TOTAL SYNTHESIS OF SESQUITERPENOIDS
(+)-EREMOPHILENOLIDE, (+)-TETRAHYDROLIGULARENOLIDE,
(+)-ARISTOLOCHENE, (-)-YLANGOCAMPHOR,
(-)-YLANGOBORNEOL, (-)-YLANGOISOBORNEOL

BY

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We accept this thesis as conforming to the
required standard

THE UNIVERSITY OF BRITISH COLUMBIA
June, 1973
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Department of Chemistry

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Date June 11, 1973
ABSTRACT

The first part of this thesis is concerned with the successful development of a general synthetic approach to the eremophilane class of sesquiterpenoids, which culminated in the total synthesis of (+)-eremophileneolide 6, (+)-tetrahydroligularenolide 44 and (+)-aristolochene 34. The octalone 92 was converted via an efficient, regioselective route into the keto ester 105, which served as a common synthetic intermediate for the preparation of all three sesquiterpenoids. Successive subjection of 105 to alkylation, hydrolysis and decarboxylation afforded the keto acid 111. Hydrogenation of the latter provided both the cis-fused keto acid 113, which was readily converted into (+)-eremophileneolide 6, and the trans-fused keto acid 112, which was similarly transformed into (+)-tetrahydroligularenolide 44. Conversion of 105 into the dithio-ketal 127, followed by desulfurization and treatment of the resultant olefinic ester 124 with excess methyllithium, provided the olefinic alcohol 130. Dehydration of the latter yielded (+)-aristolochene 34.

In the second part of this thesis, a stereoselective total synthesis of the ylango-type sesquiterpenoids, (-)-ylangocamphor 7, (-)-ylango-borneol 23 and (-)-ylangoisoborneol 143, is described. The (+)-ketol 222, of known absolute stereochemistry, was converted by an efficient route into the keto ester 216. The latter was transformed into the bicyclo[3.2.1]octadione 203 by an intramolecular Claisen condensation. Homologation of 203 to the keto aldehyde 245 was achieved by an efficient three-step sequence of reactions. Reaction of keto aldehyde 245 with methoxymethylenetriphenylphosphorane afforded the (+)-keto olefin 204.
which could hopefully be used as a common intermediate in the synthesis of the majority of known ylango sesquiterpenoids. Transformation of 204 into (−)-ylangocamphor 7 was achieved by successive hydroboration, mesylation and intramolecular alkylation. Ylangocamphor was converted in (−)-ylangoborneol 23 and (−)-ylangoisoborneol 143 by two completely stereoselective reductions.
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INTRODUCTORY REMARKS

1. General

The sesquiterpenoids are a group of compounds within the biogenetically related family of natural products which are collectively referred to as the terpenoids. The terpenoids are considered to be derived from two or more multiples of a basic building unit, isoprene $\text{\textsubscript{1}}$.\textsuperscript{1,2} Thus monoterpenoids contain the equivalent of two isoprene units,

\begin{center}
\includegraphics{isoprene.png}
\end{center}

sesquiterpenoids three units, diterpenoids four units, sesterterpenoids five units, triterpenoids six units and carotenoids eight units.

The sesquiterpenoids, normally containing fifteen carbon atoms, have been known for a long time as constituents of the essential oils. However, it is only in relatively recent times that the chemistry of these compounds has been extensively investigated. This is partly due to the fact that in the essential oils sesquiterpenoids often occur
as very complex mixtures which could not be resolved by the classical methods available. With the advent of modern separation techniques such as gas-liquid chromatography (g.l.c.), and modern spectroscopic methods such as proton magnetic resonance (p.m.r.), the structure and stereochemistry of a very large number of sesquiterpenoids have been established. Furthermore, polyfunctional sesquiterpenoids are rarely found in essential oils because of their low volatility. The substitution of solvent extraction of plant materials for steam distillation as the extraction process, has, in recent years, been fruitful in providing a large variety of polyoxygenated sesquiterpenoids.

As a result of these investigations, over fifty different sesquiterpenoid skeletal types have been found to exist in nature. The diversity of sesquiterpenoid compounds is multiplied further by stereochemical variations, the range of functional groups and by positional isomerism. Thus sesquiterpenoids may occur as acyclic, monocyclic, bicyclic, tricyclic or tetracyclic hydrocarbons, alcohols, ketones, oxides or lactones, with structures as widely differing as farnesene, tun, and ishwarane.
One large class of sesquiterpenoids is the eremophilane class, which possesses the basic carbon skeleton 5, as exemplified by eremophilenolide 6. For some years, the first isolated members of this class represented the only known exceptions to the "isoprene rule" in the sesquiterpenoid field. Thus the carbon skeleton of the eremophilanes could not be rationalized in terms of a simple linkage of isoprene units.

Because of the existence of structures such as the eremophilanes, the "isoprene rule" was revised to accommodate such structures, by allowing for skeletal rearrangements of the previously head-to-tail linked isoprene units. The eremophilane class of sesquiterpenoids will be the subject of discussion in the first part of this thesis.

The second part of this thesis is concerned with a small group of sesquiterpenoids, the ylango sesquiterpenoids. This group of compounds, which includes structures such as ylangocamphor 7, and sativene 8, is part of a larger class of structurally related sesquiterpenoids which possess the bicyclo[2.2.1]heptane skeletal moiety or the related bicyclo[3.1.1]heptane moiety. Thus, other examples of this class of compounds are campherenone 9, cyclocopacamphene 10 and α-longipinene 11. The structural relationships within this class of sesquiterpenoids will be discussed later in greater detail (see Introduction Part II).
2. **Biosynthesis of Eremophilane- and Ylango-type Sesquiterpenoids**

The biosynthesis of sesquiterpenoids is believed to arise from the combination of the biological equivalent of three isoprene units, followed by subsequent cyclization of the resultant fifteen carbon unit in a number of different ways.\(^{15,16}\) The specific fifteen carbon unit involved in these transformations is generally considered to be farnesyl pyrophosphate \(^{13}\). The biosynthesis of the latter from acetyl CoA via the intermediacy of mevalonic acid \(^{12}\) has been experimentally verified.\(^{17-19}\) On the other hand, the proposed biogenesis\(^{16}\) of
virtually all sesquiterpenoids from farnesyl pyrophosphate $\text{13}$ has received relatively little experimental proof. Nevertheless, this proposal offers an interesting rationalization of the biological derivation of the quite diverse skeletal structures found in the sesquiterpenoid field. Since a recent comprehensive review* summarizes well the present state of this hypothesis, the proposed biosynthesis of the eremophilane and ylang sesquiterpenoids will be discussed here in outline only.

In order to accommodate the non-isoprenoid skeleton of the eremophilanes, trans-farnesyl pyrophosphate $\text{13}$ is considered to undergo a solvolytic cyclization (or a related biogenetic process) to give a structure such as $\text{14}$. Further cyclization of $\text{14}$ gives a bicyclic intermediate $\text{15}$ which undergoes a 1,2-methyl shift as shown, thus forming the intermediate $\text{16}$ which possesses the basic carbon skeleton of the eremophilanes.

* The representation of a formal cation in this discussion is only a convenient symbolism, since the biosynthetic cyclizations are undoubtedly enzymatically controlled and may occur via concerted processes.
An analogous cyclized form 18 (see Chart 1) of cis-farnesyl pyrophosphate 17 is postulated as the precursor to the ylango sesquiterpenoids. By a 1,3-hydride shift, cation 18 is converted into 19 which then cyclizes to give the bicyclic derivative 20. The latter can cyclize further in two different ways. Thus Markownikoff cyclization, followed by deprotonation affords α-ylangene 21. On the other hand, anti-Markownikoff cyclization of 20 gives cation 22 which, by simple neutralization with water, affords ylangoborneol 23, or by a 1,3-deprotonation produces cyclosativene 24. Alternatively, a Wagner-Meerwein rearrangement of 22, followed by deprotonation, results in sativene 8.
Chart 1
De Mayo and coworkers have postulated that a structure such as sativene might be the biological precursor to the sesquiterpenoid toxin, helminthosporal. Thus oxidative cleavage of sativene at the point indicated, followed by isomerization of the double bond, would result in helminthosporal. Indeed, these workers have shown by a tracer study using [2-14C]-mevalonic acid that the unsaturated aldehyde carbon atom in helminthosporal contained approximately one-third of the total incorporated activity. Thus if the postulated derivation of helminthosporal from sativene is correct, this result supports the general outline of the biogenetic scheme given above for sativene.

An alternative hypothesis for the biogenesis of ylango sesquiterpenoids from a fifteen carbon isoprenoid precursor has recently been proposed. Thus, dihydrocryptomerion enol phosphate is envisaged as undergoing cyclization to give campherenone. The enol phosphate derivative of the latter could again cyclize in an analogous manner to give ylangocamphor. Reduction of ylangocamphor to ylangoborneol and solvolysis of the latter gives the previously encountered cation (see Chart 1). The formation of other ylango sesquiterpenoids from this cation is considered to occur by the mechanisms previously mentioned.
PART I

TOTAL SYNTHESIS OF (+)-EREMOPHILENOLIDE,
(+)-TETRAHYDROLIGULARENOLIDE AND (+)-ARISTOLOCHENE
PART I

INTRODUCTION

1. Perspective

The first naturally occurring sesquiterpenoids found to possess the eremophilane carbon skeleton 5, eremophilone 27, hydroxydihydro-eremophilone 28 and hydroxyeremophilone 29, were isolated in 1935 from the wood of *Eremophila Mitchelli* by Bradfield, Penfold and Simonsen.24,25 The work concerned with the structural elucidation of these compounds extended over a number of years, leading eventually to the formulation of the correct skeletal structures.25 Confirmation of the gross structures and a determination of the relative configuration of all three of the natural products was finally secured in the late 1950's by the X-ray crystallographic analysis26,27 of hydroxydihydro-eremophilone 28, and by the unambiguous correlation28 of 27 and 29 with 28. At about that time, further examples of the presence in plants of the biogenetically anomalous eremophilanes began to emerge, and the number of known naturally occurring eremophilanes3 has grown rapidly ever since. To date, approximately seventy different eremophilanes have been isolated and characterized.3 Because of space requirements, it is not feasible to include a chart of all of these structures. However, it does seem desirable to comment on the
variations on the basic eremophilane skeleton which have given rise to such a large group of related compounds.

The distinguishing feature of the eremophilanes, apart from their non-isoprenoid carbon skeleton, is the cis related vicinal methyl groups. In addition, approximately one-half of the known naturally occurring eremophilanes possess the interesting cis-fused decalin system as exemplified by fukinone (See Chart 2. Structures shown do not necessarily imply absolute configurations). The occurrence of trans-fused and of C_{10}-oxygenated eremophilane-type natural products is rare. However, furanoligularenone and euryopsol provide, respectively, an example of each type. The remainder of the
eremophilane-type sesquiterpenoids possess a double bond at the C\textsubscript{10} bridgehead position. This double bond can occur in either ring, as exemplified by the isomeric pair valencene \textsuperscript{33}\textsuperscript{32,33} and aristolochene \textsuperscript{34}.34

Despite the restrictions imposed by the basic carbon skeleton, by the thus far invariable presence of \textit{cis} vicinal methyl groups and by the presence of mainly two types of ring fusion, a great variety of compounds exists within the eremophilane family of sesquiterpenoids. The isopropyl-type side-chain provides the basis for some of this variety. For example, this three-carbon fragment is found as the saturated isopropyl group in nardostachone \textsuperscript{35}\textsuperscript{35,36} and as the tertiary alcohol moiety in valerianol \textsuperscript{36}.37,38 More often it is encountered in the unsaturated forms, both as the isopropenyl group (see valencene \textsuperscript{33}) and as the isopropylidene moiety (see fukinone \textsuperscript{30}). In the former case, the question of stereochemistry at C\textsubscript{7} arises, and compounds possessing both \textit{alpha} and \textit{beta} substituents have been isolated, including the epimeric pair valencene \textsuperscript{33} and eremophilene \textsuperscript{37}.39 In approximately one-half of the known cases this side-chain is further oxidized, giving rise to either the \textit{\alpha},\textit{\beta}-unsaturated \textit{\gamma}-lactone system as in the petasitolides \textsuperscript{38}\textsuperscript{40} or the closely related furan system as in 9-hydroxyfuranoeremophilane \textsuperscript{39}.41

The remaining structural variations in the eremophilanes are based mainly on annular unsaturation and the presence of ketonic and hydroxyl functional groups at one or more of the secondary annular carbon atoms. The former can vary from the highly conjugated warburgin \textsuperscript{40,42} to aristolochene \textsuperscript{34} which possesses only a single,
Chart 2
isolated annular double bond. The hydroxyl-containing compounds are exemplified by 9-hydroxyfuranoeremophilane 39 and the trihydroxy compound, euryopsol 32.

Two small groups of recently isolated sesquiterpenoids are considered within the eremophilane family, although they possess modified carbon skeletons. One group, the bakkanes, have the basic structure of bakkenolide A 41, 43, 44 which is functionally the simplest known member. Approximately nine bakkanes are known to date, the others differing from 41 in the nature of the substituents at C1 and C9. The bakkanes can be regarded as eremophilanes which have undergone a ring contraction from a six- to a five-membered ring. The second group, containing ishwarone 42 (R = 0) 45, 46 and ishwarane 4 (R = H2), 7 as the only known members to date, possesses an interesting carbon skeleton whose relationship to the eremophilanes is evident. For the sake of completeness, it is appropriate to mention here the aristolanes, possessing the carbon skeleton 43, which are now generally regarded as a separate class of sesquiterpenes from the eremophilanes.

Even though, as mentioned previously, the number of known eremophilane-type sesquiterpenoids is large, and in spite of considerable total effort on the part of a number of research groups, only a few of
the structurally fairly simple members of this class have yielded to total synthesis.* The work described in the first part of this thesis was aimed at the development of a general synthetic pathway to the eremophilanes. Since, as mentioned earlier, so many of the eremophilanes contain either the α,β-unsaturated γ-lactone or furan functionalities and since a facile method of converting the former functional group into the latter was available, it was decided to synthesize two sesquiterpenoids containing the unsaturated lactone moiety. In all, three eremophilanes were totally synthesized, eremophilenolide 6, tetrahydroligularenolide 44, and aristolochene 34, each containing a differently fused decalin system. It seems appropriate to describe next the work which led to the establishment of the structure and stereochemistry of these three sesquiterpenoids.

* To date, the following eremophilane-type and structurally closely related aristolane-type sesquiterpenoids have been totally synthesized: (+)-aristolone,47,48 (+)-calarene,49 (+)-dehydrofukinone,50 (+)-eremoligenol,51,52 (+)-eremophil-3,11-diene,53 (+)-eremophilene,51,52 (+)-fukinone,54-58 (+)-hydroxyeremophilone,58 (+)-ishwarane,59 (+)-isonootkatone (α-vetivone)60,61 (-)-isonootkatone (α-vetivone),62 (+)-nootkatone,61,63-65 (-)-nootkatone,62 (+)-7-epi-nootkatone,36,61 (+)-tetrahydroeremophilone,66 (+)-valencene,52 and (+)-valerianol.52
2. **Origin and Structural Elucidation of Eremophilenolide, Tetrahydro-ligularenolide and Aristolochene**

(+)-Eremophilenolide was isolated\(^{68}\) from *Petasites officinalis* Moench. by Sorm and coworkers in 1961 and was subsequently shown\(^{8}\) to possess structure and absolute stereochemistry as depicted in 6. This structural determination will be summarized in the following paragraphs.

![Diagram of molecule 6]

Absorption bands at 1760 and 1693 cm\(^{-1}\) in the infrared spectrum of eremophilenolide (C\(_{15}\)H\(_{22}\)O) indicated the presence of an \(\alpha,\beta\)-unsaturated \(\gamma\)-lactone, while the ultraviolet absorption maximum at 220-224 \(\text{m}\upmu\) (log \(\varepsilon = 4.16\)) was consistent with this chromophore. Catalytic hydrogenation (acetic acid-platinum oxide) gave dihydroeremophilenolide 45 (see Chart 3) which exhibited an infrared absorption at 1780 cm\(^{-1}\) typical of a saturated \(\gamma\)-lactone.

Reduction of 45 with lithium aluminum hydride afforded the diol 46. Further reduction of the ditosylate derivative of 46 with lithium aluminum hydride gave a mixture of compounds from which the tetrahydrofuran derivative 47 could be isolated. This compound was identical with the product of catalytic hydrogenation of the naturally occurring furanoeremophilane 48.\(^{69}\)
In order to determine whether the termination point of the lactone in eremophilenolide was C₆ or C₈, dihydroeremophilenolide 45 was reduced with lithium aluminum hydride under controlled conditions, thus yielding the hydroxy aldehyde 49. The latter was subjected to Huang-Minlon reduction, followed by Jones oxidation of the resulting alcohol 50 to give the base-labile ketone 51. Epimerization of the latter under basic conditions afforded the base-stable ketone 52.

Ketone 52 was also obtained in the following manner. Catalytic hydrogenation of the acetate of hydroxyeremophilone 29, of known absolute stereochemistry, followed by successive reductive removal of the acetate groups in the resulting keto acetates 53 with calcium in liquid ammonia and oxidation of the over-reduced keto group, produced a mixture of two ketones in the ratio of 1:1. Since both of these ketones were base-stable, and since one was shown to be identical with the known trans-fused decalene 54, the remaining one had to be the cis-fused decalene derivative 52. In keeping with this, 52 exhibited a negative Cotton effect, superimposed on a positive background, which is characteristic of A/B cis-fused 3-keto steroids. Decalene 52, thus obtained, was identical with the sample obtained from eremophilenolide 6. This conversion of eremophilenolide 6 and hydroxyeremophilone 29 into a common intermediate, established C₈ as the lactone terminus in 6, and it also proved the absolute configuration of (+)-eremophilenolide as that depicted in structure 6.

If the lactone terminus in eremophilenolide 6 is α-oriented, the catalytic hydrogenation of this compound should occur predominantly
Chart 3
from the beta face of the molecule (see 6a), thus giving rise eventually to the ketone 51. Consideration of the conformational equilibria of 51 and its C7 epimer 52 shows that 52a, the preferred conformation of 52, is thermodynamically more stable than 51a', the favored conformation of 51. This is due mainly to the fact that in 51a', the secondary methyl group possesses an axial orientation (with
respect to ring A). Therefore decalone \textit{51} should be base-labile as was actually observed. Application of the modified Klyne-Hudson rule,\textsuperscript{71} using the molecular rotation values of -12° for \textit{45} and +42° for \textit{47}, supported the 8α (R)\textsuperscript{72} stereochemical assignment.

Although tetrahydroligularenolide \textit{44} has not yet been isolated from natural sources, it has been obtained,\textsuperscript{73,74} in high yield, by palladium-catalyzed hydrogenation of the naturally occurring (-)-ligularenolide \textit{55}. The latter was isolated\textsuperscript{73} in 1968 from the herb "San-Shion", the root of a \textit{Ligularia} species. The assignment of structure and absolute configuration to both compounds\textsuperscript{73,74} was based upon spectral evidence and upon the correlation of \textit{44} with a compound of known absolute stereochemistry.

\begin{center}
\begin{tikzpicture}
  \node (A) at (0,0) {\includegraphics[width=0.4\textwidth]{ligularenolide}};
  \node (B) at (0.4,0) {\includegraphics[width=0.4\textwidth]{ligularenolide}};
\end{tikzpicture}
\end{center}

\textit{Ligularenolide \textit{55}} (C\textsubscript{15}H\textsubscript{18}O\textsubscript{2}) exhibited absorption bands in the infrared spectrum characteristic of an α,β-unsaturated γ-lactone (1764, 1648 and 1621 cm\textsuperscript{-1}), while the ultraviolet spectrum indicated the presence of a conjugated system [\(\lambda_{\text{max}}\) 261 and 331 μ (ε = 3560 and 20,700)]. The p.m.r. spectrum showed the presence of three methyl groups, primary, secondary and vinyl at τ 9.03, 9.00 and 8.09 respectively; of two vinyl protons at τ 4.21 and 4.08; and of an allylic methylene group which gave rise to a doublet (\(J = 16.5\) Hz) at τ 7.15 and a broadened doublet (\(J = 16.5\) Hz) at τ 7.78.
By extensive use of proton magnetic double and triple resonance experiments, it was shown that long-range spin-couplings existed between the two vinyl protons \((J = 0.8 \, \text{Hz})\), between the allylic proton \((\tau 7.78)\) and the tertiary methyl group \((J = 0.5 \, \text{Hz})\), and between the same allylic proton and the vinyl methyl group \((J = 1.7 \, \text{Hz})\). This suggested that the vinyl methyl group was attached to the double bond in the lactone ring and that the angular methyl group and the allylic proton \((\tau 7.78)\) were both axial. These observations led to the partial working structure 56 which was extended to the full structure 55 from biogenetic considerations and on the basis of the observed features of long-range spin-couplings.

Catalytic hydrogenation of \((+)-\text{ligularenolide} \, 55\) yielded the \((-)-\text{tetrahydro} \, \text{derivative} \, \left(C_{15}H_{22}O_2\right) \, 44\) which was named \text{tetrahydroligularenolide}. The ultraviolet \(\lambda_{\text{max}} = 222 \, \text{nm} \, (e = 24,000)\) and the infrared \(\nu_{\text{max}} = 1765, 1745\) and \(1678 \, \text{cm}^{-1}\) spectral data indicated that the \(\alpha,\beta\)-unsaturated \(\gamma\)-lactone system was still intact. In the p.m.r. spectrum, the vinyl proton signals were absent and a complex multiplet (width at half height = ca. 22 Hz) due to the proton at the lactone terminus \((C_8)\) was evident. The large width at half height of this \(C_8\) proton signal, and the presence of long-range spin-couplings between it and the olefinic methyl protons, implied that the \(C_8\) proton was axial.

That tetrahydroligularenolide did indeed possess structure 44 was shown by the conversion of compound 57 into tetrahydroligularenolide. The former, a known compound prepared\(^{30}\) from naturally occurring \((+)-\text{furanoligularenone} \, 31\) of known absolute stereochemistry,\(^{30}\) when treated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), afforded the enol
lactone 58, contaminated with 44. Hydrogenation of this mixture over 5% palladium on charcoal gave pure 44, the infrared and p.m.r. spectra of which were identical with those of tetrahydroligularenolide. A molecular model indicates that hydrogenation of 58 is less hindered from the alpha face and thus the expected product should have an \(\alpha\)-oriented \(\text{C}_8\) hydrogen, as was implied also by the p.m.r. spectrum. The absolute configuration of (-)-tetrahydroligularenolide and the (+)-ligularenolide follow from the conversion of (+)-furanoligularenone 31 into (-)-tetrahydroligularenolide and are those represented in structure 44 and 55 respectively.
The hydrocarbon (-)-aristolochene $^{34}$ was recently (1970) isolated$^7$ from the roots of *Aristolochia indica*. The structure and absolute stereochemistry were determined$^7$ from spectral data of $^{34}$ and derivatives thereof, and by direct correlation of $^{34}$ with (+)-nootkatane, of known absolute stereochemistry.

The infrared spectrum of aristolochene ($\text{C}_{15}\text{H}_{24}$) $^{34}$, different from that of the structurally closely related valencene $^{33}$, showed the presence of a terminal methylene group with absorptions at 3080, 1648 and 886 cm$^{-1}$, and of a trisubstituted double bond with a band at 810 cm$^{-1}$. The ultraviolet spectrum showed that the double bonds were not conjugated. In the p.m.r. spectrum, the presence of a primary, a secondary and a vinyl methyl group was evident from the singlet at $\tau$ 9.05, the doublet ($J = 6$ Hz) at $\tau$ 9.17 and the broad signal at $\tau$ 8.30 respectively. The terminal olefinic protons and the vinyl protons of the trisubstituted double bond gave rise to a broad singlet at $\tau$ 5.33 and a broad multiplet at $\tau$ 4.75 respectively.

Selenium-dehydrogenation of aristolochene $^{34}$ afforded eudalene $^{59}$ (see Chart 4), suggesting either the eremophilane or the eudesmane carbon skeleton for the former compound. Hydrogenation of aristolochene, using deactivated Raney nickel, afforded the dihydro derivative ($\text{C}_{15}\text{H}_{26}$)
Chart 4
the p.m.r. spectrum of which indicated the selective saturation of the terminal olefin. The latter was subjected to successive hydroboration with oxidative workup (alkaline hydrogen peroxide), chromium trioxide oxidation of the resulting mixture of alcohols and homogenization of the product over basic alumina, to afford the trans-fused decalone. This decalone was converted into its ethylene dithioketal derivative, the mass spectrum of which showed an intense peak at m/e 173 due to the ion. This suggested that the trisubstituted double bond was in the ring to which the isopropyl side-chain was attached.

Catalytic hydrogenation of aristolochene over platinum oxide afforded two hydrocarbons. One was 7-epi-eremophilane. The other was (+)-nootkatane, which was identical in all respects with an authentic sample of (+)-nootkatane, prepared from (+)-valencene. This correlation provided a direct chemical proof for the assignment of structure to aristolochene, including absolute stereochemistry.

3. Other Synthetic Approaches to Eremophilane-Type Sesquiterpenoids

While it is not possible, in the interests of brevity, to discuss here each of the syntheses of eremophilane-type sesquiterpenoids reported to date, it does seem pertinent to present a few representative examples.

