Synthesis of
Limonoid and Steroidal Intermediates

By

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(Department of Chemistry)

We accept this thesis as conforming
to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA
October 1993
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Department of **CHEMISTRY**

The University of British Columbia
Vancouver, Canada

Date *Oct 15th 1993*
Abstract

The cyclopentyl intermediate 4 is an easily obtained, highly enantiopure starting material for the synthesis of numerous triterpenoids. Prepared from (+)-endo-3-bromocamphor (2) in a four-step sequence, 4 has been converted into two advanced triterpenoid intermediates.

In an eleven-step sequence 4 was transformed into the bicyclic intermediate (42) that could be used in an enantiospecific approach to the limonoids. The enone 42 was subsequently dialkylated in a regio- and stereoselective manner to produce the intermediate 45. Removal of the silyl protecting group followed by oxidation and acid-catalysed annulation produced the tricyclic enone 53. Structure 53 represents a highly advanced ent-limonoid intermediate with correct relative and absolute stereochemistry with obvious similarities to limonoids such as ent-azadirone (6).

Further investigations illustrated 4's utility in the synthesis of the steroidal hydrindane system. Using an analogous pathway 4 was again converted to a bicyclic enone 104 in eight steps. Regiospecific alkylation followed by medium pressure hydrogenation and epimerization yielded the hydrindane 110. Extensive NMR analysis of this compound was used to provide conclusive evidence of 110's absolute stereochemistry. This route is therefore potentially useful in an approach to natural products such as 1α, 25-dihydroxyvitamin D3 (58).
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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
<td>Anal.</td>
<td>microanalytically determined mass %</td>
</tr>
<tr>
<td>APT</td>
<td>Attached Proton Test (13C NMR)</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous solution</td>
</tr>
<tr>
<td>b</td>
<td>broad absorption (IR)</td>
</tr>
<tr>
<td>nBu</td>
<td>normal butyl</td>
</tr>
<tr>
<td>tBu</td>
<td>tertiary butyl</td>
</tr>
<tr>
<td>Calc.</td>
<td>Calculated mass %</td>
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<tr>
<td>Calc. Mass</td>
<td>Calculated exact Mass</td>
</tr>
<tr>
<td>cat.</td>
<td>catalytic amount</td>
</tr>
<tr>
<td>conc.</td>
<td>concentrated</td>
</tr>
<tr>
<td>CSA</td>
<td>camphorsulfonic acid</td>
</tr>
<tr>
<td>d</td>
<td>doublet (NMR); days</td>
</tr>
<tr>
<td>dAB</td>
<td>AB doublet, i.e. one branch of an AB quartet (NMR)</td>
</tr>
<tr>
<td>DEAD</td>
<td>diethyl azodicarboxylate</td>
</tr>
<tr>
<td>DHP</td>
<td>dihydropyran</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DIPA</td>
<td>diisopropylamine</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulphoxide</td>
</tr>
<tr>
<td>ent-</td>
<td>enantiomer (of)</td>
</tr>
<tr>
<td>eq.</td>
<td>equivalent (s)</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>Et₂O</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>Et₃N</td>
<td>triethylamine</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>-------------</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>EtOH</td>
<td>ethanol</td>
</tr>
<tr>
<td>GC</td>
<td>gas liquid chromatography</td>
</tr>
<tr>
<td>h</td>
<td>hours</td>
</tr>
<tr>
<td>H</td>
<td>proton(s) (NMR)</td>
</tr>
<tr>
<td>HetCor</td>
<td>heteronuclear correlation ((^{13})C, (^{1})H NMR experiment)</td>
</tr>
<tr>
<td>(H_c)</td>
<td>cis protons (NMR)</td>
</tr>
<tr>
<td>(H_t)</td>
<td>trans protons (NMR)</td>
</tr>
<tr>
<td>IR</td>
<td>infrared spectrum</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant (Hz) (NMR)</td>
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<td>J-resloved</td>
<td>resolved coupling constant (NMR experiment)</td>
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<tr>
<td>m</td>
<td>multiplet (NMR)</td>
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<td>m/z</td>
<td>mass to charge ratio (Mass Spec.)</td>
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<tr>
<td>(M^+)</td>
<td>molecular ion (MS)</td>
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<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>Meas. Mass</td>
<td>exact mass determined by high resolution MS</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>min</td>
<td>minutes</td>
</tr>
<tr>
<td>mm</td>
<td>millimeters of mercury (distillation pressure)</td>
</tr>
<tr>
<td>MMC</td>
<td>magnesium methyl carbonate</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrum</td>
</tr>
<tr>
<td>n-</td>
<td>normal (primary)</td>
</tr>
<tr>
<td>NaHSO(_3)</td>
<td>sodium bisulfite</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance (spectrum)</td>
</tr>
<tr>
<td>NOE</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>Nuc(^-)</td>
<td>nucleophile</td>
</tr>
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</table>
p  pentet
PDC  pyridinium dichromate
ppm  parts per million (NMR)
q  quartet (NMR)
\(\pi\)  room temperature
s  singlet (NMR); strong absorption (IR)
sat.  saturated solution (aqueous)
SiO\(_2\)  silica gel
t  triplet (NMR)
\(t\)-  tertiary
TBAF  tetra-n-butylammonium fluoride
TBDPS  \(t\)-butyldiphenylsilyl
TFAA  trifluoroacetic anhydride
THF  tetrahydrofuran
Tig-  tigloyl ((E)-2-methyl-2-butenoyl-)
TLC  thin layer chromatography
p-TsOH  \(p\)-toluenesulphonic acid
X-ray  X-ray crystallograph
\([\alpha]^T\)  specific rotation at 589nm at \(T^\circ\)C
\(\delta\)  chemical shift (ppm) (NMR)
\(\nu\)  absorption wave number (cm\(^{-1}\)) (IR)
Acknowledgments

I would like to thank Mike Wong for his excellent advice in many areas of this thesis. His advice on experimental procedure and his editorial skills have been greatly appreciated. Monica Palme also deserves acknowledgement as she has been the source of insightful and valuable comment with respect to the writing of this thesis.

I would also like to thank S. Rak (glass blowing) and the mechanical and electrical workshops for their prompt and talented repair of laboratory equipment. I would also like to thank, collectively the spectral services of the U.B.C. chemistry department for their assistance in the analysis of the products reported in this thesis.

Finally, I would like to thank Professor Thomas Money for making my graduate school experience as enjoyable as it has been. From the discussion of current research to the history of organic chemistry, Dr. Money has made the past several years as entertaining as they have been educational.
Dedication

I dedicate this thesis to my parents,
Patricia and Ronald Richardson,
for their answering of my first questions and later for
their encouragement
and support in seeking answers to others.
General Introduction

Camphor (1) is a naturally occurring monoterpenoid that is commercially available in both enantiomeric forms. An important feature of camphor is the availability of procedures for the regiospecific functionalisation of the molecule at C(3), C(5), C(6), C(8), C(9) or C(10) position. (Scheme 1)

The mechanisms of some of these transformations have been fully investigated and described in recent publications. In general they are often the result of multiple Wagner-Meerwein rearrangements.

Scheme 1
The potential utility of camphor as a chiral starting material is not immediately obvious. In fact, retrosynthetic analysis of only a few natural products would lead to

Scheme 2
camphor as an obvious starting material. To illustrate this point a selection of synthetic transformations is given in scheme 2.

The investigations reported in this thesis explore the utility of camphor as an enantiopure starting material in a synthetic route to the *ent-*limonoid (6) and steroid (7).

![Scheme 3](image)

Systems. Beginning with the commercially available (+)-*endo-*3-bromocamphor (2), (+)-9,10-dibromocamphor (3) is easily prepared in multi-gram quantities using a three step reaction sequence. The key reaction in both of the investigations reported is the Grob-type fragmentation of 3\(^{1e}\) yielding the hydroxy-acid (4).\(^{1f}\) It should be noted that this compound possesses absolute stereochemistry [at C(13) and C(17) position] that is appropriate for its subsequent use in triterpenoid and steroid synthesis. (Scheme 3)

For convenience, commercially available (+)-*endo-*3-bromocamphor (2) was used as a starting material in both investigations as both syntheses share a common intermediate, the enone ester (5). Although (+)-*endo-*3-bromocamphor (2) yields the *ent-*series of the limonoids (6), the work presented is valid as a synthetic route to the natural series of
compounds because (−)-endo-3-bromocamphor (ent-2) can be easily synthesised from (−)-camphor (ent-1).

The ent-limonoid (6) and steroid (7) systems are structurally similar and during this discussion particular carbon centres will be referred to by the steroidal numbering system shown in structures 6 and 7. The convention of ring nomenclature (A through D) will also be used throughout this thesis.

The first chapter of this thesis describes efforts to develop a simple synthetic route to a potentially useful intermediate in ent-limonoid synthesis. The second chapter discusses recent approaches to a key intermediate for steroid synthesis.
1.1 Limonoid Introduction:

The limonoids are a large complex family of natural products that exist in relatively large concentrations in many citrus plants. Limonin (8), which lends its name to this family of compounds is the bitter principle of citrus fruits and was the first of the limonoids to be isolated.9 Though limonin (8) was isolated some 150 years ago, its structural and stereochemical complexity was not fully elucidated until 1960.10 Barton, Robertson, and their respective co-workers independently, over a three year period, determined the correct constitution of limonin. Barton and co-workers10a approached the problem through classical spectroscopic analysis (IR, UV, NMR and mass spectrometry) of limonin and products produced by the systematic degradation of limonin. Their structural assignment was in agreement with the result obtained by Robertson and co-workers,10b who used X-ray crystallography to determine both the relative and absolute stereochemistry of limonin.

These results stimulated a great deal of interest in this family of compounds. The relative abundance and obvious complexity of the limonoids were ideal challenges for chemists interested in structure elucidation.11a-c A recent review, for example, lists just under 300 fully characterized limonoids found in the Meliaceae family of plants.11a

The limonoids are defined by several common characteristics: i) they are tetrannortriterpenoids [i.e. they are formed by the loss of a four-carbon unit from the normal
of the triterpenoid side chain and iii) they often contain lactone rings formed by the biological equivalent of the Baeyer-Villiger oxidation reaction on ring A and ring D ketones.

Some representative examples of limonoids are shown above. These examples have been chosen to illustrate some of the structural complexity and diversity found within this group of natural products.

Structure-activity relationships in the limonoids are not well understood. It is known that many, if not most, limonoids are powerful insect anti-feedants but the specifics of the insect-limonoid interactions are not known. The large number of limonoids present in these plants (albeit in small concentrations) appears to offer a very good chemical defense system against insect predators. Feeding studies have shown that although indigenous insects are able to adapt to specific anti-feedants, the sheer number of different limonoids present in these plants ensure adequate protection. Early investigations on the biological activity of the limonoids attracted interest with respect to their possible use in chemotherapy. However
limonoids attracted interest with respect to their possible use in chemotherapy. However Jolad and co-workers have reported limited success in the use of these compounds as chemotherapeutic agents.\textsuperscript{13} The limonoids remain a novel yet synthetically unexplored family of compounds.
1.2 The Biosynthesis of the Limonoid System:

As the number of known limonoids increased, speculation on their biosynthesis was inevitable. The limonoids are believed to be biosynthesised by structural modification of euphol (11) or tirucallol (12). As shown in scheme 4, euphol (11) and tirucallol (12) are formed by cyclisation of squalene epoxide (9) in the chair-chair-chair-boat conformation. This conformation ensures the relative orientation of the methyl groups and hydrogen atoms at the various ring junctions, which then are able to undergo a series of 1,2-shifts to attain a limonoid-like structure. There is some evidence to support the specific proposal that the limonoid biosynthesis involves rearrangement of an epoxide (13 or 14) derived from euphol (11) or tirucallol (12) to provide apo-euphol (15) or apo-tirucallol (16) derivatives with structure and stereochemistry appropriate for its subsequent conversion to the limonoids.

Although the biosynthetic route from the parent triterpenoid(s) (15 and/or 16) to individual limonoids has not been determined, it seems obvious that the overall transformation involves a series of recognisable reactions. For example, a common biosynthetic process is the partial oxidative degradation of the C(17) side-chain in the triterpenoid precursor to produce the characteristic C(17) furan ring that is common to all limonoids. Other biosynthetic transformations likely to occur are epoxidations, allylic oxidations and the biological equivalent of the Baeyer-Villiger reaction. The latter process produces A-ring and D-ring lactones that are a common structural feature to these compounds. Protolimonoids [e.g. grandifoliolenone] are intact triterpenoids with highly functionalised side-chains that are likely biological precursors of the limonoids. They exhibit the basic tetracyclic ABCD ring structure of the limonoids along with the proper stereochemistry at the various ring junctions.
Scheme 4
1.3 Previous Synthesis of the Limonoid System:

Possessing structural and stereochemical complexity, triterpenoids in general have been popular target molecules to showcase synthetic organic methodologies ever since the synthesis of (±)-lanosterol was reported by Woodward, Barton and co-workers in 1957. Yet despite the numerous reviews outlining the isolation and structural elucidation of many limonoids since 1960 there has only been one reported synthetic approach to the limonoid system.

