EVALUATION OF CAMPHOR DERIVATIVES
IN TERPENOID SYNTHESIS

By

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B.Sc., University of British Columbia, 1988

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

in

THE FACULTY OF GRADUATE STUDIES
(Department of Chemistry)

We accept this thesis as conforming
to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA

April 1993

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Department of Chemistry
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Date June 10, 1993
Abstract

New enantiospecific syntheses of 5,6-dehydrocamphor (36) and 5-methyl-5,6-dehydrocamphor (178) are reported, and these two compounds were evaluated as intermediates in terpenoid synthesis. Addition of an alkenyl unit to (+)-5,6-dehydrocamphor (36) and subsequent anionic oxy-Cope rearrangement of the resulting 1,5-diene (64) provided hydrindenone 66. Ring expansion of 66 provided decalin intermediate 69 which contains the A/B ring system common to many terpenoids; however, the stereospecific introduction of an angular methyl group to provide a system such as 40 eluded us. Therefore, a similar synthetic strategy using (-)-5-methyl-5,6-dehydrocamphor (178) was investigated. Isopropenyl addition to 178 and subsequent anionic oxy-Cope rearrangement provided hydrindenone 190 which contained the desired angular methyl group. (-)-5-Methyl-5,6-dehydrocamphor (178) was also converted to enone 204, but stereoselective conjugate addition to this enone (204) was not satisfactory. Addition of a more complex alkenyl unit to (-)-5-methyl-5,6-dehydrocamphor (178) provided 1,5-diene 179, however, anionic oxy-Cope rearrangement to provide hydrindenone 180 did not occur, presumably due to steric effects.

The first enantioselective synthesis of (-)-4-methylcamphor (229) is also reported. It is expected that 229 will undergo reactions analogous to those reported for camphor (25) and therefore would provide a route to trans hydrindenone 232. The latter compound is a potentially useful intermediate in the synthesis of the lanostane group of triterpenoids whereas its enantiomer (ent-232) derived from (+)-4-methylcamphor (ent-178) could gain access to the euphane group of triterpenoids.
# Table of Contents

Abstract ii
Table of Contents iv
List of Tables vi
List of Figures vii
Contents of Appendix vii
List of Abbreviations viii
Acknowledgements xiii
Dedication xiv

Chapter 1: The Evaluation of 5,6-Dehydrocamphor (36) and 5-Methyl-5,6-dehydrocamphor (178) as Intermediates in Terpenoid Synthesis 1

1.1: Introduction: The Anionic Oxy-Cope Rearrangement 2

1.2: Discussion 10

   1.2.1: Introduction 10
   1.2.2: Synthesis of 5,6-Dehydrocamphor (36) 13
   1.2.3: Synthesis of a Decalin System from 5,6-Dehydrocamphor (36) 21
   1.2.4: Angular Functionalization Approaches 23

      1.2.4.1: Hydroxyl-directed Cyclopropanation 23
      1.2.4.2: Radical Cyclization and γ-Alkylation 32
      1.2.4.3: Anionic Oxy-Cope Rearrangement 41

   1.2.5: Elaboration of A and B Rings 51

      1.2.5.1: In Situ Methylation 52
      1.2.5.2: C(1)-Oxygenation of Ring A 57

   1.2.6: Evaluation of 5-Methyl-5,6-dehydrocamphor (178) as an Intermediate in Terpenoid Synthesis 59
**List of Tables**

Table 1: Comparison of reaction rates of the oxy-Cope rearrangement and the corresponding anionic oxy-Cope rearrangement 4

Table 2: Camphor derivatives in natural product synthesis 11

Table 3: Conditions used in the attempted cyclopropanation of compound 87 28

Table 4: Results of COSY experiment done on compound 138 47

Table 5: Results of NOE experiments done on compound 138 48

Table 6: Results of decoupling experiments done on major isomer of compound 210 75

Table 7: Results of NOE experiments done on major isomer of compound 210 77

Table 8: Results of NOE experiments done on compound 214 79

Table 9: Results of NOE experiments done on compound 255 101

Table 10: Specific rotation of (+)-4-methylisoborneol (267) 106

Table 11: Specific rotation of (-)-4-methylcamphor (229) 109
List of Figures

Figure 1: Chromatograms obtained for Samples A and B of (+)-4-methylisoborneol (267) 108

Figure 2: $^1$H NMR (400 MHz) spectra after [Eu(hfc)$_3$] addition to Sample C of (-)-4-methylcamphor (229) 110

Figure 3: $^1$H NMR (400 MHz) spectra after [Eu(hfc)$_3$] addition to Sample D of (-)-4-methylcamphor (229) 112

Contents of Appendix

1. X-ray crystal structure of alcohol 158 222
2. X-ray crystal structure of ketone 171 223
**List of Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AcO⁻</td>
<td>acetate</td>
</tr>
<tr>
<td>Ac₂O</td>
<td>acetic anhydride</td>
</tr>
<tr>
<td>AIBN</td>
<td>azobis(isobutyronitrile)</td>
</tr>
<tr>
<td>Anal.</td>
<td>microanalytically determined mass %</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>atm</td>
<td>atmosphere</td>
</tr>
<tr>
<td>ax.</td>
<td>axial</td>
</tr>
<tr>
<td>B⁻</td>
<td>base</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>BnBr</td>
<td>benzyl bromide</td>
</tr>
<tr>
<td>bp</td>
<td>boiling point</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>Bu</td>
<td>primary butyl</td>
</tr>
<tr>
<td>n-Bu</td>
<td>primary butyl</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tertiary butyl</td>
</tr>
<tr>
<td>c</td>
<td>concentration (g/100 mL, specific rotation)</td>
</tr>
<tr>
<td>Calc.</td>
<td>calculated mass %</td>
</tr>
<tr>
<td>Calc. Mass</td>
<td>calculated exact mass</td>
</tr>
<tr>
<td>conc</td>
<td>concentrated</td>
</tr>
<tr>
<td>COSY</td>
<td>$^1$H-$^1$H correlation spectroscopy</td>
</tr>
<tr>
<td>18-crown-6</td>
<td>18-crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane)</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>dd</td>
<td>doublet of doublets</td>
</tr>
<tr>
<td>ddd</td>
<td>doublet of doublets of doublets</td>
</tr>
</tbody>
</table>
ddm    doublet of doublets of multiplets
DHP    dihydropyran
DIBAL  diisobutylaluminum hydride
diglyme bis(2-methoxyethyl)ether
dm     doublet of multiplets
DMAP   4-dimethylaminopyridine
DME    1,2-dimethoxyethane
DMF    dimethyl formamide
DMS    dimethylsulfide
DMSO   dimethyl sulfoxide
dq     doublet of quartets
dt     doublet of triplets
E+     electrophile
e.e.   enantiomeric excess
ent-   enantiomer (of)
eq.    equatorial
Et     ethyl
Et2O   diethyl ether
EtOAc  ethyl acetate
Et3N   triethylamine
EtOH   ethanol
[Eu(hfc)3] tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium(III)
3,2-exo-Me 3,2-exo methyl shift
GC     gas liquid chromatography
h      hour
6,2-H  6,2-hydride shift
HMDS   1,1,1,3,3,3-hexamethyldisilazane
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>HMPT</td>
<td>hexamethylphosphorous triamide</td>
</tr>
<tr>
<td>HOAc</td>
<td>acetic acid</td>
</tr>
<tr>
<td>HOBu(^t)</td>
<td>tertiary butanol</td>
</tr>
<tr>
<td>i.d.</td>
<td>inner diameter (capillary gas liquid chromatography column)</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>k</td>
<td>rate constant</td>
</tr>
<tr>
<td>KOBu(^t)</td>
<td>potassium tertiary butoxide</td>
</tr>
<tr>
<td>KHMDS</td>
<td>potassium hexamethyldisilazide</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>lit</td>
<td>literature reference</td>
</tr>
<tr>
<td>L-Selectride(^\text{®})</td>
<td>lithium tri-secondary-butylborohydride</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>M</td>
<td>metal or molarity (mol/L)</td>
</tr>
<tr>
<td>M(^+)</td>
<td>molecular ion (mass spectrometry) or metal cation</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>m/e</td>
<td>mass to charge ratio</td>
</tr>
<tr>
<td>MeI</td>
<td>methyl iodide</td>
</tr>
<tr>
<td>Meas. Mass</td>
<td>exact mass determined by high resolution mass spectrometry</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>min</td>
<td>minute</td>
</tr>
<tr>
<td>mmHg</td>
<td>millimeters of mercury</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrum</td>
</tr>
<tr>
<td>n</td>
<td>normal (primary)</td>
</tr>
</tbody>
</table>
NaOMe  sodium methoxide
NMR  nuclear magnetic resonance
NOE  nuclear Overhauser effect
Nu-  nucleophile
PCC  pyridinium chlorochromate
PE  low boiling (30-60 °C) petroleum ether
Ph  phenyl
ppm  parts per million
i-Pr  isopropyl
i-Pr₂NH  diisopropylamine
py  pyridine
q  quartet
R  alkyl group
R’  alkyl group different from R
RBF  round bottomed flask
rt  retention time
RT  room temperature
s  singlet
SiO₂  silica gel
SM  starting material
t  triplet
t-  tertiary
T  temperature
TBAF  tetrabutylammonium fluoride
TBDMS  tertiary-butyldimethylsilyl
TBDMSCI  tertiary-butyldimethylsilyl chloride
td  triplet of doublets
Tf         trifuoromethanesulfonic (triflic)
Tf$_2$O     trifluoromethanesulfonic anhydride
THF        tetrahydrofuran
THP        tetrahydropyranyl
TLC        thin layer chromatography
TMS        trimethylsilyl
TMSCl      trimethylsilyl chloride
p-TsOH     para-toluenesulfonic acid
Ts         para-toluenesulfonyl
WM         Wagner Meerwein rearrangement
wt         weight
$[\alpha]^{T}_{D}$ specific rotation at 589 nm at T °C
δ          chemical shift
ν          absorption frequency
1°         primary
2°         secondary
3°         tertiary
Acknowledgements

I would like to thank my research supervisor, Professor Thomas Money, for his guidance and support throughout the years I have studied under his direction. Even during those times when results came slowly, he could always inspire me to try another of his exciting ideas, which came from an apparently limitless supply. His enthusiasm and encouragement increased both my knowledge of chemistry and my confidence, and I will always consider Professor Money as my mentor who guided me at the critical beginning of my career in chemistry. I shall always strive to achieve his level of knowledge in so many diverse areas of chemistry, although this will no doubt be a difficult goal.

I would like to thank Mike Wong and Scott Richardson, my co-workers, for their friendship, help and advice over the years. It was wonderful to share so much time with two undoubtedly diverse personalities who nevertheless complemented each other and each contributed to the lab atmosphere in a positive way. I would also like to thank the many friends, colleagues, and departmental staff members who made my graduate school years among the best of my life.

Finally, I would like to thank my mother, Daisy Palme, for her consistent support and encouragement throughout my studies, for her genuine interest in what I do, and for listening to an amazing amount of technical information, especially considering that she thought I should have become a chartered accountant.
This thesis is dedicated to
the memory of my father, Kurt Palme,
from whom I inherited curiosity, patience and perseverance
and to
my mother, Daisy Palme,
from whom I inherited drive, ambition and independence.
Chapter 1

The Evaluation of 5,6-Dehydrocamphor and 5-Methyl-5,6-dehydrocamphor As Intermediates In Terpenoid Synthesis
1.1 Introduction: The Anionic Oxy-Cope Rearrangement

The anionic oxy-Cope rearrangement is a versatile reaction that has been used extensively in the synthesis of natural products. The work described in Chapter 1 of this thesis utilizes the anionic oxy-Cope rearrangement as a key step in our route to a decalin system and relies on its stereospecificity to introduce three chiral centers.

The anionic oxy-Cope rearrangement is a variation of the Cope rearrangement which is a thermal [3,3] sigmatropic rearrangement of 1,5-dienes. A sigmatropic process involves a concerted reorganization of electrons during which a group attached by a σ-bond migrates to a more distant terminus of an adjacent π-electron system; there is a simultaneous shift of the π electrons. The [3,3] nomenclature comes from splitting the molecule at the migrating sigma bond and numbering the carbon atoms in each resulting fragment from that end. The two digits reflect the numbers of the carbon atoms of each fragment which are joined as a new sigma bond is formed.

The Cope rearrangement is reversible, giving an equilibrium mixture of two 1,5-dienes (starting material and product), with the ratio of the two reflecting their relative thermodynamic stabilities. Any 1,5-diene will rearrange, but will do so at lower temperature if there is a substituent on the C(3) or C(4) atom with which the new double bond that is formed can conjugate. If the group is hydroxyl (Z=OH), then the reaction is
called an oxy-Cope\textsuperscript{5} rearrangement and the product, an enol, tautomerizes to the ketone or aldehyde, causing the equilibrium to lie far to the right.

In 1975, Evans and Golob\textsuperscript{6} reported that the oxy-Cope rearrangement is accelerated by factors of $10^{12}$-$10^{17}$ if an alkoxide rather than an alcohol is used, and this variation became known as the anionic oxy-Cope rearrangement. The product is an enolate, which may be utilized \textit{in situ} as will be discussed in Section 1.2.5.1 (p. 52), or may simply be protonated to provide an aldehyde or ketone. Evans and Golob studied the effects of various cations on the anionic oxy-Cope rearrangement of alkoxide 1 in THF (Scheme 1).

In all cases, the temperature was kept at 66 $^\circ$C and the following results were obtained: If the cations were Li\textsuperscript{+} or MgBr\textsuperscript{+}, then even after 24 hours, no reaction was observed. When Na or K were used, the half lives of the reactions were 1.2 hours and 1.4 minutes respectively, and upon protonation during work-up, the product was found to be ketone 2. Having established that potassium as the counterion resulted in the greatest rate increase, the effect of added ionophore 18-crown-6 was investigated. It was found that addition of up to 3 equivalents of 18-crown-6 resulted in a limiting 180-fold acceleration in rate of

\[\text{Scheme 1}\]
reaction of 1b (M=K) at 0°C in THF. When HMPT was used as solvent and the reaction
was run under similar conditions (except T=10°C), the same results were obtained,
suggesting that rate dependence on the dielectric constant of the solvent is negligible and
that ion pair dissociation results in maximal rate acceleration.

Another set of experiments probed the actual rate accelerations observed when the
potassium alkoxides 1b (M=K) and 3b (M=K) were used instead of the corresponding
alcohols (Scheme 2). The effect of added ionophore 18-crown-6 was again investigated
and the results are summarized in Table 1.

![Scheme 2]

Table 1: Comparison of the reaction rates of the oxy-Cope rearrangement and the
corresponding anionic oxy-Cope rearrangement

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Alkoxide</th>
<th>Temp (°C)</th>
<th>Equiv. 18-cr-6</th>
<th>Rate Accel. ( \frac{k_{1b}}{k_{1a}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a, M=H</td>
<td>1b, M=K</td>
<td>25</td>
<td>1.1</td>
<td>10^{12}</td>
</tr>
<tr>
<td>3a, M=H</td>
<td>3b, M=K</td>
<td>40</td>
<td>0</td>
<td>10^{12}</td>
</tr>
<tr>
<td>3a, M=H</td>
<td>3b, M=K</td>
<td>0</td>
<td>1.1</td>
<td>10^{17}</td>
</tr>
</tbody>
</table>
These experiments dramatically showed the exceptionally large increases in rate \( k \) which were observed when alkoxides 1b (M=K) and 3b (M=K) were used instead of the corresponding alcohols (1a, M=H and 3a, M=H). These results also confirmed the previously described reports of rate increases attainable when an ionophore is used as an additive. In 1984, Bartmess and co-workers\(^7\) suggested that a faster rate observed for tertiary alkoxides (as compared to secondary alkoxides) is due to steric hindrance around the anionic site, which results in decreased ion pairing and solvation at that location. This suggestion is consistent with the fact that an increase in rate is produced by the addition of 18-crown-6 which complexes potassium ions and hence reduces ion pairing.

In order to explain the rate increases observed in the anionic oxy-Cope rearrangement, Evans and co-workers\(^8\) carried out \textit{ab initio} C-H bond strength calculations for methanol, sodium methoxide, potassium methoxide and the methoxide anion and found that the bond strength decreased with increasing degree of ionization. The decrease calculated upon going from the alcohol to an alkoxide was attributed to increased charge transfer from the cation to the organic fragment and thus a tendency for the oxygen π electrons to delocalize back onto the carbon, resulting in a weaker C-H bond. In the case of the bare, unsolvated methoxide anion, there is further oxygen-centered electron delocalization and the C-H bond becomes even weaker. If this explanation is extended to a C-C bond where one carbon atom bears a hydroxyl substituent, then the C-C bond strength should be weaker in the alkoxide than in the parent alcohol, and cleavage of the bond should be more facile. This explanation accounts for the rate increases observed in the anionic oxy-Cope reaction; furthermore, it also supports the rate acceleration observed upon the addition of ionophore which should further weaken the C-C bond.

In 1980, Evans and co-workers\(^9\) established that the anionic oxy-Cope rearrangement, as the Cope rearrangement itself, is a concerted process which usually proceeds through a chair-like transition state. Thus the stereochemical outcome of a
reaction can usually be predicted in terms of a preference for the chair-like transition state which minimizes steric interactions. As shown in Scheme 3, for example, the Cope rearrangement of the meso isomer of 3,4-dimethyl-1,5-hexadiene can exist in one possible pseudo-chair conformation (5). Rearrangement of this isomer (5) via a concerted process leads to the formation of only one product, the cis, trans isomer 6, which was observed.\textsuperscript{10} Reaction of the meso isomer via either possible boat conformation 7 or 9 would lead to either the trans, trans product 8 or the cis, cis product 10, neither of which were observed.\textsuperscript{10}

The Cope rearrangement of systems such as 11 (Scheme 4) that can proceed via two possible chair-like transition states has also been examined.\textsuperscript{11} Rearrangement of 11 was found to give 12 as the major product, and only minor amounts of 13 were formed. This can be rationalized by the fact that the more sterically demanding phenyl substituent would favor the equatorial position in the transition state 11a, as opposed to the axial
position as in 11b, where it would experience greater 1,3-diaxial interaction than the methyl group. When enantiopure 11 was used, it was found that the major product 12 had an enantiomeric purity of at least 95%. Thus, not only can the stereochemistry of the newly formed double bonds be predicted, but also, when the starting 1,5-diene is optically active, the chirality of newly formed tetrahedral centers. A recent example of such a chirality transfer was reported by Nakai and co-workers\textsuperscript{12} in their approach to (+)-faranal (18), an ant pheromone (Scheme 5).
Diene 14 was prepared in >96% e.e. and upon treatment with KH and 18-crown-6 formed alkoxide 15 which rearranged via a chair-like transition state to give, upon protonation, enol 16 which tautomerized to aldehyde 17. The stereochemistry of 17 was determined to be as predicted, and the enantiomeric purity was 91%.

In cases where the starting 1,5-diene is rigid, a chair-like transition state may not be possible; the anionic oxy-Cope rearrangement may then proceed via a boat-like transition state. An example of such a molecule is the bicyclo[2.2.1]heptenol intermediate 19 that Paquette and co-workers\textsuperscript{13} used in their synthesis of (+)-ikarugamycin (21) (Scheme 6). Although forced to proceed via a boat-like transition state, diene 19 rearranged in reasonable yield, and the stereochemistry of product 20 was as predicted.

Although the anionic oxy-Cope rearrangement commonly is used to synthesize acyclic or 6-membered ring products, it can also be used to make medium ring products.
A striking example is Paquette and co-workers' synthesis of intermediate 23 (Scheme 7).

Treatment of 22 with KHMDMS caused rearrangement to provide enolate 23. Instead of protonation of 23 by the addition of water, methyl iodide was added instead, which resulted in alkylation of the intermediate enolate 23 to provide 24. This *in situ* methylation of an enolate resulting from anionic oxy-Cope rearrangement will be discussed further in Section 1.2.5.1 (p. 52); however, reaction of 22 to provide 24 is an example of how the anionic oxy-Cope rearrangement can be utilized to provide a highly functionalized, medium ring product.

The predictable stereospecificity of the anionic oxy-Cope rearrangement makes it a very useful reaction in organic synthesis. If the starting 1,5-diene is substituted, however, steric interactions may prevent the rearrangement from occurring, thus limiting the scope of the reaction. We have utilized the anionic oxy-Cope rearrangement in our efforts towards the enantiospecific synthesis of natural product intermediates. Our use of this versatile reaction, and also its limitations due to steric effects, is described in the discussion of Chapter 1 of this thesis.
1.2: Discussion

1.2.1: Introduction

The use of (+)-camphor (25) or its enantiomer (ent-25) in natural product synthesis\textsuperscript{15} is due to the fact that camphor can be functionalized at the C(3), C(5), C(6), C(8), C(9) and C(10) positions. In addition, cleavage of the C(1)-C(2), C(2)-C(3), and C(1)-C(7) bonds in camphor and camphor derivatives can be accomplished to provide synthetically useful intermediates (Scheme 8).

![Scheme 8](image-url)
Table 2 shows examples of camphor derivatives and some natural products or synthetic intermediates that have been synthesized using them as precursors. Each derivative can be synthesized in either enantiomeric form, and thus either enantiomer of the natural product is accessible.

Table 2: Camphor derivatives in natural product synthesis

<table>
<thead>
<tr>
<th>Camphor Derivative</th>
<th>Natural Products or Intermediates</th>
</tr>
</thead>
<tbody>
<tr>
<td>camphor-10-sulfonic acid (26)</td>
<td>khusimone,\textsuperscript{16} zizanoic acid,\textsuperscript{16}</td>
</tr>
<tr>
<td></td>
<td>quadrone,\textsuperscript{17} \textit{epi}-zizanoic acid\textsuperscript{16}</td>
</tr>
<tr>
<td>9-bromocamphor (27)</td>
<td>\textit{\alpha}-santalene,\textsuperscript{18,19,20} \textit{\alpha}-santol,\textsuperscript{21,22,23,24,25}</td>
</tr>
<tr>
<td></td>
<td>\textit{\beta}-santol,\textsuperscript{23,24} furodysin,\textsuperscript{26}</td>
</tr>
<tr>
<td></td>
<td>\textit{epi}-\textit{\beta}-santalone,\textsuperscript{19,27} furodysin,\textsuperscript{26}</td>
</tr>
<tr>
<td></td>
<td>isoepticampherolen,\textsuperscript{27} cannabidiol,\textsuperscript{28}</td>
</tr>
<tr>
<td></td>
<td>cannabidiol dimethyl ether,\textsuperscript{28} hapalindole Q,\textsuperscript{29} helenanolide intermediate,\textsuperscript{30} vitamin B\textsubscript{12} intermediate,\textsuperscript{31} steroid intermediates\textsuperscript{32,33,34}</td>
</tr>
<tr>
<td>8-bromocamphor (29)</td>
<td>campheronenone,\textsuperscript{27,35} \textit{\alpha}-santalene,\textsuperscript{27}</td>
</tr>
<tr>
<td></td>
<td>sativene,\textsuperscript{27,36} copacamphene,\textsuperscript{27,36}</td>
</tr>
<tr>
<td></td>
<td>copaborneol,\textsuperscript{27,36} campherolen,\textsuperscript{27}</td>
</tr>
<tr>
<td></td>
<td>longiborneol,\textsuperscript{35} longifolene,\textsuperscript{35} \textit{\beta}-santalone\textsuperscript{27}</td>
</tr>
<tr>
<td>9,10-dibromocamphor (28)</td>
<td>estrone,\textsuperscript{37,38} California red scale pheromone,\textsuperscript{39} ophiobolin C,\textsuperscript{40}</td>
</tr>
<tr>
<td></td>
<td>helenanolide intermediate,\textsuperscript{41} steroid intermediates\textsuperscript{42,43,44}</td>
</tr>
<tr>
<td>5-ketoisobornyl acetate (33)</td>
<td>nojigiku alcohol\textsuperscript{45}</td>
</tr>
<tr>
<td>5-ketobornyl acetate (34)</td>
<td>\textit{epi}-\textit{\beta}-necrodol\textsuperscript{46}</td>
</tr>
<tr>
<td>camphorquinone (30)</td>
<td>patchouli alcohol,\textsuperscript{47} taxusin,\textsuperscript{48} vitamin B\textsubscript{12} intermediates\textsuperscript{49,50,51,52}</td>
</tr>
</tbody>
</table>
Part of the continuing interest in our laboratory is to further investigate camphor (25) as a chiral starting material in natural product synthesis. The objective of the research described in this thesis was to develop a general strategy towards the enantiospecific synthesis of sesquiterpenoids, diterpenoids, sesterterpenoids and triterpenoids that contain 4,4,10-trimethyl decalin (35) as a structural sub-unit (A/B ring system) in their carbon skeleton (Scheme 9).

Scheme 9

It was envisioned that an alkoxide (37) derived by the formal addition of a trans-alkenyl unit to (+)-5,6-dehydrocamphor (36) or its enantiomer could undergo anionic
oxy-Cope rearrangement resulting in hydrindenone intermediate 38. The structure of the alkenyl unit would, of course, depend upon the class of terpenoid to be synthesized. For sesquiterpenoids, R\(^1\)=H and R\(^2\)=CH\(_3\), CH\(_2\)OH or CHO. For the larger terpenoids, R\(^1\) represents an appropriate C\(_5\), C\(_{10}\), or C\(_{15}\) unit.

Due to the stereospecificity of the anionic oxy-Cope rearrangement, the ring junction in hydrindenone 38 is cis, and the C(9) substituent trans to the ring junction hydrogens. In addition, the absolute configurations of C(5), C(9) and C(10) are dependent upon which enantiomer of 5,6-dehydrocamphor (36) is used as starting ketone. Initially, the enolate of the hydrindenone (38) is formed, and therefore the stereochemistry of the R\(^2\) substituent is dependent upon which face of the enolate is protonated upon work-up; the C(8) center is, of course, epimerizable. Ring expansion of 38 should provide the decalin system and intermediate 39 contains most structural features inherent in the A/B ring system of many terpenoids: oxygen functionality at C(3) and C(7), the geminal dimethyl groups at C(4), and alkyl substitution at C(8) and C(9). Missing, however, is the angular methyl group at C(10). It was expected, however, that either the C(11) hydroxyl group or the A ring enone functionality in 39 could be used to introduce, stereoselectively, the angular methyl group.

1.2.2: Synthesis of 5,6-Dehydrocamphor (36)

Literature methods for the synthesis of (+)-5,6-dehydrocamphor (36) or its enantiomer (ent-36) involve laborious multi-step sequences. The first synthesis of (+)-5,6-dehydrocamphor (36) was Asahina's nine-step route outlined in Scheme 10.\(^{53}\)

(+)-Camphor (25) is converted to (+)-bornyl acetate (32) in two steps. Oxidation of (+)-bornyl acetate (32) with CrO\(_3\)/HOAc yields a mixture from which the desired product, 5-ketobornyl acetate (34) is obtained in only 24% yield. Further oxidation of 5-ketobornyl acetate (34) with SeO\(_2\) in Ac\(_2\)O gave 5,6-dioxobornyl acetate (42) in 56%
yield. (+)-5,6-Dehydrocamphor (36) was ultimately obtained after diazotization, reduction, bromination, and dehydrohalogenation steps.

Hietaniemi and Malkonen's nine-step synthesis\textsuperscript{54} of (-)-5,6-dehydrocamphor (ent-36) also uses (+)-camphor (25) as a starting material (Scheme 11) and is dependent
on remote oxidation of (+)-bornyl acetate (32) to provide 5-ketobornyl acetate (34) as a key intermediate. Replacement of the acetyl protective group with the tetrahydropyranyl protective group, reduction, and treatment with CS₂/CH₃I yielded xanthate 50. After pyrolysis and oxidation (-)-5,6-dehydrocamphor (ent-36) was finally obtained.

Scheme 11

The syntheses described above both involve remote oxidation of bornyl acetate (32) as a key step. Considerable experience in our laboratory has shown that this
produces 5-ketobornyl acetate (34) in variable yield.\textsuperscript{45} Separation of the desired isomer from the other major product, 6-ketobornyl acetate, is tedious.

Recent investigations in our laboratory have resulted in the development of two alternative synthetic routes to 5,6-dehydrocamphor (36). The first route (Scheme 12) was based on the discovery that commercially available (+)-endo-3-bromocamphor (52) undergoes acid-catalyzed rearrangement to provide (-)-endo-6-bromocamphor (53) in \(~40\%\) yield.\textsuperscript{55} The mechanism proposed (Scheme 13) for the acid-catalyzed rearrangement of (+)-endo-3-bromocamphor (55, \(X=\text{Br}, Y=\text{H}\)) to (-)-endo-6-bromocamphor (56, \(X=\text{Br}, Y=\text{H}\)) is analogous to that reported for the acid-catalyzed racemization of camphor (55, \(X=Y=\text{H}\))\textsuperscript{56} and is supported by the observation that (+)-endo-3-bromo-10-deuteriocamphor (55, \(X=\text{Br}, Y=\text{D}\)) rearranged to (-)-endo-6-bromo-8-deuteriocamphor (56, \(X=\text{Br}, Y=\text{D}\)).\textsuperscript{57}

A minor by-product in the rearrangement of 52 to 53 was 7-bromofenchone (57) and its formation can be rationalized by the mechanism outlined in Scheme 14 (p. 18).
(-)-endo-6-Bromocamphor (53) was dehydrobrominated with KOH in DMSO/H₂O to give (+)-5,6-dehydrocamphor (36, mp: 145-148 °C, lit mp 148 °C) in ~40% yield. The poor yield in this reaction is due to the competing ring-cleavage reaction that produces campholenic acid (54) as a co-product (cf. Scheme 12).
A simple two-step synthesis of (+)-5,6-dehydrocamphor (36) is therefore available, and it is also possible to obtain (-)-5,6-dehydrocamphor (ent-36) by the same sequence, starting with commercially available (-)-endo-3-bromocamphor (ent-52).

The development of a new six-step synthetic route to (-)-5,6-dehydrocamphor (ent-36) (or its enantiomer) was the starting point of the work described in this thesis. Although longer than the synthesis described above, each step of the new synthesis is easily carried out and occurs in good to high yield (Scheme 15). In the first step of the

Scheme 15

1) Br₂, CH₃CO₂H, reflux, 2.5 h  ii) Et₂Zn, benzene, reflux, 24 h  iii) 48% HBr, Ac₂O, 65 °C, 3 h  iv) TMSCl, ethylene glycol, RT, 2.5 h  v) KOH, DMSO/H₂O, 100 °C, 2.5 h  vi) 1 M HCl, acetone, RT, 1.5 h
synthesis addition of bromine to (+)-endo-3-bromocamphor (52) in refluxing glacial acetic acid\textsuperscript{58} provided (+)-3,3-dibromocamphor (58) in 88\% yield. Subsequent treatment with Et\textsubscript{2}Zn in refluxing benzene\textsuperscript{59} gave cyclocamphanone (59) as a white solid in 78\% yield. The spectral characteristics of cyclocamphanone (59) were identical to those reported in the literature and the melting point is 168-169 °C (lit mp: 168-170 °C).\textsuperscript{59} The mechanism proposed\textsuperscript{59} for this reaction is outlined in Scheme 16. The reaction was monitored by GC and an intermediate was seen whose retention time matched that of an authentic sample of endo-3-bromocamphor (52). Further heating showed disappearance of the intermediate as the tricyclic product (59) was formed, presumably via a carbene insertion reaction. Thus, the GC data is consistent with the proposed mechanism.\textsuperscript{59}

Cyclocamphanone (59) was heated at 65 °C with 48\% hydrobromic acid in acetic anhydride\textsuperscript{60} to provide exo-5-bromocamphor (60) in 78\% yield as a white crystalline solid (mp: 109-111 °C, lit mp\textsuperscript{58}: 110-111 °C). The position of the bromine is confirmed by the C(5) endo proton signal in the \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) spectrum of 60. As expected, it is downfield at 4.06 ppm, due to the electron withdrawing properties of the
C(5) bromine. It appears as a doublet of doublets, showing no coupling with the C(4)H with which it forms an angle of approximately 90°. The C(5) endo proton does show coupling of 8 Hz with the C(6) endo proton, and of 5 Hz with the C(6) exo proton. Thus, bromination occurred at the C(5) exo position as expected.

With the C(5) position now functionalized, it was hoped that treatment with base would result in dehydrohalogenation to provide (-)-5,6-dehydrocamphor (ent-36). However, treatment with a variety of bases resulted in enolate formation and subsequent loss of bromide to provide cyclocamphanone (59). Thus protection of the carbonyl group was required. This was done using ethylene glycol and TMSCl to form ketal 61 in 92% yield. The infrared spectrum (CHCl₃) of 61 showed the absence of the carbonyl stretch which was present at 1745 cm⁻¹ in exo-5-bromocamphor (60) and its ¹H NMR (400 MHz, CDCl₃) spectrum also showed both C(3) protons to be more shielded (1.41 vs 1.84 ppm for C(3) endo H and 2.11-2.17 vs 2.46 ppm for C(3) exo H) than in the corresponding carbonyl compound (60).

Treatment of ketal 61 with KOH in DMSO/H₂O at 100 °C provided 5,6-dehydrocamphor ketal (62) in 92% yield and subsequent hydrolysis with 1 M HCl in acetone gave (-)-5,6-dehydrocamphor (ent-36) as a white crystalline solid (92% yield):

[α]D²⁵ -714° (c 2.10, 95% EtOH), lit [α]D²⁵ -735° (c 1.0, 95% EtOH).⁵³,⁵⁴ This compound was identical in all respects to (+)-5,6-dehydrocamphor (36) prepared via the two-step synthesis (cf. Scheme 12, p. 16) except for the sign of optical rotation.
1.2.3: Synthesis of a Decalin System from 5,6-Dehydrocamphor (36)

With 5,6-dehydrocamphor (36) easily accessible in either enantiomeric form, the next goal was to add an allenyl unit to the carbonyl group in this compound and to investigate the subsequent anionic oxy-Cope rearrangement of this product (Scheme 17).

![Scheme 17](image)

i) LiC≡CCH₂OLi, THF, -78°C, RT, 76%  
ii) LiAlH₄, THF, 40°C, 1 h, 85%  
iii) KH, THF, 40°C, 15 min, 85%

The dianion of propargyl alcohol, formed by addition of n-BuLi at -78°C in THF⁶¹ was added to (+)-5,6-dehydrocamphor (36) to give alkyne diol 63 as a white crystalline solid in 76% yield. Reduction of 63 using LiAlH₄ in THF⁶² afforded trans-alkene diol 64 as a white solid in 85% yield. This compound was quite insoluble in common organic solvents such as Et₂O and CHCl₃; however, its ¹H NMR spectrum was obtained as a solution in CD₃CN. The ¹H NMR (400 MHz, CD₃CN) spectrum of 64 supported the reduction of the alkyne to the alkene; however, the signals due to the vinyl protons of the newly formed alkene overlapped with the C(6) vinyl proton signal. That the reduction had occurred trans and not cis could not be proven at this point. In later
experiments, however, alkene diol 64 was derivatized and X-ray crystallographic evidence supported the trans stereochemistry (see p. 54).

Treatment of alkene diol 64 with excess KH in THF at 40°C resulted in facile anionic oxy-Cope rearrangement to give hydrindenone 66 in 85% yield. The relative stereochemistry of the product was confirmed by X-ray crystallographic analysis of a later derivative (see p. 54). It was predicted at this point, however, based on the presumed trans-geometry of the alkene diol and the stereospecificity of the concerted anionic oxy-Cope rearrangement. Therefore, the ring junction hydrogens were assumed to be cis and the C(9) hydroxymethylene substituent to be equatorial (trans to the ring junction protons). Ring expansion of hydrindenone 66 to decalin intermediate 69 was accomplished by the reaction sequence shown in Scheme 18.

Thus protection of the hydroxyl group in 66 to provide acetate 67, followed by ozonolysis and reductive work-up provided keto-aldehyde 68. Subsequent treatment with p-TsOH·H2O in refluxing benzene resulted in acid-catalyzed aldol condensation to provide enone 69. The structure of 69 was confirmed by the presence of IR carbonyl absorptions for the ester (1740 cm⁻¹), ketone (1720 cm⁻¹) and enone (1680 cm⁻¹) functionalities. The ¹H NMR (400 MHz, CDCl₃) spectrum of 69 also showed the absence of the original vinyl proton (5.17 ppm in the acetate 67) and the appearance of
new vinyl protons: 6.16 (1H, dd, J=11, 3 Hz, C(2)H); 6.82 (1H, dt, J=11, 1 Hz, C(1)H) which were downfield, as expected for an α,β-unsaturated ketone.

Enone 69 is obviously related to the familiar A/B ring system of many terpenoids. It possesses the geminal dimethyl groups at C(4), oxygenation at C(3) and C(7) and the hydroxymethylene group at C(9). As a result we concluded that enone 69 could be a potentially useful intermediate in terpenoid synthesis. A missing structural feature, however, is the C(10) angular methyl group and our next objective was, therefore, to introduce, stereoselectively, a C(10) angular methyl group into enone 69.

1.2.4: Angular Functionalization Approaches

1.2.4.1: Hydroxyl-directed Cyclopropanation

Traditional approaches to introducing an angular methyl group in the synthesis of terpenoids have often included elaboration of the 10-methyldecalin system (cf. 72) by Robinson annulation\(^6\) or modifications thereof.\(^6\)

![Chemical Structure](image)

Other approaches have also been explored. One of these involves cyclopropanation reactions, and the subsequent opening of the cyclopropane ring provides a methyl group.\(^6\) For example, such a sequence was used in a reported synthesis of 10-epi-testosterone (77)\(^6\) (Scheme 19).

Classical Simmons-Smith conditions\(^6\) were used to cyclopropanate 73 and provide intermediate 74. The stereochemistry of the cyclopropane ring in 74 derives
from the established tendency for allylic and homoallylic hydroxyl groups to direct the methylene carbene attack on the double bond so that the cyclopropane ring is formed cis to the directing group. Not only can an allylic or homoallylic hydroxyl substituent act as a directing group, it also enhances the rate of the cyclopropanation, and often may be necessary for reaction to occur at all. Oxidation of 74 followed by removal of the protective group produced intermediate 76. Treatment of 76 with base resulted in removal of a C(4) proton with subsequent opening of the cyclopropane ring and led to the formation of 10-epi-testosterone (77).

A second example of a base-promoted cyclopropane ring opening to provide an angular methyl group is shown in Scheme 20. In this work, isomeric cyclopropyl alcohols 78 and 80 were both prepared. Treatment of 78 (which has the C(2) hydroxyl group cis to the cyclopropane ring) with KOBu\(^+\) in HOBu\(^+\) and DMSO gave 79 in high yield. However, under identical conditions, 80 (which has the C(2) hydroxyl group trans to the cyclopropane ring) failed to react at all. This result suggests that a ketone adjacent to the cyclopropane ring, in some cases, may not be enough for base-promoted ring
opening to occur. A hydroxyl group homoallylic to the double bond from which the
cyclopropane ring was derived may also be required to assist in ring opening;
furthermore, the stereochemistry of the alcohol can be crucial.

Our first attempt to introduce, stereoselectively, a C(10) angular methyl group
into enone 69 was based on this methodology (Scheme 21). Thus we considered that
decoupling of the C(1)-C(2) enone double bond in 69 to the C(1)-C(10) position
followed by cyclopropanation directed by homoallylic oxygen substituents at C(3) or
C(11) would provide intermediate 83. Subsequent cleavage of the cyclopropane ring in
83 could then provide the required angularly methylated intermediate 84.

By analogy with the related studies in the steroid area (Scheme 20)71 we also
assumed that the hydroxymethyl group at C(9) could assist in the base-promoted ring
cleavage reaction. Evaluation of this general approach to angular methylation is outlined
in Schemes 22 and 23.
Thus treatment of enone 69 with ethylene glycol and p-TsOH-H2O in refluxing benzene for 45 minutes provided the monoketalized acetate 85 in 77% yield. Further treatment with ethylene glycol and p-TsOH-H2O in refluxing benzene overnight provided a mixture of diketal-acetate 86 and diketal-alcohol 87 in 37% and 48% yields respectively. The two compounds could easily be separated chromatographically and the acetate (86) converted to the alcohol (87) by treatment with KOH in aqueous MeOH. The alcohol 87 showed an absence of any C=O absorptions in its infrared spectrum and the presence of a broad O-H absorption as expected. The $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 87 showed eight ethylene ketal proton signals. That deconjugation of the double bond had occurred was apparent by the presence of only one vinyl proton signal at 5.33 ppm due to the C(1)H. In addition, the C(10) proton signal in the $^1$H NMR (400 MHz, CDCl$_3$) spectrum of the starting enone (69) was a distinctive broad singlet at 3.06 ppm. This signal was absent in the spectrum of the deconjugated alcohol (87).
Several classical cyclopropanation reactions on 87 were attempted; unfortunately, none yielded any cyclopropyl-containing product as determined by $^1$H NMR and mass spectrometry. Table 3 summarizes the reagents used and products obtained. This complete lack of success was unexpected and we concluded that the reaction could be inhibited by steric effects. Examination of the structure of alcohol 87 led to the possibility that either the β C(3) ketal substituent or the β C(4) methyl group may be blocking the β face of the C(1)-C(10) double bond and preventing cyclopropanation from occurring.
Table 3: Conditions used in the attempted cyclopropanation of compound 87

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>172</td>
<td>CHCl₃, BuN⁺Et₃Cl⁻, 50% NaOH(aq)</td>
<td>complex mixture</td>
</tr>
<tr>
<td>2⁷³,⁷⁴</td>
<td>Et₂Zn, toluene, CH₂I₂, O₂</td>
<td>39% recovered alcohol 87 and side-products</td>
</tr>
<tr>
<td>3⁶⁷</td>
<td>Zn-Cu, I₂, CH₂I₂, Et₂O</td>
<td>17% recovered alcohol 87 and side-products</td>
</tr>
<tr>
<td>4⁷⁵</td>
<td>Zn, CuCl, Et₂O, CH₂Br₂, TiCl₄</td>
<td>complex mixture</td>
</tr>
</tbody>
</table>

Scheme 23
We decided, therefore, to remove the C(3) ketal group and use a C(3)β hydroxyl group to direct the cyclopropanation. For simplicity, and to check the feasibility of this approach, the hydroxymethyl group and the C(7) hydroxyl group obtained after reduction of the C(7) carbonyl group in 66 were protected as methyl ethers (Scheme 24).

