Novel Transition Metal Catalysts for Intramolecular Ene-reaction

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by

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This thesis is dedicated to my mum and dad,
and to my wife Monaza, and our children, Nafisa and Kamran
with much love
Abstract

We have designed a new class of \(\text{M}^{\text{II}}\)-catalysts, namely molybdenum and tungsten (II) complexes of the type \(\text{PhCH}_2\text{(Et)}_3\text{N}^+\text{[M(CO)}_4\text{ClBr}_2\text{]}^-\) and \(\text{M(CO)}_5\text{(OTf)}_2\) (\(\text{M} = \text{Mo or W}\)), which induce intramolecular cyclization of olefinic aldehydes to afford products with a \textit{cis}-configuration at the newly formed chiral centres in some cases. These catalysts can be tuned to drive the reaction either toward the ene or Prins-type product (32 or 89). The latter reaction occurs via an \textit{anti} addition of the carbonyl carbon and OH across the \(\text{C}=\text{C}\) bond, as evidenced by isotopic labeling. A chair-like transition state with an axial carbonyl oxygen is proposed to rationalise the stereoselectivities observed.
Acknowledgements

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Chapter 1

Introduction and Review of the Ene reaction
1.1. Introduction

The success of the late transition metals in catalytic chemistry is due to the ease with which they change their coordination number and exist as 18-, 16-, and 14-electron species.\(^1\) Similar changes in the coordination sphere of the Group 6 metals are usually more difficult to accomplish. Thus, relatively few catalytic processes using the latter metals in lower oxidation states have been developed to date.\(^1\)\(^2\) However, one successful example is the Mo(0)- and W(0)-catalysed allylic substitution (Scheme I).\(^3\)\(^4\) For instance, reaction of 1 in toluene or diglyme with silyl enol ether, generated from dimethylmalonate and \(N,O\)-bis(trimethylsilyl)-acetamide (BSA), in the presence of Mo(CO)\(_6\) gave the allylic substitution product 2.\(^5\) Its variant proceeds much more readily by the use of Pd(0) as the catalyst,\(^6\)\(^7\) usually at room temperature. Whereas, Mo- and W-carbonyl complexes generally require refluxing in higher boiling solvents for several hours.\(^3\)\(^4\) This remarkable difference can be ascribed, partly, to the readiness of ligand dissociation in the case of palladium catalysts,\(^1\) i.e., \((\text{Ph}_3\text{P})_4\text{Pd} \rightleftharpoons (\text{Ph}_3\text{P})_3\text{Pd} + \text{Ph}_3\text{P}\), in contrast to the relative stability of Mo(CO)\(_6\), W(CO)\(_6\), and analogous complexes.

![Scheme 1](image)

We reasoned that the intrinsic coordination rigidity of the Group 6 metal complexes could be offset by introducing one or two weakly coordinating ligands in place of the CO group(s), that can be more easily substituted by the reactants.\(^8\)\(^9\)\(^10\) In conjunction with the ability of Mo and W to form heptacoordinated complexes,\(^1\)\(^11\) this ligand property may result in an improved or even new catalytic activity.
In this thesis we examine the effects of replacing the strongly coordinating chloride in benzyltriethylammonium and bis(triphenylphosphine)ammonium (PPN) complexes of molybdenum and tungsten of the type \([\text{M(CO)}_5\text{Cl}]^-\) (\(\text{M} = \text{Mo or W}\)) by weakly coordinating trifluorosulfonate anion (\(\text{TfO}^-\)) and on the associated redox processes. We also investigate the effect of the counterion and the solvent polarity on the formation and properties of these new complexes, and their catalytic activity in the intramolecular carbonyl-ene reaction.\(^{12}\)

### 1.2. Ene reaction

The reaction between an alkene bearing an allylic hydrogen (an ene component) and an electron-deficient multiple bond (an enophile) to form a new \(\sigma\)-bond with migration of the ene double bond and a 1,5-hydrogen shift is referred to as an "ene" reaction.\(^{12}\) It was discovered in 1943\(^{13}\) by Alder who, in his Nobel lecture, described it as an "indirect substitution" or "ene synthesis" in 1950.\(^{14}\) The ene reaction is mechanistically related to the better known Diels-Alder addition because both reactions can be concerted, proceeding through cyclic transition states involving six electrons (Scheme 2).

**Scheme 2**

\[\text{diene} \quad \xrightarrow{\text{ene}} \quad \text{enophile} \quad \xrightarrow{\text{ene}} \quad \text{dienophile}\]

Diels-Alder

Ene
Since the enophile, like the dienophile in a Diels-Alder reaction, should be electron deficient, complexation of Lewis acids to the enophile with basic groups can be expected to result in acceleration in the ene reaction. Therefore, a number of Lewis acid catalysts have been developed, such as AlCl₃, BF₃·Et₂O, TiCl₄, SnCl₄ and also alkylaluminium halides (RₙAlX₃-n); the latter prevent undesired proton-catalyzed side reactions (see below), since these compounds act as Bronsted bases (proton scavengers) as well as Lewis acids.¹⁵

Acrylate and propiolate esters require strongly acidic Lewis acids such as AlCl₃ or EtAlCl₂.¹⁶,¹⁷ The more reactive acrolein and methyl vinyl ketone have had limited success with milder Lewis acids such as Me₂AlCl or zinc halides. SnCl₄ and BF₃·Et₂O have been exploited as Lewis acid catalysts with formaldehyde.¹⁸ Catalysis of electron-deficient aldehydes such as chloral has been achieved with mild Lewis acids such as FeCl₃ as well as by BF₃, AlCl₃, SnCl₄, or TiCl₄.¹⁹ For the reactions of glyoxylate esters, FeCl₃ is optimal.²⁰ Zinc halides, SnCl₄, and TiCl₄ selectively promote the ene cyclization of citronellal to afford isopulegol.²¹

A serious drawback in Lewis acid promoted ene reactions has been proton initiated side reactions i.e. polymerization of the ene component and isomerization of the double bonds in the ene component or ene products. For instance, methylenecyclohexane isomerizes partially to 1-methylcyclohexene in the ene reaction with methyl propiolate using AlCl₃ as the catalyst.¹⁷b The ene product from the reaction of isoprene with chloral in the presence of SnCl₄ at room temperature partly isomerizes to a dihydoropyran under the reaction conditions (Scheme 3).²²

**Scheme 3**

```
\[
\begin{align*}
\text{CH₂CH} & \quad + \quad \text{HCCl}_3 \\
\text{SnCl}_4, \text{rt} & \quad \rightarrow \\
\text{CH₂CHC} & \quad + \quad \text{OCCl}_3
\end{align*}
\]
```

95% 5%
However, Snider has shown that the use of alkylaluminium halides eliminates proton-catalysed side reactions, since these reagents act as Bronsted bases (proton scavengers) as well as Lewis acids (eq. 1). $\text{Me}_2\text{AlCl}$ is a particularly useful catalyst for the ene reactions of $\alpha,\beta$-unsaturated aldehydes and ketones and also for saturated aldehydes.\textsuperscript{23} $\text{EtAlCl}_2$ is very effective with $\alpha,\beta$-unsaturated esters.\textsuperscript{17b,d} Its acidity is comparable with that of $\text{AlCl}_3$ but gives much better yields of the ene products as proton catalysed isomerization does not occur.

\[
\text{HX} + \text{RAICl}_2 \rightarrow \text{RH} + \text{AlCl}_2\text{X} \tag{1}
\]

One disadvantage of the use of alkylaluminium halides is that the alkyl group can act as a nucleophile as well as a base. This is not generally a problem with monoalkylated aluminium halides. However, with $\text{Et}_2\text{AlCl}$ the problem is very severe when unreactive ene components are used.\textsuperscript{23} This necessitates the use of more expensive, but less nucleophilic, $\text{Me}_2\text{AlCl}$. Therefore, the use of alkylaluminium Lewis acids as proton scavengers is only beneficial when the nucleophilicity of the alkyl substituents is not a problem.

1.2.1. The ene component

The ene reaction involves suprafacial orbital interaction, here the two electrons of the allylic C-H $\sigma$-bond replace the two $\pi$-electrons of the diene required in the Diels-Alder reaction. Therefore, ene reactions typically occur at higher temperatures, which is the main reason why ene reactions have remained over-shadowed for a long time in comparison to Diels-Alder counterpart. Thus, Lewis acid catalysed ene reactions have been exploited, and the mechanistic differences from thermal reactions have been examined carefully. Whether the mechanism is concerted or stepwise, positive charge is formed to certain extent at the ene component in Lewis acid catalysed reactions. Thus, alkenes with at least 1,1-disubstituted double bond are much more reactive than mono- or 1,2-disubstituted alkenes. In this respect,
the Lewis acid catalysed ene reactions differ from thermal ene reactions where steric accessibility of the double bond and allylic C-H is of great importance. These differences have been quantified by Salomon, who demonstrated that the reaction constant $\rho = -1.2$ for the thermal ene reaction of para-substituted 1-arylcyclopentenes with diethyloxomalonate, while $\rho = -3.9$ for the reaction catalysed by SnCl$_4$. The influences of steric effects in thermal reactions vs electronic effects in Lewis acid catalysed reactions are shown in the different product ratios obtained with diethyl oxomalonate and 6-methyl-1,5-heptadiene (Scheme 4).

**Scheme 4**

![Scheme 4](image)

180 °C 48h 92 : 8 (75%)

SnCl$_4$ (0.2 equiv) 2.5 : 97.5 (40%)

$0 \text{ °C, 5 min}$

The reactivity order for alkenes in Lewis acid-promoted ene reactions is generally 1,1-di- > tri- > tetra- >> mono- > 1,2-disubstituted. However, steric requirements of the enophile can have a significant effect on this order. For instance, methyl propiolate, with little steric requirements, shows only 2:1 preference for the 1,1-disubstituted double bond of limonene in Lewis acid-mediated ene reactions. In contrast, aldehydes,$^{18a,23}$ acrolein,$^{25}$ and methyl acrylate$^{25}$ exhibit much greater selectivities.
1.2.2. The enophile

Propiolates.

Thermal ene reactions with methyl propiolate esters afford regioisomeric mixtures. For instance, reaction of methyl propiolate with 1-heptene at 200 °C for 30 h produces a 4:1 mixture of regioisomers in 30% yield. A similar reaction with isobutylene furnishes a 93:7 regioisomeric mixture in 45% yield (Scheme 5). On the other hand, AlCl₃ catalysed reactions of propiolate with 1,1-di-, tri-, and tetra-substituted alkenes give exclusively one regioisomer in marked contrast to the thermal reactions which give a mixture of ene products (Scheme 5). Presumably, complexation of AlCl₃ to the ester, makes the double bond electron-deficient and hence polarises it so that the reaction proceeds regioselectively at the electron deficient β-carbon.

Scheme 5

```
HC = CC02Me

CO2Me

220 °C  93 : 7  (45%)
AlCl₃ 25 °C  100 : 0  (61%)
```
However, 1,2-disubstituted alkenes afford exclusively stereospecific cycloaddition products, and monosubstituted alkenes provide ene products along with cyclobutenes. EtAlCl$_2$ was found to be a more effective catalyst. Ethynyl $p$-tolyl sulfone undergoes similar reactions with EtAlCl$_2$ as catalyst in CH$_2$Cl$_2$. Use of ZnCl$_2$ as catalyst enables the isolation of similar products from 3-butyne-2-one.

**Chloral**

Thermal ene reactions of chloral with 1,1-di- and 1,1,2-trisubstituted alkenes occurs at lower temperatures (90-130 °C) because of the electron-withdrawing effect of the trichloromethyl substituent. Thus, reaction of 2-methylbut-2-ene at 130 °C yields *anti*-isomer in 84% diastereoselectivity (Scheme 6). By contrast, Lewis acid promoted reaction gives the opposite diastereomer in 85% selectivity. Recently Gill has reported a complete account on the chloral ene reaction.

### Scheme 6

\[
\begin{align*}
&\text{130 °C} & \quad 16 : 84 \\
&\text{AlCl}_3 \quad 25 °C & \quad 85 : 15
\end{align*}
\]
Formaldehyde

The formaldehyde-ene reaction has been extensively explored.\textsuperscript{33} Thermal ene reactions of paraformaldehyde with 1,1-disubstituted including trisubstituted alkenes proceed at 180-220 °C.\textsuperscript{34,35} \textsuperscript{34} \textsuperscript{35} SnCl\textsubscript{4}-catalysed reaction with a symmetrical diene readily occurs providing lavanduol in 55% yield (Scheme 7).\textsuperscript{36} A similar reaction with limonene occurs selectively at the more reactive 1,1-disubstituted double bond to furnish the ene product in 80% yield.\textsuperscript{37} Recently, Yamamoto and co-workers have reported the generation of formaldehyde from trioxane and its stabilization as a complex with a very bulky aluminium reagent, MAPH which gives excellent regioselectivity.\textsuperscript{38}

\textbf{Scheme 7}

![Scheme 7](image)

Glyoxylate

Thermal ene reactions of glyoxylate as the enophile occur at 150 °C. However, SnCl\textsubscript{4}- and AlCl\textsubscript{3}-mediated ene reactions of glyoxylates take place at lower temperatures even with less reactive cyclohexenes and 1-alkenes.\textsuperscript{39} The introduction of a chiral ester auxiliary can lead to high asymmetric induction in the ene product (Scheme 8).\textsuperscript{40} For this reason glyoxylate-ene reactions are synthetically of great importance.
Aliphatic and Aromatic Aldehydes

Aliphatic and aromatic aldehydes are thermally unreactive. Snider has shown that Me₂AlCl accelerates ene reactions with reactive 1,1-di-, tri-, and also tetra-substituted alkenes. Mono- and 1,2-disubstituted alkenes are less reactive. However, reaction of a monosubstituted alkene with an aliphatic aldehyde in the presence of EtAlCl₂, a stronger Lewis acid than Me₂AlCl, in CH₂Cl₂ at 0 °C gives a 4:1 mixture of (E)- and (Z)- isomers respectively (Scheme 9).
Quite recently, Kuwajima and co-workers reported that the reaction of an aromatic aldehyde with (S)-2-(ethylthio)-3-siloxy-1-butene derived from lactate affords $\gamma$-hydroxy carbonyl compounds as their silyl enol ethers (Scheme 10).\textsuperscript{43} Interestingly, they found a high level of chirality transfer (99%) by the correct choice of enophile and used the product for the synthesis of anthracycline antibiotics.\textsuperscript{44}

Scheme 10

\[
\begin{align*}
\text{MeO} & \quad \text{TBSO} \\
\text{CHO} & \quad \text{TBSO} \\
\end{align*}
\]

\[
\begin{align*}
\text{SMe} & \quad \text{OTBS} \\
\text{OTBS} & \quad \text{Me}_2\text{AlCl} \\
\text{MeO} & \quad \text{OH} \\
\text{TBSO} & \quad \text{OTBS} \\
\end{align*}
\]

99% e.e.

**Oxomalonates and Pyruvates**

Thermal and SnCl\textsubscript{4}-mediated ene reactions of diethyl oxomalonates have been extensively studied by Salomon.\textsuperscript{24,45} A range of alkenes furnish the ene products with stoichiometric amounts of diethyl oxomalonates at 80-185 °C. Comparable yields are obtained at 0 °C using SnCl\textsubscript{4} as the catalyst. The use of clay as a catalyst has also been exploited.\textsuperscript{46} Thermal ene reactions of $\beta$-pinene with methyl pyruvate can be carried out in quantitative yield at 40 kbar for 17 h at 25 °C.\textsuperscript{47} Reaction of trans-2-phenylcyclohexyl
pyruvate with 1-hexene in the presence of TiCl₄ (2 equiv) at 0 °C provides the ene product in 86% diastereomeric excess (Scheme 11).⁴₈

**Scheme 11**

Furthermore, dialkyl dioxosuccinate esters,⁴⁹ carbonyl cyanide,⁵⁰ carbonyl sulfide,⁵¹ hexafluoroacetone⁵²-⁵⁴ as well as 1,1,1-trifluoro methyl ketones⁵⁵ have also been studied. A variety of alkenes give the ene products with hexafluoro acetone under mild conditions. AlCl₃ catalysed ene reactions of 1,1,1-trifluoromethyl ketones reportedly proceed in good yields at -78 °C.⁵⁵

**Aliphatic ketones**

Ketones are less enophilic, and the ene products are homoallylic alcohols which are acid labile. However, moderate yields of the ene products can be obtained with EtAlCl₂, cyclic ketones, and reactive 1,1-disubstituted alkenes.⁵⁶
Until recently, the ene reaction of hetero-substituted aldehydes such as hydroxy and amino aldehydes has proved unsuccessful. For example, reaction of glycolaldehyde with 3-hydroxybutanal in the presence of a range of aluminium halides leads to a mixture of products.\textsuperscript{57} However, the ene reactions of protected hydroxy and amino aldehydes have been examined to provide a new entry into the asymmetric synthesis of diols\textsuperscript{58} and amino alcohols.\textsuperscript{59} Thus, 22(R)-(methoxymethyl)oxy aldehyde, obtained via glyoxylate-ene reaction, reacts with isobutylene on exposure to tin(IV) chloride to furnish exclusively the syn-isomer in quantitative yield (Scheme 12).\textsuperscript{58}

Moreover, \(\gamma\)-lactols, the cyclic equivalent of \(\gamma\)-hydroxy aldehydes, undergo reactions with 1,1-disubstituted alkenes to provide ene products.\textsuperscript{12b}
Thiocarbonyl compounds

The title compounds such as methyl cyanodithioformate, thiogloxylates and hexafluorothioacetone are very reactive as enophiles. It is pertinent to note that the orientation is opposite to that observed for ene reactions with carbonyl compounds i.e. C-S rather than C-C bond formation occurs (Scheme 13).

Scheme 13

In the ene reactions involving Schiff’s bases, the nitrogen analogues of aldehydes, C-C bond formation occurs site selectively at the imino double bond. However, ene reactions with imine derivatives of aldehydes have been restricted either to reactions with reactive N-sulfonyl imine derivatives of glyoxylate (Scheme 14) or to reactions employing highly reactive ene component for instance an allenyl sulfide.

Scheme 14
1.2.3. Diastereoselectivity

The diastereoselectivity of methyl glyxoylate has been examined using a number of Lewis acids such as (alkoxy)titanium chloride, boron triluoride etc. Interestingly, a dramatic changeover in diastereoselectivity has been observed by changing the Lewis acid from dimethylaluminium triflate to tin(IV) chloride (see below). Thus, methyl glyoxylate reacts with an excess of (Z)-but-2-ene in the presence of Me₂AlOTf to afford a 91:9 ratio of syn- and anti-isomers respectively (Scheme 15). This is rationalised in terms of greater repulsion between the substituents on the monodentate aluminium reagent and the ene methyl group in (3) than between the ester group and the same methyl group in (4).

**Scheme 15**

\[ 	ext{MeO}_2\text{C} - \text{AlMe}_2\text{OTf} \]

\[ \text{MeO}_2\text{C} \rightarrow \text{CH}_3 \]

\[ \text{CH}_2\text{Cl}_2, -78 \, ^\circ\text{C} \]

\[ \text{MeO}_2\text{C} \rightarrow \text{OH} \]

\[ \text{65\%} \]
By contrast, the SnCl\textsubscript{4}-mediated ene reaction of but-2-ene exhibits anti selectivity, irrespective of the ene geometry. Reaction with (E)-but-2-ene affords a 82:18 diastereomeric mixture in quantitative yield. The predominance of the anti-diastereoisomer (7) in this reaction is attributed to greater steric interaction between Lewis acid and the methyl group in 6 (Scheme 16).

![Scheme 16](image)

The reaction with (Z)-but-2-ene gives predominantly the same anti-isomer, although in this case lower diastereoselectivity is observed (Scheme 17), perhaps there is some interaction between the substituents on the coordinated tin and the olefinic H\textsubscript{a} proton.
The introduction of an additional group into the ene component further enhances the diastereoselectivity (Scheme 18) (cf. Scheme 16). However, in the presence of this 2-trimethylsilyl group a reversal in the sense of diastereoselectivity has been observed with trans-vinylsilane (Scheme 19) (cf. Scheme 17). This can be explained in terms of greater steric interaction between the trimethylsilyl moiety and the substituents on the complexed Lewis acid in transition state resembling 8 than between the methyl group and the coordinated Lewis acid in 9 (Scheme 19).
1.2.4. Regioselectivity

Nakai and co-workers have shown that, in the intramolecular glyoxylate ene reaction, allylic ethers afford single regioisomers with a range of protecting groups except for trifluoroacetate which gives a 3:1 regioisomeric mixture (Scheme 20).
The ene reaction of 1-silyloxy-substituted \((E)\)-pent-2-ene with methyl glyoxylate using tin(IV) chloride is both highly regio- and diastereoselective (Scheme 21).\textsuperscript{71} Moreover, a double bond is formed, which, in the absence of a substituent at the 3-position, is generally \(E\) configured irrespective of the ene geometry.

![Scheme 21](image_url)

More importantly, the reaction with homoallylic ether also affords the \(E\) configured \(anti\)-ester as a single isomer, irrespective of the geometry in the parent ene component (Scheme 22).\textsuperscript{71}
With the successful regio- and stereocontrol in the ene reaction with (homo)allylic ethers (see above), the bishomoallylic cases have also been investigated. Interestingly however, the opposite regioisomer is obtained exclusively with $E$ configured double bond and high *anti* selectivity (Scheme 23).

**Scheme 23**

<table>
<thead>
<tr>
<th>R</th>
<th>Yield</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Si^{i}Pr_3$</td>
<td>99</td>
<td>:</td>
</tr>
<tr>
<td>$SiPh_2^{t}Bu$</td>
<td>96</td>
<td>:</td>
</tr>
</tbody>
</table>
1.2.5. Asymmetric catalysis

Recently, Yamamoto and co-workers have shown that by using equimolar amount of the chiral aluminium reagent generated from trimethylaluminium and 3,3'-bis(triphenylsilyl)binaphthol the asymmetric ene reaction of electron deficient aldehydes such as perfluorobenzaldehyde, chloral and 2,6-dichlorobenzaldehyde with alkenes proceeds with high enantioselectivity (Scheme 24). In the presence of molecular sieves the reaction proceeds without loss of the optical purity of the ene product, even when catalytic amounts of the aluminium reagent are used.

However, the asymmetric catalysis for the carbonyl-ene reaction especially with prochiral glyoxylate has remained fairly unexplored, despite its potential for the asymmetric synthesis of $\alpha$-hydroxy esters, a class of compounds of biological and synthetic importance. A substrate-based asymmetric glyoxylate-ene reaction employing a chiral glyoxylate enophile using stoichiometric amounts of Lewis acid has been reported (Scheme 25).
More recently, an extremely efficient asymmetric catalysis of the glyoxylate-ene reaction has been successfully developed as illustrated (Scheme 26). The catalyst in this reaction is prepared \textit{in situ} from optically pure binaphthol (BINOL) and diisopropoxytitanium dihalide in the presence of 4Å molecular sieves; even as little as 1% is effective.
The authors have demonstrated that the catalyst derived from \((R)\)-BINOL affords the \((R)\)-enantiomer, whereas the catalyst prepared from \((S)\)-BINOL consistently leads to the \((S)\)-homoallylic alcohol. Moreover, the present asymmetric catalysis is applicable to a wide range of 1,1-disubstituted alkenes to furnish the ene products in extremely high enantiomeric purities by the judicious choice of the dichloro or dibromo chiral catalyst.\(^{75a,c}\) Interestingly, the dibromide is superior to the dichloride in both reactivity and enantioselectivity with a methylene hydrogen transfer in particular (Scheme 27).

**Scheme 27**

\[
\begin{align*}
\text{Catalyst} & \quad \text{H} & \quad \text{CO}_2\text{Me} \\
4\text{Å mol sieves} & \quad \text{OH} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\((\text{i-PrO})_2\text{TiCl}_2 / (\text{R})\)-BINOL (10 mol%), 8h, 93%, (88% e.e.)

\((\text{i-PrO})_2\text{TiBr}_2 / (\text{R})\)-BINOL (5 mol%), 3h, 92%, (89% e.e.)

**Ene cyclization**

Intramolecular ene reactions (ene cyclization) are much more facile than their intermolecular counterparts.\(^{76}\) Therefore, even simple enophiles such as alkenes and acetylenes can undergo thermal ene reactions. Conceptually, ene cyclizations can be classified into six different modes of cyclization (Scheme 28)\(^{77}\) according to Ziegler’s notation originally proposed for the cyclic Claisen sigmatropic shifts.\(^{78}\) In the ene cyclizations, the carbons, to which the tether connecting the \([1,5]\)-hydrogen shift system is attached are exemplified in \((m,n)\) fashion. The ring size may be designated by a numerical
prefix I-. (3,4) ene cyclizations are limited to the formation of 5-, 6- and 7-membered rings. The formation of a 5-membered ring is a facile process for olefinic enophiles. An analogous 6-(3,4) ene cyclization is known to be less facile. For carbonyl enophiles this order is reversed. The formation of larger rings by (3,4) ene cyclizations is less common. (2,4) ene cyclizations are restricted to the formation of 6- and 7-membered rings.\(^7\) (1,5) ene cyclization only give medium sized rings.\(^8\) Oppolzer described these three modes of ene cyclizations as types I, II, and III.\(^7\)

**Scheme 28**

Occasionally, (3,5) ene cyclization has also been observed. The attachment of an electron-withdrawing moiety to the interior adjacent carbon of the enophile favors the type 6-(3,5) rather than 5-(3,5) ene cyclizations.\(^8\) Recently, EtAlCl\(_2\)-mediated (1,4) ene cyclization has been observed with reactive trifluoromethyl ketones which affords cyclohexenol and cycloheptenol in good yields.\(^8\)
Asymmetric catalysis of ene reactions was initially investigated in the intramolecular version, since intramolecular ene reactions are much more facile. Such a trial of asymmetric (3,4) ene cyclization of prochiral aldehyde with geminal dimethyl groups has been made using a binaphthol-derived zinc reagent. Thus, treatment of 3-methylcitronellal (Scheme 29) and (Z)-methylfarnesal with the above zinc reagent gives the corresponding ene products in high enantiopurity (ca. 90% e.e.). However, this was successful only in the presence of an excess of zinc reagent (at least 3 equivalents).

