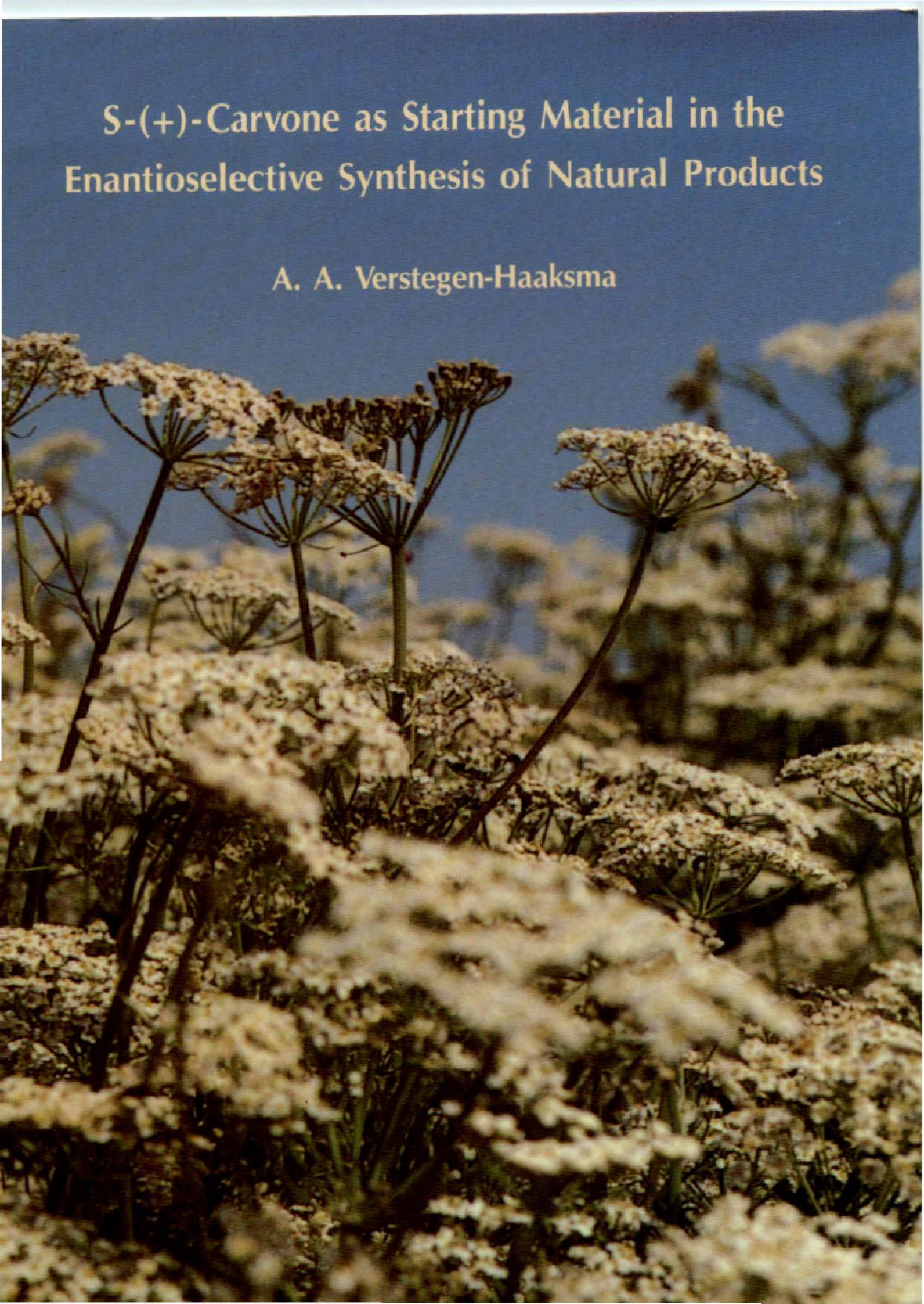
S-(+)-Carvone as Starting Material in the Enantioselective Synthesis of Natural Products

A. A. Verstegen-Haaksma

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Voorwoord

In 1990 startte een onderzoeksprogramma in Nederland, dat zich richtte op het verbeteren van de karwijteelt èn op het vinden van nieuwe toepassingen voor karwijzaad buiten de voedingsmiddelensector. Dit "Nationaal Karwijonderzoeksprogramma" werd gefinancierd door de ministeries van Economische Zaken en Landbouw, Natuurbeheer en Visserij. S-(+)-carvon is de belangrijkste component van de essentiële olie van karwijzaad. Het toepassen van S-(+)-carvon in de chirale synthese, was één van de onderwerpen binnen dit Nationaal Karwijonderzoeksprogramma en de resultaten hiervan zijn beschreven in dit proefschrift. Bij mijn onderzoek ben ik door een groot aantal mensen geholpen en/of aangemoedigd. Hierbij wil ik alle mensen die een bijdrage geleverd hebben aan het tot stand komen van dit proefschrift bedanken. Een aantal wil ik bij name noemen.

Allereerst Henk Swarts. Weinig AIO's zitten in de luxe positie dat ze een persoonlijke assistent hebben. Henk voerde een groot aantal reakties uit, waarbij o.a. de verbindingen gemaakt werden voor twee volledige publicaties. Bovendien was hij een aangename lab- en kamergenoot waar ik gezellig mee geluncht en geborreld heb.

Ben Jansen kende ik al van een praktikum en afstudeervak. Door de plezierige sfeer die er op zijn lab heerste, hoefde ik niet lang na te denken om terug te komen voor een promotieonderzoek. Behalve de kennis en de ervaring die hij overdroeg op het gebied van de Organische Chemie, heeft hij me ook geleerd dat geduld een schone zaak is.

Aede de Groot bood me de mogelijkheid om dit onderzoek uit te voeren. Zijn grote belangstelling voor het onderzoek en de verslaglegging daarvan heb ik altijd zeer gewaardeerd.

Beb van Veldhuizen, Cees Teunis, Hugo Jongejan en Rien van Dijk hebben de analytische bepaling van de gesynthetiseerde stoffen op een snelle en accurate manier uitgevoerd. Ook Gerrit Lelieveld wil ik niet vergeten, al viel zijn werk pas op als de voorraad silicaplaten verdwenen was. Gelukkig hield hij meestal een paar reserveplaten achter de hand.

Zichtbare invloed van buiten de vakgroep Organische Chemie kwam van Willem Meijer, die de inleiding van dit proefschrift van kritisch commentaar voorzien heeft en van Hille Toxopeus, die de foto voor de omslag van dit boekje gemaakt heeft.

Tenslotte wil ik Jos noemen, die in het laatste jaar van mijn onderzoek steeds minder ruimte kreeg tussen al mijn papieren. Zijn belangstelling voor mijn onderzoek is van grote waarde voor mij geweest.

Anja

Contents

1 Introduction

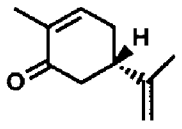
1.1 Caraway essential oil

Caraway fruit (*Carum carvi* L.), usually referred to as seed, has an aromatic fresh taste and smell caused by the essential oil contained in ducts in the pericarb (2-7% of air-dry fruit weight)[1]. The essential oil consists mainly of the two monoterpenes S-(+)-carvone (50-60%) and R-(+)-limonene (35-45%)(figure 1.1)[1]. The olfactory characteristic of caraway oil is dominated by S-(+)-carvone. This monoterpene can also be obtained from dill (*Anethum graveolens*) and Indian dill (*Anethum sowa*) essential oils. The common source for R-(+)-limonene is orange oil.

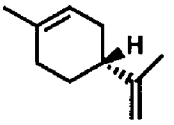
Both S-(+)-carvone and R-(+)-limonene belong to the secondary plant compounds, which are characterized by a limited distribution, storage in special organs and an absence of obvious function in the metabolism of the producer plant[2]. The investment in DNA, enzymes and photosynthate to produce the secondary compounds is considerable[2b]. Since plants are considered to be efficient, it is presumed that there is some selective advantage in producing them[2b]. Some secondary plant compounds are important in the chemical defence against herbivores, competing plants and micro-organisms, thereby exhibiting antifeedant, phytotoxic or antimicrobial activities.

Biological activities that have been reported for S-(+)-carvone or caraway essential oil include antifungal, antibacterial, antioxidant (section 1.1.1), insecticidal, repellent (section 1.1.2), phytotoxic (section 1.1.3), antitumor (section 1.1.4) and plant growth regulatory activity (section 1.1.5).

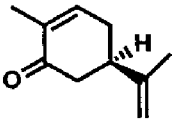
Figure 1.1



S-(+)-carvone



R-(+)-limonene



R-(-)-carvone

1.1.1 Antifungal, antibacterial and antioxidant activity

The antibacterial and antifungal activities of essential oils are directly related to their ability to penetrate the cell walls of bacteria or fungi and therefore due to their solubility in the phosholipid bilayer of cell membranes[3]. Caraway oil of an unusual

composition* inhibits mycelial growth of *Aspergillus parasiticus* and also prevents aflatoxin formation by this fungus at a concentration of 0.6 mg/ml[4]. The same caraway oil* shows antibacterial activity against a number of bacteria and a yeast[5]. The inhibition zones produced by this caraway oil* (2-2.5 mg/ml) for the yeast *Saccharomyces cerevisiae*, the acid-fast bacterium *Mycobacterium phlei* and the Gram-positive bacteria *Micrococcus spp.*, *Staphylococcus aureus* and *Bacillus subtilis* are a little larger than for the Gram-negative bacteria *Pseudomonas fluorescens*, *Serratia marcescens* and *Escherichia coli*. Caraway oil is very effective as an antioxidant on linoleic acid oxidation[6].
R-(-)-carvone (figure 1.1), the enantiomer of S-(+)-carvone that can be isolated from spearmint *(Mentha viridis)*, also exhibits antifungal activity. R-(-)-carvone is more effective in the inhibition of mycelial growth of *Aspergillus niger* than R-(+)-limonene[7]. Papers, in which the antifungal, antibacterial and antioxidant activities of S-(+)-carvone and R-(-)-carvone are compared, were not found.

1.1.2 Insecticidal and repellent activity

S-(+)-Carvone is biologically active against several species of storage insects and gives long lasting repellency against the confused flour beetle *Tribolium confusum*[8]. The essential oil of Indian dill (*Anethum sowa*) shows marked nematicidal activity against larvae of root-knot nematode, *Meloidogyne incognita*, the most menacing pest of major Indian soils[9]. The chemical components responsible for this insecticidal activity are both S-(+)-carvone and R-(+)-limonene. The essential oils of caraway, dill and spearmint all show high acaricidal activities against the house mites *Dermatophagoides pteronyssinus*, *Dermatophagoides fasinae* and *Tyrophagus putrescentiae*. The amount to give 100% mortality (LD_{100}) ranged from 1-5 µl/petridish[10]. S-(+)-carvone (caraway and dill) and R-(-)-carvone (spearmint) are the active compounds.

1.1.3 Phytotoxic activity

Secondary plant compounds can also be phytotoxic to the producing plant cells[11]. Undifferentiated plant cell cultures of *Pelargonium fragrans*, produce carvone** and limonene** in concentrations toxic to the cultures. The essential oil production in whole plants is probably not limited by end-product toxicity, because the storage in ducts in the pericarb prevents the inhibition of further formation of the monoterpenes.

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* The composition of this oil according to the authors is 81.3% of S-(+)-carvone and 15.8% of *p*-cymene. Probably an error was made in the determination of the composition of the oil!

** Optical rotation not mentioned by the authors

1.1.4 Antitumor activity

S-(+)-Carvone induces the activity of the detoxifying enzyme glutathione S-transferase in several mouse target tissues and inhibits N-nitrosodiethylamine induced carcinogenesis[12, 13]. The glutathione S-transferase enzymes catalyze the conjugation of glutathione with electrophilic species to form less toxic, water soluble substances that are readily excreted. Since electrophiles are the reactive forms of chemical carcinogens, induction of glutathione S-transferase activity is believed to be a major mechanism for carcinogen detoxification. The α,β-unsaturated ketone system of S-(+)-carvone is critical for the high enzyme-inducing activity.

1.1.5. Plant growth regulatory activity

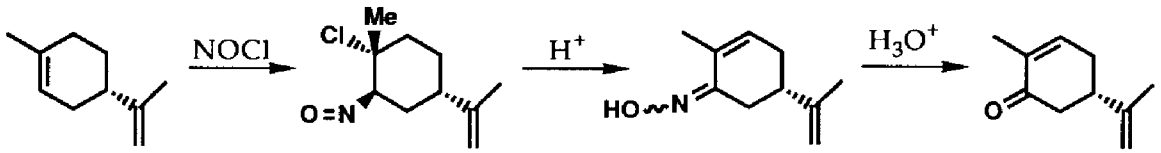
The germination of lettuce (*Lactuca sativa L.*) fruits is inhibited by many monoterpenes, including S-(+)-carvone, R-(-)-carvone and R-(+)-limonene[14]. The minimal inhibition concentration (MIC) is low for both carvones (MIC S-(+)-carvone = 0.052 mM, MIC R-(-)-carvone = 0.38 mM), while R-(+)-limonene is not very effective (MIC > 2mM). The activity of the compounds is therefore not just determined by the presence of a double bond conjugated with an electron withdrawing group and the lipophilicity of the molecule, but also by the steric orientation of the isopropenyl group.
A very interesting activity of carvone is its effective inhibition of the sprouting of potatoes. From previously published reports of the inhibiting effect of carvone on the sprouting of potatoes it was not clear which carvone was used, neither the optical rotation of the carvone nor its origin was mentioned[15,16]. The possible effect of chirality on the inhibition of sprouting was therefore totally neglected. Later on in a national caraway research program the biological effects of both S-(+)-carvone and R-(-)-carvone on the inhibition of the sprouting of potatoes were studied at the ATO-DLO (see section 1.2.2)[17].

1.2 The National Caraway Research Program

Until recently, caraway was only cultivated for consumption of the seeds and the essential oil. The seeds were used as spices in food stuffs and the essential oil was applicated as a flavour in certain liquors. In the Netherlands the potential of caraway for the production of non-food products was investigated during the last four years in the "National Caraway Research Program". New applications were particularly sought for S-(+)-carvone, the major compound of the essential oil. In a connected industrial program, the application of S-(+)-carvone as a sprouting inhibitor for potatoes was developed and

the necessary information for approval was collected.
In 1989, almost all commercially available S-(+)-carvone and R-(-)-carvone was synthetically produced[18]. The synthesis of S-(+)-carvone started from S-(-)-limonene, which was obtained from pine needle oil. The synthetic sequence[19] started with the reaction of nitrosyl chloride with S-(-)-limonene to give the nitroso chloride **1**. Dehydrohalogenation of adduct **1** afforded oxime **2**, which upon hydrolysis gave S-(+)-carvone in an overall yield of 30-35% (scheme 1.1).

Scheme 1.1



S-(-)-limonene **1** **2** S-(+)-carvone

The low yield of the synthetic conversion of S-(-)-limonene into S-(+)-carvone is an important drawback in the synthetic production of S-(+)-carvone, as about 60% of the S-(-)-limonene is converted to useless by-products. By this, the cost of S-(-)-limonene is strongly reflected in the production cost of S-(+)-carvone, and S-(-)-limonene is not inexpensive! The prospects of an economic S-(+)-carvone production by steam distillation of caraway essential oil are therefore favourable at first sight.
An important drawback in the production of S-(+)-carvone by steam distillation of caraway is the unreliable supply of caraway seed. The price of caraway seed fluctuates, as a result of decreases and increases in acreages planted and from crop variations because of weather conditions. From data of farmers in the Oldambt region from 1986 to 1990 it appeared that the seed and essential oil yields of caraway showed great variations between years *and* between farmers[1]. Diseases and pests in caraway probably also had a great influence on the seed and essential oil yields per ha. The essential oil content, and in particular the S-(+)-carvone content of the seed is for the steam distillation process of course a very important quality aspect.
New applications for S-(+)-carvone will only lead to a larger demand for caraway seed, if the steam distillation of caraway is an economic alternative to the synthetic production of S-(+)-carvone. Therefore a part of the research within the "National Caraway Research Program" aimed at the improvement of the primary production of caraway and the quality of caraway seed, *i.e.*, the S-(+)-content. The results of these projects are given in section 1.2.1. The results of the projects that examined potential new applications for S-(+)-carvone are given in section 1.2.2.

1.2.1 Improvement of primary production and the quality of caraway seed

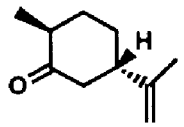
The influences of weather conditions, the contamination of caraway with two fungi and an aphid, and cultivation measures on the primary production of caraway were examined within the "National Caraway Research Program". Breading research was used to increase the S-(+)-carvone production potential.
Plant and crop physiological research at AB-DLO[20] has shown that the phase of seed setting is critical. Abundant supply of assimilates in that period increases the seed production. High crop photosynthesis throughout the period from flowering till ripening increases the essential oil content and also the ratio of S-(+)-carvone/ R-(+)-limonene. Weather conditions can not be manipulated, but breeding and cultivation measures can improve the efficiency of light use or reduce the competition for assimilates in the plants, and by that increase the yield of S-(+)-carvone.
Selection for S-(+)-carvone content of the seed was conducted in the Oldambster landrace of caraway by researchers of CPRO-DLO[21]. The selected population showed in a few field experiments a 20% higher S-(+)-carvone content compared to the older landrace[1]. Selection response is expected to increase in the next generations. In cooperation with the tissue-culture laboratory of the Prof. H. C. van Hall institute[22], routine vegetative reproduction of plants with high S-(+)-carvone content has been initiated.
The susceptibility of caraway for the fungus *Mycocentrospora acerina* was researched at PAGV[23]. The symptoms of the disease brought about by this fungus are severe. Infection with *M. acerina* causes lesions in the stem, and thereby death of the upper parts of the plant. Spreading of the contamination can be reduced by a few cultivation measures. The best way to prevent infection of the crop by *M. acerina*, is to start with *M. acerina* free soil and sowing seed.
The damage caused by the fungus *Sclerotinia sclerotiorum* in caraway was researched at IPO-DLO[24]. Both caraway and most preceding crops are susceptible for *S. sclerotiorum*, but control of the infection is possible. The application of the antagonistic fungus *Coniothyrium minitans* is very effective in the control of an infection with *S. sclerotiorum*.
Another group of researchers at IPO-DLO[25] have examined the biology and control of the caraway root aphid *Pemphigus passeki*. During the project, the knowledge of the ecology of this insect was increased, but ecological measures to prevent the damage caused by this aphid, are not yet found. However, chemical control is possible.

1.2.2 New applications for caraway essential oil

In section 1.1 an impression of the biological activities of caraway oil and S-(+)-carvone is given. For the industrial use of caraway oil, the biological properties of R-(+)-limonene are of less importance, because it can easily be obtained from citrus oil in bulk quantities. In a number of cases, R-(-)-carvone, the enantiomer of S-(+)-carvone shows the same or similar biological activities as S-(+)-carvone. Since R-(-)-carvone is cheaper than S-(+)-carvone, the possible competition of this compound for the preparation of bioactive compounds should not be neglected.
In section 1.1.5 the potential of S-(+)-carvone as inhibitor of the sprouting of potato tubers is shown. A research group of ATO-DLO[17] has examined the biological effects of S-(+)-carvone and R-(-)-carvone on potato tubers. S-(+)-carvone inhibits the sprouting of potatoes faster than R-(-)-carvone. The effect of the carvone treatment is reversible for both enantiomers. After ceasing the treatment with R-(-)-carvone, the sprouts grow lengthier than after ceasing the treatment with S-(+)-carvone. The company Luxan has developed, in cooperation with the ATO-DLO, a new sprout inhibiting agent, called Talent®, with S-(+)-carvone as the active component. A possitive side-effect of Talent® is the inhibition of potato storage fungi like *Fusarium sp.* and *Helminthosporium solani.*
The mechanism of the antimicrobial activity of S-(+)-carvone was examined at the Microbiology Department of Groningen University[26]. The inhibition of bacterial growth is correlated with the accumulation of S-(+)-carvone in the cytoplasmic membranes, causing disruptions and disturbance of the energy metabolism of the bacteria.
The insecticidal and antifungal activities of S-(+)-carvone against some storage insects and fungi were examined at the Prof. H. C. van Hall institute[27]. A cyclodextrine slow-release formulation of S-(+)-carvone kills under laboratory conditions the corn weevil *Sitophilus granarius* within ten days. S-(+)-Carvone also inhibits the growth of the storage fungi *Fusarium culmorum, Pythium ultimum* and *Rhizoctonia solani,* but a potential application of this biological effect in the disinfection of flower bulbs is not possible, because of the phytotoxic effect of S-(+)-carvone on flower bulbs in the concentrations necessary for fungi inhibition.
A feasibility study of the bioconversion of S-(+)-carvone to fine chemicals was performed at the Groningen Biotechnology Centre[28]. A few bacteria and a fungus were tested in batch-cultures for their capacity to convert S-(+)-carvone stereoselectively into interesting products. The selected bacteria all reduce S-(+)-carvone, thereby forming predominantly dihydrocarvone **3** or iso-dihydrocarvone **4** (figure 1.2) in purities up to 93%. The fungus *Trychoderma pseudokoningii* reduces S-(+)-carvone mainly to neo-isodihydrocarveol **5** (figure 1.2) in yields up to 71%. Unfortunately, the sensitivity of this fungus for the starting material S-(+)-carvone limits the yields of **5** to 0.2 g/l. The bacteria

are less sensitive to S-(+)-carvone, but their product yields are even lower, probably due to product inhibition.

Figure 1.2



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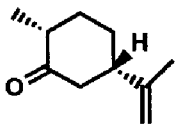

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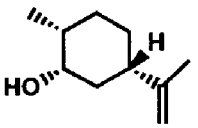

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The application of S-(+)-carvone in the synthesis of biologically active natural products, was investigated at the Department of Organic Chemistry of the Agricultural University and is the subject of this thesis. The results obtained in this research project are descibed in the chapters 2-6.

1.3 S-(+)-Carvone and R-(-)-carvone as starting material in the enantioselective synthesis of natural compounds

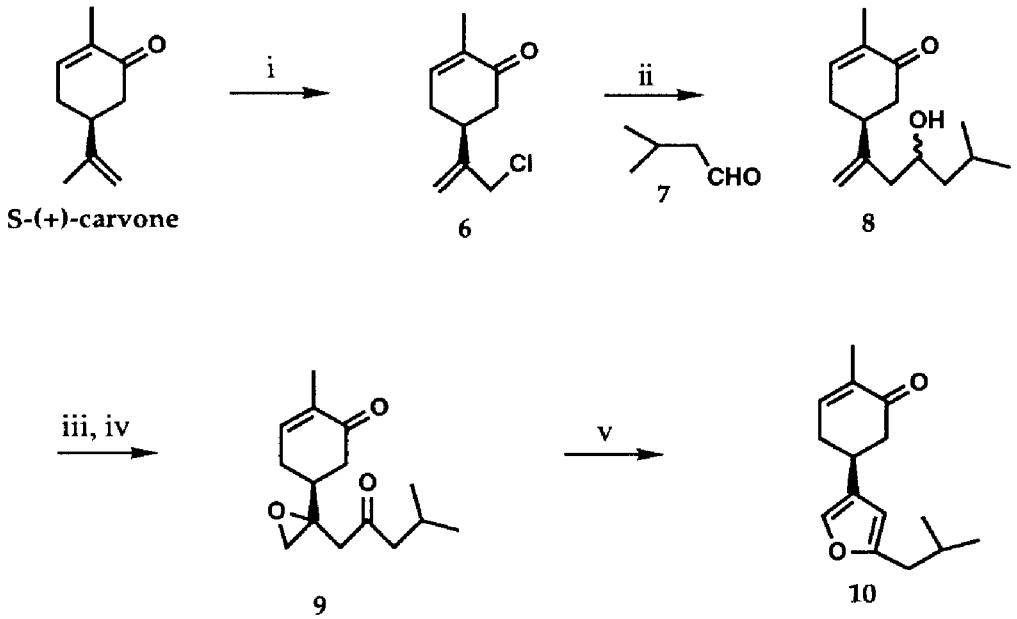
Both S-(+)-carvone and R-(-)-carvone have been widely used as starting material in the synthesis of natural compounds[29]. In this section a limited selection of the approaches from both carvones to other natural products is discussed. The synthetic strategies are divided into sections, each dealing with an important transformation possibility of carvone.

In section 1.3.1 the isopropenyl group is the major target of modification. A number of possible approaches of this functional group of carvone are shown. In section 1.3.2 some annulation methods to polycyclic intermediates are given. This section involves not just direct annulation methods, but also annulation methods in which first an alkyl group is introduced *via* alkylation, conjugate addition or aldol condensation, later on followed by and intramolecular cyclization reaction. Section 1.3.3 deals with radical cyclization reactions of carvone to bicyclic intermediates. The fragmentation of carvone into a linear carbon chain is discussed in section 1.3.4. The major topic of section 1.3.5 is the conversion of the six-membered cyclohexanone ring into rings of different size.

1.3.1 Modification of the isopropenyl group

The correlation between (+)-bilobanone (**10**), a furano sesquiterpene isolated from the heartwood of *Ginko biloba* L, and S-(+)-carvone is obvious[30]. Hedge *et al.* transformed the isopropenyl side chain into the furano moiety in four steps (scheme 1.2)[30b].
Allylic chloride **6** was formed by a two-phase reaction of hypochlorous acid with the double bond of the isopropenyl group of S-(+)-carvone. The addition of metallic zinc gave an organometallic compound, that reacted with isovaleraldehyde **7** to afford homoallylic alcohol **8** as a mixture of stereoisomers. This mixture was oxidized to a diketone with chromium trioxide and subsequently converted into epoxy ketone **9** with *m*-chloroperbenzoic acid. Treatment of this epoxy ketone with boron trifluoride etherate gave (+)-bilobanone (**10**) in an overall yield of 28% from S-(+)-carvone.

Scheme 1.2



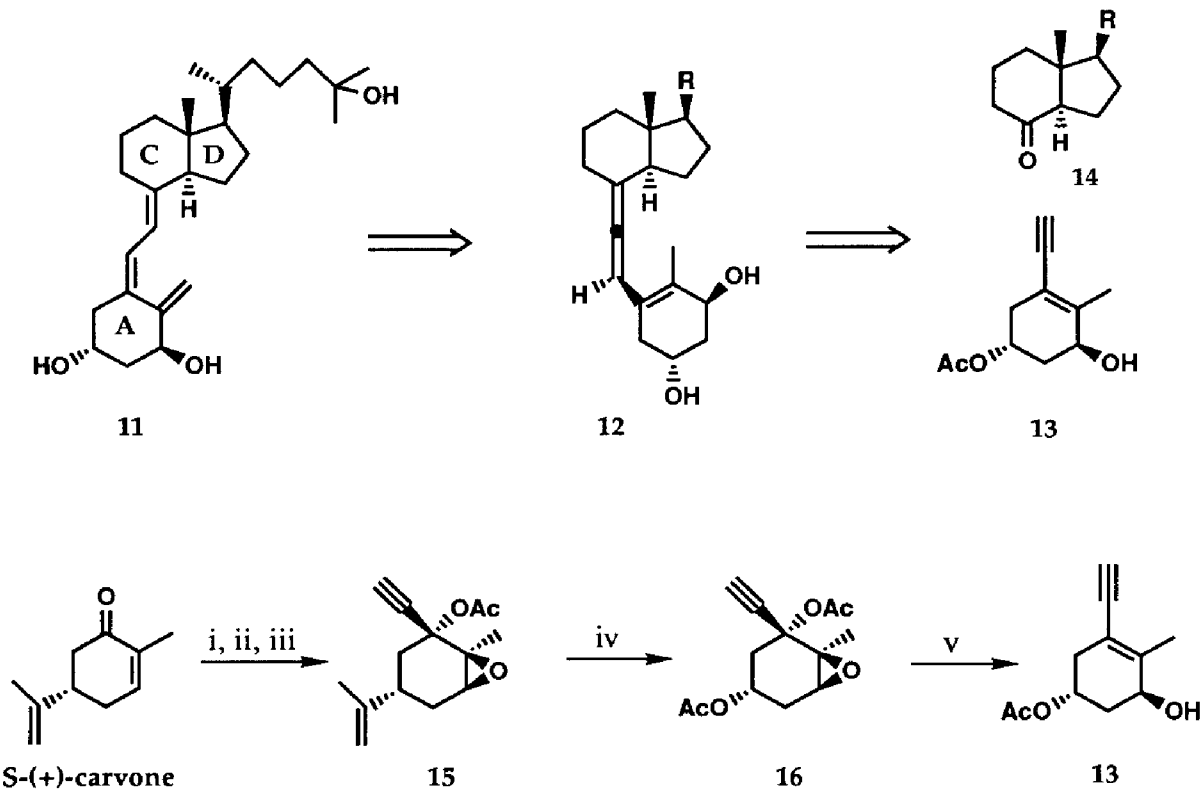
Reagents i: HOCl, H_2O, CH_2Cl_2; ii: Zn; iii: CrO_3; iv: *m*-CPBA; v: $BF_3.Et_2O$.

Both R-(-)-carvone and S-(+)-carvone are suitable starting materials in the synthesis of ring-A synthons of 1α,25-dihydroxycholecalciferol (**11**)[31]. This known vitamin D_3 metabolite is considered to be the most potent stimulator of calcitropic effects and has also been found to suppress proliferation and to induce differentiation in human myeloid leukemia cells.

A key step in the synthesis of ring-A synthons from S-(+)-carvone or R-(-)-carvone is the conversion of the isopropenyl group into an oxygen functionality with retention of configuration. A five step sequence to a suitable ring-A enyne **13** from S-(+)-carvone for coupling with an appropriate CD-ring fragment **14** is shown in scheme 1.3[31a] and a somewhat longer sequence from R-(-)-carvone to ring-A synthon **22** is shown in scheme 1.4[31d].

Stereoselective epoxidation of S-(+)-carvone, followed by ethynylation and acetylation gave acetate **15**. The isopropenyl group was degraded by ozonolysis, acylation with *p*-nitrobenzoyl chloride and *in situ* Criegee rearrangement to afford the diacetate **16**. Samarium iodide-promoted reductive elimination of the epoxypropargyl acetate with concomitant ring opening of the epoxide moiety gave ring-A synthon **13** in an overall yield of 37% from S-(+)-carvone[31a].

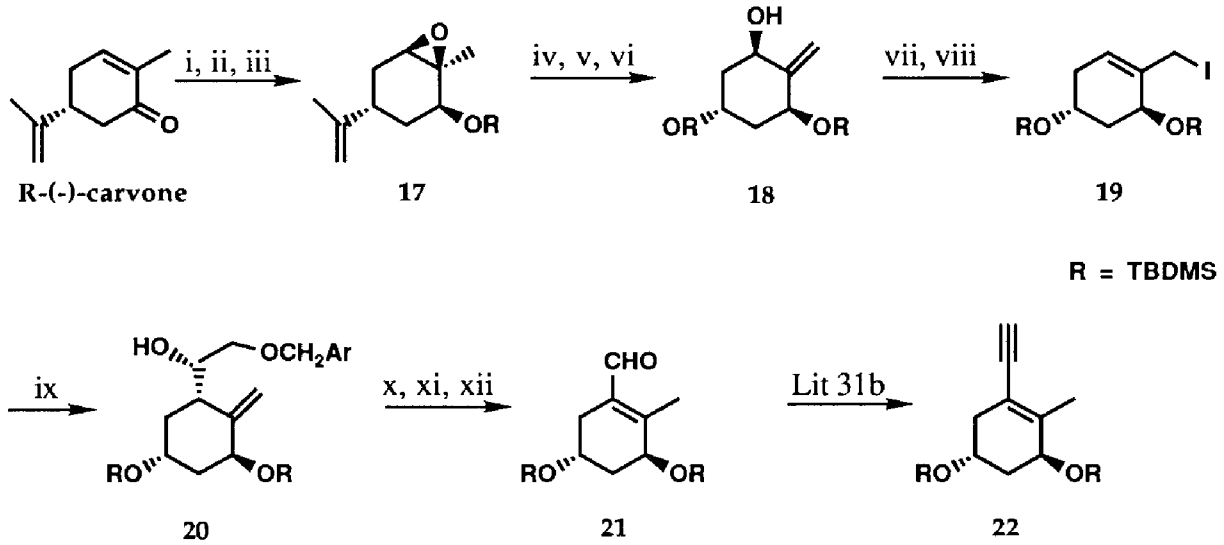
Scheme 1.3



Reagents i: H_2O_2, OH^-; ii: Li acetylide; iii: Ac_2O, Et_3N, DMAP; iv: O_3; ArCOCl, py; Δ; v: SmI_2, $(Ph_3P)_4Pd$

The epoxide obtained from R-(-)-carvone was reduced with lithium selectride to give an axial alcohol which was protected as its *tert*-butyldimethylsilyl ether **17** (scheme 1.4)[31d]. Then the isopropenyl group was oxidatively degraded to an hydroxy group *via* ozonolysis, Criegee rearrangement and hydrolysis and then protected as an TBDMS ether. Treatment of the diprotected compound with diethylaluminum-2,2,6,6-tetramethylpiperidide led to the allylic alcohol **18**. Iodide **19** was formed *via* the corresponding mesylate. The crucial chromium (II)-mediated condensation with an α-alkoxyacetaldehyde yielded alcohol **20** with excellent diastereoselectivity. Oxidative deprotection and cleavage furnished aldehyde **21** after isomerization in an overall yield of 35% from R-(-)-carvone. This compound has been transformed previously into acetylene **22**[31b].

Scheme 1.4



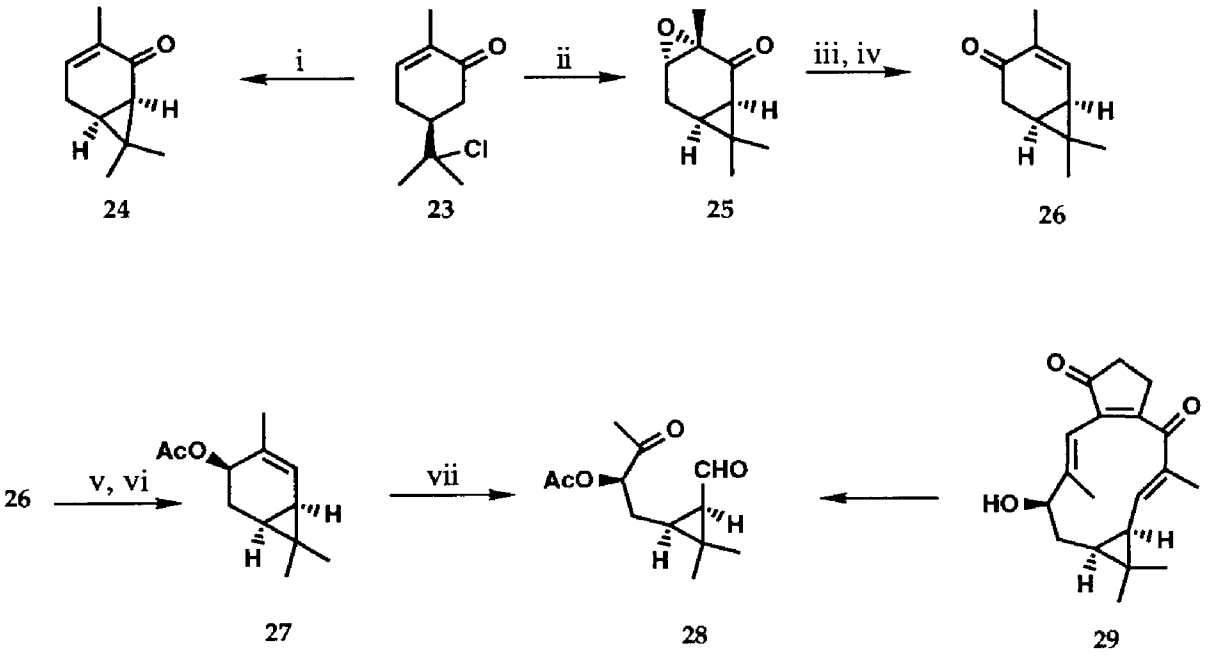
R-(-)-carvone **17** **18** **19** **20** **21** **22**

Reagents i: H_2O_2, OH^-; ii: Li-selectride; iii: TBDMSCl, imidazole; iv: O_3; Ac_2O, Et_3N, DMAP; K_2CO_3; v: TBDMSCl, imidazole; vi: Et_2Al TMP; vii: MsCl, DMAP; viii: NaI, Δ; ix: $CrCl_3$, $LiAlH_4$; *p*$MeOC_6H_4CH_2OCH_2CHO$; x: DDQ; xi: K_2CO_3; xii: $NaIO_4$; DBU.

Intramolecular cyclization of the isopropenyl group of both R-(-)-carvone and S-(+)-carvone to carenones like **24** and **26** is interesting because there is a large group of natural sesqui- and diterpenes with a dimethylcyclopropane fragment in its structure[32]. Ring closure of carvone hydrochloride **23** at the α'-carbon of the cross-conjugated enolate gave car-3-en-2-one **24** directly (scheme 1.5)[32b]. The synthesis of car-2-en-4-one **26** required a longer synthetic sequence, while γ-alkylation of the enantiomer of **23** was unsuccessful. Treatment of carvone hydrochloride **23** with basic hydrogen peroxide afforded compound **25** in one step.

The desired carenone **26** was obtained by a Wharton rearrangement followed by oxidation of the allylic hydroxy group. The correlation between carenone **26** and bertyadionol (**29**) was proven by the transformation of **26** into keto aldehyde **28**, a degradation product of bertyadionol. This transformation was performed by reduction of the carbonyl functionality of **26** and acylation to afford acetate **27**. This acetate was transformed by ozonolysis into the keto aldehyde **28** in an overall yield of 44% from carvone hydrochloride **23**.

Scheme 1.5



24 23 25 26

26 27 28 29

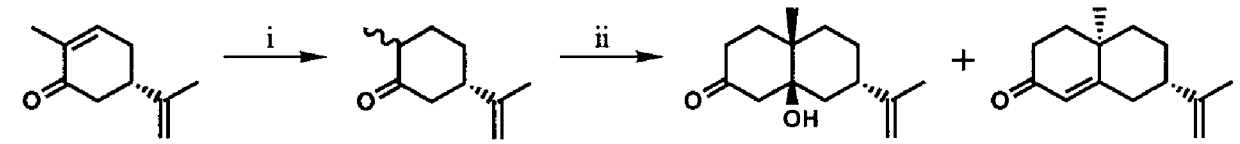
Reagents i: NaOH, 25% aq. DMSO; ii: H_2O_2, OH^-; iii: N_2H_4; iv: PCC; v: $NaBH_4$, $CeCl_3$; vi: Ac_2O, DMAP; vii: O_3, Me_2S.

1.3.2 Annulation reactions

The Robinson annulation reaction is a time-tested method for ring annulation. This reaction can provide for large quantities of bicyclic compounds from the monocyclic carvones (scheme 1.6)[33].

The Robinson annulation of methyl vinyl ketone (MVK) and (-)-dihydrocarvone **30**, the lithium bronze reduction product of S-(+)-carvone, yields two easily separable products **31** and **32** in a ratio of ~ 3:1, if the dehydration of the major diastereomer **31** is prevented by careful control of the reaction conditions (scheme 1.6)[33]. After separation from enone **32**, the major Robinson annulation product **31**, with the angular methyl group and the isopropenyl group in a *trans*-position can be dehydrated to decalone **33** (see scheme 1.7).

Scheme 1.6

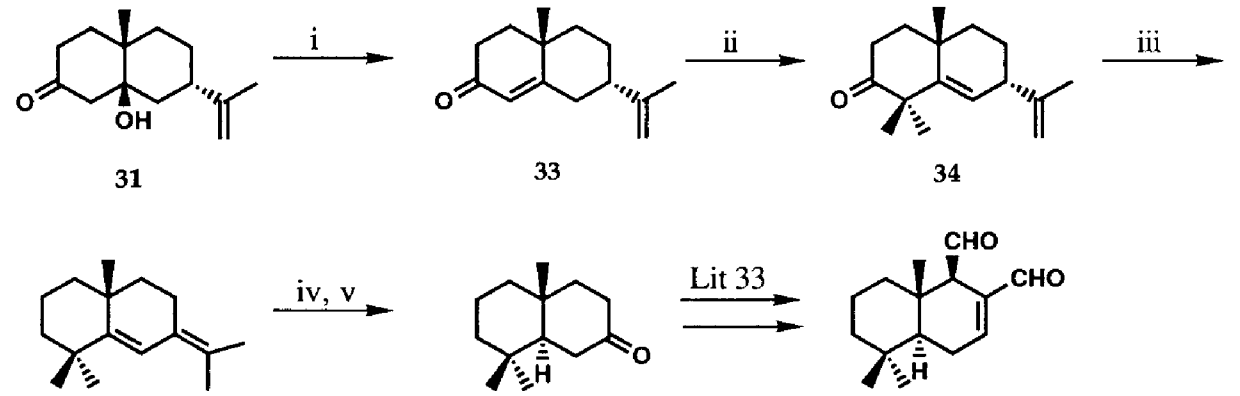


S-(+)-carvone **30** **31** **32**

Reagents i: Li, NH_3, *t*-BuOH, ether; ii: MVK, KOH, 0 °C.

(-)-Polygodial (**37**) is a drimane sesquiterpene with a strong insect-antifeedant activity, that can be isolated from *Polygonum hydropiper* L. The synthesis of chiral intermediate **36**, that previously was transformed into (-)-polygodial (**37**)[34] is shown in scheme 1.7.
After dehydration of the Robinson annulation product **31** to **33**, the *gem*-dimethyl group was introduced to afford **34**. The carbonyl functionality was removed by a Wolff-Kishner reduction with concomitant isomerization of the double bond of the isopropenyl group to the exocyclic position, to give product **35**. Ozonolysis and reduction with lithium in ammonia gave decalone **36** in an overall yield of 20% from S-(+)-carvone. Decalone **36** was further transformed into (-)-polygodial (**37**) by the known procedure[34].

Scheme 1.7



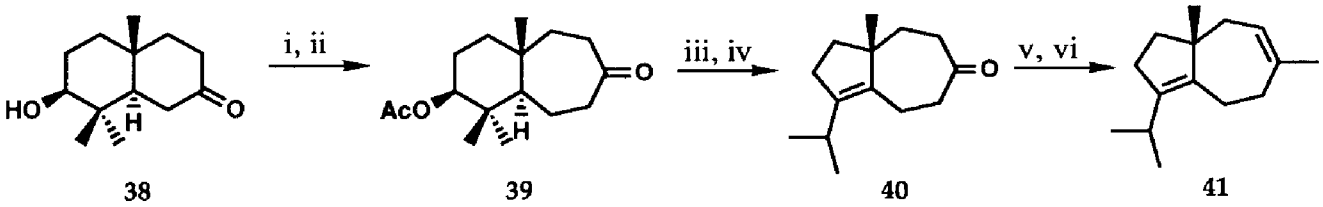
31 **33** **34**

35 **36** **37**

Reagents i: KOH, MeOH, rt; ii: MeI, *t*-BuOK; iii: N_2H_4, KOH, 200 °C; iv: O_3, Me_2S; v: Li, NH_3.

The Robinson annulation products also can be converted into 5,7 fused ring-systems. This is shown in the synthesis of (+)-daucene (**41**), a constituent of *Daucus carota*, from hydroxy ketone **38**[35]. Hydroxy ketone **38** can be obtained from S-(+)-carvone *via* the methodology used for decalone **36** in scheme 1.7, with only small modifications.
Hydroxyketone **38** was treated with diazo methane to give a ring enlargement (scheme 1.8). After acylation, product **39** could be obtained pure. Hydrolysis of the acetate followed by ring contraction and isomerization gave olefin **40**. A Grignard reaction with methylmagnesium iodide followed by dehydration gave (+)-daucene (**41**)[35].

Scheme 1.8

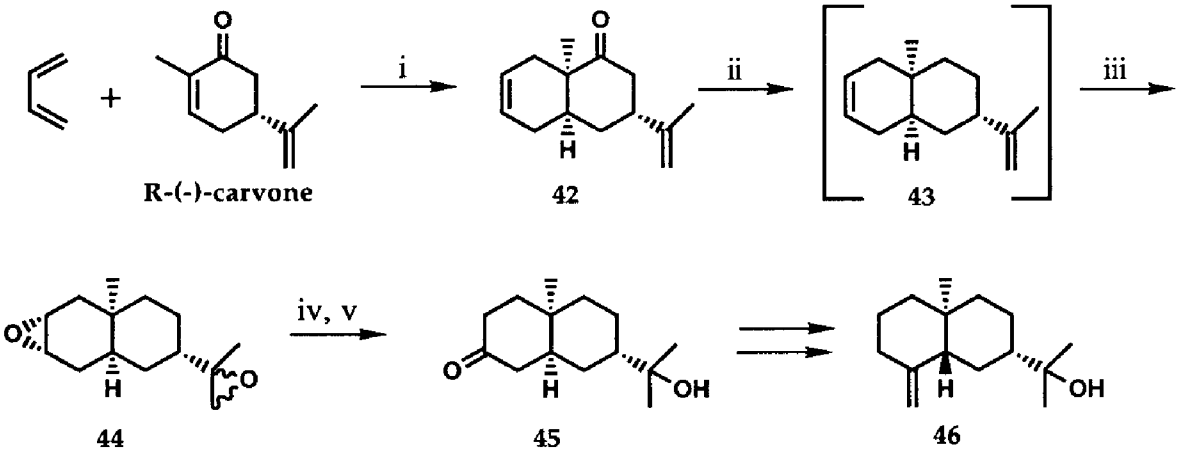


38 **39** **40** **41**

Reagents i: CH_2N_2; ii: Ac_2O, py; iii: OH^-; iv: PCl_5; H^+; v: MeMgBr; vi: $SOCl_2$.

The construction of sesquiterpenes with the angular methyl group and the alkyl side chain in a *cis*-position *via* the Diels-Alder reaction of R-(-)-carvone and butadiene is shown in scheme 1.9[36].

Scheme 1.9



R-(-)-carvone **42** **43**

44 **45** **46**

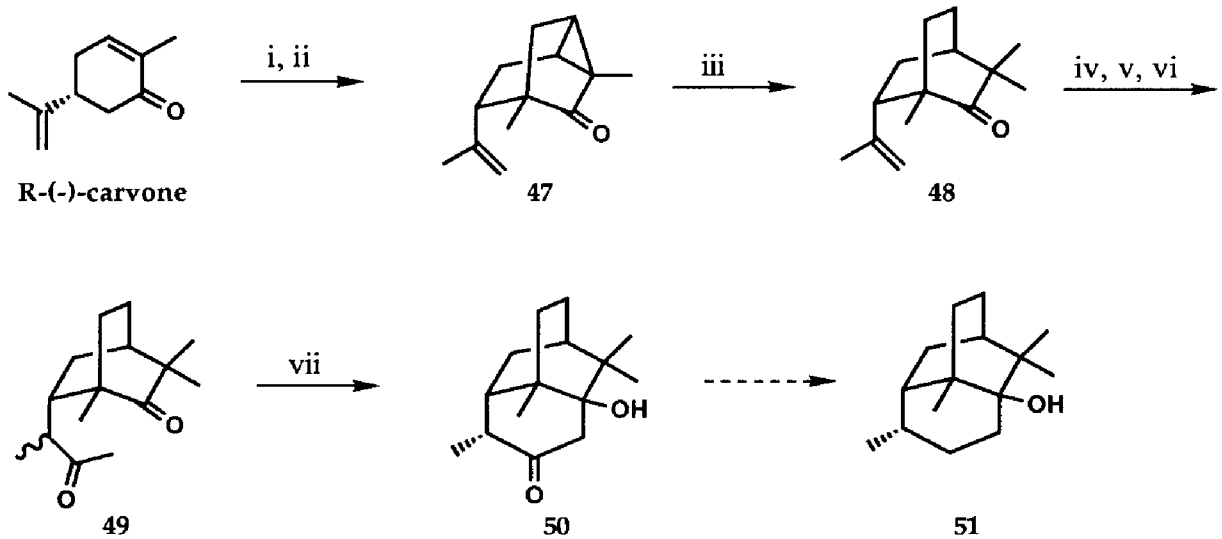
Reagents i: $AlCl_3$, benzene, rt; ii: *p*-Tosylhydrazine, $NaBH_4$; iii: *m*-CPBA; iv: $LiAlH_4$; v: Jones oxidation.

The Diels-Alder reaction of R-(-)-carvone and butadiene in the presence of the Lewis acid aluminum chloride yielded the *anti*-addition product **42** in 40% yield. The oxygen functionality was removed by successive treatments with *p*-tosylhydrazine and sodium

borohydride. Then *m*-chloroperbenzoic acid was added without isolation of the intermediate hydrocarbon **43** to give diepoxide **44** in a yield of 25%. Reductive diaxial cleavage of both epoxides with lithium aluminum hydride followed by Jones' oxidation gave hydroxyketone **45** in a yield of 60%. The enantiomer of **45** was previously converted to (+)-β-eudesmol[37], so this is a formal synthesis of (-)-β-eudesmol (**46**).

Tricyclic intermediates are also obtainable in a few steps from the carvones. The synthesis of the sesquiterpene (-)-patchouli alcohol (**51**), a constituent of patchouli oil (*Pogostemon patchouli*) is shown in scheme 1.10[38].
α'-Methylation of R-(-)-carvone followed by vinyl phosphonium bicycloannulation gave tricyclo-octanone **47** in excellent yield. Octanone **48** was formed by reductive cleavage-alkylation of this tricyclo-octanone. Chromyl chloride oxidation followed by Grignard reaction and oxidation afforded diketone **49**. An intramolecular aldol condensation resulted in 3-oxopatchouli alcohol **50** in an overall yield of 18% from R-(-)-carvone. Removal of the carbonyl group from the tricyclic ketol would give (-)-patchouli alcohol (**51**)[38].

Scheme 1.10

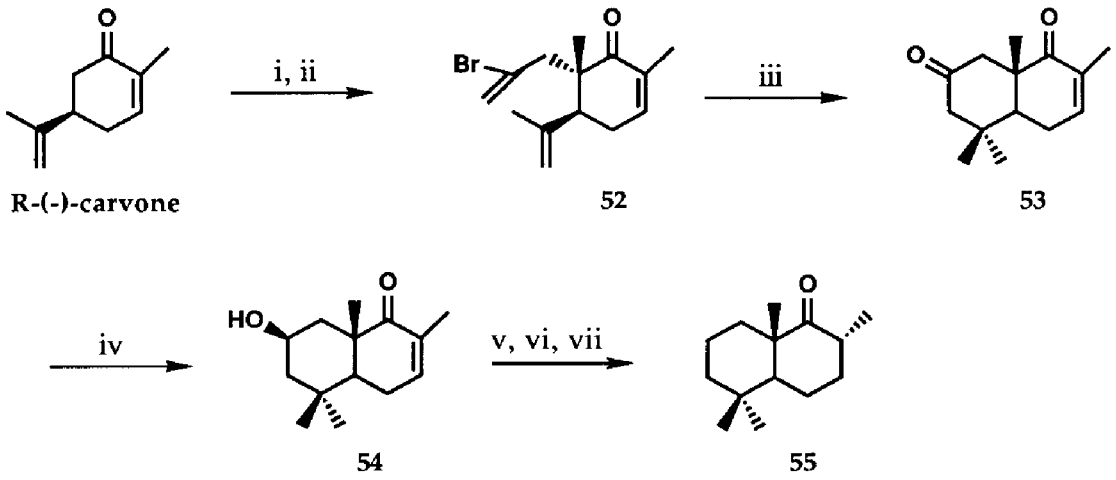


Reagents i: LDA, MeI; ii: LDA, 0 °C; CH_2=$CHPPh_3Br$, Δ; iii: Li/ NH_3; MeI; iv: CrO_2Cl_2, Zn; v: MeMgBr; vi: PCC; vii: LDA.

Besides the Robinson annulation, other annulation methods are very suitable for the synthesis of chiral *trans*-fused 6,6-decalones from carvone. An example from R-(-)-carvone is presented in scheme 1.11[39].

Two consecutive alkylations of the kinetic enolate of R-(-)-carvone, first with methyl iodide and then with 2,3-dibromopropene, gave product **52** stereoselectively. An acid-catalyzed cyclization by treatment with aqueous sulfuric acid yielded diketone **53**. Reduction with sodium borohydride gave the axial alcohol **54**. Dehydration, hydrogenation and epimerization of the methyl group afforded decalone **55** in an overall yield of 17% from R-(-)-carvone[39].

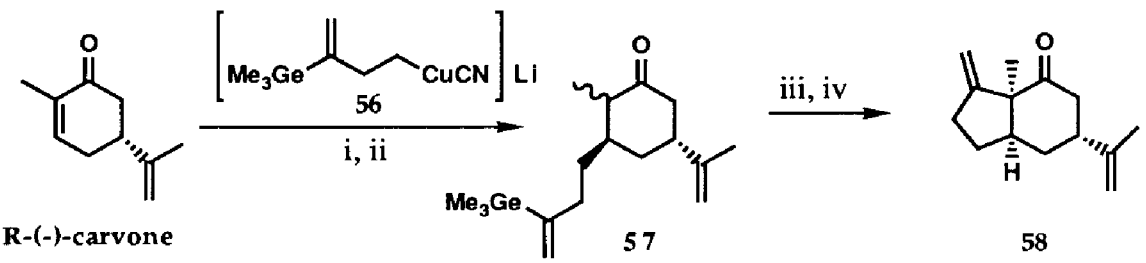
Scheme 1.11



Reagents i: LDA, MeI; ii: LDA, CH_2=$CBrCH_2Br$; iii: aq. H_2SO4; iv: $NaBH_4$; v: $POCl_3$, py: vi: H_2, Pd/C; vii: NaOMe.

An example of a five-membered ring annulation is shown in scheme 1.12[40]. The conjugate addition of cuprate reagent **56** to R-(-)-carvone gave after hydrolysis of the resultant enol silyl ether vinylgermane **57** as a mixture of epimers. Compound **57** was transformed into the corresponding iodide, and then annulated to the *cis*-fused product **58** by treatment with a palladium triphenylphosphine complex and potassium *tert*-butoxide. Compound **58** was obtained in an overall yield of 46% from R-(-)-carvone.

Scheme 1.12

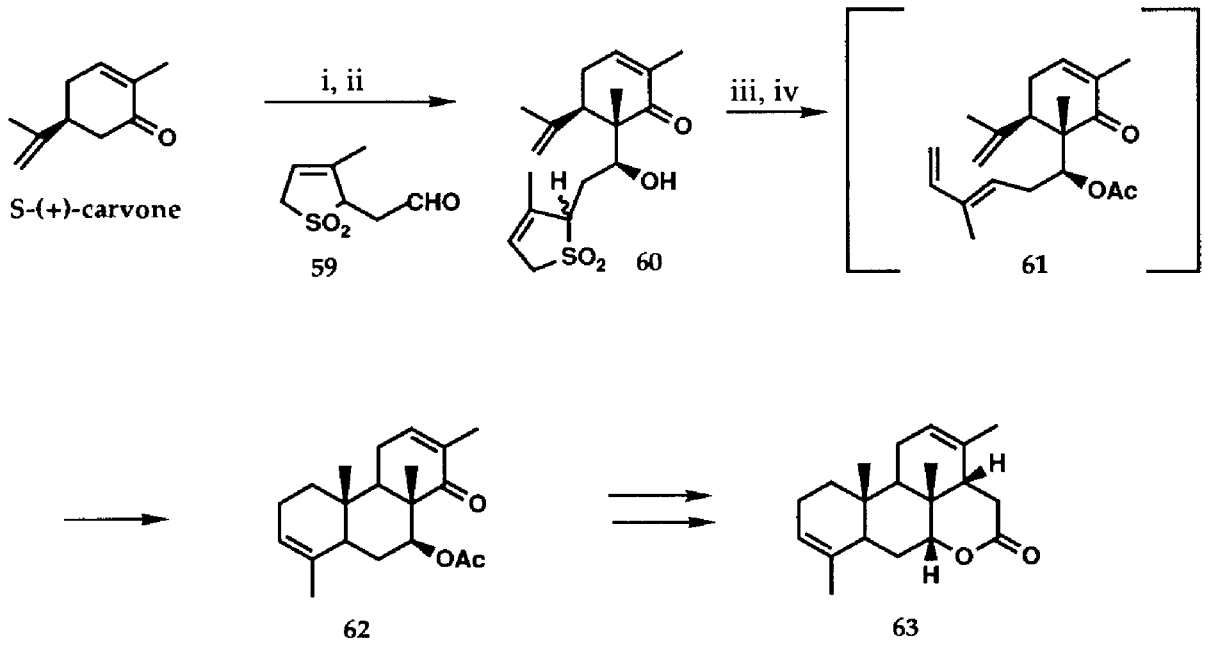


Reagents i: cuprate **56**, Me_3SiCl, THF, -78 °C; ii: NH_4Cl, H_2O; iii: I_2; iv: $[Ph_3P]_4Pd$, *t*-BuOK

The synthesis of the quassinoid skeleton **62** from S-(+)-carvone is shown in scheme 1.13[41b] The triterpenoid quassinoids, found in the *Simaroubacea* plant family, exhibit a wide spectrum of biological activities, *e.g.*, anticancer, antimalarial, insecticidal and growth inhibitory activities[42].

Methylation of the kinetic enolate of S-(+)-carvone, followed by the aldol reaction with aldehyde **59** afforded a 1: 1 mixture of diastereomers **60**. This aldol reaction[41b] was more reproducable than that with the *in situ* prepared unstable E-4-methylhexa-3,5-dienal[41a]. After protection of the hydroxy group as an acetate, the sulfonene was heated in benzonitrile and sulfur dioxide was extruded. Intermediate **61** underwent an *endo*-selective intramolecular Diels-Alder reaction to give the trans-fused tricyclic compound **62**. This tricycle, obtained in an overall yield of 40% from S-(+)-carvone, was further transformed into the tetracyclic quasssinoid skeleton **63**[41b].

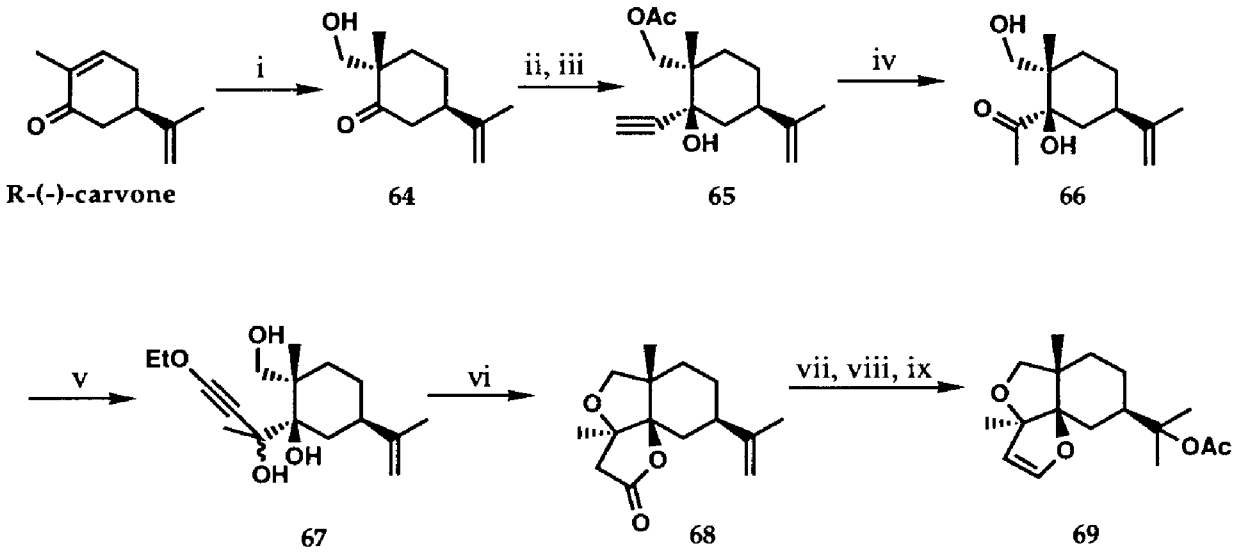
Scheme 1.13



Reagents i: LDA, MeI; ii: LDA, then followed by aldehyde **58**, DMPU, -78°C; iii: Ac_2O, py, DMAP; iv: PhCN, Methylene blue, 190 °C, 110 h.

The approach of Findlay *et al.* to the phytoalexin (-)-phytotuberin (**69**), a stress metabolite found in potato tubers, is shown in scheme 1.14[43]. The aldol condensation of the lithium enolate of R-(-)-carvone with formaldehyde gave a mixture of C-2 epimers with the desired epimer **64** as the minor product (2: 3). The yield of compound **64** could be augmented substantially by pyrolysis of the undesired epimer to give a new mixture (4: 5) of hydroxyketone **64** and its epimer *via* a retroaldol-aldol reaction. Ethynylation and acetylation afforded acetate **65**. Hydration to methyl ketone **66** was performed using mercury (II) sulfate as a catalyst. Ethoxy ethynylation provided for compound **67** as a mixture of diastereomers. Hydration of both isomers gave the tricyclic lactone **68**. Modification of the side chain was performed via epoxidation and reduction with lithium aluminum hydride, which also reduced the lactone to a lactol. Acetylation gave a diacetate which after pyrolysis afforded (-)-phytuberin (**69**) in an overall yield of 10%[43].

Scheme 1.14

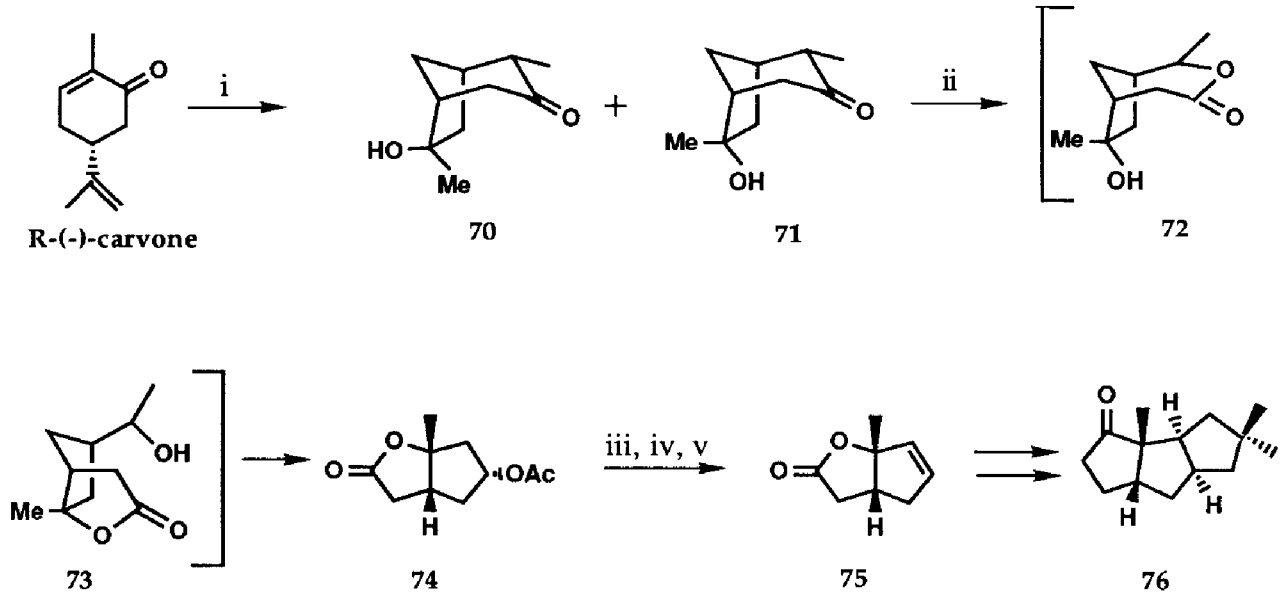


Reagents i: Li, NH_3; HCHO; ii: Li-acetylide, -78 °C; iii: Ac_2O, py; iv: $HgSO_4$, aq. MeOH; v: EtO-acetylene, *n*-BuLi; vi: H_3O^+; vii: *m*-CPBA; viii: $LiAlH_4$; ix: Ac_2O, py; Δ

1.3.3 Radical cyclization reactions

The last few years, the radical cyclization of both enantiomers of carvone to bicyclic ketones like **70** and **71** received a lot of attention[44]. In scheme 1.15, the conversion of R-(-)-carvone into (-)-hirsuten (**76**) is shown[44d]. Hirsuten (optical rotation not determined) is a tricyclic sesquiterpene extracted from the mycelium of *Coriolus consors*. A diastereomeric 1: 1 mixture of the hydroxy ketones **70** and **71**, was formed upon radical cyclization of R-(-)-carvone using mercuric acetate. After separation of the diastereomers, the Bayer-Villiger reaction of **71** formed the seven-membered intermediate lactone **72** that immediately rearranged to the more stable five-membered lactone **73**. This alcohol **73** was oxidized by the excess of *m*-chloroperbenzoic acid and the corresponding ketone gave a second Bayer-Villiger reaction to afford lactone **74**[44b]. Saponification of the acetate, replacement of the hydroxy substituent with bromide and dehydrohalogenation gave alkene **75** in an overall yield of 15% from R-(-)-carvone. Alkene **75** was further transformed into (-)-hirsuten (**76**)[44d].

Scheme 1.15



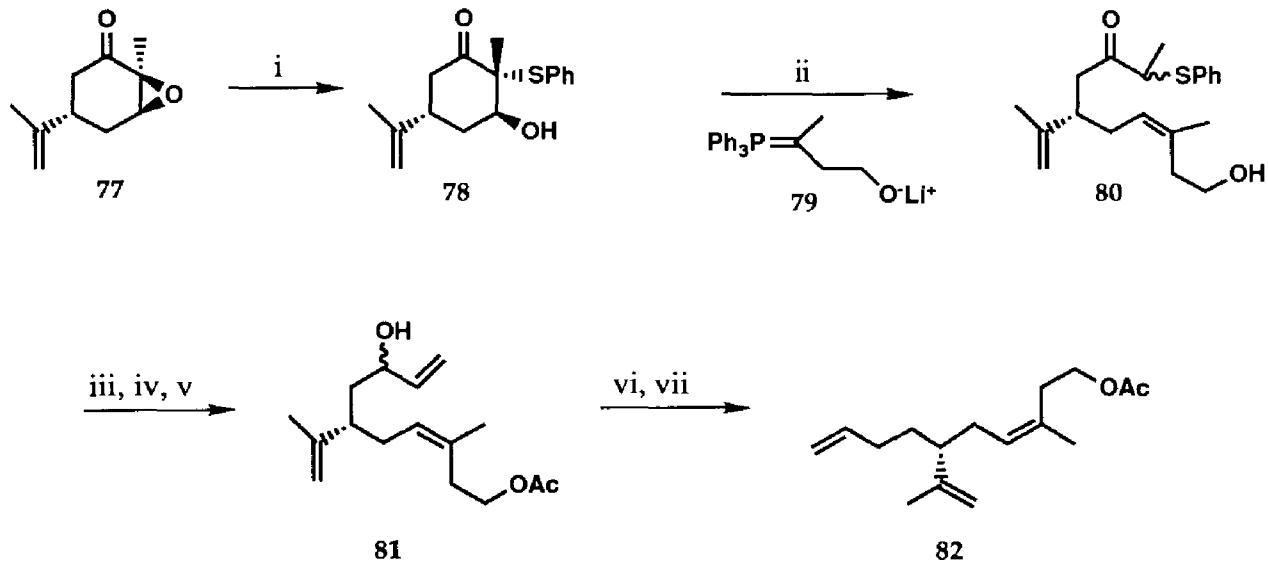
Reagents i: $Hg(OAc)_2$, THF, H_2O, then $NaBH_4$; ii: *m*-CPBA, 40 °C; iii: K_2CO_3; iv: Ph_3P, $ZnBr_2$, DEAD; v: DBU

1.3.4 *Fragmentation of the cyclohexanone ring*

Opening of the cyclohexanone ring of carvone makes the synthesis possible of some open chain natural products. The sex pheromone of the California red scale, (3Z,6R)-3-methyl-6-isopropenyl-3,9-decadien-1-yl acetate (**82**) was synthesized from S-(+)-carvone (scheme 1.16)[45].

The cis-carvone epoxide **77** gave hydroxy sulfide **78** upon treatment with thiophenol and triethylamine. The *in situ* prepared Wittig reagent **79** induced the tandem retroaldol-Wittig olefination process[46] to give the Z-trisubstituted olefin **80** stereoselectively. Acetylation, oxidation and thermal elimination of the sulfoxide gave a trienone acetate that was reduced to a mixture of alcohols **81**. Acetylation and chemoselective hydrogenolysis of the allylic acetate gave acetate **82** in an overall yield of 20% from *cis*-carvone epoxide **77**[45].

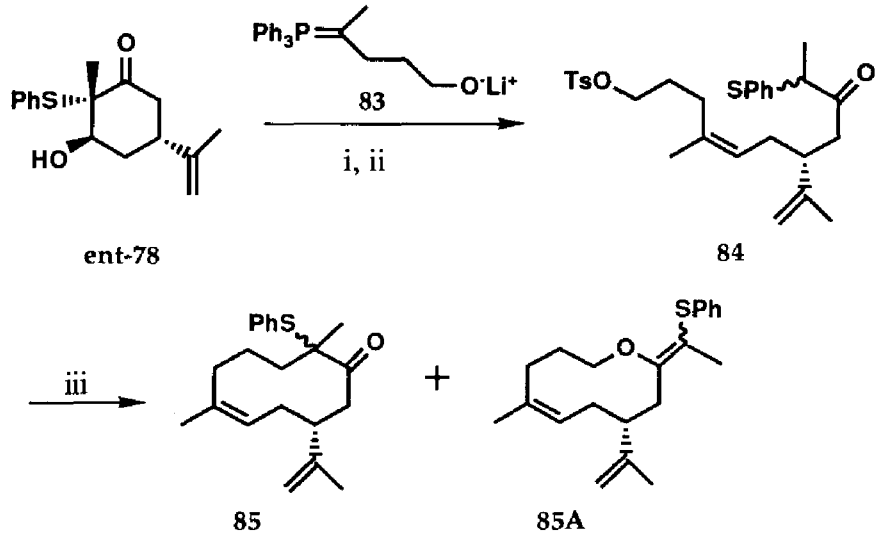
Scheme 1.16



Reagents i: PhSH, NEt_3; ii: retroaldol-Wittig olefination; iii: Ac_2O, py; iv: *m*-CPBA, Δ; v: $NaBH_4$, $CeCl_3$; vi: Ac_2O, py; vii: $PdCl_2(PPh_3)_2$, HCO_2NH_4.

Ent-**78**, obtained from R-(-)-carvone, was converted into a cyclodecane ring system (scheme 1.17)[47]. The retroaldol-Wittig olefination of *ent*-**78** with oxido-ylid **83**, followed by tosylation gave a diastereomeric mixture of tosylates **84**. Intramolecular alkylation using sodium hydride in 1,2-dimethoxyethane gave the C-alkylation product **85** in 70% yield and the O-alkylation product **85A** as a minor product in 7% yield. Compound **86** was obtained in an overall yield of 38% from *ent*-**78**[47].

Scheme 1.17



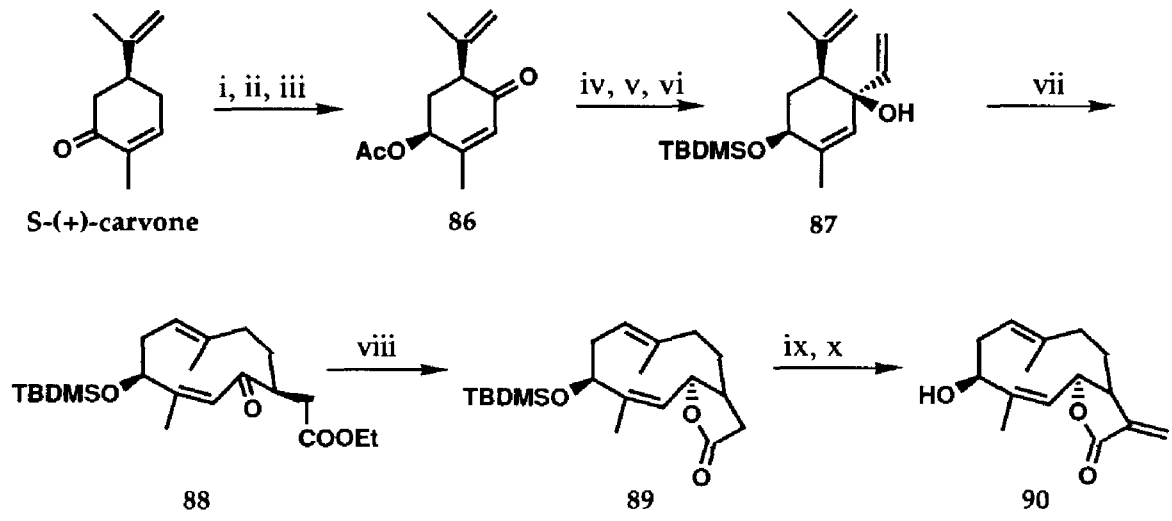
Reagents i: retroaldol-Wittig olefination; ii: TsCl, py; iii: NaH, DME, Δ

1.3.5 Cyclomutation reactions

The conversion of S-(+)-carvone into (-)-heliangolide (**90**) is another example of the construction of 10-membered rings from carvone (scheme 1.18)[48]. (-)-Heliangolide (**90**) can be isolated from *Tanacetum tanacetioides*.

Reduction, acetylation and oxidation of S-(+)-carvone gave enone **86** in a yield of 41%[48a]. A Grignard reaction with vinyl magnesium bromide, followed by protection with *tert*-butyldimethylsilyl chloride afforded product **87** in a yield of 30%. Treatment of the TBDMS ether **87** with potassium bis(trimethylsilyl)amide gave the oxy-Cope rearrangement product, which was quenched with ethyl bromoacetate to give the cyclodecadiene **88** in a yield of 32%. Reduction with sodium borohydride gave the *trans*-lactone **89** in 50% yield. The introduction of the exo-methylene moiety proceeded in two steps in an overall yield of 21%. Deprotection of the hydroxyl functionality gave natural (-)-heliangolide (**90**)[48a].

Scheme 1.18

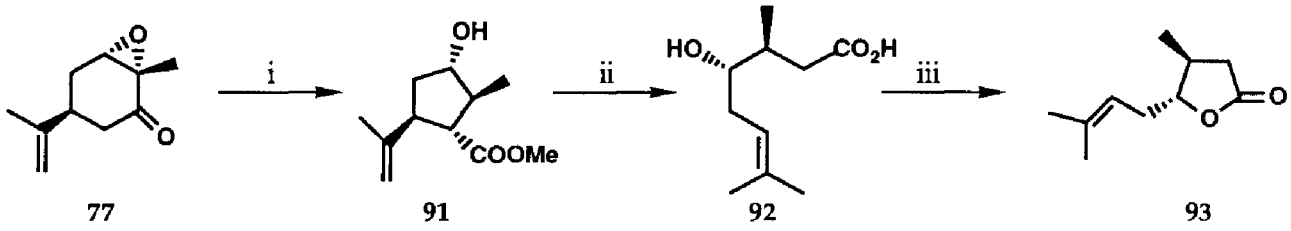


Reagents i: $LiAlH_4$; ii: Ac_2O, py; iii: $(t\text{-}BuO)_2CrO_2$; iv: vinyl MgBr; v: K_2CO_3, MeOH; vi: TBMSCl, imidazole; vii: $KN(SiMe_3)_2$, $BrCH_2COOEt$; viii: $NaBH_4$; ix: LDA, HCHO; MsCl, DMAP, py; x: Bu_4NF.

The Favorskii rearrangement product **91**, obtained by treatment of epoxycarvone **77** with sodium methoxide, and its enantiomer, have often been used as chiral building blocks in the synthesis of biologically active compounds[49]. The synthesis of (+)-eldanolide (**93**), a sex attractant pheromone isolated from the male wing glands of the African sugar cane borer *Eldana Sacharina*, is shown in scheme 1.19[49d].

The key feature of this synthetic sequence was the regioselective fragmentation reaction of **91** by treatment with sodium metal in hexamethylphosphoric triamide to the desired cleavage product **92**. Inversion of the hydroxy group and an intramolecular esterification was performed by a Mitsunobu reaction with diethyl azodicarboxylate (DEAD) and triphenyl phosphine to give (+)-eldanolide (**93**) in an overall yield of 33% from **77**[49d].

Scheme 1.19

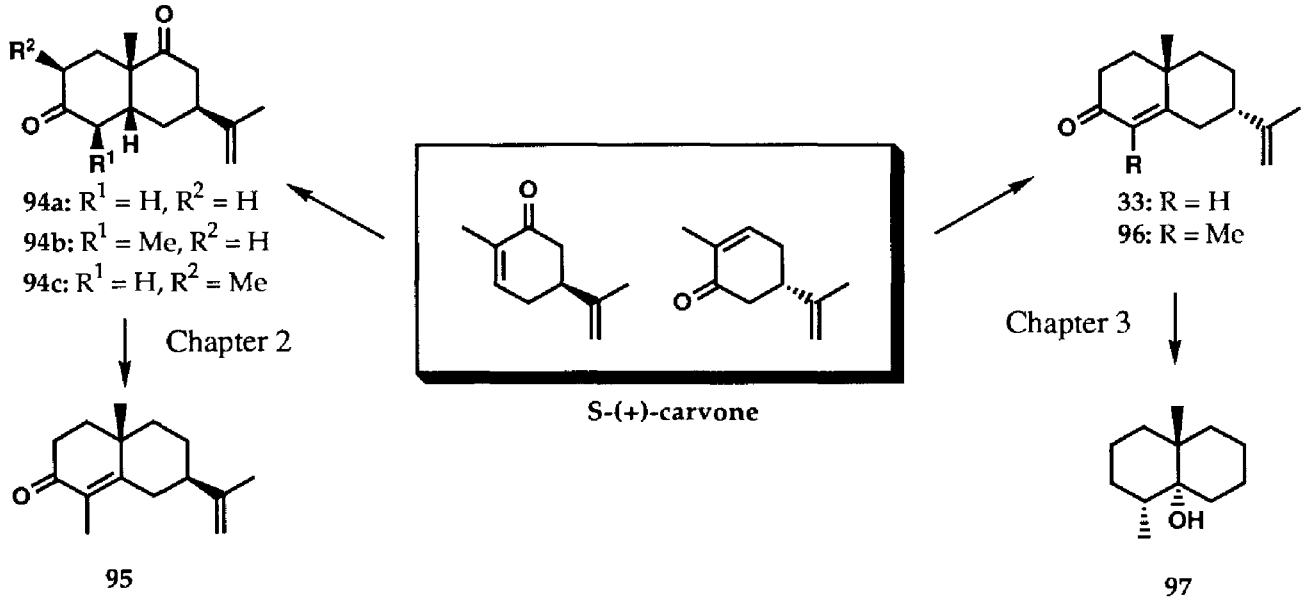


Reagents i: NaOMe; ii: Na, HMPA, H_2O; iii: PPh_3, DEAD, AcOEt

1.4 Scope of this thesis

S-(+)-carvone, the major compound of caraway essential oil, is a versatile starting material for the synthesis of biologically active natural products. The availability of interesting biologically active compounds from natural sources is often too small for commercial application. Then enantioselective syntheses of these compounds can be attractive. In this thesis approaches *via* the Diels-Alder reaction of S-(+)-carvone and (variations of) the Robinson annulation of dihydrocarvone derivatives are researched. These annulation methods are complementary in the formation of bicyclic compounds from S-(+)-carvone (scheme 1.20).

Scheme 1.20



The intramolecular Diels-Alder reaction of S-(+)-carvone with functionalized dienes is described in chapter 2. The *anti*-addition products, **94a-c**, with the angular substituents and the isopropenyl group in a *cis*-position, are the major products of the Lewis acid catalyzed Diels-Alder reaction of S-(+)-carvone with some silyloxy dienes. The total synthesis of (+)-α-cyperone (**95**) from one of the adducts **94** is described to show the synthetic utility of these adducts.

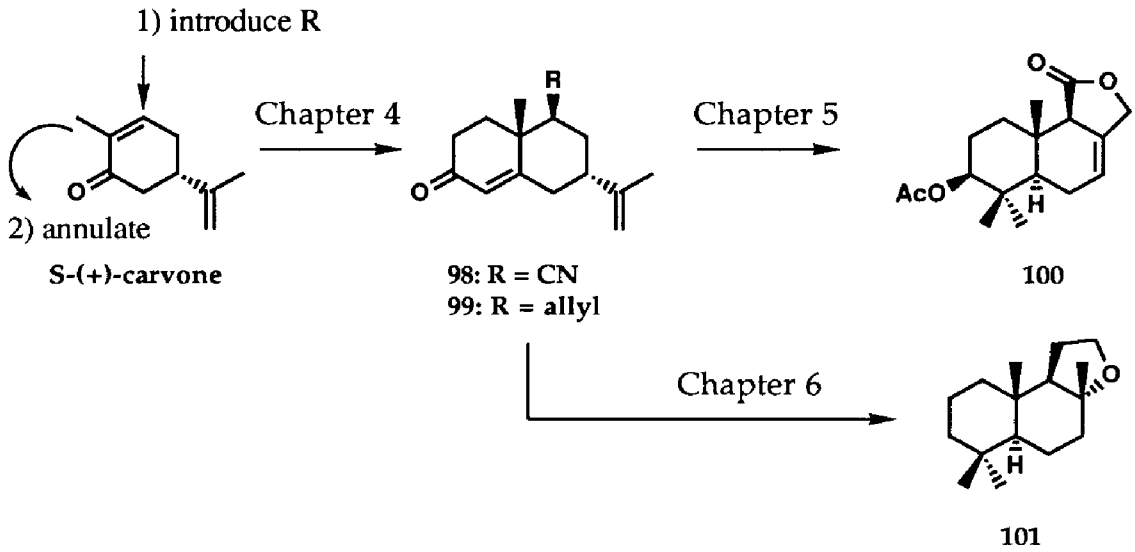
The Robinson annulation of (-)-dihydrocarvone, the lithium-bronze product of S-(+)-carvone, and methyl vinyl ketone or ethyl vinyl ketone gives predominantly the products **33** or **96**, respectively, with the angular methyl group and the isopropenyl group in a *trans*-position. The conversion of the Robinson annulation products **33** and **96** into compounds like (+)-geosmin (**97**) is shown in chapter 3. The removal of the isopropenyl group plays an important role in this chapter.

In chapter 4, two different conjugate addition/annulation methodologies from S-(+)-carvone to cyano and alkyl substituted decalones like **98** and **99** are reported (scheme 1.21).

The transformation of the cyano substituted decalone **98** into 3-oxygenated drimane sesquiterpenes like (-)-3β-acetoxydrimenin (**100**) is described in chapter 5.

The conversion of both the decalones **98** and **99** into the interesting olfactive compound (-)-Ambrox® (**101**) is the subject of chapter 6.

Scheme 1.21



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2. Lewis Acid Catalyzed Diels-Alder Reactions of S-(+)-Carvone with Silyloxy Dienes. Total Synthesis of (+)-α-Cyperone*

2.1 Introduction

As shown in section 1.3, both enantiomers of carvone have been widely used as starting materials in the enantioselective synthesis of miscellaneous natural products[1]. The intermolecular Diels-Alder reaction has not often been applied as a method of ring annulation in the total synthesis of bicyclic natural products from S-(+)- or R-(-)-carvone. Other annulation methods, *e.g.*, the Robinson annulation received more attention than the Diels-Alder reaction, because of the low reactivity of carvone as a dienophile[2].
Nerdel and Dahl executed the Diels-Alder reaction of carvone with 1,3-butadiene under drastic thermal conditions but this cycloaddition reaction proceeded in very low yield and with low stereospecificity[3]. The discovery of Lewis acid catalysis in Diels-Alder reactions of low-reactive dienophiles in 1960[4] made the cycloadditions with carvone more attractive for total synthesis. The first reported Lewis acid catalyzed Diels-Alder reaction, using R-(-)-carvone as a dienophile, was executed by Harayama *et al.*[5] The Lewis acid catalyzed Diels-Alder reaction of R-(-)-carvone with alkyl substituted 1,3-butadienes was further improved by Angell *et al.*[6] to give the *anti*-addition products in high yield. Unfortunately these adducts were low-functionalized and could be converted to eudesmane type sesquiterpenes only with difficulty[5]. On the other hand, the highly functionalized Danishefsky diene[7] was susceptible to Lewis acids and the reactions with R-(-)-carvone and other 2-cycloalkenones under thermal conditions (without Lewis acids) gave the desilylated products in 39% yield and with a low selectivity for the *anti*-addition product (2:1)[8].

2.2 Diels-Alder reactions of S-(+)-carvone with functionalized, Lewis acid stable silyloxydienes

The functionalized dienes 2-trimethylsilyloxy-1,3-butadiene (**102a**)[9], 3-trimethylsilyloxy-1,3-pentadiene (**102b**)[10] and 2-*tert*-butyldimethyl-silyloxy-3-methyl-1,3-butadiene (**102c**)[11] were often used in synthesis, but usually without Lewis acids. In our laboratory, diene **102c** was used previously[11b,c] in the presence of $ZnCl_2$. The dienes **102a**, **102b** and **102c** proved to be stable in the presence of aluminum chloride and ethylaluminum dichloride ($EtAlCl_2$). $EtAlCl_2$ was found to be the most effective

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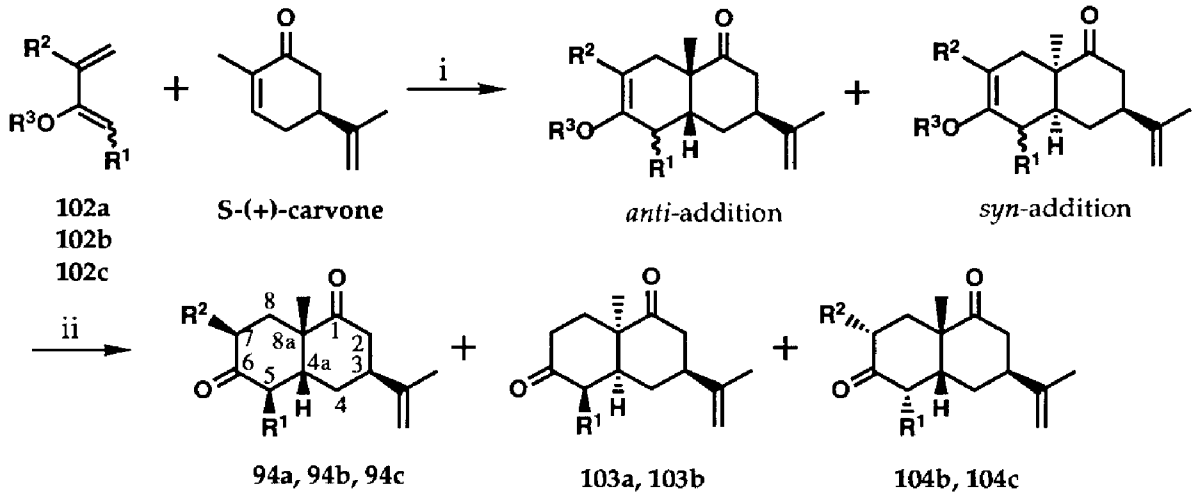
catalyst in the Diels-Alder reaction with S-(+)-carvone, but in a quantity of 0.5 eq. and not in a catalytic amount! So, the Diels-Alder reactions of S-(+)-carvone with **102a**, **102b** and **102c** were performed in the presence of 0.5 eq of $EtAlCl_2$ in toluene solution at room temperature for 2 - 4 h to give both *anti*- and *syn*-addition products. The adducts were separated by column chromatography after hydrolysis by the addition of aqueous 4 M hydrochloric acid to obtain the *cis* decalones **94 (a,b,c)**, **103 (a,b)** and **104 (b,c)** in a yield of 73-77% yield (scheme 2.1 and table 2.1).

