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

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

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Voorwoord

In 1990 startte een onderzoeksprogramma in Nederland, dat zich richtte op het verbeteren van de karwijteelt én op het vinden van nieuwe toepassingen voor karwijzaad buiten de voedingsmiddelensector. Dit "Nationale 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 naam 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 geborrelde heb.

Ben Jansen kende ik al van een practicum 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.

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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 pericarp (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 monoterpane 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\(^2\)\(_b\). Since plants are considered to be efficient, it is presumed that there is some selective advantage in producing them\(^2\)\(_b\). 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](image)

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 phospholipid 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. The same caraway oil* shows antibacterial activity against a number of bacteria and a yeast. 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.

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. 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*. 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. 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 farinae* and *Tyrophagus putrescentiae*. The amount to give 100% mortality (LD$_{100}$) ranged from 1-5 μl/petridish. 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. 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 pericarp prevents the inhibition of further formation of the monoterpenes.

---

* 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\textsuperscript{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 $\alpha,\beta$-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\textsuperscript{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\textsuperscript{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)\textsuperscript{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 applied 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\textsuperscript{18}. The synthesis of S-(+)-carvone started from S-(−)-limonene, which was obtained from pine needle oil. The synthetic sequence\textsuperscript{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).

\begin{center}
\textbf{Scheme 1.1}
\end{center}

![Scheme 1.1](image)

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 acres 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 \textit{and} between farmers\textsuperscript{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, \textit{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". Breeding research was used to increase the S-(+)-carvone production potential.

Plant and crop physiological research at AB-DLO\textsuperscript{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 cannot 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\textsuperscript{21}. The selected population showed in a few field experiments a 20% higher S-(+)-carvone content compared to the older landrace\textsuperscript{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\textsuperscript{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\textsuperscript{23}. The symptoms of the disease brought about by this fungus are severe. Infection with \textit{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 \textit{M. acerina}, is to start with \textit{M. acerina} free soil and sowing seed.

The damage caused by the fungus Sclerotinia sclerotiorum in caraway was researched at IPO-DLO\textsuperscript{24}. Both caraway and most preceding crops are susceptible for \textit{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 \textit{S. sclerotiorum}.

Another group of researchers at IPO-DLO\textsuperscript{25} have examined the biology and control of the caraway root aphid \textit{Pemphigus paseki}. 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\textsuperscript{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®\textsuperscript{26}, with S-(+)-carvone as the active component. A positive 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\textsuperscript{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\textsuperscript{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\textsuperscript{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 \textbf{3} or iso-dihydrocarvone \textbf{4} (figure 1.2) in purities up to 93%. The fungus \textit{Trychoderma pseudokoningii} reduces S-(+)-carvone mainly to neo-isodihydrocarveol \textbf{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 \textbf{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](image)

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 described 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 Ginkgo biloba L, and S-(+)-carvone is obvious\textsuperscript{30}. Hedge et al. transformed the isopropenyl side chain into the furano moiety in four steps (scheme 1.2)\textsuperscript{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 \textit{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

\begin{center}
\begin{tikzpicture}
\node at (0,0) {S-(+)-carvone};
\node at (2,0) {6};
\node at (4,0) {8};
\node at (0,-2) {9};
\node at (2,-2) {10};
\draw[->] (0.3,0.3) -- (1.7,0.3) node[midway, above] {i};
\draw[->] (1.7,0.3) -- (3.1,0.3) node[midway, above] {ii};
\draw[->] (3.1,0.3) -- (4.5,0.3) node[midway, above] {ii, iv};
\draw[->] (4.5,0.3) -- (5.9,0.3) node[midway, above] {v};
\end{tikzpicture}
\end{center}

Reagents i: HOCl, H\textsubscript{2}O, CH\textsubscript{2}Cl\textsubscript{2}; ii: Zn; iii: CrO\textsubscript{3}; iv: \textit{m}-CPBA; v: BF\textsubscript{3}.Et\textsubscript{2}O.

Both R-(−)-carvone and S-(+)-carvone are suitable starting materials in the synthesis of ring-A synthons of 1α,25-dihydroxycholecalciferol (11)\textsuperscript{31}. This known vitamin D\textsubscript{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\textsuperscript{31a} and a somewhat longer sequence from R-(−)-carvone to ring-A synthon 22 is shown in scheme 1.4\textsuperscript{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 \textit{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\textsuperscript{31a}.

\begin{center}
\textbf{Scheme 1.3}
\end{center}

\begin{center}
\includegraphics[width=\textwidth]{scheme13.png}
\end{center}

\textit{Reagents} i: H$_2$O$_2$, OH$^-$_; ii: Li acetylide; iii: Ac$_2$O, Et$_3$N, DMAP; iv: O$_3$; ArCOCl, py; Α; v: SmI$_2$, (Ph$_3$P)$_4$Pd
The epoxide obtained from R-(−)-carvone was reduced with lithium selectride to give an axial alcohol which was protected as its tert-butylidimethylsilyl ether 17 (scheme 1.4)\textsuperscript{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\textsuperscript{31b}.

Scheme 1.4

Reagents i: H\textsubscript{2}O\textsubscript{2}, OH\textsuperscript{−}; ii: Li-selectride; iii: TBDMSCl, imidazole; iv: O\textsubscript{3}; Ac\textsubscript{2}O, Et\textsubscript{3}N, DMAP; K\textsubscript{2}CO\textsubscript{3}; v: TBDMSCl, imidazole; vi: Et\textsubscript{2}Al TMP; vii: MsCl, DMAP; viii: NaI, Ar; ix: CrCl\textsubscript{3}, LiAlH\textsubscript{4}; pMeOC\textsubscript{6}H\textsubscript{4}CH\textsubscript{2}OCH\textsubscript{2}CHO; x: DDQ; xi: K\textsubscript{2}CO\textsubscript{3}; xii: NaIO\textsubscript{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\textsuperscript{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)\textsuperscript{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

Reagents  i: NaOH, 25% aq. DMSO; ii: H₂O₂, OH⁻; iii: N₂H₄; iv: PCC; v: NaBH₄, CeCl₃; vi: Ac₂O, DMAP; vii: O₃, Me₂S.

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).
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)\textsuperscript{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**

\[
\begin{align*}
\text{S- (+)-carvone} & \xrightarrow{i} \text{30} \xrightarrow{ii} \text{31} + \text{32} \\
\text{Reagents} & \quad i: \text{Li, NH}_3, \text{t-BuOH, ether;} \quad ii: \text{MVK, KOH, 0 °C.}
\end{align*}
\]

(-)-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)\textsuperscript{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\textsuperscript{34}.