Examination of the tetracyclic structure of the non-lactonic limonoids (e.g. ent-azadirone, 6, scheme 3) leads to the conclusion that synthesis of the basic framework could be accomplished by methods similar to those previously used in steroidal and triterpenoid synthesis. (scheme 5) The three examples given below illustrate disconnections that have been used in the complete synthesis of various tetracyclic triterpenoids. The specifics of these approaches will not be discussed further, yet they do illustrate retrosynthetically several plausible routes to a complete limonoid synthesis.

* After the completion of this thesis a communication was published which outlined another approach to the limonoid system. It has been presented in Appendix B without comment
In the only reported synthetic approach to the limonoid system, Corey and co-workers, however, used a biomimetic-type route (scheme 6) in which the key step was the stereoselective cyclisation of enol phosphate 18. This compound was prepared by the reaction of farnesyl bromide (17) with the dianion derivative of methyl acetoacetate18, followed by the capture of the intermediate enolate with diethyl chlorophosphate. Cyclisation of 18 was promoted by mercuric trifluoroacetate and produced the tricyclic β-keto-ester (19) in an isolated yield of 27-30 % over three steps. This cyclisation process therefore produced the correct stereochemistry at the AB and BC ring junction. [Note: the stereochemistry is only correct in a relative sense as the cyclisation produces a racemic product.]
The chloromercurio functionality in compound 19 was photolytically replaced with a phenylselenenyl group which was then oxidatively eliminated with MCPBA to provide olefin 20. (Scheme 7) The β-keto ester (20) was then converted to an enol phosphate and the methyl ester group was reduced with DIBAL to yield phosphoenolate 21.

In a typical Michael reaction a nucleophile is added in a conjugate manner to an enone system. In Corey's synthetic route, the phosphoenolate (21) is converted in situ to enone 21b under basic conditions. A reasonable description of bond rearrangements involve an
intermediate cyclic enol phosphate (21a). The formation of enone 21b in the presence of the sodium salt of 3-(2-nitroethyl)-furan resulted in a Michael reaction to provide the nitroketone (21c). A Nef reaction then converted nitroketone (21c) to the diketone (22) and base-catalysed aldol condensation provided the pentacyclic enone (23). (Scheme 9)

(i) 12 N HCl, ethanol (1:3.3), 10°C
(ii) 1M NaOEt, EtOH, 56°C

At this point the basic carbon skeleton was complete except for the angular methyl at the C(13) position. Steric hindrance precluded the use of conjugate methylation of the enone (23); numerous organocopper reagents with and without electrophilic promoters failed to add in the desired conjugate manner. Cyclopropanation of the Δ^{13,17} double bond and subsequent cleavage would introduce this methyl group; however without a directing
hydroxyl group (Simmons-Smith reaction) limited control of stereochemistry is likely. L-Selectride reduction of the enone resulted in formation of an allylic alcohol (24) with a \( \beta \)-oriented hydroxyl group. (Scheme 10) This, however, is the opposite stereochemistry required for a hydroxyl-directed Simmons-Smith \( \beta \)-cyclopropanation. Therefore 24 was converted to the \( \alpha \)-hydroxy compound (25) by the Mitsunobu DEAD inversion technique (50% yield). Hydroxyl-directed stereoselective cyclopropanation of (25) then occurred to produce (26) in 89% yield. Oxidation of the tetracyclic alcohol (26) followed by dissolving metal reduction (Li, NH\(_3\)) resulted in cleavage of the cyclopropyl group and production of the advanced limonoid intermediate (28). (13% yield overall)

This synthetic approach to the limonoids remains unfinished, although future publications from Corey's group can be anticipated. Nonetheless, this synthesis illustrates
the advantage of using biosynthetic ideas to devise synthetic strategies for complex carbon skeletons.
1.4 Discussion:

The particular research reported in this chapter stems naturally from previous investigations in our laboratory. It was previously established that the Grob-type fragmentation of 9,10-dibromocamphor (ent-3 or 3) gave the hydroxy acids (ent-4 or 4). They were immediately recognized as a potentially useful synthetic intermediates for the synthesis of steroids and tetracyclic triterpenoids. (Scheme 11)

Since hydroxy-acid 4 is more conveniently accessible than its enantiomer (ent-4) the former compound was used as a common enantiopure intermediate in the limonoid project and the steroid project (to be discussed in the following chapter). Specifically, 4 was seen as an enantiopure starting material from which an enantiospecific synthesis of the ent-limonoid C,D ring system could be based. With two stereocentres exhibiting the correct absolute stereochemistry, it was envisioned that the subsequent alkylations and annulations could be
achieved stereoselectively resulting in the highly stereoselective synthesis of an advanced limonoid intermediate.

(+)-9,10-Dibromocamphor (3) is readily available from (+)-3-bromocamphor (2) through a series of bromination and debromination reactions. (Scheme 12) The mechanisms proposed for the individual steps involve a combination of Wagner-Meerwein rearrangements and 3,2-exo-methyl shifts. The particulars of these reactions will not be addressed here as they have been dealt with extensively in previous theses and their resultant publications.

The debromination of (+)-3,9,10-tribromocamphor (30) can be explained by Zn acting as a Lewis base, complexing with the carbonyl's oxygen and causing a displacement of bromine at C(3). Protonation of the zinc enolate and tautomerization of the resultant enol readily yields (3).

Ring cleavage of (+)-9,10 dibromocamphor (3), however, is central to the research that will be described in this thesis and is conveniently accomplished in the following way. (Scheme 13) Treatment of (+)-9,10-dibromocamphor (3) with KOH in DMSO:H₂O (5:1) at room temperature for one hour produces bromo-acid (3a). When this reaction is carried out at 65°C for 24 hours the product is hydroxy-acid (4). TLC evidence indicates that during
this conversion a stable intermediate does exist. If the fragmentation is carried out under anhydrous conditions the 'stable intermediate' described above is the only product which is isolable. Analysis of the intermediate and structural confirmation by X-ray crystallography\(^{19}\) indicates that it is the lactone 31. The proposed mechanism illustrated in scheme 13 also helps to explain the unusual observation of hydroxide substitution of a neopentyl bromide.

\[
\text{Scheme 13}
\]

Indications by TLC suggest that the conversion (+)-9,10-dibromocamphor to hydroxy-acid (4) is quantitative; however, the isolation of this compound is complicated by its solubility in water. Optimum yields were obtained when numerous (>5) solvent-solvent extractions were incorporated into the work-up procedure.

Subsequent reaction of acid 4 with methyl iodide in the presence of K\(_2\)CO\(_3\) yields the hydroxy-ester (32) as an easily purified oil. (Scheme 14) Swern oxidation\(^{20}\) of the hydroxy-ester readily provided the aldehyde (33), and reaction of this compound with the stabilized trimethyl phosphonoacetate anion led to the trans-\(\alpha,\beta\)-unsaturated ester (34).\(^{21}\) This elaboration of the hydroxy-acid (4) has achieved several objectives. The esterification at C(21) allows for a future enolate alkylation in the preparation of the furan ring, and the Wadsworth-Emmons (33 \(\rightarrow\) 34) reaction has introduced the precursor to ring C.
Prior to cyclisation of ring C, reduction of the α,β-unsaturated ester (34) was required. This reduction could have been achieved through several methods, but obviously the other functionalisations of the molecule limited the possible choices. Dissolving metal reductions would have likely caused the reduction of the C(21) ester to the alcohol, whereas catalytic hydrogenation would have destroyed the exocyclic double bond. α,β-Unsaturated esters, however, can be selectively reduced when treated with magnesium in dry methanol and this methodology was used to convert 34 to 35. Work-up of the reaction mixture entailed acidification, followed by immediate extraction of the diester into an organic medium to avoid isomerization of the exocyclic double bond.
Hydrolysis of the isolated diester (35) was readily achieved through treatment with KOH, MeOH and H2O. However in repetition of this work it was found convenient not to isolate the diester (35). Instead, 35 was directly hydrolysed by quenching the reaction mixture from Mg/MeOH reduction with 5 equivalents of KOH dissolved in a sufficient amount of water so as to allow efficient mixing of the resultant slurry.

Cyclisation of diacid (36) to produce ring C was now possible. Treatment of 36 with TFAA in methylene chloride followed by removal of solvent and addition of anhydrous methanol and a catalytic amount of p-TsOH provided the hydrindenone 5. It is likely that in this reaction the initial cyclisation product is the mixed anhydride (36b), and is subsequently converted to the methyl ester.

Hydrindenone (5) has considerable potential as an intermediate for the synthesis of limonoids and steroids. Its evaluation as an intermediate in limonoid synthesis is described below.

The limonoids' characteristic furan ring, like furan rings in general, are known to be acid sensitive. As a result we decided to elaborate this structural sub-unit at a later stage in
the synthesis. It was convenient at this point, however, to establish the basic carbon framework of the furan ring. This was accomplished by the conversion of the enone ester (5) into the ketal ester (37), and the alkylation of 37 with methyl bromoacetate. \(^{(28)}\) (Scheme 16) This provided the diastereoisomers 38 and 39.

As expected (see below) this alkylation occurred stereoselectively. Although the stereocentre created in this reaction will be removed later by the formation of the furan ring this reaction provides a useful way of introducing stereochemistry at the C(20) centre for other related structures, such as steroidal side chains. NMR analysis of the resultant diester suggests that the stereoselectively of the reaction produces a \(~19:1\) mixture of 38:39 as indicated by integration of the appropriate peaks (A slight twinning of the angular methyl signal (1.05 ppm) was noted and expanded to measure the relative proportion of 38 to 39). Similar alkylations reported by our research group are consistent with these observations.\(^{(24,28)}\)

The stereoselective alkylations of ketal ester (37) can be explained in the following way.\(^{(26)}\) As shown below the ester enolate (37a) can adopt a conformation in which the double bond eclipses or nearly eclipses the \(\alpha\) hydrogen at C(17). The electrophile (E\(^+\)) then approaches the enolate preferentially from the least hindered face (as illustrated). Clearly the
least sterically congested face of the molecule is that on which the C(16) methylene group resides \((re\text{-face})\), as the \(si\text{-face}\) attack would require the electrophile to accommodate a quaternary carbon at C(13).

With the ketal diester (38) in hand, reduction with LiAlH\textsubscript{4} provided ketal diol 40.\textsuperscript{27} (Scheme 17) Infrared spectroscopy showed the expected emergence of a strong hydroxyl peak centered at approximately 3340 cm\(^{-1}\) and the disappearance of the carbonyl peak at 1733 cm\(^{-1}\). The hydroxyl groups were then protected as the corresponding methyl ethers (41). Spectral proof of structure 41 was most apparent in the NMR spectrum as there was a disappearance of a very broad singlet at 2.85 ppm, which integrated to two hydrogens (2 x OH) and the emergence of two 3H singlets at 3.27 and 3.30 ppm (2 x OMe). Subsequent hydrolysis of the ketal yielded enone 42. NMR analysis showed the disappearance of the ketal hydrogens (4H, m, 3.36 - 3.45 ppm), and a strong carbonyl peak at 1665 cm\(^{-1}\) in the IR spectrum consistent with what is expected for an \(\alpha,\beta\)-unsaturated carbonyl.
Retrochemically it was observed that ring B of the limonoids could be synthesized through an intramolecular aldol condensation (scheme 18) involving compound 52. Therefore the dialkylation of enone 42, suitable for this elaboration, was our next major objective.
It was reasoned that the methyl and the n-pentyl groups at C(8) of compound 52 could be added by successive alkylations of the thermodynamic dienolate of 42. The stereochemistry would be dictated by the 1,3-interactions of the angular methyl group [C(18), steroidal numbering] with the second of the two alkylating agents added. The first alkylating agent would add producing a planar α-substituted α,β-unsaturated carbonyl. The second alkylation would produce a sp³ center α to the carbonyl at the C(8) position moving the double bond out of conjugation. The stereochemistry at the C(8) center would depend on which face of the dienolate would be attacked by the second alkylating agent. In the dienolate 43a, the C(18) methyl group was seen to present significant steric hindrance along the β-face of the molecule. (Scheme 19) Therefore it was assumed that the second alkylation (methylation) would occur preferentially from the α-face producing the required stereochemistry.

Scheme 19

The obvious choice for the n-pentyl alkylating agent, in view of the retrosynthetic analysis presented in scheme 18, was an appropriately protected 1-iodo-3-pentanol (50).
The choice of iodo-alkane (50) was determined by consideration of the alkylating tendencies (to be discussed later) of the various alkyl halides and the stability of the tert-butyldiphenylsilyl ether. The procedure used to synthesize 50 is outlined in scheme 20. The spectral detail of the compounds shown below agree favourably with a similar compound (TBDMS ether) reported by Mander and co-workers.30

Based on literature precedence we expected that α-alkylation of enone 42 with the electrophilic iodo-alkane (50) may not occur in high yields.30 (Scheme 21) A review of the literature shows that alkylations of this type (1,2-additions of dienolates) rarely produce yields greater than 70 %.31 Specifically, to achieve the intended alkylation (42 -> 43, scheme 16) the thermodynamic enolate must be formed, C-alkylation must predominate over O-alkylation and dialkylation must be avoided.
It is known that, in the presence of NaH/DMSO, conjugated enones are converted to thermodynamic dienolates. As DMSO has a pK of ~35 and the enone α-protons have a pK of ~25 any proton abstraction by the dimsyl sodium base is essentially irreversible. However, the reaction with DMSO to form the dimsyl sodium is slow and as a result, the effective concentration of the dimsyl sodium in solution is low relative to that of the substrate enone. Thus the initially formed, kinetic dienolate (42a) can equilibrate with the more stable, thermodynamic dienolate (42b) via the unreacted enone (42).

