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Synthetic approaches to cleomeolide and ceroplastol I

Philippo, Christophe M. G., Ph.D.

The Ohio State University, 1991
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SYNTHETIC APPROACHES TO CLEOMEOLIDE AND CEROPLASTOL I

DISTRIBUTION

Presented in Partial Fulfillment of the Requirements
for the Degree Doctor of Philosophy in the
Graduate School of The Ohio State University

by

Christophe M. G. Philippo

****

The Ohio State University
1991

Dissertation Committee:

Prof. Leo A. Paquette
Prof. David J. Hart
Prof. Matthew S. Platz

Approved by

Leo A. Paquette
Adviser
Department of Chemistry
To my Parents
ACKNOWLEDGEMENTS

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Above all, I would like to thank my family for their love, encouragement, and understanding throughout this time.
VITA

July 26, 1962 ........................................... Born-Roubaix, France

1980 ............................................................... Baccalauréat C,
Collège de La Salle, Estaimpuis
Belgium

1980-1983 ................................................ Preparatory School,
Lycée Faidherbe, Lille, France

1983-1989 ................................................ School for Engineer in Chemistry
Ecole Supérieure de Chimie
Industielle de Lyon, France

1985-1986 ................................................ Military Service

1986-1987 ................................................ Graduate Teaching Associate,
Department of Chemistry,
The Ohio State University,
Columbus, Ohio

1986-1990 ................................................ Graduate Research Associate,
Department of Chemistry,
The Ohio State University,
Columbus, Ohio

FIELD OF STUDY

MAJOR FIELD: Chemistry
Studies in Organic Chemistry
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CHAPTER I
SYNTHETIC APPROACHES TO CLEOMEOLIDE

A. INTRODUCTION

1. Isolation and Structure

Cleomeolide (1) is a bicyclic diterpene isolated from the organic extract of the leaves and twigs of Cleome viscosa Linn.\(^1\) This plant, also called Cleome icosandra Linn., is a sticky herb with yellow flowers and strong penetrating odor. It is commonly found in India, where it is well-known for its anthelmintic properties.\(^2\)

\[
\text{OH} \quad \text{I : cleomeolide} \quad \text{2 : verticillol}
\]

\[\text{H} \quad \text{OH}
\]

Figure 1 : Structures of Cleomeolide and Verticillol.

Pronounced biological properties are often encountered in macrocyclic diterpenic natural products.\(^3\) Cembrene\(^4\) and casbene\(^5\) may be considered as the prototypes of these compounds. The
structural features of cleomeolide, which are related to those of verticillol (2), include a twelve-membered carbocyclic ring cis-fused in 1,3 fashion to a cyclohexane ring and a seven-membered \( \alpha,\beta \)-unsaturated lactone (Figure 1). This carbon framework is the first member of a hitherto unknown class.\(^1\)\(^{(a)}\) The absolute stereochemistry of cleomeolide has been established by X-ray diffraction. As a result of its biological activity and its inherent structural novelty, cleomeolide is viewed as an attractive and challenging synthetic target.

2. Biosynthesis

The biogenetic pathway envisaged for formation of the cleomeolide skeleton involves a cationic polyene cyclization. The first proposed route rationalizes the structural formation by a head-to-tail cyclization of geranyl geranyl pyrophosphate, followed by hydride shift, methyl migration, and proton loss (Scheme 1).\(^1\)\(^{(b)}\)

**Scheme 1 : Biogenetic Pathway to 1 from Geranyl Geranyl Pyrophosphate.**
The second possible biosynthesis involves the same process, but starts with a more highly oxygenated substrate, geranyl linalool epoxide (Scheme 2).1(a)

Scheme 2: Biosynthesis of 1 from Geranyl Linalool Epoxide.

B. THE FIRST APPROACH

1. Retrosynthetic Strategy

Before embarking on an enantioselective synthesis of cleomeolide (1), there was a need to develop an efficient retrograde strategy for introduction of different functionalities and stereochemical features of the molecule, as outlined in Scheme 3. We envisioned that cleomeolide could arise from the selective epoxidation and consequent lactonization of the macrocyclic acid 3.1(b) The twelve-membered ring would be formed by an
intramolecular cyclization of α-keto ester phosphonate 4. The precursor of the macrocyclized product would be prepared by introduction of the exo-methylene moiety into ketone 5 and alkylation of keto ester 6. Finally, the Wieland-Miescher ketone6 7 appeared to be the most suitable chiral pool precursor to deliver 6 by elaboration of the cis,vic-dimethyl stereochemistry from its saturated ketone functionality, followed by oxidative cleavage of the enone double bond.

**Scheme 3 : Retrosynthetic Analysis for Cleomeolide (1).**

2. Results and Discussion

Optically active Wieland-Miescher ketone 7 was prepared from commercially available 2-methyl-1,3-cyclohexanedione.7 The literature procedure presents problems for the purification of the crude material, which can be avoided by Kugelrohr distillation.
Others have recently published modified procedures to circumvent the same inconvenience.\textsuperscript{7(b)}

Differentiation of the two carbonyls of 7 is achieved by selective dithioketalisation, providing ketone 8 in an almost quantitative yield.\textsuperscript{8} This compound is homologated by treatment with the Wittig salt derived from methoxymethyl chloride (MOMCl),\textsuperscript{9} followed by acidic hydrolysis. It should be noted that this Wittig reaction does not differentiate between the ketone and enone moieties of 7. Resulting aldehyde 9 is constituted of a 7 to 1 mixture in favor of the desired cis isomer (Scheme 4).

**Scheme 4 : Homologation of Ketone 7.**

\[
\begin{align*}
\text{7} & \xrightarrow{1. \text{AcOH}} \text{8} \\
& \xrightarrow{2. \text{S-Proline}} \xrightarrow{(\text{CH}_2\text{SH})_2} \xrightarrow{\text{AcOH, PTSA}} \text{8} \\
& \xrightarrow{1. \text{(Ph)}_3\text{P=CHMe}} \xrightarrow{2. \text{HCl}} \text{9}
\end{align*}
\]

The conversion of 9 to the cis-dimethyl intermediate 10 was first attempted following Wolff-Kischner conditions,\textsuperscript{10} but only polar materials were formed. A two-stage procedure was then implemented as a replacement. Condensation of 9 with tosylhydrazine\textsuperscript{11} provided hydrazone 11, which was reduced with
lithium aluminum hydride or sodium cyanoborohydride. Desired product was isolated in only moderate yield and the mixture problem was not resolved. Therefore a four-step sequence, which proved itself to be much more efficient, was adopted. First, aldehydes 9 were reduced with sodium borohydride to provide alcohols 12. These compounds, being more polar, could be separated by preparative H.P.L.C. to give the cis alcohol, pure by capillary G.C.. Then mesylation, in the presence of methanesulfonyl chloride and triethylamine, followed by displacement of the mesylate group in 13 with lithium triethylborohydride provided cis-methyl thioketal 10 in excellent yield (Scheme 5).

Scheme 5: Introduction of the cis-Dimethyl Stereochemistry.

At this stage, removal of the protecting group was the only remaining step to have access to octalone 14, which has been used
as a building block for the synthesis of several natural products. Methods involving the use of methyl iodide, amyl nitrite and thallium trifluoroacetate were attempted without very much success. However, the use of thallium trinitrate trihydrate gave enone 14 in 94% yield on a small scale (1g or less) (Scheme 6). All attempts to scale-up this reaction led to lower yield. However, since the reaction time is only 5 minutes, this inconvenience in scale is greatly reduced. A new, efficient, and optically active synthesis of octalone 14 has been developed. The previous preparations of this compound were mostly racemic and involved Diels-Alder methodologies.

Scheme 6: Deprotection of Thioketal 10.

Now that the cis, vic-dimethyl moiety has been introduced, the next important step involved oxidative cleavage of the enone double bond. Numerous literature precedents report that double bond cleavages of enones, allylic alcohols, and allylic acetates or benzoates occur with decarboxylation. To avoid this problem, octalone 14 was stereoselectively reduced with sodium borohydride in methanol at 0°C, and resulting allylic alcohol 15.
was protected as the silyl ether 16. The first attempts at ozonolysis of its double bond in dichloromethane, with adoption of either triphenylphosphine or dimethyl sulfide as reducing agent, gave only poor results. Oxidations with potassium permanganate or ruthenium tetroxide were similarly unsuccessful. The double bond of the tert-butyldimethylsilyl ether was therefore functionalized as epoxide 17 and as diol 18 by hydroxylation with osmium tetroxide. Unfortunately, these compounds were relatively unreactive in the presence of periodic acid or sodium periodate. Finally, the proper conditions for ozonolysis were found and required the presence of small amounts of methanol and pyridine to provide a quantitative yield of keto aldehyde 19 (Scheme 7).

**Scheme 7 : Oxidative Cleavage of 16.**
To gain access to the desired keto ester 6, a mild way to oxidize aldehyde 19 was needed. The first attempts involving pyridinium dichromate in dimethylformamide\(^{24(a)}\) as well as silver nitrate and sodium hydroxide\(^{24(c)}\) were unsuccessful. Masamune’s conditions,\(^{25}\) consisting of potassium permanganate and tert-butanol in a buffered aqueous media, provided an acid. However the method was plagued by loss of the tert-butyldimethyl silyl group, which was supposed to be stable under these conditions. This silyl group was then replaced by the bulkier tert-butyldiphenyl silyl ether 20. Ozonolysis to keto aldehyde 21 and the subsequent oxidation went smoothly, providing acid 22 which was converted to its corresponding methyl ester 23 with an excess of diazomethane (Scheme 8).

**Scheme 8 : Preparation of Keto Ester 23.**

The next important transformation involved connection of the lower side-chain of the molecule. This side-chain was prepared by
application of Corey's method for transforming propargylic alcohols into trans-trisubstituted allylic alcohols.\textsuperscript{26} Protection of 1-butyn-4-ol as its tetrahydropyranyl ether\textsuperscript{27} followed by deprotonation of the terminal alkyne product \textsuperscript{24} and addition of excess paraformaldehyde delivered propargylic alcohol \textsuperscript{25}. Reduction of the triple bond with lithium aluminium hydride and sodium methoxide in tetrahydrofuran with subsequent quenching of the aluminum intermediate with elemental iodine, provided vinyl iodide \textsuperscript{26}. Displacement of the iodine by lithium dimethyldicuprate furnished the desired \textsuperscript{27}, which was ultimately converted to allylic acetate \textsuperscript{28} (Scheme 9).

\textbf{Scheme 9 : Preparation of the Side-Chain via Vinyl Iodide \textsuperscript{26}.}

An alternative route to the same intermediate was developed later. This more efficient route involved selective ozonolysis of geranyl acetate,\textsuperscript{28} reduction of the resulting aldehyde \textsuperscript{29} with
sodium borohydride, and protection of alcohol 30 with dihydropyran (Scheme 10).

**Scheme 10**: Preparation of 28 via Selective Ozonolysis of Geranyl Acetate.

Because keto ester 23 possesses two enolizable centers, with one of then chiral, Lewis acid-catalyzed alkylation was tried first. Upon treatment with trimethylsilyl triflate and triethylamine, 23 was converted to its silyl enol ether 31. However, admixture of 31 with 28 in the presence of a catalytic amount of zinc iodide resulted in no reaction. This reaction was repeated with the silyl enol ether of 2,6-dimethylcyclohexanone as a model. After a long reaction time, only degradation of the THP protected alcohol was observed. The tetrahydropyranyl protecting group, which had been chosen for the ease of its conversion to bromide, was inappropriate for this use. This reaction was tested further with prenyl acetate and the silyl enol ether of 2,6-dimethylcyclohexanone; alkylated product 32 was formed efficiently. Alcohol 30 was protected as *tert*-butyldimethyl silyl ether 33, converted to bromide 34, and
condensed in an Arbuzov reaction with triethyl phosphite and a catalytic amount of nickel chloride\textsuperscript{31} to give the phosphonate 35. The zinc iodide-catalyzed alkylation was attempted with 33 and 35 and gave a good yield of the alkylated products 36 and 37 respectively, with the model enol ether, but no reaction with 31 (Scheme 11).

**Scheme 11**: Zinc Iodide-Promoted Alkylations.
Another alkylation reaction was then considered. Trost has reported that tin enolates undergo smooth alkylation with allylic acetates in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium.\textsuperscript{32} The tin enolates were prepared by deprotonation with lithium diisopropylamide in THF at -78°C, followed by addition of tributyltin triflate\textsuperscript{33} or chloride. Allylic acetate 34, obtained by conversion of the THP group of 26 to bromide, was then added to the palladium catalyst. Again, although the model ketone efficiently gave alkylated product 38, no desired product was observed with 23 (Scheme 12).

Scheme 12: Palladium-Catalyzed Alkylation of a Tin Enolate.

A related and milder reaction was also tried. Ketone 23 was converted with Manders' reagent\textsuperscript{34} to its β-keto ester 39, which was deprotonated with sodium hydride and reacted with allylic acetate 99 under palladium catalysis.\textsuperscript{35} The same lack of reactivity was encountered (Scheme 13).
Scheme 13: Palladium-Catalyzed Alkylation of β-Keto Ester.

At this time, because of the lack of reactivity encountered under the previous conditions, direct alkylation involving the enolate of 23 and dibromide 41 was attempted. The dibromoalkene was prepared by hydrolysis of the acetate in 30 and conversion of diol 40 to 41 by treatment with bromine and DIPHOS. Deprotonation of 23 with LDA at -78°C and reaction with 40 gave the desired alkylated product 42 in low yield (15%). A switch from the lithium to the potassium enolate improved the yield to 36%. The addition of 3 equivalents of DME to the reaction mixture increased the yield further to 46%. Finally, addition of HMPA, along with the DME, and very slow warming of the reaction mixture to room temperature allowed optimization of the yield to 88%. Bromide 42 was converted to phosphonate 43 by the Arbuzov reaction. The presence of a catalytic amount of nickel chloride is critical to obtain a satisfactory yield. Direct alkylation of 23 with bromo phosphonate 44 was possible, but a lower yield of 43 was obtained (Scheme 14).
Scheme 14: Direct Alkylation of Potassium Enolates.

Alkylated products of these reactions were always obtained as diastereoisomeric mixtures, whose ratios were determined by integration of the $^1$H NMR olefinic hydrogen signals. Several attempts to equilibrate ketones 42 and 43 gave rise to only a modest shift in the equilibrium slightly enriched in the desired isomer (Table 1).
Table 1: Conditions for Equilibration of Ketones 42 and 43.

<table>
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<tr>
<th>CONDITIONS</th>
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<tr>
<td>Alkylation with dibromide</td>
<td>1.0 : 2.1</td>
</tr>
<tr>
<td>Alkylation with bromophosphonate</td>
<td>2.3 : 1.0</td>
</tr>
<tr>
<td>Et₃N, Et₂O, MeOH, overnight, R.T.</td>
<td>1.0 : 2.0</td>
</tr>
<tr>
<td>Na₂CO₃, MeOH, overnight, R.T.</td>
<td>1.0 : 1.9</td>
</tr>
<tr>
<td>0.5 eq tBuOK, tBuOH, overnight, R.T.</td>
<td>1.0 : 1.1</td>
</tr>
<tr>
<td>7% NaOCH₃, MeOH, overnight, R.T.</td>
<td>1.0 : 1.7</td>
</tr>
<tr>
<td>1) TMSOTf, Et₃N, Et₂O 2) H₂O, R.T.</td>
<td>1.0 : 1.7</td>
</tr>
<tr>
<td>1) TMSOTf, Et₃N, Et₂O 2) THF, 0°C, tBuOH, cat H⁺</td>
<td>1.2 : 1.0</td>
</tr>
<tr>
<td>KN(TMS)₂, -78°C, tBuOH, -78°C to R.T.</td>
<td>2.0 : 1.0</td>
</tr>
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The next key transformation was associated with introduction of the exocyclic methylene moiety. Various reaction conditions for the olefination of ketones were tried. The methyl ester was found too sensitive in several instances, being replaced by a tert-butyl ester (Scheme 15).

Scheme 15: Preparation of tert-Butyl Ester Derivatives.
In spite of this ester modification, ketone 44 remained unreactive to many different attempted reaction conditions (Table 2).\textsuperscript{38} This unreactivity must be attributed to the extreme steric hindrance of the ketone moiety and its probable ease of enolization.

<table>
<thead>
<tr>
<th>CONDITIONS</th>
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<tbody>
<tr>
<td>(Ph)\textsubscript{3}PCH\textsubscript{3}Br, KHMDS, Diisopropyl ether, 5°C</td>
<td>lost methyl ester</td>
<td></td>
</tr>
<tr>
<td>CH\textsubscript{2}I\textsubscript{2}, Zn, TiCl\textsubscript{4}</td>
<td>no reaction</td>
<td></td>
</tr>
<tr>
<td>NaH, DMSO, (Ph)\textsubscript{3}PCH\textsubscript{3}Br, 80°C</td>
<td>no reaction</td>
<td></td>
</tr>
<tr>
<td>(Ph)\textsubscript{3}PCH\textsubscript{3}Br, KHMDS, THF, R.T.</td>
<td>Br displaced</td>
<td></td>
</tr>
<tr>
<td>Lombardo's reagent</td>
<td>no reaction</td>
<td></td>
</tr>
<tr>
<td>Tebbe's reagent</td>
<td>no reaction</td>
<td></td>
</tr>
<tr>
<td>(Ph)\textsubscript{3}PCH\textsubscript{3}Br, BuLi, THF, R.T.</td>
<td>lost methyl ester</td>
<td></td>
</tr>
<tr>
<td>(Ph)\textsubscript{3}PCHLi, THF:HMPA, tBuOH</td>
<td>no reaction</td>
<td></td>
</tr>
<tr>
<td>(Ph)\textsubscript{3}PCH\textsubscript{3}Br, BuLi, Diisopropyl ether, RT</td>
<td>no reaction</td>
<td></td>
</tr>
<tr>
<td>(Ph)\textsubscript{3}PCH\textsubscript{3}Br, KHMDS, THF, R.T.</td>
<td>no reaction</td>
<td></td>
</tr>
<tr>
<td>(Ph)\textsubscript{3}PCH\textsubscript{3}Br, BuLi, THF:HMPA (9:1), R.T.</td>
<td>no reaction</td>
<td></td>
</tr>
<tr>
<td>MeMgBr (2.5 eq), THF, -78°C to R.T.</td>
<td>no reaction</td>
<td></td>
</tr>
<tr>
<td>(Ph)\textsubscript{3}PCH\textsubscript{3}Br, KHMDS, DME, reflux</td>
<td>no reaction</td>
<td></td>
</tr>
<tr>
<td>(Ph)\textsubscript{3}PCH\textsubscript{3}Br, KO\textsubscript{t}Bu, Benzene, reflux</td>
<td>no reaction</td>
<td></td>
</tr>
<tr>
<td>MeLi, CeCl\textsubscript{3}, THF, -78°C to -40°C</td>
<td>no reaction</td>
<td></td>
</tr>
</tbody>
</table>

All the reagents used for the attempted olefinations are rather bulky. If the problem of unreactivity stems from steric encumbrance, an effort to add a nitrile anion, much smaller in size, should be more effective. Treatment of ketone 44 with trimethylsilyl cyanide, potassium cyanide, and crown ether resulted in very efficient conversion to trimethyl cyanohydrin 47.\textsuperscript{39} Under similar conditions, trisubstituted ketone 46 reacted somewhat more
slowly and trimethylsilylated cyanohydrin 48 was obtained from a high pressure reaction at 100,000 psi. Unfortunately, elimination of the trimethylsiloxy group did not occur, even under forcing conditions. However, when an equilibrium was established between 44 and its corresponding cyanohydrin, the latter could be quantitatively dehydrated to unsaturated nitrile 49 (Scheme 16). Trimethylsilylated cyanohydrins can deliver cyanohydrins in a non-equilibrating fashion by acidic hydrolysis of the silyl group. In the case of 44, steric hindrance necessitated the use of elevated acidic concentrations which caused degradation. A similar outcome was observed in the treatment of 44 with diethylaluminum cyanide.

Scheme 16: Introduction of a Nitrile.
Again, the steric problem did not allow us to take full advantage of the good nucleophilicity of cyanide anion. The investigation nonetheless moved forward, consideration next being given to a cyclized product that might make the ketone carbonyl more accessible. Deprotection of the silyl group of 44 was best realized with pyridinium hydrofluoride to furnish 50, a mixture of hydroxy ketone and hemiketal. Similar treatment of 46 delivered 51 which when oxidized under Swern conditions gave a good yield of α-keto ester 52 (Scheme 17). Several attempts to cyclize 52 were unsuccessful, and this lack of reactivity was
attributed to the fact that formation of a double bond by means of a phosphonate anion does not occur easily unless there is an electron-withdrawing group α to the phosphonate moiety.\(^{42}\)

At this stage, it seemed that neither the problem of introducing the exo-methylene moiety nor the unreactivity in macrocyclization could be easily solved. Thus it became necessary to develop an alternative route which was not plagued with such inconveniences.

C. THE MODIFIED APPROACH

1. Carbopalladation and Ensuing Experiments

The synthetic efforts described in the previous section illustrate those difficulties that can arise during addition of a one-carbon unit to a sterically hindered trisubstituted ketone. Only a few important modifications have to be incorporated into the original synthetic scheme, as outlined in Figure 2. In particular, a reversal in the order of introduction of the functionalities is needed. The exocyclic methylene group must be elaborated first from disubstituted ketone 44, and the lower side chain of the molecule incorporated subsequently. Also, to improve the probability of macrocyclization, the silyl protected alcohol will be converted to a phosphonate group to attempt the well-documented Horner-Emmons reaction.
The alternative route began by homologating ketone 5. Previously prepared nitrile 49 already has the one carbon-unit in place. However, it is not possible to reduce the nitrile group selectively in the presence of the tert-butyl ester. When recourse to the Wittig salt of methoxymethyl chloride (MOMCl) gave no reaction, it became clear that disubstituted ketone 44 is also very sterically encumbered and easily enolizable. Other processes which could deliver a homologated aldehyde would therefore suffer from the same complication as before. A two-step protocol, the palladium-catalyzed carbonylation of a vinyl triflate, which is known to be quite insensitive to steric hindrance, was therefore considered. At first, ketone 44 appeared to be reluctant toward conversion into its vinyl triflate. All attempts to capture its enolate, generated with different bases and in different solvents, with N-phenyl triflimide failed. The same unreactivity was observed...
during attempts to prepare the enol phosphate with dimethylchlorophosphite. Nonetheless use of triflic anhydride with a hindered pyridine base at room temperature and overnight resulted in smooth conversion to vinyl triflate 53. The palladium-catalyzed carboxylation required some forcing conditions, at least 80°C for 3 days, to deliver the desired carboxyl function (Scheme 18). A mixture of unsaturated acid 54 and ester 55 was obtained and converted to the latter by treatment with diazomethane.

**Scheme 18 : Carbopalladation of 44.**

At this point, the first methodology considered for introduction of the lower side chain involved a 1,4 addition process. To insure the proper stereochemical outcome in the delivery of this chain, the use of a chiral auxiliary group as described by Koga was evaluated. Unsaturated methyl ester 55 was selectively reduced by DIBAL-H at -78°C without affecting the tert-butyl ester group.
To improve the moderate yield of this reaction, a two-step protocol was tried. Unsaturated acid 54 was treated with ethyl chloroformate to give mixed anhydride 57, but its reduction with sodium borohydride in the presence of cerium trichloride did not result in any enhanced efficiency. Allylic alcohol 56 was then oxidized under Swern conditions to give the unsaturated aldehyde 58 (Scheme 19).

Scheme 19: Reduction of Unsaturated Ester 55.

The condensation of 58 with D-valine tert-butyl ester\textsuperscript{50} in the presence of magnesium sulfate could not be driven to more than 90% conversion, probably because of steric hindrance. The chain to be added to enamine 59 was prepared by ketalization, according to Noyori’s procedure,\textsuperscript{51} of aldehyde 29, followed by deprotection of the acetate group in 60 and conversion of the resulting alcohol 61 to an allylic halide. All attempts to obtain the allylic bromide were
unsuccessful and even the extremely mild conditions described by Meyers resulted in a rather low yield of chloride 62.\textsuperscript{52} The ensuing preparation of the Grignard reagent of 62 was tried with ultrasound-activated magnesium powder,\textsuperscript{53} but its addition of enimine 59 did not give rise to any 1,4-addition product (Scheme 20). After several unsuccessful attempts to effect conjugate addition and in light of the instability of 62, a different approach was considered.

**Scheme 20**: Chiral 1,4-Addition to Eneimine 59.

The next sequence for construction of the side-chain consists in formation of the exocyclic double bond by Claisen rearrangement. This protocol, which has been used in the synthesis of several natural products,\textsuperscript{54} involves the conversion of allylic alcohol 55 to its vinyl ether 63 by mercury-catalyzed transetherification with
ethyl vinyl ether used as solvent. Toluene solutions of 63, placed in KOH-washed pyrex sealed tubes, delivered a mixture of isomeric aldehydes 64 when thermally activated (Scheme 21). These compounds are not stable on silica gel and must be used as a crude mixture for the next step. This [3,3] sigmatropic rearrangement allowed us to access reasonable amounts of both isomers which were epimeric at the newly created stereogenic center. Aluminum-promoted Claisen rearrangement was also tried, but Tribal reduced the tert-butyl ester and the milder diethylaluminum chloride-triphenylphosphine complex proved unreactive.

Scheme 21: Claisen Rearrangement to Introduce the Exo-Double Bond.

For the purpose of completing construction the side-chain from aldehydes 64, Wittig reaction was first considered. Although the non-stereospecificity of trisubstituted double bond formation55
by the Wittig reaction is well-known, Corey has introduced a modification which delivers only a trans double bond.\textsuperscript{56} Wittig salt 68 was prepared by one-carbon homologation of bromo dioxolane 65, conversion of alcohol 66 to bromide 67, and subsequent reaction with triphenylphosphine, as shown in Scheme 22. The Wittig reaction was first tested on trimethylacetaldehyde and furnished the trans trisubstituted product in low yield.

Scheme 22: Stereospecific Modification of the Wittig Reaction.

Alternatively, the trans double bond was prepared by a second Claisen sequence. Addition of 2-propenylmagnesium bromide to aldehydes 64 delivered a mixture of two pairs of diastereoisomeric secondary allylic alcohols 69, which are separable on silica gel. As previously, mercury-catalyzed transetherification to
allyl vinyl ether 70 and thermal activation\textsuperscript{57} of a toluene solution of this compound delivered aldehyde 71 as outlined in Scheme 23.

Scheme 23: Second Claisen Rearrangement to Build the Trisubstituted Double Bond.

To identify the stereochemistry of the stereogenic center created in the first Claisen protocol, each of the pairs of diastereoisomeric alcohols 69 was submitted to NOE analysis (Figure 3). In the major series, irradiation of the quaternary methyl resulted mainly in enhancement of the integral of one the exo-methylene proton. This suggests that this methyl has an equatorial disposition and therefore the two larger chains of that molecule are oriented trans. In the minor isomer, the same irradiation shows an enhancement for an axial hydrogen and
consequently is believed that this compound possesses the correct stereochemistry for cleomeolide. An X-ray crystallographic analysis would, of course, be conclusive. Unfortunately, however, conversion of aldehyde 71 to its 2-4-dinitrophenylhydrazone 72 did not result in formation of a crystalline substance.

![Chemical structures](image)

**Figure 3**: NOE Experiments to Determine the Stereochemistry of 64.

Nevertheless, the synthesis was continued by protecting aldehyde 71 as its dioxolane 73 following Noyori's procedure. The silyl group was removed by treatment with pyridinium hydrofluoride in acetonitrile and the resulting alcohol 74 was converted to bromide 75. Arbuzov reaction with trimethyl phosphite occurred readily, even without nickel chloride catalysis, and delivered phosphonate 76. Finally, deprotection of the ketal moiety by treatment with a catalytic amount of p-toluenesulfonic
acid in aqueous acetone furnishes aldehydo phosphonate 77, the penultimate macrocyclization precursor (Scheme 24).

Scheme 24: Preparation of the Macrocyclization Precursor.
2. The Problem of Macrocyclization

Intramolecular Horner-Emmons reactions have frequently been used as the key macrocyclisation step in the synthesis of "cembrene-like" diterpenes. Among the numerous reaction conditions adopted for this cyclization, those described by Masamune and Roush seem to be the most efficient. When such were applied to aldehyde phosphonate 72, no reaction was observed. Inverse addition or warming the reaction mixture to 40°C did not help. Other reaction conditions only resulted in the loss of starting material. These disappointing results were believed to stem from the fact that the major stereoisomer possesses stereochemistry epimeric to that of cleomeolide. As a consequence, the two arms of 77 may have a problem to reach. For this reason, the diastereoisomeric aldehydo phosphonate 77 was prepared by the same pathway and submitted to analogous macrocyclization conditions.

Unfortunately, aldehyde 77 proved also to be unreactive. Careful examination of Dreiding models of 77 revealed that the estimated preferred formation of the Z double bond would force the bulky tert-butyl ester residue into a sterically hindered environment - an unlikely event. Attempts to cleave the ester group only led to degradation. Thus, it became clear that no macrocyclization product can accommodate a tert-butyl ester and suitable replacement of this group has to be done early in the synthesis. Modification in the reaction scheme can be realized by
converting aldehyde 22 to its corresponding dimethylhydrazone, which after quaternization and treatment with base, delivers cyanide 78 (Scheme 25). The same previously described chemistry will be applied. We feel confident from the literature precedence that new attempts at macrocyclization, with equal to cyano or carbomethoxy, will be fruitful and eventuate in completion of the enantioselective total synthesis of cleomeolide.

Scheme 25: Proposed Modification of the Route to Cleomeolide.

C. CONCLUSION

The synthetic effort described in this chapter illustrates those difficulties that can arise during construction of highly congested or structurally rigid sites within a natural product. However, considering the novelty of the carbon framework of cleomeolide, several significant synthetic contributions to our quest of the target molecule have been realized. First, a new and enantioselective access to octalone 14 and its cis,vic-dimethyl stereochemistry has been achieved. Then, the introduction, in an extremely hindered site, of a one-carbon unit by palladium-catalyzed carbonylation was
achieved. Finally, through the implementation of two consecutive Claisen rearrangements, the establishment of the exo-methylene moiety and lower side-chain of the molecule was completed. Moreover, this latter key transformation allows access to a reasonable amount of each isomer of the newly created stereogenic center. Overall, a reasonably efficient route to an optically active precursor of the macrocyclization product has been realized.

The only important remaining task for the future is the key macrocyclization step by the Horner-Emmons methodology. This will deliver a known intermediate obtained from a study of the characterization of cleomeolide. The ultimate objective of this research was to develop an effective enantioselective route to cleomeolide. In the light of the numerous intramolecular Horner-Emmons reactions found in the literature, we feel confident that this goal will be met in the near future.
EXPERIMENTAL

General Procedures

Melting points were taken on a Thomas Hoover (Uni-Melt) Capillary Melting Point Apparatus and are uncorrected. Optical rotations were obtained using a Perkin-Elmer Model 241 Polarimeter and concentrations are expressed in grams/100 ml. Infrared (IR) spectra were recorded on a Perkin-Elmer 1320 Spectrometer and are reported in reciprocal centimeters (cm⁻¹). Proton magnetic resonance spectra (¹H NMR) were recorded at 300 MHz (Bruker WP 300 and Bruker AC 300 FT NMR spectrometers) and the splitting pattern were designated as: s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet; and b, broad. Carbon-13 NMR were recorded at 75 MHz (Bruker WP 300 and Bruker AC 300 FT NMR spectrometers). The chemical shift are reported in parts per million (δ).

Elemental analyses were obtained from the Scandinavian Microanalytical Laboratory, Herlev, Denmark. Exact mass determinations were obtained at the Ohio State University Chemical Instrument Center by use of a Kratos MS-30 mass spectrometer. Capillary GC analyses were carried out on a Carlo Erba Strumentazione Fractovap 4130 using a 30m x 0.25 mm J and W Scientific, Inc. 0.25 m DB-5 Durabond column at a flow rate of
2ml/min calibrated at 100°C and split ratio of 30:1 on injection.

All sovents were reagent grade and pre-dried via standard methods. Unless otherwise indicated, all reactions involving non-aqueous solution were performed under an inert atmosphere.

(4'aS)-4',4'a,7',8'-Tetrahydro-4'a-methylspiro[1,3-dithiolane-2,2'(3'H)-naphtalen]-5'(6'H)-one (8).

![Structure of compound 8](image)

To a solution of Wieland-Miescher ketone 7 (5.87 g, 33.0 mmol, [α]$_{25}^{25}$D +100° (c 1.00, toluene)) in glacial acetic acid (14 ml) was added 1,2-ethanedithiol (3.41 g, 36.3 mmol), p-toluenesulfonic acid (2.94 g), and glacial acetic acid (34 ml). The mixture was stirred at room temperature for 5 h, poured into water, and stirred for 15 minutes more. The white solid was filtered off, washed successively with water, dilute NaHCO$_3$ solution, and water, and dried to yield 8.31 g of thioketal 8 (99%) as a white solid; mp 138°C; [α]$_{25}^{25}$D +112° (c 1.15, CHCl$_3$); IR (KBr, cm$^{-1}$) 2910, 1705, 1640; $^1$H NMR (300 MHz, CDCl$_3$) δ 5.56 (s, 1H), 3.39-3.32 (m, 3H), 3.31-3.22 (m, 1H), 2.68-1.96 (series of m, 6H), 1.78-1.30 (series of m, 4H), 1.29 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 212.75, 141.23, 128.11, 64.87, 49.49, 40.13, 39.66, 37.95, 37.65, 30.86, 30.79, 24.77, 24.62; MS m/z (M$^+$) calcd 254.0799, obsd 254.0799.
(4'aR,5'S)-4',4'a,5',6',7',8'-Hexahydro-4'a-methylspiro[1,3-dithiolane-2,2'(3'H)-naphtalene]-5'-carboxaldehyde and (4'aR,5'R)-4',4'a,5',6',7',8'-Hexahydro-4'a-methylspiro[1,3-dithiolane-2,2'(3'H)-naphtalene]-5'-carboxaldehyde (9).

To a cold solution (-30°C) of methoxymethyl triphenylphosphonium chloride (4.05 g, 11.8 mmol) in THF (40 ml) was added KHMDS (0.5 M in toluene, 19.7 ml, 9.85 mmol). The resulting red solution was stirred at 0°C for 15 min before being treated with a solution of thioketal 8 (1.00 g, 3.94 mmol) in THF (10 ml). The mixture was stirred at room temperature for 24 h. A solution of CH₃OH:THF (1:1) (10 ml), followed by a 4 N HCl solution (10 ml) were added to the mixture at 0°C. The resulting solution was allowed to stir at room temperature for 36 h, then poured into water (40 ml) and extracted with ether (4 x 30 ml). The combined organic layers were washed with brine, dried, concentrated, and purified by flash chromatography on silica gel (elution with 2.5% ethyl acetate in petroleum ether) to give 0.977 g of a mixture of aldehydes 9 (93%) as a white solid; mp 98°C; IR (KBr, cm⁻¹) 2985, 2940, 2860, 1715, 1440, 1195; ¹H NMR (300 MHz, CDCl₃) δ 9.81 (d,
J=2.0 Hz, 1H), 5.57 (s, 1H), 3.45-3.32 (m, 3H), 3.32-3.17 (m, 1H),
2.26-2.10 (m, 4H), 2.10-1.95 (m, 3H), 1.95-1.82 (m, 1H), 1.82-1.69
(m, 2H), 1.42-1.22 (m, 1H), 1.14 (s, 3H); ¹³C NMR (75 MHz, CDCl₃)
ppm 203.85, 143.05, 125.76, 64.95, 60.35, 39.91, 39.34, 37.14,
37.02, 36.61, 31.58, 25.81, 22.01, 19.42; MS m/z (M⁺) calcd
268.0956, obsd 268.0965.