**Scheme 1.7**

\[
\begin{align*}
\text{31} & \xrightarrow{i} \text{33} \xrightarrow{ii} \text{34} \xrightarrow{iii} \\
\text{35} & \xrightarrow{iv, v} \text{36} \xrightarrow{Lit 33} \text{37} \\
\text{Reagents} & \quad i: \text{KOH, MeOH, rt;} \quad ii: \text{MeI, t-BuOK;} \quad iii: \text{N}_2\text{H}_4, \text{KOH, 200 °C;} \quad iv: \text{O}_3, \text{Me}_2\text{S;} \quad v: \text{Li, NH}_3.
\end{align*}
\]
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\textsuperscript{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)\textsuperscript{35}.

**Scheme 1.8**

Reagents  
\textsuperscript{i}: CH\textsubscript{2}N\textsubscript{2};  \textsuperscript{ii}: Ac\textsubscript{2}O, py;  \textsuperscript{iii}: OH\textsuperscript{+};  \textsuperscript{iv}: PCl\textsubscript{5}; H\textsuperscript{+};  \textsuperscript{v}: MeMgBr;  \textsuperscript{vi}: SOCl\textsubscript{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\textsuperscript{36}.

**Scheme 1.9**

Reagents  
\textsuperscript{i}: AlCl\textsubscript{3}, benzene, rt;  \textsuperscript{ii}: *p*-Tosylhydrazine, NaBH\textsubscript{4};  \textsuperscript{iii}: *m*-CPBA;  \textsuperscript{iv}: LiAlH\textsubscript{4};  \textsuperscript{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 (\textit{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**

```
\[ \text{R-(-)-carvone} \xrightarrow{\text{i, ii}} 47 \xrightarrow{\text{iii}} 48 \xrightarrow{\text{iv, v, vi}} \]

\[ \text{49} \xrightarrow{\text{vii}} 50 \xrightarrow{\text{51}} \]
```

**Reagents**  
i: LDA, MeI; ii: LDA, 0 °C, CH\(_2\)CH=CHPH\(_3\)Br, \(\Delta\); iii: Li/ NH\(_3\), MeI; iv: CrO\(_2\)Cl\(_2\), Zn; v: MeMe\(_2\)MgBr; 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.

Scheme 1.11

Reagents i: LDA, MeI; ii: LDA, CH₂=CH(CBr)₂Br; iii: aq. H₂SO₄; iv: NaBH₄; v: POCl₃, py; vi: H₂, Pd/C; vii: NaOMe.

An example of a five-membered ring annulation is shown in scheme 1.12. 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, Me₃SiCl, THF, -78 °C; ii: NH₄Cl, H₂O; iii: I₂; iv: [Ph₃P]₄Pd, t-BuOK
The synthesis of the quassinoid skeleton 62 from S-(+)-carvone is shown in scheme 1.13\textsuperscript{41b} The triterpenoid quassinoids, found in the *Simaroubaceae* plant family, exhibit a wide spectrum of biological activities, e.g., anticancer, antimalarial, insecticidal and growth inhibitory activities\textsuperscript{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\textsuperscript{41b} was more reproducible than that with the *in situ* prepared unstable E-4-methylhexa-3,5-dienal\textsuperscript{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\textsuperscript{41b}.

**Scheme 1.13**

\[
\begin{align*}
\text{S-(+)-carvone} & \xrightarrow{\text{i, ii}} \begin{array}{c}
\text{CHO} \\
\text{SO_2} \\
59
\end{array} & \xrightarrow{\text{iii, iv}} & \begin{array}{c}
\text{OH} \\
\text{SO_2} \\
60
\end{array} & \xrightarrow{} & \begin{array}{c}
\text{Ac} \\
61
\end{array} & \xrightarrow{} & \begin{array}{c}
\text{OAc} \\
62
\end{array} & \xrightarrow{} & \begin{array}{c}
\text{OAc} \\
63
\end{array}
\end{align*}
\]

*Reagents* i: LDA, MeI; ii: LDA, then followed by aldehyde 58, DMPU, -78\°C; iii: Ac\(_2\)O, 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 1.14⁴³. 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 (-)-phytotuberin (69) in an overall yield of 10%⁴³.

Scheme 1.14

Reagents i: Li, NH₃; HCHO; ii: Li-acetylide, -78 °C; iii: Ac₂O, py; iv: HgSO₄, aq. MeOH; v: EtO-acetylene, n-BuLi; vi: H₃O⁺; vii: m-CPBA; viii: LiAlH₄; ix: Ac₂O, 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\textsuperscript{44}. In scheme 1.15, the conversion of R-(-)-carvone into (-)-hirsuten (76) is shown\textsuperscript{44d}. Hirsuten (optical rotation not determined) is a tricyclic sesquiterpene extracted from the mycelium of \textit{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 \textit{m}-chloroperbenzoic acid and the corresponding ketone gave a second Bayer-Villiger reaction to afford lactone 74\textsuperscript{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)\textsuperscript{44d}.

\textbf{Scheme 1.15}

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {R-(-)-carvone};
\node (B) at (2,0) {70};
\node (C) at (4,0) {71};
\node (D) at (6,0) {72};
\node (E) at (8,0) {73};
\node (F) at (10,0) {74};
\node (G) at (12,0) {75};
\node (H) at (14,0) {76};

\draw[->] (A) -- node[above] {i} (B);
\draw[->] (B) -- node[above] {\textcolor{red}{+}} (C);
\draw[->] (C) -- node[above] {\textcolor{red}{\textit{ii}}} (D);
\draw[->] (E) -- node[above] {\textcolor{red}{\textit{iii, iv, v}}} (F);
\draw[->] (F) -- node[above] {\textcolor{red}{\textit{\rightarrow}}} (G);
\draw[->] (G) -- node[above] {\textcolor{red}{\textit{\rightarrow}}} (H);
\end{tikzpicture}
\end{center}

\textit{Reagents} \hspace{1cm} i: Hg(OAc)\textsubscript{2}, THF, H\textsubscript{2}O, then NaBH\textsubscript{4}; ii: \textit{m}-CPBA, 40 °C; iii: K\textsubscript{2}CO\textsubscript{3}; iv: Ph\textsubscript{3}P, ZnBr\textsubscript{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 \textit{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 triene 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\(^{45}\).

