STEREOSELECTIVE TOTAL SYNTHESIS OF SESQUITERPENOIDS: (-)-COPACAMPHENE AND (-)-CYCLOCOPACAMPHENE

BY

ROBERT DEAN SMILLIE

B.Sc. (Hons.), University of British Columbia, 1966
M.Sc. University of British Columbia, 1969

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in the Department

of

CHEMISTRY

We accept this thesis as conforming to the

required standard

THE UNIVERSITY OF BRITISH COLUMBIA

January, 1972

In presenting this thesis in partial fulfilment of the requirements for an advanced degree at the University of British Columbia, I agree that the Library shall make it freely available for reference and study. I further agree that permission for extensive copying of this thesis for scholarly purposes may be granted by the Head of my Department or by his representatives. It is understood that copying or publication of this thesis for financial gain shall not be allowed without my written permission.

Department of CHEMISTRY

The University of British Columbia
Vancouver 8, Canada

Date Jan 14, 1972

ABSTRACT

An efficient, 6-step synthesis of the (-)-diketone (122) from (+)-carvomenthone (123) is described. Conversion of 123 into the corresponding n-butylthiomethylene derivative (131), followed by alkylation of the latter with ethyl 2-iodopropionate and successive removal of the n-butythiomethylene blocking group and esterification of the resulting acid (134), gave the keto ester (135). Treatment of 135 with sodium bis(trimethylsilyl)amide in dimethoxyethane resulted in an efficient intramolecular Claisen condensation, affording the (-)-diketone 122 in 90% yield.

The stereochemistry of the (-)-diketone (122) was proven unambiguously in the following way. Successive subjection of the (+)-ketol (142), of known absolute stereochemistry, to hydrogenation, dehydration, condensation with ethyl formate, and oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone, afforded the (+)-dienone aldehyde (153). Conjugate addition of lithium dimethylcuprate to 153, followed by trapping of the intermediate enolate anion with acetyl chloride gave the keto enol acetate (154). Ozonolysis of the latter, followed by esterification of the resulting acid (157) gave the (+)-keto ester (138), which was clearly epimeric with the previously prepared keto ester (135). Intramolecular Claisen condensation of 135 afforded the (+)-diketone (139), which was clearly different from the (-)-diketone (122).

The (-)-diketone (122) was utilized in the synthesis of (-)-copacamphene (23) and of (-)-cyclocopacamphene (24). Several methods for the conversion of the (-)-diketone (122) into the (-)-keto olefin

(125) were investigated. The most efficient sequence found was as follows. Reduction of 122 with sodium borohydride gave the (-)-keto alcohol (169) which was readily converted into the corresponding p-tosylhydrazone (170). Treatment of the latter with methyllithium, followed by Jones oxidation afforded the (-)-keto olefin (125) in good yield.

Reaction of 125 with methoxymethylenetriphenylphosphorane gave the isomeric olefinic enol ethers (172). Successive subjection of the latter to acid hydrolysis and base-catalyzed equilibration afforded the (-)-olefinic aldehyde (174). The latter was reacted with methylenetriphenylphosphorane, and the resulting (+)-diene (175) was subjected to hydroboration-oxidation, to produce the (+)-olefinic alcohol (178). Treatment of 178 with p-toluenesulfonyl chloride in pyridine produced the corresponding p-tosylate (180), which underwent a high-yielding eliminative cyclization to afford (-)-copacamphene (23).

Although a number of routes directed towards the synthesis of (-)-cyclocopacamphene (24) were investigated, the most efficient sequence employed the (+)-olefinic alcohol (178) as starting material. Oxidation of the latter with Collins reagent afforded the (-)-olefinic aldehyde (194), which was readily converted into the corresponding p-tosylhydrazone (210). Pyrolysis of the lithium salt of the latter produced the (+)-pyrazoline (213), which, upon photolysis in ether, afforded (-)-cyclocopacamphene (24) in 93% yield.

TABLE OF CONTENTS

LIST OF FIGURES

ACKNOWLEDGEMENTS

I would like to express my sincere thanks to Dr. Edward Piers for his invaluable advice, guidance and enlightening discussions throughout the course of this research, and the preparation of this manuscript.

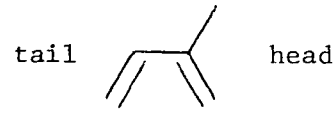
I would also like to thank Dr. Ronald W. Britton and Mr. Robert J. Keziere, my co-workers in this research, and all the members of Dr. Piers' research group, for their helpful discussions and suggestions.

The able typing of Miss Diane Johnson is greatly appreciated.

INTRODUCTION

1. General

The terpenoids are a large family of natural products which have widespread distribution in the realm of nature. They are compounds which have structures that are normally based on head to tail linkings of isoprene units (1)[1,2] and usually contain two (monoterpenoids), three (sesquiterpenoids), four (diterpenoids), five (sesterterpenoids), six (triterpenoids) or eight (carotenoids) multiplets of the basic unit. However, during biogenesis of terpenoids,



1

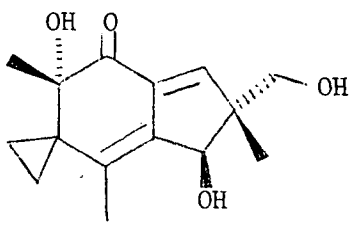
the linked isoprene units may rearrange to give a vast array of different carbon skeletons.[2]

The sesquiterpenoids are a large group in the terpenoid family which are formed by the combination of three isoprene units. The virtuosity of nature in the construction of intricate molecules is nowhere more evident than in this sesquiterpenoid group. Within this

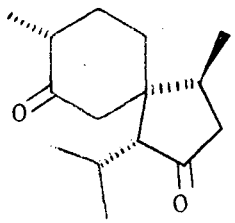
group can be found an especially concentrated and impressive display of synthetic expertise, with over fifty different sesquiterpenoid skeletal types known to exist in nature.[3]

Sesquiterpenoids may occur as acyclic, monocyclic, bicyclic, tricyclic, or tetracyclic hydrocarbons, alcohols, ketones, oxides or lactones. They have been known as constituents of the essential oils, and have formed the basis for a wide range of exotic scents and perfumes for centuries. However, it is only in comparatively recent times that the chemistry of these compounds has been investigated in detail. One of the reasons for this was that in the essential oils, sesquiterpenoids often occur as very complex mixtures which could not be resolved by the classical methods that were available. The isolation of pure homogeneous compounds was quite difficult, and characterization of inseparable mixtures, which under the circumstances appeared homogeneous, led to inaccurate results and conclusions. With the development of new separation techniques such as gas-liquid chromatography and thin layer chromatography, and the introduction of modern spectroscopic methods such as nuclear magnetic resonance and optical rotatory dispersion, the structure and stereochemistry of a large number of sesquiterpenes have been established.

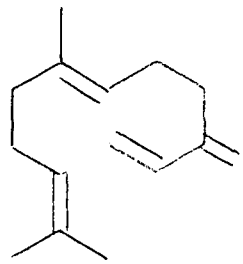
Three examples which illustrate this great diversity of structure which can be found in the sesquiterpenoids are the highly oxygenated illudin-S (2),[4] acorone (3)[5,6] which contains a spirane carbon skeleton, and the acyclic hydrocarbon farnesene (4).[7]



2

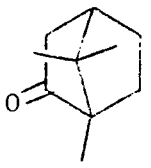


3

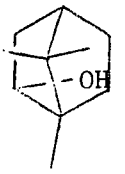


4

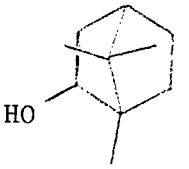
The structures of one interesting and structurally related group of bicyclic, tricyclic and tetracyclic sesquiterpenoids are illustrated in Chart 1. The sesquiterpenoids listed in this chart are arranged and drawn in a manner which emphasizes their structural similarities to particular monoterpenoids. Also, the structural similarities among the sesquiterpenoids themselves is clear from an examination of Chart 1. For example, the sesquiterpenoids campherenone (8), copacamphor (11), ylangocamphor (14), and longicamphor (17) all have the structural features of the monoterpenoid camphor (5) incorporated into their structure. In other words, these four sesquiterpenoids listed can be considered to be "isoprenologs" of the monoterpenoid camphor. Similarly, sesquiterpenoids listed in the other five columns of Chart 1 can be considered to be structural "isoprenologs" of the monoterpenoids which head these columns. There are also marked structural similarities among the sesquiterpenoids in a given row. For example, copacamphor (11), copaborneol (12), and copaisoborneol (13) each contain a six-membered ring with an axial



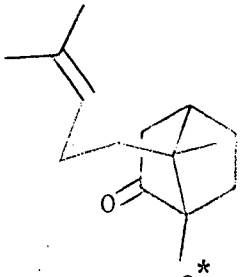
5
camphor



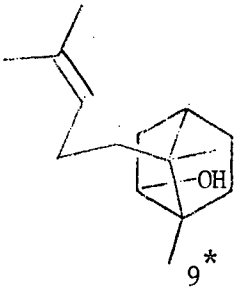
6
borneol



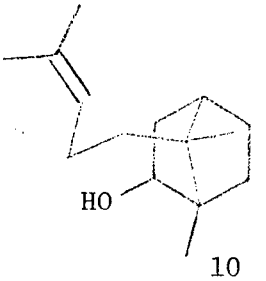
7
isoborneol



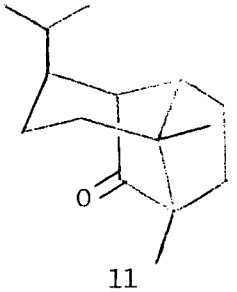
8*
(-)-campherenone[8-10]



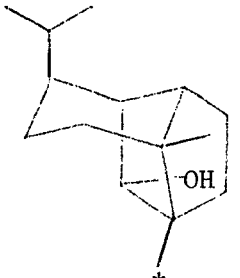
9*
(-)-campherenol[8-10]



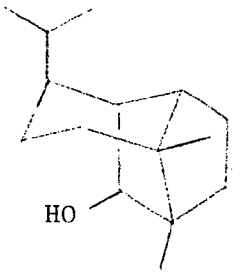
10
(+)-isocampherenol[8-10]



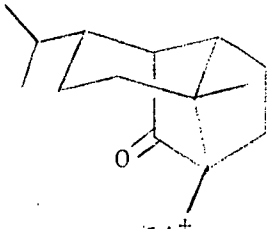
11
(+)-copacamphor[11-13]



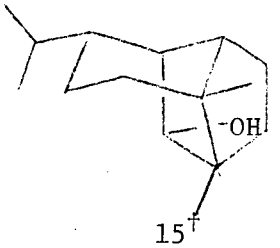
12*
(+)-copaborneol[11-13]



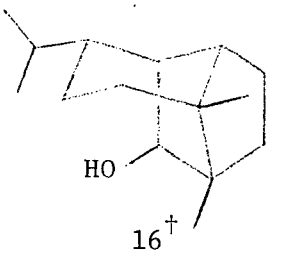
13
(+)-copaisoborneol[11-13]



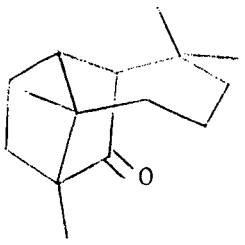
14†
ylangocamphor



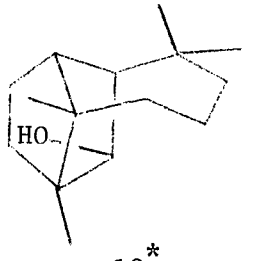
15†
ylangoborneol



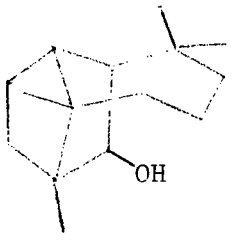
16†
ylangoisoborneol



17
(+)-longicamphor[14]

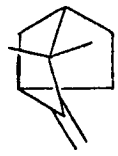


18*
(+)-longiborneol[14]

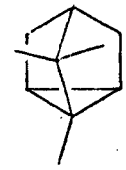


19
(+)-longiisoborneol[14]

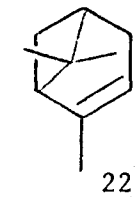
CHART 1††



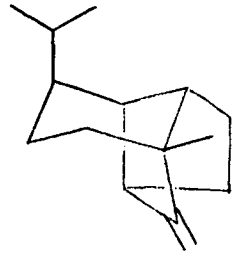
20
camphene



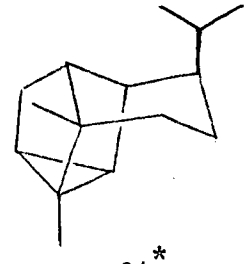
21
tricyclene



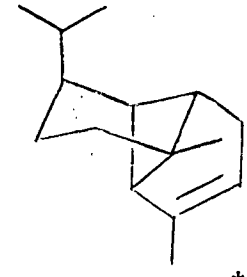
22
α-pinene



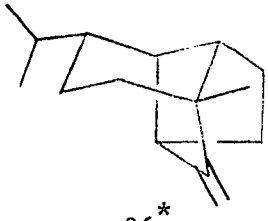
23
(-)-copacamphene[11,12,15-17]



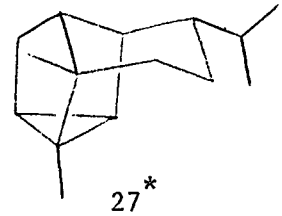
24*
(+)-cyclocopacamphene[17,18]



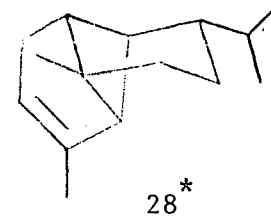
25*
(-)-α-copaene[19-21]



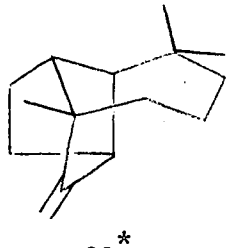
26*
(-)-sativene[22,23]



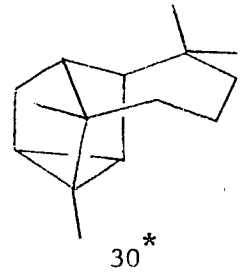
27*
(+)-cyclosativene[24-26]



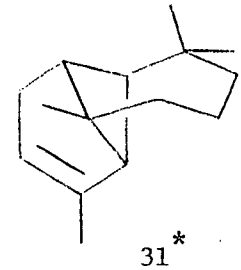
28*
(+)-α-ylangene[27-30]



29*
(+)-longifolene[31-35]



30*
(+)-longicyclene[36]



31*
(+)-α-longipinene[37,38]

CHART 1 (cont'd)††

---

* These compounds have been isolated from naturally occurring sources.

† These compounds are as yet unknown.

†† Absolute configurations are depicted by these structures.

isopropyl group.

The sesquiterpenoids ylangocamphor (14), ylangoborneol (15) and ylangoisoborneol (16), as yet unknown compounds, have been added for the sake of completeness in Chart 1. The names that are proposed for these terpenoids are based on their structural relationship both to the corresponding monoterpenoids (camphor, borneol, isoborneol, respectively) and to the sesquiterpene α-ylangene (28).

Throughout this thesis, the groups of sesquiterpenoids under discussion here will be referred to as "copa-", "ylango-" and "longi-" type sesquiterpenoids. Dealing with each of these prefixes, the first, "copa", refers to sesquiterpenoids in Chart 1 which possess a six-membered ring with an axial isopropyl group.* The prefix "copa" is derived from copaene (25), which was the first sesquiterpene of this type to be isolated (from African copaiba balsam oil) and named.[19] "Ylango" refers to sesquiterpenoids in Chart 1 which possess a six-membered ring with an equatorial isopropyl group.* In this case, the prefix "ylango" was derived from ylangene (28) (isolated from ylang-ylang oil), which again was the first sesquiterpene of this type to be isolated and named.[27] Finally, the prefix "longi" refers to the group of sesquiterpenoids in Chart 1 which have a seven-membered ring possessing gem-dimethyl groups. Longifolene (29) was the first sesquiterpene of this type to be isolated (from Pinus longifolia,Roxb.) and named,[31] hence the prefix "longi".

The work described in this thesis was concerned with the successful

---

* It is assumed that the cyclohexane ring is in a chair conformation.

attempt to synthesize (-)-copacamphene (23) and (-)-cyclocopacamphene (24).

2. Sesquiterpene Biosynthesis

It is generally believed[1,2,39] that all sesquiterpenoids can be derived from the appropriate cyclization of either trans-farnesyl pyrophosphate (39) or cis-farnesyl pyrophosphate (40)[40] followed by appropriate rearrangements, oxidations and reductions. The biosynthesis of farnesyl pyrophosphate from acetyl CoA (32) via the intermediacy of mevalonic acid (35) has been experimentally verified[41-43] and is outlined in Chart 2.

The successive condensation of three molecules of acetyl CoA (32) can occur in two ways. A linear condensation (path A) leads to a straight chain product 33, generally considered to be the precursor of groups of natural products such as the phenolic resins and the acetogenins.[44-46] The other mode of condensation (path B) leads to the formation of the branched β-hydroxy-β-methyl glutaryl CoA (34). Reduction of 34 with nicotinamide-adenine dinucleotide phosphate (NADPH) affords mevalonic acid (35), which upon phosphorylation with adenine triphosphate (ATP) and subsequent decarboxylation, gives Δ^3-isopentenyl pyrophosphate (36). Isomerization of the terminal double bond of 36 results in the formation of dimethylallyl pyrophosphate (37), which upon condensation with 36 gives geranyl pyrophosphate (38). Subsequent condensation of geranyl pyrophosphate (38) with Δ^3-isopentenyl pyrophosphate (36) affords trans- and cis-farnesyl pyrophosphates, 39 and 40, respectively.