Quite recently, an asymmetric olefin-ene cyclization was reported using stoichiometric amount of the tartrate-derived chiral titanium complex (Scheme 30). In this 6-(3,4) ene cyclization a gem-disubstituent effect is observed, and the presence of geminal dimethyl and dithioacetal groups accelerates the reaction to provide cyclohexane and cyclopentane derivatives with high enantiopurity.
Mikami and co-workers have recently reported the enantioselective catalysis of ene cyclization of type (3,4) (Scheme 31) as well as of type (2,4) (Scheme 32) which are catalysed by a BINOL-derived titanium complex (R)-13, modified by the perchlorate ligand.\textsuperscript{77,86}
The titanium perchlorate \((R)-13\) can readily be prepared by the treatment of the corresponding chloride complex (see above) with silver perchlorate. Thus, the \(\textit{trans}\)-tetrahydropyran is preferentially obtained in 84% ee (Scheme 31). However, 6-(2,4) \((n = 0)\) ene cyclization does not afford any ene product (Scheme 32), presumably because of the lower ene-reactivity of the allylic ether group. By contrast, the seven-membered type (2,4) cyclization of the homoallylic ether \((n = 1)\) provides the oxepane in high enantiomeric excess, in the absence of geminal-dimethyl substituents (Scheme 32).

\[
\text{Scheme 32}
\]

\[
\text{(R)-13} \quad \text{(20 mol\%)} \quad \text{MS 4Å} \quad \text{rt}
\]

\[
\begin{align*}
\text{OH} \\
\text{O} \\
\text{R} = H & \quad 91\% \text{ ee (R)} \\
\text{R} = \text{Me} & \quad 82\% \text{ ee (R)}
\end{align*}
\]

In the presence of the chiral titanium perchlorate 13, cyclisation of the carbo-analogue was accomplished in high enantioselectivity to afford preferentially the \textit{trans}-isomer (Scheme 33).
Scheme 33

\[
\text{(R)-13} \quad (20 \text{ mol\%}) \quad \text{MS 4Å} \quad \text{CH}_2\text{Cl}_2
\]

\[
\begin{align*}
\text{69} & \quad (55\% \text{ ee}) \\
\text{31} & \quad (64\% \text{ ee})
\end{align*}
\]
Chapter 2

Review of Lewis acids
2.1. Structural Studies on the Lewis Acid Carbonyl Complexation

Lewis acid is an electron deficient species which coordinates to lone pairs in a molecule, thereby increasing its electrophilic nature. They can be described as being monodentate, for instance BF$_3$ (eq 1), or polydentate such as SnCl$_4$ and titanium (IV) chloride etc.

\[
\text{BF}_3 + \text{OEt}_2 \rightarrow \text{BF}_3:\text{OEt}_2
\]  

(1)

Carbonyl compounds are activated upon coordination with Lewis acids (see below). Discussion on the precise nature of the complexes in solution is rather difficult. However, X-ray crystallographic and theoretical studies on the complexes of carbonyl compounds and Lewis acids have provided us with considerable information on their structure.

X-ray crystallography of the complex between boron trifluoride and benzaldehyde clearly indicates that the boron atom lies in the plane of aldehyde and \textit{anti} to the larger phenyl substituent as shown in Scheme 34. Similar complexation in solution, \textit{anti} to the phenyl moiety, is also suggested by the NOE measurements between fluoride and the benzaldehyde proton.

\textbf{Scheme 34}

\[
\text{HN}_{\text{BF}_3} \quad \text{BF}_3
\]

MNDO calculations of the acetaldehyde-BF$_3$ complex indicate that the \textit{anti} (to the methyl substituent) adduct is the lowest energy species and the \textit{syn} complex lies 1.8 Kcal/mol higher in energy. Furthermore, the linear (C=O-B) complex is not a minimum on the energy
surface. However, it represents the transition state for intramolecular anti \( \Leftrightarrow \) syn isomerization.\(^8\(^7\)

Complexation of Lewis acids with esters, generally leads to anti adducts (to the alkoxy moiety) in which the M-O=C-C skeletons lie in a common plane. For instance, the crystalline 2:2 complex of ethyl acetate and titanium tetrachloride has been clearly shown to exhibit the anti conformation to the ethoxy moiety by X-ray analysis (Scheme 35).\(^8\(^8\)

![Scheme 35](image)

Regarding the complexes between Lewis acids and acrylate derivatives, ab initio calculations have been carried out on the conformations of the complex of methyl acrylate and BF\(_3\). There is a greater preference for the s-cis geometry in the conformations of methyl acrylate itself, whereas the borane complex prefers the geometry in which the borane atom is coordinated anti to the methoxy moiety and the acryloyl group is s-trans configured. (Scheme 36).\(^8\(^9\)

![Scheme 36](image)
Appparently, the tin(IV) chloride-ethyl cinnamate adduct (1:2) exhibits the *s-trans* conformation, as revealed by the crystal structure. In the octahedral complex the tin atom is at the center of inversion. Moreover, SnCl₄ also lies *anti* to the ethoxy moiety with both of the cinnamoyl substituents being *s-trans* (Scheme 37). The Sn-O-C-C dihedral angle of 21° suggests some out of plane bonding, although less than that of in the analogous titanium complexes.⁹⁰

**Scheme 37**

Fp(4-methoxy-3-butenone)PF₆ also adopts the *s-trans* geometry, with the iron coordinated *syn* to the double bond (Scheme 38). In addition, there is no evidence for π-bonding in the crystal structure of the above complex.⁹¹

**Scheme 38**

Recently, a tungsten-derived Lewis acid, [(Me₃P)(CO)₃(NO)W]⁺SbF₆⁻ has been employed in the catalysis of diene polymerisation and the Diels-Alder reactions.⁹² Despite
any obvious steric interactions in the s-cis conformer, acrolein-adduct exhibits the s-trans conformation, with tungsten σ-coordinated \([\tau(W-O=C-C) = 180^\circ]\), syn to hydrogen, at an angle of 137.1° (Scheme 39). It appears from the crystal structure that the behaviour of the tungsten complex is analogous to classical Lewis acids. Thus, its structure can be determined using the same principles.

Scheme 39

Generally, complexation with a Lewis acid stabilizes the s-trans conformation of an \(\alpha,\beta\)-unsaturated ester relative to the s-cis conformation (see above). However, in a particular case where a Lewis acid is chelated with an unsaturated ester it is possible for the conformation of the ester to become s-cis. Evidence for such an s-cis conformation is provided by the crystal structure of the TiCl4-adduct of an acrylate bearing a lactate substituent. The titanium lies syn to the alkoxy group of the acrylate by the 7-membered chelate formation. The acrylate exhibits the s-cis geometry (Scheme 40).93

Scheme 40
The inverse asymmetric induction has been observed in the Diels-Alder reaction of acrylate 14 and cyclopentadiene in the presence of either nonchelating Lewis acids (Et₂AlCl, BF₃·OEt₂) or chelating Lewis acids such as TiCl₄ and SnCl₄. These results can be rationalised by considering nonchelating (s-trans) and the chelating (s-cis) intermediates, 15 and 16 respectively (Scheme 41). The high diastereoselectivity (93:7) observed in the case of TiCl₄ can be ascribed to a shielding of the Re face of the ene part of the enoate by one of the chlorine substituents. SnCl₄ shows similar reactivity as for titanium tetrachloride.

**Scheme 41**
The association of Lewis acids in solution is another aspect of their behaviour which influences their structure and reactivity. For instance, titanium primary alkoxides have been known to associate in dry nonpolar solvents to afford a mixture of species, mainly trimers, whereas secondary and tertiary alkoxides are mostly monomers due to the steric effects.\textsuperscript{94} Furthermore, association decreases the Lewis acidity as in the case of TiCl\textsubscript{2}(OPr-\textit{i})\textsubscript{2}.\textsuperscript{95} Association as a result of coordination has also been observed in a dioxane solution of alkoxytitanium such as propoxide, butoxide, and pentoxide. With the increase in concentration, the molecular weight rises and oligomerization also continues to increase.\textsuperscript{96}

2.2. Use of Lewis acids in Diels-Alder reactions

Lewis acids have a strong influence on the rate and regiochemistry of the Diels-Alder reactions which can be attributed to lowering of the frontier orbital energies, as well as a redistribution of the orbital electron densities. Thus, Cu(BF\textsubscript{4})\textsubscript{2} catalysed Diels-Alder reaction\textsuperscript{97} of $\alpha$-acrylonitrile and 5-substituted cyclopentadiene (17) takes advantage of this rate enhancement to afford the desired product, thus avoiding the 1,5-hydrogen shift reaction, which isomerizes the double bond (Scheme 42).

![Scheme 42](image)

In the natural product synthesis, reaction between isoprene and 3-methylbut-2-ene-2-one furnished a mixture of ketones in which the para-regioisomer proved to be very difficult to separate from the undesired meta-isomer (Scheme 43). However, in the presence of stannic...
chloride the para-isomer was obtained exclusively.\textsuperscript{98} This clearly demonstrates the great practical utility of Lewis acids.

![Scheme 43](image)

Also accompanying these large rate accelerations, greatly increased regioselectivity is also observed. For example, methylbutadiene reacts with methyl acrylate to give ortho:meta ratios of 90:10 and 98:2 for the uncatalysed and AlCl\textsubscript{3}-catalysed reactions respectively (Scheme 44).\textsuperscript{99} The greater preference for the ortho-regioisomer can be rationalised in terms of the increase in the polarisation of the lowest unoccupied molecular orbital (LUMO) of the C=C double bond of the dienophile as depicted in Scheme 45, where the size of the circles represents the magnitude of the coefficients on the interacting lobes.

![Scheme 44](image)

| Without AlCl\textsubscript{3} | 90 : 10 |
| With AlCl\textsubscript{3}   | 98 : 2  |
Diastereoselectivity (endo:exo ratios) also dramatically increases upon Lewis acid catalysis of Diels-Alder reactions. Hence, cyclopentadiene reacts with methyl acrylate to provide endo:exo ratios of 82:18 and 99:1 in uncatalysed and aluminium chloride-catalysed reactions, respectively (Scheme 46). The secondary orbital interaction between the carbonyl carbon and the diene C-2 is greatly enhanced in the presence of Lewis acid because of the increased coefficient on the carbonyl carbon. For this reason, greater endo selectivity is observed in contrast to the uncatalysed reaction.
Enantioselective Diels-Alder reactions have been successfully mediated in the presence of Lewis acids bearing enantiopure ligands. Complexation with chiral Lewis acids makes the two enantiofaces of the dienophile diastereotopic, which leads to the formation of an unequal mixture of enantiomers. However, in certain cases enantiomerically pure products are obtained.\textsuperscript{101}

The reaction between 2-methyl-2-propenal and cyclopentadiene in the presence of menthylaluminium dichloride (Koga’s reagent) gives the exo-adducts in 72\% e.e. (Scheme 47).\textsuperscript{102}

The use of lanthanide chiral shift reagents such as tris[3-(heptafluoropropyl hydroxymethylene)-(+-)camphorato]europium(III) [Eu(hcf)$_3$], provides only modest enantioselectivity in the Diels-Alder reaction between achiral but prochiral Danishefsky dienes 18 and benzaldehyde (Scheme 48).\textsuperscript{103}
However, the reaction of diene 19 bearing \(l\)-menthoxy as a chiral auxiliary with benzaldehyde in the presence of \((+)-\text{Eu}(hfc)_3\) gives 20 in high diastereoselectivity (Scheme 49). But with achiral \(\text{Eu}(\text{fod})_3\) there is a slightly greater preference for the opposite diastereoisomer 21. This seems to suggest that there is some specific interaction between the menthoxy substituent and the shift reagent in the double asymmetric induction.\(^{104}\)

**Scheme 49**

1. \((+)-\text{Eu}(hfc)_3\)  
2. TFA

19, \(R = l\)-menthyl
Chiral titanium reagents have also successfully been employed in the asymmetric Diels-Alder reactions. For example, the reaction between N-crotonoyl-1,3-oxazolidin-2-one 22 and cyclopentadiene proceeds with catalytic amount of tartrate-derived chiral titanium complex to furnish 23 enantioselectively with 91% ee in the presence of molecular sieves 4Å (Scheme 50).\textsuperscript{105}

\textbf{Scheme 50}

\begin{center}
\includegraphics[width=\textwidth]{Scheme_50.png}
\end{center}

Strikingly, the enantiopure binaphthol-derived aluminium reagent also promotes the hetero Diels-Alder reaction of Danishefsky diene 24 and benzaldehyde to afford the dihydropyrrone with high enantioselectivity (Scheme 51).\textsuperscript{106} Although, in this case the dienophile cannot exhibit the \textit{s-cis} and \textit{s-trans} conformation unlike \(\alpha,\beta\)-unsaturated ketones (see above); coordination is assumed to be \textit{trans} to the phenyl ring of benzaldehyde.\textsuperscript{106} Additionally, by altering the aryl substituents from phenyl to 3,5-dimethylphenyl an increase
in both diastereoselectivity and enantioselectivity is observed.

\[ \text{Scheme 51} \]

\[
\begin{align*}
\text{MeO} & \quad \text{Me} \\
\text{Me} & \quad \text{MeO} \quad \text{SiMe}_3 \\
\text{24} & \quad + \\
\text{O} & \quad \text{Ph} \\
\end{align*}
\]

1. (10 mol%)
   toluene, -20 °C

2. CF\(_3\)CO\(_2\)H

\[
\begin{align*}
\text{Me} & \quad \text{O} \\
\text{Ph} & \quad \text{Me} \\
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{O} \\
\text{Ph} & \quad \text{Me} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ar} = \text{Ph} & \quad 77\% \\
& \quad 95\% \text{ e.e.} \\
\text{Ar} = 3,5-\text{Me}_2\text{C}_6\text{H}_3 & \quad 90\% \\
& \quad 97\% \text{ e.e.} \\
\end{align*}
\]
Recently, a highly enantio- and diastereoselective Diels-Alder reaction has been reported using chiral aluminium reagent, prepared \textit{in situ} by the treatment of enantiopure bis(sulfonamides) 25 with trimethylaluminium or DIBAL-H. The highly enantiomerically enriched bicyclo[2.2.1]heptene derivative 26, an intermediate in prostaglandin synthesis, was isolated in 94% yield (Scheme 52).\textsuperscript{107}

\textbf{Scheme 52}

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{O} \\
\text{Bn} \\
\end{array}
+ \\
\begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{CF}_3\text{SO}_2\text{HN} \\
\text{NH}_2\text{SO}_2\text{CF}_3 \\
\end{array}
\xrightarrow{\text{AlCl}_3, \text{10 mol\%}} \\
\begin{array}{c}
\text{BnO} \\
\text{H} \\
\text{Ph} \\
\text{Ph} \\
\text{26} \\
\end{array}
\]

94% yield, 95% e.e.

Chiral boron reagents have also been examined as catalysts in the asymmetric Diels-Alder reactions. Thus, for instance, anthraquinone derivative 28 is obtained with high enantioselectivity by the use of boron derivative of 3,3'-bis(aryl)binaphthol 27 (Scheme 53).\textsuperscript{108} However, stoichiometric amount of the chiral reagent is needed.
By the use of acyloxyborane 29 obtained from monoacylated (R)-tartaric acid and borane, the Diels-Alder reaction has been accomplished in high enantioselectivity using 2-methyl-2-propenal and cyclopentadiene (Scheme 54). \(^{101b}\)

**Scheme 53**

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{BLn}^* (100 \text{ mol\%}) & \quad \text{AcOH, THF, -78 °C} \\
\end{align*}
\]

By the use of acyloxyborane 29 obtained from monoacylated (R)-tartaric acid and borane, the Diels-Alder reaction has been accomplished in high enantioselectivity using 2-methyl-2-propenal and cyclopentadiene (Scheme 54). \(^{101b}\)

**Scheme 54**

\[
\begin{align*}
\text{Me CHO} & \quad \text{Me} \\
\text{CH}_2\text{Cl}_2, -78 °C & \quad \text{CHO} \\
\end{align*}
\]

96% e.e.
2.3. Sharpless asymmetric epoxidation

In the Sharpless asymmetric epoxidation (SAE) reaction, an achiral allylic alcohol is converted into the corresponding epoxide with high enantioselectivity using titanium (IV) isopropoxide, \( \text{Ti(O}^\text{Pr})_4 \), which coordinates in polydentate fashion, tert-butyl hydroperoxide and an enantiopure diethyl tartrate (Scheme 55). In the presence of molecular sieves, the SAE reaction can be achieved by employing catalytic amounts (10 mol%) of diethyl tartrate and titanium (IV) isopropoxide.

**Scheme 55**

![Scheme 55](image)

L-(+)-diethyl tartrate

Using L-(+)-diethyl tartrate (natural), the oxygen atom is transferred to the bottom face of the olefin when the allylic alcohol is oriented as shown in Scheme 55. By contrast, epoxide formation occurs on the top face of the olefin with the unnatural D-(-)-diethyl tartrate. Since both enantiomers of diethyl tartrate are readily available, this approach leads to just as easily to the formation of one enantiomer of glycidol as to the other.

The Sharpless asymmetric epoxidation reaction is presumed to occur via coordination of diethyl tartrate, tert-butyl hydroperoxide and allylic alcohol to the same titanium atom as illustrated in Scheme 56, epoxidation followed by subsequent decomplexation then leads to tert-butyl alcohol and the product glycidol.
Scheme 56

\[ E = \text{CO}_2\text{Et} \]
Chapter 3

Results and discussion
3.1. Introduction

The carbonyl ene reaction has been thoroughly studied and developed into a reliable methodology. Thus, for example, in its intramolecular variant, citronellal 30 has been found to cyclize by the use of Lewis acids (1 - 20 equiv) to afford predominantly iso-pulegol 31 (Scheme 57);\textsuperscript{110} the ratios of trans- and cis-diastereoisomers vary from 95:5 (ZnI\textsubscript{2}) to 43:57 (SbCl\textsubscript{5}).\textsuperscript{110,111} The methylated homologue 11 reacts in a similar manner (Scheme 3).\textsuperscript{111} A reversal in the sense of diastereoselectivity has been observed (but not explained) for the stoichiometric reaction of citronellal with (Ph\textsubscript{3}P)\textsubscript{3}RhCl, which produced a 1:3 mixture of iso-pulegol 31 and neo-iso-pulegol 32.\textsuperscript{112,113}

![Scheme 57](image)

We have now found that a complex, generated from M(CO)\textsubscript{5}Cl\textsuperscript{-} (M = Mo or W) and bromine is also capable of catalysing the reaction of citronellal (30) to give mainly the cis-diastereoisomer (32) (see below). By contrast, complexes prepared from M(CO)\textsubscript{5}Cl\textsuperscript{-} (M = Mo or W) and silver trifluorosulfonate (TfOAg) afforded Prins-type products. This observation prompted us to carry out a thorough investigation, including the structure elucidation of Mo and W complexes and to prepare a series of model compounds (Scheme 58) to survey the generality of this reaction.
3.2. Preparation of starting materials.

(Z)-6-octen-1-al 33 was synthesized as illustrated in Scheme 59. Reaction of cis-1-bromopropene with Grignard reagent, prepared from 5-bromo-1-tetrahydropyran-1-yl ether 51 and Mg turnings in THF, in the presence of bis-(triphenylphosphine) nickel(II)chloride as a catalyst afforded 52 (67%). Deprotection (52 → 53) with p-toluenesulfonic acid, followed by Swern oxidation produced the desired aldehyde 33 which contained 7% of the (E)-isomer.

Scheme 59

![Scheme 59](image_url)
(E)-6-Octen-1-ol \(34^{116}\) was prepared via a Wittig-Horner type of reaction employed earlier in the synthesis of a pheromone of the Mediterranean Fruit Fly.\(^{117,118}\) Acylation of the lithium salt of ethylidiphenylphosphine oxide \(54^{119}\) with \(\varepsilon\)-caprolactone afforded \(55\) (Scheme 60). Reduction of the carbonyl group in \(55\) gave a mixture of diastereoisomers, from which the \textit{threo}-alcohol \(56\) was isolated in 81\% yield by chromatography. Elimination of \(\text{Ph}_2\text{P}O^2^-\) on treatment with two equivalents of \(\text{NaH}\) produced (E)-6-octen-1-ol \(57\) in a very high yield, which gave the corresponding aldehyde \(34\) on Swern oxidation. The (Z)-isomer \(33\) was found to be absent by GLC analysis.

(Z)-8-(Dimethylphenylsilyl)oct-6-en-1-al \((37)\) was obtained in eight steps from aldehyde \(58^{120}\) which was processed according to a procedure developed by Kishi\(^{121}\) to furnish acetylenic ester \(59\) (Scheme 61) in 75\% overall yield. Lindlar hydrogenation of the acetylene bond followed by reduction of the resulting ester \(60\) with DIBAL-H afforded the allylic alcohol \(61\). The corresponding acetate \(62\) gave allylsilane \(64\) on reaction with organosilicon cuprate followed by methanolysis of the tetrahydropyranyl protecting group. Oxidation of alcohol \(64\) with chromium trioxide-dipyridine complex\(^{122}\) in dichloromethane furnished \(37\).
Scheme 61: 

- **a**, Zn dust, CBr₄, PPh₃;  
- **b**, n-BuLi, ClCO₂Me  
- **c**, H₂, Lindlar catalyst;  
- **d**, DIBAL-H, 2 equiv;  
- **e**, Ac₂O, py  
- **f**, (PhMe₂Si)₂CuLi;  
- **g**, p-TsOH

58

**Scheme 61:**

- **a**, Zn dust, CBr₄, PPh₃;  
- **b**, n-BuLi, ClCO₂Me  
- **c**, H₂, Lindlar catalyst;  
- **d**, DIBAL-H, 2 equiv;  
- **e**, Ac₂O, py  
- **f**, (PhMe₂Si)₂CuLi;  
- **g**, p-TsOH

58

- **Collins oxidation**

61, X = CH₂OH
62, X = CH₂OAc
63, X = CH₂SiMe₂Ph

58

- **reflux**

65

- **Collins oxidation**

66, X = CH₂OH
67, X = CH₂OAc
68, X = CH₂SiMe₂Ph
(E)-8-(Dimethylphenylsilyl)oct-6-en-1-al (38) was synthesised in a similar manner. Olefination of 58 with the stabilised Wittig reagent (carbethoxymethylene)triphenylphosphorane furnished the unsaturated ester 65 (97:3) in almost quantitative yield, which was subsequently reduced with DIBAL-H to furnish allylic alcohol (66). Acetylation (56 → 57), followed by allylic substitution (67 → 68), deprotection (68 → 69) and Collins oxidation as previously described for the synthesis of the (Z)-isomer (37) then gave 38.

Scheme 62

(Z)- and (E)-6-nonen-1-al 35 and 36 were prepared from the corresponding commercially available cis- and trans-6-hexen-1-ol in a similar manner to (E)-7-Trimethylsilyloct-6-en-1-al 41. Homoallylic alcohol 73 was stereoselectively synthesized in 95% yield via a Ni°-catalysed coupling of MeMgBr with 5-trimethylsilyl-2,3-dihydrofuran 72 (Scheme 62).
Mesylation followed by a Finkelstein reaction (NaI, acetone, 75 °C) produced iodide 74. The corresponding copper derivative 75,124 generated by the slow addition of a THF solution of the iodide 74 to an excess of activated124,125 zinc (2.5 equiv) at 30 °C followed by transmetallation with CuCN.2LiCl126 (0.86 equiv, 0 °C, 10 min), was treated with acrolein to afford 41 in 75% isolated yield.

Ethyl 3,7-dimethyl-1-oxo-6(E)-octenoate 42127 was synthesized from aldehyde 76, which in turn was obtained from citronellol following a literature procedure128 involving ozonization of O-benzyl citronellol (Scheme 63). Wittig reaction between ethyl 2-(triphenylphosphoranylidene)propionate and 76 furnished (E)-ester 77 (95:5) which was subsequently deprotected129 using trimethylsilyl iodide to produce alcohol 78. The corresponding aldehyde 42 was obtained upon Swern oxidation.

Scheme 63

![Scheme 63](image)

Ethyl 4-[N-(3′-methylbut-2′-enyl)amino]but-2(E)-enoate (43)130 was obtained on alkylation of 1-amino-3-methylbut-2-ene131 with commercially available trans-ethyl 4-bromocrotonate in 69% yield (Scheme 64).
Scheme 64

[N-(4-methylpent-3-enyl)methyl]ethanalamine (44). Sarcosine methyl ester hydrochloride was alkylated with 1-bromo-4-methylpent-3-ene (79) in the presence of catalytic amounts of sodium iodide to afford 80 in 93% isolated yield (Scheme 65). Reduction of the ester (80) with lithium aluminium hydride gave the corresponding alcohol (81), which on Swern oxidation produced the desired aldehyde (44).

Scheme 65
7-Methyl-3-oxa-6-octenal \( \text{45}^{133} \) and 2-[(3'-methyl-2'-butenyl)oxy]benzaldehyde \( \text{46}^{134} \) were also successfully prepared. The synthesis of the latter substrate began with commercially available 2-bromophenol (Scheme 66), reaction of which with 3-methyl-2-buten-1-ol in the presence of triphenylphosphine and diethyl azodicarboxylate (Et\(_2\)CN=NC\(_2\)Et) afforded isoprenyl ether \( \text{82} \) (94\%).\(^{135} \) Metallation of the latter intermediate in THF at -70 °C with an excess of \( \text{n-BuLi} \) resulted in a lemon-yellow solution and, when treated with \( \text{N,N-dimethylformamide (DMF)} \), furnished the desired aldehyde \( \text{46} \) in 74\% yield.

**Scheme 66**

![Scheme 66](image)

3-(3-Methoxyphenyl)propanal (\( \text{47}^{136} \)) was conveniently obtained from the readily available carboxylic acid \( \text{83} \) (Scheme 67): treatment with borane-dimethyl sulfide gave the corresponding trialkoxyboroxine, which was subsequently oxidised with pyridinium chlorochromate (PCC) to produce the required aldehyde \( \text{47} \) (64\% yield).
Scheme 67

6-Octyn-1-ol (48) was synthesized from dibromoolefin (58a) (see above) which was obtained in 92% yield by the addition of 6-(tetrahydro-2′-pyranyloxy)hexanal to a reagent prepared from interaction of zinc dust (2 equiv), triphenylphosphine (2 equiv), and carbontetrabromide (2 equiv) in dichloromethane at 23 °C for 24-30 h. Reaction of the dibromide 58a with 2 equiv of n-BuLi in tetrahydrofuran at -78 °C for 30 min, resulted in the formation of the lithio derivative of 58a, which was treated with a solution of methyl iodide in hexamethylphosphoramide (HMPT) to yield acetylene 84 (87%) (Scheme 68). Deprotection (84 → 85), followed by Swern oxidation furnished aldehyde 48.

Scheme 68: THP = tetrahydropyranyl

---

56
As outlined in Scheme 69, our approach to the synthesis of 4,8-dimethylnon-7-enal (49) began with commercially available citronellol 86. Thus, on treatment with p-toluenesulfonyl chloride a solution of alcohol 86 in pyridine gave the corresponding tosylate 87, which on substitution by cyanide (87 → 88), and then reduction with diisobutylaluminium hydride (DIBAL-H) produced aldehyde 49 in 76% yield.

Scheme 69
3.3. Preparation of Group 6 metal complexes

In the search for new Group 6 metal catalysts, we strived to generate Lewis-acidic, carbonyl complexes of Mo and W bearing a weakly coordinating anion, such as triflate (TfO⁻), in their coordination sphere. We reasoned that such complexes could be prepared from the halopentacarbonylmetalate(0) salts [M(CO)₅X]⁺, whose halogen atom (X) could be substituted by the required anion on treatment with the corresponding silver(I) salt.

