A GENERAL SYNTHETIC ROUTE TO MONOTERPENES AND SESQUITERPENES

BY

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We accept this thesis as conforming to the required standard

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September, 1972
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Department of Chemistry

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Date Sept 29, 1972
ABSTRACT

A biogenetic hypothesis concerned with an alternative route to monoterpenes and sesquiterpenes bearing the bicyclo(2.2.1)heptane framework has led to a general synthetic route to this class of compound. In particular, consideration of an oxygenated monocyclic cyclohexenyl substrate resembling dihydrocarvone enol phosphate as possible intermediate in the biogenesis of camphor has resulted in development of an efficient laboratory synthesis of (±)-camphor and related compounds including borneol, tricyclene and camphene. Extention of this work in the monoterpenic field to the related sesquiterpenes provided synthetic entry to (±)-campherenone, (±)-epicampherenone, (±)-α-santalene, (±)-β-santalene and (±)-epi-β-santalene. As a further simplification of the biogenesis of sesquiterpenes, campherenone enol phosphate was considered a possible precursor of such polycyclic sesquiterpenes as copacamphor, ylangocamphor, longicamphor and structurally related compounds. Laboratory analogy for this biogenetic relationship was established in the synthesis of (±)-copacamphor, (±)-ylangocamphor and related compounds starting from campherenone.
The success of the synthetic investigations led to refinements in the initial biogenetic postulate and necessitated the establishment of the absolute configurations of various sesquiterpenes encompassed in the postulate. (-)-Cryptomerion 99a was prepared starting from (-)-carvone 79a. A synthesis of (+)-epicamphenone 45a and (-)-camphenone 42b starting from (+)-camphor has allowed assignment of absolute configuration to these compounds and to β-santalene and epi-β-santalene. Formal access to optically active copacamphor, ylangocamphor and related compounds is implied from the synthesis of (-)-camphenone.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>ii</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>iv</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>v</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>vi</td>
</tr>
<tr>
<td>DEDICATION</td>
<td>vii</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>31</td>
</tr>
<tr>
<td>EXPERIMENTAL</td>
<td>133</td>
</tr>
<tr>
<td>BIBLIOGRAPHY</td>
<td>210</td>
</tr>
</tbody>
</table>
LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N.M.R. Spectrum (100 M Hz) of (±)-Campherenone 42</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>Infrared Spectrum of (±)-Campherenone 42</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>N.M.R. Spectrum (100 M Hz) of (±)-Epicampherenone 45</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>Infrared Spectrum of (±)-Epicampherenone 45</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>N.M.R. Spectrum (100 M Hz) of (±)-Copacamphor 52</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>Infrared Spectrum of (±)-Copacamphor 52</td>
<td>96</td>
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<tr>
<td>7</td>
<td>N.M.R. Spectrum (100 M Hz) of (±)-Ylangocamphor 53</td>
<td>97</td>
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<td>98</td>
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<tr>
<td>9</td>
<td>N.M.R. Spectrum (100 M Hz) of (±)-Sativene 60</td>
<td>104</td>
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<tr>
<td>10</td>
<td>Infrared Spectrum of (±)-Sativene 60</td>
<td>105</td>
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<tr>
<td>11</td>
<td>N.M.R. Spectrum (100 M Hz) of (+)-Epi-β-santalene 50a</td>
<td>120</td>
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To my loving wife and daughter
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INTRODUCTION

Biogenetic-type synthetic studies offer the organic chemist the opportunity to trespass the boundary between chemistry and bio-chemistry and to pursue the wealth of chemical knowledge that remains to be revealed in biological phenomena. Laboratory analogies for biosynthetic processes not only lend support to biosynthetic postulates and establish guidelines for further biosynthetic investigation but, more important to the chemist, also unveil new synthetic methods and even new classes of reactions. A single example from the files of terpene chemistry should demonstrate this point. The chemistry of
1,5-dienes has developed largely from model studies conducted in search of laboratory support for terpene biosynthetic postulates. These model studies have recently culminated in useful routes to total synthesis of complex triterpenes such as malabaricanediol $\text{2}_2$. This entire complex of ring systems was established in a one step biogenetic-type cyclization of the acyclic epoxy diol substrate $\text{1}_1$ (1). Later in this thesis it will be shown that an alternative hypothesis for the biogenesis of monoterpenes and sesquiterpenes possessing the bicyclo(2.2.1)heptane (bornane) skeleton has led to a general synthetic route to numerous compounds of this type.

Though biosynthetic studies and biogenetic-type synthetic studies have been concerned with various metabolic pathways, the chemist has concentrated mainly on secondary metabolites, leaving primary metabolites to the realm of the biochemist. One such group of secondary metabolites comprising an ever expanding list of interesting structures is the terpene or isoprenoid compounds.

As early as 1887 Wallach commented on this group of natural products indicating that they could be constructed by head to tail linking of isoprene $\text{3}_3$ units. Later, more extensive structural studies resulted in a restatement of the original hypothesis in the form of the "biogenetic isoprene rule" (2-4). In these papers Ruzicka postulated that nearly all the structurally diverse isoprenoids could be biogenetically accommodated by head to tail linking of two or more isoprene units forming key acyclic intermediates which could then undergo various cyclizations and modifications.
Linking of two isoprene units would afford the C-10 series of isoprenoids known as the monoterpenes. Today it is felt that the key acyclic intermediate(s) leading to these compounds is one or more of three possible compounds; geranyl pyrophosphate 4, neryl pyrophosphate 5 or linalyl pyrophosphate 6. All three are formed in nature by joining isopentenyl pyrophosphate 7 (the biological equivalent of Ruzicka's isoprene unit) with dimethylallyl pyrophosphate 8, a rearrangement product of 7 (scheme I). Addition of another C-5 unit of isopentenyl pyrophosphate 7 to geranyl pyrophosphate 4 produces the C-15 acyclic intermediate (farnesyl pyrophosphate, cis 9 or trans 10) postulated to be the precursor of the sesquiterpenes. The various structural types of sesquiterpenes have been postulated to arise by cyclization of either cis-farnesyl pyrophosphate 9 or trans-farnesyl pyrophosphate 10 to one of six intermediate cations, 11-16 (scheme II), followed by further transformations and elaborations (5,6). Detailed accounts of the above biosynthetic postulates for monoterpenes, sesquiterpenes, diterpenes, triterpenes and steroids have been presented elsewhere (3-11 and references therein).

Of all the vast number of known terpene compounds camphor 17 has enjoyed the longest and perhaps most colorful record of chemical
Scheme I: Biosynthesis of C-10 and C-15 Acyclic Intermediates

(OPP equals pyrophosphate)
Scheme II: Postulated Intermediate Cations in Sesquiterpene Biosynthesis
exploration (12). Our interest in terpenes bearing the camphane and related skeletons (e.g., camphor 17, borneol 18, tricyclene 19 and camphene 20) developed from an initial curiosity concerning the biological formation of the bicyclo(2.2.1)heptane nucleus which is a common denominator of these compounds. The general proposals for the biogenesis of bicyclic and tricyclic monoterpenes have not changed significantly from those initially laid down by Ruzicka and co-workers (cf. 3,4 and 11). Cyclization of neryl phophosphate 5 (or its counterpart linalyl pyrophosphate 6, OPP equals pyrophosphate) affords the monocyclic substrate 21 where Z is a cation or an appropriate biological leaving group. There are strong indications that geranyl pyrophosphate 4
may serve as the acyclic precursor of many monocyclic and bicyclic monoterpenes (11). However the trans double bond of this substrate prohibits direct cyclization to 21 and it has been suggested that 4 is transformed to 5 or 6.

Monoterpenes possessing the bicyclo(2.2.1)heptane skeleton are postulated to be derived from the monocyclic substrate 21 by interaction of the \( \pi \)-electrons of the double bond with the Z group (Z equals cation, pyrophosphate, \( \ddagger \)-Enz., etc.) to form cation 22 directly (anti-Markovnikov cyclization) or to form cation 23 initially followed by Wagner--Meerwein rearrangement to 22. The nonclassical version of this interaction is shown in 24. Cation 22 can then lose a proton from C\(_6\) to form tricyclene 19 on the one hand or lose a proton from the C\(_{10}\) methyl with concomitant Wagner--Meerwein shift affording camphene 20. Simple hydration of 22 leads to borneol 18 which then could be oxidized to camphor 17.

While such proposals are compelling from their schematic simplicity, Banthorpe, Charlwood, and Francis in a recent and extensive review of monoterpane biosynthesis (11) emphasize the paucity of meaningful data presently available from which to judge such hypotheses. One possible significant result from biosynthetic studies was the incorporation of \( (^{14}\text{C})\alpha \)-terpineol 25 into camphor 17 in \( \text{T. vulgare} \). However it was not determined if the incorporation was specific and it was also shown that in the same plant system \( (^{14}\text{C})\text{terpenen-4-ol} \) 26 was likewise incorporated and to the extent of 0.5%. With significant incorporations into monoterpenes usually falling in the range of 0.01 to 0.1% (excluding methylcyclopentanoids where percentages are often higher) the
obvious conclusion to be drawn from these two results is that much remains to be disclosed concerning the nature of the biological precursor of the bornane skeleton.

At the outset of our work, laboratory analogy for the biogenetic proposed cyclization of monocyclic substrates to bicyclo-(2.2.1)heptane systems was nonexistent. Despite considerable efforts to effect cyclization of monocyclic substrates such as \( \text{21}\) where \( Z \) has been hydroxyl (13), orthophosphate and pyrophosphate (14,15,16), chloride (17) and para-nitrobenzoate (17,18), detectable amounts of bicyclic materials were not produced*. Similarly no bicyclic materials were detected in cyclization attempts with acyclic substrates such as \( \text{27}, \text{28} \) or \( \text{29} \) with \( Z \) equal to hydroxyl (19), orthophosphate and pyrophosphate (14,15,16), diphenyl phosphate (20), or para-nitrobenzoate (18); however, in several cases considerable amounts of monocyclic materials

* Efforts in our laboratory to achieve cyclization of limonene (21, double bond between \( \text{C}_7 \) and \( \text{C}_8 \)) or \( \text{\textgamma-terpineol} (21, Z equals OH) \) with various acid catalysts (for example: boron trifluoride, boron trifluoride etherate, stannic chloride, silica gel or ion exchange resin) have failed to produce bicyclic products.
were produced. In connection with their solvolysis studies on compounds such as 21 (Z equals chloride or para-nitrobenzoate), Wilcox and Chibber estimated that "participation in cyclohexenyl systems is just below the energetic threshold of observation and that accessible systems with appropriate substituents can be expected to give participation."(17)

Structural analysis of terpenes bearing the camphane skeleton (for example camphor 17 and borneol 18) led us to consider an oxygen function (or the equivalent) at the C2 position of 21 as an "appropriate substituent" capable of promoting cyclization. Our reason for this proposal was the common occurrence of oxidation at the analogous C2 position of terpenes based on the bicyclo(2.2.1)heptane framework. A possible model substrate for the study of this proposal might be 30 where Z could be the cation or an appropriate leaving group. We were aware however from classical terpene chemistry that one would require regiospecific enol (enolate) formation to effect this cyclization since cyclization of 30 (Z equals Br) in the presence of base leads entirely to carone 31 (21). Similar treatment of dihydrocryptomerion dihydrobromide 32 in our laboratory afforded sesquicarones 33 and 34 with no
indication of the alternative cyclization to the bicyclo(2.2.1)heptane skeleton (22).

Specific enols (enolates) are commonly generated in the laboratory by decomposition of appropriate enol derivatives (enol esters, enol ethers, etc.) (23). In Nature enol derivatives are also involved in biosynthesis. Phosphoenolpyruvate 35 appears at a key stage of the shikimic acid pathway to aromatic compounds and condenses with erythrose-4-
phosphate 36 to form 2-deoxy-D-arabino-heptulosonic acid-7-phosphate 37. Later in this same biosynthetic route shikimic acid 38 is converted to prephenic acid 40 by cyclization of enol ether 39 (chorismic acid)(24). Enamines are also postulated as intermediates in biosynthesis, for example, in carbon-carbon bond formation reactions involving thiamine pyrophosphate (25). Combining the synthetic qualities of enol derivatives and
the biological precedent for such structures with our previously proposed substrate we arrived at structure 41 (Z equals a cation or an appropriate biological leaving group; X equals pyrophosphate).

Thus the monocyclic substrate 41 could undergo cyclization directly to camphor 17 which could be reduced in vivo to borneols 18a,b. Dehydration of 18(a or b) in Nature could occur by analogy with the known processes in the laboratory to produce tricyclene 19 and camphene 20(12). The relationship of compounds 17-20 is supported by the fact that the five apparently co-occur in _Picea rubens_ Sarg. (26). The chief difference between this proposal and earlier biogenetic schemes is the appointment of camphor 17 as the key intermediate of the quartet of compounds 17-20, a result which follows directly from the nature of the proposed monocyclic precursor 41. Later in this thesis it will be shown that this biogenetic proposal forms the basis of biogenetic-type synthetic studies in the monoterpenene and sesquiterpenene area.
The direct extension of our biogenetic proposals for bicyclic monoterpenes to the sesquiterpenes is obvious if one considers the structural relationships between camphor 17 and campherenone 42 or between borneol 18 and longiborneol 43. Cyclization in vivo of a monocyclic substrate such as 44 (Z equals cation, pyrophosphate, $\frac{S}{H}$-Enz., etc.; X equals pyrophosphate) would lead to campherenone 42 (27,28) and epicampherenone 45 (29). In analogy with the scheme for camphor,
Campherenone could be the precursor of camphenols 46a,b (27,28), \( \alpha \)-santalene 47 and \( \beta \)-santalene 48 (30). A similar quartet of compounds would emanate from epicampherenone 45 providing epicamphenols 49a,b (29), \( \alpha \)-santalene 47 and epi-\( \beta \)-santalene 50 (30).

\* Epi-\( \beta \)-santalene could alternatively be derived from campherenone 42 through the intermediacy of \( \alpha \)-santalene 47.
A further extension of this proposal would be the utilization of campherenone 42 as precursor of the polycyclic sesquiterpenes. Thus, for example, enol phosphate 51 (X = pyrophosphate) could be transformed into copacamphor 52 (29), ylangocamphor 53 (29) or longicamphor 54 (29). Each of the parent ketones (52-54) leads to sesquiterpene analogues of borneol, camphene and tricyclene and thus twelve polycyclic sesquiterpene skeletons can be derived in theory from campherenone 42 (scheme III). Copacamphor 52 could provide copaborneols 55a,b (32,33), cyclocopacamphene 56 (34) and copacamphene 57 (29). From ylangocamphor 53 one
Scheme III

52

55a \( R_1 = H, \ R_2 = OH \)

b \( R_1 = OH, \ R_2 = H \)

53

58a \( R_1 = H, \ R_2 = OH \)

b \( R_1 = OH, \ R_2 = H \)

54

61a \( R_1 = H, \ R_2 = OH \)

b' \( R_1 = OH, \ R_2 = H \)
obtains ylangoborneols 58a,b (29), cyclosativene 59 (35) and sativene 60 (36). Longicamphor 54 provides longiborneols 61a,b (37), longicyclene 62 (38), and longifolene 63 (30).

The overall simplicity of the above proposed biogenetic scheme (39,40) involving the generation of numerous skeletal types by simple transformations of analogous intermediates compare favourably with previous biogenetic proposals. Previous postulated routes to the santalenes and to campherenol and campherenone hinge on the formation of cation 64 (6,28). Transformations of 64 (exactly analogous to those mentioned for cation 22) lead to α-santalene 47, β-santalene 48, campherenol 46a and campherenone 42.
More complex problems are encountered in the previous postulates for the biogenesis of the copacamphane and ylangocamphane systems (6)(scheme IV). Cation 13 derived from cis-farnesyl pyrophosphate 9 must undergo 1,3-hydride transfer to form cation 65 which presumably upon cyclization forms the cis-decalin cation 66. Cyclization of 66 affords cation 67 or 68 depending on the relative stereochemistry of the isopropyl group in 66. As tricyclic analogues of 64, cations 67 and 68 could likewise be rearranged or oxidized to the various members of their quartets. Cation 66 could alternatively be derived by anti-Markovnikov cyclization of γ-curcumene 69 to cation 70 followed by 1,2-hydride transfer (6). In previous proposals a third route stemming from completely different intermediates is required to rationalize the biogenesis of the longicamphane quartet (6)(scheme V). Anti-Markovnikov cyclization of cis-farnesyl pyrophosphate 9 could lead to eleven membered cation 14. A 1,3-hydride shift converts 14 to 71 which on cyclization could lead to the cis-fused bicyclo(5.4.0)undecane intermediate 72. Further cyclization of 72 provides cation 73 bearing the longicamphane skeleton. Elaboration of 73 to the quartet members follows the route previously outlined for cation 64. An alternative route to cation 72 from γ-curcumene 69 via cation 74 has also been suggested (6).

The ability of enzyme systems to utilize common intermediates and elaborate numerous variations on the same theme is perhaps nowhere better exemplified than in the terpene field. In the triterpenes, for example, the lanosterol skeleton is elaborated in a multitude of variations but holding to the same basic skeletal theme. In this context
Scheme IV

13 → 65 → 66

69 → 70

67, 68 → 56, 59

57, 60

55, 58 → 52, 53
the use of common intermediates such as enol phosphates 44 and 51 to produce numerous skeletal variations which are further elaborated by analogous transformations is highly attractive from a biosynthetic perspective. A survey of the literature reveals that many of the members of the various analogous quartets presented above have already been found in nature. If one allows for optical isomerism, ten quartets in all could theoretically exist, stemming from enantiomers of campher-enone 42, epicampher-enone 45, copacamphor 52, ylangocamphor 53, and longicamphor 54. In fact members of nearly every quartet are known and these are shown in the following tables (naturally occurring compounds indicated by **; see key to Tables I and II on page 27.)

Analysis of Tables I and II could stimulate studies in several areas. First, one immediately notices that several structures do not correspond to naturally occurring compounds. It seems highly plausible that a thorough investigation of uncharacterized fractions of appropriate essential oils or other sources of sesquiterpenes could reveal the "missing" members. The absolute configurations of co-occurring members of the various structural quartets is of crucial importance as each member, according to our postulate, is derived through the corresponding camphor analogue and thus should belong to the same antipodal series as the other quartet members. Such correlations serve as a useful check on this and previous biogenetic hypotheses. Research in each of the areas outlined above is already underway in our laboratory.

A third area of investigation from our hypothesis would be biosynthetic studies aimed at identifying or verifying postulated intermediates between cis-farnesol pyrophosphate and the quartet members. For example, the establishment of oxidized monocyclic precursors such
Table I: Terpenes Structurally Related to D-\(\text{(+)}\)-Camphor

**Monoterpenes**

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<tr>
<td>Borneol</td>
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**Sesquiterpenes**

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<td><strong>(F)(27)</strong> ?</td>
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Table I: (Cont'd.)

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<td></td>
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<td>**(H)(42),(L)(30)</td>
</tr>
<tr>
<td>Juniperol acetate</td>
<td>*(C,+)(53)</td>
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<tr>
<td></td>
<td>**(M)(53)</td>
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<tr>
<td>Longifol-7(15)-en-5β-ol</td>
<td>*(C,+)(53)</td>
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<tr>
<td></td>
<td>**(M)(53)</td>
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<tr>
<td>Longifolan-3α,7α-oxide</td>
<td>*(C,-)(53)</td>
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<tr>
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<td>**(M)(53)</td>
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Table II: Terpenes Structurally Related to L-(-)-Camphor

### Monoterpenes

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>Configuration</th>
<th>(N)</th>
<th>(O)</th>
<th>(H)</th>
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<tbody>
<tr>
<td>Camphor</td>
<td><img src="image" alt="Camphor" /></td>
<td><em>(E,−)</em></td>
<td><em>(N)(26?)</em>, <em>(O)(12)</em></td>
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<td></td>
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<tr>
<td>Borneol</td>
<td><img src="image" alt="Borneol" /></td>
<td><em>(E,−)</em></td>
<td><em>(N)(26)</em>, <em>(O)(12)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricyclene</td>
<td><img src="image" alt="Tricyclene" /></td>
<td><em>(H)(42)</em>, <em>(N)(26)</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Camphene</td>
<td><img src="image" alt="Camphene" /></td>
<td><em>(E,−)</em></td>
<td><em>(N)(26)</em></td>
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### Sesquiterpenes

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<th>Compound</th>
<th>Structure</th>
<th>Configuration</th>
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<th>(O)</th>
<th>(H)</th>
<th>(I)</th>
<th>(F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campheranone</td>
<td><img src="image" alt="Campheranone" /></td>
<td><em>(B,−)(22)</em></td>
<td></td>
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<tr>
<td>Campherenol</td>
<td><img src="image" alt="Campherenol" /></td>
<td><em>(B,+)</em>(45)</td>
<td><em>(I)(30)</em>, <em>(F)(60)</em></td>
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<td></td>
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<tr>
<td>α-Santalene</td>
<td><img src="image" alt="α-Santalene" /></td>
<td><em>(B,+)</em>(45)</td>
<td><em>(I)(30)</em></td>
<td><em>(F)(60)</em></td>
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<td></td>
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<tr>
<td>β-Santalene</td>
<td><img src="image" alt="β-Santalene" /></td>
<td><em>(B,−)(22)</em></td>
<td><em>(I)(30)</em>, <em>(F)(60)</em></td>
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<tr>
<td>α-Santalol</td>
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<td><em>(B,+)</em>(46)</td>
<td><em>(I)(30)</em></td>
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<tr>
<td>β-Santalol</td>
<td><img src="image" alt="β-Santalol" /></td>
<td><em>(I)(30)</em></td>
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<td><em>(I)(54)</em></td>
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<td><em>(I)(30)</em></td>
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### Other Monoterpenes

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>Configuration</th>
<th>(N)</th>
<th>(O)</th>
<th>(H)</th>
<th>(I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epicampheranone</td>
<td><img src="image" alt="Epicampheranone" /></td>
<td><em>(E,−)</em></td>
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<td></td>
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<tr>
<td>Epicampherenol</td>
<td><img src="image" alt="Epicampherenol" /></td>
<td><em>(E,−)</em></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>α-Santalene</td>
<td><img src="image" alt="α-Santalene" /></td>
<td><em>(E,−)</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epi-β-santalene</td>
<td><img src="image" alt="Epi-β-santalene" /></td>
<td><em>(E,−)</em></td>
<td></td>
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</tr>
</tbody>
</table>
Table II: (Cont'd.)

- Copacamphor
  \[\text{*(B,+)}(55)\]

- Copaborneol
  \[\text{*(C,+)}(32,33), \text{**(P)}(32,33)\]

- Cyclocopacamphene
  \[\text{*(B,-)}(56)\]

- Copacamphene
  \[\text{*(B,-)}(56)\]

- Ylangocamphor

- Ylangoborneol

- Cyclosativene
  \[\text{*(E,-)}\]

- Sativene
  \[\text{*(E,-)}, \text{**(Q)}(36)\]

- Longicamphor
  \[\text{*(E,-)}\]

- Longiborneol
  \[\text{*(E,-)}, \text{**(R)}(57)\]

- Longicyclene
  \[\text{*(E,-)}\]

- Longifolene
  \[\text{*(E,-)}, \text{**(R)}(57)\]

- Culmorin
  \[\text{*(C,-)}(58), \text{**(S)}(59)\]
Key to Tables I and II

*—Absolute configuration assigned, pertinent data indicated as follows:

(A,+) (26) — Reference

Rotational sign, 589 or 578 nm (may vary with solvent)

Method of assigning absolute configuration:

A. X-ray crystallography.
B. Total synthesis.
C. Chemical correlation to compound of known absolute configuration.
D. ORD and/or CD.
E. Enantiomer of known absolute configuration.

**—Natural product

(F) (27) — Reference

Source

F. Cinnamomum camphora Siebold (lauraceae)
G. Dryobalanops aromatica
H. Abies magnifica A. Murray
I. Santalum album Linn
J. Vetiveria zizanioides
K. Cedrus deodar Loud.
L. Pinus longifolia Roxb.
M. Juniperus conferta Parl.
N. Picea rubens Sarg.
O. \textit{Blumea balsamifera}

P. \textit{Pinus sylvestris} \textit{L.}

Q. \textit{Helminthosporium sativum}

R. \textit{Scapania undulata} \textit{(L.) Dum.}

S. \textit{Fusarium culmorum} \textit{(Link)}

T. \textit{Thuya occidentalis}
as dihydrocryptomerion 75 or dihydrocarvone 76 or analogous compounds*

will be a crucial test of the validity of our hypothesis. Furthermore, sequence studies to test in vivo the interconversion patterns of quartet members (e.g., camphor 17 → borneol 18 → tricyclene 19 + camphene 20) are exciting possibilities. As a result of our synthetic program we have developed suitable synthetic routes which can be adapted to the preparation of radioactive monocyclic and bicyclic substrates necessary for these biosynthetic studies.

Finally, consideration of simple structural relations between the members of the quartets, particularly when viewed from our biogenetic hypothesis has stimulated an exceedingly fruitful synthetic study of polycyclic monoterpenes and sesquiterpenes. The use of enol derivatives

* E.g. epoxides:
to promote and direct cyclization has been the basis of synthetic entry

to the skeletal systems of the majority of the quartet members. Bond

formation in a sequence analogous to our biogenetic postulate has

proven to be an efficient route to the complex polycyclic systems.

Syntheses incorporating the use of suitable optically active starting

materials have led to the establishment of the absolute configurations

of a number of these sesquiterpenes while at the same time establishing

a synthetic route to optically pure members of the quartets. This

synthetic work surrounding our biogenetic hypothesis will be discussed

in detail in the remainder of this thesis.
DISCUSSION

Prompted by an alternate biogenetic scheme for the formation and interrelation of various monoterpenes bearing the bicyclo(2.2.1)-heptane skeleton, we sought laboratory support for our proposed cyclization of intermediate 41 (Z equals cation, pyrophosphate, $^+\text{H}^-$-Enz. etc.; X equals pyrophosphate). We anticipated that by analogy with our biogenetic scheme the direct synthesis of camphor 17, from a C$_2$ oxygenated monocyclic precursor might be a feasible laboratory route to members of this skeletal series. The conversions of camphor to the borneols 18a, b to tricyclene 19, and to camphene 20 were known from

\[
\begin{align*}
41 & \xrightarrow{X} 17 \\
& \xrightarrow{\text{Camphor}} 20
\end{align*}
\]

18a $R_1 = H, R_2 = OH$

18b $R_1 = OH, R_2 = H$
classical terpene chemistry (12) and thus the synthesis of camphor would constitute a synthetic entry to the entire quartet of compounds. We were further encouraged along these lines by the work of Felkin and Lion involving the solvolytic cyclization of enol ether 77 to 1-methylnorcamphor 78 (61). While the yield of this reaction was rather low, this constituted the first reported formation of the bicyclo(2.2.1)heptane system by solvolytic cyclization of a monocyclic cyclohexenyl substrate. Furthermore this reaction established the feasibility and potential usefulness of enol derivatives in promoting and directing cyclization. We envisioned a terpenoid analogy to this cyclization proceeding through substrate 41 where Z equals the carbonium ion and X is a suitable enol derivative.

Dihydrocarvone 76 seemed to possess the necessary functionalities to test our synthetic proposals and in addition, the compound was readily available by reduction of carvone 79 with zinc in ethanolic potassium hydroxide (62). We chose as the enolic derivative, enol acetate 80, partially due to literature precedent (63) and partially due to the greater synthetic accessibility of enol esters as compared to enol ether derivatives. Thus treatment of (-)-carvone 79a, $^3_d\alpha=-58.6^\circ$, 

\[
\begin{align*}
\text{OCH}_3
\end{align*}
\]

\[
\begin{align*}
\text{OR}
\end{align*}
\]

77 R=p-bromobenzenesulfonate
with zinc powder and potassium hydroxide in 7:2 ethanol-water under reflux with vigorous stirring afforded an 87% yield of (+)-dihydrocarvone, \((\alpha)^{29}\_D +18.3^\circ\), as a 3:1 mixture of epimers 76a and 76b [estimate based on the integral of the epimeric C\textsubscript{1} methyl in the nuclear magnetic resonance (n.m.r.) spectrum]. Considerable effort was made to improve the yield in this reaction (62) since dihydrocarvone became an important substrate for our later synthetic work.

Wallach's conditions were reported to yield 64 to 74% dihydrocarvone but in our hands we found difficulty in reproducing such yields. Wallach had reported isolating from this reaction a crystalline side product of imperical formula C\textsubscript{10}H\textsubscript{15}O (mp 148-149\textdegree) for which he proposed the molecular formula C\textsubscript{10}H\textsubscript{14}\_OH\_H\textsubscript{2}O\_C\textsubscript{10}H\textsubscript{14} describing the material as possibly carvone pinacol. In the interest of improving our reaction yield we likewise isolated this material (mp 153-154\textdegree) and sought its identity spectroscopically. Wallach's assignment of molecular formula C\textsubscript{20}H\textsubscript{30}O\textsubscript{2} was confirmed in the mass spectrum by a molecular ion of m/e 302 which appeared as the base peak of the spectrum. The dimeric type of structure was also supported by a monomer fragment ion of m/e 151 (relative intensity 52.5). The
pinacol structure was nevertheless invalidated by the infrared spectrum which indicated no hydroxyl absorption but instead a strong carbonyl band at 1705 cm\(^{-1}\). The presence of terminal double bond was also indicated by absorptions at 3090, 1650 and 892 cm\(^{-1}\). The ultraviolet spectrum confirmed the presence of saturated carbonyl (probably ketone) by an absorption at 288 nm (\(\varepsilon 90\)) and the large extinction coefficient suggested the presence of two similar ketones. The n.m.r. spectrum of this compound was found very similar to that of dihydrocarvone with the exception that most of the peaks were doubled in integral area. Thus a doublet at 9.03\(\delta\) (six protons, \(J = 6.5\) Hz) indicated the presence of two secondary methyls and signals at 8.22\(\delta\) (multiplet, six protons) and 5.18\(\delta\) (multiplet, four protons) suggested two isopropenyl groups. Combination of the foregoing spectral evidence with mechanistic arguments has led us to assign structure 82 to this compound. Mechanistically this compound could be produced in the reaction by attack of enolate anion 81 (formed from the reduced material, dihydrocarvone) in Michael fashion on the enone system of the starting material 79a.

As compound 82 frequently comprised from 5 to 10\% (isolated) of the reaction products, an attempt was made to adjust reaction conditions so as to disfavour Michael addition. Indeed, very slow addition of carvone to the vigorously stirred reduction medium, utilizing a considerably greater ethanol to water ratio than described by Wallach, decreased the isolable yield of 82 to less than 0.2\% and correspondingly increased the yield of dihydrocarvone to 87\%. Other products from the reaction included phenolic materials (ca. 1\%, probably largely carvacrol 83) and a resinous material (ca. 9\%) exhibiting strong ketone
and hydroxyl absorptions in the infrared spectrum.

We next turned our attention to the preparation of the enol acetate derivative of dihydrocarvone. Two of the common methods of acid catalyzed enol acetylation [acetic anhydride/p-toluenesulfonic acid (64,65), and acetic anhydride/perchloric acid/carbontetrachloride (66,67)] isomerized the acid labile terminal double bond of 76a,b. However, it was found that isopropenyl acetate with a catalytic amount of p-toluenesulfonic acid (65,68) afforded the desired enol acetate 80a and the isomeric compound 84 in a 3:1 ratio respectively. The stereochemical integrity of the terminal double bond was apparent from both the infrared spectrum (3090, 1645 and 892 cm\(^{-1}\)) and the n.m.r.
spectrum (ca. 5.25\(\tau\), two vinyl protons) of the enol acetate mixture. Pure samples of 80a and 84 were obtained by preparative gas-liquid chromatography (g.l.c.) and were readily distinguishable by their n.m.r. spectra. Thus enol acetate 80a exhibited two vinyl methyl signals (8.51 and 8.26\(\tau\)) and no additional olefinic signals to those mentioned above, while isomer 84 showed one signal for vinyl methyl (8.26, three protons) and an olefinic proton (4.86\(\tau\)) due to the enol acetate double bond. The use of (-)-carvone 79a as starting material afforded optically active 80a, \(\alpha\)\(^D\) +81.1°, which in view of the method of synthesis must have the absolute configuration shown.