For this purpose keto-alcohol 66 was treated with LiAlH₄ in THF to give a crude diol that was converted directly to its dimethyl ether (91) using KH and MeI in an overall yield of 83%. The diastereomeric ratio resulting from the stereoselective reduction was determined by ¹H NMR spectroscopy to be ~4:1. Based on the following analysis, the major isomer (91) was predicted to be that with a β C(7) methoxy substituent.

There are two considerations when predicting which face of a carbonyl group will be attacked by a hydride reducing agent (or other nucleophile). The first is the presence
of substituents which may block the approach of the hydride reagent. In our cyclohexanone derivative 66 these are the C(5) and C(9) axial hydrogens. If the reducing agent is bulky enough, these two substituents would hinder approach from the \( \alpha \) face. Therefore, a large hydride reducing agent would approach from the \( \beta \) face to give an \( \alpha \)-hydroxyl group (i.e. an axial hydroxyl group upon reaction with 66). However, the reducing agent used was LiAlH\(_4\) which is relatively small, and may not be subject to severe steric hindrance from the C(5) and C(9) axial hydrogens and therefore a second factor, torsional strain, must be considered.

If one looks down the C(7)-C(8) bond of hydrindenone 66, one sees Newman projection A:

If the hydride approaches from the \( \alpha \) face, then the new C-OH bond is formed without eclipsing the vicinal C-H bonds (cf. B). If, however, the hydride approaches from the \( \beta \) face, the new C-OH bond is formed with eclipsing of a vicinal C-H bond (cf. C) and this results in torsional strain. When a small reducing agent such as LiAlH\(_4\) is used, the torsional strain factor outweighs any other factors and in cyclohexanone derivatives this results, primarily, in the formation of an equatorial hydroxyl group. Thus, LiAlH\(_4\).
reduction of ketone 66 was predicted to result in the β orientation (i.e. in the equatorial position) of the C(7) hydroxyl group. This stereochemistry was not established at this time since it was irrelevant to the cyclopropanation investigation. However, as the synthetic sequence progressed and each compound was purified, the mixture of diastereomers became more and more enriched in the major isomer as small amounts of the minor isomer were separated.

The dimethyl ether (91) was treated with ozone and a reductive work-up using Zn and HOAc to give a keto-aldehyde intermediate which was immediately cyclized under acid-catalyzed aldol conditions to give enone 92 in 52% yield (Scheme 24, p. 29). The enone was deconjugated as before by prolonged treatment with p-TsOH·H2O and ethylene glycol in refluxing benzene to give ketal 93 in 53% yield. The ketal could be removed without reconjugation of the double bond by short (15 min) acid treatment at 70 °C to provide deconjugated enone 94 in 95% yield. Infrared spectroscopy showed the C=O absorption to be at 1714 cm⁻¹, which is significantly higher frequency than what one would expect if the enone were conjugated (cf. 1679 cm⁻¹ in enone 92). The ¹H NMR (300 MHz, CDCl₃) spectrum of 94 showed only one vinyl proton signal at 5.26 ppm due to the C(1)H and the distinctive broad singlet due to the C(10)H at 3.12 ppm in the ¹H NMR (400 MHz, CDCl₃) spectrum of enone 92 was absent. Ketone 94 was reduced with LiAlH₄ to give alcohol 95 in 89% yield. Based on the same rationale described above for the reduction of the C(7) carbonyl group in compound 66, the C(3) hydroxyl group in 95 was predicted to be in the β (i.e. equatorial) orientation.

Alcohol 95 was treated with Zn-Cu couple and CH₂I₂ under classical Simmons-Smith conditions.⁶⁷ Two compounds were obtained and the ¹H NMR (400 MHz, CDCl₃) spectrum showed these to be mainly unreacted starting alcohol (95) and a compound which was probably the cyclopropanation product (96) as shown by a proton signal at 0.45 ppm. As a satisfactory result could not be obtained under these reaction conditions, cyclopropanation of 95 was attempted using Et₂Zn, CH₂I₂ and O₂ (as a rate
accelerator). Under these conditions, cyclopropyl compound 96 was formed, although in an extremely poor yield of 4%! This low yield suggests that the β C(4) methyl group (as opposed to the β C(3) ketal substituent) may be the cause of the steric hindrance which makes the β face of 95 inaccessible. It is unlikely that cyclopropanation would occur from the α face as an alternative because that face is the hindered concave face of 95. Evidence that a small amount of cyclopropyl compound 96 was formed was given by the high resolution mass spectrum of 96 which showed a parent ion peak corresponding to compound 96 (C16H28O3 Calc. Mass: 268.2038, Meas. Mass: 268.2029) and the 1H NMR (300 MHz, CDCl3) spectrum of 96 showed two characteristic cyclopropyl proton signals at 0.45 and 0.67 ppm.

Although the cyclopropyl compound 96 was finally obtained, this route to an angular methyl group was not pursued further, due to the unacceptable yields obtained in the cyclopropanation reactions.

1.2.4.2: Radical Cyclization and γ-Alkylation

Another approach to the stereoselective introduction of an angular methyl group at C(10) involved radical cyclization. It was envisioned that the hydroxymethyl group at C(9) could be used for this purpose. It was expected that a radical intermediate such as 97 (Scheme 25) could undergo radical cyclization to produce the synthetically useful intermediate 98. Intermediate 97 would be designed such that Y=carbon or a heteroatom
such as silicon so that facile cleavage of cyclized product 98 would provide an angularly functionalized decalin (99).

![Diagram](image)

Scheme 25

Literature reports indicate that **exo** ring closure of the hex-5-enyl radical and analogous systems is kinetically preferred over **endo** ring closure to give a 5-membered ring product.\textsuperscript{76,77,78}

With radical intermediate 97 (Scheme 25), however, the possible cyclization products were either a 6-membered ring by **exo** closure or a 7-membered ring by **endo** closure and
it was hoped that in this case a 6-membered ring would form preferentially. It is experimentally observed in the formation of 5- and 6-membered bicyclic ring products that the newly formed ring junction is predominantly cis. Therefore, if 6-membered ring cyclization of radical could be induced, the new bond to C(10) would be expected to be cis to the C(9) group in bicyclic product, i.e. the C(10) substituent would be in the β orientation, as required. The carbon-centered radical is usually formed from a bromide, and the two-atom chain in intermediate should be such that the Y-O bond in can ultimately be cleaved to give angularly functionalized decalin.

Stork and co-workers have used compounds such as and and have shown that 6-membered ring formation is possible using the acetal linkage in (Scheme 26).

![Scheme 26](image)

More recently, Koreeda and co-workers have reported successful 6-membered ring formation using the bromomethyldimethylsilyl chain tethered to an allylic hydroxyl group (Scheme 27).
The silicon tether appealed to us because it is easily cleaved, either reductively with TBAF in DMF/THF to give Y' = H, or oxidatively using 30% H₂O₂ and KF in DMF to give Y' = OH in 99 (Scheme 25, p. 33). Therefore, both the possibility for introducing an angular methyl group or an angular aldehyde existed. Although an angular methyl group is more common, some natural products exist in which this methyl group has been oxidized. Our route is outlined in Scheme 28.

Scheme 27

Scheme 28
The diketalized alcohol (87), obtained as before (Scheme 22, p. 27) for use in the cyclopropanation work, was treated with bromomethyldimethylsilyl chloride, Et3N and DMAP in CH2Cl2 for 30 minutes to give the silylated alcohol 106 in 76% yield. Bromine abstraction and radical formation was induced by Bu3SnH in refluxing benzene using AIBN as initiator. Both concentrated conditions with rapid Bu3SnH addition and highly dilute conditions with Bu3SnH addition over hours were tried. In all cases, no cyclization products were detected, and only the reduction product 107 was formed in 65-80% yield. The structure of the latter compound was confirmed by the presence of one vinyl proton signal at 5.18 ppm and a singlet due to the trimethylsilyl protons at 0.10 ppm in the 1H NMR (400 MHz, CDCl3) spectrum of 107. A small sample of 107 was treated with TBAF in THF and the product from this reaction was identical to starting alcohol 87, further confirming the structure of 107. The fact that reduction rather than cyclization had occurred shows that hydrogen radical abstraction to quench the initially formed methylene radical is faster than interaction with the double bond. The usual source of the quenching hydrogen radical is Bu3SnH and a common solution to this type of problem is to use high dilution techniques. However, these reaction conditions also failed to induce cyclization and therefore another source of the quenching hydrogen had to be considered.

Stork has reported that in homoallylic systems, [1,5] hydrogen atom transfer is common (Scheme 29). If compound 110, for example, is treated with Bu3SnH and AIBN, the major product is the cyclized compound 111; however, significant amounts of 112 are also produced. It is believed that 112 is formed by quenching of the radical that is initially formed at position 1, not by hydrogen radical abstraction from the Bu3SnH, but from the hydrogen that is present in 110 at position 5.
In our case, this hydrogen atom source is the C(9) hydrogen. A possible solution to the problem is to replace the C(9) hydrogen with an alkyl group; however, in view of our general synthetic objectives, this approach was not investigated.

Stork has also reported that conjugating the double bond with an ester or ketone functionality leads to increased yields of cyclization product and decreased yields of reduction product (Scheme 29). Thus, introducing an ester group at the C(1) position of our compound 87 may encourage cyclization. Again, however, this solution would involve too many steps to be practical.
A final solution would be to convert our homoallylic system to an allylic system by conversion of the hydroxymethyl group at C(9) to a hydroxyl group. Thus, [1,5] hydrogen abstraction is no longer a problem, and it is expected that the 5-membered ring cyclization product would form in reasonable yield. This idea is unattractive, however, because it involves losing an important carbon atom of the terpenoid framework. Also, during either its removal or re-introduction at a later stage, the C(9) center would likely become trigonal with subsequent loss of the initially introduced stereochemistry.

Although the radical cyclization route was unsuccessful, we thought that the bromomethyldimethylsilyl group used in that approach might be useful as an intramolecular alkylating agent. An enone functionality in ring A of our decalin system was readily accessible to us as a result of the ring expansion sequence described previously (Scheme 18, p. 22). Extensive investigations by Fleming and Paterson have led to the recommended use of electrophiles such as 1,3-dithienium fluoroborate and chloroalkylphenyl sulfides for the γ-alkylation of dienolates. However, even in cases where the yields of the γ-alkylated products were reasonable, the alkylations have not
been stereoselective and few have been reported where the γ position has been tertiary. Scheme 30 shows some representative examples.87

Scheme 30

In our work, γ-alkylation at the C(10) position must be stereoselective for this route to be synthetically useful, as a C(10) methyl group or equivalent is tertiary and therefore not epimerizable.
Thus we considered the possibility of achieving stereoselective \( \gamma \)-alkylation by an intramolecular approach that involved the use of the bromomethyldimethylsilyl group in 122 (Scheme 31) as a potential alkylation agent.

**Scheme 31**

The monoketalized acetate 85, obtained as before (Scheme 22, p. 27), was treated with KOH\(_{\text{aq}}\) and MeOH for 30 min at room temperature to provide alcohol 122 in 86% yield. This was converted quantitatively to the silyl ether 123 using bromomethyl-dimethylsilyl chloride, Et\(_3\)N and DMAP in CH\(_2\)Cl\(_2\). Upon treatment with base, it was hoped that alkylation to compound 124 would occur. With compound 123, \( \alpha \)-alkylation is hardly possible as the C(2) center is far from the bromomethyl terminus; however, the \( \gamma \), or C(10), position is in reasonable proximity for a 6-membered ring to be formed. As
in the radical cyclization approach, it was assumed that if this 6-membered ring could be formed, the C(10) stereochemistry of 124 would be dictated by the C(9) stereochemistry of 123 and therefore would be β as desired. As before, the silicon could be either oxidatively or reductively removed from compound 124 to give an angular C(10) aldehyde or methyl group. Unfortunately, however, treatment of 123 with either LDA or KH in THF gave a mixture of products. In both cases, some alcohol 122 was isolated (20-35% yield), a result of silyl ether cleavage. None of the other products isolated were identified, but they were not γ-alkylation products, as determined by 1H NMR and mass spectrometry. As a result, this approach to the introduction of a C(10) angular methyl group was also abandoned.

1.2.4.3: Anionic Oxy-Cope Rearrangement

A final approach to introducing an angular methyl group into our A/B decalin system involved a second anionic oxy-Cope rearrangement. It was previously shown in connection with our C(3) hydroxyl-directed cyclopropanation approach (Scheme 24, p. 29) that the A ring enone in 92 could be deconjugated to give 94 and the ketone (94) was subsequently reduced. If, however, a vinyl group were added to the ketone of a similar deconjugated derivative (125, Scheme 32), a 1,5-diene (126) would be produced which could potentially undergo anionic oxy-Cope rearrangement to provide 127.

![Scheme 32](image-url)
It is expected that a small nucleophile such as vinylmagnesium bromide would attack as a small hydride reducing agent does, that is, to give a $\beta$ hydroxyl group at C(3) as in structure 126. If anionic oxy-Cope rearrangement were successful, the C(2)-C(3) bond in 126 would be broken as the vinyl terminus forms a bond to C(10). As the vinyl group was originally added $\alpha$ to the C(3) ketone in 125, it must also attack the C(10) position from the $\alpha$ side, and becomes part of the new ring A in structure 127. The newly formed C(10) vinyl group actually originates from the A ring of 125 and therefore has $\beta$ stereochemistry.

There were two concerns with this approach. Firstly, the C(3) ketone in 125 is quite hindered due to the geminal dimethyl groups at C(4). Vinyl addition could be a problem, since the nucleophile can potentially act as a base and abstract a proton at C(2) instead of adding to the hindered carbonyl group of 125. Secondly, anionic oxy-Cope rearrangements are quite sensitive to steric hindrance, and thus in a fairly substituted compound such as 126, the rearrangement might not occur. However, upon examining molecular models, it was felt that the system was only moderately hindered and that this approach should be attempted. An advantage of this route is that, if created, the angular group in 127 is vinyl and therefore has the potential of being converted to either a methyl group, or an oxidized substituent (eg. -CHO or -CO$_2$R). The synthetic route to the required deconjugated enone (135) is shown in Scheme 33.

The trans alkene diol (64, obtained as before, Scheme 17, p. 21) was reacted with TBDMSCl and imidazole in DMF to give primary silyl ether 128 in 97% yield. Anionic oxy-Cope rearrangement using n-BuLi in THF at 40 °C for 15 minutes gave hydridenone 129 in 73% yield. L-Selectride® reduction of 129 at -78 °C in THF gave alcohol 130 in 78% yield. As this hydride reducing agent is bulky, approach from the $\alpha$ face of the carbonyl group would be hindered by the 1,3-diaxial hydrogen atoms and therefore addition from the $\beta$ face would be preferred. Thus we assumed that the hydroxyl group in 130 is axial ($\alpha$).
Protection of this hydroxyl group as its methyl ether was accomplished using KH and MeI in THF at room temperature to give 131 in 95% yield. Ring expansion of compound 131 using ozonolysis, reductive work-up and acid-catalyzed aldol condensation provided enone 132 in only 28% yield. The low yield of 132 was believed to be due to the acid sensitivity of the TBDMS protective group, which was partially hydrolyzed under these conditions and caused by-products to be formed. The analogous reaction using acetate or
methyl ether as the protective groups proceeded in good yield. At this point, however, the sequence was continued with the TBDMS ether. Ketalization of 132 using ethylene glycol and p-TsOH•H2O in refluxing benzene for 24 hours gave 133 in only 25% yield. Again, the low yield is attributed to the poor choice of protective group. When the ketal in 133 was removed using 1 M HCl and acetone at 70 °C, the keto-alcohol 134 was obtained in 97% yield. Under these acid conditions, the TBDMS group was hydrolyzed completely; however, in this reaction no side-products were obtained and the yield was not adversely affected. In the last step, the primary alcohol was re-protected to give the TBDMS ether 135. Both infrared and 1H NMR spectroscopy confirmed that the double bond was deconjugated to the C(1)-C(10) position in structure 135. The carbonyl absorption in the infrared spectrum was at 1715 cm⁻¹, a significantly higher frequency than that of the carbonyl absorption at 1680 cm⁻¹ in the spectrum of the conjugated enone 132. The 1H NMR (400 MHz, CDCl₃) spectrum of 135 showed only one vinyl proton signal at 5.23 ppm as compared to the two downfield signals (5.97 and 6.78 ppm) seen in the spectrum of the enone 132. Also, the characteristic broad singlet at 3.18 ppm due to the C(10)H of the enone 132 was absent in the spectrum of 135.

Freshly prepared vinylmagnesium bromide was added to ketone 135 (Scheme 34) to give alcohol 136 in 57% yield. Because the C(3) carbonyl group in 135 is somewhat sterically hindered due to the geminal dimethyl groups at C(4), we were concerned that deprotonation at C(2) to form an enolate may compete with vinyl addition to the carbonyl group. Imamoto and co-workers have reported improved yields of addition products when the Grignard reagent is complexed with CeCl₃. The complexed reagent has increased nucleophilicity and decreased basicity and therefore there is a reduced tendency to form the enolate of the substrate ketone. Thus addition is favored, and fewer side reactions such as reduction or condensation reactions are observed. We therefore tried the conversion of 135 to 136 using vinylmagnesium bromide complexed to CeCl₃, but found no improvement in yield. In fact, only 6% of alcohol 136 was isolated, in addition
to 6% of starting ketone 135. Although the CeCl₃ methodology is useful for reaction with highly enolizable ketones, it is also very sensitive in practice (rigorous drying of the initial CeCl₃·7H₂O is essential) and, in fact, led to a decrease in yield in our conversion of 135 to 136.

![Scheme 34](image)

i) CH₂=CHMgBr, THF, reflux, 1h, 57%  ii) KH, THF, 18-cr-6, reflux, 12 h, 16%  iii) KHMDS, 18-cr-6, RT, 21 h, 98%  iv) KH, THF, 0 °C, 30 min; Mel, 0 °C, 20 min,12%  v) KH, 18-cr-6, xylenes, reflux, 2 days

Scheme 34

Anionic oxy-Cope rearrangement of 136 was attempted using the commonly used conditions of KH and 18-crown-6 in refluxing THF. After 12 h, the only isolated product was alcohol 137 in 16% yield. A similar reaction using KHMDS and 18-crown-6 in THF at room temperature also gave 137 in 98% yield. There was no evidence of any anionic oxy-Cope rearrangement product, as shown by the lack of a C=O absorption in the infrared spectrum of any side-products. Once again, it was apparent that the TBDMS protective group was unstable and therefore attempts were made to convert the primary alcohol (137) to its methyl ether (138) using KH and MeI in THF at 0 °C. Unfortunately this product (138) was obtained in only 12% yield, although enough was obtained to attempt the anionic oxy-Cope rearrangement under more rigorous conditions. The yield
of 138 was not optimized; in fact, in the C(3) hydroxyl-directed cyclopropanation work described on p. 29 it was found that protection of the C(11) and C(7) hydroxyl groups early in the synthetic sequence occurred in good yield and avoided the problems encountered here. However, it was established that the low yield of 138 was due to side reactions such as dimethylation, and was not due to anionic oxy-Cope rearrangement occurring during the protection. This was confirmed by the lack of a carbonyl absorption in the infrared spectrum of the crude reaction mixture before isolation of 138. While these investigations were proceeding, COSY and NOE $^1$H NMR experiments were done in an attempt to confirm the assumed stereochemistries at C(3) and C(7). Both experiments were performed on a CDCl$_3$ solution of compound 138 using a 400 MHz spectrometer and the following structure shows the numbering used to assign proton resonances in both analyses.

![Chemical Structure](image)

Table 4 shows the results of the COSY experiment. Chemical shift and proton assignments are listed in columns 1 and 2. Chemical shifts and assignments of protons coupled to the signal listed in column 1 are shown in columns 3 and 4. Signals which showed no coupling, such as the geminal dimethyl groups at C(4) are omitted for simplicity. In the case of the signal at 2.11 ppm, this was a multiplet due to three overlapping signals and therefore three protons are assigned to the one signal.

The COSY experiment confirmed all proton assignments, although axial and equatorial C(8), C(6) and C(2) protons were not distinguished. The NOE experiment results are shown in Table 5. The chemical shift of the irradiated signal is shown in column 1 with the corresponding proton assignment in column 2. Any resonance which
was affected by the irradiation is shown in column 3, with the proton assignment of that signal in column 4.

Table 4: Results of COSY experiment done on compound 138

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Table 5: Results of NOE experiment done on compound 138

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<td>C(1)H</td>
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Overall, the NOE experiment re-confirmed the proton assignments obtained from both the COSY experiment and analysis of the simple one dimensional $^1$H NMR spectrum of compound 138. As the C(6) and C(8) axial and equatorial protons could not
be distinguished, there was no direct evidence that the C(7) proton was equatorial (\(\beta\)). However, the stereochemistry of the hydroxyl group formed at C(7) by L-Selectride\textsuperscript{\textregistered} reduction of a similar derivative (157) was unambiguously established to be axial (\(\alpha\)) by X-ray crystallographic analysis as discussed on p. 54 and one can therefore infer that the C(7) methyl ether group is also axial (\(\alpha\)) in 138.

The NOE experiment was useful in confirming the stereochemistry at C(3). When the signal due to the C(2)H was irradiated (2.19 ppm) there was an enhancement seen in the C(5)H signal at 1.58 ppm. The stereochemistry of the C(5)H was definitely \(\alpha\) (axial). This was a result of the original anionic oxy-Cope rearrangement used to obtain the hydrindenone intermediate (129) from the 5,6-dehydrocamphor derivative (64) (Scheme 33, p. 43). Since the C(5)H and the C(2)H are near enough to experience an NOE effect, it can be deduced that the C(2)H at 2.19 ppm must be \(\alpha\) (pseudo-axial). The H(12) proton on the vinyl group also experienced enhancement when the C(2) \(\alpha\) H was irradiated. Therefore, the vinyl substituent at C(3) is assumed to be \(\alpha\) also. Further confirmation of this C(3) stereochemistry is seen when the H(12) signal at 6.09 ppm is irradiated. The C(5)H signal showed enhancement, again suggesting that the vinyl group at C(3) is \(\alpha\).

With the stereochemistry at C(3) established, compound 138 was treated with KH and 18-crown-6 in refluxing xylenes. This time, with methyl ethers as the protective groups, no side-products were formed. Yet even after 2 days under these rigorous conditions, no anionic oxy-Cope rearrangement occurred. Starting alcohol 138 was almost quantitatively recovered (98% yield). Although this result was disappointing, it is known that the anionic oxy-Cope rearrangement is sensitive to steric effects. A striking example of this sensitivity was reported by Koreeda and co-workers\textsuperscript{89} in their route to desmosterol. When the steroidal derivative 140 (Scheme 35) was treated with KH in refluxing dioxane for 1 h, ketone 141 was obtained in 94% yield. The stereospecific generation of the 20R stereochemistry was attributed to a chair-like transition state (144).
When the isomeric alcohol 142 was treated under the same reaction conditions, no anionic oxy-Cope rearrangement occurred; instead, a mixture of E and Z isomers of enone 143 was isolated. That absolutely no anionic oxy-Cope product was obtained when the Z isomer (142) was used was attributed to a quasi 1,3-diaxial interaction between the C(16)-alkoxide and the C(20)-methyl group in the chair-like transition state (146).

In our alcohol 138 one could envision a similar steric interaction in the transition state: as the vinyl terminus approached the $\alpha$ face to form a bond to C(10), it would
experience steric interaction with the substituents at C(5) and C(9), presumably sufficient to prevent any rearrangement of 138 from occurring. The product (139) that would be obtained upon rearrangement has a 1,3-diaxial interaction between the newly formed vinyl group at C(10) and the β C(4) methyl group and the interaction in the transition state that leads to this steric arrangement may also prevent reaction of 138.

As this route, also, failed to provide any angularly functionalized product, we decided to re-direct our approach by introducing the C(10) methyl group at a much earlier stage in the synthetic sequence. This new approach will be discussed later in Section 1.2.6, p. 59.

1.2.5: Elaboration of A and B Rings

In the course of the angular methylation work, we also investigated the functionalization of positions other than the C(10) center of our decalin system.
Many natural products contain oxygen functionality at the C(1) position, as well as an alkyl substituent at C(8). Therefore, another objective was to use the existing oxygen substituents at C(3) and C(7) to introduce these functionalities.

1.2.5.1 *In Situ* Methylation

There have been several reported examples where the enolate resulting from anionic oxy-Cope rearrangement has been utilized to introduce further functionality. In their approach to the ophiobolin ring system, for example, Paquette and co-workers reported\(^90\) *in situ* methylation of such an enolate (Scheme 36).

![Scheme 36](image)

Treatment of ketone 148 with the lithium anion generated from 1-bromocyclopentene at -78 °C in THF resulted in addition followed by anionic oxy-Cope rearrangement of the intermediate alkoxide 149. That this rearrangement occurred at such a low temperature is attributed to a low activation energy due to the decrease in
strain when the 4-membered ring is cleaved. The resulting enolate (150) was treated *in situ* with methyl iodide and the methylated ketone 151 was isolated in 96% overall yield.

In an analogous fashion we expected that anionic oxy-Cope rearrangement of 152 (Scheme 37) followed by *in situ* methylation of the intermediate enolate (154) would provide bicyclic ketone 155 with the required methyl group at C(8). To evaluate this proposal the primary hydroxyl group in 64 was selectively protected using KH and Mel.

\[
\text{Scheme 37}
\]

\[
\begin{align*}
\text{64} & \xrightarrow{\text{i}} \text{152} & \text{153} & \xrightarrow{\text{X}} \text{155} & \xrightarrow{\text{ii}} \text{156} & \xrightarrow{\text{iii}} \text{157} & \xrightarrow{\text{X}} \text{158} \\
\text{i) } & \text{KH, THF, } 0^\circ \text{C, 15 min; Mel, } 0^\circ \text{C, 45 min, 63%} & \text{ii) } & \text{KH, THF, } 40^\circ \text{C, 20 min; Mel, } -78^\circ \text{C to RT, 12 h, 92%} & \text{iii) } & \text{L-Selectride, } -78^\circ \text{C, THF; } \text{H}_2\text{O}_2, \text{NaOH, 79%}
\end{align*}
\]
in THF at 0 °C to give methyl ether 152 in 63% yield. Upon treatment with KH in THF at 40 °C, anionic oxy-Cope rearrangement of 152 occurred and when the rearrangement was complete, (as indicated by TLC and GC), the reaction mixture was cooled to -78 °C and MeI was added. The product of this reaction was obtained in 92% yield and our initial assumption was that the expected product 155 had been formed. That methylation had occurred was established by the presence of a new methyl proton signal (1.19 ppm, 3H, d, J=8 Hz) in the 1H NMR (400 MHz, CDCl3) spectrum. Overlapping signals made proof of the position of the new methyl group difficult via NMR techniques such as NOE and COSY experiments. Therefore, the methylated ketone was stereoselectively reduced to a crystalline alcohol using L-Selectride® in THF at -78 °C. Subsequent X-ray crystallographic analysis led to structure 158 being assigned to this compound and hence the original ketone was assigned structure 157. This evidence established the totally unexpected result that the newly introduced methyl group was in the 6α (equatorial) position and not at C(8) as originally predicted. This result will be discussed further, but first it is pertinent to point out that the structure of 158 confirmed assumptions previously made (cf. p. 22) about stereochemistry of the product in our anionic oxy-Cope rearrangements. Thus it was originally postulated that as a result of the anionic oxy-Cope rearrangement of 152 the ring junction in the product 157 would be cis. Furthermore, if the alkene diol 64 was trans (as predicted from the LiAlH4 reduction of alkyne 63 shown in Scheme 17, p. 21) then the hydroxymethyl group at C(9) would be trans to the ring junction hydrogens. Finally, reduction of the carbonyl at C(7) in 157 was predicted to give a C(7) α (axial) hydroxyl group in 158 since L-Selectride® is a bulky hydride reducing agent. All of these assumptions were validated by the X-ray crystallographic analysis of 158.

That the methylation occurred at the C(6) and not the C(8) position in 157 suggests that the enolate resulting from anionic oxy-Cope rearrangement (154) equilibrated to 156 before alkylation occurred (Scheme 37). Such an isomerization,
although unusual (and unknown to us at the time), is not unprecedented. In their
approach to forskolin, for example, Paquette and co-workers have reported a similar
result (Scheme 38).

Upon treatment with KH and 18-crown-6 in refluxing THF, alcohol 159
underwent anionic oxy-Cope rearrangement to provide intermediate 160. In situ
treatment with PhSeCl at -78 °C provided 162 in 79% yield. The position of the PhSe-
substituent at C(6) in 162 rather than at C(8) shows that enolate 160 must have
isomerized to enolate 161.

Another example of enolate isomerization was reported by Evans and Golob. In
this first report of anionic oxy-Cope rearrangement, the enolate resulting from
rearrangement of 163 was trapped as its enol silyl ether using TMSCl (Scheme 39).
In this case, the enolate did not isomerize completely, but a 1:9 mixture of isomers 165:167 was obtained. The minor isomer (165) is the one actually derived from the initially formed enolate (164) of the anionic oxy-Cope rearrangement, and the major isomer (167) was derived from the isomerized enolate (166).

It is generally assumed that for an enolate to isomerize, a proton source must be present so that the parent ketone is formed. Subsequent loss of a proton to form the thermodynamically more stable enolate can then occur. In all the reported examples, a possible proton source is the starting alcohol if the rearrangement is faster than initial deprotonation. To our knowledge, no examples of enolate isomerization have occurred without an alcohol as the starting material. For example, anionic oxy-Cope
rearrangement can occur after nucleophilic addition to a ketone, such as described on page 52. In cases such as this, where the starting material is a ketone and the source of the alkoxide is not deprotonation of an alcohol, no isomerization occurs. Our own work in the in situ rearrangement of an alkoxide derived from Grignard addition to 5-methyl-5,6-dehydrocamphor (178) is discussed in Section 1.2.6.2 (p. 64). Trapping of the enolate in this case showed no evidence of isomerization and this supports the theory that a proton source such as an alcohol is necessary for enolate equilibration to occur.

1.2.5.2: C(1)-Oxygenation of Ring A

In 1989 Ayer and Craw\textsuperscript{92} reported the isolation and structural elucidation of several natural products which lacked the angular methyl group usually present at C(10) in terpenoids (e.g. 175-177, Scheme 40). It was apparent that our decalin system (69) could be a key intermediate in the synthesis of these compounds if we were able to introduce oxygen functionality at C(1). This was accomplished by the following synthetic sequence. Enedione 69 was monoketalized and the acetate protective group removed as described previously (p. 27 and p. 40) to give 122. Protection of the C(11) hydroxyl group using TBDMSCl and imidazole in DMF at room temperature for 12 h gave 168 in 99% yield. Epoxidation of the A ring enone was accomplished using alkaline H\textsubscript{2}O\textsubscript{2}\textsuperscript{93} in MeOH. Epoxide 169 was obtained in 80% yield and its structure was supported by the carbonyl absorption at 1705 cm\textsuperscript{-1} in its infrared spectrum which was at significantly higher frequency than that of the enone 168 (1675 cm\textsuperscript{-1}). The \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) spectrum of 169 showed characteristic signals for the C(1) and C(2) protons: 3.14 (1H, d, J=3 Hz, C(1)H) and 3.45 (1H, br s, C(2)H). These protons were significantly more upfield than in the \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) spectrum of enone 168 (5.98 ppm, 1H, dd, J=10, 3 Hz, C(2)H and 6.78 ppm, 1H, dt, J=10, 2, Hz, C(1)H), as expected. Epoxide 169 was opened using NaSePh which was generated in situ from
PhSeSePh and NaBH₄ according to the method of Sharpless and Lauer.⁹⁴ The use of this reagent for the reduction of α,β-epoxyketones was first reported by Yoshikoshi and
co-workers in 1987, and gave the desired keto-alcohol 170 in 60% yield. The enone (168) resulting from dehydration was also isolated in 10% yield. Therefore the unstable keto-alcohol (170) was immediately protected using TBDMSOTf and 2,6-lutidine in CH₂Cl₂ to give the silyl ether 171 as a crystalline compound in 50% yield. X-ray crystallographic analysis confirmed the structure of 171 and established the α C(1) protected hydroxyl group stereochemistry. Thus, it was established that the epoxidation of enone 168 occurred from the α face to give 169.

Having successfully introduced oxygenation at C(1), this investigation was not carried further. However, structural similarities between intermediates 169 and 171 and target structures 175-177 are obvious and it seems reasonable to assume that appropriate functional group transformations could lead to advanced intermediates for the synthesis of these compounds. Reduction of the C(3) carbonyl group in 171 would lead to the A ring of 176, whereas deoxygenation using classical techniques such as thioketalization followed by Raney nickel desulfurization would lead to 177. The epoxide 169 could be converted to mesylate 173 for elimination and ring opening to 174. Alternatively, epoxide 169 could be directly converted to 174 using a Wharton reaction. In addition to these transformations, the cis ring junction of our intermediates must be converted to trans, presumably via an epimerization of the C(10) proton as there exists a carbonyl group at the adjacent C(1) center in the natural products 175-177.

1.2.6: Evaluation of 5-Methyl-5,6-dehydrocamphor (178) as an Intermediate in Terpenoid Synthesis

Since we were unable to angularly functionalize the decalin system obtained after our initial anionic oxy-Cope rearrangement, we decided to introduce the methyl group much earlier in our sequence. Our overall synthetic plan (Scheme 41) remained similar to our original route to a decalin system; however, the methyl group which would
ultimately become the C(10) methyl group in the decalin system (181) would originate from the camphor derivative (178) which would be the precursor to the 1,5-diene (179) used in the anionic oxy-Cope rearrangement.

![Chemical structures and reactions](image)

Scheme 41

The simplest such camphor derivative is 5-methyl-5,6-dehydrocamphor (178). For the C(10) methyl group to have β stereochemistry, as in 180, the 5-methyl-5,6-dehydrocamphor (178) must have the absolute configuration shown in Scheme 41. As before, formal addition of an appropriately substituted alkene to 178 would provide a 1,5-diene (179) which has the potential of undergoing anionic oxy-Cope rearrangement to provide a hydrindenone such as 180. Since the desired stereochemistry of a C(9) substituent in 180 is β (i.e. cis to the ring junction protons), the double bond of alkene 179 must be cis. It was proposed that if the anionic oxy-Cope rearrangement of 179 to 180 were successful under these steric requirements, the hydrindenone 180 would be expanded to a decalin such as 181 using the ozonolysis, reductive work-up and acid-catalyzed aldol condensation sequence described earlier. Finally, the ring junction would
be converted from cis to trans; the C(5) proton could presumably be epimerized via an enone derived from the ketone at C(7) and subsequent reduction.

1.2.6.1: Synthesis of 5-Methyl-5,6-dehydrocamphor (178)

Our first objective was the enantiospecific synthesis of (-)-5-methyl-5,6-dehydrocamphor (178) and this was accomplished by the reaction sequence shown in Scheme 42.

Scheme 42
exo-5-Bromocamphor ketal (61) was obtained from commercially available (+)-endo-3-bromocamphor (52) in 4 steps as previously outlined in Scheme 15, p. 18. A modification of the Kornblum oxidation using AgBF$_4$ and DMSO followed by Et$_3$N gave the desired 5-ketocamphor ketal (183) in 43% yield and cyclocamphanone ketal (184) in 40% yield. If the mechanism of this reaction is similar to other DMSO oxidations such as the Swern oxidation, then one can assume that an intermediate ylide (187) is formed (Scheme 43).

Subsequent removal of a C(5) proton via path a gives the desired ketone 183, whereas loss of a C(3) proton via path b gives the by-product 184. As these two compounds were formed in a 1:1 ratio, both protons must be equally accessible. The by-product 184 was easily recycled, however, to exo-5-bromocamphor ketal (61). Acid hydrolysis of the ketal in 184 provided cyclocamphanone (59) quantitatively. exo-5-Bromocamphor ketal (61) was originally synthesized from cyclocamphanone (59) by hydrobromic acid ring opening to give 60 and ketalization to give 61 as shown previously in Scheme 15, p. 18.
The structure of ketone 183 was supported by the infrared spectrum which showed a strong carbonyl absorption at 1752 cm\(^{-1}\). The \(^1\)H NMR (400 MHz, CDCl\(_3\)) spectrum of 183 showed the absence of the C(5) endo proton signal which was a distinctive doublet of doublets (J=8, 5 Hz) at 4.05 ppm in the spectrum of bromide 61. Mass spectrometry also showed the absence of characteristic twin peaks due to bromine-containing fragments, and the high resolution spectrum showed the exact mass of the ketone 183 as expected (Calc. Mass: 210.1256, Meas. Mass: 210.1259).

Ketone 183 was treated with trifluoromethanesulphonic (triflic) anhydride and 2,6-di-t-butyl-4-methylpyridine\(^{103}\) in CH\(_2\)Cl\(_2\) to provide enol triflate 185 in 95% yield. The infrared spectrum of 185 showed the absence of the carbonyl absorption and the \(^1\)H NMR (400 MHz, CDCl\(_3\)) spectrum showed a characteristic vinyl proton singlet at 5.34 ppm due to the C(6) proton.

Enol triflate\(^{104}\) 185 was coupled with Me\(_2\)CuLi (prepared \textit{in situ} from CuBr-DMS and MeLi\(^{105}\)) and 5-methyl-5,6-dehydrocamphor ketal (186) was obtained in 93% yield; the new vinyl methyl group at C(5) appeared at 1.62 ppm in the \(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)) spectrum of 186. Unfortunately, ketal 186 obtained in this way was always contaminated with a small amount (~5%) of 5,6-dehydrocamphor ketal (62), resulting from protonation of the intermediate in the coupling reaction. We have no explanation for this result, but found that optimum conditions for the preparation of methylated product 186 occurred when 5 equivalents of cuprate in a 1 M Et\(_2\)O solution at -20 °C were used. Simple acid hydrolysis of ketal 186 provided (-)-5-methyl-5,6-dehydrocamphor (178) in 95% yield. Due to the presence of a small amount of (-)-5,6-dehydrocamphor (ent-36) (not separable from 178), an accurate specific rotation for 178 could not be obtained. Specific rotations of samples of (-)-5-methyl-5,6-dehydrocamphor (178) which were taken ranged from [α]\(_D\)^25\(-489^\circ\) (c 1.98, 95% EtOH) to [α]\(_D\)^25\(-642^\circ\) (c 2.09, 95% EtOH). There are no steps in this route to 178 where racemization could occur, and since the starting material (52) is enantiopure, one can assume that the
(-)-5-methyl-5,6-dehydrocamphor (178) has a similar enantiomeric purity. No experiments were done, however, to confirm this. It should be noted that the enantiomeric starting material, (-)-endo-3-bromocamphor (ent-52) is also commercially available and therefore a route to ent-178 also exists.

1.2.6.2: Isopropenyl Addition to 5-Methyl-5,6-dehydrocamphor (178) and Anionic Oxy-Cope Rearrangement

Our initial objective was to add a simple alkenyl unit to (-)-5-methyl-5,6-dehydrocamphor (178) and to determine whether anionic oxy-Cope rearrangement would occur. The Grignard reagent of 2-bromopropene was made and added to (-)-5-methyl-5,6-dehydrocamphor (178) at room temperature (Scheme 44). The reaction was monitored by GC, and when addition was complete (after 2 h), the mixture was refluxed for an additional 5.5 h. This resulted in in situ anionic oxy-Cope rearrangement of alkoxide...
188, and bicyclic ketone 190 was obtained in 85% yield. Since protonation of the initially formed enolate 189 could occur from either face, 190 was obtained as a mixture of diastereomers at the C(8) center. The $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 190 showed the diastereomeric mixture to be 1:1. Evidence that rearrangement had occurred was a single vinyl proton signal for each diastereomer (5.18 and 4.95 ppm) as well as a doublet due to the newly introduced C(8) methyl group (1.01 and 1.03 ppm). The angular methyl group was also apparent (1.28 and 1.20 ppm) as well as the vinyl methyl group (1.60 and 1.50 ppm) and the geminal dimethyl groups (0.87, 1.00 and 0.83, 1.09 ppm). Having established that a simple hydridenone (190) was accessible through this route, ring expansion to a decalin (191) was performed (Scheme 45). Hydridenone 190 was subjected to ozonolysis, reductive work-up and acid-catalyzed aldol condensation to provide enone 191 (also a mixture of diastereomers) in 59% yield. Absorptions due to both saturated (1709 cm$^{-1}$) and $\alpha,\beta$-unsaturated (1673 cm$^{-1}$) carbonyl groups were apparent in the infrared spectrum of 191, and the $^1$H NMR (400 MHz, CDCl$_3$) spectrum showed two vinyl proton signals downfield at 5.88 and 6.56 ppm as expected.