\textbf{Scheme 1.16}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {77} edge[->] node[above] {i} (1,0) edge[->] node[above] {ii} (2,0) edge[->] node[above] { iii, iv, v} (3,0) edge[->] node[above] {vi, vii} (4,0);
\node at (1,0) {78} edge[->] node[below] {Ph\textsubscript{3}P} (2,0) edge[->] node[below] {O'Li\textsuperscript{+}} (3,0) edge[->] node[below] {80} (4,0);
\node at (2,0) {81} edge[->] node[below] {82} (4,0);
\end{tikzpicture}
\end{center}

\textit{Reagents} i: PhSH, NEt\textsubscript{3}; ii: retroaldol-Wittig olefination; iii: Ac\textsubscript{2}O, py; iv: m-CPBA, \(\Delta\); v: NaBH\textsubscript{4}, CeCl\textsubscript{3}; vi: Ac\textsubscript{2}O, py; vii: PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2}, HCO\textsubscript{2}NH\textsubscript{4}. 

19
Ent-78, obtained from R-(-)-carvone, was converted into a cyclodecane ring system (scheme 1.17)\textsuperscript{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\textsuperscript{47}.

**Scheme 1.17**

![Scheme 1.17](image)

*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)\textsuperscript{48}. (-)-Heliangolide (90) can be isolated from Tanacetum tanacetioides.

Reduction, acetylation and oxidation of S-(+)-carvone gave enone 86 in a yield of 41\%\textsuperscript{48a}. A Grignard reaction with vinyl magnesium bromide, followed by protection with tert-butylidimethylsilyl 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)\textsuperscript{48a}.
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\(^\text{49}\). 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\(^\text{49d}\).

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\(^\text{49d}\).
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 olfactory compound (-)-Ambrox® (101) is the subject of chapter 6.

1.5 References


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 Danshofsdyne 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 silyloxydiienes

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-buta diene (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

* This chapter has been published in a revised form: Haaksma, A.A.; Jansen, B. J. M.; de Groot, Ae. Tetrahedron 1992, 48, 3121-3130.
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 EtAlCl₂ 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 decalone 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

\[ \text{S-(+)-carvone} \rightarrow \text{anti-addition} + \text{syn-addition} \]

\[ \begin{align*}
102a & \quad 94a, 94b, 94c \\
102b & \quad 94b, 103b, 104b \\
102c & \quad 94c, 104c
\end{align*} \]

\[ a: R^1 = H, R^2 = H, R^3 = \text{TMS}, \quad b: R^1 = \text{Me}, R^2 = H, R^3 = \text{TMS}, \quad c: R^1 = H, R^2 = \text{Me}, R^3 = \text{TBDMS} \]

Reagents i: EtAlCl₂, toluene, rt; ii: H⁺, H₂O.

Table 2.1: EtAlCl₂ "catalyzed" Diels-Alder reactions of S-(+)-carvone with dienes 102

<table>
<thead>
<tr>
<th>Diene</th>
<th>products</th>
<th>product ratio</th>
<th>% anti-addition</th>
<th>product yield (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>102a</td>
<td>94a, 103a</td>
<td>19:1</td>
<td>95</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>(R¹ = H, R² = H)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>102b</td>
<td>94b, 103b, 104b</td>
<td>variable**</td>
<td>91</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>(R¹ = Me, R² = H)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>102c</td>
<td>94c, 104c</td>
<td>10:11</td>
<td>100</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>(R¹ = H, R² = Me)</td>
<td></td>
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</tbody>
</table>

*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 $^1\text{H}$ and $^{13}\text{C}$ 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 $^1\text{H}$ NMR spectrum. The hydrogen at C-5 appeared as a quintet, located at $\delta$ 2.85 with a coupling constant of 7 Hz with the three hydrogens of the methyl group 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 $\delta$ 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](image)

The $^1\text{H}$ 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-butadienes6.

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

<table>
<thead>
<tr>
<th></th>
<th>94a</th>
<th>103a</th>
<th>94b</th>
<th>103b</th>
<th>104b</th>
<th>94c</th>
<th>104c</th>
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<tr>
<td>C-1</td>
<td>213.2</td>
<td>213.2</td>
<td>213.2</td>
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<td>39.4</td>
<td>44.2</td>
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<td>41.3</td>
<td>39.9</td>
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<td>30.8</td>
<td>31.1</td>
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<td>30.9</td>
<td>30.3</td>
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<tr>
<td>C-4a</td>
<td>44.5</td>
<td>44.7</td>
<td>51.8</td>
<td>51.6</td>
<td>46.4</td>
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<tr>
<td>C-5</td>
<td>42.1</td>
<td>41.8</td>
<td>44.1</td>
<td>43.8</td>
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<tr>
<td>i-Pr Me</td>
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<tr>
<td>i-Pr CH$_2$</td>
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<tr>
<td>i-Pr C</td>
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<tr>
<td>C-8a Me</td>
<td>25.2</td>
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<tr>
<td>C-5 Me</td>
<td>-</td>
<td>-</td>
<td>11.1</td>
<td>11.8</td>
<td>11.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C-7 Me</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>13.9</td>
<td>14.0</td>
</tr>
</tbody>
</table>
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\(^1\). 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%\(^1\). 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\(^1\). Until now, (+)-α-cyperone was used mainly as a starting compound for the synthesis of various other fused-ring sesquiterpenes\(^1\). Recently it was shown that (+)-α-cyperone (95) has in vitro activity against Plasmodium falciparum strain K1, a multidrug resistant malaria parasite\(^1\) which made this compound again an interesting target molecule.

Scheme 2.2

![Scheme 2.2](image)

**Reagents** i: MED, \(p\)-TsOH, glycol; ii: LiAlH\(_4\), ether; iii: NaH, CS\(_2\), MeI, THF, \(\Delta\); \(n\)-Bu\(_3\)SnH, AIBN, toluene, \(\Delta\); iv: \(H^+\), H\(_2\)O, acetone; v: TMSiCl, Et\(_3\)N, DMF, \(\Delta\). 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\(^\text{18}\) 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\(^\text{19}\), 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.\(^\text{20}\) in 90% yield. Oxidation of 109 with dichlorodicyanoquinone (DDQ)\(^\text{21}\) in benzene at room temperature afforded \((+)-\alpha\)-cyperone (95) in 87% yield and dehydro-\(\alpha\)-cyperone 110 as a byproduct in 8% yield. \((+)-\alpha\)-Cyperone (95) was obtained \textit{via} this 7-step procedure in an overall yield of 40% from S-(+)carvone. The Diels-Alder approach of \((+)-\alpha\)-cyperone (95) therefore is a competitive alternative for the other known total syntheses of \((+)-\alpha\)-cyperone (95).

2.4 Experimental Section

\textit{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 (\(\delta\) 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-octahydroporphthalene-1,6-dione (94a)
mp: 56 - 57 °C. 1H 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 C14H20O2: C, 76.32; H, 9.15; found: C, 76.12; H, 9.11. [α]D = -39.9 (c = 0.3).

(3S,4aS,8aR)-3-Isopropenyl-8a-methyl-2,3,4,4a,5,7,8,8a-octahydroporphthalene-1,6-dione (103a)
mp: 97 °C. 1H 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. [α]D = -120.6 (c = 0.2).

(3S,4aR,5R,8aS)-5,8a-Dimethyl-3-isopropenyl-2,3,4,4a,5,7,8,8a-octahydroporphthalene-1,6-dione (94b)
1H 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. [α]D = -36.7 (c = 0.3).

(3S,4aS,5R,8aR)-5,8a-Dimethyl-3-isopropenyl-2,3,4,4a,5,7,8,8a-octahydroporphthalene-1,6-dione (103b)
mp: 128 - 129 °C. 1H 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. [α]_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. [α]_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. [α]_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. [α]_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 MgSO₄ 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: calc'd (M\(^+\)) m/e 278.1882; found m/e 278.1883. [\(\alpha\)]\(_D\) = −35.8 (c = 0.3).

\((1S,3S,4aR,5R,8aS)-5,8a-\text{Dimethyl}-6,6-(\text{ethylenedioxy})-3-\text{isopropenyl-perhydro-naphthalene-1-ol}\) (106) and \((1R,3S,4aR,5R,8aS)-5,8a-\text{dimethyl}-6,6-(\text{ethylenedioxy})-3-\text{isopropenyl-perhydro-naphthalene-1-ol}\) (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 1 h. 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: \(^1\)H 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: calc'd (M\(^+\)) m/e 280.2038; found m/e 280.2044. [\(\alpha\)]\(_D\) = +14.0 (c = 0.4).

107: \(^1\)H 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: calc'd (M\(^+\)) m/e 280.2038; found m/e 280.2038. Anal.: calc'd 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).

\((1R,4aS,7R,8aR)-1,4a-\text{Dimethyl}-2,2-(\text{ethylenedioxy})-7-\text{isopropenyl-perhydro-naphthalene}\) (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 MgSO4. 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 aozoisobutyronitrile 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.

1H 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). 13C 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. [α]D = 29.4 (c = 0.3).

(daS,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 MgSO4. 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-octahyronaphthalene-2(1H)-one as a colourless oil.

1H 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). 13C 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. [α]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 MgSO4. Column chromatography (eluent PE) yielded 1.21 g (4.14 mmol, 90%) of 109 as a colourless oil. 1H 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). 13C 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. [α]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-quatrohydropranhthalene-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: 1H NMR: δ 1.19 (s, 3H); 1.76 (s, 6H); 1.0 - 2.9 (m, 11H); 4.74 (s, 2H). 13C 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. [α]D = +91.1 (c = 0.7).
110: 1H 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).
13C 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. [α]D = −149.0 (c = 0.1).

2.5 References and Notes
9. For previous reactions with diene 102a, see
      103, 6677-6685.
10. For previous reactions with diene 102b see
11. For previous reactions with diene 102c see
       25, 2593-2596.
     6677-6685.
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](image)

Reagents i: Mel, \(t\)-BuOK; ii: \(N_2H_4\), KOH, 200 °C; iii: \(O_3\), Me\(_2\)S; 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](image)

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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 benzylation 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**

![Scheme 3.2](image)

Reagents i: PhCHO, NaOH; ii: LiAlH$_4$, AlCl$_3$; iii: O$_3$, thiourea; iv: PBB, HOAc; v: LiBr, Li$_2$CO$_3$, DMF, 120 °C; vi: H$_2$O$_2$, NaOH; vii: H$_2$NNH$_2$, 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 decomposition 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**

![Scheme 3.3](image)

Reagents i: KOH, DEG, 200 °C; ii: O₃, thiourea; iii: O₃, MeOH; Cu(OAc)₂, FeSO₄; iv: Li/NH₃, t-BuOH; v: H₂NNH₂, 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 \(\delta\)-acetoxy-\(\alpha,\beta\)-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.

\[\text{Scheme 3.4}\]

\[\text{Reagents } i: \text{O}_3, \text{MeOH}; \text{Ac}_2\text{O}, \text{Et}_3\text{N}, \text{DMAP}; ii: \text{NaOCH}_3; iii: \text{Li-selectride, DMPU}; iv: m\text{-CPBA}; v: \text{NaBH}_4; vi: \text{TsCl, py; LiAlH}_4, \Delta.\]

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: \(\delta\) 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 \textit{in vacuo} and the residue was filtered over silicagel (eluent PE). The solvent was evaporated \textit{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 \textit{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\(^3\): 88 - 90 °C).

\(^1\)H NMR: \(\delta\) 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. \([\alpha]_D = -81.0\) (c = 0.37), (Lit\(^3\): \([\alpha]_D = -86.1\)).

\((4aS,8aS)-4a,5,6,7,8,8a-Hexahydro-4a,8,8-trimethyl-naphthalen-2(1H)-one\) (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: \(\delta\) 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: calcld (M⁺) m/e 272.0776; found m/e 272.0779. Anal: calcld for C₁₃H₂₁BrO: C, 57.14; H, 7.74; found: C, 56.86; H, 7.70. [α]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 MgSO₄, 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: calcld (M⁺) m/e 192.1514; found m/e 192.1511. [α]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-octahydror-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: calcld (M⁺) m/e 208.1463; found m/e 208.1456. Anal: calcld for C₁₃H₂₀O₂: C, 74.95; H, 9.67; found: C, 74.78; H, 9.84. [α]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 MgSO₄, 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.

\[ ^1H \text{NMR: } \delta 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)-3,4a,5,6,7,8,8a-Octahydrop-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-hexahydrop-5,5,8a-trimethyl-naphthalen-1(4H)-one as a colourless oil, which solidified on standing, mp 30 - 34 °C.

\[ ^1H \text{NMR: } \delta 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.

\[ ^1H \text{NMR: } \delta 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 194.1672; 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-octahydrop-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\(^I\) 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

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solvent was dried over anhydrous MgSO₄, 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.

¹H 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 C₁₆H₂₆O: C,81.99; H, 11.18; found: C, 82.01; H, 11.10. [α]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 34¹ 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 MgSO₄. 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.

¹H 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. [α]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 34¹ 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.

¹H 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. [α]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 MgSO₄, 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.

¹H 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. [α]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 ethereal 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.

¹H 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. [α]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 until 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.

¹H 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. [α]D = -23 (c = 0.45).
A solution of 710 mg (3.0 mmol) of 34 in 50 ml of methanol was cooled to \(-80^\circ\text{C}\) and ozonized until 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.

\((4\text{aR},7\text{S})-7\text{-Hydroxy-4,4a,5,6,7,8-hexahydro-4a,8,8-trimethyl-naphthalen-2(3H)-one}\) (123)

A stirred solution of 1.95 g (8.3 mmol) of 120 in 50 ml of methanol was cooled to \(-80^\circ\text{C}\) and ozonized until 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\text{H NMR: }\delta \text{ 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 \text{ 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 \(-80^\circ\text{C}\) and ozonized until 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 until a light blue color 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.

1H 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. [α]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, (Lit5d: 91.6 - 92 °C).

1H 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. [α]D = −4.9 (c = 0.81), (Lit5d: [α]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 MgSO4, filtered and evaporated in vacuo to give 105 mg (81%) of 113 as a white solid, mp 85 - 87 °C. (Lit5d: 86.5 - 87.4 °C).

1H 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. [α]D = −9.4 (c = 0.32), (Lit5d: [α]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 962 in a mixture of 170 ml of dichloromethane and methanol (5:1) was cooled to -80 °C and ozonized until 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 MgSO4, 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.

1H 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. [α]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.

1H 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. [α]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-chloroanisole. 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.

1H 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: calc (M+) m/e 194.1307; found m/e 194.1299. [α]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.

1H 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: calc (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.

1H 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: calc (M+) m/e 182.1670; found m/e 182.1662. [α]D = +15.5 (c= 1.2). Lit:6a: [α]D = -16.5 (-)-geosmin.

3.6 References and Notes

2039-2044.


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 olfactory compound (-)-Ambrox® (101) (Scheme 4.1).

Scheme 4.1

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. 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. Although one step procedures for conjugate addition-alkylation are often successful, only a few examples of the tandem conjugate addition-Michael reactions are known, probably because the intermediate organocopper enolate requires a not commercially available α-trimethylstilyl ketone as Michael acceptor, to avoid multiple addition and polymerization. Trapping of the intermediate enolates as their silyl enol ethers usually proceeds quite well and therefore the Lewis acid catalyzed silyl enol ether variation of the Robinson annulation 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.Me2S), 2 equivalents of trimethylchlorosilane (TMSCl) and hexamethyolphosphoric triamide (HMPA) at -40 °C, afforded the 1,4-addition products 127a and 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.Me2S) 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 (Et3N) in acetonitrile at 80 °C to give 127d in 85% yield accompanied with 6% of the kinetic silyl enol ether.

Scheme 4.2

Reagents for 127a, 127b and 127c i: RMgX, Me2S.CuBr, TMSCl, HMPA, THF, low temperature (see text); for 127d: ii: Li/NH3, t-BuOH; iii: TMSCl, NEt3, NaI, acetonitrile, Δ.
The conditions of Duhamel\textsuperscript{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 \(-65\) \(\text{oC}\) instead of \(-20\) \(\text{oC}\), 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\textsuperscript{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).

\[ \text{Scheme 4.3} \]

\[ \text{127a: } R = \text{Me} \]
\[ \text{127b: } R = \text{vinyl} \]
\[ \text{127c: } R = \text{allyl} \]
\[ \text{127d: } R = \text{H} \]
\[ \text{129a: } R = \text{Me} \]
\[ \text{129b: } R = \text{vinyl} \]
\[ \text{129c: } R = \text{allyl} \]
\[ \text{129d: } R = \text{H} \]
\[ \text{130a: } R = \text{Me} \]
\[ \text{130b: } R = \text{vinyl} \]
\[ \text{130c: } R = \text{allyl} \]
\[ \text{130d: } * \]
\[ \text{131: } R = \text{Me} \]
\[ \text{132: } R = \text{vinyl} \]
\[ \text{99: } R = \text{allyl} \]

\textit{Reagents} i: MVK, BF\textsubscript{3}.Et\textsubscript{2}O, isopropanol, CH\textsubscript{2}Cl\textsubscript{2}, nitromethane, \(-65\) \(\text{oC}\); ii: NaOMe, MeOH; * see scheme 4.4.

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

<table>
<thead>
<tr>
<th>Silyl enol ether</th>
<th>Ketone 129 yield (%)\textsuperscript{a}</th>
<th>Diketone 130 yield (%)\textsuperscript{a} (de) (%)</th>
<th>Cyclization yield (%)\textsuperscript{b} (de) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>127a (R=Me)</td>
<td>25</td>
<td>65\textsuperscript{c} 92\textsuperscript{c}</td>
<td>87\textsuperscript{c} 98\textsuperscript{c}</td>
</tr>
<tr>
<td>127b (R=vinyl)</td>
<td>23</td>
<td>65\textsuperscript{c} 94\textsuperscript{c}</td>
<td>89\textsuperscript{c} 98\textsuperscript{c}</td>
</tr>
<tr>
<td>127c (R=allyl)</td>
<td>15</td>
<td>75\textsuperscript{c} 92\textsuperscript{c}</td>
<td>95\textsuperscript{c} 96\textsuperscript{c}</td>
</tr>
<tr>
<td>127d (R=H)</td>
<td>19</td>
<td>70 40</td>
<td>90 (d)</td>
</tr>
</tbody>
</table>

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

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

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\textsuperscript{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).

\textbf{Scheme 4.5}

\[ \begin{array}{c}
\text{S-(-)-carvone} \quad \text{i} \quad \text{135} \quad \text{ii} \quad \text{136} \quad \text{iii} \quad \text{98}
\end{array} \]

Reagents i: KCN, HAc, EtOH, H$_2$O; 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 drimanones and into (-)-Ambrox\textsuperscript{®} (101) are the subjects of the chapters 5 and 6, respectively.

\textbf{4.4 Experimental Section}

\textit{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 hexamethyldiphosphoric 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.

1H 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). 13C 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. [α]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 hexamethyldiphosphoric 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.

1H 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). 13C 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. [α]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 magnesium chloride 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: 1H 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). 13C 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+1) m/e 264.1909; found m/e 264.1909. [α]D = −43.5 (c = 0.5).