The desired chloromolybdate and chlorotungstate complexes I and II were synthesized according to a literature procedure i.e. by heating the corresponding metal carbonyls with benzyltriethylammonium chloride in diglyme at 120 °C (Scheme 70). The reaction can also be achieved in refluxing DME at 80 °C. However, in this case both the ammonium salt and the solvent need to be dry (see below). Similar [Ph₃P=N=PPh₃]⁺ salts (PPN) III and IV were obtained in an analogous way. The structure of these complexes was substantiated by comparison of their data with those described in literature for analogous complexes. Thus, for example, in accordance with the data published by other authors, the Mo-complex I exhibited four carbonyl vibrations in the IR spectrum [at 1853 (s), 1926 (vs), 1982 (w), and 2061 (w) cm⁻¹; in CH₂Cl₂]. The complexes II - IV, generated in a similar manner, displayed analogous characteristics. However, using wet BnEt₃ N⁺ Cl⁻ the reaction of Mo(CO)₆ took an alternative course when carried out in DME (but not in diglyme). Thus, a sparingly soluble salt was obtained instead of the formation of the soluble complex I, which showed distinct carbonyl bands at 1723 (s), 1741 (s), 1782 (w), and 1887 (w) cm⁻¹ in the IR spectrum (in KBr), the first three vibrations being indicative of the presence of bridged carbonyl substituent(s). The ¹H NMR spectrum (in DMSO-d₆) exhibited a signal for water (singlet at 3.49 ppm exchangeable with D₂O), that was in ca 1:1 ratio to the PhCH₂ signal. Furthermore, a broad peak at 3260-3500 cm⁻¹ in the IR spectrum (in KBr or nujol), clearly suggested the presence of water which is in accord with the behavior of related aqua complexes. Elemental analysis (C, H, N, Mo) was in good agreement with the proposed formula V. The latter complex, on consumption with MeCN, afforded a new, sparingly soluble material, whose IR spectrum (in KBr) showed four carbonyl bands that were very close to those of I:
1866 (s), 1920 (s), 1977 (w), and 2064 (w) cm\(^{-1}\). Apparently, it seems that the original polymeric structure is broken up by coordination with the solvent to furnish I (or a related species). The tungsten complex prepared in the same way using wet BnEt\(_3\)N\(+\)Cl\(^-\), showed similar spectral characteristics compatible with the structure VI. However, the elemental analysis did not fit the proposed formula as well as that for V, suggesting contamination by another species. Again, the same effect was observed for V on consumption with MeCN.

**Scheme 70**: Bn = PhCH\(_2\); PNP\(^+\) = [Ph\(_3\)P=N=PPh\(_3\)]\(^+\); M = Mo or W

\[
\text{BnEt}_3\text{N}^+\text{Cl}^- + \text{M(CO)}_6 \xrightarrow{\text{heat, diglyme}} \text{BnEt}_3\text{N}^+\text{[M(CO)}_5\text{Cl}]^- + \text{CO}
\]
I, M = Mo  
II, M = W

\[
(PNP)^+\text{Cl}^- + \text{M(CO)}_6 \xrightarrow{\text{heat, diglyme}} (PNP)^+\text{[M(CO)}_5\text{Cl}]^- + \text{CO}
\]
III, M = Mo  
IV, M = W

\[
\text{BnEt}_3\text{N}^+\text{Cl}^- + \text{M(CO)}_6 \xrightarrow{\text{heat, DME, H}_2\text{O}} \{(\text{BnEt}_3\text{N})_4\text{[M}_3\text{(CO)}_9\text{Cl}_4\}.3\text{H}_2\text{O}\}_n + \text{CO}
\]
V, M = Mo  
VI, M = W

**3.3.1. Treatment of the Complexes I - IV with Silver(I)**

Reaction of the zero valent halopentacarbonyl metalate halides R\(_4\)N\(^+\)[M(CO)\(_5\)X\(^-\)] with silver(I) or thallium(I) carboxylates has been found to provide the expected carboxylate complexes R\(_4\)N\(^+\)[M(CO)\(_5\)(O\(_2\)CR)]\(^-\) and the AgCl precipitate (M = Mo, W);\(^{144}\) silver tosylate is also reported to react in a similar way.\(^{144}\) By contrast, we have discovered that silver trifluorosulfonate (TfOAg) behaves quite differently. Thus, reaction of I with 1 equiv. of TfOAg results in the formation of a white precipitate of AgCl (in DME), whereas the addition of an excess of TfOAg mainly affords a grey suspension of Ag(0).\(^{149}\) Similarly, the tungsten complex II reacted in an analogous manner.
The reactions between the complexes I - IV and TfOAg were monitored by electrochemical methods. Thus, results of the cyclic voltammograms for the starting Mo and W halopentacarbonyl complexes I - IV were in accord with those described by Bond,\textsuperscript{150}: all samples indicated an irreversible, one-electron transfer process at about +0.7 V using \( \text{Bu}_4\text{N}^+\text{[M(CO)\(_X\)\text{X}]}^+ \).\textsuperscript{151} The reaction of TfOAg with each of the complexes I - IV was examined by cyclic voltammetry (see below). Strikingly, the reactions were greatly influenced by the type of the quaternary ammonium counterion and the polarity of the solvent in which the reaction was conducted.

3.3.2. Treatment of \([\text{W(CO)}\(_5\)\text{Cl}]^-\) with TfOAg in Dimethoxyethane

The parent benzyltriethylammonium complex \( \text{BnEt}_3\text{N}^+\text{[W(CO)}\(_5\)\text{Cl}]^- \) (II) exhibits three oxidation processes on a sweep from 0 to +2 V (Figure 1a), that can be presumed to correspond to the oxidation of II to the W\(^I\), W\(^{II}\), and W\(^{III}\) states, respectively. The former two processes are irreversible and can be ascribed to the electrochemical reactions reported by Bond;\textsuperscript{150} while the latter process is found to be quasi reversible.

The addition of one equiv. of TfOAg resulted in an instantaneous formation of a predominantly white precipitate upon reaction with II (in DME) and altered the voltammogram of the solution as shown in Figure 1b (full line). It is pertinent to note that no signal was observed for Ag\(^+\) ions, in the reaction with II, which indicates that they were removed from the solution. Furthermore, the observed signal for the oxidation of W\(^0\) to W\(^I\) did not stay constant, suggesting that some of the complex had undergone oxidation. This result can be explained by assuming that two reactions proceed simultaneously (eq. 1 and 2). Apparently, the major process 1 can also be succeeded by oxidation of the corresponding triflate complex (eq 3),\textsuperscript{152} provided the latter reaction undergoes with a comparable rate.

\begin{align*}
[\text{W}^0\text{(CO)}\(_5\)\text{Cl}]^- + \text{TfOAg} & \rightarrow [\text{W}^0\text{(CO)}\(_5\)\text{OTf}]^- + \text{AgCl} \downarrow \quad (1) \\
[\text{W}^0\text{(CO)}\(_5\)\text{Cl}]^- + \text{TfOAg} & \rightarrow \text{W}^I\text{(CO)}\(_5\)\text{Cl} + \text{TfO}^- + \text{Ag}^0 \downarrow \quad (2) \\
[\text{W}^0\text{(CO)}\(_5\)\text{OTf}]^- + \text{Ag}^+ & \rightarrow \text{W}^I\text{(CO)}\(_5\)\text{OTf} + \text{Ag}^0 \downarrow \quad (3)
\end{align*}
Figure 1. Elucidation of the reaction of complex II with TfOAg in DME by cyclic voltammetry. (a) Voltammogram of the parent complex II. (b) Voltammogram of II after addition of the 1st equiv of TfOAg (full line) and 80 seconds later (dashed line). (c) Voltammogram after addition of the 2nd equiv of TfOAg. (d) Voltammogram after addition of the 3rd equiv of TfOAg.
The cyclic voltammetry signal for the oxidation of $\text{W}^1 \rightarrow \text{W}^\text{II}$ gradually decreased with time, while that for $\text{W}^0 \rightarrow \text{W}^1$ has been found to increase (Figure 1b; dashed line). This is clearly suggestive of a disproportionation\textsuperscript{150} process that can be assumed to occur as indicated in eq 4. The kinetics of this disproportionation correspond to an expected 2nd order process with the rate constant 1.87 mol\textsuperscript{-1}dm\textsuperscript{3}s\textsuperscript{-1} at 20 °C. Thus, the disproportionation is fairly slow ($\tau/2 \sim 3$ min), which suggests that at least 5% of this species should still remain after 30 min at rt, so that it could be examined by ESR spectroscopy (see below).

$$2[\text{W}^1(\text{CO})_5\text{OTf}] \rightarrow [\text{W}^\text{II}(\text{CO})_5(\text{OTf})]^+ + [\text{W}^0(\text{CO})_5(\text{OTf})]^-$$(4)

The addition of two equivs of TfOAg led to the formation of a grey precipitate and to a decrease of the current corresponding to the oxidation of $\text{W}^0 \rightarrow \text{W}^1$ and $\text{W}^1 \rightarrow \text{W}^{1\text{I}}$ was observed in the cyclic voltammogram (Figure 1c). This behavior indicates that reaction 1 occurs preferentially on addition of first equiv. and reaction 3 proceeds when the second equiv. is added. Moreover, treatment with second equiv. of TfOAg would also lead to the substitution of Cl\textsuperscript{-} in $\text{W}^1(\text{CO})_5\text{Cl}$ (formed in the reaction 2) by TfO\textsuperscript{-}. If we consider that each step occurs quantitatively and no other, undetected side-reactions proceed, 1 equiv of II would give 0.5 equiv. of $[\text{W}^\text{II}(\text{CO})_5(\text{OTf})]^+$ and 0.5 equiv. of $[\text{W}^0(\text{CO})_5(\text{OTf})]^-$, using up 2 equivs of TfOAg. Another equiv. of TfOAg would be required for the oxidation of the latter species. Therefore, in total 3 equivs of TfOAg will be needed for the complete oxidation of $\text{W}^0$ to $\text{W}^\text{II}$. Addition of a third equiv of TfOAg led to the distinctive deposition and stripping peaks in the voltammogram (Figure 1d). The latter features correspond to the electrochemical reduction of Ag\textsuperscript{1} to Ag\textsuperscript{0} (eq 5), indicating that there is an excess of Ag\textsuperscript{+} in the solution and the reaction is complete.

$$\text{Ag}^+ + e^- \rightleftharpoons \text{Ag}^0$$ (5)

The ESR spectrum, acquired at 77K for the DME solution of the complex prepared from II and 1 equiv of TfOAg, exhibited a broad, weak feature with $g_{\parallel} = 1.801$ and $g_{\perp} = 1.764$
(species A). By the use of 2 equiv of TfOAg, the spectrum (Figure 2) became much stronger and better resolved but with the central feature shifted to $g_{\parallel} = 1.963$ and $g_{\perp} = 1.932$ (species B). The $^{183}$W isotope, which has a nuclear spin of 1/2 and natural abundance of 14.28%, showed weak satellite lines with hyperfine couplings of $A_{\parallel} = 188$ G and $A_{\perp} = 125$ G. A trace of signal associated with species A was also observed. The structure $W^1(CO)_5OTf$ (see eq 3) is proposed for the species B, whereas the species A, could arise via a minor reaction of the original complex with the 1st equiv of Ag$, [for which the structure $W^1(CO)_5Cl$ is assumed (eq 2)]. Both the major and minor products (eq 1 and 2) are then converted (via oxidation or halogen exchange, respectively) to the same species B by the reaction with second equivalent of TfOAg. Furthermore, the absence of the species B after the addition of the first equiv of TfOAg clearly indicates that the process 3 does not compete with either reactions 1 or 2.

Theoretically, the stoichiometry of the whole process would need exactly 3 equivs of TfOAg. However, the above experiments suggest that, to drive the reaction to completion, slightly less than 3 equivs are sufficient. This observation can be ascribed to a non-quantitative conversion in some of the transformation(s), presumably due to undetected side-reaction(s).

Substitution of BnEt$_3$N$^+$ by (PPN)$^+$ as the counterion had a remarkable effect on the reaction of the complex with TfOAg. The cyclic voltammogram for a DME solution of IV, prior to the addition of TfOAg, was analogous to that obtained for the BnEt$_3$N$^+$ complex II. However, in this case no signal associated with the oxidation of W$^\text{II}$ to W$^\text{III}$ was detected (Figure 3; full line). The addition of one equiv. of TfOAg resulted in the deposition of a grey precipitate and suppression of peaks corresponding to W$^0$ to W$^1$ transition (Figure 3; dashed line). Moreover, little or no disproportionation was subsequently observed. After the addition of a second equiv. of TfOAg to this solution, a sharp decrease of the current associated with the reduction of Ag$^+$ was observed (Figure 3; dotted line), indicating that the reaction had gone to completion. This behaviour suggests that reaction 2 occurs in preference to 1.
Figure 2. ESR spectrum of $\text{W}^{\dagger}(\text{CO})_3\text{OTf}$ in DME.
Figure 3. Elucidation of the reaction of complex IV with TfOAg in DME by cyclic voltammetry.

- - - - Voltammogram of the parent complex IV.

----- Voltammogram of IV after addition of the 1st equiv of TfOAg

---------- Voltammogram after addition of the 2nd equiv of TfOAg.
It can be considered that the difference in the reactivity of these two complexes toward TfOAg is due to the interaction of ions in DME, which is a medium of relatively low polarity. Recently, it has been shown that small anions can fit into the pockets of bulky quaternary ammonium anions, resulting in the formation of a "penetrating ion pair". The (PPN)$^+$ ion has a cavity between the phenyl substituents into which the [W(CO)$_5$Cl]$^-$ ion could penetrate. The firm association between these two ions would prevent the replacement of Cl$^-$ by TfO$^-$ ligands. Thus, the role of TfOAg is only to oxidize the [W(CO)$_5$Cl]$^-$ anion as in reaction 2. The latter oxidation reinforces the W-Cl bond, thereby further inhibiting the ligand substitution. By contrast, the BnEt$_3$N$^+$ cation, which does not possess such a cavity, allows the exchange to take place between Cl$^-$ and TfO$^-$ ligand.

3.3.3. Treatment of [Mo(CO)$_5$Cl]$^-$ with TfOAg in Dimethoxyethane

The effect of the Mo(0) complexes I and III was similar to that for their W(0) analogues II and IV, respectively, which suggests that the characteristics of these species is independent of the metal core. In analogy with the tungsten complex, the ESR spectrum of the solution prepared by the addition of 1 equiv of TfOAg to I showed a broad weak feature with $g_{||} = 1.911$ and $g_{\perp} = 1.881$ flanked by very weak satellite lines. Upon addition of 2 equiv of TfOAg, the spectrum (Figure 4) became much stronger and better resolved with the same central feature and satellite lines, associated with $^{95,97}$Mo isotopes that have a nuclear spin of 5/2 and a combined natural abundance of 25.35%. These hyperfine couplings were $A_{||} = 84$ G and $A_{\perp} = 40$ G. This spectrum can be ascribed to the Mo(CO)$_5$OTf species.
Figure 4. ESR spectrum of Mo\(\text{I}(\text{CO})_5\text{OTf}\) in DME.
3.3.4. Treatment of [W(CO)₅Cl]⁻ and [Mo(CO)₅Cl]⁻ with TfOAg in Acetonitrile

We assumed that increasing the polarity of the solvent would result in reduction of the degree of association between the complex anion and (PPN)⁺ (see below). Hence, acetonitrile, that has a greater relative permittivity (ε = 35.9) than DME (ε = 7.2),¹⁴ was chosen to test this reasoning.

In acetonitrile, all of the complexes (I - IV) showed the same electrochemical behaviour, irrespective of the metal core or the quaternary ammonium counterion. A white precipitate of AgCl was observed on the addition of first equiv. of TfOAg in each case; on addition of the second equiv a grey precipitate was then formed. These observations indicate that reaction 1 is the dominant process. Furthermore, the absence of any disproportionation signal shows that the chemical reaction, in which M(CO)₅OTf species furnishes the new complex, is dramatically accelerated in MeCN in comparison with DME.

3.3.5. Treatment of V and VI with TfOAg in Dimethoxyethane

Addition of the first equiv. of TfOAg to the yellow-grey suspension of V in DME resulted in deposition of a black precipitate of Ag(0). No visual change was observed on addition of the second and third equiv. Apparently, reactions analogous to eq. 1 - 4 take place again. The new complex, presumably containing Mo(II), remained sparingly soluble. The tungsten complex VI exhibited the same behavior.
3.3.6 Summary of the preparation of Mo and W complexes

Elucidation of the reaction between TfOAg and each of complexes I - IV by cyclic voltammetry and ESR spectroscopy, indicates that complex redox processes occur in combination with chloride exchange. The M(0) species undergoes oxidation to afford M(I), which then disproportionates to produce the more stable M(II) complex. The reaction of tetraalkylammonium complexes I and II, proceeds contemporaneously with the exchange of chloride anion by TfO⁻ ligand. By contrast, the latter reaction is precluded for the PPN complexes III and IV, presumably due to strong interaction of the counterion. However, this interaction can be overcome by the use of MeCN in place of DME as the solvent, which allows the substitution of Cl⁻ to occur. Attempted preparation of I and II in DME in the presence of a small amount of water took a different course, giving polymeric material, for which structures V and VI are proposed, respectively. The catalytic activity of M(II) complexes generated from I, II, V, and VI is described below.
3.4. Catalytic activity of the Mo(II) and W(II) complexes

In the presence of PhCH₂(Et)₃N⁺[Mo(CO)₄ClBr₂]⁺ (complex VII) (5 mol%), generated on bromination of V via a known procedure, citronellal 30 (rt, 24 h), gave a mixture of 31 and 32 in 25:75 ratio, from which neo-iso-pulegol 32 was isolated in 68% yield (Scheme 71). The tungsten analogue exhibited similar reactivity. The complexes prepared from I and II in an analogous manner are capable of catalysing the same reaction; although, their activity is somewhat lower.

Scheme 71: VII = BnEt₃N⁺[Mo(CO)₄ClBr₂]⁺; VIII = Mo(CO)₅(OTf)₂

<table>
<thead>
<tr>
<th>reagent</th>
<th>trans : cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>L.A.</td>
<td>≤ 95 : 5</td>
</tr>
<tr>
<td>Rh</td>
<td>1 : 3</td>
</tr>
<tr>
<td>VII</td>
<td>25 : 75</td>
</tr>
<tr>
<td>VIII</td>
<td>20 : 80</td>
</tr>
</tbody>
</table>

By contrast, complexes of the type M(CO)₅(OTf)₂ (M = Mo or W) obtained from V and VI and 3 equivs of TfOAg (see above) afforded the major cis-diol 90 with a significant preference for cis-configuration at the newly formed vicinal centers of chirality (4:1). Again, the complexes generated from I and II reacted sluggishly. However, the PPN complexes, obtained from III and IV and TfOAg (in DME) proved inert, which suggests that the replacement of Cl⁻ ligand by TfO⁻ is crucial for catalytic activity.

The cyclization of citronellal 30 was also investigated with other complexes prepared from V and VI in the same way (Table 1).
<table>
<thead>
<tr>
<th>entry</th>
<th>complex (amount)</th>
<th>temp (°C)</th>
<th>time</th>
<th>cis/trans ratio</th>
<th>isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>VII (1 equiv)</td>
<td>20</td>
<td>1.5 h</td>
<td>50 : 50 a</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>VII (5 mol%)</td>
<td>20</td>
<td>24 h</td>
<td>75 : 25 a</td>
<td>79 d</td>
</tr>
<tr>
<td>3</td>
<td>VIII (1 equiv)</td>
<td>20</td>
<td>2 h</td>
<td>50 : 50 a</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>VIII (5 mol%)</td>
<td>20</td>
<td>2 h</td>
<td>49 : 51 a</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>IX (1 equiv)</td>
<td>20</td>
<td>24 h</td>
<td>78 : 22 a</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>IX (10 mol%)</td>
<td>20</td>
<td>3 h</td>
<td>80 : 20 b</td>
<td>84 e</td>
</tr>
<tr>
<td>7</td>
<td>X (1 equiv)</td>
<td>20</td>
<td>30 min</td>
<td>46 : 54 a</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>X (10 mol %)</td>
<td>20</td>
<td>1.5 h</td>
<td>48 : 52</td>
<td>91</td>
</tr>
<tr>
<td>9</td>
<td>XI (1 equiv)</td>
<td>-40</td>
<td>3 h</td>
<td>84 : 16 b,c</td>
<td>89 f</td>
</tr>
<tr>
<td>10</td>
<td>XI (10 mol %)</td>
<td>20</td>
<td>30 min</td>
<td>76 : 24 a</td>
<td>93 g</td>
</tr>
<tr>
<td>11</td>
<td>XI (1 mol %)</td>
<td>80</td>
<td>10 min</td>
<td>63 : 37 a</td>
<td>96 h</td>
</tr>
<tr>
<td>12</td>
<td>XII (1 equiv)</td>
<td>20</td>
<td>30 min</td>
<td>56 : 44 a</td>
<td>91 i</td>
</tr>
<tr>
<td>13</td>
<td>XII (5 mol%)</td>
<td>20</td>
<td>1 h</td>
<td>50 : 50 a</td>
<td>88</td>
</tr>
<tr>
<td>14</td>
<td>XIII (1 equiv)</td>
<td>20</td>
<td>24 h</td>
<td>78 : 22 a</td>
<td>100</td>
</tr>
</tbody>
</table>

* Determined by NMR. ** Determined by GC. ** NMR gave 88 : 12 ratio.

d 68% cis and 11% trans. e 67% cis and 17% trans. f 80% cis and 9% trans.

g 71% cis and 22% trans. h 62% cis and 36% trans. i 51% cis and 40% trans.
Surprisingly, 3-methylcitronellal 11 (see above) reacted very sluggishly, whereas both cis- and trans-6-octen-1-ol 33 and 34 were unreactive even if stoichiometric amounts of VII and VIII were used. Furthermore, aldehydes 35 and 36 also proved inert, whereas cyclizability on treatment with 1 equiv of Me₂AlCl for 2 h at 0 °C has been reported to afford exclusively (E)-cis-2-(1-propenyl)cyclohexan-1-ol 91 from 35 and mainly the trans-isomer 92 from 36 (Scheme 72). Thus, we envisioned activating the less reactive 1,2-disubstituted double bond by introducing an allylic silane moiety.

(Z)-8-(dimethylphenylsilyl)-6-octen-1-ol (37) was catalytically cyclized in the presence of either VII or VIII (5 mol%) to afford a mixture of products 93 and 94 in a 90:10 ratio respectively. Similarly, the (E)-isomer 38 also gave the same two products (36:64); however, in this case much lower stereoselectivity was observed. Note, that in each case the latter complex of the two was found to be more efficient catalyst.
For the cyclization of the (Z)-isomer 37, the formation of the predominant cis-product 93 can be rationalized by the syn-synclinal transition state 95 (Scheme 73), with the silicon bearing methylene syn disposed to the carbonyl oxygen, which is considered to be the most favourable conformer among the number of accessible synclinal geometries enroute to product 93. The increased population of the transition state 95 can be attributed to secondary orbital interaction i.e., the LUMO of the carbonyl interacts with the HOMO of the terminal carbon of the allylsilane which results in lowering of energy by secondary orbital overlap. On the other hand, trans-product 94 results from anti-synclinal transition state (96); here the silicon bearing methylene is anti to the carbonyl oxygen and thus cannot benefit from secondary orbital overlap stabilization.

Similarly, with (E)-8-(dimethylphenylsilyl)oct-6-enal (38), transition state 97 would be expected to benefit from stabilization through secondary orbital interaction leading to the major trans-product 94, which is in accord with our results.

Scheme 73
In order to further elucidate the scope of these reactions the effect of the double bond was studied. Thus, 5-methyl-5-hexen-1-al (39) (a type II ene reaction substrate), which was synthesized by Wittig olefination of commercially available ethyl 4-acetylbutyrate, followed by ester reduction with DIBAL-H, and 40, which was obtained from ethyl 3-(2-oxocyclohexyl)propionate in a similar manner, are readily cyclized on treatment with either complexes VII or VIII as illustrated (Scheme 74). The regioselectivity for the cyclization of aldehyde 39 can be controlled by the choice of catalysts. On treatment with VII (5 mol%), 40 gave two bicyclic products 101 and 102 in a ratio of 83:17 respectively, whose proton and $^{13}$C NMR spectra were identical with literature values. However, essentially no regio-control was observed with complex VIII.

**Scheme 74:** VII = BnEt$_3$N$^+$[Mo(CO)$_4$ClBr$_2$]; VIII = Mo(CO)$_5$(OTf)$_2$
In the next stage, we examined a number of other model compounds (Scheme 75) to ascertain the reactivity pattern of complexes VII and VIII, and to investigate the effect of the length of the carbon chain on the stereoselectivity of the reaction. However, substrates 41, 42, 48 and 49 including the hetero- and aromatic aldehydes 43, 44, 45, 46 and 47 proved inert under various reaction conditions even if a stoichiometric amount of either reagents was used.

Scheme 75
On the other hand, when 2,6-dimethyl-5-hepten-1-al (50), a one-carbon-fewer analog of 30 (see above), was treated with stoichiometric amounts of complex VII, only trans-product 103 was isolated in 73% yield (Scheme 76).\textsuperscript{180} The configuration assignment was based on the NOE difference of 2.19% and 1.54% observed between 1-CHOH and 5-CH\textsubscript{2}CH\textsubscript{3}, and 2-H and 5-CH\textsubscript{2}CH\textsubscript{3} respectively. By contrast, VIII (1 equiv) surprisingly afforded 104. The configuration of secondary alcohol and isopropenyl groups in product 104 was not determined.

![Scheme 76](image)

3.4. Mechanism of the carbonyl-ene and Prins reactions

Several reaction mechanisms can be suggested to rationalize the Mo-catalyzed cyclization of 30 (Scheme 77). Thus, since the reaction gives rise either to an olefin (32) or a tertiary alcohol (90), a carbocationic intermediate 106a can be envisaged.\textsuperscript{181} On the other hand, concerted or semi-concerted processes, involving 105a or 107a, can also be considered. However, the greater preference for the cis-products seems to suggest a template effect, i.e., the C-C bond formation occurring in the coordination sphere of the metal (108 $\rightarrow$ 109),\textsuperscript{182}
both β-elimination (109 → 32) and hydration (110 → 90) appear to be viable pathways. In the former reaction, the required β-H would be available from either methyl group, so that the elimination step may not be selective. By contrast, the hydration (via 110) should be stereospecific, i.e., the reaction should proceed as an overall syn-addition across the C=C bond. Similar considerations can be applied to the other pathways: thus, an overall anti-addition would result if the reaction proceeded via 107a, whereas a lack of, or little stereodifferentiation can be assumed for quenching the carbocation 106a; the ene-product should be formed by a regioselective deprotonation via 105a.

Scheme 77: a, R = CH₃; b, R = CD₃

This analysis suggests that the mechanistic issues can be addressed by isotopic labelling, namely via replacement of one of the olefinic methyls by a CD₃ group. Hence, the required (E)- and (Z)-d₃-citronellal were synthesised.
3.4.1. Preparation of (E) and (Z)-d$_3$-citronellal

(E)-[8,8,8-$^2$H$_3$]-3,7-dimethyl-6-octen-1-al (111) was obtained from (E)-ester 77, which in turn was readily synthesised from commercially available citronellol following a literature procedure (see above). The unsaturated ester (77) was reduced with LiAl$_2$H$_4$ to furnish deuterated alcohol 112 (Scheme 78). The corresponding chloride (113) was prepared via allylic substitution (OH → Cl), and reduced with LiAl$_2$H$_4$ to the $d_3$-compound 114. Reductive cleavage of the benzyl group was cleanly accomplished with lithium in ammonia at -78 °C and the resulting alcohol 115 was subjected to Swern oxidation to afford the desired aldehyde 111.

