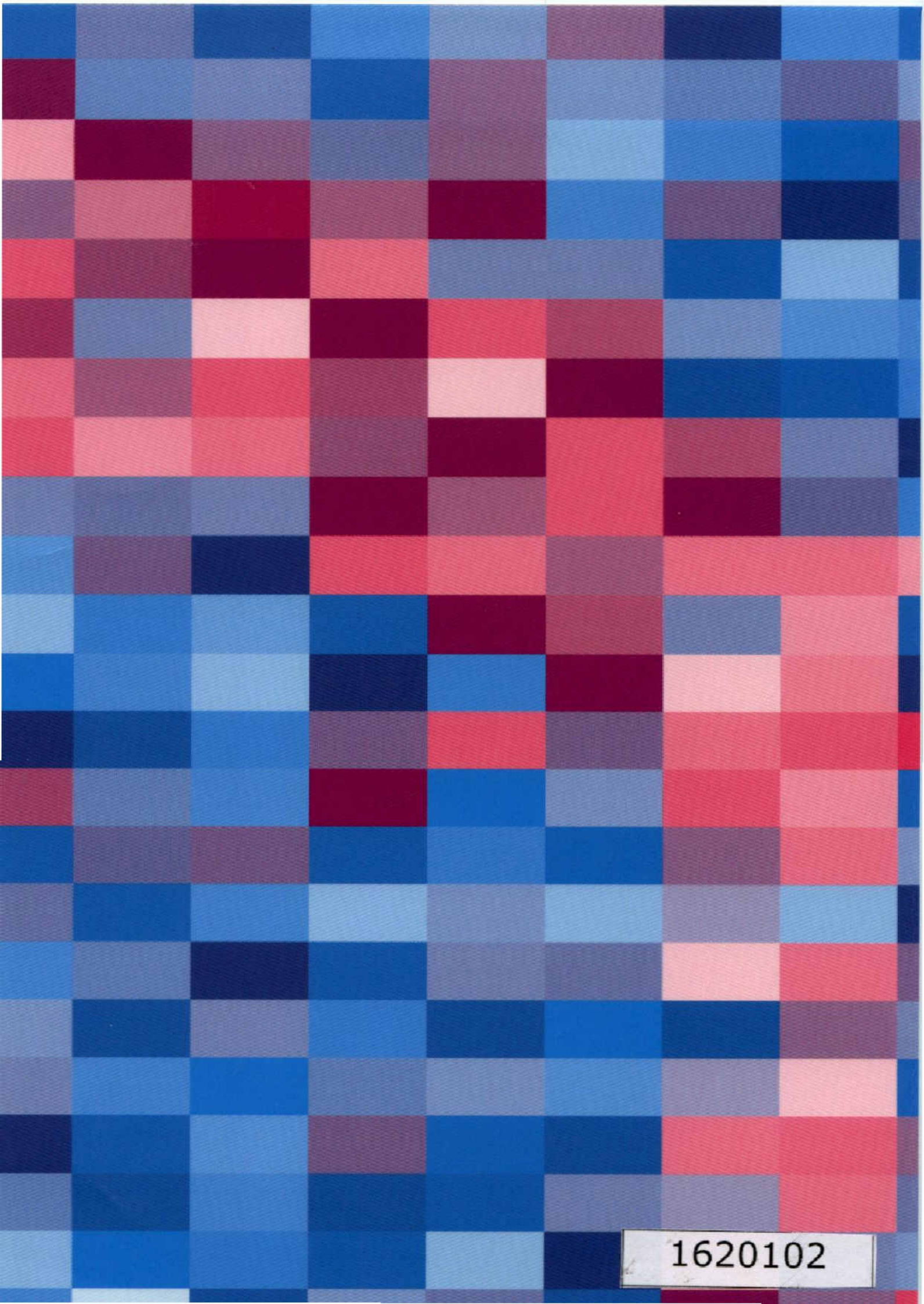
Ambergris Fragrance Compounds from Labdanolic acid and Larixol

M.G. Bolster



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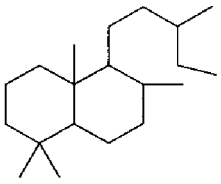
Chapter 1

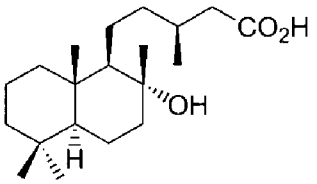
Labdanes

Abstract

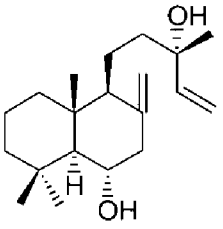
A general introduction to the occurrence, function, biosynthesis and bioactivity of labdanes is presented. Two abundantly available labdanes, e.g. labdanolic acid and larixol, can be considered as potentially versatile starting materials in synthesis and a selection of the chemistry of both compounds is presented.



labdane skeleton



labdanolic acid



larixol

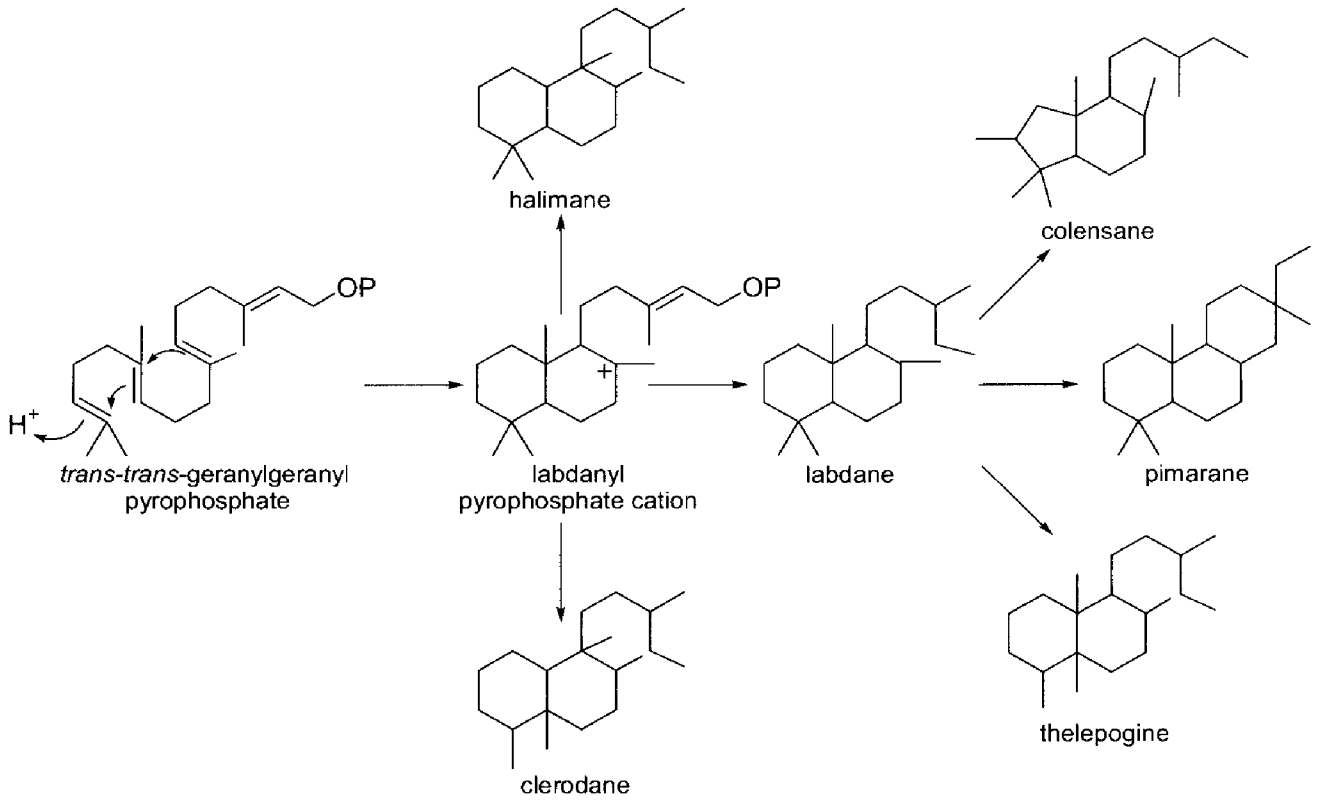
1.1 Structure and nomenclature

Isoprenoids, also known as terpenes, terpenoids, or isopentenoids, form one of the main classes of secondary metabolites and are amongst the most widespread natural products. They are typically found in all parts of higher plants and also occur in mosses, liverworts, algae and lichens, some insects, mammals and fungi.[1] Despite their structural diversity, isoprenoids have a simple common feature. All isoprenoids originate from isopentenyl pyrophosphate[2] thus giving rise to hemiterpenes (C(5)), monoterpenes (C(10)), sesquiterpenes (C(15)), diterpenes (C(20)), sesterpenes (C(25)), triterpenes (C(30)), carotenoids (C(40)), and polyisoprenoids ($(C(5))_n$).

The history of isoprenoids spans centuries of civilization. Essential oils, particularly oil of turpentine, were known to the Ancient Egyptians whilst they also are mentioned in Dioscorides 'De Materia Medica'. It is easy to understand that man employs the natural functions of isoprenoids, for instance to improve agriculture. Examples are the use of pheromones in order to monitor and control insect populations,[3] and the use of insect antifeedants as natural pesticides,[4] but the application of isoprenoids is not restricted to their original functions. Since ancient times, isoprenoids are applied as food additives and as medicines, mostly in the form of plant extracts or the whole plant, and to improve the quality of life as flavour and fragrance compounds.

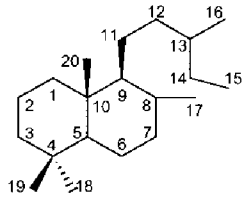
This thesis deals with labdanes, which are diterpenes derived from geranylgeranyl pyrophosphate. They are widely spread in the plant kingdom and can be considered as the central intermediates in the biosynthesis of several other diterpenes like colensanes, pimaranes, thelepogines, halimanes and clerodanes as is depicted in Scheme 1.1.[1]

Scheme 1.1



The name labdane is used for the saturated hydrocarbon that is structurally characterized by a 4,4,10-trimethyl substituted *trans* decalin system with a β-orientated substituted side chain at C(9). The C atoms are numbered as depicted in Figure 1.1, and throughout this and the following chapters the numbering of the carbon skeleton will be used as given in **1**. Labdanes occur in both enantiomeric series and prefixes are used to indicate changes to the normal terpenoid skeleton. [5]

Figure 1.1

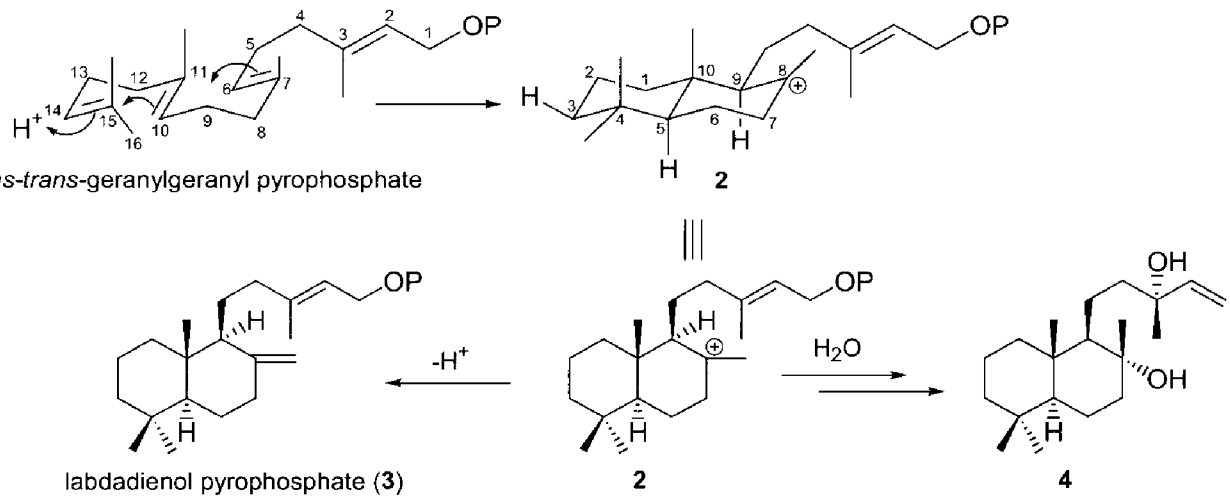


labdane diterpene (**1**)

1.2 The biosynthesis of labdane diterpenes

All structural classes of labdanes can be derived from geranylgeranyl pyrophosphate, through cyclizations.[6] The cyclization normally progresses directly to the bicyclic decalin system which is subsequently discharged by addition of water or proton elimination. The configuration of C(5,8,9,10) is determined by the folding of the *trans-trans*-geranylgeranyl pyrophosphate chain. Proton induced cyclization of the folded chair-chair conformation gives the labdanyl pyrophosphate cation (**2**) (Scheme 1.2).

Scheme 1.2

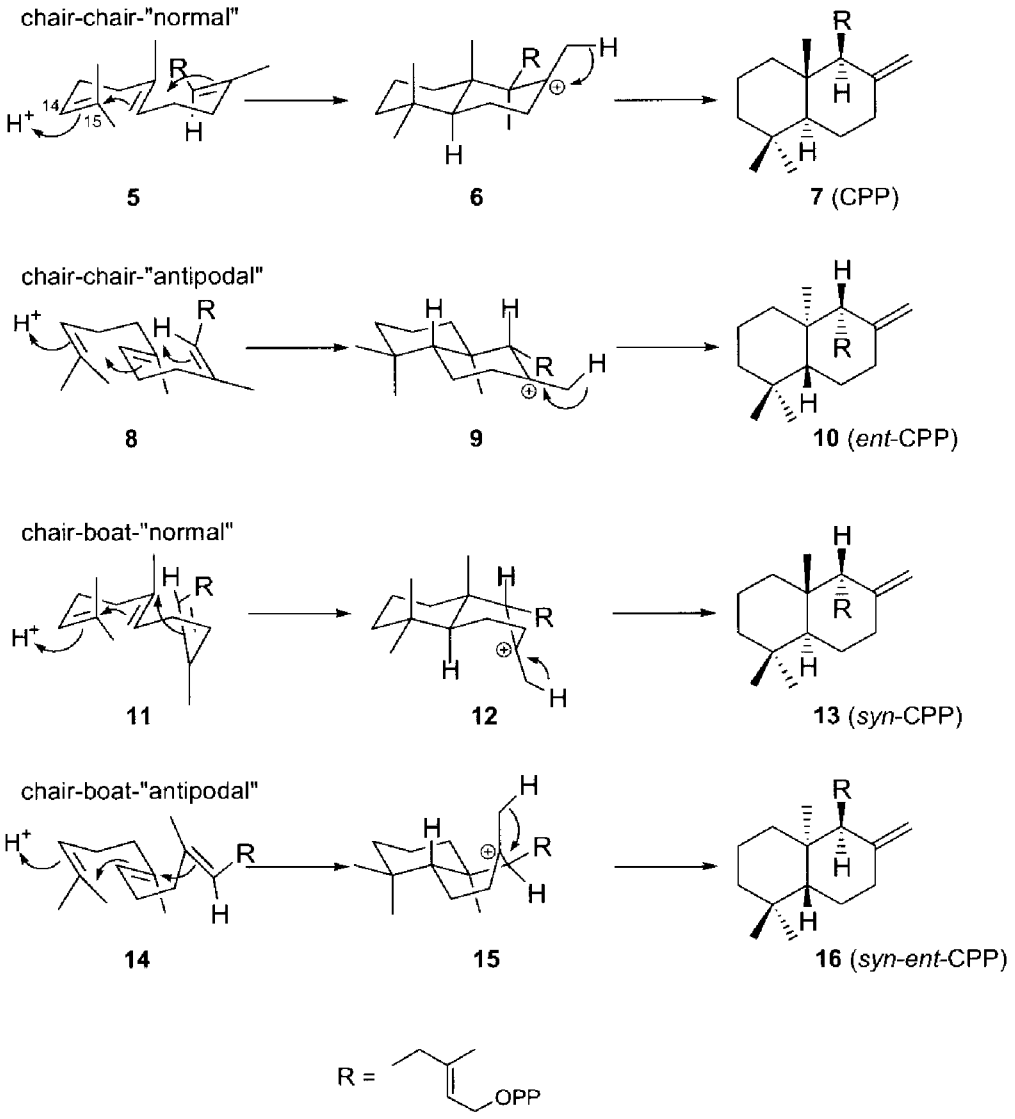


Hydratation of the C(8)-carbocation and allylic rearrangement in the side chain than leads to sclareol (**4**). Deprotonation to the C(8) exocyclic double bond produces labdadienol

pyrophosphate, which is an important intermediate in the biosynthesis of tri- and tetracyclic diterpenes.

Often both enantiomeric forms (*enantio-* or *ent-*) are produced, in the same series of diterpenes. Apparently the mode of cyclization is not entirely determined by the topology of the enzyme but must be highly favoured stereoelectronically as cyclization can often be carried out with great success under purely chemical conditions of acid catalysis.

Scheme 1.3

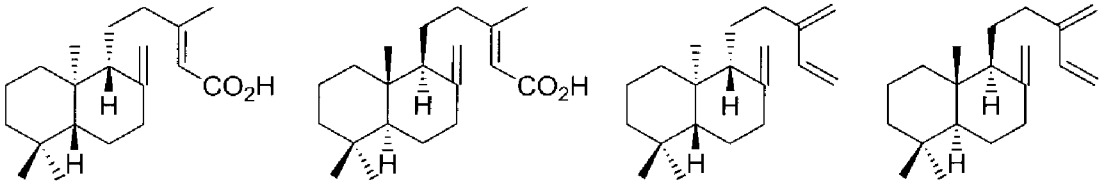


The most favourable conformation of the folded polyenic chain during the cyclization is the 'chair (pre-ring A) - chair (pre-ring B)' conformation. *A priori*, such a conformation can exist in two enantiomeric forms.[7] Protonation of the Δ^{14}-double bond of all *trans* geranylgeranyl pyrophosphate (*E,E,E*-GGPP), followed by the attack of the Δ^{10} double bond on the C(15) carbocation, can give four possible products, depending on the conformation of the *pro*chiral substrate. The chair-chair conformation **5** gives the C(8)-carbocation **6** of copalyl diphosphate (CPP, (**7**)) with the "normal" *anti,anti* absolute stereochemistry (Scheme 1.3). The antipodal chair-chair conformation **8** of

GGPP gives upon cyclization *ent*-copalyl diphosphate (*ent*-CPP, (**9**)) with the enantiomeric *anti,anti* absolute stereochemistry. The chair-boat conformation **11** gives rise to the "normal" *syn*-CPP (**13**) and the chair-boat conformation **14** leads to *syn-ent*-CPP (**16**). The *trans*-junction between the rings A and B, found in all labdanes is in agreement with the stereoelectronic requirements of a concerted mechanism, in which multiple additions on non-conjugated double bonds take place.
Few biosynthetic studies have been reported about labdanes and it has been suggested that a two-step cyclization of GGPP *via* monocyclic intermediates may occur as well. The presence of variable amounts of acyclic, mono- and bicyclic diterpenoids in *Bellardia trixago* has been mentioned as support for this supposition.[8]

The normal labdanes are biosynthesized *via* **6**, and the less common *ent*-labdanes, are obtained *via* **9**. The co-occurrence of labdanes and *ent*-labdanes indicates that both biosynthetic routes can take place, sometimes even in the same plant. For example, the enantiomers **17** and **18** occur in the resin of *Eperua purporea*. *ent*-Sclarene (**19**) and sclarene (**20**) have been isolated from different specimens of *Dacridium intermedium* (Figure 1.2).[9] It is supposed that the enzyme responsible for the cyclization of geranylgeranyl pyrophosphate to the labdane skeleton allows enantiomeric leakage to yield optically impure products.

Figure 1.2



17 **18** **19** **20**

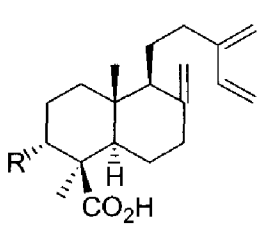
The absolute stereochemistry that has been assigned to some labdanes is not always secure. In view of the reported co-occurrence of members of both enantiomeric series, there is a need for a critical survey of this area.[10g]

1.3 Occurrence of labdane diterpenes

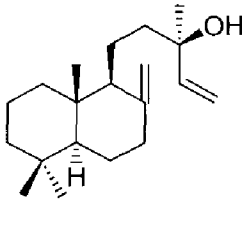
The labdanes isolated from nature up to 2000 have been reviewed and will not be repeated here.[1,10,11] The examples mentioned below are ment to give an *impression* about the structures and occurrence of labdanes in Nature, it is not the intention to be complete in this summary.

Conifer oleoresins are a rich source of labdanes. *Auraucaria* species gave a number of labdanes with communic acid (**21**) and manool (**22**) as the most important compounds.[12] Some labdanes with a carboxylic group in the side chain are isolated from *Pinus* species like dehydropinifolic acid (**23**),[13] anticopalic acid (8(17)-E-13-labdadien-15-oic acid),[14] cyclo-anticopalic

acid (**24**)[15] and its fission product **25**. In the genus *Juniperus* the communic acids (**21**) can be used as chemotaxonomic markers.[16] The berries of *Juniperus excelsa* are an important source of the cytoxic juniperexcelsic acid (**26**).[17] Imbricatolic acid (**27**) co-occurs with *cis*- and *trans*-communic acids in all *Cupressus* resins except in *Cupressus sempervirens*.[18] A series of 3,15- and 19-oxygenated labdanes (*e.g.* **28**) are amongst the diterpenoid constituents of *Juniperus thurifera* (Cupressaceae).[19]



21: R=H
26: R=OAc



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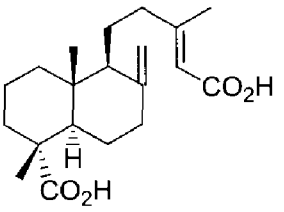

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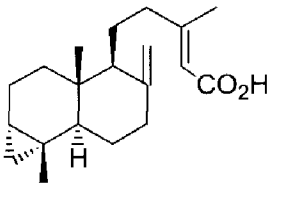

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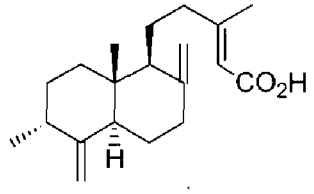

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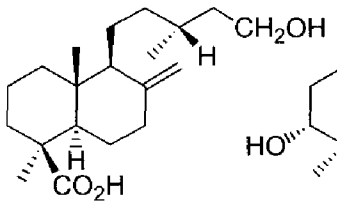

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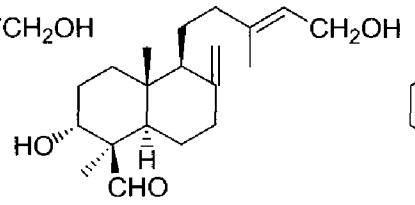

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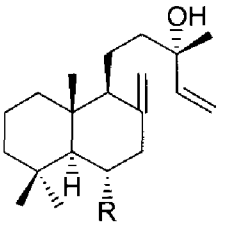
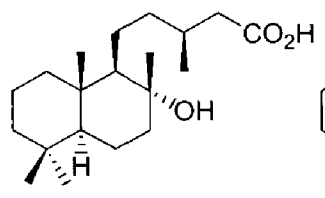


29: R=H
30: R=OH
31: R=OAc

Larix (larch) oleoresin contains several diterpenes[20,21] and especially *epi*-manool (**29**),[22] larixol (**30**) or its C(6)-acetate (**31**) should be mentioned. Heartwood extracts of *Larix gmelini* contains large amounts of larixol. *Larix decidua* Miller resin, formerly available commercially under the name of Venice turpentine, contains large amounts of larixyl acetate (**31**) together with lesser amounts of the free diol larixol (**30**) and *epi*-manool (**29**).

The mediterranean shrub *Cistus ladaniferus* gives an exudate in which labdanolic acid (**32**) is the main component. *Cistus* species also give rise to oxidized derivatives of labdanolic acid like cistadienic acid (**33**), cistenolic acid (**34**)[23] and acetoxy-ketone **35**.[24] In the latter the configuration at C(13) has not been established but from biogenetic considerations it may be assumed that it is the same as in the other labdanes.



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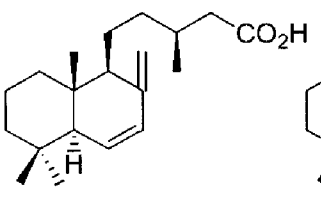

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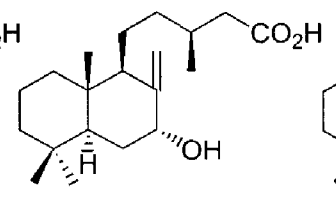

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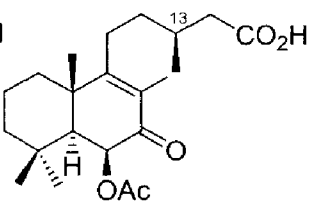
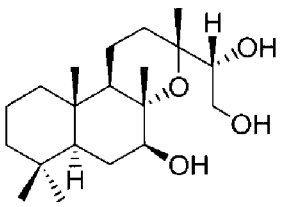


35

Sideritis (Compositae) species have been a fruitful source of labdanes. A new derivative of manoyl oxide, borjatriol (**36**),[25] has been obtained from *S. mugronensis* whilst barbatol (**37**) has been isolated from *S. arborescens*.[26] Andalusol (**38**)[27] which has been reported to have antiinflammatory properties and andalusol derivatives like 6-deoxyandalusol[28] have been obtained from *S. arborescens*. 6-Deoxyandalusal (**39**) and *ent*-3β,12α,dihydroxy-13-*epi*-manoyl oxide (varodiol (**40**)) were obtained from *S. varoi*.[29] The manoyl oxide derivatives sidnutol (**41**) and gomerol (**42**) were isolated from *Sideritis nutans*.[30] 13-*Epi*-manoyl oxide derivatives including ribenol (**43**) and its 12-hydroxy derivative are constituents of *Sideritis varoi* subsp. *nijarensis*.[31]



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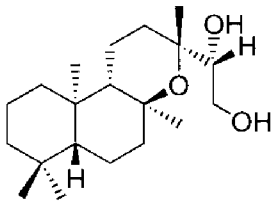

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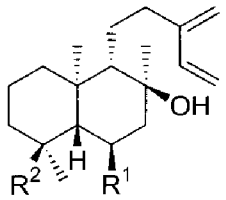
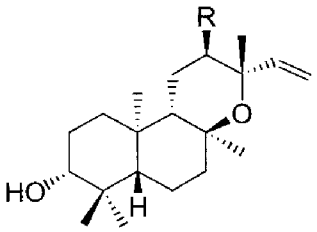
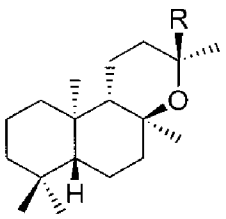


38: R^1=OH, R^2=CH_2OH
39: R^1=H, R^2=CHO

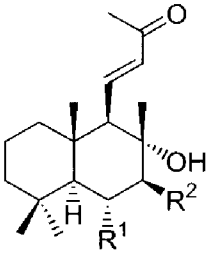


40: R=OH
43: R=H

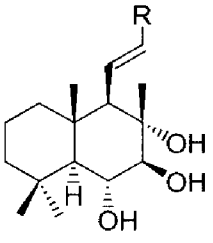


41: R=CH_2OH
42: R=CH_2CH_2OH

Compositae regularly have yielded labdanes. The highly oxygenated sterebins A-D (**44a-d**)[32] and the sterebins E (**45a**)[33] and F (**45b**),[33] which are Δ^{13} isomers were isolated from *Stevia rebaudiana*. The sterebins G and H (**46**), from the same source are epimers at C(14).[33]

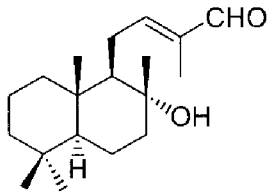


44a: R^1=R^2=OH
44b: R^1=OAc, R^2=OH
44c: R^1=OH, R^2=OAc
44d: R^1=H



45a: R=
45b: R=
46: R=

The genus *Nicotiana* is a rich source of labdanes or *nor*-labdanes like (**47**), (**48**)[34] and raimonol (**49**).[35] The diterpenes that occur in the leaf surface gum are considered to be precursors for the aromatic properties, which develop after curing and fermentation.[36]



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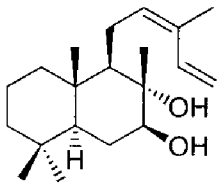

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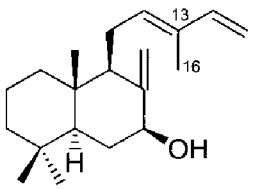
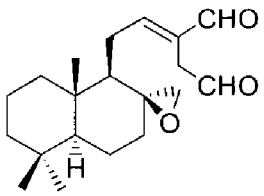


49

Aldehydes are not very common in Nature, but the Zingiberaceae contain a number of labdane dialdehydes like Afromodial (**50**)[37] and (**51**)[38] from *Afromomun* species.



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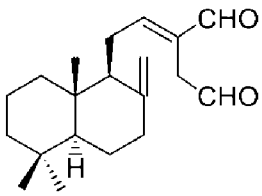

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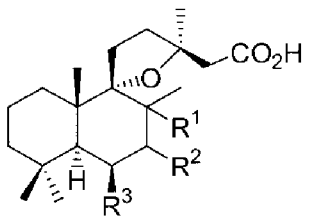
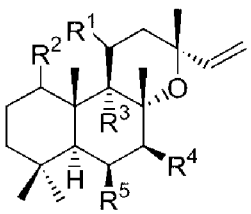


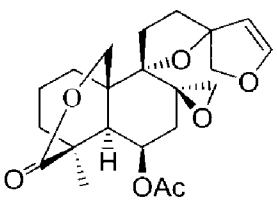
52: R^1, R^2=Δ, R^3=H
53: R^1, R^2=Δ, R^3=OH
54: R^1, R^2=, R^3=H

Characteristic labdanes with a spiro tetrahydrofurane structure were isolated from *Grindelia* species including grindelic acid (**52**)[39] from *G. robusta* and *G. squarrosa*, **53** and **54** were found in *Grindelia camporum*.[40]

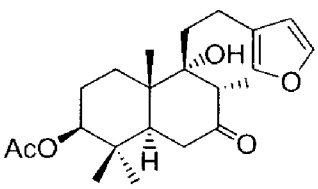
Phytochemical investigations of Labiatae gave rise to several highly oxygenated labdanes. Some of these have interesting properties like forskolin (**55**)[41] and coleosol (**56**),[42] isolated from *Coleus forskohlii*, nepetaefolin (**57**)[43] from the medicinal plant *Leonotis nepetaefolia*, and calyone (**58**) and precalyone (**59**),[44] isolated from *Roylea calycina*, the latter showing tumour inhibitory activity.



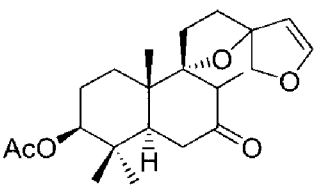
55: R^1=O, R^2=  OH, R^3=OH, R^4=OAc, R^5=OH
56: R^1=O, R^2=H, R^3=OH, R^4=H, R^5=OH
60: R^1=  OAc, R^2=  OAc, R^3=H, R^4=OH, R^5=OAc



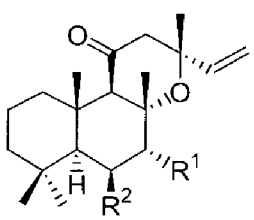
57



58



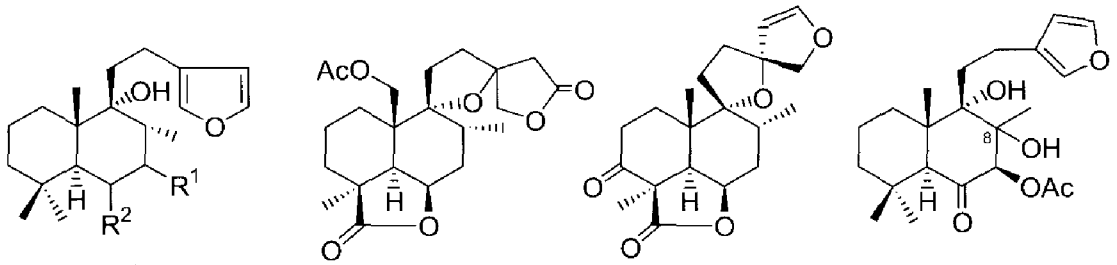
59



61a: R^1=OH, R^2=OAc
61b: R^1=OAc, R^2=OH

The ptychantins, *e.g.* (**60**), are relatives of forskolin and were isolated from the liverwort *Ptychanthus striatus*.[45] Some 11-oxomanoyl oxide derivatives, coleonol E (**61a**) and F (**61b**), were also obtained from *Coleus forskohlii*.[46] Their oxygenation pattern is reminiscent of that of the tricyclic diterpenoids which have been obtained from other *Coleus* species.

Ballota species gave rise to diterpenes with a furan-ring in the side chain as characteristic feature. Examples are hispanolone (**62**)[47] from *B. hispanica* and ballotinone (**63**)[48] from *B. aucheri*. *Leonotis leonotis*, *Marrubium friwaldskyanum* and *Galeopsis reuteri* are Labiatae which contain for example the labdanes leonitin (**64**),[49] preperegrinine (**65**),[50] and galeuterone (**66**)[51] with a spiro ether group. The stereochemistry in **66** was not ascertained. However, on biogenetic grounds it is supposed that **66** belongs to the normal labdane series since this absolute configuration has been found in all the diterpenoids isolated from *Galeopsis* species.

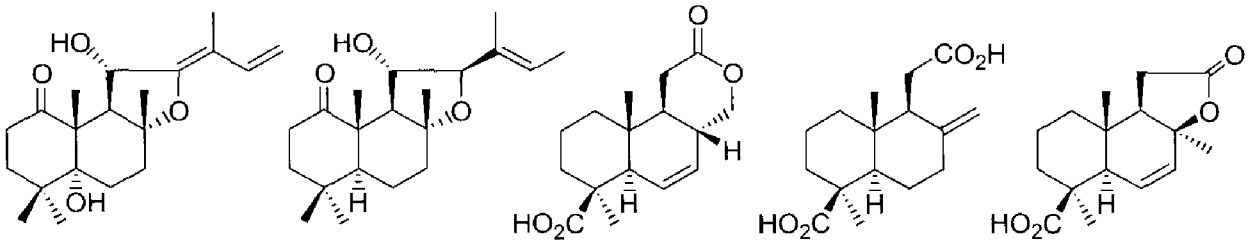


62: R^1=O, R^2=H
63: R^1= ⟝ OH, R^2=O

64 **65** **66**

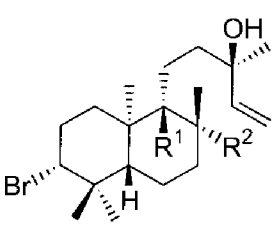
Some variants of the manoyl oxide skeleton, the scapanins A (**67a**) and B (**67b**), were isolated from the liverwort *Scapania undulata*.[52]

Nor-labdanes such as acrostalic acid (**68**) and the related products acrostalidic acid (**69**) and isoacrostalidic acid (**70**) from *Acrostalagmus* species are often found as fungal metabolites.[53]

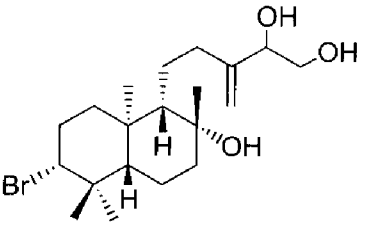


67a **67b** **68** **69** **70**

Marine organisms are a still growing source for labdanes.[54] The red alga *Laurencia concinna* contains concinndiol (**71**),[55] in which the bromine atom may represent the residue of a cyclization initiator. Other species of *Laurencia* synthesized the related bromolabdanes isoconcinndiol (**72**)[56] and venustanol (**73**).[57]



71: R^1=OH, R^2=H
72: R^1=H, R^2=OH

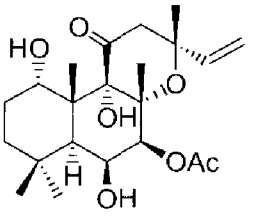


73

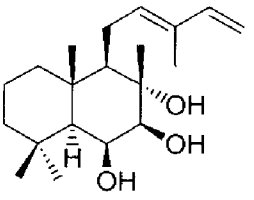
1.4 Biological activities of labdanes

Natural products often possess pharmacological properties which can be of use to humans.[58] They may provide lead compounds for the development of new drugs or may act as tools in biomedical research. Their role as plant secondary metabolites is often not clear, but many are substrates for life process, are toxins for self-defence, hormones, or molecules with other functions.

Figure 1.3



55



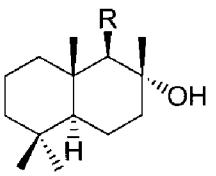
74

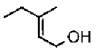
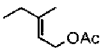
The biological activity of only a few labdanes have had more than a passing interest.[59,60] This does not necessarily mean that biological activity is rare among labdanes. Most compounds have only been tested for one specific biological activity, or have not been tested at all. Many labdanes did show activities, but mostly these were not good enough to reach medicinal application. Well-known is the labdane forskolin (**55**), a component of *Coleus forskohlii*, which has attracted considerable interest because of its antihypertensive activity (Figure 1.3).[61] Another example is crotomachlin (**74**), a labdane diterpene from the East African plant *Croton macrostachyus*, which possesses, *in vitro*, antilipoxygenase activity.[62] In the next sections an account of the bioactive labdanes from plants and marine sources is summarized.

1.4.1 Antibacterial activity

13-*Epi*-sclareol (**75**), labdan-14-ene-8,13-diol (**76**), 5*R*,8*R*,9*R*,10*R*-labdan-13(*E*)-ene-8a,15-diol (**77**), and 5*R*,8*R*,9*R*,10*R*-labdan-13(*E*)-en-8a-ol-15-yl acetate (**78**), isolated from *Cistus incanus* (Cistaceae), were found to be more active than ampicillin, a standard antibiotic, when

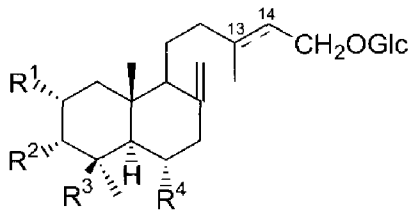
tested on *Klebsiella pneumoniae*, *Staphylococcus aureus* and *Pseudomonas aeruginosae* at a concentration of 100 μg/mL.[63]



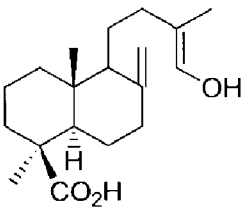
	R		R
75		**77**	
76		**78**	

A series of labdane diterpenes was isolated from the leaves of *Viburnum suspensum* (Caprifoliaceae), these labdanes were termed as gomojosides.[64] Gomojoside B (**79a**), C (**79b**), E (**79c**), and F (**79d**) were found to exhibit antibacterial activity at a concentration of 500 ppm in nutritional agar medium against *E. coli*. Monoglycosides gomojosides K-O (**79e-i**) exhibited potent antibacterial activity against *Aeromonas salmonishida* at a concentration of 100 ppm in nutrition agar medium. Gomojoside M (**79g**) was also found to be active against *Bacillus subtilis*.[65]

From the bark of *Juniperus procera* (Cupressaceae)[66] isocupressic acid (**80**) and cryptotrienolic acid (**81**) were tested against *B. aureus*, *Streptococcus durans*, *Enterococcus faecalis* and *Mycobacterium intracellular*. Cryptotrienolic acid (**81**) was found to exhibit weak antibacterial activity whereas isocupressic acid was found to be inactive.



79a-i



80

	R^1	R^2	R^3	R^4	Δ
79a	H	H	COOGlc	H	-
79b	H	H	CH_2OGlc	H	Δ^{13}
79c	H	H	CH_2OGlc	OH	Δ^{13}
79d	H	H	CH_2OGlc	OH	-
79e	OH	OH	CH_2OH	OH	Δ^{13}
79f	H	H	CH_2OH	OH	-
79g	H	OH	CH_2OH	H	Δ^{13}
79h	OH	H	CH_2OH	H	Δ^{13}
79i	H	OH	CH_3	OH	Δ^{13}

The twigs of the shrub *Premna oligotricha* (Verbenaceae) are used in East Africa as chewing sticks while the smoke formed by burning the plant is used to sterilise milk containers. These uses suggest the probable presence of antibacterial compounds. The crude ethanolic extract of *P. oligotricha*[67] showed antimicrobial activity against a wide range of Gram-positive bacteria, *e.g. Streptococcus* sp. are responsible for dental caries and *Lactobacillus* sp. are an important group of acid-forming bacteria which are also responsible for dental problems.

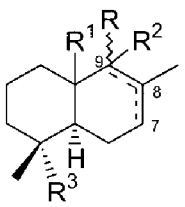
Compound **81**, which was isolated from the crude extract, was found to be active against a number of Gram-positive bacteria and streptomycin was used as standard for comparison.

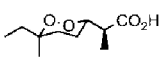
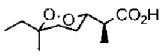
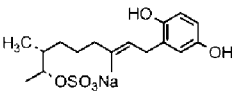
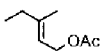
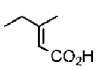
From the methanolic extract of the Thai sponge *Mycale*, mycaperoxides A (**82a**) and B (**82b**) were isolated.[68] Both exhibited antibacterial activity by inhibiting the growth of Gram-positive bacteria *B. subtilis* and *S. aureus*. Besides both labdanes exhibited antiviral activity (IC_{50} 0.25-1.0 μg/ml) against vesicular stomatitis and herpes simplex type-1 virus.

1.4.2 Antifungal activity

From the seeds of *Alpina galanga* (Zingiberaceae), some antifungal labdanes, *E*-8β(17)-epoxylabd-12-ene-15,16-dial (**50**), (*E*)-8(17),12-labdadiene-15,16-dial (**51**) and galanolactone (**83**), were isolated and tested against various strains of *Candida*.[69] Extraction of the seeds of *Aframonum daniellii* (Zingiberaceae)[70] with hexane yielded the hot tasting antifungal compounds **50** and **51**.

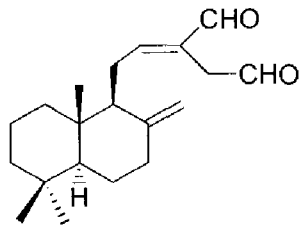
Sclareol (**4**) at a concentration of 100 μg/ml gave good control of rust fungi of french bean, broad bean and wheat, reducing infection to less than 10% of the control. [71]



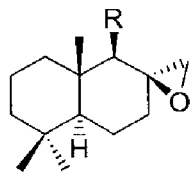
	R	R^1	R^2	R^3	Δ
81		α-CH_3	H	CH_3	-
82a		α-OH	β-CH_3	CH_3	-
82b		β-CH_3	α-OH	CH_3	-
84		β-CH_3	H	CH_3	Δ^7
89		β-CH_3	H	CH_3	Δ^7
90		β-CH_3	H	CH_3	Δ^7
96		β-CH_3	-		Δ^8

Compounds isolated from the leaves of *Cistus incanus*[63] were tested for antifungal activity against *C. albicans*, *Torulopsis glabrata* and the infectious fungus *Saccharomyces cerevisiae*. 5*R*,8*R*,9*R*,10*R*-Labdane-13(*E*)-ene-8a,15-diol (**77**) was the only compound found to be active against the fungus *C. albicans* at a concentration of 1 μg/mL.

Halisulfate (**84**) isolated from a dark brown sponge[72] (Halichondriidae) was found to inhibit the growth of *C. albicans* at a concentration of 5 μg/disk.



51



50: R= 

83: R= 

1.4.3 Anti-inflammatory activity

The leaves of a Japanese plant *Cryptomeria japonica* (Taxodiaceae) are used in traditional medicine for the treatment of eczema, swelling and injury by topical application. The activity was found to be due to the compound *cis*-communic acid (**21**).[73] The activity testing was done using the carrageenaninduced paw edema (CPE) method in rats. *cis*-Communic acid (**21**) was found to inhibit the histamine induced contraction in guinea pig ileum, as histamine is used in the CPE test. This is the first time that a compound having a labdane skeleton was reported to show anti-inflammatory activity.

1.4.4 Antileishmanial activity

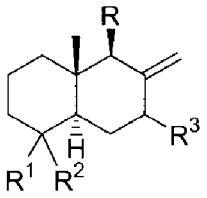
In the search for new leishmanicidal agents the neutral extract of the stem bark of *Polyalthia macropoda* (Annonaceae) was subjected to *in vitro* bioassay on cultures of *Leishmania donovani*, a visceral leishmaniasis agent.[74] Labdane **85** at a concentration of 0.25 mg/mL inhibits the parasites cell division with a LD_{50} of 0.75 mg/mL.

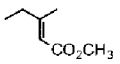
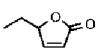
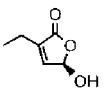
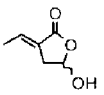
1.4.5 Cardiotonic activity

Medigenin (**86**) and medigenin acetate (**87**), isolated from *Melodinus monogynus* (Apocyanaceae), exhibited cardiotonic activity in isolated frog heart and in isolated mammalian heart. Medigenin (**86**) increased the tone and force of contraction of the heart and the heart rate was decreased.[75] Similar positive inotropic and negative chronotropic effects were observed on isolated rabbit heart. The acetylated derivative also increased the tone and force of myocardial contraction and decreased the heart rate and was more potent than medigenin.

1.4.6 Cytotoxic agents

On screening the chloroform extract of the rhizomes of *Hedychium coronarium* (Zingiberaceae), it was found to inhibit the growth of Chinese hamster V-79 cells and sarcoma 180 ascites in mice.[76] Detailed chemical analysis led to the isolation of the known (*E*)-labda-8(17),12-diene-15,16-dial (**51**) along with four new coronarins A-D (**88a-d**). All compounds exhibited cytotoxicity, whereas coronarin A and B exhibited significant activity. The cytotoxicity of various compounds was assessed by determing T/C (number of stained colonies of test group/those of control groups) x IC_{50}. Solutions of 10 µL each of various concentrations (1, 3, 10, 30 µg/mL) were added to the cultures of cloned Chinese hamster V-79 cells.

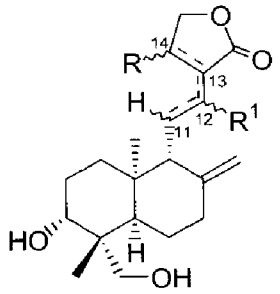


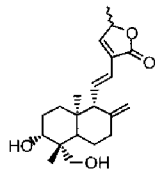
	R	R^1	R^2	R^3
79h		β-CO_2H	α-CH_3	H
83		CH_3	CH_3	H
21		β-CO_2H	α-CH_3	H
85		β-CH_3	α-CO_2H	H
86		CH_2OH	CH_3	H
87		CH_2OAc	CH_3	H
88a		CH_3	CH_3	β-OH
88b		CH_3	CH_3	H
88c		CH_3	CH_3	H
88d		CH_3	CH_3	H

Several compounds have been isolated from the resin 'ladano' obtained from the plant *Cistus creticus* (Cistaceae).[77] The labdanes **77**, **89**, **90** along with other diterpenes were tested for cytotoxic activity using different cell lines: MOLT 3, a human cell T cell line originating from a patient with acute lymphoblastic leukemia (ALL); RAJI cells, a pre-B-cell line originating from a patient with Burkitt lymphoma; and H 9 cells originating from a patient (ALL). All tests were carried out at three different concentrations (15, 7.5 and 3.75 μg/mL) and using tethotrexate as a standard drug. After *in vitro* testing it was found that the isolated compounds **77**, **88**, **80** proved to be active against RAJI, MOLT 3 and H 9 cell lines. The compouds were also found to be active against the murine leukemia P-388 (3 PS) and KB cell lines.

Cell differentiation inducers may act as new types of antitumour agent and hence there is a need for naturally occurring substances, which induce differentiation of leukemia cells. The methanolic extract of the aerial parts of *Andrographis paniculata* (Acanthaceae) showed potent differentiation inducing activity.[78] Monomeric compounds like **91** and **92** showed cell differentiation activity, but dimeric compounds **93**, **94**, **95** were found to be more active that the monomers.

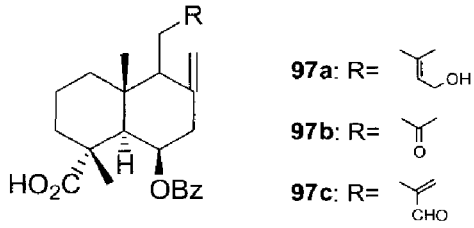
Mycaperoxides A (**82a**) and B (**82b**) isolated from the sponge *Mycale* sp.[68] showed significant cytotoxicity (IC_{50} = 0.5-1.0 μg/mL) against cell lines of P-388, A-549 and HT-29. (*E*)-8β(17)-Epoxylabd-12-ene-15,16-dial (**50**) and galanolactone (**83**) exhibited mild cytotoxicity against KB cells (ED_{50}) = 38.5 μg/mL and 22.5 μg/mL, respectively.[69]



	R	R^1	
91	α-OH	H	Δ^{12}
92	H	OCH_3 (α or β)	Δ^{13}
93 – 95	H		Δ^{13}

1.4.7 Inhibitors of aldose reductase, β-glucuronidase and phospholipase A_2

Accumulation of sugar sorbitol formed from D-galactose by alsose reductase enzyme results in the appearance of cataract of the lens of eyes in galactosemic patients. Due to the increasing therapeutic demand new inhibitors of aldose reductase are needed. From the marine sponge *Dysidea* sp.[79] some metabolites inhibiting the activity of enzyme aldose reductase were isolated. The active principle isolated was dysideapalaunic acid (**96**) with a labdane unit. Total synthesis along with elucidation of the absolute stereochemistry of natural (+)-dysideapalaunic acid (**96**) has been carried out.[80]



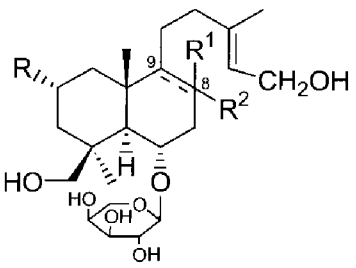
The scoparic acids A-C (**97a-c**) have been isolated from the Paraguayan drug Typycha Kurata: *Scoparia dulcis* (Scrophulariaceae), a perennial sub-tropical herb, widely used in folk medicine. Scoparic acid A (**97a**) was found to inhibit the activity of β-glucuronidase isolated from bovine liver (IC_{50} = 6.8 x 10^{-6} M).[81]

Halisulfate (**84**), isolated from the marine dark brown sponge (Halichondriidae), showed 100% inhibition of the enzyme phospholipase A_2 at a concentration of 16 μg/mL.[82]

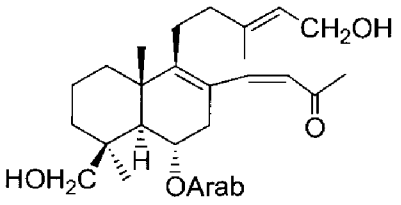
1.4.8 Natural sweetening agents

Searching for natural sweetening compounds *Baccharis gaudichaudiana* (Compositae), a plant commonly known as "Chilca melosa" and used traditionally as an antidiabetic remedy, was investigated and gave five labdane type glycosides of which gaudichaudioside A (**98a**) was found to be highly sweet. It exhibits about 55 times the sweetening potency of a 2% w/v aqueous sucrose solution.[31] Gausichaudiosides B-E (**98b-e**) were found to be sweet bitter, neutral tasting, wholly bitter and sweet bitter, respectively, when tested as 0.5% w/v aqueous solutions.

Gaudichaudioside F (**98f**)[15] is a bitter-tasting arabinoside constituent of the glycosides of *Baccharis gaudichaudiana*.

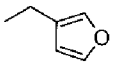
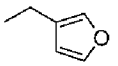


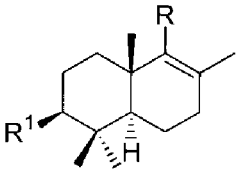
	R	R^1	R^2	
98a	H	CHO	H	Δ^8
98b	H	CH_2OH	H	Δ^8
98c	OH	CH_2OH	H	Δ^8
98d	H	β-CH_3	α-OH	
98e	OH	CH_3	H	Δ^8



98f

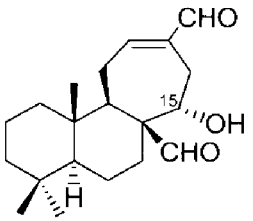
The roots of *Phlomis younghushbandii* (Labiatae) contain a sweet furanolabdane glucoside phlomisoside I (**99**).[83] From the roots of *P. medicinalis* another sweet furanolabdane was isolated and named baiyunoside (**100**). Both were isolated earlier from the roots of a Chinese plant *Salvia digitaloides* known under the name of the crude drug "Bai-Yun-Shen".[54,84]

	R	R^1
99		$OGlc^2$-Rha
100		$OGlc^2$-Xyl

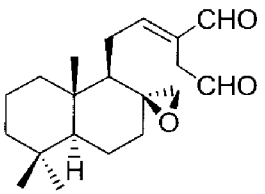


1.4.9 Pungent taste

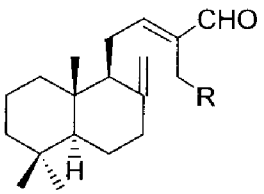
The Zingiberaceae contain a number of labdane dialdehydes, which have a pungent taste. Galanal A (**101a**) and its 15-epimer (galanal B) (**101b**) have been isolated from *Alpinia galanga*.[85] This plant is used for flavouring purposes in food in the preparation of meat dishes and curries in Malaysia. The seeds of *Afromomun* species are used as a West African food spice. Afromodial (**50**)[37] (from *A. daniellii*) and the hot-tasting dialdehyde **51**[38] have been isolated from these plants. The seeds of *Alpinia zerumbet*, which are used in Chinese medicine for stomach problems, have been shown to contain zerumin A (**102**).[86]



101a



50



51: R=CHO
102: R=CO_2H

The variety of biological activities encountered in labdane diterpenes indicates that the plants hold many keys to new drug discovery. Synthesis and modification of the decaline system which is the basic unit of all the labdane diterpenes is a viable proposition. Therefore the preparation of new analogues of this skeletal type could be carried out to get new leads in drug development.

1.5 Abundantly available labdanes and their (potential) use

Total synthesis of complex natural products can often be achieved starting from congeners that occur abundantly in Nature. Only a limited number of labdanes is available in (multi)gram quantities from Nature, which means that labdanes are not used much as starting material in synthesis. There is however one commercial important product in the flavour and fragrance industry called Ambrox® (**103**) which can be synthesized most easily from natural labdanes and for this reason the chemistry of many labdanes has been investigated extensively, mostly for this purpose. This compound is known by various trade names as *Amberlyn*® (Quest), *Ambrofix*® (Givaudan Roure), *Ambroxan* (Henkel) or *Ambrox*®, which is the Firmenich name. In this thesis this last name Ambrox® will be used.

Labdanolic acid (**32**) is a readily accessible compound from labdanum, which is a natural oleoresin from *Cistus ladaniferus*, a small wild-growing shrub found in all countries around the Mediterranean Sea. The production of labdanum is concentrated in Spain, although smaller quantities are produced in Portugal, Morocco, Yugoslavia and Greece. Next to labdanolic acid labdanum contains labdane diol, waxes and some volatile oil, but less than most of the other natural labdane containing extracts.[87]

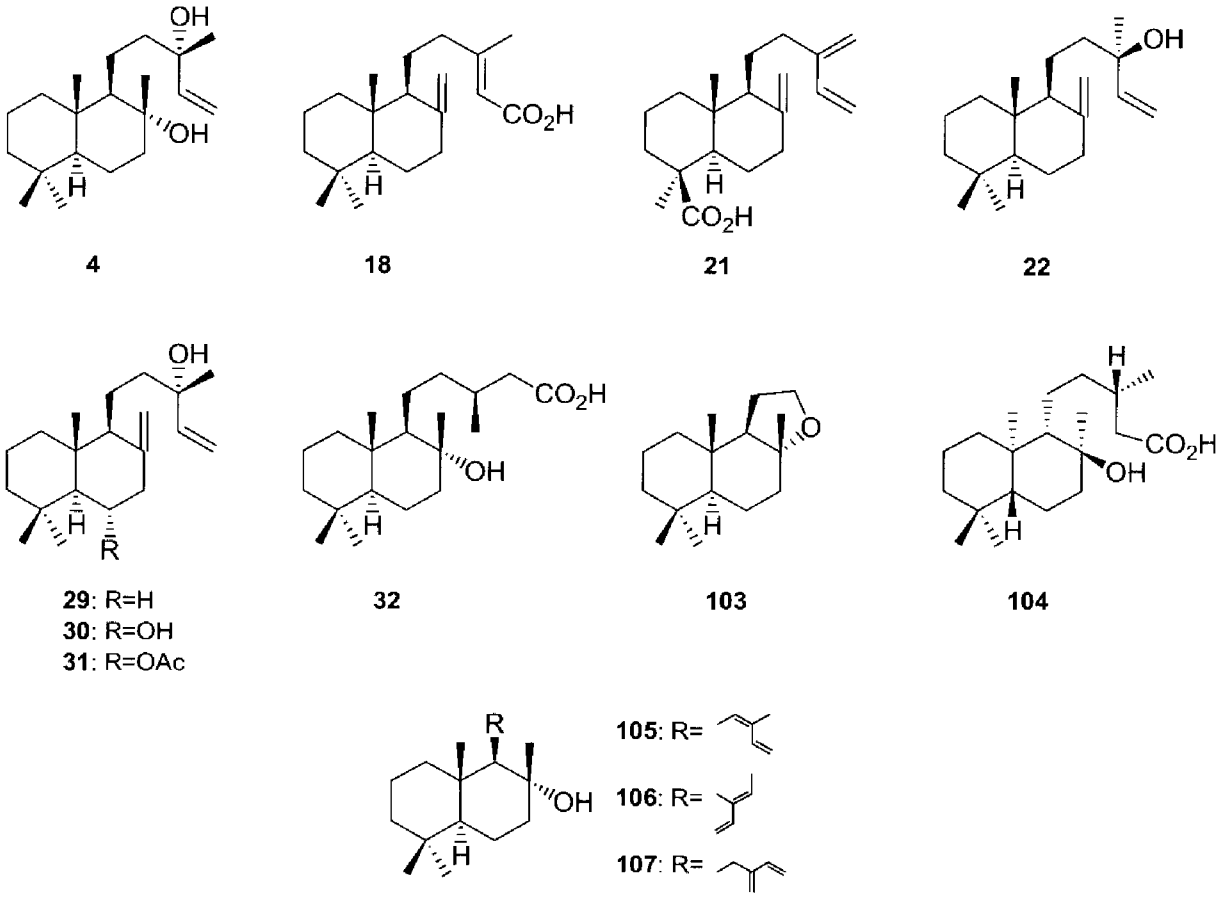
Although heartwood extracts of *Larix gmelini* contains large amounts of larixol (**30**) as well, large quantities of larixol can be isolated easier from *Larix decidua*. Larch turpentine of the latter contains large amounts of larixyl acetate (**31**) together with lesser amounts of the free diol larixol (**30**) and (+)-*epi*-manool (**29**). Upon hydrolysis larixol can be obtained easily by crystallization. The chemistry of these compounds has been well-studied and will be described in paragraph 1.7.[88]

Sclareol (**4**) is not widely distributed in Nature, but nevertheless it is the most used labdane in industry since it is the starting material[89] for the production of Ambrox® (**103**). The most convenient source is from the leaves of *Nicotiana glutinosa* (Solanaceae) and from the flower heads of *Salvia sclarea*,[71] the latter being the source for industry. Manool (**22**)[90] is a byproduct from the isolation of sclareol (**4**).

The tropical American genus *Eperua*, which occurs extensively in British Guiana, is the source of a highly durable gummy timber commonly known as wallaba. The wood is used locally for constructional purposes and as fuel. Due to its abundance, it has been examined for possible commercial applications, *e.g.* for papermaking and as a tanning agent. From the living tree a pale

viscous oleoresin can be obtained which consists mainly of eperuic acid (**104**) (Figure 1.4).[91] The acid has also been extracted from the wood. Labdanolic acid (**32**) and eperuic acid (**104**) are two representative labdane-type diterpenoids,[92] which possess the same *S* configuration at C(13), but otherwise belong to antipodal series.

Figure 1.4



Cis/trans-Abienol (**105a,b**)[93] is a constituent of *Pinus strobus*, *neo*-abienol (**106**)[94] is a constituent of *Abies sibirica*, and *iso*-abienol (**107**)[95] is found in the needles of *Pinus sylvestris* and *Jungermannia infusca*. (+)-*cis*-Abienol can also be isolated from the non-acid fraction of commercial Canadian balsam (oleoresin of *Abies balsamea* L. Mill.).[96] Abienol derivatives are used as agent for improving the taste and flavor of tobacco, harmonizing well with the original flavor of tobacco, suppressing the irritation, mildening the flavor and making the effect last.[97]

Communic acid (**21**) can be found in considerable amounts in the berries and wood of *Juniperus sabina* L.[98] (Cupressaceae) and in berries of *J. thurifers* L.[99] Communic acid (**21**) is very sensitive to acids and polymerizes on keeping and has not been obtained in a crystalline form.[100]

Due to the high price and unique olfactive and fixative properties of (-)-Ambrox® (**103**), a large number of syntheses has been reported since its first preparation in 1950. Most of them start from naturally occuring sesqui- or diterpenes such as (-)-sclareol,[101] (-)-drimenol,[102] (+)-manool,[103] manoyl oxide,[104] (-)-labdanolic acid,[105] (+)-abietic acid,[106,107] (-)-levopimaric acid,[108] and also from the monoterpenes (+)-carvone[109] and thujone[110] as will be discussed in Chapter 2. New syntheses

of (-)-Ambrox® (**103**) from the naturally occuring sources, communic acids and *cis*-abienol are reported.[111,112] This is the first time that communic acids and *cis*-abienol, major diterpene constituents of non-polar extracts of several *Juniperus*[98] and *Abies*[96] species, respectively, have been employed as starting materials. Their structural features (*trans*-decalin junction, β side chain and a diene system prone to cleavage of the C(12)-C(13) bond) converts both the communic acids (**21**) and *cis*-abienol (**104a**) in good chiral synthons for the synthesis of (-)-Ambrox® (**103**). The use of the *trans*- and *cis*-communic acids is also reported as a new natural source for the synthesis of amber-type odorants, like (+)-ambraketal.[113] Abienol is also used in the production of sclareolide.[114] The preparation of ambergris odorants is also reported from copalic acid (**18**).[115]

1.6 The chemistry of labdanolic acid

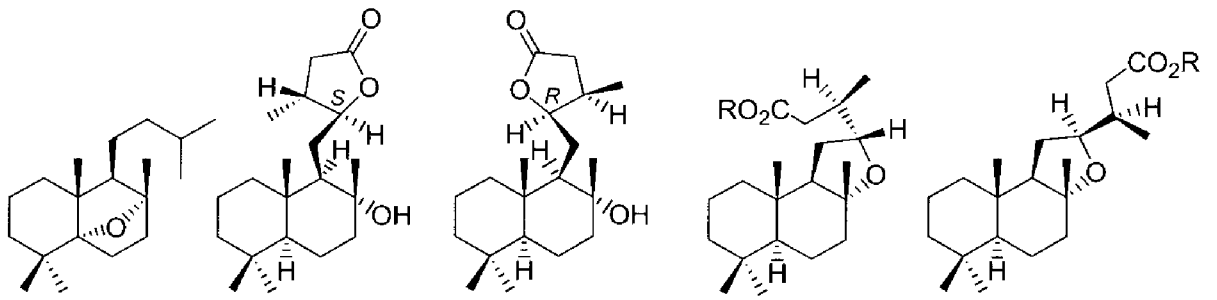
In this thesis investigations will be described on two abundantly available labdanes, *e.g.* labdanolic acid (**32**) and larixol (**30**), both can be considered as potentially versatile starting materials in synthesis and a selection of the chemistry of both compounds is presented in the next paragraphs.

The chemistry of labdanolic acid (**30**) is described with emphasis on transformations of the side chain, which give rise to precursors suitable for the synthesis of levanenolides, levantanolides, drimanes and Ambrox® (**103**). Next to the carboxyl group in the side chain, labdanolic acid also possesses a hydroxyl group at C(8) which may or may not take part in reactions. First the chemistry of labdanolic acid is described in which this hydroxyl group at C(8) is unprotected and does take part in the reaction (paragraph 1.6.1), which leads mostly to functionalization of the side chain. When the hydroxyl group at C(8) is protected as its acetate reactions of labdanolic acid take a different course, which lead mostly to decarboxylation (paragraph 1.6.2). In paragraph 1.6.3 the further degradation of the C(9) side chain is mentioned.

1.6.1 Functionalization of labdanolic acid

Reaction of labdanolic acid (**32**) with $Pb(OAc)_4$ led to a plethora of products in varying amounts (Figure 1.5).[116] From the neutral fraction products from oxidative cyclization (**108**), or lactonization (**109**) and (**110**), could be isolated. From the acid fraction the oxidative cyclization products **111** and **112** were isolated after esterification.

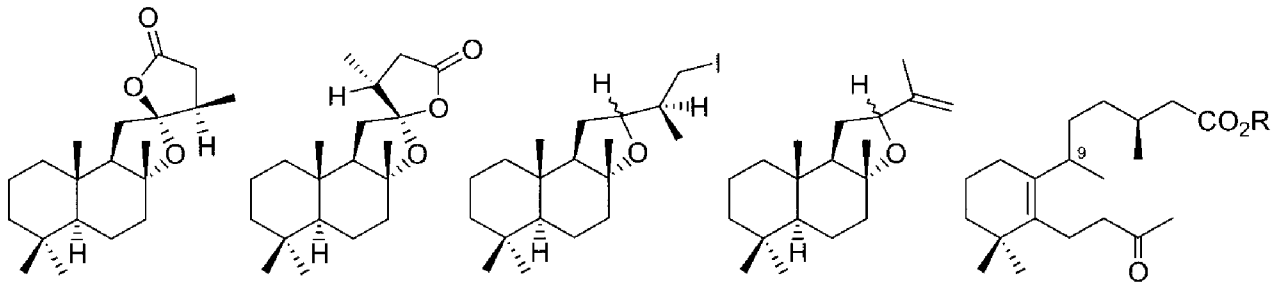
Figure 1.5



108 (2-5%) **109** (6-14%) **110** (1-2%) **111a**: R=H (1-15%) **112a**: R=H (1-15%)
111b: R=CH_3 **112b**: R=CH_3

When the reaction was performed under "hypoiodite" conditions ($Pb(OAc)_4$, I_2) further cyclization took place in the side chain leading again to unattractive mixtures of products. The lactones **109** and **110**, the desired spirolactones **113** and **114**, and the decarboxylation products **115** and **116** were obtained. From this mixture the levantanolides **113** and **114** could be isolated in low yield (Figure 1.6). Treatment of methyl labdanolate (**118**) with lead tetraacetate leads to fragmentation and fission of ring B to products **117c-d**.

Figure 1.6

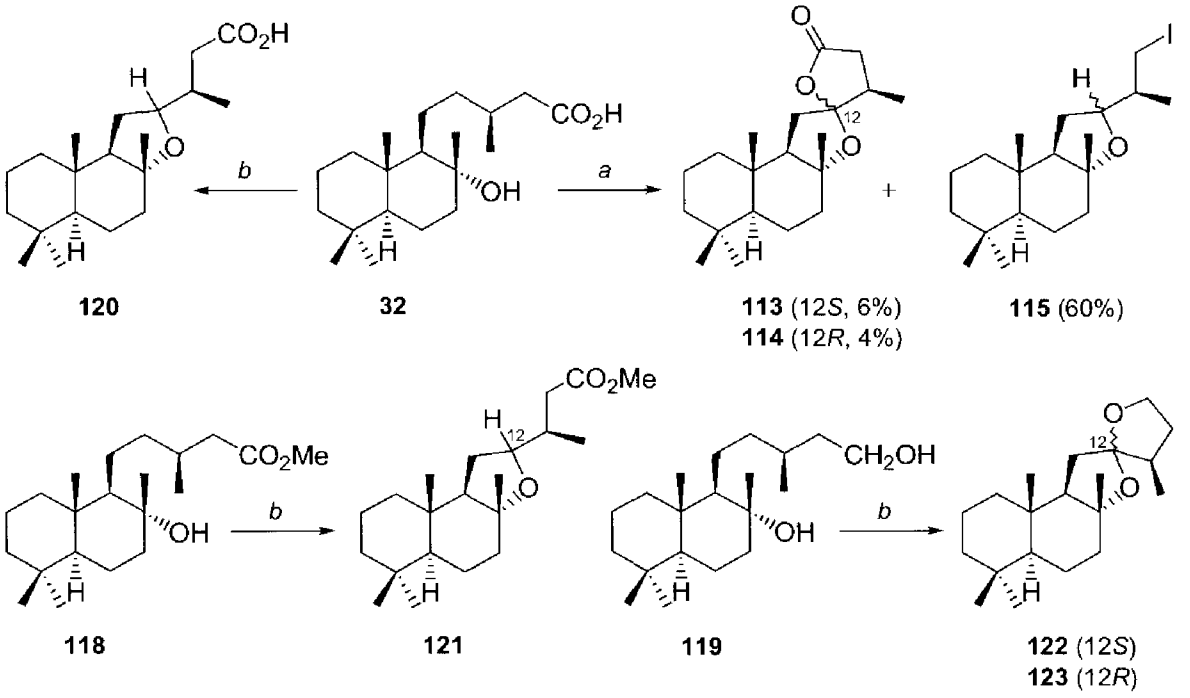


113 (9-20%) **114** (3-6%) **115** (1-13%) **116** (2-6%) **117a**: R=H (9*R*, 1%)
117b: R=H (9*S*, 1%)
117c: R=CH_3 (9*R*)
117d: R=CH_3 (9*S*)

In situ photolysis of labdanolic acid (**32**) with visible light in the presence of iodosobenzene diacetate (IBDA) and iodine leads to an alkoxyl radical which undergoes intramolecular abstraction of a suitably positioned hydrogen atom to produce the C(12) epimeric iodo derivatives **115** as the main products (Scheme 1.4).[117,118] The formation of the isomeric lactones **113** and **114** can be explained by a double hydrogen abstraction.

Irradiation with visible light in cyclohexane containing IBDA and iodine at 30 °C of the labdane derivatives **32**, **118**, and **119** gave the compounds **120**, **121**, and **122** and **123** respectively in good yield, no selectivity in the abstraction of the pro-*R* or pro-*S* hydrogen was observed.

Scheme 1.4

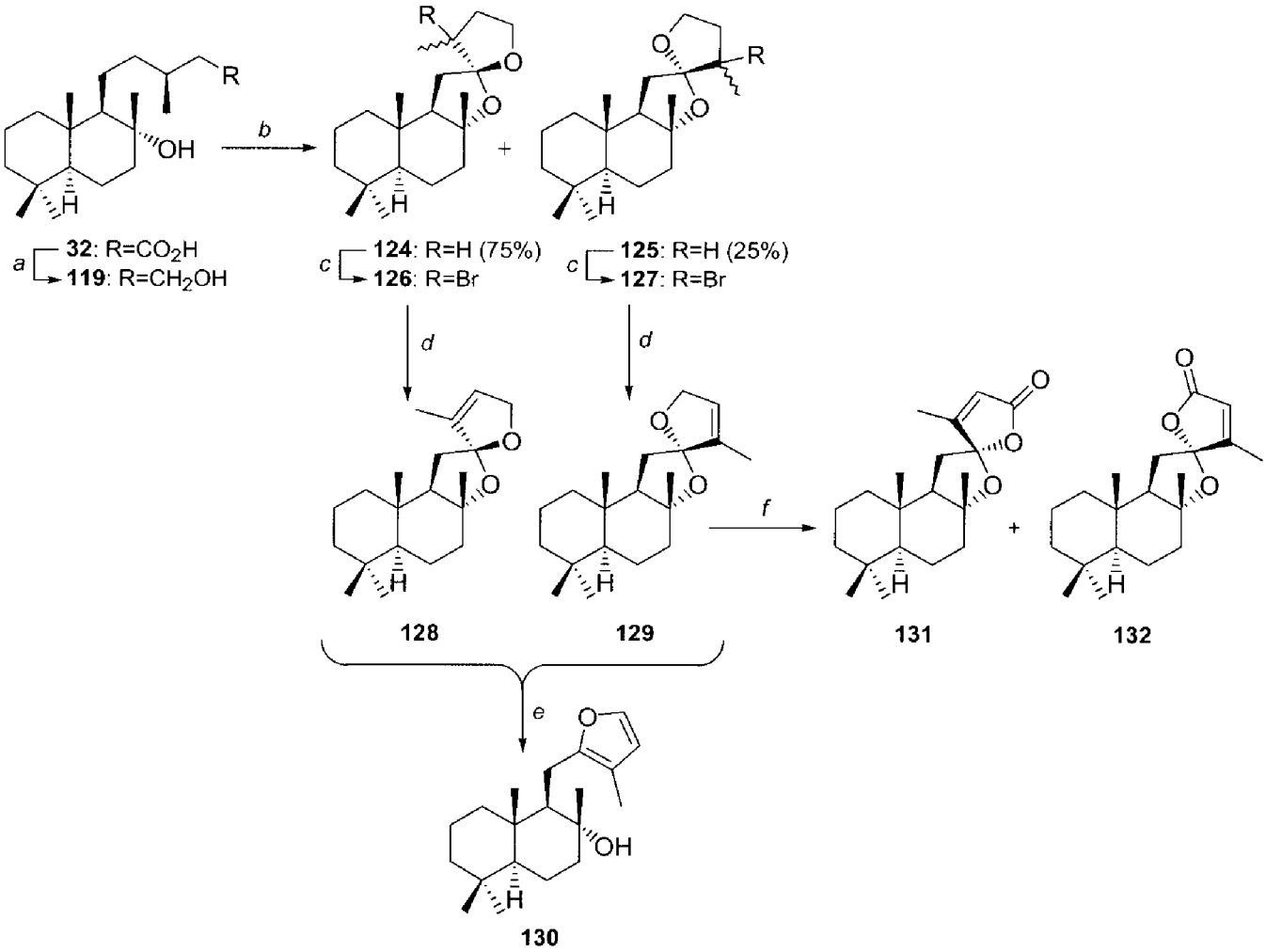


Reagents and conditions: (*a*) IBDA, I_2, CCl_4, ΔT, 100W, 70%; (*b*) IBDA, I_2, C_6H_6, hv, 30°C.

Several C(12) oxygenated labdanolic diterpenes have been isolated, mainly from species of *Nicotiana*, such as the lactones α- and β-levantenolide (**131** and **132**), from Turkish tobacco.[119,120] After the functionalization at C(12) of labdanolic acid (**32**), as mentioned in Scheme 1.4, a simple synthesis of these lactones is possible (Scheme 1.5).

Reduction of labdanolic acid (**32**) gave diol **119** which was transformed upon irradiation with a 100W tungsten-filament lamp with $Pb(OAc)_4/I_2$ into a 3:1 mixture of spiro compounds **124** and **125**. Bromination of **124** or **125** proceeded regioselectively to give two monobromides **126** and **127**, respectively. Dehydrobromination of **126** with potassium *t*-butoxide gave **128**, while **127** afforded **129**. The olefins **128** and **129** are transformed quantitatively into furan derivative **130** by adsorption on SiO_2. Oxidation of **130** with *m*-CPBA, afforded only a small quantity (4%) of α-levantenolide. However when the olefin **128** was oxidized with modified Collins reagent, α- and β-levantenolide (**131**) and (**132**) were formed in 35 and 60% yield, respectively. The stereoselectivity was improved using NBS in the presence of $CaCO_3$ as oxidizer for **128** and **129**. In the first case, the ratio between **131** and **132** was 4:1 while in the second, it was 3:7. In both cases the anomalous C(12) isomer may be formed *via* the furan intermediate since **130** was also transformed by this oxidation reaction to a mixture of **131** and **132**.

Scheme 1.5



Reagents and conditions: (*a*) $LiAlH_4$; (*b*) $Pb(OAc)_4/I_2$, 77%; (*c*) Br_2, HOAc, 5°C, 5 min, 80%; (*d*) KO*t*Bu, C_6H_6-DMSO 4:1, 0°C, 30 min; (*e*) SiO_2, quantitative; (*f*) Collins reagent or NBS, dioxane/H_2O, $CaCO_3$, 95%.

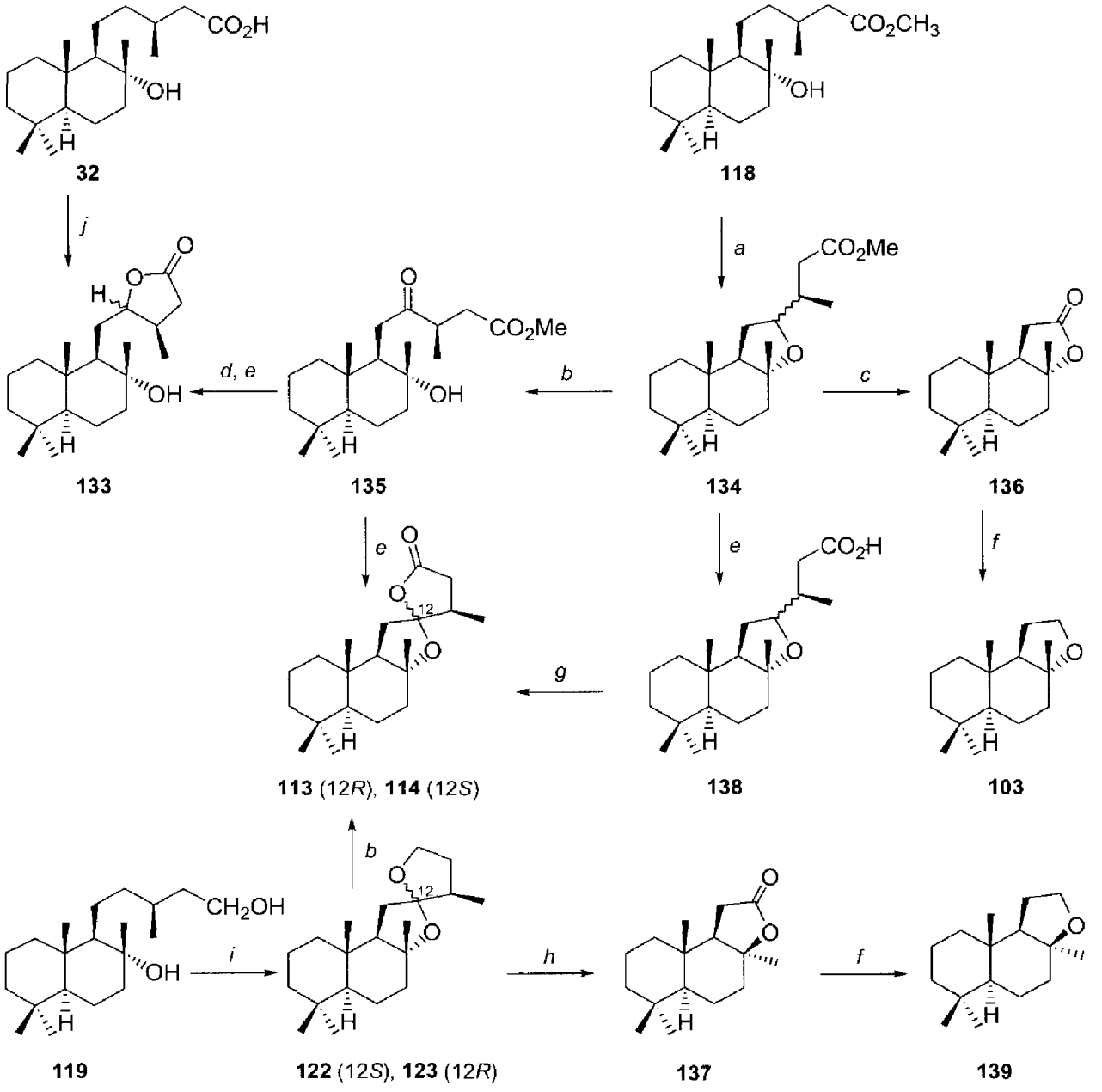
Several lactones, such as labdanolide and 12-*epi*-labdanolide (**133**), α- and β-levantanolides (**113** and **114**), sclareolide (also called 12-*nor*-ambreinolide) (**136**) and 8-*epi*-sclareolide (**137**)[121] have been isolated from *Cistus ladaniferus L.*[122] All have economical interest since they can be transformed into Ambrox® (**103**) and *iso*-Ambrox (**139**) (Scheme 1.6). The synthesis of these perfume fixers with ambergris smell was undertaken starting from labdanolic acid (**32**). Oxidation of the methyl ester of labdanolic acid (**118**) with $Pb(OAc)_4$ followed by CrO_3 oxidation of the intermediate **134** gave rise to lactone **136**, which upon reduction afforded Ambrox® (**103**).[123]

If the oxidation of **134** is carried out with $RuO_2/NaIO_4$, the ketoester **135** is obtained. Saponification and subsequent acidification of **135** leads to a mixture of spirolactones **133**. These spirolactones can also be directly synthesized by reaction of **32** with $Pb(OAc)_4/I_2$, but in much lower yield.

Oxidative cyclization of labdanediol (**119**) with $Pb(OAc)_4/I_2$ yields a (3:1) mixture of spiroketals **122** and **123** which, when oxidized with $RuO_2/NaIO_4$ give the spirolactones **113** and

114. If the oxidation of **122** and **123** is carried out with $(t\text{Bu})_2CrO_4/Ac_2O/AcOH$ lactone **137** is obtained, which can be reduced to *iso*-Ambrox (**139**). The spirolactones **113** and **114** can also be prepared from the acids **138** by the 'dry ozonation' method.

Scheme 1.6



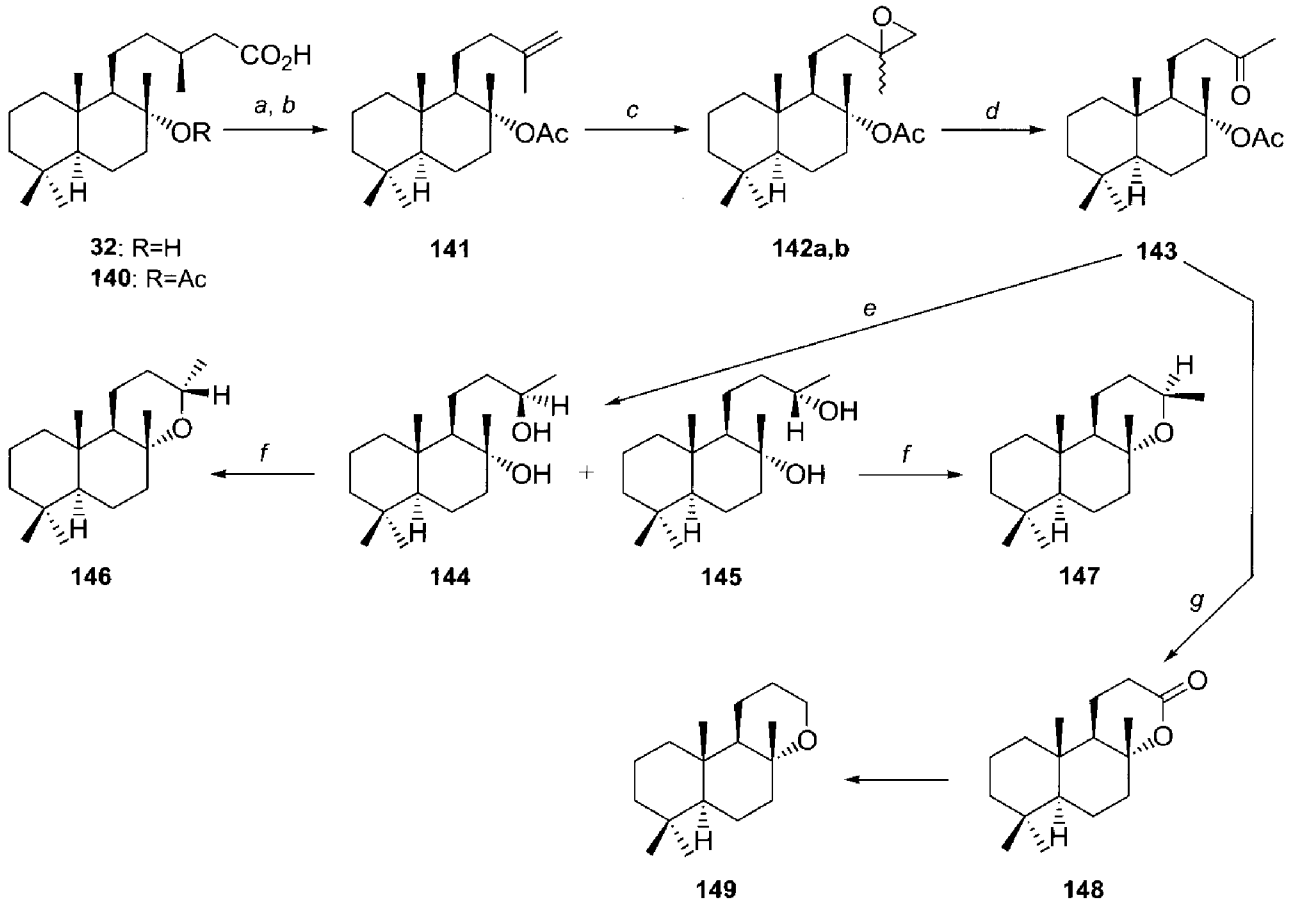
Reagents and conditions: (*a*) $Pb(OAc)_4$, I_2, C_6H_6, py, 10°C, 65%; (*b*) RuO_2, $NaIO_4$, acetone, H_2O, 100%; (*c*) CrO_3, AcOH, 77%; (*d*) $NaBH_4$, MeOH, 100%; (*e*) *i*) KOH, MeOH; *ii*) HCl, H_2O, 100%; (*f*) B_2H_6, $BF_3{\cdot}OEt_3$, or $LiAlH_4$, Et_2O, *p*-TsCl, py, ΔT, 90%; (*g*) O_3, SiO_2, -80°C, 76%; (*h*) $(t\text{Bu})_2CrO_4$, Ac_2O, AcOH, 73%; (*i*) $Pb(OAc)_4$, I_2, cyclohexane, $CaCO_3$, 80°C, 80%; (*j*) $Pb(OAc)_4$, I_2, benzene, 26%.

1.6.2 Functionalization of 8-acetoxy labdanolic acid

Radical reactions of labdanolic acid take a different course when the C(8) hydroxyl group is protected as its acetate, which does not take part in radical processes such as hydrogen

abstraction at C(12). So decarboxylation of the acetate **140** with $Pb(OAc)_4$ and $Cu(OAc)_2$ produced the alkene **141** in 60% yield (Scheme 1.7).

Scheme 1.7

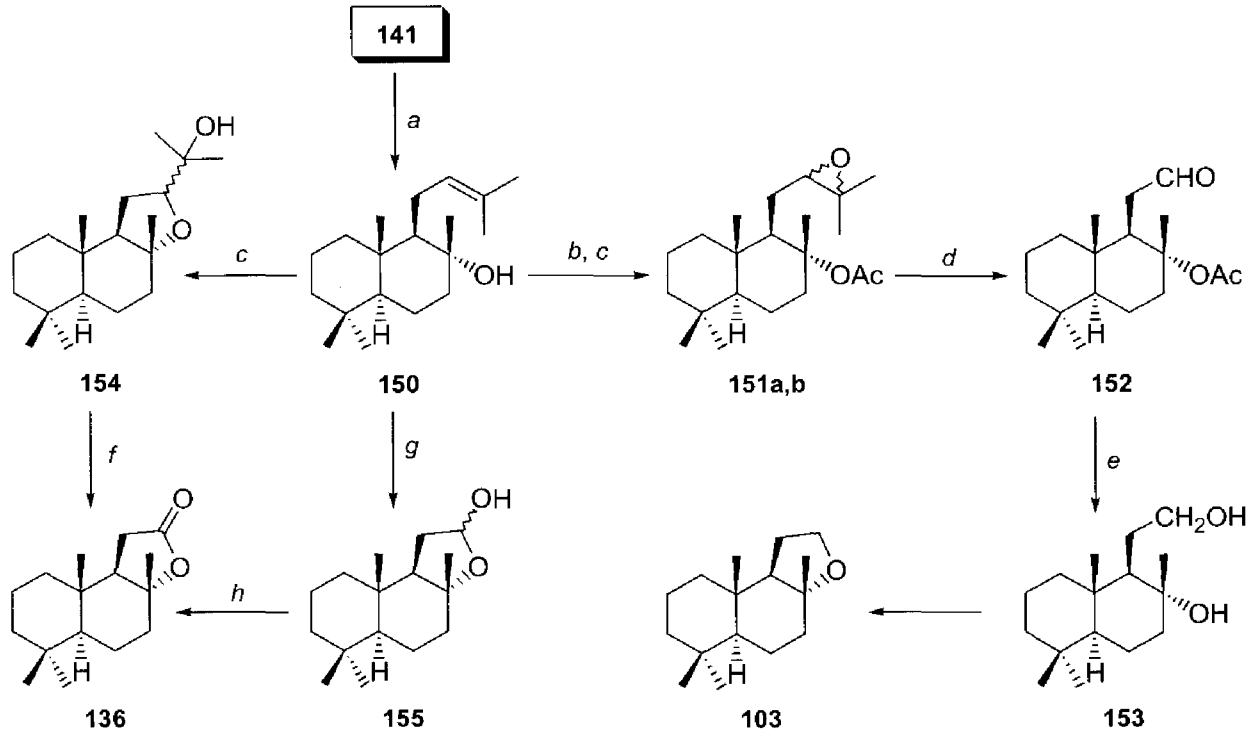


Reagents and conditions: (*a*) Ac_2O, py, DMAP, 75%; (*b*) $Pb(OAc)_4$, C_6H_6, $Cu(OAc)_2$, 60%; (*c*) *m*-CPBA, 90%; (*d*) HIO_4, acetone, 93%; (*e*) Br_2, OH^-, 93%; (*f*) MsCl, py, 65%; (*g*) $LiAlH_4$, 97%.

Epoxidation followed by a rearrangement of the epoxides **142a,b** gave a crystalline product **143**, with a pleasant amber odour.[124] When **143** is reduced with lithium aluminium hydride a mixture of separable diols **144** and **145** is obtained. Mesylation of the secondary hydroxyl group in the side chain of the separated diols and cyclization gave the Ambra oxides **146** and **147** respectively. Treatment of **143** with Br_2 in basic medium led to lactone **148**, a precursor of the corresponding Ambra oxide (**149**).

Treatment of **141** with lithium/ethylenediamine led to isomerization of the double bond and the obtained alkene **150** could be converted into the sclareolide (**136**) and ambroxdiol (**153**) as is indicated in Scheme 1.8. Epoxidation of **150** with *m*CPBA gave the tetrahydrofuran derivative **154**. Oxidation of **154** with Na_2CrO_4 led to sclareolide **136** in 99% yield. Another route to **136** was achieved by ozonolysis of **150** to hemi-acetal **155** and oxidation of the latter with Jones reagent. Alkene **150** was also transformed to ambroxdiol **153**, according to the sequence of reactions indicated in Scheme 1.8. This diol could be transformed into Ambrox® (**103**) in the usual way.[125]

Scheme 1.8



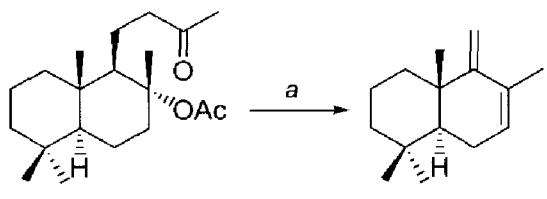
Reagents and conditions: (*a*) Li/ethylenediamine, 92%; (*b*) AcCl, *N,N*-dimethylaniline, 87%; (*c*) *m*-CPBA, 68-91%; (*d*) HIO_4, 98%; (*e*) $LiAlH_4$, 94%; (*f*) Na_2CrO_4, 99%; (*g*) O_3, 96%; (*h*) Jones reagent, 70%.

1.6.3 Degradation of the C(9) side chain

Labdanolic acid (**32**) proved to be a suitable starting material for the synthesis of drimanic sesquiterpenoids as well,[126] and drima-7,9(11)-diene (**156**) and 8α-acetoxydriman-11-oic acid (**162**), intermediates suitable for the preparation of biologically active natural drimanes, could be obtained from **32** (Scheme 1.9 and 1.10).[127]

For this purpose labdanolic acid (**32**) was converted into acetoxyketone **143** as described in Scheme 1.7. Norrish II photochemical cleavage of acetoxy ketone **143** afforded diene **156** in 23% overall yield (over 5 steps), based on labdanolic acid (Scheme 1.9). In addition to the photochemical fragmentation reaction, elimination of the acetoxyl group on C(8) also occurred, leading directly to the diene. This intermediate drimadiene **156** is a versatile synthon and has been used in the synthesis of polygodial (**193**) and warburganal (**194**) (see paragraph 1.7).

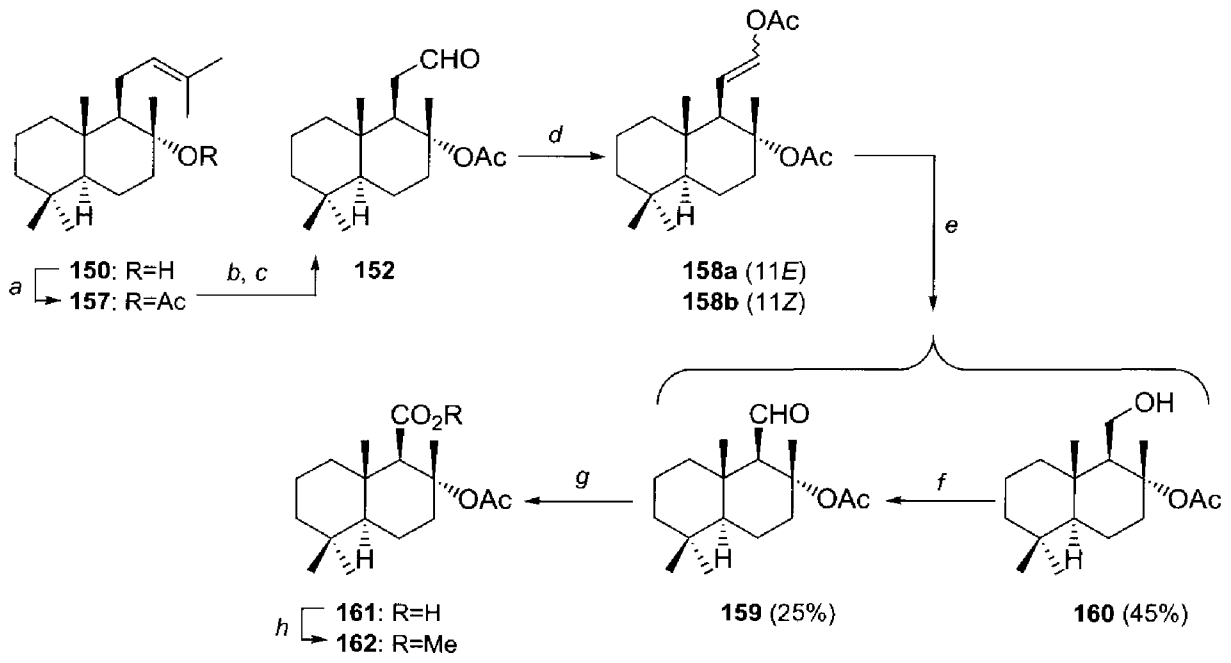
Scheme 1.9



Reagents and conditions: (*a*) hν, 60%.

Acetylation of the hydroxyl group of alkene **150** (see Scheme 1.8) followed by cleavage of the double bond in the acetate **157** gave acetoxy aldehyde **152**,[128] which was subsequently converted into a mixture of *E*- and *Z*-enol acetates **158a** and **158b** (Scheme 1.10).

Scheme 1.10



Reagents and conditions: (*a*) AcCl, *N,N*-dimethyl aniline, 87%; (*b*) *m*-CPBA, 90%; (*c*) HIO_4, 93%; (*d*) Ac_2O, NEt_3, DMAP, 70%; (*e*) O_3, $NaBH_4$, 87%; (*f*) $(COCl)_2$/DMSO, 45%; (*g*) $NaClO_2$; (*h*) CH_2N_2, 99%.

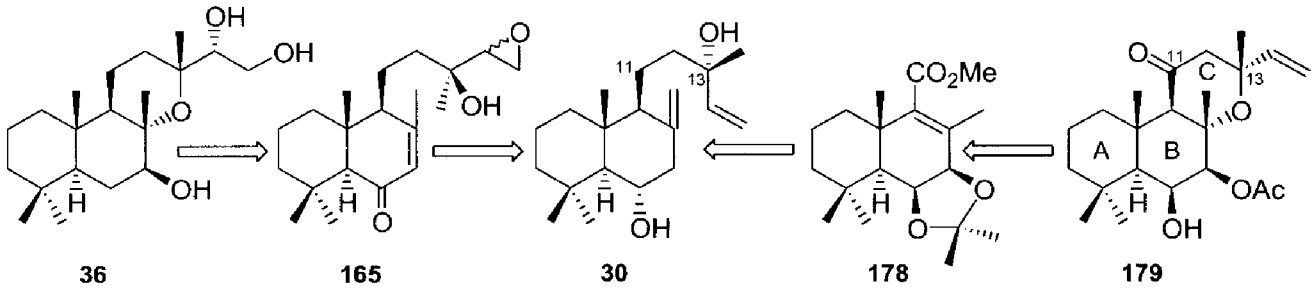
Ozonization of this mixture and a reductive work up resulted in a mixture of acetoxy aldehyde **159** and hydroxy acetate **160**, the latter gave aldehyde **159** upon oxidation by the Swern method. Compound **159** was further oxidized to acetoxy acid **161** and the latter was methylated by CH_2N_2 to yield ester **162**, which is suitable as an intermediate in the synthesis of biologically active natural drimanes.[126,127,129]

1.7 The chemistry of larixol

Larixol (**30**) has a more accessible side chain than labdanolic acid (**32**), besides additional functional groups are present at C(6) and C(8), which makes it to a more flexible starting material. The oxidative degradation of the side chain has been well studied and will be described in Chapter 3. In this paragraph total syntheses starting from larixol, *e.g.* the synthesis of polyoxygenated diterpenes and drimanes are described.