An enone in ring B could potentially be used to introduce functionality at the C(9) position (cf. 197, Scheme 45), and therefore the enone functionality already present in ring A was first protected via the following sequence. Selective ketalization of the carbonyl group in ring B was accomplished using ethylene glycol and p-TsOH·H$_2$O in refluxing benzene for 1 h. The ketal 192 was isolated in 70% yield and infrared spectroscopy established that the $\alpha,\beta$-unsaturated carbonyl group in ring A was still present (1671 cm$^{-1}$) and that the carbonyl group in ring B was absent. Dissolving metal reduction$^{106}$ of 192 using Li in NH$_3$(l), Et$_2$O and EtOH gave the alcohol 193 in 54% yield. The $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 193 showed the absence of any vinyl proton signals, indicating that 1,4- and not 1,2-reduction had occurred. As the reduction was done in the presence of a proton source (EtOH) it was expected that the initially formed enolate would be protonated to give a ketone which would be subject to
further reduction to provide the alcohol 193. A broad O-H absorption (3615 cm\(^{-1}\)) in the infrared spectrum of 193 and the lack of a carbonyl absorption confirmed that complete reduction had occurred. Protection of the hydroxyl group in 193 using KH and MeI in THF gave the methyl ether 194 in 94% yield. The \(^1\)H NMR (400 MHz, CDCl\(_3\)) spectrum of 194 clearly showed the presence of 4 signals due to the methyl ether protons, indicating that all 4 possible diastereomers were obtained and that the dissolving metal reduction had not occurred stereoselectively. However, no attempt was made to separate
the diastereomers since the C(8) center would later become trigonal in the synthetic sequence and the stereochemistry at C(3) was not relevant to subsequent functional group transformations. Hydrolysis of ketal 194 using 1 M HCl and acetone at room temperature for 1 h provided ketone 195 in 91% yield.

Compound 195 is a potentially useful decalin intermediate in terpenoid synthesis as it contains oxygenation at C(3) and C(7), an angular methyl group at C(10), geminal dimethyl groups at C(4) and a methyl group at C(8). However, its potential could only be realized if it possessed a β C(9) substituent which could be used in the elaboration of sesquiterpenoids, diterpenoids or triterpenoids. We believed that such a group could be stereoselectively introduced via conjugate addition to an α,β-unsaturated ketone, and therefore enone 197 was prepared in the following way.

The thermodynamic enolate of 195 was formed and trapped as its enol silyl ether (196) using HMDS and TMSI\textsuperscript{107} generated \textit{in situ} from TMSCl and LiI\textsuperscript{108} in THF. This product (196) was not purified, but was used directly in the next reaction. However, the $^1$H NMR (400 MHz, CDCl$_3$) spectrum clearly showed the loss of the C(8) methyl doublet which was at 0.96 ppm in the spectrum of starting ketone 195 and showed a singlet at 1.53 ppm due to the C(8) methyl group which is vinyl in 196. A singlet due to the trimethylsilyl protons was also obvious at 0.18 ppm. Compound 196 was treated with PhSeCl at -78 °C in THF for 1.25 h. The reaction was monitored by TLC and when all starting enol silyl ether was absent, the α-phenylseleno ketone intermediate was oxidized \textit{in situ} by treatment with H$_2$O$_2$, H$_2$O and HOAc. Warming to room temperature caused elimination of the phenylselenoxide to provide enone 197 in 58% yield. The structure of 197 was confirmed by infrared and $^1$H NMR spectroscopy. The infrared spectrum of 197 showed a carbonyl absorption at 1671 cm$^{-1}$ as expected for an α,β-unsaturated ketone. The $^1$H NMR (400 MHz, CDCl$_3$) spectrum showed the C(8) methyl group to be vinyl (1.68 ppm) and showed one vinyl proton signal, downfield at 6.40 ppm as expected. Enone 197 was suitable for subsequent conjugate addition to introduce a substituent at
C(9). Such transformations have been extensively investigated on similar systems.$^{109,110}$ For example, Kutney and co-workers$^{109}$ have reported successful vinyl addition to 198 to provide 199 in 70% yield (Scheme 46).

![Scheme 46](image)

i) CH$_2$=CHMgBr, CuI, DMS:THF (1:1), 70%  
ii) LDA, DME; MeI; KOH, MeOH, 60-70%  
iii) LDA, THF; PhSeCl; H$_2$O$_2$, py, 65% (based on 25% recovered SM)  
iv) Li, NH$_3$(aq), 90%

The stereochemistry at C(9) in compound 199 was predicted to be $\beta$ based on conformational analysis and $^1$H NMR spectroscopy confirmed that this was indeed the case. Subsequently, a C(8) methyl group was introduced by alkylation of the kinetic enolate generated with LDA to give 200. Initially a mixture of diastereomers, compound 200 was epimerized using KOH and MeOH to give the isomer shown in an overall yield of ~65%. The cis ring junction in 200 was converted to trans by conversion to the enone 201 and subsequent dissolving metal reduction to give 202.

As our own compound 197 was very similar to 198, it is expected that the reactions done by Kutney and co-workers would yield similar results on our system;
therefore, we did not pursue this route any further. However, having established that addition of propenyl-2-magnesium bromide to (-)-5-methyl-5,6-dehydrocamphor (178) and subsequent anionic oxy-Cope rearrangement occurred readily, we decided to use the enolate generated from the anionic oxy-Cope rearrangement (189) to introduce a ring B enone at this stage, and to investigate conjugate additions to this hydrindenone (203, Scheme 47).

![Reaction Scheme](image)

i) CH₂=C(CH₃)MgBr, THF, RT, 1h; 40 °C, 30 min; reflux, 8.5 h  
ii) PhSeCl, -78 °C to RT; H₂O₂, HOAc, H₂O, 0 °C to RT, 75%  
iii) 6 M HCl, acetone, 70 °C, 30 min, 81%

Scheme 47

The Grignard reagent of 2-bromopropene was freshly prepared, added to (-)-5-methyl-5,6-dehydrocamphor (178), and subsequent heating resulted in anionic oxy-Cope rearrangement as before. Instead of quenching the resulting enolate (189) by the addition of water, the reaction mixture was cooled to -78 °C and PhSeCl was added. After warming to room temperature to allow selenation to occur, the mixture was cooled to 0 °C and the intermediate α-phenylseleno ketone was oxidized with H₂O₂, HOAc and H₂O. Warming to room temperature caused elimination to provide enone 203 as a mixture of exo-and endocyclic double bond isomers as determined by ¹H NMR spectroscopy. The mixture was purified by column chromatography to give the mixture
of isomers (203) in 75% yield. Treatment with 6 M HCl and acetone at 70 °C for 30 minutes caused isomerization to the thermodynamically more stable endocyclic isomer (204) which was isolated in 60% overall yield. Infrared spectroscopy showed a carbonyl absorption at 1662 cm⁻¹ as expected for an α,β-unsaturated ketone. The ¹H NMR (400 MHz, CDCl₃) spectrum of 204 showed two vinyl proton signals: 5.16 (1H, d, J=1 Hz, C(1)H) and 6.30 (1H, t, J=1 Hz, C(9)H) as expected. Signals due to two vinyl methyl groups (1.63 and 1.72 ppm) and three tertiary methyl groups (0.76, 1.00 and 1.24 ppm) were also observed.

The cis hydrindenone 204 can exist in either conformation A or B. One might expect conformation B to be favored over A because in B the smallest of the 6-membered ring substituents, a hydrogen atom, is in the axial position and the largest, a tertiary alkyl substituent, is in the equatorial position. However, although the large tertiary alkyl substituent is in the axial position in A, there are no 1,3-diaxial interactions because the 3 positions with respect to that center are trigonal. The doublet due to the C(1) proton in the ¹H NMR spectrum of 204, however, showed a coupling constant of 1 Hz which is suggestive of W coupling with the proton at C(5). This W coupling is only possible in conformation B and therefore it is likely that conformation B is preferred. In both conformations A and B, however, the bottom (α) face is concave due to the cis ring junction and therefore it is assumed that the top (β) face is more accessible. Thus it was predicted that conjugate addition to the enone (204) would occur from the top face to give β stereochemistry at C(9).
Our first attempt at conjugate addition to 204 used lithium dimethylcuprate (Me₂CuLi), generated in situ from CuBr·DMS and MeLi.¹⁰⁵ This addition was done in the presence of TMSCl which accelerates the rate of reaction and often improves yields.¹¹¹ Treatment of enone 204 under these conditions (Scheme 48) resulted in conjugate addition and trapping of the intermediate enolate to provide enol silyl ether 205 in 89% yield.

![Scheme 48](image)

The ¹H NMR (300 MHz, CDCl₃) spectrum of 205 showed a singlet due to nine trimethylsilyl proton signals (0.18 ppm) and two vinyl methyl proton signals at 1.51 ppm (3H, d, J=1.5 Hz) and 1.60 ppm (3H, d, J=1.5 Hz) as expected. A doublet (J=7 Hz) at 0.93 ppm due to the newly introduced C(9) methyl group was also diagnostic, although the stereochemistry of this methyl group was not determined at this stage. Treatment of 205 with 1 M HCl and acetone at room temperature for 2 h gave the corresponding ketone (206) as a 2:1 mixture of diastereomers (as determined by GC) in 70% yield.
Isomerization of the mixture using a 9:1 mixture of HOAc:HCl\textsubscript{(conc)} at 80 °C for 1 h gave clean conversion to the single isomer 207 in 52% yield.

Although we expected that the C(9) methyl group in 207 would be introduced from the convex (β) face of 204, analysis of the \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) spectrum of 207 suggested that it had, in fact, approached from the concave face and was in the α (equatorial) position in 207. Analysis of 207 suggests that conformation B is favored over conformation A since in B the largest 6-membered ring substituent, a tertiary alkyl group at C(5) is in the equatorial position and the smallest, a hydrogen atom at C(5) is in the axial position. Thus the severe 1,3-diaxial interactions between the C(10) methyl group and the axial C(8) substituent and between the C(5) tertiary alkyl group and the axial C(9) group which occur in conformation A are avoided. Furthermore, upon epimerization of 206 to 207 the C(8) methyl group is assumed to be equatorial, as shown in conformation B. The stereochemistry of the C(9) methyl group was determined using conformation B and the coupling constant that was observed between the C(9) and C(8) protons. The C(9)H signal in the \textsuperscript{1}H NMR spectrum of 207 showed a coupling constant of 7 Hz with the C(9) methyl group and a coupling constant of 13 Hz with the C(8)H. Similarly, the C(8)H signal showed a coupling constant of 7 Hz with the C(8) methyl group and a coupling constant of 13 Hz with the C(9)H. This large J=13 Hz value is characteristic of a diaxial relationship between the adjacent C(8) and C(9) protons, whereas axial-equatorial or diequatorial coupling is commonly in the range of 2-4 Hz. A
diallial relationship between the C(8) and C(9) protons establishes that the C(9) methyl group is in the equatorial (α) position and therefore conjugate addition to 204 must have occurred from the bottom (α) face.

To be synthetically useful, we required the addition of a functionalized substituent at C(9) and therefore conjugate addition using both vinyl and cyanide nucleophiles was attempted (Scheme 49). Treatment of 204 with Et₂AlCN¹¹² in THF at room temperature

\[
\begin{align*}
\text{i) } & \text{Et}_2\text{AlCN, THF, RT, 5.5 h, 68\%} \\
\text{ii) } & \text{CH}_2=\text{CHMgBr, CuBr•DMS, TMSCl, THF, -78 °C to RT, 24\% (and 23\% SM)} \\
\text{iii) } & \text{NaOMe, MeOH, RT, 3.5 h, 100\%}
\end{align*}
\]

Scheme 49

for 5.5 hours gave 208 in 68% yield. GC and ¹H NMR spectroscopy showed that this was a complex mixture of diastereomers, due to conjugate addition to both faces of the enone and not just due to a mixture of epimers at the C(8) center. Evidence that conjugate addition had occurred, however, was the presence of a characteristic nitrile absorption (2236 cm⁻¹) in the infrared spectrum of 208 as well as the carbonyl absorption at 1718 cm⁻¹ as compared to the carbonyl absorption which was at 1662 cm⁻¹ in
the \( \alpha,\beta \)-unsaturated ketone 204. High resolution mass spectrometry also confirmed the presence of the parent mass (Calc. Mass: 231.1623, Meas. Mass: 231.1623). For this reaction to be synthetically useful, we required predominant, if not exclusive, attack to the \(\beta\) face of enone 204. We assumed that due to the small size of the cyanide nucleophile it did not experience much steric interaction in its attack from either side of the enone (204) and thus no stereoselectivity was observed. Therefore, we focussed our attention on the conjugate addition of a vinyl group; since this was a slightly more sterically demanding group, the addition would presumably be more stereoselective.

The Grignard reagent of vinyl bromide was freshly prepared and added to enone 204 in the presence of both a Cu(I) species (to promote 1,4 addition)\(^{113}\) and TMSCl (a rate accelerator).\(^{111}\) Ketone 209 was isolated in 24% yield, as well as 23% starting enone 204. That ketone 209 and not the corresponding enol silyl ether was isolated was probably due to hydrolysis of the enol silyl ether which occurred either during the aqueous work-up or upon purification by column chromatography using silica gel. The diastereomeric mixture (209) was treated with NaOMe in MeOH to epimerize the C(8) center. Ketone 210 was isolated in quantitative yield and \(^1\)H NMR spectroscopy determined this to be a 2:1 mixture of diastereomers. A small amount of the major isomer was isolated and the following \(^1\)H NMR experiments were done to establish the stereochemistry at the C(9) center. It was possible, on the basis of chemical shift and coupling constant analyses, to assign all proton signals in the \(^1\)H NMR (300 MHz, CDCl\(_3\)) spectrum of 210. The geminal dimethyl groups at C(4) and the C(10) methyl group were not distinguished, however, nor were the C(6) axial and equatorial protons. Decoupling experiments verified several of these assignments, particularly the C(8) and C(9) protons of interest, and the results are shown in Table 6:
Table 6: Results of decoupling experiments done on major isomer of compound 210

<table>
<thead>
<tr>
<th>Irradiation (ppm)</th>
<th>Proton Assignment</th>
<th>Affected Signal (ppm)</th>
<th>Proton Assignment</th>
<th>Change in Signal (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.14</td>
<td>C(9)H</td>
<td>5.60</td>
<td>RCH=CH₂</td>
<td>ddd (J=17, 10, 12) to dd (J=17, 10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.94</td>
<td>H trans to RCH=CH₂</td>
<td>dd (J=17, 2) to d (J=17) m to br m</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.24</td>
<td>C(8)H</td>
<td></td>
</tr>
<tr>
<td>2.24</td>
<td>C(8)H</td>
<td>2.14</td>
<td>C(9)H</td>
<td>dd (J=12, 9) to br m</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.95</td>
<td>C(8)Me</td>
<td>d (J=7) to s</td>
</tr>
<tr>
<td>0.95</td>
<td>C(8)Me</td>
<td>2.24</td>
<td>C(8)H</td>
<td>m to d (J=12)</td>
</tr>
</tbody>
</table>

In addition to confirming proton assignments, irradiation at the frequency of the C(8) methyl group (0.95 ppm) gave valuable information about coupling constants. Originally a multiplet, the C(8) proton resonance collapsed to a doublet (J=12 Hz) when the C(8) methyl group frequency was irradiated. The coupling constant of 12 Hz must reflect the coupling of the C(8) proton with the C(9) proton, and not with the C(8) methyl protons, and as discussed in the analysis of methylated compound 207 (p. 72), a coupling constant as large as 12 Hz suggests coupling between two axial protons. Therefore, we concluded that the C(8) and C(9) protons were trans with respect to each other. Upon examining the two possible conformations of a cis hydrindenone such as 210, we again assumed that conformation B is favored over A and the rationale is analogous to that already discussed for compound 207 (p. 72). As we concluded from the coupling constant between the C(8) and C(9) protons, the C(9) proton is axial (β), and therefore, conjugate addition of the vinyl group occurred predominantly from the α face of enone 204. Having some evidence for the stereochemistries at C(8) and C(9), the major isomer of compound 210
is considered to have the conformation and configuration shown:

An NOE experiment was also performed on the major isomer of compound 210 and it confirmed the stereochemical deductions made. The results of the NOE experiment are shown in Table 7. Due to the stereospecificity of the anionic oxy-Cope rearrangement it was known that the stereochemistry of the C(5) proton must be $\beta$ and cis to the C(10) angular methyl group. Irradiation at the frequency of the C(5) proton signal showed enhancement of the C(9) proton. Upon examination of possible conformations of 210 it is apparent that an NOE enhancement is only likely if the C(9) proton is cis to the C(5) proton, i.e. also $\beta$. Thus, this experiment also supported the assumption that the conjugate addition of the vinyl group had occurred from the $\alpha$ face of the enone 204. Irradiation of the C(5) proton signal also caused enhancement of the signal at 2.35 ppm. This had previously been determined to be a C(6) proton signal; now it was assigned more specifically to the C(6) $\beta$ proton and therefore the signal at 2.51 ppm was assumed to be the C(6) $\alpha$ proton resonance. Irradiation at the C(8) methyl group frequency
Table 7: Results of NOE experiments done on major isomer of compound 210

<table>
<thead>
<tr>
<th>Irradiation (ppm)</th>
<th>Proton Assignment</th>
<th>Enhanced Signal (ppm)</th>
<th>Assignment of Enhanced Signal</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.95</td>
<td>C(8)Me</td>
<td>2.24</td>
<td>C(8)H</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.35</td>
<td>C(6)βH</td>
</tr>
<tr>
<td>1.96</td>
<td>C(5)H</td>
<td>2.35</td>
<td>C(6)βH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.15</td>
<td>C(9)H</td>
</tr>
<tr>
<td>2.15</td>
<td>C(9)H</td>
<td>5.60</td>
<td>RCH=CH₂</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.94</td>
<td>H trans to RCH=CH₂</td>
</tr>
<tr>
<td>2.24</td>
<td>C(8)H</td>
<td>1.07</td>
<td>C(4)Me</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.95</td>
<td>C(8)Me</td>
</tr>
<tr>
<td>2.35</td>
<td>C(6)βH</td>
<td>2.51</td>
<td>C(6)αH</td>
</tr>
<tr>
<td>2.51</td>
<td>C(6)αH</td>
<td>2.35</td>
<td>C(6)βH</td>
</tr>
</tbody>
</table>

appeared to cause enhancement of the C(6) β proton signal. It is more likely, however, that simultaneous irradiation of the C(4) β methyl group had occurred and that this caused enhancement of the C(6) β proton signal.

As a result of these investigations, it was determined that conjugate addition of both a methyl group and a vinyl group occurred from the bottom (concave) face of enone 204 resulting in α stereochemistry of that group at C(9). When the nucleophile was less sterically demanding, however, as in the case of cyanide, no selectivity was observed. These results were disappointing because we required β selectivity and had hoped to add even more sterically demanding groups to the C(9) center. However, a recent paper by Taguchi and coworkers shows similar results (Scheme 50).

Conjugate addition of cyanide to enone 211 occurred from the β face to give 212. The β stereochemistry at C(9) was expected as the cis ring junction of decalin 211 results in a concave α face and a more accessible convex β face. However, vinyl addition to the same enone 211 resulted in α approach to give ketone 213 with the resulting α
stereochemistry at C(9). This was attributed to the steric interaction that would be felt between the angular trifluoromethyl substituent and the vinyl group if it approached from the same (β) side. Thus, attack by a sterically demanding group such as vinyl was governed by the stereochemistry of the angular substituent whereas addition of a small nucleophile such as cyanide was governed by the folded shape of the cis decalin structure. Although our enone 204 was a hydrindenone with an angular methyl group as opposed to the angular trifluoromethyl containing decalin 211 shown in this example, the same arguments apply and the experimental results are similar.

\[
\begin{align*}
&\text{i)} \quad \text{KCN, NH}_4\text{Cl, DMF} \quad \text{ii)} \quad \text{CH}_2=\text{CHMgBr, CuI} \\
\end{align*}
\]

Scheme 50

1.2.6.3: Allyl Addition to Hydrindenone 204 and Attempted Anionic Oxy-Cope Rearrangement

The previously described approach to C(9) functionalization involved conjugate addition to enone 204. Another route to C(9) functionalization would be 1,2-addition of an allyl group to the carbonyl at C(7), followed by anionic oxy-Cope rearrangement of the resulting 1,5-diene (214, Scheme 51). Addition of commercially available allyl-magnesium bromide to enone 204 was complete after 30 minutes at room temperature, as indicated by GC and TLC. Heating of the intermediate alkoxide for 3 hours, however, gave no indication of any anionic oxy-Cope rearrangement occurring, therefore the reaction was quenched by the addition of water and alcohol 214 was isolated as a 9:1 mixture of isomers (as determined by GC and 1H NMR spectroscopy) in 78% yield. The
The structure of 214 was confirmed by the presence of an O-H absorption (br, 3413 cm\(^{-1}\)) in the infrared spectrum and the lack of a C=O absorption. All proton signals in the \(^1\)H NMR (400 MHz, CDCl\(_3\), major isomer) spectrum of 214 were identified and NOE experiments were done to confirm the stereochemistry at C(7). The NOE results are shown in Table 8.

**Table 8: Results of NOE experiments done on compound 214**

<table>
<thead>
<tr>
<th>Irradiation (ppm)</th>
<th>Proton Assignment</th>
<th>Enhanced Signal (ppm)</th>
<th>Assignment of Enhanced Signal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.90</td>
<td>C(5)H</td>
<td>5.12-5.20</td>
<td>C(9)H and -CH=CH(_2) -CH(_2)-CH=CH(_2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.23, 2.40</td>
<td></td>
</tr>
<tr>
<td>1.76</td>
<td>C(6)(\beta)H</td>
<td>5.90</td>
<td>-CH=CH(_2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.90</td>
<td>C(5)H</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.36</td>
<td>C(6)(\alpha)H</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.92</td>
<td>C(4)CH(_3)</td>
</tr>
<tr>
<td>1.15</td>
<td>C(10)CH(_3)</td>
<td>1.90</td>
<td>C(5)H</td>
</tr>
</tbody>
</table>
Based on conformational analysis of the cis fused hydrindenone system (cf. p. 70), it was expected that nucleophilic attack would occur predominantly from the top (β) face of enone 204, and the NOE experiment results were consistent with this prediction.

Irradiation at the C(5) proton frequency resulted in enhancement of the multiplet at 5.12-5.20 ppm and of the signals at 2.23 and 2.40 ppm. The multiplet was due to overlapping signals due to the C(9)H and the terminal allyl methylene protons and therefore analysis of this enhancement is not valid as it cannot be distinguished with which of the 3 protons the C(5) proton is interacting. That enhancement was observed with the signals at 2.23 and 2.40 ppm, however, suggests that the allyl group is syn to the C(5)H, i.e. β, because those signals are assigned to the methylene protons of the allyl group. Irradiation at the frequency of the C(6)β H showed enhancement of the signals at 1.90, 1.36 and 0.92 ppm as could be expected. However, the most informative enhancement was seen in the signal at 5.90 ppm, which is due to the -CH=CH₂ of the allyl group. This result further suggests that the allyl group must have been added to the β face of enone 204. Finally, irradiation at the frequency of the C(10) methyl group showed enhancement of the signal due to the C(5)H. While this did not give information about the C(7) stereochemistry directly, it did support the proton assignments that were made based on coupling constant information from the one-dimensional ¹H NMR (400 MHz, CDCl₃) spectrum of 214. All other NOE experiment results also supported these assignments.

The anionic oxy-Cope rearrangement of 214 was first attempted using the commonly used conditions of KH in refluxing THF. The only product isolated from this reaction was enone 204 in 30% yield. There was no evidence of any rearrangement product as determined by the lack of a C=O absorption in the infrared spectrum of the crude product. The formation of enone 204 can be explained by a retro-ene reaction which could occur if the alcohol (214) were not deprotonated before heating began. We are aware of at least one similar report in the literature. Koreeda and co-workers found
that the E isomer 140 (Scheme 35, p. 50) rearranged smoothly to give ketone 141, but the Z isomer 142 gave a mixture of isomeric enones (143). No explanation was given regarding the mechanism of the enone formation, however, it was also the loss of an allyl group that occurred, presumably via a retro-ene reaction. The retro-ene reaction can only occur if alcohol, and not alkoxide, is the reacting species, and therefore we treated alcohol 214 with an excess of a strong, readily soluble base (n-BuLi) before anionic oxy-Cope rearrangement was attempted. Thus alcohol 214 was allowed to stand in contact with n-BuLi for 1 hour at -78 °C, for 1 hour at 0 °C and for 2.5 hours at room temperature. Subsequent heating at reflux did not result in anionic oxy-Cope rearrangement, and starting alcohol 214 was isolated in 74% yield. That no enone 204 was recovered, however, supported our assumptions that a retro-ene reaction of alcohol 214 had occurred previously. In a subsequent experiment alcohol 214 was treated with KH and 18-crown-6 in diglyme for 3 days at room temperature to ensure complete deprotonation, and then was refluxed for 24 hours. A complex mixture of products was isolated, as determined by GC and TLC. None was the desired rearrangement product 215, as indicated by the lack of a carbonyl absorption in the infrared spectrum of the crude mixture. A final reaction using oxy-Cope conditions was tried. Treatment of alcohol 214 with K₂CO₃ in refluxing decalin for 3 days resulted in the formation of 40% enone (204) and the recovery of 38% unreacted starting material (214). After these investigations it seemed evident that neither oxy-Cope nor anionic oxy-Cope rearrangement of alcohol 214 to ketone 215 was feasible.
1.2.6.4: Alkynyl Addition to 5-Methyl-5,6-dehydrocamphor (178) and Attempted Anionic Oxy-Cope Rearrangement

After the previously described initial investigations in which we determined that addition of propeny1-2-magnesium bromide to (-)-5-methyl-5,6-dehydrocamphor (178) followed by anionic oxy-Cope rearrangement was feasible, we returned to our initial objective of adding a more complex and therefore potentially more useful alkenyl unit to 178 (cf. Scheme 41, p. 60). In particular, the alkenyl unit would be designed so that upon anionic oxy-Cope rearrangement of the intermediate alcohol (179), the product hydrindenone (180) would possess the C(9) substituent which could not be successfully introduced in the previously described work.

Propargyl alcohol was protected as its enol silyl ether and upon treatment with n-BuLi at -78 °C for 2.75 h the resulting anion$^{61}$ was added to (-)-5-methyl-5,6-dehydrocamphor (178) to provide alkyne 216 in 96% yield (Scheme 52). Subsequent reduction with H$_2$ using Lindlar's catalyst$^{114}$ provided alkene 217 in 77% yield. The $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 217 showed three vinyl proton signals: 5.16 (1H, br s, C(6)H), 5.43 (1H, m, -CH=CHCH$_2$OTBDMS) and 5.52 (1H, dt, J=12, 1 Hz, -CH=CHCH$_2$OTBDMS). The coupling constant of 12 Hz between the two adjacent vinyl proton signals suggests that the hydrogenation did occur cis as expected. Irradiation at the frequency of one of the -CH$_2$OTBDMS protons simplified the vinyl proton signal which was a multiplet to a doublet of doublets with the coupling constant
i) LiC=CCH₂OTBDMS, THF, -78 °C to RT, 96%  
ii) H₂, Lindlar's catalyst, 2:1 hexane:EtOAc, RT, 30 min, 77%  
iii) KH, 18-crown-6, THF, reflux, 3 h, 41% (diol)  
iv) KHMDS, THF, reflux, 17 h  
v) toluene, 140 °C, sealed tube, 14 h  
vi) toluene, propylene oxide, reflux, 66 h  
vii) K₂CO₃, decalin, reflux, 2.75 h  
viii) TBAF, THF, RT, 15 min, 91%  
ix) KH, 18-crown-6, THF, reflux, 47 h  
x) K₂CO₃, decalin, reflux, 5 h

Scheme 52

of 12 Hz between adjacent cis protons and the coupling constant of 5 Hz between the vinyl proton and the non-irradiated CH₂OTBDMS proton. For the subsequent C(9) substituent of hydrindenone 218 to possess β stereochemistry, the alkene 217 must be cis; rearrangement of the corresponding trans alkene would result in α stereochemistry at the
subsequent C(9) center. The 1,5-diene 217 was subjected to various conditions in an attempt to effect anionic oxy-Cope rearrangement. Treatment of 217 with KH and 18-crown-6 in refluxing THF for 3 hours failed to induce anionic oxy-Cope rearrangement as determined by the lack of a carbonyl absorption in the infrared spectrum of the crude product mixture. The diol (219) resulting from enol silyl ether cleavage was isolated in 41% yield. Treatment of 217 with KHMDS in refluxing THF for 17 hours resulted in a complex mixture of products as indicated by TLC and GC. Again, infrared spectroscopy was used to determine that none of the products was the desired rearrangement product 218.

These discouraging results led us to believe that the basic conditions were too harsh and caused decomposition of 217; thus we tried the rearrangement under oxy-Cope conditions using higher temperatures but no base. Heating of 217 in toluene in a sealed tube\textsuperscript{115} at 140 °C for 14 hours, however, also gave a complex mixture of products. Heating of 217 for 66 hours in refluxing toluene in the presence of propylene oxide which acts as a proton scavenger\textsuperscript{116} resulted in less decomposition but only starting material (35%) was isolated. Finally, 217 was heated in refluxing decalin for 2.75 hours in the presence of K\textsubscript{2}CO\textsubscript{3}.\textsuperscript{117} A new compound was isolated which could not be identified, but which was determined not to be the desired rearrangement product 218. The unknown compound had the same molecular weight as the starting alkene 217 as determined by mass spectrometry, and it contained two carbonyl absorptions (1718 and 1663 cm\textsuperscript{-1}) in its infrared spectrum as well as an O-H absorption (3571 cm\textsuperscript{-1}); however, \textsuperscript{1}H NMR spectroscopy established that the compound was not ketone 218. The \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) spectrum of the unknown compound showed three vinyl proton signals: 5.07 (1H, m), 5.13 (1H, br s) and 6.30 (1H, d, J=10 Hz) as compared to the one signal expected if compound 218 had been produced. In particular, the proton signals downfield at 5.13 and 6.30 ppm suggest that the product is an α,β-unsaturated ketone;
this was supported by a strong carbonyl absorption at 1663 cm\(^{-1}\) in addition to the carbonyl absorption at 1718 cm\(^{-1}\) in the infrared spectrum.

To ensure that the large silyl protecting group in 217 was not interfering with rearrangement, it was removed by treatment of 217 with TBAF in THF for 15 minutes at room temperature and diol 219 was isolated in 91% yield. The diol (219) was then treated with KH and 18-crown-6 in refluxing THF for 47 hours; however the only product that could be isolated was recovered starting material (12%). Since anionic oxy-Cope rearrangement of 219 did not occur, the diol (219) was heated in refluxing decalin in the presence of K\(_2\)CO\(_3\) under oxy-Cope conditions for 5 hours. This led to a complex mixture of products, none of which was the desired rearrangement product 220 as determined by infrared spectroscopy.

Finally, we prepared the trans compound 222 (Scheme 53). Although rearrangement of the trans compound would give \(\alpha\) and not \(\beta\) C(9) stereochemistry in the product (223), we felt it would be interesting to see if rearrangement would occur; if so, this would suggest that it was the cis stereochemistry which prevented rearrangement of 217. Alkyne 216 was treated with TBAF in THF at room temperature for 30 minutes to provide alkyne diol 221 in 91% yield. Treatment of 221 with LiAlH\(_4\)\(^{62}\) in THF at 40 °C for 2 hours gave trans alkene diol 222 in 31% yield. The trans stereochemistry was supported by coupling constant evidence in the \(^1\)H NMR (400 MHz, CDCl\(_3\)) spectrum of 222: the large coupling constant (J=16 Hz) of the doublet signal at 5.67 ppm due to one of the adjacent vinyl protons (-CH=CHCH\(_2\)OH) is consistent with a trans relationship between these two protons. Subsequent treatment of 222 with KHMDS and 18-crown-6 at room temperature for 3 days showed no sign of reaction as indicated by TLC and GC. Therefore, the reaction mixture was heated at reflux for 2 days, which resulted in a complex mixture of products. There was no evidence for the formation of the rearrangement product (223) as determined by infrared spectroscopy.
It was evident from these investigations that the anionic oxy-Cope rearrangement is very sensitive to steric effects. Paquette and co-workers\textsuperscript{118} have extensively investigated the anionic oxy-Cope rearrangement of 1,5-dienes (cf. Scheme 54) derived from bicyclo [2.2.2] octenones and these are comparable, to some extent, with the results described above for 1,5-dienes derived from bicyclo [2.2.1] heptenones. For example, compound 224 rearranged using KHMDS and 18-crown-6 in THF at room temperature while 225 required KH and 18-crown-6 in refluxing THF. As indicated previously, 5,6-dehydrocamphor derivatives 64, 128 and 152 rearranged using KH in THF at 40 °C. On the other hand, compound 188 which can be likened to structure 225 required refluxing THF and longer reaction time when the corresponding alkoxide was generated \textit{in situ} from Grignard addition to (-)-5-methyl-5,6-dehydrocamphor (178). The longer
reaction time is attributed to the steric effect of the 5-methyl substituent as well as to the fact that magnesium was used as the cation, as opposed to potassium; nevertheless yields were excellent. Finally, it is interesting to note that compounds 226-228 completely failed to rearrange. Paquette and co-workers used KH and 18-crown-6 in both refluxing THF and diglyme as well as KHMDS and 18-crown-6 under identical conditions and were only able to isolate starting material in all cases. Paquette's compounds 226-228 are
similar to structures 217, 219 and 222, and as discussed previously, we had a complete lack of success in our attempts to effect rearrangement of these compounds using a variety of reaction conditions. It is apparent, therefore, that substitution at various positions of the 1,5-dienes can inhibit or completely prevent anionic oxy-Cope rearrangement, and these observations have been attributed to steric effects.

1.3: Conclusion

5,6-Dehydrocamphor (36) can be synthesized in either enantiomeric form using one of several enantiospecific routes. It has been used as a precursor to 1,5-diene systems (37) which can undergo anionic oxy-Cope rearrangement to provide hydrindenones (38) which have three fixed predictable chiral centers based on the stereospecificity of the concerted rearrangement reaction (Scheme 55).
Hydrindenone 38 could be easily ring expanded to the familiar A/B decalin system of terpenoids (39), however, the stereospecific introduction of an angular methyl group to provide a system such as 40 eluded us. The introduction of the methyl group was tried using such diverse approaches as hydroxyl-directed cyclopropanation, radical cyclization, γ-alkylation and anionic oxy-Cope rearrangement. All routes relied on a C(1)-C(10) double bond as a means toward C(10) functionalization and conformational analysis of such systems shows that the β face is rather sterically hindered. It was attempted to alleviate some of these steric interactions by removal of, for example, a β C(3) substituent; in the case of γ-alkylation, the dienolate ion generated in ring A of an enone such as 39 flattens the A ring considerably. However, the β C(4) methyl group may well have been the major contributor to steric hindrance at the C(10) center, and of course, removal of this substituent is not feasible. Future investigations in this area could involve the introduction of the angular methyl group utilizing a C(10)-C(9) double bond in ring B; however, this would involve losing the C(9) stereochemistry which was originally introduced stereospecifically, and therefore such a route did not appeal to us.

We did, however, develop an enantiospecific route to (-)-5-methyl-5,6-dehydrocamphor (178) which via a similar synthetic strategy to that outlined for 5,6-dehydrocamphor (36) led to a hydrindenone (190) that contained the angular methyl group (Scheme 56).

It was found that anionic oxy-Cope rearrangement of a simple 1,5-diene derivative (188) of (-)-5-methyl-5,6-dehydrocamphor (178) occurred readily to give hydrindenone (190) which was expanded to decalin 197. Conjugate addition to enone 197 and to the B ring enone derived from the enolate of 190 (189 to 204, Scheme 47, p. 69) was attempted to introduce a substituent at C(9) and varying degrees of success were achieved. Thus, the 1,5-dienes 217 and 219 were prepared. Anionic oxy-Cope rearrangement of 217 and 219 would provide hydrindenones 218 and 220 respectively which contain both the angular methyl group and a C(9) substituent; however,
rearrangement could not be induced under a variety of conditions. This lack of success was attributed to steric interaction between the C(5) methyl group and the CH$_2$OR substituent in dienes 217 and 219, and these results are consistent with reports by Paquette and co-workers$^{118}$ who studied similar systems. Therefore, future work would probably focus on the simpler system which provided hydrindenone 190 and goals would include more diverse functionalization of 190 than was achieved in the work described in this thesis. There is no doubt that the work described in Chapter 1 of this thesis proved disappointing; although both 5,6-dehydrocamphor (36) and 5-methyl-5,6-dehydrocamphor (178) appeared to be potentially useful chiral starting materials, it became evident that their use in our synthetic strategy was limited due (to a great extent) to the steric sensitivity of the anionic oxy-Cope rearrangement which was the basis for many of our functional group transformations.
Chapter 2

A New Enantiospecific Synthesis of 4-Methylcamphor
2.1: Introduction

As described in Chapter 1, (+)-camphor (25) or its enantiomer (ent-25) is a useful chiral starting material for the synthesis of natural products because it can be functionalized at many positions. For example, (-)-camphor (ent-25) is readily converted to (-)-9,10-dibromocamphor (ent-28) in 4 steps via a series of bromination and selective debromination reactions\(^{55,119}\) and it has been shown that ent-28 can be converted to a trans-hydrindenone intermediate 231 that has been used in an enantiospecific synthesis of (+)-estrone (233, Scheme 57).\(^{37,38,43}\) If (-)-4-methylcamphor (229) could be similarly transformed to the corresponding 9,10-dibromo derivative 230, a useful route to trans-hydrindenone 232 could be realized. The latter compound (232) is a potentially useful intermediate in the synthesis of the lanostane group of triterpenoids (cf. Scheme 58) while its enantiomer (ent-232) derived from (+)-4-methylcamphor (ent-229) could be used to gain access to the euphane group of triterpenoids. The successful outcome of this route
is, however, initially dependent on the availability of enantiopure 4-methylcamphor (229). Camphor (25) is commercially available in high enantiomeric purity in either enantiomeric form and as no racemization occurs in any of the steps leading to hydrindenone 231, this product is obtained in high enantiomeric purity as well. 

(-)-4-Methylcamphor (229), however, must be synthesized, and no enantiospecific synthesis has yet been reported.

Literature methods\textsuperscript{120,121,122,123} for the synthesis of (-)-4-methylcamphor (229) use commercially available, enantiopure (+)-camphor (25) or (+)-fenchone (237) as starting materials (Scheme 59). Acid-catalyzed rearrangement of derivatives 236 or 238 provide (+)-4-methylisobornyl acetate (239) which is easily converted to (-)-4-methylcamphor (229). The enantiomeric purity of the (-)-4-methylcamphor (229) obtained via these routes, however, was not determined. A shorter synthesis of (-)-4-methylcamphor (229) which utilizes an acid-catalyzed rearrangement similar to those shown in Scheme 59
Scheme 59

has been developed in our laboratory (Scheme 60)\textsuperscript{124} and the mechanism of the rearrangement has been thoroughly investigated.\textsuperscript{124} Conversion of (+)-camphor (25) to

\[
\begin{align*}
25 & \xrightarrow{H_2C=\text{PPh}_3} 240 \\
240 & \xrightarrow{\text{HOAc}:H_2SO_4} 239 \\
239 & \xrightarrow{1) \text{LiAlH}_4} 240 \\
240 & \xrightarrow{2) \text{PCC}} 229
\end{align*}
\]

Scheme 60

(-)-2-methylenebornane (240) in excellent yield was easily accomplished using a Wittig reaction.\textsuperscript{125} Subsequent treatment of 240 with a 40:1 mixture of HOAc:H_2SO_4 at room temperature for 15 minutes gave (+)-4-methylisobornyl acetate (239) in ~75% yield. Subsequent removal of the acetate protective group and oxidation provided (-)-4-methylcamphor (229) in an overall yield of ~60%. The acid-catalyzed rearrangement of 240 to provide 239 is believed to occur via the mechanism outlined in Scheme 61, and deuterium labelling studies have supported this mechanism.\textsuperscript{124} Although intermediates are represented and referred to as carbocations, they are only used as a model to explain our results; in fact, there is evidence that \textit{exs}-methylene intermediates (cf. 242b, 243b) are involved in this rearrangement. Wagner Meerwein rearrangement of
241 followed by a 3,2-exo methyl shift provides 243a. A second Wagner Meerwein rearrangement occurs to give 244 and this carbocation reacts with acetate to provide (+)-4-methylisobornyl acetate (239). However, this intermediate (244) can undergo a 6,2-hydride shift to provide ent-244 and hence (-)-4-methylisobornyl acetate (ent-239) can also be formed. (+)-4-Methylisobornyl acetate (239) was isolated in ~75% yield and since partial racemization could occur by the mechanism shown in Scheme 61, the enantiomeric purity of this compound was determined. The lanthanide shift reagent [Eu(hfc)₃] and ¹H NMR spectroscopy were used to determine that the enantiomeric purity of the (+)-4-methylisobornyl acetate (239) obtained in this reaction was ~60%. Thus partial racemization had occurred via a 6,2-hydride shift in intermediate 244 to provide an 80:20 ratio of 239:ent-239. The optical rotation of (+)-4-methylisobornyl
acetate (239) prepared via our route ([\(\alpha\)]_D^{21.5} = +35.79, \(c\) = 2.28, EtOH) was compared to the rotations reported in the literature ([\(\alpha\)]_D^{20} = +18.90\(^0\) and +35.84\(^0\))\(^{122,127,128}\) and confirmed that those methods of preparation also did not provide enantiopure 239. This was not surprising since these routes also relied on a similar acid-catalyzed rearrangement reaction where partial racemization could occur by the 6,2-hydride shift shown in Scheme 61. The results of these investigations confirmed that an enantiospecific route to (-)-4-methylcamphor (229) did not exist, since the precursor to 229, (+)-4-methyl-isobornyl acetate (239), had not been obtained as an enantiopure compound.

2.2: Discussion

Since (-)-4-methylcamphor (229) and its enantiomer (ent-229) are potentially useful starting materials for the synthesis of triterpenoids (cf. Scheme 58, p. 93), our objective was to develop an enantiospecific route to these compounds. Our initial approach was to use a camphor derivative which would undergo acid-catalyzed rearrangement to lead to (-)-4-methylcamphor (229) or its enantiomer (ent-229), but where the 6,2-hydride shift (cf. 244 to ent-244, Scheme 61, p. 95) is prevented or restricted. Our first approach involved the synthesis of the thioketal derivative of 5-keto-2-methylenebornane (245, Scheme 62).