(Z)-[8,8,8-$^2$H$_3$]-3,7-dimethyl-6-octen-1-al (116) was prepared from 6-(benzyloxy)-4-methylhexanal (76) which was transformed via a procedure known as the Schlosser modification of the Wittig reaction to afford the allylic alcohol 117 (93:7) (45% yield). On treatment with active MnO$_2$ in the presence of NaCN and MeOH, alcohol 117 was converted into methyl (Z)-2,6-dimethyl-8-benzyloxy-2-octenoate (118) in 48% yield, and subsequently to aldehyde 116 via procedures previously described for the preparation of 111.
Scheme 78: a, LiAl₂H₄; b, NCS, Me₂S; c, Li, NH₃;
d, Ph₃P=CHCH₃, then BuLi, CH₂O;
e, MnO₂, NaCN, MeOH

\[ 77 \xrightarrow{a,b,a} 112, X = C₂H₂OH \]
\[ 113, X = C₂HCl \]
\[ 114, X = C₂H₃ \]
3.4.2. Cyclization of (E) and (Z)-d$_3$-citronellal

Treatment of the stereospecifically labeled d$_3$-citronellal 111 with VIII (5 mol%) gave the expected cis-diol 123 as an 85:15 mixture of the C-8 epimers$^{188}$ (Scheme 79). In order to determine the configuration at C-8, 123 was converted into the conformationally fixed carbonate 124. In the $^1$H NMR spectrum of its non-deuterated counterpart 125, the geminal methyls appeared as singlets at 1.38 (equatorial CH$_3$) and 1.51 (axial CH$_3$) ppm, respectively. The latter substituent showed a significant NOE with 3-H, and the same effect was observed for 124; also, the singlet at 1.38 ppm was substantially reduced in the spectrum of 124 (giving, again, an 85:15 epimeric ratio). Therefore, the configuration at C-8 in 124 and 125 must be ($S^*$), which is consistent with anti-addition across the C=C bond (107b).

**Scheme 79**

In the carbonyl-ene cyclization (30 $\rightarrow$ 32), the deprotonation occurs from CH$_3$ and CD$_3$ in a 70:30 ratio (i.e., preferentially via 105b), as revealed by the relative intensities of the signals corresponding to the vinylic and CHOH protons in the $^1$H NMR spectrum of the
product. This ratio mainly reflects the kinetic isotope effect as shown by comparison with the reactivity of the (Z)-isomer of 111, which gave a 64:36 mixture. With less bulky reagents, a proton is removed selectively from MeE of citronellal (30 → 31).111b

These experiments indicate that both VII and VIII act mainly as Lewis acids so that Mo should form an η1-complex with the usual trans-geometry189 of the C=O bond. Two chair-like transition states (Scheme 80), 126 and 127, can be envisaged, of which the latter, having an axial O[M] group, appears to exhibit greater A1,3-strain. However, the magnitude of A1,3-strain is apparently dependent on the Lewis acid, with the relatively small reagents (ZnCl2, AlCl3, BF3, etc.)110 preferring TS+ 126, the bulky Rh(I)112 and our Mo(II) complexes favoring TS+ 127, and SbCl5110 showing no preference.

![Scheme 80](image.png)

The dominance of TS+ 127 in our reactions is reinforced by the absence of an accelerating effect of the geminal dimethyl group in 11 (see above): note that the additional Me would impose a 1,3-diaxial interaction with O[M] (128), which is consistent with the lack of reactivity of 11.190 However, we asked ourselves, what is it that renders the seemingly more crowded TS+ 127 lower in energy than 126? Inspection of 126 and 127 suggests that, as usually, the equatorially disposed vicinal substituents in 126 should repel each other (see the arrows), whereas in 127 the axial O[M] should lean toward the equatorial isopropylidene group.191 This distortion in the case of 127 would partly release the steric interaction of [M] with MeZ, whereas in 126 the [M] group would move from a relatively less hindered position to an eclipsing one with MeE.192 Hence, the bulkier the Lewis acid [M], the more important...
the latter effect should become, which is in accord with the experiment.

3.5. Conclusion

We have designed a new class of catalysts, which induce intramolecular cyclization of olefinic aldehydes to afford products with a cis-configuration at the newly formed chiral centres in some cases. These catalysts can be tuned to drive the reaction either toward the ene or Prins-type product (32 or 90).\textsuperscript{193} Note that cyclized are only those alkenals with electron rich double bond; trisubstituted or with an allylic silane moiety. However, Lewis-basic groups ($N,O$) prevent the reaction presumably due to coordination with the catalyst and thus rendering it inactive. Control experiments have demonstrated that $M^{II}$ ($M = Mo$ or $W$) is, indeed, responsible for the reactivity rather than $\text{BnEt}_3\text{N}^+\text{TfO}^-$ or $\text{TfOAg}$. Our experiments shed more light on the mechanism of these reactions and show that formation of a cis-product\textsuperscript{194} in reactions such as these, may not always involve a C-C bond formation occurring on the metal template. Currently, new $M^{II}$-catalysts are being developed in the laboratory e.g. $[\text{Mo(CO)}_4\text{Br}_2]_2$ which have the promise to be more reactive and selective.
Chapter 4

Experimental section
General Procedure

The reactions between the metal complexes and TfOAg were monitored using cyclic voltammetry on a 1 mm diameter Pt disc electrode. An EG&G model 173 potentiostat and a model 175 wave form generator were used in these studies. Potentials are given with respect to a saturated calomel electrode (SCE). Tetrabutylammonium tetrafluoroborate (Fluka, electrochemistry grade) [TBABF₄] (0.1 mol dm⁻³) was used as an electrolyte in all electrochemical experiments. Acetonitrile (BDH, HPLC grade) and 1,2-dimethoxyethane (Lancaster, 99+%) were used as received. The ESR spectra of frozen solutions of the complexes in DME were recorded at 77K; g-values were calculated using Mn²⁺ in MgO as an internal standard. Melting points were determined on a Kofler block and are uncorrected. The IR spectra were recorded in CHCl₃ (or CDCl₃) unless stated otherwise. The NMR spectra were recorded for CDCl₃ solutions at 25 °C on 250 or 300 MHz instruments. The coupling constants were obtained by first-order analysis. The mass spectra were measured using direct inlet and the lowest temperature enabling evaporation or in a thermospray mode; chemical ionization was used in certain cases (with NH₄). GC Analysis was carried out using capillary columns (BP10 25m x 2.65 μm). All reactions were carried out under nitrogen. Standard workup of an ethereal solution means washing 3x with 5% HCl (aqueous), water, and 3x with 5% KHCO₃ (aqueous) and drying with MgSO₄. Petroleum ether refers to the fraction boiling in the range 40-60 °C. The identity of samples prepared by different routes was checked by TLC and IR and NMR spectra. Yields are given for isolated product showing one spot on a chromatographic plate and no impurities detectable in the NMR spectrum.
Benzytriethylammonium chloromolybdate (I). A mixture of molybdenum hexacarbonyl (1.32 g; 5 mmol) and benzytriethylammonium chloride (1.14 g; 5 mmol) in dry diglyme (50 mL) was heated at 120 °C for 2 h. After cooling, the solution was filtered and to the filtrate was added petroleum ether (50 mL). The precipitate was isolated by filtration, washed with petroleum ether, and dried in vacuum to give I (1.68 g; 72%) as a yellow solid: IR (KBr) ν(C=O) 1821 (s), 1916 (vs), 2067 (w) cm⁻¹; IR (CH₂Cl₂) ν(C=O) 1853 (s), 1926 (vs), 1982 (w), 2061 (w) cm⁻¹; MS (-FAB) m/z 273 [Mo(CO)₅Cl⁺], 242 [Mo(CO)₄Cl₂⁻], 217 [Mo(CO)₃Cl₃⁻]. Anal. Calcd for C₁₈H₂₂ClMoN₂O₅: C, 46.62; H, 4.78; N, 3.02; Cl, 7.64. Found: C, 46.14; H, 5.08; N, 3.23; Cl, 7.66.

Benzytriethylammonium chlorotungstate (II). A mixture of tungsten hexacarbonyl (1.76 g; 5 mmol) and benzytriethylammonium chloride (1.14 g; 5 mmol) in dry diglyme (50 mL) was heated at 120 °C for 2 h. After cooling, the solution was filtered and to the filtrate was added petroleum ether (50 mL). The precipitate was isolated by filtration, washed with petroleum ether, and dried in vacuum to give II (2.06 g; 74%) as a yellow solid: IR (KBr) ν(C=O) 1820 (s), 1906 (vs), 2066 (w) cm⁻¹; IR (CH₂Cl₂) ν(C=O) 1848 (s), 1918 (vs), 1959 (sh), 2060 (w) cm⁻¹. Anal. Calcd for C₁₈H₂₂ClN₂O₅W: C, 39.19; H, 4.02; N, 2.54; Cl, 6.43. Found: C, 39.08; H, 4.10; N, 2.65; Cl, 6.40.

Bis(triphenylphosphine)ammonium chloromolybdate (III). A mixture of molybdenum hexacarbonyl (1.32 g; 5 mmol) and bis(triphenylphosphine)ammonium chloride (2.87 g; 5 mmol) in dry DME (50 mL) was refluxed for 4 h. After cooling, the solution was filtered and to the filtrate was added hexane (50 mL) to give rise to a brown-yellow oil. The solvent was decanted and a new portion of hexane was added. This procedure was repeated several times - until the oil begun to crystallize. The yellow solid was then isolated by filtration, washed with hexane, and dried in vacuum to give III (2.83 g; 70%): IR (KBr) ν(C=O) 1850 (s), 1919 (vs), 1977 (w), 2061 (w) cm⁻¹; IR (CH₂Cl₂) ν(C=O) 1850 (s), 1925 (vs), 1975 (w), 2062 (w) cm⁻¹, in accordance with the literature.

[^144]:
Bis(triphenylphosphine)ammonium chlorotungstate IV. A mixture of tungsten hexacarbonyl (1.76 g; 5 mmol) and bis(triphenylphosphine)ammonium chloride (2.87 g; 5 mmol) in dry DME (50 mL) was refluxed for 4 h. After cooling, the solution was filtered and to the filtrate was added hexane (50 mL) to give rise to a brown-yellow oil. The solvent was decanted and a new portion of hexane was added. This procedure was repeated several times - until the oil begun to crystallize. The yellow solid was then isolated by filtration, washed with hexane, and dried in vacuum to give IV (3.19 g; 71%): IR (KBr) v(C=O) 1855 (s), 1903 (vs), 2050 (w) cm⁻¹; IR (CH₂Cl₂) v(C=O) 1840 (s), 1909 (vs), 1968 (w), 2060 (w) cm⁻¹, in accordance with the literature.¹⁴⁴

Molybdenum Complex V. A mixture of molybdenum hexacarbonyl (1.32 g; 5 mmol) and wet benzyltriethylammonium chloride (1.14 g; 5 mmol)¹⁹⁶ in DME (50 mL) was refluxed for 2 h; gradual formation of a yellow-grey precipitate was observed. After cooling, the precipitate was isolated by filtration, washed successively with DME and petroleum ether, and dried in vacuum to give V (1.68 g; 67%): IR (KBr) v(C=O) 1723 (s), 1741 (s), 1782 (w), 1887 (w) cm⁻¹. After digestion with MeCN: IR (KBr) v(C=O) 1866 (s), 1920 (s), 1977 (w), 2064 (w) cm⁻¹. Anal. Calcd for C₆₁H₉₄Cl₄Mo₃N₄O₁₂: C, 48.53; H, 6.29; N, 3.72; Cl, 9.42; Mo, 19.7. Found: C, 48.35; H, 6.33; N, 3.69; Cl, 9.39; Mo, 19.7.

Tungsten Complex VI. A mixture of tungsten hexacarbonyl (1.76 g; 5 mmol) and wet benzyltriethylammonium chloride (1.14 g; 5 mmol) in DME (50 mL) was refluxed for 2 h; gradual formation of a yellow-grey precipitate was observed. After cooling, the precipitate was isolated by filtration, washed successively with DME and petroleum ether, and dried in vacuum to give VI (1.79 g): IR (KBr) v(C=O) 1716 (s), 1737 (s), 1877 (s), 1913 (w).

Molybdenum Complex C₆H₅CH₂(C₂H₅)₃N⁺[PhenMo(CO)₃Cl]⁻. A mixture of PhenMo(CO)₄ (0.39 g; 1.0 mmol) and benzyltriethylammonium chloride (0.34 g; 1.5 mmol) in toluene (25 mL) was refluxed for 4 h. After cooling, the precipitate was isolated by filtration, washed rapidly with a little cold methanol and dried in vacuum to give the title
compound (0.44 g, 75%):\textsuperscript{197} IR v(C=O) 1870, 1765, 1738 cm\textsuperscript{-1}.

* **Molybdenum Complex** \(\text{C}_6\text{H}_5\text{CH}_2(\text{C}_2\text{H}_5)_3\text{N}^+\text{[Mo(CO)$_4$ClBr$_2$]}^+\) (VII). The catalyst was generated freshly before the reaction as follows: to a suspension of \(\text{C}_6\text{H}_5\text{CH}_2(\text{C}_2\text{H}_5)_3\text{N}^+\text{[Mo(CO)$_5$Cl]}^+\) (23 mg, 0.05 mmol) in DME (2 mL) was added a solution of bromine (8 mg, 0.05 mmol) in DME (1 mL) and the mixture was stirred at rt for 10 min. This mixture was then used to catalyze the carbonyl-ene reaction.

* **Molybdenum Complex** \(\text{Mo(CO)}_3\text{OTf}_2\) (VIII). The catalyst was generated freshly as follows: Silver(I) trifluorosulfonate (50 mg, 3 equivs) was added to a stirred suspension of \(\text{C}_6\text{H}_5\text{CH}_2(\text{C}_2\text{H}_5)_3\text{N}^+\text{[Mo(CO)$_5$Br]}^+\text{nH}_2\text{O}\) (30 mg; 1 equiv) in DME (2 mL) at 0 °C under N\(_2\). The reaction mixture was then allowed to warm to rt and stirred for 15 min.

* **Molybdenum Complex** \(\text{C}_6\text{H}_5\text{CH}_2(\text{C}_2\text{H}_5)_3\text{N}^+\text{[PhenMo(CO)$_3$ClBr]}^+\) (IX). The catalyst was generated freshly before the reaction as follows: to a suspension of \(\text{C}_6\text{H}_5\text{CH}_2(\text{C}_2\text{H}_5)_3\text{N}^+\text{[PhenMo(CO)$_3$Cl]}^+\) (see above) (29 mg, 0.05 mmol) in DME (2 mL) was added a solution of bromine (8 mg, 0.05 mmol) in DME (1 mL) and the mixture was stirred at rt for 10 min. This mixture was then used to catalyze the carbonyl-ene reaction.

* **Molybdenum Complex** \(\text{PhenMo(CO)}_3\text{OTf}_2\) (VIII). The catalyst was generated freshly as follows: Silver(I) trifluorosulfonate (50 mg, 3 equivs) was added to a stirred suspension of \(\text{C}_6\text{H}_5\text{CH}_2(\text{C}_2\text{H}_5)_3\text{N}^+\text{[PhenMo(CO)$_3$Cl]}^+\) (see above) (38 mg; 1 equiv) in DME (2 mL) at 0 °C under N\(_2\). The reaction mixture was then allowed to warm to rt and stirred for 15 min.
3,3,7-Trimethyl-6-octen-1-al (11).

To a slurry of cuprous iodide (1.0 g, 5.25 mmol) in Et₂O (50 mL) was added methyllithium (8.0 mL, 10.5 mmol, 1.3M solution in hexane) at 0 °C under nitrogen. After 10 min, the solution was cooled to -78 °C and 3,7-dimethyl-2,6-octadienal (0.76 g, 5.0 mmol) in Et₂O (5 mL) was added slowly dropwise. The resulting mixture was stirred at -78 °C for 10 min at -20 °C for 4 h, then poured into a cold saturated aqueous solution of NH₄Cl and extracted with ether. The combined ethereal layers were dried with MgSO₄ and evaporated. The crude product was purified by flash chromatography on silica gel with a hexane-EtOAc mixture (20:1) to afford 11 (0.68 g, 81%) as a colorless oil: IR ν(C=O) 1705 cm⁻¹; ¹H NMR δ 1.04 (s, 6 H, CMe₂), 1.58 (s, 3 H, CH=CCMe), 1.66 (s, 3 H, CH=CMe₂), 1.83 (m, 2 H, CH₂CH=), 2.25 (d, J = 3.2 Hz, 2 H, CH₂CH=O), 5.06 (t, J = 7.1 Hz, CH=CMe₂), 9.82 (t, J = 3.2 Hz, 1 H, CH=O); ¹³C NMR δ 22.7 (t), 27.3 (q), 42.7 (t), 54.7 (t), 124.3 (d), 131.5 (s), 203.6 (d).
Cyclization of 3,7-dimethyl-6-octen-1-al (30).

Method 1. To a DME solution of 5 mol% of the PhCH₂(Et)₃N⁺[Mo(CO)₄ClBr₂]⁻ (VII) catalyst generated in situ (see above) was added a solution of citronellal 30 (154 mg, 1.0 mmol) in DME (1 mL). The resulting yellow solution was stirred at rt for 24 h, then diluted with ether and washed with saturated aqueous solution of NaHCO₃ and brine. The combined organic layers were dried with MgSO₄ and filtered through a pad of silica gel to remove inorganic residues. The solvent was evaporated under reduced pressure and the residue was chromatographed on a column of silica gel with a petroleum ether-ether mixture (9:1) to afford neo-iso-pulegol 32 (105 mg, 68%) as a colourless oil, whose spectral data correspond to those described in the literature:¹⁶³ IR ν 850, 900, 1025, 1125, 1300, 1375, 1450, 1650, 2900, 3560 cm⁻¹; ¹H NMR δ 0.91 (d, J = 6.4 Hz, 3 H, CH₃CH), 1.81 (s, 3 H, CH₃-C=CH₂), 4.03 (d, J = 2.3 Hz, 1 H, CH-OH), 4.81 (s, 1 H, C=CHH), 4.98 (s, 1 H, C=CHH); ¹³C NMR δ 22.30 (q), 22.75 (q), 23.92 (t), 25.79 (d), 34.74 (t), 40.89 (t), 48.37 (d), 66.28 (d), 111.23 (t), 147.27 (s). Continued elution furnished iso-pulegol 31 (17 mg, 11%), whose ¹H NMR spectrum was identical with that of an authentic sample obtained from Fluka: ¹H NMR δ 0.86 (d, J = 6.6 Hz, 3 H, CH₂CH), 1.71 (s, 3 H, CH₂-C=CH₂), 3.46 (ddd, J = 10.4, 4.3 Hz, 1 H, CH-OH), 4.86 (s, 1 H, C=CHH), 4.90 (s, 1 H, C=CHH). Further verification of the structures of 31 and 32 was based on the PCC oxidation which, in each case, gave iso-pulegone; treatment of the latter non-conjugated enone with methanolic KOH afforded pulegone, identical with an authentic sample purchased from Fluka.
Method 2. Repetition of the reaction with the Mo(CO)$_5$(OTf)$_2$ (VIII) catalyst generated in situ (see above) at 20 °C for 2 h afforded 131 mg (85%) of a 1:1 mixture of 31 and 32 as determined by $^1$H NMR.

Method 3. A mixture of molybdenum hexacarbonyl (150 mg, 0.56 mmol) and tetrabutylammonium fluoride (0.57 mL, 1M solution in THF) in DME (2 mL) was refluxed for 5 min. After cooling, a solution of bromine (90 mg, 0.56 mmol) in DME (1 mL) was added and the mixture was stirred at rt for 10 min. To the reagent thus generated in situ was added citronellal 30 (87 mg, 0.56 mmol). The resulting mixture was stirred at rt for 24 h, then diluted with ether and worked up to give 85 mg of product, which was shown by $^1$H NMR to consist of 31 (22%) and 32 (78%).

(Z)-6-Octen-1-al (33).

To a solution of oxalyl chloride (351 mg, 2.77 mmol) in CH$_2$Cl$_2$ (19 mL) was added dropwise a solution of DMSO (433 mg, 5.54 mmol) in CH$_2$Cl$_2$ (1.6 mL) at -78 °C and the resulting solution was stirred at -78 °C for 5 min. A solution of the alcohol 53 (329 mg, 2.57 mmol) in dichloromethane (1.6 mL) was then added at the same temperature. After 15 min, Et$_3$N (1.8 mL, 13 mmol) was added, the mixture was allowed to warm to room temperature, then stirred for 30 min, and poured into 1M HCl. The product was extracted with dichloromethane, the organic layer was dried with MgSO$_4$, and the solvent was evaporated. The residue was flash-chromatographed on silica gel (10 g) with a petroleum ether-ether
mixture (9:1) to afford 33 (311 mg; 96%) as a colourless oil: IR (neat) ν 2720 (CH), 1725 cm⁻¹(CO); ¹H NMR δ 1.32-1.48 (m, 4 H, remaining CH₂), 1.60 (d, J = 6.0 Hz, 3 H, CHCH₃), 2.10 (m, 2 H, CH₂CH=), 2.43 (dt, J = 7.3 and 1.9 Hz, 2 H, CH₂CHO), 5.25-5.65 (m, 2 H, CH=CH), 9.74 (m, 1 H, CH=O); ¹³C NMR δ 12.7 (q), 21.6 (t), 26.5 (t), 29.0 (t), 43.8 (t), 124.3 (d), 129.9 (d), 202.7 (d).

(E)-6-Octen-1-ol (34).

![](image)

Obtained from 57 on Swern oxidation (in the same way as 33 was prepared from 53). 34 (288 mg, 89%): ¹H NMR δ 1.4 (m, 4 H, 2 x CH₂), 1.64 (d, J = 4.4 Hz, 3 H,CHCH₃), 2.06-1.95 (m, 2 H, CH₂CH=CH), 2.42 (dt, J = 7.3 and 1.9 Hz, 2 H, CH₂CHO), 5.46-5.37 (m, 2 H, CH=CH), 9.76 (t, J = 1.8 Hz, 1 H, CHO); ¹³C NMR δ 17.89 (q), 21.52 (t), 28.98 (t), 32.21 (t), 43.77 (t), 125.35 (d), 130.68 (d), 202.82 (d).
A dry, three-necked 100-mL flask was charged with (1.7 g, 26 mmol) of zinc dust (99.99% purity) and flushed with argon. After zinc activation with 1,2-dibromoethane and Me3SiCl as reported previously124a solution of iodide 70 (3.15 g, 15 mmol) in THF (8 mL) was slowly added at 30 °C. After the end of the addition, the reaction mixture was stirred for 12 h at 35-40 °C. The resulting solution was then cooled to -10 °C, and a solution of CuCN (1.98 g, 22 mmol) and LiCl (1.9 g, 44 mmol, dried at 150 °C for 1 h) in THF (22 mL) was rapidly added. The light green solution was stirred at 0 °C for 10 min.

A solution of acrolein (0.75 mL, 11 mmol) and chlorotrimethylsilane (5.5 mL, 43 mmol) in dry ether (10 mL) was slowly added (0.5 h) dropwise to the above prepared solution of the copper reagent cooled at -78 °C. After 3 h at -78 °C, the reaction mixture was allowed to warm up to 25 °C overnight and diluted with ether, washed with saturated aqueous solution of NH4Cl, and water, and dried with MgSO4. After filtration, the solvent was evaporated and the residue was chromatographed on silica gel (35 g) using a petroleum ether-ether mixture (9:1) to furnish 35 (1.45 g, 95%) as colourless oil, whose spectral data correspond to those described in the literature:175 1H NMR δ 0.95 (t, J = 7.5 Hz, 3 H), 1.40 (q, J = 7.3 Hz, 2 H), 1.65 (quintet, J = 8.0 Hz, 2 H), 2.05 (quintet of d, J = 7.3 and 1.7 Hz, 2 H), 2.44 (triplet of d, J = 7.2 and 1.8 Hz, 2 H), 5.25-5.47 (m, 2 H), 9.76 (t, J = 1.8 Hz, 1 H). 13C NMR δ 14.2 (q), 20.4 (t), 21.5 (t), 26.6 (t), 29.1 (t), 39.7 (t), 128.2 (d), 132.0 (d), 202.5 (d).
(E)-6-Nonen-1-al (36).

Obtained from 71 (in the same manner as 35 was prepared from 70). 36 (1.43 g, 93%).

$^1$H NMR $\delta$ 0.81 (t, $J = 7.5$ Hz, 3 H), 1.25 (q, $J = 7.5$ Hz, 2 H), 1.48 (quintet, $J = 7.5$ Hz, 2 H), 1.85 (quintet, $J = 6.9$ Hz, 2 H), 2.26 (dt, $J = 7.2$ and 1.8 Hz, 2 H), 5.22-5.46 (m, 2 H), 9.76 (t, $J = 1.8$ Hz, 1 H); $^{13}$C NMR $\delta$ 13.8 (q), 21.4 (t), 25.4 (t), 28.9 (t), 32.1 (t), 43.6 (t), 128.3 (d), 132.4 (d), 202.6 (d).

(Z)-8-(Dimethylphenylsilyl)oct-6-en-1-al (37).

Chromium trioxide (448 mg, 4.5 mmol) was added in three equal portions to pyridine (0.73 mL, 9 mmol) in dry CH$_2$Cl$_2$ (7 mL). After stirring at rt for 15 min, a solution of 64 (262 mg, 1.0 mmol) in dry CH$_2$Cl$_2$ (2 mL) was added. The reaction mixture was then stirred for 3 h and quenched by pouring into a wet, reagent grade ether. The ethereal layer was successively washed with 10% NaOH (2 x 70 mL), saturated aqueous solution of CuSO$_4$ (4 x 15 mL), water (10 mL), brine (2 x 15 mL) and dried with MgSO$_4$. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel using a petroleum
ether-ether mixture (4:1) as eluent to furnish 37 as a colourless oil (163 mg, 63%): IR v(CO) 1725 cm\(^{-1}\); \(^1H\) NMR \(\delta\) 0.28 (s, 6 H, Si(CH\(_3\))\(_2\)C\(_6\)H\(_5\)), 1.06-1.65 (m, 4 H), 1.70 (d, \(J = 8.5\) Hz, 2 H, CH=CHCH\(_2\)Si), 1.92 (m, 2 H), 2.37 (dt, \(J = 7.2, 1.8\) Hz, 2 H, CH\(_2\)CHO), 5.14-5.53 (m, 2 H, CH=CH), 7.28-7.59 (m, 5 H, aryl-H), 9.72 (t, \(J = 1.7\) Hz, 1 H, CH=O); \(^{13}\)C NMR \(\delta\) -3.34 (2 x q), 17.61 (t), 21.72 (t), 26.67 (t), 29.06 (t), 43.73 (t), 125.20 (d), 127.44 (d), 127.56 (d), 128.91 (d), 133.54 (d), 138.76 (s), 202.70 (d).

(E)-8-(Dimethylphenylsilyl)oct-6-en-1-al (38).

\[\text{Obtained from 69 (in the same manner as 37 was prepared from 64).}\]

38 (153 mg, 59%): IR v(CH) 2725, 1725 (CO) cm\(^{-1}\); \(^1H\) NMR \(\delta\) 0.26 (s, 6 H, -Si(CH\(_3\))\(_2\)C\(_6\)H\(_5\)), 1.23-1.43 (m, 2 H), 1.49-1.73 (m, 4 H), 1.65 (d, \(J = 7.6\) Hz, 2 H, CH=CHCH\(_2\)Si), 1.90-2.05 (m, 2 H), 2.37 (dt, \(J = 7.5\) and 1.80 Hz, 2 H, CH\(_2\)CHO), 5.14-5.46 (m, 2 H, CH=CH), 7.28-7.56 (m, 5 H, aryl-H), 9.73 (t, \(J = 1.7\) Hz, 1 H, CH=O); \(^{13}\)C NMR \(\delta\) -3.41 (q), 21.42 (t), 21.60 (t), 29.28 (t), 32.33 (t), 43.70 (t), 126.05 (d), 127.66 (d), 128.83 (d), 128.87 (d), 133.58 (d), 138.85 (s), 202.69 (d).