The catalyst chosen to test the cyclization was gaseous boron trifluoride. Among its many chemical and catalytic properties, boron trifluoride is known to promote C-acylation of ketones in the presence of anhydrides (23), to decompose enol esters resulting again in C-acylation (23), to promote electrophilic substitution, particularly in aromatic systems, to stabilize enols as enol fluoroborates (69), and to facilitate the interaction of enol esters with double bonds (63). In spite of this generous endorsement of the capabilities of this catalyst we were nevertheless pleasantly surprised when a 0.1% solution
of enol acetate 80a in methylene chloride saturated with boron trifluoride gas (10 minutes) yielded (±)-camphor 17a,b in 90% yield as judged by g.l.c. (70). Higher concentrations of 80a and other variations in reaction conditions resulted in lower yields of camphor and corresponding increase in the yield of carvenone 85 (71) λ_max 234 nm (ε 13,200)(methanol)H; ν_max 1670 and 880 cm⁻¹; (CCl₄) 8.95 (doublet, three protons, J = 6.5 Hz), 8.89 (doublet, six protons, J = 6.5 Hz and 4.27 (singlet, one proton)) and other products. For example,

\[ \text{BF}_3/\text{CH}_2\text{Cl}_2 \]

\[ \text{OAc} \]

\[ \text{17a} \]

\[ \text{17b} \]

\[ \text{85} \]

\[ \text{86} \]

a 0.7% solution of enol acetate 80a under the cyclization conditions afforded a mixture of at least ten components as judged from g.l.c. analysis including 10% camphor, 35% carvenone and 39% a compound tentatively assigned structure 86 on the basis of the following spectral characteristics. The infrared spectrum of 86 exhibited a
carbonyl absorption at 1745 cm$^{-1}$ and a C-O stretch at 1210 cm$^{-1}$ consistent with the presence of an acetate function. The n.m.r. spectrum (CCl$_4$) was well defined with a six proton doublet at 8.97$\tau$ (J = 6.5 Hz) suggesting an isopropyl group; a broadened three proton singlet at 8.50$\tau$ consistent with a methyl group on an enol acetate double bond; a sharp three proton singlet at 7.92$\tau$ indicating an acetate function; a one proton multiplet at 7.72$\tau$ (methine proton); a four proton broadened singlet at 7.32$\tau$ typical of allylic methylenes; and a one proton broadened singlet olefinic signal at 4.65$\tau$. The alternative homoannular diene structure 87 was ruled out on the basis of the ultraviolet spectrum which exhibited no absorption in the 260-270 nm region [$\lambda_{\text{max}}$ calculated for compound 87 is 273 nm, the value found for analogous compound 88 is 262 nm (acetate function normally doesn't shift position of absorption band greatly) (72)].

As the reagent grade methylene chloride used contained about 0.01% water, we considered that the water content was a yield determining factor in the reaction. Indeed, when the reaction was run in scrupulously dry methylene chloride, the result was a negligible yield
of camphor. The choice of boron trifluoride gas as catalyst for this reaction proved fortuitous as later attempts to effect cyclization of enol acetate 80a with other acid catalysts (e.g., hydrogen chloride, hydrogen fluoride, aluminum chloride or boron trifluoride etherate) gave no detectable amount of camphor.

Though pleased by the success of the cyclization, we were somewhat perplexed by the fact that from optically active enol acetate 80a we had obtained racemic camphor rather than the (+)-camphor 17a which we had anticipated. A plausible solution to this dilemma was the known racemization of camphor under acidic conditions (73). However, (+)-camphor proved configurationally stable to our reaction conditions over prolonged periods of exposure. One remaining possibility is that disruption of the chiral center at C4 of enol acetate 80a through double bond migration or hydride shift occurs prior to cyclization.

In the above description we have assumed that formation of the enol acetate of dihydrocarvone was essential in directing and promoting cyclization. To provide some support for this argument, dihydrocarvone 76 was subjected to reaction conditions identical to those described above. The starting material 76 was consumed very rapidly, but no trace of camphor was found among the reaction products. Instead, a major product initially was an unconjugated enone tentatively assigned structure 89 on the basis of spectral evidence. The infrared spectrum of compound 89 showed a carbonyl absorption at 1710 cm⁻¹ while the n.m.r. spectrum (CCl₄) exhibited a nine proton doublet at 8.96τ (J = 6.5 Hz) for three secondary methyls, a broad singlet at 7.26τ assigned to the methylene group adjacent to the ketone
function and allylic to the double bond in 89 and a one proton olefinic signal at 4.46σ. When benzene was used as solvent the secondary methyl adjacent to the ketone function of 89 (9.01σ, doublet, three protons, J = 5.0 Hz) appeared downfield from the isopropyl methyls (9.18σ, doublet, six protons, J = 5.0 Hz). As the reaction of dihydrocarvone (BF3/CH2Cl2) proceeded, the concentration of carvenone 85 increased at the expense of compound 89. Dihydrocarvone of +10° rotation afforded (+)-carvenone, (α)D24 +67°.

Encouraged by the successful cyclization of enol acetate 80a, we next investigated enol acetate 84 which we had previously obtained as a by-product in the enol acetylation of dihydrocarvone. Treatment of 84, (α)D28 +90.5°, under analogous conditions, however, failed to produce carone 31 and instead yielded only carvenone 85. One possible reason for the failure of enol acetate 84 to yield carone could be the instability of certain strained small ring compounds to the reaction conditions. In other studies in our laboratory, aimed at preparing the bicyclo(3.1.1)heptane ring system, we attempted cyclization of enol acetate 90 with the result that no nopinone 91 was produced but rather enone 92 appeared the major product. When we
subjected nopinone 91 to the cyclization conditions (BF₃/CH₂Cl₂) the result was formation of enone 92. While these results do not obligate the intermediate formation of 91 from enol acetate 90, they do attest to the instability of ring systems such as 91 and possibly 31 to our reaction conditions. Interestingly, another ketonic compound 94, formally bearing a bicyclo(3.1.1.)heptane ring system, is apparently stable to boron trifluoride. Stork and co-workers (74) have reported that treatment of cis-dimethyloctalone 93 with boron trifluoride in methylene chloride affords ketone 94 in 90% yield.

Our success in the synthesis of camphor via monocyclic substrate 80a (95a; R = H, X = OAc) led us to consider extension of our synthetic efforts to the sesquiterpene analogues of camphor. Already in the sesquiterpene field Corey and co-workers (63) had used enol acetate 97 to effect cyclization of the norcorane skeleton 96 to the norcedrane skeleton 98 which was then elaborated to (±)-cedrol.

Our interests were mainly in the preparation of sesquiterpene analogues of camphor by extension of the cyclization reaction of monocyclic enol acetates. The simplest known sesquiterpene analogue of camphor appeared to be campherenone 42 which was isolated in 1967 from the camphor tree [Cinnamomum camphora Siebold (Lauraceae)] (27). Our biogenetic scheme (repeated for convenience in schemes VI and VII) depicted campherenone as derived from a monocyclic precursor such as 95b where R is a γ,γ-dimethylallyl side chain and X equals pyrophosphate (OPP). Compound 95b is simply the enol derivative of dihydrocryptomerion 75, which can be regarded as the sesquiterpene analogue of dihydrocarvone 76. Dihydrocryptomerion itself is not known in nature...
95a $R=H$

b $R=\text{CH}_2\text{CH}C(\text{CH}_3)_2$

\[
\begin{align*}
\text{96} & \quad \rightarrow \quad \text{97} \quad \rightarrow \quad \text{98}
\end{align*}
\]
Scheme VI

- 95b -

**Campherenone**

**Epicampherenone**

**Campherenols**

**Epicampherenols**

**β-Santalene**

**Epi-β-santalene**

**α-Santalene**
Scheme VII

- Copacamphor
- Ylangocamphor
- Longicamphor
- Copaborneols
- Ylangoborneols
- Longiborneols
- Cyclocopacamphene
- Cyclosativene
- Longicycline
- Copacamphene
- Šativene
- Longifolene
but cryptomerion 99 occurs in Cryptomeria japonica D. Don. (75).

Thus the synthesis of campherenone 42 appeared a logical extension of our synthetic work in the monoterpenes area and we hoped to obtain 42 directly by cyclization of dihydrocryptomerion enol acetate 95b (X equal to OAc). Moreover, we regarded campherenone as a key synthetic intermediate in the synthesis of the other "sesquicamphanes" (cf. biogenetic postulates, schemes VI and VII). Thus, cyclization of an enol derivative of campherenone such as 51 could lead to copacamphor 52, ylangocamphor 53 and longicamphor 54. Allowing for the possible rearrangement products of campherenone, copacamphor, ylangocamphor and longicamphor it was apparent that our synthetic scheme, if successful, could be an extremely useful, general synthetic route to a large number of polycyclic sesquiterpenes. Much of this original synthetic scheme has since been achieved in our laboratory though many of the synthetic intermediates which we originally proposed were later altered.

Our synthetic plans required a facile route to dihydrocryptomerion 75. Planning a synthesis of 75 presented no great problem as the compound had been previously synthesized by two different multi-step routes by Vig and co-workers (76,77). The more direct of the two previous synthetic routes (77)(scheme VIII) employed β-ketosulfoxide 104 which was obtained by condensation of dimsyl sodium with acetal ester 103. Ester 103 was obtained via a lengthy series of reactions from 6-methylcyclohexenone 100 as shown in scheme VIII (78). Alkylation of 104 with 1-bromo-3-methyl-2-buten yielded compound 105 which was reduced with aluminum/mercury amalgam to keto acetal 106. A simple
Wittig reaction on 106 followed by hydrolysis of the acetal group of 107, afforded 75 in approximately 10% overall yield from 100.

The route we chose initially for the preparation of compound 75 utilized the same intermediate keto acetal 106 as Vig's scheme but we felt that a simple Grignard coupling reaction to give 106 directly from acid chloride 111 would simplify the reaction sequence. While acetal acid 110 could conceivably be prepared from Vig's acetal ester 103, we felt that a simpler route might be developed from dihydrocarvone 76 which was now readily available to us. Indeed from this
reaction sequence we obtained 106 in 38% overall yield from dihydrocarvone. Thus 76 was converted in high yield to the known ethylene acetal 108 (79,80) by treatment in benzene with ethylene glycol and a catalytic amount of oxalic acid. Use of p-toluenesulphonic acid as previously described (79) to catalyze this step led to double bond isomerization, evidenced by the gradual disappearance of the 889 cm⁻¹ absorption in the infrared spectrum of compound 108. Ozonolysis of acetal 108 followed by neutral reductive work-up with dimethylsulphide (81) afforded the selectively protected keto acetal 109 in high yield. The presence and position of both the acetal and ketone functions were readily apparent from the infrared and n.m.r. spectra: \(\nu_{\text{max}}\) 1700, 1170 and 1090 cm⁻¹; \(\delta(CCl_4)\), 6.07 (four proton singlet, acetal methylene), 7.92 (sharp three proton singlet, methyl adjacent to ketone). Oxidation of 109 with hypochlorite afforded a modest yield of crystalline acetal acid 110. Treatment of 110 in dry benzene with oxalyl chloride provided acid chloride 111 \(\left(\nu_{\text{max}}\right.\) 1790, 1165 and 1090 cm⁻¹) which was used without further purification. Inverse addition of Grignard reagent 114, prepared from 2-methyl-5-bromo-2-pentene 113 [available from cyclopropyl methyl ketone 112 (82)], to an ether solution of 111 in the presence of cuprous chloride (83,84) afforded keto acetal 106 in 77% yield based on starting acid 110. Physical constants and spectral data for compound 106 were in agreement with those previously published (76,77).

The transformation of 106 to dihydrocryptomerion by treatment with methylenetriphenylphosphorane in dimethylsulfoxide (85), followed by hydrolysis, proceeded smoothly in 83% yield. Enol acetylation
\[ R = \text{CH}_2 \]

\[ X = \text{OH} \]

\[ R = \text{CH}_2 \]

\[ X = \text{Cl} \]

\[ R = \text{O} \]

\[ Z_i \]

\[ \text{HI} \]

\[ R = \text{CH}_2 \]

\[ \text{CH}_3 \text{MgI} \]

\[ \text{HBr} \]

\[ 1) \]

\[ 2) \]

\[ 112 \]

\[ 113 \]

\[ 114 \]

\[ 75 \]

\[ 95b \]

\[ 115 \]

\[ R = \text{CH}_2\text{CH} = \text{C(CH}_3\text{)}_2 \]
using isopropenyl acetate and p-toluenesulphonic acid followed by separation of the isomeric enol acetates 95b and 115 by preparative g.l.c. afforded the desired substrate 95b. Infrared absorptions at 1750, 1705, and 1210 cm\(^{-1}\) supported the presence of the enol acetate function (86) while other characteristic absorptions of 95b occurred at 3090, 1645 and 889 cm\(^{-1}\) indicating terminal olefin. The n.m.r. spectrum evidenced three vinyl methyl signals at 8.52, 8.40 and 8.33\(\tau\), an acetate methyl at 7.95\(\tau\), a terminal olefin signal (two protons) at 5.23\(\tau\) and a one proton olefinic signal at 4.92\(\tau\).

It would be appropriate to mention at this point that subsequent to the development of the above synthesis of dihydrocryptomerion, a far simpler route to this compound was developed in our laboratory. The background and particulars of this alternate route will be given in a later section in connection with further enol acetate cyclization studies. Suffice it to say at this point that metalation of dihydrocarvone acetal 116 with n-butyllithium in tetramethylethylenediamine (TMEDA) followed by alkylation with 1-chloro-3-methyl-2-butene provided 117 which upon hydrolysis of the acetal function yielded dihydrocryptomerion 75a at 88% overall yield.
With the appropriate monocyclic substrate in hand we attempted the proposed cyclization of enol acetate 95b to campherenone 42 using boron trifluoride in methylene chloride. For this reaction to succeed the cyclization must occur by selective interaction of the enol acetate function with the terminal methylene double bond. The hope was held that the remaining trisubstituted double bond of this 1,5-diene system would remain inert during the cyclization. Treatment of 95b under the previously described optimum reaction conditions afforded a complex mixture of bicyclic and tricyclic ketones with carbonyl absorptions at 1740, 1715 and 1680 cm$^{-1}$. The n.m.r. spectrum of the crude mixture indicated no protons in the proper region for the trisubstituted double bond of campherenone as described in the published n.m.r. spectrum (27,28). Separation of the volatile components of the mixture by preparative g.l.c. afforded three major components A, B and C (in the order of increasing retention times) none of which exhibited spectral characteristics corresponding to campherenone.

Component A (25-30% of the volatile products) exhibited infrared absorptions at 1740 and 1410 cm$^{-1}$ indicative of a strained five membered ring ketone flanked by a methylene group. Bands at 1375 and 1360 cm$^{-1}$ suggested the presence of a saturated dimethyl group such as a gem-dimethyl or isopropyl group. The n.m.r. spectrum (CCl$_4$) of A was dominated by sharp high field methyl signals and there were no olefinic signals. A singlet at 9.19$\tau$ had a relative integral area of three protons when compared to four sharp singlets at 9.10, 9.05, 9.00 and 8.94$\tau$ totaling six protons. Though component A was homogenous by g.l.c. analysis on several columns, spectral evidence indicated that it consisted of a mixture of diastereomers 119a and b
Elemental analysis and mass spectral data are in agreement with this assignment.

Component B (5%) was a semisolid material of low melting point exhibiting absorptions in the infrared at 1715 and 1404 cm\(^{-1}\). The n.m.r. spectrum (CCl\(_4\)) of this component showed a broadened doublet at 9.22\(\tau\) (three protons, \(J = 5\) Hz, secondary methyl), two sharp singlet methyl signals at 9.07 and 9.03\(\tau\) and a very broad signal at 8.55\(\tau\) (half peak width 7 Hz) which contained six to seven protons. Component B is stable to acids such as boron trifluoride and oxalic acid and was also stable to ozone in several solvents thus making the presence of a tetrasubstituted double bond extremely unlikely. The above spectral and chemical evidence combined with mass spectral evidence for a molecular ion of m/e 220 suggests that B may be a tricyclic compound. The presence of a secondary methyl group suggests that rearrangement may have occurred before cyclization. The carbonyl absorption (1715 cm\(^{-1}\)) is at lower frequency than expected for a ketone in a strained five membered ring and yet the absorption is of higher frequency than normally found for other six membered ring ketones in this series of compounds. The presence of an ester function is ruled out by the lack of characteristic bands in the 1200 cm\(^{-1}\) region of the infrared spectrum as well as by other data. One type of structure which would seem to fit much of the data would be a bicyclo(2.2.2)octanone compound such as structure 124a or b which can be derived on paper from enol acetate isomer 122 by methyl migration followed by cyclization of the corresponding double bond isomer 123. Present data however, make such a structural suggestion highly speculative.
Component C contained an enone functionality evidenced by an absorption in the ultraviolet spectrum at 237 nm (ε 15,000), by infrared absorptions at 1670, 1625 and 880 cm⁻¹ and by a low field olefinic absorption at 4.25 τ in the n.m.r. spectrum (CCl₄). The n.m.r. spectrum also indicated a six proton singlet at 9.03 τ (two overlapping tertiary methyl signals) and a three proton doublet at 8.93 τ (J = 6.5 Hz). The spectral data above as well as the mass spectrum and elemental analysis agree with structure 121 tentatively assigned for this component. When enol acetate 95b was exposed to the cyclization conditions for very brief periods, a new component could be isolated to which structure 120 has been assigned on the basis of spectral data and by analogy with compound 86 derived from dihydrocarvone enol acetate 80a. As reaction time was lengthened, compound 120 was depleted with a corresponding increase in enone 121. It may well be that compound 120 is thus the major precursor of the enone material.

A possible scheme accounting for components A (119a and b) and C (121) is shown above. The structures suggested for A and C are only tentative, although the evidence for these components in view of the analogous reactions of dihydrocarvone enol acetate 80a seems quite attractive. Crystalline derivatives of one of the two diastereomers of A (separated as their enol acetate derivatives by preparative g.l.c.) as well as of component B have been submitted for X-ray structural analysis. One more recent piece of data from our laboratory tends to support the structure 119a,b assigned to component A: cyclization (BF₃/CH₂Cl₂) of enol acetate 125 (87), prepared from ketone 126 (87) (see reference (88)), affords components A, B and C in the relative
ratios 5:3:1 respectively (89).

Though we were disappointed that the cyclization of the enol acetate of dihydrocryptomerion had failed to produce detectable amounts of campherenone, the presence of component A (119a,b) among the reaction products provided hope that the requisite cyclization was in fact occurring but that the presence of the additional double bond was altering the course of the reaction. At a later date when a synthetic sample of campherenone was available from an alternate route, we discovered that campherenone itself is not stable to treatment with boron trifluoride thus making the above results even less surprising. The obvious next approach to the preparation of campherenone was to eliminate the possibility of 1,5-diene interaction in the side chain of the cyclization substrate.

The availability of keto acetal 109 from our synthesis of dihydrocryptomerion led to the preparation of a series of compounds possessing the basic structure 127. Simple Wittig reactions on 109 provided compounds 127a-f or their precursors in good yield allowing us to attempt the cyclization of their corresponding enol acetate derivatives 128a-f. We first prepared 127a, the simple ethylidene analogue of dihydrocarvone, to establish that the trisubstituted double bond would participate in cyclization in the same manner as the terminal olefin of dihydrocarvone enol acetate. Treatment of the corresponding enol acetate 128a under the cyclization conditions (BF$_3$/CH$_2$Cl$_2$) provided the bicyclic homocamphor compounds 129a,b in good yield:
\[ R = \text{CH}_3 \]  
\[ R = \text{CO}_2\text{CH}_3 \]  
\[ R = \text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3 \]  
\[ R = \text{CH}_2\text{CH}_2\text{CH}_2\text{OCH}_2\text{C}_6\text{H}_5 \]  
\[ R = \text{CH}_2\text{CH}_2\text{Br} \]  
\[ R = \text{CH}_2\text{CH}_2\text{Cl} \]
\( \nu_{\text{max}} \) 1740 and 1410 cm\(^{-1}\); \((\text{CCl}_4)\) 9.15 (three proton singlet, \(C_{10}\) methyls), 9.20 and 9.08 (two singlets with combined integral of three protons, \(C_8\) and \(C_9\) methyls); \(\tau(C_6H_6)\) 9.44 and 9.39 (two singlets with combined integral of three protons, \(C_8\) and \(C_9\) methyls) and 9.10 (three proton singlet, \(C_{10}\) methyls).\(^{(90)}\) However, preliminary attempts to effect cyclization with such substrates as \(128b-e\) under analogous conditions failed to produce suitable bicyclic materials for various reasons. In particular, compounds \(128b\) and \(c\) failed to undergo cyclization with our reaction conditions while compounds \(128d\) and \(e\) apparently yielded some bicyclic materials but possessed functional groups which were labile under the conditions of reaction and/or work-up thus leading to complex mixtures of products.

Compound \(128f\) appeared to be a reasonable alternative intermediate for the synthesis of a suitably functionalized bicyclic precursor of campherenone. The appropriate Wittig salt was prepared starting from commercially available 3-chloropropan-1-ol \(130\). Treatment of \(130\) with sodium iodide in acetone provided iodo alcohol \(131\) in high yield. Protection of the hydroxyl function as the tetrahydropyranyl (THP) ether \(132\) followed by direct reaction with triphenylphosphine in benzene afforded the crystalline phosphonium salt \(133\). Condensation of keto acetal \(109\) with \(133\) in the presence of dimethyl sodium \(85\) afforded \(134\). The use of the \(\gamma\)-tetrahydropyranyl phosphonium salt for this step in preference to other functionalized salts avoided the internal interactions observed by others \(91\) and by ourselves with salts such as \(135\) upon treatment with base.
\[ \text{Cl} - \text{C-C} - \text{OH} \rightarrow \text{I} - \text{C-C} - \text{OH} \rightarrow \text{I} - \text{C-C} - \text{OTHP} \]

\[ \text{(C}_6\text{H}_5\text{)}\text{P}^+ - \text{C-C} - \text{OTHP} \]

\[ \text{I}^- \]

\[ \text{130} \quad \text{131} \quad \text{132} \quad \text{133} \]

\[ \text{109} + 133 \rightarrow \text{134} \]

\[ \text{R}_3\text{P}^+ - \text{C-C} - \text{Z} \]

\[ \text{X}^- \]

\[ \text{135} \]

\[ Z = \text{Br, CH}_2\text{Br} \]
The next step in the synthesis required selective removal of the THP protective group. This was achieved in one step by treatment in benzene with ethylene glycol and oxalic acid. Hydroxy acetal $136$ was obtained in 70% overall yield from keto acetal $109$, and was converted in 78% yield to chloro acetal $137$ by treatment with tri-n-octylphosphine and carbon tetrachloride (92). Subsequent hydrolysis and enol acetylation afforded the desired monocyclic substrate $128f$.

It would appear that nonselective hydrolysis of $134$ to hydroxy ketone $138$ followed by chlorination would provide a more direct if not higher yielding route to $127f$. In practice, consistently lower yields in the chlorination step were obtained from $138$ presumably due to attack at the ketone. It has been shown that triphenylphosphine $139$ (R equals phenyl) reacts with carbon tetrachloride to form compounds $140$ and $141$ (93,94). Both $140$ and $141$ have been shown to react with cyclohexanone to form in the case of $140$ dichloromethylene adduct $142$, while $141$ reacts to form enyl chloride $143$ (95). However, when cyclohexanone in carbontetrachloride solution is allowed to react with one mole of triphenylphosphine, there is formed 62% $143$ and 3% $142$. A mechanism has been proposed involving compound $144$ to account for the formation of greater than 50% enyl chloride $143$ (95). Similar reactions are probably occurring with tri-n-octylphosphine $139$ (R equals n-octyl) and ketone $138$.

Concurrent with our investigations of enol acetates $128a-f$ a new synthetic route to dihydrocryptomerion $75$ was developed in our laboratory involving alkylolithium species $145$ (96). Though we had already by that time developed a satisfactory route to $128f$ (and to
\[ 2R_3P + CC_4 \rightarrow R_3P = CC_2 + R_3PCl_2 \]

\[ R_3P + CC_4 \rightarrow R_3P - CC_3Cl \]

139  140  141

140  142

141  143

144
campherenone for that matter) the possibility of greatly shortening that route by direct alkylation of 145 seemed highly attractive and worthwhile investigating in view of the potential usefulness of the subsequent product, campherenone. Our interest in this reaction was initially stimulated by a preliminary paper presented by R. J. Crawford (97,98,99) concerning the metalation and alkylation of limonene 146. Treatment of limonene with the 1:1 complex of n-butyllithium and N,N,N',N'-tetramethylethylene diamine (TMEDA) selectively metalated the C10 position forming the alkyllithium species indicated as structure 147. It was found that 147 underwent many reactions typical of alkylpithiums including carbonation, oxygenation, coupling reactions with alkyl halides, addition to carbonyl compounds and addition to epoxides forming derivatives of the general structure 148. The reaction of 147 with 1-bromo-3-methyl-2-butene to afford a 4:1 mixture of β-bisabolene 149 and isomer 150 was particularly attractive in regard to our dihydro-cryptomerion work. A possible extension of this reaction would be the metalation and alkylation of dihydrocarvone acetal 108 providing acetal diene 107 directly which upon hydrolysis would yield dihydrocryptomerion in three steps from dihydrocarvone. Unfortunately 108 failed to undergo the desired metalation as evidenced by the absence of the characteristic red color of the allylic alkyllithium species in the reaction mixture as well as by the lack of alkylated products after treatment with various alkylation agents. In fact treatment of 108 with one equivalent of the n-butyllithium--TMEDA complex for 24 hours followed by the usual work-up and hydrolysis yielded dihydrocarvone 76 and a less volatile product in approximately a 1:1 ratio as judged by g.l.c.
analysis. Heathcock and co-workers (100) had previously shown that
cyclohexanone ethylene acetal $151$ reacts with $t$-butyllithium or iso-
propyllithium converting $151$ to tertiary alcohols $152$ and $153$ respectively.
The analogous reaction with n-butyllithium occurred to a small extent.
The mechanism suggested for this reaction is shown below. In keeping
with this mechanism acetal $154$ was stable in the presence of these
alkyllithium reagents.

We anticipated that the 1:1 complex of n-butyllithium--TMEDA
was a sufficiently powerful metalating agent to cause analogous decom­
position of dihydrocarvone acetal $108$. The preparation of the 1,3-
dioxane $155$ of dihydrocarvone was a possible route to circumvent this
difficulty; however, such acetals are notably difficult to prepare
(e.g., acetal $155$ was prepared in our laboratory in only 35% yield).Newman and Harper (101) found that 2,2-dimethyl-1,3-propanediol reacted
much more rapidly with cyclohexanone than did ethylene glycol while
1,3-propanediol reacted very slowly. We therefore attempted the
analogous reaction using 2,2-dimethyl-1,3-propanediol, oxalic acid
and dihydrocarvone in benzene at reflux and obtained a high yield of
material exhibiting no ketone absorption in the infrared but exhibiting
bands for terminal olefin ($3090$, $1650$ and $888 \text{ cm}^{-1}$) and for the acetal
function ($1150$ and $1100 \text{ cm}^{-1}$). The n.m.r. of this product proved
unexpectedly complex particularly in the regions of the acetal methylenes
($6-7 \tau$) and of the saturated methyls ($\sigma$above $8.8\tau$). The complexity was
felt to be partially due to the presence of two disastereomers $116a$ and $b$
and this was confirmed by g.l.c. analysis. Separation by g.l.c. provided
samples of $116a$ and $116b$ of greater than 90% purity. Compound $116a$
155

116a

116b
with both its methyl and isopropenyl group equatorial in the energetically favored conformation was assumed to be the major product (relative retention time 21 minutes compared to 23.5 minutes for 116b). The n.m.r. spectrum (CCl₄) of 116a was still complex in the region of the acetal methylenes (6-7 ppm) possibly indicating slow conformational interconversion of the 5,5-dimethylidioxane ring (102). Sharp singlets appeared at 8.88 and 9.33 ppm due to the gem-dimethyl group of the acetal function. Compound 116b on the other hand exhibited a rather simple n.m.r. spectrum (CCl₄) with a broad four proton singlet at 6.63 ppm for the acetal methylenes and two sharp singlets at 9.09 and 9.12 ppm due to the methyl groups of the acetal. A molecular model of compound 116b does not reveal significant difference in steric interactions for the various possible preferred conformations of the acetal ring (102) and thus rapid interconversions between these conformations may account for the simplicity of the n.m.r. spectrum.

Thus acetal 116a,b was obtained in 91% overall yield and metalation was again attempted with this new substrate. Reaction of 116a,b with one equivalent of the 1:1 n-butyllithium--TMEDA complex overnight produced a deep red solution of the metalated species represented by 145 which, upon alkylation with 1-chloro-3-methyl-2-butene and subsequent hydrolysis, provided dihydrocryptomerion in 88% isolated yield based in consumed acetal 116a,b. No evidence could be found for the allylic rearrangement product 156 analogous to 150 observed by Crawford et al. Indeed repetition of Crawford's synthesis of β-bisabolene, substituting 1-chloro-3-methyl-2-butene for the bromo analogue used by Crawford, likewise gave no trace of 150 (103).
The success of this alkylation led us to attempt the reaction of 145 with other alkylating agents. Notably the reaction of 145 with 1,2-dichloroethane (excess) seemed a possible direct route to ketone 160, the double bond isomer of 127f. While some success was achieved with this alkylation on a small scale, the results were not reproducible on a synthetically useful quantity, the competing reaction apparently being elimination of hydrogen chloride from the alkylation agent. Alkylation with ethylene oxide proceeded much more smoothly to afford acetal alcohol 158 in 91% overall yield (considerable starting material [ca. 48%] was recovered in this reaction). Transformation of 158 to the corresponding chloro derivative 159 (84% yield) and subsequent hydrolysis to chloro ketone 160 (91% yield) were performed as in the analogous series from hydroxy acetal 136. Enol acetylation of ketone 160 provided a 3:1 ratio of isomeric enol acetates 161 and 162 which could be separated by preparative g.l.c.

Treatment of either enol acetate 128f or 161 under the usual cyclization conditions afforded two major products in the approximate ratio 3:2 as judged by g.l.c. analysis (relative retention times 4.1 minutes and 6.0 minutes respectively). Pure samples of each could be obtained either by preparative g.l.c. or fractional distillation. The more volatile major product (55 to 60%), a fragrant, colorless oil with (α)D = 0°, exhibited absorptions in the infrared at 1740 and 1410 cm⁻¹ indicative of a five-membered ring ketone flanked by a methylene group and characteristic of our various synthetic camphor analogues. The n.m.r. spectrum of this component exhibited resonances [τ (CCl4)] 9.11 (three proton singlet, tertiary methyl), 9.16 and 9.03 (two singlets totalling three protons, disastereomeric tertiary methyls), 6.55 and
and 6.48 (two overlapping triplets totalling two protons, methylenes bearing chlorine atoms)], which are consistent with a mixture of disastereomers 163a and b. The above data combined with mass spectral evidence for parent ions at m/e 214 (relative intensity 97.3) and m/e 216 (relative intensity 33.6), indicated that the desired cyclization to 163a,b had occurred. Additional evidence for this structure was obtained by comparison of the n.m.r. spectrum of 163a,b with those of camphor and methyl homocamphor 129a,b in carbon tetrachloride and in benzene (see Table III) (104-106). Assuming that the C₈ and C₉ position methyls have analogous positions in the n.m.r. spectra of 163a,b and of camphor 17, and are similarly shifted when the solvent is changed to benzene, the ratio of product 163a to 163b was approximately 5.8:4.2.

The second main component (30-40%) in the cyclization product from 128f or 161 proved to possess an enone function as evidenced by an ultraviolet absorption at 234 nm (ε 15,000) and by infrared absorptions at 1670, 1210 and 883 cm⁻¹. The presence of an enone function immediately suggested structure 164 by analogy with the products obtained from enol acetates 80a and 95b. This structure was further corroborated by the n.m.r. spectrum (CCl₄) τ 8.91 (three proton doublet, J = 6.5 Hz, secondary methyl), 8.87 (three proton doublet, J = 6.5 Hz, secondary methyl), 6.52 (broadened triplet, two protons, J = 6 Hz, methylene bearing chlorine substituent) and 4.30 (one proton singlet, proton on enone system) and by mass spectral and elemental analysis.