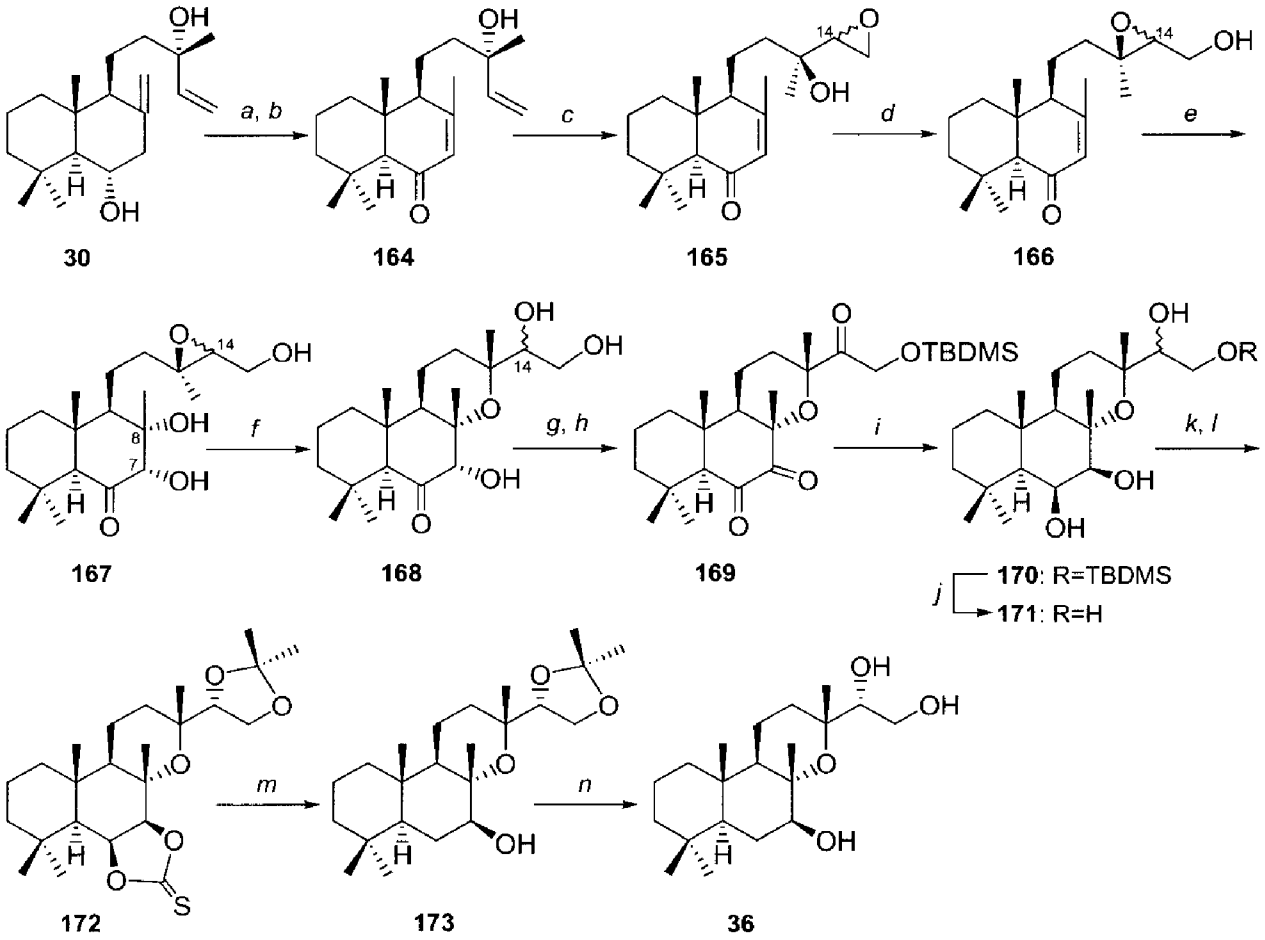
Viewing its structure, larixol (**30**) looks an excellent candidate as starting material for the (hemi)synthesis of polyoxygenated diterpenes which often possess interesting biological activities.

Scheme 1.11



The synthesis of (-)-borjatriol (**36**),[130,131] a diterpene with anti-inflammatory properties (Scheme 1.11) is the first example. The introduction of oxygen functionalities in ring B at positions C(7) and C(8) and in the side chain at positions C(14) and C(15) in the larixol skeleton are the key transformations in this synthesis. Similar conversions provide an entry for the hemisynthesis of forskolin derivatives.

Scheme 1.12

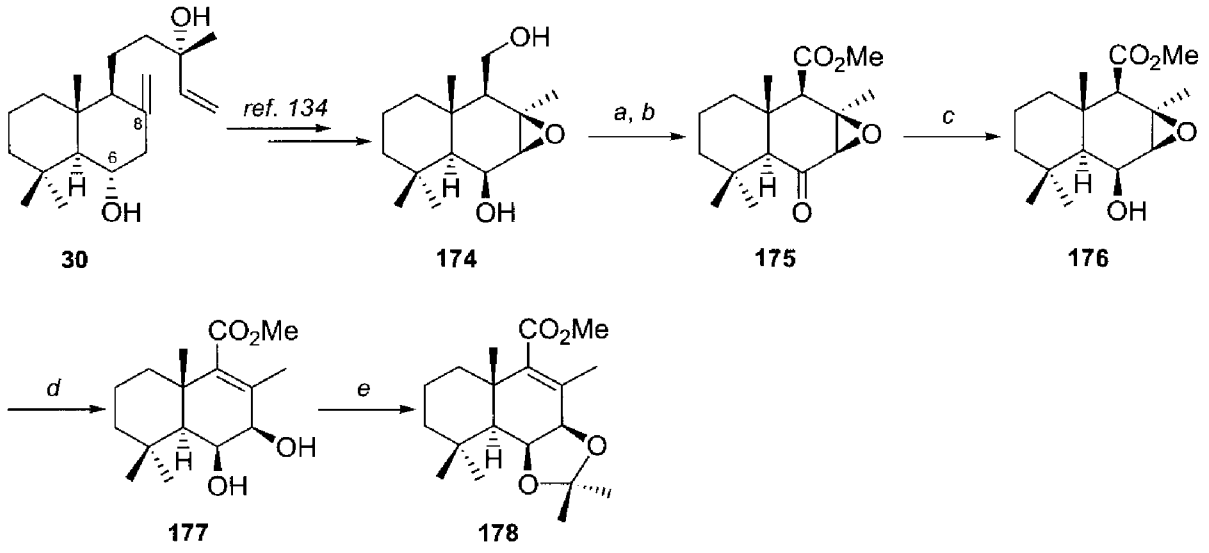


Reagents and conditions: (*a*) Dess-Martin, CH_2Cl_2, py, 95%; (*b*) NaOMe, MeOH, 98%; (*c*) *t*-BuOOH, $VO(acac)_2$, 93%; (*d*) NaOH 0.5N, *t*-BuOH, 70%; (*e*) cat. OsO_4, NMO, 70%; (*f*) cat. CSA, quant.; (*g*) TBDMSiCl, imidazole, 98%; (*h*) Dess-Martin, CH_2Cl_2, py, 49%; (*i*) $NaBH_4$, 76%; (*j*) *n*-Bu_4NF, THF, 84%; (*k*) $(CH_3)_2C(OCH_3)_2$, 78%; (*l*) thiocarbonyl diimidazole, 65%; (*m*) Bu_3SnH, 90%; (*n*) CSA, 79%.

In the 14 steps synthesis of (-)-borjatriol (**36**) from larixol (**30**) many oxidation and reduction steps were necessary to introduce the hydroxyl groups in ring B and in the side chain with the correct configuration. The hydroxyl groups at C(7) and C(8) of the B-ring were introduced by OsO_4 giving the 7α,8α,15-triols **167** (Scheme 1.12). The correct configuration of C(7) was obtained by reduction of triketone **169** arising from hydride delivery from the least hindered α-side of the carbonyl groups, but two epimeric alchohols were obtained in the side chain of **170**. After separation of the isomers and reduction, the vicinal 14,15-dihydroxyl groups of **171** were selectively protected as an acetal. The 6,7-diol was transformed into thiocarbonate **172**, and radical reduction of the thiocarbonyl group gave the deoxy-compound **173** as the major product. Deprotection of **173** gave (-)-borjatriol (**36**) in 5% overall yield.

Although larixol (**30**) has the advantage to possess a functionalized decalin system, the synthesis of forskolin derivatives from larixol is not straightforward. The different configuration at C(13) of forskolin compared with larixol necessitates the breakdown of the side chain in larixol and its reconstruction with the desired stereochemistry. Also the oxidation of C(11) is troublesome, but can be integrated in the reconstruction of ring C. In contrast to forskolin (**5**), a natural product with a wide range of biological activities, its 1,9-dideoxy analogue **179**, also isolated from *Coleus forskohlii*, has been found to selectively inhibit glucose transport in rats adipocytes. [132]

Scheme 1.13



30 **174** **175** **176** **177** **178**

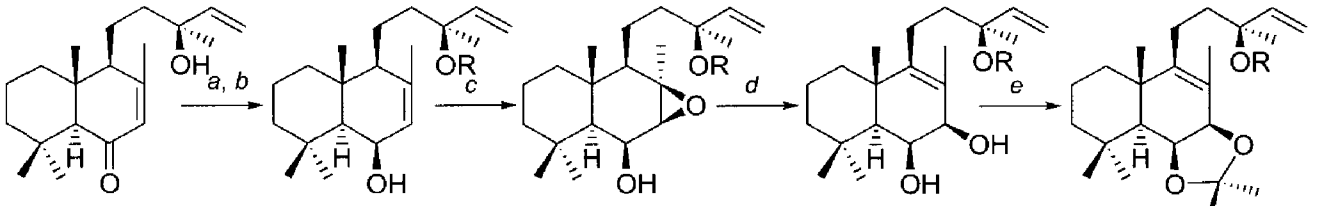
Reagents and conditions: (*a*) $RuCl_3 \cdot 3H_2O$, $NaIO_4$, $H_2O/CH_3CN/CCl_4$ (3/2/2), rt, 2h, 75%; (*b*) 0.3 M CH_2N_2, Et_2O, 0°C, 1h, 92%; (*c*) $NaBH_4$, MeOH, 0°C, 40 min, 63%; (*d*) 30% NaOMe, dry MeOH, rt to 55°C, 1h, 75%; (*e*) dimethoxypropane, cat. H^+, 1 day, 68%.

The first target for a preparation of 1-deoxy- or 1,9-dideoxy-forskolin, was the preparation of a Ziegler-type intermediate **178**[133] from uvidin-C (**174**) (Scheme 1.13), the latter has been obtained from larixol (**30**) as described in Scheme 1.16.[134] Thus, **174** was oxidized by RuO_4 and then esterified to give keto-ester **175**. Regeneration of the 6-hydroxyl group in the 6β configuration was

effected by hydride reduction to **176**. Opening of the epoxide ring to **177** was achieved with sodium methoxide and the vicinal hydroxy groups were protected as an acetal, which afforded the Ziegler-type intermediate **178**.

Several 1,9-dideoxy-forskolin analogs like **183** have been prepared from hydroxy-enone **164**, which can be prepared in two steps from larixol (**30**) (Scheme 1.14). Silylation and reduction of **164** to the 6β alcohol **180** and epoxidation of the intracyclic Δ^7 double bond provided the β-epoxide **181**. Acidic opening of the epoxide ring afforded diol **182**, which was then converted to acetal **183**.

Scheme 1.14



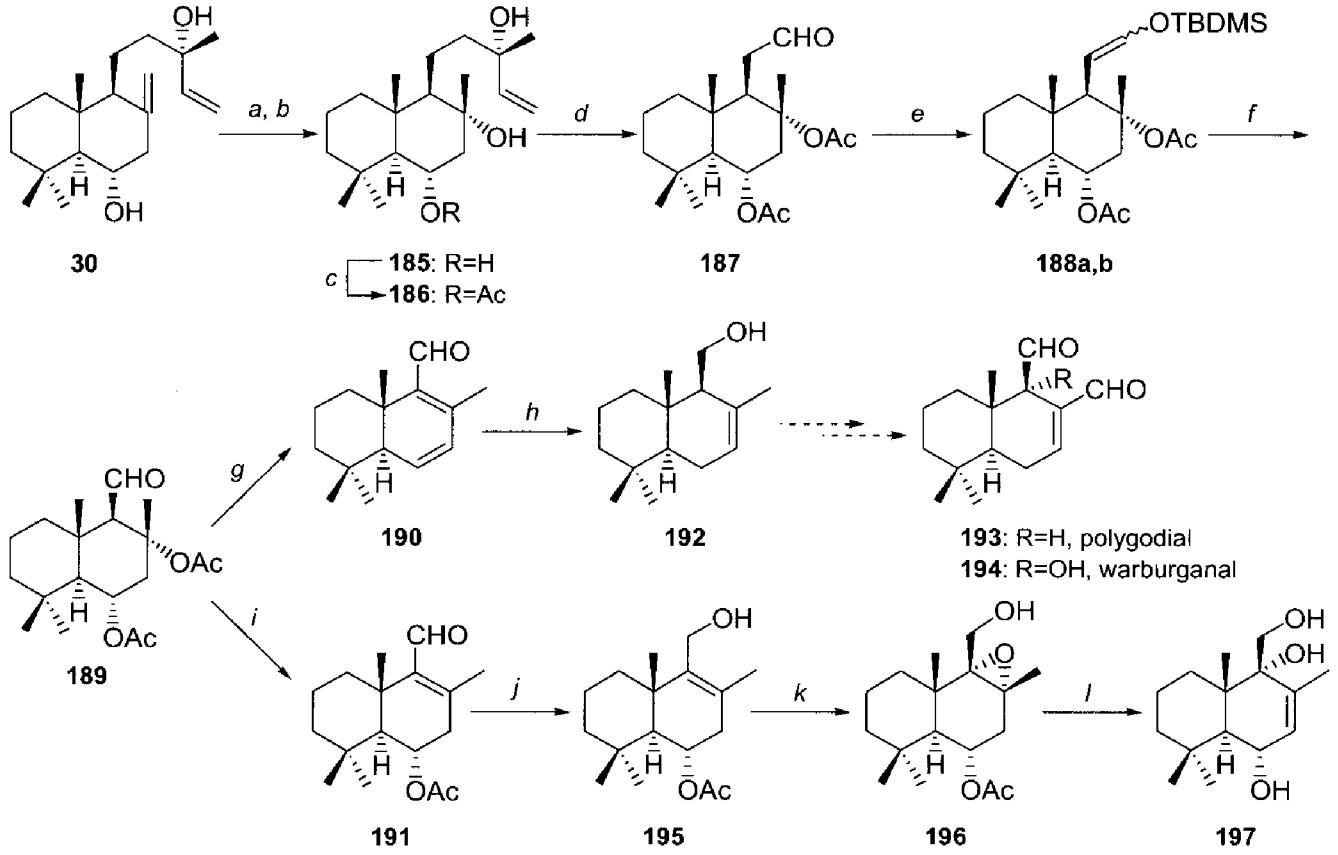
164 **180** **181** **182** **183**

R= TBDMS

Reagents and conditions: (*a*) TBDMSiCl, imidazole, 5 days, 70°C, 96%; (*b*) DIBAL-H, toluene, 1h, -78°C to rt, 96%; (*c*) TBHP, $VO(acac)_2$, 2h, rt, 34%; (*d*) H_2SO_4, 38%; (*e*) 2,2-dimethoxypropane, H^+, 96%.

The biological activities of some drimane sesquiterpenoids have greatly stimulated the development of new synthetic routes to this class of compounds. In view of the availability and the chemical structure, larixol (**30**) seems to be a suitable starting material, especially for the synthesis of C(6) functionalized drimanes. For the conversion of larixol (**30**) into drimanes, first a selective oxidative degradation of the side chain of larixol has to take place. For this purpose the double bond at C(8) was first transformed into a methyl- and a hydroxyl group so that the latter could take part in the oxidation reaction. After selective acetylation of the hydroxyl group at C(6) and oxidation, intermediate **187** was obtained in high yield as depicted in Scheme 1.15. A further breakdown of the side chain of **187** can be performed by the oxidative degradation of the corresponding enol derivatives **188** by ozonolysis to give aldehyde **189**.[134] The acetoxyaldehyde **189** underwent a regioselective elimination of the C(8)-acetate by heating with collidine to give a moderate yield of **191**. The elimination of both acetates from aldehyde **189** could be achieved in high yield using a more concentrated collidine solution. The aldehydes **189**, **190** and **191** have been used as key intermediates for the semisynthesis of (-)-albrasitriol (**197**)[135] and for the enantioselective synthesis of (-)-drimenol **192**,[134] which is an intermediate in the synthesis of the well-known drimanes (-)-polygodial (**193**)[136] and (-)-warburganal (**194**).[137] These drimanes have generated considerable interest because of their potent antifeedant and molluscicidal activities. [138]

Scheme 1.15

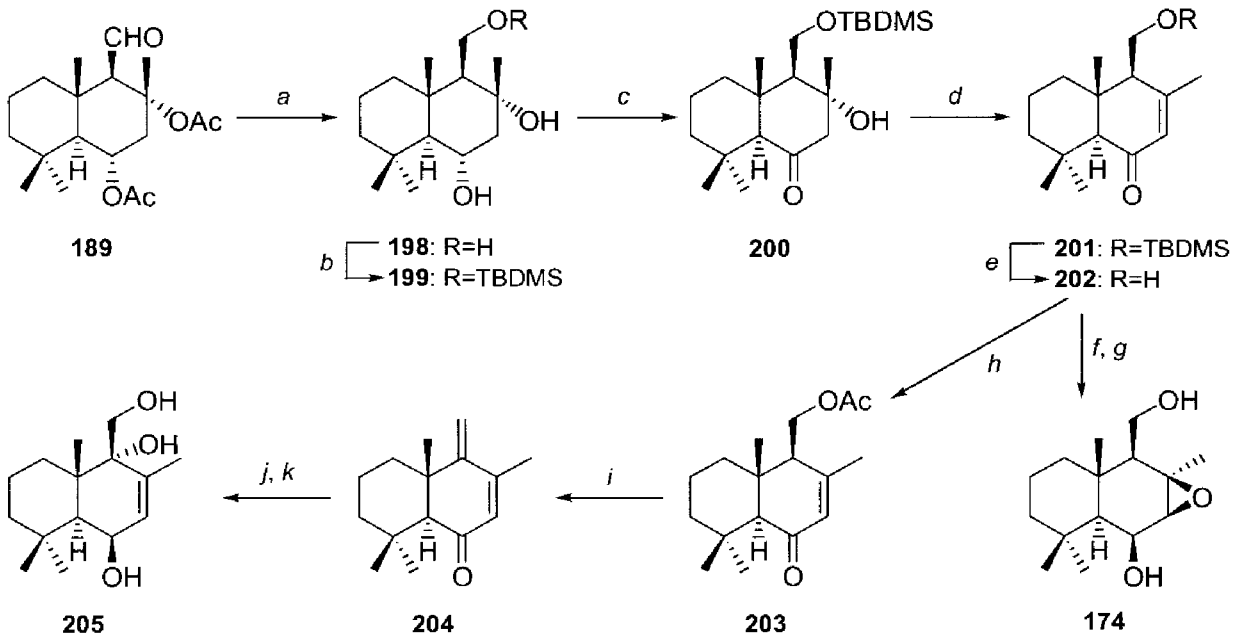


Reagents and conditions: (*a*) oxone®, CH_2Cl_2, acetone, H_2O, $NaHCO_3$, 18-crown-6, 0-3°C, 81%; (*b*) $LiAlH_4$, THF, rt, 94%; (*c*) Ac_2O, py, rt, 99%; (*d*) OsO_4, $NaIO_4$, THF, H_2O, 45°C, 84%; (*e*) TBDMSiCl, NaH, THF, rt, 96%; (*f*) *i*) O_3, CH_2Cl_2/MeOH 3:2, -78°C; *ii*) Me_2S, rt, 78%; (*g*) collidine, 200°C, 90 min, 77%; (*h*) $NaBH_4$, EtOH, 0°C to rt, 89%; (*i*) collidine, 200°C, 15 min, 40%; (*j*) $NaBH_4$, EtOH, -8°C to rt, 94%; (*k*) *m*-CPBA, CH_2Cl_2, rt, 95%; (*l*) Et_2NLi, Et_2O, 0°C, N_2, 43%.

An efficient route to (-)-*epi*-albrassitriol (**205**)[139] has been developed *via* **202**, an intermediate in the synthesis of uvidin C (**174**) (Scheme 1.16).[140] Exposure of **203** to DBU afforded the known dienone **204**, which was submitted to osmylation and reduction to give the 6β-alcohol **205** arising from hydride delivery from the least hindered α-face of the carbonyl group.

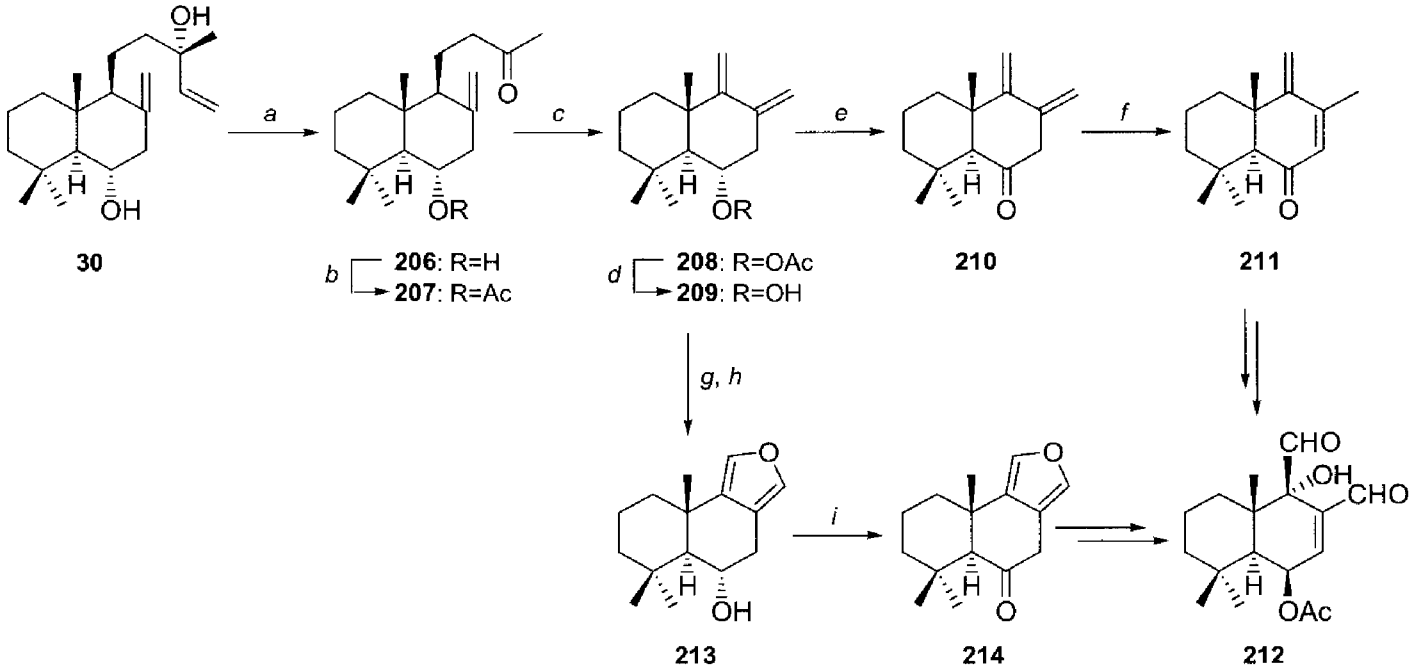
Oxidation of larixol (**30**) with potassium permanganate to methylketone **206** can be achieved in a good 68% yield.[141] Upon irradiation with a high pressure mercury lamp, **207** underwent a Norrish type II cleavage to afford the diene **208** in 75% yield based on reacted starting material (Scheme 1.17).[142] The low conversion of this photolysis (13%) is a problem which is a pity because further oxygenation of these dienes is easy and could provide for short and easy routes to highly substituted drimanes like (-)-cinnamodial (**212**) from larixol. (-)-Cinnamodial (**212**) has been prepared from **208** before *via* furan **213**.[143]

Scheme 1.16



Reagents and conditions: (*a*) $LiAlH_4$, THF, 70%; (*b*) TBDMSiCl, imidazole, 94%; (*c*) PCC, CH_2Cl_2, 3Å molecular sieves, AcOH, 78%; (*d*) $SOCl_2$, py, 0°C, 71%; (*e*) TBAF, 60%; (*f*) DIBAL-H, THF, N_2, 0°C, 95%, (*g*) *m*-CPBA, CH_2Cl_2, 92%; (*h*) Ac_2O, py, 87%; (*i*) DBU, benzene, reflux, 66%; (*j*) OsO_4, py, rt, N_2, 88%; (*k*) DIBAL-H, THF, N_2, 0°C, 83%.

Scheme 1.17



Reagents and conditions: (*a*) $KMnO_4$, 68%; (*b*) Ac_2O, py, 96%; (*c*) hexane, hv, 3h, 5°C, N_2, 75%, 13% conversion (*d*) KOH, EtOH, reflux, 100%; (*e*) PCC, CH_2Cl_2, 3Å molecular sieves, AcOH, 1h, 82%; (*f*) NaOMe, MeOH, 96%; (*g*) O_2, TPP, CCl_4, hv, 6h, 86%; (*h*) $FeSO_4$, THF, 1.5 h, 90%; (*i*) PCC, CH_2Cl_2, 3Å molecular sieves, AcOH, 1h, 82%.

1.8 Scope of this thesis

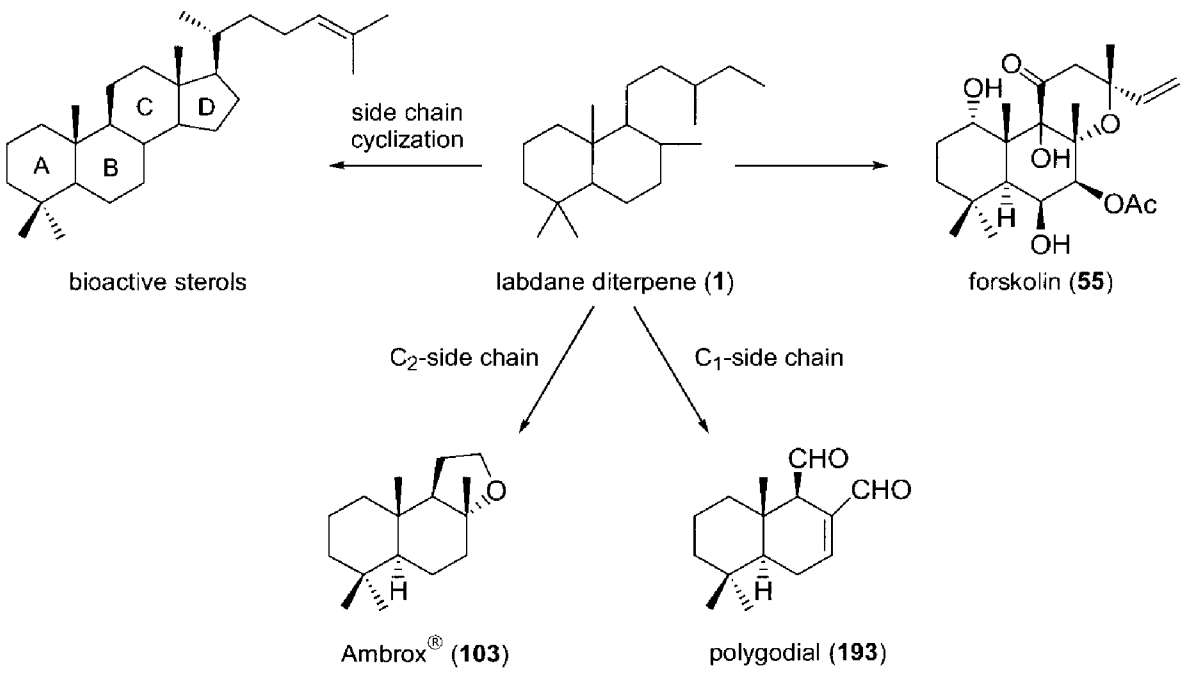
The available literature on the synthetic chemistry of labdanes can be devided into synthesis aiming at total synthesis of labdanes and synthesis with natural labdanes as starting material.

In principle one can imagine three types of products which can be synthesized from natural labdanes.

1. Modification of the labdane skeleton as it is, either to prove the structure of newly isolated labdanes, or to obtain more valuable bioactive labdanes.
2. To use the labdane and its side chain for the synthesis of larger polycyclic compounds, for instance with sterol like structures.
3. To shorten the side chain with two or more carbon atoms for the synthesis of valuable flavour compounds like ambraketals and Ambrox® or for the synthesis of interesting bioactive drimanes.

In this thesis we have concentrated our efforts on the synthesis of flavour compounds starting from the labdanes labdanolic acid (**32**) and larixol (**30**), which are easily available from the exudate of *Cistus ladaniferus* or larch turpentine, respectively.

Scheme 1.19



In Chapter 2, the chemistry of labdanolic acid (**32**) and the shortening of its side chain are described. A short literature overview is given about the synthesis of Ambrox® (**103**), the commercially most important flavour constituent of the scarce natural ambergris. A new and efficient synthesis of Ambrox®, starting from labdanolic acid (**32**) is presented.

For the synthesis of Ambrox® (**103**) or Ambrox-like compounds from larixol (**30**) the side chain has to be shortened by oxidation. In Chapter 3, a brief overview on the oxidation of larixol (**30**) is presented with emphasis on the oxidation of the side chain. A new procedure for this oxidation has been developed and its efficiency in larixol and sclareol type labdanes is compared. One of the oxidation products is investigated for its conversion into (modified) Ambraketals.

In Chapter 4 the further degradation of the methyl ketone derived from larixol is discussed. This leads to 6-hydroxy Ambrox as the key intermediate from which several C(6) derivatives of Ambrox® have been prepared. Some of these showed pleasant odour properties.

The combination of the hydroxyl group at C(6) and the exocyclic double bond at C(8) in larixol offers new possibilities for the synthesis of ring B modified Ambrox-like odour compounds. In Chapter 5, the selective synthesis of Δ^6-Ambroxene starting from larixol (**30**) is reported. This approach is extended for the synthesis of several C(13) substituted Δ^6-tricyclic tetrahydropyranyl ethers (Δ^6 Ambra oxides).

In Chapter 6, some concluding remarks and newly obtained insights about the chemistry of labdanolic acid and larixol are given.

1.9 References and notes

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5. The *abeo*-prefix indicates that a bond has migrated. Thus the prefix 5(4→3) indicates that the 5,4-bond has been replaced by a 5,3-bond. To indicate the addition of carbon atoms the *homo*-prefix is used whilst the *nor*-prefix is used to indicate loss of carbons from a skeleton. The highest available locant is always eliminated when one of a set of equivalent carbons is lost. The *seco*-prefix is used to indicate cleavage of a bond, with the locants for both ends of the broken bond given. The *friedo*-prefix is used to indicate that carbon atoms such as angular methyls and hydrogens have migrated from their normal positions. For more information see the current *Chemical Abstracts Index Guide*.
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141. The oxidation of larixol (**28**) with permanganate will be described in Chapter 3.

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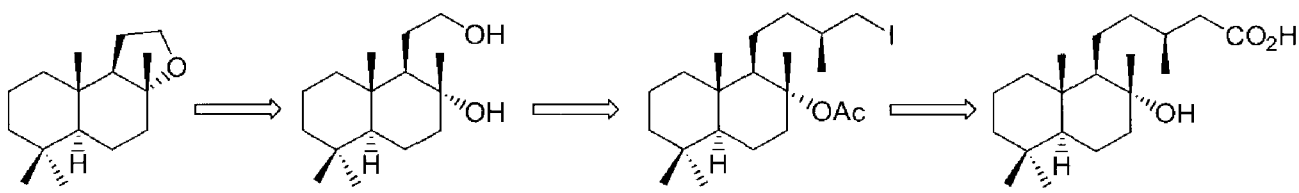
Chapter 2 Labdanolic acid as starting material in the synthesis of Ambrox®

Abstract

*The most important degradation product of ambergris, a metabolic product of the spermwhale, is Ambrox®. Its high price and limited availability has stimulated the synthetic production of Ambrox® (**103**). A large variety of syntheses has been published, based on the cyclization of linear or monocyclic precursors, starting from cyclic monoterpenoids or drimenol or syntheses starting from labdanes.*

*Labdanum is an exudate from the rock-rose Cistus ladaniferus L., and labdanolic acid (**32**) can be isolated easily from this natural oleoresin. The isolation together with the structure determination of this labdane is described in the first paragraph. Labdanolic acid has the potential to serve as a cheap starting material for the preparation of Ambrox®. After oxidative degradation of the C(9) side chain of labdanolic acid suitable synthons for the synthesis of the ambergris fragrance compound become available. The iododecarboxylation of the acetate of labdanolic acid gives the iodide **331** in 76% yield, which after dehydrohalogenation leads to alkenes **150** or **332**. Both compounds are converted into (1R,2R,4aS,8aS)-1-(2-hydroxyethyl)-2,5,5,8a-tetramethyldecahydro-2-naphthalenol (**153**), which is transformed via cyclization into (-)-Ambrox® (**103**).*



Ambrox® **153** **331** labdanolic acid

Part of this chapter has been published as: Bolster, M. G.; Jansen, B. J. M.; de Groot, Ae. *Tetrahedron* **2001**, *57*, 5657-5662.

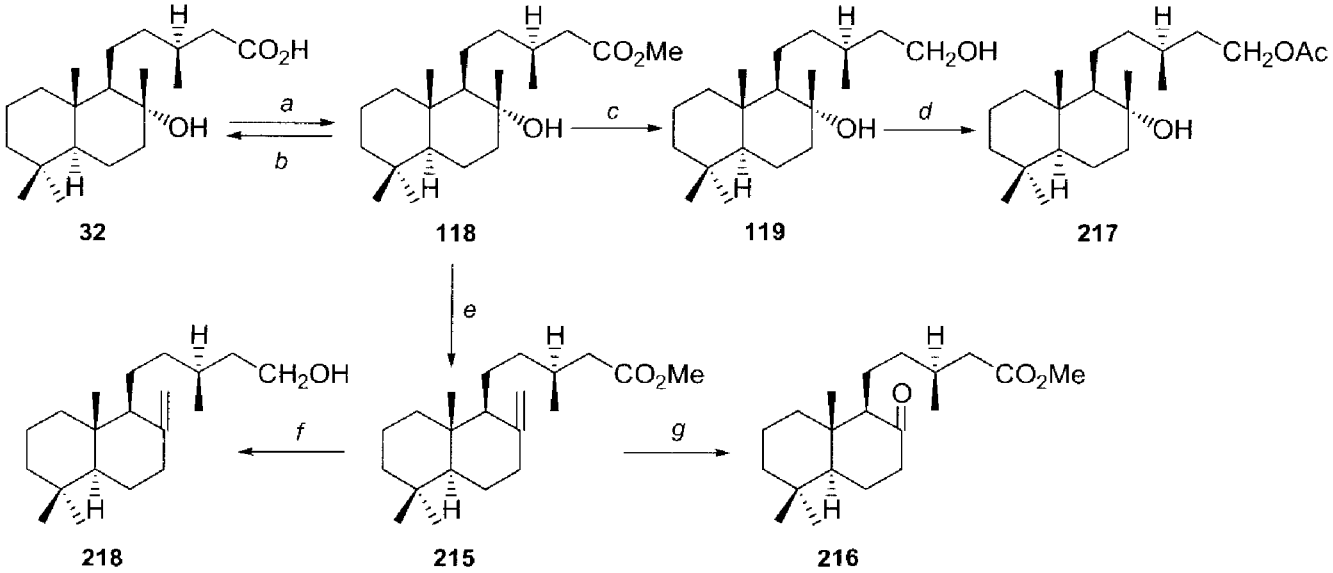
2.1 Isolation and structure determination of labdanolic acid

Labdanum, a natural oleoresin,[1,2] is an exudate from *Cistus ladaniferus* ("rock-rose"), a small wild-growing shrub found in all countries around the Mediterranean Sea. The name *labdanum* is derived from Latin *ladanum*, from Greek *ladanon*, or possibly ultimately from Akadian *ladanu*[3] which means sticky herb, and it has given this name to the whole class of labdane diterpenes.

The production of labdanum is concentrated in Spain, although smaller quantities are produced in Portugal, Morocco, Yugoslavia and Greece. Labdanum gum is obtained by boiling the wood of the bramble in water and collecting the resin from the water surface. The dark brown to black gum is used as a fixative in perfumery, and the names "black amber" or "black balsam" are used to indicate this. The acidic fraction of the gum was esterified with diazomethane and the resulting methyl esters were taken up in light petroleum and separated by chromatography. The main component in this ester mixture proved to be the methyl ester of a hydroxy-acid, $C_{20}H_{36}O_3$, named labdanolic acid (**32**).

The structure of labdanolic acid (**32**) was elucidated by spectroscopic and chemical means,[4] as depicted in Scheme 2.1. The ease with which the methylester of labdanolic acid (**118**) is hydrolyzed, shows the rather unhindered carboxyl group and its position in the side chain. The hydroxy function was unaffected upon acetylation, so it should be tertiary. Compound **119** is a known compound so that products after reduction of labdanolic acid can be compared with the reference compound **119**.[5]

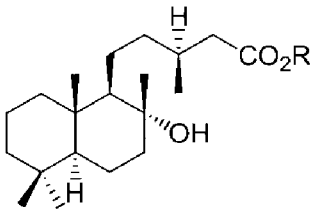
Scheme 2.1



Reagents and conditions: (*a*) CH_2N_2, Et_2O; (*b*) NaOEt, H_2O, reflux, 96%; (*c*) $LiAlH_4$, Et_2O; (*d*) Ac_2O, py; (*e*) $POCl_3$, py, 96%; (*f*) $LiAlH_4$, Et_2O, 0°C, 98%; (*g*) O_3, EtOAc, -70°C.

Dehydration of methyl labdanolate (**118**) with phosphoryl chloride in pyridine gave a homogeneous product **215**, which upon ozonolysis gave keto-ester **216**. So methyl labdanolate (**118**) must have contained a tertiairy hydroxyl group in the equatorial position to account for the formation of an exocyclic rather than an endocyclic double bond.

Figure 2.1



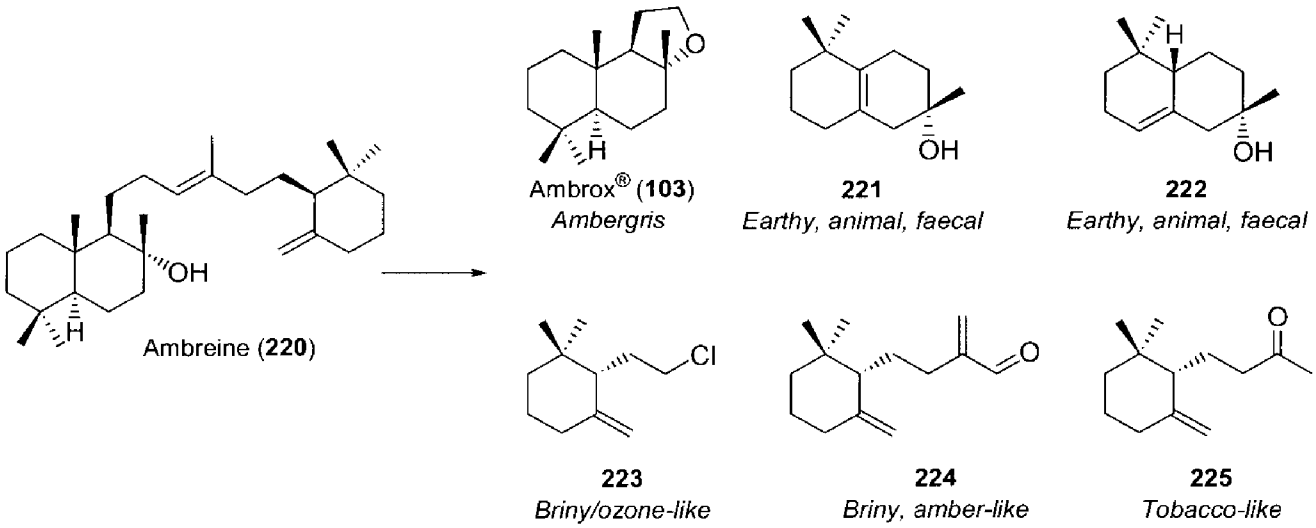
32: R=H
219: R=$CH_2COC_6H_4Br$

The configuration at C(13) remained uncertain for a long time but the crystal structure of the *p*-bromophenacyl ester of labdanolic acid (*p*-bromophenylacyl labdanolate (**219**)), determined by three-dimensional *X*-ray analysis, established the configuration for labdanolic acid (**32**) at C(13) as *S* (Prelog's notation).[6]

2.2 Ambergris flavour compounds

Ambergris is a metabolic product of the spermwhale[7] (*Physeter macrocephalus L.*), which accumulates as concretions in the gut. It contains up to 46% of cholestanol type steroids and 25-45% of a triterpene, ambreine (**220**), the structure of which is shown in Figure 2.2.[7] The reason for its formation is unknown but is is thought that it may be formed as a reaction to some irritation in the whale's intestine. Ambergris which is released into the sea takes the form of lumps which are rarely more than 20 cm in diameter. The largest piece ever found weighed 400 kg and was taken from the intestine of a whale, which had been killed. On exposure to sunlight, air and sea water, ambergris is degraded into a mixture of products of which some are depicted in Figure 2.2, like ambrinol (**221**), α-ambrinol (**222**), γ-homo cyclogeranyl chloride (**223**), and dihydro-γ-ionone (**225**). Some of the proposed degradative pathways have been simulated chemically.[8,9] Some of the degradation products are odourless but a number are responsible for the complex odour which is characteristic for ambergris.[10-12] This is a subtle odour reminiscent of seaweed, wood and moss but with a peculiar sweet, yet dry undertone of unequalled tenacity.[11] The most important of all is the perhydronaphtofuran **103**, which possess the characteristic animalic note of ambergris.[13-15]

Figure 2.2



Ambergris has always been one of the most highly valued and expensive perfumery materials but the decline in the whale population has exacerbated the situation.[10,16,17] The price and availability of the natural material essentially precluded its use in fragrance, and therefore much work has been done on synthetic substitutes. The ambergris materials used in perfumery nowadays are entirely of synthetic or semi-synthetic origin, the key material being Ambrox® and its equivalents.

Sclareol (**4**) constitutes till now the starting material for the industrial production of (-)-Ambrox® (**103**). Because the available quantity of (-)-(**103**) is limited, its price is accordingly high. The increasing demand for this valuable amber odorant on the one hand, and the fact that racemic Ambrox [(±)-**103**] is olfactorily very similar to (-)-**103** on the other hand, prompted several laboratories to design new syntheses of (±)-**103** and (-)-**103**.

2.3 Syntheses of Ambrox®

The large variety of syntheses for Ambrox® (**103**) that has been published can be divided roughly in four main approaches.

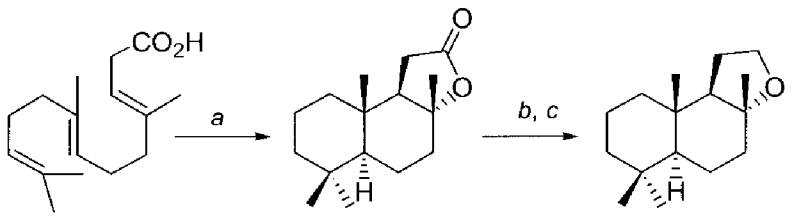
- Syntheses based on the cyclization of linear or monocyclic precursors.
- Syntheses starting from cyclic monoterpenoids or drimenol.
- Syntheses starting from labdanes.
- Syntheses starting from other natural products.

2.3.1 Syntheses of Ambrox® via biomimetic polyolefin cyclizations.

Since the fifties the acid-catalyzed cyclizations of homofarnesoic acid (**226**) and monocyclohomofarnesoic acid (**230**), to racemic sclareolide (±)-(**136**) and its diastereomers have

been reported.[18-23] The cyclization of homofarnesoic acid (**226**) at -78°C in dichloromethane, catalyzed by $SnCl_4$, afforded in high yield (82%) (±)-sclareolide ((±)-**136**) (Scheme 2.2).

Scheme 2.2

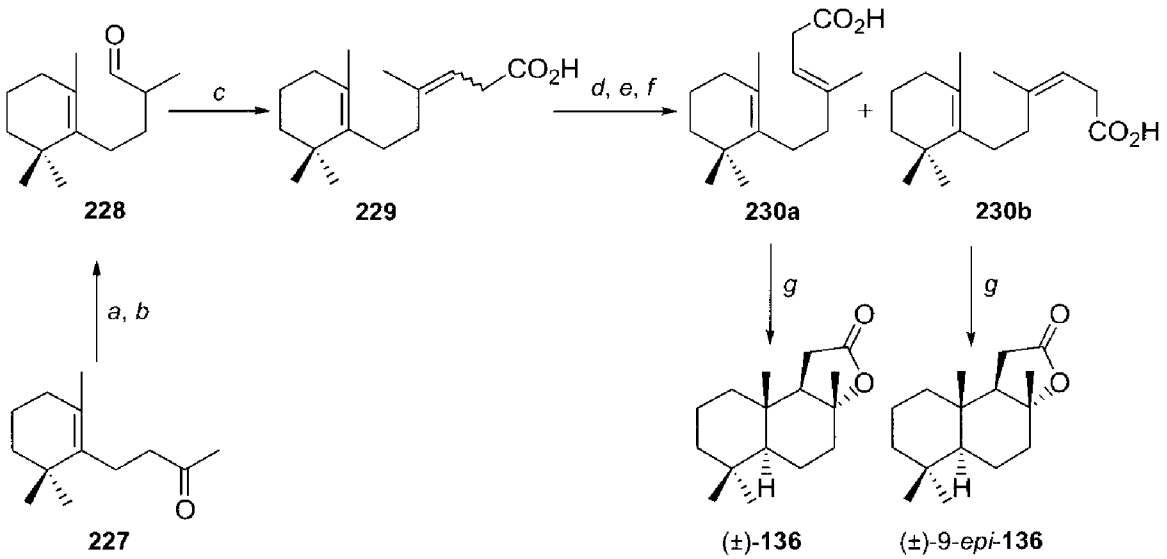


226 (±)-**136** (-)-**103**

Reagents and conditions: (*a*) $SnCl_4$, CH_2Cl_2, -78°C, 82%; (*b*) Red-Al®, 60°C; (*c*) *p*-TsCl, py, 0°C, 69%.

(*E*)- and (*Z*)-*β*-Monocyclohomofarnesoic acid have been preprared from dihydro-β-ionone (**227**) in several steps, as indicated in Scheme 2.3. Treatment of (*E*)-*β*-monocyclohomofarnesic acid (**230a**) with trifluoroacetic acid at 0°C provided (±)-**136** in 64% yield, whereas (*Z*)-*β*-monocyclohomofarnesic acid (**230b**) under the same conditions gave (±)-9-*epi*-**136** in a similar yield.

Scheme 2.3



228 **229** **230a** **230b**

227 (±)-**136** (±)-9-*epi*-**136**

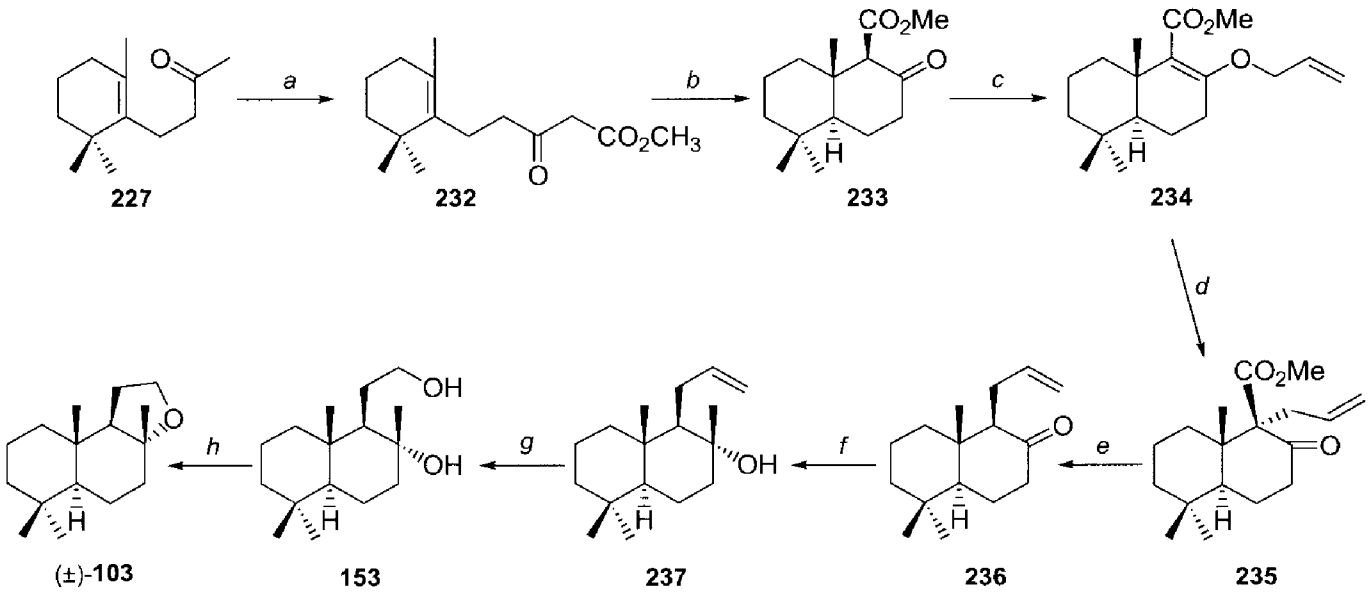
Reagents and conditions: (*a*) $ClCH_2CO_2Et$, NaOEt, 5°C; (*b*) AcONa, 200°C, $-CO_2$, 55%; (*c*) $CH_2(CO_2H)_2$, NEt_3, ΔT, 87% (ratio 1:1); (*d*) $TiCl_4$, EtOH; (*e*) fractional distillation; (*f*) 2.5 M KOH, EtOH; (*g*) CF_3CO_2H, 0°C, 2h, 64-65%.

In the cyclization of both **230a** and **226** the stereochemistry of the double bonds (*E vs Z*) is translated in the stereochemistry of the products *via* the preferred chairlike transition state.[21] Reduction of (±)-**136** with Red-Al®, followed by treatment with TsCl in pyridine gave (-)-Ambrox®

(**103**) in 69% yield, its (±)-9-epimer (**231**) was obtained in a similar way from (±)-9-*epi*-**136** in 74% yield.

β-Keto ester **232** is readily available from dihydro-β-ionone (**227**), *via* condensation with dimethyl carbonate and NaH. Stannic chloride mediated cyclization of this monocyclic *β*-keto ester **232** affords the bicyclic β-keto ester **233** in 61% yield, this ester has been converted to (±)-**101** in six steps (Scheme 2.4).[24] Attempted C-alkylation of **233** failed, but O-alkylation was found to be a facile process. The resulting crude allyl ether **234** when heated in boiling xylene afforded C-substituted β-keto ester **235**. Demethoxycarbonylation of **235** gave a mixture of the desired isomer **236** (86%) and its epimer (14%). Ketone **236** was condensed with MeMgI, and the resulting alcohol **237** was ozonolyzed and reduced to give dol **153**. Heating the diol in nitromethane in the presence of *p*-toluenesulfonic acid produced Ambrox® (**103**).

Scheme 2.4

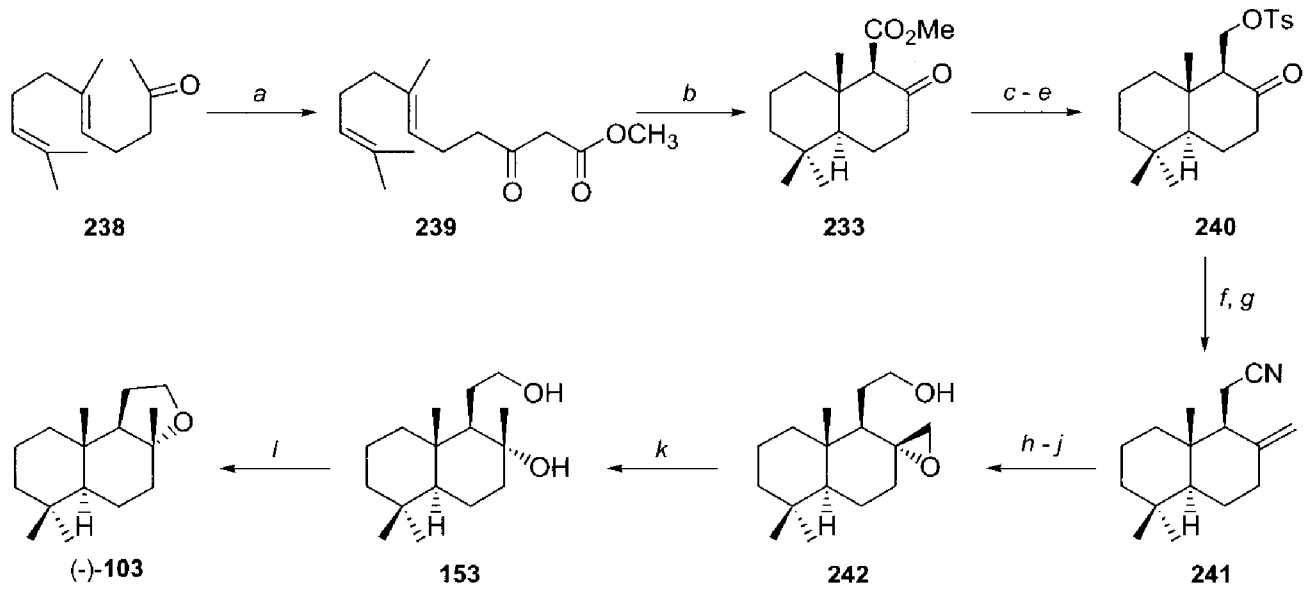


Reagents and conditions: (*a*) $(CH_3O)_2CO$, NaH; (*b*) $SnCl_4$, 61%; (*c*) allylbromide, NaH, DMF; (*d*) xylene, reflux, 62%; (*e*) $CaCl_2{\cdot}2H_2O$, DMSO, reflux, 70%; (*f*) MeMgI, Et_2O, reflux, 98%; (*g*) *i*) O_3, MeOH, -30°C; *ii*) $NaBH_4$, 62%; (*h*) *p*-TsOH, CH_3NO_2, 80°C, 75%.

The β-keto ester **233** can be obtained as well by stannic chloride mediated cyclization of the linear unsaturated keto ester **239** (Scheme 2.5).[25,26] Reduction of **233** followed by tosylation and oxidation afforded the keto tosylate **240**, which was converted into the unsaturated nitrile **241** by a reaction with sodium cyanide and a Wittig olefination. The nitrile was reduced to an aldehyde and further reduction yielded the primairy hydroxyl functionality. Epoxidation of the exocyclic double bond was quite stereoselective and gave the desired epoxide **242** and its epimer in a ratio of 18:1. The mixture of epoxides was reduced to **153** and its 8-epimer. After ring closure to a mixture of Ambrox® (**103**) and 8-*epi*-Ambrox (**139**), separation was effected by silica gel

chromatography to give pure Ambrox® (**103**) in 2% overall yield through 15 steps from geranylacetone **238**.

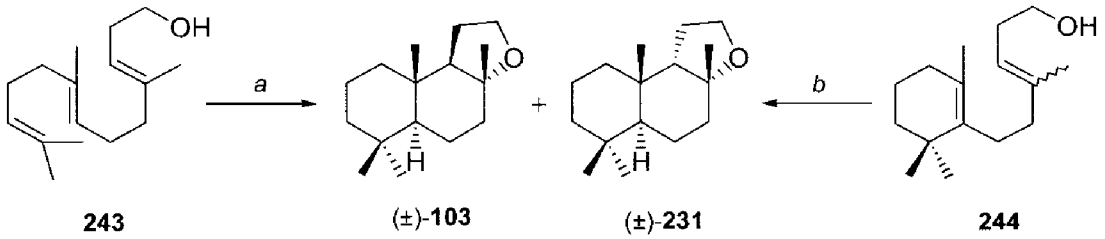
Scheme 2.5



Reagents and conditions: (*a*) $(CH_3O)_2CO$, NaH, Et_2O, ΔT, 88%; (*b*) $SnCl_4$, CH_2Cl_2, H_2O, 32%; (*c*) $LiAlH_4$, THF, 87%; (*d*) TsCl, py, 0°C, 80%; (*e*) CrO_3, acetone, 0°C, 91%; (*f*) NaCN, DMSO, 80%; (*g*) $Ph_3P{=}CH_2$, DME, 67%; (*h*) DIBAL-H, 97%; (*i*) $NaBH_4$, MeOH, 98%; (*j*) *m*-CPBA, CH_2Cl_2, 91%, (5% 8-*epi*-epoxide); (*k*) $LiAlH_4$, THF, 81%; (*l*) *p*-TsCl, py, 92%, (5% 8-*epi*-Ambrox (+)-**139**)).

A low-temperature cyclization with fluorosulfonic acid was used for the *one step* synthesis of (±)-**103** from (*E,E*)-homofarnesol [(*E,E*)-**243**] in 73% yield (Scheme 2.6).[27] Under these conditions the isomerization of (*E,E*)-**243** to (3*Z*,7*E*)-**243** is fast enough to compete with the cyclization. Thus, pure (*E,E*)-**243** furnishes a mixture of 40% (±)-**103** and 35% (±)-**231** (9-*epi*-**103**). This isomerization diminishes slightly the synthetic elegance, but since (-)-**231** is an even more powerful ambergris fragrance compound than (-)-**103**, it is no problem from the olfactory point of view. Cyclization of the monocyclic (*E*)-**244** under the same conditions provided a mixture of (±)-**103** and (±)-(9-*epi*-**103**) (**231**) in 86% yield.[28,29]

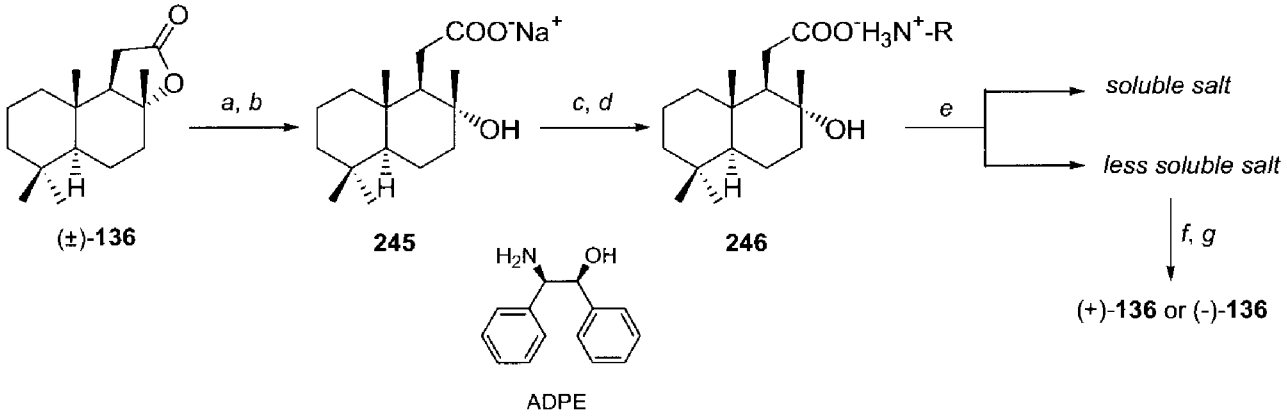
Scheme 2.6



Reagents and conditions: (*a*) FSO_3H, $nPrNO_2$, 73% (40% (±)-**103**, 35% (±)-**231** (9-*epi*-**103**); (*b*) FSO_3H, $nPrNO_2$, 86%.

It is reported that the smell of (-)-Ambrox® is much stronger than that of (+)-Ambrox and considerable effort has been paid to the syntheses of enantiomerically pure Ambrox®. In some of these syntheses, diastereomeric salt formation was applied to obtain enantiomerically pure intermediates.[25,26,30] This method is effected for the resolution of sclareolide ((±)-**136**) by diastereomeric salt formation using homochiral ADPE (*erythro*-2-amino-1,2-diphenylethanol) as the resolving agent (Scheme 2.7). Highly pure (+)- and (-)-sclareolide were obtained as the key intermediates for the synthesis of both enantiomers of Ambrox.[31]

Scheme 2.7



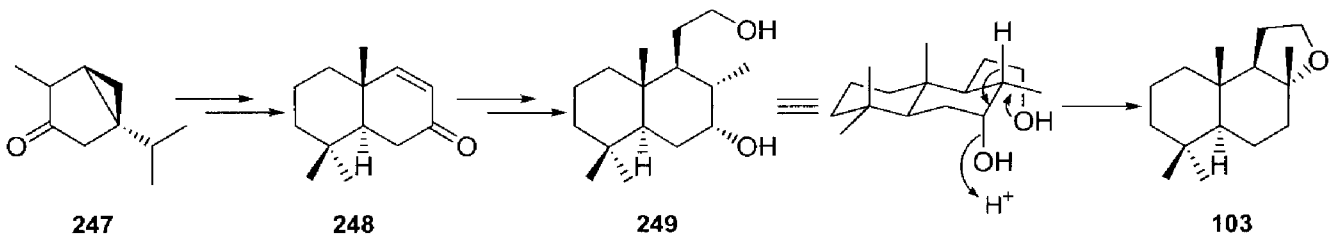
Reagents and conditions: (*a*) NaOH, MeOH; (*b*) HCl, pH 7-8; (*c*) ADPE; (*d*) HCl, pH 6-7; (*e*) solvent, recrystallization; (*f*) NaOH, liberation; (*g*) HCl, lactonization.

To prevent laborious separation procedures it is better to begin the synthesis from optically pure starting materials. It is obvious that natural terpenes have been investigated extensively for this purpose.

2.3.2 *Syntheses of Ambrox® starting from cyclic mono- and sesquiterpenoids.*

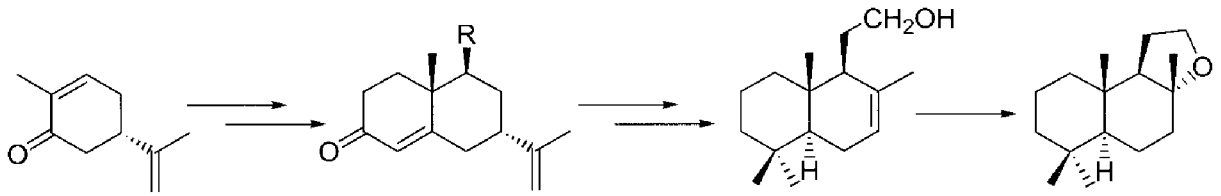
The monoterpene thujone (**247**), a waste material of the Canadian forest industry, is a less obvious starting material for the synthesis of Ambrox®. Nevertheless it has been converted[32] to Ambrox in 15 steps through the intermediates **248** and **249**, culminating in a ring closure of the 1,5-diol moiety of **249** to the tetrahydrofuran ring of (-)-**103** (Scheme 2.8).

Scheme 2.8



The synthesis of Ambrox® from (*S*)-(+)-carvone (**250**) needed 13 steps.[33] Conjugate addition of the indicated nucleophiles to S-(+)-carvone (**250**) followed by a Robinson annulation with methyl vinyl ketone gave the substituted decalones **251** and **252** stereoselectively with the chiral centres at C(9) and C(10) in the correct configuration for the preparation of (-)-Ambrox® (Scheme 2.9). The allyl and nitrile substituents both have been transformed into the hydroxy ethylene substituent in **253**. The conversion of the isopropenyl group into a carbonyl group at C(7) gives the opportunity to introduce a methyl group at C(8) and the Δ^7 double bond in **253**. The final cyclization to (-)-Ambrox® can be achieved using *p*-TsOH in nitromethane.

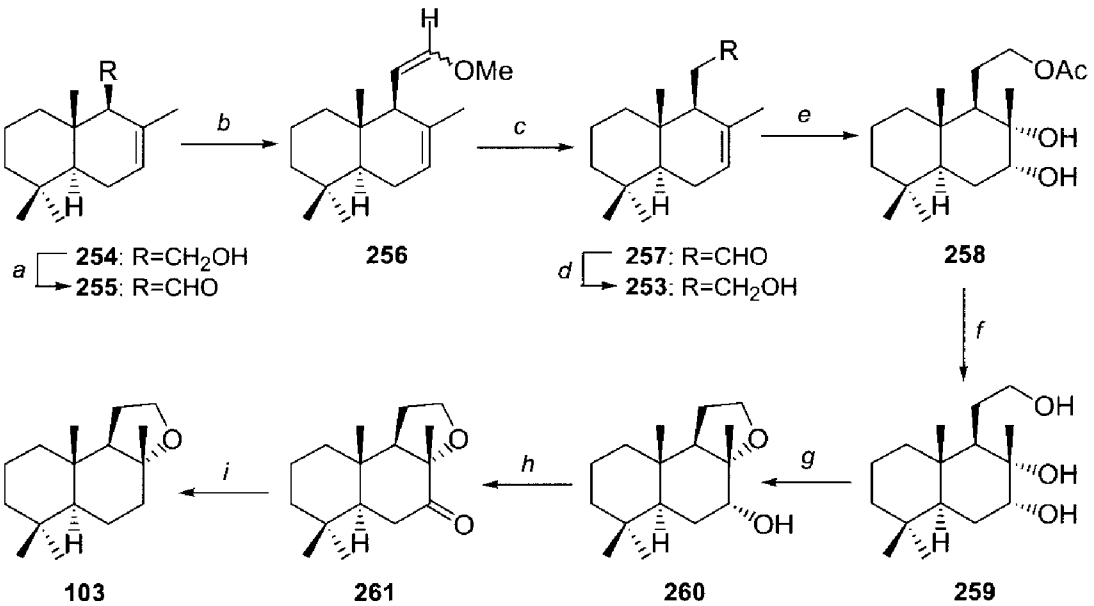
Scheme 2.9



250 **251**: R=allyl; **252**: R=CN **253** **103**

Drimenol (**254**) has been transformed to Ambrox® in 10 steps (Scheme 2.10).[34] Oxidation of **254** and reaction of the resulting aldehyde **255** with (methoxymethyl) triphenylphosphonium ylide gave the enol ether **256**. Hydrolysis of **256** and subsequent reduction of aldehyde **257** with $LiAlH_4$ afforded alcohol **253**.

Scheme 2.10



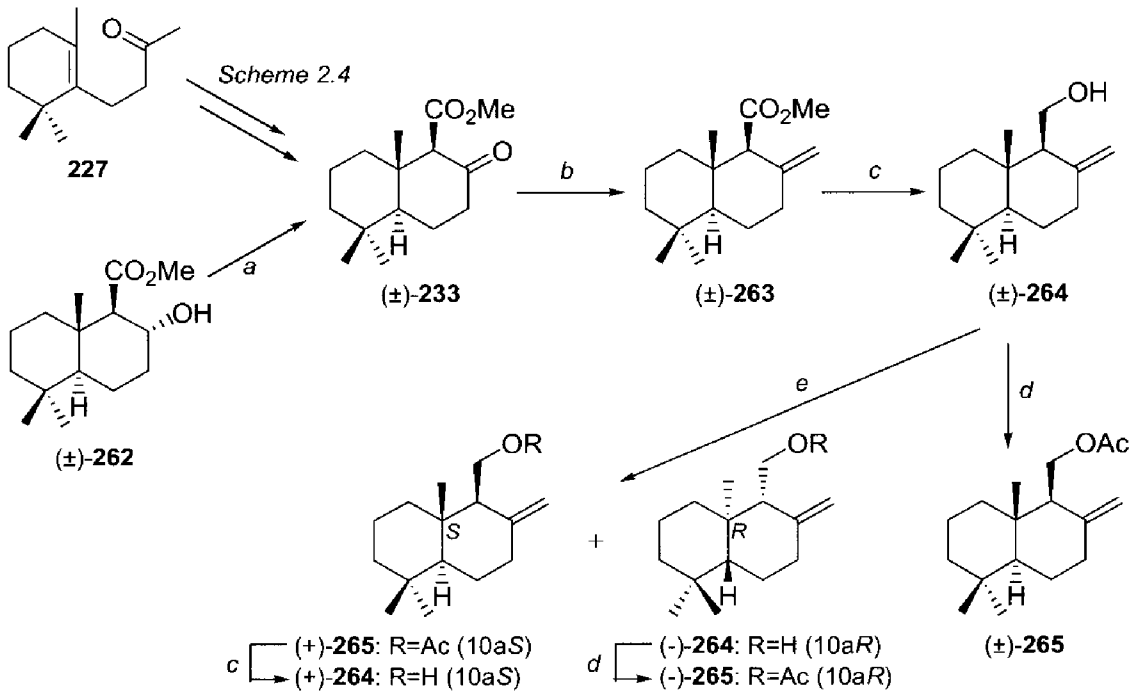
254: R=CH_2OH → **255**: R=CHO **256** **257**: R=CHO → **253**: R=CH_2OH **258** **259** **260** **261** **103**

Reagents and conditions: (*a*) PCC, CH_2Cl_2, 72%; (*b*) $(Ph_3P^+CH_2OCH_3)Cl^-$, 59%; (*c*) dioxane-HCl; (*d*) $LiAlH_4$, 82%; (*e*) *i*) Ac_2O; *ii*) OsO_4, 96%; (*f*) KOH, H_2O, 100%; (*g*) MsCl, py, 95%; (*h*) PCC, CH_2Cl_2, 98%; Huang-Minlon, 90%.

A rather roundabout route, consisting of osmylation of the double bond, cyclization, oxidation of the hydroxyl group and Huang-Minlon reduction, was used to convert **253** into Ambrox® (**103**). It can be noticed that compound **253** also is obtained in the synthesis from carvone (**250**) to Ambrox® (Scheme 2.9) and can be cyclized also directly to Ambrox®.

Racemic albicanol (±)-**264** can be synthesized easily from dihydro-β-ionone (**227**) or from Jones oxidation of the β-hydroxy ester (±)-**262**[35] as indicated. Upon reaction with isopropenyl acetate in the presence of lipase 'PL-266', it can be converted into pure (+)-albicanyl acetate **265**.[36] Deprotection afforded also (+)-albicanol **264**, which was converted into (-)-Ambrox® (**101**) following the route that is indicated in Scheme 2.12.

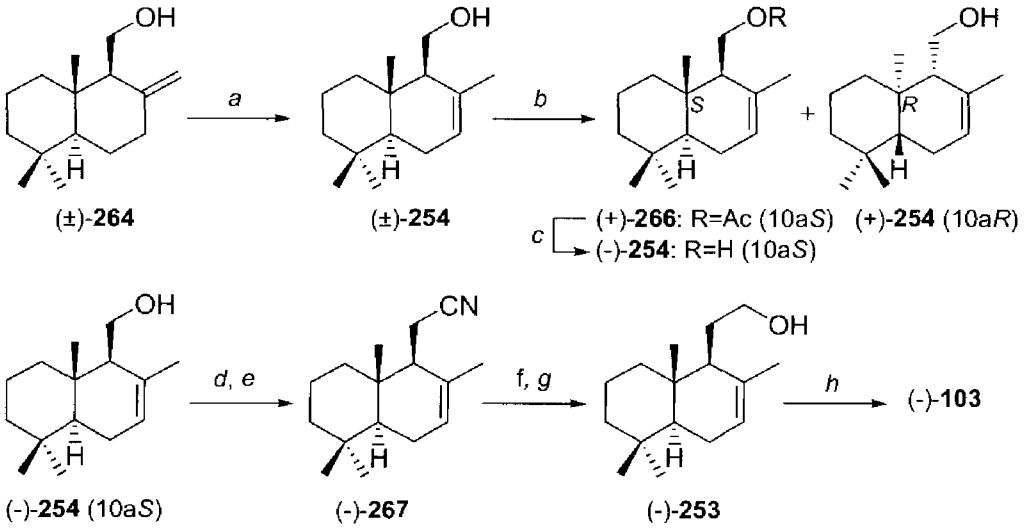
Scheme 2.11



Reagents and conditions: (*a*) CrO_3, H^+; (*b*) $Ph_3P{=}CH_2$; (*c*) $LiAlH_4$; (*d*) Ac_2O, py; (*e*) 2-propenyl acetate, lipase, $(i\text{-}Pr)_2O$, 33°C.

Racemic albicanol ((±)-**264**) can be converted also first into (±)-drimenol ((±)-**254**) using $BF_3{\cdot}Et_2O$, which than can be separated in its enantiomers as well (Scheme 2.12). When (±)-drimenol ((±)-**254**) was exposed to 'PL-266' in the presence of isopropyl acetate, acetate (+)-**266** (53%, 61% ee) and unchanged (+)-**254** (40%, 80% ee) were obtained. Homologation of the primary alcohol group of (-)-**254** has been achieved by reaction of the corresponding mesylate with NaCN to nitrile (-)-**267**. Reduction with DIBAL-H and subsequent reduction with $NaBH_4$ provided the alcohol **253**. Treatment of (-)-**253** with *p*-TsOH in acetonitrile gave (-)-Ambrox® (**103**).

Scheme 2.12



Reagents and conditions: (*a*) $BF_3{\cdot}Et_2O$, 93%; (*b*) 2-propenyl acetate, lipase, $(i\text{-}Pr)_2O$, 33°C; (*c*) $LiAlH_4$; (*d*) MsCl, pyridine, 99%; (*e*) NaCN, DMSO, 45-53%; (*f*) DIBAL-H, H^+, 81%; (*g*) $NaBH_4$, 99%; (*h*) *p*-TsOH, CH_3CN, 55%.

2.3.3 Syntheses of Ambrox® starting from labdanes.

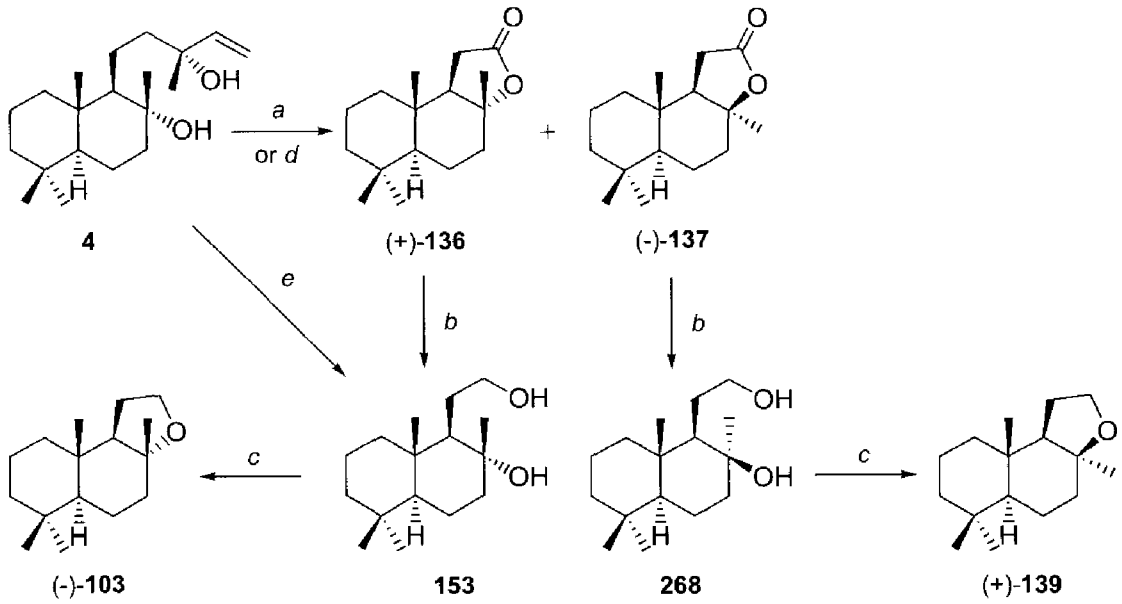
Ambrox® is a tetra*nor* labdane and it is obvious that labdanes have been used for the synthesis of Ambrox® (**103**). To achieve this goal 4 carbon atoms have to be removed from the labdane and many oxidative protocols have been investigated for this purpose.

Syntheses starting from sclareol.

(-)-Ambrox® was first prepared starting from (-)-sclareol (**4**),[37-41] which upon oxidation of the side chain with permanganate gave the γ-lactones (+)-sclareolide (**136**) and (-)-*iso*-sclareolide (**137**). Reduction of both lactones with hydride donating reagents afforded diols **153** and **268**. Cyclization of the diols then leads to the desired ether (-)-**103** and its 8-*epi*-isomer (+)-*iso*-Ambrox ((+)-**139**) as shown in Scheme 2.13. The smell of (+)-*iso*-Ambrox (**139**) is more than a hundred times weaker than Ambrox® itself.

Cyclization of diol **153** is a delicate step as epimerization at C(8) has to be avoided as much as possible. It is assumed that this acid catalyzed cyclization proceeds through the attack of the primary hydroxyl group on the tertiary carbocation, formed by elimination of the tertiary hydroxyl group in **153**.[24a] Attack fro the α-face than gives Ambrox® (**103**) and the β-face attack gives *iso*-Ambrox (**139**). The formation of the undesired *iso*-Ambrox (**139**) may be controlled by using *p*-toluenesulfonic acid as catalyst in nitromethane as solvent.[24,32,42]

Scheme 2.13



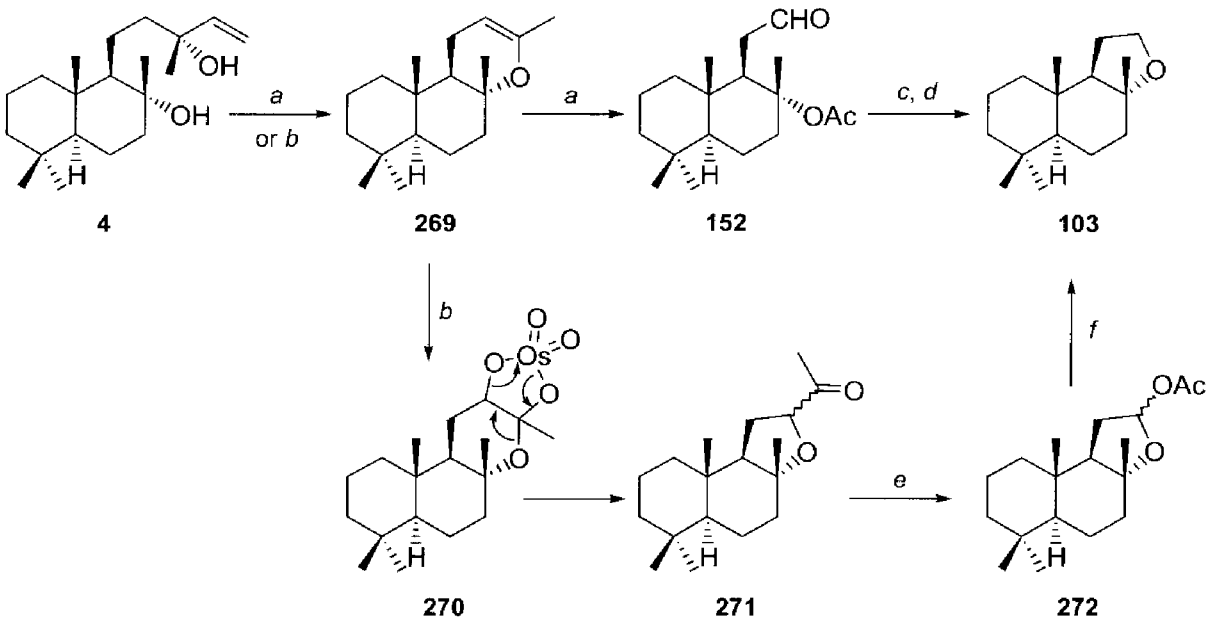
Reagents and conditions: (*a*) CrO_3, AcOH or $KMnO_4$; (*b*) $LiAlH_4$ or BH_3; (*c*) *p*-TsCl, py or CH_3NO_2; (*d*) *Cryptococcus albidus*; (*e*) *Hyphozyma roseoniger* or *Bensingtonia cilata*.

Oxidation of sclareol (**4**) with chromic acid in acetic acid is also not 100% selective and gives the γ-lactones (+)-sclareolide (**136**) and (-)-*iso*-sclareolide (**137**) as well.[40] The first on reduction and cyclization then leads to (-)-Ambrox® (**103**), while the latter leads to the 8-*epi*-isomer (+)-*iso*-Ambrox (**139**). This synthesis is still the commercial one, as the diterpene sclareol (**4**) is relatively cheap (US$ 150-200 per kg) and an abundant constituent of clary sage oil and technical improvements of the oxidation, reduction, and cyclization steps, have made it to a well established procedure.

Sclareol (**4**) is oxidized efficiently also by the microorganism *Cryptococcus albidus* to sclareolide **136**.[43,44] The chemical reduction of sclareolides **136** and **137** to the diastereomeric diols **153** and **268** can be circumvented by the direct biotransformation of sclareol (**4**) to the diol **153** by *Hyphozyma roseoniger* or *Bensingtonia cilata*.[45]

The ruthenium tetroxide oxidation of sclareol (**4**) to 12-acetyl Ambrox (**271**) is strongly dependent on the cooxidation agent used (Scheme 2.14). Sodium periodate gives only 18% yield of **271**, whereas calcium hypochlorite gives about 54%.[46] In these oxidations, the double bond of (-)-sclareol (**4**) is first cleaved to the corresponding α-hydroxy acid. This is further oxidized, under decarboxylation, to a methyl ketone, which cyclizes in the course of the reaction to enol ether **269**. Ruthenium-tetroxide oxidation of **269** then provides the aldehyde **152**, which is converted into (-)-Ambrox®. Optimalization of the oxidation procedure finally led to osmium tetroxide as oxidant of choice.

Scheme 2.14

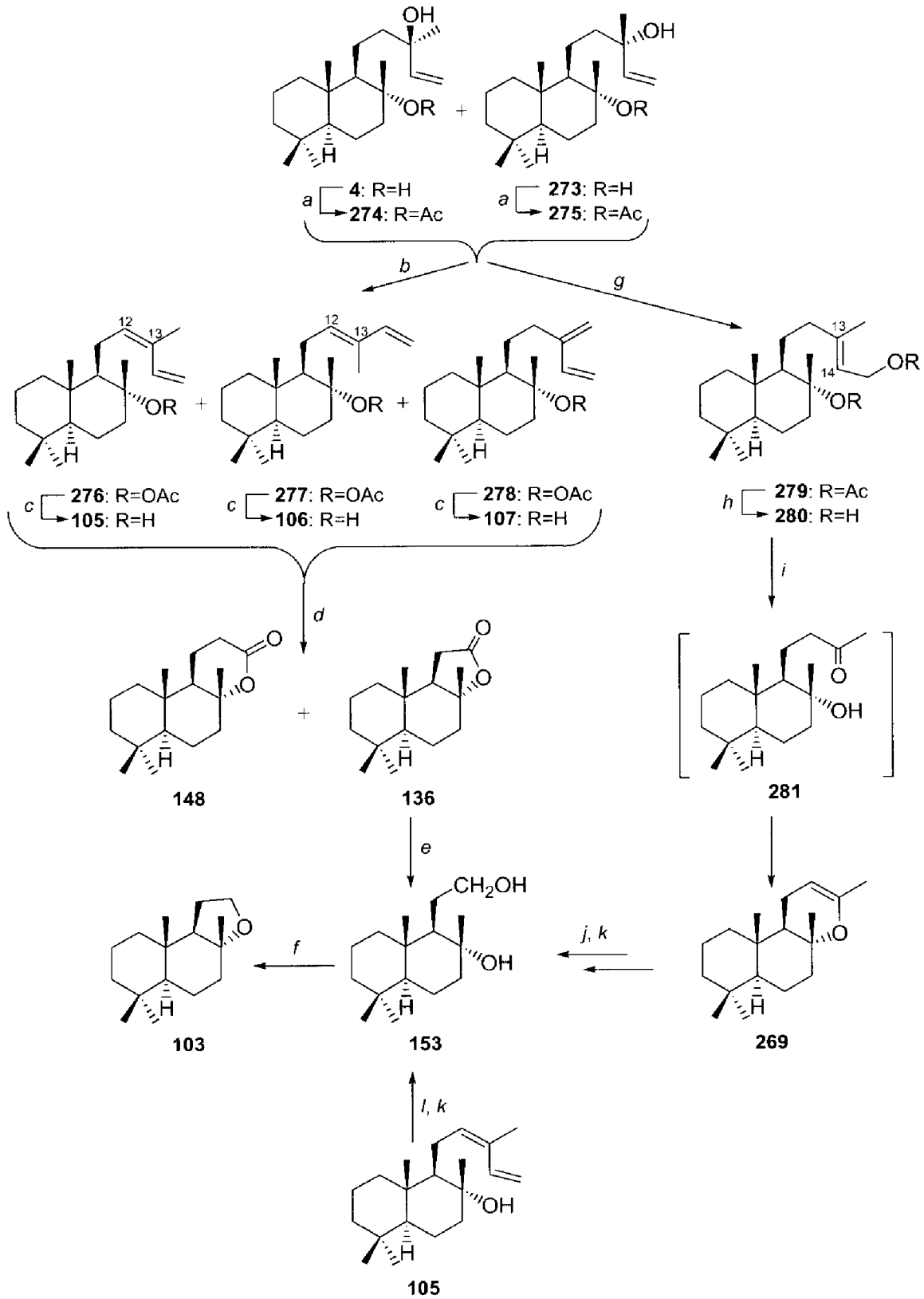


Reagents and conditions: (a) RuO_4; (*b*) O_3, or $NaIO_4$, OsO_4 (cat.); (*c*) $LiAlH_4$; (*d*) *p*-TsCl, NaH, CH_2Cl_2; (*e*) *m*-CPBA; (*f*) $LiAlH_4$, $BF_3{\cdot}OEt_3$.

Another ingenious oxidation of sclareol (**4**) has been described with the system OsO_4-$NaIO_4$ (1:70).[47] The final product of this oxidation is 12-acetyl Ambrox (**271**), which is isolated in high yield. The synthesis of Ambrox® can be completed in high yield through a Baeyer-Villiger oxidation to the acetate **272** and subsequent reduction with lithium aluminium hydride in the presence of $BF_3{\cdot}OEt_2$.

Ambrox® (**103**) has been synthesized also *via* palladium acetate catalyzed elimination of H_2O from the commercially available mixture of sclareol and *epi*-sclareol acetates (Scheme 2.15).[48] As the synthetic scheme leads to a loss of chirality at C(13), this mixture can be used as starting material. When acetates **274** and **275** were treated with a catalytic amount of palladium acetate, a 3/1/1 mixture of dienic acetates **276**, **277** and **278** was obtained in quantitative yield. The corresponding mixture of *cis*-abienol (**105**), *iso*-abienol (**106**) and *neo*-abienol (**107**) was obtained after $LiAlH_4$ reduction of the acetates, and oxidation of this mixture with $KMnO_4$ gave ambreinolide (**148**) and sclareolide (**136**). These two derivatives could be separated by column chromatography on silica gel. Finally $LiAlH_4$ reduction of sclareolide (**136**), immediately followed by cyclization using tosylchloride, gave Ambrox® (**103**). A better variant using the quantitative palladium catalyzed isomerization of **274** and **275** to the *E* isomer of *iso*-sclareyl diacetate **279** has been uses as well. $LiAlH_4$ reduction of **279** to *iso*-sclareol **280**, followed by ozonolysis gave sclareol oxide **269**, which is formed by intramolecular attack of the 8-hydroxy group on the intermediate methyl ketone **281**. Ozonolysis of **269**, followed by $LiAlH_4$ reduction and cyclization yields Ambrox® (**103**) in 70% overall yield.

Scheme 2.15

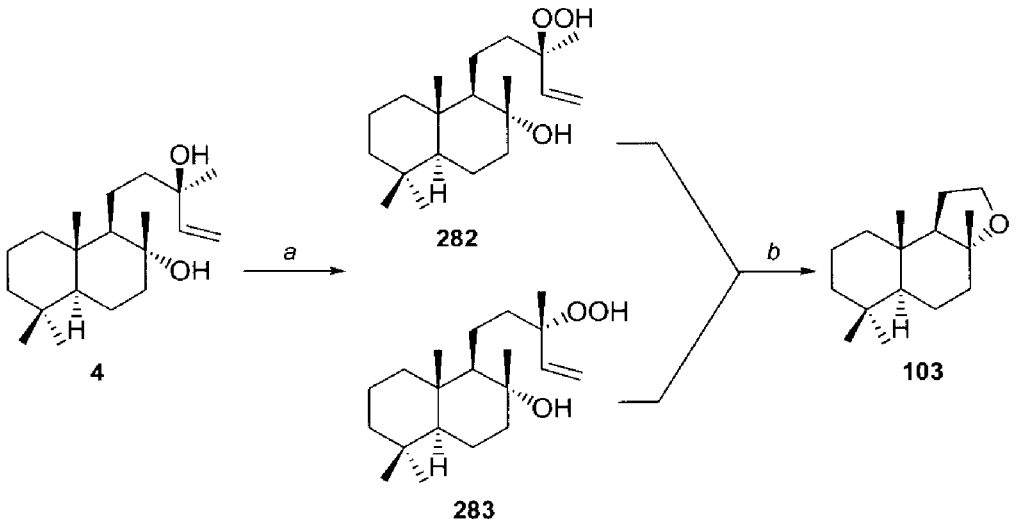


Reagents and conditions: (*a*) AcCl, *N,N*-dimethylaniline, 25°C, 1 day, 98%; (*b*) $Pd(OAc)_2$, dioxane, 100°C, 15 min, 100%; (*c*) $LiAlH_4$, Et_2O, 96%; (*d*) $KMnO_4$, 1 day, 80%; (*e*) $LiAlH_4$, THF, 25°C, 3h, 98%; (*f*) *p*-TsCl, CH_2Cl_2, 25°C, 2h, 90%; (*g*) $PdCl_2(CH_3CN)_2$, THF, 25°C, 4h, 100%; (*h*) $LiAlH_4$, Et_2O, 25°C, 98%; (*i*) O_3, MeOH, CH_2Cl_2, $(CH_3)_2S$, -70°C, 24h, 75%; (*j*) O_3, MeOH, CH_2Cl_2, $(CH_3)_2S$, -70°C, 24h; (*k*) $LiAlH_4$, Et_2O, 25°C; (*l*) O_3, CH_2Cl_2, -78°C.

(+)-*cis*-Abienol (**105**) can also be isolated by vacuum destillation of the non-acid fraction of commercial Canadian balsam (oleoresin of *Abies balsamea* Mill.).[49] A short and efficient approach to Ambrox® was developed in 84% overall yield. Ozonization of **105** and subsequent treatment with $LiAlH_4$ afforded **153** in high yield, and the cyclization of **153** into **103** using *p*-TsCl in pyridine gave Ambrox® in 98% yield (Scheme 2.15).

The over-oxidation of sclareol (**4**) to the lactone **136**, and thus the use of a powerful reductant to convert it into the diol **153**, is wasteful and a number of approaches have been investigated to stop the oxidation at a better level. Two of these are especially worth mentioning. Näf and co-workers used metal-catalyzed fragmentation of the mono-hydroperoxide of sclareol (**4**) to give an intermediate at the correct oxidation level for cyclization, when the mixture of the two hydroperoxides **282** and **283** reacted with the redox couple Fe^{II}/Cu^{II} Ambrox® (**103**) (30% isolated yield) was directly formed (Scheme 2.16).[41] Willis and colleagues achieved a similar fragmentation by fermentation using the previously unreported micro-organism *Hyphozyma roseoniger* ATCC 20624.[50]

Scheme 2.16



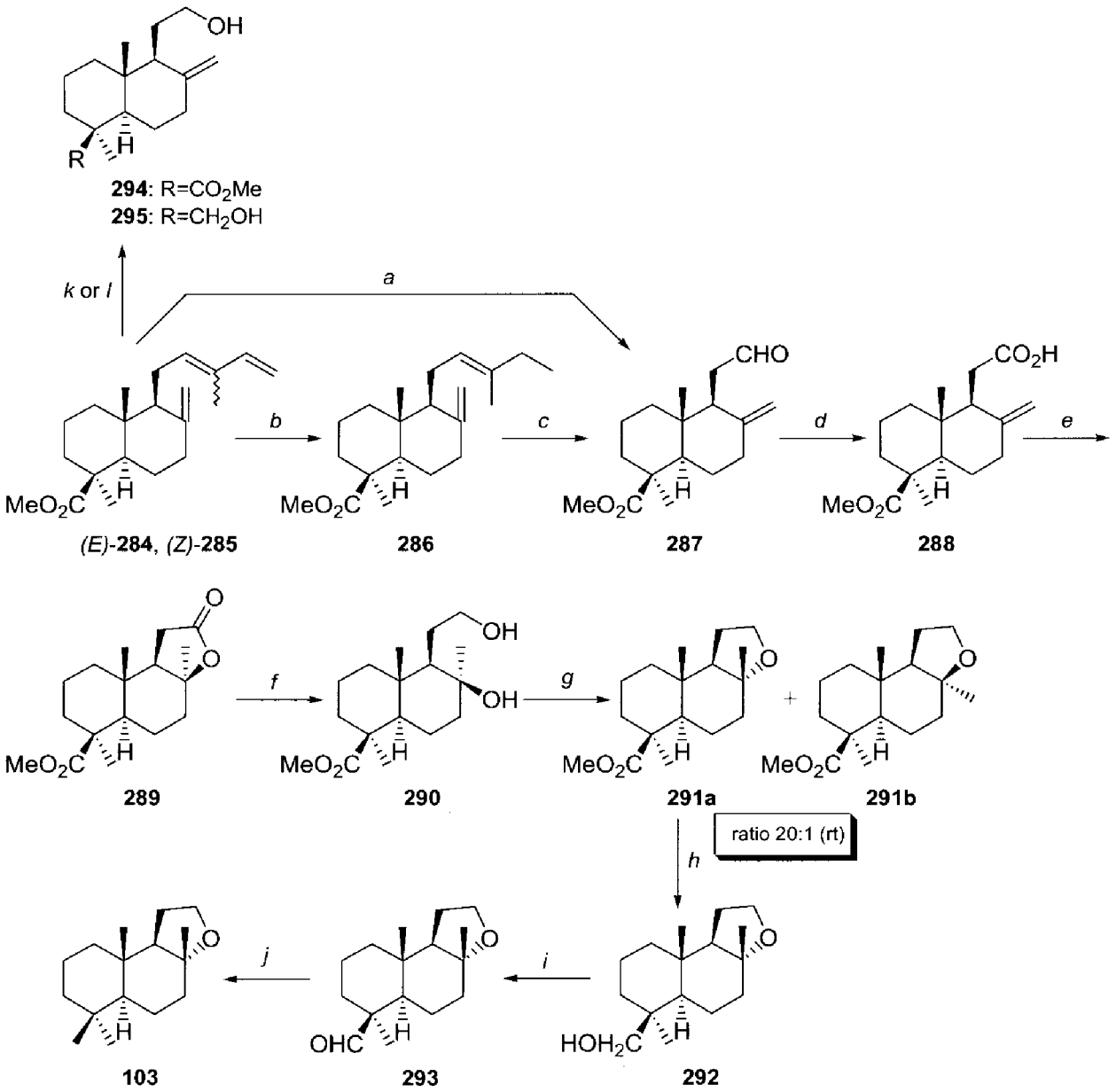
Reagents and conditions: (*a*) 70% aqueous H_2O_2, *p*-TsOH, CH_2Cl_2; (*b*) $Cu(OAc)_2 \cdot 2H_2O$, $FeSO_4 \cdot 7H_2O$, CH_3OH.

Syntheses starting from communic acid.

Communic acids are found in many species of the Cupresaceae family and they are the main components in the non-polar extracts of the genus Juniperus. For the degradation of the side chain of methyl *(E)*-(**284**) or *(Z)*-communate (**285**), or a mixture of them, two methods were followed: (a) the carefully controlled ozonolysis of **284** and/or **285** at low temperature to give aldehyde **287** (40%) and recovered starting material (40%), or (b) the Δ^{14} selective hydrogenation of **284** with diimide (70%), followed by the degradation of the Δ^{12} double bond in **286** with OsO_4-$NaIO_4$.[51] The formation of the tetrahydrofuran ring was achieved as depicted in Scheme 2.17, ultimately leading to the correct configuration at C(8). Finally, the ester functionality at C(4) was

converted into a methyl group in a traditional way *via* reduction and oxidation to an aldehyde, which was reduced by the Wolff-Kishner method.

Scheme 2.17



Reagents and conditions: (*a*) O_3, CH_2Cl_2, -78°C, Me_2S, 40%; (*b*) $N_2H_4{\cdot}H_2O$, EtOH, 30% H_2O_2, 0°C, 70%; (*c*) $NaIO_4$, 0.2% OsO_4, *t*-BuOH, H_2O, rt, 60h, 80%; (*d*) Jones reagent, acetone, 0°C, 90%; (*e*) *p*-TsOH, toluene, reflux, 1h, 75%; (*f*) $LiAlH_4$, THF, rt, 1h, 90%; (*g*) *p*-TsOH, CH_3NO_2, rt, 3h, 85%; (*h*) $LiAlH_4$, THF, reflux, 1.5h, 90%; (*i*) Jones reagent, acetone, 0°C, 88%; (*j*) $N_2H_4{\cdot}H_2O$, KOH, triethylene glycol, reflux, 1h, 71%; (*k*) *i*) O_3, CH_2Cl_2, -78°C; *ii*) $LiAlH_4$, THF, rt, 40%; %; (*l*) *i*) O_3, CH_2Cl_2, -78°C; *ii*) $LiAlH_4$, THF, reflux, 35-40%.