![Scheme 62](image)

If the acid-catalyzed rearrangement occurred as it did for (-)-2-methylenebornane (240, Scheme 61, p. 95), then intermediate 246 is analogous to intermediate 244. The
thioketalized intermediate (246), however, does not have a hydrogen atom that can undergo 6,2-hydride shift. Trapping of 246 with acetate would then provide enantiopure 247 which could subsequently be converted to enantiopure (-)-4-methylcamphor (229).

Dithiane 245 was prepared by the reaction sequence outlined in Scheme 63.

Thus treatment of cyclocamphanone (59) with H$_2$SO$_4$ and HOAc at 100 °C for 46 hours resulted in cyclopropane ring opening to provide keto-acetate 248 in 50% yield (63% yield based on recovered starting material). Compound 248 was determined to be a 5:1 mixture of exo:endo isomers by GC analysis and $^1$H NMR spectroscopy. The $^1$H NMR (400 MHz, CDCl$_3$, exo isomer) spectrum of 248 clearly showed a singlet due to the acetate methyl protons at 2.03 ppm as well as the C(5) proton signal at 4.72 ppm (1H, dd, J=8, 4 Hz). The infrared spectrum of 248 showed a broad carbonyl absorption centered at 1747 cm$^{-1}$ which was due to both the C(1) carbonyl group and that of the acetate. It was found that treatment of keto-acetate 248 with an excess of the modified "Super Wittig" reagent prepared from CH$_2$I$_2$, TiCl$_4$ and Zn in THF$^{129}$ resulted in both methylenation, as
expected, and removal of the acetate group to give alcohol 249 in 89% yield. The infrared spectrum (CHCl₃ solution) of 249 showed the absence of any carbonyl peaks and the presence of O-H absorptions at 3613 and 3445 cm⁻¹. The ¹H NMR (400 MHz, CDCl₃) spectrum of 249 showed the exo methylene proton signals as broad singlets at 4.66 and 4.72 ppm. In addition, the C(5) proton had shifted from 4.72 ppm in acetate 248 to 3.85 ppm in alcohol 249. Swern oxidation¹⁰² of 249 provided 5-keto-2-methylene-bornane (250) in 62% yield and thioketalization using ethanedithiol and BF₃·OEt₂ in CH₂Cl₂⁹⁶ provided the target dithiane 245 in 42% yield. The ¹H NMR (400 MHz, CDCl₃) spectrum of 245 showed that the exo double bond had remained intact during these transformations (4.81 and 4.95 ppm, vinyl proton signals), and also showed the expected multiplet due to the thioketal protons (3.10-3.35 ppm). The infrared spectrum of 245 showed the loss of the carbonyl absorption that had been present at 1742 cm⁻¹ in the spectrum of ketone 250. The yields of these reactions were not optimized as it was first essential to determine whether or not the acid-catalyzed rearrangement of 245 would occur.

Dithiane 245 was treated with the identical reaction conditions that were used to prepare (+)-4-methylisobornyl acetate (239) from (-)-2-methylenebornane (240), i.e. with HOAc:H₂SO₄ (40:1) at room temperature. After 1.5 hours, no reaction had occurred and therefore the mixture was heated at 100 °C for 2 hours. One product was formed almost exclusively, but it could not be identified. The infrared spectrum of this product showed a very strong absorption at 1755 cm⁻¹; however, the ¹H NMR (400 MHz, CDCl₃) spectrum showed the absence of a signal due to the methyl protons of an acetate group. The ¹H NMR spectrum also showed the presence of four methyl groups (0.89, 1.07, 1.21 and 1.23 ppm) and the absence of any vinyl protons which suggested that the exo methylene group in 245 had been converted to a fourth methyl group, as desired. A distinctive set of signals were seen at 2.43 ppm (1H, d, J=18 Hz) and at 2.52 ppm (1H, dd, J=18, 1.5 Hz), and yet signals due to thioketal protons were missing, suggesting that
the harsh reaction conditions resulted in hydrolysis of the thioketal group. That rearrangement of 245 did not occur at room temperature suggested that the thioketal group was either too sterically demanding for rearrangement to occur, or else that electronic effects due to the sulfur atoms prevented the required Wagner Meerwein rearrangement. Reaction did occur at a higher temperature, but the product could not be identified. It was hoped that rearrangement of a modified derivative would occur at a lower temperature than was required for 245, or if a higher temperature was required, that the group at C(5) would be stable so that competing reactions due to the loss of that group would not occur. Thus ethers 251 and 252 were prepared as outlined in Scheme 64.

Alcohol 249 was prepared as previously described (Scheme 63, p. 97) and upon treatment with KH in THF followed by addition of either benzyl bromide or methyl iodide, ethers 251 and 252 were respectively prepared. Alcohol 249 was an exo:endo (5:1) mixture of isomers, and after purification of the ethers 251 and 252 the ratio had become ~9:1 exo:endo as the minor isomer was partially separated.

Treatment of benzyl ether 251 with H₂SO₄ and HOAc at room temperature for 1 hour resulted in a complex mixture of products which were not separated or identified. Reaction of methyl ether 252 under the same conditions gave similar results. Thus, it was determined that the acid-catalyzed rearrangement of substituted 2-methylenebornanes is extremely sensitive to steric and/or electronic effects, resulting in complex mixtures of products which are not synthetically useful.
We believed that a ketone instead of the thioketal or ether substituents at the C(5) position of (-)-2-methylenebornane (240) would probably inhibit the second Wagner Meerwein rearrangement due to the electron withdrawing effects of the carbonyl group. However, since we had prepared 5-keto-2-methylenebornane (250) as a precursor to thioketal 245 (Scheme 63, p. 97), we decided to test this hypothesis by subjecting 250 to the normal rearrangement conditions (HOAc/H₂SO₄).

Treatment of 5-keto-2-methylenebornane (250) with H₂SO₄ and HOAc at room temperature for 4 days gave ketone 255 as the major product (55% yield, Scheme 65). Several possible intermediates and products are possible if 250 rearranges according to our proposed mechanism. The lack of signals due to acetate protons in the ¹H NMR (400 MHz, CDCl₃) spectrum of the product and the presence of exo methylene vinyl proton signals at 4.80 and 4.86 ppm led us to conclude that the product was either ketone
255 or 257. NOE experiments were done to confirm that the structure was 255, and the results are summarized in Table 9.

![Diagram of compound 255]

Table 9: Results of NOE experiments done on compound 255

<table>
<thead>
<tr>
<th>Irradiation (ppm)</th>
<th>Proton Assignment</th>
<th>Enhanced Signal (ppm)</th>
<th>Assignment of Enhanced Signal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.07</td>
<td>C(9)Me</td>
<td>1.15</td>
<td>C(8)Me</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.80</td>
<td>H_B</td>
</tr>
<tr>
<td>1.15</td>
<td>C(8)Me</td>
<td>2.29</td>
<td>C(4)H</td>
</tr>
<tr>
<td>2.29</td>
<td>C(4)H</td>
<td>1.15</td>
<td>C(8)Me</td>
</tr>
<tr>
<td>4.80</td>
<td>H_B</td>
<td>4.86</td>
<td>H_A</td>
</tr>
<tr>
<td>4.86</td>
<td>H_A</td>
<td>1.30</td>
<td>C(10)Me</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.80</td>
<td>H_B</td>
</tr>
</tbody>
</table>

That enhancement was seen in the C(8)Me signal when the C(4)H signal was irradiated suggests that the product is indeed 255 and not 257. Further evidence is provided from the enhancements seen when the vinyl protons H_A and H_B are irradiated. These results show that a carbonyl group at C(5) in the 2-methylenebornane system does not inhibit the first Wagner Meerwein rearrangement (cf. 253 to 254, Scheme 65, p. 100). It does, however, inhibit the 3,2-methyl shift that is expected to occur next, and thus by loss of a proton, ketone 255 is isolated. While the synthesis of 255 was not useful in providing a synthetic route to (-)-4-methylcamphor (229) or its enantiomer (ent-229), it did suggest that the first Wagner Meerwein rearrangement occurs readily.
At this stage we became intrigued by reports in the early literature (Houben and Pfankuch, 1931 and 1933)\textsuperscript{130,131} on the acid-catalyzed rearrangement of (-)-1-chlorocamphene (261, Scheme 66). These results dramatically illustrate the differences in enantiomeric purity obtained when different acids are used. Treatment of (-)-1-chlorocamphene (261) with 45% HBr/HOAc solution gave the brominated compound 262.\textsuperscript{130,131} Reconversion of 262 to (-)-1-chlorocamphene (261) showed no loss of optical activity; therefore, it was deduced that 262 had been formed as an enantiopure compound. When trichloroacetic acid was used instead, 263 was formed, and it too was reconverted to (-)-1-chlorocamphene (261), which only showed 69% of the optical activity of the starting material.\textsuperscript{130,131} Thus, it was concluded that 263 had been formed in 69% enantiomeric excess. A much later study by Warnhoff and co-workers\textsuperscript{132} showed that when formic acid was used, the product 264 was racemic.
(-)-1-Chlorocamphene (261) is structurally similar to the product (255) we obtained upon acid-catalyzed rearrangement of the 5-keto-2-methylenebornane (250). In addition, the carbocation intermediate 265 presumably involved in the rearrangement of 261 is very similar to the intermediate 243a proposed for the rearrangement of (-)-2-methylenebornane (240, Scheme 67).

As indicated above, the enantiomeric purity of the product obtained by rearrangement of (-)-1-chlorocamphene (261) depends upon the acid used and two competing rearrangement processes can be invoked to illustrate these results (Scheme 68). In pathway i, bromide ion adds after Wagner Meerwein rearrangement has occurred but before 6,2-hydride shift to give 262; in pathway ii, bromide adds after 6,2-hydride shift occurs to give ent-262. In the presence of 45% HBr/HOAc, it was observed that only 262 was formed, and this can be explained by the exclusive operation of pathway i. When an acid other than HBr is used, (eg. formic acid or trichloroacetic acid), then pathway ii competes with pathway i: enantiomeric products result and enantiomeric purity is lost or decreased. Based on these results, we decided to investigate the rearrangement of (-)-2-methylenebornane (240) using 45% HBr/HOAc instead of H2SO4 and HOAc as we had used previously.
(-)-2-methylenebornane (240) was prepared in 87% yield\textsuperscript{133} by reaction of (+)-camphor (25) with the Wittig\textsuperscript{125} reagent prepared from methyltriphenylphosphonium bromide (Scheme 69). Upon treatment of 240 with a 45% solution of HBr in HOAc for 5 minutes at room temperature,\textsuperscript{130,131} a single product was obtained in 87% yield, which was determined to be 4-methylisobornyl bromide (266). The $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 266 showed four singlets due to four methyl groups at 0.72, 0.91, 1.00 and 1.05 ppm as well as a characteristic doublet of doublets ($J$=8, 5 Hz) at 4.15 ppm due to the C(2) endo proton. As this compound (266) was not reported in the literature
and no specific rotation was available for comparison, the enantiomeric purity was not
determined at this stage, and it was converted to the known compound (+)-4-methyl-
isoborneol (267) (Scheme 70). The bromide (266) was found to discolor upon storage

and therefore it was always freshly prepared, purified by column chromatography and
immediately used in the next reaction to provide alcohols 267 and 268. Grignard reagent
formation from the bromide 266 followed by reaction with oxygen provided a 1:1
mixture of \textit{exo} and \textit{endo} alcohols 267 and 268 in 40\% yield. Although conversion of
bromide 266 to the corresponding Grignard derivative is slow, satisfactory results (for the
purpose of determining enantiomeric purity) were obtained when the Grignard reaction
was performed under concentrated conditions (\~1 M) with rapid addition of the bromide
to freshly ground magnesium in dry THF. Attempts to increase the yield of the
conversion of 266 to 267/268 are currently being investigated in our laboratory; other
sources of oxygen such as MoO$_5$py-HMPA$^{134}$ or (camphorylsulfonyl)oxaziridine$^{135}$will
also be investigated. That a mixture of isomers was obtained in this reaction did not
matter, since the mixture of epimeric alcohols was subsequently oxidized to (-)-4-methyl-
camphor (229). Careful column chromatography of the mixture of isomers, however, led
to the separation of (+)-4-methylisoborneol (267) so that its enantiomeric purity could be
determined. The spectral characteristics of 267 were identical to those obtained for
(+)-4-methylisoborneol (267) previously prepared in our laboratory by hydrolysis of
(+)-4-methylisobornyl acetate (239, cf. Scheme 60, p. 94). The specific rotation,
however, was significantly higher than any previously reported values and suggested a
very high enantiomeric purity. Table 10 compares literature specific rotations of
(+)-4-methylisoborneol (267) with those obtained for the alcohol prepared by our new
route. It should be noted that entries 1-3 are rotations that were taken for three different
samples of 267 prepared by acid-catalyzed (45% HBr/HOAc) rearrangement of
(-)-2-methylenebornane (240). These results indicate that the rotation is consistent
regardless of slight variations in reaction time or temperature and thus the high specific
rotations are a result of the acid catalyst used and are also reproducible.

Table 10: Specific rotation of (+)-4-methylisoborneol (267)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Specific Rotation [α]D</th>
<th>T (°C)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+32.9 0 (c 2.7, 95% EtOH)</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>+32.9 0 (c 8.1, 95% EtOH)</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>+33.0 0 (c 3.1, 95% EtOH)</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>+25.20 0 (c 10.0, EtOH)</td>
<td>20</td>
<td>121</td>
</tr>
<tr>
<td>5</td>
<td>+14.8 0</td>
<td>20</td>
<td>127</td>
</tr>
<tr>
<td>6</td>
<td>+22.69 0 (EtOH)</td>
<td>20</td>
<td>122</td>
</tr>
<tr>
<td>7</td>
<td>+19.5 0 (c 10.00, EtOH)</td>
<td>30</td>
<td>124</td>
</tr>
</tbody>
</table>

Based on the high specific rotations obtained for alcohol 267, we believed that the
alcohol synthesized via 45% HBr/HOAc catalyzed rearrangement of (-)-2-methylene-
bornane (240) was of very high enantiomeric purity, and we performed additional analyses to confirm this.

It was found that a Chirasil-val III column (Alltech, 25 m x 0.25 mm i.d.) was able to separate (+)-4-methylisoborneol (267) and (-)-4-methylisoborneol (ent-267) when an oven temperature of 60 °C and a flow rate of 1.46 mL/min (carrier gas=He) were used. A sample of (+)-4-methylisoborneol (267) prepared via the H2SO4/HOAc route ([α]D24 +20.9 °, c 9.4, 95% EtOH, Sample A) was used as standard and it was found that two peaks with relative areas of 81.7 and 18.2% (rt=29.90 and 30.70 min) were obtained. Although complete baseline resolution could not be achieved, the integration ratio of the two peaks was consistent when different oven temperatures and injection volumes were used and the results are consistent with previous determinations.124 A sample of (+)-4-methylisoborneol (267) prepared via our new route ([α]D25 +33.0 °, c 3.1, 95% EtOH, Sample B) was analyzed under the same GC conditions and only one peak was detected. The chromatograms obtained for both Sample A and Sample B are shown in Figure 1 (p. 108). Considering the resolution attainable and the GC detection limits, we believe that our new route provides (+)-4-methyl-isoborneol (267) that is at least 95% enantiomerically enriched. Future work may involve obtaining a chiral GC column that is capable of better resolution of the two enantiomers (267 and ent-267) and with ideal resolution the detection limits using this method should be at least 1%.

The final step in this project was to oxidize the mixture of exo and endo alcohols 267 and 268 to the corresponding ketone, (-)-4-methylcamphor (229, Scheme 70, p. 105). This was accomplished in 97% yield using Jones' reagent, CrO3 in H2SO4 and acetone.136 The (-)-4-methylcamphor (229) obtained through this route showed spectral characteristics identical to those reported in the literature; however, its specific rotation, as expected, was higher. Table 11 (p. 109) compares the specific rotation obtained for our compound with those reported in the literature. Entries 1 and 2 are rotations taken for two samples of 229, both prepared via our new route but in separate experiments.
Oven Temp. = 60 °C

<table>
<thead>
<tr>
<th>RT</th>
<th>Area</th>
<th>Type</th>
<th>Area %</th>
<th>[α]_D^{24} +20.9 °, c 9.4, 95% EtOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.18</td>
<td>1.93</td>
<td>BB</td>
<td>0.015</td>
<td>Sample A</td>
</tr>
<tr>
<td>29.90</td>
<td>10676.10</td>
<td>BV</td>
<td>81.745</td>
<td></td>
</tr>
<tr>
<td>38.70</td>
<td>2382.27</td>
<td>VB</td>
<td>18.241</td>
<td></td>
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</tbody>
</table>

Total Area = 13060.30

Oven Temp. = 60 °C

<table>
<thead>
<tr>
<th>RT</th>
<th>Area</th>
<th>Type</th>
<th>Area %</th>
<th>[α]_D^{25} +33.0 °, c 3.1, 95% EtOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>29.93</td>
<td>12180.00</td>
<td>BH</td>
<td>100.00</td>
<td>Sample B</td>
</tr>
</tbody>
</table>

Total Area = 10180.00

Figure 1: Chromatograms obtained for Samples A and B of (+)-4-methylisoborneol (267)
Table 11: Specific rotation of (-)-4-methylcamphor (229)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Specific Rotation $[\alpha]_D$</th>
<th>$T;(^\circ C)$</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-27.0 $^o$ (c 0.7, 95% EtOH)</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>-26.7 $^o$ (c 3.4, 95% EtOH)</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>-14.5 $^o$ (c 10.0, EtOH)</td>
<td>20</td>
<td>121</td>
</tr>
<tr>
<td>4</td>
<td>-16.0 $^o$ (c 2.00, EtOH)</td>
<td>21</td>
<td>124</td>
</tr>
</tbody>
</table>

As for the (+)-4-methylisoborneol (267), the high rotations obtained for (-)-4-methylcamphor (229) obtained via our new route suggested that it was of high enantiomeric purity, and further experiments were done to confirm this. Unfortunately, neither of the two chiral GC columns available to us (the previously described Chirasil-val III or Cyclodex-30N, 30 m x 0.25 mm i.d., film thickness 0.25 m) were able to resolve the two enantiomers present in a test mixture of 4-methylcamphor (229) prepared by the $\text{H}_2\text{SO}_4$/HOAc catalyzed rearrangement of (-)-2-methylenebornane (246). Earlier studies, however, had been done using the chiral shift reagent $[\text{Eu(hfc)}_3]$ and $^1\text{H}$ NMR spectroscopy.\textsuperscript{127} To a 0.1 M solution of (-)-4-methylcamphor (229) prepared via the $\text{H}_2\text{SO}_4$/HOAc route (Sample C) was added successively 0.10, 0.20 and 0.30 mole equivalents of the chiral shift reagent and a $^1\text{H}$ NMR (400 MHz, CDCl$_3$) spectrum was recorded after each addition. The spectra are shown in Figure 2 (p. 110) and after a total of 0.60 equivalents of reagent were added, a second signal due to the protons of a methyl group in a diastereomeric species was detected. Integration of the parent signal and of the minor new signal showed a ratio of ~4.3:1, and this suggests that the (-)-4-methylcamphor (229) as prepared by the $\text{H}_2\text{SO}_4$/HOAc route has an enantiomeric purity of ~60%.

A sample of the (-)-4-methylcamphor (229, $[\alpha]_D^{25}$ -26.7 $^o$, c 3.4, 95% EtOH, Sample D) prepared via our new route was treated under similar conditions as those used for Sample C and $^1\text{H}$ NMR (400 MHz, CDCl$_3$) spectra were recorded after the
Figure 2: $^1$H NMR (400 MHz) spectra after [Eu(hfc)$_3$] addition to Sample C of (-)-4-methylcamphor (229)

0 equiv. [Eu(hfc)$_3$]

0.1 equiv. [Eu(hfc)$_3$]

0.3 equiv. [Eu(hfc)$_3$]

0.6 equiv. [Eu(hfc)$_3$]
successive addition of 0.10, 0.30 and 0.30 mole equivalents of [Eu(hfc)_3]. The spectra are shown in Figure 3 (p. 112) and comparison with those obtained for Sample C shows a similar trend in signal broadening and chemical shift change. However, Sample D shows no extra signals that would indicate the presence of a diastereomeric species, and thus, considering the NMR detection limits, our (-)-4-methylcamphor (229) can be considered to be enantiopure.

2.3: Conclusion

A new short synthetic route to (-)-4-methylcamphor (229) has been developed which uses the acid-catalyzed (45% HBr/HOAc) rearrangement of (-)-2-methylenebornane (240) as a key step. As the starting material, (+)-camphor (25), is available in either enantiomeric form, a route to (+)-4-methylcamphor (ent-229) is also available. Comparison of the specific rotations obtained for (+)-4-methylisoborneol (267) and (-)-4-methylcamphor (229) obtained via our new route to those reported in the literature suggested that these compounds had been obtained enantiopure, and subsequent GC analyses and NMR experiments showed no evidence of the presence of enantiomers ent-267 or ent-229. The availability of enantiopure 4-methylcamphor (229) provides an opportunity to evaluate its potential as an intermediate in the enantiospecific synthesis of triterpenoids.
Figure 3: $^1$H NMR (400 MHz) spectra after $[\text{Eu(hfc)}_3]$ addition to Sample D of (-)-4-methylcamphor (229)
Experimental

General Experimental:

All reagents used were of commercial grade and were used as received unless otherwise specified. Reactions involving air- or moisture-sensitive reagents were performed in flame- or oven-dried glassware and performed under an Ar atmosphere. Dry solvents and reagents were obtained as follows: THF and Et₂O were distilled from Na/benzophenone; CH₂Cl₂, C₆H₆, toluene, MeOH, i-Pr₂NH, and diglyme were distilled from CaH₂; pyridine and DMSO were distilled from KOH; TMSCl, xylene and Et₃N were distilled from LiAlH₄; and DMF and quinoline were stored over 4 Å molecular sieves. Absolute EtOH was obtained by refluxing 95% EtOH for 6 h over oven-dried CaO, followed by distillation. Low boiling petroleum ether (PE, bp. 30-60 °C) was distilled prior to use in chromatography. Aqueous solutions used in reaction work-ups were saturated unless otherwise specified and MgSO₄ used as a drying agent was anhydrous.

Column chromatography was performed on Merck Silica Gel 60 (230-400 mesh) and radial chromatography was performed on a Harrison Research Chromatotron® 7924T, using plates of Merck Silica Gel 60, PF₂₅₄ containing gypsum, of 1, 2 or 4 mm thickness and 4.0-11.25 cm radius. Thin layer chromatography (TLC) was performed on Merck 5735 Precoated Silica Gel 60, PF₂₅₄ on plastic sheets and visualization was accomplished using I₂ vapour or an ammonium molybdate/H₂SO₄ spray. Gas liquid chromatography (GC) was performed on a Hewlett-Packard HP5830A instrument, using either a 0.2 mm x 11 m OV-101 column or a 0.25 mm x 25 m Chirasil-val III column (for the optical purity determination work) and He as the carrier gas.

Melting points were determined on a Reichert heating stage and are uncorrected. Infrared spectra were recorded using either a Perkin-Elmer 710B scanning spectrophotometer (calibrated using the 1601 cm⁻¹ band of polystyrene) or a Bomem Michelson 100 Fourier Transform Infrared spectrometer using internal calibration. Samples were
prepared as neat films between NaCl plates or as solutions in NaCl cells of 0.1 mm path length. $^1$H NMR spectra were recorded at 300 MHz on a Varian XL-300 spectrometer and at 400 MHz on a Bruker WH-400 spectrometer and signal positions are given in ppm and are referenced to tetramethylsilane. $^{31}$P NMR spectra were recorded at 121.4 MHz on a Varian XL-300 spectrometer and signal positions are given in ppm and are referenced to 85% H$_3$PO$_4$ in D$_2$O. Low resolution mass spectra were obtained using a Kratos MS-80 spectrometer and high resolution mass spectra were obtained using a Kratos MS-50 spectrometer. Specific rotations ([α]) were recorded on a Jasco J-710 spectropolarimeter in a 0.1 dm cell using the sodium D line (589 nm). Elemental analyses were performed by Mr. P. Borda, Microanalytical Laboratory, Department of Chemistry, U.B.C. and X-ray crystallographic analyses were done by Dr. S. Rettig, Department of Chemistry, U.B.C.

Conversion of (+)-endo-3-bromocamphor (52) to (+)-5,6-dehydrocamphor (36):

Chlorosulphonic acid (240 mL) was cautiously added to (+)-endo-3-bromocamphor (52, 60.0 g, 0.26 mol). The solution was heated at 55 °C for 15 min, then cooled in ice for 15 min. The reaction mixture was cautiously poured onto ice (~ 500 g) and extracted with Et$_2$O (3x). The combined extracts were washed with NaHCO$_3$(aq) solution until the washings were basic, then with brine (6x), and dried over MgSO$_4$. Removal of the solvent gave crude (-)-endo-6-bromocamphor (53) as a brown solid which was not purified. A solution of KOH (26.0 g, 0.46 mol) in water (100 mL) was added, followed by DMSO (600 mL). The solution was heated at 120 °C overnight, then cooled and diluted with water (700 mL). The reaction mixture was extracted with Et$_2$O
(3x) and the combined extracts washed with brine (5x) and dried over MgSO₄. Removal of the solvent gave a yellow solid which was purified by sublimation (20 mmHg, 50 °C) to afford (+)-5,6-dehydrocamphor (36, 4.83 g, 12% yield) as a white solid.

mp: 145-148 °C (lit 148 °C)

C₁₀H₁₄O \quad \text{Calc. Mass:} \quad 150.1044
\quad \text{Meas. Mass:} \quad 150.1036

¹H NMR (400 MHz, CDCl₃): δ=0.92 (3H, s, C(8)H); 1.02 (3H, s, C(10)H); 1.08 (3H, s, C(9)H); 1.94 (1H, d, J=16 Hz, C(3) endo H); 2.23 (1H, dd, J=16, 4 Hz, C(3) exo H); 2.69 (1H, br s, C(4)H); 5.59 (1H, d, J=6 Hz, C(6)H); 6.45 (1H, dd, J=6, 4 Hz, C(5)H).

IR (CHCl₃): ν=2969 (C-H); 1740 (C=O) cm⁻¹

MS: m/e (%)=150 (M⁺, 7.9); 108 (100); 107 (72); 93 (98); 91 (66); 77 (30).

[α]D²⁵ +731° (c 1.3, 95% EtOH) (lit [α]D -735° for enantiomer (c 1.0, EtOH))

Bromination of (+)-endo-3-bromocamphor (52) to give (+)-3,3-dibromocamphor (58):

Bromine (20 mL, 0.39 mol) was added dropwise over 1 h to a refluxing solution of (+)-endo-3-bromocamphor (52, 69.2 g, 0.299 mol) in HOAc (250 mL). After an additional 30 min, a second portion of bromine (10 mL, 0.19 mol) was added dropwise over 1 h. The reaction was cooled to RT and cautiously poured onto ice (~500 mL). Solid NaHSO₃ was added until the mixture turned from orange to pale yellow. Solid
NaHCO₃ was cautiously added until the aqueous layer was saturated. The white precipitate was dissolved with Et₂O and the mixture was diluted with water. The mixture was extracted with Et₂O (3x) and the combined extracts were washed with saturated NaHCO₃(aq) solution (5x, until basic) and brine (5x). After drying the extracts over MgSO₄, removal of the solvent gave an orange oil which was diluted with PE. Upon cooling, (+)-3,3-dibromocamphor (58, 63.00 g, 68% yield) was obtained as white crystals. A second crop of crystals yielded an additional 18.86 g (20% yield) of product.

mp: 59-60 °C (lit 68 64 °C)

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>C₁₀H₁₄O⁷⁹Br⁷⁹Br</td>
<td>307.9411</td>
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</tbody>
</table>

Calc.: C 38.74  H 4.55  Br 51.55 %
Anal.: C 38.68  H 4.53  Br 51.80 %

¹H NMR (400 MHz, CDCl₃): δ=1.01 (3H, s, CH₃); 1.10 (3H, s, CH₃); 1.23(3H, s, CH₃); 1.61-1.67 (2H, m, C(5) endo H and C(6) endo H); 2.07 (1H, m, C(6) exo H); 2.33 (1H, m, C(5) exo H); 3.82 (1H, d, J=4 Hz, C(4)H).

IR (CHCl₃): ν=2962 (C-H); 1761 (C=O) cm⁻¹

MS: m/e(%)=312, 310, 308 (M⁺, 3.4, 6.7, 3.1); 284, 282, 280 (7.2, 16, 7.7); 203 (54); 201 (55); 122 (84); 83 (100).
Debromination of (+)-3,3-dibromocamphor (58) to give cyclocamphanone (59):

![Chemical Structures]

To a solution of (+)-3,3-dibromocamphor (58, 5.89 g, 19.0 mmol) in dry benzene (100 mL) under an Ar atm was added Et₂Zn (17.3 mL, 1.1 M/toluene, 19.0 mmol). The mixture was refluxed for 24 h, then was cautiously poured onto ice (~100 mL). 1 M HCl was added to dissolve the white precipitate and the mixture was extracted with Et₂O (3x). The combined extracts were washed with water (3x, until neutral), and dried over MgSO₄. Removal of the solvent gave an orange solid which was purified by column chromatography using 24:1 PE:Et₂O as eluant. Cyclocamphanone (59) was isolated as a white solid (2.21 g, 78% yield).

mp: 168-169 °C (lit²⁹ 168-170 °C)

C₁₀H₁₄O  
Calc. Mass: 150.1044  
Meas. Mass: 150.1044  

Calc.: C 79.96 %  
Anal.: C 80.00 %  

¹H NMR (400 MHz, CDCl₃): δ=0.81 (3H, s, CH₃); 0.91 (3H, s, CH₃); 0.97 (3H, s, CH₃); 1.44 (1H, t, J=5.5 Hz, C(3)H); 1.71 (1H, d, J=11 Hz, C(6) endo H); 1.93 (1H, dd, J=11, 1.5 Hz, C(6) exo H); 1.96 (1H, t, J=5.5 Hz, C(4)H); 2.01 (1H, t, J=5.5 Hz, C(5)H).

IR (CH₂Cl₂): ν=3065, 2964, 2874 (C-H); 1747 (C=O) cm⁻¹

MS: m/e(%)=150 (M⁺, 27); 135 (44); 121 (12); 108 (22); 107 (100).
Bromination of cyclocamphanone (59) to give \textit{exo}-5-bromocamphor (60):

\[
\begin{array}{c}
59 \\
\text{O} \\
\text{Br} \\
60
\end{array}
\]

To a solution of cyclocamphanone (59, 23.10 g, 0.153 mol) in Ac\textsubscript{2}O (68 mL, 0.72 mol) was cautiously added dropwise hydrobromic acid (48%, 470 mL, 4.15 mol).\textsuperscript{60} The reaction was heated at 65 °C for 3 h, then cooled to RT and carefully poured onto ice (~500 mL). The yellow precipitate was collected by filtration, dissolved in Et\textsubscript{2}O and washed with water (2x), NaHCO\textsubscript{3}(aq) solution (2x), and brine (3x). After drying over MgSO\textsubscript{4}, removal of the solvent gave a yellow solid which was recrystallized from 4:1 PE:Et\textsubscript{2}O to give \textit{exo}-5-bromocamphor (60) as a white crystalline solid (27.60 g, 78% yield).

mp: 109-111 °C (lit\textsuperscript{60} 110-111 °C)

\[
\begin{array}{c}
\text{C}_{10}\text{H}_{15}\text{O}^{79}\text{Br} \\
\text{Calc. Mass: 230.0306} \\
\text{Meas. Mass: 230.0307} \\
\text{C}_{10}\text{H}_{15}\text{O}^{81}\text{Br} \\
\text{Calc. Mass: 232.0286} \\
\text{Meas. Mass: 232.0288}
\end{array}
\]

\[
\begin{array}{ccc}
\text{Calc.:} & \text{C 51.97} & \text{H 6.54} & \text{Br 34.57 \%} \\
\text{Anal.:} & \text{C 51.78} & \text{H 6.44} & \text{Br 34.43 \%} \\
\end{array}
\]

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \textsuperscript{8} = 0.89 (3H, s, CH\textsubscript{3}); 0.96 (3H, s, CH\textsubscript{3}); 1.37 (3H, s, CH\textsubscript{3}); 1.84 (1H, d, J=18 Hz, C(3) \textit{endo} H); 2.15 (1H, dd, J=16, 8 Hz, C(6) \textit{endo} H); 2.27 (1H, dd, J=16, 5 Hz, C(6) \textit{exo} H); 2.46 (1H, dd, J=18, 5 Hz, C(3) \textit{exo} H); 2.52 (1H, d, J=5 Hz, C(4)H); 4.06 (1H, dd, J=8, 5 Hz, C(5)H).
IR (CH₂Cl₂): ν=3058, 2969 (C-H); 1745 (C=O) cm⁻¹

MS: m/e(%)=232, 230 (M⁺, 7.2, 7.4); 151 (34); 123 (80); 110 (18); 109 (100).

Ketalization of exo-5-bromocamphor (60) to give 61:

To a solution of exo-5-bromocamphor (60, 18.93 g, 81.91 mmol) in ethylene glycol (70.0 mL, 1.23 mol) was added TMSCl (32.0 mL, 0.246 mol) under an Ar atm. After stirring at RT for 2.5 h, brine was added and the mixture was extracted with Et₂O (3x). The combined extracts were washed with NaHCO₃(aq) solution (2x), brine (3x) and dried over MgSO₄. Removal of the solvent gave a yellow solid which was recrystallized from 4:1 PE:Et₂O. The ketal 61 was isolated as a white crystalline compound (20.72 g, 92% yield).

mp: 72-74 °C

C₁₂H₁₉O₂⁷⁹Br  Calc. Mass: 274.0568
Meas. Mass: 274.0569
C₁₂H₁₉O₂⁸¹Br  Calc. Mass: 276.0548
Meas. Mass: 276.0553

Calc.:  C 52.38  H 6.96  Br 29.04 %
Anal.:  C 52.49  H 7.00  Br 29.00 %

¹H NMR (400 MHz, CDCl₃): δ=0.83 (3H, s, CH₃); 1.05 (3H, s, CH₃); 1.23 (3H, s, CH₃); 1.41 (1H, d, J=13 Hz, C(3) endo H); 2.02 (1H, dd, J=14, 5 Hz, C(6) endo
H); 2.11-2.17 (2H, m, C(4)H and C(3) exo H); 2.61 (1H, dd, J=14, 8 Hz, C(6) exo H); 3.70-3.96 (4H, m, ketal H's); 4.05 (1H, dd, J=8, 5 Hz, C(5)H).

IR (CHCl₃): ʋ=3028, 2962, 2885 (C-H) cm⁻¹

MS: m/e(%)=276, 274 (M⁺, 9.2, 9.2); 261, 259 (17, 18); 195 (55); 194 (15); 179 (38); 108 (100).

Dehydrobromination of bromide 61 to give 5,6-dehydrocamphor ketal (62):

A solution of bromoketal 61 (0.94 g, 3.4 mmol) and KOH (1.23 g, 21.9 mmol) in DMSO (34 mL) and water (4.5 mL) was heated at 100 °C for 2.5 h. After cooling to RT, water was added and the mixture was extracted with Et₂O (3x). The combined extracts were washed with brine (3x) and dried over MgSO₄. Removal of the solvent gave 5,6-dehydrocamphor ketal (62) as a pale yellow oil (0.60 g, ~91% yield) which was not purified but which was used directly in the next reaction. A small sample was purified for elemental analysis by column chromatography using 9:1 PE:Et₂O as eluant. The pure ketal 62 was isolated as a very volatile colourless liquid.

C₁₂H₁₈O₂  Calc. Mass:  194.1307
            Meas. Mass:  194.1315

Calc.: C 74.19  H 9.34 %
Ana.:  C 74.13  H 9.45 %

¹H NMR (400 MHz, CDCl₃): δ=0.90 (3H, s, CH₃); 0.92 (3H, s, CH₃); 1.05 (3H, s, CH₃); 1.45 (1H, d, J=12 Hz, C(3) endo H); 2.06 (1H, dd, J=12, 3 Hz, C(3) exo H);
2.37 (1H, br t, J=3 Hz, C(4)H); 3.65-4.00 (4H, m, ketal H’s); 5.79 (1H, d, J=6 Hz, C(6)H); 6.15 (1H, dd, J=6, 3 Hz, C(5)H).

IR (CHCl₃): ν=2954, 2873 (C-H) cm⁻¹

MS: m/e(%)=194 (M⁺, 1.6); 179 (2.5); 108 (100); 93 (80); 86 (35).

Hydrolysis of ketal 62 to provide (-)-5,6-dehydrocamphor (ent-36):

A solution of ketal 62 (0.50 g, 2.6 mmol) in acetone (13 mL) and 1 M HCl (8.0 mL) was stirred at RT for 1.5 h. After dilution with water, the mixture was extracted with Et₂O (3x). The combined extracts were washed with water (3x), dried over MgSO₄ and the solvent removed to yield a white solid. Purification by column chromatography using first PE as eluant, then gradually increasing the polarity to 9:1 PE:Et₂O gave (-)-5,6-dehydrocamphor (ent-36) as a white crystalline compound (0.33 g, 85% yield).

mp: 145-148 °C (sealed tube) (lit 148 °C)

C₁₀H₁₄O  Calc. Mass:  150.1045
               Meas. Mass:  150.1038

¹H NMR (400 MHz, CDCl₃): δ=0.90 (3H, s, CH₃); 1.00 (3H, s, CH₃); 1.06 (3H, s, CH₃); 1.93 (1H, d, J=16 Hz, C(3) endo H); 2.21 (1H, dd, J=16, 3 Hz, C(3) exo H); 2.68 (1H, br s, C(4)H); 5.58 (1H, d, J=6 Hz, C(6)H); 6.45 (1H, dd, J=6, 4 Hz, C(5)H).

IR (CHCl₃): ν=2969 (C-H); 1734 (C=O) cm⁻¹
Conversion of (+)-5,6-dehydrocamphor (36) to alkyne diol 63:

\[
\begin{array}{c}
\text{36} \\
\text{OH}
\end{array}
\xrightarrow{\text{n-BuLi (58 mL, 1.6 M/hexanes, 93 mmol)}}
\begin{array}{c}
\text{63} \\
\text{OH}
\end{array}
\]

n-BuLi (58 mL, 1.6 M/hexanes, 93 mmol) was added dropwise to a solution of propargyl alcohol (2.7 mL, 47 mmol) in dry THF (150 mL) at -78 °C under an Ar atm and stirred at -78 °C for 1 h.61 A solution of (+)-5,6-dehydrocamphor (36, 4.68 g, 31 mmol) in dry THF (40 mL) was also cooled to -78 °C and cannulated into the reaction mixture which was stirred for another hour before being allowed to warm to RT overnight. The reaction was quenched by the addition of water, diluted with NH4Cl(aq) solution and extracted with Et2O (3x). The combined extracts were washed with brine (2x), and dried over MgSO4. Removal of the solvent gave a crude pale yellow solid which was recrystallized from CH2Cl2 to afford pure alkyne diol 63 (4.84 g, 76% yield) as a white solid.

mp: 118-120 °C

C_{13}H_{18}O_2  
Calc. Mass: 206.1307  
Meas. Mass: 206.1300

Calc.: C 75.69  
Anal.: C 75.77  
H 8.79 %  
H 8.59 %
\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta=0.94\) (3H, s, CH\(_3\)); 1.10 (3H, s, CH\(_3\)); 1.11 (3H, s, CH\(_3\)); 1.45 (1H, t, J=6 Hz, exchanges with D\(_2\)O, -CH\(_2\)OH); 1.89 (1H, d, J=12 Hz, C(3) \text{endo} H); 1.97 (1H, s, exchanges with D\(_2\)O, 3\(^\circ\) OH); 2.27 (1H, dd, J=12, 4 Hz, C(3) \text{exo} H); 2.42 (1H, br t, J=4 Hz, C(4)H); 4.26 (2H, d, J=6 Hz, CH\(_2\)OH); 5.74 (1H, d, J=6 Hz, C(6)H); 6.11 (1H, dd, J=6, 4 Hz, C(5)H).

IR (Nujol mull): \(\nu=3300\) (br, O-H); 2950, 2900 (C-H) cm\(^{-1}\)

MS: m/e (%)=206 (M\(^+\), 0.3); 176 (17); 145 (40); 108 (100); 107 (55); 105 (40); 93 (98); 91 (77); 77 (46).

Reduction of alkyne diol 63 to give alkene diol 64:

A solution of alkyne diol 63 (6.04 g, 29.2 mmol) in dry THF (50 mL) was cautiously cannulated into a slurry of LiAlH\(_4\) (2.80 g, 73.0 mmol) in dry THF (100 mL) under an Ar atm\(^6\). After heating at 40 °C for 1 h, the reaction was cooled to RT and cautiously quenched by the addition of water. 1 M HCl was added to dissolve the resulting grey precipitate. The solution was extracted with Et\(_2\)O (4x) and the combined extracts washed with brine (3x, until neutral). Removal of the solvent gave a pale yellow solid which was recrystallized from Et\(_2\)O to afford the alkene diol 64 (5.16 g, 85% yield) as white crystals.

mp: 158-161 °C
C_{13}H_{20}O_2  

Calc. Mass: 208.1463  

Meas. Mass: 208.1459

^1H NMR (400 MHz, CD_{3}CN): \delta=0.90 (3H, s, CH_3); 0.92 (3H, s, CH_3); 1.17 (3H, s, CH_3); 1.56 (1H, d, J=12 Hz, C(3) \text{ endo} H); 2.10 (1H, dd, J=12, 4 Hz, C(3) \text{ exo} H); 2.38 (1H, br t, J=4 Hz, C(4)H); 3.98 (2H, d, J=6 Hz, CH_2OH); 5.65 (3H, m, C(6)H and trans vinyl H's); 6.00 (1H, dd, J=6, 4 Hz, C(5)H).

IR (Nujol mull): \nu=3350 (br, O-H); 2900 (C-H) cm^{-1}

MS: m/e (%)=208 (M^+, 3.1); 177 (18); 119 (24); 108 (100); 93 (61); 91 (32).