One difference was noted between this cyclization and those described previously in that the cyclization of dihydrocarvone enol
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<th>C₈</th>
<th>C₉</th>
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<tbody>
<tr>
<td>Camphor</td>
<td>CCl₄</td>
<td>9.19</td>
<td>9.07</td>
<td>9.18</td>
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<tr>
<td></td>
<td>C₆H₆</td>
<td>9.40</td>
<td>9.35</td>
<td>9.11</td>
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<tr>
<td>Methyl Homocamphor 129a</td>
<td>CCl₄</td>
<td>-</td>
<td>9.08</td>
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<tr>
<td></td>
<td>C₆H₆</td>
<td>-</td>
<td>9.39</td>
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<tr>
<td>Methyl Homocamphor 129b</td>
<td>CCl₄</td>
<td>9.20</td>
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<td>9.15</td>
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<td></td>
<td>C₆H₆</td>
<td>9.44</td>
<td>-</td>
<td>9.10</td>
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<tr>
<td>Keto Chloride 163a</td>
<td>CCl₄</td>
<td>-</td>
<td>9.03</td>
<td>9.11</td>
</tr>
<tr>
<td></td>
<td>C₆H₆</td>
<td>-</td>
<td>9.45</td>
<td>9.11</td>
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<tr>
<td>Keto Chloride 163b</td>
<td>CCl₄</td>
<td>9.16</td>
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<tr>
<td></td>
<td>C₆H₆</td>
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acetate 80a, for example, required less than five minutes (in fact in one experiment the reaction was shown to be complete in thirty seconds) while enol acetates 128f or 161 required approximately one hour or more for total disappearance of enol acetate material. The reason for this longer reaction time has not been illucidated; however, our previous experience with various functional groups preventing cyclization or interacting during cyclization suggests one possible area for further research.

As noted earlier, the cyclization of the various enol acetates proceeded in highest yield when carried out at approximately a one milligram per one milliliter concentration in methylene chloride. The high dilution presented certain practical problems in scaling up this reaction to produce useful synthetic quantities of 163a,b. For example, a ten gram reaction would require ten liters of solvent. It was found, however, that the reaction could be performed by the addition of several small portions of substrate to a more moderate volume of solvent with the addition of water between each portion of substrate. The presence of the previously added substrate (now partially transformed to product) had no detrimental effect on the product ratio, while the addition of water restored the water consumed during the reaction of the previous portion of enol acetate. In this manner five grams of substrate could be conveniently reacted in 1.8 liters of solvent and the methylene chloride recovered directly from the rotary evaporator after work-up could be used for further cyclizations with no diminution of yield.

The separation of enol acetate isomers 161 and 162 by preparative g.l.c. or by distillation proved tedious on a synthetic scale and
thus a mixture of the two isomers was employed for large scale cyclizations. Isomer 162 simply enhanced the amount of enone 164 which had to be separated from bicyclic material. Thus using the enol acetate mixture and the cyclization procedure described above, bicyclic ketones 163a,b were isolated by fractional distillation from the reaction mixture in 46% yield (based on enol acetate 161).

At this stage our overall reaction sequence from carvone 79 to bicyclic ketones 163a,b was highly efficient except at the point of the cyclization of the enol acetate mixture. We were not bothered by the yield of the cyclization itself (which did not improve under various changes in reaction conditions) for in view of our previous experience we were pleased that cyclization had proceeded in 55 to 60% yield (by g.l.c.). The presence of the other enol acetate isomer (approximately 25%) in the reaction however, presented problems in that it greatly reduced our overall yield from ketone 160 and at the same time increased considerably the quantity of enone 164 to be separated, after cyclization, from the bicyclic products. To circumvent this annoyance with isomer 162 we again looked at alternate enol acetylation conditions.

Our previous choice of isopropenyl acetate and p-toluenesulfonic acid was required to prevent double bond migration during the enol acetylation step. A literature report of enol acetylation using perchloric acid and acetic anhydride in ethyl acetate (107) looked promising as the reaction could be carried out at room temperature and proceeded very fast (five minutes). Indeed, on a ten milligram scale ketone 160 was converted almost completely to enol acetates 161 and
and 162 in the relative ratio 92:8 (based on g.l.c.) with very little double bond migration as judged by the n.m.r. integral of the terminal olefin signal (ca. 5.18 \( \tau \)) relative to the chloro substituted methylene group (ca. 6.55 \( \tau \)). When the reaction was scaled up to a feasible size for preparative work, a greater percentage of double bond migration occurred and the volume of reagent required was ungainly. After considerable effort to optimize reaction conditions for our substrate, it was found that addition of 500 milliliters of reagent (anhydrous ethyl acetate solution 1.06 molar in acetic anhydride and 0.23 molar in perchloric acid) to 10 grams of ketone in 100 milliliters of anhydrous ethyl acetate (5.5 minutes) provided enol acetates 161a and 162a in good yield and in the relative ratio of 93:7 respectively. Double bond isomerization was found to have occurred to the extent of 45% by n.m.r. analysis, with isomer 128f accounting for roughly 18% of the isomerized product. Since the bicyclic products produced from either enol acetate are racemic, and since double bond isomers 161 and 128f undergo cyclization in equal yield, the stereochemical integrity of the terminal double bond in 161a was not crucial. The yield of bicyclic product from 161a was again 55-60% as judged by g.l.c.

Transformation of bicyclic ketones 163a,b to campherenone and its C\(_7\) epimer proceeded without complication. The mixture of the two ketones was used as 163a and b proved extremely difficult to separate by distillation and could not be resolved by g.l.c. on a variety of columns. Treatment of the mixture with ethylene glycol and p-toluenesulfonic acid in benzene afforded acetals 165a,b in 95% yield. Though acetals 165a and b were readily resolvable by g.l.c., it was found to be more practical to wait until a later stage of the synthesis.
to perform this separation. Treatment of chloro acetals 165a,b with sodium iodide in dry acetone and in the presence of calcium carbonate afforded iodo acetals 166a,b in high yield. As compounds 166a,b proved sensitive to aqueous work-up, a non-aqueous work-up was developed in which the reaction mixture was transferred directly under dry nitrogen into dry pentane, precipitating the inorganic materials. The pentane solution was then filtered over celite and the resulting colorless solution concentrated and distilled affording 166a,b in 97% yield. Once the solution of 166a,b had been filtered over celite, it no longer colorized upon exposure to the atmosphere. Iodo acetals 166a and b were readily resolved by g.l.c. on several columns but attempts to collect samples of either compound by preparative g.l.c. led to considerable product degradation and thus the mixture was used in the next step.

The Wittig salt of 166a,b, prepared by refluxing with triphenylphosphine in dry benzene, was a colorless oil. The salt, 167a,b, proved to be very hygroscopic and highly sensitive to any moisture absorbed. Product 167a,b was also very soluble in organic solvents (such as benzene) which are normally used to extract traces of unreacted triphenylphosphine or starting halide from crude non-crystalline phosphonium salts. Circumventing a troublesome purification step, phosphonium salt 167a,b was prepared from equimolar quantities of starting halide and triphenylphosphine and, after removal of benzene, the resulting product was used without further purification. Thin layer chromatographic (t.l.c.) analysis indicated no detectable amount of either starting material or triphenylphosphine in the crude product.
Generation of the ylide with dimsyl sodium and subsequent condensation with acetone provided acetal alkenes 168a,b in 84% yield from acetal iodide 166a,b. Hydrolysis of the acetal mixture provided a mixture of bicyclic ketones exhibiting spectral properties consistent with the assumption that the mixture consisted of campherenone 42 and epicampherenone 45 in the ratio 6:4 as judged by n.m.r. Analysis of the mixture by g.l.c. on several different columns failed to separate the product into its two components. Fortunately the acetal precursors of 42 and 45, compounds 168a and b, were separated easily by preparative g.l.c. and two components were isolated having relative retention times of 42 minutes and 47 minutes. The component of shorter retention time was assigned structure 168a on the basis of subsequent conversion to (±)-campherenone.

Thus removal of the ethylene acetal from 168a (H+ / acetone) provided (±)-campherenone 42 exhibiting spectral properties (infrared, n.m.r., mass spectrum) (see Figures 1 and 2) in close agreement with published values (27,28). Unfortunately we were not able to obtain an authentic sample of (-)-campherenone 42a for direct comparison (27,28). Acetal 168b upon hydrolysis afforded a product assigned structure 45 on the basis of the mode of synthesis and on spectral characteristics (see Figures 3 and 4): $\nu_{\text{max}}$ 1745, 1412 and 835 cm$^{-1}$; $\tau$ (CCl$_4$) 9.13 (six proton singlet, C$_8$ and C$_{10}$ methyl), 8.38 and 8.32 (two broad singlets totaling six protons, C$_{14}$ and C$_{15}$ vinyl methyls) and 4.89 (one proton multiplet, olefinic signal). The n.m.r. spectra of (±)-campherenone and (±)-epicampherenone as compared to the corresponding spectrum of camphor in carbontetrachloride and in benzene are
Figure 1. N.M.R. Spectrum (100 MHz) of (-)-Camphorone 42
Figure 3. N.M.R. Spectrum (100 M Hz) of (±)-Epicampherone 45
Figure 4. Infrared Spectrum of (±)-Epicaampherenone 45
shown in Table IV. Published values for natural (-)-campherenone are shown in parenthesis. Further evidence for the structures of both 42 and 45 was obtained by various chemical transformations described in a later section. This work constituted the first total synthesis of campherenone and provided independent confirmation of the structure but not the absolute configuration assigned to this compound (108).

Campherenone occupies the key position in our proposed general synthetic route to a group of bicyclic, tricyclic, and tetracyclic sesquiterpenes. Having developed an efficient route to campherenone and epicampherenone via monocyclic enol derivatives, we now were ready to test further aspects of our synthetic proposals. Our proposed biogenetic scheme presented in the introduction indicated campherenone and perhaps epicampherenone as possible precursors of the corresponding borneol analogues, campherenol and epicampherenol, as well as of the santalenes. Our synthetic proposal stated that an analogous relationship might be established in the laboratory. Indeed by simple transformations on campherenone 42 and 45 we have subsequently established alternate synthetic routes to β-santalene 48, epi-β-santalene 50 and α-santalene 47 all in good yield.

Campherenone 42 on treatment with sodium/n-propanol afforded a 7:1 mixture of endo alcohol 46a to exo isomer 46b. Isomer 46a has the naturally occurring endo hydroxyl stereochemistry found in (-)-campherenol which co-occurs with (-)-campherenone (27,28). Reduction of 42 with lithium trimethoxyaluminohydride (109) afforded isocampherenol 46b. The trimethoxy derivative of lithium aluminum hydride was chosen in preference to the parent hydride in an attempt
**Table IV: N.M.R. Signals of Bicyclic Ketones**

<table>
<thead>
<tr>
<th></th>
<th>C₈</th>
<th>C₉</th>
<th>C₁₀</th>
<th>C₁₂</th>
<th>C₁₄, C₁₅</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CCl₄</strong></td>
<td>9.19</td>
<td>9.07</td>
<td>9.18</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Camphor</strong></td>
<td>C₆C₆</td>
<td>9.40</td>
<td>9.35</td>
<td>9.11</td>
<td>-</td>
</tr>
<tr>
<td><strong>CCl₄</strong></td>
<td>-</td>
<td>9.03(9.04)</td>
<td>9.14(9.15)</td>
<td>4.95(4.97)</td>
<td>8.35(8.36), 8.39(8.41)</td>
</tr>
<tr>
<td><strong>Camphenone</strong></td>
<td>C₆C₆</td>
<td>-</td>
<td>9.30(9.33)</td>
<td>9.07(9.10)</td>
<td>4.97(5.02)</td>
</tr>
<tr>
<td><strong>CCl₄</strong></td>
<td>9.13</td>
<td>-</td>
<td>9.13</td>
<td>4.89</td>
<td>8.32, 8.38</td>
</tr>
<tr>
<td><strong>Epicamphenone</strong></td>
<td>C₆C₆</td>
<td>9.35</td>
<td>-</td>
<td>9.06</td>
<td>4.83</td>
</tr>
</tbody>
</table>

* Literature values (27,28) in parentheses.
to avoid formation of the endo alcohol 46a. Hikino et al. found that reduction of campherenone with lithium aluminum hydride afforded isocampherenol and some campherenol (28). Brown and Deck have shown that reduction of camphor with lithium aluminum hydride produces a 9:1 mixture of exo to endo alcohols while reduction with the trimethoxy derivative yields 99% isoborneol (109). The isocampherenol obtained by reduction of 42 with lithium trimethoxyalumino hydride was shown to be one component by n.m.r. and g.l.c. analysis. Similar treatment of epicampherenone 45 afforded the corresponding epicampherenols 49a and 49b. Consideration of the n.m.r. spectra of the campherenols 46a and 46b and the epicampherenols 49a and 49b in carbon tetrachloride and in pyridine (110) in conjunction with the corresponding spectra of borneol and isoborneol (110-112) affirmed the structural assignments (see Table V). Proton assignments for the n.m.r. spectra of borneol and isoborneol have been previously worked out on the basis of comparison of spectra of a large number of derivatives (112) as well as more recently by the use of pyridine-induced solvent shifts (110) and shifts produced by rare earth metal complexes (113).

(±)-Isocampherenol 46b upon heating with p-toluenesulfonyl chloride in pyridine provided (±)-β-santalone 48 (30,114) in 80% overall yield (119). Similarly, the treatment of isoepicampherenol 49b under these reaction conditions provided (±)-epi-β-santalone (30,114). The identity of synthetic β- and epi-β-santalone was established by comparison of g.l.c. characteristics and spectral data (infrared, n.m.r.) with authentic samples (−)-β-santalone and (+)-epi-β-santalone isolated from sandalwood oil (120) and with synthetic samples obtained in our
Table V: N.M.R. Signals of Bicyclic Alcohols *

<table>
<thead>
<tr>
<th></th>
<th>C₂</th>
<th>C₈</th>
<th>C₉</th>
<th>C₁₀</th>
<th>C₁₂</th>
<th>C₁₄,C₁₅</th>
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<tbody>
<tr>
<td>Borneol</td>
<td>CCl₄</td>
<td>6.08</td>
<td>9.14</td>
<td>9.14</td>
<td>9.17</td>
<td>-</td>
</tr>
<tr>
<td>Δ **</td>
<td>- .22</td>
<td>- .01</td>
<td>- .01</td>
<td>- .13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoborneol</td>
<td>CCl₄</td>
<td>6.49</td>
<td>8.98</td>
<td>9.17</td>
<td>9.11</td>
<td>-</td>
</tr>
<tr>
<td>Δ</td>
<td>- .24</td>
<td>- .26</td>
<td>- .02</td>
<td>- .18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Campherenol</td>
<td>CCl₄</td>
<td>6.00(6.03)</td>
<td>9.11</td>
<td>9.17</td>
<td>4.94</td>
<td>8.34,8.41</td>
</tr>
<tr>
<td>Δ</td>
<td>- .35</td>
<td>- .05</td>
<td>- .19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isocampherenol</td>
<td>CCl₄</td>
<td>6.46(6.49)</td>
<td>9.18</td>
<td>9.12</td>
<td>4.92</td>
<td>8.36,8.39</td>
</tr>
<tr>
<td>Δ</td>
<td>- .33</td>
<td>- .08</td>
<td>- .24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epicampherenol</td>
<td>CCl₄</td>
<td>6.06</td>
<td>9.13</td>
<td>-</td>
<td>9.18</td>
<td>4.92</td>
</tr>
<tr>
<td>Δ</td>
<td>- .33</td>
<td>- .06</td>
<td>- .21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iso-epicampherenol</td>
<td>CCl₄</td>
<td>6.47</td>
<td>8.96</td>
<td>-</td>
<td>9.12</td>
<td>4.93</td>
</tr>
<tr>
<td>Δ</td>
<td>- .29</td>
<td>- .31</td>
<td>- .24</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Literature values (27,28) in parentheses.  ** Δ = τ pyridine - τ CCl₄
laboratory by an alternative route described in a later section (Figures 11-14).

The tricyclic nucleus of α-santalene was generated in analogy to the classical conversion of camphor to tricyclene (121). A mixture of campherenone 42 and epicampherenone 45 was converted in high yield to the corresponding hydrazones 169 and 170. When a methanolic solution of hydrazones 169 and 170 was heated with mercuric oxide, (±)-α-santalene 47 (30, 114) was obtained in 65% overall yield. Synthetic (±)-α-santalene exhibited the same spectral and g.l.c. characteristics as authentic (+)-α-santalene (120).

The next objective in our synthetic sequence was the achievement of intramolecular cyclization of campherenone, thereby constructing the tricyclic systems represented by copacamphor 52, ylangocamphor 53 and longicamphor 54. Westfelt and co-workers (33) in a previous study of the structure and absolute configuration of copaborneol 55a achieved a partial synthesis of this compound by internal Michael-type cyclization of unsaturated keto ester 171 and subsequent transformation to 55a. The cyclization of 171, a compound derived from the naturally occurring mixture of α- and β-santalols, indicated that bond formation between C3 and C12 of the campherenone-type skeleton was indeed feasible. In accord with our biogenetic hypothesis we initially considered a cyclization of campherenone 42 involving the interaction of an enol derivative such as an enol acetate, with the olefinic side chain of campherenone. In this manner we hoped to generate perhaps all three skeletons 52, 53 and 54 in one reaction.

The preparation of campherenone enol acetate 51 (X equals
OAc) was based on the previous preparation of camphor enol acetate
Warnhoff et al. (122) had shown that treatment of camphor under
various acid catalyzed enol acetylation conditions yielded only start-
ing material. However the enol acetate could be prepared by generation
of the enolate anion with butyllithium followed by O-alkylation with
acetic anhydride. Following the procedure described for camphor,
campherenone was converted to enol acetate 51 in 84\% yield as judged
by g.l.c.

Cyclization of 51 was attempted using the conditions
(BF\textsubscript{3}/CH\textsubscript{2}Cl\textsubscript{2}) previously employed in other enol acetate cyclizations.
Preliminary analysis (g.l.c. on three different columns) indicated the
presence of components in the mixture of retention times corresponding
to authentic samples of copacamphor (123) and longicamphor (124) albiet
in low yield. Subsequent work has shown the reaction to be of negli-
gible synthetic value, the major portion of product being non-volatile,
possibly polymeric material. No attempt at further characterization
of the reaction products has yet been made.

An alternate route to the polycyclic sesquiterpenes 52, 53
and 54 could involve the cyclization of a substrate such as 173 in
which X and Y equal any of a number of possible derivatives of the
double bond in campherenone. In practice the epoxide (X,Y = -O-)*

* The choice of an epoxide intermediate is in keeping with our desire
to utilize substrates of possible biological analogy and significance.
The importance of epoxides in terpene biosynthesis (e.g., squalene
epoxide) has been discussed elsewhere (125).
proved a convenient intermediate (126) and could be prepared from the parent ketone with \textit{m}-chloroperbenzoic acid in benzene affording diastereomeric keto epoxides \textit{173a,b} in good yield. Treatment of \textit{173a,b} with potassium \textit{t}-butoxide in \textit{t}-butanol afforded tricyclic keto alcohols \textit{174} and \textit{175} in the ratio 45:55 (relative retention times 5.4 minutes and 6.5 minutes respectively). A distinction between compounds \textit{174} and \textit{175} could tentatively be made on the basis of their infrared and n.m.r. spectra. A carbontetrachloride solution of compound \textit{175} exhibited two absorption bands in the hydroxyl stretch region 3620 and 3440 cm$^{-1}$, the broad band of lower energy indicating hydrogen bonding. Dilution studies on this sample resulted in a relative increase in intensity of the 3620 cm$^{-1}$ band and a corresponding decrease in the 3440 cm$^{-1}$ band. Isomeric keto alcohol \textit{174} on the other hand exhibited a strong hydrogen bonding band of moderate width (3490 cm$^{-1}$) which did not significantly vary in intensity upon dilution. This spectral behavior of the hydroxyl function of \textit{174} would be consistent with intramolecular hydrogen bonding between the hydroxyl group and the nearby ketone function. Keto alcohol \textit{175} is sterically prevented from similar intramolecular hydrogen bonding and thus the hydroxyl band at 3440 cm$^{-1}$, resulting from intermolecular hydrogen bonding, decreases upon dilution. The n.m.r. spectrum of \textit{174} (CCl$_4$, 100 MHz) indicated two sharp methyl singlets at 9.10 and 9.08 $\tau$ due to the C$_{10}$ and C$_9$ methyls and two singlets 8.95, 8.94 $\tau$ (total integral three protons) and a broadened singlet 8.76 $\tau$ (three protons) due to the tertiary methyls bearing an alpha hydroxyl function. A broad one proton singlet at 7.57 $\tau$ can be assigned to the methine proton alpha to the ketone and a very broad absorption centered at 7.26 $\tau$ (half peak width
ca. 12 Hz) was shown to be the hydroxyl proton by exchange with deuterium oxide.

The n.m.r. (CCl₄, 100 MHz) of compound 175 exhibited two sharp methyl singlets at 9.12 and 9.07 τ for the C₁₀ and C₉ methyls and two slightly broadened methyl signals at 8.87 and 8.80 τ due to the tertiary methyls with adjacent hydroxyl function. Two methine protons were distinguishable; one appeared as a broad singlet (7.80τ, half peak width 4 Hz), while a hydroxyl proton with moderate broadening (half peak width ca. 2 Hz) appeared at 7.43 τ. The one proton signal at 7.80 τ has tentatively been assigned to the proton alpha to the ketone, which by inspection of models would be expected to be a singlet in analogy to the corresponding proton in 174. The other methine signal (7.70 τ) could not be assigned with the desired degree of certainty but the low field position of this signal would not agree with either of the two remaining methines in compound 174 and thus favors structure 175. The structural assignment of 175 was confirmed by subsequent conversion to copacamphor.

Thus dehydration of keto alcohol 175 with thionyl chloride and pyridine yielded a 7:3 mixture of tricyclic alkenes 176 and 177 which were separated by preparative g.l.c. Other common reagents used in dehydration of alcohols (for example phosphorus oxychloride/pyridine; p-toluensulfonyl chloride/pyridine; aluminum oxide/pyridine/heat) showed no advantage in product ratio. The two double bond isomers were readily distinguished by their n.m.r. spectra as 177 exhibited no olefinic signals but showed two vinyl methyls at 8.37 and 8.28 τ while 176 displayed a two proton multiplet at ca. 517 τ and one vinyl methyl
at 8.28 \tau. Hydrogenation of 176 using platinum oxide as the source of catalyst provided (+)-copacamphor 52 whose g.l.c. and spectral characteristics were identical to those of authentic (+)-copacamphor (32,33,123) (see Figures 5 and 6).

Similar dehydration of 174 provided two isomeric alkenes in the ratio 4:1. The minor product was shown to be identical (g.l.c., infrared, n.m.r.) to 177 while the major component was assigned structure 178 in analogy to 176. Reduction of 178 afforded (±)-ylangocamphor 53 [$\nu_{\text{max}}$ 1730 cm$^{-1}$; n.m.r. (CDCl$_3$, 100 MHz), \( \tau \) 9.20 (three proton doublet, J = 6.5 Hz, isopropyl methyl), 9.11 and 9.10 (two singlets, tertiary methyls), 9.03 (three proton doublet, J = 6.5 Hz, isopropyl methyl) and 7.76 (broad one proton singlet)]. Comparison of our spectra (see Figures 7 and 8) with those of a sample of (-)-ylangocamphor prepared by an alternate route (127) indicated that the two compounds were identical.

Hydrogenation of the tetrasubstituted double bond isomer 177 afforded a 5:1 mixture of ylangocamphor 53 and copacamphor 52. Both terminal alkenes 176 and 178 were isomerized to 177 upon treatment with palladium on carbon in the presence of hydrogen (128) thus further establishing the isomeric relationship of the two series of compounds derived from keto alcohols 174 and 175. No trace of the possible third series of products bearing the longicamphane skeleton was found at any stage of this work despite careful search by g.l.c. and n.m.r. (129).

The availability of copacamphor and ylangocamphor opened the potential route to two more sets of rearrangement products. Copacamphor 52 already had been converted to copaborneol 55a, isocopaborneol 55b.
Figure 5. N.M.R. Spectrum (100 M Hz) of (±)-Copacamphor 52
Figure 6. Infrared Spectrum of (±)-Copacamphor 52
Figure 8. Infrared Spectrum of (±)-Ylangocamphor 53
and copacamphene 57 by Westfelt and co-workers (32,33). Cyclocopa-
camphor* 56 remains the only member of this quartet to be interrelated
to copacamphor. Ylangocamphor and the ylangoborneols were not known
previously but their potential rearrangement products, sativene 60 and
cyclosativene 59 are naturally occurring materials (35,36,42) and have
been synthesized from other routes (36,130,131). McMurry has shown that
in the presence of copper(II) acetate and acetic acid, sativene 60
exists in equilibrium with cyclosativene 59 and isosativene 179
(131, cf. 35,42) (see scheme X). While one might have anticipated that
a similar equilibrium would interrelate copacamphene 57 with cyclo-
copacamphene 56, McMurry in fact obtained upon treatment of copa-
camphene under the equilibrating conditions the identical equilibrium
mixture of sativene, cyclosativene and isosativene as obtained from
sativene itself (126b,132). Presumably the copacamphene skeleton inter-
converts with the more stable sativene skeleton (equatorial isopropyl
group) through the pathway depicted in scheme X.

For the purpose of our work we desired to complete the
transformations of copacamphor by attempting the synthesis of cyclo-
copacamphor via hydrazone 180 in analogy to our work in the santalene
series. Similarly we hoped to establish the analogous relationships
among ylangocamphor, sativene and cyclosativene (via 181). Work on
these various transformations is now in progress in our laboratory.
Thus far we have been successful in converting ylangocamphor into

* This compound is known both in nature (34) and through synthesis (56).
\[
52 \xrightarrow{\text{Westfelt}} \quad ? \quad \xrightarrow{\text{Westfelt}} \quad 56
\]

\[
55a \quad R_1\text{=}H, \quad R_2\text{=}OH
\]

\[
b \quad R_1\text{=}OH, \quad R_2\text{=}H
\]

\[
53 \xrightarrow{?} \quad 59
\]

\[
55a R_1\text{=}H, \quad R_2\text{=}OH
\]

\[
b R_1\text{=}OH, \quad R_2\text{=}H
\]

\[
57
\]

\[
59
\]

\[
60
\]
Scheme X

\[ 60 \xrightleftharpoons[H^+]{\text{H}^+} 59 \]

\[ 179 \]
sativene. Treatment of ylangocamphor 53 with lithium aluminum hydride in ether afforded isoylangoborneol 58b: $\nu_{\text{max}}$ 3500 and 1095 cm$^{-1}$; $\tau$(CCl$_4$), 9.21 (three proton singlet, tertiary methyl), 9.16 (three proton singlet, tertiary methyl), 9.08 (six proton doublet, J = 7 Hz) and 6.28 (one proton doublet, J = 7\text{ Hz}, methine on carbon bearing hydroxyl function). The splitting pattern and the coupling constant for the endo methine proton on the carbon bearing the hydroxyl function is in agreement with the assigned structure (58). Treatment of 58b under the usual rearrangement conditions (p-toluenesulfonylchloride/
pyridine) yielded only recovered starting material. In view of the steric bulk surrounding the hydroxyl function of 58b we considered employing a less sterically hindered esterifying agent. Thus when isoylangoborneol was heated with methanesulfonylchloride in pyridine, (±)-sativene was obtained exhibiting spectral characteristics (infrared, n.m.r.) in agreement with published values (36) (see Figures 9 and 10).

Encouraged by the successful achievement of much of our initial synthetic goal, we turned our attention to the more refined points of our biosynthetic hypothesis. In particular, we were concerned with the absolute configurations of several of the naturally occurring members included within the scope of our synthetic and biogenetic schemes (see pages 44, 45). We first considered the monocyclic substrates which, as we mentioned earlier, in the case of campherenone could possibly be dihydrocryptomerion 75 a logical relative to the known sesquiterpene cryptomerion 99 found in Cryptomerion japonica D. Don (75). The absolute configuration of cryptomerion had not been assigned previously and prior multi-stage syntheses were of the racemic form of the compound (76,77). We felt that since (-)-campherenone had been ascribed the (+)-camphor configuration as in 42a (27,28) it would be significant to know if (-)-cryptomerion had the related (-)-carvone configuration and thus we sought a stereospecific route to cryptomerion from (-)-carvone 79a.

In the previously mentioned work of Crawford et al. (97,99) concerning the metalation of limonene, it was shown that alkyl lithium 147 retained its optical purity in all its various reactions. Our
Figure 10. Infrared Spectrum of (±)-Sativene 60
previous success with metalation of dihydrocarvone acetal 116 with the 1:1 butyllithium--TMEDA complex led us to prepare carvone acetal 182 from (-)-carvone [(α)\textsubscript{30}\textdegree{D} - 58.6\textdegree{D}] by reaction with 2,2-dimethyl-1,3-propanediol and oxalic acid in benzene in a Dean-Stark apparatus. The reaction was followed by g.l.c. and the ratio of acetal to starting material approached 1:2 respectively after four days and did not change significantly thereafter. Addition of molecular seives to the side arm of the Dean-Stark water trap as well as other measures failed to shift the equilibrium further towards product. Fortunately isolation of 182 was simple since the acetal was a solid [mp 82-82.5\textdegree, (α)\textsubscript{30}\textdegree{D} - 71.8\textdegree{D}] which easily crystallized from a cold dry pentane solution of the reaction product leaving largely starting material in solution. Treatment of carvone acetal 182 with one equivalent of the 1:1 butyllithium--TMEDA complex rapidly formed a deep red colored solution which precipitated a red viscous mass after one hour standing at room temperature. As it was not possible to alkylate the alkyllithium species in the form produced, the solvent (hexane from the butyllithium) was removed under reduced pressure and tetrahydrofuran was added and immediately upon solution the reaction mixture was cooled to -78\textdegree and treated with 1-chloro-3-methyl-2-butene. In contrast to the reaction of dihydrocarvone acetal 116 no alkylated material was recovered but only starting acetal 182. Repetition of the above procedure using two equivalents of the metalating agent afforded after hydrolysis and distillation a recovery of about one third of the starting (-)-carvone, (α)\textsubscript{31}\textdegree{D} -58.2\textdegree{D}, a low yield of monoalkylated material and the remainder as less volatile products.
The monoalkylated material consisted of two products relative retention times 4.5 minutes and 5.4 minutes in the approximate ratio 1:4 respectively. Isolation by preparative g.l.c. of the major monoalkylated product and comparison of spectral characteristics (ultraviolet, infrared, n.m.r.) and specific rotation \([\alpha]_D^{29} -39.3^\circ\) established the identity of the product with natural \((-\))-cryptomerion \([\alpha]_D^{29} -38^\circ\) (75) which now can be assigned structure 99a. The minor component of the mixture was assigned structure 183 on the basis of the following spectral characteristics: 

- \(\lambda_{\text{max}}\) 234 nm \((\varepsilon 7,230)\);
- \(\nu_{\text{max}}\) 3100, 1675, 892 and 830 cm\(^{-1}\); n.m.r. (CCl\(_4\)), \(\tau\) 8.42 and 8.40 (two vinyl methyl singlets, isopropylidene group), 8.23 (multiplet, vinyl methyl), 5.23 (two proton multiplet, terminal olefin), 4.98 (multiplet, olefinic proton), and 3.43 (multiplet, olefinic proton on beta-carbon of enone). The allylic rearrangement product 184 analogous to compound 150 obtained by Crawford et al. (97,99) from the alkylation of limonene was not found among the reaction products, again attesting to the absence of allylic rearrangement in 1-chloro-3-methyl-2-butene.

Vig and co-workers had previously reported the conversion of dihydrocryptomerion 75 to cryptomerion 99 through the intermediacy of the bromo ketone. Using phenyltrimethylammoniumtribromide (PTT) (134) as the brominating reagent and effecting dehydrobromination by refluxing the crude bromide in pyridine, the overall conversion was reported to proceed in 92% yield (76). Though we had established the absolute configuration of \((-\))-cryptomerion through the alkylation of acetal 182, our interest in further transformations on this compound prompted us to repeat Vig's conversion using the more readily
available optically active dihydrocryptomerion 75a from our previous study of metalated acetal 145. In this way (-)-cryptomerion [(α)\textsubscript{D}\textsuperscript{29} -37°] was obtained in good yield.

While the above synthesis of (-)-cryptomerion was in progress, the structure and absolute configuration of (+)-delobanone 185, isolated from Lindera triloba Sieb, et Zucc. Blume, was published, based on spectral and chemical evidence (135). In the process of structure elucidation (+)-delobanone was dehydrated to (+)-cryptomerion [(α)\textsubscript{D}\textsuperscript{23} +21.4°] assigned structure 99b which is in accord with
our work establishing 99a as (-)-cryptomerion. Delobanone would be an equally suitable monocyclic precursor of campherenone in terms of our biosynthetic proposal and thus both antipodal forms of the proposed monocyclic substrate occur in nature.