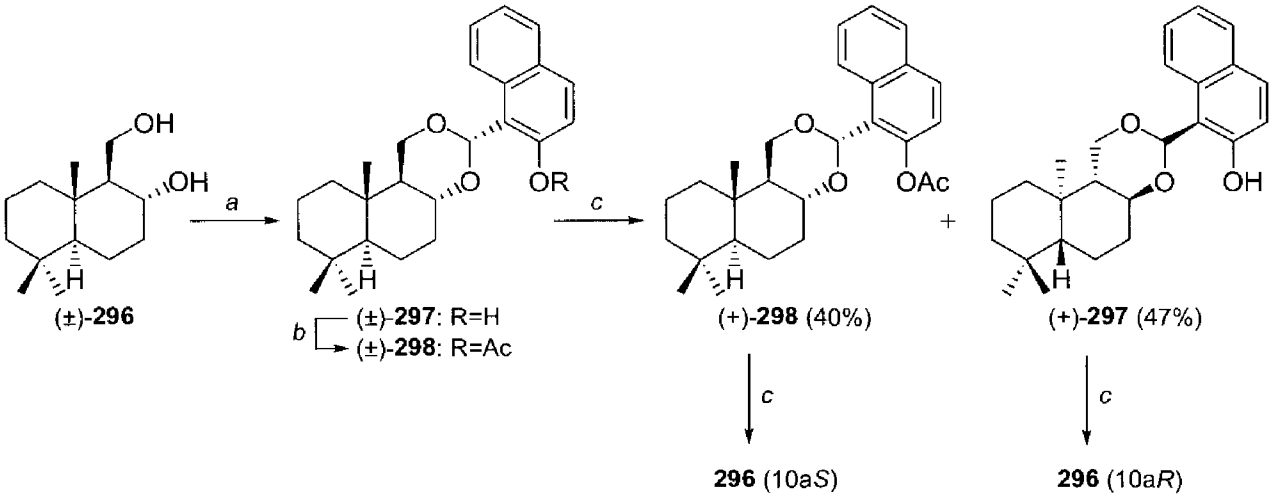
A shorter and more efficient approach to (-)-Ambrox® comprised the preparation of **294** by reductive ozonolysis of **284** and **285**, subsequent cyclization of **294** with *p*-TsOH in CH_3NO_2 (85%), and the aforementioned sequence for converting an ester into a methyl group. This route was

shortened further by the direct conversion of **284** and **285** into diol **295** by refluxing the crude reaction mixture of ozonides with $LiAlH_4$, followed by its cyclization to **292** under the established conditions (80%).

2.3.4 *Ambrox® from other natural products*

Another example based on enzymatic functionalization and its application to the synthesis of (-)-Ambrox® is the enantioselective and regioselective acetylation of (±)-**296** with the lipase 'Godo E-4' from *Pseudomonas* sp. in the presence of isopropenyl acetate (Scheme 2.18).[52]

Scheme 2.18

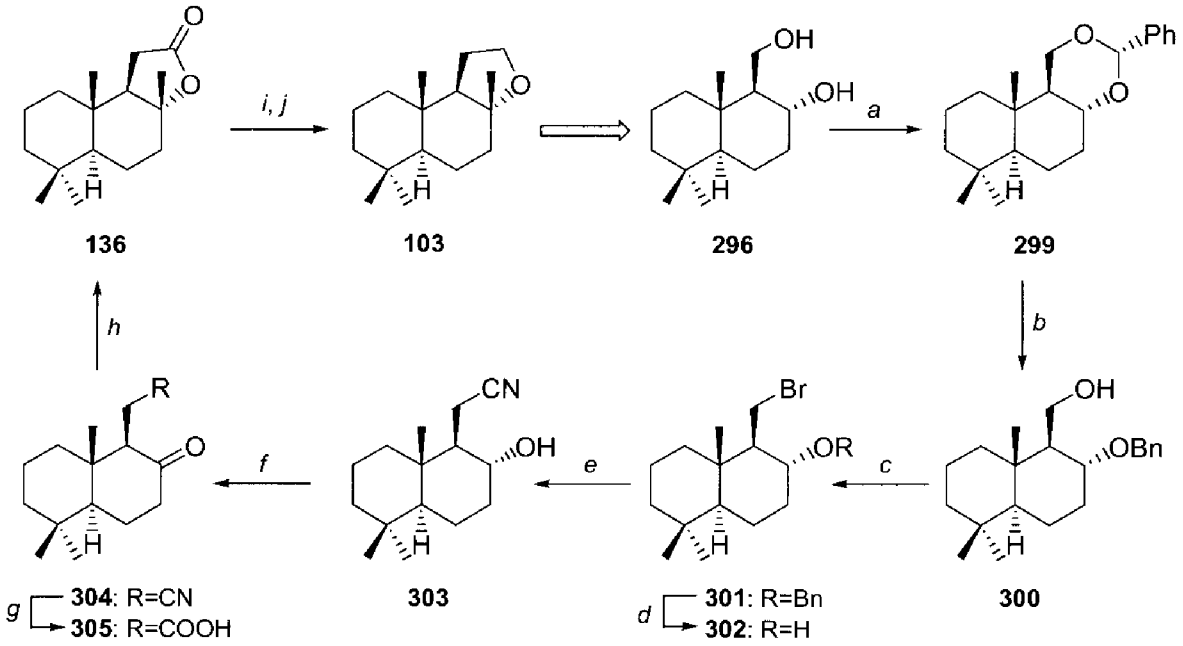


Reagents and conditions: (*a*) 2-hydroxy-1-naphtaldehyde, H_2SO_4, DMSO, 99%; (*b*) Ac_2O, py, 99%; (*c*) acylase I (*Aspergillus melleus*) in H_2O saturated $(i\text{-}Pr)_2O$; (*d*) *i*) recrystallization; *ii*) H_2, 20% $Pd(OH)_2$-C, AcOEt, 92-96%.

The reaction of (±)-**296** and 2-hydroxy-1-naphtaldehyde gave the phenolic acetal (±)-**297** as a single diastereomer in quantitative yield whose acetylation afforded the corresponding acetate (±)-**298** (Scheme 2.18). When the phenolic acetate (±)-**298** was exposed to the acylase I in water-saturated diisopropyl ether, hydrolyzed product (+)-**298** (80% ee) and unchanged (+)-**297** (92% ee) were obtained.

Treatment of (10a*S*)-**296** with benzaldehyde afforded acetal **298**, which was reduced to provide selectively primary alcohol **300** along with a small amound of secondary alcohol (Scheme 2.19). Conversion of **300** by treatment with CBr_4 and Ph_3P into the bromide **301** followed by catalytic reduction gave the 1,3-bromohydrin **303**. Treatment of **297** with NaCN provided the nitrile **303**, which was oxidized to afford keto-nitrile **304**. Hydrolysis of **304** gave the β-keto-acid **305**, which was reacted with MeLi folowed by treatment with *p*-TsOH to provide the δ-lactone **136**. Reduction of **136** yielded the diol **153** which was reacted with *p*-TsOH in nitromethane to provide the (-)-Ambrox® (**103**).

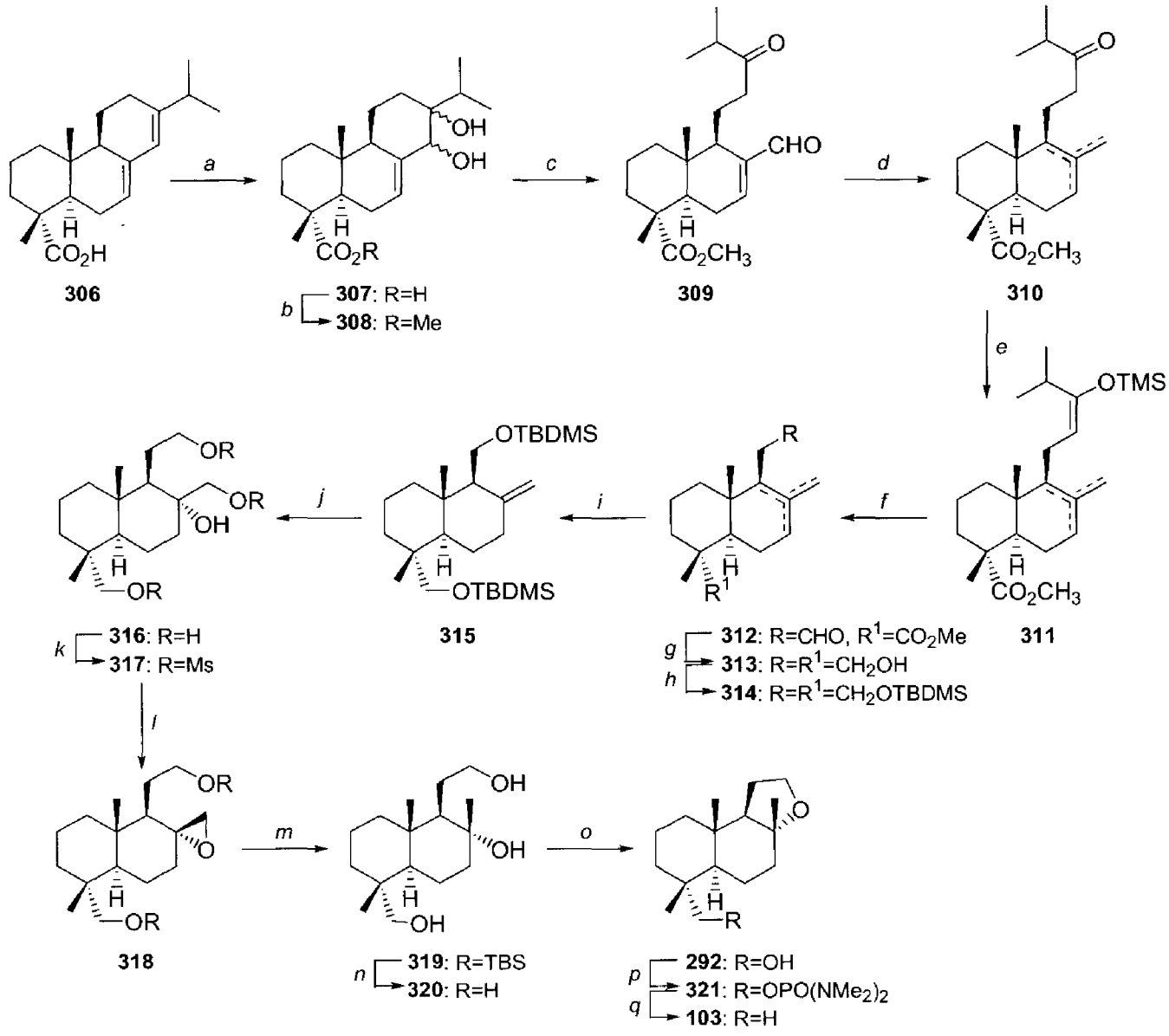
Scheme 2.19



Reagents and conditions: (*a*) *i*) PhCHO, H_2SO_4, DMSO, *ii*) H_2O, DMSO, 98%; (*b*) $LiAlH_4$, $AlCl_3$, Et_2O, 93%; (*c*) CBr_4, Ph_3P, THF, 98%; (*d*) H_2, 20% $Pd(OH)_2$-C, AcOEt, 99%; (*e*) NaCN, DMSO, 97%; (*f*) Jones reagent, acetone, 96%; (*g*) NaOH, H_2O, MeOH, 89%; (*h*) *i*) MeLi, THF, Et_2O; *ii*) *p*-TsOH, 65%; (*i*) $LiAlH_4$, Et2O, 76%; (*j*) *p*-TsOH, CH_3NO_2, 45%.

Abietic acid (**306**) is easily available from pine resin and represents a good and cheap chiral starting material (Scheme 2.20).[53] However, it is rather difficult to perform the regioselective oxidation of the conjugated double bonds located in the B and C-ring of **306**. This problem was solved by highly regioselectively oxidation with a catalytic amount of OsO_4 to give diol **307**.[54] The mixture of diols **307** was converted to methyl ester **308**, which was cleaved with $Pb(OAc)_4$ to afford keto-aldehyde **309**. The aldehyde group in **309** was transformed into an thioacetal and subsequent reduction with Raney Ni afforded a mixture of olefins **310** in a ratio of endo to exo in 3 to 1. The mixture of ketones **310** was converted into silyl enol ethers **311** and after ozonolysis aldehydes **312** were obtained. Reduction of aldehyde mixture **312** with $LiAlH_4$ and protection of the primary alcohols of **313** with TBDMSOTf yielded **314**. The mixture of olefins **314** was subjected to photo-induced isomerization (UV-irridiation with high pressure mercury lamp) to afford **315** as a single product. The exomethylene compound **315** was oxidized to glycol **316**, which was converted to the monomesylate **317** and subjected to Li-HMDS to afford the α-epoxide **318**. The epoxide **318** was reduced and after removal of the TBDMS groups in **319** cyclized product **292** was formed in 78% yield from **319** after treatment with mesitylenesulfonylchloride. The neopentyl alcohol group in **292** was reduced and treatment of **321** with Li in $EtNH_2$ finally furnished Ambrox® (**103**).

Scheme 2.20



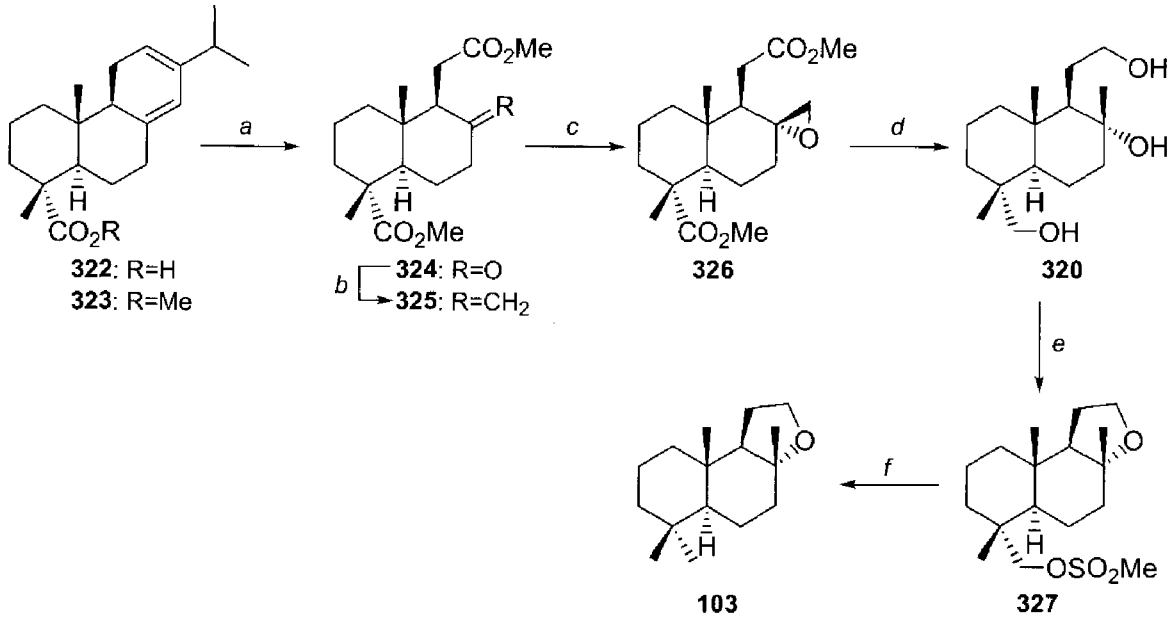
Reagents and conditions: (*a*) OsO_4, Me_3NO, *t*BuOH, H_2O, py, reflux, 86%; (*b*) CH_2N_2, CH_2Cl_2/MeOH, 99%; (*c*) $Pb(OAc)_4$, benzene, 90%; (*d*) *i*) $HSCH_2CH_2SH$, *p*TsOH, 72%; *ii*) Raney-Ni, AcOEt-EtOH, 85% (ratio endo:exo 3:1); (*e*) TMSOTf, CH_2Cl_2, -78°C, 99%; (*f*) O_3, AcOEt-py, 1.3% v/v, -78°C, 49%; (*g*) $LiAlH_4$, 93%; (*h*) TBDMSOTf, 99%; (*i*) hv, *i*PrOH-xylene, 0°C, 99%; (*j*) OsO_4-TBHP, acetone, Et_4NOH, 50°C, 71%; (*k*) MsCl, py; (*l*) Li-HMDS, THF, 99%; (*m*) $LiAlH_4$, THF, 80%; (*n*) TBAF; (*o*) $(CH_3)_3C_6H_2SO_2Cl$, py, 78%; (*p*) $(NMe_2)_2OPOCl$, py; (*q*) Li, $EtNH_2$, 93%.

Ambrox® was also efficiently synthesized starting from (-)-levopimaric acid (**322**) (Scheme 2.21).[55] Levopimaric acid (**322**) is a major component of pine oleoresin, and can be purified easily.[56] Pine oleoresin is obtained on an industrial scale from pine trees.

The keto diester **324** was obtained by ozonolysis of methyl levopimarate (**323**), followed by Jones oxidation and methylation with diazomethane. Introduction of the methyl group at C(8) was a crucial step in this approach. Addition of methyl lithium was considered to give an α-methyl goup at C(8) predominantly. Therefore, the exocyclic methylene group was introduced in a Wittig reaction

of **324** with methyltriphenylphosphonium iodide and KO*t*Bu to give **325**. Epoxidation of the exocyclic methylene diester **325** with *m*-CPBA gave the α-epoxide **326** as the major product. Reduction of **326** with lithium aluminium hydride afforded triol **320**. The triol was converted into the 8α,12-epoxy mesylate **327** by dehydration with methanesulfonyl chloride in an overall yield of 35% from **320**. Reduction of the mesylate **327** with sodium iodide and zinc dust gave (-)-Ambrox® (**103**) in 44%, along with the starting material **327**.

Scheme 2.21

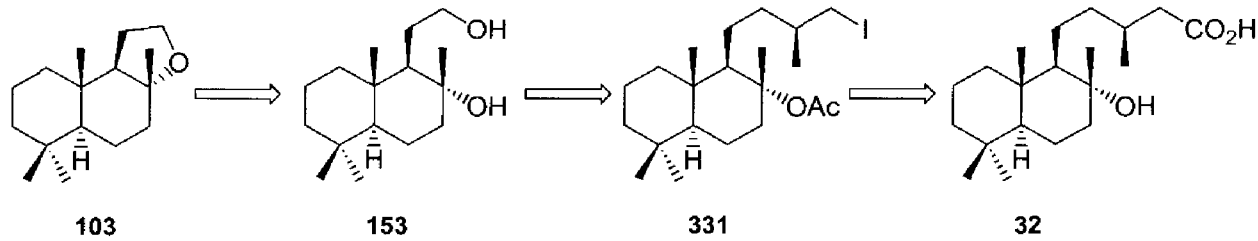


Reagents and conditions: (*a*) *i*) O_3, EtOAc, -70°C; *ii*) CrO_3, *iii*) CH_2N_2; (*b*) PPh_3CH_2I, KO*t*Bu, $((CH_3)_2CH)_2O$, 60°C, N_2, 59%; (*c*) *m*-CPBA, $CHCl_3$; (*d*) $LiAlH_4$, THF, 0°C, N_2; (*e*) $MeSO_2Cl$, py, 35%; (*f*) NaI, Zn, DMF, 115°C, 44%.

2.4 The Synthesis of (-)-Ambrox® starting from labdanolic acid

Labdanolic acid (**32**) is the main component (ca. 40%) in the acidic fraction of the *n*-hexane extract of *Cistus ladaniferus L.* ("Rock-rose")[1,57-59] and it has the potential to serve as a cheap starting material for the preparation of Ambrox®. After oxidative degradation of the C(9) side chain of labdanolic acid suitable synthons for the synthesis of (-)-Ambrox® may become available.

Scheme 2.22

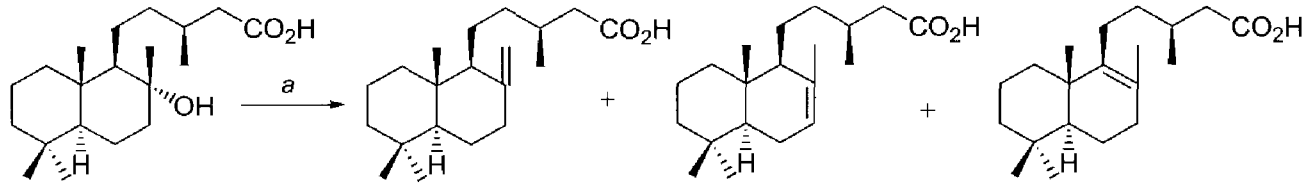


However, the degradation of labdanolic acid is not an easy task because the carboxyl group is the only available functional group in the side chain. Several studies to break down the side chain of labdanolic acid (**32**) or its methyl ester have been reported in the literature.[60,61] Lead tetraacetate is mostly used as decarboxylating reagent[60] and acetates are obtained in rather irreproducible yields. Therefore the iododecarboxylation of labdanolic acid as key step in the synthesis of (-)-Ambrox® may offer an acceptable alternative (Scheme 2.22). [62-65]

The commercial extract from *Cistus ladaniferus L.*,[66] is obtained by steam distillation of the twigs and leaves of the plants, or by treatment of the plant material with hot water or aqueous base. These conditions may cause elimination of the tertiairy hydroxyl group which results in formation of a mixture of labdenic acids. An analysis of the commercial extract confirmed this assumption. Also treatment of labdanolic acid (**32**) with urea in methanol leads to elimination of water and a mixture of unsaturated (**328** - **330**) is formed (Scheme 2.23).[58]

To prevent this dehydration the air-dried twigs and leaves of the *Cistus ladaniferus L.* were soaked with *n*-hexane and evaporation of the solvent gave rise to a sticky labdanum gum. Partial purification was performed by extracting the acid with base from an etheral solution of the gum. After acidification the crude labdanolic acid (**32**) was obtained. Further purification of this crude labdanolic acid (**32**) appeared to be difficult, but after conversion of the C(8) tertiary hydroxyl group into its acetate, the purification of the acetate **140** proved to be relatively easy, and pure acetate **140** could be obtained in 35-45% based upon the crude acidic material.

Scheme 2.23



32 **328** (69%) **329** (11%) **330** (19%)

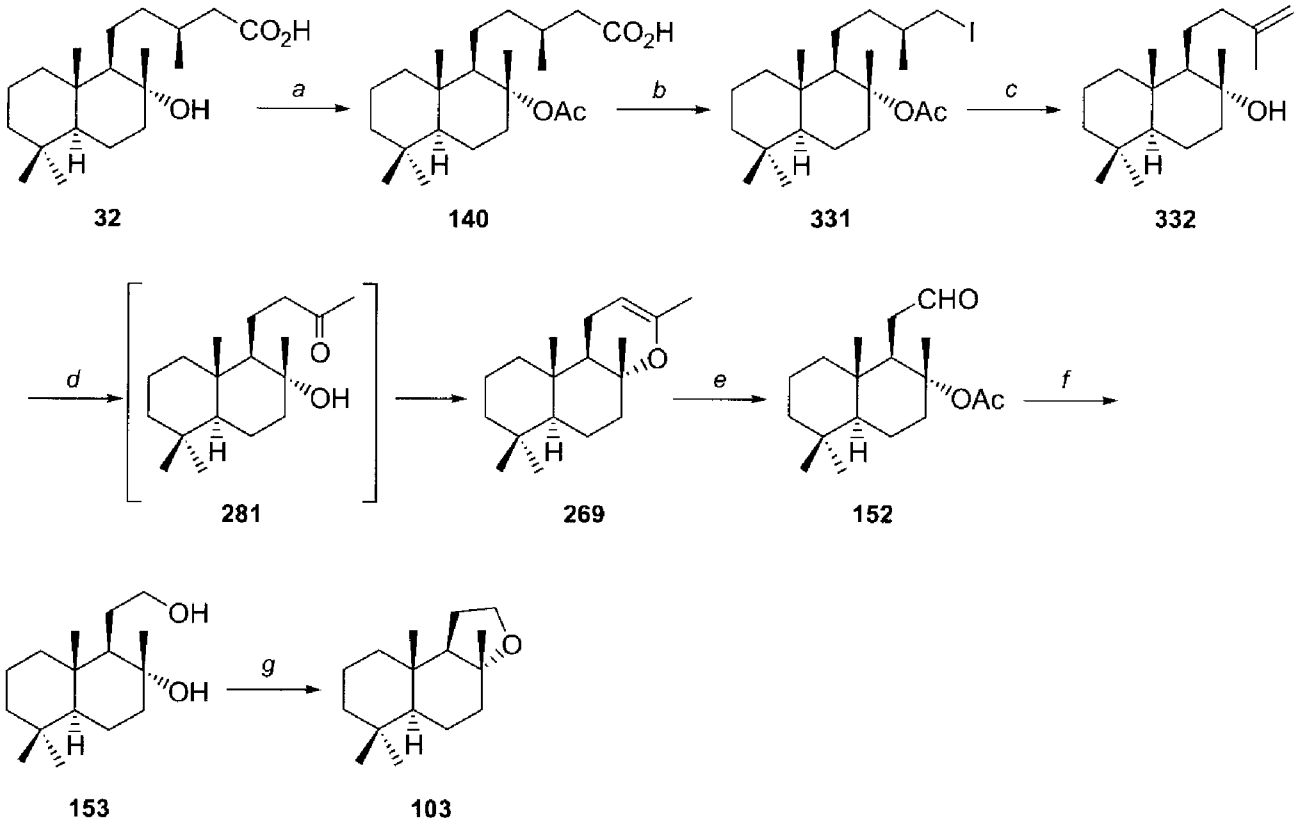
Reagents and conditions: (*a*) urea, MeOH, 99%.

The iododecarboxylation[67] of acetate **140** with iodobenzenediacetate (IBDA) could be achieved under irradiation with a 100W tungsten lamp and the iodide **331** was obtained in 76% yield. Because this iodide **331** proved to be a rather unstable compound and because it was contaminated with iodobenzene, the product was treated immediately with potassium *tert*-butoxide (*t*BuOK) in THF at room temperature to give dehydroiodination and hydrolysis of the acetate group to compound **332** in 74% yield (Scheme 2.24).

Ozonolysis of the double bond of compound **332** and reduction of the intermediate ozonides gave the methyl ketone which immediately cyclized into sclareol oxide (**269**) in a irreproducible yield of 45-90% due to the fact that **269** is fairly unstable. Therefore the enol ether in sclareol oxide (**269**) was ozonolyzed immediately, and reduction of the aldehyde and acetate group

in intermediate **152** afforded the diol **153** in 60% overall yield starting from **332**. Stirring of this diol **153** in nitromethane in the presence of *p*-toluenesulfonic acid gave the cylized product (-)-Ambrox® (**103**) in 87% yield.[33b]

Scheme 2.24



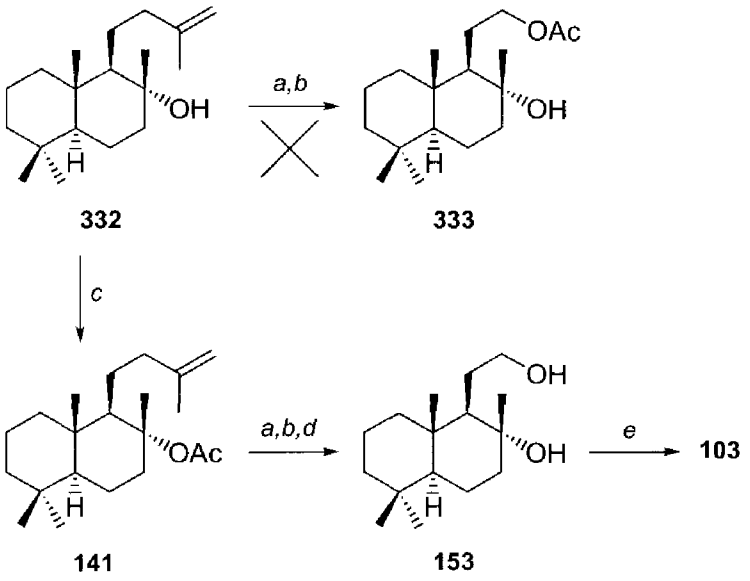
Reagents and conditions: (*a*) AcCl, *N,N*-dimethylaniline; (*b*) IBDA, I_2, CCl_4, hν, Δ, 76%; (*c*) *t*BuOK, THF, 74%; (*d*) O_3, $MeOH/CH_2Cl_2$ 1:5, -78°C, PPh_3, 44%; (*e*) O_3, CH_2Cl_2, py, -78°C; (*f*) $LiAlH_4$, THF, 60%; (*g*) *p*-TsOH, CH_3NO_2, 87%.

An obvious way to circumvent the unstable sclareol oxide was the synthesis of acetate ester **333** *via* a Criegee rearrangement[68] of the ozonide of alkene **332**, but this approach was unsuccessful (Scheme 2.25). The rearranged product **333** was not observed upon treatment of the ozonide under the usual Criegee conditions (acetic anhydride, triethylamine, and *N,N*-dimethylaminopyridine), probably because an unfavourable seven membered ring intermediate cannot be formed, and the reaction gave the *normal* ozonolysis product which cyclized as before to sclareol oxide (**269**).

Another way to circumvent the formation of sclareol oxide was to apply the Criegee rearrangement but to prevent the interference of the hydroxyl group at C(8) during the ozonolysis. So the tertiairy hydroxyl group of **332** was protected again as its acetate and the ozonolysis product of **141** was subjected to Criegee rearrangement. After reduction of the obtained

intermediate with lithium aluminum hydride ($LiAlH_4$) now indeed compound **153** was obtained in 89% overall yield from compound **141**. This diol was also transformed into (-)-Ambrox® (**103**).

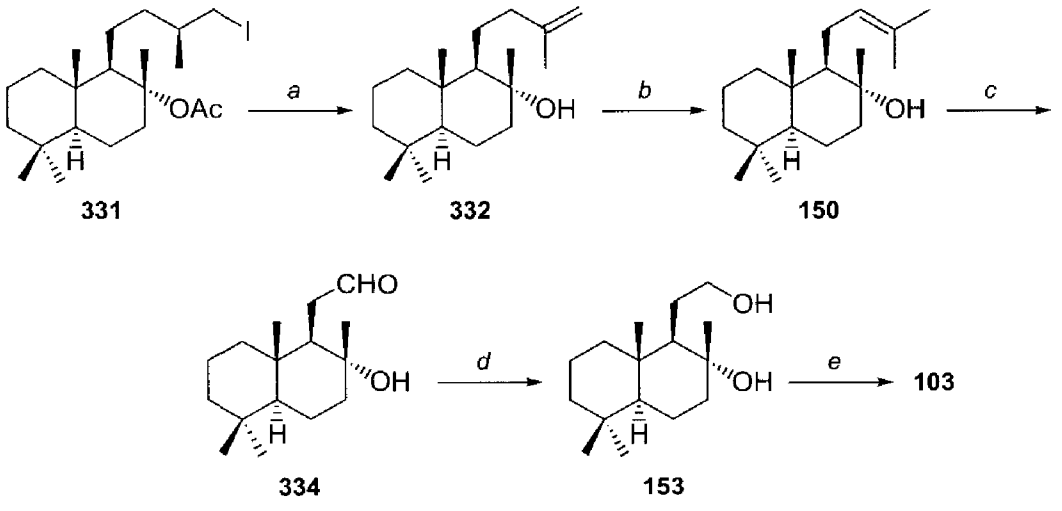
Scheme 2.25



Reagents and conditions: (*a*) O_3, MeOH/CH_2Cl_2 1:5, -78°C; (*b*) Ac_2O, NEt_3, DMAP; (*c*) AcCl, *N,N*-dimethylaniline, 83%; (*d*) $LiAlH_4$, THF, 89%; (*e*) CH_3NO_2, *p*-TsOH, 87%.

In Scheme 2.24 it was shown that treatment of **331** with *t*BuOK in THF at *room temperature* afforded compound **332**. When this dehydroiodonation was performed using the same base in *refluxing* THF (or in DMSO at room temperature), the intermediate **332** was *in situ* isomerized to **150** (Scheme 2.26).

Scheme 2.26



Reagents and conditions: (*a*) *t*BuOK, THF; (*b*) Δ, 78%; (*c*) O_3, MeOH/CH_2Cl_2 3:1, -78°C; (*d*) $NaBH_4$, 92%; (*e*) *p*-TsOH, CH_3NO_2, 87%.

Ozonolysis of the double bond and reduction with sodium borohydride ($NaBH_4$) of the intermediate ozonides gave diol **153** in 92% overall yield and this diol again was transformed into (-)-Ambrox® (**103**) upon treatment with *p*-TsOH in nitromethane.

The results of these three synthetic routes of acetate **140** to (-)-Ambrox® are summarized in Table 2.1. From this table it is clear that (-)-Ambrox® (**103**) can be obtained in a short four step procedure in 47% overall yield starting from the acetate of labdanolic acid **140**.

Table 2.1: Synthesis of (-)-Ambrox®, starting from 8-acetoxy-labdanolic acid (**140**).

route depicted in Scheme	steps	overall yield (%)	average step yield (%)
2.24	5	13	65
2.25	5	36	80
2.26	4	47	85

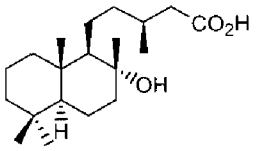
The main drawback of the method is the application of IBDA and iodine in the decarboxylation reaction. When a cheaper procedure can be found for this reaction, labdanolic acid (**32**) will become a good alternative as starting material for the industrial preparation of (-)-Ambrox® (**103**).

2.5 Experimental

General information and instrumentation.

All reagents used were purchased from Aldrich or Acros Chimica and used without further purification, unless otherwise stated. Reactions under dry conditions were performed under a steady stream of dry nitrogen or argon with glassware pre-dried at 140°C. Sonication experiments were performed using a 35 KHz Bandelin Sonorex TK 52 apparatus. Melting points were determined on a C. Reichert, Vienna, hot stage apparatus and are not corrected. Infrared spectra were recorded on a FT-IR, Biorad FTS-7 spectrometer and only characteristic absorptions are reported. ^1H and ^{13}C NMR spectra were, unless otherwise stated, recorded at 200 MHz and 50 MHz on a Bruker AC-E 200 spectrometer, respectively, using $CDCl_3$ as solvent. The chemical shift values are expressed in ppm (parts per million) (δ) relative to the residual $CHCl_3$ at 7.24 (^1H) and 77.00 (^{13}C) as internal standard. The multiplicity of the ^1H signals are expressed as: s=singlet, d=doublet, t=triplet, q=quartet, br s=broad singlet, m=multiplet. The multiplicity of the ^{13}C signals were determined with the DEPT technique, q=quartet, t=triplet, d=doublet, s=singlet. GC-MS data were determined at 70 eV on a Hewlett Packard 5890B series Mass Selective Detector, coupled with a Hewlett Packard 5973 GC provided with a DB-17 fused silica capillary column, 30 m x 0.25 mm i.d., film thickness 0.25 μm with helium as the carrier gas. The ratios m/e and relative

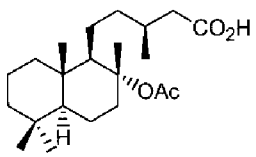
intensities (%) are indicated for the significant peaks. MS and HRMS data were obtained with a Finnigan MAT 95 spectrometer. The ratios *m/e* and relative intensities (%) are indicated for significant peaks. Elemental analyses were performed on a Carlo Erba 1106 elemental analyser. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter at 20 °C for chloroform solutions and concentrations are specified in units of g/100 mL. Gas chromatography was performed on a 5890 Series II Hewlett Packard gas chromatograph using a DB-17 fused silica bonded capillary column (30 m x 0.25 mm i.d.), programmed from 100-250°C at a rate of 10°C/min. For flash chromatography, ICN Biomedicals silica gel mean pore size 60 (32-63 μm) was used with mixtures of distilled light petroleum ether (b.p. 40-60°C) (PE) and EtOAc (EA) as eluents unless reported otherwise. Solvents were dried and freshly distilled by common practice. Usual work up refers to washing of the extract with brine, drying over anhydrous $MgSO_4$, filtration and evaporation of the solvent under reduced pressure. Reactions were monitored by GC or by TLC on Merck silica gel $60F_{254}$ plastic sheets plates. Compounds on TLC were visualized by UV detection and by spraying with basic $KMnO_4$ or with an acidic anisaldehyde solution or with a molybdate solution and subsequent heating.



(-)-(3*S*)-5-((1*R*,2*R*,4a*S*,8a*S*)-2-Hydroxy-2,5,5,8a-tetramethyldecahydro-1-naphthalenyl)-3-methylpentanoic acid (labdanolic acid (32)).

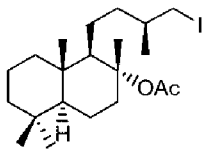
The air dried twigs and leaves of *Cistus ladaniferus L.* (300 g) were soaked with *n*-hexane (5 L) at room temperature for 3 days. The solution was separated from the solid material and the solvent was evaporated to give a sticky labdanum gum. The gum was stirred with ether and the etheral solution was washed with a 4 M aqueous NaOH solution. The aqueous basic solution was acidified with aqueous 4 M HCl solution, extracted with ether and dried. After evaporation of the solvent a crude acidic fraction (30 g) was obtained. A sample of the crude product was purified by column chromatography (eluent CH_2Cl_2/MeOH 9:1) to give pure labdanolic acid (**32**) as a sticky solid compound.

M.p. 80-82°C (lit.[60a]: 82-83°C); $[\alpha]_D$ -6.9 (*c* 0.9) (lit.[60a]: -7.2); IR (KBr) ν_{max} 3431, 2924, 1710 cm^{-1}; ^1H NMR ($CDCl_3/CD_3OD$) δ 0.62 (s, 3H), 0.69 (s, 3H), 0.77 (d, *J* = 5.0 Hz, 3H), 1.01 (s, 3H), 1.08 (s, 3H), 1.10-1.84 (m, 17H), 2.06 (m, 2H), 4.37 (br s, 2H); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 15.1 (q), 18.1 (t), 19.4 (q), 20.1 (t), 21.1 (q), 22.7 (t), 23.1 (q), 29.3 (t), 30.9 (d), 31.0 (s), 32.9 (q), 38.8 (s), 39.4 (t), 40.3 (t), 41.6 (t), 43.3 (t), 55.8 (d), 61.7 (d), 73.9 (s), 176.7 (s); HRMS: M^+, found 324.2661. $C_{20}H_{36}O_3$ requires 324.2664; MS *m/e* (%) 324 (M^+, 38), 312 (58), 235 (47), 177 (65), 171 (100), 148 (84), 123 (64), 109 (62), 69 (86); Anal.: found C, 73.50; H, 11.27%. $C_{20}H_{36}O_3$ requires C, 74.02; H, 11.18%.



(-)-(3*S*)-5-((1*R*,2*R*,4a*S*,8a*S*)-2-(Acetyloxy)-2,5,5,8a-tetramethyldecahydro-1-naphthalenyl)-3-methylpentanoic acid (140).

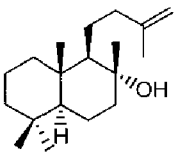
To a stirred solution of crude labdanolic acid (**32**) (10 g) in *N,N*-dimethylaniline (40 mL) was added acetyl chloride (15 mL; 16.56 g; 210.9 mmol) and the solution was left overnight. Dilute sulfuric acid was carefully added to the blue reaction mixture till the colour had disappeared. The mixture was extracted with ether and the ethereal solution was washed with aqueous 1 M sulfuric acid (150 mL), and worked up as usual. The residue was purified by flash column chromatography on silica gel (eluent PE/EA 7:1) to yield **140** (4.66 g; 12.73 mmol; 47%, based upon the crude acidic fraction) as a light yellow sticky gum. $[\alpha]_D$ -18.1 (*c* 1.8); IR (KBr) ν_{max} 3449, 2925, 2852, 1734, 1643, 1287 cm^{-1}; ^1H NMR δ 0.75 (s, 3H), 0.80 (s, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 1.20 (s, 3H), 1.90 (s, 3H), 0.65-2.38 (m, 20H), 2.62 (dt, *J* = 3.0, 12.4 Hz, 1H), 4.38 (br s, 2H); ^{13}C NMR δ 15.7 (q), 18.3 (t), 19.7 (q), 19.9 (t), 20.3 (q), 21.4 (q), 22.8 (q), 23.1 (t), 29.7 (t), 30.8 (d), 33.0 (s), 33.3 (q), 38.7 (t), 39.3 (s), 39.5 (t), 39.8 (t), 41.6 (t), 55.5 (d), 59.0 (d), 88.0 (s), 170.4 (s), 179.7 (s); HRMS: (M^+-60), found 306.2557. $C_{20}H_{34}O_2$ requires 306.2559; MS *m/e* (%) 366 (M^+, 1), 307 (29), 306 (100), 291 (66), 191 (98), 182 (65), 137 (40), 109 (42), 95 (33), 69 (36); Anal.: found C, 72.51; H, 10.49%. $C_{22}H_{38}O_4$ requires C, 72.09; H, 10.45%.



(1*R*,2*R*,4a*S*,8a*S*)-1-((3*S*)-4-Iodo-3-methylbutyl)-2,5,5,8a-tetramethyldeca-hydro-2-naphthalenyl acetate (331).

A solution of **140** (1.5 g; 4.10 mmol) in carbon tetrachloride (40 mL) containing iodobenzene diacetate (IBDA) (0.72 g; 2.25 mmol) and iodine (0.52 g; 2.05 mmol) was irradiated with a 100W tungsten filament lamp for 45 min at reflux temperature. Then another portion of IBDA (0.72 g; 2.25 mmol) and iodine (0.52 g; 2.05 mmol) was added, and the irradiation at reflux temperature was continued for 45 min. The reaction mixture was cooled to room temperature and was washed with aqueous 1 M sodium thiosulfate solution (100 mL), water and brine. Flash column chromatography of the residue (eluent PE/EA 9:1) on silica gel gave the iodo compound **331** (1.40 g; 3.12 mmol; 76%) as an oil contaminated with iodobenzene in a 1:1 molair ratio, determined *via* ^1H NMR.

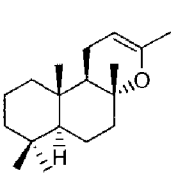
^1H NMR δ 0.76 (s, 3H), 0.81 (s, 3H), 0.85 (s, 3H), 0.97 (d, *J* = 6.4 Hz, 3H), 1.05-1.81 (m, 19H), 1.96 (s, 3H), 2.63 (dt, *J* = 2.7, 12.3 Hz, 1H), 3.18 (d, *J* = 5.2 Hz, 2H); ^{13}C NMR δ 15.7 (q), 17.8 (t), 18.4 (t), 20.0 (t), 20.4 (q), 20.8 (q), 21.5 (q), 23.2 (t), 23.3 (q), 29.7 (s), 33.1 (s), 33.4 (q), 35.7 (d), 38.8 (t), 39.4 (t), 39.6 (t), 41.9 (t), 55.6 (d), 58.9 (t), 87.8 (s), 170.3 (s); HRMS: M^+, found 448.1844. $C_{21}H_{37}IO_2$ requires 448.1838; MS *m/e* (%) 448 (M^+, 1), 389 (25), 388 (100), 373 (37), 264 (44), 191 (60), 137 (33), 95 (28), 69 (31), 43 (29).



(+)-(1*R*,2*R*,4a*S*,8a*S*)-2,5,5,8a-Tetramethyl-1-(3-methyl-3-butenyl)-decahydro-2-naphthalenol (332).

To a solution of **331** (1.61 g; 3.6 mmol) in THF (20 mL) under nitrogen was added *t*BuOK (2.02 g; 18 mmol). After stirring overnight at room temperature the mixture was quenched with an aqueous saturated solution of NH_4Cl, and worked up as usual. The residue was purified by flash column chromatography (eluent PE/EA 5:1) and **332** (0.74 g; 2.66 mmol; 74%) was obtained as a sticky solid compound.

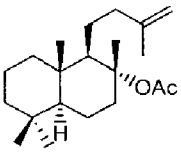
$[\alpha]_D$ +0.6 (*c* 1.6); IR (liquid film) ν_{max} 3420, 3072, 2927, 2868, 1457 cm^{-1}; ^1H NMR δ 0.76 (s, 3H), 0.78 (s, 3H), 0.84 (s, 3H), 1.11 (s, 3H), 1.71 (s, 3H), 0.87-2.36 (m, 17H), 4.67 (s, 2H); ^{13}C NMR δ 15.5 (q), 18.5 (t), 20.6 (t), 21.5 (q), 22.6 (q), 23.6 (t), 23.9 (q),, 33.3 (s), 33.4 (q), 39.2 (s), 39.7 (t), 41.3 (t), 42.0 (t), 44.6 (t), 56.1 (d), 61.5 (d), 74.1 (s), 109.7 (t), 147.1 (s); HRMS: M^+, found 278.2605. $C_{19}H_{34}O$ requires 278.2610; MS *m/e* (%) 278 (M^+, 6), 245 (36), 192 (100), 191 (71), 177 (75), 123 (39), 109 (45), 95 (50), 69 (58), 43 (32); Anal.: found C, 82.18; H, 12.62%. $C_{19}H_{34}O$ requires C, 81.95; H, 12.31%.



(+)-(4a*R*,6a*S*,10a*S*)-3,4a,7,7,10a-Pentamethyl-4a,5,6,6a,7,8,9,10,10a,10b-decahydro-1*H*-benzo[*f*]chromene (sclareol oxide (269)).

A stirred solution of **332** (0.30 g; 1.08 mmol) in a mixture of MeOH and CH_2Cl_2 1:5 (20 mL) was purged through with ozone at -78°C until a pale blue colour appeared. The excess ozone was expelled and PPh_3 (0.57 g; 2.17 mmol) was added at -78°C. The mixture was allowed to warm up to room temperature. After stirring overnight the mixture was evaporated. The residue was purified by flash column chromatography (eluent PE/EA 6:1) to yield sclareol oxide (**269**) (0.124 g; 0.47 mmol; 44%) as a light yellow oil.

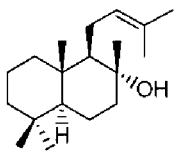
$[\alpha]_D$ +4.9 (*c* 1.3) (lit.[51a]: $[\alpha]_D$ +5.7, *c* 1.6); IR (liquid film) ν_{max} 3055, 2950, 2900, 2890, 1687, 1470, 1390, 1342, 1000 cm^{-1}; ^1H NMR δ 0.74 (s, 3H), 0.75 (s, 3H), 0.81 (s, 3H), 1.25 (s, 3H), 1.61 (s, 3H), 1.76-1.83 (m, 13H), 1.87 (dt, *J* = 4.3, 14.6 Hz, 1H), 4.30 (br s, 1H); ^{13}C NMR δ 19.3 (q), 18.2 (q), 18.6 (t), 19.8 (t), 20.7 (q), 21.0 (q), 26.6 (q), 28.6 (q), 33.1 (s), 36.7 (s), 39.3 (t), 41.1 (t), 41.9 (t), 52.4 (d), 55.2 (d), 76.2 (s), 94.6 (d), 147.8 (s); MS *m/e* (%) 262 (M^+, 100), 191 (81), 177 (39), 123 (46), 109 (97), 95 (64), 81 (72), 43 (78).



(-)-(1*R*,2*R*,4a*S*,8a*S*)-2,5,5,8a-Tetramethyl-1-(3-methyl-3-butenyl)-decahydro-2-naphthalenyl acetate (141).

To a stirred solution of **332** (0.53 g; 1.91 mmol) in *N,N*-dimethylaniline (30 mL) was added acetyl chloride (8 mL; 8.83 g; 112.5 mmol) and left overnight. An aqueous 1 M sulfuric acid solution was added carefully to the blue reaction mixture till the colour had dissapeared. The mixture was extracted with ether and worked up as usual. The residue was purified by flash column chromatography on silica gel (eluent PE/EA 10:1) to yield **141** (0.53 g; 1.58 mmol; 83%) as a white crystalline solid.

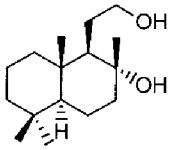
M.p. 64-66°C; $[\alpha]_D$ -23.1 (*c* 1.2); IR (KBr) ν_{max} 3431, 2926, 2852, 1728, 1253 cm^{-1}; ^1H NMR δ 0.76 (s, 3H), 0.81 (s, 3H), 0.84 (s, 3H), 1.91 (s, 3H), 1.05-2.03 (m, 21H), 2.61 (dt, *J* = 3.0, 12.4 Hz, 1H), 4.65 (s, 2H); ^{13}C NMR δ 15.7 (q), 18.3 (t), 20.4 (q), 21.4 (q), 22.5 (q), 22.9 (q), 24.5 (t), 29.7 (t), 33.1 (s), 33.3 (q), 38.7 (t), 39.3 (s), 39.4 (t), 41.1 (t), 41.9 (t), 55.6 (d), 58.6 (d), 88.0 (s), 109.3 (t), 146.9 (s), 170.1 (s); HRMS: M^+, found 320.2715. $C_{21}H_{36}O_2$ requires 320.2715; MS *m/e* (%) 320 (M^+, 4), 245 (30), 192 (100), 191 (57), 177 (55), 123 (31), 109 (32), 95 (33), 81 (34), 69 (36), 43 (33); Anal.: found C, 78.63; H, 11.45%. $C_{21}H_{36}O_2$ requires C, 78.69; H, 11.32%.



(+)-(1*R*,2*R*,4a*S*,8a*S*)-2,5,5,8a-Tetramethyl-1-(3-methyl-2-butenyl)-decahydro-2-naphthalenol (150).

Under an atmosphere of nitrogen iodide **331** (0.56 g; 1.24 mmol) was dissolved in DMSO (20 mL) and *t*BuOK (1.39 g; 12.4 mmol) was added. After stirring overnight at room temperature the mixture was quenched with saturated NH_4Cl and worked up as usual. The residue was purified by flash column chromatography (eluent PE/EA 5:1) and **150** (0.27 g; 0.97 mmol; 78%) was obtained as a yellow oil.

$[\alpha]_D$ +14.7 (*c* 1.6); IR (liquid film) ν_{max} 3446, 2924, 2867, 1457, 1387, 1083 cm^{-1}; ^1H NMR δ 0.72 (s, 3H), 0.75 (s, 3H), 0.80 (s, 3H), 1.12 (s, 3H), 1.60 (s, 6H), 0.83-2.26 (m, 15H), 5.18 (t, *J* = 4.5 Hz, 1H); ^{13}C NMR δ 15.4 (q), 17.9 (q), 18.6 (t), 20.2 (t), 21.6 (q), 23.7 (t), 24.7 (q), 25.9 (q), 33.3 (s), 33.5 (q), 38.7 (s), 40.0 (t), 41.9 (t), 56.1 (d), 61.6 (d), 74.3 (s), 127.2 (d), 130.8 (s); HRMS: (M^+-18), found 260.2500. $C_{19}H_{32}$ requires 260.2504; HRMS: (M^+-15), found 263.2377. $C_{18}H_{31}O$ requires 263.2374; MS *m/e* (%) 278 (M^+, 1), 263 (2), 260 (13), 178 (11), 136 (9), 122 (100), 109 (11), 107 (19), 95 (10), 69 (19), 43 (9).

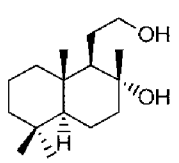


(-)-(1*R*,2*R*,4a*S*,8a*S*)-1-(2-Hydroxyethyl)-2,5,5,8a-tetramethyldecahydro-2-naphthalenol (153).

A solution of sclareol oxide (**269**) (0.124 g; 0.47 mmol) in CH_2Cl_2 (35 mL) and pyridine (0.35 mL) was ozonolyzed at -78°C. The excess of ozone was expelled and the mixture was allowed to come to room temperature. The mixture was acidified with an aqueous 1 M hydrochloric acid solution and worked up as usual. The residue was dissolved in THF (20 mL), cooled to 0°C and $LiAlH_4$ (137 mg; 3.60 mmol) was added in portions. After stirring overnight at room temperature the mixture was carefully acidified with 1 M HCl. The aqueous layer was extracted three times with ethyl acetate and worked up as usual. The crude oil was purified by flash column chromatography (eluent PE/EA 1:1) to give **153** (72 mg; 0.28 mmol; 60%) as a white crystalline solid.

M.p. 128-130°C; $[\alpha]_D$ -13.8 (*c* 1.1); IR (KBr) ν_{max} 3410, 2926, 2894, 1458, 1243, 1051 cm^{-1}; ^1H NMR δ 0.80 (s, 6H), 0.89 (s, 3H), 1.16 (s, 3H), 0.92-1.70 (m, 13H), 1.92 (dt, *J* = 4.5, 11.9 Hz, 1H), 2.67 (br s, 2H), 3.48 (dt, *J* = 6.5, 10.0 Hz, 1H), 3.81 (dt, *J* = 4.3, 10.0 Hz, 1H); ^{13}C NMR δ 15.3 (q), 18.4 (t), 20.5 (t), 21.5 (q), 24.7 (q), 27.9 (t), 33.3 (s), 33.4 (q), 39.0 (s), 39.3 (t), 41.9 (t), 44.3 (t),

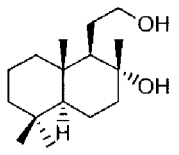
56.0 (d), 59.1 (d), 64.2 (t), 73.2 (s); HRMS: M^+, found 254.2249. $C_{16}H_{30}O_2$ requires 254.2250; MS *m/e* (%) 254 (M^+, 9), 221 (73), 195 (100), 177 (64), 151 (65), 109 (81), 95 (76), 69 (87), 43 (48); Anal.: found C, 75.98; H, 12.27%. $C_{16}H_{30}O_2$ requires C, 75.53; H, 11.89%.



(-)-(1*R*,2*R*,4a*S*,8a*S*)-1-(2-Hydroxyethyl)-2,5,5,8a-tetramethyldecahydro-2-naphthalenol (153).

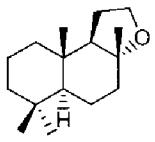
A stirred solution of **141** (0.25 g; 0.78 mmol) in a mixture of MeOH and CH_2Cl_2 1:5 (20 mL) was purged through with ozone at -78°C until a pale blue colour appeared and the solution was purged with nitrogen to remove the excess of ozone. This mixture was treated with acetic anhydride (1.16 mL; 10.5 mmol), triethylamine (0.53 mL; 7.16 mmol) and 4-*N,N*-dimethylaminopyridine (DMAP) (25 mg; 0.20 mmol). The reaction mixture was allowed to come to room temperature and stirred overnight. The solution was poured into an aqueous 1 M HCl solution and extracted with ethyl acetate and worked up as usual.

The residue was dissolved in THF (10 mL), and cooled to 0°C and $LiAlH_4$ (84 mg; 2.22 mmol) was added. After stirring for 1 h at room temperature the mixture was carefully diluted with ethyl acetate, and treated with aqueous 1 M HCl solution. The aqueous layer was extracted with ethyl acetate and worked up as usual. The crude oil was purified by flash column chromatography (PE/EA 1:1) to give **153** (0.17 g; 0.65 mmol; 89%) as a white crystalline solid. For analytical data see foregoing experiment.



(-)-(1*R*,2*R*,4a*S*,8a*S*)-1-(2-Hydroxyethyl)-2,5,5,8a-tetramethyldecahydro-2-naphthalenol (153).

A solution of **150** (0.2 g; 0.72 mmol) in a mixture of MeOH and CH_2Cl_2 3:1 (30 mL) was ozonized at -78°C. The excess of ozone was expelled and $NaBH_4$ (0.22 g; 5.79 mmol) was added at -78°C. The mixture was alllowed to warm to room temperature. The excess of $NaBH_4$ was destroyed with an 1 M aqueous HCl solution and diluted with water. The mixture was extracted with ethyl acetate and worked up as usual. The residue was purified by flash column chromatography (eluent PE/EA 2:1) to yield **153** (0.17 g; 0.66 mmol; 92%) as a white crystalline solid. The analytical data were as mentioned before.



(-)-(3a*R*,5a*S*,9a*S*,9b*R*)-3a,6,6,9a-Tetramethyldodecahydronaphtho[2,1-*b*]furan ((-)-Ambrox® (103)).

A mixture of **153** (0.10 g; 0.39 mmol) and *p*-toluenesulfonic acid (0.04 g; 0.19 mmol) in nitromethane (7 mL) was stirred at room temperature for 3 h. Ether was added and the mixture was washed with a saturated aqueous sodium bicarbonate solution and brine, dried and evaporated. Flash column chromatography (eluent PE/EA 6:1) gave Ambrox® (**103**) (0.08 g; 0.34 mmol; 87%) as white crystals.

M.p. 74-75°C (lit.[69]: 74-76°C); $[\alpha]_D$ -23.8 (*c* 1.3) (lit.[69]: -22.1, *c* 0.7); IR (KBr) ν_{max} 3441, 2922, 2884, 1130, 1120, 1005 cm^{-1}; ^1H NMR δ 0.82 (s, 6H), 0.86 (s, 3H), 1.07 (s, 3H), 0.92-1.92 (m, 14H), 3.85 (m, 2H); ^{13}C NMR δ 15.1 (q), 18.4 (t), 20.7 (t), 21.2 (q), 21.3 (q), 22.6 (t), 33.1 (s), 33.6 (q), 36.2 (s), 39.7 (t), 40.0 (t), 42.4 (t), 57.3 (d), 60.1 (d), 65.0 (t), 79.9 (s); HRMS: M^+, found 236.2143. $C_{16}H_{28}O$ requires 236.2140; MS *m/e* (%) 236 (M^+, 3), 221 (100), 137 (15), 97 (10), 95 (4), 81 (4), 69 (5), 55 (4), 43 (4); Anal.: found C, 81.10; H, 11.95%. $C_{16}H_{28}O$ requires C, 81.29; H, 11.94%.

2.6 References and notes

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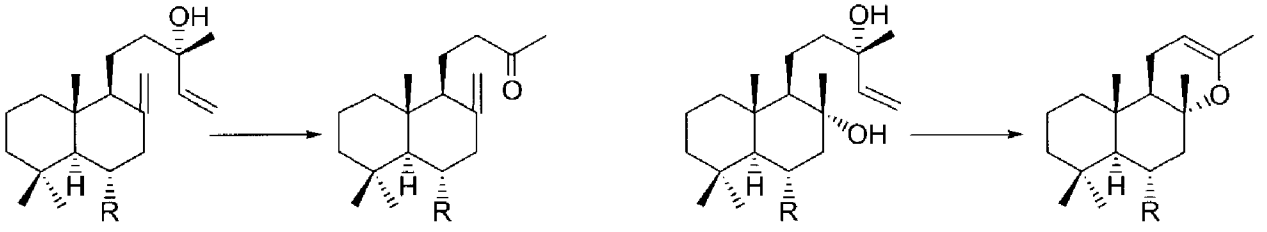
Chapter 3

Oxidation of larixol and sclareol-like labdanes

Abstract

*Larixol (**30**) is easily available from the oleoresin of Larix decidua Miller. Its isolation, structure determination and chemistry is set out in the first paragraphs. Oxidation of the C(9) side chain of larixol (**30**) may provide suitable synthons for the synthesis of Ambrox-like compounds. For this purpose the side chain of larixol (**30**) has to be shortened to a two-carbon moiety using oxidative procedures. The oxidation of the (3-hydroxy-3-methyl-4-pentenyl)-side chain at C(9) of some labdanic diterpenoids with potassium permanganate is investigated. The functional group at C(8) strongly influences the course of the reaction. Triols, ketones, or cyclic enol ethers are obtained as the main products.*

*Next to Ambrox® also the Ambraketals have intense amber odours and larixol has good potentials as starting material for the preparation of these compounds. From the standardized oxidation of larixol with potassium permanganate C(6) hydroxylated Ambraketals were already found as minor products. Starting from larixol good reaction sequences are developed for the synthesis of epi-hydroxy Ambraketal **401** and hydroxy Ambraketal **343**, which allow the preparation of several simple derivatives of these ketals.*



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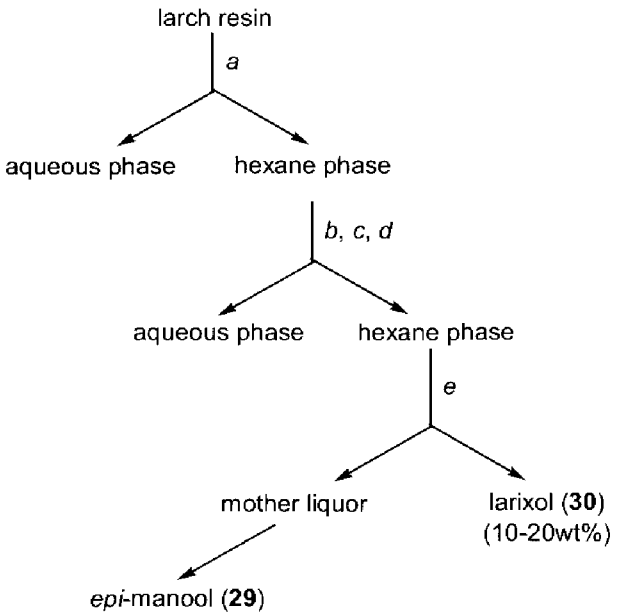
3.1 Isolation and structure determination of larixol

The genus *Larix* (or larches (Pinaceae)) comprises seven Eurasian and three North American species, three interspecies hybrids, and one entity. Like other genera of the Pinaceae the larches yield an oleoresin in which the diterpene composition varies in the different species.[1,2] Common to all are *epi*-manool (**29**), but larixol (**30**) and its acetate (**31**) are confined to *L. decidua* and *L. gemelini*. The contents of larixyl acetate (**29**) in the oleoresin of *L. decidua* Miller (*L. europae*), formerly available commercially under the name of Venice turpentine, is above 30% of the diterpene fraction. In 1947 larixol (**30**) was isolated after a troublesome procedure for the first time from *Larix europae*.[3] Nowadays an improved isolation procedure of larixol (**30**) from the resin is available (Scheme 3.1). To facilitate the isolation it is recommendable to hydrolyse larixyl acetate (**31**) first, because larixol (**30**) crystallizes easier.

Scheme 3.1

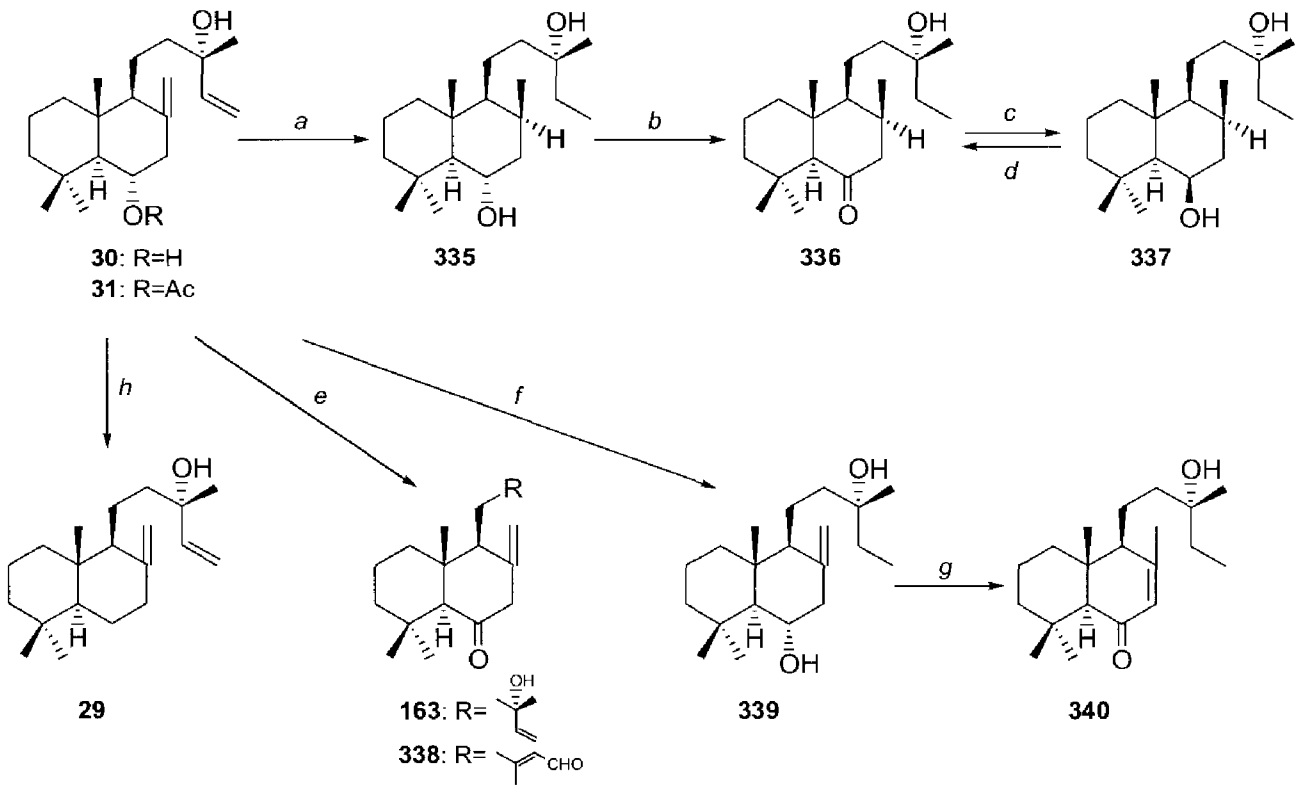


Reagents and conditions: (*a*) *i*) extraction (Et_2O); *ii*) 1N NaOH, *n*-hexane or Et_2O; *iii*) filtration; (*b*) evaporation; (*c*) saponification (4M aq, KOH, EtOH, 60°C, 12 h); (*d*) *i*) concentration; *ii*) extraction (*n*-hexane or Et_2O); (*e*) crystallization.

The structure of larixol was elucidated by chemical means and lateron confirmed by NMR spectroscopy.[4-7] The configuration at C(6) was confirmed by the following chemical experiments. Hydrogenation of larixol (**30**) using a platinum catalyst yielded tetrahydrolarixol **335**. A mild chromic acid oxidation of **335** gave ketone **336**, which upon reduction with lithium aluminium hydride gave an alcohol again, which proved to be the C(6)-epimer **337** of tetrahydrolarixol **335**. Jones oxidation of larixol (**30**) under standardized conditions furnished mainly two products, ketoalcohol **161** as the minor product and the α,β-unsaturated aldehyde **338** as the main product. Hydrogenation of larixol (**30**) using a Raney-nickel catalyst furnished 14,15-dihydrolarixol **339**. Jones oxidation of **339**

yielded α,β-unsaturated hydroxy-ketone **340**. The molecular formula gave rise to two hydroxy groups of which one was a tertiary and the other a secondary one, as can be concluded from the transformations depicted in Scheme 3.2. Since 13-*epi*-manool (**29**) has been found to be one of the main constituents of the oleoresin of *L. europaea* as well, it was assumed that larixol (**30**) has the same configuration at C(13). This could be confirmed by conversion of larixol into 13-*epi*-manool through reduction of the C(6) hydroxyl group *via* its tosylate.

Scheme 3.2



Reagents and conditions: (*a*) H_2/Pt; (*b*) CrO_3; (*c*) $LiAlH_4$; (*d*) CrO_3; (*e*) *R=H:* CrO_3; (*f*) *R=H:* H_2/Ni; (*g*) CrO_3; (*h*) *R=H: i*) *p*-TsCl; *ii*) $LiAlH_4$.

The secondary hydroxyl group at C(6) was investigated by ^{1}H NMR as well. The signal of the 6β-proton in the ^{1}H NMR spectrum showed a triplet of doublets (J = 11 Hz, J' = 5 Hz), which led unambigously to assignment in the β-position, being the only one with this multiplicity.

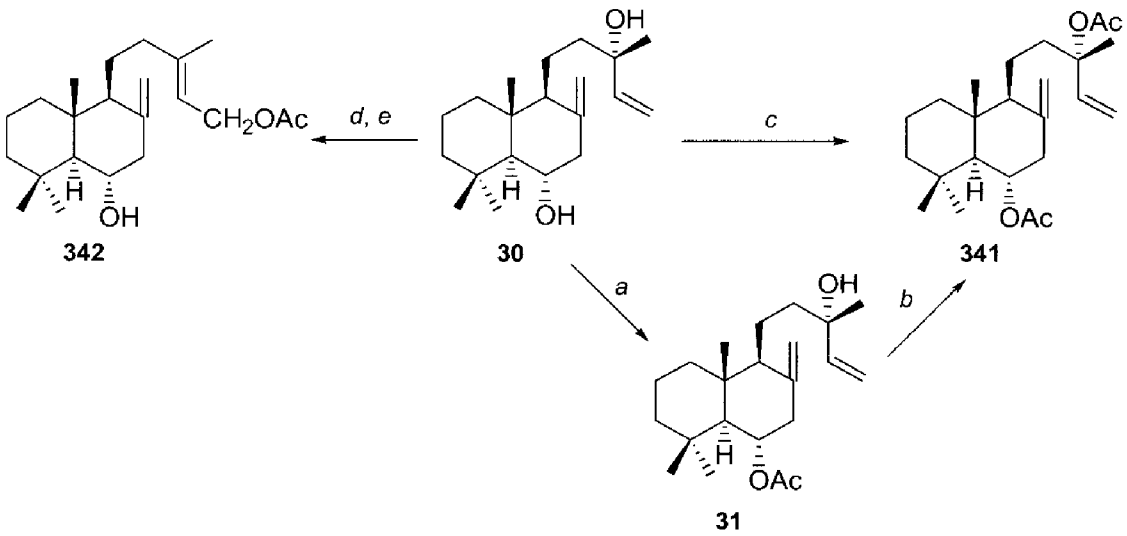
3.2 The chemistry of larixol

3.2.1 Acetylation reactions

The acetylation of larixol (**30**) gives two corresponding acetates (Scheme 3.3).[4-9] Larixyl acetate (**31**) is the monoacetate of larixol in which the secondary hydroxyl group is acetylated. On treatment with acetic anhydride in pyridine or with equimolar amounts of acetyl chloride in pyridine

or *N,N*-dimethylaniline, larixol gave larixyl acetate in good yields. The corresponding diacetate (**341**) could be prepared from larixol or from larixyl acetate using acetyl chloride and *N,N*-dimethylaniline. Depending on the reaction conditions used, it is possible to acetylate only the OH-group on C(6) or the OH-groups on both C(6) and C(13). By action of phosphorus tribromide in the presence of pyridine,[4] followed by potassium acetate at reflux, larixol (**30**) rearranges to acetate **342** in a yield of about 35%.

Scheme 3.3

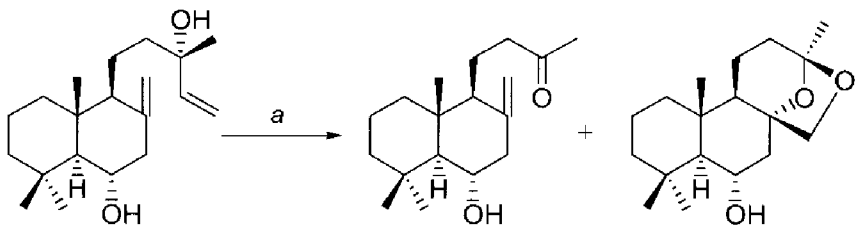


Reagents and conditions: (*a*) *i*) Ac_2O, py, 65%; *ii*) AcCl, *N,N*-dimethylaniline or py, 65-95%; (*b*) AcCl, *N,N*-dimethylaniline, 90-95%; (*c*) AcCl, *N,N*-dimethylaniline, 76%; (*d*) PBr_3 , py; (*e*) AcOH, KOAc, 35%.

3.2.2 Chemical oxydations of larixol and larixyl acetate.

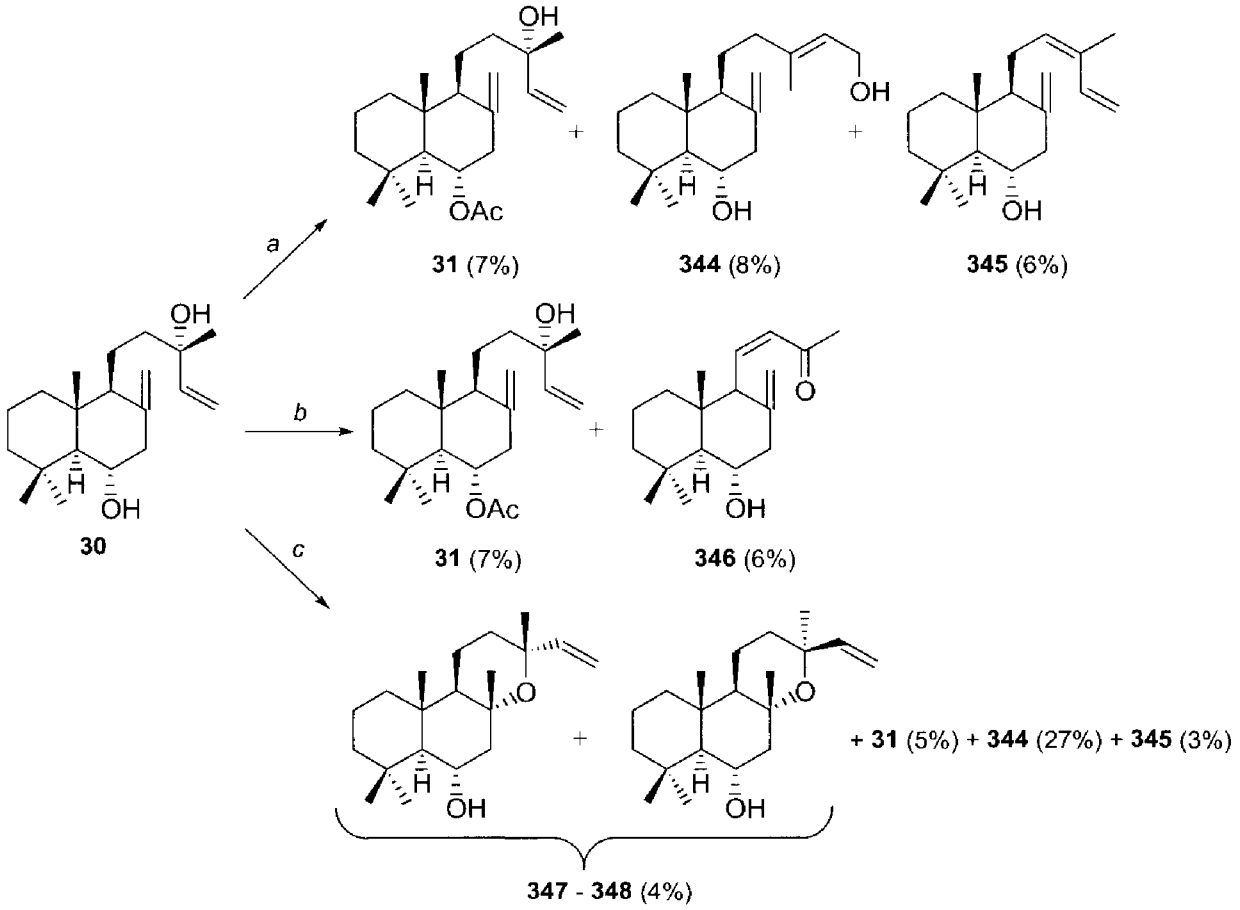
Larixol (**30**) and larixyl acetate (**31**) have been oxidized with all traditional oxidants like O_2,[10] I_2/KI,[5,11] $KMnO_4$,[5,12] CrO_3,[13,14] $Na_2Cr_2O_7$[15] and $K_2Cr_2O_7$[11] under various conditions, but seldom a clean reaction to one major oxidation product has been observed. Mostly mixtures of all kinds of oxidation products were obtained as is indicated in Schemes 3.4 - 3.6.

Scheme 3.4



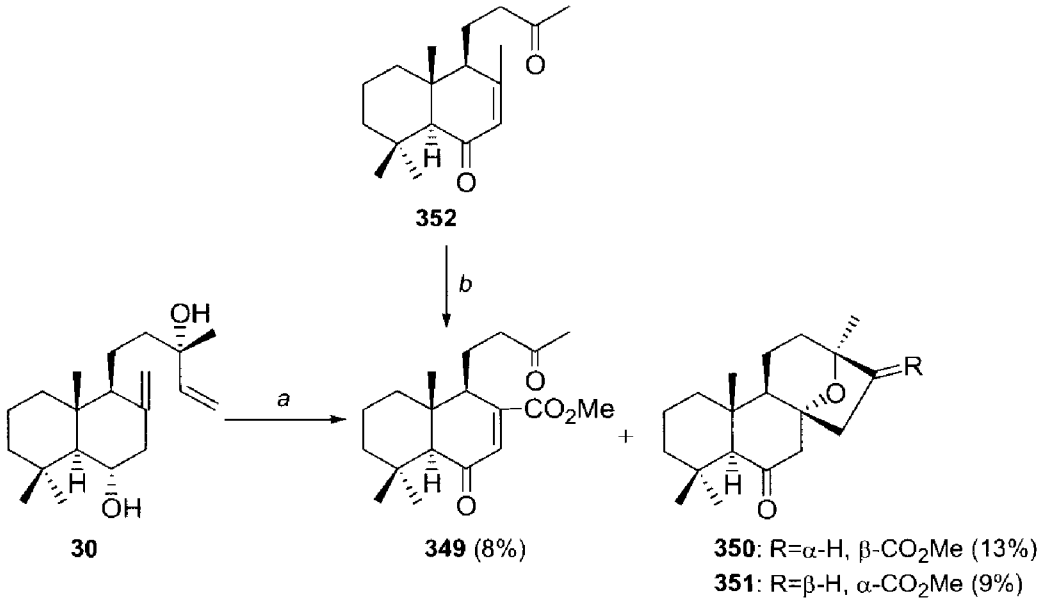
Reagents and conditions: (*a*) $KMnO_4$.

Scheme 3.5



Reagents and conditions: (*a*) O_2, HPA-3, 0.1M H_2SO_4, 80% AcOH, 25°C; (*b*) O_2, HPA-3, 80°C; (*c*) O_2, HPA-3, P = 8.3 atm.

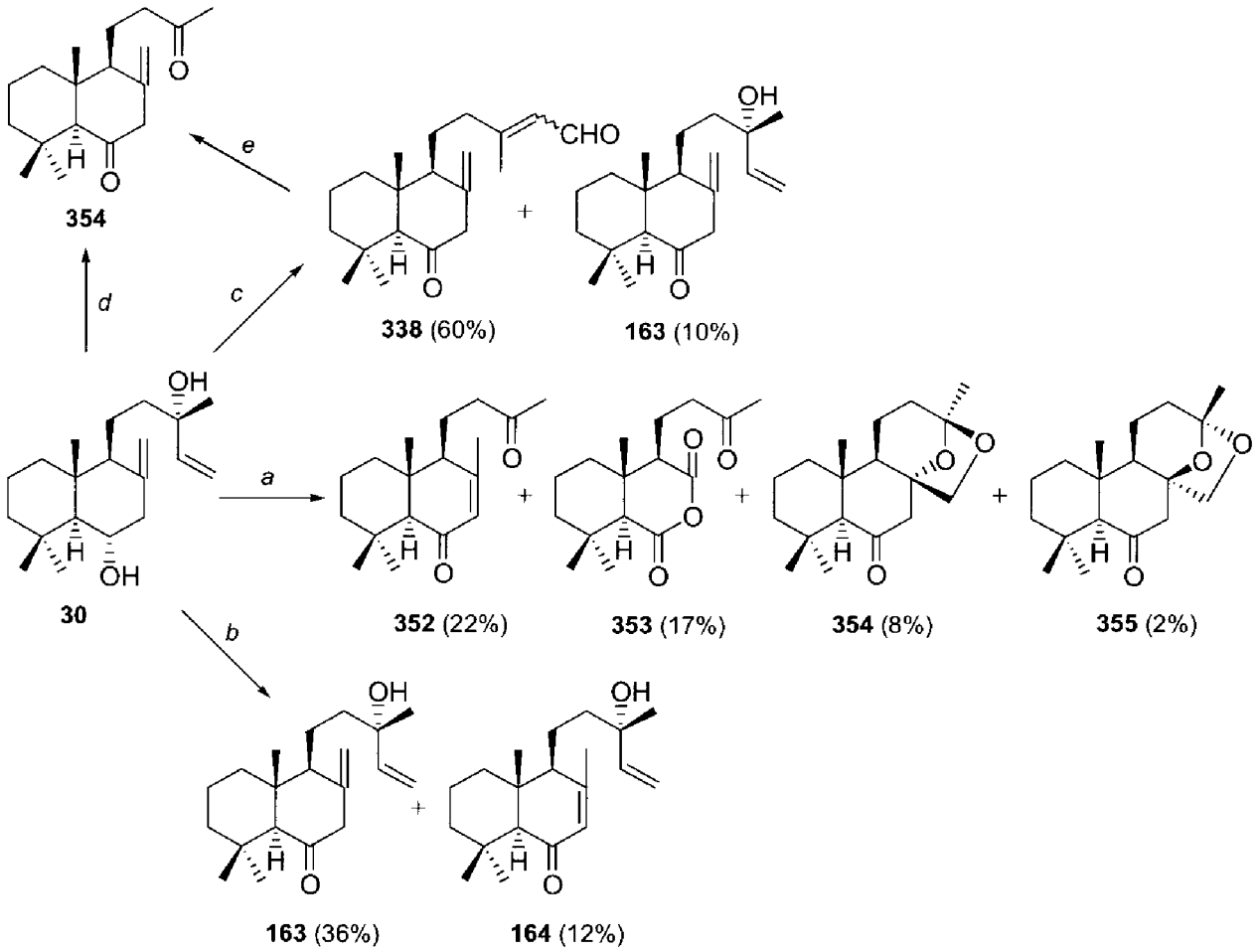
Scheme 3.6



Reagents and conditions: (*a*) $Na_2Cr_2O_7$, H_2SO_4, AcOH; (*b*) $Na_2Cr_2O_7$, H_2SO_4, CH_2N_2.

Diketone **354** can be obtained in a reasonable 50% yield *via* direct oxydation of larixol (**30**) using chromium trioxide in acetic acid, as depicted in Scheme 3.7.

Scheme 3.7

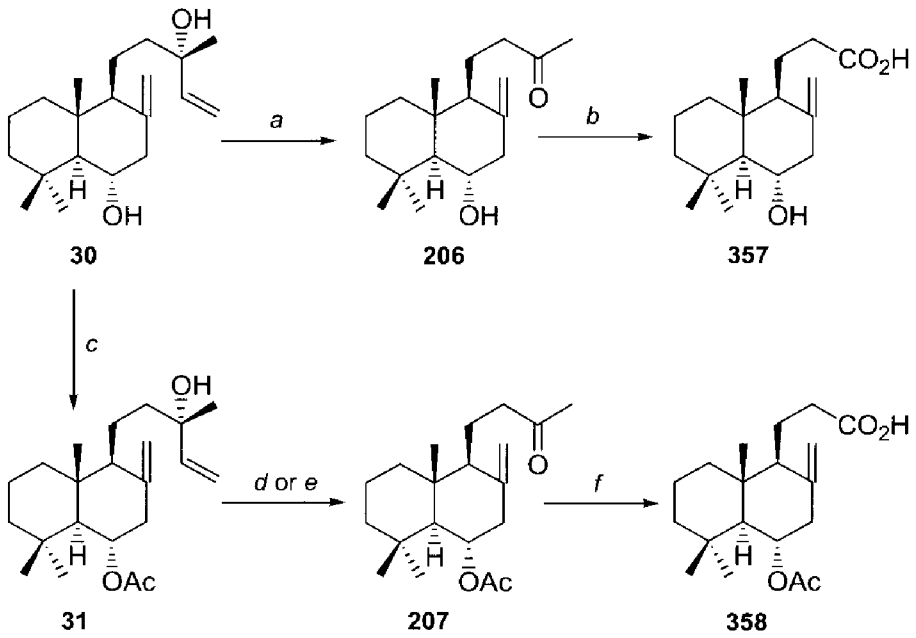


Reagents and conditions: (*a*) $Na_2Cr_2O_7$, H_2SO_4, AcOH, 49%; (*b*) H_2CrO_4, Al_2O_3, acetone, 48%; (*c*) $K_2Cr_2O_7$, 70%; (*d*) CrO_3, AcOH, 50%; (*e*) CrO_3, AcOH, 30%.

Oxidation of larixol (**30**) with potassium permanganate gave a mixture of products, from which methylketone **206** could be isolated in 17% yield (Scheme 3.8). Further degradation of the side chain by treatment of I_2/KI gave the corresponding acid **357**.[5] The oxidation of larixyl acetate (**31**) with chromic trioxide in acetic acid gave ketone **207** in a fair 60% yield. The iodoform reaction had been performed also on this acetylated methylketone **207**, which gives the carboxylic acid **358**.[11]

Ozonization of larixol (**30**) under various conditions led to the formation of many compounds **359-362** in rather low yields (Scheme 3.9). The C(13)-C(14) single bond is cleaved together with the double bond and the keto-group arising at C(8) interacts with the hydroxy-group at C(13) and with the functional group formed at C(14), which explains this multiple product formation.

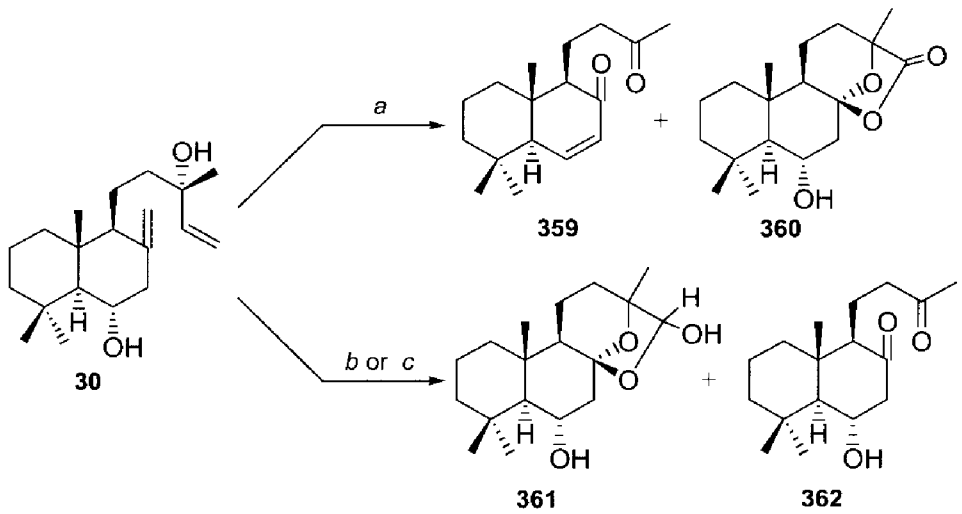
Scheme 3.8



Reagents and conditions: (*a*) $KMnO_4$, 17%; (*b*) I_2, KI, 55%; (*c*) Ac_2O, 65%; (*d*) CrO_3, AcOH, 60%; (*e*) $KMnO_4$, 30%; (*f*) I_2, KI, 75%.

Ozonolysis of larixol (**30**) in methanol at -70°C followed by addition of ammonium chloride[16-19] gave dione **359** and acetal **30**. When the ozonolysis of larixol is performed between -55 and -60°C in a mixture of CH_2Cl_2 and pyridine or in methanol followed by reduction with dimethylsulfide[16-18] the major products were acetal **361** and hydroxydione **362**.

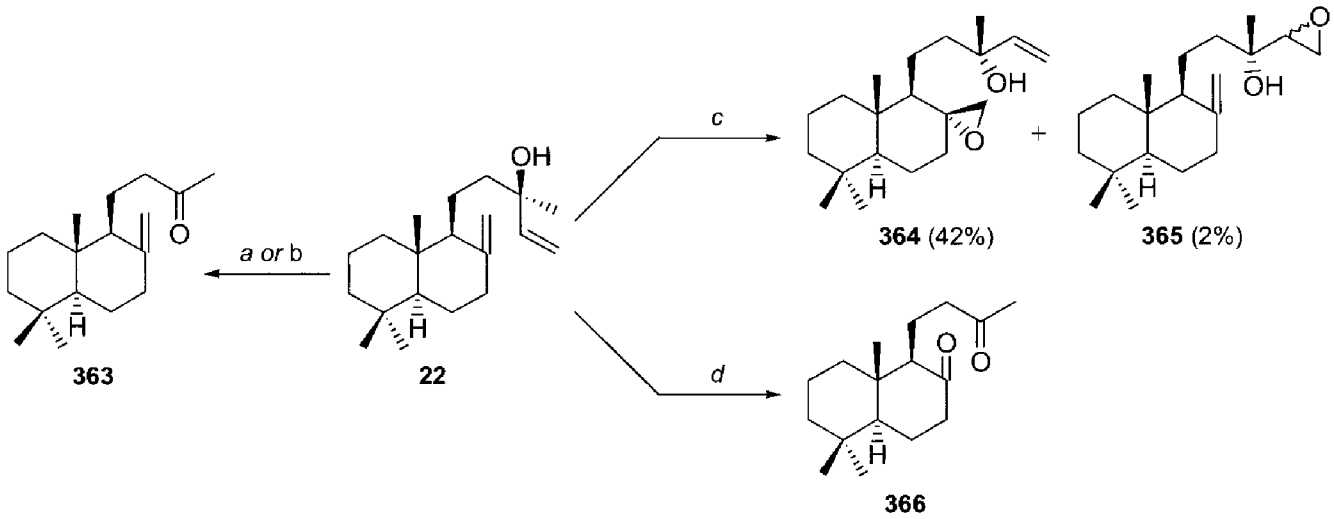
Scheme 3.9



Reagents and conditions: (*a*) *i*) O_3, MeOH, -70°C; *ii*) NH_4Cl, 20%; (*b*) *i*) O_3, MeOH, -55°C; *ii*) Me_2S; (*c*) *i*) O_3, py, CH_2Cl_2, -55°C, *ii*) Me_2S.

Several oxydations of the sclareol side chain have been mentioned in the previous chapter for the synthesis of Ambrox®. Potassium permanganate, chromic trioxide, ruthenium tetroxide, osmium tetroxide and microbial oxydation of sclareol (**4**) were described. The course of the oxydations is in sclareol (**4**) mostly determined by the presence and participation of the C(8) hydroxyl group. In this respect, manool (**22**) is a better compound for comparison with larixol (**30**) since both contain a $\Delta^{8,17}$ double bond (Scheme 3.10). Treatment of manool (**22**) with potassium permanganate gives methyl ketone **363** in low yield.[20,21] The same oxidation in the presence of a phase-transfer catalyst gave a much higher yield in comparison with the previous method.[22] After reaction of *m*-chloroperbenzoic acid in dichlormethane with manool (**22**), the epoxide **364** was synthesized, along with a small quantity of **365**.[23] Ozonization of manool (**22**) in chloroform led to diketone **366** in rather low yield.[24]

Scheme 3.10

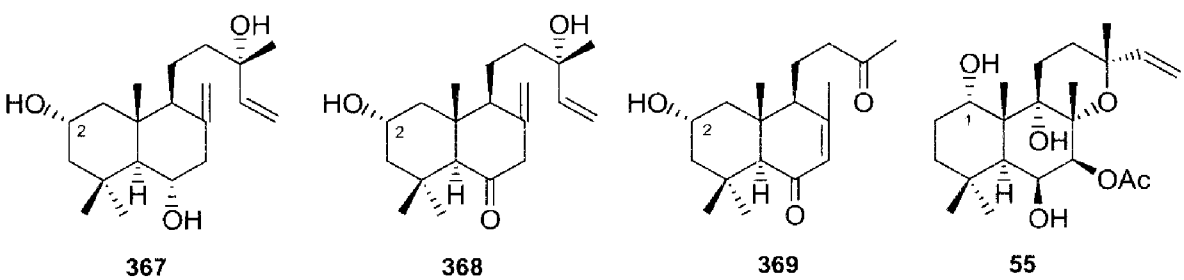


Reagents and conditions: (*a*) $KMnO_4$, acetone, 2-4°C, 28%; (*b*) $KMnO_4$, $C_6H_5CH_2N^+(CH_2CH_3)_3Cl^-$, $CHCl_3$, 93%; or in H_2O/C_6H_6, 82%; (*c*) *m*-CPBA, CH_2Cl_2, 44%; (*d*) O_3, $CHCl_3$, 0°C.

3.2.3 *Enzymatic oxydations*

The unfunctionalized A-ring of larixol is a drawback, especially in syntheses of natural products with a functionalized A-ring.

Figure 3.1



This problem may be circumvented using microbial hydroxylation (*Mucor plumbeus* LCM) of larixol (**30**) and derivatives. This leads to the 2α-hydroxylated compounds **367** (60%), **368** (37%), and **369** (35%), which can be used for the hemisynthesis of forskolin (**55**) type compounds (Figure 3.1).[25,26]

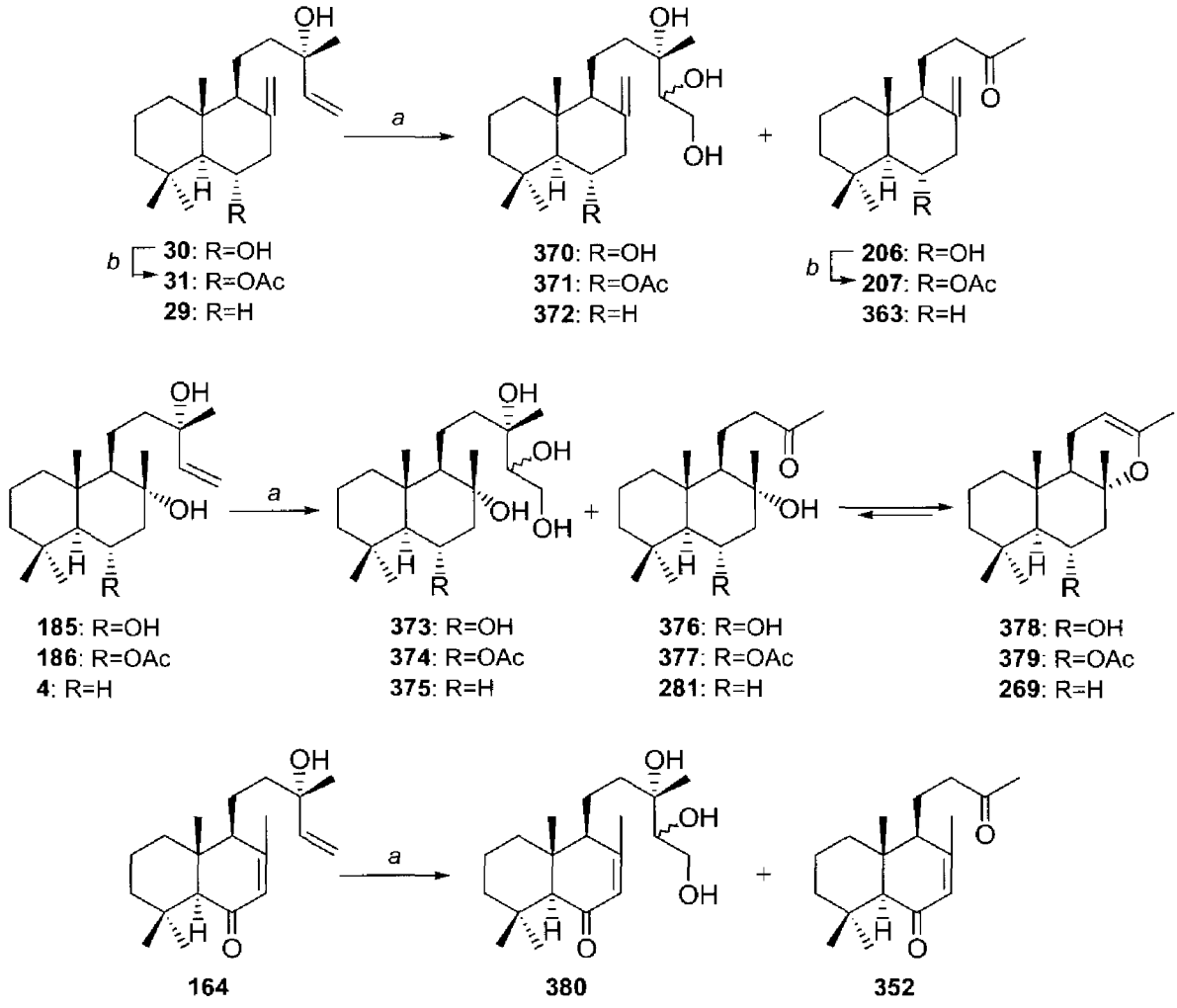
3.3 The Oxidation of Labdanes with Potassium Permanganate

Oxidation of the C(9) side chain of larixol (**30**) or larixyl acetate (**31**) may provide suitable synthons for the synthesis of Ambrox-like compounds. For this purpose the side chain of larixol (**30**)[27] has to be shortened to a two-carbon moiety using oxidative procedures. Several studies to oxidize this side chain have been reported in the former paragraphs but many use expensive, environmentally suspect oxidants, are irreproducable, or give rise to experimental difficulties during work-up (see 3.2.2). Also some special oxidation procedures, which have been developed for sclareol (**4**),[18,28-31] do not proceed in the same way for larixol (**30**) due to differences in the functional groups at C(8). The C(8) hydroxyl group of sclareol (**4**) participates in reaction intermediates of the oxidation, while such participation is not possible in larixol (**30**), its acetate (**31**) and in 13-*epi*-manool (**29**). Furthermore the presence of an exocyclic double bond at C(8) in the latter three compounds may cause selectivity problems, and this may be also the case with the hydroxyl group at C(6) in **30** and **185**.

So there is still a need for a general selective good yield procedure for the degradation of the labdane side chain and for this purpose a modification of the method of Ogino[32] *et al.* using solid potassium permanganate[33] in the presence of a phase-transfer catalyst was investigated for the oxidation of the labdanes **29**-**31**, **185**, **186**, **4**, and **164** aiming at an optimum yield for methyl ketones (Scheme 3.11).

As described before larixol (**30**), larixyl acetate (**31**),[34] and *epi*-manool (**29**)[35,36] can be obtained from the oleoresin of larch turpentine. Compound **185** was obtained from larixol (**30**) in 64% overall yield after epoxidation of the exocyclic double bond with oxone and reduction of the epoxide using lithium aluminum hydride ($LiAlH_4$) and its structure was fully determined.[37] The corresponding acetate 184 was obtained after treatment of compound **185** with acetic anhydride in pyridine. Compound **164**[25] was synthesized from larixol (**30**) in 73% overall yield by oxidation of the C(6)-hydroxyl group with pyridinium chlorochromate (PCC) to the C(6)-ketone, which was transformed into the conjugated ketone **164** *via* base catalyzed isomerization of the exocyclic 8(17) double bond using methanolic sodium methoxide. The same C(6)-ketone can also be obtained by Swern oxidation of larixol (**30**), followed by isomerization.

Scheme 3.11



Reagents and conditions: (*a*) $KMnO_4$, for details see Table 1; (*b*) Ac_2O, CH_2Cl_2, py, DMAP, 91%.

The oxidation of compounds **29-31**, **185**, **186**, **4**,[38] and **164** was investigated using two standardized methods with 1.5 or 3.0 equivalents of potassium permanganate and benzyltriethylammonium chloride respectively, at 0°C, and the results are summarized in Table 1. In all cases mixtures of triols and methyl ketones were obtained (Scheme 3.11), but it became clear that generally good yields of the desired methyl ketones could be obtained when 3.0 equivalents of potassium permanganate were used. The ratio between the two products was slightly pH dependent with alkaline conditions giving higher yields of the triols.[39,40] Longer reaction times, higher temperature or more equivalents of oxidant gave no improvement of the yield of methyl ketones and in the labdanes **29-31** products rising from oxidation of the exocyclic methylene group were found.[5,6] For substrate **164** the use of 3 equivalents of potassium permanganate did not show a significant difference in product ratio, but when this reaction was carried out at *room temperature*, the methyl ketone **352** is obtained as main product in 68% isolated yield.

