THE USE OF CAMPHOR IN SESQUITERPENOID SYNTHESIS

By

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Date December 30, 1987
This thesis is dedicated to my dearest parents,
Dr. and Mrs. Y. C. Kuo with love..............
ABSTRACT

This thesis, entitled "The use of camphor in sesquiterpenoid synthesis", consists of three chapters. Chapter One describes the conversion of (+)-8-bromocamphor (42) into a chiral dimethyl-acetal enolsilyl ether (105) that undergoes facile TiCl₄-promoted intramolecular cyclisation to provide tricyclic intermediates (195a,b), which after a series of functional group interconversions and the introduction of the gem-dimethyl group, leads to the first enantiospecific total synthesis of (+)-longiborneol (59) (ca. 13% in 21 steps from (+)-camphor (26)). Oxidation of (+)-longiborneol (59) provides (+)-longicamphor (83), which was converted into (+)-longi-isoborneol (89) by reduction. Subsequent treatment with of (+)-longiisoborneol (89) with MsCl, 4-DMAP, and pyridine, reveals (+)-longifolene (61) (ca. 52% in 3 steps from (59)).

Two other major attempts were also carried out prior to the successful synthesis of (59) and (61). Triene acetates (103a,b) were synthesised (ca. 8% in 10 steps from (+)-camphor (26)), but failed to undergo the intramolecular Diels-Alder reaction. In addition, (+)-campherenone (151) was also prepared (ca. 28% in 9 steps from (+)-camphor (26)), and both (151) and its derivatives (170), and (104) undergo SnCl₄-promoted intermolecular tertiary α-alkylation reaction to provide dimers (169a,b).

Chapter Two describes two synthetic approaches to albene (221) which involves an intramolecular ene reaction, or
an intramolecular free radical cyclisation reaction. A new enantiospecific synthesis route to (+)-β-santalene (259) (ca. 78% in 2 steps from (±)-camphenone (151)) is illustrated, however, (±)-β-santalene failed to undergo the intramolecular ene reaction to provide olefin (261). In addition, bromo-olefin (260) is also prepared (ca. 59% in 14 steps from (±)-camphor (26)), but cyclises in a 6-exo-trig mode in the intramolecular free radical cyclisation reaction to provide methyl ether (331).

Chapter Three describes an evaluation of the potential use of (+)-5,6-dehydrocamphor (323) as a chiral synthon in the synthesis of the A,B ring system (cf. 329) of several classes of terpenoid. (+)-5,6-dehydrocamphor (323) was prepared from (-)-endo-3-bromocamphor (41) in two steps, and which is then converted to bicyclic enones (368a,b, 369a,b, 376a,b) by a sequence in which the key reaction was an anionic oxy-Cope rearrangement. Bicyclic enones (368a,b) were converted to tricyclic ketals (385a,b), but attempts to convert this compound to an angularly methylated intermediate (434) were unsuccessful. Furthermore, 1,5-dienols (409a,b), synthesised from (323) in ca. 50% yield, failed to undergo an anionic oxy-Cope rearrangement to provide bicyclic ketones (410a,b). Alternative ways of constructing an angular methyl group into the C(10) position in bicyclic enones (369a,b, or 376a,b) are currently being investigated in our laboratory. In addition, bicyclic ketones (373a,b) could serve as key intermediates
in an enantiospecific synthesis of spirodysin (421), and indirectly to the synthesis of furodysin (422), and furodysinin (423).
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LIST OF ABBREVIATIONS AND TERMINOLOGY

(a) Terminology

Since many of the compounds referred to in this thesis are optically active, in order to differentiate between enantiomers the term 'ent' is used. 'Ent' refers to the enantiomer of the compound given, eg. (+)-camphor 10 has the structure:

(-)-camphor is thus denoted as ent10.

(b) Abbreviations

The following abbreviations are used in this thesis:

A - Activating group
Ac - Acetyl
AIBN - 2,2'-Azobis-(isobutyronitrile)
APT - Attached Proton Test
ax - Axial
BB - Broad Band Decouple
bp - Boiling point
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<tr>
<td>br</td>
<td>Broad (ir and $^1$H-n.m.r.)</td>
</tr>
<tr>
<td>Bu</td>
<td>tertiary-Butyl</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
</tr>
<tr>
<td>Conc.</td>
<td>Concentrated</td>
</tr>
<tr>
<td>c</td>
<td>Concentration in g/100 mL of solvent</td>
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<tr>
<td>CD</td>
<td>Circular Dichroism</td>
</tr>
<tr>
<td>d</td>
<td>Doublet ($^1$H-n.m.r.)</td>
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<tr>
<td>DHP</td>
<td>Dihydropyrrane</td>
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<td>DIBAL</td>
<td>Diisobutylaluminum hydride</td>
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<td>DIS</td>
<td>Disconnection</td>
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<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
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<tr>
<td>DMF</td>
<td>N,N-Dimethylformamide</td>
</tr>
<tr>
<td>DMS</td>
<td>Dimethylsulphide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulphoxide</td>
</tr>
<tr>
<td>E</td>
<td>Electrophile</td>
</tr>
<tr>
<td>EG</td>
<td>Ethylene Glycol</td>
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<td>eq</td>
<td>Equatorial</td>
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<td>Et</td>
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<td>FGI</td>
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<tr>
<td>LDA</td>
<td>Lithium Diisopropylamide</td>
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<tr>
<td>lit.</td>
<td>Literature</td>
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<tr>
<td>m</td>
<td>Multiplet ($^1$H-n.m.r.) or Medium (ir)</td>
</tr>
<tr>
<td>M</td>
<td>Molar</td>
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</table>
Me - Methyl
mmol - Millimole
m/e - Mass to charge ratio
MHz - Mega hertz
MOM - Methoxymethyl
mp - Melting point
Ms - Methanesulphonyl
MTPA - α-Methoxy-α-(trifluoromethyl)phenylacetyl
N - Normal (concentration)
NBS - N-Bromosuccinimide
n.m.r. - Nuclear Magnetic Resonance
NOE - Nuclear Overhauser Effect
PCC - Pyridinium Chlorochromate
PDC - Pyridinium Dichromate
ph - Phenyl
ppm - Parts per Million
py - Pyridine
q - Quartet (1H-n.m.r.)
s - Singlet (1H-n.m.r.) or Strong (ir)
t - Triplet (1H-n.m.r.)
TBAF - Tetrabutylammonium Fluoride
TBDMS - tertiary-Butyldimethylsilyl
t - tertiary
THF - Tetrahydrofuran
tlc - Thin Layer Chromatography
TMS - Trimethylsilyl

xi
triflate - Trifluoromethanesulphonate
UV - Ultra Violet
w/v - Weight to volume ratio
w - Weak (ir)
WM - Wagner Meerwein Rearrangement
Wt. - Weight
[α] - Specific Rotation at 589 nm
2,3 exo Me - 2,3-exo-Methyl shift
2,6 H - 2,6-Hydride shift
δ - Chemical shift in ppm from the tetramethylsilane signal
ν - Wavenumbers (cm⁻¹)
ACKNOWLEDGEMENTS

This thesis could not be written without extensive helps from the fine group of people at U.B.C.. First, I wish to acknowledge my research supervisor, Professor Thomas Money, for his stimulating ideas, patient enlightenment, and continuous support in many ways throughout the course of this work. I also wish to thank the former members of Professor Money's research group, Dr. S. Piper, Dr. J. Hutchinson and Mr. G. Roberts for their technical assistance at the very beginning of my research. A special thanks goes to Mr. A. Clase for proofreading my thesis. My sister Miss Feng-ni Kuo's on-going help during the preparation of this thesis is appreciated.

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Finally, I wish to thank the Department of Chemistry, U.B.C. and N.S.E.R.C., Canada for their financial support over the past four years.
"The synthesis of substances occurring in Nature, perhaps in greater measure than in any other area of organic chemistry, provides a measure of the condition and powers of the science.......

R. B. Woodward
in Perspectives in Organic Chemistry (1956)
The structural diversity of natural products has presented a considerable challenge to the organic chemists who are concerned with their laboratory synthesis, and indeed this challenge has provided impetus for great advances in synthetic methodology. The problems associated with synthetic methodology involve construction of the carbon framework, functional group transformation, and control of absolute stereochemistry. In general, however, the control of absolute stereochemistry remains the most complicated issue in developing a synthetic strategy to a particular natural product.

Most natural products exist in nature as enantiomerically pure compounds and usually only one enantiomer is responsible for the particular biological activity, while the other one is either inactive or capable of causing serious side effects [1]. Stimulated by the enantiomeric purity of most natural products and by the complete asymmetric induction of enzymic reactions occurring in biological systems, organic chemists have developed ways of preparing enantiomerically pure forms of natural products by (i) resolving some convenient intermediate or final product; (ii) constructing the target molecule from achiral intermediates by means of asymmetric induction [2]; and (iii) the utilisation of inexpensive, and readily available chiral starting materials [3]. A brief discussion of each of these approaches will be provided below.
(i) First, the conventional method of obtaining enantiomerically pure target molecules has been the employment of resolution of racemates. To separate enantiomers at the end of a synthesis, especially of multi-step ones results in the loss of at least half of the product. The resolution of racemates at the beginning of a synthesis is particularly useful in those cases where both enantiomers can either be used in the synthesis or transformed into synthetically useful building blocks. For example, in the synthesis of the macrolide, erythrynomolide B (1) [4], the racemic ketal (2) was resolved by separating the corresponding mandelate esters (3) and (4). Subsequent hydrolysis of these esters provided enantiomerically pure ketals (5) and (6) which were then used as the chiral starting materials in the construction of upper left half and lower right half of the target molecule (1) respectively.

(ii) An alternative approach to the synthesis of natural products which avoids wasteful and often time consuming resolution steps, involves asymmetric induction. Generally,
the first reaction of an achiral starting molecule to generate a chiral center will inevitably provide racemates as shown in Scheme 1. Furthermore, any subsequent reaction to generate additional chiral centers will produce both diastereomers and enantiomers in which the diastereomers could be possibly separated, whereas the enantiomers must be resolved. Thus it is desirable that the first step in the reaction sequence should
generate preferentially one enantiomer over the other. This asymmetric induction, which converts an achiral unit into a chiral unit in which the enantiomers (R)-C and (S)-C are produced in unequal amounts, usually requires a chiral auxiliary. It is this aspect of asymmetric induction which plays a central role in the reaction process and dictates which reaction product (R)-C or (S)-C will predominate, as illustrated in Scheme 2.

Scheme 2

The ratio of (R)-C/(S)-C produced is dependent on the relative rate constants \(K(R)\) and \(K(S)\) leading to the respective diastereomeric transition states (T.S.). The magnitude of the difference in free energy \(\Delta \Delta G^\ddagger\) will determine the ratio of enantiomeric products (R)-C/(S)-C since these two competing processes are a function of the respective free energies of activation \(\Delta G^\ddagger\). Approximately, a \(\Delta \Delta G^\ddagger\) of 2 kcal/mole at 0°C can produce essentially one of the enantiomers in at least 80%
enantiomeric excess [5] and this ratio may be deemed as synthetically useful. Hence it is desirable to maximise $\Delta \Delta G^+$ which would increase the enantiomeric excess of the product. Four examples of the asymmetric induction approach involving the use of chiral auxilarys are provided below.

(1) **Asymmetric Diels-Alder Reaction**

Oppolzer’s and Helmchen’s research groups [6] have demonstrated the use of a wide variety of functionalised alcohols of enantiomeric camphor derivatives as chiral auxilarys in asymmetric synthesis. This methodology in general has three advantages which include the high degree of asymmetric inductive selectivity, readily available and inexpensive precursors of the chiral auxilarys in both enantiomeric forms, and easy removal of the chiral auxilarys after introduction of new chirality has been achieved. Scheme 3 shows titanium tetrachloride promoted addition of cyclopentadiene to both enantiomers of the conformationally rigid cis-diphenylmethylbornyl acrylate, which exhibits a high degree of asymmetric induction, where (7) gave (R)-cycloadduct (8) and (9) produced (S)-cycloadduct (10).

(2) **Asymmetric 1,4-Addition**

Oppolzer and co-workers [7] have reported boron trifluoride mediated 1,4-addition of organocopper reagents to chiral derivatives of $\alpha,\beta$-unsaturated carbonyl compounds which also resulted in a high degree of asymmetric induction, as illustrated in Scheme 4. Here, 1,4-addition of organocopper reagent to (11) produced ester (12) with a high degree of
selectivity, which was subsequently hydrolysed to acid (13).

Scheme 3

Scheme 4
{3} Asymmetric Hydroboration

Brown and Zweifel [8] have developed the preparation of the highly optically pure diisopinocamphenylborane (IPC₂BH) (14) from the reaction of (+)- or (-)-α-pinene (15) and borane-tetrahydrofuran. This organoborane reagent was utilised in the asymmetric hydroboration of diene (16) to provide (17) by Corey and Noyori in the synthesis of PGF₂α (18) [9], as shown in Scheme 5.

\[
\begin{align*}
\text{(+)-}(15) & \quad \text{BH}_3 \cdot \text{SM}_{
\text{ether}_{2}} \\
\text{IPC}_2 \text{BH} & \quad \text{(14)}
\end{align*}
\]

(16) \quad (17) \quad (18)

Scheme 5

{4} Asymmetric Alkylation

Meyers and co-workers have demonstrated the use of chiral oxazoline (19) [10] in the asymmetric alkylation reaction, in which (S)-acid (20) was obtained with high enantiomeric excess, and the methoxyamino alcohol (21), as expected, was utilised to regenerate the chiral oxazoline as illustrated in Scheme 6.

In spite of these developments in the asymmetric synthesis, the control of absolute stereochemistry and the regioselective introduction of functionality at predetermined sites remain
crucial problems in the construction of even moderately functionalised chiral compounds, that is, in most cases the minor, undesired, enantiomer is also formed. To minimise this drawback in asymmetric synthesis, an alternative approach would involve the use of an enantiomerically pure starting material. In essence, this approach involves scrutinising the molecular structure of the target molecule to identify hidden elements, decode the stereochemical information, and transpose the target molecule either partially or totally, into the carbon framework of a suitable chiral starting material [11]. The choice of a chiral starting material is left to the imagination and creativity of the organic chemist and generally conforms to the following guidelines. First,
the chiral starting material must be readily available at a reasonable cost. Second, it should be available in both enantiomeric forms so that either enantiomer of the target molecule could be synthesised. Third, it must possess versatile chemical reactivity so that it can be used to construct a wide variety of large molecules. The pace of utilising chiral starting materials in natural product synthesis has been exceptionally rapid during the past several years. By now the literature has witnessed a large number of successful total syntheses employing chiral starting materials, and Schemes 7-10 illustrate the specific use of (R)-1,2-isopropylidene glyceraldehyde (22) [12], (-)- or (+)-tartaric acid (23) [13], (-)- or (+)-carvone (24) [14], and D-glucose (25) [15] respectively.

Camphor is another readily available chiral starting material which has been widely utilised in the synthesis of natural products. Camphor exists in nature in three forms (+), (-), and racemic. (+)-Camphor (28) is the most abundant enantiomer, and can be isolated from the wood of the camphor laurel (Cinnamomum camphora). On the other hand, (-)-camphor (27)
Scheme 7
IONOPHORE ANTIBIOTIC X-14547A

[13a]

COOH
H-C-OH
HO-C-H
COOH

(23)

EXO-BREVICOMIN
[13c]

DISPARLURE
[13b]

Scheme 8
EUCANNABINOLIDE [14a]

Picrotoxinin [14c]

(-)-(3Z)-CEMBPENE A [14d]

METHYL TRANS-CHRYSANTHEMATE [14e]

1,25-DIHYDROXYCHOLECALCIFEROL [14b]
Scheme 10
which is much less common, occurs in the oil of the sagebrush (Artemesia triclentata). Although (-)-camphor is not as readily available as and more expensive than (+)-camphor, it can be easily prepared by the oxidation of the more abundant and relatively inexpensive (-)-borneol (28).

At first glance, the molecular structure of camphor seems to indicate that this compound will not have the varied chemical reactivity normally required for a chiral starting material in natural product synthesis. However, the versatility of camphor as a chiral starting material is associated with its tendency to undergo molecular rearrangements which provide an opportunity for the introduction of functionality at C(3), C(4), C(5), C(6), C(8), C(9) and C(10) positions (Scheme 11). In addition, ring cleavage (Scheme 12) of C(1)-C(2), C(2)-C(3) and C(1)-C(7) bonds can produce many useful synthetic intermediates.

Camphor chemistry has been recently reviewed [16], and therefore only a brief description of the methods to functionalise camphor and the application of these derivatives in the enantiospecific synthesis of natural products will be provided below.

<1> C(4) Substitution (Scheme 13)

(-)-4-Methylcamphor (29) has recently prepared from (+)-camphor (28) in 4 steps [17]. It has the potential of being transformed into the ring D and part of ring C (30) of triterpenoids such as lanostane (31) and derivatives while
(+)-4-methylcamphor (ent-29) could lead to diastereomeric triterpenoids such as euphane (32). This synthetic potential is based on the assumption that 4-methylcamphor could be converted to 9,10-dibromo-4-methylcamphor (33) and that
(a) **Cleavage of C(1)-C(2) Bond**

(b) **Cleavage of C(2)-C(3) Bond**

(c) **Cleavage of C(1)-C(7) Bond**

Scheme 12

16
subsequent ring cleavage between C(1) and C(2) carbon-carbon bond would reveal an intermediate (30) which could be converted to the C,D ring system of lanostane (31). Efforts towards
this objective are currently being made in our laboratory [17].

\section*{2. C(5) Substitution (Scheme 14)}

Scheme 14 shows the preparation of 5-bromocamphor (34) from 3,5-cyclocamphor (35) [18]. Other routes to C(5) functionalised camphors can be carried out either microbiologically [19] or chemically [19] through remote oxidation of bornylacetate (36) to afford 5-ketobornylacetate (37) and 6-ketobornylacetate (38) as the major and minor products respectively. Both (37) and (38) have been utilised in the synthesis of (+)-nojigiku alcohol (39) by Money et al. [20].

![Scheme 14](image)
\[\text{C}(6)\] Substitution

(-)-8-endo-Bromocamphor (40) can be prepared from the rearrangement of (+)-3-endo-bromocamphor (41) with chlorosulfonic acid [21]. An evaluation of the use of (40) in the enantiospecific synthesis of terpenoids is provided in chapter 3.

\[\text{C}(8)\] Substitution (Scheme 15)

(+)-8-Bromocamphor (42) or (43) can be easily prepared from (+)- or (-)-camphor (26) or (27) in 3 steps [22]. Its usefulness as a chiral intermediate in natural product synthesis is clearly reflected in Scheme 15 [23], and chapters 1 and 2 of this thesis.

\[\text{C}(9)\] Substitution (Scheme 16)

(+)-9-Bromocamphor (44) prepared from (41) in 2 steps [22] has been used in the synthesis of (+)-\(\alpha\)-santalene (45) [24], (+)-\(\alpha\)-santalol (46) [25], (+)-isoepicampherolenol (47) [23], (+)-epi-\(\beta\)-santalene (48) [23], and the steroid intermediate (49) [26] (cf. Scheme 16).

\[\text{C}(10)\] Substitution (Scheme 17)

(+)-10-Camphorsulfonic acid (50) is derived from the treatment of (+)-camphor (26) with acetic anhydride and concentrated sulfuric acid [27]. Its enantiomeric ammonium
Scheme 15
Scheme 16
salt (51) has been applied in the synthesis of (-)-khusimone (52a) and (+)-zizanoic acid (52b) [28] as shown in Scheme 17.

\[ \text{C(8), C(10) Substitution (Scheme 18)} \]

(+)\text{-}9,10\text{-}Dibromocamphor (53), prepared from (41) in 3 steps [29] has been widely utilised as an important chiral intermediate in the synthesis of (-)-estrone (54) [30], the california red scale pheromone (55) [31], precursor of the C,D ring system of vitamin D\textsubscript{3} (56) [32], C,D ring system of 11\text{oxy-steroids} (57) [33], and the helenanolide intermediate (58) [34] (cf. Scheme 18).

One of the main aims of the research described in this thesis was to investigate the further use of C(8) functionalised camphor derivatives (Chapter 1 and Chapter 2), and C(6) functionalised camphor derivatives (Chapter 3) in the enantiospecific synthesis of terpenoids.
Scheme 18

PRECURSOR OF THE C,D RING SYSTEM OF VITAMIN D₃ (56)

CALIFORNIA RED SCALE PHEROMONE (55)

(-)-ESTRONE (54)

3 steps

HELENANOIDE INTERMEDIATE (58)

C,D Ring SYSTEM OF 11-oxy-STEROIDS (57)
Chapter 1

An Enantiospecific Synthesis of (+)-Longiborneol And (+)-Longifolene
1.1.0. INTRODUCTION

Longiborneol (59), longicyclene (60), and longifolene (61) co-occur in Pinus longifolia Roxb. [35], and their total synthesis has attracted considerable attention over the past two decades.

![Chemical structures](image)

An obvious structural feature of these compounds is the presence of the tricyclic carbon skeleton in which the bicyclo[2.2.1]heptane unit is fused with a seven-membered ring. At least 6 research groups have devised ingenious methods to construct this structural sub-unit, and their successful syntheses provide racemic longifolene, longiborneol, and longicyclene, or one of their enantiomers by using a resolution step, or employing a chiral auxiliary. An enantiospecific synthesis* of these sesquiterpenoids has not been realised prior to the research described in this thesis, and to place our synthetic endeavours in perspective, a brief account and schematic representation of previous synthetic routes to longifolene, longiborneol, and longicyclene are provided below.

* We define enantiospecific synthesis as one in which readily available enantiomeric starting materials provide enantiomeric products [36].
The initial breakthrough was made by E. J. Corey and co-workers [37] (Scheme 19) in 1964 by using the Wieland-Miescher ketone (62) to synthesise the diketone intermediate (63). Subsequent intramolecular Michael cyclisation of (63) provided the tricyclic diketone (64), which established the tricyclic carbon skeleton that was necessary for the completion of the first total synthesis of (†)-longifolene. In addition, the preparation of the optically active natural product was also accomplished by resolution of the L-(+)-2,3-butanedithiol ketal (65).

\[ \text{(65)} \]

A later synthesis, completed by J. E. McMurry and S. J. Isser [38] (Scheme 20), also started with Wieland-Miescher ketone (62) and used keto-epoxide (66) as a precursor of the tricyclic keto-alcohol (67). Ring expansion followed by fragmentation and several functional group interconversions resulted in a second total synthesis of (†)-longifolene.

A third longifolene synthesis was described by W. S. Johnson et al. [39] in 1975. In this approach (Scheme 21) the tricyclic carbinol intermediate (68) was constructed by an
Reagents and conditions:

(i) HOCH₂CH₂OH-p-Toluenesulphonic acid; (ii) CH₃CH=PPP₃; (iii) OsO₄;
(iv) p-Toluenesulphonyl chloride; (v) LiClO₄; (vi) 6N HCl;
(vii) Et₃N-HOCH₂CH₂OH-225°C; (viii) Ph₃CNa, CH₃I;
(ix) HSCH₂CH₂SH-BF₃; (x) LAH; (xi) H₂NNH₂-Na-HOCH₂CH₂OH; (xii) CrO₃-HOAc;
(xiii) MeLi; (xiv) SOCl₂-Pyridine.

Scheme 19
Reagents and conditions:
(i) HOCH₂CH₂OH-E-Toluenesulphonic acid; (ii) H₂, Pd; (iii) MeMgI; (iv) H⁺;
(v) m-Cl-C₆H₄CO₃H; (vi) NaCH₂SOCH₃; (vii) H⁺; (viii) KOTBu/CHBr₃; (ix) AgClO₄;
(x) Na/liq. NH₃; (xi) Collins reagent; (xii) Me₂CuLi; (xiii) NaBH₄;
(xiv) MsCl; (xv) KOTBu; (xvi) Tristriphenylphosphinerodium chloride/H₂;
(xvii) MeLi; (xviii) SOCl₂-Pyridine.

Scheme 20
Reagents and conditions:

(i) CuLi((CH$_2$)$_3$C$\equiv$CCH$_3$)$_2$; (ii) CH$_3$COCl; (iii) MeLi-Et$_2$O; (iv) Br$_2$-CH$_2$Cl$_2$;
(v) 2,4,6-(CH$_3$)$_3$C$_6$H$_2$CO$_2$N(CH$_3$)$_3$; (vi) LAH; (vii) CF$_3$CO$_2$H; (viii) ZnBr$_2$/NaBH$_3$CN;
(ix) p-Toluenesulphonic acid; (x) RuO$_2$/50% H$_2$O in tBuOH/H$_2$IO$_6$-NaIO$_4$;
(xi) LiN(i-Pr)$_2$-MeI; (xii) MeLi; (xiii) SOCl$_2$-Pyridine.

Scheme 21

29
acid-catalysed cyclisation of enynol (69) derived from 2-isopropylidene cyclopentanone (70). This intermediate (68) was then converted to (±)-longifolene, as described in Scheme 21.

An alternative synthetic route (Scheme 22) to (±)-longifolene was described by W. Oppolzer and T. Godel [40] in 1977 and 1984. A key feature of this route was the use of an intramolecular photoaddition/retro-aldolisation process (Intramolecular de Mayo Reaction) to construct the tricyclic intermediate (71). By resolving intermediate (72) Oppolzer and T. Godel [41] used this route to synthesise (+)-longifolene (61).

Recently, A. G. Schultz and S. Puig [42] in 1985 also reported the synthesis of both racemic and (-)-longifolene (78) (Scheme 23), in which the tricyclic carbon skeleton was constructed by the combination of an intramolecular 1,3-dipolar reaction (73 - 74) and electrocyclic reaction (75 - 76). By using optically pure benzoxazopenone (77) as the starting material [43] A. G. Schultz and S. Puig were able to use this procedure to synthesise (-)-longifolene (78).

The only synthesis of longiborneol and longicyclene was published by S. C. Welch and R. L. Walters [44] in 1973 and involved the use of (-)-carvone (79) as a chiral starting material. The route (Scheme 24) featured a reductive cyclisation step to construct the intermediate bicyclic ketol (80). This compound, (80), was then converted to tetracyclic
ketone (81) via an intramolecular carbene insertion, and finally by a series of simple reactions to (†)-longicyclene. Furthermore, cyclisation of bicyclic keto-mesylate (82) (Scheme 24) resulted in the synthesis of (†)-longicamphor and subsequent stereoselective reduction provided (†)-longiborneol.
Reagents and conditions:

(i) PhCH₂OCOC₁-Pyridine; (ii) hν; (iii) H₂-Pd/C-HOAc; (iv) CH₃PPh₃;
(v) CH₂I₂, ZnEt₂; (vi) H₂, PtO₂; (vii) NaH, CH₃I; (viii) MeLi; (ix) SOCl₂,
Pyridine.

Scheme 22
32
Reagents and conditions:

(i) Birch reduction, (ii) LDA, 2,2-dimethyl-5-iodopentanal, (iii) N-bromoacetamide, Methanol, (iv) DBN, (v) Acetone, p-toluenesulfonic acid, after silica gel chromatography, (vi) 1-amino-trans-2,3-diphenylaziridine, heat, (vii) \( \text{hv} \), heat, xylene, (viii) \( \text{H}_2 \), Pd/C,(ix) KOH, Methanol-water, (x) toluene, reflux, (xi)MeLi, THF, (xii) \( \text{SOCl}_2 \), Pyridine.

Scheme 23

33
Reagents and conditions:

(1) HBr-HOAc; (ii) KOH, MeOH; (iii) H₂-Pd/C; (iv) NaH, CH₃CHBrCH=CHCH₃;
(v) RuO₄, OsO₄, H₂O, t-BuOH, NaI₀₄; (vi) NaOAc, Ac₂O; (vii) DIBAL-H;
(viii) H⁺; (ix) MsCl; (x) Collidine; (xi) PPh₃=CHOCH₃; (xii) HClO₄;
(xiii) K₂CO₃, CH₃OH; (xiv) CrO₃, H₂SO₄; (xv) (COCl)₂; (xvi) CH₂N₂; (xvii) Cu;
(xviii) DIBAL-H; (xix) MsCl; (xx) LAH; (xxi) PPh₃=CH₂; (xxii) BH₃-THF;
(xxxii) H₂O₂, t-OH; (xxiv) MsCl; (xxv) CrO₃-Pyridine; (xxvi) Na(N(SiMe₃))₂, DME;
(xxvii) Ca, NH₃, n-PrOH.

Scheme 24
1.2.0. DISCUSSION

A desirable feature of a synthetic strategy is that it be applicable to more than one compound within any class of structurally similar natural products. This was the goal of the strategy we adopted for the synthesis of (+)-longiborneol (58), (+)-longicyclene (60), and (+)-longifolene (61). The key feature of our synthetic plan was to construct the longifolene structure by a route based on its proposed biosynthesis [45] (Scheme 25). Thus, we considered that the