During our work with cryptomerion we noticed that a sample left standing on the bench several days showed significant changes in the infrared spectrum. In particular, a new absorbance in the carbonyl region (1735 cm\(^{-1}\)) appeared at the expense of the 1670 cm\(^{-1}\) absorption. We were aware of earlier work involving the photocyclization of carvone 79 to carvonecamphor 186 (136-139) and of isopiperitenone 187 to compound 188 (140,141). In view of the analogy among the structures of cryptomerion, 79 and 187, we considered that similar phototransformation might be occurring with cryptomerion. Indeed, when (-)-cryptomerion 99a, (\(\alpha\))\(_D\) -39°, was photolyzed three days in ethanol solution using an ordinary sunlamp with a filter which essentially eliminated light of wave length shorter than 340 nm (cf. reference 138), two compounds were present in the photolysis mixture in the relative ratio of 73:27 with relative retention times 3.9 minutes and 5.4 minutes respectively. The component of greater retention time was isolated by preparative g.l.c. and shown to be starting material 99a. The major component (retention time 3.9 minutes) proved unstable to the preparative g.l.c. conditions (SE-30, 240°) though a pure sample \([(\alpha)]\(_D\) 38 -41°) was obtained by column chromatography and exhibited the following spectral characteristics: \(\nu_{\text{max}}\) 1735, 1410, and 835 cm\(^{-1}\); \(\tau\) (CCl\(_4\)) 8.93 (sharp methyl singlet), 8.40 and 8.32 (two vinyl methyls) and 4.96 (olefinic proton). The replacement of the enone carbonyl by
79 \xrightarrow{\text{hv}} 186

187 \xrightarrow{\text{hv}} 188

99a

III

189 (\text{-})-\text{Photocryptomerion}
a strained saturated carbonyl (1735 cm⁻¹) was highly indicative that cyclization had occurred. The fact that the trisubstituted double bond remained intact was evidenced by the n.m.r. absorptions for vinyl methyls and the olefinic proton. The above spectral evidence plus the analogy with similar photocyclizations all point to structure 189 and this assignment was further corroborated by high resolution mass spectral analysis. We propose the name (-)-photocryptomerion for this photoproduct and note that its formation is analogous to the conversion of carvone 79 to carvonecamphor 186.

At the outset of our work the absolute configuration of (-)-campherenone 42 and (-)-campherenol 46 had been proposed on the basis of optical rotatory dispersion and circular dichroism studies using (+)-camphor as a model. The configuration of campherenone and thus of 46 (which had been converted to 42), was stated to be the same as (+)-camphor (see structures 42a and 46a) on the grounds of similar positive Cotton effects. This configurational assignment was particularly disconcerting to us from the standpoint that (+)-(α)-santalene 47a [(α)²⁵ D +11.1°], known by total synthesis to have the absolute configuration shown [(α)²⁶ D +18.4°] (44), was identified in the same plant system in which campherenone occurs (60). Our biosynthetic postulate and indeed all previous postulates (see for example references 6 and 28) were directly contradicted by this finding, as campherenone and the santalenes were presumably derived from a common intermediate. Therefore in order to place our proposals on a credible footing it became necessary to reinvestigate the absolute configuration of campherenone. At the same time we were interested in establishing the
absolute configurations of natural $\beta$-santalene and epi-$\beta$-santalene which had not previously been assigned on a rigorous basis.

Westfelt et al. had previously prepared keto ester 171 in apparently good optical purity from a starting mixture of $\alpha$,\,$\beta$- and (presumably) epi-$\beta$-santalols through formolysis of the corresponding $\alpha$,\,$\beta$-unsaturated esters 190, 191 and 192 (33). After hydrolysis and oxidation, keto esters 171 and 193 were obtained (the presence of 193 in the reaction mixture was given as evidence for epi-$\beta$-santalol 194 in the original santalol mixture). One might expect that formolysis of the corresponding hydrocarbon $\alpha$-santalene 47a would provide a possible route to optically active ketone 42b with absolute configuration known from that of (+)-$\alpha$-santalene (45). Unfortunately Westfelt's formolysis conditions, when applied to a mixture of $\alpha$,\,$\beta$ and epi-$\beta$-santalene (relative ratio 4.3:1.0:3.0 respectively), afforded one major product (71% by g.l.c.) which was not the desired formolysis product. The absence of a carbonyl absorption in the infrared spectrum indicated that the desired formate ester(s) had not been formed. The appearance of a new absorption band at 797 cm$^{-1}$, replacing the absorption bands due to the trisubstituted double bonds, the terminal olefins and the cyclopropane ring protons of the starting hydrocarbon mixture (ca. 800 to 900 cm$^{-1}$) suggested that double bond interaction had occurred. The n.m.r. spectrum (CCl$_4$) confirmed this assumption showing only one olefinic proton, a well defined triplet at 4.68 $\tau$ (J = 2 Hz), which was coupled to an isolated allylic methylene group (7.97 $\tau$, two proton doublet, sharp, J = 2 Hz), a six hydrogen singlet at 9.05 $\tau$ and a six hydrogen doublet (J = 7 Hz) at 8.96 $\tau$, indicated the presence of four saturated methyl groups. Structures 195, 196 and 197 all appear to
be in reasonable agreement with spectral evidence and no clear distinction among the three has yet been made.

An alternate synthetic route to optically active campherenone 42 and epicampherenone 45 was stimulated by a recently reported synthesis (117) of epi-β-santalene 50 and α-santalene 47 in which iodides 198 and 199 respectively were coupled with the nickel(I) complex from 1-bromo-3-methyl-2-butene indicated by structure 200. No data was given as to the optical activity of either product so produced. We felt that an analogous reaction with iodide 201 might give access to optically pure epicampherenone which in turn could be transformed into epi-β-santalene. The same reaction on the disastereomeric iodide 202 would provide a route to campherenone and subsequently β-santalene. In fact, both the coupling reactions and the subsequent transformations proved successful.

The known bromo acetal 206 (142) was chosen as the source of iodide 201. Thus commerically available (+)-3-bromocamphor 203 was converted to 3,9-dibromocamphor 204 by treatment with chlorosulfonic acid and bromine (45). Reduction with zinc and hydrogen bromide yielded (+)-9-bromocamphor 205 (45). This sequence of reactions has previously been shown to transpire with full retention of absolute configuration, while in contrast, 9-bromination of camphor itself affords partially racemized 9-bromocamphor (143,144). Treatment of 205 with ethylene glycol and p-toluenesulfonic acid in benzene provided bromo acetal 206 (142). Reaction of 206 with sodium iodide in acetone afforded only 12% of the desired iodide 201 after four days refluxing. A much more efficient conversion (83%) to the iodide was obtained when 206 was heated with sodium iodide in dimethylsulfoxide (145).
\[ \text{198} \xrightarrow{200} \text{50} \]
\[ \text{199} \xrightarrow{200} \text{47} \]
\[ \text{Br} \]

\[ \text{200} \]

\[ \text{201} \]

\[ \text{202} \]
The nickel complex required for the coupling reaction with 201 had been prepared previously by Corey et al. (117) through a procedure involving low temperature recrystallization of the air and heat sensitive nickel compound. Sato and co-workers (146) recently reported satisfactory preparation and use of the complex with elimination of this difficult recrystallization step and we chose this modified route. Thus acetal iodide 201 was treated with eight equivalents of the nickel complex at 50° overnight affording epicampherenone acetal \(168b\) and some of the corresponding ketone \(45a\) in good yield. The keto iodide derived from 201 required considerably longer reaction time than iodide 201. The need for a large excess of the complex was probably due to decomposition of the thermally sensitive reagent. However, at lower temperatures [e.g., 22° as described by Corey et al. (117)] the reaction failed to proceed. Purification by preparative g.l.c. provided \((+)-epicampherenone \(45a\) \([\alpha]_D +84.6°\)] identical (infrared, n.m.r., g.l.c.) except in rotation with our previously synthesized \((\pm)-epi-campherenone (108)\). The circular dichroism spectrum of \(45a\) exhibited a strong positive cotton effect at 298 nm \([\theta] = 4.2 \times 10^4\] and a stronger negative curve at higher energy \([\theta]_{\text{max}} = -2.2 \times 10^4\]. The strong positive cotton effect at the n -- \(\pi^*\) transition is in accord with \((+)-camphor\) and apparently with a large number of known 9-position substituted \((+)-camphor\) derivatives (147).

Reduction of \((+)-epicampherenone\) with lithium trimethoxy-aluminohydride afforded \((+)-isoepicampherenol\) which was treated with tosyl chloride in pyridine at 95° overnight yielded \((+)-epi-\beta\)-santalene, \([\alpha]_{D}^{29} +26.9°\), (see Figures 11 and 12) in agreement with the natural isomer, \([\alpha]_{D}^{29} +23.3°\), isolated in our laboratory from Mysore oil (120).
Figure 11. N.M.R. Spectrum (100 M Hz) of (+)-Epi-β-santalene 50a
Figure 12. Infrared Spectrum of (+)-Epi-β-santalene 50a
Thus (+)-epi-β-santalene has the absolute configuration shown in 50a and is configurationally related to (+)-α-santalene 47a by formal cleavage of the bond between carbon atoms a and b of the cyclopropane ring in 47a.

The preparation of optically active campherenone required preparation of intermediate acetal iodide 202 and the route chosen to this compound was based on two previous synthetic endeavours. Corey et al. (145) had prepared lactone 212 by rearrangement of the hydroxy acid 211 derived from 9-bromocamphor, however, no data on optical activity was given. Rodig et al. (148) had prepared (±)-lactone 212 by another route and subsequently transformed it into (±)-keto iodide 216. We felt that combination of the two routes could produce the desired optically active keto iodide 216 if the formation of lactone 212 proceeded with full retention of configuration.

Acetolysis of 9-bromocamphor 205 afforded (+)-9-acetoxy camphor 208 which was hydrolyzed to (+)-9-hydroxycamphor 209 (149,145). Oxidation of 209 by the procedure of Corey et al. (145) provided (+)-trans-isoketopinic acid 210 (α) \( \Delta^D +1.4^\circ \) [lit. (α) \( \Delta^D +3.2^\circ \) (150)]. Reduction with sodium borohydride and lactonization in refluxing trifluoroacetic acid-sulfuric acid (145) provided lactone 212 with mp 199-200\(^\circ\), (α) \( \Delta^D -60.7^\circ \), which disagrees with material prepared by another route [mp 191\(^\circ\); (α) \( \Delta^D -117.9^\circ \)] starting from teresantalol (151).

Lactone 212 was converted to crystalline diol 213 by reduction with lithium aluminum hydride following the procedure of Rodig (148). Selective monotosylation with one mole of p-toluenesulfonyl chloride (-10\(^\circ\)) followed by oxidation of the crude product 214 (144,148) afforded
ketotosylate 215 as an oil which crystallized after standing two weeks at -10°. Treatment of 215 with sodium iodide in dimethylsulfoxide afforded (-)-8-iodocamphor 216, mp 40-41°, (α) D 32 -92.1° [lit. (±) mp 40-42° (148)]. Finally, treatment of keto iodide 216 with ethylene glycol and p-toluenesulfonic acid afforded the desired acetal 202 in good yield. Hydrogenolysis of keto iodide 216 with palladium on carbon provided (-)-camphor, (α) D 32 -44.8° [lit. (α) 16 -43.6° (152)].

Reaction of acetal iodide * 202 with the nickel complex 200, as previously described, afforded campherenone acetal which was purified by distillation and hydrolyzed, providing (-)-campherenone, (α) D 33 -33.6° [lit. (α) D -33.0° (27,28)]. The circular dichroism spectrum of our product ([θ] max 294 -370) did not agree with the published value ([θ] max 298 + 600 (28)) for (-)-campherenone. This anomaly between our data and that of the natural campherenone makes assignment of absolute configuration to the natural product impossible at present. It would appear that the physical constants for the natural material need reinvestigation and we are currently attempting to obtain a sample of natural campherenone for this purpose.

Reduction of (-)-campherenone with lithium trimethoxyalumino-hydride afforded (+)-isocampherenol (+)-46b which upon heating with

* Attempts to transform 216 directly to campherenone by reaction with 200 under analogous conditions led to consumption of 216 but production of no detectable amount of campherenone.
p-toluenesulfonyl chloride in pyridene provided (-)-β-santalene, 
(α)\(^{33}\)_D = 112°, identical in spectral data (see Figures 13 and 14) and 
sign of rotation with natural β-santalene [(α)\(^{28}\)_D = -102°] isolated 
from Mysore sandlewood oil (120). The absolute configuration of (-)-
β-santalene must be as shown in 48a thus relating (-)-β-santalene with 
(+)−α-santalene 47a through formal cleavage between carbon atoms a 
and c in 47a. β-Santalene of undetermined specific rotation has been 
reported to co-occur with (+)-α-santalene in the same plant species 
in which "(-)-campherenone" is found (60). This material is probably 
(-)-β-santalene in agreement with our biosynthetic postulate.

Establishment of the absolute configuration of campherenone, 
epicampherenone and the corresponding β- and epi-β-santalenes formally 
concluded the initial goals of this synthetic investigation into 
possible biogenetic routes to monoterpenes and sesquiterpenes bearing 
the bicyclo(2.2.1)heptane framework. We have demonstrated the synthetic 
utility of enol derivatives in directing and promoting cyclization of 
monocyclic cyclohexenyl substrates to functionalized camphor derivatives. 
Furthermore, this work established the feasibility of preparing many 
polycyclic sesquiterpenes utilizing campherenone as a key intermediate 
or synthon. Finally, having shown the chemical feasibility of our bio-
genetic postulate, we have used our postulate to predict the absolute 
stereochemical relationships of various sesquiterpene families or 
"quartets" resulting in our current reinvestigation of the absolute 
configurations of certain known sesquiterpenes.

While our original goals for this project have been achieved, 
the potentials of our synthetic approach have by no means been exhausted. 
In fact, as our work progressed it became apparent that a much broader,
much more general synthetic and possibly biogenetic relationship lay before us and that we had only tapped one portion of the potential resources. The utilization of campherenone as a key intermediate in the preparation of more complex polycyclic skeletons has proven to be a particularly rewarding approach. An extension of this approach would be the intramolecular cyclization of substrate 217 which should be readily obtainable from campherenone. If successful, this cyclization would generate the longicamphane skeleton providing a simple route to longicamphor 54, longiborneols 61a,b, longicyclene 62 and longifolene 63. Oxidation of longicamphor in analogy to the known oxidation of camphor (12) might open a route to culmorin 218 (58).

Similar oxidative functionalization of ylangocamphor 53 followed by rearrangement to the sativene-like skeleton 219 could provide a suitable substrate for cleavage to helminthosporal 220 in analogy with the proposed biosynthesis (153). Baeyer-Villiger oxidative cleavage of the copacamphor skeleton to 221 would generate the basic skeleton of the large group of picrotoxane sesquiterpenes including alkaloids such as dendrobine 222 and highly oxygenated sesquiterpenes such as tutin 223. Biosynthetic postulates (6,154) and labelling studies (155-158) have implicated an analogous cleavage in the biosynthesis of both 222 and 223 and the recent specific incorporation of the tritium labelled copaborneol 58* into 223 (159) confirms this route.

The synthesis of optically active campherenone now makes possible the synthesis of optically active members (both antipodes) of the copacamphor and ylangocamphor series. If the synthesis of longicamphor is achieved from a campherenone derivative, then it may be
possible to prepare every member of both antipodal quartets for campherenone 42, epicampherenone 45, copacamphor 52, ylangocamphor 53 and longicamphor 54 starting from either (+)- or (-)- campherenone.

A further extension of this work would be the modification of our cyclization reaction so as to allow the formation of compounds bearing the bicyclo(3.1.1)heptane skeleton. We have previously generated the bicyclo(4.1.0)heptane (for example 33 and 34) and the bicyclo(2.2.1)-heptane ring systems using suitable enol (enolate) derivatives. Cyclization of a substrate such as 224, isopiperitenone enol derivative, to verbenone 225 (12) or a similar cyclization of 226 to compound 227 (160) would complete the possible modes of cyclization of cyclohexenyl substrates and provide a new route to a highly interesting group of monoterpenes and sesquiterpenes.

Whether or not future investigations prove our biogenetic postulate to be correct, the success of our synthetic studies attests to the richness of chemical information that awaits discovery through consideration and experimental application of possible biosynthetic processes to the synthesis of natural products. Through biogenetic patterned synthetic studies such as these we can perhaps unlock some of the fascinating secrets surrounding enzyme mediated reactions and thus greatly broaden our synthesis capabilities in the laboratory.
EXPERIMENTAL

Unless otherwise noted the following are implied. Melting points, which were determined on a Kofler apparatus, and boiling points are uncorrected. Gas-liquid chromatography (g.l.c.) was carried out on either a Varian Aerograph, model 90-P, or an Aerograph Autoprep, model 700. The following columns were employed:

<table>
<thead>
<tr>
<th>Column</th>
<th>Length</th>
<th>Stationary Phase</th>
<th>Support</th>
<th>Mesh</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>10 ft. x 1/4 in.</td>
<td>3% SE 30</td>
<td>Varoport 30</td>
<td>100/120</td>
</tr>
<tr>
<td>B</td>
<td>&quot;</td>
<td>5% QF 1</td>
<td>Chromosorb W</td>
<td>60/80</td>
</tr>
<tr>
<td>C</td>
<td>&quot;</td>
<td>10% FFAP</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>D</td>
<td>&quot;</td>
<td>10% Carbowax</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>E</td>
<td>&quot;</td>
<td>20% DEGS</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>F</td>
<td>10 ft. x 3/8 in.</td>
<td>30% FFAP</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>G</td>
<td>20 ft. x 3/8 in.</td>
<td>30% SE 30</td>
<td>&quot;</td>
<td>45/60</td>
</tr>
<tr>
<td>H</td>
<td>&quot;</td>
<td>30% QF 1</td>
<td>&quot;</td>
<td>&quot;</td>
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</tbody>
</table>

Carrier gas (helium) flow-rate for 1/4 in columns was 60 ml/min and for 3/8 in columns was 170 ml/min. Optical rotations were measured with either a Perkin-Elmer model 141 polarimeter or a Rudolph polarimeter. Circular dichroism spectra were recorded on a JASCO J-20 spectro-polarimeter. Ultraviolet spectra were recorded on a Unicam model
S.P. 800 spectrophotometer in methanol solution. Routine infrared spectra were recorded on a Perkin-Elmer Infracord model 137 spectrophotometer; comparison spectra were recorded on Perkin-Elmer model 21 or model 457 spectrophotometer. The 60 MHz nuclear magnetic resonance (n.m.r.) spectra were recorded on Varian Associates model A-60 or model T-60 while 100 MHz spectra were recorded on Varian Associates model HA-100 or model XL-100. Signal positions are given in the Tiers tau scale with tetramethylsilane as an internal reference. Signal multiplicity and integrated area as well as proton assignments are indicated in parentheses. Mass spectra were recorded on an Atlas model CH-4 or on an AEI model MS-9 mass spectrometer. High resolution mass spectra were determined on the AEI model MS-9 instrument. Microanalyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia, Vancouver.

Solvents employed were of either Reagent grade or Certified grade. The term "petroleum ether" will refer to the low boiling fraction of Certified grade petroleum distillate (bp ca. 30-60°). Dry solvents or reagents, where indicated, were prepared as follows: benzene, ether, pentane or petroleum ether by storage over sodium followed by distillation; acetone, dimethylformamide or dimethylsulfoxide by storage over molecular seives type 4A; pyridine by storage over potassium hydroxide pellets; and tetrahydrofuran by distillation from lithium aluminum hydride. Additional purification of dimethylsulfide was effected by distillation and of thionyl chloride by distillation from triphenyl phosphite.
Preparation of Dihydrocarvone 76a,b

To a 3 liter three neck flask fitted with dropping funnel and reflux condenser was added 250 g (3.83 mole) zinc powder, 100 g (1.78 mole) potassium hydroxide, 1000 ml 95% ethanol and 400 ml water. The mixture was heated to reflux with vigorous stirring and 203 g (1.35 mole) 1-carvone [Aldrich, (α)\textsubscript{D}^0 -58.6° (c 4.78, CHCl\textsubscript{3})] dissolved in 400 ml 95% ethanol was added dropwise over a period of 6 hours. Reflux was continued for 1 hour at which time the reduction was determined complete as judged by the disappearance of the absorption at 234 nm in the ultraviolet spectrum of an aliquot. After cooling and filtering through a Büchner funnel, the solvent was removed under reduced pressure and the residue was extracted with three 250 ml portions of petroleum ether. The organic layers were washed first with water, then with dilute acetic acid until the aqueous layer tested neutral to wide range pH test paper, and finally again with water. Drying over anhydrous sodium sulfate followed by solvent removal and distillation afforded 178 g (87%) dihydrocarvone 76a,b as a mixture of epimers at C\textsubscript{1} in the ratio 1:3 cis-1,4 to trans-1,4 as judged by n.m.r.: bp 80° (6 mm) [lit. bp 100-104° (17mm)(161)]; homogeneous by g.l.c. (column A, 150°); (α)\textsubscript{D}^0 +18.3° (c 10.4, CHCl\textsubscript{3}) [in another preparation using Wallach's procedure (62) the dihydrocarvone exhibited a rotation of +12° indicating a different ratio of the C\textsubscript{1} epimers]; ultraviolet, \(\lambda_{\text{max}}\) 284 nm (ε 30); infrared (neat), \(\nu_{\text{max}}\) 3100, 1710, 1650 and 892 cm\(^{-1}\); n.m.r. (CCl\textsubscript{4}), τ 9.04 and 8.99 (two doublets, relative area 76:24 respectively, 3H, J = 6.0 Hz and 6.5 Hz respectively, epimeric secondary methyls), 8.27 (multiplet, 3H, vinyl methyl), and 5.29 (multiplet, 2H =CH\textsubscript{2}).
Isolation of Michael Addition Product 82

The residue remaining from distillation of dihydrocarvone 76 in the above reaction was triturated with petroleum ether and stored at -10°C. Filtration and recrystallization of the crude product from petroleum ether-methylene chloride (80:1) provided 0.37 g (< 0.2%) of colorless crystals [other preparations following Wallach's procedure (62) produced from 5 to 10% of this material]: mp 153-154°C [lit. mp 148-149°C (62)]; ultraviolet (95% ethanol), λ_{max} 288 nm (ε 90); infrared (KBr), ν_{max} 3090, 1705, 1650 and 892 cm^{-1}; n.m.r. (CDCl₃), δ 9.03 (doublet, 6H, J = 6.5 Hz, secondary methyls), 8.22 (multiplet, 6H, vinyl methyls) and 5.18 (multiplet, 4H, two =CH₂ groups); mass spectrum, m/e (relative intensity), 302 (100, M⁺), 259 (81.2), 151 (52.5), 109 (36.9), 97 (25.0) and 55 (30.0).

Preparation of Enol Acetates 80a and 84

Dihydrocarvone (6.00 g, 0.039 mole) was heated with 15 ml isopropenyl acetate and 100 mg p-toluenesulfonic acid monohydrate 30 hours with slow distillation of the acetone generated. The reaction mixture was cooled, diluted with petroleum ether, washed with saturated sodium bicarbonate, with water and twice with saturated sodium chloride and then dried over anhydrous sodium sulfate. Solvent removal under reduced pressure followed by distillation yielded 7.20 g (94%) of a mixture of enol acetates 84 and 80a: bp 41-44°C (0.02 mm); two components by g.l.c. analysis (column A, 140°C) in the ratio 29:71 for
compounds 84 and 80a respectively (relative retention times 3.0 minutes and 3.7 minutes respectively). (In another preparation the ratio of compounds 84 and 80a was 1:4.) Pure samples of 84 and 80a were obtained by preparative g.l.c. (column G, 175°) followed by evaporative distillation.

Enol acetate 84 exhibited the following characteristics:
($\alpha$) $^{28}_{D}$ +90.5° (c 2.56, CHCl$_3$); infrared (neat), $\nu_{\text{max}}$ 3090, 1745, 1680, 1645, 1210 and 890 cm$^{-1}$; n.m.r. (CCl$_4$), $\tau$ 9.04 (doublet, 3H, J = 6.5 Hz, secondary methyl), 8.26 (multiplet, 3H, vinyl methyl), 7.93 (singlet, sharp, 3H, acetate methyl), 5.23 (multiplet, 2H, =CH$_2$) and 4.86 (multiplet, 1H, olefinic proton); mass spectrum, m/e (relative intensity), 194 (5.5, M$^+$), 152 (90.4), 137 (79.4), 109 (35.2), 95 (35.8), 43 (100) and 41 (51.5).

Enol acetate 80a showed the following characteristics:
$n^2_{D}$ 1.4757; ($\alpha$) $^{28}_{D}$ +81.1° (c 2.46 CHCl$_3$)(another preparation gave a +77° rotation); infrared (neat), $\nu_{\text{max}}$ 3090, 1745, 1705, 1645, 1210 and 888 cm$^{-1}$; n.m.r. (CCl$_4$), $\tau$ 8.51 (singlet, broad 3H, methyl on enol acetate double bond), 8.26 (multiplet, 3H, vinyl methyl), 7.95 (singlet, sharp, 3H, acetate methyl) and 5.26 (multiplet, 2H, =CH$_2$); mass spectrum, m/e (relative intensity), 194 (5.1, M$^+$), 152 (67.0), 109 (100), 84 (37.3), 43 (72.9), and 41 (51.7).

Cyclization of Enol Acetate 80a

A solution of 203 mg (1.04 m mole) enol acetate 80a, ($\alpha$) $^{23}_{D}$ +77°, in 200 mls methylene chloride (Baker reagent grade, 0.012% water) was
saturated with boron trifluoride gas by rapid bubbling of the gas into the vigorously stirred enol acetate solution. After 10 minutes the reaction was quenched by shaking with 50 ml saturated sodium bicarbonate and the organic phase was washed twice with water and dried over anhydrous sodium sulfate. Solvent removal afforded a faintly yellow residue which became crystalline when cooled to -10°. Sublimation (50°, 14mm) afforded 103 mg (64%) (±)-camphor \( \beta \): (\( \alpha \))\( _D^{23} \) 0° (c 1.96, 95% EtOH); ultraviolet, \( \lambda_{max} \) 288 nm (\( \varepsilon \) 36); infrared (CCl\(_4\)), \( \nu_{max} \) 1740, 1422 and 1050 cm\(^{-1}\), entire spectrum superimposable on spectrum of authentic (±)-camphor; n.m.r. (CCl\(_4\)) \( \tau \) 9.17 (singlet, 3H, C\(_8\) tertiary methyl), 9.15 (singlet, 3H, C\(_{10}\) tertiary methyl) and 9.04 (singlet, 3H, C\(_9\) tertiary methyl); \( \tau \) 9.41 (singlet, 3H, C\(_8\) tertiary methyl), 9.37 (singlet, 3H, C\(_9\) tertiary methyl) and 9.10 (singlet, 3H, C\(_{10}\) tertiary methyl), entire spectrum in both solvent systems superimposable on spectrum of authentic (±)-camphor.

In other cyclizations higher yields were obtained by pre-saturation of the solvent with boron trifluoride. Thus to 50 mls of methylene chloride saturated with boron trifluoride gas was added a solution of 100 mg (0.51 m mole) enol acetate \( 80a \) in 50 ml methylene chloride in portions over a period of 4 minutes and the reaction was continued 10 minutes. Work-up as above afforded a colorless product which was estimated to be 90% camphor by g.l.c. analysis (column F, 170°).

Higher concentrations of \( 80a \) led to reduced yields of camphor. Thus 335 mg (1.7 m mole) \( 80a \) in 50 ml methylene chloride was treated 1 hour with boron trifluoride gas followed by the usual work-up afford-
ing 300 mg crude product. The product consisted of at least ten components by g.l.c. analysis and the three major components were isolated by preparative g.l.c. (column F, 170°) having retention times of 10, 25 and 29 minutes. The component of retention time 10 minutes (10%) was identified as camphor 17 by infrared and n.m.r. spectra and by its mass spectrum (M⁺, m/e 150) as compared to the corresponding spectra of authentic (±)-camphor.

Component 85 (carvenone) of retention time 25 minutes (35%) exhibited the following data: ultraviolet, λmax 234 nm (ε 13,200); infrared (neat), νmax 1670, 1210 and 880 cm⁻¹; n.m.r. (CCl₄) 8.95 (doublet, 3H, J = 6.5 Hz, vinyl methyl), 8.89 (doublet, 6H, J = 6.5 Hz, two secondary methyls) and 4.27 (singlet, 1H, olefinic proton). (162a,b, 163).

Component 86 with retention time 29 minutes (39%) showed the following spectral data: ultraviolet, end absorption; infrared (neat), νmax 1745, 1210, 840 and 805 cm⁻¹; n.m.r. (CCl₄) τ 8.97 (doublet, 6H, J = 6.5 Hz, secondary methyls), 8.50 (singlet, broad, 3H, vinyl methyl), 7.92 (singlet, 3H, acetate methyl), 7.72 (multiplet, 1H, methine proton), 7.32 (singlet, broad, 4H, two allylic methylene groups) and 4.65 (singlet, 1H, olefinic proton).

Employment of scrupulously dry methylene chloride (distilled from phosphorus pentoxide) in the cyclization of enol acetate 80a led to a mixture of products containing only a trace amount of camphor as judged by g.l.c. analysis.

Attempted Racemization of (+)-Camphor

(+)-Camphor, (α)D +46.4°, commercial grade was used without
further purification. A solution of 152 mg (+)-camphor in 150 ml methylene chloride was saturated with boron trifluoride gas, stoppered and allowed to stand 4 hours at room temperature. The mixture was washed with saturated sodium bicarbonate and two times with water and then dried over anhydrous sodium sulfate. Solvent removal followed by two sublimations (50°, 0.15 mm) afforded (+)-camphor ($\alpha$)\textsuperscript{25} +43.6° (c 1.52, 95% EtOH) [lit. ($\alpha$)\textsuperscript{20} +44.3° (95% EtOH)(164)].

Another sample of (+)-camphor (200 mg in 200 ml methylene chloride) was treated as above except that the period of exposure to boron trifluoride was extended to 66 hours. Two sublimations afforded (+)-camphor ($\alpha$)\textsuperscript{25} +43.4° (c 5.23, 95% EtOH).

Treatment of Dihydrocarvone With Boron Trifluoride

Dihydrocarvone 76a,b (100 mg, 0.66 m mole) [($\alpha$)\textsuperscript{24} +12° (c 2.70, 95% EtOH)] in 50 ml methylene chloride was added over 3.5 minutes to 50 ml of vigorously stirred methylene chloride saturated with boron trifluoride gas. After 10 minutes stirring the solution was washed with saturated sodium bicarbonate and twice with water and dried over anhydrous sodium sulfate. G.l.c. analysis (column F, 170°) indicated that the product consisted of three major components with relative retention times of 13, 20 and 25 minutes.

Component 89 of retention time 13 minutes exhibited the following spectral data: ultraviolet, end absorption; infrared (neat), $\nu_{\text{max}}$ 1710 and 805 cm$^{-1}$; n.m.r. (CCl$_4$), $\tau$ 8.96 (doublet, 9H, $J$ = 6.5 Hz,
three secondary methyls), 7.26 (singlet, broad, 2H, allylic methylene adjacent to ketone) and 4.46 (singlet, broad, 1H, olefinic proton); (C₆H₆), τ 9.18 (doublet, 6H, J = 5Hz, two secondary methyls) and 9.01 (doublet, 3H, J = 5 Hz, secondary methyl).

The component of retention time 20 minutes did not appear pure on spectral analysis but was assigned a tentative structure corresponding to a double bond isomer of dihydrocarvone (with an isopropylidene group) based on the following evidence: infrared (neat), νₘₐₓ 1705 cm⁻¹; n.m.r. (CCl₄) 8.97 (doublet, 3H, J = 6 Hz, secondary methyl) and 8.32 (singlet, broad, 6H, vinyl methyl).

Component 85 of retention time 25 minutes exhibited spectral properties (ultraviolet, infrared, n.m.r.) in agreement with those found for carvenone 85 produced in the cyclization of enol acetate 80a and was shown to have a positive specific rotation: (α)_D^24 +67° (c 2.94, 95% EtOH).

**Attempted Cyclization of Enol Acetate 84**

Enol acetate 84 (19 mg, 0.098 m mole) in 9 ml methylene chloride was added at room temperature to 10 ml of methylene chloride, saturated with boron trifluoride gas, with stirring. A slow stream of the gas was maintained through the solution for 10 minutes. The solution was washed with 5 ml saturated sodium bicarbonate and twice with water and then dried over anhydrous sodium sulfate. Solvent removal afforded a nearly pure material (93% by g.l.c.; column F, 170°, retention time 25 minutes), exhibiting spectral characteristics (ultraviolet, infrared) in agreement
with those found for carvenone \textit{85} isolated in the cyclization of enol acetate \textit{80a}.