The influence of the substituent on C(8) is also clear. When an exocyclic double bond is present at C(8) a reasonable selective oxidation of the double bond in the side chain can be

achieved to give the methyl ketones **206**, **207**, **363** in good yields. When a hydroxyl group is present at C(8), this group has a strong tendency to react with the methyl ketone in the side chain, and the cyclic enol ethers **378**, **379**, **269** are isolated as the main products in high yield. A further breakdown in a *separate* reaction with another 3.0 equivalents of $KMnO_4$ could not be achieved. Decomposition of these enol ethers was observed during longer chromatographic procedures or upon standing, so in preparative procedures it is advisable to use them immediately for further transformations without purification. Sonication[41] accelerated the oxidation appreciably, *i.e.* a shortening of the reaction time from 14 h to 2 h. However, the yield and product composition was not affected. Presumably, sonication promotes the decomposition of the cyclic manganate ester which is responsible for the formation of the products.[42] The *periodate-permanganate* system for the oxidation of olefinic double bonds[43,44] was also investigated but it did not improve the yields of the methyl ketones.

Table 3.1. Potassium permanganate oxidation of labdanes using 1.5 and 3.0 equivalents, respectively, at 0°C.

substrate	oxidation with 1.5 eq. $KMnO_4$			oxidation with 3.0 eq. $KMnO_4$		
	products			products		
	triol (%)[a]	methyl ketone (%)[a]	enol ether (%)[a]	triol (%)[a]	methyl ketone (%)[a]	enol ether (%)[a]
30	**370** (38)	**206** (45)		**370** (-)[b]	**206** (68)	
31	**371** (26)	**207** (48)		**371** (-)[b]	**207** (72)	
29	**372** (24)	**363** (48)		**372** (-)[b]	**363** (67)	
185	**373** (-)[b]	**376** (-)[b]	**378** (47)	**373** (-)[b]	**376** (-)[b]	**378** (74)
186	**374** (-)[b]	**377** (-)[b]	**379** (48)	**374** (-)[b]	**377** (-)[b]	**379** (90)
4[38]	**375** (25)	**281** (6)	**269** (51)	**375** (-)[b]	**281** (-)[b]	**269** (86)
164	**380** (56)	**352** (8)		**380** (56)	**352** (11)	

[a] isolated pure yields.

[b] not isolated, maximum yield <5%.

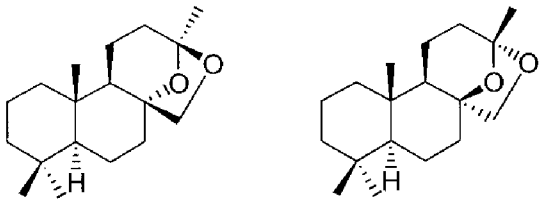
3.4 Ambraketals

3.4.1 Introduction

Next to Ambrox® (**103**), another product that has been found to possess an intense amber odour is Ambraketal (**381**) (also called Amberketal or Jeger's ketal). The diastereomeric intramolecular C(8) acetals **381** and **382**, the two cyclic ketals which occurs in small amounts in the bark of the western white pine (*Pinus montcola*).[45] have frequently been the subject of olfactory

investigation (Figure 3.2). Its structure originates from a reaction between the oxidized side chain with the oxidized exocyclic alkene.[46] These products were also found in the standardized oxidation of larixol (**30**) with potassium permanganate as minor byproducts.

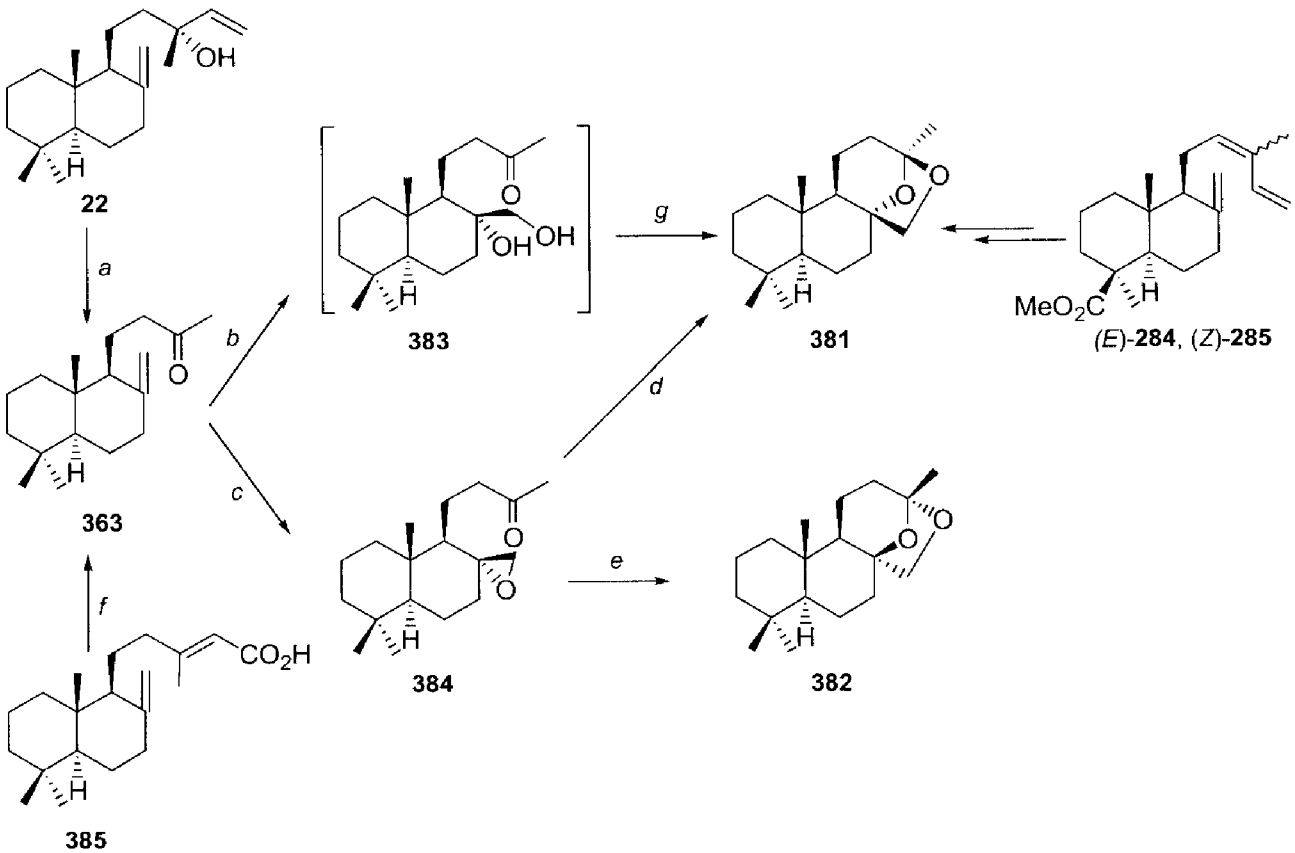
Figure 3.2



381 **382**

The Ambraketals are most readily obtained by degradation of manool (**22**)[47,48] which is a commercialized constituent of *Halocarpus biformis* (Podocarpaceae) from New Zealand,[39] or from the tree *Dacrydium biforme*, which is a relatively rare and protected species found only in New Zealand.

Scheme 3.12

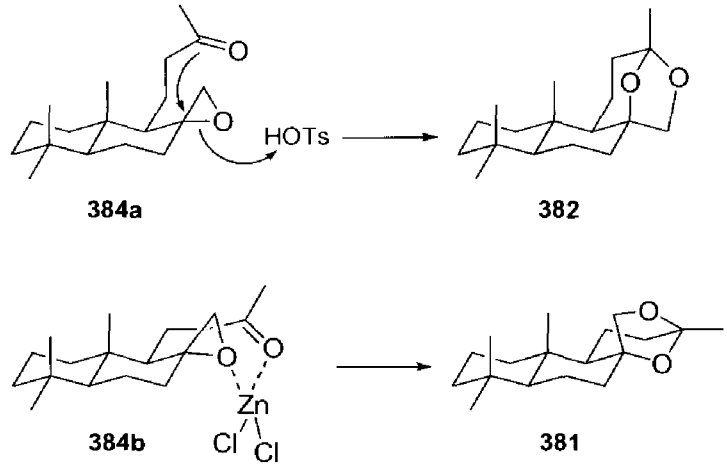


Reagents and conditions: (*a*) $KMnO_4$, $C_6H_5CH_2N^+(CH_2CH_3)_3Cl^-$, $CHCl_3$, 93%, or in H_2O:C_6H_6, 82%; (*b*) OsO_4; (*c*) *m*-CPBA, aq. $NaHCO_3$, CH_2Cl_2, 18-20°C, 100%; (*d*) *p*-TsOH, vermiculite, C_6H_6, 18°C, 100% (C_6H_{14}, 70%); (*e*) $ZnCl_2$, CH_2Cl_2/*p*-$CH_3C_6H_4SO_3H$, $CH_3C_6H_5$, 20°C, 100%, silica/alumina/vermiculite or silicalite, 100°C, 100% (*f*) $KMnO_4$, $C_6H_5N^+(CH_3)_3Cl^-$, CH_2Cl_2, 65%, H_2O:C_6H_6, 88%.

Ambraketal is, therefore, only available in restricted quantity and at a high price. Its synthesis proceeds through the intermediate methylene ketone **363**, and each synthetic variant is judged on how it solves the problem of preparing **363** and by the ratio of **381** *vs.* **382** (Scheme 3.12). The 8-*epi*-isomer **382** is virtually odourless;[49] thus, the more selective the transformation into the odorous epimer **382**, the better. Besides manool (**22**) also anticopalic acid (**385**), readily extracted from *Pinus Pinaster* Ait. needles, has been used as a starting material for **363** by oxidation of the corresponding ester.[50]

The highly diastereoselective epoxidation of **363** with *m*-chloroperbenzoic acid yields **384**, which upon treatment with *p*-toluenesulfonic acid in toluene furnishes selectively the odourless isomer **382**.

Figure 3.3

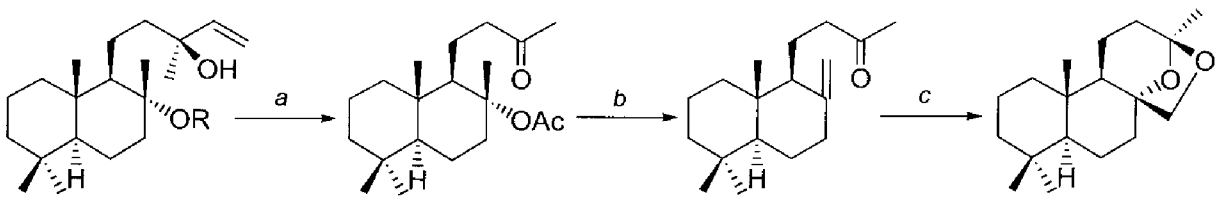


Treatment of **384** with zinc chloride in dichloromethane at 18°C, or clays, *e.g.* vermiculite,[51] yields only **381**. The striking difference in the ring-closure reaction catalyzed with *p*-toluenesulfonic acid and zinc chloride, respectively, has been rationalized as depicted in Figure 3.4. Protonation of the epoxide **384**, and subsequent attack of the carbonyl oxygen on the developing positively charged tertiary centre leads to inversion at C(8) and formation of **382**. In the case of the Lewis acid catalysis a complexation as in **384b** has been assumed, which would ensure an attack of the carbonyl group from the α-face, providing **381** (Figure 3.3).

Communic esters (*E*)-**284** and (*Z*)-**285** also have been used as a natural diterpenic starting material for **381**.[52] The handicap of this approach is the three-step sequence which is neccessary to convert the ester group into a methyl group.

Sclareol (**4**) is suited for the preparation of Ambraketal (**381**) as well, and has consequently been used for this purpose (Scheme 3.13).[52,53] The monoacetate of sclareol (**274**) could be oxidized very efficiently to the ketoacetate **143** with a catalytic amount of ruthenium trichloride and a stoichiometric amount of sodium periodate. Pyrolysis of **143** led in high yield to **363** as the main product, which finally was transformed into Amberketal (**381**) with a catalytic amount of osmium tetroxide and trimethylamine oxide as oxidant.

Scheme 3.13



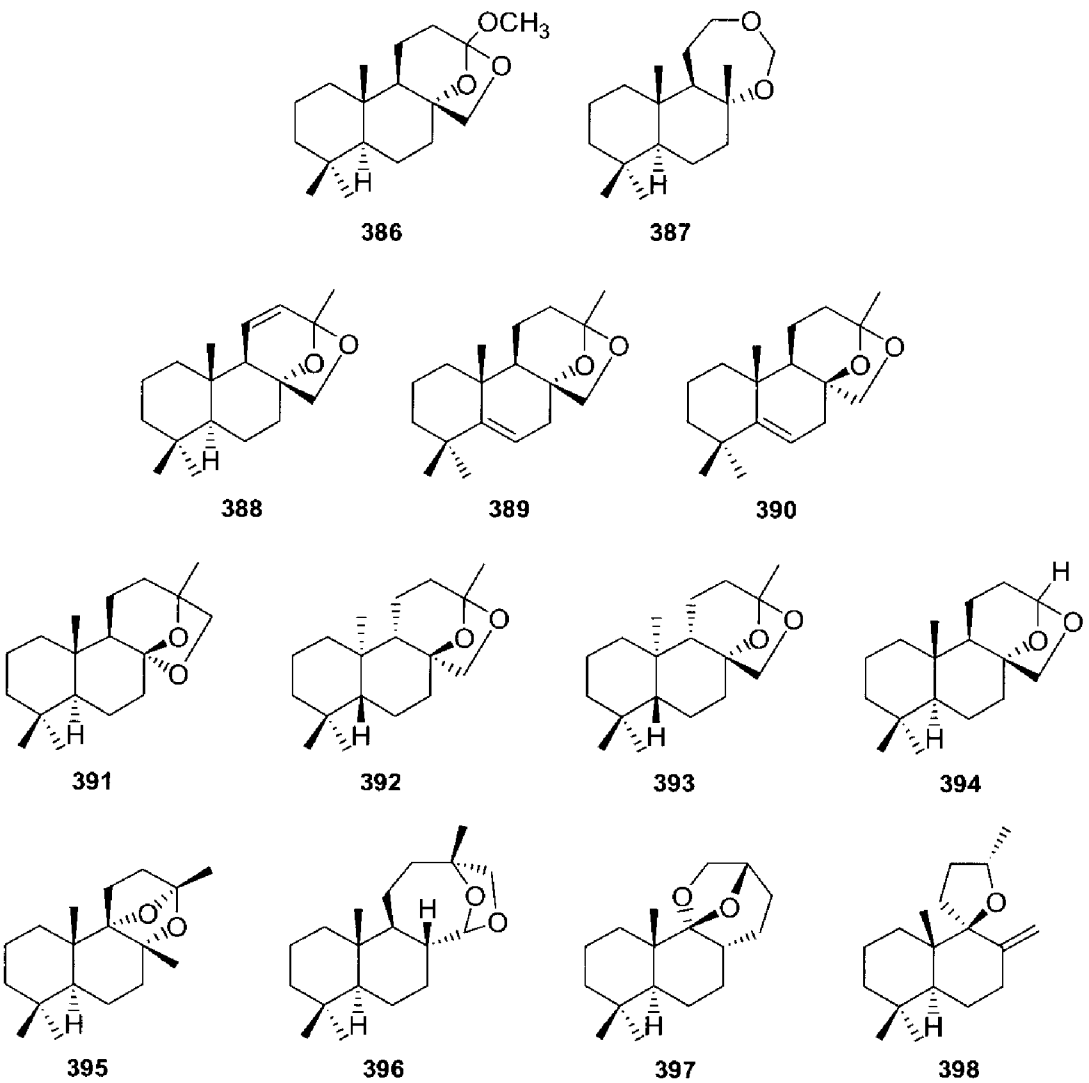
4: R=H
274: R=Ac

143 **363** **381**

Reagents and conditions: (*a*) $RuCl_3$, $NaIO_4$, 95%; (*b*) $NaHCO_3$, DMSO, 150°C, 84%; (*c*) OsO_4, Me_3NO, 55%.

Ambraketal is not an easy target for the synthetic organic chemist. Consequently, a considerable amount of research work has been carried out on structure/activity relationships (SAR) in this odour area, with the aim of identifying more accessible materials, which could be produced more cheaply.

Figure 3.4



386 **387**

388 **389** **390**

391 **392** **393** **394**

395 **396** **397** **398**

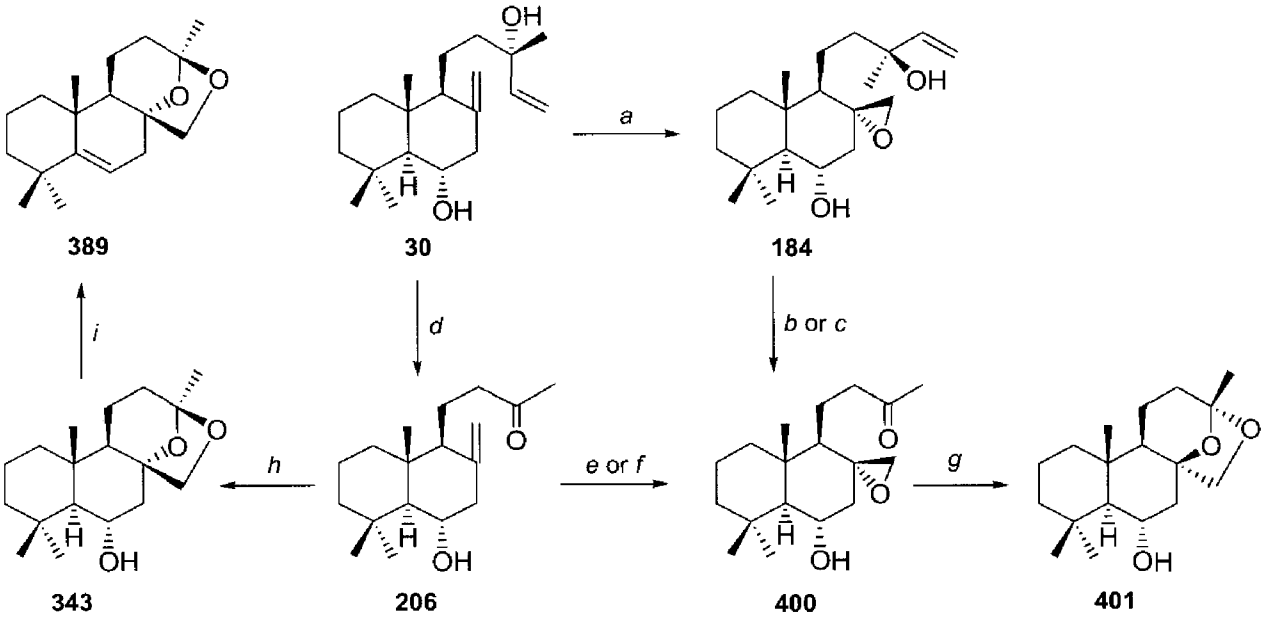
Only a few Ambraketal analogs *e.g.* **386**[54] and the tricyclic acetal **387**[55] reach the tonality and odour strength of compound **381**. Most of the synthesized analogs are weak smelling (**391**, **392**, **393**, **394**)[55,56] or odourless (**395**, **396**, **397**, **398**)[55,57-60] (Figure 3.4). A loss in intensity with unchanged tonality occurs on introduction of a double bond in the molecule, as could be shown with compounds **388**,[61,62] **389**, and **390**.[63]

3.4.2 Synthesis of Ambraketals starting from larixol

Larixol (**30**) has good potential as starting material for the preparation of Ambraketals. Oxidation of the side chain provides for the necessary methyl ketone and the exocyclic double bond is already present in the molecule as precursor for the diol or the epoxide function. From the standardized oxidation of larixol with potassium permanganate C(6) hydroxylated Ambraketals were already found as minor products.

It is already shown in Scheme 3.12 that the reaction sequence and the type of intermediate determines the stereochemistry at C(8) in these ketals.[52] When the exocyclic double bond is oxidized first to an epoxide, acid catalyzed ring closure can be effected easily. This takes place with inversion of the configuration at C(8) and the outcome is a ketal with the undesired 8*S* configuration. Epoxide **400** is obtained in low yield from larixol when the exocyclic double bond is first converted into epoxide **184** followed by oxidation of the side chain, either by the use of $KMnO_4$ or by ozonolysis (Scheme 3.14).

Scheme 3.14

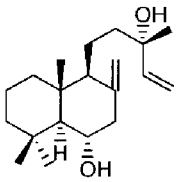


Reagents and conditions: (*a*) oxone®, acetone, H_2O, CH_2Cl_2, [18]crown-6, $NaHCO_3$, 0°C, 81%; (*b*) $KMnO_4$, TEBAC, acetone, 44%; (*c*) O_3, EtOAc, py, -40°C, 40%; (*d*) $KMnO_4$, TEBAC, CH_2Cl_2, 68%; (*e*) *m*-CPBA, Na_2CO_3, CH_2Cl_2, 87%; (*f*) oxone®, acetone, H_2O, CH_2Cl_2, [18]crown-6, $NaHCO_3$, 0°C, 79%; (*g*) PPTS, benzene, 70%; (*h*) OsO_4, py, *t*BuOH, $(CH_3)_3NO$, H_2O, 86%; (*i*) *p*-TsOH, benzene, reflux, 43%.

A better sequence is to oxidize the larixol side chain first followed by epoxidation of the exocyclic double bond, either by *m*-CPBA or oxone®. This latter sequence gives epoxide **400** in about 60% yield from larixol. Cyclization of epoxide **400** was performed with a catalytic amount of the mild acid PPTS and *epi*-hydroxy Ambraketal **401** was obtained in 70% yield.

When the double bond is first oxidized to a diol, than no inversion will occur during formation of the ketal, which results in the desired 8*R* configuration. The hydroxy Ambraketal **343** was obtained by a one step oxidation of methyl ketone **206** with OsO_4.[64] The hydroxyl group at C(6) in *epi*-hydroxy Ambraketal (**401**) and hydroxy Ambraketal (**343**) allows again the preparation of several simple derivatives of these ketals. In a first experiment, dehydration of **342** in refluxing benzene in the presence of *p*-toluenesulfonic acid,[63] Δ^5-ambraketal (**389**) was obtained in a moderate yield. Further research in this field has not been carried out.

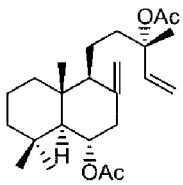
3.5 Experimental[65]



(+)-(1*S*,4*S*,4a*R*,8a*S*)-4-((3*S*)-3-Hydroxy-3-methyl-4-pentenyl)-4a,8,8-trimethyl-3-methylenedecahydro-1-naphthalenol (larixol (30)).

The oleoresin of the larch turpentine (250 g), purchased from Carl Roth GmbH and Co. (Karlsruhe, Germany), was dissolved in ether (600 mL), and washed with a 2% aqueous solution of KOH (400 mL). The organic layer was evaporated and the yellow residue was dissolved in EtOH (300 mL) and hydrolyzed with a 4 M aqueous solution of KOH (200 mL) by refluxing it for 3 h. The mixture was cooled to room temperature and acidified with a 4 M aqueous solution of HCl. Extraction with ether, followed by usual work up gave the crude larixol as a dark yellow oil. Crystallization from cyclohexane gave pure larixol (**30**) (108 g).

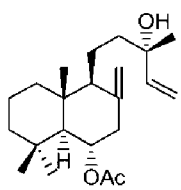
M.p. 102-103°C (lit.[6]: 103-104°C); $[\alpha]_D$ +53.0 (*c* 2.1) (lit.[6]: +50.4); IR (KBr) ν_{max} 3466, 3083, 2928, 1741, 1727, 1374, 1249, 1047 cm^{-1}; ^1H NMR δ 0.64 (s, 3H), 0.91 (s, 3H), 1.12 (s, 3H), 1.22 (s, 3H), 1.09-1.84 (m, 14H), 1.98 (t, *J* = 11.6 Hz, 1H), 2.32 (dd, *J* = 4.8, 12.1 Hz, 1H), 3.76 (td, *J* = 4.9, 10.7 Hz, 1H), 4.60 (d, *J* = 1.4 Hz, 1H), 4.89 (d, *J* = 1.4 Hz, 1H), 5.05 (dd, *J* = 2.7, 10.7 Hz, 1H), 5.20 (dd, *J* = 10.7, 17.4 Hz, 1H), 5.91 (dd, *J* = 10.7, 17.4 Hz, 1H); ^{13}C NMR δ 16.0 (q), 18.0 (t), 19.1 (t), 22.3 (q), 27.6 (q), 33.8 (s), 36.6 (q), 39.2 (t), 39.5 (s), 41.3 (t), 43.7 (t), 49.1 (t), 56.4 (d), 60.5 (d), 71.6 (d), 73.5 (s), 108.4 (t), 111.6 (t), 145.2 (d), 145.5 (s); HRMS: (M^+-18), found 288.2449. $C_{20}H_{32}O$ requires 288.2449; MS *m/e* (%) 288 [(M^+-18), 79], 273 (59), 270 (58), 255 (70), 153 (100), 135 (100), 121 (41), 109 (78), 95 (45); Anal.: found C, 78.10; H, 11.28%. $C_{20}H_{34}O_2$ requires C, 78.38; H, 11.18%.



(+)-(1*S*)-1-(2-((1*S*,4*S*,4a*S*,8a*R*)-4-(acetyloxy)-5,5,8a-trimethyl-2-methylene-decahydro-1-naphthalenyl)ethyl)-1-methyl-2-propenyl acetate (larixyl diacetate (341)).

To a solution of larixol (**30**) (5.0 g; 16.34 mmol) in pyridine (150 mL) was added acetic anhydride (5 mL; 5.44 g; 53.2 mmol) and 4-*N,N*-dimethylaminopyridine (50 mg; 0.40 mmol). The reaction mixture was stirred for 1 h, then poured into an ice-cold aqueous 4 M solution of HCl, and worked up with ethyl acetate, to give the crude larixyl acetate as a yellow oil. Purification by flash column chromatography on silica gel with PE/EA 4:1 as eluent gave larixyl diacetate (**341**) (0.58 g; 1.47 mmol; 9%) as a white solid.

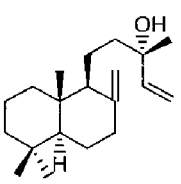
M.p. 115-116.5°C (lit.[7] 117°C); $[\alpha]_D$ +46.6 (*c* 2.2) (lit.[7]: +36.0); IR (KBr) ν_{max} 2937, 2895, 1728, 1257, 1243, 1023 cm^{-1}; ^1H NMR δ 0.72 (s, 3H), 0.85 (s, 3H), 0.99 (s, 3H), 1.47 (s, 3H), 1.01-1.95 (m, 13H), 2.02 (s, 3H), 2.04 (s, 3H), 2.57 (dd, *J* = 5.1, 12.2 Hz, 1H), 4.61 (d, *J* = 1.3, 1H), 4.91 (d, *J* = 1.3, 1H), 4.97 (dd, *J* = 4.5, 11.0 Hz, 1H), 5.08 (s, 1H), 5.14 (d, *J* = 5.1, 1H), 5.95 (d, *J* = 10.9, 17.7 Hz, 1H); ^{13}C NMR δ 15.9 (q), 17.6 (t), 19.0 (t), 21.9 (q), 22.2 (q), 22.4 (q), 23.5 (q), 33.5 (s), 36.1 (q), 39.0 (t), 39.1 (t), 39.8 (s), 43.4 (t), 44.3 (t), 56.2 (d), 57.5 (d), 73.1 (d), 83.2 (s), 109.4 (t), 113.1 (t), 141.8 (d), 144.2 (s), 169.9 (s) 170.1 (s); HRMS: (M^++1), found 391.2833. $C_{24}H_{39}O_4$ requires 391.2848; MS *m/e* (%) 391 [(M^++1), 1], 331 (5), 289 (4), 273 (6), 272 (21), 271 (100), 270 (4), 269 (5), 203 (3), 101 (3), 61 (12); Anal.: found C, 74.14; H, 9.88%. $C_{24}H_{38}O_4$ requires C, 73.80; H, 9.81%.



(+)-(1*S*,4*S*,4a*R*,8a*S*)-4-((3*S*)-3-Hydroxy-3-methyl-4-pentenyl)-4a,8,8-trimethyl-3-methylenedecahydro-1-naphthalenyl acetate (larixyl acetate (31)).

Further elution gave larixyl acetate (**31**) (5.07 g; 14.54 mmol; 89%) as a white solid.

M.p. 78-79°C (lit.[7]: 82°C); $[\alpha]_D$ +45.2 (*c* 2.4) (lit.[7]: +67.0); IR (KBr) ν_{max} 3526, 3086, 2931, 2868, 2851, 1767, 1737, 1668, 1369, 1245, 1172 cm^{-1}; ^1H NMR δ 0.70 (s, 3H), 0.83 (s, 3H), 0.97 (s, 3H), 1.21 (s, 3H), 1.02-1.81 (m, 15H), 1.99 (s, 3H), 2.64 (dd, *J* = 5.1, 12.2 Hz, 1H), 4.62 (d, *J* = 1.3 Hz, 1H), 4.90 (d, *J* = 1.3 Hz, 1H), 5.01 (dd, *J* = 1.4, 10.7 Hz, 1H), 5.16 (dd, *J* = 1.3, 17.4 Hz, 1H), 5.86 (dd, *J* = 10.7, 17.4 Hz, 1H); ^{13}C NMR δ 16.0 (q), 18.0 (t), 19.0 (t), 22.0 (q), 22.4 (q), 27.7 (q), 33.5 (s), 36.2 (q), 39.1 (t), 39.8 (s), 41.3 (t), 43.5 (t), 44.2 (t), 56.4 (d), 57.5 (d), 73.3 (d), 73.5 (s) 109.5 (t), 111.7 (t), 144.3 (s), 145.2 (d), 170.1 (s); HRMS: (M^+-60), found 288.2451. $C_{20}H_{32}O$ requires 288.2449; MS *m/e* (%) 288 [(M^+-60), 22], 270 (66), 255 (80), 187 (33), 153 (100), 123 (43), 105 (35), 95 (36), 73 (40), 43 (39); Anal.: found C, 75.38; H, 10.39%. $C_{22}H_{36}O_3$ requires C, 75.81; H, 10.41%.

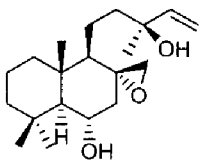


(+)-(3*R*)-5-((1*S*,4a*S*,8a*S*)-5,5,8a-Trimethyl-2-methylenedecahydro-1-naphthalenyl)-3-methyl-1-penten-3-ol (*epi*-manool (29)).

13-*Epi*-manool (**29**) was isolated from the mother liquor left after crystallization of larixol (**30**) by flash column chromatography on silica gel (eluent PE/EA 15:1) as a

very thick light yellow oil, (lit.[7]: m.p. 35-38°C).

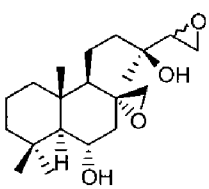
$[\alpha]_D$ +44.6 (*c* 2.6) (lit.[7]: +48.0); IR (liquid film) ν_{max} 3444, 3082, 2925, 1715, 1645, 1386, 1367, 1120 cm^{-1}; ^1H NMR δ 0.61 (s, 3H), 0.73 (s, 3H), 0.80 (s, 3H), 1.20 (s, 3H), 0.85-2.20 (m, 16H), 2.31 (dd, *J* = 4.2, 12.2 Hz, 1H), 4.44 (d, *J* = 1.5 Hz, 1H), 4.74 (d, *J* = 1.5 Hz, 1H), 4.79 (dd, *J* = 1.4, 10.7, 1H), 5.13 (dd, *J* = 1.3, 17.3 Hz, 1H), 5.84 (dd, *J* = 10.7, 17.3 Hz, 1H); ^{13}C NMR δ 14.4 (q), 17.7 (t), 19.4 (t), 21.7 (q), 24.4 (t), 27.6 (q), 33.5 (s), 33.6 (q), 38.4 (t), 39.1 (t), 39.9 (s), 41.4 (t), 42.2 (t), 55.6 (d), 57.3 (d), 73.6 (s), 106.5 (t), 111.6 (t), 145.3 (d), 148.7 (s); HRMS: M^+, found 290.2612. $C_{20}H_{34}O$ requires 290.2610; MS *m/e* (%) 290 (M^+, 1), 272 (42), 257 (63), 137 (100), 123 (36), 109 (33), 107 (30), 95 (51), 93 (35), 81 (56), 69 (37).



(+)-(1*S*,4*S*,4a*R*,8a*S*)-4((3*S*)-3-Hydroxy-3-methyl-4-pentenyl)-4a,8,8-trimethyl-3-spiro-2'-oxiran-decahydro-1-naphtalenol (184).

To a stirred solution of larixol (**30**) (6.0 g; 19.61 mmol) in CH_2Cl_2 (100 mL), acetone (100 mL), H_2O (180 mL), [18]crown-6 (600 mg) and sodium hydrogen carbonate (24 g) was added a solution of oxone® (18.08 g; 29.41 mmol) in H_2O (100 mL) at 0°C. After stirring at 0°C for 90 min the mixture was diluted with a saturated aqueous sodium hydrogen carbonate solution. The aqueous mixture was extracted with ethyl acetate and the combined organic layers were washed with a 10% aqueous solution of $Na_2S_2O_3$, saturated aqueous sodium bicarbonate and brine. Usual work up gave a crude oil which was purified by flash column chromatography (eluent PE/EA 1:1) to give first monoepoxide **184** (4.46 g; 13.33 mmol; 68%) as a white crystalline solid.

184; M.p. 114-115°C; $[\alpha]_D$ +16.3 (*c* 1.7); IR (KBr) ν_{max} 3442, 3048, 2932, 2857, 1455, 1237 cm^{-1}; ^1H NMR δ 0.81 (s, 3H), 0.99 (s, 3H), 1.19 (s, 3H), 1.24 (s, 3H), 0.94-2.05 (m, 16H), 2.59 (d, *J* = 4.3 Hz, 1H), 2.79 (dd, *J* = 1.8, 4.2 Hz, 1H), 4.01 (td, *J* = 4.8, 10.9 Hz, 1H), 5.04 (dd, *J* = 1.3, 10.7 Hz, 1H), 5.20 (dd, *J* = 1.3, 17.2 Hz, 1H), 5.84 (dd, *J* = 10.7, 17.2 Hz, 1H); ^{13}C NMR δ 15.8 (q), 16.0 (t), 18.3 (t), 22.3 (q), 28.1 (q), 33.8 (s), 36.6 (q), 39.2 (t), 40.2 (s), 43.6 (t), 43.7 (t), 47.0 (t), 51.2 (t), 53.7 (d), 57.7 (s), 60.3 (d), 69.9 (d), 73.6 (s), 111.8 (t), 145.0 (d); HRMS: (M^+-31), found 291.2323. $C_{19}H_{31}O_2$ requires 291.2324; MS *m/e* (%) 291 [(M^+-31), 8], 233 (60), 109 (91), 69 (90), 43 (59), 31 (100); Anal.: found C, 74.19; H, 10.85%. $C_{20}H_{34}O_3$ requires C, 74.49; H, 10.63%.

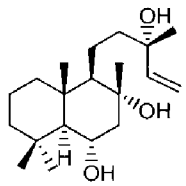


(+)-(1*S*,4*S*,4a*R*,8a*S*)-4((3*S*)-3-Hydroxy-3-methyl-4-spiro-2'-oxiran)-4a,8,8-trimethyl-3-spiro-2'-oxiran-decahydro-1-naphtalenol (399).

Further elution afforded the diepoxide **399** (1.26 g; 3.73 mmol; 19%) as white crystals.

M.p. 74-75°C; $[\alpha]_D$ +17.7 (*c* 1.9); IR (liquid film) ν_{max} 3445, 3051, 2930, 2866, 1460, 1455, 1387, 1366 cm^{-1}; ^1H NMR δ 0.76 (s, 3H), 0.97 (s, 3H), 1.12 (s, 3H), 1.18 (s, 3H), 1.03-1.91 (m, 16H), 2.51-2.84 (m, 5H), 3.96 (td, *J* = 3.5, 11.2 Hz, 1H); ^{13}C NMR δ 15.4 (t), 15.8 (q), 18.3 (t), 22.3 (q), 22.6 (q), 33.8 (s), 36.6 (q), 39.2 (s), 40.2 (s), 42.9 (t), 43.2 (t), 43.7 (t), 47.0 (t), 51.1 (t), 53.3 (d),

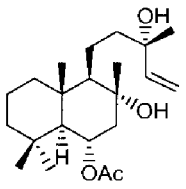
57.6 (s), 58.0 (d), 60.3 (d), 69.5 (s), 69.8 (d); HRMS: M^+, found 338.2460. $C_{20}H_{34}O_4$ requires 338.2457; MS *m/e* (%) 338 (M^+, 1), 307 (43), 213 (63), 153 (48), 109 (100), 95 (79), 93 (45), 81 (63), 69 (96), 55 (62), 43 (97), 41 (51); Anal.: found C, 70.90; H, 10.12%. $C_{20}H_{34}O_4$ requires C, 70.97; H, 10.12%.



(+)-(1*S*,3*R*,4*R*,4a*S*,8a*S*)-4-((3*S*)-3-Hydroxy-3-methyl-4-pentenyl)-3,4a,8,8-tetramethyldecahydro-1,3-naphthalenediol (185).

Epoxide **184** (5.5 g; 17.08 mmol) was added in small portions at 0°C into a stirred suspension of $LiAlH_4$ (1.3 g; 34.21 mmol) in freshly distilled THF (100 mL). After stirring overnight at room temperature the mixture was treated carefully with ethyl acetate (50 mL), and diluted with an 1 M aqueous solution of HCl (200 mL). The aqueous layer was extracted with ethyl acetate and worked up as usual. The residue was recrystallized from EA/CH_2Cl_2 1:1 to give compound **185** as white crystals (5.2 g; 16.05 mmol; 94%).

M.p. 158-159°C; $[\alpha]_D$ +43.4 (*c* 1.3, EtOH); IR (KBr) ν_{max} 3427, 2923, 2542, 2474, 1457, 1388 cm^{-1}; ^1H NMR ($CDCl_3/CD_3OD$) δ 0.72 (s, 3H), 0.90 (s, 3H), 1.08 (s, 3H), 1.11 (s, 3H), 1.18 (s, 3H), 1.04-1.48 (m, 13H), 2.00 (dd, *J* = 3.8, 11.9 Hz, 1H), 3.26 (br s, 3H), 3.70 (td, *J* = 3.8, 10.7 Hz, 1H), 4.99 (dd, *J* = 1.5, 10.7 Hz, 1H), 5.13 (dd, *J* = 1.5, 17.4 Hz, 1H), 5.77 (dd, *J* = 10.7, 17.4 Hz, 1H); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 15.9 (q), 17.8 (t), 18.7 (t), 21.5 (q), 24.7 (q), 28.6 (q), 33.3 (s), 35.9 (q), 39.2 (s), 39.4 (t), 43.5 (t), 44.3 (t), 51.1 (d), 53.3 (t), 60.7 (d), 68.3 (d), 73.9 (s), 74.0 (s), 111.6 (t), 144.1 (d); HRMS: (M^+-18), found 306.2560. $C_{20}H_{34}O_2$ requires 306.2559; MS *m/e* (%) 306 [(M^+-18), 1], 292 (6), 191 (53), 187 (56), 150 (53), 123 (81), 109 (72), 87 (100), 43 (99); Anal.: found C, 73.71; H, 11.37%. $C_{20}H_{36}O_3$ requires C, 74.02; H, 11.18%.

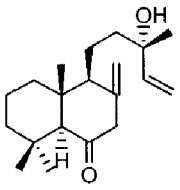


(+)-(1*S*,3*R*,4*R*,4a*S*,8a*S*)-3-Hydroxy-4-((3*S*)-3-hydroxy-3-methyl-4-pentenyl)-3,4a,8,8-tetramethyldecahydro-1-naphthalenyl acetate (186).

A solution of 6α-hydroxy **185** (1.5 g; 4.63 mmol) in CH_2Cl_2 (10 mL) and pyridine (8 mL) was treated with acetic anhydride (1.75 mL; 1.90 g; 18.6 mmol) and DMAP (25 mg; 0.20 mmol) and stirred at 0°C. After stirring for 150 min the mixture was poured into an ice cold aqueous 4 M solution of HCl, and worked up with ethyl acetate. Flash column chromatography (eluent PE/EA 3:1) of the residue gave compound **186** (1.54 g; 4.21 mmol; 91%) as white crystals.

M.p. 126-128°C; $[\alpha]_D$ +52.9 (*c* 2.1); IR (KBr) ν_{max} 3423, 2924, 2869, 1727, 1716, 1469, 1266, 1239 cm^{-1}; ^1H NMR δ 0.85 (s, 3H), 0.86 (s, 3H), 1.02 (s, 3H), 1.26 (s, 6H), 1.30-1.84 (m, 14H), 2.04 (s, 3H), 2.07 (dd, *J*=3.9, 11.7 Hz, 1H), 2.54 (br s, 2H), 5.07 (dd, *J* = 3.3, 10.8 Hz, 1H), 5.23 (dd, *J* = 1.4, 17.2 Hz, 1H), 5.87 (dd, *J* = 10.8, 17.2 Hz, 1H); ^{13}C NMR δ 16.2 (q), 18.0 (t), 19.0 (t), 22.0 (2x q), 25.6 (q), 29.2 (q), 33.3 (s), 36.1 (q), 39.5 (t), 39.7 (s), 43.5 (t), 44.3 (t), 50.0 (t), 58.4 (d), 61.0 (d), 70.9 (d), 74.1 (s), 74.2 (s), 112.0 (t), 144.9 (d), 170.3 (s); HRMS: (M^+-18), found 348.2669. $C_{22}H_{36}O_3$ requires 348.2664; MS *m/e* (%) 348 [(M^+-18), 2], 288 (44), 191 (48), 190 (81), 121 (43),

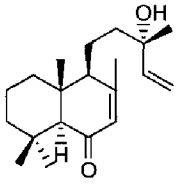
109 (50), 95 (50), 81 (50), 71 (44), 69 (48), 43 (100); Anal.: found C, 72.44; H, 10.69%. $C_{22}H_{38}O_4$ requires C, 72.09; H, 10.45%.



(+)-(4*S*,4a*R*,8a*S*)-4-((3*S*)-3-hydroxy-3-methyl-4-pentenyl)-4a,8,8-trimethyl-3-methyleneoctahydro-1(2*H*)-naphthalenone (163).

To a stirred solution of larixol (**30**) (2.5 g; 8.18 mmol) in CH_2Cl_2 (60 mL) was added 3Å molecular sieves (2.0 g) followed by pyridinium chlorochromate (PCC) (2.63 g; 12.25 mmol) and 10 drops of acetic acid. After 1 h the mixture was filtered over silica gel 60H and flushed with ethyl acetate. Purification of the crude product by flash column chromatography (PE/EA 3:1) gave **163** (2.35 g; 7.75 mmol; 95%) as a colourless oil.

$[\alpha]_D$ +74.6 (*c* 3.0); IR (liquid film) ν_{max} 3467, 2930, 1715, 1652, 1464, 1293, 1233 cm^{-1}; ^1H NMR δ 0.63 (s, 3H), 0.96 (s, 3H), 1.17 (s, 3H), 1.28 (s, 3H), 1.14-1.86 (m, 15H), 4.68 (d, *J* = 1.1 Hz, 1H), 4.85 (d, *J* = 1.1, 1H), 5.06 (dd, *J* = 1.3, 10.7 Hz, 1H), 5.20 (dd, *J* = 1.3, 17.2 Hz, 1H), 5.91 (dd, *J* = 10.7, 17.2 Hz, 1H); ^{13}C NMR δ 15.8 (q), 18.2 (t), 18.9 (t), 21.6 (q), 27.9 (q), 32.6 (s), 32.8 (q), 38.9 (t), 41.1 (t), 41.4 (s), 42.7 (t), 55.9 (t), 57.3 (d), 66.4 (d), 73.4 (s), 110.1 (t), 111.9 (t), 143.4 (s), 145.1 (d), 208.2 (s); HRMS: M^+, found 304.2400. $C_{20}H_{32}O_2$ requires 304.2402; MS *m/e* (%) 304 (M^+, 4), 287 (23), 286 (100), 258 (23), 206 (52), 151 (63), 135 (36), 109 (28), 68 (30).



(+)-(4*S*,4a*R*,8a*S*)-4-((3*S*)-3-Hydroxy-3-methyl-4-pentenyl)-3,4a,8,8-tetramethyl-4a,5,6,7,8,8a-hexahydro-1(4*H*)-naphthalenone (164).

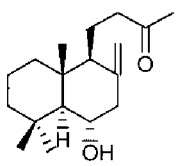
The above mentioned C(6)-ketone (**163**) (2.0 g; 6.58 mmol) was isomerized into the conjugated ketone **164** by treatment with an 1 M solution of sodium methoxide (5 mL) in methanol (35 mL) at room temperature during 2 h. The methanol was evaporated and an 1 M aquous solution of HCl (200 mL) was added. Extraction with ether followed by usual work up gave the crude product which was purified by flash column chromatography (PE/EA 2:1) to give compound **164**[25] (1.96 g; 6.45 mmol; 98%) as a light yellow oil.

$[\alpha]_D$ +43.5 (*c* 3.6); IR (liquid film) ν_{max} 3429, 3088, 2912, 1651 cm^{-1}; ^1H NMR δ 0.77 (s, 3H), 1.05 (s, 3H), 1.08 (s, 3H), 1.25 (s, 3H), 1.12-1.92 (m, 13H), 1.85 (s, 3H), 5.03 (dd, *J* = 1.2, 10.7 Hz, 1H), 5.17 (dd, *J* = 1.2, 17.3 Hz, 1H), 5.68 (t, *J* = 1.4 Hz, 1H), 5.86 (dd, *J* = 10.7, 17.3 Hz, 1H); ^{13}C NMR δ 14.6 (q), 18.2 (t), 21.4 (t), 21.5 (q), 22.1 (q), 27.8 (q), 32.3 (s), 33.4 (q), 38.7 (t), 43.2 (t), 43.4 (s), 44.6 (t), 56.6 (d), 63.6 (d), 73.4 (s), 112.3 (t), 128.4 (d), 144.6 (d), 159.0 (s), 200.4 (s); HRMS: M^+, found 304.2394. $C_{20}H_{32}O_2$ requires 304.2402; MS *m/e* (%) 286 [(M^+-18), 17], 219 (19), 218 (34), 135 (100), 109 (28), 95 (21), 73 (89), 43 (31).

General procedure for the oxidation with 1.5 equivalents of potassium permanganate.

To an ice-cooled stirred solution of labdanes **29** – **31**, **185**, **186**, **4**, and **164** (3.25 mmol) and *N,N,N'*-triethylbenzenemethanaminium chloride (1.1 g; 4.91 mmol) in dichloromethane (40 mL) was added solid $KMnO_4$ (0.77 g; 4.91 mmol) in small portions in 15 min and then the mixture was

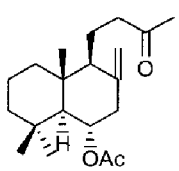
allowed to warm up to room temperature and stirring was continued until conversion of the starting material, which took about 14 h. The dark brown reaction mixture was treated with an aqueous saturated Na_2SO_3 solution (75 mL) and with a 3% aqueous solution of oxalic acid (75 mL). Extraction of the now colourless reaction mixture with ethyl acetate was followed by usual work-up and purification was performed by flash column chromatography. Gradient eluation gave first methyl ketones **206**, **207**, **363**, **352** and enol ethers **378**, **379**, **269** (eluent PE/EA 3:1), followed by triols **370 - 372**, **380** (eluent EA/MeOH 9:1).



(+)-4-((1*S*,4*S*,4a*S*,8a*R*)-4-Hydroxy-5,5,8a-trimethyl-2-methylenedecahydro-1-naphthalenyl)-2-butanone (206).

Methyl ketone **206** was isolated as a white crystalline solid in 45% yield.

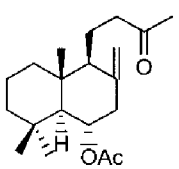
M.p. 77-79°C; $[\alpha]_D$ +43.4 (*c* 2.0); IR (liquid film) ν_{max} 3467, 2926, 1713, 1644, 1361 cm^{-1}; ^1H NMR δ 0.69 (s, 3H), 0.99 (s, 3H), 1.15 (s, 3H), 1.07-2.06 (m, 14H), 2.10 (s, 3H), 2.66 (dd, *J* = 4.9, 12.1 Hz, 1H), 3.82 (dt, *J* = 4.9, 10.6 Hz, 1H), 4.49 (d, *J* = 1.2 Hz, 1H), 4.88 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR δ 15.9 (q), 17.7 (t), 19.1 (t), 22.3 (q), 30.1 (q), 33.9 (s), 36.6 (q), 39.2 (t), 39.4 (s), 42.8 (t), 43.6 (t), 49.0 (t), 55.4 (d), 60.4 (d), 71.6 (d), 108.2 (t), 145.3 (s), 209.2 (s); HRMS: (M^+-18), found 260.2131. $C_{18}H_{28}O$ requires 260.2140; MS *m/e* (%) 260 [(M^+-18), 76], 202 (53), 153 (52), 109 (55), 95 (38), 93 (72), 43 (100); Anal.: found C, 78.12; H, 11.28%. $C_{18}H_{30}O_2$ requires C, 77.65; H, 10.86%.



(+)-(1*S*,4*S*,4a*R*,8a*S*)-4a,8,8-Trimethyl-3-methylene-4-(3-oxobutyl)-decahydro-1-naphthalenyl acetate (207).

Methyl ketone **207** was isolated as a colourless oil in 48% yield.

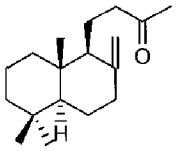
$[\alpha]_D$ +56.2 (*c* 1.8); IR (liquid film) ν_{max} 2929, 1733, 1717, 1647, 1243 cm^{-1}; ^1H NMR δ 0.71 (s, 3H), 0.83 (s, 3H), 0.91 (s, 3H), 2.02 (s, 3H), 2.07 (s, 3H), 1.01-2.42 (m, 13H), 2.64 (dd, *J* = 5.1, 12.2 Hz, 1H), 4.51 (d, *J* = 1.3 Hz, 1H), 4.89 (d, *J* = 1.3, 1H), 4.97 (dt, *J* = 5.1, 10.9 Hz, 1H); ^{13}C NMR δ 15.8 (q), 17.6 (t), 18.9 (t), 21.9 (q), 22.4 (q), 30.0 (q), 33.4 (s), 36.1 (q), 38.9 (t), 39.6 (s), 42.6 (t), 43.3 (t), 44.0 (t), 55.2 (d), 57.4 (d), 73.1 (d), 109.2 (t), 144.0 (s), 170.0 (s), 209.0 (s); HRMS: (M^+-60), found 260.2146. $C_{18}H_{28}O$ requires 260.2140; MS *m/e* (%) 260 [(M^+-60), 76], 202 (88), 189 (35), 187 (32), 159 (19), 153 (57), 135 (21), 133 (36), 123 (22), 43 (100).



(+)-(1*S*,4*S*,4a*R*,8a*S*)-4a,8,8-Trimethyl-3-methylene-4-(3-oxobutyl)-decahydro-1-naphthalenyl acetate (207).

To a solution of methyl ketone **206** (0.7 g; 2.52 mmol) in CH_2Cl_2 (20 mL) and pyridine (15 mL) was added acetic anhydride (2.17 g; 21.3 mmol) and 4-*N,N*-dimethylaminopyridine (25 mg; 0.20 mmol). The reaction mixture was stirred for 1 h, then poured into a 4 M aqueous solution of HCl, and worked up with ethyl acetate. Purification by flash column

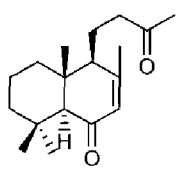
chromatography on silica gel (eluent PE/EA 15:1) gave the title compound **207** (0.73 g; 2.29 mmol; 91%) as a colourless oil. Spectral data of **207** were identical with the above mentioned.



(+)-4-((1*S*,4a*S*,8a*S*)-5,5,8a-Trimethyl-2-methylenedecahydro-1-naphthalenyl)-2-butanone (363).

Methyl ketone **363** was isolated as a colourless oil in 48% yield.

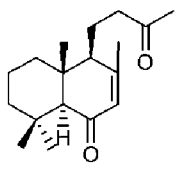
$[\alpha]_D$ +35.5 (*c* 1.8); IR (liquid film) ν_{max} 3477, 2931, 3078, 1716, 1460, 1366, 1162 cm^{-1}; ^1H NMR δ 0.44 (s, 3H), 0.55 (s, 3H), 0.62 (s, 3H), 1.02-1.79 (m, 15H), 1.85 (s, 3H), 2.29 (dd, *J* = 4.2, 12.1 Hz, 1H), 4.19 (d, *J* = 0.9 Hz, 1H), 4.57 (d, *J* = 0.9 Hz, 1H); ^{13}C NMR δ 14.3 (q), 17.5 (t), 19.3 (t), 21.7 (q), 24.4 (t), 30.1 (q), 33.6 (2x q), 38.3 (t), 39.0 (t), 39.8 (s), 42.1 (t), 42.9 (t), 55.5 (d), 56.2 (d), 106.3 (t), 148.3 (s), 209.6 (s); HRMS: M^+, found 262.2300. $C_{18}H_{30}O$ requires 262.2297; MS *m/e* (%) 262 (M^+, 52), 244 (48), 204 (51), 177 (40), 137 (100), 123 (36), 107 (40), 95 (55), 81 (51), 43 (56).



(+)-(4*S*,4a*R*,8a*S*)-3,4a,8,8-Tetramethyl-4-(3-oxobutyl)-4a,5,6,7,8,8a-hexahydro-1(4*H*)-naphthalenon (352).

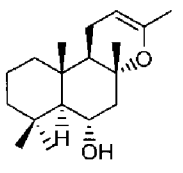
Methyl ketone **352** was isolated as a colourless oil in 8% yield.

$[\alpha]_D$ +34.0 (*c* 1.4); IR (liquid film) ν_{max} 2928, 1716, 1669, 1454, 1357, 1176 cm^{-1}; ^1H NMR δ 0.79 (s, 3H), 1.06 (s, 3H), 1.09 (s, 3H), 1.84 (s, 3H), 1.14-2.06 (m, 10H), 2.11 (s, 3H), 2.47-2.70 (m, 2H), 5.70 (dd, *J* = 1.3, 2.7 Hz, 1H); ^{13}C NMR δ 14.6 (q), 18.1 (t), 20.5 (t), 21.4 (q), 22.1 (q), 30.0 (q), 32.2 (s), 33.4 (q), 38.9 (t), 43.0 (t), 43.4 (s), 45.4 (t), 55.5 (d), 63.5 (d), 128.8 (d), 158.0 (s), 200.3 (s), 207.9 (s); HRMS: M^+, found 276.2082. $C_{18}H_{28}O_2$ requires 276.2089; MS *m/e* (%) 276 (M^+, 2), 219 (6), 135 (19), 109 (13), 95 (6), 73 (100), 69 (2), 43 (30), 41.



(+)-(4*S*,4a*R*,8a*S*)-3,4a,8,8-Tetramethyl-4-(3-oxobutyl)-4a,5,6,7,8,8a-hexahydro-1(4*H*)-naphthalenon (352).

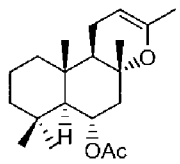
To a solution of **164** (1.0 g; 3.29 mmol) and benzyltriethylammonium chloride (2.21 g; 9.87 mmol) in dichloromethane (40 mL) was added solid $KMnO_4$ (1.55 g; 9.87 mmol) at once at room temperature. The mixture was stirred until completion of the reaction. The dark brown reaction mixture was treated with an aqueous saturated Na_2SO_3 solution and a 3% aqueous solution of oxalic acid. Extraction of the colourless reaction mixture with ethyl acetate was followed by usual work-up. Purification by flash column chromatography (eluent PE/EA 3:1) gave methyl ketone **352** (0.68 g; 2.24 mmol; 68%) as a colourless oil. The analytical data were as mentioned before.



(+)-(4a*R*,6*S*,6a*S*,10a*S*,10b*R*)-3,4a,7,7,10a-Pentamethyl-4a,5,6,6a,7,8,9,10,10a,10b-decahydro-1*H*-benzo[*f*]chromen-6-ol (378).

Compound **378** was isolated as a colourless oil in 47% yield.

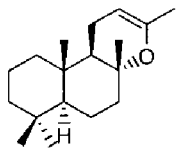
$[\alpha]_D$ +24.9 (*c* 0.4); ^{1}H NMR δ 0.82 (s, 3H), 1.00 (s, 3H), 1.13 (s, 3H), 1.15 (s, 3H), 1.75 (s, 3H), 1.10-1.94 (m, 12H), 2.23 (dd, *J* = 3.9, 11.8 Hz, 1H), 3.89 (td, *J* = 3.9, 11.2 Hz, 1H), 4.42 (br d, *J* = 2.9 Hz, 1H); ^{13}C NMR δ 16.2 (q), 18.3 (t), 18.6 (t), 20.3 (q), 21.2 (q), 22.0 (q), 33.6 (s), 36.6 (q), 37.4 (s), 39.3 (t), 43.6 (t), 52.0 (d), 52.1 (t), 61.4 (d), 68.9 (d), 75.5 (s), 94.7 (d), 147.8 (s); HRMS: M^+, found 278.2241. $C_{18}H_{30}O_2$ requires 278.2246; MS *m/e* (%) 278 (M^+, 99), 245 (29), 217 (100), 215 (30), 191 (53), 189 (52), 175 (44), 119 (30), 109 (39).



(4a*R*,6*S*,6a*S*,10a*S*,10b*R*)-3,4a,7,7,10a-Pentamethyl-4a,5,6,6a,7,8,9,10,10a,10b-decahydro-1*H*-benzo[*f*]chromen-6-yl acetate (379).

Compound **379** was isolated as a colourless oil in 48% yield.

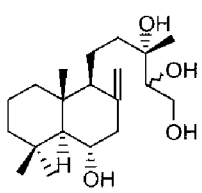
^{1}H NMR δ 0.87 (s, 3H), 0.89 (s, 3H), 1.02 (s, 3H), 1.21 (s, 3H), 1.23-1.89 (m, 14H), 2.04 (s, 3H), 2.17 (dd, *J* = 4.1, 11.7 Hz, 1H), 4.41-4.44 (m, 1H), 5.12 (td, *J* = 4.1, 11.3 Hz, 1H); ^{13}C NMR δ 16.1 (q), 18.2 (t), 18.5 (t), 20.2 (q), 21.0 (q), 21.9 (q), 22.1 (q), 33.2 (s), 36.2 (q), 37.5 (s), 39.1 (t), 43.3 (t), 47.5 (t), 51.9 (d), 58.4 (d), 70.5 (d), 75.1 (s), 94.6 (d), 147.8 (s), 170.2 (s); HRMS: M^+, found 320.2350. $C_{20}H_{32}O_3$ requires 320.2351; MS *m/e* (%) 320 (M^+, 5), 260 (37), 190 (34), 189 (90), 119 (100), 109 (36), 69 (33), 43 (95).



(+)-(4a*R*,6a*S*,10a*S*,10b*R*)-3,4a,7,7,10a-Pentamethyl-4a,5,6,6a,7,8,9,10,10a,10b-decahydro-1*H*-benzo[*f*]chromene, (sclareol oxide (269)).

Compound **269** was isolated as a light yellow oil in 51% yield.

$[\alpha]_D$ +4.9 (*c* 1.3) (lit.[66]: $[\alpha]_D$ +5.7, *c* 1.6); IR (liquid film) ν_{max} 3055, 2950, 2900, 2890, 1687, 1470, 1390, 1342, 1000 cm^{-1}; ^{1}H NMR δ 0.74 (s, 6H), 0.81 (s, 3H), 1.25 (s, 3H), 1.61 (s, 3H), 1.76-1.83 (m, 13H), 1.87 (dt, *J* = .3, 14.6 Hz, 1H), 4.30 (br s, 1H); ^{13}C NMR δ 19.3 (q), 18.2 (q), 18.6 (t), 19.8 (t), 20.7 (q), 21.0 (q), 26.6 (q), 28.6 (q), 33.1 (s), 36.7 (s), 39.3 (t), 41.1 (t), 41.9 (t), 52.4 (d), 55.2 (d), 76.2 (s), 94.6 (d), 147.8 (s); HRMS: M^+, found 262.2294. $C_{18}H_{30}O$ requires 262.2297; MS *m/e* (%) 262 (M^+, 100), 191 (81), 177 (39), 123 (46), 109 (97), 95 (64), 81 (72), 43 (78).

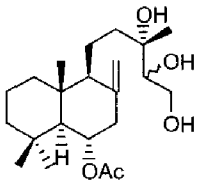


(+)-(2ζ,3*S*)-5-((1*S*,4*S*,4a*S*,8a*R*)-4-Hydroxy-5,5,8a-trimethyl-2-methylenedecahydro-1-naphthalenyl)-3-methyl-1,2,3-pentanetriol (370).

Compound **370** was isolated as a white crystalline solid in 38% yield.

M.p. 139-141°C; $[\alpha]_D$ +33.2 (*c* 1.5, EtOH); IR (KBr) ν_{max} 3389, 2939, 1644, 1382, 1271 cm^{-1}; ^{1}H NMR δ 0.42 (s, 3H), 0.71 (s, 3H), 0.85 (s, 3H), 0.87 (s, 3H), 1.02-1.84 (m, 17H), 2.34 (dd, *J* = 4.8, 12.2 Hz, 1H), 3.14-3.84 (m, 4H), 4.33 (br s, 1H), 4.58 (br s, 1H); ^{13}C NMR δ 15.3 (q), 16.9 (t), 18.6 (t), 21.2 (q), 21.5 (q), 33.3 (s), 35.8 (q), 37.3 (t), 38.8 (t), 38.9 (s), 43.3 (t), 48.2 (t), 56.2 (d), 59.6 (d), 62.4 (t), 70.5 (d), 73.7 (s), 76.1 (d), 107.3 (t), 145.4 (s); HRMS: M^+, found 340.2597. $C_{20}H_{36}O_4$ requires 340.2614; HRMS: (M^+-18), found 322.2509. $C_{20}H_{34}O_3$ requires

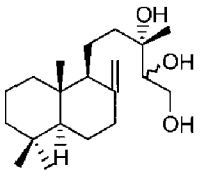
322.2508; MS *m/e* (%) 340 (M^+, 3), 322 (11), 261 (49), 243 (58), 218 (58), 153 (71), 109 (87), 95 (66), 69 (100), 43 (75); Anal.: found C, 70.24; H, 10.71%. $C_{20}H_{36}O_4$ requires C, 70.55; H, 10.66%.



(+)-(1*S*,4*S*,4a*R*,8a*S*)-4a,8,8-Trimethyl-3-methylene-4-((3*S*,4ζ)-3,4,5-trihydroxy-3-methylpentyl)-decahydro-1-naphthalenyl acetate (371).

Compound **371** was isolated as an oil in 26% yield.

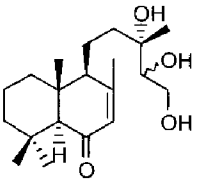
$[\alpha]_D$ +24.6 (*c* 1.9); IR (liquid film) ν_{max} 3378, 2910, 1720, 1647, 1258 cm^{-1}; ^1H NMR δ 0.71 (s, 3H), 0.83 (s, 3H), 0.97 (s, 3H), 1.10 (s, 3H), 1.16-1.84 (m, 16H), 2.00 (s, 3H), 2.63 (dd, *J* = 5.1, 12.2 Hz, 1H), 3.43 (t, *J* = 4.3 Hz, 1H), 3.64 (d, *J* = 2.6 Hz, 2H), 4.62 (s, 1H), 4.88 (s, 1H), 4.97 (dt, *J* = 5.8, 11.0 Hz, 1H); ^{13}C NMR δ 16.0 (q), 17.5 (t), 19.0 (t), 22.0 (2x q), 22.1 (q), 33.5 (s), 36.2 (q), 38.3 (t), 39.1 (t), 39.6 (s), 43.5 (t), 44.2 (t), 56.5 (d), 57.5 (d), 63.3 (t), 73.3 (d), 74.6 (s), 75.9 (d), 109.4 (s), 144.3 (s), 170.3 (s); HRMS: (M^+-18), found 364.2609. $C_{22}H_{36}O_4$ requires 364.2614; MS *m/e* (%) 382 (M^+, 2), 364 (3), 322 (26), 243 (83), 189 (44), 188 (43), 153 (54), 123 (34), 109 (30), 105 (29), 95 (29), 81 (31), 43 (100).



(+)-(2ζ,3*R*)-5-((1*S*,4a*S*,8a*S*)-5,5,8a-Trimethyl-2-methylenedecahydro-1-naphthalenyl)-3-methyl-1,2,3-pentanetriol (372).

Compound **372** was isolated as a white crystalline solid in 24% yield, as its hydrate.

M.p. 129-131°C; $[\alpha]_D$ +20.8 (*c* 0.53); IR (KBr) ν_{max} 3418, 2943, 2476, 3082, 1639, 1458, 1387 cm^{-1}; ^1H NMR δ 0.62 (s, 3H), 0.73 (s, 3H), 0.81 (s, 3H), 1.06 (s, 3H), 1.10-1.96 (m, 16H), 2.28 (dd, *J* = 4.0, 12.1 Hz, 1H), 3.36-3.66 (m, 5H), 4.46 (br s, 1H), 4.73 (br s, 1H); ^{13}C NMR δ 14.3 (q), 17.1 (t), 19.2 (t), 21.5 (q), 21.7 (q), 24.3 (t), 33.3 (s), 33.4 (q), 36.0 (t), 36.2 (t), 36.9 (t), 39.7 (s), 42.0 (t), 55.4 (d), 57.3 (d), 62.9 (t), 74.3 (s), 75.9 (d), 106.2 (t), 146.6 (s); HRMS: M^+, found 324.2664. $C_{20}H_{36}O_3$ requires 324.2664; MS *m/e* (%) 324 (M^+, 6), 306 (10), 275 (28), 245 (100), 204 (38), 137 (81), 121 (42), 109 (43), 95 (61), 69 (58), 43 (52); Anal.: found C, 70.45; H, 11.14%. $C_{20}H_{36}O_3 \cdot H_2O$ requires C, 70.13; H, 11.18%.

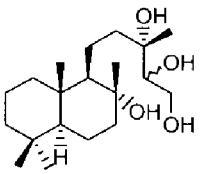


(+)-(4*S*,4a*R*,8a*S*)-3,4a,8,8-Tetramethyl-4-((3*S*)-3,4,5-trihydroxy-3-methylpentyl)-4a,5,6,7,8,8a-hexahydro-1(4*H*)-naphthalenone (380).

Compound **380** was isolated as a white crystalline solid in 56% yield.

M.p. 108-110°C; $[\alpha]_D$ +21.0 (*c* 1.1); IR (KBr) ν_{max} 3422, 2928, 1669, 1384, 1293, 1234, 1087 cm^{-1}; ^1H NMR δ 0.77 (s, 3H), 1.04 (s, 3H), 1.06 (s, 3H), 1.12 (s, 3H), 1.90 (s, 3H), 1.12-1.94 (m, 15H), 3.48 (t, *J* = 4.2 Hz, 1H), 3.76 (d, *J* = 4.2 Hz, 2H), 5.72 (br s, 1H); ^{13}C NMR δ 14.6 (q), 18.0 (t), 21.0 (t), 21.4 (q), 21.9 (q), 22.2 (q), 33.3 (q), 38.6 (t), 41.8 (t), 43.0 (t), 43.4 (s), 43.5 (s), 56.7 (d), 63.3 (t), 63.5 (d), 74.5 (s), 74.8 (d), 128.3 (d), 159.1 (s), 200.6 (s); HRMS: M^+, found 338.2449. $C_{20}H_{34}O_4$ requires 338.2457; MS 338 (M^+, 10), 320 (13), 277 (17), 219 (49), 218 (73),

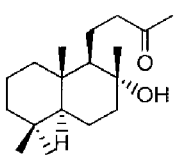
203 (12), 148 (14), 135 (100), 109 (18), 73 (17), 69 (18), 43 (22); Anal.: found C, 70.82; H, 10.12%. $C_{20}H_{34}O_4$ requires C, 70.97; H, 10.13%.



(+)-(2ζ,3*S*)-5-((1*R*,2*R*,4a*S*,8a*S*)-2-Hydroxy-2,5,5,8a-tetramethyldecahydro-1-naphthalenyl)-3-methyl-1,2,3-pentanetriol (375).

Compound **375** was isolated as a colourless oil in 25% yield.

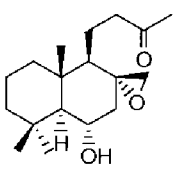
$[\alpha]_D$ +0.9 (*c* 1.5); IR (KBr) ν_{max} 3405, 2927, 2860, 1464, 1387, 1085 cm^{-1}; ^1H NMR δ 0.73-1.20 (5x s, 5x 3H), 1.26-1.98 (m, 18H), 3.31-3.77 (m, 5H); ^{13}C NMR δ 15.5 (q), 18.1 (t), 18.4 (t), 20.4 (t), 21.2 (q), 21.4 (q), 23.9 (q), 33.2 (s), 33.9 (q), 39.2 (s), 39.5 (t), 41.3 (t), 42.0 (t), 43.6 (t), 56.1 (d), 61.8 (d), 63.0 (t), 74.4 (s), 78.1 (d), 78.7 (s); HRMS: M^+, found 342.2764. $C_{20}H_{38}O_4$ requires 342.2770; MS *m/e* (%) 342 (M^+, 2), 324 (9), 306 (13), 245 (100), 177 (39), 137 (37), 109 (46), 95 (49), 81 (41), 69 (50), 43 (64).



(+)-4-((1*R*,2*R*,4a*S*,8a*S*)-2-Hydroxy-2,5,5,8a-tetramethyldecahydro-1-naphthalenyl)-2-butanone (281).

Methyl ketone **281** was isolated as a colourless oil in 6% yield. During its isolation this methyl ketone quickly cyclized to sclareol oxide (**269**).

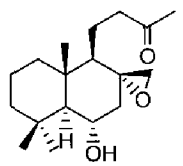
$[\alpha]_D$ +7.3 (*c* 1.3) (lit.[66]: +6.7, *c* 1.0); IR (liquid film) ν_{max} 3439, 2924, 2866, 1731, 1683, 1459, 1376, 1248, 1048 cm^{-1}; ^1H NMR δ 0.75 (s, 3H), 0.78 (s, 3H), 0.83 (s, 3H), 1.12 (s, 3H), 1.50-2.05 (m, 15H), 2.10 (s, 3H), 2.48-2.60 (m, 1H), 2.60-2.70 (m, 1H); MS *m/e* (%) 280 (M^+, 1), 262 (100), 191 (81), 177 (39), 123 (46), 109 (97), 95 (64), 43 (78).



(+)-(1*S*,4*S*,4a*S*,8a*R*)-4-(4-Hydroxy-octahydro-5,5,8a-trimethyl-spiro[naphtalene-2(1*H*),2'-oxiran]-yl)-2-butanone (400).

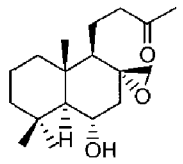
A mixture of methyl ketone **206** (0.10 g; 0.360 mmol), *m*-CPBA (0.265 g; 1.08 mmol) and Na_2CO_3 (0.076 g; 0.72 mmol) in CH_2Cl_2 (15 mL) was stirred at room temperature for 3 h. A 2% aqueous $Na_2S_2O_3$ solution was added and the mixture was extracted with ethyl acetate, washed with saturated aqueous sodium bicarbonate, brine, dried and evaporated. Flash column chromatography (eluent PE/EA 1:1) gave epoxide **400** (0.0919 g; 0.313 mmol; 87%) as a colourless oil.

$[\alpha]_D$ +19.1 (*c* 0.4); IR (liquid film) ν_{max} 3479, 2928, 2870, 1714, 1462, 1386, 1362 cm^{-1}; ^1H NMR δ 0.81 (s, 3H), 0.97 (s, 3H), 1.15 (s, 3H), 1.04-2.02 (m, 15H), 2.07 (s, 3H), 2.48-2.55 (m, 1H), 2.80 (dd, *J* = 1.9, 4.3 Hz, 1H), 3.98 (td, *J* = 4.5, 10.9 Hz, 1H); ^{13}C NMR δ 15.8 (q), 16.0 (t), 18.3 (t), 22.2 (q), 29.9 (q), 33.7 (s), 36.5 (q), 39.1 (t), 40.1 (s), 43.5 (t), 47.0 (t), 51.0 (t), 52.2 (d), 57.8 (s), 60.0 (d), 69.6 (d), 75.7 (t), 209.2 (s); HRMS: M^+, found 294.2200. $C_{18}H_{30}O_3$ requires 294.2195; MS *m/e* (%) 294 (M^+, 6), 234 (44), 206 (61), 153 (32), 109 (81), 95 (48), 81 (45), 69 (67), 43 (100).



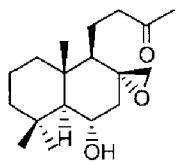
(+)-(1*S*,4*S*,4a*S*,8a*R*)-4-(4-Hydroxy-octahydro-5,5,8a-trimethyl-spiro[naphtalene-2(1*H*),2'-oxiran]-yl)-2-butanone (400).

To a stirred solution of methyl ketone **206** (0.277 g; 0.814 mmol) in CH_2Cl_2 (4 mL), acetone (4 mL), H_2O (7 mL), [18]crown-6 (0.03 g) and sodium hydrogen carbonate (1.00 g) was added a solution of oxone (0.70 g; 1.22 mmol) in H_2O (4 mL) at 0°C. After stirring at 0°C for 3 h the mixture was diluted with a saturated aqueous sodium hydrogen carbonate solution. The aqueous mixture was extracted with ethyl acetate and the combined organic layers were washed with a 10% aqueous solution of $Na_2S_2O_3$, saturated aqueous sodium bicarbonate and brine. Usual work up gave a crude oil which was purified by flash column chromatography (eluent PE/EA 1:1) to give the epoxide **400** (0.190 g; 0.645 mmol; 79%) as a white crystalline solid. Spectral data were identical with the above mentioned.



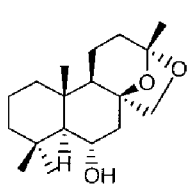
(+)-(1*S*,4*S*,4a*S*,8a*R*)-4-(4-Hydroxy-octahydro-5,5,8a-trimethyl-spiro[naphtalene-2(1*H*),2'-oxiran]-yl)-2-butanone (400).

To an ice-cooled stirred solution of epoxide **184** (0.097 g; 0.301 mmol) and benzyltrietylammonium chloride (0.206 g; 0.905 mmol) in acetone (10 mL) was added solid $KMnO_4$ (0.143 g; 0.905 mmol) at once. The mixture was allowed to warm to room temperature and stirring was continued untill completion of the reaction. The dark brown reaction mixture was treated with an aqueous saturated Na_2SO_3 solution and with a 3% aqueous solution of oxalic acid. Extraction of the now colourless reaction mixture with ethyl acetate was followed by usual work-up. Purification by flash column chromatography (eluent PE/EA 1:1) gave first epoxy ketone **400** (0.039 g; 0.132 mmol; 44%) as a white crystalline solid with the same spectral data as the epoxide obtained before. Further elution gave a mixture of **401** and **343** (0.038 g; 0.129 mmol; 40%).



(+)-(1*S*,4*S*,4a*S*,8a*R*)-4-(4-Hydroxy-octahydro-5,5,8a-trimethyl-spiro[naphtalene-2(1*H*),2'-oxiran]-yl)-2-butanone (400).

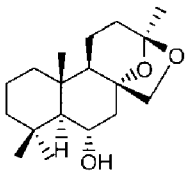
A stirred solution of epoxide **184** (0.110 g; 0.344 mmol) in a mixture of ethyl acetate (30 mL) and pyridine (1 mL) was purged through with ozone at -40°C during 4 h until most of the starting material has disappeared. The excess ozone was expelled and the mixture was allowed to warm up to room temperature. Water was added and the mixture was extracted with ethyl acetate. The combined organic layers were washed with a 10% aqueous solution of $CuSO_4$, brine, dried and evaporated. The residue was purified by flash column chromatography (eluent PE/EA 1:1) to yield epoxy ketone **400** (0.040 g; 0.136 mmol; 40%) as a crystalline solid and **401** (0.015 g; 0.0509 mmol; 15%) also as a solid. Compound **400** was obtained with analytical data as mentioned before.



(+)-(3*S*,4*S*,9*S*,10*R*,11*S*)-5,5,9,13-Tetramethyl-14,16-dioxatetracyclo-[11.2.1.$0^{1,10}$.$0^{4,9}$]-hexadecan-3-ol (401).

A mixture of **400** (0.109 g; 0.370 mmol) and a catalytic amount of PPTS (0.0125 g; 0.050 mmol) in dry benzene (5 mL) was stirred at room temperature for 4 h. Ether was added and the mixture was washed with a saturated aqueous sodium bicarbonate solution and brine, dried and evaporated. Flash column chromatography (eluent PE/EA 6:1) gave acetal **401** (0.0766 g; 0.260 mmol; 70%) as a crystalline solid.

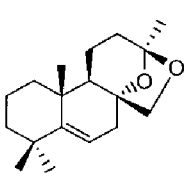
M.p. 126-128°C; $[\alpha]_D$ +17.1 (*c* 1.0); IR (KBr) ν_{max} 3457, 2985, 2923, 2849, 1460, 1385, 1030, 867 cm^{-1}; ^1H NMR δ 1.09 (s, 3H), 1.14 (s, 3H), 1.18 (s, 3H), 1.45 (s, 3H), 0.91-1.85 (m, 14H), 2.10 (dd, *J* = 4.3, 13.4 Hz, 1H), 3.38 (d, *J* = 6.8 Hz, 1H), 3.81 (d, *J* = 6.8 Hz, 1H), 4.19 (dt, *J* = 4.3, 11.0 Hz, 1H); ^{13}C NMR δ 16.9 (t), 17.8 (q), 18.3 (t), 22.5 (q), 24.9 (q), 33.6 (s), 33.6 (t), 37.2 (q), 40.3 (t), 40.4 (s), 43.9 (t), 45.6 (t), 49.6 (d), 59.8 (d), 68.2 (d), 75.8 (t), 82.4 (s), 108.6 (s); HRMS: M^+, found 294.2198. $C_{18}H_{30}O_3$ requires 294.2195; MS *m/e* (%) 294 (M^+, 11), 234 (71), 206 (100), 191 (33), 188 (44), 173 (30), 109 (35), 95 (28), 69 (36), 43 (45); Anal.: found C, 73.52; H, 10.40%. $C_{18}H_{30}O_3$ requires C, 73.43; H, 10.27%.



(+)-(3*S*,4*S*,9*S*,10*R*,11*R*)-5,5,9,13-Tetramethyl-14,16-dioxatetracyclo-[11.2.1.$0^{1,10}$.$0^{4,9}$]-hexadecan-3-ol (343).

To a solution of methyl ketone **206** (0.099 g; 0.358 mmol) in *t*BuOH (5 mL), H_2O (5 mL) and pyridine (0.1 mL; 1.25 mmol) was added trimethylamine N-oxide (0.0352 g; 0.459 mmol) and OsO_4 (0.4 mL of a 2.5 wt% solution in *t*BuOH; 0.0398 mmol). This reaction mixture was stirred at reflux temperature for 6 h. After cooling to room temperature the mixture was extracted with ethyl acetate. The organic solutions were washed with brine, dried and evaporated. The crude oil was purified by flash column chromatography (eluent PE/EA 1:1) to give **343** (0.0903 g; 0.307 mmol; 86%) as a crystalline solid.

M.p. 137-138°C; $[\alpha]_D$ +46.7 (*c* 1.14); IR (KBr) ν_{max} 3477, 2929, 1440, 1386, 1348, 1193, 1155, 1026, 936, 875, 850 cm^{-1}; ^1H NMR δ 0.87 (s, 3H), 1.01 (s, 3H), 1.16 (s, 3H), 1.40 (s, 3H), 0.89-2.04 (m, 14H), 2.14 (dd, *J* = 4.2, 12.3 Hz, 1H), 3.42 (dd, *J* = 1.0, 7.2 Hz, 1H), 3.80 (dt, *J* = 4.2, 11.6 Jz, 1H), 4.28 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR δ 15.7 (q), 17.6 (t), 18.0 (t), 22.1 (q), 24.0 (q), 33.4 (s), 35.8 (t), 36.8 (q), 37.8 (s), 38.7 (t), 43.8 (t), 46.4 (t), 52.7 (d), 60.7 (d), 68.6 (d), 73.3 (t), 81.9 (s), 106.1 (s); HRMS: M^+, found 294.2196. $C_{18}H_{30}O_3$ requires 294.2195; MS *m/e* (%) 294 (M^+, 20), 234 (69), 206 (100), 191 (27), 188 (34), 153 (27), 137 (22), 109 (31), 95 (22), 69 (26), 43 (26); Anal.: found C, 73.17; H, 10.27%. $C_{18}H_{30}O_3$ requires C, 73.43; H, 10.27%.



(-)-(9*S*,10*R*,11*R*)-5,5,9,13-Tetramethyl-14,16-dioxatetracyclo[11.2.1.$0^{1,10}$.$0^{4,9}$]-hexadec-3-ene (389).

To a solution of **343** (0.095 g; 0.323 mmol) in dry benzene (15 mL) was added *p*TsOH (0.0875 g; 0.460 mmol). The mixture was heated at reflux temperature in a

Dean Stark apparatus. After 6 h the mixture was cooled to room temperature and washed with saturated aqueous $NaHCO_3$, brine, dried and evaporated. The residual oil was purified by flash column chromatography (eluent PE/EA 15:1) to give **389** (0.0383 g; 0.139 mmol; 43%) as colourless crystals.

M.p. 68-70°C; $[\alpha]_D$ -46.5 (*c* 0.7); IR (KBr) ν_{max} 2922, 1688, 1464, 1394, 1210, 1104, 866 cm^{-1}; ^1H NMR δ 1.02 (s, 9H), 1.36 (s, 3H), 0.81-1.73 (m, 11H), 2.23 (dd, *J* = 3.7, 19.4 Hz, 1H), 2.55 (dd, *J* = 4.3, 19.4 Hz, 1H), 3.33 (d, *J* = 7.3 Hz, 1H), 4.34 (d, *J* = 7.3 Hz, 1H), 5.35 (t, *J* = 4.0 Hz, 1H); ^{13}C NMR δ 17.9 (t), 21.1 (q), 24.2 (q), 29.7 (t), 30.6 (q), 32.6 (q), 33.9 (t), 35.5 (s), 35.8 (t), 37.3 (s), 38.6 (t), 40.7 (t), 49.8 (d), 74.4 (t), 81.0 (s), 106.5 (s), 115.8 (d), 150.8 (s); HRMS: M^+, found 276.2087. $C_{18}H_{28}O_2$ requires 276.2098; MS *m/e* (%) 276 (M^+, 51), 201 (65), 188 (44), 187 (100), 173 (89), 145 (61), 131 (56), 119 (42), 118 (66), 43 (48); Anal.: found C, 75.14; H, 9.42%. $C_{18}H_{28}O_2$ requires C, 78.21; H, 10.21%.

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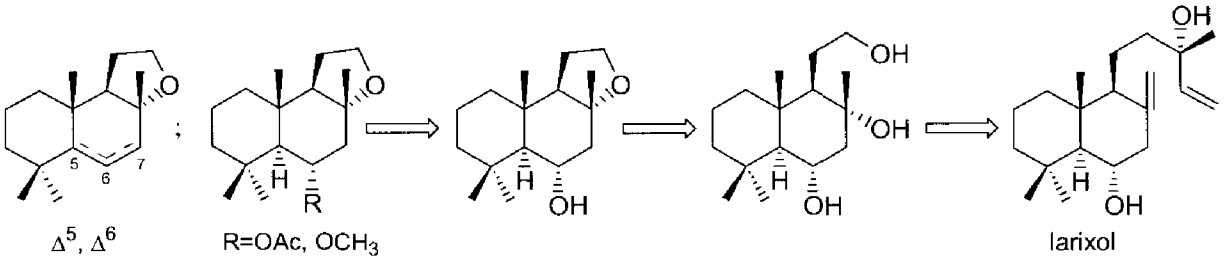
Chapter 4

The synthesis of Ambrox-like compounds

Abstract

The oxidation of the (3-hydroxy-3-methyl-4-pentenyl)-side chain at C(9) of some labdanic diterpenoids with potassium permanganate afforded ketones or cyclic enol ethers as the main reaction products, depending on the substituent at C(8). Further degradation of the methyl ketones by the Baeyer-Villiger reaction and modification of the exocyclic 8(17) double bond was troublesome but led to intermediates, which have been transformed into Ambrox-like compounds. Better results were obtained when first the exocyclic 8(17) double bond was converted into a methyl and hydroxyl group at C(8), followed by oxidation of the side chain. Synthetic routes using $OsO_4/NaIO_4$ or palladium catalyzed elimination or isomerization of allylic acetates, followed by ozonolysis have been developed for this purpose.

*Products from both routes have been cyclized to 6α-hydroxy Ambrox (**451**). This compound was used as the key intermediate for the synthesis of several other Ambrox-like compounds of which some showed pleasant odour properties.*



Δ^5, Δ^6 R=OAc, OCH_3

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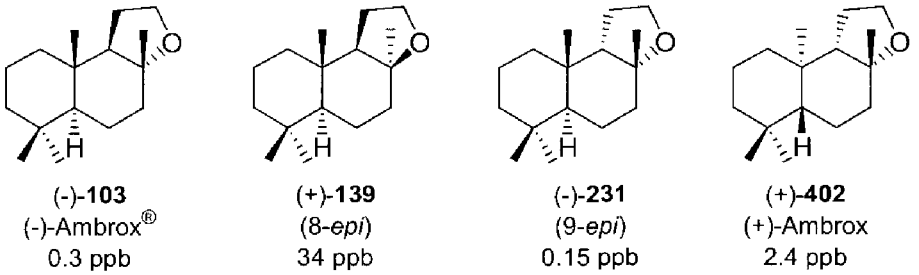
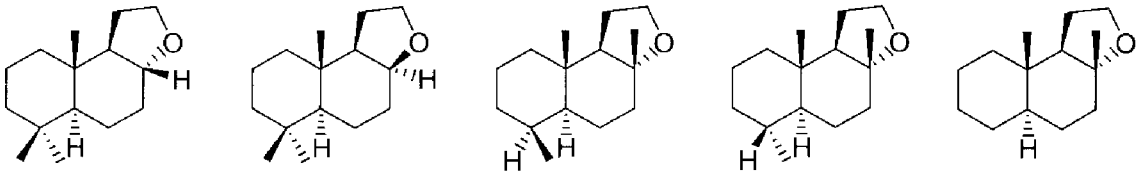
4.1 Introduction

The commercial importance of ambergris and products derived there off, have greatly stimulated the search for new compounds with ambergris-like odours, with the aim of being either cheaper or possessing additional odour properties.[1] In this search for ambery compounds diastereomers,[2a] enantiomers,[2a] *nor*-compounds,[2b] 5β-isomers[2b], ring-opened analogues[2c], substituted analogues, unsaturated analogues, homologues and lactones of (-)-Ambrox® (**103**) have been prepared. (-)-Ambrox® (**103**) has an odour treshold of 0.3 ppb. The stereoisomer (-)-9-*epi*-Ambrox® (-)-**231** is even more powerful than Ambrox® itself, although only by a factor of two (Figure 4.1). Of the distinct odours of varying quality and strength uncovered to the present, (-)-9-*epi*-Ambrox has been found to possess the strongest scent and lowest threshold concentration (0.15 ppb) of all. The enantiomer (+)-**402** is about 10 times weaker (2.4 ppb), and the 8-*epi*-isomer (+)-**139** (also called *iso*-Ambrox) even 100 times weaker (34 ppb). The racemate (±)-**103** is only slightly weaker than (-)-**103** with a treshold of 0.5 ppb, and its odour is very similar to that of (-)-**103**. The amber fragrance of the diastereomeric (±)-ethers **231** and **402** seems to be less intense that that of Ambrox® (**103**) and *iso*-Ambrox (**139**). Although (-)-9-*epi*-Ambrox (**231**) has been found to possess the strongest scent and lowest threshold concentration (0.15 ppb) of all, this compound hardly has got any synthetic attention.[3]

Figure 4.1



(-)-**103** (-)-Ambrox® 0.3 ppb | (+)-**139** (8-*epi*) 34 ppb | (-)-**231** (9-*epi*) 0.15 ppb | (+)-**402** (+)-Ambrox 2.4 ppb



403 | **404** | **405** | **406** | **407**

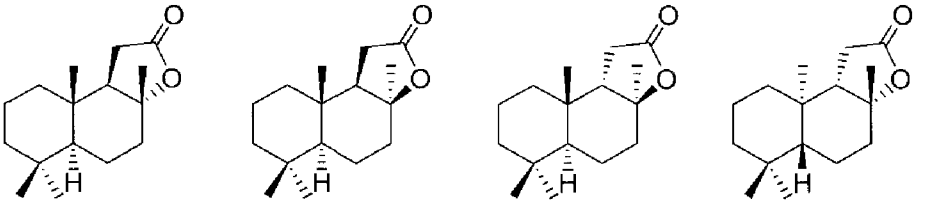
With the discovery that Ambrox® can be obtained by oxidative degradation of sclareol (**4**), a breakthrough was achieved in the commercial production of tricyclic amber odorants of woody nature. The release of ambergris scent is strongly related to structural elements of the labdane skeleton, Ambrox® (**103**) being the typical example. To assess the significance of the geminal CH_3 groups at C(4) for the specific ambergris odour sensation the diastereomeric tricyclic ethers **103**, **139**, **231** and **402** and the *nor*-ethers **405** and **406** and the 18,19-dinor-ether **407** were synthesized

(Figure 4.1). When it was established that the amber-like odour of the enol ether **269** was retained in its hydrogenation product, ambra oxide **149**, the search for structurally similar ambergris type odorants started (Figure 4.3). In Figure 4.4 and 4.5 some substituted 5- and 6-ring ethers and carboxylic analogues are presented. Some oxidized analogues are given in Figure 4.6.

The loss of a methyl group, as in the tricyclic ethers **403** and **404**, not only modifies the odour impression but is also accompanied by a 10-fold reduction in odour intensity, whereby ether **404** was considerably stronger than its diasteromer **403**. The 18-*nor*-derivateve (±)-4α-desmethyl ambrox (**405**) (1.4 ppb) shows only a small qualitative deviation when compared to Ambrox®, it is said to have an amber note whose odour quality and intensity resembles that of Ambrox®, with a side-note of Tonkin Musk.[4] The Ambrox note is still perceptible in the 19-*nor*-diastereomer **406** (3 ppb), although less pronounced than in the 18-*nor*-derivative. The woody character of Ambrox® in the 18,19-dinor ether **407** has not completely disappeared, although it is masked, in the beginning, by a relatively complex odour. Compound **407** (2.4 ppb) is dominated by a strong earthy odor reminiscent of a freshly plowed field.

Sclareolide (**136**) and *iso*-sclareolide (**137**), described as odourless crystalline compounds,[5] display a weak but still fine amber odour with a woody-resinous undertone in dilute alcoholic solutions according to Ohloff and Giersch (unpublished results),[1] as do their diastereomers **408** and **409** (Figure 4.2).

Figure 4.2



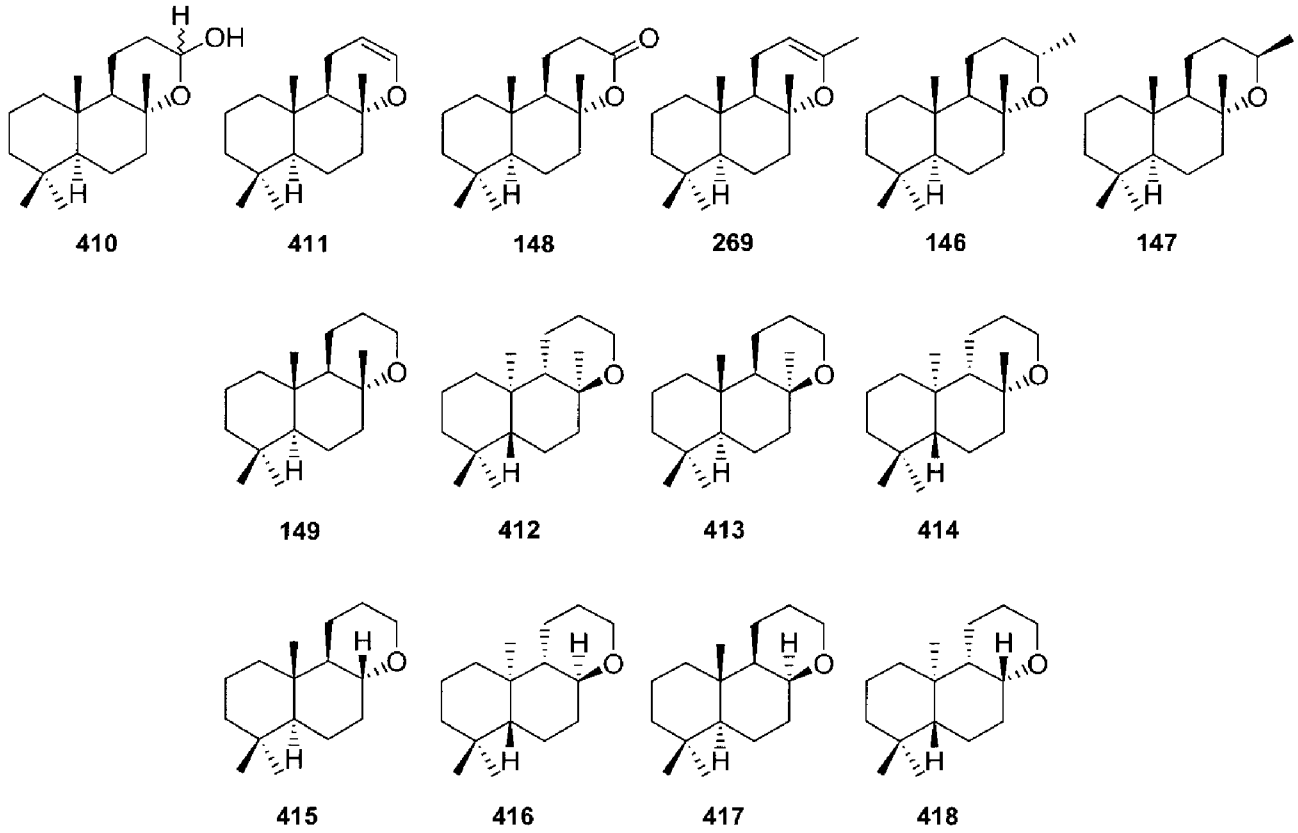
136 **137** **408** **409**

The tricyclic (-)-hemiacetal **410**,[6] also known as ambreinolal and enol ether **411**[7] are found in the volatile fraction of ambergris (Figure 4.3). Enol ether **411** is one of the compounds which appears to be responsible for the odour of ambergris. The lactone (+)-ambreinolide (**148**) is odourless.[1,8] The hemiacetal **410** is converted to (-)-enol ether **411** by heating under reduced pressure.[9] The tricyclic tetrahydropyranyl ether **149** of defined stereochemistry is conveniently obtained by hydrogenation of **411** and also by a two-step transformation of ambreinolide **148**.[6a,8,10] The amber-like odour is retained in ambra oxide **149**. Sclareol oxide **269**, an odourless enol ether, is converted by catalytic hydrogenation into two diastereomeric tetrahydropyranyl ethers **146** and **147**, of which only compound **147** possesses an amber odour.[11]

In the synthesized compounds **149**, **412** - **418**, pronounced ambergris-like odours were strongest in **149**, followed by the ethers **415** and **417**. In contrast, compound **413** was practically

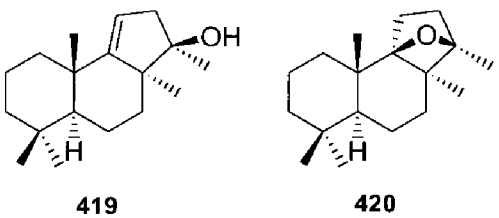
odourless.[12] The enantiomer **415**, on the other hand, has relatively strong odour which can only to a limited extent be associated with an ambergris-type odour. The enantiomers **413** and **414** are one of the first recorded examples of optical antipodes in which only one isomer possesses olfactory properties.

Figure 4.3



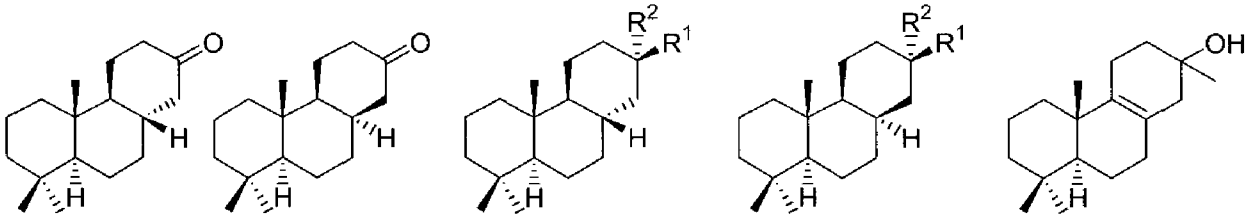
Alcohol **419** posseses also a strong amber odour and also the tetracyclic ether **420** is a relatively strong odorant of the amber type (Figure 4.4).[12]

Figure 4.4



While ketone **421** still possesses a woody amber-like odour, though of relatively low intensity, its diastereoisomer **422** is rated as practically odourless (Figure 4.5). The four secondary alcohols **423/424** and **427/428** are also without odour. The sensory properties return with the methyl-substituted alcohols **425/426** and **429/430**, although the woody odour of **425** and **426** is extremely weak. The same tonality is detected in the alcohol **430** with a grapefruit-like subnote. The tertiary alcohol **429** has an exceptionally strong amber odour. Alcohol **431** is odourless.