The first total synthesis of an eremophilane sesquiterpenoid, was that of isonootkatone (a-vetivone), reported in 1967 by Marshall, Faubl and Warne. The key reaction in their sequence was the condensation of 2-carbomethoxy-4-isopropylidenecyclohexanone with trans-3-penten-2-one in the presence of potassium t-amylate in t-amyl
alcohol. This afforded, after cyclization and dehydration, the keto ester 68 as a readily purifiable crystalline material. Ketalization of 68, and reduction of the carbomethoxy group in the resulting ketal 69 to the methyl group (69 → 70 → 71 → 72) gave, after ketal hydrolysis, isonootkatone 73. The latter showed spectral properties identical with those of the naturally occurring material.

Considerable effort has since been devoted to the synthesis of nootkatanes, but each approach (excepting one) has also involved a similar Robinson annelation of a suitably substituted cyclohexanone derivative with trans-3-pentene-2-one. Coates and Shaw also used this technique to generate the cis-dimethyl system in the dione 75 (see
Chart 5) which led to the synthesis of a number of eremophilane-type
sesquiterpenoids. Thus condensation of the pyrrolidine enamine
of 2-methylcyclohexane-1,3-dione with trans-3-pentene-2-one gave a
mixture of the cis- and trans-dimethyloctalones, varying in ratio
from 1:1 to 1:10 respectively depending on the reaction conditions
employed. Selective thio-ketalization of the 1:1 mixture, followed by
desulfurization of the resulting thio-ketals with Raney nickel, afforded
a mixture of the cis- and trans-dimethyloctalones and , which were
separated by fractional distillation of the mixture through a spinning-
band column. Reaction of the cis-dimethyl octalone with diethyl
carbonate, in the presence of sodium hydride, produced the corresponding
β-keto ester as a mixture of the keto and enol tautomers, formulated
here as . The latter, when treated with methyllithium, followed by
acid-catalyzed dehydration of the resulting β-hydroxy ketone, gave rise
to the α,β-unsaturated ketone . Treatment of this ketone with
hydrazine, followed by thermal decomposition of the resulting pyrazoline
over powdered potassium hydroxide, afforded racemic aristolone , which was identical in all respects (except optical
activity)with an authentic sample from plant sources.

Subjection of keto ester to alkylation with chloromethyl methyl
er ether in hexamethylphosphoramide afforded the enol ether derivative .
Reduction of the latter with lithium in liquid ammonia, followed by
appropriate work-up, produced the octalin ester . The formation of
the less stable axial epimer was presumably the result of kinetically
controlled protonation (during work-up) of the ester enolate from the
less hindered equatorial direction. Reaction of this ester with
Chart 5
methyllithium afforded eremoligenol 84 which, when dehydrated, yielded eremophilene 37. Eremoligenol and eremophilene thus obtained exhibited spectral properties identical with those of the corresponding naturally occurring materials.

Because of the axial nature of the carbethoxy group in 83, this compound was epimerizable to the more stable ester 85. Subjection of the latter to methyllithium addition and subsequent dehydration produced valerianol 36 and valencene 33 respectively. The spectral data of 36 and 33 were identical with those obtained for the naturally occurring materials.

A different approach to the introduction of the cis-dimethyl system in eremophilanes was explored by Piers and Keziere in their synthesis of eremophil-3,11-diene 90. Condensation of the hydroxymethylene derivative 86 of 3-isopropenylcyclohexanone with 1-diethylamino-3-pentanone methiodide 87 gave, after cyclization, the octalone 88. Stereoselective introduction of the angular methyl group was accomplished by reaction of octalone 88 with lithium dimethylcuprate, thus yielding the cis-dimethyl decalone derivative 89. The tosylhydrazone derivative of the latter was reacted with sodium ethylene glycolate in refluxing
ethylene glycol, yielding as major product racemic eremophila-3,11-diene 90. Structure 90 was originally proposed\textsuperscript{77} for naturally occurring eremophilene but a comparison of the synthetic material with an authentic sample of eremophilene showed them to be different. The structure of eremophilene was later revised\textsuperscript{39} to that of 37.
PART I
DISCUSSION

1. Total Synthesis of (+)-Eremophilene 6 and Tetrahydroligularenolide 44

In an attempt to develop a rational, general, synthetic scheme for the synthesis of compounds of the eremophilane family of sesquiterpenoids, the total synthesis of (+)-eremophilene 6, (+)-tetrahydroligularenolide 44 and (+)-aristolochene 34 was undertaken. Taken together, these three compounds incorporate most of the problems posed in the synthesis of eremophilanes. Their common stereochemical feature, the only one common to all the eremophilane sesquiterpenoids, is the presence of the distinctive, vicinal, cis-related methyl substituents. The introduction of this system at an early stage of the synthesis would be of greatest use synthetically, since at least a partial common synthesis to the three compounds was desired. The common intermediacy
of a substituted octalin-type derivative with the unsaturation at the bridgehead position (Δ¹) was also desirable. Such a compound could then be elaborated to give aristolochene, and hopefully could also be selectively hydrogenated to afford both the cis and trans ring junctions required for the synthesis of eremophilone and tetrahydroligularenolide respectively.

At the outset of this work in 1969, a number of approaches to the construction of the cis dimethyl system of various eremophilanes had been attempted, but most had failed to provide a stereoselective method of accomplishing this. In connection with a synthetic proof of the stereochemistry of aristolone, an annelation of 2,3-dimethylcyclohexanone had been developed in our laboratory, which resulted in the stereoselective synthesis of the synthetically elusive octalone. It was felt that this octalone provided an ideal synthetic precursor to the eremophilanes and it was thus adopted as an intermediate in the present synthesis. Not only did this compound satisfy the requirement with regard to the cis-related vicinal methyl groups but it also possessed the desired unsaturation at the ring junction which hopefully could be manipulated as mentioned above. In addition, the
ketone functionality was strategically placed for the introduction of
the remaining three-carbon unit required for the completion of the
syntheses. This functionality would also provide the oxygen atom at
C₈ which was necessary for the introduction of the lactone functionality
present in eremophilenolide 6 and tetrahydroligularenolide 44.

The octalone 92 was prepared from 2,3-dimethylcyclohexanone 93
by the method previously mentioned. Thus, the latter, readily
available starting material was converted in 78% yield into the 6-n-
butylthiomehtylene derivative 94 (see Chart 6) in the usual manner. Alkylation of the latter with ethyl 3-bromopropionate in the presence
of potassium t-butoxide in t-butyl alcohol produced, in 85% yield, a mixture of the keto esters 95. Removal of the n-butylthiomehtylene
blocking groups from 95 was achieved in the normal way (potassium hydroxide in hot aqueous diethylene glycol) and was accompanied by
hydrolysis of the ester group. The product, a mixture of the keto acids 96, was obtained in 90% yield. When this mixture of keto acids
was refluxed in acetic anhydride containing sodium acetate, there
was produced, in 85% yield, a crystalline material which consisted of
a mixture of the two epimeric enol lactones 97 and 98 in the approximate
ratio of 9:1 respectively (as judged by the p.m.r. spectrum). The
major desired epimer 97 could readily be separated from the mixture
in 80% yield by careful recrystallization of the latter from n-hexane.
This enol lactone 97 was converted, in 70% yield, into the desired
octalone 92 by reaction of the former with methyllithium in dry ether
at -25°, followed by successive acid hydrolysis and base-catalyzed
aldol cyclization and dehydration.
Chart 6
The octalone 92 could be selectively reduced to afford either the cis-fused decalone 99 or the trans-fused decalone 100. Thus, this octalone might be considered a suitable branch-point for the synthesis of the three sesquiterpenoids under discussion. However, while it was anticipated that the octalone 92 and the decalone 100 could be regioselectively alkylated at the desired C3 positions (and subsequently be transformed into aristolochene 34 and tetrahydroligular-enolide 44 respectively), it was felt that the cis-fused decalone 99 (the corresponding precursor to eremophilenolide 6) would present a major problem in this regard. Indeed, exploratory work performed in our laboratory on the cis-fused decalone 99, had indicated that alkylation at the C3 position was not a feasible process. Thus, attempted alkylation of 99 with ethyl 2-bromopropionate or with methyl bromoacetate in t-butyl alcohol in the presence of potassium t-butoxide, afforded a complex mixture of products. On changing the base and the solvent to triphenylmethy1sodium (tritylsodium) and 1,2-dimethoxy-ethane respectively, similar results were obtained. Furthermore, in an effort to at least avoid the problem of polyalkylation, 99 was converted by standard procedures into the mixture of enamine derivatives 101 and 102, which were obtained in a ratio of 2:3 respectively. Attempted alkylation of this mixture with ethyl 2-bromopropionate was also unsuccessful. Some alkylated product was obtained using methyl bromoacetate as alkylating agent, but the yield was low, especially low in the desired product because of the unfavorable ratio of the starting enamines.
A more favorable ratio was obtained of the corresponding enol acetates 103 and 104, formed from the decalone 99 and isopropenyl acetate under equilibrating conditions. The ratio of 103 to 104 was 3:2 respectively. When the mixture of lithium enolates corresponding to 103 and 104 was reacted with ethyl 2-bromopropionate, the spectra of the products obtained were not in agreement with those predicted for the desired compound.

In view of these preliminary results, it was felt that the elaboration of the cis-fused decalone 99 to eremophilenolide 6 would prove to be an inefficient process, and hence this transformation
was not attempted. Since the difficulty in selectively alkylating decalone 99 at the C₃ position stemmed at least partially from the cis nature of the ring fusion, it was decided to introduce the side-chain at C₃ prior to the generation of the cis-fused ring junction.

On the basis of literature precedent, the direct alkylation of octalone 92 would be expected to result in preferential alkylation at the C₁ position, not at the desired C₃ position. Therefore in order to alkylate regioselectively at the C₃ position, an activating group would first have to be introduced at this position. Since a common synthetic precursor to the three sesquiterpenoids was desirable, the keto ester 105 was chosen as the activated form of octalone 92. The direct alkylation of this keto ester would hopefully result in an intermediate which could be selectively hydrogenated to afford both the cis-fused and the trans-fused intermediates required for the synthesis of the two lactone-containing sesquiterpenoids. The elaboration of the carbomethoxy group itself (in 105) would afford the isopropenyl side-chain required for aristolochene synthesis.

The keto ester 105 was obtained from the octalone 92 by means of an efficient and completely regioselective synthetic route as outlined in Chart 7. The octalone 92 was converted into the hydroxymethylene...
derivative in quantitative yield, by standard procedures (ethyl formate in benzene in the presence of sodium methoxide).

Dehydrogenation of the latter with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in dioxan afforded, in 95% yield, the crystalline cross-conjugated keto aldehyde. The spectral properties of this material were consistent with structure. Of particular interest in the infrared spectrum were the four absorption bands at 1700, 1660, 1625 and 1600 cm\(^{-1}\). In the p.m.r. spectrum the aldehydic proton and the \(\beta\)-vinyl proton were evident as sharp singlets at \(\tau\ -0.33\) and 2.17 respectively, while the \(\alpha\)-vinyl proton gave rise to a broadened singlet at \(\tau\ 3.80\). The tertiary methyl group appeared as a singlet at \(\tau\ 8.76\) and the secondary methyl group as an unresolved multiplet at \(\tau\ 8.87\).

Oxidation of the keto aldehyde with silver oxide afforded the crystalline keto acid in 89% yield. The presence of the carboxyl group was evidenced in the infrared spectrum by the broad absorption band at 3600-2280 cm\(^{-1}\) and in the p.m.r. spectrum by the broad singlet at \(\tau\ -3.55\). The singlet due to the aldehydic proton had disappeared.

Esterification of the keto acid was carried out by reacting it with methyl iodide in the presence of silver oxide. The corresponding keto ester was thus obtained in 96% yield.

The conversion of compound into the desired keto ester required the selective reduction of one of the trisubstituted olefinic double bonds in. This was accomplished, in 86% yield, by reduction of with sodium borohydride in pyridine solution. It has been shown that such reaction conditions can be used to selectively reduce
an olefinic double bond which is conjugated with two carbonyl groups as in \(\text{109}\), without reducing either of the carbonyl functionalities themselves. The keto ester thus obtained, exhibited spectral properties in complete agreement with structure \(\text{105}\). The infrared spectrum of \(\text{105}\) showed an absorption at 1740 cm\(^{-1}\) for the ester carbonyl group, and bands at 1670 and 1620 cm\(^{-1}\) due to the \(\alpha,\beta\)-unsaturated ketone. That the desired reduction had indeed taken place was evident from the p.m.r. spectrum. Thus the signal due to the \(\beta\)-vinyl proton had disappeared and a new signal, a doublet of doublets (\(J = 13.0\) and 6.0 Hz), was evident at \(\tau\) 6.57. The latter signal was attributed to the \(C_3\) proton.

Chart 7
Since the work-up of the reduction reaction just described involved epimerizing conditions, the keto ester 105 was expected to possess the thermodynamically more stable configuration at C₃, which is that shown in structure 105. The p.m.r. spectrum supported this, since the observed C₃ proton coupling constants, J = 13.0 and 6.0 Hz, are in agreement with those expected for the coupling of an axial C₃ proton to the C₄ axial and equatorial protons respectively.⁹²

An alternative, direct conversion of the octalone 92 into the keto ester 105 involving base-promoted condensation of the former with dimethyl carbonate was also considered. However, on the basis of literature precedent,⁸⁶a it was felt that a reaction of this type would result in carboxymethoxylation of 92 at C₁ as well as at the desired position (C₃), and hence this reaction was not attempted in the present synthesis. Indeed, this direct conversion was later attempted⁵⁸ and the product, although claimed to be 105, was not obtained crystalline and no criterion of purity was given.

Attempted alkylation of the sodium enolate of keto ester 105 with ethyl 2-bromopropionate in refluxing benzene, resulted in an almost quantitative recovery of starting material. On changing the alkylating reagent to methyl bromoacetate, however, there was obtained, under the same reaction conditions, a quantitative yield of the keto diester 110. The failure to alkylate with ethyl 2-bromopropionate meant that the final carbon atom required to complete the syntheses, would have to be introduced at a later stage.

The spectral data obtained for the product of successful alkylation were in agreement with structure 110. The infrared spectrum clearly
showed the presence of the two ester carbonyl groups with absorptions at 1740 and 1720 cm\(^{-1}\). Consistent with this were the two singlets at \(\tau 6.35\) and \(\tau 6.41\) in the p.m.r. spectrum. The quartet attributed to the \(\text{C}_3\) proton in the starting material had disappeared, but the \(\text{C}_1\) vinyl proton was still evident as a broad singlet at \(\tau 4.22\). Thus the alkylation reaction had proceeded in the desired regioselective manner. In addition, since the presence of only one diastereomeric product was indicated, this reaction was also stereoselective. Although the stereochemistry of the product was not rigorously proven, literature precedent\(^9\) indicated that the newly alkylated center should possess the configuration shown in 110. In any event, this point was not crucial, since the next step of the synthesis involved hydrolysis and decarboxylative removal of the tertiary carbomethoxy group.

\[ \text{105} \rightarrow \text{110} \rightarrow \text{111} \]

Treatment of the diester 110 with sodium hydroxide in refluxing ethanol-water for thirty minutes, provided the crystalline keto acid 111 in 82\% yield. This material exhibited the expected spectral properties. Of particular pertinence in the infrared spectrum was the broad band at 3600-2400 cm\(^{-1}\) and the absorption at 1710 cm\(^{-1}\) due to the carboxyl group. The broad singlet at \(\tau -1.30\) in the p.m.r. spectrum was attributed to the exchangeable carboxylic acid proton. Since this
keto acid was formed under epimerizing conditions the stereochemistry at C₇* is undoubtedly that indicated. The epimeric compound would possess a 1,3-diaxial interaction between the angular methyl group and the acetic acid side-chain.

In order to obtain (from 111) a synthetic intermediate suitable for elaboration into eremophilenolide, it was necessary to reduce the double bond of 111 so as to produce the corresponding cis-fused decalone system. On the other hand, reduction to a trans-fused decalone was required for the production of a suitable precursor to tetrahydro-ligularenolide.

Hydrogenation of 111 in ethanol over palladium on charcoal afforded, in quantitative yield, the crystalline trans-fused keto acid 112. It was subsequently shown by an independent synthesis that compound 112 had the trans-fused configuration (vide infra). This compound gave a strong absorption band at 1705 cm⁻¹ in the infrared spectrum, due to the two carbonyl groups and, in the p.m.r. spectrum, showed no signal due to a vinyl proton. The tertiary methyl group gave rise to a singlet at τ 9.00 and the secondary methyl group to an unresolved multiplet at τ 9.12.

Subjection of keto acid 111 to hydrogenation with palladium on charcoal under basic conditions (ethanolic sodium hydroxide) afforded a quantitative yield of a mixture of the cis-fused decalone 113 and the previously obtained trans-fused compound 112 in a ratio of approximately 2:3 respectively (as determined by the p.m.r. spectrum). At this stage,

* Unless otherwise noted, eremophilane system numbering will be henceforth employed.
considerable effort was expended in order to find conditions which
would increase the proportion of the desired cis-fused keto acid 113.
Eventually it was found that hydrogenation of 111 in ethanolic sodium
hydroxide using rhodium on charcoal as catalyst, gave improved results.
However, under these conditions the ketone carbonyl group was also
reduced, and it was therefore necessary to oxidize the initially formed
hydrogenation product. This was readily accomplished by treating the
crude product with ruthenium dioxide-sodium periodate under basic
conditions. There was thus obtained, in quantitative yield, a
mixture of the cis-fused decalone 113 and the trans-fused decalone 112
in a ratio of approximately 3:2 respectively. The two keto acids were
isolated in pure form by careful fractional crystallization of this mixture from hexane-benzene.

The spectral properties of the crystalline *cis*-fused decalone 113 were in complete agreement with the structure shown. In the infrared spectrum, the carbonyl groups gave rise to a common absorption at 1708 cm\(^{-1}\), the carboxyl group exhibiting a further broad band at 3600-2400 cm\(^{-1}\). Of pertinence in the p.m.r. spectrum was the singlet at \(\tau 9.09\) due to the tertiary methyl group, and the clean doublet \(^{88}\) (\(J = 7.0\) Hz) at \(\tau 9.12\) due to the secondary methyl group.

Since both the hydrogenation and oxidation reactions were carried out under basic, epimerizing conditions, the stereochemistry (at \(C_7\)) of the
cis-fused keto acid should be as indicated in 113. The latter, on the basis of conformational analysis, would be more stable than the corresponding epimeric (at C₇) compound. Thus 113a, the preferred conformation of 113, is thermodynamically more stable than 114a' the preferred conformation of the C₇ epimer of 113. This is mainly due to the fact that the secondary methyl group is in an axial orientation (with respect to ring A) in 114a'.

The stereochemical outcome of the hydrogenation reactions just described merits further comment. The effect of increasing the ratio of cis-fused decalone products by employing basic conditions in the catalytic hydrogenation of octalone derivatives had previously been observed, in particular instances. In our own laboratory, the catalytic hydrogenation of octalone 92 and its hydroxymethylene derivative 106, when performed under basic conditions, yielded only the corresponding cis-fused products. On the basis of these latter results, a higher ratio of the cis-fused decalone 113 was expected on hydrogenation of the structurally related octalone 111 under similar reaction conditions. The low ratio actually obtained in this instance may reflect the 1,3-diaxial-type interaction generated (between -CH₂CO₂H and C₄), as the

![Chemical Structures](image-url)
acetic acid side-chain is forced towards the unstable axial position in the transition state, leading to the cis-fused product.

When the cis-fused keto acid 113 was subjected to standard lactonization conditions (refluxing acetic acid in the presence of sodium acetate\(^7\)), the expected unsaturated lactone 115 was produced in very low yield. The spectral data of the crude reaction product mixture indicated that the major component was the mixed anhydride of the keto acid 113 and acetic acid. Analogous results were obtained with the trans-fused keto acid 112. However, on treating the cis-fused keto acid 113 with p-toluenesulfonic acid in refluxing toluene under a Dean-Stark water separator, there was obtained, in 97% yield, a crystalline mixture of 11-demethyleremophilenolide 115 and 8-epi-11-demethyleremophilenolide 116, in a ratio of approximately 7:3 respectively. Recrystallization of this mixture afforded the desired (+)-11-demethyleremophilenolide 115 in 55% yield. The spectral data supported the proposed structure for this latter compound. Thus the ultraviolet spectrum of 115 exhibited on absorption maximum at 216 \(\text{m}\mu\), while the infrared spectrum showed bands at 1780, 1745 and 1650 cm\(^{-1}\) characteristic of this type of lactone functionality. The p.m.r. spectrum revealed a vinyl proton as an unresolved multiplet (width at half height = 6.0 Hz) at \(\tau 4.31\), while the very broad unresolved multiplet at \(\tau 5.26\) (width at half height = 19 Hz) was assigned to the \(\text{C}_8\) proton. The doublet (J = 14.0 Hz) at \(\tau 7.10\) was attributed to the \(\text{C}_6\) equatorial proton, the singlet at \(\tau 8.99\) to the tertiary methyl group and the doublet (J = 6.0 Hz) at \(\tau 9.23\) to the secondary methyl group.
Attempts to obtain a pure sample of 8-epi-11-demethyleremophilenolide were not successful. However, the spectral data obtained on the mother liquors (containing 115 and 116, ratio 1:2 respectively) of recrystallization of the lactonization product supported the assigned structure. Thus the infrared spectrum exhibited absorption bands at 1785, 1750 and 1640 cm\(^{-1}\). In the p.m.r. spectrum, the presence of a vinyl proton was evident from the unresolved multiplet (width at half height = 4.0 Hz) at \(\tau\) 4.24. The broad unresolved multiplet (width at half height = 20 Hz) at \(\tau\) 5.07 was attributed to the \(\text{C}_8\) proton, while the two doublets (\(J = 14.0\) Hz) at \(\tau\) 7.00 and 7.87 were assigned to the \(\text{C}_6\) protons. The secondary and tertiary methyl groups gave rise to a doublet (\(J = 6.6\) Hz) at \(\tau\) 8.97 and a singlet at \(\tau\) 9.13 respectively.

That the major product of lactonization was 11-demethyleremophilenolide 115 and not 8-epi-demethyleremophilenolide 116 was supported by the following evidence. As mentioned above, subjection of keto acid 113 to lactonization conditions (refluxing toluene in the presence of \(p\)-toluenesulfonic acid) for 3 hours afforded 115 and 116, in the ratio of approximately 70:30 respectively. When the reaction was allowed to
proceed for 6 hours, the ratio of 115 to 116 increased to approximately 85:15 respectively. Under the epimerizing conditions of the reaction, the thermodynamically more stable product should predominate. On the basis of conformational analysis, 11-demethyleremophilenolide 115 is thermodynamically more stable than 8-epi-11-demethyleremophilenolide 116. Thus a comparison of 115a, the preferred conformation of 11-demethyleremophilenolide, and 116a, the all-chair conformation of 8-epi-11-demethyleremophilenolide, shows that the latter is thermodynamically less favored, mainly because of the axial orientation (with respect to ring A) of the secondary methyl group. A similar comparison of 115a with the
alternative conformation \(^{116a*}\) of 8-epi-11-demethyleryremophilenolide, shows that the latter is also less favored thermodynamically, due to the presence in the latter of the twist-boat conformation in ring B.

The final carbon required for completion of the synthesis of eremophilenolide 6 was introduced via an alkylation reaction. Thus 11-demethyleryremophilenolide \(^{115}\) was treated with tritylsodium, and the resulting enolate was reacted with methyl iodide to give racemic eremophilenolide 6, in 61% yield. That the desired alkylation had occurred was evident from the spectral data of the product. Thus, in the ultraviolet spectrum, an absorption maximum appeared at 220 \(\text{m} \mu\), while, in the infrared spectrum, the absorption band at 1780 cm\(^{-1}\) had now disappeared, indicating the absence of the \(C_{11}\) proton. This was confirmed by the p.m.r. spectrum which, although similar to that of the starting lactone, showed no signal due to a vinyl proton. Instead, an unresolved multiplet was evident at \(\tau\) 8.21, attributed to the newly introduced vinyl methyl group. The infrared (Figure 1) and p.m.r. (Figure 2) spectra of synthetic (+)-eremophilenolide thus prepared, were identical with those of an authentic sample of natural (+)-eremophilenolide* (infrared spectrum, Figure 3; p.m.r. spectrum, Figure 4).

The previously mentioned mother liquors of recrystallization, containing a 1:2 mixture of 11-demethyleryremophilenolide \(^{115}\) and 8-epi-11-demethyleryremophilenolide \(^{116}\), also proved to be synthetically useful. Thus alkylation of this mixture with methyl iodide under conditions

* We are very grateful to Professor V. Herout for a sample of (+)-eremophilenolide.
Figure 1. Infrared Spectrum of Synthetic (+)-Fremophilinolide 6.
Figure 2. P.M.R. Spectrum of Synthetic (+)-Eremophileneolide 6.
Figure 3. Infrared Spectrum of Authentic (+)-Eremophilenolide 6.
Figure 4. P.M.R. Spectrum of Authentic (+)-Eremophilenoide 6.
identical with those used in the alkylation of pure 11-demethyl-eremophilenolide, also afforded (+)-eremophilenolide, in 52% yield.

The trans-fused keto acid 112 was converted into (+)-tetrahydroligularenolide 44 by a sequence of reactions identical with that described above for the conversion of the cis-fused keto acid 113 into (+)-eremophilenolide 6. Lactonization of 112 yielded the crystalline (+)-11-demethyltetrahydroligularenolide 117 in 94% yield. This material exhibited spectral properties similar to those of (+)-11-demethyleremophilenolide 115. Thus, the ultraviolet spectrum exhibited an absorption maximum at 216 μm and the infrared spectrum
the expected absorption bands at 1780, 1745 and 1645 cm\(^{-1}\). The p.m.r. spectrum revealed an unresolved multiplet (width at half height = 4.0 Hz) at \(\tau\) 4.34 due to the vinyl proton and a broad unresolved multiplet (width at half height = 19.0 Hz) at \(\tau\) 5.33 due to the C\(_8\) proton. The doublet \((J = 13.0\) Hz\) at \(\tau\) 7.25 was assigned to the C\(_6\) equatorial proton,\(^7\) the poorly resolved doublet \((J = 5.5\) Hz\) at \(\tau\) 9.15 to the secondary methyl group and the singlet at \(\tau\) 9.36 to the tertiary methyl group.