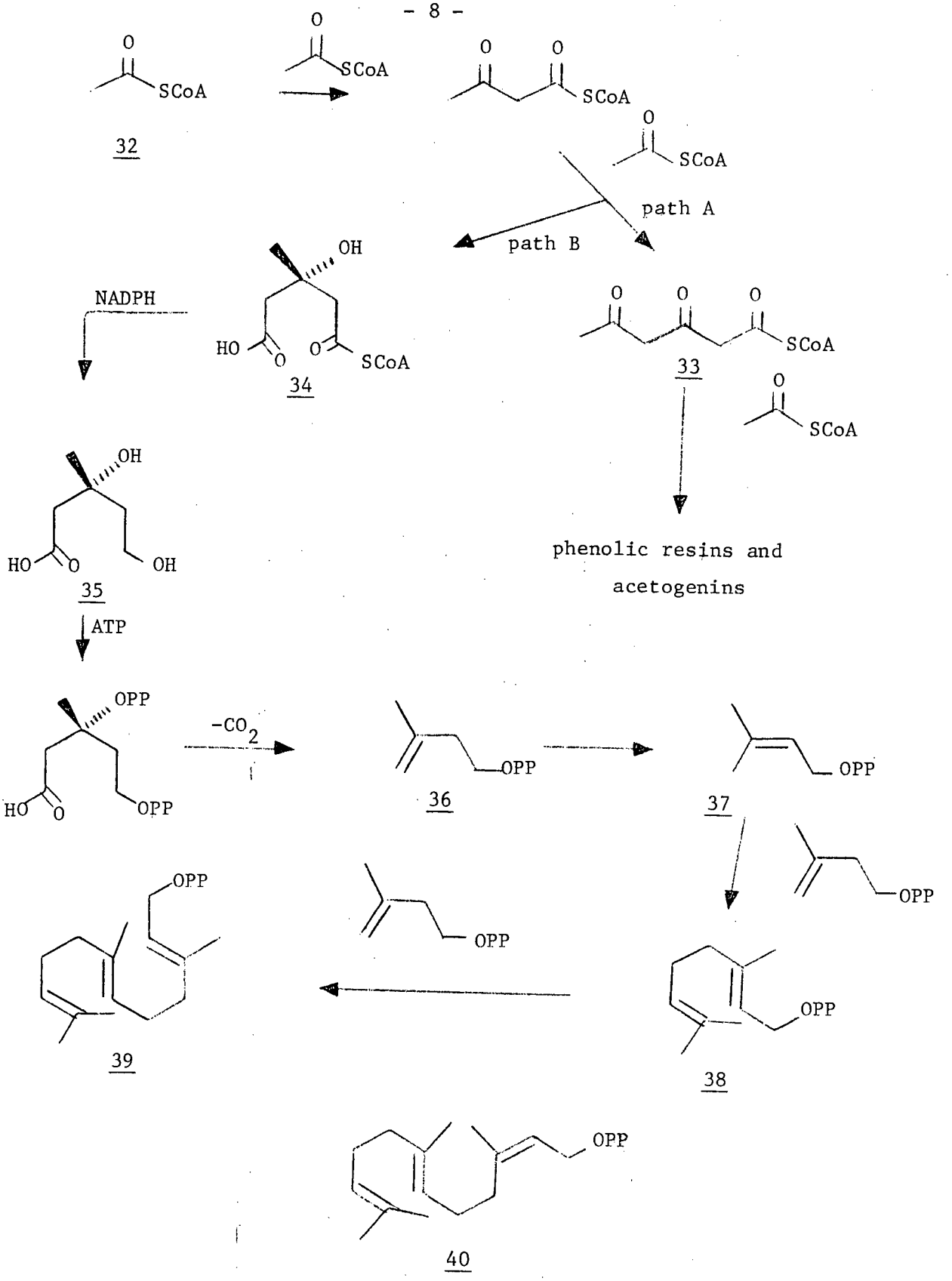

SCoA
32
path A
path B
NADPH
OH
HO
34
33
phenolic resins and
acetogenins
35
ATP
OPP
-CO2
36
37
38
39
40

CHART 2

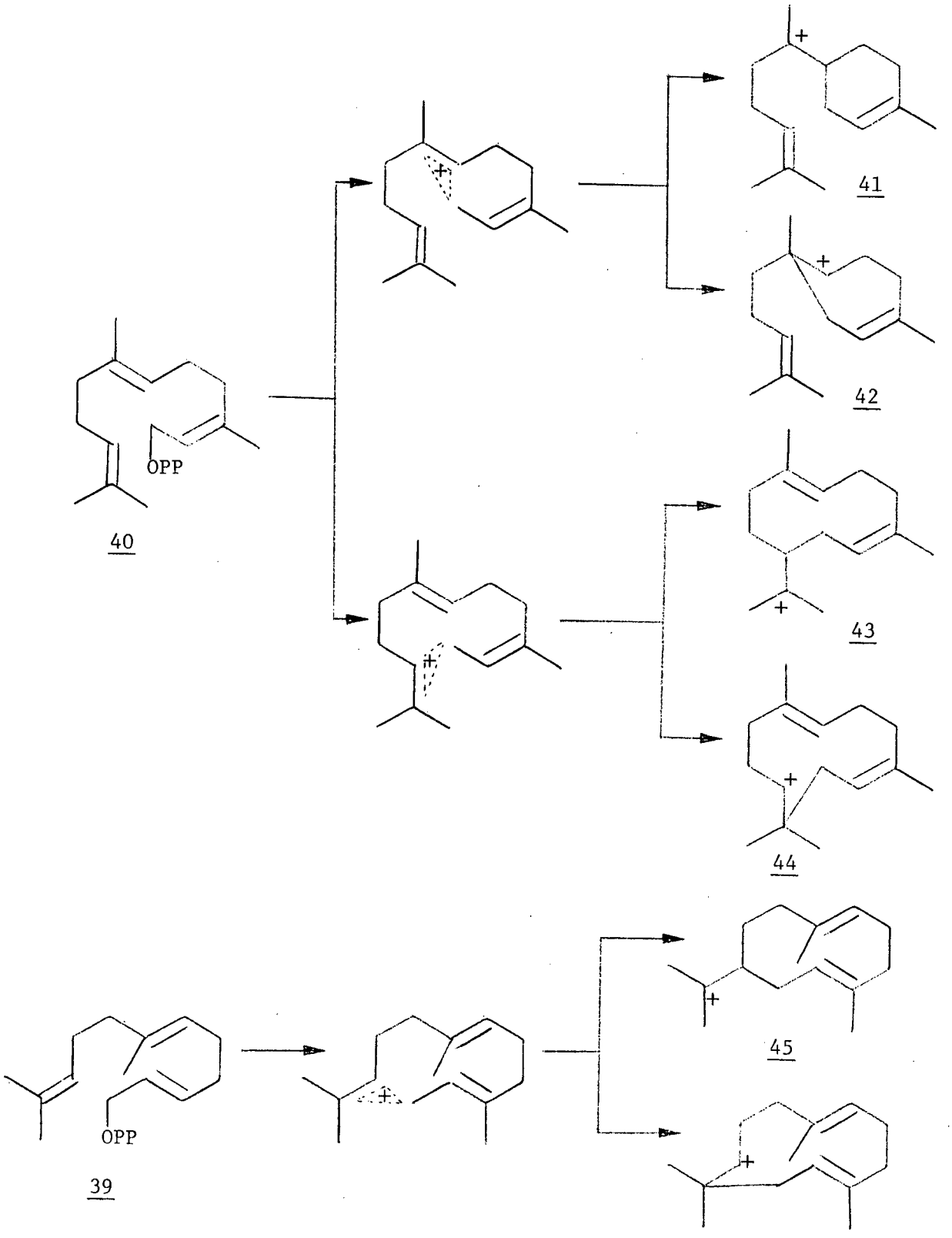


CHART 3

The next stage in the biosynthesis of sesquiterpenes is thought to be initiated by the ionization of the allylic pyrophosphates (39 and 40).[39] The unstable cations* formed could be neutralized by either the central or terminal double bond, leading to representations such as cations 41 to 46, as shown by Chart 3.

The biosynthesis of the "copa-" and "ylango-" type sesquiterpenoids probably occurs via very closely related pathways differing only in the configuration of the isopropyl group. So for convenience, only the "copa" series will be discussed in detail.

There are two distinctly different pathways which can be envisaged for the formation of the common intermediate, cation 50. In the first of these, as shown in Chart 4, cation 41 could undergo successive deprotonation, reprotonation and finally deprotonation to afford triene 47.** Subsequent cyclization of 47 would afford cation 48 which could be deprotonated and reprotonated (a 1,2-hydride shift) to afford cation 50.

In a second possible pathway, cation 43 could undergo a 1,3-hydride shift to produce cation 49. Markownikoff cyclization of the latter would form the same cation (50) as the previous pathway. Cation 51

---

* The representation of a formal cation in this and subsequent discussions is only a convenient symbolism, since the biogenetic cyclizations are undoubtedly enzymatically controlled, and probably occur via partially or fully concerted processes.

** This might also be viewed as a 1,2-hydride shift followed by deprotonation. It should be emphasized that in this and subsequent treatments, the formalism of these mechanisms must be treated with caution, as in all cases, the total process probably takes place on an enzyme surface and is probably concerted.

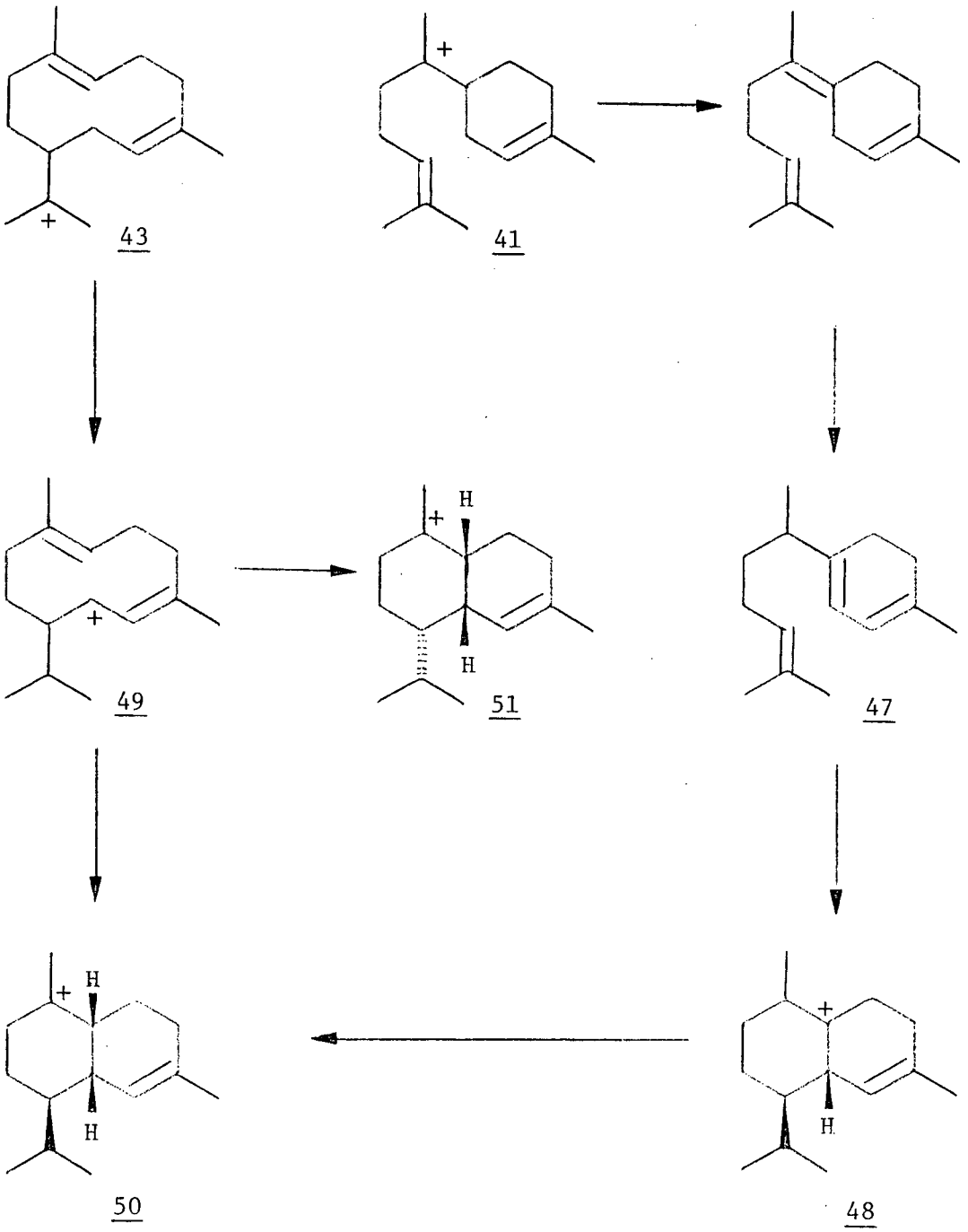


CHART 4

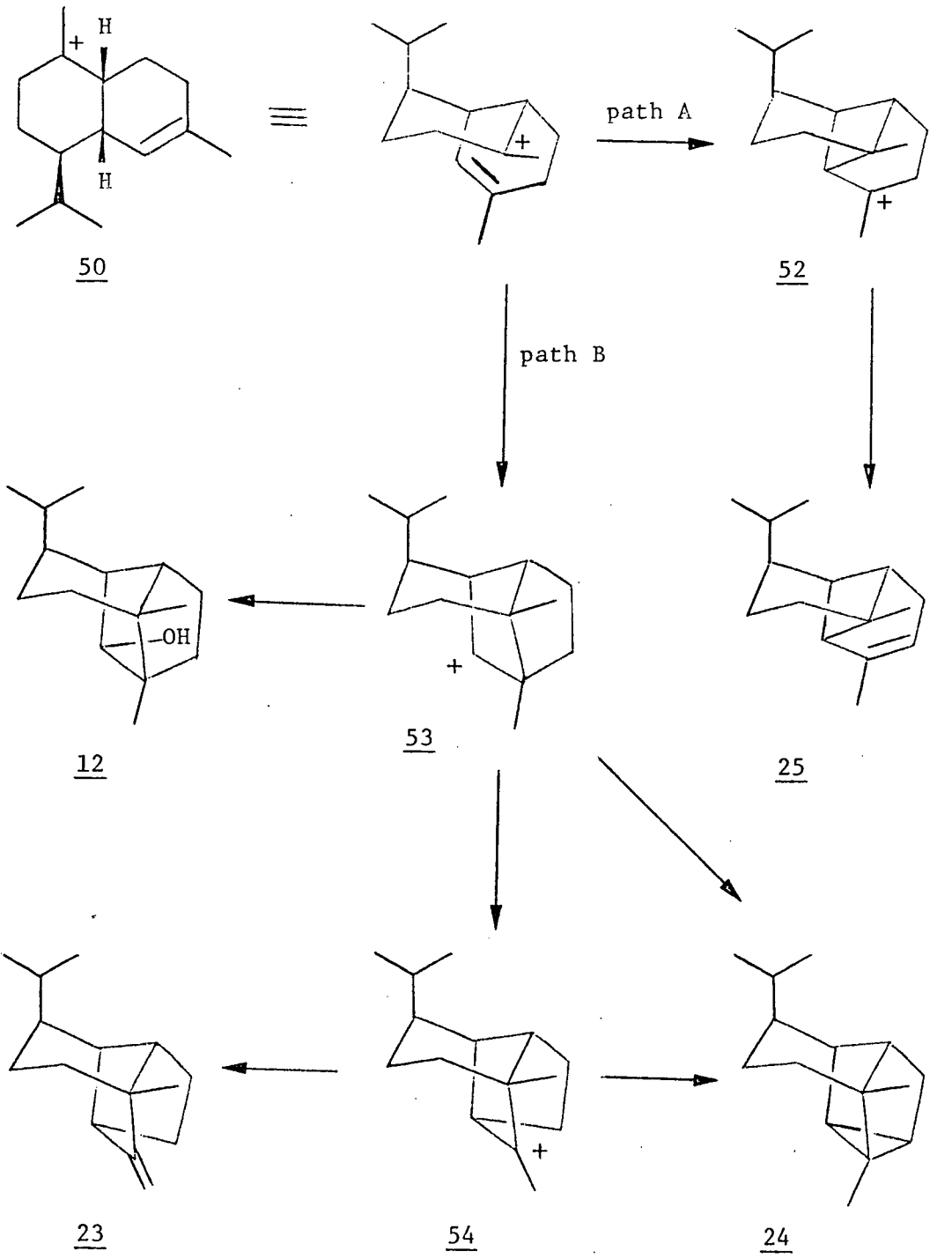


CHART 5

("ylango" series) could be formed in an analogous manner to that of cation 50.