(4'aR)-4',4'a,5',6',7',8'-Hexahydro-4'a-methylspiro[1,3-
dithiolane-2,2'(3'H)-naphtalene]-5'-carboxaldehyde  p-
tolylhydrazone (11).

A mixture of aldehydes 9 (1.00 g, 3.7 mmol), p-
toluenesulfonylhydrazine (0.45 g, 3.7 mmol), and methanol (8 ml)
was refluxed for 6 h under nitrogen, cooled, and concentrated under
vacuum. The residue was purified by flash chromatography on
silica gel (elution with 10% ethyl acetate in petroleum ether) to
afford 1.60 g of tosylhydrazone 11 (99%) as a white solid; mp 69°C;
IR (KBr, cm⁻¹) 3200, 2930, 2850, 1595, 1490, 1435, 1365, 1320,
1165, 1090, 1015, 925, 815, 675; ¹H NMR (300 MHz, CDCl₃) δ 7.81
(d, J=8.2 Hz, 1H), 7.66 (s, 1H), 7.32 (d, J=8.2 Hz, 2H), 7.09 (d, J=6.7
Hz, 2H), 5.51 (s, 1H), 3.38-3.32 (m, 3H), 3.27-3.20 (m, 1H), 2.43 (s,
3H), 2.13-1.97 (m, 4H), 1.78 (m, 1H), 1.67 (m, 3H), 1.35 (m, 2H),
1.18 (d, J=16.2 Hz, 1H), 0.89 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 153.46, 144.05, 143.53, 135.11, 129.58 (2C), 128.02 (2C), 125.79, 65.29, 51.52, 40.06, 39.63, 37.35, 37.01, 36.84, 31.65, 26.24, 25.38, 21.62, 18.96; MS m/z (M$^+$-N$_2$H$_3$C$_6$H$_4$(p-CH$_3$)) calcd 252.1006, obsd 252.1032.

(4'$aR,5'S$)-4',4'$a,5'$,6'$,7'$,8'-Hexahydro-4'$a$-methylspiro[1,3-dithiolane-2,2'(3'H)-naphtalene]-5'$-methanol (12).

To a solution of aldehydes 9 (1.07g, 4 mmol) in methanol (15 ml) was added NaBH$_4$ (645 mg, 17 mmol) in portions. The mixture was allowed to stand at 0°C for 2 h, poured into a mixture of saturated aqueous NaCl (30 ml) and 2 M NaOH solutions (6ml) and stirred for 5 minutes. After the usual extractive work-up with ether (4 x 20 ml), 1.05g of a mixture of isomeric alcohols 12 (97%) was obtained. Purification and separation by preparative HPLC on silica gel (elution with 10% ethyl acetate in petroleum ether) gave 983 mg of pure alcohol (94%); mp 76°C; [$\alpha$]$^{25}_D$ +179° (c 1.19, CHCl$_3$); IR (KBr, cm$^{-1}$) 3500, 2920, 2840, 1640, 1435, 1005; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.44 (s, 1H), 3.74 (d, J=7.8 Hz, 2H), 3.33-3.26 (m, 3H), 3.19-3.15 (m, 1H), 2.12-1.96 (m, 4H), 1.81-1.61 (m, 4H), 1.26 (m, 3H), 0.91 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) 145.46, 124.93, 65.57, 63.70,
51.45, 40.03, 39.58, 37.83, 37.28, 36.45, 32.61, 26.85, 25.56, 18.69; 
MS \textit{m/z} (M^+) \textit{calcd} 270.1112, \textit{obsd} 270.1113.

\((4'aR,5'S)-4',4'a,5',6',7',8'-\text{Hexahydro-4'a-methylspiro[1,3-dithiolane-2,2'-(3'\text{H})-naphtalene]-5'-methanol methanesulfonate} \ (13)."

\begin{center}
\begin{tikzpicture}
\draw (0,0) -- (1,0) -- (1,1) -- (0,1) -- cycle;
\filldraw[black] (0.5,0.5) circle (0.1);
\filldraw[black] (0,0) circle (0.1);
\filldraw[black] (1,0) circle (0.1);
\filldraw[black] (1,1) circle (0.1);
\filldraw[black] (0,1) circle (0.1);
\draw (0.5,0.5) -- (0,0) -- (1,0) -- (1,1) -- (0,1) -- cycle;
\end{tikzpicture}
\end{center}

To a cold solution (-25°C) of alcohol 12 (0.26 g, 0.97 mmol) in dry ether (30 ml) was added triethylamine (0.250 ml, 1.80 mmol) and methanesulfonyl chloride (0.125 ml, 1.60 mmol). The mixture was allowed to warm to 0°C and water (20 ml) was added. After the usual extractive work-up with ether (4 x 20 ml) and evaporation of solvent, 334 mg of crude mesylate 13 was obtained (99%) as a light yellow solid; mp 85°C; IR (KBr, cm\(^{-1}\)) 2940, 2860, 1640, 1460, 1005; \(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \(\delta 5.54\) (s, 1H), 4.33 (dd, J=3.8 Hz, J' =9.6 Hz, 1H), 3.99 (t, J=9.7 Hz, 1H), 3.37 (m, 3H), 3.23 (m, 1H), 3.00 (s, 3H), 2.17 (m, 4H), 1.83 (m, 4H), 1.60 (m, 1H), 1.37 (m, 3H), 1.01 (s, 2H); \(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)) ppm 143.80, 125.39, 70.49, 64.95, 47.71, 39.77, 39.28, 37.31, 37.07, 36.81, 36.05, 31.92, 26.16, 25.20, 18.46; MS \textit{m/z} (M^+) \textit{calcd} 348.0887, \textit{obsd} 348.0876.
(4'aR,5'S)-4',4'a,5',6',7',8'-Hexahydro-4'a,5'-dimethylspiro[1,3-dithiolane-2,2'(3'H)-naphtalene] (10).

To a cold solution (0°C) of mesylate 13 (334 g, 0.96 mmol) in THF (20 ml) was added Superhydride (1 M in THF, 4 ml). The mixture was stirred at room temperature for 14 h then quenched with water (5 ml). After the usual extractive work-up with ether (4 x 20 ml) and purification by chromatography on silica gel (elution with 1% ether in petroleum ether) 234 mg of thioketal 10 (95%) was obtained; mp 86°C; [α]$_D^{25}$ +162.5° (c 1.09, CHCl$_3$); IR (CHCl$_3$, cm$^{-1}$) 2970, 2930, 2860, 1465, 1440, 1210, 730; $^1$H NMR (300 MHz, CDCl$_3$) δ 5.49 (s, 1H), 3.36 (m, 3H), 3.22 (m, 1H), 2.14 (m, 2H), 1.98 (m, 2H), 1.75 (m, 2H), 1.59 (m, 1H), 1.32 (m, 4H), 0.93 (s, 3H), 0.82 (d, J=5.9 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 146.40, 124.48, 66.01, 43.35, 39.93, 39.54, 38.02, 37.09, 33.22, 32.49, 30.91, 27.36, 17.15, 15.43; MS m/z (M$^+$) calcd 254.11629, obsd 254.1163.

Anal. Calcd for C$_{14}$H$_{22}$S$_2$: C, 66.06; H, 8.72. Found: C, 66.18; H, 8.87.
(4aR,5S)-4,4a,5,6,7,8-Hexahydro-4a,5-dimethyl-2(3H)-naphtalenone (14).

A solution of thallium(III) nitrate trihydrate (190 mg, 0.43 mmol) in methanol (2 ml) was rapidly added to a solution of thioketal 10 (106 mg, 0.42 mmol) in methanol (8 ml) and THF (2 ml). A white precipitate formed immediately and after 5 min CH2Cl2 (10 ml) was added and the precipitate was filtered. The solvents were removed from the filtrate under vacuum and the residue was dissolved in CHCl3, washed with water, dried and concentrated. Purification by flash chromatography on silica gel (elution with 7.5% ethyl acetate in petroleum ether) gave 75.3 mg of enone 14 (96%) as a yellow oil; [α]25D +185.6° (c 1.63, CHCl3); IR (neat, cm⁻¹) 2930, 2850, 1675, 1615, 1465, 1445, 1435, 1235; ¹H NMR (300 MHz, CDCl3) δ 5.70 (s, 1H), 2.34 (m, 2H), 2.03 (m, 2H), 1.85 (m, 2H), 1.69 (m, 2H), 1.45 (m, 3H), 1.08 (s, 3H), 0.89 (d, J=5.5 Hz, 3H); ¹³C NMR (75 MHz, CDCl3) ppm 199.47, 171.17, 124.00, 43.13, 38.99, 35.53, 33.98, 33.33, 30.48, 26.54, 16.00, 15.17; MS m/z (M⁺) calcd 178.1358, obsd 178.1357.
(2S,4aR,5S)-2,3,4,4a,5,6,7,8-Octahydro-4a,5-dimethyl-2-naphtalenol (15).

To a solution of unsaturated ketone 14 (1.00 g, 5.6 mmol) in methanol (50 ml) at 0°C was added in portions sodium borohydride (0.854 g, 22.5 mmol). The mixture was stirred for 6 h at 0°C before water (25 ml) was carefully added. After the usual extrative work-up with ether (4 x 30 ml) and purification by flash chromatography (elution with 15% ethyl acetate in petroleum ether) 0.92 g of alcohol 15 (91%) was obtained as a colorless oil; [α]$_D^{25}$ +94.9° (c 1.16, CHCl$_3$); IR (neat, cm$^{-1}$) 3350, 2960, 2840, 1650, 1460, 1440, 1370, 1060, 1020, 855; $^1$H NMR (300 MHz, CDCl$_3$) δ 5.29 (d, J=1.6 Hz, 1H), 4.16 (m, 1H), 2.23-1.63 (series of m, 5H), 1.60-1.18 (series of m, 7H), 0.97 (s, 3H), 0.81 (d, J=6.5 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) 147.61, 123.62, 68.00, 43.65, 37.89, 35.16, 32.63, 31.09, 29.41, 27.73, 17.51, 15.24; MS $m/z$ (M$^+$) calcd 180.1514 obsd 180.1514.

$\text{tert-Butyl}[(2S,4aR,5S)-2,3,4,4a,5,6,7,8$-octahydro-$4a,5$-dimethyl-2-naphtalyl]oxy]dimethylsilane (16).
To a solution of allylic alcohol 15 (0.92 g, 5.1 mmol) in DMF (5 ml) was added tert-butyldimethylchlorosilane (1.16 g, 7.65 mmol). The mixture was stirred overnight at room temperature and water (10 ml) was added. After the usual extractive work-up with ether and purification by flash chromatography (elution with 1% ether in petroleum ether) 1.38 g of silyl ether 16 (92%) was obtained as a light yellow oil; [α]25D +45° (c 0.99, CHCl₃); IR (neat, cm⁻¹) 2960, 2920, 2840, 1650, 1435, 1370, 1250, 1130, 1075, 880, 830, 770; ¹H NMR (300 MHz, CDCl₃) δ 5.22 (d, J=1.4 Hz, 1H), 4.18 (m, 1H), 2.15-2.10 (m, 1H), 1.99-1.94 (m, 1H), 1.82-1.66 (m, 2H), 1.59-1.19 (series of m, 7H), 0.97 (s, 3H), 0.91 (s, 9H), 0.81 (d, J=6.6 Hz, 3H), 0.08 (2 s, 6H); ¹³C NMR (75 MHz, CDCl₃) ppm 146.05, 124.85, 69.03, 44.02, 37.81, 35.69, 32.68, 31.14, 29.57, 27.75, 26.06, 18.40, 17.27, 15.20, -4.38, -4.54; MS m/z (M+) calcd 294.2379, obsd 294.2397.

*tert*-Butyl[(2S,4aR,5S)-1,8a-epoxydecahydro-4a,5-dimethyl-2-naphtalyl]oxy]dimethylsilane (17).

To a solution of silyl ether 16 (0.103 g, 0.35 mmol) in dichloromethane (5 ml) was added at 0°C sodium bicarbonate (88.3 mg, 1.05 mmol) and *meta*-chloroperbenzoic acid (0.152 g, 0.88
mmol). The mixture was stirred for 6 h at room temperature and a saturated solution of sodium bicarbonate (5 ml) was added. After the usual extractive work-up with dichloromethane and purification by MPLC (elution with 2.5% ethyl acetate in petroleum ether) 0.104 g of the epoxide 17 (96%) was obtained as a colorless oil; IR (neat, cm\(^{-1}\)) 2940, 2850, 1465, 1365, 1255, 1100, 880, 840, 780; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.91 (t, \(J=8.5\) Hz, 1H), 2.82 (d, \(J=0.6\) Hz, 1H), 2.01 (m, 1H), 1.99-1.10 (series of m, 10H), 1.01 (s, 3H), 0.90 (s, 9H), 0.78 (d, \(J=6.7\) Hz, 3H), 0.08 (2s, 6H); \(^1\)C NMR (75 MHz, CDCl\(_3\)) ppm 67.09, 65.24, 40.10, 38.94, 35.91, 30.42, 29.85, 28.81, 27.60, 25.90, 23.12, 18.22, 16.09, 14.92, -4.66, -4.83; MS \(m/z\) (M\(^+\)) calcd 292.2222, obsd 292.2170.

\((2S,4aR,5S)-2-(\text{tert-Butyldimethylsiloxy})\text{octahydro-4a,5-dimethyl-1,8a(1H)-naphtalenediol} \quad (18)
\)

![Chemical Structure](image)

To a solution of silyl ether 16 (159 mg, 0.54 mmol) in pyridine (3 ml) was added a solution of osmium tetroxide (1 g in 10 ml of pyridine, 0.923 ml, 0.363 mmol). The solution was stirred for 1 day and a solution of sodium bisulfite was added. After filtration, the usual extractive work-up with ethyl acetate and purification by
flash chromatography on silica gel (elution with ether) gave 175 mg of diol 18 (97%) as a yellow oil; IR (neat, cm$^{-1}$) 3570, 3480, 2960, 2840, 1460, 1375, 1250, 1080, 910, 830, 775; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.83 (m, 3H), 3.45 (d, J=8.6 Hz, 1H), 1.92-1.18 (series of m, 11H), 0.90 (s, 9H), 0.88 (s, 3H), 0.75 (d, J=2.0 Hz, 3H), 0.05 (d, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 77.21, 76.00, 74.59, 40.22, 34.49, 30.56, 30.15, 29.69, 29.38, 26.13, 20.82, 18.28, 15.54, 14.23, -3.96, -4.41; MS $m/z$ (M$^+$) calcd 296.2171, obsd 296.2150.

($\alpha$S,1$R$,2$S$)-$\alpha$-(tert-Butyldimethylsiloxy)-1,2-dimethyl-6-oxocyclohexanebutyraldehyde (19).

To a solution of tert-butyldimethylsilyl ether 16 (300 mg, 1.02 mmol) in 10% methanol in dichloromethane (40 ml) was ozonized at -78°C until the solution turned blue. Pyridine (0.2 ml) and dimethylsulfide (1 ml) were added. The mixture was allowed to warm to 0°C and stirred overnight at this temperature. The solvent was evaporated and xylene (100 ml) was added. The solution was concentrated to yield keto aldehyde 19 quantitatively as a yellow oil; IR (neat, cm$^{-1}$) 2960, 2930, 2840, 1735, 1705, 1455, 1255, 1115, 915, 840, 770, 735; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.59 (d, J=1.6 Hz, 1H), 3.97 (m, 1H), 2.32 (m, 3H), 1.90-1.52 (series of m, 8 H), 0.99
(s, 3H), 0.92 (s, 9H), 0.89 (d, J=7.0 Hz, 3H), -0.08 (2s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 215.23, 203.58, 77.86, 51.72, 38.65, 38.20, 30.71, 28.83, 27.44, 25.76, 24.23, 18.64, 18.24, 15.38, -4.64, -4.91; MS m/z (M$^+$-[C$_4$H$_8$]) calcd 270.1651, obsd 270.1677.

**tert-Butyl[(2S,4aR,5S)-2,3,4,4a,5,6,7,8-octahydro-4a,5-dimethyl-2-naphtalyl]oxy]diphenylsilane** (20).

To a solution of allylic alcohol 15 (0.92 g, 5.1 mmol) in DMF (5 ml) was added *tert*-butyldimethylchlorosilane (1.16 g, 7.65 mmol). The mixture was stirred overnight at room temperature and water (10 ml) was added. After the usual extractive work-up with ether and purification by flash chromatography (elution with 1% ether in petroleum ether) 1.38 g of silyl ether 20 (92%) was obtained as a light yellow oil; [$\alpha$]$^2$$_D$ +31.5° (c 1.66, CHCl$_3$); IR (neat, cm$^{-1}$) 3080, 3050, 2960, 2920, 2860, 1650, 1465, 1430, 1270, 1110, 1065, 830, 790, 710; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.74 (m, 6H), 7.41 (m, 4H), 5.33 (d, J=0.8 Hz, 1H), 4.24 (m, 1H), 2.16-2.10 (m, 1H), 1.98-1.93 (m, 1H), 1.76-1.14 (series of m, 9H), 1.10 (s, 9H), 0.96 (s, 3H), 0.77 (d, J=6.7 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) 146.06, 135.90 (2C), 135.87 (2C), 135.82, 134.96, 129.40 (2C), 127.46 (2C), 127.42 (2C), 124.55,
69.74, 43.63, 37.73, 35.34, 32.62, 31.10, 29.21, 27.68, 27.08 (3C), 19.19, 17.30, 15.14; MS/FAB m/z (M⁺) calcd 418.27, obsd 418.27.


(αS,1R,2S)-α-(tert-Butyldiphenylsiloxy)-1,2-dimethyl-6-oxocyclohexanecarbonylaldehyde (22).

To a solution of tert-butyldiphenylsilyl ether 20 (0.427 g, 1.02 mmol) in 40 ml of 10% methanol in dichloromethane was ozonized at -78°C until the solution turned blue. Pyridine (0.2 ml) and dimethylsulfide (1 ml) were added. The mixture was allowed to warm up to 0°C and stirred overnight at this temperature. The solvent was evaporated and xylene (100 ml) was added. The solution was concentrated to yield keto aldehyde 22 quantitatively as a yellow oil; IR (neat, cm⁻¹) 3060, 2960, 2860, 2250, 1735, 1700, 1650, 1460, 1430, 1380, 1110, 910, 700; ¹H NMR (300 MHz, CDCl₃) δ 9.57 (s, 1H), 7.73-7.61 (m, 4H), 7.45-7.24 (m, 6H), 4.05 (t, J=5.0 Hz, 1H), 2.36-2.18 (m, 3H), 1.93-1.48 (series of m, 8H), 1.12 (s, 9H), 0.90 (s, 3H), 0.82 (d, J=6.8 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm 213.67, 203.07, 135.75 (2C), 135.70 (2C), 134.73, 133.13, 132.93, 129.94 (2C), 127.71(2C), 127.58, 78.15, 51.64, 38.47, 38.10, 30.40, 28.64,
27.36, 26.93 (3C), 23.93, 19.32, 18.63, 15.36; MS m/z (M+-[C₄H₉])
calcd 393.1865, obsd 393.1885.

**Methyl(αS,1R,2S)-α-(tert-Butyldiphenylsiloxy)-1,2-dimethyl-6-oxocyclohexanebutyrate** (23).

To a solution keto aldehyde 22 (0.225 g, 0.50 mmol) in tert-BuOH (3 ml) was added a solution of 5% KH₂PO₄ (2 ml) then a 1.25 M solution of KMnO₄ (3 ml). The mixture was stirred 10 min at room temperature and a saturated solution of sodium sulfite was added. The MnO₂ precipitate was dissolved with dilute HCl. The mixture was extracted with ether (3 x 20 ml), dried, and concentrated. The solution of crude acid in ether (2.5 ml) was treated with a solution of diazomethane in ether. The solvent was removed and the residue was purified by flash chromatography (elution with 5% ethyl acetate in petroleum ether) to give 0.199 g of keto ester 23 (83%) as a colorless oil; [α]²⁵°D 5.5° (c 1.00, CHCl₃); IR (neat, cm⁻¹) 3080, 3060, 2970, 2885, 1755, 170, 1595, 1480, 1430, 1380, 1205, 1110, 950, 810, 750, 705; ¹H NMR (300 MHz, CDCl₃) δ 7.64 (m, 4H), 7.40 (m, 6H), 4.24 (t, J=5.1 Hz, 1H), 3.51 (s, 3H), 2.29 (m, 3H), 1.88-1.49 (series of m, 8H), 1.10 (s, 9H), 1.01 (s, 3H), 0.85 (d, J=6.8 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm 215.31, 173.23,
135.88 (2C), 135.73 (2C), 133.37, 133.11, 129.73, 129.68 (2C), 127.56 (2C), 127.45, 72.65, 51.64, 51.38, 38.58, 38.16, 30.81, 29.66, 28.59 (3C), 26.88 (3C), 23.82, 19.35, 18.79, 15.40; MS m/z (M+-[C4H7]) calcd 423.1991, obsd 423.1964.

tert-Butyl(αS,1R,2S)-α-(tert-Butyldiphenylsilox)-1,2-dimethyl-6-oxocyclohexanecarboxyrate (44).

![Chemical Structure](image)

To a solution keto aldehyde 22 (0.675 g, 1.50 mmol) in tert-BuOH (9 ml) was added a solution of 5% KH₂PO₄ (6 ml) then a 1.25 M solution of KMnO₄ (9 ml). The mixture was stirred 10 min at room temperature and a saturated solution of sodium sulfite was added. The MnO₂ precipitate was dissolved with dilute HCl. The mixture was extracted with ether (3 x 50 ml), dried, and concentrated. To a solution of crude acid (0.60 g, 1.29 mmol) in ether (2.5 ml) was added isobutylene (7 ml) and concentrated sulfuric acid (0.130 ml). The mixture was stirred overnight at room temperature, poured into a 30% solution of potassium hydroxide (25 ml) extracted with ether (3 x 10 ml) dried, concentrated and purified by MPLC (elution with 5% ethyl acetate in petroleum ether) to give 0.62 g (92%) of keto ester 44; [α]°D -11° (c=1.86, CHCl₃); IR (neat, cm⁻¹) 3060, 3040, 2960, 2940, 2850, 1750, 1710, 1590, 1460,
1420, 1390, 1240, 1150, 810, 710; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$
7.73-760 (m, 4H), 7.44-7.31 (m, 6H), 4.17 (t, J=3.9 Hz, 1H), 2.29 (t, J=6.6 Hz, 2H), 1.93-1.01 (series of m, 9H), 1.34 (s, 9H), 1.11 (s, 9H), 0.94 (s, 3H), 0.86 (d, J=7.1 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm
215.42, 171.90, 135.98 (2C), 135.77 (2C), 134.78, 133.81, 129.67, 129.62, 127.57 (2C), 127.48 (2C), 80.77, 72.68, 51.64, 38.78, 30.78, 29.66, 28.57, 27.92, 26.94, 26.58, 23.72, 19.37, 18.92, 15.44;
MS/FAB $m/z$ (M$^+$) calcd 522.36, obsd 522.36.
Anal. Calcd for C$_{32}$H$_{46}$O$_4$Si: C, 73.52; H, 8.87. Found: C, 73.58. H, 8.87.


To a solution of pent-4-yn-1-ol (488 mg, 5.80 mmol) in 10 ml of dichloromethane was added PPTS (0.080 g, 0.32 mmol) and dihydropyran (0.736 g, 8.64 mmol). The mixture was stirred overnight at room temperature. After the usual extractive work-up with ether and purification by distillation 0.947 g of the tetrahydropyryanyl ether 24 (97%) was obtained; bp=70$^\circ$C/2 torr; IR (neat, cm$^{-1}$) 3290, 2940, 2860, 2120, 1460, 1450, 1435, 1350, 1200, 1135, 1125, 1030; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$
4.56 (t, J=3.5 Hz, 1H), 3.83 (m, 2H), 3.46 (m, 2H), 2.28 (dt, J=2.6 Hz, J'=7.1 Hz, 2H), 1.91 (t, J=2.6 Hz, 2H), 1.78 (m, 2H), 1.66 (m, 2H), 1.54 (m, 3H); $^{13}$C NMR (75
50

MHz, CDCl₃) ppm 98.71, 83.87, 68.34, 65.71, 62.08, 30.61, 28.69, 25.44, 19.45, 15.28.

5-[(tetrahydro-2H-pyran-2-yl)oxy]-2-pentyn-1-ol (25).

\[ \text{THPO} \quad \text{OH} \]

To a cold solution (-23°C) of THP ether 24 (34.83 g, 207.3 mmol) in ether (350 ml) were added nBuLi (1.55M in hexane, 133.8 ml, 207.4 mmol) and a suspension of paraformaldehyde (18.0 g, 600 mmol) in ether (120 ml). The mixture was stirred overnight and water (200 ml) was added. The usual extractive work-up with ether (4 X 150 ml) and distillation (bp 135°C/30 torr) gave 32.54 g of alcohol 25 (79%); IR (neat, cm⁻¹) 3420, 2935, 2860, 2220, 1425, 1350, 1195, 1135, 1070, 1025, 900, 865, 810; ¹H NMR (300 MHz, CDCl₃) δ 4.59 (t, J=3.4 Hz, 1H), 4.23 (bs, 1H), 3.84 (m, 4H), 3.49 (m, 2H), 1.74 (m, 4H), 1.56 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) ppm 98.60, 85.08, 78.83, 65.78, 62.04, 50.83, 30.49, 28.60, 25.30, 19.30, 15.50; MS m/z (M⁺) calcd 197.1178, obsd 197.1229.
To a suspension of lithium aluminum hydride (0.157 g, 4.14 mmol) and sodium methoxide (0.447 g, 8.28 mmol) in THF (30 ml) at 0°C was added a solution of alcohol 25 (0.4 g, 2.07 mmol) in 5 ml of THF. The mixture was stirred at 0°C for 1 hr then at reflux for 2 hr. The mixture was cooled down to -78°C and a solution of iodine (4.20 g, 16.56 mmol) in THF (10 ml) was added dropwise. The mixture was stirred for 30 min at -78°C then for 2 h at -23°C. A 10% aqueous solution of disodium tartrate was added to the mixture followed by a saturated aqueous solution of sodium thiosulfate (10 ml). After the usual extractive work-up with ether (4 x 30 ml) and purification by flash chromatography on silica gel (elution with 20% ethyl acetate in petroleum ether) 0.52 g of vinyl iodide 26 (77.3%) was obtained as a colorless oil; IR (neat, cm⁻¹) 3400, 2935, 2880, 1635, 1435, 1350, 1260, 1200, 1130, 1120, 1030; ¹H NMR (300 MHz, CDCl₃) δ 5.82 (t, J=5.7 Hz, 1H), 4.52 (t, J=3.5 Hz, 1H), 4.12 (d, J=5.6 Hz, 2H), 3.81 (m, 1H), 3.68 (m, 1H), 3.46 (m, 1H), 2.64 (bs, 1H), 2.57 (t, J=7.3 Hz, 2H), 1.73 (m, 4H), 1.50 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) ppm 134.24, 108.78, 98.79, 67.08, 65.60, 62.27, 41.84, 30.59, 20.14, 25.33, 19.48; MS m/z (M⁺) calcd 326.0381, obsd 326.0365.
(E)-3-Methyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-2-penten-1-ol (27).

To a suspension of CuI (1.98 g, 10.4 mmol) in 20 ml of ether at -30°C was added MeLi (1.1 M in ether, 18.92 ml, 20.8 mmol). A solution of vinyl iodide 26 (0.52 g, 1.6 mmol) in ether (5 ml) was added to the yellow solution and the mixture was stirred for 4 days at -5°C. Treatment with an excess of methyl iodide, the usual extractive work-up with ether (4 x 20 ml), and purification by flash chromatography on silica gel (20% ethyl acetate in petroleum ether) gave 0.257 g of alcohol 27 (75%); IR (neat, cm⁻¹) 3420, 2940, 2880, 1665, 1435, 1380, 1350, 1260, 1140, 1120, 1075, 1035, 910; ¹H NMR (300 MHz, CDCl₃) δ 5.40 (t, J=5.7 Hz, 1H), 4.55 (t, J=3.5 Hz, 1H), 4.11 (d, J=6.8 Hz, 2H), 3.84 (m, 1H), 3.70 (m, 1H), 3.47 (m, 1H), 3.36 (m, 1H), 2.08 (t, J=7.6 Hz, 2H), 1.76 (m, 4H), 1.63 (s, 3H), 1.55 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) ppm 139.02, 123.68, 98.88, 67.04, 62.35, 59.26, 36.06, 30.74, 27.73, 25.47, 19.64, 16.13; MS m/z (M⁺) calcd 214.1569, obsd 214.1589.

(E)-3-Methyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-2-penten-1-ol acetate (28).
To a solution of alcohol 27 (0.257 g, 1.2 mmol) in pyridine (5 ml) was added acetic anhydride (0.750 g, 6.2 mmol) and traces of DMAP. The mixture was stirred overnight and poured onto ice. After the usual work-up with ether (5 x 5 ml) and purification by flash chromatography on silica gel (elution with 5% ethyl acetate in petroleum ether) 0.27 g of acetate 28 (88%) was isolated as a yellow oil; IR (neat, cm⁻¹) 2935, 2870, 1735, 1660, 1435, 1230, 1135, 1115, 1075, 1030;¹ H NMR (300 MHz, CDCl₃) δ 5.32 (t, J=6.3 Hz, 1H), 4.53 (m, 3H), 3.85-3.78 (m, 1H), 3.68 (m, 1H), 3.45 (m, 1H), 3.33 (m, 1H), 2.16-2.00 (m, 2H), 2.00 (s, 3H), 1.82 (m, 4H), 1.67 (s, 3H), 1.55 (m, 4H);¹³C NMR (75 MHz, CDCl₃) ppm 170.81, 141.64, 118.46, 98.74, 66.89, 62.14, 61.20, 36.00, 30.67, 27.63, 25.43, 20.87, 19.53, 16.26; MS m/z (M⁺) calcd 255.1596, obsd 255.1574.

(E)-6-Hydroxy-4-methyl-4-hexenal acetate (29).

To a solution of geraniol (33.0 g, 0.210 mol) and pyridine (43.1 ml, 0.540 mol) in dichloromethane (100 ml) at 0°C was added dropwise acetic anhydride (22.3 ml, 0.240 mol). After the mixture was warmed to room temperature, stirring was continued for 4 h. The resulting solution was then diluted with dichloromethane (900 ml), cooled to -78°C, and treated with a stream of ozone. The
progress of the reaction was monitored by TLC and by GC. After only a trace of geranyl acetate could be detected, the ozone flow was discontinued, and the solution was treated with acetic acid (230 ml) followed by zinc dust (120 g). The resulting slurry was warmed to room temperature, stirred for 2 h, and then filtered through a pad of Celite. The filtrate was diluted with pentane (2 l) and washed with 0.5 M HCl. The combined aqueous washes were reextracted with pentane. The combined organic layers were washed with 5% aqueous NaHCO₃, water, and brine, then dried, and concentrated. Purification by distillation, bp 110°C (2.5 torr) gave 23.4 g (61%) of the aldehyde 29; IR (neat, cm⁻¹) 2920, 2820, 1730, 1440, 1370, 1230, 1020, 950 ; ¹H NMR (300 MHz, CDCl₃) δ 9.68 (t, J=1.4 Hz, 1H), 5.30 (t, J=7.0 Hz, 1H), 4.48 (d, J=7.0 Hz, 2H), 2.50 (t, J=7.2 Hz, 2H), 2.29 (t, J=7.5 Hz, 2H), 1.95 (s, 3H), 1.64 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm 201.00, 170.28, 139.52, 119.00, 60.55, 41.26, 31.04, 20.42, 16.07; MS m/z (M⁺) calcd 170.0942, obsd 170.0963.

(Z)-3-Methyl-2-hexene-1,6-diol 1-acetate (30).

To a solution of aldehyde 29 (0.246 g, 1.45 mmol) in methanol (20 ml) was added in portions sodium borohydride (0.120 g). The mixture was stirred for 1 h at 0°C and a diluted solution of
acetic acid was added. After the usual extractive work-up with ether, crude alcohol 30 was obtained (100%); IR (neat, cm⁻¹) 3400, 2960, 2860, 1730, 1670, 1440, 1360, 1230, 1020; ¹H NMR (300 MHz, CDCl₃) δ 5.37 (t, J=7.1 Hz, 1H), 4.58 (d, J=7.0 Hz, 2H), 3.66 (t, J=7.1 Hz, 2H), 2.13 (t, J=6.4 Hz, 2H), 2.05 (s, 3H), 1.75-1.70 (m, 3H), 1.72 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) 170.95, 141.61, 118.23, 61.82, 61.09, 35.47, 30.24, 20.69, 16.08; MS m/z (M⁺) calcd 172.1099, obsd 172.1108.

*(E)-3-Methyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-2-penten-1-ol acetate (28).*

![Chemical Structure](image)

To a solution of alcohol 30 (250 mg, 1.45 mmol) in 10 ml of dichloromethane was added PPTS (0.040 g, 0.16 mmol) and dihydropyran (0.184 g, 2.18 mmol). The mixture was stirred overnight at room temperature. After the usual extractive work-up with ether and purification by flash chromatography (elution with 10% ether in petroleum ether) 0.341 g of the tetrahydropyranyl ether 28 (92%) was obtained. This material was identical to that described above.
(E)-6-(tert-Butyldimethylsiloxy)-3-methyl-2-hexen-1-ol acetate.

To a solution of alcohol 30 (0.153 g, 1.00 mmol) in DMF (2 ml) was added tert-butyldimethylchlorosilane (0.232 g, 1.50 mmol) and imidazole (0.207 g, 3.00 mmol). The mixture was stirred overnight at room temperature and water (5 ml) was added. After the usual extractive work-up with ether and purification by flash chromatography (elution using 5% ether in petroleum ether) 0.263 g of silyl ether 33 (92%) was obtained; IR (neat, cm⁻¹) 2960, 2940, 2860, 1740, 1460, 1380, 1360, 1250, 1220, 1110, 1020, 950, 830, 770; ¹H NMR (300 MHz, CDCl₃) δ 5.33 (t, J=7.1 Hz, 1H), 4.57 (d, J=7.0 Hz, 2H), 3.58 (t, J=6.5 Hz, 2H), 2.12 (m, 2H), 2.03 (s, 3H), 1.68 (s, 3H), 1.67-1.60 (m, 2H), 0.88 (s, 9H), 0.33 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) ppm 170.99, 141.98, 118.38, 62.59, 61.34, 35.74, 30.77, 25.94, 25.65, 20.97, 18.30, 16.39, -5.31 (2C); MS m/z (M⁺) calcd 286.1964, obsd 286.1479.

(E)-6-(tert-Butydiphenylsiloxy)-3-methyl-2-hexen-1-ol acetate (33).
The same procedure was used for the preparation of the tert-butyldiphenylsilyl ether in 91% yield; IR (neat, cm$^{-1}$) 3060, 3040, 2950, 2840, 1740, 1590, 1450, 1430, 1380, 1360, 1235, 1105, 1020, 950, 820, 740, 700; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.73-7.65 (m, 4H), 7.42-7.26 (m, 6H), 5.33 (t, J=7.1 Hz, 1H), 4.56 (d, J=7.1 Hz, 2H), 3.65 (t, J=6.3 Hz, 2H), 2.07-2.03 (m, 2H), 2.05 (s, 3H), 1.70-1.54 (m, 2H), 1.67 (s, 3H), 1.07 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 171.05, 141.98, 135.51 (2C), 135.28 (2C), 135.02, 134.76, 133.96, 129.49, 127.62 (2C), 127.55 (2C), 118.31, 63.34, 61.34, 35.72, 30.51, 26.86, 26.56, 20.99, 19.20, 18.99, 16.37; MS/FAB $m/z$ (M$^+$) calcd 410.23, obsd 410.33.

$(E)$-3-Methyl-2-hexene-1,6-diol (40).

To a suspension of LiAlH$_4$ (0.894 g, 23.57 mmol) in ether (100 ml) at 0°C was added dropwise a solution of aldehyde 29 (2.0 g, 11.8 mmol) in ether (25 ml). The mixture was refluxed for 4 h and poured into a mixture of a saturated NaCl aqueous solution (30 ml) and a 2 M NaOH aqueous solution (6 ml). After extractive work-up with ethyl acetate, 1.5 g of crude diol 40 (98%) was obtained and used without purification; IR (neat, cm$^{-1}$) 3300 2940, 2840, 1660, 1370, 1230, 1050, 990; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.30 (t, J=6.9 Hz, 1H), 4.01 (d, J=6.6 Hz, 2H), 3.78 (bs, 1H), 3.68 (bs, 1H), 3.48 (t,
J=6.5 Hz, 2H), 1.98 (t, J=6.8 Hz, 2H), 1.57 (s, 3H), 1.55 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 138.06, 123.65, 61.78, 58.66, 35.48, 30.19, 15.91; MS m/z (M$^+$) calcd 130.0994, obsd 130.0982.

(E)-1,6 Dibromo-3-methyl-2-hexene (41).

To a cold solution (0°C) of 1,2-bis(diphenylphosphino)ethane (DIPHOS) (2.0 g, 5 mmol) in dichloromethane (25 ml) was added dropwise a solution of bromine (1.6 g, 10 mmol) in dichloromethane (5 ml), followed by a solution of diol 40 (0.26 g, 2 mmol) in dichloromethane (5 ml). The mixture was allowed to return to room temperature and stirred overnight. Ether (70 ml) and pentane (140 ml) were added, and the mixture was filtered through a thin pad of magnesium sulfate. The filtrate was evaporated to give 0.50 g of crude dibromide 41 (98%) which was used without further purification; IR (neat, cm$^{-1}$) 2960, 2850, 1660, 1440, 1380, 1250, 1200, 1050, 880; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.59 (t, J=8.4 Hz, 1H), 4.00 (d, J=8.3 Hz, 2H), 3.38 (t, J=6.6 Hz, 2H), 2.21 (t, J=7.3 Hz, 2H), 1.98 (t, J=6.8 7Hz, 2H), 1.73 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 141.15, 121.50, 37.32, 32.66, 30.22, 28.80, 15.63; MS m/z (M$^+$) calcd 252.9228, obsd 252.9246.
(E)-6-Bromo-3-methyl-2-hexen-1-ol acetate (34).

\[ \text{Br} \text{H}_3\text{C} \equiv \text{OAc} \]

To a cold solution (-10°C) of DIPHOS (0.83 g, 2.08 mmol) in dichloromethane (10 ml) was added a solution of bromine (0.664 g, 4.15 mmol) in dichloromethane (2 ml). A solution of alcohol 30 (0.425 g, 1.66 mmol) was added, the mixture was allowed to warm to room temperature and stirred overnight. The mixture was diluted with ether (50 ml) and pentane (100 ml), filtered through a thin pad of silica gel, and concentrated. The residue was purified by flash chromatography (elution with 1% ether in petroleum ether) to give 0.342 g of bromo acetate 34 (88%); IR (neat, cm\(^{-1}\)) 2960, 2920, 2860, 1740, 1440, 1380, 1370, 1220, 1020, 950; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.39 (t, \(J=7.0\) Hz, 1H), 4.58 (d, \(J=7.0\) Hz, 2H), 3.36 (t, \(J=6.6\) Hz, 2H), 2.19 (t, \(J=7.4\) Hz, 2H), 2.05 (s, 3H), 2.04-1.94 (m, 2H), 1.71 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) ppm 170.69, 139.93, 119.45, 60.94, 37.47, 32.84, 30.34, 20.80, 16.16; MS \(m/z\) (M\(^+\)) calcd 234.0255, obsd 234.0263.

Diethyl[(E)-6-hydroxy-4-methyl-4-hexenyl]phosphonate, acetate (35).

\[ \text{(EtO)}_2\text{(O)P} \text{H}_3\text{C} \equiv \text{OAc} \]
A mixture of bromo acetate 34 (0.470 g, 2 mmol), triethylphosphite (0.5 g, 3 mmol) and nickel chloride (10 mg) was stirred at 150°C for 4 h. The resulting solution was purified by flash chromatography (elution with ethyl acetate) to give 0.432 g of phosphonate 35 (94%); IR (neat, cm⁻¹) 2990, 2910, 2860, 1730, 1650, 1440, 1380, 1230, 1180, 950, 790; ¹H NMR (300 MHz, CDCl₃) δ 5.28 (t, J=7.0 Hz, 1H), 4.51 (d, J=7.0 Hz, 2H), 4.08-3.97 (m, 4H), 2.04 (t, J=6.8 Hz, 2H), 1.98 (s, 3H), 1.71-1.56 (m, 4H), 1.62 (s, 3H), 1.25 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) ppm 170.80, 140.55, 119.36, (61.31, 61.08), (40.08, 39.83), 25.96, 24.09, 20.89, (20.34, 20.28), (16.43, 16.35), 16.08; MS m/z (M⁺) calcd 292.1439, obsd 292.1475.

Diethyl[(E)-6-bromo-4-methyl-4-hexenyl]phosphonate (44).

A mixture of ester 35 (0.292 g, 1.00 mmol), methanol (5 ml), and a catalytic amount of potassium carbonate was stirred overnight at 0°C. The mixture was poured in water. After extractive work-up with ether, the residue was dissolved in ether (5 ml) and phosphorus tribromide (0.048 ml, 0.505 mmol) was added at 0°C. The mixture was stirred for 20 minutes and a few drops of methanol were added. The resulting solution was diluted with
pentane, washed with 5% aqueous NaHCO₃, water, and brine. The organic layer was then dried and concentrated to yield 0.306 g of bromophosphonate 44 (98%); IR (neat, cm⁻¹) 2970, 2890, 1650, 1440, 1390, 1235, 1200, 1160, 1090, 1060, 1030, 960, 780; ¹H NMR (300 MHz, CDCl₃) δ 5.50 (t, J=8.4 Hz, 1H), 4.06 (m, 4H), 3.94 (d, J= 8.3 Hz, 2H), 2.08 (d, J=6.7 Hz, 2H), 1.66 (s, 3H), 1.66 (m, 4H), 1.26 (t, J=7.0 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) ppm 141.89, 121.58, (61.41, 61.32), (39.91, 39.68), 28.90, 25.72, 23.85, (20.26, 20.19), (16.39, 16.31); MS m/z (M⁺-Br) calcd 233.1370, obsd 233.1364.

Methyl(αS,1R,2S)-α-(tert-Butyldiphenylsiloxy)-1,6-dimethyl-2-(trimethylsiloxy)-2-cyclohexene-1-butyrate (31).

To a cold solution of ketone 23 (150 mg, 0.31 mmol) in ether (5 ml) was added triethylamine (150 µl, 0.77 mmol) and trimethylsilyl triflate (85 µl, 0.39 mmol). The mixture was stirred for 14 h and purified by chromatography (elution with 20% ether in petroleum ether) to give 91.5 mg of trimethylsilyl enol ether 31 (68%); IR (CHCl₃, cm⁻¹) 3060, 2960, 2860, 1745, 1625, 1420, 1250, 1180, 1120, 920, 835; ¹H NMR (300 MHz, CDCl₃) δ 7.82 (m, 4H), 7.20 (m, 6H), 4.74 (m, 1H), 4.50 (t, J=5.3 Hz, 1H), 3.22 (s, 3H), 1.95-1.67
ZnI$_2$-Catalyzed Alkylation of TMS Enol Ether. General Procedure.

Zinc iodide (0.64 g, 2 mmol) was flame-dried under vacuum then kept under argon. To the zinc iodide was added a solution of TMS enol ether (1 mmol) in dichloromethane (2 ml) and a solution of allylic acetate (1 mmol) in dichloromethane (2 ml). The mixture was stirred at room temperature for 48 h. A saturated solution of sodium carbonate (10 ml) was added to the mixture. The usual extractive work-up with dichloromethane and purification by flash chromatography gave the alkylated product.

2,6-Dimethyl-2-(3-methyl-2-butenyl)cyclohexanone (22).

For 22 (87%); IR (neat, cm$^{-1}$) 2980, 2960, 2880, 1700, 1450, 1370, 1310, 1120, 990, 850; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.13 (t,
J=7.5 Hz, 1H major), 4.92 (t, J=3.9 Hz, 1H minor), 2.52-1.48 (series of m, 7H), 1.69 (s, 3H), 1.59 (s, 3H), 1.27 (m, 2H), 1.13 (s, 3H), 0.99 (d, J=6.5 Hz, 3H minor), 0.98 (d, J=6.5 Hz, 3H major); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 216.60 (2C), 134.06, 133.14, 120.54, 118.63, 49.11, 48.63, 41.06, 40.93, 39.94, 38.35, 37.16, 36.61, 36.41, 36.30, 35.66, 25.89, 25.78, 22.96, 22.45, 21.21, 17.82, 17.72, 14.88, 14.82; MS m/z (M$^+$) calcd 194.1671, obsd 194.1690.

2-[(E)-6-(tert-Butyldiphenylsiloxy)-3-methyl-2-hexenyl]-2,6-dimethylcyclohexanone (36).

For 36 (76%); IR (neat, cm$^{-1}$) 3040, 3020, 2960, 2920, 2850, 1700, 1580, 1460, 1425, 1370, 1110, 990, 820; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.62-7.45 (m, 4H), 7.33-7.25 (m, 6H), 5.09 (t, J=6.9 Hz, 1H major), 4.89 (t, J=6.6 Hz, 1H minor), 3.59 (m, 2H), 2.52 (m, 1H), 2.18-1.10 (series of m, 12H), 1.60 (s, 3H minor), 1.59 (s, 3H major), 0.99 (m, 9H), 0.98 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm For the major: 216.31, 136.55, 136.49 (2C), 135.34 (2C), 133.91, 133.47, 129.87, 129.32 (2C), 128.67, 127.40 (2C), 118.73, 63.47, 48.54, 40.85, 38.30, 37.10, 36.23, 36.10, 30.82, 26.76 (3C), 22.86, 21.18, 19.06, 15.93, 14.91; MS m/z calcd 476.3111, obsd 476.3121.
Diethyl[(E)-6-(1,3-dimethyl-2-oxocyclohexyl)-4-methyl-4-hexenyl]phosphonate (37).

For 37 (63%); IR (neat, cm⁻¹) 2980, 2920, 2880, 1700, 1650, 1440, 1370, 1320, 1250, 1040, 950, 760, 725; ¹H NMR (300 MHz, CDCl₃) δ 5.15 (t, J=6.8 Hz, 1H major), 4.92 (t, J=6.0 Hz, 1H minor), 4.07 (m, 4H), 2.52 (m, 1H), 2.17-1.40 (series of m, 14H), 1.66 (s, 3H), 1.27 (m, 6H), 1.12 (s, 3H), 0.97 (m, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm 216.76, 216.58, 136.57, 135.69, 121.97, 120.37, (63.61, 63.53), (61.40, 61.32), 49.15, 48.99, 48.69, 48.40, 41.21, 41.04, 40.80, 40.56, 38.52, (36.61, 36.40), 36.15, (35.61, 35.40), 25.95, 24.09, 23.93, 23.25, 23.19, 22.62, 22.45, 21.29, 21.23, 20.70, 20.63, 16.39, 16.13, 16.04, 15.91, 15.83 (two signals not observed); MS m/z (M⁺) calcld 358.2273, obsd 357.2258.

2-[(E)-6-Bromo-3-methyl-2-hexenyl]-2,6-dimethylcyclohexanone (38).
To a solution of ketone (1 mmol) in dry THF (5 ml) was added
at -78°C a solution of LDA (1 eq). After 20 minutes of stirring, a
solution of tributyltin triflate or tributyltin chloride (1.5 mmol) in
THF (2 ml) was added and the mixture was allowed to warm up to
room temperature. A solution of allylic acetate (1 mmol) in THF (2
ml) was added, followed by *tetrakis*-triphenylphosphinepalladium
(0.034 g). The mixture was stirred for 48 hr at room temperature.
Addition of water (10 ml), the usual extractive work-up with ether,
and purification by flash chromatography gave the alkylation
product.

For 38 (45%); IR (neat, cm⁻¹) 2960, 2920, 2860, 1700, 1650,
1440, 1370, 1240, 1170, 990, 730; ¹H NMR (300 MHz, CDCl₃) δ 5.35
(t, J=7.4 Hz, 1H minor), 4.96 (t, J=7.3 Hz, 1H major), 3.30 (t, J=6.7 Hz,
2H), 2.55 (m, 1H), 2.18-1.22 (series of m, 12H), 1.57 (s, 3H), 1.19 (s,
3H), 0.97 (m, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm 216.59, 216.42,
135.95, 131.59, 122.11, 120.13, 49.10, 48.84, 48.63, 41.33, 41.17,
40.46, 39.93, 38.46, 38.13, 38.02, 36.39, 36.31, 35.57, 33.08, 32.22,
30.81, 26.73, 23.12, 22.58, 21.23, 17.44, 16.08, 14.89, 13.51; MS
m/z (M⁺) calcd 300.1089, obsd 300.1103.
(αS,1R,2S)-α-(tert-Butyldiphenylsiloxy)-3-carboxy-2-hydroxy-1,6-dimethyl-2-cyclohexene-1-butyric acid, dimethyl ester (39).

\[
\text{OSi(Ph)₂tBu}
\]

\[
\begin{align*}
\text{COOMe} \\
\text{OH}
\end{align*}
\]

To a cold solution (-78°C) of ketone 23 (120 mg, 0.25 mmol) in THF (10 ml) was added a solution of LDA in THF (0.679M, 0.323 ml) and HMPA (0.25 mmol). The mixture was stirred for 30 min and Mander's reagent (0.33 mmol) was added. After 1 h of stirring at -78°C, addition of water, and the usual extractive work-up with ether, the residue was purified by flash chromatography (elution with 3% ethyl acetate in petroleum ether) 91.5 mg of β-keto ester 39 (68%) was obtained; IR (CHCl₃, cm⁻¹) 3500, 3080, 3010, 2970, 2940, 2860, 1740, 1585, 1460; ¹H NMR (300 MHz, CDCl₃) δ 12.25 (s, 1H), 7.60 (m, 4H), 7.31(m, 6H), 4.13 (t, J=5.3 Hz, 1H), 3.65 (s, 3H), 3.43 (s, 3H), 2.23-0.97 (series of m, 9H), 1.10 (s, 9H), 0.92 (s, 3H), 0.75 (d, J=7.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm 176.90, 173.32, 135.91 (2C), 135.78 (2C), 134.77, 133.51, 129.70, 129.58, 127.66, 127.55 (2C), 127.46 (2C), 97.64, 72.73, 51.35, 42.30, 33.03, 30.38, 29.97, 26.90 (3C), 26.58, 26.33, 23.84, 20.60, 19.35, 15.50; MS/FAB m/z (M⁺) calcd 538.28, obsd 538.34.
Methyl(αS,1R,3S,6S)-3-[(E)-6-bromo-3-methyl-2-hexenyl]-
α-(tert-Butyldiphenylsiloxy)-1,6-dimethyl-2-
oxocyclohexanebutyrate (42).

To a cold solution (-78°C) of keto ester 23 (0.5154 g, 1.074 mmol) in THF (20 ml) was added a solution of KHMDS (2.15 ml of 0.5 M solution in toluene) and the mixture was stirred for 1 h. DME (0.4 ml) and HMPA (0.4 ml) were introduced and the mixture was stirred for an additional hour. A solution of dibromide 41 (0.330 g, 1.288 mmol) in THF (5 ml) was then added and the mixture was allowed to warm slowly to room temperature. The resulting solution was washed with brine, dried, concentrated, and purified by MPLC (elution with 5% ethyl acetate in petroleum ether) to give 0.604 g of alkylated product 42 (86%); IR (CHCl₃, cm⁻¹) 3060, 3040, 2940, 2860, 1750, 1700, 1575, 1460, 1380, 1150, 1110, 820, 700; 
¹H NMR (300 MHz, CDCl₃) δ 7.60 (m, 4H), 7.32 (m, 6H), 5.04 (major) (t, J=7.1 Hz, 1H), 4.94 (minor) (t, J=6.5 Hz, 1H), 4.15 (t, J=5.0 Hz, 1H), 3.43 (s, 3H), 3.26 (t, J=6.7 Hz, 2H), 2.39–1.12 (series of m, 16H), 1.51 (s, 3H), 1.03 (s, 9H), 0.81 (s, 3H), 0.74 (d, J=7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm For the major: 216.43, 174.78, 135.85 (2C), 135.70 (2C), 134.78, 134.37, 130.85, 129.86, 129.83, 127.66 (2C),
tert-Butyl(αS,1R,3S,6S)-3-[(E)-6-bromo-3-methyl-2-hexenyl]-α-(tert-Butyldiphenylsiloxy)-1,6-dimethyl-2-oxocyclohexanebutyrate (45).

For the tert-butyl ester 45 (88%); IR (CHCl₃, cm⁻¹) 3080, 3060, 2950, 2920, 2850, 1740, 1700, 1585, 1460, 1425, 1370, 1260, 1140, 1115, 825, 740, 705; ¹H NMR (300 MHz, CDCl₃) δ 7.58 (m, 4H), 7.31 (m, 6H), 5.04 (t, J=7.1 Hz, 1H major), 4.93 (t, J=6.7 Hz, 1H minor), 4.16 (t, J=5.1 Hz, 1H), 3.25 (m, 2H), 2.38-0.97 (series of m, 16H), 1.52 (s, 3H), 1.25 (s, 3H), 1.03 (s, 9H), 0.89 (s, 3H), 0.87 (d, J=7.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm For the major: 216.30, 171.61, 135.91 (2C), 134.28 (2C), 134.12, 133.87, 133.58, 133.18, 129.70, 129.47 (2C), 127.45 (2C), 123.59, 80.80, 72.34, 51.94, 46.12, 40.62, 37.91, 33.37, 32.87, 30.89, 30.77, 29.75, 28.40, 28.06, 27.88 (3C), 26.91 (3C), 19.32, 18.70, 15.96, 15.75; MS/FAB m/z (M⁺-[C₄H₇]) calcd 641.35, obsd 641.35.
(αS,1R,3S,6S)-α-(tert-Butyldiphenylsiloxyl)-1,6-dimethyl-3-[(E)-3-methyl-6-phosphono-2-hexenyl]-2-oxocyclohexanebutyric acid, $P,P$-diethyl methyl ester (43).

Same procedure as previously with bromophosphonate 44 gave phosphonate 43 (68%); IR (CHCl$_3$, cm$^{-1}$) 3060, 3040, 2920, 2850, 1750, 1700, 1590, 1460, 1430, 1390, 1240, 1200, 1150, 1120, 1030, 960, 820, 740, 700; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.59 (m, 4H), 7.27 (m, 6H), 5.01 (t, J=7.0 Hz, 1H major), 4.90 (t, J=6.7 Hz, 1H minor), 4.15 (t, J=5.0 Hz, 1H), 4.07 (m, 4H), 3.43 (s, 3H), 2.34-1.03 (series of m, 18H), 1.48 (s, 3H), 1.27 (m, 6H), 1.03 (s, 9H), 0.81 (s, 3H), 0.73 (d, J=7.1 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 214.63, 173.17, 135.59 (2C), 135.31 (2C), 133.29, 133.10, 132.70, 129.62, 129.28, 127.43 (2C), 127.32 (2C), 123.27, 72.89, 61.18, (51.80, 51.75), (51.07, 51.02), 45.88, (40.28, 40.17), 38.63, 32.90, 31.85, 29.73, 29.64, 29.56, 28.73, 27.47, 26.72 (3C), 25.82, 23.88, 20.39, 19.19, 18.46, 16.23, 15.00; MS/FAB m/z (M$^+$) calcd 712.39, obsd 712.42

Alternatively, a mixture of bromide 42 (0.654 g, 1 mmol), triethylphosphite (0.5 g, 3 mmol), and nickel chloride (10 mg) was
stirred at 165°C for 8 h. The resulting solution was purified by MPLC (elution with 80% ethyl acetate in petroleum ether) to give 0.641 g of phosphonate 43 (90%).

(\(\alpha S,1R,3S,6S\))-\(\alpha\)-(\(tert\)-Butyldiphenylsiloxy)-1,6-dimethyl-3-[(\(E\)-3-methyl-6-phosphono-2-hexenyl]-2-oxocyclohexanecarboxylic acid, 1-\(tert\)-butyl diethyl ester (46).

\[
\text{OSi(Ph)2tBu} \quad \text{CO}_2\text{tBu} \\
\text{P(O)(OEt)_2}
\]

For the \(tert\)-butyl ester 46 (72%); IR (CHCl\(_3\), cm\(^{-1}\)) 3060, 3040, 2950, 2920, 2850, 1740, 1700, 1585, 1450, 1420, 1360, 1220, 1140, 1105, 1025, 960, 825; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.02-7.70 (m, 4H), 7.27-7.20 (m, 6H), 5.12 (t, J=4.6 Hz, 1H), 4.46 (t, J=6.0 Hz, 1H), 3.99-3.85 (m, 4H), 2.55-1.00 (series of m, 18H), 1.49 (s, 3H), 1.37 (s, 9H), 1.32 (m, 6H), 1.27 (s, 9H), 0.75-0.69 (m, 6H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) ppm For the major: 214.41, 171.88, 136.29 (2C), 135.52 (2C), 134.26, 134.16, 133.76, 130.11, 129.92, 129.31 (2C), 127.87 (2C), 124.34, 80.49, 72.97, 61.12, 52.04, 51.20, 46.20, (40.73, 40.52), 38.62, 33.29, 32.19, 29.87, 30.17, 29.87, 28.66, 28.00 (3C), 27.26 (3C), 26.56, 24.69, 21.19, 19.59, 19.13, 16.63, 15.87; MS/FAB m/z (M\(^{+}\)) calcd 755.49, obsd 755.49.
**tert-Butyl**$(\alpha S,1R,6S)-\alpha-(tert-Butyldiphenylsiloxy)-2-cyano-1,6-dimethyl-2-(trimethylsiloxy)cyclohexane butyrate** (47).

To a solution of keto ester 44 (46 mg, 0.088 mmol) in benzene (0.3 ml) was successively added potassium cyanide (2 mg), 18-crown-6 (2 mg), and trimethylsilyl cyanide (0.5 ml). The mixture was refluxed for 1 day. Most of the benzene and trimethylsilyl cyanide were evaporated and the residue was chromatographed to give a red oil which was purified by MPLC (elution with 2.5% ethyl acetate in petroleum ether) to give 44.5 mg of trimethylsilyl cyanohydrin 47 (85%); IR (CHCl$_3$, cm$^{-1}$) 3060, 3040, 2960, 2930, 2850, 2210, 1730, 1580, 1550, 1520, 1470, 1420, 1380, 1250, 1250, 1140, 1110, 880, 840, 690; $^1$H NMR (300 MHz, C$_6$D$_6$) $\delta$ 7.68 (m, 4H), 7.38 (m, 6H), 4.14 (t, J=5.5 Hz, 1H), 2.1-1.1 (series of m, 11H), 1.30 (s, 9H), 1.12 (s, 9H), 0.80 (m, 6H), 0.25 and 0.21 (2 s, 9H); $^{13}$C NMR (75 MHz, C$_6$D$_6$) ppm 172.08, 136.52 (2C), 136.51 (2C), 135.43, 131.29, 130.75, 129.94 (2C), 128.53 (2C), 127.86, 121.56, 80.41, 78.55, 74.14, 44.46, 37.81, 35.94, 33.65, 32.55, 31.76, 29.39, 28.01 (3C), 27.31 (3C), 22.49, 19.77, 16.50, -1.64 (3C) MS/FAB m/z (M$^+$-[$C_4H_7$]) calcd 566.34, obsd 566.34.
(αS,1R,3S,6S)-α-(tert-Butyl diphenylsiloxy)-2-cyano-1,6-dimethyl-3-[(E)-3-methyl-6-phosphono-2-hexenyl]-2-(trimethylsiloxy)cyclohexane butyric acid, 1-tert-butyl diethyl ester (48).

Keto ester 46 (52 mg, 0.066 mmol) was dissolved in trimethylsilyl cyanide (1 ml), following which 18-crown-6 (3 mg) and potassium cyanide (3 mg) were added. After a few minutes, the mixture was transferred to a teflon tube sealed at one end with a glass rod and the other end of the tube was sealed with a second glass rod such that a minimum of air was trapped. The tube was pressurized to 100,000 psi for 2 days. The mixture was transferred to a flask with ether and the excess trimethylsilyl cyanide was evaporated. The residue was chromatographed twice by MPLC (elution with 75% ethyl acetate in petroleum ether) to give 54.7 mg of trimethylsilyl cyanohydrin 48 (93%); IR (CHCl₃, cm⁻¹) 3060, 3040, 2970, 2920, 2850, 2220, 1730, 1610, 1560, 1470, 1450, 1420, 1390, 1360, 1290, 1250, 1200, 1140, 1110, 1060, 1030, 960, 840, 695; ¹H NMR (300 MHz, C₆D₆) δ 7.82 (m, 4H), 7.24 (m, 6H), 5.09 (m, 1H), 4.36 (m, 1H), 3.92 (m, 4H), 2.10-1.12 (series of m, 18H),
1.54 (s, 3H), 1.32 (s, 9H), 1.26 (s, 9H), 1.06 (m, 6H), 0.92-0.72 (series of d and s, 6H), 0.27 (2s, 9H); \(^{13}\)C NMR (75 MHz, C\(_6\)D\(_6\)) ppm 171.85, 136.45 (2C), 136.22 (2C), 135.08, 134.26, 134.11, 134.01, 133.76, 130.10, 129.96 (2C), 127.89 (2C), 123.76, 120.16, 82.12, 80.58, 73.70, 61.22, 45.96, 44.47, 43.63, 40.70, 40.48, 33.72, 31.74, 30.78, 30.14, 27.99 (3C), 27.25 (3C), 26.68, 24.79, 21.24, 19.71, 16.58, 1.97 (3C) (three signals not observed); MS/FAB \(m/z\) (M\(^+\)-[C\(_4\)H\(_7\)]) calcd 799.60, obsd 799.60.

**tert-Butyl(αS,1R,6S)-α-(tert-Butyldiphenylsiloxy)-2-cyano-1,6-dimethyl-2-cyclohexene-1-butyrate** (49).

To keto ester 44 (85 mg, 0.163 mmol) was added 18-crown-6 (20 mg) and a saturated solution of sodium bisulfate (3ml). The mixture was stirred for 15 min and potassium cyanide (0.5 g) was added. The mixture was stirred overnight and extracted with ether (3 x 10 ml). The organic extracts were dried and concentrated. The crude cyanohydrin was dissolved in pyridine (2 ml) and phosphorus oxychloride (1 ml). The mixture was stirred for 15 min at room temperature, heated at reflux for 1 h, poured onto ice, and extracted with ether (3 x 20 ml). The organic extracts were dried and concentrated, and the residue was purified by MPLC (elution
with 2.5% ethyl acetate in petroleum ether) to give 55.3 mg of unsaturated nitrile 49 (64%); [α]$_{25}^D$ -18.2° (c 0.81, CHCl$_3$); IR (CHCl$_3$, cm$^{-1}$) 3060, 3040, 3010, 2960, 2920, 2850, 2205, 1740, 1630, 1590, 1470, 1460, 1430, 1390, 1370, 1290, 1260, 1150, 1110, 1005, 995, 980, 940, 900, 860, 820, 700, 610; $^1$H NMR (300 MHz, C$_6$D$_6$) δ 7.72 (m, 4H), 7.15 (m, 6H), 5.87 (t, J=3.9 Hz, 1H), 4.35 (t, J=2.5 Hz, 1H), 2.25-1.02 (series of m, 9H), 1.32 (s, 9H), 1.21 (s, 9H), 0.72 (s, 3H), 0.61 (d, J=6.9 Hz, 3H); $^{13}$C NMR (75 MHz, C$_6$D$_6$) ppm 171.54, 144.67, 136.48 (2C), 136.19 (2C), 136.01, 135.25, 134.37, 133.89, 129.73 (2C), 127.94 (2C), 122.36, 118.37, 80.93, 72.80, 39.00, 32.18, 31.97, 30.10, 27.99 (3C), 27.27, 26.91 (3C), 25.66, 22.12, 19.68, 16.68; MS/FAB m/z (M$^+$+1) calcd 532.32, obsd 532.43.

Anal. Calcd for C$_{33}$H$_{45}$O$_3$SiN: C, 74.53; H, 8.53. Found: C, 74.26; H, 8.39.

$tert$-Butyl(αS,1R,2S)-α-hydroxy-1,2-dimethyl-6-oxocyclohexanecarboxylate and $tert$-Butyl(4aR,5S)-hexahydro-8a-hydroxy-4a,5-dimethyl-2-chromanecarboxylate (50).
To a solution of keto ester 44 (63 mg, 0.121 mmol) in acetonitrile (2 ml) was successively added pyridine (1 ml) and HF (0.250 ml of a 48% solution, 0.7 mmol). The mixture was stirred at room temperature for 1 day, poured in water, extracted with ether (3 x 10 ml), dried, concentrated and purified by MPLC (elution with 5% ethyl acetate in petroleum ether) to give 30.3 mg of keto alcohol 50 and isomeric hemiketal (minor) (88%); IR (CHCl₃, cm⁻¹) 3580, 3500, 2990, 2970, 2920, 2880 1715, 1700, 1390, 1380, 1365, 1305, 1240, 1150, 1090, 1040, 1005, 940, 905, 840; ¹H NMR (300 MHz, CDCl₃) δ 4.46 (m, 1H minor), 4.05 (m, 1H major), 3.35 (m, 1H minor), 2.89 (m, 1H major), 2.44-1.11 (series of m, 11H), 1.50 (s, 9H minor), 1.47 (s, 9H major), 0.99 (s, 3H major), 0.85 (s, 3H minor), 0.80 (d, J=6.8 Hz, 3H major), 0.75 (d, J=6.9 Hz, 3H minor); ¹³C NMR (75 MHz, CDCl₃) ppm For the major: 216.38, 175.00, 82.53, 70.59, 51.51, 38.50, 35.94, 31.26, 30.94, 29.52, 27.85 (3C), 23.80, 18.67, 15.07; MS/FAB m/z (M⁺-[OH]) calcd 284.40, obsd 284.20.
(αS,1R,3S,6S)-α-Hydroxy-1,6-dimethyl-3-[(E)-3-methyl-6-phosphono-2-hexenyl]-2-oxocyclohexanebutyric acid, 1-tert-butyl diethyl ester and (4aR,5S,8S)-hexahydro-8α-hydroxy-4a,5-dimethyl-8-[(E)-3-methyl-6-phosphono-2-hexenyl]-2-chromancarboxylic acid, 2-tert-butyl diethyl ester (51).

To a solution of keto ester 46 (75 mg, 0.10 mmol) in acetonitrile (2 ml) was successively added pyridine (1 ml) and HF (0.250 ml of a 48% solution, 0.7 mmol). The mixture was stirred at room temperature for 1 day, poured into water, extracted with ether (3 x 10 ml), dried, concentrated and purified by MPLC (elution with 65% ethyl acetate in petroleum ether) to give 47 mg of keto alcohol 51 and isomeric hemiketal (92%); IR (CHCl$_3$, cm$^{-1}$) 3500, 2960, 2920, 2840, 1710, 1450, 1380, 1360, 1260, 1200, 1150, 1090, 1060, 1020, 960, 820; $^1$H NMR (300 MHz, CDCl$_3$) δ 5.28 (t, J=6.7 Hz, 0.5H), 5.13 (t, J=7.0 Hz, 0.5H), 4.24 (t, J=5.0 Hz, 0.5H), 4.15 (t, J=5.0 Hz, 0.5H), 3.94 (m, 4H), 3.55 (m, 1H), 2.68-0.80 (series of m, 9H), 1.57 (s, 3H), 1.46 (s, 9H), 1.34 (s, 9H), 1.07 (series of m, 6H), 0.90-0.64 (series of m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm
214.60, 174.29, 136.73, 124.30, 81.51, 71.31, 61.28, 61.21, 42.53, 
(40.46, 40.27), 39.59, 38.51, 33.49, 31.48, 29.61, 28.67, 28.01 (3H), 
26.48, 24.64, 24.06, 21.16, 20.97, 19.03, 16.58, 15.89; MS/FAB m/z 
(M⁺-[C₄H₇]) calcd: 461.32, obsd: 461.43.

(1R,3S,6S)-1,6-dimethyl-3-[(E)-3-methyl-6-phosphono-2-
hexenyl]-α,2-dioxocyclohexanecarboxylic acid, 1-tert-butyl 
diethyl ester (52).

\[
\begin{align*}
\text{CO}_2\text{Bu} & \\
\text{P(O)(OEt)}_2 & 
\end{align*}
\]

To a cold solution (-78°C) of DMSO (0.20 ml) in 
dichloromethane (2 ml) was added oxalyl chloride (0.10 ml). The 
mixture was stirred for 10 min and a solution of α-hydroxy ester 
51 (68 mg, 0.132 mmol) in dichloromethane (1 ml) was added. The 
mixture was allowed to warm to -40°C and kept at this temperature 
for 15 min, then cooled down to -78°C when triethylamine (0.40 ml) 
was added. The mixture was allowed to warm to room temperature 
and water was added. After the usual extractive work-up with 
dichloromethane and purification by MPLC (elution with 75% ethyl 
acetate in petroleum ether) 50.1 mg of α-keto ester 52 (74%) was 
obtained; IR (CHCl₃, cm⁻¹) 3020, 2980, 2920, 2860, 1740, 1695, 
1460, 1370, 1205, 1150, 1060, 1020, 960; ¹H NMR (300 MHz, C₆D₆)
δ 5.16 (m, 1H), 3.94 (m, 4H), 2.92-1.01 (series of m, 18 H), 1.49 (s, 3H), 1.36 (s, 9H), 1.07 (m, 6H), 0.67 (s, 3H), 0.58 (d, J=6.6 Hz, 3H); 13C NMR (75 MHz, C6D6) ppm 213.97 (2C), 195.17 (2C), 161.87 (2C), 135.10 (2C), 124.20, 124.04, 82.82 (2C), 61.23, 61.15, 51.65, 51.02, 46.46, 46.20, 40.70, 40.46, 40.10, 39.25, 34.96, 34.31, 32.36, 29.90, 28.96, 28.70, 28.56, 28.17, 28.12, 27.82, 27.75, 27.71 (6C), 26.51, 24.63, 21.16, 21.10, 18.69, 18.22, 16.65, 16.57, 15.85, 15.21 (one signal not observed); MS/FAB m/z (M+ + 1) calcd 515.31, obsd 515.38.

tert-Butyl(αS,1R,6S)-α-(tert-butyldiphenylsiloxy)-1,6-dimethyl-2-(trifluoromethoxy)-2-cyclohexene-1-butyrate (53).

\[
\text{OSi(Ph)₂tBu} \\
\text{CO₂tBu}
\]

To a dichloromethane (10 ml) solution of ketone 44 (280 mg, 0.556 mmol) and 2,6-di-tert-butyl-4-methylpyridine (300 mg) was added dropwise triflic anhydride (0.112 ml, 0.66 mmol). The resulting solution was stirred overnight at room temperature, concentrated almost to dryness, diluted with pentane, and filtered. The filtrate was concentrated and purified by flash chromatography on silica gel (elution with 1% ethyl acetate in petroleum ether) to yield to 211 mg of enol triflate 53 (60%); IR (CHCl₃, cm⁻¹) 3060,
3040, 2960, 2920, 2840, 1740, 1660, 1460, 1420, 1410, 1360, 1240, 1205, 1140, 1105, 980, 830, 700; ¹H NMR (300 MHz, C₆D₆) δ 7.82 (m, 4H), 7.21 (m, 6H), 5.53 (t, J=3.9 Hz, 1H), 4.35 (t, J=5.1 Hz, 1H), 1.99-1.00 (series of m, 9H), 1.30 (s, 9H), 1.25 (s, 9H), 0.87 (s, 3H), 0.67 (d, J=6.8 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm 171.68, 154.49, 135.90 (2C), 135.71 (2C), 133.72, 133.37, 130.03, 129.89, 129.67 (2C), 127.53 (2C), 118.28 (q, J= 319.5 Hz), 117.41, 80.85, 72.78, 65.76, 41.38, 34.28, 29.91, 28.67 (3C), 26.91 (3C), 25.64, 23.13, 19.99 19.69, 15.18; MS/FABm/z (M⁺+1) calcd 565.27, obsd 565.35

(αS,1R,6S)-α-(tert-Butylidiphenylsiloxy)-2-carboxy-1,6-dimethyl-2-cyclohexene-1-butyric acid, 1-tert-butyl ester (54) and (αS,1R,6S)-α-(tert-Butylidiphenylsiloxy)-2-carboxy-1,6-dimethyl-2-cyclohexene-1-butyric acid, 1-tert-butyl methyl ester (55).

A solution of enol triflate 53 (200 mg, 0.397 mmol), anhydrous triethylamine (0.4 ml), dry methanol (0.6 ml), triphenylphosphine (81.4 mg, 0.116 mmol), and palladium(II) acetate (23.4 mg, 0.10 mmol) in 2 ml of dimethylformamide was prepared under argon and at room temperature. The system was
purged with carbon monoxide for 5 min and then maintained under 1 atm of carbon monoxide gas for 3 days at 90°C. The reaction mixture was poured into water and extracted with ether. The extracts were dried, concentrated and purified by flash chromatography on silica gel (elution with 5% ethyl acetate in petroleum ether) to yield 67.2 mg of unsaturated methyl ester 55 (30% yield) and to 126.7 mg of unsaturated acid 54 (58%). After esterification with diazomethane and purification by flash chromatography on silica gel (elution with 3% ethyl acetate in petroleum ether) 188.1 mg of the unsaturated methyl ester 55 (84%) was obtained.

For unsaturated acid 54; IR (CHCl₃, cm⁻¹) 3400-2400, 3060, 3020, 2960, 2920, 2860, 1740, 1685, 1630, 1460, 1430, 1370, 1270, 1210, 1160, 1120, 740; ¹H NMR (300 MHz, CHCl₃) δ 10.61 (bs, 1 H), 7.70 (m, 4H), 7.39 (m, 6H), 7.14 (t, J=3.6 Hz, 1H), 4.19 (t, J=4.8 Hz, 1H), 2.35-1.00 (series of m, 9 H), 1.34 (s, 9H), 1.15 (s, 9H), 1.11 (s, 3H), 0.92 (d, J= 6.7 Hz, 3 H); ¹³C NMR (75 MHz, CHCl₃) ppm 173.00, 171.88, 143.69, 136.54 (2C), 135.91 (2C), 134.70, 133.86, 133.49, 129.56, 129.50, 127.47 (2C), 127.40 (2C), 80.57, 72.50, 38.70, 33.79, 30.01, 29.85, 27.84 (3C), 26.90 (3C), 26.50, 25.75, 21.10, 19.27, 15.66; MS/FAB m/z (M⁺) calcd 539.32, obsd 539.38.

For methyl ester 55; [α]²⁵D -33.7° (c 1.42, CHCl₃); IR (CHCl₃, cm⁻¹) 3060, 2960, 2920, 2850, 1740, 1690, 1620, 1460, 1420, 1380, 1369, 1250, 1220, 1110, 1030, 820, 700; ¹H NMR (300 MHz,
C₆D₆) δ 7.68 (m, 4H), 7.21 (m, 6H), 6.81 (t, J=3.9 Hz, 1H), 4.38 (t, J=5.1 Hz, 1H), 3.43 (s, 3H), 2.27 (dt, J=5.2 Hz, J′=13.3 Hz, 2H), 1.96 (dt, J=3.7 Hz, J′=13.3 Hz, 2H), 1.87-1.01 (series of m, 5H), 1.33 (s, 9H), 1.27 (s, 9H), 1.24 (s, 3H), 0.84 (d, J=6.8 Hz, 3H); ¹³C NMR (75 MHz, C₆D₆) ppm 171.74, 167.22, 140.19, 137.82, 136.48 (2C), 136.24 (2C), 135.75, 135.54, 134.50, 134.16, 129.89 (2C), 127.85 (2C), 80.35, 73.42, 50.88, 39.46, 34.04, 30.76, 30.46, 28.02 (3C), 27.28 (3C), 26.17, 25.74, 21.57, 19.71, 15.86; MS/FAB m/z (M⁺) calcd 564.33, obsd 563.40.


**tert-Butyl(αS,1R,6S)-α-(tert-Butyldiphenylsiloxy)-2-(hydroxymethyl)-1,6-dimethyl-2-cyclohexene-1-butyrate (56).**

To a solution of the unsaturated methyl ester 55 (80 mg, 0.142 mmol) in dichloromethane (5 ml) at -78°C was added Dibal-H (1.0 M solution in hexane, 0.284 ml). The mixture was stirred at -78°C for 30 minutes, then quenched with a 10% solution of KOH (5 ml), allowed to warm up to room temperature, and extracted with ether. The extracts were dried, concentrated and purified by flash
chromatography on silica gel (elution with 8% ethyl acetate in petroleum ether) to yield 47.3 mg of allylic alcohol 56 (62%) along with 24.3 mg of recovered starting material. Overall yield: 92.3%; \([\alpha]^{25}_D -17.2^\circ (c 2.4, \text{CHCl}_3)\); IR (CHCl\(_3\), cm\(^{-1}\)) 3600, 3080, 3010, 2960, 2930, 2860, 1740, 1590, 1460, 1340, 1360, 1110, 910, 810, 710; \(^1\text{H}\) NMR (300 MHz, CDCl\(_3\)) \(\delta 7.85 (m, 4H), 7.55 (m, 6H), 5.75 (m, 1H), 4.12 (t, J=5.3 Hz, 1H), 3.95 (m, 2H), 2.00 (bs, 1H), 1.86-1.01 (series of m, 9H), 1.34 (s, 9H), 1.11 (s, 9H), 0.88 (s, 3H), 0.82 (d, J=6.7 Hz, 3H); \(^{13}\text{C}\) NMR (75 MHz, CDCl\(_3\)) ppm 172.27, 143.17, 135.96 (2C), 135.81 (2C), 133.76, 133.34, 129.67, 129.62, 127.53 (2C), 127.47 (2C), 124.99, 80.93, 73.00, 63.20, 39.28, 33.29, 30.99, 29.80, 27.91 (3C), 26.97 (3C), 26.54, 24.92, 21.78, 19.33, 15.35; MS/FAB \(m/z\) (M\(^{+}\)+1) calcd 537.33, obsd 537.30.

\((\alpha S,1R,6S)-\alpha-(\text{tert-Butyldiphenylsiloxy})-2\text{-carboxy-1,6-dimethyl-2-cyclohexene-1-butyr}ic\ acid, \ 1\text{-tert-butyl ester, anhydride with ethyl hydrogen carbonate (57).}

![Structure](image)

To a cold solution (0°C) of acid 54 (196 mg, 0.356 mmol) in THF (4 ml) and triethylamine (1 ml) was added ethyl chloroformate (60 \(\mu\)l, 0.534 mmol). The mixture was allowed to warm up to room
temperature and stirred for 3 hr, then filtered through a pad of Celite with ether and concentrated under vacuo to give 206.5 mg of mixed anhydride 57 (98%); [α]D 25 -11.3° (c 7.5, CHCl₃); IR (CHCl₃, cm⁻¹) 3070, 3030, 2980, 2940, 2860, 1795, 1735, 1630, 1465, 1250, 1150, 980; ¹H NMR (300 MHz, C₆D₆) δ 7.83 (m, 2H), 7.74 (m, 2H), 7.21 (m, 6H), 6.90 (t, J=3.9 Hz, 1H), 4.34 (t, J=4.2 Hz, 1H), 3.92 (q, J=7.1 Hz, 2H), 2.38-1.11 (series of m, 9H), 1.36 (s, 9H), 1.24 (s, 9H), 1.07 (s, 3H), 0.92 (t, J=7.1 Hz, 3H), 0.78 (d, J=6.8 Hz, 3H); ¹³C NMR (75 MHz, C₆D₆) ppm 171.51, 160.74, 150.27, 146.56, 136.46 (2C), 136.21 (2C), 135.71, 134.46, 134.06, 129.92 (2C), 127.95 (2C), 80.48, 72.87, 65.13, 46.73, 39.50, 33.92, 30.34, 29.71, 27.95 (3C), 27.25 (3C), 26.10, 25.67, 21.10, 19.64, 15.76, 13.83, 12.24 (two signals not observed); MS/FAB m/z (M⁺-[CO₃C₂H₅]) calcd 533.38, obsd 533.44.

**tert-Butyl(αS,1R,6S)-α-(tert-Butyldiphenylsiloxy)-2-formyl-1,6-dimethyl-2-cyclohexene-1-butyrate (58).**

![Structure of 58](image)

To a cold solution (-78°C) of DMSO (0.047 ml) in dichloromethane (3 ml) was added oxalyl chloride (0.028 ml). The mixture was stirred for 10 min and a solution of allylic alcohol 56 (72 mg, 0.134 mmol) in dichloromethane (1 ml) was added. The
mixture was allowed to warm to \(-40^\circ C\) and kept at this temperature for 15 min, then cooled at \(-78^\circ C\) when triethylamine (0.400 ml) was added. The mixture was allowed to warm up to room temperature and water was added. After the usual extractive work-up with dichloromethane and purification by flash chromatography on silica gel (elution with 5% ether in petroleum ether) 43.2 mg of enal \(58\) (60%) was obtained; IR (CHCl\(_3\), cm\(^{-1}\)) 3080, 3010, 2960, 2910, 2860, 1735, 1680, 1460, 1430, 1270, 1150, 1120, 710;\(^1\)H NMR (300 MHz, C\(_6\)D\(_6\)) \(\delta\) 9.12 (s, 1H), 7.87 (m, 2H), 7.77 (m, 2H), 7.21 (m, 6H), 5.99 (t, \(J=5.0\) Hz, 1H), 4.38 (t, \(J=5.0\) Hz, 1H), 2.39 (dt, \(J=5.0\) Hz, \(J'=13.3\) Hz, 2H), 1.99-1.00 (series of m, 7H), 1.39 (s, 9H), 1.28 (s, 9H), 1.04 (s, 3H), 0.77 (d, \(J=6.9\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) ppm 193.37, 171.58, 153.44, 147.25, 136.48 (2C), 136.28 (2C), 136.23, 134.57, 129.94, 128.11, 127.87 (2C), 127.29 (2C), 80.53, 73.15, 38.97, 33.68, 30.66, 28.91, 28.01 (3C), 27.26 (3C), 26.73, 26.16, 20.55, 19.68, 15.28; MS/FAB \(m/z\) (M\(^+\)) calcd 534.32, obsd 534.28.

\((\alpha S,1R,6S)-\alpha-(\text{tert-Butyldiphenylsiloxy})-2-[(E)-N-(1-carboxy-2-methylpropyl)formimidoyl]-1,6-dimethyl-2-cyclohexene-1-butyric\ acid, \text{di-tert-butyl ester}\ (59).\)
To a solution of enal 58 (132 mg, 0.247 mmol) in ether (4 ml) was added magnesium sulfate (700 mg), D-valine tert-butyl ester (66 ml), and acetic acid (2 ml). The mixture was stirred at room temperature for a week resulting in 90% conversion to eneimine 59; IR (CHCl₃, cm⁻¹) 3060, 3010, 2920, 2850, 2920, 1730, 1630, 1460, 1370, 1260, 1145, 1115; ¹H NMR (300 MHz, C₆D₆) δ 7.74 (m, 4H), 7.54 (s, 1H), 7.20 (m, 6H), 5.89 (t, J=4.1 Hz, 1H), 4.35 (t, J=6.0 Hz, 1H), 3.34 (d, J=6.1 Hz, 1H), 2.57-1.00 (series of m, 10H), 1.37 (s, 9H), 1.28 (s, 9H), 1.22 (s, 9H), 1.01 (d, J=3.6 Hz, 3H), 0.93 (s, 3H), 0.92 (d, J=3.6 Hz, 3H), 0.78 (d, J=5.4 Hz, 3H); ¹³C NMR (75 MHz, C₆D₆) ppm 171.87, 171.03, 165.69, 143.58, 136.52 (2C), 136.49 (2C), 136.32, 136.24, 136.18, 135.94, 129.90, 128.26 (2C), 127.88 (2C), 80.22, 79.99, 74.56, 40.18, 34.27, 31.91, 31.02, 28.14 (3C), 28.00 (3C), 27.25 (3C), 26.46, 26.36, 20.48, 19.88, 19.66, 15.85 (four signals not observed); MS/FAB m/z (M⁺) calcd 690.45, obsd 690.46.

(⁵)-5-(1,3-Dioxolan-2-yl)-3-methyl-2-penten-1-ol acetate (60).

To a stirred solution of dichloromethane (6 ml) at -78°C under argon was successively added TMS triflate (0.045ml), 1,2-bis-
(trimethylsilyloxy)ethane (620 mg, 3mmol), and aldehyde 29 (510 mg, 3mmol). The mixture was stirred overnight at -40°C, quenched with pyridine (0.200 ml) and poured in a saturated solution of sodium bicarbonate (15 ml). After the usual extractive work-up with ether and purification by flash chromatography (elution with 10% ethyl acetate in petroleum ether), 0.591 g of the dioxolane 60 (92%) was obtained; IR (CHCl₃, cm⁻¹) 2940, 2860, 1740, 1450, 1360, 1230, 1130, 1020; ¹H NMR (300 MHz, CDCl₃) δ 5.32 (t, J=4.8 Hz, 1H), 4.81 (t, J=4.7 Hz, 1H), 4.52 (d, J=7.0 Hz, 2H), 3.86 (m, 4H), 2.11 (m, 2H), 1.99 (s, 3H), 1.71 (m, 2H), 1.66 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm 170.81, 141.25, 118.43, 103.93, 64.77 (2C), 61.14, 33.49, 31.90, 20.86, 16.34; MS m/z (M⁺) calcd 214.1320, obsd 214.1205.

(E)-5-(1,3-Dioxolan-2-yl)-3-methyl-2-penten-1-ol  (61).

A mixture of dioxolane 60 (0.214 g, 1 mmol), methanol (5 ml), and a catalytic amount of potassium carbonate was stirred overnight at 0°C and poured into water. After extractive work-up with ether and purification by flash chromatography (elution 20% ethyl acetate in petroleum ether) 0.167 g of allylic alcohol 61 (97%) was obtained; IR (CHCl₃, cm⁻¹) 3300, 2940, 2920, 2860, 1660, 1440, 1400, 1130, 1030, 880; ¹H NMR (300 MHz, CDCl₃) δ 5.37 (t, J=1.9 Hz,
1H), 4.80 (t, J=9.5 Hz, 1H), 4.07 (d, J=6.9 Hz, 2H), 3.79 (m, 4H), 1.91 (m, 4H), 1.62 (s, 3H) (hydroxyl signal not observed); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 138.30, 123.57, 104.01, 64.71 (2C), 59.00, 33.51, 31.90, 16.13; MS m/z (M$^+$) calcd 171.1021, obsd 171.0950.

2-[(E)-5-Chloro-3-methyl-2-pentenyl]-1,3-dioxolane (62).

![Structure of 2-[(E)-5-Chloro-3-methyl-2-pentenyl]-1,3-dioxolane (62).]

To a DMF solution (1.6 ml) of LiCl (150 mg) at 0°C was added a solution of allylic alcohol 61 (510 mg, 3 mmol) in 2,6-lutidine (0.4 ml). The mixture was stirred for 30 minutes at 0°C and methanesulfonyl chloride (270 µl) was added at -15°C. The mixture was stirred overnight at -15°C, poured into water, and extracted with ether. The extracts were dried, concentrated and purified by flash chromatography on silica gel (elution with 5% ethyl acetate in petroleum ether) to yield 239 mg of allylic chloride 62 (42%); IR (CHCl$_3$, cm$^{-1}$) 2960, 2880, 1660, 1460, 1270, 1150, 1050, 920, 750; $^1$H NMR (300 MHz, CDCl$_3$) δ 5.44 (t, J=7.5 Hz, 1H), 4.82 (t, J=4.6 Hz, 1H), 4.04 (d, J=7.9 Hz, 2H), 3.92 (m, 2H), 3.81 (m, 2H), 2.14 (t, J=4.6 Hz, 2H), 1.74 (m, 2H), 1.70 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 141.83, 120.31, 103.79, 64.78 (2C), 40.83, 33.39, 31.75, 15.97; MS m/z (M$^+$) calcd 186.0699, obsd 186.0683.
To a solution of allylic alcohol 55 (40 mg, 0.075 mmol) in freshly distilled ethyl vinyl ether (5 ml) was added mercuric acetate (24 mg, 0.075 mmol). The mixture was heated at reflux for 24 hr, with two more 24 mg additions of mercuric acetate. The mixture was cooled to room temperature, diluted with petroleum ether, treated with a 10% solution of KOH, and extracted with petroleum ether. The extracts were dried, concentrated, and purified by flash chromatography on neutral alumina (elution with 5% ether in petroleum ether) to yield 40.5 mg of vinyl ether 63 (96%); [α]$_{25}^D$ -14.9° (c 1.83, CHCl$_3$); IR (CHCl$_3$, cm$^{-1}$) 3080, 3020, 2960, 2920, 2860, 1740, 1600, 1460, 1260, 1110, 710; $^1$H NMR (300 MHz, C$_6$D$_6$) δ 7.86 (m, 2H), 7.77 (m, 2H), 7.22 (m, 6H), 6.40 (m, 1H), 5.73 (t, J=3.7 Hz, 1H), 4.35 (t, J=5.0 Hz, 1H), 4.20 (m, 4H), 1.94-1.00 (series of m, 9H), 1.28 (s, 9H), 1.25 (s, 9H), 0.92 (s, 3H), 0.81 (d, J=6.9 Hz, 3H); $^{13}$C NMR (75 MHz, C$_6$D$_6$) ppm 171.91, 157.17, 138.90, 136.48 (2C), 134.33 (2C), 134.00, 133.68, 130.00, 129.98, 128.11 (2C), 127.89 (2C), 87.04, 80.49, 73.65, 70.16, 47.58, 39.50, 33.68,
31.74, 30.25, 27.99 (3C), 27.24, 26.68 (3C), 25.14, 21.79, 19.69, 15.54; MS/FAB m/z (M⁺+1) calcd 563.35, obsd 563.44.

Anal. Calcd for C₃₅H₅₀O₄Si: C, 74.69; H, 8.95. Found C, 75.02; H, 9.05.

tert-Butyl(αS,1R,3R,6S)-α-(tert-Butyldiphenylsiloxy)-3-(formylmethyl)-1,6-dimethyl-2-methylenecyclohexane butyrate and tert-Butyl(αS,1R,3S,6S)-α-(tert-Butyl diphenylsiloxyl)-3-(formylmethyl)-1,6-dimethyl-2-methylenecyclohexanebutyrate (64).

A solution of vinyl ether 63 (50 mg, 0.089 mmol) in toluene (1.0 ml) was introduced into a base washed pyrex tube. The tube was sealed under vacuum and heated at 160°C for 24 hr. Resulting aldehydes 64 were not stable to silica gel and not purified; IR (CHCl₃, cm⁻¹) 3070, 3010, 2960, 2860, 1720, 1630, 1460, 1430, 1370, 1220, 1120, 730; ¹H NMR (300 MHz, CDCl₃) δ 9.72 (t, J=2.1 Hz, 1H minor), 9.48 (t, J=2.2 Hz, 1H major), 7.77 (m, 4H), 7.38 (m, 6H), 4.60 (s, 1H), 4.24 (s, 1H), 4.11 (t, J=4.9 Hz, 1H), 2.53 (m, 2H), 2.26-1.00 (series of m, 10H), 1.27 (s, 9H), 1.04 (s, 9H), 0.83 (s, 3H), 0.73 (d, J=7.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm For the major:
202.77, 172.12, 152.60, 135.96 (2C), 135.77 (2C), 129.65, 128.97, 128.17, 127.77, 127.53 (2C), 127.48 (2C), 127.48 (2C), 127.48 (2C), 125.22, 108.20, 80.69, 72.77, 43.15, 38.97, 33.73, 32.81, 31.90, 29.75, 29.13, 27.92 (3C), 26.86 (3C), 19.33, 15.67; MS/FAB m/z (M+1) calcd 563.35, obsd 563.29.

**1,3-Dioxolane-2-propanol (66).**

![Chemical Structure](image)

To a magnetically slurry of magnesium turnings (1.0 g) in THF (30 ml) was added one crystal of iodine and about 3 ml of a solution of dioxolane 65 (5.0 g, 27.6 mmol) in THF (20 ml). Once the solution was refluxing, the rest of the dioxolane was added dropwise at a rate such as to maintain reflux. The solution was allowed to return, to room temperature, then cooled down at 0°C, at which point a THF solution (20 ml) of dry parformaldehyde (3.0 g, 100 mmol) was added. The mixture was allowed to warm to room temperature and quenched with a saturated solution of ammonium chloride. After ether extraction, the combined extracts were dried, concentrated, and purified by flash chromatography on silica gel (elution with 30% ethyl acetate in petroleum ether) to yield 2.40 g of alcohol 66 (66%); IR (neat, cm⁻¹) 3400, 2960, 2880, 1460, 1420, 1150, 1050, 950; ¹H NMR (300 MHz, CDCl₃) δ 4.82 (t, J=4.3 Hz, 1H), 3.91, (m, 2H), 3.79 (m, 2H), 3.57 (t, J=6.0 Hz, 2 H), 2.84 (bs, 1H), 1.68 (m, 2H), 1.63
(m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 104.19, 64.71 (2C), 62.20, 30.25, 26.76; MS $m/z$ (M$^+$) calcd 132.0717, obsd 132.0769.

2(3-Bromopropyl)-1,3-dioxolane (67).

To a cold stirred solution of alcohol 66 (0.132 g, 1.0 mmol) in dry ether (8 ml) was added triethylamine (0.25 ml, 1.8 mmol) and methanesulfonyl chloride (0.125 ml, 1.6 mmol). The mixture was allowed to warm to 0°C. Most of the solvent was evaporated and replaced by acetone (15 ml) and an excess of LiBr (0.7 g). The mixture was refluxed for 3 h, then allowed to cool and quenched with water. After the usual extractive work-up with ether (4 x 20 ml) and purification by chromatography on silica gel (elution 20% ether in petroleum ether) 0.178 g of bromide 67 (92%) was obtained; IR (CHCl$_3$, cm$^{-1}$) 2960, 2860, 1460, 1130, 1020, 980; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.85 (t, J= 4.4 Hz, 1H), 3.92 (m, 2H), 3.80 (m, 2H), 3.41 (t, J=6.8 Hz, 2H), 1.96 (m, 2H), 1.78 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 103.51, 64.81 (2C), 33.48, 32.15, 27.04; MS $m/z$ (M$^+$) calcd 193.9942, obsd 193.9964.
[3-(1,3-Dioxolan-2-yl)propyl]triphenylphosphonium bromide (68).

To a solution of primary bromide 67 (200 mg, 1.03 mmol) in benzene (2 ml) was added triphenylphosphine (300 mg, 1.14 mmol). The mixture was refluxed for 24 h, cooled to room temperature, and freed of liquid by decantation. The remaining waxy solid was triturated with ether (2 x 3 ml) and kept under high vacuum to yield 338 mg of 68 as a light yellow solid (72%); IR (CHCl₃, cm⁻¹) 3080, 2880, 1590, 1460, 1410, 1340, 1130, 1050, 930; ¹H NMR (300 MHz, CDCl₃) δ 7.65 (m, 15H), 4.77 (t, J=4.2 Hz, 1H), 3.76 (m, 4H), 1.92 (m, 4H), 1.68 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) ppm 134.41 (3C), 133.45 (3C), 132.93 (3C), 130.93 (3C), 130.20 (3C), 128.03 (3C), 102.71, 64.14 (2C), 32.34, 21.49, (16.22, 16.17); MS m/z (M⁺) calcd 375.1514, obsd 375.1555.
**tert-Butyl(αS,1R,6S)-α-(tert-Butyldiphenylsiloxy)-3-(2-hydroxy-3-methyl-3-butenyl)-1,6-dimethyl-2-methylenecyclohexanebutyrate (69).**

To a suspension of magnesium turnings (300 mg, 12.34 mmol) in THF (15 ml) was added 5% of a solution of 2-bromopropene (1.21 g, 10 mmol) in THF (15 ml). The mixture was heated with a heat gun to achieve reflux and the remaining vinyl bromide was added dropwise at a rate such as to maintain reflux. After the addition, reflux was continued for 1 h, then stirred at room temperature for 1 h. The solution was titrated with a THF solution of menthol and 1,10-phenanthroline (0.26 M, 78% yield). To a solution of aldehyde 64 (114.2 mg, 0.20 mmol) in ether:THF (5 ml : 5 ml) at -78°C was added a solution of the Grignard reagent (0.9 ml, 0.23 mmol). The mixture was stirred for 30 minutes at -78°C, then quenched with a solution of ammonium chloride. The reaction mixture was extracted with ether (3 x 20 ml). The extracts were dried, concentrated and purified by flash chromatography on silica gel (elution with 3% ethyl acetate in petroleum ether) to yield 90.2 mg of the major mixture of diastereoisomers 69 (84%).
For the major: IR (CHCl₃, cm⁻¹) 3600, 3070, 3050, 2960, 2920, 2860, 1740, 1630, 1470, 1430, 1370, 1260, 1115, 915, 825, 700; ¹H NMR (300 MHz, CDCl₃) δ 7.72 (m, 4H), 7.38 (m, 6H), 4.93 (d, J=4.2 Hz, 1H), 4.80 (m, 2H), 4.69 (d, J=8.4 Hz, 1H), 4.11 (m, 2H), 2.19-1.00 (series of m, 13H), 1.75 (s, 3H), 1.32 (s, 9H), 1.10 (s, 9H), 0.89 (s, 3H), 0.79 (d, J=6.5 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm 172.61, 172.29, 154.67, 153.81, 148.49, 148.15, 136.05 (4C), 136.02 (4C), 135.87, 135.20, 134.78, 134.04, 134.00, 129.62 (2C), 129.57 (2C), 127.69, 127.50, 127.45, 110.50, 107.12, 106.97, 80.92, 80.67, 73.84, 73.62, 73.33, 73.27, 43.39, 43.22, 39.33, 38.99, 38.92, 38.86, 35.41, 34.75, 33.99, 33.36, 30.40, 30.10, 29.84, 29.05, 28.77, 28.53, 27.95 (6C), 27.91, 26.94 (6C), 26.58, 22.85, 22.70, 19.38, 18.50, 17.78, 17.45, 15.45, 15.41 (two signals not observed); MS/FAB m/z (M⁺+1) calcd 605.39, obsd 605.40.

For the minor: IR (CHCl₃, cm⁻¹) 3600, 3070, 3050, 2960, 2930, 2870, 1740, 1630, 1465, 1430, 1260, 1115, 700; ¹H NMR (300 MHz, CDCl₃) δ 7.77 (m, 4H), 7.38 (m, 6H), 4.92 (s, 1H), 4.82 (s, 1H), 4.75 (m, 1H), 4.64 (m, 1H), 4.17 (m, 2H), 2.24 (m, 1H), 2.05-1.00 (series of m, 12H), 1.73 (s, 3H), 1.31 (s, 9H), 1.11 (s, 9H), 0.86 (s, 3H), 0.77 (m, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm 172.25 (2C), 157.36, 157.03, 147.86 (2C), 136.04 (4C), 135.83 (4C), 133.87, 133.56, 129.61, 129.57, 127.73 (4C), 127.53 (4C), 127.45 (2C), 111.21, 110.64, 104.03 (2C), 80.67 (2C), 77.21, 74.41, 73.39, 73.35, 60.37, 42.53, 42.48, 38.88, 35.69, 35.07, 34.67, 33.70, 32.15, 30.82, 30.77, 29.70, 29.36, 29.20, 27.92 (3C), 27.10, 26.97 (3C), 22.70, 20.59, 20.10,
19.37, 17.59, 17.04, 15.94, 15.41, 14.21 (eight signals not observed); MS/FAB m/z (M⁺+1) calcd 605.39, obsd 605.40.

**tert-Butyl(αS,1R,6S)-α-**(tert-Butyldiphenylsiloxy)-1,6-dimethyl-2-methylene-3-[3-methyl-2-(vinyloxy)-3-butenyl]cyclohexanebutyrate  (70).

![Chemical structure](attachment:image.png)

To a solution of allylic alcohol 69 (66 mg, 0.109 mmol) in freshly distilled ethyl vinyl ether (5 ml) was added mercuric acetate (60 mg). The mixture was stirred at room temperature for 72 hr. The mixture was diluted with petroleum ether, a 10% solution of KOH was added, and the mixture was extracted with petroleum ether. The extracts were dried, concentrated and purified by flash chromatography on neutral alumina (elution with petroleum ether) to yield to 68 mg of vinyl ether 70 (99%); IR (CHCl₃, cm⁻¹) 3060, 2960, 2920, 2860, 1740, 1630, 1460, 1360, 1260, 1100, 1020, 790; ¹H NMR (300 MHz, C₆D₆) δ 7.79 (m, 4H), 7.17 (m, 6H), 6.33 (m, 1H), 4.94 (s, 1H), 4.87 (m, 1H), 4.83 (s, 1H), 4.79 (m, 1H), 4.73 (m, 1H), 4.42 (m, 1H), 4.33 (m, 1H), 4.02 (m, 1H), 2.48-1.00 (series of m, 12H), 1.65 (s, 3H), 1.28 (s, 9H), 1.24 (s, 9H), 0.90
(s, 3H), 0.78 (d, J=6.7 Hz, 3H); $^{13}$C NMR (75 MHz, C$_6$D$_6$) ppm 171.97 (2C), 154.63, 154.23, 151.00, 150.90, 145.51 (2C), 136.52 (4C), 136.33, 136.27 (4C), 134.49, 134.42, 134.17, 129.95, 129.92 (4C), 128.13, 127.85, 127.75, 113.25, 113.14, 107.60, 107.42, 89.11, 88.90, 82.69 (2C), 80.90, 80.19, 74.06, 73.73, 43.49, 43.42, 39.22, 39.04, 37.92, 37.57, 35.89, 34.60, 34.15, 34.01, 30.39, 30.30, 29.92, 29.11, 29.03, 28.62, 27.99 (6C), 27.27 (3C), 27.25 (3C), 23.12, 23.07, 19.77, 17.04, 16.72, 15.61 (six signals not observed); MS/FAB $m/z$ (M$^+$) calcd 630.41, obsd 630.30.

**tert-Butyl($\alpha$S,$1R,6S$)-$\alpha$-(tert-Butyldiphenylsiloxy)-3-[(E)-5-formyl-3-methyl-2-pentenyl]-1,6-dimethyl-2-methylenecyclohexanebutyrate (71).**

A solution of vinyl ether 70 (68 mg, 0.108 mmol) in toluene (10 ml) was refluxed for 14 hr. The resulting product was purified by flash chromatography on silica gel (elution with 5% ether in petroleum ether) to give 66 mg of aldehyde 71 (98%); $[\alpha]^{25}_D$ -16.1° (c 1.6, CHCl$_3$); IR (CHCl$_3$, cm$^{-1}$) 3060, 2960, 2920, 2860, 1740, 1720, 1460, 1430, 1360, 1260, 1110, 1020, 700; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.70 (s, 1H), 7.80 (m, 4H), 7.34 (m, 6H), 5.02 (t, J=4.5 Hz, 1H), 4.75
(s, 1H), 4.62 (s, 1H), 4.11 (t, J=4.1 Hz, 1H), 2.43 (t, J=7.7 Hz, 1H), 2.25 (t, J=7.4 Hz, 1H), 2.15-100 (series of m, 14H), 1.54 (s, 3H), 1.30 (s, 9H), 1.08 (s, 9H), 0.86 (s, 3H), 0.77 (d, J=6.9 Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) ppm 202.65, 172.21, 154.16, 136.00 (2C), 135.71 (2C), 133.94, 133.44, 133.25, 129.63, 128.17, 127.52 (2C), 127.48 (2C), 124.67, 107.24, 80.54, 72.78, 43.04, 42.24, 39.35, 38.62, 32.76, 31.93, 31.67, 29.82, 29.68, 28.87, 27.91 (3C), 26.91 (3C), 22.80, 19.40, 16.32, 15.45; MS/FAB \(m/z\) (M+1) calcd 631.41, obsd 631.42.

tert-Butyl(\(\alpha S,1R,6S\))-\(\alpha\)-(tert-Butyldiphenylsiloxy)-3-[(\(E\))-5-formyl-3-methyl-2-pentenyl]-1,6-dimethyl-2-methylenecyclohexanecarboxylic acid (2,4-dinitrophenylhydrazone (72).

To aldehyde 71 (20 mg, 0.032 mmol) was added a 90 \(\mu\)l of solution of 2,4-dinitrophenylhydrazine (100 mg) and concentrated hydrochloric acid (5 drops) in DMF (5 ml). The mixture was stirred for 3 h and water was added, followed by methanol. The remaining sticky oil was dissolved in dichloromethane, dried, and purified by flash chromatography on silica gel (elution with 5% ether in
petroleum ether) to give 17 mg of 2,4-dinitrophenylhydrazone 72 (66%); \([\alpha]^{25\mathrm{D}}\) -19.8° (c 0.87, CHCl₃); IR (CHCl₃, cm⁻¹) 3300, 3080, 3060, 3030 2960, 2930, 2860, 1740, 1735, 1620, 1580, 1520, 1430, 1340, 1140, 1120, 840; ¹H NMR (300 MHz, CDCl₃) δ 10.97 (s, 1H), 9.11 (d, J=2.5 Hz, 1H), 8.27 (dd, J=2.6 Hz, J'=9.6 Hz, 1H), 7.91 (d, J=9.5 Hz, 1H), 7.65 (m, 4H), 7.36 (m, 6H), 5.06 (t, J=4.6 Hz, 1H), 4.77 (s, 1H), 4.64 (s, 1H), 4.12 (t, J=4.9 Hz, 1H), 2.51-1.00 (series of m, 17 H), 1.65 (s, 3H), 1.31 (s, 9H), 1.10 (s, 9H), 0.88 (s, 3H), 0.77 (d, J=6.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm 172.17, 154.16, 152.29, 145.08, 135.98 (2C), 135.89, 135.85, 135.82, 135.73, 134.00, 133.45, 133.21, 129.90, 129.64, 129.60, 127.52 (2C), 127.49 (2C), 125.46, 123.48, 116.47, 107.25, 80.58, 72.85, 43.07, 39.34, 38.69, 36.25, 32.77, 31.72, 30.93, 29.86, 29.67, 28.87, 27.92 (3C), 26.93 (3C), 22.72, 19.40, 16.24, 15.38; MS/FAB m/z (M⁺+1) calcd 811.43, obsd 811.48.

*tert*-Butyl(αS,1R,6S)-α-(tert-Butyldiphenylsiloxy)-3-[(E)-5-(1,3-dioxolan-2-yl)-3-methyl-2-pentenyl]-1,6-dimethyl-2-methylenecyclohexanebutyrate (73).
To a cold solution (-78°C) of aldehyde 71 (5 mg, 0.008 mmol) in dichloromethane (1 ml) was added TMS triflate (1 drop) and 1,2-bis(trimethylsilyloxy)ethane (20 μl, 0.08 mmol). The mixture was stirred for 6 h at -78°C, quenched with pyridine (0.20 ml) and poured into a saturated solution of sodium bicarbonate (15 ml). After the usual extractive work-up with ether and purification by flash chromatography (elution 5% ethyl acetate in petroleum ether) 4.5 mg of the dioxolane 73 (84%) was obtained; [α]$_D$$^2$ -25.8° (c 0.93, CHCl$_3$); IR (CHCl$_3$, cm$^{-1}$) 3070, 2980, 2940, 2860, 1740, 1630, 1460, 1380, 1260, 1140, 1110, 1020, 740; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.67 (m, 4H), 7.36 (m, 6H), 5.04 (t, J=6.0 Hz, 1H), 4.83 (t, J=4.6 Hz, 1H), 4.79 (s, 1H), 4.64 (s, 1H), 4.13 (t, J=4.5 Hz, 1H), 3.95 (m, 2H), 3.84 (m, 2H), 2.16-1.00 (series of m, 16H), 1.60 (s, 3H), 1.32 (s, 9H), 1.11 (s, 9H), 0.88 (s, 3H), 0.78 (d, J=6.9 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 172.25, 154.37, 136.00 (2C), 135.74 (2C), 134.51, 133.49, 130.89, 129.62, 128.81, 127.53 (2C), 127.46 (2C), 123.94, 107.12, 104.37, 80.51, 72.80, 64.82 (2C), 43.01, 39.29, 38.64, 34.03, 32.86, 32.54, 31.68, 29.80, 29.68, 28.89, 28.31, 27.91 (3C), 26.90 (3C), 22.84, 19.37, 16.86; MS/FAB m/z (M$^+$) calcd 674.44, obsd 674.44.

**tert-Butyl(αS,1R,6S)-3-[(E)-5-(1,3-dioxolan-2-yl)-3-methyl-2-pentenyl]-α-hydroxy-1,6-dimethyl-2-methylenecyclohexanebutyrate (74).**

![Chemical Structure](image)

To a solution of dioxolane 73 (2 mg, 0.003 mmol) in acetonitrile (2 ml) was added 2 ml of a freshly prepared solution of pyridium hydrofluoride in acetonitrile (pyridine (2.4 ml) and HF (1 ml of a 48% solution, 2.8 mmol)). The mixture was stirred at room temperature overnight, poured into water, extracted with ether (3 x 10 ml), dried, concentrated and purified by flash chromatography (elution with 10% ethyl acetate in petroleum ether) to give 1.2 mg of α-hydroxy tert-butyl ester 74 (92%); [α]$_{25}^{D}$ -13.4° (c 0.60, CHCl$_3$); IR (CHCl$_3$, cm$^{-1}$) 3520, 3080, 3010, 2960, 2910, 2870, 1715, 1625, 1460, 1370, 1260, 1210, 1160, 1140, 1080, 890, 730; $^1$H NMR (300 MHz, CDCl$_3$) δ 5.18 (t, J=4.8 Hz, 1H), 4.85 (t, J=4.8, 1H), 4.82 (s, 1H), 4.68 (s, 1H), 4.04 (m, 1H), 3.97 (m, 2H), 3.84 (m, 2H), 2.81 (bs, 1H), 2.28-1.00 (series of m, 16H), 1.62 (s, 3H), 1.48 (s, 9H), 0.95 (s, 3 H), 0.81 (d, J=7.0 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 174.65, 154.16, 134.57, 123.94, 107.28, 104.35, 82.24, 70.81, 64.83 (2C), 43.08, 39.33, 38.96, 34.00, 33.05, 32.48, 31.67, 29.67, 28.90, 28.65, 28.04
(3C), 22.90, 16.24, 15.45; MS/FAB m/z (M+) calcd 436.32, obsd 436.34.

tert-Butyl(1R,6S)-α-bromo-3-[(E)-5-(1,3-dioxolan-2-yl)-3-methyl-2-pentenyl]-1,6-dimethyl-2-methylene-cyclohexanebutyrate (75).

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\text{\includegraphics[width=1\textwidth]{image.png}}
\]

To a cold solution (-40°C) of hydroxy ester 74 (7.3 mg, 0.0167 mmol) in triethylamine (0.5 ml) and dichloromethane (1 ml) was added methanesulfonyl chloride (30 µl). The mixture was warmed to room temperature and THF (3 ml) and LiBr (300 mg) were added. The mixture was heated at 70°C for 3 h. Water was added and the mixture was extracted with ether (3 x 10 ml), dried, concentrated and purified by flash chromatography (elution with 5% ethyl acetate in petroleum ether) to give 7.1 mg of α-bromo tert-butyl ester 75 (85%); IR (CHCl₃, cm⁻¹) 3010, 2960, 2920, 2850, 1720, 1460, 1370, 1350, 1260, 1140, 1100, 1070, 1015; ¹H NMR (300 MHz, CDCl₃) δ 5.19 (t, J=7.4 Hz, 1H), 4.85 (s, 1H), 4.85 (t, J=4.5 Hz,1H), 4.71 (s, 1H), 4.06 (m, 1H), 3.97 (m, 2H), 3.84 (m, 2H), 2.33-0.86 (series of m, 16H), 1.62 (s, 3H), 1.48 (s, 9H) 0.97 (s, 3H), 0.82
(d, J=7.0 Hz, 3H); 13C NMR (75 MHz, CDCl₃) ppm 168.81 (2C), 153.82, 153.64, 134.83, 134.77, 123.77 (2C), 107.86, 107.78, 104.42 (2C), 82.19 (2C), 77.20 (2C), 64.86 (4C), 48.78, 48.59, 43.38, 43.32, 39.31, 39.21, 39.11, 38.99, 36.22, 34.00, 32.53, 31.65, 30.10, 29.69, 28.96, 28.57, 27.79 (6C), 22.92, 16.31, 15.45 (seven signals not observed); MS m/z (M⁺) calc'd 500.2326, obsd 500.2324.

(1R,6S)-3-[((E)-5-(1,3-Dioxolan-2-yl)-3-methyl-2-pentenyl]-1,6-dimethyl-2-methylene-α-phosphonocyclohexanecarboxylic acid, 1-tert-butyl dimethyl ester (76).

Bromo ester 75 (2 mg, 0.004 mmol) was placed in a Wheaton flask and dissolved in an excess of trimethylphosphite (0.3 ml). The mixture was heated with an oil bath at 180°C for 24 h. The crude mixture was purified by flash chromatography (elution with 90% ethyl acetate in petroleum ether) to give 1.84 mg of α-phosphono tert-butyl ester 76 (87%); IR (CHCl₃, cm⁻¹) 3010, 2960, 2920, 2860, 1720, 1460, 1370, 1260, 1150, 1060, 1040; 1H NMR (300 MHz, CHCl₃) δ 5.18 (m, 1H), 4.84 (t, J=4.5 Hz, 1H), 4.84 (s, 1H), 4.71 (s, 1H), 3.96 (m, 2H), 3.84 (m, 2H), 3.78 (d, J=10.9 Hz, 3H), 3.76 (d, J=10.9
Hz, 3H), 2.78 (dt, J=22.1 Hz, J'=4.2 Hz, 0.5H), 2.74 (dt, J=22.3 Hz, J'=4.0 Hz, 0.5H), 2.34-0.86 (series of m, 16H), 1.62 (s, 3H), 1.48 (s, 9H), 0.97 (s, 3H), 0.80 (d, J=6.9 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 168.09 (2C), 153.88, 153.75, 134.71 (2C), 123.98, 123.91, 107.70 (2C), 104.41 (2C), 81.84, 81.75, 77.20 (2C), 64.85 (4C), 51.16 (2C), 51.12 (2C), 43.42, 39.16, 39.00, 38.96, 38.75, 34.03, 32.54, 31.77, 29.69, 28.99, 28.52, 27.96 (6C), 16.27, 15.40 (13 signals not observed); MS m/z (M+) calcd 528.3215, obsd 528.3215.

$(1R,6S)-3-[(E)-5-Formyl-3-methyl-2-pentenyl]-1,6$-dimethyl-2-methylene-$\alpha$-phosphono cyclohexane butyric acid, 1-tert-butyl dimethyl ester (77).

To a solution of dioxolane 76 (2 mg, 0.0038 mmol) in acetone:water (9:1) (1 ml) was added PTSA (12 mg). The mixture was stirred for 24 h at room temperature and the solvent was removed under vacuum. Ether was added and the solution was washed with a saturated solution of sodium bicarbonate, dried, concentrated and purified by flash chromatography (elution with ethyl acetate) to give 1.5 mg of aldehyde 77 (82%); IR (CHCl$_3$, cm$^{-1}$) 3010, 2960, 2930, 2860, 1720, 1460, 1370, 1260, 1200, 1150,
1070, 1040; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.73 (t, J=1.9 Hz, 1H), 5.18 (m, 1H), 4.81 (s, 1H), 4.71 (m, 1H), 3.77 (d, J=10.9 Hz, 3H), 3.75 (d, J=10.4 Hz, 3H) 2.78 (dt, J=22.1 Hz, J'=0.7 Hz, 0.5H), 2.74 (dt, J=22.2 Hz, J'=0.7 Hz, 0.5H), 2.51 (m, 2H), 2.35-0.84 (series of m, 14H), 1.63 (s, 3H), 1.48 (s, 9H), 0.97 (s, 3H), 0.83 (d, J=7.0 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 202.70 (2C), 168.16, 168.10, 153.56, 153.52, 133.42, 133.22, 124.97, 124.83, 108.09, 107.80, 107.77, 81.85, 81.74, 77.66, 77.21, 53.17, 53.10, 47.63, 43.43, 42.20, 39.20, 39.00, 38.76, 37.59, 37.42, 37.39, (31.98, 31.93), (31.74, 31.69) (d, J=11.3 Hz, 2C), 29.69, 28.98, 28.91, 28.73, 27.95 (6C), 22.79, 21.88, 21.83, 16.34, 15.37 (seven signals not observed); MS m/z (M$^+$-[C$_4$H$_8$]) calcd 428.2328, obsd 428.2353.

tert-Butyl($\alpha$S,1R,6S)-$\alpha$-(tert-Butyldiphenylsiloxy)-1,6-dimethyl-2-methylene-3-[3-methyl-2-(vinlyoxy)-3-butenyl]cyclohexanebutyrate (70) (the minor series).

To a solution of allylic alcohol 69 (66 mg, 0.109 mmol) in freshly distilled ethyl vinyl ether (5 ml) was added mercuric acetate (60 mg). The mixture was stirred at room temperature for
72 hr, diluted with petroleum ether, treated with a 10% solution of 
KOH, and extracted with petroleum ether. The extracts were dried, 
concentrated, and purified by flash chromatography on neutral 
alumina (elution with petroleum ether) to yield 68 mg of vinyl 
ether 70 (99%); IR (CHCl₃, cm⁻¹) 3060, 2960, 2920, 2860, 1740, 
1460, 1260, 1100, 1020; ¹H NMR (300 MHz, C₆D₆) δ 7.86 (m, 2H), 
7.78 (m, 2H), 7.21 (m, 6H), 6.26 (m, 1H), 5.03 (s, 1H), 4.81 (m, 3H), 
4.43 (m, 2H), 4.24 (t, J=6.8 Hz, 1H), 3.99 (m, 1H), 2.39-1.02 (series of 
m, 12H), 1.62 (s, 3H), 1.27 (s, 9H), 1.26 (s, 9H), 0.86 (s, 3H), 0.77 (m, 
3H); ¹³C NMR (75 MHz, C₆D₆) ppm 171.98 (2C), 157.33, 157.06, 
151.12, 150.98, 145.45, 145.25, 136.55 (2C), 136.27 (2), 136.13, 
135.98, 134.76, 134.40, 134.10, 129.97 (2C), 127.86 (2C), 112.99 
(2C), 104.80, 104.55, 88.91, 88.82, 82.57, 81.20, 80.42, 80.33, 73.61, 
73.90, 42.82, 40.19, 39.92, 39.28, 39.20, 37.78, 37.74, 35.98, 35.04, 
34.94, 34.73, 33.67, 33.89, 32.81, 32.71, 32.30, 32.13, 31.01, 30.97, 
30.47, 30.15, 29.70, 29.66, 28.32, 27.96 (3C), 27.26 (3C), 23.07, 
20.93, 20.76, 20.72, 19.69, 16.84, 16.94, 16.78, 16.08, 15.60, 14.31, 
six signal not observed; MS/FAB m/z (M⁺) calcd 630.41, obsd 
630.30.
**t**ert-**Bu**tyl(α*S*, 1*R*, 6*S*)-α-(**t**ert-Butyldiphenylsiloxy)-3-[(E)-5-formyl-3-methyl-2-pentenyl]-1,6-dimethyl-2-methylenecyclohexanobutyrate (71) (the minor series).

A solution of vinyl ether 70 (68 mg, 0.108 mmol) in toluene (10 ml) was refluxed for 14 hr. The resulting product was purified by flash chromatography on silica gel (elution with 5% ether in petroleum ether) to give 67 mg of aldehyde 71 (98%); \([\alpha]_{D}^{25} +8.4^\circ\) (c 0.82, CHCl₃); IR (CHCl₃, cm⁻¹) 3040, 2970, 2920, 2870, 1740, 1460, 1110; \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 9.76 (t, \(J=1.9\) Hz, 1H), 7.66 (m, 4H), 7.38 (m, 6H), 5.17 (t, \(J=6.3\) Hz, 1H), 4.74 (s, 1H), 4.63 (s, 1H), 4.19 (t, \(J=5.2\) Hz, 1H), 2.52 (dt, \(J=7.0\) Hz, \(J'=1.8\) Hz, 2H), 2.36-1.04 (series of m, 14 H), 1.63 (s, 3H), 1.32 (s, 9H), 1.12 (s, 9H), 0.87 (s, 3H), 0.79 (d, \(J=5.6\) Hz, 3H); \(^13\)C NMR (75 MHz, CDCl₃) ppm 202.51, 172.27, 157.16, 136.04 (2C), 135.84 (2C), 135.72, 133.88, 133.58, 129.60, 129.57, 127.52 (2C), 127.44 (2C), 125.00, 104.15, 80.64, 73.35, 42.21, 39.24, 38.27, 33.35, 32.07, 31.99, 31.83, 30.77, 29.67, 29.13, 27.88 (3H), 26.95 (3C), 21.10, 19.34, 16.27, 15.88; MS/FAB \(m/z\) (M⁺⁺1) calcd 631.41, obsd 631.42.
*tert*-Butyl(α*S,1*R,6*S)-α-(*tert*-Butyldiphenylsiloxy)-3-[(E)-5-(1,3-dioxolan-2-yl)-3-methyl-2-pentenyl]-1,6-dimethyl-2-methylenecyclohexanecarboxylate (73) (the minor series).

To a cold solution (-78°C) of aldehyde 71 (67mg, 0.106 mmol) in dichloromethane (1 ml) was successively added 1 drop of TMS triflate and 1,2-bis(trimethylsilyloxy)ethane (20 μl, 0.08 mmol). The mixture was stirred for 6 h at -78°C, quenched with pyridine (0.200 ml) and poured in a saturated solution of sodium bicarbonate (15 ml). After the usual extractive work-up with ether and purification by flash chromatography (elution 5% ethyl acetate in petroleum ether) 66 mg (92%) of dioxolane 73 was obtained; [α]$_D^{25}$ +1.8° (c 1.05, CHCl$_3$); IR (CHCl$_3$, cm$^{-1}$) 3010; 2960, 2920, 2860, 1720, 1460, 1110; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.69 (m, 4H), 7.38 (m, 6H), 5.17 (t, J=6.2 Hz, 1H), 4.85 (t, J=4.8 Hz, 1H), 4.73 (s, 1H), 4.64 (s, 1H), 4.18 (t, J=5.1 Hz, 1H), 3.96 (m, 2H), 3.83 (m, 2H), 2.15-1.05 (series of m, 16H), 1.62 (s, 3H), 1.32 (s, 9H), 1.12 (s, 9H), 0.93 (s, 3H), 0.78 (d, J=5.6 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 172.25, 157.28, 136.04 (2C), 135.83 (2C), 134.55, 133.87, 133.58, 129.59, 129.55, 127.51
(2C), 127.43 (2C), 124.04, 104.37, 104.07, 80.61, 73.35, 64.82 (2C),
42.37, 39.32, 38.75, 34.00, 32.53, 32.07, 30.82, 30.37, 29.91, 27.88
(3C), 26.94 (3C), 23.76, 22.95, 19.32, 16.22, 15.98; MS/FAB m/z
(M+) calcd 674.44, obsd 674.44.

**tert-Butyl(αS,1R,6S)-3-[(E)-5-(1,3-dioxolan-2-yl)-3-
 methyl-2-penteny]-α-hydroxy-1,6-dimethyl-2-
methylenecyclohexanecarboxylate (74) (the minor series).**

![Chemical structure of tert-Butyl(αS,1R,6S)-3-[(E)-5-(1,3-dioxolan-2-yl)-3-methyl-2-penteny]-α-hydroxy-1,6-dimethyl-2-methylenecyclohexanecarboxylate (74)](image)

To a solution of dioxolane 73 (66 mg, 0.098 mmol) in acetonitrile (5 ml) was added a freshly prepared solution of pyridinium hydrofluoride (2 ml) in acetonitrile (pyridine (2.4 ml), HF (1 ml of a 48% solution, 2.8 mmol) in acetonitrile (10 ml)). The mixture was stirred at room temperature overnight, poured in water, extracted with ether (3 x 20 ml), dried, concentrated and purified by flash chromatography (elution with 10% ethyl acetate in petroleum ether) to give 39 mg of α-hydroxy tert-butylester 74 (91.5%); [α]$_D^{25}$ +10° (c 0.65, CHCl$_3$); IR (CHCl$_3$, cm$^{-1}$) 3500, 3020, 2960, 2920, 2870, 1715, 1460, 1370, 1250, 1150, 1040; $^1$H NMR (300 MHz, CDCl$_3$) δ 5.16 (t, J=6.2 Hz, 1H), 4.84 (s, 1H), 4.83 (t, J=4.7
Hz, 1H), 4.70 (s, 1H), 4.07 (t, J=5.0 Hz, 1H), 3.96 (m, 2H), 3.83 (m, 2H), 2.80 (bs, 1H), 2.20-1.08 (series of m, 16H), 1.61 (s, 3 H), 1.50 (s, 9 H), 0.91 (s, 3 H), 0.82 (d, J=5.9 Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) ppm 174.68, 157.37, 134.60, 123.99, 104.38, 104.18, 82.37, 71.02, 64.82, 42.39, 39.38, 38.30, 33.98, 33.31, 32.51, 32.16, 30.77, 28.12, 28.04 (3C), 26.56, 21.20, 16.23, 15.90 (one signal not observed); MS/FAB \(m/z\) (M\(^+\)) calcd 436.32, obsd 436.34.

**tert-Butyl(1R,6S)-α-bromo-3-[(E)-5-(1,3-dioxolan-2-yl)-3-methyl-2-pentenyl]-1,6-dimethyl-2-methylenecyclohexanebutyrate (75) (the minor series).**

![Chemical Structure](image)

To a cold solution (-40°C) of hydroxy ester 74 (38 mg, 0.087 mmol) in triethylamine (4 ml) and dichloromethane (6 ml) was added methanesulfonyl chloride (250 \(\mu\)l). The mixture was warmed to room temperature and THF (20 ml) and LiBr (1.2 g) were added. The mixture was heated at 70°C for 3 hr. Water was added and the mixture was extracted with ether (3 x 20 ml), dried, concentrated, and purified by flash chromatography (elution with 10% ether in petroleum ether) to give 41 mg of α-bromo **tert**-butyl ester 75.
(94%); IR (CHCl$_3$, cm$^{-1}$) 3010, 2960, 2930, 2860, 1725, 1465, 1260, 1095; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.16 (t, J= 6.5 Hz, 1H), 4.84 (t, J=4.8 Hz, 1H), 4.77 (s, 1H), 4.72 (s, 1H), 4.11 (t, J=1.4 Hz, 1H), 3.96 (m, 2H), 3.84 (m, 2H), 2.18-0.90 (series of m, 16H), 1.61 (s, 3H), 1.49 (s, 9H), 0.92 (s, 3H), 0.83 (d, J=4.0 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 168.85, 168.81, 157.13, 157.06, 134.82, 134.70, 123.90, 123.78, 104.39, 104.32, 104.24, 82.29, 82.26, 64.85 (4C), 48.83, 48.51, 42.78, 42.75, 39.45, 39.41, 38.35, 38.30, 35.33, 35.21, 34.00, 33.27, 33.23, 32.53, 31.86, 30.77, 30.72, 29.36, 29.22, 27.77 (6C), 26.56, 21.20, 21.15, 16.25, 15.94 (five signals not observed); MS/FAB m/z (M$^+$) calcd 500.23, obsd 500.37.

(1R,6S)-3-[(E)-5-(1,3-Dioxolan-2-yl)-3-methyl-2-pentenyl]-1,6-dimethyl-2-methylene-\(\alpha\)-phosphonocyclohexanebutyric acid, 1-\(\text{tert}\)-butyl dimethyl ester (76) (the minor series).

Bromo ester 75 (22 mg, 0.044 mmol) was placed in a Wheaton flask and dissolved in an excess of trimethylphosphite (2 ml). The mixture was heated in an oil bath at 160°C for 24 h. The
crude mixture was purified by flash chromatography (elution with 70% ethyl acetate in petroleum ether) to give 19.4 mg of \(\alpha\)-phosphono tert-butyl ester 76 (83%) as a viscous oil; IR (CHCl\(_3\), cm\(^{-1}\)) 3010, 2960, 2920, 2860, 1720, 1460, 1370, 1260, 1150, 1060, 1040; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.16 (t, \(J=6.4\) Hz, 1H), 4.84 (t, \(J=4.8\) Hz, 1H), 4.82 (s, 1H), 4.70 (s, 1H), 3.95 (m, 2H), 3.86 (m, 2H), 3.78 (d, \(J=10.9\) Hz, 3H), 3.76 (d, \(J=10.9\) Hz, 3H), 2.82 (dt, \(J=22.2\) Hz, \(J'=3.8\) Hz, 0.5H), 2.79 (dt, \(J=22.2\) Hz, \(J'=4.2\) Hz, 0.5H), 2.25-0.93 (series of m, 16H), 1.61 (s, 3H), 1.49 (2s, 9H), 0.89 (2s, 3H), 0.82 (m, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) ppm 168.25, 168.11, 157.16, 157.07, 134.70, 134.65, 123.99, 123.90, 104.39, 104.29, 103.97, 81.97, 81.93, 64.85 (4C), 53.25, 53.15, 53.11, 53.01, 47.92, 46.20, 42.87, 42.78, 39.44, 39.32, 38.27, 38.11, 36.69 (d, \(J=12.2\) Hz, 2C), 34.00, 33.38, 33.20, 32.54, 31.87, 31.85, 30.83, 30.74, 29.67, 27.94 (6C), 26.35, 23.30, 21.19, 20.98, 16.24, 15.98, 15.93 (three signals not observed); MS \(m/z\) (M\(^{+}\)) calcd 528.3215, obsd 528.3212.

\((1R,6S)-3-\left[(E)-5-\text{Formyl}-3\text{-methyl-2-pentenyl}\right]-1,6\text{-dimethyl-2-methylene-}\alpha\text{-phosphonocyclohexanebutyric acid, 1-}\text{\(\alpha\)-butyl dimethyl ester\) (77) (the minor series).}
To a solution of dioxolane 76 (16 mg, 0.030 mmol) in acetone:water (9:1) (10 ml) was added PTSA (120 mg). The mixture was stirred for 28 h at room temperature and the solvent was removed under vacuum. Ether was added and the solution was washed with a saturated solution of sodium bicarbonate, dried, concentrated and purified by flash chromatography (elution with 65% ethyl acetate in petroleum ether) to give 13.1 mg of aldehyde (89%); IR (CHCl₃, cm⁻¹) 3010, 2960, 2930, 2860, 1720, 1460, 1370, 1260, 1200, 1150, 1070, 1040; ¹H NMR (300 MHz, CDCl₃) δ 9.75 (t, J=1.9 Hz, 1H), 5.16 (t, J=4.8 Hz, 1H), 4.83 (s, 1H), 4.69 (s, 1H), 3.79 (d, J=10.9 Hz, 1.5H), 3.77 (d, J=10.9 Hz, 1.5H), 2.82 (dt, J=22.2 Hz, J'=3.7 Hz, 0.5H), 2.77 (dt, J=22.2 Hz, J'=4.0 Hz, 0.5H), 2.51 (td, J=7.0 Hz, J'=1.8 Hz, 2H), 2.33 (t, J=7.4 Hz, 2H), 2.22-1.07 (series of m, 12H), 1.62 (s, 3H), 1.49 (s, 9H), 0.90 (s, 3H), 0.81 (m, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm 202.72, 202.58, 168.16, 168.10, 153.62, 153.56, 133.43, 133.22, 124.97, 124.83, 107.80, 107.76, 81.85, 81.74, 53.17, 53.10, 53.06, 47.63, 43.42, 42.20, 39.23, 38.25, 38.10, 37.42 (2d, J=11.7 Hz, 2C), 33.40, 33.21, 31.98, 31.93, 31.74, 31.65, 28.97, 28.90, 28.72, 27.93 (6C), 27.82, 27.76, 22.78, 21.87, 21.82, 20.95, 16.27, 15.96, 15.91 (three signals not observed); MS m/z (M⁺-[C₄H₈]) calcd 428.2328, obsd 428.2378.
REFERENCES


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CHAPTER II
SYNTHETIC APPROACHES TO CEROPLASTOL I

A. INTRODUCTION

1. Isolation and Structure

*Senecio Praecox* shrubs, which grow on volcanic layers in south of Mexico City, are annually infested by the insects *Ceroplastes albolineatus*. The females of this coccidae secrete and cover themself with a thick cluster of wax which acts as a protective scale against dessication. The crude wax consists of 40% acid and 60% neutral components. One of the major constituents of the latter fraction is ceroplastol I (1).\(^1\)

\[\text{Figure 4 : Structure of Ceroplastol I.}\]
This natural product may be regarded as the prototype of the ceroplastins, which along with the ophiobolins constitute the two major subclasses of the ophiobolane class of sesterterpenes. The structural assignment to ceroplastol I is based upon chemical and spectroscopic analysis of the alcohol and X-ray crystal structure examination of the p-bromobenzoate. This analysis revealed a 5-8-5 ring system, the common carbon framework shared by this family of sesterterpenes. The five-membered A ring possesses an exomethylene group. To the second five-membered ring C is attached a steroidal-like sidechain formally derived from 2-methyl-2-heptene and encountered in many natural products. Finally, the junction between rings A and B and between B and C are both found to be trans, in contrast to the cis/trans disposition in ophiobolins.

2. Retrosynthetic Strategy.

To address the various stereochemical challenges and interesting structural features offered by the target molecule, the synthetic plan can be divided in two major subdivisions. The first one would implement introduction of ring C and unsaturation in ring B (Scheme 26). Therefore, ceroplastol is envisioned to arise from conversion of the ketone moiety in 2 into a trisubstituted double bond. The C ring would be formed by conjugate addition of the Piers reagent to enone 4 and subsequent cyclization. The proper stereochemistry should result from steric control of attack of the cuprate on the quasi-tub conformation that enone 4 likely
adopts. This latter compound is to be prepared from isomeric enone 5.

**Scheme 26 : Retro-Synthetic Construction of the C Ring of Ceroplastol I.**

The second part of the retrosynthetic strategy concerns preparation of the 5-8 ring system by expanding application of the methodology employed for the stereospecific synthesis of precapnelladiene. A Claisen rearrangement with ring expansion of allyl vinyl ether 6 would allow access to the eight-membered ring of 5. The two olefinic functionalities of 6 could be introduced by
addition of vinyllithium and subsequent Tebbe olefination of keto ester 7. This latter intermediate would result from an oxidative ring opening of bicyclic ketone 8 that would be prepared by thermal cyclization of unsaturated ketone 9 (Scheme 27).

Scheme 27: Retro-Synthetic Approach to the Eight-Membered Ring of Ceroplastol I.

B. THE FIRST APPROACH

1. The Attempted Ene Reaction Route

Our first plan to access cis-perhydropentalenone 8, with its four consecutive stereogenic centers, was to take advantage of the high stereochemical definition encountered in the ene reaction. To obtain the desired stereochemical outcome in the thermal process, a general procedure for the stereospecific preparation of a (Z)-trisubstituted olefin was needed. A titanium-mediated methylation
of a homopropargylic alcohol was selected. Thus, bromoketal 10 was added to the dilithio derivative of but-3-yn-1-ol in liquid ammonia to deliver homologated alcohol 11. Subsequent carbometalation resulted in the formation of a complex mixture of trisubstituted olefins. This unexpected outcome prompted an examination of the reaction of hex-3-yn-1-ol (12), similarly prepared with ethyl bromide. A good yield of desired homoallylic alcohol 13 was obtained. Therefore, the failure of this first reaction was attributed to the presence of the ketal group which interferes in the crucial chelation between the alcohol and the organometallic reacting species (Scheme 28).

**Scheme 28**: Model Reaction for the Carbometalation.

![Scheme 28](image)

To circumvent this problem, a silyl protected alcohol was chosen to replace the ketal functionality. 3-Chloro-propanol was first protected as its tert-butyldimethylsilyl ether 14. Subsequent conversion to the iodide allowed nucleophilic displacement by the butynol to proceed in good yield. Carbometalation with
trimethylaluminum and titanium tetrachloride then delivered the desired (Z)-homoallylic alcohol (Scheme 29).

Scheme 29: Preparation of the Side-Chain for the Ene Reaction.

At this stage, the conjugated addition was tried. Formation and titration of the Grignard reagent revealed that only moderate yields could be obtained since homoallylic Grignard reagents are prone to elimination. Recourse to a mixed cuprate was therefore considered advantageous. To test the 1,4-addition and ensuing ene reactions, the homoallylic bromide and cis-1-bromo-3-hexene were added to 3-methylcyclopentenone. Thermal cyclization of solutions of 18 and 20 in decalin occurred in sealed tubes held at 340°C for 100 min. As the degree of substitution increased on the double bond, the yield of the reaction was seen to decrease dramatically. When the same thermal cyclization was attempted on 22, a complex mixture of cyclized products was obtained in relatively low yield. Different temperatures (from 320 to 400°C) were tried, but no single product became major (Scheme 30).
Scheme 30: Models for the Thermal Cyclization.

This attempt to set up simultaneously the relative stereochemistry of four stereogenic centers by an ene reaction represents the first example involving generation of such a high order of stereochemical definition with this type of transformation. This conversion, which would set a steroidal-like side-chain, is of general interest. Unfortunately, although cyclized products are obtained, no major compound predominated and this route was abandoned.

2. The Attempted Manganese-Promoted Lactonization Route

Recourse to an alternative strategy for accessing the bicyclic ketone 23 was needed. It was envisioned that a radical cyclization-desilylation process\textsuperscript{12} involving 24 could set up the terminal
stereogenic center of 23. The three others would be obtained from 25, the product of a manganese-promoted double annulation\textsuperscript{13} of \(\beta\)-keto acid 26. This latter is prepared from 3-methylcyclopentenone (Scheme 31).

**Scheme 31**: New Retro-Synthetic Approach to Bicyclic ketone 23.

Reduction of 3-methylcyclopentenone with Dibal-H\textsuperscript{14} led in good yield to allylic alcohol 27. Because the 4-position of this enone is unsubstituted, recourse to cerium trichloride\textsuperscript{15} was not necessary. Subsequent acetylation with acetic anhydride set the stage for an Ireland-modified Claisen rearrangement.\textsuperscript{16} The necessary silyl ketene acetal was then prepared by deprotonation of 28 with LDA and addition of trimethylsilyl chloride. The intended rearrangement subsequently took place in moderate yield. However, the yield of carboxylic acid 29 improved when the lithium enolate of allylic acetate 28 was treated with tert-butyldimethylsilyl chloride in
presence of HMPA.\textsuperscript{17} This modification minimized the generation of C-silylated acetate. Acid 29 was converted to β-keto acid 26 when submitted to reaction with the mono-anion of bis[trimethylsilyl] malonate (Scheme 32).\textsuperscript{18}

Scheme 32: Preparation of Tricyclic Lactone 25.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme32.png}
\caption{Preparation of Tricyclic Lactone 25.}
\end{figure}

The manganese-promoted double annulation was reported to occur in 52% yield for an example closely related to 26. In our case, the additional methyl group was believed to bring the chain closer to the double bond, thereby presumably accelerating the reaction and improving the yield. Unfortunately, this expected effect was not observed. Decarboxylation was the predominant process and only a small amount of lactone 25 could be isolated in non-reproducible
fashion. Thus, again it became necessary to develop an alternative route.

C. A NEW ENANTIOSELECTIVE APPROACH

1. Strategy

Due to the difficulties encountered in earlier attempts at preparing bicyclic intermediate 23, and the problem of the double bond migration in the construction of (+)-7,8-epoxy-2-basmen-6-one that was encountered independently in this group, a new and enantioselective approach was considered. The major modification involves a more rapid access to the eight-membered ring and the introduction of the steroidal-like side-chain by conjugate addition of a cuprate to an enone (Figure 5).\(^{19}\)

Figure 5: Retrosynthesis Involving Cuprate Addition of the Side-Chain.

An efficient method for preparing keto esters related to 7 involves oxidative cleavage of cyclic enones. Starting with selective
protection of the ketone moiety in optically active 30 as a dioxolane,\textsuperscript{20} ensuing oxidation of resulting enone 31 with potassium permanganate and sodium periodate, and treatment with diazomethane delivered keto ester 32. It should be noted that in order to keep the ketal in place, sodium dithionite must replace the too acidic sodium thiosulfate during work-up of the cleavage reaction. Condensation of 32 with vinyllithium did not deliver the desired vinyl lactone. Because of the increased steric hindrance imposed by the quaternary center, double addition to the methyl ester and formation of tertiary alcohol 33 occurred instead (Scheme 33).

\textbf{Scheme 33 : Oxidative Cleavage of Enone 31.}

At this point, it became clear that because of the more complicated structural features found in ceroplastol I, the methodology used for the synthesis of precapnelladiene could not be applied. Nevertheless, access to an eight-membered ring by
Claisen-promoted ring expansion was still very attractive. We also wanted to fully use the six carbons of enone 31, instead of losing one of them to get to the correct oxidation level and then reintroduce it. A comprehensive search in the literature revealed that five examples of peracidic oxidation of enones to epoxy lactones with subsequent rearrangement to aldehydo lactone are known. Double olefination of the aldehydo lactone should then deliver a similar Claisen precursor to the allyl vinyl ether 6 and therefore give us an access to eight-membered ring (Figure 6)

Figure 6: Retrosythetic Pathway Involving a Peracidic Oxidation.

2. Results and Discussion

Ketal 31 was oxidized with three equivalents of m-chloroperbenzoic acid to give epoxy lactone 34. The ensuing rearrangement was somewhat troublesome because of the sensitivity of the ketal moiety. Only thermal conditions provided
access to aldehyde 35, which could not be purified without extensive degradation (Scheme 34).

Scheme 34: Peracidic Oxidation and Rearrangement of 31.

Due to the difficulties encountered, ketone 30 was selectively reduced and resulting alcohol 36 was treated with MCPBA. Even under forcing conditions, no reaction took place. Similarly, acetate 37 did not react. Silyl ether 38, along with the MEM and SEM protected alcohols 39 and 40, do deliver the corresponding epoxy lactone but only in low yield and after tedious purification (Scheme 35).

Scheme 35: Series of Functionalized Alcohols.

36, X=H
37, X=Ac
38, X=Si(Ph)2Bu
39, X=MEM
40, X=SEM
The obstacles found in the attempts to realize this oxidation were attributed to interaction between the hydroxyl group and the peracid. To effectively prevent this, tert-butylation was effected with isobutylene in the presence of sulfuric acid. Peracidic oxidation of resulting enone 41 delivered epoxy lactone 42 in good yield (Scheme 36). Unfortunately, when exposed to the rearrangement conditions, epoxy lactone 42 gave an aldehydo hydroxy acid that could not be made to lactonize. The stereochemistry of the epoxide moiety in 42 is β. Therefore the ring junction of the aldehydo lactone would be trans, which is not favored in a 6,5-ring system.

Scheme 36: Peracidic Oxidation of tert-Butyl Ether 41.

A possible way to avoid this problem is to elaborate the C-ring of the natural product later by ring contraction of a six-membered ring. Therefore, starting with the Wieland-Miescher ketone, selective reduction to alcohol 43,\(^{22}\) formation of the tert-butyl ether 44, and ensuing peracidic oxidation delivered a diastereoisomeric mixture of epoxy lactone 45. Subsequent treatment with a catalytic amount of trifluoroacetic acid furnished aldehydo lactone 46 in excellent yield. Condensation with the
Tebbe reagent resulted in very efficient double olefination. The allyl vinyl ether 47 so formed was treated with Tribal for 6 h at room temperature to deliver cyclooctenol 48. Swern oxidation completed the conversion to cyclooctenone 49 (Scheme 37).

**Scheme 37:** Access to the Eight-Membered Ring from the Wieland-Miescher Ketone.

In our quest to find a way to get access to the medium-sized ring found in ceroplastol I, a concise and effective process for effecting the enlargement of smaller functionalized rings has been discovered. Implementation of the versatility of this technology along with the advantages of the aluminum-promoted
rearrangement over the more traditional thermal Claisen procedure is of considerable interest and is discussed in the following chapter.

D. CONCLUSION

Synthetic efforts presented in this chapter describe an approach toward the A/B ring system of ceroplastol I. Several important problems have been solved. The strategy used for the synthesis of precapnelladiene cannot be applied because of the increased steric hindrance of the more highly functionalized target molecule. However a new and reliable access to 5-cyclooctenones, via Claisen-promoted ring expansion has been introduced. This technology is quite versatile and might be useful in the area of medium-ring natural product synthesis in general.

Several important tasks remain for the future. Efforts toward the incorporation of the C ring along with ring contraction of the A ring to complete the enantioselective synthesis of 1 will resume shortly. The remaining transformations have precedence in the literature and, now that the synthesis is back on track, we hope that the final goal of this research will be met promptly.
EXPERIMENTAL

2-(2-Bromoethyl)-1,3-dioxolane (10).\(^7\)

![Chemical structure of 2-(2-Bromoethyl)-1,3-dioxolane](image)

To stirred solution of hydrogen bromide (300 g, 3.75 mol) in ethylene glycol (500 ml) was added acrolein (140 g, 2.5 mol). After being stirred for 1 h at room temperature, the mixture was extracted with pentane (2 x 600ml). The combined organic layers were washed with 5% sodium bicarbonate solution, dried, and evaporated. Distillation of the residue gave 250 g of bromoacetal 10 (55%); bp 70-78°C/16 Torr; IR (neat, cm\(^{-1}\)) 2960, 2880, 1470, 1405, 1260, 1210, 1140, 1010, 880; \(^1\)H NMR (80 MHz, CDCl\(_3\)) \(\delta\) 4.79 (t, J=6.0 Hz, 1H), 3.75 (m, 4H), 3.40 (t, J=7.0 Hz, 2H), 2.20 (m, 2H).

6-(1,3-Dioxolan-2-yl)-3-hexyn-1-ol (11).

![Chemical structure of 6-(1,3-Dioxolan-2-yl)-3-hexyn-1-ol](image)
But-3-yn-1-ol (40.6 g, 0.58 mol) was added to lithium amide (from lithium (8.05 g, 1.16 mol)) in liquid ammonia (0.77 ml). After 1 h, a solution of bromoketal 10 (54.5 g, 0.33 mol) in tetrahydrofuran (400 ml) was added, the mixture was refluxed for 8 h and allowed to evaporate. Addition of dilute hydrochloric solution, usual extraction with ether and distillation gave 33.7 g of ketal 11 (60%); bp 127°C/1.5 Torr; IR (neat, cm⁻¹) 3080, 2960, 2930, 2870, 1740, 1460, 1405, 1380, 1260, 1160, 910; ¹H NMR (300 MHz, CDCl₃) δ 4.79 (t, J=4.6 Hz, 1H), 3.78 (m, 4H), 3.49 (m, 2H), 3.01 (bs, 1H), 2.22 (m, 2H), 2.13 (m, 2H), 1.67 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) ppm 103.06, 80.64, 76.77, 64.51 (2C), 60.82, 32.77, 22.71, 13.28; MS m/z (M⁺) calcd 170.0943, obsd 170.0953.

Hex-3-yn-1-ol (12).

But-3-yn-1-ol (36.8 g, 0.525 mol) was added to lithium amide (from lithium (7.3 g, 1.02 mol)) in liquid ammonia (0.70 ml). After 1 h, a solution of ethyl bromide (32.7 g, 0.30 mol) in tetrahydrofuran (300 ml) was added, the mixture was refluxed for 8 h and allowed to evaporate. Addition of dilute hydrochloric solution, usual extraction with ether and distillation gave 22.4 g of hexynol 12 (76%); bp 92°C/32 Torr; IR (neat, cm⁻¹) 3350, 2970, 2930, 2870,
(Z)-4-Methyl-3-hexen-1-ol (13).

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH} & \quad \text{CH}_2 & \quad \text{OH} \\
& \quad & \quad & \\
& \quad & \quad & \\
& \quad & \quad & 
\end{align*}
\]

To a cooled solution (0°C) of trimethylaluminum (23 ml, 0.24 mol) in dichloromethane (80 ml) was added dropwise hex-3-yn-1-ol 12 (18.24 g, 0.120 mol) in dichloromethane (40 ml). The mixture was allowed to warm to room temperature, transferred via cannula into a dropping funnel and added dropwise to a cold solution (-78°C) of titanium tetrachloride (1 M solution in dichloromethane, 160 ml). The mixture was stirred at -78°C for 6 h, quenched with methanol, followed with 5% sulfuric acid saturated with sodium chloride. The mixture was extracted with ether (3 x 80 ml), the organic extracts were dried, concentrated and purified by chromatography on silica gel (elution with 7.5% ethyl acetate in petroleum ether) to give 7.06 g of alcohol 13 (52%); IR (neat, cm⁻¹) 3350, 3050, 2960, 2930, 2870, 1460, 1370, 1045; ¹H NMR (300 MHz, CDCl₃) δ 5.02 (t, J=7.3 Hz, 1H), 3.52 (t, J=6.6 Hz, 2H), 2.19 (q, J=6.5 Hz, 2H), 1.98 (q, J=7.6 Hz, 2H), 1.64 (s, 3H), 0.91 (t, J=7.5 Hz,
3H) (hydroxyl signal not observed); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 139.70, 119.55, 62.16, 31.00, 24.59, 22.58, 12.50.

(Z)-1-Bromo-4-methyl-3-hexene (14).

To a cold solution (-25°C) of alcohol 13 (0.13 g, 1.00 mmol) in dry ether (30 ml) was added triethylamine (0.250 ml, 1.80 mmol) and methanesulfonyl chloride (0.125 ml, 1.60 mmol). The mixture was allowed to warm to 0°C and water (20 ml) was added. After the usual extractive work-up with ether (4 x 20 ml) and evaporation of solvent, the crude mesylate was dissolved in THF (30 ml) and LiBr (500 mg) was added. The mixture was heated at 70°C for 3 h. Water was added and the mixture was extracted with ether (3 x 10 ml), dried, concentrated and purified by flash chromatography (elution with 5% ethyl acetate in petroleum ether) to give 151 mg of bromide 14 (85%); IR (neat, cm$^{-1}$) 3040, 2960, 2930, 2870, 1460, 1370, 1045; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.08 (t, J=7.2 Hz, 1H), 3.32 (t, J=7.3 Hz, 2H), 2.57 (q, J=6.8 Hz, 2H), 2.03 (q, J=7.6 Hz, 2H), 1.70 (s, 3H), 0.98 (t, J=7.5 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 140.58, 120.52, 32.84, 31.46, 24.93, 22.80, 12.74.
3-Chloro-1-(tert-Butyldimethylsiloxy)-propane (15).

![Structural formula](image)

To a solution of 3-chloropropan-1-ol (32.02 g, 0.36 mol) in DMF (85 ml) was added tert-butyldimethylchlorosilane (45.3 g, 0.30 mol) and imidazole (60 g). The mixture was stirred overnight at room temperature and water (5 ml) was added. After the usual extractive work-up with ether and purification by flash chromatography (elution using 5% ether in petroleum ether) 63.10 g of silyl ether 15 (97%) was obtained; IR (neat, cm\(^{-1}\)) 2960, 2940, 2860, 1460, 1350, 1240; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.74 (t, J=4.5 Hz, 2H), 3.62 (t, J=5.1 Hz, 2H), 1.94 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H); \(^1^3\)C NMR (75 MHz, CDCl\(_3\)) ppm 59.41, 41.61, 32.93, 25.86 (3C), 18.27, -5.43, -5.50.

7-(tert-Butyldimethylsiloxy)-3-heptyn-1-ol (16).

![Structural formula](image)

To a solution of silyl ether 15 (11.5 g, 64 mmol) in methyl ethyl ketone (100 ml) was added sodium iodide (12.5 g, 83 mmol). The mixture was refluxed overnight then cooled to room temperature. Water was added and after the usual extraction with
ether and distillation 16.1 g of iodosilyl ether was obtained; bp 105°C/22 Torr. But-3-yn-1-ol (7.24 g, 0.103 mol) was added to lithium amide (from lithium (1.45 g, 0.206 mol)) in liquid ammonia (200 ml). After 1 h, a solution of silyl ether (16.1 g, 59 mmol) in tetrahydrofuran (50 ml) was added, the mixture was refluxed for 8 h and allowed to evaporate. Addition of dilute hydrochloric acid solution, usual extraction with ether and distillation gave 7.62 g of homopropargylic alcohol 16 (46%); bp 127°C/1.5 Torr; IR (neat, cm⁻¹) 3350, 2960, 2940, 2860, 1460, 1260, 1110, 840; ¹H NMR (300 MHz, CDCl₃) δ 3.64 (m, 4H), 2.34 (m, 2H), 2.20 (m, 2H), 1.64 (m, 2H), 0.83 (s, 9H), -0.06 (2s, 6H); ¹³C NMR (75 MHz, CDCl₃) ppm 81.45, 76.47, 61.49, 61.14, 31.80, 25.74 (3C), 22.87, 18.10, 14.97, -5.53 (2C); MS m/z (M⁺-[C₄H₈⁺]) calcd 186.1076, obsd 186.1032.

(Z)-7-(tert-Butyldimethylsiloxy)-4-methyl-3-hepten-1-ol (17).

\[
\text{tBu(Me)₂SiO} \quad \text{OH}
\]

To a cooled solution (0°C) of trimethylaluminum (3.8 ml, 40 mmol) in dichloromethane (40 ml) was added dropwise a solution of homopropargylic alcohol 16 (4.84 g, 20 mmol) in dichloromethane (20 ml). The mixture was allowed to warm to room temperature, transferred via cannula into a dropping funnel and added dropwise to a cold solution (-78°C) of titanium tetrachloride (1 M solution in
dichloromethane, 26.5 ml). The mixture was stirred at -78°C for 6 h, quenched with methanol, followed by 5% sulfuric acid saturated with sodium chloride. The mixture was extracted with ether (3 x 80 ml), the organic extracts were dried, concentrated and purified by chromatography on silica gel (elution with 7.5% ethyl acetate in petroleum ether) to give 2.10 g of alcohol 17 (42%); IR (neat, cm⁻¹) 3400, 2960, 2940, 2870, 1460, 1380, 1260, 1105, 840, 780; ¹H NMR (300 MHz, CDCl₃) δ 5.12 (t, J=7.2 Hz, 1H), 3.61 (m, 4H), 2.38 (q, J=6.7 Hz, 2H), 2.07 (q, J=7.4 Hz, 2H), 1.69 (s, 3H), 1.62 (m, 2H), 0.91 (s, 9H), 0.06 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) ppm 138.17, 121.00, 62.72, 62.46, 31.34, 31.09, 28.04, 25.89 (3C), 23.39, 18.24, -5.30 (2C); MS m/z (M⁺-[C₄H₈]) calcd 202.1389, obsd 202.1332.

3-(3-Butenyl)-3-methylcyclopentanone (18).

![Chemical structure](image)

To an ether solution (25 ml) of magnesium turnings (0.73 g, 30 mmol) was added dropwise a solution of 1-bromo-3-butene (2.7 g, 20 mmol) in ether (10 ml). The reaction was initiated with 1,2-dibromomethane (0.10 ml). After the addition was completed, the mixture was stirred at reflux for 1 h. (The Grignard reagent was titrated with menthol and 1,10-phenanthroline and gave 72% conversion). Methyllithium (1.12 M, 4.41 ml) was added to a cold
suspension (-30°C) of cuprous iodide (0.95 g, 5.0 mmol) in ether (10 ml). The temperature was allowed to rise to 0°C for 15 min and lowered to -40°C. The previously prepared solution of Grignard reagent was added dropwise and the mixture was stirred for 15 min. The temperature was allowed to rise to -10°C for 15 min and lowered to -40°C. A solution of 3-methyl-2-cyclopentenone (2.0 g, 20.8 mmol) in ether (10 ml) was added to the methyl cuprate solution and the temperature was allowed to rise to -10°C for 30 min. A saturated solution of ammonium chloride was added and the mixture was extracted with ether (3 x 20 ml). The organic extracts were dried, concentrated and purified by chromatography on silica gel to give 2.5 g of 1,4-addition product 18 (90%); IR (neat, cm⁻¹) 3080, 2960, 2930, 2870, 1740, 1460, 1405, 1380, 1260, 1160, 910; ¹H NMR (300 MHz, CDCl₃) δ 5.72 (m, 1H), 4.90 (m, 2H), 2.22 (t, J=4.2 Hz, 2H), 1.98 (m, 4H), 1.73 (m, 2H), 1.43 (t, J=8.4 Hz, 2H), 0.99 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm 218.82, 138.43, 114.22, 51.94, 40.79, 39.18, 36.44, 35.06, 28.96, 24.73; MS m/z (M⁺) calc 152.1201, obsd 152.1229.

Anal. Calcd for C₁₂H₁₆O: C, 78.88; H, 10.60. Found: C, 78.91; H, 10.63.

3-(3-hexenyl)-3-methylcyclopentanone (20).
The same procedure as described above, but involving cis-1-bromo-3-hexene (1.65 g, 10 mmol), delivered 1.08 g of 1,4-addition product 20 (60%); IR (neat, cm⁻¹) 3005, 2960, 2930, 2870, 1740, 1460, 1380, 1260, 1160; ¹H NMR (300 MHz, CDCl₃) δ 5.37 (m, 2H), 2.25 (m, 2H), 2.02 (m, 6H), 1.80 (m, 2H) 1.48 (t, J=8.4 Hz, 2H), 1.07 (s, 3H), 0.96 (t, J=7.5 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm 219.20, 131.70, 128.65, 52.06, 41.76, 39.44, 36.58, 35.16, 24.81, 22.53, 20.36, 14.17; MS m/z (M⁺) calcd 180.1514, obsd 180.1533.


3-Methyl-3-(4-Methyl-3-hexenyl)cyclopentanone (22).

The same procedure as described above, but with cis-1-bromo-4-methyl-3-hexene (1.80 g, 10 mmol), gave 0.81 g of 1,4-addition product 22 (45%); IR (neat, cm⁻¹) 2970, 2920, 2860, 1730, 1465; ¹H NMR (300 MHz, CDCl₃) δ 5.02 (t, J=7.4 Hz, 1H), 2.22 (m, 4H), 1.97 (m, 4H), 1.74 (m, 2H), 1.62 (s, 3H), 1.39 (t, J=8.4 Hz, 2H), 1.02 (s, 3H), 0.92 (t, J=7.6 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm 219.24, 137.09, 123.80, 52.05, 42.09, 39.38, 36.58, 35.15, 24.83, 24.68, 22.97, 22.60, 12.73; MS m/z (M⁺) calcd 194.1671, obsd 194.1692.
Thermal Cyclizations

A solution of unsaturated ketone (50 mg) in decalin (1 ml) was placed in a base-washed pyrex tube. The tube was sealed under vacuum and heated at 340°C for 100 min. The tube was opened and rinsed three times with ether. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel (elution with 5% ether in petroleum ether) and provided the bicyclic ketone.

(3aS,6S,6aS)-Hexahydro-3a,6-dimethyl-1(2H)-pentalenone (19).

For 19 (70%); IR (CHCl₃, cm⁻¹) 2970, 2940, 2870, 1740, 1465; ¹H NMR (300 MHz, CDCl₃) δ 2.35 (m, 3H), 2.02 (d, J=9.8 Hz, 1H), 1.85 (m, 2H), 1.74 (m, 2H), 1.60 (m, 2H), 1.21 (s, 3H), 1.02 (d, J=7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm 221.80, 62.68, 48.53, 40.68, 40.13, 38.52, 35.56, 35.36, 28.57, 16.35; MS m/z (M⁺) calcd 152.1201, obsd 152.1230
(3aS,6S,6aS)-Hexahydro-3a-methyl-6-propyl-1(2H)-pentalenone (21).

For 21 (40%); IR (CHCl₃, cm⁻¹) 2960, 2920, 2860, 1740, 1460; 
¹H NMR (300 MHz, CDCl₃) δ 2.21 (m, 3H), 2.04 (d, J=9.6 Hz, 1H), 1.88 
(m, 2H), 1.71 (m, 2H) 1.59 (m, 2H), 1.31 (m, 2H), 1.14 (m, 2H), 1.19 
(s, 3H), 0.88 (t, J=7.3 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm 221.63, 
61.89, 47.96, 44.36, 40.50, 40.11, 35.44, 33.35, 33.30, 28.66, 22.02, 
14.17; MS m/z (M⁺) calcd 180.1514, obsd 180.1543.

3-Methyl-2-cyclopenten-1-ol (27).

To a cold solution (0°C) of 3-methylcyclopentenone (9.80 g, 
102 mmol) in benzene (100 ml) was added a solution of DIBAL-H in 
hexane (150 ml of 1 M, 150 mmol) and benzene (150 ml). After 2h 
at 0°C, the aluminum salts were decomposed with a large excess of 
methanol and removed by filtration through Celite. The filtrate was 
concentrated and the residue was distilled to give 7.46 g of allylic 
alcohol 27 (76%); bp 70°C/20 Torr; IR (neat, cm⁻¹) 3300, 3040, 
2960, 2920, 2840, 1650, 1440, 1375, 1335, 1150, 1070, 1040, 995,
3-Methyl-2-cyclopenten-1-ol (28).

A solution of allylic alcohol 27 (4.77 g, 49 mmol), acetic anhydride (15.03, 147 mmol) and DMAP (0.2 g) in pyridine (50 ml) was stirred for 14 h at room temperature. The reaction mixture was poured in ice water and extracted with ether (3 x 50 ml). The organic extracts were washed with 10% HCl solution (40 ml), saturated sodium carbonate solution (40 ml), and brine (40 ml), dried, concentrated and purified by chromatography on silica gel to give 5.74 g of acetate 28 (83%); IR (neat, cm\(^{-1}\)) 3050, 2960.2930, 2860, 1730, 1660, 1410, 1370, 1240, 1010; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.53 (m, 1H), 5.35 (s, 1H), 2.20 (m, 4H), 1.91 (s, 3H), 1.71 (s, 3H); \(^1\)H NMR (75 MHz, CDCl\(_3\)) ppm 170.81, 148.21, 123.44, 81.11, 35.07, 30.67, 21.14, 16.55.
1-Methyl-2-cyclopentene-1-acetic acid (29).

To a cold solution (-78°C) of LDA (11 mmol) in THF (40 ml) was added HMPA (3 ml, 10.2 mmol) and acetate 28 (1.40 g, 10 mmol). The mixture was stirred for 30 min at -78°C and a solution of tert-butyldimethylsilyl chloride (1.65 g, 10.3 mmol) in THF (2 ml) was added. The reaction mixture was warmed to 70°C and kept 2 h at this temperature. The silyl ester was extracted with pentane, the solvent was removed and replaced with THF (25 ml) and 10% HCl (5 ml). The mixture was stirred at room temperature for 1 h, poured into a 5% sodium hydroxide (30 ml), and washed with ether (30 ml). The aqueous solution was acidified with concentrated HCl and extracted with ether (4 x 30 ml). The organic extracts were dried and concentrated to give 1.05 g of acid 29 (74%) as a viscous oil; IR (neat, cm\(^{-1}\)) 3300-2300, 3050, 2960, 2920, 2850, 1700, 1450, 1370, 1350, 1310, 1290, 1250, 1130, 930, 740; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 11.68 (bs, 1H), 5.65 (s, 2H), 2.38 (s, 2H), 2.35 (t, J=6.6 Hz, 2H), 1.82 (m, 2H), 1.17 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) ppm 179.01, 138.70, 129.50, 47.12, 45.49, 37.08, 31.35, 26.09; MS \(m/z\) (M\(^+\)) calcd 140.0837, obsd 140.0866.
1-Methyl-2-cyclopentene-1-acetoacetic acid (26).

To a solution of acid 29 (0.81 g, 5.74 mmol) in benzene (20 ml) was added oxalyl chloride (3 ml). The mixture was stirred for 3 h at room temperature. The solvent was evaporated and replaced with ether (10 ml). To a cold solution (-78°C) of bis-(trimethylsilyl) malonate ester (3.00 g, 12.1 mmol) in ether (70 ml) was added n-butyllithium (1.51 M, 8.04 ml). The mixture was allowed to warm to 0°C and the previously prepared ethereal solution of acid chloride was added. The mixture was stirred at this temperature for 2 h, and thoroughly shaken for 10 min with a cold 5% solution (0°C) of sodium carbonate. The aqueous layer was acidified to pH 1 with cold (0°C) 4 N sulfuric acid and extracted with ether (4 x 50 ml). The organic extracts were dried and concentrated. The residue was dissolved in benzene (30 ml), filtered and evaporated to give 0.75 g of β-keto acid 26 (71%); IR (neat, cm⁻¹) 3600-2300, 1730, 1620, 1460, 1240, 680; ¹H NMR (300 MHz, CDCl₃) δ 10.56 (bs, 1H), 5.56 (s, 2H), 4.90 (s, 1H, enol), 3.38 (s, 2H), 2.42 (s, 2H), 2.25 (m, 2H), 1.65 (m, 2H), 1.06 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm 208.87, 177.71, 139.06, 129.15, 54.08, 46.61, 37.14, 31.74, 31.35, 26.44.
(2aR,4aR,6aR,6bS)-hexahydro-4-a-methyl-2H-pentaleno[1,6-bc]furan-2,3(2aH)-dione (25).

Manganese (III) acetate (0.53 g, 1.98 mmol) was dissolved in glacial acetic acid (10 ml) at 40°C. The resulting solution was cooled to room temperature and β-keto acid 26 (0.23 g, 1.25 mmol) was added. The mixture was stirred for 1 h and the solvent was removed under reduced pressure. The residue was diluted with an aqueous solution of sodium carbonate (15 ml) and extracted with ether (3 x 10 ml). The organic extracts were dried, concentrated and purified by chromatography on Florisil to give 0.046 g of keto-lactone 25 (20%) as a light yellow solid; mp 71°C; IR (CHCl₃, cm⁻¹) 3020, 2970, 2880, 1780, 1740, 1460, 1360, 1175, 1025; ¹H NMR (300 MHz, CDCl₃) δ 5.12 (t, J=5.6 Hz, 1H), 3.56 (d, J=10.8 Hz, 1H), 3.12 (dd, J=10.7 Hz, J=6.8 Hz, 1H), 2.46 (d, J=18.5 Hz, 2H), 2.08 (m, 2H), 1.75 (m, 1H), 1.53 (m, 1H), 1.28 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm 206.29, 169.73, 85.04, 55.21, 53.64, 52.15, 45.99, 36.34, 32.91, 26.45; MS m/z (M⁺) calcd 180.0786, obsd 180.0779.
To a solution of 30 (5 g, 30.5 mmol) in methyl ethyl dioxolane (50 ml) was added p-toluenesulfonic acid (0.4 g) and ethylene glycol (1 ml). The mixture was stirred at room temperature for two days, quenched by addition of triethylamine (2 ml), poured into water and extracted with ether (3 x 20 ml). The extracts were dried, concentrated and purified by flash chromatography (elution with 30% ethyl acetate in petroleum ether) to give 5 g of monoketal 31 (85%); [α]D <sub>25</sub> +8.2° (c 2.10, CHCl₃); IR (CHCl₃, cm<sup>-1</sup>) 2980, 2960, 2880, 1660, 1460, 1170, 1140, 1040, 980; <sup>1</sup>H NMR (300 MHz, CDCl₃) δ 5.70 (s, 1H), 3.87 (m, 4H), 2.55-1.25 (series of m, 8H), 1.18 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl₃) ppm 198.42, 173.90, 122.88, 117.27, 65.50, 64.66, 47.46, 32.84, 31.43, 26.62, 26.30, 19.79; MS <i>m/z </i>(M<sup>+</sup>) calcd 208.1099, obsd 208.1109.

**Methyl(S)-6-methyl-7-oxo-1,4-dioxaspiro[4.4]nonane-6-propionate** (32).
To a solution of enone 31 (1.04 g, 5 mmol) in tert-butanol (60 ml) and potassium carbonate (3.5 g) in 20 ml of water was added a solution of sodium periodate (15 g) in water (100 ml) and a solution of potassium permanganate (0.4 g) in water (20 ml) to keep the reaction mixture pink. After 2 h, the reaction mixture was quenched by adding an excess of a solution of sodium dithionite, acidified with cold 5% hydrochloric acid, and extracted with ether (3 x 60 ml). The extracts were dried, concentrated, and treated with an ethereal solution of diazomethane. The mixture was concentrated and purified by flash chromatography (elution with 25% ethyl acetate in petroleum ether) to give 1.01 g of keto ester 32 (83%); \([\alpha]^{25}_D -5.0^\circ (c 1.19, \text{CHCl}_3)\); IR (CHCl\(_3\), cm\(^{-1}\)) 3010, 2990, 2950, 2890, 1730, 1440, 1380, 1300, 1230, 1050, 950; \(^1\)H NMR (300 MHz, CDC\(_3\)) \(\delta 3.89 (m, 4H), 3.58 (s, 3H), 2.35-1.75 (\text{series of } m, 8H), 0.95 (s, 3H)\); \(^{13}\)C NMR (75 MHz, CDC\(_3\)) ppm 217.14, 173.76, 115.90, 64.91, 64.51, 52.97, 51.29, 34.96, 29.69, 28.58, 27.04, 15.25; MS m/z (M\(^+\)) calcd 242.1154, obsd 242.1163.

\((S)-6-(3\text{-Hydroxy-3-vinyl-4-pentenyl-6-methyl-1,4-dioxaspiro[4.4]nonan-7-one}\) (33).
To a cold solution (-78°C) of vinyl bromide (0.4 ml, 5.7 mmol) in ether (20 ml) was added tert-Butyllithium (0.85 ml of a 1.7M solution, 1.44 mmol). The mixture was stirred at -78°C for 30 minutes and a cold solution of keto ester 32 (155.5 mg, 0.6425 mmol) in ether (5 ml) was added via a cannula. The mixture was stirred for 30 minutes at -78°C, then warmed to room temperature, stirred for 1 h and quenched with water. After the usual extraction with ether (3 x 15 ml), the combined extracts were dried, concentrated and purified by flash chromatography (elution with 15% ethyl acetate in petroleum ether) to give 0.108 g of tertiary alcohol 33 (63%); IR (CHCl₃, cm⁻¹) 3600, 3500, 3080, 3010, 2970, 2880, 1730, 1460, 1310, 1030, 920; ¹H NMR (300 MHz, CDCl₃) δ 5.86 (m, 2H), 5.25 (m, 2H), 5.19 (m, 2H), 3.97 (m, 4H), 2.40-1.56 (series of m, 8H), 0.98 (s, 3H) (hydroxyl signal not observed); ¹³C NMR (75 MHz, CDCl₃) ppm 217.86, 142.65, 142.53, 116.30, 112.97 (2C), 65.13, 64.91, 64.59, 53.63, 35.09, 34.42, 29.96, 26.16, 15.19; MS m/z (M⁺) calcd 266.1518, obsd 266.1529.

(5aS)-Tetrahydro-5a-methylspiro[1aH,6H-cyclopent[c]oxireno[b]oxepin-6,2’-[1,3]dioxolan]-3(4H)-one (34).
To a solution of enone 31 (0.21 g, 1 mmol) in dichloromethane (15 ml) was added sodium bicarbonate (1.5 g) and MCPBA (1.08 g, 3 mmol). The mixture was stirred for 1 day at room temperature, quenched with water, extracted with ether (3 x 60 ml). The combined extracts were dried, concentrated, and purified by flash chromatography (elution with 35% ethyl acetate in petroleum ether) to give 0.086 g of epoxy lactone 34 (36%); [α]$_{D}^{25}$ +61° (c 1.00, CHCl$_3$); IR (CHCl$_3$, cm$^{-1}$) 3010, 2990, 2890, 1740, 1460, 1340, 1220, 1100, 1070, 1030, 950; $^1$H NMR (300 MHz, CDCl$_3$) δ 5.04 (s, 1H), 3.98 (m, 4H), 2.72 (m, 1H), 2.52 (m, 1H), 2.18-1.75 (series of m, 5H), 1.61 (m, 1H), 1.02 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 170.95, 117.97, 82.03, 69.92, 65.30, 45.62, 35.16, 31.94, 30.71, 29.03, 27.97, 19.08; MS m/z (M$^+$) calcd 240.0998, obsd 240.0992.

$^{(4aS)}$-Hexahydro-4a-methyl-2-oxospirocyclopenta[b]pyran-5(7aH),2'-[1,3]dioxolane]-7a-carboxaldehyde (34).

Epoxy lactone 34 is placed in a Wheaton flask and heated in an oil bath at 175°C for 20 min. The crude mixture of aldehydo lactone 35 could not be purified; IR (CHCl$_3$, cm$^{-1}$) 3010, 2980, 2950, 2890, 1740, 1460, 1085, 950; $^1$H NMR (300 MHz, CDCl$_3$) δ 9.70 (s,
1H), 3.95 (m, 4H), 2.82-1.00 (series of m, 8H), 1.15 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 199.84, 171.50, 114.05, 91.32, 65.39, 65.36, 48.99, 33.83, 25.60, 24.92, 22.26, 17.42; MS/FAB m/z (M$^+$) calcd 240.10, obsd 240.06.

$(1S,7aS)-7,7a$-Dihydro-1-hydroxy-7$\alpha$-methyl-5(6H)-indanone (36).

To a cold solution (0°C) of 30 (10 g, 59.5 mmol) in methanol (150 ml) was added dropwise a solution of sodium borohydride (1.4 g, 37 mmol) in methanol (200 ml). The solution was stirred at 0°C for 90 min and several drops of acetic acid were added. The mixture was concentrated under vacuum, water was added and the mixture was extracted with ether (3 x100 ml), dried, concentrated and purified by flash chromatography (elution with 30% ethyl acetate in petroleum ether) to give 840 g of alcohol 36 (85%); IR (CHCl$_3$, cm$^{-1}$) 3400, 3015, 2980, 2880, 1650, 1460, 1075, 875; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.74 (s, 1 H), 3.80 (t, J=8.3 Hz, 1H), 2.97 (bs, 1H), 2.72-1.68 (series of m, 8H), 1.10 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 199.60, 175.85, 123.14, 80.35, 45.16, 33.99, 33.19, 28.89, 26.44, 14.98; MS m/z (M$^+$) calcd 166.0994, obsd 166.0997.
(1S,7aS)-7,7a-Dihydro-1-hydroxy-7a-methyl-5(6H)-indanone acetate (37).

To a solution of alcohol 36 (0.36 g, 2.17 mmol) in pyridine (5 ml) was added acetic anhydride (0.33 g, 3.25 mmol) and DMAP (50 mg). The mixture was stirred for 16 h at room temperature. Water was added and the mixture was extracted with ether (3 x 10 ml), dried, concentrated and purified by flash chromatography (elution with 30% ethyl acetate in petroleum ether) to give 0.415 g of acetate 37 (92%); IR (CHCl₃, cm⁻¹) 3010, 2980, 2940, 1740, 1660, 1460, 1050, 905; ¹H NMR (300 MHz, CDCl₃) δ 5.74 (s, 1 H), 4.75 (dd, J=4.2, J'=10.8 Hz, 1H), 2.77-1.76 (series of m, 8H), 2.04 (s, 3H), 1.14 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm 198.38, 172.73, 170.41, 123.38, 80.77, 44.46, 34.09, 32.99, 26.49, 26.15, 20.79, 16.39; MS m/z (M⁺) calcd 208.1099, obsd 208.1095.

(1S,7aS)-1-(tert-Butyldiphenylsiloxy)-7,7a-dihydro-7a-methyl-5(6H)-indanone (38).
To a solution of alcohol 36 (0.36 g, 2.17 mmol) in DMF (5 ml) was added tert-butyldiphenylchlorosilane (0.716 g, 2.6 mmol), imidazole (0.35 g) and DMAP (50 mg). The mixture was stirred for 16 h at room temperature. Water was added and the mixture was extracted with ether (3 x 10 ml). The extracts were dried, concentrated and purified by flash chromatography (elution with 20% ethyl acetate in petroleum ether) to give 0.843 g of silyl ether 38 (96%); IR (CHCl₃, cm⁻¹) 3080, 3060, 2960, 2930, 2860, 1660, 1460, 1430, 1120, 830; ¹H NMR (300 MHz, CDCl₃) δ 7.66 (m, 4H), 7.34 (m, 6H), 5.68 (s, 1H), 3.77 (dd, J=4.6 Hz, J'11.2 Hz, 1 H), 2.65-1.40 (series of m, 8H), 1.26 (s, 3H), 1.10 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) ppm 198.97, 174.49, 135.87 (2C), 135.84 (2C), 134.78 (2C), 129.87, 129.75, 127.64 (2C), 127.53 (2C), 123.17, 81.31, 45.82, 34.13, 33.28, 29.29, 26.95 (3C), 26.55, 19.25, 15.61; MS/FAB m/z (M⁺) calcd 388.22, obsd 388.31.

(1S,7aS)-7,7a-Dihydro-1-[(2-methoxyethyl)oxy]-7a-methyl-5(6H)-indanone (40).

To a solution of alcohol 36 (0.27 g, 1.63 mmol) in dichloromethane (20 ml) was added Hünig's base (2.4 ml, 2.6 mmol) and SEM chloride (2.2 ml). The mixture was stirred for 16 h at room
temperature. Water was added and the mixture was extracted with ether (3 x 20 ml), dried, concentrated and purified by flash chromatography (elution with 60% ether in petroleum ether) to give 0.415 g of SEM ether 40 (86%) as a viscous oil; IR (CHCl₃, cm⁻¹) 3020, 2970, 2900, 1660, 1460, 1255, 1060, 1040; ¹H NMR (300 MHz, CDCl₃) δ 5.72 (m, 1H), 4.66 (m, 2H), 3.66 (m, 1H), 3.58 (m, 2H), 2.68-0.84 (series of m, 10H), 1.10 (s, 3H), -0.03 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) ppm 198.84, 174.37, 123.10, 94.16, 84.95, 64.93, 44.76, 34.37, 33.16, 26.77, 26.39, 17.95, 15.77, -1.55 (3C); MS/FAB m/z (M⁺) calcd 296.18, obsd 296.15.

(1S,7aS)-7,7a-Dihydro-7a-methyl-1-[2-(trimethylsilyl)ethoxy]methoxy]-5(6H)-indanone (39).

OMEM

To a solution of alcohol 36 (0.27 g, 1.63 mmol) in dichloromethane (20 ml) was added Hüning's base (2.4 ml, 2.6 mmol) and MEM chloride (2.0 ml). The mixture was stirred for 16 h at room temperature. Water was added and the mixture was extracted with ether (3 x 20 ml), dried, concentrated and purified by flash chromatography (elution with 50% ethyl acetate in petroleum ether) to give 0.323 g of MEM ether 39 (78%) as a viscous oil; IR (CHCl₃, cm⁻¹) 2980, 2880, 1670, 1470; ¹H NMR (300 MHz, CDCl₃) δ
5.59 (m, 1H), 4.63 (m, 2H), 3.55 (m, 3H), 3.38 (m, 2H), 3.21 (s, 3H),
2.56-1.66 (series of m, 8H), 1.00 (s, 3H); \(^{13}\text{C} \text{NMR} \ (75 \text{ MHz, CDCl}_3)
\text{ppm} \ 198.30, \ 173.92, \ 122.76, \ 94.57, \ 84.78, \ 71.27, \ 66.52, \ 58.56,
44.44, \ 34.01, \ 32.83, \ 26.42, \ 26.07, \ 15.47; \ \text{MS m/z} \ (\text{M}^+) \ \text{calcd}
254.1518, \ \text{obsd} \ 254.1518

\((1S,7aS)-1\text{-tert-Butoxy-7,7a-Dihydro-7a-methyl-5(6H)-}
\text{indanone} \ (41).

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To a cold solution (-78°C) of alcohol 36 (0.90 g, 5.42 mmol) in dichloromethane (20 ml) was added liquified isobutylene (40 ml). The mixture was stirred for 16 h at room temperature, cooled to -10°C, and poured into 5% KOH. The mixture was extracted with ether (3 x 40 ml), dried, concentrated and purified by flash chromatography (elution with 60% ether in petroleum ether) to give 0.914 g of the tert-butyl ether 41 (76%) as a viscous oil; \([\alpha]^{25}_D +54.5^\circ \ (c \ 4.80, \ \text{CHCl}_3); \ \text{IR (CHCl}_3, \ \text{cm}^{-1}) \ 3010, \ 2980, \ 2940, \ 1660,
1460, \ 1195, \ 1095, \ 890; \ ^1\text{H} \ \text{NMR (300 MHz, CDCl}_3) \ \delta \ 5.60 \ (s, \ 1H), \ 3.45
(dd, \ J=11.2 \ Hz, \ J'=4.1 \ Hz, \ 1H), \ 2.54 \ (m, \ 1H), \ 2.22 \ (m, \ 3 \ H), \ 1.86 \ (m,
2H), \ 1.61 \ (m, \ 2H), \ 1.04 \ (s, \ 9H), \ 0.97 \ (s, \ 3H); \ ^{13}\text{C} \ \text{NMR (75 MHz, CDCl}_3)
\text{ppm} \ 198.68, \ 174.87, \ 122.50, \ 79.34, \ 72.61, \ 44.46, \ 34.03, \ 33.05,
29.27, 28.33, 26.50 (3C), 15.37; MS m/z (M+-[C₄H₈]) calcd 166.0994, obsd 166.0996.

(1S,7aS)-1-tert-Butoxy-7,7a-Dihydro-4α,5-epoxy-A-homo-4-oxa-7a-methyl-5(6H)-indanone (42).

To a solution of enone 41 (0.20 g, 0.9 mmol) in dichloromethane (50 ml) was added sodium carbonate (1.70 g) and MCPBA (0.80 g, 3 mmol). The mixture was refluxed for 1 day, quenched with water, and extracted with ether (3 x 60 ml). The extracts were dried, concentrated and purified by flash chromatography (elution with 60% ether in petroleum ether) to give 0.124 g of epoxy lactone 42 (54%) as a waxy white solid; [α]²⁵⁺ +41° (c 1.89, CHCl₃); IR (CHCl₃, cm⁻¹) 2980, 2940, 2880, 1755, 1460, 1365, 1080; ¹H NMR (300 MHz, CDCl₃) δ 4.93 (s, 1H), 3.42 (t, J=6.2 Hz, 1H), 2.52 (t, J=5.1 Hz, 2 H), 1.93-1.18 (series of m, 6H), 1.15 (s, 9H), 1.01 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm 171.08, 83.55, 76.42, 73.38, 71.11, 44.42, 30.67, 29.85, 29.12, 28.43 (4C), 18.32; MS m/z (M+-[C₄H₈]) calcd 198.0892, obsd 198.0896.
(4aS,5S)-4,4a,5,6,7,8-Hexahydro-5-hydroxy-4a-methyl-2(3H)-naphthalenone (43).

To a solution of Wieland-Miescher ketone (1.0 g, 5.6 mmol) in methanol (30 ml) at 0°C was added dropwise a solution of sodium borohydride (0.14 g, 3.7 mmol) in methanol (20 ml). The solution was stirred at 0°C for 30 min and several drops of acetic acid were added. The mixture was concentrated under vacuum, water was added, and the mixture was extracted with ether (3 x 20 ml), dried, concentrated, and purified by flash chromatography (elution with 30% ethyl acetate in petroleum ether) to give 0.980 g (97%) of alcohol 43 as a colorless oil; [α]$_{25}^{25}$D $+183^\circ$ (c 1.70, CHCl$_3$); IR (CHCl$_3$, cm$^{-1}$) 3600, 3450, 2990, 2940, 2870, 1665, 1620, 1460, 1205, 1060; $^1$H NMR (300 MHz, CDCl$_3$) δ 5.73 (s, 1H), 3.37 (dd, $J$=11.5 Hz, $J'$=4.4 Hz, 1H), 2.66 (bs, 1H), 2.45-2.10 (series of m, 6H), 1.82 (m, 2H), 1.64 (m, 1H), 1.45 (m, 1H), 1.15 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 199.84, 169.04, 125.17, 77.95, 41.58, 34.10, 33.59, 31.96, 30.09, 23.08, 15.19; MS m/z (M$^+$) calcd 180.1150, obsd 180.1167.
(4aS,5S)-5-tert-Butoxy-4,4a,56,7,8-hexahydro-4a-methyl-2(3H)-naphthalenone (44).

To a cold (-78 °C) solution of alcohol 43 (0.90 g, 5.42 mmol) in dichloromethane (20 ml) was added liquified isobutylene (40 ml). The mixture was stirred for 16 h at room temperature, then cooled to -10°C and poured into dilute KOH solution. The mixture was extracted with ether (3 x 40 ml), dried, concentrated, and purified by flash chromatography (elution with 60% ether in petroleum ether) to give 0.914 g of tert-butyl ether 44 (76%) as a viscous oil; [α]_D^{25} +108° (c 4.05, CHCl₃); IR (CHCl₃, cm⁻¹) 3010, 2980, 2880, 1660, 1620, 1460, 1370, 1195, 1080; ^1H NMR (300 MHz, CDCl₃) δ 5.69 (s, 1H), 3.15 (dd, J=11.2 Hz, J'=4.1 Hz, 1H), 2.30 (m, 2 H), 2.15 (m, 1H), 2.05 (m, 1H), 1.75 (m, 5H), 1.31 (m, 1H), 1.13 (s, 9H), 1.11 (s, 3H); ^13C NMR (75 MHz, CDCl₃) ppm 199.60, 169.40, 124.82, 77.36, 73.32, 41.54, 34.69, 33.87, 32.23, 30.22, 29.00 (3C), 22.99, 16.18; MS/FAB m/z (M⁺+1) calcd 237.36, obsd 237.26.
(4aS,5S)-5-tert-Butoxy-4,4a,56,7,8-hexahydro-2α,3-epoxy-A-homo-2-oxa-4a-methyl-2(3H)-naphthalenone (45).

To a solution of enone 44 (0.120 g, 0.51 mmol) in dichloromethane (30 ml) was added sodium bicarbonate (0.40 g) and MCPBA (0.26 g, 1.5 mmol). The mixture was refluxed for 1 day, quenched with water, extracted with ether (3 x 60 ml), dried, concentrated, and purified by flash chromatography (elution with 40% ether in petroleum ether) to give 0.086 g of epoxy lactone 45 (63%); IR (CHCl$_3$, cm$^{-1}$) 2980, 2950, 2870, 1750, 1460, 1195, 1090; $^1$H NMR (300 MHz, CDCl$_3$) δ 4.75 (s, 1H major), 4.67 (s, 1H minor), 3.42 (dd, J=4.2 Hz, J'=10.6 Hz, 1H), 2.54 (m, 2 H), 1.97-1.03 (series of m, 8H), 1.16 (s, 9H), 1.14 (s, 3H major), 1.12 (s, 3H minor); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 171.68, 171.55, 87.48, 84.81, 74.22, 73.91, 73.67, 73.57, 72.33, 69.63, 41.41, 41.00, 31.29, 31.08, 30.75, 29.62, 29.47, 29.24, 29.19 (6C), 28.99, 27.45, 19.84, 19.02, 17.54, 16.39; MS m/z (M$^+$-[C$_4$H$_8$]) calcd 212.1048, obsd 212.1081.
(4aR,5S)-5-tert-Butoxy-8a-formylhexahydro-4a-methyl-hydrocoumarin (46).

To a solution of epoxy lactone 45 (80 mg, 0.299 mmol) in methylene chloride (10 ml) was added trifluoroacetic acid (10 drops). The mixture was stirred for 24 h at room temperature and diluted with ether. The solution was washed with a saturated solution of sodium bicarbonate, dried, concentrated and purified by flash chromatography (elution with 15% ethyl acetate in petroleum ether) to give 70.5 mg of aldehydo lactone 46 (88%) as a white solid; mp 132-135°C; IR (CHCl₃, cm⁻¹) 2980, 2880, 1735, 1460, 1195; ¹H NMR (300 MHz, CDCl₃) δ 9.87 (s, 1H major), 9.63 (s, 1H minor), 3.77 (dd, J=10.6 Hz, J'=4.4 Hz, 1H major), 3.46 (dd, J=10.2 Hz, J'=4.2 Hz, 1H minor), 2.60 (m, 2H), 2.20-1.08 (series of m, 8H), 1.16 minor, 1.14 major (s, 9H), 1.04 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm 200.06, 199.05, 171.23, 171.05, 90.96, 88.99, 73.71, 73.58, 71.92, 67.61, 41.25, 38.39, 29.31, 29.19, 29.07 (3C), 28.85 (3C), 28.17, 27.21, 26.66, 26.58, 26.15, 18.52, 18.36, 16.61, 13.16 (one signal not observed); MS m/z (M⁺-[C₄H₈]) calcd 212.1049, obsd 212.1031.
Anal. Calcd for C\textsubscript{15}H\textsubscript{24}O\textsubscript{4}: C, 67.14; H, 9.01. Found: C, 66.96; H, 9.01.

\((4aR,5S)-5\text{-}\text{tert-}B\text{utoxyhexahydro-4a-methyl-2-methylene-8a-vinylchroman} \ (47)\). 

A solution of aldehyde lactone 46 (53 mg, 0.20 mmol), pyridine (3 drops), THF (2 ml) and dichloromethane (1 ml) was prepared under argon. The mixture was cooled to -40°C and 0.5M Tebbe reagent (1.0 ml, 0.5 mmol) in toluene was added dropwise. The solution was kept for 15 min at this temperature, then warmed to 25°C, stirred for 90 min at this temperature before being cooled to -40°C and quenched with 10% KOH solution (1 ml). A 0.5% triethylamine solution in ether was added and the mixture was filtered through a pad of basic alumina (act III). Most of the solvent was evaporated and the residue was purified by chromatography on basic alumina (act III) (elution with pentane) to provide 43.3 mg of allyl vinyl ether 47 (63%) as a light yellow oil; IR (neat, cm\textsuperscript{-1}) 3050, 2970, 2930, 2870, 1670, 1460, 1260, 1190, 1060; \textsuperscript{1}H NMR (300 MHz, C\textsubscript{6}D\textsubscript{6}) δ 6.10 (dd, J=17.1 Hz, J'=11.0 Hz, 1H), 5.63 (dd, J=17.1 Hz, J'=1.9 Hz, 1H), 5.23 (dd, J=11.0 Hz, J'=1.2 Hz, 1H), 4.52 (d,
J=1.8 Hz, 1H); 4.11 (d, J=1.7 Hz, 1H), 3.29 (m, 1H), 2.50 (m, 1H), 2.41 (m, 1H), 1.90 (m, 2H), 1.59-0.92 (series of m, 6 H), 1.24 (s, 9H), 1.02 (s, 3H); 13C NMR (75 MHz, C₆D₆) ppm 157.68, 140.16, 117.74, 89.69, 81.55, 73.34, 72.78, 31.34, 34.78, 30.25, 29.14, 29.03 (3C), 24.56, 19.81, 13.74; MS m/z (M+-[C₄H₈]) calcd 208.1463, obsd 208.1445.

(4S,4aS)-4-tert-Butoxy-1,2,3,4,4a,5,6,7,8,9-decahydro-4a-methyl-7-benzocyclooctenol (48).

To a solution of allyl vinyl ether 47 (42 mg, 0.16 mmol) in dichloromethane (2 ml) was added at room temperature and under argon a solution of Tribal in toluene (0.8 ml, 0.8 mmol). The mixture was stirred for 6 h and ether was added, followed by water. After the usual extractive work-up with ether and purification by flash chromatography (elution with 30% ether in petroleum ether) 26.2 mg (62%) of alcohol 48 was obtained as a viscous oil; IR (CHCl₃, cm⁻¹) 3600, 3005, 2980, 2940, 2860, 1460, 1190, 1060, 1010; ¹H NMR (300 MHz, CDCl₃) δ 5.34 (m, 1H), 4.07 (m, 1H major), 3.97 (m, 1H minor), 3.39 (dd, J=10.9 Hz, J'=4.5 Hz, 1H major), 3.18 (dd, J=10.7 Hz, J'=4.4 Hz, 1H minor), 2.68 (bs, 1H major), 2.49 (bs, 1H major), 2.36-0.87 (series of m, 14 H), 1.18 (2s, 9H), 1.04 (2s, 3H); ¹³C NMR (62.5 MHz, CDCl₃) ppm For the major: 145.32, 121.85, 73.08, 72.75, 65.30,
46.71, 36.14, 35.96, 35.89, 32.33, 30.82, 30.66, 29.52 (3C), 23.00, 22.21; MS m/z (M⁺-[C₄H₈]) calcd 210.1620, obsd 210.1628.

\((4S,4aS)-4\text{-tert-Butoxy-1,2,3,4,4a,5,6,7,8,9-decahydro-4a-methyl-7-benzocyclooctenone}\) (49).

\[
\text{\includegraphics[width=0.3\textwidth]{cyclooctenone.png}}
\]

To a solution of DMSO (200 µl) in dichloromethane (2 ml) was added at -78°C and under argon oxaly chloride (100 µl). The mixture was stirred for 15 min and a solution of octenol 48 (25 mg, 0.094 mmol) in dichloromethane (2 ml) was added. The mixture was warmed to -45°C, stirred for 20 min, cooled to -78°C and quenched by addition of triethylamine (400 µl). The mixture was allowed to warm to room temperature and water was added. After the usual extractive work-up with ether and purification by flash chromatography (elution with 5% ether in petroleum ether) 20.8 mg of cyclooctenone 49 (84%) was obtained as a viscous oil; \([\alpha]_{D}^{25} +46°\) (c 0.55, CHCl₃); IR (CHCl₃, cm⁻¹) 3010, 2980, 2940, 2860, 1695, 1460, 1190 ,1080; \(^1\)H NMR (300 MHz, CDCl₃) δ 5.39 (t, J=8.2 Hz, 1H), 3.31 (dd, J=10.8 Hz, J'=4.6 Hz, 1H), 2.53 (m, 4H), 2.26 (m, 4H), 1.86 (m, 2H), 1.69-1.10 (series of m, 4 H), 1.17 (s, 9H), 1.08 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl₃) ppm 213.65, 145.95, 121.36, 74.26, 73.09,
46.73, 43.72, 40.70, 35.56, 32.27, 30.21, 29.35 (3C), 24.52, 22.85, 19.71; MS m/z (M+-[C₄H₈]) calcd 208.1463, obsd 208.1441.
REFERENCES


CHAPTER III
RING EXPANSION BY TANDEM DOUBLE TEBBE-CLAISEN TECHNOLOGY

A. INTRODUCTION

Since their initial characterization, natural products possessing fused eight-membered rings have attracted considerable synthetic attention\(^1\) because of their interesting structural features and their significant biological activities.\(^2\) The aliphatic Claisen rearrangement, which is a versatile synthetic tool,\(^3\) represents an attractive route for accessing medium-ring unsaturated ketones by ring expansion.\(^4\) However this methodology has only been explored recently and requires long muti-step protocols.\(^5\,6\) The new scheme, disclosed in the previous chapter, is short, dependable and efficient, and therefore worthy of further investigation. Our purpose was to explore the capability of incorporating an eight-membered ring in steroid carbon skeletons along with a comparative study between the thermal\(^1(e)\,5\,7\) and aluminum-promoted\(^6\,8\) [3,3] sigmatropic processes.
B. RESULTS AND DISCUSSION

The strategy for effecting the ring expansion, as elucidated in synthetic studies directed toward ceroplastol I, includes three key transformations. First, the exhaustive peracidic oxidation of enone 1 with $m$-chloroperbenzoic acid (Baeyer-Villiger reaction and epoxidation) to provide epoxy lactone 2 which easily isomerized to aldehydo lactone 3. Although this conversion can be effected in one pot, yields usually improve if epoxy lactone is first isolated. Subsequent condensation of both carbonyl groups in aldehydo lactone 3 with the Tebbe reagent \(^{11}\) ([bis(cyclopentadienyl)-titanium]($\mu$-chloro)($\mu$-methylene)dimethylaluminum) results in efficient methylenation and the formation of 4. This first example of a double Tebbe olefination sets the stage for $[3,3]$ sigmatropic bond reorganization. Finally, the Tribal-promoted Claisen rearrangement\(^{8}\) is completed during 6 h at room temperature and gives a good yield of diastereoisomeric cyclooctenols 5, which provide cyclooctenone 6 under Swern conditions\(^{12}\) (Scheme 38). The overall process results in the intercalation of a $\text{CH}_2$-$\text{CH}_2$ unit between the original C-1 and C-2 atoms of a 2-cyclohexenone. Each methylene part of this carbon unit is provided by the double olefination and subsequently linked by the Claisen rearrangement.
Scheme 38: Ring Enlargement by Two-Carbon Intercalation.

Interesting peculiarities of intermediates and reactions conditions from this scheme include the following. The formation of epoxy lactone usually leads to a mixture of isomers, the stereochemical assignments to which can be easily assigned from their $^1$H NMR spectra as outlined in Figure 7. The chemical shift of the proton in the $\alpha$-epoxy lactone isomer appears as a singlet at 4.75 ppm and is more shielded in the $\beta$-isomer (4.67 ppm). This observation also extends to the aldehydic proton of the isomerized product which is seen at 9.63 ppm for the cis-fused isomer and at 9.87 ppm for the more thermodynamically stable trans compound.$^{13}$
Figure 7: Stereochemical Recognition of Epoxy Lactones and Aldehydo Lactones from their $^1$H NMR Chemical Shift Data.

Isomerization to the aldehydo lactone can be conveniently performed under a wide variety of conditions. Although in this study, the acid-catalyzed rearrangement has been used principally, acid-sensitive compounds can be isomerized under neutral (165°C for 15 min) or basic conditions (aqueous methanolic sodium hydroxide at 0°C).\textsuperscript{14}

The double Tebbe reaction did require some experimentation to successfully prevent the internalization of the vinyl ether double bond. This olefinic migration of the exocyclic double bond to an endocyclic position is thermodynamically driven and known to occur with ease.\textsuperscript{1(c)} Moreover, this prototropic isomerization has been found to be catalyzed by the aluminum reagent. It is therefore essential that only a slight excess of the Tebbe reagent (2.5 equivalent) be used, and that the quenched reaction mixture be purified as rapidly as possible. Each olefination can be done separately if desired, by initial Wittig condensation to provide 7
followed by Tebbe methylenation. This two-step process does not reduce the level of isomerization, but eventually permits the introduction of two differently functionalized olefinic moieties. Freshly prepared Tebbe reagent is equally important to minimize isomerization and to obtain cleaner reaction mixtures. Finally, all glassware used for this reaction must be base-washed. This consideration extends to the NMR tubes utilized for spectral analysis. Otherwise, the cis and trans allyl vinyl ethers slowly isomerize in deuterated benzene, but at different rates as shown in Table 3.

**Table 3 : Different Rates of Isomerization of Vinyl Ethers 4.**

<table>
<thead>
<tr>
<th>Time</th>
<th>Cis Isomer</th>
<th>Trans Isomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>t=0</td>
<td>30%</td>
<td>70%</td>
</tr>
<tr>
<td>t=36h</td>
<td>15%</td>
<td>50%</td>
</tr>
<tr>
<td>t=5d</td>
<td>0%</td>
<td>25%</td>
</tr>
<tr>
<td>t=15d</td>
<td>0%</td>
<td>6%</td>
</tr>
</tbody>
</table>

The Tribal-promoted Claisen rearrangement takes 6 h to go to completion and must be performed at room temperature. The few attempts to run this reaction at lower temperatures (-78°C and
-20°C) resulted only in isomerization of the allyl vinyl ether. The [3,3] sigmatropic product is constituted of a diastereoisomeric mixture of cyclooctenols which is oxidized under Swern conditions. The direct conversion of 4 to cyclooctenone 6 can be thermally accomplished in based-coated soft glass tubes at 190°C for 48 h. In pyrex tubes, the starting material is completely isomerized before rearranging. If organometallic residues from the Tebbe reagent remain, the prototropic isomerization becomes the dominant pathway. Isomeric ketone 8 and isomerized vinyl ether 9 are then the predominant components. Consequently, the purification of 4 is critical in order to produce a good yield of eight-membered 6 (Scheme 39).

**Scheme 39 : Different Products from the Thermal Process of 4.**

Octalone 10, a somewhat simpler example, was oxidized with MCPBA according to the DeBoer and Ellwanger protocol, and the resulting product was isomerized in the presence of trifluoroacetic...
acid to provide trans-fused aldehydo lactone 11. Subsequent double condensation with the Tebbe reagent provided ether 12 in good yield (69%). The efficiency in this case is lower than usual, probably because of product volatility. The presence of an excess of Tribal (5 equiv) induces acceleration of the Claisen process and delivers within 15 min at room temperature the stereochemically pure cyclooctenol 13. Ensuing Swern oxidation affords cylooctenone 14 in 82% isolated yield. Direct conversion of 12 to 14 by thermal activation occurred at 180°C (Scheme 40). The desired product was contaminated with only a small amount (12.9%) of isomeric ketone 15 if the Claisen precursor was sufficiently freed of traces of remaining transition metal arising from the Tebbe reagent.

Scheme 40: Two-Carbon Intercalation for \( \Delta^{1,9} \) Octalone 10.
At this stage, a few interesting observations can be cited. The Tribal-promoted Claisen rearrangement of 4 occurs approximately 20 times slower than that of 12. Similarly, the thermal process involving 12 takes place at lower temperature, for a shorter period of time, and with total disappearance of starting material. The isomerized vinyl ether 16 has been characterized by acidic treatment of 12. It is believed that this kinetic retardation is not due to the added ether functionality, but to the presence of the angular methyl group which greatly enhances steric congestion. It should also be noted that, in contrast to the thermal approach, the charge-accelerated process is not sensitive to the presence of remaining transition metal impurities.

To further explore this retardation effect, manool 17 served as starting material. Following Grant's procedure,16 manool 17 was converted to aldehydo lactone 18 and subsequently to cyclooctenone 19. Again the same facility for either of the Claisen processes was observed and attributed to the absence of an alkyl group at the proximal angular site (Scheme 41).

**Scheme 41** : Ring Expansion of the Manool Skeleton.
To fully implement the synthetic versatility of the two-carbon intercalation process, the ring enlargement was tested on steroidal frameworks. The hydroxyl group of testosterone (20) was first protected as the tert-butyldiphenylsilyl ether 21. Oxidation of the enone moiety with MCPBA in refluxing dichloromethane delivered a stereoisomeric mixture 22, which isomerized to 23 when admixed with a catalytic amount of d-camphor-10-sulfonic acid in benzene. Double condensation with Tebbe reagent and subsequent Tribal-promoted rearrangement of 24 delivered cyclooctenol 25 in 64% yield. The same kinetic retardation was observed. In this instance, a few different types of aluminum reagent such diethylaluminum chloride with triphenyl phosphine\(^8\) or methylaluminum bis(4-bromo-2-6,di-\(\text{tert}\)-butylphenoxide),\(^{17}\) were tried without success. Swern oxidation furnished cyclooctenone 26, which was also directly obtained by thermal bond reorganization of 24. This process exhibits a competitive [1,3] hydrogen migration, probably catalyzed by residual Tebbe by-products, and consequently along with 26, isomeric ketone 27 and isomerized vinyl ether 28 are isolated (Scheme 42).
Scheme 42: Ring Enlargement for Testosterone.

The 17β-methyl homologue 30 can be oxidized without hydroxyl group protection to give epoxy lactone 31. The latter was isomerized to 32 with a catalytic amount of camphorsulfonic acid. Under the harsher action of anhydrous perchloric acid in dichloromethane, dehydration of the tertiary alcohol and Wagner-
Meerwein shift occurred to deliver aldehydo lactone 33.\textsuperscript{1,8} Treatment with Tebbe reagent provided, in excellent yield, the allyl vinyl ether 34, which when exposed to an excess of Tribal underwent smooth bond reorganization within 6 h at room temperature to give Claisen product 35. Since additional oxygen substituents are not present in 34, the kinetic retardation has to be attributed to the steric hindrance imposed by the angular methyl substituent. Swern oxidation delivered cyclooctenone 36, which was also prepared by thermal activation of 34. The latter reaction also gave minor amounts of isomeric ketone 37 and isomerized vinyl ether 38 (Scheme 43).

As previously observed,\textsuperscript{1(e)} distinction between the cyclooctenone and its isomeric ketone can be readily accomplished for every case studied on the basis of the respective IR absorption (1700 vs 1705 cm\textsuperscript{-1}) and the presence of an acetyl methyl singlet in the 1H NMR of the methyl ketone.
Scheme 43: Dehydration and Ring Enlargement of 30.

1. (HClO₄)
2. Tebbe

33 X=O
34 X=CH₂

190°C
48 h

34

35

36

38

33

39

H₂C=O
CH=CH₂

OH

MCPBA

CHO

OH

(CSA)
C. CONCLUSION

The methodology herein described provides short and effective access to 4-cyclooctenones from 2-cyclohexenones. The overall ring enlargement procedure results in the intercalation of a two-carbon unit into the enone moiety. These carbons are simultaneously introduced by an unparalleled application of double-Tebbe olefination and connected by Claisen bond reorganization. The less sterically hindered examples undergo very efficient [3,3] sigmatropy when thermally activated. The presence of a quaternary center in close proximity to the reacting site gives rise to significant kinetic retardation. Consequently, the alkylaluminum-accelerated rearrangement becomes more attractive. Only recently has this procedure, which allows Claisen processes to be conducted routinely at room temperature, attracted attention as the cationic counterpart of the well-established anionic oxy-Cope process.\textsuperscript{19} The tandem double Tebbe-Claisen technology has proven its effectiveness by the successful incorporation of an eight-membered ring into the carbocyclic framework of steroids. The initial efforts to develop this methodology should be followed by additional useful and interesting synthetic applications in the near future.
EXPERIMENTAL

Thermal Claisen Rearrangement of 4.

A solution of allyl vinyl ether 4 (78 mg, 0.295 mmol) in toluene (1 ml) was sealed under vacuum in a potassium hydroxide-coated soft glass tube (8 mm O.D.) and heated at 190°C for 48 hr. The tube was opened and rinsed three times with ether. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel (elution with 5% ether in petroleum ether) and provided 10.3 mg of isomerized vinyl ether 9 (13.2%), 21.0 mg of methyl ketone 8 (26.9%) and 38.5 mg of cyclooctenone 6 (49.3%).

(4aR,5S)-5-tert-Butoxy-4a,5,6,7,8,8a-hexahydro-2,4a-dimethyl-8a-vinyl-4H-1-benzopyran  (9).
For isomerized allyl vinyl ether 9; IR (CHCl₃, cm⁻¹) 3080, 3010, 2980, 2930, 2880, 1680, 1465, 1195, 1060, 740; ¹H NMR (300 MHz, CHCl₃) δ 6.16 (dd, J=10.9 Hz, J'=17.0 Hz, 1H major), 5.93 (dd, J=10.9 Hz, J'=17.3 Hz, 1H minor), 5.28 (dd, J=1.8 Hz, J'=17.0 Hz, 1H major), 5.22 (dd, J=1.8 Hz, J'=10.9 Hz, 1H major), 5.10 (dd, J=1.7 Hz, J'=17.3 Hz, 1H minor), 4.41 (m, 1H major); 4.11 (m, 1H minor), 3.49 (dd, J=4.3 Hz, J'=10.9 Hz, 1H minor), 3.47 (dd, J=5.1 Hz, J'=10.5 Hz, 1H major), 1.88-0.88 (series of m, 8 H), 1.74 (2s, 3H), 1.16 (2s, 9H), 0.95 (2s, 3H); ¹³C NMR (75 MHz, CHCl₃) ppm For the major: 147.51, 138.03, 114.23, 95.84, 80.99, 73.07, 72.84, 39.50, 33.36, 31.73, 30.25, 29.06 (3C), 19.84, 19.64, 13.28; MS m/z (M⁺-[C₄H₈]) calcd 208.14632, obsd 208.1448.

(8'S,8'aS)-8'-tert-Butoxy-1',2',3',5',6',7',8',8'a-octahydro-8'a-methyl-2'-acetonaphtalene (8).
212.19, 211.98, 144.34, 142.96, 119.14, 118.47, 78.91, 73.35, 72.02, 44.75, 44.53, 41.58, 41.17, 39.80, 34.88, 31.70, 31.47, 31.07, 29.69, 29.29 (3C), 29.20 (3C), 28.28, 28.09, 27.89, 27.52, 26.10, 24.58, 20.89, 18.28 (one signal not observed); MS m/z (M+-[C4H8]) calcd 208.1463, obsd 208.1451.

(4aR,5S)-5-tert-Butoxyhexahydro-4a-methyl-8a-vinylhydrocoumarin (7).

To a solution of methyltriphenylphosphonium bromide (357 mg, 1 mmol) in THF (3 ml) at -10°C was added KHMDS (1.90 ml, 0.95 mmol). The mixture was stirred for 30 min and a solution of aldehydo lactone 3 (0.15 g, 0.71 mmol) in THF (1 ml) was added. The reaction mixture was stirred for 1 h at room temperature and quenched with water. After the usual extractive work-up with ether and purification by flash chromatography (elution with 5% ether in petroleum ether) 138 mg (93% yield) of vinyl lactone 2 was obtained as a white solid; mp 110°C; IR (CHCl₃, cm⁻¹) 3010, 2970, 2870, 1720, 1460, 1190, 1000, 910; ¹H NMR (300 MHz, CHCl₃) δ 6.40 (dd, J=11.1 Hz, J'=17.0 Hz, 1H major), 6.02 (dd, J=11.0 Hz, J'=17.2 Hz, 1H minor), 5.38 (dd, J=1.1 Hz, J'=17.0 Hz, 1H major), 5.32
A solution of aldehydo lactone 11 (68.0 mg, 0.37 mmol), pyridine (3 drops), THF (2 ml) and dichloromethane (1 ml) was prepared under argon. The mixture was cooled to -40°C and 0.5M Tebbe reagent (1.9 ml, 0.95 mmol) in toluene was added dropwise. The solution was kept for 15 min at this temperature, then warmed to 25°C, stirred for 90 min at this temperature before being cooled to -40°C, and quenched with 10% KOH solution (1 ml). A 0.5% triethylamine solution in ether was added and the mixture was filtered through a pad of basic alumina (act III). Most of the solvent was evaporated and the residue was purified by chromatography.
on basic alumina (act III) (elution with pentane) to provide 45.9 mg (69%) of allyl vinyl ether 12 as a light yellow oil; IR (neat, cm\(^{-1}\)) 3010, 2940, 2860, 1640, 1460, 1260, 1140, 1020; \(^1\)H NMR (300 MHz, C\(_6\)D\(_6\)) \(\delta\) 5.87 (dd, \(J=17.4\) Hz, \(J'=11.0\) Hz, 1H), 5.61 (dd, \(J=17.4\) Hz, \(J'=2.1\) Hz, 1H), 5.27 (dd, \(J=11.0\) Hz, \(J'=2.1\) Hz, 1H), 4.50 (s, 1H), 4.12 (t, \(J=2.3\) Hz, 1H), 2.20 (m, 2H), 1.97 (m, 1H), 1.64 (m, 1H), 1.47 (m, 3H), 1.33-0.92 (series of m, 6 H); \(^13\)C NMR (75 MHz, C\(_6\)D\(_6\)) ppm 157.68, 137.09, 117.74, 91.52, 79.53, 43.42, 40.65, 29.29, 29.07, 25.83, 25.08, 22.98; MS \(m/z\) (M\(^+\)) calcd 178.1358, obsd 178.1346.

\((4aS,8aS)-4a,5,6,7,8,8a\)-hexahydro-2-methyl-8a-vinyl-4\(H\)-1-benzopyran (16).

Allyl vinyl ether 12 was isomerized in an NMR tube with CHCl\(_3\) as solvent; IR (CHCl\(_3\), cm\(^{-1}\)) 3080, 3010, 2980, 2930, 2880, 1680, 1465, 1195, 1060, 740; \(^1\)H NMR (300 MHz, CHCl\(_3\)) \(\delta\) 5.87 (dd, \(J=17.4\) Hz, \(J'=11.0\) Hz, 1H), 5.61 (dd, \(J=17.4\) Hz, \(J'=2.1\) Hz, 1H), 5.27 (dd, \(J=11.0\) Hz, \(J'=2.1\) Hz, 1H), 4.50 (s, 1H), 4.12 (t, \(J=2.3\) Hz, 1H), 2.20 (m, 2H), 1.97 (m, 1H), 1.64 (m, 1H), 1.47 (m, 3H), 1.33-0.92 (series of m, 6 H); \(^13\)C NMR (75 MHz, CHCl\(_3\)) ppm 142.49, 135.51, 114.80, 111.99, 93.06, 37.45, 35.28, 27.60, 26.02, 25.64, 21.41, 20.09; MS \(m/z\) (M\(^+\)) calcd 178.1358, obsd 178.1346.
(4aS)-1,2,3,4,4a,5,6,7,8,9-Decahydr0-7-benzocyclooctenol (12).

To a solution of allyl vinyl ether 12 (74 mg, 0.42 mmol) in dichloromethane (2 ml) was added, at room temperature and under argon a solution of Tribal in toluene (2 ml, 2 mmol). The mixture was stirred for 15 min and ether was added followed by water. After the usual extractive work-up with ether and purification by flash chromatography (elution with 30% ether in petroleum ether) 64.4 mg (86%) of alcohol 13 was obtained; IR (CHCl₃, cm⁻¹) 3600, 3010, 2940, 2860, 1460, 1230, 1010; ¹H NMR (300 MHz, CDCl₃) δ 5.35 (t, J=8.0 Hz, 1H), 3.93 (m, 1H), 2.76 (m, 1H), 2.50 (m, 1H), 2.14-1.79 (series of m, 16H); ¹³C NMR (75 MHz, CDCl₃) ppm 141.85, 122.11, 71.27, 38.86, 36.40, 35.19, 32.49, 32.18, 30.20, 26.70, 22.17, 21.42; MS m/z (M⁺) calcd 180.1514, obsd 180.1551.

(4aS)-2,3,4,4a,5,6,7,8,9-Octahydro-7-benzocyclooctenone (13).
To a solution of DMSO (200 μl) in dichloromethane (2 ml) was added at -78°C and under argon oxalyl chloride (100 μl). The mixture was stirred for 15 min and a solution of octenol 13 (30 mg, 0.17 mmol) in dichloromethane (2 ml) was added. The mixture was warm to -45°C, stirred for 20 min, cooled back to -78°C and quenched by addition of triethylamine (400 μl). The mixture was allowed to warmed to room temperature and water was added. After the usual extractive work-up with ether and purification by flash chromatography (elution with 5% ether in petroleum ether), 25.5 mg of ketone 14 (86% yield) was obtained; IR (CHCl₃, cm⁻¹) 3005, 2940, 2860, 1695, 1460; ¹H NMR (300 MHz, CDCl₃) δ 5.52 (t, J=6.4 Hz, 1H), 2.57-0.77 (series of m, 17 H); ¹³C NMR (75 MHz, CDCl₃) ppm 215.74, 142.46, 121.56, 48.22, 39.82, 34.57, 31.84, 31.07, 26.66, 26.53, 22.50, 21.51; MS m/z (M⁺) calcd 178.1358, obsd 178.1358.


Thermal Claisen Rearrangement of 12.

A solution of allyl vinyl ether 12 (63 mg, 0.354 mmol) in toluene (1 ml) was sealed under vacuum in a potassium hydroxide-coated soft glass tube (8 mm O.D.) and heated at 180°C for 24 hr. The tube was opened and rinsed three times with ether. After evaporation of solvent, the residue was purified by flash
chromatography on silica gel (elution with 5% ether in petroleum ether) and provide 8.1 mg of methyl ketone 15 (12.9%) and 46.2 mg of cyclooctenone 14 (73.3%).

(8'aS)-1',2',3',5',6',7',8',8'a-Octahydro-2'-acetonaphthone (15).

For methyl ketone 15; IR (CHCl₃, cm⁻¹) 3005, 2950, 2860, 1705, 1460, 1360, 1210, 1170, 915; ¹H NMR (300 MHz, CDCl₃) δ 5.31 (m, 1H), 2.51 (m, 1H), 2.12 (s, 3H), 2.21-0.81 (series of m, 13 H); ¹³C NMR (75 MHz, CDCl₃) ppm 211.60, 211.51, 141.39, 140.46, 117.49, 116.24, 47.55, 44.70, 37.55, 36.39, 35.63, 35.07, 35.04, 34.73, 33.42, 31.61, 28.36, 27.89, 27.70, 27.46, 27.33, 26.87, 26.55, 25.99; MS m/z (M⁺) calcd 178.1358, obsd 178.1376.

17β-(tert-Butyldiphenylsiloxy)androstan-4-en-3-one (21).
To a solution of testosterone (20) (0.288 g, 1 mmol) in DMF (1 ml) was added t-butyldiphenylchlorosilane (0.33 g, 1.2 mmol), imidazole (150 mg) and DMAP (15 mg). The mixture was stirred for 16 h at room temperature. Water was added and the mixture was extracted with ether (3 x 10 ml), dried, concentrated and purified by flash chromatography (elution with 10% ethyl acetate in petroleum ether) to give 0.500 g of silyl ether 21 (95%) as a white solid; mp 138 °C; [α]_D^{25} +12.7° (c 0.56, CHCl_3); IR (CHCl_3, cm⁻¹) 3070, 3040, 2960, 2860, 1660, 1615, 1470, 1360, 1140, 1115, 1090, 830; \(^1\)H NMR (300 MHz, CDCl_3) δ 7.69 (m, 4H), 7.38 (m, 6H), 5.72 (s, 1H), 3.68 (t, J=8.2 Hz, 1 H), 2.35 (m, 4H), 2.00 (m, 1H), 1.82-0.79 (series of m, 14H), 1.18 (s, 3H), 1.12 (s, 9H), 0.95 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl_3) ppm 199.22, 171.10, 135.81 (2C), 135.78 (2C), 134.72, 129.40, 129.34, 127.41, 127.30 (2C), 127.25 (2C), 123.64, 82.13, 53.74, 49.62, 43.42, 38.47, 36.56, 35.56, 33.78, 32.64, 31.39, 30.63, 26.98 (3C), 26.51, 23.35, 20.58, 19.19, 17.26, 11.57; MS FAB \(m/z\) (M⁺+1) calcd 527.33, obsd 527.32.

\(17\beta-(\text{tert-Butyldiphenylsiloxy})-4\alpha,5\text{-epoxy-}A\text{-homo-4-oxaandrostan-3-one} \ (22)\).
To a solution of enone 21 (1.052 g, 2 mmol) in dichloromethane (40 ml) was added sodium carbonate (3.00 g) and MCPBA (2.16 g, 6 mmol). The mixture was stirred for 14 hr at reflux, quenched with water, extracted with ether (3 x 60 ml), dried, concentrated, and purified by flash chromatography (elution with 5% ethyl acetate in petroleum ether) to give 0.715 g of epoxy lactone 22 (64%) as a white solid; mp 52°C; IR (CHCl₃, cm⁻¹) 3080, 3010, 2960, 2860, 1750, 1580, 1470, 1290, 1120, 705; ¹H NMR (300 MHz, CDCl₃) δ 7.67 (m, 4H), 7.36 (m, 6H), 4.73 (s, 1H major), 4.66 (s, 1H minor), 3.64 (t, J=8.2 Hz, 1 H), 2.69 (m, 1H), 2.51 (m, 1H), 1.94 (td, J=14.1 Hz, J'=4.4 Hz, 1H), 1.81-0.89 (series of m, 16H), 1.18 (s, 3H), 1.08 (s, 9H), 0.89 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm For the major isomer: 171.51, 135.93 (2C), 135.91 (2C), 134.27, 133.73, 129.52, 129.46, 127.41 (2C), 127.37 (2C), 87.45, 82.18, 71.11, 49.73, 48.90, 43.54, 38.54, 36.55, 34.83, 31.24, 30.66, 29.48, 29.28, 27.04 (3C), 23.44, 20.90, 19.30, 18.84, 11.58 (one signal not observed); MS FAB m/z (M++1) calcd 559.32, obsd 559.34.

17β-[(tert-Butyldiphenylsiloxy)-3-oxo-4-oxaandrostan-5-carboxaldehyde (23).
To a solution of epoxy lactone 22 (342 mg, 0.613 mmol) in benzene (10 ml) was added camphorsulphonic acid (50 mg). The mixture was stirred at room temperature for 24 hr, then poured into a saturated solution of sodium bicarbonate. After the usual extractive work-up with ether and purification by flash chromatography (elution with 15% ether in petroleum ether) 321.5 mg of aldehydo lactone 23 (94% yield) was obtained as a white solid; mp 90-92 °C; IR (CHCl₃, cm⁻¹) 3070, 3005, 2940, 2860, 1740, 1460, 1120, 1090; ¹H NMR (300 MHz, CDCl₃) δ 9.95 (s, 1H major), 9.67 (m, 1H minor), 7.66 (m, 4H), 7.38 (m, 6H), 3.64 (t, J=8.2 Hz, 1H), 2.58 (m, 2H), 1.96-0.86 (series of m, 17H), 1.08 (s, 9H), 1.07 (s, 3H), 0.89 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm For the major isomer: 200.29, 170.79, 135.87 (4C), 134.65, 134.21, 129.49, 129.44, 127.38 (2C), 127.34 (2C), 88.24, 82.07, 49.66, 47.90, 43.81, 38.96, 36.40, 34.45, 30.60, 29.04, 27.29, 27.02 (3C), 26.32, 23.38, 20.97, 19.27, 14.44, 11.74 (one signal not observed); MS FAB m/z (M⁺⁺1) calcd 558.32, obsd 559.35.

Anal. Calcd for the corresponding acid, C₃₅H₄₆O₅Si: C, 73.13; H, 8.07. Found: C, 73.30; H, 8.22.
tert-Butyl[(3-methylene-5-vinyl-4-oxaandrostan-17β-y1)oxy]diphenylsilane (24).

A solution of aldehydo lactone 23 (132 mg, 0.237 mmol), pyridine (3 drops), THF (2 ml) and dichloromethane (2 ml) was prepared under argon. The mixture was cooled to -40°C and 0.5M Tebbe reagent (1.2 ml, 0.60 mmol) in toluene was added dropwise. The solution was kept for 15 min at this temperature, then warmed to 25°C and stirred for 90 min at this temperature before being cooled to -40°C and quenched with 10% KOH solution (1 ml). A 0.5% triethylamine solution in ether was added and the mixture was filtered through a pad of basic alumina (act III). Most of the solvent was evaporated and the residue was purified by chromatography on basic alumina (act III) (elution with pentane) to provide 120.6 mg of allyl vinyl ether 24 (92%) as a light yellow oil; IR (neat, cm⁻¹) 3060, 3040, 2940, 2860, 1675, 1460, 1260, 1115, 1090; ¹H NMR (300 MHz, C₆D₆) δ 7.82 (m, 4H), 7.26 (m, 6), 6.13 (dd, J=11.1 Hz, J'=17.2 Hz, 1H major), 6.03 (dd, J=11.2 Hz, J'=17.4 Hz, 1H minor), 5.62 (dd, J=1.9 Hz, J'=17.2 Hz, 1H major), 5.38 (dd, J=1.7 Hz, J'=17.4 Hz, 1H minor), 5.23 (dd, J=1.9 Hz, J'=11.0 Hz, 1H major), 5.14 (dd, J=1.7 Hz, J'=17.2 Hz, 1H minor) 4.58 (d, J=2.3 Hz, 1H minor), 4.52 (s,
1H major), 4.15 (d, J=2.3 Hz, 1H minor), 4.08 (s, 1H), 3.66 (t, J=8.3 Hz, 1H major), 3.64 (t, J=8.1 Hz, 1H minor), 2.29 (m, 2H), 1.90-0.93 (series of m, 17 H), 1.23 (s, 9H), 1.02 (s, 3H), 0.92 (3 H); $^1$H NMR (75 MHz, C$_6$D$_6$) ppm 158.18, 157.79, 140.88, 140.73, 136.45 (4C), 136.39 (4C), 135.21 (2C), 134.80 (2C), 129.98 (2C), 129.92 (2C), 129.27 (4C), 128.49 (4C), 127.85, 127.63, 117.02, 113.21, 91.64, 88.74, 82.80, 81.38, 49.93, 49.71, 48.46, 44.25, 43.72, 40.92, 38.72, 37.32, 36.96, 35.45, 35.07, 34.63, 33.00, 31.32, 31.18, 30.16, 29.48, 29.00, 27.37 (6C), 27.01, 26.17, 24.49, 23.66, 23.48, 21.37, 21.10, 20.63, 19.62, 18.58, 15.40, 12.18 (two signals not observed); MS FAB m/z (M$^+$) calcd 554.36, obsd 555.46.

$^{17}$β-(tert-Butyldiphenylsiloxyl)-A-dihomoandrost-4b-en-3-ol (25).

To a solution of allyl vinyl ether 24 (177.3 mg, 0.32 mmol) in dichloromethane (2 ml) was added at room temperature and under argon a solution of Tribal in toluene (2 ml, 2 mmol). The mixture was stirred for 6 h at room temperature, and ether followed by water were added. After the usual extrative work-up with ether and purification by flash chromatography (elution with 25% ether
in petroleum ether) 50 mg of alcohol 25 (64%) was obtained as a viscous oil; IR (CHCl₃, cm⁻¹) 3600, 3070, 3005, 2960, 2920, 2860, 1460, 1115; ¹H NMR (300 MHz, CDCl₃) δ 7.61 (m, 4 H), 7.31 (m, 6 H), 5.32 (t, J=9.1 Hz, 1H major), 5.19 (t, J=8.8 Hz, 1H minor), 4.13 (m, 1H minor), 3.81 (m, 1H major), 3.62 (t, J=8.3 Hz, 1H major), 3.58 (t, J=8.2 Hz, 1H minor), 2.75 (bs, 1H minor), 2.38 (bs, 1H major), 2.29-0.83 (series of m, 23 H), 1.07 (s, 9H), 1.03 (s, 3H) 0.86 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm For the major: 147.67, 135.92 (2C), 134.93, 134.37, 129.44, 129.36, 128.48, 127.55, 127.36 (2C), 127.32 (2C), 126.92, 82.44, 65.20, 50.28, 43.65, 43.53, 37.07, 37.01, 36.54, 36.28, 35.94, 35.82, 32.33, 31.67, 30.88, 29.65, 29.31, 27.05 (3C), 23.49, 23.20, 19.32, 11.64; MS FAB m/z (M+1) calcd 557.37, obsd 557.42.

17β-(tert-Butyldiphenyldisiloxy)-A-dihomoandrostone-4b-en-3-one (26).

To a solution of DMSO (300 µl) in dichloromethane (2 ml) was added at -78°C and under argon oxalyl chloride (150 µl). The mixture was stirred for 15 min and a solution of octenol 25 (83.4 mg, 0.15 mmol) in dichloromethane (2 ml) was added. The mixture
was warmed to -45°C, stirred for 20 min, cooled to -78°C and quenched by addition of triethylamine (700 μl). The mixture was allowed to warm to room temperature and water was added. After the usual extractive work-up with ether and purification by flash chromatography (elution with 5% ether in petroleum ether), 68 mg of cyclooctenone 26 (86%) was obtained as a viscous oil; [α]^{25}_D +16.3° (c 1.19, CHCl₃); IR (CHCl₃, cm⁻¹) 3080, 3005, 2970, 2940, 2860, 1695, 1460, 1120; ¹H NMR (300 MHz, CDCl₃) δ 7.65 (m, 4 H), 7.36 (m, 6 H), 5.29 (t, J=9.1 Hz, 1H), 3.65 (t, J=8.2 Hz, 1H), 2.70-0.81 (series of m, 23 H), 1.07 (s, 12H), 0.86 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm 212.96, 147.00, 135.92 (4C), 134.96, 134.42, 129.47, 129.29, 127.41 (2C), 127.35 (2C), 119.35, 82.41, 49.98, 47.87, 43.92, 43.81, 43.59, 41.07, 36.86, 36.45, 35.80, 33.31, 32.40, 30.87, 27.08 (3C), 23.46, 23.04, 22.94, 20.61, 19.37, 11.68; MS FAB m/z (M⁺+1) calcd 555.36, obsd 555.43.


**Thermal Claisen Rearrangement of 24.**

A solution of double vinyl ether 24 (56 mg, 0.10 mmol) in toluene (1 ml) was sealed under vacuum in a potassium hydroxide-coated soft glass tube (8 mm O.D.) and heated at 190°C for 48 hr. The tube was opened and rinsed three times with ether. After evaporation of the solvent, the residue was purified by flash
chromatography on silica gel (elution with 5% ether in petroleum ether) and provided 10 mg of isomerized vinyl ether 28 (18 %), followed by 16 mg of methyl ketone 27 (29%) and 21.5 mg of cyclooctenone 26 (39%).

\textit{tert}-Butyl[(3-methyl-5-vinyl-4-oxaandrost-2-en-17b-yl)oxy]diphenylsilane (28).

![Chemical Structure](attachment:image)

For isomerized vinyl ether 28; IR (CHCl$_3$, cm$^{-1}$) 3070, 3005, 2980, 2940, 2880, 1680, 1460, 1370, 1265, 1115, 840; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.58 (m, 4H), 7.32 (m, 6H), 6.09 (dd, J=10.9 Hz, J'=17.1 Hz, 1H ), 5.17 (dd, J=1.8 Hz, J'=17.1 Hz, 1H ), 4.98 (dd, J=1.8 Hz, J'=10.9 Hz, 1H ), 4.29 (t, J=3.2 Hz, 1H ), 3.55 (t, J=8.3 Hz, 1H), 1.76-0.83 (series of m, 17 H), 1.75 (s, 3H), 1.09 (s, 9H), 0.94 (s, 3H), 0.89 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 147.86, 138.51, 136.01 (2C), 135.97 (2C), 134.94, 134.46, 129.47, 129.41, 127.40 (2C), 127.35 (2C), 114.17, 95.58, 82.44, 80.74, 50.12, 48.02, 44.00, 37.00, 36.58, 35.17, 33.78, 32.22, 30.76, 27.10 (3C), 23.40, 21.07, 19.94, 19.35, 14.76, 11.88 (one signal not observed); MS FAB $m/z$ (M$^+$+1) calcd 555.36, obsd : 555.47.
17β-\((\text{tert-Butyldiphenylsiloxy})\text{androst-4-en-2-yl}\) methyl ketone (27).

For methyl ketone 27; IR (neat, cm\(^{-1}\)) 3060, 3005, 2970, 2930, 2860, 1705, 1460, 1115, 915, 710; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.65 (m, 4H), 7.36 (m, 6H), 5.26 (m, 1H), 3.62 (t, J=8.3 Hz, 1H), 2.60 (m, 1H), 2.16 (s, 3H major), 2.15 (s, 3H minor), 2.10-0.67 (series of m, 19H), 1.07 (s, 9H), 1.04 (s, 3H), 0.88 (s, 3H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) ppm 212.18, 211.99, 146.55, 144.77, 135.99 (4C), 135.96 (4C), 134.94 (2C), 134.42 (2C), 129.49 (2C), 129.39 (2C), 127.38 (4C), 127.33 (4C), 116.90, 116.08, 82.44, 82.39, 54.61, 50.88, 50.22, 49.99, 44.66, 44.54, 43.96, 43.62, 39.87, 38.55, 36.99, 36.87, 36.34, 36.30, 35.99, 33.80, 32.51, 32.03, 31.95, 30.85, 30.96, 29.68, 28.07, 27.97, 27.62, 27.55, 27.07 (6C), 23.55, 22.60, 21.90, 21.34, 21.12, 19.60, 19.42, 19.32, 11.82, 11.68; MS FAB \(m/z\) (M+1) calcd 555.36, obsd 555.41.
17β-(tert-Butyldiphenylsiloxy)-5-vinyl-4-oxaandrostan-3-one (29).

To a solution of methyltriphenylphosphonium bromide (178.6 mg, 0.50 mmol) in THF (3 ml) at -10°C was added KHMDS (0.96 ml, 0.48 mmol). The mixture was stirred for 30 min and a solution of aldehydo lactone 23 (0.20 g, 0.36 mmol) in THF (1 ml) was added. The reaction mixture was stirred for 1 h at room temperature and quenched with water. After the usual extractive work-up with ether and purification by flash chromatography (elution with 5% ether in petroleum ether) 191 mg of vinyl lactone 29 (96%) was obtained as a viscous oil; IR (CHCl₃, cm⁻¹) 3070, 3005, 2960, 2860, 1720, 1460, 1260, 1115, 1090, 805; ¹H NMR (300 MHz, CHCl₃) δ 7.65 (m, 4H), 7.36 (m, 6H), 6.43 (dd, J=11.2 Hz, J'=17.1 Hz, 1H ), 5.33 (dd, J=0.2 Hz, J'=17.1 Hz, 1H), 5.20 (dd, J=0.2 Hz, J'=11.1 Hz, 1H), 3.63 (t, J=8.3 Hz, 1H), 2.49 (m, 2H), 2.0-0.80 (series of m, 17 H), 1.17 (s, 3H), 1.04 (s, 9H), 0.88 (s, 3H); ¹³C NMR (75 MHz, CHCl₃) ppm 172.79, 138.72, 135.98 (2C), 135.94 (2C), 134.77, 134.35, 129.48, 129.45, 127.40 (2C), 127.37 (2C), 116.10, 86.19, 82.24, 65.83, 49.91, 48.07, 43.93, 38.79, 36.76, 34.92, 33.96, 30.68, 28.65, 27.04 (3C), 26.90,
23.34, 21.21, 19.31, 14.22, 11.83; MS FAB m/z (M+1) calcd 557.34, obsd 557.41.

4a,5-Epoxy-17α-hydroxy-17-methyl-A-homo-4-oxaandrostan-3-one (31).

Mixture of isomers (cis:trans) 8:1

To a solution of enone 30 (0.302 g, 1 mmol) in dichloromethane (30 ml) was added sodium carbonate (0.80 g) and MCPBA (0.52 g, 3 mmol). The mixture was stirred for 1 day at reflux, quenched with water, extracted with ether (3 x 50 ml), dried, concentrated, and purified by flash chromatography (elution with 35% ethyl acetate in petroleum ether) to give 0.274 g of epoxy lactone 31 (82%) as a white solid; mp 74-76°C; IR (CHCl₃, cm⁻¹) 3600, 3450, 2950, 2870, 1750, 1450, 1380, 1090; ¹H NMR (300 MHz, CDCl₃) δ 4.76 (s, 1H major), 4.69 (s, 1H minor), 2.78-0.96 (series of m, 19H), 1.21 (s, 3H), 1.18 (s, 3H), 0.87 (s, 3H) (hydroxyl signal not observed); ¹³C NMR (75 MHz, CDCl₃) ppm For the major: 171.42, 87.41, 81.39, 71.07, 50.12, 48.79, 45.33, 38.76, 38.57, 35.61, 31.31, 31.26, 30.13, 29.44, 25.74, 23.16, 20.87, 18.84, 13.77 (one signal not observed); MS m/z (M⁺) calcd 334.2142, obsd 334.2105.
17α-Hydroxy-17-methyl-3-oxo-4-oxaandrostane-5-carboxaldehyde (32).

To a solution of epoxy lactone 31 (43.2 mg, 0.129 mmol) in benzene (3 ml) was added camphorsulfonic acid (10 mg). The mixture was stirred for 24 h at room temperature and diluted with ether. The solution was washed with a saturated solution of sodium bicarbonate, dried, concentrated and purified by flash chromatography (elution with 30% ethyl acetate in petroleum ether) to give 40.6 mg of aldehydo lactone 32 (94%) as a white solid; mp 74-76 °C; IR (CHCl₃, cm⁻¹) 3600, 3450, 3010, 2960, 2860, 1740, 1460, 1260, 1180, 1085, 1040; ¹H NMR (300 MHz, CDCl₃) δ 9.95 (s, 1H major), 9.63 (s, 1H minor), 2.53 (m, 2H), 2.03-0.78 (series of m, 17 H), 1.16 (s, 3H), 1.04 (s, 3H), 0.83 (s, 3H) (hydroxyl signal not observed); ¹³C NMR (75 MHz, CDCl₃) ppm 200.30, 170.80, 88.24, 81.34, 50.07, 47.81, 45.65, 38.99, 38.76, 35.26, 31.22, 29.04, 27.32, 27.08, 26.50, 25.81, 23.04, 20.95, 14.53, 13.96; MS m/z (M⁺-H₂O) calcd 316.2038, obsd 316.2105.
17,17-Dimethyl-3-oxo-18-nor-4-oxaandrost-13-ene-5-carboxaldehyde (33).

To a solution of epoxy lactone 31 (120 mg, 0.359 mmol) in methylene chloride (10 ml) was added an anhydrous methylene chloride solution of perchloric acid (5 ml). The mixture was stirred for 24 h at room temperature and diluted with ether. The solution was washed with a saturated solution of sodium bicarbonate, dried, concentrated and purified by flash chromatography (elution with 5% ethyl acetate in petroleum ether) to give 99.9 mg of aldehydo lactone 33 (88% yield) as a white solid; mp 94°C; IR (CHCl₃, cm⁻¹) 3010, 2960, 2860, 1740, 1460, 1260, 1180, 1095, 1050; ¹H NMR (300 MHz, CDCl₃) δ 10.04 (s, 1H major), 9.70 (s, 1H minor), 2.33-0.87 (series of m, 18 H), 1.04 (s, 3H), 0.96 (s, 3H) 0.95 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) 200.30, 170.91, 142.15, 134.06, 88.17, 45.60, 45.43, 39.39, 39.10, 35.43, 29.63, 28.93, 27.82, 27.04, 26.66, 26.29, 22.80, 21.90, 14.31 (one signal not observed); MS m/z (M⁺) calcd 316.2038, obsd 316.2076.

Anal. Calcd for C₂₀H₂₈O₃: C, 75.91; H, 8.92. Found: C, 75.89; H, 8.88.
**17,17-Dimethyl-3-methylene-5-vinyl-18-nor-4-oxaandrost-13-ene (34).**

\[
\text{H}_2\text{C} \text{O} \quad \text{H} \quad \text{CH} = \text{CH}_2
\]

Aldehydo lactone 33 (126.4 mg, 0.40 mmol) was dissolved in pyridine (6 drops), THF (3 ml) and dichloromethane (2 ml), cooled to -45°C and the Tebbe reagent (2 ml, 0.5 mmol) was introduced. The reaction mixture was warmed to room temperature and stirred for 1 h. The solution was cooled to -40°C and a 5% solution of KOH was carefully added. The reaction mixture was passed through a pad of basic alumina (activity III), concentrated under vacuo, and purified by flash chromatography on basic alumina (activity III) (elution with pentane) to give 113.6 mg of allyl vinyl ether 34 (91%) as a light yellow oil; IR (neat, cm\(^{-1}\)) 3080, 3010, 2960, 2860, 1680, 1460, 1260, 1100, 1020; \(^1\)H NMR (300 MHz, C\(_6\)D\(_6\)) \(\delta\) 6.15 (dd, \(J=11.0\) Hz, \(J'=17.1\) Hz, 1H), 5.60 (dd, \(J=2.0\) Hz, \(J'=17.1\) Hz, 1H), 5.13 (dd, \(J=2.0\) Hz, \(J'=11.0\) Hz, 1H), 4.52 (d, \(J=1.1\) Hz, 1H), 4.07 (d, \(J=1.4\) Hz, 1H), 2.40-0.93 (series of m, 18 H), 1.05 (s, 3H), 1.03 (s, 3H), 1.00 (s, 3H); \(^1^3\)C NMR (75 MHz, C\(_6\)D\(_6\)) ppm 157.91, 140.82, 136.06, 128.05, 116.87, 88.09, 45.88, 39.95, 36.34, 36.12, 34.81, 32.40, 29.99, 29.24, 27.14, 27.01 (2C), 26.59, 24.36, 22.95, 22.60, 15.27; MS \(m/z\) (M\(^+\)) calcd 312.2453, obsd 312.2450.
17,17-Dimethyl-\(\Delta 5\)-dihomo-18-norandrosta-4b,13-dien-3-ol (35).

To a solution of double vinyl ether 34 (104 mg, 0.33 mmol) in dichloromethane (2 ml) was added at room temperature and under argon a solution of Tribal in toluene (2 ml, 2 mmol). The mixture was stirred for 15 min and ether was added followed by water. After the usual extractive work-up with ether and purification by flash chromatography (elution with 20% ether in petroleum ether) 90 mg of alcohol 35 (63%) was obtained as a viscous oil; IR (CHCl\(_3\), cm\(^{-1}\)) 3600, 3005, 2960, 2940, 2850, 1460, 1200; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.38 (t, \(J=9.1\) Hz, 1H major), 5.27 (t, \(J=8.9\) Hz, 1H minor), 4.20 (m, 1H minor), 3.82 (m, 1H major), 2.55-0.88 (series of m, 22 H), 1.00 (s, 3H), 0.96 (s, 3H), 0.94 (s, 3H) (hydroxyl signal not observed); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) ppm 147.36, 141.49, 136.19, 121.33, 119.16, 72.06, 68.49, 45.35, 45.29, 43.47, 43.09, 40.07, 39.66, 37.16, 37.07, 36.90, 35.90, 35.57, 33.31, 32.57, 32.41, 32.30, 32.20, 31.91, 31.46, 29.75, 29.67, 29.33, 27.28, 26.84, 26.74, 26.70,
26.50, 23.56, 23.40, 23.34, 23.14, 23.09, 22.94, 22.63, 22.50, 22.34, 21.53, 21.24; MS m/z (M+) calcd 314.2210, obsd 314.2190.


![Chemical Structure](image)

To a solution of DMSO (140 μl) in dichloromethane (2 ml) was added at -78°C and under argon oxalyl chloride (66 μl). The mixture was stirred for 15 min and a solution of octenol 35 (21 mg, 0.067 mmol) in dichloromethane (2 ml) was added. The mixture was warmed to -45°C, stirred for 20 min, cooled back to -78°C and quenched by addition of triethylamine (300 μl). The mixture was allowed to warm to room temperature and water was added. After the usual extractive work-up with ether and purification by flash chromatography (elution with 5% ether in petroleum ether) 16.1 mg of cyclooctenone 36 (86%) was obtained as a viscous oil; [α]$_{25}^{25}$D +31.4° (c 1.12, CHCl₃); IR (CHCl₃, cm$^{-1}$) 3010, 2960, 2930, 2860, 1695, 1460, 1205, 1100, 930; $^1$H NMR (300 MHz, CDCl₃) δ 5.36 (t, J=9.0 Hz, 1 H), 3.10 (m, 1 H), 2.68 (m, 2 H), 2.52-0.84 (series of m, 18 H), 1.05 (s, 3 H), 0.96 (s, 3 H), 0.95 (s, 3 H); $^{13}$C NMR (75 MHz, C₆D₆) 211.82, 146.52, 141.38, 135.90, 120.20, 45.46, 45.31, 43.65, 43.57,
40.85, 39.62, 36.92, 36.74, 32.88, 31.84, 29.74, 26.68, 26.5, 23.14,
22.68, 22.29 (one signal not observed); MS m/z (M⁺) calcd
312.2453, obsd 312.2450.

Anal. Calcd for C₂₂H₃₂O: C, 84.56; H, 10.32. Found: C, 84.35; H,
10.37.

Thermal Claisen Rearrangement of 34.

A solution of allyl vinyl ether 34 (50 mg, 0.16 mmol) in
toluene (1 ml) was sealed under vacuum in a potassium hydroxide-
coated soft glass tube (8 mm O.D.) and heated at 190°C for 46 hr.
The tube was opened and rinsed three times with ether. After
evaporation of solvent, the residue was purified by flash
chromatography on silica gel (elution with 5% ether in petroleum
ether) and provided 9 mg of isomerized vinyl ether 38 (18 %),
followed by 15 mg of methyl ketone 37 (30%) and 20 mg of
cyclooctenone 36 (40%).

3,17,17-Trimethyl-5-vinyl-18-nor-4-oxaandrosta-2,13-
diene (38).
For isomerized vinyl ether 38; IR (CHCl₃, cm⁻¹) 3080, 3010, 2960, 2940, 2860, 1680, 1460, 1370, 1115; ¹H NMR (300 MHz, CDCl₃) δ 6.29 (dd, J=10.9 Hz, J'=17.0 Hz, 1H), 5.29 (dd, J=1.7 Hz, J'=17.0 Hz, 1H), 5.10 (dd, J=1.7 Hz, J'=10.9 Hz, 1H), 4.41 (t, J=1.3 Hz, 1H), 2.20-1.00 (series of m, 16 H), 1.80 (s, 3H), 0.97 (s, 3H), 0.96 (s, 3H), 0.91 (s, 3 H); ¹³C NMR (62.5 MHz, CDCl₃) ppm 147.93, 141.27, 138.72, 135.47, 95.65, 80.88, 45.38, 45.20, 39.54, 36.57, 36.16, 34.45, 32.00, 29.66, 26.97, 26.76, 26.40, 22.94, 22.27, 19.95, 14.37; MS m/z (M⁺) calcd 312.2453, obsd 312.2458.

17,17-Dimethyl-18-norandrosta-4,13-dien-2-yl methyl ketone (37).

For methyl ketone 37; IR (CHCl₃, cm⁻¹) 3010, 2950, 2930, 2860, 1700, 1460, 1220, 720; ¹H NMR (300 MHz, CDCl₃) δ 5.32 (m, 1 H), 2.60 (m, 1H), 2.24-0.86 (series of m, 18H), 2.18 (s, 3H major), 2.17 (s, 3H minor) 1.03 (s, 3H), 0.96 (s, 3H), 0.94 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) ppm 211.98, 211.80, 145.97, 144.31, 135.85, 135.30 (2C), 117.38 (2C), 116.75, 52.19, 48.33, 45.22, 45.15, 44.67, 44.51, 39.39, 38.26, 37.72, 37.41, 36.83, 36.23, 33.30, 32.54, 32.36, 32.07, 29.68, 29.60, 27.93, 27.61, 27.53, 26.59, 26.51, 26.33, 26.30,
23.30, 22.93, 22.25, 22.04, 21.36, 19.05 (three signals not observed); MS m/z (M⁺) calcd 312.2453, obsd 312.2460.

17,17-Dimethyl-5-vinyl-18-nor-4-oxaandrost-13-en-3-one (39).

To a solution of methyltriphenylphosphonium bromide (357 mg, 1 mmol) in THF (3 ml) at -10°C was added KHMDS (1.90 ml, 0.95 mmol). The mixture was stirred for 30 min and a solution of aldehydo lactone 33 (0.20 g, 0.6 mmol) in THF (1 ml) was added. The reaction mixture was stirred 1 h at room temperature and quenched with water. After the usual extractive work-up with ether and purification by flash chromatography (elution with 5% ether in petroleum ether) 189 mg of vinyl lactone 39 (95%) was obtained as a viscous oil; IR (CHCl₃, cm⁻¹) 3080, 3010, 2960, 2870, 1720, 1460, 1195, 1100, 1005, 940; ¹H NMR (300 MHz, CHCl₃) δ 6.58 (dd, J=11.1 Hz, J'=17.1 Hz, 1H), 5.36 (dd, J=0.7 Hz, J'=17.0 Hz, 1H), 5.22 (dd, J=0.7 Hz, J'=11.5 Hz, 1H), 2.51 (m, 2H), 2.22-1.01 (series of m, 16H), 0.99 (s, 3H), 0.96 (s, 3H), 0.94 (s, 3H); ¹³C NMR (75 MHz, CHCl₃) ppm 172.77, 141.60, 138.99, 134.81, 115.89, 86.00, 45.37, 45.32, 39.42, 38.79, 35.91, 34.52, 29.61, 28.39, 27.01, 26.70, 26.30,
23.05, 22.12, 13.95 (one signal not observed); MS $m/z$ (M+) calcd 314.2246, obsd 314.2247.
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7. (a) Rhoads, S. J.; Brandenburg, C. F. J. Am. Chem. Soc. 1971, 93, 5805. (b) Rhoads, S. J.; Watson, J. M. Ibid 1971, 93, 5813. (c)


APPENDIX A

$^1$H NMR SPECTRA FOR THE SYNTHETIC APPROACH TO CLEOMEOLIDE
\[
\text{Bu(Ph)_2SO}_2\text{COC}
\]
APPENDIX B

$^1$H NMR SPECTRA FOR THE SYNTHETIC APPROACH
TO CEROPLASTOL I
APPENDIX C

$^1$H NMR SPECTRA FOR THE RING EXPANSION BY TANDEM DOUBLE TEBBE-CLAISEN TECHNOLOGY