Under these reaction conditions it was found that a reaction time of ~2 hours was sufficient to form the thermodynamic enolate exclusively as the reaction of the dienolate 42 with iodoalkane 50 produced no C(11) alkylation product.
The use of dimsyl sodium/DMSO served another purpose as DMSO has excellent solvation characteristics. DMSO is a polar aprotic solvent and is able to solvate the sodium cation extremely well, yet is unable to effectively solvate the enolate anion due to its inability to form hydrogen bonds through the 'donation' of its methyl hydrogens. Consequently this leaves the enolate unencumbered with solvent molecules and is very reactive towards electrophiles.

Controlling C- versus O-alkylation is another concern in achieving efficient conversion of 42 to 43. Enolate (42a or 42b) is an ambident nucleophile and the preference for C-alkylation or O-alkylation is best understood through the concept of hard and soft acids and bases.

Hard and soft refer to an atom's ability to attract its valence electrons. Those atoms which are moderately electronegative hold onto their valence electrons in a relatively tight manner and are considered hard. Conversely those atoms which are weakly electronegative are considered soft as their valence electrons are less tightly bound by the nucleus. [Acid and base terminology is in the Lewis sense, where bases (nucleophiles) donate electrons and acids (electrophiles) accept electron pairs.]

As enolates are ambident one must consider both the carbon and oxygen as possible nucleophiles. The oxygen anion is considered to be hard and the carbon anion is soft due to their respective electronegativities. With respect to electrophiles, a highly polarised carbon-halide bond decreases electron density about the carbon and its electrons become more closely associated with the nucleus, hence there is an increase in its hardness. A weaker or less polar carbon-halide bond allows for greater electron density about the carbon atom and the carbon is regarded as soft. In a comprehensive investigation it was shown that of all leaving groups iodide promotes C-alkylation best. As the alkylating agent (50) is an iodoalkane, theory suggests C-alkylation will predominate. In our alkylation reaction of the thermodynamic enolate (42a), in fact no O-alkylated product was isolated.
The major difficulty encountered in the alkylation of 42 was that of dialkylation. The reaction produces a mixture of unreacted starting material as well as monoalkylated (43) and dialkylated product (44). The fact that alkylated enone (43) underwent further alkylation was unexpected.

Two possible explanations would account for this observation. The first is that the alkylating agent (50) was being added too slowly. This would allow for the alkylated enone (43) to become deprotonated by contact with unreacted enolate (42b). If the addition of iodo-alkane (50) was slow enough an equilibrium could form between the enolate (42b) and alkylated enone (43), allowing for a substantial amount of dialkylation.

The second explanation for substantial dialkylation occurring can be understood by a closer examination of the reaction mechanism (below). Upon alkylation of the thermodynamic dienolate (42b) the unconjugated enone (42c) is formed. Subsequent isomerization of the $\delta,\gamma$-unsaturation may produce the more stable $\alpha,\beta$-unsaturated enone (43, path A). However, as the initial step of this isomerization is a deprotonation of 42c's $\alpha$-proton a second alkylation is possible resulting in compound 44 (path B). This explanation, though extremely similar to the first explanation, is not the result of poor experimental technique but rather a natural consequence of the reaction mechanism.
The fact that some starting material (42) was recovered may be a result of hydrolysis of some O-alkylated product during work-up. Future studies in this area will investigate the possibility of controlling these reaction difficulties.

The introduction of the α-oriented methyl group at C(8) was then addressed. Using a set of reaction conditions similar to those described in the previous alkylation, dimsyl sodium was used to produce the conjugated enolate (43b) and after several hours of equilibration, iodomethane was added and alkylation of the thermodynamic enolate (43b) was achieved as predicted. (Scheme 22) The stereochemistry of this alkylation was from the α-face. An NOE experiment was performed on compound 45. Irradiation of the C(18) signal provided no positive enhancement of the new methyl substituent introduced at C(8), and thus suggesting the stereochemistry shown for 45 is correct. The NMR spectra of this compound is extremely complex through the 1.00 to 2.50 ppm region and identification of specific hydrogens was not possible. Therefore other irradiations were not possible in an attempt to determine the stereochemistry of the C(8) centre.
Little difficulty had been expected in the deprotection of the TBDPS-protected hydroxyl group of 45 since numerous examples of the removal of TBDPS groups have been reported.\textsuperscript{25} In general treatment with 5 equivalents of TBAF or mildly acidic conditions usually result in the complete removal of the TBDPS group in a few hours. However it was found that conversion of 45 to 51 (scheme 22) required 25 equivalents of TBAF in THF stirring at room temperature for 5 days to achieve a 70% conversion. The amount of 45 that was available at this time precluded optimization of this deprotection reaction. [ It was
later found that in similar systems 2 hours of reflux in 35 - 50 excess of TBAF achieved quantitative deprotection. The availability of 51 then allowed us to attempt an oxidation followed by cyclisation of the resulting diketone (52) in an acid-catalysed intramolecular aldol reaction. (Scheme 22)

Several attempts to obtain 52 by Swern oxidation of 51 were unsuccessful. The small scale of the reaction undoubtedly had some effect on the outcome of the experiment. When a chromic acid oxidation [Jones reagent] of 51 was attempted, diketone (52) was isolated in excellent yield. Finally the diketone (52) was refluxed in an acidic methanol solution overnight to produce the tricyclic enone (53) in an isolated yield of >90%.

Tricyclic enone 53 represents a potentially useful intermediate in the projected synthesis of limonoids. For example, it is hoped that dissolving metal reaction \(^{31a}\) followed by the Stork-Boeckman annulation procedure\(^{31b,36,37}\) will provide a tetracyclic enone which can be gem-dimethylated to yield the tetracyclic ketone (57). Elaboration of the furan side chain unit and allylic oxidation could then provide a typical limonoid structure such as ent-azadirone (ent-4). (Scheme 23)

![Scheme 23 Diagram](image-url)
2.1 Stereoselective Synthesis of Steroid B,C,D Ring System:

The widespread occurrence and biological importance of the steroids has stimulated considerable interest in their total synthesis. Much of the recent synthetic work in the steroid area has been concerned with the development of synthetic routes to the biologically important* seco-steroid, calcitriol (58) [syn. 1α,25-dihydroxycholecalciferol, 1,25-dihydroxyvitamin D₃]. Thus it is not surprising that a large proportion of recently published work involves the development of synthetic routes to appropriate hydrindane derivatives (cf. 59 and 60) that represent the C,D ring system and side chain unit of this and related steroids. It is also clear that considerable importance has been given to routes that provide these intermediates with the correct absolute stereochemistry at C(13), C(14), C(17), and C(20).

A selection of synthetic routes to hydrindane derivatives that can serve as key intermediates in steroid synthesis is presented in Schemes 24-27 to provide an overview of work done in this area. In the first of these (scheme 24), Lythgoe and co-workers reported a synthetic route to the previously known bicyclic diol (61).

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* The use of calcitriol and analogues for the treatment of osteoporosis, psoriasis and leukemia is currently being investigated by a number of research groups.
Diol 61 was first described by Inhoffen and co-workers in 1958, as a degradation product of vitamin D$_2$ and is now commonly referred to as the Inhoffen-Lythgoe diol.

Key reactions in the synthetic route (scheme 24) developed by Lythgoe and co-workers are the ortho-ester Claisen rearrangement that leads to the formation of (64) and the subsequent Claisen rearrangement of the hydroxy-lactone (65) to the dimethyl amide (66) via a Meerwein-Eschenmoser reaction.
The stereochemistry of the alcohol functionality of compound 63 (a readily available enantiopure starting material) directs the ortho-ester Claisen rearrangement that produces the proper stereochemistry at C(13) and C(17) in 64 via the mechanism illustrated in scheme 25.
The Claisen rearrangement, being a concerted [3,3] sigmatropic rearrangement, proceeds with retention of configuration, transferring the stereochemistry of the α-oriented hydroxyl group of 63 to the α-oriented substituent at C(13) (64).

The β-orientation of the benzoate group of compound 64 was used in a similar manner to produce the trans cyclohexane derivative 66. Hydrolysis of 64 to allylic alcohol (65) followed by treatment with dimethylamino-1-methoxyethylene caused a Meerwein - Eschenmoser type reaction producing the intermediate (65a, scheme 26). Heating (65a) caused a spontaneous [3,3] sigmatropic rearrangement to the advanced intermediate 66.

The resultant amide (66) was readily hydrolysed, esterified as the methyl ester (67) and cyclised through a base-catalysed Claisen condensation to produce the required stereochemistry at C(13), C(14), C(17) and C(20) [steroidal numbering] as illustrated in
structure 68 in scheme 24. Subsequent functional group transformations as shown in scheme 24 converted 68 to Inhoffen-Lythgoe diol (61).

Other approaches to the Inhoffen-Lythgoe diol (61) have also been described\textsuperscript{40a-d}. As a result of its stereochemistry and functional utility, it is considered a central intermediate in vitamin D\textsubscript{3} synthesis. One of the more interesting approaches to 61 is the biomimetic-type synthesis reported by Johnson and co-workers in 1984.\textsuperscript{40a} This involves the cyclisation of the enyne acetal (76) to provide a trans-hydrindane derivative (79) that can be elaborated by an ene reaction and subsequent stereoselective reduction to the Inhoffen-Lythgoe diol (61).

\[
\begin{align*}
\text{BuLi, THF} & \rightarrow \text{Et}_3\text{SiCH}_2\text{OTf} \\
\text{NaCH(CO}_2\text{Me})_2, \text{EtOH} & \rightarrow \text{LiCl, DMSO, H}_2\text{O} \\
\text{DIBAL, THF} & \rightarrow \text{2S,4S-pentanediol, THF, oxalic acid, Linde 4A sieves} \\
\text{TiCl}_4, \text{CH}_2\text{Cl}_2, 2,4,6\text{-trimethylpyridine, } -78^\circ & \rightarrow \text{PCC, CH}_2\text{Cl}_2 \\
\text{KOH, THF, MeOH} & \rightarrow \text{Ac}_2\text{O, pyridine, DMAP, } 70^\circ \\
\text{H}_2, \text{Lindlar catalyst, MeOH} & \rightarrow \text{CH}_2\text{O, BF}_3\text{E} \rightarrow \text{H}_2, \text{PtO}_2, \text{EtOH} \\
\text{KOH, MeOH, THF} & \rightarrow \text{87% trans : 13% cis}
\end{align*}
\]

Scheme 27
The stereochemistry achieved by the cyclisation of enyne 76 is directly related to the stereochemistry of the acetal group. The stereochemistry of the dimethyl ligand is believed to affect the conformation of 76 prior to cyclisation. In this particular synthesis the (2S, 4S)-pentanediol was used to produce 77. [Johnson and co-workers report that ent-77 is produced, predictably, when (2R,4R)-pentanediol is used.] Scheme 28 illustrates the possible influence of the acetal's methyl substituents on the enyne's conformation prior to cyclisation.

The cyclic acetal assumes a chair conformation in which the enyne chain is in the equatorial orientation, minimizing 1,3-diaxial interactions.(cf. 76a & 76b) As drawn in (76b), the axial methyl group (denoted with an asterisk) is in relative proximity to what is to become C(15). The conformation (76a) in which C(15) moves away from the 'offending' methyl group (*), is the more stable and it is this conformation that defines the stereochemistry of the product (77).
Having established the stereochemistry of C(8), C(13) and C(14) by this cyclisation reaction, Johnson and co-workers used a stereoselective ene reaction to introduce the correct stereochemistry at C(20). (shown below)

Partial hydrogenation of the allene 77 produced the Z-isomer 78 which was then reacted with paraformaldehyde in an ene reaction giving 79. Catalytic hydrogenation and hydrolysis of the acetate group finally gave the Inhoffen-Lythgoe diol (61).

