Syntheses of Allelochemicals for Insect Control

Isoprenoid Synthesis

Olof Smitt

Doctoral Thesis

Akademisk avhandling som med tillstånd av Kungliga Tekniska Högskolan i Stockholm framlägges till offentlig granskning för avläggande av filosofie doktorsexamen i organisk kemi, fredagen den 27:e september 2002, kl. 10:00 i Fälldinsalen (N 109), Mälthuset, Åkroken, Mitthögskolan, Sundsvall. Fakultetsopponent: professor Torbjörn Frejd, Organisk kemi 1, Lunds Universitet. Avhandlingen förvaras på svenska.
“The synthetic chemist is more than a logician and strategist; he is an explorer strongly influenced to speculate, imagine, and even to create. These added elements provide the touch of artistry which can hardly be included in a cataloguing of the basic principles of synthesis, but they are very real and extremely important.”

E. J. Corey, Nobel Prize for chemistry, 1990

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ABSTRACT

This thesis describes the synthetic preparation of some compounds, which can serve as chemical signals for use in the development of control methods for pest insects. The compounds synthesised are of the isoprenoid type and of two kinds: carvone derivatives and germacrane. The derivatives of carvone are based on modifications of this compound, by reactions of either its endocyclic or its exocyclic double bond. One type of modifications was accomplished by chemoselective additions of thiophenol. The latter ones imply additions to the exocyclic double bond and seem to constitute general, previously rarely studied reactions.

In other modifications of its exocyclic side chain, carvone afforded some sesquiterpenoid natural products. The following compounds were synthesised in an enantioselective way: (−)-epi-delobanone, (−)-delobanone, (−)-7-hydroxy-3,10-prenyl-bisaboladien-2-one (an insecticidal constituent of Croton linearis) as well as its diastereomer and some other compounds with similar structures. All of these compounds were tested for their antifeedant/feeding deterrent capability against gnawing of the pine weevil, Hylobius abietis.

The germacrane prepared by means of enantioselective total syntheses are: (−)-1(10),5-germacradien-4-ol and (−)-germacrene D. The former is a constituent of the defence secretion (an allomone) from the larvae of the pine sawfly, and the needles of Scots pine. (−)-Germacrene D is a ubiquitous compound in nature. For example, it occurs in the peels of apples and acts as one component of a lure (a kairomone) to the apples, which attracts the codling moth, Cydia pomonella.

The main problem in the total syntheses of the germacrane was the formation of the unsaturated monocyclic 10-membered ring. This was achieved by intramolecular alkylation with a suitably functionalised/protected cyanohydrin derivative, which, after further elaboration, afforded a monocyclic 10-membered enone, that was used in the syntheses of the two germacrane mentioned above. In the initial steps in the synthetic sequence the stereochemistry was established by alkylation of an amide enolate attached to a chiral auxiliary. This approach could most likely also readily furnish the (+)-enantiomers of these germacrane (of the germacrane terpenoid class) using the opposite enantiomer of the chiral auxiliary in the initial steps.

Keywords: isoprenoids, natural product synthesis, allelochemicals, kairomones, allomones, bisabolane terpenoids, Hylobius abietis, germacrane terpenoids, Neodiprion sertifer, stereoselective synthesis.
This thesis is mainly based on the following papers and supplements, referred to in the chapters by their Roman numerals.


III  **Carvone and less volatile analogues as repellent and deterrent antifeedants against the pine weevil, Hylobius abietis (L.).** Schlyter, F.; Löfqvist, J.; Smitt, O.; Sjödin, K.; Högberg, H.-E. Manuscript for *J. Chem. Ecol.*

IV  **First Total Synthesis of (–)-1(10),5-Germacradien-4-ol.** Smitt, O.; Högberg, H.-E. *Synlett* 2002, 1273.

V  **Appendix: Total Syntheses of (–)-1(10),5-Germacradien-4-ol and (–)-Germacrene D - Experimental Part.** Smitt, O.

The papers were reprinted with kind permission from: Science Reviews Ltd., U.K. (paper I); Elsevier Science Ltd., U.K. (paper II) and Georg Thieme Verlag, Germany (paper IV).
CONTENTS

Abstract iii
List of papers iv
Abbreviations vi

1. INTRODUCTION 1
   1.1 Semiochemicals 1
   1.2 Antifeedants/feeding deterrents 3
   1.3 Isoprenoids 3
   1.4 Natural product synthesis 8
   1.5 This thesis 9

2. THIOPHENOL-BASED CARVONE ANALOGUES 11
   2.1 Biological background 11
   2.2 Hypothetical slow release system based on carvone 12
   2.3 1,4-addition of thiophenol to carvone 13
   2.4 Radical addition of thiophenol to carvone and perillaldehyde 15

3. LOW VOLATILITY CARVONE ANALOGUES 17
   3.1 Background of the aim at decreasing the volatility 17
   3.2 Terpenoids of the bisabolane type, and a synthetic strategy for their preparation 17
   3.3 Syntheses of carvone analogues with an exocyclic alkyl side chain 20
   3.4 Syntheses of carvone analogues with an exocyclic alkenyl side chain 22
   3.5 Biological activity of the carvone analogues 28

4. TOTAL SYNTHESES OF 1(10),5-GERMACRADEN-4-OL AND GERMACRENE D 31
   4.1 Biological background 31
   4.2 A literature survey of methods considered suitable for the syntheses of 1(10),5-germacraden-4-ol (9) and germacrene D (10) 33
   4.3 Retrosynthetic analysis and approach towards the synthesis of 1(10),5-germacraden-4-ol (9) and germacrene D (10) 40
   4.4 Synthesis of i-Pr substituted key fragment; (3E,7S)-7-[(tert-butyldimethylsilyl)-oxymethyl]-4,8-dimethylnon-3-en-1-ol (70) 42
   4.5 Synthesis of the monocyclic ten-membered ring compound; (2E,4S,7E)-4-isopropyl-7-methyleneclodeca-2,7-dien-1-one (82) 44
   4.6 Properties of the 10-membered monocyclic enone 82 and completion of the synthesis of 1(10),5-germacraden-4-ol (9) and Germacrene D (10) 47

5. CONCLUSIONS AND OUTLOOK 51
# ABBREVIATIONS

<table>
<thead>
<tr>
<th>Ac</th>
<th>acetyl</th>
<th>Ms</th>
<th>methanesulfonyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADP</td>
<td>adenosine 5´-diphosphate</td>
<td>MTPA</td>
<td>2-methoxy-2-(trifluoro-</td>
</tr>
<tr>
<td>AIBN</td>
<td>2,2´-azobisisobutyronitrile</td>
<td></td>
<td>methyl)phenylacetic acid</td>
</tr>
<tr>
<td>ATP</td>
<td>adenosine 5´-triphosphate</td>
<td>NADPH</td>
<td>reduced nicotinamide</td>
</tr>
<tr>
<td>9-BBN</td>
<td>9-borabicyclo[3.3.1]nonane</td>
<td></td>
<td>adenine dinucleotide phosphate</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
<td>NOE</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>bp</td>
<td>boiling point</td>
<td>NMO</td>
<td>4-methylmorpholine N-oxide</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CoA</td>
<td>coenzyme A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cp</td>
<td>cyclopentadienyl</td>
<td>NMP</td>
<td>N-methylpyrrolidinone</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift in ppm relative to TMS [(CH&lt;sub&gt;3&lt;/sub&gt;)₄Si]</td>
<td>PPTS</td>
<td>pyridinium 4-toluene-sulfonate</td>
</tr>
<tr>
<td>Δ&lt;sub&gt;x&lt;/sub&gt;</td>
<td>heat at reflux</td>
<td>R</td>
<td>generalised structure unit</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>DIBALH</td>
<td>diisobutylaluminium hydride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(dimethyl)aminopyridine</td>
<td>TBDMS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
<td>TBDPS</td>
<td>tert-butyldiphenylsilyl</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
<td>Tf</td>
<td>trifluoromethanesulfonamide</td>
</tr>
<tr>
<td>ED&lt;sub&gt;50&lt;/sub&gt;</td>
<td>dose that is effective in 50% of test subjects</td>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>EE</td>
<td>1-ethoxyethyl</td>
<td>TMS</td>
<td>trimethylsilyl or tetramethyl-silane (in NMR)</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalent</td>
<td>TPAP</td>
<td>tetrapropylammonium perruthenate</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hν</td>
<td>indicates radiation (in photo-chemical reactions)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>i-Pr</td>
<td>isopropyl</td>
<td>Ts</td>
<td>4-toluenesulfonyl</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant (in NMR)</td>
<td>X</td>
<td>halogen</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
<td>X&lt;sub&gt;c&lt;/sub&gt;</td>
<td>chiral auxiliary</td>
</tr>
<tr>
<td>Lg</td>
<td>leaving group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LHMDS</td>
<td>lithium hexamethyl-disilazane</td>
<td></td>
<td></td>
</tr>
<tr>
<td>m-CPBA</td>
<td>3-chloroperoxybenzoic acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
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</table>

Abbreviations list continues...
1. INTRODUCTION

Organic chemistry is the science dealing with the compounds containing carbon. Although called organic, such compounds do not have their own mind and consciousness, that is, they are dead materia, but despite this fact they are the building blocks of organisms. All living organisms consist of molecules containing carbon in some way. These can be linked together in a sophisticated way to form larger carbon molecules (e.g. carbohydrates, lipids, proteins), which in turn form organelles and cellular compartments, the main components of living cells. Organic molecules perform other tasks than just to serve as construction material. They are, for example, responsible for communication both at the intra- and intercellular level, and between fully developed organisms (working in parallel with the acoustic and optical stimuli, that humans normally consider as communication).

The organic chemist studies carbon-containing compounds, normally as homogeneous samples of one individual compound. This science, which is full of nuances, involves: isolation of new compounds from natural sources, investigation of their structures, studies on how they are formed, their preparation (i.e. organic synthesis) from natural and artificial starting materials, determination of their properties and so forth. There are ubiquitous examples of the use of synthetic organic compounds, which play an essential role in normal everyday life. Such useful chemicals are found in polymers, fuels, dyes, flavours, detergents, pharmaceuticals and so forth. Each carbon atom is capable of forming four covalent bonds, a fact that induces three-dimensionality (i.e. gives rise to the possibility of variations in stereochemistry). These factors and the possibility of forming stable covalent bonds also with atoms of other elements (frequently hydrogen, nitrogen, oxygen and sometimes sulfur and halogens) result in the virtually unlimited number of different carbon compounds that form our complex world.

1.1 Semiochemicals

Insect pest control and management are crucial for modern food and fibre production. In other words, efficient control of many species of insects is a necessity for mankind. About 10 000 insect species (out of 4–6 million)\(^1\) are regarded as harmful.\(^2\) The crop losses caused by insect pests are estimated at about 15%.\(^2\) In addition, insect-borne diseases are a serious problem. Increased knowledge of how

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nature itself deals with such problems may provide tools for controlling them. Many species use organic chemicals for communication or for defence against pests and predators. A chemical substance that transfers information between individuals is called a semiochemical. This term is derived from the Greek word *semio* that means a sign or a mark. Thus, semiochemicals are biological signal-compounds. The science dealing with how naturally occurring chemicals affect living organisms is called chemical ecology.

The semiochemicals can be divided into several subgroups that distinguish different categories on the basis of their biological purposes (Figure 1.1). Substances that elicit a response within species are named pheromones (Gk. *pherein* = to carry and *horman* = to excite). The pheromone class is further splitted into several subclasses: sex, alarm, aggregation, trail and so forth. Chemicals, which transmit messages between different species, are called allelochemicals (Gk. *allelon* = of each other). These are also divided into different groups depending on their functions.

![Figure 1.1. The concept of semiochemicals used to describe chemical communication.](image)

Allomones (Gk. *allo* = different) transfer signals that are advantageous to the emitter, kairomones (Gk. *kairos* = opportunistic) are advantageous to the receiver, synomones (Gk. *syn* = with or jointly) affect both the emitter and the receiver positively, and apneumones (Gk. *a-pneum* = breathless or lifeless) are substances emitted by dead material. There are also examples of multifunctional semiochemicals. Closely related species can thus use an intraspecific pheromone, which also acts as an interspecific

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This is the case of predators of several bark beetle species, which orient themselves towards their bark beetle preys with the help of the pheromone emitted by them.