5-Methyl-5-hexen-1-al (39).
To a stirred solution of ethyl 4-isopropenylbutyrate (0.48 g, 3 mmol) in dichloromethane (30 mL) at -78 °C was added diisobutylaluminium hydride (6 mmol, 1 M solution in CH₂Cl₂) over a period of 20 min under nitrogen atmosphere. After 10 min, the reaction mixture was quenched with saturated aqueous solution of ammonium chloride and allowed to warm to room temperature over 0.5 h. The product was extracted with ether and dried with MgSO₄. After filtration, the solvent was removed under reduced pressure and the residual oil was flash chromatographed on silica gel (10 g) eluting with hexane-ether mixture (16:1) to furnish 39 (218 mg, 65%) as a colourless oil: \[ ^{1}H\text{NMR } \delta 1.64 (s, 3 \text{ H, CH}_3), 1.98 (t, J = 7.4 \text{ Hz, 2 H}), 2.36 (dt, J = 7.3 \text{ and } 1.7 \text{ Hz, 2 H}), 4.62 (s, 1 \text{ H, C=CHH}), 4.68 (s, 1 \text{ H, C=CHH}), 9.71 (t, J = 1.6 \text{ Hz, 1 H, CHO}); \] \[ ^{13}\text{C NMR } \delta 19.83 (t), 22.10 (q), 36.93 (t), 43.21 (t), 110.82 (t), 144.59 (s), 202.41 (CHO). \]

3-(2'-Methylenecyclohexyl)propanal (40).

\[ \text{EtO}_2\text{C} - \text{CH}_2\text{CH}_2\text{CH}=\text{CH}-\text{C}_{\text{cyclohexyl}} \rightarrow \text{CHO} \]

Obtained as a colourless oil from ethyl 3-(2'-methylenecyclohexyl)propionate on DIBAL-H reduction (in the same way as 39 was prepared from ethyl 4-isopropenylbutyrate). 40 (120 mg, 26%): \[ ^{1}H\text{NMR } \delta 1.15-1.72 (m, 7 \text{ H}), 1.77-2.06 (m, 3 \text{ H}), 2.07-2.19 (m, 1 \text{ H}), 2.44-2.47 (m, 2 \text{ H}), 4.57 (s, 1 \text{ H, C=CHH}), 4.69 (s, 1 \text{ H, C=CHH}), 9.75 (t, J = 1.5 \text{ Hz, 1 H, CHO}); \] \[ ^{13}\text{C NMR } \delta 26.90 (t), 28.59 (t), 31.58 (t), 33.69 (t), 34.22 (t), 42.16 (t), 42.57 (d), 106.55 (t), 151.60 (s), 202.75 (d). \]
(E)-7-Trimethylsilyloct-6-enal (41).

\[
\begin{align*}
\text{74} & \quad \text{SiMe}_3 \\
\text{\rightarrow} & \quad \text{SiMe}_3 \\
\text{41}
\end{align*}
\]

Obtained from 74 (in the same manner as 35 was prepared from 70) as a colourless oil (1.63 g, 75%). 41: IR ν 2725 (CH), 1725 (CO), 1640, 1280, 830 and 740 cm\(^{-1}\); \(^1\)H NMR δ 0.00 (s, 9 H, -SiMe\(_3\)), 1.62 (d, \(J = 0.9\) Hz, 3 H, CH\(_3\)), 2.07 (m, 2 H), 2.40 (dt, \(J = 7.2\) and \(1.9\) Hz, 2 H, CH\(_2\)CHO), 5.64 (m, \(J = 1.8\) and \(6.6\) Hz, 1 H, C=CH), 9.73 (t, \(J = 2.5\), 1 H, CHO); \(^{13}\)C NMR δ -2.6 (q), 14.3 (q), 21.7 (t), 27.9 (t), 28.7 (t), 43.7 (t), 136.6 (s), 138.3 (d), 202.6 (d); HRMS m/z 198.1440 (calcd for C\(_{11}\)H\(_{22}\)OSi: 198.1440, M\(^{+}\)).

Ethyl 3,7-dimethyl-1-oxo-6(E)-octenoate (42).

\[
\begin{align*}
\text{78} & \quad \text{CO}_2\text{Et} \\
\text{\rightarrow} & \quad \text{CO}_2\text{Et} \\
\text{42}
\end{align*}
\]

Obtained from 78 on Swern oxidation (in the same way as 33 was prepared from 53) as a colourless oil (0.49 g, 90%), whose spectral data correspond to those described in the literature.\(^{127}\) 42: IR ν 2725, 1725, 1700, and 1650 cm\(^{-1}\); \(^1\)H NMR δ 0.92 (d, \(J = 6.6\) Hz, 3 H, C(3) CH\(_3\)), 1.22 (t, \(J = 7.1\) Hz, 3 H, CO\(_2\)CH\(_2\)CH\(_3\)), 1.76 (s, 3 H, C(7) CH\(_3\)), 4.12 (q, \(J = 7.1\) Hz, 2 H, CO\(_2\)CH\(_2\)CH\(_3\)), 6.65 (dt, \(J = 7.5\) and \(1.5\) Hz, 1 H, C(6) C=CH), 9.69 (t, \(J = 2.0\) Hz, 1
H, CHO); $^{13}$C NMR $\delta$ 12.25 (q), 14.19 (q), 19.60 (q), 25.99 (t), 27.71 (d), 35.43 (t), 50.76 (t), 60.35 (t), 128.05 (s), 141.24 (d), 168.01 (s), 202.32 (d); HRMS $m/z$ 212.1413 (calcd for $C_{12}H_{20}O_3$: 212.1412; M$^+$).

**Ethyl 4-[N-(3'-methylbut-2'-enyl)amino]but-2(E)-enoate (43).**

![Chemical Structure](image)

A mixture of 1-amino-3-methylbut-2-ene (1.42 g, 16.67 mmol) and (E)-ethyl 4-bromocrotonate (3.22 g, 16.67 mmol) in $CH_2Cl_2$ (100 mL) was stirred vigorously in the presence of 10% aqueous solution of Na$_2$CO$_3$ (25 mL) at rt for 1 h after which the organic layer was separated. The aqueous layer was basified with solid sodium carbonate and extracted with $CH_2Cl_2$ (20 mL). The combined organic layers were dried over MgSO$_4$, filtered, and evaporated under reduced pressure to afford 43$^{130}$ (0.88 g, 69%) as an oil. $^1$H NMR $\delta$ 1.29 (t, $J = 7.2$ Hz, 3 H, OCH$_2$CH$_3$), 1.65 (s, 3 H, CH$_3$), 1.73 (s, 3 H, CH$_3$), 1.90 (s, 1 H, NH), 3.24 (d, $J = 7.0$ Hz, 2 H, (Cl) CH$_2$), 3.42 (d, $J = 5.6$ Hz, 2 H, (C4) CH$_2$), 4.20 (q, $J = 7.1$ Hz, 2 H, OCH$_2$CH$_3$), 5.24 (t, $J = 6.9$ Hz, 1 H, CH=CM$_2$), 5.99 (d, $J = 15.7$ Hz, 1 H, (C2) CH), 7.00 (dt, $J = 15.7$, 5.6 Hz, 1 H, (C3) CH); MS $m/z$ 197 (M$^{**}$).
[N-(4-Methylpent-3-enyl)methyl]ethanalamine (44).

\[
\begin{align*}
\text{81} & \quad \xrightarrow{\text{N,O-acylation}} \quad \text{44}
\end{align*}
\]

To a solution of oxalyl chloride (323 mg, 2.6 mmol) in CH\(_2\)Cl\(_2\) (17 mL) was added dropwise a solution of DMSO (498 mg, 6.5 mmol) in CH\(_2\)Cl\(_2\) (2.0 mL) at -78 °C and the resulting solution was stirred at -78 °C for 5 min. A solution of the alcohol 81 (200 mg, 1.27 mmol) in dichloromethane (2.0 mL) was then added at the same temperature. After 15 min, Et\(_3\)N (1.78 mL, 13 mmol) was added, the mixture was allowed to warm to room temperature, then stirred for 30 min, and poured into an aqueous solution of NaHCO\(_3\). The product was extracted with dichloromethane and the combined organic extracts were washed twice with brine, water and then dried over MgSO\(_4\). Upon removal of solvent, spectrally pure 44 (180 mg, 91%) was obtained as a pale yellow oil: \(^1\)H NMR \(\delta\) 1.55 (s, 3 H, CH=CCH\(_3\)), 1.62 (s, 3 H, CH=CCH\(_3\)), 2.01-2.17 (m, 2 H, CH\(_2\)CH=), 2.28 (s, 3 H, NCH\(_3\)), 2.38 (t, \(J = 7.0\) Hz, 2 H), 5.04 (m, 1 H, CH\(_2\)CH=), 9.64 (t, \(J = 1.7\) Hz, 1 H, CH=O), \(^{13}\)C NMR \(\delta\) 17.63 (q), 25.58 (q), 26.04 (t), 42.95 (q), 57.88 (t), 67.17 (t), 121.26 (d), 132.96 (s), 202.30 (s).

2-[(3'-Methyl-2'-butenyl)oxy]benzaldehyde (46).

\[
\begin{align*}
\text{82a} & \quad \xrightarrow{\text{oxidation}} \quad \text{46}
\end{align*}
\]
To a solution of 82a (0.9 g, 3.7 mmol) in THF (20 mL) was added dropwise under nitrogen n-BuLi (1.8 mL, 4.5 mmol, 2.5M solution in hexane) over a period of 15 min at -70 °C (dry-ice/acetone). The resultant yellow solution was stirred for 1 h before slowly adding (ca. 10 min) N,N-dimethylformamide (DMF) (0.32 mL, 4.12 mmol). The reaction mixture was then stirred at the same temperature (-70 °C) for 2 h and then at room temperature for 1 h. After dilution with water and extraction with hexane the combined organic layers were washed with water, brine, and dried with Na2SO4. After filtration, the solvent was evaporated under reduced pressure and the residue was purified on silica gel eluting with a hexane-ether mixture (9:1) to yield 46 (350 mg, 74%) as a colourless oil, whose spectral data correspond to those described in the literature:134 1H NMR δ 1.75 (s, 3 H, CH3), 1.80 (s, 3 H, CH3), 4.64 (d, J = 6.59 Hz, 2 H, OCH2), 5.47-5.52 (m, 1 H, C=CH), 6.97-7.85 (m, 4 H, aryl-H), 10.49 (m, 1 H, CHO); 13C NMR δ 18.26 (q), 25.75 (q), 65.42 (t), 112.90 (d), 118.93 (d), 120.51 (d), 128.24 (d), 135.72 (d), 138.69 (s), 190.0 (d); HRMS m/z (relative intensity) 190 (M+, 3.8), 123 (8), 122 (85), 121 (37), 110 (23), 88 (5), 77 (4), 69 (100), 68 (12), 65 (15), 53 (10), (found: 190.0994. C12H14O2 requires M, 190.0994). The yield was based on the starting material recovered (300 mg).

3-(3-Methoxyphenyl)propanal (47).

To a solution of 3-(3-methoxyphenyl)propionic acid (1.80 g, 10 mmol) in Et2O (13 mL) was added dropwise borane-dimethylsulfide (BMS)(5 mL, 10 mmol, 2.0M solution in Et2O) under N2. Following the addition of initial 2-3 mL of BMS, when evolution of gas subsided,
the mixture was refluxed to complete evolution of hydrogen. The remainder of the BMS was added slowly maintaining a gentle reflux. After the addition was complete, the mixture was refluxed for 1 h. The solvent and volatiles were removed under reduced pressure, and the residue was dissolved in CH$_2$Cl$_2$ (10 mL).

The above prepared solution of trialkoxyboroxine was added to a well stirred suspension of pyridinium chlorochromate (2.37 g, 11 mmol) in CH$_2$Cl$_2$ (17 mL) under N$_2$. The resulting mixture was refluxed for 1 h, diluted with ether (30 mL) and filtered through a column of celite. The solvent was evaporated, and the residue was purified on silica gel (40 g) eluting with a petroleum ether-ether mixture (5:1) to afford the desired aldehyde 47 (1.05 g, 64%) as a colourless oil, whose spectral data correspond to those described in the literature: IR $\tilde{\nu}$ 2837, 2719, 1725, 1155, and 1037 cm$^{-1}$; $^1$H NMR $\delta$ 2.64-2.95 (m, 4 H), 3.71 (s, 3 H), 6.61-6.76 (m, 3 H), 7.07-7.20 (m, 1 H), 9.74 (t, $J = 1.3$ Hz, 1 H); $^{13}$C NMR $\delta$ 28.09 (t), 45.12 (t), 55.09 (q), 111.46 (d), 114.10 (d), 120.54 (d), 129.55 (d), 141.90 (s), 159.72 (s), 201.47 (d); HRMS (EI) $m/z$ 164.0837 (calcd for C$_{10}$H$_{12}$O$_2$: 164.0837; M$^+$).

6-Octyn-1-al (48).

Obtained from 85 on Swern oxidation (in the manner as 33 was prepared from 53). 48: IR $\tilde{\nu}$ 2255 (C=O), 1725 (CO) cm$^{-1}$. $^1$H NMR $\delta$ 1.73 (t, $J = 2.5$ Hz, 3 H, CH$_3$), 2.03-2.25 (m, 2 H, CH$_2$C≡CCH$_3$), 2.42 (dt, $J = 7.2$, 1.8 Hz, 2 H, CH$_2$CHO), 9.74 (t, $J = 1.8$ Hz, CH=O); $^{13}$C NMR $\delta$ 3.34 (q), 18.42 (t), 21.18 (t), 28.31 (t), 43.34 (t), 75.92 (s), 78.36 (s), 202.30 (d).
4,8-Dimethyl-non-7-en-1-al (49).

Diisobutylaluminium hydride (3.85 mmol, 1.0 M solution in hexane) was added dropwise to a solution of 88 (0.54 g, 3.25 mmol) in dry Et₂O at 0 °C under nitrogen. The reaction mixture was allowed to warm to rt over 45 min, and 10% aqueous H₂SO₄ was slowly added with cooling until the aqueous phase remained acidic. After stirring for 0.5 h, the organic layer was separated and the aqueous phase was extracted with ether (3 x 25 mL). The combined organic layers were washed with an aqueous solution of NaHCO₃, brine, and dried with MgSO₄. The crude product was purified on silica gel with a hexane-EtOAc mixture (20:1) to afford 49 as a colourless oil, whose spectral data correspond to those described in the literature:¹⁴² IR (neat) ν 2710, 1 727, 1 454, 1 378, 1 115, and 980 cm⁻¹; ¹H NMR δ 0.87 (d, J = 6.3 Hz, 3 H, CHCH₃), 1.58 (s, 3 H, CH=CCH₃), 1.66 (s, 3 H, CH=CCH₃), 1.82-2.10 (m, 2 H, CH₂C=), 2.31-2.47 (m, 2 H, CH₂CHO), 5.06 (t, J = 5.5 Hz, 1 H, CH=C), 9.75 (t, J = 1.9 Hz, 1 H, CH=O); ¹³C NMR δ 17.59 (q), 19.19 (q), 25.39 (t), 25.64 (q), 28.81 (t), 31.98 (d), 36.70 (t), 41.63 (t), 124.49 (d), 131.33 (s), 202.83 (d).
To a solution of cis-1-bromo-1-propene (1.0 g, 8.26 mmol) and Ni(Ph3P)2Cl2 (45 mg, 0.07 mmol) in dry THF (10 mL) was added under nitrogen Grignard reagent, which was prepared from 5-bromo-1-tetrahydropyranyl ether (2.08 g, 8.2 mmol) and dry Mg turnings (0.24 g, 9.9 mmol) in THF (15 mL). The mixture changed immediately to a brown homogeneous solution. After stirring for 18 h at rt, the mixture was hydrolysed with dilute acid in ice-water. The combined ethereal extracts were washed with water, saturated aqueous solution of NaHCO3, water, and then dried over MgSO4. After filtration, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel (20 g) eluting with a petroleum ether-ether mixture (9:1) to furnish 52 (93:7)(1.20 g, 67%) as a colourless oil, whose spectral data correspond to those described in the literature:139 1H NMR δ 1.60 (d, J = 5.4 Hz, 3 H, CH3), 2.05 (m, 2 H, CH2CH=CH), 3.30-3.97 (m, 4 H, 2 x CH2O), 4.58 (m, 1 H, OCHO), 5.27-5.56 (m, 2 H, CH=CH); 13C NMR δ 12.68 (q), 19.63 (t), 25.46 (t), 25.84 (t), 26.72 (t), 29.34 (t), 29.61 (t), 30.73 (t), 62.25 (t), 67.61 (t), 98.78 (d), 123.70 (d), 130.58 (d). A TLC analysis on silica gel impregnated with 10% silver nitrate using hexane-ether mixture (5:1) as the developing solvent showed the presence of small amounts of the trans-THP ether (Rf 0.74) along with the cis-isomer (Rf 0.68).
(Z)-Oct-6-en-1-ol (53).

![Chemical structure of (Z)-Oct-6-en-1-ol (53).](image)

A solution of (Z)-1-(tetrahydro-2-pyranyloxy)oct-6-ene (52) (0.20 g, 1.0 mmol) in methanol (15 mL) was stirred in the presence of p-toluenesulfonic acid (30 mg) at rt for 24 h. The reaction mixture was then poured into a saturated aqueous solution of NaHCO₃, and extracted with petroleum ether. The combined organic layer was dried with MgSO₄. After filtration, the solvent was evaporated, and the residue was purified by flash chromatography on silica gel (7 g) using a petroleum ether-ether mixture (9:1 to 4:1) as eluent to furnish an unpleasant-smelling alcohol 53 (150 mg, 84%):

**IR** (film) v 3340 (OH), 1455 (CH def.), and 1055 (C-O) cm⁻¹; **¹H NMR** 8 1.25-1.47 (m, 6 H, 3 x CH₂), 1.60 (d, J = 6.0 Hz, 3 H, CH₂CH₃), 1.8 (s, 1 H, OH), 2.05 (m, 2 H, CH₂CH=CH), 3.61 (t, J = 6.5 Hz, 2 H, CH₂OH), 5.45 (m, 2 H, CH=CH); **¹³C NMR** 8 12.63 (q), 25.30 (t), 26.67 (t), 29.25 (t), 32.54 (t), 62.75 (t), 123.76 (d), 130.45 (d); **MS** m/z (rel. intensity) 110 (24, M⁺-H₂O), 95 (37), 85 (80), 68 (75), 55 (100).

2-Diphenylphosphinoyl-8-hydroxyoctan-3-one (55).

![Chemical structure of 2-Diphenylphosphinoyl-8-hydroxyoctan-3-one (55).](image)

**n-Butyl-Lithium** (6.7 mL, 1.5 M solution in hexane) was added dropwise to a stirred solution of diphenylethylphosphine oxide 54 (2.30 g, 10 mmol) in dry THF (30 mL) at 0 °C.
After 15 min, the mixture was cooled to -78 °C and ε-caprolactone (1.14 g, 10 mmol) was added slowly dropwise. The temperature was maintained at -78 °C for 10 minutes. The reaction mixture was then quenched by adding a saturated aqueous solution of ammonium chloride (20 mL) and allowed to warm to room temperature. After removal of THF under reduced pressure the aqueous layer was extracted with dichloromethane (3 x 30 mL). The organic extracts were dried with MgSO₄, evaporated under reduced pressure, and the residue was chromatographed on silica gel (elution with EtOAc) to afford 55 (2.78 g, 81%) as a colourless oil: \[^{118}R_f\] (EtOAc) 0.2; IR (film) ν 3350 (OH), 1705 (C=O), 1440 (P-Ph), 1265, 1185, and 1120 cm\(^{-1}\); \(^{1}H\) NMR δ 1.1-1.17 (m, 9 H, \((C\text{H}_2\text{)}_3\text{CH}_2\text{OH and CH}_3\)), 2.58 (t, \(J = 7.1\) Hz, 2 H, COCH₂), 3.55 (t, \(J = 6.6\) Hz, 2 H, CH₂OH), 3.6-4.10 (m, 1 H, CHP), 7.9-7.2 (m, 10 H, Ph₂PO); MS \(m/z\) (rel. intensity) 344 (M⁺, 0.6), 230 (23, Ph₂POEt), 202 (81, Ph₂POH), 201 (100, Ph₂P⁺), and 77 (36, C₆H₅⁺).

(6R*,7R*)-7-Diphenylphosphinoyloctan-1,6-diol (56).

\[
\begin{array}{c}
\text{Ph}_2\text{P} \\
\text{O} \\
\text{O} \\
\text{C} \\
\text{OH}
\end{array} \quad \begin{array}{c}
\text{H} \\
\text{O} \\
\text{H}
\end{array} \\
\text{55} \quad \text{theo - 56}
\]

Sodium borohydride (135 mg, 3.56 mmol) was added in one portion to a stirred solution of 55 (1.22 g, 3.56 mmol) in ethanol (20 mL). The reaction mixture was heated under reflux for 3 h, cooled to room temperature and a saturated aqueous solution of ammonium chloride (15 mL) was added. Ethanol was removed under reduced pressure and diluted HCl (ca. 0.5 mL) was added to the aqueous residues. After dilution with brine (20 mL), the aqueous reaction mixture was extracted with dichloromethane (3 x 50 mL) and the combined organic layers were dried with MgSO₄. The crude product, which was a mixture of diastereoisomers, was chromatographed on silica gel eluting with EtOAc followed by acetone to furnish 56 (1.01 g, 82%) as needles, m.p. 109-111 °C (from EtOAc-Hexane) (literature\[^{118b}\] gives
104-105 °C): $^1$H NMR $\delta$ 0.97-1.78 [m, 11 H, (CH$_2$)$_4$ and Me], 2.80-1.80 (m, 3 H, CHP and 2 x OH), 3.61 (t, $J = 6.6$ Hz, 2 H, CH$_2$OH), 3.85 (m, 1 H, CHOH), 7.35-8.0 (m, 10 H, Ph$_2$PO);

MS $m/z$ (rel. intensity) 328 [4, (M$^{++}$-H$_2$O)], 259 [100, M-(CH$_2$)$_5$OH], 229 [35, Ph$_2$PO(CH$_2$)$_2$+], 230 (82, Ph$_2$POEt), 202 (88, Ph$_2$POH), and 201 (87, Ph$_2$PO$^+$).

*(E)-6-Octen-1-ol (57).*

\[
\begin{array}{c}
\text{Ph}_2P \hspace{1cm} \text{OH} \\
\text{H} \\
\text{HO} \\
\text{H} \\
\text{\textbf{threeo - 56}} \\
\text{\textbf{57}}
\end{array}
\]

Sodium hydride (67 mg, 1.67 mmol, 60% dispersion in oil) was added in one portion to a stirred solution of the (6R*,7R*)-adduct threo-(56) (288 mg, 0.833 mmol) in dry DMF (20 mL). The reaction mixture was heated at 50 °C for 30 min by which time a white solid had precipitated from solution. The mixture was allowed to cool to rt and the precipitate was dissolved by addition of water (25 mL). The mixture was then diluted with brine (15 mL) and extracted with Et$_2$O (3 x 40 mL). The combined organic extracts were washed with water (3 x 40 mL), dried with MgSO$_4$, and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using a petroleum ether-ether mixture (4:1) to afford an unpleasant-smelling colourless oil 57 (95 mg, 89%), whose spectral data correspond to those described in the literature:$^{203,204}$ IR (film) $\nu$ 3360 (OH) cm$^{-1}$; $^1$H NMR $\delta$ 1.0-1.62 (m, 6 H, 3 x CH$_2$), 1.64 (d, $J = 4.4$ Hz, 3 H, CHCH$_3$), 1.99 (m, 2 H, CH$_2$CH=), 3.64 (t, $J = 6.6$ Hz, 2 H, CH$_2$OH), 5.39 (m, 2 H, CH=CH); $^{13}$C NMR $\delta$ 17.91 (q), 25.23 (t), 29.34 (t), 32.51 (t), 32.66 (t), 63.04 (t), 124.85 (d), 131.29 (d); MS $m/z$ (rel. intensity) 110 (23, M$^{++}$-H$_2$O), 95 (26), 85 (100), 68 (85), 55 (88). The (Z)-isomer was found to be absent by GLC analysis.

Methyl 8-[(tetrahydro-2'H-pyran-2'-yl)oxy]-2-octynoate (59).
To a mixture of zinc dust (1.30 g, 2 equiv.) and carbontetram bromide (6.64 g, 2 equiv.) in CH$_2$Cl$_2$ (28 mL) was added triphenylphosphine (5.24 g, 2 equiv.) portionwise. After 24 h at 23 °C, a solution of 6-(tetrahydro-2'-pyranyloxy)hexanal 58 (2.0 g, 10 mmol, 1 equiv.) in CH$_2$Cl$_2$ (10 mL) was slowly added. The mixture was stirred for 90 min, poured into hexane (540 mL), and filtered, and the solvent was evaporated under reduced pressure. The residue was diluted with hexane (100 mL), and triphenylphosphine oxide was removed by filtration. Upon removal of solvent, essentially pure dibromool efin 58a (3.28 g, 92%) was obtained as a colourless oil: $^1$H NMR $\delta$ 2.10 (q, $J = 7.1$ Hz, 2 H, CH$_2$CH=), 3.27-3.93 (m, 4 H, 2 x CH$_2$O), 4.56 (m, 1 H, OCHO), 6.37 (t, $J = 7.2$ Hz, 1 H, CH$_2$CH=CB$_2$); $^{13}$C NMR $\delta$ 19.67 (t), 25.48 (t), 25.71 (t), 27.62 (t), 29.44 (t), 30.75 (t), 32.91 (t), 62.32 (t), 67.31 (t), 88.64 (s), 98.85 (d), 138.64 (d); HRMS m/z 354.9731 (calcd for C$_{12}$H$_{19}$O$_2$Br$_2$: 354.9731; M$^{+}$-H$^+)$.

To a solution of the dibromool efin 58a (847 mg, 2.38 mmol) obtained from the above reaction, in THF (30 mL), was added dropwise n-BuLi (3.14 mL, 5.02 mmol, 1.6 M solution in hexane) at -78 °C under nitrogen. After 20 min, methyl chloroformate (0.92 mL, 11.9 mmol) was added dropwise. The mixture was stirred for 10 min at -78 °C, allowed to warm to rt for 45 min, and then poured into ether and brine. The organic layer was washed with aqueous solution of NaHCO$_3$, brine, dried over MgSO$_4$, and the solvent was evaporated. The crude product was purified by flash chromatography on silica gel using a hexane-EtOAc mixture (30:1) as eluent to furnish 59 (0.49 g, 81%) as an oil, whose spectral data correspond to those described in the literature: $^{205}$ IR ν 2235, 1710, 1435, 1135, 1120, 1075, 1030, 908 cm$^{-1}$; $^1$H NMR $\delta$ 1.05-1.90 (m, 12 H), 2.31 (t, $J = 6.9$ Hz, 2 H, CH$_2$CCO$_2$Me), 3.25-3.95 (m, 4 H, 2 x CH$_2$O) and (s, 3 H, -OCH$_3$), 4.53 (m, 1 H, OCHO); $^{13}$C NMR $\delta$ 18.54 (t), 19.59 (t), 25.42 (t), 25.49 (t), 27.30 (t), 29.08 (t), 30.68 (t), 52.41 (q), 62.26 (t), 67.12 (t), 72.89 (s),
Methyl (Z)-8-[(tetrahydro-2'H-pyran-2'-yl)oxy]-2-octenoate (60).

\begin{center}
\begin{align*}
\text{Methyl (Z)-8-[(tetrahydro-2'H-pyran-2'-yl)oxy]-2-octenoate} \quad & \text{\textcopyright} \quad \text{60} \\
\text{A mixture of acetylene 69 (0.52 g, 2.04 mmol), quinoline (0.75 mL, 6.33 mmol), and Lindlar catalyst (0.37 g) in hexane (57 mL) was stirred under 1 atm of H}_2 \text{ (g) for 4.5 h. After removal of the solids by filtration through celite, the solution was washed with 1M HCl, water, aqueous solution of NaHCO}_3 \text{, and brine, and dried over MgSO}_4. \text{Upon removal of the solvent, pure 60 (517 mg, 99\%) was obtained as a colourless oil: IR } & \nu \text{ 2940, 2860, 1718, 1645, 1440, 1275, 1165, 1135, 1120, 1075, 1025, 900, 865 cm}^{-1}; ^1\text{H NMR } \delta \text{ 1.10-1.95 (m, 12 H), 2.63 (m, 2 H, CH}_2\text{CH}=\text{), 3.25-3.92 (m, 4 H, 2 x CH}_2\text{O) and (s, 3 H, -OCH}_3\text{), 4.53 (m, 1 H, OCHO), 5.73 (d, J } \text{= 11.6 Hz, 1 H, CH=CHCO}_2\text{Me), 6.19 (dt, J } \text{= 11.3, 7.6 Hz, 1 H, CH=CHCO}_2\text{Me); } ^{13}\text{C NMR } \delta \text{ 19.60 (t), 25.46 (t), 25.90 (t), 28.79 (t), 28.87 (t), 29.48 (t), 30.71 (t), 50.86 (q), 62.22 (t), 67.37 (t), 98.75 (d), 119.23 (d), 150.62 (d), 166.74 (s); HRMS m/z } \text{255.1596 (calced for C}_{14}\text{H}_{23}\text{O}_4; 255.1596; M}^{++-\text{H}^+}. \\
\end{align*}
\end{center}
the solvent was evaporated to furnish the required product 61 (96 mg, 84%): IR \( \nu(\text{OH}) \) 3618 and 3680 cm\(^{-1}\); \(^1\)H NMR \( \delta \) 1.21-1.93 (m, 12 H), 1.93-2.14 (m, 2 H, \( \text{CH}_2\text{CH}=\)), 3.28-3.91 (m, 4 H, 2 x \( \text{CH}_2\text{O} \)), 4.15 (s, 2 H, \( \text{CH}_2\text{OH} \)), 4.54 (m, 1 H), 5.39-5.67 (m, 2 H, \( \text{CH}=\text{CH} \)); \(^{13}\)C NMR \( \delta \) 19.60 (t), 25.40 (t), 25.66 (t), 27.14 (t), 29.21 (t), 29.41 (t), 30.67 (t), 58.39 (t), 62.29 (t), 67.47 (t), 98.82 (d), 128.61 (d), 132.63 (d); HRMS \( m/z \) 228.1728 (calcd for \( \text{C}_{13}\text{H}_{24}\text{O}_3 \): 228.1725; M\(^+\)).

\((Z)-8-[(\text{Tetrahydro-2'}\text{H-pyran-2'-yl})\text{oxy}]-2\text{-octenylacetate (62)}.

To a solution of alcohol 61 (1.83 g, 8.06 mmol) in dry THF (17 mL) at rt was added pyridine (0.97 mL, 12 mmol). Acetic anhydride (1.13 mL, 12 mmol) was then added and the resulting reaction mixture was stirred overnight. Evaporation of the solvent afforded a crude residue which was diluted with ether (150 mL) and washed with saturated aqueous solution of CuSO\(_4\) (2 x 15 mL), water (10 mL), saturated aqueous solution of NaHCO\(_3\) (2 x 15 mL), and brine (10 mL). The ethereal layer was dried with MgSO\(_4\), filtered and evaporated. The residue was chromatographed on a column of silica gel (50 g) with petroleum ether-ether mixture (9:1) to furnish 62 (1.98 g, 91%): IR \( \nu(\text{C}=\text{O}) \) 1730 cm\(^{-1}\); \(^1\)H NMR \( \delta \) 1.89-1.93 (m, 12 H), 2.08 (m, 2 H, \( \text{CH}_2\text{=CH} \)), 2.06 (s, 3 H, \( \text{CO}_2\text{CH}_3 \)), 3.27-3.94 (m, 4 H, 2 x \( \text{CH}_2\text{O} \)), 4.57 (m, 1 H, OCHO), 4.61 (d, \( \text{J} = 6.6 \text{ Hz} \), 2 H, \( \text{=CHCH}_2\text{OH} \)), 5.44-5.92 (m, 2 H, \( \text{CH}=\text{CH} \)); \(^{13}\)C NMR
\( \delta \) 19.62 (t), 20.92 (q), 25.44 (t), 25.79 (t), 27.41 (t), 29.20 (t), 29.52 (t), 30.71 (t), 60.30 (t), 62.26 (t), 67.42 (t), 98.79 (d), 123.35 (d), 135.18 (d), 170.90 (d); HRMS \( m/z \) 270.1830 (calcd for \( C_{15}H_{26}O_4 \): 270.1831; \( M^+ \)).

(Z)-7-[(Tetrahydro-2'H-pyran-2'-yl)oxy]-1-[(dimethylphenylsilyl)methyl]hept-1-ene (63).

Phenyldimethylchlorosilane (1.29 mL, 7.8 mmol) was added to a suspension of finely cut lithium wire (275 mg) in dry THF (15 mL). After being stirred for 90 min at rt the solution turned dark red. Continued vigorous stirring for 3 h then produced a brownish solution which was transferred with the aid of a canula to a suspension of CuCN (0.49 g, 5.5 mmol) in dry THF (7 mL) at 0 °C. After 90 min, the reaction mixture was cooled to -60 °C and a solution of acetate 62 (1.05 g, 3.9 mmol) in dry THF (7 mL) was added. The resulting mixture was stirred at -60 °C for 12 h, poured into a 1:1 mixture of saturated aqueous \( \text{NH}_4\text{Cl} \)/saturated aqueous \( \text{Na}_2\text{CO}_3 \) (250 mL) and extracted with ether. The combined ethereal layers were dried, filtered and evaporated. The residue was chromatographed on silica gel using a hexane-ether mixture (30:1 to 4:1) to furnish 63 (1.01 g, 75%) as a colourless oil: \(^1\)H NMR \( \delta \) 0.27 (s, 6 H, Si(CH\(_3\)_2Ph), 1.0-1.68 (m, 12 H), 1.72 (d, \( J = 7.9 \text{ Hz} \), 2 H, CH=CHCH\(_2\)Si), 1.90-1.99 (m, 2 H), 3.25-3.96 (m, 4 H, 2 x CH\(_2\)O), 4.57 (m, 1 H, OCHO), 5.17-5.47 (m, 2 H, CH=CH), 7.28-7.57 (m, 5 H, aryl-H); \(^{13}\)C NMR \( \delta \) -3.31 (2 x q), 17.50 (t), 19.65 (t), 25.49 (t), 26.00 (t), 27.01 (t), 29.50 (t), 29.65 (t), 30.75 (t), 62.25 (t), 67.58 (t), 98.79 (d), 124.62 (d), 127.66 (d), 128.25 (d), 128.89 (d), 133.53 (d), 138.92 (s); HRMS \( m/z \) 346.2328 (calcd for \( C_{21}H_{34}O_2\)Si: 346.2328; \( M^{+*} \)).
(Z)-7-([(Dimethylphenylsilyl)methyl]-1-hydroxy-hept-6-ene (64).

\[
\text{PhMe}_2\text{Si} \quad \text{OTHP} \quad \text{OH} \quad \text{PhMe}_2\text{Si}
\]

A solution of 63 (346 mg, 1.0 mmol) in MeOH (15 mL) was stirred in the presence of p-toluene sulfonic acid (30 mg) at rt. After 7 h, the reaction mixture was poured into a saturated aqueous solution of sodium hydrogen carbonate, and extracted with ether, and dried over MgSO₄. The solvent was evaporated under reduced pressure, and the residue was purified on silica gel (10 g) eluting with a hexane-ether mixture (4:1) to afford 64 (249 mg, 95%) as a colourless oil: IR ν(OH) 3620 cm⁻¹; $^1$H NMR δ 0.27 (s, 6 H, -Si(CH₃)₂C₆H₅), 1.16-1.64 (m, 6 H), 1.70 (d, $J = 7.9$ Hz, 2 H, CH=CHCH₂Si), 1.93 (m, 2 H, CH₂CH=C), 3.61 (t, $J = 6.4$ Hz, 2 H, CH₂OH), 5.16-5.48 (m, 2 H, CH=CH), 7.28-7.61 (m, 5 H, aryl-H); $^{13}$C NMR δ -3.32 (q), 17.52 (t), 25.44 (t), 26.98 (t), 29.41 (t), 32.65 (t), 62.93 (t), 124.75 (d), 127.66 (d), 128.09 (d), 128.90 (d), 133.55 (d), 138.88 (s). HRMS m/z 262.1753 (calcd for C₁₆H₂₆OSi: 262.1753; M⁺⁺).

Ethyl (E)-8-[(tetrahydro-2'H-pyran-2'-yl)oxy]-2-octenoate (65)

Aldehyde 58 (2.2 g, 11.0 mmol) was added dropwise over a period of 15 min to a refluxing solution of (carbethoxymethylene)triphenylphosphorane (3.83 g, 11.0 mmol) in
benzene (10 mL). TLC analysis with a hexane-EtOAC mixture (4:1) indicated that the reaction was complete after 3 h. The solvent was evaporated, and the residue was dissolved in hexane and filtered through silica gel to remove triphenylphosphine oxide. Evaporation of the solvent furnished the unsaturated ester 65 (96:4) (2.64 g, 89%) as a colorless oil, whose spectral data correspond to those described in the literature: 206 IR ν (C=O) 1710, 1657 cm⁻¹; ¹H NMR δ 1.28 (t, J = 7.1 Hz, 3 H, CH₃), 1.35-1.55 (m, 12 H), 2.13-2.59 (m, 2 H, CH₂CH=), 3.31-3.94 (m, 4 H, 2 x CH₂O), 4.18 (q, J = 7.1 Hz, 2 H, OCH₂CH₃), 4.57 (m, 1 H, OCHO), 5.81 (d, J = 15.7 Hz, 1 H, CH=CHCO₂Me), 6.19 (dt, J = 15.7, 6.9 Hz, 1 H, CH=CHCO₂Me); ¹³C NMR δ 14.20 (q), 19.64 (t), 25.43 (t), 25.74 (t), 27.79 (t), 29.43 (t), 30.70 (t), 30.03 (t), 60.04 (t), 62.31 (t), 67.31 (t), 98.83 (d), 121.33 (d), 149.07 (d), 166.65 (s); HRMS (El) m/z 269.1753 (calcd for C₁₅H₂₅O₄: 269.1753; M⁺-1).

(ZS)-8-[(Tetrahydro-2'H-pyran-2'-yl)oxy]-2-octen-1-ol (66).

\[
\begin{align*}
\text{65} & \quad \text{CO₂Et} \\
\text{66} & \quad \text{CH₂OH}
\end{align*}
\]

Obtained from 65 on DIBAL-H reduction (in the same way as 61 was prepared from 60) to afford a colourless oil 66 (103 mg, 90%), whose spectral data correspond to those described in the literature: 207 IR ν(OH) 3605, 3440 cm⁻¹; ¹H NMR δ 1.27-1.94 (m, 12 H), 1.97-2.16 (m, 2 H, CH₂CH=), 3.30-3.95 (m, 4 H, 2 x CH₂O), 4.07 (d, J = 4.4 Hz, 2 H, CH₂OH), 4.57 (m, 1 H, OCHO), 5.47-5.78 (m, 2 H, CH=CH); ¹³C NMR δ 19.61 (t), 25.42 (t), 25.69 (t), 28.87 (t), 29.49 (t), 30.69 (t), 32.04 (t), 62.29 (t), 63.62 (t), 67.48 (t), 98.80 (d), 129.03 (d), 133.01 (d). HRMS (El) m/z 227.1647 (calcd for C₁₃H₂₃O₃: 227.1647; M⁺-1).
(E)-8-[(Tetrahydro-2'H-pyran-2'-yl)oxy]-2-octenylacetate (67).

\[
\begin{align*}
\text{66} & \quad \text{O} \quad \text{THP} \\
\text{CH}_2\text{OH} & \quad \text{CH}_2\text{OAc} \\
\text{67} & \quad \text{O} \quad \text{THP}
\end{align*}
\]

Obtained from \textbf{66} on acetylation (in the same way as \textbf{62} was prepared from \textbf{61}). \textbf{67} (2.02 g, 93\%): IR \nu(C=O) 1730 cm\(^{-1}\); \(^1\)H NMR \delta 1.23-1.86 (m, 12 H), 1.97-2.17 (m, 2 H, \text{CH}_2\text{CH}=), 2.06 (s, 3 H, \text{COCH}_3), 3.31-3.94 (m, 4 H, 2 x \text{CH}_2\text{O}), 4.50 (d, \text{J} = 6.5 \text{ Hz}, 2 \text{ H}, \text{CH}_2\text{OAc}), 4.57 (m, 1 \text{ H, OCHO}), 5.47-5.66 (m, 1 \text{ H, CH=CH}), 5.68-5.86 (m, 1 \text{ H, CH=CH}); \(^1\)C NMR \delta 19.60 (t), 20.90 (q), 25.40 (t), 25.67 (t), 28.61 (t), 29.46 (t), 30.68 (t), 32.06 (t), 62.24 (t), 65.15 (t), 67.39 (t), 98.77 (d), 123.78 (d), 136.29 (d), 170.71 (s); HRMS (El) m/z 269.1753 (caled for \text{C}_{15}\text{H}_{25}\text{O}_4: 269.1753; \text{M}^{+}-1).

\[\text{(E)-7-[(Tetrahydro-2'H-pyran-2-yl)oxy]-1-[(Dimethylphenylsilyl) methyl]hept-1-ene (68).}\]

\[
\begin{align*}
\text{67} & \quad \text{O} \quad \text{THP} \\
\text{CH}_2\text{OAc} & \quad \text{SiMe}_2\text{Ph} \\
\text{68} & \quad \text{O} \quad \text{THP}
\end{align*}
\]

Obtained from \textbf{67} (in the same way as \textbf{63} was prepared from \textbf{62}). \textbf{68} (0.90 g, 67\%): \(^1\)H NMR \delta 0.25 (s, 6 H, -\text{Si(CH}_3)_2\text{C}_6\text{H}_5), 1.15-1.84 (m, 12 H), 1.65 (d, \text{J} = 7.5 \text{ Hz}, 2 \text{ H, CH=CHCH}_2\text{Si}), 1.96 (m, 2 \text{ H, CH}_2\text{CH}=\text{C}), 3.27-3.95 (m, 4 \text{ H, 2 x CH}_2\text{O}), 4.57 (m, 1 \text{ H,
OCHO), 5.14-5.46 (m, 2 H, CH=CH), 7.27-7.60 (m, 5 H, aryl-H); $^{13}$C NMR δ -3.43 (q), 19.64 (t), 21.55 (t), 25.49 (t), 25.66 (t), 29.60 (t), 29.72 (t), 30.75 (t), 32.64 (t), 62.23 (t), 67.59 (t), 98.77 (d), 125.38 (d), 127.63 (d), 128.82 (d), 129.60 (d), 133.58 (d), 138.96 (s). HRMS m/z 346.2328 (calcd for C$_{21}$H$_{34}$O$_2$Si: 346.2328; M$^{+}$).

$(E)$-7-[(Dimethylphenylsilyl)methyl]-1-hydroxy-hept-6-ene (69).

Obtained from 68 on deprotection (in the same way as 64 was prepared from 63). 69: IR v(OH) 3615 cm$^{-1}$; $^1$H NMR δ 0.25 (s, 6 H, -Si(CH$_3$)$_2$C$_6$H$_5$), 1.20-1.61 (m, 7 H), 1.65 (d, J = 7.2 Hz, 2 H, CH=CHCH$_2$Si), 1.85-2.05 (m, 2 H, CH$_2$CH=C), 3.61 (t, J = 6.6 Hz, 2 H, CH$_2$OH), 5.15-5.47 (m, 2 H, CH=CH), 7.29-7.56 (m, 5 H, aryl-H); $^{13}$C NMR δ -3.43 (q), 21.56 (t), 25.10 (t), 29.63 (t), 32.62 (t), 62.97 (t), 125.53 (d), 127.64 (d), 128.84 (d), 129.48 (d), 133.59 (d), 138.97 (s). HRMS m/z 262.1753 (calcd for C$_{16}$H$_{26}$OSi: 262.1753; M$^{+}$).

(Z)-1-Iodo-3-hexene (70).

A solution of (Z)-3-hexen-1-ol (5.0 g, 48.9 mmol) in pyridine (40 mL) was cooled to 0 °C under argon, and methanesulfonyl chloride (4.17 mL, 1.1 equiv) was added dropwise. After 1 h at 0 °C, the solution was warmed to room temperature for 5 h. The mixture was
then diluted with ether and and filtered, and the filtrate was evaporated under reduced pressure. The residual oil was dissolved in ether, washed with 10% HCl, saturated aqueous solution of NaHCO₃, and brine, and dried with Na₂SO₄. After removal of the solids by filtration, the solvent was evaporated under reduced pressure to furnish the mesylate (7.24 g, 83%) as a pale yellow oil.

Sodium iodide (9.2 g, 1.5 equiv) was added to a solution of the mesylate (7.24 g, 40.5 mmol) in acetone (90 mL) and heated to reflux (70-75 °C) for 15 h. After cooling to rt, the solution was diluted with light petroleum ether, washed three times with water, brine, and dried with Na₂SO₄. Following evaporation of solvent, distillation under reduced pressure furnished a red oil which was then passed through a short column of neutral alumina, eluting with pentane. The solvent was evaporated, and the product was distilled to afford 70 as an orange oil (7.57 g, 89%), bp 59-62 °C (12 mmHg): ²⁰⁸H NMR δ 0.98 (t, J = 7.5 Hz, 3 H), 2.04 (quintet of d, J = 7.5 and 1.3 Hz, 2 H), 2.60 (br q, J = 7.2 Hz, 2 H), 3.14 (t, J = 7.2 Hz, 2 H), 5.26-5.34 (m, 1 H), 5.49-5.59 (m, 1 H). ¹³C NMR δ 5.6 (t), 14.1 (q), 20.8 (t), 31.4 (t), 127.1 (d), 134.2 (d).

**(Z)-1-Iodo-3-hexene (71).**

\[
\text{O} \quad \rightarrow \quad \text{I}
\]

Obtained in two steps (7.14 g, 84%) from commercially available (E)-3-hexene-1-ol, via formation of the mesylate (MesCl, py, 0 °C → rt) followed by a Finkelstein reaction (in the same way as 70 was prepared from (Z)-3-hexen-1-ol). 71: ²⁰⁹H NMR δ 0.98 (t, J = 7.5 Hz, 3 H), 2.05 (quintet of d, J = 7.3, 1.0 Hz, 2 H), 2.53 (br q, J = 7.0 Hz, 2 H), 3.14 (t, J = 7.3 Hz, 2 H), 5.25-5.44 (m, 1 H), 5.47-5.67 (m, 1 H).
(E)-4-Trimethylsilylpent-3-en-1-ol (73).

\[
\begin{array}{c}
\text{SiMe}_3 \\
72
\end{array} \quad \text{HO} \quad \begin{array}{c}
\text{SiMe}_3 \\
73
\end{array}
\]

A solution of MeMgBr in Et₂O (3.6 mL, 10.9 mmol) was added to a stirred suspension of (Ph₃P)₂NiCl₂ (0.22 g, 0.3 mmol) in dry benzene (10 mL) at rt under dry nitrogen. The deep red solution was stirred for 15 min, and the solvent was then replaced with dry benzene (15 mL). A solution of 5-trimethylsilyl-2,3-dihydrofuran 72 (0.50 g, 3.4 mmol) in benzene (5 mL) was added and the mixture was refluxed. After 1.5 h, the mixture was cooled and poured into a saturated solution of ammonium hydroxide (2.0 mL) in saturated ammonium chloride (18 mL) with vigorous stirring. The mixture was stirred until decolourised, extracted with ether and the combined ethereal extracts were dried with MgSO₄. After filtration, the solvent was evaporated under reduced pressure and the residue was distilled (Kugelrohr) to afford 73 (0.51 g, 3.22 mmol, 95%) as a colourless oil:¹¹¹ b.p. 90 °C (bath)/3 mmHg. ¹H NMR δ 0.04 (s, 9 H), 1.69 (d, J = 0.8 Hz, 3 H), 1.98 (br s, 1 H), 2.37 (dt, J = 6.7 and 6.9 Hz, 2 H), 3.65 (t, J = 6.7 Hz, 2 H), 5.70 (m, J = 1.7 and 6.9 Hz, 1 H); ¹³C NMR δ -2.19 (q), 14.56 (q), 31.84 (t), 62.0 (t), 134.16 (d), 139.81 (s).

(E)-1-Iodo-4-trimethylsilylpent-3-ene (74).

\[
\begin{array}{c}
\text{HO} \\
\text{SiMe}_3 \\
73
\end{array} \quad \text{I} \quad \begin{array}{c}
\text{SiMe}_3 \\
74
\end{array}
\]
Obtained in two steps (91%) from homoallylic alcohol 73, via formation of the mesylate (MesCl, py, 0 °C → rt) followed by a Finkelstein reaction (in the same manner as 70 was prepared from commercially available (Z)-3-hexen-1-ol). 74: \( ^1H \text{ NMR} \delta 0.00 (s, 9 \text{ H}), 1.61 (d, J = 0.9, 3 \text{ H}), 2.56-2.69 (m, 2 \text{ H}), 3.09 (t, J = 7.6, 2 \text{ H}), 5.56 (m, 1 \text{ H}); ^{13}C \text{ NMR} \delta -2.2 (q), 5.1 (t), 14.7 (q), 32.5 (t), 136.7 (d), 139.3 (s).

6-(Benzyloxy)-4-methyl-hexanal (76).

\[ \text{O} \]
\[ \text{OBn} \]
\[ \text{76} \]

A steady stream of ozone in oxygen generated with a Wallace and Tiernan Ozoniser was bubbled through a solution of 1-(benzyloxy)-3,7-dimethyloct-6-ene (12.3 g, 50 mmol) and pyridine (4.3 mL, 50 mmol) in dry \( \text{CH}_2\text{Cl}_2 \) (120 mL) for 4.5 h at -78 °C. Dimethyl sulfide (8.6 mL) was added and the solution was allowed to warm to rt. After 5 h, the volatile materials were removed under reduced pressure and the residue was diluted with water and extracted with hexane. The combined organic layers were washed with 5% HCl and brine, dried with \( \text{MgSO}_4 \) and evaporated. The crude product (11 g) was purified by flash chromatography on a column of silica gel using petroleum ether-ether mixture (9:1) as eluent to furnish 76 (6.65 g, 61%), whose spectral data correspond to those described in the literature: \(^{210} \text{IR (neat)} ν 2725 (\text{CH}), 1725 \text{ cm}^{-1}(\text{C=O}); ^1H \text{ NMR} \delta 0.93 (d, J = 6.0 \text{ Hz}, 3 \text{ H}, \text{CHCH}_3), 1.37-1.88 (m, 5 \text{ H}), 2.34-2.56 (m, 2 \text{ H}, \text{CH}_2\text{CHO}), 3.54 (t, J = 6.4 \text{ Hz}, 2 \text{ H}, \text{CH}_2\text{CH}_2\text{O}), 4.52 (s, 2 \text{ H}, \text{OCH}_2\text{C}_6\text{H}_5), 7.36 (s, 5 \text{ H}, \text{aryl-H}), 9.78 (t, J = 1.7 \text{ Hz}, 1 \text{ H}, \text{CHO}); ^{13}C \text{ NMR} \delta 19.22 (q), 28.78 (t), 29.44 (d), 36.37 (t), 41.52 (t), 68.18 (t), 72.89 (t), 127.46 (d), 127.54 (d), 128.28 (d), 138.45 (s), 202.65 (d).
Ethyl 2,6-dimethyl-8-benzyloxy-2(E)-octenoate (77).

Aldehyde 76 (1.16 g, 5.26 mmol) was added dropwise over a period of 15 min to a refluxing solution containing ethyl 2-(triphenylphosphoranylidene)propionate (2.4 g, 6.64 mmol) in dichloromethane (5 mL). After 4 h, the reaction was found to be complete by TLC analysis with hexane-ethyl acetate mixture (5:1) as the developing solvent. The solvent was evaporated and the residue was dissolved in petroleum ether and filtered through silica gel (10 g) to remove starting phosphorane and triphenylphosphine oxide. Removal of the solvent under reduced pressure gave unsaturated ester 77 (1.48 g, 93 %):\(^{123}\) IR ν 1700 (C=O), 1645 (C=C), and 1270 cm\(^{-1}\) (CO); \(^1\)H NMR δ 0.69 (d, \(J = 6.3\) Hz, 3 H, CHCH\(_3\)), 1.15-1.58 (m, 5 H), 1.07 (t, \(J = 7.1\) Hz, 3 H, CO\(_2\)CH\(_2\)CH\(_3\)), 1.61 (s, 3 H, CH\(_3\)), 1.95 (m, 2 H, CH\(_2\)CH=CMeoCO\(_2\)Et), 3.28 (t, \(J = 6.5\) Hz, 2 H, CH\(_2\)OBn), 3.96 (q, \(J = 7.2\) Hz, 2 H, OCH\(_2\)CH\(_3\)), 4.28 (s, 2 H, OCH\(_2\)C\(_6\)H\(_5\)), 6.52 (t, \(J = 7.6\) Hz, 1 H, vinyl-H), 7.11 (s, 5 H, aryl-H); \(^{13}\)C NMR δ 12.27 (q), 14.26 (q), 19.37 (q), 26.16 (t), 29.67 (d), 35.72 (t), 36.53 (t), 60.34 (t), 68.42 (t), 72.92 (t), 127.47 (d), 127.58 (d), 128.40 (d), 138.54 (s), 142.29 (d), 168.24 (s). HRMS \(m/z\) 304.2039 (calcd. for C\(_{19}\)H\(_{28}\)O\(_3\): 304.2039; M\(^+\)).
Ethyl 2,6-dimethyl-8-hydroxy-2(E)-octenoate (78).

To a solution of ether 77 (0.61 g, 2.2 mmol) in CDCl$_3$ (3 mL) was added neat trimethylsilyl iodide (0.4 mL, 3.0 mmol) under N$_2$. After 1.25 h, the reaction mixture was poured into methanol (0.4 mL). The volatiles were evaporated under reduced pressure and the residue was diluted with Et$_2$O (100 mL), washed with aqueous solution of sodium bisulfite, aqueous solution of NaHCO$_3$, and brine, and dried with MgSO$_4$. The solvent was evaporated and the crude product was purified on silica gel (20 g) eluting with a hexane-ether mixture (5:1 to 1:1) to afford 78 as colourless oil (0.39 g, 97%): IR v 3620, 1700 and 1645 cm$^{-1}$; $^1$H NMR $\delta$ 0.83 (d, $J = 6.3$ Hz, 3 H), 1.19 (t, $J = 7.1$ Hz, 3 H), 1.20-1.55 (m, 6 H), 1.73 (s, 3 H), 1.95-2.23 (m, 2 H), 3.48-3.70 (m, 2 H), 4.08 (q, $J = 7.1$ Hz, 2 H), 6.65 (dt, $J = 7.5$ and 1.4 Hz, 1 H); $^{13}$C NMR $\delta$ 12.22 (q), 14.19 (q), 19.28 (q), 26.10 (t), 29.24 (d), 35.73 (t), 39.60 (t), 60.35 (t), 60.79 (t), 127.60 (s), 142.22 (d), 168.26 (s).

Methyl-[N-(4-methylpent-3-enyl)methylamino]acetate (80).
A solution of sarcosine methyl ester hydrochloride (9.83 g, 70 mmol), N-ethyldiisopropylamine (11.73 mL, 70 mmol), 1-bromo-4-methylpent-3-ene 79 (1.88 mL, 14 mmol) and 20 mL of ethanol was deoxygenated with nitrogen and treated with sodium iodide (ca. 80 mg) at room temperature. The resulting solution was heated at 75 °C for 4 h, cooled to room temperature and diluted with saturated aqueous solution of NaHCO3 (30 mL). The aqueous phase was extracted with dichloromethane (3 x 20 mL) and the combined organic layers were dried with K2CO3. After filtration, the solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel using a petroleum ether-ether mixture (5:1) to afford 80 as a colourless oil (2.4 g, 93%): 1H NMR δ 1.53 (s, 3 H, CH3), 1.60 (s, 3 H, CH3), 2.15-2.06 (m, 2 H, CH2CH=CMe2), 2.29 (s, 3 H, -NCH3), 2.40 (t, J = 7.9 Hz, 2 H, CH2NCH3CH2CO2Me), 2.19 (s, 2 H, CH2CO2Me), 3.63 (s, 3 H, CO2CH3), 4.98 (m, 1 H, C=CH); 13C NMR δ 17.67 (q), 25.66 (q), 26.18 (t), 42.37 (q), 51.50 (q), 56.97 (t), 58.35 (t), 121.48 (d), 132.9 (s), 171.41 (s).

N,N-(2-hydroxyethyl)(4'-methylpent-3'-enyl)methylamine (81).

![Diagram](image)

To a suspension of LiAlH4 (0.27 g, 7.1 mmol) in dry ether (100 mL) at -5 °C was added dropwise a solution of the ester 80 (1.31 g, 7.1 mmol) in ether (15 mL) over 15 min. When the addition was complete, the reaction mixture was allowed to reach room temperature whereupon it was stirred for 1 h. The mixture was cooled in an ice-bath, reaction product and excess of hydride were decomposed by the adding dropwise water (0.27 mL), 15 % aqueous solution of sodium hydroxide (0.27 mL) and water (0.81 mL) in succession. After vigorous stirring for a further 20 min, the mixture was filtered with suction and the granular precipitate
was washed thoroughly with ether. The combined ethereal layers were washed with brine, water, and dried over Na$_2$SO$_4$. Upon removal of solvent, pure alcohol 81 (1.01 g, 91%) was obtained: $^1$H NMR $\delta$ 1.54 (s, 3 H, CH=CCH$_3$), 1.61 (s, 3 H, CH=CCH$_3$), 2.0-2.17 (m, 2 H), 2.18 (s, 3 H, NCH$_3$), 2.33 (t, $J$ = 6.93 Hz, 2 H, CH$_2$NCH$_3$), 2.45 (t, $J$ = 5.35 Hz, 2 H, CH$_2$CH$_2$O), 2.71 (br s, 1 H, -OH), 3.49 (t, $J$ = 5.38 Hz, 2 H, CH$_2$OH), 5.05-4.98 (m, 1 H, C=CH); $^{13}$C NMR $\delta$ 17.7 (q), 25.6 (q), 25.9 (t), 41.5 (q), 57.4 (t), 58.3 (t), 58.6 (t), 121.7 (d), 132.8 (s).

2-[(3'-Methyl-2'-butenyl)oxy]-1-bromobenzene (82a).

To a stirred solution of triphenylphosphine (1.61 g, 6 mmol) in THF (10 mL) was added 3-methyl-2-buten-1-ol (0.35 g, 4 mmol), 2-bromophenol (1.04 g, 6 mmol) and of diethyl azodicarboxylate (DEAD) (0.97 mL, 6 mmol) at room temperature in succession. After 3 h the reaction mixture was diluted with hexane, washed with water, brine, and dried with MgSO$_4$. After filtration, the solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel with a hexane-ether mixture (9:1) to give 82a (0.9 g, 94 %);$^{135}$ $^1$H NMR $\delta$ 1.75 (s, 3 H, CH$_3$), 1.79 (s, 3 H, CH$_3$), 4.59 (d, $J$ = 6.60 Hz, 2 H, OCH$_2$CH=CMe$_2$), 5.47-5.53 (m, 1 H, C=CH), 6.81 (t, $J$ = 7.69 Hz, 1 H), 6.90 (d, $J$ = 8.06 Hz, 1 H), 7.22 (t, $J$ = 7.69 Hz, 1 H), 7.53 (d, $J$ = 7.69 Hz, 1 H). LRMS 242, 240 (M**)
1-(Tetrahydro-2'-pyranyloxy)oct-6-yn-1-ol (84).

To a solution of dibromoolefin 58a (0.85 g, 2.38 mmol) in THF (30 mL) was added n-BuLi (3.14 mL, 5.02 mmol, 1.6M solution in hexane) at -78 °C under nitrogen. After 0.5 h at -78 °C, methyl iodide (0.31 mL, 5.02 mmol) in HMPT (8.0 mL) was added dropwise. The resulting mixture was allowed to warm to rt, poured into ice cold water within 30 min and extracted with ether. The combined ethereal layers were dried over MgSO₄, evaporated and the residue was purified on silica gel (20 g) eluting with a hexane-ether mixture (9:1) to furnish 84 (435 mg, 87%) as a colourless oil, spectral data correspond to those described in the literature: ¹³⁹ H NMR δ 1.0-1.69 (m, 12 H), 1.75 (t, J = 2.5 Hz, 3 H, CH₃), 2.05-2.17 (m, 2 H, CH₂C≡CCH₃), 3.27-3.95 (m, 4 H, 2 x CH₂O), 4.56 (m, 1 H, OCHO); ¹³ C NMR δ 3.38 (q), 18.65 (t), 19.62 (t), 22.61 (t), 25.49 (t), 28.89 (t), 29.28 (t), 30.74 (t), 62.25 (t), 67.42 (t), 75.38 (s), 79.12 (s), 98.80 (d); HRMS m/z 210.1620 (calcd for C₁₃H₂₂O₂: 210.1620; M**).

6-Octyn-1-ol (85).

6-Octyn-1-ol (85).
Obtained from 84 on deprotection (in the same way as 64 was prepared from 63). 85 (91%): $^1$H NMR $\delta$ 1.0-1.67 (m, 6 H), 1.75 (t, $J = 2.5$ Hz, 3 H, CH$_3$), 2.01-2.24 (m, 2 H, CH$_2$C≡CCH$_3$), 3.62 (t, $J = 6.3$ Hz, 2 H, CH$_2$OH); $^{13}$C NMR $\delta$ 3.38 (q), 18.65 (t), 24.98 (t), 28.78 (t), 32.26 (t), 62.79 (t), 75.53 (s), 79.03 (s); HRMS m/z 125.0967 (calcd for C$_8$H$_{13}$O: 125.0966; M$^+$/-H$^+$).

4,8-Dimethylnon-7-enonitrile (88).

To a solution of 3,7-dimethyl-6-octen-1-ol 86 (3.07 g, 19.7 mmol) in pyridine (20 mL) was added dropwise a solution of p-toluenesulfonyl chloride (11.3 g, 59.1 mmol) in pyridine (22 mL) at 0 °C, and the mixture was stirred at 0 °C for 2 h and then at rt for 3 h. The mixture was poured into 10% aqueous HCl (200 mL) and extracted with ether. The combined organic layers were washed with water, dried with MgSO$_4$, and evaporated under reduced pressure. The residue was purified on a column of silica gel (45 g) with a petroleum ether-ether mixture (9:1) to furnish the corresponding tosylate 87 (4.2 g, 69%) as a colourless oil: $^1$H NMR $\delta$ 0.80 (d, $J = 6.3$ Hz, 3 H, CH$_3$), 0.95-1.55 (m, 5 H), 1.55 (s, 3 H, CH=CCH$_3$), 1.65 (s, 3 H, CH=CCH$_3$), 1.75-2.03 (m, 2 H, CH$_2$CH=), 2.43 (s, 3 H, CH$_3$), 4.04 (t, $J = 6.6$ Hz, 2 H, CH$_2$O), 4.95-5.07 (m, 1 H, CH=C), 7.32 (d, $J = 8.2$ Hz, 2 H, arom), 7.77 (d, $J = 8.2$ Hz, 2 H, arom); $^{13}$C NMR $\delta$ 17.56 (q), 18.96 (q), 21.56 (q), 25.19 (t), 25.65 (q), 28.77 (d), 35.57 (t), 36.62 (t), 68.99 (t), 124.25 (d), 127.81 (d), 129.75 (d), 131.38 (s), 133.12 (s), 144.60 (s); MS m/z 310 (M$^{**}$).
Sodium cyanide (487 mg, 9.94 mmol) was added to a solution of 3,7-Dimethyl-1-[(p-tolylsulfonyl)oxy]oct-6-ene 87 (2.37 g, 7.65 mmol) in DMSO (30 mL), and the mixture was stirred at 60 °C for 1 h. The mixture was then poured into ice-water (30 mL) and extracted with ether (3 x 50 mL). The combined ethereal layers were washed with water (2 x 20 mL) and dried over anhydrous CaCl₂. After filtration, the solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel using petroleum ether-ether mixture (9:1) as eluent to afford 88 (1.21 g, 96%) as a colourless oil.²¹¹ IR (neat) ν 2240, 1450, 1380, 1113, 827 cm⁻¹; ¹H NMR δ 0.91 (d, J = 6.6 Hz, 3 H, CH₃), 1.59 (s, 3 H, CH=CC₃), 1.67 (s, 3 H, CH=CC₃), 1.81-2.12 (m, 2 H, CH₂C=), 2.21-2.44 (m, 2 H, CH₂CN), 5.07 (dt, J = 7.1, 1.4 Hz, 1 H, CH=C); ¹³C NMR δ 14.86 (t), 17.62 (q), 18.67 (q), 25.22 (t), 25.65 (q), 31.62 (d), 32.22 (t), 36.28 (t), 119.93 (s), 124.08 (d), 131.71 (s); HRMS m/z 165.1518 (calcd for C₁₁H₁₉N: 165.1518; M⁺).
Cyclization of citronellal (30).

To a DME solution of 5 mol% of the Mo(CO)\(_5\)(OTf)\(_2\) (VIII) catalyst generated \textit{in situ} (see above) was added H\(_2\)O (0.3 mL) followed by a solution of citronellal 30 (200 mg, 1.3 mmol) in DME (1 mL). The resulting mixture was stirred at rt for 48 h, then diluted with ether and worked up. The crude product, which was a 1:4 mixture of 89 and 90, as determined by \(^1\)H NMR, was chromatographed on a column of silica gel (20 g) using a petroleum ether-ether mixture (2:1) to furnish the cis-diol 90 (163 mg, 73%): mp 78-81 °C (literature gives\(^{212}\) 73-74 °C or 81-82 °C\(^{213,214}\)); IR ν(OH) 3480 and 3610 cm\(^{-1}\); \(^1\)H NMR (250 MHz) δ 0.89 (d, \(J = 6.2\) Hz, 3 H, \(\text{CH}_3\)), 1.24 (3 H, \textit{pro-S*-CH}\(_3\)), 1.37 (s, 3 H, \textit{pro-R*-CH}\(_3\)), 1.60-1.90 (m, 5 H), 2.95-3.40 (br s, 2 H), 4.42 (d, \(J = 2.5\) Hz, 1 H, CHO\(_\text{H}\)); \(^1^3\)C NMR δ 20.24 (t), 22.18 (q), 25.56 (d), 28.76 (q), 28.88 (q), 34.83 (t), 42.46 (t), 48.23 (d), 67.98 (d), 73.20 (s); HRMS (EI) \textit{m/z} 154.13582 (calcd for C\(_{10}\)H\(_{18}\)O: 154.13577; M\(^{**}\) - H\(_2\)O). Continued elution afforded a more polar fraction, identified as the \textit{trans}-diol 89 (20 mg; 9%): mp 59-60 °C (petroleum ether) (literature\(^{212}\) gives 60-61 °C or 77-78 °C\(^{213,214}\)); IR ν(OH) 3480, 3600 cm\(^{-1}\); \(^1\)H NMR δ 0.92 (d, \(J = 6.5\) Hz, 3 H, \(\text{CH}_3\)), 1.23 (s, 6 H, \text{CMe}_2), 1.25-2.05 (m, 6 H), 3.72 (dt, \(J = 10.5\) and 4.3 Hz, 1 H, CHO\(_\text{H}\)), 3.88 (br s, 2 H, 2 x OH); \(^1^3\)C NMR δ 22.03 (q), 23.75 (q), 27.15 (t), 30.13 (q), 31.41 (d), 34.59 (t), 44.65 (t), 53.46 (d), 72.95 (d), 75.12 (s); HRMS (EI) \textit{m/z} 154.1358 (calcd for C\(_{10}\)H\(_{18}\)O: 154.1358; M\(^{**}\) - H\(_2\)O).
(1R*,2R*)-2-Vinylcyclohexanol (93).

Obtained from (Z)- and (E)-8-(dimethylphenylsilyl)-6-octen-1-al 37 and 38 on cyclization according to method 1 and 2, whose spectral data was consistent with the assigned structure:\textsuperscript{215} IR \nu(OH) 3590, 3660 cm\textsuperscript{-1}; \textsuperscript{1}H NMR \delta 1.05-1.78 (m, 8 H), 2.09-2.30 (m, 1 H, \textit{CHCH}=\textit{CH}_2), 3.79-3.89 (m, 1 H, \textit{CH}_2\textit{CHOH}), 5.04-5.19 (m, 2 H, \textit{CH}=\textit{CH}_2), 5.92 (ddd, \textit{J} = 6.6, 10.7, and 17.3 Hz, 1 H, \textit{CH}=\textit{CH}_2; \textsuperscript{13}C NMR \delta 20.83 (t), 24.20 (t), 25.51 (t), 32.10 (t), 45.23 (d), 69.29 (d), 115.96 (t), 140.80 (d).

(1S*,2R*)-2-Vinylcyclohexanol (94).

Obtained from (Z)- and (E)-8-(dimethylphenylsilyl)-6-octen-1-al 37 and 38 on cyclization according to method 1 and 2, whose spectral data was consistent with the assigned structure:\textsuperscript{215,216} IR \nu(OH) 3600, 3680 cm\textsuperscript{-1}; \textsuperscript{1}H NMR \delta 1.06-1.94 (m, 8 H), 1.94-2.10 (m, 1 H, \textit{CHCH}=\textit{CH}_2), 3.23 (dt, \textit{J} = 4.0, 10.0 Hz, 1 H, \textit{CH}_2\textit{CHOH}), 5.04-5.21 (m, 2 H, \textit{CH}=\textit{CH}_2), 5.66 (ddd, \textit{J} = 8.0, 10.2, and 17.3 Hz, 1 H, \textit{CH}=\textit{CH}_2; \textsuperscript{13}C NMR \delta 24.75 (t), 25.12 (t), 31.08 (t), 33.81 (t), 51.20 (d), 72.76 (d), 116.66 (t), 140.79 (d).
Cyclization of 5-methyl-5-hexen-1-ol (39).

On treatment with Mo(II) complexes VII or VIII, 5-methyl-5-hexen-1-ol (39) afforded a mixture of regioisomers 99 and 100 employing method 1 and 2. $^1$H NMR $\delta$ (only the characteristic peaks were recorded) for 99: $^{179, 217}$ 3.75 (m, 1 H, CHO), 4.70 (s, 1 H, C=CH), 4.74 (s, 1 H, C=CH); for 100: $^{218}$ 1.58 (s, 3 H, CH$_3$), 3.86 (br s, 1 H, CHO), 5.29 (m, 1 H, CH$_2$CH=).

Cyclization of 3-(2-methylenecyclohexyl)propanal (40).

Run 1. To a DME solution of 5 mol% of the PhCH$_2$(Et)$_3$N$^+$[Mo(CO)$_4$ClBr$_2$]$^-$ (VII) catalyst generated in situ (see above) was added a solution of 40 (152 mg, 1.0 mmol) in DME (1 mL). The reaction was stirred at rt for 0.5 h and worked up. Chromatography on silica gel using a hexane-ether mixture (6:1 to 4:1) afforded 101 (126 mg, 83 %): IR $\nu$(neat) 3350 (OH), 1440, 1040, and 945 cm$^{-1}$; $^1$H NMR $\delta$ 1.16-2.07 (m, 12 H), 2.17-2.29 (m, 2 H), 4.07 (t, $J = 3.4$ Hz, 1 H, CH$_2$CHOH), 5.52 (s, 1 H, C=CH); $^{13}$C NMR $\delta$ 21.14 (t), 25.59 (t), 28.71 (t), 30.58 (t), 32.33 (t), 36.93 (d), 42.55 (t), 67.15 (d), 124.02 (d), 136.11 (s). $^1$H NMR and $^{13}$C NMR data were consistent with literature values; $^{178}$ continued elution gave a more polar isomer 102 (26 mg, 17 %): $^{178}$ $^1$H NMR $\delta$ 1.10-2.58 (m, 14 H), 3.85-4.0 (m, 1 H); $^{13}$C NMR $\delta$
22.89 (t), 23.02 (t), 28.43 (t), 29.80 (t), 30.23 (t), 31.26 (t), 67.46 (d), 125.19 (s), 127.50 (s).

Run 2. Silver(I) trifluorosulfonate (50 mg, 3 equivs) was added to a stirred suspension of 
$C_6H_5CH_2(C_2H_5)_3N^+[Mo(CO)_5Br] \cdot nH_2O$ VI (30 mg; 1 equiv) in DME (2 mL) at 0 °C under 
N$_2$. The reaction mixture was allowed to warm to rt and stirred for 15 min. To the catalyst 
thus generated in situ (5 mol%) was added a solution of 40 (198 mg, 1.3 mmol) in DME (1 
mL). The resulting mixture was stirred at rt for 0.5 h, then diluted with ether and worked up. The crude product was chromatographed on silica gel using a hexane-ether mixture (5:1) to 
furnish 101 (79 mg, 40%) and 102 (95 mg, 48%).

**Cyclization of 2,6-dimethyl-5-hepten-1-al (50).**

![Cyclization of 2,6-dimethyl-5-hepten-1-al (50).](image)

On treatment with PhCH$_2$(Et)$_3$N$^+[Mo(CO)$_4$ClBr$_2$]$^-$ VII (1 equiv) generated in situ (see 
above) for 24 h at rt, 50 furnished 103 (68%) as a colourless oil: $^1$H NMR $\delta$ 1.06 (d, $J = 6$
Hz, 3 H, CH$_3$CH), 1.75 (s, 3 H, CH$_3$), 2.37 (q, $J = 12$ Hz, 1 H, CHCMe=CH$_2$), 3.42 (t, 1 H, 
CHOH), 4.81 (m, 2 H); $^{13}$C NMR $\delta$ 18.10 (q), 19.80 (q), 26.00 (t), 29.21 (t), 41.50 (d), 56.10 
(d), 81.5 (d), 110.90 (t), 146.31 (s). An NOE difference of 2.19% and 1.54% was observed 
between C$_1$H and C$_5$-CH$_3$, and C$_2$H and C$_3$H respectively.
Cyclization of 2,6-dimethyl-5-hepten-1-al (50).

On reaction with 1 equiv of Mo(CO)$_5$(OTf)$_2$ VIII generated in situ (see above) for 5h at rt, 50 gave 104 (79%): δ 0.95 (d, $J = 6$ Hz, 3 H, CH$_3$CH), 1.07 (d, $J = 4.5$ Hz, 6 H, Me$_2$C), 1.92 (q, $J = 12$ Hz, 1 H, CH), 3.18 (s, 3 H, OCH$_3$), 3.45 (t, 1 H, CHOH); $^{13}$C NMR δ 16.50 (q), 23.00 (t), 24.10 (q), 29.5 (t), 40.9 (d), 48.8 (q), 55.01 (d), 78.20 (s), 80.90 (d); Treatment of 37 with Cl$_3$CON=CN=O resulted in a δ shift of CHOH from 3.45 ppm to 4.95 ppm indicating the presence of a secondary -OH group. Also at δ 8.30 (s, 1 H, Cl$_3$CONHR) signal was observed which suggested that there was only one -OH substituent in the molecule.

(E)-[8,8,8-$^2$H$_3$]-3,7-dimethyl-6-octen-1-al (111).

Obtained from 115 on Swern oxidation (in the same way as 33 was prepared from 53).

111 (89%): IR ν(C=O) 1725, ν(CH) 2725 cm$^{-1}$; $^1$H NMR δ 0.97 (d, $J = 6.6$ Hz, 3 H, CHCH$_3$), 1.1-1.45 (m, 3 H), 1.60 (s, 3 H, CH$_3$), 1.85-2.52 (m, 4 H), 5.09 (dt, $J = 7.1$, 1.3 Hz, 1 H, CH=C), 9.75 (t, $J = 2.4$ Hz, 1 H, CH=O); $^{13}$C NMR δ 17.57 (q), 19.82 (q), 25.33 (t), 27.72 (d), 36.89 (t), 50.95 (t), 123.99 (d), 131.69 (s), 203.07 (d).
(E)-[8,8-\textsuperscript{2}H\textsubscript{2}]-1-(Benzyloxy)-3,7-dimethyl-6-octen-8-ol (112).

To a suspension of lithium aluminum deuteride (90 mg; 2.14 mmol; ≥96% \textsuperscript{2}H-enrichment) in \textit{Et\textsubscript{2}O} (30 mL) at 0 °C was added dropwise over a period of 15 min a solution of ethyl 2,6-dimethyl-8-benzyloxy-2(\textit{E})-octenoate\textsuperscript{127} 77 (650 mg; 2.14 mmol) in \textit{Et\textsubscript{2}O} (5 mL) and the mixture was stirred at rt for 10 min. Solid, anhydrous \textit{Na\textsubscript{2}SO\textsubscript{4}} was added and the excess of the reagent was decomposed by a slow addition of water. The solid was filtered off, the filtrate was washed with brine, dried with \textit{MgSO\textsubscript{4}}, and the solvent evaporated. The residue was purified by flash chromatography on silica gel (14 g) using a hexane-Ac\textit{O}Et mixture (9:1) as eluent to afford 112 (499 mg, 89%): IR \textit{v}(OH) 3610 cm\textsuperscript{-1}; \textsuperscript{1}H NMR δ 0.73 (d, \textit{J} = 6.3 Hz, 3 H, CH\textsubscript{3}), 0.90–0.68 (m, 9 H), 1.48 (s, 3 H, CH\textsubscript{3}), 1.87 (m, 2 H, CH\textsubscript{2}CH=C), 3.34 (t, \textit{J} = 6.7 Hz, 2 H, CH\textsubscript{2}CH\textsubscript{2}OCH\textsubscript{2}), 4.33 (s, 2 H, -OCH\textsubscript{2}C\textsubscript{6}H\textsubscript{5}), 5.21 (t, \textit{J} = 7.2 Hz, 1 H, C=CH), 7.16 (s, 5 H, arom); \textsuperscript{13}C NMR δ 13.5 (q), 19.4 (q), 24.9 (t), 29.4 (d), 36.6 (t), 36.7 (t), 68.5 (t), 72.8 (t), 126.5 (d), 127.4 (d), 127.5 (d), 128.3 (d), 134.4 (s), 138.5 (s); HRMS \textit{m}/\textit{z} 264.2058 (calcd for C\textsubscript{17}H\textsubscript{24}\textsuperscript{2}H\textsubscript{2}O\textsubscript{2}: 264.2058, M\textsuperscript{++}).
(E)-[8,8-\(^2\)H\(_2\)]-1-(Benzyloxy)-3,7-dimethyl-6-octen-8-yl Chloride (113).

To a solution of \(N\)-chlorosuccinimide (294 mg; 2.2 mmol) in dry \(\text{CH}_2\text{Cl}_2\) (10 mL) was added dropwise dimethyl sulfide (0.176 mL; 2.4 mmol) at 0 °C under nitrogen. The reaction mixture was cooled to -20 °C, and a solution of the alcohol 112 (528 mg; 2 mmol) in \(\text{CH}_2\text{Cl}_2\) (1 mL) was added gradually over a period of 10 min. The resulting solution was allowed to warm to 0 °C, stirred for 5h at that temperature and poured into an ice-cold brine (10 mL). The organic layer was separated, and the aqueous phase was extracted with \(\text{Et}_2\text{O}\) (2 x 5 mL). The combined organic layers were washed with two 5 mL portions of cold brine and dried over \(\text{MgSO}_4\). Upon removal of the solvent, pure allylic chloride 113 (520 mg, 92 %) was obtained as a yellow oil: \(^1\)H NMR \(\delta\) 0.89 (d, \(J = 6.6\) Hz, 3 H, \(\text{CH}_3\)), 1.10-1.71 (m, 5 H), 1.72 (s, 3 H, \(\text{CH}_3\)), 1.91-2.15 (m, 2 H, \(\text{CH}_2\text{CH}=\text{C}\)), 3.44-3.58 (m, 2 H, -\(\text{CH}_2\text{OCH}_2\text{Ph}\)), 4.49 (s, 2 H, -\(\text{OCH}_2\text{Ph}\)), 5.50 (m, \(J = 1.3\) and 7.2 Hz, 1 H, C=CH), 7.33 (s, 5 H, arom); \(^{13}\)C NMR \(\delta\) 13.99 (q), 19.44 (q), 25.47 (t), 29.53 (d), 36.37 (t), 36.60 (t), 68.52 (t), 72.90 (t), 127.47 (d), 127.59 (d), 128.31 (d), 131.16 (d), 131.32 (s), 138.59 (s).
(E)-[8,8,8-2H₃]-1-(Benzyloxy)-3,7-dimethyl-6-octene (114).

To a solution of the allylic chloride 113 (340 mg; 1.2 mmol) in ether (6.2 mL) was added lithium aluminum deuteride (51 mg; 1 eq.; 96% ²H-enrichment). After 6 h at reflux a single spot on the TLC plate was observed. Dry Na₂SO₄ was added, followed by slow addition of water to decompose the excess of the reagent. After removal of the solids by filtration, the ethereal solution was washed with brine, dried with MgSO₄, and the solvent was evaporated to yield the benzyl ether 114 (290 mg; 97%) as a colourless oil: ¹H NMR δ 0.81 (d, J = 6.3 Hz, 3 H, CH₃), 0.95-1.72 (m, 8 H), 1.52 (s, 3 H, CH₃), 1.91 (m, 2 H, CH₂CH=), 3.42 (m, J = 1.9 and 6.8 Hz, 2 H, CH₂OCH₂Ph), 4.42 (s, 2 H, PhCH₂O), 5.02 (br t, J = 7.1 Hz, 1 H, C=CH), 7.25 (s, 5 H, arom); ¹³C NMR δ 17.55 (q), 19.53 (q), 25.43 (t), 29.53 (d), 36.70 (t), 37.18 (t), 68.70 (t), 72.88 (t), 124.79 (d), 127.43 (d), 127.58 (d), 128.31 (d), 131.01 (s), 138.67 (s); HRMS m/z 249.2172 (calcd for C₁₇H₂₃₂H₃O: 249.2172; M⁺).

(Zs)-[8,8,8-2H₃]-3,7-Dimethyl-6-octen-1-ol (115).

(E)-[8,8,8-2H₃]-3,7-Dimethyl-6-octen-1-ol (115).
A solution of the benzyl ether 114 (0.88 g; 3.53 mmol) in THF (20 mL) was added slowly to a solution of lithium (containing 1% sodium) (2.58 g; 112 mmol; 30% dispersion in oil) in ammonia (70 mL) at -78 °C. After 15 min, the excess of lithium was decomposed by adding 3-hexyne until the blue color was completely dissipated and the resulting yellow solution was then quenched with methanol until colorless. At rt, water was added and the volatiles were carefully removed by rotary evaporation under reduced pressure. The resulting cloudy solution was extracted with ether (4 x 60 mL) and the combined ethereal layers were washed with water, brine, and dried with MgSO₄. After filtration, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel (45 g) with a petroleum ether-ether mixture (9:1) followed by pure ether to furnish 115 as a colourless oil (0.51 g; 91%): IR ν(OH) 3620 and 3680 cm⁻¹; ¹H NMR δ 0.78 (d, J = 6.6 Hz, 3 H, CH₃CH), 0.94-1.66 (m, 9 H), 1.48 (s, 3 H, CH=CCD₂CH₃), 1.76-1.98 (m, 2 H, CH₂CH=C), 3.40-3.67 (m, 2 H, CH₂OH), 4.97 (br t, J = 7.1 Hz, 1 H, CH=C); ¹³C NMR δ 17.54 (q), 19.46 (q), 25.39 (t), 29.11 (d), 37.16 (t), 39.84 (t), 61.11 (t), 124.66 (d), 131.15 (s).

(Z)-[8,8,8-²H₃]-3,7-Dimethyl-6-octen-1-al (116).

Obtained from 122 on Swern oxidation (in the same way as 33 was prepared from 53). 116 (92%): IR ν(C=O) 1725; ¹H NMR δ 0.95 (d, J = 6.6 Hz, 3 H, CHCH₃), 1.1-1.45 (m, 3 H), 1.67 (d, J = 1.3 Hz, 3 H, CH₃C=), 1.83-2.48 (m, 4 H), 5.07 (dt, J = 7.1 and 1.3 Hz, 1 H, C=CH), 9.74 (t, J = 2.2 Hz, 1 H, CH=O); ¹³C NMR δ 19.84 (q), 25.36 (t), 25.62 (q), 27.74 (d), 36.92 (t), 50.98 (t), 124.02 (d), 131.70 (s), 203.07 (d).
(Z)-1-(Benzyloxy)-3,7-dimethyl-6-octen-8-ol (117).

To a stirred solution of ethyltriphenylphosphonium bromide (1.86 g, 5 mmol) in THF (7 mL) was added butyllithium (1.6 M, 3.1 mL) at 0 °C. After 1 h at that temperature the mixture was cooled to -78 °C and 6-(benzyloxy)-4-methyl-hexanal (76) (1.1 g, 5 mmol) was added dropwise and the mixture was stirred for 5 min at -78 °C. Additional butyllithium (1.6 M, 3.1 mL) was then added, resulting in the formation of the deep red ylide. The mixture was allowed to reach 0 °C and then paraformaldehyde (0.30 g) was added. Stirring was continued at 0 °C for 1 h and then for 10 h at rt followed by addition of ice-water and extraction with ether. The ethereal extract was worked up and the residue was purified on silica gel (15 g), using a petroleum ether-ether mixture (7:1 to 3:1) as eluent to afford the (Z)-alcohol 117 (93:7) (590 mg, 45%) as a colourless oil, whose spectral data correspond to those described in the literature: IR v(OH) 3450, 3615 cm\(^{-1}\); \(^1\)H NMR δ 0.87 (d, \(J = 6.6\) Hz, 3 H, CH\(_3\)), 1.02-1.74 (m, 6 H), 1.78 (s, 3 H, CH\(_3\)), 1.90-2.25 (m, 2 H, CH\(_2\)CH=C), 3.41-3.59 (m, 2 H, CH\(_2\)CH\(_2\)OCH\(_2\)), 4.10 (m, 2 H, CH\(_2\)OH), 4.49 (s, 2 H, -OCH\(_2\)C\(_6\)H\(_5\)), 5.25 (t, \(J = 7.6\) Hz, 1 H, C=CH), 7.33 (s, 5 H, aryl-H); \(^{13}\)C NMR δ 19.58 (q), 21.26 (q), 24.89 (t), 28.97 (d), 36.30 (t), 37.17 (t), 61.42 (t), 68.32 (t), 72.91 (t), 127.50 (d), 127.66 (d), 128.32 (d), 128.48 (d), 134.30 (s), 138.46 (s); HRMS m/z 262.1933 (calcd for C\(_{17}\)H\(_{26}\)O\(_2\): 262.1933, M**).
Methyl (Z)-8-Benzylxy-2,6-dimethyl-2-octenoate (118).

A mixture of the allylic alcohol 117 (0.5 g), and active manganese dioxide (5.75 g) in hexane (80 mL) was stirred at 0 °C for 30 min. Filtration and evaporation of solvent under reduced pressure furnished (Z)-1-(benzyloxy)-3,7-dimethyl-6-octen-8-al (487 mg, 98%): IR ν 1095, 1380, 1455, 1670, 2865, 2925, 2955 cm⁻¹; ¹H NMR δ 0.92 (d, J = 6.3 Hz, 3 H, CH₃), 1.76 (s, 3 H, CH₃), 2.46-2.66 (m, 2 H, CH₂=CH=), 3.40-3.59 (m, 2 H, CH₂OCH₂), 4.50 (s, 2 H, -OCH₂C₆H₅), 6.49 (t, J = 8.0 Hz, 1 H, =CH), 7.33 (s, 5 H, aryl-H); ¹³C NMR δ 16.39 (q), 19.28 (q), 24.18 (t), 29.45 (d), 34.85 (t), 68.22 (t), 72.93 (t), 127.50 (d), 127.58 (d), 128.32 (d), 135.81 (s), 138.46 (s), 149.77 (d), 191.06 (d). The aldehyde thus obtained was stirred with a mixture of sodium cyanide (0.82 g), acetic acid (0.30 g), and manganese dioxide (5.75 g) in dry methanol (45 mL) for 12 h at 20-25 °C. After removal of methanol, the residue was partitioned between ether and water. Evaporation of the ethereal extract afforded the desired crude product. Further purification was carried out by flash chromatography on silica gel (20 g) using a hexane-ether mixture (9:1) as eluent to yield 118 as a colourless oil (265 mg, 48%): IR ν(CO) 1710 cm⁻¹; ¹H NMR δ 0.90 (d, J = 6.3 Hz, 3 H, CH₃), 1.03-1.77 (m, 5 H), 1.89 (d, J = 1.3 Hz, 3 H, CH₃C=), 2.35-2.58 (m, 2 H, CH₂CH=), 3.51 (m, J = 6.9, 1.9 Hz, 2 H, CH₂CH₂OCH₂), 3.72 (s, -OCH₃), 4.50 (s, 2 H, -OCH₂C₆H₅), 5.92 (t, J = 7.4 Hz, 1 H, =CH), 7.33 (s, 5 H, aryl-H); ¹³C NMR δ 19.37 (q), 20.66 (q), 27.06 (t), 29.61 (d), 36.58 (t), 36.61 (t), 51.16 (q), 68.55 (t), 72.86 (t), 126.60 (d), 127.43 (d), 127.56 (d), 128.30 (d), 138.61 (s), 143.67 (d), 168.45 (s); HRMS m/z 290.1882 (calcd for C₁₈H₂₆O₃: 290.1882, M⁺).
(Z)-[8,8-2H$_2$]-1-(Benzyloxy)-3,7-dimethyl-6-octen-8-ol (119).

![Chemical Structure](image)

Obtained from 118 on LiAl$_2$H$_4$ reduction (in the same way as 112 was prepared from 77). 119: IR ν(OH) 3615 cm$^{-1}$; $^1$H NMR δ 0.74 (d, $J = 6.3$ Hz, 3 H, CH$_3$), 1.0-1.67 (m, 5 H), 1.71 (s, 3 H, CH$_3$), 1.81-2.17 (m, 2 H, CH$_2$CH=C), 3.31-3.52 (m, 2 H, CH$_2$CH$_2$OCH$_2$), 4.33 (s, 2 H, -OCH$_2$C$_6$H$_5$), 5.19 (t, $J = 7.4$ Hz, 1 H, C=CH), 7.18 (s, 5 H, aryl-H); $^{13}$C NMR δ 19.57 (q), 21.22 (q) 24.89 (t), 28.96 (d), 36.29 (t), 37.16 (t), 68.31 (t), 72.91 (t), 127.5 (d), 127.66 (d), 128.32 (d), 128.53 (d), 134.22 (s), 138.45 (s); HRMS m/z 264.2059 (calcd for C$_{17}$H$_{24}$2H$_2$O$_2$: 264.2058, M$^{+}$).

(Z)-[8,8-2H$_2$]-1-(Benzyloxy)-3,7-dimethyl-6-octen-8-yl Chloride (120).

![Chemical Structure](image)

Obtained from 119 on OH → Cl exchange (in the same way as 113 was prepared from 112). 120: $^1$H NMR δ 0.90 (d, $J = 6.6$ Hz, 3 H, CH$_3$), 1.10-1.76 (m, 5 H), 1.80 (s, 3 H, CH$_3$), 1.95-2.21 (m, 2 H, CH$_2$CH=), 3.42-3.58 (m, 2 H, -CH$_2$OCH$_2$Ph), 4.50 (s, 2 H, -OCH$_2$Ph), 5.36 (m, $J = 1.4$ and 7.4 Hz, 1 H, C=CH), 7.33 (s, 5 H, aryl-H); $^{13}$C NMR δ 19.44 (q), 21.47
(q), 25.33 (t), 29.47 (d), 36.59 (t), 36.86 (t), 68.50 (t), 72.91 (t), 127.46 (d), 127.59 (d), 128.32 (d), 130.96 (s), 131.47 (d), 138.60 (s).

(Z)-[8,8,8-2H3]-1-(Benzyloxy)-3,7-dimethyl-6-octene (121).

\[
\begin{align*}
\text{ClD}_2C & \quad \rightarrow \\
\text{D}_3C & 
\end{align*}
\]

Obtained from 120 on LiAl\textsuperscript{2}H\textsubscript{4} reduction (in the same way as 114 was prepared from 113). 121: \textsuperscript{1}H NMR \(\delta 0.89 (d, J = 6.3 \text{ Hz}, 3 \text{ H, CH}_3), 1.04-1.76 (m, 8 \text{ H}), 1.68 (s, 3 \text{ H, CH}_3), 1.83-2.15 (m, 2 \text{ H, CH}_2CH=), 3.43-3.58 (m, 2 \text{ H, CH}_2OCH_2Ph), 4.50 (s, 2 \text{ H, -OCH}_2Ph), 5.10 (br t, J = 6.6 \text{ Hz, 1 H, C=CH}), 7.33 (s, 5 \text{ H, aryl-H}); \textsuperscript{13}C \text{ NMR } \delta 19.54 (q), 25.45 (t), 25.65 (q), 29.55 (d), 36.70 (t), 37.20 (t), 68.71 (t), 72.90 (t), 124.83 (d), 127.45 (d), 127.60 (d), 128.33 (d), 131.05 (s), 138.68 (s); \text{ HRMS } m/z 249.2172 \text{ (calcd for C}_{17}H_{23}^{2}H_3O: 249.2172; M^{++}).}

(Z)-[8,8,8-2H3]-3,7-Dimethyl-6-octen-1-ol (122).

\[
\begin{align*}
\text{D}_3C & \quad \rightarrow \\
\text{D}_3C & 
\end{align*}
\]
Obtained by deprotection of 121 (in the same way as 115 was prepared from 114). 122: IR v(OH) 3620, 3680 cm⁻¹; ¹H NMR δ 0.89 (d, J = 6.6 Hz, 3 H, CH₃CH), 1.10-1.61 (m, 5 H), 1.66 (d, J = 1.3 Hz, 3 H, CH=CCD₂CH₃), 1.83-2.10 (m, 2 H, CH₂CH=C), 3.56-3.77 (m, 2 H, CH₂OH), 5.08 (br t, J = 6.9 Hz, 1 H, C=CH); ¹³C NMR δ 19.46 (q), 25.40 (t), 25.61 (q), 29.11 (d), 37.17 (t), 39.84 (t), 61.12 (t), 124.69 (d), 131.16 (s); HRMS m/z 159.1703 (calcld for C₁₀H₁₇₂H₃O: 159.1703; M⁺). [9,9,9,-²H₃]-(1S*,3R*,4S*,8S*)-p-Menthane-3,8-diol (123).

Obtained from d₃-citronellal 111 in the same manner as its non-labelled counterpart 90: ¹H NMR δ 0.89 (d, J = 6.0 Hz, 3 H, CHCH₃), 0.90-1.20 (m, 3 H), 1.35 (s, 3 H, CH₃), 1.59-1.94 (m, 5 H), 2.59-3.30 (br s, 2 H, 2 x OH), 4.39 (d, J = 2.2 Hz, 1 H, CHO); ¹³C NMR δ 20.21 (t), 22.17 (q), 25.57 (d), 28.79 (q), 34.81 (t), 42.47 (t), 48.21 (d), 68.03 (d), 73.10 (s); HRMS m/z (rel. intensity) 157 (M⁺⁻H₂O; 8), 142 (6), 124 (3), 111 (7), 96 (61), 81 (100), 72 (8), 68 (22), 62 (56), 54 (25). [9,9,9,-²H₃]-(1S*,3S*,4S*,8S*)-p-Menthane-3,8-diol.
Obtained from $d_3$-citronellal 111 in the same manner as its non-labelled counterpart 89:

$^1$H NMR $\delta$ 0.92 (d, $J = 6.6$ Hz, 3 H, CHCH$_3$), 1.21 (s, 3 H, CH$_3$), 1.23-2.0 (m, 6 H), 3.71 (dt, $J = 10.4$, 4.2 Hz, 1 H, CHO), 4.26 (br s, 2 H, 2 x OH); $^{13}$C NMR $\delta$ 21.94 (q), 26.99 (t), 29.85 (q), 31.31 (d), 34.49 (t), 44.50 (t), 53.24 (d), 72.83 (d), 74.86 (s); HRMS $m/z$ (rel. intensity) 157 (M$^{+}$-H$_2$O; 5), 139 (6), 124 (2), 112 (4), 96 (66), 81 (100), 72 (7), 68 (21), 62 (71), 54 (25).

$[9,9,9,2H_3]-$((1$S^*,3R^*,4S^*,8S^*)-p-Menthane-3,8-diol Carbonate (124).)

Prepared from the diol 123 in the same manner as its non-labeled counterpart 125: IR (CH$_2$Cl$_2$) $\nu$ 1065, 1085, 1140, 1210, 1350, 1730 (C=O); $^1$H NMR $\delta$ 0.92 (d, $J = 6.6$ Hz, 3 H, CH$_3$CH), 1.05-1.25 (m, 1 H), 1.51 (s, 3 H, CH$_3$), 1.55-1.66 (m, 1 H), 2.12 (dd, $J = 14.5$, 3.0 Hz, 1 H), 4.85 (d, $J = 2.5$ Hz, 1 H, CHO); $^{13}$C NMR (CDCl$_3$, TMS) $\delta$ 21.23 (t), 21.56 (q), 25.22 (d), 27.91 (q), 32.91 (t), 38.49 (t), 39.12 (d), 74.45 (d), 83.0 (s), 149.67 (C=O); HRMS (El) $m/z$ 202.1523 (calcd for C$_{11}$H$_{16}$2H$_3$O$_3$: 202.1523; MH$^+$).

$[9,9,9,2H_3]-$((1$S^*,3S^*,4S^*,8S^*)-p-Menthane-3,8-diol Carbonate

Obtained from the corresponding diol (in the same way as 125 was prepared from 90):

IR $\nu$(C=O) 1730 cm$^{-1}$; $^1$H NMR $\delta$ 0.94 (d, $J = 6.6$ Hz, 3 H, CH$_3$CH), 1.37 (s, 3 H, CH$_3$-eq), 1.65-1.87 (m, 2 H), 2.02-2.19 (m, 1 H), 4.13 (dt, $J = 11.0$, 4.4 Hz, 1 H, CHO); $^{13}$C NMR $\delta$
(1S*,3R*,4S*)-p-Menthane-3,8-diol Carbonate (125).

To a solution of the cis-diol 90 (500 mg; 2.92 mmol) and pyridine (460 mg) in toluene (10 mL) was added a 20% solution of phosgene in toluene (8.25 mL; 1.93 M; 1.1 equiv.) at 0 °C. After 15 min, the reaction mixture was quenched with 1M HCl, the product was extracted into Et2O (3 x 50 mL), and the combined organic layers were washed with water, 5% aqueous NaHCO3, and brine and dried over MgSO4. The solvent was removed under reduced pressure and the solid residue was crystallized from hexane to afford the carbonate 125 (537 mg; 2.72 mmol; 93%): mp 94-95 °C; IR ν(C=O) 1730 cm⁻¹; ¹H NMR δ 0.92 (d, J = 6.5 Hz, 3 H, CH₃C), 1.05-1.25 (m, 1 H), 1.38 (s, 3 H, CH₃-equatorial), 1.51 (s, 3 H, CH₃-axial), 1.55-1.66 (m, 1 H), 2.13 (dd, J = 14.5, 3.0 Hz, 1 H), 4.85 (d, J = 2.6 Hz, 1 H, CHO); ¹³C NMR δ 21.19 (t), 21.52 (q), 25.19 (d), 25.69 (q), 27.96 (q), 32.86 (t), 38.45 (t), 39.07 (d), 74.44 (d), 83.11 (s), 149.63 (s); HRMS (EI) m/z 199.1334 (calcd for C₁₁H₁₉O₃: 199.1334; MH⁺). In the NOE difference experiments, irradiation at 4.85 ppm (CH-O) gave 2% enhancement of the signal at 1.51 ppm (CH₃-axial), while irradiation at 1.51 ppm resulted in 11% enhancement of the
signal at 4.85 ppm (CH-O); no enhancement of the latter signal was observed upon irradiation at 1.38 ppm (CH$_3$-equatorial).

(1S*,3S*,4S*)-\(\beta\)-Menthan-3,8-diol Carbonate.

![Chemical structure](image)

Obtained from the corresponding diol (in the same way as 125 was prepared from 90): IR $\nu$(C=O) 1730 cm$^{-1}$; $^1$H NMR $\delta$ 0.94 (d, $J = 6.6$ Hz, 3 H, CH$_3$CH), 1.30 (s, 3 H, CH$_3$-ax), 1.37 (s, 3 H, CH$_3$-eq), 1.65-1.87 (m, 2 H), 2.02-2.19 (m, 1 H), 4.13 (dt, $J = 11.0, 4.4$ Hz, 1 H, CHO); $^{13}$C NMR $\delta$ 21.60 (q), 22.50 (q), 24.81 (t), 27.69 (q), 30.64 (d), 33.45 (t), 39.75 (t), 46.07 (d), 76.81 (d), 84.48 (s), 149.03 (s)
References and Notes


(5) The Mo(CO)6-catalysed reaction of 1 with CH2(CO2Me)2/BSA affords mainly 2 as a 2:1 mixture of regioisomers.6


(14) Alder, K.; Pascher, F.; Schmitz, A. Ber. Dtsch. Chem. Ges. 1943, 76, 27. (b)


(41) (a) Snider, B. B.; Rodini, D. J. Tetrahedron lett. 1980, 21, 1815. (b) Snider, B. B.;
802. For a correction, see: Whitesell, J. K.; Nabona, K; Deyo, D. J. Org. Chem. 1989,
54, 2258.
(49) Beak, P.; Song, Z.; Resek, J. E. J. Org. Chem. 1992, 57, 944.
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PCC also mediates the cyclization; however, the product is instantaneously oxidized by the reagent, so that the stereochemistry of the ring closure cannot be determined: Corey, E. J.; Ensley, H. E. Suggs, J. W. *J. Org. Chem.* 1976, 41, 380.


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For the procedure, see the following: McCann, S.F.; Overman, L. E. J. Am. Chem. Soc. 1987, 109, 6112.


(a) Manas, Abdul R. B.; Smith, Robin A. J. Tetrahedron 1987, 43, 1847. (b) Brown,


(145) The striking difference between the reaction course in diglyme and DME is difficult to understand. Presumably, diglyme, being a tridentate ligand, can better coordinate water molecules, preventing their reaction with the metal complex. Moreover, the reaction in diglyme is carried out at 120 °C, whereas in DME it only runs at 80 °C (reflux), which may further add to the difference.


Cyclic voltammetry of CF$_3$CO$_2$Ag and TfOAg showed a 0.10 V difference in the redox potential of the Ag$^+$ ion, which corresponds to a difference of approximately 10 kJ/mol$^{-1}$ in the Gibbs energy of the two processes, consistent with the hypothesis on dissociation.

The slight differences between the potentials reported in this work and ref 150 result from the different reference electrodes used.

Both TfOAg and the precipitated AgCl may, a priori, serve as oxidants. For an analogous oxidation of Cu(I) to Cu(II) by means of AgCl, see: Smrčina, M.; Poláková, J.; Vyskočil, Š.; Kočovsky, P. J. Org. Chem. 1993, 58, 4534. However, AgCl should react more slowly in view of its low solubility.

The ESR spectrum obtained after addition of 3 equiv of TfOAg showed a very broad featureless signal arising from a third species of low abundance, with g = 2.08. No satellite lines arising from the $^{183}$W isotope could be resolved. Presumably, this signal originates from an impurity, which implies that most of the metal has been oxidized to W(II), which should give no signal.

Few other related systems have been investigated by ESR spectroscopy. Electrochemical oxidation of [W(CO)$_2$(CNR)$_2$(PR$_3$)$_2$] have yielded ESR spectra with similar parameters: $g_\parallel = 1.903$ and $g_\perp = 2.212$. The Mo analogues had $g_\parallel = 1.97 - 1.99$ and $g_\perp = 2.00 - 2.02$ and $A_\parallel = 50$ G.$^{155}$


(158) One slight exception was that the BnEt3N+[Mo(CO)5Cl]' complex exhibited only two signals, one for the oxidation Mo⁰ → M¹ (at +1.45 V) and one combined for Mo¹ → Mo² → Mo³ (at +1.4 V). These two signals are again resolved following the addition of 1 equiv. of TfOAg.

(159) Oxidation of the molybdenum complexes by means of Ag(I) has previously been reported to afford Mo(II) species. Thus, for instance, treatment of [Mo(CO)₂(bipy)₂]+BF₄⁻ with AgBF₄ in MeCN gives [Mo(CO)₂(bipy)₂(MeCN)]²⁺ (BF₄⁻)₂. The same product has also been obtained from Mo(CO)₂(bipy)₂ on reaction with 2 equiv. of AgBF₄.¹⁶⁰


(161) The ESR spectrum obtained after addition of 3 equiv of TfOAg showed a poorly resolved signal arising from two species, one with g∥ = 2.063 and g⊥ = 2.095 and the other with g₁ = 1.954, g₂ = 1.931, and g₃ = 1.911. No satellite lines arising from the Mo isotopes could be resolved. Due to the low intensity of the signals it was not possible to characterize these species; the signals are apparently associated with very minor byproducts.


(164) All yields refer to isolated (preparative) yields. Diastereoisomeric ratios were determined by integration of suitable signals in the ¹H NMR spectra of the crude product mixtures with usual accuracy (≤ ±2%).

(165) Abbott, A. P.; Malkov, A. V.; Zimmermann, N.; Raynor, J. B.; Ahmed, G.; Steele, J.;
Kočovsky, P.: manuscript in preparation.

(166) The complex VIII was generated in situ from BnEt₃N⁺[Mo(CO)₅Cl]⁻ via the redox reaction with CF₃SO₃Ag.¹⁶⁷ The structure elucidation of the latter species, tentatively formulated as VIII,¹⁶⁷ by electrochemical methods will be disclosed elsewhere.¹⁶⁵


(168) Essentially identical results have been obtained with the corresponding W(II) complexes.


(170) The configurational assignment for 89 and 90 is based on the coupling pattern of the CHOH in the ¹H NMR. Thus, 89, with an axial OH, shows the proton in question as a broad singlet, whereas the epimer 90 exhibits a dt with J = 10.5 and 4.3 Hz. These and other signals are in a perfect agreement with those found for the authentic samples of iso-pulegol and neo-iso-pulegol, respectively.

(171) A facile, though less stereoselective formation of the corresponding cyclopentane derivatives from 3,6-dimethyl-5-hepten-1-al has also been observed.

(172) Similar, Cp₂Ti(PMe₃)₂-catalyzed cyclization of 6-hepten-2-one and its congeners, leading to cis-disubstituted cyclopentanes, have recently been reported;¹⁷³,¹⁷⁴ attempted construction of cyclohexane homologues was unsuccessful.¹⁷³


(174) For a review on analogous cyclization of dienes, see: (a) Buchwald, S. L.; Nielsen, R. B. Chem. Rev. 1988, 88, 1047. For a recent example, see, e.g.: (b) Taber, D. F.; Wang, Y. Tetrahedron Lett. 1995, 36, 6639.


This reactivity pattern suggests development of a considerable positive charge on the sp² carbon (C-7 in 30). Further experiments showed that cyclized are only those alkenals, where this charge is sufficiently stabilized. Thus, 5-methyl-5-hexen-1-al (a type II ene reaction substrate) and 37 or 38, with electron deficiency either created on a tertiary carbon or stabilized by β-PhMe₂Si, respectively, are readily cyclized. Note that carbocationic intermediates are assumed in analogous cyclizations mediated by standard Lewis acids, such as Me₂AlCl, and MeAlCl₂: Snider, B. B.; Karras, M.; Price, R. T.; Rodini, D. J. *J. Org. Chem.* 1982, 47, 4538.


(a) Schlosser, M.; Christmann, K.-F. *Justus Liebigs Ann. Chem.* 1967, 708, 1. (b)


(187) For the method, see: Corey, E. J.; Katzenellenbogen, J. A.; Gilman, N. W.; Roman, S.; Erickson, B. W. J. Am. Chem. Soc. 1968, 90, 5618.

(188) The epimeric ratio was determined by integration of the CH$_3$ signals in the $^1$H NMR spectrum.


(190) An alternative boat-like TS$^+$ can be ruled out on similar grounds.


(192) The highest cis/trans ratio 80:20 corresponds to $\sim$1 kcal.mol$^{-1}$ difference in the energy of the transition states (at rt), which seems to be compatible with the subtle geometrical distortions in 126 and 127.


(194) Another example of a dramatic reversal of the stereochemistry has been observed for the Lewis acid-mediated oxo-ene type II reaction: Maruoka, K.; Ooi, T.; Yamamoto, H. J. Am. Chem. Soc. 1990, 112, 9011.

(195) In diglyme, the commercially available (i.e., wet) BN$_3$N$^+$Cl$^-$ is suitable. However, if DME is used as the solvent, BN$_3$N$^+$Cl$^-$ has to be rigorously dried (in vacuo over P$_2$O$_5$ at rt for 2 weeks).
Used as obtained from the manufacturer. If dried before the reaction, complex I is obtained instead.