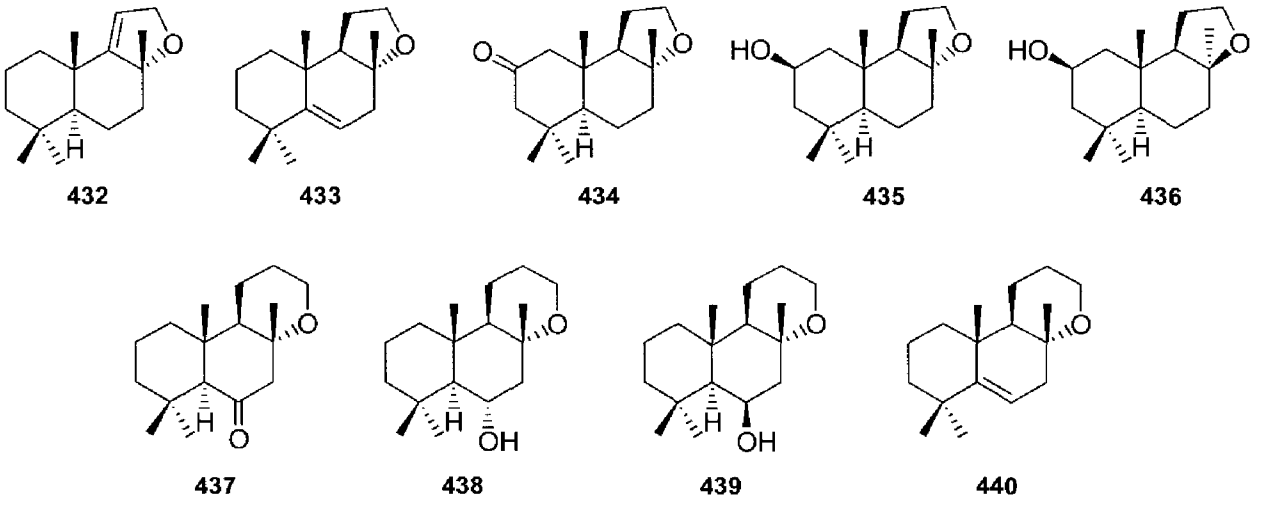
Figure 4.5



421 **422** **423**: R^1=OH, R^2=H; **424**: R^1=H, R^2=OH; **425**: R^1=OH, R^2=CH_3; **426**: R^1=CH_3, R^2=OH; **427**: R^1=OH, R^2=H; **428**: R^1=H, R^2=OH; **429**: R^1=OH, R^2=CH_3; **430**: R^1=CH_3, R^2=OH; **431**

The fragrance of dehydro-Ambrox **432** has a woody-ambery character (Figure 4.6). Compound **433** exhales a powerfull woody and ambery smell, more woody than Ambrox® (**103**) and less ambery-animale, a note which appears to be also more long-lasting than Ambrox®, especially on linen.[13]

Figure 4.6



432 **433** **434** **435** **436**

437 **438** **439** **440**

The tetra*nor*-labdanyl ethers **434** - **436**, substituted in the 2-position by oxygen, belong to the same odour type as the unsubstituted derivatives Ambrox® (**103**) and *iso*-Ambrox (**139**), although weaker and somewhat sweeter.[14] The derivatives oxidized at C(6), **437** - **439**, were odourless.[15] On going from the saturated ether **149** to the dehydrogenated compound **440** a loss in intensity with unchanged tonality is observed.[15]

4.2 Structure activity relationship studies of ambergris fragrance compounds

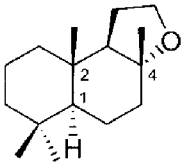
Ambrox® (**103**) is not an easy target for the synthetic organic chemist. Consequently, a considerable amount of research work has been carried out on structure/activity relationships

(SAR) in this odour area, with the aim to find easier accessible compounds which could be produced more cheaply.[16] The approach based on *molecular similarity* among compounds of the same odour note is of practical use in the search for more efficient and attractive odorants. By analogy with the term *pharmacophore*, the terms *olfactophore* and *osmophore* have been coined for a set of structural features responsible for a defined odour-type sensation, to design the (most) polar part of odoriferous compounds, which is probably responsible for the strongest interactions with their receptors. The acquisition of reliable structure-odour relationship (SOR) data is the first and indispensable step in the *olfactophore* search. The selection of useful information from the chemical and perfumery literature is not easy because of the lack of unity in perfumers language, insufficient statistical significance of most of the published data and scarcity of results obtained with olfactorily pure single stereoisomers or their mixtures of known ratio and configuration. The complex problem of the efficient measurement of the odour quantity[17] and quality[18] makes it even more difficult.

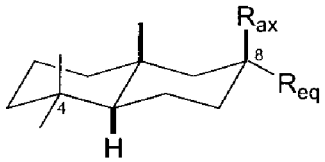
Pioneering work on amber SAR was done by Ohloff.[19] After studying a range of analogues of natural ambergris components, he concluded that, for a compound to possess an amber odour, it must have a molecular structure containing a decalin ring system with three axial groups, these groups should be located at positions 1, 2 and 4 relative to each other (Figure 4.7). The substituents in the 1- and 2-positons can be hydrogen, since their main function is to ensure the *trans*-configuration of the decalin ring system. These structural demands have been defined as the 'triaxial rule' in the olfactory recognition process. The stereochemistry of the CH_3 groups at C(8) and C(10) in Ambrox® plays an important role in the hydrophobic interaction with the hypothetical receptor site.[19]

The conclusion of this investigation is that odour qualities similar to those of ambergris are generated by compounds having a strictly determined stereochemistry.[20,21] The position of the oxygen function within the triaxial system has some influence on the odour sensation. On the other hand, the surroundings of the centre triggering the odour, as well as the chemical nature of the oxygen substituent seems to be of minor importance.

Figure 4.7



103



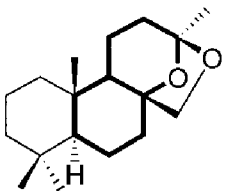
The triaxial rule has been studied in detail by Winter,[22,23] Näf[24] and Bruns.[25] Winter and Näf both state that there are compounds which satisfy Ohloff's rule but do not possess an amber odour. However, Näf does state categorically that, 'today, there are no ambergris odorants known which do not obey these broad structural limits'. They therefore conclude that the rule is not

complete and that additional criteria must be sought. Winter's work is directed towards identifying possible hydrogen-bond interactions and Näf has demonstrated that subtle changes in the molecular structure, even at sites remote from the osmophoric group, can have a profound effect on the odour. Bruns has considered the application of Ohloff's rule to Ambraketal (**381**) (Jeger's ketal) and has shown that, for that molecule, it is more meaningful to apply it to the oxadecalin system rather than the decalin system (Figure 4.8). He also notes that the rule is incomplete, as some materials which obey it have little or no amber character.

As part of her work, Winter synthesized a number of Ambrox analogues in which the furanoid ring of structure **103** is missing.[22] The distribution of groups around the remaining decalin system, however, demonstrated that the materials still obeyed Ohloff's rule.

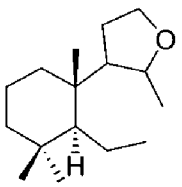
The steric accessibility (SA) of the *osmophoric* oxygen of the analogues of Ambrox® was calculated using a probe radius of 1.4Å.[23] The lower limit of the measured van der Waals surface, critical for the amber odour, was found to be 5-6Å^2. This structural feature was used as a supplementary criterion in another study based on the so-called electron-topological (ET) approach.[26,27] Two molecular fragments found indispensable for the amber odour, *e.g.* (a) O bond to a quaternary C-atom and 4 carbons (C(1), C(4), C(5), and C(6)) (b) 2 methyl groups attached to a quaternary C-atom (methyl groups at C(4) and at C(10)), correspond to two electron-topological matrices of contiguity (ETMC). These are built using effective charges as diagonal elements, and Wiberg indices for bonded as well as optimized distances for unbonded atoms. The authors report an astonishingly high degree of 95% of prediction.

Figure 4.8



381

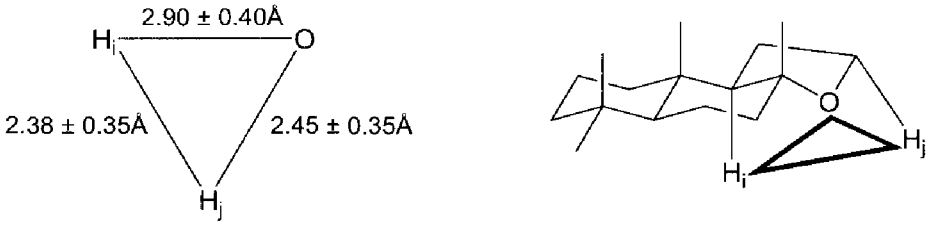
Figure 4.9



441

Vlad and co-workers prepared and analogue **441** in which the carbocyclic ring is broken (Figure 4.9).[28] This material cannot obey Ohloff's rule, but it is claimed that **441** has an amber odour.

Figure 4.10



Shortly after patenting their discovery of cyclohexyltetrahydrofuran **441**, Vlad's group published an alternative rule governing the relationship between chemical structure and amber odour.[29,30] They claim that ambergris odorants all possess a triangular arrangement of atoms, one being oxygen and the other two hydrogen, which interact electronically with the postulated amber receptor. The layout of this 'amber triangle' is shown in Figure 4.10.

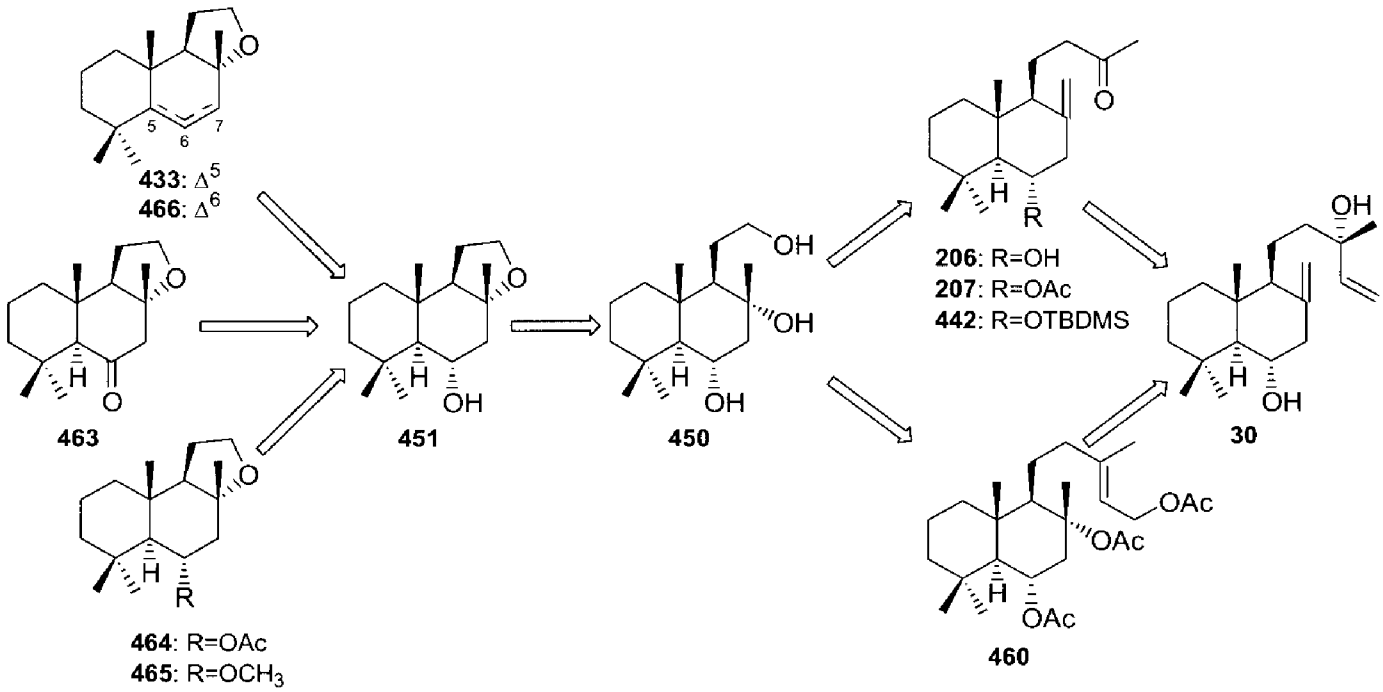
There are several criteria which should be applied to these atoms in addition to the spatial ones. The three atoms must make a major contribution to the LUMO of the molecule, or to an unoccupied orbital lying close to the LUMO. The history and current state of SOR research has been exhaustively reviewed.[31]

4.3 Synthesis of Ambrox-like compounds starting from larixol

The synthesis of (-)-Ambrox® (**103**) and other flavour compounds from (-)-sclareol (**4**) has been studied extensively.[32] Larixol (**30**) and larixyl acetate (**31**) are also easily available from Nature,[33] but have been used to a much lesser extent as starting materials in synthesis.

However, oxidation of the C(9) side chain of these labdanes also may provide suitable synthons for the synthesis of Ambrox-like compounds.[34] In Chapter 3 the degradation of the side chain oxidation of labdanes, *e.g.* larixol (**30**) using solid potassium permanganate was investigated, aiming at an optimum yield for methyl ketones.

Scheme 4.1



An obvious way to achieve further breakdown of methyl ketones into a functionalized two carbon moiety is the Baeyer-Villiger oxidation and this reaction was investigated for methyl ketone

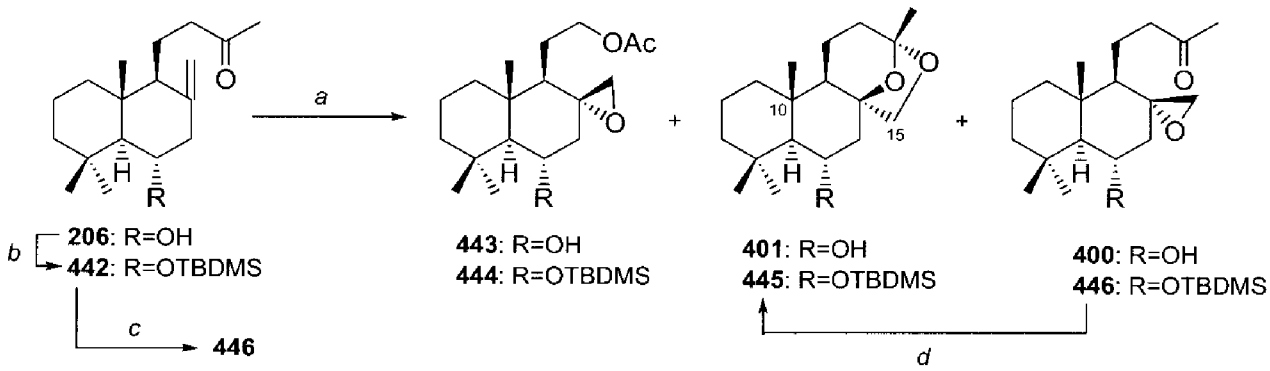
206 and for its C(6) acetate **207** and *tert*-butyldimethylsilyl (TBDMS) ether **442**. Pd catalized isomerization or elimination, followed by ozonolysis can provide for a short route to break down the side chain in labdanes as well. Both routes lead to intermediates like **450**, which are suitable for cyclization to 6α-hydroxy Ambrox (**451**). The exocyclic 8(17) methylene group has to be modified to enable the construction of the cyclic ether that is characteristic for Ambrox-type molecules. 6α-Hydroxy-Ambrox (**451**) can be considered as a key intermediate in the syntheses of other Ambrox-like compounds as depicted in Scheme 4.1.

4.4 Oxidation of the side chain with the Bayer-Villiger reaction

The side chain of larixol (**30**) was oxidized with potassium permanganate to compound **206** as described before in Chapter 3.[34] An obvious way to achieve further breakdown of methyl ketone **206** into a functionalized two carbon moiety is the Baeyer-Villiger oxidation and this reaction was investigated for **206** and for two C(6) derivatives, *viz* the *tert*-butyldimethylsilyloxy (TBDMS) ether **442** and the acetate **207**.

It is known that methyl ketones give acetate esters upon Baeyer-Villiger oxidation resulting from migration of the larger group.[35] However, under the conditions of the Baeyer-Villiger oxidation double bonds can be epoxidized as well. When methyl ketone **206** was treated with 10 equivalents of *meta*-chloroperbenzoic acid (*m*-CPBA) during 10 days acetal **401** was obtained in 50% yield and the expected epoxy acetate **443** was formed in only 35% yield. Treatment of **206** with just 2 equivalents of *m*-CPBA again gave rise to **443** and **401** in 30% and 40% yield respectively and epoxide **400** was now found as a minor byproduct (12%) (Scheme 4.2).

Scheme 4.2



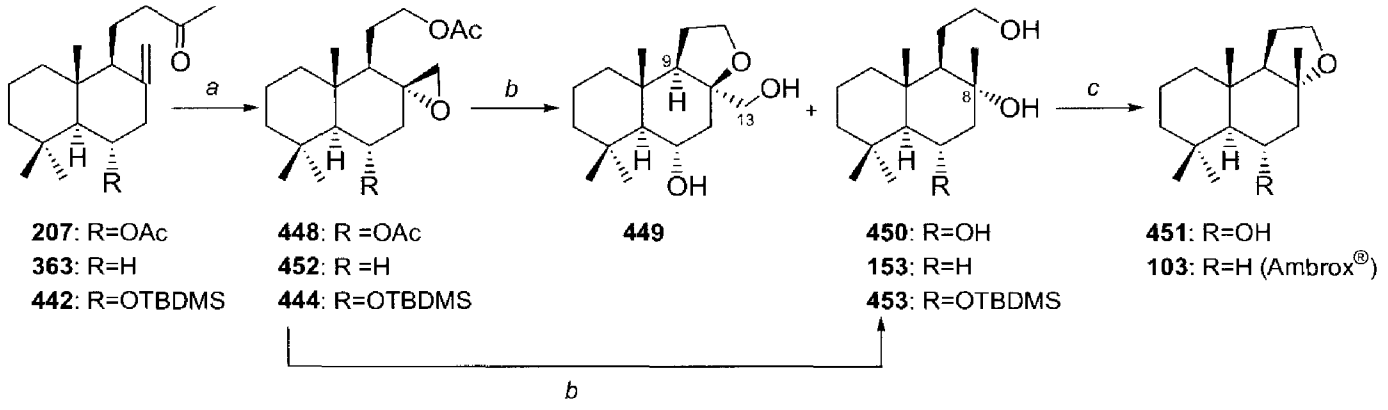
Reagents and conditions: (*a*) *for R=OH: m*-CPBA (2 eq.), CH_2Cl_2, 83%, **443**:**401**:**400**=3:4:1; *for R=OTBDMS: m*-CPBA (2.5 eq.), CH_2Cl_2, 85%, **444**:**445**:**446**=2:2:5; (*b*) TBDMSiCl, DMF, imidazole, 60°C, 87%; (*c*) MMPP, CH_2Cl_2, 60%; (*d*) spontaneously upon standing.

The structure of compound **401** was elucidated by $^1H,^1H$-NOESY-NMR and $^1H,^1H$-COSY-NMR, whereby no nOe is observed between H(15) and the protons of the C(10)-methyl group.

Apparently epoxidation of the double bond is faster than the Baeyer-Villiger oxidation of the methyl ketone and a subsequent acid catalyzed reaction of the carbonyl group with the epoxide than gives the acetal **401**. Baeyer-Villiger oxidation of the TBDMS protected compound **442** with *m*-CPBA gave again a mixture, with the desired epoxy acetate **444** as the minor product. Epoxide **446** was obtained in almost 80% yield as the major product after flash column chromatography, as was established by ^{1}H NMR. However already during the ^{13}C NMR identification of **446** in $CDCl_3$, acetal **445** was formed and upon standing a conversion of **446** into **445** was also observed.

In an attempt to obtain **444** in a better yield the oxidation was also carried out with magnesium monoperoxyphthalate hexahydrate[36] (MMPP) instead of *m*-CPBA, but this reagent epoxidized only the exocyclic double bond to give compound **446**, and left the methyl ketone unaffected. On the other hand when acetate **207** was treated with *m*-CPBA compound **448** was obtained in a good yield of 84% together with 11% of compound **447**, in which only the exocyclic double bond is epoxidized (Scheme 4.3).

Scheme 4.3



Reagents and conditions: (*a*) *for R=OAc: m*-CPBA, CH_2Cl_2, 84%; *for R=H:* see literature data[31]; (*b*) *for R=OH, OAc:* $LiAlH_4$, THF, 0°C to rt, 95%, **450**:**449**=1:8.5; *for R=OTBDMS:* $LiAlH_4$, THF, 0°C to rt, 62%; *for R=H:* see literature data[31]; (*c*) *for R=OH: p*-TsOH, CH_3NO_2, 64%.

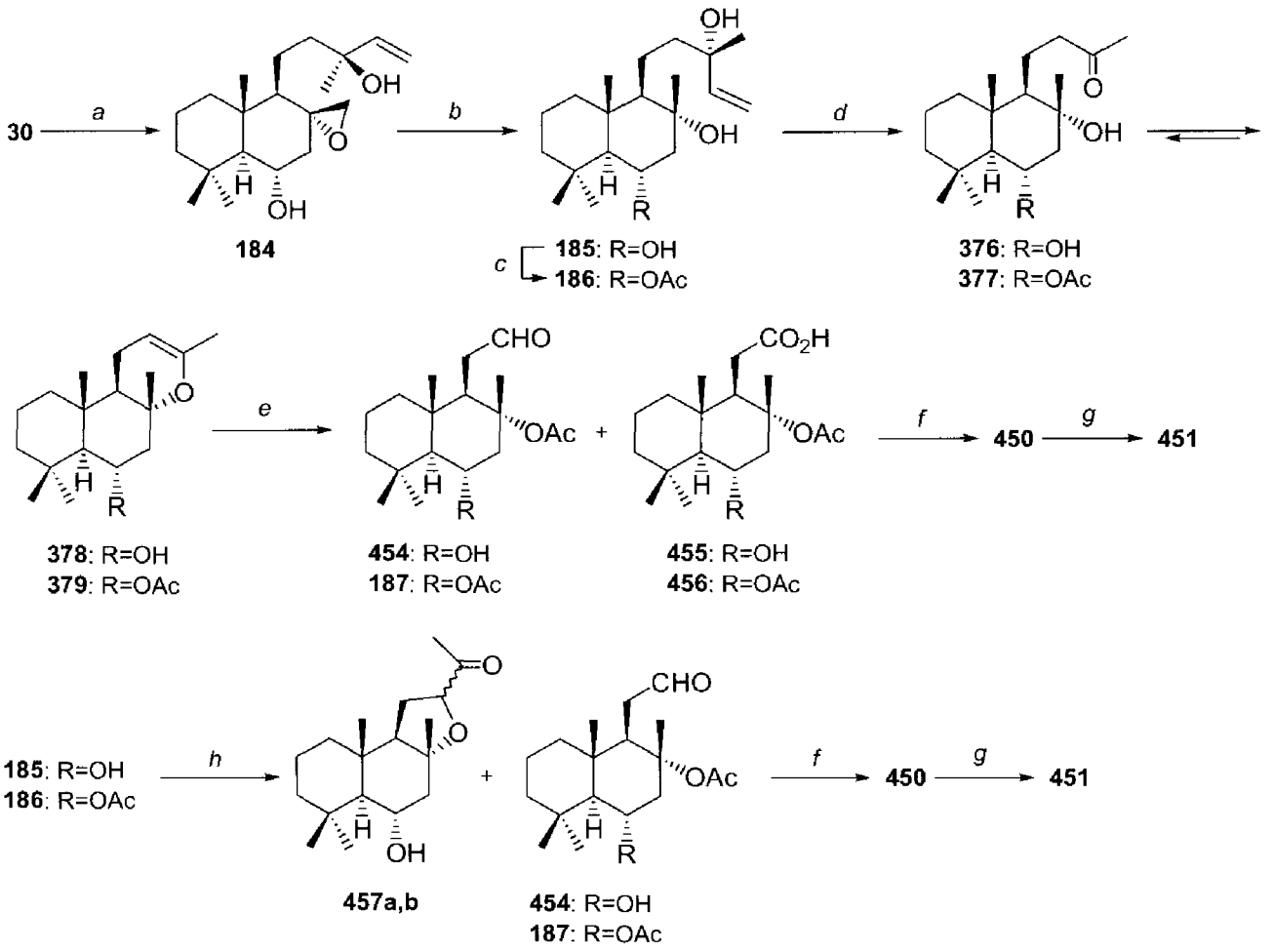
The epoxy acetates **443**, **444**, and **448** were treated with lithium aluminum hydride ($LiAlH_4$) with the aim to introduce the desired tertiary hydroxyl group at C(8), and to reduce the acetates to hydroxyl groups as well. However, the reduction of the epoxy acetates **443** and **448** both gave the cyclic ether **449** as main product and the desired triol **450** only as the minor component. Obviously the acetate group in the side chain was reduced first, and then the formed alkoxide attacked the epoxide to give the cyclic ether **449**. Its configuration was determined by $^{1}H,^{1}H$-NOESY-NMR, whereby a clear nOe was observed between H(13) and H(9). Reduction of epoxy acetate **444** gave **453** as the sole product in a reasonable 62% yield. Cyclization of **450** was achieved by stirring in nitromethane in the presence of *para*-toluenesulfonic acid (*p*-TsOH) and gave **451** in 64% yield.

When the results depicted in Schemes 4.2 and 4.3 are compared with each other and with a similar reaction sequence of methyl ketone **363**, derived from manool, it can be concluded that the C(6) substituent in larixol (**30**) and its derivatives has a definitive but rather unpredictable influence on the course and yields of the reactions involved. Treatment of methyl ketone **363** with two equivalents of *m*-CPBA effected a clean conversion into the epoxy acetate **452** by successive epoxidation and Baeyer-Villiger reaction. Reduction of this epoxy acetate with $LiAlH_4$ afforded the diol **153** in 72% yield.[37] The related compounds **206** and **442** gave mixtures in the Baeyer-Villiger reaction but the same reaction with acetate **207** gave a high yield of the desired epoxy diacetate **448**. However, the reduction of epoxide **448** proceeded in the wrong way and gave the desired triol **450** in only 10% yield. Although incidental transformations proceeded in good yield, no overall high yield conversion of **206** into the key intermediate **451** could be achieved and therefore other routes were investigated.

The major difficulties in the former route were connected with the lack of selectivity in the Baeyer-Villiger oxidation of the 3-oxo-butyl side chain and in the reduction of the resulting epoxy acetate. A new route was investigated in which these transformations could be avoided and therefore the exocyclic 8(17) double bond in larixol (**30**) was converted first into a methyl group and a hydroxyl group at C(8). This was performed by epoxidation of this double bond with oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) which proved to be the oxidant of choice compared with *m*-CPBA because its selectivity for the 8(17) exocyclic double bond was much better. Overepoxidation to give the 8(17), 14(15)-diepoxide **399** was observed in 19%.

Epoxide **184** was reduced with $LiAlH_4$ to give the triol **185**[38] which proceeded in good yield and without the competitive formation of cyclic ethers as seen before in Scheme 4.3. The C(6)-hydroxyl group in **185** could be protected selectively as its acetate **186**, and **185** and **186** were both oxidized with a catalytic amount of osmium tetroxide (OsO_4) and an excess of sodium metaperiodate ($NaIO_4$) (Scheme 4.4). This oxidation gave the aldehydes **454** and **187** respectively, as the major products along with some side products, of which two were identified as the epimers **457a** and **b**. A high ratio of $NaIO_4/OsO_4$ favoured cleavage to the aldehyde above rearrangement to methyl ketones **457a** and **b**.[39]

Scheme 4.4



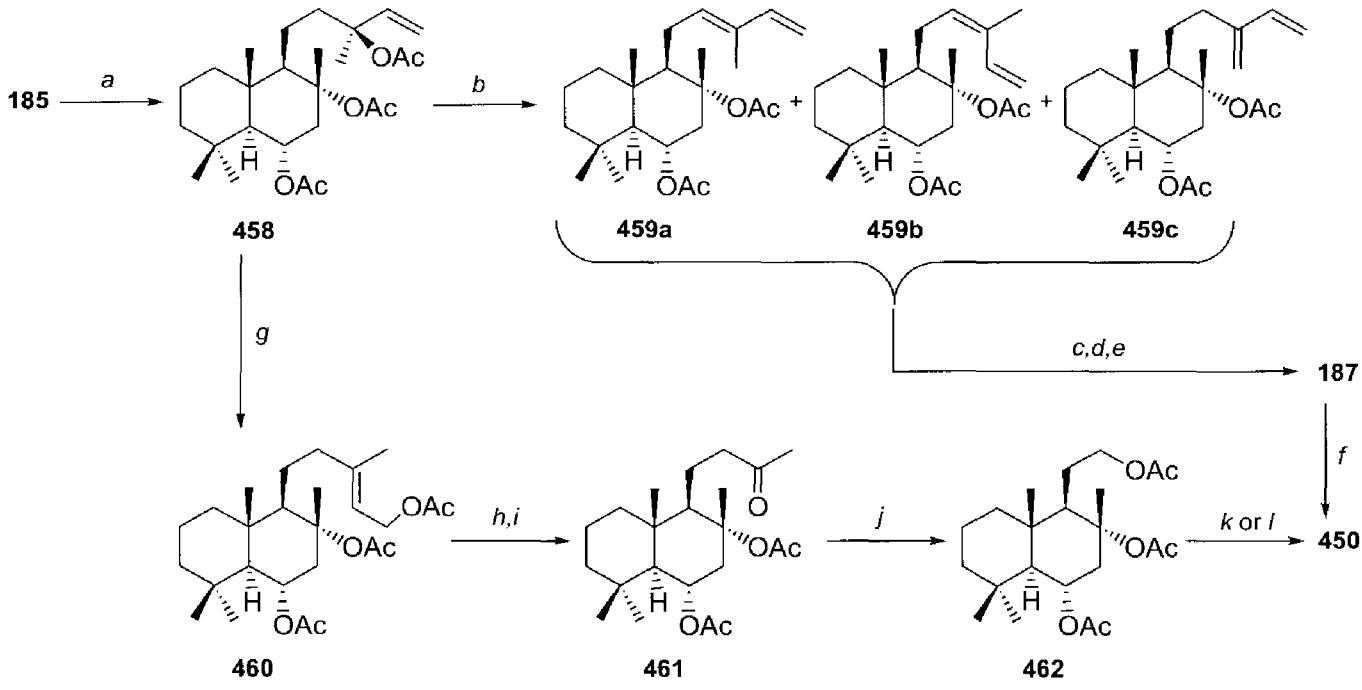
Reagents and conditions: (*a*) oxone®, acetone, H_2O, CH_2Cl_2, [18]crown-6, $NaHCO_3$, 0°C, 68%; (*b*) $LiAlH_4$, THF, 0°C to rt, 94%; (*c*) Ac_2O, CH_2Cl_2, py, DMAP, 91%; (*d*) $KMnO_4$, BTEACl, CH_2Cl_2, 0°C to rt, 70-85%; (*e*) Jones, acetone, 50%; (*f*) $LiAlH_4$, THF, 0°C to rt, 94%; (*g*) *p*-TsOH, CH_3NO_2, 64%; (*h*) *for R=OH:* cat. OsO_4, $NaIO_4$, THF, 80-90%, **457a,b**:**454**=1:2.2; *for R=OAc:* cat. OsO_4, $NaIO_4$, THF, 72%.

Some other routes starting from **185** were also investigated (Scheme 4.4). Oxidation of **185** or **186** with potassium permanganate ($KMnO_4$)[40] has been mentioned before in Chapter 3 and leads to formation of the enol ethers **378** and **379**. Attempts to cleave the double bond in these enol ethers by a second oxidation with $KMnO_4$ were unsuccesful, but Jones' oxidation[41] immediately followed by reduction of the resulting mixture of aldehydes and acids gave triol **450** in 50% yield, based on the enol ethers. Various other oxidation procedures were also applied to these enol ethers, but did not lead to improvements.[42] The aldehydes **454** and **187** isolated from the osmylation reactions, both gave triol **450** in 94% yield upon reduction with $LiAlH_4$.

4.5 Palladium-catalyzed conversion and ozonolysis of the side chain

Elimination or rearrangement of allylic acetates in the side chain of larixol or its derivatives followed by ozonolysis also could provide for an easy access to compounds with a two or four carbon moiety at C(9) and this approach was investigated as well. The acetylation of the secondary and both tertiary hydroxyl groups in **185** could be achieved with acetyl chloride in *N,N*-dimethylaniline to give the triacetate **458** (Scheme 4.5). When **458** was treated with a catalytic amount (1 mol %) of palladium acetate[32j,43c] in the presence of triphenylphosphine at 100°C, a mixture of unsaturated acetates **459a**, **b**, and **c** in a ratio of 4:2:3, determined with ^{1}H NMR, was obtained in over 90% yield. Ozonolysis of this mixture afforded aldehyde **187**, which was reduced and saponified to give triol **450** in 67% yield starting from the mixture of dienes.

Scheme 4.5



Reagents and conditions: (*a*) AcCl, *N,N*-dimethylaniline, 80%; (*b*) $Pd(OAc)_2$, $CaCO_3$, PPh_3, dioxane, Δ, 94%, **459a:b:c**=4:2:3; (*c*) O_3, MeOH/CH_2Cl_2 3:1, -78°C; (*d*) $NaBH_4$, -78°C; (*e*) NaOMe, MeOH, 67%; (*f*) $LiAlH_4$, THF, 0°C to rt, 87%; (*g*) $PdCl_2(CH_3CN)_2$, THF, 98%; (*h*) O_3, CH_2Cl_2/ MeOH 1:1, -78°C; (*i*) PPh_3, -78°C, 95%; (*j*) *m*-CPBA, CH_2Cl_2, 83%; (*k*) $LiAlH_4$, THF, 0°C to rt, 85%; (*l*) NaOMe, MeOH, 85%.

In a second variant triacetate **458** was isomerized in quantitative yield to the allylic acetate **460**[43] (Scheme 4.5). Ozonolysis of the double bond gave the methyl ketone **461,** which was transformed into triacetate **462** by a Baeyer-Villiger oxidation, now in good yield (83%). Exhaustive reduction of **462** with $LiAlH_4$ gave triol **450** in 85% yield. This triol was also obtained in the same yield from the triacetate by saponification using sodium methoxide in methanol.

When the results of the different approaches for the conversion of larixol (**30**) into 6α-hydroxy Ambrox (**451**) are summerized in Table 4.1 and compared, it can be seen that the best yield is obtained by the route described in Scheme 4.4, using the poisonous OsO_4.

Table 4.1: Synthesis of 6α-hydroxy Ambrox (**451**), starting from larixol (**30**).

route (Scheme)	steps	overall yield (%)	average step yield (%)
1 (Scheme 4.3)	5	3 [a]	50
2 (Scheme 4.4)	6	25 [b]	80
3 (Scheme 4.4)	6	16 [b]	75
4 (Scheme 4.5)	6	13	70
5 (Scheme 4.5)	8	21	80

[a] performed with the acetate **207**.

[b] performed with the acetate **186**.

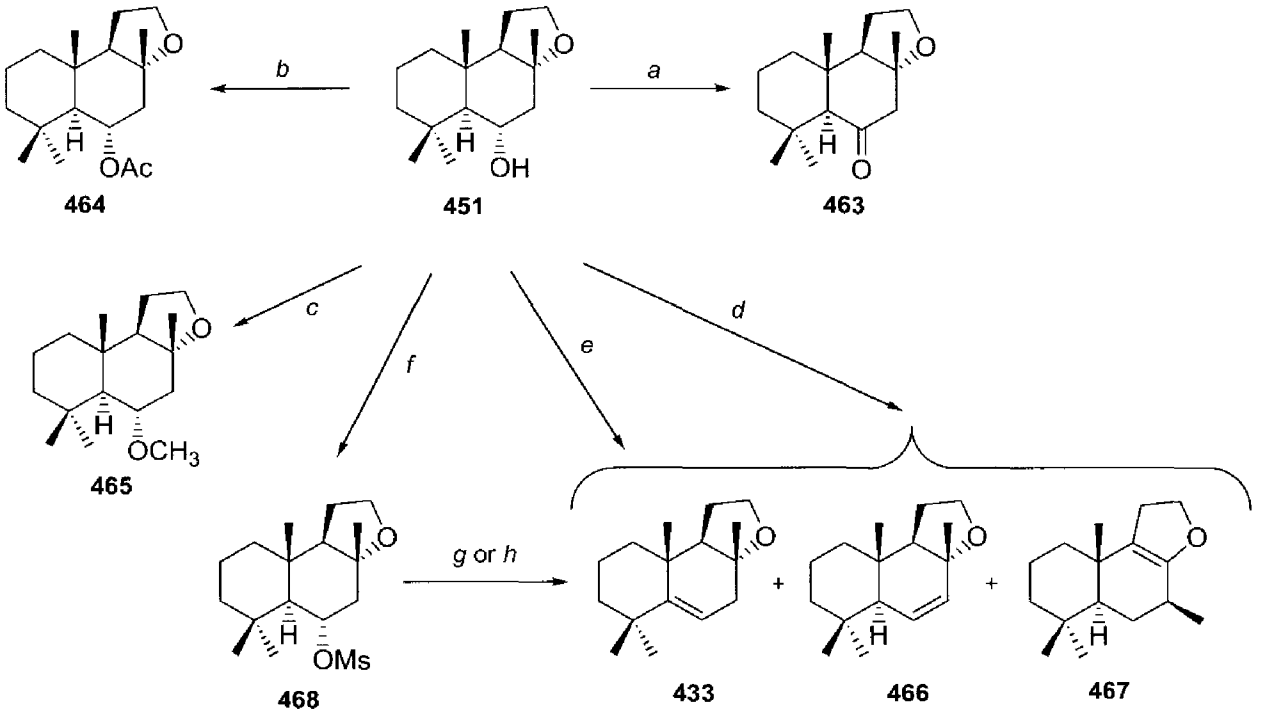
Although the second route described in Scheme 4.5 needs two steps more, the overall yield of **451** is comparable and environmentally safe chemicals are used. Furthermore, the intermediates are all formed in high yield, which avoids difficult purification procedures, so in our opinion this is the route of choice.

4.6 Preparation of Ambrox derivatives

6α-Hydroxy Ambrox (**451**) was used as the key intermediate for the preparation of some Ambrox-like compounds (Scheme 4.6). Treatment of **451** with Jones' reagent in acetone afforded ketone **463** in 91% yield. Conversion of **451** into its acetate **464** was achieved by acetic anhydride in 94% yield, and the reaction of the alkoxide of **451** with methyl iodide gave the methyl ether **465** in 95% yield. When **451** was treated with *p*-toluenesulfonic acid in benzene under Dean Stark conditions a non-separable mixture of three compounds **433**, **466**, and **467** was formed in a ratio of 2:1:1, determined with ^{1}H NMR and GC experiments. This pleasant smelling mixture was analysed on a GC-MS apparatus and on a GC-sniff apparatus, and all three compounds had a pleasant smell, with the Δ^5-alkene **433** as the most attractive one. The structure of alkene **433** was deduced from the NMR spectrum and from its MS spectrum, which showed a clear retro Diels Alder reaction. Moreover, its structure was proven by an independent synthesis (*vide infra*). Compound **466** showed two vinylic protons which coupled with each other, strongly indicating the proposed structure, which is additionally supported by the MS spectrum. The third product most likely has a rearranged skeleton, but further investigations are required to determine the precise structure.

The Δ^5-alkene **433** was produced in a more selective way in 57% yield by treating **451** with thionyl chloride in pyridine, but this approach was not compatible with the preservation of its pleasant odour. Conversion of **451** to mesylate **468** was achieved by methanesulfonyl chloride in pyridine in a 92% yield, and *syn* elimination of this mesylate by treatment with magnesium iodide in toluene afforded Δ^5-Ambroxene (**433**) in 67% yield, with preservation of its pleasant smell. This compound also was obtained in 71% yield from the same mesylate **468** by treatment with lithium bromide and lithium carbonate in *N,N*-dimethyl formamide at 120°C. Several attempts were undertaken to achieve a selective synthesis of the Δ^6-alkene, but all met with moderate success.

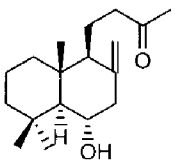
Scheme 4.6



Reagents and conditions: (*a*) $H_2Cr_2O_7$, acetone, 91%; (*b*) Ac_2O, CH_2Cl_2, py, DMAP, 94%; (*c*) NaH, MeI, DMF, 100°C, 95%; (*d*) *p*-TsOH, benzene, Δ, 80%, **433**:**466**:**467**=2:1:1; (*e*) $SOCl_2$, py, 0°C to rt, 57%; (*f*) MsCl, 0°C to rt, 92%; (*g*) LiBr, Li_2CO_3, DMF, 120°C, 71%; (*h*) MgI_2, toluene, 67%.

None of the Ambrox-like compounds **451**, **463**[44,45] - **465** showed the typical ambergris fragrance properties, only the Δ^5- and the Δ^6-alkenes **433** and **466**, respectively, and **467** had a pleasant smell.

4.7 Experimental[46]

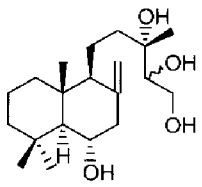


(+)-4-((1*S*,4*S*,4a*S*,8a*R*)-4-Hydroxy-5,5,8a-trimethyl-2-methylenedecahydro-1-naphtha-lenyl)-2-butanone (206).

To an ice-cooled stirred solution of larixol (**30**)[34] (1.0 g; 3.27 mmol) and benzyltriethylammonium chloride (2.2 g; 9.81 mmol) in dichloromethane (40 mL) was added solid $KMnO_4$ (1.54 g; 9.81 mmol) in small portions in 15 min. The mixture was allowed to warm to room temperature and stirring was continued until completion of the reaction. The dark brown reaction mixture was treated with an aqueous saturated Na_2SO_3 solution and a 3% aqueous solution of oxalic acid. Extraction of the colourless reaction mixture with ethyl acetate was followed by usual work-up. Purification by flash column chromatography using gradient elution gave first methyl ketone **206** (0.62 g; 2.22 mmol; 68%) (eluent PE/EA 3:1) as a white crystalline solid.

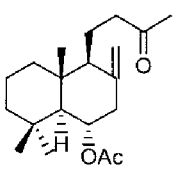
M.p. 77-79°C; $[\alpha]_D$ +43.4 (*c* 2.0); IR (liquid film) ν_{max} 3467, 2926, 1713, 1644, 1361 cm^{-1}; ^1H NMR δ 0.69 (s, 3H), 0.99 (s, 3H), 1.15 (s, 3H), 1.07-2.06 (m, 14H), 2.10 (s, 3H), 2.66 (dd, *J* = 4.9, 12.1 Hz, 1H), 3.82 (td, *J* = 4.9, 10.6 Hz, 1H), 4.49 (d, *J* = 1.2 Hz, 1H), 4.88 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR δ 15.9 (q), 17.7 (t), 19.1 (t), 22.3 (q), 30.1 (q), 33.9 (s), 36.6 (q), 39.2 (t), 39.4 (s), 42.8 (t), 43.6 (t), 49.0 (t), 55.4 (d), 60.4 (d), 71.6 (d), 108.2 (t), 145.3 (s), 209.2 (s); HRMS: (M^+-18), found 260.2131. $C_{18}H_{28}O$ requires 260.2140; MS *m/e* (%) 260 [(M^+-18), 76], 202 (53), 153 (52), 109 (55), 95 (38), 93 (72), 43 (100); Anal.: found C, 78.25; H, 11.28%. $C_{18}H_{30}O_2$ requires C, 77.65; H, 10.86%.

Further elution (eluent EA/MeOH 9:1) gave triol **370** (0.18 g; 0.52 mmol; 16%) as a white crystalline solid.



(+)-(2ζ,3*S*)-5-((1*S*,4*S*,4a*S*,8a*R*)-4-hydroxy-5,5,8a-trimethyl-2-methylenedecahydro-1-naphthalenyl)-3-methyl-1,2,3-pentanetriol (370).

M.p. 139-141°C; $[\alpha]_D$ +33.2 (*c* 1.5, EtOH); IR (KBr) ν_{max} 3389, 2939, 1644, 1382, 1271 cm^{-1}; ^1H NMR δ 0.42 (s, 3H), 0.71 (s, 3H), 0.85 (s, 3H), 0.87 (s, 3H), 1.02-1.84 (m, 16H), 2.34 (dd, *J* = 4.8, 12.2 Hz, 1H), 3.14-3.84 (m, 4H), 4.33 (br s, 1H), 4.58 (br s, 1H); ^{13}C NMR δ 15.3 (q), 16.9 (t), 18.6 (t), 21.2 (q), 21.5 (q), 33.3 (s), 35.8 (q), 37.3 (t), 38.8 (t), 38.9 (s), 43.3 (t), 48.2 (t), 56.2 (d), 59.6 (d), 62.4 (t), 70.5 (d), 73.7 (s), 76.1 (d), 107.3 (t), 145.4 (s); HRMS: (M^+-18), found 322.2509. $C_{20}H_{34}O_3$ requires 322.2508; MS *m/e* (%) 340 (M^+, 3), 322 (11), 261 (49), 243 (58), 218 (58), 153 (71), 109 (87), 69 (100), 43 (75); Anal.: found C, 70.24; H, 10.71%. $C_{20}H_{36}O_4$ requires C, 70.55; H, 10.66%.

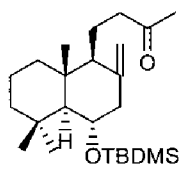


(+)-(1*S*,4*S*,4a*R*,8a*S*)-4a,8,8-Trimethyl-3-methylene-4-(3-oxobutyl)-decahydro-1-naphthalenyl acetate (207).

To a solution of methyl ketone **206** (0.7 g; 2.52 mmol) in CH_2Cl_2 (20 mL) and pyridine (15 mL) was added acetic anhydride (2.17 g; 21.3 mmol) and 4-*N*,*N*-dimethylaminopyridine (25 mg; 0.20 mmol). The reaction mixture was stirred for 1 h, then poured

into a 4 M aqueous solution of HCl, and worked up with ethyl acetate. Purification by flash column chromatography on silica gel (eluent PE/EA 15:1) gave acetate **207** (0.73 g; 2.29 mmol; 91%) as a colourless oil.

$[\alpha]_D$ +56.2 (*c* 1.8); IR (liquid film) ν_{max} 2929, 1733, 1717 cm^{-1}; ^1H NMR δ 0.71 (s, 3H), 0.83 (s, 3H), 0.91 (s, 3H), 2.02 (s, 3H), 2.07 (s, 3H), 1.01-2.42 (m, 13H), 2.64 (dd, *J* = 5.1, 12.2 Hz, 1H), 4.51 (d, *J* = 1.3 Hz, 1H), 4.89 (d, *J* = 1.3 Hz, 1H), 4.97 (td, *J* = 5.1, 10.9 Hz, 1H); ^{13}C NMR δ 15.8 (q), 17.6 (t), 18.9 (t), 21.9 (q), 22.4 (q), 30.0 (q), 33.4 (s), 36.1 (q), 38.9 (t), 39.6 (s), 42.6 (t), 43.3 (t), 44.0 (t), 55.2 (d), 57.4 (d), 73.1 (d), 109.2 (t), 144.0 (s), 170.0 (s), 209.0 (s); HRMS: (M^+-60), found 260.2146. $C_{18}H_{28}O$ requires 260.2140; MS *m/e* 260 [(M^+-60), 76], 202 (88), 189 (35), 153 (57), 133 (36), 43 (100).



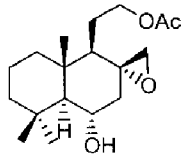
(+)-4-((1*S*,4*S*,4a*S*,8a*R*)-4-((*tert*-Butyl(dimethyl)silyl)oxy)-5,5,8a-trimethyl-2-methylenedecahydro-1-naphthalenyl)-2-butanone (442).

A mixture of methyl ketone **206** (0.30 g; 1.08 mmol), *tert*-butyldimethylsilyl chloride (1.63 g; 10.79 mmol) and imidazole (1.47 g; 21.58 mmol) in DMF (25 mL) was stirred at 60°C. After heating overnight the mixture was cooled to room temperature, diluted with ether, washed with H_2O and worked up as usual. The crude yellow oil was purified by flash column chromatography (eluent PE/EA 10:1) to give silyl ether **442** as an oil (0.32 g; 0.91 mmol; 84%).

$[\alpha]_D$ +40.7 (*c* 0.7); IR (liquid film) ν_{max} 2928, 2856, 1720, 1471, 1463, 1361, 1233 cm^{-1}; ^1H NMR δ 0.11 (s, 3H), 0.13 (s, 3H), 0.71 (s, 3H), 0.90 (s, 9H), 0.96 (s, 3H), 1.13 (s, 3H), 2.12 (s, 3H), 1.16-2.42 (m, 12H), 2.57 (m, 2H), 3.85 (td, *J* = 4.6, 10.4 Hz, 1H), 4.48 (br s, 1H), 4.85 (br s, 1H); ^{13}C NMR δ -3.7 (q), -3.5 (q), 16.0 (q), 17.7 (t), 18.1 (s), 19.0 (t), 22.3 (q), 26.1 (3x q), 30.1 (q), 33.7 (s), 36.5 (q), 39.3 (s), 39.6 (t), 42.9 (t), 44.1 (t), 49.6 (t), 55.5 (d), 60.0 (d), 72.6 (d), 107.8 (t), 145.9 (s), 209.4 (s); HRMS: (M^+-15), found 377.2878. $C_{23}H_{41}O_2Si$ requires 377.2876; MS *m/e* (%) 392 (M^+, 2), 377 (3), 335 (49), 267 (36), 243 (100), 211 (63), 119 (26), 43 (21).

*Baeyer-Villiger oxidation with m-chloroperbenzoic acid of **206**.*

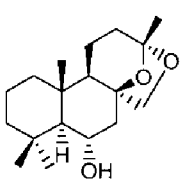
A mixture of methyl ketone **206** (0.20 g; 0.72 mmol) and *m*-CPBA (0.35 g; 1.51 mmol) in CH_2Cl_2 (15 mL) was stirred at room temperature for 13 days. Ether was added and the mixture was washed with a 2% aqueous $Na_2S_2O_3$ solution, saturated aqueous sodium bicarbonate, brine, dried and evaporated. Flash column chromatography (eluent PE/EA 5:1) gave epoxy acetate **443** (0.07 g; 0.22 mmol; 31%), acetal **401** (0.085 g; 0.29 mmol; 40%), and epoxide **400** (0.025 g; 0.09 mmol; 12%) respectively.



(+)-(1*R*,2*R*,4*S*,4a*S*,8a*S*)-2-(4-Hydroxy-3,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-spiro[naphtalene-2(1*H*),2'-oxiran]-yl-ethyl acetate (443).

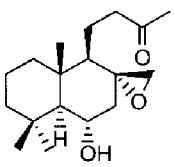
Colourless oil; $[\alpha]_D$ +16.7 (*c* 1.1); IR (liquid film) ν_{max} 3480, 3002, 2930, 2869, 1738, 1714, 1248, 1034 cm^{-1}; ^1H NMR δ 0.83 (s, 3H), 0.99 (s, 3H), 1.19 (s, 3H), 1.05-1.98 (m, 13H), 2.05 (s, 3H), 2.59 (d, *J* = 4.1 Hz, 1H), 2.76 (dd, *J* = 1.9, 4.1 Hz, 1H), 4.03 (td, *J* = 3.8,

10.4 Hz, 1H), 3.95-4.14 (m, 2H); ^{13}C NMR δ 15.8 (q), 18.2 (t), 21.0 (q), 21.5 (t), 22.2 (q), 33.7 (s), 36.5 (q), 39.6 (s), 43.6 (t), 46.7 (t), 49.6 (d), 50.8 (t), 57.0 (s), 60.1 (d), 65.2 (t), 69.7 (d), 171.6 (s); HRMS: M^+, found 310.2139. $C_{18}H_{30}O_4$ requires 310.2144; MS *m/e* (%) 310 (M^+, 1), 250 (27), 153 (39), 126 (48), 109 (100), 98 (48), 69 (70), 43 (82).



(+)-(3*S*,4*S*,9*S*,10*R*)-5,5,9,13-Tetramethyl-14,16-dioxatetracyclo[11.2.1.0^{1,10}.0^{4,9}]hexade-can-3-ol (401).

Crystalline solid; m.p. 126-128 °C; $[\alpha]_D$ +17.1 (*c* 1.0); IR (KBr) ν_{max} 3457, 2985, 2923, 2849, 1460, 1385, 1030 cm^{-1}; ^{1}H NMR δ 1.09 (s, 3H), 1.14 (s, 3H), 1.18 (s, 3H), 1.45 (s, 3H), 0.91-1.85 (m, 14H), 2.10 (dd, *J* = 4.3, 13.4 Hz, 1H), 3.38 (d, *J* = 6.8 Hz, 1H), 3.81 (d, *J* = 6.8 Hz, 1H), 4.19 (td, *J* = 4.3, 11.0 Hz, 1H); ^{13}C NMR δ 16.9 (t), 17.8 (q), 18.3 (t), 22.5 (q), 24.9 (q), 33.6 (s), 33.6 (t), 37.2 (q), 40.3 (t), 40.4 (s), 43.9 (t), 45.6 (t), 49.6 (d), 59.8 (d), 68.2 (d), 75.8 (t), 82.4 (s), 108.6 (s); HRMS: M^+, found 294.2198. $C_{18}H_{30}O_3$ requires 294.2195; MS *m/e* (%) 294 (M^+, 11), 234 (71), 206 (100), 191 (33), 188 (44), 173 (30), 109 (35), 95 (28), 69 (36), 43 (45); Anal.: found C, 73.19; H, 10.47%. $C_{18}H_{30}O_3$ requires C, 73.43; H, 10.27%.

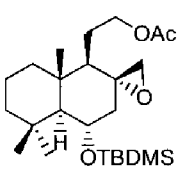


(+)-(1*S*,4*S*,4a*S*,8a*R*)-4-(4-Hydroxy-octahydro-5,5,8a-trimethyl-spiro[naphtalene-2(1*H*),2'-oxiran]-yl)-2-butanone (400).

Colourless oil; $[\alpha]_D$ +19.1 (*c* 0.4); IR (liquid film) ν_{max} 3479, 2928, 2870, 1714, 1462, 1386, 1362 cm^{-1}; ^{1}H NMR δ 0.81 (s, 3H), 0.97 (s, 3H), 1.15 (s, 3H), 1.04-2.02 (m, 15H), 2.07 (s, 3H), 2.48-2.55 (m, 1H), 2.80 (dd, *J* = 1.9, 4.3 Hz, 1H), 3.98 (td, *J* = 4.5, 10.9 Hz, 1H); ^{13}C NMR δ 15.8 (q), 16.0 (t), 18.3 (t), 22.2 (q), 29.9 (q), 33.7 (s), 36.5 (q), 39.1 (t), 40.1 (s), 43.5 (t), 47.0 (t), 51.0 (t), 52.2 (d), 57.8 (s), 60.0 (d), 69.6 (d), 75.7 (t), 209.2 (s); HRMS: M^+, found 294.2200. $C_{18}H_{30}O_3$ requires 294.2195; MS *m/e* (%) 294 (M^+, 6), 234 (44), 206 (61), 153 (32), 109 (81), 95 (48), 81 (45), 69 (67), 43 (100).

Baeyer-Villiger oxidation with m-chloroperbenzoic acid of ***442***.

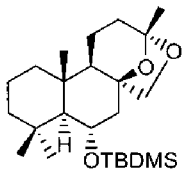
A mixture of silyl ether **442** (0.10 g; 0.25 mmol) and *m*-CPBA (0.18 g; 0.71 mmol) in CH_2Cl_2 (8 mL) was stirred at room temperature for 48 h. Ether was added and the mixture was washed with a 2% aqueous solution of sodium thiosulfate, saturated aqueous sodium bicarbonate, brine, dried and evaporated. Flash column chromatography (eluent PE/EA 15:1) of the crude product gave acetal **445** (0.023 g; 0.056 mmol; 20%), epoxy acetate **444** (0.020 g; 0.047 mmol; 17%), and epoxide **446** (0.050 g; 0.12 mmol; 48%), respectively. During the identification procedure epoxide **446** is converted into acetal **445**.



(+)-(1*R*,2*R*,4*S*,4a*S*,8a*S*)-2-(4-[(1,1-Dimethylethyl)dimethylsilyl]oxy-3,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-spiro[naphtalene-2(1*H*),2'-oxiran]-yl-ethyl acetate (444).

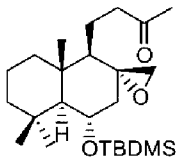
Oil; $[\alpha]_D$ +6.2 (*c* 1.1); IR (liquid film) ν_{max} 2927, 2854, 1724, 1224, 1208 cm^{-1}; ^{1}H NMR δ -0.01 (s, 3H), 0.00 (s, 3H), 0.73 (s, 3H), 0.78 (s, 9H), 0.89 (s, 3H), 1.08 (s, 3H), 1.07-1.72 (m, 12H), 1.95 (s, 3H), 2.44 (d, *J* = 4.1 Hz, 1H), 2.66 (dd, *J* = 2.0, 4.1 Hz, 1H), 3.88-4.02 (m, 3H);

^{13}C NMR δ -4.0 (q), -3.5 (q), 16.0 (q), 18.1 (s), 18.2 (t), 21.1 (q), 21.5 (t), 22.2 (q), 26.0 (3x q), 33.6 (s), 36.4 (q), 39.5 (t), 39.6 (s), 44.0 (t), 47.2 (t), 49.5 (d), 50.8 (t), 57.1 (s), 59.7 (d), 65.3 (t), 70.5 (d), 171.1 (s); HRMS: (M^+-15), found 409.2772. $C_{23}H_{41}O_4Si$ requires 409.2774; MS *m/e* (%) 409 [(M^+-15), 1], 367 (21), 233 (71), 215 (78), 183 (57), 109 (44), 105 (43), 69 (49), 43 (41), 32 (100).



(+)-(1*R*,3*S*,4*S*,9*S*,10*R*)-*tert*-Butyl(dimethyl)silyl-5,5,9,13-tetramethyl-14,16-dioxatetracyclo[11.2.1.0^{1,10}.0^{4,9}]hexadec-3-yl ether (445).

Crystals; m.p. 54-56°C; $[\alpha]_D$ +29.6 (*c* 0.7); IR (KBr) ν_{max} 3442, 2929, 1385, 1253, 1061 cm^{-1}; ^{1}H NMR δ -0.02 (s, 3H), 0.00 (s, 3H), 0.76 (s, 3H), 0.77 (s, 9H), 0.90 (s, 3H), 1.02 (s, 3H), 1.28 (s, 3H), 1.87 (dd, *J* = 4.2, 13.3 Hz, 1H), 0.95-1.80 (m, 13H), 3.23 (d, *J* = 6.7 Hz, 1H), 3.62 (d, *J* = 6.7 Hz, 1H), 4.06 (td, *J* = 4.2, 10.6 Hz, 1H); ^{13}C NMR δ -3.7 (q), -3.6 (q), 17.0 (t), 17.9 (q), 18.1 (s), 18.2 (t), 22.4 (q), 25.0 (q), 26.2 (3x q), 33.4 (s), 33.6 (t), 37.0 (q), 40.1 (s), 40.8 (t), 44.4 (t), 46.0 (t), 49.7 (d), 59.8 (d), 69.1 (d), 76.0 (t), 82.3 (s), 108.5 (s); HRMS: M^+, found 408.3050. $C_{24}H_{44}O_2Si$ requires 408.3060; MS *m/e* (%) 408 (M^+, 2), 352 (27), 351 (100), 275 (14), 119 (9), 117 (11), 75 (26), 43 (10); Anal.: found C, 70.68; H, 11.14%. $C_{24}H_{44}O_3Si$ requires C, 70.54; H, 10.85%.

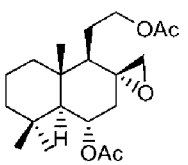


(+)-(1*S*,4*S*,4a*S*,8a*R*)-4-(4-[(1,1-Dimethylethyl)dimethylsilyl]oxy-octahydro-5,5,8a-trimethyl-spiro[naphtalene-2(1*H*),2'-oxiran]-yl)-2-butanone (446).

^{1}H NMR δ 0.05 (s, 3H), 0.07 (s, 3H), 0.83 (s, 3H), 0.87 (s, 9H), 0.97 (s, 3H), 1.12 (s, 3H), 1.08-1.98 (m, 12H), 1.58 (dd, *J* = 3.8, 11.2 Hz, 1H), 2.09 (s, 3H), 2.32-2.65 (m, 2H), 2.82 (dd, *J* = 2.1, 4.2 Hz, 1H), 4.03 (td, *J* = 4.5, 10.7 Hz, 1H).

Baeyer-Villiger oxidation with m-chloroperbenzoic acid of ***207***.

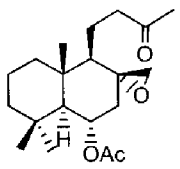
A mixture of acetate **207** (0.20 g; 0.62 mmol) and *m*-CPBA (0.38 g; 1.56 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 10 days. Ether was added and the mixture was washed with a 2% aqueous solution of $Na_2S_2O_3$, saturated aqueous sodium bicarbonate, and worked up as usual. Flash column chromatography (eluent PE/EA 5:1) afforded epoxy diacetate **448** (0.187 g; 0.53 mmol; 84%) as white crystals.



(+)-(1*R*,2*R*,4*S*,4a*S*,8a*S*)-2-(4-Acetoxy-3,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-spiro[naphtalene-2(1*H*),2'-oxiran]-1β-yl-ethyl acetate (448).

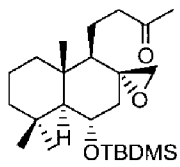
M.p. 86-88°C; $[\alpha]_D$ +8.4 (*c* 1.2); IR (KBr) ν_{max} 2928, 1721, 1735, 1245 cm^{-1}; ^{1}H NMR δ 0.89 (s, 3H), 0.91 (s, 3H), 1.06 (s, 3H), 2.05 (s, 3H), 2.06 (s, 3H), 1.11-2.03 (m, 12H), 2.67 (d, *J* = 4.1 Hz, 1H), 2.77 (dd, *J* = 2.0, 4.1 Hz, 1H), 4.03 (td, *J* = 1.5, 7.0 Hz, 2H), 5.21 (dt, *J* = 5.0, 11.2 Hz, 1H); ^{13}C NMR δ 15.8 (q), 18.2 (t), 21.0 (q), 21.5 (t), 21.8 (q), 22.3 (q), 33.4 (s), 36.1 (q), 39.0 (t), 39.8 (s), 42.1 (t), 43.3 (t), 49.6 (d), 50.7 (t), 56.6 (s), 57.2 (d), 65.1 (t), 71.1 (d), 170.0 (s), 171.0 (s); HRMS: (M^+-60), found 292.2036. $C_{18}H_{28}O_3$ requires 292.2038; MS *m/e* (%) 292 [(M^+-60), 35], 232 (96), 217 (65), 187 (24), 153 (24), 109 (33), 43 (100); Anal.: found C, 68.08; H, 9.27%. $C_{20}H_{32}O_5$ requires C, 68.15; H, 9.15%.

Further elution gave epoxidized compound **207** (**447**) (0.023 g; 0.069 mmol; 11%) as an oil.



(+)-(1*S*,4*S*,4a*S*,8a*R*)-4-(4-Acetoxy-octahydro-5,5,8a-trimethyl-spiro[naphtalene-2(1*H*),2'-oxiran]-yl)-2-butanone (447).

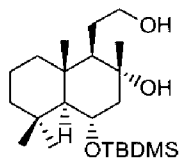
IR (KBr) ν_{max} 2929, 2869, 1731, 1714, 1366, 1244, 1027 cm^{-1}; ^1H NMR δ 0.85 (s, 3H), 0.88 (s, 3H), 0.99 (s, 3H), 1.03-1.99 (m, 12H), 2.04 (s, 3H), 2.09 (s, 3H), 2.27-2.85 (m, 3H), 2.82 (dd, *J* = 1.9, 4.2 Hz, 1H), 5.19 (td, *J* = 5.0, 11.2 Hz, 1H); ^{13}C NMR δ 15.8 (q), 16.1 (t), 18.3 (t), 21.8 (q), 22.3 (q), 29.7 (s), 29.9 (q), 36.1 (q), 39.0 (t), 40.2 (s), 42.5 (t), 43.3 (t), 44.6 (t), 50.9 (t), 52.1 (d), 57.2 (d), 57.4 (s), 71.2 (d), 170.0 (s), 208.9 (s); HRMS: (M^+-60), found 276.2085. $C_{18}H_{28}O_2$ requires 276.2089; MS *m/e* (%) 336 (M^+, 2), 292 (10), 276 (26), 203 (38), 189 (30), 188 (29), 187 (100), 109 (38), 95 (29), 69 (40), 43 (87).



(+)-(1*S*,4*S*,4a*S*,8a*R*)-4-(4-[(1,1-Dimethylethyl)dimethylsilyl]oxy-octahydro-5,5,8a-trimethyl-spiro[naphtalene-2(1*H*),2'-oxiran]-yl)-2-butanone (446).

Silyl ether **442** (0.10 g; 0.28 mmol) and MMPP (0.44 g; 0.71 mmol) were dissolved in CH_2Cl_2 (8 mL) and stirred at room temperature for 3 days. Ether was added and the mixture was treated with an aqueous 1 M solution of hydrochloric acid. The aqueous mixture was extracted with ethyl acetate. The combined organic layers were washed with a saturated aqueous sodium bicarbonate solution and worked up as usual. Flash column chromatography (eluent PE/EA 6:1) gave epoxide **446** (0.07 g; 0.17 mmol; 60%) as a colourless oil.

$[\alpha]_D$ +17.3 (*c* 0.6); IR (liquid film) ν_{max} 2931, 2868, 1721, 1209 cm^{-1}; ^1H NMR δ 0.05 (s, 3H), 0.07 (s, 3H), 0.83 (s, 3H), 0.87 (s, 9H), 0.97 (s, 3H), 1.12 (s, 3H), 1.08-1.98 (m, 12H), 1.58 (dd, *J* = 3.8, 11.2 Hz, 1H), 2.09 (s, 3H), 2.32-2.65 (m, 2H), 2.82 (dd, *J* = 2.1, 4.2 Hz, 1H), 4.03 (td, *J* = 4.5, 10.7 Hz, 1H); ^{13}C NMR δ -4.0 (q), -3.5 (q), 16.0 (q), 16.1 (t), 18.1 (s), 18.2 (t), 22.2 (q), 26.0 (3x q), 26.2 (q), 33.6 (s), 36.5 (q), 39.6 (t), 39.8 (s), 44.0 (t), 44.9 (t), 47.6 (t), 51.0 (t), 52.2 (d), 59.8 (d), 70.5 (d), 82.3 (s), 209.1 (s); MS *m/e* (%) 408 (M^+, 2), 367 (2), 233 (44), 215 (100), 159 (32), 145 (34), 117 (38), 105 (33), 75 (64), 73 (44), 69 (39), 43 (36).

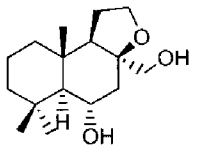


(+)-(1*R*,2*R*,4*S*,4a*S*,8a*S*)-4-((*tert*-Butyl(dimethyl)silyl)oxy)-1-(2-hydroxyethyl)-2,5,5,8a-tetramethyldecahydro-2-naphthalenol (453).

Epoxy acetate **444** (0.016 g; 0.038 mmol) was dissolved in freshly distilled THF (5 mL), cooled to 0°C and $LiAlH_4$ (0.01 g; 0.15 mmol) was added. After stirring for 3 h at room temperature, the mixture was carefully treated with ethyl acetate and diluted with 4 M HCl. The aqueous mixture was extracted with ethyl acetate, the combined organic layers were washed with brine and worked up as usual. Purification by flash column chromatography (eluent PE/EA 1:1) on silica gel gave compound **453** (0.01g; 0.023 mmol; 62%) as a sticky colourless oil.

$[\alpha]_D$ +33.6 (*c* 0.05); IR (liquid film) ν_{max} 3344, 2929, 2858, 1373, 1027 cm^{-1}; ^1H NMR δ 0.12 (s, 3H), 0.14 (s, 3H), 0.85 (s, 3H), 0.89 (s, 9H), 0.94 (s, 3H), 1.14 (s, 3H), 1.23 (s, 3H), 1.10-1.98 (m, 11H), 2.13 (dd, *J* = 3.6, 12.2 Hz, 1H), 2.46 (br s, 2H), 3.47-3.52 (m, 1H), 3.78-3.86 (m, 1H), 3.91 (td, *J* = 3.4, 10.5 Hz, 1H); ^{13}C NMR δ -3.9 (q), -3.5 (q), 16.6 (q), 18.1 (t), 22.0 (q), 25.7 (q), 26.1 (3x q), 27.7

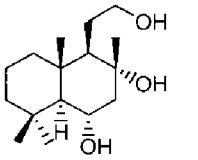
(t), 29.7 (s), 33.6 (s), 36.3 (q), 39.2 (s), 39.8 (t), 43.9 (t), 54.7 (t), 58.4 (d), 60.9 (d), 64.0 (t), 69.7 (d), 72.8 (s); HRMS: (M^+-15-18), found 351.2722. $C_{18}H_{28}O_3$ requires 351.2719; MS *m/e* (%) 351 [(M^+-15-18), 4], 309 (26), 237 (66), 217 (39), 191 (100), 119 (39), 109 (47), 95 (44), 75 (79), 73 (39), 69 (59), 43 (47).



(+)-(3a*S*,5*S*,5a*S*,9a*S*,9b*R*)-3a-(Hydroxymethyl)-6,6,9a-trimethyldodecahydro-naphtho[2,1-*b*]furan-5-ol (449).

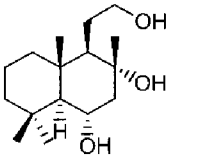
Epoxy acetate **448** (0.24 g; 0.68 mmol) was dissolved in freshly distilled THF (8 mL), cooled to 0°C and $LiAlH_4$ (110 mg; 2.89 mmol) was added in small portions. After stirring overnight, the mixture was carefully treated with ethyl acetate, and then diluted with a 4 M aqueous solution of hydrochloric acid. The aqueous mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and worked up as usual. The crude oil was purified by flash column chromatography on silica gel (eluent PE/EA 1:1) to give diol **449** (0.155 g; 0.58 mmol; 85%) and triol **450** (0.018 g; 0.068 mmol; 10%) both as white crystalline materials.

449: M.p. 133-135°C; $[\alpha]_D$ +11.0 (*c* 0.5); IR (KBr) ν_{max} 3395, 2918, 1472, 1344, 1212, 1015 cm^{-1}; ^1H NMR (400 MHz) δ 0.88 (s, 3H), 0.98 (s, 3H), 1.00 (s, 3H), 1.14-2.03 (m, 10H), 2.17 (dd, *J* = 5.6, 15.2 Hz, 1H), 2.87 (br s, 3H), 3.42 (dd, *J* = 11.0, 17.8 Hz, 2H), 3.78-3.90 (m, 2H), 4.11 (td, *J* = 1.9, 5.8 Hz, 1H); ^{13}C NMR δ 17.0 (q), 18.3 (t), 22.5 (q), 26.8 (t), 33.7 (s), 33.9 (q), 36.4 (s), 40.1 (t), 42.0 (t), 42.3 (t), 53.8 (d), 59.2 (d), 66.4 (t), 66.4 (d), 68.2 (t), 83.7 (s); HRMS: (M^+-31), found 237.1854. $C_{15}H_{25}O_2$ requires 237.1855; MS *m/e* (%) 238 [(M^+-30), 16], 237 (100), 219 (12), 113 (16), 85 (16), 69 (24), 57 (12), 55 (13), 43 (14), 32 (12); Anal.: found C, 72.28; H, 10.81%. $C_{16}H_{28}O_3$ requires C, 71.60; H, 10.52%.



(+)-(1*S*,3*R*,4*R*,4a*S*,8a*S*)-4-(2-Hydroxyethyl)-3,4a,8,8-tetramethyldecahydro-1,3-naphthalenediol (450).

M.p. 156-158°C; $[\alpha]_D$ +31.4 (*c* 0.8, EtOH); IR (KBr) ν_{max} 3462, 3287, 2925, 2872, 1463, 1378, 1247, 1051 cm^{-1}; ^1H NMR (DMSO d_6) δ 0.73 (s, 3H), 0.87 (s, 3H), 1.02 (s, 3H), 1.10 (s, 3H), 1.05-1.56 (m, 10H), 1.90 (dd, *J* = 3.4, 11.9 Hz, 1H), 2.48 (d, *J* = 1.7 Hz, 1H), 3.33 (t, *J* = 7.7 Hz, 2H), 3.48-3.55 (m, 1H), 4.09 (br s/m, 3H); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 20.3 (q), 22.0 (t), 25.7 (q), 29.0 (q), 31.6 (t), 37.5 (s), 40.1 (q), 43.1 (s), 43.4 (t), 47.5 (t), 57.7 (t), 62.2 (d), 64.7 (d), 67.4 (t), 72.3 (d), 76.2 (s); HRMS: (M^+-15), found 255.2071. $C_{15}H_{27}O_3$ requires 255.1960; HRMS: (M^+-15-18), found 237.1852. $C_{15}H_{25}O_2$ requires 237.1855; MS *m/e* (%) 270 (M^+, 2), 255 (1), 151 (6), 109 (7), 95 (6), 87 (100), 69 (9), 43 (11); Anal.: found C, 71.38; H, 11.35%. $C_{16}H_{30}O_3$ requires C, 71.07; H, 11.18%.



(+)-(1*S*,3*R*,4*R*,4a*S*,8a*S*)-4-(2-Hydroxyethyl)-3,4a,8,8-tetramethyldecahydro-1,3-naphthalenediol (450).

- Aldehyde **446** was treated with $LiAlH_4$ as described above. The triol **450** was

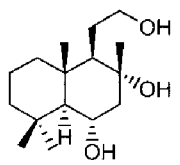
obtained in 74% yield as white crystals. For analytical data see foregoing experimental procedure.

- An unpurified mixture of aldehyde **454** and acid **455** was reduced as described above. Purification by flash column chromatography (eluent EA/MeOH 95:5) gave the same pure triol **450** as white crystals as obtained before.

- Aldehyde **454** was treated with $LiAlH_4$ as above mentioned. The triol **450** was obtained in 87% yield as white crystals. The analytical data were as mentioned before.

- Triacetate **462** was dissolved in freshly distilled THF, cooled to 0°C and treated with $LiAlH_4$. Work up as usual and after purification crystalline triol **450** was obtained in 85% yield. The analytical data were as mentioned before.

- Triacetate **462** was dissolved in MeOH and treated with an 1 M solution of sodium methoxide in methanol. Usual work up, followed by purification by flash column chromatography gave triol **450** in 85% yield as white crystals, identical with the product obtained before.

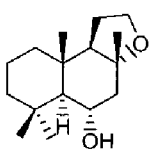


(+)-(1*S*,3*R*,4*R*,4a*S*,8a*S*)-4-(2-Hydroxyethyl)-3,4a,8,8-tetramethyldecahydro-1,3-naphthalenediol (450).

A mixture of $CaCO_3$ (0.25 g; 2.50 mmol), PPh_3 (0.65 g; 0.25 mmol), a catalytic amount of $Pd(OAc)_2$ (5 mg) and triacetate **458** (1.0 g; 2.20 mmol) in dioxane (25 mL) was refluxed for 90 min. The mixture was cooled to room temperature and diluted with ether. The ethereal solution was washed with an aqueous saturated sodium bicarbonate solution (2x), water, and brine and worked up as usual. The residual light yellow oil was purified by flash column chromatography (eluent PE/EA 6:1) to yield an unseparable mixture of dienes **459**.

A solution of a mixture of dienes **459** (0.50 g; 1.28 mmol) in a mixture of MeOH and CH_2Cl_2 3:1 (40 mL) was ozonolyzed at -78°C. The excess ozone was expelled and $NaBH_4$ (0.10 g; 2.56 mmol) was added at -78°C. The mixture was allowed to warm to room temperature. After stirring overnight an 1 M aqueous solution of hydrochloric acid was added. The aqueous mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and worked up as usual.

The crude product was dissolved in MeOH (10 mL) and an 1 M solution of sodium methoxide in methanol (2 mL) was added. After stirring overnight at room temperature the MeOH was evaporated under reduced pressure. The residue was acidified with an 1 M aqueous solution of hydrochloric acid and extracted with CH_2Cl_2. Work up as usual afforded a residue which was flash chromatographed (eluent first EA, then EA/MeOH 95:5) to yield triol **450** (0.27 g; 0.86 mmol; 67%) as a white crystalline solid, identical with the product mentioned before.

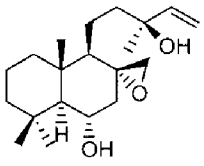


(+)-(3a*R*,5*S*,5a*S*,9a*S*,9b*R*)-3a,6,6,9a-Tetramethyldodecahydronaphtho[2,1-*b*]furan-5-ol (451).

A solution of triol **450** (1.0 g; 3.70 mmol) and *p*-toluenesulfonic acid (0.10 g; 0.52 mmol) in nitromethane (50 mL) was stirred at room temperature for 4 h. Ether was

added and the mixture was washed with saturated aqueous sodium bicarbonate and brine and worked up as usual. Flash column chromatography on silica gel (eluent PE/EA 1:1) gave 6α-hydroxy Ambrox (**451**) (0.60 g; 2.37 mmol; 64%) as white crystals.

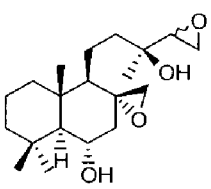
M.p. 146-148°C; $[\alpha]_D$ +15.1 (*c* 1.1); IR (KBr) ν_{max} 3423, 2964, 2844, 1463, 1414, 1379, 1247, 1051 cm^{-1}; ^1H NMR δ 0.86 (s, 3H), 1.00 (s, 3H), 1.12 (s, 3H), 1.15 (s, 3H), 1.02-1.74 (m, 12H), 2.27 (dd, *J* = 3.9, 11.1 Hz, 1H), 3.77-4.00 (m, 3H); ^{13}C NMR δ 16.7 (q), 18.6 (t), 22.1 (q), 22.9 (q), 23.0 (t), 34.1 (s), 35.8 (s), 36.7 (q), 40.3 (t), 44.4 (t), 51.7 (t), 60.3 (d), 62.8 (d), 65.7 (t), 70.9 (d), 79.1 (s); HRMS: (M^+-1), found 251.2013. $C_{16}H_{27}O_2$ requires 251.2011; MS *m/e* (%) 252 (M^+, 1), 251 (1), 237 (100), 219 (10), 125 (7), 113 (11), 109 (10), 95 (6), 69 (15), 43 (8); Anal.: found C, 76.14; H, 11.18%. $C_{16}H_{28}O_2$ requires C, 76.08; H, 11.34%.



(+)-(1*S*,4*S*,4a*R*,8a*S*)-4((3*S*)-3-Hydroxy-3-methyl-4-pentenyl)-4a,8,8-trimethyl-3-spiro-2'-oxiran-decahydro-1-naphtalenol (184).

To a stirred solution of larixol (**30**) (6.0 g; 19.61 mmol) in CH_2Cl_2 (100 mL), acetone (100 mL), H_2O (180 mL), [18]crown-6 (600 mg) and sodium hydrogen carbonate (24 g) was added a solution of oxone® (18.08 g; 29.41 mmol) in H_2O (100 mL) at 0°C. After stirring at 0°C for 90 min the mixture was diluted with a saturated aqueous sodium hydrogen carbonate solution. The aqueous mixture was extracted with ethyl acetate and the combined organic layers were washed with a 10% aqueous solution of $Na_2S_2O_3$, saturated aqueous sodium bicarbonate and brine. Usual work up gave a crude oil which was purified by flash column chromatography (eluent PE/EA 1:1) to give first monoepoxide **184** (4.46 g; 13.33 mmol; 68%) as a white crystalline solid, followed by diepoxide **399**, (1.26 g; 3.73 mmol; 19%) as white crystals.

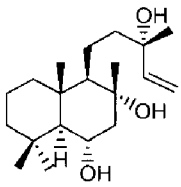
M.p. 114-115°C; $[\alpha]_D$ +16.3 (*c* 1.7); IR (KBr) ν_{max} 3442, 3048, 2932, 2857, 1455, 1237 cm^{-1}; ^1H NMR δ 0.81 (s, 3H), 0.99 (s, 3H), 1.19 (s, 3H), 1.24 (s, 3H), 0.94-2.05 (m, 16H), 2.59 (d, *J* = 4.3 Hz, 1H), 2.79 (dd, *J* = 1.8, 4.2 Hz, 1H), 4.01 (td, *J* = 4.8, 10.9 Hz, 1H), 5.04 (dd, *J* = 1.3, 10.7 Hz, 1H), 5.20 (dd, *J* = 1.3, 17.2 Hz, 1H), 5.84 (dd, *J* = 10.7, 17.2 Hz, 1H); ^{13}C NMR δ 15.8 (q), 16.0 (t), 18.3 (t), 22.3 (q), 28.1 (q), 33.8 (s), 36.6 (q), 39.2 (t), 40.2 (s), 43.6 (t), 43.7 (t), 47.0 (t), 51.2 (t), 53.7 (d), 57.7 (s), 60.3 (d), 69.9 (d), 73.6 (s), 111.8 (t), 145.0 (d); HRMS: (M^+-31), found 291.2323. $C_{19}H_{31}O_2$ requires 291.2324; MS *m/e* (%) 291 [(M^+-31), 8], 233 (60), 109 (91), 69 (90), 43 (59), 31 (100); Anal.: found C, 74.19; H, 10.85%. $C_{20}H_{34}O_3$ requires C, 74.49; H, 10.63%.



(+)-(1*S*,4*S*,4a*R*,8a*S*)-4((3*S*)-3-Hydroxy-3-methyl-4-spiro-2'-oxiran)-4a,8,8-trimethyl-3-spiro-2'-oxiran-decahydro-1-naphtalenol (399).

M.p. 74-75°C; $[\alpha]_D$ +17.7 (*c* 1.9); IR (liquid film) ν_{max} 3445, 3051, 2930, 2866, 1460, 1455, 1387, 1366 cm^{-1}; ^1H NMR δ 0.76 (s, 3H), 0.97 (s, 3H), 1.12 (s, 3H), 1.18 (s, 3H), 1.03-1.91 (m, 16H), 2.51-2.84 (m, 5H), 3.96 (td, *J* = 3.5, 11.2 Hz, 1H); ^{13}C NMR δ 15.4 (t), 15.8 (q), 18.3 (t), 22.3 (q), 22.6 (q), 33.8 (s), 36.6 (q), 39.2 (s), 40.2 (s), 42.9 (t), 43.2 (t), 43.7

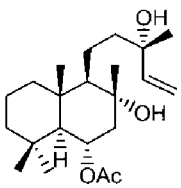
(t), 47.0 (t), 51.1 (t), 53.3 (d), 57.6 (s), 58.0 (d), 60.3 (d), 69.5 (s), 69.8 (d); HRMS: M^+, found 338.2460. $C_{20}H_{34}O_4$ requires 338.2457; MS *m/e* (%) 338 (M^+, 1), 307 (43), 213 (63), 153 (48), 109 (100), 95 (79), 93 (45), 81 (63), 69 (96), 55 (62), 43 (97), 41 (51); Anal.: found C, 70.90; H, 10.12%. $C_{20}H_{34}O_4$ requires C, 70.97; H, 10.12%.



(+)-(1*S*,3*R*,4*R*,4a*S*,8a*S*)-4-((3*S*)-3-Hydroxy-3-methyl-4-pentenyl)-3,4a,8,8-tetramethyl-decahydro-1,3-naphthalenediol (185).

To a stirred suspension of $LiAlH_4$ (1.3 g; 34.21 mmol) in freshly distilled THF (100 mL) was added epoxide **184** (5.5 g; 17.08 mmol) in small portions at 0°C. After stirring overnight at room temperature the mixture was carefully treated with ethyl acetate and diluted with an 1 M solution of hydrochloric acid in water. The aqueous mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and worked up as usual. The residue was crystallized from EA/CH_2Cl_2 1:1 to give 6α-hydroxy sclareol **185** (5.2 g; 16.05 mmol; 94%) as white crystals.

M.p. 158-159°C; $[\alpha]_D$ +43.4 (*c* 1.3, EtOH); IR (KBr) ν_{max} 3427, 2923, 2542, 2474, 1457, 1388 cm^{-1}; ^1H NMR ($CDCl_3/CD_3OD$) δ 0.72 (s, 3H), 0.90 (s, 3H), 1.08 (s, 3H), 1.11 (s, 3H), 1.18 (s, 3H), 0.95-1.60 (m, 13H), 2.00 (dd, *J* = 3.9, 11.9 Hz, 1H), 3.26 (br s, 3H), 3.70 (td, *J* = 3.8, 10.9 Hz, 1H), 4.99 (dd, *J* = 3.1, 10.8 Hz, 1H), 5.13 (dd, *J* = 3.9, 17.4 Hz, 1H), 5.77 (dd, *J* = 1.9, 17.4 Hz, 1H); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 15.9 (q), 17.8 (t), 18.7 (t), 21.5 (q), 24.7 (q), 28.6 (q), 33.3 (s), 35.9 (q), 39.2 (s), 39.4 (t), 43.5 (t), 44.3 (t), 51.1 (d), 53.3 (t), 60.7 (d), 68.3 (d), 73.9 (s), 74.0 (s), 111.6 (t), 144.1 (d); HRMS: (M^+-18), found 306.2560. $C_{20}H_{34}O_2$ requires 306.2559; MS *m/e* (%) 306 [(M^+-18), 1], 292 (6), 191 (53), 187 (56), 150 (53), 123 (81), 109 (72), 87 (100), 43 (99); Anal.: found C, 73.71; H, 11.37%. $C_{20}H_{36}O_3$ requires C, 74.02; H, 11.18%.

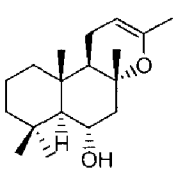


(+)-(1*S*,3*R*,4*R*,4a*S*,8a*S*)-3-Hydroxy-4-((3*S*)-3-hydroxy-3-methyl-4-pentenyl)-3,4a,8,8-tetramethyldecahydro-1-naphthalenyl acetate (186).

A solution of 6α-hydroxy sclareol (**185**) (1.5 g; 4.63 mmol) in CH_2Cl_2 (10 mL) and pyridine (8 mL) was treated with acetic anhydride (1.75 mL; 1.90 g; 18.63 mmol) and DMAP (25 mg; 0.20 mmol) and stirred at 0°C. After stirring for 150 min at room temperature the mixture was neutralized with a 4 M solution of hydrochloric acid. The pyridine was evaporated, extra water was added and the aqueous solution was extracted with ethyl acetate. The combined organic layers were washed with a 4 M solution of hydrochloric acid and worked up as usual. Flash column chromatography (eluent PE/EA 3:1) gave white crystalline acetate **186** (1.54 g; 4.21 mmol; 91%).

M.p. 126-128°C; $[\alpha]_D$ +52.9 (*c* 2.1); IR (KBr) ν_{max} 3423, 2924, 2869, 1727, 1716, 1469, 1266, 1239 cm^{-1}; ^1H NMR δ 0.85 (s, 3H), 0.86 (s, 3H), 1.02 (s, 3H), 1.26 (s, 6H), 1.08-1.74 (m, 14H), 2.04 (s, 3H), 2.07 (dd, *J* = 3.9, 11.7 Hz, 1H), 2.54 (br s, 2H), 5.07 (dd, *J* = 3.3, 10.8 Hz, 1H), 5.23 (dd, *J* = 1.4, 17.2 Hz, 1H), 5.87 (dd, *J* = 10.8, 17.2 Hz, 1H); ^{13}C NMR δ 16.2 (q), 18.0 (t), 19.0 (t), 22.0 (2x

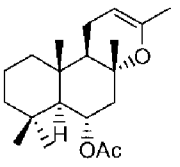
q), 25.6 (q), 29.2 (q), 33.3 (s), 36.1 (q), 39.5 (t), 39.7 (s), 43.5 (t), 44.3 (t), 50.0 (t), 58.4 (d), 61.0 (d), 70.9 (d), 74.1 (s), 74.2 (s), 112.0 (t), 144.9 (d), 170.3 (s); HRMS: (M^+-18), found 348.2669. $C_{22}H_{36}O_3$ requires 348.2664; MS *m/e* (%) 348 [(M^+-18), 2], 288 (44), 191 (48), 190 (81), 121 (43), 109 (50), 95 (50), 81 (50), 71 (44), 69 (48), 43 (100); Anal.: found C, 72.44; H, 10.69%. $C_{22}H_{38}O_4$ requires C, 72.09; H, 10.45%.



(+)-(4a*R*,6*S*,6a*S*,10a*S*,10b*R*)-3,4a,7,7,10a-Pentamethyl-4a,5,6,6a,7,8,9,10,10a,10b-decahydro-1*H*-benzo[*f*]chromen-6-ol (378).

To an ice-cooled solution of **185** (1.0 g; 3.09 mmol) and BTEAC (2.11 g; 9.26 mmol) in acetone (40 mL) was added solid $KMnO_4$ (1.46 g; 9.26 mmol) at once under sonification. Sonification was continued till completion of the reaction. The dark brown reaction mixture was treated with a saturated aqueous Na_2SO_3 solution and with a 3% aqueous solution of oxalic acid which gave a clear colourless reaction mixture. Extraction with ethyl acetate and usual work up gave crude 6α-hydroxy sclareol oxide **378** (0.98 g) as a colourless, rather unstable, oil. A sample was purified by flash column chromatography (eluent PE/EA 15:1).

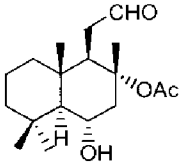
$[\alpha]_D$ +24.9 (*c* 0.4); ^{1}H NMR δ 0.82 (s, 3H), 1.00 (s, 3H), 1.13 (s, 3H), 1.15 (s, 3H), 1.75 (s, 3H), 1.10-1.94 (m, 12H), 2.23 (dd, *J* = 3.9, 11.8 Hz, 1H), 3.89 (dd, *J* = 3.9, 11.2 Hz, 1H), 4.42 (br s, 1H); ^{13}C NMR δ 16.2 (q), 18.3 (t), 18.6 (t), 20.3 (q), 21.2 (q), 22.0 (q), 33.6 (s), 36.6 (q), 37.4 (s), 39.3 (t), 43.6 (t), 52.0 (d), 52.1 (t), 61.4 (d), 68.9 (d), 75.5 (s), 94.7 (d), 147.8 (s); HRMS: M^+, found 278.2241. $C_{18}H_{30}O_2$ requires 278.2246; MS *m/e* (%) 278 (M^+, 99), 245 (29), 217 (100), 215 (30), 191 (53), 189 (52), 175 (44), 119 (30), 109 (39).



(4a*R*,6*S*,6a*S*,10a*S*,10b*R*)-3,4a,7,7,10a-Pentamethyl-4a,5,6,6a,7,8,9,10,10a,10b-decahydro-1*H*-benzo[*f*]chromen-6-yl acetate (379).

The oxidation of acetate **186** (3.0 g; 8.19 mmol) with $KMnO_4$ was performed as described for **378** and crude 6α-acetoxy sclareol oxide **379** (3.02 g) was obtained as a colourless oil. A sample was purified by flash column chromatography (eluent PE/EA 12:1).

^{1}H NMR δ 0.87 (s, 3H), 0.89 (s, 3H), 1.02 (s, 3H), 1.21 (s, 3H), 2.04 (s, 3H), 1.23-1.89 (m, 14H), 2.17 (dd, *J* = 4.1, 11.7 Hz, 1H), 4.41-4.44 (m, 1H), 5.12 (dt, *J* = 4.1, 11.3 Hz, 1H); ^{13}C NMR δ 16.1 (q), 18.2 (t), 18.5 (t), 20.2 (q), 21.0 (q), 21.9 (q), 22.1 (q), 33.2 (s), 36.2 (q), 37.5 (s), 39.1 (t), 43.3 (t), 47.5 (t), 51.9 (d), 58.4 (d), 70.5 (d), 75.1 (s), 94.6 (d), 147.8 (s), 170.2 (s); HRMS: M^+, found 320.2350. $C_{20}H_{32}O_3$ requires 320.2351; MS *m/e* (%) 320 (M^+, 5), 260 (37), 190 (34), 189 (90), 119 (100), 109 (36), 69 (33), 43 (95).



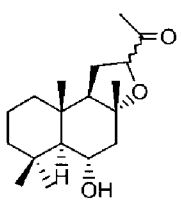
(-)-(1*R*,2*R*,4*S*,4a*S*,8a*S*)-4-Hydroxy-2,5,5,8a-tetramethyl-1-(2-oxo-ethyl)decahydro-2-naphthalenyl acetate (454).

A solution of 6α-hydroxy sclareol (**185**) (0.30 g; 0.92 mmol) and $NaIO_4$ (1.28 g; 6.0

mmol) in THF (20 mL) and water (4 mL) was treated with a 2.5 wt% OsO_4 solution in *tert*-BuOH (0.5 mL). The mixture was warmed to 45°C and stirred overnight. The reaction mixture was filtered and diluted with a saturated aqueous Na_2SO_3 solution and extracted with ethyl acetate. The combined organic layers were dried and evaporated. Purification was performed by flash column chromatography (eluent PE/EA 1:1) to yield aldehyde **454** (0.183 g; 0.58 mmol; 63%) as a colourless oil.

454; $[\alpha]_D$ -9.6 (*c* 0.2, EtOH); IR (KBr) ν_{max} 3498, 2933, 1726, 1713, 1388, 1274, 1055 cm^{-1}; ^1H NMR δ 0.87 (s, 3H), 0.98 (s, 3H), 1.13 (s, 3H), 1.52 (s, 3H), 1.88 (s, 3H), 1.17-1.93 (m, 12H), 3.02 (dd, *J* = 4.0, 12.2 Hz, 1H), 3.86 (td, *J* = 4.0, 10.9 Hz, 1H), 9.65 (t, *J* = 2.2 Hz, 1H); ^{13}C NMR δ 17.1 (q), 18.0 (t), 21.5 (q), 21.9 (q), 22.5 (q), 33.6 (s), 36.3 (q), 38.3 (s), 39.9 (t), 40.4 (t), 43.2 (t), 49.6 (t), 52.7 (d), 60.3 (d), 68.3 (d), 84.0 (s), 169.7 (s), 202.0 (d); HRMS: (M^+-15), found 295.1902. $C_{17}H_{27}O_4$ requires 295.1909; MS *m/e* (%) 295 [(M^+-15), 46], 125 (8), 124 (40), 109 (100), 97 (37), 95 (44), 87 (32), 81 (39), 69 (78), 43 (87).

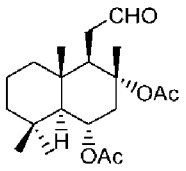
Further elution gave the acetyl compounds **457a** (0.044 g; 0.15 mmol; 16%) and **457b** (0.033 g; 0.11 mmol; 12%) as liquids.



1-((2ζ,3a*R*,5*S*,5a*S*,9a*S*,9b*R*)-5-Hydroxy-3a,6,6,9a-tetramethyldodeca-hydronaphtho-[2,1-*b*]furan-2-yl)ethanone (457a) and 1-((2ζ,3a*R*,5*S*,5a*S*,9a*S*,9b*R*)-5-Hydroxy-3a,6,6,9a-tetramethyldodeca-hydronaphtho-[2,1-*b*]furan-2-yl)ethanone (457b).

457a; $[\alpha]_D$ +0.6 (*c* 0.5); IR (KBr) ν_{max} 3483, 2924, 1711, 1459, 1245, 1047 cm^{-1}; ^1H NMR δ 0.80 (s, 3H), 0.93 (s, 3H), 1.09 (s, 3H), 1.14 (s, 3H), 0.98-2.03 (m, 12H), 2.14 (s, 3H), 2.28 (dd, *J* = 3.9, 11.1 Hz, 1H), 3.88 (td, *J* = 3.9, 10.8 Hz, 1H), 4.34 (dd, *J* = 3.2, 9.8 Hz, 1H); ^{13}C NMR δ 16.2 (q), 18.1 (t), 21.6 (q), 22.8 (q), 26.8 (q), 26.9 (t), 33.7 (s), 35.3 (s), 36.2 (q), 39.8 (t), 43.9 (t), 51.1 (t), 59.1 (d), 62.1 (d), 70.2 (d), 81.2 (d), 81.8 (s), 210.8 (s); HRMS: (M^+-43), found 251.2013. $C_{16}H_{27}O_2$ requires 251.2011; MS *m/e* (%) 251 [(M^+-43), 30], 233 (79), 189 (67), 125 (34), 119 (38), 109 (45), 43 (48), 31 (100); Anal.: found C, 73.06; H, 9.99%. $C_{18}H_{30}O_3$ requires C, 73.43; H, 10.27%.

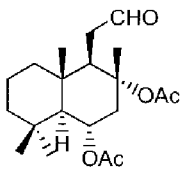
457b; $[\alpha]_D$ -5.0 (*c* 0.1); IR (KBr) ν_{max} 3470, 2926, 1717, 1459, 1385, 1058 cm^{-1}; ^1H NMR δ 0.79 (s, 3H), 0.89 (s, 3H), 1.05 (s, 3H), 1.09 (s, 3H), 1.02-1.99 (m, 12H), 2.17 (s, 3H), 2.26 (dd, *J* = 3.9, 11.2 Hz, 1H), 3.87 (td, *J* = 7.0, 10.8 Hz, 1H), 4.28 (t, *J* = 8.2 Hz, 1H); ^{13}C NMR δ 16.6 (q), 18.1 (t), 21.6 (q), 24.3 (q), 26.0 (t), 26.9 (q), 33.7 (s), 35.4 (s), 36.3 (q), 39.9 (t), 43.9 (t), 51.2 (t), 60.3 (d), 62.1 (d), 70.2 (d), 81.0 (s), 82.8 (d), 211.0 (s); HRMS: (M^+-15), found 279.1959. $C_{17}H_{27}O_3$ requires 279.1960; MS *m/e* (%) 279 [(M^+-15), 2], 233 (75), 189 (86), 125 (43), 119 (52), 109 (65), 69 (100), 43 (74); Anal.: found C, 72.98; H, 9.96%. $C_{18}H_{30}O_3$ requires C, 73.43; H, 10.27%.



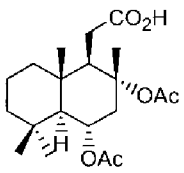
(+)-(1*R*,2*R*,4*S*,4a*S*,8a*S*)-4-(Acetyloxy)-2,5,5,8a-tetramethyl-1-(2-oxo-ethyl)-decahydro-2-naphthalenyl acetate (187).