1.2 Antifeedants/feeding deterrents

Feeding inhibitors are allelochemicals and belong to the subgroup allomones. When working with allomones one must consider several aspects: molecular structure, natural occurrence in host plants, behavioural assays, bio- and neurochemical studies of perception and usefulness in pest management. Several definitions of the term antifeedant can be found in the literature, and the lack of a stringent one is clear. It is common to all definitions that an antifeedant prevents or reduces feeding. However, olfactory deterrents in terms of volatile compounds that repel insects before they start to feed are usually not included. The difficulty lies in determining whether the feeding is inhibited before contact, during contact or after contact. The behaviour upon contact is not facile to establish unambiguously. Is the contact an olfactory- or a taste/sensory-mediated contact? Since toxic compounds are being classified as toxins or insecticides, it is obvious that the antifeedants/feeding deterrents are not toxic to the receiver of the compounds.

1.3 Isoprenoids

Compounds produced by living organisms are usually divided into classes according to the metabolic processes, from which they originate. Primary metabolites refer to substances derived via the Krebs cycle (α-amino acids, carbohydrates, fats, proteins and nucleic acids). They are vital for maintaining the life of organisms. Secondary metabolites do not play any essential roles in the biochemical events, but they contribute to the fitness and survival of the species and are usually more species specific than the primary ones. Alkaloids, aromatics, polyketides and isoprenoids are

examples of secondary metabolites. The reasons for the production of many secondary metabolites by living organisms are still the subject of speculation, and the task of distinguishing primary (biochemical) metabolites from secondary ones may be difficult due to the close relationship between these two classes of compounds. The branch of science that describes the properties, structure and formation of secondary metabolites is referred to as natural product chemistry.\textsuperscript{8}

Isoprenoids are also known as terpenes (sometimes defined as including only hydrocarbons) and terpenoids (sometimes defined as oxygen-containing terpenes). These two terms are normally used with the same meaning. The isoprenoids constitute the largest and most widely distributed class of natural products. There are more than 400 structural types characterising over 22 000 isoprenoids.\textsuperscript{9} Interestingly, isoprenoids often possess several tasks (many still unknown) in nature. Some of the purposes known are those of semiochemicals, for example antifeedants.\textsuperscript{10}

All isoprenoids are formed from units of five carbon atoms, called isopentenyl or isoprene units. Figure 1.2 shows two examples of low molecular weight isoprenoids, lavandulol and limonene, which are often produced by odoriferous plants, two of medium molecular weight, nootkatone (aroma of grapefruit), zingiberene (in ginger oil) and three of higher molecular weight, squalene (ubiquitous in many oils, \textit{e.g.} fish liver oils), cholesterol and \(\beta\)-carotene (found in carrots). The reason why there seems to be a lack of three carbon atoms in cholesterol is due to a series of biosynthetic steps, discussed further in the end of this section. The numbers of isoprenoid building blocks present in the terpenes have been used to define a systematic name classification: two linked isopentenyl units result in compounds with 10 carbon atoms, the \(\text{C}_{10}\) isoprenoids = monoterpenes; three units give \(\text{C}_{15}\) isoprenoids = sesquiterpenes; four give \(\text{C}_{20}\) = diterpenes; five give \(\text{C}_{25}\) = sesterterpenes; six give \(\text{C}_{30}\) = triterpenes; eight give \(\text{C}_{40}\) = tetraterpenes and so forth. Isoprene units can also be polymerised to give heterogeneous isoprenoids, more commonly known as natural rubbers. Terpenoids that deviate from the \(X \times \text{C}_5\) unit principle are sometimes found in nature, especially among the larger (> diterpenes) terpenoids. These are prefixed \textit{nor} if there is a lack of a carbon atom, \textit{homo} if there is an extra one.

\begin{itemize}
\end{itemize}
Figure 1.2. Some examples of isoprenoids. The isoprene units are indicated with bold lines.

The biosynthesis of terpenoids has been the subject of much research. The fact that they are built up by isoprene units was realised as early as 1887 by Otto Wallach.\cite{Wallach1887}
Ruzicka formulated the ‘biogenetic isoprene rule’ in 1953 as follows: “…the carbon skeleton of terpenes is composed by isoprene units linked in regular or irregular arrangement.”\cite{Ruzicka1953} Due to the use of sophisticated methods and modern instrumentation, the biosynthesis of most terpenoids from the isopentenyl building unit is mostly well established. Two major biosynthetic pathways leading to the isoprene unit are found.

\begin{itemize}
\item \cite{Wallach1887} Wallach, O. Justus Liebigs Ann. Chem. \textbf{1887}, 239, 1.
\item \cite{Ruzicka1953} Ruzicka, L. Experientia \textbf{1953}, 9, 357.
\end{itemize}
The first one, the mevalonate pathway starts with two enzyme catalysed Claisen condensations, which is followed by a NADPH dependent reduction to afford mevalonate (Figure 1.3). This carboxylate is in turn subjected to diphosphate formation by means of ATP. Decarboxylation coupled with dehydration gives rise to isopentenyl diphosphate (IPP, i.e. the isoprene unit).¹³

Figure 1.3. The biosynthesis of the crucial IPP unit along the mevalonate pathway.¹³

The mevalonate pathway was first believed to be the only route to the IPP unit. Somewhat surprisingly another biosynthetic pathway to the IPP unit was discovered at the end of the nineteen eighties. This seems to be even more widespread in nature than that previously discussed. This new, mevalonate independent, pathway starts with a thiamine diphosphate dependent coupling/decarboxylation to give a phosphate deoxyxylulose sugar unit (Figure 1.4).¹³ Enzyme catalysed rearrangement followed by an NADPH reduction result in a 2-methyl erythritol derivative. The further transformation of this to the IPP unit is currently under investigation. In either pathway, the individual steps are smoothly catalysed in a very efficient and selective way by enzymes. Many of these have been isolated and are well characterised.

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Figure 1.4. The alternative biosynthesis of the crucial IPP unit along the pyruvate/glyceraldehyde 3-phosphate pathway.

Enzymes also play a major role in further stages of isoprenoid biosynthesis. After initial formation of the parent, main ingredient of all isoprenoids (the IPP unit), further transformations of this are dominated by carbocation reactions. The carbocations are generated by enzymatic protonation of carbon-carbon double bonds and they sometimes undergo chain elongation or cyclisations (shown generalised in Figure 1.5). In some cases these are, in turn, followed by degradations and further rearrangements. Such degradations and rearrangements are the reasons why cholesterol does not seem to have been built up entirely from isoprene units (see Figure 1.2).

Figure 1.5. The IPP unit as the main building block in all terpenoids.
1.4 Natural product synthesis

The interest in developing practical applications by using semiochemicals constitutes one example where there is a need for syntheses of natural products. Mankind has used natural products in various applications since the dawn of its history, for example in the treatment of diseases, for dyeing, as spices, as poisons and so forth. The natural products were used as crude extracts, not as isolated pure compounds. In natural product chemistry the majority of substances studied originate from plants, and the Latin plant name is often used as an ingredient in the trivial name given to the substance. It is estimated that 40% of the pharmaceutical drugs used today are the results of using biologically active natural products as starting points.\footnote{Samuelsson, G. \textit{Drugs of Natural Origin}; Apotekarsocieten-Swedish Pharmaceutical Society, Swedish Pharmaceutical Press: Stockholm, 1999; p 17.}

Although nature seems to be the unbeatable master when it comes to the construction of complex carbon containing compounds, the science of chemical synthesis of natural products has developed tremendously during the 20\textsuperscript{th} century. Good examples (Figure 1.6) of complex natural products synthesised by predecessors in the field (among many others) are: camphor (1), a pleasantly smelling monoterpene (G. Komppa, 1903 and W. H. Perkin, 1904), tropinone (2) a stimulant of the nervous system (R. Willstätter, 1901 and R. Robinson, 1917, who made a great improvement in the economy of steps compared with the first synthesis) haemin (3), the oxygen carrier moiety in the protein hemoglobin (H. Fischer, 1929) and strychnine (4), a famous poison often occurring in detective stories (R. B. Woodward, 1954). All of these researchers contribute not only with numerous successful syntheses of target molecules of natural origin. Another main contribution of theirs is the development of retrosynthetic strategies and new chemical methods and concepts applied to the syntheses of compounds with complex molecular architecture. In this context, E. J. Corey \cite{corey1978} [\textit{e.g.} erythronolide B (5) a biosynthetic precursor of the broad-spectrum erythromycin antibiotics, 1978] and K. C. Nicolaou \cite{nicolaou1995} [\textit{e.g.} brevetoxin B (6) a neurotoxin produced by a marine alga, 1995], who carried the banner further, are also often mentioned.\footnote{(a) Nicolaou, K. C.; Sorensen, E. J. \textit{Classics in Total Synthesis}; VCH; Weinheim, 1996. (b) Nicolaou, K. C.; Sorensen, E. J.; Winssinger, N. \textit{J. Chem. Educ.} \textbf{1998}, \textit{75}, 1226. (c) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. \textit{Angew. Chem. Int. Ed.} \textbf{2000}, \textit{39}, 44.} In their case, of course, new synthetic methods and modern instru-
Figure 1.6. Famous examples of some natural products that have been made by total syntheses.

The capability of later chemists to administrating and handling (often several) large complex synthetic projects must also be acknowledged. Another contribution of Corey is that he systematically organised the retrosynthetic analysis, mainly based on thoughts that were seeded in the Woodward era, and that he formulated this in a logical way.¹⁶

1.5 This thesis

This thesis consists of two parts. Both parts deal with chemical support to the development of a use of allelochemicals in the biological projects of a MISTRA research programme: “Pheromones and Kairomones for Insect Control”.¹⁷ The first part (Chapters 2 and 3) highlights the progress made in the search for a new, environmentally friendly method to protect seedlings of pine and spruce from being gnawed by the pine weevil, *Hylobius abietis*.

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¹⁷ Foundation for Strategic Environmental Research, MISTRA.
In initial studies it was found that the spearmint flavoured monoterpenic carvone \([(R)-7]\), belonging to the menthane class of terpenoids, had a good inhibitory effect on the gnawing.\(^\text{18}\) Thus, 7 was a suitable lead candidate compound in further search for effective antifeedants/feeding deterrents. Less volatile antifeedant carvone analogues were developed as well as a slow release compound. Synthetic approaches to some naturally occurring carvone analogues of the bisabolane (8) class were also developed.

\[
\begin{align*}
(R)-7 & \\
8 & 
\end{align*}
\]

The second part (Chapter 4) describes the total syntheses of compounds of the germacrane isoprenoid class. These sesquiterpenes frequently occur in nature and have various purposes and effects,\(^\text{9}\) but in general they are difficult to obtain from natural sources. Due to the monocyclic 10-membered ring, they are often also difficult to synthesise. Their instability towards acids and UV radiation is also a reason for the preparation problem. Some of these compounds are called “simple” germacrane because of their relatively small and simple structure,\(^\text{9}\) but as mentioned above they are not simple to handle and synthesise. The germacrane that have been synthesised are \((-)-1(10),5\)-germacradien-4-ol* (9) and \((-\))-germacrene D (10).

\[
\begin{align*}
9 & \\
10 & 
\end{align*}
\]

Thus, the syntheses that are going to be discussed in this thesis are mainly directed towards isoprenoid targets. Some syntheses are pure total syntheses, where the intermediates do not necessarily belong to the isoprenoid type of compounds. Others are simple, one step syntheses that modify a well-known, readily available isoprenoid, carvone. As expected, and briefly mentioned in Section 1.3, the terpenoids prepared possess biological effects, affecting the behaviour of some insects. Although these compounds modify the behaviour of insects, the humans (chemists) perceive these compounds, sometimes, as having a pleasant smell.