Scheme 2.1



a: R^1 = H, R^2 = H, R^3 = TMS, b: R^1 = Me, R^2 = H, R^3 = TMS, c: R^1 = H, R^2 = Me, R^3 = TBDMS

Reagents i: $EtAlCl_2$, toluene, rt; ii: H^+, H_2O.

Table 2.1: $EtAlCl_2$ "catalyzed" Diels-Alder reactions of S-(+)-carvone with dienes 102

Diene	products	product ratio	% *anti*-addition	product yield (%)*
102a	**94a, 103a** (R^1 = H, R^2 = H)	19:1	95	73
102b	**94b, 103b, 104b** (R^1 = Me, R^2 = H)	variable**	91	77
102c	**94c, 104c** (R^1 = H, R^2 = Me)	10:11	100	74

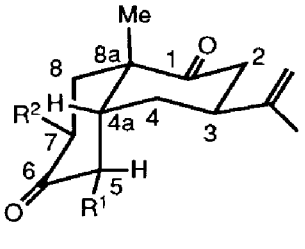
*Isolated yields after desilylation. **Under the hydrolysis conditions, some epimerization of **104b** to **94b** takes place.

The acid catalyzed epimerization of **104b** to **94b**, which was slow and incomplete, indicated that **104b** is the C-5 epimer of **94b.** Complete conversion of **104b** to **94b** was established in a 1 M solution of sodium methoxide in methanol. A similar

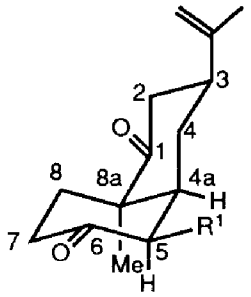
epimerization was observed for compound **104c**, which was completely converted to its C-7 epimer **94c** under the same basic reaction conditions. The structures were determined by ^{1}H and ^{13}C NMR spectroscopy.

First the regioselectivity of the Diels-Alder reactions was determined. For the adducts of S-(+)-carvone and the dienes **102a** and **102c**, the regioselectivity was quite obvious, because of the strong para-directing effect of the 2-silyloxy group. For the adducts of diene **102b** and S-(+)-carvone an alternative orientation could be possible since literature precedents suggested an opposite regioselectivity for the dienes **102a** and **102b**[10a]. The terminal methyl group should have a stronger directing influence than the non-terminal silyloxy group[12]. In our case the same regioselectivity for the three dienes in the $EtAlCl_2$-catalyzed Diels-Alder reactions was found. The regioselectivity of adduct **104b** was confirmed by its 200 MHz ^{1}H NMR spectrum. The hydrogen at C-5 appeared as a quintet, located at δ 2.85 with a coupling constant of 7 Hz with the three hydrogens of the methylgroup at C-5 and with the angular hydrogen at C-4a. The regioselectivity of **103b** was confirmed in the same way, by a quintet located at δ 2.92, J = 7 Hz. The coupling constant of 7 Hz in the two adducts indicated an axial-equatorial coupling for the angular proton and the proton at C-5 and thus a cis-orientation for the two hydrogens. These assignments were confirmed by decoupling experiments. The regioselectivity of **94b** was confirmed by its C-5 epimer relationship with **104b**, which resulted in a trans-relationship for the angular hydrogen and the C-5 hydrogen.

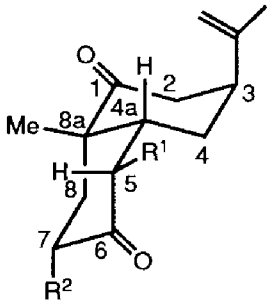
Figure 2.1



94



103



104

The ^{1}H NMR spectrum further gave information about the conformation of the adducts. The signals of the two isopropenyl olefinic hydrogens were separated only between 0.03 and 0.05 ppm for the compounds **94a, 103a, 94b, 103b** and **94c**, indicating only small differences in the environment of the two hydrogens. These adducts thus had a conformation in which the isopropenyl group resided in an equatorial position. This suggested the conformations shown in figure 2.1 for the *anti*-addition products **94** and the *syn*-addition products **103**. The olefinic hydrogens of the isopropenyl group of the compounds **104b** and **104c** appeared as separate singlets with

a shift difference of 0.24 and 0.22 ppm respectively, indicating a conformation with an axial isopropenyl group. This suggested the conformation shown in figure 2.1 for the *anti*-addition products **104**.

Additional information was obtained by the analysis of the carbon shifts of the diketones **94, 103** and **104** (table 2.2). In the adducts **103** and **104**, the angular methyl group is located at the site peri to the keto function of C-1 and thus this methyl group is shielded extraordinarily by the nonbonded interaction with the carbonyl oxygen in these conformations. This fact is substantiated in the compounds **103a, 103b, 104b** and **104c** by a shielding of ca. 6 ppm of their C-8 methyl group. As a consequence of the γ-effect imposed by the axial isopropenyl group C-4a is shielded extra in the diketones **104b** and **104c.** The shifts of C-3 of the *syn*-addition products **103a** and **103b** are ca. 5 ppm higher compared to their isomeric *anti*-addition products. This fact results from the diminished γ-effects imposed by steric hindrance on C-3 in the conformation of **103**, compared to C-3 in the conformations of **94** and **104**. In the conformation of **94**, the axial-fused ring causes a 1,3-diaxial interaction with the axial C-3 hydrogen. In the conformation of **104**, the 1,3-diaxial interaction between the axial isopropenyl and the angular hydrogen causes a γ-effect on C-3. The same shift differences were found by Angell *et al.* for the carvone derived ring carbons in the reaction products of R-(-)-carvone with methyl-substituted 1,3-butadienes[6].

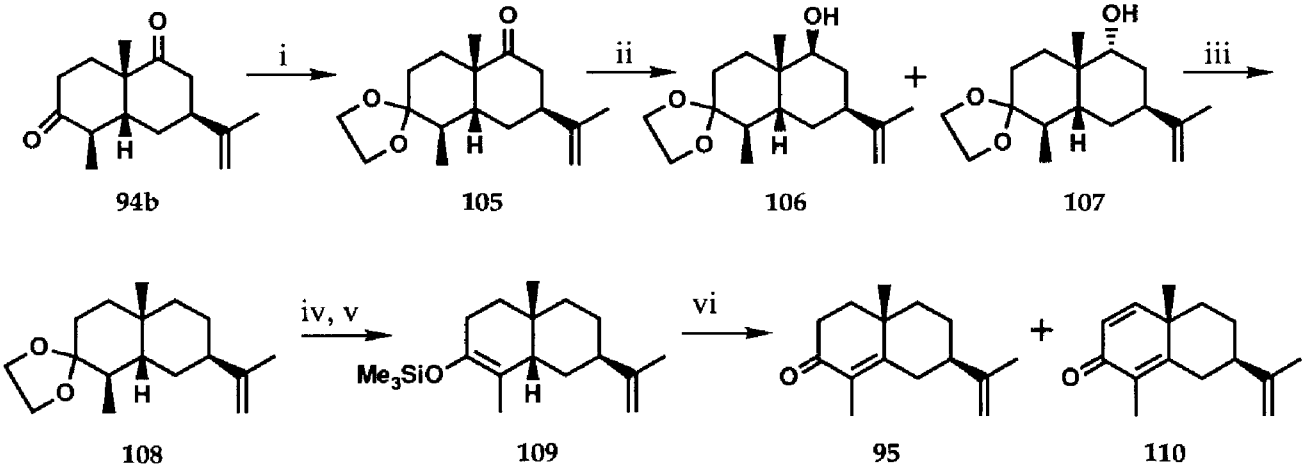
Table 2.2: ^{13}C Chemical shifts of the products

	94a	**103a**	**94b**	**103b**	**104b**	**94c**	**104c**
C-1	213.2	213.2	213.2	213.0	213.8	213.5	213.9
C-2	43.8	43.8	42.2	42.0	40.5	43.4	40.0
C-3	40.3	44.1	39.4	44.2	39.5	41.3	39.9
C-4	30.8	31.1	27.7	27.4	24.0	30. 9	30.3
C-4a	44.5	44.7	51.8	51.6	46.4	46.0	40.3
C-5	42.1	41.8	44.1	43.8	43.2	42.3	40.9
C-6	210.9	209.4	212.6	211.0	211.6	212.5	211.9
C-7	38.2	37.4	38.6	37.5	37.5	40.4	40.2
C-8	33.8	33.4	34.6	32.1	32.5	44.0	44.0
C-8a	47.5	47.3	48.4	48.8	48.9	48.4	48.2
i-Pr Me	20.3	20.1	20.3	20.0	21.7	20.3	21.5
i-Pr CH_2	110.2	109.9	109.9	110.0	112.5	110.1	111.9
i-Pr C	146.3	146.4	146.5	146.7	145.7	146.5	146.1
C-8a Me	25.2	19.0	26.4	18.9	19.0	25.8	21.2
C-5 Me	-	-	11.1	11.8	11.6	-	-
C-7 Me	-	-	-	-	-	13.9	14.0

2.3 Total synthesis of (+)-α-cyperone (95).

The major adduct of the reaction of diene **102b** with S-(+)-carvone was used to demonstrate the synthetic utility of this adduct in the synthesis of eudesmanes with a *cis*-relationship between the angular methyl group and the isopropenyl group, like (+)-α-cyperone (**95**). In (+)-α-cyperone (**95**) this *cis*-relationship has been a stereochemical problem in syntheses involving the Robinson annulation[13]. A major improvement was obtained by the approach of Caine and Gupton, who obtained (+)-α-cyperone (**95**) in three steps from (-)-2-carone in an overall yield of 20%[14]. Pierce and Cheng developed an eight step synthesis of (+)-α-cyperone (**95**) from (-)-santonin. They obtained (+)-α-cyperone (**95**) in an overall yield of 20% from (-)-santonin[15]. Until now, (+)-α-cyperone was used mainly as a starting compound for the synthesis of various other fused-ring sesquiterpenes[16]. Recently it was shown that (+)-α-cyperone (**95**) has *in vitro* activity against *Plasmodium flaciparum* strain K1, a multidrug resistent malaria parasite[17] which made this compound again an interesting target molecule.

Scheme 2.2



Reagents i: MED, *p*-TsOH, glycol; ii: $LiAlH_4$, ether; iii: NaH, CS_2, MeI, THF, Δ; *n*-Bu_3SnH, AIBN, toluene, Δ; iv: H^+, H_2O, acetone; v: TMSiCl, Et_3N, DMF, Δ. vi: DDQ, benzene.

The Diels-Alder reaction of S-(+)-carvone with **102b**, followed by hydrolysis and quantitative epimerization of **104b** gave **94b** in 69% yield. The less hindered carbonyl group in **94b** was selectively protected by acid catalyzed acetal exchange with methyl ethyl dioxolane (MED) to give the monoprotected decalone **105** in 97% (scheme 2.2). Reduction of the carbonyl group at C-1 *via* the Wolff-Kishner procedure was

unsuccessful, probably for steric reasons. Enforced conditions for the Wolff-Kishner reduction[18] resulted in the formation of the hydrazone, but the decomposition of this hydrazone gave a double bond in the $\Delta^{1,2}$ position. As an accompanying reaction the isomerization of the olefinic bond from the isopropenyl sidechain, to the conjugated exocyclic position was observed. The Barton reduction[19], which involves neutral conditions and avoids ionic processes of any type was more successful. Reduction of decalone **105** with lithium aluminum hydride gave an isomeric mixture of the alcohols **106** and **107** in 18% and 78% respectively. The mixture of alcohols was transformed into a mixture of xanthates which was refluxed in toluene with tributylstannane in the presence of a catalytic amount of azoisobutyronitrile (AIBN) to provide **108** in 86% yield. Deprotection of compound **108** and formation of the thermodynamic trimethylsilyl enol ether **109** was achieved by the procedure of House *et al.*[20] in 90% yield. Oxidation of **109** with dichlorodicyanoquinone (DDQ)[21] in benzene at room temperature afforded (+)-α-cyperone (**95**) in 87% yield and dehydro-α-cyperone **110** as a byproduct in 8% yield. (+)-α-Cyperone (**95**) was obtained *via* this 7-step procedure in an overall yield of 40% from S-(+)-carvone. The Diels-Alder approach of (+)-α-cyperone (**95**) therefore is a competitive alternative for the other known total syntheses of (+)-α-cyperone (**95**).

2.4 Experimental Section

General experimental conditions:

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were determined on a Bruker AC-E 200. Chemical shifts are reported in ppm downfield relative to tetramethylsilane (δ scale) and in $CDCl_3$ solutions. Mass spectral data and HRMS measurements were obtained on a AEI MS 902 spectrometer. Elemental analyses were carried out using a Carlo Erba Elemental Analyser 1106. Optical rotations were measured on a Perkin-Elmer 241 polarimeter in chloroform as the solvent with the concentrations denoted in g/100 ml. GLC analyses were carried out on a Fisons MEGA8000 chromatograph provided with a 30 m capillaire column (DB-5 MS).

For all dry reactions performed under a steady stream of nitrogen the equipment was dried in an oven at 150 °C for several hours, and allowed to cool in an atmosphere of dry nitrogen. Ether and toluene were dried by storage of the distilled solvent over sodium wire. Dry tetrahydrofuran was obtained by distillation of the commercial material from sodium hydride or from sodium benzophenone ketyl. Usually the reaction mixture was diluted with water and extracted three times with an organic solvent. The combined organic extracts were washed with brine and dried over anhydrous magnesium sulfate ($MgSO_4$) prior to filtration and evaporation of the

solvent under reduced pressure. Flash chromatography was performed on Merck silica gel (230 - 400 mesh) and mixtures of petroleum ether (PE, boiling range 40-60 °C) and ethyl acetate (EtOAc) were used as eluent.
2-Trimethylsilyloxy-1,3-butadiene (**102a**) and 3-trimethylsilyloxy-1,3-pentadiene (**102b**) were prepared by a modified House procedure according to literature methods[22]. 2-(*tert*-Butyldimethylsilyloxy)-3-methyl-1,3-butadiene (**102c**) was prepared by the procedure of Ireland *et al.*[11a]

General procedure of the Diels-Alder reactions
To a solution of S-(+)-carvone (2-5 g) in toluene (50-100 ml) was added by syringe 0.5 equivalent of ethylaluminium dichloride (1.8 M solution in toluene) and the reaction mixture was stirred for 15 min at room temperature. The silyloxy diene **102** was added (1.5 eq.) and the mixture was stirred at room temperature until the reaction was completed as determined by GLC (2-4 h). The reaction mixture was acidified with aqueous 4 M hydrochloric acid and the mixture was stirred at room temperature (2-48 h). Water was added and the mixture was extracted with ether (3 x 100 ml). The combined organic layers were washed with aqueous saturated sodium bicarbonate, dried and evaporated. The residue was purified by flash chromatography (eluent PE/EtOAc = 9/1).

(3S,4aR,8aS)-3-Isopropenyl-8a-methyl-2,3,4,4a,5,7,8,8a-octahydronaphthalene-1,6-dione (94a)
mp: 56 - 57 °C. ^{1}H NMR: δ 1.22 (s, 3H); 1.25 - 1.60 (m, 2H); 1.65 (s, 3H); 1.95 - 2.65 (m, 10H); 4.66 (s, 1H); 4.70 (s, 1H). HRMS: calcd (M^+) *m/e* 220.1463; found *m/e* 220.1466. Anal: calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15; found: C, 76.12; H, 9.11. $[\alpha]_D = -39.9$ (c = 0.3).
(3S,4aS,8aR)-3-Isopropenyl-8a-methyl-2,3,4,4a,5,7,8,8a-octahydronaphthalene-1,6-dione (103a)
mp: 97 °C. ^{1}H NMR: δ 1.39 (s, 3H); 1.69 (s, 3H); 1.2 - 1.85 (m, 3H); 2.1 - 2.8 (m, 9H); 4.68 (s, 1H); 4.73 (s, 1H). HRMS: calcd (M^+) *m/e* 220.1463; found *m/e* 220.1465. $[\alpha]_D = -120.6$ (c = 0.2).
(3S,4aR,5R,8aS)-5,8a-Dimethyl-3-isopropenyl-2,3,4,4a,5,7,8,8a-octahydronaphthalene-1,6-dione (94b)
^{1}H NMR: δ 0.97 (d, J = 6 Hz, 3H); 1.25 (s, 3H); 1.74 (s, 3H); 1.1 - 2.8 (m, 11H); 4.76 (s, 1H); 4.79 (s, 1H). HRMS: calcd (M^+) *m/e* 234.1620; found *m/e* 234.1617. $[\alpha]_D = -36.7$ (c = 0.3).
(3S,4aS,5R,8aR)-5,8a-Dimethyl-3-isopropenyl-2,3,4,4a,5,7,8,8a-octahydronaphthalene-1,6-dione (103b)
mp: 128 - 129 °C. ^{1}H NMR: δ 1.02 (d, J = 7 Hz, 3H); 1.46 (s, 3H); 1.69 (s, 3H); 1.1 - 2.65 (m,

10H); 2.92 (quintet, J = 7 Hz, 1H); 4.70 (s. 1H); 4.75 (s,1H). HRMS: calcd (M^+) *m/e* 234.1620; found *m/e* 234.1625. Anal: calcd for $C_{15}H_{22}O_2$: C, 76.87; H, 9.46; found: C, 76.69; H, 9.47. $[\alpha]_D = -147.1$ (c = 0.3).

(3S,4aR,5S,8aS)-5,8a-Dimethyl-3-isopropenyl-2,3,4,4a,5,7,8,8a-octahydronaphthalene-1,6-dione (104b)

mp: 108 - 109 °C. ^1H NMR: δ 0.98 (d, J = 7 Hz, 3H); 1.42 (s, 3H); 1.67 (s, 3H); 1.0 - 2.75 (m, 10H); 2.85 (quintet, J = 7 Hz, 1H); 4.62 (s, 1H); 4.88 (s, 1H). HRMS: calcd (M^+) *m/e* 234.1620; found *m/e* 234.1616. Anal: calcd for $C_{15}H_{22}O_2$: C, 76.87; H, 9.46; found: C, 76.74; H, 9.56. $[\alpha]_D = +138.4$ (c = 0.3).

(3S,4aR,7R,8aR)-7,8a-Dimethyl-3-isopropenyl-2,3,4,4a,5,7,8,8a-octahydronaphthalene-1,6-dione (94c)

^1H NMR: δ 0.95 (d, J = 6 Hz, 3H); 1.25 (s, 3H); 1.73 (s, 3H); 0.85 - 2.80 (m, 11H).; 4.74 (s, 1H); 4.78 (s, 1H). HRMS: calcd (M^+) *m/e* 234.1620; found *m/e* 234.1619. $[\alpha]_D = -42.3$ (c = 0.3).

(3S,4aR,7S,8aR)-7,8a-Dimethyl-3-isopropenyl-2,3,4,4a,5,7,8,8a-octahydro-naphthalene-1,6-dione (104c)

mp 96 °C. ^1H NMR: δ 1.00 (d, J = 6.6 Hz, 3H); 1.39 (s, 3H); 1.68 (s, 3H); 1.55 - 2.35 (m, 6H); 2.5 - 2.7 (m, 5H); 4.61 (s, 1H); 4.83 (s, 1H). HRMS: calcd (M+) *m/e* 234.1620; found *m/e* 234.1619. $[\alpha]_D = +62.2$ (c = 0.3).

Epimerizations of the diketones 104 to 94

A solution of 0.23 g of **104b** in 10 ml of a 1 M solution of sodium methoxide in methanol was stirred at room temperature for 2 h. Water was added and the mixture was extracted with ether (3 x 20 ml). The combined ethereal layers were washed with brine, dried and evaporated to yield **94b** quantitative. Diketone **94c** was obtained quantitative in the same way from diketone **104c**.

(3S,4aR,5R,8aS)-5,8a-Dimethyl-6,6-(ethylenedioxy)-3-isopropenyl-2,3,4,4a,5,7,8,8a-octahydronaphthalene-1(2H)-one (105)

A solution of 1.81 g (7.74 mmol) of **94** in 20 ml of methyl ethyl dioxolane, 0.45 g of *p*-toluenesulfonic acid and 5 drops of ethylene glycol was stirred for 15 minutes and then saturated aqueous sodium bicarbonate was added. The reaction mixture was extracted with ether (3 x 50 ml). The combined organic layers were washed with brine, dried on $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on silica gel (eluent PE/EtOAc = 19/1) to give 2.08 g (7.54 mmol, 97%) of **105** as a pale yellow oil.

^1H NMR: δ 0.82 (d, J = 6.4 Hz, 3H); 1.18 (s, 3H); 1.71 (s, 3H); 1.1 - 2.5 (m, 11H); 3.85 -

4.00(m, 4H); 4.70 (s, 1H); 4.73 (s, 1H). ^{13}C NMR: δ 10.27 (q); 20.23 (q); 26.93 (t); 27.06 (q); 31.14 (t); 31.45 (t); 38.97 (d); 39.34 (d); 42.29 (t); 47.49 (d); 48.00 (s); 64.58 (t); 64.81 (t); 109.32 (t); 110.50 (s); 147.32 (s); 214.04 (s). HRMS: calcd (M^+) *m/e* 278.1882; found *m/e* 278.1883. $[\alpha]_D = -35.8$ (c = 0.3).

(1S,3S,4aR,5R,8aS)-5,8a-Dimethyl-6,6-(ethylenedioxy)-3-isopropenyl-perhydronaphthalene-1-ol (106) and (1R,3S,4aR,5R,8aS)-5,8a-dimethyl-6,6-(ethylenedioxy)-3-isopropenyl-perhydronaphthalene-1-ol (107).

A solution of 1.92 g (6.96 mmol) of **105** in 100 ml of dry ether was added to 0.30 g (7.89 mmol) of lithium aluminum hydride in 50 ml of dry ether at room temperature under nitrogen. The mixture was stirred for 1 h and 100 ml of ether was added, followed by 0.3 ml of water. After 15 minutes 0.3 ml of aqueous 4 M sodium hydroxide was added and after another 0.5 h 0.9 ml of water was added, and stirring was continued for 1h. The reaction mixture was dried, filtered and evaporated. The residue was chromatographed on silica gel. Elution with PE/EtOAc = 6/1 gave first 1.51 g (5.43 mmol, 78%) of **107** as white crystals with a melting point of 103 - 104 °C. Further elution with PE/EtOAc = 4/1 gave 0.34 g (1.22 mmol, 18%) of **106** as a colourless oil.

106: ^1H NMR: δ 0.73 (d, J = 6.5 Hz, 3H); 0.85 (s, 3H); 1.1 - 2.3 (m, 15H); 3.83 - 4.02 (m, 5H); 4.61 (s, 2H). ^{13}C NMR: 10.76 (q); 20.60 (q); 20.98 (q); 27.27 (t); 29.98 (t); 31.62 (t); 35.52 (t); 36.71 (d); 36.99 (s); 37.78 (d); 46.73 (d); 64.43 (t); 64.84 (t); 67.49 (d); 108.41 (t); 110.89 (s); 148.89 (s). HRMS: calcd (M^+) *m/e* 280.2038; found *m/e* 280.2044. $[\alpha]_D = +14.0$ (c = 0.4).

107: ^1H NMR: δ 0.80 (d, J = 7 Hz, 3H); 0.89 (s, 3H); 1.70 (s, 3H); 1.4 - 1.9 (m, 9H); 2.1 - 2.6 (m, 3H); 3.70 (br.s, 1H); 3.8 - 4.0 (m, 4H); 4.67 (s, 2H). ^{13}C NMR: δ 11.35 (q); 20.86 (q); 28.19 (t) 28.55 (q); 32.34 (d); 33.13 (t); 35.30 (s); 36.86 (t); 36.93 (t); 37.40 (d); 44.65 (d); 64.46 (t); 64.63 (t); 77.78 (d); 108.13 (t); 112.03 (s); 150.02 (s). HRMS: calcd (M^+) *m/e* 280.2038; found *m/e* 280.2038. Anal.: calcd for $C_{17}H_{28}O_3$: C, 72.81; H, 10.06; found: C, 73.05; H, 10.35. $[\alpha]_D = -2.0$ (c = 0.3).

(1R,4aS,7R,8aR)-1,4a-Dimethyl-2,2-(ethylenedioxy)-7-isopropenyl-perhydronaphthalene (108)

A solution of 0.6 g of sodium hydride, (80%, 20 mmol), 40 mg of imidazole and 1.80 g (6.43 mmol) of a mixture of **106** and **107** in 50 ml of dry tetrahydrofuran was stirred and refluxed for 2 h under nitrogen. Carbon disulphide (2 ml, 33 mmol) was added, and after refluxing for 1 h methyl iodide (2 ml) was added and refluxing was continued for 1 h. The mixture was allowed to cool to room temperature and 2 ml of

acetic acid was added. The reaction mixture was diluted with water and extracted with ether (3 x 50 ml). The extract was washed with aqueous 1 M hydrochloric acid (2 x 10 ml) and with saturated aqueous sodium bicarbonate and dried on $MgSO_4$. After evaporation the residue was flash chromatographed (eluent PE/EtOAc = 19/1) to yield 2.29 g (6.19 mmol, 96%) of a mixture of xanthates. The xanthates were dissolved in 50 ml of toluene and 2 ml of tri-n-butyltin hydride (7.4 mmol) and a catalytic amount of azoisobutyronitrile was added. The mixture was refluxed for 2 h, the toluene was evaporated and the residue was chromatographed. Elution with PE easily removed a non-polar stannane compound from the column, raising of the EtOAc concentration to 5% gave 1.46 g (5.53 mmol, 86%) of **108** as a colourless oil.
^{1}H NMR: δ 0.81 (d, J = 6.6 Hz, 3H); 0.96 (s, 3H); 1.2 - 1.7 (m, 13H); 1.8 - 2.1 (m, 3H); 3.89 - 3.95 (m, 4H); 4.65 (br.s, 2H). ^{13}C NMR; δ 10.65 (q); 20.74 (q); 26.86 (t); 27.33 (q); 27.97 (t); 30.06 (t); 30.36 (t); 32.00 (s); 36.82 (d); 37.68 (t); 37.69 (d); 45.35 (d); 64.43 (t); 64.86 (t); 107.80 (t); 111.30 (s); 150.53 (s). HRMS: calcd (M^+) *m/e* 264.2089; found *m/e* 264.2089. $[\alpha]_D$ = +29.4 (c = 0.3).

(4aS,7R,8aS)-1,4a-Dimethyl-7-isopropenyl-3,4,4a,5,6,7,8,8a-octahydro-2-(trimethylsilyloxy)-naphthalene (109)
A solution of 1.44 g (5.45 mmol) of **108** and 10 drops of aqueous 4 M hydrochloric acid in 10 ml of acetone was refluxed for 2 h. The acetone was partly evaporated and 20 ml of water and 20 ml of ether were added. The aqueous layer was extracted 3 times with ether. The combined ethereal layers were washed with a brine and dried on $MgSO_4$. Flash chromatography (eluent PE/EtOAc = 9/1) yielded 1.11 g (5.05 mmol, 93%) of *(1R,4aS,7R,8aR)-1,4a-Dimethyl-7-isopropenyl-octahydronaphthalene-2(1H)-one* as a colourless oil.
^{1}H NMR: δ 0.96 (d, J = 6.5 Hz, 3H); 1.01 (s, 3H); 1.70 (s, 3H); 1.1 - 2.8 (m, 13H); 4.67 - 4.69 (m, 2H). ^{13}C NMR: δ 11.39 (q); 20.76 (q); 26.66 (q); 28.74 (t); 30.34 (t); 32.68 (s); 37.49 (d); 37.50 (t); 41.24 (t); 42.82 (d); 50.02 (d); 108.39 (t); 149.61 (s); 214.31 (s). HRMS: calcd (M^+) *m/e* 220.1827; found *m/e* 220.1825. $[\alpha]_D$ = +38.2 (c = 0.5).
A mixture of 1.01 g (4.59 mmol) of the above mentioned ketone, 2 g (20 mmol) of triethylamine and 2.1 g (20 mmol) of chlorotrimethylsilane in 50 ml of N,N-dimethylformamide was heated under nitrogen at 130 °C for 16 h. After cooling to room temperature 50 ml of saturated aqueous sodium bicarbonate and 50 ml of ether were added. The aqueous layer was extracted with ether (3 x 50 ml). The combined organic layers were washed with brine and dried on $MgSO_4$. Column chromatography (eluent PE) yielded 1.21 g (4.14 mmol, 90%) of **109** as a colourless oil.
^{1}H NMR: δ 0.15 (s, 9H); 0.97 (s, 3H); 1.52 (m, 3H); 1.97 (s, 3H); 0.9 - 1.2 (m, 3H); 1.3 - 2.3 (m, 9H); 4.67 (s, 2H). ^{13}C NMR: δ 0.48 (q*3); 13.32 (q); 20.99 (q); 26.46 (t);26.89 (q); 27.07

(t); 29.56 (t); 30.79 (t); 31.19 (s); 35.72 (t); 39.78 (d); 43.88 (d); 107.89 (t); 113.40 (s); 143.24 (s); 150.30 (s). HRMS: calcd (M^+) *m/e* 292.2222; found *m/e* 292.2220. $[\alpha]_D$= +36.9 (c = 0.5).

(4aS,7R)-1,4a-Dimethyl-4,4a,5,6,7,8-hexahydro-7-isopropenyl-naphthalene-2(1H)-one (95) and (4aS,7R)-1,4a-Dimethyl-7-isopropenyl-5,6,7,8-quatrohydronaphthalene-2(4aH)-one (110)

To 0.91 g (4 mmol) of dichlorodicyanoquinone in 20 ml of benzene was added 1.00 g (3.42 mmol) of **109** in 25 ml of benzene at room temperature under a nitrogen atmosphere. The solution was stirred and after 1 h the reaction mixture was quenched with water and extracted with ether (3 x 50 ml). The combined ether layers were washed with water (2 x 10 ml) and with brine (1 x 10 ml). After drying, filtration and evaporation of the ether the residue was purified by flash chromatography (eluent PE/EtOAc = 19/1) This gave 0.65 g (2.98 mmol, 87%) of (+)-α-cyperone (**95**) and 0.060 g (0.28 mmol, 8%) of **110** as colourless oils.

95: ^{1}H NMR: δ 1.19 (s, 3H); 1.76 (s, 6H); 1.0 - 2.9 (m, 11H); 4.74 (s, 2H). ^{13}C NMR: δ 10.89 (q); 20.63 (q); 22.45 (q); 26.84 (t); 32.87 (t); 33.76 (t); 35.77 (s); 37.40 (t); 41.87 (t); 45.86 (d); 109.15 (t) 128.77 (s); 149.11 (s); 162.13 (s); 199.08 (s). HRMS: calcd (M^+) *m/e* 218.1670; found *m/e* 218.1671. $[\alpha]_D$ = + 91.1 (c = 0.7).

110: ^{1}H NMR: δ 1.17 (s, 3H); 1.75 (s, 3H); 1.87 (s, 3H); 1.1 - 2.0 (m, 6H); 2.14 (t, J = 12.5 Hz, 1H); 2.70 - 2.85 (m, 1H); 4.76 (s, 2H); 6.19 (d, J = 10 Hz, 1H); 6.71 (d, J = 10 Hz, 1H). ^{13}C NMR: δ 10.30 (q); 20.55 (q); 23.27 (q); 25.97 (t); 32.59 (t); 37.61 (t); 39.97 (s); 46.32 (d); 109.28 (t); 125.90 (d); 129.03 (s); 148.28 (s); 156.36 (d); 159.45 (s); 186.21 (s). HRMS: calcd (M^+) *m/e* 216.1514; found *m/e* 216.1513. $[\alpha]_D$ = −149.0 (c = 0.1).

2.5 References and Notes

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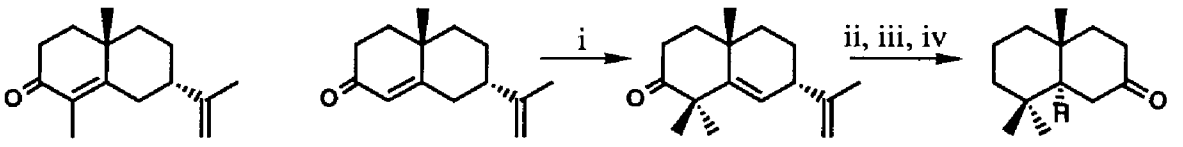
3 The Syntheses of Chiral Decalones, (-)-1,1,4a-Trimethyl-2-Decalol and (+)-Geosmin from S-(+)-Carvone*

3.1 Introduction

The chiral decalones **33** and **96** can be obtained in good yield from S-(+)-carvone *via* the Robinson annulation of its lithium-bronze reduction product with methyl vinyl ketone[1] and ethyl vinyl ketone[2], respectively. In this chapter, these chiral intermediates are further transformed into biologically active compounds and into other interesting intermediates. Decalone **33**, was previously dimethylated to **34** and then by a Wolff-Kishner, ozonolysis and conjugate reduction sequence converted into **36** (scheme 3.1)[1].

Scheme 3.1



96 33 34 36

Reagents i: MeI, *t*-BuOK; ii: N_2H_4, KOH, 200 °C; iii: O_3, Me_2S; iv: Li/NH_3.

Now an approach to the decalones **111** an **112** (figure 3.1) from intermediate **36** is given. Decalone **111** is a famous target molecule in perfumery and also a suitable starting material for the synthesis of other fragrance chemicals[3]. Decalone **112** is an important intermediate in the synthesis of several drimanes and drimane-related natural products[4]. Intermediate **34** is only a few steps away from (-)-decalol **113**, a known inhibitor of the cholesterol biosynthesis[5]. (+)-Geosmin (**97**), the enantiomer of the natural (-)-geosmin, can be synthesized from intermediate **96**. (-)-Geosmin can be isolated from actinomycetes and it is the main odor component of freshly plowed soil[6]. (+)-Geosmin (**97**) also shows an earthy smelling odor.

Figure 3.1

111 112 113 97

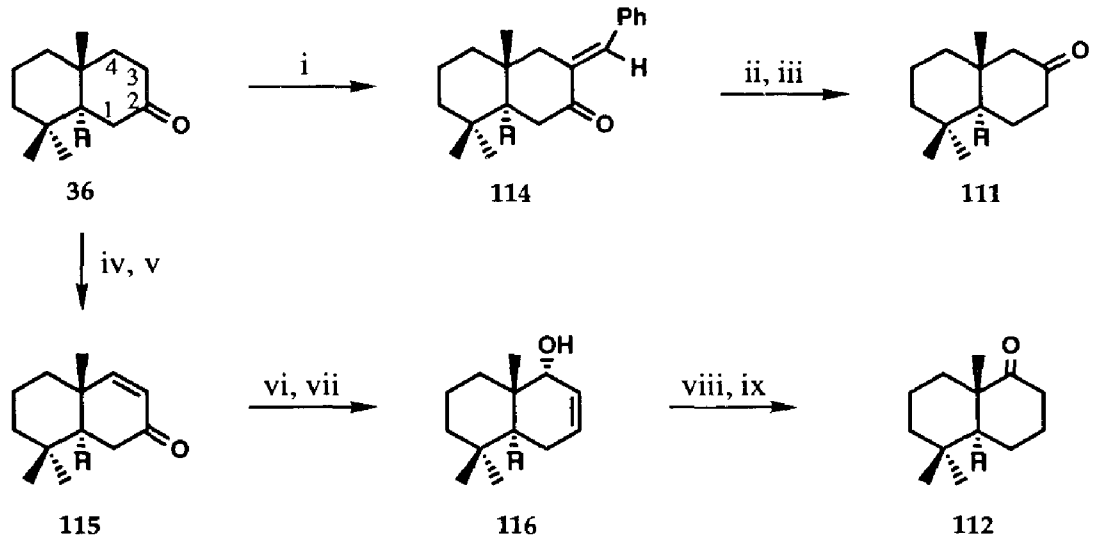
* This chapter has been published in a revised form: Swarts, H. J.; Haaksma, A. A.; Jansen, B. J. M.; de Groot, Ae. *Tetrahedron* **1992**, *48*, 5497-5508.

3.2 Synthesis of the chiral decalones 111 and 112

With ketone **36** in hand, the decalones **111** and **112** were synthesised via a 1,2[7]- and a 1,3[8]-carbonyl transposition, respectively (scheme 3.2). The 3-position of ketone **36** was functionalized by benzylidation with benzaldehyde under basic conditions. This crystalline benzylidene derivative **114** was reduced with a mixture of lithium aluminum hydride and aluminum chloride in ether to afford a mixture of double bond isomers which was submitted to ozonolysis without further purification. The desired ketone **111** was obtained as the only product though in a moderate 17% yield from **36**.

For the 1,3-carbonyl transposition, ketone **36** was brominated with pyridinium bromide perbromide (PBB) in acetic acid to give a crystalline α-bromo ketone in 82% yield[9]. Dehydrobromination in DMF at 120 °C gave the enone **115** in 93% yield[10]. The epoxidation of the olefinic bond in **115** afforded stereoselectively an α-epoxy ketone which was reduced to the α,β-unsaturated alcohol **116** in 94% yield by a Wharton-reduction[11]. Oxidation of **116** followed by catalytic reduction of the double bond finally gave **112** in an overall yield of 45% from **36**.

Scheme 3.2

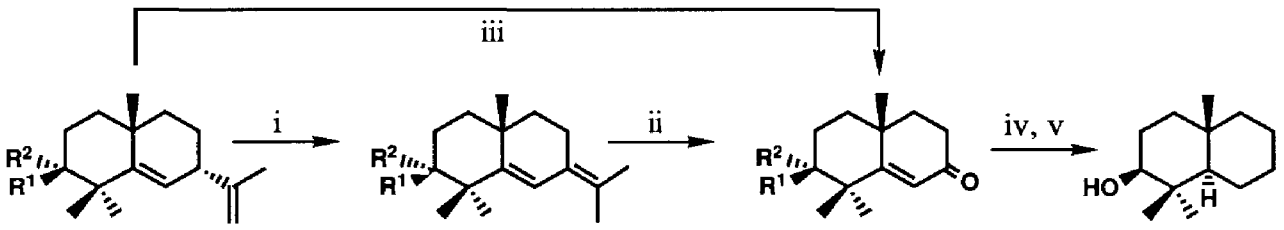


Reagents i: PhCHO, NaOH; ii: $LiAlH_4$, $AlCl_3$; iii: O_3, thiourea; iv: PBB, HOAc; v: LiBr, Li_2CO_3, DMF, 120 °C; vi: H_2O_2, NaOH; vii: H_2NNH_2, HOAc; viii: PDC; ix: H_2,10% Pd/C.

3.3 Synthesis of the cholesterol inhibitor (-)-1,1,4a-Trimethyl-2-decalol 113

The synthesis of enantiomerically pure decalol (-)-**113** from intermediate **34** was carried out as depicted in scheme 3.3. The carbonyl functionality of **34** was reduced with lithium aluminum hydride to give alcohol **117** in 90% yield. The transformation of the isopropenyl group, the former chiral handle, into a carbonyl group *via* isomerisation of the isopropenyl sidechain followed by selective ozonolysis of the exocyclic double bond[1] was also performed for ketone **34** and acetal **118**. The extreme conditions for the isomerization of the isopropenyl group to an isopropylidene group (potassium hydroxide, diethylene glycol, 200 °C) proved to be compatible with the hydroxy and acetal group in **117** and **118** and gave the dienes **120** and **121** in 98% and 90%, respectively. Ketone **34** was more vulnerable to the isomerization conditions and the carbonyl group gave rise to incomplete reactions and competing aldol condensations. The yield of diene **119** was therefore just 55%. The resulting dienes **119, 120** and **121** are rather unstable compounds and the selective ozonolyses should be carried out instantaneously to give the unsaturated ketones **122, 123** and **124** in a yield of 65%, 63% and 65%, respectively.
The isopropenyl group of **34** and **117** was also removed *via* ozonolysis in methanol at -78 °C followed by decompositon of the intermediate methoxy hydroperoxides with cupric acetate and ferrous sulfate[12] to afford the compounds **122** and **123** in one step in a yield of 26% and 47%, respectively.

Scheme 3.3



34: R^1, R^2 = =O
117: R^1 = OH, R^2 = H
118: R^1, R^2 = O-CH_2-CH_2-O

119: R^1, R^2 = =O
120: R^1 = OH, R^2 = H
121: R^1, R^2 = O-CH_2-CH_2-O

122: R^1, R^2 = =O
123: R^1 = OH, R^2 = H
124: R^1, R^2 = O-CH_2-CH_2-O

113

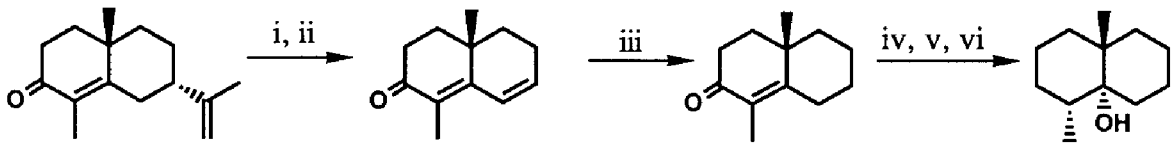
Reagents i: KOH, DEG, 200 °C; ii: O_3, thiourea; iii: O_3, MeOH; $Cu(OAc)_2$, $FeSO_4$; iv: Li/NH_3, t-BuOH; v: H_2NNH_2, KOH, DEG, 200 °C

The dissolving metal reduction[13] of **123** gave the *trans*-decaline in a yield of 81%. The following Wolff-Kishner reduction gave the inhibitor of the cholesterol biosynthesis (-)-**113** in a yield of 81%. The overall yield of (-)-**113** was 38% from **34**.

3.4 Synthesis of (+)-geosmin (97)

The Criegee rearrangement was used to remove the isopropenyl group in the reaction sequence to (+)-geosmin (**97**) (scheme 3.4). Compound **96**, obtained *via* a Robinson annulation of (-)-dihydrocarvone **30** with ethyl vinyl ketone[2], was submitted to ozonolysis in methanol followed by the addition of acetic anhydride, triethylamine and 4-N,N-dimethylaminopyridine[14]. The resulting δ-acetoxy-α,β-unsaturated ketone was treated with sodium methoxide to give the dienone **125** in 74% yield. Conjugate reduction of **125** with lithium-selectride[1] in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) gave enone **126** in a yield of 77%. Enone **126** was converted into (+)-geosmin (**97**) using the procedure of Gosselin[6f]. (+)-Geosmin was obtained in this way from S-(+)-carvone in 12% overall yield.

Scheme 3.4



96 125 126 97

Reagents i: O_3, MeOH; Ac_2O, Et_3N, DMAP; ii: $NaOCH_3$; iii: Li-selectride, DMPU; iv: *m*-CPBA; v: $NaBH_4$; vi: TsCl, py; $LiAlH_4$, Δ.

3.5 Experimental Section

General experimental conditions were as described in chapter 2

(4aR,8aS)-3(E)-Benzylidene-3,4,4a,5,6,7,8,8a-octahydro-4a,8,8-trimethyl-naphthalen-2(1H)-one (114)

To a solution of 0.73 g (3.76 mmol) of **36**[1] in 25 mL of absolute ethanol was added 1.0 g (9.4 mmol) of benzaldehyde and a solution of 0.15 g (2.7 mmol) of potassium hydroxide in 15 ml of absolute ethanol. The reaction mixture was stirred overnight at room temperature. After evaporation of the solvent, water and dichloromethane were added. The aqueous layer was extracted with dichloromethane. The combined dichloromethane layers were washed with water and brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (eluent PE/EtOAc = 97/3) to yield 0.70 g (66%) of **114** as pale

yellow crystals which were recrystallized from ethanol, mp: 94 - 100 °C.
^{1}H NMR: δ 0.87 (s, 9H); 1.1 - 1.7 (m, 7H); 2.2 - 2.8 (m, 4H); 7.37 (m, 5H); 7.54 (dd, J = 1,0 Hz, 3.1 Hz, 1H). MS: *m/e* (%): 282 (M^+, 100), 159 (22), 123 (32), 117 (21), 116 (48), 115 (35), 91 (17), 41 (30). HRMS: calcd (M^+) *m/e* 282.1983; found *m/e* 282.1982. Anal: calcd for $C_{20}H_{26}O$: C, 85.05; H, 9.28; found: C, 84.78; H, 9.24. $[\alpha]_D$ = +180 (c = 0.65).