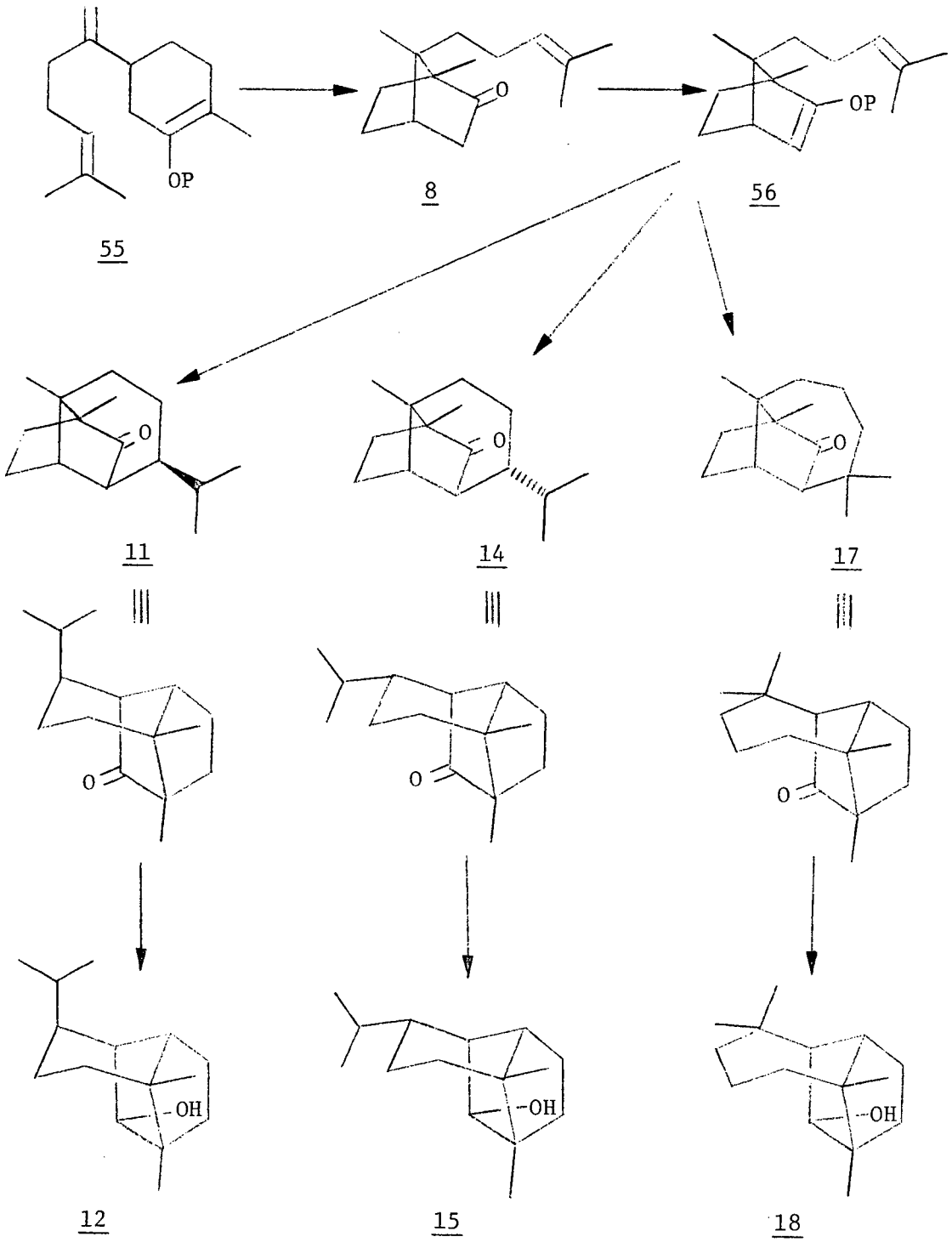
In order to obtain the "copa-"type sesquiterpenes from cation 50, it has been proposed that the latter could cyclize in a Markownikoff or anti-Markownikoff fashion (Chart 5). The former mode of cyclization (path A) would afford cation 52, which could then deprotonate to produce α-copaene (25).

Anti-Markownikoff cyclization of cation 50 (path B, Chart 5) could lead to the formation of cation 53. It can be seen that simple neutralization of cation 53 with water would afford copaborneol (12). It is also possible that this cation (53) could undergo a 1,3-deprotonation step to form cyclocopacamphene (24). Alternatively, a Wagner-Meerwein rearrangement of cation 53 could lead to cation 54 which could then undergo either 1,2- or 1,3-deprotonation to afford copacamphene (23) or cyclocopacamphene (24), respectively.*

In view of some interesting work by McMurry on the acid catalyzed conversion of copacamphene (23) to sativene (26) and cyclosativene (27),[16,47] it is interesting to speculate regarding the possibility of a conversion, (or an interconversion) of this type being used by nature in the biosynthesis of these compounds. McMurry's conversion of copacamphene to sativene will be discussed later in the Introduction.

An alternative hypothesis for the biosynthesis of the "ylango-" and "copa-"type sesquiterpenoids has recently been proposed.[48] The basic

* The structures shown in this discussion of biosynthesis do not necessarily depict the absolute configuration, and there is no attempt here to correlate the biosynthesis of these sesquiterpenes with their absolute configuration.



55 8 56

11 14 17

12 15 18

CHART 6

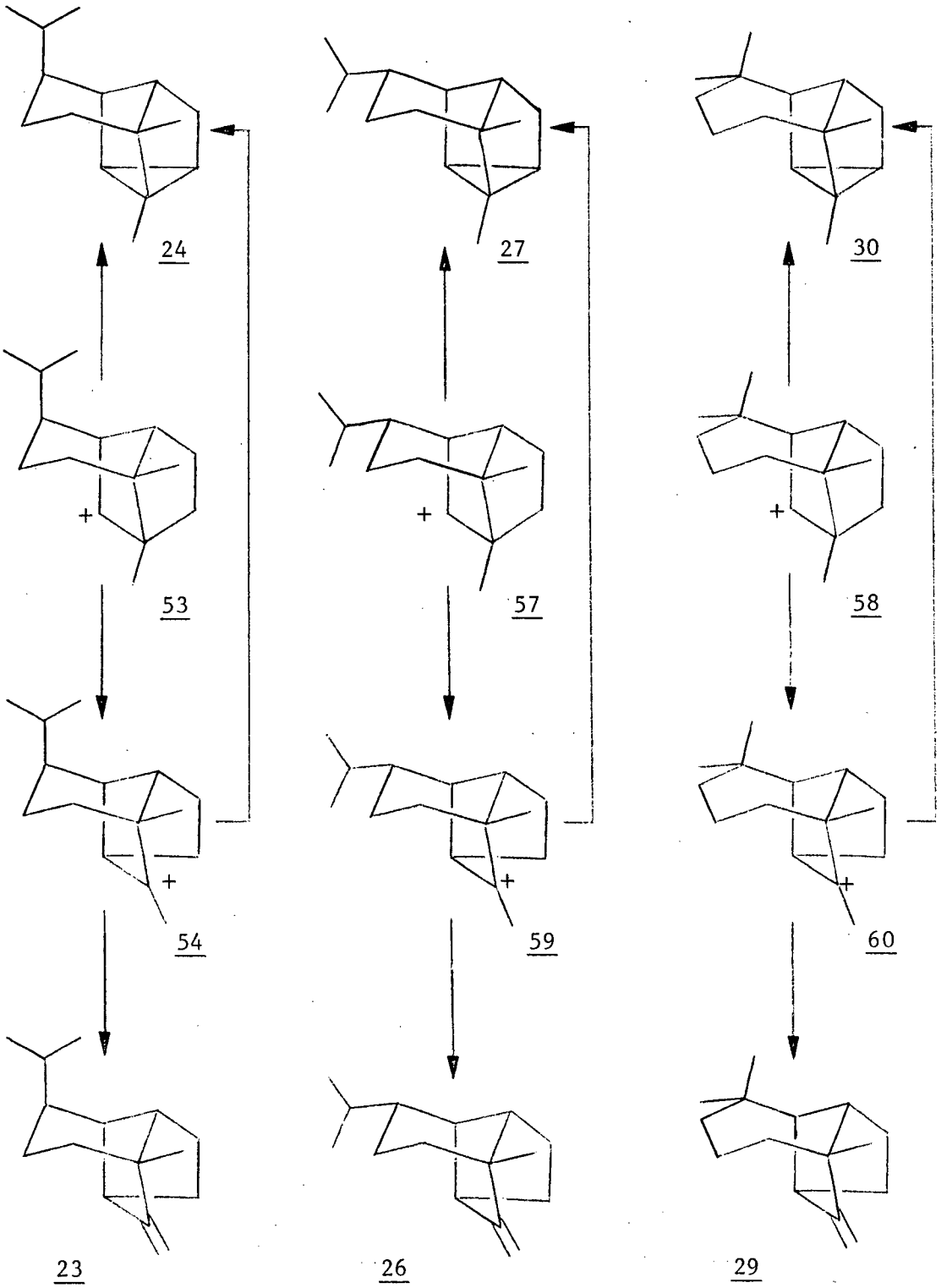


CHART 7

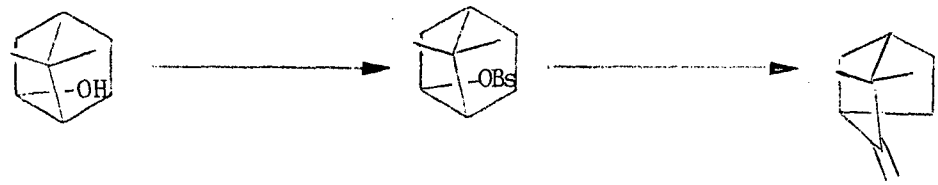
feature of this postulate is that certain bicyclic and tricyclic sesquiterpenoids could be constructed by cyclization of an appropriate enol phosphate. It was envisaged that cyclization of dihydrocryptomerion enol phosphate (55) could be involved in the biosynthesis of campherenone (8) (see Chart 6). The enol phosphate of campherenone (56) could then cyclize in each of three different ways, leading to the formation of copacamphor (11), ylangocamphor (14) or longicamphor (17). Reduction of the carbonyl function of these compounds could produce the corresponding borneol "isoprenologs" copaborneol (12), ylangoborneol (15) and longiborneol (18).

Solvolysis (or a related biogenetic process) of these three borneol "isoprenologs" could produce the corresponding cations (53, 57 and 58) as illustrated in Chart 7. In a manner analogous to that discussed previously in the biosynthesis of the "copa" series, the tetracyclic sesquiterpenes (24, 27, and 30) could be formed by deprotonation of cations 53, 57 and 58, respectively. A Wagner-Meerwein rearrangement of these cations could lead to the formation of cations 54, 59 and 60. Again, 1,3- or 1,2-deprotonation of these cations would produce the tetracyclic (24, 27 and 30) or tricyclic (23, 26 and 29) sesquiterpenes, respectively.

3. Origin and Structural Elucidation of Copacamphene and Cyclocopacamphene

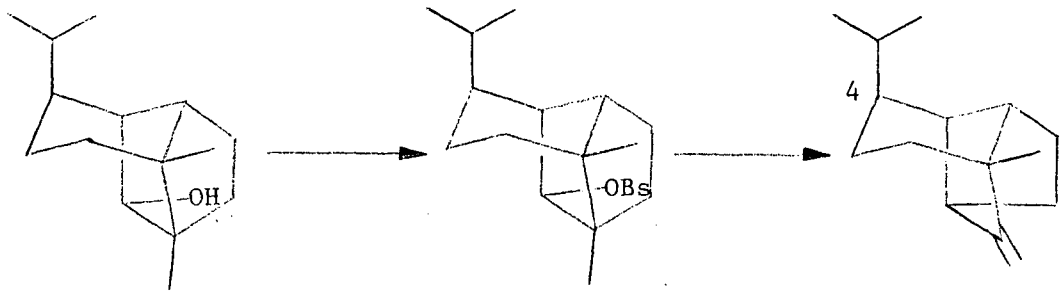
This thesis is mainly concerned with the total synthesis of copacamphene (23) and of cyclocopacamphene (24). It is therefore pertinent to discuss the origin of these compounds, and the work which led to the establishment of their structures and stereochemistry.

Copacamphene (23), although not yet isolated from a natural source, has been prepared by Westfelt,[11,12] by rearrangement of a derivative of copaborneol (12). By analogy with the elimination reaction of borneol and isoborneol derivatives[49] (cf. 6 → 20), Westfelt reasoned



6 20

that an elimination reaction of copaborneol would produce copacamphene. On treatment with p-bromobenzenesulfonyl (brosyl) chloride in pyridine at room temperature, copaborneol gave a crystalline brosylate (61). When a pyridine solution of the latter (61) was heated, a mixture of hydrocarbons was obtained, with copacamphene (23) being the major product.



12 61 23

The infrared and nuclear magnetic resonance (n.m.r.) spectra of copacamphene were very similar to those reported for sativene.[22,23]

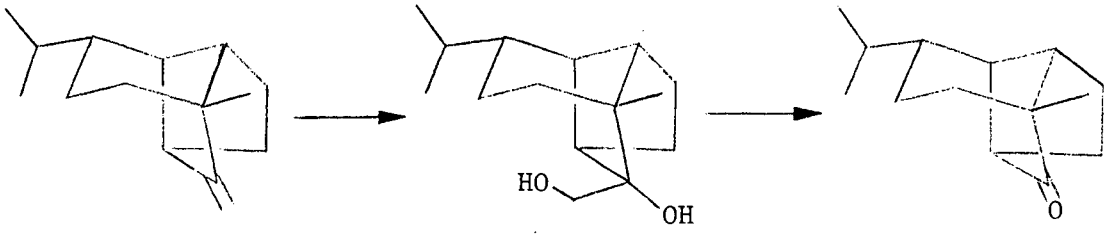
However, as Westfelt reported, the hydrocarbons were not identical, and different diols were obtained from osmium tetroxide oxidation. Westfelt therefore concluded that the hydrocarbons were epimeric at the isopropyl position, C_4 (see copacamphene (23) numbering).

As for the absolute stereochemistry of copacamphene, Westfelt has synthesized (+)-copaborneol (12)[12] from (+)-α-santalol, a compound of known absolute configuration.[50] This established the absolute configuration of (+)-copaborneol (12) which in turn established the absolute configuration of (-)-copacamphene (23).*

It is perhaps pertinent at this point to discuss the structural elucidation of (-)-sativene (26) since Westfelt assigned the structure and stereochemistry of copacamphene (23) mainly on the basis of its structural similarity to sativene (26). (-)-Sativene (26) was first isolated by de Mayo and co-workers from Helminthosporium sativum.[22] This hydrocarbon exhibited a rotation of -186° and infrared absorptions at 3.27, 6.03 and 11.30 μ, compatible with an exocyclic methylene group. This interpretation was corroborated by the n.m.r. spectrum which exhibited two one-proton signals at τ 5.28 and 5.60, which could readily be assigned to the exocyclic methylene protons. A singlet at τ 8.95 (3H) and a pair of doublets (6H, J ∿ 5 Hz) at 9.10 and 9.13 suggested the presence of a tertiary and isopropyl methyl groups respectively. A crystalline diol derivative of sativene was prepared by reacting sativene with osmium tetroxide. This diol (62) showed no

* Although Kolbe-Haugwitz and Westfelt[12] were correct in their assignments regarding absolute stereochemistry, we found that copacamphene of absolute configuration as shown in 23 is levorotatory ($[\alpha]_D^{21}$ -159°, vide infra) and not dextrorotatory ($[\alpha]_D$ +28.9°) as reported.[11,12] Neither we nor Dr. Westfelt (private communication) have as yet been able to trace the reason for this discrepancy.

absorption above 200 mμ in the ultraviolet, requiring the presence of but one double bond in the original hydrocarbon. Periodate cleavage of 62 gave ketone 63 whose carbonyl absorption in the infrared (5.75 μ) was characteristic of a saturated five-membered ring. De Mayo noted that the spectral data was in accord with the proposed structure, but



26 62 63

this in itself did not constitute irrefutable proof of structure. However, conclusive evidence was provided by the actual synthesis of (+)-sativene, as outlined in Section 5 of the Introduction (p. 31).

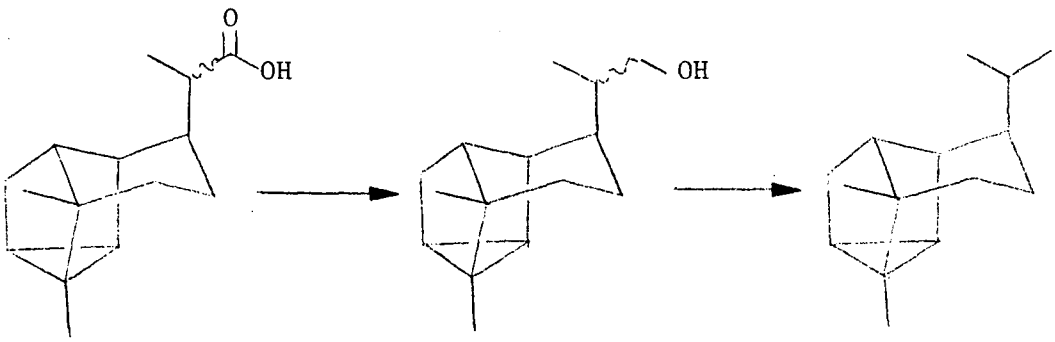
Closely related to copacamphene (23) is the tetracyclic hydrocarbon (+)-cyclocopacamphene (24) which was obtained from the reduction of the naturally occurring cyclocopacamphenic acids (64)[18] by Yoshikoshi and co-workers.*

The epimeric mixture of the cyclocopacamphenic acids (64) were esterified with diazomethane, then reduced with lithium aluminum hydride to afford the epimeric mixture of the corresponding alcohols (65).** These alcohols were converted to their corresponding tosylates by reaction with p-toluenesulfonyl chloride, and the resulting

* Cyclocopacamphene apparently occurs naturally in vetiver oil.[18]

** The epimeric alcohols, cyclocopacamphenol and epicyclocamphenol (65) were subsequently isolated from vetiver oil by Yoshikoshi and co-workers.[51]

tosylates were reacted again with lithium aluminum hydride to produce (+)-cyclocopacamphene (24).



64 65 24

The infrared and n.m.r. spectra of cyclocopacamphene were compared with the corresponding spectra of cyclosativene (27). The spectra of the two compounds were found to be quite similar, but not identical. Therefore, it was felt that cyclocopacamphene was a stereoisomer of cyclosativene, and specifically, that the two compounds were epimeric with respect to the configuration of the isopropyl group.

This supposition was confirmed by conversion of the epimeric cyclocopacamphenic acids (64) into cyclosativene (27) (Chart 8). Decarboxylative acetoxylation of the epimeric acids (64) with lead tetra-acetate produced the epimeric acetates (66). Hydrolysis of the latter (66), followed by Jones oxidation afforded a single acetyl derivative, compound 67. This compound was subjected to epimerizing conditions (sodium methoxide in methanol) and the corresponding epimeric acetyl compound (68) was isolated. A Wittig reaction with methylenetriphenylphosphorane on compound 68 produced the desired isopropenyl derivative (69), which was then hydrogenated using tris(triphenylphosphine)-rhodium chloride as a catalyst, to obtain (+)-cyclosativene (27).