This reaction was performed as described for **454**. Purification by flash column chromatography (eluent PE/EA 3:2) afforded aldehyde **187** (0.174 g; 0.49 mmol; 72%) as a white crystalline solid.

M.p. 114-116°C; $[\alpha]_D$ +31.2 (*c* 0.5); IR (KBr) ν_{max} 2929, 1719, 1710, 1239, 1045 cm^{-1}; ^1H NMR δ 0.87 (s, 3H), 0.95 (s, 3H), 1.04 (s, 3H), 1.57 (s, 3H), 1.07-1.89 (m, 11H), 1.90 (s, 3H), 2.05 (s, 3H), 2.94 (dd, *J* = 4.1, 12.2 Hz, 1H), 5.14 (td, *J* = 4.1, 11.2 Hz, 1H), 9.69 (t, *J* = 2.1 Hz, 1H); ^{13}C NMR δ 16.9 (q), 17.9 (t), 21.4 (q), 21.8 (q), 21.9 (q), 22.5 (q), 33.2 (s), 35.9 (q), 38.5 (s), 39.8 (t), 40.4 (t), 43.0 (t), 45.2 (t), 52.4 (d), 57.8 (d), 69.6 (d), 84.3 (s), 169.5 (s), 170.0 (s), 201.7 (d); HRMS: (M^+-15), found 337.2006. $C_{19}H_{29}O_5$ requires 337.2015; MS *m/e* (%) 337 [(M^+-15), 1], 293 (4), 233 (64), 190 (70), 109 (29), 43 (100); Anal.: found C, 67.95; H, 9.15%. $C_{20}H_{32}O_5$ requires C, 68.15; H, 9.15%.



187

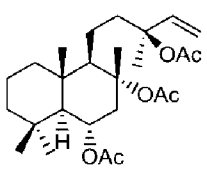


456

(+)-(1*R*,2*R*,4*S*,4a*S*,8a*S*)-4-(Acetyloxy)-2,5,5,8a-tetramethyl-1-(2-oxo-ethyl)decahydro-2-naphthalenyl acetate (187) and (+)-((1*R*,2*R*,4*S*,4a*S*,8a*S*)-2,4-Bis(acetyloxy)-2,5,5,8a-tetramethyldecahydro-1-naphthalenyl)acetic acid (456).

A stirred solution of the crude enol ether **379** (3.2 g; max. 8.12 mmol) in acetone (80 mL) was treated dropwise with Jones' reagent (20 mL; 53.44 mmol) at 0°C. Stirring was continued for 1 h and water (300 mL) was added. The aqueous mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and worked up as usual to give a mixture of aldehyde **187** and acid **456** (2.73 g). A sample was purified by flash column chromatography on silica gel (eluent EA) to give crystalline **187** (26%) and oily **456** (24%). Spectral data of **187** were identical with the above mentioned.

456; $[\alpha]_D$ +45.5 (*c* 0.4); IR (KBr) ν_{max} 3437, 2929, 1740, 1709, 1244, 1134, 1033 cm^{-1}; ^1H NMR δ 0.85 (s, 3H), 0.93 (s, 3H), 1.02 (s, 3H), 1.56 (s, 3H), 1.89 (s, 3H), 1.11-1.95 (m, 10H), 2.04 (s, 3H), 2.33-2.42 (m, 2H), 2.88 (dd, *J* = 4.0, 12.1 Hz, 1H), 5.11 (td, *J* = 4.0, 11.1 Hz, 1H); ^{13}C NMR δ 16.7 (q), 17.9 (t), 21.2 (q), 21.8 (q), 22.0 (q), 22.4 (q), 30.4 (t), 33.1 (s), 35.9 (q), 38.6 (t), 38.9 (s), 43.0 (t), 45.0 (t), 54.3 (d), 57.5 (d), 69.7 (d), 84.3 (s), 169.8 (s), 170.1 (s), 180.2 (s); HRMS: (M^+-60), found 308.1988. $C_{18}H_{28}O_4$ requires 308.1988; MS *m/e* (%) 308 [(M^+-60), 2], 266 (26), 249 (26), 248 (100), 233 (22), 188 (43), 173 (23), 119 (31), 69 (27), 43 (54).

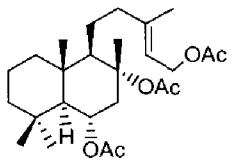


(+)-(1*R*,2*R*,4*S*,4a*S*,8a*S*)-4-(Acetyloxy)-1-((3*S*)-3-(acetyloxy)-3-methyl-4-pentenyl)-2,5,5,8a-tetramethyldecahydro-2-naphthalenyl acetate (458).

6α-Hydroxy **185** (0.50 g; 1.54 mmol) was dissolved in *N,N*-dimethylaniline (15 mL) and acetyl chloride (8.83 g; 112.5 mmol) was added dropwise and stirred overnight. The reaction mixture was acidified cautiously by a 4 M aqueous solution of sulfuric acid

and worked up as usual. The residual yellow oil was purified by flash column chromatography on silica gel (eluent PE/EA 3:1) to yield triacetate **458** (0.57 g; 1.23 mmol; 80%) as white crystals.

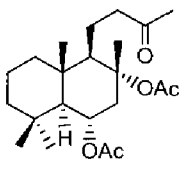
M.p. 100-102°C; $[\alpha]_D$ +38.8 (*c* 2.2); IR (KBr) ν_{max} 3441, 2931, 1737, 1732, 1372, 1258, 1239, 1021 cm^{-1}; ^1H NMR δ 0.81 (s, 3H), 0.88 (s, 3H), 0.97 (s, 3H), 1.49 (s, 3H), 1.01-1.92 (m, 16H), 1.93 (s, 3H), 1.98 (s, 3H), 1.99 (s, 3H), 2.74 (dd, *J* = 4.1, 12.0 Hz, 1H), 5.03 (td, *J* = 4.1, 11.0 Hz, 1H), 5.07 (dd, *J* = 0.9, 17.5 Hz, 1H), 5.15 (dd, *J* = 0.9, 10.7 Hz, 1H), 5.92 (dd, *J* = 10.9, 17.5 Hz, 1H); ^{13}C NMR δ 16.6 (q), 17.9 (t), 19.4 (t), 21.7 (q), 21.8 (q), 21.9 (q), 22.1 (q), 22.7 (q), 23.6 (q), 33.1 (s), 35.9 (q), 39.4 (t), 39.4 (s), 42.1 (t), 43.3 (t), 44.9 (t), 57.7 (d), 57.9 (d), 70.0 (d), 83.0 (s), 85.8 (s), 113.2 (t), 141.7 (d), 169.7 (s), 169.9 (s), 170.1 (s); HRMS: M^+, found 450.2977. $C_{26}H_{42}O_6$ requires 450.2981; MS *m/e* (%) 450 (M^+, 1), 435 (1), 270 (68), 262 (63), 202 (69), 190 (88), 189 (100), 43 (83); Anal.: found C, 69.07; H, 9.48%. $C_{26}H_{42}O_6$ requires C, 69.30; H, 9.40%.



(+)-(1*R*,2*R*,4*S*,4a*S*,8a*S*)-4-(Acetyloxy)-1-((3*E*)-5-(acetyloxy)-3-methyl-3-pentenyl)-2,5,5,8a-tetramethyldecahydro-2-naphthalenyl acetate (460).

A mixture of triacetate **458** (1.0 g; 2.22 mmol) and $PdCl_2(CH_3CN)_2$ (25 mg; 0.10 mmol) in freshly distilled THF (25 mL) was stirred at room temperature for 1 h. Ether was added and the mixture was washed with brine and worked up as usual. Flash column chromatography (eluent PE/EA 6:1) gave **460** (0.98 g; 2.18 mmol; 98%) as a sticky solid.

M.p. 58-61°C; $[\alpha]_D$ +38.2 (*c* 2.5); IR (KBr) ν_{max} 3443, 2931, 1735, 1367, 1025 cm^{-1}; ^1H NMR δ 0.78 (s, 3H), 0.81 (s, 3H), 0.94 (s, 3H), 1.47 (s, 3H), 1.65 (s, 3H), 1.12-1.87 (m, 13H), 1.88 (s, 3H), 1.95 (s, 3H), 2.00 (s, 3H), 2.72 (dd, *J* = 4.1, 12.0 Hz, 1H), 4.52 (d, *J* = 7.1 Hz, 2H), 5.04 (dt, *J* = 4.1, 11.1 Hz, 1H), 5.27 (dt, *J* = 1.2, 7.2 Hz, 1H); ^{13}C NMR δ 16.0 (q), 16.5 (q), 17.9 (t), 21.0 (q), 21.7 (q), 21.8 (q), 21.9 (q), 22.7 (q), 24.2 (t), 33.5 (s), 35.9 (q), 38.2 (t), 39.1 (t), 39.6 (s), 43.4 (t), 44.1 (t), 55.2 (d), 57.5 (d), 61.3 (t), 73.2 (d), 118.2 (d), 142.6 (s), 144.1 (s), 169.9 (s), 170.0 (s), 171.0 (s); HRMS: (M^+-60), found 390.2767. $C_{24}H_{38}O_4$ requires 390.2770; MS *m/e* (%) 390 [(M^+-60), 1], 330 (6), 270 (12), 190 (100), 140 (34), 119 (19), 81 (11), 69 (10).

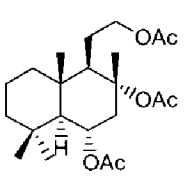


(+)-(1*R*,2*R*,4*S*,4a*S*,8a*S*)-4-(Acetyloxy)-2,5,5,8a-tetramethyl-1-(3-oxobutyl)-decahydro-2-naphthalenyl acetate (461).

A solution of compound **460** (2.0 g; 4.44 mmol) in a mixture of CH_2Cl_2 and MeOH 1:1 (60 mL) was ozonolyzed at -78°C. The excess ozone was expelled and PPh_3 (2.33 g; 8.88 mmol) was added at -78°C. The mixture was allowed to warm up to room temperature. After stirring overnight the solvents were evaporated and the residue was purified by flash column chromatography (eluent PE/EA 3:1) to yield **461** (1.6 g; 4.22 mmol; 95%) as a white solid.

M.p. 128-129°C; $[\alpha]_D$ +42.8 (*c* 1.1); IR (KBr) ν_{max} 3433, 2931, 1722, 1708, 1369, 1248, 1025 cm^{-1}; ^1H NMR δ 0.81 (s, 3H), 0.90 (s, 3H), 0.97 (s, 3H), 1.51 (s, 3H), 1.21-1.85 (m, 12H), 1.90 (s, 3H), 2.01 (s, 3H), 2.07 (s, 3H), 2.51 (dd, *J* = 7.0, 10.5 Hz, 1H), 2.74 (dd, *J* = 4.1, 12.1 Hz, 1H), 5.06 (td,

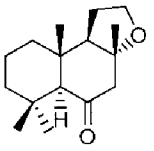
J = 4.1, 11.0 Hz, 1H); ^{13}C NMR δ 16.5 (q), 17.9 (t), 19.4 (t), 21.7 (q), 21.9 (q), 22.0 (q), 22.8 (q), 29.9 (q), 33.2 (s), 35.9 (q), 39.4 (s), 39.6 (t), 43.2 (t), 44.9 (t), 46.2 (t), 57.1 (d), 57.8 (d), 69.9 (d), 85.9 (s), 169.9 (s), 170.0 (s), 208.8 (s); HRMS: (M^+-60), found 320.2334. $C_{20}H_{32}O_3$ requires 320.2351; MS *m/e* (%) 320 [(M^+-60), 4], 260 (100), 242 (23), 202 (58), 189 (69), 187 (55), 153 (25), 119 (54), 43 (34); Anal.: found C, 69.52; H, 9.68%. $C_{22}H_{36}O_5$ requires C, 69.44; H, 9.54%.



(+)-(1*R*,2*R*,4*S*,4a*S*,8a*S*)-4-(Acetyloxy)-1-(2-(acetyloxy)ethyl)-2,5,5,8a-tetramethyldecahydro-2-naphthalenyl acetate (462).

Methyl ketone **461** (0.20 g; 0.52 mmol) and *m*-CPBA (0.18 g; 1.04 mmol) in CH_2Cl_2 (25 mL) were stirred at room temperature for 1 week. Ether was added and the mixture was washed with a 2% aqueous solution of $Na_2S_2O_3$, saturated aqueous sodium bicarbonate and brine, respectively, and worked up as usual. Flash column chromatography (eluent PE/EA 6:1) of the residual oil gave triacetate **462** (0.17 g; 0.42 mmol; 83%) as white crystals.

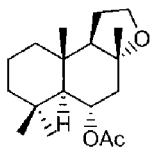
M.p. 142-144°C; $[\alpha]_D$ +25.4 (*c* 0.9); IR (KBr) 3428, 2934, 1729, 1718, 1706, 1239, 1026 cm^{-1}; ^{1}H NMR δ 0.82 (s, 3H), 0.90 (s, 3H), 0.99 (s, 3H), 1.53 (s, 3H), 1.18-1.86 (m, 11H), 1.92 (s, 3H), 2.00 (s, 3H), 2.03 (s, 3H), 2.80 (dd, *J* = 4.1, 12.1 Hz, 1H), 3.94-4.18 (m, 2H), 5.08 (td, *J* = 4.1, 11.2 Hz, 1H); ^{13}C NMR δ 16.7 (q), 17.9 (t), 21.6 (q), 21.9 (2x q), 22.0 (q), 22.8 (q), 24.8 (t), 33.2 (s), 35.9 (q), 39.0 (s), 39.4 (t), 43.2 (t), 44.9 (t), 54.0 (d), 57.8 (d), 65.6 (t), 69.8 (d), 85.2 (s), 169.9 (s), 170.0 (s), 171.0 (s); HRMS: (M^+-60), found 336.2296. $C_{20}H_{32}O_4$ requires 336.2301; MS *m/e* (%) 336 [(M^+-60), 1], 276 (30), 217 (19), 216 (68), 201 (35), 189 (21), 119 (20), 109 (20), 69 (25), 43 (100); Anal.: found C, 66.99; H, 9.30%. $C_{22}H_{36}O_6$ requires C, 66.64; H, 9.15%.



(-)-(3a*R*,5a*S*,9a*R*,9b*R*)-3a,6,6,9a-Tetramethyldecahydronaphtho[2,1-*b*]furan-5(2*H*)-one (463).

6α-hydroxy Ambrox (**451**) (0.30 g; 1.19 mmol) in acetone (10 mL) was treated with Jones' reagent (2 mL; 5.34 mmol) at 0°C. After 1 h the excess of Jones' reagent was destroyed by adding *i*-PrOH (3 mL) and the mixture was diluted with water (150 mL). Extraction with ethyl acetate, followed by usual work up gave after flash column chromatography on silica gel (eluent PE/EA 5:1) ketone **463** (0.27 g; 1.08 mmol; 91%) as a crystalline solid.

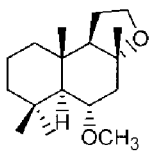
M.p. 66-68 °C; $[\alpha]_D$ -34.1 (*c* 1.3); IR (KBr) ν_{max} 3412, 2927, 1705, 1451, 1388, 1361, 1267 cm^{-1}; ^{1}H NMR δ 0.88 (s, 3H), 0.96 (s, 3H), 1.06 (s, 3H), 1.13 (s, 3H), 1.09-1.94 (m, 8H), 2.13 (dd, *J* = 6.2, 13.0 Hz, 2H), 2.65 (dd, *J* = 6.2, 17.3 Hz, 2H), 3.95-4.07 (m, 2H); ^{13}C NMR δ 15.9 (q), 18.0 (t), 21.3 (q), 21.5 (q), 22.2 (t), 32.2 (s), 32.2 (q), 36.8 (s), 40.3 (t), 42.8 (t), 58.0 (t), 60.0 (d), 65.4 (t), 66.9 (d), 81.0 (s), 209.4 (s); HRMS: M^+, found 250.1935. $C_{16}H_{26}O_2$ requires 250.1933; MS *m/e* (%) 250 (M^+, 12), 236 (14), 235 (100), 151 (15), 123 (16), 111 (23), 109 (16), 43 (12); Anal.: found C, 77.17; H, 10.74%. $C_{16}H_{26}O_2$ requires C, 76.75; H, 10.47%.



(+)-(3a*R*,5*S*,5a*S*,9a*S*,9b*R*)-3a,6,6,9a-Tetramethyldodecahydronaphtho[2,1-*b*]furan-5-yl acetate (464).

A solution of 6α-hydroxy Ambrox (**451**) (0.30 g; 1.19 mmol) in dichloromethane (10 mL) and pyridine (5 mL) was treated with acetic anhydride (0.5 mL; 0.54 g; 5.32 mmol) and DMAP (25 mg; 0.20 mmol). After 2 h the reaction mixture was neutralized with a 4 M solution of hydrochloric acid. Usual work up gave the crude product which was purified by flash column chromatography (eluent PE/EA 5:1) to give acetate **464** (0.33 g; 1.12 mmol; 94%) as white crystals.

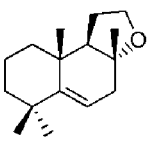
M.p. 73-74°C; $[\alpha]_D$ +23.9 (*c* 1.2); IR (liquid film) ν_{max} 2927, 2875, 1738, 1378, 1242, 1030 cm^{-1}; ^1H NMR δ 0.89 (s, 3H), 0.94 (s, 3H), 1.00 (s, 3H), 1.19 (s, 3H), 1.08-1.81 (m, 11H), 2.05 (s, 3H), 2.20 (dd, *J* = 4.1, 11.2 Hz, 1H), 3.79-4.00 (m, 2H), 5.19 (td, *J* = 4.1, 11.2 Hz, 1H); ^{13}C NMR δ 16.1 (q), 18.1 (t), 21.7 (q), 21.9 (q), 22.3 (q), 22.5 (t), 33.2 (s), 35.2 (s), 35.8 (q), 39.8 (t), 43.7 (t), 43.7 (t), 59.5 (d), 59.8 (d), 65.3 (t), 71.6 (d), 78.4 (s), 170.1 (s); HRMS: (M^+-15), found 279.1957. $C_{17}H_{27}O_3$ requires 279.1960; MS *m/e* (%) 294 (M^+, 1), 279 (1), 220 (16), 219 (100), 123 (10), 69 (6), 43 (14); Anal.: found C, 73.11; H, 10.30%. $C_{18}H_{30}O_3$ requires C, 73.43; H, 10.27%.



(+)-(3a*R*,5*S*,5a*S*,9a*S*,9b*R*)-3a,6,6,9a-Tetramethyldodecahydronaphtho[2,1-*b*]furan-5-yl methyl ether (465).

A 60% suspension of sodium hydride in mineral oil (0.08g; 2.0 mmol) and 6α-hydroxy Ambrox (**451**) (0.10 g; 0.397 mmol) in dry DMF (15 mL) was heated at 100°C under nitrogen for 1 h. Iodomethane (0.86 mL; 1.97 mmol) was added dropwise and the mixture was heated overnight. The mixture was cooled, poured into water and acidified with a 4 M solution of hydrochloric acid and the mixture was worked up as usual. Flash column chromatography with PE/EA 3:1 as the eluent gave ether **465** (0.10 g; 0.377 mmol; 95%) as a colourless oil.

$[\alpha]_D$ +41.9 (*c* 0.2); IR (liquid film) ν_{max} 3372, 2929, 2877, 1724, 1462, 1455, 1380, 1098 cm^{-1}; ^1H NMR δ 0.89 (s, 3H), 0.92 (s, 3H), 1.11 (s, 3H), 1.14 (s, 3H), 1.08-1.80 (m, 11H), 2.44 (dd, *J* = 3.8, 11.3 Hz, 1H), 3.35 (s, 3H), 3.87 (td, *J* = 3.9, 10.7 Hz, 1H), 3.85-3.97 (m, 2H); ^{13}C NMR δ 16.5 (q), 18.2 (t), 22.0 (q), 22.6 (q), 22.7 (t), 33.6 (s), 35.2 (s), 36.1 (q), 39.9 (t), 43.8 (t), 45.0 (t), 56.2 (q), 59.9 (d), 60.7 (d), 65.3 (t), 78.6 (s), 79.8 (d); HRMS: (M^+-15), found 251.2014. $C_{16}H_{27}O_2$ requires 251.2011; MS *m/e* (%) 266 (M^+, 3), 251 (33), 219 (11), 109 (7), 101 (20), 85 (10), 84 (100), 43 (12), 31 (9).

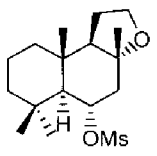


(-)-(3a*R*,9a*R*,9b*R*)-3a,6,6,9a-Tetramethyl-1,2,3a,4,6,7,8,9,9a,9b-decahydro-naphtho[2,1-*b*]furan (Δ^5-Ambroxene) (433).

To a stirred mixture of 6α-hydroxy Ambrox (**451**) (0.05 g; 0.20 mmol) in pyridine (5 mL) was added thionyl chloride (5 mL; 8.16 g; 68.5 mmol) at 0°C. The mixture was allowed to come to room temperature and stirring was continued overnight. The reaction mixture was

quenched with ice-water and the aqueous mixture was extracted with ethyl acetate and usual work up afforded a yellow oil which was purified by flash column chromatography on silica gel (eluent PE/EA 15:1) to yield odorous compound **433** (0.027 g; 0.115 mmol; 57%) as a colourless oil.

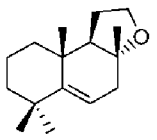
$[\alpha]_D$ -70.0 (*c* 0.4); IR (KBr) ν_{max} 3420, 2926, 1468, 1377, 1165, 1048 cm^{-1}; ^1H NMR δ 1.07 (s, 3H), 1.10 (s, 3H), 1.13 (s, 3H), 1.14 (s, 3H), 1.16-1.94 (m, 9H), 2.26 (d, *J* = 4.0 Hz, 2H), 3.94 (m, 2H), 5.45 (t, *J* = 4.0 Hz, 1H); ^{13}C NMR δ 18.3 (t), 19.5 (q), 21.8 (q), 23.4 (t), 28.9 (q), 33.2 (q), 36.2 (s), 38.3 (s), 41.4 (t), 41.9 (t), 42.2 (t), 57.2 (d), 65.4 (t), 78.3 (s), 117.5 (d), 149.8 (s); HRMS: M^+, found 234.1981. $C_{16}H_{26}O$ requires 234.1984; MS *m/e* (%) 234 (M^+, 23), 219 (54), 151 (13), 150 (98), 135 (100), 105 (12), 91 (11), 43 (18).



(+)-(3a*R*,5*S*,5a*S*,9a*S*,9b*R*)-3a,6,6,9a-tetramethyldodecahydronaphtho[2,1-*b*]furan-5-yl methanesulfonate (468).

To a stirred solution of 6α-hydroxy Ambrox (**451**) (0.30 g; 1.19 mmol) in pyridine (10 mL) was added MsCl (0.16 g; 0.11 mL; 1.42 mmol) at 0°C. The mixture was allowed to warm to room temperature and stirring was continued for **1** h. The reaction mixture was neutralized with a 4 M solution of hydrochloric acid and diluted with ether. The organic layer was washed with saturated aqueous sodium bicarbonate solution and worked up as usual. Purification of the residue by flash column chromatography (eluent PE/EA 3:1) gave **468** (0.36 g; 1.09 mmol; 92%) as a white crystalline solid.

M.p. 114-115°C; $[\alpha]_D$ +12.7 (*c* 1.3); IR (KBr) ν_{max} 3431, 2929, 1344, 1168, 954, 943 cm^{-1}; ^1H NMR δ 0.95 (s, 3H), 1.05 (s, 3H), 1.10 (s, 3H), 1.20 (s, 3H), 1.24-1.92 (m, 11H), 2.61 (dd, *J* = 4.0, 11.0 Hz, 1H), 3.05 (s, 3H), 3.81-4.02 (m, 2H), 5.01 (td, *J* = 4.1, 11.2 Hz, 1H); ^{13}C NMR δ 16.2 (q), 17.9 (t), 21.3 (q), 22.4 (q), 22.5 (t), 33.4 (s), 35.6 (q), 35.8 (s), 40.0 (q), 40.3 (t), 44.0 (t), 47.9 (t), 59.6 (q), 60.2 (d), 65.5 (t), 78.2 (s), 80.6 (d); HRMS: M^+, found 330.1869. $C_{17}H_{30}O_4S$ requires 330.1865; MS *m/e* (%) 330 (M^+,1), 220 (16), 219 (100), 75 (21), 73 (19), 69 (16), 43 (16); Anal.: found C, 61.45; H, 9.20%. $C_{17}H_{30}O_4S$ requires C, 61.78; H, 9.15%.



(-)-(3a*R*,9a*R*,9b*R*)-3a,6,6,9a-Tetramethyl-1,2,3a,4,6,7,8,9,9a,9b-decahydro-naphtho[2,1-*b*]furan (433).

The above mentioned mesylate **468** (0.025 g; 0.075 mmol) in toluene (5 mL) was purged through with nitrogen and MgI_2 (0.042 g; 0.15 mmol) was added quickly. After stirring for 150 min the mixture was diluted with ether and washed with a 2% aqueous solution of $Na_2S_2O_3$ and brine and worked up as usual. Flash column chromatography (eluent PE/EA 15:1) yielded **433** (0.012 g; 0.050 mmol; 67%) as an odorous, colourless oil, with spectral data in accordance with the above mentioned.

A mixture of mesylate **468** (0.025 g; 0.075 mmol), Li_2CO_3 (34 mg; 0.43 mmol) and LiBr (34 mg; 0.39 mmol) in dry DMF (7 mL) was heated to 120°C under nitrogen for 4 h. The mixture was cooled and water was added. The aqueous mixture was extracted with light petroleum ether and

worked up as usual. The crude oil was purified by flash column chromatography (eluent PE/EA 15:1) to give fragrance compound **433** (0.013 g; 0.053 mmol; 71%) as an odorous colourless oil with spectral data in agreement with the above mentioned.

4.8 References and Notes

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42. The following oxidation procedures were performed: O_3, dimethyl sulfide; O_3, pyridine; O_3, $NaBH_4$; *m*-CPBA, lutidine (2,6-dimethylpyridine); *m*-CPBA, 2,6-di-*tert* butylpyridine.
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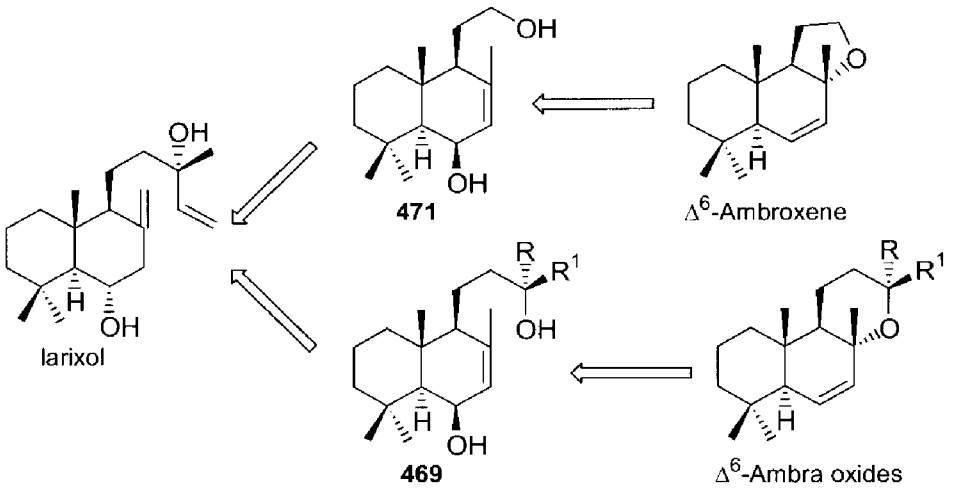
Chapter 5

The synthesis of Δ^6-Ambrox-like compounds

Abstract

*Several Δ^6-Ambrox-like compounds were synthesized in an enantiomerically pure form starting from (+)-larixol (**30**) using diols **471**, **469** and silyl protected alcohol **480** as important intermediates. Abstraction of the allylic hydroxyl group at C(6) in these diols followed by interception of the resulting mesomeric carbocation at C(8) by the hydroxyl group in the side chain allows the synthesis of a Δ^6-tetrahydrofuranylether and some Δ^6-tetrahydropyranylethers. In the latter syntheses the formation of $\Delta^{6,8}$-dienes proves to be a seriously competing reaction.*



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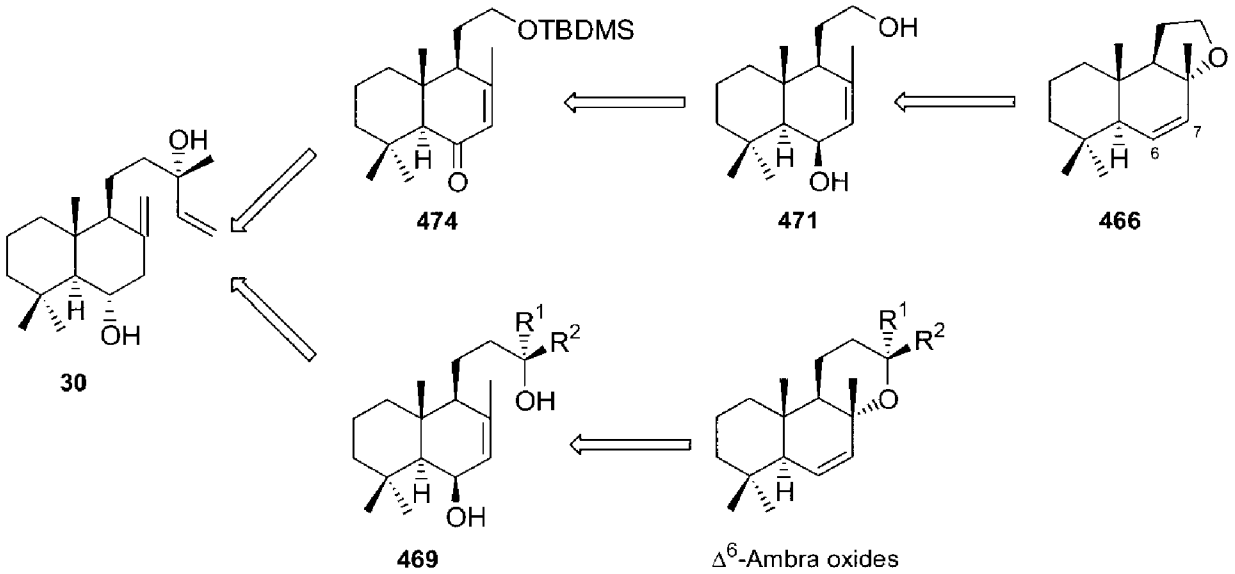
5.1 Introduction

Larixol (**30**) and larixyl acetate (**31**) may provide for suitable synthons for the synthesis of several unsaturated Ambrox® related compounds[1] like Δ^6-Ambroxene (**466**) or Δ^6-Ambra oxides as well. It is known that small structural changes such as the introduction of a double bond in Ambrox® can change the odour properties to a great extend. Derivatives functionalized in ring B at position C(5), C(6) and C(7) are amber odoriferous, in some cases even more intense than the non functionalized analogues. [1,2]

Larixol (**30**) can be easily transformed into intermediates with an hydroxyl group at C(6), a Δ^7 double bond and a substituted side chain at C(9) with a second hydroxyl group. Abstraction of the allylic hydroxyl group at C(6) followed by interception of the resulting mesomeric carbocation at C(8) by the hydroxyl group in the side chain should allow the synthesis of Δ^6-Ambroxene and of some C(13) modified Δ^6-tricyclic tetrahydropyranyl ethers (Δ^6-Ambra oxides) (Scheme 5.1).[3,4] In this chapter the feasibility of this approach is described.

Scheme 5.1

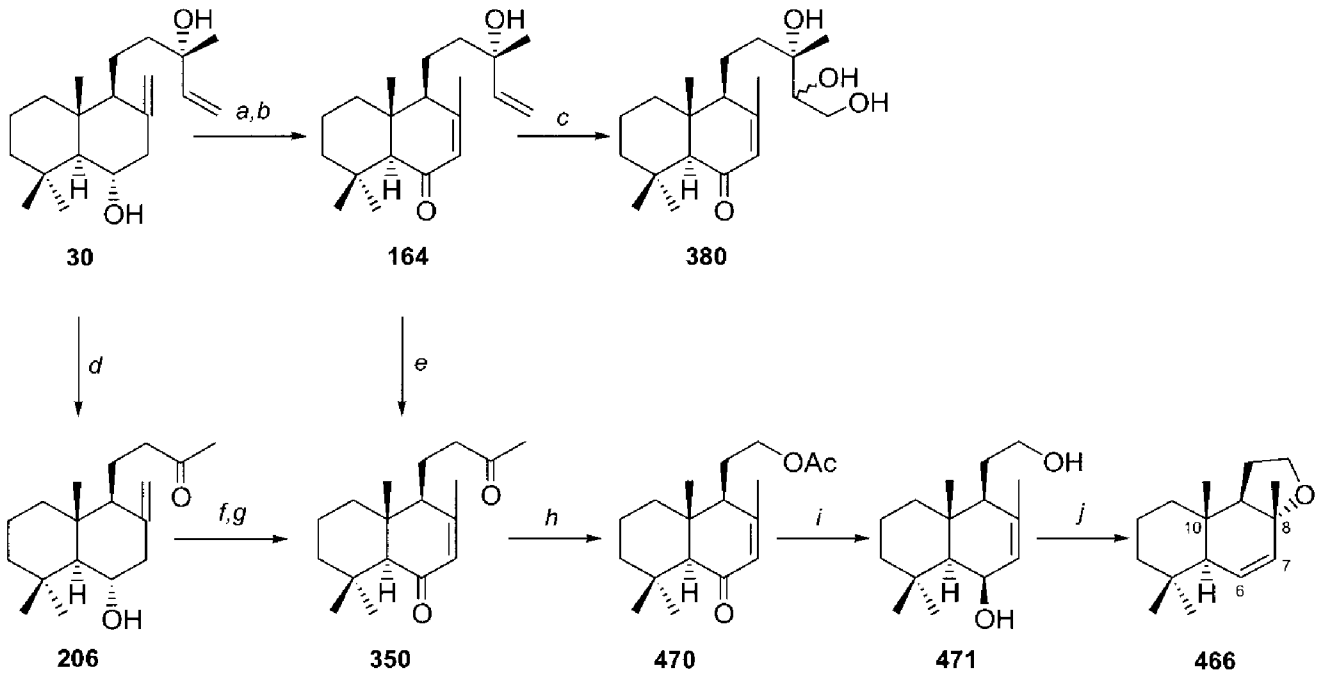


5.2 The synthesis of Δ^6-Ambroxene *via* a new cyclization approach

For the synthesis of the known conjugated enone **350**,[5,6] a more efficient route was developed and starting from larixol (**30**) two reaction sequences have been investigated (Scheme 5.2). First the hydroxyl group at C(6) was oxidized with pyridinium chlorochromate (PCC) followed by base catalyzed isomerization of the double bond to give the conjugated enone **164** in high yield. The standard $KMnO_4$ oxidation (3.0 eq. $KMnO_4$, 0°C) of the side chain in **164** did not give the

desired methyl ketone **350**, but triol **380** as the main product.[1] However, sonication of **164** at room temperature gave the desired diketone **350** in 68% yield.

Scheme 5.2



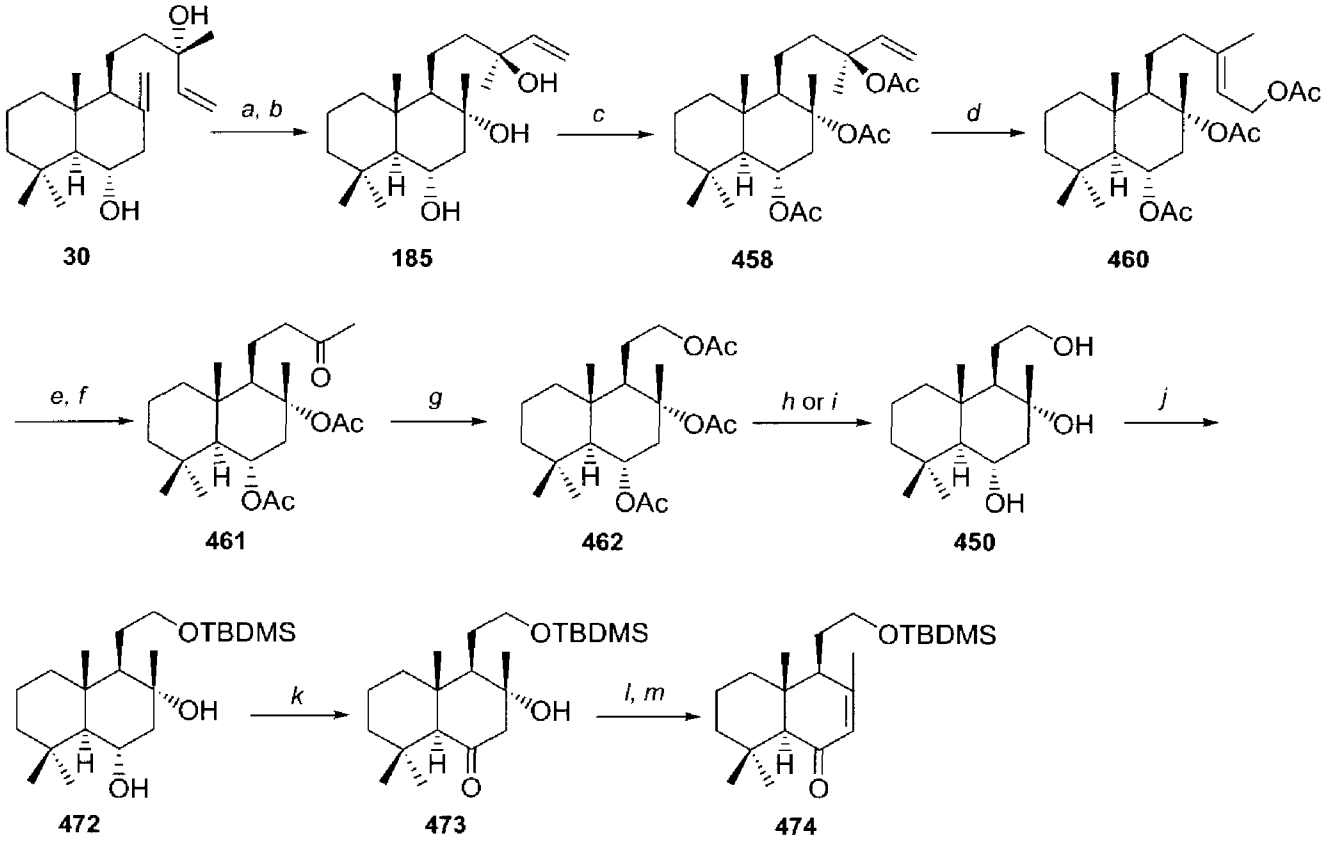
Reagents and conditions: (*a*) PCC, CH_2Cl_2, 95%; (*b*) $NaOCH_3$, MeOH, 98%; (*c*) $KMnO_4$, BTEACl, CH_2Cl_2, 0°C to rt, 56%; (*d*) $KMnO_4$, BTEACl, CH_2Cl_2, 0°C to rt, 68%; (*e*) $KMnO_4$, BTEACl, CH_2Cl_2, rt,))), 68%; (*f*) PCC, CH_2Cl_2, 89%; (*g*) NaOMe, MeOH, 92%; (*h*) *m*-CPBA, $BF_3{\cdot}OEt_2$, 30%; (*i*) $LiAlH_4$, THF, 0°C to rt; (*j*) *p*-TsOH, CH_3NO_2, 37% (2 steps).

An alternative procedure is to oxidize first the side chain of larixol with $KMnO_4$ to methyl ketone **206**,[1] followed by oxidation of the hydroxyl group at C(6) and isomerization of the double bond. In this way diketone **350** was obtained in 56% overall yield.[7] However, also in our hands the Bayer-Villiger oxidation of **350** to **470**, using various conditions, could be accomplished only in a moderate 30% yield, along with unreacted starting material (ca. 50%).[6b] Also the reduction of **470** to diol **471** could not be effected in a good yield, but acid catalyzed cyclization of **470** did give the desired compound **466** in an overall of 37% yield. The configuration of **466** was determined by $^1H,^1H$-NOESY-NMR, whereby a clear nOe was observed between the protons of the C(8)-methyl-group and the C(10)-methyl-group. For these reasons this route to diol **471** was not elaborated further, but the good result in the cyclization reaction encouraged us to look for a better synthesis of **471**. The reduction of the carbonyl group in enone **474** (Scheme 5.3) could provide a solution for this problem.

The oxidative breakdown of the side chain to a hydroxyethyl group can be accomplished in several ways and a modified version of one of the routes described before [1] is depicted in Scheme 5.3. In this route the exocyclic double bond of larixol (**30**) was first converted into compound **185** by

epoxidation with oxone® followed by reduction of the epoxide with $LiAlH_4$.[8] Its structure was determined unambiguously by spectroscopy and X-ray.[9] Peracetylation,[10] palladium catalyzed isomerization[11] of the allylic acetate in the side chain and ozonolysis afforded methyl ketone **461**, which upon Baeyer-Villiger oxidation gave triacetate **462** in good yield. In general it was noticed that the Baeyer-Villiger reaction of acetates proceeds in good yields while other functional groups (*e.g.* **470**) regularly cause difficulties and low yields. Conversion of the acetates into triol **450** and selective monosilylation[12] of the primary hydroxyl group in the side chain gave the protected diol **472**. Oxidation of the secondary hydroxyl group at C(6) with pyridinium dichromate (PDC),[13] and regioselective elimination of the tertiary hydroxyl group at C(8), with thionylchoride in pyridine,[14] then gave the desired enone **474** in 34% overall yield, starting from (+)-larixol (**30**). This enone **474** is also an important intermediate in the total synthesis of the polyoxygenated diterpenes crotomachlin and 8-*epi*-crotomachlin.[15]

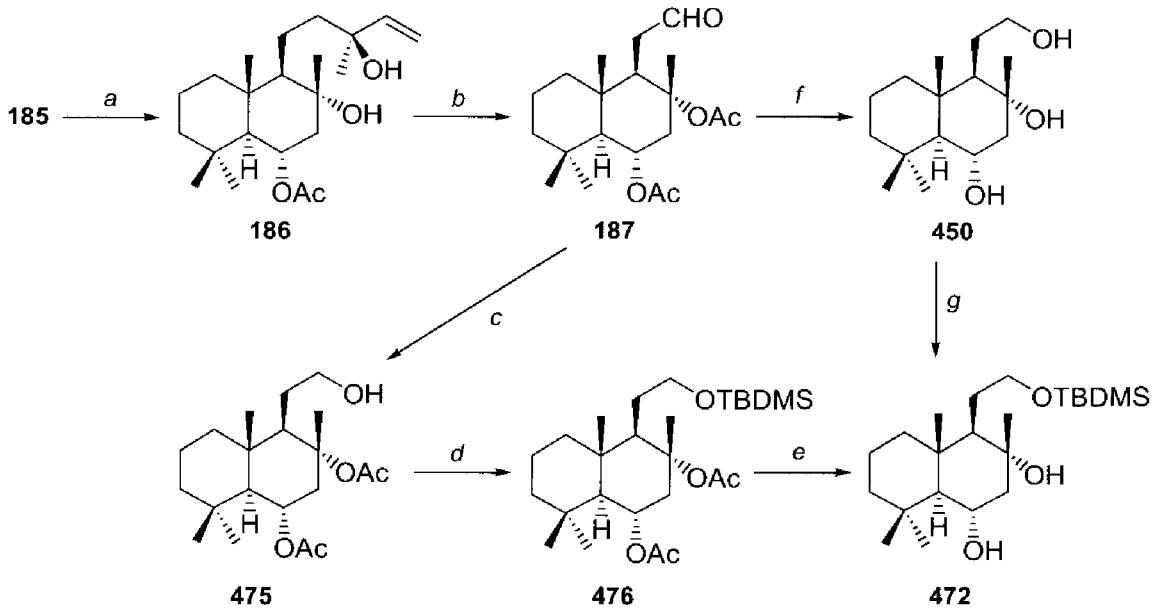
Scheme 5.3



Reagents and conditions: (*a*) oxone®, acetone, H_2O, CH_2Cl_2, [18]crown-6, $NaHCO_3$, 0°C, 81%; (*b*) $LiAlH_4$, THF, 0°C to rt, 94%; (*c*) AcCl, *N,N*-dimethylaniline, 93%; (*d*) $PdCl_2(CH_3CN)_2$, THF, 98%; (*e*) O_3, CH_2Cl_2/MeOH 1:1, -78°C; (*f*) PPh_3, -78°C, 95% (2 steps); (*g*) *m*-CPBA, CH_2Cl_2, 83%; (*h*) $LiAlH_4$, THF, 0°C to rt, 94%; (*i*) NaOMe, MeOH, 85%; (*j*) TBDMSiCl, DMF, imidazole, N_2, 95%; (*k*) PDC, CH_2Cl_2, 3Å molecular sieves, 86%; (*l*) $SOCl_2$, py, DMAP, 0°C to rt; (*m*) NaOMe, MeOH, 82% (2 steps).

Another synthesis of the selectively protected **472** is depicted in Scheme 5.4. The C(6)-hydroxyl group in **185** could be protected selectively as its acetate, with acetic anhydride in pyridine,[16] and now a sclareol type oxidation[17] of **186** with a catalytic amount of OsO_4 and an excess of $NaIO_4$ afforded in high yield the aldehyde **187**, which upon reduction with $LiAlH_4$ gave triol **450** in a overall yield of 54%, starting from (+)-larixol (**30**). This triol could be converted into **472** as described before (Scheme 5.3). An alternative route to **472** was performed *via* selective reduction of the aldehyde group in **187**, by the use of $NaBH_4$, followed by protection of the hydroxyl group and transesterification of the acetates with sodium methoxide. However, complete transesterification proved difficult and easily led to mixtures of partly acylated and especially desilylated products, so for practical reasons the route *via* selective protection of **450** has our preference.

Scheme 5.4

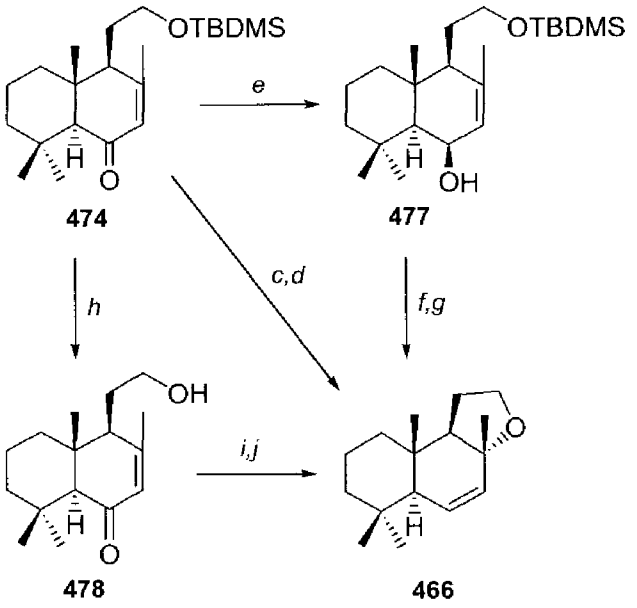


Reagents and conditions: (*a*) Ac_2O, py, DMAP, CH_2Cl_2, 91%; (*b*) cat. OsO_4, $NaIO_4$, THF, 84%; (*c*) $NaBH_4$, MeOH, 80%; (*d*) TBDMSiCl, imidazole, DMF, N_2, 92%; (*e*) NaOMe, MeOH, 50°C, 5 h, 34%; (*f*) $LiAlH_4$, THF, 0°C to rt, 93%; (*g*) TBDMSiCl, imidazole, DMF, N_2, 95%.

A selective synthesis of Δ^6-Ambroxene (**466**) from enone **474** proved to be possible in one pot, but a two step procedure gave better results. Reduction of the carbonyl group at C(6) with $LiAlH_4$ was accompanied by deprotection of the hydroxyl group in the side chain, and acid catalyzed cyclization of diol **471** afforded Δ^6-Ambroxene (**466**) in a moderate 40% yield. A more than 90% yield of **477** was obtained when the reduction of the enone was performed with DIBAL-H in toluene. Deprotection of the hydroxyl group in **477** by TBAF,[15] followed by acid catalyzed cyclization then gave Δ^6-Ambroxene (**466**) in 78% overall yield, based on **474**. This reaction sequence also could be reversed, so deprotection of the hydroxyl group followed by reduction with

DIBAL-H and acid catalyzed cyclization also led to Δ^6-Ambroxene (**466**) in a slightly lower 71% overall yield.

Scheme 5.5



Reagents and conditions: (*c*) $LiAlH_4$, dry THF, 0°C to rt; (*d*) *p*-TsOH, CH_3NO_2, 40% (2 steps); (*e*) DIBAL-H, dry THF, 0°C, N_2, 90%; (*f*) TBAF, dry THF; (*g*) *p*-TsOH, CH_3NO_2, 87% (2 steps); (*h*) TBAF, dry THF, 1 h, 93%; (*i*) DIBAL-H, dry THF, 0°C, N_2; (*j*) *p*-TsOH, CH_3NO_2, 71% (2 steps).

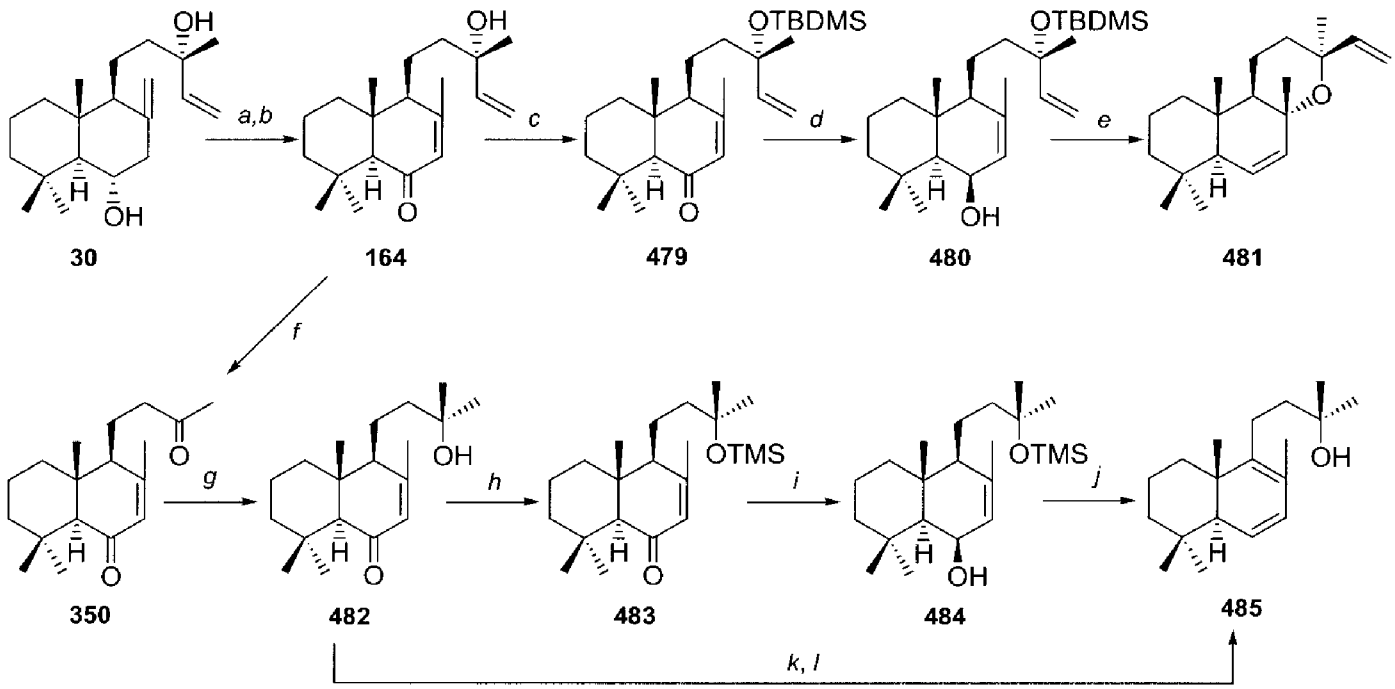
5.3 The synthesis of Δ^6-Ambra oxides from larixol

Enones **164** and **350**, which can be obtained in a few reaction steps from larixol (**30**), are in principle good starting materials for the selective syntheses of a variety of C(13) modified Δ^6-tricyclic tetrahydropyranyl ethers (Δ^6-Ambra oxides) (Scheme 5.6).[1] Enone **164** can be synthesized easily (Scheme 5.2) and after protection of the hydroxyl group in the side chain, the reduction of the carbonyl group at C(6) in **479** could be carried out in high yield with DIBAL-H. Deprotection of this hydroxyl group in the side chain with an aqueous HF solution[18] was accompanied by cyclization of the intermediate diol during its purification as was demonstrated in the synthesis of ether **481**, thus providing the first example of the successful synthesis of six-membered cyclic ethers. This encouraged to investigate a similar approach for the whole series of C(13) modified compounds.

Oxidation of the side chain in **164** with $KMnO_4$ gave diketone **350**, in which the non-conjugated carbonyl group in the side chain could be manipulated selectively (Scheme 5.6). Addition of methyl lithium[19] to **350** proceeded selectively in high yield to give **482**, and after protection of the hydroxyl group, as its trimethylsilyl (TMS) ether, the reduction of the carbonyl

group at C(6) to compound **484** also went without difficulties. However, in this case the combined deprotection cyclization reaction did not give cyclization and dehydrated diene **485** was isolated as the only product in 61% yield based on **482**. Reduction with DIBAL-H without protection of the hydroxy group at C(13) in **482** immediately followed by treatment with a catalytic amount of acid to cause cyclization also gave diene **485**, but now in only 30% yield.

Scheme 5.6



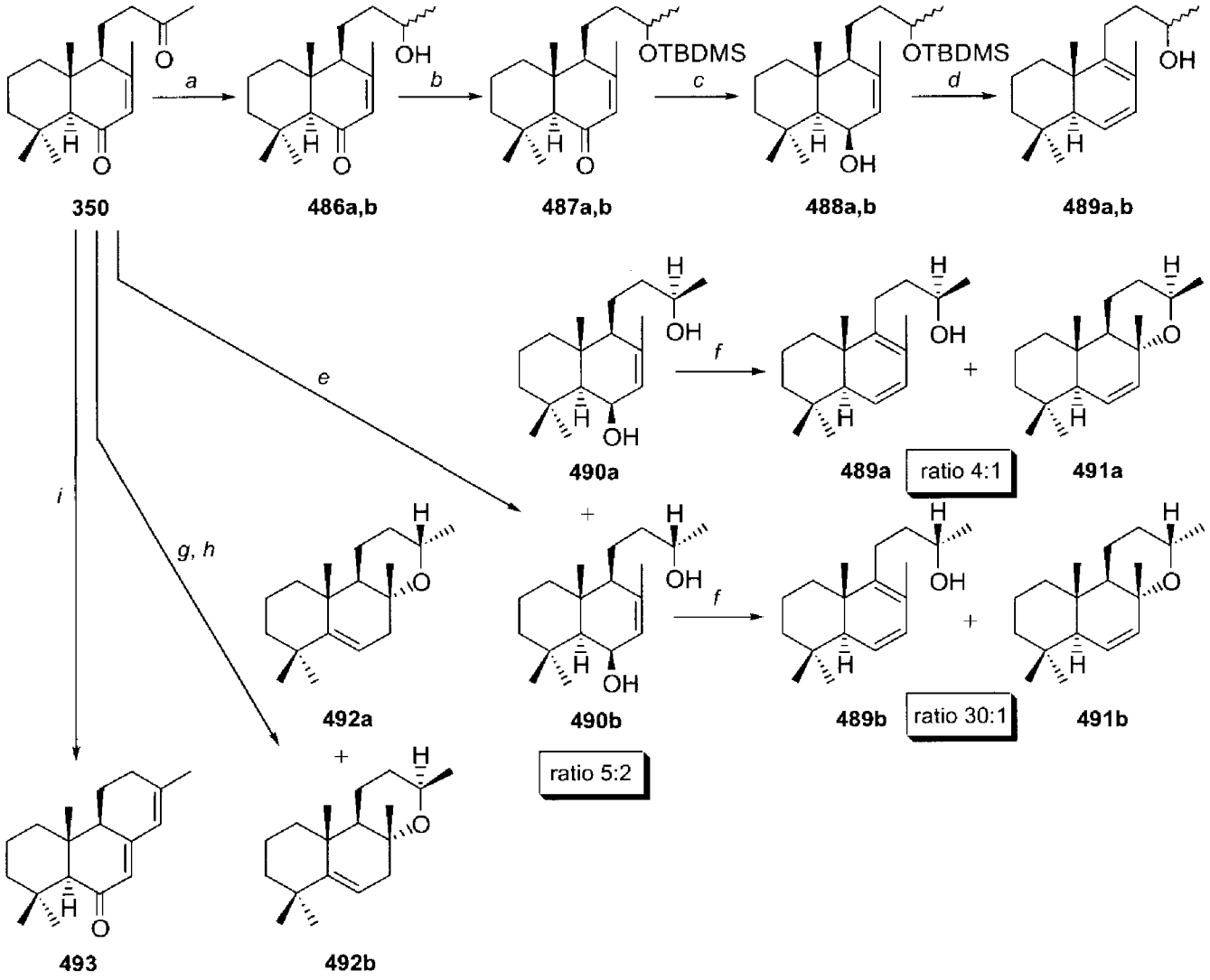
Reagents and conditions: (*a*) PCC, CH_2Cl_2, 95%; (*b*) $NaOCH_3$, MeOH, 98%; (*c*) TBDMSiCl, DMF, imidazole, 70°C, 3 days, 92%; (*d*) DIBAL-H, toluene, -78°C, 98%; (*e*) *i*) HF (50% aqueous solution), CH_3CN; *ii*) SiO_2, 67%; (*f*) $KMnO_4$, BTEAC, CH_2Cl_2, rt,))), 68%; (*g*) MeLi, Et_2O, -78°C, 81%; (*h*) TMSiCl, DMF, imidazole, 99%; (*i*) DIBAL-H, toluene, -78°C, 76%; (*j*) *i*) HF (50% aqueous solution), CH_3CN; *ii*) SiO_2, 80%; (*k*) DIBAL-H, toluene, -78°C, 40%; (*l*) PPTS, CH_3NO_2, 79%.

Selective reduction of the carbonyl group in the side chain of **350** gave a mixture of two C(13) epimeric alcohols. When this mixture was submitted to the similar reaction sequence as described before for the synthesis of **481** (Scheme 5.6) *viz* protection of the hydroxyl group in the side chain, reduction of the carbonyl group at C(6), deprotection of the hydroxyl group in the side chain and cyclization, again an epimeric mixture of C(13)-mono-methyl substituted dienes **489a,b** was obtained (Scheme 5.7). It should be mentioned that separation of the epimers **487a,b** and **488a,b** is possible but for convenience this was only done for analytical purposes. Especially **488a,b** proved to be very unstable and should be used as such.

The reduction of both carbonyl groups in **350** was carried out simultaneously with DIBAL-H at low temperature, to give a separable 5:2 mixture of the two diols **490a** and **490b** respectively, after aqueous work up. After chromatographic separation each diol was treated with a catalytic amount of PPTS in an attempt to cyclize it into the cyclic ethers **491a** and **491b**, but again only the

dienes **489a** and **489b** were obtained. After treatment with aqueous hydrochloric acid both diols **490a** and **490b** gave a small to very small amount of the cyclized products **491a** and **491b** respectively, but also in this case the dienes **489a** and **489b** were obtained as the main products. The formation of the cyclic ethers **491a** and **491b** allowed the assignment of the correct configuration at C(8) and C(13), because a clear nOe between the methyl groups at C(8) and C(13) could be detected only in the NMR spectrum of **491a**. Moreover the observed coupling constants for H_{13} in the NMR spectra of **491a** and **491b** (**491a**: J = 3.6 Hz; **491b**: J = 4.3 Hz) is fully consistent with the supposed structures. Consequently also the configuration at C(13) in their precursors **490a** and **490b** respectively and in the two dienes **489a** and **489b** respectively, could also be established.

Scheme 5.7



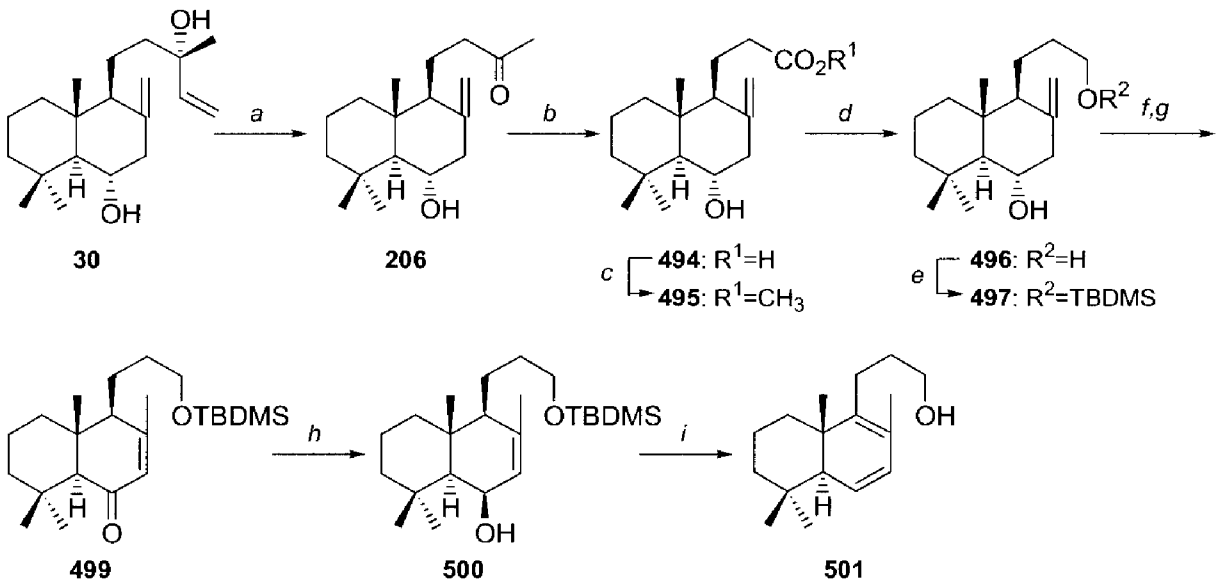
Reagents and conditions: (*a*) $NaBH_4$, MeOH, 0°C, 94%; (*b*) TBDMSiCl, DMF, imidazole, 98%; (*c*) DIBAL-H, toluene, -78°C, 80%; (*d*) *i*) HF (50% aqueous solution), CH_3CN; *ii*) SiO_2, 89%; (*e*) DIBAL-H, toluene, -78°C, NaOH, H_2O, 78%; (*f*) 4 M aq. HCl, Et_2O, 80-95%; (*g*) DIBAL-H, toluene, -78°C, HCl, H_2O; (*h*) *p*-TsOH, CH_3NO_2, 29%; (*i*) KI, I_2, KOH, 1,4-dioxane, 92%.

When the reduction of both carbonyl groups in **350** was carried out with DIBAL-H and an aqueous acidic work up was practiced, compounds **492a** and **492b** were obtained with the double bond in the Δ^5 position. So acidic work-up in the DIBAL-H reduction should be avoided if Δ^6 derivatives are desired and an aqueous basic work-up should be used preferentially. Also NMR spectroscopy measurements of the Δ^6-Ambra oxides or the intermediates in deuterated chloroform led to degradation and isomerization. However when the NMR spectroscopy experiments were performed in deuterated benzene all compounds were stable and the recording of both ^1H and ^{13}C NMR spectra, and 2-D NMR spectra, was no problem.

The synthesis of the unsubstituted C(13) analog **501** was first tried by shortening the side chain in **350** with one carbon atom through an iodoform reaction,[20] but this reaction did not give the desired compound. Under the *basic reaction conditions* a seldom observed type of intramolecular aldol condensation took place to give the dienone **493** (Scheme 5.7). A similar cyclization of **350** could be realized in high yield by simple treatment with base (4 M aq. KOH in 1,4-dioxane).

Therefore a different route was followed in which the side chain in larixol (**30**) was shortened to the desired length followed by a modification of ring B (Scheme 5.8). The oxidation with $KMnO_4$ of (+)-larixol (**30**) to the methyl ketone **206** has been described before[1] and in this compound the iodoform reaction could be accomplished in an acceptable yield.

Scheme 5.8

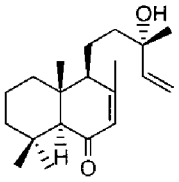


Reagents and conditions: (*a*) $KMnO_4$, BTEAC, CH_2Cl_2, 0-3°C, 68%; (*b*) KI, I_2, KOH, 1,4-dioxane, 56%; (*c*) CH_2N_2, MeOH/Et_2O 1:1; 98%; (*d*) R^1=CH_3: $LiAlH_4$, THF, 0°C, 93%; (*e*) TBDMSiCl, DMF, imidazole, 94%; (*f*) R^2=*TBDMS:* PCC, CH_2Cl_2, 82%; (*g*) $NaOCH_3$, MeOH, 78%; (*h*) DIBAL-H, toluene, -78°C, 87%; (*i*) *i*) HF (50% aqueous solution), CH_3CN; *ii*) SiO_2, 88%.

The acid was converted into its methyl ester **495** and reduction of the ester into an alcohol and selective protection of the primary hydroxyl group in the side chain gave compound **497**. Now

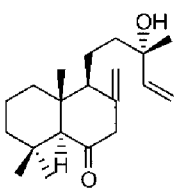
the β-orientated allylic alcohol in ring B was constructed by oxidation of the hydroxyl group at C(6), isomerization of the double bond to enone **499**, and stereoselective reduction of the carbonyl group to give the allylic alcohol **500**. Upon deprotection of the silyl ether in the side chain the corresponding diene **501** was formed again, and no cyclized product could be detected.

5.4 Experimental[21]



(+)-(4*S*,4a*R*,8a*S*)-4-((3*S*)-3-Hydroxy-3-methyl-4-pentenyl)-3,4a,8,8-tetramethyl-4a,5,6,7,8,8a-hexahydro-1(4*H*)-naphthalenone (164).

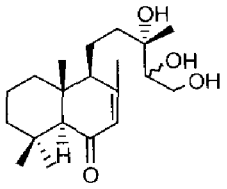
To a stirred solution of (+)-larixol[1] (**30**) (2.5 g; 8.18 mmol) in CH_2Cl_2 (60 mL) were added 3Å molecular sieves (2.0 g) followed by pyridinium chlorochromate (PCC) (2.63 g; 12.25 mmol) and 10 drops of acetic acid. After 1 h the mixture was filtered over silica gel and flushed with ethyl acetate. Purification of the crude product by flash column chromatography (PE/EA 3:1) gave **(+)-(4*S*,4a*R*,8a*S*)-4-((3*S*)-3-hydroxy-3-methyl-4-pentenyl)-4a,8,8-trimethyl-3-methyleneoctahydro-1(2*H*)-naphthalenone** (**163**) (2.35 g; 7.75 mmol; 95%) as a colourless oil.



$[\alpha]_D^{20}$ +74.6 (*c* 3.0) (lit.[22] +76); IR (liquid film) ν_{max} 3467, 2930, 1715, 1652, 1464, 1293, 1233 cm^{-1}; ^1H NMR δ 0.63 (s, 3H), 0.96 (s, 3H), 1.17 (s, 3H), 1.28 (s, 3H), 1.14-1.86 (m, 15H), 4.68 (d, *J* = 1.1 Hz, 1H), 4.85 (d, *J* = 1.1, 1H), 5.06 (dd, *J* = 1.3, 10.7 Hz, 1H), 5.20 (dd, *J* = 1.3, 17.2 Hz, 1H), 5.91 (dd, *J* = 10.7, 17.2 Hz, 1H); ^{13}C NMR δ 15.8 (q), 18.2 (t), 18.9 (t), 21.6 (q), 27.9 (q), 32.6 (s), 32.8 (q), 38.9 (t), 41.1 (t), 41.4 (s), 42.7 (t), 55.9 (t), 57.3 (d), 66.4 (d), 73.4 (s), 110.1 (t), 111.9 (t), 143.4 (s), 145.1 (d), 208.2 (s); HRMS: M^+, found 304.2400. $C_{20}H_{32}O_2$ requires 304.2402; MS *m/e* (%) 304 (M^+, 4), 287 (23), 286 (100), 258 (23), 206 (52), 151 (63), 135 (36), 109 (28), 68 (30).

The C(6)-ketone **163** (2.0 g; 6.58 mmol), obtained above, was isomerized into the conjugated ketone **164** by treatment with a 0.125 M solution of sodium methoxide in methanol (40 mL) at room temperature for 2 h. The methanol was evaporated and an 1 M aqueous solution of HCl (200 mL) was added. Extraction with ether followed by the usual work-up gave the crude product which was purified by flash column chromatography (PE/EA 2:1) to give compound **164** (1.96 g; 6.45 mmol; 98%) as a light yellow oil.

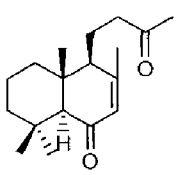
$[\alpha]_D^{20}$ +43.5 (*c* 3.6) (lit[22] +144, lit.[23] +70); IR (liquid film) ν_{max} 3429, 3088, 2912, 1651 cm^{-1}; ^1H NMR δ 0.77 (s, 3H), 1.05 (s, 3H), 1.08 (s, 3H), 1.25 (s, 3H), 1.12-1.92 (m, 13H), 1.85 (s, 3H), 5.03 (dd, *J* = 1.2, 10.7 Hz, 1H), 5.17 (dd, *J* = 1.2, 17.3 Hz, 1H), 5.68 (t, *J* = 1.4 Hz, 1H), 5.86 (dd, *J* = 10.7, 17.3 Hz, 1H); ^{13}C NMR δ 14.6 (q), 18.2 (t), 21.4 (t), 21.5 (q), 22.1 (q), 27.8 (q), 32.3 (s), 33.4 (q), 38.7 (t), 43.2 (t), 43.4 (s), 44.6 (t), 56.6 (d), 63.6 (d), 73.4 (s), 112.3 (t), 128.4 (d), 144.6 (d), 159.0 (s), 200.4 (s); HRMS: M^+, found 304.2394. $C_{20}H_{32}O_2$ requires 304.2402; MS *m/e* (%) 286 [(M^+-18), 17], 219 (19), 218 (34), 135 (100), 109 (28), 95 (21), 73 (89), 43 (31).



(+)-(4*S*,4a*R*,8a*S*)-3,4a,8,8-Tetramethyl-4-((3*S*)-3,4,5-trihydroxy-3-methylpentyl)-4a,5,6,7,8,8a-hexahydro-1(4*H*)-naphthalenone (380).

To an ice-cooled stirred solution of **164** (1.00 g; 3.29 mmol) and benzyltriethylammonium chloride (1.10 g; 4.94 mmol) in dichloromethane (40 mL) was added solid $KMnO_4$ (0.77 g; 4.94 mmol) in small portions over 15 min and the mixture allowed to warm to room temperature and stirred for an additional 14 h untill complete conversion of the starting material. The dark brown reaction mixture was treated with an aqueous saturated Na_2SO_3 solution (75 mL) and with a 3% aqueous solution of oxalic acid (75 mL). Extraction of the now colourless reaction mixture with ethyl acetate (3x 75 mL) was followed by usual work-up. Purification was performed by flash column chromatography (eluent EA/MeOH 9:1) and gave compound **380** as a white crystalline solid (0.62 g; 1.84 mmol; 56%).

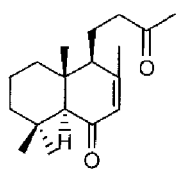
M.p. 108-110°C; $[\alpha]_D^{20}$ +21.0 (*c* 1.1); IR (KBr) ν_{max} 3422, 2928, 1669, 1384, 1293, 1234, 1087 cm^{-1}; ^1H NMR δ 0.77 (s, 3H), 1.04 (s, 3H), 1.06 (s, 3H), 1.12 (s, 3H), 1.90 (s, 3H), 1.12-1.94 (m, 15H), 3.48 (t, *J* = 4.2 Hz, 1H), 3.76 (d, *J* = 4.2 Hz, 2H), 5.72 (br s, 1H); ^{13}C NMR δ 14.6 (q), 18.0 (t), 21.0 (t), 21.4 (q), 21.9 (q), 22.2 (q), 33.3 (q), 38.6 (t), 41.8 (t), 43.0 (t), 43.4 (s), 43.5 (s), 56.7 (d), 63.3 (t), 63.5 (d), 74.5 (s), 74.8 (d), 128.3 (d), 159.1 (s), 200.6 (s); HRMS: M^+, found 338.2449. $C_{20}H_{34}O_4$ requires 338.2457; MS *m/e* (%) 338 (M^+, 10), 320 (13), 277 (17), 219 (49), 218 (73), 135 (100), 109 (18), 43 (22); Anal.: found C, 70.82; H, 10.12%. $C_{20}H_{34}O_4$ requires C, 70.97; H, 10.13%.



(+)-(4*S*,4a*R*,8a*S*)-3,4a,8,8-Tetramethyl-4-(3-oxo-butyl)-4a,5,6,7,8,8a-hexahydro-1(4*H*)-naphthalenone (350).

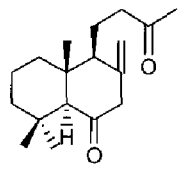
A solution of enone **164** (0.50 g; 1.64 mmol), benzyltriethylammonium chloride (1.12 g; 4.93 mmol) and $KMnO_4$ (0.78 g; 4.93 mmol) in dichloromethane (25 mL) was sonicated at 30-40°C untill completion of the reaction. After 90 min the dark brown reaction mixture was treated with an aqueous saturated Na_2SO_3 solution and with a 3% aqueous solution of oxalic acid. Extraction of the now colourless reaction mixture with ethyl acetate (3x 40 mL) was followed by usual work-up. Purification by flash column chromatography (eluent PE/EA 5:1) gave methyl ketone **350** (0.62 g; 2.22 mmol; 68%) as a colourless oil. (Lit.[6b] Mp 59°C)

$[\alpha]_D^{20}$ +34.8 (*c* 0.5) (lit.[6b]+43); IR (film) ν_{max} 2928, 2870, 1716, 1669, 1464, 1379, 1359, 1234, 1163 cm^{-1}; ^1H NMR δ 0.84 (s, 3H), 1.10 (s, 3H), 1.13 (s, 3H), 1.86 (s, 3H), 1.12-2.05 (m, 10H), 2.15 (s, 3H), 2.41-2.77 (m, 2H), 5.74 (br s, 1H); ^{13}C NMR δ 14.6 (q), 18.1 (t), 20.5 (t), 21.4 (q), 22.1 (q), 30.0 (q), 32.2 (s), 33.4 (q), 38.9 (t), 43.0 (t), 43.4 (s), 45.3 (t), 55.5 (d), 63.5 (d), 128.8 (d), 158.0 (s), 200.3 (s), 207.9 (s); HRMS: M^+, found 276.2082. $C_{18}H_{28}O_2$ requires 276.2089; MS *m/e* (%) 276 (M^+, 1), 261 (2), 135 (19), 109 (13), 95 (5), 73 (100), 69 (6), 57 (27), 43 (30).



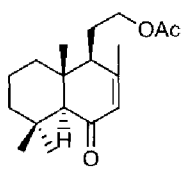
(+)-(4*S*,4a*R*,8a*S*)-3,4a,8,8-Tetramethyl-4-(3-oxo-butyl)-4a,5,6,7,8,8a-hexahydro-1(4*H*)-naphthalenone (350).

A mixture of methyl ketone **206**[1] (1.0 g; 3.60 mmol), PCC (1.16 g; 5.40 mmol), 4 drops of acetic acid and 3Å molecular sieves (0.5 g) in CH_2Cl_2 (25 mL) was stirred at room temperature for 1 h. The black mixture was filtered over silica gel, flushed with ethyl acetate and evaporated. Purification by flash column chromatography (eluent PE/EA 5:1) gave the pure ketone **(+)-(4*S*,4a*R*,8a*S*)-4a,8,8-trimethyl-3-methylene-4-(3-oxobutyl)octahydro-1(2*H*)-naphthalenone** (**356**) (0.88 g; 3.20 mmol; 89%) as white crystals.



M.p. 72-74°C; $[\alpha]_D^{20}$ +80.4 (*c* 1.0); IR (KBr) ν_{max} 2940, 2873, 1702, 1645, 1390, 1228 cm^{-1}; ^1H NMR δ 0.65 (s, 3H), 0.96 (s, 3H), 1.14 (s, 3H), 2.12 (s, 3H), 1.20-2.20 (m, 13H), 2.67 (dd, *J* = 4.0, 9.6 Hz, 1H), 4.88 (br s, 1H), 5.29 (br s, 1H); ^{13}C NMR δ 15.7 (q), 17.5 (t), 18.4 (t), 26.1 (q), 28.1 (q), 29.8 (q), 32.5 (s), 38.8 (t), 41.1 (t), 42.5 (s), 42.6 (t), 55.7 (t), 55.8 (d), 57.4 (d), 109.9 (t), 141.2 (s), 207.8 (s), 208.9 (s); HRMS: M^+, found 276.2074. $C_{18}H_{28}O_2$ requires 276.2089; MS *m/e* (%) 276 (M^+, 54), 258 (20), 151 (57), 124 (20), 123 (94), 109 (100), 107 (26), 95 (40), 81 (45), 43 (57); Anal.: found C, 78.53; H, 10.50%. $C_{18}H_{28}O_2$ requires C, 78.21; H, 10.21%.

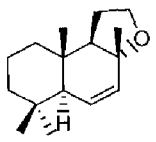
A solution of the above ketone (**356**) (0.50 g; 1.81 mmol) in a 0.2 M solution of sodium methoxide in MeOH (12 mL) was stirred at room temperature for 2 h. After evaporation of the solvent, ether (30 mL) was added and the mixture was acidified with a 4 M solution of hydrochloric acid (5 mL). The mixture was extracted, washed with brine, dried and evaporated. Purification by flash column chromatography (eluent PE/EA 5:1) gave enone **350** (0.46 g; 1.67 mmol; 92%) as a colourless oil. Spectral data were identical with the above mentioned.



(+)-2-((1*S*,4a*S*,8a*R*)-2,5,5,8a-Tetramethyl-4-oxo-1,4,4a,5,6,7,8,8a-octahydro-1-naphthalenyl)ethyl acetate (470).

A mixture of enone **350** (0.270 g; 1.0 mmol), *m*-CPBA (0.370 g; 1.5 mmol), and boron trifluoride etherate ($BF_3{\cdot}OEt_2$) (1.5 mmol; 0.19 mL) in CH_2Cl_2 (10 mL) was stirred at room temperature for 4 days. The mixture was diluted with ether, washed with a 10% aqueous solution of $Na_2S_2O_3$ and with a saturated aqueous sodium bicarbonate solution, brine, dried and evaporated. Flash column chromatography (eluent PE/EA 5:1) gave acetate **470** (0.088 g; 0.30 mmol; 30%) as a colourless oil besides unreacted starting material **350** (0.139 g; 0.50 mmol; 50%).

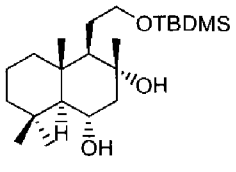
$[\alpha]_D^{20}$ +15.0 (*c* 0.7); IR (film) ν_{max} 2928, 1741, 1671, 1463, 1382, 1238, 1041 cm^{-1}; ^1H NMR δ 0.78 (s, 3H), 1.06 (s, 3H), 1.09 (s, 3H), 1.12-1.85 (m, 10H), 1.87 (s, 3H), 2.01 (s, 3H), 3.99-4.29 (m, 2H), 5.72 (br s, 1H); ^{13}C NMR δ 14.6 (q), 18.1 (t), 21.0 (q), 21.5 (q), 22.1 (q), 26.1 (t), 32.3 (s), 33.4 (q), 38.7 (t), 42.8 (s), 43.1 (t), 52.4 (d), 63.4 (d), 65.0 (t), 128.9 (d), 157.3 (s), 171.0 (s), 199.8 (s); HRMS: M^+, found 276.2082. $C_{18}H_{28}O_2$ requires 276.2089; MS *m/e* (%) 292 (M^+, 14), 232 (48), 203 (14), 150 (13), 149 (100), 135 (15), 109 (26), 108 (57), 95 (16), 43 (19).



(-)-(3a*R*,5a*S*,9a*S*,9b*R*)-3a,6,6,9a-Tetramethyl-1,2,3a,5a,6,7,8,9,9a,9b-decahydronaphtho-[2,1-*b*]furan (Δ^6-Ambroxene) (466).

To a stirred solution of enone **470** (0.05 g; 0.171 mmol) in dry THF (10 mL) was added $LiAlH_4$ (0.033 g; 0.86 mmol) at 0°C. After stirring overnight at room temperature the mixture was diluted with Et_2O and carefully treated with an 1 M aqueous solution of hydrochloric acid. The aqueous mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried and evaporated to obtain the crude **(1*R*,4*S*,4a*R*,8a*S*)-4-(2-hydroxyethyl)-3,4a,8,8-tetramethyl-1,4,4a,5,6,7,8,8a-octahydro-1-naphthalenol** (**471**). This oil was not purified but directly converted into **466** by treatment with *p*-toluenesulfonic acid (0.05 g; 0.26 mmol) in nitromethane (5 mL) at room temperature for 4 h. Ether (25 mL) was added and the mixture was washed with saturated aqueous sodium bicarbonate and brine and worked up as usual. Flash column chromatography on silica gel (eluent PE/EA 5:1) gave **466** (0.015 g; 0.064 mmol; 37%) as a clear oil.

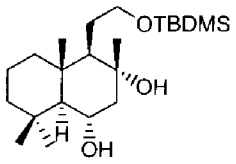
$[\alpha]_D^{20}$ -46.0 (*c* 0.4); IR (film) ν_{max} 2925, 1729, 1462, 1367, 1164, 1073, 1049 cm^{-1}; ^1H NMR (C_6D_6) 0.80 (s, 3H), 0.84 (s, 3H), 0.86 (s, 3H), 1.24 (s, 3H), 0.81-2.48 (m, 10H), 3.80-3.91 (m, 2H), 5.74 (dd, *J* = 2.8, 10.1 Hz, 1H), 5.87 (dd, *J* = 2.8, 10.1 Hz, 1H); ^{13}C NMR (C_6D_6) 14.1 (q), 18.8 (t), 22.2 (q), 25.6 (t), 27.5 (q), 32.7 (s), 33.3 (q), 36.5 (s), 38.8 (t), 41.8 (t), 53.1 (d), 58.2 (d), 65.8 (t), 80.2 (s), 127.5 (d), 132.8 (d); HRMS: M^+, found 234.1983. $C_{16}H_{26}O$ requires 234.1984; MS *m/e* (%) 234 (M^+, 11), 220 (16), 219 (100), 201 (14), 147 (13), 135 (5), 123 (17), 119 (6), 69 (5), 43 (5).



(+)-(1*S*,3*R*,4*R*,4a*S*,8a*S*)-4-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-3,4a,8,8-tetra-methyldecahydro-1,3-naphthalenediol (472).

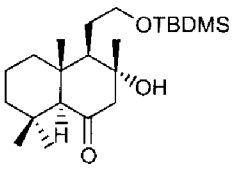
A mixture of triol **450** (0.77 g; 2.85 mmol), *tert*-butyldimethylsilyl chloride (0.47 g; 3.13 mmol) and imidazole (0.31 g; 4.56 mmol) in DMF (30 mL) was stirred at room temperature. After 1 h the mixture was diluted with ether, washed with H_2O and worked up as usual. The crude yellow oil was purified by flash column chromatography (eluent PE/EA 5:2) to give silyl ether **472** (1.04 g; 2.71 mmol; 95%) as white crystals.

M.p. 160-162°C; $[\alpha]_D^{20}$ +9.8 (*c* 0.8); IR (KBr) ν_{max} 3420, 2924, 1471, 1362, 1257 cm^{-1}; ^1H NMR δ 0.04 (s, 6H), 0.78 (s, 3H), 0.86 (s, 9H), 0.94 (s, 3H), 1.12 (s, 3H), 1.15 (s, 3H), 1.25-1.67 (m, 13H), 2.17 (dd, *J* = 3.7, 12.0 Hz, 1H), 3.41 (dt, *J* = 4.3, 9.7 Hz, 1H), 3.71-3.84 (m, 2H); ^{13}C NMR δ -5.4 (2x q), 16.5 (q), 18.1 (t), 18.2 (s), 22.0 (q), 25.8 (q), 25.9 (3x q), 27.6 (t), 33.7 (s), 36.4 (q), 39.3 (s), 39.5 (t), 43.5 (t), 54.4 (t), 58.4 (d), 61.2 (d), 64.7 (t), 69.0 (d), 71.5 (s); HRMS: (M^+-CH_3), found 369.2825. $C_{21}H_{41}O_3Si$ requires 369.2821; MS *m/e* (%) 369 [(M^+-15), 1], 241 (30), 217 (36), 191 (100), 151 (40), 109 (27), 95 (26), 75 (51), 69 (33), 32 (43), 31 (54).



(+)-(1*S*,3*R*,4*R*,4a*S*,8a*S*)-4-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-3,4a,8,8-tetra-methyldecahydro-1,3-naphthalenediol (472).

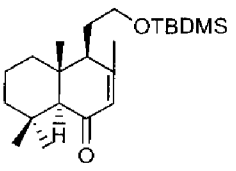
A solution of compound **476** (1.00 g; 2.25 mmol) in a 0.2 M solution of sodium methoxide in MeOH (25 mL) was stirred at 50°C for 5 h. After evaporation of the solvent ether was added and the mixture was acidified with a 4 M solution of hydrochloric acid (5 mL). The mixture was extracted, washed with brine, dried and evaporated. Purification by flash column chromatography (eluent PE/EA 5:1) gave **472** (0.294 g; 0.765 mmol; 34%) as white crystals, identical in all aspects with the product obtained before. Further elution (eluent PE/EA 1:1) gave triol **450** (0.273 g; 1.012 mmol; 45%) as white crystals with analytical data as mentioned before.



(+)-(3*R*,4*R*,4a*R*,8a*S*)-4-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-3-hydroxy-3,4a,8,8-tetramethyloctahydro-1(2*H*)-naphthalenone (473).

A mixture of silylether **472** (0.8 g; 2.08 mmol), PDC (1.18 g; 3.13 mmol), and 3Å molecular sieves (0.5 g) in CH_2Cl_2 (30 mL) was stirred at room temperature. After 90 min the black mixture was filtered over silica gel, flushed with ethyl acetate and the solvent was evaporated. Purification of the residue by flash column chromatography (eluent PE/EA 10:1) gave pure **473** (0.68 g; 1.79 mmol; 86%) as white crystals.

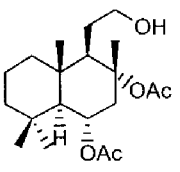
M.p. 86-88°C; $[\alpha]_D^{20}$ +3.3 (*c* 0.8); IR (KBr) ν_{max} 3425, 2933, 1713, 1491, 1387, 1252, 1088 cm^{-1}; ^1H NMR δ 0.11 (s, 6H), 0.76 (s, 3H), 0.89 (s, 9H), 0.91 (s, 3H), 1.11 (s, 3H), 1.16 (s, 3H), 1.22-1.84 (m, 10H), 2.19 (s, 1H), 2.52-2.63 (m, 2H), 3.49-3.58 (m, 1H), 3.83-3.90 (m, 1H); ^{13}C NMR δ -5.4 (2x q), 16.2 (q), 18.2 (t), 18.3 (s), 21.6 (q), 25.3 (q), 25.9 (3x q), 27.8 (t), 32.1 (s), 32.3 (q), 39.8 (t), 41.5 (s), 42.6 (t), 59.6 (d), 60.4 (t), 64.5 (t), 66.1 (d), 74.8 (s), 209.7 (s); HRMS: (M^+-C_4H_9), found 325.2199. $C_{18}H_{33}O_3Si$ requires 325.2196; MS *m/e* (%) 325 [(M^+-57), 100], 267 (35), 201 (36), 123 (86), 109 (40), 105 (90), 95 (30), 81 (26), 75 (58), 73 (29); Anal.: found C, 69.92; H, 11.11%. $C_{22}H_{42}O_3Si$ requires C, 69.07; H, 11.07%.



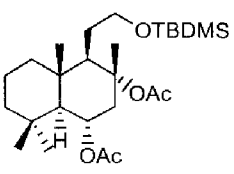
(+)-(4*S*,4a*R*,8a*S*)-4-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-3,4a,8,8-tetramethyl-4a,5,6,7,8,8a-hexahydro-1(4*H*)-naphthalenone (474).

To a solution of **473** (0.63 g; 1.65 mmol) and DMAP (25 mg; 0.20 mmol) in dry pyridine (15 mL) was added $SOCl_2$ (0.3 mL; 4.12 mmol) at 0°C. The reaction mixture was allowed to warm slowly to room temperature. After stirring for 2 h the mixture was quenched with ice and extracted with ethyl acetate. The organic solution was washed with water, saturated aqueous $NaHCO_3$, and brine and worked up as usual. The crude oil was isomerized into the conjugated ketone **474** by treatment with an 1 M solution of sodium methoxide (3 mL) in methanol (25 mL) at room temperature during 2 h. The methanol was evaporated and an 1 M aqueous solution of HCl (100 mL) was added. Extraction with ether followed by usual work up gave

the crude product which was purified by flash column chromatography (eluent PE/EA 25:1) to give compound **474** (0.49 g; 1.346 mmol; 82%) as a colourless oil, which crystallizes upon standing.
M.p. 48-50°C; $[\alpha]_D^{20}$ +7.3 (*c* 1.2); IR (film) ν_{max} 2928, 1672, 1462, 1385, 1255, 1098 cm^{-1}; ^1H NMR δ 0.06 (s, 6H), 0.83 (s, 3H), 0.90 (s, 9H), 1.14 (s, 3H), 1.17 (s, 3H), 1.18-2.14 (m, 8H), 1.89 (s, 3H), 2.04 (s, 1H), 2.16 (br s, 1H), 3.56-3.79 (m, 2H), 5.76 (br s, 1H); ^{13}C NMR δ -5.5 (2x q), 14.4 (q), 17.9 (t), 18.3 (s), 21.2 (q), 22.0 (q), 25.7 (3x q), 29.9 (t), 32.2 (q), 33.2 (q), 38.5 (t), 42.8 (s), 42.9 (t), 51.9 (d), 63.3 (d), 63.7 (t), 128.4 (d), 158.6 (s), 200.2 (s); HRMS: M^+, found 364.2801. $C_{22}H_{40}O_2Si$ requires 364.2798; MS *m/e* (%) 364 (M^+, 1), 308 (24), 307 (100), 249 (20), 232 (70), 173 (15), 149 (54), 147 (26), 95 (18), 75 (23), 73 (16); Anal.: found C, 72.13; H, 10.94%. $C_{22}H_{40}O_2Si$ requires C, 72.07; H, 11.55%.

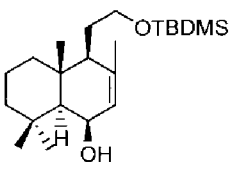


(+)-(1*R*,2*R*,4*S*,4a*S*,8a*S*)-4-(Acetyloxy)-1-(2-hydroxyethyl)-2,5,5,8a-tetramethyl-decahydro-2-naphthalenyl acetate (475).
To a solution of aldehyde **187** (0.100 g; 0.28 mmol) in methanol (10 mL) was added sodium borohydride (0.044 g; 1.14 mmol) at 0°C. The reaction mixture was stirred for an additional hour at room temperature, and the methanol was evaporated. Water and 4 M aqueous hydrochloric acid were added to the residue and the aqueous mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried and evaporated. The crude oil was purified by flash column chromatography (eluent PE/EA 2:1) to give compound **475** (0.080 g; 0.226 mmol; 80%) as a clear oil.
$[\alpha]_D^{20}$ +43.0 (*c* 0.9); IR (film) ν_{max} 3501, 3000, 2931, 2872, 1732, 1715 cm^{-1}; ^1H NMR δ 0.85 (s, 3H), 0.93 (s, 3H), 0.98 (s, 3H), 1.57 (s, 3H), 1.96 (s, 3H), 2.03 (s, 3H), 1.20-2.05 (m, 12H), 2.86 (dd, *J* = 4.0, 12.1 Hz, 1H), 3.60-3.69 (m, 2H), 5.12 (dt, *J* = 4.1, 11.2 Hz, 1H); ^{13}C NMR δ 16.3 (q), 18.0 (t), 21.1 (q), 21.9 (q), 22.0 (q), 24.4 (t), 25.1 (q), 33.3 (s), 36.0 (q), 39.2 (s), 39.5 (t), 43.3 (t), 50.2 (t), 57.2 (d), 58.3 (d), 66.3 (t), 70.7 (d), 72.8 (s), 170.2 (s), 171.2 (s); HRMS: (M^+-$C_2H_4O_2$), found 294.2220. $C_{18}H_{30}O_3$ requires 294.2195; MS *m/e* (%) 294 [(M^+-60), 15], 219 (46), 176 (32), 129 (89), 109 (36), 95 (33), 87 (75), 69 (40), 43 (100); Anal.: found C, 67.37; H, 9.66%. $C_{20}H_{34}O_5$ requires C, 67.77; H, 9.67%.



(+)-(1*R*,2*R*,4*S*,4a*S*,8a*S*)-4-(Acetyloxy)-1-(2-{[*tert*-butyl(dimethyl)silyl]-oxy}ethyl)-2,5,5,8a-tetramethyldecahydro-2-naphthalenyl acetate (476).
A mixture of alcohol **475** (0.50 g; 1.41 mmol), *tert*-butyldimethylsilyl chloride (0.276 g; 1.83 mmol) and imidazole (0.250 g; 3.67 mmol) in DMF (30 mL) was stirred at room temperature. After 1 h the mixture was diluted with ether, washed with H_2O and worked up as usual. The crude yellow oil was purified by flash column chromatography (eluent PE/EA 15:1) to give silyl ether **476** (0.607 g; 1.297 mmol; 92%) as white crystals.
M.p. 87-89°C; $[\alpha]_D^{20}$ +40.4 (*c* 1.1); IR (KBr) ν_{max} 2930, 2857, 1729, 1368, 1251, 1072 cm^{-1}; ^1H NMR δ 0.00 (s, 6H), 0.78 (s, 3H), 0.83 (s, 9H), 0.84 (s, 3H), 0.99 (s, 3H), 1.50 (s, 3H), 1.88 (s, 3H), 1.96

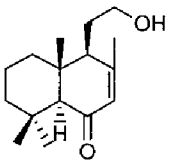
(s, 3H), 0.82-1.82 (m, 11H), 2.78 (dd, J = 4.1, 12.0 Hz, 1H), 3.42-3.65 (m, 2H), 5.04 (dt, J = 4.1, 11.2 Hz, 1H); ^{13}C NMR δ -5.1 (2x q), 16.7 (q), 17.9 (t), 18.4 (s), 21.6 (q), 21.9 (q), 22.9 (q), 25.6 (q), 26.1 (3x q), 29.4 (t), 33.2 (s), 36.0 (q), 39.0 (s), 39.5 (t), 43.3 (t), 45.1 (t), 54.0 (d), 57.9 (d), 64.9 (t), 70.0 (d), 85.6 (s), 169.9 (s), 170.0 (s); HRMS: (M^+-$C_4H_8O_4$), found 348.2844. $C_{22}H_{40}OSi$ requires 348.2848; MS *m/e* (%) 348 [(M^+-120), 9], 291 (49), 217 (76), 201 (28), 191 (100), 190 (50), 119 (30), 117 (27), 75 (32), 73 (28), 69 (24), 43 (23).



(-)-(1*R*,4*S*,4a*R*,8a*S*)-4-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-3,4a,8,8-tetra-methyl-1,4,4a,5,6,7,8,8a-octahydro-1-naphthalenol (477).

To a solution of **474** (0.02 g; 0.055 mmol) in dry toluene (3 mL) at -78 °C under N_2 was added DIBAL-H (0.15 mL of an 1.5 M solution in toluene; 0.22 mmol). After stirring for 1 h, the excess of Dibal-H was quenched with ethyl acetate and an 1 M solution of HCl. The mixture was then extracted with ethyl acetate and the organic layers were washed with brine, dried and evaporated. The residue was purified by flash column chromatography (eluent PE/EA 25:1) to afford **477** (0.018 g; 0.049 mmol; 90%) as a colourless oil.

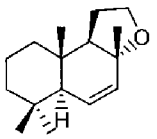
$[\alpha]_D^{20}$ -32.1 (*c* 1.2); IR (film) ν_{max} 3474, 2927, 2859, 1668, 1462, 1386, 1255, 1098, 1029, 938 cm^{-1}; ^{1}H NMR δ 0.05 (s, 6H), 0.89 (s, 9H), 1.01 (s, 3H), 1.04 (s, 3H), 1.30 (s, 3H), 1.73 (s, 3H), 0.82-2.00 (m, 11H), 3.47-3.59 (m, 1H), 3.67-3.93 (m, 1H), 4.36 (br s, 1H), 5.59 (br d, J = 4.9 Hz, 1H); ^{13}C NMR δ -5.2 (2x q), 16.3 (q), 18.4 (s), 19.0 (t), 22.1 (q), 24.8 (q), 26.0 (3x q), 30.6 (t), 32.7 (q), 34.2 (s), 36.3 (s), 41.4 (t), 44.7 (t), 51.3 (d), 54.3 (d), 64.6 (t), 66.2 (d), 125.6 (d), 138.0 (s); HRMS: (M^+-H_2O), found 348.2843. $C_{22}H_{40}OSi$ requires 348.2848; MS *m/e* (%) 348 [(M^+-18), 12], 291 (41), 201 (29), 191 (25), 190 (100), 173 (19), 147 (18), 138 (16), 119 (28), 75 (30), 73 (26).



(+)-(4*S*,4a*R*,8a*S*)-4-(2-Hydroxyethyl)-3,4a,8,8-tetramethyl-4a,5,6,7,8,8a-hexa-hydro-1(4*H*)-naphthalenone (478).

To a solution of **474** (0.49 g; 1.34 mmol) in dry THF (25 mL) was added TBAF (1.34 mL of an 1.1 M solution in THF; 1.47 mmol). After 1 h, the mixture was diluted with H_2O and extracted with ethyl acetate. The organic layers were washed with brine, dried and concentrated to yield the crude product as an oil. This oil was purified by flash column chromatography (eluent PE/EA 2:1) to afford **478** (0.31 g; 1.25 mmol; 93%) as a colourless oil.