The assignment of configuration to the C\(_8\) position of the lactone product 117 was based on the fact that, as in 11-demethyleremophilenolide 115, the thermodynamically more stable product was expected under the equilibrating conditions of the reaction. Thus structure 117a is thermodynamically favored over 118a, since ring B in the latter possesses the twist-boat conformation.

Methylation of 117 afforded racemic tetrahydroligularenolide 44, in 59\% yield. The expected changes in the spectral data were observed. Accordingly, there was a shift in the absorption maximum in the ultraviolet spectrum to 220 \(\mu\)m, and the absorption band at 1780 cm\(^{-1}\) in the infrared spectrum of the starting material disappeared. In the p.m.r. spectrum the signal due to the vinyl proton had disappeared, and an unresolved multiplet was now evident at \(\tau\) 8.21, attributed to the newly introduced vinyl methyl group. Although an authentic sample of \((-)\)-tetrahydroligularenolide was not obtained, the infrared (Figure 5) and p.m.r. (Figure 6) spectra of the synthetic racemate thus prepared, agree very well with the published data.\(^7\)\(^3\),\(^7\)\(^4\)
Figure 5. Infrared Spectrum of Synthetic (+)-Tetrahydroligularenolide 44.
Figure 6. P.M.R. Spectrum of Synthetic (+)-Tetrahydroligularenolide 44.
2. Stereochemical Proof of trans-Fused Keto Acid 112

Since one of the objectives of the synthesis of a natural product is generally to provide unambiguous evidence for a structural proposal, it was important to prove unequivocally the stereochemistry of the ring junction in the two decalones, 112 and 113, obtained by hydrogenation of the corresponding octalone 111. The hydrogenation reactions which afforded a mixture of two products were performed under basic, equilibrating conditions, and it could therefore readily be concluded that the two products were not merely C7 epimers of one type of ring-fused product. Consequently, the configurational difference was at the C10
ring junction position. Thus an unambiguous synthesis of one of the keto acids 112 or 113 would provide proof of the stereochemistry of the other keto acid also.

In view of the previously mentioned (see p. 36) failure to alkylate the cis-fused decalene 99, it was decided to use the corresponding, known, trans-fused decalene 100 for the present stereochemical proof.

Decalene 100 was prepared from octalene 92 by successive Birch reduction and oxidation. Treatment of this trans-fused decalene 100 with isopropenyl acetate-p-toluenesulfonic acid afforded a mixture of the corresponding enol acetates 119 and 120, in a ratio of approximately
3:2 respectively. Reaction of this mixture with two equivalents of methyllithium in dimethoxyethane, followed by the addition of methyl bromoacetate, gave a mixture of compounds from which a sample of the keto ester \( \text{121} \) could be isolated by column chromatography. Alkaline hydrolysis of \( \text{121} \) yielded the keto acid \( \text{112} \), which was identical in all respects (m.p., mixed m.p., infrared and p.m.r. spectra) with the product obtained by hydrogenation of octalone \( \text{111} \) under neutral conditions (vide supra).

The above synthetic proof of the \( \text{C}_{10} \) stereochemistry of the trans-fused keto acid \( \text{112} \) established the trans nature of the ring fusion in tetrahydroligularenolide \( \text{44} \). Similarly, it confirmed the cis relationship
of the ring fusion in eremophilenolide 6. The assignment of stereochemistry to the asymmetric lactone terminal positions (C<sub>8</sub>) in eremophilenolide 6 and tetrahydroligularenolide 44, was based on the generation of these centres under equilibrating conditions, the structures 6 and 44 being in each case the thermodynamically more stable epimers (vide supra).

3. Total Synthesis of (+)-Aristolochene 34

Aristolochene 34 was also successfully synthesized from the key intermediate keto ester 105. An ideal precursor to aristolochene was the olefinic ester 124 and hence the initial objective was reduction of the C<sub>2</sub> keto group in 105 to the methylene group. It was felt that a convenient method of accomplishing this was by reduction of 105 to the corresponding alcohol 122, acetylation (or equivalent) of the latter, and, finally, reductive cleavage of the resulting acetate 123 (or equivalent).
When the keto ester 105 was treated with excess sodium borohydride in methanol at room temperature for one hour, the crude product obtained consisted of three compounds. These were the starting material 105, the desired alcohol 122 and a third component which appeared to be the diol 125. While such unwanted reductions of β-carbonyl esters to the corresponding diols are known to occur, sometimes the reaction conditions can be controlled to give a good yield of the monoalcohol product. All efforts in the present instance failed in this regard. Indeed, attempts to obtain the diol in high yield were also unsuccessful, so this approach was not investigated further.
An alternative method of reducing a keto group to the methylene group is by successive thioketalization and desulfurization. When the keto ester 105 was reacted neat with 1,2-ethanediithiol in the presence of boron trifluoride-etherate, a crystalline product was obtained in good yield. This was not the desired thioketal 127 however, rather it appeared to be the interesting thioketal lactone 126, as deduced from a preliminary analysis. When the reaction conditions were modified by employing acetic acid as solvent, there was produced, in quantitative yield, a crystalline mixture of the desired thioketal 127 and its C₃ epimer 128 in a ratio of approximately 4:1 respectively. The former could very readily be isolated in pure form by recrystallization of the mixture from methanol. The spectral properties of this material were in complete agreement with structure 127. Accordingly, the infrared spectrum showed one carbonyl absorption at 1728 cm⁻¹ due to the ester functionality. The p.m.r. spectrum revealed a singlet at τ 4.32 due to the vinyl proton, and a multiplet at τ 6.52-6.99 which was assigned to the -SCH₂CH₂S- group and the C₃ proton. The three methyl groups gave rise to a singlet at τ 6.32 (methoxy methyl), a singlet at τ 9.07 (tertiary methyl) and an unresolved multiplet at τ 9.15 (secondary methyl).
Desulfurization of 127 with Raney nickel in refluxing ethanol, followed by purification of the crude product by preparative g.l.c., afforded the desired olefinic ester 124 in 63% yield. In the p.m.r. spectrum of this compound the expected broadening of the vinyl proton signal had occurred. It now appeared as a broad unresolved multiplet at $\tau$ 4.72. The signals due to the three methyl groups were also clearly evident.

The mother liquors remaining from the recrystallization of thioketal 127 were also found to be synthetically useful. These mother liquors were composed of a mixture of 127 and 128 in a ratio of approximately 1:2 respectively. Desulfurization of this mixture yielded a mixture
of the olefinic esters 124 and 129 (ratio 1:2 respectively). Equilibration of the latter mixture with sodium methoxide in methanol, followed by purification of the resultant material (ratio of 124 to 129 = 9:1) by preparative g.l.c., also provided pure 124.

Because the olefinic ester 124 is thermodynamically more stable than its C₃ epimer 129, the formation of the former is favored under equilibration conditions. Consequently, the equilibration reaction just described firmly established the configuration (at C₃) of the keto ester derived from the major product of thioketalization as that shown in structure 124. Hence the major thioketal product itself must possess the stereochemistry shown in 127.
When the olefinic ester 124 was allowed to react with an excess of methyllithium in refluxing ether, the corresponding olefinic alcohol 130 was obtained in 95% yield. The infrared spectrum of this material showed a strong hydroxyl absorption at 3380 cm\(^{-1}\) while the p.m.r. spectrum exhibited two singlets at \(\tau\) 8.84 and \(\tau\) 8.85, attributed to the newly introduced methyl groups.

\[ \text{124} \quad \rightarrow \quad \text{130} \quad \rightarrow \quad \text{34} \]

Dehydration of 130 with thionyl chloride in pyridine at 0\(^\circ\)C, followed by purification of the crude product by column chromatography on silver nitrate-impregnated silica gel, gave pure racemic aristolochene 34, in 43% yield. The presence of the terminal olefin was evidenced in the infrared spectrum by absorption bands at 3075, 1645 and 887 cm\(^{-1}\), and in the p.m.r. spectrum by the unresolved multiplet at \(\tau\) 5.31. The infrared (Figure 7) and p.m.r. (Figure 8) spectra, and g.l.c. retention times of this synthetic product were identical with those of authentic (-)-aristolochene* (infrared spectrum, Figure 9; p.m.r. spectrum, Figure 10).

* We are indebted to Dr. T.R. Govindachari for a sample of (-)-aristolochene.
Figure 7. Infrared Spectrum of Synthetic (+)-Aristolochene 34.
Figure 9. Infrared Spectrum of Authentic (-)-Aristolochene 34.
In conclusion, a general synthetic approach to the eremophilane class of sesquiterpenoids has been developed. The construction of a large number of eremophilanes is conceivable from an intermediate such as the synthetically versatile keto ester 105. The feasibility of this approach is demonstrated by the unambiguous total synthesis of (+)-eremophilenolide, (+)-tetrahydroligularenolide and (+)-aristolochene. This synthesis fully corroborates the structures proposed for these three sesquiterpenoids.
**PART I**

**EXPERIMENTAL**

Melting points, which were determined on a Kofler block, and boiling points are uncorrected. Ultraviolet spectra were measured in methanol solution on a Unicam, model SP 800, spectrophotometer. Optical rotations were measured with a Perkin-Elmer, model 141, polarimeter. Routine infrared spectra were recorded on either a Perkin-Elmer model 137, 710 or 457 spectrophotometer. The latter instrument was employed for all comparison infrared spectra. The p.m.r. spectra were taken in deuterochloroform solution (unless otherwise noted) on Varian Associates spectrometers, models A-60, T-60 and/or HA-100 or XL-100. Signal positions are given in the Tiers τ scale, with tetramethysilane as an internal standard; the multiplicity, integrated peak areas and proton assignments are indicated in parentheses. Gas-liquid chromatography (g.l.c.) was carried out on Aerograph g.l.c. units, models 700 or 90-P. 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>
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<tbody>
<tr>
<td>A</td>
<td>10 ft x 1/4 in</td>
<td>20% SE 30</td>
<td>Chromosorb W</td>
<td>60/80</td>
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<tr>
<td>B</td>
<td>&quot;</td>
<td>20% Carbowax</td>
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<tr>
<td>C</td>
<td>5 ft x 1/4 in</td>
<td>20% SE 30</td>
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<tr>
<td>D</td>
<td>10 ft x 3/8 in</td>
<td>30% SE 30</td>
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The specific column used, along with column temperature and carrier gas (helium) flow-rate (in ml/min), are indicated in parentheses. Column chromatography was performed using florisil (Fisher Scientific Co.), neutral silica gel (Camag or Macherey, Nagel and Co.) or neutral alumina (Camag or Macherey, Nagel and Co.). The alumina was deactivated as required by addition of the correct amount of water. Microanalyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia, Vancouver.

Preparation of the Hydroxymethylene Derivative

To an ice-cooled, stirred suspension of powdered sodium methoxide (26.0 g, 0.50 mole) in 700 ml of dry benzene and 25 g (0.338 mole) of ethyl formate, under an atmosphere of nitrogen, was added 40 g (0.222 mole) of octalone. The ice-bath was removed and the reaction mixture was stirred overnight at room temperature. Water was added with external cooling, and the layers were separated. The organic layer was extracted with two portions of 10% aqueous sodium hydroxide. The combined aqueous layer and alkaline extracts were washed once with ether, acidified with 6 N hydrochloric acid and thoroughly extracted.
with ether. The combined ether extracts were washed with water, with brine, and dried over anhydrous magnesium sulfate. Removal of the solvent and distillation of the resulting residue afforded 32.0 g (100%, based on unrecovered starting material) of the hydroxymethylene derivative 106 as yellow crystals, b.p. 115-120° at 0.3 mm. An analytical sample, obtained by vacuum sublimation, exhibited m.p. 68-71°; ultraviolet, $\lambda_{\text{max}}$ 248 μm (ε = 9,280), 311 μm (ε = 3,860); infrared (CHCl₃), $\nu_{\text{max}}$ 1645, 1560 cm⁻¹; p.m.r., τ 0.0 (broad multiplet, 1H, =CHOH), 2.61 (broad singlet, 1H, =CHOH), 4.21 (broad singlet, 1H, vinyl H), 9.04 (singlet, 3H, tertiary methyl), 9.08 (unresolved multiplet, 3H, secondary methyl).

Anal. Calcd. for $\text{C}_{13}\text{H}_{18}\text{O}_2$: C, 75.69; H, 8.79. Found: C, 75.99; H, 8.73.

The combined benzene layer and ether wash were washed twice with brine and dried over anhydrous magnesium sulfate. Removal of the solvents gave 11.84 g of the starting material, octalone 92.

* In the p.m.r. spectrum of each of the compounds 34, 106-112, inclusive, 124, 127, and 130, the signal due to the secondary methyl group appeared as a broad band, with very little resolution, while in compounds 44 and 117 this signal appeared as a poorly resolved doublet. Presumably this was, in each case, due to virtual coupling. In contrast, the secondary methyl group of compounds 6, 113 and 115 gave rise, in each case, to a clean, well-resolved doublet with the expected coupling constant (6-7 Hz). This observation was eventually used quite consistently to distinguish between those compounds of this series possessing a trans (or trans-like) ring fusion and those possessing a cis ring fusion.
Preparation of Keto Aldehyde 107

To a solution of 5.0 g (24.2 mmoles) of the hydroxymethylene derivative 106 in 250 ml of dry dioxan was added a solution of 5.8 g (29.8 mmoles) of 2,3-dichloro-5,6-dicyanobenzoquinone (DEQ) in 250 ml of dry dioxan. The reaction mixture was stirred under an atmosphere of nitrogen at room temperature for 10 min and then diluted with 1150 ml of dichloromethane. The resulting mixture was filtered and the filtrate was passed quickly through a short column of neutral alumina. The alumina was eluted with an additional 500 ml of dichloromethane. Evaporation of the combined dichloromethane solution afforded 4.7 g (95%) of the crystalline keto aldehyde 107. An analytical sample, obtained by recrystallization of the crude product from hexane, exhibited m.p. 64.5-66°; ultraviolet, $\lambda_{\text{max}}$ 245 nm ($\varepsilon = 12,600$); infrared (CHCl$_3$), $\nu_{\text{max}}$ 1700, 1660, 1625, 1600 cm$^{-1}$; p.m.r. $\tau$ -0.33 (singlet, 1H, -CHO), 2.17 (singlet, 1H, $\beta$-vinyl H), 3.80 (broad singlet, 1H, $\alpha$-vinyl H), 8.76 (singlet, 3H, tertiary methyl), 8.87 (unresolved multiplet, 3H, secondary methyl).

Anal. Calcd, for C$_{13}$H$_{16}$O$_2$: C, 76.44; H, 7.90. Found: C, 76.64; H, 7.70.

Preparation of Keto Acid 108

To a stirred solution of silver nitrate (19.1 g, 0.112 mole) and the keto aldehyde 107 (11.0 g, 0.054 mole) in a mixture of ethanol (200 ml) and water (160 ml) was added dropwise, over a period of 1 h, a solution of sodium hydroxide (8.8 g, 0.22 mole) in water (300 ml). After the reaction mixture had been stirred for an additional 2 h, it was filtered through celite. The filtrate was evaporated under reduced
pressure to a small volume. The residue was diluted with water, washed once with ether and acidified with 6 N hydrochloric acid. The resulting mixture was thoroughly extracted with ether. The combined extracts were washed with brine and then dried over anhydrous magnesium sulfate. Removal of the solvent gave 10.7 g (89%) of the crystalline keto acid \textit{108}. An analytical sample was obtained by recrystallization from hexane-benzene and exhibited m.p. 105°; ultraviolet, \( \lambda_{\text{max}} \) 253 m\( \mu \) (\( \varepsilon \) = 9,740); infrared (CHCl\(_3\)), \( \nu_{\text{max}} \) 3600-2280, 1745, 1650, 1600 cm\(^{-1}\); p.m.r., \( \tau \) -3.55 (broad singlet, 1H, \(-\text{COOH}\)), 1.57 (singlet, 1H, \( \beta \)-vinyl H), 3.67 (broad singlet, 1H, \( \alpha \)-vinyl H), 8.72 (singlet, 3H, tertiary methyl), 8.84 (unresolved multiplet, 3H, secondary methyl).

\textit{Anal. Calcd. for C}_{13}\text{H}_{16}\text{O}_3: \text{C}, 70.89; \text{H}, 7.32. Found: C, 70.88; H, 7.30.}

\textit{Preparation of the Keto Ester 109}

Silver oxide (18.5 g, 0.080 mole) was added to a solution of the keto acid \textit{108} (8.8 g, 0.040 mole) in 240 ml of methanol. To the resultant mixture was added a solution of methyl iodide (11.3 g, 0.078 mole) in 160 ml of methanol. The reaction mixture was stirred at room temperature for 45 min, filtered, and the filtrate was evaporated under reduced pressure. The residue was dissolved in ether and the resulting solution was washed with aqueous sodium bicarbonate, with brine, and then dried over anhydrous magnesium sulfate. Removal of the solvent and distillation of the residue under reduced pressure afforded 9.0 g (96%) of the keto ester \textit{109}, b.p. 147° at 0.1 mm; \( n^\text{D}_{19.5} \) 1.5388; ultraviolet, \( \lambda_{\text{max}} \) 245 m\( \mu \) (\( \varepsilon \) = 10,550);
infrared (film), $v_{\text{max}}$ 1740, 1720 (shoulder 1660, 1640 (shoulder) cm$^{-1}$; p.m.r., $\tau$ 2.25 (singlet, 1H, $\beta$-vinyl H), 3.85 (broad singlet, 1H, $\alpha$-vinyl H), 6.12 (singlet, 3H, $-\text{COOCH}_3$), 8.79 (singlet, 3H, tertiary methyl), 8.90 (unresolved multiplet, 3H, secondary methyl).

Anal. Calcd. for C$_{14}$H$_{18}$O$_3$: C, 71.77; H, 7.74. Found: C, 71.53; H, 7.84.

Preparation of Keto Ester 105

To a solution of 7.02 g (0.030 mole) of the keto ester 109 in 45 ml of pyridine was added 1.13 g (0.030 mole) of powdered sodium borohydride. External cooling (ice-bath) was required initially to keep the temperature of the reaction mixture below 50°. After the solution had been stirred for 30 min, it was poured into rapidly stirring 2 N hydrochloric acid (360 ml). The resulting mixture was extracted thoroughly with ether. The combined extracts were washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. Recrystallization of the residual crude crystalline material from hexane-ethyl acetate gave 5.35 g (76%) of pure keto ester 105. Column chromatography (silica gel) of the mother liquors afforded an additional 0.7 g (10%) of the desired compound 105. An analytical sample of keto ester 105 exhibited m.p. 108-108.5°; ultraviolet, $\lambda_{\text{max}}$ 240 mu ($\epsilon$ =14,920); infrared (CHCl$_3$), $v_{\text{max}}$ 1740, 1670, 1620 cm$^{-1}$; p.m.r., $\tau$ 4.31 (broad singlet, 1H, vinyl H), 6.30 (singlet, 3H, $-\text{COOCH}_3$), 6.57 (doublet of doublets, 1H, $-\text{CH-COOCH}_3$, $J = 13.0, 6.0$ Hz), 8.88 (singlet, 3H, tertiary methyl), 9.08 (unresolved multiplet, 3H, secondary methyl).
Preparation of the Keto Diester

To a solution of the keto ester (5.29 g, 22.4 mmoles) in dry benzene (180 ml), under an atmosphere of nitrogen, was added 1.04 g (24.6 mmoles) of sodium hydride (56% in dispersion oil). When the evolution of hydrogen had ceased (approximately 20 min), 7.5 g (49.0 mmoles) of methyl bromoacetate was added all at once. The reaction mixture was gradually heated to 80°, and was then refluxed for 2.5 h. The cooled reaction mixture was poured into dilute hydrochloric acid, and the layers were separated. The aqueous layer was extracted further with ether. The combined benzene layer and ether extracts were washed twice with brine and dried over anhydrous magnesium sulfate. Removal of the solvent and distillation of the residual oil under reduced pressure gave a quantitative yield of the keto diester as a viscous oil, b.p. 162-164° at 0.07 mm; ultraviolet, λmax 242 μm (ε = 13,760); infrared (film), νmax 1740, 1720 (shoulder), 1665, 1640 (shoulder) cm⁻¹; p.m.r., τ 4.22 (broad singlet, 1H, vinyl H), 6.35, 6.41 (singlets, 6H, methoxy methyls), 8.98 (singlet, 3H, tertiary methyl), 9.12 (unresolved multiplet, 3H, secondary methyl).

Anal. Calcd. for C₁₇H₂₄O₅: C, 66.21; H, 7.84. Found: C, 66.29; H, 7.82.
Preparations of Keto Acid 111

The keto diester 110 (6.5 g, 21.1 mmoles) was dissolved in 210 ml of 5:1 ethanol-water containing 30 g (0.75 mole) of sodium hydroxide and the resulting solution was refluxed under an atmosphere of nitrogen for 30 min. Most of the ethanol was removed under reduced pressure. The residue was diluted with water, washed once with ether, and then acidified with 6 N hydrochloric acid. The resulting mixture was extracted with ether, the combined extracts were washed with brine and then dried over anhydrous magnesium sulfate. Removal of the ether gave 5.0 g of a viscous oil which crystallized on standing. Recrystallization from benzene-hexane gave 3.1 g of pure keto acid 111. Distillation of the mother liquors [b.p. 190-205° (hot box) at 0.2 mm], followed by recrystallization of the distillate afforded an additional 1.0 g of keto acid 111 (total yield = 82%). An analytical sample exhibited m.p. 127.5-128°; ultraviolet, \( \lambda_{\text{max}} = 238 \text{ nm} (\epsilon = 14,750) \); infrared (CHCl₃), \( \nu_{\text{max}} = 3600-2400, 1710, 1665, 1620 \text{ cm}^{-1} \); p.m.r., \( \tau = 1.30 \) (broad singlet, 1H, -COOH), 4.28 (broad singlet, 1H, vinyl H), 8.85 (singlet, 3H, tertiary methyl), 9.10 (unresolved multiplet, 3H, secondary methyl).

Anal. Calcd. for C₁₄H₂₀O₃: C, 71.16; H, 8.53. Found: C, 71.15; H, 8.47.

Preparation of the trans-Fused Keto Acid 112 by Hydrogenation of 111

Under Neutral Conditions

A solution of the keto acid 111 (21 mg, 0.089 mmole) in 2 ml of ethanol was hydrogenated at atmospheric pressure and room temperature over palladium on charcoal (11 mg) until uptake of hydrogen ceased.
Filtration of the reaction mixture, followed by evaporation of the filtrate under reduced pressure afforded a quantitative yield of the trans-fused keto acid 112. An analytical sample, obtained by recrystallization from hexane-benzene, exhibited m.p. 139-140°; infrared (CHCl₃), v max 3600-2400, 1705 cm⁻¹; p.m.r., τ 0.04 (broad singlet, 1H, -COOH), 9.00 (singlet, 3H, tertiary methyl), 9.12 (unresolved multiplet, 3H, secondary methyl).


Preparation of the cis-Fused Keto Acid 113 and the trans-Fused Keto Acid 112

Hydrogenation of the keto acid 111 was carried out at atmospheric pressure and room temperature. A solution of 111 (118 mg, 0.5 mmole) in 3 ml of freshly prepared 0.2 N ethanolic sodium hydroxide containing 30 mg of 5% rhodium on charcoal was hydrogenated until two equivalents of hydrogen were taken up (approximately 5 h). The reaction mixture was filtered and the filtrate was evaporated to dryness. The residue was dissolved in distilled water (4 ml) and 6 mg of ruthenium dioxide was added. To the resulting stirred mixture was added, dropwise, a freshly prepared 5% solution of sodium periodate in distilled water, until the yellowish color of ruthenium tetroxide persisted. The reaction mixture was treated with a few drops of 2-propanol, and then filtered. The filtrate was acidified with dilute hydrochloric acid and then thoroughly extracted with ether. The combined ether extracts were washed with brine and dried over anhydrous magnesium sulfate.
Removal of the solvent gave 120 mg of crystalline material, which consisted of a mixture of the cis-fused keto acid 113 and the trans-fused keto acid 112 in a ratio of approximately 3:2, respectively (based on the p.m.r. spectrum). Both of the compounds could be obtained in pure form by repeated fractional crystallization of the mixture from varying proportions of hexane-benzene. Although the actual amount of each isomer isolated from the mixture varied somewhat from experiment to experiment, the less soluble compound (trans-fused keto acid 112) was secured in approximately 30% yield, while the more soluble isomer (cis-fused keto acid 113) was obtained in approximately 30-35% yield. The trans-fused keto acid thus obtained was shown to be identical (m.p., infrared and p.m.r. spectra) with the product obtained by hydrogenation of 111 under neutral conditions (vide supra).

The cis-fused keto acid 113 exhibited m.p. 114.5-115°; infrared (CHCl₃) ν max 3600-2400, 1708 cm⁻¹; p.m.r., τ -1.27 (broad singlet, 1H, -COOH), 9.09 (singlet, 3H, tertiary methyl), 9.12 (doublet, 3H, secondary methyl, J = 7.0 Hz).


(+)-11-Demethyleremophilenolide 115

(a) Cyclization: 3-hour reaction

A solution of the keto acid 113 (100 mg, 0.42 mmole) in 24 ml of dry toluene containing 30 mg of p-toluenesulfonic acid was refluxed gently under a Dean-Stark water separator in a nitrogen atmosphere for 3 h. The cooled solution was washed with dilute aqueous sodium bicarbonate, with brine, and then dried over anhydrous magnesium sulfate.
Removal of the solvent, followed by distillation of the residue gave 90 mg of lactone material (97%) which crystallized on standing. Recrystallization from hexane yielded 51 mg (55%) of pure 11-demethyl-eremophilenolide 115, m.p. 112-112.5°; ultraviolet, \( \lambda_{\text{max}} \) 216 μm (ε = 14,830); infrared (CHCl₃), \( \nu_{\text{max}} \) 1780, 1745, 1650 cm⁻¹; p.m.r., \( \tau \) 4.31 (unresolved multiplet, 1H, vinyl H, width at half height = 4.0 Hz), 5.26 (broad, unresolved multiplet, 1H, \( \mathrm{C}_6\mathrm{H} \), width at half height = 19.0 Hz), 7.10 (doublet, 1H, \( \mathrm{C}_6\mathrm{H} \)-equatorial, \( J = 14.0 \) Hz), 8.99 (singlet, 3H, tertiary methyl), 9.23 (doublet, 3H, secondary methyl, \( J = 6.0 \) Hz).


The mother liquors from the above recrystallization consisted of an oily mixture of 11-demethyleremophilenolide 115 and 8-epi-11-demethyleremophilenolide 116 in a ratio of approximately 1:2 respectively, as judged by the p.m.r. spectrum. Column chromatography of this mixture on silica gel yielded no separation of the two components. The mixture exhibited infrared (film), \( \nu_{\text{max}} \) 1785, 1750, 1640 cm⁻¹. By comparing the p.m.r. spectrum of the 1:2 mixture of lactones with that of pure 11-demethyleremophilenolide, it was possible to identify the signals due to 8-epi-11-demethyleremophilenolide. Thus the latter exhibited p.m.r., 4.24 (unresolved multiplet, 1H, vinyl H, width at half height = 4.0 Hz), 5.07 (broad, unresolved multiplet, 1H, \( \mathrm{C}_6\mathrm{H} \), width at half height = 20 Hz), 7.00 (broadened doublet, 1H, \( \mathrm{C}_6\mathrm{H} \), \( J = 14.0 \) Hz), 7.87 (doublet, 1H, \( \mathrm{C}_6\mathrm{H} \), \( J = 14.0 \) Hz), 8.97 (doublet, 3H, secondary methyl, \( J = 6.6 \) Hz), 9.13 (singlet, 3H, tertiary methyl).
(b) **Cyclization: 6-hour reaction**

A solution of the keto acid $113$ (12.0 mg, 0.05 mmole) in 4 ml of dry toluene containing 9 mg of p-toluenesulfonic acid, was refluxed under a Dean-Stark water separator in a nitrogen atmosphere for 3 h. At this point, a further 9 mg of p-toluenesulfonic acid was added and refluxing was continued for a further 3 h period. The reaction mixture was worked up as above. Distillation (hot box) of the resulting crude product afforded 10.5 mg (95%) of crystalline material which consisted mainly of a mixture of 11-demethyleremophilenolide $115$ and 8-epi-11-demethyleremophilenolide $116$ in the ratio of approximately 85:15 (as judged from the p.m.r. spectrum).

**(+)-Eremophilenolide 6**

(a) **From pure 11-demethyleremophilenolide $115$**

To a stirred solution of (+)-11-demethyleremophilenolide $115$ (68 mg, 0.31 mmole) in 3 ml of dry benzene under an atmosphere of nitrogen was added, dropwise, an ethereal solution of tritylsodium until the red color of the base persisted. After the resulting solution had been stirred at room temperature for 30 min, methyl iodide (142 µl, 2.28 mmoles) was added all at once. The solution was stirred for 6 h, diluted with ether, washed with cold water, with brine, and then dried over anhydrous magnesium sulfate. Removal of the solvents gave a crude product which was chromatographed over silica gel. Elution with hexane afforded triphenylmethane. Further elution with ether gave 73 mg of material which crystallized on standing. Recrystallization from ether gave 31 mg of pure (+)-eremophilenolide 6. Subjection of the
mother liquors to column chromatography on silica gel yielded an additional 13 mg of 6 (total yield = 61%). An analytical sample of (±)-eremophilenolide 6 exhibited m.p. 110.5-111.5°; ultraviolet, $\lambda_{max}$ 220 mμ ($\epsilon = 14,600$); infrared (CHCl₃), $\nu_{max}$ 1740, 1690 cm⁻¹; p.m.r., $\tau$ 5.37 (broad, unresolved multiplet, 1H, $C_8H$, width at half height = 20.5 Hz), 7.11 (doublet, 1H, $C_6H$-equatorial, $J = 14.5$ Hz), 8.21 (unresolved multiplet, 3H, vinyl methyl), 8.97 (singlet, 3H, tertiary methyl), 9.20 (doublet, 3H, secondary methyl, $J = 6.0$ Hz). The infrared and p.m.r. spectra of this material were identical with those of an authentic sample of natural (±)-eremophilenolide.

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.58; H, 9.60.

(b) From the mixture of 115 and 116

A mixture of 11-demethyleremophilenolide 115 and 8-epi-11-demethyl-eremophilenolide 116 (34 mg, 1:2, respectively), the mother liquors of recrystallization of impure 115 (vide supra), was subjected to alkylation under conditions identical with those described above. Purification of the crude product, as above, afforded 19 mgs (52%) of (±)-eremophilenolide 6.

(±)-11-Demethyltetrahydroligularenolide 117

A solution of the trans-fused keto acid 112 (44 mg, 0.19 mmole) in 12 ml of dry toluene containing 15 mg of $p$-toluenesulfonic acid was refluxed gently for 3 h in an atmosphere of nitrogen under a Dean-Stark water separator. The cooled solution was washed with cold,
dilute aqueous sodium bicarbonate, with brine and then dried over anhydrous magnesium sulfate. Removal of the solvent and distillation of the residual material afforded 38 mg (94%) of (+)-11-demethyltetrahydroligularenolide \textsuperscript{117}, m.p. 94-95°. An analytical sample, obtained by recrystallization of this material from hexane, exhibited m.p. 98-99°; ultraviolet, $\lambda_{\text{max}}$ 216 m\(\mu\) (\(\epsilon = 14,870\)); infrared (CHCl\(_3\)), $\nu_{\text{max}}$ 1780, 1745, 1645 cm\(^{-1}\); p.m.r., $\tau$ 4.34 (unresolved multiplet, 1H, vinyl H, width at half height = 4.0 Hz), 5.33 (unresolved multiplet, 1H, C\(_8\)H, width at half height = 19 Hz), 7.25 (doublet, 1H, C\(_8\)H-equatorial, J = 13.0 Hz), 9.15 (poorly resolved doublet, 3H, secondary methyl, J \(\approx\) 5.5 Hz), 9.36 (singlet, 3H, tertiary methyl).

Anal. Calcd. for C\(_{14}\)H\(_{20}\)O\(_2\): C, 76.33; H, 9.15. Found: C, 76.15; H, 9.03.

(+)–Tetrahydroligularenolide \textsuperscript{44}

To a stirred solution of the lactone \textsuperscript{117} (85 mg, 0.39 mmole) in 4 ml of dry benzene under an atmosphere of nitrogen was added, dropwise, an ethereal solution of tritylsodium until the red color of the base persisted. After the resulting solution had been stirred at room temperature for 35 min, methyl iodide (160 \(\mu\)l, 2.5 mmole) was added in one portion. The reaction mixture was stirred at room temperature for 6 h, then diluted with ether and poured into ice-water. The organic layer was separated, washed with brine, and dried over anhydrous magnesium sulfate. Removal of the solvents gave 234 mg of residual material which was subjected to column chromatography on silica gel. Elution of the column with hexane yielded triphenylmethane, while
elution with ether afforded 82 mg of crude crystalline product.

Recrystallization from hexane-ether, followed by further purification (column chromatography) of the mother liquors, provided 53 mg (59%) of pure (+)-tetrahydroligularenolide 44, m.p. 91.5-92°; ultraviolet, $\lambda_{\text{max}}$ 220 m$\mu$ ($\varepsilon = 14,990$); infrared (CHCl$_3$), $\nu_{\text{max}}$ 1740, 1685 cm$^{-1}$; p.m.r., $\tau$ 5.38 (unresolved multiplet, 1H, C$_0$H, width at half height = 21.0 Hz), 7.24 (doublet, 1H, C$_6$H-equatorial, $J = 14.0$ Hz), 8.21 (unresolved multiplet, 3H, vinyl methyl), 9.09 (poorly resolved doublet, 3H, secondary methyl, $J = 5.5$ Hz), 9.42 (doublet, 3H, tertiary methyl, $J = 0.6$ Hz). Although an authentic sample of (-)-tetrahydroligularenolide was not obtained, the infrared and p.m.r. data given above agree very well with the published data. 73, 74


Preparation of the trans-Fused Keto Acid 112 by Alkylation of the

Decalone 100

A solution of the decalone 100 (180 mg, 1 mmole) in 25 ml of isopropenyl acetate containing 100 mg of p-toluenesulfonic acid was slowly heated under a Dean-Stark water separator. The acetone-isopropenyl acetate mixture was slowly distilled until the residual volume was about 4 ml. The cooled reaction mixture was poured into aqueous sodium bicarbonate and the resulting mixture was extracted thoroughly with ether. The combined ether extracts were washed with brine and dried over anhydrous magnesium sulfate. Removal of the ether, followed by distillation of the residual oil, afforded 220 mg of the mixture of
enol acetates \textsuperscript{119} and \textsuperscript{120} b.p. 80-90° (hot box) at 0.1 mm, in a ratio of approximately 3:2. (On the basis of the p.m.r. spectrum, the major compound was the $\Delta^2$-isomer). This mixture exhibited infrared (film), $v_{\text{max}}$ 1750 cm\(^{-1}\); p.m.r., $\tau$ 4.75, 5.00 (unresolved multiplets, 1H, vinyl protons, width at half height = 9 Hz and 5.5 Hz respectively).

A solution of the mixture of enol acetates \textsuperscript{119} and \textsuperscript{120} in dry dimethoxyethane was added dropwise \textit{via} a syringe to a stirred solution of methyllithium (2 mmoles) in 1.5 ml of dimethoxyethane. To the resulting solution was added, all at once, 0.5 ml of methyl bromoacetate, stirring was continued for 1 min, and the reaction mixture was then poured into cold dilute hydrochloric acid. The resulting mixture was extracted with ether, the combined ether extracts were washed with water and dried over anhydrous magnesium sulfate. Removal of the solvents gave 273 mg of crude material. Subjection of the latter to column chromatography on silica gel afforded the keto ester \textsuperscript{121} which, upon hydrolysis at room temperature with potassium hydroxide in methanol, provided the crystalline keto acid \textsuperscript{112}. The latter was shown to be identical (m.p., mixed m.p., i.r. and p.m.r. spectra) with the keto acid \textsuperscript{112} prepared by hydrogenation of keto acid \textsuperscript{111} under neutral conditions (\textit{vide supra}).

**Preparation of the Thioketal Derivative \textsuperscript{127}**

To a solution of the keto ester \textsuperscript{105} (1.22 g, 5.2 mmoles) in 30 ml of acetic acid was added 2.5 ml of 1,2-ethanedithiol and 1.5 ml of boron trifluoride etherate. The mixture was stirred under nitrogen for 26 h and then diluted with ether. Excess solid sodium bicarbonate was added and the resulting mixture was carefully diluted with cold water. The
organic layer was separated, washed successively with aqueous sodium bicarbonate, water and brine, and then dried over anhydrous magnesium sulfate. Removal of the solvent afforded 1.67 g (100%) of crude crystalline material. The p.m.r. spectrum of this material indicated that it was an epimeric mixture of 127 and 128 in a ratio of approximately 4:1, respectively. One recrystallization of this material from methanol yielded 1.16 g (72.5%) of the pure dithioketal 127, m.p. 110.5-111°; infrared (CHCl₃), v max 1728 cm⁻¹; p.m.r., τ 4.52 (broad singlet, 1H, vinyl H), 6.32 (singlet, 3H, -COOCH₃), 6.52-6.99 (multiplet, 5H, -SCH₂CH₂S- and C₇H), 9.07 (singlet, 3H, tertiary methyl), 9.15 (unresolved multiplet, 3H, secondary methyl).

Anal. Calcd. for C₁₆H₂₄O₂S₂: C, 61.50; H, 7.74; S, 20.52. Found: C, 61.64; H, 7.84; S, 20.35.

The mother liquors of the above recrystallization consisted of compounds 127 and 128 in a ratio of approximately 1:2, respectively. Attempts to isolate a pure sample of 128 by column chromatography of this material were not successful.

Preparation of the Olefinic Ester 124

(a) From the dithioketal 127

To a solution of the dithioketal 127 (594 mg, 1.9 mmoles) in 80 ml of ethanol was added about 20 g of W-2 Raney nickel and the resulting mixture was refluxed with stirring under nitrogen for 15 min. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. Distillation of the residual material gave 373 mg of an oil, b.p. 120° (hot box) at 0.15 mm, which was shown by gas-liquid chromatographic analysis (column F, 205°, 105) to consist mainly of one
compound, accompanied by two minor components. The desired, major component was isolated by preparative g.l.c. (column F, 200°, 90), yielding 264 mg (63%) of pure olefinic ester \(124\), \(n_D^{20} 1.4979\); infrared (film), \(\nu_{\text{max}}\) 1735, 808 cm; p.m.r., \(\tau\) 4.72 (unresolved multiplet, 1H, vinyl H), 6.36 (singlet, 3H, \(-\text{COOCH}_3\)), 9.06 (singlet, 3H, tertiary methyl), 9.14 (unresolved multiplet, 3H, secondary methyl).


(b) From a mixture of dithioketals \(127\) and \(128\)

A mixture of compounds \(127\) and \(128\) (180 mg, 1:2, respectively), obtained from the mother liquors of recrystallization of impure \(127\) (\textit{vide supra}), was subjected to desulfurization with Raney nickel under conditions identical with those described above. Distillation of the crude product gave 102 mg of material which was shown by g.l.c. analysis (column F, 205°, 105) to consist mainly (85%) of the epimeric olefinic esters \(124\) and \(129\) (approximately 1:2, respectively). A solution of this material in 10 ml of 0.82 M sodium methoxide in methanol was refluxed under nitrogen for 20 h. The cooled solution was poured into dilute aqueous acetic acid and the resulting mixture was extracted with ether. The combined extracts were washed with water, with brine, and then dried over anhydrous magnesium sulfate. Removal of the solvents, followed by distillation of the residual material, afforded 65 mg of an oil. Gas-liquid chromatographic analysis (column F, 205°, 105) of the latter revealed that the ratio of \(124\) and \(129\) was now approximately 9:1, respectively. The major component, isolated from the mixture by
preparative g.l.c. (column F, 205°, 105), was shown (i.r. and p.m.r. spectra) to be identical with 124 prepared as described above.

Preparation of the Olefinic Alcohol 130

An ethereal solution of methyllithium (6 mmoles) was added to a cold (0°) solution of the olefinic ester 124 (222 mg, 1 mmole) in 8 ml of anhydrous ether. The resulting solution was refluxed under nitrogen for 2.5 h, cooled, and poured into a mixture of dry ice in water. The ether layer was separated, successively washed with water and brine, and dried over anhydrous magnesium sulfate. Removal of the solvent gave an oil which, upon distillation under reduced pressure, afforded 212 mg (95%) of the olefinic alcohol 130, b.p. 125-130° (hot box) at 0.25 mm; n\textsubscript{D}\textsuperscript{20} 1.5075; infrared (film), ν\textsubscript{max} 3380, 810 cm\textsuperscript{-1}; p.m.r., τ 4.71 (unresolved multiplet, 1H, vinyl H), 8.68 (singlet, 1H, exchangeable, -OH), 8.84, 8.85 (singlets, -C(OH)(CH\textsubscript{3})\textsubscript{2}), 9.08 (singlet, 3H, tertiary methyl), 9.14 (unresolved multiplet, 3H, secondary methyl).

Anal. Calcd. for C\textsubscript{15}H\textsubscript{26}O: C, 81.02; H, 11.79. Found: C, 80.93; H, 11.67.

(+)-Aristolochene 34

To a solution of the olefinic alcohol 130 (160 mg, 0.72 mmole) in 5.2 ml of pyridine at 0° was added, dropwise, 520 μl of thionyl chloride. The resulting solution was stirred under a nitrogen atmosphere at 0° for 1 h and then poured into cold, aqueous sodium bicarbonate. The resulting mixture was extracted with ether and the combined extracts were evaporated under reduced pressure. The residue was taken up in
ether and the resulting solution was washed successively with water and brine, and then dried over anhydrous magnesium sulfate. Removal of the solvent gave 134 mg of crude material. Subjection of the latter to column chromatography on silver nitrate-impregnated silica gel (15%) gave, upon elution with hexane-ether, 57 mg (43%) of pure (+)-aristolochene. Infrared (film), \( \nu \_{\text{max}} \) 3075, 3030, 1645, 887, 810 cm\(^{-1}\); p.m.r. \( \delta \) 4.70 (unresolved multiplet, 1H, vinyl H, width at half height = 9.0 Hz), 5.31 (unresolved multiplet, 2H, =CH\(_2\), width at half height = 3.0 Hz), 8.29 (unresolved multiplet, 3H, vinyl methyl), 9.06 (singlet, 3H, tertiary methyl), 9.17 (unresolved multiplet, 3H, secondary methyl). This material exhibited infrared and p.m.r. spectra identical with authentic (-)-aristolochene.

PART II
STEREOSELECTIVE TOTAL SYNTHESIS OF
(-)-YLANGOCAMPHOR, (-)-YLANGOBORNEOL AND (-)-YLANGOISOBORNEOL
PART II

INTRODUCTION

1. **Perspective**

The ylangosesquiterpenoids belong to the interesting family of structurally related sesquiterpenoids whose skeletal structures incorporate the bicyclo[2.2.1]heptane nucleus \[131\] or the related bicyclo[3.1.1]heptane nucleus \[132\]. This group includes bicyclic, tricyclic and tetracyclic members as shown in Chart 8. The sesquiterpenoids listed in this chart are arranged and drawn in a manner which emphasizes their structural similarity to known monoterpenoids which also possess either the bicyclo[2.2.1]heptane or the bicyclo[3.1.1]heptane moieties. For example, the sesquiterpenoids listed in the first vertical column in Chart 8, campherenone, copacamphor, ylangocamphor and longicamphor, all incorporate the structural features of the monoterpenoid camphor. Thus, these four sesquiterpenoids can be considered "isoprenologs" of camphor.
These compounds have been isolated from naturally occurring sources. Absolute configurations are depicted by these structures.
Similarly the sesquiterpenoids listed in the other vertical columns in Chart 8 can be considered "isoprenologs" of the monoterpenes which head these columns. The sesquiterpenoids in Chart 8 are also arranged in horizontal rows in a manner which emphasizes the structural similarities among the sesquiterpenoids themselves. Thus longicamphor, longiborneol, longiisoborneol, longifolene, longicyclene and \( \alpha \)-longipinene all possess a seven-membered ring containing geminal dimethyl groups.

At the outset of the work described in this thesis, the sesquiterpenoids ylangocamphor 7, ylangoborneol 23, and ylangoisoborneol 143 were unknown compounds. The names that have been proposed for these sesquiterpenoids are based on their structural relationship both to the corresponding monoterpenoids (camphor, borneol, and isoborneol respectively) and to the sesquiterpenoid \( \alpha \)-ylangene 21. \( \alpha \)-Ylangene (isolated from ylang-ylang oil) was the first ylango-type sesquiterpenoid to be isolated and named. For convenience, throughout this thesis all the sesquiterpenoids in this group (horizontal row 4) in Chart 8 (ylangocamphor, ylangoborneol, ylangoisoborneol, sativene, cyclosativene and \( \alpha \)-ylangene) will be referred to collectively as the ylango sesquiterpenoids. Similarly the copa sesquiterpenoids will refer to the sesquiterpenoids in row 3, and the longi sesquiterpenoids to those in row 5.

Apart from the compounds listed in Chart 8, other members of this family of sesquiterpenoids are also known. Thus, a series which bears an epimeric relationship to the sesquiterpenoids in row 2 is known, epicampherenone 149 being a representative example. Many of the other
known structurally related sesquiterpenoids are merely oxygenated derivatives of structures listed in Chart 8. Thus (+)-α-santalol is related to (+)-α-santalene in row 2 of Chart 8.

The naturally occurring cyclocopacamphenols are related to cyclocopacamphene of the copa series, while culmorin is an oxidized form of longiborneol of the longi series.

No naturally occurring ylango sesquiterpenoids are known which contain intact the bicyclo[2.2.1]heptane or bicyclo[3.1.1]heptane nuclei other than those shown in Chart 8. However, a group of sesquiterpenoids are known whose common carbon skeleton can be related to that of sativene. These naturally occurring compounds are
helminthosporal 25,22, helminthosporol 153,134, prehelminthosporal* 154,135 (R = H) and prehelminthosporol 155.135 Thus theoretical cleavage of the sativene carbon skeleton 8 at the point indicated, results in the

* This compound has been isolated only as the acetal 154 (R = Et).
formation of the skeletal structure \( \text{156} \), which is common to the helmintho sesquiterpenoids. Indeed, de Mayo and co-workers have obtained evidence \( \text{21} \) which supports the biogenesis of these compounds from an intermediate such as sativene \( \text{8} \) (see Introductory Remarks p. \( \text{8} \)). For convenience therefore, throughout the remainder of this thesis the helmintho sesquiterpenoids will also be included in the term "ylango sesquiterpenoids".

Because of the interesting tricyclic and tetracyclic carbon skeletons of the copa, ylango and longi sesquiterpenoids, attention was directed in our laboratory towards the development of synthetic approaches to these sesquiterpenoids. The initial effort in this area was concentrated on synthetic access to the copa group of sesquiterpenoids. This effort has resulted in the stereoselective total syntheses \( \text{107,109} \) of \((+)-\text{copacamphor 138}\), \((+)-\text{copaborneol 139}\), \((+)-\text{copaisoborneol 140}\), \((-)-\text{copacamphene 141}\) and \((-)-\text{cyclocopacamphene 10}\). The work described in the second part of this thesis is concerned with the development of a similar general synthetic approach to the ylango group of sesquiterpenoids. This work has led to the stereoselective total synthesis \( \text{9} \) of \((-)-\text{ylangocamphor 7}, (-)-\text{ylango-borneol 23}\) and \((-)-\text{ylangoisoborneol 143}\).

2. Other Synthetic Approaches to Copa and Ylango Sesquiterpenoids

Because of the epimeric relationship between the copa and ylango series of sesquiterpenoids, it is appropriate here to discuss synthetic approaches to compounds of both series.
In connection with the structural elucidation of copaborneol $\text{139}$, Kolbe-Haugwitz and Westfelt$^{105,106}$ reported the conversion of ($\pm$)-$\alpha$-santalol $\text{150}$ into ($\pm$)-copaborneol (see Chart 9). The key step in this conversion was the construction of the third ring in copaborneol by a stereoselective intramolecular Michael-type addition reaction. The starting material employed was a commercial mixture (ca. 7:3) of ($\pm$)-$\alpha$-santalol $\text{150}$ and (-)-$\beta$-santalol $\text{157}$. For convenience, the reactions of only the major component $\text{150}$ will be discussed here.

Oxidation of $\text{150}$ with selenium dioxide, followed by further oxidation of the resulting santalal with silver oxide afforded the unsaturated keto acid $\text{158}$. The initial oxidation reaction conditions also effected total isomerization of the olefinic double bond. Formolysis of $\text{158}$ caused the cyclopropane ring to open in two ways, thus giving rise to the syn and anti formates $\text{159}$ and $\text{160}$ respectively. (The other component of the starting material, (-)-$\beta$-santalol $\text{157}$, on subjection to the same series of reactions gave rise to only the syn formate $\text{159}$.) Hydrolysis of this mixture, followed by Jones oxidation and esterification, produced a mixture of the corresponding keto esters $\text{161}$ and $\text{162}$.

Subjection of the keto ester mixture to cyclization conditions (potassium t-butoxide in dioxan), resulted in the facile intramolecular alkylation of the syn isomer $\text{161}$, the anti isomer $\text{162}$ remaining virtually unchanged. The cyclized product $\text{163}$ was separated from the mixture by column chromatography on silica gel. This product was stereochemically homogeneous with respect to the important $C_{10}$ position (see structure $\text{163}$ for numbering).
Chart 9
The carbomethoxy group in 163 was reduced to the desired methyl group by the following series of conversions: \(-\text{CO}_2\text{Me} \rightarrow -\text{CO}_2\text{H} \rightarrow -\text{COCl} \rightarrow -\text{CH}_2\text{OH} \rightarrow -\text{CH}_2\text{OMs} \rightarrow -\text{CH}_3\). The final reaction, reductive removal of the mesylate group with lithium aluminum hydride, also effected reduction of the ketone functionality. Thus, the isolated product was copaisoborneol 140. Chromic acid oxidation of the latter afforded copacamphor 138. Reduction of copacamphor with sodium in ethanol gave (+)-copaborneol 139, identical in all respects with the naturally occurring product. Since \(\alpha\)-santalol 150 has already been synthesized, this represents a formal total synthesis of copaborneol, copacamphor and copaisoborneol.

A similar type of approach to the construction of the third ring in copacamphor 138 and ylangocamphor 7 was reported very recently by Hodgson, MacSweeney and Money. The starting material used in this instance was (+)-camphenone 9 (see Chart 10). Reaction of 9 with \(m\)-chloroperbenzoic acid gave rise to the diastereomeric mixture of keto epoxides 164. Subjection of 164 to cyclization with potassium \(t\)-butoxide in \(t\)-butanol, afforded a mixture of the tricyclic keto alcohols 165 and 166, which were separated by preparative g.l.c. Dehydration of 166 gave a mixture (7:3) of the keto olefins 167 and 168. This mixture of compounds was also separated by preparative g.l.c. Catalytic hydrogenation of keto olefin 167 produced copacamphor 138, while hydrogenation of 168 gave rise to a mixture (5:1) of ylangocamphor 7 and copacamphor 138.

The same sequence of reactions was applied to the epimeric keto alcohol 165, thus also yielding ylangocamphor 7 via the terminal olefin 169. Copacamphor 138, thus synthesized, exhibited gas-liquid chromatographic and spectral characteristics identical with those of an authentic
Chart 10
sample. The spectral properties of ylangocamphor 7 thus obtained, were identical with those of (-)-ylangocamphor prepared as described in this thesis. Since Money and co-workers had previously totally synthesized\textsuperscript{97} campherenone 9, this work represents a total synthesis of both copacamphor 138 and ylangocamphor 7.

De Mayo and Williams\textsuperscript{11} reported the conversion of (+)-longifolene 147 into (-)-sativene 8 (see Chart 11) in connection with their structural elucidation of the latter. The over-all result of this multi-step transformation was the contraction of the cycloheptane ring in longifolene to the cyclohexane ring in sativene. Thus longifolene 147 was reacted with bromotrichloromethane to give the halogenated derivative 170 via a previously studied\textsuperscript{136} free-radical transannular hydrogen transfer. Dehydrochlorination of 170 afforded the acetylene derivative 171. Oxidation of the latter to the acid, followed by esterification, yielded the bromo ester 172. Distillation of 172 from iron powder, under reduced pressure, produced the cyclohexene derivative 173. Hydrogenation of the latter gave the ester 174. This particular product of hydrogenation was expected, since it resulted from the approach of the catalyst from the less hindered side of the olefinic double bond in 173. Reduction of the ester 174 with lithium aluminum hydride, and acetylation of the resulting alcohol gave the acetate 175. Pyrolysis of this acetate at 550° gave rise to sativene 8. (-)-Sativene, thus obtained, was identical with the naturally occurring material except for the sign of its optical rotation. Since longifolene 147 has been totally synthesized,\textsuperscript{125} this represents a formal total synthesis of sativene 8.
Chart 11
Another approach to the synthesis of sativene was reported by McMurry. The starting material chosen for this synthesis was the readily available Wieland-Miescher ketone (see Chart 12). Selective ketalization of the saturated ketone, followed by catalytic hydrogenation of the resulting ketal, resulted in the cis-fused decalone. Treatment of this decalone with isopropyllithium, followed by acid-catalyzed hydrolysis and dehydration of the resulting ketal alcohol, afforded the keto olefin. Since attempted hydroboration of resulted in preferential reduction of the carbonyl group, the latter was first protected with a blocking group. Thus the keto olefin was converted into the 2,4-dinitrophenylhydrazone (2,4-DNP) derivative. Subjection of the latter to hydroboration, followed by oxidative work-up and removal of the blocking group by ozonolysis, gave the desired keto alcohol. Intramolecular alkylation of the tosylate derivative of was accomplished by reaction with methylsulfinyl carbanion in dimethylsulfoxide, thus producing the tricyclic ketone. Reaction of the latter with methyllithium, and dehydration of the resulting tertiary alcohol, afforded racemic sativene. The infrared and p.m.r. spectra of this material were identical with those of the naturally occurring compound.

McMurry also succeeded in synthesizing copacamphene (see Chart 13), the epimer of sativene, from an intermediate used in his sativene synthesis. Thus keto olefin was transformed into the keto epoxide. Reaction of the latter with methylsulfinyl carbanion in dimethyl sulfoxide at 60° for four days, effected the required cyclization. Acid-catalyzed dehydration of the resulting keto alcohol
Chart 12
gave rise to a mixture (7:3) of two keto olefins. The major product was the **endo-cyclic olefin** \( 185 \), the minor product being the corresponding **exo-cyclic olefin**.

Catalytic hydrogenation of keto olefin \( 185 \) gave a product which possessed the wrong orientation of the isopropyl group for the purpose of synthesizing copacamphene \( 141 \). Consequently, this keto olefin \( 185 \) was first reduced with lithium in liquid ammonia to afford a 6:4 mixture of alcohols \( 186 \) and \( 187 \) respectively. It was felt that by hydrogenating \( 186 \) in a non-polar solvent, the hydroxyl group might bond to the catalyst and thus promote hydrogenation of the olefinic double bond from the more hindered side. Catalytic hydrogenation of \( 186 \) in hexane solution over 10% palladium on charcoal, followed by Collins oxidation of the resulting product, produced a mixture of the two ketones \( 188 \) and \( 182 \). Reaction of this mixture with methyllithium, followed by dehydration of the resulting tertiary alcohols, afforded a mixture of (+)-copacamphene \( 141 \) and (+)-sativene \( 8 \) in a ratio of 85:15 respectively. This mixture was separated by chromatography on silver nitrate-impregnated silica gel. Copacamphene, thus obtained, exhibited spectral properties identical with those of a sample prepared from naturally occurring copaborneol.

The final synthetic approach to copa- and ylango-type sesquiterpenoids to be considered here is the total synthesis of helminthosporal \( 25 \), reported by Corey and Nozoe. The starting material, (-)-carvomenthone \( 189 \), (see Chart 14) was converted via its hydroxymethylene derivative to the diketo aldehyde \( 190 \), using methyl vinyl ketone as alkylation agent. Deformylation of \( 190 \) under mildly basic conditions
Chart 13
resulted in the diketone 191. The desired bicyclic bridged system was constructed by subjection of this diketone to cyclization under acidic conditions (boron trifluoride in methylene chloride). The resulting product consisted of a mixture of the desired keto olefin 192 and its C_1, C_3 epimer in a ratio of 4:1 respectively. This mixture was resolvable by preparative g.l.c. or by recrystallization of the semicarbazone derivatives. Reaction of ketone 192 with methoxymethylene-triphenylphosphorane in dimethylsulfoxide, and subjection of the resulting Wittig product 193 to acetalization conditions, resulted in the formation of the ethylene acetal 194 (together with lesser amounts of the C_2 epimer). Cleavage of the double bond in 194 was accomplished by osmolation and oxidation of the resulting diol with lead tetraacetate, thus affording the keto aldehyde 195. Cyclization of the latter under basic conditions produced the unsaturated aldehyde 196. Hydrolysis of 196 yielded (-)-helminthosporal 25, the properties of which were completely identical with those of the naturally derived material.
Chart 14

189 \[ \rightarrow \]

190 \[ R_1 = \text{CHO} \\
R_2 = \text{CH}_2\text{CH}_2\text{COCH}_3 \]

191 \[ R_1 = \text{H} \\
\downarrow \quad R_2 = \text{CH}_2\text{CH}_2\text{COCH}_3 \]

192

193

194 \[ \rightarrow \]

195 \[ \downarrow \]

196

25

Chart 14
PART II
DISCUSSION

1. General

In the construction of complex sesquiterpenoids such as ylangocamphor a variety of synthetic approaches are possible. The sequence in which the substituents or functional groups are introduced may vary considerably, but the variety is based mainly on the order and the manner in which the tricyclic skeleton itself can be assembled. An analysis of the structure of ylangocamphor showed that there are a number of ways in which the third ring of this carbon skeleton could be formed by an intramolecular alkylation of a suitably substituted bicyclic precursor. For example, the tricyclic system could possibly be constructed from any one of the four different bicyclic structures shown in Chart 15. A choice of one of these intermediates, and hence, in principle, of a synthetic pathway to ylangocamphor, depended on a
number of considerations. Of importance amongst these were the synthetic availability of the intermediate and the probability of the intermediate undergoing the crucial cyclization.

Since the factors influencing stereochemistry in the generation of asymmetric centres in perhydroazulene derivatives are not well understood, the bicyclic keto tosylate 197 was eliminated as a precursor to ylangocamphor 7. Keto tosylate 198 was also rejected because the required cyclization was considered unlikely to occur. The cyclization of either of the remaining two intermediates, 199 and 200, seemed attractive, hence a choice between these two was based on other considerations.

As was mentioned in the introduction, the purpose of the present synthetic study was the development of a general stereoselective synthetic approach to ylango-type sesquiterpenoids (see Chart 15). It was felt that a synthetic pathway leading to keto tosylate 199 could not be readily adapted to the syntheses of ylango sesquiterpenoids other than ylangocamphor. In addition, the stereoselective synthesis of ylangocamphor via intermediate 199 required the difficult construction of a side-chain in 199 containing a centre of asymmetry. By ignoring this difficulty and synthesizing a mixture of two epimers at this centre, it should be possible to perform a cyclization which leads to a mixture of ylangocamphor 7 and copacamphor 138. This type of cyclization has, in fact, recently been reported 10 (see Introduction, p. 102).

Since the introduction of the leaving group in the remaining keto tosylate 200 involved no stereochemical problems and since the substituted bicyclo[3.2.1]octanone 200 could hopefully be constructed in
$X = OTs$ (or other leaving group)

Chart 15
a stereoselective fashion, this approach to the synthesis of ylangocamphor was chosen. Moreover, an analysis of the other ylango-type sesquiterpenoid structures showed that the syntheses of these compounds could also be rationalized from a proposed intermediate in this ylangocamphor synthesis. These synthetic proposals will now be discussed.

The structures of the ylango-type sesquiterpenoids are reproduced in Chart 16. All of these compounds, except α-ylangene 21, incorporate the basic structural moiety 201. In addition, ylangocamphor 7, ylangoborneol 23, ylangoisoborneol 143, sativene 8, and cyclosativene 24 also have in common a two-carbon unit attached to the one-carbon bridge as in 202. The theoretical transfer of the terminal carbon atom on this two-carbon side-chain to the two-carbon bridge to give structure 156, affords the basic skeleton of the helmintho sesquiterpenoids: Helminthosporal 25, prehelminthosporal 154, helminthosporol 153, and prehelminthosporol 155. Thus it becomes evident that a structure such as 202, with appropriate functional groups, could act as a common intermediate in the synthesis of all the sesquiterpenoids shown in Chart 16, excepting α-ylangene 21. (From here onwards, α-ylangene will not be included in the discussion of the synthesis of the ylango-type sesquiterpenoids.)
Chart 16

1. ylangocamphor
2. ylangoborneol
3. ylangoisoborneol
4. sativene
5. cyclosativene
6. α-ylangene
7. helminthosporal
8. prehelminthosporal
9. helminthosporol
10. prehelminthosporol

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The initial synthetic objective, therefore, was the construction of the bicyclo[3.2.1]octane-type carbon skeleton 201, with functionality on the one-carbon bridge which would allow for the introduction of the two-carbon side-chain, and a suitable functional group on the two-carbon bridge which would allow for the later cyclizations leading to the individual sesquiterpenoids. Keeping in mind also the importance of synthetic availability, it was felt that the diketone 203 best fulfilled all of these requirements. Even though this compound contains two keto groups, it is possible to differentiate between them synthetically, since only one is enolizable. By virtue of this distinction it should be possible to introduce the two-carbon side-chain selectively onto the one-carbon bridge, to give the required fifteen-carbon compound with the carbon skeleton 202.
The desirability of having to synthesize just one such fifteen-carbon precursor to all of the "goal" sesquiterpenoids led to the choice of the keto olefin 204 as this precursor. Since the synthesis of this compound will be discussed later (vide infra) it seems appropriate here to show only how this single intermediate, containing all fifteen carbons required for sesquiterpenoid synthesis, could be converted into each of the ylango-type sesquiterpenoids to be synthesized.

Hydroboration of 204 (see Chart 17), followed by tosylation and cyclization of the resulting keto tosylate 200 under basic conditions, should give ylangocamphor 7. Ylangoborneol 23 and ylangoisoborneol 143 could then be derived from ylangocamphor by selective reductions. Thermal decomposition of the tosylhydrazone derivative of 204 in the presence of methyllithium, followed by selective hydroboration of the resulting diene 206 should give the olefinic alcohol 207. A facile cyclization of the tosyl derivative 208 of this alcohol to give sativene 8 would be expected under solvolytic conditions. Oxidation of this olefinic alcohol 207, and thermal decomposition of the tosylhydrazone derivative of the resulting olefinic aldehyde 209 in the presence of methyllithium, should result in the formation of cyclosativene 24 directly, or allow for the subsequent formation of cyclosativene from the pyrazoline 210. Acid-catalyzed cyclization of olefinic aldehyde 209 to the olefinic alcohol 211, followed by oxidation of the latter, should give the keto olefin 212.

Conversion of keto olefin 212 into the diene 213 (cf. 204 into 206), followed by selective osmolation, would result in the olefinic diol 214. Oxidative cleavage of the latter under neutral conditions would hopefully
Chart 17
Chart 17 (cont'd)
give the dialdehyde 215, which should be readily isomerizable to helminthosporal 25 under basic conditions. Helminthosporal has previously been converted 134 into helminthosporol 153 by reduction with sodium borohydride, followed by oxidation of the resulting diol with manganese dioxide. Treatment of helminthosporol with aqueous acid would afford prehelminthosporol 155. Prehelminthosporal 154 (R = H) has been isolated only as its acetal derivative 154 (R = CH$_3$CH$_2$). This derivative could hopefully be obtained from 215 by exposure to ethanol under acidic conditions.

The feasibility of the synthetic proposal outlined in this general discussion was confirmed by the stereoselective total synthesis of the (+)-keto olefin 204, and its subsequent conversion 9 into the sesquiterpenoids (-)-ylangocamphor 2, (-)-ylangoborneol 23, and (-)-ylangoisoborneol 143. This synthesis will now be discussed.

2. Synthesis of (+)-Keto Olefin 204

The first goal in the proposed synthetic route to the keto olefin 204 was an unambiguous synthesis of the diketone 203. 138 Basically this structure is a bridged cyclohexanone system containing two substituents, a methyl group and an isopropyl group, in a trans relationship to each other. Because of the substitution pattern, one obvious approach to the synthesis of this compound would be the alkylation of carvomenthone 189, thus leading to an intermediate such as keto ester 216. The latter could then be cyclized to the required diketone 203.
Previous work in our laboratory had shown, however, that such an approach was not feasible. Thus, attempts to alkylate carvomenthone directly with ethyl-2-bromopropionate under a variety of reaction conditions were unsuccessful. Similarly, the use of allylic halides as alkylating agents did not look promising. On forming the

* Recently, Welch and Walters have succeeded in reacting (+)-carvomenthone directly with 4-chloro-2-pentene. The alkylated material was obtained in 65% yield and consisted of a mixture of 218 and 219. The major product was keto olefin 218.
2-n-butylthiomethylene derivative of carvomenthone, however, alkylation with 2-iodopropionate did take place in good yield. The only product isolated, however, after removal of the blocking group and reesterification of the resulting keto acid, was not the keto ester \(216\) required for the present synthesis, but the \(C_2\) epimeric compound \(217\).

In spite of these results, it was still felt that the most direct approach to the synthesis of the desired keto ester \(216\) was by alkylation of a monoterpene such as carvomenthone. It was important however, that the stereochemical outcome of the successful alkylation could be easily established or be already known. For these reasons, the starting material chosen for this synthetic sequence was the known \((+)-ketol\) \(222\) (see Chart 18). The structure of this ketol had been well documented,\(^{142-144}\) and the important trans relationship between the \(C_{10}\) methyl group and the isopropyl side-chain had been confirmed by other work.\(^{**}\) The absolute stereochemistry of this ketol was known by virtue

\(^{*}\) It is now general practice to number eudesmane-type sesquiterpenoids according to the steroid numbering system, as indicated in structure \(222\).

\(^{**}\) For example, \((-\)-santonin \(235\), of known absolute stereochemistry,\(^{145}\) has been converted\(^{146}\) into \((+)-\alpha\)-cyperone \(224\), one of the dehydration products formed in the synthesis\(^{142b}\) of \((+)-ketol\) \(222\) (see Chart 18). Therefore, the other dehydration product, \((-\)-epi-\(\alpha\)-cyperone, must possess structure \(223\), and this compound was obtained\(^{142b}\) by dehydration of \((+)-ketol\) \(222\). Thus, the \((+)-ketol\) \(222\) has the \(C_{10}\) stereochemistry shown.
of its synthesis from (+)-dihydrocarvone 221, itself of known absolute stereochemistry. 147

(+)-Dihydrocarvone was obtained by a simple literature procedure, 148 from (-)-carvone 220, a readily available and inexpensive monoterpenoid. Thus Birch reduction of (-)-carvone, followed by oxidation of the crude product, gave a high yield of (+)-dihydrocarvone (see Chart 18).

The procedure used for the synthesis of (+)-ketol 222 was essentially that reported by Howe and McQuillan. 142 Thus condensation of (+)-dihydrocarvone 221 with l-diethylamino-3-pentanone methiodide 87 in the presence of sodium amide, afforded as major product the (+)-ketol 222, accompanied by an epimeric mixture of (+)-α-cyperone 223 and (~)-7-epi-α-cyperone 224. The ketol was readily separated from the distilled product mixture by recrystallization of the latter.

![Chart 18](image-url)
In our hands, the use of a slightly higher proportion of 1-diethylamino-3-pentanone methiodide than that reported resulted in a reaction product which did not crystallize. The product consisted mainly of one component which was not the desired ketol, as determined by g.l.c. Consideration of the reaction involved and of the physical and spectral properties (b.p., 133-140° at 0.04 mm, infrared spectrum, very strong carbonyl absorption at 1705 cm\(^{-1}\)) of this product mixture suggested that the major component was the diketone. This was confirmed by the facile cyclization of this material to give the desired ketol. Thus, subjection of the distilled product mixture to cyclizing conditions (sodium methoxide in methanol at 0°), afforded, after workup and recrystallization of the crude product, a 68% yield of the (+)-ketol. This represented a substantial increase over the previously reported yields for the synthesis of this compound.

The physical and spectral properties of the ketol were in agreement with structure and with the data reported in the literature for this compound. Thus the infrared spectrum showed hydroxyl absorptions at 3605 and 3580-3280 cm\(^{-1}\), and a saturated carbonyl absorption
at 1705 cm$^{-1}$. The presence of the terminal olefinic functionality was evidenced in the infrared spectrum by bands at 1638 and 895 cm$^{-1}$, and in the p.m.r. spectrum by a multiplet at $\tau$ 5.33. The quartet at $\tau$ 7.13 ($J = 6.8$ Hz) was assigned to the $C_4$ proton and consistent with this the doublet at $\tau$ 8.98 ($J = 6.8$ Hz) was assigned to the secondary methyl group. The exchangeable hydroxyl proton appeared as a singlet at $\tau$ 8.14, and the vinyl methyl group as an unresolved multiplet at $\tau$ 8.33. The sharp singlet at $\tau$ 8.77 was attributed to the angular methyl group.

Hydrogenation of the (+)-ketol 222 (one equivalent of hydrogen) over palladium on charcoal gave a quantitative yield of the crystalline (+)-ketol 227. The physical and spectral properties of this compound were in accord with the published data$^{149}$ and with structure 227. Of particular interest in the infrared spectrum was the absence of olefinic absorptions. The p.m.r. spectrum was very similar to that of the starting ketol 222, except for the disappearance of the signals due to the olefinic protons and the vinyl methyl group, which were replaced by two doublets ($J = 6.0$ Hz) at $\tau$ 9.15 and 9.16, attributable to the isopropyl methyl groups.

The possibility of using (+)-carvomenthone 189 instead of (+)-dihydrocarvone 221 in the Robinson annelation reaction was also considered. This would result in the direct synthesis of the saturated (+)-ketol 227, thus eliminating the hydrogenation step. This condensation reaction had already been performed$^{139}$ in our laboratory and the expected ketol 227 was formed in reasonable yield. However, this ketol
did not crystallize* from the product mixture and thus its isolation required extensive column chromatography. Consequently, this approach was not attempted in the present synthesis.

The (+)-ketol was dehydrated using refluxing ethanolic potassium hydroxide to give the corresponding unsaturated ketone 228 in 97% yield. The physical properties of this octalone were in agreement with the published data\textsuperscript{149} and with structure 228. Thus the ultraviolet spectrum showed the presence of the $\alpha,\beta$-unsaturated ketone with a strong absorption at 250 nm. The infrared spectrum supported this with absorptions at 1658 and 1607 cm$^{-1}$. In the p.m.r. spectrum the vinyl methyl group gave rise to a doublet ($J = 1.1$ Hz) at $\tau$ 8.20, and the tertiary methyl group appeared as a singlet at $\tau$ 8.96. The pair of doublets at $\tau$ 9.04 and 9.12 ($J = 6.0$ Hz) were attributable to the isopropyl methyl groups.

* This reluctance of the ketol 227 to crystallize was also noted in the present synthesis. Hikino and co-workers, who have also performed the hydrogenation reaction described above, report their product as a colorless oil.\textsuperscript{149}
At this point it seems appropriate to discuss the planned conversion of the octalone 228 into the desired keto ester 216. In order to obtain the keto ester carbon skeleton from the octalone 228, the introduction (into the latter) of a methyl group at C₃, followed by oxidative cleavage of the C₂-C₃ and C₄-C₅ bonds was required. Presumably the latter transformations would involve an intermediate such as 229, where R = H or OAc, for example.

The introduction of the methyl group at C₃ could hopefully be accomplished by a selective Michael-type addition to the dienone 230. The conversion of the octalone 228 into this dienone would normally be carried out by direct oxidation of the former with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). However in our laboratory the DDQ oxidation of the closely related epi-α-cyperone 223 was found to be a
very poor yielding reaction. This problem had been overcome by first making the hydroxymethylene derivative 233 and then oxidizing this compound with DDQ to give the cross-conjugated dienone aldehyde 234 in good overall yield.

In view of these results the direct DDQ oxidation of octalone 228 was not attempted. Instead, the octalone 228 was transformed first into the hydroxymethylene derivative 235 and then into the dienone aldehyde 236. Presumably, the synthesis of the desired keto ester 216 from this latter compound could then be accomplished in a manner similar to that proposed for the conversion of the dienone 230 into the same keto ester.
Thus, treatment of the (-)-octalone 228 with ethyl formate in benzene, in the presence of sodium methoxide, gave the (-)-hydroxy-methylene derivative 235 in 98% yield. This crystalline material showed the expected spectral properties. Of particular interest in the p.m.r. spectrum was the very broad singlet at \( \tau = -3.73 \) due to the exchangeable hydroxyl proton, and the doublet \( (J = 1.6 \text{ Hz}) \) at \( \tau = 2.68 \) due to the vinyl proton.

Dehydrogenation of 235 with DDQ\(^8\) in dioxan for ten minutes afforded the crystalline (+)-dienone aldehyde 236 in 93% yield. The infrared spectrum of this compound showed four absorptions at 1700, 1648, 1623 and 1600 cm\(^{-1}\), due to the unsaturated bonds. Of pertinence in the p.m.r. spectrum was the very sharp vinyl proton singlet at \( \tau = 2.51 \), and the singlet at \( \tau = -0.31 \) attributable to the aldehydic proton. The remaining assignable signals were similar in chemical shift and multiplicity to the corresponding resonances in the octalone 228.

Treatment of compound 236 with excess lithium dimethylcuprate\(^{152}\) at 0°, followed by quenching of the resulting enolate with acetyl chloride gave the enol acetate 237, in good yield (see Chart 19). In order to prevent decomposition of the product during work-up of the reaction...
mixture, the latter was poured into rapidly stirring, cold ammonium hydroxide and the product was quickly isolated by extraction of the resulting mixture with cold ether. Even after isolation, the crude product was somewhat unstable, and it was therefore used in the next reaction without further purification. However, the spectral data obtained from the crude product supported the assigned structure 237.

The infrared spectrum showed the presence of the enol acetate functionality with absorptions at 3110 and 1768 cm\(^{-1}\), while absorption bands at 1672 and 1612 cm\(^{-1}\) indicated the presence of the \(\alpha,\beta\)-unsaturated ketone functionality. A sharp singlet at \(\tau\) 1.85 in the p.m.r. spectrum was assigned to the vinyl proton, while a quartet (\(J = 7.0\) Hz) at \(\tau\) 7.12 was attributed to the newly generated tertiary proton. In addition to the signals for the vinyl methyl group (a broad singlet at \(\tau\) 8.13), the tertiary methyl group (a singlet at \(\tau\) 8.82), and the isopropyl methyl groups (poorly resolved multiplet at \(\tau\) 9.06), the newly introduced acetyl methyl group and the secondary methyl group appeared as a singlet at \(\tau\) 7.76 and a doublet (\(J = 7.0\) Hz) at \(\tau\) 8.96, respectively.

The crude enol acetate product consisted of only one component as shown by the p.m.r. spectrum, thus indicating that the conjugate addition reaction was both regioselective and stereoselective. Although the stereochemistry of the newly introduced secondary methyl group was not rigorously established, it could readily be assigned on the basis of considerable literature precedent. The latter clearly indicated that, in additions of this type, the expected configuration of the product is that in which the newly introduced group bears a \textit{trans} relationship to the angular methyl group as shown in 237. In any case, for the purpose
of the present synthesis, the configuration at this centre of the enol acetate 237 was not crucial, since the stereochemical integrity at this centre would be lost at a later stage in the synthetic sequence.

Oxidative cleavage of compound 237 was effected by ozonolysis in methylene chloride at -78° to -25°, followed by decomposition of the resulting ozonide with basic hydrogen peroxide. The resulting crude crystalline keto acid 23 was used in the next reaction without further purification. However, an analytical sample of the keto acid was obtained by recrystallization of the crude material from hexanes–ethyl acetate, and this material showed interesting spectral properties. The infrared spectrum of the crystals (nujol mull) showed a strong hydroxyl absorption at 3415 cm\(^{-1}\) and a carbonyl absorption at 1750 cm\(^{-1}\). The infrared spectrum of a chloroform solution of these crystals on the other hand, exhibited hydroxyl absorptions at 3590 and 3560-2500 cm\(^{-1}\), and carbonyl absorptions at 1770 and 1705 cm\(^{-1}\). These data indicated that the keto acid 238 crystallized in the lactol form 238b, while in chloroform solution there existed an equilibrium mixture of the ring-open form 238a and the cyclized form 238b. The p.m.r. spectrum of this material indicated that the ratio of the two forms in deuterochloroform solution at 40° was approximately 1:1. Two quartets, at \(\tau\) 6.88 (\(J = 7.2 \text{ Hz}\)) and at \(\tau\) 7.13 (\(J = 7.2 \text{ Hz}\)), whose combined integrated area corresponded to one proton, were assigned to the protons adjacent to the carboxylic acid carbonyl (of 238a) and to the lactol carbonyl (of 238b) in the mixture. The signals due to the methyl groups were not assignable.

Esterification of the total crude keto acid with ethereal diazomethane, followed by distillation of the crude product, afforded the keto ester
216 in 60% overall yield from the dienone aldehyde 236. This compound showed the expected spectral properties. In the infrared spectrum the presence of the two different carbonyl groups was evident from the absorptions at 1732 cm$^{-1}$ and 1705 cm$^{-1}$. The p.m.r. spectrum showed a sharp singlet at $\tau$ 6.30 for the methoxy methyl group and a quartet ($J = 7.1$ Hz) at $\tau$ 6.91 which was assigned to the proton adjacent to the ester carbonyl group. Signals for the tertiary methyl group appeared as a singlet at $\tau$ 9.00, for the secondary methyl group as a doublet ($J = 7.1$ Hz) at $\tau$ 9.03 and for the isopropyl methyl groups as doublets ($J = 6.3$ Hz) at $\tau$ 9.07 and 9.08.

![Chart 19](chart.png)
Having now achieved the first objective of this synthetic sequence, namely an unambiguous and good-yielding (54% overall yield from the starting ketol 222) synthesis of the keto ester 216, the next step involved the cyclization of this compound to give the important bicyclo[3.2.1]octadione intermediate 203. This type of cyclization had already been successfully attempted by Roberts and co-workers in their synthesis \(^{133}\) of culmorin, and by Piers and co-workers in their synthesis \(^{107}\) of (+)-copacamarphor and related compounds. Thus, Roberts and co-workers \(^{133}\) discovered that treatment of the keto ester 239 with sodium hydride in dimethoxyethane for 17 h at 75° gave the diketone 240 in 67% yield. It should be noted that, in this instance, the product of cyclization was a bicyclo[4.2.1]nonadione system while our work required the production of a bicyclo[3.2.1]octadione system.

Upon application of this procedure to the cyclization of compound 217, Piers and co-workers found \(^{139}\) that the diketone 241 was formed in only poor yield. When, however, this latter cyclization reaction was performed using sodium bis(trimethylsilyl)amide \(^{154}\) as base in refluxing dimethoxyethane, the diketone 241 was obtained in 90% yield. \(^{107}\)

The intramolecular Claisen condensation of the keto ester 216 proved to be much more difficult and capricious than expected on the basis of the above results. Thus, subjection of this compound to either of the condensation conditions outlined above resulted in the formation of only poor yields of the desired diketone 203 in each case. The crude product from both reactions contained unidentified, high-boiling material. At this stage considerable effort was expended in order to find conditions which would increase the yield of the
diketone 203. A number of different bases (sodium hydride, sodium bis(trimethylsilyl)amide, lithium bis(trimethylsilyl)amide, trityllithium, and tritylsodium) and/or different solvents (benzene, dimethoxyethane, tetrahydrofuran) were employed under a variety of conditions. In general, although the degree of success varied somewhat from experiment to experiment, most of the attempted reactions proved unsatisfactory. Eventually it was found that the conditions which afforded by far the highest yield (75%), and which gave reproducible results, were the following. A benzene solution of the keto ester 216 was added over a period of 65 min to a solution of sodium bis(trimethylsilyl)amide
(2.6 equivalents) in benzene kept at 79-80° (internal temperature). This temperature was maintained for a further 75 min. The reaction mixture was then quenched by pouring it into aqueous acetic acid. It was found that the choice of reaction temperature was crucial, because at lower temperatures some starting material was recovered, while at higher temperatures the crude product contained considerable amounts of high-boiling material. Similarly, longer reaction times also gave high-boiling products.

The crystalline material obtained from this cyclization reaction showed spectral properties consistent with structure 203. The infrared absorptions at 1765 and 1725 cm\(^{-1}\) are characteristic of this type of 1,3-dione. In the p.m.r. spectrum, a broad singlet at \(\tau\) 7.07 was assigned to the bridgehead (C\(_5\)) proton, while the quartet of doublets (\(J = 7.1, 1.5\) Hz) at \(\tau\) 7.68 was attributed to the C\(_7\) proton. That the latter proton was coupled (\(J = 1.5\) Hz) to the C\(_5\) proton was shown by a decoupling experiment in which the C\(_5\) proton at \(\tau\) 7.07 was irradiated, thus causing the quartet of doublets at \(\tau\) 7.68 to collapse to a quartet (\(J = 7.1\) Hz). The doublet (\(J = 7.1\) Hz) at \(\tau\) 8.80 was assigned to the secondary methyl (C\(_7\) methyl) group, the sharp singlet at \(\tau\) 8.88 to the bridgehead methyl group and the two doublets (\(J = 6.0\) Hz)
at \( \tau \) 8.99 and 9.12 to the isopropyl methyl groups.

Although the stereochemistry at C\(_7\) in the diketone 203 was not rigorously established, the stereochemistry shown in structure 203 was assigned on the basis of analogy with similar compounds. For example, Roberts and co-workers\(^{133}\) found that on quenching the enolate corresponding to diketone 240 with acetic acid, the product formed was 240, not its C\(_8\) epimer. Likewise, Piers and co-workers\(^{139}\) found that the quenching, with acetic acid, of the enolate corresponding to diketone 241, resulted in the exclusive formation of the diketone 241, not its C\(_7\) epimer. The reaction conditions employed in the present synthesis of diketone 203 similarly involved the quenching, with acetic acid, of the enolate corresponding to diketone 203, and hence the expected product was 203, not its C\(_7\) epimer.

Piers and co-workers had also shown\(^{139}\) that the diketone 241 was thermodynamically more stable than the C\(_7\) epimeric diketone. Likewise the diketone 203 was found to be thermodynamically more stable than its C\(_7\) epimer. Thus, when diketone 203 (obtained by cyclization of ketoester 216) was subjected to epimerizing conditions (potassium carbonate in aqueous dioxan at room temperature), the diketone was recovered unchanged. That these conditions were sufficiently strong to effect epimerization of the diketone, was shown by employing deuterium oxide, instead of water, as the cosolvent in the above reaction. In this case, deuterium was incorporated at C\(_7\) in diketone 203 as shown by the p.m.r. spectrum. The p.m.r. spectrum of deuterated diketone 203a was identical with that of diketone 203, except for the absence (in 203a) of the C\(_7\)H signal, the presence (in 203a) of a singlet (at \( \tau \) 8.81) rather than a
doublet for the C₇ methyl group, and the sharpening (in 203a) of the C₅H signal (width at half height = 3.0 Hz).

Finally, the coupling constant in diketone 241 (the C₇ stereochemistry of which has been firmly established¹³⁹) between C₅H and C₇H has been shown¹³⁹ to be 1.5 Hz. A coupling constant of similar magnitude would be expected between C₅H and C₇H in diketone 203, if the latter possessed the C₇ stereochemistry shown. This, indeed, was found to be the case. Thus, it was shown, by a proton magnetic double resonance experiment (vide supra), that JᵢC₅H-C₇H in 203 was 1.5 Hz.
With the important substituted bicyclo[3.2.1]octadione 203 in hand, the synthesis of the key intermediate, keto olefin 204, now required only the introduction of a vinyl side-chain to this dione. However, it was important to carry out this transformation in a regioselective and stereoselective manner. In order to satisfy the stereoselectivity requirement, it was felt that a successive addition of two one-carbon units, rather than a simultaneous introduction of both of the carbon atoms, would be the more rewarding approach. The solution to the problem of regioselectivity had already been incorporated into the structure of the diketone itself, since only one of the keto groups was enolizable. Thus, the first carbon of the required vinyl side-chain was introduced by an efficient three-step homologation sequence.

The (+)-diketone 203 was reacted with excess sodium bis(trimethylsilyl)amide in hexamethylphosphoramide and the resulting enolate was trapped with isopropyl bromide to give the O-alkylated product 242 in 88% yield. Of note in the infrared spectrum of this material was the carbonyl absorption at 1760 cm\(^{-1}\) and the strong olefinic absorption at 1660 cm\(^{-1}\). That O-alkylation had indeed taken place was evident from the p.m.r. spectrum of the product. A septet (J = 6.1 Hz) at \(\tau\) 5.95 and
doublets \((J = 6.1 \text{ Hz})\) at \(\tau\) 8.74 and 8.89 accounted for the tertiary proton and the isopropyl methyl groups respectively of the newly introduced isopropyl group, while the doublet \((J = 0.9 \text{ Hz})\) at \(\tau\) 8.32 was attributed to the vinyl methyl group. The remaining assignable signals, due to the \(\text{C}_5\) proton, the tertiary methyl group and the isopropyl methyl groups were similar in chemical shift and multiplicity to the corresponding resonances in the diketone \text{203}.

The alkylation reaction just described also produced a second product, to the extent of about 10%. Consideration of the reaction involved, and of the physical and spectral properties of this crystalline product indicated that this material was the C-alkylated product \text{243}.

Thus, in the infrared spectrum, the carbonyl absorption region was similar to that of diketone \text{203} with absorptions at 1758 and 1722 cm\(^{-1}\). The p.m.r. spectrum showed the \(\text{C}_5\) bridgehead proton as a broad singlet at \(\tau\) 7.15, and also two sharp singlets at \(\tau\) 8.85 and 8.90, attributed to the tertiary methyl groups. The two pairs of doublets at \(\tau\) 8.97 and 9.12 \((J = 6.1 \text{ Hz})\) and at \(\tau\) 9.00 and 9.22 \((J = 6.9 \text{ Hz})\), were assigned to the methyl groups of the two isopropyl moieties. While the configuration at \(\text{C}_7\) in this product was not established, it was evident
from a study of a molecular model of the enolate of diketone 203 that
approach of the alkylating agent is much less hindered from the exo
side (i.e., the side away from the three-carbon bridge), and thus the
alkylation reaction should have produced a product with the stereo-
chemistry shown in structure 243.

The reaction conditions used in the alkylation reaction merit
further comment. Hexamethylphosphoramidc was selected as solvent since
this medium has been found to promote O-alkylation.156 The use of
other solvents with similar properties was also studied in the
present instance. It was found, however, that when the reaction was
carried out in dimethylsulfoxide or sulfolane, the expected products
242 and 243 were indeed formed, but in each case the proportion of the
desired O-alkylated material 242 was considerably less than in
hexamethylphosphoramidc.

Treatment of the (+)-keto enol ether 242 with excess methoxymethylene-
triphenylphosphorane in refluxing ether for thirty minutes afforded,
in quantitative yield, a mixture of the diastereomeric diethers 244.
The ratio of the two diastereomers varied considerably from experiment
to experiment. No attempt was made to separate these isomers, since both
gave rise to the same products in the next reaction. Of importance in
the infrared spectrum of this mixture were the two olefinic absorptions
at 1707 and 1664 cm⁻¹. The presence of the two components was evident
in the p.m.r. spectrum of the mixture which showed two vinyl proton
singlets at δ 4.43 and 4.52, two tertiary proton (adjacent to oxygen)
septets (J = 6.1, 6.1 Hz) at δ 5.92 and 5.97 and two methoxy methyl
singlets at δ 6.49 and 6.56.
Total hydrolysis of both of the enol ether functionalities in the mixture \(244\) was achieved by exposure of this material to aqueous perchloric acid in ether for 1.5 hours. The resulting keto aldehydes \(245\) and \(246\) were produced in a ratio of approximately 1:1. On allowing the hydrolysis reaction to proceed for a longer time, it was found that the ratio of keto aldehydes gradually changed in favor of the desired product \(245\). It was felt, however, that an equilibrium mixture could be achieved more rapidly under basic conditions. Consequently the 1:1 mixture of keto aldehydes was treated with potassium carbonate in aqueous methanol until an equilibrium mixture of the two epimers was achieved (1.5 hours). On the basis of gas-liquid chromatographic analysis,
this ratio was found to be approximately 82:18, with the major epimer being the desired compound 245.

The overall yield for the hydrolysis and epimerization reactions was 80%, although the yield decreased somewhat if the crude product of hydrolysis was not distilled before being subjected to epimerization. Attempted separation of the two epimers (245 and 246) by column chromatography (silica gel or activity III neutral alumina) resulted in extensive decomposition of both compounds. Consequently, the next reaction was performed on the equilibrium mixture of the compounds. The spectral data obtained from this mixture supported the proposed structures, 245 and 246. Thus the infrared spectrum exhibited absorptions at 2745, 1735, and 1715 cm\(^{-1}\). In the p.m.r. spectrum, the presence of the two components was evident from the two doublets at \(\tau\) 0.10 (\(J = 1.0\) Hz) and \(\tau\) 0.03 (\(J = 2.0\) Hz), attributed to the aldehydic protons. The signals due to the methyl groups were not assignable.

The final carbon required for the completion of the synthesis of the \(C_{15}\)-carbon skeleton was also added by means of a Wittig reaction. The equilibrium mixture of keto aldehydes 245 and 246 was first allowed to react with methylenetriphenylphosphorane under conditions similar to the previous high-yielding Wittig reaction, but this resulted in the formation of only poor yields of the corresponding keto olefinic products 204 and 247. The use of other ether-type solvents, as well as experimentation with a variety of reaction temperatures, failed to appreciably increase the yield of the desired products. However, on performing the reaction in dry dimethylsulfoxide at room temperature, the keto olefins 204 and 247 were produced in quantitative yield, in the expected ratio of approximately 82:18 respectively.
The two components (204 and 247) were separable by column chromatography on t.l.c. silica gel. The physical and spectral properties of each were in agreement with the proposed structures. Thus the infrared spectrum of the desired major epimer 204 (Figure 11) showed the presence of the terminal olefinic group with bands at 3080, 1634 and 910 cm\(^{-1}\), while the carbonyl group gave rise to a strong absorption at 1730 cm\(^{-1}\). In the p.m.r. spectrum of 204 (Figure 12), the vinyl group exhibited a multiplet at \(\tau\) 3.99-4.37 for the C\(_9\) proton and a multiplet at \(\tau\) 4.86-5.10 for the C\(_{10}\) protons. The broad singlet at \(\tau\) 7.41 was assigned to the bridgehead C\(_5\) proton, the doublet (\(J = 7.9\) Hz) at \(\tau\) 7.79 to the allylic C\(_8\) proton, and the quartet (\(J = 7.2\) Hz) at \(\tau\) 7.97 to the
Figure 11. Infrared Spectrum of (+)-Keto Olefin 204.
The secondary methyl group ($C_7$ methyl) appeared as a doublet ($J = 7.2$ Hz) at $\tau$ 9.06, while the tertiary methyl group ($\tau$ 8.99) and the isopropyl methyl groups (doublets, $\tau$ 8.99 and 9.20, $J = 6.2$ Hz) were also distinguishable.

The spectral data for the crystalline minor keto olefinic product were similar to, but not identical with that of its epimer $204$. The olefinic double bond gave rise to absorptions at 3080, 1633 and 916 cm$^{-1}$ in the infrared spectrum, while the carbonyl group produced a strong band at 1724 cm$^{-1}$. In the p.m.r. spectrum, the vinyl group gave rise to multiplets at $\tau$ 3.71-4.08 and 4.68-4.92 corresponding to the $C_9$ and $C_{10}$ protons respectively. The $C_5$ bridgehead proton appeared as a broadened doublet ($J = 5.6$ Hz) at $\tau$ 7.42, the $C_8$ allylic proton as a doublet of doublets ($J = 5.6, 8.3$ Hz) at $\tau$ 7.64 and the $C_7$ proton as a quartet ($J = 7.0$ Hz) at $\tau$ 8.17. The signals for the various methyl groups were also readily assignable.

The assignment of the stereochemistry at the point of attachment of the vinyl side-chain to the one-carbon bridge of the bicyclo[3.2.1]-octanone system merits comment. It had been assumed that in the mixture of keto aldehydes $245$ and $246$, the major component at equilibrium was the desired compound $245$ with the formyl group in an equatorial orientation with respect to the six-membered ring. Consequently, the major product in the corresponding mixture of keto olefins was also assumed to be $204$. The first indication that this assumption was indeed correct was provided by a comparison of the p.m.r. spectra of the two keto olefin products. The $C_5$ proton of the major product $204$ appeared as a broad singlet (width at half height = 4.5 Hz) at $\tau$ 7.41 with little or no coupling to
the C₈ proton. The C₅ proton of the minor product 247, on the other hand, was clearly coupled with the C₈ proton with \( J_{C₅H-C₈H} = 5.6 \text{ Hz} \). An analysis of a molecular model of keto olefin 204 showed that the dihedral angle between C₅H and C₈H is approximately 70°, and on the basis of the Karplus equation only a very small coupling constant should exist between these two protons. This is, in fact, the situation observed in the p.m.r. spectrum of the major keto olefinic product. On the other hand, a molecular model of the other keto olefin 247 showed that the dihedral angle between C₅H and C₈H in this compound is about 45°, and for this angle the Karplus equation predicts a coupling constant \( J_{C₅H-C₈H} \) of magnitude similar to that observed (5.6 Hz) in the p.m.r. spectrum of the minor component of the keto olefin mixture. Chemical confirmation that the major component was indeed compound 204 was provided later (vide infra) by the cyclization of a derivative of the major keto olefin to give ylangocamphor. Obviously, the analogous derivative of the keto olefin 247 could not undergo such a cyclization.

The successful, stereoselective synthesis of the (+)-keto olefin 204 made available a C-15 intermediate which could hopefully be transformed into the various ylango sesquiterpenoids. The feasibility of such transformations is demonstrated by the successful synthesis of (-)-ylango-camphor 7, (-)-ylangoborneol 23, and (-)-ylangoisoborneol 143 from this (+)-keto olefin.
3. Synthesis of (-)-Ylangocamphor 7, (-)-Ylangoborneol 23, and (-)-Ylangoisoborneol 143

The planned conversion of the (+)-keto olefin 204 into ylangocamphor required the introduction of a leaving group at the terminal position of the olefinic side-chain of the former compound, so that an internal alkylation could be attempted. Hydroboration, followed by mesylation (or tosylation), seemed a promising method of accomplishing this required transformation and this sequence of reactions was therefore adopted.

Because of the fact that ketones are susceptible to reduction by diborane, and because of the proximity of the keto functionality to the olefinic side-chain in compound 204, it was felt that selective hydroboration of the olefinic double bond in 204 with diborane would not be feasible. What was required was a hydroborating reagent which delivered only one hydride per molecule and which was relatively unreactive towards ketone carbonyl groups. The selective hydroborating reagent, disiamylborane (Sia₂BH), which is easily prepared by treating tetrahydrofuran-borine complex with two or more equivalents of 2-methyl-2-butene at 0°, was therefore chosen for this reaction.

It should be noted that an additional advantage in the use of disiamylborane is that the product of hydroboration of monosubstituted olefins (such as 204) with this reagent, is almost exclusively the corresponding primary alcohol.

Subjection of the (+)-keto olefin 204 to hydroboration with disiamylborane in tetrahydrofuran at 0° for 45 minutes, followed by oxidative decomposition of the resulting trialkylborane with alkaline hydrogen peroxide afforded, in 81% yield, a mixture of the desired keto
alcohol 205 and the diol 248 in a ratio of approximately 85:15 respectively. The two components were not separable by column chromatography.

It was desirable at this stage to separate these compounds in order to show that the minor component was indeed the diol 248, and in order to obtain an analytical sample of the keto alcohol 205. However, for the purpose of synthesizing ylangocamphor 7, this separation was not necessary. It was felt that the remaining reactions (mesylation and intramolecular alkylation) leading to ylangocamphor would not be disadvantageously influenced by the presence of this diol impurity, and that ylangocamphor could readily be separated from the final product mixture by distillation. This proved to be the case (vide infra).

For purposes of characterization, the keto alcohol 205 and the diol 248 were separated as their trimethylsilyl ether derivatives. Thus, treatment of the hydroboration product with a mixture of trimethylchlorosilane and hexamethyldisilazane in pyridine at room temperature for fifteen minutes, gave a quantitative yield of the corresponding trimethylsilyl ether derivatives 249 and 250 (in the ratio of approximately 85:15 respectively). These derivatives were readily separated by preparative g.l.c., and both were collected in high yield. The keto trimethylsilyl ether 249 showed the expected carbonyl absorption
at 1727 cm\(^{-1}\) and bands at 1250, 1090, 840 and 745 cm\(^{-1}\) attributed to the trimethylsilyl ether group. Of interest in the p.m.r. spectrum was the sharp singlet at \(\tau\) 9.88 due to the methyl groups of trimethylsilyl blocking group. The remainder of the p.m.r. spectrum was almost identical with that of the corresponding keto alcohol 205, except for the absence of the hydroxyl proton.

The (+)-keto alcohol 205 was easily regenerated in pure form and in high yield from the trimethylsilyl ether derivative 249 by hydrolysis of the latter in refluxing aqueous ethanol.\(^{161}\) The infrared spectrum of the product 205 exhibited a strong hydroxyl absorption at 3400 cm\(^{-1}\) and the usual cyclopentanone carbonyl absorption at 1724 cm\(^{-1}\). In the p.m.r. spectrum, the complex multiplet at \(\tau\) 6.34 was assigned to the pair of protons on the oxygen-bearing carbon, and the broad singlet at \(\tau\) 7.46 to the \(C_5\), bridgehead proton. The angular methyl group and the secondary methyl group appeared as a singlet at \(\tau\) 8.96 and a doublet (\(J = 7.1\) Hz) at \(\tau\) 9.03 respectively. The two doublets (\(J = 6.1\) Hz) at \(\tau\) 8.99 and 9.18 were attributed to the isopropyl methyl groups.

The minor component collected by preparative g.l.c., the bistrimethylsilyl ether derivative 250, showed no hydroxyl or carbonyl absorptions in the infrared spectrum. Absorption bands due to the trimethylsilyl ether groups were present at 1250, 1060, 840 and 750 cm\(^{-1}\). Of particular interest in the p.m.r. spectrum were the two singlets at \(\tau\) 9.89 and 9.85 due to the methyl groups of the two trimethylsilyl groups. The remainder of the p.m.r. spectrum was similar to that of diol 248. The latter was obtained in high yield from the bistrimethylsilyl ether derivative 250 by the same type of mild hydrolysis as that employed
in the case of compound 249. The infrared spectrum of the product 248 exhibited a strong hydroxyl absorption at 3350 cm\(^{-1}\). The p.m.r. spectrum showed a doublet of doublets (J = 6.9, 10.6 Hz) at \(\tau\) 5.60 and a complex multiplet at \(\tau\) 6.41, attributed to the C\(_6\) proton and the protons on the carbon bearing the primary hydroxyl group, respectively. The tertiary methyl group was apparent as a singlet at \(\tau\) 9.25, the secondary methyl group as a doublet (J = 7.1 Hz) at \(\tau\) 9.29 and the isopropyl methyl groups as doublets (J = 6.6 Hz) at \(\tau\) 9.18 and 9.28, respectively.

It seems appropriate here to comment on the stereochemistry at C\(_6\) of the diol 248. Molecular models indicated that the dihedral angle between the protons on C\(_5\) and C\(_6\) was approximately 15-25° and in agreement
with the Karplus equation the observed coupling constant, $J_{C_5 H-C_6 H'}$ was 6.9 Hz. Likewise, the dihedral angle between the $C_6$ and $C_7$ protons was near to 0°, giving rise to the observed coupling constant, $J_{C_6 H-C_7 H'}$ of 10.6 Hz, also in good agreement with that expected on the basis of the Karplus equation. If the configuration at $C_6$ of the diol had been epimeric with that shown in 248, the dihedral angles between the protons on $C_5$ and $C_6$ would be approximately 90°, and between the protons on $C_6$ and $C_7$ approximately 125°. On the basis of the Karplus equation, the expected coupling constants would then be approximately zero and 3.0 Hz respectively. Finally, it was evident from a consideration of a molecular model of the keto olefin 204 that attack on the ketone functionality by the hydride complex would be more facile from the exo side of the bicyclo[3.2.1]octane system, (that is, the side away from the three-carbon bridge) thus giving rise to the endo-alcohol.

The pure (+)-keto alcohol 205 was treated with methanesulfonyl chloride in pyridine for 2.25 hours at room temperature. The resulting crude keto mesylate 251 was subjected to cyclization conditions without purification. This intramolecular alkylation proved to be very facile. Thus, exposure of 251 to sodium bis(trimethylsilyl)amide in dimethoxyethane for 40 minutes, and distillation of the resulting crude product, afforded (-)-ylangocamphor 7, in 84% overall yield from the (+)-keto alcohol 205. This distilled product crystallized on cooling, and a recrystallized sample (from hexanes) exhibited a sharp melting point of 25-25.5°, and $[\alpha]_{D}^{26} = -58°$. The spectral properties of this compound were in complete agreement with the assigned structure. Of importance in the infrared spectrum (Figure 13) was the carbonyl absorption at 1733 cm$^{-1}$. 
Figure 13. Infrared Spectrum of (-)-Ylangocamphor 7.
In the p.m.r. spectrum (Figure 14) the bridgehead proton adjacent to the carbonyl group was evident as a broad singlet (width at half height = 3.0 Hz) at $\tau$ 7.76, while the isopropyl methyl groups appeared as a pair of doublets ($J = 6.5$ Hz) at $\tau$ 9.02 and 9.19. The singlets at $\tau$ 9.10 and 9.11 were assigned to the two tertiary methyl groups.

As mentioned earlier, the rather tedious though efficient separation of the mixture of keto alcohol 205 and diol 248 could be avoided by performing the mesylation and cyclization reactions on the mixture, under conditions identical with those used on the pure keto alcohol. Thus, reaction of the mixture of 205 and 248 with methanesulfonyl chloride in pyridine, and treatment of the resulting mixture of mesylate derivatives with sodium bis(trimethylsilyl)amide in dimethoxyethane, gave a crude product which, on simple distillation, yielded pure ylangocamphor (50% overall yield from the keto olefin 204).

(-)-Ylangocamphor 7 was converted into the two corresponding alcohols, ylangoborneol 23 and ylangoisoborneol 143, by two completely stereo-selective reductions. Thus treatment of 7 with calcium in anhydrous liquid ammonia afforded (-)-ylangoborneol as the sole product, in 95% yield. This crystalline compound exhibited a sharp m.p. of 60.5-61° and $[\alpha]_D^{25} = -23^\circ$. In the infrared spectrum (Figure 15) the presence of the
hydroxy group was evident from absorptions at 3610 and 3460 cm$^{-1}$. The p.m.r. spectrum (in CCl$_4$, Figure 16) displayed a broad singlet (width at half height = 3.2 Hz) at $\tau$ 6.26 for the hydrogen on the oxygen-bearing carbon. The doublets ($J = 6.5$ Hz) at $\tau$ 9.06 and 9.14 and the singlets at $\tau$ 9.15 and 9.19 were assigned to the isopropyl methyl groups and the two tertiary methyl groups, respectively.

The stereochemical outcome of the reaction, and the particular reaction conditions employed in the reduction of (-)-ylangocamphor 7 to (-)-ylangoborneol 23 merit further comment. The metal-ammonia reduction of keto compounds generally favors the production of the thermodynamically more stable alcohol product. Consideration of molecular models of ylangoborneol 23 and ylangoisoborneol 143 indicates that the hydroxyl group is in a less crowded environment in ylangoborneol, and consequently this should be the thermodynamically more stable epimer. It has also been shown in the reduction of camphor and related compounds that the use of calcium metal, rather than lithium, sodium or potassium, under anhydrous conditions, has the combined attractiveness of favoring the formation of endo-alcohols and of producing high yields of monomeric products. While in the reduction of ylangocamphor the use of metals other than calcium was not studied, an excellent yield of monomeric product was
obtained using calcium metal under anhydrous conditions. Furthermore, the reaction showed complete stereoselectivity in favor of the endo-alcohol (endo with respect to the bicyclo[2.2.1]heptane moiety).

The transformation of (-)-ylangocamphor 7 into (-)-ylangoisoborneol 143 was also accomplished in a stereoselective fashion. Thus subjection of 7 to reduction with lithium aluminum hydride in refluxing ether for 1 hour afforded, as the sole product, (-)-ylangoisoborneol in 91% yield. This product, though pure by gas-liquid chromatographic analysis, proved difficult to recrystallize. However, despite its high solubility in the solvent, a recrystallized sample was obtained by recrystallization from hexane at -10°. The resulting crystalline material, which had a soft appearance at room temperature (22°), exhibited a melting point range of 31.5-32.5° and [α]D^26 = -28°. The infrared and p.m.r. spectra of this material were clearly different from those of (-)-ylangoborneol 23. Of pertinence in the infrared spectrum (Figure 17) were the hydroxyl absorptions at 3630 and 3495 cm^-1. In the p.m.r. spectrum (in CCl₄, Figure 18), the proton on the oxygen-bearing carbon gave rise to a doublet (J = 7.7 Hz) at τ 6.27. This proton was coupled with the proton on the adjacent bridgehead carbon which appeared as a broadened doublet (J = 7.7 Hz) at τ 7.91. The chemical shift assigned to this bridgehead hydrogen was confirmed by a decoupling experiment in which the proton at τ 6.27 was irradiated, thus causing the doublet at τ 7.91 to collapse to a broadened singlet. The pair of doublets (J = 6.5 Hz) at τ 9.08 and 9.20 were assigned to the isopropyl methyl groups, and the singlets at τ 9.18 and 9.20 to the two tertiary methyl groups.
Figure 17. Infrared Spectrum of (-)-Ylangoisoborneol 143.
It has been pointed out above that the expected product of dissolving metal reduction of ylangocamphor \(7\) was the alcohol \(23\), ylangoborneol. The expected product of hydride reduction, on the other hand, was the epimeric alcohol \(143\). The latter prediction arose from a study of a molecular model of ylangocamphor \(7\), which showed that the approach by the hydride complex to the carbonyl group is much less hindered on the eno side (endo with respect to the bicyclo[2.2.1]heptanone moiety), and attack from this side gives rise to the exo-alcohol \(143\), ylangoisoborneol.

That the products of metal-ammonia reduction and hydride reduction of (-)-ylangocamphor \(7\) were indeed (-)-ylangoborneol \(23\) and (-)-ylangoisoborneol \(143\) respectively, was confirmed by the p.m.r. spectra of the two alcohols. Thus, as shown by inspection of molecular models, the dihedral angle between the proton on the oxygen-bearing carbon and the proton on the adjacent bridgehead carbon in ylangoborneol was about 110°. Therefore in keeping with the Karplus equation, the expected coupling constant between these two protons would be in the order of 1.0 Hz. The observed signal for the proton on the oxygen-bearing carbon in the product of metal-ammonia reduction was a broad singlet. In the p.m.r.
spectrum of the product of hydride reduction, on the other hand, this proton appeared as a doublet with a coupling constant of 7.6 Hz. Again, this coupling constant was in agreement with that predicted on the basis of the Karplus equation, since an analysis of a molecular model of indicated that the dihedral angle between the proton on the oxygen-bearing carbon and the proton on the adjacent bridgehead carbon was near to 0°.

In summary, a general stereoselective approach to the synthesis of ylango-type sesquiterpenoids has been developed. The feasibility of this approach has been demonstrated by the stereoselective total synthesis of (-)-ylangocamphor 7, (-)-ylangoborneol 23 and (-)-ylango-isoborneol 143, via the key intermediate keto olefin 204. This unambiguous synthesis provides proof for the structure and absolute stereochemistry of these three sesquiterpenoids. The synthesis of other ylango-type sesquiterpenoids from this same intermediate 204 is currently being investigated in our laboratory.
PART II
EXPERIMENTAL

For general experimental information see p. 73.

Preparation of (+)-Ketol 222

A solution of (+)-dihydrocarvone 221 (142 g, 0.93 mole) in 1250 ml of anhydrous ether containing 40 g (1.025 moles) of sodium amide was stirred at 0° for 2 h under an atmosphere of nitrogen. To this solution at 0° was added, over 50 min, a cold solution of 1-diethylamino-3-pentanone methiodide 87 (290 g, 0.97 mole) [prepared by reaction of 1-diethylamino-3-pentanone (152.5 g, 0.97 mole) with methyl iodide (142 g, 1.0 mole)] in 300 ml of dry pyridine. The resulting mixture was stirred with a mechanical stirrer at 0° for 8 h and then for a further 5 h at reflux. The cooled reaction mixture was poured into cold water, the layers were separated and the aqueous layer extracted with ether. The ether layers were combined, the ether was removed at aspirator pressure and most of the pyridine was taken off under vacuum. The resulting residue was dissolved in ether and washed with a 5% solution of hydrochloric acid, with brine, and then dried over anhydrous magnesium sulfate. Removal of solvent afforded a yellow oil which was distilled to give 60 g of the starting material, (+)-dihydrocarvone 221 (b.p. 55-60° at 0.4 mm) and 106.8 g of a liquid product with b.p. 133-140° at 0.04 mm. Analysis of this material by g.l.c. (column A,
182°, 120) showed that only a small amount of the desired ketol 222 was present. (The relative amount of ketol present varied somewhat from experiment to experiment.) The p.m.r. and infrared spectra confirmed this, and the indications were that most of the condensation product had failed to cyclize under these reaction conditions. Consequently this material was treated with 63 ml of 0.136 M sodium methoxide solution in methanol at 0° for 2 h. The reaction mixture was poured into brine and the product isolated by extraction with ether. The ether solution was washed with brine and dried over anhydrous magnesium sulfate. Removal of the solvent gave a crystalline compound which was recrystallized from hexanes to give 85.5 g of the desired (+)-ketol 222 (68% based on unrecovered (+)-dihydrocarvone). An analytical sample exhibited m.p. 107.5-108°; [α]_D^28 +43.5° (c,2.5 in CHC_l_3) [lit. 142b m.p. 106°; [α]_D +54° (c,3.0 in CHC_l_3)]; infrared (CHC_l_3), ν_{max} 3605, 3580-3280, 1705, 1638, 895 cm^{-1}; p.m.r., τ 5.33 (multiplet, 2H, CH_3-C=CH_2), 7.13 (quartet, 1H, C_4H, J = 6.8 Hz), 8.14 (singlet, 1H, exchangeable -OH), 8.33 (unresolved multiplet, 3H, vinyl methyl, width at half height = 3.0 Hz), 8.77 (singlet, 3H, tertiary methyl), 8.98 (doublet, 3H, secondary methyl, J = 6.8 Hz).

Anal. Calcd. for C_{15}H_{24}O_2: C, 76.23; H, 10.24. Found: C, 76.05; H, 10.03.

* The reason for this discrepancy is not known. The enantiomeric compound which has been synthesized by Halsall and co-workers was reported 144 to have [α]_D -48° (c,2.3 in CHC_l_3).
Preparation of (+)-Ketol 227

A solution of the (+)-ketol 222 (114.5 g, 0.385 mole) in 750 ml of ethanol was hydrogenated over 10.5 g of 10% palladium on charcoal at room temperature, until the uptake of hydrogen was complete (approximately 50 min). The solution was filtered and the solvent was removed to give a quantitative yield of the (+)-ketol 227, which crystallized on standing. An analytical sample was obtained by recrystallization from hexanes to give colorless crystals, m.p. 62.5-63°; $[\alpha]_D^{27}$ +50.1° (c, 2.5 in CHCl$_3$) [lit. $149 [\alpha]_D^{27}$ +101.5° (c, 5.20 in CHCl$_3$)]; infrared (CHCl$_3$), $\nu$ max 3610, 3580-3320, 1707 cm$^{-1}$; p.m.r., $\tau$ 7.14 (quartet, 1H, CH$_3$, J = 6.8 Hz), 8.10 (singlet, 1H, exchangeable, -OH), 8.79 (singlet, 3H, tertiary methyl), 8.96 (doublet, 3H, secondary methyl, J = 6.8 Hz), 9.15, 9.16 (doublets, 6H, isopropyl methyls, J = 6.0 Hz).

Anal. Calcd. for C$_{15}$H$_{26}$O$_2$: C, 75.58; H, 10.99. Found: C, 75.58; H, 10.90.

Preparation of (-)-11,12-Dihydro-7-epi-a-cyperone 228

A solution containing 166.4 g (0.697 mole) of the (+)-ketol 227 in 2000 ml of 10% ethanolic potassium hydroxide was refluxed gently for 10 h under an atmosphere of nitrogen. The cooled solution was poured into water and this mixture was thoroughly extracted with petroleum ether (b.p. 30-60°). The combined extracts were washed with 2% hydrochloric

* This literature rotation was taken on a sample of non-crystalline (+)-ketol and this might account for the high reading obtained. The (-)-ketol has also been synthesized, $^{143}$ and the reported data for this compound are: m.p. 64-65°; $[\alpha]_D^{27}$ -57° (c 3.8 in CHCl$_3$).
acid, with brine, and dried over anhydrous magnesium sulfate. Removal of the solvent, followed by distillation of the residue, gave 150.5 g (97%) of the octalone 228 as a colorless oil, b.p. 97° at 0.15 mm. An analytical sample, obtained by preparative g.l.c. (column B, 220°, 100) exhibited $n^D_{20}$ 1.5187; $[\alpha]D_{26}^o$ -145° (c,0.6 in CHCl₃) [lit. 149 $[\alpha]D$ -145° (c,9.35 in CHCl₃)]; ultraviolet, $\lambda_{max}$ 250 mμ (ε = 14,000); infrared (film), $\nu_{max}$ 1658, 1607 cm$^{-1}$; p.m.r., $\tau$ 8.20 (doublet, 3H, vinyl methyl, $J = 1.1$ Hz), 8.76 (singlet, 3H, tertiary methyl), 9.04, 9.12 (doublets, 6H, isopropyl methyls, $J = 6.0$ Hz).

Anal. Calcd. for C$_{15}$H$_{24}$O: C, 81.76; H, 10.98. Found: C, 81.62; H, 10.78.

Preparation of the (-)-Hydroxymethylene Derivative 235

To a stirred suspension of powdered sodium methoxide (102.5 g, 1.9 moles) in 1400 ml of dry benzene containing 153 ml (2.25 moles) of ethyl formate was added at 0° 140 g (0.635 mole) of the (-)-octalone 228 in 1400 ml of dry benzene. The cooling bath was removed and the reaction mixture was stirred at room temperature in an atmosphere of nitrogen for 4 days. The cooled mixture was acidified with 6 N hydrochloric acid, the layers were separated and the aqueous layer was extracted with ether. The combined organic extracts were washed twice with brine and dried over anhydrous magnesium sulfate. Removal of the solvent gave 157 g (98%) of the hydroxymethylene derivative 235 as yellow crystals. An analytical sample of pale yellow crystals, obtained by recrystallization from hexanes, exhibited m.p. 64.5-65°; $[\alpha]D_{27}^o$ -8.5° (c,2.5 in CHCl₃); infrared (CHCl₃), $\nu_{max}$ 1638, 1563 cm$^{-1}$; p.m.r. (CCl₄),
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$\tau -3.73$ (broad signal, 1H, exchangeable, $=\text{CHOH}$), 2.68 (doublet, 1H, $=\text{CHOH}$, $J = 1.6$ Hz), 8.17 (doublet, 3H, vinyl methyl, $J = 1.2$ Hz), 8.90 (singlet, 3H, tertiary methyl), 9.01, 9.07 (doublets, 6H, isopropyl methyls, $J = 6.0$ Hz).

Anal. Calcd. for $C_{16}H_{20}O_2$: C, 77.38; H, 9.74. Found: C, 77.31; H, 9.86.

Preparation of (+)-Dienone Aldehyde 236

A solution of 2,3-dichloro-5,6-dicyanobenzoquinone (5.0 g, 22.0 mmoles) in 75 ml of dry dioxan was added to a solution of the hydroxy-methylen derivative 235 (5.0 g, 20.1 mmoles) in 75 ml of dry dioxan. The resulting mixture was stirred at room temperature in an atmosphere of nitrogen for 10 min, and then 300 ml of methylene chloride was added. The precipitate was removed by filtration and the solution was passed quickly through a short column of neutral alumina (activity III). The column was thoroughly eluted with methylene chloride. Removal of the solvents gave 4.6 g (93%) of the desired dienone aldehyde 236 as pale yellow crystals. An analytical sample was obtained by recrystallization from hexanes and it exhibited m.p. 78.5-79°; $[\alpha]_D^{27} +161^\circ$ (c,2.5 in CHCl$_3$); ultraviolet, $\lambda_{\text{max}}$ 228 mu ($\epsilon = 10,200$), 239 mu ($\epsilon = 9,800$) (shoulder), 266 mu ($\epsilon = 6,800$) (shoulder); infrared (CHCl$_3$), $\nu_{\text{max}}$ 1700, 1648, 1623, 1600, 855, 824 cm$^{-1}$; p.m.r., $\tau -0.31$ (singlet, 1H, aldehydic H), 2.51 (singlet, 1H, vinyl H), 8.03 (doublet, 3H, vinyl methyl, $J = 1.2$ Hz), 8.67 (singlet, 3H, tertiary methyl), 9.04, 9.17 (doublets, 6H, isopropyl methyls, $J = 6.0$ Hz).

Anal. Calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.18; H, 9.09.
Preparation of (+)-Keto Ester

To a stirred suspension of anhydrous cuprous iodide (15.6 g, 82.0 mmoles) in 300 ml of anhydrous ether at -25° was added, over 5 min, 73.7 ml of 2.2 M ethereal methyllithium. The resulting solution was stirred in an atmosphere of nitrogen for 10 min and then the temperature was raised to 0°. A solution of the (+)-dienone aldehyde (11.6 g, 47.0 mmoles) in 300 ml of anhydrous ether was added over 40 min and the resulting mixture was stirred at 0° for 2 h. A solution of acetyl chloride (12 ml) in 240 ml of anhydrous ether was then added over 5 min and stirring was continued at 0° for a further 10 min, by which time the reaction mixture was composed of a clear supernatant and a sticky precipitate. The clear solution was poured into a rapidly stirred mixture (1200 ml) of concentrated ammonium hydroxide and crushed ice (1:2) and the ether layer was quickly separated. The aqueous layer was rapidly extracted twice with cold ether and the combined ether extracts were washed with cold brine until neutral, dried over anhydrous magnesium sulfate and concentrated to give 11.1 g of the enol acetate as a viscous oil. This material was somewhat unstable and was used without further purification in the next reaction (ozonolysis). It exhibited infrared (film), $\nu_{\text{max}}$ 3110, 1768, 1672, 1612 cm$^{-1}$; p.m.r., $\tau$ 1.85 (singlet, 1H, vinyl H), 7.12 (quartet, 1H, CH$_3$CH$^-$, J = 7.0 Hz), 7.76 (singlet, 3H, CH$_3$COO$^-$), 8.13 (singlet, 3H, vinyl methyl), 8.82 (singlet, 3H, tertiary methyl), 8.96 (doublet, 3H, secondary methyl, J = 7.0 Hz), 9.06 (poorly resolved multiplet, 6H, isopropyl methyls).

The solid residue remaining in the reaction flask was treated with 500 ml of concentrated ammonium hydroxide and crushed ice (1:1) and 500 ml of ether. This mixture was stirred vigorously for 15 min, sodium
chloride was added and the layers separated. The aqueous layer was extracted twice with cold ether and the combined ether extracts were washed with cold brine until neutral. Drying over anhydrous magnesium sulfate and removal of the solvent gave 3.0 g of a gum-like material. Infrared and p.m.r. spectra indicated that about one-half of this material was the desired enol acetate 237, so it was combined without further purification with the material obtained above.

The combined crude enol acetate product (14.1 g) in 200 ml of methylene chloride was treated with ozone at -78° until the solution turned blue, and then for a further 30 min at -25°. The cooling bath was removed and 300 ml of a 5% solution of sodium hydroxide in methanol/water (7:1) was added, followed by the careful addition of 120 ml of 30% hydrogen peroxide. This mixture was gradually heated and the methylene chloride was distilled off. The temperature was then raised to reflux, and refluxing was continued until the foaming ceased. The solution was cooled to 40° and 60 ml of 30% hydrogen peroxide was added, followed by refluxing as before. This process was repeated once more with a further 60 ml of hydrogen peroxide. The methanol was removed at aspirator pressure, the residue was diluted with water and acidified with 6 N hydrochloric acid. This mixture was thoroughly extracted with ether, the ether layer was washed twice with brine and dried over anhydrous magnesium sulfate. Removal of the solvent gave 10.9 g of a viscous oil which solidified overnight. A small sample of this solid was recrystallized from hexanes and then from hexanes/ethyl acetate to give an analytical sample of the keto acid 238 which exhibited m.p. 83.5-84°; infrared (i) (CHCl₃), 3590, 3560-2500, 1770, 1702 cm⁻¹; (ii) (nujol),
3415, 1750 cm$^{-1}$; p.m.r., $\tau$ 6.88, 7.13 (quartets, 1H, CH$_3$CHCO$_2$H and CH$_3$CHCO$_2$C(OH)$^-$ (lactol), $J$ = 7.2, 7.2 Hz).


The total crude keto acid 238 product was esterified by treatment with excess ethereal diazomethane. The excess diazomethane was then destroyed with acetic acid, the mixture was washed with sodium bicarbonate solution, with brine, and dried over anhydrous magnesium sulfate. Removal of the solvent and distillation of the residual oil gave 6.75 g (60% overall from the dienone aldehyde) of the desired keto ester 216, b.p. 98-106° at 0.15 mm. An analytical sample was obtained by preparative g.l.c. (column D, 205°, 180) and it exhibited $n_D$ 1.4699; $[\alpha]_D^{25}$ +151° (c, 2.0 in CHCl$_3$); infrared (film), $\nu_{\text{max}}$ 1732, 1705 cm$^{-1}$; p.m.r., $\tau$ 6.30 (singlet, 3H, -OCH$_3$), 6.91 (quartet, 1H, CH$_3$CHCO$_2$CH$_3$, $J$ = 7.1 Hz), 9.00 (singlet, 3H, tertiary methyl), 9.03 (doublet, 3H, secondary methyl, $J$ = 7.1 Hz), 9.07, 9.08 (doublets, 6H, isopropyl methyls, $J$ = 6.3 Hz).


Preparation of (+)-Diketone 203

To a solution of sodium bis(trimethylsilyl)amide (30 g, 164 mmoles) in 400 ml of dry benzene, kept at 79-80° (internal temperature) under an atmosphere of nitrogen, was added over 65 min a solution of the keto ester 216 (15.0 g, 62.5 mmoles) in 650 ml of dry benzene. This temperature was maintained for a further 75 min, the reaction mixture was cooled and poured into 1000 ml of cold water containing 30 ml of
acetic acid. The layers were separated and the aqueous layer was extracted once with ether. The combined organic layers were washed twice with sodium bicarbonate solution, with brine, and dried over anhydrous magnesium sulfate. Removal of the solvent and distillation of the resulting crystalline residue gave 10.9 g of the crystalline diketone \textit{203}, b.p. 90-105° at 0.2 mm. Analysis of this material by g.l.c. (column A, 165°, 110) showed that it consisted of 91% diketone and two unidentified minor components. Recrystallization of this material from hexane yielded 9.8 g (75%) of pure diketone. This compound exhibited m.p. 77.5-78°; \([\alpha]_D^{27} +102° \text{ (c,1.6 in CHCl}_3\text{)};\) infrared (CHCl\(_3\)), \(v_{\text{max}}\) 1765, 1725 cm\(^{-1}\); p.m.r., \(\tau\) 7.07 (broad singlet, 1H, \(\text{C}_7\text{H}\), width at half height = 3.5 Hz), 7.68 (quartet of doublets, 1H, \(\text{C}_7\text{H}, J = 7.1, 1.5 \text{ Hz}\)), 8.80 (doublet, 3H, secondary methyl, \(J = 7.1 \text{ Hz}\)), 8.88 (singlet, 3H, tertiary methyl), 8.99, 9.12 (doublets, 6H, isopropyl methyls, \(J = 6.0 \text{ Hz}\)). A frequency-swept decoupling experiment in which the H at \(\tau\) 7.07 was irradiated, thus causing the quartet of doublets at \(\tau\) 7.68 to collapse to a quartet (\(J = 7.1 \text{ Hz}\)), showed that the \(\text{C}_7\text{H}\) is coupled with the bridgehead \(\text{C}_5\text{H}\) (\(J = 1.5 \text{ Hz}\)).

Anal. Calcd. for \(\text{C}_{13}\text{H}_{20}\text{O}_{2}\): C, 74.96; H, 9.68. Found: C, 74.98; H, 9.80.
**Attempted Epimerization of Diketone 203**

To a solution of diketone 203 (52 mg) in 2.5 ml of anhydrous dioxan was added a solution of potassium carbonate (anhydrous, 15 mg) in 1.2 ml of distilled water. The resulting solution was stirred at room temperature for 19 h. The dioxan was removed at aspirator pressure, the residue was diluted with water and was thoroughly extracted with ether. The combined ether extracts were washed twice with brine and dried over anhydrous magnesium sulfate. Removal of the solvent afforded 51.5 mg of crystalline material. This material was identical with the starting diketone 203.

**Deuterated Diketone 203a**

Diketone 203 (47.5 mg) was reacted with deuterium oxide (1.2 ml) (instead of water) under conditions identical with those described above for the attempted epimerization of diketone 203. The crystalline, crude product (48 mg) thus obtained, consisted of monodeuterated diketone 203a and small amount of starting diketone 203 (as shown by the p.m.r. spectrum). The deuterated compound 203a exhibited p.m.r., \( \tau \) 7.07 (singlet, 1H, C\(_5\)H, width at half height 3.0 Hz), 8.81 (slightly broadened singlet, 3H, C\(_7\) methyl, width at half height = 2.2 Hz), 8.88 (singlet, 3H, tertiary methyl), 8.99, 9.12 (doublets, 6H, isopropyl methyls, J = 6.0 Hz).
Preparation of (+)-Keto Enol Ether 242

A solution of (+)-diketone 203 (10.4 g, 50 mmoles) in 100 ml of dry hexamethylphosphoramide was added in one batch to a solution of sodium bis(trimethylsilyl)amide (25 g, 136 mmoles) in 150 ml of dry hexamethylphosphoramide. This mixture was stirred at room temperature in an atmosphere of nitrogen for 15 min, then cooled to 0° and 25 ml of 2-bromopropane was added over 3 min. The cooling bath was removed and stirring was continued at room temperature for 45 min. The reaction was quenched by pouring into cold brine and this mixture was thoroughly extracted with ether. The ether extract was washed three times with brine and dried over anhydrous magnesium sulfate. Removal of the solvent gave 12.3 g of a mobile oil. A g.l.c. analysis of this material (column C, 168°, 100) showed the presence of three components. These were shown to be starting material (diketone 203), the desired O-alkylated product 242, and the C-alkylated product 243 in the ratio of 13:76.5:10.5 respectively. Distillation of this crude product through a 2-inch Vigreux column gave 11.0 g of material (b.p. 73-81° at 0.025 mm), which consisted of the starting material, the desired O-alkylated product and a trace of the C-alkylated product. The keto enol ether was readily separated from this mixture by chromatography on activity III neutral alumina. Elution with 2%-15% benzene in petroleum ether (b.p. 65-110°) separated out 9.55 g of pure keto enol ether 242 (88% based on unrecovered starting material). This material exhibited $n_D^{20}$ 1.4747; $[\alpha]_D^{25}$ +145° (c,2.0 in CHCl₃); infrared (film), $\nu_{\text{max}}$ 1760, 1660 cm⁻¹; p.m.r., $\tau$ 5.95 (septet, 1H, $-\text{OCH}(\text{CH}_3)_2$, $J = 6.1$ Hz), 6.99 (broad singlet, 1H, C₅H, width at half-height = 3.3 Hz), 8.32 (doublet, 3H, vinyl methyl, $J = 0.9$ Hz),
8.74, 8.89 (doublets, 6H, -OCH(CH₃)₂, J = 6.1 Hz), 8.98 (singlet, 3H, tertiary methyl), 9.04, 9.13 (doublets, 6H, isopropyl methyls, J = 6.4 Hz).

Anal. Calcd. for C₁₆H₂₆O₂: C, 76.75; H, 10.47. Found: C, 76.55; H, 10.46.

Further elution of the column with higher benzene concentrations gave 1.37 g of the crystalline starting material (diketone 203) containing the small amount of C-alkylated material. A pure sample of the latter compound was obtained as follows. Hot box distillation of the still-pot residue yielded 1.2 g of crystalline material, b.p. 115° at 0.3 mm. Recrystallization of this material from hexanes gave a sample with m.p. 60.5°; infrared (CHCl₃), νmax 1758, 1722 cm⁻¹; p.m.r., τ 7.15 (broad singlet, 1H, C₅H, width at half height = 4.3 Hz), 8.85, 8.90 (singlets, 6H, tertiary methyls), 8.97, 9.12 (doublets, 6H, isopropyl methyls, J = 6.5 Hz), 9.00, 9.22 (doublets, 6H, isopropyl methyls, J = 6.9 Hz).

Anal. Calcd. for C₁₆H₂₆O₂: C, 76.75; H, 10.47. Found: C, 76.60; H, 10.55.

Preparation of Diethers 244

A slurry of methoxymethyltriphenylphosphonium chloride (71.5 g, 208 mmol) in 615 ml of anhydrous ether was cooled to 0° under an atmosphere of nitrogen. To this stirred mixture was added, via a syringe, 73.5 ml of a 2.34 M hexane solution of n-butyllithium over a two minute period. The resulting phosphorane solution was stirred for a further 10 min. A solution of the (+)-keto enol ether 242 (11.65 g,
46.5 mmoles) in 170 ml of anhydrous ether was then added over 4 min, the cooling bath was removed and the reaction mixture was refluxed for 30 min. The cooled solution was poured into cold water, the layers were separated and the aqueous layer was extracted once with ether. The combined ether layers were washed twice with brine and dried over anhydrous magnesium sulfate. Removal of the solvent and distillation of the resultant crude material (55.0 g) gave 14.2 g of colorless oil with b.p. 94-103° at 0.2 mm. Analysis by g.l.c. (column C, 155°, 110) showed that this material contained three unidentified minor components to the extent of approximately 10%, thus indicating that the desired diethers were formed in quantitative yield. The ratio of the component diastereomers as determined by g.l.c. (same column and conditions) varied considerably from experiment to experiment but the average ratio was approximately 65:35, with the same isomer always predominating. Attempts to remove the impurities from this distilled material by column chromatography (neutral alumina - activity I and III, and florisil) were unsuccessful due to poor recovery of the diethers from the columns and/or due to similarity in retention times. Consequently, this mixture was used in the next reaction without further purification. An analytical sample of the diastereomeric diether mixture was obtained, however, by preparative g.l.c. (column B, 185°, 105) and it exhibited infrared (film), \( \nu_{\text{max}} \) 1707, 1664 cm\(^{-1}\); p.m.r., \( \tau \) 4.43, 4.52 (singlets, 1H, vinyl hydrogens), 5.92, 5.97 (septets, 1H, \( J = 6.1, 6.1 \) Hz), 6.49, 6.56 (singlets, 3H, methoxy methyls).

Anal. Calcd. for C\(_{18}\)H\(_{30}\)O\(_2\): C, 77.65; H, 10.86. Found: C, 77.52 H, 11.11.
Preparation of Keto Aldehydes 245 and 246

A solution of the impure diethers 244 (10.8 g) from above, in 180 ml of ether was added to a solution of 70% perchloric acid (120 ml) in 700 ml of ether. The resulting mixture was stirred at room temperature under a nitrogen atmosphere for 1.5 h. It was then washed successively with ice-water, with dilute sodium bicarbonate solution and with brine, and dried over anhydrous magnesium sulfate. Removal of the solvent and distillation of the residual oil gave 7.7 g of material with b.p. 108-110° at 0.07 mm. A g.l.c. analysis (column H, 168°, 110) of this material showed that the ratio of the keto aldehydes 245 and 246 was approximately 1:1.

This material (7.7 g) was dissolved in 325 ml of methanol and was added to a solution of anhydrous potassium carbonate (9.5 g) in 800 ml of water. The resultant mixture was stirred at room temperature under a nitrogen atmosphere for 1.5 h. It was then diluted with water and extracted three times with petroleum ether (b.p. 68°)-ether (4:1). The combined extracts were washed with water, with brine, and dried over anhydrous magnesium sulfate. Removal of the solvent and distillation of the residue gave 7.05 g of a colorless oil, b.p. 106-109° at 0.05 mm. A g.l.c. analysis (column H, 168°, 110) of this material showed that it was composed of the desired products (88%), keto aldehydes 245 and 246 in a ratio of 82:18 respectively, and impurities (12%) which were not identified, but were presumably related to those in the starting material. Thus the effective overall yield for the hydrolysis and epimerization reactions was 80%. Because of extensive decomposition of the epimeric keto aldehydes 245 and 246 on the columns
it was not possible to separate these epimers from each other or from
the other contaminants by column chromatography (silica gel and
activity III neutral alumina). Consequently, this material was used
in the next reaction without further purification. The impure keto
aldehyde product mixture exhibited infrared (film), $\nu_{\text{max}}$ 2745, 1735,
1715 (shoulder) cm$^{-1}$; p.m.r., $\tau$ -0.10, -0.03 (doublets, 1H, aldehydic
hydrogens, J = 1.0, 2.0 Hz, respectively).

Preparation of Keto Olefins 204 and 247

A mixture of 50% sodium hydride in dispersion oil (1.028 g, 22.5
mmoles) and dry dimethyl sulfoxide (52 ml) was heated to 74° in an
atmosphere of nitrogen. This temperature was maintained for 45 min,
by which time the evolution of hydrogen gas had ceased. The solution
was cooled to 20°, 9.64 g (27.0 mmoles) of methyltriphenylphosphonium
bromide was added in one batch and the resulting solution was stirred
at room temperature for 10 min. To this solution was added over a
period of 3 min 1.046 g (approximately 4.15 mmoles) of the impure
keto aldehyde mixture (245 and 246) from above in 26 ml of dry DMSO.
Stirring was continued for a further 1 h at room temperature. The
solution was poured into ice-water and this mixture was extracted
three times with petroleum ether (b.p. 68°). The combined extracts
were washed with brine and dried over anhydrous magnesium sulfate.
Removal of the solvent and distillation of the residue gave 991 mg of
a colorless oil with b.p. (hot box) 82-95° at 0.07 mm. A g.l.c.
analysis (column I, 175°, 110) showed that this material was composed
of a mixture of the keto olefins (92%), 204 and 247 in a ratio of 82:18
respectively, and unidentified minor components (8%). This represents a quantitative yield of keto olefins based on pure starting material. The two epimers were only partially separated by column chromatography on silica gel. However, total separation was achieved by column chromatography using Camag Kieselgel for TLC (without binder) and 98:2 petroleum ether (b.p. 68°)-ether as eluting solvent. A positive pressure (nitrogen) was required to maintain a reasonable flow rate. The ratio of compound to silica gel was 1:100. The recovery of both keto olefins from the column was quantitative. However, while the minor epimer 247, a colorless crystalline compound, was obtained in pure form, the major epimer 204 contained minor impurities (approximately 4% as determined by g.l.c.). Thus an analytical sample of the keto olefin 204 was obtained by preparative g.l.c. (column D, 198°, 170) of the material obtained from chromatography on silica gel. This analytical sample, a colorless oil, exhibited $[\alpha]_D^{25}$ +51.5° (c,2.0 in CHCl$_3$); infrared (film), $\nu_{\text{max}}$ 3080, 1730, 1634, 910 cm$^{-1}$; p.m.r., $\tau$ 3.99-4.37 (multiplet, 1H, $C_9$H), 4.86-5.10 (multiplet, 2H, $C_{10}$ protons), 7.41 (broad singlet, 1H, $C_5$H, width at half height = 4.5 Hz), 7.79 (doublet, 1H, $C_8$H, $J = 7.9$ Hz), 7.97 (quartet, 1H, $C_7$H, $J = 7.2$ Hz), 8.99 (singlet, 3H, tertiary methyl), 8.99, 9.20 (doublets, 6H, isopropyl methyls, $J = 6.2$ Hz), 9.06 (doublet, 3H, secondary methyl, $J = 7.2$ Hz).

Anal. Calcd. for C$_{15}$H$_{24}$O: C, 81.76; H, 10.98. Found: C, 81.64; H, 11.07.

The crystalline keto olefin 247 (the minor component) was recrystallized from pentane and this sample exhibited m.p. 28.5-29°; $[\alpha]_D^{25}$ +130° (c,2.5 in CHCl$_3$); infrared (CHCl$_3$), $\nu_{\text{max}}$ 3080, 1724, 1633, 916 cm$^{-1}$; p.m.r.
3.71-4.08 (multiplet, 1H, C₉H), 4.68-4.92 (multiplet, 2H, Cₒ protons), 7.42 (broadened doublet, 1H, C₅H, Jₖ₅H-C₈H = 5.6 Hz), 7.64 (doublet of doublets, 1H, C₈H, J = 8.3, 5.6 Hz), 8.17 (quartet, 1H, C₇H, J = 7.0 Hz), 9.01 (doublet, 3H, secondary methyl, J = 7.0 Hz), 9.05 (singlet, 3H, tertiary methyl), 9.05, 9.18 (doublets, 6H, isopropyl methyls, J = 5.9 Hz).


Preparation of (+)-Keto Alcohol 205

To a solution of 2-methyl-2-butene (1.78 g, 25.5 mmoles) in 7.5 ml of dry tetrahydrofuran was added 9 ml of 1.4 M borane solution in tetrahydrofuran (12.6 mmoles) at 0°. Stirring was continued in an atmosphere of nitrogen at 0° for 30 min. To this solution was then added 661 mg (3 mmoles) of the (+)-keto olefin 204 in 7.5 ml of dry tetrahydrofuran and stirring was continued at 0° for a further 45 min. The reaction was quenched by the careful addition at 0° of 6 ml of 3 N aqueous sodium hydroxide followed by 6 ml of 30% hydrogen peroxide. The cooling bath was removed and stirring was continued at room temperature for 1 h. The tetrahydrofuran was removed at aspirator pressure, water was added to the residue and this mixture was thoroughly extracted with ether. The organic extract was washed with brine and dried over anhydrous magnesium sulfate. Removal of the solvent and distillation of the residue gave 579 mg (81%) of a viscous oil b.p. 135-145° (hot box) at 0.2 mm. A g.l.c. analysis (column G, 175°, 100) of this material indicated the presence of two components in the approximate ratio of
85:15 (this g.l.c. column did not totally resolve the two components and more polar columns caused decomposition of the products. This ratio was confirmed later, however, by g.l.c. analysis of the silyl ether derivatives of this mixture (vide infra). Chromatography on silica gel or activity III neutral alumina afforded no useful separation of the two products.

Pure samples of the desired keto alcohol 205, and of the contaminating diol 248 were obtained for analytical purposes via their silyl ether derivatives. Thus 239 mg (1.0 mmole) of the product mixture in 2 ml of dry pyridine containing 0.4 ml of hexamethyldisilazane and 0.2 ml of trimethylchlorosilane was stirred in an atmosphere of nitrogen at room temperature for 15 min. This mixture was filtered, the solvent was evaporated and the residue was distilled to give 323 mg of a mobile oil, b.p. 125-130° (hot box) at 0.25 mm. This material showed two peaks on analysis by g.l.c. (column C, 190°, 100), in the ratio of 85:15. An attempt to separate the components on a silica gel column resulted in the partial hydrolysis of the silyl ether blocking groups, but an efficient separation was effected by preparative g.l.c. (column D, 220°, 200). Thus 300 mg of the mixture yielded, after collection and distillation, 204 mg of the pure keto trimethylsilyl ether 249 and 44 mg of the bistrimethylsilyl derivative 250. The keto trimethylsilyl ether exhibited infrared (film), ν_max 1727, 1250, 1090, 840, 745 cm⁻¹; p.m.r., τ 6.39 (complex multiplet, 2H, -CH₂OTMS), 7.45 (broad singlet, 1H, C₅H, width at half height = 4.6 Hz), 8.97 (singlet, 3H, tertiary methyl), 9.00, 9.18 (doublets, 6H, isopropyl methyls, J = 6.1 Hz), 9.04 (doublet, 3H, secondary methyl, J = 7.0 Hz), 9.88 (singlet, 9H, -OSi(CH₃)₃).
Hydrolysis of this keto trimethylsilyl ether 249 gave the desired keto alcohol 205. Thus a solution of the silyl ether (220 mg, 0.71 mmole) in 3 ml of ethanol and 0.1 ml of water was refluxed in an atmosphere of nitrogen for 4 h. The solvent was removed at aspirator pressure and the residue was distilled to give 150 mg (89%) of a viscous oil b.p. 127-128° (hot box) at 0.04 mm. Analysis of this material by g.l.c. (column G, 175°, 100) showed that it was one component. It exhibited $[\alpha]_D^{25} +30.5^\circ$ (c,0.7 in CHCl$_3$); infrared (film), $\nu_{\text{max}}$ 3400, 1724 cm$^{-1}$; p.m.r., $\tau$ 6.34 (complex multiplet, 2H, $-\text{CH}_2\text{OH}$), 7.46 (broad singlet, 1H, C$_5$H, width at half height = 4.8 Hz), 7.87 (singlet, 1H, exchangeable, $-\text{OH}$), 8.96 (singlet, 3H, tertiary methyl), 8.99, 9.18 (doublets, 6H, isopropyl methyls, J = 6.1 Hz), 9.03 (doublet, 3H, secondary methyl, J = 7.1 Hz).


The minor component in the silyl ether mixture was also g.l.c. collected as mentioned above. It exhibited infrared (film), $\nu_{\text{max}}$ 1250, 1060, 840, 750 cm$^{-1}$; p.m.r., $\tau$ 5.53 (doublet of doublets, 1H, $-\text{CHOTMS}$, J = 6.8, 10.5 Hz), 6.40 (complex multiplet, 2H, $-\text{CH}_2\text{OTMS}$), 7.73 (broadened doublet, 1H, C$_5$H, J = 6.8 Hz), 9.10, 9.20 (doublets, 6H, isopropyl methyls, J = 6.5 Hz), 9.15 (singlet, 3H, tertiary methyl), 9.23 (doublet, 3H, secondary methyl, J = 7.0 Hz), 9.89, 9.95 (singlets, 18H, $-\text{OTMS}$ groups). This material was hydrolyzed to the diol 248 in a manner similar to the hydrolysis of the keto silyl ether 249 using 0.75 ml of ethanol and 25 ml of water. From 44 mg there was obtained 25 mg of the viscous diol which exhibited infrared (film), $\nu_{\text{max}}$ 3350 cm$^{-1}$; p.m.r.
\[ \tau 5.60 \text{ (doublet of doublets, } 1H, -\text{CHOH, } J = 6.9, 10.6 \text{ Hz)}, 6.41 \text{ (complex multiplet, } 2H, -\text{CH}_2\text{OH)}, 7.83 \text{ (broadened doublet, } 1H, \text{ C}_5\text{H, } J = 6.9 \text{ Hz)}, 9.18, 9.28 \text{ (doublets, } 6H, \text{ isopropyl methyls, } J = 6.6 \text{ Hz}), 9.25 \text{ (singlet, } 3H, \text{ tertiary methyl)}, 9.29 \text{ (doublet, } 3H, \text{ secondary methyl, } J = 7.1 \text{ Hz}). \] This diol decomposed slowly on standing in deuterochloroform solution at room temperature.

**(-)-Ylangocamphor**

(a) From pure keto alcohol 205

A solution of keto alcohol 205 (109 mg, 0.458 mmole) in 3.5 ml of dry pyridine containing 229 mg (1.0 mmole) of methanesulfonyl chloride was stirred in an atmosphere of nitrogen at room temperature for 2.25 h. The reaction mixture was then poured into 25 ml of cold water and the water layer was extracted 3 times with ether. The combined ether extracts were washed with cold 10% hydrochloric acid, with water and with brine, and dried over anhydrous magnesium sulfate. Removal of the solvent gave 173 mg of a viscous oil which exhibited infrared (film), \( \nu_{\text{max}} \) 1728 cm\(^{-1}\). This crude keto mesylate in 2 ml of dry dimethoxyethane was added to a solution of sodium bis(trimethylsilyl)amide (450 mg, 2.46 mmole) in 5 ml of dry dimethoxyethane at 0°. The cooling bath was immediately removed, the reaction mixture was stirred at room temperature in an atmosphere of nitrogen for 40 min and it was then poured into 25 ml of cold water. The organic layer was washed with water and brine and dried over anhydrous magnesium sulfate. Removal of the solvent and distillation of the residue gave 85 mg (84% from keto alcohol) of (-)-ylangocamphor b.p. 72-74° (hot box) at 0.04 mm. This material
was pure by gas-liquid chromatographic analysis (columns: A, 170°, 115; B, 190°, 110; F, 201°, 118) and it crystallized on refrigeration. A sample was recrystallized from hexanes at -35° to -40° yielding colorless crystals with m.p. 25-25.5°; \([\alpha]_D^{26} -58° (c,1.0 \text{ in } \text{CHCl}_3);\) infrared (film), \(v_{\text{max}} 1733 \text{ cm}^{-1};\) p.m.r., \(\tau 7.76\) (broad singlet, 1H, bridgehead H adjacent to -C=O, width at half height = 3.0 Hz), 9.02, 9.19 (doublets, 6H, isopropyl methyls, \(J = 6.5 \text{ Hz}), 9.10, 9.11, (\text{singlets, 6H, tertiary methyls}).\)

Anal. Calcd. for \(\text{C}_{15}\text{H}_{24}\text{O}:\) C, 81.76; H, 10.98. Found: C, 81.9; H, 11.18.

(b) From the mixture of keto alcohol 205 and diol 248

The keto alcohol-diol mixture (239 mg) obtained from hydroboration was converted into the mesylate derivative mixture in the same manner as the pure keto alcohol, using 7 ml of pyridine and 229 mg (2.0 mmole) of methanesulfonyl chloride. Similarly, the crude keto mesylate mixture thus obtained was cyclized (without purification) as above, using 915 mg (5 mmoles) of sodium bis(trimethylsilyl)amide and 14 ml of dry dimethoxyethane. Simple distillation of this product (hot box) separated out the (-)-ylangocamphor, 135 mg (50% overall yield from the keto olein 204). This material was pure by gas-liquid chromatographic analysis.

(-)-Ylangoborneol 23

To a reaction vessel containing 12.5 ml of refluxing anhydrous ammonia was added 50 mg (1.25 mmoles) of calcium metal followed,
5 min later, by a solution of (-)-ylangocamphor \( \mathbf{2} \) (57 mg, 0.259 mmole) in 1.1 ml of anhydrous ether. This mixture was stirred at reflux temperature for 30 min and 150 \( \mu \)l of anhydrous ethanol was then added. Care was taken at all times to exclude water from the system. When the blue color was discharged, ether was added and the mixture was poured into water. The water layer was thoroughly extracted with ether, and the organic layer was washed with brine until neutral and then dried over anhydrous magnesium sulfate. Filtration through celite and removal of the solvent gave a residue which was distilled to yield 55 mg (96%) of crystalline (-)-ylangoborneol, b.p. 108° (hot box) at 0.04 mm. This material consisted of only one component by gas-liquid chromatographic analysis (columns: B, 188°, 110; C, 168°, 100; E, 190°, 100; F, 195°, 105. Note: columns B and F resolve a mixture of ylangoborneol and ylangoisoborneol). Recrystallization from hexanes gave a sample exhibiting m.p. 60.5-61°; \([\alpha]^{25}_D -23°\) (c,0.4 in \( \text{CHCl}_3 \)); infrared (\( \text{CHCl}_3 \)), \( \nu_{\text{max}} \) 3610, 3460 cm\(^{-1}\); p.m.r., (i) (\( \text{CDCl}_3 \)), \( \tau \) 6.17 (broad singlet, 1H, -CHOH, width at half height = 3.2 Hz), 8.60 (singlet, 1H, exchangeable, -OH), 9.05, 9.15 (doublets, 6H, isopropyl methyls, \( J = 6.4 \) Hz), 9.13, 9.19 (singlets, 6H, tertiary methyls); (ii) (\( \text{CCl}_4 \)), 6.26 (broad singlet, 1H, -CHOH, width at half height = 3.2 Hz), 8.90 (singlet, 1H, exchangeable, -OH), 9.06, 9.14 (doublets, 6H, isopropyl methyls, \( J = 6.5 \) Hz), 9.15, 9.19 (singlets, 6H, tertiary methyls).

Anal. Calcd. for \( \text{C}_{15}\text{H}_{26} \text{O} \): C, 81.02; H, 11.79. Found: C, 80.75; H, 11.69.
(-)-Ylangoisoborneol 143

An anhydrous ether solution (5 ml) of (-)-ylangocamphor 7 (110 mg, 0.5 mmole) containing 25 mg of lithium aluminum hydride was refluxed under an atmosphere of nitrogen for 1 h. The reaction mixture was cooled to 0°, 1 ml of saturated aqueous ammonium chloride solution was added and stirring was continued for 45 min at room temperature. This mixture was filtered through celite and the celite was thoroughly washed with ether. The ether layer was washed with brine and dried over anhydrous magnesium sulfate. Removal of the solvent followed by distillation of the residue gave 101 mg of (-)-ylangoisoborneol 143 (91%), b.p. 100-102° (hot box) at 0.12 mm. This material consisted of only one component on analysis by g.l.c. (columns and conditions: same as ylangoborneol), and it crystallized on refrigeration. Recrystallization from hexanes at -10° gave colorless crystals which were somewhat soft at room temperature (22°) and exhibited m.p. 31.5-32.5°; \([\alpha]_D^{26} -28°\) (c,1.0 in CHCl₃); infrared (film), \(\nu_{\text{max}}\) 3630, 3495 cm\(^{-1}\); p.m.r. (i) (CDCl₃), \(\delta\) 6.22 (doublet, 1H, \(-\text{CHOH}, J = 7.6\) Hz), 7.88 (broadened doublet, 1H, bridgehead H adjacent to \(-\text{CHOH}, J = 7.6\) Hz), 8.68 (singlet, 1H, exchangeable, \(-\text{OH}\)), 9.04, 9.17 (doublets, 6H, isopropyl methyls, \(J = 6.5\) Hz), 9.15, 9.21 (singlets, 6H, tertiary methyls); (ii) (CCl₄), \(\delta\) 6.27 (doublet, 1H, \(-\text{CHOH}, J = 7.7\) Hz), 7.91 (broadened doublet, 1H, bridgehead H adjacent to \(-\text{CHOH}, J = 7.7\) Hz), 8.87 (singlet, 1H, exchangeable, \(-\text{OH}\)), 9.08, 9.20 (doublets, 6H, isopropyl methyls, \(J = 6.5\) Hz), 9.18, 9.22 (singlets, 6H, tertiary methyls). The chemical shift assigned to the bridgehead H adjacent to the \(-\text{CHOH}\) was confirmed by a frequency-swept decoupling experiment
in which the H at τ 6.27 was irradiated, thus eliminating the coupling with the bridgehead H, and causing the doublet at τ 7.91 to collapse to a broadened singlet.

Anal. Calcd. for C$_{15}$H$_{26}$O: C, 81.02; H, 11.79. Found: C, 80.99; H, 11.86.
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78. See ref. 55 and refs. cited therein.


88. See footnote, p. 75.


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