STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF RETIGERANIC ACID

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LA THÈSE A ÉTÉ MICROFILMÉE TELLE QUE NOUS L'AVONS RÉCU
STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF RETIGERANIC ACID

by

© Ralph Stephen Smith, B.Sc.

A Thesis submitted in partial fulfillment of the requirements for the degree of Master of Science

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Abstract

Studies directed at the total synthesis of retigeranic acid (1) have revealed that compounds of type 81a and 87 cyclize in intramolecular fashion to give the conjoint ring systems 91 and 90 rather than the fused bicyclo [3.3.0] octanes 48 and 88. Increasing the acidity of the \( \gamma \)-proton did not result in alkylative cyclization.

The Wittig reagents 124, 125, and 126 have been synthesized and shown to react in normal fashion with aldehydes to give enol-ether-dienes such as 126 and \( \alpha,\beta \)-unsaturated ketones 129 after hydrolysis. A route to a suitable triene 111 for the construction of the hydrindane portion of retigeranic acid has been developed, but unfortunately conditions were not found that allowed the intramolecular Diels-Alder reaction to proceed.
Acknowledgements

The author wishes to express his appreciation to Dr. Alex G. Fallis for the guidance, enthusiasm and patience he provided throughout this work.

The author would also like to thank his wife, Cheryl, for her encouragement and understanding, without which this effort would not have been possible.

Thanks are also due to Ms. Marian Baggs for recording mass spectra, and to Mr. Avery Earle who recorded the 80 MHz n.m.r. spectra.

Financial assistance from Memorial University of Newfoundland is gratefully acknowledged.
This Thesis is dedicated to the memory of

Barbara Lynn Charters

whose courage was an inspiration to all who knew her.
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Introduction

The unique sesterterpene retigeranic acid (1) was first isolated in 1965 by Seshadri et al. from lichens of the Lobaria retigera group collected in the western Himalayas. In 1972 Schibata and co-workers² revised the molecular formula to \( \text{C}_{25}\text{H}_{38}\text{O}_{2} \) based on high resolution mass spectrometry and determined the skeletal structure by means of x-ray analysis. They also proposed that the biogenetic pathway to this pentacyclic sesterterpene involved the cyclization of geranyl-farnesylpyrophosphate (2) as outlined in Scheme 1². Since then, work by Cané and Tillman³ has determined by means of enzymatic cyclization that the biosynthesis of the structurally related triquinane skeleton compound, penetelene (2), involves a similar sequence of steps starting from farnesyl pyrophosphate (4) (Scheme 2).

Although retigeranic acid (1) does not resemble any previously known sesterterpene, its triquinane ring portion is found in many related natural products including pentalenic acid (5)⁴, isococene (6)⁵,⁶, silphine (7)⁷,⁸, and laurgenine (8)⁹. Structural features such as eight asymmetric carbons, three quaternary centers, a tetrasubstituted olefin and four ring junctures make retigeranic acid (1) a synthetically challenging molecule, as evident by the fact that it has yet to be totally synthesized.

Before the early sixties there were relatively few examples of natural cyclopentanoids other than the iridoids and cadranes and the D ring of steriods. Rarer still were
polycondensed natural products. During the mid-1970's interest in synthesizing fused cyclopentane ring systems grew rapidly as these new natural products containing di and triquinane skeletons were isolated. Since then the amount of research dealing with such polyquinane systems has increased dramatically, resulting in a number of new methods that have met the challenge of producing five membered ring systems.

In particular, functionalized bicyclo[3.3.0]octane synthons have received significant attention.

Five membered ring forming reactions include the classical Dieckman cyclization, Friedel Crafts acylation and aldol condensation. Although they may be used for a variety of ring sizes, problems arise due to the strain of five membered rings. For example, (Scheme 3) the analogous aldol condensation to the well known Wieland-Mieschler ketone gave only 30-40% yield of the diquinane. Intramolecular alkylations show a stereoselective preference for O-alkylation over G-alkylation, which is opposite to the six membered ring case, (Scheme 4). In fact, extrapolating cyclization methods that work for six membered rings to five membered rings can be "painfully deceptive". Representative preparative methods for condensed five-membered rings are outlined below (for recent reviews see Paquette, Trost, and Demuth and Schaffner).

Several types of annulation reactions have given fused cyclopentâncoid products. Cyclodehydration procedures analogous to aldol condensations (Scheme 5) resulted in
the synthesis of the elusive bicyclic enone 10\textsuperscript{15}, while a
modified sequence employing a vinyl silane gave 11\textsuperscript{16}. The
use of Wadsworth-Emmons reagents such as 12\textsuperscript{17} gave desirable
results as did aldol condensation of 12\textsuperscript{18}. Intramolecular
Michael additions as in the sequence 14-15\textsuperscript{19} were highly
efficient, while the intramolecular Claisen condensation was
used to produce highly functionalized bicyclo[3.3.0]octanes
such as 16\textsuperscript{20}. Similarly, the intramolecular Wittig cyclization
developed by Trost and Curran\textsuperscript{21} for the synthesis of 17
provided entry to a highly functionalized system. Some of
the new techniques have involved the use of silicon containing
intermediates as in the adaptations of the Nazarov cyclization
outlined in Scheme 6 to produce cyclopentenone annulation\textsuperscript{22}.

Ring contraction and expansion are both available to the
synthetic chemist interested in these fused cyclopentane
systems. The Favorskii rearrangement is an example of ring
contraction that has been used as part of a sequence towards
diquinanes as illustrated by the conversion of 18-19\textsuperscript{24} (Scheme
7). Two types of ring expansion reactions have proved useful.
One involved treating the dichlorocyclobutanone\textsuperscript{20}, resulting
from dichloroketene addition to an olefin, with diazomethane
to give\textsuperscript{21}\textsuperscript{25}; while in the other case a trimethylthio inter-
mediate was reacted with tetrakis (acetonitrile) copper (I)
perchlorate, 22-22\textsuperscript{26}.

The N-bromosuccinimide induced closure to bromohydrin\textsuperscript{27},
thiolation in the presence of Lewis acids\textsuperscript{28} and the \(\text{Me}_2\text{AlCl}\)
catalyzed ene reaction with formaldehyde\textsuperscript{27} of 1,5-cyclo-
Scheme 5

a) Me₃Si₂⁺[OSO₂CH₃, NaI, NaH, DME
b) Bu₄NF, THF

12

13
Scheme 6

14 → 15

16

a) AcO, Li, OEt, Pd(Ph3P)4, DBU (2) NBS
b) Ph3P, C6H6, Δ (2) K2CO3, H2O, Δ

c) FeCl3, CH2Cl2

17
Scheme 7

\begin{align*}
{\text{Ketone 18}} & \xrightarrow{\text{H}_2\text{SO}_4} \text{Ketone 19} \\
\text{Ketone 19} & \xrightarrow{} \text{Ketone 20} \\
{\text{Cyclopentadiene}} & \xrightarrow{} \text{Cyclopentane-2,4-dione} \\
\text{Cyclopentane-2,4-dione} & \xrightarrow{\text{Me$_2$S}} \text{Cyclopentane-2,4-dione} \\
{\text{Ketone 22}} & \xrightarrow{\text{CuClO$_4$} \cdot 4\text{CH}_3\text{CN}} \text{Ketone 23}
\end{align*}
octadiene (24) are new adaptations of the well known trans-
annular bond formations of eight membered rings, which gave
25, 26, and 27 respectively (Scheme 8). An analogy to a
[4 + 2] cycloaddition that would result in a cyclopentane
ring annulation 28 has been developed by Hudlicky and models
of these reactions of carbenes with conjugated dienes have
been studied30-32. Pyrolysis of the vinylcyclopropane inter-
mediates resulted in the formation of the desired fused ring
compounds (Scheme 9).

Another thermolytic vinylcyclopropane rearrangement
scheme employed the condensation of cyclopentanone with a
silylcyclopropyl anion followed by dehydration and pyrolysis
as in the case of 29-3033, 34. Work by Conia et al35, 36 has
pointed out the synthetic value of the intramolecular ene
reaction, 31, and a slight variation involving the pyrolysis
of a diene ester has provided promising results.37

Many of these techniques for producing fused pentacyclic
systems have been applied to the synthesis of both the linear
and angular triquinane skeletons found in natural products.
As an example, isocomene (6) has been synthesized via several
routes. It was first synthesized in 1979 by three different
groups concurrently. The key step in the approach of
Oppolzer and co-workers6a,b was an intramolecular ene reac-
tion followed by ring contraction, to give the [6.3.0.04,8]
triquinane skeleton as outlined in Scheme 10.

Paquette's6c,d successful approach to isocomene (6) was
by a stannic chloride induced cyclization and the lithium
Scheme 8

Scheme 9

a) Cu(acac)₂, C₆H₆, Δ
29. \[ \text{Ketone} \rightarrow \text{Cyclopropane} \rightarrow \text{Cyclopentadiene} \]

30. \[ \text{Cyclopropane} \rightarrow \text{Cyclopentadiene} \]

31. \[ \text{Dien} \rightarrow \text{Cyclopentadiene} + \text{Cyclopentadiene} \]

32. \[ \text{Indene} \rightarrow \text{Cyclopentadiene} \]
dimethylcuprate 1,4-addition of the final methyl group in the
penultimate step (Scheme 11). It also involved a cuprous
bromide-dimethyl sulfide complex catalyzed 1,4-conjugate
addition of a ketal grignard reagent, which he has since
used in several other synthetic schemes to related
molecules.\(^{38}\)

The third approach of the original trika, by
Pirrung,\(^{6e,f}\), is the shortest route and featured \([2 + 2]\)
photocycloaddition and a Wagner-Meerwein rearrangement step
(Scheme 12). Subsequent synthesis of isocomene \((6)\) have
been achieved by two other research groups\(^{6g, h}\). Metaphoto-
cycloaddition of an olefinic substituent aromatic ring
followed by thermolysis and controlled hydrogenation was
used by Wender and Dryer\(^{6h}\) (Scheme 13) in their novel syn-
thesis. A synthetic scheme published by Chatterjee\(^{39}\) has
been rebuked several times in the literature and is generally
considered mythical.

Although retigeranic acid has yet to be totally syn-
thesized, a few approaches to portions of it have appeared
in the literature. Paquette and co-workers\(^{40 a, b}\) are working
on a synthetic scheme based on two bond disconnections in
the B ring (Scheme 14) which gave a functionalized angular
triquinane segment \(33\) and a highly functionalized 1,1,2,3-
tetrasubstituted cyclopentane \(24\) as synthons. They have
described their attempts to synthesize \(24\) in proper
enantiomeric form in an interim report on 1,2,3-trisub-
stituted cyclopentanes as being "more vexacious than
originally expected.\textsuperscript{40b}

In Paquette's exhaustive review on "Recent Synthetic Developments in Polyquinane Chemistry"\textsuperscript{40b}, he states that the triquinane portion of retigeranic acid has been prepared by his research group in both racemic and optically active forms. Although not yet published, the racemic synthetic route is outlined in Scheme 15. Preparation of the fused bicyclic enone \textsuperscript{26} was achieved by means of an aldol type condensation, followed by cuprous bromide-dimethylsulfide promoted conjugate addition of the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxane. Acid hydrolysis permitted the formation of \textsuperscript{27}. With \textsuperscript{27} in hand they then prepared two tricyclic enones \textsuperscript{33} and \textsuperscript{35} by alternate routes. Enone \textsuperscript{35} was obtained by condensing \textsuperscript{37} with methylphenylthiochloroformate followed by pyrolysis, Wolff-Kishner reduction and sodium chromate oxidation. The route to \textsuperscript{33} was a little more involved requiring the protection of the alcohol function, Wolff-Kishner reduction of the ketone, deprotection, PCC oxidation of the alcohol and finally condensation with phenylselenium chloride followed by oxidative elimination.

A brief outline of the route to the optically active analogues is illustrated in Scheme 16. The chiral starting material, (+)-pulegone (\textsuperscript{38}), was converted to the dibromide and then underwent Favorskii rearrangement. Since the stereochemistry of the methyl substituted carbon was unaltered during the rearrangement, this stereocenter is fixed. The three additional chiral centers were then attained via
Scheme 16

\[ \text{38} \rightarrow \text{39} \rightarrow \text{several steps} \]

Scheme 17

\[ \text{a} \text{ cycle propanation} \]
\[ \text{b} \text{ rearrangement} \]
the reactions discussed in the racemic synthetic route. They hope that fusion of the final two rings will be possible now that these \(\alpha,\beta\)-unsaturated ketones have been obtained.

Hudicky and Short \(^{41}\) have also successfully synthesized the triquinane portion of retigeranic acid by means of their general scheme, which they hope to use for several terpenic acids. This scheme centers around a carbenoid cyclopropanation and subsequent rearrangement of the resulting vinyl acrylates (Scheme 17). Their specific route to the triquane portion began 'exactly like Paquette's with a Favorskii rearrangement of dibromo (+)pukegone followed by ozonolysis to the keto-ester \(^{40}\), as shown in Scheme 18. Then, under Reformatsky conditions, the keto-ester \(^{41}\) was condensed with ethyl bromocrotonate to give the lactone \(^{42}\). The acid produced by DBU elimination was converted via the acid chloride to the diazo ketone \(^{43}\) which was in turn subjected to carbenoid intermediate cyclopropanation to produce \(^{44}\). Flash pyrolysis over a lead carbonate treated column gave the tricyclic ketone \(^{45}\) in 50% yield. This was followed by removal of the ketone functionality by way of the alcohol xanthate which was reduced by reaction with freshly prepared \((n\text{Bu})_3\text{SnH}\) to give the tricyclic ester \(^{46}\).

Our retrosynthetic scheme for retigeranic acid begins with two bond disconnections in the C-ring resulting in two pretargets distinctly different from the approaches of Paquette and Hudicky (Scheme 19). This scheme is a major undertaking in our laboratory and is part of a general method
Scheme 18

\[
\begin{align*}
\text{40} & \rightarrow \text{41} \\
\text{41} & \rightarrow \text{42} \\
\text{42} & \rightarrow \text{43} \\
\text{43} & \rightarrow \text{44} \\
\text{44} & \rightarrow \text{45} \\
\text{45} & \rightarrow \text{46}
\end{align*}
\]
we are developing for the construction of quaternary, spiro-fused tricyclic skeletons of varying ring size which relies on a Diels-Alder: oxy-Cope rearrangement sequence. This route is highly convergent and offers good stereochemical control. The two pretargets are a substituted \([4,3,0]\) nonane or hydridane (left-hand piece) \(^{47}\) and a bicyclo \([3,3,0]\) octane \(^{48}\) which may be transformed to a tricyclo \([4,2,2,0^{4,8}]\) decene (right hand piece) \(^{49}\).

Coincident with research in our own group, in which the hydridanone \(^{47}\) has been prepared by both an intramolecular Michael and complementary intramolecular Diels-Alder sequence (still under study, see below), Corey and Engler \(^{52}\) reported a different synthesis of this left-hand piece. They make no mention of retigeranic acid in their paper which deals with the stereospecific conversion of the hydridanone \(^{51}\) to either the trans or cis fused hydridanone (\(^{47}\) or \(^{50}\) respectively) (Scheme 20).

Using the method of Snider and co-workers \(^{43}\), they obtained \(^{50}\) in two steps from 2,6-dimethyl-5-heptenal, and after LiAlH\(_4\) reduction isolated the allylic alcohol \(^{52}\) in 99\% yield stereospecifically. Treatment of this alcohol with thiolacetic acid, triphenylphosphine and diethylazodicarboxylate followed by LiAlH\(_4\) reduction to the thiol and the subsequent oxidation with two equivalents of 5-chloroperoxybenzoic acid gave the sulfinic acid \(^{53}\). Thermal decomposition to the olefin \(^{54}\) occurred during purification of the sulfinic acid. Conversion of the olefin to the trans fused hydridanone \(^{47}\);
Scheme 20

\[ \text{Diagram of molecular structures with reactions} \]

\[ 50 \quad \xrightarrow{\text{a}} \quad 51 \quad \xrightarrow{\text{b}} \quad 52 \]

\[ 47 \quad \xrightarrow{\text{c}} \quad 54 \]

53a) \( X = \text{SH} \)
53b) \( X = \text{SO}_2\text{H} \)

1) m-CIP3A
2) LiAlH_4
3) Na_2Cr_2O_7, H_2SO_4
involved epoxidation with m-chloroperoxybenzoic acid, formation of an epimeric mixture of alcohols and finally sodium dichromate oxidation of the mixed alcohols.

Preliminary routes to both halves of retigeranic acid have been studied. In order to prepare the requisite bicyclo[3.3.0]octane synthon \(^48\), a new cyclopentanone intramolecular alkylation sequence was investigated.

Previous studies\(^44\) with \(\alpha\beta\)-unsaturated ketones have established that the kinetically controlled formation of the \(\alpha\)'enolate anion results from treatment with strong non-nucleophilic bases under aprotic conditions. Intramolecular alkylation then affords the \(\alpha\)'alkylation product provided anion equilibration is relatively slow. In contrast, equilibrating conditions (protic solvent) favour thermodynamic control so that alkylation at the \(\sigma\)-carbon generally results. In addition to the effect of the base-solvent combination, the balance between competing pathways in intramolecular alkylation, is influenced by the nature of the electrophile and the length of the sidechain. This is exemplified by the octalones \(^55\) and \(^56\) studied by Piers et al\(^45\) (Scheme 21). They found that the product distribution (\(\sigma'=57, \sigma=58, \gamma=59\)) could be partially controlled by the reaction conditions.

Thus, the \(\sigma'\) and \(\sigma\) products predominated for \(n=3\), whereas for \(n=1\) only the \(\gamma\) and \(\sigma\) products were encountered. Johnson and Vajš\(^65\) found that the related cyclohexenone \(^60\) afforded only \(\sigma\) alkylation product \(^61\) with potassium tert-butoxide (t-BuO\(^-\)). whereas conditions which facilitated proton transfer
Scheme 21

55 \( n = 3 \), \( X = Cl \)
56 \( n = 1 \), \( X = OMs \)

57(a)
58(a)
59(y)

60

61(a)

62M

63

64(a')
(KOH, H₂O, dimethyl sulfoxide) gave the γ alkylation product 62.

In contrast to cyclohexenones, enolate anion generation and intramolecular alkylation of cyclopentenones have received much less attention. However, Cargill and Jackson 47 demonstrated that treatment of 62 with potassium tert-butoxide (t-BuOK) resulted in selective formation of the δ'-product 64.

Clearly, substrate structure and the experimental conditions have a significant influence on the site of intramolecular alkylation of α,β-unsaturated cycloenones. As Scheme 22 illustrates, intramolecular cyclization of 65 could afford a complex product mixture. Excluding δ' and α-alkylated products, both of which are improbable due to the anti-Markovnikov olefins which would result, the most likely bicyclic systems are 71 to 74. If the initial enolate is 66 or 67 it may be regarded as a masked cyclopentadiene and treatment with a second mole of strong base should generate 69 to give a different product ratio.

A variety of dianion systems have been gainfully employed in synthesis 48 and cyclopentenones appear to satisfy the general criteria of dianion species. However, with the exception of a methoxyindanone example 49, a report of some reactions of the dianions from 3-isobutoxy-2-cyclopentenones 50 and the in situ generation of the dianion of 3-methyl-2-cyclopentenone in an early hydroxyferrocene preparation 51, their potential as versatile synthetic inter-
Scheme 22

\[ \text{Diagram showing chemical structures and reactions.} \]
mediates remains unexplored. It was anticipated that for retigeranic acid, appropriate dianions could be utilized to generate the desired diquinâne skeleton.
Discussion

As outlined above, our approach to the pentacyclic sesterterpene retigeranic acid was divided into two major synths based on breaking two carbon-carbon bonds in the C-ring of the molecule. These two pretargets are the bicyclo[3.3.0]octane 48 which can be converted to the tricyclo[4.2.2.0^2,8]decene 49 (right hand piece), and the substituted bicyclo[4.3.0]nonane or hydrindane 47 (left hand piece). It was anticipated that once these two pretargets had been achieved, that the synthesis of retigeranic acid (I) could be completed by means of the route detailed in Scheme 23.

Conversion of the hydridane 47 (left hand piece) to the Grignard or alkyllithium reagent 75 followed by reaction with the right hand piece (tricyclo[4.2.2.0^2,8]decene) 49 would give the alkylation product 76. Subsequent treatment with a base such as potassium hydride should provide the oxy-Cope rearrangement product 77. Hydrogenation of the olefin would then be followed by ring contraction of the C-ring from six to five carbon. This contraction could involve a diazotization followed by photochemical or thermal rearrangement to give 78. Then the final requirement, a double bond in the C-ring, could be achieved via condensation with phenylselenium chloride and subsequent oxidative elimination to produce retigeranic acid (1).
Part A: General Route to Substituted Cyclopentenones and Results of Cyclization Attempts

The complete synthetic pathway that was originally envisioned to the right hand piece of the molecule is outlined in Scheme 24. Preparation of the olefinic sidechain substituted \( \alpha,\beta \)-unsaturated ketone 80 was based on analogous procedures developed by S.J. Alward in our labs. It was anticipated that the addition of hydrogen halide across the double bond in Markovnikov fashion would give the alkyl halide 81. Cyclization of the halide 81 involving a dianion intermediate seemed quite feasible based on literature precedents mentioned above, to produce the fused bicyclo[3.3.0] octane 48 as the thermodynamically favoured product. Reduction to the alcohol 82 followed by the generation of the cyclopentadiene intermediate 83 at low temperature based on work by Greco et al.\(^5\), should then lead to the Diels-Alder product, tricyclo[4.3.3.0\(^4,8\)]decene 84, using the methods of Corey.\(^5\)

As expected the olefin 80 was obtained by means of the 2% Na/Li alloy mediated alkylation of the enol ether 79 in an ultrasonic bath in 73%. This enol ether 79 was prepared in greater than 99% yield by refluxing 2-methyl-1,3-cyclopentanedi-one in acidic ethanol/benzene solution. The ultrasonic bath was employed because alkylation reactions involving a related sidechain had failed to work for a co-worker without such a device. It was later discovered that standard Grignard conditions in an ethyl ether/tetrahydrofuran solvent mixture increased the yield to 95% in
Scheme 24

\[ 79 \xrightarrow{\text{Et}} 80 \]

[Diagram of molecular structures and reactions]

\[ 82 \xrightarrow{\text{HCl}} 86 \]
this particular case where 4-bromo-1-butene was used with magnesium turnings.

With the olefin 80 in hand it appeared straightforward to convert the molecule to an alkyl halide, however this did not prove to be the case. Neither aqueous nor gaseous hydrogen chloride could be induced to add across the double bond of 80 in a number of solvents and varying reaction times, nor could hydrobromic acid or gaseous hydrogen bromide under various conditions of solvent or time, (Table 1). It was possible to add HCl across the olefin portion of the related molecule 85 under relatively mild conditions, but this is not particularly surprising as trisubstituted olefins are more reactive than terminal olefins.

In view of the difficulty of this halide addition step the synthetic route was altered slightly to epoxidize the olefin. This would result in an alcohol 88 product from the dianion intermediate cyclization reaction, but this slight inconvenience could be dealt with by converting the alcohol 88 to a methyl group by means of a zinc amalgam reduction of the tosylate 89 intermediate. The original synthetic route could then be continued after this short detour (Scheme 25).

Reaction of the olefin 80 with m-chloroperoxybenzoic acid gave the desired epoxide 87 in 70% yield. The $^1$H nmr spectrum displayed peaks between 2.6-3.0 ppm representing three protons, indicative of epoxide protons and infrared
Table 1 - Hydrogen Halide Addition Attempts

<table>
<thead>
<tr>
<th>Olefin</th>
<th>Hydrogen Halide</th>
<th>Solvent</th>
<th>Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>HCl (aq)</td>
<td>Ether</td>
<td>2 hrs</td>
<td>N.R.</td>
</tr>
<tr>
<td>80</td>
<td>HCl (aq)</td>
<td>Ether</td>
<td>16 hrs</td>
<td>N.R.</td>
</tr>
<tr>
<td>80</td>
<td>HCl (aq)</td>
<td>Ether</td>
<td>24 hrs</td>
<td>N.R.</td>
</tr>
<tr>
<td>80</td>
<td>HCl gas</td>
<td>CCl₄</td>
<td>1 hr</td>
<td>N.R.</td>
</tr>
<tr>
<td>80</td>
<td>0.5M HBr/AcOH</td>
<td>AcOH</td>
<td>3 hrs</td>
<td>N.R.</td>
</tr>
<tr>
<td>80</td>
<td>0.5M HBr/AcOH</td>
<td>AcOH</td>
<td>6 hrs</td>
<td>N.R.</td>
</tr>
<tr>
<td>80</td>
<td>0.5M HBr/Benzene</td>
<td>Benzene</td>
<td>3 hrs</td>
<td>N.R.</td>
</tr>
<tr>
<td>80</td>
<td>HBr gas</td>
<td>Dioxane</td>
<td>3 hrs</td>
<td>N.R.</td>
</tr>
<tr>
<td>85</td>
<td>HCl (aq)</td>
<td>Ether</td>
<td>45 min</td>
<td>86</td>
</tr>
<tr>
<td>80</td>
<td>HCl (aq)</td>
<td>Dioxane</td>
<td>1 hr</td>
<td>N.R.</td>
</tr>
</tbody>
</table>

N.R. = no reaction
Scheme 25

80 \rightarrow 87 \rightarrow 88

\downarrow

\rightarrow 82

\leftrightarrow 48

\leftrightarrow 89

80 \rightarrow 87 \rightarrow 88

82 \leftrightarrow 48

\leftrightarrow 89

90 \quad \rightarrow \quad \rightarrow 92
bands at 1265 and 845 cm\(^{-1}\) were also consistent with an epoxide functionality.

Efforts were then begun to determine the optimum conditions for the dianion intermediate cyclization reactions. A number of bases were employed with varying results. The use of two equivalents of sodium hydride in a tetrahydrofuran solution gave a clear oil (48\% yield). A broad infrared absorption between 3500-3300 cm\(^{-1}\) suggested an alcohol and bands at 1680 and 1630 cm\(^{-1}\) indicated the unsaturated ketone was still present. Inspection of the 60 MHz \(^1\text{H} \) nmr spectrum with broad multiplet signals at 0.8-1.3, 2-2.5 and 3.6 ppm, a methyl singlet at 1.8 ppm and a possible alcohol peak at 3.2 ppm suggested that the product was either the fused system 88 or the conjoint ring system 90. Since both of these products have the same molecular weight, the high resolution mass of 166.0991 indicated only that the mass was correct for a \(\text{C}_{10}\text{H}_{14}\text{O}_2\) molecule. With the aid of a 400 MHz \(^1\text{H} \) nmr spectrum it was possible to establish the identity of the product as the conjoint-ring system 90 based on the excellent resolution of the three cyclopropyl protons at 1.00, 1.14, and 1.55 ppm and the allylic cyclopropyl proton at 1.94 ppm. Also, the allylic protons and the two protons \(\alpha\) to the carbonyl were resolved, falling at 2.18 and 2.33 ppm respectively on the 400 MHz spectrum. Changing the base to three equivalents of lithium diisopropylamide in tetrahydrofuran gave the same product in only a 13\% yield. Cyclization attempts involving two equivalents of potassium
hydride gave the conjoint ring system as well in a slightly higher yield of 57%. The use of potassium amide in liquid ammonia as the base failed to give any reaction product, only recovered starting material. Since the results achieved were not the desired ones, it was decided to return to better leaving group systems.

It was found that the addition of hydrogen bromide across the double bond in the desired Markovnikov fashion could be achieved in the presence of a catalytic amount of zinc bromide. Thus, stirring the olefin 80 in a hydrogen bromide in acetic acid solution with this catalyst provided the bromide 81a in 91% yield. The distinguishing characteristics of this molecule in its 1H nmr spectrum were the new sextet at 4.02 ppm representing one proton which identified the proton on the carbon bearing the bromide, and the absence of any olefinic signals. The proof of the structure was provided by the exact mass determination of 230.0299 which corresponds very well with the calculated value of 230.0307 for C10H15Br0.

With the bromide 81a in hand studies were begun to cyclize the molecule to the desired fused ring system 48. Reacting the bromide at room temperature for fifteen hours with two equivalents of potassium hydride gave 45% yield of an oil. Unfortunately, interpretation of the 1H nmr spectrum showed cyclopropyl protons which indicated that the conjoint ring system 91 was formed. This product resulted from the dianion intermediate formed when the base abstracts a proton
exocyclic to the ring system rather than from two points in the ring as had been hoped (Scheme 26). When the base was changed to two equivalents of sodium hydride and the reaction repeated under the same conditions of time and temperature the same results were achieved.

It was then felt that perhaps the desired results might be achieved if a better leaving group was employed. Thus, the bromide 81a was converted to the iodide 81b by refluxing the bromide in acetone with potassium iodide for three hours. The $^1$H nmr spectrum of the product showed that the proton attached to the halide bearing carbon was shifted downfield slightly to 4.10 ppm, and the mass spectrum showed a molecular ion at (m/z) 278 which indicated that the iodide 81b was in fact achieved in 80% yield. Attempted cyclizations of the iodide 81b, with two equivalents of potassium hydride again provided the undesired conjoint ring system rather than the fused bicyclic desired product. Related studies in our laboratory have established that one mole of base also produced the conjoint ring system 21, and fused rings are only obtained when the Y(sidechain) position is blocked.

To verify that the alkylations followed a parallel course conversion of the conjoint ring alcohol 90 isolated from the epoxide cyclization reaction to the conjoint ring product 21 by way of the tosylate intermediate was attempted. As expected the alcohol 90 was readily converted to the tosylate 92 by the action of p-toluenesulfonyl chloride in pyridine in 71% yield. The infrared spectra
of the tosylate showed the characteristic sulfonyl absorption bands at 1360 and 1170 cm\(^{-1}\) as well as an aromatic proton band at 3020 cm\(^{-1}\). Four aromatic protons in the \(^1\)H nmr spectrum and a peak at 320(M/z) in the mass spectra corresponding to the molecular ion were consistent with the tosylate structure. The conditions employed to reduce the tosylate to a methyl functionality however resulted in conversion of the tosylate not to the desired product, but rather reversion to the original olefinic side-chain molecule 80 (Scheme 27) by cyclopropane ring opening as a consequence of zinc promoted enolization of the ketone. These studies showed that direct cyclization of these cyclopentadienyl systems proceeded easily to conjoint ring systems but was not a viable route to fused ring systems.

In view of these results, this dianion approach was abandoned in favour of a different route.

An alternate route to the bicyclo[3.3.0]octane synthon 48 was then attempted. The crucial steps of this approach were a lithium/ammonia alkylation-aldol condensation sequence as outlined in Scheme 28. The acid chloride 24 was prepared in 76% yield from propionic acid (23) by treatment with thionyl chloride on a warm water bath. The \(^1\)H nmr spectrum showed only the ethyl peaks and the boiling point range of 76-79\(^{0}\)C agreed with the literature value of 76-79\(^{0}\)C. Using the method of Catch and co-workers\(^{54}\) the acid chloride was converted to the \(\alpha\)-bromoketone 96 via the diazo ketone 25 in 21% yield. The two new protons
Scheme 28

CH₃CH₂COH → CH₃CH₂CO → CH₃CH₂Cl → CH₃CH₂CO

CH₃CH₂CO ← CH₃CH₂CO + CH₂CH₂CH₂Br

CH₃CH₂CH₃ → CH₃CH₂CH₂Br + CH₃CH₂CH₂Br
appeared as a sharp singlet at 3.87 ppm in the $^1$H nmr spectrum. Diazomethane was prepared in the manner described on the bottle of Diazald (Aldrich) beginning with twenty-five grams of Diazald.

Because of the relatively poor yield of $\alpha$-bromoketone acquired by this method and due to the restriction of the scale of the reaction imposed by our abiding respect for diazomethane generation, it was decided to prepare the $\alpha$-bromoketone by an alternate route. This route involved a one step bromination of 2-butanone 99 based on the work of the French chemists Gaudry and Marquet 55 to give the bromides 100 and 95. Though the yield was poor, this route was preferable because the starting materials were inexpensive and the technique straightforward.

The modified route involved an enone reduction-enolate alkylation step with lithium ammonia that was analogous to procedures developed by the research groups of Caine 56 and Stork 57 for six-membered ring cases. All attempts to alkylate 3-methyl-2-cyclopenten-1-one (27) by this method were unsuccessful. Model studies involving both 4-bromo-1-butene and benzyl chloride as the alkylating agent likewise met with disappointing results in that no reaction was observed. It would appear that this reaction is one of the cases that Paquette was referring to when he commented on the success rate of extrapolating from a six-membered ring method to a five membered ring situation. 13

It was at this point that a different synthetic
approach to the right-hand piece of retigeranic acid (1) was designed.

Part B: Increasing the Acidity of the Cyclopentenone Allylic Proton and Attempted Cyclizations

This final synthetic scheme for making the fused bicyclic synthon involved increasing the acidity of the proton at the Υ position in the cyclopentenone ring as outlined in detail in Scheme 29. We believed that the introduction of an alkyl- or arylthio substituent would increase the acidity of the requisite proton (Υ position), such that the use of one equivalent of base would be sufficient to initiate the intramolecular alkylation reaction required to achieve the fused bicyclic system. In addition, this substituent would block the sigmatropic rearrangement of the cyclopentadiene and direct the alkenyllithium addition in the required endo direction.

The direct introduction of the thio group at the required Υ position in compound 80 could not be achieved, based on the results of our earlier cyclization attempts which showed that the preferred anion was at the exocyclic position. Thus, the thio group was introduced σ to the carbonyl function in the enol-ether 72 prior to the alkenyllithium addition. After acidic workup of the alkylation reaction, the thio group would be in the desired Υ position of the new σ,β-unsaturated ketone product. Removal of the thio group could be conducted at a later point in the synthesis.
It was decided to add a phenylthio substituent to the enol-ether 79 by treating it with one equivalent of lithium diisopropylamide and N-thiophenylsuccinimide\textsuperscript{58}. When this failed to give the desired results a series of model studies using cyclopentenone 108 were initiated (Table 2). Work by the Japanese chemist Mukaiyama and co-workers\textsuperscript{59} suggested that N-thiophenylphthalimide might act as a better sulfur transfer reagent. The N-thiophenylphthalimide was prepared by the method of Behforuz and Kerwood\textsuperscript{60}. Eventually encouraging results were obtained when two equivalents of potassium hydride were used as the base and N-thiophenylphthalimide was used as the sulfur transfer reagent on the model compound. When these conditions were applied to the enol-ether they unfortunately did not result in the preparation of the desired product. No reaction was observed for two equivalents of potassium hydride nor for two equivalents of lithium diisopropylamide in dry dimethoxyethane.

Attempts to add a methylthio substituent α to the carbonyl of the enol-ether met with much more successful results. It was found that treating the anion, formed by the action of one equivalent of lithium diisopropylamide on the enol-ether, with dimethyl disulfide at -78°C provided ready access to the methyl sulfide enol-ether 102 in 72% yield. The distinguishing spectral feature was the appearance in the $^1H$ nmr of a singlet at 2.17 ppm which integrated for three protons corresponding to the methyl group.
Table 2 - Thiophenyl Addition Conditions

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Base</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>79</td>
<td>LDA</td>
<td>a</td>
<td>THF</td>
<td>3 hrs</td>
<td>N.R.</td>
</tr>
<tr>
<td>cyclopentanone</td>
<td>NaH</td>
<td>a</td>
<td>DME</td>
<td>16 hrs</td>
<td>N.R.</td>
</tr>
<tr>
<td>cyclopentanone</td>
<td>NaH</td>
<td>b</td>
<td>DME</td>
<td>6 hrs</td>
<td>N.R.</td>
</tr>
<tr>
<td>cyclopentanone</td>
<td>LDA</td>
<td>b</td>
<td>DME/HMPA</td>
<td>6 hrs</td>
<td>N.R.</td>
</tr>
<tr>
<td>cyclopentanone</td>
<td>1.2 NaH</td>
<td>b</td>
<td>DME</td>
<td>24 hrs</td>
<td>N.R.</td>
</tr>
<tr>
<td>cyclopentanone</td>
<td>2 NaH</td>
<td>b</td>
<td>DME</td>
<td>24 hrs</td>
<td>N.R.</td>
</tr>
<tr>
<td>cyclopentanone</td>
<td>1.2 KH</td>
<td>b</td>
<td>DME</td>
<td>24 hrs</td>
<td>N.R.</td>
</tr>
<tr>
<td>cyclopentanone</td>
<td>2 KH</td>
<td>b</td>
<td>DME</td>
<td>72 hrs</td>
<td>108</td>
</tr>
<tr>
<td>79</td>
<td>2 KH</td>
<td>b</td>
<td>DME</td>
<td>24 hrs</td>
<td>N.R.</td>
</tr>
<tr>
<td>cyclopentanone</td>
<td>2 KH</td>
<td>b</td>
<td>DME</td>
<td>24 hrs</td>
<td>N.R.</td>
</tr>
<tr>
<td>cyclopentanone</td>
<td>2 LDA</td>
<td>b</td>
<td>THF</td>
<td>16 hrs</td>
<td>N.R.</td>
</tr>
<tr>
<td>cyclopentanone</td>
<td>2 LDA</td>
<td>b</td>
<td>THF</td>
<td>24 hrs</td>
<td>N.R.</td>
</tr>
</tbody>
</table>

a = N-thiophenylsuccinimide
b = N-thiophenylphthalimide
N.R. = no reaction
attached to the sulfur atom. The exact mass of 186.0730 was in reasonable agreement with the calculated value of 186.0714 for a C₉H₁₄SO₂ molecule. Since then, D. Scholz has published a paper dealing with the addition of the methylthio substituent to a number of cyclic ketones, including the model compound worked on.

The next step in the sequence was addition of the olefin sidechain by means of an organometallic reaction. Initially, this was accomplished by means of a 2% Na/Li alloy alkylation with 4-bromo-1-butene using an ultrasonic bath. Characteristic olefin multiplet signals in the ¹H nmr at 4.8-5.18 ppm and 5.48-6.02 ppm which integrated for two and one protons respectively and an exact mass of 196.0907 for a C₁₁H₁₆SO molecule proved that the olefin 103a had been obtained. However, due to the abysmal yields isolated by this method (6-15%) it was decided to switch to Grignard conditions using an alkylmagnesium halide reagent, since it appeared that enolization of the thioketone was competing with the desired reaction. Model studies using methylmagnesium chloride (2.9 M in tetrahydrofuran) in varying amounts and in various solvents, indicated that two equivalents of Grignard reagent in a mixed ether/tetrahydrofuran solvent might give better results while three equivalents of Grignard reagent did not. An improved yield of 34% was achieved with 1.5 equivalents of 3-butenylmagnesium bromide.

Hydridobromination of the olefin using the technique
developed earlier was successful and the bromide product 104 had a sextet corresponding to one proton at 4.06 ppm in the $^1$H nmr spectrum characteristic of a secondary bromide. A molecular ion of (m/z) 276 indicated that the correct product had been obtained. Unfortunately attempts to cyclize this bromide 104a to the corresponding fused ring system using one equivalent of potassium hydride in tetrahydrofuran and 1.5 equivalents of potassium hydride in dimethoxyethane both failed and starting material was recovered.

Not willing to surrender, we anticipated that converting the sulfide to a higher oxidation state such as the sulfoxide 103b or sulfone 103c would facilitate the desired proton abstraction. The crude spectra of the sulfoxide 102b indicated that this should indeed be the case. The proton attached to the sulfur bearing carbon appeared farther downfield than in the sulfide case as a result of deshielding effects. Attempted epoxidation of the olefin sidechain and concomitant oxidation of the sulfide 103a to the sulfoxide 104d by employing two equivalents of m-chloroperoxybenzoic acid gave instead the methyl sulfone with the olefin sidechain. A molecular ion of (m/z) 228 indicated that two oxygen atoms had indeed been added and the infrared spectra contained absorption bands at 1300 and 1130 cm$^{-1}$ characteristic of a sulfone. Also, the proton at the allylic position was further deshielded and appeared as a multiplet at 4.27 ppm. Epoxidation of the sulfone 103c
was achieved when it was reacted with an additional equivalent of the oxidizing reagent. Subsequently the epoxysulfone \textbf{104c} was obtained from the sulfide olefin by refluxing it with three equivalents of \textit{m}-chloroperoxybenzoic acid in dichloromethane for forty-eight hours. Attempts to cyclize the epoxysulfone \textbf{104c} with 1.5 equivalents of potassium hydride in dimethoxyethane, 1.1 equivalents of lithium diisopropylamide in dimethoxyethane or 1.1 equivalents of sodium hydride in tetrahydrofuran all resulted in recovering only starting material.

In a final bid to synthesize the bicyclic synthon the sulfone olefin \textbf{102c} was treated with hydrogen bromide and zinc bromide to produce the bromide \textbf{104b} in 21% yield. This bromide has the characteristic multiplet for a proton attached to a carbon bearing a bromide functionality. Unfortunately the use of potassium hydride as the base in either dimethoxyethane or dimethylformamide failed to achieve the desired results. All that was recovered from these attempts were decomposition products.

Unfortunately, it appears that the geometric requirements for this intramolecular alkylation cannot be readily achieved and that the steric bulk of the activating group may also interfere. At this point, after all these variations had proven unsuccessful, in our bid to synthesize the fused bicyclic system, it was decided to step work on the right hand piece of retigeranic acid (\textbf{1}), and concentrate on the left hand piece (hydrindane portion).
Part C: Route to Hydrindanone via Wittig-Intramolecular Diels-Alder Sequence

The two key steps of our initial approach to the hydrindane 47 (left hand piece) portion of retigeranic acid involved alkylating the cyclic sulfone 109 with bromide 110, followed by an intramolecular Diels-Alder cyclization based on work by Oppolozer and co-workers 62.

The alkylation of the cyclic sulfoxide step was an extrapolation of work on linear alkyl sulfones by Kondo and Tunemoto 63. Several attempts to alkylate sulfone 109 with 2-bromopropane or methyl iodide using lithium diisopropylamide to form the required anion all met with failure.

An alternative route to the triene molecule necessary for the Diels-Alder reaction was then envisioned as seen in Scheme 30, which proved to be much more successful. It was anticipated that once the triene 111 had been isolated that conditions would be found for the Diels-Alder reaction to provide the hydrindane skeleton. Either acidic work up condition or subsequent reaction with dilute acid would then be sufficient to convert the vinylc ethoxy Diels-Alder product to the hydrindanone 47. This would be followed by conversion of the ketone 47 to the alkylating reagent 75 needed for the final series of steps to retigeranic acid (1) as outlined earlier in Scheme 23. The preparation of the triene molecule was divided into two sub-routes, preparation of the Wittig reagent 112 and the aldehyde 113.

A paper published by Ramirez and Dershowitz 64 indicated that the Wittig salt 122 should be easily attainable from
Scheme 30

109 + 110 → 47

114 → 115 → 116 → 117

113 + QG2H5 + CH2=C=CH-P(C6H5)3 → 119 → 118

111 → 47 → 75
chloroacetone (120) and triphenylphosphine (121) (Scheme 31). The first two steps of this sequence were in fact achieved by their methodology, but repeated attempts to form the required salt 124 using their conditions of refluxing the phosphinemethylene 123 in ethyl bromide gave only an oily sludge. We were able to successfully synthesize the required Wittig salt 124 in 93% yield by refluxing the phosphinemethylene with one equivalent of ethyl bromide for 24 hours. Subsequently this methodology was applied in the synthesis of two new Wittig salts 125 and 126.

It was necessary to convert the Wittig salt to the Wittig reagent before reacting it with the appropriate ketone. Martin and Desal65 have used this phosphonium salt 124 for the in situ generation of the Wittig reagent which they then reacted with a variety of α,β-unsaturated ketones to prepare monocyclic, fused bicyclic, and spiro bicyclic ring systems. Under these conditions a two-step sequence of events occurred, first an ene reaction and then intramolecular Wittig reaction. We hoped that the reagent would undergo the standard Wittig reaction only. Therefore a model study involving benzaldehyde was undertaken (Scheme 32). Addition of benzaldehyde (127) to a solution of the Wittig salt which has been treated with an equivalent of n-butyl-lithium produced the known compound trans-4-phenyl-3-buten-2-one (129). This product was the result of the desired Wittig reaction followed by hydrolysis of the enol ether 128 to the conjugated ketone 129 during purification by
Scheme 31

\[ \text{CH}_3\text{CCH}_2\text{Cl} + (\text{C}_6\text{H}_5)_3\text{P} \rightarrow \text{CH}_3\text{CCH}_2\text{H}_6\text{Cl} \]

\[ \rightarrow \text{CH}_3\text{CCH}_2\text{H}_6\text{Cl} \]

124 R = \text{C}_2\text{H}_5, X = \text{Br}
125 R = \text{C}_2\text{H}_5, X = \text{I}
126 R = \text{CH}_3, X = \text{I}

Scheme 32

127

128

129

130
flash chromatography.

Since it was known that the Wittig salt would react with an aldehyde functionality, the synthesis of the required aldehyde 113 was undertaken. An extrapolation of work done by Ireland et al.66 on ionophore antibiotic synthesis provided the means for conversion of alcohol 114 to the bromide 116 via a mesylate intermediate 115 in 90% yield. The crucial step towards the aldehyde synthesis is the alkylation of isovaleric acid (117) with a bromide. It was accomplished by a modification of a procedure developed by Pfeffer and co-workers67 for the generation of α-anilines of carboxylic acids, in 96% yield.

Once the acid 118 had been achieved it was an easy matter to reduce it with lithium aluminium hydride to the alcohol 119, and then oxidize it to the desired aldehyde 113 by stirring it in a dichloromethane solution of pyridinium chlorochromate. The aldehyde did not appear to be very stable and was used immediately for the Wittig reaction. Using the method developed for the model studies on benzaldehyde, the aldehyde was added to a tetrahydrofuran solution of the Wittig reagent. During the work up of the initial attempts the hydrolyzed product, conjugated ketone 120, was isolated as had been the case with the benzaldehyde model. This hydrolysis was believed to occur on the silica gel during flash chromatographic purification. The triene itself 111 was isolated by vacuum distillation of the reaction mixture.
Unfortunately Diels-Alder conditions have yet to be determined that will convert the triene to the hydrindane skeleton. An attempt in refluxing toluene and a trace of pyridine in a sealed tube failed, as did an attempt with pyridine as the solvent in a sealed tube reaction. It was thought that basic conditions should be employed based on the results of a related system worked on in our labs in which conjugated trienes bearing carbomethoxy functions have been successfully cyclized.

Our work in this area is continuing. These studies have helped increase our understanding of the activity in these systems, and will ultimately facilitate the successful total synthesis of retigeranic acid.
Experimental

Melting points were determined in capillary tubes with a Thomas Hoover Uni-Melt apparatus, or a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 237B or 451 grating spectrometer and were calibrated against polystyrene film. Proton magnetic resonance spectra were measured at 400 MHz with a Bruker WA 400 spectrometer at the University of Alberta, at 80 MHz with a Bruker WP 80 spectrometer employing a chloroform lock or at 60 MHz with a Varian EM 360 spectrometer. Signal positions are reported in ppm downfield from tetramethylsilane (delta scale) as an internal standard, the number of protons, multiplicity, coupling constants, and proton assignments are indicated in parentheses. Mass spectra were determined on a V.G. Micromass 7070 H5 instrument using an ionization energy of 70 electron volts.

Thin layer chromatographic analyses were carried out on 7.5 x 2.5 cm glass plates coated with silica gel PF 254-360 type 60 (E. Merck) or commercial precoated silica plates with fluorescent indicator (Eastman-Kodak silica gel 13181). Flash chromatography using BDH silica gel kieselgel 60, 230-400 mesh was employed for column chromatography.

Petroleum ether refers to a fraction with boiling range 30-60° C. Anhydrous, diethyl ether (ether), tetrahydrofuran (THF), dimethoxyethane (DME) and dioxane were obtained by distillation from lithium aluminium hydride or potassium/benzophenone. Absolute ethanol and methanol were dried by
distillation from magnesium. Dry hexamethyolphosphoramidone (HMPA), dimethylformamide (DMF) and diisopropylamine were prepared by distillation from calcium hydride. In certain cases spectrometric solvents were used without further purification; i.e., CH₂Cl₂ and acetone and sometimes just distilled. Also, for Grignard reactions the anhydrous ether was taken directly from freshly opened small cans (Fisher). Solutions in organic solvents were dried over anhydrous magnesium sulfate and stripped of solvent with a Buchi rotary evaporator connected to a water aspirator. Unless otherwise indicated all reactions were conducted under an atmosphere of dry argon.

2-Methyl-3-ethoxy-2-cyclopenten-1-one (79)

A solution (benzene:ethanol, 13:5, 850 mL) of 2-methyl-1,3-cyclopentanediene (25 g, 0.22 mol, Aldrich) containing a catalytic amount of p-toluenesulfonic acid (1 g) was refluxed through molecular sieves (30 g, 4 Å) for 24 hours. The molecular sieves were exchanged for fresh molecular sieves and the refluxing continued for an additional 24 hours.

The solvent was then removed and the residual yellow oil distilled b.p. 92-105°C/0.3 Torr, to give enol ether 79, m.p. 36-38°C, 31.1 g (100%); ir (film): 2920 (C-H), 1680 (C=O), 1625 (C=C), 1125 (C-O) cm⁻¹; ¹H nmr (CCl₄, 80 MHz) δ: 1.4 (t, 3H, J=7Hz, CH₂-CH₂-O), 1.51 (t, 3H, J=1.5Hz, CH₂-C=O), 2.35 (m, 2H, CH₂-C=O), 2.65 (m, 2H, CH₂-C=O), 4.15 (q, 2H, J=7Hz, CH₂-O); m.s. (m/z) 140 (M⁺), 112 (M-C₂H₅), 83 (M-C₂H₃O). Exact mass calculated for C₈H₁₂O₂:
3-((3-Butenyl)-2-methyl-2-cyclopentenone (80)

An ether solution (100 mL) of 4-bromo-1-butene (5.43 mL, 7.22 g, 53 mmol, Aldrich) was added dropwise (1 hour) to a solution of an anhydrous ether (200 mL) containing 2-methyl-3-ethoxy-2-cyclopenten-1-one (5.0 g, 0.036 mol) and 2% Na/Li alloy (1 g, 3 equiv.) maintained at 0°C in an ultrasonic bath (Branson 50/60 Hz). Ultrasonic agitation initiated when addition was commenced and for a further three hours after the addition was complete. The mixture was quenched (3N HCl, 200 mL), the organic layer separated, washed with brine, extracted with ether, the combined ether extracts dried, filtered, concentrated and the product purified by chromatography (20% ethyl acetate in petroleum ether (30–60)) to give the enone olefin 80, 3.67 g (68%); ir (film): 3080 (C=C-H), 1705 (C=O), 1650 (C=C) cm⁻¹; ¹H nmr (CDCl₃)δ: 1.62 (s, 3H, CH₂-C=C), 2.25-2.75 (m, 8H), 4.8-5.12 (m, 2H, CH₂=C), 5.42-6.0 (m, 1H, -CH=CH); M.S. (m/z) 150 (M⁺). Exact mass calculated for C₁₀H₁₄O: 150.1045, found: 150.1041.

3-((3-Butenyl)-2-methyl-2-cyclopenten-1-one (80)

A tetrahydrofuran solution (25 mL) of 2-methyl-3-ethoxy-2-cyclopenten-1-one 79 (1.0 g, 7 mmol) was added dropwise to a solution of anhydrous ether (15 mL) containing 4-bromo-1-butene (1.1 mL, 1.45 g, 11 mmol, Aldrich) and
magnesium turnings (0.26 g, 11 mmol) at 23°C. The reaction mixture was allowed to stir for 30 minutes at 23°C and was then warmed to 50°C for an additional 30 minutes.

The mixture was quenched (3N HCl, excess), the organic layer separated, the aqueous layer extracted with ether (3x), and the combined ether layers washed with saturated aqueous sodium bicarbonate, dried, filtered and concentrated to give the enone olefin 80 as a yellow oil, 5.36 g (72%); ir (film): 3080 (C=O-H), 1705 (C=O), 1650 (C=C) cm⁻¹; ¹H nmr (CDCl₃) δ: 1.62 (s, 3H, CH₃-C=C), 2.25-2.75 (m, 8H), 4.8-5.12 (m, 2H, CH₂=C), 5.42-6.0 (m, 1H, CH=CH); m.s. (m/z) 150 (M⁺). Exact mass calculated for C₁₀H₁₄O: 150.1045, found: 150.1041.

2-(3-Bromobutyl)-2-methyl-2-cyclopenten-1-one (81a)

To glacial acetic acid (2 mL) containing 3-(3-butenyl)-2-methyl-2-cyclopenten-1-one (1.5 g, 10 mmol) and zinc bromide (0.3 g) was added hydrogen bromide solution (15 mL, 2.55 M in acetic acid) and the flask wrapped in aluminium foil to protect the reaction from light.

After stirring for 72 hours at 23°C the reaction mixture was poured into ice water (50 mL); extracted into ether (3 x 50 mL), washed with aqueous saturated sodium bicarbonate, washed with brine, dried, filtered, concentrated and chromatographed (40% hexane in ether) to give bromide 81a, 2.11 g (91%); ir (film): 1685 (C=O), 1640 (C=C) cm⁻¹; ¹H nmr (CDCl₃, 80 MHz) δ: 1.67 (d, 3H, J=7Hz, CH₃-CH), 1.75 (s, 3H, CH₃-C=C), 2.0 (m, 2H, CH₂-CBr), 2.4 (m, 6H), 4.02
(sextet, 1H, \( J=7\text{Hz} \), CHBr); M.S. (m/z) 232 (M\(^+\)), 230 (M\(^+\)).

Exact mass calculated for \( C_{10}H_{15}BrO \): 230.0307, found: 230.0299.

\( 3-(3\text{-Iodobutyl})-2\text{-methyl-2-cyclopenten-1-one (81b)} \)

An acetone solution (30 mL) of \( 3-(3\text{-bromobutyl})-2\text{-methyl-2-cyclopenten-1-one (0.97 g, 4.2 mmol) and sodium iodide (0.63 g, 4.2 mmol) was refluxed for 3 hours.

Filtration of the reaction mixture, concentration of the resulting solution and chromatography (ether: petroleum ether, 3:2) gave the iodide 81b as an oil, 0.93 g (79%); ir (film): 1680 (C=O), 1640 (C=C) cm\(^{-1}\); \( ^1\text{H} \) nmr (CDCl\(_3\)) 8: 1.7 (s, 3H, CH\(_2\)-C=O), 1.92 (d, 3H, J=7Hz, CH\(_3\)-CH) 2.15-2.75 (m, 8H), 4.10 (sextet, 1H, J=7Hz, -CHI-); M.S. (m/z) 278 (M\(^+\)).

\( 3-(3,4\text{-Epoxybutyl})-2\text{-methyl-2-cyclopenten-1-one (87)} \)

A dichloromethane solution (200 mL) of \( 3-(3\text{-butenyl})-2\text{-methyl-2-cyclopenten-1-one (8.69 g, 58 mmol) and m-chloroperoxybenzoic acid (13.1 g, 76 mmol, 80%, Aldrich) was stirred magnetically at 23\(^\circ\)C for 24 hours. Then aqueous sodium bisulfite solution (100 mL, 10%) was added to destroy excess peroxy acid and the reaction mixture extracted into ether, washed with saturated aqueous sodium bicarbonate, dried, filtered, concentrated and the product purified by chromatography (ethyl acetate: pet. ether, 1:1) to give the epoxide 87 as an oil, 6.26 g (65%); ir (film): 1685 (C=O),
1640 (C=O), 1265, 845 (C-O) cm\(^{-1}\); \(^1\)H nmr (CDCl\(_3\), 80 MHz) \(\delta\):
1.60 (s, 3H, CH\(_3\)-C=O), 1.7 (m, 2H, -CH\(_2\)-), 2.45 (m, 6H, CH\(_2\)-C=C), 2.6-3.0 (m, 3H, epoxide protons); M.S. (m/z) 166 (M\(^+\)). Exact mass calculated for C\(_{10}H_{14}O_2\): 166.0994, found: 166.1033.

3-[2-(hydroxymethyl) cyclopropyl]-2-methyl-2-cyclopentenone (90)

A tetrahydrofuran solution (25 mL) of 3-(3,4-epoxybutyl)-2-methyl-2-cyclopentenone (500 mg, 3 mmol) was added dropwise to a suspension of sodium hydride (0.23 g, 60% in oil, 6 mmol, Aldrich) in tetrahydrofuran (25 mL) cooled in an ice bath and stirred magnetically. After 30 minutes at 0°C, the reaction mixture was stirred at 22°C for 14 hours, quenched with saturated aqueous ammonium chloride and diluted with ether. After separating the layers, the aqueous phase was extracted with ether (4 x) and the combined organic layers were dried, filtered, concentrated and the product purified by preparative layer chromatography (ethyl acetate:pet. ether, 1:1) to give the cyclized alcohol 90, 240 mg (48%); ir (film): 3300-3500 (br, OH), 1680 (C=O), 1630 (C=C) cm\(^{-1}\); \(^1\)H nmr (CDCl\(_3\), 80 MHz) \(\delta\): 0.85-1.22 (m, 7H, CH\(_3\) and cyclopropyl H), 1.80 (t, 3H, J=1.8 Hz, CH\(_3\)-C=C), 3.60 (m, 2H, J=6.2 Hz, CH\(_2\)-O); M.S. (m/z) 166 (M\(^+\)). Exact mass calculated for C\(_{10}H_{14}O_2\): 166.0994, found: 166.0991.
3-(2-(Hydroxymethyl) cyclopropyl)-2-methyl-2-cyclopentenone (90)

A tetrahydrofuran solution (50 mL) of 3-(3, 4-epoxybutyl)-2-methyl-2-cyclopentenone (4.7 g, 28 mmol) was added dropwise to a stirred suspension of potassium hydride (7.2 g, 35% in oil, 56 mmol, Aldrich) in tetrahydrofuran (50 mL) cooled in an ice bath. After 30 minutes at 0°C, the reaction mixture was stirred at 22°C for 12 hours, quenched with saturated aqueous ammonium chloride, and diluted with ether. The layers were separated, the aqueous layer extracted with ether (3 x), and the combined organic layers were dried, filtered, concentrated and chromatographed (3% methanol in ether) to give the cyclized alcohol 20, 2.6 g (57%); ir (film): 3300-3500 (br OH), 1680 (C=O), 1630 (C=C) cm⁻¹; ¹H nmr (CDCl₃, 80 MHz) δ: 0.85-1.22 (m, 7H, CH₃ and cyclopropyl H), 1.8 (t, 3H, J=8 Hz, CH₃-C=C), 3.6 (m, 2H, J=6 Hz, CH₂-O), 5.09 (m). Exact mass calculated for C₁₀H₁₄O₂: 166.0994, found: 166.0991.

3-(2-(Hydroxymethyl) cyclopropyl)-2-methyl-2-cyclopentenone (90)

3-(3, 4-Epoxybutyl)-2-methyl-2-cyclopentenone (0.3 g, 1.8 mmol) in tetrahydrofuran (20 mL) was added dropwise to a tetrahydrofuran solution (20 mL) containing diisopropylamine (0.8 mL, 5.4 mmol, Aldrich), n-butyllithium (0.5 mL, 2.2M in hexane, Aldrich), triphenylmethane (5 mg) and hexamethylphosphoramide (1 mL) cooled to -78°C. After the addition was complete, the reaction mixture was stirred at
22°C for 16 hours, quenched with saturated aqueous ammonium chloride and diluted with ether. The aqueous layer was extracted with ether (3x) and the combined organic layers dried, filtered, concentrated and purified by preparative layer chromatography (ethyl acetate: ether, 1:1) to give the cyclized alcohol 20, 40 mg (19%); ir (film): 3300-3500 (br. OH), 1680 (C=O), 1630 (C=C) cm⁻¹; ¹H nmr (CDCl₃, 80 MHz)δ: 0.85-1.22 (m, 7H, CH₃ and cyclopropyl H), 1.8 (t, 3H, J=1.8 Hz, CH₂-C=C), 3.6 (m, 2H, J=6 Hz, CH₂-0), M.S. (m/z) 166 (M⁺). Exact mass calculated for C₁₀H₁₄O₁: 166.0994, found: 166.0991.

2-(2-Methylcyclopropyl)-2-methyl-2-cyclopenten-1-one (91)

To a magnetically stirred suspension of potassium hydride (7.1 g, 60 mmol, 35% oil suspension, Aldrich) in dimethoxyethane (50 mL) cooled in an ice bath, 3-(3-bromo-butyl)-2-methyl-2-cyclopenten-1-one (6.5 g, 28 mmol) in dimethoxyethane (50 mL) was added dropwise. After stirring for 10 minutes at 0°C, stirring was continued at 22°C for 15 hours, and the reaction mixture quenched with saturated aqueous ammonium chloride and diluted with ether. The aqueous layer was extracted with ether (3x) and the combined organic layers were dried, filtered, concentrated and chromatographed (petroleum ether: ether, 3:2) to give 91 as an oil, 1.85 g (45%), ir (film): 1690 (C=O), 1650 (C=C) cm⁻¹; ¹H nmr (CDCl₃, 80 MHz)δ: 0.80 (m, 1H, cyclopropyl H), 1.0-1.35 (m, 5H, cyclopropyl H and CH₃-CH), 1.65 (m, 1H,
cyclopropyl H), 1.7 (t, 3H, J=1.8 Hz, CH₂ - C=C), 2.0-2.4 (complex, 4H). Exact mass calculated for C₁₀H₁₄O: 150.1044; found: 150.1044.

3-(2-Methylcyclopropyl)-2-methyl-2-cyclopenten-1-one (91)

To a magnetically stirred suspension of sodium hydride (0.54 g, 4.3 mmol, 35% in oil, Aldrich) in dimethoxyethane (5 mL) cooled in an ice bath, 3-(3-bromobutyl)-2-methyl-2-cyclopenten-1-one (600 mg, 2.2 mmol) in dimethoxyethane (5 mL) was added dropwise. After stirring for 10 minutes at 0°C, stirring was continued to 22°C for 15 hours, and the reaction mixture quenched with saturated aqueous ammonium chloride and diluted with ether. The aqueous layer was extracted with ether (3 x) and the combined organic layers were dried, filtered, concentrated and chromatographed (petroleum ether: ethyl acetate, 4:1) to give 91, 120 mg (37%), ir (CHCl₃): 1695 (C=O), 1650 (C=C) cm⁻¹; ¹H nmr (CDCl₃): 0.75-1.0 (m, 2H, cyclopropyl), 1.0-1.35 (br s, 5H, cyclopropyl H and CH₂-CH), 1.65 (m, 1H, cyclopropyl H), 1.8 (br s, 3H, CH₂-C=C), 2.0-2.45 (m, 4H, CH₂-CH₂), M.S. (m/z) 150 (M⁺).

3-(2-p-Toluene sulfonyloxy)methylcyclopropyl)-2-methyl-2-cyclopentenone (92)

A pyridine solution (5 mL) of 3-[(2-hydroxymethyl)cyclopropyl]-2-methyl-2-cyclopentenone (350 mg, 2.1 mmol) and p-toluene sulfonyl chloride (810 mg, 4.2 mmol) was stirred at -20°C for 22 hours. The reaction mixture was then
poured over ice water (60 mL) and extracted into ether (5 x 30 mL). The combined organic layers were washed with dilute hydrochloric acid (1N, 20 mL, 4 x), aqueous sodium bicarbonate (5%), dried over Na₂SO₄ for 6 hours, filtered and concentrated to give the tosylate 22, 0.48 g (71%), mp 87-91° C; ir (CHCl₃): 3020 (aromatic C-H), 1690 (C=O), 1630 (C=C), 1360 (S=O, assym), 1170 (S=O, sym.) cm⁻¹; ¹H nmr (CDCl₃)δ: 0.70-1.35 (m, 4H, cyclopropyl H), 1.72 (3H, CH₃-C=C), 2.1 (m, 2H, CH₂-C=O), 2.3 (m, 2H, CH₂-C=C), 2.44 (S, 3H, CH₃-aromatic), 4.0 (m, 2H, CH₂-0), 7.2-7.8 (m, 4H, aromatic); M.S. (m/z) 320 (M⁺).

Propionyl Chloride (94)

Propionic acid (25 g, 25.2 mL, 0.337 mol) was added dropwise to thiophenyl chloride (50.2 g, 30.7 mL, 0.42 mol) at 22° C. After the addition was complete the mixture was warmed to 65° C for 30 minutes and then the crude product was distilled off. The crude product was purified by fractional distillation, b.p. 76-79° C to give propionyl chloride (24), 23.6 g (76%), ¹H nmr (CCl₄)δ: 1.3 (t, 3H, J=7 Hz, CH₃-CH₂), 3.00 (q, 2H, J=7 Hz, -CH₂-C=O).

1-Bromo-2-butanone (96)

To a well stirred dry methanol solution (800 mL) of 2-butanone (50 g, 62 mL, 0.69 mol) at 0° C was added bromine (110 g, 36 mL, 0.69 mol). Stirring was continued until decolorization had occurred (4½ hours) and then sulfuric
acid (900 ml, 2M) was added and the stirring continued for an additional 16 hours. The reaction mixture was extracted into ether and neutralized with saturated aqueous sodium bicarbonate, the ether phase washed with water (4 x), dried over Na₂SO₄, filtered, concentrated and the product purified by distillation, to give a clear oil, 5.54 g (6%) b.p. 105°C/120 Torr; ¹H nmr (CDCl₃) δ: 1.03 (t, 3H, J=7 Hz, CH₃-), 2.62 (q, 2H, J=7 Hz, -CH₂-C=O), 3.87 (s, 2H, -CH₂-Br).

2-Phenylthio-1-cyclopentanone (108)

A dry dimethoxyethane solution (5 mL) of cyclopentanone (168 mg, 0.178 mL, 2 mmol) was added dropwise to a dimethoxyethane suspension (5 mL) of potassium hydride (458 mg, 4 mmol, 35% in oil, Aldrich) cooled to 0°C. The reaction mixture was allowed to warm to 22°C and a dimethoxyethane solution (40 mL) of N-thiophenylphthalimide (510 mg, 2 mmol) was added dropwise. The reaction mixture was stirred for an additional 72 hours, quenched with water, extracted into ether (4 x), washed with brine, dried, filtered, concentrated and purified by preparative layer chromatography (hexane: ethyl acetate, 4:1) to give the phenyl sulfide 108, 71 mg (81%); ir (CHCl₃): 3020 (C-H, aromatic), 1735 (C=O) cm⁻¹; ¹H nmr (CDCl₃) δ: 2.2 (br m, 6H), 3.61 (m, 1H, -CH-S-), 7.32 (m, 5H, aromatic).
**Acetonyltriphenylphosphonium Chloride (122)**

A benzene solution (100 mL) of triphenylphosphine (28.85 g, 100 mmol) and chloroacetone (9.25 g, 100 mmol) was refluxed for 1 hour. The reaction mixture diluted with petroleum ether and filtered under aspirator vacuum to give the phosphonium salt 122, 30.2 g (85%), m.p. 238-241°C; ir (CHCl₃): 3070 (C-H, aromatic), 1715 (C=O), 1600 and 1520 (C=C, aromatic) cm⁻¹; ¹H nmr (CDCl₃, 80 MHz)δ: 2.49 (d, 3H, J=1.5 Hz, CH₂-C=O), 6.10 (d, 2H, J=10 Hz, O=C-CH₂-P), 7.28 (m, 15H, aromatic).

**Triphenylphosphineacetymethylenne (123)**

A mixture of acetonyltriphenylphosphonium chloride (15.7 g, 44 mmol) and 10% aqueous sodium carbonate (125 mL) was stirred at 22°C for 8 hours. Filtration under reduced pressure (water aspirator) gave the crystalline product 123, 14.1 g (91%), m.p. 203-205°C; ir (CHCl₃): 3070 (C-H, aromatic), 1525 (C=C, aromatic) cm⁻¹; ¹H nmr (CDCl₃, 80 MHz)δ: 2.07 (d, 3H, J=1.5 Hz, CH₂-C=O), 3.65 (d, 1H, J=26 Hz, HC=P), 7.45 (m, 15H, aromatic H), M.S. (m/z) 318 (M⁺).

**2-Ethoxy-1-propenyltriphenylphosphonium bromide (124)**

A tetrahydrofuran solution (15 mL) of triphenylphosphine acetylumethylene (1.0 g, 3.1 mmol) and ethyl bromide (0.26 mL, 3.5 mmol, Aldrich) was refluxed for 48 hours. The oily residue was crystallized (methanol: ethyl acetate, 1:20) to give the ether phosphonium bromide salt 124, 0.82 g.
(61%), m.p. 165-167°C; ir (CHCl₃): 3060 (C-H, aromatic), 1600 (C=O), 1490 (C=C, aromatic), 1120 (C-O) cm⁻¹; ¹H nmr (CDCl₃, 80 MHz)δ: 0.70 (t, 3H, J=7 Hz, CH₂-CH₂), 2.65 (s, 3H, CH₃-C=), 4.06 (q, 2H, J=7 Hz, CH₂-O), 5.80 (d, 1H, J=18 Hz, -CH-P), 7.73 (m, 15H, aromatic).

2-Ethoxy-1-propenyltriphenylphosphonium iodide (125)

A tetrahydrofuran solution (150 mL) of triphenylphosphineacetylmethylene (20 g, 62.4 mmol) and freshly distilled ethyl iodide (10.7 g, 69 mmol, Aldrich) was refluxed for 15 hours to give a tawny viscous oil. This oil was crystallized (methanol: ethyl acetate, 1:20) to give the ether phosphonium salt 125 as needles, 27.7 g (93%), m.p. 160-161°C; ir (CHCl₃): 3060 (C-H, aromatic), 1600 (C=O), 1485, 1440 (C=C, aromatic), 1110 (C-O, ether) 1000-870 (=CH) cm⁻¹; ¹H nmr (CHCl₃, 80 MHz)δ: 0.69 (t, 3H, J=7 Hz, CH₂-CH₂), 2.57 (s, 3H, CH₃-C=O), 4.05 (q, 2H, J=7 Hz, CH₂-O), 5.52 (d, 1H, J=18 Hz, =CH-R), 7.6 (m, 15H, aromatic).

2-Methoxy-1-propenyltriphenylphosphonium iodide (126)

A tetrahydrofuran solution (15 mL) of triphenylphosphine acetylmethylene (1.0 g, 3.1 mmol) and methyl iodide (0.50, 3.5 mmol) was stirred at 22°C for 48 hours. Filtration under reduced pressure (water aspirator) gave the crystalline product 126, 1.13 g (78%), m.p. 138-141°C; ir (CHCl₃): 1720 (C=O), 1600 (C=O), aromatic), 1125 (C-O)
3-Ethoxy-2-methyl-5-methylthio-2-cyclopenten-1-one (102)

3-Ethoxy-2-methyl-cyclopenten-1-one (10 g, 71 mmol) in tetrahydrofuran (200 mL) was added dropwise to the tetrahydrofuran solution (100 mL) containing diisopropylamine (15 mL, 110 mmol, Aldrich) and n-butyllithium (51 mL, 2.1M in hexane, 110 mmol, Aldrich) at -78° C. After stirring the anion at -78° C for 30 minutes and at 0° C for 45 minutes, a tetrahydrofuran solution (150 mL) of dimethyl disulfide (6.44 mL, 6.74 g, 71 mmol, Aldrich) was added rapidly (1 minute).

After stirring at 23° C for 1 hour the reaction mixture was quenched with saturated aqueous ammonium chloride and the layers separated. The aqueous phase was extracted with ether (150 mL, 3 ×) and the combined organic layers were dried, filtered, concentrated and chromatographed to give the sulfide 102, 9.58 g (72%); ir (film): 1680 (C=O), 1625 (C=C), 1125 (C-O) cm⁻¹; ¹H nmr (CDCl₃, 80 MHz) δ: 1.40 (t, 3H, J=7 Hz, CH₃-CH₂), 1.52 (t, 3H, J=1.5 Hz, CH₃-C=C), 2.17 (s, 3H, CH₃-S), 2.8-3.35 (br m, 2H, CH₂-C=), 4.2 (q, 2H, J=7 Hz, CH₂-CH₂); M.S. (m/z) 186 (M⁺). Exact mass calculated for C₉H₁₄SO₂: 186.0714, found: 186.0730.
3-(3-Butenyl)-2-methyl-4-methylthio-2-cyclopenten-1-one (120a)

A tetrahydrofuran solution (5 mL) of 3-ethoxy-2-methyl-5-methylthio-2-cyclopenten-1-one (1.32 g, 7.1 mmol) was added dropwise to a solution of anhydrous ether (5 mL) containing 4-bromo-1-butene (1.1 mL, 1.45 g, 10.7 mmol, Aldrich) and magnesium turnings (260 mg, 10.7 mmol). The reaction mixture was allowed to stir at 65° C for 15 hours.

The mixture was quenched (3N HCl, excess), the organic layer separated and the aqueous layer extracted with ether (3 x). The combined ether layers were washed with saturated sodium bicarbonate, dried, filtered and concentrated to give 102a as an oil, 312 mg (34%); ir.(film): 1695 (C=C), 1635 (C=C) cm⁻¹; ¹H nmr (CDCl₃, 80 MHz): 1.60 (s, 3H, CH₃-C=), 1.73 (s, 3H, CH₂-S), 2.06-2.8 (m, 6H), 3.77 (m, 1H, =CH-S), 4.8-5.18 (m, 2H, CH₂=), 5.48-6.02 (m, 1H, -CH=C); M.S. (m/z) 196 (M⁺). Exact mass calculated for C₁₁H₁₆S0 196.0922, found: 196.0907.

3-(3-Bromobutyl)-2-methyl-4-methylthio-2-cyclopenten-1-one (104a)

3-(3-Butenyl)-2-methyl-4-methylthio-2-cyclopenten-1-one (850 mg, 4.5 mmol) was added to glacial acetic acid (5 mL) containing zinc bromide (100 mg). Hydrogen bromide in acetic acid solution (5 mL, 30%) was added to the stirred reaction mixture, and the flask wrapped in aluminium foil to protect the reaction from light.
After stirring for 48 hours at 23° C the reaction mixture was poured into ice water (50 mL), extracted into ether (3 x 50 mL), washed with saturated aqueous sodium bicarbonate, washed with brine, dried, filtered, concentrated and the product purified by chromatography (ether: petroleum ether, 3:2) to give the bromide 104a as an oil, 88 mg (13%); \( ^1H \) nmr (CDCl\(_3\))\( \delta \): 1.70 (s, 3H, CH\(_3\)-C=C), 1.8 (s, 3H, CH\(_3\)-S-), 2.02 (m, 2H, -CH\(_2\)CHBr-), 2.33-2.90 (m, 4H), 4.06 (sextet, 1H, -CHBr-), M.S. (m/z) 276 (M\(^+\)).

3-(3-Butenyl)-2-methyl-4-methylsulfonyl-2-cyclopenten-1-one (103c)

A dichloromethane solution (50 mL) of 3-(3-butenyl)-2-methyl-4-methylthio-2-cyclopenten-1-one (1.0 g, 5.1 mmol) and m-chloroperoxybenzoin acid (2.32 g, 10.3 mmol, 80%, Aldrich) was refluxed for 6 hours. Then 10% aqueous sodium bisulfite (20 mL) was added to destroy excess peroxy acid and the reaction mixture extracted into dichloromethane (4 x 30 mL). The combined extracts were washed with saturated aqueous sodium bicarbonate, followed by 0.5M aqueous sodium hydroxide (excess), then dried, filtered, concentrated and chromatographed (ether) to give the sulphone (103c) 785 mg (68%); ir (CHCl\(_3\)) 1710 (C=O), 1635 (C=C), 1300 (S=O) cm\(^{-1}\); \( ^1H \) nmr (CDCl\(_3\))\( \delta \): 1.80 (d, 3H, J=1.5 Hz, CH\(_3\)-C=C), 2.3-2.55 (m, 2H), 2.65-3.0 (m, 7H, 4.27 (m, 1H, -CH-SO\(_2\) -)), 4.83-5.2 (m, 2H, CH\(_2\)=), 5.5-6.05 (m, 1H, -CH-C=); M.S. (m/z) 228 (M\(^+\)).
3-(3-Bromobutyl)-2-methyl-4-methylsulfonyl-2-cyclopenten-1-one (104b)

3-(3-Butenyl)-2-methyl-4-methylsulfonyl-2-cyclopenten-1-one (1.4 g, 6.3 mmol) and zinc bromide (0.25 g) in glacial acetic acid (10 mL) were added to a stirred hydrogen bromide in acetic acid solution (20 mL, 30-32%) and the flask wrapped in aluminium foil to protect the reaction from light.

After stirring for 96 hours, the reaction mixture was poured into ice water (50 mL), extracted into ether (3 x 50 mL), washed with saturated aqueous sodium bicarbonate, brine, dried, filtered, concentrated, and chromatographed (ethyl acetate: hexane, 1:9) to give the bromide 104b, 400 mg (21%); ir (film): 1700 (C=O), 1640 (C=O), 1310 (S=O), 1230 (C-Br), 1130 (S=O) cm⁻¹, ¹Hnmr (CDCl₃): 1.71 (s, 3H, CH₃-C=C), 2.17 (d, 3H, J=2 Hz, CH₃-CHBr), 3.91 (m, 1H, -CH-SO₂Me), 5.0 (m, 1H, -CHBr-Me).

A dichloromethane solution (50 mL) of 3-(3-butenyl)-2-methyl-4-methylsulfonyl-2-cyclopenten-1-one (795 mg, 3.5 mmol) and m-chloroperoxybenzoic acid (750 mg, 3.5 mmol, 80% Aldrich) was refluxed for 48 hours. Then 10% aqueous sodium bisulfite (excess) was added to destroy any residual peroxy acid and the reaction mixture extracted into dichloromethane (4 x 25 mL). The combined extracts were washed with saturated aqueous sodium bicarbonate (2 x), followed by 10% aqueous sodium hydroxide (2 x), then dried, filtered,
concentrated and chromatographed (ethyl acetate) to give the sulfone epoxide 104c, as a clear oil, 640 mg (75%); ir (film), 1700 (C=O), 1635 (C=C), 1300 (S=O) cm⁻¹; ¹H nmr (CDCl₃)δ: 1.83 (s, 3H, CH₂-C=), 1.9-2.1 (m, 2H, -CH₂-), 2.35-3.15 (m, 10H), 4.5 (m, iH, -CH-SO₂).

3-Methyl-3-buten-1-ol mesylate (115)

To a dichloromethane solution (100 mL) of 3-methyl-3-buten-1-ol (114) (8.61 g, 0.1 mol) at 0° C was added a dichloromethane solution (20 mL) of triethylamine (20 mL, 14.4 g, 0.14 mol) and methanesulfonyl chloride (7.6 mL, 0.1 mol). After stirring for 1 hour 0.5M aqueous sodium bicarbonate (50 mL) was added and the reaction mixture stirred vigorously for 10 minutes. The layers were separated, the aqueous layer back extracted with dichloromethane and the combined organic layers washed with brine, dried filtered and concentrated to give the mesylate (115), 13.94 g (85%); ir (CDCl₃): 1665 (C=C), 1030 (S=O) cm⁻¹; ¹H nmr (CDCl₃)δ: 1.78 (s, 3H, CH₂-C=), 2.40 (t, 2H, J=7 Hz, CH₂-C=C), 2.95 (s, 3H, CH₃-S), 4.21 (t, 2H, J=7 Hz, -CH₂-O), 4.80 (br. s, 2H, CH₂=); M.S. (m/z) 164 (M⁺).

4-Bromo-2-methyl-1-butene (116)

An acetone solution (1000 mL) of 3-methyl-3-buten-1-ol mesylate (90.0 g, 0.549 mol) and lithium bromide (52 g, 0.600 mol) was refluxed for 1 hour. Then ether (500 mL) and water (500 mL) were added, the layers separated, the aqueous layer re-extracted with ether (3 x) and the combined ether
layers washed with brine, dried, filtered, concentrated and
the bromide 116 purified by distillation, b.p. 120°-130° C/
760 torr, 74.0 g (90%); ir (CDCl₃): 1660 (C=O) cm⁻¹; ¹H nmr
(CDCl₃)δ: 172 (s, 3H, CH₃-C=), 2.53 (t, 2H, J=7 Hz, CH₂-C=),
3.45 (t, 2H, J=7 Hz, CH₂-Br), 4.75 (br s, 2H, CH₂=).

5-Methyl-2-isopropyl-5-hexenoic acid (118)

Isovaleric acid (117) (1.53 g, 15.0 mmol, Aldrich) was
added to a stirred suspension of sodium hydride (0.6 g, 15.0
mmol, 60% dispersion in oil) in dry tetrahydrofuran (15 mL)
and diisopropylamine (1.53 g, 15.0 mmol). The reaction was
refluxed for 10 minutes, cooled to 0° C with an external ice
bath, and n-butyllithium (7.14 Ml, 15.0 mmol, 2.1 M in hexane)
added. The mixture was warmed to 35° C for 20 minutes,
cooled to 22° C and 4-bromo-2-methyl-1-butene (2.22 g,
15.0 mmol) added. Stirring was continued at 30° C for 24
hours, the cold reaction mixture (0° C) quenched slowly with
water, acidified with 10% aqueous hydrochloric acid and
extracted with ether. The combined ether extracts were
washed with brine, dried, filtered and concentrated to
afford the acid 118, 2.04 g (80%); ir (film): 3500-2500
(OH), 1700 (C=O) cm⁻¹, ¹H nmr (CDCl₃)δ: 1.02 (d, 6H, J=7 Hz,
(CH₃)₂C), 1.72 (s, 3H, CH₃-C=), 4.71 (br s, 2H, H₂C=C), 10.90
(br s, 1H, COOH); M.S. (m/z) 170 (M⁺).

5-Methyl-2-isopropyl-5-hexen-1-ol (119)

5-Methyl-2-isopropyl-5-hexenoic acid (2.04 g, 12.0 mmol)
in anhydrous ether (15 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (0.456 g, 12 mmol) in anhydrous ether (15 mL) maintained at 0°C. Stirring was continued for 1 hour at 22°C after addition was complete. Additional ether (50 mL) added, followed by water (1 mL) dropwise and anhydrous sodium sulfate. The solution was dried, filtered, concentrated and the product purified by chromatography (ethyl acetate: hexane, 1:9) to give the alcohol [112], 1.8 g (96%); i.r. (film): 3300 (br, OH), 3060 (H-C=) cm⁻¹; ¹H nmr (CD₂Cl₂) 6: 0.90 (d, 6H, J=7 Hz, (CH₃)₂C), 1.75 (s, 3H, CH₃-C=C), 3.50 (d, 2H, J=5 Hz, CH₂-O), 3.77 (s, 1H, OH), 4.64 (br s, 2H, CH₂-C); M.S. (m/z) 156 (M⁺).

5-Methyl-2-isopropyl-5-hexen-1-al ([113])

A dry dichloromethane solution (2 mL) of 5-methyl-2-isopropyl-5-hexenol (1.7 g, 10.9 mmol) was added to a well stirred suspension of pyridinium chlorochromate (6.0 g, 27.9 mmol) and sodium acetate (0.5 g, 6.2 mmol) and the reaction stirred at 22°C for 3 hours. The reaction mixture was diluted with ether (150 mL), filtered under vacuum through a short column of silica gel, concentrated and the product purified by chromatography (2% ethyl acetate/hexane) to give the aldehyde [113], 1.4 g (88%); i.r. (film): 3060 (H-C=O), 1730 (C=O), 1670 (C=C) cm⁻¹; ¹H nmr (CD₂Cl₂) 6: 0.89 (d, 6H, J=7 Hz, (CH₃)₂C), 1.63 (s, 3H, CH₃-C=), 4.54 (br s, 2H, H₂C=C), 9.54 (d, 1H, J=1 Hz, H-C=O); M.S. (m/z) 142 (M⁺).
2-Ethoxy-5-isopropyl-8-methyl-1, 2, 8-nonatriene (III)

n-Butyllithium (4.8 mL, 12.6 mmol, 2.6M in hexane, Aldrich) was added to a well stirred anhydrous tetrahydrofuran solution (30 mL) of the phosphonium salt (6.0 g, 12.6 mmol) cooled to -78° C. After the addition was complete the red-orange mixture was allowed to warm to -23° C and the stirring continued for 2 hours. The reaction mixture was then recooled to -78° C and a tetrahydrofuran solution (15 mL) of 5-methyl-2-isopropyl-2-hexenal (1.30 g, 8.3 mmol), III, was added dropwise. The reaction mixture was warmed to 23° C and stirred for 18 hours. Cold water (75 mL) was added, the layers separated, the organic layer washed with water, and the aqueous layer back extracted with ether (2 x). The combined organic extracts were dried, filtered, concentrated and distilled by Kugelrohr (90° C/0.1 torr) to give the triene III as an oil, 7.50 mg (27%); ir (film): 3080 (C=C-H, stretch), 1575, 1450 (C=C), 1080 (C-O) cm⁻¹, ¹H nmr (CDCl₃) 6: 0.75-0.90 (overlapping d, 6H, J=7 Hz, (CH₃)₂CH), 1.31 (t, 3H, J=7 Hz, CH₃-CH₂-0), 1.50-2.1 (M, 6H, -CH₂-, R₂CH-), 1.69 (s, 3H, CH₃-C=C), 3.7 (q, 2H, J=7 Hz, Me-CH₂-0), 3.9 (s, 2H, CH₂-C=O), 4.6 (s, 2H, H₂C=C=Me), 5.69 (br s, 2H, -CH=CH-); M.S. (m/z) 222 (M⁺). From an attempted preparative layer chromatography purification (ether: petroleum ether, 1:9) of the crude triene (500 mg), recovered the hydrolysed product, 8-methyl-5-isopropyl-1, 8-nonadien-2-one (I₃₀), 170 mg; ir (film): 3080 (C=C-H, stretch), 1689 (C=O), 1625, 1450 (C=C) cm⁻¹, ¹H nmr (CDCl₃) 6: 0.87 (overlapping, d,
trans-4-Phenyl-3-butene-2-one (benzalacetone) (129)

n-Butyllithium (4.4 mL, 11.3 mmol, 2.6M in hexane, Aldrich) was added slowly to a well stirred anhydrous tetrahydrofuran suspension (20 mL) of the phosphonium iodide salt 125 (5.35 g, 11.3 mmol) at -78° C. After the addition was complete, the dark red mixture was allowed to warm to -23° C and the stirring continued for 2 hours. The reaction mixture was recooled to -78° C and a tetrahydrofuran solution (10 mL) of benzaldehyde (1.0 g, 9.4 mmol, Aldrich) was added dropwise. The resulting reddish-brown mixture was quenched with water (30 mL), extracted into dichloromethane (3 x), and the combined organic layers dried, filtered, concentrated and purified by preparative layer chromatography (petroleum ether/ether, 9:1) to give the aromatic unsaturated ketone 129, 0.210 g (15%) m.p. 35-38° C, (purification required 3 columns and a preparative plate, contributing to low yield); ir (film): 1670 (C=O), 1610 (C=C), 1495, 1450 (C=C, aromatic) cm⁻¹; H nmr (CDCl₃) δ: 2.23 (s, 3H, CH₃-C=O), 6.52 (d, 1H, J=16 Hz, -C=CH), 7.36 (d, 1H, J=16 Hz, -C=CH), 7.29 (s, 5H, aromatic); M.S. (m/z) 146 (M⁺).
Bibliography