Along with the Inhoffen-Lythgoe diol, the enedione 84 is one of the most widely used enantiopure intermediates in steroid synthesis. The stereoselective synthesis of enedione 84 was independently reported by research groups at Hoffmann-La Roche, Inc. and Schering Corp. and involves the use of (S)-(−)-proline (82) as a chiral auxiliary in the intramolecular aldol condensation of monocyclic diketone 81. Hajos and Parrish's synthesis and elaboration of 84 to an advanced steroidal intermediate is given in scheme 29.
By using S-(-) proline (82), the initial cyclisation is mediated by a chiral ligand present in the transition state. It is reasoned that proline (82) reacts with the methyl ketone of 81 to form a chiral enamine (81a, scheme 30), which in turn causes stereoselective annulation, giving the chiral products 83 or 84 in 87-97 % e.e.
One of the main problems associated with the elaboration of hydridenone 84 to more advanced steroidal intermediates is the stereoselective reduction of the enone group to produce the required trans-hydridane ring system. Simple hydrogenation of the enedione (84) will produce a cis-hydridanone.\textsuperscript{42c} This is due to the fact that formation of the hydridane involves addition of hydrogen to the less hindered convex side of the enedione (84). Hajos and Parrish were able to obtain the trans-hydridane (87, scheme 31), however, by incorporating an acid functionality at C(8). The carboxylic acid group is thought to form a 'pseudo C ring' by hydrogen bonding with the C(9) carbonyl group and this effectively obstructs the upper face of the molecule (86, scheme 29). Using a platinum catalyst Hajos and Parrish hydrogenated compound 86 and obtained a β-keto acid (87) that could be decarboxylated to provide the trans-hydridanone (88). In addition they also reported the synthesis of enone 89 from the crude β-keto acid 87.
In more recent investigations Haynes and co-workers\textsuperscript{43a} have determined that the presence of large substituents at C(17) and C(8) [steroidal numbering] in hydrindenones (90) promote $\alpha$-face hydrogenation and the formation of \textit{trans}-hydrindanes.

\begin{center}
\includegraphics[width=0.25\textwidth]{90.png}
\end{center}

Haynes and co-workers have reported the synthesis of hydrindenones by using the reaction sequence outlined in scheme 31,\textsuperscript{43b} which when followed by reasonably high pressure catalytic hydrogenation produced \textit{trans}-hydrindanes almost exclusively.
The key step in this synthesis is the stereoselective conjugate addition of the allylic anion of a chiral phosphonate (91) to 2-methylcyclopent-2-en-1-one to produce enone 92 as a pure enantiomer. The rationale proposed for the stereoselectivity of this reaction is the formation of the "chair-chair" ten-membered cyclic conformation of the transition state.
Facial selectivity arises from the preferred axial orientation of the phenyl over that of the larger t-butyl group. (below)

Scheme 32

In this research both the natural (94 and 96) and 'unnatural' (ent-94 and ent-96) hydrindenone intermediates were synthesized by using S-(+)-91 or R-(−)-91 as starting materials, respectively.
2.2 Discussion:

Our interest in the hydrindane system is due in part to the common structural and stereochemical features it shares with the hydroxy-acid (2) formed by the ring cleavage of (+)-9,10-dibromocamphor (4, below).

In the previous section several representative examples were given to illustrate approaches that have been taken towards the synthesis of the hydrindane system. They are similar in that chiral ligands are used to introduce stereochemistry to otherwise achiral systems. In our approach chiral induction is not required as our enantiopure starting material, (+)-endo-3--bromocamphor (2), is transformed into the hydroxy-acid (4) with retention of configuration at the C(4) and C(7) positions [camphor numbering] (above). Thus the enantiomeric purity of our product is directly related to the enantiomeric purity of the starting material.44

Previous investigations in our laboratory have resulted in the development of an enantiospecific approach to enone (101; scheme 33) with the correct absolute configuration at C(13), C(17) and C(20) [steroidal numbering].24 In addition, the nature of the side-chain unit at C(20) can be pre-determined by the choice of electrophilic agent used in the alkylation of ketal ester (37).**

** The biological activity of steroids is often related directly to the nature of the side chain used.
Scheme 33
The objective of further studies in this area was the development of an amended procedure to provide a steroidal intermediate with the correct absolute configuration at C(8), C(13), C(14), C(17) and C(20) and with the capability of being converted to specific steroids with structurally different C(20) side chain units. To achieve this objective ketal ester (37) (cf Scheme 33, p 45) was reduced and the resulting alcohol (102) converted to enone 104 by O-methylation and hydrolysis of the ketal protecting group.

\[
\begin{align*}
\text{i) LiAlH}_4, \text{THF} & \quad \text{ii) KH, MeI, THF} \quad \text{iii) IN HCl, acetone / H}_2\text{O} \\
37 & \rightarrow 102 \rightarrow 103 \rightarrow 104
\end{align*}
\]

Scheme 34

Reaction of (104) with sodium hydride in DMSO followed by alkylation with 1-iodo-3-(t-butyldiphenylsilyloxy)pentane (50) provided enone (105) in a ~55% yield. The dialkylated product (106) was a co-product in this reaction.

\[
\begin{align*}
\text{NaH, DMSO} & \quad \text{OMe} \\
104 & \rightarrow \text{105} + \text{106}
\end{align*}
\]

Scheme 35

By analogy with the work of Haynes and co-workers it seemed likely that 105 would undergo stereoselective reduction to some degree. Previous studies by Haynes and
co-workers\textsuperscript{43a} showed that reduction of enone 107 could be accomplished with excellent stereoselectivity when the hydrogenation was carried out at 820 psi. (Scheme 36).

Subsequent epimerization of the C(8) centre was achieved by reaction with KOH-MeOH and the saturated product (108) was obtained in good yield.

\begin{align*}
\text{Scheme 36}
\end{align*}

It was suggested by Haynes and co-workers that the stereochemical bulk of substituents at C(8) and C(17) would effectively promote \(\alpha\)-face hydrogenation. They found that under several atmospheres of pressure (conditions used successfully on similar systems) substantial amounts of product with \(\beta\)-face hydrogenation was formed. Since the formation of a \textit{trans}-hydrindane compound seemed to require the presence of groups at the C(8) and C(17) position we considered the reduction of 105 could be expected to undergo hydrogenation at the \(\alpha\)-face of the enone system.
Hydrogenation of 105 under the same conditions (820 psi, EtOH, Pd·C) used by Haynes and co-workers, followed by epimerization with sodium methoxide resulted in the formation of ketone 110. The stereoselectivity of these reactions, however, was not immediately obvious and detailed NMR analysis and an extensive comparison of chemical shift values reported in the literature (appendix A) eventually convinced us that the stereochemistry of 110 is indeed as indicated in scheme 37.

\[ \text{A priori it seemed that the stereochemistry of compound 110 could be readily verified by a series of decoupling experiments to identify specific protons, followed by NOE measurements to determine the orientation of the C(8) and C(14) hydrogens relative to the angular methyl at C(13).} \]

\[ \delta = 0.79 \text{ ppm, s} \] Several factors however made these determinations difficult. For example, the methylene and methine region of the NMR spectra appears as complex multiplets ranging from 1.3 to 1.9 ppm, effectively obscuring the C(14) proton signal. Also, the C(8) and C(11) protons (α to the carbonyl), at 2.0 to 2.4 ppm, exhibit complex splitting patterns due to the number of neighbouring diastereotopic hydrogens, making the analysis of coupling interactions very difficult.(Spectrum 1)
Though the C(8) proton of compound 110 appears as a well-resolved multiplet (2.03 to 2.16 ppm) its orientation relative to the C(14) proton is not immediately apparent. As the C(14) proton signal is completely obscured, the C(14) and C(8) coupling interactions must be obtained solely through the analysis of the C(8) proton signal.

The complete stereochemical analysis of 110 begins with the comparison of the H(8) signal before and after epimerization of 109. The splitting pattern of the signal representing
H(8) is shown in spectrum 2 for both 109 and 110. As one can see they are both complex but sufficiently different as to suggest epimerization has occurred.

As one can see they are both complex but sufficiently different as to suggest epimerization has occurred.

Spectrum 2

A NOE experiment showed that after epimerization of (109) the C(8)-H was in the β-orientation, as a positive enhancement was observed when the angular methyl group at C(13) was irradiated. This is good evidence that after catalytic hydrogenation but prior to epimerization, the C(8)-H was oriented on the α-face of the molecule along with C(14)-H, suggesting a trans ring junction in (109) or (110). Further NMR experiments were carried out to provide further evidence to support this conclusion.

Numerous NMR experiments were carried out (including J-resolved, HETCOR, APT and a series of 1H homonuclear decoupling experiments) yet little additional information was gained with respect to the stereochemistry of the ring junction. It was only through close examination of C(8)-H's splitting pattern that the stereochemistry of the ring junction could be inferred. One would expect that C(8)-H signal would appear as a doublet of doublets of doublets due to coupling with C(7)-H', C(7)-H'' and C(14)-H.
Experimentally it was found that C(8)-H appears as a multiplet of 13 distinguishable peaks in the 400 MHz spectrum. This is substantially more than the eight expected and may be due to the presence of diastereoisomers (110a and 110b). The presence of diastereoisomers was investigated by running a simple 500 $^1$H MHz NMR. The H(8) signal in the 500 $^1$H MHz NMR spectrum was then compared with the H(8) signal in the $^1$H 400 MHz spectrum. As seen in spectrum 3 the overall symmetry of the signal in the $^1$H 400 MHz spectrum is different from that in the 500 $^1$H MHz spectrum.

$H_8$ multiplet of 110

Spectrum 3

If the complexity of the multiplets was simply due to coupling interactions no change would have been noted between the two when observed at different field strengths. Coupling interactions and their respective magnitudes are independent of the applied magnetic field;
signal frequencies, however, are not and the frequency difference between signals will change according to magnetic field strength. That is what spectrum 3 illustrates: an increased separation of the overlapping C(8)-H signals in the two diastereoisomers 110a and 110b.

Careful examination of the C(8)-H multiplet in the 500 MHz spectrum indicates that the two diastereoisomers have signals at 2.12 ppm and 2.07 ppm. Each signal is composed of a doublet of doublets of doublets with the approximate coupling of 3.3 Hz, 9.2 Hz and 13.2 Hz. All three couplings are consistent with those reported by Haynes for compound (108) [2.8 Hz, 9.7 Hz and 12.7 Hz] (scheme 36). The unequal coupling of C(8)-H with C(7)-H' and C(7)-H" indicates an unequal dihedral angle in the most stable conformation of (110). The larger coupling of 13.3 Hz coupling is consistent with an axial-axial relationship between C(8)-H and C(14)-H. This in turn is consistent with our original assumption that C(14)-H is in the α-orientation and is trans to the angular C(13) methyl group.

At this point the NMR evidence had strongly suggested that the stereochemistry of (110) at the CD ring junction was trans. Examination of the chemical shifts of angular methyl groups at C(13) in other steroidal systems increased our confidence. It was observed that the chemical shift of the angular methyl group at C(13) was correlated to its relative orientation to the hydrogen at C(14). The C(13) methyl hydrogens typically resonate at a chemical shift of approximately 0.70 to 0.95 ppm when in a trans ring junction, whereas a cis ring junction often showed the C(13) methyl group hydrogens resonate between 0.90 to 1.25 ppm.\(^{45-52}\) (Appendix A) As compound 110 exhibits a methyl resonance at 0.79 ppm it is reasonable to suggest a trans ring junction.

Though this research is not complete, the results observed illustrate a simple, effective way of synthesising advanced intermediates for steroid synthesis.
Experimental

General Experimental

Unless otherwise stated the following statements are implied.

All reagents were of commercial grade and were used as received unless otherwise specified. The solvents that were used were spectral grade and were purified as follows: THF and Et2O were distilled from Na/benzophenone; CH2Cl2, i-Pr2NH and MeOH were distilled from CaH2; and DMSO and Et3N were distilled from KOH.

Thin layer chromatography (TLC) was carried out under specified solvent conditions using Merck 5735 Precoated Silica Gel 60 F254 on plastic backing (0.2 mm in thickness). Development of TLC plates were carried out using one or several of the following methods: I2 vapour, UV light or ammonium molybdate/H2SO4. Flash chromatography was carried out using Merck Silica Gel 60 (230 - 400 mesh) and various solvents as noted. Radial chromatography was accomplished using SiO2 coated plates (Silica Gel 60 F254 with gypsum) at thickness of 1 or 2 mm. The chromatotron used was a Harrison Research Chromatotron® 7924T. Gas chromatography was performed using a Hewlett-Packard HP5830A instrument, which was equipped with a 0.2 mm x 11 m OV-101 column. Helium was used as the carrier gas.

Infrared spectra were carried out using a Bomem Michelson 100 Fourier Transform Infrared spectrophotometer, equipped with an internal standard. Samples were prepared as neat films between NaCl plates or as solutions in a NaCl cell (0.1 mm path length). Proton NMR was carried out on a Bruker WH-400 spectrometer (field strength 400 MHz) or Bruker AMX-500 (field strength 500 MHz). Signals are reported on the δ scale and are positioned relative to the chloroform singlet (7.24 ppm). Low resolution mass spectra were recorded on a Kratos MS-80 spectrometer and high resolution mass spectra were recorded on a Kratos MS-50 spectrometer.
Elemental analyses were performed by Mr. P. Borda, Microanalytical Laboratory, Department of Chemistry, U.B.C.

(+)-3,9-Dibromocamphor (29):

(+)-endo-3-Bromocamphor (2, 100 g, 0.43 mol) was cooled to 0°C in a large round-bottom flask and a solution of Br₂ (35 mL, 110 g, 1.5 eq.) in chlorosulfonic acid (80 mL) was slowly added over 5 min. After 20 min, the ice bath was removed and the reaction mixture was allowed to warm to room temperature (1.5 h) before being quenched by careful addition to NaHSO₃ (50 g) and ice (0.5 L). The resultant yellow solid was collected by filtration, dissolved in CH₂Cl₂ (600 mL) and the organic layer washed with sat. NaHCO₃ solution (2 × 100 mL), H₂O (2 × 100 mL) and brine (200 mL). The organic extract was dried over MgSO₄, filtered and the solvent removed to provide (29) as a crude yellow solid (230 g). Recrystallization from MeOH produced (+)-3,9-dibromocamphor (29) as a white solid (105.5 g) that was shown by GC analysis to be 85% pure. A small sample was recrystallised from MeOH to yield a pure sample for ¹H NMR analysis.