Anionic oxy-Cope rearrangement of alkene diol 64 to give keto-alcohol 66:

A solution of alkene diol 64 (3.51 g, 16.8 mmol) in dry THF (70 mL) was cannulated into a slurry of KH (2.03 g, 50.6 mmol) in dry THF (100 mL) under an Ar atm. After 15 min at 40 °C the reaction was cooled to RT, cautiously quenched by addition of n-propanol and diluted with water. The reaction was extracted with Et_2O (3x) and the combined extracts washed successively with 1 M HCl and brine (3x). Drying over MgSO_4 followed by removal of the solvent gave a red oil which was purified by column chromatography using 2:1 PE:Et_2O as eluant. The keto-alcohol 66 was isolated as a yellow liquid (2.98 g, 85% yield).

C_{13}H_{20}O_2  

Calc. Mass: 208.1463  

Meas. Mass: 208.1466
Protection of keto-alcohol 66 to give keto-acetate 67:

To a solution of keto-alcohol 66 (3.66 g, 17.6 mmol) in dry CH$_2$Cl$_2$ (~100 mL) under an Ar atm were added successively Ac$_2$O (2.0 mL, 21 mmol), Et$_3$N (4.9 mL, 35 mmol) and a catalytic amount of DMAP. After stirring at RT overnight the reaction mixture was diluted with water and extracted with CH$_2$Cl$_2$ (3x). The combined extracts were washed successively with water, 1 M HCl, brine (2x) and dried over MgSO$_4$. Removal of the solvent gave a pale yellow liquid which was purified by column chromatography using 4:1 PE:Et$_2$O as eluant. The keto-acetate 67 was isolated as a colourless oil (4.17 g, 95% yield).

C$_{13}$H$_{20}$O$_2$  
Calc. Mass: 250.1569  
Meas. Mass: 250.1572
Calc:  C 71.97  H 8.86 %  
Anal.:  C 71.68  H 8.90 %

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$=0.94 (3H, s, CH$_3$); 1.04 (3H, s, CH$_3$); 1.62 (3H, br s, vinyl CH$_3$); 2.09 (3H, s, -O$_2$CCH$_3$); 2.20-2.55 (6H, m); 3.20 (1H, br s, C(10)H); 4.03 (1H, dd J=11, 7 Hz, -CHHOAc); 4.17 (1H, dd, J=11, 7 Hz, -CHLHOAc); 5.17 (1H, s, vinyl H).

IR (neat): $\nu$=2950, 2900 (C-H); 1730, 1710 (C=O) cm$^{-1}$.

MS: m/e (%)=250 (M+, 0.2); 190 (99); 175 (100); 148 (67); 107 (34); 91 (33); 43 (53).

Ring expansion of keto-acetate 67 to enone 69:

A solution of keto-acetate 67 (3.66 g, 14.6 mmol) in CH$_2$Cl$_2$ (60 mL) and MeOH (60 mL) was cooled to -78 °C and O$_3$ was bubbled through the solution until a blue colour persisted (~1 h). Excess O$_3$ was removed by bubbling O$_2$ through the solution until it became colourless. The reaction mixture was poured onto Zn (7.75 g, 118 mmol), HOAc (15 mL, 266 mmol) was added, and the reaction was stirred at RT for 1 h. The mixture was filtered, washed successively with water, 5% NaOH(aq) solution, water (4x, until neutral) and dried over MgSO$_4$. Removal of the solvent yielded the crude keto-aldehyde 68 as a yellow oil which was not purified but which was used directly in the next reaction. The IR and $^1$H NMR spectra were consistent with those expected for the aldehyde 68.
IR (neat): $\nu = 2970$ (C-H); 1735, 1715, 1705 (C=O) cm$^{-1}$

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.15$ (3H, s, CH$_3$); 1.16 (3H, s, CH$_3$); 2.05 (3H, s, -O$_2$CCH$_3$); 2.16 (3H, s, -COCH$_3$); 2.30-2.50 (6H, m); 2.65-2.82 (2H, m); 3.05 (1H, d, J=3 Hz, C(10)H); 4.03 (2H, d, J=7 Hz, -CH$_2$OAc); 9.10 (1H, d, J=3 Hz, -CHO).

A catalytic amount of p-TsOH·H$_2$O was added to a solution of crude keto-aldehyde 68 in dry benzene (~100 mL). The reaction was refluxed in a Dean-Stark apparatus under an Ar atm for 1 h. After cooling to RT, brine was added. The mixture was extracted with Et$_2$O (3x), and the combined extracts were washed with NaHCO$_3$(aq) solution and brine (2x). After drying over MgSO$_4$ and removal of the solvent, a yellow liquid was obtained. The crude product was purified by column chromatography using 1:1 PE:Et$_2$O as eluant to yield the enone 69 as a pale yellow liquid (3.23 g, 83% yield). A small amount was distilled (bp ~150 °C at 0.1 mmHg) to yield a colourless oil for microanalysis.

C$_{15}$H$_{20}$O$_4$  
Calc. Mass: 264.1361  
Meas. Mass: 264.1357

<table>
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<tr>
<th>Calc.</th>
<th>C 68.16</th>
<th>H 7.63 %</th>
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<tbody>
<tr>
<td>Anal.</td>
<td>C 67.97</td>
<td>H 7.63 %</td>
</tr>
</tbody>
</table>

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.09$ (3H, s, CH$_3$); 1.28 (3H, s, CH$_3$); 2.12 (3H, s, -O$_2$CCH$_3$); 2.14-2.40 (4H, m); 2.48 (2H, dd, J=14, 4 Hz); 3.22 (1H, br s, C(10)H); 4.18 (1H, dd, J=11, 6 Hz, -CHHOAc); 4.32 (1H, dd, J=12, 7 Hz, -CHHOAc); 6.16 (1H, dd, J=11, 3 Hz, C(2)H); 6.82 (1H, dt, J=11, 1 Hz, C(1)H).

IR (neat): $\nu = 3050$, 2980, 2900 (C-H); 1740, 1720, 1680 (C=O) cm$^{-1}$
MS: m/e (%) = 264 (M+, 0.4); 204 (63); 153 (12); 135 (16); 108 (100); 107 (40); 69 (35).

Monoketalization of enone 69 to give ketal 85:

To a solution of enone 69 (3.23 g, 12.2 mmol) in dry benzene (~100 mL) were added a catalytic amount of p-TsOH-H2O and ethylene glycol (8.25 mL, 148 mmol), and the mixture was refluxed under an Ar atm for 45 min in a Dean-Stark apparatus. After cooling to RT, the mixture was poured onto brine and extracted with Et2O (3x). The combined extracts were washed with NaHCO3(aq) solution, brine (2x) and dried over MgSO4. Removal of the solvent gave a yellow oil which was purified by column chromatography using 2:1 PE:Et2O as eluant. The ketal 85 was isolated as a colourless oil (2.91 g, 77% yield).

C17H24O5  Calc. Mass: 308.1623
Meas. Mass: 308.1623

1H NMR (400 MHz, CDCl3): δ = 1.09 (3H, s, CH3); 1.21 (3H, s, CH3); 1.22-1.45 (2H, m); 1.62 (1H, d, J=12 Hz); 1.73 (1H, dt, J=12, 4 Hz); 2.05 (1H, m); 2.10 (3H, s, -O2CCl3); 2.32 (1H, br s); 3.06 (1H, br s, C(10)H); 3.93 (4H, s, ketal H's); 4.12 (1H, dd, J=11, 6 Hz, -CHHOAc); 4.22 (1H, dd, J=11, 8 Hz, -CHHOAc); 6.02 (1H, dd, J=11, 3 Hz, C(2)H); 6.67 (1H, dt, J=11, 1 Hz, C(1)H).

IR (neat): ν = 2980, 2900 (C-H); 1740, 1680 (C=O) cm⁻¹
Ketalization of enone 85 to give diketalized acetate 86 and diketalized alcohol 87:

Ethylene glycol (3.9 mL, 70 mmol) and a catalytic amount of p-TsOH·H₂O were added to a solution of acetate 85 (1.08 g, 3.5 mmol) in dry benzene (~50 mL). After refluxing under an Ar atm in a Dean-Stark apparatus overnight, the reaction was cooled to RT and poured onto brine. The mixture was extracted with Et₂O (3x) and the combined extracts were washed with NaHCO₃(aq) solution and brine (2x). After drying over MgSO₄ the solvent was removed to yield a yellow oil which was purified by radial chromatography (4 mm plate) using 1:1 PE:Et₂O as eluant. Two compounds were isolated: the diketalized acetate 86 as a colourless oil (0.46 g, 37% yield) and the diketalized alcohol 87 also as a colourless oil (0.52 g, 48% yield).

Data for diketalized acetate 86:

C₁₉H₂₈O₆  Calc. Mass: 352.1886
Meas. Mass: 352.1885

¹H NMR (300 MHz, CDCl₃): δ=0.89 (3H, s, CH₃); 0.99 (3H, s, CH₃); 1.40 (1H, t, J=12 Hz); 1.79-1.96 (3H, m); 2.06 (3H, s, -O₂CC₃H₃); 2.21 (3H, br s); 2.55 (1H, br s); 3.84-4.03 (8H, m, ketal H's); 4.10 (1H, dd, J=11, 7 Hz, -CHHOAc); 4.33 (1H, dd, J=11, 5 Hz, -CH₂HOAc); 5.22 (1H, br s, C(1)H).

IR (neat): ν=2960, 2880 (C-H); 1740 (C=O) cm⁻¹
MS: m/e (%)=352 (M+, 2.0); 309 (30); 223 (32); 171 (81); 114 (100); 86 (66).

Data for diketalized alcohol 87:

\[ \text{C}_{17}\text{H}_{26}\text{O}_5 \quad \text{Calc. Mass:} \quad 310.1780 \]
\[ \text{Meas. Mass:} \quad 310.1786 \]

\(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)): \( \delta = 0.89 \) (3H, s, CH\(_3\)); \( 0.98 \) (3H, s, CH\(_3\)); \( 1.24 \) (1H, t, \( J=6 \) Hz); \( 1.37 \) (1H, br, s, exchanges with D\(_2\)O, -OH); \( 1.43 \) (1H, t, \( J=12 \) Hz); 2.74 (1H, br d, \( J=9 \) Hz); \( 2.84 \) (1H, dt, \( J=12, 4 \) Hz); \( 2.91 \) (1H, dt, \( J=12, 4 \) Hz); 2.15-2.30 (2H, br m); \( 2.45 \) (1H, br s); 3.69-3.77 (2H, br m, -CH\(_2\)OH); 3.80-4.02 (8H, m, ketal H's); \( 5.33 \) (1H, br s, C(1)H).

IR (neat): \( \nu = 3400 \) (br, O-H); \( 2950, 2860 \) (C-H) cm\(^{-1}\)

MS: m/e (%)=310 (M\(^+\), 5.3);267 (36); 181 (28); 129 (36); 114 (100); 99 (48); 86 (34).

Deprotection of diketalized acetate 86 to give diketalized alcohol 87:

\[ \text{86} \quad \xrightarrow{\text{KOH \text{in water}}} \quad \text{87} \]

To a solution of diketalized acetate 86 (0.429 g, 1.18 mmol) in MeOH (10 mL) was added a solution of KOH (0.20 g, 3.5 mmol) in water (10 mL). After stirring at RT for 30 min, the mixture was diluted with water and extracted with Et\(_2\)O (3x). The combined extracts were washed with brine (3x), dried over MgSO\(_4\) and the solvent removed to provide a pale yellow oil. Purification by column chromatography using 1:1 PE:Et\(_2\)O as eluant gave the diketalized alcohol 87 as a colourless oil (0.34 g, 95% yield). Spectral characteristics were identical to those of the alcohol 87 described previously.
Attempted cyclopropanation of diketalized alcohol 87:

Cyclopropanation attempt A⁷²:

To a solution of diketalized alcohol 87 (0.115 g, 0.40 mmol) in CHCl₃ (2 mL) at
0 °C were added BuN⁺Et₃Cl⁻ (0.002 g, 0.008 mmol), then NaOH (0.5 mL, 50%/H₂O)
dropwise. The mixture was stirred at 0 °C for 2.5 h, then at RT for 3 days. Water was
added and the mixture extracted with Et₂O (3x). Drying over MgSO₄ and removal of the
solvent gave a yellow oil which was purified by column chromatography using 1:1
PE:Et₂O as eluant. None of the products obtained showed evidence of being a cyclo-
propanation product by either ¹H NMR or mass spectrometry.

Cyclopropanation attempt B⁷³,⁷⁴:

To a solution of diketalized alcohol 87 (0.268 g, 0.860 mmol) in dry toluene
(10 mL) under an Ar atm was added Et₂Zn (1.9 mL, 1.1 M/toluene, 2.1 mmol) followed
by CH₂I₂ (0.21 mL, 2.6 mmol). The system was flushed with O₂ and the reaction stirred
at RT 1.5 h. The reaction was then heated at 45 °C for 1 h, then at 95 °C overnight.
After cooling to RT, NH₄Cl(aq) solution was added and the mixture extracted with Et₂O
(3x). The combined extracts were dried over MgSO₄ and the solvent removed to yield a
yellow oil which was a complex mixture by TLC and GC. The mixture was purified by
column chromatography using 1:1 PE:Et₂O as eluant to give starting material (0.105 g,
39% yield). There was no evidence of a cyclopropanation product as determined by ¹H
NMR and mass spectrometry.
Cyclopropanation attempt C67:

To a slurry of Zn-Cu (0.37 g, 5.0 mmol) and I2 (0.37 g, 1.4 mmol) in dry Et2O (5 mL) under an Ar atm was added a solution of diketalized alcohol 87 (0.19 g, 0.62 mmol) in dry Et2O (5 mL). CH2I2 (0.15 mL, 1.8 mmol) was added and the reaction was stirred at RT for 30 min, then refluxed for 1 h. Additional CH2I2 (0.15 mL, 1.8 mmol) was added dropwise and the mixture was refluxed for a further 8 h. A final portion of CH2I2 (0.15 mL, 1.8 mmol) was added and the reaction was refluxed overnight. After cooling to RT, NH4Cl(aq) solution was added and the mixture was filtered through Celite. The organic layer was separated and washed with NaHCO3(aq) solution, brine (3x), dried over MgSO4, and the solvent removed to give a yellow oil. Purification by column chromatography using 2:1 PE:Et2O as eluant gave recovered starting material as the major product (0.033 g, 17% recovery). Minor products showed no evidence of being cyclopropanation products as determined by 1H NMR or mass spectrometry.

Cyclopropanation attempt D75:

To a slurry of Zn (0.20 g, 3.1 mmol) and CuCl (0.03 g, 0.31 mmol) in dry Et2O (1 mL) under an Ar atm were added CH2Br2 (0.16 mL, 2.3 mmol) and a solution of diketalized alcohol 87 (0.24 g, 0.77 mmol) in dry Et2O (3 mL). TiCl4 (5.0 μL, 0.046 mmol) was cautiously added and the mixture diluted with dry Et2O (3 mL). After refluxing for 2 h, the reaction was cooled to RT and NH4Cl(aq) solution was added. After filtration and extraction with pentane (3x) the combined extracts were washed with 10% NaOH(aq) solution (3x) and brine. Drying over MgSO4 and removal of the solvent gave a yellow liquid which was purified by column chromatography using 4:1 PE:Et2O as eluant. Many products were obtained, none of which appeared to be cyclopropanation products as determined by 1H NMR and mass spectrometry.
Reduction and protection of keto-alcohol 66 to give dimethyl ether 91:

To a slurry of LiAlH₄ (0.12 g, 3.2 mmol) in dry THF (15 mL) at -78 °C under an Ar atm was added a solution of keto-alcohol 66 (0.554 g, 2.60 mmol) in dry THF (30 mL). The reaction mixture was allowed to warm to RT over ~1 h. Water was cautiously added, then the mixture was diluted with 1 M HCl and extracted with Et₂O (3x). The combined extracts were washed with brine (3x) and dried over MgSO₄. Removal of the solvent gave a yellow gum (0.606 g) which was not purified but which showed the following spectral characteristics, suggesting that the diol was formed:

C₁₃H₂₂O₂  Calc. Mass: 210.1619
Meas. Mass: 210.1613

¹H NMR (300 MHz, CDCl₃, major diastereomer) δ=0.95 (3H, s, CH₃); 1.00 (3H, s, CH₃); 1.10-1.30 (2H, m); 1.60 (3H, m, vinyl CH₃); 1.75-2.00 (4H, m); 2.95 (1H, br s, C(7)H); 3.50-3.80 (5H, m); 5.15 (1H, s, vinyl H).

IR (neat): ν=3350 (br, O-H); 2900 (C-H) cm⁻¹

MS: m/e (%)=210 (M⁺, 23); 192 (34); 177 (100); 174 (28); 159 (91).

The crude diol was dissolved in dry THF (15 mL) and cannulated into a slurry of KH (0.26 g, 6.5 mmol) in dry THF (10 mL) under an Ar atm. The reaction was stirred at RT for 45 min and then MeI (0.40 mL, 6.5 mmol) was added. After stirring for an additional 60 min, water was cautiously added, and the reaction was extracted with Et₂O.
(3x). The combined extracts were washed with brine (3x) and dried over MgSO₄. Removal of the solvent gave a yellow liquid which was purified by column chromatography using 15:1 PE:Et₂O as eluant. The dimethyl ether 91 was isolated as a colourless liquid (0.515 g, 83% yield from keto-alcohol 66). ¹H NMR spectroscopy showed the diastereomeric mixture to be ~4:1.

C₁₅H₂₆O₂  Calc. Mass: 238.1932
Meas. Mass: 238.1927

¹H NMR (400 MHz, CDCl₃, major diastereomer) δ=0.94 (3H, s, CH₃); 0.99 (3H, s, CH₃); 1.58 (3H, m, vinyl CH₃); 1.70-1.80 (1H, m); 1.80-1.95 (3H, m); 2.94 (1H, br s, C(7)H); 3.80 (1H, m); 3.30-3.50 (10H, m); 5.14 (1H, s, vinyl H).

IR (neat): ν=2900 (C-H) cm⁻¹

MS: m/e(%)=238 (M⁺, 4.5); 223 (1.1); 207 (4.2); 206 (27); 191 (20); 159 (100).

Ring expansion of dimethyl ether 91 to give enone 92:

A solution of dimethyl ether 91 (0.91 g, 3.8 mmol) in CH₂Cl₂ (10 mL) and MeOH (10 mL) was cooled to -78 °C and O₃ was bubbled through the solution until a blue colour persisted (~45 min). Excess O₃ was removed by bubbling O₂ through the solution until it became colourless. The reaction mixture was poured onto Zn (2.49 g, 38.1 mmol), HOAc (4.5 mL, 76 mmol) was added, and the reaction was stirred at RT for 1 h. The mixture was filtered, washed successively with water (2x), 5% NaOH(aq)
solution (2x), water (4x, until neutral) and dried over MgSO₄. Removal of the solvent gave the crude keto-aldehyde as a yellow oil which was not purified. To the keto-aldehyde in dry C₆H₆ (~50 mL) was added a few crystals of p-TsOH·H₂O and the mixture was refluxed in a Dean-Stark apparatus under an Ar atm for 1 h. After cooling to RT brine was added and the mixture was extracted with Et₂O (3x). The combined extracts were washed with NaHCO₃(aq) solution, brine (3x) and dried over MgSO₄. Removal of the solvent gave a yellow liquid which was purified by column chromatography using 4:1 PE:Et₂O as eluant. The enone 92 was isolated as a colourless oil (0.502 g, 52 % yield).

C₁₅H₂₄O₃    Calc. Mass:  252.1725
               Meas. Mass:  252.1719

¹H NMR (400 MHz, CDCl₃): \( \delta = 1.00-1.25 \) (2H, m); 1.09 (3H, s, CH₃); 1.21 (3H, s, CH₃); 1.77 (1H, br d, J=14 Hz); 1.93 (1H, br d, J=14 Hz); 2.06 (1H, br d, J=14 Hz); 2.33 (1H, br m); 3.12 (1H, br s, C(10)H); 3.30 (3H, s, -CHRR'OCH₃); 3.38 (3H, s, -CH₂OCH₃); 3.40-3.55 (3H, m, -CH₂OCH₃ and C(7)H); 5.98 (1H, dd, J=10, 3 Hz, C(2)H); 6.75 (1H, dt, J=10, 2 Hz, C(1)H).

IR (neat): \( \nu = 2924, 2357, 2331 \) (C-H); 1679 (C=O) cm⁻¹

MS: m/e(%)=252 (M⁺, 11); 221 (4.9); 220 (30); 205 (3.1); 189 (5.0); 188 (22); 45 (100).

Conversion of enone 92 to ketal 93:
A solution of enone 92 (0.50 g, 1.9 mmol), ethylene glycol (1.1 mL, 19 mmol), and a catalytic amount of p-TsOH·H₂O in dry C₆H₆ (~50 mL) was refluxed under an Ar atm in a Dean-Stark apparatus for 3 days. After cooling to RT, brine was added and the mixture was extracted with Et₂O (3x). The combined extracts were washed with NaHCO₃(aq) solution, brine (3x) and dried over MgSO₄. Removal of the solvent gave a pale yellow oil which was purified by column chromatography using 15:1 PE:Et₂O as eluant. The ketal 93 was isolated as a colourless liquid (0.301 g, 53% yield).

C₁₇H₂₈O₄  Calc. Mass: 296.1987

¹H NMR (300 MHz, CDCl₃): δ=0.88 (3H, s, CH₃); 0.99 (3H, s, CH₃); 1.12-1.30 (2H, m); 2.00-2.40 (5H, m); 2.55 (1H, br s); 3.33 (3H, s, -CHRR'OCH₃); 3.34 (3H, s, -CH₂OCH₃); 3.43 (1H, m, C(7)H); 3.54 (1H, m, -CHHOCH₃); 3.65 (1H, m, -CHHOCH₃); 3.85-4.00 (4H, m, ketal H's); 5.19 (1H, br s, C(1)H).

IR (neat): υ=2900 (C-H) cm⁻¹

MS: m/e(%)=296 (M⁺, 2.9); 251 (7.1); 221 (13); 114 (100).

Conversion of ketal 93 to deconjugated enone 94:

A solution of ketal 93 (0.38 g, 1.3 mmol) in acetone (5 mL) and 1 M HCl (5 mL) was heated at 70 °C for 15 min. After cooling to RT, the reaction was extracted with Et₂O (3x) and the combined extracts were washed with brine (3x) and dried over MgSO₄.
Removal of the solvent gave the deconjugated enone 94 as a colourless liquid (0.31 g, 95% yield) which was not purified but which was used directly in the next reaction.

\[ \text{C}_{15}\text{H}_{24}\text{O}_3 \]

Calc. Mass: 252.1725
Meas. Mass: 252.1733

\(^1\text{H NMR}\) (300 MHz, \(\text{CDCl}_3\)): \(\delta = 1.03\) (3H, s, \(\text{CH}_3\)); 1.07-1.22 (2H, m); 1.29 (3H, s, \(\text{CH}_3\)); 2.11 (1H, br d, \(J = 4\) Hz); 2.17 (1H, br d, \(J = 4\) Hz); 2.52 (1H, dd, \(J = 14, 4\) Hz);
\(-\text{CHRR'}\text{OCH}_3\); 3.39 (3H, s, \(-\text{CH}_2\text{OCH}_3\)); 3.39-3.41 (1H, m, \(\text{C}(7)\text{H}\)); 3.50-3.63 (2H, m, \(-\text{CH}_2\text{OCH}_3\)); 5.26 (1H, br s, \(\text{C}(1)\text{H}\)).

\(\text{IR}\) (neat): \(\nu = 2974, 2925, 2870, 2822\) (C-H); 1714 (C=O) cm\(^{-1}\)

\(\text{MS}\): \(m/e(\%)=252\) (M\(^+\), 6.8); 221 (1.9); 220 (21); 189 (3.3); 188 (13); 45 (100).

Reduction of deconjugated enone 94 to give alcohol 95:

A solution of deconjugated enone 94 (0.31 g, 1.2 mmol) in dry \(\text{THF}\) (5.0 mL) was cooled to -78 °C and was cannulated into a slurry of \(\text{LiAlH}_4\) (0.053 g, 1.4 mmol) in dry \(\text{THF}\) (5.0 mL), also at -78 °C and under an \(\text{Ar}\) atm. The mixture was allowed to warm to RT over 2 h, then was cautiously quenched by the addition of water. After dilution with 1 M \(\text{HCl}\), the mixture was extracted with \(\text{Et}_2\text{O}\) (3x) and the combined extracts were washed with water and brine (2x). Drying over \(\text{MgSO}_4\) and removal of the solvent gave the alcohol 95 as a colourless liquid (0.275 g, 89% yield).
C_{15}H_{26}O_{3} \quad \text{Calc. Mass:} \quad 254.1881
\text{Meas. Mass:} \quad 254.1881

^{1}H \text{ NMR (300 MHz, CDCl}_{3}\): \delta=0.80 (3H, s, CH_{3}); 0.98 (3H, s, CH_{3}); 1.15-1.40 (2H, m); 2.00-2.12 (4H, m); 2.20-2.31 (1H, m); 2.50 (1H, br s); 3.34 (3H, s, \text{CHRR'}\text{OCH}_{3}); 3.35 (3H, s, -\text{CH}_{2}\text{OCH}_{3}); 3.36-3.58 (3H, m, -\text{CH}_{2}\text{OCH}_{3} \text{ and } \text{C(7)H}); 3.65 (1H, br t, J=4 \text{ Hz, C(3)H}); 5.26 (1H, br s, C(1)H).

IR (neat): \nu=3436 (br, O-H); 2865 (C-H) cm\(^{-1}\)

MS: m/e(\%)=254 (M\(^{+}\), 0.1); 236 (1.3); 222 (5.4); 204 (8.6); 159 (100); 105 (35); 91 (54).

Conversion of alcohol 95 to cyclopropane 96:

\[
\begin{array}{c}
\text{HO} \\
95
\end{array}
\rightarrow
\begin{array}{c}
\text{HO} \\
96
\end{array}
\]

Cyclopropanation attempt E^{67}:

A slurry of Zn-Cu (0.032 g, 0.50 mmol) and CH\(_2\)Cl\(_2\) (0.040 mL, 0.50 mmol) in dry Et\(_2\)O (1.0 mL) was refluxed under an Ar atm for 20 min. A solution of alcohol 95 (0.061 g, 0.24 mmol) and CH\(_2\)I\(_2\) (0.040 mL, 0.50 mmol) in dry Et\(_2\)O (2.0 mL) was added dropwise. The mixture was refluxed for 5 h, then an additional portion of CH\(_2\)I\(_2\) (0.040 mL, 0.50 mmol) was added. After 30 min at reflux, the reaction mixture was cooled to RT and stirred under an Ar atm overnight. It was then warmed to 50 °C and another portion of CH\(_2\)I\(_2\) (0.040 mL, 0.50 mmol) was added. After 30 min, the reaction was cooled to RT, another portion of Zn-Cu (0.032 g, 0.50 mmol) was added and the mixture was refluxed for 45 min. One last portion of CH\(_2\)I\(_2\) (0.040 mL, 0.50 mol) was added and reflux was continued 5 h. After cooling to RT, 0.5 M HCl was added and the
mixture was extracted with Et$_2$O (3x). The combined extracts were washed with brine, dried over MgSO$_4$ and the solvent removed to give a yellow oil. Purification by column chromatography using 9:1 PE:Et$_2$O as eluant gave a colourless liquid (0.028 g) which was a mixture of 2 compounds as determined by GC. $^1$H NMR (400 MHz, CDCl$_3$) determined this to be a mixture of recovered starting material 95 and a cyclopropyl compound (tentatively assigned structure 96), as indicated by an NMR signal at 0.45 ppm. It was not possible to obtain a pure sample of the cyclopropyl compound.

Cyclopropanation attempt F$^{73,74}$:

To a solution of alcohol 95 (0.127 g, 0.499 mmol) in dry toluene (2.0 mL) and Et$_2$Zn (2.3 mL, 1.1 M/toluene, 2.5 mmol) at 50 °C under an Ar atm was added dropwise CH$_2$I$_2$ (0.20 mL, 2.5 mmol) in dry toluene (2.0 mL). After heating for 30 min, the system was flushed with O$_2$ and heated for a further 1 h. After cooling to RT, 0.5 M HCl was added, and the mixture was extracted with Et$_2$O (3x). The combined extracts were washed with brine (3x) and dried over MgSO$_4$. Removal of the solvent gave a brown oil which was subjected twice more to the above cyclopropanation conditions. After the final work-up, the oil was purified by column chromatography using 9:1 PE:Et$_2$O as eluant. The cyclopropyl compound 96 was isolated as a colourless oil (0.006 g, 4% yield).

C$_{16}$H$_{28}$O$_3$  
Calc. Mass:  268.2038  
Meas. Mass:  268.2029

$^1$H NMR (300 MHz, CDCl$_3$): δ=0.45 (1H, dd, J=4, 11 Hz, cyclopropyl H); 0.67 (1H, m, cyclopropyl H); 0.80 (3H, s, CH$_3$); 0.81-0.82 (1H, m); 0.92 (3H, s, CH$_3$); 0.95-0.99 (1H, m); 1.55 (2H, br m); 1.70-1.80 (1H, m); 1.88 (1H, d, J=14 Hz); 2.01 (1H, dd, J=11, 6 Hz); 2.10-2.20 (1H, m); 3.30 (3H, s, -CHRR'OCH$_3$); 3.32 (3H, s, -CH$_2$OCH$_3$); 3.33-3.42 (3H, m, -CH$_2$OCH$_3$ and C(7)H); 3.76 (1H, m, C(3)H).
MS: m/e(%)=268 (M⁺, 0.7); 250 (2.4); 235 (11); 218 (15); 173 (66); 171 (40); 159 (35);
131 (45); 119 (45); 45 (100).

Conversion of alcohol 87 to silyl ether 106:

![Chemical structure diagram]

To a solution of diketalized alcohol 87 (0.408 g, 1.39 mmol), Et₃N (0.24 mL, 1.7 mmol) and a catalytic amount of DMAP in dry CH₂Cl₂ (20 mL) was added bromomethyldimethylsilyl chloride (0.24 mL, 1.7 mmol) and the mixture was stirred at RT under an Ar atm for 30 min. Water was added and the mixture was extracted with CH₂Cl₂ (3x). The combined extracts were washed with brine (3x) and dried over MgSO₄. Removal of the solvent gave an orange liquid which was purified by column chromatography using 4:1 PE:Et₂O as eluant. The silyl ether 106 was isolated as a colourless liquid (0.46 g, 76% yield).

C₂₀H₃₃O₅Si⁷⁹Br
Calc. Mass: 460.1280
Meas. Mass: 460.1288

C₂₀H₃₃O₅Si⁸¹Br
Calc. Mass: 462.1260
Meas. Mass: 462.1270

¹H NMR (400 MHz, CDCl₃): δ=0.26 (3H, s, -SiCH₃); 0.30 (3H, s, -SiCH₃); 0.88 (3H, s, CH₃); 0.98 (3H, s, CH₃); 1.29 (1H, t, J=13 Hz); 1.70-1.78 (1H, br m); 1.83 (1H, dt, J=12, 4 Hz); 1.99-2.05 (1H, m); 2.17-2.30 (3H, br m); 2.39 (1H, br s); 2.48 (1H, s, -SiCH₂Br); 2.50 (1H, s, -SiCH₂Br); 3.65 (1H, dd, J=10, 8 Hz, -CHHOSi(CH₃)₂CH₂Br); 3.86-4.20 (9H, m, 8 ketal H's and
-CH₂OSi(CH₃)₂CH₂Br); 5.18 (1H, br s, C(1)H).

IR (neat): υ=2970, 2890 (C-H) cm⁻¹

MS: m/e(%)=462, 460 (M⁺, 0.8, 0.7); 419, 417 (6.2, 5.9); 333, 331 (1.6, 1.4); 279 (5.2); 193 (6.9); 165 (8.5); 114 (100); 99 (12).

Reduction of bromosilyl ether 106 to give silyl ether 107:

Radical cyclization attempt A (concentrated conditions):

A solution of bromosilyl ether 106 (0.42 g, 0.91 mmol), Bu₃SnH (0.37 mL, 1.4 mmol) and a catalytic amount of AIBN in dry benzene (10 mL) was refluxed under an Ar atm for 45 min. The solvent was removed and the residue was purified by column chromatography using first PE as eluant, then gradually increasing the polarity until the eluant was 4:1 PE:Et₂O. A colourless liquid was isolated, which was not the desired cyclization product, but which was determined to be the trimethylsilyl ether 107 (0.235 g, 67% yield) resulting from radical reduction of the bromide 106.

¹H NMR (400 MHz, CDCl₃): δ=0.10 (9H, s, -Si(CH₃)₃); 0.88 (3H, s, CH₃); 0.98 (3H, s, CH₃); 1.19-1.30 (2H, m); 1.83 (1H, dt, J=12, 4 Hz); 2.03 (1H, dt, J=12, 4 Hz); 2.17-2.28 (3H, br m); 2.37 (1H, br s); 3.55 (1H, dd, J=10, 8 Hz, -CHHOTMS); 3.86-4.00 (9H, m, 8 ketal H's and -CHHOTMS); 5.18 (1H, br s, C(1)H).

IR (neat): υ=2950, 2890 (C-H) cm⁻¹
A small sample of 107 was treated with TBAF in THF. The product, as expected, was the diketalized alcohol 87, showing spectral characteristics identical to the previously prepared product.

Radical cyclization attempt B (dilute conditions):

A solution of Bu3SnH (0.27 mL, 0.99 mmol) and a catalytic amount AIBN in dry benzene (10 mL) was added dropwise over 7 h to a refluxing solution of silyl ether 106 (0.46 g, 0.99 mmol) in dry benzene (20 mL) under an Ar atm. The solvent was removed and the residue was purified by column chromatography using 9:1 PE:Et2O as eluant. As before, no cyclization product was obtained, only the trimethylsilyl ether reduction product 107 as a colourless liquid (0.30 g, 79% yield).

De-protection of acetate 85 to give alcohol 122:

To a solution of acetate 85 (2.90 g, 9.4 mmol) in MeOH (40 mL) was added a solution of KOH (1.58 g, 28 mmol) in water (40 mL). After stirring at RT for 30 min, the reaction was diluted with water and extracted with Et2O (3x). The combined extracts were washed with brine (2x) and dried over MgSO4. Removal of the solvent yielded the alcohol 122 as a pale yellow oil (2.16 g, 86% yield). A small amount could be crystallized from Et2O for microanalysis.

mp: 149-151 °C

C15H22O4  Calc. Mass:  266.1518
            Meas. Mass:  266.1524
Calc. C 67.64     H 8.32 %  
Anal. C 67.70     H 8.25 %  

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$=1.08 (3H, s, CH$_3$); 1.12-1.30 (4H, m); 1.40 (1H, t, J=12 Hz); 1.60 (1H, d, J=12 Hz); 1.72 (1H, d, J=12 Hz); 2.02 (1H, d, J=12 Hz); 2.15 (1H, br s); 3.15 (1H, br s, C(10)H); 3.68-3.82 (2H, m, -CH$_2$OH); 3.93 (4H, s, ketal H's); 6.00 (1H, dd, J=11, 3 Hz, C(2)H); 6.23 (1H, d, J=11 Hz, C(1)H).

IR (neat): $\nu$=3400 (br, O-H); 2980, 2900 (C-H); 1670 C=O) cm$^{-1}$

MS: m/e(%)=266 (M$^+$, 15); 140 (24); 129 (100); 86 (25).

Conversion of alcohol 122 to silyl ether 123:

![Diagram of conversion](image)

A solution of alcohol 122 (0.617 g, 2.32 mmol), Et$_3$N (0.50 mL, 3.5 mmol), bromomethyldimethylsilyl chloride (0.40 mL, 2.5 mmol) and a catalytic amount DMAP in dry CH$_2$Cl$_2$ (20 mL) was stirred under an Ar atm for 30 min. Water was added and the mixture was extracted with CH$_2$Cl$_2$ (3x). The combined extracts were washed with brine (3x) and dried over MgSO$_4$. Removal of the solvent gave a yellow liquid which was purified by column chromatography using 1:1 PE:Et$_2$O as eluant. The silyl ether 123 was isolated as a colourless liquid (0.96 g, 100% yield).

C$_{18}$H$_{29}$O$_4$Si$^{79}$Br    Calc. Mass: 416.1018  
Meas. Mass: 416.1018
C\textsubscript{18}H\textsubscript{29}O\textsubscript{4}Si\textsuperscript{81}Br \quad \text{Calc. Mass: 418.0998} \\
\quad \text{Meas. Mass: 418.0995}

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \delta=0.29 (6H, s, -Si(CH\textsubscript{3})\textsubscript{2}); 1.08 (3H, s, CH\textsubscript{3}); 1.22 (3H, s, CH\textsubscript{3}); 1.39 (1H, t, J=13 Hz); 1.45 (1H, br m); 1.55-1.70 (2H, m); 2.00-2.05 (1H, m); 2.16 (1H, br m); 2.50 (2H, m, -CH\textsubscript{2}OSiMe\textsubscript{2}CH\textsubscript{2}Br); 3.16 (1H, br s, C(10)H); 3.71-3.80 (2H, m, -CH\textsubscript{2}OSiMe\textsubscript{2}CH\textsubscript{2}Br); 3.92-3.98 (4H, m, ketal H's); 6.00 (1H, dd, J=11, 3 Hz, C(2)H); 6.75 (1H, br d, J=11 Hz, C(1)H).

IR (neat): v=2960, 2890 (C-H); 1675 (C=O) cm\textsuperscript{-1}

MS: m/e(%)=418, 416 (M\textsuperscript{+}, 8.4, 7.6); 281, 279 (100, 99); 235 (70); 165 (65); 140 (81); 99 (64); 86 (72).

Conversion of silyl ether 123 to alcohol 122:

\[
\begin{align*}
\text{Br} & \quad \text{Si} \\
\text{H} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{OH} \\
\text{H} & \quad \text{OH} \\
\end{align*}
\]

\[
\begin{align*}
\text{123} & \quad \rightarrow \\
\text{122} & \\
\end{align*}
\]

\gamma-Alkylation attempt A:

A solution of LDA was prepared by adding n-BuLi (1.7 mL, 1.6 M/hexane, 2.5 mmol) to a solution of diisopropylamine (0.35 mL, 2.5 mmol) in dry THF (10 mL) at -78 °C under an Ar atm. After 15 min, the solution was stirred at 0 °C for 15 min and then re-cooled to -78 °C. A solution of silyl ether 123 (0.96 g, 2.3 mmol) in dry THF (20 mL) was added. The yellow mixture was stirred at -78 °C for 4 h, allowed to warm gradually to RT and stirred overnight. Water was added and the mixture was extracted with Et\textsubscript{2}O (3x). The combined extracts were washed with brine (3x) and dried over MgSO\textsubscript{4}. Removal of the solvent gave a red liquid which was purified by column
chromatography using 2:1 Et$_2$O:PE as eluant. A colourless liquid (0.207 g, 34% yield) was isolated and was determined to be the alcohol 122 resulting from silyl ether cleavage. Spectral characteristics were identical to those of the alcohol 122 prepared previously. None of the other side-products isolated were the desired γ-alkylation product, as determined by $^1$H NMR, IR, and MS.

γ-Alkylation attempt B:

To a solution of silyl ether 123 (0.15 g, 0.36 mmol) in dry THF (20 mL) under an Ar atm was added KH (0.022 g, 0.55 mmol). The mixture was stirred at RT overnight. Water was added and the mixture was extracted with Et$_2$O (3x). The combined extracts were washed with 1 M HCl and brine (3x) and dried over MgSO$_4$. Removal of the solvent gave a yellow liquid which was a complex mixture by GC and TLC. Purification by column chromatography using 2:1 PE:Et$_2$O as eluant gave the alcohol 122 resulting from silyl ether cleavage as a colourless liquid (0.021 g, 22% yield). Spectral characteristics were identical to the alcohol 122 prepared previously. None of the other side-products isolated were the desired γ-alkylation product as determined by $^1$H NMR and MS.

Protection of alkene diol 64 to give silyl alcohol 128:

To a solution of alkene diol 64 (4.47 g, 21.4 mmol) in dry DMF (~100 mL) under an Ar atm were added successively TBDMSCI (3.85 g, 25.6 mmol) and imidazole (2.18 g, 32.1 mmol). After stirring at RT overnight, the reaction was diluted with water, extracted with Et$_2$O (3x) and the combined extracts washed with brine (3x). After drying
over MgSO₄ and removal of the solvent, a yellow oil was isolated which was purified by column chromatography using 4:1 PE:Et₂O as eluant. The silyl alcohol 128 was isolated as a white solid (6.66 g, 97% yield).

mp (sealed tube): 108-110 °C

\[ C_{19}H_{34}O_2Si \quad \text{Calc. Mass:} \quad 322.2328 \]
\[ \text{Meas. Mass:} \quad 322.2334 \]

Calc.  C 70.75  H 10.62 %
Anal.  C 70.36  H 10.55 %

\(^1\text{H NMR (400 MHz, CDCl}_3\): \( \delta = 0.04 \) (6H, s, -Si(CH₃)₂); 0.89 (9H, s, t-Bu); 0.92 (6H, s, 2x CH₃); 1.16 (3H, s, CH₃); 1.60 (1H, d, J=12 Hz, C(3) \text{ endo H}); 2.13 (1H, dd, J=12, 3 Hz, C(3) \text{ exo H}); 2.40 (1H, br t, J=3 Hz, C(4)H); 4.16 (2H, d, J=3 Hz, -CH₂OTBDMS); 5.55-5.70 (3H, m, C(6)H and trans vinyl H's); 5.98 (1H, dd, J=6, 3 Hz, C(5)H).

IR (CHCl₃): \( \nu = 3610 \) (O-H); 3010, 2950, 2930, 2870 (C-H) cm\(^{-1}\)

MS: m/e (%)=265 (M\(^+\)-t-Bu, 5.9); 177 (17); 108 (100); 93 (29); 75 (26).