* Two systems of numbering 9 occur in the literature. This thesis applies the germacrane numbering system described in ref 9.
2. THIOPHENOL-BASED CARVONE ANALOGUES\textsuperscript{I,III}

2.1 Biological background

The seedling mortality during the first two years, caused by stem gnawing of the pine weevil, \textit{H. abietis}, and its relatives is the main and most serious issue in conifer forestry in the temperate part of the northern hemisphere. If the gnawing is not controlled, it is estimated that the economic loss caused by the gnawing may be at least 150 million SEK annually, in Sweden alone.\textsuperscript{19} To prevent gnawing, the pine and spruce plants are at present coated with an insecticide, permethrin (11) before being planted. In conditions where the activity of the pine weevils is severe, it is necessary to recoat the plants after one season.

\begin{center}
\includegraphics[width=0.5\textwidth]{permethrin.png}
\end{center}

The structure of the synthetic pyrethroid permethrin was developed from a natural insecticide (cyclopropane monoterpenoid class) produced by a Kenyan, oxeye daisy-like flower, \textit{Chrysanthemum cinerariaefolium}. The natural insecticide was synthetically modified to be more stable towards light, with preserved activity and still with a low mammalian toxicity.\textsuperscript{20} However, permethrin showed toxicity against fishes and other water living organisms in rivers near treated plantations. It also induced allergic reactions in forestry workers.\textsuperscript{21} These effects led to a ban of the use for conifer plant protection. The ban was issued by the National Chemicals Inspectorate in Sweden and is effective after the year 2003.

Since pine weevils, as well as many other insects,\textsuperscript{1} are polyphagous generalists,\textsuperscript{22} a solution of the survival problem of the seedlings can be a treatment with an antifeedant/feeding deterrent (see Section 1.2) applied to their preferred nutritional source, the conifer seedlings. The weevils will then be directed to feed either on alternative untreated plant species of low commercial value or on mature conifers.


In an early initial study it was found that carvone (7) was a good inhibitor of gnawing.\(^{18}\) This study was based on results obtained with the closely related North American species, *Hylobius pales*.\(^{23}\) However, carvone was too volatile to fulfil the demands for practical use. It should at least be effective long enough to protect the plants over two summer seasons. Some initial laboratory studies revealed that carvone evaporated quite fast. Virtually no carvone remained within two weeks after the treatment. This also correlated well with biological results, which showed that the antifeedant/feeding deterrent effect was significantly reduced after two weeks. The two other main practical requirements for a good antifeedant/feeding deterrent (low toxicity and high stability) were, however, well fulfilled. With the aim of studying whether there was a possibility to circumvent the effects of the high volatility of carvone with preserved activity, an investigation using carvone as a model substance was initiated.

### 2.2 Hypothetical slow release system based on carvone

Three methods for possible modifications in order to reduce the problem with the volatile properties of carvone were identified. One was to encapsulate it in a suitable carrier that would slowly emit carvone. Such carriers could be polymers, waxes, latex rubbers or a suitable zeolite. Another solution to the problem could be to prepare chemically modified carvone of higher molecular weight with retained activity but lower volatility. (For this, see Chapter 3.) A third approach to the problem was to prepare “pro-carvones”, rather labile compounds of low volatility, slowly decomposing to carvone. We envisaged a thiol Michael adduct of carvone as such a possible pro-carvone. This would slowly undergo autoxidation to a sulfoxide, followed by a slow spontaneous thermal elimination to give carvone and a sulfenic acid (Scheme 2.1).

![Scheme 2.1. Hypothetic slow release system of carvone, the pro-carvone methodology.](image)

---

2.3 1,4-addition of thiophenol to carvone

To verify whether this method could be successful, we prepared the thiophenol derivative 12 from carvone by a previously known procedure (Scheme 2.2). Thus the α,β-unsaturated double bond of carvone was treated with thiophenolate under kinetically controlled conditions to afford the Michael adduct (2S,3R,5S)-12. However, this compound did not revert spontaneously to carvone. It was too stable and did not undergo autoxidation fast enough. Therefore, the adduct 12 was oxidised with sodium m-periodate to afford the sulfoxide 13. Indeed, the sulfoxide 13 was unstable in chloroform, and when the compound as a white foam was stored neat, it decreased in weight and a smell of carvone was noticeable, even after a period of one month. The decomposition (i.e. elimination) product, benzenesulfenic acid and its oxidised relatives are probably not enough environmentally friendly in an eventual practical use. Initial biological tests with the sulfoxide 13 revealed that it was less active than carvone. The preparation of an analogue of 13, from natural starting (possibly more environmentally friendly) materials, carvone and the amino acid cysteine was also planned. However, due to the rather discouraging results in the initial biological tests with compound 13, this somewhat lengthy synthesis is not realised yet.

Based on preliminary studies of a large library of various types of compounds in the pine weevil project, it was noticed that α,β-unsaturated aldehydes were also potent gnawing inhibitors. Being an aldehyde of this type, perillaldehyde [(R)-14] was subjected to the previously known thiophenol addition in a way similar to that

\[
\begin{align*}
(R)-7 & \quad \stackrel{a}{\longrightarrow} \quad \begin{array}{c}
(2S,3R,5S)-12 \\
\end{array} \\
& \quad \stackrel{b}{\longrightarrow} \quad \begin{array}{c}
13
\end{array}
\end{align*}
\]

Scheme 2.2. Reagents and conditions (yield): (a) PhSH, Et₃N, CH₂Cl₂, 0 °C; (b) NaIO₄, MeOH, rt (20%).

References:

[27] (a) Schlyter, F. Växtskyddsnotiser: Sveriges Lantbruksuniversitet-Swedish University of Agricultural Science, 2002, 65 (3–4), 47. (b) Schlyter, F. et al. to be submitted for publication.
described above (Scheme 2.3). In contrast to the sulfide 12, the resulting 1,4-adduct 15 slowly decomposed to the starting materials. In fact the sulfide 15 was too labile to allow purification by conventional methods.

\[
\begin{align*}
\text{(R)-14} & \quad \text{a} \quad \text{15} \\
\text{Scheme 2.3.} \quad \text{Reagents and conditions: (a) PhSH, Et₃N, CH₂Cl₂, 0 °C.}
\end{align*}
\]

The stereochemistry of the produced adducts 12 and 15 was as drawn in the schemes above. Despite the simple conditions, 0 °C and only one recrystallisation [for \((2S,3R,5S)-12\)], two continuous stereocentres were formed simultaneously and with high efficiency. This was due to addition of the thiophenolate to the conjugated double bond from the least hindered side under kinetic control, which furnished \((2S,3R,5S)-12\). This was readily established by \(^1\)H NMR spectroscopy. It was known that the \(\delta\) of H\(^3\) (Figure 2.1) was shifted downfield for compounds that contained an axial phenylthio isomer.\(^{24a,29a}\) The isomer formed under thermodynamic conditions [(\(2S,3S,5S\))-12] gave a more shielded H\(^3\), and hence a lower \(\delta\) value.\(^{24a,29b}\) Similar observations in the NMR spectrum of the sulfide 15 established its stereochemistry.

\[
\begin{align*}
\text{(2S,3R,5S)-12} & \quad \delta = 3.9 \\
\text{(2S,3S,5S)-12} & \quad \delta = 3.3 \\
\end{align*}
\]

Figure 2.1. \(^1\)H NMR differences in the kinetic vs the thermodynamic Michael-type products.\(^{24a,29b}\)

2.4 Radical addition of thiophenol to carvone and perillaldehyde

Thiophenol can be incorporated into an \( \alpha,\beta \)-unsaturated framework of an organic molecule by a non-polar, radical reaction.\(^{30}\) It is also well known that thiophenol can react with non-conjugated carbon-carbon double bonds via a radical mechanism.\(^{31}\) Far less studied is the competitive radical addition of thiophenol to a conjugated \textit{versus} a non-conjugated double bond. To my knowledge this is known only through studies made by Oswald and Naegele.\(^{32}\) Their work shows that the reactant, diallyl fumarate, displays a 60:1 preference for 1,2-addition to one of the two allylic double bonds, over 1,4-addition to the conjugated double bond in the fumarate moiety.

An investigation of the radical addition reaction of thiophenol to the somewhat more complex bisolefinic carvone molecule was therefore performed, and heating a mixture of a catalytic amount of a radical source (AIBN) plus carvone and thiophenol in equimolar amounts indeed resulted in the thio ether **16** (Scheme 2.4). The thio ether **17** was produced as a 1:1 mixture of inseparable diastereomers, as evidenced by inverse gated \(^{13}\)C NMR. This was the expected result of a reaction proceeding \textit{via} an anti-Markovnikov radical mechanism. None of the possible 1,4-addition products were detected. Only the exocyclic isopropenyl group was affected. However, when an excess of thiophenol was used instead of an equimolar amount, thiophenol added to both of the double bonds of carvone. Thus, although the exocyclic isopropenyl group reacted first,\(^{32}\) it was possible to form the diadduct **17** under radical conditions.

Scheme 2.4. Reagents and conditions (yields): (a) 1 equiv PhSH, AIBN, 65 °C (62%); (b) excess PhSH, AIBN, 65 °C; (c) PhSH, Et\(_3\)N, CH\(_2\)Cl\(_2\), 0 °C (54%).

---


This diadduct was a complex mixture of isomers. In order to obtain a product that consisted of a more homogeneous isomeric mixture, the monoadduct 16 was subjected to the same conditions as those described for the preparation of \((2S,3R,5S)-12\) (see Scheme 2.2). Under kinetic control this gave the diastereomers \((2S,3R,5S)-17\), as a 1:1 mixture regarding the exocyclic \(-\text{CH}_2\text{-SPh}\) side chain (Scheme 2.4). This was corroborated by the \(^1\text{H}\) NMR spectrum of the diadduct \((2S,3R,5S)-17\) in the same manner as that described for 12 (see Section 2.3, and Figure 2.1). To establish the shift of H\(^3\) in the isomeric diadduct with an equatorial PhS group we needed access to \((2S,3S,5S)-17\). In analogy to what was described for preparation of the thermodynamical isomer \((2S,3S,5S)-12\), thio ether 16 was subjected to reaction conditions that should provide thermodynamically controlled products. Thus, the thio ether 16 was refluxed with Et\(_3\)N and PhSH. Indeed this experiment gave \((2S,3S,5S)-17\) (\(\delta 3.4\) for H\(^3\)) in a mixture with \((2S,3R,5S)-17\) (\(\delta 3.9\) for H\(^3\)).

In order to confirm that this kind of chemoselectivity could be extended to other \(\alpha,\beta\)-unsaturated substances than ketones, we made perillaldehyde (14) react under the same radical conditions. Gratifyingly this afforded the phenylthio ether 18, again as an inseparable mixture of diastereomers (1:1) with respect to the exocyclic \(-\text{CH}_2\text{-SPh}\) side chain.

Even though the phenylthio ethers 16-18 were furnished as diastereomeric mixtures, they could provide a good starting point of further multistep organic syntheses. Their variety of functional groups could be either further manipulated or used in subsequent carbon-carbon bond formations. For example, 16 and 18 could be valuable intermediates in terpenoid syntheses where, in some cases, there is a need for compounds containing an enantiomerically highly pure isopropyl substituent.

There are not many sources of enantiopure compounds, containing such an aliphatic isopropyl branch, commercially available. There are some terpenoids available (mainly menthol and derivatives thereof) as well as the amino acid valine (and its derivatives). To my knowledge there are no others. Therefore there is a need for alternative isopropyl sources. After, hypothetic, further transformations the PhS-moiety at the isopropyl group can probably be removed by various methods (e.g. Na/Hg, Raney nickel). However, the rather sluggish conditions in the radical reaction described may be a problem in connection with transformations of advanced, highly functionalised intermediates.
3. LOW VOLATILITY CARVONE ANALOGUES

3.1 Background of the aim at decreasing the volatility

According to what was written in Section 2.2, another approach towards a decrease of the volatile properties of carvone was to prepare active analogues of it with higher molecular weight. These should still contain the active functional group, which, in carvone, was supposed to be the α-methyl-α,β-unsaturated cyclic ketone part. An obvious consequence of this was to modify the exocyclic part of carvone by an increase of its atomic weight. Thus, the monoterpenes (still of the menthane class) hydroxydihydrocarvone (19) and epoxycarvone (20) were prepared according to the published procedures (Scheme 3.1).\textsuperscript{33,34} Both of these carvone analogues displayed promising biological activity, at least at the initial test level (see Section 3.5). Compound 19 was, therefore, synthesised on a large scale (~50 g) and subjected to a field-test. Due to its high water solubility the formulation of 19 was problematic, and the results from the field-test were difficult to evaluate.