128: 1H 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). 13C 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. [α]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.

1H NMR: δ 0.15 (s, 9H); 1.54 (s, 3H); 1.70 (s, 3H); 1.2 - 2.3 (m, 7H); 4.70 (bs, 2H). 13C 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. [α]D = −73.4 (c = 0.4).

General procedure for the synthesis of the diketones 130.

Silyl enol ether 127 was dissolved in dichloromethane (1 mmol/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 $-65^\circ$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: $\delta$ 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: $\delta$ 0.95 (d, $J = 6.8$ Hz, 3H); 1.70 (s, 3H); 4.68 (s, 1H); 4.79 (s, 1H). HRMS: calcld (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: $\delta$ 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: $\delta$ 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: calcld (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: $\delta$ 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: $\delta$ 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: calcld (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: $\delta$ 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: $\delta$ 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: calcld (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: $\delta$ 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: $\delta$ 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: calcld (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 \text{H NMR: } \delta 0.96 \text{ (s, 3H)}; \ 1.68 \text{ (s, 3H)}; \ 2.10 \text{ (s, 3H)}; \ 1.6 - 2.7 \text{ (m, 12H)}; \ 4.64 \text{ (s, 1H)}; \ 4.77 \text{ (s, 1H)}; \ 4.95 \text{ (m, 1H)}; \ 5.02 \text{ (s, 1H)}; \ 5.65 - 5.70 \text{ (m, 1H)}. \ ^{13} \text{C NMR: } \delta 18.8 \text{ (q); } 20.9 \text{ (q); } 27.6 \text{ (t); } 29.8 \text{ (q); } 29.9 \text{ (t); } 33.2 \text{ (t); } 38.1 \text{ (t); } 39.6 \text{ (d); } 40.6 \text{ (d); } 42.3 \text{ (t); } 50.9 \text{ (s); } 110.5 \text{ (t); } 116.2 \text{ (t); } 136.6 \text{ (d); } 147.0 \text{ (s); } 208.3 \text{ (s); } 215.3 \text{ (s). \ HRMS: calculd (M^+) m/e 262.1932 ; found m/e 262.1932. [α]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 \text{H NMR: major signals of the major epimer: } \delta 0.96 \text{ (s, 3H)}; \ 1.69 \text{ (s, 3H)}; \ 2.08 \text{ (s, 3H)}; \ 4.67 \text{ (s, 1H)}; \ 4.72 \text{ (s, 1H). \ ^1 \text{H NMR: major signals of the minor epimer: } \delta 1.09 \text{ (s, 3H)}; \ 1.69 \text{ (s, 3H)}; \ 2.11 \text{ (s, 3H)}; \ 4.67 \text{ (s, 1H)}; \ 4.72 \text{ (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 (elucent PE/EtOAc = 10/1) to give the cyclization products as colourless oils.

(4aR,5S,7S)-4a,5-Dimethyl-4,4a,5,6,7,8-Hexahydrro-7-isopropenyl-naphthalene-2(3H)-one (131)

\[ ^1 \text{H NMR: } \delta 0.82 \text{ (d, J = 6.6 Hz, 3H)}; \ 1.08 \text{ (s, 3H)}; \ 1.66 \text{ (s, 3H)}; \ 1.4 - 2.7 \text{ (m, 10H)}; \ 4.70 \text{ (s, 1H)}; \ 4.80 \text{ (s, 1H)}; \ 5.76 \text{ (s, 1H). \ ^{13} \text{C NMR: } \delta 14.8 \text{ (q); } 15.7 \text{ (q); } 22.5 \text{ (q); } 32.0 \text{ (t); } 33.8 \text{ (t); } 35.1 \text{ (d); } 35.2 \text{ (t); } 36.0 \text{ (t); } 38.6 \text{ (s); } 39.5 \text{ (d); } 111.9 \text{ (t); } 125.2 \text{ (d); } 146.8 \text{ (s); } 170.8 \text{ (s); } 199.0 \text{ (s). \ HRMS: calculd (M^+) m/e 218.1671 ; found m/e 218.1677. [α]D = +155 (c = 0.4).}

(4aR,5R,7S)-4a,5,6,7,8-Hexahydrro-7-isopropenyl-4a-methyl-5-vinlynaphthalene-2(3H)-one (132)

\[ ^1 \text{H NMR: } \delta 1.14 \text{ (s, 3H)}; \ 1.68 \text{ (s, 3H)}; \ 1.6 - 2.8 \text{ (m, 10H)}; \ 4.74 \text{ (s, 1H)}; \ 4.85 \text{ (s, 1H)}; \ 4.99 \text{ (dd, J = 10.7 Hz, J = 2.0 Hz, 1H)}; \ 5.07 \text{ (d, J = 1.8 Hz, 1H)}; \ 5.64 - 5.82 \text{ (m, 1H)}; \ 5.79 \text{ (s, 1H). \ ^{13} \text{C NMR: } \delta 16.9 \text{ (q); } 22.4 \text{ (q); } 29.2 \text{ (t); } 33.7 \text{ (t); } 35.5 \text{ (t); } 35.6 \text{ (t); } 38.3 \text{ (s); } 39.1 \text{ (d); } 46.4 \text{ (d); } 112.3 \text{ (t); } 116.5 \text{ (t); } 125.6 \text{ (d); } 137.4 \text{ (d); } 146.4 \text{ (s); } 169.7 \text{ (s); } 198.9 \text{ (s). \ HRMS: calculd (M^+) m/e 230.1668 ; found m/e 230.1668. [α]D = +54.7 (c = 0.3).}

(4aR,5S,7S)-4a,5,6,7,8-Hexahydrro-7-isopropenyl-4a-methyl-5-(prop-2'-enyl)-naphthalene-2(3H)-one (99)

\[ ^1 \text{H NMR: } \delta 1.11 \text{ (s, 3H)}; \ 1.65 \text{ (s, 3H)}; \ 1.2 - 2.7 \text{ (m, 12H)}; \ 4.69 \text{ (s, 1H)}; \ 4.81 \text{ (s, 1H)}; \ 4.96 \text{ (m, 1H)}; \ 5.03 \text{ (s, 1H)}; \ 5.69 \text{ (m, 1H)}; \ 5.80 \text{ (s, 1H). \ ^{13} \text{C NMR: } \delta 16.5 \text{ (q); } 22.3 \text{ (q); } 28.2 \text{ (t); } 33.3 \text{ (t);}

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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 [α]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). 13C 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. [α]D = −51.9 (c = 1.0).

(4aR,7S)-4,4a,5,6,7,8-Hexahydro-7-isopropenyl-4a-methylnapthalene-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). 13C 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). [α]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 28.1 g (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. [α]D = +10.2 (c = 0.2).

(1S,3S,4aS,8aR)-Decahydro-4a-hydroxy-3-isopropenyl-8a-methyl-6-oxo-1-naphthalene-carbonitrile (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. [α]$_D$ = −41.3 (c = 0.3).

(1S,3S,8aR)-3-Isopropenyl-8a-methyl-1,2,3,4,6,8a-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.

$^1$H 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: calcd. (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. [α]$_D$ = +202 (c = 0.4).

4.5 References and Notes


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

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\(^4\) 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.

\(^{*}\) This chapter has been published in a revised form: Swarts, H. J.; Verstegen-Haaksma, A. A.; Jansen, B. J. M.; de Groot, A. Tetrahedron 1994, 50, 10083-10094.
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 \textit{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 \textit{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.

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.

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**

![Scheme 5.2](image)

**Reagents**

i: MeI, KO-t-Bu, HO-t-Bu; ii: NaBH₄, 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**

\[
\begin{align*}
144 & \xrightarrow{i} 145 & 146 & 147 & 148 \\
& \xrightarrow{ii} & & & \\
& & \xrightarrow{iii} & & \\
& & & \xrightarrow{iv} & \\
R & = & \text{TBDMS} & & \\
\end{align*}
\]

**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-butylidimethylsilyl 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

Reagents  i: HCO₂Et, 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 occurred after acylation of the intermediate and rising the temperature to room temperature 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

Reagents  i: O₃, MeOH; Ac₂O, NEt₃, DMAP; ii: NaOMe, MeOH; iii: NaBH₄; iv: MnO₂, 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) 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**

Reagents i: H₂, 10% Pd/C, 4 bar; ii: Bredereck's reagent; HCl, H₂O, acetone; iii: Ac₂O, DMAP; iv: H₂, PtO₂, 2 bar; v: NaBH₄, 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 of 157 with trifluoromethanesulfonyl chloride (TfCl) in the presence of 4-N₂,N-dimethylaminopyridine finally led to (-)-3β-acetoxydrimenin (100) and (+)-3β-acetoxyisodrimenin (158) in 53% and 12% respectively.

Sierra et al. 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.

(IS,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. [α]$_D$ = -32.6 (c = 3.5).

(IS,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 (IS,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. [α]$_D$ = -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 (3q); 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. [α]$_D$ = -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 (3q); 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$_2$Si: C, 73.36; H, 10.71; found: C, 73.09; H, 10.81. [α]$_D$ = -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). 13C 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 C23H42O2Si: C, 72.97; H, 11.18; found: C, 72.82; H, 11.22. [α]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.

1H 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). 13C 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. [α]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.

1H 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). 13C 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
(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 mgat) 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). 13C 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 C20H38O3Si: C, 67.76; H, 10.80; found: C, 67.65; H, 10.92. [α]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-Butyldimethylsilyloxy)-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 364.2428. [α]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.

$^1$H 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.

1H 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). 13C NMR: δ 21.3 (q); 22.9 (q); 25.6 (q); 26.0 (t); 35.4 (2*); 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 C14H19NO2: C, 72.06; H, 8.21; N, 6.00; found: C, 72.05; H, 8.13; N, 5.87. [α]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.

1H 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). 13C 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: calc for C14H21NO2: C, 71.45; H, 9.00; N, 5.95; found: C, 71.21; H, 9.06; N, 5.89. [α]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.

1H 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). 13C 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. [α]_D = +31.3 (c = 0.4).

(3aS,5aR,7S,9aS,9bS)-7-Acetoxyl-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.

1H 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). 13C 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. [α]_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.

1H 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). 13C 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. [α]_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.

1H 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: calc'd (M+ - 60) m/e 250.1569; found m/e 250.1564. Anal: calc'd for C$_{17}$H$_{26}$O$_{5}$: C, 65.78; H, 8.44; found: C, 65.95; H, 8.51. [α]$_D$ = -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 $^1$H 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: calc'd (M+) m/e 292.1674; found m/e 292.1673. Anal: calc'd for C$_{17}$H$_{24}$O$_{4}$: C, 69.83; H, 8.27; found: C, 69.84; H, 8.25. [α]$_D$ = -6.1 (c = 0.4).

158 $^1$H 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: calc'd (M+ - 60) m/e 232.1463, found m/e 232.1463. [α]$_D$ = +100 (c = 0.11).

5.4 References and Notes


5. The numbering system of drimane sesquiterpenes is used throughout the discussion.


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. 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. For this reason, diverse synthetic routes to (-)-Ambrox® (101) and its racemate have been developed. (-)-Ambrox® (101) was previously prepared starting from geranylacetone, which made an optical resolution step necessary, and from naturally occurring sesquiterpenes or diterpenes. The racemate was prepared by a number of total syntheses employing biogenetic-type cyclizations from farnesic or monocyclofarnesic acids or derivatives of these.

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 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 Δ^7,8^ double bond in 159 which is necessary for the final cyclization to (-)-Ambrox® (101).

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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: O3, MeOH, -78 °C; NaBH4; iv: MnO2, acetone; v: (Me)2N-CH2-N(Me)2, Ac2O; vi: Li, NH3, EtOH; vii: TBDMSiCl, DMF, imidazole; viii: MsCl, DMAP, CH2Cl2; LiCO3, LiBr, Δ; ix: HF, acetonitrile; x: p-TsOH, nitromethane.

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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

![Chemical structures](image)

Enone 163 gave diene 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 Wüst\(^6a\) 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-toluencesulfonic 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 dekalone 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 chloride 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. Methylolation 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 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: NaBH₄; iv: TsCl, pyridine; v: NaCN, DMF; vi: HCl, H₂O; vii: Mel, KO-t-Bu, HO-t-Bu; viii: Hydrazine, KOH, DEG, 220 °C; ix: O₃, MeOH; NaBH₄; x: LiAlH₄.

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 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. 

1H 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). 13C 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. [α]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 oC and then the excess of hydrazine hydrate and water was removed by distillation. The temperature was raised to 220 oC 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. 

1H 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). 13C 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. [α]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 oC. 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 oC. 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 oC after flash chromatography (eluent PE/EtOAc = 3/2).