Anionic oxy-Cope rearrangement of silyl alcohol 128 to give ketone 129:

To a solution of silyl alcohol 128 in dry THF (5.0 mL) under an Ar atm was added dropwise n-BuLi (0.16 mL, 1.6 M/hexanes, 0.26 mmol). The resulting yellow
solution was warmed to 40 °C for 15 min then water was added. The mixture was extracted with Et₂O (3x) and the combined extracts were washed with brine (3x), dried over MgSO₄, and the solvent removed to give a yellow liquid. Purification by column chromatography using 9:1 PE:Et₂O as eluant gave ketone 129 as a pale yellow liquid (0.040 g, 73% yield).

C₁₉H₃₄O₂Si  Calc. Mass: 322.2328  
Meas. Mass: 322.2325

¹H NMR (400 MHz, CDCl₃): δ=0.05 (6H, s, Si(CH₃)₂); 0.90 (9H, s, t-Bu); 0.92 (3H, s, CH₃); 1.02 (3H, s, CH₃); 1.61 (3H, br s, vinyl CH₃); 2.01 (1H, dd, J=16, 12 Hz); 2.22-2.40 (4H, m); 2.47 (1H, m); 3.22 (1H, br s, C(5)H); 3.59 (1H, dd, J=10, 6 Hz, -CHHOTBDMS); 3.67 (1H, dd, J=10, 7 Hz, -CHHOTBDMS); 5.19 (1H, br s, vinyl H).

IR (neat): v=2940, 2910, 2890, 2840 (C-H); 1715 (C=O) cm⁻¹

MS: m/e(%)=265 (M⁺-t-Bu, 59); 173 (30); 157 (25); 143 (41); 131 (40); 105 (42); 75 (100); 59 (35); 41 (53).

Reduction of ketone 129 to give alcohol 130:

To a solution of ketone 129 (3.51 g, 10.8 mmol) in dry THF (70 mL) at -78 °C under an Ar atm was added dropwise L-Selectride® (21.6 mL, 1 M/THF, 21.6 mmol). After stirring at -78 °C for 1.5 h, NaOH (5.4 mL, 3 M, 16.2 mmol) was cautiously added, followed by H₂O₂ (27 mL, 30%). The mixture was allowed to warm to RT and was
diluted with water. After saturation with K$_2$CO$_3$, the mixture was extracted with Et$_2$O (4x) and the combined extracts were dried over MgSO$_4$. Removal of the solvent gave a pale yellow oil which was purified by column chromatography using 15:1 PE:Et$_2$O as eluant. Some starting material 129 (0.26 g, 7% yield) was recovered along with the alcohol 130 (2.73 g, 78% yield) as a colourless oil.

C$_{19}$H$_{36}$O$_2$Si  
\text{Calc. Mass: 324.2484}  
\text{Meas. Mass: 324.2486}  
\text{Calc.: C 70.31 \quad H 11.18 \%}  
\text{Anal.: C 70.25 \quad H 11.31 \%}  

$^1$H NMR (400 MHz, CDCl$_3$): \( \delta=0.06 \) (6H, s, -Si(CH$_3$)$_2$); 0.90 (9H, s, t-Bu); 0.94 (3H, s, CH$_3$); 0.98 (3H, s, CH$_3$); 1.03-1.18 (2H, m); 1.30-1.42 (1H, m); 1.58 (3H, dd, J=3, 1.5 Hz, vinyl CH$_3$); 1.67 (1H, br d, J=13 Hz); 2.02-2.10 (1H, m); 2.11-2.21 (1H, m); 3.01 (1H, br s, C(10)H); 3.56 (1H, dd, J=10, 7 Hz, -CHHOTBDMS); 3.63 (1H, dd, J=10, 6 Hz, -CHHOTBDMS); 4.12 (1H, br s, C(7)H); 5.19 (1H, s, vinyl H).

IR (neat): \( \nu=3380 \) (br, O-H); 3040, 2930, 2740 (C-H) cm$^{-1}$

MS: m/e(%)=267 (M$^+$/t-Bu, 22); 249 (20); 192 (100); 175 (74); 159 (75); 135 (61); 105 (66); 75 (90); 73 (73).

Protection of alcohol 130 to give methyl ether 131:
A solution of alcohol 130 (1.62 g, 5.0 mmol) in dry THF (40 mL) was cannulated into a slurry of KH (0.30 g, 7.5 mmol) in dry THF (20 mL) under an Ar atm. After stirring at RT for 1.5 h, MeI (0.50 mL, 7.5 mmol) was passed through basic alumina directly into the reaction mixture. After stirring overnight, NH₄Cl(aq) solution was cautiously added and the reaction was extracted with Et₂O (3x). The combined organic extracts were washed with brine (3x) and dried over MgSO₄. Removal of the solvent gave a yellow liquid which was purified by column chromatography using 24:1 PE:Et₂O as eluant. The methyl ether 131 was obtained as a colourless liquid (1.60 g, 95% yield).

C₂₀H₃₈O₂Si  Calc. Mass: 338.2641
Meas. Mass: 338.2644

¹H NMR (400 MHz, CDCl₃): δ=0.05 (6H, s, -Si(CH₃)₂); 0.90 (9H, s, t-Bu); 0.91 (3H, s, CH₃); 0.98 (3H, s, CH₃); 1.20-1.30 (2H, m); 1.57 (3H, br s, vinyl CH₃); 1.69 (1H, br d, J=12 Hz); 1.86 (1H, br d, J=12 Hz); 1.98-2.10 (2H, m); 2.97 (1H, br s, C(10)H); 3.29 (3H, s, -OCH₃); 3.50-3.63 (3H, m, -CH₂OTBDMS and C(7)H); 5.19, (1H, br s, vinyl H).

IR (neat): v=2960, 2940, 2860 (C-H) cm⁻¹

MS: m/e(%)=338 (M⁺, 17); 281 (52); 249 (64); 206 (100); 193 (79); 175 (87); 159 (87); 148 (69); 134 (73); 122 (68); 119 (75); 89 (93).

Ring expansion of alkene 131 to give enone 132:
A solution of alkene 131 (0.836 g, 2.46 mmol) in CH₂Cl₂ (20 mL) and MeOH (20 mL) was cooled to -78 °C and O₃ was bubbled through until a blue colour persisted (~30 min). Excess O₃ was removed by bubbling O₂ through the solution until it became colourless. The mixture was poured onto Zn (4.84 g, 74.0 mmol), HOAc (7.0 mL, 0.12 mol) was added and the reaction mixture was stirred at RT for 1.25 h. The mixture was filtered, washed successively with water (2x), 5% NaOH(aq) solution (2x), water (4x, until neutral) and dried over MgSO₄. Removal of the solvent gave the crude keto-aldehyde as a yellow oil which was not purified but which was immediately dissolved in dry benzene (~50 mL). A catalytic amount of p-TsOH·H₂O was added, and the solution was refluxed under an Ar atm in a Dean-Stark apparatus for 3 h. After cooling to RT, the mixture was poured onto brine and extracted with Et₂O (3x). The combined extracts were washed with NaHCO₃(aq) solution, brine (3x) and dried over MgSO₄. Removal of the solvent gave a yellow oil which was purified by column chromatography using 9:1 PE:Et₂O as eluant. The enone 132 was obtained as a colourless liquid (0.244 g, 28% yield).

¹H NMR (400 MHz, CDCl₃): δ=0.08 (6H, s, Si(CH₃)₂); 0.90 (9H, s, t-Bu); 0.96-1.08 (2H, m); 1.10 (3H, s, CH₃); 1.21 (3H, s, CH₃); 1.76 (1H, br d, J=12 Hz); 1.92 (1H, br d, J=14 Hz); 2.04 (1H, br d, J=12 Hz); 2.20 (1H, br m); 3.18 (1H, br s, C(10)H); 3.29 (3H, s, -OCH₃); 3.53 (1H, t, J=3 Hz, C(7)H); 3.66 (2H, d, J=8 Hz, -CH₂OTBDMS); 5.97 (1H, dd, J=3, 10 Hz, C(2)H); 6.78 (1H, dt, J=10, 1.5 Hz, C(1)H).

IR (neat): ν=2950, 2870 (C-H); 1680 (C=O) cm⁻¹

MS: m/e(%)=295 (M⁺-t-Bu, 31); 265 (28); 189 (61); 161 (30); 147 (30); 119 (71); 105 (27); 91 (36); 89 (100).
Protection of enone 132 to give ketal 133:

A solution of enone 132 (0.244 g, 0.69 mmol), ethylene glycol (0.38 mL, 6.9 mmol) and a catalytic amount of p-TsOH•H2O in dry benzene (~50 mL) was refluxed under an Ar atm in a Dean-Stark apparatus for 24 h. After cooling to RT, the mixture was poured onto brine and extracted with Et2O (3x). The combined extracts were washed with NaHCO3(aq) solution and brine (3x). Drying over MgSO4 and removal of the solvent gave a yellow oil which was purified by column chromatography using 15:1 PE:Et2O as eluant. The ketal 133 was isolated as a colourless liquid (0.068 g, 25% yield).

C22H40O4Si Calc. Mass: 396.2695  
Meas. Mass: 396.2701

1H NMR (400 MHz CDCl3): δ=0.05 (6H, s, Si(CH3)2); 0.88 (9H, s, t-Bu); 0.89-0.91 (4H, m); 0.98 (3H, s, CH3); 1.12 (1H, td, J=12, 4 Hz); 1.20-1.30 (1H, m); 2.06 (1H, br d, J=12 Hz); 2.17 (1H, br s); 2.27 (1H, br d, J=12 Hz); 2.40 (1H, br s); 3.23 (3H, s, -OCH3); 3.56 (1H, t, J=8 Hz); 3.66 (1H, br s, C(7)H); 3.83-3.96 (6H, m, -CH3OTBDMS and ketal H's); 5.10 (1H, br s, C(1)H).

IR (neat): ν=2950, 2900 (C-H) cm⁻¹

MS: m/e(%)=396 (M⁺, 8.0); 353 (27); 339 (52); 251 (37); 171 (43); 119 (28); 115 (33); 114 (100); 99 (48).
Hydrolysis of ketal 133 to give deconjugated enone 134:

A solution of ketal 133 (0.062 g, 0.156 mmol) in 1 M HCl (2.0 mL) and acetone (2.0 mL) was heated to 70 °C for 30 min. After cooling to RT, water was added and the mixture was extracted with Et2O (3x). The combined extracts were washed with brine (3x) and dried over MgSO4. Removal of the solvent gave the keto-alcohol 134 as a colourless liquid (0.036 g, 97% yield) which was not purified but was used directly in the next reaction.

C_{14}H_{22}O_3  
Calc. Mass: 238.1568  
Meas. Mass: 238.1567

^1H NMR (400 MHz, CDCl3): δ=0.93 (3H, s, CH3); 1.05 (3H, s, CH3); 1.13 (2H, m); 2.17 (2H, br d, J=12 Hz); 2.53 (1H, dd, J=16, 4 Hz); 2.56 (1H, br s); 2.77 (1H, dd, J=20, 4 Hz, C(2)H); 3.12 (1H, dt, J=20, 2 Hz, C(2)H); 3.34 (3H, s, -OCH3); 3.68 (1H, dd, J=11, 4 Hz, -CHOH); 3.84 (1H, dd, J=11, 7 Hz, -CHHOH); 5.32 (1H, br s, C(1)H).

IR (neat): v=3400 (br, O-H); 2970, 2940, 2890 (C-H); 1715 (C=O) cm\(^{-1}\)

MS: m/e(%)=238 (M\(^+\), 14); 220 (48); 206 (50); 175 (88); 145 (65); 119 (91); 117 (48); 107 (50); 105 (93); 91 (100).
Protection of alcohol 134 to give silyl ether 135:

To a solution of alcohol 134 (0.036 g, 0.15 mmol) in dry DMF (1.0 mL) was added imidazole (0.021 g, 0.31 mmol) and TBDMSCl (0.035 g, 0.23 mmol) and the mixture was stirred under an Ar atm at RT overnight. Water was added, the mixture was extracted with Et2O (3x) and the combined extracts were washed with NH4Cl(aq) solution and brine (3x). Drying over MgSO4 and removal of the solvent gave the silyl ether 135 as a pale yellow oil (0.050 g, 95% yield) which was not purified but which was used directly in the next reaction.

C20H36O3Si  Calc. Mass: 352.2433
               Meas. Mass: 352.2428

1H NMR (400 MHz, CDCl3): δ=0.02 (3H, s, SiCH3); 0.06 (3H, s, SiCH3); 0.90 (9H, s, t-Bu); 0.93 (3H, s, CH3); 1.04 (3H, s, CH3); 1.06-1.18 (2H, m); 2.13 (1H, dq, J=13, 3 Hz); 2.26 (1H, dq, J=13, 3 Hz); 2.43 (1H, br s); 2.51 (1H, dd, J=13, 4 Hz); 2.73 (1H, dd, J=20, 4 Hz, C(2)H); 3.07 (1H, dt, J=20, 3 Hz, C(2)H); 3.33 (3H, s, -OCH3); 3.56-3.63 (2H, m, C(7)H and -CHHOTBDMS); 3.81 (1H, dd, J=11, 6 Hz, -CHHOTBDMS); 5.23 (1H, br s, C(1)H).

IR (neat): ν=2950, 2850 (C-H); 1715 (C=O) cm⁻¹

MS: m/e(%)=295 (M⁺- t-Bu, 33); 263 (54); 237 (42); 171 (71); 89 (100); 75 (97); 73 (94).
Vinyl addition to ketone 135 to give alcohol 136:

Preparation A:

To flame-dried Mg (0.055 g, 2.3 mmol) in a 3-necked, 25 mL round bottomed flask equipped with an addition funnel and condenser and kept under an Ar atm was added dry THF (5.0 mL) and a crystal of I2. A solution of vinyl bromide (0.13 mL, 1.9 mmol) in dry THF (1.0 mL) was added dropwise via the addition funnel to initiate the Grignard reaction, then at a rate to maintain reflux. After refluxing for a further 5 min after the addition was complete, the reaction mixture was cooled to RT and a solution of ketone 135 (0.135 g, 3.83 mmol) was added. The mixture was refluxed for 1 h, cooled to RT and NH₄Cl(aq) solution was cautiously added. The mixture was extracted with Et₂O (3x) and the combined extracts were washed with brine (3x) and dried over MgSO₄. Removal of the solvent gave a yellow oil which was purified by column chromatography using 4:1 PE:Et₂O as eluant. The alcohol 136 was isolated as a white solid (0.082 g, 57% yield).

C₂₂H₄₀O₃Si  Calc. Mass:  380.2746
                      Meas. Mass:  380.2750

¹H NMR (400 MHz, CDCl₃):  δ=0.05 (6H, s, Si(CH₃)₂); 0.90 (16 H, br s, t-Bu and 2x CH₃); 1.08-1.17 (2H, m); 2.10 (2H, br d, J=12 Hz); 2.15 (1H, br s); 2.25 (1H, br d, J=12 Hz); 2.66 (1H, br s, C(9)H); 3.33 (3H, s, –OCH₃); 3.57 (1H, dd, J=10,
8 Hz, -CHHOTBDMS); 3.68 (1H, t, J=3 Hz, C(7)H); 3.88 (1H, dd, J=10, 6 Hz, -CHHOTBDMS); 5.11 (1H, dd, J=11, 1.5 Hz, vinyl H \textit{cis} to -CH=CH2); 5.20 (1H, br s, C(1)H); 5.30 (1H, dd, J=17, 1.5 Hz, vinyl H, \textit{trans} to -CH=CH2); 6.09 (1H, dd, J=17, 11 Hz, -CH=CH2).

IR (CHCl3): \nu=3630 (br, O-H); 3030; 2950; 2870 (C-H) cm\textsuperscript{-1}

MS: m/e(%)=380 (M+, 0.6); 323 (61); 291 (26); 273 (31); 231 (34); 199 (71); 185 (47); 157 (57); 143 (53); 119 (50); 105 (63); 91 (48); 89 (99); 75 (100); 73 (98).

Preparation B\textsuperscript{91}:

To CeCl\textsubscript{3}·7H\textsubscript{2}O (0.87 g, 2.34 mmol) which was dried at 140 °C under vacuum for 2 h was added dry THF (20 mL) and the slurry was kept under an Ar atm and cooled to 0 °C. A solution of vinylmagnesium bromide, prepared as described above by the addition of vinyl bromide (0.16 mL, 2.34 mmol) in dry THF (5.0 mL) to flame-dried Mg (0.057 g, 2.34 mmol) and a crystal of I\textsubscript{2} in dry THF (15 mL), was added dropwise to the slurry. A solution of ketone 135 (0.552 g, 1.56 mmol) in dry THF (10 mL) was added and the mixture was allowed to warm to RT overnight. Water (20 mL) and HOAc (1.0 mL) were added and the mixture was extracted with Et\textsubscript{2}O (3x). The combined extracts were washed successively with brine, NaHCO\textsubscript{3}(aq) solution and brine. After drying over MgSO\textsubscript{4}, removal of the solvent gave a yellow oil which was purified by column chromatography using 15:1 PE:Et\textsubscript{2}O as eluant. Starting material 135 (0.032 g, 6% yield) and the desired alcohol 136 (6% yield) were isolated and showed spectral characteristics as described previously.
Conversion of alcohol 136 to diol 137:

Anionic oxy-Cope rearrangement attempt A:

To a slurry of KH (0.0032 g, 0.079 mmol) in dry THF (1.0 mL) under an Ar atm was added alcohol 136 (0.0060 g, 0.016 mmol) in dry THF (1.0 mL). The mixture was stirred at RT for 1 h, then 18-crown-6 (0.028 g, 0.079 mmol) was added. After refluxing for 12 h, the mixture was cooled to RT and water was cautiously added. The mixture was extracted with Et2O (3×) and the combined extracts were washed with brine (3×). After drying over MgSO4, removal of the solvent gave a brown-yellow solid which was purified by column chromatography using 1:1 PE:Et2O as eluant. A colourless liquid (0.004 g, 16% yield) was isolated which was not the desired anionic oxy-Cope rearrangement product, but which was identified as the diol 137 resulting from silyl ether cleavage.

C16H2603  
Calc. Mass: 266.1881  
Meas. Mass: 266.1887

1H NMR (400 MHz, CDCl3): δ=0.86 (3H, s, CH3); 0.87 (3H, s, CH3); 1.20-1.40 (3H, m); 1.50 (1H, br t, J=10 Hz); 2.06 (4H, m); 2.16 (1H, br s); 2.40 (1H, br s, C(5)H); 3.30 (3H, s, -OCH3); 3.65 (1H, t, J=3 Hz, C(7)H); 3.71 (1H, dd, J=12, 7 Hz, -CHHOH); 3.79 (1H, dd, J=12, 7 Hz, -CHHOH); 5.08 (1H, dd, J=11, 1.5 Hz, vinyl H cis to -CH=CH2); 5.26 (1H, dd, J=17, 1.5 Hz, vinyl H trans to -CH=CH2); 5.30 (1H, br s, C(1)H); 6.04 (1H, dd, J=17, 11 Hz, -CH=CH2).

IR (CHCl3): ν=3620 (br, O-H); 2940 (C-H) cm⁻¹
Anionic oxy-Cope rearrangement attempt B:

To a solution of 18-cr-6 (0.034 g, 0.13 mmol) in dry THF (0.50 mL) under an Ar atm was added KHMDS (0.33 mL, 0.39 M/THF, 0.13 mmol). A solution of alcohol 136 (0.044 g, 0.11 mmol) in dry THF (1.0 mL) was added, and the solution was stirred at RT for 21 h. NH₄Cl(aq) solution was added and the mixture was extracted with Et₂O (3x). The combined extracts were washed with 1 M HCl and brine (3x). Drying over MgSO₄ and removal of the solvent gave a yellow gum. Purification by column chromatography using 2:1 PE:Et₂O as eluant gave a pale yellow liquid (0.030 g, 98% yield) which was not the desired anionic oxy-Cope product, but which was identified as the diol 137 resulting from silyl ether cleavage as before. Spectral characteristics of the diol 137 were identical to those described above.

Protection of alcohol 137 to give methyl ether 138:

To a slurry of KH (0.012 g, 0.30 mmol) in dry THF (1.0 mL) under an Ar atm and at 0 °C was added a solution of diol 137 (0.040 g, 0.15 mmol) in dry THF (2.0 mL).

After 30 min, Mel (0.010 mL, 0.15 mmol) was added. After a further 20 min at 0 °C, NH₄Cl(aq) solution was added and the mixture was extracted with Et₂O (3x). The combined extracts were washed with brine (3x) and dried over MgSO₄. Removal of the solvent gave an orange oil which was purified by column chromatography using 9:1
PE: Et\(_2\)O as eluant. The dimethyl ether \(138\) was isolated as a white solid (0.0050 g, 12% yield).

\[
C_{17}H_{28}O_3 \quad \text{Calc. Mass: 280.2038} \\
\text{Meas. Mass: 280.2034}
\]

\(^1\)H NMR (400 MHz, CDCl\(_3\)):
- \(\delta=0.90\) (6H, br s, 2x CH\(_3\))
- \(1.24\) (1H, d, J=2 Hz, C(8)H)
- \(1.28\) (1H, d, J=3 Hz, C(8)H)
- \(1.58\) (1H, m, C(5)H)
- \(2.11\) (3H, m, 2x C(6)H and C(2)H)
- \(2.19\) (1H, br s, C(2)H)
- \(2.51\) (1H, br s, C(9)H)
- \(3.34\) (3H, s, -OCH\(_3\))
- \(3.35\) (3H, s, -OCR\(_3\))
- \(3.45\) (1H, dd, J=10, 6 Hz, -CHOCH\(_3\))
- \(3.57\) (1H, dd, J=10, 6 Hz, -CHOCH\(_3\))
- \(3.67\) (1H, t, J=3 Hz, C(7)H)
- \(5.11\) (1H, dd, J=11, 1.5 Hz, vinyl H \text{cis} to -CH=CH\(_2\))
- \(5.27\) (1H, br s, C(1)H)
- \(5.30\) (1H, dd, J=17, 1.5 Hz, vinyl H \text{trans} to -CH=CH\(_2\))
- \(6.09\) (1H, dd, J=17, 11 Hz, -CH=CH\(_2\)).

IR (CHCl\(_3\)):
- \(\nu=3620\) (br, O-H)
- \(2940, 2890\) (C-H) cm\(^{-1}\)

MS:
- \(m/e(\%)=280\) (M\(^+\), 1.4)
- \(230\) (13)
- \(185\) (89)
- \(183\) (35)
- \(143\) (35)
- \(133\) (41)
- \(119\) (31)
- \(105\) (61)
- \(98\) (100)
- \(91\) (69)
- \(45\) (71).

Anionic oxy-Cope rearrangement attempt of alcohol \(138\):

To a slurry of KH (0.0014 g, 0.036 mmol) in dry xylenes (0.5 mL) was added a solution of alcohol \(138\) (0.0050 g, 0.018 mmol) and 18-cr-6 (0.0094 g, 0.036 mmol). The mixture was refluxed under an Ar atm for 23 h, then another portion of KH (0.0014 g, 0.036 mmol) and 18-cr-6 (0.0094 g, 0.036 mmol) was added. After another 5 h at reflux,
third portion of KH (0.0014 g, 0.036 mmol) and 18-cr-6 (0.0094 g, 0.036 mmol) was added and reflux was continued for another 21 h. The mixture was cooled to RT, water was cautiously added, and the mixture was extracted with Et2O (3x). The combined extracts were washed with brine (3x), dried over MgSO4 and the solvent removed to yield a yellow solid. Purification by column chromatography using 9:1 PE:Et2O as eluant gave a white solid (0.0049 g, 98% recovery) which was determined to be starting material 138.

Protection of alcohol 64 to give methyl ether 152:

\[
\begin{align*}
64 & \quad \text{OH} \\
& \quad \text{OH} \\
152 & \quad \text{OCH}_3
\end{align*}
\]

To a slurry of KH (0.96 g, 24 mmol) in dry THF (30 mL) at 0 °C under an Ar atm was added a solution of diol 64 (2.53 g, 12.1 mmol) in dry THF (30 mL) also cooled to 0 °C. After 15 min, Mel (0.76 mL, 12 mmol) was passed through basic alumina directly into the reaction mixture. After another 45 min at 0 °C, NH4Cl(aq) solution was cautiously added and the mixture was extracted with Et2O (3x). The combined extracts were washed with brine (3x) and dried over MgSO4. Removal of the solvent gave a yellow liquid which was purified by column chromatography using 4:1 PE:Et2O as eluant. The methyl ether 152 was isolated as pale yellow liquid (1.67 g, 63% yield).

C14H22O2  Calc. Mass: 222.1619  
Meas. Mass: 222.1629

\[^{1}H\text{ NMR (400 MHz, CDCl}_3): \delta=0.94 (6H, s, 2x CH}_3); 1.20 (3H, s, CH}_3); 1.58 (1H, s, exchanges with D2O, -OH); 1.63 (1H, d, J=13 Hz, C(3) endo H); 2.17 (1H, dd, J=13, 3.5 Hz, C(3) exp H); 2.43 (1H, t, J=3 Hz, C(4)H); 3.32 (3H, s, -OCH}_3); 3.91
(2H, d, J=4 Hz, -CH$_2$OCH$_3$); 5.64 (1H, d, J=6 Hz, C(6)H); 5.71 (2H, m, trans vinyl H's); 6.03 (1H, dd, J=6, 3 Hz, C(5)H).

IR (neat): $\nu$=3450 (O-H); 2950, 2870 (C-H) cm$^{-1}$

MS: m/e(%)=222 (M$^+$, 1.2); 204 (20); 186 (31); 171 (34); 161 (100); 145 (35); 129 (79); 108 (91); 91 (77).

Anionic oxy-Cope rearrangement of methyl ether 152 to give ketone 157:

A solution of alcohol 152 (0.24 g, 1.1 mmol) in dry THF (6.0 mL) was cannulated into a slurry of KH (0.051 g, 1.3 mmol) in dry THF (10 mL) under an Ar atm. The mixture was warmed to 40 °C for 20 min (at which point rearrangement had occurred, as indicated by TLC and GC), then cooled to -78 °C. Mel (0.66 mL, 11 mmol) was passed through basic alumina, dissolved in dry THF (1.0 mL), cooled to -78 °C and the solution was added to the reaction mixture. After warming to RT overnight, NH$_4$Cl(aq) solution was cautiously added and the mixture was extracted with Et$_2$O (3x). The combined extracts were washed with brine (3x) and dried over MgSO$_4$. Removal of the solvent gave a yellow oil which was purified by radial chromatography (1 mm plate) using 2:1 PE:Et$_2$O as eluant. The ketone 157 was isolated as a pale yellow oil (0.23 g, 92% yield).

C$_{15}$H$_{24}$O$_2$  Calc. Mass:  236.1776
Meas. Mass:  236.1770
\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 0.97\) (3H, s, CH\(_3\)); 1.06 (3H, s, CH\(_3\)); 1.19 (3H, d, J=8 Hz, C(6)CH\(_3\)); 1.64 (3H, m, vinyl CH\(_3\)); 2.09-2.18 (2H, m); 2.37 (1H, ddd, J=16, 4, 1 Hz, C(8)H); 2.33-2.48 (2H, m); 3.18 (1H, br s, C(10)H); 3.29 (1H, dd, J=9, 7 Hz, -CHHOCH\(_3\)); 3.26 (3H, s, -OCH\(_3\)); 3.41 (1H, dd, J=9, 7 Hz, -CHHOCH\(_3\)); 5.20 (1H, br s, vinyl H).

IR (neat): \(\nu = 2950\) (C-H); 1705 (C=O) cm\(^{-1}\)

MS: m/e(%)=236 (M\(^+\), 0.7); 204 (40); 189 (23); 161 (19); 148 (22); 133 (20); 121 (27); 108 (19); 45 (23).

Reduction of ketone 157 to give alcohol 158:

To a solution of ketone 157 (1.88 g, 7.98 mmol) in dry THF (40 mL) at -78 °C under an Ar atm was added dropwise L-Selectride® (16 mL, 1 MfTHF, 16 mmol). The solution was stirred at -78 °C for 1 h, then 3 M Na\(_2\)OH\(_{aq}\) solution (4.2 mL) was cautiously added followed by H\(_2\)O\(_2\) (21 mL, 30%). After warming to RT, water (40 mL) was added and the aqueous layer was saturated with K\(_2\)CO\(_3\). After extraction with Et\(_2\)O (4x) the combined extracts were dried over MgSO\(_4\) and the solvent removed to give a yellow liquid. Purification by column chromatography using 4:1 PE:Et\(_2\)O as eluant gave recovered starting material (0.187 g, 9% yield) and the desired alcohol 158 (1.49 g, 79% yield) as a white crystalline solid.

mp (sealed tube): 109-110 °C
C\textsubscript{15}H\textsubscript{25}O\textsubscript{2}  \hspace{1cm} \text{Calc. Mass:} \; 238.1933  \\
\hspace{1cm} \text{Meas. Mass:} \; 238.1937  \\
\hspace{1cm} \text{Calc.:} \; \text{C} \; 75.58 \hspace{1cm} \text{H} \; 10.99 \%  \\
\hspace{1cm} \text{Anal.:} \; \text{C} \; 75.56 \hspace{1cm} \text{H} \; 10.97 \%  \\

\begin{align*}
\text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\text{):} & \quad \delta = 1.00 (3\text{H, s, CH}_3); 1.05 (3\text{H, s, CH}_3); 1.09 (3\text{H, d, J=7 Hz, C(6)CH}_3); 1.28 (1\text{H, td, J=13, 2 Hz, C(8)H}); 1.58 (3\text{H, m, vinyl CH}_3); 1.66 (1\text{H, dtd, J=13, 3, 1.5 Hz, C(8)H}); 1.77 (1\text{H, dd, J=9, 7 Hz}); 2.33 (1\text{H, m}); 3.01 (1\text{H, br s, C(10)H}); 3.32 (1\text{H, dd, J=9, 7 Hz, -CHHOCH}_3); 3.36 (3\text{H, s, -OCH}_3); 3.41 (1\text{H, dd, J=9, 7 Hz, -CHHOCH}_3); 3.77 (1\text{H, br s, C(7)H}); 5.19 (1\text{H, br s, vinyl H}).
\end{align*}

\text{IR (neat):} \; \nu = 3630 (O-H); 2940 (C-H) \text{ cm}^{-1}

\text{MS: m/e(\%)=238 (M\textsuperscript{+}, 52); 206 (25); 193 (95); 175 (49); 173 (100); 135 (46); 121 (36).}

\text{Protection of alcohol 122 to give silyl ether 168:}

\begin{align*}
\text{A solution of alcohol 122 (0.128 g, 0.481 mmol), imidazole (0.049 g, 0.72 mmol) and TBDMScI (0.0865 g, 0.576 mmol) in dry DMF (10 mL) was stirred at RT under an Ar atm overnight. Water was added and the mixture was extracted with Et}_2\text{O (3x). The combined extracts were washed with NH}_4\text{Cl(aq) solution and brine (3x) and dried over MgSO}_4. \text{ Removal of the solvent gave a yellow liquid which was purified by column}
\end{align*}
chromatography using 2:1 PE:Et2O as eluant. The silyl ether 168 was isolated as a
colourless liquid (0.18 g, 99% yield).

C21H36O4Si  Calc. Mass:  380.2383  
 Meas. Mass:  380.2382

1H NMR (400 MHz, CDCl3):  δ=0.07 (3H, s, -SiCH3); 0.08 (3H, s, -SiCH3); 0.90 (9H,  
s, t-Bu); 1.09 (3H, s, CH3); 1.19-1.25 (1H, m); 1.22 (3H, s, CH3); 1.40 (1H, t,  
J=13 Hz); 1.54 (1H, br d, J=13 Hz); 1.72 (1H, dm, J=13 Hz); 2.02 (1H, dm,  
J=13 Hz); 2.34 (1H, br m); 3.17 (1H, br s, C(10)H); 3.70 (2H, d, J=6 Hz,  
-CH2OTBDMS); 3.93 (4H, br s, ketal H's); 5.98 (1H, dd, J=10, 3 Hz, C(2)H;  
6.78 (1H, dt, J=10, 2 Hz, C(1)H).

IR (neat): ν=2950, 2890 (C-H); 1675 (C=O) cm⁻¹

MS: m/e(%)=323 (M⁺-t-Bu, 39); 279 (22); 243 (20); 159 (24); 119 (24); 108 (100); 105  
(26); 93 (79); 91 (35); 86 (37); 84 (39); 75 (84); 73 (51); 49 (53).

Conversion of enone 168 to epoxide 169:

To a solution of enone 168 (0.18 g, 0.47 mmol) in MeOH (8.0 mL) and H2O2  
(1.9 mL, 30%) at 0 °C was added dropwise NaOH (2.5 mL, 4 M/H2O, 0.010 mol).93 The  
mixture was allowed to warm to RT, then was stirred for 1.5 h. After dilution with water,  
the mixture was extracted with CH2Cl2 (3x). The combined extracts were dried over
MgSO₄ and the solvent removed to give the epoxide 169 as a pale yellow liquid (0.15 g, 80% yield) which was not purified but used directly in the next reaction.


¹H NMR (400 MHz, CDCl₃): δ=0.08 (6H, br s, -Si(CH₃)₂); 0.90 (9H, s, t-Bu); 1.03 (3H, s, CH₃); 1.10-1.25 (1H, m); 1.30-1.40 (1H, m); 1.32 (3H, s, CH₃); 1.65 (1H, br d, J=12 Hz); 1.80 (2H, d, J=12 Hz); 2.09 (1H, br m); 2.90 (1H, br s, C(10)H); 3.14 (1H, d, J=3 Hz, C(1)H); 3.45 (1H, br s, C(2)H); 3.74 (2H, d, J=6 Hz, -CH₂OTBDMS); 3.91 (4H, br s, ketal H's).

IR (neat): ν=2950, 2900 (C-H); 1705 (C=O) cm⁻¹

MS: m/e(%)=396 (M⁺, 0.6); 339 (66); 295 (77); 277 (26); 251 (53); 195 (33); 157 (24); 99 (38); 75 (100).

Conversion of epoxide 169 to alcohol 170:

To a solution of PhSeSePh (0.72 g, 2.3 mmol) in absolute EtOH (6.0 mL) under an Ar atm was added in portions NaBH₄ (0.17 g, 4.6 mmol).⁹⁴,⁹⁵ Into the colourless solution was cannulated a solution of epoxide 169 (0.305 g, 0.77 mmol) in absolute EtOH (4.0 mL) and the resulting yellow solution was stirred at RT overnight. The mixture was diluted with EtOAc and washed once with brine. Drying over MgSO₄ and removal of the solvent gave a yellow oil which was purified by column chromatography using 4:1
PE:Et₂O as eluant. Two compounds were isolated, the desired keto-alcohol 170 as a colourless liquid (0.183 g, 60% yield) and the enone 168 resulting from dehydration as a colourless liquid (0.028 g, 10% yield). The enone 168 had spectral characteristics identical to those of the previously prepared sample.

Data for keto-alcohol 170:

C₂₁H₂₈O₅Si  Calc. Mass:  398.2481
   Meas. Mass:  398.2481

¹H NMR (400 MHz, CDCl₃): δ=0.10 (3H, s, -SiCH₃); 0.11 (3H, s, -SiCH₃); 0.92 (9H, s, t-Bu); 1.00 (3H, s, CH₃); 1.06 (1H, t, J=13 Hz, C(6)H); 1.33 (3H, s, CH₃); 1.42 (1H, dt, J=13, 3 Hz, C(8)H); 1.68 (1H, dt, J=13, 3 Hz, C(6)H); 1.85-1.94 (2H, m); 2.09 (1H, br dd, J=13, 3 Hz); 2.37 (1H, dt, J=13, 3 Hz, C(10)H); 2.67 (1H, s, C(2)H); 2.70 (1H, d, J=2 Hz, C(2)H); 3.78 (1H, dd, J=11, 3 Hz, -CHHOTBDMS); 3.90-3.98 (4H, m, ketal H's); 4.00 (1H, dd, J=11, 1.5 Hz, -CHHOTBDMS); 4.12 (1H, m, C(1)H); 5.49 (1H, br s, exchanges with D₂O, -OH).

IR (neat): ν=3400 (br, O-H); 2960, 2940, 2890 (C-H); 1705 (C=O) cm⁻¹

MS: m/e(%)=398 (M⁺, 0.2); 323 (24); 279 (22); 205 (21); 181 (21); 159 (26); 119 (26); 105 (22); 99 (27); 86 (21); 77 (21); 75 (100); 73 (58); 41 (30).

Protection of keto-alcohol 170 to give silyl ether 171:
To a solution of keto-alcohol 170 (0.116 g, 0.290 mmol) and 2,6-lutidine (0.070 mL, 0.58 mmol) in dry CH$_2$Cl$_2$ (10 mL) at 0 °C under an Ar atm was added dropwise TBDMSOTf (0.10 mL, 0.44 mmol). After stirring at 0 °C for 1 h, the mixture was stirred at RT for 3 h. Water was added, and the mixture was extracted with Et$_2$O (3x). The combined extracts were washed with 0.25 M HCl solution and brine (3x), and dried over MgSO$_4$. Removal of the solvent gave a pale yellow oil which was purified by column chromatography using 9:1 PE:Et$_2$O as eluant. The silyl ether 171 was isolated as a white crystalline solid (0.0745 g, 50% yield).

mp: 105-106 °C (sealed tube)

C$_{23}$H$_{43}$O$_5$Si$_2$ (M$^+$-t-Bu)  Calc. Mass: 455.2649  
Meas. Mass: 455.2641

C$_{27}$H$_{52}$O$_5$Si$_2$  Calc.: C 63.23  H 10.22 %  
Anal.: C 63.31  H 10.12 %

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$=0.04 (3H, s, -SiCH$_3$); 0.05 (3H, s, -SiCH$_3$); 0.08 (3H, s, -SiCH$_3$); 0.09 (3H, s, -SiCH$_3$); 0.90 (18 H, s, 2x t-Bu); 1.00 (3H, s, CH$_3$); 1.14 (1H, t, J=13 Hz, C(6)H); 1.32 (3H, s, CH$_3$); 1.38 (1H, t, J=13 Hz, C(8)H); 1.69 (1H, dt, J=13, 2 Hz, C(6)H); 1.92 (1H, dt, J=14, 4 Hz, C(5)H); 1.98-2.05 (2H, m, C(8)H and C(9)H); 2.42 (1H, dt, J=10, 3 Hz, C(10)H); 2.56 (1H, dd, J=14, 6 Hz, C(2)H); 2.64 (1H, dd, J=14, 10 Hz, C(2)H); 3.63 (1H, t, J=10 Hz, -CHHOTBDMS); 3.80 (1H, dd, J=10, 3 Hz, -CHHOTBDMS); 3.90-3.99 (4H, m, ketal H's); 4.20 (1H, dddd, 6 lines, J=10, 10, 6 Hz, C(1)H).

IR (CHCl$_3$): $\nu$=2960, 2940, 2890, 2860 (C-H); 1705 (C-O) cm$^{-1}$

MS: m/e(%)=455 (M$^+$-t-Bu, 8.4); 323 (12); 249 (18); 195 (30); 171 (20); 147 (18); 75 (100); 41 (29).
Oxidation of bromide 61 to give ketone 183 and cyclocamphanone ketal (184):

Silver tetrafluoroborate (2.56 g, 13.1 mmol) was added to a solution of bromide 61 (2.41 g, 8.76 mmol) in dry DMSO (40 mL) under an Ar atm. After stirring in the dark at RT overnight, dry Et₃N (1.8 mL, 13 mmol) was added and the reaction was stirred for another hour. Water was cautiously added and the mixture was filtered through Celite. The filter cake was washed well with Et₂O, and the filtrate was extracted with Et₂O (4x). The combined extracts were dried over MgSO₄ and the solvent was removed to give a yellow liquid. Column chromatography using 9:1 PE:Et₂O as eluant gave the ketone 183 as a colourless solid (0.784 g, 43% yield) and cyclocamphanone ketal (184) as a colourless liquid (0.674 g, 40% yield).

Data for ketone 183:

C₁₂H₁₈O₃  Calc. Mass:  210.1256

¹H NMR (400 MHz, CDCl₃):  δ=0.95 (6H, s, 2x CH₃); 1.15 (3H, s, CH₃); 1.73 (1H, d, J=14 Hz, C(3) endo H); 2.05 (1H, dd, J=18, 1 Hz, C(6) endo H); 2.20 (1H, br d, J=5 Hz, C(4)H); 2.29 (1H, dd, J=14, 5 Hz, C(3) exo H); 2.55 (1H, d, J=18 Hz, C(6) exo H); 3.80 (1H, m, ketal H); 3.90 (2H, m, 2 ketal H's); 4.00 (1H, m, ketal H).

IR (CHCl₃):  ν=2970, 2887 (C-H); 1752 (C=O) cm⁻¹

MS: m/e(%)=210 (M⁺, 54); 195 (88); 141 (28); 127 (46); 126 (100).
Data for cyclocamphanone ketal (184):

\[ C_{12}H_{18}O_2 \]

Calc. Mass: 194.1306
Meas. Mass: 194.1302

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 0.72 \) (3H, s, CH\(_3\)); 0.86 (3H, s, CH\(_3\)); 1.15 (3H, s, CH\(_3\)); 1.19-1.32 (3H, m, C(3)H, C(4)H, C(5)H); 1.58 (1H, d, \( J = 10 \) Hz, C(6) endo H); 1.76 (1H, d, \( J = 10 \) Hz, C(6) exo H); 3.79-4.12 (4H, m, ketal H's).

IR (neat): \( \nu = 2959, 2873 \) (C-H) cm\(^{-1}\)

MS: m/e(%) = 194 (M\(^+\), 35); 179 (95); 150 (12); 138 (42); 135 (34); 121 (25); 108 (61); 107 (100).