3.2 Terpenoids of the bisabolane type, and a synthetic strategy for their preparation

Another approach to carvone analogues of low volatility is compounds containing a long exocyclic side chain. Terpenoids with this type of ‘tails’ occur in nature and belong to the bisabolane class.\textsuperscript{9} Their biosynthesis resembles that of carvone but originates from farnesyl- or geranylgeranyl diphosphate instead of geranyl diphosphate, the precursor of carvone (Figure 1.5, Section 1.3). The former

\textbf{Scheme 3.1.} Reagents and conditions: (a) H\textsubscript{2}SO\textsubscript{4} (5 M), 0 °C,\textsuperscript{33} (b) m-CPBA, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C, 2:3 mixture of diastereomers.\textsuperscript{34}

\textsuperscript{34} Baldwin, J. E.; Broline, B. M. J. Am. Chem. Soc. 1982, 104, 2857.
phosphates undergo isomerisation and carbocation formation, followed by cyclisation between carbon atoms 1 and 6 (**Figure 3.1**), finally to give the bisabolane sesqui- or prenylbisabolane diterpenes.\(^{35}\) Various other terpenoid bisabolanes have been formed from these by further reactions such as: allylic oxidation, hydration and/or dehydration. Several total syntheses of bisabolanes have been reported,\(^ {36}\) but to my knowledge no total synthesis of a prenylbisabolane has hitherto been reported. Only a few isolations of these diterpenes from natural sources have been accomplished.\(^ {9}\)

An increase of the exocyclic side chain length could probably be accomplished by means of a \(\beta\)-alkyl Suzuki-Miyaura cross-coupling reaction.\(^ {37}\) With this short strategy, the electron-rich, exocyclic double bond of carvone (7) would be mildly coupled with the suitable chain to give carvone analogues of the type 21 (**Scheme 3.2**). The carvone derivative 21 does not, however, contain a tertiary alcohol moiety at C-7. Judging from the initial tests with hydroxydihydrocarvone 19, such a moiety seems to be beneficial for antifeedant activity. If such a tertiary alcohol moiety should be present in the

**Figure 3.1.** Cyclisation of acyclic precursors that give rise to the bisabolane (R = -CH\(_3\)) and prenylbisabolane [R = -CH\(_2\)CH\(_2\)CH=C(CH\(_3\))\(_2\)] skeletons.\(^ {35}\)

**Scheme 3.2.** A potential strategy of the synthesis of carvone analogues with extended exocyclic side chain, using the \(\beta\)-alkyl Suzuki-Miyaura cross-coupling reaction.\(^ {37}\)

\[\text{9-BBN-H} \rightarrow \text{Pd}^0 \text{base RX} \rightarrow \text{R}\]


synthetic analogues, a suitable precursor of these is epoxycarvone \(20\), which after opening with a variety of nucleophiles would give the suitable hydroxycarvone analogues \(22\). Organocuprate nucleophiles \(23\) are known to open epoxides in that manner, as first reported by Gilman and Jones in 1952.\[^{38}\] Application of this approach results in a potential strategy for the synthesis of hydroxycarvone analogues as shown below (Scheme 3.3).

\[
\begin{align*}
\text{R}_2\text{CuLi} & \quad + \quad 20 \\
\end{align*}
\]

Scheme 3.3. A potential strategy for the synthesis of hydroxycarvone analogues.

A sesquiterpene isomer of the hypothetical bisabolane \(22\) has been isolated from natural sources, namely the root of \textit{Lindera triloba}, a Japanese spicebush.\[^{39}\] The structure of this compound, named \((+)-\text{delobanone} [(6S,7R)-24]\), has been unambiguously established by NMR studies.\[^{39}\] Delobanone and a diastereomer of this, \((+)-7\text{-}\text{epi}-\text{delobanone} [(6S,7S)-24]\), have been synthesised in a rather sluggish manner (acidic condensation of carvone and 2-methyl-3-butene-2-ol), that also gave racemisation of the remaining substrate.\[^{40}\] A prenylbisabolane analogue of \(22\) has also been found in nature. The diterpene \((-)\text{-}25\) occurred in the neutral fraction of an extract from the Jamaican plant \textit{Croton linearis}, and exhibited insecticidal properties against another weevil species than \textit{H. abietis}, namely the sweetpotato weevil, \textit{Cylas formicarius elegantulus}.\[^{41}\] NMR experiments have established the gross structure of \(25\), but no conclusive evidence has appeared regarding the absolute and relative configurations of C-6 and C-7 (bisabolane numbering system, see Figure 3.1).\[^{41}\]

Of course the prenylbisabolane 25 appeared especially interesting as regards to the biological applications. A synthetic strategy leading to the prenyl and geranyl derivatives (24 and 25) of 22 could probably not include the use of the “lower order” cuprate 23 approach proposed for analogues with saturated exocyclic side chains (see Scheme 3.3). Instead “higher order” cuprates [e.g. a cyanocuprate, R₂Cu(CN)Li₂] should probably be more appropriate.⁴² Since the nucleophile in the latter cases would be allylic and, therefore, a bit awkward to acquire, some special considerations had to be made,⁴³ but there were inspiring examples in the literature of this type of transformation of fairly simple to very complex substrates.⁴⁴

3.3 Syntheses of carvone analogues with an exocyclic alkyl side chain

The syntheses of compounds with an aliphatic, saturated side chain R in the hydroxycarvone 22 were first attempted. In a test to establish the chemoselectivity in additions to epoxycarvone 20, this was treated with the lower order organocuprate (Bu₂CuLi), which resulted in the undesired conjugate addition product 26 (Scheme 3.4), a non-predictable outcome of chemoselectivity.⁴⁵ In order to secure the chemoselective opening of the epoxide moiety instead of conjugate addition to the endocyclic double bond, there was a need for deactivation of the α,β-unsaturated ketone system. One way to achieve this was reduction of the ketone, followed by protection of the resulting alcohol as a silyl ether. However, this process was not as straightforward as anticipated. To prevent undesired saturation of the conjugated double bond as the result, the Luche reduction protocol (NaBH₄, CeCl₃, MeOH) was applied.⁴⁶ Indeed this gave a chemoselective 1,2-reduction. However, this was followed by an intramolecular Lewis acid catalysed cyclisation to yield a mixture of the known (and previously synthesised) [3.2.1]-oxabicyclooctane monoterpenes

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(+)-bottrospicatol (27) and (+)-iso-bottrospicatol (28) (Scheme 3.4). Although some other hydride donors (e.g. LiAlH₄) could be expected to be 1,2-chemoselective, they were probably too efficient, resulting in reduction of the epoxide moiety as well.

Therefore, an alternative reducing agent was needed. In a literature survey, a method describing an aqueous NaBH₄ reduction in combination with sucrose as a “reactant transfer” agent was found. Indeed, application of this method to the epoxycarvone 20, afforded the unstable epoxycarveol, in a highly stereoselective manner. Due to its

.Scheme 3.4. Reagents and conditions (yields): (a) BuLi (2 equiv), CuI (1 equiv), Et₂O, −78 °C to rt; (b) see text; (c) NaBH₄, sucrose, H₂O, rt; (d) TMSCl, Et₃N, DMF, rt (84% from 20, >90% 1R isomer); (e) for 30a: (1) BuLi (2 equiv), CuI (1 equiv), THF, −72 °C to 0 °C, (2) TsOH, MeOH, rt (76% over 2 steps); for 30b: (1) OctylMgBr (2 equiv), CuI (1 equiv), THF, −30 °C to rt, (2) TsOH, MeOH, rt (75% over 2 steps); (f) MnO₂, CH₂Cl₂, rt (~60%, 1:1 mixture of diastereomers in both cases).

Therefore, an alternative reducing agent was needed. In a literature survey, a method describing an aqueous NaBH₄ reduction in combination with sucrose as a “reactant transfer” agent was found. Indeed, application of this method to the epoxycarvone 20, afforded the unstable epoxycarveol, in a highly stereoselective manner. Due to its

proclivity to undergo cyclisation to the bottrospicatol monoterpenes (see above), this was directly reconstituted in its TMS ether form, \(29\) (Scheme 3.4). Although TMS ethers being unsuitable protective groups when alkylolithiums and Grignard reagents are applied,\(^{50}\) the TMS ether epoxide \(29\) could be used with both lower and higher order cyanocuprates (Bu\(_2\)Cu(CN)Li\(_2\)). The lower order (Gilman) cuprates were prepared either from butyllithium or octylmagnesium bromide, and cuprous iodide. After subsequent removal of the TMS-group (using a catalytic amount of TsOH) the diols \(30a\) or \(30b\), respectively, were obtained. Finally oxidation with MnO\(_2\) furnished the desired, less volatile hydroxycarvone analogues \(31a\) and \(31b\). Since this oxidation is chemoselective for allylic alcohols, it would leave any possible by-product (the saturated, non allylic alcohol, arising from saturation of the conjugated double bond in the first reduction step) unaffected. This being a multistep synthesis, however, it was desirable to work with homogeneous materials. Therefore, the efficient sucrose-mediated 1,2-selective reduction mentioned above was a more appropriate choice.

### 3.4 Syntheses of carvone analogues with an exocyclic alkenyl side chain

With the successful syntheses of the bisabolane model compounds of type \(31\), containing a saturated side chain, focus was turned to the natural products elongated with prenyl- and geranyl side chains \(i.e.\) isoprenoids \(24\) and \(25\), page 19). At the start, all attention was turned towards the synthesis of prenylbisabolane \(25\), by application of the synthetic strategy described in Scheme 3.3. In an optimistic test reaction, the cuprate formed from geranyl magnesium bromide,\(^{51}\) was treated with the TMS ether epoxide \(29\). However, this straightforward approach to the target was not successful. Had it been so, there might have been problems to conserve the \(E\)-geometry of the double bond between the carbon atoms C-10 and C-11 (see Figure 3.1).\(^{52}\) Lipshutz et al. developed an attractive approach for the preparation of allylic cuprates that were able to react with epoxides.\(^{53}\) According to this method, the allylic cyanocuprate was derived from an allylic stannane precursor. In order to apply this method to this particular synthesis, geranyltributylstannane \(32\) was needed. This was prepared from geraniol \(33\), by a “one-pot operation” (Scheme 3.5).\(^{54}\) This stannane was then subjected to the conditions described in the literature on the formation of higher order

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\(^{50}\) Greene, T. W.; Wuts, P. G. M. Protective groups in organic synthesis; Wiley & Sons: New York, 1999; p 709.


\(^{54}\) Weigand, S.; Brückner, R. Synthesis 1996, 475.
cuprates.\textsuperscript{44,53} Although the reactants were rigorously purified, and reaction characteristics such as colour changes were observed, which were indicative of the formation of the higher order cyanocuprate 34, there was no trace of the expected product 35 after addition of the electrophile 29. Epoxide 29 still remained unaffected, despite several attempts. Reaction with the five carbon atoms shorter stannane, prenyltributylstannane, which had previously been used with success in the opening of epoxides, were also attempted,\textsuperscript{53a} but, again disappointingly, no traces of the expected products were detected. The reason for the lack of success was difficult to understand. Terminal epoxides have been previously reacted successfully according to this method, and hence the reasons for our unsuccessful attempts should probably not originate in the epoxide 29.\textsuperscript{44,53} Instead, an explanation could be the high reactivity of the lithiated allylic intermediate, which had been described as extremely reactive, and hence sensitive.\textsuperscript{53a}

Due to the failure of the allylic cuprate – epoxide route, an alternative synthetic strategy for achieving terpenoids 24 and 25 (see page 19) was developed by means of more reliable reactions. In the new strategy, one extra methylene group was incorporated into the nucleophile. This would circumvent the problems associated with the allylic nucleophiles. Consequently the electrophile had to be shortened by one carbon atom. This could for example be realised by cleavage of the terminal epoxide by means of periodic acid. As the TMS ether in 29 was very sensible towards acidic conditions, the allylic alcohol was instead protected as the TBDPS ether. A slight
modification of the reaction conditions (Scheme 3.6) compared with those previously used for the formation of TMS ether 29 (see Scheme 3.4) gave the suitable TBDPS-protected epoxycarveol derivative 36. TBDPS ethers is in general ~5 million times more stable towards acid hydrolysis than a TMS ones, and indeed, was epoxide moiety of 36 readily cleaved with periodic acid to afford the norterpene (see Section 1.3) ketone 37, without serious deprotection.

Scheme 3.6. Reagents and conditions (yields): (a) NaBH₄, sucrose, H₂O, rt; (b) TBDPSCl, imidazole, DMAP, CH₂Cl₂, rt (73% over 2 steps); (c) HIO₄·2H₂O, Et₂O, THF (82%, 94/6 syn/anti ratio).

The literature described three procedures for the synthesis of homogeraniol, 38 (a homoterpen, see Section 1.3). Because the method developed by Kocieński et al. had been used successfully in our laboratory for the synthesis of pine sawflies pheromones, this alternative was chosen. The procedure prescribed the use of lithiated 2,3-dihydrofuran (39) that was alkylated with the appropriate iodide (Scheme 3.7). The iodide 40 was obtained from the commercially available homoprenyl bromide, which was simply converted to 40 by a Finkelstein reaction (NaI, acetone). The crude homoprenylated dihydrofuran, 41, was subjected directly to Ni⁰-catalysed ring opening with methylmagnesium bromide. This gave homogeraniol, as an essentially pure isomer (> 99% trans).

Scheme 3.7. Synthesis of homogeraniol 38 via Ni⁰-catalysed coupling of MeMgBr.

[55] Ref 50, p 114.
With the C₉ norterpene ketone 37, and the necessary C₆ and C₁₁ homoterpenoid building blocks (e.g. 38 and 40) in hand, the syntheses of the bisabolane 24 and prenylbisabolane 25 natural products could be resumed. First in line (towards the synthesis of bisabolane 24) to react with the ketone 37 was the Grignard reagent, formed from the precursor of 40 (Scheme 3.8), homoprenyl bromide. Indeed this reaction was possible, although the yield was moderate. After desilylation using TBAF, and chromatographic separation of the diastereomeric mixture, the pure diols 42a and 42b were obtained. Separate MnO₂ oxidation of each of these converted the allylic alcohol moiety to a α,β-unsaturated ketone, and this stereogenic centre was by this destroyed. This afforded the desired sesquiterpenes: (−)-7-epi-delobanone [(6R,7R)-24] and (−)-delobanone [(6R,7S)-24] in their pure forms.

![Scheme 3.8. Reagents and conditions (yields): (a) homoprenylmagnesium bromide, Et₂O, 0 °C to rt; (b) TBAF, THF, separation [42a vs 42b, 1:1, 21% (combined for both isomers) over 2 steps]; (c) MnO₂, CH₂Cl₂, rt (~70%).](image)

The data of (6R,7S)-24 correlated well with those reported for the opposite enantiomer isolated from natural sources (6S,7R)-24. The optical rotation value was of the expected opposite sign, but slightly higher than the absolute value reported for (6S,7R)-24.³⁹
Second in line was the synthesis of the prenylbisabolane 25. That synthesis commenced with the transformation of homogeraniol (38) (see page 24) to the corresponding bromide (44) by treatment with Ph₃P and bromine (Scheme 3.9). By analogy with what has been described above regarding the synthesis of sesquiterpenes 24, the Grignard reaction was attempted. In this case the reaction was even more inefficient. Only a trace of the TBDPS ether 45 was formed. The reason for this failure could be either a Wurtz coupling of the Grignard reagent with the bromide during the formation of this reagent, or a β-elimination of the bromide 44 induced by the Grignard reagent.⁵⁸ Some unfavourable elimination and enolisation properties of Grignard reagents were known, and organolithiums had been described as being more reliable nucleophiles in 1,2 additions.⁵⁹ A useful method for the preparation of the latter was lithium-iodine exchange by means of tert-butyllithium.⁶⁰ Using the Finkelstein reaction again, the necessary iodide 46 was obtained from the bromide 44. Conversion of the iodide 46 to the corresponding homoallyllithium followed by addition of the ketone 37 (see page 24) efficiently afforded the desired prenylbisabolane skeleton in the form of compound 45. Desilylation of this, separation of the diastereomeric mixture of diols 47, followed by MnO₂ oxidation of each of these in the same manner as described above in the synthesis of delobanones, afforded the two pure diastereomers \((6R,7R)-25\) and \((6R,7S)-25\). A comparison of the NMR-shifts of diastereomers 25, with the ones of the two synthetic delobanone diastereomers \([(6R,7R)-24\) and \((6R,7S)-24\)], indicated that the configuration of the tertiary hydroxyl group (at C-7) should be as drawn in Scheme 3.9.

---

Scheme 3.9. Reagents and conditions (yields): (a) Ph$_3$P, Br$_2$, CH$_2$Cl$_2$, 0 °C (90%); (b) Mg, Et$_2$O, 0 °C then 37; (c) NaI, acetone, rt (93%); (d) t-BuLi, degassed Et$_2$O, –78 °C, to –35 °C, then 37, Et$_2$O, –78 °C to –10 °C; (e) TBAF, THF, separation [47a vs 47b, 3:2 (80% combined for both isomers) over 2 steps]; (f) MnO$_2$, CH$_2$Cl$_2$, rt [89% for (6R,7R)-25, 76% for (6R,7S)-25].

NOE measurements on the [4.3.1] bicyclic silyl derivatives 48 (Figure 3.2) were performed to secure that this hypothesis was correct regarding the configuration at C-7 of the diterpenes (6R,7R)-25 and (6R,7S)-25. The formation of the diastereomers 49a and 49b from the diols 47a and 47b was accomplished through silylation of each of them by di-tert-butyldimethyl ditriflate.$^{61}$

Figure 3.2. Significant NOE enhancements in the [4.3.1] bicyclic silyl derivatives of 48.

The structure originally drawn (with no evidence),\textsuperscript{41} resembled that of (6\textit{R},7\textit{S})-25. Indeed, although only a few of the NMR-shifts (especially regarding $\delta$ in $^{13}$C) of (6\textit{R},7\textit{S})-25 differed slightly from those of the isomer (6\textit{R},7\textit{R})-25, the shifts of (6\textit{R},7\textit{S})-25 were most similar to the ones reported.\textsuperscript{41} Compared with the literature value of 25 isolated from natural sources,\textsuperscript{41} the optical rotation value was slightly higher for the synthetic (6\textit{R},7\textit{S})-25, and significantly lower for synthetic (6\textit{R},7\textit{R})-25. When all these facts were summarised, they strongly indicated that (6\textit{R},7\textit{S})-25, was identical with the prenyl bisabolane diterpene isolated from \textit{C. linearis}. There were minor, although significant differences in the $^1$H NMR spectra of the two synthesised isomers of 25, but these signals had not been reported in the original paper.\textsuperscript{41} One problem (unfortunately not uncommon) in natural product chemistry is that of erroneous identifications. In order to ensure that the proposed structure of the natural product from \textit{C. linearis} was correct, we compared the $^1$H NMR spectrum of our synthetic sample of the isomer (6\textit{R},7\textit{S})-25 with the $^1$H NMR spectrum of the authentic, original specimen of that compound, kindly provided by Dr Williams. Indeed, these two spectra matched each other perfectly, whereas the $^1$H NMR spectrum derived from the other diastereomer [(6\textit{R},7\textit{R})-25] differed clearly.

3.5 Biological activity of the carvone analogues

The antifeedant activity against the feeding behaviour of pine weevils of the carvone analogues described above was tested at five different levels.\textsuperscript{27a} The two initial levels consisted of tests made by depositions of the compound on 5 $\times$ 5 mm TLC plates with a cellulose adsorbent layer.\textsuperscript{62} Two plates were used in each test (choice test). One of the two plates was treated with 1.5 $\mu$l of a 10\% solution of the test compound (treated), whereas the other was covered with the same volume of the solvent only (blank). After adding a sucrose solution to both plates, they were placed in a Petri dish together with a pine weevil, which had been starving for 24 h prior to the start of the experiment. In order to obtain significant results for each compound, at least 5 male and 5 female weevils had to be tested in each experiment. Normally, 2 or 3 replicates of such experiments were run for each compound. After 4 h, the area eaten was measured, and an anti-feedant index (AFI) was calculated,\textsuperscript{18,27a,62} obtained from the following equation:

$$AFI = \frac{\text{Area eaten on blank} - \text{Area eaten on treated}}{\text{Total area eaten on blank and treated}}$$

\textsuperscript{[62]} Schlyter, F. \textit{et al.} to be submitted for publication.
This gave values ranging between +1 and −1. A value of +1 represented no feeding on the test plate indicating a perfect antifeedant/feeding deterrent, whereas a value of −1 indicated a strong feeding stimulant. The compounds that gave an AFI higher than 0.5 in these tests were subjected to further tests, using the same TLC plate system. In these tests, solutions of three different concentrations of the test compound (0.1, 1 and 10%) were used together with blanks. The results provided estimates of the effective dose required for obtaining a 50% reduction of the feeding (the ED$_{50}$-value). The most promising substances from this second series of tests were subjected to further tests using natural material, pine twigs. These tests were performed in Petri dishes and the treated twigs were tested alone (no-choice test). The 1 cm twigs were treated with the same concentrations of the test compound as described above. A treated twig was placed between the bottom and lid of a Petri dish, so that only the bark was accessible when the lid of the dish was put on. After a pine weevil had spent 48 h in the Petri dish, the area eaten was measured and an additional ED$_{50}$ value was calculated. Provided that the compound still seemed promising after this sequence of tests, it was finally subjected to field-test. Thus, conifer seedlings were coated with the compound and the area subjected to gnawing was registered at intervals ranging from weeks to several months. The biological activity, together with volatility data are summarised in Table 3.1. The compounds are sorted according to the antifeedant index obtained in the first TLC test.

The results of antifeedant/feeding deterrent activity tests revealed that the low volatile analogues of carvone were less active than carvone itself. If the volatility of the carvone analogues prepared was sufficiently decreased (i.e. bp > ~300 °C at normal atmospheric pressure), the activity was lost. In other words, the signals of most of these compounds were probably olfactory. The odour was thus responsible for the activity, and therefore analogues with a high molecular weight were not very active feeding deterents. The activity of carvone is probably due to the α,β-unsaturated enone moiety and according to our tests, allylic alcohols, for example 30a, do not possess any feeding deterrent activity. Another striking example of this is that the commercially available allylic alcohol sobrerol (49) actually is a feeding stimulant. In contrast to what was described in the literature, we observed no insecticidal properties against the pine weevil for neither diastereomers of the prenylabisabolane diterpene 25.

Even though some of the carvone analogues gave promising results at the first level of tests using an artificial substrate (sucrose on a TLC-plate), they were less promising when subjected to more demanding tests on natural host material (twigs). One explanation for this might be that once the starving pine weevil starts to feed it will not stop (provided it does not die, for example by consuming enough amounts of an
insecticidal compound such as permethrin, 11). The ingestion of the preferred natural feeding source probably represents a very potent positive tactile and chemical signal for the pine weevil.

<table>
<thead>
<tr>
<th>Structure</th>
<th>AFI TLC (10%)</th>
<th>ED_{0} TLC (10%)</th>
<th>ED_{0} Twig (10%)</th>
<th>mp (°C)</th>
<th>bp (°C at 760 mm Hg)</th>
<th>Exp. bp (°C at pressure X)</th>
<th>Calc. bp (°C at 760 mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>1.0</td>
<td>0.5</td>
<td>&gt;100</td>
<td></td>
<td>58–61/0.05 mm Hg</td>
<td>290\textsuperscript{\textdegree}</td>
<td></td>
</tr>
<tr>
<td>(S)-7</td>
<td>0.9</td>
<td>1.3</td>
<td>2.1</td>
<td>230\textsuperscript{63}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>0.9</td>
<td>1.9</td>
<td>&gt;100</td>
<td></td>
<td>88/0.1 mm Hg\textsuperscript{33}</td>
<td>290\textsuperscript{\textdegree}</td>
<td></td>
</tr>
<tr>
<td>(R)-7</td>
<td>0.8</td>
<td>2.6</td>
<td>4.8</td>
<td>230\textsuperscript{63}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31a</td>
<td>0.8</td>
<td>0.1</td>
<td></td>
<td></td>
<td>175/0.6 mbar\textsuperscript{ii}</td>
<td>400\textsuperscript{\textdegree} (±21)\textsuperscript{3}</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>0.8</td>
<td></td>
<td></td>
<td></td>
<td>180/0.1 mbar\textsuperscript{i}</td>
<td>450\textsuperscript{\textdegree} (±21)\textsuperscript{3}</td>
<td></td>
</tr>
<tr>
<td>(6R,7S)-25</td>
<td>0.7</td>
<td>1.7</td>
<td></td>
<td></td>
<td>215/0.3 mbar\textsuperscript{ii}</td>
<td>470\textsuperscript{\textdegree} (±24)\textsuperscript{3}</td>
<td></td>
</tr>
<tr>
<td>(6R,7R)-25</td>
<td>0.5</td>
<td>1.8</td>
<td></td>
<td></td>
<td>220/0.35 mbar\textsuperscript{ii}</td>
<td>470\textsuperscript{\textdegree} (±24)\textsuperscript{3}</td>
<td></td>
</tr>
<tr>
<td>31b</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
<td>220/0.4 mbar\textsuperscript{ii}</td>
<td>460\textsuperscript{\textdegree} (±21)\textsuperscript{3}</td>
<td></td>
</tr>
<tr>
<td>30a</td>
<td>0.5</td>
<td>&gt;100</td>
<td></td>
<td></td>
<td>200/0.65 mbar\textsuperscript{ii}</td>
<td>430\textsuperscript{\textdegree} (±30)\textsuperscript{3}</td>
<td></td>
</tr>
<tr>
<td>(2S,3R,5S)-12</td>
<td>0.0</td>
<td>&gt;100</td>
<td></td>
<td></td>
<td>76–78\textsuperscript{29b}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>−0.3</td>
<td></td>
<td></td>
<td>148–149\textsuperscript{63}</td>
<td>270\textsuperscript{63}</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3.1. Biological activities of prepared carvone analogues.


ψ Calculated by using a pressure/temperature nomograph.

4. TOTAL SYNTHESES OF 1(10),5-GERMACRADIEN-4-OL AND GERMACRENE D\textsuperscript{IV,V}

Sesquiterpenoids with the germacrane carbon skeleton occur rather frequently in nature.\textsuperscript{9} Even though they contain only fifteen carbon atoms, ten of which form a monocyclic ring, the structural variability among the germacrines is large. A search of ‘germacrane or germacrene’ in the Chemical Abstracts Database, for example, gives more than two thousand answers. Most of these articles concern the occurrence of such terpenoids in various natural extracts (\textit{i.e.} essential oils) and only a few germacrines are easily accessible in their pure form. As mentioned in Chapter 1, one reason for the difficulties associated with their isolation from natural sources is their inherent instability. This originates from the parallel and closely proximate double bonds, which, in the presence of acid traces or upon heating, sometimes are very favourably located for undergoing ring closures that give bicyclic cadinenes.\textsuperscript{64} Tricyclic bourbonane structures are formed upon exposure to UV radiation.\textsuperscript{64a-d} Another case of isolation difficulties is the fact that these extracts often contain complex mixtures of substances that will co-elute on attempted chromatographic separation. Moreover, since many of them are oils, crystallisation is often not possible.

4.1 Biological background

The germacrane isoprenoids are typical secondary metabolites in nature (see Section 1.3). Many of their biological functions are still unknown, which may be due to the lack of large enough amounts of germacrines in their pure forms. The research group in which I have been working has been involved in two research programmes: PHERODIP\textsuperscript{65} and the MISTRA\textsuperscript{17} programme previously mentioned. This class of sesquiterpenes has emerged as a very interesting one in both of these projects.

One of the species studied in the PHERODIP programme, the pine sawfly \textit{Neodiprion sertifer}, is one of the most serious pine sawfly pests regarding its

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\end{flushleft}

\begin{flushleft}
\textsuperscript{[65]} \textit{Pine sawfly pheromones for sustainable management of European forests}, PHERODIP.
\end{flushleft}
economic importance of forestry in the northern hemisphere. The periodic outbreaks of the colony living larvae cause serious defoliation upon feeding on the needles of the pines. The resin from the needles digested is stored in pouches of the foregut and used as a defence secretion against predators such as ants, spiders, wasps and birds. When attacked, the larva rears its front and emits a droplet of a viscous mixture of terpenoids, which is smeared on the attacker (an example of the use of an allomone, see Section 1.1). This terpenoid mixture consists of various amounts of monoterpenes and acids, plus a major sesquiterpene constituent, (−)-1(10),5-germacradien-4-ol, a compound first isolated in 1977 from Senecio phonolithicus by a research group led by F. Bohlmann. The mixture of terpenoids in the larval secretion resembles that of the needle resin, which remains rather conserved in the foregut of the larvae. An efficient [1‰ (w/w)] isolation of pure (−)-9 from needles of Scots pine (Pinus sylvestris) is known. Isomerisation to known sesquiterpenes establishes the 7S configuration, and NMR-studies supported by molecular mechanics calculations strongly indicate that the other stereogenic centre should have a 4S configuration. In summary, this gives the exact structure as drawn above.

Another germacrane terpene emerged as an interesting semiochemical within a subproject in the MISTRA research programme. This programme concerned the volatile compounds from apple (Malus domestica) and it was found that the widely

occurring sesquiterpene germacrene D (10) and some other non-polar sesquiterpenes acted as kairomones between apples and the codling moth, *Cydia pomonella*, the globally most economically important pest on apples. Germacrene D was first isolated from *Pseudotsuga japonica*, a Japanese Douglas fir, by Yoshihara *et al.* in 1969.\(^{64a}\) The importance of germacrene D in insect host communication was further proved by the strong response it caused from the antennal neurons of the tobacco budworm moth, *Heliothis virescens*.\(^{72}\)

Even though the occurrence of 10 is common in nature, its instability towards acids and UV radiation,\(^{64a}\) and its low polarity makes the compound very difficult to isolate in a pure form from its natural sources. Unfortunately, even if it can be possible to isolate chemically pure 10, many attempts to do so will result in mixtures of enantiomers.\(^{73}\) This could be established by gas chromatography using a chiral stationary phase.\(^{73}\) The two compounds above were examples (among others) where natural product synthesis could serve as a tool for the supply of semiochemicals suitable for the study of the complicated language of nature, occurring (often overlooked by humans) at every moment in our environment.\(^{74}\)

### 4.2 A literature survey of methods considered suitable for the syntheses of 1(10),5-germacradien-4-ol (9) and germacrene D (10)

The total syntheses of the two germacradienes mentioned in this heading (a more specific name of them is germacradienes) were challenging tasks, and much effort was devoted to searching the literature for efficient synthetic strategies. In contrast to the syntheses of the bisabolanes (Chapter 3), there were no suitable ‘advanced’ starting materials available. Although the carbocyclic skeleton contained two *trans* double bounds (one of them trisubstituted) and one (in 10) or two (in 9) stereogenic centres, the main issue to be addressed was the formation of the monocyclic 10-membered


ring. No synthesis of 9 was found in the literature, but there was one of \((\pm)-10\), reported by Schreiber and Hawley.\(^{75}\) In this particular synthesis (an adjunct to a rather classical germacrane synthesis of the American cockroach pheromone, periplanone B),\(^{76}\) the monocyclic ketone 50 was regioselectivity enolised under kinetic conditions with a 10:1 site-selectivity at the somewhat more accessible \(\alpha\)-hydrogen at C-1 (Scheme 4.1). The enolate was then trapped as the triflate and subsequently methylated with lithium dimethylcuprate,\(^{77}\) which gave germacrene D mixed with a minor regioisomer (see Scheme 4.1). The starting material, ketone 51 (cryptone, a norterpene see Section 1.3) was also later prepared in 70% ee by the same group.\(^{78}\) The elegant sigmatropic oxy-Cope rearrangement approach (e.g. the reaction that produces the ketone 52) was used several times in the synthesis of cyclodecanoid germacrane frameworks mainly based on methods developed by W. C. Still.\(^{79}\)

![Scheme 4.1](image)

Scheme 4.1. Single reported synthesis (summarised) of germacrene D (10), which resulted in a mixture of regioisomers.\(^{75}\)

The total syntheses of germacrane sesquiterpenes have rather recently been reviewed.\(^{80,81}\) The following discussion will focus on the synthetic methods that I have considered as possible strategies for the syntheses of 9 and 10. Ring-closing of acyclic molecules in the ‘upper-right’ bonds (a in Figure 4.1), as well as some bicyclic ring-cleavage of the central bond of the decalin systems, and ring-expansion reactions been

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\(^{81}\) Ref 36, pp 114–128.
performed earlier in syntheses of germacrane and compounds with similar skeletons, but these have not been considered as suitable strategies in my work. One reason for this is that the germacradienes 9 and 10 and their precursors have been considered to be too sensitive and labile to be acquired by means of ring-cleavage or expansion reactions. Most important, there were only a limited number of synthetic alternatives, in a possible failure of projected reactions due to disconnection at site a.

![Figure 4.1. Possible areas of retrosynthetic bond disconnection of compounds studied.](image)

The nowadays quite popular ring-closing olefin metathesis (RCM) utilising the commercially available Grubbs’ catalyst (53)\textsuperscript{82} can be used in approaches towards 9. Indeed, RCM reactions are elegant and often result in considerable simplifications of syntheses.\textsuperscript{83} Reactions leading to 10-membered unsaturated rings as well as other medium (8–11) sized rings with inherent ring strain are often difficult to perform.\textsuperscript{84} The reactions are frequently characterised by the formation of unwanted geometrical double bond isomers, whose stereochemistry is difficult to predict. The stereochemistry seems to be dependent on remote functional groups and their conformation effects on the substrates.\textsuperscript{84,85} Development of more effective, but also more trans-selective catalysts is under progress.\textsuperscript{86}


Some racemic nor-10 methyl 1(10),5-germacradien-4-ol precursors were recently prepared, based on the RCM methodology (Scheme 4.2) constituting the first examples of RCM syntheses of 10-membered purely carbocyclic ring compounds, and moreover, nor-10 methyl 9 was synthesised from one of these precursors.

Scheme 4.2. RCM methodology used for the synthesis of 1(10),5-germacradien-4-ol skeletons and its limitations/characteristics.

However, based on earlier RCM experiences in our group, this reaction did not seem to be possible when $R^1 = \text{Me}$. This result was the reason why the RCM synthetic approach was abandoned by our group, and alternative strategies via a disconnection in bonds of the molecules (see Figure 4.1) were considered more appropriate. Disconnection at these ‘lower-left’ bonds of the molecules on the other hand opened several alternatives towards ring-closure. Three general reaction methodologies were identified, as depicted in Scheme 4.3. Examples of such potentially useful reactions were found in the literature. For example, Takahashi et al. developed a procedure that seems to be a general one for the formation of macrocyclic...
If R = O, then X = Cl
If R = CH₂, then X = I, Br, Cl or OTf

Scheme 4.3. Possible disconnections and their consequent reactions, leading to the monocyclic 10-membered ring framework of 1(10),5-germacratrien-4-ol and germacrene D.

ketones, which was based on an intramolecular alkylation of the anion formed from a protected cyanohydrin. This method was later applied to syntheses of many monocyclic terpenoids. A particularly encouraging example was the synthesis of the ten-membered enone (Scheme 4.4), which was used further in the synthesis of dicyclohumulenone. Besides the efficiency in the example below, it is worth noting, that no elimination products were observed although a homoallylic tosylate was involved in the reaction.

Scheme 4.4. Example of intramolecular alkylation developed by Takahashi et al.

Low-valent titanium-induced formation of medium-sized rings by the intramolecular McMurry keto ester cyclisation reaction might be another alternative for the target germacrenes. An example of its use, with a substrate that somewhat resembles what has to be used in the syntheses of precursors of 9 and 10, is the synthesis of (±)-acoragermacrone (Scheme 4.5).

Scheme 4.5. Titanium-induced keto ester cyclisation by Li et al.

The intramolecular Stille reaction was also utilised in germacrane synthesis in inspiring examples from the research group led by D. M. Hodgson (Scheme 4.6). Another important achievement developed in connection with these syntheses was the chain elongation with two carbon atoms that afforded the trans alkenyl stannane precursor via a CrII-mediated reaction of the stannane precursor aldehydes. Access to the ten carbon monocyclic enones (i.e. the immediate precursor of germacradienol 9) might also be possible, using the intramolecular Stille cross coupling with an acid chloride as the electrophilic coupling partner (see Scheme 4.3, $R = O$). A potential

Scheme 4.6. Germacrane syntheses utilising the intramolecular Stille reaction.

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problem associated with the intramolecular Stille reactions if applied to these targets, may be competing or dominating intramolecular Heck reactions (4-exo or 5-endo, cascade like) due to a more unsaturated precursor than previously used (compare Scheme 4.3 with Scheme 4.6). Presumably bicyclic molecules might be produced from this, instead of the desired monocyclic ones.96 Such Heck reactions are not possible for the substrate shown in Scheme 4.6 above, but this is not immediately obvious when the literature regarding Stille and Heck reactions is examined.

Corey and Hortmann mentioned synthetic strategies that resemble the biomimetic synthesis of germacranes as early as in the first germacrane synthesis, published by them in 1965. They stated: “…the laboratory synthesis of these sesquiterpenes by such a cyclization has not yet been realized, despite its apparent simplicity...”.97 Since then a few syntheses of germacranes have been completed using the biomimetic connection between C-6 and C-7 (germacrane numbering). For example Kodama et al. have used an intramolecular ring-closing alkylation with a reverse electron flow relative to the biosynthesis of germacranes (Scheme 4.7).98 This approach could probably also be applied to a synthesis of racemic 9, since a diterpene with a very similar framework has been synthesised in this manner.99

![Scheme 4.7](image)

**Scheme 4.7.** Intramolecular alkylation between C-6 and C-7 by Kodama et al.98

In principle, intramolecular Wittig reactions or probably more preferably, Horner-Wadsworth-Emmons (HWE) reactions,100 might also offer a route to the germacrane ring by disconnection of bonds in the b area of the molecules (see Figure 4.1), but the potential of such reactions were not investigated in detail for use in our work.

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4.3 Retrosynthetic analysis and approach towards the syntheses of 1(10),5-germacradien-4-ol (9) and germacrene D (10)

The flexibility and number for alternatives for the disconnection of the bonds in part b (see Figure 4.1) discussed above, led to the choice of this strategy toward the germacradienes 9 and 10. At a late stage in the syntheses, this strategy provided three potentially useful intramolecular ring-closing reactions, the Takahashi, McMurry and Stille ones, discussed in Section 4.2. For the retrosynthetic scheme, see Scheme 4.8. The synthesis of nor-10 methyl 9 revealed that 54 in its enone form (R^1 = O) might serve as the direct precursor of germacradienol 9 upon treatment with MeLi. Moreover, this enone could probably also be methylenated to afford germacrene D (10). All of these three methods converged in all-trans isopropyl substituted precursors such as 55 with suitable (R^2 ≠ R^3) functionalities installed. In any of the ring-closure methodologies chosen, the C-5/C-6 double bond was to be introduced via an aldehyde (56), using a Wittig or HWE reaction. Alternatively, if Stille reactions were to be used, the stannane required could also be obtained from the same aldehyde.

The stereogenic centre (i-Pr) can most probably be introduced by some method based on a chiral auxiliary, but it is not obvious whether it should be introduced before or after the formation of the trisubstituted E-double bond. It is desirable to form a stereogenic centre at a late stage of the synthesis, because the molecules discussed do not contain any other stereogenic centres that could receive stereoorientation from the first one. If the centre was introduced at an early stage, this should give loss of valuable enantiomerically enriched material in later synthetic steps. A formation of this stereogenic centre from a late fusion of C-7/C-8 would lead to a large electrophile and most likely to a propitious stereochemical outcome. Such a process would, however, involve a reaction with a homoallylic electrophile that might be prone to extensive elimination. To avoid involving reactants with this inclination, a different route was selected instead.

Useful methods of trisubstituted double bond formation as in 56 were: Negishi carboalumination of alkynes (e.g. 57), rearrangement of cyclopropylcarbinyl compounds developed by Johnson et al. and Ni\(^0\)-catalysed coupling and ring-opening of dihydrofurans 58 with synchronous methyl insertion (see Scheme 3.7).

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developed by Kocieński et al. If possible elimination problems associated with homoallylic alkylation of a chiral auxiliary should be circumvented, the method of Johnson was excluded as well as carboalumination, if this was made before the C-7/C-8 bond formation. On the other hand, the sequence could be reversed, starting with C-7/C-8 formation and finishing with C-1/C-2 formation with simultaneous methyl insertion (see Scheme 4.8). However, due to previous good experience with the reliable Kocieński method (see Section 3.4), and because of its advantage in large-scale reactions, this method was selected. The first steps in the synthesis would then be the introduction of the stereogenic centre via an alkylation with of a two-carbon fragment (the C-7/C-8 formation) to produce the intermediate 59. In summary, this strategy resulted in a linear sequence with quite small building blocks as starting materials. The strategy gave room for the choice of a number of different options in the most critical step, the ring formation at the end of the synthesis, a situation quite common in natural product syntheses of macrocyclic targets. All the other transformations were considered to be rather reliable.

Scheme 4.8. Retrosynthetic scheme (generalised) for 9 and 10 (R₁ = O or CH₂).

4.4 Synthesis of i-Pr substituted key fragment; (3E,7S)-7-[(tert-butylidimethylsilyl)oxymethyl]-4,8-dimethylnon-3-en-1-ol (70)

The synthesis of germacradienes 9 and 10 commenced by alkylation of the amide 60, formed by reaction of (+)-pseudoephedrine with i-valeryl chloride (Scheme 4.9).\textsuperscript{105} Although a suitable electrophile precursor 61 was commercially available, it was easily prepared on a large scale by benzylation of ethylene glycol. Functional group conversion to the iodide 62\textsuperscript{106} and alkylation of the amide 60 with this, using the general methodology developed by Myers, furnished the isovaleryl-amide 63,\textsuperscript{105,107} with high efficiency and a high diastereomeric ratio (> 96/4). Another suitable electrophile precursor in this reaction might be the TBDMS protected iodide 64, which most probably should give even higher diastereomeric outcome in the reaction.\textsuperscript{105} The benzyl group as a hydroxyl protecting moiety of this two carbon unit was chosen due to its expected facile differentiation from other protecting groups. However, silyl ethers (as in the case of electrophile 64),\textsuperscript{108} and other protecting groups could also be differentiated rather easily.\textsuperscript{50} After that reaction, the pseudoephedrine auxiliary was removed (and recovered) by reduction of the amide 63 using lithium amidotrihydroborate (LAB) to afford the i-Pr substituted primary alcohol 65.\textsuperscript{109} This reduction proceeded with essentially no epimerisation of the α-stereogenic centre,\textsuperscript{109} and the ee was ~92–93%, established by NMR on the MTPA-ester formed from 65 and (R)-(−)-MTPACl.\textsuperscript{110} Subsequent silylation of the alcohol 65 using standard conditions afforded the diether 66. A reason for the choice of benzyl as a protecting group was that it could be easily unveiled in the presence of the TBDMS group upon

\[
\begin{align*}
X & \quad \text{OBn} \\
61 & \quad X = \text{OH} \\
62 & \quad X = \text{I} \\
\end{align*}
\]

\[X \quad \text{OTBDMS} \]

\[64 \]

\[66 \]


catalytic hydrogenation a priori, but this unmasking was very inefficient in MeOH. THF was a better solvent, but caused unacceptable migration of the silyl ether group that produced a mixture of primary alcohols 67, 68 and a completely deprotected diol.\textsuperscript{111} On the other hand, dissolving metal reduction (Na in ammonia) nicely removed the benzyl group, which gave the alcohol 67 in a homogeneous form.

The alcohol 67 was transformed into the primary iodide 69, the electrophile necessary for subsequent E-double introduction. Deprotonation of 2,3-dihydrofuran using tert-BuLi, and addition of 69 to this gave elongated 2,3-dihydrofuran (i.e. 58 with $R^5 = $ TBDMS, see Scheme 4.8).\textsuperscript{104} To prevent potential double bond migration of this, it was added immediately in its crude form to a solution of MeMgBr and (Ph$_3$P)$_2$NiCl$_2$,\textsuperscript{104} which gave concomitant opening of the dihydrofuran ring, accomplished by methyl introduction to furnish the primary trans trisubstituted homoallylic alkenol 70. This constituted a useful building block that could be employed in any of the ring forming strategies previously discussed.

\textsuperscript{111} For other examples of this, see Ref 50, pp 114–116 and references cited therein.
4.5 Synthesis of the monocyclic ten-membered ring compound; \((2E,4S,7E)-4\)-isopropyl-7-methylcyclodeca-2,7-dien-1-one (82)

Since one of the targets in this project was germacrene D (10), some initial efforts were made towards precursors that could be used in a ring-closure using intramolecular Stille conditions.\(^{92,93}\) Thus the alcohol 70 was tosylated and subjected to ethyne elongation (Scheme 4.10). In this case sodium acetylide was completely unreactive. Lithium acetylide-ethylenediamine complex with DMSO as solvent provided an alternative, and gave the expected alkenyne 71, albeit in low yield and as a mixture with the elimination product (71 vs 72, ~3:1). Using mixed solvents (DMSO/THF, 2:1) at 0 °C gave the same result.\(^ {112}\) Lithium TMS-acetylide in THF at −78 °C also gave elimination and a poor yield. Preliminary experiments displayed, however, that 71 could be iodoborated to the vinyl iodide 73,\(^ {112,113}\) a suitable precursor of further reactions that should culminate with the intramolecular Stille fusion. Unfortunately the vinyl iodide 73 was not separable from the elimination product 72, formed in the previous step. Other approaches to terminal alkynes were described in the literature. A common way in the preparation of these led from aldehydes (which could be synthesised in one step from 70) either via Wittig reactions to afford 1,1-dihaloolefins or vinyl halides which after subsequent base induced elimination gives terminal alkynes,\(^ {114}\) or by using HWE methodology to afford terminal alkynes in a one-pot procedure from the precursor aldehydes.\(^ {115}\) The preparation of terminal alkynes could be expected to increase by virtue of the alkyne metathesis recently developed.\(^ {83}\)

\[ \text{Scheme 4.10. Synthetic efforts towards a terminal alkyne a intramolecular Stille precursor, and iodoboration of this.}\]

\[^{112}\] Smitt, O. Unpublished results.
Recently published work on germacrene B syntheses from the research group led by K. Mori,\textsuperscript{116} and their use of the intramolecular alkylation methodology developed by Takahashi \textit{et al.},\textsuperscript{88} inspired us to apply this method to our targets. The synthesis of Stille intermediates was thereby abandoned, and the focus was switched to intermediates that could be used in intramolecular alkylations. The experiments started with the acetylation of 70, followed by desilylation to yield the primary acetoxyalkenol 74 (Scheme 4.11). Oxidation of this of with TPAP gave the aldehyde 75. The choice of oxidation method (TPAP is a rather expensive oxidative agent) was made to circumvent a possible decrease in enantiomeric purity due to epimerisation of the stereogenic centre in the α-carbonyl position.\textsuperscript{117} The aldehyde 75 in its crude form was subjected to a salt free Wittig reaction, using methyl α-(triphenylphosphonium)-acetate for the unsaturated two-carbon atoms chain elongation. This reaction required elevated temperature (refluxing acetonitrile) and a long reaction time to produce a satisfactory yield of the α,β-unsaturated methyl ester 76.\textsuperscript{118} This was reduced using DIBALH, a hydride known not to give deleterious saturation of α,β-diesters upon reduction of these. This property of DIBALH was preserved and the reaction resulted in the diol 77.

\begin{align*}
70 & \xrightarrow{\text{a, b}} & \text{HO} & \xrightarrow{\text{c}} & \text{OAc} \\
& & 74 & & 75 \\
& & & & \\
& & \text{d} & \xrightarrow{\text{e}} & \text{HO} & \xrightarrow{\text{d}} & \text{OAcMeO} & \xrightarrow{\text{e}} & \text{OH} & \xrightarrow{\text{f}} & \text{OAc} \\
\end{align*}

\textbf{Scheme 4.11.} (a) Ac$_2$O, pyridine, rt, 20 h (100%); (b) TBAF, THF, rt, 8 h, (91%); (c) TPAP, NMO, 3Å sieves, rt, 1.5 h (87%); (d) Ph$_3$PCHCO$_2$Me, MeCN, Δ, 56 h (94%); (e) DIBALH, CH$_2$Cl$_2$, $-78^\circ$C, 1.5 h (94%).

\begin{thebibliography}{99}
\bibitem{117} For a review, see: Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. \textit{Synthesis} \textbf{1994}, 639.
\end{thebibliography}
As mentioned previously (see Chapter 3) MnO₂-oxidation was the method of choice for the oxidation of allylic alcohols to aldehydes. Important for the further steps in the synthesis was the fact that only the allylic OH group of diol 77 should be chemoselectively oxidised to an aldehyde group. This was indeed possible in this reaction, which furnished the desired hydroxyaldehyde 78 (Scheme 4.12). Tosylation of the remaining, unaffected homoallylic alcohol group at the other end of the chain of the aldehyde 78 resulted in the labile intermediate 79, with all necessary functionalities in place. The insertion of an additional carbon atom, localised in an electron withdrawing cyanide group, by dissolving 79 in TMSCN,¹¹⁹ and adding a catalytic amount of KCN·18-crown-6 complex was almost quantitative.¹²⁰ The resulting diastereomeric mixture of TMS-protected cyanohydrin isomers was reconstituted as the complex diastereomeric mixture 80, displaying the somewhat more tolerant hydroxyl protecting 1-ethoxyethyl ether group,⁵⁰ the preferred protective group in these kind of reactions. The EE-protected cyanohydrin tosylate 80 represents the ultimate synthon for monocyclic ring synthesis, containing all functionalities needed in an intramolecular alkylation reaction. Gratifyingly, the general conditions⁸⁸,⁸⁹ was fidelity also to the crucial cyclisation of compound 80, providing the suitably substituted 1(10),5-dienic monocyclic ring (compound 81) in a good yield. On the basis of former experiences (see Scheme 4.10) with a homoallylic tosylate of a similar kind, it was with contentment observed that no base-induced elimination had occurred.

Scheme 4.12. (a) MnO₂, CH₂Cl₂, rt, 4 h; (b) TsCl, DMAP, CH₂Cl₂, rt, 18 h (77% over two steps); (c) TMSCN, KCN·18-crown-6 complex, rt, 3 h; (d) 1 M HCl/THF (1:9), 0 °C, 30 min; (e) EtOCH=CH₂, cat. H⁺, benzene, 0 °C, 1.5 h (89% over three steps); (f) 80 added to LHMDS (9 equiv) in dioxane at 80 °C over a 5.5 h period; (g) PPTS, MeOH, 40 °C, 7 h; (h) NaOH (2% aq)/Et₂O, rt, 5 min (80% over three steps).

Deprotection of the EE ether gave the corresponding cyanohydrin that was subjected to retro-hydro-cyanation under weakly basic conditions, giving the key intermediate enone 82 in one sequence. A useful synthetic approach to the main core of this germacrene skeleton was thus finally confirmed.

4.6 Properties of the 10-membered monocyclic enone and completion of the synthesis of 1(10),5-germacradien-4-ol (9) and germacrene D (10)

It was a bit troublesome to establish the exact structure of the enone 82. TLC and the NMR spectrum revealed that the enone was a mixture (~4:1) of two compounds. Initially the olefinic β-proton (dd) at δ 6.6 (J = 16, 10 Hz) of the minor compound was assigned to a trans-enone (5E), and the olefinic β-proton of the major compound at δ 6.1 (unusual pattern) seemed to belong to the cis-enone (5Z) as judged by coupling constants and their splitting patterns. Such an unfavourable isomerisation in the preceding reaction leading to an enone had been reported to occur during the base treatment that affected the retro-hydro-cyanation. Computer-assisted simulation of the NMR spectrum revealed, however, that the signal with the odd appearance at δ 6.1 in fact originated from a trans-enone, in which the δ-values of the olefinic β-proton (dd) and the olefinic α-proton (d) were similar, and which had a typical trans coupling constant (Figure 4.2.).

Figure 4.2. (a) Simulation of dd at δ 6.08 (J = 16, 10 Hz) and d at δ 6.06 (J = 16 Hz) coupled to a proton at δ 2.00 obtained using gNMR. (b) The same part of the experimental ¹H NMR of enone 82.

These experiments implied that compound 82 existed either as two very slowly interconverting, or stable, conformers, and that the assignment of the stereochemistry of the double bond was unambiguously trans for both conformers. The same observation had been made with a 10-membered heterocyclic ring compound of this kind, and a similar phenomenon appeared in the $^1$H NMR spectrum of the nor-10-methyl relative of 82. This was also ultimately corroborated by $^1$H NMR experiments at higher temperatures, in which the minor signal diminished, and it was re-established on cooling to rt. It is no coincidence that germacrane compounds often has been popular compounds in theoretical chemistry calculations. Three conformers with small differences (~1 kcal/mole) in their low energy global minima were found in minimisations using various force fields (Figure 4.3), similar to what was found in previous estimations of energies in relatives of enone 82. Of these, the one with crossed double bonds (CR) was quite dissimilar to the others (enone 82 CR-1). The rotation barrier \[i.e.\] the movement of the methyl group from an upward position in the ones with parallel double bonds (P), to a downwards position (CR)] between these two has not yet been calculated. Most probably, the difference between $\delta$ of the $\beta$-proton, and some other signals, was due to the different chemical anisotropies in the crossed versus the parallel conformer(s).

Figure 4.3. Minimum energy conformers of enone 82.

Treatment of the enone 82 with MeLi at low temperature, followed by chromatographic purification, resulted in a single isomer as the major product, namely (−)-9 (Scheme 4.13). This result supported the structure determination for 82. Thus, the nucleophile attacked from the less hindered face (from beneath in Figure 4.3) of the enone under kinetical conditions. A mixture of more polar isomers, probably arising from 82 CR-1 among others, was also isolated, which might consist of diastereomers or possible stable conformers. All analytic data of (−)-9 were identical with those reported in the literature, except the optical rotation value, which was somewhat lower than that reported for (−)-9 isolated from Scots pine. Provided that

the sample of (–)-9 isolated from natural sources was enantiomerically pure, the synthetic sample was estimated to be of ~85% ee. Even though epimerisation at the carbon atom bearing the i-Pr substituent might be expected during the conditions of the Wittig reaction that gave 76, Rychnovsky and Hoye did not observe this for similar compounds,\textsuperscript{118} but others noted this propensity for this reaction.\textsuperscript{126} If epimerisation occurred during the Wittig reaction, the Roush-Masamune modification of the HWE reaction could offer a better alternative for the synthesis of the diester 76.\textsuperscript{100,127}

As suggested,\textsuperscript{85f} and according to the retrosynthetic plan (see Section 4.3), the enone 82 could serve as the immediate precursor towards synthesis of germacrene D (10), which could be obtained by treatment of 82 with the Tebbe reagent (Cp\textsubscript{2}TiCH\textsubscript{2}AlClMe\textsubscript{2}).\textsuperscript{128} Some of the features of this reagent, as compared with Wittig ylides,\textsuperscript{100} were its lower basicity, its tolerance to hindered substrates and its faster reaction rate.\textsuperscript{129} This reagent had also been successful earlier, when applied to the germacrane enone system.\textsuperscript{130} And indeed, its reaction with enone 82 gave germacrene D [(–)-10], but unfortunately in a complex mixture with other sesquiterpenes. These probably originated in subsequent Lewis acid catalysed cyclisations after the formation of (–)-10, induced by the reagent or reagent residues. The enone seemed to survive

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{scheme_4_13.png}
\caption{Scheme 4.13. (a) MeLi, Et\textsubscript{2}O, −78 °C to −25 °C, separation (55% of pure isomer); (b) Cp\textsubscript{2}TiCH\textsubscript{2}AlClMe\textsubscript{2}, THF/Toluene, 0 °C, [mixture of sesquiterpenes containing (–)-10].}
\end{figure}

Wittig reaction conditions upon attempted methylene addition, which had also been applied to other enone systems. However, the Wittig reaction has so far not been successful to give (–)-10. A change of reaction conditions (solvent/temperature) might overcome this. If not, the Peterson olefination reaction could be an alternative.


5. CONCLUSIONS AND OUTLOOK

Even though organic syntheses of pharmaceuticals are high priority goals of mankind, syntheses of semiochemicals and other natural products are by no means unimportant areas for organic chemists. Many naturally occurring compounds remain to be discovered and their properties and functions are still unknown. This thesis discusses some examples of organic synthesis being an important tool for the preparation and biological investigation of potential allelochemicals. These have further use in biological studies of the behaviour of some insects, mainly that of the pine weevil *H. abietis*.

In the project dealing with carvone analogues as antifeedants for the pine weevil, different kinds of thio ethers have been prepared in well-defined isomeric forms, and the chemoselectivity of various reaction types for the synthesis of these has been studied. Carvone analogues with increased molecular weight have been synthesised employing different strategies. Some of these synthetic targets have been naturally occurring compounds belonging to the bisabolane (the delobanones 24) and the prenylbisabolane (*e.g.* 25) terpenoid classes. The carvone analogues prepared have not fulfilled all requirements for being efficient substitutes of the insecticide permethrin used at present, in seedling protection against stem gnawing by *H. abietis*. Therefore, some additional, easily accessible carvone analogues (*e.g.* ethers of the type 83) should also be prepared and tested.133 The main problem associated with the potential practical application of the compound prepared as gnawing inhibitors, as well as with the use of many other promising ones from of the large library of compounds screened, is a general and practically useful formulation method for these. A strong interdisciplinary cooperating effort between biologists and chemists is needed to develop such a method.

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The germacrane project has demonstrated that the intramolecular alkylation procedure developed by Takahashi\textsuperscript{88} is a convenient method in the total synthesis of a sensible 1,5-cyclodecanoid framework (\textit{e.g.} enone 82). This enone could then be used in germacrane sesquiterpene syntheses. Using this approach, the synthesis of (−)-1(10),5-germacadien-4-ol (9) has been disclosed. It has also been shown that the ubiquitous sesquiterpene germacrene D (10) can be prepared in trace amounts \textit{via} the same monocyclic enone 82, using a Tebbe reaction.

Whether this enone will be a useful precursor of pure germacrene D or not, is still an open question. There are some minor improvements that can be made in this multistep synthesis (\textit{i.e.} to increase the ee, to conserve the ee throughout the whole sequence, to synthesise all possible isomers and perhaps also to decrease the number of synthetic steps). Although the strategy using the Takahashi coupling for ring-closure is successful, the competing ring-closing metathesis methodology may also turn out to be an attractive strategy in germacrane syntheses.\textsuperscript{83,85d,85f} However, at the moment this strategy is not developed enough for successful syntheses of the fully substituted germacranoid skeletons. Ongoing efforts in catalyst design and increased understanding of the reaction might overcome these problems.