¹H NMR (CDCl₃): δ = 1.04 (3H, s, C(10)H₃); 1.12 (3H, s, C(8)H₃); 1.43 - 1.58 (1H, m, C(6) endo H); 1.73 (1H, ddd, J = 16, 12, 4 Hz, C(5) endo H); 1.84 - 1.94 (1H, m, C(5) exo H); 2.19 (1H, m, C(6) exo H); 2.70 (1H, t, J = 4 Hz, C(4) exo H); 2.29, 3.65 (2H, qAB, J = 11Hz, C(9)H₂Br ); 4.57 (1H, dd, J = 4,1 Hz, C(3)H).
(+)-3,9,10-Tribromocamphor (30):

A solution of Br₂ (155 g, 0.98 mol, 1.5 eq.) in chlorosulfonic acid (200 mL) was slowly added to (+)-3,9-dibromocamphor (29) (201.2 g, 92% purity by GC, 0.60 mol) at 0°C. The reaction mixture was allowed to warm to room temperature and after 4 days an additional amount of Br₂ (15 mL) and ClSO₃H (15 mL) were added. This was repeated on the 11th day and after a further 16 h the reaction mixture was added to a mixture of ice (600 g) and NaHSO₃ (150 g). The reaction mixture was extracted with CH₂Cl₂ (1 × 500 mL, 2 × 250 mL) and the organic layer washed with saturated NaHCO₃ solution (3 × 200 mL). The organic extracts were then washed with brine, dried over MgSO₄, filtered, and the solvent removed to provide crude (+)-3,9,10-tribromocamphor (30) as a dark brown oil (208 g; 48% pure by GC) that was used without further purification.
Crude (±)-3,9,10-tribromocamphor (30, 190 g, 50% purity) was dissolved in a 1:1 solution of diethyl ether and acetic acid (700 mL) and cooled to 0 °C. Zinc dust (84 g, 1.28 mol) was slowly added over 1 h and after warming to room temperature the reaction mixture was filtered through Celite. The filtrate was washed successively with water (3 × 200 mL), saturated NaHCO₃ (2 × 100 mL) and brine (2 × 200 mL), and then dried over MgSO₄. Removal of solvent provided a brown solid that was crystallised from MeOH to yield (±)-9,10-dibromocamphor (3) as a white solid (49.45 g, 0.128 mol; yield 64%).

C₁₀H₁₄Br₂O  Calc. Mass: 311.9371
Meas. Mass: 311.9377

IR (CHCl₃): ν = 2975, 2900 (C–H); 1740 cm⁻¹ (C=O).

MS (70 eV) : m/z (%) = 312, 310, 308 (M⁺, 0.5, 0.9, 0.4)

¹H NMR (CDCl₃): δ = 1.10 (3H, s, C(8)H₃); 1.43 - 1.58 (2H, m, C(5) and C(6) endo H); 1.98 (1H, dAB, J = 18 Hz, C(3) endo H); 2.05 (1H, dddAB, JAB=18 Hz, J= 5, 4 Hz, C(3) exo H); 2.25 - 2.35 (1H, m, C(6) exo H); 2.41 (1H, dt, J= 19, 4 Hz, C(5) exo); 2.66 (1H, t, J=5Hz, C(4) ); 3.48 and 3.59 (1 H each); 3.70 (2H) 3 dAB, J = 12 Hz, C(9)H₂Br and C(10)H₂Br).
Hydroxy-acid (4):

\[
\begin{align*}
\text{O} & \quad \text{Br} & & \quad \text{Br} \\
& \quad \text{Br} & \quad \text{Br} & \quad \text{H} \quad \text{O} \\
& \quad \text{CO}_2 \\
\end{align*}
\]

A solution of (+)-9,10-dibromocamphor (3, 45.35 g, 0.146 mol) in DMSO (1 L), 150 mL H₂O and 33.6 g of KOH (0.730 mol, 5 eq.) were stirred at 90 °C for 21 h. The solution was then allowed to cool to room temperature at which point it was acidified to pH 1 by the addition of 6 M HCl. The product was then extracted with EtOAc (4 × 150 mL) and the organic extracts dried over MgSO₄. Removal of solvent produced hydroxy-acid (4) as a yellow crystalline solid (18.77 g, 0.10 mol; yield 70%).

C₁₀H₁₆O₃

Calc. Mass: 184.1099
Meas. Mass: 184.1103

IR (CHCl₃) ν = 3400 - 2600 (COOH, OH); 2975, 2895 (C-H); 1705 (C=O); 1650 (C=CH₂); 900 cm⁻¹ (=C-H).

MS (70 eV): m/z(%) = 184 (M⁺, 0.3); 166 (4.9); 154 (7.7) 94 (100).

¹H NMR (CDCl₃): δ = 0.88 (3H, s, CH₃); 1.33 - 1.44 (1H, m); 1.95-2.03 (1H, m); 2.23 (1H, dd, J = 15, 9Hz); 2.28 - 2.40 (1H, m); 2.43 - 2.55 (4H, m) 3.43, 3.54 (2H, dAB, J = 11.5 Hz, CH₂-O-); 4.83, 5.03 (1 each, 2t, J = 2.5 Hz, (=CH₂).
**Hydroxy-ester (32):**

![Chemical structure diagram]

Anhydrous K$_2$CO$_3$ (7.51 g, 54.3 mmol) was added to a solution of hydroxy-acid (4, 5.00 g, 27.0 mmol) in DMF (200 mL). The reaction mixture was stirred for 2 h under argon and then iodomethane (3.4 mL, 7.7 g, 53.6 mmol) was added by syringe. After 3 h the reaction mixture was quenched with water (250 mL) and extracted with Et$_2$O (5 x 50 mL). The ethereal layer was washed and dried and removal of solvent produced crude hydroxy-ester (32) as an orange oil (5.69 g). Flash chromatography (230 - 400 mesh SiO$_2$, 7 x 15 cm) using 35% EtOAc / 65% hexane as eluant, afforded pure hydroxy-ester (32) as a colorless oil (5.28 g; yield 98%).

IR (neat): $\nu = 3450$ (OH); 3090 (vinyl C-H); 2950, 2880 (C-H); 1730 (C=O); 1665 (C=CH$_2$); 885 cm$^{-1}$ (vinyl C-H).

MS (70 eV): m/z(%) = 169 (M$^+$ – OCH$_3$, 1.8); 168 (M$^+$ – CH$_3$OH, 23.0); 167 (17.9); 135 (7.7); 107 (100).

$^1$H NMR (CDCl$_3$): $\delta = 0.87$ (3H, s, CH$_3$); 1.31 - 1.43 (1H, m); 1.90 - 1.99 (1H, m); 2.21 (1H, dd, J = 17, 11 Hz); 2.28 - 2.40 (1H, m); 2.42 - 2.55 (3H, m); 3.41, 3.54 (2H, d$_{AB}$ 12 Hz); 3.70 (3H, s, CO$_2$CH$_3$); 4.83, 5.02 (1H each, 2t, J = 2 Hz, =CH$_2$).
Aldehyde-ester (33):

A solution of oxalyl chloride (4.12 g; 32.4 mmol, 1.2 eq.) in dry CH₂Cl₂ (30 mL) was cooled to -78°C. DMSO (2.3 mL) and dry CH₂Cl₂ (50 mL) were added and after 35 min a solution of hydroxy-ester (32) (5.28 g, 26.6 mmol) dry CH₂Cl₂ (75 mL) was added over a 1 h period. Stirring was continued for 1.5 h at -78°C and Et₃N (11.3 mL, 8.2 g, 81 mmol) was added. The reaction mixture was allowed to warm to room temperature (18 h) and washed with water (100 mL), 1 M HCl (2 × 100 mL), saturated NaHCO₃ (100 mL) and brine (100 mL). Removal of solvent yielded aldehyde (33) as a colorless viscous oil (4.43 g; yield 82%) that required no further purification.

IR (neat): \(\nu = 2960, 2920, 2840 \text{ (C-H)}; 1740 \text{ (C=O, ester)}; 1710 \text{ (C=O)}; 1650 \text{ (C=CH₂)}; 895 \text{ cm}^{-1} (=\text{C-H}).\)

MS (70 eV): \(m/z\) (%): 182 (M⁺, 10.5); 168 (12.6); 167 (24.5); 166 (11.8); 107 (100).

\(^1\text{H NMR} \text{ (CDCl}_3\text{)}: \delta = 1.05 \text{ (3H, s, CH}_3\text{)}; 1.98 - 2.06 \text{ (1H, m)}; 2.34 \text{ (2H, dd, } J = 7, 1.5 \text{ Hz)}; 2.38 - 2.51 \text{ (3H, m)} 2.77 \text{ (1H, dq, } J = 12, 7 \text{ Hz); 3.67 \text{ (3H, s, -OCH}_3\text{)}; 4.78 \text{ and 5.12 (1H each } J = 2 \text{ Hz, =CH}_2\text{); 9.30 (1H, s, CHO).}\)
Ester (34):

A solution of trimethyl phosphonoacetate (5.28 g, 29.0 mmol) in dry THF (50 mL)
was added dropwise over a 30 min period to a slurry of KH (0.70 g, 29.0 mmol) and dry
THF (50 mL). After 1 h a solution (50 mL) of ester-aldehyde (33, 4.43 g, 24.3 mmol) in
THF (50 mL) was added dropwise over 30 min and the reaction mixture allowed to stand
for 18 h. Addition of water (100 mL), extraction with Et2O (4 x 100 mL), and removal of
solvent provided colorless diester (34) that was purified by flash chromatography (230 -
400 mesh SiO2, 5.5 x 17 cm; 40% EtOAc / 60% hexane as eluant ) to provide pure diester
(34, 4.99 g; yield 80%).

IR (neat); v = 2970 - 2850 (C-H); 1735 (C=O, saturated ester); 1720 (C=O, α,β-
unsaturated ester); 1650 (C=C); 890 cm⁻¹ (=CH2).

MS (70 eV): m/z (%): 252 (M⁺, 10.6); 232 (1.7); 221 (23.6); 222 (72.6); 205 (8.4); 192
(26.8); 119 (100).

¹H NMR (CDCl₃): δ = 1.05 (3H, s, CH₃), 1.43-1.53 (1H, m) 1.97-2.05 (1H, m) 2.11-
2.20 (1H, m) 2.28-2.39 (2H, m); 2.40-2.48 (1H, m); 2.50-2.58 (1H, m); 3.65
and 3.75 (3H each, 2 s, 2x(-OCH₃); 4.70 and 4.93 (1 each, 2 t, J = 2.5 Hz,
=CH₂); 5.85 (1H, d, J = 16 Hz, -C(O)CH=CHR); 6.88 (1H, d, J = 16 Hz, –
C(O)CH=CHR).
Diester (35):

A solution of diester (34, 5.95 g, 23.6 mmol) in dry MeOH (150 mL) was added to flame-dried Mg turnings (1.43 g). After stirring for 4.5 h under argon at room temperature the reaction mixture was quenched with water (100 mL) and the Mg(OH)$_2$ suspension dissolved by addition of 6 M HCl. The aqueous reaction mixture was extracted with ether (3 x 100 mL) and the combined extracts washed with saturated NaHCO$_3$ (100 mL), water (100 mL) and brine (100 mL). Removal of the solvent provided diester (35) as a pale yellow oil (5.513 g, 21.7 mmol; yield 92%).

IR (neat): $\nu = 3090$ (=C-H); 2955, 2880, 2850 (C-H); 1740 (C=O); 1650 (C=C); 885 cm$^{-1}$ (=CH$_2$).

MS (70 eV): $m/z$ (%) = 254 (M+, 3.2); 224 (11.4); 223 (51.3); 222 (56.3); 220 (10.8); 207 (15.5); 180 (65.2); 107 (100).

$^1$H NMR (CDCl$_3$): $\delta = 0.89$ (3H, s, CH$_3$); 1.27 - 1.37 (1H, m); 1.70 - 1.85 (2H, m); 1.86 - 1.94 (1H, m); 2.10 - 2.18 (2H, m); 2.22 - 2.34 (3H, m); 2.36 - 2.47 (2H, m); 3.66 and 3.68 (3H each, 2s, 2 x -OCH$_3$); 4.73 and 4.93 (1 H each, 2 t, J = 2 Hz, 2 Hz, =CH$_2$).
Preparation of Diacid (36) from Diester (35):

![Chemical structure of 35 and 36]

The diester (35, 5.024 g, 22.2 mmol) was dissolved in a 1:1 solution of methanol and water (300 mL). KOH (6.3 g, 0.11 mmol) was added to the vigorously stirred solution at room temperature and after 8.5 h the reaction was quenched by acidifying to pH 1 with 6 M HCl. Extraction with Et2O (6 x 75 mL) followed by removal of solvent provided crude diester (36) as a yellow oil (5.2 g) that was further purified by redissolving in Et2O, extraction with 1 M KOH, acidification, and extraction with ether. Removal of solvent provided diacid (36) as a pale yellow oil (4.56 g, 20.1 mmol; yield 91%).