1H NMR: (with a drop of CDOD₃) 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). 13C 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 C₁₅H₂₆O₂: C, 75.58; H, 11.00; found: C, 75.78; H, 11.14. [α]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. [α]$_D$ = -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-naphthaleneethanol (164)
To a solution of 0.62 g (2.64 mmol) of hydroxyketone 163 in 2 ml of N,N,N',N'-tetramethylethylammonium methane 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. [α]$_D$ = -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-naphthaleneethanol (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-naphthaleneethanol (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 mEq) 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: 1H 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). 13C 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. [α]D = -12.3 (c = 1.0).

166: 1H 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 (dd, J = 6.2 Hz, 12.0 Hz, 12.5 Hz, 1H); 3.40 - 3.70 (m, 2H). 13C 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. [α]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 tert-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.

1H 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 (dd, J = 5.4 Hz, 10.5 Hz, 11.4 Hz, 1H); 3.33 - 3.67 (m, 2H). 13C 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 C22H44O2Si: C, 71.69; H, 12.03; found: C, 71.89; H, 12.38. [α]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-butyldimethylsilyloxy)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 (elucent PE/EtOAc = 7/3) gave a second crop of alcohol 159 of 0.089 g (0.38 mmol, 51%).

TBDMS ether: 1H 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). 13C 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: calcld (M+ -57) m/e 293.2301; found m/e 293.2301. [α]D = -6.7 (c = 0.7).

159: 1H 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). 13C 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: calcld (M+) m/e 236.2140; found m/e 236.2142. [α]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 (MgSO4). Flash chromatography (elucent 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 ºC (ref.6a: mp 74 - 76 ºC).

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 (elucent 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): 1H 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). 13C 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: calcld (M+) m/e 236.2140; found m/e 236.2144. Anal: calcld for C16H28O: C, 81.29; H, 11.94; found: C, 80.98; H, 12.02. [α]D = -24.6 (c = 0.5) (ref. 6a: [α]D = -22.1 (c = 0.7)).
168: $^1$H NMR (90 MHz, major signals): $\delta$ 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-(Ethlenedioxy)-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: $\delta$ 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: $\delta$ 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: calcld (M$^+$) $m/e$ 273.1729; found $m/e$ 273.1729.

Anal: calcld for C$_{17}$H$_{23}$O$_2$N: 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-(Ethlenedioxy)-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 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: $\delta$ 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: $\delta$ 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: calcld (M$^+$) $m/e$ 276.1725; found $m/e$ 276.1725. Anal: calcld 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.

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).

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. [α]_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.

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).

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_{5}S: C, 66.64; H, 7.46; found: C, 66.59; H, 7.65. [α]_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.

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$^1$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$_2$N: C, 75.22; H, 8.77; N, 4.87; found: C, 74.87; H, 8.82; N, 4.67. [α]$_D$ = -116.7 (c = 0.5).

(1R,3S,8aR)-3-Isopropenyl-8a-methyl-1,2,3,4,6,7,8,8a-octahydro-6-oxo-1-naphthalene-acetonitrile (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$_1$N: C, 78.97; H, 8.70; N, 5.76; found: C, 78.55; H, 8.74; N, 5.67. [α]$_D$ = +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$_1$N: C, 79.66; H, 9.28; N, 5.16; found: C, 79.47; H, 9.47; N, 5.08. [α]$_D$ = -66.6 (c = 0.4).
(1R,8aR)-3-Isopropylidene-1,2,3,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-1-naphthaleneacetic 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.

^1H 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-naphthaleneacetic acid (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.

^1H 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 MgSO4. 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.

95
6.4 References and Notes


7. The numbering system of drimane sesquiterpenes, as indicated in compound 160, is used throughout the discussion.


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 falciparum K1, a multidrug resistant malaria parasite. The activity of (+)-α-cyperone (IC\(_{50} = 5.5 \mu g/ml\))^2 is nevertheless substantially lower than the activity of artemisin, another sesquiterpene with antimalaria activity (IC\(_{50} = 3.4 \text{ng/ml}\))\(^3\).

![Scheme 7.1](image)

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**

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**
(+)-Geosmin (97), the enantiomer of the natural (-)-geosmin, is an interesting olfactory 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

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

\[ \text{S-(+)-carvone} \rightarrow \text{127a: } R = \text{Me} \]
\[ \text{127b: } R = \text{vinyl} \]
\[ \text{127c: } R = \text{allyl} \]
\[ \text{130a: } R = \text{Me} \]
\[ \text{130b: } R = \text{vinyl} \]
\[ \text{130c: } R = \text{allyl} \]
\[ \text{99: } R = \text{allyl} \]
\[ \text{131: } R = \text{Me} \]
\[ \text{132: } R = \text{vinyl} \]
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.

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 7.6](image)

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\(^6\).
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%. Optimization 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-dimethylamino-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 optimization of the reaction conditions. So, the overall yield of (+)-3β-acetoxydrimenin (100) was only 4.5% from S-(-)-carvone.

Scheme 7.8
The synthesis of the commercially interesting olfactory 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

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 diene 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

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

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

The synthesis of (-)-Ambrox® (101) from S-(+)-carvone is probably not competitive with the known short synthetic routes from (-)-scclareol7, 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**

![Chemical Structures](image)

7.2 References and notes

   
   


   


   
   
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**

\[
\begin{array}{c}
\text{S-(+)-carvone} \\
\rightarrow \\
\text{94a: } R^1 = H, R^2 = H \\
\text{94b: } R^1 = \text{Me}, R^2 = H \\
\text{94c: } R^1 = H, R^2 = \text{Me} \\
\text{95}
\end{array}
\]

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 olfactory compound was synthesized from decalone 96 (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.
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](image)

In chapter 6 the total synthesis of (-)-Ambrox® (101), a commercially interesting olfactory 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](image)

98: R = allyl
99: R = CN
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.

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 moleculaire, 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 Cypereus rotundus L. en heeft een interessante in vitro activiteit tegen Plasmodium flaciparium K1, een malariaparasiet met een resistentie tegen een groot aantal bestaande malaria-medicijnen.

Schema 9.1

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 synthese 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

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 ozonolys/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**

![Chemical structure](image)

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**

![Chemical structure](image)

98: R = allyl  
99: R = CN
Curriculum Vitae

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.

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.

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

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.

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.

![structuur 1](image1)
![structuur 2](image2)
![structuur 3](image3)
6. De "unieke" stereoselectiviteit die Harrison et al. vonden bij de reductie van een aantal alkyl gesubstitueerde cyclohexancarboxylaat met aminoborohydrides is vergelijkbaar met de stereoselectiviteit van lithiumaluminiumhydride en natriumborohydride.

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