Hydrolysis of cyclocamphanone ketal (184) to give cyclocamphanone (59):

A solution of cyclocamphanone ketal (184, 0.873 g, 4.49 mmol) was stirred in acetone (10 mL) and 1 M HCl (10 mL) at RT for 1 h. The mixture was diluted with water, extracted with Et\(_2\)O (3x) and the combined extracts were washed with brine (3x). After drying over MgSO\(_4\) and removal of the solvent, cyclocamphanone (59, 0.67 g, 100% yield) was obtained as a white solid. Spectral characteristics were identical to those of cyclocamphanone (59) prepared previously.
Conversion of ketone 183 to enol triflate 185:

A solution of ketone 183 (1.80 g, 0.856 mmol) in dry CH2Cl2 (30 mL) was cannulated into a solution of triflic anhydride (1.5 mL, 8.9 mmol) and 2,6-di-t-butyl-4-methylpyridine (1.84 g, 8.96 mmol) in dry CH2Cl2 (80 mL) under an Ar atm. After stirring at RT for 4 h, the solvent was removed, pentane (80 mL) was added, and the tan residue was filtered off. The filtrate was washed successively with NH4Cl(aq) solution, NaHCO3(aq) solution and brine (2x). After drying over MgSO4, the solvent was removed to yield a yellow liquid which was purified by column chromatography using 9:1 PE:Et2O as eluant. The enol triflate 185 was isolated as a colourless liquid (2.76 g, 95% yield).

C12H17O3 (M+-SO2CF3)  Calc. Mass:  209.1178  
Meas. Mass:  209.1179

1H NMR (400 MHz, CDCl3):  δ=0.82 (3H, s, CH3); 0.96 (3H, s, CH3); 0.98 (3H, s, CH3); 1.65 (1H, d, J=12 Hz, C(3) endo H); 1.94 (1H, dd, J=12, 4 Hz, C(3) exo H); 2.23 (1H, br s, C(4)H); 3.25 (1H, m, ketal H); 3.32-3.48 (3H, m, 3 ketal H's); 5.34 (1H, s, C(6)H).

IR (neat):  ν=2961, 2880 (C-H) cm⁻¹

MS:  m/e(%)=209 (M+-Tf, 100); 137 (35); 123 (15); 109 (32); 86 (45).
Conversion of enol triflate 185 to 5-methyl-5,6-dehydrocamphor ketal (186):

A slurry of CuBr·DMS (17.66 g, 85.90 mmol) in dry Et2O (~100 mL) was cooled to -20 °C under an Ar atm. MeLi (~120 mL, 1.4 M/Et2O, ~172 mmol) was added dropwise until a colourless solution was obtained. The triflate (5.656 g, 16.50 mmol) was dissolved in dry Et2O (20 mL) and added dropwise. After stirring at -20 °C for 2 h, 5% NH4OH in a saturated NH4Cl(aq) solution was cautiously added. The reaction mixture was extracted with Et2O (3x) and the combined extracts were washed with 5% NH4OH in a saturated NH4Cl(aq) solution and brine (3x). After drying over MgSO4, the solvent was removed to yield a pale yellow liquid which was purified by column chromatography using 15:1 PE:Et2O as eluant. 5-Methyl-5,6-dehydrocamphor ketal (186) was isolated as a colourless liquid (3.21 g, 93% yield). It was, however, contaminated with 5% of 5,6-dehydrocamphor ketal (62) which could not be separated.

\[
\text{C}_{13}\text{H}_{20}\text{O}_2 \quad \text{Calc. Mass: 208.1463} \\
\text{Meas. Mass: 208.1465}
\]

\(^1\text{H NMR (400 MHz, C}_6\text{D}_6\text{):} \delta = 1.00 (3\text{H, s, CH}_3\text{)}; 1.05 (3\text{H, s, CH}_3\text{)}; 1.22 (3\text{H, s, CH}_3\text{)}; 1.48 (1\text{H, d, J}=12\text{ Hz, C}(3) \text{ endo H}); 1.62 (3\text{H, d, J}=1\text{ Hz, C}(5)\text{CH}_3\text{)}; 1.95 (1\text{H, d, J}=4\text{ Hz, C}(4)\text{H}); 2.10 (1\text{H, dd, J}=12, 4\text{ Hz, C}(3) \text{ exo H}); 3.30-3.40 (1\text{H, m, ketal H}); 3.40-3.58 (3\text{H, m, 3 ketal H's}); 5.43 (1\text{H, br s, C}(6)\text{H}).
\]

\text{IR (neat): } \nu=2952, 2872, 2726 \text{ (C-H cm}^{-1} \text{).}

\text{MS: } m/e(\%)=208 (M^+, 2.5); 193 (1.3); 122 (100); 107 (63).
Hydrolysis of 5-methyl-5,6-dehydrocamphor ketal (186) to give (-)-5-methyl-5,6-dehydrocamphor (178):

After stirring a solution of ketal 186 (0.379 g, 1.81 mmol) in acetone (8 mL) and 1 M HCl (8 mL) at RT for 15 min, water was added and the reaction was extracted with Et₂O (3x). The combined extracts were washed with NaHCO₃(aq) solution, brine (3x) and dried over MgSO₄. Removal of the solvent gave a colourless liquid which was purified by column chromatography using 4:1 PE:Et₂O as eluant. (-)-5-Methyl-5,6-dehydrocamphor (178) was isolated as a colourless liquid (0.297 g, 99% yield). It was contaminated with ~5% (-)-5,6-dehydrocamphor (ent-36) which could not be separated.

\[ \text{C}_{11}\text{H}_{16}\text{O} \quad \text{Calc. Mass:} \quad 164.1201 \]
\[ \text{Meas. Mass:} \quad 164.1196 \]

\[ \text{H NMR (400 MHz, C}_{6}\text{D}_{6}): \delta = 0.65 (3\text{H}, \text{s, CH}_3); 0.85 (3\text{H}, \text{s, CH}_3); 1.00 (3\text{H}, \text{s, CH}_3); 1.44 (3\text{H}, \text{s, C(5)CH}_3); 1.61 (1\text{H}, \text{d, J=14 Hz, C(3) endo H}); 1.85 (1\text{H}, \text{br s, C(4)H}); 1.96 (1\text{H}, \text{dd, J=14, 4 Hz, C(3) exo H}); 4.81 (1\text{H}, \text{br s, C(6)H}). \]

\[ \text{IR (neat): } \nu = 2963 \text{ (C-H)}; 1743 \text{ (C=O)} \text{ cm}^{-1} \]

\[ \text{MS: m/e(%)} = 164 \text{ (M⁺, 7.1); 149 (8.3); 122 (86); 121 (51); 107 (100).} \]

Isopropenyl addition to (-)-5-methyl-5,6-dehydrocamphor (178) and anionic oxy-Cope rearrangement to give ketone 190:
A 3-necked 100 mL round bottomed flask equipped with condenser and addition funnel and containing a stir bar and Mg (0.52 g, 0.021 mol) was flame dried and cooled under Ar. A crystal of I$_2$ and dry THF (12 mL) were added and a small amount of 2-bromopropene was added to initiate Grignard formation. A solution of 2-bromopropene (1.3 mL, 0.014 mol) in dry THF (12 mL) was then added dropwise to maintain the exothermic reaction. After 30 min, a solution of (-)-5-methyl-5,6-dehydrocamphor (178, 1.16 g, 7.08 mmol) in dry THF (12 mL) was added dropwise and the mixture was stirred at RT for 2 h, at which point addition had occurred as evidenced by TLC and GC. Rearrangement was induced by heating at reflux for 5.5 h. The reaction was cooled to RT and NH$_4$Cl(aq) solution was cautiously added. The mixture was extracted with Et$_2$O (3x) and the combined extracts were washed with brine (3x). Removal of the solvent gave a yellow liquid which was purified by column chromatography using 15:1 PE:Et$_2$O as eluant. The ketone 190 was obtained as a colourless liquid (1.237 g, 85% yield). $^1$H NMR spectroscopy showed the diastereomeric mixture to be 1:1.

$^1$H NMR (400 MHz, CDCl$_3$, one diastereomer): $\delta=0.87$ (3H, s, CH$_3$); 1.00 (3H, s, CH$_3$); 1.01 (3H, d, J=6 Hz, C(8)CH$_3$); 1.28 (3H, s, C(10)CH$_3$); 1.60 (4H, m, vinyl CH$_3$ and 1 H); 1.77 (1H, dd, J=13, 5 Hz, C(9)H); 2.04 (1H, t, J=6 Hz); 2.38-2.50 (3H, m, 2xC(6)H and C(8)H); 5.18 (1H, br s, vinyl H).

$^1$H NMR (400 MHz, CDCl$_3$, second diastereomer): $\delta=0.83$ (3H, s, CH$_3$); 1.03 (3H, d, J=6 Hz, C(8)CH$_3$); 1.09 (3H, s, CH$_3$); 1.20 (3H, s, C(10)CH$_3$); 1.50-1.65 (6H, m,
vinyl CH₃ and 3H); 2.05 (1H, q, J=3 Hz); 2.10 (1H, m); 2.39-2.45 (2H, m); 4.95 (1H, br s, vinyl H).

IR (neat): ν=2926 (C-H); 1714 (C=O) cm⁻¹

MS: m/e(%)=206 (M⁺, 15); 191 (17); 177 (10); 135 (100); 121 (52); 107 (44); 91 (35); 69 (43).

Ring expansion of ketone 190 to give enone 191:

A solution of ketone 190 (0.404 g, 1.96 mmol) in CH₂Cl₂ (10 mL) and MeOH (10 mL) was cooled to -78 °C and O₃ was bubbled through the solution until a blue colour persisted (~30 min). Excess O₃ was removed by bubbling O₂ through the solution until it became colourless. The reaction mixture was poured onto Zn (2.56 g, 39.1 mmol), HOAc (4.5 mL, 78 mmol) was added, and the mixture was stirred at RT for 1 h. The reaction mixture was filtered, washed successively with water (2x), 5% NaOH(aq) solution, water (4x, until neutral) and dried over MgSO₄. Removal of the solvent gave the crude aldehyde as a yellow oil (0.36 g, 77% yield). It was not purified, but was immediately dissolved in dry benzene (~50 mL). A catalytic amount of p-TsOH·H₂O was added, and the mixture was refluxed in a Dean-Stark apparatus under an Ar atm for 1 h. Brine was added and the mixture was extracted with Et₂O (3x). The combined extracts were washed with brine (3x), dried over MgSO₄ and the solvent removed to yield a yellow oil. Purification by column chromatography using 1:1 PE:Et₂O as eluant gave the enone 191 as a white crystalline solid (0.255 g, 59% yield from ketone 190).
mp: 115-116 °C

C_{14}H_{20}O_2  \quad \text{Calc. Mass: 220.1463}
Meas. Mass: 220.1454

\text{Calc.: C 76.33 H 9.15 \%}
\text{Anal.: C 76.46 H 8.99 \%}

^{1}H \text{ NMR (400 MHz, CDCl}_3): \delta=0.99 (3H, s, CH}_3; 1.05 (3H, d, J=8 Hz, C(8)CH}_3); 1.20 (3H, s, CH}_3); 1.48 (3H, s, C(10)CH}_3); 1.82-1.88 (2H, m, 2x C(9)H); 2.22 (1H, dd, J=8, 2 Hz, C(5)H); 2.53-2.68 (3H, m, 2x C(6)H and C(8)H); 5.88 (1H, d, J=8 Hz, C(2)H); 6.56 (1H, d, J=8 Hz, C(1)H).

IR (CHCl\textsubscript{3}): \nu=2964 (C-H); 1709, 1673 (C=O) cm\textsuperscript{-1}

MS: m/e(\%)=220 (M\textsuperscript{+}, 7.8); 124 (37); 107 (11); 95 (100); 77 (24); 69 (41); 67 (34); 40 (82).

Conversion of enone 191 to ketal 192:

A solution of enone 191 (0.341 g, 1.55 mmol), ethylene glycol (0.43 mL, 7.7 mmol) and a catalytic amount of p-TsOH•H\textsubscript{2}O in dry benzene (~60 mL) was refluxed in a Dean-Stark apparatus under an Ar atm for 1 h. After cooling to RT, brine was added, and the mixture was extracted with Et\textsubscript{2}O (3x). The combined extracts were washed with brine (3x), dried over MgSO\textsubscript{4} and the solvent removed to yield a yellow oil. Purification by column chromatography using 4:1 PE:Et\textsubscript{2}O as eluant gave starting material 191.
(0.035 g, 10% yield) and the desired ketal 192 as a colourless oil (0.284 g, 70% yield).

$^1$H NMR spectroscopy showed the diastereomeric mixture to be ~2:1.

C$_{16}$H$_{24}$O$_3$  
Calc. Mass: 264.1725  
Meas. Mass: 264.1723

$^1$H NMR (400 MHz, CDCl$_3$, major diastereomer): $\delta$=0.92 (3H, d, J=7 Hz, C(8)CH$_3$);
1.15 (3H, s, CH$_3$); 1.31 (3H, s, CH$_3$); 1.34 (3H, s, C(10)CH$_3$); 1.45-1.78 (4H, m);
1.80-1.95 (2H, m); 3.85-4.00 (4H, m, ketal H's); 5.79 (1H, d, J=10 Hz, C(2)H);
6.47 (1H, dd, J=10, 1.5 Hz, C(1)H).

IR (neat): $\nu$=2935 (C-H); 1671 (C=O) cm$^{-1}$

MS: m/e(%)=264 (M$, 1.7$); 2.50 (3.5); 140 (100); 113 (40); 100 (12); 95 (15); 86 (20);
40 (57).

Reduction of enone 192 to give alcohol 193:

A solution of enone 192 (0.284 g, 1.07 mmol) in dry Et$_2$O (3.0 mL) and EtOH
(5.0 mL) was added to NH$_3$(l) (~20 mL) kept cold by a dry ice/acetone bath. Li (0.075 g, 10.7 mmol) was added in small pieces and after stirring the blue mixture for 1 h,
NH$_4$Cl(s) was cautiously added, and the NH$_3$(l) was allowed to evaporate overnight.$^{106}$
The residue was taken up in Et$_2$O and water was added to dissolve the white precipitate.
The mixture was extracted with Et$_2$O (3x), the combined extracts were washed with brine
(3x) and dried over MgSO$_4$. Removal of the solvent gave a yellow oil which was
purified by column chromatography using 4:1 PE:Et$_2$O as eluant. A pale yellow solid
was obtained which was recrystallized from 4:1 PE:Et₂O to give the alcohol 193 as a white crystalline solid (0.156 g, 54% yield). ¹H NMR spectroscopy showed the diastereomeric mixture to be 1:1.

**C₁₆H₂₈O₃**
- **Calc. Mass:** 268.2038
- **Meas. Mass:** 268.2037

**Calc.: C 71.60**
**H 10.51 %**
**Anal.: C 71.69**
**H 10.42 %**

¹H NMR (400 MHz, CDCl₃, one diastereomer):  δ=0.90 (3H, d, J=6 Hz, C(8)CH₃); 1.00 (6H, s, 2x CH₃); 1.07-1.10 (4H, m, CH₃ and 1H); 1.25-1.35 (3H, m); 1.50-1.55 (1H, m); 1.65-1.75 (3H, m); 1.89 (1H, dd, J=15, 8 Hz); 2.05 (1H, m); 3.38 (1H, m, C(3)H); 3.85-4.00 (4H, m, ketal H's).

IR (CHCl₃): v=3615 (O-H); 2968 (C-H) cm⁻¹

MS: m/e(%)=268 (M⁺, 21); 198 (6.3); 151 (18); 140 (51); 113 (100); 100 (31); 99 (80).

**Protection of alcohol 193 to give methyl ether 194:**

To a slurry of KH (0.022 g, 0.54 mmol) in dry THF (1.0 mL) under an Ar atm was added a solution of alcohol 193 (0.12 g, 0.45 mmol) in dry THF (6.0 mL) and the mixture was stirred at RT for 25 min. Mel (0.050 mL, 0.67 mmol) was passed through basic alumina directly into the reaction mixture. After stirring overnight, water was cautiously added and the mixture was extracted with Et₂O (3x). The combined extracts
were washed with brine (3x), dried over MgSO₄ and the solvent was removed to give a yellow liquid. Purification by column chromatography using 4:1 PE:Et₂O as eluant gave the methyl ether 194 as a pale yellow oil (0.119 g, 94% yield). ¹H NMR spectroscopy and GC showed this to a mixture of all 4 possible diastereomers.

C₁₇H₃₀O₃  Calc. Mass:  282.2195  
Meas. Mass:  282.2195

¹H NMR (400 MHz, CDCl₃, major diastereomer): δ=0.81 (3H, d, J=7 Hz, C(8)CH₃); 0.99 (3H, s, CH₃); 1.10 (3H, s, CH₃); 1.13 (3H, s, CH₃); 1.35-2.05 (10H, m); 2.99 (1H, dd, J=12, 5 Hz, C(3)H); 3.35 (3H, s, -OCH₃); 3.85-4.00 (4H, m, ketal H's).

IR (neat): ν=2924, 2818 (C-H) cm⁻¹

MS: m/e(%)=282 (M⁺, 4.9); 268 (8.0); 250 (3.7); 140 (22); 113 (69); 99 (100); 41 (21).

Hydrolysis of ketal 194 to give ketone 195:

A solution of ketal 194 (0.124 g, 0.439 mmol) in acetone (3.0 mL) and 1 M HCl (3.0 mL) was stirred at RT for 1 h. Water was added and the mixture was extracted with Et₂O (3x). The combined extracts were washed with brine (3x), dried over MgSO₄, and the solvent was removed to give a yellow solid. Purification by column chromatography using 9:1 PE:Et₂O as eluant gave ketone 195 as a white crystalline solid (0.096 g, 91% yield). ¹H NMR spectroscopy and GC showed the diastereomeric mixture to be 1:1.
Conversion of ketone 195 to enol silyl ether 196:

\[ \text{CH}_3O^+ \text{CH}_3O^+ \]

To a solution of ketone 195 (0.056 g, 0.23 mmol) and HMDS (70 µL, 0.33 mmol) in dry CH\(_2\)Cl\(_2\) (2.0 mL) at 0 °C under an Ar atm were added successively LiI (0.037 g, 0.28 mmol) and TMSCl (35 µL, 0.28 mmol).\(^{107,108}\) After stirring at 0 °C for 1 h, the mixture was poured onto ice and diluted with CH\(_2\)Cl\(_2\). The layers were separated, and
the CH₂Cl₂ solution was washed with NaHCO₃(aq) solution (2x). After drying over MgSO₄, the solvent was removed to yield the enol silyl ether \textbf{196} (0.0765 g, >100\% weight recovery) as a pale yellow liquid which was not purified but which was used directly in the next reaction.

\[
\text{C}_{18}\text{H}_{34}\text{O}_{2}\text{Si} \quad \text{Calc. Mass: } 310.2328 \\
\text{Meas. Mass: } 310.2330
\]

\textbf{1H NMR} (400 MHz, CDCl₃): \( \delta = 0.18 \) (9H, s, -Si(CH₃)₃); 0.80 (3H, s, CH₃); 0.92 (3H, s, CH₃); 0.93 (3H, s, CH₃); 0.99-1.12 (2H, m); 1.34 (1H, br d, J=17 Hz); 1.53 (3H, s, vinyl CH₃); 1.62-1.74 (2H, m); 1.86 (1H, br d, J=17 Hz); 2.22 (1H, br d, J=17 Hz); 2.33 (1H, br d, J=17 Hz); 2.29 (1H, br s); 3.28 (3H, s, -OCH₃); 3.29-3.35 (1H, m, C(3)H).

\textbf{IR (neat)}: \( \nu = 2960 \) (C-H); 1656 (C=C) cm⁻¹

\textbf{MS}: m/e(%)=310 (M⁺, 24); 278 (16); 196 (32); 156 (27); 141 (100); 75 (48); 73 (93); 41 (26).

Conversion of enol silyl ether \textbf{196} to enone \textbf{197}:

A solution of PhSeCl (0.064 g, 0.33 mmol) in dry Et₂O (2.0 mL) was added to a solution of enol silyl ether \textbf{196} (0.069 g, 0.22 mmol) in dry Et₂O (2.0 mL) at -78 °C under an Ar atm. After stirring at -78 °C for 1.25 h, the solution was warmed to 0 °C and water (0.12 mL), HOAc (30 \( \mu \)L) and H₂O₂ (0.11 mL) were successively added. The mixture was warmed to RT, NaHCO₃(aq) solution was added, and the mixture was
extracted with Et₂O (3x). The combined extracts were washed with 1 M HCl, water, brine (2x), and dried over MgSO₄. Removal of the solvent gave a yellow oil which was purified by column chromatography using 9:1 PE:Et₂O as eluant. The enone 197 was isolated as a white solid (0.030 g, 58% yield).

C₁₅H₂₄O₂  Calc. Mass: 236.1776  
Meas. Mass: 236.1785

¹H NMR (400 MHz, CDCl₃): δ=0.72 (3H, s, CH₃); 0.98 (3H, s, CH₃); 1.18 (3H, s, CH₃); 1.38 (1H, m); 1.68-1.78 (6H, m, C(8)CH₃ and 3 H's); 2.01 (1H, dt, J=7, 2 Hz, C(5)H); 2.48 (1H, dd, J=18, 2 Hz, C(6)eq H); 2.74 (1H, dd, J=18, 7 Hz, C(6)ax H); 2.83 (1H, br d, J=2 Hz); 3.35-3.40 (4H, m, -OCH₃ and C(3)H); 6.40 (1H, br s, C(9)H).

IR (CHCl₃): ν=2934 (C-H); 1671 (C=O) cm⁻¹

MS: m/e(%)=236 (M⁺, 20); 204 (21); 189 (37); 161 (30); 91 (23); 79 (25); 71 (100); 41 (49).

Conversion of (-)-5-methyl-5,6-dehydrocamphor (178) to enone 204:

Freshly ground Mg (0.55 g, 23 mmol) was added to a 3-necked 200 mL round bottomed flask equipped with condenser and addition funnel. After flame drying and cooling under Ar, dry THF (25 mL) and a crystal of I₂ were added. A solution of 2-bromopropene (1.7 mL, 19 mmol) in dry THF (25 mL) was added dropwise and the Grignard reagent was allowed to form over 30 min. A solution of (-)-5-methyl-5,6-dehydrocamphor (178, 1.56 g, 9.50 mmol) in dry THF (20 mL) was added dropwise and
the reaction was stirred at RT for 30 min. After heating at 40 °C for 30 min, the reaction was refluxed for 8.5 h. The mixture was cooled to -78 °C and a solution of PhSeCl (3.64 g, 19.0 mmol) in dry THF (25 mL) was added and the reaction was allowed to warm to RT overnight. The mixture was cooled to 0 °C and water (6.0 mL), HOAc (1.5 mL) and H₂O₂ (6.0 mL, 30%) were added successively. The reaction was warmed to RT and was stirred until a white precipitate was formed (~30 min). NaHCO₃(aq) solution was added, the mixture was extracted with Et₂O (3x) and the combined extracts were washed successively with 1 M HCl, water and brine (2x). Drying over MgSO₄ and removal of the solvent gave a yellow liquid which was purified by column chromatography using 24:1 PE:Et₂O as eluant. The enone 203 was obtained as a yellow liquid (1.448 g, 75% yield) and ¹H NMR spectroscopy showed this to be a mixture of exo- and endocyclic double bond isomers. Therefore, the liquid was dissolved in acetone (20 mL) and 6 M HCl (20 mL) and was heated at 70 °C for 30 min. After cooling to RT, the reaction was extracted with Et₂O (3x) and the combined extracts were washed with brine (3x). Drying over MgSO₄ and removal of the solvent gave an orange liquid which was purified by column chromatography using 24:1 PE:Et₂O as eluant. The enone 204 was isolated as a colourless liquid (1.17 g, 60% yield from (-)-5-methyl-5,6-dehydrocamphor, 178). A small amount could be crystallized from Et₂O for elemental analysis.

C₁₄H₂₀  
Calc. Mass: 204.1514  
Meas. Mass: 204.1514  

Calc.: C 82.30  
Anal.: C 82.15  

¹H NMR (400 MHz, CDCl₃): δ=0.76 (3H, s, CH₃); 1.00 (3H, s, CH₃); 1.24 (3H, s, CH₃); 1.63 (3H, d, J=1 Hz, vinyl CH₃); 1.72 (3H, d, J=1 Hz, vinyl CH₃); 2.06 (1H, dt, J=7, 1.5 Hz, C(5)H); 2.53 (1H, dd, J=17, 1.5 Hz, C(6) eq. H); 2.64 (1H,
dd, J=17, 7 Hz, C(6) ax. H); 5.16 (1H, d, J=1 Hz, C(1)H); 6.30 (1H, t, J=1 Hz, C(9)H).

IR (CHCl₃): ν=2953 (C-H); 1662 (C=O) cm⁻¹

MS: m/e(%)=204 (M⁺, 16); 189 (59); 162 (11); 161 (16); 147 (14); 40 (50).

Conversion of enone 204 to enol silyl ether 205:

To a slurry of CuBr-DMS (0.10 g, 0.50 mmol) in dry THF (3.0 mL) at -78 °C under an Ar atm was added dropwise MeLi (~0.6 mL, 1.5 M/THF, ~1.0 mmol) until the mixture became a colourless solution. Following the addition of TMSCl (0.16 mL, 1.3 mmol), a solution of enone 204 (0.052 g, 0.25 mmol) in dry THF (3.0 mL) was added. The solution immediately became yellow, and was stirred at -78 °C for 30 min. A 5% NH₄OH in saturated NH₄Cl(aq) solution was added, and the mixture was extracted with Et₂O (3x). The combined extracts were washed with brine and dried over MgSO₄. Removal of the solvent gave a yellow liquid which was purified by column chromatography using 15:1 PE:Et₂O as eluant. The enol silyl ether 205 was isolated as a colourless oil (0.065 g, 89% yield).

C₁₈H₃₂OSi  Calc. Mass:  292.2222
  Meas. Mass:  292.2226

¹H NMR (300 MHz, CDCl₃): δ=0.18 (9H, s, -Si(CH₃)₃); 0.82 (3H, s, CH₃); 0.88 (3H, s, CH₃); 0.93 (3H, d, J=7 Hz, C(9)CH₃); 0.95 (3H, s, CH₃); 1.51 (3H, q, J=1.5 Hz, vinyl CH₃); 1.60 (3H, d, J=1.5 Hz, vinyl CH₃); 1.71 (1H, dd, J=9, 3 Hz, C(5)H);
1.95 (1H, dm, J=17 Hz, C(6) eq H); 2.10 (1H, br d, J=7 Hz, C(9)H); 2.20 (1H, ddm, J=17, 9 Hz, C(6) ax H); 5.39 (1H, br s, vinyl H).

IR (neat): v=2936 (C-H); 1680 (C=O) cm⁻¹

MS: m/e(%)=292 (M⁺, 15); 170 (12); 155 (51); 122 (100); 107 (51); 75 (31); 73 (46).

Conversion of enol silyl ether 205 to ketone 207:

A solution of enol silyl ether 205 (0.057 g, 0.19 mmol) in 1 M HCl (1.0 mL) and acetone (1.0 mL) was stirred at RT for 2 h. After dilution with water, the mixture was extracted with Et₂O (3x) and the combined extracts were washed with NaHCO₃ (aq) solution and brine (3x). Drying over MgSO₄ and removal of the solvent gave a yellow liquid which was purified by column chromatography using 24:1 PE:Et₂O as eluant. The ketone 206 was isolated as a colourless liquid (0.030 g, 70% yield). The diastereomeric mixture was determined to be 2:1 by GC. A sample of this mixture (0.021 g, 0.095 mmol) in a 9:1 mixture of HOAc:HCl(conc) (1.0 mL) was heated at 80 °C for 1 h to epimerize the C(8) center. After cooling to RT, the mixture was added to water and extracted with Et₂O (3x). The combined extracts were washed with water, NaHCO₃ (aq) solution and water (3x) and dried over MgSO₄. Removal of the solvent gave a yellow liquid which was only one diastereomer by GC. Purification by column chromatography using 24:1 PE:Et₂O as eluant gave the ketone 207 as a colourless liquid (0.011 g, 52% yield).
\[ C_{15}H_{24}O \quad \text{Calc. Mass:} \quad 220.1827 \]
\[ \text{Meas. Mass:} \quad 220.1818 \]

\(^1\text{H NMR} (300 \text{ MHz, CDCl}_3)\): \(\delta=0.91 (3\text{H, s, CH}_3)\); 0.93 (3H, d, J=7 Hz, C(9)CH\(_3\)); 1.00 (3H, s, CH\(_3\)); 1.03 (3H, d, J=7 Hz, C(8)CH\(_3\)); 1.05 (3H, s, CH\(_3\)); 1.62 (3H, d, J=1.5 Hz, vinyl CH\(_3\)); 1.69 (1H, m, C(9)H); 1.99 (1H, dd, J=8, 7 Hz, C(5)H); 2.09 (1H, m, C(8)H); 2.37 (1H, ddd, J=13, 8, 1 Hz, C(6) ax H); 2.52 (1H, dd, J=13, 7 Hz, C(6) eq H); 5.33 (1H, d, J=1.5 Hz, vinyl H).

IR (neat): \(v=2940 \text{ (C-H)}\); 1714 \text{ (C=O) cm}^{-1}

MS: m/e(\%)=220 (M\(^+\), 4.9); 135 (100); 122 (35); 121 (32); 107 (18); 91 (14); 40 (45).

Conversion of enone 204 to ketone 208:

Et\(_2\)AlCN (1.9 mL, 1 M/THF, 1.9 mmol) was added dropwise to a solution of enone 204 (0.095 g, 4.6 mmol) in dry THF (5.0 mL) under an Ar atm. After stirring at RT for 5.5 h, the mixture was poured onto 5% NaOH(aq) solution and extracted with Et\(_2\)O (3x). The combined extracts were washed with 1 M HCl solution and brine (3x). Drying over MgSO\(_4\) and removal of the solvent gave a yellow oil which was purified by column chromatography using 4:1 PE:Et\(_2\)O as eluant. The ketone 208 was isolated as a yellow oil (0.073 g, 68% yield). GC and \(^1\text{H NMR} \) spectroscopy showed this to be a complex mixture of diastereomers.
C_{15}H_{21}ON  \quad \text{Calc. Mass: 231.1623}
\text{Meas. Mass: 231.1623}

^1\text{H NMR (400 MHz, CDCl}_3\text{, a complex mixture of diastereomers) characteristic signals:}
\delta=0.7-1.7 \text{ (methyl groups); 5.2-5.4 (vinyl H's)}

\text{IR (neat): } \nu=2929 \text{ (C-H); 2236 (C=\text{N}); 1718 (C=\text{O}) cm}^{-1}

\text{MS: } m/e \% = 231 (M^+, 16); 135 (100); 122 (92); 107 (42); 40 (29).

\text{Conversion of enone } 204 \text{ to ketone } 210:

To flame-dried Mg (0.41 g, 17 mmol) was added a crystal of I\text{2} and dry THF (15 mL). Vinyl bromide (~0.4 mL, ~8 mmol) was added dropwise to initiate and maintain Grignard formation and after 30 min at RT, the solution was cooled to -78 °C. An additional portion of dry THF (10 mL) was added, followed by CuBr-DMS (0.28 g, 1.4 mmol). After stirring at -78 °C for 1 h, TMSCl (1.9 mL, 15 mmol) was added and the mixture was stirred for an additional 15 min before the enone 204 (0.075 g, 0.36 mmol) was added. After 2 h at -78 °C, the reaction was allowed to warm to RT overnight. A solution of 5% \text{NH}_4\text{OH in saturated NH}_4\text{Cl(aq)} was cautiously added and the mixture was extracted with \text{Et}_2\text{O (3x). The combined extracts were washed with brine (3x) and dried over MgSO}_4. Removal of the solvent gave an orange oil which was purified by column chromatography using 24:1 PE:Et}_2\text{O as eluant. The hydrolyzed product (209) of the intermediate enol silyl ether was isolated as a yellow liquid (0.02 g, 24\% yield) as well as recovered starting enone 204 (0.017 g, 23\% yield). GC and ^1\text{H}
NMR spectroscopy determined the ketone 209 to be a complex mixture of diastereomers. A solution of this mixture (0.017 g, 0.077 mmol) in MeOH (2 mL) was added to a solution of NaOMe prepared by adding Na (0.007 g, 0.3 mmol) to MeOH (1 mL). The mixture was stirred at RT for 3.5 h, diluted with water and extracted with Et2O (3x). The combined extracts were washed with brine (3x) and dried over MgSO4. Removal of the solvent gave a yellow liquid which was purified by column chromatography using 24:1 PE:Et2O as eluant. The isomerized ketone 210 was isolated as a yellow liquid (0.017 g, 100% yield). 1H NMR spectroscopy determined this to be a 2:1 mixture of isomers.

C16H24O  
Calc. Mass: 232.1833  
Meas. Mass: 232.1825

1H NMR (300 MHz, CDCl3, major diastereomer): δ=0.91 (3H, s, CH3); 0.95 (3H, d, J=7 Hz, C(8) CH3); 1.00 (3H, s, CH3); 1.07 (3H, s, CH3); 1.59 (3H, d, J=1.5 Hz, vinyl CH3); 1.96 (1H, t, J=7 Hz, C(5)H); 2.14 (1H, dd, J=12, 9 Hz, C(9)H); 2.24 (1H, m, C(8)H); 2.35 (1H, dd, J=14, 7 Hz, C(6)H); 2.51 (1H, dd, J=14, 7 Hz, C(6)H); 4.94 (1H, dd, J=17, s, vinyl H trans to RCH=CH2); 5.08 (1H, dd, J=10, 2, vinyl H cis to RCH=CH2); 5.16 (1H, d, J=1.5 Hz, C(1)H); 5.60 (1H, ddd, J=17, 10, 12 Hz, RCH=CH2).

IR (neat): ν=2963, 2930 (C-H); 1706 (C=O) cm⁻¹

MS: m/e(%)=232 (M⁺, 7.7); 135 (100); 122 (46); 107 (23); 91 (16).

Allyl addition to enone 204 to give alcohol 214:
To a solution of enone 204 (0.053 g, 0.26 mmol) in dry THF at 0 °C under an Ar atm was added dropwise a solution of allylmagnesium bromide (0.52 mL, 1 M/THF, 0.52 mmol). The solution was warmed to RT and after stirring for 30 min it was heated at reflux for 3 h. NH₄Cl(aq) solution was cautiously added and the mixture was extracted with Et₂O (3x). The combined extracts were washed with brine (3x), dried over MgSO₄ and the solvent removed to give a yellow oil. Purification by column chromatography using 9:1 PE:Et₂O as eluant gave the alcohol 214 as a colourless liquid (0.050 g, 78% yield). GC and ¹H NMR spectroscopy showed this to be a 9:1 mixture of isomers.

C₁₇H₂₆O  
Calc. Mass: 246.1984  
Meas. Mass: 246.1985

Calc.: C 82.87  
Anal.: C 82.70  
H 10.64 %  
H 10.73 %

¹H NMR (400 MHz, CDCl₃, major isomer): δ=0.92 (3H, s, CH₃); 1.13 (3H, s, CH₃); 1.15 (3H, s, CH₃); 1.36 (1H, t, J=13 Hz, C(6) axial H); 1.53 (3H, d, J=1 Hz, vinyl CH₃); 1.70 (3H, d, J=1.5 Hz, vinyl CH₃); 1.76 (1H, dd, J=13, 5 Hz, C(6) equatorial H); 1.90 (1H, dd, J=13, 5 Hz, C(5)H); 2.23 (1H, dd, J=15, 10 Hz, -CHHCH=CH₂); 2.40 (1H, ddd, J=15, 10, 2 Hz, -CHHCH=CH₂); 4.97 (1H, s, C(1)H); 5.12-5.20 (3H, m, C(9)H and -CH=CH₂); 5.90 (1H, m, -CH=CH₂).

IR (neat): ν=3413 (O-H); 2949, 2862 (C-H) cm⁻¹

MS: m/e(%)=228(M⁺-H₂O, 23); 213 (36); 205 (100; 187 (55); 157 (28) 107 (28) 83 (99).
Attempted rearrangement of alcohol 214:

Anionic oxy-Cope rearrangement attempt A:

A solution of alcohol 214 (0.048 g, 0.19 mmol) in dry THF (4.0 mL) was added to a slurry of KH (0.016 g, 0.39 mmol) in dry THF (0.5 mL) under an Ar atm. The mixture was refluxed for 36 h, cooled to RT and water was cautiously added. The mixture was extracted with Et2O (3x) and the combined extracts were washed with brine (3x). Drying over MgSO4 and removal of the solvent gave an orange oil which was purified by column chromatography using 24:1 PE:Et2O as eluant. The only product isolated was enone 204 (0.012 g, 30% yield).

Anionic oxy-Cope rearrangement attempt B:

To a solution of alcohol 214 (0.046 g, 0.14 mmol) in dry THF (4.0 mL) at -78 °C under an Ar atm was added dropwise n-BuLi (0.28 mL, 1.6 M/THF, 0.45 mmol). The solution was stirred at -78 °C for 1 h, then at 0 °C for 1 h. After a further 2.5 h at RT, the mixture was refluxed for 19 h. After cooling to RT, water was added and the mixture was extracted with Et2O (3x). The combined extracts were washed with brine (3x), dried over MgSO4, and removal of the solvent gave a yellow liquid which was purified by column chromatography using 24:1 PE:Et2O as eluant. Starting alcohol 214 was recovered (0.034 g, 74% yield).
Anionic oxy-Cope rearrangement attempt C:

A solution of alcohol 214 (0.032 g, 0.095 mmol) and 18-cr-6 (0.13 g, 0.48 mmol) in dry diglyme (1.0 mL) was added to a slurry of KH (0.019 g, 0.48 mmol) in dry diglyme (0.5 mL) under an Ar atm. The mixture was stirred at RT for 3 d, then was refluxed for 24 h. The mixture was cooled to RT and passed through silica (230-400 mesh) using 1:1 PE:Et₂O as eluant to remove polar decomposition products. Removal of the solvent gave a yellow liquid which was a complex mixture by GC and TLC. There was no evidence of any anionic oxy-Cope rearrangement product, as indicated by IR spectroscopy.

Oxy-Cope rearrangement attempt:

A mixture of alcohol 214 (0.050 g, 0.15 mmol) and anhydrous K₂CO₃ (0.10 g, 0.74 mmol) in dry decalin (3.0 mL) was refluxed for 3 d. After cooling to RT the reaction mixture was passed through silica (230-400 mesh) using PE as eluant until all decalin had been eluted, then increasing the polarity to 24:1 PE:Et₂O. Starting alcohol 214 (0.019 g, 38% yield) was recovered, as well as enone 204 (0.012 g, 40% yield).

Protection of propargyl alcohol as its TBDMS ether:

OTBDMS

OH

A solution of propargyl alcohol (10 mL, 0.17 mol), imidazole (17.5 g, 0.258 mol) and TBDMSCl (30.9 g, 0.206 mol) was stirred overnight at RT under an Ar atm. Brine was added and the mixture was extracted with Et₂O (3x). The combined extracts were washed with brine (3x), dried over MgSO₄ and the solvent removed to give a yellow oil. Purification by distillation (T=-80 °C, P=-15 mmHg) afforded silyl-protected propargyl alcohol as a colourless liquid (25 g, 86% yield).
C$_9$H$_{18}$OSi  
Calc. Mass: 170.1127  
Meas. Mass: 170.1124

$^1$H NMR (400 MHz, CDCl$_3$): $\delta=0.11$ (6H, s, Si(CH$_3$)$_2$); 0.90 (9H, s, t-Bu); 2.37 (1H, t, J=2.5 Hz, HC=$\equiv$C-); 4.30 (2H, d, J=2.5 Hz, -CH$_2$OTBDMS).

IR (neat): $\nu=3300$ (C-H); 2930, 2900, 2870, 2830 (C-H) cm$^{-1}$

MS: m/z(%)=170 (M$^+$, 1.0); 113 (99); 83 (100); 75 (59).

Conversion of (-)-5-methyl-5,6-dehydrocamphor (178) to alkyne 216:

To a solution of silyl-protected propargyl alcohol (0.864 g, 5.07 mmol) in dry THF (20 mL) at -78 °C under an Ar atm was added dropwise n-BuLi (2.9 mL, 1.6 M/hexane, 4.6 mmol). After stirring at -78 °C for 2.75 h, a solution of (-)-5-methyl-5,6-dehydrocamphor (178, 0.562 g, 3.42 mmol) in dry THF (20 mL) was cooled to -78 °C and cannulated into the reaction mixture. The solution was gradually allowed to warm to RT overnight. Water was added, the mixture was extracted with Et$_2$O (3x) and the combined extracts were washed with brine (3x). Drying over MgSO$_4$ and removal of the solvent gave an orange liquid which was purified by column chromatography using 15:1 PE:Et$_2$O as eluant. The alcohol 216 was isolated as a white solid (1.10 g, 96% yield).

mp: 78-79 °C
C₂₀H₃₄O₂Si  Calc. Mass: 334.2328  
Meas. Mass: 334.2322

¹H NMR (400 MHz, CDCl₃): δ=0.09 (6H, s, Si(CH₃)₂); 0.89 (9H, s, t-Bu); 0.91 (3H, s, CH₃); 1.04 (3H, s, CH₃); 1.05 (3H, s, CH₃); 1.67 (3H, d, J=1.5 Hz, vinyl CH₃); 1.81 (1H, d, J=13 Hz, C(3) endo H); 2.04 (1H, d, J=3 Hz, C(4)H); 2.18 (1H, dd, J=13, 3 Hz, C(3) exo H); 4.29 (2H, s, -CH₂OTEDMS); 5.22 (1H, br s, C(6)H).

IR (CHCl₃): ν=3596 (O-H); 2943, 2862 (C-H) cm⁻¹

MS: m/e(%)=334 (M⁺, 0.4); 278 (26); 277 (100); 249 (20); 173 (26); 155 (36); 123 (26); 122 (81); 107 (30).