IR (CHCl3): \( \nu = 3450 - 2300 \) (broad, =COOH); 2960, 2945 (C-H); 1710 (C=O); 1655 (C=C); 885 cm\(^{-1}\) (=CH2).

MS (70 eV): m/z (%) = 208 (M\(^+\) - H2O, 23.0); 190 (6.7); 180 (5.7); 166 (50.7); 153 (100).

\(^1\)H NMR (CDCl3): \( \delta = 0.89 \) (3H, s, CH3); 1.30 - 1.42 (1H, m); 1.85 and 1.91 (2H, q\(_{AB}\)t, \( J = 14 \) Hz, 7.5 Hz, -CH\(_2\)CH\(_2\)CO\(_2\)H); 2.00 - 2.10 (2H, m); 2.13 - 2.20 (1H, m); 2.24 - 2.38 (3H, m); 2.43 - 2.55 (2H, m); 4.72 and 4.93 (1H each, 2 t, \( J = 2.5 \) Hz, 2 Hz, =CH\(_2\)H); 11.20 - 12.50 (2H, broad singlet, 2 x =COOH).
Preparation of Diacid (36) from Diester (34):

A solution of diester (34, 5.28 g, 20.9 mmol) in dry MeOH (75 mL) was added to flame-dried magnesium turnings (1.53 g, 62.7 mmol) under argon at room temperature. After 15 h a solution of KOH (5.9 g, 0.10 mol) in water (150 mL) was added to the vigorously stirred reaction mixture and after 7.5 h the reaction mixture was acidified with 6 N HCl. Extraction with EtOAc (4 × 125 mL) followed by washing with brine (125 mL) and removal of solvent produced diacid (36) as a crude yellow oil (5.1 g). Although this represents slightly more than 100% weight recovery the crude product was used without further purification. Spectral data for the crude diacid (36) is consistent with that previously reported.

Enone-ester (5):

Trifluoroacetic anhydride (2.54 g, 12.1 mmol) was added via syringe to the crude diacid (36, 1.09 g, ~5.0 mmol) dissolved in dry CH2Cl2 (100 mL). After 2 h at room temperature the solvent was removed by rotary evaporation, with care been taken to minimize exposure to atmospheric moisture. Dry MeOH (35 mL) and a catalytic amount of
p-toluenesulfonic acid was added and the reaction mixture was stirred for 15 h at room temperature under an argon atmosphere. The MeOH was then removed and replaced by EtOAc (50 mL) which was partitioned with water (100 mL). The product was extracted with Et2O (3 × 25 mL), washed with brine, dried over MgSO4, filtered and the solvent removed. This extraction process was sufficient to yield a pure sample of the enone-ester (5, 1.04 g, 4.7 mmol; yield 97%).

IR (neat): ν = 2950 (C-H); 1740 (C=O, ester); 1660 cm⁻¹ (C=O, enone).

MS (70 eV): m/z (%) = 222 (M⁺, 33.6); 207 (15.4); 194 (22.4); 191 (21.8); 180 (43.2); 121 (100.0).

¹H NMR (CDCl₃): δ = 1.05 (3H, s, CH₃); 1.54 - 1.66 (1H, m); 1.80 (1H, dABdd, J = 15, 14, 5 Hz); 1.97 (1H, dABdd, J = 15, 6, 2 Hz); 2.05 - 2.14 (2H, m); 2.30 (1H, dABd, J = 15, 9 Hz); 2.39 (1H, dABdd, J = 18, 5, 2 Hz); 2.44 - 2.57 (3H, m); 2.68 (1H, dABdt, J = 20, 11, 2 Hz); 3.71 (3H, s, -OCH₃); 5.80 (1H, s, =CH₂).

Ketal-ester (37):

A Dean-Stark apparatus was charged with a solution of benzene, ethylene glycol (1.70 mL, 1.88 g, 30.3 mmol), PPTS (0.115 g, 0.45 mmol) and the enone-ester (5, 670 mg, 3.03 mmol) and the solution was refluxed overnight. The reaction mixture was cooled.
to room temperature, diluted with Et₂O (100 mL) and the organic layer washed with H₂O (3 x 100 mL), brine (50 mL) and finally dried over MgSO₄. Filtration and solvent removal yielded a yellow mobile oil (1.26 g). The crude material was purified by radial chromatography, eluting with 15% EtOAc / 85% hexane. This provided ketal (37) as a colorless mobile oil (645 mg, 2.62 mmol; yield 80%).

IR (neat): ν = 3050 (=C-H); 2960, 2900, 2860 (C-H); 1740 cm⁻¹ (C=O).

MS (70 eV): m/z (%) = 266 (M⁺, 2.1); 235 (1.2); 99 (100.0).

¹H NMR (CDCl₃): δ = 0.92 (3H, s, CH₃); 1.51 - 1.59 (1H, m); 1.65 - 1.74 (2H, m); 1.79 - 1.88 (1H, m); 1.99 - 2.07 (1H, m); 2.32 - 2.52 (6H, m); 3.67 (3H, s, -OCH₃); 3.93 - 4.00 (4H, m, O(CH₂)₂O-); 5.33 (1H, s, =CH₂).

Ketal-diester (38):

A solution of diisopropylamine (1.40 mL, 1.26 g, 12.4 mmol) and dry THF (30 mL) was cooled to 0°C under an argon atmosphere and n-BuLi (1.55 M, 7.1 mL, 11.3 mmol) was added by syringe. The reaction mixture was stirred for 45 min and then cooled to -78°C. Ketal-ester (37, 3.02 g, 11.3 mmol) in dry THF (20 mL) was added via syringe and allowed to react for a further 1 h. Methyl bromoacetate (2.65 g, 17.3 mmol) was then
added and the reaction mixture was kept at -78°C for 1 h and was then allowed to warm to room temperature overnight (14 h). The reaction mixture was quenched by addition of saturated NH₄Cl solution (100 mL). Extraction with Et₂O (3 × 100 mL) followed by removal of solvent yielded a red-brown oil (3.5 g). Flash chromatography using a 65 x 180 mm column of silica gel (230 - 400 mesh) and elution with 40% Et₂O / 60% petroleum ether afforded unreacted starting material (1.66 g) and diester (38) (1.94 g).

IR (CHCl₃): ν = 2934 (C-H); 1733 (C=O); 1156 cm⁻¹ (C-O).

MS (70 eV) : m/z (%) = 338 (M⁺, 1.9), 307 (M⁺ - OMe, 2.5); 192 (2.0); 179 (2.0); 131 (4.3); 99 (100.0).

¹H NMR (CDCl₃): δ = 1.05 (3H, s, C-13-Me); 1.43(1H, ddd, J = 4, 11, 11 Hz); 1.50 - 1.64 (2H, m); 1.75 (1H, ddd, J = 4, 14, 14 Hz); 1.94 - 2.03 (1H, m); 2.27 - 2.36 (3H, m); 2.47 (1H, dd, J = 4, 16 Hz, C-22 H); 2.12 (1H, ddd, J = 4, 11, 11 Hz, C-17 H); 2.65 ( 1H, dd, J = 11, 16 Hz, C-22 H); 2.93 (1H, ddd, J = 4, 11, 11 Hz); 3.63 (3H, s, CO₂Me); 3.64 (3H, s, CO₂Me); 3.86 - 3.94 (4H, m, -OCH₂CH₂O-); 5.30 (1H, s, =CH).
Ketal-diol (39):

To a stirred suspension of LiAlH₄ (0.83 g, 21.9 mmol) and dry THF (60 mL) at 0°C was added a solution of ketal-diester (38, 1.24 g, 3.66 mmol) in dry THF (15 mL) via syringe over 15 min. The reaction mixture was stirred at room temperature under argon for 13.5 h and then carefully quenched by slow addition of NaSO₄·10 H₂O and H₂O (100 mL). Extraction with Et₂O (4 x 100 mL) followed by removal of the solvent (dried over MgSO₄) yielded ketal-diol (39, 0.73 g; yield 71%) which was used without further purification.

IR (neat): ν = 3340 (s, b; OH); 2930 (C-H); 1620 (C=C); 1110 cm⁻¹ (C-O).

MS (DCI, NH₃) : m/z (%) = 283 ((M+H)+, 96.0); 282 (M+, 5.2); 265 (M+-OH, 13.2); 221 (23.5); 99 (100.0).

¹H NMR (CDCl₃): δ = 0.97 (3H, s, C-13-Me); 1.52 - 1.68 (3H, m); 1.75 - 2.04 (6H, m); 2.25 - 2.40 (3H, m); 2.60 - 3.10 (2H, broad singlet, 2 x OH); 3.50 - 3.55 (1H, m, C-21-HHOH); 3.62 - 3.70 (1H, m, C-21-HHOH); 3.72 - 3.80 (2H, m, C-22-H₂OH); 3.87 - 3.97 (4H, m, -OCH₂CH₂O-); 5.29 (1H, s, =CH).
Dimethoxy-ketal (41):

Ketal-diol 40 (0.733 g, 26.0 mmol) in dry THF (50 mL) was treated with KH (2.92 g, 73 mmol) for 0.5 h. Methyl iodide (2.53 mL, 1.11 g, 78 mmol) was added and after 1.5 h the reaction mixture was quenched by the careful addition of H2O (100 mL). Extraction with Et2O (4 x 100 mL) followed by removal solvent from the dried, combined extracts provided dimethoxy-ketal as a pale yellow oil (> 95% pure by GC) that was used without further purification.

C18H30O4  
Calc. mass 310.2144  
Meas. mass 310.2143

IR (neat): ν = 2900 (C-H); 1455 (C-H); 1106 cm⁻¹ (C-O).

MS (70 eV) : m/z (%) = 310 (M⁺, 9.1); 278 ((M⁺– MeOH), 1.1); 265 (12.0); 193 (5.0); 147 (10.9); 99 (100.0).

¹H NMR (CDCl₃): δ = 0.90 (3H, s, C-13-H₃); 1.50 - 1.65 (3H, m); 1.70 - 1.90 (4H, m); 1.90 - 2.05 (2H, m); 2.27 - 2.40 (3H, m); 3.27 (3H, m, OCH₃); 3.30 (3H, s, OCH₃); 3.36 - 3.45 (4H, m, -OCH₂CH₂O⁻); 5.28 (1H, s, =CH).
Dimethoxy-enone (42):

A solution of dimethoxy-ketal (41, 37 mg, 0.11 mmol), 1 M HCl (2 mL) and acetone (4 mL) was refluxed for 1.5 h. TLC and GC analysis showed complete conversion of starting material to a single product. The reaction mixture was cooled to room temperature, diluted with H2O (10 mL) and extracted with Et2O (3 x 30 mL). The ether extracts were washed with sat. NaHCO3 and dried over MgSO4. Removal of solvent afforded dimethoxy-enone (42) as a yellow oil (25.8 mg; yield 84%). Purification of this compound was accomplished by column chromatography (SiO2; 230-400 mesh) using 60% EtOAc / 40% hexane.

<table>
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<th>C16H26O3</th>
<th>Calc. Mass</th>
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</tr>
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<tr>
<td>Meas. Mass</td>
<td></td>
<td>266.1880</td>
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</table>

IR (neat): ν = 2900 (C-H); 1665 (C=O); 1456 (C-H); 1110 cm⁻¹ (C-O).

MS (70 eV) : m/z (%) = 266 (M⁺, 16.6); 251 (M⁺-CH₃, 46.5); 234 (M⁺-MeOH);
202(15.1); 121 (94.0).

¹H NMR (CDCl₃): δ = 1.11 (3H, s, C-13-Me); 1.53 (2H, m); 1.74 - 1.84 (3H, m); 1.89
(1H, dt, J = 5, 14 Hz); 2.34 (1H, ddd, J = 1, 4, 18 Hz); 2.38 - 2.59 (2H, m); 2.65
(1H, dddd(2, 2, 11, 20 Hz); 3.31 (3H, s, OCH3); 3.34 (3H, s, OCH3); 3.38 (2H, 
d, J = 4 Hz, -CHCH2O); 3.40 (2H, t, J = 7 Hz); 5.75 (1H, s, =CH-).

1-Chloro-3-hydroxypentane (48):

Freshly distilled 1-chloropentan-3-one (47, 9.16 g, 76.0 mmol) was dissolved in 
dry THF (30 mL) and cooled to 0°C. LiAlH4 (1.10 g, 28.5 mmol) was added in three 
equal portions over 15 min and after 1 h the reaction mixture was quenched by careful 
addition of Na2SO4·10H2O (~ 5 g) and H2O (20 mL). The gelatinous precipitate was 
dissolved in 1 M HCl and the mixture extracted with Et2O (4 x 100 mL). Removal of 
solvent from the dried extract gave 3-hydroxy-1-chloropentane (48) as a mobile oil (7.86 
g). The IR spectrum of the crude product showed no carbonyl stretching bands, and the 
crude product was used without further purification. For spectral analysis 300 mg of the 
crude sample was purified by radial chromatography (2 mm plate, PF-254 SiO2) eluting 
with 1:1 hexane/CH2Cl2.

IR (neat): v = 3332 (OH); 2966, 2931, 2879 (-C-H); 1459 cm⁻¹ (OH bend).