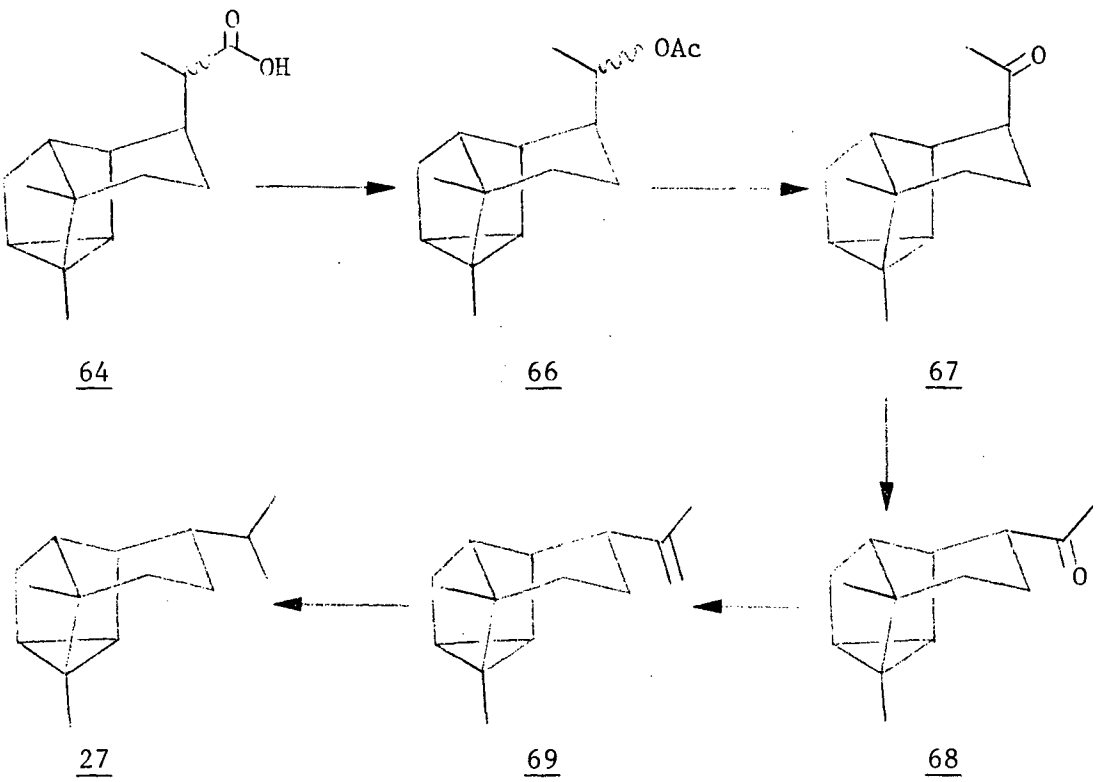


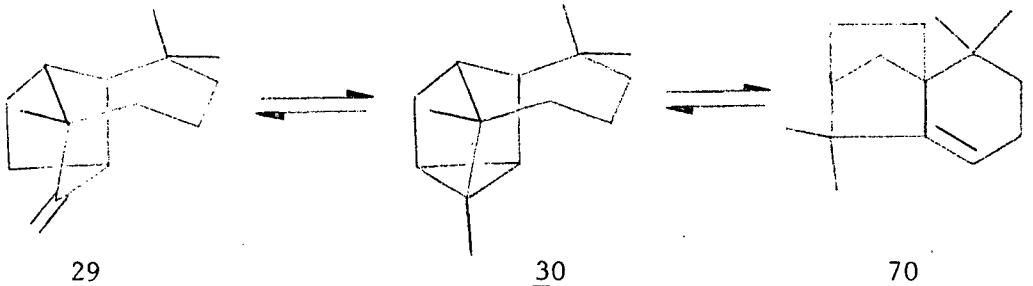
CHART 8

Although it has been suggested that (+)-cyclocopacamphene has absolute stereochemistry as depicted in 24[18] this point did not receive unambiguous verification until the completion of our synthesis of (-)-cyclocopacamphene.[17]

The structural elucidation of cyclocopacamphene (24) is dependent on the correct assignment of the cyclosativene (27) structure and stereochemistry. However, the structural elucidation of cyclosativene involved some of the interesting chemistry of these compounds and these features will be discussed in the next section of the Introduction.

4. Acid Rearrangements

Longifolene (29) is known to undergo some deep-seated rearrangements in the presence of acid.[36,52-54] When treated with cupric acetate in acetic acid at reflux (+)-longifolene underwent isomerization to a mixture of racemic (or partially racemic) hydrocarbons which contained longifolene (29), longicyclene (30) and isolongifolene (70).



29 30 70

When the reaction was stopped after twenty-two hours, there was obtained 55% longifolene (29), 24% longicyclene (30) and 19% isolongifolene (70). If the isomerization was allowed to proceed for five days, there was obtained 53% longifolene, 17% longicyclene and 30% isolongifolene. When longicyclene (30) was treated under the same conditions the same mixture of hydrocarbons was obtained.[36] This in fact was one of the methods used in the structural elucidation of the naturally occurring (+)-longicyclene (30).[36]

A mechanistic pathway accounting for these results was originally proposed by Ourisson[55,56] and is formulated for simplicity as proceeding through classical carbonium ions (Chart 9). The exocyclic methylene group of 29 could be protonated to produce cation 71. A 1,2- Wagner-Meerwein shift would afford cation (-)-71 which is the mirror image of

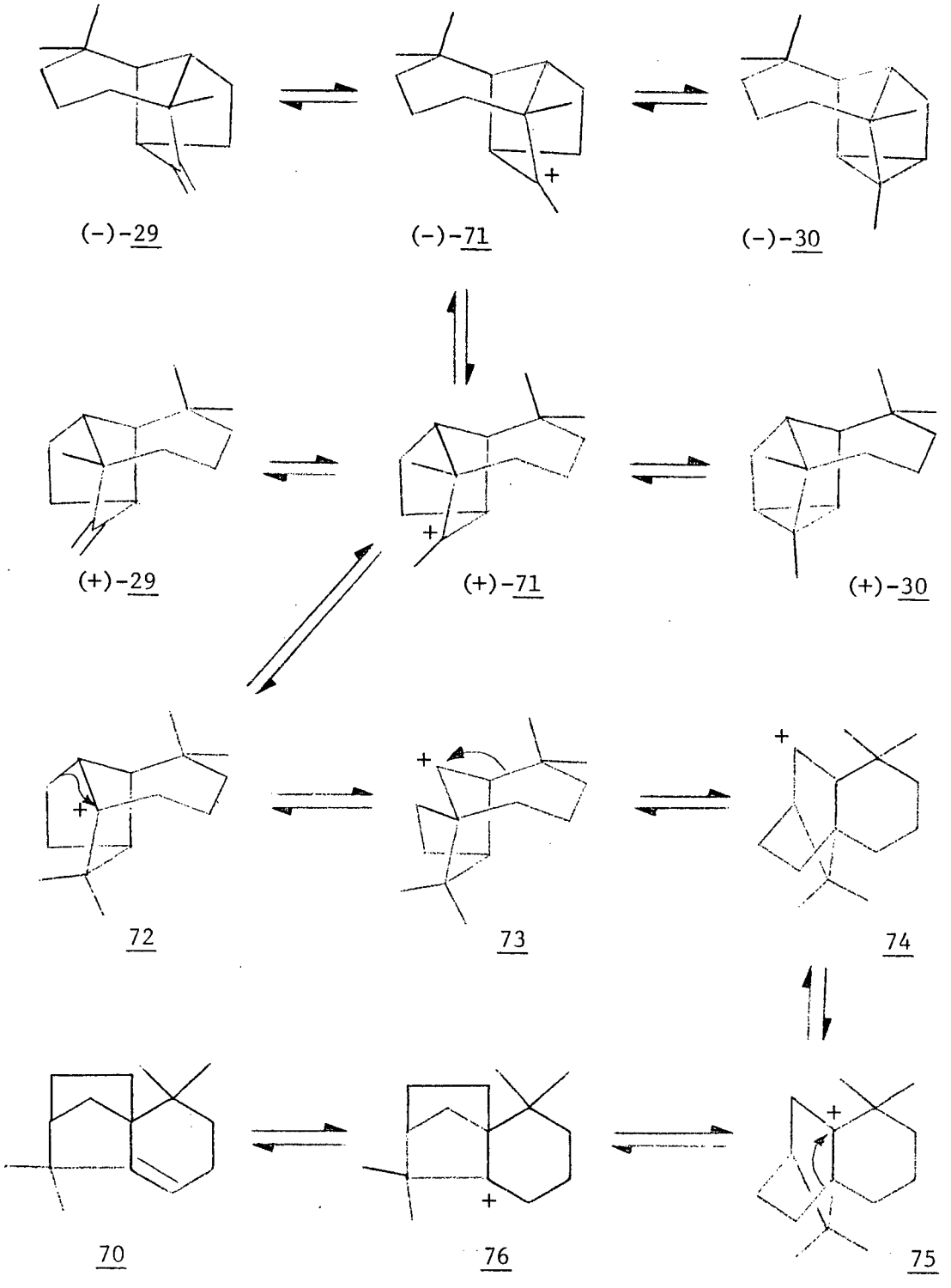
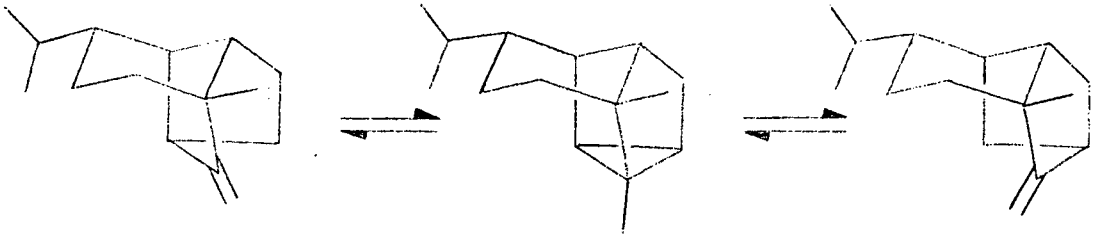


CHART 9

the original cation ((+)-71), and would account for the fact that the products in this isomerization were largely racemized. A 1,2- or 1,3-deprotonation of cations (+)-71 and (-)-71 would produce the enantiomeric forms of longifolene (29) and longicyclene (30) respectively.

The formation of isolongifolene (70) is postulated to involve a more deep seated skeletal change. Both enantiomeric forms of cation 71 would be involved, giving rise to racemic isolongifolene but only the rearrangement involving cation (+)-71 is shown diagramatically (Chart 9). A methyl migration in cation 71 could lead to the formation of cation 72. Migration of the two carbon bridge of cation 72 would produce cation 73. Ring contraction of 73 would afford cation 74 which could undergo a 1,2-hydride shift to produce cation 75. A further 1,2-Wagner-Meerwein shift in the latter cation could produce cation 76, which could undergo 1,2-deprotonation to afford isolongifolene (70).

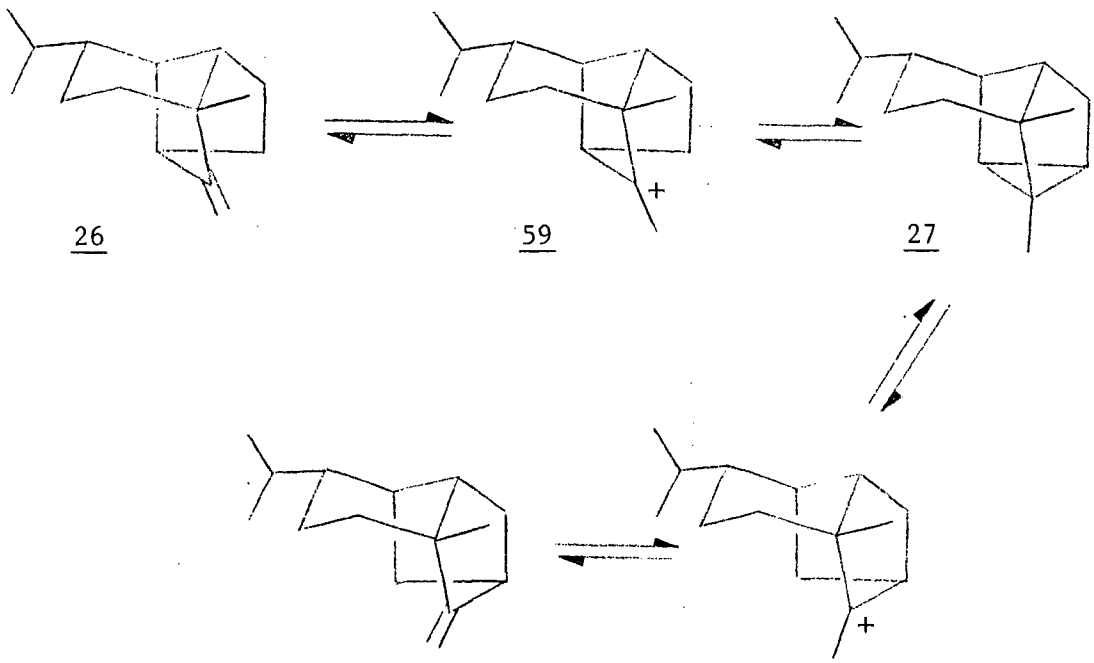
Because of its structural similarity to longifolene, sativene (26) would be expected to exhibit the same type of chemistry when treated with cupric acetate and acetic acid at reflux. This is indeed what has been observed.[24-26]



26 27 77

Treatment of sativene with acetic acid-cupric acetate (two days at reflux) gave an equilibrium mixture which consisted of 7% sativene (26), 32% cyclosativene (27) and 61% isosativene (77). McMurry[26] demonstrated that a true equilibrium did exist between these isomeric sesquiterpenes, since subjection of samples of pure cyclosativene or isosativene to cupric acetate-acetic acid treatment produced the same equilibrium mixture of products. The fact that cyclosativene could be converted to sativene was instrumental in the structural elucidation of cyclosativene,[24,25] by analogy with the structural elucidation of longicyclene (30).[36]

McMurry[26] suggested the following mechanism for the acid-catalyzed equilibrium between sativene, cyclosativene and isosativene.

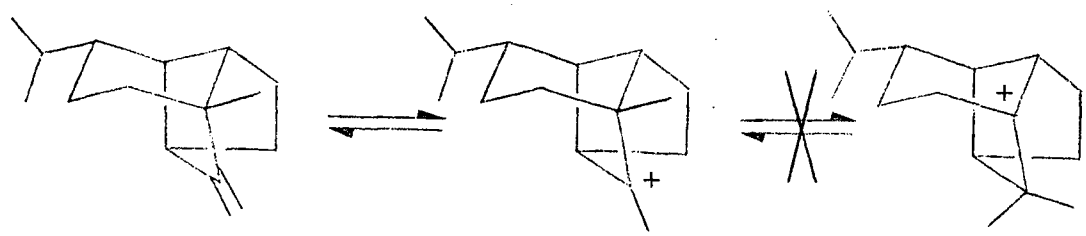


26 59 27

77 78

Protonation of sativene (26) could lead to the formation of cation 59 which could undergo 1,3-deprotonation to form cyclosativene (27). The cyclopropyl ring of cyclosativene could then be opened by protonation in either of two directions to generate a new tertiary cation 78 or to regenerate cation 59. Deprotonation of cation 78 would give rise to isosativene (77).

There are both similarities and differences in the acid catalyzed isomerization of longifolene and sativene. Each undergoes one unique type of transformation (leading to the two different iso products) and one common type of transformation (leading to the two analogous tetracyclic products). One of the differences is that sativene does not undergo a deep-seated rearrangement analogous to the formation of isolongifolene (see Chart 9). If such a rearrangement were to occur in the sativene case, the analogous bridgehead cation 79 would be formed. In 79, the cation is contained in a bicyclo[3.2.1]octane



26 59 79

system while in 72, the cation is in the more flexible bicyclo[4.2.1]-nonane system. Thus, McMurry[16] postulated that the consequent strain increases on moving to the smaller ring system, preventing this

rearrangement from occurring.

One further point of difference between the isomerization of longifolene and sativene is the carbonium ion rearrangement ((+)-71 → (-)-71, Chart 9) that accounts for the racemization in the longifolene series. If a rearrangement of this type were to occur in the sativene series, it would not lead to racemic sativene, but to a compound which is epimeric at the isopropyl group, namely copacamphene. However, this product was never found in the sativene isomerization. This is not surprising, since the isopropyl group in sativene has an equatorial orientation, while in copacamphene the isopropyl group is axial to the six-membered ring.* Therefore, sativene, possessing the equatorial isopropyl group, would clearly be the thermodynamically more stable product and to demonstrate the existence of an interconversion between sativene and its epimer (copacamphene), it would be necessary to start with the latter, and examine its rearrangement under acid catalysis.

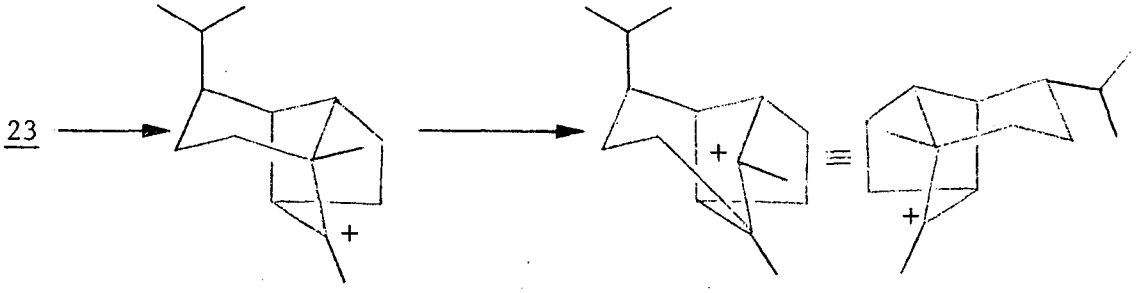
When (-)-copacamphene (23)** was treated with cupric acetate in refluxing acetic acid, rearrangement did indeed take place.[16,47] The products obtained were (+)-cyclosativene, sativene and isosativene in a ratio of 32:7:61 respectively. The obvious conclusion[16] was that copacamphene was being isomerized to sativene, with the latter compound undergoing further rearrangement as described previously (see p. 25).

---

* It is assumed that the six-membered rings in sativene and copacamphene are in the chair conformation.

** See the footnote on p. 18.

Mechanistically, protonation of copacamphene, followed by Wagner-Meerwein rearrangement of the resulting cation (54) would lead to the formation of cation 59. The latter is structurally identical with the cation which was postulated as an intermediate in the sativene rearrangement.



23 54 59

5. Other Synthetic Approaches to "Copa-" and "Ylango-"type Sesquiterpenoids.

Recently, Westfelt[12] has reported the synthesis of (+)-copaborneol (12) in conjunction with the structural elucidation of this compound, with the key synthetic step involving a stereoselective intramolecular Michael cyclization. The starting material employed was (+)-α-santalol (80), (see Chart 10). When this compound (80) was oxidized with selenium dioxide a mixture of santalals (81) was obtained. The configuration at the double bond had been partially inverted during the oxidation, but this stereochemical point was unimportant for the outcome of the synthesis. Silver oxide oxidation of 81 produced the corresponding acids (82). This product was treated with formic acid, and since the cyclopropyl ring of 82 could be

opened in two different ways, a mixture of the syn (83) and anti (84) formates was obtained in a ratio of 11:7 respectively. Hydrolysis of the formates (83 and 84) with ethanolic sodium hydroxide, followed by Jones oxidation of the resulting alcohols and Fischer esterification of the allylic acids, generated the corresponding anti (85) and syn (86) keto esters, respectively.

When the mixture of saturated syn and anti keto esters was treated with potassium t-butoxide in dioxan at room temperature, the syn isomer (86) cyclized rapidly to afford the keto ester 87, while the anti isomer (85) remained unchanged. Compound 87 was readily separated from compound 85 by column chromatography. The copacamphoric ester (87) was stereochemically homogeneous with respect to the orientation of the C_{10} side chain (see structure 87 for numbering), but epimeric with respect to the secondary methyl group (C_{11}).

Next, the carbomethoxy group (of 87) was transformed into a methyl group. Hydrolysis (ethanolic sodium hydroxide) of the copacamphoric ester (87) produced the corresponding acid, which was treated with thionyl chloride in benzene to afford the corresponding acid chloride. The latter was reduced with sodium borohydride in dioxan at room temperature to generate copacamphoric alcohol 88. This keto alcohol (88) was then treated with methanesulfonyl chloride in pyridine to produce the corresponding methanesulfonate derivative. Lithium aluminum hydride reduction of the latter afforded copaisoborneol (13), which was readily oxidized by Jones reagent to give copacamphor (11). Since the configuration of the hydroxyl group in copaborneol (12)

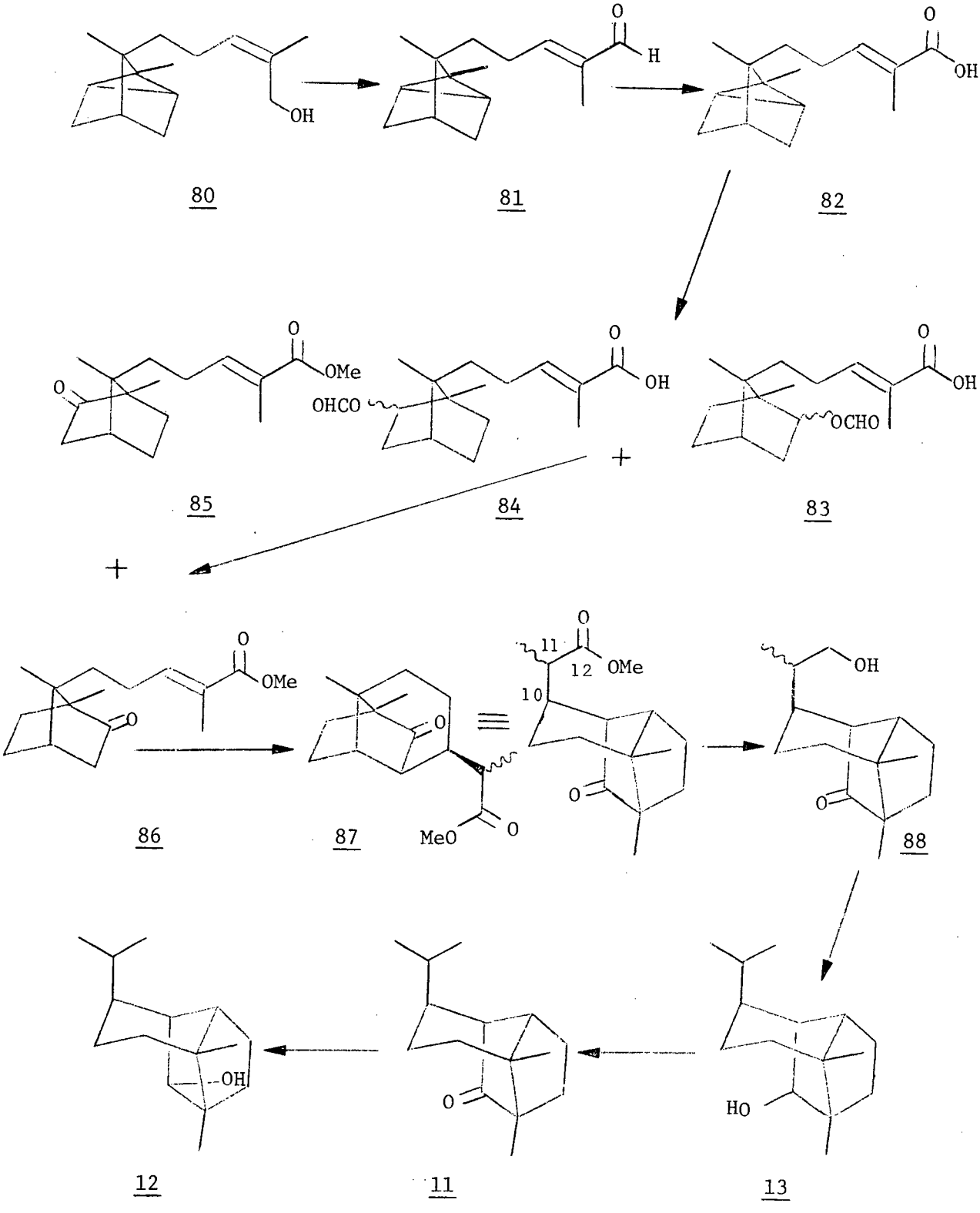
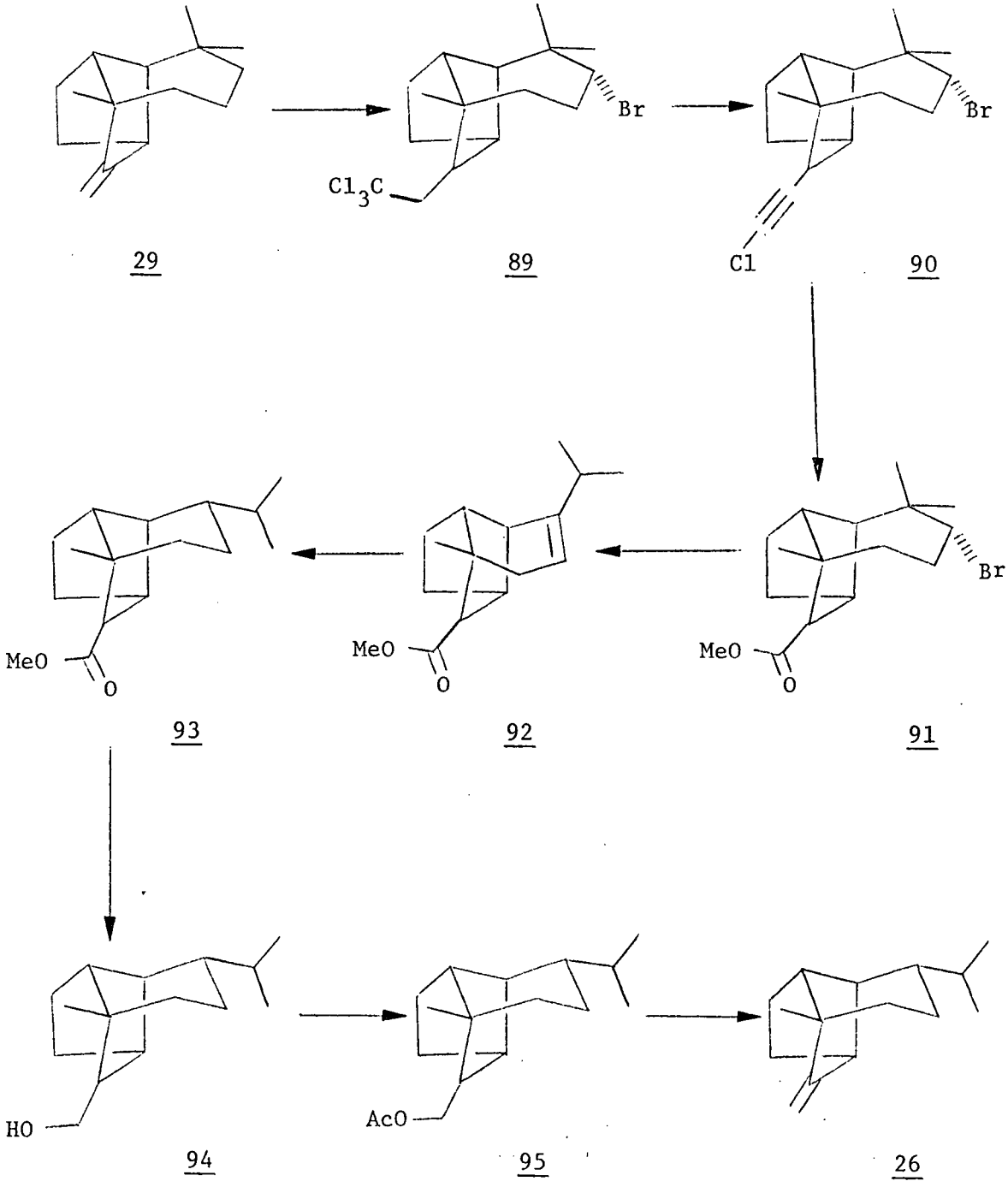

OH
O
H
OH
80
81
82
O
OMe
O
OHCO
OH
O
OH
OCHO
85
84
83
+
+
O
OMe
O
O
11
12
OMe
10
O
≡
MeO
O
OH
O
86
87
88
HO
O
--OH
12
11
13

CHART 10

is the thermodynamically more favoured orientation, reduction of copacamphor (11) with sodium in alcohol yielded synthetic (+)-copaborneol (12), identical in every respect to the natural product. Since the latter compound (12) had previously been converted into (-)-copacamphene (23),[11] Westfelt's synthesis formally represented a total synthesis of this sesquiterpene.

De Mayo reported the synthesis of (+)-sativene[22] as part of the structural elucidation of the naturally occurring (-)-sativene. Longifolene (29)[33-35] of known absolute stereochemistry, was reacted with bromotrichloromethane[57] to give the trichlorobromo derivative (89) (see Chart 11) via a well documented free-radical transannular hydrogen transfer.[55] Compound 89 was dehydrochlorinated to afford the chloroacetylene 90. Oxidation of the latter, followed by esterification of the resulting acid produced the bromoester (91). On distillation of this compound from iron powder under reduced pressure (0.2 mm), olefinic ester 92 was obtained in 45% yield. Hydrogenation of the double bond of 92 produced ester 93. Because of the convex nature of the six-membered ring, and the steric hinderance of the bridged system on the α-side of compound 92, hydrogenation would be expected to take place from the β-side of the molecule, to produce the compound possessing an equatorial isopropyl group. The ester group of 93 was then reduced with lithium aluminum hydride to afford alcohol 94. Acetylation of the latter produced acetate 95, which was pyrolyzed[58] in the vapour phase at 550° to give (+)-sativene (26). The latter was identical with the natural (-)-sativene, except that its optical rotation was opposite in sign. Since the absolute configuration of the starting material

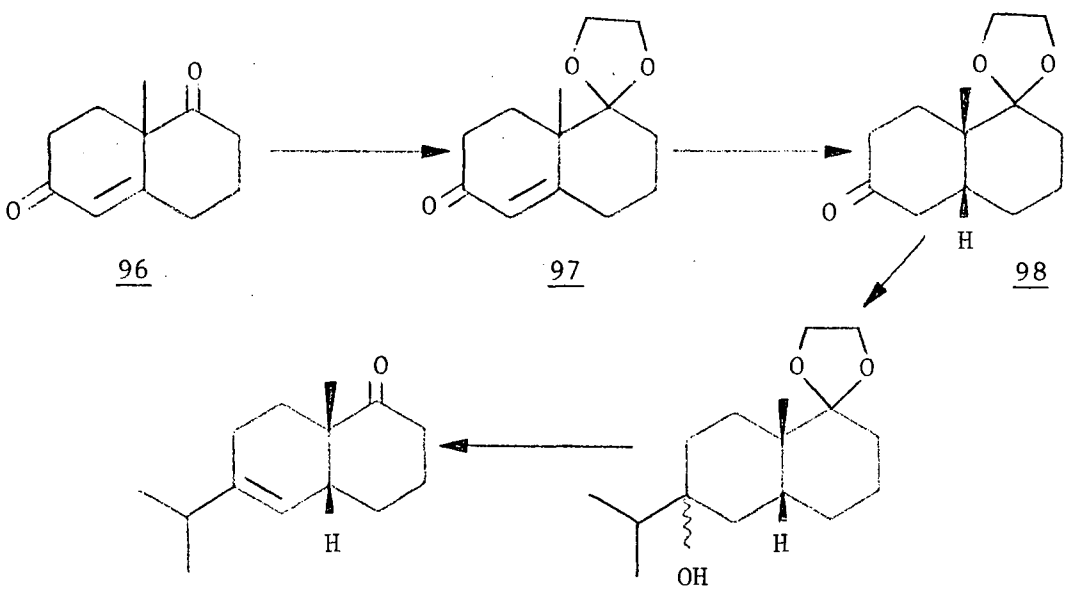


29 89 90 91 92 93 94 95 26

CHART 11

((+)-longifolene) was known, this synthesis established not only the stereochemistry, but also the absolute configuration of natural (-)-sativene.

McMurry has succeeded in synthesizing both (±)-sativene (26)[23] and (±)-copacamphene (23).[15,16] Dealing first with the sativene synthesis, McMurry's starting material was the well known Wieland-Miescher ketone (96).[59] Under carefully controlled conditions, this compound (96) was reacted with ethylene glycol using p-toluenesulfonic acid as a catalyst. The saturated carbonyl (of 96) was selectively ketalized, forming the keto ketal 97. Catalytic hydrogenation of 97 with 10% palladium on charcoal in ethanol resulted in the formation of the cis fused decalone (98). Reaction of the decalone 98 with isopropyllithium in refluxing pentane generated alcohol 99. Dehydration and deketalization of this alcohol-ketal was accomplished by stirring compound 99 overnight in a two-phase system of hexane-50% aqueous sulfuric acid, to afford the keto olefin (100).



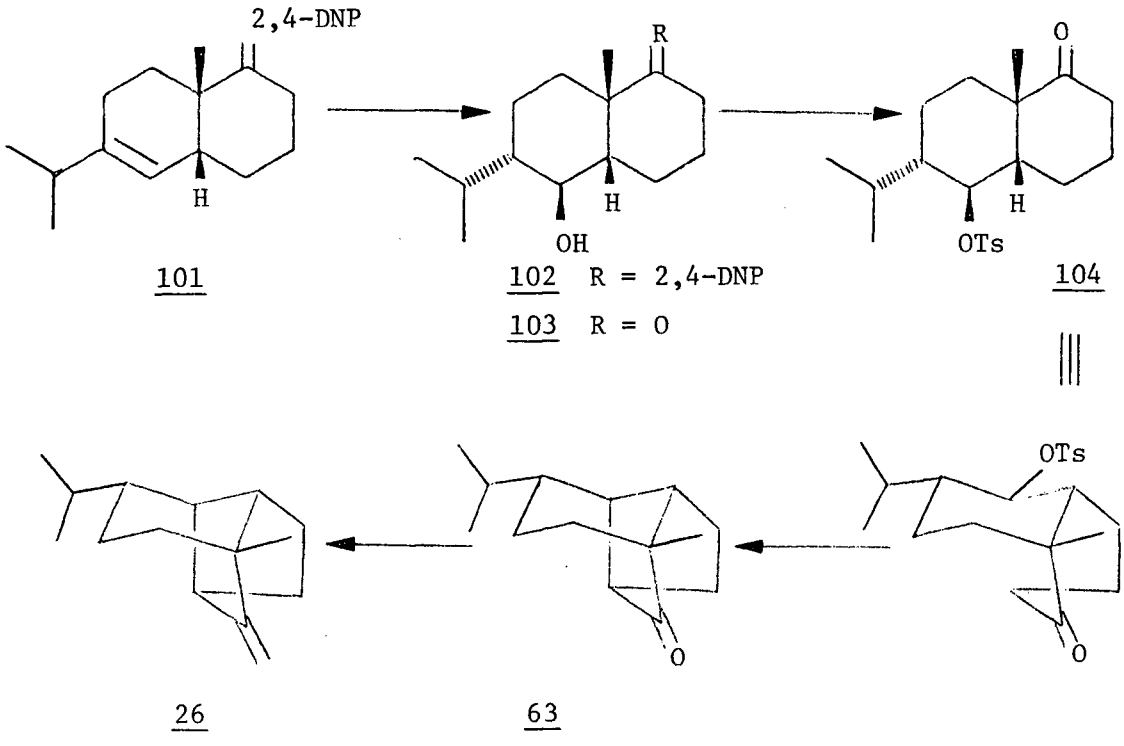
96 97 98

100 99

Treatment of 100 with borane in tetrahydrofuran showed that this reagent affected reduction of the carbonyl group faster than it hydroborated the carbon-carbon double bond. Furthermore, attempts at protecting the carbonyl group (of 100) by ketalization resulted in at least partial migration of the carbon-carbon double bond. However, the carbonyl was protected by forming the 2,4-dinitrophenylhydrazone (2,4-DNP) derivative (101)[60] and this compound was reacted with borane in tetrahydrofuran. The resulting dialkylborane intermediate was oxidized with basic hydrogen peroxide to form the 2,4-DNP alcohol (102). Removal of the 2,4-DNP protecting group was readily accomplished[61] by ozonolysis of 102 in ethyl acetate at -78°, and after reductive workup with sodium bisulfite, keto alcohol 103 was obtained.

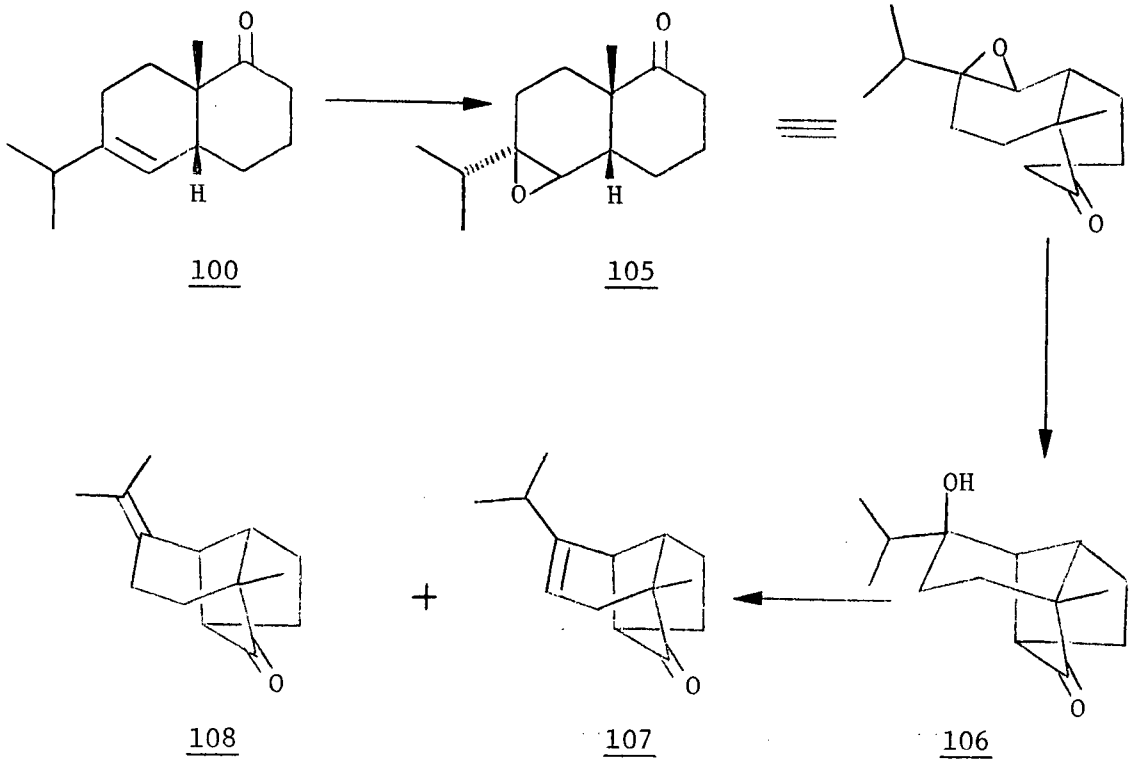
The keto alcohol (103) was reacted with p-toluenesulfonyl (tosyl) chloride in pyridine at room temperature for three days to form the corresponding keto tosylate (104). Intramolecular alkylation was accomplished by reacting the keto tosylate (104) with methylsulfinyl carbanion in dimethyl sulfoxide[62] at 60° for two hours to produce tricyclic ketone 63. Treatment of the latter (63) with methyllithium followed by dehydration of the resulting tertiary alcohol with thionyl chloride in pyridine yielded racemic sativene (26).

McMurry, in his synthesis of racemic copacamphene (23)[16] utilized as his starting material an intermediate from the sativene synthesis. Keto olefin 100 was treated with m-chloroperbenzoic acid in chloroform to give the β-epoxide (105). On treatment with either methylsulfinyl



carbanion in dimethyl sulfoxide for two days at 65° or with a refluxing solution of potassium t-butoxide in t-butanol for seven days, compound 105 underwent an intramolecular epoxide opening to generate the tricyclic keto alcohol (106). Dehydration was accomplished by stirring the keto alcohol 106 briefly in a two phase hexane-50% aqueous sulfuric acid system, to produce the trisubstituted olefin (107) and the tetrasubstituted olefin (108) in a ratio of 7:3 respectively.

Hydrogenation of keto olefin 107 over Adams catalyst in acetic acid gave tricyclic ketone 63 (sativene series) as the only product. By analogy with de Mayo's work on the synthesis and structural

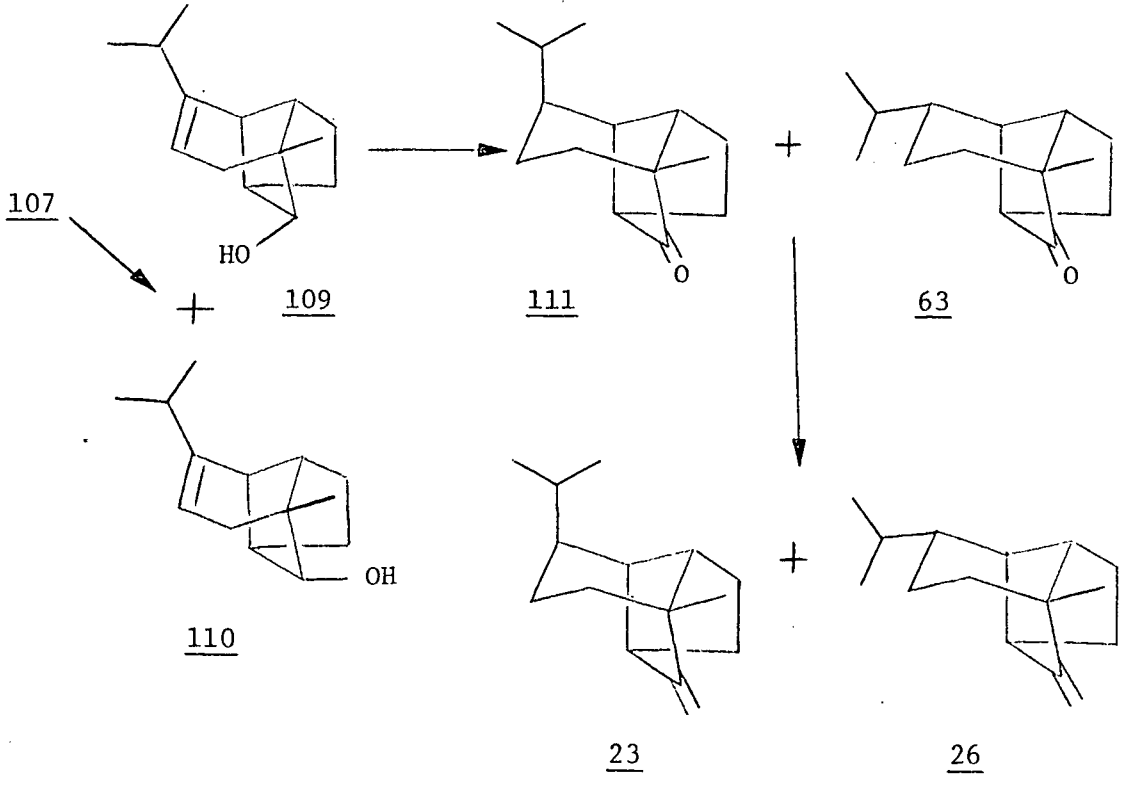


100 105 108 107 106

elucidation of sativene (92 → 93; Chart 11)[22] the hydrogenation would be expected to take place completely stereoselectively from the less hindered side.

Reduction of the carbonyl group of keto olefin 107 with lithium aluminum hydride in ether gave olefinic alcohols 109 and 110 in a ratio of 4:6 respectively. However, the olefinic alcohol 109 was formed as the major product when the reduction of compound 107 was carried out with lithium in liquid ammonia. Under these conditions, a 6:4 ratio of 109 to 110 was obtained. The hydroxyl group of compound 109 is in close proximity to the double bond. This relationship was important as hydrogenation was carried out in a non-polar solvent

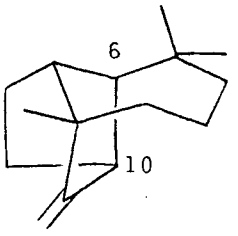
(hexane) so that the catalyst (palladium on charcoal) might bond to the hydroxyl group and deliver hydrogen from the more hindered side of the carbon-carbon double bond.[63] Although, in practice, hydrogenation was slow, it did reach completion after five days. Collins oxidation[64] of the hydrogenated alcohols gave a mixture of tricyclic ketones 111 and 63 in a ratio of 85:15 respectively. Treatment of this mixture (111 and 63) with methyllithium followed by dehydration with thionyl chloride in pyridine afforded (±)-copacamphene (23) and (±)-sativene (26) which could be separated by column chromatography on silver nitrate impregnated silica gel.



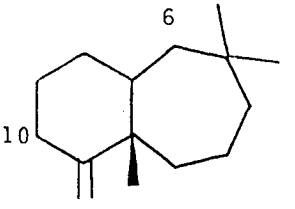
DISCUSSION

1. General

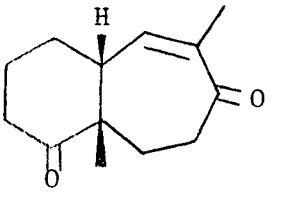
Because of the great diversity in the number of pathways by which complex natural products such as copacamphene, cyclocopacamphene and copaborneol could, in theory, be constructed, some consideration of various synthetic approaches to these sesquiterpenoids will be discussed briefly. The theoretical cleavage of a bond in a polycyclic sesquiterpenoid would produce an intermediate which often possesses a greatly simplified structure as compared with the original structure of the natural product itself. To regenerate the desired polycyclic skeleton, one would then have to carry out the cyclization of the appropriately functionalized intermediate. This approach is well illustrated by Corey and co-workers,[65] in the synthesis of longifolene (29). The theoretical cleavage of the C_6-C_{10} bond in longifolene (29) produced a simplified structure (112) as compared with 29. The appropriately functionalized intermediate (113) underwent an intramolecular Michael cyclization to produce the tricyclic diketone (114).



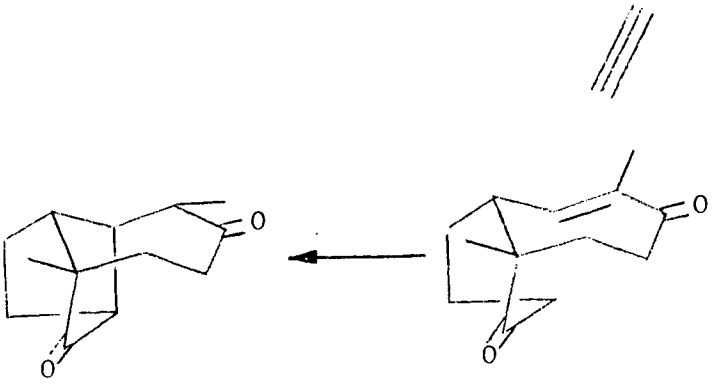
29



112

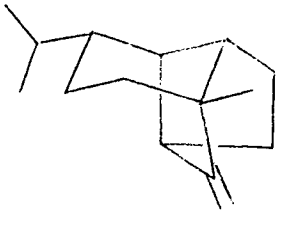


113

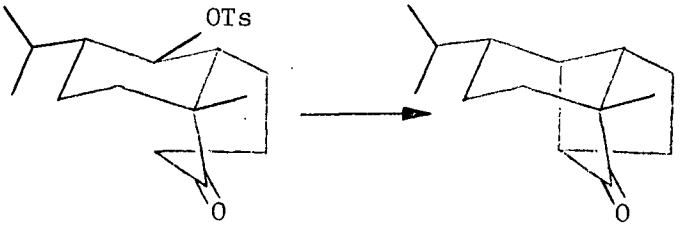


114

This same basic approach was used by McMurry in his synthesis of (±)-sativene (26).[23] The key step in this synthesis involved the intramolecular alkylation of an appropriately functionalized intermediate, the bicyclic keto tosylate (104), to afford the tricyclic ketone (63).

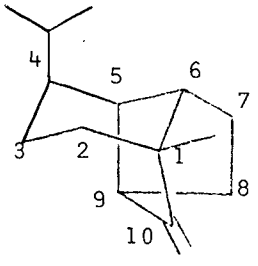


26



104 63

Following this general outline, the theoretical cleavage of several carbon-carbon bonds in copacamphene (23) were considered (see Chart 12). Cleavage of the C_5-C_9, C_1-C_6 and C_8-C_9 bonds of copacamphene (23) (see numbering below) would lead to the hypothetical intermediates 115, 116, and 117 respectively. The appropriately functionalized synthetic intermediates that might be envisaged for the regeneration of the required tricyclic carbon skeleton were 118, 119, and 120 respectively.

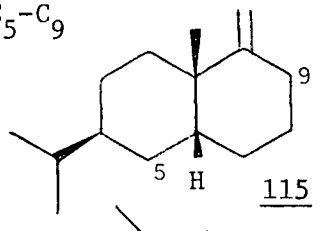


23

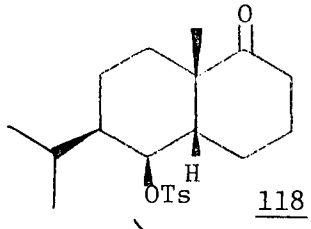
Cleavage of:

Proposed intermediate for cyclization

C_5-C_9

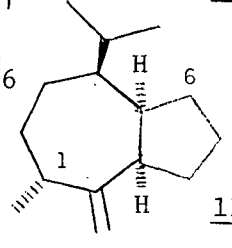


115

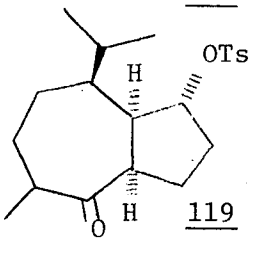


118

C_1-C_6

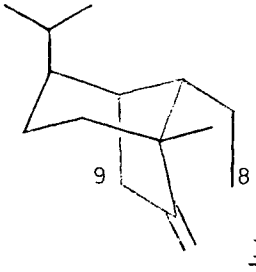


116

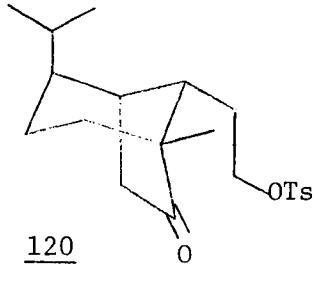


119

C_8-C_9



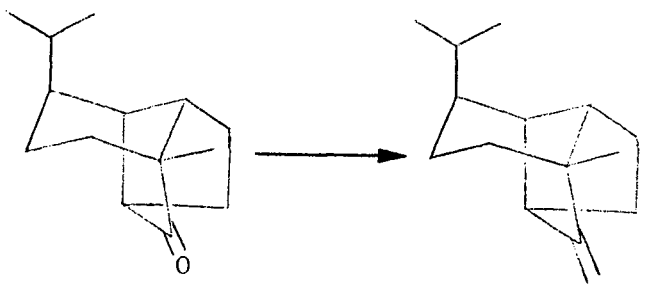
117



120

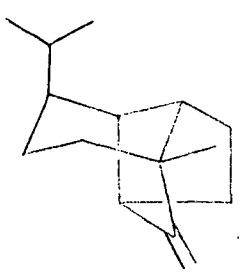
CHART 12

Thus, it was felt that the bicyclic keto tosylate intermediates (118, 119 and 120) would undergo intramolecular alkylation to afford the tricyclic ketone (111). Conversion of the carbonyl group of 111 to an exocyclic methylene group would then produce copacamphene (23).

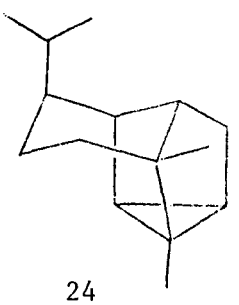


111 23

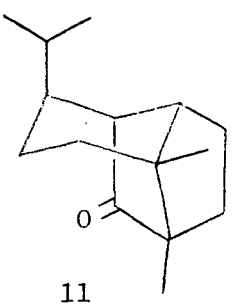
Apart from the obvious difficulties in synthesizing complex intermediates such as 118, 119 and 120, it was felt that this whole synthetic approach was too narrow in scope, in that only copacamphene could be synthesized via these schemes. What was desired was an intermediate that could be utilized not only for the synthesis of copacamphene (23) but also for the synthesis of cyclocopacamphene (24) and of copacamphor (11).*



23

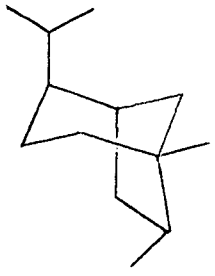


24



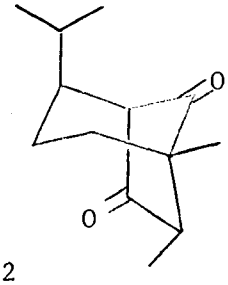
11

* Since (+)-copacamphor (11) had previously been converted[11,12] into both (+)-copaborneol (12) and (+)-copaisoborneol (13), the synthesis of copacamphor would also complete the total synthesis of these two sesquiterpenoids.



121

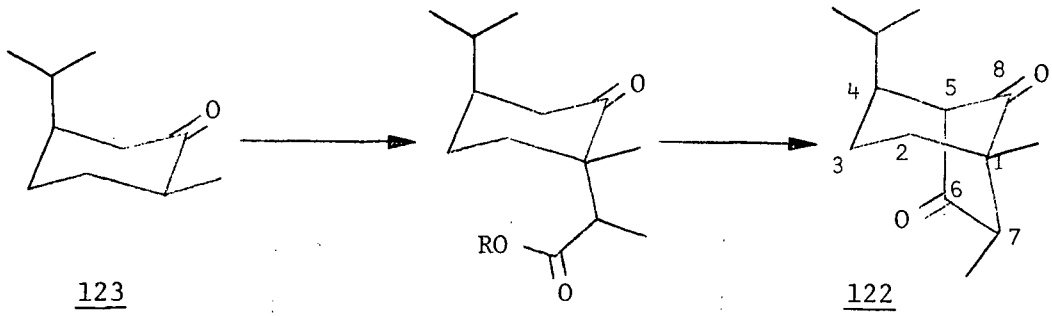
Inspection of the structures of the sesquiterpenoids in question [copacamphene (23), cyclocopacamphene (24), and copacamphor (11)] revealed that these compounds could be considered to possess a basic, common substituted bicyclo[3.2.1]octane unit (121), with an additional two carbon unit attached in various ways, to form the tricyclic skeletons of copacamphene (23) and copacamphor (11), or the tetracyclic skeleton of cyclocopacamphene (24). Therefore, the functionalized bicyclo[3.2.1]octane derivative that we believed would be synthetically useful was diketone 122.



122

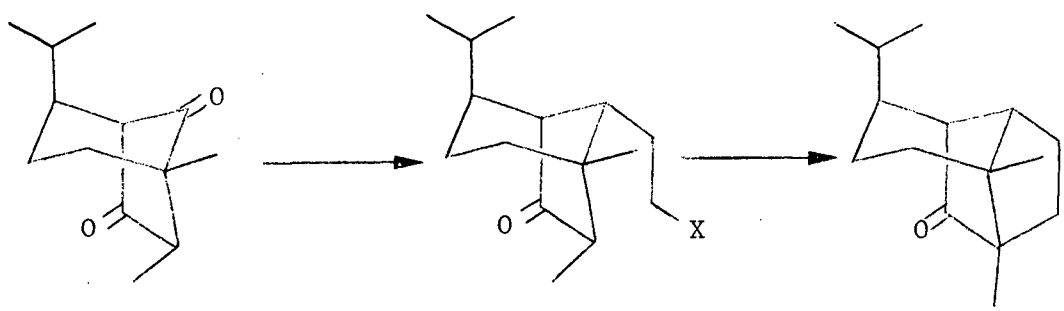
Synthetically, the diketone (122) could be considered as a cyclohexane derivative with an added two carbon bridge. The judicious choice of a starting material is a critical step in any synthetic sequence, and it was felt that the monoterpenoid (+)-carvomenthone (123) could be

utilized as the required cyclohexane derivative. This readily available compound is optically active and of known absolute configuration[66] and provides ten of the fifteen carbons that are required in the synthesis of a sesquiterpenoid. Alkylation of carvomenthone with a suitable α-halopropionate, and the subsequent cyclization of the resulting product would, if successful, produce the desired diketone.



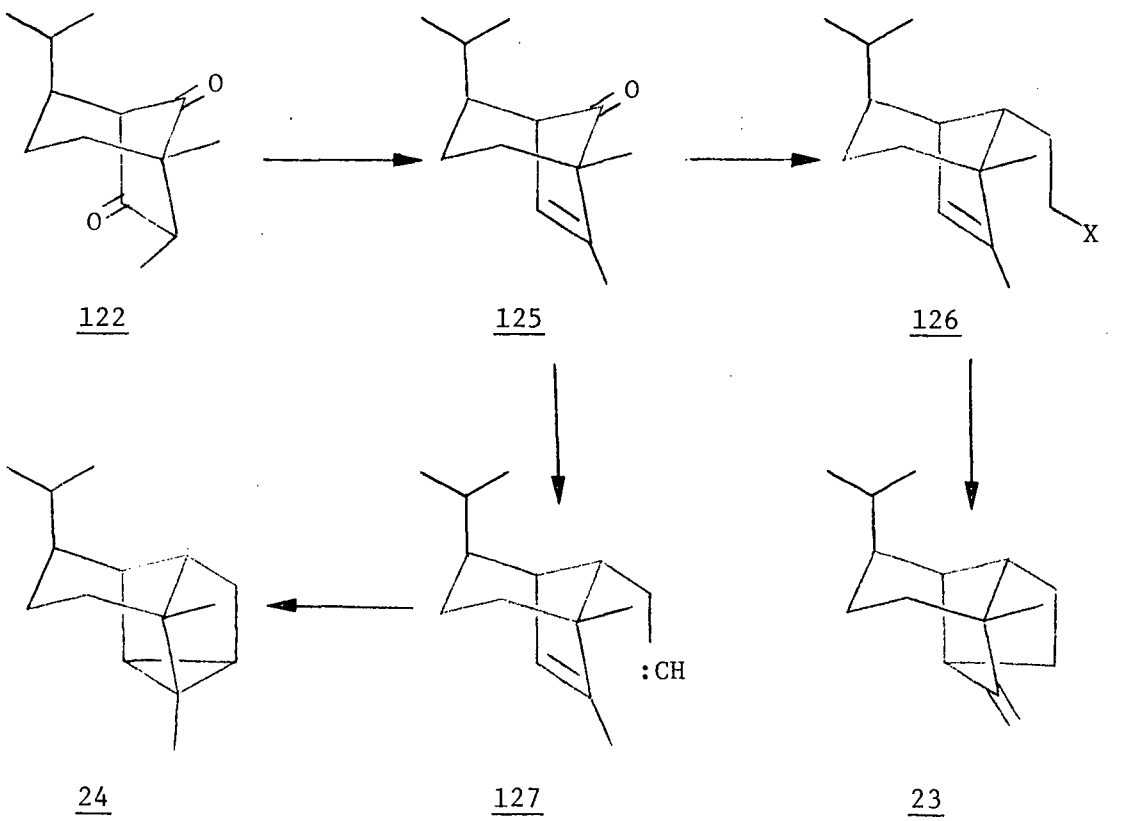
123 122

Even though compound 122 possesses two saturated carbonyl groups, it can readily be seen that only the C_6 carbonyl group (see numbering above) would be capable of enolate formation. Therefore, synthetically, it would be possible to differentiate between the two carbonyl groups. In this manner, it should be possible to introduce at C_8 a two carbon unit with an appropriate leaving group. Intramolecular alkylation of such a compound (124) would be expected to produce copacamphor (11).



122 124 11

By conversion of diketone 122 into the keto olefin (125), and subsequent introduction of appropriate two carbon units at C_8, it was felt that the syntheses of copacamphene and cyclocopacamphene could be accomplished. Thus, it was felt that solvolytic eliminative cyclization of a compound such as 126 could produce copacamphene (23), whereas intramolecular addition to the carbon-carbon double bond of an olefinic carbenoid such as compound 127 could produce cyclocopacamphene (24).



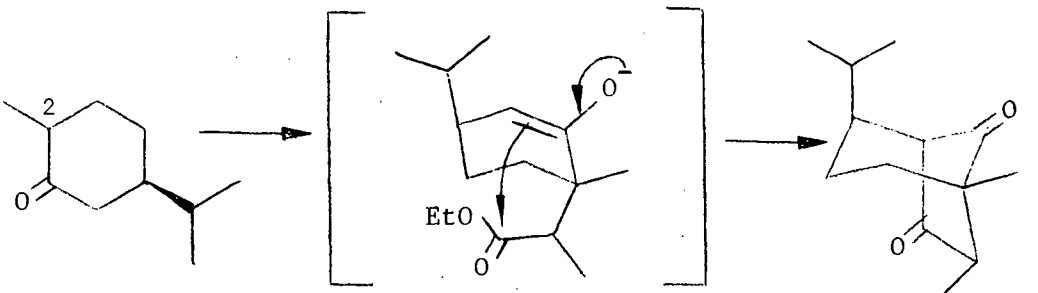
122 125 126

24 127 23

2. Synthesis of the Substituted Bicyclo[3.2.1]octadione 122

The first synthetic objective was the synthesis of the critical intermediate, diketone 122. As mentioned before, the starting material for the preparation of 122 was (+)-carvomenthone (123). This material was prepared by catalytic hydrogenation of commercially available (-)-carvone (128) in ethanol over a Raney nickel catalyst, followed by chromic acid oxidation of the resulting alcohol.

The possibility of forming diketone 122 in a one step reaction, involving alkylation of (+)-carvomenthone (123) with ethyl-2-bromo-propionate, followed by cyclization *in situ* of the resulting keto ester was quite attractive. Once alkylation had taken place at C_2 of (+)-carvomenthone (123), the product could react with base to form the cyclohexanone enolate (129), which could then undergo an intramolecular Claisen condensation to produce the diketone (122).



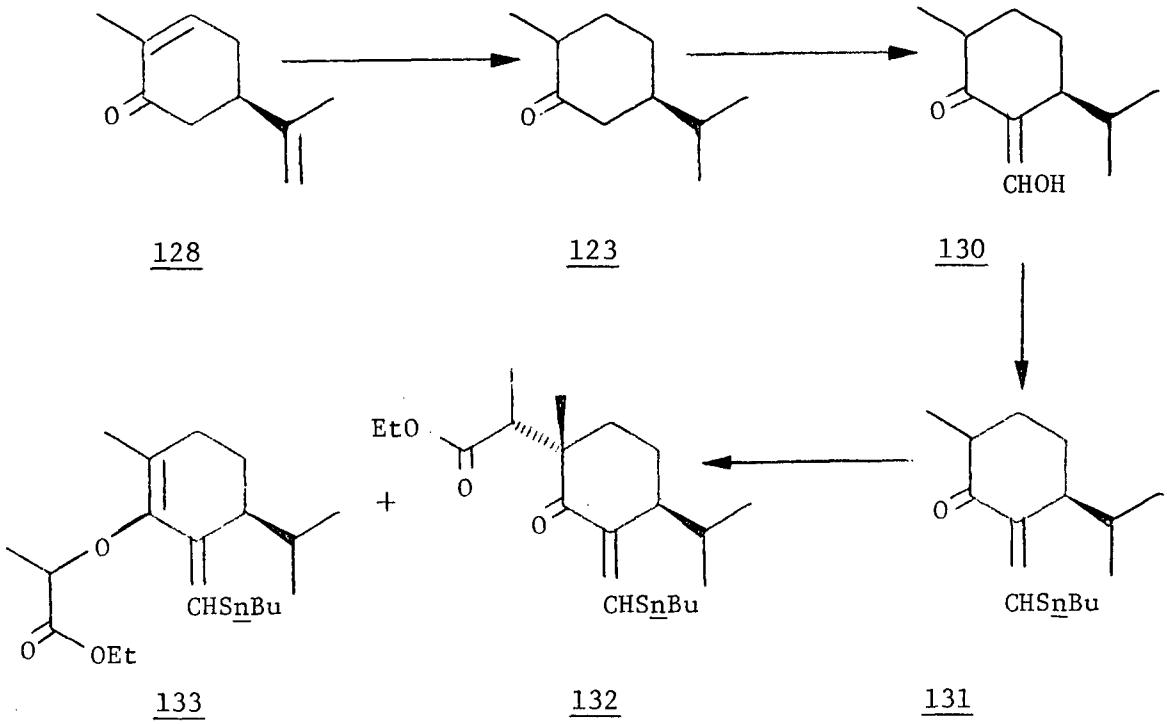
123 129 122

However, extensive experimentation ruled this possibility out, because the initial alkylation was not taking place. Therefore, (+)-carvomenthone (123) was treated with ethyl formate and sodium methoxide in dry benzene to produce the corresponding hydroxymethylene derivative (130) in 83% yield. Reaction of the latter (130) with n-butanethiol in the presence of a catalytic amount of p-toluenesulfonic

acid in benzene afforded the 2-n-butylthiomethylene derivative (131) in 83% yield.

Alkylation of 131 with ethyl 2-bromopropionate in t-butyl alcohol in the presence of potassium t-butoxide[67] gave a mixture of products. Gas-liquid chromatographic analysis indicated that the product consisted of 50% starting material (131), 25% of the desired C-alkylated product (132) and 25% of an undesired O-alkylated product (133).

Analytical samples of both the carbon- and oxygen-alkylated products (132 and 133 respectively) were obtained by preparative g.l.c., and their spectral data were in accord with their assigned structures. In the infrared spectrum of 132, the ester carbonyl and the unsaturated carbonyl absorptions appeared at 5.79 and 6.00 μ respectively. The O-alkylated product (133) exhibited infrared absorptions at 5.78 and 5.99 μ, in accord with ester carbonyl and enolic carbon-carbon double bond absorptions, respectively. The n.m.r. spectra of both of these products were very complex, as each product apparently possessed geometric isomers (with respect to the blocking group) and stereoisomers (with respect to the secondary methyl group adjacent to the ester carbonyl group). Nevertheless, the most distinguishing trait between the n.m.r. spectra of the two products was the appearance of signals due to vinyl methyl groups at τ 8.25 in the O-alkylated product (133) and the absence of these peaks in the C-alkylated products (132).



These results were not acceptable, and led us to investigate this alkylation reaction in more detail. There are a number of variables that can be altered in this type of reaction, such as the structure of the alkylating reagent, the reaction solvent, the size and nature of the cation associated with the enolate anion, and the concentration of the reactants in solution.[68]

Alkylation on the carbon atom of an enolate anion can normally be maximized[68] by utilizing a non-polar reaction solvent such as benzene, small cations (lithium and sodium) associated with the enolate anion, and fairly high concentrations of reactants in solution. However, applying these maximizing parameters to our particular alkylation increased the carbon/oxygen alkylation ratio only slightly.

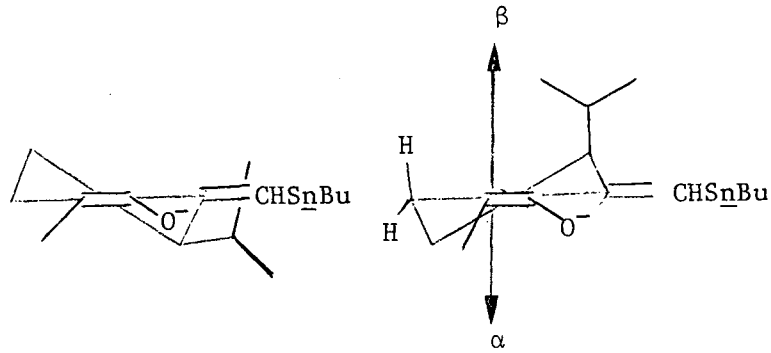
By modifying the alkylating reagent, satisfactory results were obtained. Thus, use of ethyl 2-iodopropionate in place of ethyl 2-bromopropionate, and performing the alkylation in t-butyl alcohol in the presence of potassium t-butoxide, produced the carbon-alkylated product (132) in 73% yield.

Two important features of this reaction are its regioselectivity and its stereoselectivity. Dealing first with the former phenomenon, virtually all recent studies[68] have come to the same conclusion regarding the effect of the leaving group in the alkylating agent on the carbon- vs oxygen-alkylation of enolate anions. For high C/O alkylation ratios the order of preference of leaving groups is $I^- \rangle Br^- \rangle Cl^- \rangle TsO^-$. These leaving groups are arranged in an order of decreasing "softness".[69] The preference for C/O alkylation may be rationalized on the basis of symbiosis, which is the special stabilization associated with the combinations of "hard" acids with "hard" bases, or of "soft" acids with "soft" bases.[70] These terms are qualitatively defined in the following ways[70]: soft base-donor atom is of high polarizability, low electronegativity, easily oxidized, and associated with empty low-lying orbitals; hard base-donor atom is of low polarizability, high electronegativity, hard to oxidize, and associated with empty orbitals of high energy and hence inaccessible. If one considers the ambident anion of compound 131, the carbon centre (C_6) should be a softer base than the oxygen centre. Furthermore, in the alkylating agents, the iodide is a softer base than the bromide. Thus, in ethyl 2-iodopropionate, the carbon centre (C_2) to which the iodide is bonded would be a softer acid than the corresponding carbon centre (C_2) of ethyl 2-bromopropionate. Because of the special

stabilization associated with combination of soft acids with soft bases, the combination of the softer acid (C_2 of ethyl 2-iodopropionate) with the softer base (C_6 of compound 131) would be the more energetically favourable alkylation. In any event, alkylation of compound 131 employing the ethyl 2-halopropionate with an iodide leaving group, as opposed to a bromide leaving group, resulted in the product being completely C-alkylated.

The stereochemistry of alkylation of compound 131 to produce the alkylated derivative 132 is the most critical step in this particular reaction sequence which is concerned with the synthesis of diketone 122. The fact that this alkylation was completely stereoselective was not readily evident from a spectral analysis of compound 132, in that the geometric and stereoisomers of 132 made the spectral interpretation of this compound very difficult. However, removal of the blocking group eliminated the geometric isomerism, and spectral interpretation of the corresponding unblocked alkylated products (vide infra) indicated that the alkylation was completely stereoselective. That the stereochemistry of alkylation of compound 131 was indeed as indicated by structure 132 was not confirmed until the proof of the stereochemistry of diketone 122 (vide infra) was carried out.