Reduction of alkyne 216 to give alkene 217:

Lindlar's catalyst (Pd on CaCO₃, poisoned with Pb, 0.15 g, 40% by wt of alkyne) and quinoline (14 μL, 0.015 g, 10% by wt of catalyst) in a 2:1 mixture of hexane:EtOAc (~15 mL) were stirred under a H₂ atm in a hydrogenation apparatus for 30 min.¹¹⁴ A solution of alkyne 216 (0.37 g, 1.1 mmol) in 2:1 hexane:EtOAc (~15 mL) was added and the mixture was stirred under H₂ until the rate of uptake of H₂ slowed (~1 h). The mixture was filtered and the solvent removed to give a colourless oil which was purified by column chromatography using 15:1 PE:Et₂O as eluant. The cis alkene 217 was isolated as a soft white solid (0.285 g, 77% yield).
mp: 27-28 °C

C_{20}H_{36}O_2Si  Calc. Mass: 336.2484  
Meas. Mass: 336.2491

$^1$H NMR (400 MHz, CDCl$_3$): $\delta=0.08$ (6H, s, Si(CH$_3$)$_2$); 0.90 (12H, br s, t-Bu and CH$_3$); 0.95 (3H, s, CH$_3$); 1.12 (3H, s, CH$_3$); 1.61 (1H, d, J=13 Hz, C(3) endo H); 1.64 (3H, d, J=1.5 Hz, vinyl CH$_3$); 2.24 (1H, d, J=3.5 Hz, C(4)H); 2.28 (1H, dd, J=3.5, 13 Hz, C(3) exo H); 4.30 (1H, ddd, J=13, 6, 1 Hz, -CHHOTBDMS); 4.37 (1H, ddd, J=13, 5, 1 Hz, -CHHOTBDMS); 5.16 (1H, br s, C(6)H); 5.43 (1H, m, -CH=CHCH$_2$OTBDMS); 5.52 (1H, dt, J=12, 1 Hz, -CH=CHCH$_2$OTBDMS).

IR (CHCl$_3$): $\nu=3599, 3401$ (O-H); 2860 (C-H) cm$^{-1}$

MS: m/e(%)=318 (M$^+$-H$_2$O, 2.7); 261 (6.4); 205 (14); 145 (40); 143 (30); 122 (68); 84 (53); 75 (100).

Attempted rearrangement of alcohol 217:

Anionic oxy-Cope rearrangement attempt A:

A solution of alcohol 217 (0.37 g, 0.11 mmol) in dry THF (5.0 mL) was cannulated into a slurry of KH (0.032 g, 0.80 mmol) in dry THF (2.0 mL) under an Ar atm. After stirring at RT for 15 min, 18-cr-6 (0.21 g, 0.80 mmol) was added and the reaction mixture was refluxed for 3 h, then cooled to RT. NH$_4$Cl$_{(aq)}$ solution was cautiously added, and the mixture was extracted with $\text{Et}_2\text{O}$ (3x). The extracts were dried
over MgSO₄ and the solvent removed to give a yellow oil. Purification by column chromatography using 1:1 PE:Et₂O as eluant gave a white solid (0.010 g, 41% yield) which was determined to be diol 219 resulting from silyl ether cleavage.

mp: 54-55 °C

C₁₄H₂₂O₂  Calc. Mass: 222.1619
               Meas. Mass: 222.1613

¹H NMR (400 MHz, CDCl₃): δ=0.90 (3H, s, CH₃); 0.95 (3H, s, CH₃); 1.10 (3H, s, CH₃); 1.64 (3H, d, J=1.5 Hz, vinyl CH₃); 1.67 (1H, d, J=12 Hz, C(3) endo H); 2.08 (1H, d, J=4 Hz, C(4)H); 2.35 (1H, dd, J=12, 4 Hz, C(3) exo H); 2.58 (2H, br s, exchanges with D₂O, 2xΟH); 4.21-4.32 (2H, m, -CH₂OH); 5.09 (1H, s, C(6)H); 5.50-5.10 (2H, m, cis vinyl H's).

IR (CHCl₃): ν=3394 (O-H); 2940, 2869 (C-H) cm⁻¹

MS: m/e(%)=204 (M⁺-18, 6.1); 161 (24); 143 (29); 133 (56); 131 (30); 122 (100).

Anionic oxy-Cope rearrangement attempt B:

To a slurry of KH (0.115 g, 2.87 mmol) in dry THF (5.0 mL) under an Ar atm was added HMDS (0.61 mL, 2.9 mmol) and the mixture was stirred at RT for 1 h. A solution of alcohol 217 (0.162 g, 0.481 mmol) in dry THF (5.0 mL) was added and the reaction mixture was refluxed for 17 h, then cooled to RT. NH₄Cl(aq) solution was cautiously added and the mixture was extracted with Et₂O (3x). The combined extracts were washed with brine (3x) and dried over MgSO₄. Removal of the solvent gave a yellow oil which was a complex mixture of products as determined by GC and TLC. Purification by column chromatography using 15:1 PE:Et₂O as eluant was attempted. None of the major products isolated was the desired anionic oxy-Cope product, as determined by IR and ¹H NMR spectroscopy.
Oxy-Cope rearrangement attempt A:

A solution of alcohol 217 (0.050 g, 0.15 mmol) in dry toluene (0.60 mL) was sealed under vacuum (~15 mmHg) in an oven-dried Pyrex tube which had been soaked in 35% KOH solution for 2 days, then washed with deionized water. The tube was heated at 140 °C for 14 h. Removal of the solvent gave a yellow liquid which was a complex mixture as determined by TLC and GC. Isolation of some of the major compounds by purification by column chromatography using 9:1 PE:Et2O as eluant showed no evidence of being the desired product as determined by IR and 1H NMR spectroscopy.

Oxy-Cope rearrangement attempt B:

A solution of alcohol 217 (0.068 g, 0.20 mmol) and propylene oxide (0.42 mL, 6.1 mmol) in dry toluene (4.0 mL) was heated under an Ar atm at reflux for 66 h. Removal of the solvent gave a yellow liquid which was purified by column chromatography using 24:1 PE:Et2O as eluant. Starting alcohol 217 (0.024 g, 35% yield) was isolated. There was no evidence of the desired rearrangement product as indicated by IR spectroscopy.

Oxy-Cope rearrangement attempt C:

Anhydrous K2CO3 (0.127 g, 0.920 mmol) was added to a solution of alcohol 217 (0.062 g, 0.18 mmol) in dry decalin (3.7 mL) and the mixture was refluxed under an Ar atm for 2.75 h. After cooling to RT, the liquid was purified by column chromatography eluting first with PE then switching to 24:1 PE:Et2O after all the decalin had been eluted. A colourless liquid (0.037 g) was obtained. It was determined not to be the desired oxy-Cope rearrangement product, and yet it could not be identified.

1H NMR (400 MHz, CDCl3): δ=0.12 (6H, s); 0.80-0.90 (18 H, m); 1.55 (3H, br s); 2.23 (1H, br m); 2.30 (1H, dd, J=7, 18 Hz); 2.45 (1H, dd, J=7, 18 Hz); 2.68 (1H, t, J=7 Hz); 2.97 (2H, d, J=7 Hz); 5.07 (1H, m); 5.13 (1H, br s); 6.30 (1H, d, J=10 Hz).
IR (neat): $\nu=3571$ (O-H); $2959$ (C-H); $1718$, $1663$ (C=O) cm$^{-1}$

MS: $m/e(\%)=336$ (3.6); $171$ (54); $123$ (78); $122$ (100); $115$ (61); $81$ (24); $75$ (38); $73$ (90).

Deprotection of silyl ether 217 to give diol 219:

A solution of silyl alcohol 217 (0.107 g, 0.318 mmol) and TBAF (0.64 mL, 1.0 M/THF, 0.64 mmol) in dry THF (2.0 mL) was stirred at RT under an Ar atm for 15 min. Water was added and the mixture was extracted with $\text{Et}_2\text{O}$ (3x). The combined extracts were washed with brine (3x) and dried over $\text{MgSO}_4$. Removal of the solvent gave a yellow liquid which was purified by column chromatography using 1:1 $\text{PE}:\text{Et}_2\text{O}$ as eluant. The diol 219 was isolated as a white solid (0.064 g, 91% yield). Spectral characteristics were identical with those of the diol 219 previously described.

Attempted rearrangement attempt of diol 219:

Anionic oxy-Cope rearrangement attempt:

A solution of diol 219 (0.051 g, 0.23 mmol) and 18-cr-6 (0.30 g, 1.1 mmol) in dry THF (5.0 mL) was cannulated into a slurry of KH (0.046 g, 1.1 mmol) in dry THF.
(5.0 mL) under an Ar atm. The reaction was stirred at RT for 1 h, then at reflux for 47 h. After cooling to RT, NH₄Cl(aq) solution was cautiously added and the mixture was extracted with Et₂O (3x). The combined extracts were washed with brine (3x) and dried over MgSO₄. Removal of the solvent gave an orange oil which was purified by column chromatography using 1:1 PE:Et₂O as eluant. The only compound which was isolated was starting diol 219 (0.006 g, 12% yield).

Oxy-Cope rearrangement attempt:

Anhydrous K₂CO₃ (0.10 g, 0.77 mmol) was added to a solution of diol 219 (0.034 g, 0.15 mmol) in dry decalin (3.0 mL) and the mixture was refluxed under an Ar atm for 5 h. After cooling to RT, the complex mixture was purified by column chromatography using first PE as eluant until all the decalin had been eluted, then increasing the polarity of eluant until a 1:1 mixture of PE:Et₂O was used. None of the products isolated were determined to be the desired rearrangement product, as determined by IR and ¹H NMR spectroscopy.

Deprotection of silyl ether 216 to give diol 221:

A solution of silyl ether 216 (0.29 g, 0.86 mmol) and TBAF (1.3 mL, 1.0 M/THF, 1.3 mmol) in dry THF (15 mL) was stirred at RT under an Ar atm for 30 min. Water was added, and the mixture was extracted with Et₂O (3x). The combined extracts were washed with brine (3x) and dried over MgSO₄. Removal of the solvent gave an orange
liquid which was purified by column chromatography using 1:1 PE:Et2O as eluant. The
diol 221 was isolated as a yellow oil (0.174 g, 91% yield).

C_{14}H_{20}O_2  
Calc. Mass: 220.1463  
Meas. Mass: 220.1457

^1H NMR (400 MHz, CDCl3): 8=0.94 (3H, s, CH3); 1.08 (6H, s, 2x CH3); 1.63 (2H, br s,
exchanges with D2O, 2x OH); 1.70 (3H, d, J=2 Hz, C(5)CH3); 1.83 (1H, d,
J=13 Hz, C(3) endo H); 2.09 (1H, d, J=4 Hz, C(4)H); 2.23 (1H, dd, J=13, 4 Hz,
C(3) exo H); 4.27 (2H, s, -CH2OH); 5.22 (1H, br s, C(6)H).

IR (neat): υ=3467 (O-H); 2953 (C-H) cm\(^{-1}\)

MS: m/e(%)=220 (M+, 1.2); 177 (20); 122 (100); 107 (88); 91 (45); 77 (26); 41 (36).

Reduction of alkyne diol 221 to give alkene diol 222:

To a slurry of LiAlH4 (0.078 g, 2.1 mol) in dry THF (10 mL) under an Ar atm
was added a solution of alkyne 221 (0.174 g, 0.789 mmol) in dry THF (10 mL).\(^62\) The
mixture was heated at 40 °C for 2 h, then cooled to RT and water was cautiously added.
1 M HCl was added to dissolve the white precipitate that formed. The mixture was
extracted with Et2O (4x) and the combined extracts were washed with brine (3x). Drying
over MgSO4 and removal of the solvent gave a yellow liquid which was purified by
column chromatography using 1:1 PE:Et₂O as eluant. The alkene diol 222 was isolated as a white solid (0.054 g, 31% yield).

1H NMR (400 MHz, CDCl₃): 8=0.90 (3H, s, CH₃); 0.92 (3H, s, CH₃); 1.16 (3H, s, CH₃); 1.57 (1H, d, J=13 Hz, C(3)endo H); 1.70 (3H, s, C(5)CH₃); 2.11 (1H, d, J=4 Hz, C(4)H); 2.15 (1H, dd, J=13, 4 Hz, C(3)exo H); 4.15 (2H, t, J=5 Hz, -CH₂OH); 5.13 (1H, br s, C(6)H); 5.67 (1H, d, J=16 Hz, -CH=CHCH₂OH); 5.77 (1H, m, -CH=CHCH₂OH).

IR (CHCl₃): ν=3606 (O-H); 2948, 2871 (C-H) cm⁻¹

Attempted anionic oxy-Cope rearrangement of alkene diol 222:

![Diagram](image)

To a slurry of KH (0.084 g, 2.1 mmol) in dry THF (3.0 mL) under an Ar atm was added HMDS (0.45 mL, 2.1 mmol), and the mixture was stirred at RT for 4 h. A solution of alkene diol 222 (0.047 g, 2.1 mmol) and 18-cr-6 (0.55 g, 2.1 mmol) in dry 11-IF (2.0 mL) was added. After 3 days at RT, the mixture was refluxed 2 days, then cooled to RT and water was cautiously added. After extraction with Et₂O (3x) the combined extracts were washed with brine (3x) and dried over MgSO₄. Removal of the solvent gave a yellow liquid which was a complex mixture of compounds as indicated by TLC and GC. There was no evidence of the desired rearrangement product as determined by IR and 1H NMR spectroscopy.
Conversion of cyclocamphanone (59) to keto-acetate 248:

\[
\begin{align*}
59 & \quad \rightarrow \\
& \\
248
\end{align*}
\]

To a solution of cyclocamphanone (59, 8.2 g, 54 mmol) in HOAc (35 mL) was added H_{2}SO_{4\text{(conc)}} (0.9 mL) and the mixture was heated at 100 °C under an Ar atm for 46 h. The black solution was cooled to RT, diluted with water and extracted with Et_{2}O (3x). The combined extracts were washed with NaHCO_{3(aq)} solution (4x), brine (3x) and dried over MgSO_{4}. Removal of the solvent gave a yellow liquid which was purified by column chromatography using 4:1 PE:Et{2}O as eluant. Some starting material 59 was recovered (1.05 g, 13% yield) and the product which was obtained as a yellow liquid. Further purification by Kugelrohr distillation gave the keto-acetate 248 as a colourless liquid (5.65 g, 50% yield). GC and \textsuperscript{1}H NMR spectroscopy showed the diastereomeric mixture to be 5:1 \textit{exo}:\textit{endo}.

\[
\begin{align*}
C_{12}H_{18}O & \quad \text{Calc. Mass: } 210.1256 \\
& \quad \text{Meas. Mass: } 210.1258 \\
& \quad \text{Calc.: C 68.55 } \quad \text{H 8.63 }\% \\
& \quad \text{Anal.: C 68.39 } \quad \text{H 8.56 }\%
\end{align*}
\]

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, major (\textit{exo}) diastereomer): \delta=0.83 (3H, s, CH\textsubscript{3}); 0.91 (3H, s, CH\textsubscript{3}); 1.12 (3H, s, CH\textsubscript{3}); 1.80 (1H, d, J=18 Hz, C(3) \textit{endo} H); 1.91 (1H, dd, J=14, 8 Hz, C(6) \textit{endo} H); 2.03 (3H, s, -O\textsubscript{2}CCH\textsubscript{3}); 2.07 (1H, d, J=5 Hz, C(4)H); 2.33 (1H, dd, J=14, 5 Hz, C(6) \textit{exo} H); 2.37 (1H, dd, J=18, 5 Hz, C(3) \textit{exo} H); 4.72 (1H, dd, J=8, 4 Hz, C(5)H).

IR (neat): v=2966 (C-H); 1747 (br, C=O) cm\textsuperscript{-1}
Conversion of keto-acetate 248 to alcohol 249:

\[
\begin{align*}
\text{OAc} & \rightarrow \text{OH} \\
248 & \rightarrow 249
\end{align*}
\]

\[
\begin{align*}
\text{CH}_2\text{I}_2 (9.6 \text{ mL}, 0.12 \text{ mol}) & \text{ was cautiously added over 30 min to a vigorously} \\
stirred slurry of Zn (14.0 \text{ g}, 0.214 \text{ mol}) in dry THF (220 mL) under an Ar atm. \text{ After an induction period (~15 min) the reaction became highly exothermic and was kept under} \\
control by periodic cooling with an ice bath. \text{ Upon completion of the CH}_2\text{I}_2 \text{ addition the} \\
mixture was stirred at RT for 30 min. \text{ After cooling to 0 °C, TiCl}_4 (2.6 \text{ mL}, 24 \text{ mmol}) \\
was cautiously added and after vigorous fuming had subsided the mixture was warmed to} \\
RT and stirred for 30 min. \text{ A solution of keto-acetate 248 (1.00 g, 4.8 mmol) in dry THF} \\
(20 mL) was added and the mixture was stirred for 1.25 h. \text{ Et}_2\text{O (120 mL) was cautiously added, then brine. The layers were separated and the organic layer was} \\
washed with brine (3x). \text{ Drying over MgSO}_4 \text{ and removal of solvent gave a pale yellow} \\
liquid which was purified by column chromatography using 4:1 PE:Et}_2\text{O as eluant. The} \\
alcohol 249 \text{ was isolated as a colourless liquid (0.70 g, 89% yield) which solidified upon} \\
standing. \\
\]

C\text{\textsubscript{11}}H\text{\textsubscript{18}}O \quad \text{Calc. Mass: 166.1358} \\
Meas. Mass: 166.1359 \\
Calc.: C 79.47 \quad H 10.91 % \\
Anal.: C 79.19 \quad H 11.10 % \\

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \delta=0.73 (3H, s, CH\textsubscript{3}); 0.93 (3H, s, CH\textsubscript{3}); 1.13 (3H, s, CH\textsubscript{3}); 1.58 (1H, d, J=3 Hz, exchanges with D\textsubscript{2}O, -OH); 1.68-1.85 (4H, m, C(3))
endo H, C(4)H and C(6) exo and endo H's); 2.34 (1H, dm, J=16 Hz, C(3) exo H); 3.85 (1H, br dd, J=12, 5 Hz, C(5)H); 4.66 (1H, br s, vinyl H); 4.72 (1H, br s, vinyl H).

IR(CHCl₃): ν=3613, 3445 (O-H); 3013, 2957, 2874 (C-H) cm⁻¹

MS: m/e(%)=166 (M⁺, 30); 133 (70); 123 (87); 105 (100); 95 (80); 93 (83); 91 (75).

Oxidation of alcohol 249 to give ketone 250:

A solution of DMSO (38 µL, 0.54 mmol) in dry CH₂Cl₂ (1.0 mL) was added dropwise to a solution of oxalyl chloride (47 µL, 0.54 mmol) in dry CH₂Cl₂ (1.0 mL) at -78 °C under an Ar atm. After 15 min, a solution of alcohol 249 (0.075 g, 0.45 mmol) in dry CH₂Cl₂ (2.0 mL) was added dropwise, and the reaction mixture was stirred at -78 °C for 1 h. Et₃N (0.19 mL, 1.4 mmol) was added and the reaction was allowed to warm to RT overnight. Water was added and the mixture was extracted with CH₂Cl₂ (3x). The combined extracts were washed with brine (3x), dried over MgSO₄ and the solvent removed to give a yellow liquid. Purification by column chromatography using 4:1 PE:Et₂O as eluant gave the ketone 250 as a colourless solid (0.046 g, 62% yield).

C₁₁H₁₆O

Calc. Mass: 164.1201
Meas. Mass: 164.1196

Calc.: C 80.44       H 9.82 %
Anal.: C 80.27       H 9.72 %
$^1$H NMR (300 MHz, CDCl$_3$): $\delta$=0.85 (3H, s, CH$_3$); 0.96 (3H, s, CH$_3$); 1.06 (3H, s, CH$_3$); 1.83 (1H, d, J=17 Hz, C(6) endo H); 2.15-2.25 (3H, m, C(6) exo H, C(3) endo H and C(4)H); 2.60 (1H, dm, J=15 Hz, C(3) exo H); 4.85 (1H, br s, vinyl H); 4.90 (1H, br s, vinyl H).

IR(CH$_2$Cl$_2$): v=2924, 2877 (C-H); 1742 (C=O) cm$^{-1}$

MS: m/e(%)=164 (M$^+$, 7.5); 121 (12); 93 (100); 79 (13); 40 (12).

Protection of ketone 250 to give dithiane 245:

To a solution of ketone 250 (0.034 g, 0.21 mmol) in dry CH$_2$Cl$_2$ (2.0 mL) under an Ar atm were added successively ethanedithiol (0.020 mL, 0.25 mmol) and BF$_3$·OEt$_2$ (13 µL, 0.10 mmol). After stirring at RT overnight, the reaction mixture was diluted with Et$_2$O and washed successively with 5% NaOH(aq) solution (3x), water and brine (3x). The organic layer was dried over MgSO$_4$ and the solvent removed to yield a pink liquid. Purification by column chromatography using 15:1 PE:Et$_2$O as eluant gave the dithiane 245 as a colourless liquid (0.021 g, 42% yield).

C$_{13}$H$_{20}$S$_2$  
Calc. Mass: 240.1006  
Meas. Mass: 240.1008

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$=0.96 (6H, br s, 2xCH$_3$); 1.02 (3H, s, CH$_3$); 1.58 (1H, d, J=12 Hz, C(3) endo H); 1.81 (1H, ddd, J=12, 4, 2 Hz, C(3) exo H); 1.94 (1H, d, J=18 Hz, C(6) endo H); 2.46 (1H, dd, J=18, 4 Hz, C(6) exo H); 2.67 (1H, br s,
C(4)H); 3.10-3.35 (4H, m, thioketal H's); 4.81 (1H, s, vinyl H); 4.95 (1H, vinyl H).

IR (neat): $\nu=2961, 2923, 2869$ (C-H) cm$^{-1}$

MS: m/e(%)=240 (M+, 53); 212 (44); 121 (75); 118 (63); 107 (100); 105 (72); 91 (38).

Attempted acid-catalyzed rearrangement of dithiane 245:

To a solution of dithiane 245 (0.013 g, 0.054 mmol) in HOAc (1.0 mL) was added H$_2$SO$_4$ (0.024 mL) and the mixture was stirred at RT for 1.5 h. As no reaction occurred, as indicated by TLC and GC, the mixture was heated at 100 °C for 2 h. After cooling to RT, water was added and the mixture was extracted with Et$_2$O (3x). The combined extracts were washed with NaHCO$_3$ solution (3x) and brine (3x). Drying over MgSO$_4$ and removal of the solvent gave a yellow oil which was purified by column chromatography using 15:1 PE:Et$_2$O as eluant to give a white solid (5 mg) which could not be identified, but which was determined not to be the desired acetate 247.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta=0.89$ (3H, s, CH$_3$); 1.07 (3H, s, CH$_3$); 1.21 (3H, s, CH$_3$); 1.23 (3H, s, CH$_3$); 1.40-1.46 (1H, m); 1.63-1.85 (3H, m); 2.43 (1H, d, J=18 Hz); 2.52 (1H, dd, J=18, 1.5 Hz).

IR (CHCl$_3$): $\nu=2958$ (C-H); 1755 (C=O) cm$^{-1}$

MS: m/e(%)=258 (6.6); 172 (14); 139 (46); 122 (12); 112 (33); 86 (53); 69 (81); 55 (50); 43 (66).
Protection of alcohol 249 to give benzyl ether 251:

\[
\begin{align*}
\text{249} & \quad \text{OH} \\
\text{251} & \quad \text{OBn}
\end{align*}
\]

A solution of alcohol 249 (0.13 g, 0.77 mmol) in dry THF (5.0 mL) was added to a slurry of KH (0.062 g, 1.6 mmol) in dry THF (1.0 mL) under an Ar atm. After stirring at RT for 30 min, BnBr (0.11 mL, 0.92 mmol) was added. After 30 min, water was cautiously added and the mixture was extracted with Et₂O (3x). The combined extracts were washed with brine (3x), dried over MgSO₄ and removal of the solvent gave a yellow liquid. Purification by column chromatography using first PE as eluant then increasing the polarity to 24:1 PE:Et₂O gave the benzyl ether 251 as a colourless liquid (0.165 g, 84% yield).

C₁₈H₂₄O  
Calc. Mass: 256.1827  
Meas. Mass: 256.1819

Calc.: C 84.32 H 9.43 %  
Anal.: C 84.63 H 9.53 %

¹H NMR (400 MHz, CDCl₃): 8=0.75 (3H, s, CH₃); 0.95 (3H, s, CH₃); 1.14 (3H, s, CH₃); 1.65 (1H, dd, J=13, 8 Hz, C(6)_{endo} H); 1.71 (1H, dt, J=16, 1 Hz, C(3)_{endo} H); 1.83 (1H, dd, J=13, 4 Hz, C(6)_{exo} H); 2.04 (1H, d, J=5 Hz, C(4)H); 2.37 (1H, dm, J=16 Hz, C(3)_{exo} H); 3.52 (1H, dd, J=8, 4 Hz, C(5)H); 4.40 (1H, d, J=12 Hz, -OCH₂HPh); 4.48 (1H, d, J=12 Hz, -OCH₂HPh); 4.66 (1H, br s, vinyl H); 4.72 (1H, br s, vinyl H).

IR (neat): ν=2950, 2870 (C-H) cm⁻¹

MS: m/e(%)=256 (M⁺, 5.4); 150 (36); 121 (36); 91 (100); 69 (25).
Protection of alcohol 249 to give methyl ether 252:

![Chemical structure](image)

A solution of alcohol 249 (0.17 g, 1.0 mmol) in dry THF (5.0 mL) was added to a
slurry of KH (0.081 g, 2.0 mmol) in dry THF (2.0 mL) under an Ar atm. After stirring at
RT for 15 min, Mel (0.075 mL, 1.2 mmol) was added. After 15 min, water was
cautiously added and the mixture was extracted with Et₂O (3x). The combined extracts
were washed with brine (3x), dried over MgSO₄ and removal of the solvent gave a
colourless liquid. Purification by column chromatography using 9:1 PE:Et₂O as eluant
gave the methyl ether 252 as a colourless liquid (0.153 g, 85% yield).

C₁₂H₂₀O

Calc. Mass: 180.1514
Meas. Mass: 180.1511

Calc.: C 79.94
Anal.: C 79.70
H 11.18 %
H 11.21 %

¹H NMR (400 MHz, CDCl₃): δ=0.74 (3H, s, CH₃); 0.94 (3H, s, CH₃); 1.07 (3H, s, CH₃); 1.63 (1H, dd, J=13, 8 Hz, C(6) exo H); 1.68-1.75 (2H, m, C(6) endo H and C(3) endo H); 1.99 (1H, d, J=5 Hz, C(4)H); 2.37 (1H, dm, J=16 Hz, C(3) exo H); 3.26 (3H, s, -OCH₃); 3.33 (1H, m, C(5)H); 4.67 (1H, br s, vinyl H); 4.72 (1H, br s, vinyl H).

IR (neat): ν=2954 (C-H) cm⁻¹

MS: m/e(%)=180 (M⁺, 22); 148 (59); 133 (100); 105 (82); 87 (84); 79 (45).
Attempted acid-catalyzed rearrangement of benzyl ether 251:

\[
\begin{align*}
\text{OBn} & \quad \rightarrow \quad \text{complex mixture}
\end{align*}
\]

To a solution of benzyl ether 251 (0.136 g, 0.53 mmol) in HOAc (2.0 mL) was added H\textsubscript{2}SO\textsubscript{4}(conc) (0.048 mL) and the mixture was stirred under an Ar atm at RT for 1 h. The reaction was added to water and the mixture was extracted with Et\textsubscript{2}O (3x). The combined extracts were washed with NaHCO\textsubscript{3}(aq) solution (3x) and brine (3x). Drying over MgSO\textsubscript{4} and removal of the solvent gave a yellow liquid (0.165 g) which was a highly complex mixture as determined by TLC and GC.

Attempted acid-catalyzed rearrangement of methyl ether 252:

\[
\begin{align*}
\text{OMe} & \quad \rightarrow \quad \text{complex mixture}
\end{align*}
\]

To a solution of methyl ether 252 (0.115 g, 0.639 mmol) in HOAc (1.0 mL) was added dropwise H\textsubscript{2}SO\textsubscript{4}(conc) (24 \mu L) and the solution was stirred under an Ar atm at RT for 45 min. After addition to water, the mixture was extracted with Et\textsubscript{2}O (3x) and the combined extracts were washed successively with NaHCO\textsubscript{3}(aq) solution (3x), water, and brine (2x). After drying over MgSO\textsubscript{4} the solvent was removed to give a yellow oil (0.085 g) which was a complex mixture as determined by TLC and GC.
Acid-catalyzed rearrangement of ketone 250 to give ketone 255:

To a solution of ketone 250 (0.011 g, 0.067 mmol) in HOAc (1.0 mL) was added H$_2$SO$_4$(conc) (24 µL) and the reaction was stirred under an Ar atm at RT for 4 d. After addition to water, the mixture was extracted with Et$_2$O (3x) and the combined extracts were washed with NaHCO$_3$(aq) solution (3x) and brine (3x). After drying over MgSO$_4$ and removal of the solvent a pale yellow oil was isolated which was purified by column chromatography using 24:1 PE:Et$_2$O as eluant. A colourless liquid was isolated (6 mg, 55% yield) which was determined to be ketone 255.

C$_{11}$H$_{16}$O  
Calc. Mass: 164.1201  
Meas. Mass: 164.1208

$^1$H NMR (400 MHz,CDCl$_3$): $\delta$=1.07 (3H, s, CH$_3$); 1.15 (3H, s, CH$_3$); 1.30 (3H, s, CH$_3$); 1.63 (1H, d, J=11 Hz); 1.78-1.90 (2H, m); 2.29 (1H, s, C(4)H); 4.80 (1H, s, vinyl H); 4.86 (1H, s, vinyl H).

IR (neat): $\nu$=2961, 2927 (C-H); 1741 (C=O) cm$^{-1}$

MS: m/e(%)=164 (M$^+$, 4.4); 121 (15); 107 (18); 71 (30); 57 (56); 43 (100); 32 (26).

Conversion of (+)-camphor (25) to (-)-2-methylenebornane (240):
To methyltriphenylphosphonium bromide (79.7 g, 0.223 mol) which had been dried under vacuum (~0.1 torr) for 12 h to remove traces of moisture was added dry THF (~200 mL) and the slurry was kept under an Ar atm. n-BuLi (~139 mL, 1.6 M/hexane, 0.223) was added dropwise until a red solution was obtained. After heating the solution at 50 °C for 2 h, a solution of (+)-camphor (25, 21.2 g, 0.139 mol) in dry THF (80 mL) was slowly added. A white precipitate was obtained and the yellow-orange reaction mixture was refluxed for 24 h. After cooling to RT, approximately half of the solvent was removed and water was added to the remaining mixture which was then extracted with pentane (3x). The combined extracts were washed with water (3x), dried over MgSO4, and the solvent removed to give a mixture of yellow liquid and white solid. The mixture was purified by column chromatography using PE as eluant to provide (+)-2-methylenebornane (240) as a white solid (18.17 g, 87% yield).

C11H18  
Calc. Mass: 150.1409  
Meas. Mass: 150.1400  

Calc.: C 87.93  
Anal.: C 87.87  

1H NMR (400 MHz, CDC13): δ=0.76 (3H, s, CH3); 0.89 (3H, s, CH3); 0.92 (3H, s, CH3); 1.15-1.30 (2H, m, C(5) and C(6) endo H's); 1.64 (1H, ddd, J=12, 12, 4 Hz, C(6) exo H); 1.73 (1H, dd, J=8, 4 Hz, C(4)H); 1.78 (1H, m, C(5) exo H); 1.91 (1H, dt, J=16, 1.5 Hz, C(3) endo H); 2.38 (1H, br d, J=16 Hz, C(3) exo H); 4.63 (1H, s, vinyl H); 4.69 (1H, s, vinyl H).

IR (CHCl3): ν=2942, 2873 (C-H); 1655 (C=C); 878 (vinyl C-H) cm⁻¹

MS: m/e(%)=150 (M+, 22); 135 (38); 107 (100); 93 (66); 79 (72); 67 (19).
Acid-catalyzed rearrangement of (-)-2-methylenebornane (240):

To a solution of (-)-2-methylenebornane (240, 1.91 g, 12.7 mmol) in HOAc (8.0 mL) was added 45% HBr/HOAc solution (8.0 mL). After 5 min, the mixture was cautiously poured onto water, extracted with Et₂O (3x) and the combined extracts were washed with water (3x), NaHCO₃(aq) solution (3x) and water (3x). Drying over MgSO₄ and removal of the solvent gave a yellow solid which was purified by flash column chromatography using 15:1 PE:Et₂O. 4-Methylisobornyl bromide (266) was isolated as a white solid (2.55 g, 87% yield). This compound discoloured upon storage and was therefore always freshly prepared and immediately used in the next reaction.

C₁₁H₁₉⁷⁹Br  Calc. Mass: 230.0670  
               Meas. Mass: 230.0663
C₁₁H₁₉⁸¹Br  Calc. Mass: 232.0650  
               Meas. Mass: 232.0645

¹H NMR (CDCl₃): δ=0.72 (3H, s, CH₃O); 0.91 (3H, s, CH₃); 1.00 (3H, s, CH₃); 1.07 (3H, s, CH₃); 1.15-1.22 (2H, m); 1.42-1.49 (1H, m); 1.70-1.76 (1H, m); 2.10-2.15 (2H, m, C(3) exo and endo H's); 4.15 (1H, dd, J=8, 5 Hz, C(2) endo H).

IR (CHCl₃):  ν=2955, 2872 (C-H) cm⁻¹

MS: m/e(%)=232, 230 (M⁺, 0.4, 0.5); 217, 215 (4.2, 3.7); 151 (89); 150 (71); 135 (82); 121 (75); 107 (100); 95 (91); 81 (86).
Conversion of 4-methylisobornyl bromide (266) to (+)-4-methylisoborneol (267) and 4-methylborneol (268):

\[
\text{266} \quad \text{Br} \quad \text{267 (exo OH)} \quad \text{268 (endo OH)}
\]

To freshly ground, flame-dried Mg (0.60 g, 0.025 mol) under an Ar atm was added a crystal of I\(_2\) and dry THF (6.0 mL). After the dropwise addition of dibromoethane (0.51 mL, 6.0 mmol) to initiate Grignard formation, a solution of 4-methylisobornyl bromide (266, 2.76 g, 11.9 mmol) in dry THF (5.0 mL) was added at a rate to maintain vigorous reaction. The mixture was stirred until exothermicity ceased (~30 min), then dry THF (19.0 mL) was added to increase the volume. In the next step of the reaction, potentially explosive peroxides are formed and therefore the use of a blast shield is recommended. O\(_2\) (dried by passage through 4Å molecular sieves and Drierite\textsuperscript{®}) was bubbled through the reaction mixture for 1.5 h and the mixture was kept under a positive Ar atm overnight. 1 M HCl was cautiously added to decompose any unreacted Mg and to hydrolyze the Grignard complex, and the mixture was extracted with Et\(_2\)O (3x). The combined extracts were washed with water (2x), NaHC\(_3\)(aq) solution (2x) and water (2x), dried over MgSO\(_4\) and the solvent removed to give a pale yellow liquid. Purification by column chromatography using 9:1 PE:Et\(_2\)O as eluant gave (+)-4-methylisoborneol (267, 0.2592 g, 13% yield) as a white solid and a 6:1 mixture of (+)-4-methylisoborneol (267) and 4-methylborneol (268) (0.5300 g, 27% yield) also as a white solid.

\[
\text{C}_{11}\text{H}_{20}\text{O} \quad \text{Calc. Mass:} \quad 168.1514 \\
\text{Meas. Mass:} \quad 168.1511
\]
Calc.:  C 78.51      H 11.98 %
Anal.:  C 78.53      H 12.12 %

$^1$H NMR (400 MHz, CDCl$_3$, 267): $\delta$=0.68 (3H, s, CH$_3$); 0.87 (3H, s, CH$_3$); 0.90 (3H, s, CH$_3$); 0.94 (3H, s, CH$_3$); 0.95-1.11 (2H, m, C(5) and C(6) endo H's); 1.35-1.46 (2H, m, C(6) and C(3) endo H's); 1.51 (1H, ddd, J=8, 8, 4 Hz, C(5) exo H); 1.74 (1H, dd, J=14, 8 Hz, C(3) exo H); 3.61 (1H, dd, J=8, 4 Hz, C(2)H).

$^1$H NMR (400 MHz, CDCl$_3$, 268): $\delta$=0.71 (3H, s, CH$_3$); 0.73 (3H, s, CH$_3$); 0.83 (3H, s, CH$_3$); 0.86 (3H, s, CH$_3$); 1.02 (1H, dd, J=13, 4 Hz); 1.18-1.30 (2H, m); 1.44-1.51 (1H, m); 1.82-1.90 (1H, m); 1.93-2.03 (1H, m); 3.94 (1H, br d, J=11 Hz, C(2)H).

IR (CHCl$_3$): ν=3615 (O-H); 2951, 2871 (C-H) cm$^{-1}$

MS: m/e(%)=168 (M+, 2.6); 124 (28); 109 (100); 84 (29); 55 (28); 41 (35).

$[\alpha]_{D}^{26}$ +32.9 ° (c 8.1, 95% EtOH) for (+)-4-methylisoborneol (267).

Separation of 267 and ent-267 by GC using a chiral column:

Sample A of (+)-4-methylisoborneol (267, previously prepared by the H$_2$SO$_4$/HOAc rearrangement of (-)-2-methylenebornane (240) route) was known to contain both enantiomers 267 and ent-267 and its specific rotation was determined to be +20.9 ° (c 9.4, 95% EtOH). Separation of the two enantiomers was accomplished by using a Chirasil-val III capillary column (Alltech, 25 m x 0.25 mm i.d.). With a He flow rate of 1.46 mL/min and an oven temperature of 60 °C, the rt of (+)-4-methylisoborneol (267) was 29.90 min (br peak) and the rt of (-)-4-methylisoborneol (ent-267) was 30.70 min. Sample B of (+)-4-methylisoborneol (267) was prepared by the 45% HBr/HOAc route described above. When a GC was taken under the identical conditions
as for Sample A, there was no evidence of (-)-4-methylisoborneol (ent-267); a single peak (rt=29.36 min) corresponding to (+)-4-methylisoborneol (267) was obtained.

Oxidation of (+)-4-methylisoborneol (267) and 4-methylborneol (268) to (-)-4-methylcamphor (229):

![Chemical structure]

A solution of CrO3 (0.089 g, 0.89 mmol) in water (1.2 mL) and H2SO4(conc) (0.3 mL) was added dropwise to a solution of mixture of (-)-4-methylisoborneol (267) and 4-methylborneol (268) (0.075 g, 0.45 mmol) in acetone (5.0 mL) at 0 °C.136 After the addition of the orange reagent was complete, the reaction mixture turned green and was stirred at RT for 1 h. Water was added and the mixture was extracted with Et2O (3x). The combined extracts were washed successively with water (3x), NaHCO3(aq) solution (2x) and water (2x), dried over MgSO4 and the solvent removed to give a white solid. Purification by column chromatography using 15:1 PE:Et2O as eluant gave (-)-4-methyl-camphor (229) as a white solid (0.072 g, 97% yield).

C11H18O  
Calc. Mass: 166.1358
Meas. Mass: 166.1358

Calc.:  C 79.47   H 10.91 %
Anal.:  C 79.79   H 10.91 %

1H NMR (400 MHz, CDCl3): δ=0.71 (3H, s, CH3); 0.83 (3H, s, CH3); 0.92 (3H, s, CH3); 1.04 (3H, s, CH3); 1.35-1.43 (2H, m, C(5) and C(6) endo H's); 1.57-1.75 (2H, m, C(5) and C(6) exo H's); 1.87 (1H, d, J=18 Hz, C(3) endo H); 2.08 (1H, dd, J=18, 3 Hz, C(3) exo H).
IR (CHCl₃): ν=2959, 2874 (C-H); 1734 (C=O).

MS: m/e(%)=166 (M⁺, 30); 122 (44); 109 (90); 82 (100); 55 (33).

[α]₀²⁵ D -26.7 ° (c 3.4, 95% EtOH)

Chiral shift reagent and ¹H NMR experiment done on (-)-4-methylcamphor (229):

Sample C of (-)-4-methylcamphor (229, 0.014 g, 0.086 mmol) was taken from the preparation described above, dissolved in CDCl₃ (1.0 mL, dried by passage through basic alumina), and transferred to a 5 mm NMR tube. A 0.17 M stock solution was prepared by dissolving [Eu(hfc)₃] (0.099 g, 0.17 mmol) in CDCl₃ (0.50 mL, also passed through basic alumina). A ¹H NMR (400 MHz, CDCl₃) spectrum was recorded before the addition of any shift reagent and was identical to the spectrum described above. [Eu(hfc)₃] solution (50 μL, 0.17 M/CDCl₃, 0.0086 mmol) was added and the NMR tube was vigorously shaken. Another ¹H NMR spectrum was recorded which showed broadening of most signals and changes in chemical shift. Another portion of [Eu(hfc)₃] solution (0.15 mL, 0.17 M/CDCl₃, 0.026 mmol) was added and after vigorous shaking, another ¹H NMR spectrum was recorded. A final addition of [Eu(hfc)₃] solution (0.15 mL, 0.17 M/CDCl₃, 0.026 mmol) was done and a ¹H NMR spectrum taken. The results of these studies have been presented in discussion of Chapter 2 (p. 109).
References and Notes


    c) *ibid.* 1973, 33, 145.


96. for a review see Olsen and Currie In *The Chemistry of the Thiol Group, Pt.2*; Patai, S., Ed.; Wiley: New York, 1974; p. 521-532.

97. for reviews see a) Pettit; van Tamelen, E. E. *Org. React.* 1962, 12, 356.


125. for a general review of the Wittig reaction see Maercker, A. *Org. React.* 1965, 14, 270.


Appendix

1. X-ray crystal structure of alcohol 158:
2. X-ray crystal structure of ketone 171: