An improved technique for synthesis of β-hydroxy esters via the Reformatsky reaction was developed. The method involves passage of the carbonyl compound and ethyl bromoacetate through a heated column of activated zinc. The intermediate β-alkoxyzinc ester was hydrolyzed with cold, dilute sulfuric acid. Two aldehydes and six ketones were reacted, with product yields consistently higher than those obtained by the conventional procedure. This continuous flow method was also used with carbonyl compounds and allylic bromides to form, after hydrolysis, high yields of homoallylic alcohols including artemisia alcohol (41). Six aldehydes, six ketones, and one ester were reacted with allylic bromides by this method.

Diazoketones 69 and 70 were converted to tricyclic ketones 49 and 50 with copper powder in refluxing cyclohexane. Routes were established for converting 49 and 50 into spiro[4.5]decanones and
spiro[5, 5]undecanones respectively, as well as into bicyclic[5. 3. 0] and bicyclic [5. 4. 0] systems respectively. Treatment of 49 and 50 with concentrated hydrochloric acid gave chloroketones 74 and 75 respectively, which were convertible back to 49 and 50 on alumina. Lithium-ammonia reduction of 49 and 50 afforded spiro-ketones 72 and 73 respectively. Fused, bicyclic ketones 76 and 77 were obtained by treatment of 49 and 50 with p-toluenesulfonic acid in refluxing methanol. In addition, cis fused systems 84 and 85 were obtained by perchloric acid treatment of the sodium borohydride reduction products of ketones 49 and 50 respectively. Cis isomer 85 was converted to the more stable trans isomer 86 by further reaction.

The naturally occurring spiro[4, 5]decane sesquiterpene (-)-acorenone B (1) was synthesized starting from R-(+)-limonene (103), and proceeded via cyclopentencarboxaldehyde 29, which underwent condensation with ethyl 2-bromomethylacrylate (28) to give α-methylene-γ-lactone 42. Hydrogenation of 42 over Adam's catalyst followed by hydrogenolysis over palladium-on-calcium carbonate gave carboxylic acid 109, which was converted to tricyclic ketone 112. Treatment of 112 with hydrogen chloride in chloroform gave olefin 116, which was hydrogenated over rhodium-on-carbon to give spiroketone 117. The required unsaturation of enone 1 was introduced via enol acetate 118 and α-bromoketone 119, to give (-)-acorenone B ([α]20D -19° ). Reductive cleavage of 112 with lithium-ammonia
produced 120, with inversion at the C-4 methyl group. Introduction of an \( \alpha \beta \)-unsaturation led to 4-epiacorenone B \( ([\alpha]_D^{20} - 50^\circ) \).

The synthesis of mycosporin (P 310) was approached, starting from cyclohexenones 137 and 138, which were derived from 3-methoxybenzoic acid (140) and 3,4,5-trimethoxybenzoic acid (141) respectively via Birch reduction. Treatment of 138 with bromine and silver acetate gave bicyclic bromoketone 149. Reduction of 149 to alcohol 150, followed by acid catalyzed hydrolysis, led to \( \alpha \)-bromocyclohexenone 139. After acetylation, the enone function of 151 was epoxidized with basic hydrogen peroxide to afford 152. In another approach, the acetate from 137 was oxidized at the enone function to diol 156 with osmium tetroxide-potassium chlorate. Controlled acetylation of 156 gave the \( \alpha \)-acetoxycyclohexanone 157. Ortho-nitrophenylselenocyanate (160) and 138 were treated with tri-\( n \)-butylphosphine to form selenide 161. Condensation of the hydrolysis product of 138 with 2-aminopropan-1, 3-diol (166) took place under mild conditions to give the vinylogous amide 167.
Part 1. The Total Synthesis of (-)-Acorenone B
Part 2. Approaches to the Synthesis of Mycosporin (P 310)

by

John Fredrick Ruppert

A THESIS

submitted to

Oregon State University

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the requirements for the
degree of

Doctor of Philosophy

Completed July 1977
Commencement June 1978
DEDICATED

To my Parents

and all my

Huckleberry Friends

who have seen

The Moon River,

wider than a mile.

We're crossin' you in style

some day.

Old dream maker,

you heart breaker,

wherever you're goin',

We're goin' your way.
ACKNOWLEDGEMENTS

Thanks, Dr. White. It has been a rare privilege.

Mitch Avery, you did a fine job on your part of the acorenone B synthesis.

To my fellow workers, who returned my persistent questions with valuable advice, I owe many successes.
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PART I. THE TOTAL SYNTHESIS OF (-)-ACORENONE B

I. INTRODUCTION

Many natural products have been found which contain spiro rings. Among the sesquiterpenes, (-)-acorenone B (1) (1), lubimin (2) (2, 3), and α-cedrene (3) (4, 5) serve as examples.

\[ \text{Skeletal types such as those above include a number of structural pairs, in which the ring frames are differentiated by a single carbon-carbon bond transposition (6). Examples include the acorane (4)-carotane (5) (7), vetispirane (6)-eudesmane (7), and chamigrane (8)-himachalane (9) families (8, 9, 10). The synthesis of spiro and} \]

\[ \text{Structures of compounds 1, 2, 3, 4, 5, and 6 are shown.} \]
fused systems of these types (11, 12) in a controlled fashion from a common intermediate is of considerable interest, since it should be both economical and versatile (13, 14, 15).

Naturally occurring spiro compounds have been synthesized by a wide variety of methods, and extension of these methods remains today an active area of endeavor (16-40). The most comprehensive review of spiroannellation methodology is that of Krapcho (11), and a review by Marshall, Brady, and Andersen (41) thoroughly covers spiro [4, 5] decane sesquiterpenes. Our approach to a solution of the problem of generating fused and spiroannellated systems by a single route derives from earlier work of Deslongchamps (13), in which intramolecular addition of a carbenoid to an endocyclic olefin produced a tricyclic intermediate (10). It was our hope that intermediates of this type could be induced to undergo selective fission of the cyclopropane ring bonds to give 11 and 12. Such processes, while they have ample precedent in simple systems, are more exacting when applied to the complex, functionalized frameworks required for natural product synthesis. In particular the question
of regioselectivity and stereoselectivity must be resolved.

Before attempting the synthesis of a natural material (acorenone B) along these lines, it was decided to test the validity of this approach in two simplified, model systems. Since the starting materials for both of these model routes (and ultimately for acorenone B itself) required a chain extension by reaction of an organozinc intermediate with a ketone, an initial investigation was directed toward development of an improved technique for this reaction. Chapter II describes a method whereby the Reformatsky reaction and the reaction of allylzinc bromides with carbonyl compounds can be carried out in high yield, without the inconvenience and risk associated with the conventional procedure. Chapter III describes work carried out with model systems, which established the viability of the concept outlined above. In Chapter IV, this approach is applied successfully in a total synthesis of natural (-)-acorenone B.
II. CONTINUOUS FLOW REACTIONS ON ZINC

An Improved Procedure for Preparation of β-Hydroxy Esters

The conventional Reformatsky synthesis of β-hydroxy esters (15) (43) is performed by placing in the reaction flask a stoichiometric

\[
\begin{align*}
R \text{C}=O + \text{BrCH}_2\text{COOEt} + \text{Zn} & \rightarrow \text{C}=O + \text{BrCH}_2\text{COOEt} + \text{Zn} \\
\end{align*}
\]

quantity of zinc granules, along with a small portion of the reactant solution containing the carbonyl compound (13) and the α-bromoester in benzene. The stirred mixture is heated to initiate reaction where-upon a further quantity of the reactant solution is added to maintain reflux. The final product (15) is obtained by hydrolysis of the β-alkoxyzinc ester (14).

This method encourages a number of competing side reactions, including self-condensation of the α-bromoester and elimination or retrograde aldol condensation of the intermediate β-alkoxyzinc ester (14). These diversions cause poor yields and give product mixtures
containing troublesome contaminants. Much of the difficulty may be traced to the fact that, although heat is generally required to initiate the Reformatsky reaction, once started it becomes vigorously exothermic, often requiring careful moderation. This problem and attendant side reactions are particularly severe on a large scale.

Of the several published improvements for conducting the Reformatsky reaction (44, 45), that of Rathke and Lindert (46), in which the reaction is carried out at room temperature in trimethyl borate-tetrahydrofuran (TMB-THF) solvent, appears to offer special promise. Our own approach (47) has been based on the supposition that a continuous-flow system, having a minimum contact of starting material and product in the reaction zone, could both enhance the yield and avoid the repetition of a batch procedure.

The procedure found to be most effective involves the dropwise addition of a 1:2 molar mixture of the carbonyl component (13) and ethyl bromoacetate in benzene to a benzene-presaturated column containing granular zinc. The apparatus for this purpose is shown in Figure 1. Sufficient heat was applied to the column to maintain a gentle reflux at the column head. The resulting zinc alkoxide (14) is delivered by the column as a pale yellow, benzene solution, and successive washings of this solution with 15% sulfuric acid, saturated sodium bicarbonate solution, and brine gave the hydroxy ester (15) in high yield.
Figure 1. Apparatus for conducting continuous-flow Reformatsky reaction.
The results obtained from reaction of ethyl bromoacetate with a number of aldehydes and ketones are summarized in Table I. It can be seen that yields from the present procedure represent substantial improvements over those obtained by conventional methods, and compare favorably with those of Rathke and Lindert (46).

Product hydroxy esters 16-23 were purified by short-path distillation, and were identified by ir, nmr, and mass spectral data. All showed a single peak upon gc, but nmr evidence indicated that the products 20-23 were, in each case, a mixture of stereoisomers. No attempt was made to separate these isomers.

An Efficient Synthesis of Homoallylic Alcohols

Allylzinc bromides were readily prepared from allylic bromides (25) by the zinc-column method described above. They reacted

\[
\begin{align*}
    &\text{R} + \text{Zn} \\
    &\text{H}_3\text{O}^+ \\
    &\text{OZnBr} \\
    &\text{OH}
\end{align*}
\]

smoothly with carbonyl compounds (24) in a manner very similar to that of α-bromo esters under the continuous flow conditions (47). This improved method (48) was employed in the condensation of ethyl 2-(bromomethyl)acrylate (28) with aldehyde 29 in the synthesis of acorenone B (40) (Table II and Figure 9).
<table>
<thead>
<tr>
<th>Carbonyl compound</th>
<th>Product</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Butanal</td>
<td>( \text{CH}_3(\text{CH}_2)_2\text{CH(OH)}\text{CH}_2\text{COOEt} ) (16)</td>
<td>89</td>
</tr>
<tr>
<td>Cyclopentanone</td>
<td>( \text{CH}_2\text{COOEt} ) (17)</td>
<td>95</td>
</tr>
<tr>
<td>Cyclohexanone</td>
<td>( \text{CH}_2\text{COOEt} ) (18)</td>
<td>93</td>
</tr>
<tr>
<td>Benzaldehyde</td>
<td>( \text{C}_6\text{H}_5\text{CH(OH)}\text{CH}_2\text{COOEt} ) (19)</td>
<td>94</td>
</tr>
<tr>
<td>Carbonyl compound</td>
<td>Product</td>
<td>Yield, %</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------</td>
<td>----------</td>
</tr>
<tr>
<td>2, 2, 6-Trimethylcyclohexanone</td>
<td><img src="#" alt="Chemical Structure" /></td>
<td>Zinc column(^a) 49</td>
</tr>
<tr>
<td>4-Phenylcyclohexanone</td>
<td><img src="#" alt="Chemical Structure" /></td>
<td>96</td>
</tr>
<tr>
<td>(-)-Carvomenthone</td>
<td><img src="#" alt="Chemical Structure" /></td>
<td>83</td>
</tr>
<tr>
<td>1-Methyl-4-(5-methylhex-4-enoyl) cyclohexene</td>
<td><img src="#" alt="Chemical Structure" /></td>
<td>86</td>
</tr>
</tbody>
</table>

\(^a\) Based upon glpc analysis using internal standards.
\(^b\) Data from ref. 46
\(^c\) Data from ref. 44
\(^d\) Data from ref. 42
Table II
Reaction of Allylzinc Bromides with Carbonyl Compounds

<table>
<thead>
<tr>
<th>Carbonyl compd.</th>
<th>Bromide</th>
<th>Product</th>
<th>Yield, %&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzaldehyde</strong></td>
<td>Allyl</td>
<td><img src="image1" alt="Structure" /></td>
<td>96</td>
</tr>
<tr>
<td><strong>Cyclohexanone</strong></td>
<td>Allyl</td>
<td><img src="image2" alt="Structure" /></td>
<td>97</td>
</tr>
<tr>
<td><strong>Acetophenone</strong></td>
<td>Allyl</td>
<td><img src="image3" alt="Structure" /></td>
<td>97</td>
</tr>
<tr>
<td><strong>2-Methylcyclohexanone</strong></td>
<td>Allyl</td>
<td><img src="image4" alt="Structure" /></td>
<td>93</td>
</tr>
<tr>
<td>Carbonyl compd.</td>
<td>Bromide</td>
<td>Product</td>
<td>Yield, %</td>
</tr>
<tr>
<td>------------------------------------------------------</td>
<td>-----------</td>
<td>-------------------------------------------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>2-Methyl-5-isopropyl-cyclopent-1-ene-carboxaldehyde</td>
<td>Allyl</td>
<td><img src="image1.png" alt="Image" /></td>
<td>90</td>
</tr>
<tr>
<td>Ethyl pelargonate</td>
<td>Allyl</td>
<td><img src="image2.png" alt="Image" /></td>
<td>94</td>
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<tr>
<td>3-Pentanone</td>
<td>Crotyl</td>
<td><img src="image3.png" alt="Image" /></td>
<td>96</td>
</tr>
<tr>
<td>Benzaldehyde</td>
<td>Crotyl</td>
<td><img src="image4.png" alt="Image" /></td>
<td>95</td>
</tr>
<tr>
<td>α-Tetralone</td>
<td>Crotyl</td>
<td><img src="image5.png" alt="Image" /></td>
<td>93</td>
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Table II (Continued)

<table>
<thead>
<tr>
<th>Carbonyl compd.</th>
<th>Bromide</th>
<th>Product</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetone</td>
<td>Geranyl&lt;sup&gt;e&lt;/sup&gt;</td>
<td><img src="image" alt="Acetone Geranyl" /></td>
<td>80</td>
</tr>
<tr>
<td>Isobutyraldehyde</td>
<td>Geranyl</td>
<td><img src="image" alt="Isobutyraldehyde Geranyl" /></td>
<td>74</td>
</tr>
<tr>
<td>3-Methyl-2-butenal (44)</td>
<td>1-Bromo-3-methyl-2-butene (45)</td>
<td><img src="image" alt="3-Methyl-2-butenal" /></td>
<td>91</td>
</tr>
<tr>
<td>2-Methyl-5S-isopropyl-cyclopent-1-enecarbox-aldehyde (29)</td>
<td>Ethyl 2-(bromomethyl) acrylate (28)</td>
<td><img src="image" alt="2-Methyl-5S-isopropyl-cyclopent-1-enecarbox-aldehyde" /></td>
<td>&gt;50</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield following distillation except for 41 and 42
<sup>b</sup> Ref. 61
<sup>c</sup> Ref. 62
<sup>d</sup> Ref. 63
<sup>e</sup> Ref. 59
Optimum yield required the slow addition of a 1:1.5 molar mixture of the carbonyl component (24) and allylic bromide (25) in tetrahydrofuran to the column containing granular zinc heated to just below the reflux temperature of the solvent. After addition was complete, the column was flushed with tetrahydrofuran and the collected zinc alkoxide (26) was hydrolyzed with dilute sulfuric acid to yield the homoallylic alcohol (27).

The results are summarized in Table II. Yields of alcohols (30-41) are consistently higher than those obtained from allylzinc bromides and aldehydes or ketones under conventional reaction conditions (49), and are also superior to those obtained in the Barbier-Grignard reaction using allylmagnesium halides (50). A noteworthy feature of the zinc column method is the absence of Wurtz coupling product derived from the allylic halide. The method is especially well suited to the large-scale preparation of homoallylic alcohols and, as judged from 35, is applicable to esters as well as aldehydes and ketones. However, the method is ineffective with allylic chlorides and with saturated bromides.

Product bromides were purified by short-path distillation and identified by means of infrared, nmr, and mass spectral data. In the case of the alcohol derived from crotyle bromide and \( \alpha \)-tetralone (43), dehydration occurred upon distillation, leading to diene 38. Also of note is formation of lactone 42, derived from aldehyde 29 (60) and
allylic bromide 28 (40). In this case, elimination of zincbromide-ethoxide during the reaction is in agreement with the results of previous workers (51, 52). The structures of products 36-42 reveal that attack on the unsymmetrical allylic moiety takes place solely at the β-carbon in this reaction, in agreement with similar observations made with allylmagnesium (53) and allylzinc halides (54). This feature ("allylic transposition") lent itself to an efficient, one-step synthesis of (±)-artemisia alcohol (41) (55). Thus, passage through a heated zinc column of a mixture of 3-methyl-2-butenal (44) (56) and 1-bromo-3-methyl-2-butene (45) (57) gave, after hydrolysis, a 91% yield of 41. The structure of artemisia alcohol (41) was confirmed by oxidation with chromium trioxide in pyridine to the corresponding ketone (55) (58).