$[\alpha]_D^{20}$ +12.9 (*c* 1.5); IR (film) ν_{max} 3437, 2927, 1667, 1460, 1379, 1235, 1166, 1038 cm^{-1}; ^{1}H NMR δ 0.83 (s, 3H), 1.11 (s, 3H), 1.14 (s, 3H), 1.91 (s, 3H), 1.17-2.29 (m, 11H), 3.60-3.88 (m, 2H), 5.76 (br s, 1H); ^{13}C NMR δ 14.2 (q), 17.9 (t), 21.2 (q), 21.9 (q), 27.8 (s), 29.7 (t), 33.2 (q), 38.5 (t), 42.8 (s), 43.0 (t), 51.8 (d), 63.3 (d), 63.4 (t), 128.5 (d), 158.3 (s), 200.2 (s); HRMS: M^+, found 250.1927. $C_{16}H_{26}O_2$ requires 250.1933; MS *m/e* (%) 250 (M^+, 21), 167 (13), 149 (56), 127 (8), 126 (100), 109 (14), 95 (56), 81 (7), 69 (8), 41 (9).

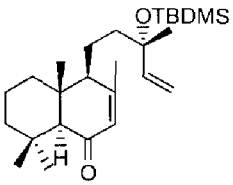


(-)-(3a*R*,5a*S*,9a*S*,9b*R*)-3a,6,6,9a-Tetramethyl-1,2,3a,5a,6,7,8,9,9a,9b-decahydro-naphtho[2,1-*b*]furan (Δ^6-Ambroxene) (466).

- To a solution of **477** (0.25 g; 0.068 mmol) in dry THF (3 mL) was added TBAF (0.07 mL of an 1.1 M solution in THF; 0.075 mmol). After 1 h, the mixture was diluted with H_2O and extracted with ethyl acetate. The organic layers were washed with brine, dried and concentrated to yield the crude diol **471** (20 mg). This residue was not purified, but directly converted into **466** by treatment with *p*-toluenesulfonic acid (0.05 g; 0.26 mmol) in nitromethane (5 mL) at room temperature. After 4 h the mixture was diluted with ether and washed with saturated aqueous sodium bicarbonate and brine and worked up as usual. Flash column chromatography on silica gel (eluent PE/EA 5:1) gave compound **466** (0.0138 g; 0.059 mmol; 87%) as a clear oil. For analytical data see before.

- To a solution of **478** (0.05 g; 0.20 mmol) in dry toluene (5 mL) at -78°C under N_2 was added Dibal-H (0.067 mL of a 1.5 M solution in toluene; 1.00 mmol). After stirring for 1 h, the excess of Dibal-H was quenched with ethyl acetate and an 1 M solution of aqueous HCl was added. The mixture was then extracted with ethyl acetate. The organic layers were washed with brine , dried and evaporated to afford **471** as an oil which was not purified, but directly converted into **466** as described above. Compound **466** (0.024 g; 0.102 mmol; 71%) is obtained as a clear oil with analytical data in all aspects as before.

The conversion of **474** into **466** *via* **471** was performed as described above, compound **466** (0.018 g; 0.077 mmol; 40%) is obtained as a clear oil with analytical data as before.

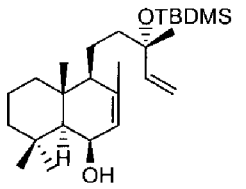


(+)-(4*S*,4a*R*,8a*S*)-4-((3*S*)-3-([*tert*-Butyl(dimethyl)silyl]oxy)-3-methyl-4-pentenyl)-3,4a,8,8-tetramethyl-4a,5,6,7,8,8a-hexahydro-1(4*H*)-naphthalenone (479).

To a stirred solution of enone **164**[1] (0.98 g; 3.22 mmol) in DMF (35 mL) were added *tert*-butyldimethylsilyl chloride (4.86 g; 32.24 mmol) and imidazole (4.39 g; 64.47 mmol). The reaction mixture was stirred at 60°C for 3 days. After cooling to room temperature a saturated aqueous solution of $NaHCO_3$ was added and the mixture was extracted with ethyl acetate. The organic solution was washed with H_2O and worked up as usual. The crude yellow oil was purified by flash column chromatography (eluent PE/EA 25:1) to give **479** (1.24 g; 2.96 mmol; 92%) as a colourless oil.

$[\alpha]_D$ +26.0 (*c* 0.9); IR (film) ν_{max} 2929, 1673, 1462, 1254, 1120, 1037 cm^{-1}; ^1H NMR δ 0.06 (s, 6H), 0.82 (s, 3H), 0.88 (s, 9H), 1.11 (s, 3H), 1.14 (s, 3H), 1.32 (s, 3H), 1.89 (s, 3H), 0.86-2.02 (m, 12H), 5.03 (dd, *J* = 1.4, 10.7 Hz, 1H), 5.14 (dd, *J* = 1.4, 17.4 Hz, 1H), 5.73 (br s, 1H), 5.87 (dd, *J* = 10.7, 17.4 Hz, 1H); ^{13}C NMR δ -2.0 (2x q), 14.7 (q), 18.2 (t), 18.3 (s), 21.4 (t), 21.5 (q), 22.2 (q), 25.9 (3x q), 26.9 (q), 32.3 (s), 33.5 (q), 38.8 (t), 43.2 (t), 43.5 (s), 46.8 (t), 56.6 (d), 63.6 (d), 75.7 (s), 112.3 (t), 128.4 (d), 145.4 (d), 159.3 (s), 200.4 (s); HRMS: (M^+-15), found 403.3030. $C_{25}H_{43}O_2Si$ requires

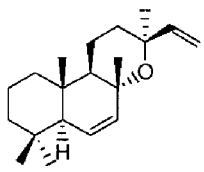
403.3032; MS *m/e* (%) 403 [(M^+-15), 5], 363 (8), 362 (30), 361 (100), 286 (19), 186 (9), 185 (57), 135 (11), 81 (9), 75 (30), 73 (17).



(-)-(1*R*,4*S*,4a*R*,8a*S*)-4-((3*S*)-3-([*tert*-Butyl(dimethyl)silyl]oxy)-3-methyl-4-pentenyl)-3,4a,8,8-tetramethyl-1,4,4a,5,6,7,8,8a-octahydro-1-naphthalenol (480).

To a solution of the above mentioned silyl ether **479** (0.10 g; 0.239 mmol) in dry toluene (5 mL) at -78°C under N_2 was added DIBAL-H (0.64 mL of an 1.5M solution in toluene; 0.957 mmol). After stirring for 1 h, the excess of DIBAL-H was quenched with ethyl acetate and then with an aqueous solution of 1M HCl. The mixture was extracted with ethyl acetate. The organic layers were washed with brine, dried and evaporated. The residue was purified by flash column chromatography (eluent PE/EA 25:1) to obtain **480** (0.094 g; 0.234 mmol; 98%) as a colourless oil.

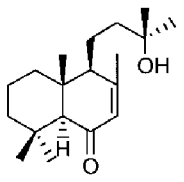
$[\alpha]_D$ -6.6 (*c* 1.6); IR (film) ν_{max} 3472, 2927, 2858, 1461, 1254, 1041, 919 cm^{-1}; ^1H NMR δ 0.06 (s, 6H), 0.86 (s, 3H), 0.87 (s, 9H), 1.01 (s, 3H), 1.03 (s, 3H), 1.30 (s, 3H), 1.72 (s, 3H), 1.00-2.42 (m, 13H), 4.34 (br s, 1H), 4.99 (dd, *J* = 1.5, 10.6 Hz, 1H), 5.12 (dd, *J* = 1.5, 17.4 Hz, 1H), 5.54 (br s, 1H), 5.91 (dd, *J* = 10.6, 17.4 Hz, 1H); ^{13}C NMR δ -1.9 (2x q), 16.1 (q), 18.3 (s), 19.1 (t), 21.8 (t), 22.2 (q), 24.7 (q), 26.0 (3x q), 26.6 (q), 32.7 (q), 34.1 (s), 36.9 (s), 41.4 (t), 44.8 (t), 46.9 (t), 54.3 (d), 55.7 (d), 65.6 (d), 75.9 (s), 111.8 (t), 125.9 (d), 138.0 (s), 145.7 (d); HRMS: M^+, found 420.3429. $C_{26}H_{48}O_2Si$ requires 420.3424; MS *m/e* (%) 420 (M^+, 1), 277 (21), 270 (24), 220 (33), 203 (24), 185 (100), 133 (19), 119 (32), 81 (21), 75 (74), 73 (35).



(+)-(3*S*,4a*R*,6a*S*,10a*S*,10b*R*)-3,4a,7,7,10a-Pentamethyl-3-vinyl-2,3,4a,6a,7,8,9,10,10a,10b-decahydro-1*H*-benzo[*f*]chromene (481).

A solution of **480** (0.171 g; 0.407 mmol) in CH_3CN (6 mL) was treated with HF (0.144 mL of a 50% aqueous solution) at room temperature. After stirring for 30 min the mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with ethyl acetate. The organic layers were washed with brine, dried and evaporated to give the corresponding diol, according to NMR spectroscopy. This residue was purified by flash column chromatography (eluent PE/EA 25:1) which gave the *cyclized* compound **481** (0.078 g; 0.273 mmol; 67%) as a colourless oil.

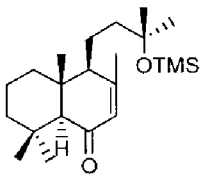
$[\alpha]_D$ +8.8 (*c* 0.25); IR (film) ν_{max} 2925, 1464, 1370, 1214, 921 cm^{-1}; ^1H NMR (benzene-d_6) δ 0.98 (s, 3H), 1.01 (s, 3H), 1.03 (s, 3H), 1.23 (s, 3H), 1.78 (s, 3H), 0.81-2.15 (m, 12H), 5.02 (dd, *J* = 1.5, 10.7 Hz, 1H), 5.24 (dd, *J* = 1.5, 17.3 Hz, 1H), 5.70-5.91 (m, 2H), 5.98 (dd, *J* = 3.2, 9.6 Hz, 1H); ^{13}C NMR (benzene-d_6) δ 15.6 (q), 17.5 (q), 19.1 (t), 21.6 (t), 22.8 (q), 27.9 (q), 32.5 (q), 32.9 (s), 33.4 (t), 39.3 (s), 41.2 (t), 42.5 (t), 53.1 (d), 53.2 (d), 53.4 (s), 72.8 (s), 111.4 (t), 126.3 (d), 129.9 (d), 145.1 (d); HRMS: M^+, found 288.2448. $C_{20}H_{32}O$ requires 288.2453; MS *m/e* (%) 288 (M^+, 28), 189 (39), 188 (45), 187 (60), 173 (39), 133 (32), 119 (100), 69 (35), 55 (30), 43 (37).



(+)-(4*S*,4a*R*,8a*S*)-4-(3-Hydroxy-3-methylbutyl)-3,4a,8,8-tetramethyl-4a,5,6,7,8,8a-hexahydro-1(4*H*)-naphthalenone (482).

To a solution of **350**[1] (0.18 g; 0.652 mmol) in dry ether (10 mL) at -78°C under N_2 was added MeLi (0.49 mL of an 1.6 M solution in Et_2O; 0.78 mmol). After stirring for 1 h, the mixture was quenched with H_2O and extracted with ethyl acetate and worked up as usual. The crude oil was purified by flash column chromatography (eluent PE/EA 4:1 to 2:1) to yield alcohol **482** (0.154 g; 0.528 mmol; 81%) as a colourless oil.

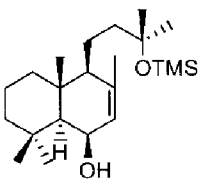
$[\alpha]_D$ +20.0 (*c* 0.4); IR (film) ν_{max} 3432, 2972, 1668, 1468, 1379, 1292, 1211, 1154, 942 cm^{-1}; ^1H NMR δ 0.84 (s, 3H), 1.11 (s, 3H), 1.14 (s, 3H), 1.24 (s, 6H), 1.91 (s, 3H), 1.04-1.90 (m, 11H), 2.00-2.03 (m, 2H), 5.74 (br s, 1H); ^{13}C NMR δ 14.7 (q), 18.2 (t), 21.5 (q), 21.7 (t), 22.1 (q), 29.1 (q), 29.4 (q), 32.3 (s), 33.5 (q), 38.7 (t), 43.2 (t), 43.4 (s), 46.3 (t), 58.6 (d), 63.6 (d), 71.1 (s), 128.5 (d), 158.3 (s), 200.3 (s); HRMS: M^+, found 292.2399. $C_{19}H_{32}O_2$ requires 292.2402; MS *m/e* (%) 292 (M^+, 2), 277 (15), 274 (44), 219 (31), 218 (86), 136 (12), 135 (100), 109 (19), 108 (27), 95 (16), 69 (13).



(+)-(4*S*,4a*R*,8a*S*)-3,4a,8,8-Tetramethyl-4-{3-methyl-3-[(trimethylsilyl)oxy]-butyl}-4a,5,6,7,8,8a-hexahydro-1(4*H*)-naphthalenone (483).

To a stirred solution of **482** (0.122 g; 0.418 mmol) in DMF (10 mL) were added trimethylsilyl chloride (0.136 g; 1.253 mmol; 0.16 mL) and imidazole (0.171 g; 2.507 mmol). The reaction mixture was stirred at room temperature. After 30 min the mixture was diluted with ethyl acetate and water was added. The mixture was extracted with ethyl acetate. The organic solution was washed with H_2O and worked up as usual. The crude oil was purified by flash column chromatography (eluent PE/EA 25:1) to give silyl ether **483** (0.151 g; 0.415 mmol; 99%) as a colourless oil.

$[\alpha]_D$ +19.9 (*c* 0.9); IR (film) ν_{max} 2929, 1673, 1463, 1382, 1250, 1152, 1041, 839 cm^{-1}; ^1H NMR δ 0.00 (s, 9H), 0.75 (s, 3H), 1.01 (s, 3H), 1.05 (s, 3H), 1.13 (s, 6H), 1.80 (s, 3H), 1.04-1.93 (m, 12H), 5.63 (br s, 1H); ^{13}C NMR δ 2.6 (3x q), 14.7 (q), 18.2 (t), 21.5 (q), 21.6 (t), 22.1 (q), 29.6 (q), 29.7 (q), 32.3 (s), 33.5 (q), 38.8 (t), 43.2 (t), 43.4 (s), 47.5 (t), 56.7 (d), 63.7 (d), 73.9 (s), 128.4 (d), 159.4 (s), 200.4 (s); HRMS: (M^+-15), found 349.2564. $C_{21}H_{37}O_2Si$ requires 349.2563; MS *m/e* (%) 349 [(M^+-15), 13], 274 (47), 219 (34), 218 (100), 148 (15), 135 (87), 131 (89), 109 (16), 108 (28), 75 (22), 73 (38).

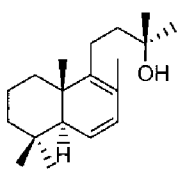


(-)-(1*R*,4*S*,4a*R*,8a*S*)-3,4a,8,8-Tetramethyl-4-{3-methyl-3-[(trimethylsilyl)oxy]-butyl}-1,4,4a,5,6,7,8,8a-octahydro-1-naphthalenol (484).

To a solution of silyl ether **483** (0.108 g; 0.297 mmol) in dry toluene (8 mL) at -78°C under N_2 was added DIBAL-H (0.79 mL of an 1.5 M solution in toluene; 1.188 mmol). After stirring for 1 h, the reaction mixture was diluted with Et_2O (5 mL) and H_2O (3 drops) was added. After stirring for 15 min a 4 M aqueous solution of NaOH (3 drops) was added,

followed by addition of H_2O (3 drops) again after 15 min of stirring in between. The mixture was dried by addition of $MgSO_4$, filtrated and evaporated to afford an oil. This residue was purified by flash column chromatography (eluent PE/EA 25:1) to obtain **484** (0.082 g; 0.224 mmol; 75%) as a colourless oil, which crystallizes upon standing.

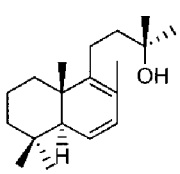
M.p. 65-67°C; $[\alpha]_D$ -33.4 (*c* 0.35); IR (film) ν_{max} 3376, 2926, 1459, 1382, 1364, 1249, 1055, 839 cm^{-1}; ^1H NMR (benzene-d_6) δ 0.24 (s, 9H), 1.14 (s, 6H), 1.20 (s, 6H), 1.55 (s, 3H), 1.77 (s, 3H), 0.89-1.96 (m, 13H), 4.33 (br s, 1H), 5.47 (br d, *J* = 4.8 Hz, 1H); ^{13}C NMR (benzene-d_6) δ 2.5 (3x q), 16.2 (q), 19.2 (t), 22.1 (q), 22.2 (t), 24.8 (q), 29.5 (q), 29.6 (q), 32.7 (q), 34.2 (s), 36.9 (s), 41.5 (t), 44.8 (t), 47.8 (t), 54.3 (d), 55.9 (d), 65.7 (d), 74.1 (s), 126.0 (d), 137.6 (s); HRMS: (M^+-15), found 351.2713. $C_{21}H_{39}O_2Si$ requires 351.2719; HRMS: (M^+-18), found 348.2845. $C_{22}H_{40}OSi$ requires 348.2848; MS *m/e* (%) 351 [(M^+-15), 1], 348 (1), 276 (15), 261 (11), 221 (16), 220 (100), 205 (44), 152 (11), 131 (60), 109 (27), 73 (17), 69 (10); Anal.: found C, 71.24; H, 11.56%. $C_{22}H_{42}O_2Si$ requires C, 72.07; H, 11.55%.



(-)-4-[(4a*S*,8a*S*)-2,5,5,8a-Tetramethyl-4a,5,6,7,8,8a-hexahydro-1-naphthalenyl]-2-methyl-2-butanol (485).

A solution of **484** (0.056 g; 0.153 mmol) in CH_3CN (8 mL) was treated with HF (0.10 mL of a 50% solution) at room temperature. After stirring for 30 min the mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and was then extracted with ethyl acetate. The organic layers were washed with brine, dried and evaporated. The residue was purified by flash column chromatography (eluent PE/EA 10:1 to 5:1) and the intermediate diol spontaneaously dehydrated to diene **485** (0.034 g; 0.123 mmol; 80%), which was obtained as a colourless oil.

$[\alpha]_D$ -71.7 (*c* 0.75); IR (film) ν_{max} 3385, 2958, 1460, 1369, 1212, 908 cm^{-1}; ^1H NMR (benzene-d_6) δ 0.96 (s, 3H), 1.03 (s, 3H), 1.04 (s, 3H), 1.13 (s, 6H), 1.78 (s, 3H), 0.91-2.34 (m, 12H), 5.80 (dd, *J* = 2.8, 9.5 Hz, 1H), 5.98 (dd, *J* = 3.1, 9.5 Hz, 1H); ^{13}C NMR (benzene-d_6) δ 15.6 (q), 17.5 (q), 19.1 (t), 22.0 (t), 22.8 (q), 28.9 (q), 29.0 (q), 32.5 (q), 32.9 (s), 35.3 (t), 39.3 (s), 41.2 (t), 44.0 (t), 53.1 (d), 70.1 (s), 124.8 (s), 126.3 (d), 129.9 (d), 144.1 (s); HRMS: M^+, found 276.2456. $C_{19}H_{32}O$ requires 276.2453; MS *m/e* (%) 276 (M^+, 40), 189 (56), 188 (43), 187 (88), 173 (37), 159 (14), 133 (32), 131 (15), 120 (14), 119 (100).



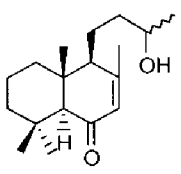
(-)-4-[(4a*S*,8a*S*)-2,5,5,8a-Tetramethyl-4a,5,6,7,8,8a-hexahydro-1-naphthalenyl]-2-methyl-2-butanol (485).

To a solution of **482** (0.070 g; 0.2397 mmol) in dry toluene (7 mL) at -78°C under N_2 was added DIBAL-H (0.71 mL of an 1.5M solution in toluene; 1.068 mmol). After stirring for 1 h, the reaction mixture was diluted with Et_2O (5 mL) and H_2O (3 drops) was added. After stirring for 15 min a 4 M aqueous solution of NaOH (3 drops) was added, followed by addition of H_2O (3 drops) again after 15 min of stirring in between. The mixture was dried by

addition of $MgSO_4$, filtrated and evaporated. The residue was purified by flash column chromatography (eluent PE/EA 10:1) to afford diol *(1R,4S,4aR,8aS)-4-(3-hydroxy-3-methylbutyl)-3,4a,8,8-tetramethyl-1,4,4a,5,6,7,8,8a-octahydro-1-naphthalenol* (0.028 g; 0.095 mmol; 40%) as a colourless oil.

$[\alpha]_D$ -50.8 (*c* 0.7); IR (film) ν_{max} 3406, 2924, 1459, 1378, 1027, 914 cm^{-1}; ^1H NMR δ 1.03 (s, 6H), 1.22 (s, 6H), 1.29 (s, 3H), 1.74 (s, 3H), 0.95-1.91 (m, 14H), 4.35 (br s, 1H), 5.55 (br s, 1H); ^{13}C NMR δ 16.3 (q), 19.0 (t), 21.9 (t), 22.1 (q), 24.8 (q), 29.0 (q), 29.3 (q), 32.7 (q), 34.2 (s), 36.9 (s), 41.4 (t), 44.7 (t), 46.6 (t), 54.3 (d), 55.9 (d), 66.2 (d), 71.3 (s), 125.5 (d), 138.3 (s); HRMS: M^+, found 294.2556. $C_{19}H_{34}O_2$ requires 294.2559; MS *m/e* (%) 294 (M^+, 17), 261 (50), 220 (61), 205 (60), 189 (35), 187 (45), 135 (35), 119 (68), 109 (100), 95 (35), 69 (50).

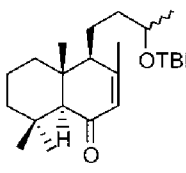
The above obtained diol (0.050 g; 0.170 mmol) was submitted to a catalytic amount of PPTS (0.025 g; 0.0994 mmol) in nitromethane (5 mL) at room temperature for 90 min. Ether was added and the mixture was washed with a saturated aqueous sodium bicarbonate solution and brine, dried and evaporated. Flash column chromatography (eluent PE/EA 10:1 to 3:1) gave diene **485** (0.037 g; 0.134 mmol; 79%) as a colourless oil with analytical data as before.



(4*S*,4a*R*,8a*S*)-4-(3ζ-Hydroxybutyl)-3,4a,8,8-tetramethyl-4a,5,6,7,8,8a-hexahydro-1(4*H*)-naphthalenone (486a and 486b).

To a solution of **350**[1] (0.100 g; 0.362 mmol) in MeOH (5 mL) at 0°C was added $NaBH_4$ (0.018 g; 0.471 mmol). After stirring for 15 min, the mixture was quenched with an 1 M aqueous solution of HCl, extracted with ethyl acetate and worked up as usual. The crude residue was purified by flash column chromatography (eluent PE/EA 2:1) to give alcohols **486a** and **486b** (0.095 g; 0.342 mmol; 94%) as a colourless oil as an inseparable C(13) diastereomeric mixture in a ratio of 5:2, determined by ^1H NMR.

IR (film) ν_{max} 3421, 2925, 1654, 1458, 1376, 1129, 974 cm^{-1}; ^1H NMR (major peaks) δ 0.84 (s, 3H), 1.14 (s, 3H), 1.19 (s, 3H), 1.28 (d, J = 16.3 Hz, 3H), 0.81-1.91 (m, 11H), 1.93 (s, 3H), 2.01-2.05 (m, 2H), 3.82 (m, 1H), 5.75 (br s, 1H); ^1H NMR (minor peaks) δ 3.81 (m, 1H), 5.74 (br s, 1H); ^{13}C NMR (major peaks) δ 14.6 (q), 18.2 (t), 21.5 (q), 22.1 (q), 23.2 (t), 23.8 (q), 32.3 (q), 33.5 (q), 38.8 (t), 41.5 (t), 41.7 (s), 43.2 (t), 56.3 (d), 63.6 (d), 68.0 (d), 128.5 (d), 158.8 (s), 200.3 (s); ^{13}C NMR (minor peaks) δ 14.7 (q), 21.6 (q), 23.7 (q), 56.5 (d), 67.9 (d), 128.6 (d), 158.7 (s); HRMS: M^+, found 278.2244. $C_{18}H_{30}O_2$ requires 278.2246; MS *m/e* (%) 278 (M^+, 42), 247 (41), 218 (35), 177 (29), 154 (22), 135 (100), 109 (60), 108 (33), 95 (25), 69 (28).



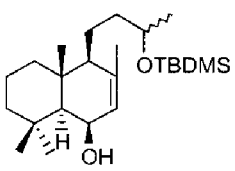
(4*S*,4a*R*,8a*S*)-4-((3ζ)-3-([*tert*-Butyl(dimethyl)silyl]oxy)butyl)-3,4a,8,8-tetra-methyl-4a,5,6,7,8,8a-hexa-hydro-1(4*H*)-naphthalenone (487a and 487b).

To a stirred solution of diastereomeric mixture of alcohols **486a** and **486b** (0.095 g; 0.342 mmol) in DMF (12 mL) were added *tert*-butyldimethylsilyl chloride (0.081 g; 0.513 mmol) and imidazole (0.070 g; 1.026 mmol). The reaction mixture was

stirred at 0°C. After 150 min the mixture was diluted with ethyl acetate and water and extracted with ethyl acetate. The organic solution was washed with H_2O and worked up as usual. The crude oil was purified by flash column chromatography (eluent PE/EA 50:1) to separate the diastereomeric silyl ethers **487a** (0.094 g; 0.239 mmol; 70%) and **487b** (0.037 g; 0.096 mmol; 28%). Both silyl ethers were obtained as colourless oils.

487a: R_f 0.70 (eluent PE/EA 3:1); $[\alpha]_D$ +28.7 (*c* 1.5); IR (film) ν_{max} 2930, 1674, 1472, 1378, 1255, 1137, 1047, 837 cm^{-1}; ^1H NMR δ 0.04 (s, 6H), 0.82 (s, 3H), 0.87 (s, 9H), 1.11 (s, 3H), 1.14 (s, 3H), 1.15 (d, *J* = 13.0 Hz, 3H), 1.02-1.85 (m, 10H), 1.90 (s, 3H), 2.02-2.05 (m, 2H), 3.74-3.82 (m, 1H), 5.73 (br s, 1H); ^{13}C NMR δ -4.8 (q), -4.4 (q), 14.2 (s), 14.6 (q), 18.1 (t), 21.5 (q), 22.1 (q), 23.3 (t), 23.7 (q), 25.9 (3x q), 32.2 (s), 33.5 (q), 38.8 (t), 42.3 (t), 43.2 (t), 43.3 (s), 56.5 (d), 63.5 (d), 68.7 (d), 128.4 (d), 158.9 (s), 200.3 (s); HRMS: M^+, found 392.3110. $C_{24}H_{44}O_2Si$ requires 392.3111; MS *m/e* (%) 392 (M^+, 17), 336 (45), 335 (72), 294 (22), 293 (100), 218 (72), 159 (19), 145 (23), 135 (34), 75 (43), 73 (21).

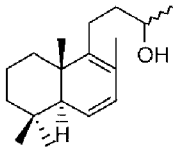
487b: R_f 0.67 (eluent PE/EA 3:1); $[\alpha]_D$ +38.0 (*c* 0.5); IR (film) ν_{max} 2928, 1673, 1470, 1379, 1257, 1134, 1045, 832 cm^{-1}; ^1H NMR δ 0.05 (s, 6H), 0.83 (s, 3H), 0.88 (s, 9H), 1.11 (s, 3H), 1.14 (s, 3H), 1.16 (d, *J* = 13.2 Hz, 3H), 0.96-1.88 (m, 10H), 1.90 (s, 3H), 2.01-2.04 (m, 2H), 3.73-3.81 (m, 1H), 5.74 (br s, 1H); ^{13}C NMR δ -4.7 (q), -4.4 (q), 14.3 (s), 14.6 (q), 18.2 (t), 21.5 (q), 22.1 (q), 23.3 (t), 23.7 (q), 25.9 (3x q), 32.3 (s), 33.5 (q), 38.8 (t), 42.3 (t), 43.2 (t), 43.3 (s), 56.6 (d), 63.6 (d), 68.7 (d), 128.4 (d), 159.0 (s), 200.4 (s); HRMS: M^+, found 392.3110. $C_{24}H_{44}O_2Si$ requires 392.3110; MS *m/e* (%) 392 (M^+, 5), 336 (27), 335 (100), 293 (39), 218 (28), 201 (13), 159 (13), 145 (16), 135 (18), 119 (17), 75 (26).



(1*R*,4*S*,4a*R*,8a*S*)-4-((3ζ)-3-([*tert*-Butyl(dimethyl)silyl]oxy)butyl)-3,4a,8,8-tetra-methyl-1,4,4a,5,6,7,8,8a-octahydro-1-naphthalenol (488a and 488b). To a solution of a diastereomeric mixture of **487a** and **487b** (0.089 g; 0.227 mmol) in dry toluene (5 mL) at -78°C under N_2 was added DIBAL-H (0.60 mL of an 1.5M solution in toluene; 0.908 mmol). After stirring for 1 h, the excess of DIBAL-H was quenched with ethyl acetate and an aqueous solution of 1M HCl. The mixture was then extracted with ethyl acetate. The organic layers were washed with brine, dried and evaporated to afford both diastereoisomers of **489** as an oil. The residue was purified by flash column chromatography (eluent PE/EA 50:1) to obtain **488a** (0.021 g; 0.054 mmol; 24%) as a colourless oil and **488b** (0.050 g; 0.127 mmol; 56%) also as an oil.

488a: R_f 0.32 (eluent PE/EA 15:1); ^1H NMR δ 0.04 (s, 6H), 0.87 (s, 9H), 1.01 (s, 3H), 1.03 (s, 3H), 1.11 (d, *J* = 10.1 Hz, 3H), 1.33 (s, 3H), 1.74 (s, 3H), 0.88-2.03 (m, 13H), 3.72-3.79 (m, 1H), 4.35 (br s, 1H), 5.55 (br d, *J* = 4.5 Hz, 1H); ^{13}C NMR (benzene-d_6) δ -4.1 (q), -4.2 (q), 16.0 (q), 19.2 (t), 19.5 (q), 22.3 (s), 23.9 (q), 24.7 (q), 25.8 (3x s), 32.7 (q), 34.1 (s), 36.6 (s), 41.3 (t), 41.4 (t), 42.6 (t), 44.9 (t), 54.2 (d), 55.6 (d), 65.6 (d), 69.0 (d), 126.2 (d), 137.4 (s).

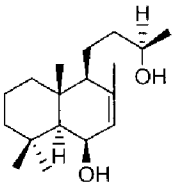
488b: R_f 0.29 (eluent PE/EA 15:1); ^{1}H NMR δ 0.04 (s, 6H), 0.88 (s, 9H), 1.01 (s, 3H), 1.03 (s, 3H), 1.10 (d, *J* = 11.6 Hz, 3H), 1.32 (s, 3H), 1.73 (s, 3H), 0.83-2.04 (m, 13H), 3.70-3.78 (m, 1H), 4.35 (br s, 1H), 5.55 (br s, 1H); ^{13}C NMR (benzene-d_6) δ -4.8 (q), -4.5 (q), 16.2 (q), 18.0 (s), 19.1 (t), 22.0 (q), 23.8 (q), 24.7 (q), 25.9 (3x s), 32.7 (q), 34.1 (s), 36.8 (s), 41.4 (t), 42.7 (t), 44.7 (t), 44.9 (t), 54.2 (d), 55.7 (d), 65.7 (d), 69.0 (d), 126.1 (d), 137.3 (s).



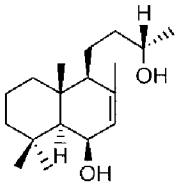
4-[(4a*S*,8a*S*)-2,5,5,8a-Tetramethyl-4a,5,6,7,8,8a-hexahydro-1-naphthalenyl]-2-butanol (489a and 489b).

To a solution of a diastereomeric mixture of **487a** and **487b** (0.100 g; 0.255 mmol) in dry toluene (10 mL) at -78°C under N_2 was added DIBAL-H (0.68 mL of a 1.5 M solution in toluene; 1.02 mmol). After stirring for 1 h, the reaction mixture was diluted with Et_2O (5 mL) and H_2O (3 drops) was added. After stirring for 15 min a 4 M aqueous solution of NaOH (3 drops) was added, followed by addition of H_2O (3 drops) again after 15 min of stirring in between. The mixture was dried by addition of $MgSO_4$, filtrated and evaporated to afford crude **488** as an oil. This mixture of crude **488** (max. 0.255 mmol) in CH_3CN (8 mL) was treated with HF (0.10 mL of a 50% solution) at room temperature. After stirring for 30 min the mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with ethyl acetate. The organic layers were washed with brine, dried and evaporated. The residue was purified by flash column chromatography (eluent PE/EA 10:1 to 5:1) to obtain a mixture of diastereomeric dienes **489a** and **b** (0.034 g; 0.123 mmol; 80%) as a colourless oil in a ratio of about 2:5.

^{1}H NMR (major peaks) δ 0.78 (s, 3H), 0.82 (s, 3H), 0.89 (s, 3H), 1.16 (d, *J* = 13.9 Hz, 3H), 1.75 (s, 3H), 0.90-2.11 (m, 12H), 3.54-3.65 (m, 1H), 5.59 (dd, *J* = 2.6, 10.3 Hz, 1H), 5.74 (dd, *J* = 3.1, 10.3 Hz, 1H); ^{13}C NMR (major peaks) δ 16.7 (q), 17.8 (t), 18.6 (t), 21.6 (q), 21.7 (q), 22.8 (q), 32.6 (q), 32.8 (s), 35.7 (t), 36.6 (t), 37.2 (s), 41.3 (t), 53.1 (d), 67.9 (d), 124.9 (s), 126.4 (d), 129.9 (d), 143.9 (s).



490a



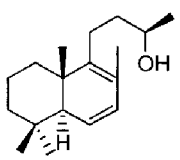
490b

(-)-(1*R*,4*S*,4a*R*,8a*S*)-4-[(3*R*)-3-Hydroxybutyl]-3,4a,8,8-tetra-methyl-1,4,4a,5,6,7,8,8a-octahydro-1-naphtha-lenol and (-)-(1*R*,4*S*,4a*R*,8a*S*)-4-[(3*S*)-3-hydroxybutyl]-3,4a,8,8-tetrmethyl-1,4,4a,5,6,7,8,8a-octahydro-1-naphthalenol (490a and 490b).

To a solution of **350**[6] (0.100 g; 0.362 mmol) in dry toluene (8 mL) at -78°C under N_2 was added DIBAL-H (1.21 mL of an 1.5M solution in toluene; 1.81 mmol). After stirring for 1 h, the reaction mixture was diluted with Et_2O (5 mL) and H_2O (3 drops) was added. After stirring for 15 min a 4 M aqueous solution of NaOH (3 drops) was added, followed by addition of H_2O (3 drops) again after 15 min of stirring in between. The mixture was dried by addition of $MgSO_4$, filtrated and evaporated to afford an oil. The residue was purified by flash column chromatography (eluent PE/EA 10:1) to give **490a** (0.056 g; 0.201 mmol; 56%) as an oil and **490b** (0.022 g; 0.080 mmol; 22%) as an oil, which crystallizes upon standing.

490a: R_f 0.22 (eluent PE/EA 3:1); $[\alpha]_D$ -60.7 (*c* 0.7); IR (film) ν_{max} 3421, 2926, 1725, 1459, 1374, 1247, 1135, 1025, 991 cm^{-1}; ^1H NMR (benzene-d_6) δ 1.08 (s, 3H), 1.10 (d, *J* = 14.0 Hz, 3H), 1.14 (s, 3H), 1.57 (s, 3H), 1.80 (s, 3H), 0.92-1.94 (m, 14H), 3.53-3.61 (m, 1H), 4.34 (br s, 1H), 5.47-5.49 (m, 1H); ^{13}C NMR (benzene-d_6) δ 16.1 (q), 19.2 (t), 22.0 (q), 23.5 (q), 23.7 (t), 24.8 (q), 32.7 (q), 34.2 (s), 36.7 (s), 41.3 (t), 42.1 (t), 44.8 (t), 54.2 (d), 55.7 (d), 65.7 (d), 68.0 (d), 126.1 (d), 137.2 (s); HRMS: M^+, found 280.2401. $C_{18}H_{32}O_2$ requires 280.2402; MS *m/e* (%) 280 (M^+, 35), 265 (33), 247 (43), 189 (46), 125 (45), 123 (39), 119 (62), 109 (100), 95 (62), 69 (48).

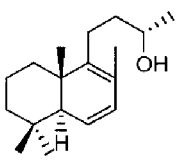
490b: R_f 0.18 (eluent PE/EA 3:1); M.p. 90-92°C; $[\alpha]_D$ -57.1 (*c* 0.9); IR (KBr) ν_{max} 3418, 2917, 1721, 1462, 1370, 1243, 1129, 1019, 989 cm^{-1}; ^1H NMR (benzene-d_6/CD_3OD) δ 0.72 (s, 3H), 0.74 (s, 3H), 0.82 (d, *J* = 14.0 Hz, 3H), 1.10 (s, 3H), 1.43 (s, 3H), 0.64-1.50 (m, 14H), 3.27-3.38 (m, 1H), 4.00 (br s, 1H), 5.17 (br d, *J* = 5.0 Hz, 1H); ^{13}C NMR (benzene-d_6/CD_3OD) δ 15.8 (q), 19.2 (t), 22.0 (q), 23.3 (q), 23.7 (t), 24.6 (q), 32.6 (q), 34.1 (s), 36.6 (s), 41.3 (t), 41.9 (t), 44.9 (t), 54.3 (d), 55.6 (d), 65.5 (d), 67.7 (d), 125.8 (d), 137.6 (s); HRMS: M^+, found 280.2402. $C_{18}H_{32}O_2$ requires 280.2402; MS *m/e* (%) 280 (M^+, 38), 247 (58), 189 (54), 138 (38), 125 (53), 123 (42), 119 (70), 109 (100), 95 (76), 69 (47).



(-)-(2*R*)-4-[(4a*S*,8a*S*)-2,5,5,8a-Tetramethyl-4a,5,6,7,8,8a-hexahydro-1-naphthalenyl]-butan-2-ol (489a).

Diol **490a** (0.046 g; 0.164 mmol) in nitromethane (5 mL) was dehydrated by treatment with a catalytic amount of PPTS (0.025 g; 0.0994 mmol) at room temperature for 30 min. Ether was added and the mixture was washed with a saturated aqueous sodium bicarbonate solution and brine, dried and evaporated. Flash column chromatography (eluent PE/EA 6:1) gave diene **489a** (0.031 g; 0.118 mmol; 72%) as a colourless oil.

R_f 0.44 (eluent PE/EA 3:1); $[\alpha]_D$ -172.6 (*c* 0.35); IR (film) ν_{max} 3346, 3032, 2924, 1459, 1369, 1127 cm^{-1}; ^1H NMR (benzene-d_6) δ 0.98 (s, 3H), 1.01 (s, 3H), 1.03 (s, 3H), 1.12 (d, *J* = 12.1 Hz, 3H), 1.76 (s, 3H), 0.96-2.23 (m, 12H), 3.60 (dt, *J* = 6.0, 12.1 Hz, 1H), 5.77 (dd, *J* = 2.7, 9.5 Hz, 1H), 5.97 (dd, *J* = 3.1, 9.5 Hz, 1H); ^{13}C NMR (benzene-d_6) δ 15.6 (q), 17.6 (q), 19.1 (t), 22.8 (q), 23.4 (q), 23.6 (t), 32.5 (q), 32.9 (s), 35.8 (t), 39.3 (s), 39.9 (t), 41.2 (t), 53.1 (d), 67.9 (d), 124.9 (s), 126.4 (d), 129.9 (d), 144.0 (s); HRMS: M^+, found 262.2295. $C_{18}H_{30}O$ requires 262.2297; MS *m/e* (%) 262 (M^+, 26), 229 (17), 189 (48), 187 (27), 173 (17), 133 (26), 120 (21), 119 (100).

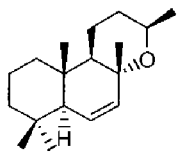


(-)-(2*S*)-4-[(4a*S*,8a*S*)-2,5,5,8a-Tetramethyl-4a,5,6,7,8,8a-hexahydro-1-naphthalenyl]-butan-2-ol (489b).

Diol **490b** (0.057 g; 0.204 mmol) was dehydrated as described above. Flash column chromatography (eluent PE/EA 6:1) of the residue gave diene **489b** (0.042 g; 0.164 mmol; 81%) as a colourless oil.

R_f 0.45 (eluent PE/EA 3:1); $[\alpha]_D$ -69.3 (*c* 0.95); IR (film) ν_{max} 3348, 3034, 2925, 1461, 1367, 1128 cm^{-1}; ^1H NMR (benzene-d_6) δ 0.98 (s, 3H), 1.01 (s, 3H), 1.03 (s, 3H), 1.12 (d, *J* = 9.8 Hz, 3H), 1.77

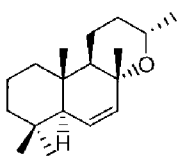
(s, 3H), 0.97-2.35 (m, 12H), 3.60 (dt, *J* = 6.2, 12.1 Hz, 1H), 5.79 (dd, *J* = 2.7, 9.5 Hz, 1H), 5.97 (dd, *J* = 3.1, 9.5 Hz, 1H); ^{13}C NMR (benzene-d_6) δ 15.6 (q), 17.6 (q), 19.1 (t), 22.8 (q), 23.4 (q), 23.6 (t), 32.5 (q), 32.9 (s), 35.4 (t), 39.2 (s), 39.8 (t), 41.1 (t), 53.1 (d), 67.9 (d), 124.9 (s), 126.4 (d), 129.9 (d), 143.9 (s); HRMS: M^+, found 262.2297. $C_{18}H_{30}O$ requires 262.2297; MS *m/e* (%) 262 (M^+, 26), 229 (17), 189 (43), 187 (26), 173 (18), 159 (16), 133 (26), 131 (14), 120 (21), 119 (100).



(3*R*,4a*R*,6a*S*,10a*S*,10b*R*)-3,4a,7,7,10a-pentamethyl-2,3,4a,6a,7,8,9,10,10a,10b-decahydro-1*H*-benzo[*f*]chromene (491a).

A solution of **490a** (0.075 g; 0.268 mmol) in Et_2O (4 mL) was treated with an aqueous solution of HCl (1 M; 0.5 mL) at room temperature. After stirring for 14 h, the mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and then extracted with ethyl acetate. The organic layers were washed with brine, dried and evaporated. The residue was purified by flash column chromatography (eluent PE/EA 6:1) to give first the Ambra oxide **491a** (0.013 g; 0.048 mmol; 18%) as a colourless oil. Further elution (eluent PE/EA 4:1) gave diene **489a** (0.049 g; 0.189 mmol; 71%) as a colourless oil. For analytical data of diene **489a** see the foregoing experimental procedure.

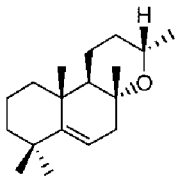
491a: R_f 0.71 (eluent PE/EA 3:1); ^{1}H NMR (benzene-d_6) δ 0.87 (s, 3H), 0.92 (s, 3H), 0.96 (s, 3H), 1.30 (d, *J* = 3.6 Hz, 3H), 1.47 (s, 3H), 0.98-1.76 (m, 10H), 1.93-1.96 (m, 2H), 3.87 (dt, *J* = 3.6, 9.7 Hz, 1H), 5.73 (dd, *J* = 2.0, 10.4 Hz, 1H), 5.94 (dd, *J* = 3.6, 10.4 Hz, 1H); ^{13}C NMR (benzene-d_6) δ 17.1 (q), 18.3 (t), 19.1 (t), 21.9 (q), 22.2 (q), 23.4 (q), 32.9 (q), 33.0 (s), 36.4 (t), 37.0 (t), 37.5 (s), 41.7 (t), 56.4 (d), 57.2 (d), 65.7 (d), 74.7 (s), 126.2 (d), 135.3 (d).



(3*S*,4a*R*,6a*S*,10a*S*,10b*R*)-3,4a,7,7,10a-pentamethyl-2,3,4a,6a,7,8,9,10,10a,10b-decahydro-1*H*-benzo[*f*]chromene (491b).

Diol **490b** (0.185 g; 0.661 mmol) was treated with an aqueous HCl solution as described above. Flash column chromatography (eluent PE/EA 6:1) of the residue gave Ambra oxide **491b** (0.005 g; 0.019 mmol; 3%) as a colourless oil. Further elution (eluent PE/EA 3:1) gave diene **489b** (0.152 g; 0.58 mmol; 88%) as a colourless oil with spectral data in accordance with the above mentioned.

491b: R_f 0.73 (eluent PE/EA 3:1); ^{1}H NMR (benzene-d_6) δ 0.81 (s, 3H), 0.85 (s, 3H), 0.90 (s, 3H), 1.09 (d, *J* = 4.3 Hz, 3H), 1.38 (s, 3H), 0.99-1.65 (m, 10 H), 1.85-1.88 (m, 1H), 2.10-2.20 (m, 1H), 4.03 (dt, *J* = 4.3, 9.8 Hz, 1H), 5.58 (dd,*J* = 1.7, 10.3 Hz, 1H), 5.86 (dd, *J* = 3.3, 10.3 Hz, 1H); ^{13}C NMR (benzene-d_6) δ 14.9 (q), 15.1 (t), 18.3 (t), 21.3 (q), 23.3 (q), 28.2 (q), 29.3 (q), 32.1 (s), 32.3 (q), 36.0 (q), 37.6 (s), 41.0 (q), 49.1 (d), 56.5 (d), 65.7 (d), 74.4 (s), 124.2 (d), 135.0 (d).



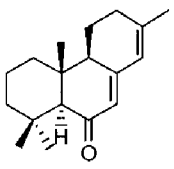
492a 492b

(3*S*,4a*R*,10a*R*,10b*R*)-3,4a,7,7,10a-pentamethyl-2,3,4a,5,7,8,9,10,10a,10b-decahydro-1*H*-benzo[*f*]chro-mene (492a) and (3*R*,4a*R*,10a*R*,10b*R*)-3,4a,7,7,10a-pentamethyl-2,3,4a,5,7,8,9,10,10a,10b-decahydro-1*H*-benzo[*f*]chro-mene (492b).

To a solution of **350**[1] (0.200 g; 0.725 mmol) in dry toluene (8 mL) at -78°C under N_2 was added DIBAL-H (2.4 mL of an 1.5 M solution in toluene, 3.62 mmol). After stirring for 90 min, the excess of DIBAL-H was quenched with ethyl acetate and an aqueous solution of 1 M HCl. The residue was treated with ethyl acetate and worked up as usual. The crude residue was not purified but treated with *p*-TsOH (0.025 g; 0.119 mmol) in nitromethane (5 mL). After 2 h ethyl acetate was added and the mixture was washed with saturated aqueous $NaHCO_3$, brine, dried and evaporated. The residue was purified by flash column chromatography (eluent PE/EA 50:1) to yield the cyclized compounds **492a** (0.018 g; 0.069 mmol; 9%) and **492** (0.037 g; 0.141 mmol; 19%) both as colourless oils.

492a: R_f 0.37 (eluent PE/EA 25:1); ^{1}H NMR δ 0.80 (s, 3H), 0.87 (s, 3H), 0.89 (s, 3H), 1.26 (d, *J* = 5.9 Hz, 3H), 1.71 (s, 3H), 0.83-2.04 (m, 13H), 3.92 (m, *J* = 6.0, 12.0, 6.0 Hz, 1H), 5.50 (br d, *J* = 3.7 Hz, 1H); ^{13}C NMR δ 15.7 (q), 18.6 (t), 19.4 (q), 21.2 (q), 22.4 (q), 23.9 (t), 29.6 (t), 31.9 (t), 33.1 (q), 33.2 (s), 36.3 (t), 42.0 (t), 42.2 (s), 43.3 (d), 76.7 (d), 89.2 (s), 125.6 (d), 134.9 (s); HRMS: M^+, found 262.2294. $C_{18}H_{30}O$ requires 262.2297; MS *m/e* (%) 262 (M^+, 2), 139 (8), 138 (100), 109 (3), 96 (4), 91 (2), 83 (2), 82 (4), 55 (3), 43 (2), 41 (3).

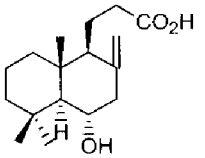
492b: R_f 0.32 (eluent PE/EA 25:1); ^{1}H NMR δ 0.85 (s, 3H), 0.86 (s, 3H), 0.89 (s, 3H), 1.22 (d, *J* = 6.0 Hz, 3H), 1.74 (s, 3H), 0.84-2.14 (m, 13H), 4.20-4.34 (m, *J* = 6.0, 2.5, 2.5 Hz, 1H), 5.53 (br d, *J* = 5.5 Hz, 1H); ^{13}C NMR δ 17.1 (q), 18.6 (t), 21.6 (q), 21.7 (q), 22.1 (q), 24.2 (t), 27.5 (t), 32.2 (t), 33.0 (q), 33.1 (d), 35.0 (t), 40.4 (s), 41.9 (t), 42.5 (d), 76.6 (d), 89.8 (s), 125.6 (d), 135.8 (s); HRMS: M^+, found 262.2296. $C_{18}H_{30}O$ requires 262.2297; MS *m/e* (%) 262 (M^+, 1), 139 (8), 138 (100), 109 (4), 96 (4), 91 (3), 82 (5), 69 (3), 55 (4), 43 (3), 41 (4).



(-)-13-Methylpodocarpa-7,13-dien-6-one (493).

To **350** (0.100 g; 0.362 mmol) in 1,4-dioxane (5 mL) was added a 4 M aqueous solution of NaOH (5 mL) and the mixture was stirred at room temperature. A 10% solution of I_2 in a 20% KI solution was added dropwise until the typical iodine colour just had disappeared after about 2 min. No precipitate of iodoform was formed immediately, so the mixture was heated to 100°C for 3 h until the starting material had disappeared. The mixture was cooled to room temperature and acidified with an aqueous solution of 4 M HCl and extracted and the combined organic layers are washed with saturated aqueous $NaHSO_3$ followed by brine, dried and evaporated. The residue was purified by flash column chromatography (eluent PE/EA 10:1 to 2:1) to obtain **493** (0.086 g; 0.333 mmol; 92%) as a colourless oil.

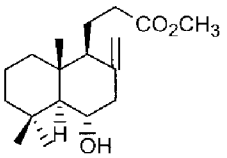
$[\alpha]_D$ -206.7 (*c* 2.0); IR (film) ν_{max} 2927, 1661, 1633, 1442, 1383, 1294, 1158, 890 cm^{-1}; ^1H NMR δ 0.88 (s, 3H), 1.12 (s, 3H), 1.16 (s, 3H), 1.83 (s, 3H), 1.28-2.25 (m, 12H), 5.56 (br s, 1H), 5.92 (br s, 1H); ^{13}C NMR δ 14.5 (q), 18.2 (t), 21.4 (t), 21.7 (q), 24.2 (q), 31.1 (t), 32.4 (s), 33.7 (q), 39.2 (t), 41.1 (s), 43.1 (t), 50.8 (d), 64.0 (d), 123.3 (d), 124.7 (d), 148.6 (s), 153.3 (s), 201.0 (s); HRMS: M^+, found 258.1988. $C_{18}H_{26}O$ requires 258.1984; MS *m/e* (%) 258 (M^+, 40), 243 (17), 187 (6), 176 (13), 175 (100), 173 (9), 135 (12), 134 (23), 91 (10).



(+)-3-[(1*S*,4*S*,4a*S*,8a*R*)-4-Hydroxy-5,5,8a-trimethyl-2-methylenedecahydro-1-naphthalenyl]propanoic acid (494).

To methyl ketone **206**[1,3] (0.250 g; 0.899 mmol) in 1,4-dioxane (7 mL) was added a 4 M aqueous solution of NaOH (8 mL) and the mixture was stirred at room temperature. A 10% solution of I_2 in a 20% KI solution was then added dropwise until the typical iodine colour just had disappeared after about 2 min. A yellow precipitate indicated the formation of iodoform. After 1 h the mixture was acidified with an aqueous solution of 4 M HCl and extracted and the combined organic layers were washed with a saturated aqueous $NaHSO_3$ followed by brine, dried and evaporated. The residue was purified by flash column chromatography (eluent PE/EA 3:1 to 2:1) to yield acid **494** (0.141 g; 0.503 mmol; 56%) as a white solid.

M.p. 146-148°C; $[\alpha]_D$ +38.2 (*c* 0.77); IR (KBr) ν_{max} 3328, 2931, 1684, 1437, 1219, 1058, 1013, 902 cm^{-1}; ^1H NMR δ 0.65 (s, 3H), 0.94 (s, 3H), 1.10 (s, 3H), 1.04-2.42 (m, 14H), 2.61 (dd, *J* = 4.8, 12.2 Hz, 1H), 3.15 (br s, 1H), 3.75 (dt, *J* = 4.9, 10.7 Hz, 1H), 4.51 (br s, 1H), 4.85 (br s, 1H); ^{13}C NMR δ 15.9 (q), 19.1 (t), 19.3 (t), 22.2 (q), 33.0 (t), 33.8 (s), 36.5 (q), 39.2 (t), 39.3 (s), 43.7 (t), 48.7 (t), 55.3 (d), 60.2 (d), 71.4 (d), 108.2 (t), 145.0 (s), 176.8 (s); HRMS: M^+, found 280.2034. $C_{17}H_{28}O_3$ requires 280.2038; MS *m/e* (%) 262 [(M^+-18), 100], 153 (82), 138 (37), 125 (48), 109 (67), 95 (41), 81 (42), 55 (53), 43 (37), 41 (61).

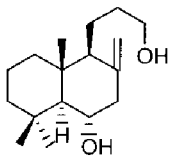


(+)-Methyl 3-[(1*S*,4*S*,4a*S*,8a*R*)-4-hydroxy-5,5,8a-trimethyl-2-methylenedecahydro-1-naphthalenyl]pro-panoate (495).

A solution of **494** (0.23 g; 0.82 mmol) in MeOH/Et_2O (1:1) (30 mL) was stirred at room temperature and treated with diazomethane until N_2 generation ceased. The excess of diazomethane was destroyed by addition of acetic acid (2 drops). The mixture was washed (2x) with an ice-cold solution of 1 M aqueous KOH, followed by brine, dried and evaporated. The residue was purified by flash column chromatography (eluent PE/EA 5:1) to give methyl ester **495** (0.236 g; 0.804 mmol; 98%) as a colourless oil.

$[\alpha]_D$ +47.2 (*c* 1.6); IR (film) ν_{max} 3515, 2928, 1739, 1645, 1439, 1166, 1013, 893 cm^{-1}; ^1H NMR δ 0.68 (s, 3H), 0.98 (s, 3H), 1.14 (s, 3H), 1.07-2.45 (m, 14H), 2.65 (dd, *J* = 4.8, 12.2 Hz, 1H), 3.64 (s, 3H), 3.81 (dt, *J* = 4.8, 10.6 Hz, 1H), 4.54 (br s, 1H), 4.88 (br s, 1H); ^{13}C NMR δ 15.9 (q), 19.0 (t), 19.3 (t), 22.3 (q), 32.9 (t), 33.8 (s), 36.6 (q), 39.1 (t), 39.3 (s), 43.6 (t), 49.0 (t), 51.5 (q), 55.3 (d), 60.3 (d), 71.5 (d), 108.3 (t), 144.9 (s), 174.5 (s); HRMS: M^+, found 294.2192. $C_{18}H_{30}O_3$ requires

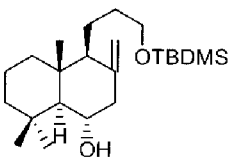
294.2195; MS *m/e* (%) 294 (M^+, 1), 276 (100), 189 (33), 153 (67), 119 (32), 109 (56), 95 (34), 82 (39), 81 (32), 69 (86), 55 (32).



(+)-(1*S*,4*S*,4a*R*,8a*S*)-4-(3-Hydroxypropyl)-4a,8,8-trimethyl-3-methylenedecahydro-1-naphthalenol (496).

To a solution of methyl ester **495** (0.060 g; 0.204 mmol) in dry THF (8 mL) at 0°C under N_2 was added $LiAlH_4$ (0.077 g; 2.04 mmol). After stirring for 1 h, the reaction mixture was diluted with Et_2O (15 mL) and H_2O (8 drops) was added. After stirring for 15 min a 4 M aqueous solution of NaOH (8 drops) was added, followed by addition of H_2O (8 drops) again after 15 min of stirring in between. The mixture was dried by addition of $MgSO_4$, filtrated and evaporated to afford an oil. The residue was purified by flash column chromatography (eluent PE/EA 2:1) to give alcohol **496** (0.051 g; 0.190 mmol; 93%) as a colourless oil.

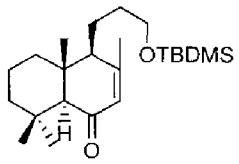
$[\alpha]_D$ +34.5 (*c* 0.5); IR (film) ν_{max} 3356, 2925, 1645, 1443, 1381, 1249, 1050, 1011, 980, 890 cm^{-1}; ^1H NMR δ 0.66 (s, 3H), 0.98 (s, 3H), 1.14 (s, 3H), 1.07-2.08 (m, 15H), 2.65 (dd, *J* = 4.8, 12.2 Hz, 1H), 3.59 (t, *J* = 6.4 Hz, 2H), 3.80 (dt, *J* = 4.8, 10.7 Hz, 1H), 4.56 (d, *J* = 1.3 Hz, 1H), 4.86 (d, *J* = 1.3 Hz, 1H); ^{13}C NMR δ 15.9 (q), 19.1 (t), 20.0 (t), 22.3 (q), 31.8 (t), 33.8 (s), 36.6 (q), 39.1 (s), 39.3 (t), 43.2 (t), 49.0 (t), 55.8 (d), 60.4 (d), 63.1 (t), 71.6 (d), 108.2 (t), 145.5 (s); HRMS: M^+, found 266.2245. $C_{17}H_{30}O_2$ requires 266.2246; MS *m/e* (%) 266 (M^+, 3), 248 (67), 153 (93), 109 (70), 96 (34), 95 (56), 93 (43), 81 (41), 69 (100), 55 (40), 41 (40).



(+)-(1*S*,4*S*,4a*R*,8a*S*)-4-(3-([*tert*-Butyl(dimethyl)silyl]oxy)propyl)-4a,8,8-trimethyl-3-methylenedeca-hydro-1-naphthalenol (497).

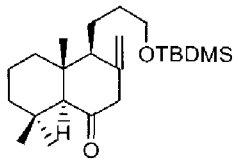
To a stirred solution of alcohol **496** (0.237 g; 0.891 mmol) in DMF (15 mL) were added *tert*-butyldimethylsilyl chloride (0.134 g; 0.89 mmol) and imidazole (0.121 g; 1.782 mmol). The reaction mixture was stirred at 0°C. After 30 min the mixture was diluted with ethyl acetate and water and extracted with ethyl acetate. The organic solution was washed with H_2O and worked up as usual. The crude oil was purified by flash column chromatography (eluent PE/EA 25:1) to yield silyl ether **497** (0.318 g; 0.837 mmol; 94%) as a colourless oil which turns into a wax-like solid upon standing.

M.p. 53-55°C; $[\alpha]_D$ +30.5 (*c* 0.6); IR (KBr) ν_{max} 3421, 2928, 2361, 1647, 1472, 1255, 1103, 1011, 894, 836, 775 cm^{-1}; ^1H NMR δ 0.04 (s, 6H), 0.68 (s, 3H), 0.88 (s, 9H), 1.00 (s, 3H), 1.16 (s, 3H), 0.90-1.74 (m, 13H), 2.04 (br t, *J* = 12.3 Hz, 1H), 2.67 (dd, *J* = 4.9, 11.8 Hz, 1H), 3.58 (t, *J* = 5.5 Hz, 2H), 3.77-3.88 (m, 1H), 4.60 (d, *J* = 1.3 Hz, 1H), 4.87 (d, *J* = 1.3 Hz, 1H); ^{13}C NMR δ -5.2 (2x q), 16.0 (q), 18.3 (s), 19.2 (t), 20.1 (t), 22.4 (q), 26.0 (3x q), 31.9 (t), 33.9 (s), 36.7 (q), 39.3 (t), 39.4 (s), 43.8 (t), 49.2 (t), 55.8 (d), 60.6 (d), 63.4 (t), 71.7 (d), 108.4 (t), 145.6 (s); HRMS: (M^+-15), found 365.2875. $C_{22}H_{41}O_2Si$ requires 365.2876; MS *m/e* (%) 365 [(M^+-15), 1], 323 (15), 306 (24), 305 (100), 231 (16), 135 (11), 109 (12), 95 (14), 75 (22), 73 (10), 69 (18); Anal.: found C, 72.85; H, 12.14%. $C_{23}H_{44}O_2Si$ requires C, 72.57; H, 11.65%.



(+)-(4*S*,4a*R*,8a*S*)-4-(3-{[*tert*-Butyl(dimethyl)silyl]oxy}propyl)-3,4a,8,8-tetramethyl-4a,5,6,7,8,8a-hexahydro-1(4*H*)-naphthalenone (499).

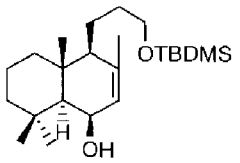
To a stirred solution of silyl ether **497** (0.276 g; 0.726 mmol) in CH_2Cl_2 (20 mL) were added 3Å molecular sieves (0.5 g) followed by pyridinium chlorochromate (PCC) (0.235 g; 1.080 mmol) and 5 drops of acetic acid. After 1 h the mixture was filtered over silica gel and flushed with ethyl acetate. Purification of the crude product by flash column chromatography (PE/EA 3:1) gave **(+)-(4*S*,4a*R*,8a*S*)-4-(3-{[*tert*-butyl(dimethyl)silyl]oxy}-propyl)-4a,8,8-trimethyl-3-methyleneocta-hydro-1(2*H*)-naphthalenone** (**498**) (0.225 g; 0.595 mmol; 82%) as a colourless oil.



$[\alpha]_D$ +59.3 (*c* 0.6); IR (film) ν_{max} 2929, 1719,1644, 1471, 1387, 1255, 1104, 981, 892, 836, 776 cm^{-1}; ^1H NMR (benzene-d_6) δ -0.15 (s, 6H), 0.54 (s, 3H), 0.91 (s, 9H), 1.03 (s, 3H), 1.29 (s, 3H), 0.76-1.71 (m, 12H), 2.64 (br d, J = 13.4 Hz, 1H), 2.92 (d, J = 13.4 Hz, 1H), 3.47 (t, J = 6.2 Hz, 2H), 4.57 (br s, 1H), 4.66 (br s, 1H); ^{13}C NMR (benzene-d_6) δ -5.6 (2x q), 15.4 (q), 18.5 (s), 18.7 (t), 20.1 (t), 21.4 (q), 25.6 (3x q), 31.6 (t), 32.5 (q), 32.8 (s), 38.4 (t), 41.2 (s), 42.4 (t), 55.3 (t), 56.1 (d), 62.9 (t), 65.5 (d), 109.2 (t), 144.1 (s), 206.4 (s); HRMS: (M^+-15), found 363.2716. $C_{22}H_{39}O_2Si$ requires 363.2719; MS *m/e* (%) 378 (M^+, 1), 363 (3), 322 (26), 321 (100), 170 (7), 169 (43), 151 (9), 123 (8), 109 (7), 95 (8), 75 (19), 73 (9).

The above obtained C(6)-ketone (**498**) (2.000 g; 6.58 mmol), was isomerized into the conjugated ketone by treatment with a 0.125 M solution of sodium methoxide in methanol (20 mL) at room temperature for 1 h. The methanol was evaporated and an 1 M aqueous solution of HCl (200 mL) was added. Extraction with ether followed by the usual work-up gave the crude product which was purified by flash column chromatography (PE/EA 15:1) to give compound **499** (0.140 g; 0.370 mmol; 78%) as a colourless oil.

$[\alpha]_D$ +24.1 (*c* 0.3); IR (film) ν_{max} 2930, 1673, 1471, 1385, 1360, 1255, 1104, 978, 836, 776 cm^{-1}; ^1H NMR δ 0.05 (s, 6H), 0.83 (s, 3H), 0.89 (s, 9H), 1.12 (s, 3H), 1.15 (s, 3H), 1.91 (s, 3H), 0.93-2.07 (m, 12H), 3.62 (t, J = 5.5 Hz, 2H), 5.75 (br s, 1H); ^{13}C NMR δ -5.3 (2x q), 14.6 (q), 18.2 (t), 18.3 (s), 21.5 (q), 22.1 (q), 23.4 (t), 25.9 (3x q), 32.3 (s), 33.5 (q), 35.2 (t), 38.8 (t), 43.1 (s), 43.2 (t), 56.2 (d), 62.8 (t), 63.6 (d), 128.5 (d), 159.0 (s), 200.3 (s); HRMS: M^+, found 378.2954. $C_{23}H_{42}O_2Si$ requires 378.2954; MS *m/e* (%) 378 (M^+, 73), 322 (22), 321 (100), 159 (15), 135 (20), 119 (27), 95 (12), 75 (32), 73 (14).

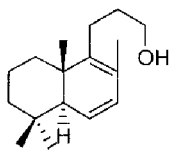


(-)-(1*R*,4*S*,4a*R*,8a*S*)-4-(3-{[*tert*-Butyl(dimethyl)silyl]oxy}propyl)-3,4a,8,8-tetramethyl-1,4,4a,5,6,7,8,8a-octahydro-1-naphthalenol (500).

To a solution of **499** (0.120 g; 0.317 mmol) in dry toluene (10 mL) at -78°C under N_2 was added DIBAL-H (0.85 mL of an 1.5 M solution in toluene; 1.27 mmol). After stirring for 1 h, the reaction mixture was diluted with Et_2O (10 mL) and H_2O (5 drops) was added. After stirring for 15 min a 4 M aqueous solution of NaOH (5 drops) was added,

followed by addition of H_2O (5 drops) again after 15 min of stirring in between. The mixture was dried by addition of $MgSO_4$, filtrated and evaporated to afford an oil. The residue was purified by flash column chromatography (eluent PE/EA 6:1) to yield alcohol **500** (0.105 g; 0.276 mmol; 87%) as a colourless oil.

$[\alpha]_D$ -28.3 (*c* 0.2); IR (film) ν_{max} 3470, 2927, 1461, 1387, 1254, 1102, 1030, 971, 917, 835, 775 cm^{-1}; ^1H NMR (benzene-d_6) δ -0.01 (s, 6H), 0.92 (s, 9H), 0.95 (s, 3H), 1.00 (s, 3H), 1.43 (s, 3H), 1.68 (s, 3H), 0.88-1.69 (m, 13H), 3.45 (t, *J* = 4.3 Hz, 2H), 4.18 (br s, 1H), 5.32 (br d, *J* = 4.3 Hz, 1H); ^{13}C NMR (benzene-d_6) δ -5.4 (2x q), 16.1 (q), 18.2 (s), 19.2 (t), 22.0 (q), 23.7 (t), 24.7 (q), 25.9 (3x q), 32.7 (q), 34.2 (s), 35.5 (t), 36.6 (s), 41.4 (t), 44.8 (t), 54.2 (d), 55.3 (d), 63.1 (t), 65.7 (d), 128.1 (d), 137.4 (s); HRMS: (M^+-18), found 362.3003. $C_{23}H_{42}OSi$ requires 362.3005; MS *m/e* (%) 362 [(M^+-18), 17], 323 (46), 305 (81), 215 (50), 189 (100), 119 (77), 109 (64), 95 (39), 75 (78), 73 (39), 69 (52).



(-)-3-[(4a*S*,8a*S*)-2,5,5,8a-Tetramethyl-4a,5,6,7,8,8a-hexahydro-1-naphthalenyl]-1-propanol (501).

A mixture of alcohol **500** (0.085 g; 0.224 mmol) in CH_3CN (6 mL) was treated with HF (0.09 mL of a 50% aqueous solution) at room temperature. After stirring for 20 min the mixture was quenched with a saturated aqueous solution of $NaHCO_3$. The mixture was then extracted with ethyl acetate. The organic layers were washed with brine, dried and evaporated. The residue was purified by flash column chromatography (eluent PE/EA 4:1) to obtain diene **501** (0.049 g; 0.184 mmol; 88%) as a colourless oil.

$[\alpha]_D$ -70.9 (*c* 0.53); IR (film) ν_{max} 3327, 2926, 1459, 1369, 1058 cm^{-1}; ^1H NMR (benzene-d_6) δ 0.97 (s, 3H), 0.99 (s, 3H), 1.02 (s, 3H), 1.75 (s, 3H), 1.09-1.79 (m, 9H), 2.06-2.23 (m, 3H), 3.45 (t, *J* = 6.3 Hz, 2H), 5.78 (dd, *J* = 2.7, 9.5 Hz, 1H), 5.96 (dd, *J* = 3.0, 9.5 Hz, 1H); ^{13}C NMR (benzene-d_6) δ 15.6 (q), 17.6 (q), 19.1 (t), 22.8 (q), 23.7 (t), 32.5 (q), 32.9 (s), 33.5 (t), 35.4 (t), 39.2 (s), 41.1 (t), 53.0 (d), 62.7 (t), 125.0 (s), 126.4 (d), 129.9 (d), 143.7 (s); HRMS: M^+, found 248.2140. $C_{17}H_{28}O$ requires 248.2140; MS *m/e* (%) 248 (M^+, 23), 189 (39), 145 (14), 133 (23), 131 (10), 120 (18), 119 (100), 105 (11), 91 (10), 41 (11).

5.5 References and Notes

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Chapter 6

Discussion

Abstract

In this chapter, the results of the research described in chapters 2-5 are discussed. In the first paragraph, the syntheses of Ambrox® starting from labdanolic acid are commented. The oxidation of the labdane side chain and the synthesis of ambraketal starting from larixol is discussed in the second paragraph. In the third paragraph, about the synthesis of Ambrox-like compounds, mainly the observed problems with the hydroxyl group at C(6) in larixol are compared with similar compounds in literature. The synthesis of the unsaturated Ambrox-like compounds Δ^6-Ambroxene and Δ^6-Ambra oxides is discussed in the last paragraph.

6.1 Introduction

In Chapter 1 and in the introduction paragraphs of Chapters 2, 3, and 4, short reviews have been presented about the investigations that have been performed on labdanes with emphesis on those about labdanolic acid, larixol and congeners. The development of high yield oxidation procedures for the breakdown of the C(9) side chain of labdanes, in particular aiming at suitable industrially applicable oxidation procedures for the synthesis of Ambrox® (**103**), has been the driving force for this research. In the last ten years these efforts have been concentrated on the oxidation of sclareol, which nowadays is the industrially used starting material for the production of Ambergris fragrance compounds. Regularly other labdanes have been investigated for this purpose as well. Labdanolic acid (**32**), being one on the main constituents of the commercially available labdanum gum, has been regurlarly investigated as starting material for the production of fragrance compounds. Another abundantly available labdane is larixol (**30**) and its acetate, as the main constituents of larix turpentine, also known as Venice turpentine, but not many investigations about its use in the preparation of fragrance compounds have been published until now.

In the literature on the general chemistry of labdanolic acid (**32**) and larixol (**30**) has been reported. The applications of labdanolic acid and larixol as starting compounds in total syntheses have been focussed on:

- functionalization in the side chain of labdanolic acid for the synthesis of the α- and β-levantanolides **113** and **114** and α- and β-levantenolides **131** and **132**, and the synthesis of the Ambrox® precursors sclareolide (**136**) and 8-*epi*-sclareolide (**137**).
- the conversion of larixol into (-)-borjatriol (**36**), which possesses anti-inflammatory properties, and the synthesis of a target for 1-deoxy- or 1,9-dideoxy-forskolin (**183**).
- the synthesis of drimanes from both larixol and labdanolic acid.

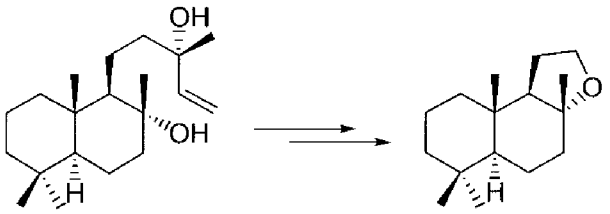
The synthetic research presented in this thesis was carried out in the framework of the 'Euterpe project' which was funded by the European Union. The general aim of this project was to investigate the application of natural and agricultural products for the preparation of non-food products. In this thesis new chemistry starting from labdanolic acid and larixol, aiming at the synthesis of ambergris fragrance compounds, is described.

6.2 The synthesis of Ambrox® starting from labdanolic acid

Ambergris, a metabolic product of the spermwhale, has always been one of the most highly valued and expensive perfumery material but the decline in the whale population has exacerbated the situation. The price and availability of the natural material essentially precluded its use in fragrances and therefore, much work has been done on synthetic substitutes. The ambergris materials used in perfumery nowadays are entirely of synthetic or semisynthetic origin, the key

material being Ambrox® (**103**) and its equivalents, which posses a dominating exotic woody note of strong warm animal tonality.

Scheme 6.1



4 **103**

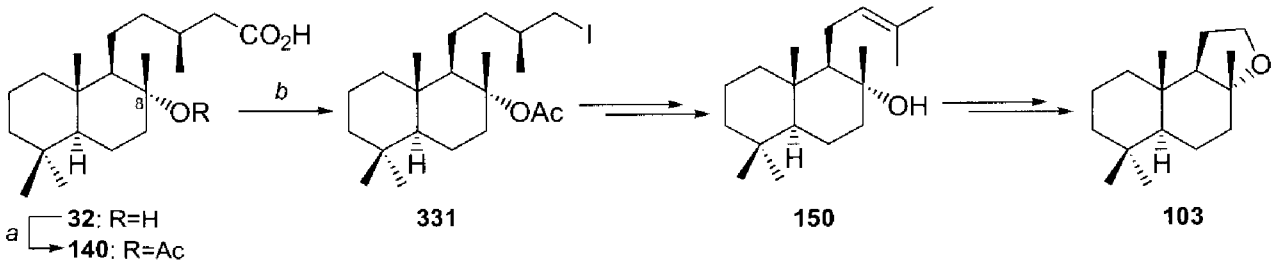
Sclareol (**4**) is nowadays the starting material for the industrial preparation of (-)-Ambrox® (**103**) (Scheme 6.1). The price of (-)-Ambrox® is relatively high and this together with the increasing demand for this valuable amber odorant prompted several laboratories to search for new syntheses for Ambrox® starting from other cheap, abundantly available labdanes.

One of such labdanes that has the potential to fulfill this role is labdanolic acid (**32**) because it is easily available from Nature. Labdanolic acid (**32**) is the main component in the acidic fraction of the *n*-hexane extract of the wild-growing shrub *Cistus ladaniferus* ("rock-rose"), found in all countries around the Mediterranean Sea. On the other hand, labdanolic acid (**32**) is not an easy starting material because for the oxidative breakdown of the side chain just the carboxyl group is available as reactive handle. The hydroxyl group at C(8) also may serve as a starting point for functionalization of the side chain but until now only radical reactions have been used for this purpose. This mostly has led to mixtures of reaction products in moderate yields. Also for the breakdown of the side chain mostly radical type decarboxylations have been investigated and competing radical reactions of the C(8) hydroxyl group have been observed regurlarly. To avoid such complications this hydroxyl group has to be protected, for instance as its acetate. Conversion of labdanolic acid into its C(8) acetate (**140**) also facilitates its isolation from the natural material and in this way both problems can be solved in one operation.

For the decarboxylation of the side chain mostly metal catalyzed reactions using lead or copper salts have been investigated with moderate and varying yields. An alternative route consists of the introduction of an α,β unsaturation using the carboxylic ester, followed by ozonolysis of the double bond to a known enol ether intermediate.

We have used the iododecarboxylation as key reaction and in a good reproducable yield the alkene **150** can be obtained and this compound can be converted into Ambrox® (**103**) in a standard way (Scheme 6.2).[1] Although our synthesis of Ambrox® is not the first reported one starting from labdanolic acid (**32**), our four step procedure starting from the acetate of labdanolic acid (**140**) leads to Ambrox® in 47% overall yield.[2,3]

Scheme 6.2



Reagents and conditions: (*a*) AcCl, *N,N*-dimethylaniline; (*b*) IBDA, I_2, CCl_4, hν, Δ, 76%.

The main drawback of our route is the application of IBDA and iodine in the decarboxylation step. The use of iodine makes this step to a rather expensive one. When a cheaper procedure can be found for this reaction or when the iodide can be reconverted to iodine, labdanolic acid (**32**) will become a good alternative starting material for the industrial preparation of Ambrox® (**103**).

6.3 Synthesis of Ambraketals

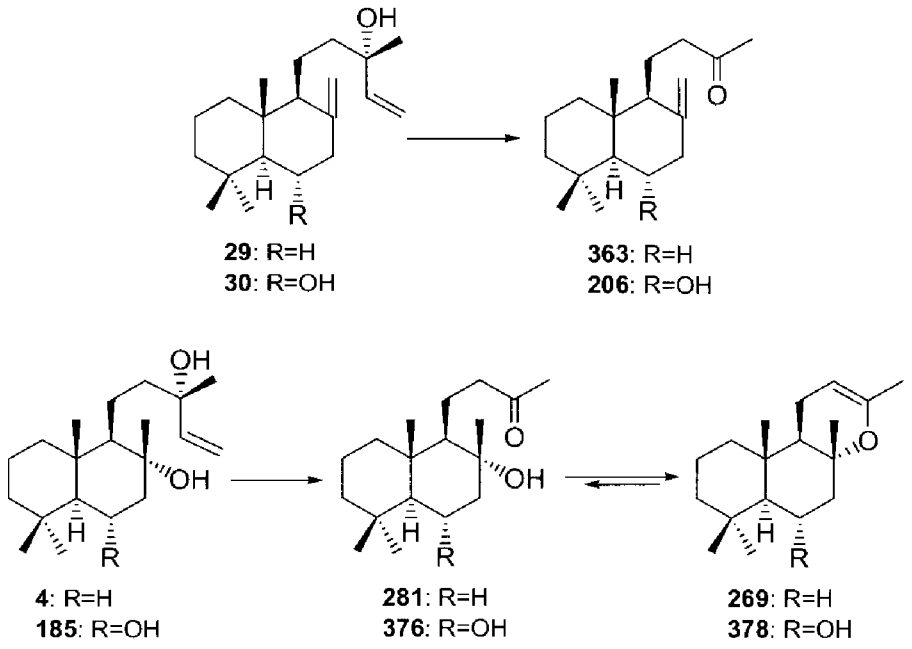
Larixol (**30**) and its C(6)-acetate (**31**) are easily available from Nature, but have not been used extensively as starting material in synthesis. However, oxidation of the C(9) side chain of these labdanes also may provide suitable synthons, for instance for the synthesis of Ambrox-like compounds. For this purpose the side chain of larixol (**30**) has to be shortened to a two carbon moiety using oxidative procedures and the exocyclic 8(17) methylene group has to be modified to enable the construction of the cyclic ether that is characteristic for Ambrox-type molecules.

The procedure for oxidative breakdown of the side chain depends of course on the functional groups, that are present in the side chain itself and in the whole molecule. Some remarks about these aspects have already been made about labdanolic acid (**32**), in Chapter 3 we concentrate on molecules with a (3-hydroxy-3-methyl-4-pentenyl)-side chain. A first step in these oxidations proceeds mostly to a methyl ketone as the first stable intermediate. The fate of this methyl ketone strongly depends on the functional group at C(8). When a hydroxyl group is present at C(8), it will react with the ketone to a hemiacetal which easily dehydrates to an enol ether that may be isolated or oxidized further. When a double bond is present at C(8), as is the case in larixol (**30**), it usually does not take part in the oxidation reaction and a selective high yield transformation to a stable methyl ketone is possible.

A good general procedure for the oxidation of both types of labdanes proved to be the method of Ogini using solid potassium permanganate in the presence of a phase-transfer catalyst. This method was investigated for several labdanes, aiming at an optimum yield for methyl ketones.[4] The oxidation has a good selectivity for the side chain and a double bond at C(8) and/or

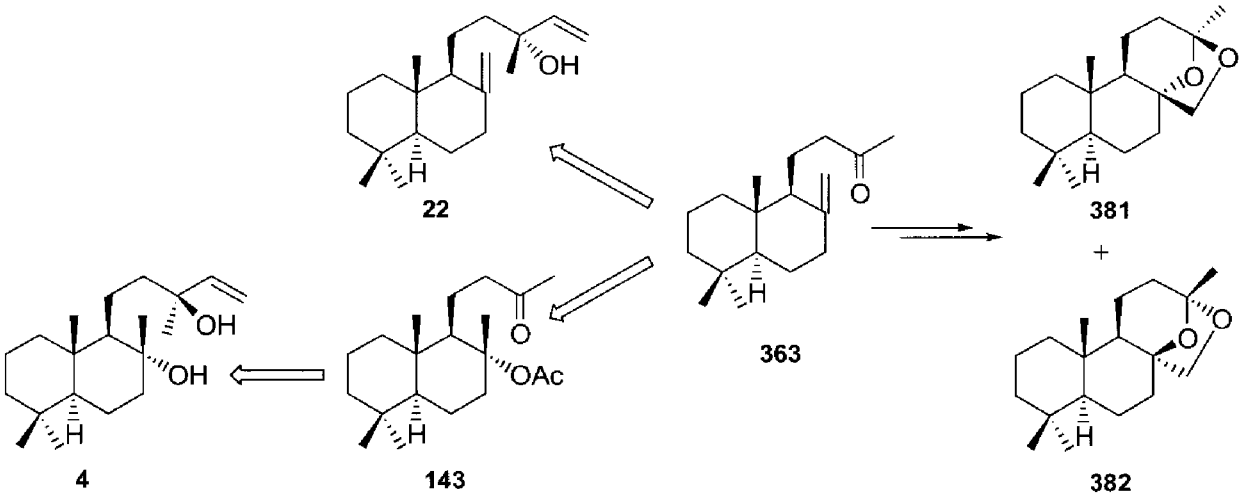
a hydroxyl group at C(6) are not affected. This also opens up possibilities for the preparation of Ambraketals from labdanes like manool (**29**) or larixol (**30**).

Scheme 6.3



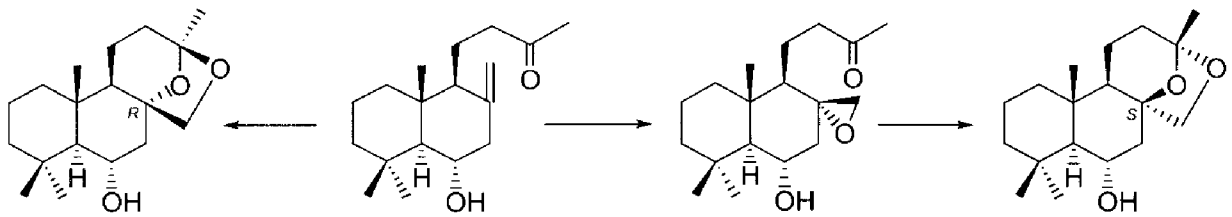
Ambraketal (**381**) (also called Jeger's ketal) which possess an intense amber odour, has already a long history, and it is most readily obtained by degradation of manool (**22**) (Scheme 6.4). Sclareol (**4**) is also suited for the preparation of Ambraketal (**381**), and has been used for this purpose as well. Both syntheses proceed through the intermediate methylene ketone **363**, and each synthetic variant is judged on how it solves the problem of preparing **363**, and on how oxidation of the C(8) double bond may lead to the desired Ambraketal. The 8-*epi*-isomer **382** is virtually odourless; thus, the more selective the transformation of **363** into the odorous epimer **381**, the better.

Scheme 6.4



Larixol (**30**) has good potential as starting material for the preparation of Ambraketals. From the standardized oxidation of larixol with potassium permanganate C(6) hydroxylated Ambraketals were already found as minor products. Oxidation of the side chain provides for the necessary methyl ketone and the exocyclic double bond is already present in the molecule as precursor for the diol or the epoxide function. The reaction sequence and the type of intermediate determines the stereochemistry at C(8) in these ketals. After epoxidation of the exocyclic double bond to epoxide **400**, acid catalyzed ring closure can be effected easily, which takes place with inversion at C(8) to the undesired 8*S* configuration. Dihydroxylation, *via* osmylation of the exocyclic double bond prevents inversion during formation of the ketal, which gives the desired 8*R* configuration. Starting from larixol (**30**) good reaction sequences are developed for the synthesis of *epi*-hydroxy Ambraketal **401** and hydroxy Ambraketal **343** (Scheme 6.5). The hydroxyl group at C(6) allows the preparation of several simple derivatives of these ketals.

Scheme 6.5

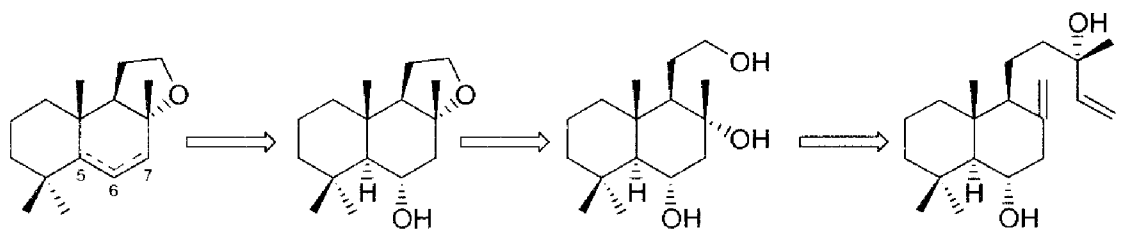


343 **206** **400** **401**

6.4 The synthesis of Ambrox-like compounds starting from larixol

The commercial importance of (-)-Ambrox® (**103**) and later that of (±)-Ambrox prompted several, mostly industrial, laboratories to search for new analogues with the aim of being either cheaper or possessing additional odour aspects. Although larixol (**30**) has the advantage of a functionalized decalin system, which makes it to a suitable starting material for the synthesis of Ambrox analogues, the synthesis of such compounds like **433** and **466** (Scheme 6.6), is not straightforward.

Scheme 6.6

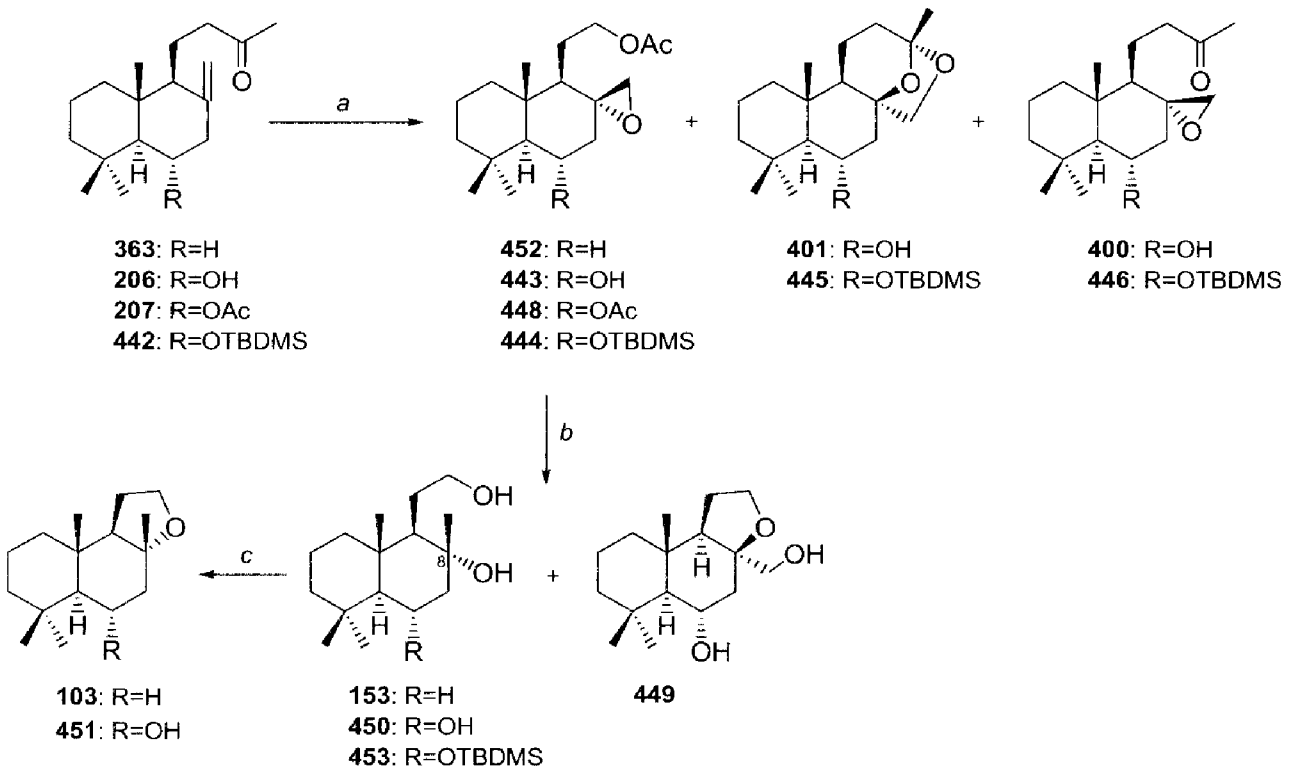


433: Δ^5
466: Δ^6 **451** **450** **30**

In principle larixol (**30**) can be used for the synthesis of Ambrox or Ambraketal by removing its C(6) hydroxyl group. It is more interesting to make use of this extra hydroxyl group for example for the synthesis of Δ^5-Ambroxene (**433**) or Δ^6-Ambroxene (**466**) as is described in Chapter 4. In this chapter 6α-hydroxy Ambrox (**451**) has been used as a key intermediate for the preparation of these Ambroxenes and of other Ambrox-derivatives.

Oxidation of the labdane side chain with potassium permanganate gives methyl ketones as **206** and **207** (Scheme 6.3). An obvious way to achieve further breakdown of the methyl ketones into a functionalized two carbon moiety is the Bayer-Villiger oxidation and this reaction was investigated for **206** and for two C(6) derivatives, *e.g.* the *tert*-butyldimethylsilyloxy ether (**442**) and the acetate (**207**) (Scheme 6.7). It is known that methyl ketones give acetate esters upon Baeyer-Villiger oxidation resulting from migration of the larger group. However, under Baeyer-Villiger conditions double bonds can be epoxidized as well. According to literature, the methyl ketone derived from manool indeed gives epoxy acetate **452** in high yield. The same result was found for **207**, but the C(6) substituent in the oxidation of **206** or **442** had a rather unpredictable influence on the course and yields of the reactions involved. In these compounds besides **443** and **444** also acetals **401**, **446** and epoxides **400** and **446** were found as products. In compounds **400** and **446** the epoxidation of the double bond has been faster than the Bayer-Villiger oxidation of the methyl ketone and a subsequent acid catalyzed reaction of the carbonyl group with the epoxide gives formation of the acetals **401** and **445**.

Scheme 6.7



363: R=H
206: R=OH
207: R=OAc
442: R=OTBDMS

452: R=H
443: R=OH
448: R=OAc
444: R=OTBDMS

401: R=OH
445: R=OTBDMS

400: R=OH
446: R=OTBDMS

103: R=H
451: R=OH

153: R=H
450: R=OH
453: R=OTBDMS

449

Reagents and conditions: (*a*) *m*-CPBA, CH_2Cl_2; (*b*) $LiAlH_4$, THF, 0°C to rt; (*c*) *p*-TsOH, CH_3NO_2.

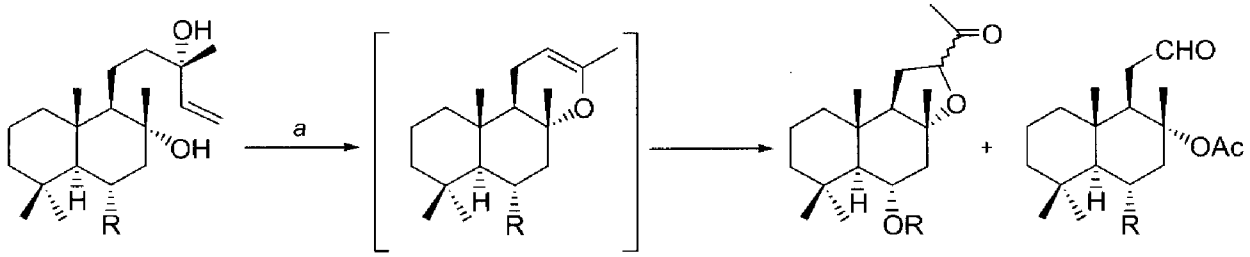
To introduce the tertiary hydroxyl group at C(8) and to reduce the acetate in the side chain to a hydroxyl group the epoxides **443**, **444**, **448**, and **452** were treated with lithium aluminum hydride. The epoxy derived from manool (**452**) gave diol **153** in high yield and epoxy silyl ether **444** showed a comparable result. However, the reduction of the epoxides **443** and **448** led to triol **450** only in low yields. Obviously the acetate group in the side chain was reduced first followed by attack of the formed alkoxide on the epoxide to give the cyclic ether **449** as the major products. The reason for this different behaviour is not yet clear, but has been observed in some other reactions of larixol and its derivatives as well.

Treatment of diol **153** or triol **450** with *p*-toluenesulfonic acid in nitromethane gives in both cases cyclization to **103** and **451** respectively, although the yield in the case of R=OH is somewhat lower (64%) compared with R=H (87%) (Scheme 6.7).

The reaction sequence in which first the side chain is degraded and next the epoxide is reduced cause difficulties with several individual reaction steps, dependent on the substituent at C(6). To circumvent these problems the reaction sequence was changed and the 8(17) double bond was first epoxidized and reduced, followed by oxidation of the side chain. In this way the functional groups at C(8) and in the side chain were transformed from the 'larixol situation' into the 'sclareol situation'.

The oxidative cleavage of sclareol (**4**) and sclareol-like compounds **185** and **186** affords methyl ketones which under acidic conditions cyclize to enol ethers. Osmylation of the double bond in the enol ethers gives the key intermediate aldehydes as the major products along with some minor products like ketones **457** (Scheme 6.8). For sclareol (**4**) it is found that the ratio of aldehyde and methyl ketones is strongly dependent on the ratio of OsO_4 and $NaIO_4$. If the ratio is high then the cleavage to the aldehydes is favored over rearrangement to the methyl ketones. Apparently the $OsO_4/NaIO_4$ ratio is not the only criterium to guide the product formation; also the substituent on C(6) shows some influence.

Scheme 6.8



4: R=H
185: R=OH
186: R=OAc

269: R=H
378: R=OH
379: R=OAc

457: R=OH

152: R=H
454: R=OH
187: R=OAc

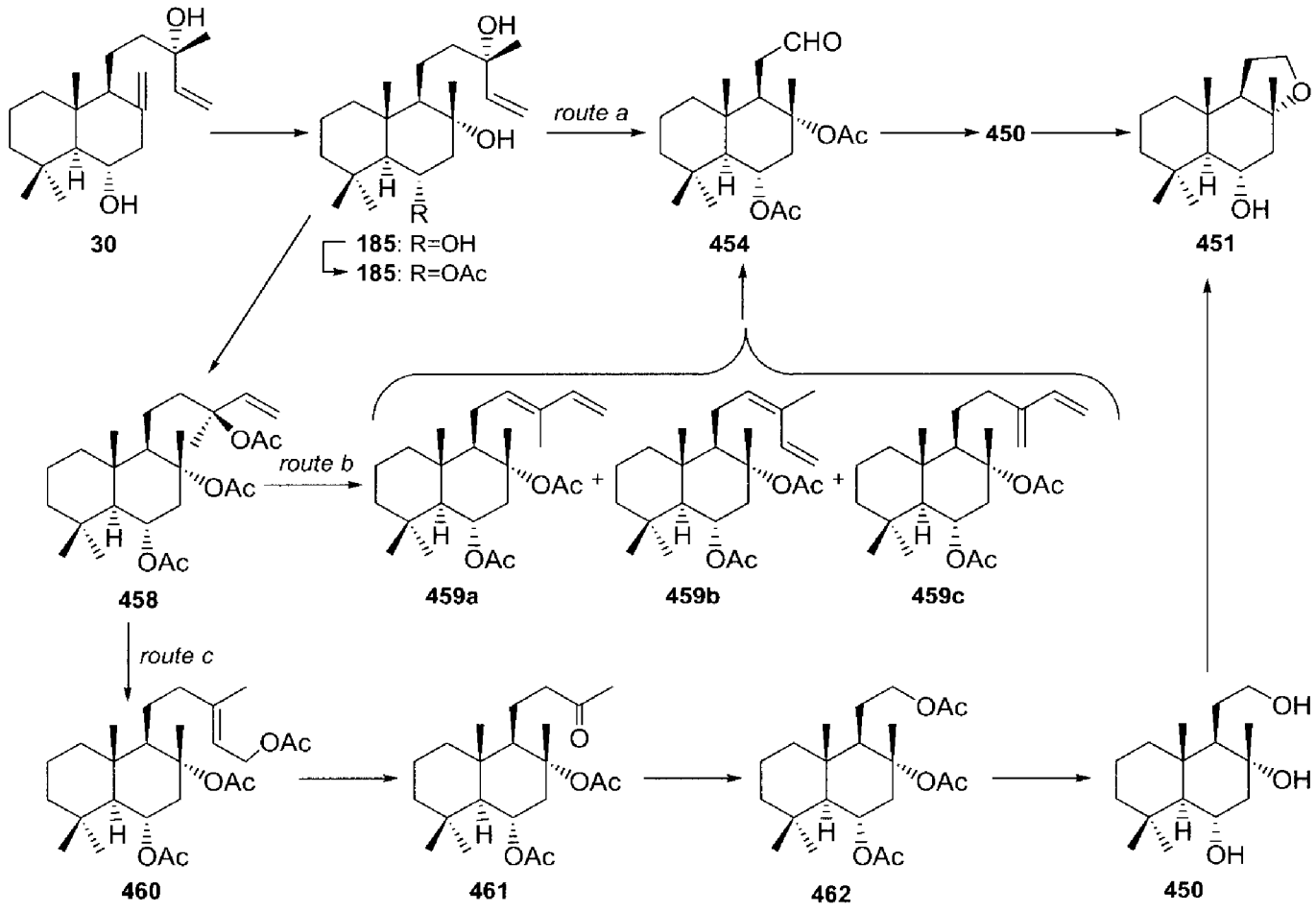
Reagents and conditions: (*a*) cat. OsO_4, $NaIO_4$, THF.

A little decrease in yield is found in going from R=H (73%) to R=OAc (72%) to R=OH (63%) in the oxidation of compounds **4**, **185**, and **186** with osmium tetroxide and sodium metaperiodate to

aldehydes **152**, **454**, and **187** accompanied by an increasing yield of a mixture of epimeric methyl ketones (route *a*, Scheme 6.9).

To avoid the use of poisonous oxidation reagents also two other routes were investigated using a $Pd(OAc)_2$ catalyzed elimination (route *b*) or a $PdCl_2(CH_3CN)_2$ catalyzed isomerization (route *c*), respectively. In the eliminated products of route *b* breakdown of the side chain was achieved by ozonolysis to give again the aldehyde **454** in reasonable yield. In the isomerized acetate **460** ozonolysis was applied as well but had to be followed by a Bayer-Villiger reaction of the resulting methyl ketone, which went in good yield in this case and without the side reactions observed in the 'larixol situation'.

Scheme 6.9



Comparing the results of the different approaches for the conversion of larixol (**30**) into 6α-hydroxy Ambrox (**451**), it is obvious that it is not necessary to consider the route depicted in Scheme 6.7 in which the larixol side chain is oxidized with the Bayer-Villiger oxidation mainly because of the lack of selectivity in this oxidation.

The best yield is obtained by route *a* (Scheme 6.9) using the poisonous OsO_4. Although route *c* involving isomerization of triacetate **458** needs two steps more, the overall yield of **451** is comparable and environmentally safe chemicals are used. Furthermore, the intermediates are all

formed in high yield, which avoids difficult purification procedures, so for us this is the route of choice.

The exocyclic double bond at C(8) in larixol makes its chemistry different from that of sclareol. Sclareol possesses a hydroxyl group at C(8) which may or may not take part in reactions of the side chain, depending on protection of this group or not. The exocyclic double bond in larixol (**30**) mostly does not take part in reactions of the side chain. Apart from this, the normal differences between a hydroxyl group and a double bond of course play a role. When the exocyclic double bond is converted to a methyl-hydroxyl group as in **185**, the chemistry still shows some differences with that of sclareol due to the presence of the C(6) hydroxyl group.

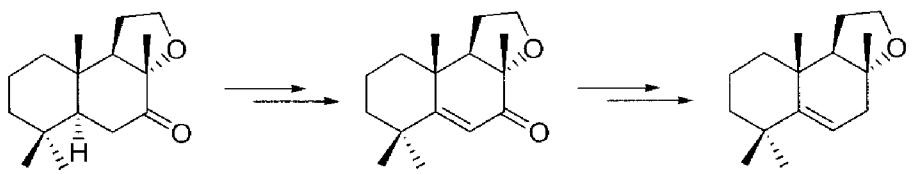
The presence of this group at C(6) in larixol can be seen as a benefit or as a drawback. The extra functional group can be used as a handle to make B-ring derivatives, something that is not possible with sclareol or (*epi*)-manool. On the other hand, reactions sometimes take an unexpectedly different course, and for the preparation of Ambrox® (**103**) itself or Ambraketal (**381**) always two extra reactionsteps have to be performed to remove this hydroxyl group.

6.5 The synthesis of unsaturated Ambrox-like Compounds

6α-Hydroxy Ambrox (**451**) was used as key intermediate for the preparation of a number of simple Ambrox derivatives of which Δ^5-Ambroxene (**433**) appeared to be the most attractive one (Chapter 4). This Δ^5-alkene **433** was produced selectively by elimination of methanesulfonic acid from the corresponding mesylate of **451** (**468**).

Compound **433** exhales a powerfull woody and ambery smell, more woody than Ambrox® (**103**) and less ambery-animal, a note which appears to be also more long-lasting than Ambrox®. This interesting Ambrox-like compound is patented and synthesized from **506** *via* enone **507** (Scheme 6.10).[5]

Scheme 6.10

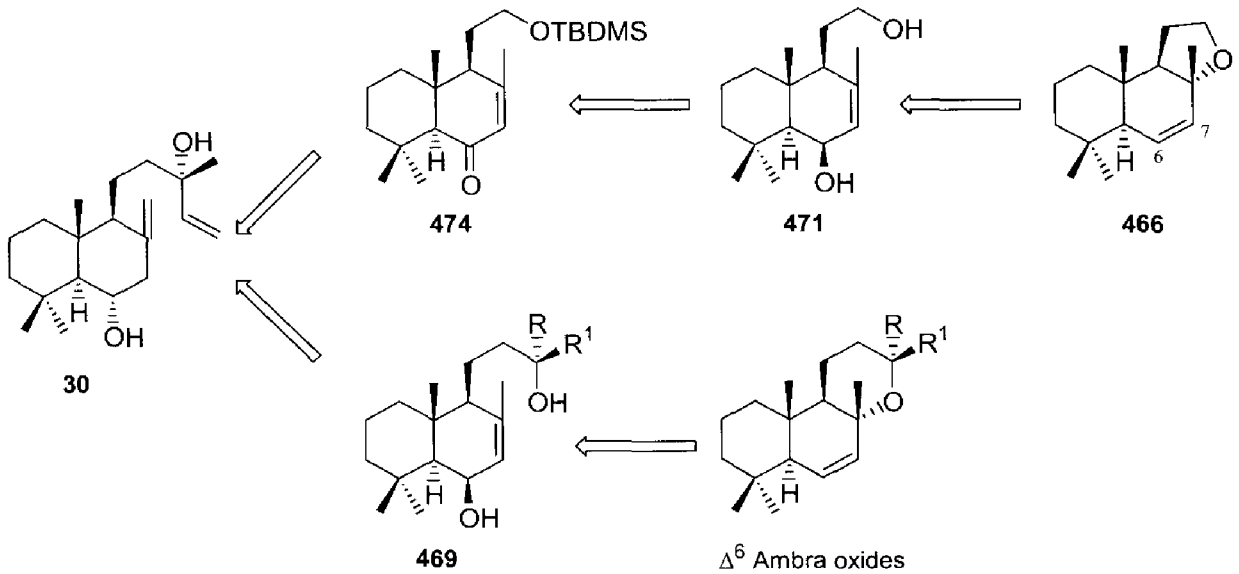


506 **507** **433**

A selective synthesis of Δ^6-Ambroxene (**466**) proved to be more difficult and laborious. Ultimately **466** was obtained in enantiomerically pure form from larixol (**30**) *via* ringclosure of allylic alcohol **471** (Scheme 6.11). The selective synthesis of Δ^6-Ambroxene (**466**) should be noted because this compound can not be obtained easily by selective elimination of the hydroxyl group at

C(6). Such type of eliminations lead to mixtures of alkenes with the Δ^5-compound as the main product.[6] The key transformation to Δ^6-Ambroxene consisted of the easy abstraction of the axial oriented allylic hydroxyl group at C(6) followed by interception of the resulting mesomeric carbocation at C(8) by the nucleophilic hydroxyl group in the side chain. The cyclization *via* ionization of the allylic alcohol in ring B is a new approach in the formation of Ambrox-type ethers. Δ^6-Ambroxene (**466**) exhibits (also) a pleasant Ambrox-like smell.

Scheme 6.11



It turned out that the already described successful cyclization to a five-membered cyclic ether[6] could not be extended to an equally successful cyclization of the corresponding homologues to the six-membered cyclic ethers (Δ^6-tetrahydrofuranylethers), *e.g.* Δ^6-Ambra oxides. In all but one of the latter cases, elimination of the 6β-hydroxyl group to the corresponding $\Delta^{6,8}$-dienes was observed as the major reaction. Although the new formed 5-ring has a higher strain energy than the 6-ring, the relative rate of cyclization is also higher and apparently this allows cyclization to take place before deprotonation can occur. When ring closure to a six-membered ring has to take place, deprotonation occurs more quickly in most cases, which leads to the corresponding dienes.

6.6 Outlook

6.6.1 Isolation and analysis of useful labdanes

Sclareol (**4**) is nowadays the industrially used starting material for the preparation of Ambrox® (**103**). Other labdanes like labdanolic acid (**32**) and labdanediol (**119**), to be extracted from the gum of *Cistus ladaniferus L.*, larixol (**30**), larixyl acetate (**31**) and *epi*-manool (**29**), to be

extracted from the turpentine of *Larix decidua Miller* (*L. europae D.C.*), can be used as natural starting material for the preparation of Ambrox® as well.

Labdanolic acid (**32**) is the main component (ca. 40%) in the acidic fraction from the *n*-hexane extract of *Cistus ladaniferus L.* ("rock-rose"). The commercial extract from *Cistus ladaniferus L.* is obtained by steam distillation of the twigs and leaves of the plants, or by treatment of the plants with hot neutral or alkaline water. However, these conditions easily cause dehydratation of the tertiary hydroxyl group from labdanolic acid, which results in a mixture of labdenic acids. To prevent this dehydratation the dried twigs and leaves of the *Cistus ladaniferus L.* were soaked with *n*-hexane to give a sticky labdanum gum from which labdanolic acid could be isolated as its acetate. No large scale procedures for the isolation of labdanolic acid from the gum of *Cisutus ladaniferus L.* are known and the development of such procedures should be studied. No large scale procedures are known for the isolation of other valuable compounds from this gum such as labdanediol (**119**). Also this compound has potentials for conversion into Ambrox® (**103**) and its large scale isolation should be studied as well.

The oleoresin of the Venice larch turpentine of the *Larix decidua Miller* consists mainly of larixyl acetate (**31**) and *epi*-manool (**29**). To facilitate purification, the extract is hydrolyzed to give larixol (**30**) as the main constituent, which can be obtained in pure form *via* crystallization from cyclohexane. The most apolar compound in the residual motherliquor is *epi*-manool (**29**), which can be isolated by chromatography. Also in this case large scale isolation procedures should be developed for the easy and industrial applicable isolation of larixol (**30**), larixyl acetate (**31**) and *epi*-manool (**29**) from the turpentine of *Larix decida*.

In the search for easy isolation procedurs, the application of modern extraction methods like solid phase extraction or supercritical extraction could be investigated. The development of novel procedures using mainly water with small quantities of added surfactants or water at elevated temperatures (110-150°C) under pressure, for the isolation of apolar secondary metabolites from plants could circumvent the use of inflamable or poisonous organic solvents, which are normally used. The isolated compounds can be recovered by filtration, centrifugation or passing the aqueous solution through apolar solid phase extraction materials. The solid phase extraction material in theory can be re-used up to ca. a hundred times, which makes the extraction method inexpensive.

Also a cheap and easy to perform quantitative analytical procedure for the determination of these labdanes in the plant extracts is not available and should be developed using modern analytical tools.

6.6.2 Conversion of labdanes into ambergris fragrance compounds

In this thesis mainly the research of labdanolic acid (**32**) and larixol (**30**) as starting material is described. The industrial applicability of the gum of *Cistus ladaniferus L.* and the resin of *Larix decidua* could be improved when also the other labdanes from these natural sources can be used

as starting material in synthesis. Next to labdanolic acid (**32**), also labdanediol (**119**) could be converted to Ambrox®. This will need the development of new synthetic procedures.

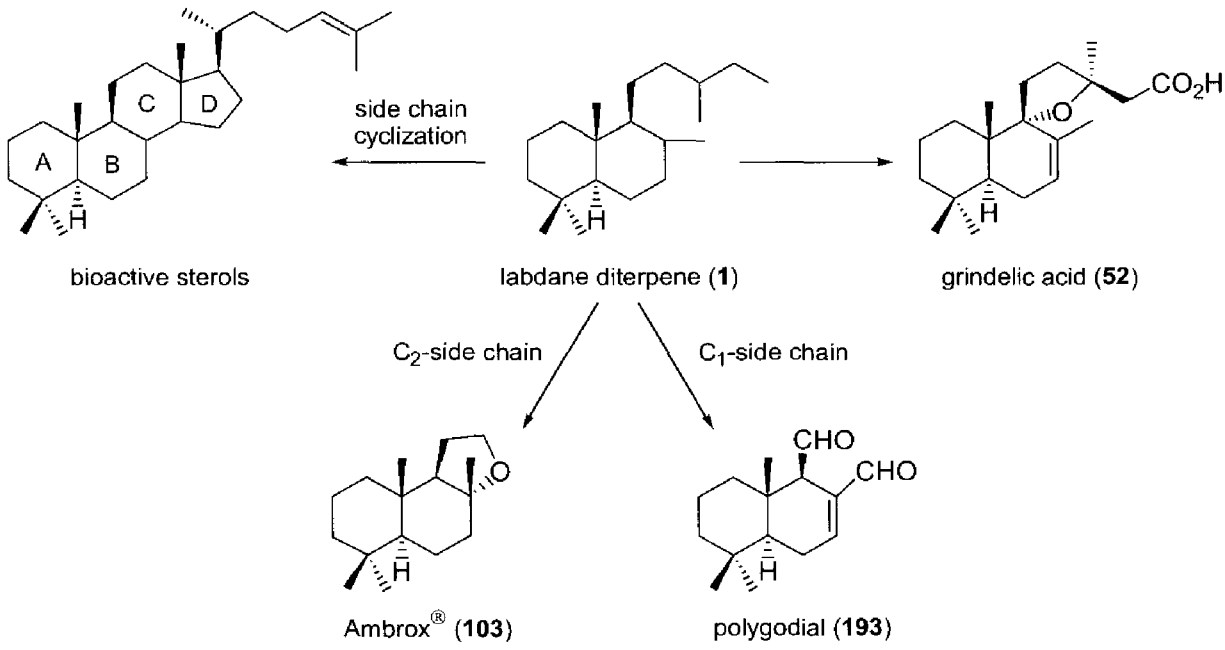
Ambraketal (**381**) can be prepared from larixol (**30**), larixyl acetate (**31**) and from *epi*-manool (**29**), but large scale procedures, suitable for industrial application have to be developed.

6.6.3 Conversion of labdanes into other bioactive natural products

Although we have concentrated our efforts on the synthesis of ambergris flavour compounds starting from the labdanes labdanolic acid (**32**) and larixol (**30**) in principle the following types of useful products can be synthesized from these labdanes as well (Scheme 6.12).

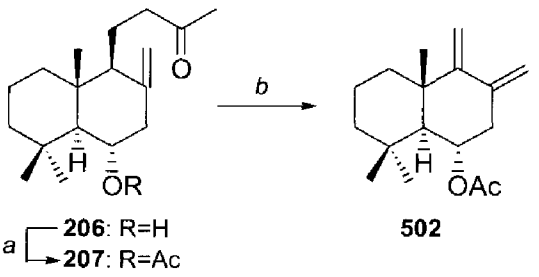
1. Modification of the labdane skeleton as it is, to obtain more valuable bioactive labdanes.
2. To use the labdane and its side chain for the synthesis of larger polycyclic compounds, for instance with sterol-like structures.
3. To shorten the side chain to one carbon atom for the synthesis of interesting bioactive drimanes.

Scheme 6.12



The decalin part of the labdane diterpenes resembles that of the drimane sesquiterpenes. Degradation of the C(9) side chain of the labdane starting compound like larixol will lead to suitable intermediates like **502** (Scheme 6.13) for conversion into several physiologically interesting drimanes, like polygodial (**193**). A Norrish type II photochemical reaction *via* irradiation of **207** with an UV-lamp showes a 75% yield of **502**, however, the conversion is only 13% (Scheme 6.13). Studies should be undertaken to improve this conversion.

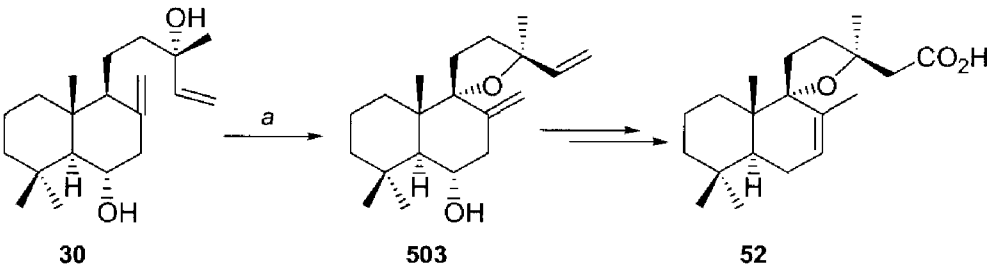
Scheme 6.13



Reagents and conditions: (*a*) Ac_2O, 92%; (*b*) hv, hexane, 5°C, 3h, 75% (13% conversion).

Grindelic acid (**52**), the most prominent member of the grindelane class of bicyclic diterpenoids, is widely considered to be the genetic precursor of many structurally interesting, highly oxygenated metabolites.[7] Investigations could be started to use labdanes for the synthesis of biological active grindelic acid (**52**). When larixol was treated with iodine in the presence of $KHCO_3$ compound **503** was obtained in 25% yield (Scheme 6.14). The reaction to **503** could be investigated and optimalized. Also *epi*-manool (**29**), which in principle is a better starting material for the synthesis of grindelic acid (**52**), could be converted into a similar spiro-compound. Further research has to be carried out to convert compounds like **503** into grindelic acid (**52**) .

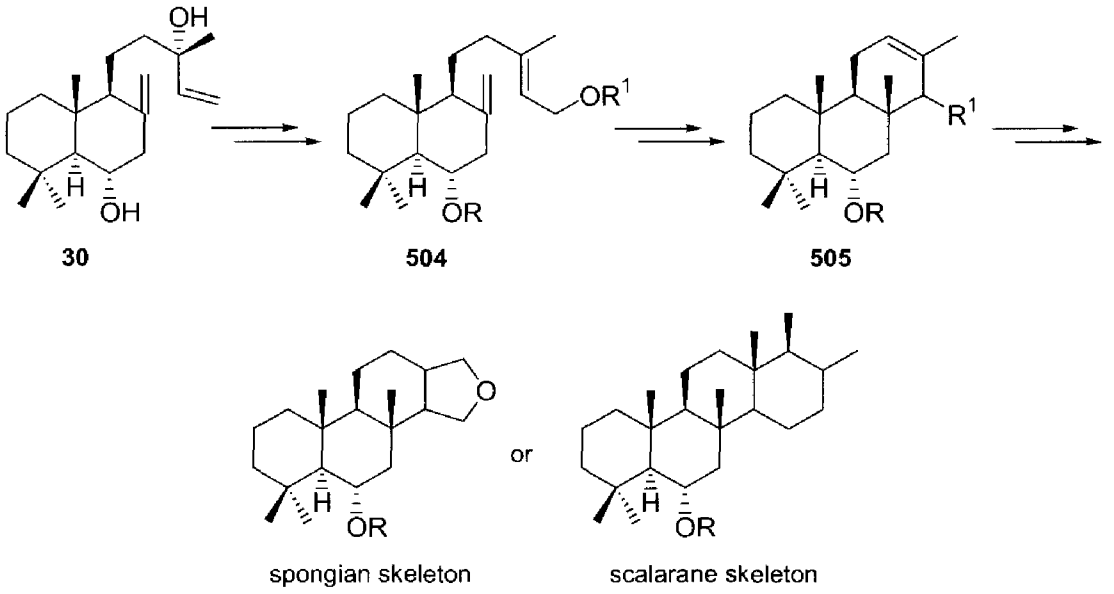
Scheme 6.14



Reagents and conditions: (*a*) I_2, $KHCO_3$, Et_2O, H_2O, 25%.

Cyclization, leading to polycyclic tri- and tetracyclic terpenes with an ABC and eventually ABCD ringsystem, could be investigated. Cyclization of the labdane side chain should give rise to bioactive sterols or to terpenes like the biological active spongianes or scalaranes (Scheme 6.15).

Scheme 6.15



30 **504** **505**

spongian skeleton scalarane skeleton

6.7 References and Notes

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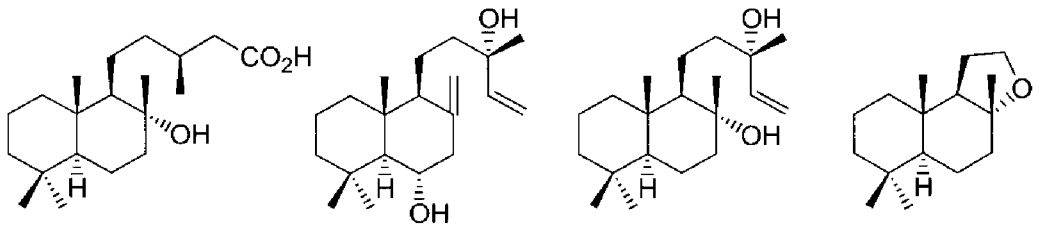
Summary

Since ancient times, ambergris has been one of the most highly valued perfumery materials. Ambergris is a metabolic product of the spermwhale (*Physeter macrocephalus* L.), which accumulates as concretions in the gut. (-)-Ambrox® (**4**), the commercially most important constituent of natural ambergris, is recognized as the prototype of all ambergris odorants. For this reason, various synthetic routes to (-)-Ambrox® and its racemate have been developed, preferrably starting from cheap, abundantly available natural labdanes. Sclareol (**3**) is nowadays the industrially used starting material for the preparation of (-)-Ambrox®. Labdanolic acid (**1**) and larixol (**2**) are both easily and abundantly available from labdanum gum and larix turpentine, respectively, but have found little use as starting material in syntheses of Ambergris odour compounds. In this thesis new chemistry in this field is described.

Figure 1



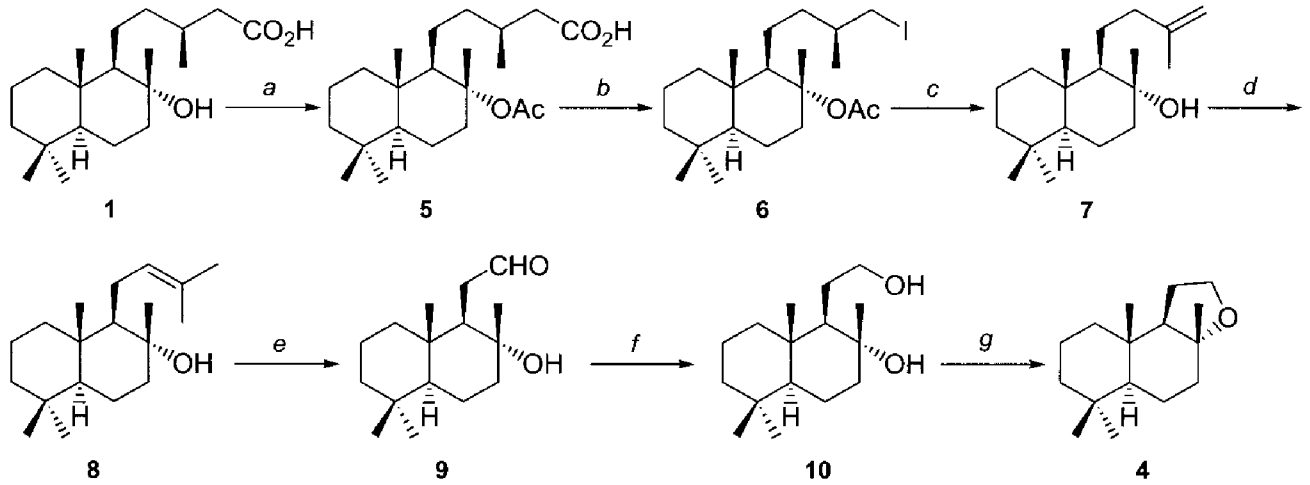
labdanolic acid (**1**) larixol (**2**) sclareol (**3**) Ambrox® (**4**)

The synthesis of Ambrox® starting from labdanolic acid

Labdanolic acid (**1**) is the main component (ca. 40%) in the acidic fraction of the *n*-hexane extract of *Cistus ladaniferus L.* ("Rock-rose"). The oxidative degradation of the C(9)-side chain of labdanolic acid (**1**) can in principle provide suitable synthons for the synthesis of (-)-Ambrox®.
The degradation of the side chain of labdanolic acid or its methyl ester is not an easy task because the carboxyl group is the only available functional group. We have used the iododecarboxylation of labdanolic acid (**1**) as the key step in its conversion into Ambrox® (**4**) (Scheme 1).

The iododecarboxylation of acetate **5** could be achieved by treatment with iodine and iodobenzene diacetate (IBDA) under irradiation and the iodide **6** was obtained in a good yield of 76% (Chapter 2). When the dehydrohalogenation of iodide **6** is performed with KO*t*Bu in *refluxing* THF (or in DMSO at room temperature), the initially formed alkene is *in situ* isomerized to **8** (Scheme 1). Ozonolysis of the double bond and reduction of the intermediate ozonides with sodium borohydride gave diol **10** in 92% overall yield from **6**. Stirring of diol **10** in nitromethane in the presence of *p*-toluenesulfonic acid gave the cyclized product Ambrox® (**4**) in 87% yield.

Scheme 1



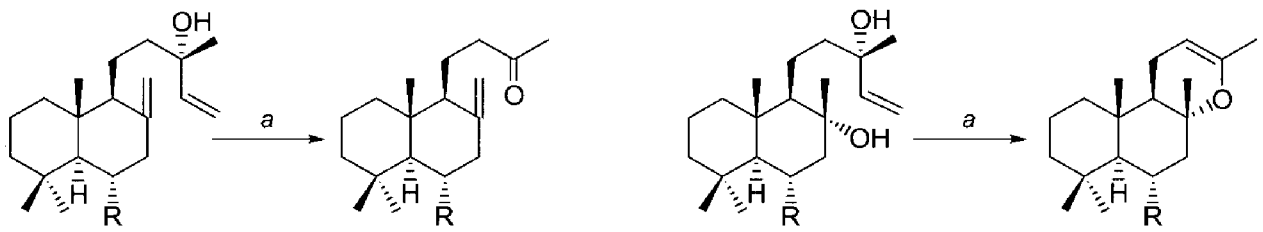
Reagents and conditions: (*a*) AcCl, *N,N*-dimethylaniline; (*b*) IBDA, I_2, CCl_4, hν, Δ, 76%; (*c*) *t*BuOK, THF; (*d*) Δ, 78%; (*e*) O_3, MeOH/CH_2Cl_2 3:1, -78°C; (*f*) $NaBH_4$, 92%; (*g*) *p*-TsOH, CH_3NO_2, 87%.

In this way Ambrox® can be obtained in a short procedure of 4 steps in 47% overall yield starting from the acetate of labdanolic acid (**5**). The main drawback of the method is the necessary application of iodine in the decarboxylation reaction. When a cheaper procedure can be found for this reaction, labdanolic acid (**1**) may become a good alternative as starting material for the industrial preparation of Ambrox®.

The synthesis of Ambrox-like compounds starting from larixol

To use the bicyclic part of the labdanes in the synthesis of other natural products the C(9) side chain has to be shortened. A modification of the method of Ogino *et al*, using anhydrous potassium permanganate in the presence of a phase-transfer catalyst, was investigated for the oxidation of several labdanes using standardized methods with 1.5 or 3.0 equivalents of potassium permanganate (Chapter 3). From the results it becomes clear that generally good to high yields of single products can be obtained (Scheme 2).

Scheme 2



2: R=OH
11: R=OAc
12: R=H

13: R=OH (68%)
14: R=OAc (72%)
15: R=H (67%)

16: R=OH
17: R=OAc
3: R=H

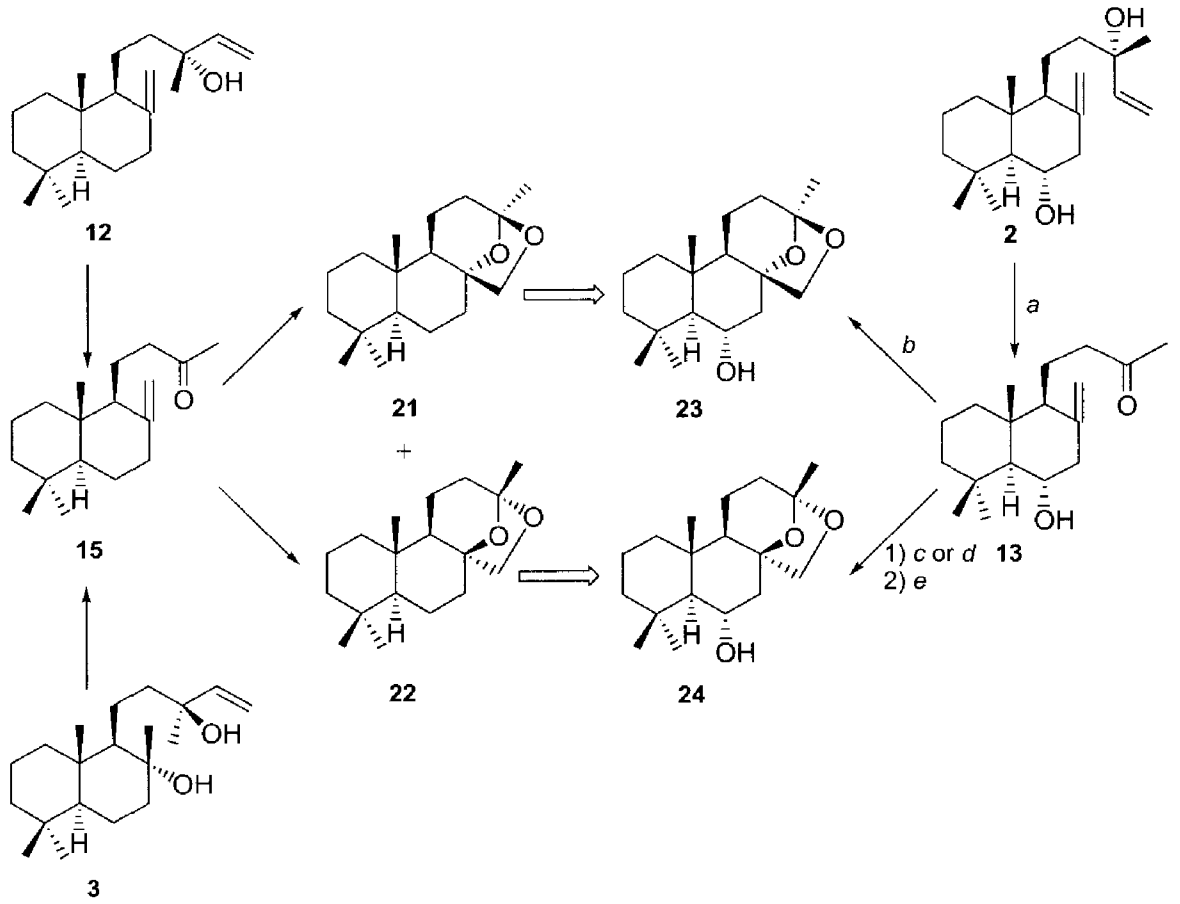
18: R=OH (74%)
19: R=OAc (90%)
20: R=H (86%)

Reagents and conditions: (*a*) 3.0 eq. $KMnO_4$, BTEAC, CH_2Cl_2, 0-3°C.

The influence of the substituent on C(8) is also clear. When an exocyclic double bond is present at C(8) a reasonable selective oxidation of the double bond in the side chain can be achieved to give the desired methyl ketones (**13** - **15**) in good yields. When a hydroxyl group is present at C(8), this group has a strong tendency to react with the methyl ketone in the side chain, and cyclic enol ethers (**18** - **20**) are isolated as the main reaction products in high yield. The application of sonification accelerates the oxidation appreciably, and shortens the reaction time from 14 to 2 hours, but the yield and product distribution is not affected.

Another compound which has been found to possess an intense amber odour is Ambraketal (**21**) (also called Amberketal or Jeger's ketal). It is nowadays most readily obtained by degradation of manool (**12**) or sclareol (**3**) (Scheme 3) *via* the intermediate methylene ketone **15**.

Scheme 3



Reagents and conditions: (*a*) $KMnO_4$, TEBAC, CH_2Cl_2, 68%; (*b*) OsO_4, py, *t*BuOH, $(CH_3)_3NO$, H_2O, 86%; (*c*) *m*-CPBA, Na_2CO_3, CH_2Cl_2, 87%; (*d*) oxone®, acetone, H_2O, CH_2Cl_2, [18]crown-6, $NaHCO_3$, 0°C, 79%; (*e*) PPTS, benzene, 70%.

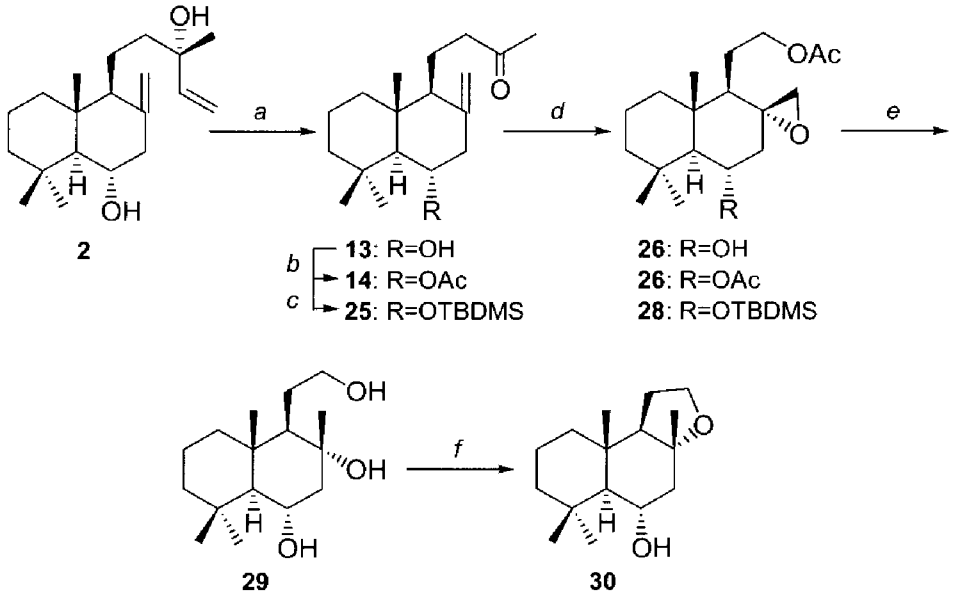
Larixol (**2**) is an excellent starting material for the preparation of Ambraketal. Oxidation of the side chain provides for the necessary methyl ketone and the exocyclic double bond is already present in the molecule as the precursor for a diol or epoxide function. When the exocyclic double

bond is oxidized first to an epoxide, an acid catalyzed ringclosure can be effected easily, which takes place with inversion of the configuration at C(8) and the outcome is a ketal with the undesired 8*S* configuration. When the double bond is first oxidized to a diol, than no inversion will occur during formation of the ketal, which results in the desired 8*R* configuration. The hydroxy Ambraketal **23** was obtained by a one step oxidation of alkene **13** with OsO_4. Epoxidation of the exocyclic double bond in **13** gave an epoxide. Cyclization of this epoxide with a catalytic amount of mild PPTS gave *epi*-hydroxy Ambraketal **24**. The hydroxyl group at C(6) of *epi*-hydroxy Ambraketal **24** and hydroxy Ambraketal **23** allows the preparation of several simple derivatives of these ketals.

The oxidation of the C(9)-side chain of larixol (**2**) or its acetate (**11**) provides suitable synthons for the synthesis of several Ambrox-like compounds. 6α-hydroxy Ambrox (**30**) can be considered to be a key intermediate in such syntheses and the conversion of larixol (**2**) into this intermediate is described in Chapter 4.

The side chain of larixol (**2**) can be oxidized with potassium permanganate to a methyl ketone and an obvious way to achieve further breakdown to a functionalized two carbon side chain is the Baeyer-Villiger oxidation. This reaction was investigated for three derivatives, which had an hydroxyl, a *tert*butyldimethylsilyloxy or an acetoxy group at C(6) (Scheme 4).

Scheme 4



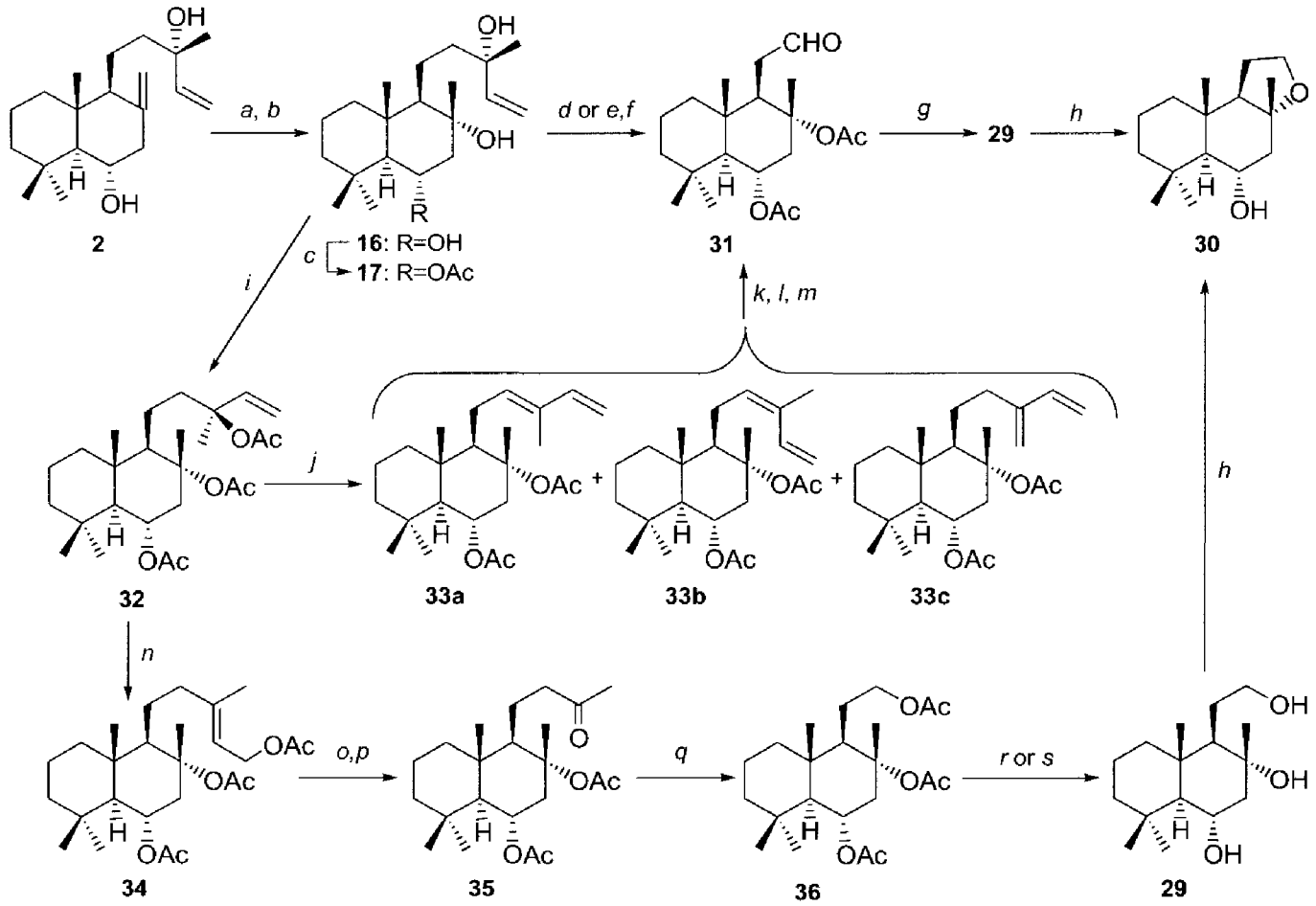
Reagents and conditions: (*a*) 3.0 eq. $KMnO_4$, BTEAC, CH_2Cl_2, 0-3°C, 68%; (*b*) Ac_2O, CH_2Cl_2, py, DMAP, 91%; (*c*) TBDMSiCl, DMF, imidazole, 60°C, 87%; (*d*) *for R=OH: m*-CPBA (2 eq.), CH_2Cl_2, 31%; *for R=OAc: m*-CPBA, CH_2Cl_2, 84%; *for R=OTBDMS: m*-CPBA (2.5 eq.), CH_2Cl_2, 17%; (*e*) *for R=OH, OAc:* $LiAlH_4$, THF, 0°C to rt, 10%; (*f*) *p*-TsOH, CH_3NO_2, 64%.

These first attempts to obtain 6α-hydroxy Ambrox from larixol did not give very satisfactory results. Although incidental transformations proceeded in good yield, no overall high yield conversion could

be achieved and therefore other routes to **30** were investigated, in which the exocyclic double bond at C(8) in larixol was first converted into 6α-hydroxy sclareol **16**.

Oxidation with a catalytic amount of OsO_4 and an excess of $NaIO_4$ afforded aldehydes **31** in high yield (Scheme 5). When the aldehydes were reduced with $LiAlH_4$ triol **29** was obtained in 94% yield, and this could be cyclized easily to 6α-hydroxy Ambrox (**30**). Two other routes starting from 6α-hydroxy sclareol **16**, based on Pd catalyzed elimination or isomerization of allylic acetates in the side chain, followed by ozonolysis, were investigated as well (Scheme 5) and in both cases triol **29** was obtained in a good yield.

Scheme 5

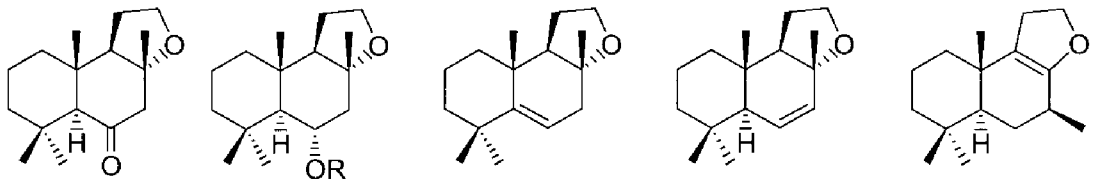


Reagents and conditions: (*a*) oxone®, acetone, H_2O, CH_2Cl_2, [18]crown-6, $NaHCO_3$, 0°C, 68%; (*b*) $LiAlH_4$, THF, 0°C to rt, 94%; (*c*) Ac_2O, CH_2Cl_2, py, DMAP, 91%; (*d*) *for R=OH:* cat. OsO_4, $NaIO_4$, THF, 55-62%; *for R=OAc:* cat. OsO_4, $NaIO_4$, THF, 72%. (*e*) $KMnO_4$, BTEACl, CH_2Cl_2, 0°C to rt, 70-85%; (*f*) Jones, acetone, 50%; (*g*) $LiAlH_4$, THF, 0°C to rt, 94%; (*h*) *p*-TsOH, CH_3NO_2, 64%; (*i*) AcCl, *N,N*-dimethylaniline, 80%; (*j*) $Pd(OAc)_2$, $CaCO_3$, PPh_3, dioxane, Δ, 94%, **33a:b:c**=4:2:3; (*k*) O_3, MeOH/CH_2Cl_2 3:1, -78°C; (*l*) $NaBH_4$, -78°C; (*m*) NaOMe, MeOH, 67%; (*n*) $PdCl_2(CH_3CN)_2$, THF, 98%; (*o*) O_3, CH_2Cl_2/ MeOH 1:1, -78°C; (*p*) PPh_3, -78°C, 95%; (*q*) *m*-CPBA, CH_2Cl_2, 83%; (*r*) $LiAlH_4$, THF, 0°C to rt, 85%; (*s*) NaOMe, MeOH, 85%.

When the results, obtained in the conversion of larixol (**2**) into 6α-hydroxy Ambrox are compared, it can be concluded that the first route described in Scheme 5 gives the highest yield in the shortest number of reaction steps. On the other hand, the third route of Scheme 5 is the easiest one to perform and has our preference.

6α-Hydroxy Ambrox (**30**) was used as the key intermediate for the preparation of a number of simple Ambrox derivatives, such as 6-oxo-Ambrox **37**, 6-methoxy-Ambrox **39**, and 6-acetoxy-Ambrox **38** (Figure 2). When **30** was treated with *p*-toluenesulfonic acid in benzene under Dean Stark conditions a non-separable mixture of three compounds **40**, **41**, and **42** was formed in a ration of 2:1:1. The structures of **40** and **41** were confirmed by independent synthesis (*vide infra*), the structure of compound **42** is still tentative. This pleasant smelling mixture was separated on a GC-MS apparatus and on a GC-sniff apparatus, and all three compounds showed a pleasant smell, with the Δ^5-alkene **40** as the most attractive one.

Figure 2



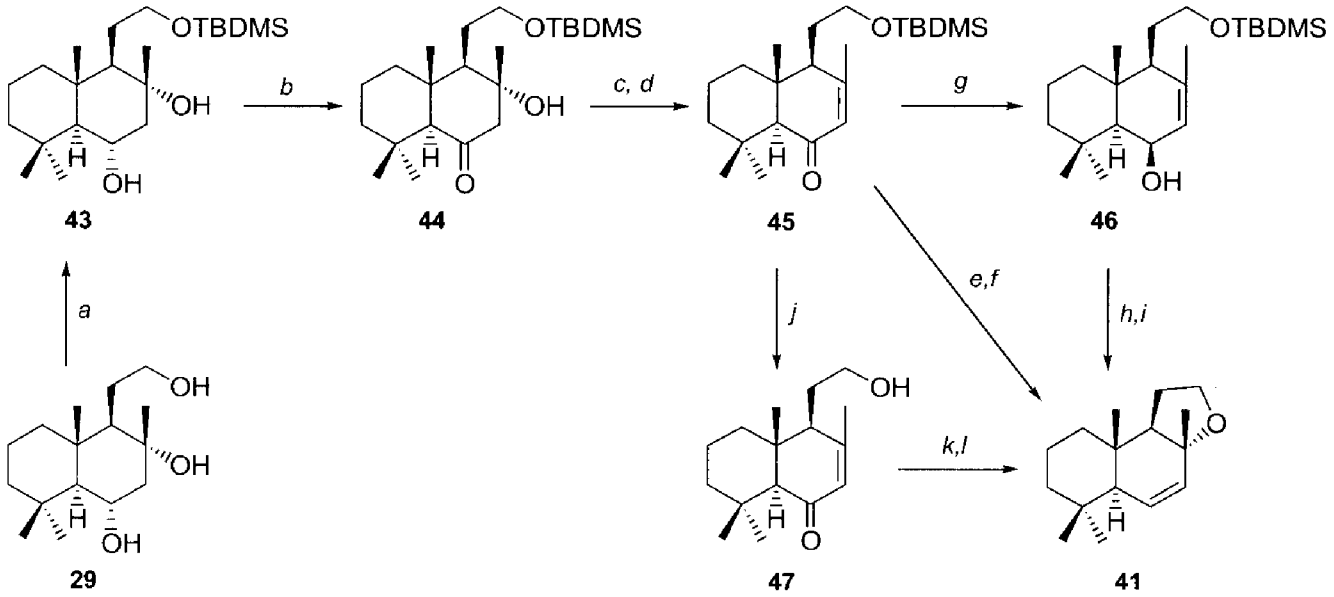
37 **38**: R=Ac **39**: R=CH_3 **40** **41** **42**

This Δ^5-alkene **40** was produced in a more selective way by elimination of methanesulfonic acid from the corresponding mesylate of **30**. A selective synthesis of Δ^6-Ambroxene **41** proved to be more difficult and laborious. Several approaches were investigated, and ultimately the one *via* ringclosure of allylic alcohol **46** proved to give good results (Scheme 6).

The oxidative breakdown of the side chain of larixol to an hydroxyethyl moiety as in triol **29**, can be accomplished in several ways as was described in Schemes 4 and 5. Selective protection of the primary hydroxyl group in the side chain of triol **29**, followed by oxidation of the secondary hydroxyl group at C(6) and elimination of the tertiairy hydroxyl group at C(8), gave the enone **45** in 67% overall yield starting from triol **29** (Scheme 6).

Reduction of the carbonyl group at C(6) with DIBAL-H in toluene at low temperature, deprotection of the hydroxyl group in the side chain of **46** and acid catalyzed cyclization afforded Δ^6-Ambroxene **41** in high yield in three simple steps. The approach described in Scheme 6 is new and very suitable for the *selective* synthesis of Δ^6-Ambrox-like compounds.

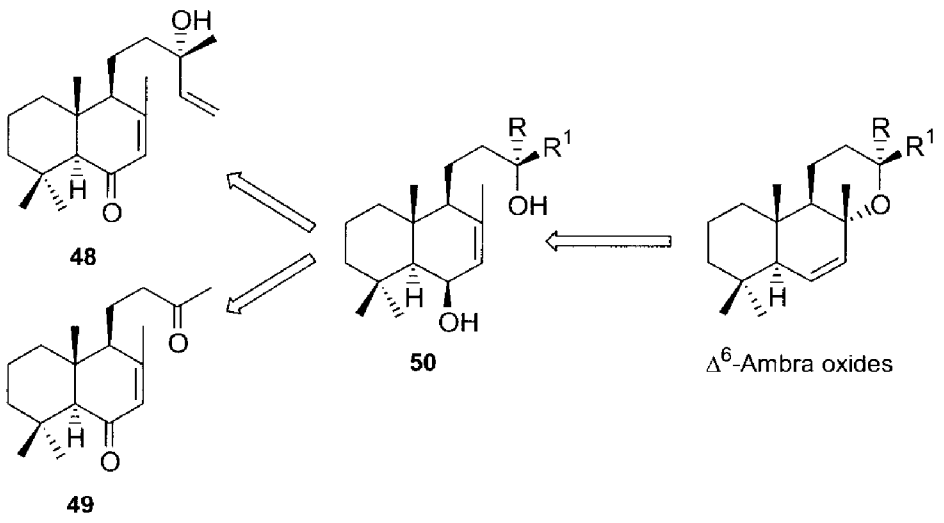
Scheme 6



Reagents and conditions: (*a*) TBDMSiCl, DMF, imidazole, N_2, 95%; (*b*) PDC, CH_2Cl_2, 3Å molecular sieves, 86%; (*c*) $SOCl_2$, py, DMAP, 0°C to rt; (*d*) NaOMe, MeOH, 82% (2 steps); (*e*) $LiAlH_4$, dry THF, 0°C to rt; (*f*) *p*-TsOH, CH_3NO_2, 40% (2 steps); (*g*) DIBAL-H, dry THF, 0°C, N_2, 90%; (*h*) TBAF, dry THF; (*i*) *p*-TsOH, CH_3NO_2, 87% (2 steps); (*j*) TBAF, dry THF, 1 h, 93%; (*k*) DIBAL-H, dry THF, 0°C, N_2; (*l*) *p*-TsOH, CH_3NO_2, 71% (2 steps).

The enones **48** and **49**, which can be obtained in a few reaction steps from larixol, are in principle good starting materials for the selective syntheses of a variety of Δ^6-Ambrox-like compounds, following a similar appraoch, and therefore the formation of ring C *six membered* ethers (Δ^6 Ambra oxides) has been investigated as well (Scheme 7).

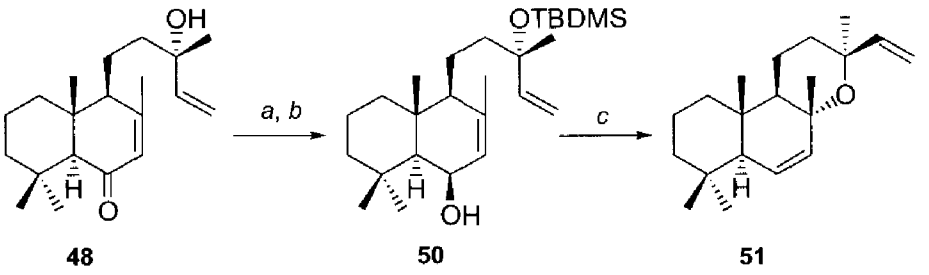
Scheme 7



The reduction of the carbonyl group at C(6) in **48** could be carried out in high yield with DIBAL-H, provided that the hydroxyl group in the side chain was protected (Scheme 8). On the

other hand, the deprotection of this hydroxyl group in the side chain with an aqueous HF solution was accompanied by cyclization of the intermediate diol as was demonstrated in the synthesis of ether **51**, thus providing the first example of the successful synthesis of sixmembered cyclic ethers (Chapter 5).

Scheme 8

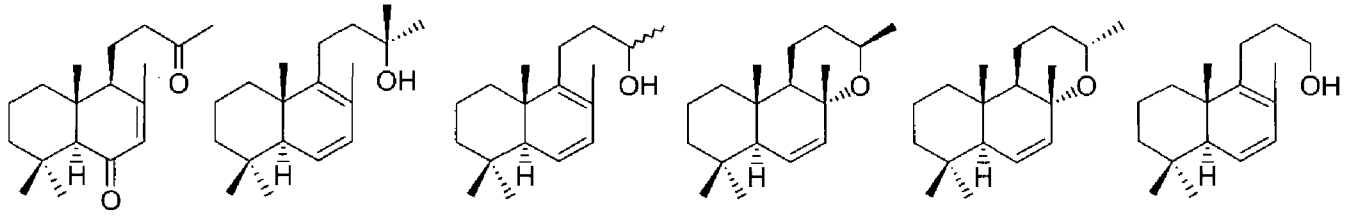


48 **50** **51**

Reagents and conditions: (*a*) TBDMSiCl, DMF, imidazole, 70°C, 3 days, 92%; (*b*) DIBAL-H, toluene, -78°C, 98%; (*c*) *i*) HF (50% aqueous solution), CH_3CN; *ii*) SiO_2, 67%.

Oxidation of the side chain in **48** with $KMnO_4$ gave diketone **49**, in which the nonconjugated carbonyl group in the side chain could be manipulated selectively. In the case of the C(13) disubstituted compound the combined deprotection cyclization reaction does not give cyclization and the dehydrated diene **52** was isolated as the only product. This prompted us to investigate the cyclization behaviour of the C(13) monosubstituted and C(13) unsubstituted compounds as well. It turned out that the already described successful cyclization to a fivemembered cyclic ether could not be extended to an equally successful cyclization of the corresponding homologues to the sixmembered cyclic ethers, *e.g.* Δ^6-Ambra oxides. In all but one of the latter cases, elimination of the 6β-hydroxyl group to the corresponding $\Delta^{6,8}$-dienes was observed as the major reaction and only minor quantities of the monomethyl compounds **54a** and **54b** could be obtained (Figure 3).

Figure 3

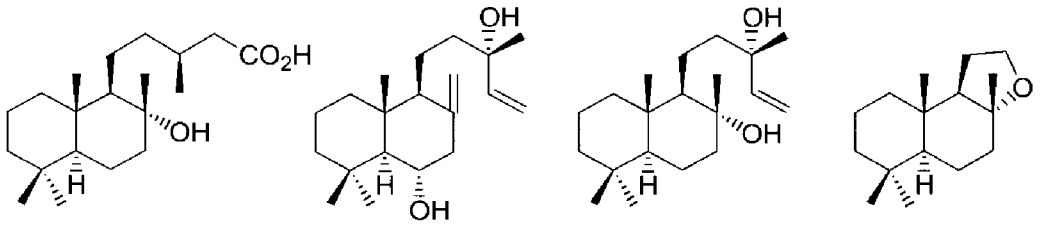


49 **52** **53a,b** **54a** **54b** **55**

Samenvatting

Sinds mensenheugenis is ambergrijs een van de meest waardevolle geurstoffen. Ambergrijs is een metabool product van de potvis (*Physeter macrocephalus* L.) en hoopt zich op als klompen in de darmen. (-)-Ambrox® (**4**) is het belangrijkste commerciële bestanddeel van natuurlijk ambergrijs en wordt gezien als het prototype van de ambergrijs geurstoffen. Vandaar dat er verschillende synthetische routes voor het racemaat en voor (-)-Ambrox® zijn ontwikkeld, de laatste bij voorkeur uitgaande van goedkope, veel voorkomende natuurlijke labdanen. Sclareol (**3**) wordt tegenwoordig als uitgangsstof gebruikt om op industriële schaal Ambrox® te maken. Labdaanzuur (**1**) en larixol (**2**) zijn beide eenvoudig te isoleren uit het in ruime mate beschikbare labdanum gom van *Cistus ladaniferus* en uit lariks hars van de *Larix decidua*, respectievelijk, maar zijn tot dusver weinig gebruikt als uitgangsmateriaal in de synthese van Ambergrijs geurstoffen. In dit proefschrift wordt nieuwe chemie op dat gebied beschreven.

Figuur 1



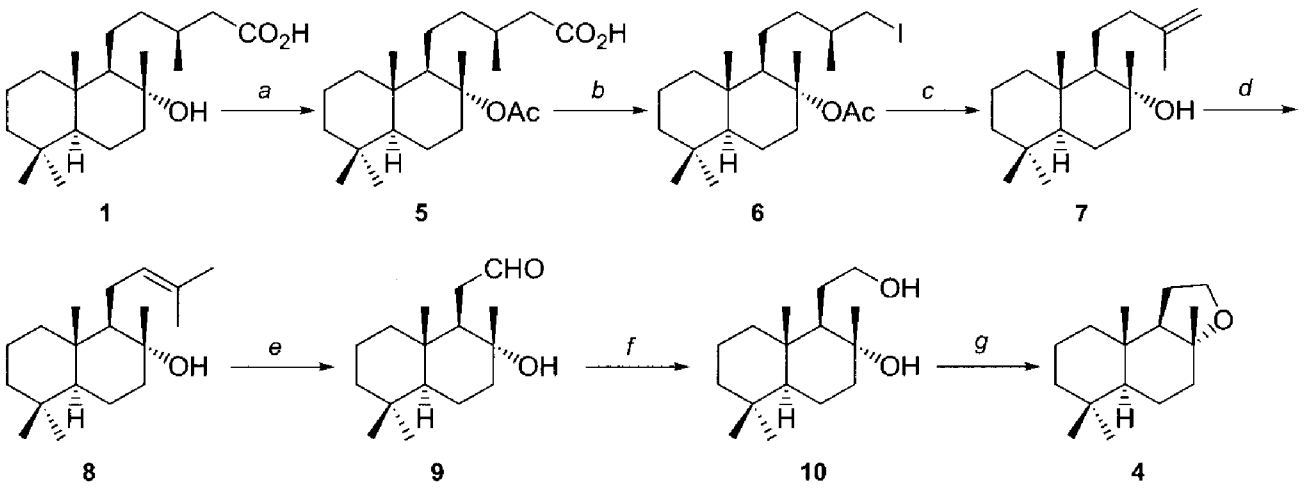
labdaanzuur (**1**) larixol (**2**) sclareol (**3**) Ambrox® (**4**)

De synthese van Ambrox® uitgaande van labdaanzuur

Labdaanzuur (**1**) is het hoofdbestanddeel (ca. 40%) van de zure fractie van het *n*-hexaan extract van *Cistus ladaniferus L.* ("Rock-rose" of "Cisteroos"). Oxydatieve degradatie van de C(9)-zijstaart van labdaanzuur (**1**) kan leiden tot geschikte synthons voor de synthese van (-)-Ambrox®, maar afbraak van de zijstaart van labdaanzuur is geen eenvoudige zaak omdat de carboxylgroep de enige beschikbare functionele groep is. Voor de omzetting van labdaanzuur tot Ambrox® (**4**) is door ons de jododecarboxylatie als sleutelstap gebruikt (Schema 1).

De decarboxylatie van acetaat **5** is bewerkstelligd met behulp van jodium en jodobenzeen-diacetaat (IBDA) onder bestraling met licht (100W) waarbij jodide **6** in een goede opbrengst van 76% verkregen is (Hoofdstuk 2). Wanneer de dehydrohalogenering van jodide **6** uitgevoerd wordt met behulp van KO*t*Bu in refluxerende THF (of in DMSO bij kamertemperatuur), dan isomeriseert het verkregen alkeen **7** *in situ* tot alkeen **8** (Schema 1). Ozonolyse van de dubbele band en reductie van de intermediaire ozonides met natriumboorhydride geeft diol **10** in een totaalopbrengst van 92% uitgaande van **6**. Roeren van diol **10** in nitromethaan in de aanwezigheid van *p*-tolueensulfonzuur levert met een opbrengst van 87% het cyclisatie-product Ambrox® (**4**) op.

Schema 1



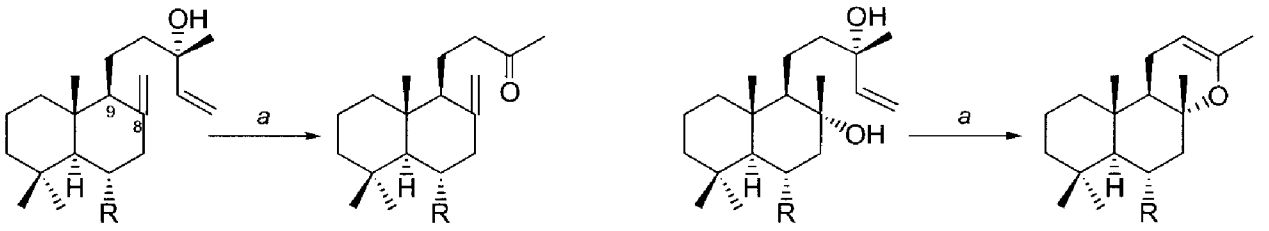
Reagentia en condities: (*a*) AcCl, *N,N*-dimethylaniline; (*b*) IBDA, I_2, CCl_4, hν, Δ, 76%; (*c*) *t*BuOK, THF; (*d*) Δ, 78%; (*e*) O_3, MeOH/CH_2Cl_2 3:1, -78°C; (*f*) $NaBH_4$, 92%; (*g*) *p*TsOH, CH_3NO_2, 87%.

Op deze manier kan Ambrox® worden verkregen via een vierstaps route in een opbrengst van 47% uitgaande van het acetaat van labdaanzuur (**5**). Een nadeel van deze methode is het noodzakelijk gebruik van jodium bij de decarboxylatie stap. Als er een goedkopere procedure voor deze reactie gevonden wordt, dan kan labdaanzuur (**1**) een goed alternatief vormen als uitgangsmateriaal voor de industriële bereiding van Ambrox®.

De synthese van Ambrox-achtige verbindingen uitgaande van larixol

Om het bicyclische gedeelte van labdanen te kunnen gebruiken in de synthese van andere natuurlijke stoffen moet de C(9) zijstaart worden ingekort. Een modificatie van de methode van Ogino *et al*, welke gebruik maakt van watervrij kaliumpermanganaat in aanwezigheid van een fase-transfer katalysator, is onderzocht voor de oxydatie van verschillende labdanen via gestandaardiseerde methodes met respectievelijk 1,5 en 3,0 equivalenten kaliumpermanganaat (Hoofdstuk 3). In het algemeen blijkt dat er goede tot hoge opbrengsten van eenduidige producten verkregen kunnen worden (Schema 2).

Schema 2



2: R=OH
11: R=OAc
12: R=H

13: R=OH (68%)
14: R=OAc (72%)
15: R=H (67%)

16: R=OH
17: R=OAc
3: R=H

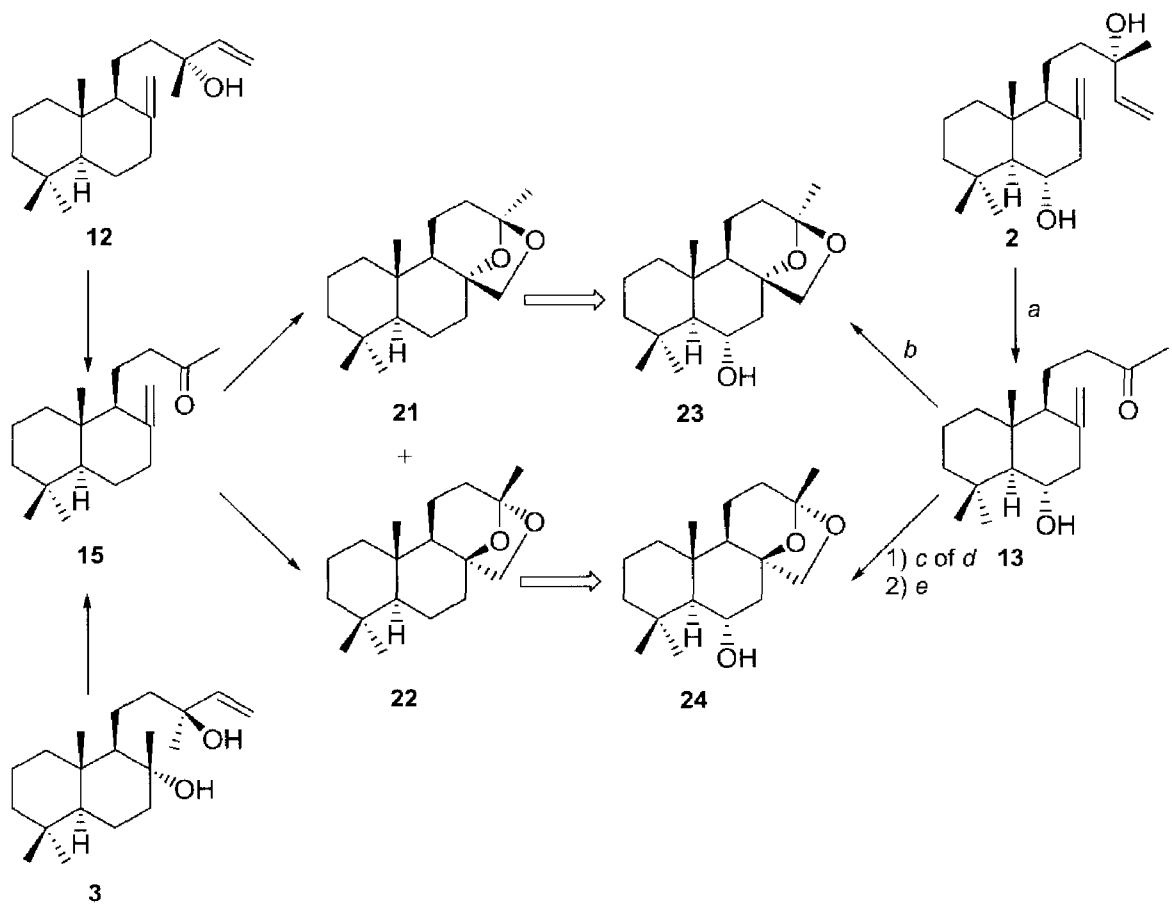
18: R=OH (74%)
19: R=OAc (90%)
20: R=H (86%)

Reagentia en condities: (*a*) 3,0 eq. $KMnO_4$, BTEAC, CH_2Cl_2, 0-3°C.

De invloed van de substituent op C(8) is duidelijk. Als er een exocyclische dubbele band op C(8) aanwezig is dan kan een redelijk selectieve oxydatie van de dubbele band in de zijstaart worden bewerkstelligd tot de gewenste methylketonen (**13** - **15**). Als er een hydroxyl-groep op C(8) aanwezig is dan heeft deze groep een sterke neiging om te reageren met het methylketon in de zijstaart en worden cyclische enolethers (**18** - **20**) in hoge opbrengst als hoofdproduct geïsoleerd. Door gebruik te maken van sonificatie wordt de reactietijd teruggebracht van 14 naar 2 uur, maar de opbrengst en de verhouding van de producten blijft hetzelfde.

Ambraketaal (**21**) (ook wel Amberketaal of Jeger's ketaal genoemd) is ook een verbinding met een sterke ambergeur. Tegenwoordig wordt het verkregen door degradatie van manool (**12**) of sclareol (**3**) (Schema 3) via het intermediaire methyleenketon **15**.

Schema 3



Reagentia en condities: (*a*) $KMnO_4$, TEBAC, CH_2Cl_2, 68%; (*b*) OsO_4, py, *t*.BuOH, $(CH_3)_3NO$, H_2O, 86%; (*c*) *m*-CPBA, Na_2CO_3, CH_2Cl_2, 87%; (*d*) oxon, aceton, H_2O, CH_2Cl_2, [18]crown-6, $NaHCO_3$, 0°C, 79%; (*e*) PPTS, benzeen, 70%.

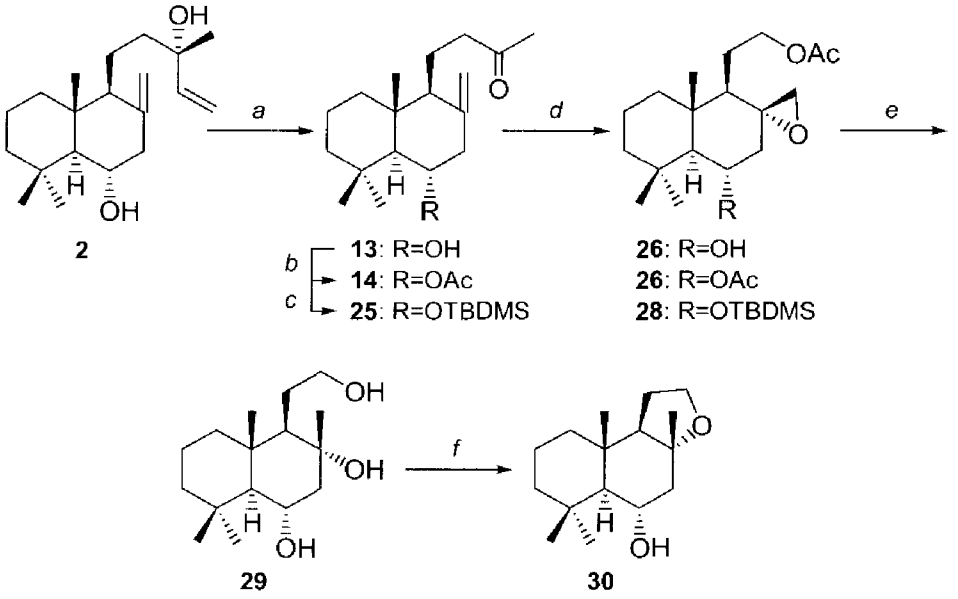
Larixol (**2**) is in principe een goed uitgangsmateriaal voor de bereiding van Ambraketaal. Oxydatie van de zijstaart levert het noodzakelijke methylketon op en de exocyclische dubbele band is al in het molecuul aanwezig. Het hydroxy-ambraketaal **23** is verkregen door oxydatie van

alkeen **13** met OsO_4 gevolgd door spontane ketalisering. Epoxydatie van de exocyclische dubbele band in **13**, gevolgd door cyclisatie met een katalytische hoeveelheid PPTS, geeft *epi*-hydroxy-ambraketaal **24**. De aanwezigheid van de hydroxyl-groep op C(6) in **23** en **24** maakt de synthese van verschillende eenvoudige derivaten mogelijk.

Oxydatie van de C(9)-zijstaart van larixol (**2**) of larixylacetaat (**11**) geeft geschikte synthons voor de synthese van verschillende Ambrox-achtige verbindingen. 6α-Hydroxy-Ambrox (**30**) kan beschouwd worden als een belangrijk intermediair in dergelijke syntheses. Een vijftal syntheses van 6α-hydroxy-Ambrox uitgaande van larixol (**2**) is beschreven in Hoofdstuk 4.

De zijstaart van larixol kan geoxydeerd worden tot een methylketon met kaliumpermanganaat. Een voor de hand liggende reactie voor verdere afbraak tot een gefunctionaliseerde zijstaart van twee koolstofatomen, is de Baeyer-Villiger oxydatie. Deze reactie is onderzocht voor derivaten met een hydroxyl-, een *tert*-butyldimethylsilyloxy- of een acetoxy-groep op C(6) (Schema 4).

Schema 4

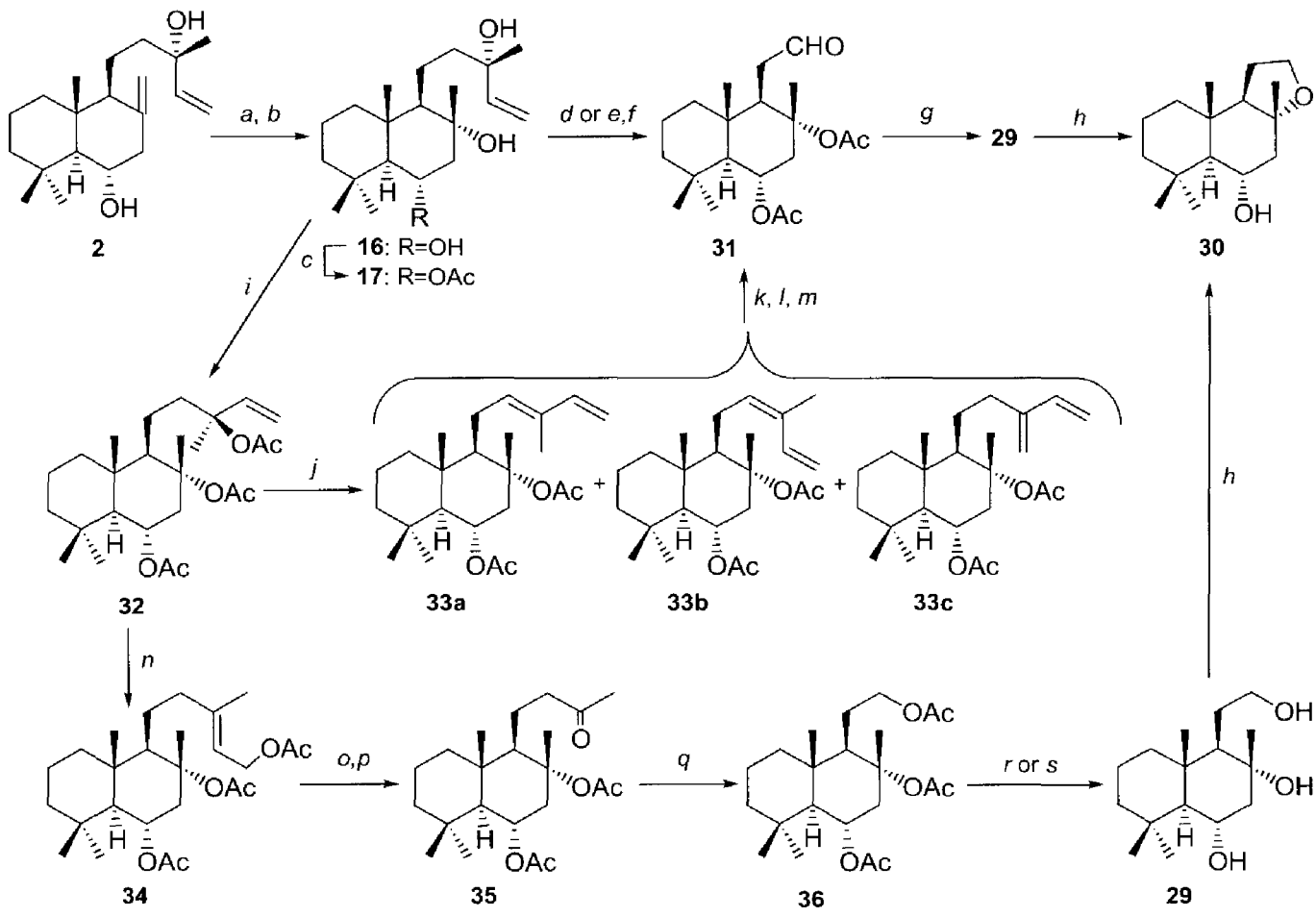


Reagentia en condities: (*a*) 3,0 eq. $KMnO_4$, BTEAC, CH_2Cl_2, 0-3°C, 68%; (*b*) Ac_2O, CH_2Cl_2, py, DMAP, 91%; (*c*) TBDMSiCl, DMF, imidazool, 60°C, 87%; (*d*) *voor R=OH:* *m*-CPBA (2 eq.), CH_2Cl_2, 31%; *voor R=OAc:* *m*-CPBA, CH_2Cl_2, 84%; *voor R=OTBDMS:* *m*-CPBA (2.5 eq.), CH_2Cl_2, 17%; (*e*) *voor R=OH, OAc:* $LiAlH_4$, THF, 0°C naar kt, 10%; (*f*) *p*-TsOH, CH_3NO_2, 64%.

De Baeyer-Villiger reactie verliep alleen goed voor het acetaat **14** maar verdere pogingen om 6α-hydroxy-Ambrox te verkrijgen uit **26** waren niet erg succesvol. Hoewel enkele omzettingen met andere substituenten op C(6) in goede opbrengst verliepen, kon er geen hoge totaalopbrengst verkregen worden. Daarom zijn andere routes tot **30** onderzocht, waarbij larixol eerst is omgezet in 6α-hydroxy-sclareol **16** en het overeenkomstige acetaat **17**.

Oxydatie van **17** met een katalytische hoeveelheid OsO_4 en een overmaat $NaIO_4$ geeft het aldehyde **31** in een goede opbrengst (Schema 5). Bij reductie van dit aldehyde met $LiAlH_4$ wordt triol **29** verkregen in 94% opbrengst, en dit triol kon eenvoudig worden gecycliseerd tot 6α-hydroxy Ambrox (**30**).

Schema 5



Reagentia en condities: (*a*) oxon, aceton, H_2O, CH_2Cl_2, [18]crown-6, $NaHCO_3$, 0°C, 68%; (*b*) $LiAlH_4$, THF, 0°C naar kt, 94%; (*c*) Ac_2O, CH_2Cl_2, py, DMAP, 91%; (*d*) *voor R=OH:* kat. OsO_4, $NaIO_4$, THF, 55-62%; *voor R=OAc:* kat. OsO_4, $NaIO_4$, THF, 72%. (*e*) $KMnO_4$, BTEACl, CH_2Cl_2, 0°C naar kt, 70-85%; (*f*) Jones, aceton, 50%; (*g*) $LiAlH_4$, THF, 0°C naar kt, 94%; (*h*) *p*-TsOH, CH_3NO_2, 64%; (*i*) AcCl, *N,N*-dimethylaniline, 80%; (*j*) $Pd(OAc)_2$, $CaCO_3$, PPh_3, dioxaan, Δ, 94%, **33a:b:c**=4:2:3; (*k*) O_3, MeOH/CH_2Cl_2 3:1, -78°C; (*l*) $NaBH_4$, -78°C; (*m*) NaOMe, MeOH, 67%; (*n*) $PdCl_2(CH_3CN)_2$, THF, 98%; (*o*) O_3, CH_2Cl_2/ MeOH 1:1, -78°C; (*p*) PPh_3, -78°C, 95%; (*q*) *m*-CPBA, CH_2Cl_2, 83%; (*r*) $LiAlH_4$, THF, 0°C naar kt, 85%; (*s*) NaOMe, MeOH, 85%.

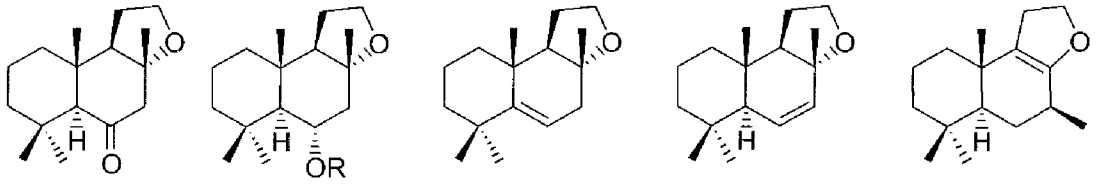
Ook zijn er twee routes onderzocht uitgaande van 6α-hydroxy-sclareol **16** die gebaseerd zijn op Pd-gekatalyseerde eliminatie of isomerisatie van allylacetaten in de zijstaart, gevolgd door ozonolyse. In beide gevallen werd triol **29** verkregen in een goede opbrengst (Schema 5).

Als de resultaten van de verschillende routes voor de omzetting van larixol (**2**) naar 6α-hydroxy-Ambrox met elkaar worden vergeleken, dan kan geconcludeerd worden dat de eerste

route beschreven in Schema 5 de hoogste opbrengst geeft in het minste aantal reactiestappen. Echter, de derde route in Schema 5 is het eenvoudigst om uit te voeren en heeft onze voorkeur.

6α-Hydroxy-Ambrox (**30**) is als intermediair gebruikt voor de bereiding van een aantal eenvoudige Ambrox-derivaten, zoals 6-oxo-Ambrox **37**, 6-methoxy-Ambrox **39** en 6-acetoxy-Ambrox **38** (Figuur 2). Bij behandeling van **30** met *p*-tolueensulfonzuur in benzeen onder Dean-Stark condities wordt een moeilijk te scheiden mengsel van drie verbindingen **40**, **41** en **42** gevormd in de verhouding 2:1:1. De structuren van **40** en **41** zijn vastgesteld door een onafhankelijke synthese (*vide infra*). Dit aangenaam, prettig ruikende mengsel is gescheiden in zijn componenten en op de geureigenschappen onderzocht m.b.v. een GC-sniff opstelling. De drie verbindingen blijken alle een prettige geur te bezitten, met Δ^5-alkeen **40** als de meest aantrekkelijke.

Figuur 2



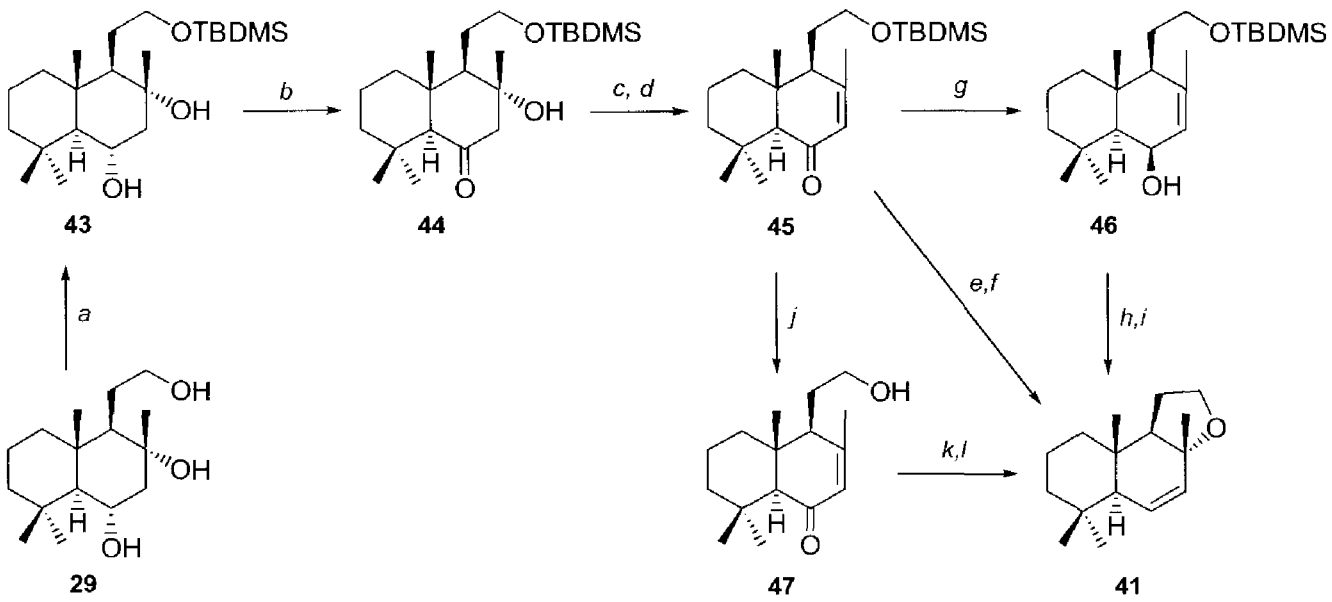
37 **38**: R=Ac **39**: R=CH_3 **40** **41** **42**

Dit Δ^5-Ambroxeen (**40**) is op een meer selectieve manier gesynthetiseerd door eliminatie van methaansulfonzuur uit het mesylaat van 6α-hydroxy-Ambrox (**30**). Een selectieve synthese van Δ^6-Ambroxeen (**41**) bleek echter veel bewerkelijker. Verschillende benaderingen zijn hierbij onderzocht, en uiteindelijk gaf de route via ringsluiting van allyl-alcohol **46** goede resultaten (Schema 6).

Oxydatieve afbraak van de larixol-zijstaart tot een hydroxyethyl eenheid zoals in triol **29** kan op verschillende manieren worden bewerkstelligd, dit is beschreven in Schema's 4 en 5. Selectieve bescherming van de primaire hydroxyl-groep in de zijstaart van triol **29**, gevolgd door oxydatie van de secondaire hydroxyl-groep op C(6) en eliminatie van de tertiaire hydroxyl-groep op C(8), geeft eenon **45** in een totaalopbrengst van 67% uitgaande van triol **29** (Schema 6).

Reductie van de carbonyl-groep op C(6) met DIBAL-H in tolueen by lage temperatuur, gevolgd door ontscherming van de hydroxyl-groep in de zijstaart van **46** en vervolgens zuur-gekatalyseerde cyclisatie geeft in drie stappen Δ^6-Ambroxeen (**41**) in een hoge opbrengst. De volgorde van deze omzettingen kan gevarieerd worden. De benadering zoals beschreven in Schema 6 is nieuw en toepasbaar voor de *selectieve* synthese van Δ^6-Ambrox-achtige verbindingen.

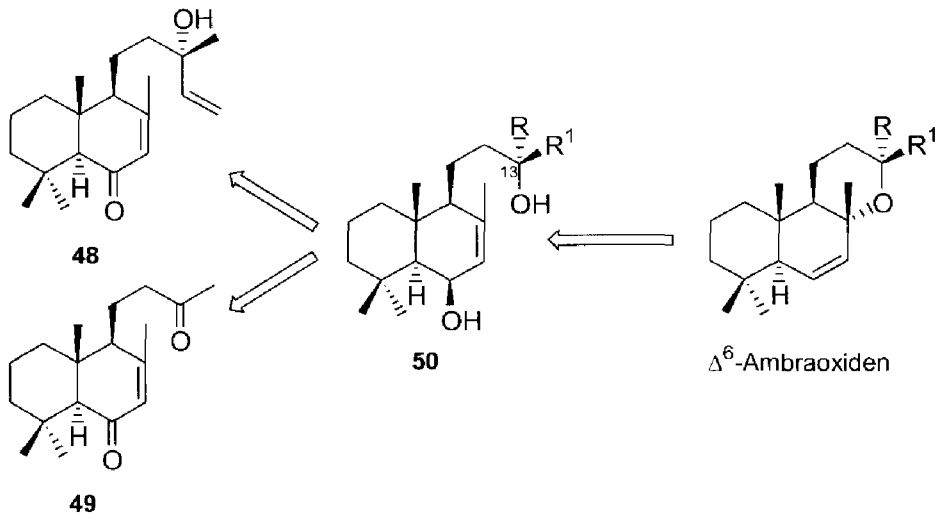
Schema 6



Reagentia en condities: (*a*) TBDMSiCl, DMF, imidazool, N_2, 95%; (*b*) PDC, CH_2Cl_2, 3Å moleculaire zeef, 86%; (*c*) $SOCl_2$, py, DMAP, 0°C naar kt; (*d*) NaOMe, MeOH, 82% (over 2 stappen); (*e*) $LiAlH_4$, droge THF, 0°C naar kt; (*f*) *p*-TsOH, CH_3NO_2, 40% (over 2 stappen); (*g*) DIBAL-H, droge THF, 0°C, N_2, 90%; (*h*) TBAF, droge THF; (*i*) *p*-TsOH, CH_3NO_2, 87% (over 2 stappen); (*j*) TBAF, droge THF, 1 h, 93%; (*k*) Dibal-H, droge THF, 0°C, N_2; (*l*) *p*-TsOH, CH_3NO_2, 71% (over 2 stappen).

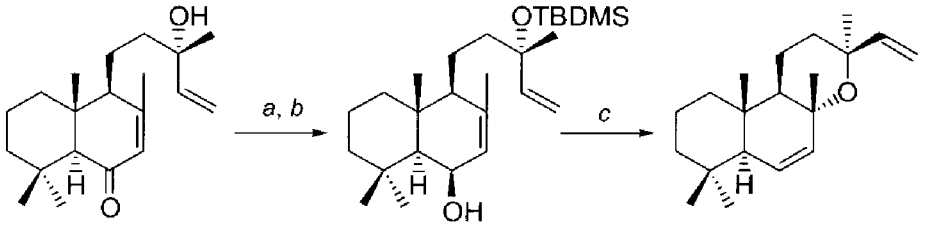
Door een zelfde benadering voor de introductie van de Δ^6 dubbele binding als hierboven beschreven toe te passen op de eenonen **48** en **49**, die in een paar reactiestappen uit larixol verkregen kunnen worden, ontstaat er in principe de mogelijkheid om een scala aan Δ^6-Ambrox-achtige verbindingen te synthetiseren. Tevens is de vorming van onverzadigde gesubstitueerde zesring ethers (Δ^6-Ambraoxiden) onderzocht (Schema 7).

Schema 7



Reductie van de carbonyl-groep op C(6) in **48** kan met hoge opbrengst uitgevoerd worden met behulp van DIBAL-H, mits de hydroxyl-groep in de zijstaart beschermd is (Schema 8). De ontscherming van deze hydroxyl-groep in de zijstaart met een waterige HF oplossing gaat samen met cyclisatie van het intermediaire diol zoals te zien is in de synthese van ether **51**. Dit is het eerste voorbeeld van een succesvolle synthese van een zesvoudige cyclische ether (Hoofdstuk 5).

Schema 8

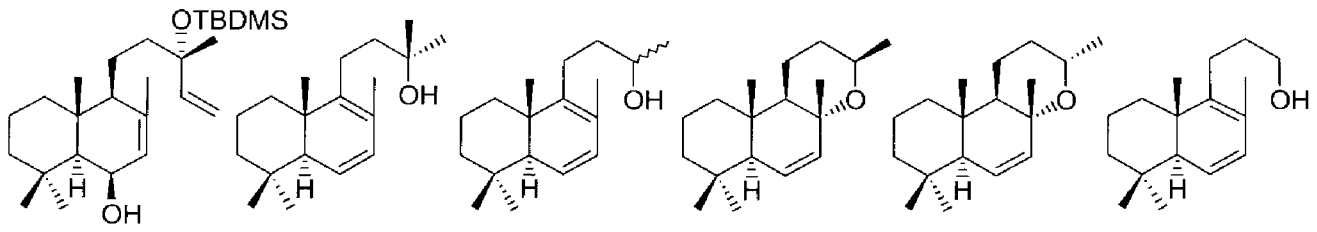


48 **50** **51**

Reagentia en condities: (*a*) TBDMSiCl, DMF, imidazool, 70°C, 3 dagen, 92%; (*b*) DIBAL-H, tolueen, -78°C, 98%; (*c*) *i*) HF (50% waterige oplossing), CH_3CN; *ii*) SiO_2, 67%.

Door oxydatie van de zijstaart in **48** met $KMnO_4$ ontstaat diketon **49**, waarin de niet-geconjugeerde carbonyl-groep selectief gemanipuleerd kan worden. In het geval van de C(13)-dimethyl verbinding geeft de combinatie van ontscherming en cyclisatie geen cyclisatie-product, maar het gedehydrateerde dieen **52** wordt als enig product geïsoleerd. Ook het cyclisatie gedrag van de C(13)-monogesubstitueerde en C(13)-niet-gesubstitueerde verbindingen zijn onderzocht, maar de eerder beschreven succesvolle cyclisatie tot een vijfring ether bleek niet te kunnen worden uitgebreid naar eenzelfde cyclisatie van de homologe diolen tot zesring ethers (Δ^6-Ambra-oxides). De eliminatie van de 6β-hydroxyl-groep tot de corresponderende $\Delta^{6,8}$-dienen is als hoofdreactie gevonden en slechts kleine hoeveelheden van de monomethyl-verbindingen **54a** en **54b** zijn geïsoleerd (Figuur 3).

Figuur 3



50 **52** **53a,b** **54a** **54b** **55**

Curriculum Vitae

De schrijfster van dit proefschrift is op 5 februari 1972 geboren in Neede. Na het behalen van het HAVO diploma aan de Scholengemeenschap De Bouwmeester te Haaksbergen, begon zij in 1989 aan het Hoger Laboratorium Onderwijs (H.L.O.) aan de Hogeschool Enschede, destijds gevestigd in Hengelo. Ze prefereerde de chemische studierichting en specialiseerde zich in de preparatieve organische chemie. De stage- en afstudeerperiode van deze studie werd doorgebracht bij de Katholieke Universiteit Nijmegen, alwaar ze werd begeleid door dr. J. H. van Maarseveen en dr. J. W. Scheeren. Na het getuigschrift te hebben ontvangen in 1993 werd de opleiding vervolgd met de studie Scheikunde aan de Katholieke Universiteit Nijmegen. Na een uitgebreid hoofdvak Organische Chemie bij dr. J. Zhu, dr. A. J. H. Klunder en prof. dr. B. Zwanenburg werd het doctoraalexamen afgelegd in 1996. Vanaf april 1997 volgde een vierjarige aanstelling als Assistent in Opleiding (A.I.O.) bij het Laboratorium voor Organische Chemie van het departement Agrotechnologie en Voedingswetenschappen aan de Wageningen Universiteit onder leiding van prof. dr. A. de Groot en dr. B. J. M. Jansen. De verkregen onderzoeksresultaten staan beschreven in dit proefschrift. Vanaf oktober 2001 is de auteur werkzaam bij MercaChem b.v. in Nijmegen als Research Scientist.

Dankwoord

De Nederlandse vertaling van de titel van mijn proefschrift luidt: ambergrijs geurstoffen uit labdaanzuur en larixol. Labdaanzuur en larixol zijn twee labdanen die tot de diterpenen behoren. Maar wat wist ik vanuit mijn studie scheikunde van terpeenchemie? Dat terpenen opgebouwd zijn uit eenheden van vijf koolstoffen en dat terpenen onderverdeeld zijn naar het aantal van die eenheden was wel zo ongeveer het enige. Van ambergrijs geurstoffen had ik nog nooit gehoord. Maar inmiddels weet ik donders goed hoe met die labdanen om te gaan en hoe die ambergrijs geurstoffen behoren te ruiken. Ambrox® is een van de meest belangrijke commerciële ingrediënten van parfums. De welriekende geur ervan wordt door experts omschreven als 'a dominating exotic woody note of strong warm animal tonality', kortom heel aangenaam. Het is dan ook maar moeilijk te begrijpen dat Ambrox® een bestanddeel is van het natuurlijke ambergrijs, wat geproduceerd wordt in het darmkanaal van potvissen! Na ruim vijf jaar is er dan dit proefschrift over het synthetiseren van Ambrox® en Ambrox-achtige geurstoffen. Het was een lange maar mooie periode die voorbij is gevlogen doordat ik met ontzettend veel plezier aan dit onderzoek heb gewerkt. Die periode was erg leerzaam en daarbij zijn leuke resultaten geboekt, met als gevolg dat deze doctorandus Doctor wordt. Dat heb ik niet alleen aan mezelf te danken, daar hebben veel mensen aan meegeholpen. Die wil ik graag hieronder bedanken.

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Béatrice, par ta perseverance tu as tres rapidement acquis de bonnes connaissances en neerlandais, c'est pour cela que moi, maintenant, je vais tenter le francais. Nous avons toutes les deux travaille sur le larixol, toi en fesant des derives de forskolin, tandis que de mon cote,

j'essayais d'en faire des substances aromatiques. Les neuf moix que tu aurais du passer a Wageningen sont devenus presque deux ans, mais etait-ce reellement a cause du larixol? Merci pour le bon temps que nous avons passe ensemble, et bonne chance pour le futur. Erasmus studente An Gea wil ik graag bedanken voor haar bijdrage aan het ambraketaal-onderzoek. Heel veel succes met je eigen promotieonderzoek in Gent. Dear Natasha, although your post-doc work cannot be directly seen in this thesis, I would like to thank you for your contribution.

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This research was part of the Euterpe project with the goal syntheses of chiral flavours, fragrances, pharmaceuticals and biocontrol agents starting from natural terpenes. I would like to thank all the participants of this project for their contribution to the useful discussions during the meetings twice a year. My special thanks go to Bert de Vries (Destilaciones Bordas) and to Charles Sell (Quest Int.) for their interest and discussions in this project.

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Marjon

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Euterpe project (FAIR CT96-1781) and was financially supported by the European Union.

Als de experimentele beschrijving aangeeft dat de opwerking na één uur reactietijd moet plaatsvinden, is het niet altijd zinvol de reactie langer te laten staan, ook al is er uitgangsmateriaal aanwezig.

- Dit proefschrift, pag. 157.

Het hanteren van verschillende namen voor één en dezelfde verbinding pleit niet voor de chemie als een exacte wetenschap.

Dit proefschrift, verbinding **103**: Ambrox®, Amberlyn®, Ambrofix®, Ambroxan®.

- Sell, C. *Chem. Ind.* **1990**, 516-520.

Dit proefschrift, verbinding **381**: Ambraketal, Jeger's ketal, Amberketal.

- Martres, P.; Perfetti, P.; Zahra, J.-P.; Waegell, B. *Tetrahedron Lett.* **1991**, *32*, 765-766.
- De Céu Costa, M.; Tavares, R.; Motherwell, W. B.; Curto M. J. M. *Tetrahedron Lett.* **1994**, *35*, 8839-8842.
- Kongkathip, B.; Kongkathip, N.; Janthorn, S.; Virarangsiyakorn, D. *Chem. Lett.* **1999**, 51-52.

Dit proefschrift, verbinding **136**: Sclareolide, 12-*nor*-Ambreinolide.

- De Pascual Teresa, J.; Urones, J. G.; Pedrero, A. M.; Barcala, P. B. *Tetrahedron Lett.* **1985**, *26*, 5717-5720.
- Coste-Manière, I. C.; Zahra, J. P.; Waegell, B. *Tetrahedron Lett.* **1988**, *29*, 1017-1020.

Groepen die ogenschijnlijk niet meedoen aan de reactie, kunnen verregaande invloed hebben op de reactie resultaten.

Basische ring opening van isatines.

- Hulme C.; Cherrier, M.-P. *Tetrahedron Lett.* **1999**, *40*, 5295-5299.

Introductie van een acetonitril eenheid.

- Makosza , M.; Wenall, M.; Golinski, M.; Kinowski, A. *Bull. Pol. Acad. Sci. Chem.* **1985**, *33*, 427-432.

Het gebruik van de subtitel "Reduction Reactions" door Bombarda *et al.* suggereert ten onrechte dat reductie van de betreffende verbindingen heeft plaats gevonden.

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

Het is niet waarschijnlijk dat het door Appendino *et al.* beschreven intermediair in de biosynthese van 3β-acetoxy-4β-hydroxypallenone in *Pallenis spinosa* (L.) Cass. de voorgestelde homo-fragmentatie kan ondergaan.

- Appendino, G.; Jakupovic, J.; Jakupovic, S. *Phytochemistry* **1997**, *46*, 1039-1043.

De aanduiding "synthetisch" voor een stof sluit niet uit dat deze stof ook in de natuur voorkomt.

Het opschrift "bevat geen chemicaliën" suggereert een materieloze inhoud.

- Etiket flesje Duvel-bier.

Een overstap van wetenschappelijk onderzoek naar contract research geeft niet meer garantie voor goede resultaten.

Stellingen behorende bij het proefschrift:

Ambergris Fragrance Compounds from Labdanolic acid and Larixol.

Wageningen, 12 juni 2002 M. G. Bolster