¹H NMR (CDCl3): δ = 0.95 (3H, t, J = 8Hz, -CH₂CH₃); 1.46 - 1.58 (2H, m); 1.82 - 
1.96 (2H, m); 2.06 (1H, broad singlet, -OH); 3.65 - 3.80 (3H, m, -CH₂I, 
CHOH)
1-Chloro-3-(t-butyldiphenylsilyloxy)pentane (49):

\[
\begin{align*}
\text{OH} & \quad \text{Cl} \\
48 & \quad \rightarrow \\
\text{OTBDPS} & \quad \text{Cl}
\end{align*}
\]

A solution of 1-chloro-3-hydroxypentane (48, 6.03 g, 49.2 mmol), imidazole (16.7 g, 0.246 mol, 5 eq.) and TBDPSCI (13.2 mL, 13.9 g, 50.8 mmol) in DMF (150 mL) was stirred for 11 h at room temperature. TLC analysis showed a substantial amount of product as well as starting material in the reaction mixture. After addition of H2O (200 mL) the reaction mixture was extracted with Et2O (4 x 100 mL). The organic layer was washed with saturated NaHCO3 solution (200 mL), brine (200 mL) and dried over MgSO4. Removal of solvent yielded crude product (18.1 g). Column chromatography of a sample (3.3 g) of product provided (49) (1.56 g) and starting material (48) (0.4 g).

IR (neat): \( \nu = 3070 \) (aromatic C-H); 2955, 2940, 2857 (-CH); 1427 (CH bend); 1109 cm\(^{-1}\) (-C-O stretch).

\(^1\)H NMR (CDCl3): \( \delta = 0.73 \) (3H, t, \( J = 8 \) Hz, -CH\( _2 \)CH\(_3 \)); 1.04 (9H, s, -C(CH\(_3 \))\(_3 \)); 1.42 - 1.48 (2H, m); 1.87 - 1.95 (2H, m); 3.53 (2H, t, \( J = 11.5 \) Hz, -CH\(_2 \)Cl); 3.82 (1H, q, \( J = 9 \) Hz, R\(_2 \)CHOR); 7.25 - 7.40 (6H, m, phenyl); 7.60 - 7.70 (4H, m, phenyl).
**1-Iodo-3-(t-butyldiphenylsilyloxy)pentane (50):**

A solution of 1-chloro-3-(t-butyldiphenylsilyloxy)pentane (49, 2.50 g, 6.70 mmol) and NaI (4.02 g, 26.8 mmol) in acetone (100 mL) was refluxed for 65 h and then cooled to room temperature. The reaction mixture was diluted Et₂O (200 mL) and washed with saturated NaHSO₃ solution (100 mL). Solvent removal afforded 50 as a colorless oil (2.50 g, 5.50 mmol; yield 80%).

**C₂₁H₃₀SiOI**

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>453.1115</td>
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</tbody>
</table>

**IR (neat):**  
\( \nu = 3070 \text{ (C-H, phenyl); 2947, 2857 (C-H); 1466 (C-H); 1100 cm}^{-1} \text{ (C-O).} \)

**MS (DCI, NH₃):**  
m/z (%) = 453 ((M+H)+, 58); 412 (37); 395 (55); 196 (100).

**¹H NMR (CDCl₃):**  
\( \delta = 0.67 \text{ (3H, t, J = 8 Hz, -CH₂CH₃); 0.99 (9H, s, -C(CH₃)₃); 1.30 - 1.46 (2H, m); 1.80 - 2.00 (2H, m); 3.07 (1H, t, J = 8 Hz, -CH₃H₃I); 3.08 (1H, t, J = 8Hz, -CH₃H₃I); 3.63 (1H, t, J= 6Hz, -CH(OR)); 7.25 - 7.40 (6H, m, phenyl); 7.60 - 7.70 (4H, m, phenyl).} \)
Dimethoxy-enone (43):

![Chemical Structure](image)

A slurry of freshly distilled DMSO (20 mL) and NaH (67 mg; 60% oil dispersion; 40.2 mg, 1.68 mmol, 1.37 eq.) was stirred under argon for 1 h at room temperature and then at 85 °C for 45 min. After cooling, a solution of dimethoxy-enone (42, 326 mg, 1.22 mmol) in dry DMSO (10 mL) was added via syringe and the mixture allowed to react for 2.5 h. The alkylating agent (50, 1.10 g, 2.44 mmol, 2 eq.) in DMSO (2 mL) was then added via syringe and the reaction mixture allowed to stir for 18 h at room temperature. Addition of saturated NH₄Cl solution (50 mL) followed by extraction with Et₂O (4 × 50 mL) and subsequent removal of solvent followed by column chromatography (35 x 150 mm SiO₂, 230 - 400 mesh; 10% EtOAc / 90% hexane) provided dimethoxy-enone (43) (500 mg), dialkylated product (44) (465 mg), and recovered starting material (42) (205 mg). Radial chromatography of the alkylated product (43) using a 2 mm SiO₂ plate and the same solvent system yielded pure dimethoxy-enone (43, 413 mg; yield 57% (based on recovered starting material)).

Dimethoxy-enone (43):

IR (neat): ν = 3100 (C-H, phenyl); 2907 (C-H); 1671 (C=O); 1428(C-H); 1100 cm⁻¹ (C-O).
MS (DCI, NH₃) : m/z (%) = 592 ((M+H)+, 100.0); 591 (M+, 29.5); 514 (53.5).

¹H NMR (CDCl₃): δ = 0.78(3H, t, J = 8Hz, -CH₂CH₃); 1.00(3H, s, C-13-H₃); 1.04 (9H, s, C(CH₃)₃); 1.28 - 1.38 (1H, m); 1.39 - 1.62 (5H, m); 1.84 - 1.94 (1H, m); 1.97 - 2.10 (3H, m); 2.18 - 2.39 (3H, m); 2.42 - 2.54 (1H, m); 3.28 (3H, s, OCH₃); 3.32 (3H, s, OCH₃); 3.30 - 3.38 (2H, m, CHCH₂OMe); 3.43 (2H, t, CH₂CH₂OMe); 3.60 (1H, p, (CH-OTBDPS); 7.30 - 7.41 (6H, m, phenyl); 7.63 - 7.70 (4H, m, phenyl).

Elemental Analysis:  

Calc.  C  75.19 %  Measured  C  75.30 %
H  9.23 %  H  9.10 %

Dialkylated Product (44):

IR (neat): v = 3070, 3049 (C-H, phenyl); 2912 (C-H); 1705 (C=O); 1461(C-H); 1075 cm⁻¹ (C-O).

MS (DCI, NH₃) : m/z (%) = 934 (M++NH₄+, 54); 918 (15.5); 860 (15.5); 660 (M+-OTBDPS, 100.0).

¹H NMR (CDCl₃): δ = 0.65 - 0.80 (6H, m, 2 x CH₂CH₃); 0.94 - 1.09 (21 H, m, C-13-H₃, 2 x -C(CH₃)₃); 1.13 - 1.28 (6H, m); 1.32 - 1.48(5H, m); 1.55 - 1.67 (3H, m); 1.68 - 1.83 (4H, m); 1.84 - 2.01 (2H, m); 2.16 - 2.42 (2H, M); 3.28 (3H, s, OCH₃); 3.32 (3H, s, OCH₃); 3.30 - 3.38 (2H, m, CHCH₂OMe); 3.43 (2H, t, CH₂CH₂OMe); 3.60 (1H, p, (CH-OTBDPS); 7.30 - 7.41 (12H, m, phenyl); 7.63 - 7.70 (8H, m, phenyl).
Dimethoxy-ketone (45):

A slurry of freshly distilled DMSO (20 mL) and NaH (34 mg; 60% oil dispersion; 20.1 mg, 0.84 mmol) was stirred under argon for 1 h at room temperature and then at 85°C for 45 min. After cooling, a solution of enone (43, 413 mg, 0.70 mmol) in DMSO (5 mL) was added at room temperature and stirring was continued under argon for 3 h. Methyl iodide (0.119 g, 0.84 mmol) was added and after 1 h the reaction mixture was quenched with saturated NH₄Cl solution (150 mL) and extracted with Et₂O (5 × 50 mL). The ether extracts were washed with brine and dried over MgSO₄. Solvent removal followed by radial chromatography of the crude product using 30% EtOAc / 70% hexane and a 2 mm SiO₂ plate afforded dimethoxy-ketone (45, 301 mg; yield 83% (based on recovered starting material)) and starting material (43, 57 mg).

C₃₈H₅₆O₄Si
Calc. mass 604.3948
Meas. mass 604.3904

IR (neat): ν = 2916 (C-H); 1708 (C=O); 1460 (C-H); 1108 cm⁻¹ (C-O).

MS (70 eV): m/z (%) = 604 (M⁺, 0.6); 547 (M⁺-tBu, 44.7); 299 (11.3); 199 (100.0).
\(^1\)H NMR (CDCl\(_3\)): \(\delta = 0.70 - 0.80\) (3H, m, CH\(_2\)CH\(_3\)); 0.90, 0.92 (3H, 2 s (diastereomers), C-11-H\(_3\)); 1.00 (9H, s, C(CH\(_3\))\(_3\)); 1.06 (3H, s, C-13-H\(_3\)); 1.22 - 1.48 (6H, m); 1.53 - 1.68 (2H, m); 1.69 - 2.08 (6H, m); 2.21 - 2.32 (3H, m); 2.44 - 2.59 (1H, m); 3.26 (3H, s, -OCH\(_3\)); 3.29 - 3.38 (5H, m); 3.40 - 3.49 (2H, m); 3.60 (1H, p, CH-OTBDPS); 5.23, 5.31 (1H, broad singlet (diastereomers), =CH); 7.30 - 7.68 (10H, m, phenyl).

**Hydroxy-ketone (51):**

A solution of dimethoxy-ketone (45, 251 mg, 0.415 mmol) and 1 M TBAF (2 eq.) in dry THF (10 mL) was stirred at room temperature under for 48 h. Addition of H\(_2\)O (20 mL) and Et\(_2\)O extraction (4 \times 20 mL) and removal of solvent yielded a crude product (246 mg) that was purified by radial chromatography (2 mm SiO\(_2\) plate, 30% EtOAc/70% hexane) to provide hydroxy-ketone (51, 113 mg; yield 99% (based on recovered starting material)) and unreacted starting material (62 mg).

IR (CHCl\(_3\)): \(\nu = 3456\) (OH); 2906 (C-H); 1709 (C=O); 1457 (C-H); 1109 cm\(^{-1}\) (C-O).
$^1$H NMR (CDCl$_3$): $\delta = 0.87$ (3H, $t$, $J = 4$ Hz, CH$_2$CH$_3$); 1.05 (3H, s, C-13-H$_3$); 1.16 (3H, s, C-11-H$_3$); 1.18 - 1.60 (10H, m); 1.63 - 2.03 (8H, m); 2.06 - 2.16 (1H, m); 2.28 - 2.40 (2H, m); 2.53 - 2.63 (1H, m); 3.28 (3H, s, OCH$_3$); 3.31 (3H, s, OCH$_3$); 3.31 - 3.37 (2H, m); 3.39 - 3.48 (3H, m); 5.43 (1H, s, =CH).

**Diketone (52):**

Hydroxy-ketone (51, 23 mg, 0.062 mmol) was added to a solution of CrO$_3$ (12 mg), H$_2$SO$_4$ (0.2 mL) and H$_2$O (3 mL) and the reaction mixture was stirred for 0°C for 1 h and then 2.5 h at room temperature. Work-up in the usual way yielded pure diketone (52) (12 mg; yield 99%).

C$_{22}$H$_{36}$O$_4$  
Calc. mass  364.2643  
Meas. mass  364.2622

IR (CHCl$_3$): $\nu = 2927$ (C-H); 1713 (C=O); 1460 (C-H); 1114 cm$^{-1}$ (C-O).

MS (70 eV) : m/z (%) = 364 (M+, 4.7); 349 (M+CH$_3$, 31.2); 332 (29.8); 314 (21.1); 57 (100.0).
$^1$H NMR (CDCl$_3$): $\delta = 1.00$ (3H, $t$, $J = 12$ Hz, -CH$_2$CH$_3$); 1.03 (3H, s, C-13-H$_3$); 1.15 (3H, s, C-11-H$_3$); 1.47 - 2.12 (9H, m); 2.12 - 2.45 (6H, m); 2.48 - 2.68 (1H, m);
3.27 (3H, s, OCH$_3$); 3.31 - 3.36 (2H, m, OCH$_2$); 3.37 - 3.47 (2H, m, OCH$_2$);
5.47 (1H, broad singlet, =CH).

**Tricyclic enone (53):**

A solution of diketone (52, 14 mg, 0.038 mmol) in MeOH (5 mL) containing 3 M HCl (1 mL) was refluxed for 22 h. The reaction mixture was extracted with Et$_2$O (75 mL) and the ether extracts washed with H$_2$O and saturated NaHCO$_3$ solution. Removal of solvent followed by radial chromatography (1 mm SiO$_2$ plate, 20% EtOAc / 80% hexane) of the crude product yielded tricyclic enone (53, 8 mg; yield 77% (based on recovered starting material)) and starting material (52, 3 mg).