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Biosynthesis of longifolene
Scheme 25
```

35
longifolene structure could be produced by Wagner-Meerwein rearrangement of the synthetic equivalent of the tricyclic secondary carbocation (84). Laboratory analogy for this approach is provided by the synthesis of (+)-camphene (85), a monoterpenoid analogue of (+)-longifolene (61), by Wagner-Meerwein rearrangement of (-)-isoborneol (86) derived from (+)-camphor (26) (Scheme 26). Prompted by this analogy, we postulated that (+)-longifolene (61) could be synthesised from (+)-longicamphor (83) by a similar reaction sequence, that is, reduction of (+)-longicamphor (83) followed by the Wagner-Meerwein rearrangement of the resulting (+)-longiisoborneol (89) as depicted in Scheme 27. It is clear therefore, that the synthesis of (+)-longicamphor (83) is of synthetic importance since there is a
potential synthetic relationship among (+)-longicamphor (83), (+)-longiborneol (59), (+)-longiisoborneol (89), (+)-longicyclene (60) and (+)-longifolene (61). In fact, the recognition of (+)-longicamphor (83) as a key intermediate was an integral part of previous studies in our laboratory on the development of stereoselective synthetic approaches from camphor to a wide variety of sesquiterpenoids (Scheme 28). These sesquiterpenoids were grouped together in structural quartets and the parent ketones in each set were identified as (+)-epicampherenone (90), (+)-copacamphor (91), (-)-campherenone (92), (+)-ylangocamphor (93), and (+)-longicamphor (83). Furthermore, the transformation of each of the parent ketones to other members of the quartet involved reduction, dehydration-rearrangement, and intramolecular cyclopropanation processes similar to those used in
(+)-isoepicampherenol (47)
(+)-epi-β-santalene (48)
(+)-α-santalene (45)

(+)-epicampherenone* (47)
(+)-camphor (26)
(+)-longcamphor* (83)
(+)-longifieone† (61)
(+)-longicyclene (60)

(-)-camphor (27)
(+)-copabornene (94)
(-)-copacamphene* (95)
(+)-copacamphor* (91)
(-)-campherenone(92)
(+)-ylangocamphor* (93)
(-)-sativene† (100)
(-)-cyclosativene† (99)

(+)-cyclocopacamphene† (96)
(+)-α-santalene (45)
(-)-campherenol (97)
(-)-β-santalene (98)

† enantiomer also known
* unknown in nature

Scheme 28
the conversion of (+)-camphor (26), to (+)-borneol (87), (+)-camphene (85), and tricyclene (88) (Scheme 26). The success of our earlier studies came from the development of synthetic routes from camphor to most of the parent ketones listed above. This success was based on a new three-step procedure, developed in our laboratory [22], to brominate camphor regiospecifically at the C(8) position. As a result, the enantiospecific synthesis of (+)-isoepicampherenol (47), (+)-epi-β-santalene (48), (+)-α-santalene (45), (+)-copaborneol (94), (-)-copacamphene (95), (-)-cyclocopacamphene (96), (-)-campherenol (97), (-)-β-santalene (98), (-)-cyclosativene (99), (-)-sativene (100), and (+)-ylangoborneol (101) [23] were completed. However, these earlier efforts failed to complete the synthetic connection between (+)-camphor (26) and (+)-longicamphor (83), and hence (+)-longiborneol (59), (+)-longicyclene (60), and (+)-longifolene (61) (Scheme 28).

In order to construct the (+)-longicamphor (83) skeleton using (+)-camphor (26) as the chiral starting molecule, two carbon-carbon bond formations, that is, "Bond 1" and "Bond 2"
of (102) must be achieved. All previous attempts in our labor-
atory to synthesise (+)-longicamphor (83) in this way were un-
successful [46]. Nevertheless, the lack of an enantiospecific
synthesis of (+)-longiborneol (59) and (+)-longifolene (61) in
the literature prompted us to undertake this challenge again.

Like a lengthy journey, the management of a successful
synthesis from its starting point to its destination requi-
res a carefully planned outline, the flexibility to accomo-
date diversions along the way, and the endurance to see the
journey through to a satisfactory conclusion. The enantiospe-
cific synthesis of (+)-longiborneol (59), and (+)-longifolene
(61) represents fairly accurately a synthesis that is built
around a rather specific approach. Synthetic approaches that we
investigated to construct the tricyclic skeleton of longicam-
phor (83) included (1.3.1) INTRAMOLECULAR DIELS-ALDER REACTION
APPROACH of triene acetate (103b), (1.3.2) INTRAMOLECULAR LEWIS
ACID-INDUCED TERTIARY ALKYLATION of campherenone hydrochloride
enol-trimethylsilyl ether (104), and (1.3.3) INTRAMOLECULAR
MUKAIYAMA CYCLISATION of an dimethyl-acetal enolsilyl ether
(105). These approaches will be discussed chronologically.
1.3.0. RESULTS

1.3.1. INTRAMOLECULAR DIELS-ALDER REACTION APPROACH

The striking utility of the intramolecular Diels-Alder reaction in the construction of carbocycles of a wide variety of natural products [47] led us to consider the application of this reaction to the construction of the tricyclic skeleton of (+)-longicamphor (83). This reaction involves the interaction between a conjugated diene and a monoene to form two bonds generating a six-membered ring (Scheme 29).

Several generalisations concerning this reaction can be categorised in terms of reactivity, regioselectivity, and stereoselectivity. First, the dienophile reactivity is increased by electron-withdrawing groups, whereas the diene reactivity is increased by electron-donating groups. For example, in the cyclopentadiene (106), replacement of the hydrogen by a carbomethoxy group (107) reduces the cyclisation temperature from 250° to 110° C [48]. Furthermore, placing activating groups
on both the terminal and non-terminal carbon atoms of the dienophile of compound (108) results in greatly enhanced reactivity as shown by the cyclisation temperatures [49].

Regiochemically, the intramolecular Diels-Alder reaction can give either fused or bridged products as shown in Scheme 30. In general, most intramolecular Diels-Alder reactions give the fused products (109) and (110) [50]. The bridged products (111) and (112) can also be produced for a trans-diene having at least a five carbon chain with a reasonable unstrained
transition state (Scheme 31). In the case of cis-diene (113), a
possible situation for the formation of bridged product (114) [51] is only when anti-addition occurs perhaps due to a less strained transition state.

![Chemical structure](image)

Stereochemically, the intramolecular Diels-Alder reaction may give rise to cis or trans fused products depending on the orientation of the diene relative to the dienophile in the transition state. Generally, trans dienes give trans-fused products via an anti-transition state, and cis-fused products via a syn-transition state. On the contrary, cis-dienes give cis-fused products via an anti-transition state and trans-fused products via a syn-transition state as shown in Scheme 32. Factors such as chain length, substituents on the chain, type of diene, type of dienophile, and catalysts may limit the number of above possibilities. For example, the ester (115) and its geometric isomer (116) cyclise favorably via an anti-transition state to provide the trans-fused products (117) and (118) as the major products, as shown in Scheme 33 [52]. A possible explanation for
trans-DIENE $\xrightarrow{\text{anti}}$ trans-FUSED

cis-DIENE $\xrightarrow{\text{syn}}$ cis-FUSED

cis-DIENE $\xrightarrow{\text{anti}}$ cis-FUSED

Scheme 32
this result is the fact that during the formation of the five-membered ring, the two substituents on the cyclopentane ring are eclipsed in the syn-transition state (119) which is thus energetically less favored than the anti-transition state (120) with staggered substituents. Furthermore, non-bonded interactions within the chain between the hydrogen atoms on carbon 4 and carbon 8 appear to be more severe in the
syn-transition state. Notice that in the presence of a Lewis acid, ester (115) gives more trans-fused product because of the enhanced *endo*-selectivity. However, the Lewis acid failed to affect ester (116), probably due to the increased secondary orbital interaction which is not able to overcome the preference for the anti-transition state.

To use an intramolecular Diels-Alder reaction in the construction of the tricyclic skeleton of longicamphor (83), a possible intermediate molecule such as triene acetate (103), which possesses a cis-diene with electron-donating methyl groups attached and a dienophile with an acetoxy group attached, was considered. In this approach, it was hoped that on thermolysis, triene acetate (103) would cyclise to afford tetracyclic acetate (124). Subsequent hydrolysis of (124) followed by hydrogenation of (125) could provide (+)-longicamphor (83) as illustrated in Scheme 34. Once the
possible feasibility of employing the intramolecular Diels-Alder reaction had been recognised, the main challenge became the preparation the intermediate, triene acetate (103).

It was envisaged that the cis-diene moiety in triene acetate (103) could be incorporated via a Wittig reaction between a non-stabilised Wittig reagent (126) and an aldehyde (127) to produce diene-ketal (128) as shown in Scheme 35. Furthermore, (126) could be derived from a C(8) function-alised (+)-camphor derivative (42).
A synthetic plan for the preparation of the Wittig reagent (126) is outlined in Scheme 36. Thus, treatment of (+)-camphor

Reagents and conditions:
(i) \( \text{Br}_2, \text{HBr}, \text{HOAc}, 110^\circ \text{C} \); (ii) \( \text{Br}_2, \text{ClSO}_2\text{H} \); (iii) \( \text{Zn}, \text{HOAc}, \text{Et}_2\text{O}, 0^\circ \text{C} \); (iv) \( \text{Me}_3\text{SiCl}, \text{HOCH}_2\text{CH}_2\text{OH} \).
(26) with bromine, catalysed by HBr gas at high temperature afforded (+)-3,3-dibromocamphor (129) in 99% yield. At room temperature this bromination reaction does not proceed to any significant extent. Wagner-Meerwein rearrangement and bromination of (129) in bromine and chlorosulfonic acid provided 3,3,8-tribromocamphor (130) in about 50-60% yield. The mechanism of this rearrangement-bromination reaction was proposed as shown in Scheme 37, which features an unusual 2,3[endo] methyl shift in intermediate (132) followed by bromination regiospecifically at the C(8) position of compound (129). Efforts have been made to improve the yield of (130) with other acids such as trifluoroacetic acid and concentrated hydrochloric acid, but chlorosulfonic acid remains the best choice for this rearrangement-bromination step. Debromination of (130) in the presence of zinc dust and acetic acid produced (+)-8-bromocamphor (42) in about 45-50% yield over these three steps. Ketalisation of (42) with chlorotrimethylsilane and ethylene glycol [53] produced (+)-8-bromocamphor ethylene ketal (131), but, unfortunately treatment of (131) with triphenylphosphine failed to produce the desired Wittig reagent (126). Likewise, there was no reaction when (+)-8-iodocamphor ethylene ketal (133) was
[* or $\Delta = ^2H$; WM = Wagner-Meerwein rearrangement; 2,3-Me = 2,3-methyl shift]
treated with triphenylphosphine. It seems likely that the failure of these reactions is due to severe steric hindrance at C(8) by the ketal group of (131) or (133). As a result, we decided to introduce an aldehyde or equivalent functionality at the C(8) position of camphor, and then couple this compound (134) with a prenyl Wittig reagent (135) to obtain dienone (136). It was anticipated, however, that this Wittig reaction would result in the trans-isomer (136a) as the major product since a stabilised Wittig reagent would be used. It was our hope that by varying reaction conditions [54] it might be possible to obtain the cis-isomer (136b) as the major product. It occurred to us then that lactol (137) presents a good
candidate for this Wittig reaction, since it is in equilibrium with hydroxy-aldehyde (138). The synthetic route to the lactol (137), outlined in Scheme 38, involved treatment of (+)-8-bromocamphor (42) with potassium acetate and dimethyl sulfoxide at high temperature to afford (+)-8-acetoxy-camphor (139) in 93% yield. Hydride reduction of (139) at 0°C provided epimeric diols (140) in 75% yield. The epimeric ratio (4:1, exo:endo) of diols was determined from $^1$H-n.m.r. integrations of the C(2) proton signals. Oxidation of diols (140) with silver carbonate on celite in refluxing benzene [55] gave

Reagents and conditions:

(i) KOAc, DMSO, 110°C; (ii) LAH, THF; (iii) Ag$_2$CO$_3$, PhH; (iv) DIBAL-H, PhCH$_3$, -78°C.

Scheme 38
lactone (141) in 77% yield. DIBAL reduction [129] of (141) then provided a mixture of epimeric lactols (137) (93% yield) which was condensed with the Wittig reagent (135) [56] derived from prenyl bromide to provide a mixture of dienols (142a,b) in 82% yield. Surprisingly, the ratio of cis to trans isomers of dienols (142b:142a) was indicated by $^1$H-n.m.r. integration (page 270) to be 7:1. The assignment of the stereoselectivity of this Wittig reaction is similar to that reported by G. Pattenden and co-workers for the synthesis of (E)-2,2,6-trimethylhepta-3,5-dienoic acid (143) [57]. This unusual observation in which a stabilised Wittig reagent such as (135) resulted in the cis-isomer as the major product is an interesting one. We are not sure of the actual course of this reaction, however a possible suggestion (Scheme 40) is coordination of the phosphorous of the ylide (145) with the alkoxide anion of lactol (144) followed by nucleophilic attack of the ylide on the aldehyde functionality of (144) to give (146). Subsequent rotation around the newly formed carbon-carbon bond to form an oxaphosphetane intermediate (147) followed by decomposition in the usual way would produce the cis-
dienol (142b) and triphenylphosphine oxide. The p-bromobenzoate

Scheme 40
derivative (148) of (142b) was a colorless oil and thus prevented us confirming the stereochemistry of this compound by X-ray crystallographic analysis.

Oxidation [69] of dienols (142a,b) provided (136a,b) which, on treatment with lithium diisopropylamide in tetrahydrofuran followed by acetic anhydride provided triene acetates (103a,b). The ratio of cis to trans isomers in both dienones (136b:136a) (page 271) and triene acetates (103b:103a) (page 271) was indicated by $^1$H-n.m.r. integration to be about 7:1.

Scheme 54
Unfortunately, all attempts to induce this compound to undergo intramolecular Diels-Alder reaction were unsuccessful (Table 1). A variety of reaction conditions were examined such as varying solvents, temperatures, and reaction times [58]. In addition, catalysts such as diethylaluminum chloride [52] and cuprous triflate-benzene complex [59] which were reputed to aid the cycloaddition process by chelating aluminum (150a) or copper (150b) with the diene and dienophile, had no effect on this reaction (Scheme 41).

![Scheme 41](image)

To account for the failure of the intramolecular Diels-Alder reaction, it was thought that for steric reasons the cis-triene acetate (103b) would exist in the s-trans conf-
ormation (149). As a result, the geometry of the diene and dienophile could not be properly aligned for cycloaddition.

(103b) \[ \rightarrow \] (149)

Scheme 55

It is also possible that the electron-rich nature of the dienophile made the reaction energetically unfavorable.
<table>
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<td>-</td>
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<td>(iii) 120</td>
<td>24 hrs.</td>
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<td>(iv) 140</td>
<td>40 hrs.</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(v) 160</td>
<td>16 hrs.</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(vi) 180</td>
<td>16 hrs.</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(vii) 190</td>
<td>13 hrs.</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(viii) 205</td>
<td>6 days</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>REFLUX</td>
<td>0-DICHLO- BENZENE</td>
<td>180</td>
<td>16 hrs</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>SEALED TUBE</td>
<td>0-DI-CHLORO- BENZENE</td>
<td>180</td>
<td>3 days</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 1**
1.3.2. **INTRAMOLECULAR LEWIS ACID INDUCED \(\alpha\)-TERTIARY ALKYLATION**

A retro-synthetic analysis (Scheme 42) of (+)-longi-camphor (83) shows a possible disconnection at the C(6)-C(7) carbon-carbon bond to provide (+)-campherenone (151). As shown in the previous studies [23] (-)-campherenone (92) can be synthesised by prenylation of a C(8) functionalised (-)-camphor and therefore, (+)-camphor (26) was chosen as the chiral starting material. Our immediate research objective was therefore

\[ \begin{align*}
     & \text{(83)} \quad \text{DIS} \quad \text{(151)} \quad \text{DIS} \quad \text{FGI} \quad \text{(152)} \\
     \downarrow & \text{DIS} \quad \text{FGI} \\
     & \text{(26)}
\end{align*} \]

Scheme 42
the formation of the carbon-carbon bond between C(3) and C(13) in (151). This synthetic strategy has been previously examined in our laboratory using a variety of methods [46], but no success was achieved. Recently, however, a new method of intramolecular alkylation of a ketone with a di-substituted alkene, catalysed by SnCl$_4$ has been reported by Reetz and co-workers [60], and examples cited from the literature included the SnCl$_4$-mediated cyclisations of (153), (154), and (155) which led to the formation of (156), (157), and (158) respectively as depicted in Scheme 44. The mechanism of these favored 6- and 7-endo-trigonal cyclisations was proposed by Reetz to be O-stannylation of the enolised form (159) to generate (160) and HCl. Protonation of the alkene results in cyclisation of the tertiary cation (161) to give (162) as shown in Scheme 43.
Scheme 44

(a), \( R = \text{CH}_3\text{O}, \ n = 1, \ 96\% \)

(b), \( R = \text{CH}_2\text{O}, \ n = 2, \ 62\% \)

(c), \( R = \text{CH}_3, \ n = 1, \ 80\% \)
Motivated by these analogies, we decided to test the validity of this intramolecular d-tertiary alkylation on (+)-campherenone (151). The synthetic route to the longicamphor skeleton from (+)-campherenone (151) was an extension of previous studies in our laboratory on the development of stereoselective synthetic approaches from camphor to a variety of complex sesquiterpenoids using (-)-campherenone (92) as a key intermediate (Scheme 28). To evaluate this intramolecular alkylation approach, our first preoccupation was to synthesise (+)-campherenone (151) by the route outlined in Scheme 46. This new route is relatively less hazardous than the previous one (Scheme 45) which involved reaction of (-)-8-iodocamphor ethylene ketal (163) with a prenyl complex (164) to provide (-)-campherenone (92). In this amended route to (+)-campherenone (151), (+)-8-cyanocamphor ethylene ketal (166) was synthesised from (+)-camphor (26) in 48% overall yield by the sequence previously developed in our laboratory [61]. Alkylation of (166) with lithium diisopropylamide and prenyl bromide in tetrahydrofuran at -78°C afforded a mixture of
Reagents and conditions:
(i) Br₂, HBr, HOAc, 110°C; (ii) Br₂, HSO₃Cl; (iii) Zn, HOAc, Et₂O, 0°C; (iv) KI, DMSO, 110°C, 3 days; (v) Me₃SiCl, HOCH₂CH₂-OH; (vi) NaCN, DMSO, 70°C, 2 days; (vii) LDA, THF, -78°C; Prenyl Bromide; (viii) K, HMPA, Et₂O, tBuOH, 0°C; (ix) HCl, Me₂CO.

Scheme 46

C(8) epimers (167a,b) of the desired products in 95% yield (6:1 ratio, determined by ¹H-n.m.r.) (page 272). Since the new chiral center created would be destroyed in the following step, the stereoselectivity in this alkylation reaction [62] is not significant (page 69). Decyanation of (167a,b) using potassium
metal in hexamethylphosphoramide [63] followed by hydrolysis of (168) furnished (+)-camphenone (151) in 75% overall yield from (167a,b). Having (+)-camphenone (151) available, we proceeded to examine the intramolecular $\alpha$-tertiary alkylation step with the hope that the cyclisation would take place to form the carbon-carbon bond between C(3) and C(13) and thus provide the longicamphor skeleton. When (+)-camphenone (151) was reacted with SnCl$_4$ a mixture of epimers of dimeric compounds (169a,b) was isolated. The evidence for this structural assignment of the products of this reaction included the occurrence of a signal at 440(M$^+$) in the mass spectrum (page 272). The ratio of epimers was determined to be about 2.3:1 from the integration in the $^1$H-n.m.r. spectrum (page 273). Thus intermolecular coupling rather than intramolecular coupling between C(3) and C(13) of (+)-camphenone (151) had occurred. As an extension of these investigations, camphenone hydrochloride enoltrimethylsilyl ether (104), and camphenone hydrochloride enolacetate (170) were prepared from (151). When (104) and (170) were separately treated with SnCl$_4$ under high dilution to attempt to promote intramolecular rather than intermolecular alkylation, dimers (169) (Scheme 47) were again the only products isolated.
Reagents and conditions:

(i) HCl, Et$_2$O; (ii) LDA, THF, -78°C; Me$_3$SiCl; (iii) LDA, THF, -78°C; Ac$_2$O; (iv) SnCl$_4$, CH$_2$Cl$_2$, 0°C.

Scheme 47
1.3.3. **INTRAMOLECULAR MUKAIYAMA REACTION APPROACH**

In view of the failure of the intramolecular α-tertiary alkylation approach, we decided to investigate the intramolecular variant of a method of cyclisation developed initially by Mukaiyama and co-workers [64]. The few examples of its application to natural product synthesis include the synthesis of hydroazulenone (172) [65], jatrophone (174) [66], and isoclovene (177) [67] as shown in Schemes 48, 49, and 50 respectively. In essence this reaction involves TiCl$_4$-directed intramolecular condensation between acetals and enol silyl ethers and, as illustrated above, has been used for the

![Scheme 48](image)

![Scheme 49](image)
synthesis of seven- and eleven-membered rings. Thus, our initial goal was to construct trimethylsilyl enol ether (178) with the expectation that cyclisation mediated by TiCl$_4$ would result in the formation of the basic tricyclic longicamphor skeleton. The synthetic route to (178) is outlined in Scheme 51, and involves alkylation of (+)-8-cyanocamphor ethylene ketal (166) with lithium diisopropylamide and 1-tert-butyldimethylsilyloxy-3-bromopropane (179) in tetrahydrofuran at $-78^\circ$C. A mixture of C(8) epimers (about 7:1 ratio) of the desired products (180a,b) were produced and the major epimer (180a) was isolated by column chromatography and converted to the crystalline p-bromobenzoate derivative (186) (Scheme 52). Subsequent X-ray crystallographic analysis [88] showed that the chiral center at C(8) in this compound (186) had the (R)-configuration (page 273). Although the chiral center will be destroyed in the following step, the
Reagents and conditions:

(i) LDA, THF, -78°C; tBuMe₂SiOCH₂CH₂Br; (ii) K, Hexamethylphosphoramide, Et₂O, tBuOH, 0°C; (iii) HCl, Me₂CO;
(iv) PDC, CH₂Cl₂; (v) p-Toluenesulfonic acid, EG, PhH;
(vi) LDA, THF, -78°C; Me₃SiCl; (vii) TiCl₄, CH₂Cl₂, -78°C;
(viii) p-Bromobenzoyl Chloride, Pyridine.

Scheme 51
Reagents and conditions:
(i) TBAF; (ii) p-Bromobenzoyl chloride, Pyridine

Scheme 52

stereoselectivity resulting from this alkylation [62] is interesting. It is probable that alkylation from the "re" face of the enolate (187) to give the (R)-product (180a) is due to the steric effect imposed by both C(9) and C(10) methyl groups as depicted in Scheme 53. Presumably a

Scheme 53

similar stereoselectivity occurs during the previously noted alkylation of (167) (page 65). Decyanation of (180a,b) with
potassium metal in tert-butanol and hexamethylphosphoramide also resulted in desilylation to afford hydroxy-ketal (181) [63] in 82% yield as well as small amounts of silyl ether (188) and hydroxy-nitriles (185a,b) (Scheme 56).

\[(185a,b) \quad (188)\]

Hydrolysis of (181), followed by oxidation [69] of the resulting hydroxy-ketone (182) provided keto-aldehyde (183) in 96% yield. Further quantities of (183) were prepared from silyl-ether (188) (Scheme 54), and nitriles (185a,b) (Scheme 55). Selective acetalisation of the aldehyde over the ketone functionality in (183) with ethylene glycol and catalytic p-toluene-sulfonic acid in refluxing benzene provided keto-acetal (184) (Scheme 51) which was then converted to the corresponding enol-silyl ether acetal (178) in about 88% overall yield. Cyclisation of (178) with TiCl4 in methylene chloride at -78°C provided two diastereomeric products (192a,b) in 78% yield. The 2:1 ratio of epimers was indicated from \(^1\)H-n.m.r. (page 274). It was
Reagents and conditions:
(i) TBAF; (ii) HCl, Me₂CO; (iii) PDC, CH₂Cl₂.

Scheme 54

Reagents and conditions:
(i) PCC, CH₂Cl₂; (ii) p-Toluenesulfonic acid, EG, PhH;
(iii) K, HMPA, Et₂O, tBuOH, 0°C; (iv) HCl, Me₂CO.

Scheme 55
particularly interesting to note the disappearance of the C-H bending band (\(\text{CH}_2-\text{CO}\)) at about 1413 cm\(^{-1}\) (page 275) since this is a useful diagnostic test for carbon-carbon bond formation at the C(3) position of (+)-camphor (26) [70] (page 275). Attempts to prepare a crystalline p-bromobenzoate derivative (193a,b) of hydroxy-ketones (192a,b) failed.

In order to make subsequent functional group transformations easier, we decided to attempt the cyclisation reaction on the dimethyl acetal enolsilyl ether (105) (Scheme 56). This compound was synthesised from keto-aldehyde (183) in 83% overall yield and on treatment with TiCl\(_4\) in methylene chloride at -78\(^\circ\)C, (105) provided two diastereomeric products (195a,b).

\[
\text{(183)} \quad \xrightarrow{(i)} \quad \text{(194)}
\]

\[\text{R}_1 = \text{H}, \quad \text{R}_2 = \text{OMe} \quad (195\text{b})\]

\[\text{R}_1 = \text{OMe}, \quad \text{R}_2 = \text{H} \quad (195\text{a})\]

Reagents and conditions:

(i) HC(O\text{Me})_3, CeCl\(_3\), MeOH; (ii) LDA, THF, -78\(^\circ\)C; Me\(_3\)SiCl;
(iii) TiCl\(_4\), CH\(_2\)Cl\(_2\).

Scheme 56
(Scheme 56) in a ratio of 3:1 determined from the $^1$H-n.m.r. spectrum (page 276). The major diastereomer, (R)-methoxy-ketone (195a), proved to be crystalline and its structure and absolute configuration were confirmed by X-ray crystallographic analysis (page 277) [68].

Although the mechanism of this Lewis acid directed aldol reaction has not been studied in detail, Kocienski et al. [71] recently suggested that ring closure involved nucleophilic addition to an electrophilic oxonium ion in the conversion of (196) into the $\alpha$-alkoxy-benzocyclooctanone (199) as shown in Scheme 57. We are not sure the actual course of the reaction in our case, but it seems likely that the intramolecular nucleophilic addition which results in ring closure could take place either at the "si face" (200) or the "re face" (201) of the oxonium ion (Scheme 58). Thus, (R)-methoxy-ketone
(195a) would result from addition to the "si face" of the oxonium ion and (S)-methoxy-ketone (195b), from addition to the "re face". The stereoselectivity ((R):(S),3:1) observed is probably due to the more favorable conformation of the nucleophilic addition at the "si face" of the oxonium ion.

Scheme 58

Having constructed the tricyclic skeleton of the (+)-longicamphor framework, we now considered the problem of introducing gem-dimethyl groups at the C(6) position. To avoid a possible retro-aldol process occurring during the demethylation of the methoxy group in (195a,b), we decided to reduce the ketone group of (195a,b) first and then protect the alcohols resulted. Lithium aluminum hydride reduction of methoxy-ketones (195a,b) was straightforward but we found that acetylation of the epimeric alcohols (202a,b) afforded acetate (203) and recovered alcohol (202a). The resistance of the (R)-methoxyalcohol (202a)
to acetylation is due to the proximity of the oxygen of the *exo*-alcohol and the (R)-methoxy group (Scheme 59). Since (202a)

Reagents and conditions:
(i) LAH, THF; (ii) AC$_2$O, 4-DMAP, Pyridine.

Scheme 59

was the major product, we decided to amend our synthetic route by reducing (195a,b) with calcium metal in liquid ammonia [23, 72] to provide *endo*-alcohols (204a,b) in 98% yield. Subsequent acetylation provided methoxy-acetates (205a,b) in 89% yield. Demethylation with boron tribromide/sodium iodide/15-crown-5 in methylene chloride [73] followed by oxidation [69] provided keto-acetate (207) in 85% overall yield (Scheme 60).

To introduce the gem-dimethyl moiety, we first investigated direct geminal dimethylation of keto-acetate (207) using Me$_2$TiCl$_2$, a reagent developed by Reetz et al. [74]. This was
Reagents and conditions:
(i) Ca/NH$_3$, Et$_2$O; (ii) Ac$_2$O, 4-DMAP, Pyridine; (iii) BBr$_3$, (15-Crown-5, NaI, CH$_2$Cl$_2$; (iv) PDC, CH$_2$Cl$_2$.

unsuccessful, however, and therefore we resorted to the traditional three step-procedure of converting a ketone group to a gem-dimethyl moiety, that is, methylenation, cyclopropagation, and hydrogenolysis (Scheme 61).

Wittig olefination of (207) with methylenetriphenylphosphorane in tetrahydrofuran afforded alkene acetate (208), which was reduced with lithium aluminum hydride to provide hydroxy-olefin (209) in 85% overall yield. Cyclopropanation of the exocyclic double bond of (209) using the modified Simmons-Smith reagent (Et$_2$Zn/CH$_2$I$_2$) [75], afforded the tetracyclic alcohol (210) in 99% yield. Finally, hydrogenolysis of the cyclopropane ring in (210) using Adam's catalyst (PtO$_2$) [76] in acetic acid at 40 p.s.i. occurred quantitatively, to complete the first enantiospecific total synthesis of (+)-longiborneol (59).

Scheme 60
Reagents and conditions:

(i) Ph₃MePBr, BuLi, -78°C-20°C; (ii) LAH, THF; (iii) Et₂Zn, CH₂I₂, PhMe; (iv) H₂/PtO₂, HOAc, 2.5 Atmosphere.

Scheme 61

The specific rotation ([α]D²⁵ +15.83°) of our synthetic (+)-longiborneol (59) compares favorably with those reported in the literature [77] (cf. Table 2). In addition, our synthetic (+)-longiborneol (59) has very similar infrared spectrum (page 277), ¹H-n.m.r. spectrum (page 278), and gas-liquid chromatographic retention time as that of racemic longiborneol [78] and naturally occurring longiborneol [79]. The corresponding "Mosher ester" derivative (211) [80] of our synthetic (+)-longiborneol (59) was prepared and the ¹H-n.m.r. (page 279), ¹⁹F-n.m.r. (page 280), and ¹³C-n.m.r. (page 281) spectra of this compound confirmed the enantiomeric purity of our synthetic material.
<table>
<thead>
<tr>
<th>GROUPS</th>
<th>LONGIBORNEOL</th>
<th>$[\alpha]_D$</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Money and Kuo</td>
<td>(+)</td>
<td>15.83°</td>
<td>[84]</td>
</tr>
<tr>
<td>Doi and co-workers</td>
<td>(+)</td>
<td>18.50°</td>
<td>[77a]</td>
</tr>
<tr>
<td>Akiyoshi and co-workers</td>
<td>(+)</td>
<td>18.40°</td>
<td>[77b]</td>
</tr>
<tr>
<td>Matsuo and co-workers</td>
<td>(-)</td>
<td>16.30°</td>
<td>[77c]</td>
</tr>
</tbody>
</table>

Table 2

\[ (+)-\text{MTPA-Chloride, Pyridine, } \text{CCl}_4 \rightarrow \]

(59)  

(211)
To complete the synthesis of (+)-longifolene (61), (+)-longiborneol (59) was oxidised [69] to (+)-longicamphor (83) which was then reduced with lithium aluminum hydride to provide (+)-longiisoborneol (89) (Scheme 62). Treatment

\[
\begin{align*}
&\text{(59)} \quad (i) \quad \rightarrow \quad \text{(83)} \quad (ii) \quad \rightarrow \quad \text{(89)} \\
&\text{(61)} \quad (iii)
\end{align*}
\]

Reagents and conditions:
(i) PCC, CH$_2$Cl$_2$; (ii) LAH, THF; (iii) MeSO$_2$Cl, Pyridine, 4-DMAP, 100°C, 16 hours.

Scheme 62 of (+)-longiisoborneol (89) with methanesulfonyl chloride in 4-dimethylaminopyridine and pyridine at high temperature, followed by column chromatography of the product, afforded a colorless oil. The infrared spectrum (page 282) of this product showed bands at 1661 cm$^{-1}$ and 871 cm$^{-1}$ which indicated the presence of an exocyclic double bond. This, together with $^1$H-n.m.r. spectrum (page 282), mass spectrum (page 283), and elemental microanalysis prompted us to conclude that the Wagner-Meerwein rearrangement had occurred successfully to
provide (+)-longifolene (61). In addition, the specific rotation ([\(\alpha\])\(\text{D}^{25}\) +51.77°) of our synthetic (+)-longifolene (61) was very similar to the literature values [81] (cf. Table 3).

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>LONGIFOLENE</th>
<th>[(\alpha])(\text{D})</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oppolzer and co-workers</td>
<td>(+)</td>
<td>51.5°</td>
<td>[81a]</td>
</tr>
<tr>
<td>G. Ourisson and co-workers</td>
<td>(-)</td>
<td>51.0°</td>
<td>[81b]</td>
</tr>
<tr>
<td>Money and Kuo</td>
<td>(+)</td>
<td>51.7°</td>
<td>[84]</td>
</tr>
</tbody>
</table>

Table 3

Scheme 25 (page 35) provides an outline of longifolene (61) biosynthesis and shows that the final step in the construction of this natural product is probably a Wagner-Meerwein rearrangement of the tricyclic secondary carbocation (84) followed by deprotonation. Similarly, the key step in our
synthetic route to (+)-longifolene (61) is the Wagner-Meerwein rearrangement of (+)-longiisoborneol (89) and therefore, the final step in our synthesis of (+)-longifolene (81) is analogous to its postulated biosynthetic process.

"If there is one way better than another, it is the way of nature"

Aristotle

Finally, we hoped to synthesised (+)-longicyclene (60) from the hydrazone derivative (212) of (+)-longicamphor (83) by a reaction analogous to that used in the synthesis of tricyclene (88) [82], and α-santalene (45) [24] (cf. Scheme 63). However, all our attempts to prepare the required hydrazone (212) failed. An examination of the molecular model reveals that steric hindrance around the carbonyl group of (+)-longicamphor (83) is quite severe (cf. Scheme 64).

\[ \text{Scheme 63} \]
Although this direct approach to synthesise (+)-longicyclene (60) from (+)-longicamphor (83) was not successful, it is interesting to note that in 1964 Dev and co-workers [83] demonstrated the rearrangement of (+)-longifolene (61) to (+)-longicyclene (60), isolongifolene (215), and (±)-longifolene as shown in Scheme 65.

Scheme 64

Scheme 65

(83)  \[\rightarrow\]  (212)  \[\rightarrow\]  (60)

(61)  \[\rightarrow\]  (60)  +  (215)

(±)-Longifolene
In summary, attempts to synthesise (+)-longicamphor (83) by an intramolecular Diels-Alder reaction or by intramolecular Lewis acid induced α-tertiary alkylation were unsuccessful. However, the intramolecular Mukaiyama reaction provided a tricyclic intermediate (195a,b) which was used in the enantiospecific total synthesis of (+)-longiborneol (59), and (+)-longifolene (61). Since (+)-camphor (26) can lead to (+)-longiborneol (59), (+)-longicamphor (82), and (+)-longifolene (61), (-)-camphor (27) should provide the naturally occurring (-)-longiborneol (216), and (-)-longifolene (78) as shown in Scheme 66.

In conclusion, Scheme 67 illustrates a series of structurally related natural products that have been synthesised in our laboratory from either (+)-8-bromocamphor (42) or (-)-8-bromocamphor (43), and includes the more recent investigations described above [84].
Scheme 66
Scheme 67

† enantiomer also known
* unknown in nature
1.4.0. **EXPERIMENTAL**

**General**

Melting points (mp) were determined on a Kofler micro heating stage and are uncorrected. Infrared (ir) spectra were recorded on a Perkin-Elmer model 710 B spectrophotometer and were calibrated using the 1601 cm\(^{-1}\) band of polystyrene. Absorption positions (\(\nu_{\text{max}}\)) are given in cm\(^{-1}\). Optical rotations ([\(\alpha\])\(_D\)) were measured on a Perkin-Elmer 141 polarimeter at a ambient temperature. The proton nuclear magnetic resonance (\(^1\)H n.m.r.) spectra were taken in deuterochloroform and recorded at 80 MHz on a Bruker WP-80 spectrometer, at 300 MHz on a Varian XL-300 spectrometer, at 400 MHz on a Bruker WH-400, 100 MHz on a Varian XL-100 spectrometer or at 270 MHz on a unit consisting of an Oxford instrument 63.4 KG superconducting magnet, a Nicolet 32K computer and Bruker TT-23 console. Signal positions are given in parts per million downfield from tetramethylsilane using the scale. In the case of compounds containing trialkylsilyl groups the chemical shifts were determined relative to chloroform signal (\(\delta 7.25\)). Signal multiplicity, coupling constants and assignments of selected signals are indicated in parentheses. \(^{13}\)C n.m.r. spectra were made in deuterochloroform and determined on a Bruket WP-400 instrument at 100.6 MHz with signal postions given in parts per million downfield from tetramethylsilane (used as an external standard). \(^{19}\)F n.m.r. spectra were obtained in deuterochloroform using either a Varian XL-100
instrument operating at 94.1 MHz or a Bruker HXS-270 spectrometer at 254 MHz. The signals are quoted in parts per million downfield from trifluoroacetic acid (used as an external reference). Low resolution mass spectra were obtained using a Varian MAT CH-4B spectrometer and exact masses were obtained by high resolution mass spectroscopy on a Kratos MS-50 mass spectrometer. All compounds characterised by high resolution mass spectrometry exhibited 1 spot on tlc. Low resolution gas liquid chromatography/mass spectra (gc/ms) were obtained on a Carlo Erba 41 60/Kratos MS80 RFA instrument using a 0.25 mm x 15 m column with helium as the carrier gas. Gas-liquid chromatography was performed on either a Hewlett Packard model 5830A gas chromatograph with a 6 ft x 1/8 in. column of 3% OV-17 or a Hewlett Packard model 5880A gas chromatograph using a 50 m or 12 m x 0.2 mm column of Carbowax 10 M or a 12 m x 0.2 mm column of OV-101. The carrier gas was nitrogen for the 5830A and helium for the 5880A. In all cases a flame ionisation detector was used. X-Ray crystallographic analyses were carried out by Dr. S. Rettig and microanalyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia, Vancouver.

All reactions involving moisture sensitive reagents were performed under an atmosphere of dry argon using either oven or flame dried glassware. All reaction products were dried by allowing the solutions to stand over anhydrous magnesium sulphate. The solvents and reagents used were purified as follows: tetra-
hydrofuran and dimethoxyethane were distilled from calcium hydride and then from lithium aluminum hydride (LAH). Diethyl ether was distilled from LAH and hexamethylphosphoramide (HMPA), benzene, methylene chloride, diisopropylamine, triethylamine, dimethylsulphoxide (DMSO), and pyridine were distilled from calcium hydride. Methanol was obtained by distillation from magnesium methoxide. Petroleum ether (the hydrocarbon fraction of boiling range 30-60°C) was distilled prior to use.

Flash chromatography was performed using Merck silica gel 60, 230-400 mesh and thin layer chromatography (tlc) using Bakerflex silica gel 1B2-F sheets. All chemicals were supplied by Aldrich Chemical Company unless otherwise stated.
(-)-Isoborneol (86)

Lithium tributoxy aluminum hydride (3.8 g, 15 mmol) was suspended in dry tetrahydrofuran (40 mL) at 0°C, and a solution of (+)-camphor (26) (1.5 g, 9.8 mmol) in dry tetrahydrofuran (10 mL) was slowly added. The reaction mixture was stirred at 0°C under an argon atmosphere for 3 hours. After dilution with water (10 mL), carefully followed by extraction with ether, the combined organic layers were washed with hydrochloric acid (1.0 N) and brine, and dried (MgSO₄). Upon removal of solvent under vacuo, the crude product was purified by column chromatograph (silica gel, pet. ether) to afford (-)-isoborneol (86) (1.5 g, 99%) as a white solid, which was recrystallised from pentane (25°C) as colorless prisms; mp 212°C (sealed tube); (lit.* mp 214°C (sealed tube)); [α]ᵣ°D -19.6° (c 2.04, CHCl₃), [α]₀D²⁰ -34.4° (c 1.80, C₂H₅OH); (lit.* [α]₀D -34.6° (c 0.50, al)); δ (80 MHz, CDCl₃): 0.83 (s, 3H, CH₃), 0.93 (s, 3H, CH₃), 1.0 (s, 3H, CH₃), 3.6 (dd, 1H, RHOH, J=2 Hz, 7 Hz).

* CRC Handbook of Chemistry and Physics, 56th ed. 1975-1976, C-345.
(+)‐Camphene (85)

(86) → (85)

(−)‐Isoborneol (86) (3.2 g, 21 mmol) was treated with methanesulphonyl chloride (3.2 mL, 41 mmol) and 4‐dimethylaminopyridine (0.10 mg) in dry pyridine (15 mL) at 105°C under an argon atmosphere for 16 hours. After dilution with water (10 mL) and extraction with ether, the combined organic layers were washed with hydrochloric acid (1.0 N), saturated sodium bicarbonate solution and water, and dried (MgSO₄). Upon removal of solvent under vacuo, the crude product was purified by column chromatography (silica gel, pet. ether) to obtain (+)‐camphene (85) (1.9 g, 67%) as a colorless oil; [α]D⁺25° +108° (c 1.87, C₂H₅OH), [α]D⁺25° +118° (c 1.77, C₆H₆) (lit.* [α]D +104° (c 0.40, C₂H₅OH)); δ (80 MHz, CDCl₃): 1.05 (s, 3H, CH₃), 1.07 (s, 3H, CH₃), 4.50 (s, 1H, RC:CHH), 4.70 (s, 1H, RC:CHH).

* CRC Handbook of Chemistry and Physics, 56th ed. 1975‐1976, C‐228
Bromine (292 mL, 5.70 mol) was added to (+)-camphor (26) (102 g, 0.670 mmol; Aldrich Chemical Co.) dissolved in glacial acetic acid (326 mL, 5.70 mol) and hydrogen bromide gas was bubbled through the reaction mixture for 1 hour at 110°C. Stirring was continued at 110°C for 16 hours in the dark and the reaction mixture was then poured into water and excess bromine destroyed with sodium bisulphite. The aqueous layer was extracted with ether and the combined organic extracts were washed with water, saturated sodium bicarbonate, saturated brine, and dried over MgSO₄. Removal of solvent gave a pale yellow oil which solidified upon cooling in ice-bath. Crystallisation from petroleum ether provided (+)-3,3-dibromocamphor (129) (205 g, 99.0%); mp 60°C; [α]D²⁵ +37.1° (c 1.67, C₂H₅OH); νmax (CCl₄): 2950, 1770 cm⁻¹; δ (CDCl₃, 80 MHz): 1.05 (s, 3H, CH₃), 1.15 (s, 3H, CH₃), 1.27 (s, 3H, CH₃), 2.82 (d, 1H; J=4 Hz, C₄H); m/e (relative intensity): 308/310/312(0.59/1.15/0.66, M+2/M+4), 284 (1.43), 282 (2.92), 280 (1.09), 232 (8.28), 230 (7.97), 203 (11.3), 201 (11.7), 123 (66.8), 107 (44.1), 95.0 (28.0), 91.0 (32.0). 83.0 (100): **Exact mass** calcd. for C₁₀H₁₄OBr₂:
307.9411/309.9391/311.9370; found (high resolution mass spectrometry): 307.9418/309.9397/311.9375. Anal. calcd. for C₁₀H₁₄OBr₂: C 38.74, H 4.55; found: C 38.63, H 4.58.

(+)-8-Bromocamphor (42)[22a]

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\begin{align*}
\text{O} & \\
\text{Br} & \\
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\text{O} & \\
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\text{O} & \\
\end{align*}
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A solution of (+)-3,3-dibromocamphor (129) (19.7 g, 63.5 mmol) in bromine (3.30 mL, 63.5 mmol) was cooled in an ice-water bath while chlorosulphonic acid (25.0 mL, 372 mmol) was added dropwise. The ice bath was then removed and stirring was continued for 3.5 hours before the reaction mixture was carefully poured onto ice. Excess bromine was destroyed with sodium bisulphite and the aqueous solution was extracted with ether. The combined organic layers were washed with sodium bicarbonate solution and brine, and dried (MgSO₄). Upon removal of solvent, crude 3,3,8-tribromocamphor (130) (24.2 g) was obtained as a viscous brown oil which was used in the next step without further purification.

Crude 3,3,8-tribromocamphor (130) (300 g, 0.771 mol) was dissolved in glacial acetic acid (450 mL) and cooled by an ice-
water bath. Zinc dust (75.0 g, 1.15 mol), was slowly added with vigorous stirring. The ice-water bath was then removed and stirring was continued for 4.5 hours at room temperature. The reaction mixture was poured into ice-water containing sodium bicarbonate, and extracted with ether. The combined organic extract was washed with saturated sodium bicarbonate solution and brine, and then dried (MgSO₄). Removal of solvent gave a brown oil (190 g) which upon fractional distillation provided (+)-8-bromocamphor (42) (107 g, 60.0%) as a colorless crystalline solid; bp (range, 0.05 mmHg) 70-110°C. Sublimation followed by crystallisation from petroleum ether (30-60°C) provided colorless crystals; mp 83-85°C; [α]D²⁵ +73.1° (c 1.17, C₂H₅OH); [α]D²⁵ +76.7° (c 1.24, CHCl₃); Rf 0.39 (petroleum ether:ether, 9:1); $\nu_{max}$ (CHCl₃): 2975, 1751 cm⁻¹; δ (CDCl₃, 400 MHz): 0.93 (s, 3H, CH₃), 1.15 (s, 3H, CH₃), 3.10, 3.17 (AB quartet, 2H, $J_{AB}$=10 Hz); m/e (relative intensity): 230/232(3.57/2.79, M⁺/M⁺+2), 205 (1.18), 188 (1.93), 186 (2.05), 175 (1.07), 159 (1.45), 151 (5.36), 149 (15.1), 109 (28.4), 108 (42.7), 107 (46.6), 95.0 (10.0); Exact mass calcd. for C₁₀H₁₅OBr: 230.0308/232.0286; found: 230.0308/232.0290; Anal. calcd. for C₁₀H₁₅OBr: C 38.74, H 4.550; found: C 38.63, H 4.580.
(+)-8-Bromocamphor ethylene ketal (131)

To a solution of (+)-8-bromocamphor (42) (9.8 g, 4.3 mmol) in dry ethylene glycol (140 mL, 354 mmol) under an argon atmosphere was added chlorotrimethylsilane (31.0 mL, 244 mmol) and the reaction mixture stirred for 6 hours at room temperature. Water (50 mL) was then added and worked up by extraction with ether, and the combined organic layers were washed with sodium bicarbonate solution (10%) and brine, and dried (MgSO$_4$). Upon removal of solvent under vacuo, the crude product was purified by column chromatography on silica gel (pet. ether:ether, 15:1) to afford the (+)-8-bromocamphor ethylene ketal (131) (10 g, 88%) as a colorless oil; $[\alpha]_D^{25} +12.1^\circ$ (c 1.02, CHCl$_3$); $\nu_{\text{max}}$ (film): 2981 cm$^{-1}$; $\delta$ (CDCl$_3$, 400 MHz): 0.82 (s, 3H, CH$_3$), 1.06 (s, 3H, CH$_3$), 3.70-4.00 (m, 4H, ROCH$_2$CH$_2$OR), 3.24, 4.22 (AB quartet, 2H; $J_{AB}=10$ Hz); m/e (relative intensity): 274/276 (0.200/0.160, M$^+$/M$^+2$), 273 (1.72), 197 (1.27), 196 (13.5), 195 (100); Exact mass calcd. for C$_{12}$H$_{19}$O$_2$Br (M$^+1$): 275.0568; found: 275.0468; Anal. calcd. for C$_{12}$H$_{19}$O$_2$Br: C 52.38, H 6.96; found: C 52.60, H 6.93.
Dry potassium iodide (31.2 g, 188 mmol) was added to a stirred solution of (+)-8-bromocamphor (42) (14.4 g, 63.0 mmol) in dry dimethylsulfoxide (60 mL) and stirring was continued at 110°C under an argon atmosphere for 40 hours. The cooled reaction mixture was added to water (200 mL), extracted with ether, and the combined organic layers were washed with brine, and dried (MgSO₄). Upon removal of solvent under vacuo, the crude product was purified by column chromatography (silica gel, pet. ether:ether, 15:1) to afford (+)-8-iodocamphor (165) (17 g, 95%) as a colorless oil; R_f 0.30 (pet. ether:ether, 9:1); [α]_D^25+72.1° (c 14.5; CHCl₃); ν_max (film): 2981, 1741 cm⁻¹; δ (CDCl₃, 270 MHz): 0.94 (s, 3H, CH₃), 1.12 (s, 3H, CH₃), 2.91, 3.00 (AB quartet, 2H, RCH₂I, J_AB=10 Hz); m/e (relative intensity): 278 (23.1, M⁺), 277 (1.90), 223 (1.90), 182 (3.30), 1.52 (7.30), 151 (50.0), 123 (28.0), 109 (69.4), 107 (100); Exact mass calcd. for C₁₀H₁₅OI: 278.0167; found: 278.0169; Anal. calcd. for C₁₀H₁₅OI: C 43.18, H 5.440, I 45.63; found C 43.30, H 5.430, I 45.45.
Chlorotrimethylsilane (31.0 mL, 242 mmol) was added to a solution of (+)-8-iodocamphor (165) (16.8 g, 60.4 mmol) in dry ethylene glycol (80 mL) under an argon atmosphere and the reaction mixture stirred for 6 hours at room temperature. Water (50 mL) was added and the mixture was extracted with ether, and the combined organic layers were washed with sodium bicarbonate solution (10%), brine, and dried (MgSO₄). The solvent was removed under vacuo and the crude product was purified by column chromatography (silica gel, pet. ether:ether, 15:1), to provide (+)-8-iodocamphor ethylene ketal (133) (18 g, 94%) as a colorless oil: Rf 0.63 (pet. ether:ether, 9:1); [α]D²⁵ +34.3° (c 0.70, CHCl₃); Ψmax (film): 2973 cm⁻¹; δ (CDCl₃, 400 MHz): 0.82 (s, 3H, CH₃), 1.05 (s, 3H, CH₃), 3.04, 4.07 (AB quartet, 2H, ICH₂R, JAB=10 Hz), 3.74-3.98 (m, 4H, ROCH₂CH₂OR); m/e (relative intensity): 321 (0.270, M⁺-1), 304 (0.220), 262 (0.290), 221 (0.590), 197 (1.38), 196 (13.4), 195 (100); Exact mass calcd. for C₁₂H₁₉IO₂ (M⁺-1): 321.0350; found: 321.0350; Anal. calcd. for C₁₂H₁₉IO₂: C 44.74, H 5.940; found: C 45.03, H 6.100.
(+)-8-Cyanocamphor ethylene ketal (166) [22a]

(a) Dry sodium cyanide (9.00 g, 184 mmol) was added to a stirred solution of (+)-8-bromocamphor ethylene ketal (131) (10.3 g, 37.6 mmol) in dry dimethyl sulfoxide (150 mL) and stirring continued at 60°C under an argon atmosphere for 7 days. After cooling, the reaction mixture was added to water (200 mL), extracted with ether, and the combined organic layers were washed with brine, and dried (MgSO₄). The solvent was removed under vacuo, and the crude product was purified by column chromatography (silica gel, pet. ether:ether, 6:1) to provide (+)-8-cyanocamphor ethylene ketal (166) (4.5 g, 54%) as a colorless oil; Rᵢ 0.48 (pet. ether:ether, 4:1); [α]迪⁰_25 +5.06° (c 2.35, C₂H₅OH); ν max (film): 2950, 2250 cm⁻¹; δ (CDCl₃, 400 MHz): 0.85 (s, 3H, CH₃), 1.09 (s, 3H, CH₃), 2.30, 2.98 (AB quartet, 2H, NCCH₂R, JAB=16 Hz), 3.70-4.00 (m, 4H, ROCH₂CH₂OR); m/e (relative intensity): 221 (1.07, M⁺), 182 (3.14), 181 (24.8), 166 (1.94), 140 (1.30), 133 (1.01), 127 (1.76), 125 (3.87), 113 (11.7), 95.0 (100); Exact mass calcd. for C₁₃H₁₉O₂N: 221.1416; found: 221.1416; Anal. calcd. for C₁₃H₁₉O₂N: C 70.56, H 8.650, N 6.330; found: C 70.72, H 8.800, N 6.220.
(b) Dry sodium cyanide (1.46 g, 29.8 mmol) was added to a stirred solution of (+)-8-iodocamphor ethylene ketal (133) (2.4 g, 7.5 mmol) in dry dimethyl sulphoxide (35 mL) and stirring continued at 60°C under an argon atmosphere for 3 days. After cooling, the reaction mixture was poured onto water (50 mL), extracted with ether and worked up in the usual way. Column chromatography (silica gel, pet. ether:ether, 6:1) of the crude product gave (+)-8-cyanocamphor ethylene ketal (166) (1.5 g, 92%) as a colorless oil.

Cyanoketals (167a,b)

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\begin{align*}
\text{(166)} & \\
\text{NC} & \\
\text{O} & \\
\text{O} & \\
\end{align*}
\]

\[
\begin{align*}
\text{(167a,b)} & \\
\text{NC} & \\
\end{align*}
\]

n-Butyllithium (1.6 M; hexane) (3.6 mL, 5.7 mmol) was added to a stirring solution of diisopropylamine (0.80 mL, 5.7 mmol) in dry tetrahydrofuran (8.0 mL) and stirring continued under an argon atmosphere at 0°C for 30 minutes. The solution was then cooled to -78°C and (+)-8-cyanocamphor ethylene ketal (166) (1.0 g, 4.7 mmol) in dry tetrahydrofuran (23 mL) was added to this cooled solution at -78°C. Stirring was continued for 2 hours before prenyl bromide (0.8 mL, 7.1 mmol) was introduced
at $-78^\circ$C. The reaction mixture was stirred for 10 hours while warming to room temperature, and worked up by adding water (10 mL) and extracting with ether. The combined organic layers were washed with saturated ammonium chloride solution and brine solution, and dried ($\text{MgSO}_4$). Removal of solvent followed by column chromatography (silica gel, pet. ether:ether, 10:1) provided a mixture of epimers of cyanoketals (167a,b) (1.3 g, 95%) as a colorless oil; the ratio (6:1) of epimers was determined from the proton integrations in the n.m.r. spectrum; $R_f$ 0.22 (pet. ether:ether, 9:1); $\nu_{\text{max}}$ (film): 2975, 2250 cm$^{-1}$; $\delta$ (CDCl$_3$, 400 MHz): $^1$H-n.m.r. assignments of major diastereomer:

$1.03$ (s, 3H, CH$_3$), $1.10$ (s, 3H, CH$_3$), $1.65$ (s, 3H, CH$_3$), $1.75$ (s, 3H, CH$_3$), $3.38$ (dd, 1H, $R_2$CHCN, $J=4$ Hz, 12 Hz), $3.70-4.00$ (m, 4H, ROC$_2$H$_4$OR), $5.24$ (t, 1H, $(\text{CH}_3)_2C:CHR$, $J=8$ Hz); m/e (relative intensity): 289 (4.62, $M^+$), 181 (17.8), 125 (15.6), 107 (1.10), 99.0 (1.30), 96.0 (7.50), 95 (100); **Exact mass** calcd. for $C_{18}H_{27}O_2N$: 289.2024; found: 289.2045; **Anal.** calcd. for $C_{18}H_{27}O_2N$: for C 74.70, H 9.400, N 4.840; found: C 74.39, H 9.550, N 4.900.
To a solution of potassium (0.36 g, 92.0 mmol) in dry hexamethylphosphoramide (7.0 mL) under an argon atmosphere at 25°C was added a solution of cyanoketal epimers (167a,b) (1.3 g, 4.6 mmol) in anhydrous ether (7.0 mL), followed by tert-butanol (0.65 mL, 6.9 mmol). Stirring was continued for 12 hours and worked up by adding brine solution (10 mL) and extracting with ether. The combined organic layers were washed with brine solution and dried (MgSO$_4$). The solvent was removed and the crude product was purified by column chromatography (silica gel, pet. ether:ether, 10:1) to provide (-)-campherenone ethylene ketal (168) (0.72 g, 78%) as a colorless oil; R$_f$ 0.89 (pet. ether:ether, 9:1); $[\alpha]_D^{25}$ -14.5° (c 0.58, CHCl$_3$); $\nu_{\text{max}}$ (film): 2776, 1661 cm$^{-1}$ (w); $\delta$ (CDC$_3$, 400 MHz): 0.80 (s, 3H, CH$_3$), 0.88 (s, 3H, CH$_3$), 1.62 (s, 3H, CH$_3$), 1.69 (s, 3H, CH$_3$), 3.7-4.0 (m, 4H, ROC$_2$H$_4$OR), 5.15 (t, 1H, Ha, J=8 Hz); m/e (relative intensity): 264 (10.9, M$^+$), 221 (2.67), 195 (2.16), 187 (2.74), 180 (6.82), 165 (4.44), 159 (2.10), 155 (2.29), 153 (7.49), 149 (2.00), 140 (3.57), 135 (6.66), 133 (4.02), 125 (100); Exact mass calcd. for C$_{17}$H$_{28}$O$_2$: 264.2089; found:
264.2086; Anal. calcd. for C_{17}H_{28}O_2: C 77.22, H 10.67; found: C 77.50, H 10.70.

\((+)-\)Campherenone (151)

\((-)-\)Campherenone ethylene ketal (168) (0.51 g, 2.0 mmol) was dissolved in acetone (5.0 mL) and treated with hydrochloric acid (1.0 N, 3.0 mL) for 3 hours at 25°C. After work-up by extracting with ether, the combined organic layers were washed with saturated sodium bicarbonate solution and brine, and dried (MgSO_4) to provide a crude product which was purified by column chromatography (silica gel, pet. ether:ether, 10:1) to provide \((+)-\)campherenone (151) (0.42 g, 96%) as a colorless oil; R_f 0.50 (pet. ether:ether, 9:1); [α]^{D}_{25}+30.8° (c 2.78, CHCl_3) (lit. [23] for \((-)-\)campherenone; [α]^{D}_{23}-30.6° (c 10.7, CHCl_3)); ν_{max} (film): 2979, 1748 cm^{-1}; δ (CDCl_3, 400 MHz): 0.90 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 5.05 (t, 1H, (CH_3)_2C:CHR, J=8 Hz); m/e (relative intensity): 220 (19.0, M^+), 163 (3.98), 137 (6.83), 135 (12.7), 121 (12.7), 109 (34.2), 95.0 (29.0), 69.0 (45.0); Exact mass calcd. for C_{15}H_{24}O: 220.1827;
found: 220.1827; Anal. calcd. for C$_{15}$H$_{24}$O: C 81.76, H 10.98;
found: C 82.00, H 11.00.

(+)-Campherenone hydrochloride (426)

(+)-Campherenone (151) (0.28 g, 1.3 mmol) was dissolved in
anhydrous ether (8.0 mL) and concentrated hydrochloric acid
(3.0 mL, 13 mmol) was added slowly at 25°C. Stirring was con­
tinued for 8 hours before water (10 mL) was added and the re­
action mixture was extracted with ether and the combined organic
layers were washed with saturated sodium bicarbonate solution,
brine, and dried ($\text{MgSO}_4$). Removal of solvent followed by column
chromatography of the crude product on silica gel (pet. ether:
ether, 10:1) afforded (+)-campherenone hydrochloride (426)
(0.32 g, 96%) as a colorless oil; $R_f$ 0.38 (pet. ether:ether, 9:1); [$\alpha$]$_D^{25} +37.9^\circ$ (c 0.47 , CHCl$_3$); $\nu_{\text{max}}$ (film): 1741,
2964 cm$^{-1}$; $\delta$ (CDC$_3$, 400 MHz): 0.8 (s, 3H, CH$_3$): 0.93 (s, 3H, CH$_3$), 1.55 (s, 6H, R'RC:C(CH$_3$)$_2$); m/e (relative intensity): 256
(9.92, $M^+$), 221 (10.0), 220 (23.3), 177 (8.38), 163 (17.6), 151
(10.8), 137 (15.1), 135 (19.6), 123 (15.1), 111 (39.5), 109
Campherenone hydrochloride enol trimethylsilyl ether (104)

Lithium diisopropylamide was generated by reacting n-butyllithium (1.6 M; hexane) (0.29 mL, 0.43 mmol) with diisopropylamine (0.06 mL, 0.43 mmol) in dry tetrahydrofuran (4.0 mL) at 0°C under an argon atmosphere for 30 minutes. This was cooled to -78°C and a solution of (+)-campherenone hydrochloride (426) (91 mg, 0.35 mmol) in dry tetrahydrofuran (2.0 mL) was added to the reaction mixture. After 2 hours, freshly distilled chlorotrimethylsilane (0.07 mL, 0.53 mmol) was added and stirring was continued for 1 hour at room temperature. The solvent was filtered through a column of celite and evaporated to provide campherenone hydrochloride enol trimethylsilyl ether (104) (112 mg, 97%) as a colorless oil. $\nu_{\text{max}}$ (film): 2977, 1618 cm$^{-1}$; $\delta$ (CDCl$_3$, 80 MHz): 0.2 (s, 9H, R$\text{Si(CH}_3)_3$), 0.7 (s, 3H, CH$_3$), 0.85 (s, 3H, CH$_3$), 1.55 (s, 6H, (CH$_3$)$_2$CClR), 4.58 (d, 1H (TMSO)R$\text{C:CHR}^+$, 105
A solution of (+)-campherenone hydrochloride (426) (89 mg, 0.30 mmol) in dry tetrahydrofuran (5.0 mL) was treated at 25°C with n-butyllithium (1.6 M; hexane) (0.3 mL, 0.4 mmol) for 15 minutes. The enolate anion thus generated was cooled to -50°C and treated with dry acetic anhydride (0.06 mL, 0.60 mmol). After 15 minutes, the reaction mixture was warmed to 25°C and saturated sodium bicarbonate solution (5 mL) was added to quench excess acetic anhydride. The mixture was then extracted with pet. ether and the combined organic layers were washed with brine solution and dried (MgSO₄). After removal of solvent, the crude product was purified by column chromatography (silica gel, pet. ether:ether, 6:1) to provide campherenone hydrochloride enolacetate (170) (92 mg, 95%) as a colorless oil. \( R_f \) 0.65 (pet. ether:ether, 4:1); \( \nu_{\text{max}} \) (film): 2980, 1760 cm\(^{-1}\); \( \delta \) (CDCl\(_3\), 400 MHz): 0.78 (s, 3H, CH\(_3\)), 0.92 (s, 3H, CH\(_3\)), 1.56 (s, 3H, CH\(_3\)), 1.57 (s, 3H, CH\(_3\)), 2.15 (s, 3H, CH\(_3\) CO R), 5.53 (d, 1H,
(AcO)RC:CHR’, J=4 Hz); m/e (relative intensity): 298 (3.20, M+), 258 (18.2), 256 (54.6), 220 (72,2), 192 (16.5), 179 (55.8), 177 (21.5), 161 (20.6), 149 (16.1), 137 (77.1), 135 (75.2), 123 (25.5), 110 (100); Exact mass calcd. for C_{17}H_{27}O Cl: 298.1699; found: 298.1700.

**Attempted Cyclisation of Campherenone Derivatives**

(a) To a cooled (0°C), well stirred solution of (+)-campherenone (151) (25 mg, 0.10 mmol) in dry methylene chloride (2 mL) under an argon atmosphere was added dropwise stannic chloride (0.003 mL, 0.020 mmol). After 24 hours the reaction mixture was diluted with water (10 mL) and extracted with ether. The combined organic layers were washed with saturated sodium bicarbonate solution and water, and dried (MgSO₄). After removal of
solvent, the crude product was purified by column chromatography (silica gel, pet. ether:ether, 5:1) to give campherenone dimers (169a,b) (13 mg) as a colorless oil; Rf 0.1 (pet. ether:ether, 9:1); $\nu_{\text{max}}$ (film): 2986, 1736 cm$^{-1}$; $\delta$ (CDCl$_3$, 400 MHz): $^1$H-n.m.r. of major diastereomer: 0.81 (s, 6H, (CH$_3$)$_2$), 0.90 (s, 6H, (CH$_3$)$_2$), 0.93, 0.98 (s, s, 6H, (CH$_3$)$_2$), 1.62 (s, 3H, CH$_3$), 1.86 (s, 3H, CH$_3$), 5.00 (t, 1H, (CH$_3$)$_2$C:CHR, J= 8 Hz); m/e (relative intensity): 440 (8.45, M$^+$), 277 (5.94), 262 (3.45), 233 (3.16), 222 (13.3), 220 (16.7), 177 (8.11), 149 (11.7), 138 (10.6), 135 (13.1), 121 (12.9), 109 (41.2), 95.0 (51.0); Exact mass calcd. for C$_{30}$H$_{48}$O$_2$: 440.3654; found: 440.3650.

(b) Titanium tetrachloride (0.055 mL, 0.500 mmol) was added dropwise to a cooled (-78°C), well-stirred solution of campherenone hydrochloride enol trimethylsilyl ether (104) (0.13 g, 0.42 mmol) in dry methylene chloride (26 mL) under an argon atmosphere. After 12 hours, the reaction mixture was diluted with water (10 mL) and extracted with ether. The combined organic layers were washed with saturated sodium bicarbonate solution and water, and dried (MgSO$_4$). After removal of solvent, the crude product was purified by column chromatography (silica gel, pet. ether:ether, 5:1) to give a mixture of epimers of campherenone dimers (169a,b) (47 mg).

(c) To a cooled (0°C), well-stirred solution of dry stannic chloride (6x10$^{-3}$ mL, 5.4x10$^{-2}$ mmol) in dry methylene chloride (6.0 mL) was added a solution of (+)-campherenone hydrochloride (426) (68 mg, 0.27 mmol) in methylene chloride (8.0 mL) dropwise,
under an argon atmosphere. After 2 days, the reaction mixture was diluted with water (10 mL) and extracted with ether. The combined organic layers were washed with saturated sodium bicarbonate solution and water, and dried (MgSO$_4$). After removal of solvent, the crude product was purified by column chromatography (silica gel, pet. ether:ether, 5:1) to give a mixture (3.5:1.0 by n.m.r.) of epimers of campherenone dimers (169a,b) (57 mg) as a colorless oil.

(d) To a cooled (0°C), well-stirred solution of campherenone hydrochloride enolacetate (170) (76 mg, 0.27 mmol) in dry methylene chloride (5 mL) under an argon atmosphere was added stannic chloride (6.4x10$^{-3}$ mL, 5.4x10$^{-2}$ mmol). After 16 hours, the reaction mixture was diluted with water (10 mL) and extracted with ether. The combined organic layers were washed with saturated sodium bicarbonate solution and water, and dried (MgSO$_4$). After removal of solvent, the crude product was purified by column chromatography (silica gel, pet. ether:ether, 5:1) to give campherenone dimers (169a,b) (20 mg) as a colorless oil.
tert-Butyldimethylsilyl trifluoromethanesulfonate (TBDMS triflate).

\[
CF_3SO_3H + \text{Si-Cl} \rightarrow CF_3SO_3\text{Si-Cl}
\]

Trifluoromethanesulphonic acid (20.5 mL, 232 mmol) was added dropwise to freshly sublimed tert-butyldimethylsilyl chloride (35.0 g, 232 mmol) at room temperature and the resulting mixture heated at 60°C for 16 hours. The product was then distilled from the reaction flask to afford TBDMS triflate 56.0 g, 91.0%) as a colorless oil (bp 65-67°C; 12 mmHg).

3-Bromo-1-tert-butyldimethylsilyloxypropane (179)

\[
\text{Br-OH} + CF_3SO_3\text{Si-Cl} \rightarrow \text{Br-O-Si-Cl}
\]

(179).

Freshly distilled TBDMS triflate (13 g, 49 mmol) was added dropwise to a solution of 3-bromo-1-propanol (6.8 g, 49 mmol) and 2,6-lutidine (5.3 g, 49 mmol) in dry methylene
chloride (35 mL) at 0°C and stirred under an argon atmosphere for 4 hours. The reaction mixture was added to water (51 mL) and extracted with methylene chloride. The combined organic layers were washed with hydrochloric acid (1.0 N), saturated ammonium chloride solution and water, and dried (MgSO₄). Upon removal of solvent under vacuo, the crude product was purified by column chromatography (silica gel, pet. ether:ether, 9:1) to afford the 3-bromo-tert-butyldimethylsilyloxypropane (179) (10.1 g, 85.0%) as a colorless oil; Rf 0.95 (pet. ether: ether, 9:1); δ (CDCl₃, 270 MHz): 0.08 (s, 6H, RSi(CH₃)₂), 0.91 (s, 9H, (CH₃)₂C-SiR), 1.96-2.08 (m, 2H, ROCH₂CH₂CH Br), 3.72 (t, 2H, RCH₂OSi, J=6 Hz), 3.50 (t, 2H, RCH₂Br, J=6 Hz); m/e (relative intensity): 253/255(7.04/6.69, M⁺+1/M⁺+3) 213 (1.38), 207 (1.04), 205 (1.02), 197 (52.1), 195 (53.4), 169 (63.5), 167 (66.1), 139 (90.3), 137 (89.7), 115 (100).
**Ketal-nitriles (180a,b)**

![Chemical structure](image)

\[
\begin{align*}
R_1 &= \text{H}, R_2 = \text{CN} \quad (180a) \\
R_1 &= \text{CN}, R_1 = \text{H} \quad (180b)
\end{align*}
\]

N-Butyllithium (1.60 M; hexane) (31 mL, 31 mmol) was added to a stirred solution of diisopropylamine (4.4 mL, 31 mmol) in dry tetrahydrofuran (50 mL) under an argon atmosphere at 0°C, and stirred for 30 minutes. (+)-8-Cyanocamphor ethylene ketal (166) (5.7 g, 26 mmol) in dry tetrahydrofuran (20 mL) was added to this cooled solution at -78°C and stirring was continued for 2 hours before a solution of 3-bromo-1-tert-butyldimethylsilyloxypropane (179) (9.3 g, 39 mmol) in tetrahydrofuran (20 mL) was introduced at -78°C. The reaction mixture was stirred for 10 hours while warming to room temperature and worked up by adding water (10 mL) and extracting with ether. The combined organic extracts were washed with saturated ammonium chloride solution and brine, and dried (MgSO₄). After removal of solvent and column chromatography (silica gel, pet. ether:ether, 5:1) a mixture of (R)-ketal-nitrile (180a) and its epimer (180b) (9.5 g, 94%) was obtained as a colorless oil. The ratio (6:1) of epimers (180a:180b) was determined by proton integrations in the n.m.r.; \( R_f \) 0.85 (pet. ether:ether, 1:1); \( \nu_{\text{max}} \) (film): 2980, 2257 cm\(^{-1}\); \( \delta \) (CDCl\(_3\), 400 MHz): 0.55 (s, 6H, \( \text{RSi(CH}_3\text{)}_2 \)).
0.89 (s, 9H, (CH₃)₃CSiR), 1.25 (s, 3H, CH₃), 1.75 (s, 3H, CH₃), 3.40-3.50 (m, 1H, R₁CHCNR₂), 3.58-3.98 (m, 6H, ROCH₂CH₂OR, and RCH₂OSi); m/e (relative intensity): 393 (0.410, M⁺), 378 (1.14) 338 (1.64), 226 (26.3), 293 (2.10), 292 (9.14), 274 (2.63), 265 (1.35), 181 (39.7), 113 (15.1), 95 (100); Exact mass calcd. for C₂₂H₃₉O₃SiN: 393.2699; found 393.2707; Anal. calcd. for C₂₂H₃₉O₃SiN: C 67.13, H 10.00, N 3.560; found: C 67.10, H 10.12, N 3.780.

(-)-Hydroxy-ketal (181)

Potassium (0.14 g, 3.6 mmol) was added to dry hexamethylphosphoramide (6.0 mL) under an argon atmosphere at 25°C and to the dark blue solution was added a solution of nitriles (180a,b) (0.71 g, 1.8 mmol) in anhydrous ether (5.0 mL) and tert-butanol (0.25 mL, 2.7 mmol). Stirring was continued for 10 hours and
the reaction was worked up in the usual way. The crude product was purified by column chromatography (silica gel, pet. ether: ether, 5:1) to afford (−)-hydroxy-ketal (181) (0.36 g, 83%) as a colorless oil; Rf 0.32 (pet. ether:ether, 1:1); [α]D²⁵ -14.7° (c 0.45, CHCl₃); νmax (film): 2964, 3407 cm⁻¹; δ (CDCl₃, 400 MHz): 0.80 (s, 3H, CH₃), 0.85 (s, 3H, CH₃), 3.70-4.00 (m, 4H, ROCH₂CH₂OR), 3.66 (t, 2H, RCH₂OH, J= 6 Hz); m/e (relative intensity): 254 (6.48, M⁺), 224 (1.79), 223 (1.73), 199 (2.26), 195 (1.19), 181 (11.7), 143 (36.5), 135 (13.4), 125 (99.9), 99.0 (41.0), 95.0 (100); Exact mass calcd. for C₁₅H₂₆O₃: 254.1882; found: 254.1879; Anal. calcd. for C₁₅H₂₆O₃: C 70.83, H 10.30; found: C 70.56, H 10.41.

A later fraction provided silyl ether (188) (11 mg) as a colorless oil; Rf 0.81 (pet. ether:ether, 1:1); [α]D²⁵ -6.9° (c 0.77, CHCl₃); νmax (film): 2886 cm⁻¹; δ (CDCl₃, 400 MHz): 0.60 (s, 6H, RSi(CH₃)₂), 0.79 (s, 3H, CH₃), 0.84 (s, 3H, CH₃), 0.91 (s, 9H, RSiC(CH₃)₃), 3.62 (t, 2H, RCH₂OSi, J= 6 Hz), 3.71-3.96 (m, 4H, ROCH₂CH₂OR); m/e (relative intensity): 368 (4.43, M⁺), 353 (2.31), 311 (20.7), 268 (11.8), 267 (54.6), 257 (24.8), 193 (53.7), 181 (14.9), 175 (29.4), 125 (74.9), 119 (33.9), 95.0 (100); Exact mass calcd. for C₂₁H₄₀O₃Si: 368.2746; found: 368.2737; Anal. calcd. for C₂₁H₄₀O₃Si: C 68.42, H 10.94; found: C 68.71, H 10.88. A final fraction provided a mixture of epimers of nitriles (185a,b) (89 mg) as a colorless oil; Rf 0.28 (pet. ether:ether, 2:3); νmax (film): 3420, 2970, 2248 cm⁻¹; δ (CDCl₃, 400 MHz): 1.03 (s, 3H, CH₃), 1.08 (s, 3H, CH₃), 3.45, 3.46 (dd,
1H, R_1R_2CHCN, J= 10 Hz, 4 Hz), 3.70-4.00 (m, 6H, ROCH_2CH_2OR, and RCH_2OH); m/e (relative intensity): 279 (0.480, M^+), 239 (0.790), 182 (4.47), 181 (35.8), 144 (2.02), 113 (11.6), 95.0 (100); Exact mass calcd. for C_{16}H_{25}O_3N: 279.1834; found: 279.1819; Anal. calcd. C_{16}H_{25}O_3N: C 68.79, H 9.020, N 5.010; found: C 68.70, H 9.000, N 4.900.

A further quantity of hydroxy-ketal (181) was obtained when tetra-n-butyl ammonium fluoride (0.10 L, 1.0 M solution in tetrahydrofuran) was added to (-)-silyl-ether (188) (10.5 g, 28.5 mmol) at 25°C under an argon atmosphere. Stirring was continued for 6 hours before water (50 mL) was added. The reaction mixture was extracted with ether and the combined organic layers were washed with saturated sodium bicarbonate solution, brine, and dried (MgSO_4). Upon removal of solvent under vacuo, the crude product was purified by column chromatography (silica gel, pet. ether:ether, 5:1) to give the (-)-hydroxy-ketal (181) (7.0 g, 97%) as a colorless oil.
(+)-Hydroxy-ketone (182)

Hydroxyketal (181) (1.0 g, 3.9 mmol) was dissolved in acetone (20 mL), hydrochloride solution (1.0 N, 12 mL) was added dropwise and the reaction mixture stirred at 25°C for 2 hours. The reaction mixture was added to water (20 mL) and worked up in the usual way to provide a crude product which was purified by column chromatography (silica gel, pet. ether:ether, 10:1) to afford (+)-hydroxy-ketone (182) (0.81 g, 99%) as a colorless oil; R_f 0.30 (pet. ether:ether, 7:2); [α]_D^25+41.9° (c 0.16, CHCl_3); ν_max (film): 3340, 2980, 1745 cm^{-1}; δ (CDCl_3, 400 MHz): 0.91 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 3.64 (t, 2H, RCH_2OH, J=6 Hz); m/e (relative intensity): 210 (22.9 M^+), 192 (1.59), 177 (1.63), 168 (1.31), 167 (2.08), 153 (3.85), 151 (9.99), 149 (5.32), 138 (18.5), 137 (25.1), 135 (17.7), 111 (14.2), 110 (15.1), 109 (100); Exact mass calcd. for C_{13}H_{22}O_2: 210.1620; found: 210.1615; Anal. calcd. for C_{13}H_{22}O_2: C 74.24, H 10.54; found: C 73.96, H 10.80.
(+)-Keto-aldehyde (183)

A solution of (+)-hydroxy-ketone (182) (0.76 g, 3.6 mmol) and pyridinium dichromate (2.7 g, 7.2 mmol) in dry methylene chloride (25 mL) was stirred at 25°C under an argon atmosphere for 10 hours. The reaction mixture was then diluted with ether and filtered through a pad of silica gel. Removal of solvent gave a crude product which was purified by column chromatography (silica gel, pet. ether:ether, 4:1) to provide (+)-keto-aldehyde (183) (0.72 g, 96%) as a colorless oil. Rf 0.49 (pet. ether:ether, 2:7); [α]_D^25 +27.5° (c 1.18, CHCl₃); ν_max (film): 2735 cm⁻¹; δ (CDCl₃, 400 MHz): 0.91 (s, 3H, CH₃), 0.98 (s, 3H, CH₃), 9.76 (t, 1H, RCHO, J = 1.5 Hz); m/e (relative intensity): 208 (14.1, M⁺), 180 (6.03), 175 (9.95), 162 (6.56), 147 (14.4), 137 (24.9), 136 (14.7), 135 (24.9), 133 (21.9), 109 (57.1), 95.0 (81.0); Exact mass calcd. for C₁₃H₂₀O₂: 208.1463; found: 208.1467; Anal. calcd. for C₁₃H₂₀O₂: C 74.96, H 9.680; found: C 74.89, H 9.730.
Keto-acetal (184)

A solution of (+)-keto-aldehyde (183) (38 mg, 0.18 mmol), ethylene glycol (0.01 mL, 0.23 mmol) and p-toluenesulfonic acid (catalytic amount) in benzene (5.0 mL) was refluxed in a Dean-Stark apparatus for 1.25 hours. Water (20 mL) was added and the reaction mixture was extracted with ether, and the combined organic layers were washed with sodium hydroxide solution (5%), and brine, and dried (MgSO₄). Removal of solvent gave a crude product which was purified by column chromatography (silica gel, pet. ether:ether, 5:1) to provide keto-acetal (184) (40 mg, 89%) as a colorless oil; R_f 0.41 (pet. ether:ether, 1:1); ν_max (film): 1740, 2979 cm⁻¹; δ (CDCl₃, 400 MHz): 0.91 (s, 3H, CH₃), 0.97 (s, 3H, CH₃), 3.80-4.00 (m, 4H, ROCH₂CH₂OR), 4.84 (t, 1H RCH(OR₁)₂, J=4.5 Hz); m/e (relative intensity): 252 (4.52 M⁺), 238 (1.24), 191 (2.90), 190 (6.89), 95.0 (15.0), 73.0 (100); Exact mass calcd. for C₁₅H₂₄O₃: 252.1725; found: 252.1722; Anal. calcd. for C₁₅H₂₄O₃: C 71.39, H 9.590; found: C 71.12, H 9.550.
Lithium diisopropylamide was generated by reacting n-butyllithium (1.6 M; hexane) (1.3 mL, 2.0 mmol) with diisopropylamine (0.28 mL, 2.0 mmol) in dry tetrahydrofuran (5.0 mL) at 0°C under an argon atmosphere for 30 minutes. A solution of ketoacetal (184) (0.41 g, 1.7 mmol) in dry tetrahydrofuran (5.0 mL) was then added to this cooled reaction mixture at -78°C and, after 2 hours, dry chlorotrimethylsilane (0.37 mL, 2.6 mmol) was introduced. Stirring was continued for 1 hour and the temperature increased to 25°C. The solvent was removed under vacuo and a solution of the residue in ether was filtered through a pad of celite and sand. Removal of ether under vacuo provided enol silyl ether acetal (178) (0.54 g, 98%) as a colorless oil; 
$\nu_{\text{max}}$ (film): 2951, 1616 cm$^{-1}$; $\delta$ (CDCl$_3$, 80 MHz): 0.13 (s, 9H, RSi(CH$_3$)$_3$), 0.67 (s, 3H, CH$_3$), 0.81 (s, 3H, CH$_3$), 3.50-4.00 (m, 4H, ROCH$_2$CH$_2$OR), 4.54 (d, 1H, RCH:CORR, $J=4$ Hz), 4.78 (t, 1H, RCH(OR)$_2$, $J=4.5$ Hz); m/e (relative intensity): 324 (4.57, M$^+$), 281 (1.22), 253 (3.11), 252 (5.29), 251 (16.0), 209 (8.96), 183 (15.6), 99.0 (9.51), 95.0 (7.19), 73.0 (100); Anal. calcd. for C$_{18}$H$_{32}$O$_3$Si: C 66.62, H 9.940; found: C 66.68, H 9.880.
Hydroxyethoxy-ketones (192a,b)

To a solution of trimethylsilyl enol ether (178) (0.13 g, 0.40 mmol) in dry methylene chloride (25 mL) under an argon atmosphere was added titanium tetrachloride (0.05 mL, 0.48 mmol), and the reaction was stirred at -78°C for 20 minutes. Saturated sodium bicarbonate solution (10 mL) was added at -78°C and after warming, the reaction mixture was extracted with ether and the combined organic layers were washed with saturated sodium bicarbonate solution, brine and water, and dried (MgSO₄). Removal of solvent gave a crude product which was purified by column chromatography (silica gel, pet. ether:ether, 4:1) to afford a mixture of epimers of hydroxyethoxy-ketones (192a,b) (78 mg, 78%) as a colorless oil. The ratio (1.2:1.0) of epimers (192a:192b) was determined from proton integration in the n.m.r. spectrum. 192a: R_f 0.22 (pet. ether:ether, 3:7), \( \nu_{max} \) (film): 3457, 1734, 2950 cm\(^{-1}\); \( \delta \) (CDCl₃, 270 MHz): 0.92 (s, 3H, CH₃), 0.97 (s, 3H, CH₃), 2.48 (d, 1H, H₇, J=6 Hz), 3.60-3.70 (m, 4H, ROCH₂CH₂OR), 3.70-3.80 (m, 1H, R₂CHOR); m/e (relative intensity): 252 (2.83, \( M^+ \)), 234 (1.16), 222 (3.18), 209 (2.27), 207 (3.44), 192 (3.38), 191 (6.82), 190 (9.91), 179 (1.99), 177 (1.36), 175
(6.70), 173 (6.07), 164 (3.60), 163 (18.3), 147 (59.0), 137 (10.7), 135 (29.8), 134 (26.6), 132 (23.2), 107 (22.4), 95.0 (27.1); **Exact mass** calcd. for $C_{15}H_{24}O_3$: 252.1725; found: 252.1725.

**192b:** $R_f$ 0.28 (pet. ether:ether, 3:7); $\nu_{\text{max}}$ (film): 3457, 2950, 1734 cm$^{-1}$; $\delta$ (CDCl$_3$, 270 MHz): 0.92 (s, 3H, CH$_3$), 2.30-2.40 (m, 2H, C(3)H, C(4)H). 3.50-3.75 (m, 4H, ROCH$_2$CH$_2$OR), 3.76-3.86 (m, 1H, R$_2$CHOR); m/e (relative intensity): 252 (35.1, M$^+$), 234 (3.92), 224 (1.18), 222 (6.04), 209 (4.46), 208 (5.97), 107 (31.6), 191 (22.4), 190 (70.9), 175 (40.2), 163 (47.3), 162 (41.7), 161 (19.9), 149 (13.8), 148 (27.4), 147 (100); **Exact mass** calcd. for $C_{15}H_{24}O_3$: 252.1725; found: 252.1721.

**p-Bromobenzoate (193a,b)**

p-Bromobenzoyl chloride (0.15 g, 0.70 mmol) was added to a solution of the major epimer of hydroxyethoxy-ketones (192a,b)
(20 mg, 0.08 mmol) in dry pyridine (5.0 mL) at 25°C under an argon atmosphere. The reaction mixture was stirred for 3 hours and hydrochloric acid (1.0 N, 10 mL) was added and then extracted with ether. The combined organic layers were washed with hydrochloric acid (1.0 N), potassium hydroxide (1.0 N), brine and water and dried (MgSO₄). Upon removal of solvent under vacuo, the crude product was triturated with ethanol and the mother liquor was concentrated down under reduced pressure and the residue was then purified by column chromatography (silica gel, pet. ether: ether, 5:1) to provide (+)-p-bromobenzoate (193a,b) (34 mg, 97%) as a colorless oil; Rf 0.97 (pet. ether:ether, 3:7); [α]D 25° +62.1° (c 0.35, CHCl₃); \( \nu_{\text{max}} \) (film): 2960, 1725 cm⁻¹; δ (CDCl₃, 400 MHz): 0.92 (s, 3H, CH₃), 0.96 (s, 3H, CH₃), 2.04 (d, 1H, C(4)H, J=4 Hz), 2.44 (d, 1H, C(3)H, J=6 Hz), 3.86 (dd, 1H, R₂CH₂OR, J=12 Hz, 5 Hz), 3.70-3.80, 2.98-4.10, 4.40-4.58 (m, m, m, 1H, 1H, 2H, ROC₂H₄OH), 7.58 (d, 2H, BrC₆H₂H₂R, J=8 Hz), 7.93 (d, 2H, BrC₆H₂H₂R, J=8 Hz); m/e (relative intensity): 434/436 (3.03/2.87, M⁺/M⁺+2), 251 (1.19), 247 (1.47), 245 (1.37), 234 (2.27), 231 (1.11), 230(12.3), 229 (97.7), 228 (12.9), 227 (100); Exact mass calcd. for C₂₂H₂₇O₄Br: 434.1102/436.1090; found: 434.1094/436.1082; Anal. calcd for C₂₂H₂₇O₄Br: C 60.70, H 6.250, Br 18.35; found: C 60.62, H 6.400, Br 18.16.
(+)-Dimethoxyketone (194)

(+)-Keto-aldehyde (183) (0.64 g, 3.1 mmol) was treated with a methanolic solution of cerium trichloride heptahydrate (0.4 M, 6.7 mL) and trimethyl orthoformate (2.3 mL, 21 mmol). Stirring was continued at 25°C for 2 hours before sodium bicarbonate solution (5.0%, 20 mL) was added and the reaction mixture was extracted with ether, and the combined organic layers were washed with brine and dried (MgSO4). The crude product was purified by column chromatography (silica gel, pet. ether:ether, 1:1) to provide (+)-dimethoxyketone (194) (0.63 g, 83%) as a colorless oil; Rf 0.72 (pet. ether:ether, 2:7); [α]D25 +32.1° (c 0.98, CHCl3); \( \nu_{\text{max}} \) (film): 2960, 1742, 1121 cm\(^{-1}\); \( \delta \) (CDCl3, 270 MHz): 0.90 (s, 3H, CH3), 0.95 (s, 3H, CH3), 3.30 (s, 6H, RCH(OCH3)2), 4.33 (t, 1H, RCH(OCH3)2, J=4 Hz); m/e (relative intensity): 254 (0.98, M\(^+\)), 224 (2.28), 223 (13.7), 222 (19.4), 207 (3.88), 191 (15.2), 190 (22.6), 175 (14.9), 162 (10.4), 149 (11.3), 148 (16.5), 147 (18.4), 75.0 (100); Exact mass calcd. for C\(_{15}\)H\(_{26}\)O\(_3\): 254.188; found: 254.188; Anal. calcd. for C\(_{15}\)H\(_{26}\)O\(_3\): C 70.83, H 10.30; found: C 71.12, H 10.26.
Lithium diisopropylamide was generated by adding n-butylithium (1.6 M; hexane) (2.4 mL, 3.6 mmol) with diisopropylamine (0.50 mL, 3.6 mmol) in dry tetrahydrofuran (10 mL) at 0°C under an argon atmosphere for 30 minutes. A solution of (+)-dimethoxyketone (194) (0.74 g, 2.9 mmol) in dry tetrahydrofuran (10 mL) was then introduced to this cooled reaction mixture at -78°C. After 2 hours, freshly distilled chlorotrimethylsilane (0.56 mL, 4.4 mmol) was added and stirring was continued for 1 hour while the temperature warmed slowly to 25°C. The solvent was removed and a pentane solution of the crude product was filtered through a column of celite and sand. Removal of solvent provided (+)-dimethyl acetal enolsilyl ether (105) (0.960 g, 100%) as a colorless oil; $[\alpha]_D^{25} +1.6^\circ$ (c 0.61, CHCl$_3$); $\nu_{\text{max}}$ (film): 1620, 2975 cm$^{-1}$; $\delta$ (CDCl$_3$, 270 MHz): 0.18 (s, 9H, RSi(CH$_3$)$_3$), 0.69 (s, 3H, CH$_3$), 0.84 (s, 3H CH$_3$), 3.28 (d, 6H, RHC(OCH$_3$)$_2$, J=2.0 Hz), 4.31 (t, 1H, RCH(OCH$_3$)$_2$, J=4 Hz), 4.51 (d, 1H, R$_3$CH:CR$_1$R$_2$, J=3.5 Hz); m/e (relative intensity): 326 (1.35, M$^+$), 312 (1.57), 311 (6.78), 296 (2.18), 293 (7.68), 294 (15.9), 251 (8.93), 209 (18.9), 208 (17.1), 182
(28.5), 75.0 (100); *Exact mass* calcd. for C\(_{18}H_{34}O_3Si\): 326.2277; found: 326.2271; Anal. calcd. for C\(_{18}H_{34}O_3Si\): C 66.21, H 10.50, found: C 66.32, H 10.63.

*(R)-and (S)-Methoxy-ketones (195a,b)*

![Chemical structures](image)

(R)-methoxy-ketone (195b) (83 mg, 21%) as a colorless oil, followed by (R)-methoxy-ketone (195a) (261 mg, 66%) as a white solid. Rerystallisation from pentane provided (195a) as colorless prisms: mp 40 °C; R\(_f\) 0.64 (pet. ether:ether, 2:7); [\(\alpha\)\(_D\)]\(_{25}\) +91.5° (c 0.34, CHCl\(_3\)); \(\nu\) max (CHCl\(_3\)): 2951, 1741, 1100 cm\(^{-1}\); \(\delta\) (CDCl\(_3\), 400 MHz): 0.91 (s, 3H, CH\(_3\)), 0.97 (s, 3H, CH\(_3\)), 2.45 (d, 1H, H, J=6 Hz),

To a solution of (+)-dimethyl acetal enolsilyl ether (105) (0.57 g, 1.8 mmol) in dry methylene chloride (40 mL) under an argon atmosphere was added titanium tetrachloride (0.23 mL, 2.1 mmol) at -78 °C and the reaction mixture was stirred for 45 minutes. Saturated sodium bicarbonate solution (10 mL) was added at -78 °C and the reaction mixture was worked up in the usual way. The crude product was purified by column chromatography (silica gel, pet. ether:ether, 1:1) to provide (S)-methoxy-ketone (195b) (83 mg, 21%) as a colorless oil, followed by (R)-methoxy-ketone (195a) (261 mg, 66%) as a white solid. Rerystallisation from pentane provided (195a) as colorless prisms: mp 40 °C; R\(_f\) 0.64 (pet. ether:ether, 2:7); [\(\alpha\)\(_D\)]\(_{25}\) +91.5° (c 0.34, CHCl\(_3\)); \(\nu\) max (CHCl\(_3\)): 2951, 1741, 1100 cm\(^{-1}\); \(\delta\) (CDCl\(_3\), 400 MHz): 0.91 (s, 3H, CH\(_3\)), 0.97 (s, 3H, CH\(_3\)), 2.45 (d, 1H, H, J=6 Hz),

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3.42 (s, 3H, ROCH₃), 3.65 (dd, 1H, R₂CHOHMe, J=6 Hz, 4 Hz); m/e (relative intensity): 222 (17.9, M⁺), 207 (3.55), 193 (4.92), 192 (26.4), 191 (3.36), 190 (15.4), 179 (5.00), 177 (10.9), 175 (18.4), 163 (32.4), 162 (20.5), 148 (20.0), 147 (59.5), 135 (18.8), 134 (35.9), 107 (67.7), 95.0 (88.0), 71.0 (100); **Exact mass** calcd. for C₁₄H₂₂O₂: 222.1619; found: 222.1619; **Anal.** calcd. for C₁₄H₂₂O₂: C 75.63, H 9.970; found: C 75.43, H 9.870.

Methoxy-ketone (195b): Rf 0.87 (pet. ether:ether, 2:7); [α]ᵢ²⁵D +72.7° (c 1.7, CHCl₃); V max (film): 2951, 1741, 1100 cm⁻¹; δ (CDCl₃, 400 MHz): 0.92 (s, 3H, CH₃), 0.94 (s, 3H, CH₃), 2.38 (d, 1H, C H, J=2 Hz), 3.35 (s, 3H, ROCH₃), 3.68 (ddd, 1H, R₂CHOHMe, J=11 Hz, 7 Hz, 2 Hz); m/e (relative intensity): 222 (21.1, M⁺), 211 (15.1), 190 (26.3), 175 (23.8), 162 (22.1), 149 (43.8), 147 (59.0), 135 (31.4), 121 (33.1), 109 (57.2), 107 (61.9), 105 (47.2), 95.0 (100); **Exact mass** calcd. for C₁₄H₂₂O₂: 222.1620; found: 222.1635; **Anal.** calcd. for C₁₄H₂₂O₂: C 75.63, H 9.970; found: C 75.80, H 9.990.
To a cold (0°C), stirred solution of lithium aluminum hydride (73 mg, 1.9 mmol) in dry tetrahydrofuran (20 mL) under an argon atmosphere was added a solution of a mixture of epimers of methoxy-ketones (195a,b) (0.43 g, 1.9 mmol) in dry tetrahydrofuran (5.0 mL). Stirring was continued for 2 hours and, after dilution with water (10 mL), the reaction mixture was worked up by extraction with ether and the combined organic layers were washed with hydrochloric acid (1.0 N) and brine, and dried (MgSO₄). The solvent was removed under vacuo and the crude product was purified by column chromatography (silica gel, pet. ether: ether, 10:1) to give a mixture of methoxy-alcohols (202a,b) (0.4 g, 91%) as a colorless oil; \( \nu_{\text{max}} \) (film): 3500, 2950, 1080 cm\(^{-1}\); \( \delta \) (CDCl\(_3\), 80 MHz): \( ^1\text{H}-\text{n.m.r. assignments of major diastereomer}: 0.83 (s, 3H, CH\(_3\)), 0.99 (s, 3H, CH\(_3\)), 3.41 (s, 3H, R\(_1\)R\(_2\)CHOCH\(_3\)), 3.50-3.70 (m, 1H, R\(_1\)R\(_2\)CHOMe), 3.94 (d, 1H, R\(_2\)CHOH, J=8 Hz); m/e (relative intensity): 223 (0.42), 222 (3.64), 207 (1.49), 206 (6.61), 192 (17.1), 177 (15.9), 174 (19.0), 161 (19.8), 159 (35.0), 149 (24.7), 147 (21.1), 133 (23.8), 131 (29.3), 121 (32.3), 119 (35.4), 105 (54.7), 109 (67.0), 95.0 (100); Exact
mass calcd. C\textsubscript{14}H\textsubscript{24}O\textsubscript{2}: 224.1776; found: 224.1775; **Anal**. calcd. for C\textsubscript{14}H\textsubscript{24}O\textsubscript{2}: C 74.95, H 10.78; found: C 74.89, H 10.72.

**(S)-Methoxy-acetate (203)**

Dry acetic anhydride (0.12 g, 1.2 mmol) was added to a solution of a mixture of epimeric methoxyalcohols (202a,b) (0.13 g, 0.59 mmol) and 4-dimethylaminopyridine (15 mg, 0.12 mmol) in dry pyridine (5.0 mL) at 25°C under an argon atmosphere. Stirring was continued for 12 hours and the reaction mixture was diluted with water (10 mL) and extracted with ether, and the combined organic layers were washed with hydrochloric acid solution (1.0 N) and brine, and dried (MgSO\textsubscript{4}). Removal of solvent provided a crude product which was purified by column chromatography (silica gel, pet. ether:ether, 5:1) to afford (S)-meth-
oxyacetate (203) (29 mg) and (R)-methoxyalcohol (202a) (89 mg), respectively, as colorless oils. Acetate (203): Rf 0.70 (pet. ether:ether, 3:2); $\nu_{\text{max}}$ (film): 2975, 1740 cm$^{-1}$; $\delta$ (CDCl$_3$, 80 MHz): 0.85 (s, 3H, CH$_3$), 0.88 (s, 3H, CH$_3$), 2.12 (s, 3H, ROCOCH$_3$), 3.10-3.25 (m, 1H, $\text{R}_1\text{R}_2\text{CHOOMe}$), 3.30 (s, 3H, ROCH$_3$), 4.95 (d, 1H, $\text{R}_2\text{CHOAc}$, J=9 Hz); m/e (relative intensity): 251 (0.39), 224 (1.03), 219 (1.87), 207 (10.2), 206 (36.7), 191 (12.8), 175 (17.2), 174 (53.0), 163 (15.7), 161 (10.2), 160 (16.5), 159 (100); Exact mass calcd. for C$_{16}$H$_{26}$O$_3$: 266.1882; found: 266.1873; Anal. calcd. for C$_{16}$H$_{26}$O$_3$: C 72.14, H 9.840; found: C 72.20, H 9.840.

Methoxy-endo-alcohols (204a,b)

Calculated (0.84 g, 21 mmol) was treated with dry liquid ammonia (80 mL) at -78°C for 5 minutes under an argon atmosphere and a solution of methoxyketone (195a,b) (0.72 g, 3.2 mmol) in dry ether (6.0 mL) was then added. The reaction mixture was stirred at reflux for 30 minutes and dry 1-propanol (3.0 mL) was added. Care was taken at all times to exclude water from
the system. When the blue color was discharged the reaction mixture was diluted with water and extracted with ether and the organic layers were washed with hydrochloric acid (1.0 N) and brine, and dried (MgSO₄). Removal of solvent gave a crude product which was purified by column chromatography (silica gel, pet. ether:ether, 5:1) to give a mixture of epimeric methoxy-endo-alcohols (204a,b) (0.71 g, 98%) as a colorless oil; \( R_f \) 0.30 (pet. ether:ether, 1:1); \( \nu_{\text{max}} \) (film): 3492, 2967 cm⁻¹; \( \delta \) (CDCl₃, 400 MHz): \(^1\text{H}-\text{n.m.r. assignments of major diastereomer:} 0.80 \text{ (s, 3H, CH}_3\text{)}, 0.97 \text{ (s, 3H, CH}_3\text{)}, 3.38 \text{ (s, 3H, ROCH}_3\text{)}, 3.50-3.60 \text{ (m, 1H, R}_2\text{CHOCH}\text{)}, 3.92 \text{ (d, 1H, R}_2\text{CHOH, J=8 Hz); m/e (relative intensity): 224 (0.88, M}^+\text{), 206 (2.67), 193 (2.62), 192 (20.3), 191 (2.08), 177 (23.8), 174 (15.0), 161 (25.5), 159 (23.9), 108 (32.7), 107 (76.4), 95.0 (100); Exact mass calcd. for C\(_{14}\)H\(_{24}\)O\(_2\): 224.1776; found: 224.1776; Anal. calcd. for C\(_{14}\)H\(_{24}\)O\(_2\): C 74.95, H 10.78; found: C 74.73, H 10.68.

**Methoxy-endo-acetates (205a,b)**

![Diagram of reaction](image)

Dry acetic anhydride (7.3 mL, 77 mmol) was added to a
solution of epimeric methoxy-endo-alcohols (204a,b) (5.7 g, 26 mmol) and 4-dimethylaminopyridine (9.4 g, 77 mmol) in dry pyridine (0.15 L) at 25°C under an argon atmosphere. Stirring was continued for 5 hours before water (50 mL) was added and the reaction mixture worked up in the usual way. Removal of solvent gave a crude product which was purified by column chromatography (silica gel, pet. ether:ether, 5:1) to provide a mixture of epimeric methoxy-endo-acetates (205a,b) (6.08 g, 89%) as a colorless oil; Rf 0.58 (pet. ether:ether, 1:1); \( \nu_{\text{max}} \) (film): 2947, 1741 cm\(^{-1}\); \( \delta \) (CDCl\(_3\), 400 MHz): \(^1\)H-n.m.r. assignments of major diastereomer: 0.82 (s, 3H, CH\(_3\)), 0.85 (s, 3H, CH\(_3\)), 2.06 (s, 3H, ROCOCH\(_3\)), 3.25 (s, 3H, ROCH\(_3\)), 3.25-3.34 (m, 1H, RCHOMe), 5.30 (dd, 1H, RCHOAc, J=5 Hz, 2 Hz); m/e (relative intensity): 251 (1.28), 236 (7.53), 224 (17.3), 207 (34.0), 206 (44.0), 174 (82.1), 159 (66.3), 119 (55.7), 107 (79.0), 105 (64.9), 95.0 (91.5), 91.0 (77.3), 83.0 (71.5), 79.0 (82.8), 71.0 (100); \textbf{Exact mass} calcd. for \( \text{C}_{16}\text{H}_{26}\text{O}_3 \): 266.1881; found: 266.1873; \textbf{Anal.} calcd. for \( \text{C}_{16}\text{H}_{26}\text{O}_3 \): C 72.14, H 9.840; found: C 72.11, H 9.800.
**Hydroxy-acetates (206a,b)**

![Diagram](image)

To a well stirred solution of a mixture of epimeric methoxy-endo-acetates (205a,b) (2.0 g, 7.5 mmol) in dry methylene chloride (10 mL) at -30°C under an argon atmosphere was added 15-crown-5 (0.30 M, 8.9 mL) saturated with dry sodium iodide in dry methylene chloride followed by boron tribromide (1.3 M, 1.5 mL) in dry methylene chloride. Stirring was continued for 4 hours and the reaction worked up by dilution with saturated sodium bicarbonate solution (20 mL) followed by extraction with methylene chloride. The combined organic layers were washed with saturated sodium bicarbonate solution, hydrochloric acid (1.0 N), saturated sodium bisulphite solution and water, and dried (MgSO₄). Removal of solvent gave a crude product which was purified by column chromatography (silica gel, pet. ether:ether, 5:1) to yield a mixture of epimeric hydroxyacetates (206a,b) (1.7 g, 89%) as a colorless oil; Rₜ 0.29 (pet. ether:ether, 1:1); νₘₐₓ (film): 3467, 2967, 1717 cm⁻¹; δ (CDCl₃, 400 MHz):

^1^H-n.m.r. assignments of major diastereomer: 0.88 (s, 3H, CH₃), 0.89 (s, 3H, CH₃), 2.01 (s, 3H, ROCOCH₃), 3.33 (d, 1H, R₂CHOH, J=12 Hz, exchangeable with D₂O), 3.53-3.80 (m, 1H, R₂CHOH), 4.74
(dd, 1H, R₂CHOAc, J=4.5 Hz, 1.5 Hz); m/e (relative intensity): 252 (0.59, M⁺), 250 (1.38), 210 (1.87), 209 (1.23), 208 (7.09), 207 (3.85), 206 (1.95), 193 (10.5), 192 (49.2), 190 (12.6), 174 (53.7), 159 (63.1), 121 (100); Exact mass calcd. for C₁₅H₂₄O₃: 252.1725; found: 252.1731; Anal. calcd. for C₁₅H₂₄O₃: C 71.39, H 9.590; found: C 71.62, H 9.600.

(+)-Keto-acetate (207)

A solution of epimeric hydroxy-acetates (206a,b) (90 mg, 0.35 mmol) and pyridinium dichromate (0.40 g, 1.1 mmol) in dry methylene chloride (10 mL) was stirred at 60°C under an argon atmosphere for 10 hours. The reaction mixture was then diluted with ether and filtered through a pad of silica gel. Removal of solvent gave a crude product which was purified by column chromatography (silica gel, pet. ether:ether, 10:0) to give (+)-keto-acetate (207) (85 mg, 95%) as a white solid, which was recrystallised from pentane as colorless prisms; mp 77-79°C; Rf 0.48 (pet. ether:ether, 1:1); [α]D₂⁵ +101° (c 0.65, CHCl₃); νmax (CHCl₃): 2969, 1717, 1699 cm⁻¹; δ (CDCl₃, 400 MHz): 0.94 (s, 3H, CH₃), 0.98 (s, 3H, CH₃), 2.07 (s, 3H, ROCOCH₃), 5.05 (dd,
$^{1}H, R_{2}CHOAc, J=4.5 \text{ Hz, 1.5 Hz}; m/e$ (relative intensity): 250 ($23.9, M^+$), 208 (32.6), 207 (54.5), 191 (18.7), 190 (100);

Exact mass calcd. for $C_{15}H_{22}O_{3}: 250.1569$; found: 250.1572; Anal. calcd. for $C_{15}H_{22}O_{3}: C$ 71.97, H 8.860; found: C 72.06, H 8.850.

($^{+}$)-Alkene-acetate (208)

Methyltriphenylphosphonium bromide (1.5 g, 4.2 mmol) was suspended in dry tetrahydrofuran (20 mL) under an argon atmosphere and cooled to $-78^\circ C$. n-Butyllithium (1.3 M; hexane) (3.2 mL, 4.2 mmol) was added and after 10 minutes the cold bath was removed and the reaction mixture was stirred for 1 hour. During this time all the solid disappeared and the solution became dark orange. A solution of ($^+$)-keto-acetate (207) (0.70 g, 2.8 mmol) in dry tetrahydrofuran (10 mL) was then introduced. Stirring was continued for 1 hour and the reaction mixture was then diluted with water (10 mL) and extracted with petroleum ether. Removal of solvent gave a crude product which was purified by column chromatography (silica gel, pet. ether:ether, 15:1) to provide ($^{+}$)-alkene-acetate (208) (0.59 g, 85%) as a colorless
oil; \( R_f \) 0.94 (pet. ether:ether, 1:1); \([\alpha]_D^{25}\) +18.3° (c 0.16, CHCl$_3$); \( \nu_{\text{max}} \) (film): 2960, 1738, 1640, 885 cm$^{-1}$; \( \delta \) (CDCl$_3$, 270 MHz): 0.82 (s, 3H, CH$_3$), 0.88 (s, 3H, CH$_3$), 2.05 (s, 3H, ROCOCH$_3$), 4.55 (s, 1H, \( \text{R}_2\text{R}_1\text{C} : \text{CHH} \)), 4.57 (s, 1H, \( \text{R}_1\text{R}_2\text{C} : \text{CHH} \)), 5.12 (dd, 1H, \( \text{R}_2\text{CHOAc} \), \( J=4.5 \) Hz, 2 Hz); m/e (relative intensity): 247 (0.10), 239 (2.37), 207 (2.41), 206 (7.15), 205 (4.22), 191 (12.7), 188 (67.7), 173 (48.6), 160 (44.5), 145 (43.1), 131 (50.6), 121 (40.2), 108 (42.2), 107 (64.4), 95.0 (67.8), 93.0 (82.4), 91.0 (100); Anal. calcd. for C$_{16}$H$_{24}$O$_2$: C 77.38, H 9.740, found: C 77.56, H 9.690.

\[ (+)\text{-Hydroxy-olefin (209)} \]

\[ \text{(208)} \quad \text{HAC} \quad \text{OH} \quad \text{(209)} \]

To a cold (0° C) stirred solution of lithium aluminum hydride (10 mg, 0.28 mmol) in dry tetrahydrofuran (1.0 mL) under an argon atmosphere was added a solution of (+)-alkene-acetate (208) (68 mg, 0.28 mmol) in dry tetrahydrofuran (3.0 mL). Stirring was continued for 2 hours and the reaction mixture worked up in the usual way. Removal of solvent gave a crude product which was purified by column chromatography (silica gel, pet. ether:ether,
10:1) to give (+)-hydroxy-olefin (209) (56.0 mg, 99.6%) as a colorless oil; \( R_f \) 0.67 (pet. ether:ether, 1:1); \([\alpha]_{D}^{25} +64^\circ\) (c 0.5, CHCl\(_3\)); \( \nu_{\text{max}} \) (film): 3375, 2950, 1640, 885 cm\(^{-1}\); \( \delta \) (CDCl\(_3\), 270 MHz): 0.89 (s, 3H, CH\(_3\)), 0.90 (s, 3H CH\(_3\)), 3.91 (dd, 1H, RCH\(_2\)OH, J=4.5 Hz, 2 Hz), 4.62 (s, 1H, R\(_2\)R\(_1\)C:CH\(_2\)), 4.67 (s, 1H, R\(_2\)R\(_1\)C:CH\(_2\)); m/e (relative intensity): 206 (9.49, M\(^+\)), 204 (2.33), 191 (38.8), 188 (31.1), 173 (30.3), 163 (22.2), 161 (23.2), 146 (39.6), 136 (69.6), 132 (29.0), 123 (25.0), 121 (85.7), 109 (40.5), 108 (66.9), 107 (100); **Exact mass** calcd. for C\(_{14}\)H\(_{22}\)O: 206.1672; found: 206.1671; **Anal.** calcd. for C\(_{14}\)H\(_{22}\)O: C 81.49, H 10.75; found: C 81.27, H 10.60.

**(+)-Tetracyclic alcohol (210)**

![Diagram](image)

To a well stirred heated (60°C) solution of (+)-hydroxy-olefin (209) (0.42 g, 2.0 mmol) in dry toluene (5.0 mL) was added successively a solution of diethylzinc (1.4 mL, 2.8 mmol, 25% w/v) in toluene and methylene iodide (0.23 mL, 2.8 mmol). A stream of dry air was passed through the reaction mixture for 3.5 hours. After acidification with hydrochloric acid (1.0 N), the
reaction mixture was extracted with ether, and the organic layers were washed with brine and dried (MgSO₄). Removal of solvent gave a crude product which was purified by column chromatography (silica gel, pet. ether:ether, 10:1) to afford (+)-tetra-cyclic alcohol (210) (0.45 g, 99%) as a white solid, which was recrystallised from pentane as colorless prisms; mp 109-111°C; [α]$_D^{25}$ +31.6° (c 0.31, CHCl₃); $R_f$ 0.21 (pet. ether:ether, 8:2); $\nu_{max}$ (CHCl₃): 3643, 3010, 2965 cm$^{-1}$; $\delta$ (CDCl₃, 400 MHz): 0.20-0.28 (m, 2H, cyclopropyl(H)), 0.40-0.53 (m, 2H, cyclopropyl(H)), 0.88 (s, 6H, Me₂), 4.03 (dd, 1H, R₁R₂CHOH, J=4 Hz, 2 Hz); m/e (relative intensity): 220 (2.89, M$^+$), 205 (8.42), 203 (1.53), 202 (5.91), 189 (15.1), 187 (18.8), 177 (11.0), 161 (10.2), 159 (13.4), 149 (19.2), 147 (16.0), 146 (12.2), 145 (18.7), 135 (29.8), 121 (45.1), 119 (33.7), 107 (81.3), 105 (54.8), 95.0 (81.6), 93.0 (91.2), 91.0 (86.6), 79.0 (100); Exact mass calcd. for C$_{15}$H$_{24}$O: 220.1827; found: 220.1821; Anal. calcd. for C$_{15}$H$_{24}$O: C 81.76, H 10.98; found: C 81.89, H 10.88.
To a solution of (+)-tetracyclic alcohol (210) (0.38 g, 1.7 mmol) in glacial acetic acid (3.0 mL) was added platinum oxide (16 mg, 0.07 mmol). The resultant suspension was stirred under 2.7 atm of hydrogen at room temperature for 12 hours. Saturated sodium bicarbonate solution was added until the mixture was neutral and the aqueous slurry was extracted with ether. The combined organic layers were washed with hydrochloric acid (1.0 N) and brine, and dried (MgSO₄). Removal of solvent yielded a crude product which was purified by column chromatography (silica gel, pet. ether:ether, 5:1) to provide (+)-longiborneol (59) (0.38 g, 100%) which crystallised from pentane as colorless prisms; mp 105-107°C (lit. [77] mp for (-)-longiborneol, 106-107°C); R_f 0.41 (pet. ether:ether, 4:1); [α]_D^{25} +15.8° (c 0.54, CHCl₃) (lit. [77] for (-)-longiborneol, [α]_D^{25} -16.3° (c 0.66, CHCl₃)); ν_max (CHCl₃): 3643, 2943 cm⁻¹; δ (CDCl₃, 400 MHz): 0.84 (s, 3H, CH₃), 0.87 (s, 3H, CH₃), 0.94 (s, 6H, CH₃, CH₃), 3.77 (dd, 1H, R₂CH₂OH, J=5 Hz, 2 Hz); m/e (relative intensity): 222 (7.36, M⁺), 208 (4.52), 207 (28.4), 204 (50.5), 189 (59.9), 161 (25.9), 133 (26.5), 121 (26.3), 119 (81.1),
109 (58.5), 95.0 (100); **Exact mass** calcd. for $\text{C}_{15}\text{H}_{26}\text{O}$: 222.1983; found: 222.1979; **Anal.** calcd. $\text{C}_{15}\text{H}_{26}\text{O}$: C 81.02, H 11.79; found: C 81.16, H 11.69.

**Longiborneol MTPA Ester (211)**

To a stirred solution of (+)-longiborneol (59) (15.0 mg, 0.067 mmol) in dry carbon tetrachloride (0.5 mL) and pyridine (2.0 mL) was added R-(+)-α-methoxy-α-trifluoromethylphenylacetly chloride ((+)-MTPA-chloride; 26 mg, 0.10 mmol) at 25°C under an argon atmosphere. After 20 hours, the solution was diluted with water (10 mL) and extracted with ether and the combined organic layers were washed with hydrochloric acid (1.0 N) and brine, and dried (MgSO$_4$). Removal of solvent gave a crude product which was purified by column chromatography (silica gel, pet. ether: ether, 10:1) to yield pure longiborneol MTPA ester (211) (28 mg, 95%) as a white solid. Crystallisation from pentane afforded (211) as
corless prisms; mp 89-91 C; Rf 0.88 (pet. ether: ether, 4:1);

$\nu_{\text{max}}$ (CHCl$_3$): 1750 cm$^{-1}$; $\delta$ (CDCl$_3$, 270 MHz): 0.80 (s, 3H, CH$_3$), 0.81 (s, 3H, CH$_3$), 0.83 (s, 3H, CH$_3$), 0.94 (s, 3H, CH$_3$), 3.57 (q, 3H, ROCH$_3$, J=1.2 Hz), 5.41 (dd, 1H, R$_1$R$_2$CHOH$_3$, J=4 Hz, 2 Hz), 7.36-7.44, 7.58-7.66 (m, m, 3H, 2H, RC$_6$H$_5$); $^{13}$C-n.m.r. (CDCl$_3$, 100.6 MHz): 22.237, 26.979, 30.035, 33.297, 35.201, 40.685, 50.626, 52.000, 60.597, (quaternary and methylene carbons); 13.210, 22.279, 28.798, 29.402, 44.019, 55.463, 60.597, 23.990 (methyl and methine carbons), 83.772 (RCF$_3$), 125.383, 127.456, 128.215, 129.450 (aromatic carbons), 166.000 (carbonyl carbon).

$^{19}$F-n.m.r. (CDCl$_3$, 254 MHz): singlet at 5.08 in the resolution enhanced proton decoupled spectrum; m/e (relative intensity): 220 (1.20), 205 (49.1), 189 (58.4), 95.0 (100); **Exact mass** calcd. for C$_{25}$H$_{33}$O$_3$F$_3$: 438.2381; found: 438.2377; **Anal calcd.** for C$_{25}$H$_{33}$O$_3$F$_3$, C 68.47, H 7.590; found: C 68.44, H 7.690.
Pyridinium chlorochromate (0.51 g, 2.4 mmol) was suspended in dry methylene chloride (2.0 mL), and a solution (+)-longiborneol (59) (0.35 g, 1.6 mmol) in dry methylene chloride (4.0 mL) was added rapidly at room temperature. After 3 hours under argon the black reaction mixture was diluted with ether and filtered through a pad of silica gel. Removal of the solvent provided a crude product which was purified by column chromatography (silica gel, pet. ether) to afford (+)-longicamphor (83) (0.29 g, 85%) as a colorless oil; $R_f$ 0.87 (pet. ether:ether, 4:1); $[\alpha]_{D}^{25}+18.9^\circ$ (c 0.74, C$_2$H$_5$OH); $\nu_{max}$ (film): 2971, 1739 cm$^{-1}$; $\delta$ (CDCl$_3$, 400 MHz), 0.89 (s, 3H, CH$_3$), 0.92 (s, 3H, CH$_3$), 1.00 (s, 3H, CH$_3$), 1.07 (s, 3H, CH$_3$); m/e (relative intensity): 220 (100, M$^+$), 206 (7.00), 205 (28.4), 178 (12.6), 177 (86.7), 163 (19.9), 150 (20.1), 149 (25.7), 137 (34.7), 136 (43.5), 135 (34.8), 124 (52.9), 95.0 (95.4); Exact mass calcd. for C$_{15}$H$_{24}$O: 272.1827; found: 220.1826; Anal. calcd. for C$_{15}$H$_{24}$O: C 81.76, H 10.98; found: C 81.67, H 11.00.
Lithium aluminum hydride (22 mg, 0.59 mmol) was suspended in dry tetrahydrofuran (2.0 mL) at 0°C, and a solution of (+)-longicamphor (83) (0.13 g, 0.59 mmol) in dry tetrahydrofuran (1.5 mL) was added slowly. The reaction mixture was stirred at 0°C under an argon atmosphere for 3 hours, and then diluted with water (10 mL) and extracted with ether. The combined organic layers were washed with hydrochloric acid (1.0 N), brine and water, and dried (MgSO₄). After removal of solvent the crude product was purified by column chromatography (silica gel, pet. ether) to yield (+)-longiisoborneol (89) (0.12 g, 92%) as a colorless oil; R_f 0.94 (pet. ether:ether, 9:1); [α]D²⁵ +45.8° (c 0.69, CHCl₃); ν max (film): 3436, 2965 cm⁻¹; δ (CDCl₃, 400 MHz): 0.80 (s, 3H, CH₃), 0.94 (s, 3H, CH₃), 0.98 (s, 3H, CH₃), 1.12 (s, 3H, CH₃), 3.84 (dd, 1H, R₂CHOH, J=8 Hz, 4 Hz); m/e (relative intensity): 222 (4.50, M), 221 (1.80), 220 (5.30), 219 (2.20), 208 (3.80), 207 (17.1), 205 (11.3), 204 (48.1), 189 (34.4), 161 (24.7), 137 (31.1), 133 (35.9), 119 (100); Exact mass calcd. for C₁₅H₂₆O: 221.1984; found: 222.1987; Anal. calcd. for C₂₅H₂₆O: C 81.02, H 11.79; found: C 81.28, H 11.80.
(+)-Longifolene (61)

(+)-Longiisoborneol (89) (0.12 g, 0.54 mmol) was treated with methanesulphonyl chloride (0.08 mL, 1.1 mmol) and 4-di-methylaminopyridine (30 mg) in dry pyridine (1.0 mL) at 105°C under an argon atmosphere for 16 hours. After dilution with water (10 mL) and extraction with ether, the combined organic layers were washed with hydrochloric acid (1.0 N), saturated sodium bicarbonate solution and water, and dried (MgSO₄). Removal of solvent provided a crude product which was purified by column chromatography (silica gel, pet. ether) to give (+)-longifolene (61) (73 mg, 66%) as a colorless oil; \( [\alpha]_D^{25} +51.8^\circ \) (c 1.07, CHCl₃) (lit. [81] \( [\alpha]_D^{25} +51.7^\circ \) (c 0.35); \( \nu_{\text{max}} \) (film): 2964, 1661, 871 cm⁻¹; \( \delta \) (CDCl₃, 400 MHz): 0.90 (s, 3H, CH₃), 0.95 (s, 3H, CH₃), 1.00 (s, 3H, CH₃), 4.50 (s, 1H, R₁R₂C:CHH), 4.75 (s, 1H, R₁R₂C:CHH); m/e (relative intensity): 204 (47.6, M⁺), 203 (15.4), 190 (11.8), 189 (63.2), 175 (27.2), 163 (19.6), 162 (18.4), 161 (76.0), 133 (56.7), 121 (59.0), 119 (66.2), 109 (65.2), 108 (55.0), 107 (86.5), 95.0 (96.6), 91.0 (100); **Exact mass** calcd. for C₁₅H₁₄: 204.1878; found: 204.1877; **Anal. calcd.** for C₁₅H₂₄: C 88.16, H 11.84;
found: C 87.94, H 11.72.

p-Bromobenzoate (186)

p-Bromobenzoyl chloride (0.63 g, 2.9 mmol) was added to a solution of nitrile (185a) (0.10 g, 0.36 mmol) in dry pyridine (10 mL) at 25°C under an argon atmosphere. The mixture was stirred for 2.5 hours and hydrochloric acid (1.0 N, 20 mL) was added and then extracted with ether. The combined organic layers were washed with hydrochloric acid (1.0 N), potassium hydroxide solution and brine, and dried (MgSO₄). Upon removal of solvent under vacuo, the crude product was triturated with ethanol and the mother liquor was concentrated down under vacuo and the residue was purified by column chromatography to provide the p-bromo-benzoate (186) (0.16 g, 99%) as a white solid. Recrystallisation from a mixture of pet. ether:ether (4:1) afforded colorless prisms; mp 100-102°C; Rf 0.89 (pet. ether:ether, 3:2); \( \nu_{max} \) (CCl₄): 2972, 2240, 1592 cm⁻¹; \( \delta \) (CDCl₃, 270 MHz): 103 (s, 3H, CH₃), 1.09 (s, 3H, CH₃), 3.53 (dd, 1H, \( R_1 R_2 CHCN \), J=12 Hz, 4 Hz), 3.80 (m, 4H ROOR), 4.37 (t, 2H, RCH₂OCOR₁, J=8 Hz), 7.58-8.00
(m, 4H, RC₆H₄Br); m/e (relative intensity): 461 (0.200, M⁺), 421 (0.210), 181 (56.2), 95.0 (100); M. mass calcd. for C₂₃H₂₈NO₄Br: 461.1177; found: 461.1177; Anal. calcd. for C₂₃H₂₈NO₄Br: C 59.75, H 6.100, N 3.030, Br 17.28; found: C 59.59, H 6.150, N 2.930, Br 17.35.

**Aldehydes (189)**

\[ \text{CN} \quad \text{HO} \quad \text{CN} \]
\((185a,b) \quad \rightarrow \quad (189)\)

A solution of mixture of epimers of nitriles (185a,b) (3.6 g, 13 mmol) and pyridinium chlorochromate (6.9 g, 32 mmol) in dry methylene chloride (20 mL) was stirred at room temperature under an argon atmosphere for 4 hours. The reaction mixture was then diluted with ether and filtered through a pad of silica gel. After washing the silica gel with more ether, the solvent was removed under vacuo and the crude product was purified by column chromatography (silica gel, pet. ether:ether, 2:1). This afforded a mixture of epimers of aldehydes (189) (3.0 g, 84%) as a colorless oil; \( R_f \) 0.28 (pet. ether:ether, 1:1); \( \nu_{\text{max}} \) (film): 2975, 2750, 2250, 1730 cm⁻¹; \( \delta \) (CDCl₃, 80 MHz): \(^1H\)-n.m.r. assignments of major
diastereomer: 1.05 (s, 3H, CH$_3$), 1.10 (s, 3H CH$_3$), 2.78 (t, 2H, RCH$_2$CHO, J=7 Hz), 3.49 (dd, 1H, R$_1$R$_2$CHCN, J=12 Hz, 6 Hz), 3.70-4.00 (m, 4H, RO(CH$_2$)$_2$OR), 9.87 (s, 1H, CHO); m/e (relative intensity): 277 (0.030, M$^+$), 181 (20.0), 113 (19.1), 96.0 (12.0), 95.0 (100); **Exact mass** calcd. for C$_{16}$H$_{23}$NO$_3$: 277.1677; found: 277.1672.

**Acetal-nitriles (190)**

A solution of aldehydes (189) (2.2 g, 7.8 mmol), ethylene glycol (0.86 mL, 16 mmol) and p-toluenesulfonic acid (catalytic amount) in benzene (50 mL) was refluxed in a Dean-Stark apparatus for 3 hours. The reaction mixture was diluted with water (20 mL) and then extracted with ether and the combined organic layers were washed with sodium hydroxide solution (5%) and brine, and dried (MgSO$_4$). Upon removal of solvent under vacuo, the crude product was purified by column chromatography (silica gel, pet. ether:ether, 10:1) to give a mixture of epimers of acetalnitriles (190) (2.3 g, 92%) as a colorless oil; $R_f$ 0.30 (pet. ether:ether, 1:1); $\nu_{\text{max}}$ (film): 2980, 2255 cm$^{-1}$; $\delta$ (CDCl$_3$, 146
400 MHz): \(^1\)H-n.m.r. assignments of major diastereomer: 1.04 (s, 3H, CH\(_3\)), 1.08 (s, 3H, CH\(_3\)), 3.48 (dd, 1H, \(R_1R_2CHCN\), J=12 Hz, 4 Hz), 3.80-4.00 (m, 4H, ROC\(_2\)H\(_4\)OR), 4.92 (t, 1H, \((R_1O)_2CHR_2\), J=4 Hz); m/e (relative intensity): 321 (0.260, M\(^+\)), 181 (38.6), 113 (12.3), 95.0 (100); Exact mass calcd. for C\(_{18}\)H\(_{27}\)N\(_4\): 321.1939; found: 321.1932; Anal. calcd. for C\(_{18}\)H\(_{27}\)N\(_4\): C 67.26, H 8.470, N 4.360; found: C 67.49, H 8.430, N 4.470.

**Acetal-ketal (191)**

To a 100 mL round-bottom flask containing dry hexamethylyphosphoramide (15 mL) was added metallic potassium (0.61 g, 16 mmol) under an argon atmosphere at 0°C. To the resultant navy blue solution was introduced a solution of a mixture of epimers of acetal-nitriles (190) (2.5 g, 7.8 mmol) in dry ether (15 mL) followed by tert-butanol (1.5 mL, 16 mmol). Stirring was continued for 10 hours, worked up by adding brine (50 mL), and then the reaction mixture was extracted with ether. The combined organic layers were washed with brine and dried (MgSO\(_4\)). Upon removal of solvent under vacuo, the crude product
was purified by column chromatography (silica gel, pet. ether: ether, 5:1) to provide acetal-ketal (191) (1.8 g, 80%) as a colorless oil; Rf 0.52 (pet. ether:ether, 1:1); $\nu_{\text{max}}$ (film): 2870 cm$^{-1}$; $\delta$ (CDCl$_3$, 400 MHz): 0.80 (s, 3H, CH$_3$), 0.86 (s, 3H, CH$_3$), 4.87 (t, 1H, $(R)_{2}$CHR$_2$, J=4 Hz); m/e (relative intensity): 296 (5.10, M$^+$), 224 (6.14), 185 (25.3), 126 (14.3), 125 (100); Exact mass calcd. for C$_{17}$H$_{28}$O$_4$: C 68.89, H 9.520; found: C 69.05, H 9.510.

(+)-Keto-aldehyde (183)

Acetal-ketal (191) (1.4 g, 4.7 mmol) was dissolved in acetone (40 mL), hydrochloric acid (1.0 N, 20 mL) was added slowly and the reaction mixture was stirred at 25 C for 2 hours. The reaction mixture was added to water (20 mL) and worked up in the usual way to provide a crude product which was purified by column chromatography (silica gel, pet. ether:ether, 10:1) to afford (+)-keto-aldehyde (183) (0.95 g, 56%). (Spectral data cf. page 112)
Dry potassium acetate (31.9 g, 325 mmol) was added to a well-stirred solution of (+)-8-bromocamphor (42) (25.0 g, 108 mmol) in dry dimethyl sulphoxide (100 mL) at 110°C under an argon atmosphere for 5 days. After cooling, water (100 mL) was added and the reaction mixture was extracted with ether, and the combined organic layer was washed with saturated sodium bicarbonate solution, brine and dried (MgSO₄). After removal of solvent, the crude product was column chromatographed (silica gel, pet. ether:ether, 10:1) to give (+)-8-acetoxycamphor (139) (21.1 g, 93.0%) as a colorless oil; Rf 0.59 (pet. ether:ether, 1:1); [α]D₂⁵ +10.0° (c 2.49, CHCl₃); νmax (film): 2996, 1746, 1234 cm⁻¹; δ (CDCl₃, 400 MHz): 0.92 (s, 3H, CH₃), 1.02 (s, 3H, CH₃), 2.03 (s, 3H, ROCOCH₃), 3.81, 3.85 (AB quartet, 2H, RCH₂OAc, JAB=16 Hz); m/e (relative intensity) : 210 (8.82, H⁺), 192 (3.05), 182 (5.27), 168 (8.39), 167 (20.1), 153 (3.91), 152 (3.03), 151 (3.53), 150 (19.5), 149 (4.02), 135 (5.74), 125 (3.39), 122 (17.4), 109 (26.3), 108 (100); Exact mass calcd. for C₁₂H₁₈O₃: 210.1256; found: 210.1249; Anal. for C₁₂H₁₈O₃: C 68.54, H 8.630; found: C 68.44, H 8.560.
Diols (140)

A solution of (+)-8-acetoxy camphor (139) (11.6 g, 55.4 mmol) in dry tetrahydrofuran (80 mL) was introduced slowly to a suspension of lithium aluminum hydride (3.78 g, 100 mmol) in dry tetrahydrofuran (100 mL) at 0°C under an argon atmosphere. After 4 hours, water (20 mL) was carefully added and the reaction mixture was extracted with ether, and the combined organic layers were washed with hydrochloric acid (1.0 N), saturated sodium bicarbonate solution and brine, and dried (MgSO₄). After removal of solvent, the crude product was purified by column chromatography (silica gel, pet. ether:ether, 2:1) to yield diols (140) (7.0 g, 75%) as a white solid, which recrystallised from ethyl acetate as colorless prisms. The ratio of exo- to endo- diols was determined from proton integrations in the n.m.r. to be 4:1, respectively; mp 275°C; Rf 0.048, 0.072 (pet. ether:ether, 1:1); νmax (CHCl₃): 3326, 2936 cm⁻¹; δ (CDCl₃, 400 MHz): ¹H-n.m.r. assignments of major diastereomer: 0.92 (s, 3H, CH₃), 0.97 (s, 3H, CH₃), 3.64, 3.94 (AB quartet, 2H, RCH₂OH, JAB=12 Hz), 3.68 (d, 1H, R₁R₂CHOH, J=4 Hz); m/e (relative intensity): 170 (0.04, M⁺), 168 (0.19), 152 (2.55),
140 (7.68), 139 (13.6), 138 (2.20), 137 (10.2), 121 (17.8), 108 (90.7), 105 (10.0), 95.0 (100); **Exact mass** calcd. for $\text{C}_{10}\text{H}_{18}\text{O}_2$: 170.1307; found: not observed; **Anal. calcd.** for $\text{C}_{10}\text{H}_{18}\text{O}_2$: $\text{C}$ 70.55, $\text{H}$ 10.66; found: $\text{C}$ 70.58, $\text{H}$ 10.72.

**(-)**-Lactone (141)

![Diagram](image)

A mixture of diols (140) (0.49 g, 2.9 mmol) and silver carbonate on celite (16 g, 29 mmol) in dry benzene (40 mL) was refluxed in a Dean-Stark apparatus for 1.5 days. The mixture was filtered and, after removal of benzene, the crude product was purified by column chromatography (silica gel, pet. ether:ether, 4:1) to provide (-)-lactone (141) (0.37 g, 77%) as a white solid which recrystallised from pentane as colorless prisms; mp 199-200°C; $[\alpha]_D^{30}$ -60.7° (c 2.22, C$_2$H$_5$OH); $R_f$ 0.47 (pet. ether:ether, 1:1); $\nu_{\text{max}}$ (CHCl$_3$): 2960, 1760 cm$^{-1}$; $\delta$ (CDCl$_3$, 400 MHz): 1.05 (s, 3H, CH$_3$), 1.10 (s, 3H, CH$_3$), 4.25 (d, 1H, R$_2$CHOR, J=4 Hz); m/e (relative intensity): 166 (5.78, M$^+$), 151 (4.99), 139 (5.65), 138 (48.4), 137 (10.9), 124 (9.15), 123 (42.3), 109 (21.2), 95.0 (100); **Exact mass** calcd. for $\text{C}_{10}\text{H}_{14}\text{O}_2$: 166.0994; found:
Anal. calcd. for C₁₀H₁₄O₂: C 72.26, H 8.490; found: C 72.16, H 8.600.

Lactols (137)

To a solution of (-)-lactone (141) (1.1 g, 6.6 mmol) in dry toluene (20 mL) cooled to -78°C under an argon atmosphere was added diisobutylaluminum hydride (1.0 M, hexane) (16 mL, 16 mmol). After 45 minutes, the reaction was cautiously quenched at -78°C with methanol (10 mL) until evolution of gas ceased. The reaction mixture was extracted with ether, and several drops of sodium bisulphate solution (2.0 N) were added to break up the gelatinous precipitate. After removal of solvent, the crude product was purified by column chromatography (silica gel, pet. ether:ether, 1:1) to produce a mixture of epimers of lactols (137) (1.1 g, 97%) as a white solid; the ratio of epimers was determined from proton integrations in the n.m.r. to be 2:1; Rf 0.30 (pet. ether:ether, 1:1); νmax (CHCl₃): 3421, 2988 cm⁻¹; δ (CDCl₃, 400 MHz): ¹H-n.m.r. assignments of major diastereomer: 0.96 (s, 3H, CH₃), 1.00 (s, 3H, CH₃), 2.83
(d, 1H, R<sub>1</sub>R<sub>2</sub>CHOH, J=4 Hz), 3.74 (d, 1H, R<sub>1</sub>R<sub>2</sub>CHOR, J=4 Hz); 5.16 (d, 1H, RC\(\text{H}(\text{OR})_2\), J=4 Hz); m/e (relative intensity): 168 (0.78, M<sup>+</sup>), 156.0 (23.32), 150 (2.15), 139 (2.57), 135 (3.53), 125 (11.3), 124 (16.8), 106 (20.0), 95.0 (100); Exact mass calcd. for C<sub>10</sub>H<sub>16</sub>O<sub>2</sub>: 168.1150; found: 168.1138; Anal. calcd. for C<sub>10</sub>H<sub>16</sub>O<sub>2</sub>: C 71.39, H 9.590; found: C 71.20, H 9.800.

**Prenyl Triphenylphosphonium Bromide (135)**

\[
\text{Br}+\text{PPh}_3 \rightarrow \text{Br}+\text{PPh}_3
\]

Triphenylphosphine (13 g, 48 mmol) was dissolved in dry benzene (20 mL) under an argon atmosphere and prenyl bromide (7.1 g, 48 mmol) was added. Stirring was continued at 25°C for 12 hours and worked up by filtering and washing the precipitate with benzene and pentane. After drying, the crude product was recrystallised from methylene chloride to provide prenyl triphenylphosphonium bromide (135) (19.6 g, 100%) as colorless prisms; mp 234-235°C (lit. [56b] mp 242°C); δ (CDCl<sub>3</sub>, 400 MHz): 1.18 (d, 3H, CH₃, J=4 Hz), 1.55 (d, 3H, CH₃, J=6 Hz), 4.40, 4.50 (dd, 2H, RCH₂PPh₃Br, J=14 Hz, 40 Hz), 4.75-5.25 (m, 1H, Me₂C:CHR), 7.50-8.00 (m, 15H, RP(C₆H₅)₃Br).
Dienols (142a,b)

An aliquot of sodium methylsulfinylmethide (28 mL, 31 mmol), prepared from sodium hydride (3.4 g) in dry dimethyl sulfoxide (0.10 L), was treated with prenyl triphenylphosphonium bromide (135) (5.1 g, 12 mmol) at 80°C under an argon atmosphere for 20 minutes. A solution of lactol (137) (1.0 g, 6.2 mmol) in dry dimethyl sulfoxide (30 mL) was then added and after 3.5 hours, the reaction mixture was cooled, water (30 mL) was added, and extracted with petroleum ether. The combined organic extract was evaporated to provide a crude product which was purified by column chromatography (silica gel, pet. ether:ether, 5:1) to yield a mixture of isomers of dienols (142a,b) (1.1 g, 82%) as a colorless oil; the ratio (1:7) of isomers (142a,b) was determined from proton integrations in the n.m.r.; (142b): Rf 0.27 (pet. ether:ether, 4:1); ν_{max} (film): 3426, 2991, 1641 cm^{-1}; δ (CDCl₃, 400 MHz): 0.96 (s, 3H, CH₃), 1.03 (s, 3H, CH₃), 1.73 (s, 3H, CH₃) 1.82 (s, 3H, CH₃), 3.45 (dd, 1H, R₂CHOH, J=8 Hz, 4 Hz), 5.55 (d, 1H, Ha, J=12 Hz), 6.20 (d, 1H, Hc, J=12 Hz), 6.14 (dd, 1H, Hb, J=12 Hz, 24 Hz); m/e (relative intensity): 220 (61.5, M⁺), 218 (9.33),
202 (21.6), 176 (42.1), 161 (21.0), 159 (38.2), 133 (77.4), 131 (22.3), 125 (67.7), 121 (35.5), 119 (39.9), 110 (14.8), 109 (100); (142a): $R_f$ 0.34 (pet. ether:ether, 4:1); $\nu_{\text{max}}$ (film): 3426, 2991, 1641 cm$^{-1}$; $\delta$ (CDCl$_3$, 400 MHz): 0.92 (s, 3H, CH$_3$), 1.01 (s, 3H, CH$_3$), 3.74 (s, 3H, CH$_3$), 3.75 (s, 3H, CH$_3$), 3.48 (t, 1H, R$_2$CHOH, $J=6$ Hz), 5.8 (d, 1H, Ha, $J=16$ Hz), 5.81 (d, 1H, Hc, $J=10$ Hz), 6.27 (dd, 1H, Hb, $H=16$ Hz, 10 Hz): m/e (relative intensity): see before. Exact mass calcd. for C$_{15}$H$_{24}$O: 220.1827; found: 220.1829; Anal. calcd. for C$_{15}$H$_{24}$O: C 81.76, H 10.89; found: C 81.46, H 11.00.

**p-Bromobenzoyl Ester (148)**

![Diagram](attachment:image.png)

p-Bromobenzoyl chloride (0.14 g, 0.64 mmol) was added to a solution of dienol (142a,b) (17 mg, 0.08 mmol) in dry pyrine (3.0 mL) at 25 C under an argon atmosphere. The mixture was stirred for 22 hours and in hydrochloric acid (1.0 N, 10 mL) was added and extracted with ether. The combined organic layers were washed with hydrochloric acid (1.0 N), potassium hydroxide (1.0 N), brine and water, and dried (MgSO$_4$). After removal of solvent, the
crude product was purified by column chromatography to give p-bromobenzoyl ester (148) (25 mg, 78%) as a colorless oil. Rf 0.92 (pet. ether:ether, 1:1); $\nu_{\text{max}}$ (film): 2985, 1710, 1592 cm$^{-1}$; 
$\delta$ (CDCl$_3$, 270 MHz): 0.98 (s, 3H, CH$_3$), 0.99 (s, 3H, CH$_3$), 1.67 (s, 3H, CH$_3$), 1.75 (s, 3H, CH$_3$), 4.78 (dd, 1H, $R_1R_2$CHOH, J=4 Hz, 8 Hz), 5.65 (d, 1H, $H_A$, J=12 Hz), 6.05 (dd, 1H, $H_B$, J=24 Hz, 12 Hz), 6.12 (d, 1H, $H_C$, J=12 Hz); m/e (relative intensity): 402 (7.18, M$^+$), 219 (39.8), 202 (87.1), 187 (55.9), 185 (84.5), 183 (83.6), 174 (37.6), 159 (76.6), 147 (42.4), 133 (71.1), 122 (50.6), 119 (50.9), 107 (80.4), 91.0 (65.5), 55.0 (58.1), 41.0 (100); Exact mass calcd. for C$_{22}$H$_{27}$O$_2$Br: 402.1193; found: 402.1189. Anal. calcd. for C$_{22}$H$_{27}$O$_2$Br: C 65.51, H 6.750; found: C 65.30, H 6.950.

Dienones (136a,b)

A solution of dienols (142a,b) (1.1 g, 5.1 mmol) and pyridinium dichromate (9.5 g, 25 mmol) in dry methylene
chloride (35 mL) was stirred at room temperature under an argon atmosphere for 12 hours. The reaction mixture was then diluted with ether and filtered through a pad of silica gel. After removal of solvent, the crude product was purified by column chromatography (silica gel, pet. ether:ether, 15:1) to yield a mixture of dienones (136a,b) (0.68 g, 62%) as a colorless oil; the ratio (1:7) of isomers (136a:136b) was determined from proton integration in the n.m.r.; (136b): R_f 0.56 (pet. ether:ether, 4:1); ν_max (film): 2931, 1744 cm^{-1}; 6 (CDCl_3, 400 MHz): 1.01 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 5.13 (d, 1H, Ha, J=8 Hz), 6.15 (d, 1H, Hc, J=10 Hz), 6.16 (dd, 1H, Hb, J=24 Hz, 12 Hz); (136b): 0.99 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 1.81 (s, 3H, CH_3), 5.41 (d, 1H, Ha, J=16 Hz), 5.73 (d, 1H, Hc, J=10 Hz), 6.28 (dd, 1H, Hb, J=16 Hz, 10 Hz); m/e (relative intensity): 218 (27.3, M), 203 (12.3), 175 (16.6), 161 (14.4), 149 (34.7), 147 (14.8), 135 (13.2), 107 (100); Exact mass calcd. for C_{15}H_{22}O: 218.1671; found: 218.1672; Anal. calcd. for C_{15}H_{22}O: C 82.51, H 10.15; found: C 82.18, H 10.04.
Triene-acetates (103a,b)

A solution of dienones (136a,b) (0.18 g, 0.83 mmol) in dry tetrahydrofuran (10 mL) was treated at 25 C with n-butyllithium (1.6 M, hexane) (0.700 mL, 1.06 mmol) for 15 minutes. The enolate anion thus generated was cooled to -50°C and treated with dry acetic anhydride (0.16 mL, 1.7 mmol). After 15 minutes, the reaction mixture was warmed to room temperature and saturated sodium bicarbonate solution (5.0 mL) was added to quench excess acetic anhydride. The mixture was then extracted with pet. ether and the combined organic layers were washed with brine and dried (MgSO₄). After removal of solvent, the crude product was purified by column chromatography (silica gel, pet. ether:ether, 20:1) to afford a mixture of isomers of triene-acetates (103a:b) (0.14 g, 64%) as a colorless oil; the ratio (1:7) of isomers (103a:103b) was determined from proton integrations in the n.m.r.;
(103b): \( R_f \) 0.81 (pet. ether:ether, 4:1); \( \gamma_{\text{max}} \) (film): 2925, 1759, 1620 cm\(^{-1}\); \( \delta \) (CDCl\(_3\), 400 MHz): 0.94 (s, 3H, CH\(_3\)), 1.06 (s, 3H, CH\(_3\)), 1.71 (s, 3H, CH\(_3\)), 1.81 (s, 3H, CH\(_3\)), 2.13 (s, 3H, ROCOCH\(_3\)), 5.49 (d, 1H, Ha, J=10 Hz), 5.59 (d, 1H, Hd, J=4 Hz), 6.10 (d, 1H, Hc, J=10 Hz), 6.10 (dd, 1H, Hb, J=24 Hz, 12 Hz); (103a): 0.90 (s, 3H, CH\(_3\)), 0.95 (s, 3H, CH\(_3\)), 1.73 (s, 6H, \( R_2(\text{CH}_3)_2 \)), 2.17 (s, 3H, ROCOCH\(_3\)), 5.63 (d, 1H, Hd, J=4 Hz), 5.80 (d, 1H, Ha, J=10 Hz), 5.19 (d, 1H, Hc, J=16 Hz), 6.19 (dd, 1H, Hb, J=16 Hz, 10 Hz); m/e (relative intensity): 260 (2.92, \( \text{M}^+ \)), 219 (1.47), 218 (8.32), 217 (3.44), 203 (3.15), 185 (4.06), 175 (8.84), 162 (8.91), 161 (4.23), 147 (18.2), 109 (17.3), 91.0 (23.8), 78.0 (15.7); Exact mass calcd. for \( \text{C}_{17}\text{H}_{24}\text{O}_2 \): 260.1776; found: 260.1775; Anal. calcd. for \( \text{C}_{17}\text{H}_{24}\text{O}_2 \): C 78.42, H 9.290; found: C 78.36, H 9.180.
CHAPTER 2

Synthetic Approaches to Albene
2.1.0. **INTRODUCTION**

(−)-Albene (221), a tricyclic C_{12}H_{18} [85] trisnorsesquiterpenoid, was first isolated from *Petasites albus* in 1962. Despite extensive efforts involving a variety of degradative and synthetic studies, the correct structure and absolute configuration of this elusive molecule has been a subject of controversy for nearly two decades.

The first tentative structural proposal (222) was made by L. Novotny and V. Herout in 1964 [86]. Later, F. Sorm and co-workers [87], on the basis of spectroscopic evidence and chemical correlation between "(−)-albene" (223) and (+)-camphene (224), proposed a new structure (223) for (−)-albene.

Structure (223) was supported in 1973 by P. T. Lansbury and R. M. Boden [88] who synthesised albanone (228) from camphenilone (225) as shown in Scheme 68. The key step in this
synthetic route was the formic acid catalysed cyclisation of the bicyclic chloro-alkene (228). The well-known preference of exo-2,3-methyl shifts over the corresponding endo shifts in norbornyl cations (Scheme 69) prompted Lansbury to conclude that this cyclisation step would provide (227) rather than (232). In 1979, however, W. Kreiser and co-workers repeated Lansbury's experiments (Scheme 70), and reported that X-ray crystallographic analysis of the 2,4-dinitrophenylhydrazone derivative of albanone (234) [89] clearly showed that this compound, albanone, had the exo configuration (235). Hence
they proposed that the formic acid catalysed cyclisation

\[ \text{Scheme 69} \]

\[ \text{2,3 Me } \text{exo} \]

\[ \text{2,3 Me } \text{endo} \]

\[ \text{2,3 Me } \text{exo} - \text{exo-2,3-methyl shift} \]

\[ \text{2,3 Me } \text{endo} - \text{endo-2,3-methyl shift} \]
Reagents and conditions:

(i) (CF₂CO)₂O, H₂O (80%), H₂SO₄ (cat.)/HOAc; (ii) Saponification; (iii) CrO₃, Pyridine; (iv) 2,4-(NO₂)₂C₆H₄NNH₂, H⁺; (v) Pb(OAc)₄.

Scheme 70

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of (233) involved an endo-2,3-methyl shift as shown in Scheme 69.

With experience gained from studies of the rearrangement of the bicyclo[2.2.1]heptane skeleton, T. Money pointed out in 1979 [90] that the 2,3-exo-methyl shift reported by Lansbury and R. M. Boden earlier was probably correct, but suggested that this was followed by Wagner-Meerwein rearrangement, 2,6 hydride shift, Wagner-Meerwein rearrangement and cyclisation reaction sequences (Scheme 71) to provide structure (243) as a cyclisation product. Thus it was suggested that (−)-albene had the enantiomeric structure (221). This conclusion was independently made by J. E. Baldwin and T. C. Barden who went on to confirm the structure of (−)-albene (221) by elegant mechanistic and synthetic studies [91].

The challenge presented by the structure of albene has led to the successful completion of four total syntheses. A brief account of these synthetic approaches is provided below.

Lansbury's initial synthesis in 1973 (Scheme 68) was repeated by W. Kreiser and L. Janitschke in 1978 and the tricyclic product was reassigned as the exo-five membered ring structure (232). In 1981, J. E. Baldwin and T. C. Barden [91] reported a synthesis of (†)-albene that featured the conversion of hemiacetal (246) into cyclopentenone (247) (Scheme 72). In 1982, B. M. Trost and P. Renaut [92] (Scheme 73) utilised the palladium catalysed cycloaddition of
Scheme 71

2,3 Me _exo_ — _exo_-2,3-methyl shift
WM = Wagner-Meerwein rearrangement
2,6 H = 2,6-hydride shift
Reagents and conditions:

(i) MeLi; (ii) DHP, TsOH; (iii) (tBu)_2AlH; (iv) KOH; (v) (tBu)_2AlH; (vi) Ac_2O, NaOAc; (vii) Li/EtNH_2.

Scheme 72
Reagents and conditions:

(i) \((i-C_3H_7)_3P, \text{Pd(OAc)}_2, \text{THF, Reflux; (ii) LAH, Ether, 0}^\circ \text{C; (iii) } \text{O}_3, \text{CH}_2\text{Cl}_2, \text{CH}_3\text{OH, -78}\,^\circ \text{C; (CH}_3)_2S; (iv) \text{KN(Me}_3\text{Si), DME, HMPA, [(CH}_3)_2\text{N]}_2P(0)\text{Cl, 0}\,^\circ \text{C; (v) Li, C}_2\text{H}_5\text{NH}_2, \text{THF, } t_C_2\text{H}_5\text{OH, -5}\,^\circ \text{C.}

\text{Scheme 73}

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2-[(trimethylsilyl)methyl]-3-iodo-1-propane (249) with diester (248) as the key reaction and produced the desired cycloadduct (250) which after reduction and ozonolysis provided the basic tricyclic skeleton (252) of albene. Reduction of the corresponding triphosphate (253) then provided (±)-albene. In 1983, A. S. Dreiding et al. [93] completed another synthesis of (±)-albene (Scheme 74) in which terminal cyclisation of alkynone (258) resulted in successful annulation to provide cyclopentenone (247). The required olefin functionality was then introduced via the Shapiro reaction to produce (±)-albene.

Synthetic routes to albene have been considered in our laboratory [94] since the proposal for the absolute configuration of albene was made [90]. The main object of this work was to develop an enantiospecific synthesis of (+)-albene (221). Two synthetic approaches, including an intramolecular ene reaction of (+)-β-santalene (259), and an intramolecular free radical cyclisation reaction of bromo-olefin (260) respectively will be described.

![Image of molecules](259) (260)
Reagents and conditions:

(i) Heat; (ii) \( \text{CH}_3\text{SiC}=\text{CSiCH}_3 \), \( \text{AlCl}_3 \); (iii) \( \text{Na}_2\text{B}_4\text{O}_7 \);
(iv) 580°C; (v) \( \text{H}_2 \), \( \text{Pd/C} \); (vi) \( \text{TsNHNH}_2 \); (vii) \( \text{MeLi} \).

Scheme 74

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2.2.0. DISCUSSION AND RESULTS

2.2.1. INTRAMOLECULAR ENE REACTION

From a biosynthetic standpoint [90], (-)-albene (221) could be produced in nature by cyclisation of (+)-β-santalene (259) followed by elimination of the isoprenyl group. Previous attempts in our laboratory to synthesise albene via acid catalysed cyclisation of (+)-β-santalene (259) and (+)-epi-β-santalene (48) were unsuccessful [70,94]. A close examination of molecular model of (+)-β-santalene (259) revealed that the ene and enophile portions of this molecule could align favorably in the transition state (263) (Scheme 75). It was hoped that
thermal cyclisation of (+)-β-santalene (259) would take place smoothly to produce the desired olefin (261). Ozonolysis of olefin (261) followed by Baeyer-Villiger oxidation and elimination of the corresponding acetate (264) could then provide (-)-albene (221) as shown in Scheme 76.

Before describing the synthesis of (+)-β-santalene (259), the substrate for the projected intramolecular ene reaction, a brief general description of the intramolecular ene reaction is provided below. The intramolecular ene reaction [95] usually involves thermolysis of an olefin with an allylic
hydrogen attached (ene) and an enophile (an electron-deficient multiple bond) (265) intramolecularly with either \textit{exo}- or \textit{endo}-transition state to give a cyclic olefin (266).

\begin{equation}
Z = CR_2, O
\end{equation}

Three different cyclisation modes are possible and these are outlined in Scheme 77. In Baldwin terminology [96], reaction types 1-3 represent \textit{exo}-\textit{exo}, \textit{exo}-\textit{endo} and \textit{endo}-\textit{endo} cyclisations respectively. For our own purpose, only intramolecular ene reaction of type 1 will be discussed here. Type 1 cyclisation is mainly associated with the thermolysis of a 1,6 diene such as compound (267) which provides compound (268) as the major product and compound (269) as the minor product [97]. Examination of transition states illustrates that the \textit{exo}-transition state (270), which gives the trans-substituted product (269), appears to be highly strained, thus favoring the almost exclusive formation of the
cis-substituted product (268) via the relatively unstrained endo-transition state (271) (Scheme 78):
Use has been made of this general principle in a recent stereoselective synthesis of a spiro-sesquiterpenoid, (+)-β-acorenol (274) [98]. The spirocyclic skeleton (273) of this compound was constructed by an intramolecular ene reaction of diene (272), and its stereochemistry results from the endo-transition state (275) rather than the less favored exo-transition state (276) which shows a non-bonded interaction between the bridge C(4) and the cyclohexene unit C(6), as shown in Scheme 79.

\[\text{Scheme 79}\]
Previous investigations [23] in our laboratory have established that \((-\)-\(\beta\)-santalene (98) can be synthesised from \((-\)-campherenone (82) which, in turn, was derived from \((-\)-camphor (27). \((+\)-\(\beta\)-santalene (259) was synthesised in a similar fashion with the exception that a less hazardous sequence (Scheme 80) was used to convert \((+\)-camphor (28) to \((+\)-campherenone (151) (cf. page 66) [61]. Subsequent hydride reduction of (151) followed by Wagner-Meerwein rearrangement of \((+\)-campherenol (278) provided \((+\)-\(\beta\)-santalene (259) in 74% yield from \((+\)-campherenone (151).

With \((+\)-\(\beta\)-santalene (259) available, attempts were made to carry out the intramolecular ene reaction to form the desired olefin (261). This reaction was carried out at different temperatures ranging from 200\(^\circ\)C-550\(^\circ\)C in sealed tubes. However, after several attempts we were forced to conclude that the desired compound (261) was not produced under these conditions. Subsequent to this attempt, we noted that J. E. Baldwin et al. have previously reported that thermolysis of olefin (262) provided \((-\)-\(\beta\)-santalene (98) via a retro-ene process [91c]. This is a possible explanation for our failure in the attempt of an intramolecular ene reaction on \((+\)-\(\beta\)-santalene (259).
Reagents and conditions:
(i) Br₂, HBr, HOAc, 110°C; (ii) Br₂, HSO₄Cl; (iii) Zn, HOAc, Et₂O, 0°C; (iv) KI, DMSO, 110°C, 3 days; (v) Me₃SiCl, HOCH₂CH₂OH; (vi) NaCN, DMSO, 70°C, 2 days; (vii) LDA, THF, -78°C; Prenyl Bromide; (viii) K, HMPA, Et₂O, tBuOH, 0°C; (ix) HCl, Me₂CO; (x) LAH, THF; (xi) MeSO₂Cl, Pyridine, 4-DMAP, 100°C, 16 hours.

Scheme 80

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2.2.2. **INTRAMOLECULAR FREE RADICAL CYCLISATION APPROACH**

Our second synthetic approach to the synthesis of albene involved an intramolecular free radical cyclisation reaction. Recently, there has been an increase in the use of free radical reactions for the synthesis of cyclic compounds. These cyclisation reactions exhibit interesting regioselectivities and stereoselectivities. For example, A. L. J. Beckwith and C. H. Schiesser [99] have shown that the 5-hexenyl radical (279) cyclised regioselectively to produce the smaller ring (281), that is, the less stable primary radical (280) was formed faster than the more stable secondary radical (282). The preferential formation of (281) is consistent with Baldwin's

![Diagram](image)

Scheme 81

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rules [86] which state that 5-exo-trigonal cyclisations are more favorable than 6-endo-trigonal cyclisation processes. Beckwith explained the regioselective formation of (281) via the most favored transition state (284) (Scheme 81).

The stereoselectivity of free radical cyclisation has also been reported by Beckwith [99], and two useful guidelines governing the ring closure of substituted hexenyl radicals were formulated. The first guideline is that 1- or 3-substituted radicals preferentially give cis-disubstituted cyclopentyl products, and the second one is that 2- or 4-substituted radicals give mainly trans-disubstituted cyclopentyl products. For example, cyclisation of 3-methyl-5-hexenyl radical (285) gives more cis-isomer (287). On the other hand, cyclisation of 2-methyl-5-hexenyl radical (288) gives more trans-isomer (289) than cis-isomer (290). Similarly, cyclisation of 4-methyl-5-hexenyl radical (291) also produced more trans isomer (292) (Scheme 82). Beckwith explained these results on the basis of the transition state structure (294) of these radicals in which the more favorable conformer should bear the substituents in the equatorial position.
Scheme 82
Many applications of free radical cyclisation in natural product synthesis have been published during the past decade. Examples, include the synthesis of (†)-copacamphene (296) and (†)-sativene (297) by P. Bakuzis et al. in 1976 [100] (Scheme 83), dihydroagarofuran (299) by Buchi and H. Wuest in 1979 [101] (Scheme 84), and norseychelllanone (301) by G. Stork and N. H. Baine in 1985 [102] (Scheme 85).

Scheme 83

Scheme 84

Scheme 85
In the key reactions leading to these compounds, alkyl radicals produced from alkyl halides (295), (298), and (300) react intramolecularly with an alkene functionality to form the cyclised products.

An extension of this methodology involves double radical cyclisation to form two rings, and an elegant example of this technique is provided by the recent synthesis of butenolide (304) (Scheme 86) described by Stork and R. Mook [103].

Successive radical cyclisation has also been used in the recent synthesis of hirsutene (306a) [104] (Scheme 88), silphiperfol-6-ene (305b) and 9-episilpriperfol-6-ene (305d)
The successful syntheses described above prompted us to consider that the construction of the cyclopentane ring of (-)-albene (221) could be accomplished by a free radical cyclisation reaction. The proposed synthetic plan outlined in Scheme 89 envisages intramolecular free radical cyclisation of the bromo olefin (307). It was hoped that the radical intermediate (308) would add to the double bond in a 5-\textit{exo}-trig fashion to produce the albene framework (310) and dehydration would then provide (+)-albene (311).

Retro-synthetic analysis (Scheme 90) reveals that bromo olefin (307) could be constructed, in theory, from alkene aldehyde (312) and an appropriate unit (313). Finally, alkene aldehyde (312) could be derived from compound (314), which could be formed by Wagner-Meerwein rearrangement of a C(8) functionalised camphor derivative (315) [94]. In the proposed enantiospecific synthesis of albene, (+)-camphor (26) was therefore chosen as the chiral starting material (Scheme 91). Treatment of (+)-8-bromocamphor (42) derived from (+)-camphor (26) in 3 steps as described earlier (page 50) with potassium
acetate in dimethyl sulfoxide at high temperature (Scheme 91) gave (+)-8-acetoxy camphor (139), which underwent selective reduction with sodium borohydride in ammonium chloride and ethanol to provide hydroxy-acetate (316). Subsequent reaction of (316) with methanesulfonyl chloride, 4-dimethylaminopyridine and pyridine resulted in Wagner-Meerwein rearrangement and
formation of alkene acetate (317). Hydride reduction of alkene acetate (317) followed by oxidation with pyridinium chlorochromate [69] afforded alkene aldehyde (312) which was treated with methyl acetate (313) and lithium diisopropylamide in tetrahydrofuran to afford (319) in over 33% yield from (+)-8-bromocamphor (42). Hydride reduction of hydroxy-ester (319) provided the diols (320) in 89% yield. The primary
Reagents and conditions:

(i) Br₂, HBr, HOAc, 110°C; (ii) Br₂, CISO₃H; (iii) Zn, HOAc, Et₂O, 0°C; (iv) KOAc, DMSO, 110°C; (v) NaBH₄, NH₄Cl, EtOH; (vi) MeSO₂Cl, Pyridine, 4-DMAP, 100°C, 16 hours; (vii) LAH, THF; (viii) PCC, CH₂Cl₂; (ix) LDA, THF, -78°C; CH₃CO₂Me; (x) LAH, THF.

Scheme 91

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alcohol in this compound (320) was selectively protected as the bulky tert-butyldiphenylsilyl ether (321) [108] (Scheme 92). Acetylation of (321) provided silyl ether ester (322) which was treated with tetrabutylammonium fluoride in tetrahydrofuran to give the desired hydroxy-acetate (323), and a by-product. The infrared spectrum (cf. page 283) of this by-product showed absorptions at 3460 cm\(^{-1}\), and 1740 cm\(^{-1}\) which indicated the presence of alcohol and ester functionalities. When its \(^1H\)-n.m.r, spectrum (page 284) was compared with that of hydroxy-ester (323) (page 284), we concluded that this by-product was the isomeric hydroxy-ester (324) (Scheme 92). To account for the formation of (324) in the desilylation reaction of (322), we proposed that a 1,3-acyl transfer reaction (Scheme 93) had taken place during the desilylation reaction. 1,3-Acyl transfers of this type have reported in the literature [107].

Since desilylation of (322) provided a mixture of isomeric hydroxy-esters (323) and (324), we decided to replace the acetate group in (324) with a methyl ether (Scheme 94). Treatment of silyl ether (321) with potassium hydride and

![Scheme 93](image_url)
Reagents and conditions:
(i) t-Butyldiphenylsilyl Chloride, Imidazole, DMF; (ii) NaH, THF, MeI; (iii) TBAF; (iv) PPh₃, Br₂, CH₂Cl₂.

Scheme 94
Reagents and conditions:
(i) t-Butyldiphenylsilyl Chloride, Imidazole, DMF; (ii) Ac$_2$O, 4-DMAP, Pyridine; (iii) TBAF.

Scheme 92

methyl iodide in tetrahydrofuran afforded the methoxy-silyl ether (325) which was desilylated to provide methyl ether alcohol (326) as the only product. With the protecting group problem solved, we then proceeded with the synthesis of bromo-olefin (260) by bromonating methyl ether alcohol (326) with bromine and triphenylphosphine in methylene chloride [108].
The synthesis of bromo-olefin (260) allowed us to investigate the crucial intramolecular free radical cyclisation reaction. Treatment of bromo-olefin (260) with azobis-(isobutyronitrile) and tributyltin hydride in benzene at 60°C [109] provided a single product. The $^1$H-n.m.r. spectrum (page 285) of this product indicated the presence of only one methyl group and was clearly inconsistent with the spectrum expected for the desired product (329). Indeed, the $^1$H-n.m.r. spectrum led us to conclude that the reaction product was the tricyclic methyl ether (331) (Scheme 95). The cyclisation of the intermediate radical (327) could occur by either a 5-exo-trig or a 6-endo-trig mode. Although the 5-exo-trig mode would usually be preferred for geometric reasons, this cyclisation involves steric interaction and torsional strain between the CH$_3$ and CH$_2$ groups attached to adjacent carbon atoms of the intermediate framework (328). In contrast, the geometrically less favored 6-endo-trig cyclisation involves a secondary free radical intermediate (330) and is not accompanied by serious steric interaction. Therefore, due to steric effects, the formation of cycloalkyl radical (330) was preferred over cycloalkyl methyl radical (328), and we obtained the undesired product (331) as the favored one.

In summary, synthetic approaches to construct the basic tricyclic carbon framework of (+)- or (-)-albene (221) include the intramolecular ene reaction and the intramolecular free radical cyclisation reaction. A new enantiospecific synthetic
route to (+)-β-santalene (259) from (+)-camphor (26) was described, but this compound unfortunately failed to undergo an intramolecular ene reaction to provide (261). In addition, bromo-olefin (260), was also synthesised from (+)-camphor (26) but cyclised in a 6-exo-trig mode in the intramolecular free radical reaction approach to provide a six-membered ring product (331).

Scheme 95
2.3.0. EXPERIMENTAL (cf. page 88)
(-)-Isocampherenol (278)

Lithium aluminum hydride (0.26 g, 6.8 mmol) was suspended in dry tetrahydrofuran (30 mL) at 0°C, and a solution of (+)-campherenone (151) (1.0 g, 4.5 mmol) in dry tetrahydrofuran (15 mL) was slowly introduced. The reaction mixture was stirred at 0°C under an argon atmosphere for 3 hours. After dilution with water (20 mL) carefully followed by extraction with ether, the combined organic layers were washed with hydrochloric acid (1.0 N), brine and water, and dried (MgSO₄). Upon removal of solvent under vacuo, the crude product was purified by column chromatography (silica gel, pet. ether) to yield (-)-isocampherenol (278) (0.99 g, 98%) as a colorless oil; R_f 0.20 (pet. ether:ether, 9:1); [α]_D^25 -24.7° (c 0.90, CHCl₃); ν_max (film): 3420, 2970 cm⁻¹; δ (CDCl₃, 400 MHz): 0.85 (s, 3H, CH₃), 0.91 (s, 3H, CH₃), 1.62 (s, 3H, R₁R₂C:CCH₃CH₃), 1.68 (s, 3H, R₁R₂C:CCH₃CH₃), 3.64 (dd, 1H, R₁R₂CHOH, J=12 Hz, 4 Hz), 5.14 (m, 1H, R₁R₂C:CHR₃); m/e (relative intensity): 222 (0.110, M⁺), 220 (1.86), 204 (2.22), 1.59 (4.34), 135 (4.38), 122 (72.1), 109 (14.5) 107 (12.6), 94.0 (25.2), 94.0 (100); Exact mass calcd. for C₁₅H₂₆O: 222.1984; found: 222.1987; Anal. calcd. for C₁₅H₂₆O:
C 81.02, H 11.79; found: C 81.00, H 11.91.

(+)-β-Santalene (259)

(-)-Isocampherenol (278) (1.0 g 4.5 mmol) was treated with methanesulphonyl chloride (1.0 g, 9.0 mmol) and 4-dimethylaminopyridine (0.15 g) in dry pyridine (10 mL) at 100°C under an argon atmosphere for 16 hours. After dilution with water (10 mL), followed by extraction with ether, the combined organic layers were washed with hydrochloric acid (1.0 N), saturated sodium bicarbonate solution and water, and dried (MgSO₄). Upon removal of solvent under vacuo, the crude product was purified by column chromatography (silica gel, pet. ether) to accomplish (+)-β-santalene (259) (0.73 g, 80%) as a colorless oil; Rf 0.93 (pet. ether:ether, 4:1); [α]₀²⁵⁺112.6° (c 1.60, CHCl₃) (lit. [23] for (-)-β-santalene [α]₀²⁸⁻112° (c 5.01, CHCl₃)); ν max (film): 2979, 1658, 878 cm⁻¹; δ (CDCl₃, 400 MHz): 1.05 (s, 3H, CH₃), 1.61 (s, 3H, R₁R₂C:CCH₃CH₃), 1.68 (s, 3H, R₁R₂C:CCH₃CH₃), 4.46 (s, 1H, R₁R₂C:CHH), 4.73 (s, 1H, R₁R₂C:CHH), 5.10 (t, 1H, R₁R₂C:CHR₃, J=8 Hz); m/e (relative intensity): 204 (1.48, M⁺),
189 (1.30), 161 (3.83), 148 (1.24), 147 (2.11), 133 (3.54),
122 (38.7), 94.0 (100); **Exact mass** calcd. for C_{15}H_{24}: 204.1878;
found: 204.1878; **Anal.** calcd. for C_{15}H_{24}: C 88.16, H 11.84;
found: C 88.19, H 11.91.

**Hydroxy-acetate (316)**

![Diagram of chemical structures](image)

Sodium borohydride (0.77 g, 20 mmol) was added to a solution of ammonium chloride (5.45 g, 101 mmol) in 95% ethanol (40 mL), followed by the addition of a solution of (+)-8-acetoxycamphor (139) (2.0 g, 0.52 mmol) in 95% ethanol (25 mL). The reaction mixture was stirred at 0°C for 30 minutes and at room temperature for 15 hours. It was then carefully poured into hydrochloric acid (1.0 N) in a separatory funnel and extracted with ether. The combined organic layers were washed with saturated sodium bicarbonate and brine, and dried (MgSO₄). Removal of solvent gave a crude product which was purified by column chromatography (silica gel, petroleum ether:ether, 5:1) to yield pure hydroxy-acetate (316) (1.7 g, 86%) as a colorless oil. R_f 0.41 (pet. ether:ether, 1:1); ν_max (film): 3498,
2955, 1730 cm$^{-1}$; $\delta$ (CDCl$_3$, 80 MHz): $^1$H-n.m.r. assignments of major diastereomer: 0.95 (s, 3H, CH$_3$), 1.00 (s, 3H, CH$_3$), 2.10 (s, 3H, CH$_3$), 4.05 (d, 1H, RCHOH, $J=4$ Hz); m/e (relative intensity): 212 (0.000, M$^+$), 194 (0.080), 152 (8.49), 137 (6.00), 123 (6.20), 121 (7.59), 108 (100); Exact mass calcd. for C$_{12}$H$_{20}$O$_3$: 212.1412; found: (not observed); Anal. calcd. for C$_{12}$H$_{20}$O$_3$: C 67.89, H 9.500; found: C 68.10, H 9.430.

Alkene-acetate (317)

Hydroxy-acetate (316) (17 g, 80 mmol) was treated with methanesulphonyl chloride (26 g, 0.23 mmol) and 4-dimethylaminopyridine (1.0 g) in dry pyridine (100 mL) was refluxed under an argon atmosphere for 12 hours. After dilution with water (20 mL) and extraction with ether, the combined organic layers were washed with hydrochloric acid (1.0 N), saturated sodium bicarbonate solution and brine, and dried (MgSO$_4$). Removal of solvent provided a crude product which was purified by column chromatography (silica gel, pet. ether:ether, 5:1) to give alkene-acetate (317) (9.4 g, 60%) as a colorless oil. $R_f$ 0.93
(pet. ether:ether, 1:1); $\nu_{max}$ (film): 2981, 1744, 1664, 891 cm$^{-1}$; 
$\delta$ (CDCl$_3$, 270 MHz): 1.15 (s, 3H, CH$_3$), 2.06 (s, 3H, CH$_3$), 3.75, 3.92 (AB quartet, 2H, RCH$_2$OAc, $J_{AB}$=12 Hz), 4.58 (s, 1H, RC:CHH), 4.82 (s, 1H, RC:CH$_2$); m/e (relative intensity): 194 (9.93, M$^+$), 152 (3.28), 134 (29.1), 121 (94.6), 119 (14.4), 106 (29.5), 93.0 (100); Exact mass calcd. for C$_{12}$H$_{18}$O$_2$: 194.1307; found: 194.1314; Anal. calcd. for C$_{12}$H$_{18}$O$_2$: C 74.19, H 9.340; found: C 74.00, H 9.180.

Hydroxy-olefin (318)

To a cold (0°C), stirred solution of lithium aluminum hydride (68 mg, 1.8 mmol) in dry tetrahydrofuran (5.0 mL) under an argon atmosphere was added a solution of alkene-acetate (317) (0.35 g, 1.8 mmol) in dry tetrahydrofuran (5.0 mL). Stirring was continued for 3 hours and the reaction mixture was worked up in the usual way. Removal of solvent gave a crude product which was purified by column chromatography (silica gel, pet. ether:ether, 10:1) to give hydroxy-olefin (318) (0.23 g, 84%) as a colorless oil. $R_f$ 0.36 (pet. ether:ether, 1:1); $\nu_{max}$ (film): 3396, 2971,
1668, 890 cm⁻¹; δ (CDCl₃, 270 MHz): 1.12 (s, 3H, CH₃), 3.28 (dd, 1H, RCHHOH, J=12 Hz, 4.5 Hz), 3.46 (dd, 1H, RCHHOH, J=12 Hz, 7.5 Hz); 4.52 (s, 1H, RC:CHH), 4.83 (s, 1H, RC:CHH); m/e (relative intensity): 152 (6.63, M⁺), 134 (0.730), 124 (23.4), 121 (92.5), 108 (4.32), 105 (9.10), 93.0 (100); Exact mass calcd. for C₁₀H₁₆O: 152.1201; found: 152.1204; Anal. calcd. for C₁₀H₁₆O: C 78.90, H 10.59; found: C 78.77, H 10.40.

Alkene-aldehyde (312)

Pyridinium chlorochromate (3.0 g, 14 mmol) was suspended in dry methylene chloride (15 mL), and a solution of hydroxyolefin (318) (0.70 g, 4.6 mmol) in dry methylene chloride (10 mL) was added rapidly at room temperature. After 4 hours under an argon atmosphere the black reaction mixture was diluted with ether and filtered through a pad of silica gel. Removal of solvent provided a crude product which was purified by column chromatography (silica gel, pet. ether:ether, 5:1) to afford alkene-aldehyde (312) (0.61 g, 88%) as a colorless oil. Rf 0.89 (pet. ether:ether, 1:1); νmax (film): 2995, 2850,
2749, 1736, 1666, 896 cm\(^{-1}\); \(\delta\) (CDCl\(_3\), 270 MHz): 1.14 (s, 3H, CH\(_3\)), 4.58 (s, 1H, RC:CH\(_2\)), 4.98 (s, 1H, RC:CH\(_2\)), 9.33 (s, 1H, RCHO); m/e (relative intensity): 150 (4.18, M\(^+\)), 121 (58.9), 105 (17.5), 93.0 (100); Exact mass calcd. for C\(_{10}\)H\(_{14}\)O: 150.1045; found: 150.1044.

**Hydroxy-esters (319)**

![Diagram of 312 and 319](image_url)

n-Butyllithium (1.6 M; hexane) (3.0 mL, 4.6 mmol) was added to a stirred solution of diisopropylamine (0.47 g, 4.6 mmol) in dry tetrahydrofuran (10 mL) under an argon atmosphere at 0°C and stirred for 30 minutes. Methyl acetate (313) (0.31 g, 4.2 mmol) in dry tetrahydrofuran (5.0 mL) was added to this cooled solution at -78°C. Stirring was continued for 2 hours before alkene-aldehyde (312) (0.57 g, 3.8 mmol) was introduced at -78°C. The reaction mixture was stirred for 5 minutes, worked up by adding water (5.0 mL) and extracted with ether. The combined organic layers were washed with saturated ammonium chloride solution and brine, and dried (MgSO\(_4\)). Removal of solvent under vacuo and subsequent column chromatography (silica gel, pet.
ether:ether, 15:1) afforded a mixture of hydroxy-esters (319) (0.72 g, 93%) as a colorless oil. The ratio of the epimeric hydroxy-esters was determined by $^1$H-n.m.r. integration to be about 1:1. $R_f$ 0.17 (pet. ether:ether, 1:1); $\nu_{\text{max}}$ (film): 3541, 2981, 1733, 1651, 889 cm$^{-1}$; $\delta$ (CDCl$_3$, 400 MHz): $^1$H-n.m.r. of one of the diastereomers: 1.03 (s, 3H, CH$_3$), 3.71 (s, 3H, CH$_3$), 3.96 (dd, 1H, RCHOH, J=10 Hz, 4 Hz), 4.70 (s, 1H, RC:CHH), 4.89 (s, 1H, RC:CHH); m/e (relative intensity): 224 (0.000, M$^+$), 206 (7.58), 178 (7.88), 167 (1.93), 149 (6.57), 121 (18.6), 105 (14.1), 103 (47.4), 94.0 (100); Exact mass calcd. for C$_{13}$H$_{20}$O$_3$: 224.1412; found: 206.1312; Anal. calcd. for C$_{13}$H$_{20}$O$_3$: C 69.61, H 8.99; found: C 69.65, H 9.10.

Diols (320)

![Diagram](image)

To a cold ($0^\circ$C), stirred solution of lithium aluminum hydride (64 mg, 1.7 mmol) in dry tetrahydrofuran (5.0 mL) under an argon atmosphere was added a solution of a mixture of hydroxy-esters (319) (0.19 g, 0.85 mmol) in dry tetrahydrofuran (5 mL). Stirring was continued for 4 hours and the reaction mixture
was worked up in the usual way. Removal of solvent gave a crude product which was purified by column chromatography (silica gel, pet. ether:ether, 4:1) to give diols (320) (0.15 g, 89%) as a colorless oil. Rf 0.37 (pet. ether:ether, 9:1); $\nu_{\text{max}}$ (film): 3350, 2855, 1645, 870 cm$^{-1}$; $\delta$ (CDCl$_3$, 400 MHz): $^1$H-n.m.r. of one of the diastereomers: 1.05 (s, 3H, CH$_3$), 3.64 (dd, 1H, RCHOH, J=4 Hz, 8.5 Hz), 3.79-3.89 (m, 2H, RCH$_2$OH), 4.63 (s, 1H, RC:CH$_2$), 4.93 (s, 1H, RC:CH$_2$); m/e (relative intensity): 196 (0.30, M$^+$), 178 (2.83), 168 (1.23), 160 (0.280), 133 (2.62), 122 (27.9), 105 (11.7), 94.0 (100); Exact mass calcd. for C$_{12}$H$_{20}$O$_2$: 196.1463; found: 196.1459; Anal. calcd. for C$_{12}$H$_{20}$O$_2$: C 73.43, H 10.27; found: C 73.20, H 10.16.

Silyl ethers (321)

Dry tert-butyldiphenylsilyl chloride (0.94 mL, 3.6 mmol) was added to a stirring mixture of diols (320) (0.65 g, 3.3 mmol) and imidazole (0.49 g, 7.3 mmol) in dry dimethylformamide (5.0 mL) at 25°C under an argon atmosphere. Stirring was continued for 2 hours before water (10 mL) was added and the reaction
mixture was extracted with ether and the combined organic layers were washed with hydrochloric acid (1.0 N), brine, and dried (Mg-SO₄). Upon removal of solvent under vacuo, the crude product was purified by column chromatography (silica gel, pet. ether:ether, 10:1) to give silyl ethers (321) (1.4 g, 99%). Rf 0.77 (pet. ether:ether, 1:1); $\nu_{\text{max}}$ (film): 3450, 3070, 2950, 1652, 1598, 896 cm⁻¹; $\delta$ (CDCl₃, 400 MHz): $^1$H-n.m.r. of one of the diastereomers: 1.09 (s, 9H, $^{t}$Bu), 3.71 (d, broad, 1H, RCH$_2$OH, J=10 Hz), 3.80-3.94 (m, 2H, RCH$_2$OSi), 4.68 (s, 1H, RC:CH$_2$H), 4.92 (s, 1H, RC:CH$_2$H), 7.34-7.47 (m, 5H, RC$_6$H$_5$), 7.65-7.74 (m, 5H, RC$_6$H$_5$); m/e (relative intensity): 434 (0.000, M$^+$), 377 (23.7), 360 (4.68), 313 (6.27), 289 (28.1), 255 (100); Exact mass calcd. for C$_{28}$H$_{38}$O$_2$Si: 434.2641; found: (not observed); Anal. calcd. for C$_{28}$H$_{38}$O$_2$Si: C 77.37, H 8.810; found: C 77.14, H 8.930.
Silylv ether esters (322)

Dry acetic anhydride (0.59 mL, 5.9 mmol) was added to a stirred solution of silyl ethers (321) (0.85 g, 2.0 mmol) and 4-dimethylaminopyridine (0.12 g, 0.98 mmol) in dry pyridine (15 mL) at 25°C under an argon atmosphere. Stirring was continued for 2.5 hours before water (15 mL) was added. The reaction mixture was extracted with ether, and the combined organic layer was washed with hydrochloric acid (1.0 N) and brine, and dried (MgSO₄). Upon removal of solvent under vacuo, the crude product was purified by a column chromatography (silica gel, pet. ether:ether, 15:1) to obtain silyl ether esters (322) (0.87 g, 93%) as a colorless oil. Rₜ 0.67 (pet. ether:ether, 9:1); ν max (film): 3078, 2966, 1736, 1651, 1591, 891 cm⁻¹; δ (CDCl₃, 400 MHz); ¹H-n.m.r. of one of the diastereomers: 1.06, (s, 3H, CH₃), 1.94 (s, 3H, CH₃), 3.58-3.67 (m, 2H, RCH₂OSi), 4.49 (s, 1H, RC:CHH), 4.77 (s, 1H, RC:CHH), 5.10-5.19 (m, 1H, RCHOAc), 7.34-7.46, 7.64-7.76 (m, m, 5H, 5H, RO-Si(C₆H₅)₂Bu); m/e (relative intensity): 476 (0.00, M⁺), 419 (2.92), 360 (3.07), 359 (9.90), 289 (44.1), 259 (20.2), 241 (21.7), 211
n-Tetrabutylammonium fluoride (17.6 mL, 1.0 M solution in tetrahydrofuran) was added to silyl ether esters (322) 0.84 g, 1.7 mmol) at 25°C under an argon atmosphere. Stirring was continued for 3 hours before water (10 mL) was added. The reaction mixture was extracted with ether, and the combined organic layers were washed with saturated sodium bicarbonate solution and brine, and dried (MgSO₄). Upon removal of solvent under vacuo, the crude product was purified by column chromatography (silica gel, pet. ether:ether, 5:1) to provide a mixture of hydroxy-acetates (324) (0.21 g, 52%) and hydroxy-acetates (323) (0.12 g, 30%) as colorless oils (324) Rf 0.32 (pet. ether:ether, 1:1); νmax (film): 3460, 2974, 1740, 1660, 204
899 cm\(^{-1}\); \(\delta (\text{CDCl}_3, 400 \text{ MHz})\): \(^1\text{H}-\text{n.m.r. of one of the diastereomers: } 1.01 (s, 3\text{H}, \text{CH}_3), 2.06 (s, 3\text{H}, \text{CH}_3), 3.61 (d, 1\text{H}, \text{RC}H-O\text{H}, J=12 \text{ Hz}), 4.25 (dd, 2\text{H}, \text{RC}H_2\text{OAc}, J=8 \text{ Hz}, 4 \text{ Hz}), 4.57 (s, 1\text{H}, \text{RC}:\text{CHH}), 4.86 (s, 1\text{H}, \text{RC}:\text{CHH}); \text{ m/e (relative intensity): } 238 (0.00, M^+)\), 220 (0.200), 178 (0.800), 151 (0.900), 136 (2.10), 122 (17.2), 117 (22.5), 105 (7.00), 89.0 (12.4), 94.0 (100); (323) \(R_f \) 0.13 (pet. ether:ether, 1:1); \(\nu_{\text{max}} \) (film): 3445, 2951, 1728, 1655, 890 cm\(^{-1}\); \(\delta (\text{CDCl}_3, 400 \text{ MHz})\): \(^1\text{H}-\text{n.m.r. of one of the diastereomers: } 1.11 (s, 3\text{H}, \text{CH}_3), 2.09 (s, 3\text{H}, \text{CH}_3), 3.40-3.49, 3.59-3.69 (m, m, 1\text{H}, 1\text{H}, \text{RC}H_2\text{OH}), 4.56 (s, 1\text{H}, \text{RC}:\text{CHH}), 5.00 (s, 1\text{H}, \text{RC}:\text{CHH}), 5.10 (dd, 1\text{H}, \text{RC}H\text{OAc}, J=12 \text{ Hz}, 2 \text{ Hz}); \text{ m/e (relative intensity): } 238 (0.100, M^+), 220 (0.100), 205 (0.200), 178 (13.8), 164 (6.10), 136 (50.5), 133 (15.7), 121 (26.5), 105 (12.6), 93.0 (89.1); \text{ Exact mass calcd. for } C_{14}H_{22}O_3: 238.1569; \text{ found: } 238.1550.

\text{Methoxyl-silyl ethers (325)}

\begin{align*}
\text{(321)} & \xrightarrow{\text{Ph}} \text{(325)}
\end{align*}

\text{At } 0^\circ \text{C, a solution of hydroxy-silyl ethers (321) (0.68 g, 1.6 mmol) in dry tetrahydrofuran (10 mL) under an argon atmosph-}

205
ere was added to a suspension of sodium hydride (38 mg, 1.6 mmol) in dry tetrahydrofuran (10 mL) followed by methyl iodide (0.22 g, 1.6 mmol). The resulting reaction mixture was then refluxed for 12 hours before water (10 mL) was carefully added. Extraction with ether was followed by washing with hydrochloric acid (1.0 N) and brine, and dried (MgSO₄). Upon removal of solvent the crude product was purified by column chromatography (silica gel, pet. ether:ether, 5:1) and provided methoxyl-silyl ethers (325) (0.68 g, 96%) as a colorless oil; υ_{max} (film): 3155, 2950, 1650, 1590, 890 cm⁻¹; δ (CDCl₃, 400 MHz): ¹H-n.m.r. of one of the diastereomers: 1.06 (s, 3H, CH₃), 3.36 (s, 3H, CH₃), 3.30-3.43 (m, 1H, RCHOMe), 3.89-4.07 (m, 2H, RCH₂OSi), 4.82 (s, 1H, RC:CHH), 4.84 (s, 1H, RC:CHH), 7.40-7.52, 4.70-4.79 (m, m, 5H, 5H, ROSi(C₆H₅)₂tBu); m/e (relative intensity): 448 (0.000, M⁺), 416 (0.300), 391 (2.50), 359 (29.0), 269 (5.50), 255 (7.70), 225 (18.9), 213 (46.7), 197 (27.5), 183 (62.3), 165 (15.7), 161 (58.1), 135 (78.3), 119 (38.4), 105 (93.0); Exact mass calcd. for C₂₉H₄₀O₂Si: 448.2797; found: (not observed); Anal. calcd. for C₂₉H₄₀O₂Si: C 77.62, H 8.990; found: C 77.88, H 8.900.
Methyl ether alcohols (326)

n-Tetrabutylammonium fluoride (5.7 mL, 1.0 M solution in tetrahydrofuran) was added to methoxyl-silyl ethers (325) (0.64 g, 1.4 mmol) at 25°C under an argon atmosphere. Stirring was continued for 1.5 hours before water (10 mL) was added. The reaction mixture was extracted with ether and the combined organic layers were washed with saturated sodium bicarbonate solution and brine, and dried (MgSO₄). Upon removal of solvent under vacuo, the crude product was purified by column chromatography (silica gel, pet. ether:ether, 10:1) to afford methyl ether alcohols (326) (0.24 g, 93%; based on recovered starting material). Rₓ 0.15 (pet. ether:ether, 3:2); Vₓₓ (film): 3368, 2950, 1643, 888 cm⁻¹; δ (CDCl₃, 400 MHz):

¹H-n.m.r. of one of the diastereomers: 1.07 (s, 3H, CH₃), 3.22 (dd, 1H, RCHOMe, J=10 Hz, 3 Hz), 3.41 (s, 3H, CH₃), 3.70-3.89 (m, 2H, RCHOH), 4.81 (s, 1H, RC:CHH), 4.84 (s, 1H, RC:CHH);
m/e (relative intensity): 180 (1.40), 178 (0.700), 178 (7.00), 93.0 (18.2), 92.0 (23.0), 89.0 (100); Exact mass calcd. for C₁₃H₂₂O₂: 210.1619; found: (not observed); Anal. calcd. for C₁₃H₂₂O₂: C 74.24, H 10.54; found: C 74.33, H 10.69.

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Bromo-olefin (260)

Bromine (0.30 mL) was added dropwise to a solution of triphenylphosphine (0.15 g, 0.57 mmol) in dry methylene chloride (7.0 mL) at 0°C under an argon atmosphere. To this pale yellowish reaction mixture was then added a solution of methyl ether alcohols (326) (90 mg, 0.38 mmol) in dry methylene chloride (5.0 mL) and stirring was continued for 15 minutes. After removal of solvent, the reaction mixture was extracted with pet. ether and the combined organic layers were then washed with sodium bisulfite solution and brine, and dried (MgSO4). Upon removal of solvent the crude product was purified by column chromatography (silica gel, pet. ether:ether, 10:1) to afford bromo-olefin (260) (0.22 g, 95%: based upon recovered starting material) as a colorless oil. Rf 0.91 (pet. ether:ether, 1:1); \( \nu_{\text{max}} \) (film): 2950, 1655, 900 cm\(^{-1}\); \( \delta \) (CDCl\(_3\), 400 MHz): \( ^1H \)-n.m.r. of one of the diastereomers: 1.04 (s, 3H, CH\(_3\)), 3.24 (dd, 1H, RCHOMe, J=5 Hz, 7 Hz), 3.44 (s, 3H, CH), 3.45-3.65 (m, 2H, RCH\(_2\)Br), 4.80 (s, 1H, RC:CHH), 4.85 (s, 1H, RC:CHH); m/e (relative intensity): 272/274 (1.50/1.30, M\(^+\)/M\(^+\)+2), 246 (6.20), 244 (7.40), 193 (0.70), 153 (94.3), 151 (100); Exact
mass calcd. for C<sub>13</sub>H<sub>21</sub>Br, 274.0755/272.0775; found: 274.0752/272.0775; Anal. calcd. for C<sub>13</sub>H<sub>21</sub>Br: C 57.15, H 7.75, Br 29.25; found: C 57.22, H 7.74, Br 29.10.

Methyl ether (331)

A mixture of bromo-olefin (260) (0.12 g, 0.44 mmol, 0.05 M) azobis-(isobutyronitrile) (0.02 mmol, 0.05 M), and tributyltin hydride (0.14 mL, 0.53 mmol, 0.05 M) as a benzene solution of appropriate molarity was refluxed under an argon atmosphere for 3 hours. Work-up was carried out by removal of benzene and the crude product was purified by column chromatography (silica gel, pet. ether:ether, 10:1) afforded methyl ether (331) (35.6 mg, 53%; based on recovered starting material). R<sub>f</sub> 0.89 (pet. ether:ether, 10:1); v<sub>max</sub> (film): 2936, 1382, 1102 cm<sup>-1</sup>; δ (CDCl<sub>3</sub>, 400 MHz): <sup>1</sup>H-n.m.r. of one of the diastereomers: 0.92 (s, 3H, CH<sub>3</sub>), 2.93 (t, 1H, RC<sub>H</sub>OMe, J=4 Hz), 3.29 (s, 3H, CH<sub>3</sub>); m/e (relative intensity): 194 (18.0, M<sup>+</sup>), 179 (5.60),
166 (18.6), 165 (5.30), 162 (10.6), 134 (100); **Exact mass**
calcd. for $\text{C}_{13}\text{H}_{22}\text{O}$: 194.1670; found: 194.1667.
Chapter 3

A Synthetic Approach to the A,B Ring System of Terpenoids
3.1.0. INTRODUCTION

While several research groups have reported synthetic approaches to the A,B structural sub-unit (322) [110] of some specific terpenoids, a general enantiospecific synthetic route has not yet been reported.

\[
\begin{align*}
\text{(322)}
\end{align*}
\]

A general synthetic route to terpenoids containing this A,B structural sub-unit (322) must have the potential to produce compounds in which the \(R_1\) and \(R_2\) groups could be elaborated to the remainder of a specific terpenoid. In addition, a general synthetic route should be capable of producing compounds with oxygen functionality at the C(1), C(3) and (7) positions. This chapter describes an evaluation of the potential use of (+)-5,6-dehydrocamphor (323) as a chiral synthon in the enantiospecific synthesis of selected sesquiterpenoids, diterpenoids, sesterterpenoids, and triterpenoids (Scheme 96).

The basic feature of our general synthetic approach is the initial conversion of (+)-5,6-dehydrocamphor (323) to various tertiary alcohols (325) by treatment with
Sesquiterpenoids

Polygodial

Warburganal

Cinnamodial

Nordrimenone

Diterpenoids

Cassaic acid

Manool

Forskolin

Sesterterpenoid

Cheilanthtriol

Triterpenoids

Lanosterol

Tetrahymanol

Scheme 96

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appropriate alkenyl Grignard reagents (324). The alkoxides (326) derived from these tertiary alcohols (325) would be expected to undergo anionic oxy-Cope rearrangement, the products of which could be subsequently transformed to the conjugated enones (328). Finally, stereoselective introduction of an angular methyl group at the C(10) position could provide (329) (Scheme 97) which could then serve as a key intermediate in the synthesis of specific compounds belonging to the various classes of terpenoids shown above (cf. Scheme 96).

The synthesis of alkenyl halides and alkenyl Grignard reagents has received considerable attention and a variety of these compounds (Scheme 98) [111] could be used synthetically to gain access to a variety of intermediates, represented by structure (329).
Scheme 97
Scheme 98
3.2.0. DISCUSSION AND RESULTS

The anionic oxy-Cope rearrangement has become firmly established [112] as an important reaction in synthetic methodology. Alkoxides derived from norbornenone derivatives (336), (338), (340), and (342) undergo this rearrangement and provide compounds (337) [113], (339) [114], (341) [115], and (343) [116] which have been used as key intermediates in natural product synthesis (Scheme 99). The development in our laboratory of a simple synthesis of either (-) or (+)-5,6-dehydrocamphor (323) led us to consider that anionic oxy-Cope rearrangement of alkoxides derived from this compound would provide bicyclic ketone (327) (cf. Scheme 97), which could serve as a chiral intermediate in a general enantiospecific synthetic approach to a wide variety of terpenoids.

Literature routes to 5,6-dehydrocamphor involve five to nine steps [117], and therefore we devised an alternative two step procedure [21] which involves acid-catalysed rearrangement of (+)-endo-3-bromocamphor (41) to (-)-endo-6-bromocamphor (40), followed by dehydrohalogenation. The remarkable rearrangement of (+)-endo-3-bromocamphor (41) to (-)-endo-6-bromocamphor (40) is based on an earlier report by Nishikawa and co-workers [118] who described the rearrangement of (+)-3,9-dibromocamphor (344) to (-)-6,9-dibromocamphor (345), but noted that the corresponding reaction with (+)-3-endo-brocamphor (41) in fuming sulfuric acid resulted only in C(9)-sulfonation (Scheme 100). In contrast, we discovered that
Scheme 99

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treatment of (+)-endo-3-bromocamphor (41) with chlorosulfonic acid for 15 minutes at 20°C provided (−)-endo-6-bromocamphor (40) in about 50% yield (Scheme 101). It seems reasonable to assume that the mechanism of this remarkable rearrangement (Scheme 102), which converts (+)-endo-3-bromocamphor (41) to (−)-endo-6-bromocamphor (40) or (+)-endo-3,9-dibromocamphor (344) to (−)-endo-6,9-dibromocamphor (345) is analogous to that proposed for the acid-catalysed racemisation of (+)-camphor (28) (cf. Scheme 102). Support for this view is provided by our observation that (+)-endo-3-bromo-10-deuterio-camphor (346; *=^2H, Scheme 106) rearranges to (−)-endo-bromo-8-deuteriocamphor (347; *=^2H, Scheme 102). The structure of
Reagents and conditions:
(i) HSO₃Cl; (ii) KOH, DMSO, H₂O, 100°C.

Scheme 101

this latter compound (347) was confirmed by ¹H-n.m.r. (400 MHz), and by its conversion to (-)-8-deuteriocamphor (348, *=²H, Scheme 102) [21,119].

Dehydrobromination of (-)-endo-6-bromocamphor (40) with potassium hydroxide/dimethyl sulfoxide/water provided (+)-5,6-dehydrocamphor (323), and therefore an opportunity to prepare a series of chiral alkoxides which could undergo the anionic oxy-Cope rearrangement. α-Campholenic acid (360) was also produced in this reaction, by cleavage of the β-bromo-ketone functionality in (-)-endo-6-bromocamphor (40).

In our initial investigation we discovered that, in contrast with (+)-camphor (26) [120], addition of vinylmagnesium bromide to (+)-5,6-dehydrocamphor (323) occurs in excellent yield (99%) to provide 2-vinyl-5,6-dehydroisoborneol (361).
Scheme 102

X = Y = H (26)
X = Br, Y = H (346)
X = Y = Br (349)

X = Y = H (348)
X = Br, Y = H (347)
X = Y = Br (350)
Reagents and conditions:

(i) Vinyl Magnesium Bromide, THF, (or 2-Bromo-propenyl-Magnesium Bromide, THF); (ii) KH, THF; (iii) LAH, THF, (or L-Selectride, THF, -78°C); (iv) Ac₂O, 4-DMAP, Pyridine, (or KH, MeI,THF); (v) O₃, CH₂Cl₂, CH₃OH; (vi) PPh₃; (vii) PhH, p-Toluenesulfonic acid.

Scheme 103

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Treatment of (361) with potassium hydride in tetrahydrofuran at room temperature for about 10 minutes promoted the anionic oxy-Cope rearrangement of alkoxide (362) and led to the formation of cis-bicyclic ketone (364) in about 95% yield. Stereoselective reduction of (364) with L-selectride in tetrahydrofuran at -78°C afforded a mixture of epimeric alcohols (365a:365b; ratio 6:1) (page 285) which were then treated with acetic anhydride and dimethylaminopyridine in pyridine to provide the corresponding acetates (366a:366b; ratio 6:1) (cf. page 286). The stereochemistry of the acetate groups in (366a,b) was deduced from the splitting pattern of the signal (1H-n.m.r.) associated with the CHOAc group in each compound (page 286). The stereoselectivity of the reduction leading to epimeric alcohols (365a,b) is governed by the fact that addition of L-selectride to the carbonyl group is sterically hindered by α-axial hydrogen atoms. In contrast, addition of a less bulky hydride reducing agent (lithium aluminum hydride), occurs with the opposite stereoselectivity to provide (365a:365b; ratio 1:3). In this case the steric factor is less important and addition is presumably governed by torsional strain (Scheme 104).

Ozonolysis of (366a,b) in methanol and methylene chloride (1:1), followed by reductive work-up with triphenylphosphine provided crude keto-aldehydes (377a,b) which were then treated with a catalytic amount of p-toluenesulfonic acid in refluxing benzene to provide bicyclic enones (368a,b) in
L-Selectride:

\[ \text{LiAlH}_4: \]

\[ \text{Torsional strain:} \]

Scheme 104
about 60% overall yield from \(368a,b\).

When \((+)-5,6\)-dehydrocamphor \(323\) was treated with 2-propenylmagnesium bromide in refluxing tetrahydrofuran for 2.5 hours, anionic oxy-Cope rearrangement occurred in situ and diastereomeric bicyclic ketones \(373a,b\) were obtained directly in about 80% yield. At room temperature, however, the product (ca. 80% yield) was a mixture (ratio ca. 2:1) of bicyclic ketones \(373a,b\) and the expected tertiary alcohol \(370\). Treatment of compound \(370\) with potassium hydride in tetrahydrofuran at 20°C for five minutes provided the bicyclic ketones \(373a,b\) (ratio ca. 2:1) in about 90% yield. Although the stereochemistry of the methyl group at C(8) is not unique, our synthetic plan envisages subsequent control at this center (cf. page 240). Hydride reduction of \(373a,b\) followed by treatment with potassium hydride and methyl iodide in tetrahydrofuran provided \(375a,b\). Subsequent
conversion of (375a,b) to bicyclic enones (376a,b) was accomplished by ring cleavage and intramolecular aldol condensation as described above (Scheme 103).

The stereochemistry at C(10) in bicyclic enones (368a,b) and (376a,b), and (369a,b) was not established at this stage of our synthetic route, and attempts to prepare a suitable crystalline derivative of either compound (381) [122] or (383) (Scheme 105) for x-ray analysis are continuing in the laboratory.

![Scheme 105](image)

**Reagents and conditions:**

(i) NaBH₄, CeCl₃·7H₂O, CH₃OH; (ii) p-Bromobenzoyl Chloride, Pyridine; (iii) H₂, Pd/C, Hexane; (iv) H₂SO₄, 2,4-Dinitrophenylhydrazine, Ethanol.

Scheme 105

Indirect evidence has been obtained (page 235) to support the trans stereochemistry at the ring junction in enones (368a,b), (369a,b), and (376a,b).
With the enones available, both a cyclopropanation approach and an anionic oxy-Cope rearrangement approach were carried out in the attempt to introduce the required angular methyl group at the C(10) position of the A,B structural sub-unit (322).
The next objective in our synthetic route was the introduction of an angular methyl group at the C(10) position. In our initial approach (Scheme 106), Simmons-Smith cyclopropanation (Et₂Zn/CH₂I₂/Toluene) [75] of the deconjugated ketal (384a,b) derived from enones (368a,b) [123,112e] provided the cyclopropane derivatives (385a,b) in 85% yield. In this reaction, methylene carbene can add either from β or α face of the double bond to provide (β-385a) and (α-385b) respectively (Scheme 107). One approach to control the stereochemistry of this cyclopropanation reaction would be to use intermediate

Reagents and conditions:
(i) H⁺, EG, PhH; (ii) CH₂I₂, Et₂Zn, PhCH₃; (iii) PtO₂, H₂.

Scheme 106
Scheme 107

(387) (Scheme 108), derived from an appropriate alkenyl Grignard reagent. This would present the opportunity to carry out a hydroxyl-directed cyclopropanation reaction.

Scheme 108
Hydrogenolysis of (385a,b) in the presence of PtO$_2$ in ethanol at 2.5 atmosphere was unsuccessful. Increasing the hydrogen pressure was also found ineffective, although further investigations in this area are anticipated. Acid-catalysed ring opening of cyclopropane derivatives has previously been reported. For example, Grieco et al. [124] have shown that treatment of cyclopropyl ketal (390) with perchloric acid, ring cleaved product (391) was obtained (Scheme 109). When (385a,b) was treated with perchloric acid in methylene chloride, enone (392) was isolated in 82% yield (Scheme 110). The structure and absolute configuration of this product were deduced from $^1$H-n.m.r. spectrum (page 286) and confirmed by X-ray crystallographic analysis (page 287) [88].
The formation of (392) presumably involves protonation of the cyclopropane ring of (385a,b), followed by ring opening to provide the tertiary carbocation (393) rather than the secondary carbocation (395). Independent hydrolysis of the ketal functionality (393) then provided enone (392) (Scheme 111).

In future investigations attempts will be made to cleave the dibromocyclopropane ring (397) under basic conditions (Scheme 112). Another possible approach is outlined in Scheme 113, which features a Wharton reaction [125] of hydrazone (402) followed by a silyloxydihaloxypropanation reaction [126].
It is expected that basic hydrolysis of (404) would then reveal the A,B structural sub-unit with the angular methyl group introduced.
An alternative means of introducing the angular methyl group at the C(10) position is to synthesise the 1,5-dienols (409a,b) with the expectation that it would undergo anionic oxy-Cope rearrangement to provide ketones (410a,b) (Scheme 114).

![Diagram of chemical structures]

Reagents and conditions:
(i) LDA, THF-HMPA, -78°C; AcOH, Et₂O, -78°C; (ii) Vinyl Magnesium Bromide, THF; (iii) (a) KH, THF, 25°C; (b) KH, THF-HMPA, Reflux; (c) KH, THF, 15-Crown-5, Reflux; (d) KH, KH, HMPA, 200°C.

Scheme 114

118). The preparation of 1,5-dienols (409a,b) were carried out by first deconjugating the bicyclic enones (369a,b) with lithium diisopropylamide in tetrahydrofuran followed by kinetic quenching with glacial acetic acid [123] to provide ketones (408a,b). It is interesting to note that an attempt to decon-
jugate bicyclic enones (368a,b) in this way led to the formation of a dimer (411) (Scheme 115) whose structure and absolute configuration were established by X-ray crystallographic analysis [68] (page 287). Incidentally, this result provides indirect evidence for the trans stereochemistry of the enones (368a,b), (369a,b), and (376a,b) (cf. page 226).

In order to avoid this complication, the methyl ether protecting group was used instead of the acetates. Enone methyl ethers (369a,b) were deconjugated to provide the enones (408a,b), which reacted with vinylmagnesium bromide in tetrahydrofuran to provide 1,5-dienols (409a,b) in 80% yield. This was then treated with potassium hydride in tetrahydrofuran at 25°C, but starting material was recovered completely. More vigorous reaction conditions (KH/15-crown-5 ether/HMPA/heat or KH/HMPA/200°C) also failed to promote conversion of (409a,b) to bicyclic ketones (410a,b). At this stage we consider that the failure of (409a,b) to undergo anionic oxy-Cope rearrangement is due to 1,3-diaxial steric interaction between a methyl
Scheme 117
group and the developing vinyl group in the transition state (Scheme 116). That anionic oxy-Cope rearrangements can be inhibited by steric factors has been clearly established by previous investigations. For example, the steroid intermediate (412) having the (E)-configuration underwent anionic oxy-Cope rearrangement to provide (414), while the corresponding (Z)-isomer (416), failed to produce any rearranged products. It has been suggested that this is due to the "quasi-1,3-diaxial interaction" between C(16)-O-K⁺ and C(20)-CH₃ (Scheme 121) [117]. It has also been shown that treatment of (417) with potassium hydride in tetrahydrofuran provided (418) in 78% yield (Scheme 118). In contrast, similar treatment of (419) provided (420) in only 11% yield [112b]. In the
latter case, 1,3-diaxial interactions between methyl group in the transition state (419a) can be invoked to explain the poor yield.

In addition to these investigations concerning the stereoselective introduction of angular methyl substituents into intermediates (368a,b), (369a,b) and (376a,b), it is worth noting that bicyclic ketones (373a,b) have considerable potential as chiral intermediates in the synthesis of spirodysin (421),
a marine natural product. Scheme 119 illustrates a possible synthetic route from (373a,b) to an intermediate ester (428) by allylic oxidation of the vinylic methyl group of (424). It is expected that this compound could then be chemically transformed to spirodysin (421). The scheme would also represents a formal synthesis of the marine natural products, furodysin (422) and furodysinin (423) since R. J. Wells and co-workers [128] have previously demonstrated that spirodysin (421) can be converted to furodysin (422) and furodysinin (423) (1:1) in the presence of BF$_3$-etherate in benzene (Scheme 120).

![Scheme 120](image)

In conclusion, we have investigated the potential use of (+)-5,6-dehydrocamphor (323) as a chiral synthon in terpenoid synthesis, and, as a result, have developed a synthetic route to bicyclic ketones (373a,b) and bicyclic enones (368a,b), (369a,b) and (376a,b). Attempts have been made to introduce angular functionality into the C(10) position of bicyclic
Scheme 119

(373a,b) \rightarrow (424) \rightarrow (430)

\[ \rightarrow \]

(432) \rightarrow (425) \rightarrow (431)

\[ \rightarrow \]

(433) \rightarrow (421)

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enones (368a,b), (389a,b), and (376a,b), but so far these have been unsuccessful. However, alternative synthetic routes to this research objective are being investigated. In addition, bicyclic ketones (373a,b) are being evaluated as intermediates in the enantiospecific synthesis of spirodysin (421), and, indirectly to the synthesis of furodysin (422) and furodysinin (423).
3.3.0. **EXPERIMENTAL** (cf. page 88)
(−)-6-endo-Bromocamphor (40)

(+)-3-endo-Bromocamphor (41) (55.0 g, 238 mmol) (Aldrich Chemical Co.) in chlorosulfonic acid (180 mL) was stirred at 55°C for 15 minutes and then poured onto ice. After extraction with ether, the combined organic layers were washed with saturated sodium bicarbonate solution and brine, and dried (MgSO₄). Removal of the solvent under vacuo provided a crude solid which was purified by column chromatography (silica gel, pet. ether:ether, 15:1) to provide (−)-6-endo-bromocamphor (40) (27 g, 50%) as a white crystalline solid. Rf 0.53 (pet. ether:ether, 4:1); mp 56°C (sealed tube); [α]D²⁵ = -51.8° (c 4.96, CH₂Cl₂); νmax (film): 1745 cm⁻¹; δ (CDCl₃, 400MHz): 0.92 (s, 3H, CH₃), 0.98 (s, 3H, CH₃), 1.00 (s, 3H, CH₃), 4.22 (dd, 1H, RCHBr, J=3.5 Hz, 10 Hz); m/e (relative intensity): 230/232 (1.8 0/1·20, M⁺/M⁺+2), 167 (11.0), 151 (39.0), 149 (30.0), 109(100); Exact mass calcd. for C₁₀H₁₅OBr: 230.0306/232.0286; found (high resolution mass spectrometry): 230.0303/232.0274; Anal. calcd. for C₁₀H₁₅OBr: C 51.97, H 8.54, Br 34.57; found: C 51.93, H 6.45, Br 34.88.
(+) 5.6-Dehydrocamphor (323)

(-)-6-endo-Bromocamphor (40) (7.0 g, 30 mmol), potassium hydroxide (8.33 g, 143 mmol), dimethyl sulfoxide (250 mL) and water (50 mL) were stirred together at 100°C for 16 hours. Upon cooling, the reaction mixture was diluted with water, extracted with ether and the combined organic layers were washed with brine and dried (MgSO₄). Upon removal of solvent under vacuo, the crude product was purified by column chromatography (silica gel, pet. ether:ether, 15:1) to afford (+)-5,6-dehydrocamphor (323) (2.4 g, 50%) as a white solid; mp 149-151°C (sealed tube) (lit. [117] mp 148°C for enantiomer); Rf 0.68 (petroleum ether:ether, 4:1); [α]²⁵ +756° (c 0.500, CH₂Cl₂), (lit. [α]D -735° (c 1.00, EtOH) for enantiomer [117]); V max (CHCl₃): 1735 cm⁻¹; δ (CDCl₃, 400 MHz): 0.91 (s, 3H, CH₃), 1.01 (s, 3H, CH₃), 1.07 (s, 3H, CH₃), 5.58 (d, 1H, C(6)H, J=6 Hz), 6.45 (dd, 1H, C(5)H, J=6 Hz, 3 Hz); m/e (relative intensity): 150 (12.0, M⁺), 93.0 (58.0), 85.0 (59.0), 71.0 (92.0), 69.0 (100); Exact mass calcd. for C₁₀H₁₄O: 150.1045; found: 150.1049;
Dienol (361)

To a stirred solution of (+)-5,6-dehydrocamphor (323) (9.2 g, 61 mmol) in dry tetrahydrofuran (50 mL) at 0°C under an argon atmosphere was added vinyl magnesium bromide solution (1.0 M in THF, Aldrich Chemical Co.) (184 mL 184 mmol) dropwise. After the completion of the addition, the ice bath was removed and stirring was continued at 25°C for 2.5 hours before saturated aqueous ammonium chloride (50 mL) was very carefully added. Following extraction with ether, the combined organic layers were washed with hydrochloric acid (0.5 N), brine, and dried (MgSO₄). Removal of solvent under vacuo provided the dienol (361) (11 g, 99%) as a pale yellow oil which was used directly for the anionic oxy-Cope rearrangement without further purification. Rf 0.44 (pet. ether:ether, 4:1).

νₘₐₓ (film): 349, 2975, 1637, 1584 cm⁻¹; δ (CDCl₃, 400MHz):
0.93 (s, 3H, CH₃), 0.95 (s, 3H, CH₃), 1.20 (s, 3H, CH₃), 5.01 (dd, 1H, Ḧb, J=10 Hz, 2 Hz), 5.16 (dd, 1H, Ḧa, J=18 Hz, 2 Hz), 5.62 (d, 1H, Ḧc, J=6 Hz), 5.85 (dd, 1H, Ḧo, J=10 Hz, 18 Hz), 6.01 (dd, 1H, Ḧd, J=4 Hz, 6 Hz); m/e (relative intensity):
178 (0.990, M⁺), 163 (2.70), 161 (0.500), 145 (2.51), 135 (2.28), 108 (98.5), 93.0 (100); **Exact mass** calcd. for C₁₂H₁₈O: 178.2762; found: 178.1362; **Anal.** calcd. for C₁₂H₁₈O: C 80.85, H 10.18; found: C 81.00, H 10.23.

**Bicyclic ketone (364)**

![Bicyclic ketone](image)

To a stirred mixture of potassium hydride (0.71 g, 18 mmol) in dry tetrahydrofuran (20 mL) at 25°C under an argon atmosphere was introduced a solution of dienol (361) (2.1 g, 12 mmol). Stirring was continued for 10 minutes before propanol (5.0 mL) was very carefully added. After dilution with water (25 mL) followed by extraction with ether, the combined organic layers were washed with hydrochloric acid (1.0 N) and brine, and dried (MgSO₄). Removal of solvent under vacuo, the crude product was purified by column chromatography (silica gel, pet. ether:ether, 10:1) to provide bicyclic ketone (364) (2.0 g, 95%) as a colorless oil. Rₐ 0.6 (pet. ether: ether, 4:1); [α]₂⁵° -119° (c 0.550, CHCl₃); νₘₐₓ (film): 2990, 1715, 1662 cm⁻¹; δ (CDCl₃, 400MHz): 0.93 (s, 3H, CH₃), 1.03
(s, 3H, CH₃), 1.62 (t, 3H, CH₃, J=2.0 Hz), 5.16 (t, 1H, RHC:CR, J=2.0 Hz); m/e (relative intensity): 178 (35.8, M⁺), 164 (12.2), 163 (100); Exact mass calcd. for C₁₂H₁₈O: 178.2762; found: 178.2759;

Bicyclic Alcohols (365a,b)

At -78°C, under an argon atmosphere, L-selectride (27 mL, 19 mmol; 1.0 M in THF, Aldrich Chemical Co.) was slowly added to a stirred solution of bicyclic ketone (364) (1.1 g, 6.2 mmol) in THF (20 mL). After 1.5 hours, the reaction was quenched at -78°C with H₂O (5.0 mL) carefully. H₂O₂ (30 Wt.% solution in H₂O (2.0 mL) was added and the mixture was extracted with ether. The combined organic layers were washed with hydrochloric acid (1.0 N), and brine and dried (MgSO₄). Upon removal of solvent under vacuo, the crude product was purified by column chromatography (silica gel; pet. ether:ether, 8:1) to provide a mixture of epimeric bicyclic alcohols (365a, b) (1.0 g, 90%) as a colorless oil. The ratio of the epimeric alcohols was determined from ¹H-n.m.r. proton integration to be 6:1. Rf
0.34 (pet. ether:ether, 1:1); $\nu_{\text{max}}$ (film): 3375, 2943, 1650 cm$^{-1}$; \( \delta \) (CDCl$_3$, 400MHz): $^1$H-n.m.r. of major diastereomer: 0.94 (s, 3H, CH$_3$), 0.97 (s, 3H, CH$_3$), 1.63 (t, 3H, CH$_3$, J = 2.0 Hz), 3.80-3.90 (m, 1H, RCH$_2$OH), 5.25 (s, 1H, RHC=CR);

m/e (relative intensity): 180 (63.8), 179 (11.2), 165 (16.9), 162 (12.1), 147 (100); **Exact mass** calcd. for C$_{12}$H$_{20}$O: 180.2922; found: 180.1510.

**Bicyclic Acetates (366a,b)**

\[ \text{Dry acetic anhydride (0.69 mL, 7.3 mmol) was added to a} \]
\[ \text{stirred solution of epimeric bicyclic alcohols (365a,b) (0.44} \]
\[ \text{g, 2.4 mmol) and 4-dimethylaminopyridine (0.15 g, 1.2 mmol) in} \]
\[ \text{dry pyridine (15 mL) at 25°C under an argon atmosphere.} \]
\[ \text{Stirring was continued for 3 hours before water (20 mL) was} \]
\[ \text{The reaction mixture was extracted with ether, and the} \]
\[ \text{combined organic layers were washed with hydrochloric acid} \]
\[ \text{(1.0 N) and brine, and dried (MgSO$_4$). Upon removal of solvent} \]
\[ \text{under vacuo, the crude product was purified by column chromatography (silica gel, pet. ether: ether, 10:1) to give a} \]

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mixture of epimeric bicyclic acetates (366a,b) (0.53 g, 98%) as a colorless oil. \( R_f = 0.55 \) (pet. ether:ether, 4:1). \( \nu_{\text{max}} \) (film): 2957, 1735 cm\(^{-1}\); \( \delta \) (CDCl\(_3\), 400MHz): \( ^1H \) n.m.r. of major diastereomer: 0.97 (s, 3H, CH\(_3\)), 0.98 (s, 3H, CH\(_3\)), 1.60 (t, 3H, CH\(_3\), J=2.0 Hz), 2.04 (s, 3H, CH\(_3\)), 4.88-4.97 (m, 1H, RHC\(_2\)COAc), 5.22 (s, 1H, RHC:CR); m/e (relative intensity): 222 (1.08, M\(^+\)), 217 (3.23), 162 (40.4), 147 (61.1), 145 (20.8), 121 (100); Exact mass calcd. for C\(_{14}\)H\(_{22}\)O\(_2\): 222.1619; found: 222.1607; Anal. calcd. for C\(_{14}\)H\(_{12}\)O\(_2\): C 75.63, H 9.97; found: C 75.57, H 10.07.

**Bicyclic enones (368a,b)**

\[ \text{R}_1=H, \text{R}_2=O\text{Ac} \quad (366a) \]
\[ \text{R}_1=O\text{Ac}, \text{R}_2=H \quad (366b) \]

At -78\(^\circ\)C, ozone (condition: E= 80 V, air inlet= 8.0 psi, ozone outlet= 0.06 psi) was allowed to pass through a stirred solution of bicyclic acetates (366a,b) (0.95 g, 4.3 mmol) in dry dichloromethane (20 mL) and methanol (20 mL) until persistent blue color was obtained. The mixture was gradually warmed to about -25\(^\circ\)C under an argon atmosphere and triphenylphosphine (1.1 g, 4.3 mmol) was added. Stirring was continued at
-25°C for 2.5 hours and at 25°C for 0.5 hour. Following removal of solvent under vacuo, the crude keto-aldehydes (377a,b) ($\nu_{\text{max}}$ 2820, 1730 cm$^{-1}$) were dissolved in dry benzene (40 mL). p-Toluenesulfonic acid (100 mg) was added, and the resulting mixture was refluxed for 4 hours in a Dean-Stark apparatus. After cooling and extraction with ether, the combined organic layers were washed with saturated sodium bicarbonate solution, and brine, and dried (MgSO$_4$). Upon removal of solvent under vacuo, the crude product was purified by column chromatography (silica gel, pet. ether:ether,10:1) to provide bicyclic enones (368a,b) (0.54g, 60%) as a colorless oil. $R_f$ 0.68 (pet. ether:ether,1:1); $\nu_{\text{max}}$ (film): 2950, 1735, 1678, 1380, 1368 cm$^{-1}$; $\delta$ (CDCl$_3$, 400MHz): $^1$H-n.m.r. of major diastereomer: 1.05 (s, 3H, CH$_3$), 1.21 (s, 3H, CH$_3$), 2.07 (s, 3H, CH$_3$), 5.05 (t, 1H, R$_2$CHOAc, J=3 Hz), 5.96 (dd, 1H, O:R'CH:CHR', J=10 Hz, 3 Hz), 6.57 (d, 1H, O:CHR:CHR', J=10 Hz): m/e (relative intensity): 236 (24.1, M$^+$), 198 (1.90), 194 (10.2), 193 (2.90), 176 (100); Exact mass calcd. for $C_{14}H_{20}O_3$: 236.1535; found: 236.1416; Anal. calcd. for $C_{14}H_{20}O_3$: C 71.16, H 8.53; found: C 71.30, H 8.66.
Bicyclic ketals (384a,b)

\[ \begin{align*}
  \text{H} & \quad \text{OAc} \\
  (368a,b) & \quad \rightarrow \\
  (384a,b) & \quad + \quad (427a,b)
\end{align*} \]

p-Toluenesulfonic acid (5.0 mg) was added to a stirred solution of bicyclic enones (368a,b) (0.10 g, 0.50 mmol) in freshly distilled ethylene glycol (0.30 mL, 50 mmol) and dry benzene (20 mL) under an argon atmosphere. The resulting mixture was refluxed for 20 hours in a Dean-Stark apparatus. After cooling and extraction with ether, the combined organic layers were washed with saturated sodium bicarbonate solution, and brine and dried (MgSO\(_4\)). Upon removal of solvent under vacuo, the crude product was purified by column chromatography (silica gel, pet. ether:ether,15:1) to provide a mixture of bicyclic ketals (384a,b) (96 mg, 70%) and bicyclic ketal alcohols (427a,b) (24 mg) as a colorless oil. (384a,b): R\(_f\) 0.63 (pet. ether:ether,1:1); \(\nu\)\(_{max}\) (film): 2950, 1735, 1382 cm\(^{-1}\); \(\delta\) (CDCl\(_3\), 400MHz): \(^1\text{H}-\text{n.m.r.}\) of major diastereomer: 0.86 (s, 3H, CH\(_3\)), 0.93 (s, 3H, CH\(_3\)), 2.06 (s, 3H, CH\(_3\)), 3.85-4.00 (m, 4H, ROCH\(_2\)CH\(_2\)-O-R), 5.18 (t, 1H, RCHOAc, J=3 Hz), 5.29 (dd, 1H, RHC:CR\(_2\), J=5 Hz, 2 Hz); m/e (relative intensity): 280 (2.50, M\(^+\)), 239 (3.20), 220 (6.90), 205 (2.30),
177 (52.5), 114 (100); Exact mass calcd. for $C_{16}H_{24}O_4$: 280.1674; found: 280.1668; Anal. calcd. for $C_{16}H_{24}O_4$: C 68.55, H 8.63, found: C 68.28, H 8.86. (427a,b): $R_f$ 0.14 (pet. ether: ether, 1:1); $\nu_{\text{max}}$ (film): 3408, 2943, 1384 cm$^{-1}$; $\delta$ (CDCl$_3$, 400 MHz): $^1$H-n.m.r. of major diastereomer: 0.87 (s, 3H, CH$_3$), 0.94 (s, 3H, CH$_3$), 3.87-4.00 (m, 4H, ROCH$_2$CH$_2$OR), 4.21 (t, 1H, R$_2$CHOH, J=3 Hz), 5.26 (s, 1H, R'HC:CR"R"'); m/e (relative intensity): 238 (4.30, M$^+$), 220 (0.50), 195 (35.00), 151 (15.1), 114 (100); Exact mass calcd. for $C_{14}H_{22}O_3$: 238.1568; found: 238.1563.

Bicyclic ketals (384a,b)

Dry acetic anhydride (0.09 mL, 0.97 mmol) was added to a mixture of bicyclic ketal alcohols (427a,b) (0.12 g, 0.48 mmol) and 4-dimethylaminopyridine (30 mg, 0.24 mmol) in dry pyridine (10 mL) at 25°C under an argon atmosphere. Stirring was continued for 3 hours before water (20 mL) was added. The reaction mixture was extracted with ether and the combined organ-
ic layers were washed with hydrochloric acid (1.0 N) and brine, and dried (MgSO₄). Removal of solvent under vacuo followed by column chromatography (silica gel, pet. ether: ether, 10:1) afforded bicyclic ketals (384a,b) (0.13 g, 97%) as a colorless oil.

**Cyclopropyl-ketals (385a,b)**

![Diagram of cyclization](image)

To a well stirred, heated (60°C) solution of bicyclic ketals (384a,b) (0.07 g, 0.27 mmol) in dry toluene (5.0 mL) was added successively a solution of diethylzinc (0.38 mL, 0.38 mmol, 25% w/v) and methylene iodide (0.03 mL, 0.38 mmol). Stirring was continued at 60°C under an argon atmosphere for 6 hours. After cooling, hydrochloric acid (0.5 N) was carefully added and the mixture was extracted with ether. The combined organic layers were washed with hydrochloric acid (0.5 N) and brine, and dried (MgSO₄). Upon removal of solvent under vacuo, the crude product was purified by column chromatography (silica gel, pet. ether:ether, 20:1) to provide cyclopropyl ketals (385a,b) (65 mg, 94%; based on the reco-
vered starting material); as a colorless oil. $R_f$ 0.71 (pet. ether:ether, 1:1); $\nu_{\text{max}}$ (film): 3050, 2950, 1730, 1380 cm$^{-1}$; $\delta$ (CDCl$_3$, 400MHz): $^1$H-n.m.r. of major diastereomer: 0.33-0.54 (m, 3H, H$_2$CRCHR'), 0.76 (s, 3H, CH$_3$), 1.01 (s, 3H, CH$_3$), 2.05 (s, 3H, CH$_3$), 3.68-3.98 (m, 4H, ROCH$_2$CH$_2$OR), 5.20-5.26 (m, 1H, RCHOAc).

**Enone (392)**

![Chemical structure](image)

To a stirred solution of cyclopropyl-ketals (385a,b) (60 mg, 0.20 mmol) in dry dichloromethane (10 mL) at 0°C under an argon atmosphere was added perchloric acid (1.0 mL) dropwise. Stirring was continued for 4 hours before water (10 mL) was added. Following extraction with ether, the combined organic layers were washed with saturated sodium bicarbonate solution and brine and dried (MgSO$_4$). Upon removal of solvent under vacuo, the crude product was purified by column chromatography (silica gel, pet. ether:ether, 10:1) to provide enone (392) (41 mg, 82%) as a white solid. Recrystallisation from pet. ether: ether, 10:1) afforded colorless prisms, mp 150-152°C. $R_f$
0.49 (pet. ether:ether,1:1); $\nu_{\text{max}}$ (CHCl$_3$): 2986, 1726, 1662, 1387, 1371 cm$^{-1}$; $\delta$ (CDCl$_3$, 400MHz): 0.94 (s, 3H, CH$_3$), 1.07 (s, 3H, CH$_3$), 2.05 (s, 3H, CH$_3$), 5.19 (t, 1H, RCHOAc, $J$=3 Hz), 5.83 (s, 1H, HRCRCH$_3$); m/e (relative intensity): 250 (20.3, M$^+$), 190 (52.1), 175 (34.5), 162 (26.5), 147 (51.0), 121 (54.0), 108 (68.2), 93 (69.5); Exact mass calcd. for C$_{15}$H$_{22}$O$_3$: 250.1568; found: 250.1571; Anal. calcd. for C$_{15}$H$_{22}$O$_3$: C 71.97, H 8.860; found: C 71.69, H 8.700.

**Bicyclic ketones (373a,b)**

![Diagram](image)

A 3-neck flask fitted with a condenser was charged with freshly crushed magnesium turnings (1.73 g, 70.9 mmol) in dry tetrahydrofuran (35 mL) and a crystal of iodine. The reaction mixture was stirred vigorously under an argon atmosphere at room temperature, and a solution of 2-bromopropene in dry tetrahydrofuran (10 mL) was then introduced. The mixture was refluxed for 20 minutes, after which time a solution of (+)-5,6-dehydrocamphor (323) (1.53 g, 2.30 mmol) in dry tetrahydrofuran (25 mL) was slowly added. The mixture was stirred...
vigorously at room temperature for 20 minutes and then refluxed for 1.5 hours. Saturated ammonium chloride (50 mL) was added and the mixture was extracted with ether. The combined organic layers were washed with water and brine, and dried (MgSO₄). Removal of solvent gave a crude product which was purified by column chromatography (silica gel, pet. ether:ether, 9:1) to yield pure bicyclic ketones (373a,b) (1.74 g, 89%) as a colorless oil. Rf 0.41 (pet. ether:ether, 4:1). The ratio (ca. 2:1) of the epimers of (373a,b) was determined by ¹H-n.m.r. integration. νₘₐₓ (film): 2950, 1715, 1643 cm⁻¹; δ (CDCl₃, 400 MHz): ¹H-n.m.r. of major diastereomer: 0.91 (s, 3H, CH₃), 1.01 (s, 3H, CH₃), 1.04 (d, 3H, CH₃, J=8 Hz), 1.32 (q, 1H, RCHCH₃), 1.60-1.61 (m, 3H, CH₃), 5.21 (s, 1H, H₃CCR:CHR'); m/e (relative intensity): 192 (46.4, M⁺), 177 (100); Exact mass calcd. for C₁₃H₂₀O: 192.1514; found: 192.1514; found: 192.1506; Anal. calcd. for C₁₃H₂₀O: C 81.20, H 10.48; found: C 80.90, H 10.47.

**Bicyclic alcohols (374)**

![Diagram of bicyclic alcohols](image)
To a cold (0°C), stirred solution of lithium aluminum hydride (0.56 g, 15 mmol) in dry tetrahydrofuran (10 mL) under an argon atmosphere was added a solution of bicyclic ketones (373a,b) (1.2 g, 5.9 mmol) in dry tetrahydrofuran (10 mL). Stirring was continued for 1 hour and the reaction mixture was quenched by careful addition of water (10 mL) followed by dilution with hydrochloric acid (1.0 N), and extraction with ether. The combined organic layers were then washed with water, brine and dried (MgSO$_4$). Removal of solvent provided a crude product which was purified by column chromatography (silica gel, petroleum ether:ether, 4:1) to provide mixture of diastereomeric bicyclic alcohols (374) (1.1 g, 98%) as a colorless oil. R$_f$ 0.37 (pet. ether:ether, 1:1); $\nu_{max}$ (film): 3350, 1645 cm$^{-1}$; $\delta$ (CDCl$_3$, 400MHz): $^1$H-n.m.r. of major diastereomer: 0.91-1.01 (m, 9H, CH$_3$, CH$_3$, CH$_3$), 1.56-1.57 (m, 3H, CH$_3$), 3.72-3.75 (m, 1H, RR'CHOH), 5.11 (s, 1H, H$_3$CCR:CHR'); m/e (relative intensity): 194 (16.5, M$^+$), 179 (16.3), 176 (13.0), 161 (100); Exact mass calcd. for C$_{13}$H$_{22}$O: 194.1671; found: 194.1675.
Bicyclic methyl ethers (375)

A solution of bicyclic alcohols (374) (0.90 g, 4.6 mmol) in dry tetrahydrofuran (10 mL) was added to a suspension of potassium hydride (0.28 g, 7.0 mmol) and methyl iodide (0.49 mL, 7.9 mmol) in dry tetrahydrofuran (10 mL). Stirring was continued for 15 minutes and the reaction was then carefully quenched with water (10 mL) and extracted with ether. The combined organic layers were washed with water and brine, and dried (MgSO₄). Removal of solvent provided a crude product which was purified by column chromatography (silica gel, pet. ether:ether,9:1) to provide mixture of diastereomeric bicyclic methyl ethers (375) (85 mg, 99%) as a colorless oil. Rf: 0.61 (pet. ether:ether,4:1); νmax (film): 1643 cm⁻¹; δ (CDCl3, 400MHz): ¹H-n.m.r. of major diastereomer: 0.86-1.00 (m, 9H, CH₃, CH₃, CH₃), 1.54-1.55 (m, 3H, CH₃), 3.30 (s, 3H, OCH₃), 3.15-3.21 (m, 1H, RR'CHOCH₃), 5.11 (s, 1H, H₃CCR:CHR'); m/e (relative intensity): 208 (14.1, M⁺), 193 (9.50), 176 (18.7), 161 (100); Exact mass calcd. for C₁₄H₂₄O: 208.1827; found: 208.1826.
Bicyclic enones (378)

At -78°C, ozone (condition: E=80 V, air inlet=8.0 psi, ozone outlet=0.06 psi) was allowed to pass through a stirred solution of bicyclic methyl ethers (375) (0.72 g, 3.4 mmol) in dry dichloromethane (15 mL) and methanol (15 mL) until a persistent blue color was obtained. The mixture was gradually warmed to about -25°C under an argon atmosphere and triphenylphosphine (0.90 g, 3.4 mmol) was added. Stirring was continued at -25°C for an hour and at 25°C for 30 minutes. After removal of solvent under vacuo, the crude keto-aldehydes (479a,b) ($\nu_{\text{max}}$, 2820, 1730 cm$^{-1}$) were dissolved in dry benzene (30 mL). p-Toluenesulfonic acid (0.10 g) was added and the mixture was refluxed for 5 hours in a Dean-Stark apparatus. After cooling and extraction with ether, the combined organic layers were washed with saturated sodium bicarbonate solution and brine, and dried (MgSO$_4$). Removal of solvent afforded a crude product was purified by column chromatography (silica gel, pet. ether: ether, 9:1) to provide mixture of diastereomeric bicyclic enones (376) (0.55 g, 74%) as a pale yellow oil. $R_f$: 0.43 (pet. ether: ether, 1:1); $\nu_{\text{max}}$ (film): 1675, 1616 cm$^{-1}$; $\delta$ (CDCl$_3$, 400MHz): 259
$^1$H-n.m.r of major diastereomer: 0.78-1.22 (m, 9H, \( (\text{CH}_3)_2 \) and \( \text{CH}_3 \)), 3.17-3.45 (m, 1H, \( R_2\text{CHOCH}_3 \)), 3.17-3.45 (m, 3H, \( R-O\text{CH}_3 \)), 5.97 (dd, 1H, \( R\text{HC:C(CO)HR} \), \( J=10 \text{ Hz, 4 Hz} \)), 6.55, 6.58 (dt, 1H, \( R\text{H(CO)C:CCHR} \), \( J=10 \text{ Hz, 2 Hz} \)); m/e (relative intensity): 222 (18.5, \( M^+ \)), 190 (28.6), 175 (14.7), 120 (48.1), 83.0 (63.7), 81.0 (100).

**Methyl ethers (367a,b)**

A solution of bicyclic alcohols (365a,b) (0.78 g, 4.36 mmol) in dry tetrahydrofuran (15 mL) was added to a suspension of potassium hydride (0.22 g, 5.4 mmol) and methyl iodide (0.41 mL, 6.5 mmol) in dry tetrahydrofuran (10 mL). Stirring was continued for 25 minutes and then carefully quenched with water (10 mL) and extracted with ether. The combined organic layers were washed with water and saturated brine and dried (\( \text{MgSO}_4 \)). Removal of solvent provided a crude product which was purified by column chromatography (silica gel, pet. ether:ether, 9:1) to give methyl ethers (367a,b) (0.85 g, 99%) as a pale yellow oil. \( R_f: 0.45 \) (pet.ether:ether, 4:1);
\( \nu_{\text{max}} \) (film): 1641 cm\(^{-1} \); \( \delta \) (CDCl\(_3\), 400 MHz): \(^1\)H-n.m.r. of major diastereomer: 0.91 (s, 3H, CH\(_3\)), 0.98 (s, 3H, CH\(_3\)), 1.54-1.56 (m, 3H, CH\(_3\)), 2.97-3.08 (m, 1H, RR'CH\(_2\)CH\(_3\)), 3.32 (s, 3H, CH\(_3\)), 5.01 (s, 1H, H\(_3\)CCR:CHR'); m/e (relative intensity): 194 (11.6, M\(^+\)), 162 (14.5), 147 (55.1), 119 (100); Exact mass calcd. for C\(_{13}\)H\(_{22}\)O: 194.1670; found: 194.1668.

Bicyclic Enones (369a,b)

At -78°C, ozone (condition: E=80 V, air inlet=8 psi, ozone outlet=0.06 psi) was allowed to pass through a stirred solution of methyl ethers (367a,b) (1.5 g, 7.5 mmol) in dry dichloromethane (20 mL) and methanol (20 mL) until a persistent blue color was obtained. The mixture was gradually warmed to about -25°C under an argon atmosphere and triphenylphosphine (2.0 g, 7.5 mmol) was added. Stirring was continued at -25°C for 30 minutes and 25°C for 30 minutes. After removal of solvent under vacuo, the crude keto-aldehydes (378a,b) (\( \nu_{\text{max}} \): 2820, 1730 cm\(^{-1} \)) was dissolved in dry benzene (20 mL). p-Toluenesulfonic acid (20 mg) was added and
the resulting mixture was refluxed for 4.5 hours in a Dean-Stark apparatus. After cooling and extraction with ether, the combined organic layers were washed with saturated sodium bicarbonate solution and brine, and dried (MgSO₄). Removal of solvent under vacuo afforded a crude product which was purified by column chromatography (silica gel, pet. ether:ether, 5:1) to afford bicyclic enones (369a,b) (1.4 g, 89%) as a colorless oil. Rₛ 0.29 (pet. ether:ether,2:1); νₘₐₓ (film): 1673, 1633 cm⁻¹; δ (CDCl₃, 400 MHz): ′H-n.m.r. of major isomer: 1.10 (s, 3H, CH₃), 1.21 (s, 3H, CH₃), 3.05-3.12 (m, 1H, RR′CHOCH₃), 3.32 (s, 3H, CH₃), 5.95 (dd, 1H, RC(=O)CH:CHR′, J=4 Hz, 10 Hz), 6.56 (dt, 1H, RC(=O)CH:CHR′, J=10 Hz, 2Hz); m/e (relative intensity): 208 (23.7, M⁺), 176 (23.4), 161 (17.0), 81 (100); Exact mass calcd. for C₁₃H₂₀O₂: 208.1463; found: 208.1459.

Ketones (408a,b)

Lithium diisopropylamide was generated by stirring n-butyllithium (1.6 M; hexane) (2.0 mL, 3.2 mmol) with diisopropylamine (0.45 mL, 3.2 mmol) at 0°C under an argon atmos-
phere in dry tetrahydrofuran (10 mL) and hexamethylphosphoramide (0.37 mL, 2.3 mmol) for 30 minutes. This solution was then cooled to -78°C and a solution of bicyclic enones (369a,b) (0.46 g, 2.2 mmol) in dry tetrahydrofuran (10 mL) was added. The resulting mixture was stirred at -78°C for 1 hour, after which time it was transferred via a cannula to a cold (-78°C) solution of acetic acid (0.62 mL, 11 mmol) in anhydrous ether (15 mL). This solution was allowed to warm to room temperature, extracted with ether and washed with saturated sodium bicarbonate solution and brine, and dried (MgSO₄). Removal of solvent provided a crude ketones (408a,b) (0.41 g, 87%). Rₓ: 0.33 (pet. ether:ether,1:1); νₓₘₐₓ (film): 1707 cm⁻¹; δ (CDCl₃, 400MHz): ¹H-n.m.r. of major diastereomer: 1.06 (s, 3H, CH₃), 1.18 (s, 3H, CH₃), 3.18-3.38 (m, 1H, RR’CHOMe), 3.37 (s, 3H, ROCH₃), 5.35-5.42 (m, 1H, Ha).

Dienols (409a,b)

(408a,b) → (409a,b)

To a solution of ketones (408a,b) (0.4 g, 1.9 mmol) in dry tetrahydrofuran (15 mL) was added vinylmagnesium bro-
mide (1.0 M, THF) (1.9 mL, 1.9 mmol) at 0°C under an argon atmosphere. Stirring was continued at 25°C for 2.5 hours and then refluxed for 0.5 hour. After cooling, the reaction mixture was quenched carefully with saturated ammonium chloride solution (50 mL) followed by extraction with ether. The combined organic layers were washed with water and brine, and dried (MgSO₄). Removal of solvent gave a crude product which was purified by column chromatography (silica gel, pet. ether:ether, 9:1) to afford dienols (409a,b) (0.34 g, 76%) as a colorless oil. R_f: 0.65 (pet. ether:ether, 1:1); ν_max (film): 3440, 1640 cm⁻¹; δ (CDCl₃, 400 MHz): ¹H-n.m.r. of major diastereomer: 0.91 (s, 3H, CH₃), 0.92 (s, 3H, CH₃), 3.17-3.26 (m, 1H, RR'CHOCH₃), 3.37 (s, 3H, ROCH₃), 5.11 (dd, 1H, Hb, J=11 Hz, 1.5 Hz), 5.30 (dd, 1H, Ha, J=17.5 Hz, 1.5 Hz), 5.31-5.33 (m, 1H, Hd), 6.45 (dd, 1H, Ha, J=11 Hz, 17.5 Hz); m/e (relative intensity): 236 (17.2, M⁺), 218 (3.90), 204 (6.10), 186 (4.00), 98.0 Exact mass calcd. for C₁₅H₂₄O₂: 236.1776; found: 236.1774; Anal. calcd. for C₁₅H₂₄O₂: C 78.23, H 10.23; found: C 75.89, H 10.29.
p-Bromobenzoates (381a,b)

At -78°C, NaBH₄ (23 mg, 0.60 mmol) was added to a stirred solution of enones (369a,b) (0.12 g, 0.60 mmol) and CeCl₃·7H₂O (0.22 g, 0.60 mmol) in methanol (10 mL). Stirring was continued at -78°C for 10 minutes and at 25°C for 1 hour, before water (2.0 mL) was added. Extraction with ether was followed by washing with hydrochloric acid (0.5 N) and brine, and dried (MgSO₄). Removal of solvent under vacuo provided allylic alcohols (428a,b) (0.13 g, 99%) as a yellowish oil. \( \nu_{\text{max}} \) (film): 3410 cm\(^{-1}\). This crude product was directly used in the next step without further purification.

p-Bromobenzoyl chloride (0.42 g, 1.9 mmol) was added to a solution of allylic alcohols (428a,b) (0.13 g, 0.59 mol) in dry pyridine (10 mL) at 25°C under an argon atmosphere. The mixture was stirred for 2 hours and hydrochloric acid (1.0 N, 10 mL) was then added and the mixture extracted with ether. The combined organic layers were washed with hydrochloric acid (1.0 N), potassium hydroxide solution (1.0 N) and brine, and dried (MgSO₄). Upon removal of solvent under vacuo the
crude product was triturated with ethanol, and the mother liquor was concentrated. The residue was purified by column chromatography (pet. ether:ether,5:1) to give p-bromobenzoates (381a,b) (0.16 g, 66%), as a colorless oil. 

R_f: 0.56 (pet. ether:ether,1:1); \(\nu_{max}\) (film): 1720 cm\(^{-1}\); 
\(\delta\) (CDCl\(_3\), 300MHz): \(^1\)H-n.m.r. of major diastereomer: 1.05 (s, 3H, CH\(_3\)), 1.14 (s, 3H, CH\(_3\)), 3.36 (s, 3H, ROCH\(_3\)), 3.10 (m, 1H, RCHOCH\(_3\)), 5.4-5.7 (m, 2H, RCH=CHR'), 7.58 (d, 2H, aromatic Hs', J=7.5 Hz), 7.92 (d, 2H, aromatic Hs', J=7.5 Hz); m/e (relative intensity): 392/394 (0.200/0.200, M\(^+\)/M\(^+\)+2), 360 (10.0), 185 (98.0).

**Hydrazones (383a,b)**

![Hydrazones diagram]

Enones (376a,b) (95 mg, 0.42 mmol), and Pd/C (10 mg) in hexane (2 mL) was treated with hydrogen at 50 psi at 25°C for 2 hours. After filtering off the catalyst, the filtrate was concentrated to provide ketones (429a,b) (85 mg, 89%) as
a colorless oil. $\nu_{\text{max}}$ (film): 1705 cm$^{-1}$.

H$_2$SO$_4$ (concentrated, 1 mL) was slowly added to a stirred solution of ketones (429a,b) (85 mg, 0.37 mmol), and 2,4-dinitrophenylhydrazine (0.15 g, 0.76 mmol) in ethanol (5 mL). The reaction mixture was refluxed for 5 minutes, cooled, and filtered. The filtrate was concentrated and purified by column chromatography (pet. ether: ether, 10:1) to provide hydrazones (383a,b) (0.14 g, 91%) as a yellow solid. $\delta$ (CDCl$_3$, 300 MHz): $^1$H-n.m.r. of major diastereomer: 0.9-1.4 (m, 9H, gem-dimethyl and CH$_3$), 3.36 (s, 3H, ROCH$_3$), 3.2-3.4 (m, 1H, RCHOH), 7.96 (d, 1H, H$_a$, J=9 Hz), 8.30 (d, 1H, H$_b$, J=9 Hz), 9.15 (s, 1H, H$_o$), 11.2 (d, 1H, R'NHR'', J=9 Hz); m/e (relative intensity): 404 (25.1, M$^+$), 85.0 (88.2), 41.0 (100).

Dimer (411)

Lithium diisopropylamide was generated by stirring n-butyllithium (1.6 M, hexane) (0.83 mL, 1.0 mmol) with
diisopropylamide (0.1 mL, 1.0 mmol) at 0°C under an argon atmosphere in dry tetrahydrofuran (10 mL) for 30 minutes. The reaction mixture was then cooled to -78°C and a solution of bicyclic enone (368a) (0.24 g, 1.0 mmol) in dry tetrahydrofuran (10 mL) was added. The resulting mixture was stirred at -78°C for one hour, after which time it was cannulated into a cold (-78°C) solution of acetic acid (1.7 mL, 30 mmol) in anhydrous ether (10 mL). This solution was allowed to warm to room temperature, extracted with ether, and washed with saturated sodium bicarbonate solution and brine, and dried (MgSO₄). After removal of solvent, the crude product was purified by column chromatography (pet. ether:ether, 5:1) to provide dimer (411) as colorless prisms (0.22 g, 91%). mp 218°C; \( \nu_{\text{max}} \) (CDCl₃): 3496(w), 1715 cm⁻¹; \( \delta \) (CDCl₃, 300MHz): 0.84 (s, 3H, CH₃), 0.93 (s, 3H, CH₃), 4.59 (s, 1H, ROH), 5.38-5.53 (m, 3H, RCH:CHR', and R''CHOAc); m/e (relative intensity): 472 (4.90, M⁺), 454 (75.3), 236 (51.3), 176 (28.9), 159 (100).
SPECTRA APPENDIX
$^1$H-n.m.r. (400MHz)

(142a)

$^1$H-n.m.r. (400MHz)
$^1$H-n.m.r. (400MHz)

(136a,b)

(103a,b)

$^1$H-n.m.r. (400MHz)
$^1$H-n.m.r. (400MHz)

Dimers (169a,b)

Low Resolution Mass Spectrum
Stereoviews of compound (186), analysed by X-ray Crystallography.
$^1\text{H-n.m.r. (270MHz)}$

(192a)

(192b)
Infra-red spectrum of compounds (192a,b)

Infra-red spectrum of compound (26)
$^1$H-n.m.r. (400MHz)
Stereoviews of compound (195a), analysed by X-ray crystallography.

Infra-red spectrum of (59)
(+)-Longiborneol (59)
[Money and co-worker]

$^1$H-n.m.r. (400MHz)

(+)-Longiborneol (59)
[Anderson and co-worker]
(Natural source)

$^1$H-n.m.r. (400MHz)
(±)-Longiborneol
[Welch and co-worker]

\[ ^1H-n.m.r. (400MHz) \]

\[ ^1H-n.m.r. (270MHz) \]
$^{19}$F-n.m.r. (254 MHz): Singlet at 5.08 in the resolution enhanced proton decoupled spectrum.
$^{13}$C-n.m.r. of compound (211)
Infra-red spectrum of (+)-Longifolene (61)

$^1$H-n.m.r. (400MHz)
Low resolution mass spectrum of compound (61)

Infra-red spectrum of compound (324)
$^1$H-n.m.r. (400MHz)

(324)

(323)

$^1$H-n.m.r. (400MHz)
$^1$H-n.m.r. (400MHz)
\[ ^1H\text{-n.m.r. (400MHz)} \]
Stereoviews of compound (392), analysed by X-ray crystallography.

Stereoviews of compound (411), analysed by X-ray crystallography.
$^1$H-n.m.r. (400MHz)

$^1$H-n.m.r. (400MHz)
$^1$H-n.m.r. (400MHz)

1

$^1$H-n.m.r. (400MHz)
$^1$H-n.m.r. (400MHz)

$^1$H-n.m.r. (300MHz)
1H-n.m.r. (400MHz)


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This reaction was first carried out by B. Yokoyama (NSERC summer student, 1986) using sodium hydride which gave (364) in about 16 hours (ca. 80%).