(4aS,8aR)-3,4,4a,5,6,7,8,8a-Octahydro-5,5,8a-trimethyl-naphthalen-2(1H)-one (111)
A mixture of 0.66 g (4.9 mmol) of aluminum chloride and 0.19 g (4.9 mmol) of lithium aluminum hydride in 25 ml of dry ether was stirred for 15 min at room temperature. A solution of 0.70 g (2.48 mmol) of **114** and 0.33 g (2.48 mmol) of aluminum chloride in 25 ml of dry ether was added dropwise. The reaction mixture was stirred for 15 min and then refluxed for an additional 30 min. After cooling the excess of lithium aluminum hydride was destroyed with 1 ml of water and 1 ml of aqueous 4 M sodium hydroxide and $MgSO_4$ were added. The solvent was filtered and evaporated *in vacuo* and the residue was filtered over silicagel (eluent PE). The solvent was evaporated *in vacuo* and the residue was dissolved in 30 ml of methanol and 10 ml of dichloromethane. The solution was cooled to -80 °C and ozonized. When the reaction was finished, 0.20 g (2.6 mmol) of thiourea was added and the mixture was allowed to come to room temperature and stirred for an additional hour. The solvents were evaporated under reduced pressure and the residu was dissolved in dichloromethane and washed with water and brine. The solvent was dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by flash chromatography (eluent PE/EtOAc = 98/2) to yield 121 mg (25%) of **111** as white crystals, mp: 89 - 91 °C; (Lit[3b]: 88 - 90 °C).
^{1}H NMR: δ 0.83 (s, 3H); 0.87 (s, 3H); 0.94 (s, 3H); 1.2 - 1.7 (m, 7H); 1.9 - 2.5 (m, 6H). HRMS: calcd (M^+) *m/e* 194.1670; found *m/e* 194.1674. [a]$_D$ = -81.0 (c = 0.37), (Lit[3b]: $[\alpha]_D$ = -86.1).

(4aS,8aS)-4a,5,6,7,8,8a-Hexahydro-4a,8,8-trimethyl-naphthalen-2(1H)-one (115)
To a stirred solution of 2.12 g (10.9 mmol) of **36**[1] in 40 ml of acetic acid at room temperature was added 3.8 g (11.9 mmol) of pyridinium bromide perbromide. The orange reaction mixture was stirred for 3 h and then water was added. After the usual work up the residue was purified by flash chromatography (eluent PE/EtOAc = 95/5) to give 2.45 g (82%) of a white solid which was recrystallized from ethanol to give white needles of *(3S,4aR,8aS)-3-bromo-3,4,4a,5,6,7,8,8a-octahydro-4a,8,8-trimethyl-naphthalen-2(1H)-one,* mp 145 - 148 °C.
^{1}H NMR: δ 0.81(s, 3H); 0.83 (s, 3H); 1.16 (s, 3H); 1.0 - 1.9 (m, 8H); 2.1 - 2.4 (m, 2H); 2.66

(dd, J = 3 Hz, 14 Hz, 1H); 4.74 (dd, J = 6 Hz, 13 Hz, 1H). MS: *m/e* (%): 274 (M^+, 18), 272 (18), 193 (33), 164 (79), 162 (78), 109 (45), 95 (37), 81 (66), 70 (46), 69 (82), 67 (50), 55 (94), 41 (100). HRMS: calcd (M^+) *m/e* 272.0776; found *m/e* 272.0779. Anal: calcd for $C_{13}H_{21}BrO$: C, 57.14; H, 7.74; found: C, 56.86; H, 7.70. $[\alpha]_D = -19.9$ (c = 0.52).

A suspension of 1.0 g (11.5 mmol) of lithium bromide and 1.42 g (19.2 mmol) of lithium carbonate in 25 ml of dry dimethylformamide was heated to 120 °C. To this mixture was added 2.1 g (7.7 mmol) of the bromide. The temperature was kept at 120 °C for 2 h. The reaction mixture was cooled to room temperature, diluted with water and extracted with dichloromethane. The combined organic layers were washed with water and brine and dried over $MgSO_4$, filtered and evaporated *in vacuo*. The yellow residue was submitted to flash chromatography (eluent PE/EtOAc = 95/5) to give 1.37 g (93%) of **115** as a colourless oil.

^1H NMR: δ 0.85 (s, 3H); 0.88 (s, 3H); 1.06 (s, 3H); 1.1 - 1.8 (m, 7H); 2.3 - 2.4 (m, 2H); 5.72 (d, J = 10 Hz, 1H); 6.60 (d, J = 10 Hz, 1H). MS: *m/e* (%) 192 (M^+, 27), 150 (90), 135 (44), 109 (40), 95 (47), 79 (51), 69 (87), 67 (47), 55 (44), 41 (100), 39 (50). HRMS: calcd (M^+) *m/e* 192.1514; found*m/e* 192.1511. $[\alpha]_D = +9.2$ (c = 1.2).

(1R,4aS,8aS)-1,4,4a,5,6,7,8,8a-Octahydro-5,5,8a-trimethyl-naphthalen-1-ol (116)

To a solution of 1.0 g (5.2 mmol) of **115** in 25 ml of methanol was added 1.36 ml (1.66 g; 16 mmol) of aqueous 35% hydrogen peroxide and 0.45 ml (2.7 mmol) of aqueous 6 M sodium hydroxide. The reaction mixture was stirred at room temperature for 1.5 h. After the usual work up a yellow oil was obtained which was purified by flash chromatography (eluent PE/EtOAc = 95/5) to give 0.82 g (76%) of *(3S,4S,4aS,8aS)-3,4-epoxy-3,4,4a,5,6,7,8,8a-octahydro-4a,8,8-trimethyl-naphthalen-2(1H)-one* as a colourless oil, which solidified on standing, mp 74 - 75 °C.

^1H NMR: δ 0.80 (s, 6H); 0.92 (s, 3H); 1.1 - 1.7 (m, 6H); 1.8 - 2.1 (m, 2H); 2.36 (dd, J = 5,2 Hz, 1H); 3.03 (d, J = 4 Hz, 1H); 3.22 (d, J = 4 Hz, 1H). MS: *m/e* (%) 208 (M^+, 1), 147 (32), 123 (33), 109 (43), 107 (25), 95 (44), 93 (25), 81 (41), 79 (26), 69 (57), 67 (41), 55 (43), 43 (33), 41 (100), 39 (40). HRMS: calcd (M^+) *m/e* 208.1463; found *m/e* 208.1456. Anal: calcd for $C_{13}H_{20}O_2$: C, 74.95; H, 9.67; found: C, 74.78; H, 9.84. $[\alpha]_D = -122$ (c = 0.85).

A solution of 0.80 g (3.84 mmol) of the epoxide in 25 ml of methanol was cooled to 0 °C. To this solution 0.55 ml (11.5mmol) of hydrazine hydrate was added dropwise. After stirring for 20 min 50 ml of acetic acid was added and stirring was continued for 1 h. Water was added and the mixture was extracted with ether. The combined ethereal layers were washed with water, saturated aqueous sodium bicarbonate and brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by flash chromatography (eluent PE/EtOAc = 93/7) to give 0.70 g (94%) of **116** as a

white solid, mp 82 - 87 °C.
^{1}H NMR: δ 0.79 (s, 3H); 0.86 (s, 3H); 0.88 (s, 3H); 1.1 - 2.1 (m, 10H); 3.24 (d, J = 5 Hz, 1H); 5.7 - 5.9 (m, 2H). MS: *m/e* (%) 194 (M^+, 8), 124 (36), 109 (100), 81 (21), 70 (74), 55 (25), 41 (39). HRMS: calcd (M^+) *m/e* 194.1671; found *m/e* 194.1677. Anal: calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41; found: C, 79.97; H, 11.49. $[\alpha]_D$ = -168 (c=0.65).

4aS,8aS)-3,4,4a,5,6,7,8,8a-Octahydro-5,5,8a-trimethyl-naphthalen-1(2H)-one (112)
To a stirred solution of 445 mg (2.29 mmol) of **116** in 25 ml of dichloromethane was added 1.30 g (3.44 mmol) of pyridinium dichromate. The orange reaction mixture was stirred overnight at room temperature. The mixture was diluted with dichloromethane and filtered over anhydrous $MgSO_4$ and silicagel. Evaporation of the solvent *in vacuo* yielded 410 mg (92%) of the desired *(4aS,8aS)-4a,5,6,7,8,8a-hexahydro-5,5,8a-trimethyl-naphthalen-1(4H)-one* as a colourless oil, which solidified on standing, mp 30 - 34 °C.
^{1}H NMR: δ 0.86 (s, 3H); 0.93 (s, 3H); 1.01(s, 3H); 1.0 - 1.6 (m, 6H); 1.7 - 1.9 (m, 1H); 2.1 - 2.4(m, 2H); 5.80 (ddd, J = 1.5 Hz, 2.5 Hz, 10 Hz, 1H); 6.84 (m, 1H). MS: *m/e* (%) 192 (M^+, 28), 177 (29), 109 (100), 91 (24), 81 (25), 79 (36), 68 (36), 55 (39), 41 (72), 39 (51). HRMS: calcd (M^+) *m/e* 192.1514; found *m/e* 192.1515. Anal: calcd for $C_{13}H_{20}O$: C, 81.19; H, 10.48; found: C, 81.04; H, 10.68. $[\alpha]_D$ = -49.9 (c = 0.88).
To a stirred solution of 380 mg (1.98 mmol) of the above obtained enone in 25 ml of methanol was added 25 mg of 10% palladium on activated carbon, and the solution was purged with hydrogen and stirred for 1 h. The reaction mixture was filtered through hyflo and the solvent was evaporated *in vacuo*. The residue was purified by flash chromatography (eluent PE/EtOAc = 96/4) to give 355 mg (92%) of **112** as a colourless oil.
^{1}H NMR: δ 0.85(s, 3H); 0.88(s, 3H); 1.12(s, 3H); 1.3 - 1.8 (m, 7H); 2.0 - 2.2 (m, 4H); 2.55 (m, 2H). MS: *m/e* (%) 194 (M^+, 51), 179 (37), 161 (60), 123 (76), 111 (48), 109 (50), 95 (64), 81 (55), 69 (57), 67 (80), 55 (80), 41 (100). HRMS: calcd (M^+) *m/e* 194.1670; found *m/e* 194.1672. $[\alpha]_D$ = -40.0 (c = 1.1), (Lit[4c]: $[\alpha]_D$ = -39.1).

(2S,4aS,7S)-7-Isopropenyl-1,2,3,4,4a,5,6,7-octahydro-1,1,4a-trimethyl-naphthalen-2-ol (117)
To a stirred suspension of 0.27 g (7,0 mmol) of lithium aluminum hydride in dry ether was added dropwise a solution of 2.0 g (13.4 mmol) of **34**[1] in 50 ml of dry ether. The mixture was stirred for 1 h, then 0.45 ml of water and 0.45 ml of aqueous 4 M sodium hydroxide were added. This mixture was stirred for 15 min and another 0.45 ml of water was added and stirring was continued for an additional 30 min. The

solvent was dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by flash chromatography (eluent PE/EtOAc = 9/1) to give 1.82 gram (90%) of **117** as a white solid, mp 90 - 92 °C.
^{1}H NMR: δ 1.03 (s, 3H); 1.13 (s, 3H); 1.14 (s, 3H); 1.73 (s,3H); 0.8 - 1.9 (m, 9H); 2.63 (m, 1H); 3.24 (dd, J = 5,1 Hz, 1H); 4.54 (br.s, 1H); 4.76 (br.s, 1H); 5.42 (d, J = 6 Hz, 1H); MS: *m/e* (%) 234 (M^+, 24), 216 (95), 201 (100), 148 (41), 135 (79), 133 (41), 121 (38), 108 (48), 93 (38). HRMS: calcd (M^+) *m/e* 234.1983; found *m/e* 234.1992. Anal: calcd. for $C_{16}H_{26}O$: C,81.99; H, 11.18; found: C, 82.01; H, 11.10. $[\alpha]_D = -125$ (c = 0.85).

(4aS,7S)-2,2-(Ethylenedioxy)-7-isopropenyl-1,2,3,4,4a,5,6,7-octahydro-1,1,4a-trimethyl-naphthalene (118)
A mixture of 2.0 g (8.6 mmol) of **34**[1] and 100 mg of *p*-toluenesulfonic acid and 4.9 ml (86 mmol) of ethylene glycol in 150 ml of benzene was refluxed for 21 h using a Dean-Stark apparatus. The reaction mixture was washed with saturated aqueous sodium bicarbonate and brine and dried over $MgSO_4$. The solvent was filtered and evaporated and the residue was purified by flash chromatography (eluent PE/ether = 98/2) to give 1.90 g (80%) of **118** as a colourless oil.
^{1}H NMR: δ 1.04 (s, 3H); 1.20 (s, 6H); 1.76 (s, 3H); 1.0 - 2.3 (m, 8H); 2.5 - 2.8 (m, 1H); 3.91 (s, 4H); 4.68 (br.s, 1H); 4.79 (br.s, 1H); 5.37 (d, J = 5 Hz, 1H). MS: *m/e* (%) 276 (M^+, 5), 261 (0.3), 135 (1), 119 (12), 105 (8), 99 (100), 91 (5). HRMS : calcd (M^+) *m/e* 276.2089; found *m/e* 276.2086. $[\alpha]_D = -139$ (c = 3.7).

(4aS)-7-Isopropylidene-3,4,4a,5,6,7-hexahydro-1,1,4a-trimethyl-naphthalene-2(1H)-one (119)
A solution of 1.81 g (7.8 mmol) of ketone **34**[1] and 0.68 g (12 mmol) of potassium hydroxide in 30 ml of diethylene glycol was heated under nitrogen at 200 °C. After 15 min the reaction mixture was poured into 200 ml of water and worked up as usual. The residue was purified by flash chromatography (eluent PE/EtOAc = 96/4) to afford 1.13 g (55%) of **119** as a colourless oil.
^{1}H NMR: δ 1.03 (s, 3H); 1.27(s, 6H); 1.73 (s, 3H); 1.80 (s, 3H); 0.8 - 2.7 (m, 8H); 6.38 (s, 1H); MS: *m/e* (%) 232 (M+, 100), 217 (70), 189 (78), 161 (35), 146 (38), 133 (45), 119 (38), 105 (33), 91 (32), 55 (28), 41 (44). HRMS: calcd (M^+) *m/e* 232.1827; found *m/e* 232.1831. $[\alpha]_D = -55.7$ (c = 1.0).

(2S,4aS)-7-Isopropylidene-1,2,3,4,4a,5,6,7-octahydro-1,1,4a-trimethyl-naphthalen-2-ol (120)
To a solution of 4.74 g (20.2 mmol) of **117** in 150 ml of diethylene glycol was added 3.42 g (61 mmol) of potassium hydroxide. The reaction mixture was heated under nitrogen at 200 °C for 2.5 h. The mixture was allowed to cool and 75 ml of water was added. The reaction mixture was neutralized with aqueous 4 M hydrochloric acid and the solution was extracted with ether. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by flash chromatography (eluent PE/EtOAc = 9/1) to give 4.65 g (98%) of **120** as a yellow oil.
^{1}H NMR: δ 1.03 (s, 3H); 1.12 (s, 3H); 1.20 (s, 3H); 1.70 (s, 3H); 1.78 (s, 3H); 0.7 - 2.5 (m, 9H); 3.20 (dd, J = 5,1 Hz, 1H); 6.40 (s, 1H). MS: *m/e* (%) 234 (M^+, 100), 219 (21), 201 (60), 177 (55), 148 (51), 85 (57), 83 (83). HRMS: calcd (M^+) *m/e* 234.1983; found *m/e* 234.1982. $[\alpha]_D$ = −96 (c = 1.3).

(4aS)-2,2-(Ethylenedioxy)-7-isopropylidene-1,2,3,4,4a,5,6,7-octahydro-1,1,4a-trimethyl-naphthalene (121)
A solution of 0.98 g (3.6 mmol) of **118** and 0.68 g (12 mmol) of potassium hydroxide in 30 ml of diethylene glycol was heated at 200 °C under a nitrogen atmosphere for 15 min. The mixture was poured into 100 ml of water and neutralized with aqueous 4 M hydrochloric acid. The mixture was extracted with ether. The combined etheral layers were washed with water and brine and dried over calcium chloride, filtered and evaporated *in vacuo*. The crude oil was submitted to flash chromatography (eluent PE/ether = 98/2) to give 0.88 g (90%) of **121** as a colourless oil.
^{1}H NMR: δ 1.12 (s, 3H); 1.20 (s, 3H); 1.23 (s, 3H); 1.72 (s, 3H); 1.79 (s, 3H); 0.9 - 2.5 (m, 8H); 3.93 (s, 4H); 6.38 (s, 1H). MS: *m/e* (%) 276 (M^+, 6); 261 (7), 177 (1), 162 (3), 99 (100), 91 (100). HRMS: calcd (M^+) *m/e* 276.2089; found *m/e* 276.2084. $[\alpha]_D$ = −105 (c = 4.0).

(4aS)-1,3,4,4a,5,6-Hexahydro-1,1,4a-trimethyl-naphthalen-2,7-dione (122)
A solution of 1.16 g (5.0 mmol) of **119** in 50 ml of methanol was ozonized at −80 °C untill a pale blue colour appeared. The excess of ozone was expelled by a stream of nitrogen and 0.21 g (2.8 mmol) of thiourea was added. After being stirred for 3 h at room temperature the reaction mixture was concentrated *in vacuo* and dissolved in water and worked up as usual to give after flash chromatography (eluent PE/ether = 7/3) 0.67 g (65%) of the dienone **122** as an oil.
^{1}H NMR: δ 1.20 (s, 3H); 1.32 (s, 6H); 1.4 - 3.0 (m, 8H); 5.97 (s, 1H). MS: *m/e* (%) 206 (M^+, 100), 191 (18), 178 (23), 163 (19), 152 (44), 151 (41), 135 (26), 123 (49), 107 (26), 70 (60). HRMS : calcd (M^+) *m/e* 206.1307; found *m/e* 206.1303. $[\alpha]_D$ = −23 (c = 0.45).

A solution of 710 mg (3.0 mmol) of **34**[1] in 50 ml of methanol was cooled to -80 °C and ozonized untill a pale blue colour appeared and the solution was purged with nitrogen to remove the excess of ozone. To this mixture was added 1.2 g (6.0 mmol) of cupric acetate monohydrate and 850 mg (3 mmol) of ferrous sulfate heptahydrate. The reaction mixture was allowed to come to room temperature and was stirred for an additional 2 h. The solvent was evaporated *in vacuo* and water and aqueous 1 M hydrochloric acid were added. The aqueous layer was worked up as usual. The residue was purified by flash chromatography (eluent PE/EtOAc = 17/3) to give 163 mg (26%) of **122** as an oil, which solidified on standing, with all data corresponding to the above mentioned.

(4aR,7S)-7-Hydroxy-4,4a,5,6,7,8-hexahydro-4a,8,8-trimethyl-naphthalen-2(3H)-one (123)
A stirred solution of 1.95 g (8.3 mmol) of **120** in 50 ml of methanol was cooled to -80 °C and ozonized untill a pale blue colour appeared. The excess of ozone was removed by flushing with nitrogen and 0.80 g (10.5 mmol) of thiourea was added. The reaction mixture was stirred for 3 h at room temperature. The methanol was partly evaporated *in vacuo* and water was added followed by the usual work up procedure. The residue was purified by flash chromatography (eluent PE/EtOAc = 3/1) to give 1.10 g (63%) of **123** as a colourless oil.
^{1}H NMR: δ 1.02 (s, 3H); 1.12 (s, 3H); 1.23 (s, 3H); 0.9 - 2.6 (m, 8H); 2.81 (br.s, 1H); 3.32 (dd, J = 5,1 Hz, 1H); 5.90 (s, 1H). MS: *m/e* (%) 208 (M^+, 41), 193 (50), 152 (100), 123 (48), 109 (41), 43 (39). HRMS: calcd (M^+) *m/e* 208.1462; found *m/e* 208.1461. $[\alpha]_D$ = -76.6 (c = 3.0).

A solution of 234 mg (1.0 mmol) of **117** in 25 ml of methanol was cooled to -80 °C and ozonized untill a pale blue colour appeared and the solution was purged with nitrogen to remove the excess of ozone. To this mixture was added 400 mg (2.0 mmol) of cupric acetate monohydrate and 330 mg (1.2 mmol) of ferrous sulfate heptahydrate. The reaction mixture was allowed to come to room temperature and was stirred for an additional 2 h. The solvent was evaporated *in vacuo* and water and aqueous 1 M hydrochloric acid were added. The aqueous layer was worked up as usual. The residue was purified by flash chromatography (eluent PE/EtOAc = 3/1) to give 97 mg (47%) of **123** as a colourless oil, with all data corresponding to the above mentioned.

(4aS)-7,7-(Ethylenedioxy)-4,4a,5,6,7,8-hexahydro-4a,8,8-trimethyl-naphthalen-2(3H)-one (124)

A solution of 2.32 g (10.0 mmol) of **121** in 50 ml of methanol was ozonized at -80 °C untill a light blue colour appeared. The excess of ozone was expelled by a stream of nitrogen and 0.42 g (5.6 mmol) of thiourea was added. After being stirred for 3 h at room temperature the reaction mixture was concentrated *in vacuo*. The residue was dissolved in water and worked up as usual to give after flash chromatography (eluent PE/EtOAc = 1/1) 1.34 g (65%) of the enone **124** as a colourless oil.
^{1}H NMR: δ 1.10 (s, 3H); 1.27 (s, 3H); 1.38 (s, 3H); 1.4 - 2.8 (m, 8H); 3.96 (br.s, 4H); 5.95 (s, 1H). MS: *m/e* (%) 250 (M^+, 2), 235 (4), 99 (100). HRMS: calcd (M^+) *m/e* 250.1569; found *m/e* 250.1571. $[\alpha]_D = -90$ (c = 2.3).

(2S,4aS,8aR)-Perhydro-1,1,4a-trimethyl-naphthalen-2-ol (113)

To a solution of 10 mg of lithium in 4 ml of ammonia was added 10 ml of dry ether. A solution of 208 mg (1.0 mmol) of **123** in 5 ml of dry ether was added dropwise. After 15 min solid ammonium chloride was added and the ammonia was allowed to evaporate. Water was added and the mixture was worked up as usual. The crude product was purified by flash chromatography (eluent PE/EtOAc = 17/3) to give 170 mg (81%) of *(4aR,7S,8aR)-7-Hydroxy-3,4,4a,5,6,7,8,8a-octahydro-4a,8,8-trimethyl-naphthalen-2(1H)-one* as a white solid, mp 88 - 90 °C, (Lit[5d]: 91.6 - 92 °C).
^{1}H NMR: δ 0.78 (s, 3H); 0.91 (s, 3H); 1.10 (s, 3H); 1.0 - 1.8 (m, 7H); 2.1 - 2.5 (m, 5H); 3.22 (dd, J = 7,9 Hz, 1H); MS: *m/e* (%) 210 (M^+, 100), 167 (44), 111 (35), 97 (48), 69 (36). HRMS: calcd (M^+) *m/e* 210.1620; found *m/e* 210.1618. $[\alpha]_D = -4.9$ (c = 0.81), (Lit[5d]: $[\alpha]_D = -5.2$).
A solution of 140 mg (0.66 mmol) of the above mentioned hydroxy ketone in 12 ml of diethylene glycol and 0.6 mL of hydrazine hydrate was heated at 150 °C under a nitrogen atmosphere for 1.5 h, after which 0.75 g (13.4 mmol) of potassium hydroxide was added. The excess hydrazine was removed by distillation and the reaction was heated at 210 °C for 2 h. The solution was cooled, poured into ice water and extracted three times with dichloromethane. The combined dichloromethane layers were washed with aqueous 1 M hydrochloric acid, water, aqueous sodium bicarbonate and brine. The solvent was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 105 mg (81%) of **113** as a white solid, mp 85 - 87 °C. (Lit[5d]: 86.5 - 87.4 °C).
^{1}H NMR: δ 0.70 (s, 3H); 0.86 (s, 3H); 0.90 (s, 3H); 0.7 - 1.8 (m, 14H); 3.17 (dd, J = 7,9 Hz, 1H); HRMS: calcd (M^+) *m/e* 196.1827; found *m/e* 196.1828. $[\alpha]_D = -9.4$ (c = 0.32), (Lit[5d]: $[\alpha]_D = -11.3$).

(4aS)-4,4a,5,6-Tetrahydro-1,4a-dimethyl-naphthalen-2(3H)-one (125)

A stirred solution of 12.2 g (55.9 mmol) of **96**[2] in a mixture of 170 ml of dichloromethane and methanol (5:1) was cooled to -80 °C and ozonized untill a pale blue colour appeared. The mixture was treated with 75 ml (795 mmol) of acetic anhydride, 75 ml (536 mmol) of triethylamine and 0.3 g of 4-N,N-dimethylaminopyridine. The reaction mixture was allowed to come to 0 °C and stirred for an additional 2 h. The solution was poured into aqueous 1 M hydrogen chloride and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with water and saturated aqueous sodium bicarbonate. The solvent was dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was dissolved in 50 ml of methanol, and 150 ml of 1M sodium methoxide was added. After stirring for 15 min the methanol was partly evaporated under reduced pressure, followed by the usual work-up procedure. The crude oil was purified by flash chromatography (eluent PE/EtOAc = 96/4) to give 7.31 g (74%) of **125** as a colourless oil.

^{1}H NMR: δ 1.03 (s, 3H); 1.73 (s, 3H); 1.4 - 1.9 (m, 2H); 2.1 - 2.7 (m, 6H); 6.15 (m, 1H); 6.39 (m, 1H). MS: *m/e* (%) 176 (M^+, 100), 161 (65), 148 (44), 134 (53), 133 (87), 119 (63), 105 (91), 91 (69), 77 (43), 41 (42), 39 (47). HRMS: calcd (M^+) *m/e* 176.1201; found *m/e* 176.1204. $[\alpha]_D$ = +442 (c = 3.1).

(4aS)-4,4a,5,6,7,8-Hexahydro-1,4a-dimethyl-naphthalen-2(3H)-one (126)

A solution of 2.5 g (14.1 mmol) of **125** in 15 ml of dry tetrahydrofuran was added dropwise to a stirred solution of 16.5 ml (16.5 mmol) of lithium-selectride and 9.8 ml (77 mmol) of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone in 85 ml of dry tetrahydrofuran at 0 °C. After 5 h the temperature was raised to room temperature and stirring was continued for 2 h. Water was added and the reaction mixture was worked up as usual. The residue was purified by flash chromatography (eluent PE/EtOAc = 98/2) to give 1.96 g (77%) of **126** as a colourless oil.

^{1}H NMR: δ 1.10 (s, 3H); 1.64 (s, 3H); 1.1 - 2.1 (m, 9H); 2.2 - 2.7 (m, 3H). MS: *m/e* (%) 178 (M^+, 100), 163 (77), 136 (88), 135 (55), 121 (88), 107 (57), 93 (76), 91 (49), 79 (67), 77 (46), 67 (32), 55 (35), 53 (35), 41 (73), 39 (60). HRMS: calcd (M^+) *m/e* 178.1357; found *m/e* 178.1356. $[\alpha]_D$ = +197 (c = 2.2).

(+)-geosmin (97)

To a solution of 1.4 g (7.8 mmol) of **126** in 75 ml of dichloromethane was added 2.05 g (9.4 mmol) of *m*-chloroperbenzoic acid. The reaction mixture was stirred overnight and water was added. After the usual work up procedure the residue was purified by flash chromatography (eluent PE/EtOAc = 98/2) to give 1.17 g (76%) of *(1S,4aS,8aS)-*

1,4a-dimethyl-1,8a-epoxy-1,4,4a,5,6,7,8,8a-octahydro-naphthalen-2(3H)-one as a colourless oil.

^{1}H NMR: δ 0.97 (s, 3H); 1.30 (s, 3H); 1.05 - 1.25 (m, 1H); 1.3 - 2.5 (m, 11H). MS: *m/e* (%) (194 (M^+, 1), 176 (22), 133 (22), 109 (93), 81 (33), 67 (60), 55 (34), 43 (100), 41 (51), 39 (37); HRMS: calcd (M^+) *m/e* 194.1307; found *m/e* 194.1299. $[\alpha]_D$ = -52 (c = 2.1).

A solution of 0.95 g (4.9 mmol) of the above obtained oil in 10 ml of methanol was added dropwise to a solution of 175 mg (4.6 mmol) of sodium borohydride in 20 ml of methanol. The reaction mixture was stirred at room temperature for 3 h, 0.5 ml of water was added. The methanol was partly evaporated *in vacuo* and water was added followed by the usual work-up procedure. The residue was purified by flash chromatography (eluent PE/EtOAc = 4/1) to afford 0.85 g (88%) of a stereoisomeric mixture of *(1S,2R/S,4aS,8aS)-1,4a-Dimethyl-1,8a-epoxy-perhydronaphthalen-2-ol* as a colourless oil.

^{1}H NMR: δ 1.01 (s, 3H); 1.35 (s, 3H); 0.7 - 1.0 (m, 1H); 1.3 - 1.9 (m, 11H); 2.45(d, J = 11 Hz, 1H); 3.71 (dd, J = 5 Hz, 10 Hz, 1H). MS: *m/e* (%) 196 (M^+, 0.1), 112 (100), 84 (31), 67 (28), 55 (26), 43 (70), 41 (36). HRMS: calcd (M^+) *m/e* 196.1463; found *m/e* 196.1465.

To an ice cold solution of 0.80 g (4.1 mmol) of the mixture of alcohols in 25 ml of chloroform was added 1.3 mL (16 mmol) of pyridine and 1.2 g (6.0 mmol) of *p*-toluenesulfonyl chloride. The reaction mixture was stirred overnight, and poured into water followed by the usual work up procedure. The crude oil was dissolved in 35 ml of dry tetrahydrofuran and was added dropwise to a suspension of 0.26 g (6.8 mmol) of lithium aluminum hydride in 25 mL of dry tetrahydrofuran. The reaction mixture was refluxed for 1.5 h, and after cooling to room temperature 0.45 ml of water and 0.45 ml of aqueous 4 M sodium hydroxide were added and stirring was continued for 30 min, followed by the usual work up. The residue was purified by flash chromatography (eluent ether/pentane = 2/98) to give 0.37 g (60%) of (+)-geosmin (**97**) as a yellow oil.

^{1}H NMR: δ 0.74 (d, J = 7 Hz, 3H); 0.99 (s, 3H); 1.16 (s, 1H); 0.9 - 1.8 (m, 15H).MS: *m/e* (%) 182 (M^+, 4), 112 (100), 69 (22), 55 (50), 43 (58), 41 (75), 39(33). HRMS: calcd (M^+) *m/e* 182.1670; found *m/e* 182.1662. $[\alpha]_D$ = +15.5 (c= 1.2), Lit[6a]: $[\alpha]_D$ = −16.5 (-)-geosmin).

3.6 References and Notes

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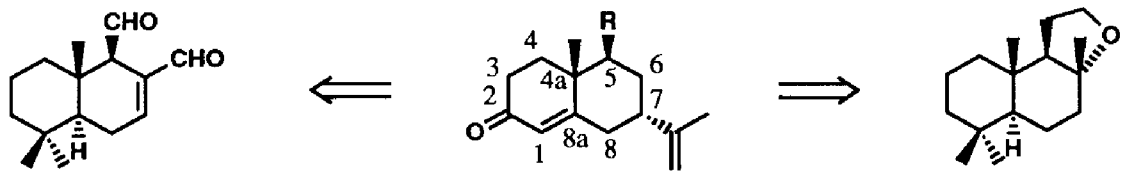
4 Conjugate Addition of Cyanide and Grignard Nucleophiles Followed by Annulation to Functionalized Decalones*

4.1 Introduction

The synthesis of chiral decalones from R-(-) and S-(+)-carvone starting *via* a Robinson annulation or a Diels-Alder reaction was shown in the chapters two and three, respectively. In this chapter the synthesis of more functionalized decalones, like **98** and **99**, *via* two different conjugate addition-annulation methodologies is discussed. Dependent on the choice of the substituent R, the C-5 substituted decalones are potentially useful chirons for the synthesis of drimane sesquiterpenes like the insect antifeedant (-)-polygodial (**37**) and of the olfactive compound (-)-Ambrox® (**101**) (Scheme 4.1).

Scheme 4.1



37 **98:** R = CN; **99:** R = allyl **101**

From the literature it is known that the Robinson annulation of sterically hindered cyclohexanones, like 2,3-dialkylated cyclohexanones proceeds in low yield and with poor stereoselectivity under the normal basic conditions[1]. The acid-catalyzed Michael addition of methyl vinyl ketone, followed by cyclization of the intermediate diketones sometimes gives a considerable improvement of the Robinson annulation in yield and in stereoselectivity[2]. Although one step procedures for conjugate addition-*alkylation* are often successful[3], only a few examples of the tandem conjugate addition-*Michael reactions* are known[4], probably because the intermediate organocopper enolate requires a not commercially available α-trimethylsilyl ketone[5] as Michael acceptor, to avoid multiple addition and polymerization. Trapping of the intermediate enolates as their silyl enol ethers usually proceeds quite well[6] and therefore the Lewis acid catalyzed silyl enol ether variation of the Robinson annulation[6a,7] seems to be the best option for the synthesis of C-5 substituted decalones from S-(+)-carvone.

The first approach to the C-5 alkylated decalones was the conjugate addition of a few

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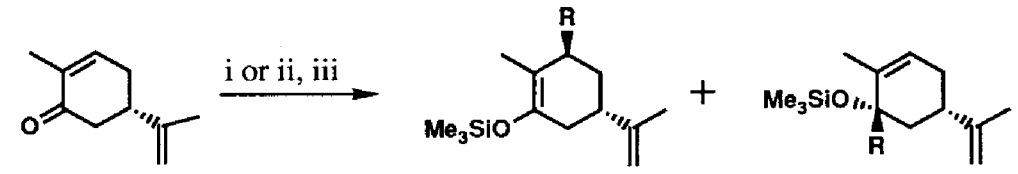
alkyl Grignard reagents to S-(+)-carvone, trapping of the intermediate enolates as their silyl enol ethers, followed by the Lewis acid catalyzed silyl enol ether variation of the Robinson annulation.
The second method was the base catalyzed Robinson annulation of dihydrocarvone derivatives, at C-3 substituted with a thiophenolate, hydroxy or nitrile group.

4.2 Conjugate addition of Grignard reagents followed by the silyl enol ether variation of the Robinson annulation with methyl vinyl ketone

The conjugate addition of methyl magnesium bromide and vinyl magnesium bromide to S-(+)-carvone in the presence of a catalytic amount of cuprous bromide-dimethyl sulfide complex (CuBr.Me_2S), 2 equivalents of trimethylchlorosilane (TMSCl) and hexamethylphosphoric triamide (HMPA) at -40 °C, afforded the 1,4-addition products **127a** en **127b** in 86% and 80% yield, respectively, with a diastereomeric excess (*de* = % major diastereomer - % minor diastereomer) for the *trans* isomer of 86% and 94% respectively (scheme 4.2). Allyl magnesium chloride yielded under the same reaction conditions solely the 1,2-addition product **128**[8] (scheme 4.2). Addition to the carbonyl group was diminished by the use of a stoichiometric amount of the copper complex (CuBr.Me_2S) and by lowering of the temperature to -100 °C. Under these conditions silyl enol ether **127c** was obtained in 73% yield, with a *de* for the *trans* isomer of 88%, together with 7% of the 1,2 addition product **128.** The thermodynamic silyl enol ether **127d** was synthesized by heating the lithium bronze reduction product of S-(+)-carvone, (-)-dihydrocarvone **30**, with trimethylchlorosilane, sodium iodide and triethylamine (Et_3N) in acetonitrile at 80 °C to give **127d** in 85% yield accompanied with 6% of the kinetic silyl enol ether.

Scheme 4.2



S-(+)-carvone

127a: R = Me
127b: R = vinyl
127c: R = allyl
127d: R = H

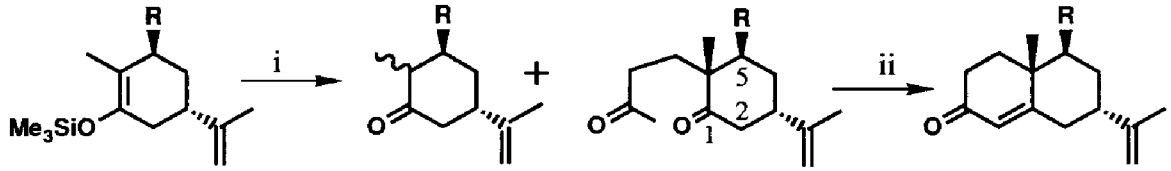
128: R = allyl

Reagents for **127a**, **127b** and **127c** i: RMgX, Me_2S.CuBr, TMSCl, HMPA, THF, low temperature (see text); for **127d**: ii: Li/NH_3, *t*-BuOH; iii: TMSCl, NEt_3, NaI, acetonitrile, Δ.

The conditions of Duhamel[6a] for the formation of diketones from silyl enol ethers and methyl vinyl ketone were applied to the silyl enol ethers **127**, but appreciable amounts of desilylated products **129** were obtained together with the diketones **130**. An adaptation of these conditions and a lowering of the temperature to -65 °C instead of -20 °C, improved the yield of the diketones **130** to 65-75% and the formation of the desilylated products **129** was diminished to 15-25% (table 4.1, scheme 4.3). The stereoselectivity for the alkyl substituted silyl enol ethers **127a-c** was excellent with *de* 's for the major diketones **130** of 92 - 94 %. Silyl enol ether **127d** gave a mixture of diketones **130d** in a ratio of 7:3 (scheme 4.4).

The diketones **130a-c** were easily cyclized by stirring in basic medium (0.2 M sodium methoxide in methanol) for 20 hours to afford even better *de* 's for the C-5 substituted decalones after purification (Table 4.1) in agreement with a previous report[6a]. The mixture of diketones **130d** was stirred for a shorter period in basic medium (3 h) to afford hydroxyketone **31** and decalone **32** in 66% and 24%, respectively (scheme 4.4).

Scheme 4.3



127a: R = Me
127b: R = vinyl
127c: R = allyl
127d: R = H

129a: R = Me
129b: R = vinyl
129c: R = allyl
129d: R = H

130a: R = Me
130b: R = vinyl
130c: R = allyl
130d: *

131: R = Me
132: R = vinyl
99: R = allyl
*

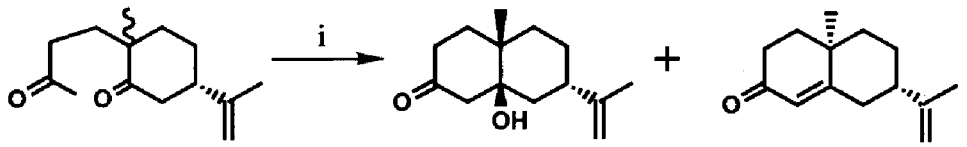
Reagents i: MVK, $BF_3.Et_2O$, isopropanol, CH_2Cl_2, nitromethane, -65 °C; ii: NaOMe, MeOH; * see scheme 4.4.

Table 4.1: Preparation of C-5 substitued Decalones from Silyl enol ethers 127

Silyl enol ether	Ketone 129 yield (%)[a]	Diketone 130 yield (%)[a]	*de* (%)	Cyclization yield (%)[b]	*de* (%)
127a (R=Me)	25	65	92[c]	87	98[c]
127b (R=vinyl)	23	65	94[c]	89	98[c]
127c (R=allyl)	15	75	92[c]	95	96[c]
127d (R=H)	19	70	40	90	d

a: from **127**; b: from **130** c: besides the major isomer, 2 minor isomers were present in the mixture; d: the two products were obtained pure after column chromatography (scheme 4.4).

Scheme 4.4



130d 31 32

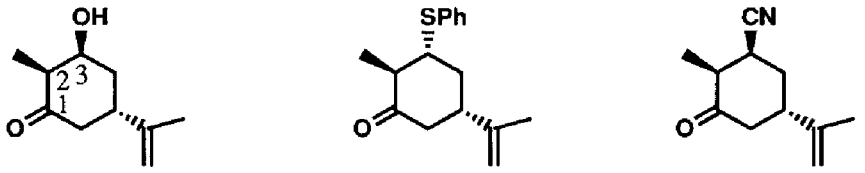
Reagents i: NaOMe, MeOH.

The overall yield of the products **31** and **32** from (-)-dihydrocarvone **30** were in this case 39% and 14%, respectively. So the stereoselectivity and the yield of the Robinson annulation of (-)-dihydrocarvone **30** was not improved by this Lewis acid catalyzed silyl enol ether variation and the normal basic conditions gave better results in this case[9]. The high stereoselectivity of the alkylated silyl enol ethers **127a-c** is probably caused by the steric effect of the alkyl substituent.

4.3 Annulation of the C-3 substituted dihydrocarvones 133, 134 and 135

The preparation of functionalized decalones with other substituents than alkyl groups at C-5 can also lead to very useful intermediates. The silyl enol ether variation of the Robinson annulation was not suitable for **133**[10], **134**[11] and **135**[12] (figure 4.1). The silyl enol ethers of **133** and **134** could not be prepared in our hands and the silyl enol ether of **135** gave in the Lewis acid catalyzed reaction mainly desilylation, resulting in **135**.

Figure 4.1

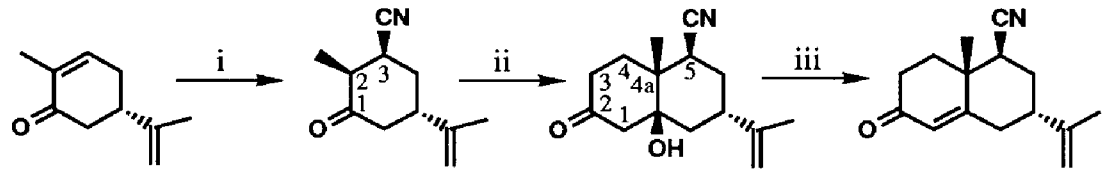


133 134 135

The base catalyzed Robinson annulation of **133** and **134** gave elimination of water and thiophenol, respectively and S-(+)-carvone was the only isolated product in both cases.
The base catalyzed Robinson annulation of 2,3-dialkylated cyclohexanones normally proceeds in a low yield and with poor stereoselectivity. To our surprise, the Robinson annulation of cyano ketone **135** with methyl vinyl ketone under basic conditions gave the Robinson annulation product **136** in high yield (90%) and with excellent stereoselectivity. This result was very encouraging for further research, especially because the adduct **136** crystallized from the reaction mixture and the starting cyano

ketone **135** could be obtained easily in a crystalline state in 95% yield.
Some special remarks have to be made to enable the production of **135** and **136** in an easy way and on a scale up to 100 g or more. It proved to be important to use crystalline **135** for the Robinson annulation; this stereoisomer crystallized directly out of the reaction mixture when *potassium* cyanide was used for the conjugate addition. Further purification of the adduct mostly was not necessary but could be done by crystallization from ethanol. The use of *sodium* cyanide for the conjugate addition reaction gave an emulsion and workup of the reaction mixture by extraction yielded an oily mixture which gave unsatisfactory results in the following annulation reaction[13]. When crystalline **135** was used for the Robinson annulation, the adduct **136** also crystallized from the reaction mixture and could be isolated simply by filtration. Refluxing of this hydroxyketone **136** with a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) in toluene afforded the cyano decalone **98** in high yield (91%) (Scheme 4.5).

Scheme 4.5



Reagents i: KCN, HAc, EtOH, H_2O; ii: MVK, NaOMe, MeOH; iii: *p*-TsOH, toluene, reflux.

The Robinson annulation of **135** with methyl vinyl ketone yielded exclusively the annulation product with the nitrile and angular methyl group in a *cis*-relationship. Consequently the nitrile group in **135** had a strong stimulating and directing effect on the yield and the stereoselectivity in the base catalyzed Robinson annulation.
The multi functionalized cyano decalone **98** is an excellent starting material for the synthesis of many terpenes and steroids. The conversion of decalones **98** and **99** into drimanes and into (-)-Ambrox® (**101**) are the subjects of the chapters 5 and 6, respectively.

4.4 Experimental Section

General experimental conditions were as described in chapter 2

(3S,5S)-2,3-Dimethyl-5-isopropenyl-1-trimethylsilyloxy-cyclohex-1-ene (127a)

To a solution of 0.35 g of cuprous bromide-dimethyl sulfide (1.7 mmol) and 10 ml of hexamethylphosphoric triamide (57 mmol) in 40 ml of tetrahydrofuran was added dropwise, 15 ml of a 3 M methyl magnesium bromide solution in diethyl ether under a nitrogen atmosphere at -40 °C. After 10 min, 4.00 g of S-(+)-carvone (26.7 mmol) and 6.68 ml of trimethylchlorosilane (53 mmol) were added. After stirring for 1h at -40 °C, 5.05 g of triethylamine (50 mmol) was added, followed by 50 ml of water. The mixture was extracted 3 times with ether. The combined organic layers were washed with water, dried and evaporated. The residue was purified by flash chromatography (eluent PE) to give 5.46 g of silyl enol ether **127a** as a colourless oil (22.9 mmol, 86%) as a 93/7 *trans/cis* mixture according to GLC.

^{1}H NMR: δ 0.15 (s, 9H); 1.02 (d, J = 7.0 Hz, 3H); 1.72 (s, 3H); 1.4 - 2.5 (m, 9 H); 4.70 (bs, 2H). ^{13}C NMR: δ 0.5 (q*3); 14.4 (q); 19.4 (q); 20.5 (q); 33.3 (d); 34.9 (t); 35.5 (t); 36.9 (d); 108.4 (t); 115.7 (s); 142.2 (s); 149.1 (s). HRMS: calcd (M^+) *m/e* 238.1753 ; found *m/e* 238.1750. $[\alpha]_D$ = -72.4 (c = 0.6).

(3R,5S)- 5-Isopropenyl-2-methyl-1-trimethylsilyloxy-3-vinylcyclohex-1-ene (127b)

To a solution of 0.34 g of cuprous bromide-dimethyl sulfide (1.7 mmol) and 11.6 ml of hexamethylphosphoric triamide (67 mmol) in 30 ml of tetrahydrofuran was added dropwise 50 ml of a 1 M vinyl magnesium bromide solution in tetrahydrofuran under a nitrogen atmosphere at - 40 °C. After 30 min at -40 °C, a mixture of 5.0 g of S-(+)-carvone (33.3 mmol) and 8.45 ml of trimethylchlorosilane (67 mmol) was added in 25 ml of tetrahydrofuran. After 30 min 6.77 g of triethylamine (67 mmol) was added, followed by 50 ml of water. The mixture was extracted 3 times with ether. The combined organic layers were washed with water, dried and evaporated. The residue was purified by flash chromatography (eluent PE) to give 6.70 g of silyl enol ether **127b** as a colourless oil (26.8 mmol, 80%) as a 97/3 *trans-cis* mixture according to GLC.

^{1}H NMR: δ 0.17 (s, 9H); 1.53 (s, 3H); 1.70 (s, 3H); 1.4 - 1.7 (m, 2H); 1.96 - 2.05 (m, 2H); 2.35 (septet, J = 5.3 Hz, 1H); 2.71 (m, 1H); 4.69 (bs, 2H);4.97 (t, J = 12.3 Hz, 2H); 5.76 (m, 1H). ^{13}C NMR: δ 0.5 (q*3); 14.8 (q); 20.5 (q); 33.1 (t); 35.3 (t); 36.8 (d); 43.3 (d); 108.6 (t); 112.0 (s); 114.4 (t); 140.9 (d); 144.1 (s); 148.9 (s). HRMS: calcd (M^+) *m/e* 250.1753; found *m/e* 250.1753. $[\alpha]_D$ = -186 (c = 0.3).

(3S,5S)-5-Isopropenyl-2-methyl-3-(prop-2'-enyl)-1-trimethylsilyloxy-cyclohex-1-ene (127c)

To a solution of 11.0 g of cuprous bromide-dimethyl sulfide (53.5 mmol) in 100 ml of tetrahydrofuran was added under an nitrogen atmosphere 25 ml of a 2 M solution of

allyl magnesiumchloride in tetrahydrofuran at -100 °C. After 15 min at -100 °C a mixture of 5.0 g of S-(+)-carvone (33.3 mmol) and 8.45 ml of trimethylchlorosilane (67 mmol) in 25 ml of tetrahydrofuran was added dropwise in 30 min. After 1.5 h 5.97 g of hexamethylphosphoric triamide (33.3 mmol) and 6.73 g (67 mmol) of triethylamine were added. Water was added and the mixture was extracted 3 times with PE. The combined organic layers were washed with water, dried and evaporated. The residue was purified by flash chromatography (eluent PE) to give first 0.59 g of the 1,2-addition product **128** (2.2 mmol, 7%) as a colourless oil, followed by 6.42 g of the 1,4 addition product **127c** as a 94/6 *trans/cis* mixture according to GLC (24.3 mmol, 73%).

127c: ^{1}H NMR: δ 0.18 (s, 9H); 1.58 (s, 3H); 1.70 (s, 3H); 1.2 - 1.4 (m, 1H); 1.5 - 2.5 (m, 7H); 4.69 (bs, 2H); 4.95 (s, 1H); 5.01 (d, J = 9 Hz, 1H); 5.65 - 5.90 (m, 1H). ^{13}C NMR: δ 0.5 (q*3); 14.6 (q); 20.6 (q); 30.6 (t); 35.2 (t); 36.7 (d); 37.2 (t); 38.6 (d); 108.4 (t); 114.3 (s); 115.5 (t); 137.9(d); 143.2 (s); 149.0 (s). HRMS: calcd (M^+) *m/e* 264.1909 ; found *m/e* 264.1909. $[\alpha]_D$ = -43.5 (c = 0.5).

128: ^{1}H NMR: δ 0.08 (s, 9H); 1.67 (s, 3H); 1.69 (s, 3H); 1.46 - 2.47 (m, 7H); 4.67 - 4.69 (m, 2H); 4.95 - 5.06 (m, 2H); 5.36 - 5.39 (m, 1H); 5.75 - 5.96 (m, 1H). ^{13}C NMR: δ 1.9 (q*3); 17.2 (q); 20.4 (q); 30.7 (t); 39.3 (d); 40.4 (t); 44.5 (t); 108.4 (t); 116.5 (t); 122.3 (d); 135.1 (d); 139.2 (s); 148.9 (s). HRMS: calcd (M^+-15) *m/e* 249.1674; found *m/e* 249.1673. $[\alpha]_D$ = + 63.3 (c = 1.0).

(5S)-5-Isopropenyl-2-methyl-1-trimethylsilyloxy-cyclohex-1-ene (127d)

To 1.70 g of a mixture of isomers of (-)-dihydrocarvone **30** (11.2 mmol) in 50 ml of acetonitrile was added 2.02 g of triethylamine (20 mmol), 2.16 g of trimethylchlorosilane (20 mmol) and 3.00 g of sodium iodide (20 mmol). The mixture was heated to 80 °C and stirred for 4 h. Water was added and the reaction mixture was extracted 3 times with PE and the combined organic layers were washed with water, dried and evaporated. Flash chromatography (eluent PE) gave 2.12 g (9.5 mmol, 85%) of silylenolethers **127d** as a 94/6 *thermodynamic/kinetic* mixture as a colourless oil.

^{1}H NMR: δ 0.15 (s, 9H); 1.54 (s, 3H); 1.70 (s, 3H); 1.2 - 2.3 (m, 7H); 4.70 (bs, 2H). ^{13}C NMR: δ 0.5 (q*3); 15.9 (q); 20.5 (q); 27.7 (t); 29.8 (t); 35.3 (t); 42.2 (d); 108.4 (t); 111.1 (s); 142.0 (s); 149.1 (s). HRMS: calcd (M^+) *m/e* 224.1596 ; found *m/e* 224.1595. $[\alpha]_D$ = -73.4 (c = 0.4).

General procedure for the synthesis of the diketones 130.

Silyl enol ether **127** was dissolved in dichloromethane (1mmol/ml) with 2 equivalents of nitromethane under a nitrogen atmosphere. The solution was cooled to -78 °C and 2 equivalents of methyl vinyl ketone and isopropanol were added. After 30 minutes 1 equivalent of boron trifluoride etherate was added dropwise. The temperature was

raised to −65 °C and the mixture was stirred for 2 h. A saturated aqueous sodium bicarbonate solution was added and the aqueous layer was extracted 3 times with dichloromethane. The organic layers were washed with water, dried and evaporated. Flash chromatography of the residue (eluent PE/EtOAc = 10/1) gave first an epimeric mixture of desilylated products **129**, followed by the diketones **130**.

(2R,3S,5S) and (2S,3S,5S)-2,3-Dimethyl-5-isopropenylcyclohexanone as a mixture of C2-epimers (129a)

^{1}H NMR: major signals of the major epimer: δ 0.79 (d, J = 7.3 Hz, 3H); 1.70 (s, 3H); 4.70 (s, 1H); 4.73 (s, 1H). ^{1}H NMR: major signals of the minor epimer: δ 0.95 (d, J = 6.8 Hz, 3H); 1.70 (s, 3H); 4.68 (s, 1H); 4.79 (s, 1H). HRMS: calcd (M^+) *m/e* 166.1358 ; found *m/e* 166.1354.

(2R,3S,5S)-2,3-Dimethyl-5-isopropenyl-2-(3-oxobutyl)-cyclohexanone (130a)

^{1}H NMR: δ 0.85 (d, J = 7.1 Hz, 3H); 0.91 (s, 3H); 1.68 (s, 3H); 2.08 (s, 3H); 1.4 - 2.7 (m, 10H); 4.65 (s, 1H); 4.75 (s, 1H). ^{13}C NMR: δ 15.9 (q); 18.5 (q); 20.8 (q); 29.8 (q); 30.3 (t); 32.3 (t); 36.5 (d); 38.2 (t); 40.2 (d); 42.5 (t); 50.8 (s); 110.3 (t); 147.1 (s); 208.0(s); 215.3 (s). HRMS: calcd (M^+) *m/e* 236.1776 ; found *m/e* 236.1776 $[\alpha]_D$ = −38.3 (c = 0.3).

(2R,3R,5S) and (2S,3R,5S)-5-Isopropenyl-2-methyl-3-vinylcyclohexanone as a mixture of C2-epimers (129b)

^{1}H NMR: major signals of the major epimer: δ 0.91 (d, J = 6.7 Hz, 3H); 1.68 (s, 3H); 4.68 (s, 1H); 4.73 (s, 1H); 4.94 - 5.07 (m, 2H); 5.46 - 5.64 (m, 1H). ^{1}H NMR: major signals of the minor epimer: δ 0.99 (d, J = 6.2 Hz, 3H); 1.68 (s, 3H); 4.64 (s, 1H); 4.81 (s, 1H); 4.94 - 5.07 (m, 2H); 5.46 - 5.64 (m, 1H). HRMS: calcd (M^+) *m/e* 178.1358; found *m/e* 178.1355.

(2R,3R,5S)-5-Isopropenyl-2-methyl-2-(3-oxobutyl)-3-vinylcyclohexanone (130b)

^{1}H NMR: δ 0.90 (s, 3H); 1.67 (s, 3H); 2.07 (s, 3H); 1.6 - 2.7 (m, 10H); 4.64 (s, 1H); 4.77 (s, 1H); 4.96 (m, 1H); 5.02 (s, 1H); 5.57 - 5.75 (m, 1H). ^{13}C NMR: δ 19.5 (q); 20.8 (q); 29.7 (q); 30.3 (t); 31.0 (t);38.0 (t); 40.4 (d); 42.3 (t); 47.3(d); 49.8 (s); 110.6 (t); 116.4 (t); 137.5 (d); 146.8 (s); 207.8 (s); 214.6 (s). HRMS: calcd (M^+) *m/e* 248.1776 ; found *m/e* 248.1779. $[\alpha]_D$ = −38.1 (c = 0.4).

(2R,3S,5S) and (2S,3S,5S)-5-Isopropenyl-2-methyl-3-(prop-2'-enyl)cyclohexanone as a mixture of C2-epimers (129c)

^{1}H NMR: major signals of the major epimer: δ 0.99 (d, J = 6.8 Hz, 3H); 1.69 (s, 3H); 4.68 (s, 1H); 4.73 (s, 1H); 4.95 - 5.06 (m, 2H); 5.54 - 5.80 (m, 1H). ^{1}H NMR: major signals of the minor epimer: δ 1.09 (d, J = 6.7 Hz, 3H); 1.69 (s, 3H); 4.65 (s, 1H); 4.78 (s, 1H); 4.95 - 5.06 (m, 2H); 5.54 - 5.80 (m, 1H). HRMS: calcd (M^+) *m/e* 192.1514; found *m/e* 192.1514.

(2R,3S,5S)-5-Isopropenyl-2-methyl-2-(3-oxobutyl)-3-(prop-2'-enyl)cyclohexanone (130c)
^{1}H NMR: δ 0.96 (s, 3H); 1.68 (s, 3H); 2.10 (s, 3H); 1.6 - 2.7 (m, 12H); 4.64 (s, 1H); 4.77 (s, 1H); 4.95 (m, 1H); 5.02 (s, 1H); 5.65 - 5.70 (m, 1H). ^{13}C NMR: δ 18.8 (q); 20.9 (q); 27.6 (t); 29.8 (q); 29.9 (t); 33.2 (t); 38.1 (t); 39.6 (d); 40.6 (d); 42.3 (t); 50.9 (s); 110.5 (t); 116.2 (t); 136.6 (d); 147.0 (s); 208.3 (s); 215.3 (s). HRMS: calcd (M^+) *m/e* 262.1932 ; found *m/e* 262.1932. $[\alpha]_D = -62.2$ (c = 0.2).

(2R,5S) and (2S,5S)-5-Isopropenyl-2-methyl-2-(3-oxobutyl)cyclohexanone as a mixture of C2-epimers (130d)
^{1}H NMR: major signals of the major epimer: δ 0.96 (s, 3H); 1.69 (s, 3H); 2.08 (s, 3H); 4.67 (s, 1H); 4.72 (s, 1H). ^{1}H NMR: major signals of the minor epimer: δ 1.09 (s, 3H); 1.69 (s, 3H); 2.11 (s, 3H); 4.67 (s, 1H); 4.72 (s, 1H).

General procedure for the cyclization of the diketones 130.
The diketones **130** were dissolved into a 0.2 M solution of sodium methoxide in methanol and the mixture was stirred for 20 h at room temperature. Water was added and the mixture was extracted 3 times with ether. The combined organic layers were washed with water, dried and evaporated. The residue was flash chromatographed (eluent PE/EtOAc = 10/1) to give the cyclization products as colourless oils.

(4aR,5S,7S)-4a,5-Dimethyl-4,4a,5,6,7,8-Hexahydro-7-isopropenyl-naphthalene-2(3H)-one (131)
^{1}H NMR: δ 0.82 (d, J = 6.6 Hz, 3H); 1.08 (s, 3H); 1.66 (s, 3H); 1.4 - 2.7 (m, 10H); 4.70 (s, 1H); 4.80 (s, 1H); 5.76 (s, 1H). ^{13}C NMR: δ 14.8 (q); 15.7 (q); 22.5 (q); 32.0 (t); 33.8 (t); 35.1 (d); 35.2 (t); 36.0 (t); 38.6 (s); 39.5 (d); 111.9 (t); 125.2 (d); 146.8 (s); 170.8 (s); 199.0 (s). HRMS: calcd (M^+) *m/e* 218.1671 ; found *m/e* 218.1677. $[\alpha]_D = +155$ (c = 0.4).

(4aR,5R,7S)-4,4a,5,6,7,8-Hexahydro-7-isopropenyl-4a-methyl-5-vinylnaphthalene-2(3H)-one (132)
^{1}H NMR: δ 1.14 (s, 3H); 1.68 (s, 3H); 1.6 - 2.8 (m, 10H); 4.74 (s, 1H); 4.85 (s, 1H); 4.99 (dd, J = 10.7 Hz, J = 2.0 Hz, 1H); 5.07 (d, J = 1.8 Hz, 1H); 5.64 - 5.82 (m, 1H); 5.79 (s, 1H). ^{13}C NMR: δ 16.9 (q); 22.4 (q); 29.2 (t); 33.7 (t); 35.5 (t); 35.6 (t); 38.3 (s); 39.1 (d); 46.4 (d); 112.3 (t); 116.5 (t); 125.6 (d); 137.4 (d); 146.4 (s); 169.7 (s); 198.9 (s). HRMS: calcd (M^+) *m/e* 230.1668 ; found *m/e* 230.1668. $[\alpha]_D = +54.7$ (c = 0.3).

(4aR,5S,7S)-4,4a,5,6,7,8-Hexahydro-7-isopropenyl-4a-methyl-5-(prop-2'-enyl)-naphthalene-2(3H)-one (99)
^{1}H NMR: δ 1.11 (s, 3H); 1.65 (s, 3H); 1.2 - 2.7 (m, 12H); 4.69 (s, 1H); 4.81 (s, 1H); 4.96 (m, 1H); 5.03 (s, 1H); 5.69 (m, 1H); 5.80 (s, 1H). ^{13}C NMR: δ 16.5 (q); 22.3 (q); 28.2 (t); 33.3 (t);

33.7 (t); 35.0 (t); 36.0 (t); 38.7 (s); 39.3 (d); 41.3 (d); 112.1 (t); 116.2 (t); 125.6 (d); 137.2 (d); 146.3 (s); 170.4 (s); 199.0 (s). HRMS: calcd (M^+) *m/e* 244.1827; found *m/e* 244.1830 $[\alpha]_D$ = +74.0 (c = 0.3).

(4aS,7S,8aS)-8a-Hydroxy-7-isopropenyl-4a-methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene-2(1H)-one (31)

^1H NMR: δ 1.16 (s, 3H); 1.64 (s, 3H); 1.3 - 2.9 (m, 14H); 4.63 (d, J = 5.4 Hz, 2H). ^{13}C NMR: δ 20.7 (q); 21.4 (q); 25.7 (t); 31.4 (t); 34.5 (t); 36.4 (s); 37.3 (t); 39.5 (t); 39.6 (d); 53.1 (t); 75.2 (s); 108.7 (t); 148.7 (s);209.3 (s). mp = 109-110 °C. $[\alpha]_D$ = -51.9 (c = 1.0).

(4aR,7S)-4,4a,5,6,7,8-Hexahydro-7-isopropenyl-4a-methylnaphthalene-2(3H)-one (32)

^1H NMR: δ 1.19 (s, 3H); 1.70 (s, 3H); 1.3 - 2.6 (m, 11H); 4.70 (s, 2H); 5.69 (s, 1H). ^{13}C NMR: δ 20.4 (q); 21.9 (q); 26.9 (t); 33.7 (t); 35.3 (s); 37.5 (t); 37.6 (t); 41.0 (t); 45.9 (d); 109.1 (t); 124.3 (d); 148.3 (s); 169.5 (s); 199.3 (s). $[\alpha]_D$ = -79 (c = 1.2).

(1S,2S, 5S)-5-Isopropenyl-2-methyl-3-oxo-cyclohexane-1-carbonitrile (135)

To a solution of 25.0 g (0.167 mol) of S-(+)-carvone in 75 ml of ethanol (96%) at 0 °C was added slowly a solution of 15 g (0.23 mol) of potassium cyanide in 35 ml of water to give a brown mixture. To this mixture was added 11 ml (0.17 mol) of glacial acetic acid in 2 h. After some time the product started to crystallize. Stirring was continued overnight at 0 °C. The reaction mixture was filtered, and the precipitate was washed with water/ethanol (1/2) and recrystallized from ethanol to give 28.1g (0.159 mmol, 95%) of **135** as white crystals, mp 95 - 96 °C.

^1H NMR: δ 1.30 (d, J = 6.5 Hz, 3H); 1.75 (s, 3H); 1.8 - 2.9 (m, 6H); 3.35 (m, 1H); 4.77 (s, 1H); 4.87 (s, 1H). HRMS: calcd (M^+) *m/e* 177.1153; found *m/e* 177.1154. $[\alpha]_D$ = +10.2 (c = 0.2).

(1S,3S,4aS,8aR)-Decahydro-4a-hydroxy-3-isopropenyl-8a-methyl-6-oxo-1-naphthalenecarbonitrile (136)

To a solution of 50.0 g (282 mmol) of cyanocarvone **135** and 75 ml (0.9 mol) of methyl vinyl ketone in 600 ml of methanol was added dropwise 150 ml of a 1 M sodium methoxide solution in methanol at 0 °C. After stirring overnight the product crystallized from the reaction mixture. Water (1000 ml) was added and the mixture was allowed to stand at 0 °C overnight. The mixture was filtered and washed with water. The resulting crystals **136** (62.7 g, 254 mmol, 90%) were dried under vacuum over phosphorus pentoxide and were used without further purification, mp 191 - 192 °C.

^1H NMR: δ 1.52 (s, 3H); 1.70 (s, 3H); 1.4 - 2.1 (m, 5H); 2.2 - 2.4 (m, 3H); 2.5 (dd, J = 6.9 Hz,

14.2 Hz, 1H); 2.6 - 2.9 (m, 3H); 4.70 (s, 1H); 4.77 (s, 1H). ^{13}C NMR: δ 19.5 (q); 20.8 (q); 28.7(t); 31.5 (t); 35.7 (d); 36.5 (d); 36.8 (t); 38.6 (s); 39.1 (t); 53.0 (s); 74.7 (t); 110.0 (t); 121.3 (s); 146.7 (s); 207.3 (s). HRMS: calcd. (M^+) *m/e* 247.1576; found *m/e* 247.1572. Anal: calcd for $C_{15}H_{21}NO_2$: C, 72.83; H, 8.55; N, 5.66; found: C, 72.71; H, 8.50; N, 5.68. $[\alpha]_D$ = -41.3 (c = 0.3).

(1S,3S,8aR)-3-Isopropenyl-8a-methyl-1,2,3,4,6,8,8a-octahydro-6-oxo-1-naphthalene-carbonitrile (98)

To a solution of 134 g (0.54 mol) of alcohol **136** in 1000 ml of toluene was added at reflux temperature 0.9 g of *p*-toluenesulfonic acid. The solution was refluxed for 1 h in a Dean-Stark apparatus.The organic layer was washed with a saturated aqueous sodium bicarbonate solution and brine and dried over $MgSO_4$. After evaporation of the solvent and recrystallization from ethanol 112 g (0.49 mol, 91%) of **98** was obtained as pale yellow crystals, mp 106 - 107 °C.

^1H NMR: δ 1.39 (s, 3H); 1.69 (s, 3H); 1.74 - 1.90 (m, 1H); 2.11 - 2.21 (m, 3H); 2.41 - 2.71 (m, 6H); 4.73 (s, 1H); 4.91 (s, 1H); 5.82 (s, 1H). ^{13}C NMR: δ 18.3 (q); 22.3 (q); 27.1 (t); 33.4 (t); 34.5 (t); 35.7 (t); 35.9 (d); 37.3 (s); 38.1 (d); 113.8 (t); 119.6 (s); 126.9 (d); 144.7 (s); 164.0 (s); 197.3 (s). HRMS: calc. (M^+) *m/e* 229.1467; found *m/e* 229.1472. Anal: calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.10.; found: C, 78.43; H, 8.47; N, 6.03. $[\alpha]_D$ = +202 (c = 0.4).

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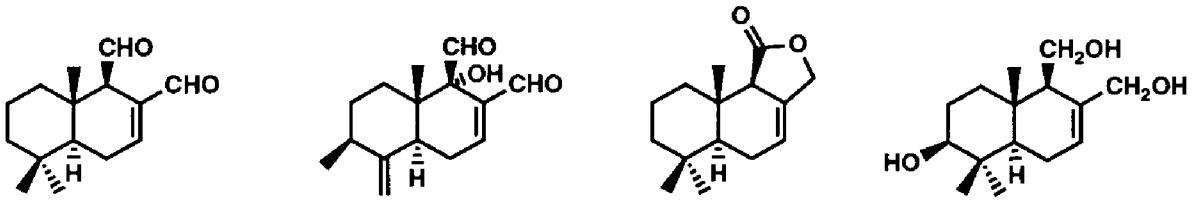
b) Taillades, J.; Garrel, L.; Lagriffoul, P. H.; Commeyras, A. *Bull. Soc. Chim. Fr.* **1992**, *129*, 191-198.
13. The unsuitability of sodium cyanide in the conjugate addition reaction of S-(+)-carvone was observed by dr. V. A. Khripach of the Institute of Bio organic Chemistry, Academy of Sciences of Belarus in Minsk, Belarus.

5 Total Synthesis of Drimane Sesquiterpenes from S-(+)-Carvone*

5.1 Introduction

The insect antifeedant properties of drimane sesquiterpenes, *e.g.*, polygodial (**37**) and the related coloratanes, *e.g.*, muzigadial (**137**) (figure 5.1) are well known[1]. This interesting biological activity has greatly stimulated the development of new and general synthetic routes to this class of compounds. Besides the ene-dialdehyde functionality, other oxidized functionalities in the B-ring, like annulated lactones and furans are common in drimanes (*e.g.*, drimenin (**138**), figure 5.1). Also ring A-oxidized drimanes are common in nature[2] , *e.g.*, drim-7-ene-3,11,12-triol (**139**).

Figure 5.1



37 137 138 139

Numerous syntheses of drimanes have appeared in the last two decades[3]. In our laboratory several new methods for the regioselective introduction of the required functionalities were explored[4] and a new approach to drimanes was developed[4e] starting from *trans*-decalones, with the carbonyl group at C-7[5]. The total synthesis of enantiomerically pure drimanes and the coloratane muzigadial was performed starting from S-(+)- and R-(-)-carvone, respectively[6].

In chapter 4, the stereoselective synthesis of cyano decalone **98** from S-(+)-carvone was discussed. This highly functionalized decalone can be obtained in high yield via a conjugate addition of cyanide followed by a Robinson annulation with methyl vinyl ketone and dehydration (scheme 4.5). It seemed worthwhile to investigate a new route to drimane sesquiterpenes, starting from this cyano decalone **98**. The differences between this new route and the former one *via* the decalone **33**[6], the Robinson annulation product of dihydrocarvone **30** and methyl vinyl ketone, are shown in scheme 5.1.

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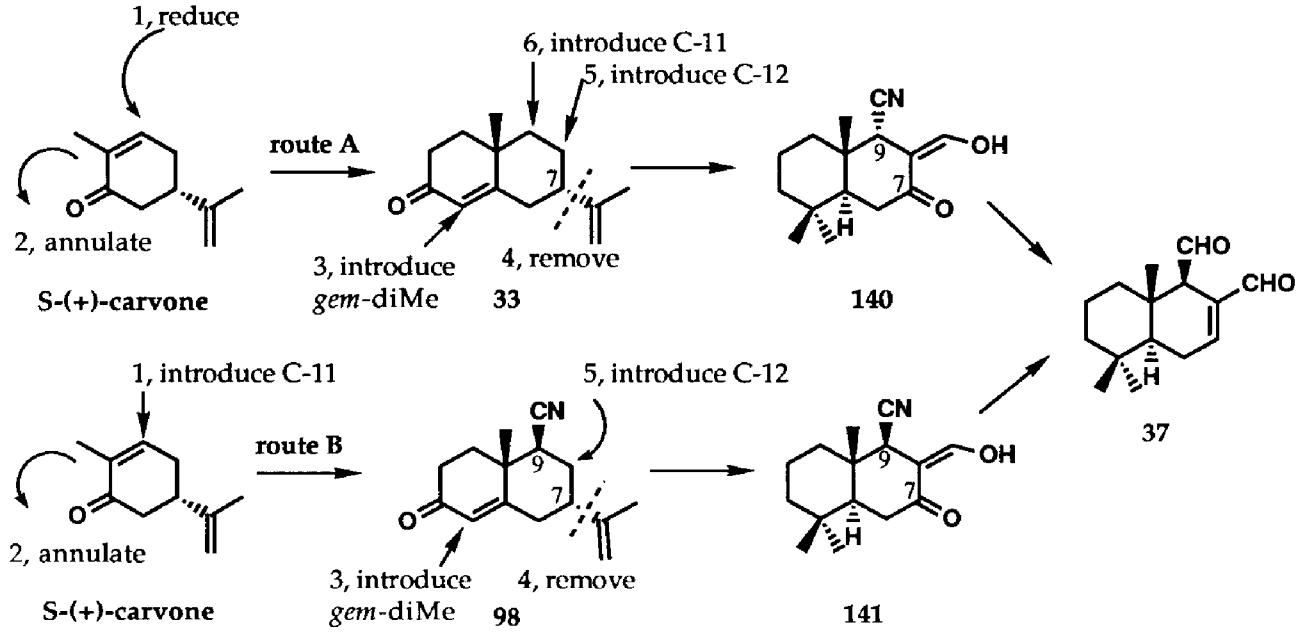
* This chapter has been published in a revised form: Swarts, H. J.; Verstegen-Haaksma, A. A.; Jansen, B. J. M.; de Groot, Ae. *Tetrahedron* **1994**, *50*, 10083-10094.

Scheme 5.1



In the former approach to drimanes, S-(+)-carvone was first reduced, annulated, and dehydrated to decalone **33** in an overall yield of 48% from S-(+)-carvone[6]. After methylation the chiral handle was removed and transformed into a carbonyl group at C-7. Next, the functionalized C-12 and C-11 carbon atoms were introduced to afford compound **140** with the *wrong* stereochemistry of the nitrile group at C-9. Finally a number of functional group transformations led to drimanes like polygodial (**37**) (scheme 5.1, route A).

In the new approach, the introduction of a nitrile group at C-9 and the 'reduction' of the double bond in S-(+)-carvone were combined in the first step of the sequence and the following Robinson annulation and dehydration gave decalone **98** in an overall yield of 78% from S-(+)-carvone. Methylation, removal of the isopropenyl group and the introduction of C-12 would lead to compound **141** with the *correct* stereochemistry at C-9 (scheme 5.1, route B).

5.2 Synthesis of C-3 oxygenated drimane sesquiterpenes

Several hydroxy drimanes have shown antitumour activity and other hydroxy drimanes are also expected to show bioactivity[7]. The hydroxylation of an unfunctionalized drimane A-ring is possible by microbial transformation[7b], but this reaction proceeds usually in low yield and with poor selectivity. C-3 Oxygenated drimane sesquiterpenes were therefore chosen as the target molecules from decalone **98**.

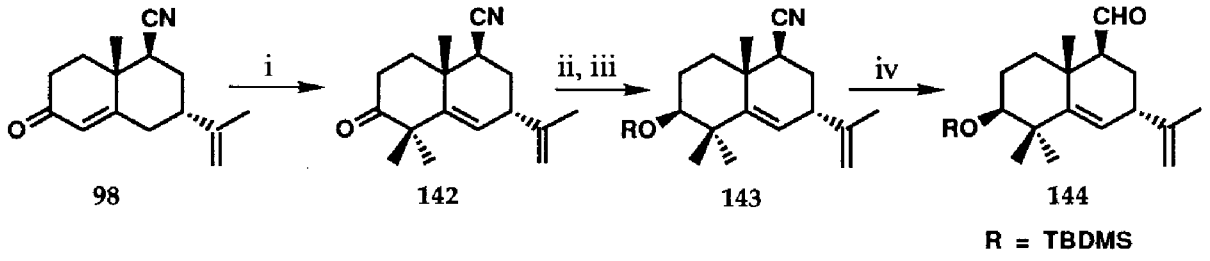
Decalone **98** was methylated with methyl iodide and potassium *tert*-butoxide in tert-butanol to give the cyano ketone **142** in a yield of 80%, without epimerization of the nitrile group (scheme 5.2). The next key step in the synthesis of drimane sesquiterpenes from cyano ketone **142** was the transformation of the isopropenyl group into a carbonyl group *via* oxidative methods. The first method that we explored to effect this conversion, was the isomerization of the isopropenyl group to an isopropylidene group under strong basic conditions, followed by selective ozonolysis of the exocyclic double bond[6].

As shown in chapter 3, a carbonyl functionality is not compatible with the strongly basic conditions of the isomerization process. Functional groups like nitriles and aldehydes are not suitable in this reaction either, since competing reactions like saponification, epimerization or aldol condensation will occur[8].

We therefore transformed both the nitrile and the carbonyl group into the less vulnerable hydroxy group. The C-3 hydroxy functionality was protected as its *tert*-butyldimethylsilyl (TBDMS) ether, to avoid purification problems later on in the reaction sequence (scheme 5.2).

Reduction of the keto group in **142** gave the desired alcohol in 90% yield. Protection of the hydroxy group as its *tert*-butyldimethylsilyl (TBDMS) ether gave compound **143** in 83% yield. The nitrile group in **143** was reduced with diisobutylaluminum hydride (DIBAH) to give the aldehyde **144** in 99% yield.

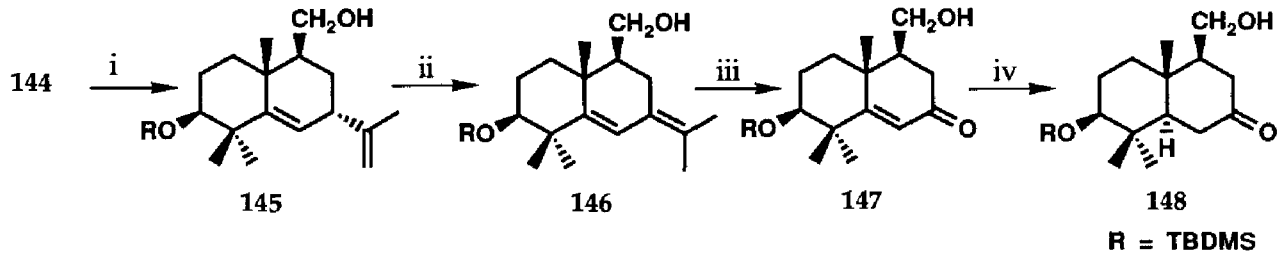
Scheme 5.2



Reagents i: MeI, KO-*t*-Bu, HO-*t*-Bu; ii: $NaBH_4$, MeOH; iii: TBDMSCl, DMF, imidazole; iv: DIBAH, toluene.

Further reduction of aldehyde **144** with sodium borohydride afforded the alcohol **145** in 95% yield (scheme 5.3). Isomerization of the isopropenyl group gave diene **146** in a 74% yield. Ozonolysis of **146** gave enone **147** in a moderate yield of 60%. Enone **147** was submitted to a dissolving metal reduction[9] to give the *trans*-decalone **148** in 78% yield.

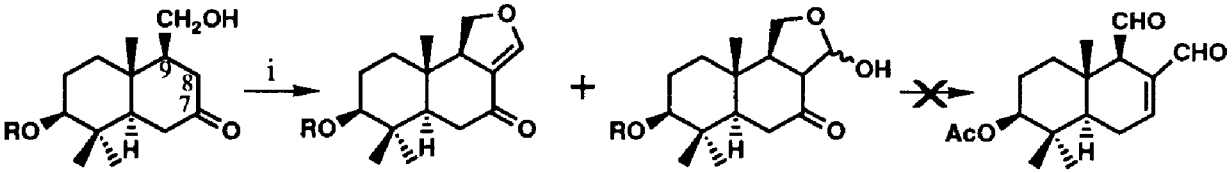
Scheme 5.3



Reagents i: $NaBH_4$, MeOH; ii: KOH, DEG, 220 °C; iii: O_3, MeOH; thiourea; iv: Li/NH_3, HO-*t*-Bu.

In scheme 5.4 an attempted total synthesis of 3β-acetoxypolygodial (**151**) from *trans*-decalone **148** is shown. 3β-Acetoxypolygodial (**151**) can be isolated from the stem bark of *Canella winterana*[2a]. The introduction of C-12 of trans-decalone **148** was now required and direct formylation was used to achieve this goal. Formylation at C-8 of **148** gave a mixture of two products, which were identified as the dihydrofuran **149** and the hemiacetal **150** in 33% and 52% yield, respectively (scheme 5.3). Protection of the primary alcohol functionality of **148** as its *tert*-butyldimethylsilyl ether, followed by submission to the same formylation conditions resulted in no reaction at all, probably due to steric hindrance. Similar products and findings were found by Lallemand *et al.*[10] in formylation reactions of monocyclic model compounds for **148**. Further elaboration of the rather unstable compounds **149** or **150** did not give satisfactory results and another route was examined for the introduction of a functional group at C-8.

Scheme 5.4



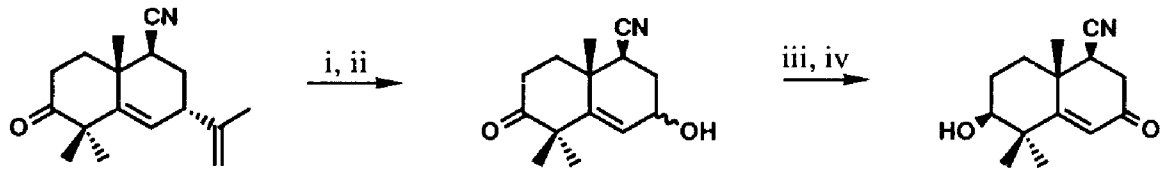
148 149 150 151

R = TBDMS

Reagents i: HCO_2Et, NaH.

Since both ketones and nitriles are resistant to ozonolysis, a procedure of direct ozonolysis followed by a Criegee rearrangement was used to effect the transformation of the isopropenyl group into a carbonyl group (scheme 5.5)[11]. Cyano ketone **142** was submitted to ozonolysis at -78 °C in the presence of methanol to obtain an intermediate methoxy hydroperoxide. A Criegee rearrangement occured after acylation of the intermediate and rising the temperature to room termperature to afford a 1 : 1 mixture of α- and β-acetates. Hydrolysis of the acetates gave the alcohol mixture **152** in an overall yield of 69% from **142**. The keto group at C-3 was reduced with sodium borohydride to give a mixture of diols. The unpurified mixture was oxidized with manganese dioxide to give enone **153** in 95% yield.

Scheme 5.5



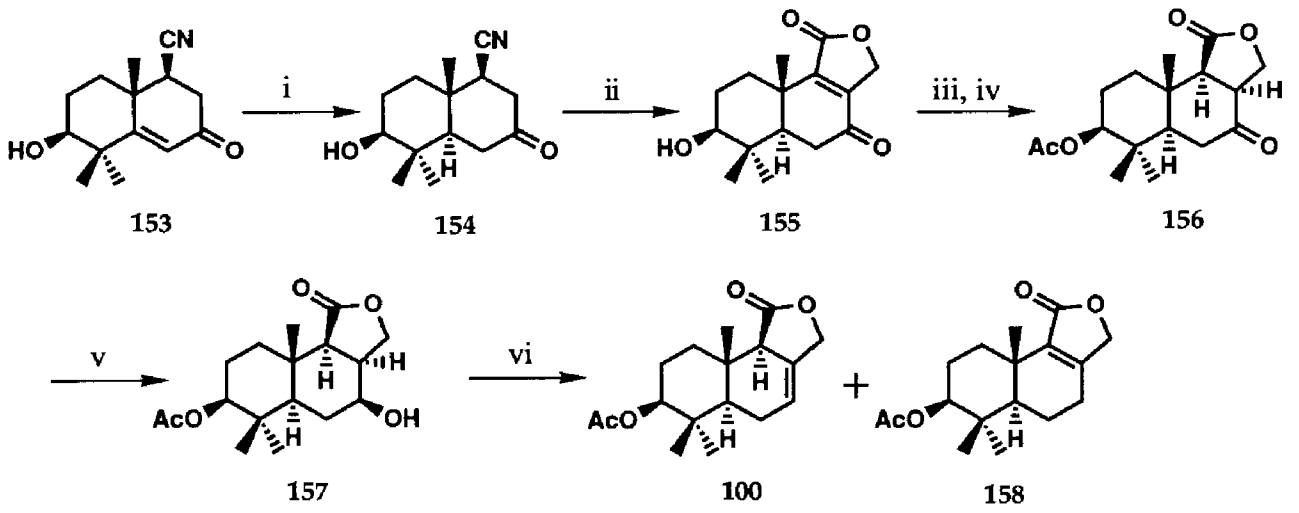
142 152 153

Reagents i: O_3, MeOH; Ac_2O, NEt_3, DMAP; ii: NaOMe, MeOH; iii: $NaBH_4$; iv: MnO_2, acetone.

Cyano decalone **153** was used in the synthesis of enantiomerically pure (-)-3β-acetoxydrimenin (**100**), which can be isolated from the leaves of *Drimys winteri*[12]. (scheme 5.6).

Enone **153** was submitted to catalytic hydrogenation, with palladium on activated carbon as catalyst, to give the saturated cyano ketone **154** in a yield of 91%. The introduction of C-12 in **154** *via* the common formylation conditions (sodium hydride, ethyl formate), also gave partial epimerization of the nitrile group and other unwanted side reactions. To avoid these problems the formylation was carried out under neutral conditions using bis-dimethylamino-*t*-butoxymethane (Bredereck's Reagent)[13] followed by hydrolysis of the resulting enamine with hydrochloric acid, which gave the α,β-unsaturated keto lactone **155** directly in a yield of 49%. Lactone **155** is a suitable intermediate for the synthesis of several natural 3β-oxygenated drimane sesquiterpenes (scheme 5.6).

Scheme 5.6



153 154 155 156 157 100 158

Reagents i: H_2, 10% Pd/C, 4 bar; ii: Bredereck's reagent; HCl, H_2O, acetone; iii: Ac_2O, DMAP; iv: H_2, PtO_2, 2 bar; v: $NaBH_4$, MeOH; vi: TfCl, DMAP.

Acylation of **155** and hydrogenation of the double bond of the α,β-unsaturated lactone using platinum(IV)oxide as catalyst, gave the lactone **156** in a yield of 49%. Selective reduction of the C-7 carbonyl group in **156** with sodium borohydride gave **157** in a yield of 95%. Dehydration[14] of **157** with trifluoromethanesulfonyl chloride (TfCl) in the presence of 4-N,N-dimethylaminopyridine finally led to (-)-3β-acetoxydrimenin (**100**) and (+)-3β-acetoxyisodrimenin (**158**) in 53% and 12% respectively.

Sierra *et al.*[12] have converted (-)-3β-acetoxydrimenin (**100**) to drim-7-ene-3,11,12-triol (**139**) (figure 5.1). So, this procedure is also a formal synthesis for this compound. It is obvious that also other 3-oxygenated drimanes are accessible *via* this synthetic route.

5.3 Experimental Section

General experimental conditions were as described in chapter 2

(1S,3S,8aR)-3-Isopropenyl-1,2,3,5,6,7,8,8a-octahydro-6-oxo-5,5,8a-trimethyl-1-naphthalenecarbonitrile (142)

To a solution of 111.5 g (1.0 mol) of potassium *tert*-butoxide in 1500 ml of *tert*-butyl alcohol was added dropwise a solution of 110.0 g (0.48 mol) of enone **98** in 2000 ml of *tert*-butyl alcohol. After stirring at room temperature for 1.5 h, 90.2 ml (1.46 mol) of methyl iodide was added and stirring was continued for another 2 h. The reaction mixture was concentrated *in vacuo* and worked up as usual to afford an oily residue which was distilled (160 - 163 °C, 0.01 bar) to give 98.8 g (0.38 mol, 80%) of **142** as a yellow oil.

^{1}H NMR: δ 1.09 (s, 3H); 1.22 (s, 3H); 1.25 (s, 3H); 1.76 (s, 3H); 1.8 - 1.9 (m, 2H); 2.0 - 2.2 (m, 2H); 2.5 - 2.6 (m, 3H); 2.77 (t, J = 5.6 Hz, 1H); 4.53 (bs, 1H); 4.88 (bs, 1H); 5.47 (d, J = 4.8 Hz, 1H). ^{13}C NMR: δ 19.5 (q); 21.9 (q); 25.1 (t); 26.7 (q); 29.5 (q); 32.7 (t); 33.1 (t); 34.9 (d); 36.1 (s); 39.6 (d); 48.6 (s); 113.1 (t); 120.7 (s); 122.4 (d); 146.2 (s); 147.8 (s); 213.8 (s). HRMS: calcd (M^+) *m/e* 257.1779; found *m/e* 257.1767. Anal: calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44; found: C, 79.04; H, 8.95; N, 5.55. $[\alpha]_D$ = -32.6 (c = 3.5).

(1S,3S,6S,8aR)-6-(*tert*-Butyldimethylsilyloxy)-3-isopropenyl-1,2,3,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-1-naphthalenecarbonitrile (143)

To a solution of 10.5 g (40.6 mmol) of **142** in 75 ml of methanol was added carefully 845 mg (22.3 mmol) of sodium borohydride. After stirring for 30 min a few drops of acetic acid were added and stirring was continued for 30 min. The reaction mixture was concentrated *in vacuo* and worked up as usual with ether. The residue was purified by flash chromatography (eluent PE/EtOAc = 5/1) to give 9.5 g (36.6 mmol, 90%) of *(1S,3S,6S,8aR)-6-Hydroxy-3-isopropenyl-1,2,3,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-1-naphthalenecarbonitrile* as a white solid, mp: 80 - 81 °C.

^{1}H NMR: δ 1.05 (s, 3H); 1.16 (s, 3H); 1.31 (s, 3H); 1.76 (s, 3H); 1.2 - 1.3 (m, 1H); 1.53 (bs, 1H); 1.7 - 1.9 (m, 2H); 1.9 - 2.2 (m, 3H); 2.42 (dd, J = 2.6, 13.0 Hz, 1H); 2.73 (dd, J = 4.5 Hz, 6.9 Hz, 1H); 3.26 (m, 1H); 4.53 (br s, 1H); 4.86 (br s, 1H); 5.47 (d, J = 4.2 Hz, 1H). ^{13}C NMR: δ 21.8 (q); 22.3 (q); 22.5 (q); 25.1 (t); 26.6 (t); 26.7 (q); 36.0 (s); 36.6 (t); 37.9 (d); 40.3 (d); 41.6 (s); 77.0 (d); 112.7 (t); 121.3 (s); 122.3 (d); 146.5 (s); 147.7 (s). HRMS: calcd (M^+) *m/e* 259.1936; found *m/e* 259.1934. $[\alpha]_D$ = -121 (c = 1.4).

To a solution of 14.1 g (54.4 mmol) of the above-mentioned alcohol in 200 ml of N,N-dimethylformamide was added 14.8 g (220 mol) of imidazole and 16.4 g (110 mmol) of *tert*-butyldimethylsilyl chloride. The reaction mixture was stirred

overnight at room temperature and worked up as usual with ether. The residue was recrystallized from methanol to give 16.9 g (45.3 mmol, 83%) of **143** as white crystals, mp: 89 - 90 °C.
^{1}H NMR: δ 0.00 (s, 3H); 0.02 (s, 3H); 0.86 (s, 9H); 1.00 (s, 3H); 1.06 (s, 3H); 1.28 (s, 3H); 1.74 (s, 3H); 1.2 (m, 1H); 1.5 - 2.2 (m, 5H); 2.38 (dd, J = 2.5 Hz, 13.1 Hz, 1H); 2.70 (dd, J = 4.6 Hz, 6.8 Hz, 1H); 3.21 (dd, J = 4.6 Hz, 11.2 Hz, 1H); 4.55 (bs, 1H); 4.84 (bs, 1H); 5.43 (d, J = 4.3 Hz, 1H). ^{13}C NMR: δ - 5.2 (q); - 4.1 (q); 17.8 (s); 21.8 (q); 22.3 (q); 23.1 (q); 25.2 (t); 25.6 (3*q); 27.0 (t); 27.1 (q); 35.9 (s); 36.5 (t); 37.9 (d); 40.3 (d); 42.3 (d); 77.5 (d); 112.6 (t); 121.1 (s); 121.9 (d); 146.6 (s); 148.1 (s). HRMS: calcd (M^+) *m/e* 373.2800; found *m/e* 373.2797. Anal: calcd for $C_{23}H_{39}NOSi$: C, 73.95; H, 10.52; N, 3.75; found: C, 73.87; H, 10.51; N, 3.58. $[\alpha]_D$ = -74.9 (c = 1.7).

(1S,3S,6S,8aR)-6-(*tert*-Butyldimethylsilyloxy)-3-isopropenyl-1,2,3,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-1-naphthalenecarboxaldehyde (144)
To a solution of 16.9 g (45.2 mmol) of **143** in 350 ml of dry toluene at - 80 °C was added dropwise 80 ml of 1 M diisobutylaluminum hydride in toluene. Stirring was continued for 4 h, then water was added slowly. The aqueous layer was extracted twice with PE. The combined organic layers were washed with water and brine and dried. The solvent was filtered and evaporated *in vacuo* to give 16.9 g (44.9 mmol, 99%) of pure **144** as a pale yellow oil, which solidified upon standing, mp: 60 - 61 °C.
^{1}H NMR: δ 0.02 (s, 3H); 0.03 (s, 3H); 0.88 (s, 9H); 1.02 (s, 3H); 1.09 (s, 3H); 1.16 (s, 3H); 1.74 (s, 3H); 1.0 - 2.2 (m, 7H); 2.74 (m, 1H); 3.26 (dd, J = 4.6 Hz, 11.0 Hz, 1H); 4.56 (bs, 1H); 4.79 (bs, 1H); 5.48 (d, J = 4.4 Hz, 1H); 9.87 (s, 1H). ^{13}C NMR: δ - 5.2 (q); - 4.1 (q); 17.8 (s); 21.2 (t); 21.9 (q); 22.2 (q); 23.3 (q); 25.6 (3*q); 27.1 (t); 27.6 (q); 36.5 (t); 37.2 (s); 40.4 (d); 42.5 (s); 55.7 (d); 77.6 (d); 111.7 (t); 122.9 (d); 147.6 (s); 149.3 (s); 205.7 (s). HRMS: calcd (M^+) *m/e* 376.2797; found *m/e* 376.2792. Anal: calcd for $C_{23}H_{40}O_2Si$: C, 73.36; H, 10.71; found: C, 73.09; H, 10.81. $[\alpha]_D$ = -67 (c = 1.1).

(1S,3S,6S,8aR)-6-(*tert*-Butyldimethylsilyloxy)-3-isopropenyl-1,2,3,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-1-naphthalenemethanol (145)
To a solution of 4.20 g (11.2 mmol) of **144** in 75 ml of ethanol was added carefully 0.21 g (5.6 mmol) of sodium borohydride. The solution was stirred at room temperature for 2 h. A few drops of acetic acid were added and stirring was continued for 1.5 h. The mixture was worked up as usual with ether. The residue was purified by flash chromatography (eluent PE/EtOAc = 9/1) to give 4.01 g (10.6 mmol, 95%) of **145** as white crystals, mp: 92 - 94 °C.
^{1}H NMR: δ 0.01 (s, 3H); 0.02 (s, 3H); 0.86 (s, 9H); 0.97 (s, 3H); 1.01 (s, 3H); 1.07 (s, 3H); 1.75 (s, 3H); 1.0 - 1.4 (m, 3H); 1.5 - 1.9 (m, 5H); 2.68 (m, 1H); 3.19 (dd, J = 4.5 Hz, 11.1 Hz,

1H); 3.27 (dd, J = 8.9 Hz, 10.3 Hz, 1H); 3.76 (dd, J = 3.6 Hz, 10.4 Hz, 1H); 4.56 (bs, 1H);.4.76 (bs, 1H); 5.49 (d, J = 4.2 Hz, 1H). ^{13}C NMR: δ - 5.2 (q); - 4.1 (q); 17.8 (s); 20.6 (q); 22.0 (q); 23.7 (q); 24.6 (t); 25.6 (3*q); 27.4 (t); 27.8 (q); 36.2 (t); 36.5 (s); 41.2 (d); 43.3 (s); 45.5 (d); 63.0 (t); 77.9 (d); 111.0 (t); 123.1 (d); 148.5 (s); 150.1 (s). HRMS: calcd (M^+) *m/e* 378.2954; found *m/e* 378.2953. Anal: calcd for $C_{23}H_{42}O_2Si$: C, 72.97; H, 11.18; found: C, 72.82; H, 11.22. $[\alpha]_D$ = -70 (c = 0.5).

(1S,6S,8aR)-6-(*tert*-Butyldimethylsilyloxy)-3-isopropylidene-1,2,3,5,6,7,8,8a-octahydro-5,8,8-trimethyl -1-naphthalenemethanol (146)

A solution of 13.7 g (36.2 mmol) of **145** and 4.1 g (72.4 mmol) of potassium hydroxide in 250 ml of diethylene glycol was heated at 220 °C for 3 h. The reaction mixture was poured into water and worked up as usual with ether. The residue was purified by flash chromatography (eluent PE/EtOAc = 9/1) to give 10.2 g (27.0 mmol, 74%) of diene **146** as a yellow oil.

^{1}H NMR: δ 0.01 (s, 3H); 0.02 (s, 3H); 0.87 (s, 9H); 0.96 (s, 3H); 1.02 (s, 3H); 1.13 (s, 3H); 1.74 (bs, 3H); 1.77 (bs, 3H); 1.2 - 2.1 (m, 7H); 2.69 (dd, J = 3.7 Hz, 15.4 Hz, 1H); 3.25 (dd, J = 4.5 Hz, 11.2 Hz, 1H); 3.38 (dd, J = 8.9 Hz, 10.4 Hz, 1H); 3.84 (dd, J = 3.7 Hz, 10.4 Hz, 1H); 6.44 (s, 1H). ^{13}C NMR: δ - 5.2 (q); - 4.1 (q); 17.8 (s); 19.4 (q); 20.6 (q); 20.7 (q); 24.2 (q); 25.7 (3*q); 26.2 (t); 27.1 (q); 27.4 (t); 36.1 (s); 36.1 (t); 42.5 (s); 49.6 (d); 63.4 (t); 77.4 (d); 119.9 (d); 125.7 (s); 127.0 (s); 150.1 (s). HRMS: calcd (M^+) *m/e* 378.2954; found *m/e* 378.2951. $[\alpha]_D$ = -48 (c = 1.2).

(1S,6S,8aR)-6-(*tert*-Butyldimethylsilyloxy)-1,2,3,5,6,7,8,8a-octahydro-3-oxo-5,8,8-trimethyl-1-naphthalenemethanol (147)

A solution of 9.8 g (25.9 mmol) of diene **146** in 96 ml of a mixture of methanol and dichloromethane (1: 5) was ozonized at - 80 °C for 30 min. Then nitrogen was purged through for 15 min and 1.20 g (15.7 mmol) of thiourea was added. Stirring was continued for 30 min at - 80 °C, and 2 h at room temperature. The solvent was evaporated and water and dichloromethane were added. The organic layer was washed with water and dried, filtered and evaporated *in vacuo*. The crude oil was purified by flash chromatography (eluent PE/EtOAc = 7/3) to give 5.5 g (15.6 mmol, 60%) of **147** as a yellow oil which solidified on standing, mp: 121 - 123 °C.

^{1}H NMR: δ 0.00 (s, 3H); 0.01 (s, 3H); 0.84 (s, 9H); 1.06 (s, 3H); 1.11 (s, 3H); 1.15 (s, 3H); 1.2 - 2.0 (m, 5H); 2.25 (dd, J = 13.7 Hz, 17.8 Hz, 1H); 2.58 (dd, J = 4.2 Hz, 17.9 Hz, 1H); 2.70 (bs, 1H); 3.32 (dd, J = 4.6 Hz, 10.7 Hz, 1H); 3.46 (dd, J = 8.1 Hz, 10.6 Hz, 1H); 3.80 (dd, J = 4.1 Hz, 10.7 Hz, 1H); 6.01 (s, 1H). ^{13}C NMR: δ - 5.3 (q); - 4.1 (q); 17.8 (s); 20.0 (q); 23.8 (q); 25.6 (3*q); 26.4 (q); 26.8 (t); 34.0 (t); 36.5 (t); 37.8 (s); 43.4 (s); 48.9 (d); 61.8 (t); 76.1 (d); 124.8

(d); 178.5 (s); 200.4 (s). HRMS: calcd (M^+ - 57) *m/e* 295.1729; found *m/e* 295.1731. Anal: calcd for $C_{20}H_{36}O_3Si$: C, 68.14; H, 10.29; found: C, 68.44; H, 10.47. $[\alpha]_D$ = -38 (c = 0.6).

(1S,4aR,6S,8aS)-6-(*tert*-Butyldimethylsilyloxy)-1,2,3,5,6,7,8,8a-octahydro-3-oxo-5,8,8-trimethyl-1-naphthalenemethanol (148)

To a stirred solution of 120 mg (17.5 mgrat) of lithium in 40 ml of ammonia and 20 ml of dry ether was added dropwise a solution of 2.80 g (7.9 mmol) of **147** and 1.65 ml (17.5 mmol) of *tert*-butyl alcohol in 25 ml of dry ether in 30 min. After stirring for 30 min 2.0 g of solid ammonium chloride was added and the ammonia was allowed to evaporate. The mixture was worked up as usual with ether. The crude oil was purified by flash chromatography (eluent PE/EtOAc = 7/3) to give 2.10 g (6.2 mmol, 78%) of **148** as a white solid, mp: 106 - 107 °C.

^1H NMR: δ 0.00 (s, 3H); 0.01 (s, 3H); 0.77 (s, 3H); 0.84 (s, 12H); 0.99 (s, 3H); 1.0 - 1.4 (m, 3H); 1.4 - 1.7 (m, 3H); 1.7 - 1.9 (m, 2H); 2.1 - 2.4 (m, 2H); 2.55 (ddd, J = 1.1 Hz, 4.3 Hz, 10.1 Hz, 1H); 3.18 (dd, J = 5.6 Hz, 10.1 Hz, 1H); 3.38 (dd, J = 8.1 Hz, 10.6 Hz, 1H); 3.79 (dd, J = 4.1 Hz, 10.5 Hz, 1H). ^{13}C NMR: δ - 5.2 (q); - 4.1 (q); 13.6 (q); 15.1 (q); 17.8 (s); 25.6 (3*q); 27.3 (q); 27.9 (q); 35.6 (s); 36.3 (t); 38.8 (t); 39.5 (s); 40.8 (t); 52.1 (d); 52.8 (d); 62.4 (t); 78.6 (d); 211.5 (s). HRMS: (M^+) *m/e* 339.2355; found *m/e* 339.2361. Anal: calcd for $C_{20}H_{38}O_3Si$: C, 67.76; H, 10.80; found: C, 67.65; H, 10.92. $[\alpha]_D$ = +2.5 (c = 1.2).

(5aR,7S,9aS,9bR)-7-(*tert*-Butyldimethylsilyloxy)-1,4,5,5a,6,7,8,9,9a,9b-decahydro-4-oxo-6,6,9a-trimethyl-naphtho-[1,2-c]-furan (149) and (3ξ,3aξ,5aR,7S,9aS,9bS)-7-(*tert*-Butyl-dimethylsilyloxy)-3-hydroxy-4-oxo-6,6,9a-trimethyl-perhydronaphtho-[1,2-c]-furan (150)

To a suspension of 180 mg (6 mmol) of 80% sodium hydride in 5 ml of dry benzene was added dropwise a solution of 355 mg (1 mmol) of **148** and 160 µl (2 mmol) of ethyl formate in 5 ml of dry benzene. The mixture was stirred for 6 h at room temperature. Water was added carefully, followed by ether and 10 ml of aqueous 4 M hydrochloric acid. The aqueous layer was extracted twice with ether and the combined organic layers were washed with water, saturated aqueous sodium bicarbonate and brine. The solvent was dried, filtered and evaporated *in vacuo*. The residue was purified by flash chromatography (eluent PE/EtOAc = 9/1) to give 120 mg (0.33 mmol, 33%) of **149** and 200 mg (0.52 mmol, 52%) of **150** as rather unstable compounds.

149: ^1H NMR: δ - 0.06 (s, 3H); - 0.05 (s, 3H); 0.74 (s, 3H); 0.78 (s, 12H); 0.80 (s, 3H); 1.0 - 1.2 (m, 2H); 1.3 - 1.6 (m, 4H); 2.3 (m, 1H); 2.95 (m, 1H); 3.14 (dd, J = 4.9 Hz, 10.5 Hz, 1H);

4.19 (t, J = 9.9 Hz, 1H); 4.48 (dd, J = 9.9 Hz, 10.8 Hz, 1H); 7.09 (d, J = 2.0 Hz, 1H). ^{13}C NMR: δ - 5.2 (q); - 4.1 (q); 13.2 (q); 14.6 (q); 17.7 (s); 25.6 (3*q); 27.1 (t); 27.7 (q); 35.4 (s); 36.5 (t); 36.6 (t); 39.1 (s); 50.4 (d); 54.3 (d); 74.0 (t); 78.7 (d); 116.6 (s); 153.5 (d); 195.9 (s). HRMS: (M^+) *m/e* 364.2433; found *m/e* 364.2426. $[\alpha]_D = -16$ (c = 1.1).
150: ^1H NMR: δ - 0.02 (s, 3H); - 0.01 (s, 3H); 0.63 (s, 3H); 0.78 (s, 3H); 0.83 (s, 12H); 1.0 - 1.2 (m, 2H); 1.4 - 1.7 (m, 4H); 2.2 - 2.5 (m, 3H); 2.86 (dd, J = 1.7 Hz, 10.8 Hz, 1H); 3.19 (dd, J = 4.9 Hz, 9.9 Hz, 1H); 3.8 - 4.1 (m, 2H); 5.72 (d, J = 1.2 Hz, 1H). ^{13}C NMR: δ - 5.2 (q); - 4.1 (q); 13.7 (q); 14.8 (q); 17.8 (s); 25.6 (3*q); 27.1 (t); 27.6 (q); 34.5 (s); 36.6 (t); 37.9 (t); 39.3 (s); 48.6 (d); 53.2 (d); 57.5 (d); 67.0 (t); 78.9 (d); 99.3 (d); 210.4 (s). HRMS: (M^+ - 57) *m/e* 325.1835; found *m/e* 325.1834.

(1S,3R,8aR) and (1S,3S,8aR)-3-Hydroxy-1,2,3,5,6,7,8,8a-octahydro-6-oxo-5,5,8a-trimethyl-1-naphthalenecarbonitrile (152)
A solution of 41.1 g (160 mmol) of ketone **142** in 78 ml of methanol and 390 ml of dichloromethane was ozonized at - 80 °C until a pale blue colour appeared. The solution was purged with nitrogen and 214 ml (2.26 mol) of acetic anhydride, 214 ml (1.54 mol) of triethylamine and 0.86 g of 4-N,N-dimethylaminopyridine were added. The resulting mixture was stirred overnight at ambient temperature, poured into 1000 ml of aqueous 6 M hydrochloric acid and stirred for 2 h. The mixture was extracted twice with dichloromethane. The combined organic layers were washed with water and saturated aqueous sodium bicarbonate and dried over $MgSO_4$. After evaporation of the solvent *in vacuo*, the residue (42.2 g) was dissolved in 300 ml of methanol and 2.3 g of potassium carbonate was added. Stirring was continued overnight. The mixture was concentrated and worked up as usual with EtOAc. The remaining residue was purified by flash chromatography (eluent PE/EtOAc = 1/1) to give 25.8 g (111 mmol, 69%) of a 1: 1 mixture of α- and β-alcohols **152.**
^1H NMR of the mixture of alcohols: δ 0.98 (s, 3H); 1.06 (s, 3H); 1.10 (s, 3H); 1.13 (s, 6H); 1.16 (s, 3H); 1.6 - 2.7 (m, 13H); 2.84 (dd, J = 5.0 Hz, 11.2 Hz, 1H); 3.3 - 3.6 (m, 2H); 4.15 - 4.30 (m, 2H); 5.48 (d, J = 1.9 Hz, 1H); 5.61 (d, J = 5.0 Hz, 1H).

(1S,6S,8aR)-6-Hydroxy-1,2,3,5,6,7,8,8a-octahydro-3-oxo-5,5,8a-trimethyl-1-naphthalene-carbonitrile (153)
To a solution of 30.2 g (130 mmol) of the mixture of alcohols **152** in 200 ml of methanol was added 2.43 g (64 mmol) of sodium borohydride and the mixture was stirred for 1 h. The mixture was concentrated, and worked up as usual with EtOAc. The residue (28.8 g), was dissolved in 250 ml of acetone and 31.5 g (245 mmol) of manganese dioxide was added. After stirring overnight an extra amount of 10.5 g (80

mmol) of manganese dioxide was added and stirring was continued for 18 h. The mixture was filtered over hyflo and the solvent was evaporated *in vacuo*, to give 28.4 g (122 mmol, 94%) of pure enone **153**, mp: 129 - 130 °C.
^{1}H NMR: δ 1.06 (s, 3H); 1.15 (s, 3H); 1.39 (s, 3H); 1.3 - 1.5 (m, 1H); 1.7 - 1.9 (m, 2H); 2.00 (dt, J = 3.2 Hz, 13.4 Hz, 1H); 2.6 (m, 2H); 2.83 (d, J = 5.1 Hz, 1H); 2.94 (dd, J = 6.5 Hz, 11.8 Hz, 1H); 3.30 (m, 1H); 5.98 (s, 1H). ^{13}C NMR: δ 21.3 (q); 22.9 (q); 25.6 (q); 26.0 (t); 35.4 (2*t); 37.0 (s); 40.3 (d); 42.9 (s); 74.9 (d); 118.4 (s); 124.3 (d); 174.9 (s); 194.6 (s). HRMS: calcd (M^+) *m/e* 233.1416; found *m/e* 233.1416. Anal: calc for $C_{14}H_{19}NO_2$: C, 72.06; H, 8.21; N, 6.00; found: C, 72.05; H, 8.13; N, 5.87. $[\alpha]_D$ = -50.2 (c = 0.3).

(1S,4aR,6S,8aS)-6-Hydroxy-3-oxo-perhydro-5,5,8a-trimethyl-1-naphthalenecarbonitrile (154)
A mixture of 27.0 g (106 mmol) of enone **153** and 0.8 g of 10% palladium on activated carbon in 170 ml of ethanol was hydrogenated (4 bar) for 6 h. The mixture was filtered over hyflo and the solvent was evaporated *in vacuo* to give 24.8 g (106 mmol, 91%) of pure **154** as a pale yellow solid, mp: 139 - 140 °C.
^{1}H NMR: δ 0.79 (s, 3H); 0.91 (s, 3H); 1.23 (s, 3H); 1.2 - 1.3 (m, 2H); 1.6 - 1.8 (m, 2H); 1.93 (bs, 1H); 2.00 (dt, J = 3.7 Hz, 13.3 Hz, 1H); 2.30 (dd, J = 14.0 Hz, 15.7 Hz, 1H); 2.40 (dd, J = 3.6 Hz, 11.5 Hz, 1H); 2.5 - 2.6 (m, 3H); 3.20 (dd, J = 4.4 Hz, 11.5 Hz, 1H). ^{13}C NMR: δ 14.3 (q); 14.5 (q); 26.5 (t); 27.0 (q); 35.8 (s); 36.5 (t); 37.9 (t); 38.9 (s); 39.4 (t); 42.6 (d); 50.1 (d); 77.6 (d); 118.5 (s); 205.8 (s). HRMS: calcd (M^+) *m/e* 235.1572; found *m/e* 235.1572. Anal: calcd for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00; N, 5.95; found: C, 71.21; H, 9.06; N, 5.89. $[\alpha]_D$ = -0.7 (c = 0.4).

(5aR,7S,9aS)-7-Hydroxy-4,5,5a,6,7,8,9,9a-octahydro-4-oxo-6,6,9a-trimethyl-naphtho-[1,2-c]-furan-1(3H)-one (155)
A mixture of 4.0 g (17 mmol) of ketone **154** and 15.8 ml (76.6 mmol) of bis-dimethylamino-*tert*-butoxymethane (Bredereck's Reagent) was heated at 55 °C for 4 h, and then poured into an ice cold aqueous 1 M hydrochloric acid solution. The mixture was stirred for 1 h and worked up as usual with EtOAc. The residue, 4.30 g of a brown oil, was dissolved in 50 ml of acetone and 30 ml of aqueous 4 M hydrochloric acid. The reaction mixture was stirred for four days. Water was added and the mixture was worked up as usual with EtOAc. The residue was purified by flash chromatography (eluent PE/EtOAc = 3/2) to give 2.21 g (8.4 mmol, 49%) of **155** as a pale yellow solid, mp: 199 - 200 °C.
^{1}H NMR: δ 0.90 (s, 3H); 1.01 (s, 3H); 1.26 (s, 3H); 1.3 - 1.9 (m, 5H); 2.4 - 2.7 (m, 3H); 3.29 (dd, J = 5.2 Hz, 11.0 Hz, 1H); 4.83 (s, 2H). ^{13}C NMR: δ 15.1 (q); 18.1 (q); 26.9 (t); 27.7 (q); 31.7 (t); 35.9 (t); 36.4 (s); 38.8 (s); 50.9 (d); 67.3 (t); 77.6 (d); 149.0 (s); 151.7 (s); 170.7 (s);

195.8 (s). HRMS: calcd (M^+) *m/e* 264.1361; found *m/e* 264.1361. Anal: calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63; found: C, 67.72; H, 7.79. $[\alpha]_D$ = +31.3 (c = 0.4).

(3aS,5aR,7S,9aS,9bS)-7-Acetoxy-4-oxo-perhydro-6,6,9a-trimethyl-naphtho-[1,2-c]-furan-1(3H)-one (156)

To a solution of 2.06 g (7.8 mmol) of **155** in 30 ml of pyridine was added 2.21 ml (23.4 mmol) of acetic anhydride and 25 mg of 4-N,N-dimethylaminopyridine. The reaction mixture was stirred for 2.5 h, then poured into an ice cold aqueous 2 M hydrochloric acid solution and worked up with EtOAc to give 2.26 g (7.4 mmol, 95%) of *(5aR,7S,9aS)-7-Acetoxy-4,5,5a,6,7,8,9,9a-octahydro-4-oxo-6,6,9a-trimethyl-naphtho-[1,2-c]-furan-1(3H)-one* as a pale yellow solid, mp: 220 - 221 °C.

^{1}H NMR: δ 0.89 (s, 3H); 0.97 (s, 3H); 1.27 (s, 3H); 1.5 - 1.9 (m, 4H); 2.03 (s, 3H); 2.3 - 2.4 (m, 3H); 4.54 (dd, J = 4.9 Hz, 11.2 Hz, 1H); 4.82 (s, 2H). ^{13}C NMR: δ 16.2 (q); 18.1 (q); 21.2 (q); 23.3 (t); 27.7 (q); 31.4 (t); 35.7 (t); 36.2 (s); 37.7 (s); 50.9 (d); 67.4 (t); 79.0 (d); 149.1 (s); 151.6 (s); 170.6 (2*s); 195.4 (s). HRMS: calcd (M^+) *m/e* 306.1464; found *m/e* 306.1467. Anal: calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24; found: C, 66.43; H, 7.13. $[\alpha]_D$ = +36.1 (c= 0.4).

To a solution of 1.45 g (4.7 mmol) of the above-mentioned acetate in 75 ml of EtOAc and 10 ml of methanol was added 100 mg of platinum(IV)oxide hydrate. The mixture was hydrogenated for 2.5 h (2 bar), and then filtered over hyflo. The solvent was evaporated *in vacuo*. The crude oil was purified by flash chromatography (eluent PE/EtOAc = 3/2) to give 0.71 g (2.3 mmol, 49%) of **156** as white crystals, mp: 182 - 183 °C.

^{1}H NMR: δ 0.83 (s, 3H); 0.86 (s, 3H); 0.94 (s, 3H); 1.5 - 1.8 (m, 4H); 1.88 (dd, J = 8.6 Hz, 11.2 Hz, 1H); 2.04 (s, 3H); 2.44 (m, 2H); 2.80 (d, J = 12.5 Hz, 1H); 3.29 (ddd, J = 6.4 Hz, 9.8 Hz, 12.4 Hz, 1H); 4.3 - 4.6 (m, 3H). ^{13}C NMR: δ 14.9 (q); 15.6 (q); 21.0 (q); 23.1 (t); 27.1 (q); 35.9 (s); 35.9 (t); 36.8 (t); 37.9 (s); 44.1 (d); 48.2 (d); 52.8 (d); 66.2 (t); 79.3 (d); 170.5 (s); 175.3 (s); 208.6 (s). HRMS: calcd (M^+ - 60) *m/e* 248.1412; found *m/e* 248.1415. Anal: calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85; found: C, 66.48; H, 7.85. $[\alpha]_D$ = -77 (c= 0.5).

(3aS,4S,5aR,7S,9aS,9bS)-7-Acetoxy-4-hydroxy-perhydro-6,6,9a-trimethyl-naphtho-[1,2-c] -furan-1-one (157)

To a solution of 0.62 g (2.0 mmol) of **156** in 20 ml of methanol was added 38 mg (1 mmol) of sodium borohydride. The reaction mixture was stirred for 1 h and worked up as usual with EtOAc to give 0.59 g (1.9 mmol, 95%) of pure **157** as a white solid, mp: 215 - 217 °C.

^{1}H NMR: δ 0.89 (s, 6H); 1.04 (s, 3H); 1.1 - 1.9 (m, 6H); 2.03 (s, 3H); 2.1 - 2.3 (m, 2H); 2.41

(bs, 1H); 2.99 (m, 1H); 4.0 - 4.4 (m, 3H); 4.48 (dd, J = 5.0 Hz, 11.0 Hz, 1H). ^{13}C NMR: δ 16.7 (2*q); 21.0 (q); 22.0 (t); 26.8 (t); 28.1 (q); 35.5 (s); 37.6 (s); 37.9 (t); 40.2 (d); 49.5 (d); 54.1 (d); 68.8 (t); 69.2 (d); 79.6 (d); 170.7 (s); 177.5 (s). HRMS: calcd (M^+ - 60) *m/e* 250.1569; found *m/e* 250.1564. Anal: calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44; found: C, 65.95; H, 8.51. $[\alpha]_D$ = -36 (c = 0.4).

(5aR,7S,9aS,9bR)-7-Acetoxy-5,5a,6,7,8,9,9a,9b-octahydro-6,6,9a-trimethyl-naphtho-[1,2-c]-furan-1(3H)-one (100) and (5aR,7S,9aS)-7-Acetoxy-4,5,5a,6,7,8,9,9a-octahydro-6,6,9a-trimethyl-naphtho-[1,2-c]-furan-1(3H)-one (158)

To a solution of 0.20 g (0.65 mmol) of **157** and 0.47 (3.8 mmol) of 4-N,N-dimethylaminopyridine in 15 ml of dry dichloromethane was added dropwise a solution of 156 µl (1.47 mmol) of trifluoromethanesulfonyl chloride in 3 ml of dichloromethane at -5 °C and the mixture was stirred for 20 min. Then the mixture was stirred for 1 h at room temperature. Water and dichloromethane were added, the aqueous layer was extracted twice with dichloromethane. The combined organic layers were washed with water, saturated aqueous sodium bicarbonate and brine. The solvent was dried, filtered and evaporated *in vacuo*. The residue was purified by flash chromatography (eluent PE/EtOAc = 3/2) to give 99 mg (53%) of **100** as white crystals, mp: 150 - 165 °C and 23 mg (12%) of **158** as a pale yellow oil.

100 ^1H NMR (500 MHz): δ 0.89 (s, 6H); 0.95 (s, 3H); 1.3 - 1.8 (m, 5H); 2.06 (s, 3H); 2.16 (m, 1H); 2.53 (dt, J = 3.4 Hz, 6.8 Hz, 1H); 2.76 (m, 1H); 4.56 (dd, J = 5.0 Hz, 10.8 Hz, 1H); 4.68 (m, 2H); 5.75 (m, 1H). ^{13}C NMR: δ 14.0 (q); 15.9 (q); 21.2 (q); 23.0 (t); 23.5 (t); 27.6 (q); 33.9 (s); 35.9 (t); 37.8 (s); 49.2 (d); 53.6 (d); 69.8 (t); 80.3 (d); 120.7 (d); 129.8 (s); 170.8 (s); 174.9 (s). HRMS: calcd (M^+) *m/e* 292.1674; found *m/e* 292.1673. Anal: calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27; found: C, 69.84; H, 8.25. $[\alpha]_D$ = -6.1 (c = 0.4).

158 ^1H NMR: δ 0.92 (s, 6H); 1.15 (s, 3H); 1.1 - 1.9 (m, 6H); 2.05 (s, 3H); 2.35 (m, 2H); 2.60 (dt, J = 3.5 Hz, 13.6 Hz, 1H); 4.53 (dd, J = 5.3 Hz, 11.2 Hz, 1H); 4.57 (s, 2H). ^{13}C NMR: δ 16.6 (q); 17.9 (t); 20.1 (q); 21.3 (q); 23.6 (t); 25.3 (t); 28.2 (q); 32.3 (t); 34.5 (s); 37.8 (s); 51.6 (d); 70.7 (t); 80.1 (d); 135.0 (s); 159.1 (s); 172.4 (s); 176.4 (s). HRMS: calcd (M^+-60) *m/e* 232.1463, found *m/e* 232.1463. $[\alpha]_D$ = +100 (c = 0.11).

5.4 References and Notes

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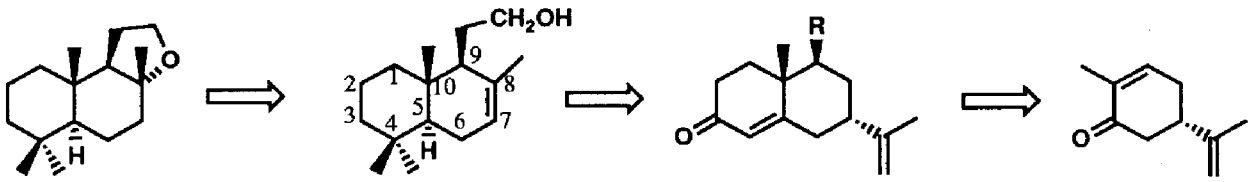
6 Total Synthesis of (-)-Ambrox® (101) from S-(+)-Carvone*

6.1 Introduction

Since ancient times, ambergris has been one of the most highly valued perfumery materials[1]. Ambergris is a metabolic product of the spermwhale (*Physeter macrocephalus L.*), which accumulates as concretions in the gut. Due to excessive whaling, ambergris is disappearing from the world market. (-)-Ambrox® **(101)** (scheme 6.1), the commercially most important constituent of the scarce natural ambergris, is recognized as the prototype of all ambergris odorants, both structurally and organoleptically[2]. For this reason, diverse synthetic routes to (-)-Ambrox® **(101)** and its racemate have been developed. (-)-Ambrox® **(101)**was previously prepared starting from geranylacetone[3], which made an optical resolution step necessary, and from naturally occurring sesquiterpenes[4] or diterpenes[5]. The racemate was prepared by a number of total syntheses employing biogenetic-type cyclizations from farnesic or monocyclofarnesic acids or derivatives of these[6].

Scheme 6.1



101 **159** **98:** R = allyl **99:** R = CN **S-(+)-carvone**

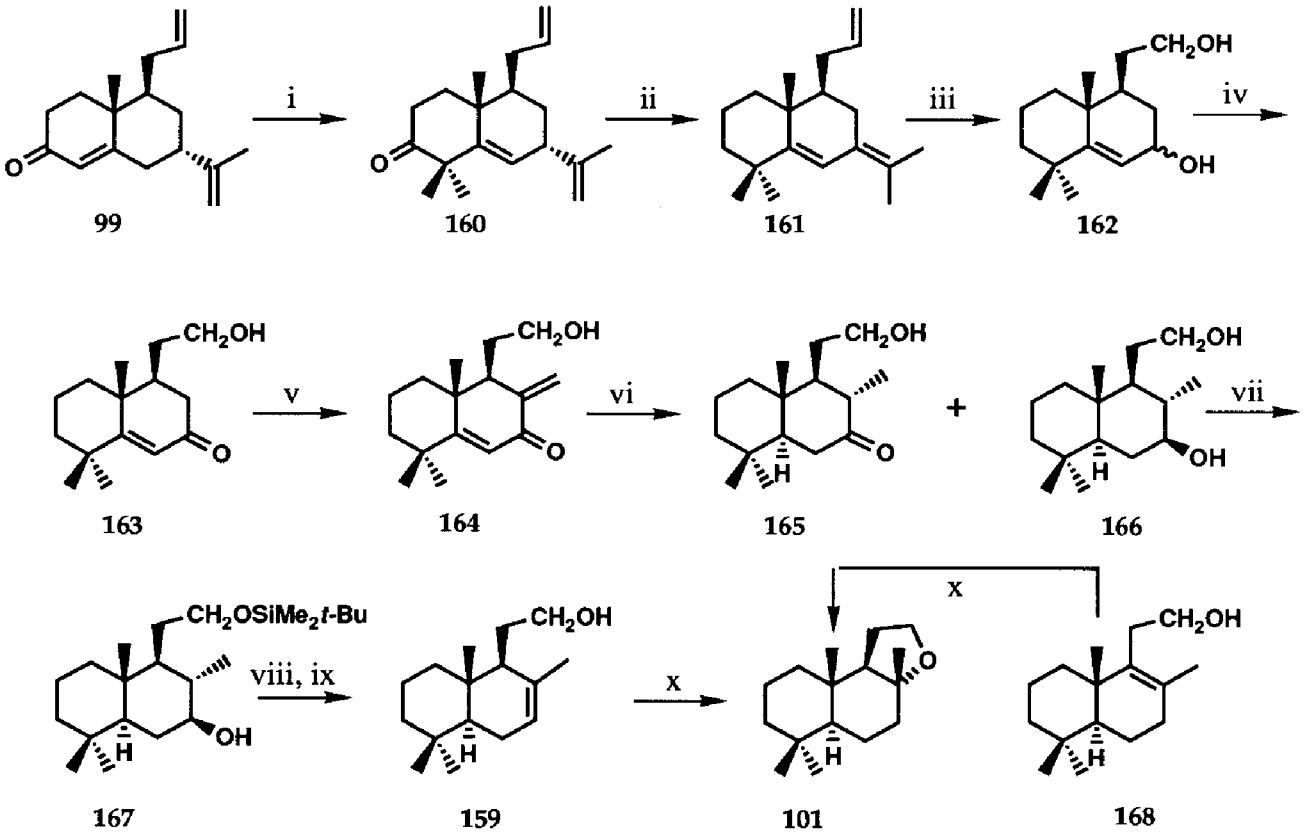
Our retrosynthetic plan to (-)-Ambrox® **(101)** starting from S-(+)-carvone is shown in scheme 6.1. Conjugate addition of the indicated nucleophiles to S-(+)-carvone followed by a Robinson annulation with methyl vinyl ketone gives the substituted decalones **98** and **99** (chapter 4) stereoselectively with the chiral centers at C-9[7] and C-10 in the correct configuration for the preparation of (-)-Ambrox® **(101)**. The allyl and nitrile substituents both can be transformed into the hydroxy ethylene substituent in **159**. The conversion of the isopropenyl group into a carbonyl group at C-7 gives the opportunity to introduce a methyl group at C-8. This carbonyl group can be used later on for the introduction of the $\Delta^{7,8}$ double bond in **159** which is necessary for the final cyclization to (-)-Ambrox® **(101)**.

* This chapter has been published in a revised form: Verstegen-Haaksma, A. A.; Swarts, H. J.; Jansen, B. J. M.; de Groot, Ac. *Tetrahedron* **1994**, *50*, 10095-10106.

6.2 Synthesis of (-)-Ambrox® (101) from decalone 99.

Decalone **99** in scheme 6.2 was obtained from S-(+)-carvone *via* conjugate addition of allyl magnesium chloride (scheme 4.2), followed by annulation of the corresponding silyl enol ether with methyl vinyl ketone (scheme 4.3). The required *gem* dimethyl groups were introduced using methyl iodide and standard basic conditions to give ketone **160** in 88% yield. Removal of the carbonyl group and isomerization of the olefinic bond of the isopropenyl group to the exocyclic isopropylidene group were performed in one step under the conditions of the Wolff-Kishner reduction to afford triene **161** in 85% yield. Ozonolysis of the allylic and exocyclic double bonds in **161** and reduction of the intermediate ozonides with sodium borohydride gave diol **162** in 80% yield. The allylic hydroxyl group was selectively oxidized with manganese dioxide to give the α,β-unsaturated ketone **163** in 90% yield.

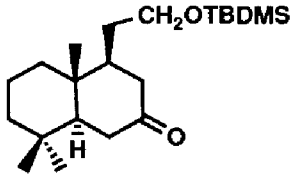
Scheme 6.2



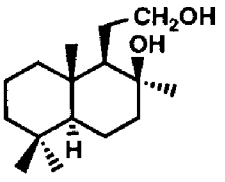
Reagents i: MeI, KO-*t*-Bu, HO-*t*-Bu; ii: Hydrazine, KOH, DEG, 220 °C; iii: O_3, MeOH, -78 °C; $NaBH_4$; iv: MnO_2, acetone; v: $(Me)_2N\text{-}CH_2\text{-}N(Me)_2$, Ac_2O; vi: Li, NH_3, EtOH; vii: TBDMSCl, DMF, imidazole; viii: MsCl, DMAP, CH_2Cl_2; $LiCO_3$, LiBr, Δ; ix: HF, acetonitrile; x: *p*-TsOH, nitromethane.

An obvious way to proceed from this point was the synthesis of hydroxyketone **165** *via* the saturated decalone **169** (figure 6.1), but this approach was unsuccessful. Although the *trans*-fused decalone **169** was obtained in good yield *via* catalytic hydrogenation of enone **163** with palladium on activated carbon in ethanol followed by protection of the primary hydroxyl group with *tert*-butyldimethylsilyl chloride, the subsequent methylation gave very disappointing results. Under the usual kinetic methylation conditions (lithium diisopropylamide, tetrahydrofuran, hexamethylphosphoramide) a large recovery of the starting material was observed. The reaction could not be improved by using a small excess of lithium diisopropylamide (1.5 eq) and/or a higher temperature of 40 °C, because then dimethylation was a competing reaction, in addition to a large recovery of starting material. The introduction of an α-methylene group to **169** by a Mannich reaction followed by β-elimination[8] was unsuccessful too. Heating decalone **169** in a mixture of N,N,N',N'-tetramethyldiaminomethane and acetic anhydride gave a product that according to GC-MS and ^{1}H NMR analysis had an α-methylene group at both C-6 and C-8.

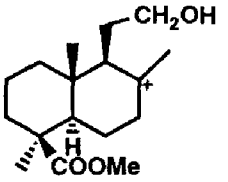
Figure 6.1



169



170



171

Enone **163** gave dienone **164** in 70% yield in the Mannich reaction[8] with N,N,N',N'-tetramethyldiaminomethane and acetic anhydride (scheme 6.2). Reduction of compound **164** by a large excess of lithium in ammonia and ethanol as the proton donor gave diol **166** in 73% and decalone **165** as a byproduct in 10% yield. Selective protection of the primary hydroxyl group in **166** by *tert*-butyldimethylsilyl chloride (TBDMSCl) gave the monoprotected diol **167** in 98% yield. Dehydration of **167** was performed by mesylation, substitution by bromide and dehydrobromination. Deprotection of the TBDMS ether with hydrofluoric acid gave alcohol **159** in 80% from **167**.

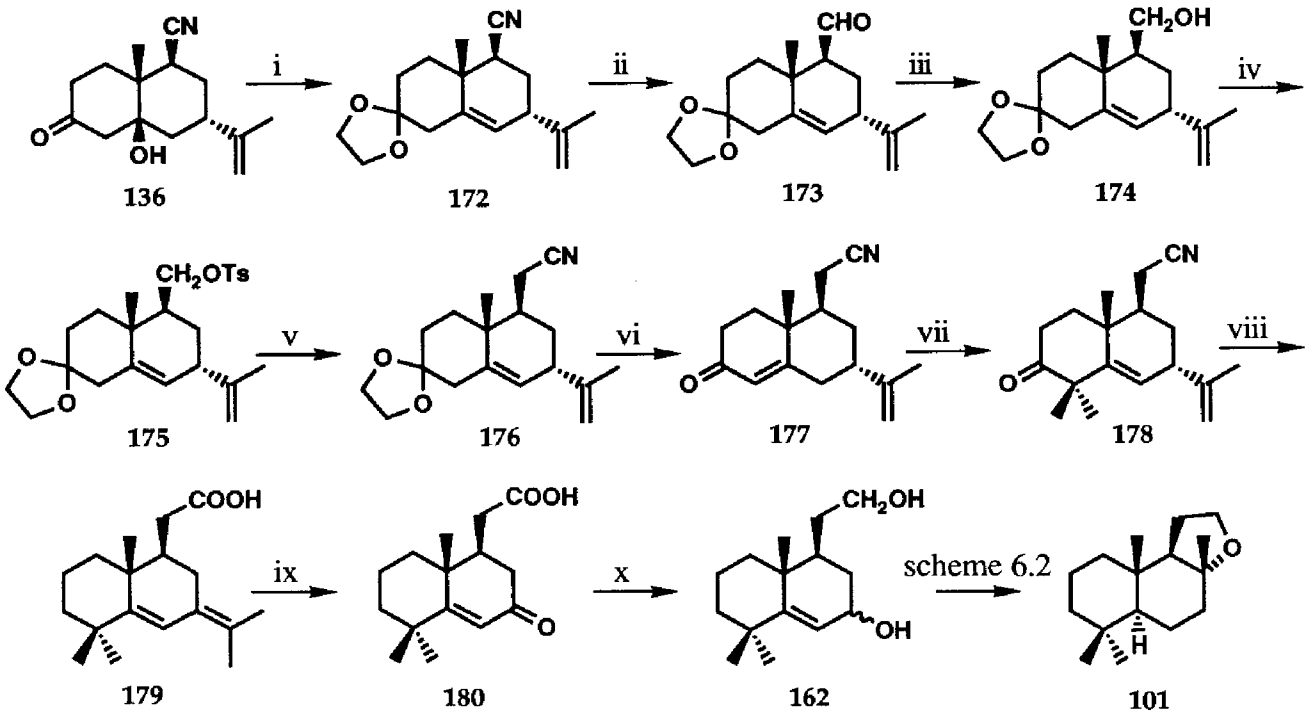
The unsaturated alcohol **159** was transformed into (-)-Ambrox® (**101**) before *via* a six step procedure[4]. The successful dehydration of racemic alcohol **170** (figure 6.1) to (±)-Ambrox® by Büchi and Wüest[6a] encouraged us to try the cyclization of alcohol **159** to (-)-Ambrox® (**101**) in one step, because the same tertiary carbocationic intermediate is assumed to be formed from **159** and **170**. Refluxing of **170** in nitromethane in the presence of *p*-toluenesulfonic acid gave the kinetic cyclization product Ambrox® (**101**) in

excess. The ratio of the thermodynamic and kinetic diastereoisomers in the cyclization of **170** [5a] proved to be only temperature dependent. Decreasing the temperature from 80 °C to 20 °C afforded the kinetic diastereomer almost exclusively.
We therefore investigated the cyclization of alcohol **159** *at room temperature* in nitromethane in the presence of *p*-toluenesulfonic acid and indeed in this way (-)-Ambrox® (**101**) was obtained directly in 80% yield. When the mixture was not stirred long enough, the yield of (-)-Ambrox® was lower and the isomerized alcohol **168** was found as byproduct. Alcohol **168** could be cyclized to (-)-Ambrox® (**101**) too under the same acidic conditions at room temperature.

6.3 Synthesis of (-)-Ambrox® (101) from decalone 98

A second route to (-)-Ambrox® (**101**) was developed starting from hydroxyketone **136**, which was obtained from S-(+)-carvone in two steps in an overall yield of 86% (chapter 4, scheme 4.5). Although the synthetic sequence involves more steps than the reaction path from **99**, it is more suitable for large scale production.
Hydroxyketone **136** was dehydrated and protected as its acetal in a "one-pot reaction" by refluxing in toluene with a catalytic amount of *p*-toluenesulfonic acid. Hydroxyketone **136** was first transformed completely into the intermediate decalone **97** and then glycol was added to give the acetal **172** in 90% yield (scheme 6.3). Compound **172** was reduced with diisobutylaluminum hydride (DIBAH) to give aldehyde **173** in 95% yield and further reduction with sodium borohydride gave alcohol **174** in 99%. The hydroxyl group was tosylated with *p*-toluenesulfonyl choride in pyridine to give tosylate **175** in 96% yield. The tosyl group was replaced by a nitrile group in 99% yield and then the acetal functionality was deprotected with hydrochloric acid to give enone **177** in 93% yield. Methylation with methyl iodide under standard basic conditions gave compound **178** in 80% yield. The conditions of the Wolff-Kishner reduction changed three substituents in one procedure. The C-3 carbonyl group was removed, the isopropenyl group was isomerized into an isopropylidene group and the nitrile substituent was saponified[9] to give acid **179** in 98% yield. Ozonolysis followed by reduction with sodium borohydride gave enone **180** in 90% yield. Reduction of enone **180** with lithium aluminum hydride gave diol **162** in 80% yield. This diol was transformed into (-)-Ambrox® (**101**) according to scheme 6.2.

Scheme 6.3



Reagents i: *p*-TsOH, toluene, glycol, Δ; ii: DIBAH, toluene; iii: $NaBH_4$; iv: TsCl, pyridine; v: NaCN, DMF; vi: HCl, H_2O; vii: MeI, KO-*t*-Bu, HO-*t*-Bu; viii: Hydrazine, KOH, DEG, 220 °C; ix: O_3, MeOH; $NaBH_4$; x: $LiAlH_4$.

Although the synthesis of (-)-Ambrox® (**101**) itself from S-(+)-carvone is not a short one, the approach is flexible and a number of other ambergris derivatives with attractive organoleptic properties[10] can also be synthesized *via* this route. Especially in the synthesis of derivatives with a more functionalized A-ring, S-(+)-carvone is an attractive starting material.

6.4 Experimental Section

General experimental conditions were as described in chapter 2

(4aR,5S,7S)-3,4,4a,5,6,7-Hexahydro-7-isopropenyl-5-(prop-2'-enyl)-1,1,4a-trimethyl-naphthalene-2(1H)-one (160)

To a solution of 5.0 g (45 mmol) of potassium-*tert*-butoxide in *tert*-butyl alcohol (80 ml) was added dropwise a solution of 4.47 g (18.3 mmol) of enone **99** in *tert*-butyl alcohol (20 ml) at room temperature. After stirring for 30 min, 3.4 ml (7.8 g, 55 mmol) of methyl iodide was added in one portion and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was concentrated *in vacuo* and worked up as usual to

afford an oily residue which was purified by flash chromatography (eluent PE/EtOAc = 97/3) to give 4.40 g (16.2 mmol, 88%) of ketone **160** as a pale yellow oil.
^{1}H NMR: δ 0.74 (s, 3H); 1.23 (s, 3H); 1.27 (s, 3H); 1.73 (s, 3H); 1.3 - 1.8 (m, 5H); 1.9 - 2.8 (m, 5H); 4.54 (s, 1H); 4.79 (s, 1H); 4.93 (m, 1H); 5.00 (s, 1H); 5.50 (dd, J = 4.8 Hz, 1.0 Hz, 1H); 5.63 (m, 1H). ^{13}C NMR: δ 17.2 (q); 22.0 (q); 25.6 (t); 26.9 (q); 30.1 (q); 31.3 (t); 33.4 (t); 33.9 (t); 37.4 (s); 39.1 (d); 40.9 (d); 48.4 (s); 111.3 (t); 115.6 (t); 123.0 (d); 137.7 (d); 148.0 (s); 150.4 (s); 216.1 (s). HRMS: calcd (M^+) *m/e* 272.2140; found *m/e* 272.2143. $[\alpha]_D$ = −109 (c = 0.3).

(1S,8aR)-3-Isopropylidene-1,2,3,5,6,7,8,8a-octahydro-1-(prop-2'-enyl)-4a,8,8-trimethyl-naphthalene (161)
A solution of 4.40 g (16.2 mmol) of ketone **160**, 5 ml of hydrazine hydrate and 2.70 g (48 mmol) of potassium hydroxide in diethylene glycol (80 ml) was heated for 2 h at 120 °C and then the excess of hydrazine hydrate and water was removed by distillation. The temperature was raised to 220 °C and after 3 h cooled, poured into water and worked up as usual. The residue was purified by flash chromatography (eluent PE) to afford 3.57 g (13.8 mmol, 85%) of triene **161** as a colourless oil.
^{1}H NMR: δ 1.04 (s, 3H); 1.14 (s, 6H); 1.70 (s, 3H); 1.78 (s, 3H); 0.8 - 2.0 (m, 10H); 2.2 - 2.6 (m, 2H); 5.01 (m, 2H); 5.73 (m, 1H). ^{13}C NMR: δ 18.3 (t); 19.3 (q); 19.9 (q); 20.4 (q); 28.2 (t); 31.1 (q); 32.3 (q); 34.1 (t); 35.9 (s); 37.0 (s); 38.3 (t); 40.8 (t); 46.5 (d); 115.1 (t); 118.3 (d); 124.6 (s); 127.5 (s); 138.6 (d); 151.4 (s). HRMS: calcd (M^+) *m/e* 258.2347; found *m/e* 258.2349. $[\alpha]_D$ = −64.6 (c = 0.3).

(1S,3R/S,8aR)-3-Hydroxy-1,2,3,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-1-naphthalene-ethanol (162)
A solution of 3.05 g (11.8 mmol) of triene **161** in 100 ml of methanol/dichloromethane (3/1) was ozonized at -78 °C. The excess of ozone was expelled by purging the solution with nitrogen for 15 min. Then 0.90 g (23.7 mmol) of sodium borohydride was added at -78 °C. The cooling bath was removed and the mixture was stirred for 3 h at room temperature. Water was added and the mixture was worked up as usual to give 2.25 g (9.5 mmol, 80%) of diol **162** as white crystals, mp 122-126 °C after flash chromatography (eluent PE/EtOAc = 3/2).
^{1}H NMR: (with a drop of $CDOD_3$) δ 1.03 (s, 6H); 1.09 (s, 3H); 0.70 - 1.95 (m, 11H); 2.79 (bs, 2H); 3.45 - 3.80 (m, 2H); 4.12 - 4.30 (m, 1H); 5.42 - 5.48 (m, 1H). ^{13}C NMR: δ 18.4 (t); 20.6 (q); 30.0 (q); 32.4 (t); 32.9 (q); 33.3 (t); 35.8 (s); 37.7 (s); 38.2 (t); 41.0 (t); 42.8 (d); 61.4 (t); 68.0 (d); 122.9 (d); 153.6 (s). HRMS: calcd (M^+) *m/e* 238.1933; found *m/e* 238.1924. Anal: calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00; found: C, 75.78; H, 11.14. $[\alpha]_D$ = +10.9 (c =

0.4).

(1S,8aR)-1,2,3,5,6,7,8,8a-Octahydro-3-oxo-5,5,8a-trimethyl-1-naphthaleneethanol (163)
A mixture of 2.00 g (8.4 mmol) of diol **162** and 7.3 g (84 mmol) of manganese dioxide in acetone was stirred for 8 h. After filtration over hyflo the acetone was evaporated and the residue was purified by flash chromatography (eluent PE/EtOAc = 3/2) to afford 1.78 g (7.5 mmol, 90%) of enone **163** as a colourless oil.
^{1}H NMR: δ 1.13 (s, 3H); 1.15 (s, 3H); 1.18 (s, 3H); 1.00 - 2.55 (m, 12H); 3.50 - 3.80 (m, 2H); 5.99 (s, 1H). ^{13}C NMR: δ 17.8 (t); 19.5 (q); 30.5 (q); 31.7 (q); 31.8 (t); 37.1 (s); 37.2 (t); 38.7 (s); 39.0 (t); 39.5 (t); 43.2 (d); 60.6 (t); 123.8 (d); 179.8 (s); 200.2 (s). HRMS: calcd (M^+) *m/e* 236.1776; found *m/e* 236.1776. $[\alpha]_D$ = -36.7 (c = 0.4).

(1R,8aR)-2-Methylene-1,2,3,5,6,7,8,8a-octahydro-3-oxo-5,5,8a-trimethyl-1-naphthlene-ethanol (164)
To a solution of 0.62 g (2.64 mmol) of hydroxyketone **163** in 2 ml of N,N,N',N'-tetramethyldiaminomethane was added 2 ml of acetic anhydride. The reaction mixture was heated for 2 h at 90 °C under a nitrogen atmosphere. Water was added and the mixture was worked up as usual. The residue was dissolved into methanol and stirred for 1 h at room temperature with 0.18 g (1.3 mmol) of potassium carbonate. The mixture was worked up as usual. The residue was purified by flash chromatography (eluent PE/EtOAc = 7/3) to give 0.64 g (1.85 mmol, 70%) of **164** as a colourless oil.
^{1}H NMR: δ 1.06 (s, 3H); 1.17 (s, 6H); 1.10 - 2.00 (m, 9H); 2.53 (dd, J = 2.0 Hz, 12.5 Hz, 1H); 3.45 - 3.90 (m, 2H); 5.24 (d, J = 2.0 Hz, 1H); 6.13 (s, 2H). ^{13}C NMR: δ 18.2 (t); 20.9 (q); 27.6 (t); 30.4 (q); 31.5 (q); 37.3 (s); 37.5 (t); 39.6 (t); 41.3 (s); 49.4 (d); 61.1 (t); 118.5 (t); 123.6 (d); 144.6 (s); 179.7 (s); 190.6 (s). HRMS: calcd (M^+) *m/e* 248.1776; found *m/e* 248.1779. $[\alpha]_D$ = -145.1 (c = 0.3).

(1S,2S,4aS,8aR)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-3-oxo-2,5,5,8a-tetramethyl-1-naphtha-leneethanol (165) and (1S,2S,3S,4aS,8aR)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-3-hydroxy-2,5,5,8a-tetramethyl-1-naphthalene-ethanol (166)
To a solution of dienone **164** (0.40 g,1.6 mmol) in a mixture of anhydrous ether (1 ml), ethanol (1 ml) and ammonia (20 ml), lithium (0.30 g, 43 mgrat) was added slowly in small pieces under a nitrogen atmosphere. The mixture was stirred for 3 h at -33 °C, while a persistent blue color remained. Then solid ammonium chloride was introduced to quench the excess of lithium. After evaporation of the ammonia, water was added and the mixture was worked up as usual. Flash chromatography (eluent PE/EtOAc= 3/2) gave 0.04 g (0.16 mmol, 10%) of hydroxyketone **165** as a colourless oil and 0.30 g

(1.17 mmol, 73%) of diol **166** as white crystals, mp 120 - 122 °C.
165: ^{1}H NMR: δ 0.80 (s, 3H); 0.81 (s, 3H); 0.98 (s, 3H); 1.01 (d, J = 6.5 Hz, 3H); 0.90 - 1.95 (m, 10H); 2.10 - 2.50 (m, 4H); 3.38 - 3.68 (m, 2H). ^{13}C NMR: δ 12.8 (q); 13.6 (q); 18.4 (t); 21.1 (q); 32.7 (q); 32.7 (t); 33.7 (s); 38.1 (s); 38.5 (t); 38.9 (t); 41.7 (t); 47.8 (d); 54.0 (d); 54.1 (d); 63.5 (t); 213.1 (s) . HRMS: calcd (M^+) *m/e* 252.2089; found *m/e* 252.2091. $[\alpha]_D$ = −12.3 (c = 1.0).
166: ^{1}H NMR: δ 0.81 (s, 6H); 0.84 (s, 3H); 1.01 (d, J = 6.2 Hz, 3H); 0.40 - 0.55 (m, 1H); 0.80 - 1.92 (m, 14H); 3.12 (ddd, J = 6.2 Hz, 12.0 Hz, 12.5 Hz, 1H); 3.40 - 3.70 (m, 2H). ^{13}C NMR: δ 14.2 (q); 16.2 (q); 18.5 (t); 21.7 (q); 31.2 (t); 32.0 (t); 33.1 (s); 33.2 (q); 37.8 (s); 38.8 (t); 41.9 (t); 42.0 (d); 51.6 (d); 52.1 (d); 64.2 (t); 76.7 (d) . HRMS: calcd (M^+-18) *m/e* 236.2140; found *m/e* 236.2134. $[\alpha]_D$ = + 16.2 (c = 0.3).

(2S,3S,4S,4aR,8aS)-4-[2'-*tert*-Butyldimethylsilyloxy)ethyl]-1,2,3,4,4a,5,6,7,8,8a-decahydro-3,4a,8,8-tetra-methyl-2-naphthalenol (167)
To a solution of 0.190 g (0.748 mmol) of diol **166** in 20 ml of N,N-dimethylformamide was added 0.135 g (0.898 mmol) of *t*-butyldimethylsilyl chloride and 0.15 g (2.2 mmol) of imidazole. The mixture was stirred at room temperature for 1 h. Water was added and the mixture was worked up as usual. The monosilylated alcohol **167** was obtained pure after evaporation of the solvent (0.270 g, 0.734 mmol, 98%) as white crystals, mp 86 - 87 °C.
^{1}H NMR: δ 0.03 (s, 6H); 0.30 - 0.46 (m, 1H); 0.80 (s, 6H); 0.84 (s, 3H); 0.88 (s, 9H); 1.13 (d, J = 9.4 Hz, 3H); 1.05 - 1.92 (m, 13H); 3.09 (ddd, J = 5.4 Hz, 10.5 Hz, 11.4 Hz, 1H); 3.33 - 3.67 (m, 2H). ^{13}C NMR: δ -5.2 (2 * q); 14.2 (q); 16.3 (q); 18.4 (s); 18.5 (t); 21.7 (q); 26.0 (3*q); 31.2 (t); 32.1 (t); 33.1 (s); 33.3 (q); 37.8 (s); 38.8 (t); 42.0 (d); 42.0 (t); 51.5 (d); 52.2 (d); 64.6 (t); 76.8 (d). HRMS: calcd (M^+-57) *m/e* 311.2406; found *m/e* 311.2408. Anal: calcd for $C_{22}H_{44}O_2Si$: C, 71.69; H, 12.03; found: C, 71.89; H, 12.38. $[\alpha]_D$ = +15.3 (c = 0.8).

(1S,4aS,8aS)-1,4,4a,5,6,7,8,8a-Octahydro-2,5,5,8a-tetramethyl-1-naphthaleneethanol (159)
A mixture of 0.27 g (0.734 mmol) of **167**, 0.7 g (5.6 mmol) of 4-N,N-dimethylaminopyridine and 0.3 ml (3.9 mmol) of methanesulfonyl chloride in 10 ml of dichloromethane was stirred at room temperature for 1 h. Water was added and the mixture was worked up as usual. After evaporation of the solvent 0.3 g (3.4 mmol) of lithium bromide and 0.26 g (3.4 mmol) of lithium carbonate in 2 ml of N,N-dimethylformamide were added and the mixture was heated at 150 °C for 2 h. Water was added and the mixture was worked up as usual. Flash chromatography with PE as the eluent gave 0.15 g (0.42 mmol, 58%) of *(1S,4aS,8aS)-1,4,4a,5,6,7,8,8a-Octahydro-2,5,5,8a-tetramethyl-1-[2'-tert-butyldimethyl-silyloxy)ethyl]-naphthalene.* Further elution (eluent PE/EtOAc =7/3) gave 0.05 g (0.21 mmol, 29%) of alcohol **159**. The TBDMS ether

was dissolved in 5 ml of acetonitrile and 5 drops of 48% aqueous hydrofluoric acid were added and the mixture was stirred at room temperature for 1 h. The mixture was poured into saturated aqueous sodium bicarbonate solution (5 ml) and extracted twice with ether. The extract was washed with water, dried and evaporated. Flash chromatography (eluent PE/EtOAc =7/3) gave a second crop of alcohol **159** of 0.089 g (0.38 mmol, 51%).
TBDMS ether: ^{1}H NMR: δ 0.05 (s, 6H); 0.75 (s, 3H); 0.84 (s, 3H); 0.87 (s, 3H); 0.91 (s, 9H); 1.0 - 2.15 (m, 15H); 3.35 - 3.82 (m, 2H); 5.39 (bs, 1H). ^{13}C NMR: δ -5.2 (2 * q); 13.5 (q); 18.4 (s); 18.7 (t); 21.8 (q); 22.1 (q); 23.8 (t); 26.0 (3*q); 30.4 (t); 32.9 (s); 33.1 (q); 36.5 (s); 39.1 (t); 42.3 (t); 50.1 (d); 50.6 (d); 64.7 (t); 122.3 (d); 134.9 (s). HRMS: calcd (M^+-57) *m/e* 293.2301; found *m/e* 293.2301. $[\alpha]_D$ = -6.7 (c = 0.7).
159: ^{1}H NMR: δ 0.74 (s, 3H); 0.82 (s, 3H); 0.85 (s, 3H); 1.64 (bs, 3H); 0.75 - 2.03 (m, 12H); 2.21 (s, 1H); 3.42 - 3.60 (m, 1H); 3.65 - 3.84 (m, 1H); 5.38 (m, 1H). ^{13}C NMR: δ 13.5 (q); 18.7 (t); 21.8 (q); 22.0 (q); 23.7 (t); 29.7 (t); 32.9 (s); 33.1 (q); 36.4 (s); 39.1 (t); 42.2 (t); 50.0 (d); 50.7 (d); 64.2 (t); 122.6 (d); 134.5 (s). HRMS: calcd (M^+) *m/e* 236.2140; found *m/e* 236.2142. $[\alpha]_D$ = -11.8 (c = 0.9).

(3aR,5aS,9aS,9bR)-Dodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1-b]furan (Ambrox®)
A mixture of 0.050 g (0.21 mmol) of **159** and 0.03 g (0.16 mmol) of *p*-toluenesulfonic acid in 3 ml of nitromethane was stirred at room temperature for 18 h. Ether was added and the mixture was washed with saturated aqueous sodium bicarbonate and dried ($MgSO_4$). Flash chromatography (eluent PE/EtOAC =19/1) removed the small amount of iso-ambrox (< 5% according to GLC) and gave 0.040 g (0.17 mmol, 80%) of (-)-Ambrox® (**101**) as white crystals, mp 74 - 75 °C (ref.[6a]: mp 74 - 76 °C).

A mixture of 0.089 g (0.375 mmol) of **159** and 0.06 g (0.32 mmol) of *p*-toluenesulfonic acid in 5 ml of nitromethane gave after stirring for 8 h and the same work-up and purification procedure 0.051 g (0.214 mol, 57%) of (-)-Ambrox® (**101**) and after further elution (eluent PE/EtOAc = 4/1) 0.020 g (0.085 mmol, 23%) of isomerized alcohol **168**. Stirring of alcohol **168** in 5 ml of nitromethane with 0.03 g (0.16 mmol) of *p*-toluenesulfonic acid for 48 h gave a second crop of (-)-Ambrox® (**101**) after the same work-up and purification procedure of 0.014 g (0.06 mmol, 16%).
(-)-Ambrox® (101): ^{1}H NMR (500MHz): δ 0.81 (s, 3H); 0.82 (s, 3H); 0.86 (s, 3H); 0.94 (dd, J = 12.4 Hz, 2.8 Hz, 1H); 1.02 (td, J = 12.7 Hz, 3.7 Hz, 1H); 1.07 (s, 3H); 1.17 (td, J = 14.1 Hz, 4.6 Hz, 1H); 1.22 - 1.50 (m, 6H); 1.60 - 1.78 (m, 4H); 1.92 (dt, J = 11.6 Hz, 3.3 Hz, 1H); 3.80 (q, J = 8.2 Hz, 1H); 3.83 - 3.94 (m, 1H). ^{13}C NMR: δ 15.0 (q); 18.4 (t); 20.6 (t); 21.1 (2*q); 22.6 (t); 33.0 (s); 33.5 (q); 36.1 (s); 39.7 (t); 39.9 (t); 42.4 (t); 57.2 (d); 60.1 (d); 64.9 (t); 79.9 (s). HRMS: calcd (M^+) *m/e* 236.2140; found *m/e* 236.2144. Anal: calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94; found: C, 80.98; H, 12.02. $[\alpha]_D$ = -24.6 (c = 0.5) (ref.[6a]: $[\alpha]_D$ = -22.1 (c = 0.7)).

168: ^{1}H NMR (90 MHz, major signals): δ 0.90 (s, 3H); 0.93 (s, 3H); 0.96 (s, 3H); 1.65 (s, 3H); 3.60 (t, J = 8 Hz, 2H))

(1S,3S,8aR)-6,6-(Ethylenedioxy)-3-isopropenyl-8a-methyl-1,2,3,5,6,7,8,8a-octahydro-1-naphthalene-carbonitrile (172)

A solution of 23.0 g of hydroxyketone **136** (93.1 mmol) in 200 ml of toluene was heated under reflux with a water separator in the presence of 1.5 g of *p*-toluenesulfonic acid. After 1.5 h 10 ml of ethylene glycol was added and refluxing was continued for 2 h. Saturated sodium bicarbonate was added and the mixture was worked up as usual. The residue was recrystallized from methanol to afford 22.8 g (83.5 mmol, 90%) of acetal **172** as white crystals, mp 99 - 100 °C.

^{1}H NMR: δ 1.23 (s, 3H); 1.74 (s, 3H); 1.30 - 2.25 (m, 7H); 2.40 - 2.72 (m, 3H); 3.91 (bs, 4H); 4.70 (s, 1H); 4.90 (s, 1H); 5.20 (d, J = 4.9 Hz, 1H). ^{13}C NMR: δ 19.2 (q); 21.9 (q); 25.6 (t); 30.6 (t);35.3(d); 35.9 (s); 36.3 (t); 40.3 (d); 41.4 (t); 64.0 (t); 64.2 (t); 108.5 (s); 114.0 (t); 121.2 (s); 123.6 (d); 138.4 (s); 145.5 (s). HRMS: calcd (M^+) *m/e* 273.1729 ; found *m/e* 273.1729. Anal: calcd for $C_{17}H_{23}O_2N$: C, 74.69; H, 8.48; N, 5.12; found: C, 74.40; H, 8.52; N, 4.88. $[\alpha]_D = -118.4$ (c = 0.3).

(1S,3S,8aR)-6,6-(Ethylenedioxy)-3-isopropenyl-8a-methyl-1,2,3,5,6,7,8,8a-octahydro-1-naphthalene-carboxaldehyde (173)

To 10.0 g (36.6 mmol) of **172** in 250 ml of dry toluene was added dropwise under nitrogen 37 ml of 1.2 M diisobutylaluminum hydride in toluene at -78 °C. After 1 h 5 ml of water was added dropwise and the solution was stirred at room temperature for a 0.5 h. Then 5 ml of aqueous 4N sodium hydroxide was added dropwise. After 1 h $MgSO_4$ was added and stirring was continued for a 0.5 h. Purification by a short column of silica (eluent PE/EtOAc =9/1) gave 9.55 g (34.6 mmol,95%) of aldehyde **173** as white crystals, mp 104 - 105 °C.

^{1}H NMR: δ 1.14 (s, 3H); 1.79 (s, 3H); 1.65 - 2.45 (m, 8H); 2.50 (dt, J = 2.2 Hz, 14.1 Hz, 1H); 2.69 (bs, 1H); 3.99 (s, 4H); 4.78 (s, 1H); 4.92 (s, 1H); 5.31 (d, J = 5.6 Hz, 1H); 9.93 (s, 1H). ^{13}C NMR: δ 18.47 (q);21.50 (t); 21.98 (q); 30.64 (t); 36.35 (t); 36.65 (s); 40.42 (d); 40.97 (t); 53.67 (d); 64.00 (t); 64.15 (t); 108.56 (s); 113.11 (t); 124.65 (d); 139.48 (s); 146.40 (s); 205.02 (d). HRMS: calcd (M^+) *m/e* 276.1725; found *m/e* 276.1725. Anal: calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75; found: C, 73.98; H, 8.97. $[\alpha]_D = -114.9$ (c = 0.4).

(1S,3S,8aR)-6,6-(Ethylenedioxy)-3-isopropenyl-8a-methyl-1,2,3,5,6,7,8,8a-octahydro-1-naphthalenemethanol (174)

To 8.72 g (31.6 mmol) of **173** in 200 ml of ethanol was added 1.0 g of sodium borohydride (26 mmol) at 0 °C. After 30 min the ethanol was partly evaporated and water was added. The residue was worked up as usual. Recrystallization of the residue from PE/EtOAc gave 8.70 g (31.3 mmol, 99%) of **174** as white crystals, mp 82 - 83 °C.

^{1}H NMR: δ 0.99 (s, 3H); 1.80 (s, 3H); 1.35 - 2.05 (m, 8H); 2.14 (dd, J = 2.8 Hz, 13.9 Hz, 1H); 2.50 (dt, J = 2.2 Hz, 13.9 Hz, 1H); 2.69 (bs, 1H); 3.36 (dd, J = 8.0 Hz, 10.5 Hz, 1H); 3.77 (dd, J = 3.5 Hz, 10.6 Hz, 1H); 3.97 (bs, 4H); 4.78 (bs, 1H); 4.89 (bs, 1H); 5.31 (d, J = 4.9 Hz, 1H). ^{13}C NMR: δ 17.2 (q); 22.1 (q); 24.8 (t); 30.9 (t); 36.0 (t); 36.2 (s); 41.1 (t); 41.2 (d); 43.3 (d); 63.3 (t); 63.9 (t); 64.0 (t); 109.0 (s); 112.4 (t); 125.0 (d); 140.2 (s); 147.1 (s) . HRMS: calcd (M^+) *m/e* 278.1882; found *m/e* 278.1883. Anal: calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41; found: C, 72.96; H, 9.48. $[\alpha]_D$ = −105.9 (c = 0.4).

(1S,3S,8aR)-6,6-(Ethylenedioxy)-3-isopropenyl-8a-methyl-1,2,3,5,6,7,8,8a-octahydro-1-tosyloxymethyl-naphthalene (175)

To 5.33 g (19.2 mmol) of **174** in 50 ml of pyridine was added 5.0 g of tosylchloride (26.2 mmol, 1.36 eq). After 2 h 50 ml of water was added and the mixture was extracted with ether (3 x 100 ml). The combined organic layers were washed with a saturated bicarbonate solution and with brine and dried, filtrated and evaporated. Purification by flash chromatography (eluent PE/EtOAc = 17/3) gave 7.99 g (18.49 mmol,96%) of **175** as white crystals, mp 78 - 79 °C.

^{1}H NMR: δ 0.93 (s, 3H); 1.74 (s, 3H); 1.20 - 1.90 (m, 7H); 2.16 (dd, J = 2.6 Hz, 4.0 Hz, 1H); 2.47 (s, 3H); 2.45 - 2.70 (m, 2H); 3.94 (bs, 4H); 3.83 - 4.05 (m, 1H); 4.16 (dd, J = 4.4 Hz, 9.7 Hz, 1H);4.70 (s, 1H); 4.84 (s, 1H); 5.27 (d, 4.6 Hz, 1H); 7.36 (d, J = 8.2 Hz, 2H); 7.79 (d, J = 8.1 Hz, 2H). ^{13}C NMR: δ 17.2 (q); 21.4 (q); 21.9 (q); 24.6 (t); 30.7 (t); 35.8 (t); 36.1 (s); 40.0 (d); 40.8 (d); 41.1 (t); 63.9 (t); 64.1 (t); 71.4 (t); 108.7 (s); 112.7 (t); 124.9 (d); 127.6 (2*d); 129.6 (2*d); 132.9 (s); 139.5 (s); 144.4 (s); 146.5 (s). HRMS: calcd (M^+) *m/e* 432.1970; found *m/e* 432.1969. Anal: calcd for $C_{24}H_{32}O_5S$: C, 66.64; H, 7.46; found: C, 66.59; H, 7.65. $[\alpha]_D$ = −76.4 (c = 0.3).

(1R,3S,8aR)-6,6-(Ethylenedioxy)-3-isopropenyl-8a-methyl-1,2,3,5,6,7,8,8a-octahydro-1-naphthalene-acetonitrile (176)

A mixture of 12.40 g (28.7 mmol) of **175** and 3.0 g (61 mmol) of sodium cyanide in 100 ml of N,N-dimethylformamide was heated to 90 °C for 3 h. Water was added and the mixture was worked up as usual. Purification by flash chromatography (eluent PE/EtOAc =17/3) gave 8.14 g (28.3 mmol,99%) of **176** as white needles, mp 66 - 67 °C.

^{1}H NMR: δ 1.00 (s, 3H); 1.83 (s, 3H); 1.20 - 1.95 (m, 7H); 2.05 - 2.30 (m, 2H); 2.43 - 2.80 (m, 3H); 3.96 (bs, 4H); 4.78 (s, 1H); 4.92 (s, 1H); 5.33(d, J = 4.5 Hz, 1H) ^{13}C NMR: δ 16.8 (q); 18.4 (t); 21.9 (q); 27.2 (t); 30.8 (t); 35.6 (t); 36.8 (s); 38.3 (d); 41.1 (t); 41.2 (d); 64.0 (t); 64.1 (t); 108.7 (s); 112.9 (t); 119.6 (s); 125.0 (d); 139.3 (s); 146.4 (s). HRMS: calcd (M^+) *m/e* 287.1885; found *m/e* 287.1884. Anal: calcd for $C_{18}H_{25}O_2N$: C, 75.22; H, 8.77; N, 4.87; found: C, 74.87; H, 8.82; N, 4.67. $[\alpha]_D = -116.7$ (c = 0.5).

(1R,3S,8aR)-3-Isopropenyl-8a-methyl-1,2,3,4,6,7,8,8a-octahydro-6-oxo-1-naphthaleneacetonitrile (177)

To a solution of 3.54 g(12.3 mmol) of **176** in 50 ml of acetone was added 1 ml of an aqueous 4N hydrochloric acid solution. The mixture was stirred for 1 h. The mixture was concentrated *in vacuo*. Water was added and the mixture was worked up as usual. Flash chromatography (eluent PE/EtOAc = 7/3) gave 2.78 g (11.4 mmol, 93 %) of **177** as pale yellow crystals, mp 69 - 70°C.

^{1}H NMR: δ 1.14 (s, 3H); 1.71 (s, 3H); 1.65 - 2.75 (m, 12H); 4.73 (s, 1H); 4.88 (s, 1H); 5.82 (s, 1H). ^{13}C NMR: δ 16.3 (q); 18.0 (t); 22.3 (q); 29.0 (t); 33.4 (t); 35.0 (t); 35.5 (t); 38.3 (s); 38.7 (d); 39.2 (d); 112.9 (t); 118.8 (s); 126.2 (d); 145.5 (s); 167.3 (s); 197.5 (s). HRMS: calcd (M^+) *m/e* 243.1623; found *m/e* 243.1623. Anal: calcd for $C_{16}H_{21}O_1N$: C, 78.97; H, 8.70; N, 5.76; found: C, 78.55; H, 8.74; N, 5.67. $[\alpha]_D = +112.2$ (c = 0.3).

(1R,3S,8aR)-3-Isopropenyl-1,2,3,5,6,7,8,8a-octahydro-6-oxo-5,5,8a-trimethyl-1-naphthaleneacetonitrile (178)

To 100 ml of *tert*-butyl alcohol was added 7.0 g (62.4 mmol) of potassium *tert*-butoxide. Then 6.55 g (28.6 mmol) of enone **177** was added and the mixture was stirred at room temperature. After 1 h 6 ml (96.4 mmol) of methyl iodide was added in one portion and the mixture was stirred for 1 h at room temperature. The reaction mixture was concentrated *in vacuo* and worked up as usual. Flash chromatography of the residue (eluent PE/EtOAc = 19/1) gave 5.88 g (22.9 mmol, 80%) of **178** as white crystals, mp 99 - 100 °C.

^{1}H NMR: δ 0.79 (s, 3H); 1.26 (s, 3H); 1.31 (s, 3H); 1.81 (s, 3H); 1.55 - 2.03 (m, 5H); 2.12 (dd, J = 9.4 Hz, 16.4 Hz, 1H); 2.40 - 2.73 (m, 3H); 2.80 (t, J = 5.0 Hz, 1H); 4.59 (bs, 1H); 4.88 (bs, 1H); 5.57 (d, J = 5.0 Hz, 1H). ^{13}C NMR: δ 17.0 (q); 18.6 (t); 22.0 (q); 26.7 (t); 26.8 (q); 30.1 (q); 31.4 (t); 33.0 (t); 37.1 (s); 37.6 (d); 40.5 (d); 48.5 (s); 112.2 (t); 119.2 (s); 123.3 (d); 147.0 (s); 149.1 (s); 214.8 (s). HRMS: calcd (M^+) *m/e* 271.1936; found *m/e* 271.1935. Anal: calcd for $C_{18}H_{25}O_1N$: C, 79.66; H, 9.28; N, 5.16; found: C, 79.47; H, 9.47; N, 5.08. $[\alpha]_D = -66.6$ (c = 0.4).

(1R,8aR)-3-Isopropylidene-1,2,3,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-1-naphthalene-acetic acid (179)

A solution of 4.00 g (14.8 mmol) of ketone **178**, 5 ml of hydrazine hydrate and 3.0 g (53.6 mmol) of potassium hydroxide in diethylene glycol (150 ml) was heated for 3 h at 120 °C and then the excess of hydrazine hydrate and water was removed by distillation. The mixture was heated to 220 °C for 18 h and then cooled, poured into water and acidified with hydrochloric acid. The mixture was extracted with ether (3 x 200 ml). The combined ethereal layers were extracted with an aqueous 1 N sodium hydroxide solution (3 x 50 ml). The last obtained combined aqueous layers were acidified with hydrochloric acid and extracted with ether. The last obtained ethereal layers were washed with water, dried and evaporated to give 4.00 g (14.5 mmol, 98%) of carboxylic acid **179**, which was used immediately for the next reaction, without further purification.

^{1}H NMR (90 MHz, major signals): δ 1.00 (s, 3H); 1.20 (s, 6H); 1.72 (s, 3H); 1.82 (s, 3H); 6.40 (s, 1H); 8.50 - 9.30 (bs, 1H)

(1R,8aR)-1,2,3,5,6,7,8,8a-Octahydro-3-oxo-5,5,8a-trimethyl-1-naphthaleneaceticacid (180)

A solution of 4.00 g (14.5 mmol) of carboxylic acid **179** in methanol (50 ml) was ozonolysed at -78 °C. The excess of ozone was expelled by purging the solution with nitrogen for 15 min. Then 0.65 g (14.5 mmol) of sodium borohydride was added at -78 °C. The cooling bath was removed and the mixture was stirred for 3 h at room temperature. Water was added and the mixture was acidified with hydrochloric acid and extracted with ether (3 x 50 ml). The combined ethereal layers were washed with water, dried and evaporated to give 3.26 g (13 mmol, 90%) of carboxylic acid **180** which was used without further purification.

^{1}H NMR (90 MHz, major signals): δ 1.16 (s, 6H);1.21 (s, 3H); 6.05 (s, 1H), 7.5-8.4 (bs, 1H)

(1S,3R/S,8aR)-3-Hydroxy-1,2,3,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-1-naphthalene-ethanol (162)

A solution of 3.00 g (12 mmol) of **180** in 50 ml of dry ether was added dropwise to 0.85 g (22 mmol) of lithium aluminum hydride under a nitrogen atmosphere and the mixture was stirred for 18 h. Then 0.9 ml of water was added, after 30 min followed by 0.9 ml of a 4N sodium hydroxide solution. The mixture was stirred for 30 min and 2.7 ml of water was added, after 30 min followed by $MgSO_4$. The mixture was filtered after 2 h and the solvent was evaporated *in vacuo* , purified by flash chromatography (eluent PE/EtOAc = 3/2) to give 2.28 g (9.6 mmol, 80%) of diol **162** as white crystals, mp 122 - 126 °C.

6.4 References and Notes

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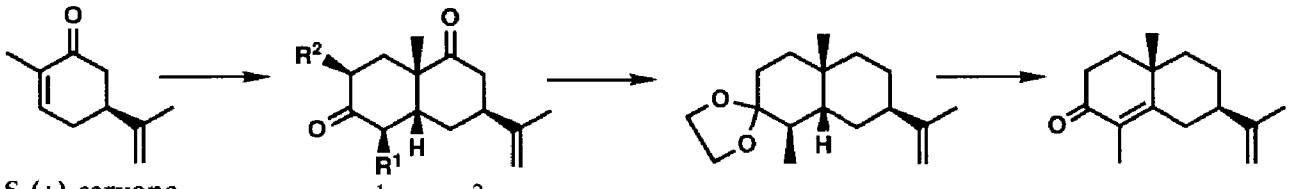
7 General Discussion

The synthetic research presented in this thesis was performed within the framework of the "National Caraway Research Program", that examined the potential for caraway and in particular for S-(+)-carvone, the main component of its essential oil, as a feedstock for the production of non-food products. In this thesis, the applicability of S-(+)-carvone in the enantioselective synthesis of interesting biologically active compounds was researched.

Although S-(+)-carvone is generally considered as a poor dienophile, the Lewis-acid catalyzed Diels-Alder reaction of S-(+)-carvone with some silyloxy dienes proceeded in good yields. The *anti*-addition products **94**, with the angular substituents and the isopropenyl group in a *cis*-position were formed almost exclusively (chapter 2). The synthetic usefulness of the Diels-Alder adducts was demonstrated by the total synthesis of (+)-α-cyperone from diketone **94b** (scheme 7.1). One of the carbonyl functionalities was selectively protected as its acetal and then the other carbonyl group was selectively removed by the Barton reduction to give acetal **108**. This acetal was further transformed to give (+)-α-cyperone (**95**) in 40% overall yield from S-(+)-carvone. This means that the Diels-Alder approach to (+)-α-cyperone (**95**) proceeds in a better overall yield and in a competitive number of steps compared to other known total syntheses of (+)-α-cyperone (**95**)[1].

(+)-α-Cyperone (**95**), can be isolated from the tubers of *Cuperus rotundus* L. in minute amounts and it exhibits an *in vitro* activity against *Plasmodium flaciparum* K1, a multidrug resistant malaria parasite. The activity of (+)-α-cyperone (IC_{50} = 5.5 μg/ml)[2] is nevertheless substantially lower than the activity of artemisin, another sesquiterpene with antimalaria activity (IC_{50} = 3.4 ng/ml)[3].

Scheme 7.1



S-(+)-carvone

94a: R^1 = H, R^2 = H
94b: R^1 = Me, R^2 = H
94c: R^1 = H, R^2 = Me

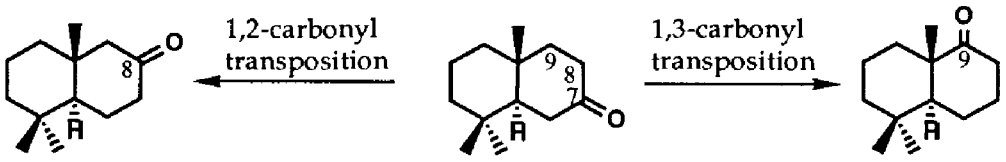
108

95

In chapter 3, some chiral intermediates obtained from the Robinson annulation of (-)-dihydrocarvone and methyl vinyl ketone (scheme 7.2 and 7.3) or ethyl vinyl ketone (scheme 7.4) were transformed into (known intermediates of) interesting biologically active compounds.

The C-7 carbonyl functionality of decalone **36** was moved to C-8 and C-9 *via* a 1,2 and 1,3-carbonyl transposition, respectively (scheme 7.2). The 1,2-carbonyl transposition afforded decalone **111**, a famous target molecule in perfumery, in a moderate overall yield of 17% from **36**. The 1,3-carbonyl transposition gave decalone **112** in a reasonable overall yield of 45% from **36**. Decalone **112** is an important intermediate in the synthesis of several drimanes and drimane-related natural products. Although the yields of the carbonyl transpositions are not very high, the possibility of moving the oxygen functionality in the B-ring also makes various other transformations in the B-ring possible. By this, a large number of natural products come within reach.

Scheme 7.2

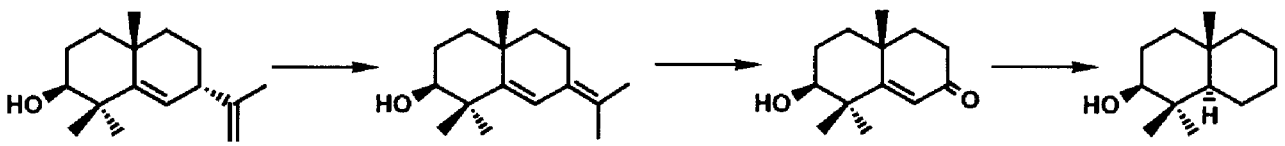


111 **36** **112**

Intermediate **117** was transformed into decalol **113**, which is a potent inhibitor of the cholesterol biosynthesis. The transformation of the isopropenyl group, the former chiral handle, into a carbonyl group was performed in two steps. First the isomerization of the isopropenyl group into an isopropylidene group under strong basic conditions (3 eq. of KOH) at high temperature (200 °C) gave diene **120** in 98% yield (scheme 7.3). Then ozonolysis of **120** gave hydroxy ketone **123** in 63%. Decalol **113** was obtained by a dissolving metal reduction of **123** followed by a Wolff-Kishner reduction in an overall yield of 40% from **117**.

The synthesis of compound **123** via an isomerization/ozonolysis sequence of the isopropenyl group showed that in the A-ring the oxygen functionality also could be preserved. This may be an advantage in the synthesis of derivatives of natural products. The isomerization/ozonolysis gave good results in the presence of an acetal functionality too. The presence of a carbonyl group was not compatible with the isomerization conditions.

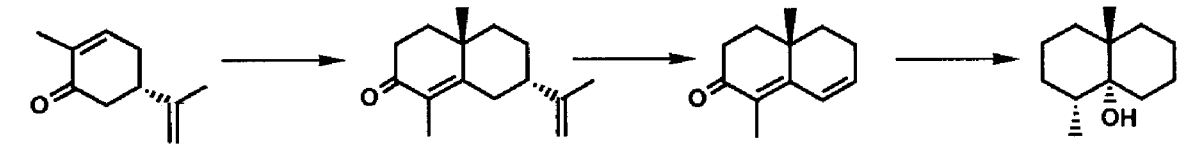
Scheme 7.3



117 **120** **123** **113**

(+)-Geosmin (**97**), the enantiomer of the natural (-)-geosmin, is an interesting olfactive compound. (+)-Geosmin (**97**) can be synthesized from the Robinson annulation product of (-)-dihydrocarvone and ethyl vinyl ketone, **96** (scheme 7.4). In this case the isopropenyl group was removed by a Criegee rearrangement followed by treatment with sodium methoxide to give the dienone **125** in 74%. Conjugate reduction with lithium-selectride and further conversion *via* a known procedure[2] gave (+)-geosmin (**97**) in an overall yield of 12% from S-(+)-carvone.

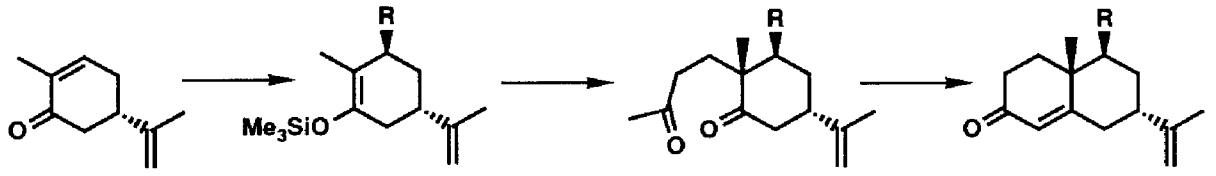
Scheme 7.4



S-(+)-carvone 96 125 97

The synthesis of the more functionalized decalones **98**, **99**, **131** and **132** from S-(+)-carvone via two different conjugate addition methodologies is presented in chapter 4. The silyl enol ethers **127** were formed by the conjugate addition of the corresponding Grignard reagents, followed by trapping of the intermediate enolates with trimethyl chlorosilane (scheme 7.5). A Lewis acid catalyzed Michael addition of the silyl enol ethers **127** to methyl vinyl ketone gave the intermediate diketones **130** in good yield. The diketones were cyclized to the substituted decalones **98**, **131**, and **132** in overall yields of 52%, 49% and 54%, respectively from S-(+)-carvone. Although the yields of these conjugate addition/annulation sequences were reasonable, there were some problems with the scaling up of these reactions.

Scheme 7.5



S-(+)-carvone

127a: R = Me
127b: R = vinyl
127c: R = allyl

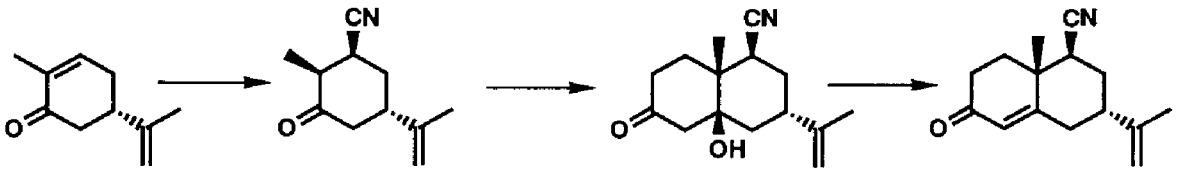
130a: R = Me
130b: R = vinyl
130c: R = allyl

99: R = allyl
131: R = Me
132: R = vinyl

A much better result was obtained in the conjugate addition of potassium cyanide to S-(+)-carvone which gave cyano ketone **135** in 95% yield after recrystallization. The base catalyzed Robinson annulation of **135** with methyl vinyl ketone afforded the hydroxy ketone **136** stereoselectively and in 90% yield by filtration of the reaction mixture. Dehydration of hydroxy ketone **136** gave decalone **98** in 91%. The overall yield of decalone **98** was therefore 78% from S-(+)-carvone and the reaction scale could be extended to a 100 g scale without any difficulty.

The high yield, the possibility of large scale operations and the stereoselectivity of the Robinson annulation of **135** to **136** and **98**, make these products very interesting for total synthesis. In this thesis, the application of hydroxy ketone **136** and decalone **98** is restricted to the total synthesis of C-3 oxygenated drimanes and the total synthesis of (-)-Ambrox® (**101**). It would be interesting to examine the application of these functionalized chiral compounds more extensively, for instance for the synthesis of steroids. Several interesting approaches are possible in this field, some of these also can use Robinson type annulation reactions with modified α,β-unsaturated ketones.

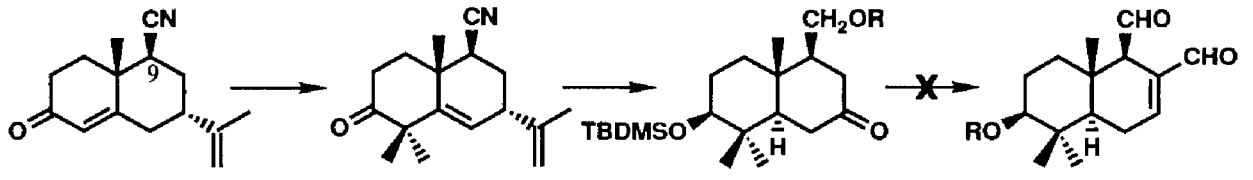
Scheme 7.6



S-(+)-carvone 135 136 98

Several hydroxy drimanes have shown antitumour activity and other types of bioactivity[5]. The hydroxylation of an unfunctionalized drimane A-ring is possible by microbial transformation[5b], but this reaction proceeds usually in low yield and with poor selectivity. Therefore the conversion of decalone **98** into 3-oxygenated drimanes gives interesting possibilities and was examined. This chiral decalone **98** already has a cyano substituent at C-9 with the *correct* stereochemistry, this in contrast to the chiral decalones that were used previously for transformation to drimanes in our laboratory[6].

Scheme 7.7

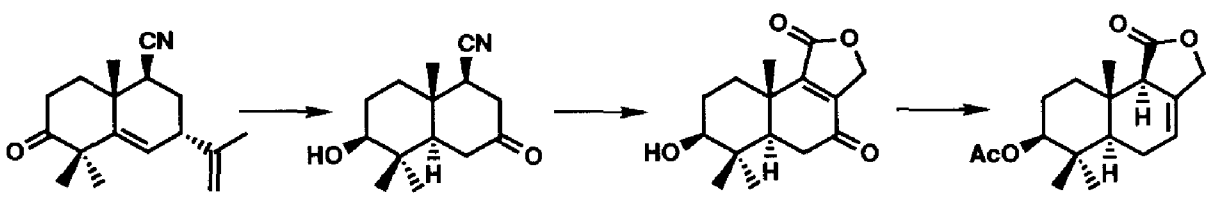


98 142 148: R = H 182: R = TBDMS 151: R = AcO

Methylation of decalone **98** to **142** proceeded without isomerization in 80% yield. Further conversion of this decalone **142** to 3β-acetoxypolygodial (**151**), via the intermediates in scheme 7.7 was not very successful. The isomerization/ozonolysis procedure for the conversion of the isopropenyl group into a carbonyl functionality proceeded in a moderate yield of 44%. Optimalization of this yield was not tried, because later on in the sequence the formylation of alcohol **148** gave a mixture of rather unstable products, that could not be transformed into 3β-acetoxypolygodial (**151**). The formylation of the TBDMS ether **182** did not proceed at all under the common formylation conditions (sodium hydride, ethyl formate). Another approach to C-3 oxygenated drimanes was therefore investigated.

In the new approach, the isopropenyl group was converted into a carbonyl group by an ozonolysis/Criegee rearrangement procedure of decalone **142**. The nitrile and the carbonyl functionalities proved to be compatible with the used conditions. Hydroxy ketone **154** was obtained in 60% overall yield from decalone **142** in five steps (scheme 7.8). Also in **154**, the formylation gave some problems. The common formylation conditions (sodium hydride, ethyl formate) gave partial epimerization of the nitrile group. The use of bis-dimethyldamino-*t*-butoxymethane (Bredereck's reagent) afforded the α,β-unsaturated lactone **155** in a yield of 49%. (+)-3β-Acetoxydrimenin (**100**) was synthesized in an overall yield of 25% from lactone **155**. Unfortunately there was no time for optimalization of the reaction conditions. So, the overall yield of (+)-3β-acetoxydrimenin (**100**) was only 4.5% from S-(+)-carvone.

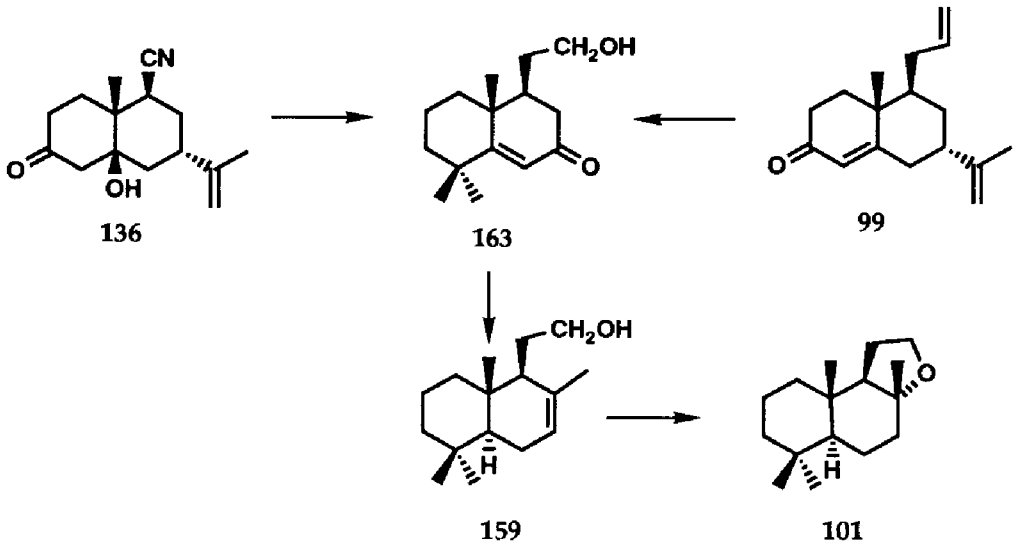
Scheme 7.8



142 154 155 100

The synthesis of the commercially interesting olfactive compound (-)-Ambrox® (**101**) from decalone **99** and hydroxy ketone **136** *via* the intermediate **159** and **163**, is described in chapter 6 (scheme 7.9).

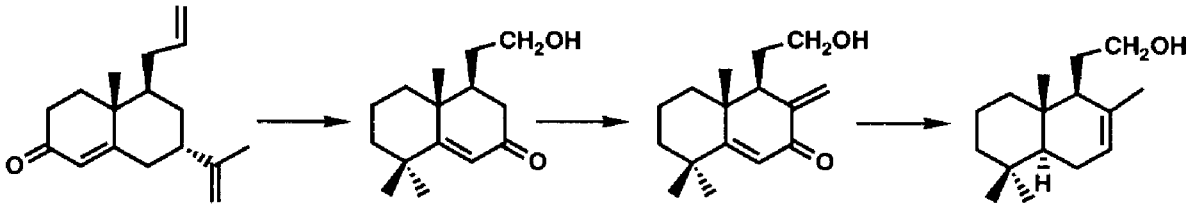
Scheme 7.9



136 **163** **99** **159** **101**

In scheme 7.10 the shortest sequence to key intermediate **159** from S-(+)-carvone is presented. Decalone **99**, obtained in 52% from S-(+)-carvone, was methylated, and the carbonyl group was removed by a Wolff-Kishner reaction. In the subsequent ozonolysis, the intermediate methoxy hydroperoxides were reduced to hydroxy groups. The allylic hydroxyl group was selectively oxidized by manganese dioxide to give compound **163** in an overall yield of 54% from decalone **99**. A Mannich reaction of **163** then gave dienone **164** in a yield of 70%. A dissolving metal reduction, protection of the primary hydroxyl group, dehydration of the secondary hydroxyl group and deprotection gave compound **159** in 57% yield from **164**.

Scheme 7.10

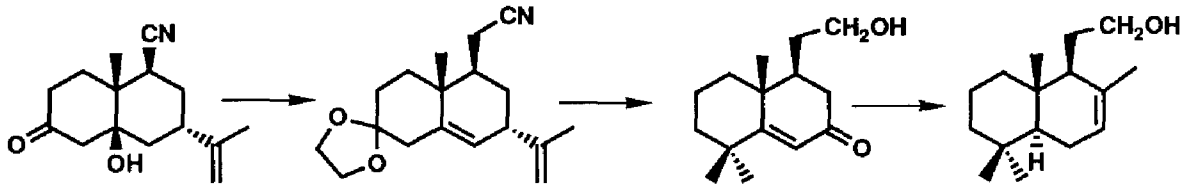


99 **163** **164** **159**

The sequence from hydroxy ketone **136**, which was obtained in an overall yield of 86% from S-(+)-carvone, to intermediate **159** is shown in scheme 7.11. Hydroxy ketone **136** was dehydrated and protected as its acetal. Then the nitrile substituent was homologated and acetal **176** was obtained in 5 steps in an overall yield of 80% from **136**.

After hydrolysis of the acetal functionality, the *gem*-dimethyl group was introduced and a Wolff-Kishner reduction was performed. By the Wolff-Kishner reaction conditions, the carbonyl functionality was removed, the isopropenyl group was isomerized and the nitrile substituent was hydrolyzed to a carboxylic acid. Ozonolysis, reduction with lithium aluminum hydride and allylic oxidation gave enone **163** in 47% from **176**. The conversion of enone **163** into compound **159** was performed as in scheme 7.10.

Scheme 7.11

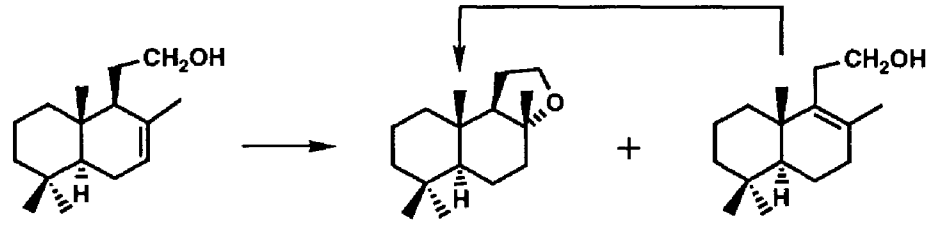


136 **176** **163** **159**

The synthetic sequence from decalone **136** to alcohol **159** involves more steps than the one from decalone **99**, but for large-scale production of alcohol **159** or derivatives of this compound, the preference should be given to the longer sequence from **136**. This hydroxy ketone could be synthesized on a 100 g scale easily, while the synthesis of decalone **99** was restricted to 5-10 g. The overall yield of alcohol **159** from S-(+)-carvone was 11% *via* decalone **99** and 13% *via* decalone **136**.

In scheme 7.12 the conversion of the unsaturated alcohol **159** into (-)-Ambrox® (**101**) is shown. The cyclization of **159** at room temperature in the presence of *p*-toluenesulfonic acid afforded (-)-Ambrox® (**101**) directly in 80% yield. The isomerized alcohol **168** was obtained as a by-product, when the cyclization was not entirely completed. Fortunately, this alcohol also gave (-)-Ambrox® (**101**) as the product under the same reaction conditions.

Scheme 7.12

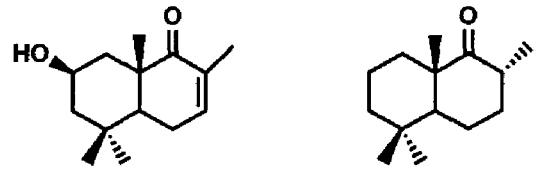


159 **101** **168**

The synthesis of (-)-Ambrox® (**101**) from S-(+)-carvone is probably not competitive with the known short synthetic routes from (-)-sclareol[7], but the application of S-(+)-carvone as a starting material makes the synthesis of ring-A derivatives of (-)-Ambrox® possible,

which otherwise can be obtained only with difficulty. In this way, the relationship of the structure of an ambergris odorant and its organoleptic activity can be studied.
The isomerized alcohol **168** seems easier to synthesize than alcohol **159**. The discovery that this alcohol **168** also cyclizes to (-)-Ambrox® (**101**) makes further research to other, simpler routes from S-(+)-carvone to (-)-Ambrox® attractive. Other chiral compounds, *e.g.*, hydroxy ketone **54** and decalone **55** (figure 7.1) already mentioned in section 1.3 also seem interesting starting materials for hydroxylated Ambrox and Ambrox®, respectively.

Figure 7.1



54 **55**

7.2 References and notes

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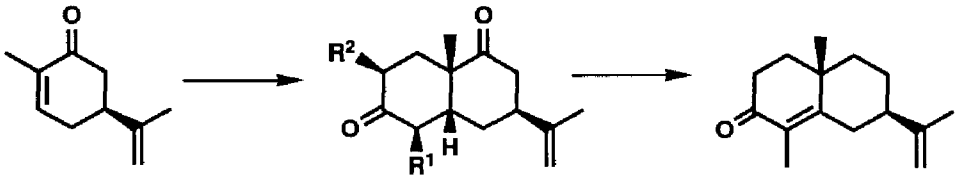
8 Summary

In this thesis the applicability of S-(+)-carvone as chiral starting material in the synthesis of biologically active compounds is examined. S-(+)-carvone is the major compound of caraway essential oil. The essential oil content of caraway seed may vary from 2-7% and it contains about 50-60% of S-(+)-carvone.

S-(+)-carvone exhibits a number of interesting biological activities, *e.g.*, antifungal, insecticidal and plant growth regulatory activities. Especially the inhibiting effect of S-(+)-carvone on the sprouting of potatoes attracted a lot of attention, and this was important for the start of a national caraway research program in the Netherlands. Within the framework of this "National Caraway Research Program" the potential of caraway for the production of non-food products was investigated. The outlines of this research are sketched in chapter 1. An overview of the application of S-(+)-carvone and R-(-)-carvone as chiral starting material in the synthesis of natural products is also given in chapter 1.

The Lewis acid catalyzed Diels-Alder reaction of S-(+)-carvone with some silyloxy dienes is described in chapter 2. The *anti*-addition products **94**, with the angular methyl group and the isopropenyl group in a *cis*-position, are formed in high yields. The synthetic utility of these Diels-Alder adducts was demonstrated by the total synthesis of (+)-α-cyperone (**95**) from diketone **94b**. (+)-α-Cyperone (**95**), that can be isolated from the tubers of *Cuperus rotundus* L., exhibits an interesting *in vitro* activity against *Plasmodium flaciparum* K1, a multidrug resistant malaria parasite (scheme 8.1).

Scheme 8.1



S-(+)-carvone

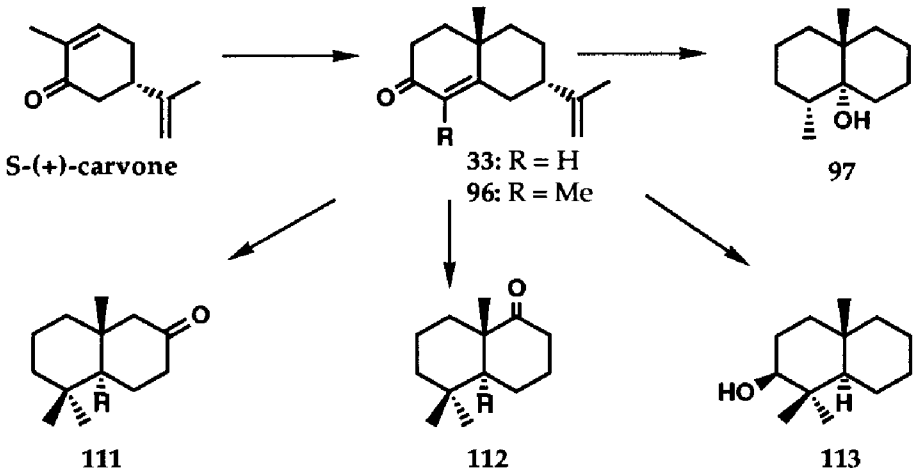
94a: R^1 = H, R^2 = H
94b: R^1 = Me, R^2 = H
94c: R^1 = H, R^2 = Me

95

In chapter 3, the Robinson annulation products **33** and **96** were transformed into interesting chiral intermediates for organic synthesis and also into some biologically active compounds. The decalones **111** and **112**, were formed from **33**. Decalone **111** is a famous molecule in perfumery and **112** is an important intermediate in the synthesis of several drimanes and drimane-related natural products. Compound **33** was also converted into decalol **113**, a potent inhibitor of the cholesterol biosynthesis.

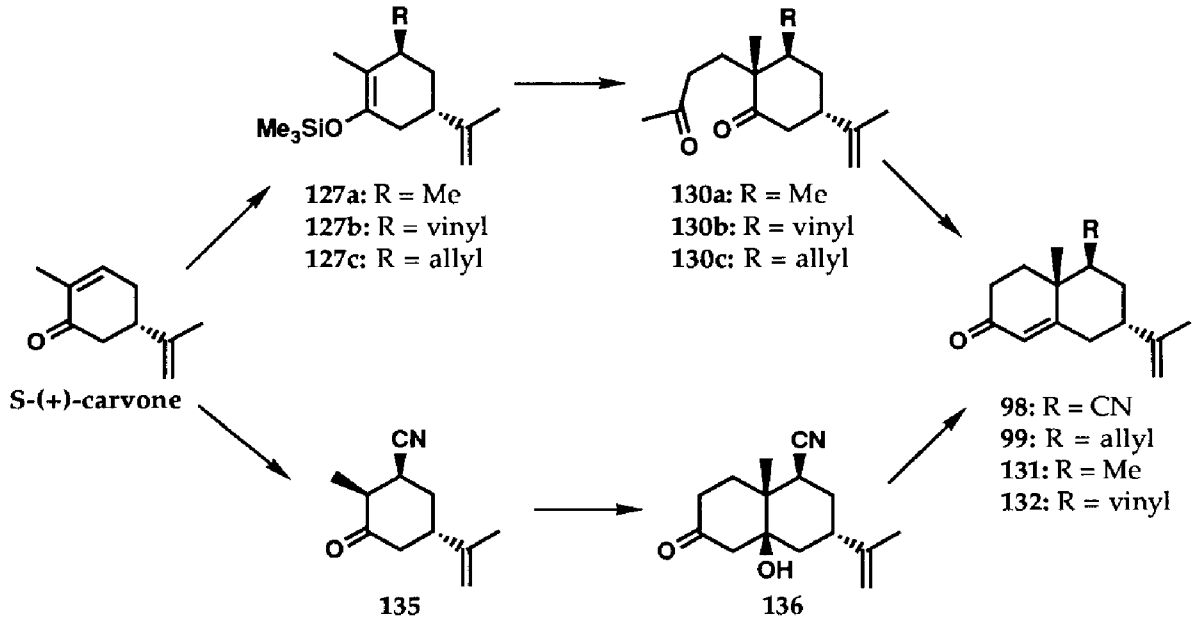
(+)-Geosmin (**97**), an interesting olfactive compound was synthesized from decalone **96** (scheme 8.2).

Scheme 8.2



In chapter 4, the syntheses of the more functionalized decalones **98, 99, 131** and **132** from S-(+)-carvone *via* two different conjugate addition annulation methodologies are presented (scheme 8.3). The conjugate addition of potassium cyanide to S-(+)-carvone gave cyano ketone **135** in high yield. The base catalyzed Robinson annulation of **135** with methyl vinyl ketone followed by dehydration gave decalone **98** stereoselectively and also in high yield.

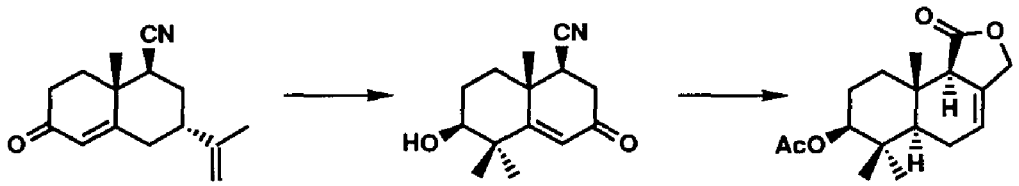
Scheme 8.3



The copper catalyzed conjugate addition of Grignard reagents gave alkyl substituted dihydrocarvones, which were annulated *via* their silyl enol ethers **127**. A Lewis acid catalyzed Michael addition of the silyl enol ether **129** to methyl vinyl ketone gave the intermediate diketones **130** in good yield. The diketones were cyclized to the substituted decalones **99**, **131** and **132** under basic conditions.

Decalone **98** was used for a new chiral approach to 3-oxygenated drimanes as is described in chapter 5. Hydroxyketone **153** was formed *via* an ozonolysis/Criegee rearrangement procedure of the isopropenyl substituent (scheme 8.4). Hydroxyketone **153** was by total synthesis further transformed into (-)-3-β-acetoxydrimenin (**100**), that can be isolated from the leaves of *Drimys winteri*,.

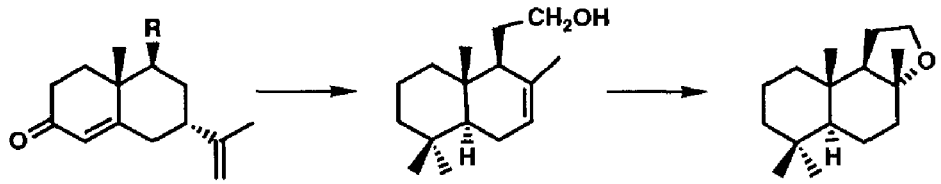
Scheme 8.4



98 **153** **100**

In chapter 6 the total synthesis of (-)-Ambrox® (**101**), a commercially interesting olfactive compound, from both the allyl substituted decalone **99** and the nitrile substituted decalone **98** is presented (scheme 8.5). In both synthetic sequences, alcohol **159** was formed as the key intermediate. (-)-Ambrox® (**101**), was synthesized by simple cyclization of alcohol **159** at room temperature under acidic conditions.

Scheme 8.5



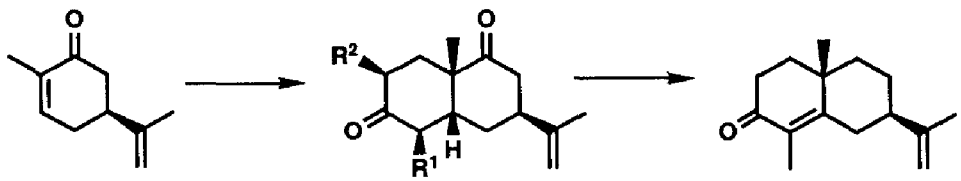
98: R = allyl
99: R = CN

159 **101**

9 Samenvatting

In dit proefschrift wordt een onderzoek beschreven waarin de toepassingsmogelijkheden van S-(+)-carvon als chirale uitgangsstof voor de synthese van biologisch actieve verbindingen centraal staan. S-(+)-carvon is de hoofdcomponent van de essentiële olie van karwijzaad. Het gehalte van de essentiële olie in het zaad kan varieren van 2-7% en ongeveer de helft hiervan bestaat uit S-(+)-carvon.
S-(+)-carvon is een monoterpeen met een aantal interessante biologische activiteiten. Voorbeelden hiervan zijn de werking van S-(+)-carvon tegen schimmels en insekten en als groeiregulator bij planten. Vooral het remmende effect van S-(+)-carvon op de spruitgroei bij aardappels trok veel aandacht en vormde mede de basis voor een nationaal onderzoeksprogramma naar nieuwe toepassingen voor karwijzaad. De mogelijkheden van karwijzaad voor agrificatie werden binnen dit "Nationale Karwij Onderzoeksprogramma" onderzocht. De hoofdlijnen van dit programma staan aangegeven in hoofdstuk 1. Verder wordt daar een overzicht gegeven van de toepassing van S-(+)-carvon en R-(-)-carvon als chirale uitgangsstof in de synthese van natuurprodukten.
De Lewis zuur gekatalyseerde Diels-Alder reaktie van S-(+)-carvon met enkele silyloxy dienen is beschreven in hoofdstuk 2. De *anti*-additie produkten **94**, met de angulaire methyl groep en de isopropenyl groep aan dezelfde kant van het molekuul, worden in hoge opbrengst gevormd (schema 9.1). Het nut van deze Diels-Alder produkten wordt aangetoond met de totaalsynthese van (+)-α-cyperon (**95**) uit diketon **94b**. (+)-α-Cyperon (**95**) kan in zeer kleine hoeveelheden geïsoleerd worden uit de wortels van *Cuperus rotundus L.* en heeft een interessante *in vitro* activiteit tegen *Plasmodium flaciparum* K1, een malariaparasiet met een resistentie tegen een groot aantal bestaande malariamedicijnen.

Schema 9.1



S-(+)-carvon

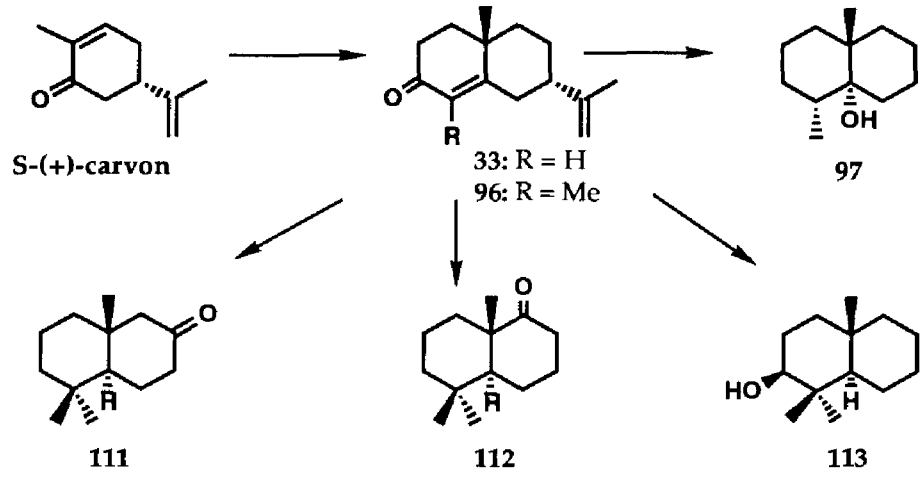
94a: R^1 = H, R^2 = H
94b: R^1 = Me, R^2 = H
94c: R^1 = H, R^2 = Me

95

In hoofdstuk 3 worden de Robinson annuleringsprodukten **33** en **96** omgezet in interessante chirale tussenprodukten voor de organische synthese en ook in een aantal biologisch actieve verbindingen (schema 9.2). De decalonen **111** en **112** werden

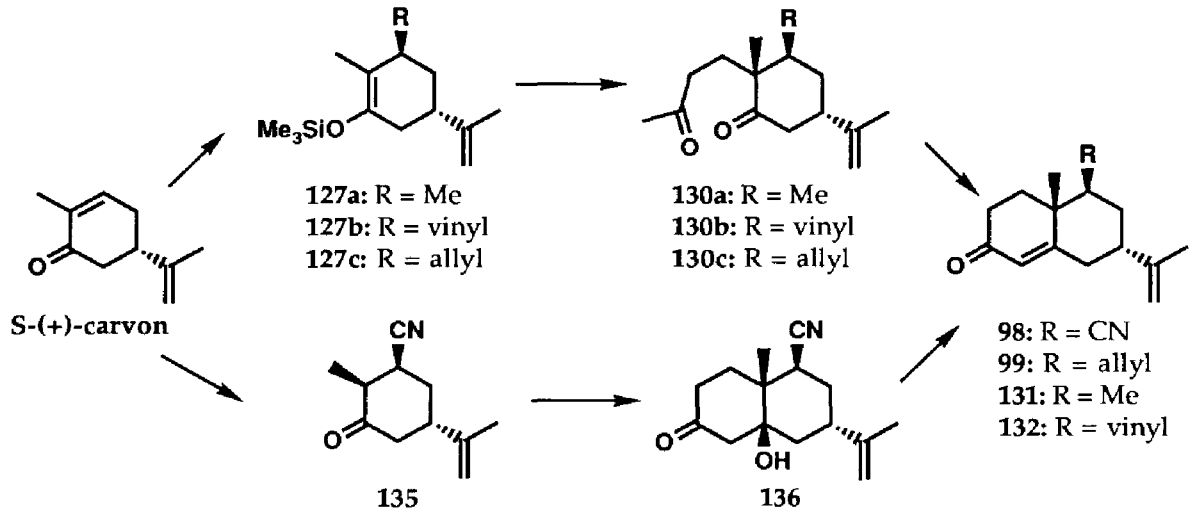
gesynthetiseerd uitgaande van verbinding **33**. Decalon **111** is een belangrijke verbinding in de geurstoffenindustrie en **112** is een tussenprodukt in de synthese van een groot aantal drimanen en drimaan-achtige natuurprodukten. Verbinding **33** werd ook omgezet in decalol **113**, een remmer van de cholesterol biosynthese. (+)-Geosmin (**97**), een interessant geurende verbinding, werd gesynthetiseerd uitgaande van decalone **96**.

Schema 9.2



In hoofdstuk 4 worden de syntheses van de meer gefunctionaliseerde decalonen **98**, **99**, **131** en **132** uit S-(+)-carvon *via* twee verschillende geconjugeerde additie/annulerings methoden gepresenteerd (schema 9.3).

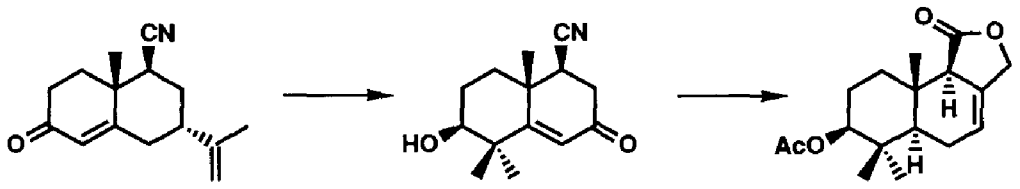
Schema 9.3



De geconjugeerde additie van kalium cyanide aan S-(+)-carvon gaf het cyano keton **135** in hoge opbrengst. De base gekatalyseerde Robinson annulering van **135** met methyl vinyl keton gaf het hydroxy keton **136** stereoselectief en in hoge opbrengst. Dehydratatie

van **136** gaf decalone **98**. De koper gekatalyseerde geconjugeerde additie van een aantal Grignard reagentia resulateerde in een aantal alkyl gesubstitueerde dihydrocarvonen, die geannuleerd werden *via* hun silyl enol ethers **127** (schema 9.3). Een Lewis zuur gekatalyseerde Michael additie van de silyl enol ethers **127** aan methyl vinyl keton gaf de tussenprodukten **130** in goede opbrengst. De diketonen werden gecycliseerd tot de gesubstitueerde decalonen **99, 131** en **132** onder basische omstandigheden.
Het in hoofdstuk 4 verkregen decalon **98** werd in hoofdstuk 5 toegepast in een nieuwe chirale benadering van C-3 geoxygeneerde drimanen. Hydroxy keton **153** werd gevormd *via* een ozonolyse/Criegee omlegging van de isopropenyl groep (schema 9.4). Hydroxy keton **153** werd door middel van totaal synthese verder omgezet in (-)-3β-acetoxydrimenin (**100**), dat geïsoleerd kan worden uit de bladeren van *Drimys winteri*.

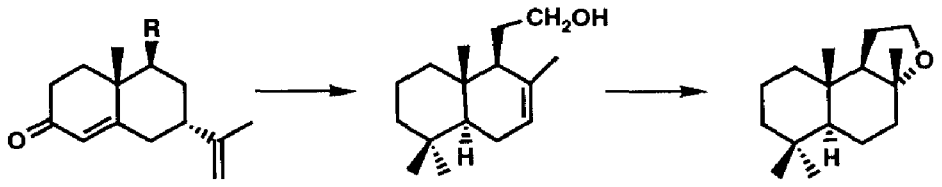
Schema 9.4



98 153 100

In hoofdstuk 6 worden zowel decalon **98** met een nitril substituent en decalon **99** met een allyl substituent omgezet in (-)-Ambrox® (**101**), een commercieel interessante geurstof (schema 9.5). In beide syntheseroutes is verbinding **159** een sleutelintermediair. (-)-Ambrox® (**101**), werd gesynthetiseerd door een eenvoudige zuur gekatalyseerde cyclisatie van alcohol **159**, die bij kamertemperatuur uitgevoerd moet worden.

Schema 9.5



98: R = allyl
99: R = CN

159 **101**

Curriculum Vitae

Anja Alida Verstegen-Haaksma werd op 22 november 1966 geboren te Anjum, gemeente Oost-Dongeradeel. In 1985 behaalde zij het ongedeeld VWO-diploma aan de Christelijke Scholengemeenschap Oostergo te Dokkum. In hetzelfde jaar begon zij aan de studie Molekulaire Wetenschappen aan de Landbouwuniversiteit te Wageningen. Tijdens de doctoraalfase werden afstudeervakken gedaan bij de vakgroepen Organische Chemie (dr. B. J. M. Jansen en prof. dr. Æ de Groot) en Toxicologie (dr. J. J. W. M. Mertens en prof. dr. J. H. Koeman). Daarna volgde een stage van 6 maanden bij de afdeling Bleekkatalysatoren van Unilever Research te Vlaardingen. Het doctoraalexamen werd afgelegd in maart 1990. Van april 1990 tot april 1994 was zij werkzaam als assistent in opleiding (AIO) bij de vakgroep Organische Chemie van de Landbouwuniversiteit, alwaar het in dit proefschrift beschreven onderzoek verricht werd, onder leiding van dr. B. J. M. Jansen en prof. dr. Ae. de Groot.

Stellingen

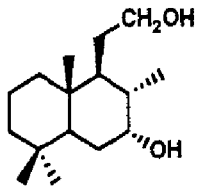
1. Het belang van chiraliteit wordt nog altijd door een groot aantal wetenschappers onderschat.
   - Brophy, J. J.; Goldsack, R. J.; Forster, P. I. *J. Essent. Oil.Res.* **1994**, *6*, 139-143.
   - Garg, S. N.; Agarwal, S. K. *J. Essent. Oil Res.* **1994**, *6*, 145-148.

2. Het negatieve effect van een S-(+)-carvon behandeling op het glutathion niveau in verschillende weefsels van A/J muizen, maakt S-(+)-carvon ongeschikt als chemopreventief middel.
   - Zheng, G.-Q.; Kenney, P. M.; Lam, L. K. T. *J. Agric. Food Chem.* **1992**, *40*, 751-755.

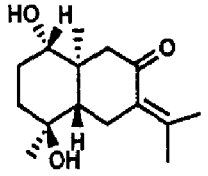
3. Het is twijfelachtig of de zuurgekatalyseerde cyclisatie van diol 4 (structuur 1) tot Ambrox® bij Kutney *et al.* verloopt *via* een hydride migratie.
   - Dit proefschrift
   - Kutney, J. P.; Chen, Y.-H. *Can. J. Chem.* **1994**, *72*, 1570-1581.

4. De verwachting van Sheffield *et al.*, dat het broomperoxidase geïsoleerd uit *Corallina officinalis* goede mogelijkheden biedt voor biotechnologische synthese van nieuwe gehalogeneerde verbindingen is gebaseerd op commerciële overwegingen en niet op kennis van zaken.
   - Sheffield, D. J.; Mort, A. J.; Harry, T.; Smith, A. J.; Rogers, L. *J. Biochem. Soc. Trans.* **1992**, *20*, 284S.

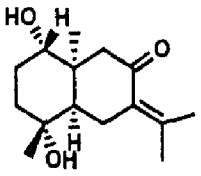
5. De bewering van Sakamoto *et al.* dat verbinding **13** (structuur 3) een *cis*-verknoopt stereoisomeer is van verbinding **5** (structuur 2), wordt niet door hun analysegegevens ondersteund.
   - Sakamoto, S.; Tsuchiya, N.; Kuroyanagi, M.; Ueno, A. *Phytochemistry* **1994**, *35*, 1215-1219.



structuur 1



structuur 2



structuur 3

6. De "unieke" stereoselectiviteit die Harrison *et al.* vonden bij de reductie van een aantal alkyl gesubstitueerde cyclohexanonen met aminoborohydrides is vergelijkbaar met de stereoselectiviteit van lithiumaluminiumhydride en natriumboorhydride.
   - Harrison, J.; Fuller, J. C.; Goralski, C. T.; Singaram, B. *Tetrahedron Letters* **1994**, *35*, 5201-5204.

7. Het bepalen van uitsluitend vetpercentages als maat voor de gezondheid van verschillende broodjes is wel een beetje mager.
   - Consumentengids **1994**, *3*, 174-177

8. Het afschaffen van maximale openingstijden voor winkels werkt prijsverhogend en is dus niet erg sociaal ten opzichte van de minima.

9. Bij een te laag budget voor studiefinanciering is een toelatingsexamen op universiteiten en HBO-instellingen te verkiezen boven een verdere verlaging van de basisbeurs.

Stellingen behorende bij het proefschrift: "S-(+)-Carvone as starting material in the enantioselective synthesis of natural products".

Te verdedigen op 7 december 1994 door Anja A. Verstegen-Haaksma