**Preparation of Dihydrocarvone Ethylene Acetal \textit{108}**

A mixture of 15.0 g (0.986 mole) dihydrocarvone \textit{76a,b}, 25 ml ethylene glycol and 500 mg oxalic acid in 300 ml benzene was heated to reflux temperature in a Dean-Stark apparatus and refluxed 20 hours using "Drierite" in the side arm to aid in water removal. The reaction mixture was cooled, the solvent removed under reduced pressure and the residue was extracted with petroleum ether. Washing of the extract with saturated sodium bicarbonate and saturated sodium chloride solution followed by drying over sodium sulfate and solvent removal provided a colorless oil. Distillation yielded 18.8 g (97%) acetal \textit{108}: bp 52° (0.25 mm); \( n^\text{25} \) 1.4749; \( (\alpha)^\text{24}_D \) -7.5° (c 10.2, CHCl\(_3\)) [lit. bp 69-71° (1.0 mm; \( n^\text{22}_D \) 1.4737; \( (\alpha)^\text{24}_D \) -6.1° (c 3.3, CHCl\(_3\))\textit{79})]; infrared (neat), \( \nu_{\text{max}} \) 3100, 1650, 1170, 1090 and 889 cm\(^{-1}\); n.m.r. (CCl\(_4\)), \( \tau \) 9.18 (doublet, broad, 3H, J = 5.5 Hz, secondary methyl), 8.30 (multiplet, 3H, vinyl methyl), 6.15 and 6.12 (two singlets, 4H, -OCH\(_2\)CH\(_2\)O-) and 5.33 (singlet, broad, 2H, -CH\(_2\)). (162a, \textit{79})

**Preparation of Keto Acetal \textit{109}**

A solution of 15.0 g (0.076 mole) of dihydrocarvone acetal \textit{108} in 400 ml methanol cooled in a dry ice -- acetone bath was treated with a stream of ozone intrained in oxygen until the blue color of ozone
in solution persisted. Excess ozone was removed by bubbling nitrogen into the solution (-70°) until the solution became colorless. Reductive work-up was effected by addition of 15 ml (0.13 mole) of dimethyl-sulfide to the solution, still maintained at low temperature, followed by slow warming to room temperature overnight. Excess dimethylsulfide was removed by bubbling nitrogen through the solution (in fume hood). The solvent was removed under reduced pressure and the residue diluted with petroleum ether, washed with water and saturated sodium chloride solution and dried over anhydrous sodium sulfate. Solvent removal and vacuum distillation afforded 14.7 g (97%) keto-acetal 109 as a colorless oil: bp 78° (0.2 mm); n^25_D 1.4708; (α)_{D}^{24} -18.0° (c 12.5, CHCl_3); ultraviolet, \lambda_{max} 280 nm (ε 34); infrared (neat), ν_{max} 1710, 1170 and 1090 cm^{-1}; n.m.r. (CCl_4), τ 9.18 (doublet, 3H, J = 6 Hz, secondary methyl), 7.92 (singlet, sharp, 3H, methyl adjacent ketone) and 6.07 (singlet, broad 4H, -OCH_2CH_2O-); mass spectrum, m/e (relative intensity), 198 (3.6, M^+) 155 (100), 113 (27.2), 99 (16.8), 55 (13.2) and 43 (19.8).

Anal. Calcd. for C_{11}H_{18}O_3: C, 66.64; H, 9.15. Found: C, 66.74; H, 9.27.

Preparation of Acetal Acid 110

A solution of potassium hypochlorite was prepared (165) by dissolving 30.0 g calcium hypochlorite (Fisher Certified, 72.7% available chlorine) in 120 ml warm water and adding a solution of 21.0 g potassium carbonate and 6.00 g potassium hydroxide in 60 ml warm water to form a slurry of calcium carbonate precipitate in the sodium hypo-
chlorite solution. Suction filtration followed by washing of the filter pad with 25 ml water and combining of filtrates provided a clear pale green solution of the oxidant. Keto acetal 109 (12.0 g, 6.06 mole) was added to the vigorously stirred hypochlorite solution at such a rate as to maintain the reaction temperature between 55 and 60°. Stirring was continued for 3 hours at room temperature after which time the excess sodium hypochlorite was destroyed by addition of a 20% solution of sodium metabisulfite until the aqueous reaction mixture no longer colorized starch and potassium iodide test paper (ca. 20 ml). After washing with petroleum ether and cooling to 5° in an ice bath, the solution of crude acid salt was acidified to pH 5 by dropwise addition of 12 N hydrochloric acid. The precipitated acid was filtered cold yielding 6.97 g of white solid. Recrystallization from 9:1 petroleum ether-ether yielded 6.29 g (52%) of the desired product 110, mp 71-74°. An analytical sample recrystallized from petroleum ether exhibited the following: mp 73-75.5°; (α) 25° D -31.1° (c 9.43, CHCl₃); ultraviolet, λ max 212 nm (ε 75); infrared (CCl₄), ν max 3300-3000 (shoulder) and 2650, 1700, 1170 and 1090 cm⁻¹; n.m.r. (CCl₄), τ 9.08 (doublet, broad, 3H, J = 6 Hz, secondary methyl), 6.05 (singlet, 4H, -OCH₂CH₂O-) and -1.09 (singlet, broad, 1H, -CO₂H); mass spectrum, m/e (relative intensity), 200 (22.1, M⁺), 155 (100), 113 (77.4), 69 (36.8), 55 (47.9) and 41 (62.9).

Anal. Calcd. for C₁₀H₁₆O₄: C, 59.98; H, 8.05. Found: C, 60.16; H, 7.92.
Preparation of 2-Methyl-5-bromo-2-pentene

Magnesium turnings (5.00 g, 0.206 mole, freshly ground with mortar and pestle) were covered with 15 ml anhydrous ether and treated with 29.2 g (0.206 mole) methyl iodide in 60 ml anhydrous ether at sufficient rate to maintain reflux (ca. 30 min). Reflux was continued for 30 minutes after completion of the addition. To the resulting Grignard solution was added with vigorous stirring a solution of 15.0 g (0.178 mole) cyclopropyl methyl ketone in 90 ml anhydrous ether maintaining reflux temperature by the rate of addition (ca. 30 min). The resulting slurry was refluxed for an additional 1 hour period after which time the excess Grignard reagent was destroyed by the addition of saturated ammonium chloride solution. The product was decanted and extracted with ether while the remaining solid was dissolved in water by the addition of 6N hydrochloric acid and was extracted with ether. Combined ether extracts were washed with saturated sodium chloride and dried over anhydrous sodium sulfate. Solvent removal provided the crude dimethyl cyclopropyl carbinol which was used without further purification: infrared (neat), $\nu_{\text{max}}$ 3400, 3100, 1150, 845 and 825 cm$^{-1}$. The entire product was cooled in an ice bath and treated over a period of 2 minutes with 60 ml of 48% hydrobromic acid (chilled in an ice bath) in 10 ml portions with vigorous shaking and frequent cooling in ice. The organic layer was separated and the aqueous phase extracted with petroleum ether. The combined organic layers were washed with saturated sodium chloride, saturated sodium bicarbonate and three times with saturated sodium chloride and then dried over anhydrous sodium sulfate. Solvent removal under reduced pressure followed by vacuum distillation
afforded 18.0 g (62% based on starting ketone) of bromide 113:
bp 58-60° (25 mm) [lit. bp 84-85° (84 mm)(82)]; homogeneous by g.l.c.
analysis (column A, 125°); infrared (neat), $v_{\text{max}}$ 835 cm$^{-1}$ and no
absorption for hydroxyl; n.m.r. (CCl$_4$), 8.36 and 8.30 (two singlets, broad, 6H, vinyl methyls), 7.49 (quartet, broad, 2H, J = 7 Hz, $\text{C}=$CHCH$_2$), 6.73 (triplet, 2H, J = 7 Hz, -CH$_2$Br) and 4.89 (multiplet, 1H, olefinic proton).

**Preparation of Keto Acetal 106**

Acetal acid 110 (6.00 g, 0.0300 mole) in 10 ml benzene at reflux temperature (dry nitrogen atmosphere) was treated with 6.00 ml 0.070 mole) oxalyl chloride and refluxed 30 minutes. Excess oxalyl chloride was removed on the rotary evaporator (with "Drierite" guard tube to prevent entrance of moisture) by addition and evaporation of small portions of dry benzene and finally one portion of anhydrous ether. The crude acid chloride 111 was used without further purification: infrared (neat), $v_{\text{max}}$ 1790, 1170 and 1090 cm$^{-1}$ (no absorption for hydroxyl).

The Grignard reagent 114 of 2-methyl-5-bromo-2-pentene was prepared by dropwise addition of 5.87 g (0.036 mole) of the bromide 113 in 40 ml anhydrous ether to 900 mg (0.037 mole) magnesium turnings covered with 20 ml anhydrous ether maintained at reflux temperature with a dry nitrogen atmosphere. Refluxing was continued 1 hour after completion of addition and the reaction mixture was cooled and transferred under nitrogen to a dropping funnel. Crude acid chloride 111
prepared above (0.03 mole) in 25 ml anhydrous ether was treated in the presence of 200 mg cuprous chloride (0-5°, dry nitrogen atmosphere, vigorous stirring) with the Grignard solution dropwise over 1 hour. The resulting slurry was allowed to stir overnight at room temperature. Aqueous bicarbonate was added to hydrolyze remaining acid chloride and the entire mixture, aqueous and organic, was filtered through a Buchner funnel. Following separation of the organic phase, the aqueous layer was further extracted with ether and the combined organic phases were washed with water and dried over anhydrous sodium sulfate for 1 hour. Solvent removal yielded 7.70 g crude product which was immediately distilled under reduced pressure providing 6.15 g (77% based on starting acid) keto acetal 106: bp 103-104° (0.03 mm); n D 1.4852 [lit. bp 180-185° (7 mm); n D 1.4682 (77)]; (α) 25° -13.9° (c 10.6 CHCl₃); ultraviolet, λ max 285 nm (ε 58); infrared (neat), ν max 1705, 1170, 1090 and 835 cm⁻¹; n.m.r. (CCl₄), τ 9.18 (doublet, broad, 3H, J = 6 Hz, secondary methyl), 8.35 (multiplet, broad 6H, vinyl methyls), 6.09 (singlet, 4H, -OCH₂CH₂O-) and 4.98 (multiplet, 1H, olefinic proton); mass spectrum, m/e (relative intensity), 266 (42.8, M⁺), 155 (97.4), 69 (84.2), 55 (100), 43 (92.3), and 42 (81.3). (162a, 77)


Preparation of Dihydrocryptomerion Ethylene Acetal 107

Sodium hydride (0.806 g, 50% oil dispersion, 0.0168 mole) in a flame dried flask (dry nitrogen atmosphere) was washed with a small
portion of anhydrous ether and then heated with 5 ml dry dimethylsulfoxide in a 70° oil bath until liberation of hydrogen ceased. The resulting solution of dimsyl sodium was cooled in an ice bath and 6.00 g (0.0168 mole) methyltriphenylphosphonium bromide in 10 ml dimethylsulfoxide was added slowly after which the light yellow solution of ylide was allowed to warm to room temperature. Keto acetal 106 (3.01 g, 0.0113 mole) in 10 ml dry tetrahydrofuran was added after the ylide had stirred 5 minutes at room temperature and the resulting light brown solution was stirred 24 hours. The reaction mixture was extracted with three 70 ml portions of petroleum ether, washing each with dimethylsulfoxide, twice with water and finally with saturated sodium chloride solution. The dimethylsulfoxide layers were combined, diluted with water and extracted with a further 70 ml portion of petroleum ether, washing as before, and the combined organic phases were dried over sodium sulfate. Concentration followed by column chromatography over 20 g of alumina, eluting with petroleum ether, provided 2.45 g (82%) of acetal diene 107: homogeneous by g.l.c. analysis (column A, 200°); infrared (neat), \( \nu_{\text{max}} \) 3090, 1645, 1170, 1090, 890 and 830 cm\(^{-1}\); n.m.r. (CCl\(_4\)), \( \tau \) 9.17 (doublet, broad, 3H, \( J = 6 \) Hz, secondary methyl), 8.38 and 8.32 (singlets, overlapping, 6H, vinyl methyls), 4.10 (singlet, 4H, -OCH\(_2\)CH\(_2\)O-), 5.33 (singlet, broad, 2H, =CH\(_2\)) and 4.94 (multiplet, 1H, olefinic proton). (162a, 77)

Preparation of Dihydrocryptomerion 75.

Acetal diene 107 prepared in the manner described above but
from 2.66 g (0.0100 mole) of keto acetal 106 was hydrolyzed directly in 100 ml acetone with 3 ml 6N hydrochloric acid added and the reaction was quenched after 4 hours by the addition of saturated bicarbonate solution and subsequent evaporation of solvent. The residue was taken up in petroleum ether, washed with water and dried over sodium sulfate. Concentration provided 2.14 g crude ketone which was distilled under reduced pressure providing 1.82 g (83% from keto acetal 106) dihydro-cryptomerion: bp 80-82° (0.04 mm) [lit. bp 135-138° (5 mm)(77)]; infrared (neat), νmax 3100, 1710, 1650, 892 and 835 cm⁻¹; n.m.r. (CCl₄), τ 9.02 and 8.97 (two doublets, 3H, J = 6.0 Hz and 6.5 Hz respectively, epimeric secondary methyls), 8.38 and 8.32 (two singlets, broad, 6H, vinyl methyls), 5.23 (singlet, broad, 2H, =CH₂) and 4.96 (multiplet, broad, 1H, olefinic proton). (162a, 77)

Preparation of Dihydrocryptomerion Enol Acetate 95b

Dihydrocryptomerion 75 (1.2g, 5.5m mole) and p-toluenesulfonic acid monohydrate (60 mg) in 20 ml isopropenyl acetate were heated 24 hours with slow distillation of volatile materials. After washing with saturated sodium bicarbonate and drying over anhydrous sodium sulfate, the crude product was chromatographed over 35 g aluminum oxide affording 1.3 g of a mixture of enol acetates 115 and 95b. Pure samples of 115 and 95b were obtained by preparative g.l.c. (column G, 250°) relative retention times 58 minutes and 66 minutes respectively (ratio 1:3) followed by evaporative distillation.
Compound 115 was identified by the following characteristics: infrared (neat), \( \nu_{\text{max}} \) 3090, 1750, 1680, 1645, 1210, 895 and 830 cm\(^{-1}\); n.m.r. (CCl\(_4\)), \( \tau \) 9.03 (doublet, 3H, J = 7 Hz, secondary methyl), 8.39 and 8.33 (two broadened singlets, 6H, vinyl methyls), 7.92 (singlet, 3H, acetate methyl), 5.17 (multiplet, 2H, =CH\(_2\)) and 4.87 (multiplet, 2H, olefinic protons); mass spectrum m/e (relative intensity), 262 (0.6, \( M^+ \)), 220 (96.9), 151 (99.9), 109 (61.4), 107 (6.13) and 69 (100).

Compound 95b showed the following: infrared (neat), \( \nu_{\text{max}} \) 3100, 1750, 1715, 1645, 1210, 890 and 830 cm\(^{-1}\); n.m.r. (CCl\(_4\)), \( \tau \) 9.18 (singlet, broad, 3H, methyl on enol acetate double bond), 8.41 and 8.34 (two broadened singlets, 6H, vinyl methyls), 7.96 (singlet, 3H, acetate methyl), 5.23 (multiplet, 2H, =CH\(_2\)) and 4.92 (multiplet, 1H, olefinic proton); mass spectrum, m/e (relative intensity), 262 (20.1, \( M^+ \)), 220 (100), 202 (68.8), 151 (70.7), 135 (65.0) and 109 (69.4).

Anal. Calcd. for C\(_{17}\)H\(_{26}\)O\(_2\): C, 77.81; H, 9.98. Found: C, 78.00; H, 10.11.

Cyclization of Dihydrocryptomerion Enol Acetate 95b (89)

To 1500 ml wet methylene chloride saturated with boron trifluoride gas was added a solution of 5.4g (0.02 mole) enol acetate 95b in 500 ml methylene chloride over a period of 30 minutes (reaction was vigorously stirred and a slow stream of boron trifluoride was maintained). After two hours stirring the reaction mixture was neutralized with saturated sodium bicarbonate, washed twice with water and dried over anhydrous sodium sulfate. Solvent removal afforded 4.4g crude product which was chromatographed over silica gel and distilled. G.l.c. analysis (column B, 155°) indicated that the distillate contained three main com-
ponents A, B and C with retention times of 3.8, 5.6 and 7.5 minutes respectively. Separation by preparative g.l.c. (column G, 240°) afforded pure samples of the three major components.

Component A (119a,b) (25-30%) exhibited the following spectral characteristics: infrared (neat), $\nu_{\text{max}}$ 1740 and 1410 cm$^{-1}$; n.m.r. (CCl$_4$), $\tau$ 9.19 (singlet, 3H, tertiary methyl), 9.10, 9.05, 9.00 and 8.94 (four singlets, 6H, diastereomeric tertiary methyls); mass spectrum, m/e (relative intensity), 220 (22.5), 105 (68.4), 77 (100), 69 (31.6), 53 (34.9) and 43 (34.6).

Component B (5%) showed the ensuing data: infrared (neat), $\nu_{\text{max}}$ 1715 and 1404 cm$^{-1}$, n.m.r. (CCl$_4$), $\tau$ 9.22 (doublet, broad, 3H, $J = 5$ Hz, secondary methyl), 9.07 (singlet, 3H, tertiary methyl), 9.03 (singlet, 3H, tertiary methyl) and 8.55 (broad singlet, 6 or 7 H, half peak with 7 Hz); mass spectrum, m/e (relative intensity), 220 (22.5), 111 (68.9), 110 (100), 109 (94.1), 69 (81.3) and 43 (67.3).

Component C (121) (40-45%) was identified by the following data: ultraviolet, $\lambda_{\text{max}}$ 237 nm (e 15,000); infrared (neat), $\nu_{\text{max}}$ 1670, 1625, 1210 and 880 cm$^{-1}$; n.m.r. (CCl$_4$), $\tau$ 9.03 (singlet, 6H, tertiary methyls), 8.93 (doublet, 3H, $J = 6.5$ Hz, secondary methyl) and 4.25 (singlet, 1H, olefinic proton); mass spectrum, m/e (relative intensity), 220 (64.6, M$^+$), 178 (59.8), 163 (66.6), 95 (93.5), 79 (58.0) and 41 (100).

Anal. Calcd. for C$_{15}$H$_{24}$O: C, 81.76; H, 10.98. Found: C, 81.85; H, 10.93.
Preparation of Dihydrocarvone Acetal 116a,b

(+)-Dihydrocarvone [120 g, 0.79 mole; (α)\text{D}^{29} +18.3 \text{ (CHCl}_3\text{)}] was refluxed with a mixture of 90.0 g (0.86 mole) 2,2-dimethyl-1,3-propanediol and 3.0 g oxalic acid in 150 ml benzene in a Dean-Stark apparatus for 4 days. G.1.c. analysis (column A, 160°) of the reaction mixture indicated 93% product and 7% starting material. Longer reaction time failed to significantly improve the yield of product. The reaction mixture was washed with saturated sodium bicarbonate and twice with saturated sodium chloride and dried over anhydrous sodium sulfate. Solvent removal and distillation afforded 155 g pure 116a,b (82%) and 22 g of a material containing starting ketone. Retreatment of the lower fraction and distillation provided 16 g 116a,b or an overall yield of 91%: bp 50° (0.025 mm); n\text{D}^{20} 1.4748; (α)\text{D}^{24} -9.4 (c 10.3, CHCl\text{3}); infrared (neat), ν\text{max} 3100, 1650, 1150, 1100 and 888 cm\textsuperscript{-1}.

Anal. Calcd. for C\textsubscript{15}H\textsubscript{25}O\textsubscript{2}: C, 75.58; H, 10.99. Found: C, 75.58; H, 11.15.

The n.m.r. of compound 116a,b was very complex and analysis by g.l.c. (column E, 100°) indicated two components of relative retention times 70 and 79 minutes in the ratio 3:1 respectively. Samples of each component were collected using the analysis conditions above. The component of retention time 70 minutes (greater than 90% pure by n.m.r. analysis) was assigned structure 116a: (α)\text{D}^{25} -20° (c 4.05, CHCl\text{3}); n.m.r. (CCl\text{4}) (100M Hz) τ 9.33 (singlet, 3H, tertiary methyl), 9.05 (multiplet, 3H, secondary methyl), 8.88 (singlet, 3H, tertiary methyl), 8.33 (multiplet, 3H, vinyl methyl), 7.32 (multiplet, 1H, major coupling J = 13 Hz), 6.79 (multiplet, 2H, major coupling J = 11 Hz,
acetal methylenes), 6.46 and 6.30 (two doublets, 2H, J = 11 Hz, acetal methylenes) and 5.38 (multiplet, 2H, -CH); mass spectrum, m/e (relative intensity) 238 (24.7, M\(^+\)), 155 (69.2), 95 (69.4), 69 (100), 56 (85.3), 55 (89.2), 43 (83.9), 41 (83.3).

The component of 79 minutes retention time \(116b\) (greater than 90% pure by n.m.r. analysis) exhibited the following: \((\alpha)^{25}_D + 23^\circ\) (c 0.90, CHCl\(_3\)); n.m.r. \((\text{CCl}_4)(100\text{M Hz})\) \(\tau 9.12\) (singlet, 3H, tertiary methyl), 9.10 (doublet, 3H, J = 7 Hz, secondary methyl), 9.09 (singlet, 3H, tertiary methyl), 8.31 (multiplet, 3H, vinyl methyl), 6.63 (multiplet, 4H, half peak width 4 Hz, acetal methylenes) and 5.37 (multiplet, 2H, =CH\(_2\)); mass spectrum, m/e (relative intensity), 238 (3.4, M\(^+\)), 181 (53.5), 155 (50.4), 69 (100), 55 (51.6) and 41 (67.5).

**Alternative Synthesis of Dihydrocryptomerion 75 (96)**

A solution of \(_n\)-butyllithium--TMEDA (tetramethylethylene-diamine) as the 1:1 complex was prepared by slow addition of 15 mls (0.1 mole) TMEDA to 43 mls (0.1 mole) of 2.35 molar \(_n\)-butyllithium in hexane with stirring under a dry nitrogen atmosphere. To the resultant yellow solution was added 19.5 g (0.082 mole) of the 2,2-dimethyl-1,3-dioxane of dihydrocarvone(\(116a,b\)) and the solution was stirred under nitrogen 18 hours. The deep red solution thus formed was cooled to -50° and treated slowly with 10.5 g (0.1 mole) 1-chloro-3-methyl-2-butene. After warming to room temperature, water was added cautiously and the mixture was extracted with ether and washed with 3N HCl. Removal of the acetal function (3N HCl/acetone) followed by distillation
afforded 5 g recovered dihydrocarvone (40%) and 9.5 g (88% based on consumed starting material) of dihydrocryptomerion, bp 100-103° (0.04 mm), which was identical (g.l.c., infrared, n.m.r.) to authentic dihydrocryptomerion 75 prepared from our previous route.

Preparation of Compounds 128a-e (90)

Dimsyl sodium (85) was prepared in the usual way (see preparation of 107) and the appropriate phosphonium salt was added at 0° followed by addition of keto acetal 109 at room temperature. The Wittig products were hydrolyzed with 6N HCl in acetone and enol acetylation was performed with isopropenylacetate and p-toluenesulfonic acid. Thus from 109 and ethyltriphenylphosphonium bromide was obtained after hydrolysis ketone 127a (67%): bp 54° (0.15 mm), infrared (neat), $\nu_{\text{max}}$ 1705 and 815 cm$^{-1}$; n.m.r. (CCl$_4$), $\tau$ 9.03 and 8.98 (two doublets, 3H, J = 6 Hz, secondary methyl), 8.37 (singlet, 6H, vinyl methyls) and 4.84 (multiplet, 1H, olefinic proton). Enol acetylation followed by separation of the isomers by preparative g.l.c. afforded enol acetate 128a: infrared (neat), $\nu_{\text{max}}$ 1750, 1705, 1210, 845 and 810 cm$^{-1}$; n.m.r. (CCl$_4$), $\tau$ 8.45 and 8.37 (broad, 6H, vinyl methyls) and 4.83 (multiplet, 1H, olefinic proton).

Condensation of 109 with trimethylphosphonoacetate in the presence of sodium hydride in dimethoxyethane followed by hydrolysis yielded keto ester 127b: infrared (neat), $\nu_{\text{max}}$ 1710, 1640, 1210 and 860 cm$^{-1}$; n.m.r. (CCl$_4$), $\tau$ 9.02 (doublet, 3H, J = 6 Hz, secondary methyl), 7.83 (multiplet, 3H, vinyl methyl), 6.33 (singlet, 3H, OCH$_3$) and 4.33
(multiplet, 1H, olefinic proton). Enol acetylation provided mainly enol acetate \textit{128a}: infrared (neat), $\nu_{\text{max}}$ 1750, 1720, 1640, 1210 and 860 cm$^{-1}$; n.m.r. (CCl$_4$), $\tau$ 8.47 (singlet, 3H, methyl on enol acetate double bond), 7.90 (singlet, 3H, acetate methyl), 7.82 (multiplet, 3H, vinyl methyl), 6.00 (singlet, 3H, OCH$_3$) and 4.28 (multiplet, 1H, olefinic proton).

Compound \textit{128c} was prepared by condensation of \textit{109} with the Wittig salt prepared by heating 4-chlorobutyric acid with triphenylphosphine (150°, 24 hours). A mixture of the salt and \textit{109} in 1:1 dimethylsulfoxide-tetrahydrofuran with excess sodium hydride was stirred 24 hours at room temperature under nitrogen. Careful acidification to pH 6 and extraction provided the crude acid which was esterified with diazomethane, hydrolyzed, and distilled affording \textit{172c}: bp 100° (0.06 mm); infrared (neat), $\nu_{\text{max}}$ 1735, 1705, 1200 and 850 cm$^{-1}$; n.m.r. (CCl$_4$), $\tau$ 9.03 (doublet, 3H, $J = 6$ Hz, secondary methyl), 8.33 (multiplet, 3H, vinyl methyl), 7.7 (multiplet, 3H, isomeric vinyl methyls), 6.40 (singlet, 3H, OCH$_3$) and 4.92 (multiplet, 1H, olefinic proton).

Enol acetylation followed by preparative g.l.c. provided \textit{128c}: infrared (neat), $\nu_{\text{max}}$ 1750, 1220 and 850 cm$^{-1}$; n.m.r. (CCl$_4$), $\tau$ 8.49 (singlet, 3H, methyl on enol acetate double bond), 8.37 (singlet, 3H, vinyl methyl), 7.93 (singlet, 3H, acetate methyl), 6.40 (singlet, 3H, OCH$_3$) and 4.97 (multiplet, 1H, olefinic proton).

Compound \textit{128d} was prepared by condensation of \textit{109} under the above stated Wittig conditions with (4-benzyloxybutyl)triphenyl-phosphonium iodide followed by the usual removal of the acetal function and enol acetylation. The Wittig, salt (166) was prepared starting from 1,4-butandiol which was reacted with one equivalent of sodium metal in
m-xylene at 120°, followed by one equivalent of benzyl chloride. Chlorination of the 4-benzyloxybutanol with thionyl chloride in the presence of dimethylaniline (167) followed by reaction with sodium iodide in acetone afforded 1-iodo-4-benzyloxybutane in good yield. Refluxing the iodide with triphenylphosphine in benzene yielded the desired salt. Compound 127d, the Wittig product after hydrolysis, exhibited the following data: infrared (neat), $\nu_{\text{max}}$ 3040, 1705, 1500, 1100, 740 and 700 cm$^{-1}$; n.m.r. (CCl$_4$), $\tau$ 9.08 (doublet, 3H, J = 6 Hz, secondary methyl), 8.38 (multiplet, 3H, vinyl methyl), 6.65 (triplet, 2H, J = 6 Hz, CH$_3$CH$_2$O-), 5.60 (singlet, 2H, benzyl methylenes), 4.92 (multiplet, 1H, olefinic proton) and 2.75 (singlet, 5H, -C$_6$H$_5$). Enol acetylation provided largely 128d: infrared (neat), $\nu_{\text{max}}$ 3040, 1750, 1710, 1500, 1210, 1100, 740 and 700 cm$^{-1}$.

Compound 128e was prepared starting from hydroxy acetal 136 whose preparation is described subsequently. Treatment of 136 with carbon tetra bromide and tri-n-octylphosphine in ether (92), followed by chromatography over silica afforded keto bromide 127e directly: infrared (neat), $\nu_{\text{max}}$ 1705 and 850 cm$^{-1}$; n.m.r. (CCl$_4$), $\tau$ 9.02 (doublet, 3H, J = 6 Hz, secondary methyl), 8.30 (singlet, 3H, vinyl methyl), 6.80 (multiplet, 2H, CH$_2$Br) and 4.90 (multiplet, 1H, olefinic proton). Enol acetylation and column chromatography afforded nearly pure 128e: infrared (neat), $\nu_{\text{max}}$ 1750, 1710, 1210 and 815 cm$^{-1}$; n.m.r. (CCl$_4$), $\tau$ 8.50 (singlet, 3H, methyl on enol acetate double bond), 8.35 (multiplet 3H, vinyl methyl), 7.95 (singlet, 3H, acetate methyl), 6.73 (multiplet, 2H, CH$_2$Br) and 4.90 (multiplet, 1H, olefinic proton).
Preparation of Methyl Homocamphors 129a,b (90)

Enol acetate 128a (250 mg, 1.2m mole) in 125 ml methylene chloride was added to wet methylene chloride (125 ml) presaturated with boron trifluoride gas and stirred 5 minutes followed by the usual work-up. Separation by preparative g.l.c. afforded two main components with ratio 5.3:1.0. The minor (and less volatile) component was apparently a mixture of double bond isomers of starting ketone 127a. The major component (a semi solid material) exhibited the following data: infrared (neat), $\nu_{\text{max}}$ 1740 and 1410 cm$^{-1}$; n.m.r. (CCl$_4$), $\tau$ 9.15 (singlet, 3H, tertiary methyls), 9.20 and 9.08 (two singlets, 3H, diastereomeric tertiary methyls); (C$_6$H$_6$) $\tau$ 9.44 and 9.39 (two singlets, 3H, diastereomeric tertiary methyls) and 9.10 (singlet, 3H, tertiary methyls).

Attempted Cyclization of Enol Acetates 128b-e

Enol acetates 128b-e were treated under the previously described cyclization conditions. Compound 128b slowly hydrolyzed to a mixture of keto ester 127b and the corresponding keto acid as judged by the infrared spectrum. Compound 128c was slowly hydrolyzed and isomerized to various double bond isomers of keto ester 127c as judged by g.l.c., ultraviolet, infrared and n.m.r. spectral analysis.

Compound 128d afforded a mixture of components as judged by g.l.c., thin layer chromatography (t.l.c.), and the infrared spectrum. Column chromatography over aluminum oxide afforded two main fractions.
(both complex mixtures) of which the less polar fraction was shown to have lost the benzyl protecting group (absence of absorption at 3040, 1500, 740 and 700 cm\(^{-1}\)).

Compound 128e yielded a product with an absorption at 1730 cm\(^{-1}\) in the infrared spectrum and no olefinic signals in the n.m.r. spectrum. However, the product darkened rapidly on standing and chromatography over silica gel failed to provide any identifiable product.

Preparation of 3-Iodopropan-1-ol 131

3-Chloropropan-1-ol (30.0 g, 0.317 mole) in 500 ml acetone was treated with sodium iodide (100 g, 0.667 mole) and the solution was refluxed in an atmosphere of nitrogen for 48 hours. Concentration followed by dilution of the residue with ether, washing first with a dilute solution of metabisulfite and then with water and drying over anhydrous sodium sulfate, yielded, after concentration, 57.6 g crude iodide. Distillation under reduced pressure provided 55.2 g (93\%) of the desired compound 131: bp 97-99° (15 mm); \(n_\text{D}^{25}\) 1.5520 [lit. bp 88° (4 mm); \(n_\text{D}^{20}\) 1.5585 (168)]; infrared (neat), \(v_{\text{max}}\) 3350 and 1040 cm\(^{-1}\); n.m.r. (CCl\(_4\)), \(\tau\) 7.93 (pentet, 2H, J = 6, -CH\(_2\)-), 6.67 (triplet, -2H, J = 6 Hz, -CH\(_2\)I), 6.29 (triplet, 2H, J = 6 Hz, -CH\(_2\)OH) and 5.97 (singlet, 1H, -CH\(_2\)OH).