The continuous-flow column procedure appears to be a generally useful method for allylation of carbonyl functions where mild reaction conditions are necessary. The operational simplicity and high efficiency of the method afford significant advantages over the Grignard reaction in certain cases.
III. SYNTHESIS OF FUSED AND SPIRO SYSTEMS FROM A COMMON INTERMEDIATE

For the reasons outlined in Chapter I, a synthetic entry into either spiro or fused carbon systems from a single intermediate could prove invaluable (39). A tricyclic structure such as 46 is an attractive candidate for this purpose, since selective fission of the cyclopropane ring can, in principle, afford either spiro (47) or fused (48) skeletons. These frames are representative of a larger group of spiro[4.5]decane and perhydroazulene sesquiterpenes respectively.

(±)-Chamigrene has been synthesized by White and coworkers (64) using this approach. There remain, however, crucial questions concerning (i) the regioselectively to be expected from the two ring-cleavage modes and (ii) the configuration at the spiro center and ring fusion, as well as adjacent centers, resulting from the cyclopropane fragmentation. The work described herein is relevant to both these questions, and establishes the validity of this concept as a general method for synthesis of fused and spiro rings.

Tricyclic ketones 49 and 50 were chosen as substrates for testing the feasibility of this approach to ring synthesis. The
\[
\begin{align*}
\text{CH}_2\text{Br} & \quad \text{PBr}_3 \quad \text{CH}_2\text{OH} \quad \text{LiAlH}_4 \\
\text{(CH}_2\text{)}_n & \quad \text{(CH}_2\text{)}_n & \quad \text{(CH}_2\text{)}_n
\end{align*}
\]

1. KOH
2. H_3O^+ 

\[
\begin{align*}
\text{(CH}_2\text{)}_n & \quad \text{COOEt}_2 \\
\text{(CH}_2\text{)}_n & \quad \text{COOH}_2 \\
\text{(CH}_2\text{)}_n & \quad \text{COOH}
\end{align*}
\]

Figure 2
carboxylic acids 51 and 52 appeared to be suitable precursors to ketones 49 and 50 respectively. Their preparation was undertaken following the method of Cook and Lawrence (Figure 2) (66).

The Reformatsky reaction of cyclohexanone 54 with ethyl bromoacetate, carried out according to the modified protocol described in Chapter II (47) gave β-hydroxyester 18 in 93% yield. Dehydration of 18 was accomplished by treatment with thionyl chloride in pyridine-ether to give unsaturated ester 58 in 77% yield. Formation of the endocyclic isomer 58 as the predominant olefin was confirmed by the nmr spectrum, which showed a two-proton multiplet at δ 2.94 for the allylic methylene group. Chain extension of ester 58 by two carbon atoms was effected by an alkylative attachment of diethyl malonate.

In order to prepare a halide suitable for this alkylation, 58 was reduced with lithium aluminum hydride in ether to alcohol 60 (primary O-H absorption at 3320 cm \(^{-1}\)) in 92% yield, which was brominated with phosphorus tribromide in ligroin to give 62 in 68% yield. Diester 64 was formed in 66% yield upon alkylation of the pre-formed mono-sodium enolate of diethylmalonate with bromide 62 in refluxing ethanol. Saponification of 64 took place in methanolic potassium hydroxide solution at reflux to give crystalline dicarboxylic acid 66 in 81% yield. Finally, heating and melting of 66 at 180° C, followed by distillation gave monocarboxylic acid 52 in 96% yield. The acid 51 was obtained in an exactly analogous manner, starting from cyclopentanone (53).
The synthesis of tricyclic ketones 49 and 50 from 51 and 52 is depicted in Figure 3. Treatment of 52 with an excess of oxalyl chloride without solvent gave acyl chloride 68, which was in turn treated with an ethereal solution of diazomethane to afford the yellow diazoketone 70. The decomposition of 70 in refluxing cyclohexane in the presence of copper bronze gave the crystalline ketone 50 in 38% yield after chromatography on alumina. An analogous sequence starting from 51 gave the corresponding, oily ketone 49 in 33% yield.

The dissolving metal reduction of fused cyclopropyl ketones (67) has been shown to fall under firm stereoelectronic control. In general, the cyclopropyl bond which cleaves is the one possessing the greater overlap with the \( \pi \)-orbital system of the carbonyl group (125). White and coworkers (64) have suggested that the tricyclic system 71 adopts the conformation shown, in which the peripheral cyclopropane bond is parallel to the carbonyl \( \pi \) axis and therefore has the greatest overlap. In agreement with this, the peripheral cyclopropane bonds of 49 and 50
Figure 3
underwent preferential reductive scission upon treatment with lithium in ammonia-ether to give spiro[4.5]ketone 72 (C=O absorption at 1712 cm\(^{-1}\)) in 52\% yield and spiro[5.5]ketone 73 (C=O absorption at 1710 cm\(^{-1}\)) in 53\% yield respectively after chromatography.

In contrast, when ketones 49 and 50 were placed in a two-phase system, consisting of concentrated hydrochloric acid and ether, a single, bicyclic chloro-ketone was formed in each case. The structures of these two products were established as 74 and 75 on the basis of spectral evidence (C=O absorption at 1715 cm\(^{-1}\); CH-Cl multiplet at δ3.8), and also from the findings that chromatography on alumina regenerated the cyclopropyl precursors 49 and 50 in quantitative yield in each case. The latter result strongly implies the configurations indicated in 74 and 75, in which the ready displacement of chloride results from a stereoelectronically favorable relationship of leaving group and internal enolate anion.

Treatment of 49 and 50 in methanol with p-toluenesulfonic acid gave the bicyclo[5.3.0]decanone 76 (C=O absorption at 1712 cm\(^{-1}\)) in 38\% yield and the bicyclo[5.4.0]undecanone 77 (C=O absorption at 1710 cm\(^{-1}\)) in 73\% yield respectively, after chromatography. The formation of fused structures in these cases is accompanied by a tertiary methyl ether substituent (CH\(_3\)-O singlet at δ3.3). Each ketone, 76 and 77, was found by gas chromatography to consist of a pair of cis/trans stereoisomers which could not be separated. Only
the cis-isomers are shown in Figure 3.

The contrasting results obtained when tricyclic ketones 49 and 50 were treated with acid (hydrochloric acid in aqueous ether) in one case to give spiro products (74, 75), and with acid (p-toluenesulfonic acid in methanol) in another case to give fused products (76, 77), demand a mechanistic rationale. The conditions of pathway a (low temperature, short reaction time, non-polar solvent, and the presence of a good nucleophile) suggest that formation of the spiro product 75 occurs with nearly concerted protonation of the carbonyl oxygen and chloride attack at the cyclopropane, the peripheral bond of which is vulnerable due to its overlap with the carbonyl π system, as discussed above. The formation of a single chloroketone isomer supports this mechanism. By comparison, the conditions of pathway b (reflux, polar solvent, longer reaction time, and absence of a good nucleophile) allow formation of intermediate carbonium ion 78, which gives rise to the product via a 1,2-alkyl shift (Wagner-Meerwein rearrangement) as shown above. This is followed by quenching of the subsequently formed tertiary carbonium ion 79 with solvent.
Another route to bicyclic, fused systems was found which employed acid treatment of the alcohols derived from tricyclic ketones 49 and 50 (Figure 4). Reduction of 49 and 50 with sodium borohydride

\[
\begin{align*}
\text{49} \quad & \quad \text{NaBH}_4 \quad \text{MeOH} \\
\text{or} \quad & \quad \text{MeOH} \\
\text{50} \\
\end{align*}
\]

in methanol gave a 1:3 mixture of exo-80 and endo-81 in 71% total yield and a 1:4 mixture of exo-82 and endo-83 in 82% total yield respectively. The exo/endo ratios were determined by nmr spectroscopy which indicated a higher field resonance (δ4.1-4.2) for the proton CH-O signal in the exo-alcohols than for the endo-alcohols.

Figure 4
Only partial separation of these exo/endo-alcohol pairs was possible by thin-layer chromatography. The observed predominance of the endo-alcohol in each case is presumably the result of hydride delivery to the carbonyl group from its least hindered side as shown for 50.

Perchloric acid treatment of a mixture containing exo-82 and endo-83 alcohols in methanol gave predominantly the cis fused isomer 85 and a small amount of the trans fused isomer 86. In an analogous manner, treatment of 80 and 81 led to a mixture from which only the cis fused isomer 84 was isolated in 37% yield.

Preparative gas chromatography allowed separation of pure cis-85 and trans-86 and quantitation of their relative amounts. The data in Table III show that the cis:trans product ratio in the case of the alcohols derived from 50 is independent of the configuration of the hydroxy group in the starting material and, when taken with the observation that the cis-isomer 85 was slowly converted into its more stable trans counterpart 86 under the reaction conditions, indicate that the cis stereoisomers were initially formed in this reaction with virtually complete stereoselectivity. A reason for this
Table III
Acid Catalyzed Methanolsysis of exo-82 and endo-83 Alcohols

<table>
<thead>
<tr>
<th>Alcohols 82:83</th>
<th>Yield of 85 (%)</th>
<th>cis:trans ratio of product</th>
</tr>
</thead>
<tbody>
<tr>
<td>47:53&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>69</td>
<td>3:1</td>
</tr>
<tr>
<td>5:95&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>75</td>
<td>3:1</td>
</tr>
<tr>
<td>20:80&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>75</td>
<td>9:1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions were carried out for 0.5 h in methanol containing one drop of 70% perchloric acid.

<sup>b</sup> At 20°C.

<sup>c</sup> At 0°C.

Stereocontrol can be derived by postulating that an intermediate carbonium ion 88 is formed from 87. This undergoes a 1,2-shift

\[
\begin{array}{c}
\text{H} \quad \text{H} \\
87 \quad 88
\end{array}
\]

of the vinylic carbon (homoallylic participation) with concurrent attack at the forming tertiary center by solvent to yield the cis-product 85. An inversion of configuration at the origin of migration in a 1,2-alkyl shift is commonly observed (126).

Thus, it is established that tricyclic intermediates such as 49 and 50 can lead efficiently to both spiro and fused systems. The
extension of these techniques to the synthesis of intermediates which can be selectively converted to either spiro or fused structures of natural products was a further goal of this project. Chapter IV deals with the preparation of such an intermediate and its conversion to the natural spiro[4.5]sesquiterpene, (-)-acorenone B.
IV. THE TOTAL SYNTHESIS OF (-)-ACORENONE B

The steam-volatile oil oil of a hybrid grass prepared from two parent races of Bothriochloa intermedia has been found to contain, as a major component, the sesquiterpene acorenone B (1) (1, 124). Acorenone B is similar to acorenone (89), a substance previously isolated from Acorus calamus (68), both in physical properties and in its ir spectrum. The structure of acorenone B (1) was determined by X-ray crystallography. Three total synthetic routes to racemic 1 have been published (35, 36, 37). In addition a total synthesis of racemic 89 has recently been reported starting from racemic 1 (69). This chapter describes the first total synthesis of natural (-)-acorenone B (1) (40).

The first synthesis of racemic 1, by a partially stereoselective route, was reported by Wolf and Kolleck (35), who prepared the spiro[4, 5] frame by acid-catalyzed cyclization of 90 to 91 (Figure 5).

The stereoselectivity of a kinetically controlled, intramolecular ene-reaction was exploited by Oppolzer and Mahalanabis (36) (Figure 6).
Wolf Route

\[
\text{Ketone} + \text{Br}(\text{CH}_2)_3\text{CH}==\text{CH}_2 \xrightarrow{\text{Mg}} \text{Alcohol} (90)
\]

\[
\text{HCOOH} \xrightarrow{\text{HCHO}} \text{Aldehyde} (91)
\]

\[
\text{Ketone} \xrightarrow{\text{H}_2/\text{Pt}/\text{C}} \text{Ketone} (90)
\]

\[
\text{Ketone} \xrightarrow{\text{OH}^-} \text{Ketone} \xrightarrow{\text{Cr}^{+6}, \text{H}^+} \text{Ester} (91)
\]

\[
\text{Ketone} \xrightarrow{\text{t-BuOK}, \text{CH}_3\text{I}} \text{Ketone}
\]

\[
\text{Ketone} \xrightarrow{\text{Br}_2} \text{Ketone} \xrightarrow{\text{Li}_2\text{CO}_3/\text{DMF}} \text{Product} (\pm) 1
\]
Oppolzer Route

92

EtOOCC

280°C

EtOOCC

93

CH₃Li

HO

Al₂O₃

Py

Na₂Cr₂O₇

H₂

(Ø₃P)₃RhCl

Pb(OAc)₄

OAc

CH₃Li

p-TSOH

Figura 6
Trost Route

Figure 7 (Continued)
Thermal cyclization of 92 furnished a separable mixture (1:1) of ester 93 and the isomer with the carboethoxy group and methyl group trans. The configurational relationship of the methyl group and spiro carbon shown in 93 was achieved with 100% stereoselectivity.

A third route to racemic 1 is that of Trost and coworkers (37), who utilized spiroannelation of ketone 94 with ylide 95, followed by rearrangement of the oxaspiropentane 96 to give 97 (Figure 7). This cyclobutanone derivative is reported to be formed with complete stereoselectivity, although the cyclopentanone precursor (94) was a mixture of cis and trans isomers. The explanation advanced by Trost for the stereohomogeneity of 97 was threefold. The interconversion of the E and Z isomers of 94 is faster than ylide addition to the carbonyl group. Of the two isomers, the Z isomer, which can present a sterically unhindered face to the bulky ylide, reacts selectively. Finally, the rearrangement of the oxaspiropentane (96) to the cyclobutanone (97) is stereospecific.

The three routes to racemic 1 all suffer from significant limiting features. Wolf and Oppolzer utilized nonstereospecific cyclization steps in their routes to obtain, in each case, mixtures of spiro[4, 5]decane intermediates. The route of Trost suffers from excessive length due, in part, to a cumbersome 1, 2-dicarbonyl transposition.

The approach described in Chapter III for synthesis of
Figure 8
spirocarbocyclic systems, based upon the intramolecular cycloaddition of a diazoketone to an olefin, is applicable, in principle, to the synthesis of \( \mathbf{1} \). In this chapter a total synthesis of \((-\)-\( \mathbf{1} \)) is described, using this strategy in a manner which permits development of the appropriate configurations at the three contiguous, chiral centers of the sesquiterpene in a fully stereocontrolled manner.

\( \text{R-}(\,\text{+}\,)-\text{Limonene (99)} \) was chosen as starting material, since its absolute configuration at the isopropyl bearing carbon (C-4) is identical to the absolute configuration found at C-1 in \((-\)-acorenone B (Figure 8). This center was preserved in configuration throughout the synthesis. A sequence outlined by van Tamelen and coworkers (60) for \( \text{S-}(-)-\text{limonene} \) was followed to transform 99 into aldehyde 29. Selective, catalytic hydrogenation of 99 at the less substituted double bond, using Adam's catalyst, gave olefin 100 in 87% yield. Epoxide 101 was formed in 87% yield by treatment of 100 with peracetic acid in the presence of sodium carbonate. Hydrolysis of 101 gave diol 102 in 76% yield. Oxidative cleavage of the glycol 102 was performed with sodium metaperiodate to give ketoaldehyde 103.

Attempts to cyclize ketoaldehyde 103 by the method of van Tamelen (60) gave low yields of impure aldehyde 29. In view of these results, a modified two-step procedure was worked out which allowed a directed internal aldol cyclization to occur in a controlled manner. The enamine of 103 was formed (with piperidine in
ether at 0° C) exclusively at the more reactive carbonyl, the aldehyde function, to give 104. Intramolecular condensation of 104 and subsequent hydrolysis in a mixture of refluxing ether and glacial acetic acid gave aldehyde 29 in 83% overall yield from 103. None of the condensation product 105 was produced in this sequence, although

![](image)

105 was formed, along with 29, in a one-step cyclization of 103 initially attempted with hydroxide as the base. The uv spectrum of 29 closely matches the literature value (60) and the melting point of the 2, 4-dinitrophenylhydrazone is in good agreement with that reported (60, 82).

Attempts to condense 106, prepared from triphenylphosphine

![Chemical structure](image)
Figure 9
and β-bromopropionic acid, with aldehyde 29 in a Wittig reaction (75) were disappointing, and this route was abandoned when no reaction conditions which would produce 107 in useful purity could be found. In addition to poor yield, this approach is burdened by the necessity of an alkylation step to introduce the C-8 methyl group in acorenone B (1).

An alternative and more attractive approach to elaboration of 29 towards an intermediate suitable for spiroannelation appeared to lie through use of the alkylation methodology described in Chapter II. Thus, 29 underwent condensation with ethyl-2-bromomethyl acrylate (28) (77-80), upon passage of the mixture in tetrahydrofuran through a heated column of granular zinc (48), to give the α-methylene-γ-lactone 42 (81) (Figure 9). Hydrogenation of 42 in ethanol, first over Adam's catalyst to give 108, and then over palladium on calcium carbonate (hydrogenolysis), afforded the carboxylic acid 109 in 50% yield based on 29. Conversion of 109 into the diazoketone 111 via the acyl chloride 110 (83) was effected as previously described (84) (Chapter III), and decomposition of 111 with copper powder (13) in refluxing cyclohexane gave the cyclopropyl ketone 112 as an oil in 34% yield, based on 109. The gas chromatogram and subsequent transformations of 112 showed it to be an epimeric mixture with respect only to the methyl group α to the carbonyl group, and thus established that carbenoid addition, following decomposition of 111,
occurred with complete stereoselectivity at the face of the cyclopentene double bond opposite the isopropyl group. This stereoselectivity is in agreement with that found by previous workers (13, 14) who obtained a mixture of 114 and 115 in the ratio of 9:1 upon decomposition of diazoketone 113.

Treatment of 112 with hydrogen chloride (13, 72, 73, 74) in chloroform (Figure 10) led cleanly to 116, which was hydrogenated (73, 74) over a rhodium-on-carbon catalyst to give 117 in 60% yield from 112.

Introduction of the enone function was effected in 34% yield from 117 via the enol acetate 118 (85) prepared from 117 with acetic anhydride containing a catalytic amount of perchloric acid. The bromo-ketone 119 derived from 118 with bromine and mixture of sodium acetate and acetic acid in chloroform (86), was dehydrobrominated using lithium chloride and lithium carbonate in dimethylformamide (35) to give (-)-acorenone B. Although a sample of natural acorenone B was not available, identity of the synthetic material was confirmed.
(−)-Acorenone B

by comparison of its ir, nmr, and mass spectra, as well as retention time on gas chromatography, with an authentic sample of (±)-acorenone B provided by Dr. H. Wolf (35). The synthetic acorenone B had a rotation \([\alpha]_{D}^{20}\) of -19°.

Reduction of 112 with lithium in liquid ammonia (Figure 11) produced 120 in 49% yield, with a configuration at the cyclopentane ring position C-4 corresponding to the acorone 121 (87) rather than the acorenone series. Proton of the dilithio intermediate 122
from 112 thus occurs predominately by route a with inversion of the methyl-bearing cyclopropane carbon atom (C-4), a result in
agreement with the findings of Piers and Worster (88). These workers found that the alkali metal-in-ammonia reduction of 123 gave 124 as a major component and 125 as a minor component of the product mixture. The enone 128 was prepared from 120 in a manner analogous to that for 1, giving 4-epi-acorenene B (71) (128, \([\alpha]_D^{20} -50^\circ\)) in 30% yield based on 120.

The tricyclic intermediate 112 can thus be converted to either (-)-acorenene B, via acid cleavage followed by catalytic hydrogenation, or to the C-4 epimer of acorenene B (128), via lithium-ammonia reduction. In addition, previous work of White and coworkers (64) in their synthesis of (±)-chamigrene (129) and that of Deslongchamps
and coworkers (13) in the synthesis of (±)-agarospirol (130) from similar tricyclic intermediates serves to establish the usefulness of this approach as a general entry to natural spiro systems. Furthermore, the possibility of extending this scheme of synthesis of fused systems such as the perhydroazulene sesquiterpene (+)-carotol (131) is foreshadowed in the preparation of 84 from 81.
PART II. APPROACHES TO THE SYNTHESIS OF MYCOSPORIN (P 310)

V. INTRODUCTION

Light is an absolute requirement for the formation of reproductive organs in many species of fungi. All the major groups of true fungi, as well as some myxomycetes, include light sensitive species (89). With certain photosensitive fungi, the stimulation of the phenomenon of reproduction is accompanied by the formation within the mycelium of substances which have maximum absorptions at 310 nm (90). These compounds, conventionally called "P 310" (Leach, 1964) (91), have been the subject of studies by Leach (92, 93), Trione et al. (89), Vargas and Wilcoxon (94), van den Ende and Cornelius (95), Hite (96), Tan and Epton (97), and Dehorter (90). In contrast, Weste (98) and Stallings (90) report that they could not find these products in the mycelium of fertile, irradiated Ophiobolus grammis and Aspergillus ornatus.

The sporogenic property of "P 310" has been demonstrated by the experiments of Leach and Trione (89, 99), Tan and Epton (97) and Dehorter (90). According to these authors, P 310's, when added to the growing culture, replace the stimulus of the light by inducing in the dark the sporulation of Ascochyta pisi, Stemphyllum solani, Botrytis cinerea, and Nectria galligena. However, this work which
seems to establish a relationship between photoinduction, reproduction, and the synthesis of "P 310" is contradicted by certain observations—in particular those of Vargas and Wilcoxon (94), of van den Ende and Cornelius (95) and of Hite (96). Vargas noted that introduction of "P 310" in the nutrient medium of Helminthosporium dictyoides did not restore fertility delayed by constant darkness. Van den Ende and Cornelius consider "P 310" a simple photoproduct without sporogenic activity, since experiments on Sclerotina fructicola indicated that nonsporulating, irradiated mycelium had an absorption at 310 nm, while sporulating, non-irradiated mycelium did not contain "P 310."

Finally, Hite observed that application of "P 310," extracted from cultures of non-irradiated Botrytis cinerea, induced sporulation in fungi which normally require light for sporulation.

Literature references to "P 310" are often ambiguous, since this designation actually refers to three substances, P 310A, P 310B, and P 310C. The last is the major component (92). Each of these fractions is homogeneous by uv monitoring of eluent from an ion-exchange column. They each absorb differently at shorter wavelengths than the 310 nm maximum and contain several amino acids (89) and possibly other significant contaminants. Thus interpretation of experimental observations must be made with caution.

Trione, Leach, and Mutch (89) have found that the three forms of P 310 differ in their sporogenic activity when added to the culture
medium of *Ascochyta pisi* and *Pleospora herbarium* in amounts comparable to a normal hormonal activity level. An increase in activity was generally observed with increasing P 310 concentration up to a point, beyond which sporulation began to decline. The sporogenic effect was localized to young mycelium near the droplet sites. Apparently the sporogens are not translocated through the fungus colony to the older mycelium. Either they are completely utilized at the site of application or are diluted beyond the threshold by diffusion through the medium.

Trione and Leach (89, 100) have isolated "P 310" from the ethanolic extract of sporulating mycelium grown in near ultraviolet irradiation. The condensed extract was washed with ether and the ether soluble material discarded. Separation of the polar substances on a 'Dowex-50W' ion-exchange column (acid form) gave two overlapping zones of "P 310," eluted with 0.1 M hydrochloric acid. All eluted fractions containing "P 310" were combined, neutralized, concentrated, and placed on a column of 'Dowex-1' (bicarbonate form). Two well-separated P 310 fractions (A and B) were washed through the column with deionized water. A third fraction was absorbed on the resin and was eluted with 0.1 M triethyl-ammonium bicarbonate. The pH of the solutions were deionized with 'Dowex AG-11A8' resin. On thin-layer chromatography, using ethanol, glacial acetic acid, water (6:2:2, v/v) as solvent with silica gel as absorbent, P 310A, B,
and C can be readily separated. The P 310's are amorphous in appearance and do not have sharp melting points. They dissolve in polar solvents but are insoluble in non-polar solvents. They are rapidly destroyed by 2 M sodium hydroxide at 20°C and slowly destroyed by 2 M sulfuric acid at 20°C.

Favre-Bovin, Arpin, and Brevard (101) have completed a structural study on P 310C, which they isolated from Sterium hirsutum and named mycosporin, and have determined its structure to be that of 132. A more recent study by Arpin, Favre-Bovin, and

![Chemical Structures](image)

Thivend (102) has established 133 to be a minor component isolated from Botrytis cinerea, and have named this mycosporin-2. The
structural elucidation of 132 relied heavily upon nmr spectroscopy, particularly the spectrum of tetraacetate 134 which was obtained from 132 by treatment with acetic anhydride-pyridine. This transformation has precedent in the literature (103-106). Off-resonance spin-decoupling experiments on 134 and some of its derivatives, as well as comparisons of nmr splitting constants and chemical shifts with those of known substances, were interpreted in favor of 132.

The biogenetic pathway leading to mycosporin has not yet been established. However, reasonable intermediates could include 5-dehydroquinic acid (135) and serine (136), the latter forming the side chain. Subsequent biological transformations would involve oxidation, reduction, and methylation.
VI. APPROACHES TO THE SYNTHESIS OF MYCOSPORIN (P 310)

Attempts to reproduce the carbon framework of mycosporin (132) (101) have focused primarily upon routes which begin with cyclohexenone substrates possessing the hydroxymethyl function at

\[
\begin{align*}
\text{OCH}_3 & \quad \text{CH}_2\text{OH} & \quad \text{O} \\
\text{OH} & \quad \text{CH}_2\text{OH} & \quad 7 \text{ CH}_2\text{OH}
\end{align*}
\]

(137), \(R_1 = \text{H}, R_2 = \text{H}\)  
(138), \(R_1 = \text{H}, R_2 = \text{OCH}_3\)  
(139), \(R_1 = \text{Br}, R_2 = \text{H}\)

C-5 (137, 138, and 139).

Cyclohexenones 137 and 138 were obtained from readily available, aromatic precursors in accordance with known methods (107-109 (Figure 12). Birch reduction of 3, 4, 5-trimethoxybenzoic acid (141) with excess sodium in liquid ammonia and methanol gave dihydrobenzoic acid 143 in 72% yield, and reduction of this material with lithium aluminum hydride in ether afforded alcohol 145 in 74% yield. The crystalline cyclohexenone 138 was obtained (by treatment of 145 with acidic methanol) in 92% yield. The ketone 137 was
prepared in a manner analogous to 138 from 3-methoxybenzoic acid (140) (109).

![Chemical structures](image)

Figure 12

The functionalization exhibited by mycosporin (132) at C-1, C-2, and C-3 does not appear to be widespread among secondary metabolites and has little precedent in the synthetic literature. The generation of a substrate possessing an oxygen function for R₁ and an amino, hydroxyl, or halo substituent for R₂ has been the major
goal of this research effort.

Acetylation of 138, followed by bromination in the presence of silver acetate and methanol, gave 147. However, attempted displacement of bromide by acetate or methoxide led instead to elimination product 148. This substance was inert to reaction at the vinyl bromide function.

Epoxidation of 138, using either basic hydrogen peroxide (111) or meta-chloroperbenzoic acid in chloroform (112), failed to take place and, therefore, bromoketone 139 was prepared in the hope that it would submit to epoxidation (Figure 13). Intramolecular trapping of the bromonium ion, generated from 138 by treatment with bromine in the presence of an equivalent amount of silver acetate, gave bicyclic ketone 149, which was reduced by sodium borohydride in methanol, to afford bromohydrin 150 in 85% yield based on 138. Aqueous acid treatment of 150, followed by chromatography on alumina, gave crystalline bromoketone 139 in 64% yield. Acetylation of 139 followed by brief treatment of acetate 151 with 90% hydrogen peroxide in ice-cold methanol containing a catalytic amount of
sodium hydroxide, afforded a product believed to be bromoepoxide 152.

Figure 13

Structure 152 is assigned on the basis of its nmr spectrum which shows no vinyl proton, its greatly diminished uv absorption, its mass spectrum which indicates parent peaks at m/e 262 and 264, and its lack of reactivity with diazomethane (113). The alternative structure 153 should retain uv absorption and would be expected to react with diazomethane to give methylation at the C-2 oxygen in a manner similar to 154, according to the findings of Ibuka, Tanaka, and Inubushi (113).
Although the usefulness of 152 was not fully explored, a more direct route via oxygenation at C-2 with osmium tetroxide was examined, starting from cyclohexenone 137 (Figure 14). It was

![Chemical structures](image)

Figure 14
believed that such a strategy might be more efficient, in that further oxidation at C-3 could be delayed until later in the sequence. In this connection, 137 was acetylated and then oxidized with osmium tetroxide in catalytic amount, by using potassium chlorate as a re-oxidant (114), to give crystalline diol 156 in 51% yield after chromatography. Further oxidation of diol 156 was not attempted since the initial product 158 was expected to be very reactive toward oxidation to a triketone. This could eventually lead to ring-cleavage products, by analogy with results obtained by Wolfrom and Bobbitt (115) on 159.

To circumvent this anticipated difficulty, the oxygen function at C-2 was protected by acetylation with acetic anhydride-pyridine. By careful control of the time and temperature of reaction, the crystalline diacetate 157 was obtained in 62% yield. Jones' oxidation (116) of this substrate appears promising but the product has not been isolated. A method for the selective methylation of the C-2 oxygen would be required to make this a viable pathway.

A major obstacle to a total synthesis of mycosporin (132) is
the tertiary hydroxyl group at C-5. Unfortunately, this function is both acid and base sensitive (100), with a strong tendency towards elimination thereby plunging the compound into aromaticity, a condition from which there is no easy recovery. This sensitivity imposes restrictions on any synthetic scheme which seeks to introduce the C-5 hydroxyl group near the beginning of the scheme, since it demands that strongly acidic or basic operations not be employed thereafter.

The options are limited.

A recent method for the introduction of an olefin function under neutral conditions, using oxidation of an aromatic selenide (117, 118), coupled with diol formation using osmium tetroxide, constitutes one plausible approach. Pursuing this tactic, ketone 138 and ortho-nitrososelecoyanate 160 (119-121) were treated with tri-n-butylphosphine to form the yellow, crystalline selenide 161 in quantitative yield (Figure 15). Completion of the scheme by oxidative removal of the

\[
\begin{align*}
\text{MeO} & \quad \text{O}2\text{N} \\
\text{CH}_2\text{OH} & \quad \text{SeCN} \\
\text{O}2\text{N} & \quad \text{MeO} \\
\text{CH}_2\text{Se} \quad \text{NO}_2 \\
\end{align*}
\]

Figure 15
aromatic selenium moiety of 161 was delayed, pending modification of functionality at C-2, but appears to present no serious difficulty.

The strategy for attachment of the aminopropanediol side chain of 132 follows precedent set forth in the work of Halpern and James (123). They found that the reaction of dimedone (162) with aminoacid esters (163) proceeds readily at room temperature, with formation of well-defined, crystalline products (164). Following this approach,

diketone 165 (which could not be isolated due to its propensity toward polymerization upon solvent removal) was prepared by treatment of ketone 138 with water containing a catalytic amount of acid (Figure 16). Addition of an equivalent of 2-amino-propan-1,3-diol (166) (122) afforded the vinylogous amide 167 directly in 53% yield after recrystallization.

In summary, several facets of the mycosporin total synthesis have been illuminated, including formation of a potentially useful
cyclohexenone structure, functionalization at four of the five oxygenated carbons of the ring, and attachment of the aminediol side chain. However, if the methods presented here are to lead to a synthesis of the metabolite itself, it seems that a certain, invariable ordering of synthetic steps must be embraced. The methoxy function at C-2 must be incorporated before either the side chain or the C-5 alcohol is added. Also, since the selenocyanate 160 (Figure 15) will attach to any and all hydroxyl groups, it must be incorporated before condensation of the side chain. Oxidative elimination of the selenide, followed by selective osmium tetroxide oxidation of the exocyclic olefin provides, in concept, a complete synthesis of mycosporin.
EXPERIMENTAL

General

Melting points were determined on a Kofler hot stage microscope and are corrected; boiling points are uncorrected. Infrared (ir) spectra were recorded on a Perkin-Elmer Model 137 or 727B infrared spectrophotometer. Ultraviolet (uv) spectra were obtained using a Cary Model 15 ultraviolet spectrophotometer. Optical rotation ([α]_D^20) was determined using a Perkin-Elmer Model 141 polarimeter. Nuclear magnetic resonance (nmr) spectra were determined on a Varian Associates Model EM-360 or HA-100 spectrometer with tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in δ units. Mass spectra and exact mass determinations were obtained using a CEC-103B spectrometer at an ionizing potential of 70 eV and were provided by Dr. Rottschaefer and Dr. Wielesek at the Department of Chemistry, University of Oregon, Eugene, Oregon. Elemental analyses were performed by Micro-Tech Laboratories, Inc., Skokie, Illinois. G. l. c. separations and analysis were carried out using (1) a 10 ft X 0.375 in column of 30% Carbowax 20M Chromosorb W, or (2) a 5 ft X 0.25 in column of 20% SE-30 on Chromosorb W with an Aerograph Autoprep 700 instrument. The abbreviations s, d, t, q, m refer to singlet, doublet, triplet, quartet, multiplet respectively. The term "variable" implies
change of $\delta$ with change in temperature.

Ethyl 2-(1-hydroxycyclopentyl)acetate (17)

The following procedure for the conversion of cyclopentanone to 17 is representative of the continuous flow method by which compounds 16-23 were obtained. A solution of cyclopentanone 53 (24.46 g, 0.291 mol) and 97.2 g (0.582 mol) of ethyl bromoacetate in 250 ml of anhydrous benzene was passed dropwise through a column of activated zinc granules (No. 10 mesh) saturated with benzene and preheated to gentle reflux. After 5.5 h, when addition was complete, the column was flushed with 50 ml of benzene. The light yellow benzene solution was hydrolyzed with 600 ml of ice-cold, 15% sulfuric acid in a separatory funnel, neutralized with saturated aqueous sodium bicarbonate, and dried ($\text{MgSO}_4$). After filtration, the solvent was removed in vacuo, and the residue was distilled to give 47.58 g (95%) of 17: bp 51-55°C/0.03 mm; ir (film) 3525, 2965, 2875, 1735, 1365, 1330, 1190, 1095, 1035 cm$^{-1}$; nmr ($\text{CDCl}_3$) $\delta$ 1.26 (3H, t, $J=7$ Hz), 1.4-2.0 (8H, m), 2.60 (2H, s), 3.42 (1H, broad s, variable), 4.21 (2H, q, $J=7$ Hz).

4-Ethyl-4-hydroxy-3-methylhex-1-ene (36)

The following procedure for the reaction of 3-pentanone with crotyl bromide to yield 36 is representative of the continuous flow method by which compounds 30-41 were obtained. A solution of
3-pentanone (3.05 g, 35.4 mmol) and 7.16 g (53.0 mmol) of 1-bromo-2-butene in 50 ml of tetrahydrofuran was passed dropwise through a column of activated zinc granules (No. 10 mesh) saturated with tetrahydrofuran and preheated to gentle reflux. After 1 h, when addition was complete, the column was flushed with 25 ml of tetrahydrofuran and the combined eluate, after dilution with 50 ml of ether, was treated with ice-cold 5% sulfuric acid, followed by sodium bicarbonate solution and saturated brine. The organic layer was dried (MgSO₄), the solvent was removed in vacuo, and the residue was purified by short-path distillation to give 4.81 g (95.6%) of 36: bp 70-73°C/16 mm; ir (film) 3530, 1635, 1455, 1368, 1250, 1120, 1000, 947, 910 cm⁻¹; nmr (CDCl₃) δ 0.8 (6H, d, J=6 Hz), 1.5 (4H, q, J=6 Hz), 1.5 (1H, s, variable), 2.3 (1H, pentuplet, J=6 Hz), 4.8-5.3 (2H, m), 5.5-6.2 (1H, m).

_Artemisia Alcohol (41)_

A mixture of 3-methylbut-2-enal 44 (1.15 g, 13.6 mmol) and 1-bromo-3-methylbut-2-ene 45 (3.05 g, 20.4 mmol) in 20 ml of tetrahydrofuran was passed dropwise through a heated column of activated zinc granules (No. 10 mesh) saturated with tetrahydrofuran and preheated to gentle reflux. After 0.5 h, when addition was complete, the column was flushed with 25 ml of tetrahydrofuran and the combined eluate, after dilution with 25 ml of ether, was treated with
ice-cold 5% sulfuric acid, followed by sodium bicarbonate solution and saturated brine. The organic layer was dried (MgSO₄), and the solvent was removed in vacuo to give 1.68 g (91%) of 41: ir (film) 3440, 1670, 1630, 1460, 1405, 1365, 1260, 1180, 1048, 1010, 990, 913, 880, 843 cm⁻¹; nmr (CDCl₃) δ 1.0 (6H, s), 1.7 (1H, s, variable), 1.75 (6H, d of d, J=2, 6 Hz), 4.1 (1H, d, J=9 Hz), 5.0 (1H, d, J=7 Hz), 5.1-5.35 (2H, m), 5.7-6.2 (1H, m); mass spectrum m/e 136 (M⁺-18).

3,3,6-Trimethylhepta-1,5-diene-4-one (55)

A solution of alcohol 41 (0.776 g, 5.03 mmol) in 3 ml of dichloromethane was added to a solution prepared from 3 g (30 mmol) of anhydrous chromium trioxide and 5 ml of pyridine in 70 ml of freshly distilled dichloromethane. After stirring at room temperature for 0.2 h, the solid material was separated by decantation and washed with 100 ml of ether. The combined organic extract was washed with aqueous 5% hydrochloric acid, sodium bicarbonate solution, saturated brine, and was dried (MgSO₄). Filtration followed by solvent removal in vacuo and distillation gave 414 mg (53%) of 55: bp 75-85° C/15 mm; ir (film) 3000, 1680, 1623, 1460, 1440, 1370, 1100, 1020, 995, 915 cm⁻¹; nmr (CDCl₃) δ 1.22 (6H, s), 1.90 (3H, d, J=1 Hz), 2.13 (3H, d, J=1 Hz), 5.07 (1H, m), 5.22 (1H, m), 5.97 (1H, d of d, J=11, 16 Hz), 6.27 (1H, m).
Ethyl 2-(1-hydroxycyclohexyl)acetate (18)

A solution of cyclohexanone (1.64 g, 16.7 mmol) and 5.6 g (33.6 mmol) of ethyl bromoacetate in 25 ml of anhydrous benzene was passed dropwise through a column of activated zinc granules (No. 10 mesh), saturated with benzene and preheated to gentle reflux. After 0.5 h, when addition was complete, the column was flushed with 50 ml of benzene. The light yellow benzene solution was hydrolyzed with 100 ml of ice-cold, 10% sulfuric acid in a separatory funnel, neutralized with saturated aqueous sodium bicarbonate, and dried (MgSO₄). After filtration, the solvent was removed in vacuo, and the residue was distilled to give 2.87 g (93%) of 18: bp 58-65°C/0.04 mm; ir (film) 3500, 1725, 1195; 1038 cm⁻¹; nmr (CDCl₃) δ 1.26 (3H, t, J=7 Hz), 1.9-1.38 (10H, m), 2.45 (2H, s), 3.45 (1H, s, variable), 4.18 (2H, q, J=7 Hz).

Ethyl 2-(1-cyclopentenyl)acetate (57)

A solution of 55 (47.58 g, 0.277 mmol) and 51.4 g (0.304 mol) of diphenylamine in 500 ml of anhydrous ether was stirred at ice temperature for 1 h while being treated dropwise with 36.2 g (0.304 mol) of thionyl chloride. When addition was complete, the solution was maintained at ice temperature for 20 h and at room temperature for 4 h. After salt removal by filtration, the ethereal solution was
washed once with ice-cold, 50% acetic acid, twice with warm water,
extice with concentrated aqueous sodium bicarbonate, twice with
saturated brine, and was dried (MgSO₄). After filtration and solvent
removal in vacuo, the residue was distilled to give 34.3 g (90%) of 57:
bp 35-43°C/0.06 mm.

A sample of 57 was purified by preparative Glpc (SE-30 column):
ir (film) 2940, 2840, 1735, 1645, 1443, 1370, 1330, 1297, 1245, 1160,
1122, 1090, 1035, 970, 667 cm⁻¹; nmr (CDCl₃) δ 1.25 (3H, t, J=7 Hz),
1.93 (2H, m), 2.36 (4H, t, J=6 Hz), 3.12 (2H, s), 4.16 (2H, q, J=7
Hz), 5.58 (1H, m).

**Ethyl 2-(1-cyclohexenyl)acetate (58)**

A solution of 56 (142 g, 0.76 mol) and 160 g (2.03 mol) of
freshly distilled pyridine in 325 ml of anhydrous ether was stirred
at ice temperature for 2 h while being treated dropwise with 103 g
(0.87 mol) of thionyl chloride. When addition was complete, the
solution was maintained at ice temperature for 2 h longer. Water
(200 ml) was added to dissolve the solid material, and the separated
organic layer was washed with 2 X 500 ml of saturated aqueous
cupric sulfate, with 2 X 500 ml of saturated brine, and was dried
(MgSO₄). After the solvent was removed in vacuo, the residue was
distilled to give 97 g (77%) of 58: bp 40-44°C/0.03 mm; ir (film)
2930, 1735, 1435, 1365, 1328, 1295, 1252, 1155, 1033, 920 cm⁻¹;
nmr (CDCl₃) δ 1.24 (3H, t, J=7 Hz), 1.62 (4H, m), 2.02 (4H, m),
2.94 (2H, m), 4.14 (2H, q, J=7 Hz), 5.60 (1H, m).

2-(1-Cyclopentenyl)ethanol (59)

Ester 57 (90 g, 0.548 mol) was added dropwise over a 1.5 h period to a stirred suspension of lithium aluminum hydride (24.4 g, 0.643 g-atom) in 1200 ml of anhydrous ether stirred at ice temperature. After stirring at room temperature for 12 h, 100 ml of water was added dropwise to produce a granular precipitate. The precipitate was removed by filtration and washed with 3 x 400 ml of ether. The washings were added to the product solution which was then extracted with saturated brine and dried (MgSO₄). After filtration, the solvent was removed in vacuo, and the residue was distilled through a 15 cm Vigreau column to give 44.1 g (72%) of 59: bp 50-54°C/1.1 mm.

A sample of 59 was purified by preparative gc: ir (film) 3340, 2940, 2840, 1645, 1440, 1337, 1292, 1048, 1022, 940, 820 cm⁻¹; nmr (CDCl₃) δ 1.76 (1H, broad s, variable), 1.79-2.1 (2H, m), 2.34 (6H, m), 3.74 (2H, t, J=6 Hz), 5.50 (1H, m).

2-(1-Cyclohexenyl)ethanol (60)

Ester 58 (91.13 g, 0.542 mol) was added dropwise over a 1.5 h period to a stirred suspension of lithium aluminum hydride (22.5 g,
0.596 g-atom) in 1200 ml of anhydrous ether stirred at ice temperature. After stirring at room temperature for 12 h, 100 ml of water was added dropwise to produce a granular precipitate. The precipitate was removed by filtration and washed with 3 X 400 ml of ether. The washings were added to the product solution which was then extracted with saturated brine and dried (MgSO₄). After filtration, the solvent was removed in vacuo, and the residue was distilled through a 15 cm Vigreux column to give 62.62 g (92%) of : bp 62-64°C/1.2 mm; ir (film) 3320, 2920, 1665, 1438, 1133, 1045, 1015, 920, 805 cm⁻¹; nmr (CDCl₃) δ 1.58 (4H, m), 1.97 (4H, m), 2.20 (2H, t, J=6 Hz), 2.6 (1H, broad s, variable), 3.65 (2H, t, J=6 Hz), 5.53 (1H, m).

2-(1-Cyclohexenyl)ethyl Bromide (62)

A solution of 60 (102 g, 0.81 mol) and 13 g (0.077 mol) of diphenylamine in 150 ml of anhydrous ligroin was stirred at ice temperature and treated dropwise with 84 g (0.311 mol) of phosphorous tribromide over a 0.5 h period. After stirring for a further 2 h, 20 ml of water was slowly added. The solid material which formed was separated by filtration and washed with 400 ml of ether. The ether and ligroin portions were combined and extracted with 2 X 250 ml of saturated brine, with saturated aqueous sodium bicarbonate, and dried (MgSO₄). After filtration and solvent removal in vacuo, the residue was distilled to give 95 g (68%) of 62: bp 40-45°C/0.02 mm;
ir (film) 2900, 1665, 1448, 1262, 1205, 1135, 920, 800 cm⁻¹; nmr (CDCl₃) δ 1.59 (4H, m), 1.96 (4H, m), 2.50 (2H, t, J=7 Hz), 3.42 (2H, t, J=7 Hz), 5.53 (1H, m).

2-(1-Cyclopentenyl)ethyl Bromide (61)

A solution of 59 (89.24 g, 0.796 mol) and 5.0 g (29.6 mmol) of diphenylamine in 150 ml of anhydrous ligroin was stirred at ice temperature and treated dropwise with 82.5 g (0.305 mol) of phosphorous tribromide over a 0.3 h period. After stirring for a further 2 h, 20 ml of water was slowly added. The solid material which formed was removed by filtration. The solution was washed with 2 x 300 ml of saturated brine, with 2 x 200 ml of saturated aqueous sodium bicarbonate, and was dried (MgSO₄). After filtration, the solvent was removed in vacuo, and the residue was distilled to give 41.0 g (29%) of unstable 61: bp 25-30°C/0.04 mm; ir (film) 2940, 2840, 1660, 1438, 1270, 1260, 1205, 1040, 953, 912, 855, 815 cm⁻¹.

Ethyl 2-ethoxycarbonyl-4-(1-cyclopentenyl)butanoate (63)

A solution of 61 (41 g, 0.234 mol) in 80 ml of absolute ethanol was added dropwise to a gently refluxing, stirred solution of sodium diethylmalonate, prepared from 5.4 g (0.234 g-atom) of sodium and 37.4 g (0.234 mol) of diethylmalonate in 300 ml of absolute ethanol. After 0.1 h when addition was complete, the solution was refluxed
for a further 2 h during which a solid formed. The mixture was allowed to cool overnight. After solvent removal in vacuo, the residue was taken up in 400 ml of ether, washed with 2 X 300 ml of saturated brine, dried (MgSO₄), and was filtered. Solvent removal in vacuo followed by distillation gave 34.64 g (60%) of 63: bp 86-91°C / 0.03 mm; ir (film) 2930, 1750, 1730, 1445, 1370, 1335, 1235, 1150, 1090, 1032, 945, 860 cm⁻¹; nmr (CDCl₃) δ 1.25 (6H, t, J=7 Hz), 3.37 (1H, m), 4.22 (4H, q, J=7 Hz), 5.91 (1H, m).

**Ethyl 2-ethoxycarbonyl-4-(1-cyclohexenyl)butanoate (64)**

Bromide 62(99.57 g, 0.527 mol) was added dropwise to a refluxing stirred solution of sodium diethylmalonate, prepared from 12.1 g (0.527 g-atom) of sodium and 84.3 g (0.527 mol) of diethylmalonate in 600 ml of absolute ethanol. After 0.25 h when addition was complete, the solution was refluxed for a further 2 h during which a solid formed. The mixture was allowed to cool overnight. After solvent was removed in vacuo, the residue was taken up in 300 ml of ether, washed with water and with saturated brine, dried (MgSO₄), and was filtered. Solvent removal in vacuo followed by distillation of the residue gave 93.58 g (66%) of 64: bp 90-95°C / 0.03 mm; ir (film) 2920, 1750, 1730, 1448, 1370, 1225, 1150, 1038, 862 cm⁻¹; nmr (CDCl₃) δ 1.27 (6H, t, J=7 Hz), 1.59 (4H, m), 1.99 (8H, m), 3.35 (1H, m), 4.23 (4H, q, J=7 Hz), 5.46 (1H, m).
2-Carboxy-4-(1-cyclopentenyl)butanoic Acid (65)

A solution of 63 (34.64 g, 0.136 mol) and 21.6 g (0.328 g-atom) of potassium hydroxide pellets dissolved in 1070 ml of absolute methanol was refluxed for 5.5 h. The solvent was removed in vacuo and the residue was taken up in 300 ml of water. The solution was extracted with 2 X 200 ml of ether and the extracts were discarded. After acidification using 7% hydrochloric acid, the aqueous solution was extracted with 3 X 300 ml of ether. The combined organic extract was washed with saturated brine, dried (MgSO₄), and was filtered. Solvent removal in vacuo gave a white solid which was recrystallized from 1500 ml of refluxing cyclohexane to give 20.7 g (77%) of 65: mp 110-116° C; ir (Nujol) 1705, 1455, 1418, 1330, 1295, 1220, 920, 820, 795, 785, 676 cm⁻¹; nmr (Acetone-d₆) δ 1.4-2.45 (10H, m), 3.38 (1H, t, J=7 Hz), 5.43 (1H, m), 7.4 (2H, broad s).

2-Carboxy-4-(1-cyclohexenyl)butanoic Acid (66)

A solution of 64 (93.58 g, 0.345 mol) and 54.4 g (0.828 g-atom) of potassium hydroxide pellets dissolved in 2700 ml of absolute methanol was refluxed for 5 h. The solvent was removed in vacuo, and the residue was taken up in 1000 ml of water. The solution was extracted with 2 X 500 ml of ether and the extracts were discarded. After acidification using 1200 ml of 4% hydrochloric acid, the aqueous
solution was extracted with 3 X 1000 ml of ether. The combined organic extract was washed with saturated brine, dried (MgSO$_4$), and was filtered. Solvent removal in vacuo gave a white solid which was recrystallized from 3500 ml of refluxing cyclohexane to give 60.4 g (81%) of 66; mp 110-116°C; ir (Nujol) 1702, 1457, 1375, 1325, 1223, 1135, 913, 827, 802, 782, 720, 680 cm$^{-1}$; nmr (DMSO-d$_6$) $\delta$ 1.53 (6H, m), 1.89 (8H, m), 3.17 (1H, m), 5.41 (1H, m).

4-((1-Cyclopentenyl)butanoic Acid (51)

Diacid 65 (3.84 g, 19.4 mmol) upon heating for 0.5 h at 160°C evolved a colorless gas. Distillation gave 2.74 g (92%) of impure 51: bp 76-78°C/0.02 mm; ir (film) 2880, 1710, 1410, 1365, 1025, 947 cm$^{-1}$; nmr (CDC$_3$) $\delta$ 5.37 (1H, m), 11.9 (1H, broad s, variable).

4-((1-Cyclohexenyl)butanoic Acid (52)

Diacid 66 (9.75 g, 46 mmol) upon heating for 0.5 h at 180°C evolved a colorless gas. Distillation gave 7.46 g (96%) of 52: bp 78-83°C/0.03 mm; ir (film) 2950, 2700, 1705, 1400, 1225, 920, 801 cm$^{-1}$; nmr (CDC$_3$) $\delta$ 1.2-2.6 (14H, m), 5.45 (1H, m), 10.67 (1H, broad s, variable).
4-(1-Cyclopentenyl)butanoyl Chloride (67)

A solution of 51 (2.74 g, 17.8 mmol) in 7.5 g (61 mmol) of oxalyl chloride was stirred at room temperature for 0.1 h and then at 40° C for 0.2 h. A colorless gas was evolved. Excess oxalyl chloride was removed in vacuo to give 2.73 g of crude 67, as a yellow oil; ir (film) 2960, 1800, 1445, 1250, 1150, 1022 cm⁻¹.

4-(1-Cyclohexenyl)butanoyl Chloride (68)

A solution of 52 (0.50 g, 3.0 mmol) in 1.4 g (11.2 mmol) of oxalyl chloride was stirred at room temperature for 0.1 h and then at 40° C for 0.2 h. A colorless gas was evolved. Excess oxalyl chloride was removed in vacuo to give 0.497 g of crude 68, as a yellow oil: ir (film) 2920, 1800, 1670, 1440, 1223, 1037, 990, 953, 863, 800, 720, 676 cm⁻¹.

1-Diazo-5-(1-cyclopentenyl)pentan-2-one (69)

A solution of crude 67 (2.73 g) in 10 ml of hexane was slowly added to an ice-cold, stirred solution of diazomethane, prepared from 10 g (56 mmol) of N, N'-Dimethyl-N, N'-dinitrosoterephthalamide in 110 ml of ether and distilled twice from potassium hydroxide pellets. After 1 h, solvent was removed in vacuo, and the residue was taken up in ether and filtered. Solvent removal in vacuo gave 2.34 g of
unstable, crude \textbf{69}, as a yellow oil: ir (film) 2990, 2110, 1645, 1365, 1150, 1020 cm$^{-1}$.

\textbf{1-Diazo-5-(1-cyclohexenyl)pentan-2-one (70)}

A solution of crude \textbf{68} (0.457 g) in 2 ml of hexane was slowly added to an ice-cold, stirred solution of diazomethane prepared from 3 g (17 mmol) of N,N'-Dimethyl-N,N'-dinitrosoterephthalamide in 40 ml of ether and distilled twice from potassium hydroxide pellets. After 1 h, solvent was removed \textit{in vacuo}, and the residue was taken up in ether and filtered. Solvent removal \textit{in vacuo} gave 0.391 g of unstable, crude \textbf{70}, as a yellow oil: ir (film) 2940, 2110, 1640, 1440, 1360, 1138 cm$^{-1}$.

\textbf{Tricyclo[5.3.0.0$^{1.6}$]decan-5-one (49)}

A mixture of crude \textbf{75} (2.34 g) and 15 g of copper-bronze powder in 900 ml of cyclohexane was heated at 75$^\circ$C for 4 h with rapid stirring. A colorless gas was slowly evolved. Filtration and solvent removal \textit{in vacuo} followed by purification on a column of neutral, activity II alumina (100 g) gave 0.894 g (33% from \textbf{51}) of oily \textbf{49}; ir (film) 2960, 1685, 1320, 1240, 1195, 1080, 1040, 1015, 933, 895, 870 cm$^{-1}$; nmr (CDCl$_3$) 1.0-2.8 (m); mass spectrum m/e 150 (M$^+$).

The DNP derivative or \textbf{49} was prepared: mp 171-174$^\circ$C.

\textbf{Anal. Calcd for C$_{16}$H$_{18}$N$_4$O$_4$:} C, 58.17; H, 5.49; N, 16.96.
Found: C, 58.16; H, 5.34; N, 17.24.

**Tricyclo[5.4.0.0^1,6]undecan-5-one (50)**

A mixture of crude 70 (0.391 g) and 2 g of copper-bronze powder in 180 ml of cyclohexane was heated at 65°C for 0.7 h with rapid stirring. A colorless gas vigorously evolved soon after 65°C was attained. Filtration and solvent removal in vacuo followed by purification on a column of neutral, activity II alumina (35 g) gave 135 mg (38% from 52) of white, crystalline 50: mp 50-51°C; ir (Nujol) 1690, 1443, 1315, 1265, 1247, 1191, 1135, 1038, 947, 914, 883 cm⁻¹; nmr (CDCl₃) δ 1.15-1.5 (4H, m), 1.5-2.5 (12H, m); mass spectrum m/e 164 (M⁺).

The DNP derivative of 50 was prepared: mp 173-176°C; Anal. Calcd for C₁₇H₂₀N₄O₄: C, 59.29; H, 5.85; N, 16.27. Found: C, 58.92; H, 5.77; N, 16.39.

**Spiro[4,5]decan-7-one (72)**

A solution of 49 (146 mg, 0.97 mmol) in 15 ml of distilled ammonia and 2 ml of anhydrous ether was stirred at -40°C and treated with 27 mg (3.9 mg-atom) of lithium added in small pieces. After 2.5 h, when the solution had turned blue, 180 mg of ammonium chloride was gradually added, and the cooling bath was removed to allow the ammonia to evaporate. The residue which remained was
taken up in 50 ml of ether, washed with aqueous concentrated tartaric acid, with saturated brine, and was dried (MgSO₄). Filtration and solvent removal in vacuo followed by purification on preparative silica gel TLC gave 77 mg (52%) of oily 72: ir (film) 2990, 1712, 1440, 1420, 1304, 1223 cm⁻¹; nmr (CDCl₃) δ 1.0-2.4 (m); mass spectrum m/z 152 (M⁺).


Spiro[5,5]undecan-3-one (73)

A solution of 50 (152 mg, 0.927 mmol) in 15 ml of distilled ammonia and 2 ml of anhydrous ether was stirred at -40°C and treated with 27 mg (3.9 mg-atom) of lithium in small pieces. After 2.5 h, when the solution had become blue, 180 mg of ammonium chloride was gradually added, and the cooling bath was removed to allow the ammonia to evaporate. The residue which remained was taken up in 50 ml of ether, washed with aqueous concentrated tartaric acid, with saturated brine, and was dried (MgSO₄). Filtration and solvent removal in vacuo followed by purification on a column of neutral activity II alumina (25 g) gave 82 mg (53%) of oily 73: ir (film) 2950, 1710, 1443, 1305, 1223, 1065 cm⁻¹; nmr (CDCl₃) δ 0.75-2.1 (16H, m), 2.1-2.4 (2H, m); mass spectrum m/z 166 (M⁺).
The DNP derivative was prepared: mp 116-141°C.  

Calcd for C_{17}H_{22}N_{4}O_{4}: C, 58.95; H, 6.40; N, 16.17.  

Found: C, 57.44; H, 6.22; N, 16.03.

2-Chlorospiro[4.5]decan-7-one (74)

A solution of 49 (248 mg, 1.66 mmol) in 30 ml of ether was stirred at ice temperature and treated dropwise with 5 ml of concentrated hydrochloric acid over a 0.1 h period. After 41 h, the ether layer was separated and washed with saturated brine, with 5% aqueous sodium bicarbonate, dried (MgSO_{4}) and was filtered. Solvent removal in vacuo and purification on a column of activity II silica gel (25 g) gave 221 mg (72%) of oily 74:  

ir (film) 2990, 1710, 1445, 1421, 1307, 1226, 947 cm^{-1}; nmr (CDCl_{3}) δ 1.0-2.6 (14H, m), 3.90 (1H, 5, J=6 Hz); mass spectrum m/e 186 (M^{+}).

The DNP derivative was prepared: mp 113-116°C.  

Calcd for C_{16}H_{19}ClN_{4}O_{4}: C, 52.3; Cl, 9.68; N, 15.3; H, 5.22.  

Found: C, 52.49; H, 5.17; Cl, 9.62; N, 15.56.

7-Chlorospiro[5.5]undecan-3-one (75)

A solution of 50 (289 mg, 1.76 mmol) in 30 ml of ether was stirred at ice temperature and treated dropwise with 5 ml of concentrated hydrochloric acid over a 0.1 h period. After 0.5 h, the ether layer was separated and washed with saturated brine, with 5% aqueous
sodium bicarbonate, dried ($\text{MgSO}_4$), and was filtered. The solvent was removed in vacuo to give 339 mg (90%) of 75 which produced a single spot on silica gel TLC: ir (film) 2970, 1715, 1445, 1225, 1138, 931 cm$^{-1}$; nmr (CDCl$_3$) $\delta$ 0.8-2.5 (15H, m), 2.75 (1H, d, J=13 Hz), 3.65-3.95 (1H, m); mass spectrum m/e 200 (M$^+$).

The DNP derivative was prepared: mp 113-116°C; Anal. Calcd for C$_{17}$H$_{21}$ClN$_4$O$_4$: C, 53.6; H, 5.6; Cl, 9.32; N, 14.46. Found: C, 53.62; H, 5.56; Cl, 9.35; N, 14.92.

**Tricyclo[5.3.0.0$^1$,0$^6$]decan-5-one (49) from 74**

Chloroketone 74 (169 mg, 0.91 mmol) was added to a column of neutral, activity II alumina (28 g). Elution with ether-hexane over a 7 h period gave 109 mg (80%) of 49: The ir and nmr spectra of this product match those of the product obtained from 69.

**Tricyclo[5.4.0.0$^1$,0$^6$]undecan-5-one (50) from 75**

Chloroketone 75 (100 mg, 0.5 mmol) was added to a column of neutral, activity II alumina (25 g). Elution with ether-hexane over a 4 h period gave 74 mg (90%) of crystalline 50: The melting point, nmr, and ir spectra of this product match those of the product obtained from 70.
I-Methoxybicyclo[5.3.0]decan-5-one (76)

A solution of 49 (96 mg, 0.64 mmol) and 0.6 g (3.1 mmol) of p-toluenesulfonylic acid in 10 ml of absolute methanol was maintained at 35°C for 20 h. After solvent removal in vacuo, the residue was taken up in 30 ml of ether, washed with 2 x 25 ml of saturated brine, and dried (MgSO₄). Filtration and solvent removal in vacuo followed by purification on a column of neutral activity II alumina (25 g) gave 44.4 mg (38%) of oily 76: \( \text{ir} \ (\text{film}) \ 2990, 1712, 1440, 1308, 1225, 1096 \ \text{cm}^{-1}; \ \text{nmr} \ (\text{CDCl}_3) \ \delta \ 1.0-2.6 \ (15 \text{H, m}), 3.30 \ (3 \text{H, s}); \ \text{mass spectrum} \ m/e \ 182 (M^+) \).

1-Methoxybicyclo[5.4.0]undecan-5-one (77)

A solution of 50 (64.5 mg, 0.393 mmol) and 0.6 g (3.1 mmol) of p-toluenesulfonylic acid in 10 ml of absolute methanol was refluxed for 24 h. After solvent removal in vacuo, the residue was taken up in 30 ml of ether, washed with 2 x 25 ml of saturated brine, and was dried (MgSO₄). Filtration and solvent removal in vacuo followed by purification on a column of activity II silica gel (20 g) gave 56 mg (73%) of oily 77: \( \text{ir} \ (\text{film}) \ 2980, 1710, 1445, 1225, 1185, 1100, 1000 \ \text{cm}^{-1}; \ \text{nmr} \ (\text{CDCl}_3) \ \delta \ 1.0-2.1 \ (13 \text{H, m}), 2.30 \ (2 \text{H, t, } J=6 \ \text{Hz}), 2.69 \ (2 \text{H, d, } J=14 \ \text{Hz}), 3.32 \ (3 \text{H, s}); \ \text{mass spectrum} \ m/e \ 196 (M^+) \).

Anal. Calcd for C₁₂H₂₀O₂: C, 73.43; H, 10.27. Found: C, 73.74; H, 10.42.
**Exo and Endo-tricyclo[5, 3, 0.0^1, 6^1]decan-5-ol (80 and 81)**

A solution of 49 (154 mg, 1.02 mmol) in 20 ml of absolute methanol was stirred at ice temperature and treated with 135 mg (3.56 mg-atom) of sodium borohydride for 1.5 h. After solvent removal in vacuo, the residue was taken up in ether, washed with aqueous ammonium chloride, with saturated brine, and was dried (MgSO₄). Filtration and solvent removal in vacuo followed by partial separation on preparative, silica gel TLC (25 g) gave a fraction containing 33 mg (21%) of a mixture of endo-81 and exo-80 (1:1 by nmr) and another fraction containing 78 mg (50%) of pure endo-81 which was distilled: bp 60-65°C/1.0 mm; ir (film) 3400, 2960, 2890, 1440, 1345, 1290, 1150, 1090, 1060, 1045, 1028, 1008, 985, 940 cm⁻¹; nmr (CDCl₃) 0.65-0.85 (2H, m), 0.9-2.0 (12H, m), 2.41 (1H, broad s, variable), 3.72-4.00 (1H, m); mass spectrum m/e 152 (M⁺).

**Exo and Endo-tricyclo[5. 4. 0. 0^1, 6^1]undecan-5-ol (82 and 83)**

A solution of 50 (154 mg, 0.94 mmol) in 20 ml of absolute methanol was stirred at ice temperature and treated with 135 mg (3.56 mg-atom) of sodium borohydride for 1.5 h. After solvent removal in vacuo, the residue was taken up in ether, washed with aqueous ammonium chloride, with saturated brine, and was dried (MgSO₄). Filtration and solvent removal in vacuo followed by partial
separation on preparative, silica gel TLC (25 g) gave a higher RF fraction containing 66 mg (42%) of a mixture of endo-83 and exo 82 (7:3 by nmr) and a lower RF fraction containing 62 mg (40%) of pure endo-83: ir (film) 3400, 2980, 2900, 1440, 1330, 1280, 1075, 1050, 1012, 970 cm\(^{-1}\); nmr (CDCl\(_3\)) \(\delta\) 0.4-0.8 (2H, m), 0.8-2.1 (15H, m), 2.3 (1H, broad s, variable), 3.95 (1H, t, \(J\) 7=Hz); mass spectrum m/e 166 (M\(^+\)).

\textit{Cis-1-methoxybicyclo[5.3.0]dec-5-ene (84)}

A solution of endo-81 (77 mg, 0.48 mmol) and 1 drop (22 mg, 0.15 mmol) of 70% perchloric acid in 5 ml of absolute methanol was stirred at ice temperature for 3 h. The solution was neutralized with concentrated, aqueous sodium bicarbonate, diluted with water, and extracted with 2 X 15 ml of ether. The combined extract was dried (MgSO\(_4\)), filtered, and the solvent was removed by distillation at atmospheric pressure. Distillation followed by chromatography on activity II silica gel gave 31 mg (37%) of cis-84: by 35-40\(^\circ\) C/. 05 mm; ir (film) 3000, 1450, 1320, 1270, 1200, 1090, 1060, 963 cm\(^{-1}\); nmr (CDCl\(_3\)) \(\delta\) 1.1-2.6 (12H, m), 2.6-2.9 (1H, m), 3.20 (3H, s), 5.3-5.8 (2H, m); mass spectrum m/e 166 (M\(^+\)).
A solution of endo-83 and exo-82 (56 mg, 0.30 mmol) in the ratio of 4:1 and 5 drops (110 mg, 0.8 mmol) of 70% perchloric acid in 5 ml of absolute methanol was stirred at ice temperature for 0.5 h. The solution was neutralized with concentrated, aqueous sodium bicarbonate, diluted with water, and extracted with 2 X 15 ml of ether. The combined extract was dried (MgSO₄), filtered, and the solvent was removed by distillation at atmospheric pressure. Vacuum distillation (bp 42-45°C/0.04 mm) gave 46 mg (73%) of a mixture of cis-85 and trans-86 (9:1 by nmr) which were separated by preparative gas chromatography.

Cis-85 gave the following spectral data: ir (film) 2970, 1460, 1355, 1190, 1140, 1095, 943, 910, 870, 793, 725 cm⁻¹; nmr (CDCl₃) δ 1.1-2.2 (14H, m), 2.47-2.64 (1H, m), 3.20 (3H, s), 5.3-5.9 (2H, m); mass spectrum m/e 180 (M⁺).


Trans-86 gave the following spectral data: ir (film) 2990, 1450, 1080, 965, 940, 855, 800, 735, 700 cm⁻¹; nmr (CDCl₃) δ 1.0-1.9 (12H, m), 1.9-2.1 (2H, m), 2.87-3.04 (1H, m), 3.34 (3H, s), 5.4-5.9 (2H, m); mass spectrum m/e 180 (M⁺).
1-Methyl-4R-isopropylcyclohex-1-ene (100)

A mixture of 99 (63.5 g, 0.46 mol) and 160 mg of platinum oxide catalyst in 200 ml of 95% ethanol was rapidly stirred at room temperature under 1 atmosphere of hydrogen. After 11.21 (0.46 mol) of hydrogen was absorbed, the solution was dried (MgSO₄) and filtered. The solvent was removed in vacuo and the residue was distilled to give 55.2 g (87%) of 100: bp 55-60°C/20 mm; ir (film) 1450, 1380, 1360, 1090, 1055, 798 cm⁻¹; nmr (CDCl₃) δ 0.85 (6H, d, J=6 Hz), 1.0-2.3 (8H, m), 1.60 (3H, s), 5.18-5.47 (1H, m).

1-Methyl-4R-isopropyl-7-oxabicyclo[4.1.0]heptane (101)

A mixture of 100 (55.2 g, 0.40 mol) and 73 g (0.69 g-atom) of sodium carbonate in 500 ml of dichloromethane was stirred at ice temperature and treated dropwise with 120 g (0.63 mol) of 40% peracetic acid over a 1.5 h period. After a further 2.5 h, the mixture was washed with water, concentrated, aqueous sodium bicarbonate, concentrated brine, and dried (MgSO₄). Filtration followed by solvent removal in vacuo and distillation of the residue gave 54.9 g (89%) of 101: bp 33-35°C/0.07 mm; ir (film) 1465, 1430, 1208, 1120, 1040, 1020, 870, 843, 760 cm⁻¹; nmr (CDCl₃) δ 0.81 (6H, d, J=6 Hz), 0.9-2.2 (8H, m), 1.30 (3H, s), 2.84-3.04 (1H, m).
1-Methyl-4R-isopropylcyclohexa-1, 2-diol (102)

A solution of 101 (54.4 g, 0.352 mol) and 20 ml of 3% aqueous perchloric acid in 300 ml of tetrahydrofuran was stirred at ice temperature. After 5 h, the solution was diluted with 300 ml of water and extracted with 3 x 200 ml of dichloromethane. The combined extract was dried (CaCl₂), filtered, and the solvent was removed in vacuo. The residue was taken up in 150 ml of dichloromethane and purified on a short column of activity IV silica gel (500 g). Solvent removal in vacuo and distillation of the residue gave 47.45 g (76%) of 102 which crystallized on standing: mp 77-80°C; bp 90-95°C/.07 mm; ir (Nujol) 3500, 1460, 1370, 1170, 1030, 960, 860 cm⁻¹; nmr (CDCl₃) δ 0.88 (6H, d, J=6 Hz), 1.22 (3H, s), 1.0-1.9 (8H, m), 2.30 (2H, broad s, exchanges with D₂O), 3.60 (1H, t, J=4 Hz); mass spectrum m/e 172 (M⁺).

3R-Isopropyl-6-oxoheptanal (103)

A solution of 102 (45.65 g, 0.266 mol) in 700 ml of 95% ethanol was added to a solution of 69 g (0.32 g-atom) of sodium meta-periodate in 700 ml of water. A white solid formed as the reaction temperature rose to 37°C. After 1.3 h, 1000 ml of water was added and the mixture was extracted with 3 x 300 ml of ether. The combined organic extract was washed with saturated, aqueous sodium bicarbonate,
saturated brine, and dried \((\text{MgSO}_4)\). After filtration, the solvent was removed in vacuo and the residue was distilled to give 41.43 g (91%) of \(\text{103} \): bp 83-86° C/0.05 mm; ir (film) 2760, 1730, 1460, 1410, 1385, 1360, 1160 cm\(^{-1}\); nmr (CDCl\(_3\)) \(\delta 0.77 \text{ (3H, d, } J=6 \text{ Hz)}, 0.82 \text{ (3H, d, } J=6 \text{ Hz)}, 1.0-2.0 \text{ (4H, m)}, 2.13 \text{ (3H, s), 2.2-2.7 (4H, m), 9.75 (1H, t, } J=2 \text{ Hz)}; \text{ mass spectrum m/e } 170 (M^+)\).

\[1\text{-Piperidino-3S-isopropyl-6-oxohept-1-ene (104)}\]

A solution of \(\text{103} \) (35.6 g, 0.209 mol) in 150 ml of anhydrous ether was stirred at ice temperature and treated dropwise with 19.6 g (0.23 mol) of freshly distilled piperidine over a 0.5 h period. After a further 3 h at ice temperature, the solution was washed with saturated brine and dried \((\text{MgSO}_4)\). Filtration followed by solvent removal in vacuo gave 47.90 g (96%) of oily \(\text{104} \): ir (film) 1720, 1650, 1445, 1380, 1194, 1117, 943, 860 cm\(^{-1}\); nmr (CDCl\(_3\)) \(\delta 0.80 \text{ (3H, d, } J=6 \text{ Hz)}, 0.85 \text{ (3H, d, } J=6 \text{ Hz)}, 1.1-2.0 \text{ (10H, m), 2.15 (3H, s), 2.2-2.6 (2H, m), 2.6-3.0 (4H, m), 4.05 (1H, d of d, } J=8, 14 \text{ Hz), 5.72 (1H, d, } J=14 \text{ Hz)}; \text{ mass spectrum m/e } 237 (M^+)\).

\[2\text{-Methyl-5S-isopropylcyclopent-1-enecarboxaldehyde (29)}\]

A solution of \(\text{104} \) (46.04 g, 0.194 mol) in 600 ml of anhydrous ether was heated to reflux and treated dropwise with 28 g (0.468 mol) of glacial acetic acid over a 0.5 h period. After 6 h at reflux, the
solution was cooled and neutralized with saturated aqueous sodium bicarbonate. The mixture was washed with saturated brine, dried (MgSO₄) and filtered. Solvent removal in vacuo followed by two consecutive vacuum distillations gave 25.66 g (87%) of 29: bp 50-55°C/0.07 mm; uv (95% ethanol) λ max 254 nm, ε 9,750 (Lit. λ 254-255 nm, ε 10,800); if (film) 2750, 1660, 1630, 1460, 1375, 1340, 1275 cm⁻¹; nmr (CDCl₃) δ 0.65 (3H, d, J=6.8 Hz), 0.90 (3H, d, J=6.8 Hz), 1.0-2.7 (3H, m), 1.75 (1H, q, J=6.8 Hz), 2.17 (3H, s), 2.7-3.3 (2H, m), 10.02 (1H, s).

The DNP derivative was prepared: mp 173.5-174.5°C (Lit. 169 or 176°C).

3-Methylene-5-(2-methyl-5S-isopropyl-1-cyclopentenyl)oxacyclopentan-2-one (42)

A solution of 29 (3.0 g, 19.7 mmol) and 4.6 g (23.8 mmol) of 28 in 50 ml of anhydrous tetrahydrofuran was passed dropwise through a column of activated zinc granules (No. 10 mesh), saturated with tetrahydrofuran and preheated to mild reflux. After 1.5 h, when addition was complete, the column was flushed with 50 ml of tetrahydrofuran. The dark product solution was diluted with 100 ml of ether and hydrolyzed with ice-cold, 1% sulfuric acid. The organic layer was separated and washed with saturated brine, dried (MgSO₄), and filtered. Solvent removal in vacuo gave 5.0 g of crude
3-Methyl-5-(2-methyl-5S-isopropyl-1-cyclopentenyl)oxacyclopentan-2-one (108)

A mixture of crude 42 (5.0 g) and 100 mg of platinum oxide catalyst in 20 ml of 95% ethanol was rapidly stirred at room temperature under 1 atmosphere of hydrogen. After 4 h, when 475 ml (19.7 mmol) of hydrogen was absorbed, the mixture was diluted with 100 ml of ether, washed with water, saturated brine, and dried (MgSO4). Filtration followed by solvent removal in vacuo and purification on a column of neutral, activity II alumina gave 2.20 g (50% from 29) of 108 after distillation: bp 100-105°C/0.05 mm; ir (film) 1775, 1460, 1375, 1330, 1195, 1106, 1107, 927, 890 cm⁻¹; nmr (CDCl3) δ 0.66 (3H, d of d, J=1.7 Hz), 0.85 (3H, d of d, J=1.7 Hz), 1.22 (3H, d, J=7 Hz), 1.72 (3H, s), 1.4-3.0 (9H, m), 4.85-5.4 (1H, m).

2-Methyl-4-(2-methyl-5S-isopropyl-1-cyclopentenyl)butanoic Acid (109)

A mixture of 108 (1.5 g, 6.80 mmol) and 0.5 g of 10% palladium-on-calcium carbonate catalyst in 20 ml of 95% ethanol was rapidly stirred at room temperature under 1 atmosphere of hydrogen. After 3 h, when 224 ml (9.3 mmol) of hydrogen was absorbed, the mixture was diluted with ether and washed with aqueous ammonium chloride,
saturated brine, and dried (MgSO₄). Filtration followed by solvent removal in vacuo gave 1.51 g of crude 109: ir (film) 1710, 1460, 1405, 1375, 1285, 1240, 943 cm⁻¹; nmr (CDCl₃) δ 0.64 (3H, d, J=6.5 Hz), 0.90 (3H, d, J=6.5 Hz), 1.20 (3H, d, J=6.5 Hz), 1.61 (3H, s), 11.8 (1H, broad s, variable).

The methyl ester was prepared with diazomethane and was purified by preparative G LPC (carbowax column): mass spectrum m/e 283.193 (M⁺); Calcd for C₁₅H₂₆O₂: 283.193.

2-Methyl-4-(2-methyl-5S-isopropyl-1-cyclopentenyl)butanoyl Chloride (110)

A solution of crude 109 (1.51 g) in 5.0 g (39 mmol) of freshly distilled oxalyl chloride was stirred at room temperature for 0.1 h. A colorless gas was evolved. Removal of excess oxalyl chloride in vacuo, followed by addition of 1 ml of hexane and removal again in vacuo gave 1.64 g of crude 110: ir (film) 1790, 1450, 1370, 943 cm⁻¹.

1-Diazo-3-methyl-5-(2-methyl-5S-isopropyl-1-cyclopentenyl)pentan-2-one (111)

A solution of crude 110 (1.64 g) in 5 ml of hexane was slowly added to an ice-cold, stirred solution of diazomethane, prepared from 10 g (56 mmol) of N,N'-Dimethyl-N,N'-dinitrosoterephthalamide in
110 ml of ether and distilled twice from potassium hydroxide pellets. After 1 h, solvent was removed in vacuo, and the residue was taken up in ether, filtered, and dried (MgSO₄). Filtration followed by solvent removal in vacuo gave 1.65 g of crude 111 as an unstable, orange oil: ir (film) 2110, 1640, 1360, 1312, 1140, 1040 cm⁻¹; nmr (CDCl₃) δ 0.63 (3H, d, J=7 Hz), 0.90 (3H, d, J=7 Hz), 1.13 (3H, d, J=7 Hz), 1.63 (3H, s), 5.30 (1H, s).

4,7R-Dimethyl-10S-isopropyltricyclo-
[5.3.0.0₁, 6]dec-5-one (112)

A mixture of crude 111 (1.65 g) and 3 g of copper-bronze powder in 350 ml of cyclohexane was heated at reflux for 0.2 h with rapid stirring. A colorless gas was evolved slowly. Filtration followed by solvent removal in vacuo and purification on preparative gas chromatography (carbowax column) gave 514 mg (34% from 109) of oily 112: ir (film) 1680, 1460, 1385, 1310, 1207, 1145 cm⁻¹; nmr (CDCl₃) δ 0.5-2.5 (m); mass spectrum m/e 220.186 (M⁺); Calcd for C₁₅H₂₄O: 220.183.

1,8-Dimethyl-4S-isopropyl-5S-spiro-
[4.5]dec-1-en-7-one (116)

A solution of 112 (514 mg, 2.34 mmol) in 30 ml of chloroform was stirred at ice temperature and treated with a stream of dry hydrogen chloride gas passed through the solution. After 6.5 h, the
solution was washed with aqueous sodium bicarbonate, dried (MgSO₄), and filtered. Solvent removal in vacuo gave 537 mg of crude 116:

\[ \text{ir (film) 1710, 1460, 1370, 1208, 1160, 1065, 806 cm}^{-1}; \text{nmr (CDCl₃) } \delta 5.23-5.4 \text{ (1H, m).} \]

**4S, 8-Dimethyl-1S-isopropyl-5R-spiro[4.5]decan-7-one (117)**

A mixture of crude 116 (537 mg) and 100 mg of 5% rhodium-on-carbon catalyst in 40 ml of absolute ethanol was rapidly stirred at room temperature under 1 atmosphere of hydrogen. After 22 h, when 54.5 ml (2.26 mmol) of hydrogen was absorbed, the mixture was filtered and the solvent removed in vacuo. The product was purified by preparative gas chromatography (carbowax column) to give 307 mg (60% from 112) of oily 117: ir (film) 1710, 1450, 1370, 1045 cm⁻¹; mass spectrum m/e 222.197 (M⁺); Calcd for C_{15}H_{26}O: 222.198.

**7-Acetoxy-4S, 8-dimethyl-1S-isopropyl-5R-spiro[4.5]decan-7-ene (118)**

Ketone 117 (307 mg, 1.38 mmol) in 30 ml of reagent B (prepared by dissolving 4.8 ml of acetic anhydride and 0.05 ml of 70% perchloric acid in 45 ml of ethyl acetate) was stirred at room temperature for 0.1 h and neutralized with saturated aqueous sodium bicarbonate. The organic layer was separated, dried (MgSO₄), and filtered. Solvent removal in vacuo gave 349 mg of crude 118: ir
A solution of crude \(118\) (349 mg) in 30 ml of buffer (prepared by dissolving 2 g of sodium acetate in 160 ml of glacial acetic acid and 40 ml of carbon tetrachloride) was stirred at ice temperature and treated dropwise with a solution of bromine (110 mg, 1.38 mmol) in 1 ml of buffer. After 0.1 h, when addition was complete, the solution was diluted with chloroform, washed with water, with saturated aqueous sodium bicarbonate, and was dried (\(\text{MgSO}_4\)). Filtration followed by solvent removal in vacuo gave 474 mg of crude \(119\): ir (film) 1715, 1460, 1370, 1285, 1120 cm\(^{-1}\).

\((-\))-Acorenone B (1)

A mixture of crude \(119\) (474 mg), 1.0 g (13 mg-atom) of lithium carbonate, and 0.5 g (12 mg-atom) of lithium chloride in 30 ml of dimethylformamide was stirred and heated at 140° C for 0.25 h. The mixture was diluted with ether, washed twice with water, once with saturated brine and was dried (\(\text{MgSO}_4\)). Filtration followed by solvent removal in vacuo and purification on preparative gas chromatography (carbowax column) gave, in order of elution, 20 mg of \(128\) (see
synthesis of \( \text{H}_2\text{O} \) for spectral data) and 103 mg (34% from \( \text{I} \)) of \( \text{I} \):
\[ \text{[d]}_{20} \text{(chloroform)} -19^\circ; \text{uv (methanol)} \lambda_{\text{max}} 240 \text{ nm, } \log \varepsilon 3.81; \text{ir (film)} 1670, 1460, 1425, 1375, 1360, 1160, 1115, 1085, 1072, 925 \text{ cm}^{-1}; \text{nmr (CDCl}_3) 0.77 (3H, d, J=6.0 Hz), 0.86 (3H, d, J=6.5 Hz), 0.95 (3H, d, J=6.5 Hz), 1.05-2.0 (7H, m), 1.76 (3H, d, J=1.8 Hz), 2.05-2.3 (2H, m), 2.24 (1H, d, J=8.2 Hz), 2.72 (1H, d, J=8.2 Hz), 6.58-6.73 (1H, m); \text{mass spectrum } m/e 220 (M^+); \text{Comparison of spectral data and Glpc retention time (10 ft X 1/4 inch carbowax column) of } \text{I} \text{ with an authentic sample of racemic Acorenone B indicate their identity in everything except optical activity.}

4R, 8-Dimethyl-1S-isopropyl-5R-spiro[4,5]decan-7-one (120)

A solution of \( \text{II} \) (90 mg, 0.41 mmol) and 150 mg (2.05 mmol) of t-butanol in 10 ml of distilled ammonia and 0.5 ml of anhydrous ether was stirred at -40° C and treated with 60 mg (8.5 mg-atom) of lithium in small pieces over a 0.1 h period. After 0.5 h, when the solution had turned blue, ammonium chloride was slowly added to discharge the blue color. The cooling was removed to allow the ammonia to evaporate. The residue which remained was taken up in ether, washed with water, with saturated brine, was dried (MgSO\(_4\)), and was filtered. Solvent removal in vacuo followed by chromatography on neutral, activity II alumina gave 70 mg of impure 120: ir
Ketone 120 (63 mg, 0.284 mmol) in 6 ml of reagent B (prepared by dissolving 4.8 ml of acetic anhydride and 0.05 ml of 70% perchloric acid in 45 ml of ethyl acetate) was stirred at room temperature for 0.1 h and neutralized with saturated sodium bicarbonate solution. The organic layer was separated, dried \((\text{MgSO}_4)\), and was filtered. Solvent removal in \textit{vacuo} gave 75 mg of crude 126: ir (film) 3000, 2920, 1760, 1460, 1360, 1212, 1112 cm\(^{-1}\).

A solution of crude 126 (75 mg) in 5 ml of buffer (prepared by dissolving 2 g of sodium acetate in 160 ml of glacial acetic acid and 40 ml of carbon tetrachloride) was stirred at ice temperature and treated dropwise with a solution of bromine (45 mg, 0.29 mmol) in 5 ml of buffer solution. After 0.1 h, when addition was complete, the solution was diluted with chloroform, washed with water, with saturated aqueous sodium bicarbonate, and was dried \((\text{MgSO}_4)\). Filtration followed by solvent removal in \textit{vacuo} gave 88 mg of crude 127:
ir (film) 3000, 2920, 1720, 1440, 1370, 1268, 1195 cm⁻¹.

(-)-4-Epiacorenone B (128)

A mixture of crude 127 (88 mg), 0.3 g (4 mg-atom) of lithium carbonate, and 0.15 g (3.6 mg-atom) of lithium chloride in 5 ml of dimethylformamide was stirred and heated at 140°C for 0.25 h. The mixture was diluted with ether, washed twice with water, once with saturated brine, and was dried (MgSO₄). Filtration followed by solvent removal in vacuo and separation by preparative gas chromatography (carbowax column) gave 6 mg of 1 (see synthesis of 1 for spectral data) and 17 mg (30% from 120) of 128: [α]D²⁰ (ether) -50°; ir (film) 1670, 1445, 1425, 1360, 1235, 1140, 1115, 1080, 925 cm⁻¹; nmr (CDCl₃) δ 0.82 (3H, d, J=2.5 Hz), 0.88 (6H, d, J=3 Hz), 0.95-2.17 (7H, m), 1.76 (3H, d, J=2.0 Hz), 2.17-2.57 (2H, m), 2.36 (2H, d, J=2.0 Hz), 6.63-6.78 (1H, m); mass spectrum m/e 220.180; Calcd for C₁₅H₂₄O: 220.183.

3-Methoxyxyclohexa-2,5-diene-1-carboxylic Acid (142)

A solution of 3-methoxybenzoic acid (21.0 g, 0.138 mol) in 500 ml of distilled ammonia and 175 ml of absolute methanol was stirred at -33°C and treated with 17.5 g (0.75 g-atom) of sodium in small pieces. After 0.5 h, when addition was complete, 73 g (1.4
(g-atom) of ammonium chloride was cautiously added and cooling was removed to allow the ammonia to evaporate. The residue which remained was dissolved in ice-water, acidified to congo-red with 2 N hydrochloric acid, and extracted with 3 X 100 ml of dichloromethane. The combined extract was dried (MgSO₄), filtered, and the solvent was removed in vacuo to give 15.78 g (74%) of crude 142:

\[
\text{IR (film) } 2950, 1700, 1650, 1592, 1395, 1280, 1210, 1170, 1028, 900, 840, 740 \text{ cm}^{-1}; \text{nmr (Acetone-d₆) } \delta 2.50-2.80 (2H, m), 3.58 (3H, s), 4.70-4.85 (2H, m), 9.40 (1H, broad s).
\]

3, 5-Dimethoxycyclohexa-2, 5-diene-1-carboxylic Acid (143)

A solution of 3, 4, 5-trimethoxybenzoic acid (80 g, 0.378 mol) in 1500 ml of distilled ammonia and 480 ml of absolute methanol was stirred at -33°C and treated with 48 g (2.19 g-atom) of sodium in small pieces. After 0.5 h, when addition was complete, 200 g of ammonium chloride was cautiously added and cooling was removed to allow the ammonia to evaporate. The residue which remained was dissolved in ice-water, acidified to congo-red with 2 N hydrochloric acid, and extracted with 3 X 300 ml of dichloromethane. The combined extract was dried (MgSO₄), filtered, and the solvent was removed in vacuo to give 49.8 g (72%) of crude 143: nmr (DMSO-d₆) \(\delta 2.72 (2H, d, J=7 \text{ Hz}), 3.60 (6H, s), 3.88 (1H, m), 4.87 (2H, d, J=3 \text{ Hz})\).
3-Methoxy-1-(hydroxymethyl)cyclohexa-2, 5-diene (144)

A solution of crude 142 (15.58 g, 0.101 mol) in 100 ml of anhydrous ether was added dropwise to a well stirred suspension of 8.4 g (0.22 g-atom) of lithium aluminum hydride in 200 ml of anhydrous ether over a 0.4 h period. After stirring for a further 1 h, the mixture was cautiously treated with moist sodium sulfate to produce a granular precipitate which was subsequently removed by filtration. Solvent removal in vacuo gave 10.4 g (74%) of crude 144 which proved unstable to distillation: bp 75-80°C/.05 mm; ir (film) 3350, 3030, 2935, 2870, 1691, 1653, 1592, 1458, 1385, 1220, 1170, 1069, 1028, 820, 700 cm⁻¹; nmr (CDCl₃) δ 2.50-2.80 (2H, m), 3.55 (3H, s), 4.40-4.62 (1H, m), 5.45-5.80 (2H, m).

3,5-Dimethoxy-1-(hydroxymethyl)cyclohexa-2,5-diene (145)

A solution of crude 143 (49.3 g, 0.269 mol) in 100 ml of anhydrous ether was added dropwise to a well stirred suspension of 22.4 g (0.56 g-atom) of lithium aluminum hydride in 400 ml of anhydrous ether over a 0.5 h period. After stirring for a further 1 h, the mixture was cautiously treated with moist sodium sulfate to produce a granular precipitate which was subsequently removed by filtration. Solvent removal in vacuo followed by distillation of the
residue gave 33.7 g (74%) of 145 which solidified on standing: bp 105-107°C/0.05 mm; ir (Nujol) 3300, 2950, 1700, 1660, 1455, 1395, 1235, 1208, 1033, 1014, 1008, 900, 816, 713 cm⁻¹; nmr (CDCl₃) δ 2.03 (1H, broad s, variable), 2.80 (2H, d, J=7 Hz), 3.60 (6H, s), 3.56 (2H, d, J=6 Hz), 4.66 (2H, d, J=3 Hz).

5-(Hydroxymethyl)cyclohex-2-en-1-one (137)

A solution of crude 144 (9.41 g, 67.3 mmol) and 10 ml of aqueous 5% hydrochloric acid in 70 ml of dimethoxyethane was stirred at room temperature for 17 h and neutralized with saturated aqueous sodium bicarbonate. After most of the solvent was removed in vacuo, the residue was taken up in 300 ml of saturated brine and extracted with 15 X 50 ml of dichloromethane. The combined extract was dried (MgSO₄) and filtered. Solvent removal in vacuo gave 8.47 g (100%) of crude 137: ir (film) 3415, 2920, 2880, 1678, 1430, 1392, 1251, 1087, 1040, 881, 738 cm⁻¹; nmr (CDCl₃) δ 3.40-3.80 (2H, m), 5.98 (1H, d, J=10 Hz), 6.70-7.15 (1H, m).

3-Methoxy-5-(hydroxymethyl)cyclohex-2-en-1-one (138)

A solution of 145 (26.5 g, 0.156 mol) and 10 drops of concentrated hydrochloric acid in 500 ml of absolute methanol was stirred at ice temperature for 1.5 h. After adding 5 ml of 5% hydrochloric acid, the solution was stirred at room temperature for a further 3 h.
Propylene oxide (15 ml) and 50 g of 4 angstrom molecular sieves were added and the solution was left overnight. Solvent removal in **vacuo** followed by purification of the residue on a column of neutral, activity II alumina (600 g) gave 22.3 g (92%) of 138 which solidified on standing and was recrystallized from chloroform-ether: mp 66-67 °C (lit. 71-72.5 °C); **uv** (water) λ̴ max 254, log ε 4.23; **ir** (Nujol) 3400, 2980, 1625, 1600, 1450, 1380, 1225, 1135, 1088, 1008, 943, 857 cm⁻¹; **nmr** (Acetone-d₆) δ 2.15-2.55 (5H, m), 3.57 (2H, m), 3.74 (3H, s), 3.93 (1H, t, J=5 Hz, variable), 5.32 (1H, s); mass spectrum m/e 156 (M⁺).

3-Methoxy-5-(acetoxymethyl)cyclohex-2-en-1-one (168)

A solution of 138 (156 mg, 1 mmol) in 0.5 ml of pyridine and 0.5 ml of acetic anhydride was stirred at 50 °C for 0.5 h. After dilution with dichloromethane, the solution was washed with water, saturated aqueous cupric sulfate solution, was dried (MgSO₄), and was filtered. Solvent removal in **vacuo** gave 198 mg (100%) of 168: **ir** (film) 2990, 1740, 1660, 1615, 1435, 1380, 1215, 1145, 1043, 1008 cm⁻¹; **nmr** (CDCl₃) δ 2.06 (3H, s), 2.15-2.20 (5H, m), 3.72 (3H, s), 4.10 (2H, d, J=5 Hz), 5.45 (1H, s).
2-Bromo-3, 3-dimethoxy-5-(acetoxy methyl) 
cyclohexan-1-one (147)

A solution of 168 (214 mg, 1 mmol) in 5 ml of absolute methanol 
containing 184 mg (1.1 mg-atom) of silver acetate was treated drop-
wise with 160 mg (1 mmol) of bromine and stirred for 0.1 h at room 
temperature. Filtration followed by solvent removal in vacuo and 
chromatography on activity II silica gel gave 267 mg (80%) of 147; ir 
(film) 2980, 1745, 1720, 1460, 1360, 1240, 1175, 1108, 1045 cm⁻¹; 
nmr (CDCl₃) δ 2.07 (3H, s), 1.8-3.0 (5H, m), 3.22 (3H, s), 3.30 
(3H, s), 4.10 (2H, d, J=5 Hz), 4.20 (1H, m).

2-Bromo-3-methoxy-5-(acetoxy methyl) 
cyclohex-2-en-1-one (148)

A solution of 168 (214 mg, 1 mmol) in 5 ml of glacial acetic 
acid containing 184 mg (1.1 mg-atom) of silver acetate was treated 
dropwise with 160 mg (1 mmol) of bromine. After stirring at room 
temperature for 0.1 h, solvent was removed in vacuo and the product 
was dissolved in dichloromethane and filtered. Solvent removal in 
vacuo followed by chromatography on activity II silica gel gave 205 mg 
(70%) of 148: ir (film) 3000, 1740, 1665, 1548, 1375, 1285, 1240, 
1040, 963, 917 cm⁻¹; nmr (CDCl₃) 2.10 (3H, s), 2.10-2.90 (5H, m), 
4.02 (3H, s), 4.14 (2H, m).
2-Bromo-1-methoxy-7-oxabicyclo[3.2.1]octan-3-one (149)

A mixture of 138 (312 mg, 2.0 mmol) and 370 mg (2.2 mg-atom) of silver acetate in 10 ml of dichloromethane was stirred at room temperature and treated dropwise with a solution of bromine (320 mg, 2.0 mmol) in 1 ml of dichloromethane over a 0.1 h period. After a further 0.5 h, the solid was removed by filtration. Solvent removal in vacuo gave 470 mg of crude 149: ir (film) 2980, 1725, 1445, 1325, 1213, 1130, 1075, 1037, 967, 843 cm\(^{-1}\); nmr (CDCl\(_3\)) \(\delta\) 2.20-2.90 (5H, m), 3.43 (3H, s), 3.76 (1H, d, J=8 Hz), 4.12 (1H, d, J=8 Hz), 4.33 (1H, m); mass spectrum m/e 233.989, 235.985 (M\(^+\)); Calcd for C\(_{8}\)H\(_{11}\)BrO\(_3\): 233.989, 235.987.

2-Bromo-1-methoxy-7-oxabicyclo[3.2.1]octan-3-ol (150)

A solution of crude 149 (470 mg, 2 mmol) in 10 ml of absolute methanol was stirred at ice temperature and treated with 146 mg (3.9 mg-atom) of sodium borohydride in several portions over a 0.5 h period. Ammonium chloride (0.5 g) was added, and the mixture was stirred for 2 h. The solvent was removed in vacuo and the residue was taken up in 10 ml of water and extracted with 3 X 10 ml of dichloromethane. The combined extract was dried (MgSO\(_4\)) and filtered. Solvent removal in vacuo gave 400 mg (85%) of crude 150: ir (film) 3420, 2940, 2860, 1458, 1338, 1284, 1214, 1189, 1140, 1080, 1046,
1012, 968, 870 cm\(^{-1}\); nmr (CDCl\(_3\)) \(\delta\) 1.38-1.72 (1H, m), 1.72-2.16 (2H, m), 1.98 (1H, broad s, variable), 2.23-2.52 (2H, m), 3.42 (3H, s), 3.76-3.88 (1H, m), 3.97-4.16 (2H, m), 4.56-4.65 (1H, m); mass spectrum m/e 219, 221 (M\(^+\)-17).

The p-toluenesulfonate derivative of 150 was prepared and recrystallized from hexane-ether: mp 87-89°C.

2-Bromo-5-(hydroxymethyl)cyclohex-2-en-1-one (139)

A solution of 150 (1.42 g, 6.0 mmol) and 10 ml of 5% aqueous perchloric acid in 15 ml of dimethoxyethane was heated at 90-100°C for 1 h. After cooling and dilution with 25 ml of water, the solution was extracted with 3 X 25 ml of dichloromethane. The combined extract was dried (MgSO\(_4\)) and filtered. Solvent removal in vacuo followed by purification on a column of activity II silica gel gave 0.785 g (64%) of solid 139 which was recrystallized from hexane-ether: mp 65-67°C; uv (water) \(\lambda_{max}\) 255 nm, log \(\varepsilon\) 3.76; ir (Nujol) 3440, 2930, 1680, 1600, 1418, 1320, 1079, 1040, 1000, 950, 885 cm\(^{-1}\); nmr (CDCl\(_3\)) \(\delta\) 2.05-2.90 (6H, m), 3.65 (2H, d, J=4 Hz), 7.46 (1H, t, J=5 Hz); mass spectrum m/e 203.979, 205.977 (M\(^+\)); Calcd for C\(_7\)H\(_9\)BrO\(_2\): 203.979, 205.977.
2-Bromo-5-(acetoxymethyl)cyclohex-2-en-1-one (151)

A solution of 139 (0.785 g, 3.84 mmol) in 2 ml of pyridine and 2 ml of acetic anhydride was heated at 50°C for 0.5 h. The solution was diluted with water and extracted with 3 X 25 ml of dichloromethane. The combined extract was washed with 2 X 10 ml of saturated cupric sulfate, dried (MgSO₄), and filtered. Solvent removal in vacuo gave 0.95 g (100%) of 151: uv (95% ethanol) λ max 251 nm, log ε 3.82; ir (film) 2950, 2900, 1740, 1690, 1606, 1414, 1374, 1315, 1240, 1042, 958 cm⁻¹; nmr (CDCl₃) δ 2.02 (3H, s), 2.20-3.02 (5H, m), 4.02 (2H, d, J=4 Hz), 7.35 (1H, t, J=3 Hz).

1-Bromo-7-oxa-4-(acetoxymethyl)bicyclo[4.1.0]heptan-2-one (152)

A solution of 151 (0.948 g, 3.84 mmol) and 0.122 ml (4.4 mmol) of 90% hydrogen peroxide in 15 ml of absolute methanol was stirred at ice temperature and treated with 12 drops of 1 N methanolic sodium hydroxide. After 0.5 h, 2 drops of glacial acetic acid were added and the solvent was removed in vacuo. The residue was taken up in ether, dried (MgSO₄), and filtered. Solvent removal in vacuo gave 1.07 g of crude 152: ir (film) 2950, 1740, 1725, 1440, 1375, 1245, 1041 cm⁻¹; nmr (CDCl₃) δ 2.03 (3H, s), 2.0-2.9 (5H, m), 3.78-4.15 (3H, m); mass spectrum m/e 262 and 264 (M⁺).
5-(Acetoxymethyl)cyclohex-2-en-1-one (155)

A solution of crude 137 (8.47 g, 67.3 mmol) in 10 ml of pyridine and 10 ml of acetic anhydride was stirred at room temperature for 12 h. After dilution with dichloromethane, the solution was washed with water, saturated aqueous cupric sulfate, dried (MgSO₄), and filtered. Solvent removal in vacuo gave 8.0 g (70%) of crude 155 which proved unstable to distillation: bp 60-72°C/0.05 mm.

A small quantity of 155 was chromatographed on activity II silica gel: uv (95% ethanol) λ_{max} 224 nm, log ε 3.99; ir (film) 2950, 2900, 1740, 1680, 1435, 1390, 1372, 1240, 1040, 883, 740 cm⁻¹; nmr (CDCl₃) δ 1.90-2.60 (5H, m), 2.05 (3H, s), 4.00 (2H, d, J=4 Hz), 5.96 (1H, d, J=10 Hz), 6.92 (1H, d of t, J=3, 10 Hz).

2,3-Dihydroxy-5-(acetoxymethyl)cyclohexan-1-one (156)

A solution of 155 (2.0 g, 11.9 mmol) and 0.53 g (4.3 mg-atom) of potassium chlorate in 33 ml of water and 25 ml of aqueous 1% osmium tetroxide was stirred at room temperature for 1 h and 1.06 g (8.7 mg-atom) of additional potassium chlorate was added. After a further 1.5 h, the solution was washed with 25 ml of carbon tetrachloride, and the washing was discarded. The solution was saturated with sodium chloride and extracted with 10 X 25 ml of dichloromethane. The combined extract was dried (MgSO₄) and filtered.
Solvent removal in vacuo followed by purification of the residue on a short column of activity II silica gel (24 g) and eluted with ether gave 1.22 g (51%) of 156 which solidified on standing and was recrystallized from benzene: mp 87-89°C; ir (Nujol) 3450, 2950, 2900, 1740, 1720, 1428, 1391, 1371, 1245; 1150, 1105, 1055, 736 cm⁻¹; nmr (CDCl₃) δ 1.74 (1H, t, J=12 Hz), 2.08 (3H, s), 2.10-2.80 (4H, m), 3.37 (1H, m, variable), 4.08 (2H, d, J=5 Hz), 4.10 (1H, m, variable), 4.20 (1H, d, J=3 Hz), 4.43 (1H, m); mass spectrum m/e 202.085 (M⁺); Calcd for C₉H₁₄O₅: 202.084.

2-Acetoxy-3-hydroxy-5-(acetoxyethyl)cyclohexan-1-one (157)

A solution of 156 (174 mg, 0.86 mmol) in 2.0 g (2.5 mmol) of pyridine and 0.2 g (2 mmol) of acetic anhydride was stirred at ice temperature for 1.5 h. After dilution with dichloromethane, the solution was washed with water, saturated aqueous cupric sulfate, was dried (MgSO₄), and was filtered. Solvent removal in vacuo followed by chromatography of the residue on activity II silica gel gave 130 mg (62%) of solid 157 which was recrystallized from chloroform-carbon tetrachloride: mp 123-125°C; ir (Nujol) 3470, 2920, 2850, 1750, 1730, 1700, 1460, 1380, 1250, 1155, 1040, 944, 911, 888, 839, 718 cm⁻¹; nmr (CDCl₃) δ 1.82 (1H, t, J=13 Hz), 2.05-2.85 (5H, m), 2.10 (3H, s), 2.23 (3H, s), 4.09 (2H, d, J=5 Hz), 4.52 (1H, m), 5.27 (1H, d, J=3 Hz); mass spectrum m/e 244.094 (M⁺);
A solution of 138 (312 mg, 2.0 mmol) and 546 mg (2.4 mmol of o-nitrophenyl selenocyanate (160, sublimed at 125°C, 0.05 mm) in 6 ml of tetrahydrofuran was stirred at ice temperature and treated dropwise with 488 mg (2.4 mmol) of tri-n-butylphosphine. After addition was complete, cooling was removed and the solution was stirred at room temperature for 1.5 h. The solvent was removed in vacuo, and the residue was triterated with ether. The solvent was again removed in vacuo and the residue was triterated twice with 1 ml portions of benzene. The benzene extracts were removed by pipet and in vacuo to give 650 mg (95%) of yellow, solid 161 which was recrystallized from benzene: mp 120-123°C; uv (95% ethanol) λ max 251 nm, log ε 4.46; λ max 382 nm, log ε 3.38; ir (Nujol) 3090, 2965, 2928, 2860, 1645, 1600, 1562, 1513, 1450, 1438, 1380, 1340, 1337, 1304, 1250, 1227, 1204, 1178, 1170, 1144, 1099, 1036, 1000, 869, 850, 818, 783, 735 cm⁻¹; nmr (DMSO-d₆) 2.08-2.74 (5H, m), 3.16 (2H, d, J=5 Hz), 3.70 (3H, s), 5.36 (1H, s), 7.38-7.58 (1H, m), 7.58-7.87 (2H, m), 8.22-8.36 (1H, m).
3-Bis(hydroxymethyl)methylamino-5-(hydroxymethyl)cyclohex-2-en-1-one (167)

A solution of 138 (780 mg, 5.0 mmol) and 2 drops of 5% hydrochloric acid in 2 ml of water was stirred at 35°C for 1 h. After the solution was cooled to room temperature, 450 mg (5.0 mmol) of solid 2-aminopropane-1,3-diol (166, distilled at 120°C/.05 mm) was added and dissolved with 0.2 h stirring. The solution was cooled to ice temperature and diluted with 10 ml of acetone. After stirring for 0.1 h, the solvent was removed by pipet and the product was again treated with 10 ml of acetone and again the acetone was removed. The product was dissolved with 10 ml of isopropyl alcohol and re-crystallized by dropwise addition of 10 ml of acetone. Solvent was removed by pipet, and 10 ml of acetone was added. After stirring for 0.1 h, solvent was removed in vacuo to give 569 mg (53%) of white, crystalline 167: mp 94-96°C; uv (water) λ max 279, log ε 4.26; ir (Nujol) 3270, 3180, 2920, 2850, 1650, 1535, 1485, 1415, 1380, 1270, 1257, 1227, 1156, 1085, 1046, 912, 868 cm⁻¹; nmr (DMSO-d⁶) δ1.77-2.23 (5H, m), 2.93 (0.5H, 5, J=6 Hz), 2.98 (0.5H, t, J=6 Hz), 3.36 (2H, d, J=4 Hz), 3.48 (2H, d, J=6 Hz), 3.50 (2H, d, J=6 Hz), 5.0 (1H, broad s), 5.33 (7H, s, water); mass spectrum m/e 215.114 (M⁺); Calcd for C₁₀H₁₇NO₄: 215.116.


80. J. Dickstein, M. Bodnar, and R. Hoegerlie, Chem. Abs., 59, 12647h.


121. H. Bauer, Ber., 46, 92 (1913).


APPENDIX

Table IV contains boiling points, proton nuclear magnetic resonance data, infrared absorption data, and mass spectral data for compounds 16 and 19-23, which were obtained from the continuous flow reactions of ethyl bromoacetate with aldehydes and ketones in the presence of zinc. Table V contains similar data for products 30-35 and 37-40, which were obtained from the continuous flow reactions of allylic bromides with aldehydes, ketones, and an ester in the presence of zinc.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Bp, °C</th>
<th>NMR, δ</th>
<th>IR, cm⁻¹</th>
<th>Mass, m/e</th>
</tr>
</thead>
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<tr>
<td>Ethyl 3-hydroxyhexanoate (16)</td>
<td>45 (0.03)</td>
<td>0.75-1.05 (3H, m), 1.22 (3H, t, J=7 Hz), 1.3-1.7 (4H, m), 2.35-2.55 (2H, m), 3.1 (1H, variable singlet), 4.1 (1H, m), 4.17 (2H, q, J=7 Hz).</td>
<td>3550 (O-H), 1735 (C=O), 1180, 1030.</td>
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<tr>
<td>Ethyl 3-hydroxy-3-phenylpropanoate (19)</td>
<td>95 (0.02)</td>
<td>1.17 (3H, 5, J=6 Hz), 2.6-2.7 (2H, m), 3.46 (1H, variable singlet), 4.12 (2H, q, J=7 Hz), 7.30 (5H, m).</td>
<td>3540 (O-H), 3010, 1735 (C=O), 1180, 1038, 760, 700.</td>
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<tr>
<td>Ethyl 2-(2,2,6-trimethylcyclohexan-1-olyl)acetate (20)</td>
<td>73 (0.02)</td>
<td>0.7-1.9 (19H, m), 2.3 (1H, d, J=16 Hz), 2.68 (1H, d, J=15 Hz), 4.16 (2H, q, J=7 Hz), 4.4 (1H, variable singlet).</td>
<td>3460 (O-H), 1735 (C=O), 1190, 1035.</td>
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<td>Ethyl 2-(2-methyl-5-isopropylcyclohexan-1-olyl)acetate (22)</td>
<td>70 (0.02)</td>
<td>1.24 (3H, t, J=6 Hz), 1.3-2.2 (9H, m), 2.44 (1H, s), 2.66 (1H, s), 3.4 (.5H, variable s), 3.9 (.5H, variable s), 4.15 (2H, q, J=7 Hz), 7.24 (5H, m).</td>
<td>3500 (O-H), 3020, 262 (M⁺), 1732 (C=O), 1180, 1030, 758, 700.</td>
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<tr>
<td>Compound</td>
<td>Bp, °C (mm)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NMR, δ</td>
<td>IR, cm&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>Mass, m/e</td>
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<td>Ethyl 2-(4-phenyl-cyclohexan-1-olyl)-acetate (21)</td>
<td>126 (0.02)</td>
<td>0.5-1.9 (2H, m), 2.4</td>
<td>3500 (O-H), 1730 (C=O), 1190, 1030.</td>
<td>242 (M&lt;sup&gt;+&lt;/sup&gt;)</td>
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<td></td>
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<td>(1H, d, J=15 Hz), 2.7</td>
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<td>(1H, d, J=11 Hz), 3.08</td>
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<td>(.5H, variable s) 3.68</td>
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<td>(.5H, variable s), 4.17</td>
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<td>(2H, q, J=7 Hz).</td>
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<tr>
<td>Ethyl 3-hydroxy-7-methyl-3-(4-methyl-cyclohex-3-enyl)-oct-5-enoate (23)</td>
<td>118 (0.02)</td>
<td>1.24 (3H, t, J=6 Hz), 2.2-1.4 (20H, m), 2.4-2.6 (2H, m), 3.56 (1H, variable s), 4.17 (2H, q, J=7 Hz), 5.1 (1H, t, J=7 Hz), 5.38 (1H, s).</td>
<td>3490 (O-H), 1715 (C=O), 1185, 1035.</td>
<td>276 (M&lt;sup&gt;+&lt;/sup&gt;-18)</td>
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<sup>a</sup>Evaporative distillation on a Short Path. Analyzed samples, see Table I.
<table>
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<tr>
<th>Compound</th>
<th>Bp, °C (mm)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>NMR, δ</th>
<th>IR, cm&lt;sup&gt;-1&lt;/sup&gt;</th>
<th>Mass, m/e</th>
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<td>1-Phenylbut-3-en-1-ol (30)</td>
<td>50-54 (0.05)</td>
<td>2. 35 (2H, t, J=6. 5 Hz), 2.7 (1H, variable s), 4. 55 (1H, t, J=6. 5 Hz), 4. 7-5. 2 (2H, m), 5. 3-6. 1 (1H, m, J=6. 5, 9, 17. 5 Hz), 7. 1-7. 3 (5H, m).</td>
<td>3400 (O-H), 3100, 1635, 1590, 1490, 1440, 1290, 1190, 1040, 995, 915, 870, 757, 697.</td>
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<tr>
<td>1-Allylcyclohexan-1-ol (31)</td>
<td>32-34 (0.05)</td>
<td>1. 0-1. 9 (10H, m), 2. 0 (1H, variable s), 2. 2 (2H, d, J=6. 5 Hz), 4. 9-5. 4 (2H, m), 5. 6-6. 3 (1H, m, J=6. 5, 8, 19 Hz).</td>
<td>3430 (O-H), 1635, 1440, 1345, 1258, 1163, 1136, 1035, 1000, 973, 911, 874, 850, 834, 746.</td>
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<td>1-Methyl-1-phenylbut-3-en-1-ol (32)</td>
<td>54-56 (0.05)</td>
<td>1. 5 (3H, s), 2. 4 (1H, s, variable), 2. 4-2. 8 (2H, m), 4. 9-5. 4 (2H, m), 5. 4-6. 1 (1H, m), 7. 1-7. 7 (5H, m).</td>
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<td>1-Allyl-2-methylcyclohexan-1-ol (33)</td>
<td>40-42 (0.05)</td>
<td>0. 7-1. 1 (3H, m), 1. 1-2. 0 (10H, m), 2. 0-2. 5 (2H, d, J=7 Hz), 4. 8-5. 3 (2H, m), 5. 4-6. 2 (1H, m).</td>
<td>3510 (O-H), 1630, 1437, 1362, 1280, 1200, 1140, 992, 963, 910, 883, 795.</td>
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<td>Compound</td>
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<td>1-(2-Methyl-4-isopropylcyclopent-1-eneyl)-but-3-en-1-ol (34)</td>
<td>65-67 (0.05)</td>
<td>0.7 (3H, d, J=7 Hz), 0.9</td>
<td>3460 (O-H), 1660,</td>
<td>176(M⁺-18)</td>
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<td>(3H, d, J=7 Hz), 1.7 (3H,</td>
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<td>m), 2.5-3.0 (1H, m), 4.2-4.7</td>
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<td>5.4-6.2 (1H, m).</td>
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<td>4-Allyldodec-1-en-4-ol (35)</td>
<td>75-79 (0.03)</td>
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<td>3450 (O-H), 1635,</td>
<td>206(M⁺-18)</td>
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<td>(2H, m).</td>
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<td>2-Methyl-1-phenylbut-3-3n-1-ol (37)</td>
<td>65-67 (0.05)</td>
<td>0.9 (3H, d of d, J=6 Hz)</td>
<td>3500 (O-H), 1640,</td>
<td></td>
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<td></td>
<td>2.3 (1H, s, variable), 2.4</td>
<td>1700, 1490, 1450,</td>
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<tr>
<td></td>
<td></td>
<td>(1H, sextuplet, J=6 Hz),</td>
<td>1410, 1360, 1190,</td>
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<tr>
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<td></td>
<td>4.4 (1H, d of d, J=6 Hz),</td>
<td>1100, 1068, 1013,</td>
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<td>4.7-5.3 (2H, m), 5.3-6.1</td>
<td>911, 760, 700.</td>
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<td>(1H, m), 7.1-7.4 (5H, m).</td>
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<tr>
<td>3,4-Dihydro-1-(3-but-1-eneylnaphthalene (38)</td>
<td>79-83 (0.05)</td>
<td>1.3 (3H, d, J=6 Hz), 2.0-</td>
<td>3100, 1635, 1590</td>
<td>182(M⁺-2)</td>
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<tr>
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<td></td>
<td>2.5 (2H, m), 2.5-3.0 (2H,</td>
<td>1480, 1443, 1360,</td>
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<td></td>
<td></td>
<td>m), 3.5 (1H, t, J=6 Hz),</td>
<td>1000, 913, 818,</td>
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<td>4.9-5.3 (2H, m), 5.7-6.3</td>
<td>769, 735.</td>
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<td></td>
<td>(2H, m), 7.0-7.5 (4H, m).</td>
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<tr>
<td>Compound</td>
<td>Bp, °C (mm)</td>
<td>NMR, δ</td>
<td>IR, cm⁻¹</td>
<td>Mass, m/e</td>
</tr>
<tr>
<td>--------------------------------</td>
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</tr>
<tr>
<td>2, 3, 7-Trimethyl-3-vinylcyclooct-6-en-2-ol (39)</td>
<td>63-67 (0.05)</td>
<td>1.0 (3H, s), 1.2 (6H, s), 1.3-2.2 (11H, m), 4.5-5.4 (3H, m), 5.9 (1H, d of d, J=11, 17 Hz).</td>
<td>3500 (O-H, 1630, 1440, 1400, 1360, 1104, 1009, 945, 910, 877, 836, 815.</td>
<td>178 (M⁺-18)</td>
</tr>
<tr>
<td>2, 4, 8-Trimethyl-4-vinylcyclooct-7-en-3-ol (40)</td>
<td>71-75 (0.03)</td>
<td>0.7-1.1 (9H, m), 1.1-2.1 (12H, m), 3.2 (1H, d, J=2 Hz), 4.6-5.3 (3H, m), 5.5-6.2 (1H, m).</td>
<td>3500 (O-H, 1630, 1460, 1400, 1365, 1237, 1164, 1108, 1000, 909, 835.</td>
<td>192 (M⁺-18)</td>
</tr>
</tbody>
</table>

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*aPurity as determined by glc was 95% except for 45 (2%), 49 (90%), 51 (93%), and 55 (93%). See Table II.*