C$_{22}$H$_{34}$O$_3$  

<table>
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<th></th>
<th>Calc. mass</th>
<th>Meas. mass</th>
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<tr>
<td></td>
<td>346.2508</td>
<td>346.2510</td>
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</table>

IR (neat): $\nu = 2909$ (C-H), 1661 ($\alpha,\beta$-unsaturated C=O), 1454 (C-H, bend), 1108 (C-O).
MS (70 eV): m/z (%) = 346 (M⁺, 9.6); 331 (M⁺ - CH₃, 11.6); 314 (19.2); 299 (29.0); 213 (100).

¹H NMR (CDCl₃): δ = 0.81 (3H, s, C-13-H₃); 1.32 (3H, s, C11-H₃); 1.57 - 1.68 (1H, m); 1.75 - (3H, s, vinyl methyl); 1.76 - 1.87 (4H, m); 1.93 - 2.07 (5H, m); 2.25 - 2.35 (2H, m); 2.40 (1H, dm, J = 16 Hz); 2.51 - 2.61 (2H, m); 3.29 (3H, s, OCH₃); 3.32 (3H, s, OCH₃); 3.34 - 3.40 (2H, m, OCH₂); 3.41 - 3.46 (2H, dd, J = 7, 7 Hz, OCH₂CH₂).

Hydroxy-ketal (37):

![Chemical structure](image-url)

A solution of ketal ester (37, 248 mg, 0.93 mmol) in dry THF (10 mL) was added via syringe to a slurry of LiAlH₄ (45 mg, 1.22 mmol) and dry THF (20 mL) at 0°C. After stirring for 1 h the ice bath was removed and the mixture stirred at room temperature overnight. The reaction mixture was quenched with Na₂SO₄·10 H₂O (150 mg) and the gelatinous mass filtered and rinsed with Et₂O (50 mL). The filtrate washed with H₂O (50 mL) and brine (50 mL). Evaporation of solvent afforded hydroxy-ketal (102) as a colorless oil (186 mg, 0.78 mmol; yield 84%). NMR and TLC analysis showed no impurities and this product was used without further purification.

IR (neat): v = 3388 (-OH); 2915 (C-H); 1691 (C=C).
MS (70 eV): m/z (%) = 238 (M+, 2.3); 169 (1.0); 141 (1.2); 105 (4.6); 99 (100.0).

$^1$H NMR (CDCl$_3$): $\delta = 0.82$ (3H, s, -CH$_3$); 1.40 (2H, m); 1.61 (4H, m); 1.80 (1H, m); 2.15 (3H, m); 3.27 (1H, m); 3.38 - 3.60 (2H, m); 3.75 (4H, -OCH$_2$CH$_2$O-); 5.32 (1H, =CH-).

**Methoxy-ketal (103):**

![Diagram of the reaction]

KH (36 mg, 0.89 mmol) was added to a stirred solution of hydroxy-ketal (102, 152 mg, 0.64 mmol) in dry THF (35 mL). After 1 h H$_2$ evolution ceased and MeI (60 µL, 126 mg, 0.89 mmol) was added via micro-syringe. After 2.5 h an additional portion of KH (15 mg) was added and then, after a further 2 h MeI (25 µL) was added and the reaction mixture left for 16 h. The reaction mixture of diluted with Et$_2$O, washed with brine, and dried over anhydrous MgSO$_4$. Evaporation of the solvent yielded a dark viscous oil that was purified by column chromatography (5% EtOAc / 95% hexane, 12 x 170 mm of 230-400 µm SiO$_2$) to produce methoxy-ketal (103, 57 mg; yield 35% (unoptimized)).

IR (neat): $\nu = 2916$ (C-H); 1667 (C=C); 1116 cm$^{-1}$ (C-O).

MS (70eV) : m/z (%) = 252 (M+, 3.9); 165 (1.0); 121 (1.9); 105 (2.9); 99 (100.0).
\(^1\)H NMR (CDCl\(_3\)): 0.91 (3H, s, -CH\(_3\)); 1.45-2.0 (7H, complex overlapping multiplet); 2.39 (4H, m, allylic H's); 3.35 (3H, OCH\(_3\)); 3.39 (2H, m, CH\(_2\)-OMe); 3.95 (4H, m, -OCH\(_2\)CH\(_2\)O-); 5.32 (1H, s, =CH).

Methoxy-enone (104):

A solution of ketal ester (103, 350 mg, 1.38 mmol), acetone (20 mL) and 1 M HCl (10 mL) was refluxed for 1.5 h. The reaction mixture was cooled to room temperature, neutralized with a sat. NaHCO\(_3\) solution and extracted with Et\(_2\)O (4 \times 100 mL). The combined extracts were washed with brine (100 mL) and dried over MgSO\(_4\). Evaporation of the solvent followed by radial chromatography (2 mm plate; 30% EtOAc / 70% hexane) afforded methoxy-enone (104) as a colorless oil (285 mg).

C\(_{13}\)H\(_{20}\)O\(_2\)  
Calc. mass 208.1463  
Meas. mass 208.1463  

IR (neat): \(\nu = 2933, 2870, 2830\) (C-H); 1731 (C=O); 1679 cm\(^{-1}\) (C=C).

MS (70 eV) m/z: 208 (M\(^+\), 28.2); 193 (M\(^+\)-CH\(_3\), 35.6); 180 (10.0); 176 (15.4); 148 (66.0); 121 (100.0).
\(^1\)H NMR (CDCl\(_3\)): \(\delta = 1.00\) (3H, s, -CH\(_3\)); 1.41 - 1.55 (2H, m); 1.60 - 1.80 (3H, m); 1.92 - 2.03 (2H, m); 2.26 - 2.68 (4H, m, allylic and \(\alpha\) protons to the carbonyl); 3.32 (3H, s, -OCH\(_3\)); 3.38 (4H, m, -OCH\(_2\)CH\(_2\)O-); 5.73 (1H, s, =CH\(_2\)).

**Methoxy-enone (105):**

A mixture of NaH (83 mg of 60% oil dispersion; 50 mg, 2.1 mmol) and freshly distilled DMSO (15 mL) was stirred at room temperature under argon for 30 min, and at 80 °C for a further 40 minutes. After cooling to room temperature, a solution of enone (104, 393 mg, 1.89 mmol) in DMSO (8 mL) was added and after an additional 5 h, the iodide (50, 1.03 g, 2.227 mmol), dissolved in dry DMSO (4 mL) was added. After 16 h the reaction mixture was acidified with 1 N HCl and extracted with Et\(_2\)O (4 \(\times\) 100 mL). Removal of solvent followed by radial chromatography (2 mm SiO\(_2\) plate; 25% EtOAc / 75% hexane) of the crude product provided methoxy-enone (105, 478 mg), dialkylated ketone (106, 526 mg), and starting material (77 mg).

**Methoxy-enone (105):**

\[
\text{C}_{34}\text{H}_{48}\text{O}_{3}\text{Si} \quad \text{Calc. mass} \quad 532.3373
\]
Meas. mass 532.3372

IR (neat): \( \nu = 3070 \) (aromatic C-H); 2914 (-C-H); 1656 cm\(^{-1}\) (C=O, C=C).

MS (70 eV): \( m/z \) (%) = 503 (1.3); 475 (M\(^+\) - C(CH\(_3\))\(_3\), 82.8); 285 (1.2); 277 (2.1); 199 (100.0).

\(^1\)H NMR (CDCl\(_3\)) = 0.79 (3H, t, \( J = 7\)Hz, -CH\(_{13}\)); 0.92 (3H, s, CH\(_3\)); 1.05 (9H, s, -C(CH\(_3\))\(_3\)); 1.30 - 1.38 (1H, m); 1.41 -1.80 (9H, m); 1.90 - 1.98 (2H, m); 2.03 - 2.13 (2H, m); 2.26 - 2.39 (2H, m); 2.43 - 2.53 (1H, m); 3.34 ( 3H, s, -OCH\(_3\)); 3.35 - 3.44 (2H, m); 3.71 (1H, q, \( J = 5.3\)Hz); 7.30 - 7.42 (6H, m, phenyl); 7.65 - 7.72 (4H, m, phenyl).

Elemental Analysis:  

<table>
<thead>
<tr>
<th></th>
<th>Calc.</th>
<th>Meas</th>
</tr>
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<tbody>
<tr>
<td>C</td>
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<td>76.55</td>
</tr>
<tr>
<td>H</td>
<td>9.10</td>
<td>9.14</td>
</tr>
</tbody>
</table>

Ketone (106):

IR (neat): \( \nu = 3070 \) (phenyl C-H); 2914 (C-H); 1704 (C=O); 1589 cm\(^{-1}\) (C=C).

MS (70 eV): \( m/z \) (%): 857 (M\(^+\), 0.4); 800 (M\(^+\)-C(CH\(_3\))\(_3\), 12.9); 544 (42.3); 543 ( M\(^+\)-(OTBDPS + tBu), 73.8); 475 (23.7); 199 (100.0).

\(^1\)H NMR (CDCl\(_3\)): \( \delta = 0.64 - 0.79 \) (9H, m, C-13 Me, 2 x RCH\(_2\)-CH\(_3\)); 0.98- 1.08 (18 H, 4 singlets - representative of diastereoisomers present, 2 x tBu); 1.12 - 1.28 ( 5H, m); 1.32- 1.57 (9 H, m); 1.64 - 1.76 ( 3H, m); 1.76 - 1.86 (1H, m); 3.32 -3.38
Methoxy-ketone (109):

A solution of enone (105, 165 mg, 0.31 mmol) in EtOH (10 mL) and a catalytic amount of 10% Pd•C were placed in a high pressure hydrogenation bomb and pressurised to 1000 psi H₂. The reaction slurry was stirred at room temperature for 24.5 h and then filtered through Celite. Evaporation of solvent yielded (109) as a viscous oil (132 mg; crude yield 81%) that was used without further purification.

IR (CHCl₃): ν = 3072 (C-H, phenyl); 2918 (C-H); 1700 (C=O); 1100 cm⁻¹ (C-O).

¹H NMR (CDCl₃): δ = 0.70 - 0.85 (6H, m, C-13-Me, RCH₂CH₃); 1.03 (9H, s, tBu);
1.27 - 1.51 (11H, m); 1.51 - 1.62 (2H, m); 1.64 - 1.78 (2H, m); 1.80 - 1.98 (2H, m); 2.05 - 2.29 (2H, m); 2.32 - 2.50 (1H, m); 3.27 - 3.32 (3H, 2 s representing diastereoisomers, OCH₃); 3.32 - 3.43 (2H, m, CH₂-OMe); 3.60 - 3.72 (1H, m, CH- OTBDPS); 7.29 - 7.42 (6H, m, phenyl); 7.60 - 7.70 (4H, m, phenyl).
Methoxy-ketone (110):

A aliquot (0.18 mL; 0.4 eq.) of 0.25 M NaOMe in MeOH was injected into a solution of ketone (109, 58 mg, 0.11 mmol) in dry MeOH (5 mL). The reaction mixture was refluxed for 4 h and then quenched with saturated NH₄Cl solution (50 mL). Extraction with Et₂O (4 × 50 mL) followed by removal of solvent from the dried combined extracts yielded a colorless oil (59 mg) that was purified by radial chromatography (1 mm plate (SiO₂); 5% EtOAc / 95% hexane) to provide pure methoxy-ketone (110, 55 mg; yield 94%).

IR (CHCl₃): v = 3073 (C-H, phenyl); 2939, 2859 (C-H); 1705 (C=O); 1100 cm⁻¹ (C-O).

MS (DCI, NH₃) : m/z (%) = 536 ((M+H)+, 5.6); 535 (M+, 5.6); 479 (15); 477 (67.0); 279 (100.0).

¹H NMR (CDCl₃): δ = 0.70 (3H, t, J=3Hz, -CH₂CF₃); 0.75 (3H, s, C-13-Me); 1.06 (9H, s, tBu); 1.30 - 1.55 (11H, m); 1.62 - 1.96 (5H, m); 2.05 - 2.42 (3H, m); 3.31 (3H, s, OCH₃); 3.34 - 3.45 (2H, m, CH₂-OMe); 3.60 - 3.73 (1H, m, CH-OTBDPS); 7.32 - 7.43 (6H, m, phenyl); 7.63 - 7.74 (4H, m, phenyl).


Appendix A

Correlation of C(13) methyl chemical shifts (ppm) with respect to the relative stereochemistry of the CD ring junction in hydrindane systems.

![Chemical structures with references 45 to 53]

ref. 45

ref. 46

ref. 47

ref. 48

ref. 48

ref. 49

ref. 49

ref. 50

ref. 50

ref. 51

ref. 51

ref. 52

ref. 53
Appendix B\textsuperscript{53}

i) HS(CH\textsubscript{2})\textsubscript{2}SH, BF\textsubscript{3}Et\textsubscript{2}O, MeOH; ii) 3-furyl lithium, THF; iii) Ti(NO\textsubscript{3})\textsubscript{3}H\textsubscript{2}O, MeOH; iv) MsCl, NE\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2}; v) MCPBA, CH\textsubscript{2}Cl\textsubscript{2}-phosphate buffer; vi) Si\textsubscript{O}