Preparation of Phosphonium Salt 133

The hydroxyl function of 3-iodopropan-1-ol 131 was first
protected as the tetrahydropyranyl ether by treatment of 37.2 g (0.200 mole) of the iodide with 50 ml dihydropyran and one drop 12 N hydrochloric acid at room temperature overnight. Excess dihydropyran was removed under reduced pressure and the heat sensitive iodo ether was used without further purification. Triphenylphosphine (53.0 g, 0.202 mole) was dissolved in 200 ml sodium dried benzene and 20 ml were distilled. To this solution was added the crude iodide along with 50 ml dry benzene and 10 ml more benzene were distilled. Refluxing for 85 hours followed by cooling, filtering, washing with dry benzene, and suction drying provided the crude phosphonium salt. Vacuum drying in a desiccator over phosphorus pentoxide (8 hours, ca. 1 mm) yielded 98.2 g of 133 (92%), mp 162-164°.

Preparation of Acetal Alcohol 136

A solution of dimsyl sodium anion was prepared by washing 8.00 g (0.167 mole) sodium hydride (50% oil dispersion) twice with dry benzene and then heating with 50 ml dimethylsulfoxide in a dry nitrogen atmosphere (70° oil bath) until evolution of hydrogen ceased. Cooling the anion in an ice bath and adding 88.0 g (0.165 mole) of phosphonium salt 133 (in 150 ml warm dimethylsulfoxide) produced a deep red solution of the ylide phosphorane. After the ylide had stirred at room temperature 10 minutes, keto acetal 109 (25.0 g, 0.126 mole) was added and the mixture stirred 43 hours at room temperature. Work-up was effected by several extractions with petroleum ether washing each extract with dimethylsulfoxide and then water. The extracts were concentrated and
dried by sequential addition and evaporation of several portions of benzene. The crude product (ca. 50 g) exhibited peaks at 1160, 1080, and 835 cm$^{-1}$ in the infrared spectrum and no hydroxyl or carbonyl absorption. Without further purification selective removal of the tetrahydropranyl protecting group was performed by treating the crude Wittig product with 106 ml ethylene glycol, 1 g oxalic acid, and 200 ml benzene at reflux over the weekend in a Dean-Stark apparatus. The cooled reaction mixture was washed with saturated sodium bicarbonate solution and water and then concentrated. Distillation at reduced pressure provided 17.3 g (57%) of pure acetal alcohol 136. Retreatment of the involatile residue under the hydrolysis conditions above followed by distillation afforded 4.0 g more or a total of 70% of compound 136: bp 100-102° (0.02 mm); ($\alpha$) $^{24}_D +20.4^\circ$ (c 10.9, CHCl$_3$); infrared (neat), $\nu_{max}$ 3450, 1165, 1080 and 835 cm$^{-1}$; n.m.r. (CCl$_4$), $\tau$ 9.18 (doublet, 3H, J = 5.5 Hz, secondary methyl), 8.41 (doublet, 3H, J = 1.5 Hz, vinyl methyl), 7.00 (singlet, 1H, CH$_2$OH), 6.52 (triplet, 2H, J = 7 Hz, CH$_2$OH), 6.11 (singlet, 4H, -OCH$_2$CH$_2$O-), and 4.95 (triplet, broad, 1H, J = 7 Hz, olefinic proton); mass spectrum, m/e (relative intensity), 240 (65.3, M$^+$), 183 (100, 113 (100), 87 (72.6), 86 (62.1), and 41 (81.0).


Preparation of Acetal Chloride 137

A solution of acetal alcohol 136 (21.5 g, 0.0892 mole) in 150 ml carbontetrachloride (dried over calcium chloride) was treated dropwise with 37.0 g (0.0997 mole) tri-$n$-octylphosphine. The mildly
exothermic reaction was moderated during the addition with a cold water bath and rapid stirring. Stirring was continued 1 hour at room temperature after which the solvent was removed under reduced pressure. Distillation at oil pump pressure afforded 17.8 g (78%) of acetal chloride 137; bp 109-111° (0.02 mm); nD\(^{20}\) 1.4960; (α)D\(^{24}\) +17.8° (c 10.8, CHCl\(_3\)); infrared (neat), \(\nu_{max}\) 1168, 1090 and 835 cm\(^{-1}\) with no absorption for hydroxyl; n.m.r. (CCl\(_4\)), 9.18 (doublet, 3H, J = 5.5 Hz, secondary methyl), 8.38 (multiplet, 3H, vinyl methyl), 7.48 (multiplet, 2H, C=CH-CH\(_2\) ), 6.57 (triplet, 2H, J = 7 Hz, CH\(_2\)Cl), 6.10 (singlet, 2H, -OCH\(_2\)CH\(_2\)O-) and 4.92 (sextet, 1H, J = 7 and J = 1.5 Hz, olefinic proton); mass spectrum, m/e (relative intensity), 260 (25.7,M\(^+\)), 258 (63.2,M\(^+\)), 203 (86.2), 202 (54.0), 201 (100), 113 (76.4) and 86 (62.6).

Anal. Calcd. for C\(_{14}\)H\(_{23}\)O\(_2\)Cl: C, 64.98; H, 8.96; Cl, 13.70.
Found: C, 64.82; H, 8.83; Cl, 13.56.

Preparation of Keto Chloride 127f

Acetal chloride 137 (12.0 g, 0.463 mole), dissolved in 125 ml acetone, was treated with 50 drops 6N hydrochloric acid and stirred overnight. The reaction was quenched with 15 ml saturated bicarbonate and most of the volatile materials were removed on the rotary evaporator. The residue was washed with water and then retreated under the hydrolysis conditions above. Quenching with bicarbonate and concentration followed by aqueous washing and drying over anhydrous magnesium sulfate yielded 10.0 g crude produce from which was distilled 8.48 g (85%) keto chloride 127f; bp 80-85° (0.02 mm); infrared (neat), \(\nu_{max}\) 1710, 1660, 850 and
Preparation of Enol Acetate \textbf{128f}

Keto chloride \textbf{127f} (8.90 g, 0.414 mole) was treated with isopropenyl acetate (15 ml) and $p$-toluenesulphonic acid monohydrate (100 mg) for 48 hours under slow distillation conditions (head temperature 50-70°). The reaction mixture was cooled to room temperature, diluted with petroleum ether, washed with saturated bicarbonate and then water, and dried over anhydrous sodium sulfate. Solvent removal provided a crude mixture which was distilled at reduced pressure yielding 9.61 g (90%) of a mixture of isomeric enol acetates: $\text{bp}\ 89-92^\circ$ (0.02 mm); two main components by g.l.c. analysis (column A, 175°) in the ratio 5.5:1.0 for compounds \textbf{128f} and its isomer respectively (relative retention times 5.1 and 4.2 minutes respectively). A pure sample of compound \textbf{128f} was obtained by preparative g.l.c. (column G, 225°): infrared (neat), $\nu_{\text{max}}\ 1750, 1710, 1210$ and $850\ cm^{-1}$; n.m.r. (CCl$_4$), $\tau\ 8.50$ (singlet, 3H, methyl on enol acetate double bond), $8.34$ (doublet, 3H, $J = 1.5$ Hz, vinyl methyl), $7.95$ (singlet, 3H, acetate methyl), $6.58$ (triplet, 2H, $J = 7$ Hz, $-\text{CH}_2\text{Cl}$) and $4.87$ (multiplet, 1H, olefinic proton).
Preparation of Acetal Alcohol 158

To 135 ml (0.322 mole) n-butyllithium (2.38 molar in hexane) in a dry nitrogen atmosphere was added with cooling 48.0 ml (0.414 mole) tetramethylethylenediamine followed by 75.7 g (0.317 mole) dihydrocarvone acetal (2,2-dimethyl-1,3-dioxane)116a,b. The reaction was allowed to stand under a static atmosphere of nitrogen at room temperature 32 hours during which time a deep red color developed. The solution of anion was allowed to react with ethylene oxide by passing the gas in a carrier stream of nitrogen rapidly into the ice bath cooled solution until the red anion color disappeared. The addition of ethylene oxide required ca. 15 minutes and the resulting yellow solution was purged of remaining traces of ethylene oxide by continued bubbling of nitrogen accompanied by warming of the solution to 40°. Crushed ice was added carefully until all the initially formed inorganic precipitate redissolved. The organic phase was separated and washed twice with water and then neutralized by sequential adding and shaking with dilute sodium bisulfate until the aqueous phase tested neutral to pH test paper. All aqueous washes were re-extracted with petroleum ether and neutralized as above. After drying over anhydrous sodium sulfate the combined organic extracts were concentrated and distilled under reduced pressure to provide 35.2 g (48%) recovered starting material and 42.6 g (48%; 91% based on consumed starting material) of acetal alcohol 158 as a colorless viscous liquid:
bp 120° (0.02 mm); nD 1.4901; (α)D -16.5° (c 6.05 CHCl₃); infrared (neat); v max 3420, 1645, 1148, 1098 and 890 cm⁻¹; n.m.r. (CCl₄), 9.0 (multiplet, 9H, methyl signals), 8.22 (broad, 1H, CH₂OH), 6.5 (multiplet, 6H, methylenes adjacent oxygen) and 5.27 (singlet, 2H, =CH₂); mass spectrum, m/e (relative intensity), 282 (16.6, M⁺), 225 (41.9), 155 (73.2),
Preparation of Acetal Chloride 159

Acetal alcohol 158 (81.3 g, 0.288 mole) in solution with 50 ml spectral grade carbontetrachloride was treated with tri-n-octylphosphine (113 g, 0.305 mole) by careful addition with vigorous stirring and cooling of the exothermic reaction in an ice bath. When the addition was completed, the reaction was stirred 1 hour at room temperature and then the solvent was removed under reduced pressure. Distillation under reduced pressure provided the crude acetal chloride [distilled until temperature of distillate reached 165° (0.07 mm)] which was redistilled to afford 72.2 g (84%) acetal chloride 159: bp 110-112° (0.07 mm); n\textsubscript{D} 1.4910; (\alpha)\textsubscript{D} ^{25} -10.6° (c 10.7, CHCl\textsubscript{3}); infrared (neat), \nu\textsubscript{max} 1145, 1098 and 892 cm\textsuperscript{-1}; n.m.r. (CCl\textsubscript{4}), \tau 9.0 (multiplet, 9H, methyl signals), 6.5 (multiplet, 6H, CH\textsubscript{2}Cl and acetal methylenes), 5.21 (multiplet, 2H, =CH\textsubscript{2}); mass spectrum, m/e (relative intensity), 302 (9.4, M\textsuperscript{+}), 300 (26.0, M\textsuperscript{+}), 265 (43.1), 243 (69.9), 155 (100), 69 (60.2) and 55 (48.8).

Anal. Calcd. for C\textsubscript{17}H\textsubscript{29}O\textsubscript{2}Cl: C, 67.87; H, 9.72; Cl, 11.78. Found: C, 68.16; H, 9.72; Cl, 11.61.

Preparation of Keto Chloride 160

Chloro-acetal 159 (55.2 g, 0.184 mole) dissolved in 1400 ml
acetone was treated with 5 ml 6N hydrochloric acid at room temperature and allowed to stand 16 hours. The reaction was quenched by the addition of 50 ml saturated aqueous bicarbonate. Solvent was removed under reduced pressure and the residue was washed with water and saturated sodium chloride re-extracting each wash with ether and drying the combined organic layers over anhydrous sodium sulphate. Solvent removal afforded the crude chloride (51.7 g). Distillation under reduced pressure yielded (after a forrun of the 2,2-dimethyl-1,3-propanediol acetal of acetone) 36.0 g (91%) ketone chloride 160: bp 82° (0.03 mm Hg); (α)\textsubscript{D} +6.9° (c 2.31, CHCl\textsubscript{3}); n\textsubscript{D} 1.4946; ultraviolet, λ\textsubscript{max} 284 nm (ε 32); infrared (film), ν\textsubscript{max} 1710, 1645, 895 and 730 cm\textsuperscript{-1}; n.m.r. (CCl\textsubscript{4}), τ 9.05 and 8.98 (two doublets, 3H, J = 7 and 6 Hz respectively, secondary methyl), 6.08 (triplet, 2H, J = 6 Hz, CH\textsubscript{2}Cl) and 5.15 (multiplet, 2H, =CH\textsubscript{2}); mass spectrum, m/e (relative intensity), 216 (19.2, M\textsuperscript{+}), 214 (86.0, M\textsuperscript{+}), 137 (90.0), 109 (86.6), 95 (86.6), 81 (96.6), 68 (86.6) and 55 (100).

Anal. Calcd. for C\textsubscript{12}H\textsubscript{19}O Cl: C, 67.12; H, 8.92; Cl, 16.51.
Found: C, 67.05; H, 9.03; Cl, 16.32.

Preparation of Enol Acetate 161

Slow distillation of a mixture of 30.7 g (0.143 mole) of keto chloride 160, 76 ml isopropenyl acetate and 500 mg p-toluenesulphonic acid monohydrate 4 days with addition of more isopropenyl acetate as needed (head temperature maintained at 50-60°) effected total conversion of the ketone into enol acetate as judged by g.l.c. analysis. The reaction was cooled, diluted with petroleum ether and washed with
saturated sodium bicarbonate, water and saturated sodium chloride. After drying over anhydrous sodium sulfate, the solvent was removed and the residue was distilled under reduced pressure through a 12 cm Vigreux column affording quantitatively a mixture of chloro enol acetates 162 and 161 in the ratio 28:72 as judged by g.l.c. analysis (column A, 175°, retention times 4.2 and 5.2 minutes respectively). A fraction of pure enol acetate 161 could be obtained by collection of the final fraction (3-4 g) of the distillate followed by redistillation. Pure enol acetate 161 showed the following characteristics: bp 95° (0.03 mm); n\textsuperscript{20} D 1.4948; (\textalpha)\textsuperscript{25} D +56.2 (c 10.6, CHCl\textsubscript{3}); infrared (neat), \nu\textsubscript{max} 3100, 1745, 1710, 1645, 1210 and 895 cm\textsuperscript{-1}; n.m.r. (CCl\textsubscript{4}), \tau 8.50 (singlet, 3H, vinyl methyl), 7.93 (singlet, 3H, acetate methyl), 6.51 (triplet, 2H, J = 6 Hz) and 5.17 (multiplet, 2H, olefinic protons); mass spectrum, m/e (relative intensity), 258 (5.5, M\textsuperscript{+}), 256 (11.4, M\textsuperscript{+}), 211 (67.7), 132.5 (59.9), 104 (68.9) and 89 (100).

Anal. Calcd. for C\textsubscript{14}H\textsubscript{21}O\textsubscript{2}Cl: C, 65.49; H, 8.24; Cl, 13.81. Found: C, 65.37; H, 8.39; Cl, 13.55.

Cyclization of Enol Acetates 128f and 161

Cyclization conditions and results were identical for both enol acetates 128f and 161. The reaction was conveniently run on a 5 g scale as follows: a 2 liter three neck flask was fitted with two addition funnels (one 250 ml funnel and another smaller funnel), a gas inlet tube (extending nearly to the bottom of the flask) and a magnetic stirring device. A solution of 5.00 g (0.0195 mole) enol acetate in
1000 ml methylene chloride was added in 200 ml portions at 20 minute intervals (through the large addition funnel) to a vigorously stirred mixture of 800 ml methylene chloride and 2 ml water (mixture was pre-saturated with boron trifluoride gas and a moderate flow of the gas was maintained throughout addition process). Water was added in 2 ml portions 5 min immediately prior to each addition of enol acetate (small addition funnel; all additions made under 5 lbs nitrogen pressure). With additions complete the reaction was allowed to stir 2 hours. The reaction mixture was transferred to a 2 liter separatory funnel and a lower layer dark yellow in color was discarded. Shaking 5 minutes with 100 ml water produced a clear, colorless organic phase which was neutralized with dilute sodium bicarbonate, shaking until the aqueous phase tested neutral to pH test paper. Further washing with 100 ml water and 100 ml saturated sodium chloride followed by drying over anhydrous sodium sulfate and solvent removal afforded a nearly colorless oil (solvent recovered in this step could be used in next run without further purification with no diminution of yield). Filtration over 5 g of celite (petroleum ether) and solvent removal afforded 3.91-4.06 g (94-97% recovery) of a colorless oil. Analysis by g.l.c. (column A, 160°) indicated the presence of 55-60% bicyclic chloro ketones 163a,b and 35-40% chloro enone 164 (retention times 4.6 and 6.5 minutes respectively). Two minor components (retention times 3.1 and 3.6 minutes) were present to the extent of ca. 2% and 4% respectively.

The difficulty entailed in separating isomeric enol acetates 161 and 162 led to the use of the mixture of isomers in the cyclization step. Thus from 23.0 g enol acetates 161 and 162 (ratio 76:24 respec-
tively), treated in portions under the conditions described above, was obtained 18.4 g of colorless oil shown by g.l.c. analysis to consist of 43% bicyclic ketones \textit{163a,b} and 48% enone \textit{162}. Distillation twice under reduced pressure with refractionation of the higher and lower boiling fractions provided 6.68 g bicyclic chloro ketones \textit{163a,b} (46% based on enol acetate \textit{161}), 7.03 g enone \textit{164} and 800 mg of the minor volatile components previously mentioned.

Component \textit{163a,b}, bp 64-65° (0.03 mm), was greater than 95% pure by g.l.c. analysis (\textit{163a} and \textit{163b} did not resolve on columns A, B, C or D) containing less than 1% \textit{164} and ca. 4% of the more volatile minor components: (\textit{a}) $\lambda_{\text{max}}^{25} 0^\circ$ (c 10.0, CHCl$_3$); n$^{20} 1.4980$; ultraviolet, $\lambda_{\text{max}}$ 285 nm (\epsilon 44); infrared (neat), $\nu_{\text{max}}$ 1740 and 1410 cm$^{-1}$; n.m.r. (CCl$_4$), $\tau$ 9.11 (singlet, 3H, tertiary methyl), 9.16 and 9.03 (two singlets, 3H, diastereomeric tertiary methyls), 6.55 and 6.48 (two overlapping triplets, 2H, J = 6 Hz, CH$_2$Cl); (C$_6$H$_5$), $\tau$ 9.52 and 9.45 (two singlets, 3H, diastereomeric tertiary methyls), 9.12 (singlet, 3H, tertiary methyl), 7.04 and 6.92 (two overlapping triplets, 2H, J = 7 Hz, CH$_2$Cl); mass spectrum, m/e (relative intensity), 216 (33.6, \textit{M}^+), 214 (97.3, \textit{M}^+), 157 (92.6), 109 (100), 81 (93.3) and 69 (85.2).

Component \textit{164} exhibited the following characteristics:

bp 76° (0.05 mm); n$^{20} 1.5032$; (\textit{a}) $\lambda_{\text{max}}^{25} +0.2^\circ$ (c 10.0, CHCl$_3$); ultraviolet, $\lambda_{\text{max}}$ 234 (\epsilon 15,000), 339 (\epsilon 58); infrared (neat), $\nu_{\text{max}}$ 1670, 1210 and 883 cm$^{-1}$; n.m.r. (CCl$_4$), $\tau$ 8.91 (doublet, 3H, J = 6.5 Hz, secondary methyl), 8.87 (doublet, 3H, J = 6.5 Hz, secondary methyl), 6.52 (triplet, broad, 2H, J = 6 Hz, CH$_2$Cl) and 4.30 (singlet, 1H, olefinic proton); mass spectrum, m/e (relative intensity), 216 (33.0,
M⁺), 214 (73.5, M⁺), 172 (63.0), 137 (45.9), 109 (65.3), 96 (100) and 95 (67.0).

Anal. Calcd. for C₁₂H₁₉O Cl: C, 67.12; H, 8.92; Cl, 16.51.
Found: C, 67.40; H, 8.83; Cl, 16.31.

Samples of the two minor components retention times 3.1 and 4.6 minutes from the cyclization of 161 were isolated by preparative g.l.c. The component of retention times 3.1 minutes showed the following: ultraviolet, \( \lambda_{\text{max}} \) 299 (\( \epsilon \) 48), infrared (neat), \( \nu_{\text{max}} \) 1760 cm⁻¹; n.m.r. (CCl₄), 8.96 (singlet, 3H, tertiary methyl), 8.77 (singlet, 3H, tertiary methyl), 7.37 (singlet, 2H) and 6.54 (multiplet, 2H, CH₂Cl).

The minor component of retention time 4.6 minutes was characterized by the following data: infrared (neat), \( \nu_{\text{max}} \) 1760 cm⁻¹; n.m.r. (CCl₄), τ 8.96 (singlet, 3H, tertiary methyl), 8.78 (singlet, 3H, tertiary methyl), 7.51 and 7.37 (two singlets, 2H) and 6.53 (multiplet, 2H, CH₂Cl).

Alternative Enol Acetylation of Keto Chloride 161

Keto chloride 161 could be conveniently enol acetylated in 10 g quantities by the following procedure: a 10.0 g quantity of ketone dissolved in 100 ml anhydrous ethyl acetate was treated at room temperature for 5.5 minutes (vigorous stirring) with 500 ml of a reagent comprised of an ethyl acetate solution 1.06 M in acetic anhydride and 0.023 M in perchloric acid (prepared by adding 50.0 ml acetic anhydride and 1.0 ml 70% perchloric acid to 300 ml anhydrous ethyl acetate and making the volume up to 500 ml with anhydrous ethyl acetate). Solid sodium bicarbonate (10.0 g) was added to the auburn solution with vigorous stirring.
When the mixture had stirred 5 minutes producing a nearly colorless solution, the solvent was removed on a rotary evaporator (room temperature) and the excess acetic anhydride was removed with an oil pump (40°, 1 mm). The crude enol acetate was taken up in petroleum ether, washed with cold saturated sodium bicarbonate and dried over anhydrous sodium sulfate. When 70.0 g (0.326 mole) keto chloride 161 was treated as above in 10 g batches and the resulting product distilled there was obtained 49.6 g (59%) of enol acetates 161a and 162a, bp 94-96° (0.05 mm) and 21.8 g of material containing 31% ketone. Retreatment of the ketone containing fraction and distillation afforded a further 17.5 g enol acetate mixture or an overall yield of 80%. Analysis by g.l.c. (column A, 160°) indicated that enol acetates 161a and 162a (greater than 97% purity, ca. 2% ketone) were in the ratio 93:7 respectively. Analysis by n.m.r. demonstrated that isomerization of the terminal olefin had occurred to the extent of 45%. Treatment of this enol acetate mixture under the same cyclization conditions as described for 161 afforded bicyclic ketones 163a,b in 55 to 60% yield as judged by g.l.c. analysis (column A, 160°).

Preparation of Bicyclic Chloro Acetals 165a,b

Bicyclic chloro ketones 163a,b (6.50 g, 0.0303 mole) were treated with 17 ml ethylene glycol, 600 mg p-toluenesulfonic acid monohydrate and 30 ml benzene at reflux in a Dean-Stark apparatus for 4 days. The cooled reaction mixture was washed with saturated sodium bicarbonate, water, and saturated sodium chloride. After drying over anhydrous sodium sulfate, the solvent was removed and the residue distilled under reduced pressure yielding 7.43 g (95%) bicyclic chloro acetals 165a,b: bp 73° (0.04 mm); n^20_D 1.5010; (α)^25_D 0° (c 10.4, CHCl₃);
infrared (neat), $\nu_{\text{max}}$ 1120 and 1044 cm$^{-1}$; n.m.r. (CCl$_4$), $\tau$ 9.23 (singlet, 3H, tertiary methyl), 9.16 and 9.00 (singlets, 3H, diastereomeric tertiary methyls), 6.57 and 6.53 (overlapping triplets, 2H, $J = 6$ Hz, CH$_2$Cl) and 6.23 (multiplet, 4H, -OCH$_2$CH$_2$O-); mass spectrum, m/e (relative intensity), 260 (41.3, M$^+$), 258 55.5, M$^+$), 69 (79.2), 55 (93.0), 43 (100) and 42 (90.4).

Anal. Calcd. for C$_{14}$H$_{23}$O$_2$Cl: C, 64.97; H, 8.96; Cl, 13.70. Found: C, 65.03; H, 8.79; Cl, 13.50.

Preparation of Iodo Acetals 166a,b

Bicyclic chloro acetals 165a,b (5.15 g, 0.0199 mole), sodium iodide (7.50 g, 0.050 mole) and 700 mg anhydrous calcium carbonate in 10 ml dry acetone were refluxed in a dry nitrogen atmosphere 48 hours. After cooling, the reaction mixture was transferred under nitrogen into 100 ml dry pentane precipitating the inorganic materials. The solution was immediately filtered over 10 g of celite (oven dried, 100° overnight) eluting with another 100 ml of dry pentane. Distillation afforded 6.75 g (97%) iodo acetals 166a,b: bp 89-90° (0.02 mm); $n^\text{20}_D$ 1.5409; $\alpha^\text{25}_D$ 0° (c 2.09, CHCl$_3$); infrared (neat), $\nu_{\text{max}}$ 1116 and 1045 cm$^{-1}$; n.m.r. (CCl$_4$), $\tau$ 9.22 (singlet, 3H, tertiary methyl); 9.15 and 8.98 (two singlets, 3H, diastereomeric tertiary methyls); 6.84 (triplet, 2H, $J = 6$ Hz, CH$_2$I) and 6.20 (multiplet, 4H, -OCH$_2$CH$_2$O-); mass spectrum, m/e (relative intensity), 350 (10.0, M$^+$), 223 (81.8), 125 (34.7), 113 (30.6), 95 (100) and 87 (32.7).
Preparation of Campherenone and Epicampherenone Ethylene Acetals 168a and 168b

Triphenylphosphine (4.60 g, 0.0176 mole) was dissolved in 10 ml dry benzene and 2 ml of the benzene were slowly distilled to remove final traces of water. Acetal iodides 166a,b (6.00 g, 0.0171 mole) was added along with 2 ml more benzene and the solution was refluxed under nitrogen 38 hours. The solvent was removed and the salt, a viscous oil, was used without further purification. Dimsyl sodium was prepared as follows: sodium hydride (0.864 g, 50% oil dispersion, 0.018 mole) was washed twice with dry pentane and heated under nitrogen with 5 ml dry dimethylsulfoxide in a 65-75° bath until evolution of hydrogen ceased (ca. 45 minutes). The reaction mixture was chilled in an ice bath and the crude Wittig salt prepared above (dissolved in 5 ml dry dimethylsulfoxide) was added dropwise at a rate sufficient to prevent freezing of the dimethylsulfoxide from the reaction mixture. The deep red ylide solution was allowed to warm to room temperature and to stand 5 minutes after which time 1.50 ml (0.0203 mole) dry acetone was added. The reaction was allowed to stir over the weekend (70 hours) and then was extracted with three 70 ml portions of petroleum ether, washing each extract in turn with dimethylsulfoxide, water, and saturated brine. The combined colorless extracts were dried over anhydrous sodium sulphate and, after solvent removal

Anal. Calcd. for C_{14}H_{23}O_{2}I:  C, 48.05;  H, 6.61;  I, 36.26.  
Found:  C, 48.00;  H, 6.52;  I, 36.10.
under reduced pressure, the mixture of acetal alkenes was vacuum distilled yielding 3.83 g (84%) of a mixture of the acetals of campherenone and epicampherenone: bp 75-76° (0.03 mm Hg). Separation by preparative g.l.c. (column A, 240°) afforded two components of retention times 42 and 47 minutes which were further purified by evaporative distillation. The component of retention time 42 minutes, 168a, showed the following characteristics: n\textsuperscript{D} \(1.4956\); (α) \(\text{c 1.31, CHCl}_3\); infrared (neat), \(\nu_{\text{max}}\) 1120 and 1050 cm\(^{-1}\); n.m.r. (CCl\(_4\)), τ 9.23 (singlet, 3H, tertiary methyl), 9.13 (singlet, 3H, tertiary methyl), 8.40 and 8.33 (two singlets, 6H, vinyl methyls), 6.22 (multiplet, 4H, -OCH\(_2\)CH\(_2\)O-) and 4.90 (multiplet, 1H, olefinic proton); mass spectrum, m/e (relative intensity), 264 (59.7, M\(^+\)), 125 (100), 95 (81.6), 87 (61.4), 69 (75.7), and 41 (74.0).

Anal. Calcd. for C\(_{17}\)H\(_{28}\)O\(_2\): C, 77.22; H, 10.67. Found: C, 76.96; H, 10.63.

The component of retention time 47 minutes, 168b, exhibited the following: n\textsuperscript{D} \(1.4965\); (α) \(\text{c 1.03, CHCl}_3\); infrared (neat), \(\nu_{\text{max}}\) 1115 and 1045 cm\(^{-1}\); n.m.r. (CCl\(_4\)), τ 9.23 (singlet, 3H, tertiary methyl), 8.97 (singlet, 3H, tertiary methyl), 8.40 and 8.33 (two singlets, 6H, vinyl methyls), 6.22 (multiplet, 4H, -OCH\(_2\)CH\(_2\)O-) and 4.92 (multiplet, 1H, olefinic proton); mass spectrum, m/e (relative intensity), 264 (9.7, M\(^+\)), 109 (35.5), 95 (100), 69 (51.6), 55 (32.2) and 41 (64.5).

Anal. Calcd. for C\(_{17}\)H\(_{28}\)O\(_2\): C, 77.22; H, 10.67. Found: C, 76.99; H, 10.86.
Preparation of \((\pm)-\text{Campherenone 42}\)

Ethylene acetal \(168a\) (491 mg, 1.86 mmole) in 50 ml acetone was treated with 10 drops of 6N hydrochloric acid and allowed to stand 24 hours. Saturated sodium bicarbonate was added (ca. 2 ml) and the solvent was removed on a rotary evaporator. The residue was diluted with petroleum ether and washed with saturated sodium chloride. After drying over anhydrous sodium sulfate, the solvent was removed and the crude ketone distilled affording 404 mg (99%) \((\pm)-\text{campherenone 42}\). The purity of the campherenone at this stage was dependent on the care taken earlier in the fractionation of keto chlorides \(163a,b\) from the more volatile minor components of the cyclization mixtures (as these materials were carried through and isolated with the ketal \(168a\) during preparative g.l.c.). Typically, a small percentage of impurity was detectable by g.l.c. (column B, 175°) with retention time 2.0 minutes compared to 2.8 minutes for campherenone 42. A pure sample of campherenone obtained by preparative g.l.c. (column G, 220°) followed by evaporative distillation (60° oil bath, 0.05 mm), exhibited the following characteristics: \(n^\circ D 1.4888\); \((\alpha )^\circ D \) 0° (c 1.02, CHCl₃); infrared (neat), \(v_{\text{max}}\) 1738, 1415 and 830 cm\(^{-1}\); n.m.r. (CCl₄), \(\tau\) 9.14 (singlet, 3H, tertiary methyl), 9.03 (singlet, 3H, tertiary methyl), 8.39 and 8.35 (two broad overlapping signals, 6H, vinyl methyls) and 4.95 (multiplet, 1H, olefinic proton); \((C_6H_6)\), \(\tau\) 9.30 (singlet, 3H, tertiary methyl), 9.07 (singlet, 3H, tertiary methyl), 8.48 and 8.35 (two broad singlets, 6H, vinyl methyls) and 4.97 (multiplet, 1H, olefinic proton); mass spectrum, m/e (relative intensity) 220 (82.2, \(M^+\)), 135 (44.6), 109
(93.8), 95 (46.4), 81 (33.9), 69 (99.0), 55 (47.2), and 41 (100).

(162a,b,c, 27,28)

Anal. Calcd. for \( \text{C}_15\text{H}_{24}O \): C, 81.76; H, 10.98. Found: C, 82.00; H, 10.83.

Preparation of (±)-Epicampherenone 45

Removal of the acetal function of 168b (934 mg, 3.54 mmole) under identical conditions to those described for acetal 168a afforded after distillation 746 mg (96%) epicampherenone: bp (bath temperature) 69° (0.05 mm); \( n^25 \) D 1.4887; homogeneous by g.l.c. analysis (column B, 175°, retention time 2.8 minutes); \( \langle \alpha \rangle^20 \) D 0° (c 2.81, CHCl₃); infrared (neat), \( \nu_{\max} \) 1738, 1415 and 835 cm⁻¹; n.m.r. (CCl₄), \( \tau \) 9.13 (singlet, 6H, tertiary methyls), 8.38 and 8.32 (two broad signals, 6H, vinyl methyls) and 4.89 (multiplet, 1H, olefinic proton); (C₆H₆), \( \tau \) 9.35 (singlet, 3H, tertiary methyl), 9.06 (singlet, 3H, tertiary methyl), 8.41 and 8.28 (two broad singlets, 3H, vinyl methyls) and 4.83 (multiplet, 1H, olefinic proton); mass spectrum, m/e (relative intensity), 220 (46.4, \( M^+ \)), 135 (45.5), 109 (100), 95 (92.7), 81 (52.7), 69 (98.3), 67 (46.4) and 41 (87.3).

Anal. Calcd. for \( \text{C}_15\text{H}_{24}O \): C, 81.76; H, 10.98. Found: C, 82.00; H, 10.94.
Preparation of (±)-Camphenenol 46a (169)

Camphenenone 42 (35 mg, 0.16 mole) was dissolved in 12 ml n-propanol and sodium metal (0.6 g, excess) was added in small pieces. The mixture was refluxed 2 hours, the solvent was removed under reduced pressure and the residue was diluted with water and extracted with ether. The isolated product (a 7:1 mixture of camphenol and iso-camphenol) after drying and solvent removal (35 mg, >95%) exhibited the following data: infrared (neat), \( \nu_{\text{max}} \) cm\(^{-1} \) 3400 and 835 cm\(^{-1} \); n.m.r. (CCl\(_4\)), \( \tau \) 9.17 (singlet, 3H, tertiary methyl), 9.11 (singlet, 3H, tertiary methyl), 8.41 and 8.34 (two broad singlets, 6H, vinyl methyls), 6.46 (triplet) and 6.00 (broadened doublet, J = 10 Hz) (relative integral areas 1:7 respectively, -CHOH, largely endo alcohol) and 4.94 (multiplet, 1H, olefinic proton); (C\(_5\)H\(_5\)N), \( \tau \) 9.06 (singlet, 3H, tertiary methyl), 8.98 (singlet, 3H, tertiary methyl), 6.13 and 5.65 (relative integral areas 1:7 respectively, -CHOH). (162a,b; 27,28)

Preparation of (±)-Isocamphenenol 46b and (±)-β-Santalene 48 (169)

Camphenenone 42 (100 mg, 0.45 mole) was stirred overnight (under nitrogen atmosphere) with 4 equivalents of lithium trimethoxy-aluminoalumohydride (109) in tetrahydrofuran. Addition of water and extraction with ether followed by solvent removal and chromatography over 5 g of silica gel afforded 96 mg (95%) (±)-isocamphenenol: homogeneous by g.l.c. analysis (column A, 160\(^\circ\)); infrared (neat), \( \nu_{\text{max}} \) 3400 and 835 cm\(^{-1} \); n.m.r. (CCl\(_4\)), \( \tau \) 9.18 (singlet, 3H, tertiary methyl), 9.12 (singlet, 3H,
tertiary methyl), 8.39 and 8.36 (two doublets, 6H, J = 1.5 Hz and J = 2 Hz respectively, vinyl methyls), 6.46 (triplet, 1H, J = 6 Hz, -CHOH, exo alcohol) and 4.92 (multiplet, 1H, olefinic proton); (C₅H₅N), τ 9.10 (singlet, 3H, tertiary methyl), 8.88 (singlet, 3H, tertiary methyl) and 6.13 (multiplet, 1H, -CHOH).

Treatment of 45 mg (0.02 m mole) isocampherenol 46b with 100 mg p-toluenesulfonyl chloride in 4 ml dry pyridine at 95° for 22 hours effected smooth dehydration and rearrangement. β-Santalene was isolated by dilution with water and extraction with pentane, washing with 6 N hydrochloric acid, saturated sodium bicarbonate and water and drying over anhydrous sodium sulfate. Solvent removal and chromatography over silica gel, eluting with petroleum ether, afforded 32 mg (80%) β-santalene: homogeneous by g.l.c. analysis (column A, 110°) with identical retention time to authentic (-)-β-santalene (120) (relative retention times of β-santalene and epi-β-santalene at this temperature are 17 minutes and 16 minutes respectively); infrared (neat), \( \nu_{\text{max}} \) 3060, 1655, 878 and 830 cm\(^{-1}\); n.m.r. (CCl\(_4\)), τ 8.97 (singlet, 3H, tertiary methyl), 8.42 and 8.35 (two broadened singlets, 6H, vinyl methyls), 7.36 (singlet, broad, 1H, allylic methine), 5.57 and 5.31 (two singlets, 2H = CH\(_2\)) and 4.96 (multiplet, 1H, olefinic proton). (162a,b; 31)

Preparation by (±)-Epicampherenol 49a (169)

Epicampherenol was prepared from epicampherenone 45 in direct analogy to the preparation of campherenol 46a, using 0.7 g sodium metal in n-propanol to reduce 40 mg (0.18 m mole) of epicampherenone. Epi-
campherenol (as a 3:2 mixture with isoepicampherenol) exhibited the following: infrared (neat), Band max 3400 and 825 cm\(^{-1}\); n.m.r. (CCl\(_4\)), \(\tau\) 9.18 (singlet, 3H, tertiary methyl), 9.13 (singlet, 3H, tertiary methyl), 8.40 and 8.33 (two broadened singlets, 6H, vinyl methyls), 6.47 (triplet) and 6.06 (broadened doublet, \(J = 10\) Hz) (relative integral area 2:3 respectively, -CHOH, predominantly endo alcohol) and 4.92 (multiplet, 1H, olefinic proton); (C\(_5\)H\(_5\)N), \(\tau\) 9.07 (singlet, 3H, tertiary methyl), 8.97 (singlet, 3H, tertiary methyl), 6.18 and 5.73 (relative integral areas 2:3 respectively, -CHOH).

Preparation of (±)-Isoepicampherenol 49b and (±)-Epi-β-Santalene 50 (169)

The transformation of epicampherenone into 49b and 50 was performed in direct analogy to the similar transformations of campherenone 42 into 46b and 48. Thus reduction of epicampherenone with lithium trimethoxyaluminoxydride in tetrahydrofuran afforded isoepicampherenol 49b: homogeneous by g.l.c. analysis (column A, 175\(^{\circ}\)); infrared (neat), Band max 3440 and 838 cm\(^{-1}\); n.m.r. (CCl\(_4\)), \(\tau\) 9.12 (singlet, 3H, tertiary methyl), 8.96 (singlet, 3H, tertiary methyl), 8.39 and 8.33 (two broadened singlets, 6H, vinyl methyls), 6.47 (triplet, 1H, \(J = 5\) Hz, -CHOH, exo alcohol) and 4.93 (multiplet, 1H, olefinic proton); (C\(_5\)H\(_5\)N), \(\tau\) 8.88 (singlet, 3H, tertiary methyl), 8.65 (singlet, 3H, tertiary methyl) and 6.18 (triplet, 1H, \(J = 5\) Hz, -CHOH).

Treatment of isoepicampherenol 49b under the same conditions employed with isocampherenol 46b (p-toluenesulfonylchloride/pyridine/A) afforded (±)-epi-β-santalene: homogeneous with identical retention time
to authentic (+)-epi-β-santalene (120) by g.l.c. analysis (column A, 110°); infrared (neat), $\nu_{\text{max}}$ 3060, 1655, 878 and 835 cm$^{-1}$; n.m.r. (CCl$_4$), $\tau$ 9.00 (singlet, 3H, tertiary methyl), 8.40 and 8.35 (two broadened singlets, 6H, vinyl methyls), 7.35 (singlet, broad, 1H, allylic methine), 5.57 and 5.34 (two singlets, 2H, -CH$_2$) and 4.93 (multiplet, 1H, olefinic proton). (162a,b; 31)

**Preparation of (±)-α-Santalene 47 (169)**

A mixture (ca. 1:1) of campherenone 42 and epicampherenone 45 (35 mg, 0.16 mm mole) was refluxed in a solution of 60 mg of hydrazine 0.1 ml acetic acid and 2 ml absolute ethanol for 4 hours. The solvent was removed and the residue was diluted with water and extracted with ether, washing with saturated sodium bicarbonate and water and drying over anhydrous sodium sulfate. The crude hydrazone obtained after solvent removal was treated in 3 ml dry methanol with 100 mg of red mercuric oxide at reflux for 16 hours. The solution was filtered, rinsing the solid with pentane, and the filtrate was evaporated leaving the crude α-santalene which was diluted with pentane, washed with water and dried over anhydrous sodium sulfate. Solvent removal afforded 30 mgs of material which was 35% α-santalene and 65% starting material by g.l.c. analysis. Chromatography over silica gel afforded 10 mg (±)-α-santalene (31%) and 18 mg starting ketone (51%) or an overall yield of 64% α-santalene (based on consumed starting material): homogeneous by g.l.c. analysis (column A, 110°) with retention time identical to authentic (+)-α-santalene (120); infrared (neat), $\nu_{\text{max}}$ 3080,
855 and 840 cm⁻¹; n.m.r. (CCl₄), δ 9.17 (singlet, 3H, tertiary methyl), 8.99 (singlet, 3H, tertiary methyl), 8.41 and 8.34 (two broadened singlets, 6H, vinyl methyls) and 4.92 (multiplet, 3H, olefinic proton).

**Preparation of Campherenone Enol Acetate 51 (X = OAc)**

Campherenone 42 (120 mgs, 0.55m mole) in 2 mls dry tetrahydrofuran was treated at room temperature with 0.275 ml (0.65m mole) of n-butyllithium (2.38 M solution in hexane) 15 minutes. The enolate anion thus generated was cooled to -50° and treated with 0.107 ml (1.1m mole) acetic anhydride (freshly opened bottle). After 15 minutes the reaction was allowed to warm slowly to room temperature and after 15 minutes at room temperature the excess acetic anhydride was destroyed by stirring 15 minutes with saturated sodium bicarbonate. Dilution with petroleum ether and washing with water and saturated sodium chloride afforded, after drying and solvent removal, 148 mg of material (theoretical, 144 mg) which was 85% enol acetate 51 as judged by g.l.c. analysis (column A, 175°, retention time 3.4 minutes as compared to 2.8 minutes for campherenone 42): infrared (neat), ν_max 1755, 1205, 835 and 810 cm⁻¹; n.m.r. (CCl₄), δ 9.24 (singlet, 3H, tertiary methyl), 9.10 (singlet, 3H, tertiary methyl), 8.44 and 8.36 (two broadened singlets, 6H, vinyl methyls), 7.90 (singlet, 3H, acetate methyl), 7.57 (triplet, 1H, J = 1.5 Hz, allylic methine), 4.93 (multiplet, 1H, olefinic proton) and 4.85 (doublet, 1H, proton on enol acetate double bond).
Cyclization Attempts With Enol Acetate 51

Campherenone enol acetate 51 was treated under the previously stated optimum cyclization conditions (BF3/CH2Cl2/.1% enol acetate by volume). G.l.c. analysis (columns A, C, D; 160°) indicated only a very small percentage of volatile products. Peaks were present on all three g.l.c. traces which corresponded to authentic longicamphor 54 and copacamphor 52 (123,124). Analysis on column B (160°) however, failed to indicate similar correspondence. In view of the large percentage of involatile material encountered in this reaction (even when the reaction was performed at a concentration of 100 mg in 1500 mls) other means were sought to obtain cyclization of campherenone. [Other acids used to attempt this cyclization, e.g., stannic chloride, boron trifluoride etherate, perchloric acid, hydrochloric acid, silica gel or phosphate buffer (pH 7) led to partial or complete regeneration of starting ketone.]

Preparation and Cyclization of Campherenone Epoxides 173a,b

Campherenone 42 (500 mg, 2.27 m mole) in 5 ml dry benzene (cooled in ice bath) was treated with 480 mg (2.36 m mole) 85% m-chloroperbenzene acid in 15 ml dry benzene over a period of 1 hour and the reaction was stirred an additional 2 hours. The reaction mixture was washed with saturated sodium bicarbonate and just enough sodium bisulfite to give a negative starch-potassium iodide test for the aqueous bicarbonate phase. Washing with water and saturated sodium chloride
followed by drying (anhydrous sodium sulfate) and solvent removal yielded 508 mg (95%) of the mixture of epoxides \textit{173a,b} which was greater than 85% pure as judged by g.l.c. (column A, 160°): infrared (neat), \(\nu_{\text{max}}\) 1240, 870 and 800 cm\(^{-1}\). The crude epoxide (495 mg) was added directly to a solution of potassium t-butoxide [prepared by refluxing a mixture of 390 mg (10 m mole) potassium metal and 8 ml dry t-butoanol until all the metal had reacted] and refluxed 36 hours under a dry nitrogen atmosphere. The reaction mixture was poured into water and extracted with several portions of petroleum ether, washing with water and saturated sodium chloride. After drying over anhydrous sodium sulfate, solvent removal afforded 488 mg (99% recovery) of crude cyclic products \textit{(174 and 175)}. G.l.c. analysis indicated two main components in the approximate ratio 45:55 with retention times 5.4 and 6.6 minutes respectively (column A, 175°). Separation by preparative g.l.c. (column G, 230°) afforded pure samples of each component (retention times 53 and 60 minutes).

Alcohol \textit{174} (retention time 53 minutes) exhibited the following: infrared (CCl\(_4\)), \(\nu_{\text{max}}\) 3620 (weak), 3490 (strong), 1734 (weak) and 1728 cm\(^{-1}\) (strong)(relative strengths of bands at 3620 and 3490 cm\(^{-1}\) did not change upon dilution from 0.08 M to 0.01 M solutions); n.m.r. (CCl\(_4\)) (100 M Hz), \(\tau\) 9.10 (singlet, 3H, tertiary methyl), 9.08 (singlet, 3H, tertiary methyl), 8.95 and 8.94 (two overlapping singlets, 3H, O-C-CH\(_3\)), 8.76 (singlet, 3H, O-C-CH\(_3\)), 7.57 (singlet, broad, 1H, methine alpha to ketone) and 7.26 (broad, 1H, half peak width 12 Hz, -C-OH); mass spectrum, m/e (relative intensity), 236 (11.6, M\(^+\)), 178 (60.5), 163 (54.2), 95 (100), 51 (60.0) and 41 (81.5).
Mole. Wt. Calcd. for C$_{15}$H$_{24}$O$_{2}$: 236.1775. Found (high resolution mass spectrometry): 236.1782.

Alcohol 175 (retention time 60 minutes) showed data as follows: infrared (CCl$_{4}$), $\nu_{\max}$ 3620, 3440 and 1740 cm$^{-1}$ (dilution from 0.064 M to 0.01 M increased the intensity of the band at 3620 relative to the 3440 cm$^{-1}$ absorption); n.m.r. (CCl$_{4}$) (100 M Hz), $\tau$ 9.12 (singlet, 3H, tertiary methyl), 9.07 (singlet, 3H, tertiary methyl), 8.87 (singlet, broad, 3H, O-C-CH$_{3}$), 8.80 (singlet, broad, 3H, O-C-CH$_{3}$), 7.80 (singlet, broad, 1H, methine), 7.70 (doublet, broad, 1H, methine) and 7.43 (singlet, broad, 1H, half peak width 2 Hz, -C-OH); mass spectrum. m/e (relative intensity), 236 (13.6, M$^{+}$), 95 (52.9), 93 (39.9), 59 (100), 51 (35.6) and 41 (44.8).

Mole. Wt. Calcd. for C$_{15}$H$_{24}$O$_{2}$: 236.1775. Found (high resolution mass spectrometry): 236.1793.

Preparation of Alkenes 176 and 177

Alcohol 175 (44 mg, 0.19m mole) in 1 ml dry pyridine was treated with 0.050 ml thionyl chloride for 30 minutes. The mixture was diluted with petroleum ether and washed with water (three portions) and saturated sodium chloride and dried over anhydrous sodium sulfate. Solvent removal on a rotary evaporator and final removal of pyridine traces at 0.03 mm afforded 37 mg (91%) of a 7:3 mixture of keto alkenes 176 and 177 as judged by g.l.c. analysis (column B, 150$^o$, relative
times 9.0 and 11.5 minutes). Preparative g.l.c. (column B, 150°) afforded pure samples of each component.

Component 176 exhibited the following: infrared (neat), \( \nu_{\text{max}} \) 3100, 1740, 1650 and 890 cm\(^{-1}\); n.m.r. (CCl\(_4\)), \( \tau \) 9.12 (singlet, 3H, tertiary methyl), 9.08 (singlet, 3H, tertiary methyl), 8.27 (singlet, 3H, vinyl methyl) and 5.15 (multiplet, 2H, =CH\(_2\)); mass spectrum, m/e (relative intensity), 218 (51.5, M\(^+\)), 95 (99.5), 79 (48.6), 69 (60.6), 55 (48.1), 43 (89.4) and 41 (100).

Component 177 showed: infrared (neat), \( \nu_{\text{max}} \) 1740 cm\(^{-1}\); n.m.r. (CCl\(_4\)), \( \tau \) 9.07 (singlet, 6H, tertiary methyls), 8.37 and 8.28 (two singlets, 6H, vinyl methyls) and 7.06 (singlet, 1H, allylic methine).

Preparation of (±)-Copacamphor 52

Hydrogenation of 176 using platinum oxide as the source of catalyst with ethyl acetate-acetic acid (19:1) as solvent and an external sodium borohydride source of hydrogen afforded (±)-copacamphor. A sample purified by preparative g.l.c. (column H, 220°) followed by evaporative distillation exhibited the following data: \( n_D \) 1.4898; homogeneous by g.l.c. analysis with identical retention times (co-injection) to authentic (+)-copacamphor (123) on four columns (A, 150°; B, 150°, C, 150°, D, 175°); infrared (neat), \( \nu_{\text{max}} \) 1735 cm\(^{-1}\); n.m.r. (CDCl\(_3\)), \( \tau \) 9.11 (doublet, 3H, J = 6.5 Hz, secondary methyl), 9.10 (singlet, 3H, tertiary methyl), 9.09 (doublet, 3H, J = 6.5 Hz, secondary methyl), 9.06 (singlet, 3H, tertiary methyl) and 7.84 (multiplet, 1H, methine alpha to ketone); mass spectrum, m/e (relative
intensity), 220 (82.2, M⁺), 149 (36.6), 135 (40.5), 124 (100), 95 (55.5) and 41 (42.8).


Preparation of Keto Alkenes 178 and 177

Keto alcohol 174 (39 mg, 0.17 mmole) was dehydrated under analogous conditions to those employed for 175 (1 ml pyridine, 0.050 ml thionyl chloride, 30 minutes). Work-up provided 26 mgs (72%) of a 5:1 mixture of 178 and 177, relative retention times 9.0 and 11.5 minutes respectively (column B, 150°). Preparative g.l.c. (column B, 150°) provided pure samples of the two components and 177 exhibited identical characteristics (g.l.c., infrared, n.m.r.) to those of 177 isolated in the dehydration of alcohol 175.

Keto alkene 178 was characterized by the following data: infrared (neat), ν_max 3100, 1740, 1650 and 890 cm⁻¹; n.m.r. (CCl₄), τ 9.12 (singlet, 3H, tertiary methyl), 9.08 (singlet, 3H, tertiary methyl), 8.26 (singlet, 3H, vinyl methyl) and 5.23 (singlet, broad, 2H, =CH₂); mass spectrum, m/e (relative intensity), 218 (96.5, M⁺), 124 (40.0), 123 (49.4), 107 (47.1), 95 (100) and 55 (37.4).

Preparation of (+)-Ylangocamphor 53

Hydrogenation of keto alkene 178 under analogous conditions to those used in the preparation of copacamphor 52 afforded (+)-ylango-
camphor: $n^D_{25} = 1.4909$; homogeneous by g.l.c. analysis on four columns (A, 150°; B, 150°; C, 150°; D, 150°); infrared (neat), $v_{\text{max}} = 1730 \text{ cm}^{-1}$; n.m.r. (CDCl$_3$), $\tau = 9.20$ (doublet, 3H, J = 6.5 Hz, secondary methyl), 9.11 (singlet, 3H, tertiary methyl), 9.10 (singlet, 3H, tertiary methyl), 9.03 (doublet, 3H, J = 6.5 Hz, secondary methyl) and 7.77 (singlet, broad, 1H, methine alpha to ketone); mass spectrum, m/e (relative intensity), 220 (100, M$^+$), 124 (73.1), 110 (72.3), 95 (69.8), 93 (62.5) and 41 (78.0). (162a,b; 127)

Anal. Calcd. for C$_{15}$H$_{24}$O: C, 81.6; H, 10.98. Found: C, 81.90; H, 10.84.

Hydrogenation of Keto Alkene 177

Tetrasubstituted olefin 177 was hydrogenated in glacial acetic acid over platinum oxide as the source of catalyst (24 hours, atmospheric pressure) affording a 5:1 mixture of ylangocamphor 53 and copacamphor 52 as judged by g.l.c. analysis (column B, 150°, relative retention times 6.5 and 8.5 minutes respectively). Infrared and n.m.r. spectra were in accord with this assignment.

Isomerization of Alkenes 176 and 178 to 177

Treatment of either 176 or 178 (separate or as the mixture) for 1 hour (ethyl acetate as solvent) with palladium on carbon in the presence of hydrogen afforded one component by g.l.c. analysis (column B, 150°) with infrared and n.m.r. spectra identical to tetrasubstituted keto alkene 177.
Large Scale Preparation of Copacamphor 52 and Ylangocamphor 53

For large scale preparations of 52 and 53 it was found more convenient to employ a mixture of campherenone 42 and epicampherenone 45 as starting material. Epoxidation of 4.80 g of a 1:1 mixture of 42 and 45 as previously described followed by cyclization in potassium t-butoxide (prepared from 4 g potassium metal and 100 ml dry t-butanol) afforded 4.99 g crude product. Dehydration with thionyl chloride in pyridine followed by distillation afforded 2.03 g of mixed keto alkenes (epicampherenone epoxide yields an allylic alcohol, resulting from epoxide opening in the reaction medium, and this alcohol is easily removed in the distillation step). Hydrogenation over 700 mg platinum oxide (9:1 ethyl acetate-acetic acid) afforded quantitatively a mixture of copacamphor and ylangocamphor (ca. 84% overall based on campherenone) in the approximate ratio 45:55 respectively. Preparative g.l.c. (column H, 220°) followed by evaporative distillation afforded pure copacamphor 52 and ylangocamphor 53.

Preparation of (±)-Sativene 60

Ylangocamphor 45 (200 mg, 0.91m mole) was treated with 35 mg (0.92 mole) lithium aluminum hydride in dry tetrahydrofuran overnight. Careful addition of water followed by ether extraction (washing with water and saturated sodium chloride), drying (anhydrous sodium sulfate) and solvent removal afforded the crude alcohol which was chromatographed over 5 g silica gel yielding 180 mgs (89%) an oil which crystal-
lized on standing overnight, mp 41-42°. The solubility of compound 58b (isoylangoborneol) made recrystallization very difficult: infrared (neat), \( \nu_{\text{max}} \) 3500 and 1095 cm\(^{-1}\); n.m.r. (CCl\(_4\)), \( \tau \) 9.21 (singlet, 3H, tertiary methyl), 9.16 (singlet, 3H, tertiary methyl), 9.08 (doublet, 1H, \( J = 7.5 \) Hz, -CHOH, exo alcohol); (C\(_5\)H\(_5\)N), \( \tau \) 9.13 (singlet, 3H, tertiary methyl), 8.94 (singlet, 3H, tertiary methyl), 8.94 (doublet, 6H, secondary methyls) and 5.97 (multiplet, 1H, -CHOH).

Treatment of 150 mg (0.68m mole) of 58b with 0.10 ml (1.3m mole) methanesulfonylchloride in 1 ml dry pyridine (105°) overnight followed by the usual work-up (see preparation of (±)-β-santalene) afforded after column chromatography, 73 mg (53%) (±)-sativene 60. Distillation provided 60 mg pure compound: bp (bath temperature) 60° (1 mm); infrared (neat), \( \nu_{\text{max}} \) 3080, 1660 and 875 cm\(^{-1}\); n.m.r. (CCl\(_4\)), \( \tau \) 9.15 (doublet, 3H, \( J = 3.5 \) Hz, secondary methyl), 9.09 (doublet, 3H, \( J = 3.5 \) Hz, secondary methyl), 8.98 (singlet, 3H, tertiary methyl), 7.40 (singlet, broad, 1H, allylic methine), 5.59 and 5.27 (two singlets, 2H, -CH\(_2\)); mass spectrum, m/e (relative intensity), 204 (52.3, M\(^+\)), 161 (57.5), 108 (100), 105 (41.8), 91 (43.8), and 41 (44.4). (160a,b; 36)

Preparation of Acetal 182

A solution of 25.0 g (0.167 mole) (−)-carvone [(\( \alpha \))\(^{30} \)D -58.6° (c 4.78, CHCl\(_3\))], 20 g 2,2-dimethyl-1,3-dioxane and 250 mg oxalic acid in 350 ml benzene was refluxed 5 days in a Dean-Stark apparatus with molecular seives added to the side arm trap to aid in water removal.
G.l.c. analysis (column A, 160°) indicated roughly 30% conversion to acetal and the ratio of product to starting material did not change significantly with longer reaction time. The cooled reaction mixture was washed with saturated sodium bicarbonate and saturated sodium chloride and dried over anhydrous sodium sulfate. Solvent removal followed by solution in dry pentane and storage at -10° afforded four batches of crystals totalling 12.8 g (32%, mp 80.5-82.5°). From the mother liquor was obtained a near quantitative recovery of carvone and ketal by distillation of the carvone (16.5 g, 66%; bp 48°, 0.3 mm) and recrystallization of the residue. A recrystallized sample of the acetal 182 gave the following data: mp 82-82.5°; (α)°D -71.8° (c 10.26, CHCl₃); infrared (mull), νmax 3100, 1650, 1125, 1105, 1070 and 890 cm⁻¹; n.m.r. (CCl₄, τ 9.25 (singlet, 3H, tertiary methyl), 8.77 (singlet, 3H, tertiary methyl), 8.23 (multiplet, 3H, vinyl methyl), 7.67 (multiplet, 1H, major coupling J = 12 Hz, methine), 6.75 (multiplet, 2H, major coupling J = 11.5 Hz, acetal methylenes), 6.32 (quartet, 2H, J = 11.5 Hz and J = 3.5 Hz) acetal methylenes), 5.28 (singlet, broad, 2H, =CH₂) and 4.52 (multiplet, 1H, olefinic proton); mass spectrum, m/e (relative intensity), 236 (4.4, M⁺), 168 (100), 109 (18.9), 82 (76.3), 69 (35.4) and 41 (25.8).


Preparation of (-)-Cryptomerion 99a

(-)-Carvone acetal 182 (6.00 g, 0.0254 mole) in 20 ml dry
pentane was treated at 0° with 22 ml (0.052 mole) n-butyllithium (2.38 M in hexane) followed by 7.7 ml (6.0 g, 0.051 mole) TMEDA (dried over molecular seives) and the reaction stood overnight in a dry nitrogen atmosphere. The solvent was pumped off from the dark red residue which had formed and, after an atmosphere of dry nitrogen had been restored, 20 ml of dry tetrahydrofuran was added with rapid swirling to effect solution. Immediately upon solution the reaction mixture was cooled to -70° and 3.0 ml (2.8 g, 0.027 mole) 1-chloro-3-methyl-2-butene was added dropwise. Slow warming to room temperature and the usual work-up (see preparation of 117) followed by hydrolysis (150 ml acetone, 1 ml 6N hydrochloric acid) and distillation afforded 1.20 g (32%) recovered (-)-carvone, (α)\textsuperscript{31}D = -58.2° (c 5.43, CHCl\textsubscript{3}), followed by 728 mg of two monoalkylated products (91% pure by g.l.c. analysis, therefore 19% yield of monoalkylated material based on consumed carvone acetal). The two products were in the ratio 1:4 by g.l.c. analysis (column A, 175°, retention times 4.5 and 5.4 minutes respectively). Pure samples were isolated by preparative g.l.c. (column G, 240°) followed by evaporative distillation.

The minor product 183 exhibited the following: ultraviolet, \( \lambda_{\text{max}} \) 234 nm (c 7230); infrared (neat), \( \nu_{\text{max}} \) 3100, 1675, 892 and 830 cm\(^{-1}\); n.m.r. (CCl\textsubscript{4}), \( \tau \) 8.42 and 8.40 (two singlets, broad 6H, vinyl methyls), 8.23 (multiplet, 3H, vinyl methyl), 5.23 (multiplet, 2H, =CH\textsubscript{2}), 4.98 (multiplet, 1H, olefinic proton), and 3.43 (multiplet, 1H, olefinic proton).

The major component, retention time 5.4 minutes, was identified as (-)-cryptomerion 99a on the basis of the following evidence:
n_D 1.5058; (α)_D 29 -39.3° (c 1.45, CHCl_3); ultraviolet (EtOH), λ_max 235 and 317 nm (ε 8800 and 43) [lit. n_D 1.5050; (α)_D -38° (c 1.45 chloroform)]; λ_max (EtOH), 236 and 304 nm (ε 9600 and 110)(75)]; infrared (neat), ν_max 3100, 1680, 1645, 897 and 825 cm^{-1}; n.m.r. (CCl_4), τ 8.38 (singlet, 3H, vinyl methyl), 8.30 (multiplet, 6H, vinyl methyls), 5.18 (singlet, 2H, =CH_2), 4.93 (multiplet, 1H, olefinic proton) and 3.38 (multiplet, 1H, olefinic proton); mass spectrum, m/e (relative intensity), 218 (10.9, M^+), 148 (33.2), 135 (27.6), 109 (49.5), 69 (100) and 41 (85.2). (162a,b; 75)

Anal. Calcd. for C_{15}H_{22}O: C, 82.51; H, 10.16. Found: C, 82.77; H, 10.07.

Alternative Preparation of (-)-Cryptomerion 99a (169)

To 250 mg (1.1m mole) dihydrocryptomerion 75a (prepared by alkylation of dihydrocarvone acetal 116a,b) in 6 ml tetrahydrofuran was added 600 mg phenyltrimethylammonium tribromide (134). Reaction appeared instantaneous as judged by the disappearance of color from the reagent. Saturated sodium bicarbonate was added and stirred 10 minutes after which time the crude bromo ketone was recovered by ether extraction, washing with saturated sodium chloride and drying over anhydrous sodium sulfate. After solvent removal, the crude product was dissolved in 5 ml pyridine and refluxed 40 minutes. The cooled reaction mixture was extracted with ether, washing with dilute hydrochloric acid, saturated sodium bicarbonate and water. After drying (anhydrous sodium sulfate) and solvent removal, chromatography
over silica gel provided 180 mg (72%) of (-)-cryptomerion 99a. A distilled sample exhibited specific rotation \([\alpha]_D^{29} -37^\circ (c 2.65, \text{CHCl}_3)\] and spectral data (infrared, n.m.r.) in agreement with (-)-cryptomerion obtained by alkylation of carvone acetal 182.

**Photolysis of (-)-Cryptomerion 99a**

(-)-Cryptomerion 99a (250 mg, 1.10m mole) in 250 ml 95% ethanol (degassed with nitrogen) was photolyzed in a pyrex vessel 74 hours with the radiation from a Westinghouse 275 Watt sun lamp passed through a 20 mm Corning No. 7380 filter (transmittance approaches zero at wavelengths shorter than 340 nm). Essentially one product was formed in the photolysis. The ratio of starting material to photoproduct was tested at intervals by g.l.c. as indicated below (column A, 175°, retention times 3.9 and 5.4 minutes for photoproduct and starting material respectively).

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>% Starting Material</th>
<th>% Product</th>
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<tbody>
<tr>
<td>11</td>
<td>93</td>
<td>7</td>
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<tr>
<td>31</td>
<td>68</td>
<td>32</td>
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<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>74</td>
<td>27</td>
<td>73</td>
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</tbody>
</table>

Longer periods of irradiation failed to improve the ratio of photoproduct to starting material. Preparative g.l.c. (column G, 240°) allowed recovery of starting material which was identical (infrared spectrum, g.l.c. retention time) with our synthetic (-)-cryptomerion.
Attempts to isolate the photolysis product under identical g.l.c. conditions led to degradation as indicated by the appearance of a new product (30%) in the analytical g.l.c. trace of the isolated photoproduct (column A, 175°, retention time 4.5 minutes). Column chromatography of the photolysis mixture over silica gel and over aluminum oxide allowed isolation of a pure sample of the photoproduct, photocryptomerion \textit{189}: \((\alpha)_{D}^{28} -41^\circ\) (c 1.5, CHCl\textsubscript{3}); ultraviolet, absence of strong absorbance in the 235 nm region; infrared (neat), \(v_{\text{max}}\) 1735, 1410 and 835 cm\(^{-1}\); n.m.r. (CCl\textsubscript{4}), \(\tau\) 8.93 (singlet, 3H, tertiary methyl), 8.40 and 8.32 (two singlets, broad, 6H, vinyl methyls) and 4.96 (multiplet, 1H, olefinic proton); mass spectrum, \(m/e\) (relative intensity), 218 (53.6, \(M^+\)), 151 (42.5), 110 (42.2), 108 (41.1), 92 (42.8) and 70 (100).

Mole. Wt. Calcd. for \(C_{15}H_{22}O\): 218.1670. Found (high resolution mass spectrometry): 218.1662.

\textbf{Formolysis of Natural \(-\), \(\beta\)-, and Epi-\(\beta\)-Santalene}

A mixture of the naturally occurring santalenes (3.10 g; in the relative ratio 4.3:1.0:3.0 for \(-\), \(\beta\)- and epi-\(\beta\)-santalene respectively) in 10 ml formic acid (> 98%) was stirred at 50° for 44 hours. Work-up (washing twice with saturated sodium chloride, saturated bicarbonate, and again with saturated sodium chloride followed by drying over anhydrous sodium sulfate and solvent removal) and subsequent distillation afforded one major product in good yield (71% by g.l.c.) which showed the following: infrared (neat), \(v_{\text{max}}\) 797 cm\(^{-1}\);
n.m.r. (CCl₄), δ 9.05 (singlet, 6H, tertiary methyls). 8.96 (doublet, 6H, J = 7 Hz, secondary methyls), 7.97 (doublet, 2H, J = 2 Hz, allylic methylenes) and 4.68 (triplet, 1H, J = 2 Hz, olefinic proton).

Preparation of (+)-3,9-Dibromocamphor 204

Following the procedure of Corey et al. (45), 120 ml chlorosulfonic acid, cooled in an ice bath, was treated with 36 ml (112 g, 0.70 mole) bromine followed by 150 g (0.65 mole) of (+)-3-bromocamphor [[(α) D] +134° (c 14.6, CHC₁₃)] in one portion. After approximately 1 hour stirring, the exothermic reaction required cooling with a water bath to moderate the reaction temperature. Rapid evolution of hydrogen bromide was observed throughout the reaction. After 4 hours the reaction mixture was poured into 500 cc crushed ice and additional ice was added with stirring until the product became granular. Excess bromine was destroyed with sodium bisulfite and the product was filtered and washed (500 ml water, 200 ml 5% sodium hydroxide and 400 ml water). After pressing dry, the crude product was dissolved in methylene chloride and dried over anhydrous sodium sulfate. The solution was diluted with methanol and the solvent removed under vacuum until crystals formed. The solution was allowed to stand at 25° and than at 0°. Filtration afforded 107 g (53%) mp 151-155° (majority melting 145-156°) [lit. mp 152-156° (45)]. Concentration of the mother liquor yielded another 54 g which was difficult to purify through further recrystallizations. A sample of the initial crop of crystals was recrystallized from methanol and exhibited the following characteristics: mp 156-158.5°, (α) D +136°
(c 10.01, CHCl₃)[lit. (α) D + 98.8° (c 4.0, CHCl₃)(170)]; ultraviolet, λ_max 306 nm (ε 230); infrared (KBr), ν_max 1745 cm⁻¹, n.m.r. (CDCl₃), τ 8.95 (singlet, 3H, tertiary methyl), 8.89 (doublet, 3H, J = 1.5 Hz, tertiary methyl), 6.34 (doublet of multiplets) and 6.71 (doublet) (ABX pattern, 2H, J_AB = 10 Hz, J_AX = 1.5 Hz, J_BX = 0 Hz, CH₂Br) and 5.42 (doublet, 1H, J = 5 Hz, -CHBr); mass spectrum, m/e (relative intensity), 312 (15.7, M⁺), 310 (29.5, M⁺), 308 (16.9, M⁺), 232 (65.6), 230 (66.2), 204 (62.6), 202 (66.9), 122 (84.4), 81 (81.4), 69 (73.5) and 41 (100). (162a,b; 144)

Preparation of (+)-9-Bromocamphor 205

Reduction of (+)-3,9-dibromocamphor was achieved as previously described (45) by treatment of a vigorously stirred solution of 100 g (0.322 mole) of the dibromide in 400 ml methylene chloride with 70 g (1.1 mole) zinc powder and a slow stream of hydrogen bromide bubbled into the reaction mixture. After 4 hours the mixture was filtered, washed with water, saturated sodium bicarbonate and saturated sodium chloride, and dried over anhydrous sodium sulfate. Removal of solvent and recrystallization from petroleum ether afforded 63.5 g (85%) of (+)-9-bromocamphor, mp 93-94.5°. One further recrystallization provided a pure sample: mp 95-95.5° (α) D + 110° (c 0.934, absolute ethanol); ultraviolet, λ_max 290 nm (ε 64) [lit. mp 93-95° (45); (α) D +109° (c 0.93, 95% ethanol)(144); infrared (KBr), ν_max 1740 and 1418 cm⁻¹; n.m.r. (CDCl₃), τ 9.02 (singlet, 3H, tertiary methyl), 8.99 (doublet, 3H, J = 1 Hz, tertiary methyl),
6.76 (doublet) and 6.41 (doublet of multiplets) (ABX pattern, 2H, \( J_{AB} = 10 \text{ Hz} \), \( J_{AX} = 1 \text{ Hz} \), \( J_{BX} = 0 \text{ Hz} \), \( \text{CH}_2\text{Br} \)); mass spectrum, m/e (relative intensity), 232 (17.5, \( \text{M}^+ \)), 230 (17.5, \( \text{M}^+ \)), 109 (53.7), 108 (57.0), 107 (75.9), 81 (100) and 41 (53.2). (162a,b; 144)

Preparation of 9-Bromocamphor Ethylene Acetal 206

(+)-9-Bromocamphor (5.00 g, 0.0216 mol) in benzene was treated with 8 ml ethylene glycol and 500 mg \( p \)-toluenesulfonic acid at reflux in a Dean-Stark water separator for 36 hours. The reaction mixture was cooled, washed with saturated sodium bicarbonate and saturated sodium chloride and dried over anhydrous sodium sulfate. Solvent removal followed by vacuum distillation afforded, after a forerun of 740 mg of the acetal containing trace of ketone, 4.68 g (79%) 206:
bp 64-65° (0.06 mm); \( n^\circ_{25} 1.5208; (\alpha)^{24}_D +1.2 \) (c 7.46, \( \text{CHCl}_3 \)); infrared (neat), \( \nu_{\max} 1120 \text{ cm}^{-1} \); n.m.r. (CCl\(_4\)), \( \tau 9.20 \) (singlet, 3H, tertiary methyl), 8.83 (doublet, 3H, \( J = 1.5 \text{ Hz} \), tertiary methyl), 6.90 (doublet) and 6.47 (doublet of quartets) (ABX pattern, 2H, \( J_{AB} = 10.5 \text{ Hz} \), \( J_{AX} = 1.5 \text{ Hz} \), \( J_{BX} = 0 \text{ Hz} \), \( \text{CH}_2\text{Br} \)) and 6.20 (multiplet, 4H, -OHCH\(_2\)CH\(_2\)O-); mass spectrum, m/e (relative intensity), 276 (1.3, \( \text{M}^+ \)), 274 (1.3, \( \text{M}^+ \)), 195 (100), 109 (44.2), 95 (37.7), 87 (56.8) and 41 (21.4). (162b; 142)

Preparation of 9-Iodocamphor Ethylene Acetal 201

A solution of bromo acetal 206 (4.40 g, 0.016 mole) in 40 ml dry dimethylsulfoxide was treated with 15 g (0.10 mole) sodium iodide
(dried over phosphorus pentoxide, 1mm, 24 hours) in the presence of 5 g anhydrous calcium carbonate at 110° for three days (dry nitrogen atmosphere). The cooled reaction mixture was diluted with sodium bicarbonate solution and extracted with three 100 ml portions of petroleum ether, washing each with saturated sodium bicarbonate and saturated sodium chloride and drying over anhydrous sodium sulfate. Analysis by g.l.c. indicated two components in the approximate ratio 1:4 (column A, 175°, retention times 4.2 and 6.3 minutes respectively) corresponding to starting material and iodo acetal 201. Distillation twice afforded 1.48 g mixed starting material and 201 followed by 2.83 g (55%) acetal 201 or an overall yield of greater than 83%. Pure iodo acetal 201 was characterized as follows: bp 75° (0.05 mm); n\textsuperscript{D} 1.5502; (α)\textsuperscript{D} -2.2° (c 5.00, CHCl\textsubscript{3}); infrared (neat), ν\textsubscript{max} 1120 cm\textsuperscript{-1}; n.m.r. (CCl\textsubscript{4}), τ 9.19 (singlet, 3H, tertiary methyl), 8.85 (doublet, 3H, J = 1.5 Hz, tertiary methyl), 7.08 (doublet) and 6.62 (doublet of quartets)(ABX pattern, 2H, J\textsubscript{AB} = 9.5 Hz, J\textsubscript{AX} = 1.5 Hz, J\textsubscript{BX} = 0 Hz, -CH\textsubscript{2}I) and 6.11 (multiplet, 4H, -OCH\textsubscript{2}CH\textsubscript{2}0-); mass spectrum, m/e (relative intensity), 195 (85.0, M\textsuperscript{+}-I), 109 (100), 87 (95.9), 67 (78.1) and 41 (90.4).

Anal. Calcd. for C\textsubscript{12}H\textsubscript{19}O\textsubscript{2}I: C, 44.73; H, 5.94; I, 39.39. Found: C, 44.90; H, 6.03; I, 39.21.

Preparation of (+)-Epicamphorenone 45a

To 20 ml dry benzene was added 6 ml (7.9 g, 45m mole) nickel carbonyl (fume hood)(171) and 3 ml (3.8 g, 25m mole) 1-bromo-3-methyl-2-butene and the reaction was stirred 2.5 hours at 50° under an atmos-
phere of dry nitrogen. Solvent was removed under vacuum and 20 ml of dry dimethylformamide was added. When all the red-brown solid was dissolved, 1.50 g (4.7 m mole) acetal iodide in 5 ml dry dimethylformamide was added and the reaction stirred 14 hours at 55-60° (nitrogen atmosphere). G.l.c. analysis of an aliquot indicated only partial reaction and thus more of the nickel complex (prepared externally from 12.5 m mole of 1-bromo-3-methyl-2-butene) was added and the reaction continued 48 hours at 55-60°. The reaction mixture was poured into dimethylsulfoxide and extracted with several portions of petroleum ether, washing with water and saturated sodium chloride and drying (anhydrous sodium sulfate). Solvent removal and distillation followed by column chromatography over silica gel afforded 468 mg of material which was largely epicampherenone (before chromatography epicampherenone and epicampherenone acetal were present in the ratio of 3:7). Estimated yield of coupled product was ca. 40-45%. Pure (+)-epicampherenone, obtained by preparative g.l.c. (column G, 240°), followed by evaporative distillation, exhibited the following: \( [\alpha]_D^{27} +84.4^{\circ} \) (c 4.88, CHCl₃); \( [\alpha]_{203}^{\text{max}} -2.2 \times 10^4 \) (c 0.0027, CH₃CN) \( [\alpha]_{298}^{\text{max}} +1.4 \times 10^4 \) (c 0.054, CH₃CN); identical in g.l.c. and spectral characteristics (infrared, n.m.r.) with (+)-epicampherenone previously synthesized.

Preparation of (+)-Epi-β-Santalene 50a

(+)-Epicampherenone (150 mg, 0.68 m mole) was reduced (as previously described for the racemic material) with lithium trimethoxyaluminohydride in tetrahydrofuran affording, after chromatography over 5 g silica gel, 140 mg (93%) isoepicampherenol (+)-49b:
(α) $^{30}$D +7.0° (c 5.10, CHCl₃); g.l.c. analysis and spectral characteristics (infrared and n.m.r.) were in full agreement with previously synthesized (±)-isoepicamphenol. The entire sample of (+)-isoepicamphenol was treated with 500 mg p-toluenesulfonyl chloride in 1 ml pyridine and the mixture heated 19 hours at 90-92°. Isolation as previously described followed by preparative g.l.c. (column G, 160°) and evaporative distillation afforded pure (+)-epi-β-santalene:

(α) $^{29}$D $^{26.9}$° (c 2.6, CHCl₃) [a sample of natural (+)-epi-β-santalene isolated in our laboratory from sandalwood oil (120) exhibited:
(α) $^{29}$D $^{23.3}$° (c 4.12, CHCl₃)]; infrared and n.m.r. spectra were in full agreement with racemic material previously prepared; mass spectrum, m/e (relative intensity), 204 (9.6, M⁺), 122 (55.9), 94 (100), 93 (24.3), 79 (19.2) and 41 (39.0).

Preparation of (+)-9-Acetoxycamphor 208

In accordance with the procedure of Guha and Bhattacharyya, 60.0 g (0.260 mole) (+)-9-bromocamphor and 120 g (1.2 mole) anhydrous potassium acetate were dissolved in 115 ml acetic acid with heating and the resulting solution was refluxed (175-185° oil bath) 48 hours. The hot reaction mixture was poured into cold water, neutralized by careful addition of solid sodium bicarbonate and extracted with four 350 ml portions of ether, washing each portion twice with water. The solvent was removed and the residue was taken up in petroleum ether and dried over anhydrous sodium sulfate. Evaporation of solvent yielded 54 g crude acetate which was distilled affording 52.0 g (95%)
(+)-9-acetoxycamphor 208: bp 70° (0.05 mm) [lit. bp 123°, 5 mm (149)];
$\eta^2_{D} 1.4760; (\alpha)^{30}_{D} +53.2^\circ$ (c 0.881, CHCl$_3$); ultraviolet, $\lambda_{max}$ 288 nm
($\epsilon$ 34) [lit. $\lambda_{max}$ (ethanol) 289 nm ($\epsilon$ 40)] (147); infrared (neat), $\nu_{max}$
1745 and 1230 cm$^{-1}$; n.m.r. (CDCl$_3$), $\tau$ 9.05 (singlet, 3H, tertiary methyl),
9.01 (singlet, 3H, tertiary methyl), 7.89 (singlet, 3H, acetate methyl),
6.02 and 5.82 (AB quartet, 2H, $J = 11.5$ Hz, CH$_2$-0-); mass spectrum, m/e,
210 ($M^+$), 122, 108, 107, 95, 93 and 43. (162a,b; 144)

Preparation of (+)-9-Hydroxycamphor 209

This compound was prepared following the procedure of Corey
et al. (145). A solution of 50 g (0.89 mole) potassium hydroxide in
400 ml 95% ethanol was heated to reflux temperature and 52.0 g (0.247 mole)
(+)-9-acetoxycamphor in 100 ml 95% ethanol was added. After reflux
with vigorous stirring for 1 hour the solvent was evaporated under
reduced pressure until crystals formed. The residue was diluted with
water and saturated sodium chloride and extracted with ether, washing
twice with saturated sodium chloride and drying over anhydrous sodium
sulfate. Solvent removal afforded crude crystalline 208 which was
rinsed with small portions of petroleum ether until colorless (44.5 g).
Recrystallization from 1:5 petroleum ether-ether provided 38.0 g (91%)
of the hydroxy camphor (mp 237-239°). One further recrystallization
afforded a pure sample exhibiting the following characteristics:
mp 237-239°; $\alpha^{32}_{D} +61.2^\circ$ (c 0.873, absolute ethanol); ultraviolet,
$\lambda_{max}$ 290 ($\epsilon$ 33) [lit. mp 238-240° (145); 243.5-244° (144); $\alpha^{23}_{D} +63.1^\circ$
(c 0.87, 95% ethanol)] (144); $\lambda_{max}$ (ethanol) 290 ($\epsilon$ 34) (147); infrared
Preparation of (+)-trans-Isoketopinic Acid 210

The oxidation of (+)-9-hydroxycamphor was performed in accordance with the procedure of Corey et al. (145). To a solution of 86 g (0.86 mole) chromium trioxide and 146 g (0.86 mole) manganous sulfate monohydrate in 220 ml water was added slowly 26 ml (ca. 0.48 mole) concentrated sulfuric acid followed by the addition with vigorous stirring of 36.2 g (0.215 mole) (+)-9-hydroxycamphor in 600 ml water over a period of 1.5 hours. The reaction mixture was stirred 8 hours at 25° and 8 hours more at 65°. After cooling and diluting with saturated sodium chloride solution, the acid was removed by extraction with four 250 ml portions of ether, washing each extract with saturated sodium chloride. Purification of the acid by extraction with 2 N aqueous sodium hydroxide followed by acidification with 6 N hydrochloric acid and re-extraction with three 250 ml portions of ether afforded after solvent removal 34.3 g of nearly pure acid. Recrystallization from acetone yielded 30.8 g (79%) of 210 mp 255-257°. One further recrystallization afforded a pure sample: mp 256-257°; $\alpha_D^{32} +1.4°$ (c 0.899, absolute ethanol)[lit. mp 248-251° (145),
Preparation of Lactone 212a

Lactone 212a was prepared after the procedure of Corey et al. (145). (+)-Trans-isoketopinic acid 210 (9.10 g, 0.050 mole) was dissolved in 250 ml methanol and neutralized with 10% methanolic potassium hydroxide until just alkaline to phenolphthalein. Sodium borohydride (20 g, 0.53 mole) was added in one portion and the reaction was stirred at room temperature 12 hours using a cold water bath as needed to moderate the reaction. The solvent was removed under reduced pressure and the residue taken up in water, acidified with 6 N hydrochloric acid, and extracted four times with ether, washing each extract with saturated sodium chloride. The ether extracts were evaporated and the residue was taken up in methylene chloride and dried over anhydrous sodium sulfate. Removal of solvent afforded 9.39 g (9.2 g theoretical yield) of the crude hydroxy acid 211: n.m.r. (CDCl₃), τ 8.73 (singlet, 3H, tertiary methyl), 8.59 (singlet, 3H, tertiary methyl), 6.40 (triplet, J = 6 Hz) and 6.03 (multiplet) (total of 1H, epimeric -CHOH) and 3.56 (singlet, broad, 2H -CHOH and -COOH). The crude hydroxy acid (a mixture
of the exo and endo alcohols in the ratio 6:4 is judged by the relative integral areas of the protons at 6.40 and 6.03 \( \tau \) respectively in the n.m.r. spectrum) was used without further purification in the lactonization step. Thus 9.39 g of 211 was dissolved in a solution of 100 ml trifluoroacetic acid to which 20 ml concentrated sulfuric acid had been added and the solution was refluxed 2.5 hours. Approximately 80% of the trifluoroacetic acid was recovered by distillation from the reaction vessel and the remaining reaction mixture was diluted with ether, washed successively with two portions of saturated sodium chloride, saturated sodium bicarbonate (until neutral) and again with saturated sodium chloride and the ether portion was dried over anhydrous sodium sulfate. Solvent removal followed by sublimation (110°, 0.05 mm) and recrystallization from petroleum ether afforded 6.18 g (74% from trans-isoketopinic acid 210) mp 198-200°. One further sublimation afforded material exhibiting the following: mp 199-200°; \((\alpha)_{D}^{30} -60.7°\) (c 2.22, absolute ethanol) [lit. mp 190-196° (145), 191° (151); \( [\alpha]_{D}^{17} -117.9° \)]; infrared (KBr), \( \nu_{\max} \) 1770 and 1070 cm\(^{-1}\); n.m.r. (CDCl\(_3\)), \( \delta 8.93 \) (singlet, 3H, tertiary methyl), 8.89 (singlet, 3H, tertiary methyl) and 5.73 (doublet, 1H, \( J = 3 \) Hz, -CHO--;); mass spectrum, m/e (relative intensity), 166 (34.2, M\(^+\)), 138 (64.7), 95 (75.8), 94 (100), 79 (19.7) and 41 (22.3). (162a,b; 148)

**Preparation of Diol 213**

Lactone 212a (16.6 g, 0.10 mole) dissolved in 40 ml anhydrous ether was added dropwise to a stirred mixture of 4 g (0.11 mole) lithium
aluminum hydride in 100 ml anhydrous ether and the resulting mixture was stirred overnight [cf. reference (148)]. The mixture was refluxed for 1 hour and the excess hydride decomposed by dropwise addition of water. Extraction with ether (three portions), followed by washing with water and saturated sodium chloride and drying over anhydrous sodium sulfate, afforded after solvent removal 15.3 g crude diol. Sublimation afforded 15.1 g (94) mp ca. 275°. Recrystallization from ethyl acetate and petroleum ether (bp 60-80°) yielded 13.6 g of material (mp unchanged). A small sample was further purified by recrystallization from ethyl acetate and exhibited the following characteristics: mp ca. 275° [lit. mp 273-275° (148)]; \( (\alpha)_D^{22.4} \) (c 2.03, CHCl₃); infrared (KBr), \( \nu_{\text{max}} \) 3380 (broad) and 1010 (broad cm⁻¹); n.m.r. (CDCl₃), \( \tau \) 9.08 (singlet, 3H, tertiary methyl), 9.03 (singlet, 3H, tertiary methyl), 6.68 (singlet, 2H, COH and 6.3 (overlapping multiplets, 3H, \(-\text{CH}_2\text{OH}\) and \(-\text{CH}_2\text{O}\)H); mass spectrum, m/e (relative intensity), 152 (8.9, M⁺-H₂O), 108 (100), 95 (91.1), 94 (40.5), 93 (38.0) and 41 (55.7). (162a,b,c; 148)

Preparation of 8-Iodocamphor 216

The preparation of 8-iodocamphor was accomplished direct from diol 213 without purification of intermediates. A solution of 8-hydroxyisoborneol 213 (13.6 g, 0.080 mole) in 40 ml dry pyridine (under a dry nitrogen atmosphere) was cooled to ca. -10° (ice/acetone bath) and a solution of 15.3 g (0.080 mole) \( p \)-toluenesulfonylchloride in 40 ml dry pyridine was added at a moderate rate with vigorous stirring of the diol. After stirring 4 hours at 0 to -10°, the reaction mixture was allowed to
stand 18 hours at -10°. This crude solution of crude 8-tosyloxyisoborneol 214 was used directly without isolation. Oxidation of 214 was achieved by addition of the crude monotosylate/pyridine solution to a cold slurry of 24 g chromic anhydride in 175 ml dry pyridine followed by stirring 7 hours at room temperature under a nitrogen atmosphere. The reaction mixture was extracted with three portions of ether washing each with water, 6 N hydrochloric acid and saturated sodium chloride. The combined extracts were dried over anhydrous sodium sulfate, solvent was removed and further drying was effected by addition and removal under vacuum of several portions of dry benzene providing crude 8-tosyloxy-camphor 215: largely one component on g.l.c. analysis (column A, 225°, retention time 26 minutes). A sample stored at -10° two weeks solidified affording crystalline material of mp ca. 75° but it was found more convenient to perform the next step of the synthesis on the crude tosylate. Crude keto tosylate 215 was treated with 60 g sodium iodide (dried over phosphorus pentoxide at 1 mm 24 hours) in 200 ml dry dimethylsulfoxide at 110° (dry nitrogen atmosphere) for 84 hours. After cooling and diluting with water, the product was extracted with four 150 ml portions of petroleum ether, washing each extract with dilute sodium metabisulfite solution and saturated sodium chloride and drying the combined extracts over anhydrous sodium sulfate. Solvent removal and crystallization from cold petroleum ether afforded 5.8 g (26%) 8-iodocamphor 216, mp 39-41°. A recrystallized sample exhibited the following characteristics: the mp 40-41° [lit. (±) mp 40-42°]; (α) D32 −92.1° (c 1.14, CHCl₃); ultraviolet, λ max 256 nm (ε 580); infrared (KBr), ν max 1740 and 1415 cm⁻¹; n.m.r. (CDCl₃), 9.05 (singlet, 3H, tertiary methyl), 8.86
(singlet, 3H, tertiary methyl), and 7.02 (singlet, 2H, CH₂I); mass spectrum, m/e (relative intensity), 278 (71.1, M⁺), 151 (49.5), 109 (94.5), 107 (100), 81 (94.8), 55 (74.2) and 41 (75.2). (162a,b,c; 148)

Preparation of Acetal Iodide 202

A mixture of 8-iodo-camphor 216 (4.50 g, 0.0162 mole), 10 ml ethylene glycol, 500 mg p-toluenesulfonic acid and 50 ml benzene was refluxed 18 hours in a Dean-Stark apparatus. After cooling to room temperature, the reaction mixture was washed with saturated sodium bicarbonate and saturated sodium chloride and dried over anhydrous sodium sulfate. Solvent removal and distillation under reduced pressure afforded first 530 mg (ca. 10%) of 202 containing less than 10% starting ketone followed by the main fraction of 4.51 g (86%) pure acetal iodide 202: bp 76° (0.03 mm); nD²⁵ 1.5480; homogeneous by g.l.c. analysis (column A, 175°); (α) 34D = -37.3° (c 5.12, CHCl₃); infrared (neat), νmax 1120 cm⁻¹; n.m.r. (CCl₄), τ 9.21 (singlet, 3H, tertiary methyl), 8.96 (doublet, 3H, J = 2 Hz, tertiary methyl), 7.67 (doublet) and 6.00 (doublet of multiplets) (ABX pattern, 2H, JAB = 10.5 Hz, JAX = 2 Hz, JBX = 0 Hz, -CH₂I) and 6.20 (multiplet, 4H, -OCH₂CH₂O-); mass spectrum, m/e (relative intensity), 195 (82.5, M⁺-I), 109 (95.0), 87 (100), 67 (60.0), 43 (50.0) and 41 (57.5).

Anal. Calcd. for C₁₂H₁₉O₂I: C, 44.73; H, 5.94; I, 39.39.
Found: C, 44.71; H, 6.12; I, 39.24.
Preparation of (-)-Camphor

Hydrogenolysis of 8-iodo-camphor was performed according to the procedure of Rodig et al. (148). A solution of 175 mg (0.63 mmole) 8-iodo-camphor in 20 ml of ethanol was mixed with a slurry of 500 mg 10% palladium on charcoal in 2 ml of water containing 45 mg potassium hydroxide. Hydrogenation of the mixture for 12 hours under 40 psi of hydrogen (Parr apparatus) followed by filtration over celite, aqueous washing and solvent removal afforded crude crystalline camphor. Two sublimations (60°, 15 mm) afforded 78 mg (82%) (-)-camphor: mp 32 -44.8° (c 1.82 absolute ethanol) [lit. mp 178°; (-)D -43.6 (ethanol)(164)]; infrared and n.m.r. spectra are in agreement with authentic (+)-camphor.

Preparation of (-)-Campherone 42b

A solution of 20 ml dry benzene and 6.5 ml nickel carbonyl (171) was treated with 3.5 ml 1-bromo-3-methyl-2-butene (4.5 g, 30 mmole) in a dry nitrogen atmosphere and the reaction was stirred 2.5 hours at 50°. After cooling and removal of solvent under vacuum, 20 ml dry dimethylformamide was added and the mixture stirred until all of the red solid had dissolved. Acetal iodide (2.00 g 6.22 mmole) was added in 10 ml dry dimethylformamide and the reaction was stirred 36 hours at 55-65° under dry nitrogen. The cooled reaction mixture was poured into 20 ml dimethylsulfoxide and extracted 4 times with petroleum ether, washing with water and saturated sodium chloride. Drying over anhydrous sodium sulfate and solvent removal afforded 3.22 g crude
product. Distillation afforded 1.51 g (92%) of campherenone ethylene acetal bp 74° (0.06 mm), which was greater than 95% pure by g.l.c. analysis (column A, 175°). A middle fraction of the distillate was collected and shown by g.l.c. (column A, 150°) to contain no detectable trace of impurity: (α)\textsubscript{D}\textsuperscript{32} +14.5° (c 4.98, CHCl\textsubscript{3}); infrared and n.m.r. spectra in complete agreement with spectra of the (±)-campherenone acetal previously synthesized. Hydrolysis of the pure fraction (H\textsuperscript{+}/acetone) and evaporative distillation provided pure (−)-campherenone 42b: bp (bath temperature) 60° 0.1 mm; (α)\textsubscript{D}\textsuperscript{33} -33.6° (c 10.0, CHCl\textsubscript{3}); [ε]\textsubscript{max}\textsuperscript{294} -370 (0.11 g/100 ml or 0.0050 M, methanol) [lit. (α)\textsubscript{D} -33.0 (c 10.0, CHCl\textsubscript{3}); [ε]\textsubscript{max}\textsuperscript{298} +600 (c 0.1097, methanol) (28)]; infrared and n.m.r. spectra in complete agreement with previously synthesized (±)-campherenone.

Preparation of (−)-β-Santalene

Reduction of (−)-campherenone with lithium trimethoxyalumino-hydride (as previously described for (±)-campherenone) afforded, after chromatography over silica, (+)-isocampherenol: [α]\textsubscript{D}\textsuperscript{32} +25° (c 2.60, CHCl\textsubscript{3}) [lit. (α)\textsubscript{D} +15.3 (c 2.6, CHCl\textsubscript{3}) (28)]; spectral data (infrared, n.m.r.) in accord with previously synthesized racemic material. Treatment of 86 mg (0.39 mole) with 120 mg (0.64 mole) p-toluenesulfonyl chloride in 1 ml pyridine 18 hours at 95° under nitrogen, followed by the previously described work-up, afforded crude (−)-β-santalene which was chromatographed first over 5 g silica gel and then over 5 g aluminum oxide (Woelm grade I) with petroleum ether elution yielding 55 mg (69%)
β-santalene. Evaporative distillation afforded pure (-)-β-santalene: bp (bath temperature) 60° (1 mm); (α) $^3_{D} -112°$ (c 4.19, CHCl$_3$) [A sample of natural (-)-β-santalene isolated in our laboratory from sandalwood oil (120) exhibited: (α) $^2_{D} -102°$ (c 5.01, CHCl$_3$).]; spectral data (n.m.r., infrared) were in accord with previously synthesized (±)-β-santalene as well with the natural material.
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29. This compound has not yet been found in nature but is known through synthesis.

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(b) J.C. Fairlie, G.L. Hodgson and T. Money, as presented before the Northwest Regional Conference of the American Chemical Society, Seattle, Washington, July, 1970.


84. J.A. MacPhee and J.E. Dubois, Tetrahedron Letters, 467 (1972) and references therein.
87. Spectral data (infrared, n.m.r. and mass spectrum) and elemental analysis are in accord with this structure.
88. Ketone 126 was the major volatile product produced from a brief treatment of dihydrocryptomerion 75a with boron trifluoride in methylene chloride.
89. Parts of the work involving dihydrocryptomerion enol acetate 95b and related compounds were carried out by Dr. D.F. MacSweeney.
90. The work involving the preparation of homocamphor compounds 129a,b as well as compounds 128b,c is largely accredited to Dr. J.C. Fairlie.
96. We are grateful to Mr. R. Bradshaw for his developmental work on the synthesis of dihydrocryptomerion.

98. We are grateful to Dr. Crawford for kindly supplying experimental details of the metalation and alkylation of limonene prior to publication.


103. T. Money, unpublished results.


114. Synthetic routes to β-santalene (31,115,116), epi-β-santalene (31,115,117) and α-santalene (44,117,118) have previously been reported.

119. The conversion of natural campherenone to β-santalene has recently been described (28).
120. We are grateful to Fritzsche, Dodge and Olcott, Inc., New York, and Norda Essential Oil and Chemical Co., Inc., New York, for generous samples of Mysore sandalwood oil.
121. H. Meerwein and K. van Emster, Ber., 53, 1815 (1920); cf. reference (117).
123. We are grateful to Professor E. Piers of this department for providing us with an authentic sample and spectral characteristics of copacamphor: cf. reference (55).
124. We are grateful to Professor D.H.R. Barton for an authentic sample of culmorin diketone dithioketal the precursor of (-)-longicamphor: cf. reference (58).
126. For another example of intramolecular alkylation of a ketone involving an epoxide see the total synthesis of copacamphene:
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162. This compound exhibited spectral characteristics in accord with previously reported spectra or spectral data in the reference cited:
   a. Infrared
   b. N.M.R.
   c. Mass spectrum


166. We are grateful to Dr. J.R. Cannon for experimental details concerning the preparation of (4-benzyloxybutyl)triphenyl-phosphonium iodide.


169. The preparation of compounds 46a, 47, 48, 49a, and 50 was done in collaboration with Dr. D.F. MacSweeney as was the alternative preparation of (-)-cryptomerion 99a.


171. Extreme caution must be used in handling this toxic and spontaneously inflammable compound.