If one considers the transition state in this alkylation (131 → 132) to be reactant-like in geometry,[72] then the direction of alkylation can be readily rationalized. The ground state, "half-chair" conformations of 131 are indicated by structures 131a and 131b.



131a 131b

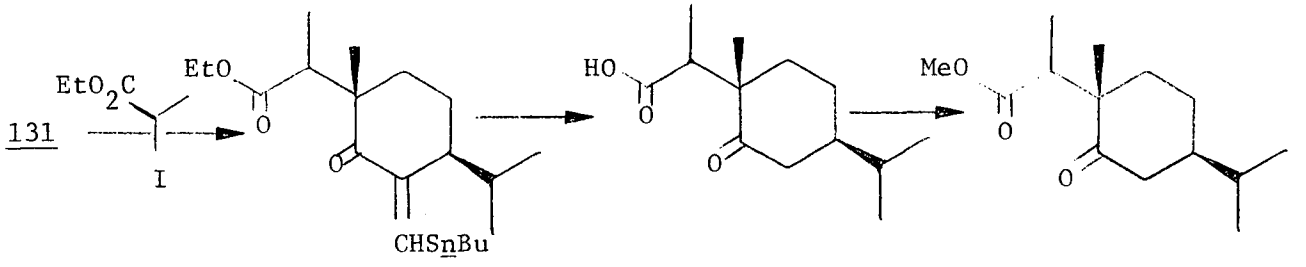
In conformer 131a there exists a sizable $A^{(1,3)}$ strain[71] associated with the exocyclic carbon-carbon double bond of the blocking group and the isopropyl group. Accordingly, 131b would be the preferred conformation in that this conformer would undoubtedly be of lower energy than conformer 131a. If, as suggested by House,[72] the geometry of transition states in alkylations of enolate anions are reactant-like, then it is reasonable to suggest that the relative stabilities of various ground state conformations will be reflected in the relative stabilities of the corresponding transition states. Therefore, in the alkylation of compound 131, the transition state for alkylation should resemble conformer 131b rather than conformer 131a.

In this particular conformer (131b) there are two steric factors which could influence the direction of alkylation. The isopropyl group and the pseudoaxial hydrogen (α- to the vinyl methyl) sterically hinder the approach to the alkylating agent from the β-side* (see 131b) of the molecule. Therefore because of these overriding steric factors

* For stereoelectronic reasons, the enolate anion must attack the alkylating agent perpendicular to the plane of the enolate anion.[73]

the 2-n-butylthiomethylene derivative 131 would be expected to alkylate on the α-side of 131b and produce, stereoselectively, the corresponding alkylated derivative 132.

Treatment of the alkylated n-butylthiomethylene derivative (132) with potassium hydroxide in refluxing aqueous diethylene glycol[67] resulted in the removal of the blocking group and in the hydrolysis of the ethyl ester functionality, affording keto acid 134. Esterification of the latter with an ethereal solution of diazomethane produced the keto ester (135) in 85% yield from compound 132.

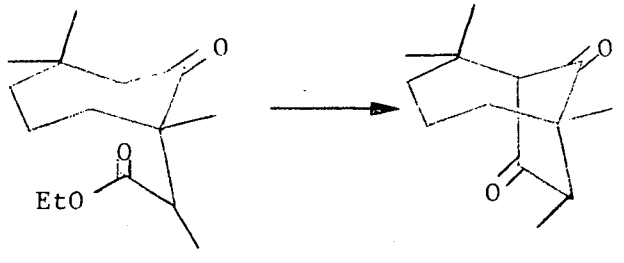


132 134 135

Because of the epimerizable nature of secondary methyl groups adjacent to the carbomethoxy functionality, the keto ester (135) was obtained as an epimeric mixture of diastereomers. No attempt was made to separate these epimers, since it was anticipated that this stereochemical ambiguity would be resolved when the material was cyclized. An analytical sample of the keto ester (135) exhibited spectral data in complete accord with the assigned structure. Accordingly, absorptions at 5.77 and 5.89 μ in the infrared spectrum were attributed to the ester and ketone absorptions respectively. The epimeric mixture (approximately 1:1 ratio) was most evident from the

n.m.r. spectrum (Figure 1). The protons of the methyl groups of the ester functionality appeared as singlets at τ 6.34 and 6.36. The protons adjacent to the ester carbonyl groups were present as quartets at τ 7.00 (J = 7.5 Hz) and 7.13 (J = 7.0 Hz). Two singlets at τ 8.76 and 8.87 were assigned to the tertiary methyl groups whereas the three-proton doublets at τ 8.84 (J = 7.5 Hz) and 8.89 (J = 7.0 Hz) were designated as the secondary methyl groups adjacent to the ester carbonyl groups. Finally, the protons of the isopropyl methyl groups appeared as a doublet (J = 6.0 Hz) at τ 9.09.

A cyclization similar to the type that we desired (keto ester 135 → diketone 122) had been reported by Roberts and co-workers[74] in the synthesis of (±)-culmorin. By reacting keto ester 136 with sodium



136 137

hydride in dimethoxyethane for seventeen hours at 75°, and quenching the reaction with aqueous acetic acid, these workers were able to obtain dione 137 in 67% yield. It should be noted, however, that while the cyclization carried out by Roberts and co-workers produced a substituted bicyclo[4.2.1]nonadione system, our synthetic work neccessitated a cyclization that would produce a substituted bicyclo[3.2.1]octadione system.

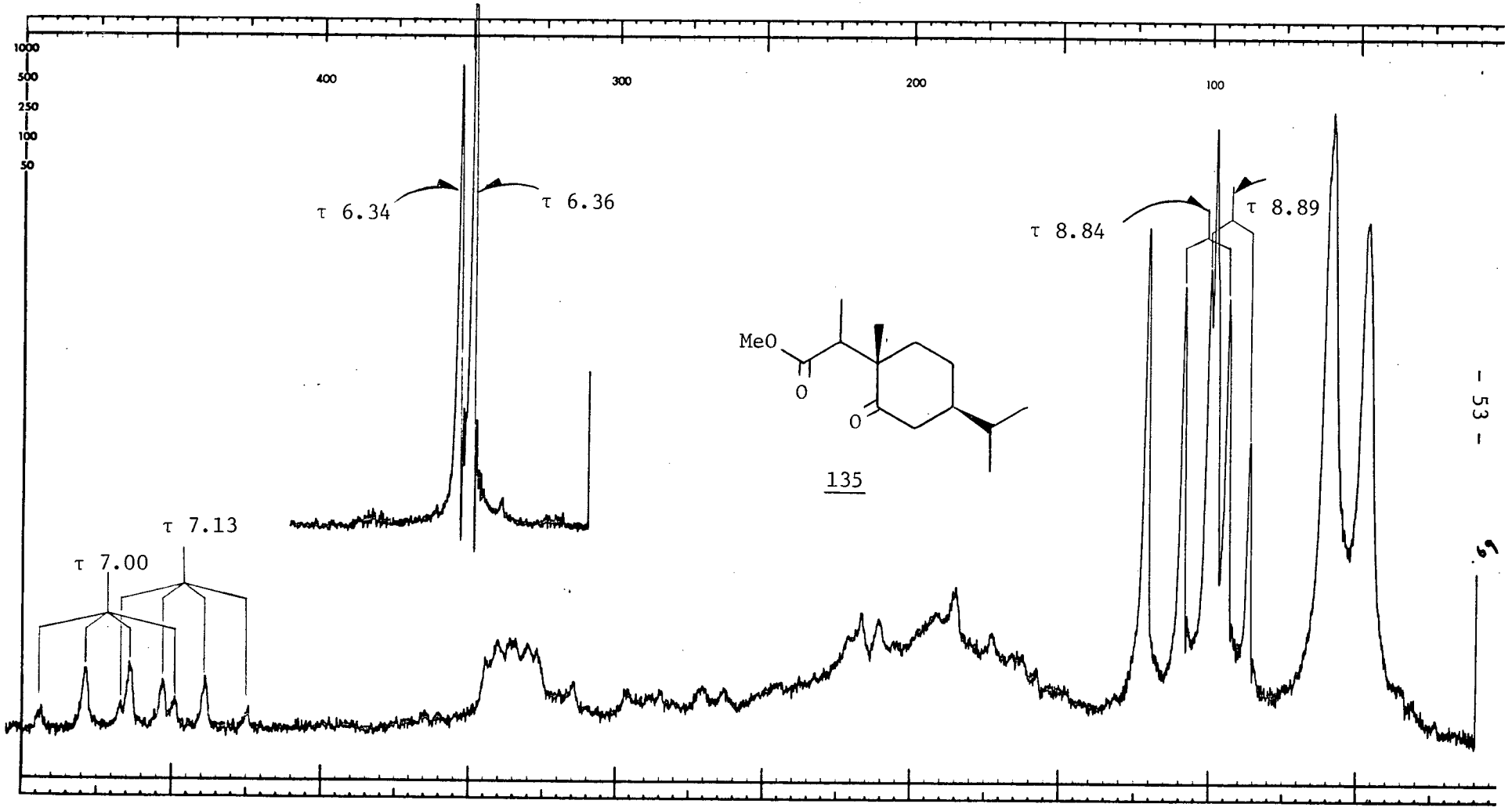
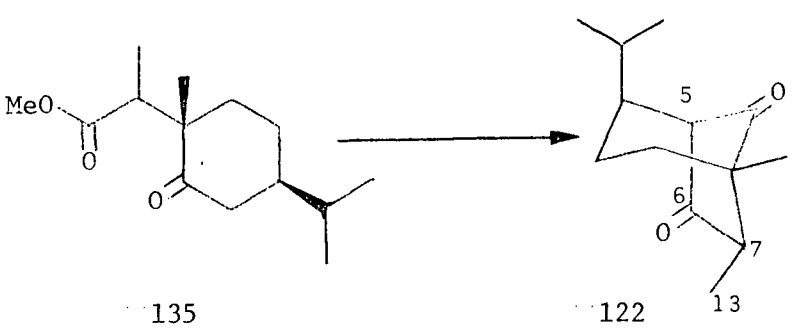


Figure 1. N.M.R. Spectrum of the Keto Ester (135).

When the procedure of Roberts was applied to keto ester 135, the desired diketone was obtained, but only in very poor yield. When sodium hydride is used as a base, the enolate is formed relatively slowly, because the base is only slightly soluble in the solvent. Thus, when the enolate is formed, there would also be present a considerable quantity of the keto ester (135) which had not enolized, setting up the possibility of intermolecular condensation. This could explain the fact that unidentified very high-boiling products were also obtained from this particular reaction.

In view of the fact that sodium hydride was unsatisfactory in effecting the desired intramolecular condensation, it was decided to investigate the use of other bases. It was found that sodium bis(trimethylsilyl)amide[75] was a very useful base for several reasons. It is a white crystalline material that is very stable and easily handled, although somewhat hygroscopic. It is a strong base and quite soluble in most organic solvents. By refluxing the keto ester (135) with sodium bis(trimethylsilyl)amide in dimethoxyethane for one hour, followed by quenching the reaction mixture with aqueous acetic acid, the desired (-)-diketone (122) was obtained in 90% yield, as a white crystalline solid.



135 122

This crystalline material exhibited spectral characteristics which were in complete agreement with the proposed structure 122. The infrared absorptions at 5.66 and 5.79 μ are characteristic of the carbonyl absorptions of this type of bicyclic dione.[74] Furthermore, the n.m.r. spectrum (Figure 2) exhibited a one-proton broadened doublet at τ 7.08 (J = 4.8 Hz) which was designated as the bridgehead proton (C_5H). A one-proton quartet of doublets at τ 7.66 was attributed to C_7 proton ($J_{C_7H-C_{13}H}$ = 7.0 Hz, $J_{C_5H-C_7H}$ = 1.5 Hz), with the secondary methyl appearing as a doublet (J = 7.0 Hz) at τ 8.75. These assignments were confirmed by a frequency-swept decoupling experiment in which the C_7 proton was irradiated causing the signal at τ 7.08 to appear as a clean doublet (J = 4.8 Hz), and the doublet at τ 8.75 to collapse to a singlet. The three-proton singlet at τ 8.90 and the three-proton doublets (J=6.0Hz) at τ 9.00 and 9.10 were assigned as the tertiary methyl group and the isopropyl methyl groups respectively.

There are two stereochemical features of the (-)-diketone (122) which warranted further investigation. These are the stereochemistry at C_7 and at C_1 of 122. The former stereochemical point refers to the orientation of the secondary methyl group at C_7. With regard to the latter (C_1), it should be noted that the factors which affect the stereochemical outcome of the alkylation of cyclohexanone derivatives are not well understood in detail.[72] Therefore, it was rather difficult to predict a priori, and with complete certainty, the stereochemistry of the alkylation (131 → 132). Thus, it became necessary to obtain unambiguous proof concerning this point. It was subsequently proved that this alkylation produced a product in which the isopropyl and propionate groups were in a trans relationship.

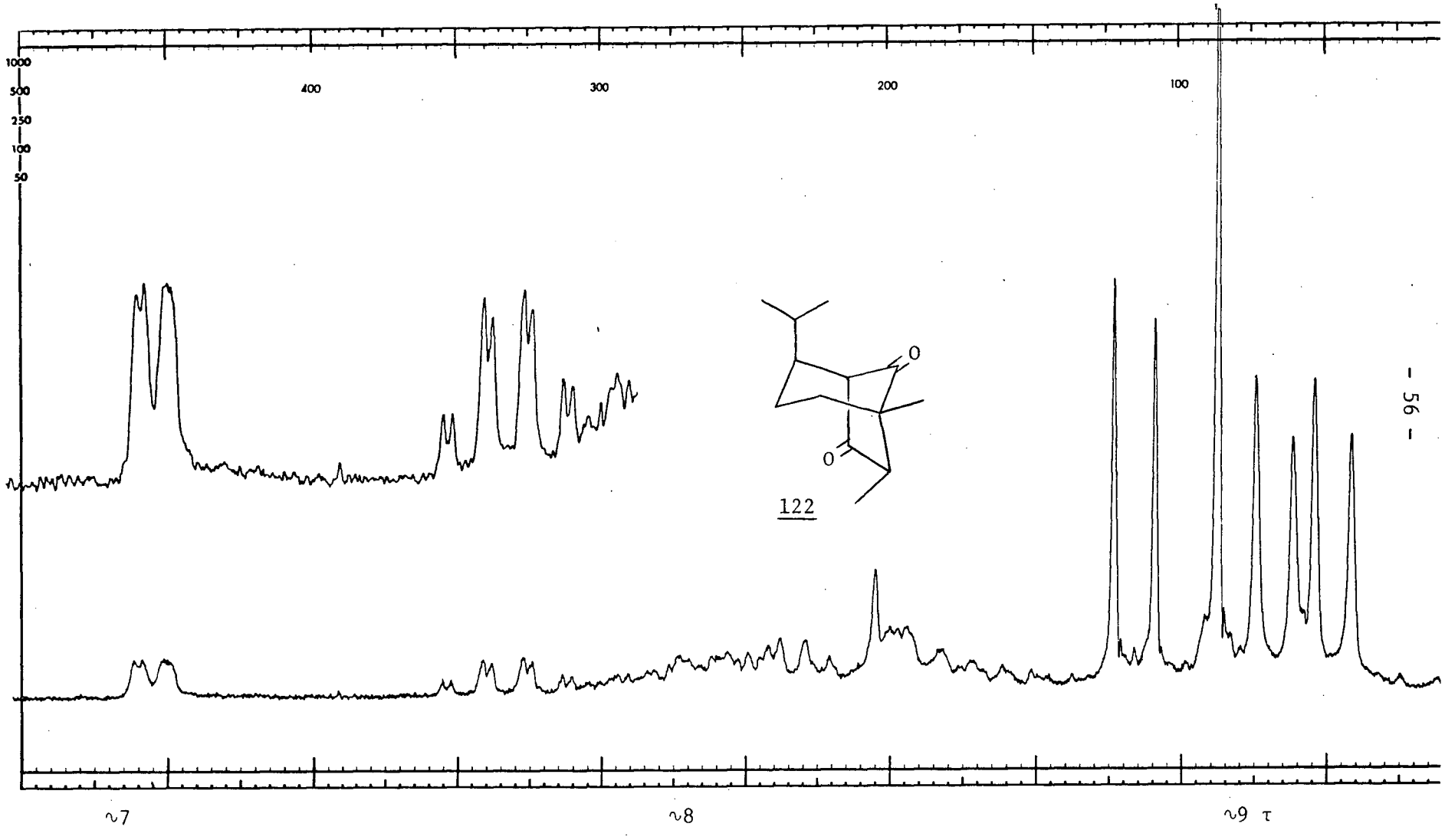
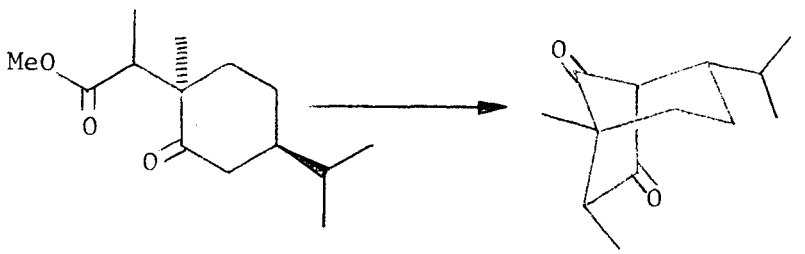


Figure 2. N.M.R. Spectrum of the (-)-Diketone (122).

3. Stereochemical Proof of Diketone 122

It was felt the easiest and synthetically most satisfying method of establishing the C_1 stereochemistry would be the unambiguous synthesis of a compound which possessed isopropyl and propionate groups in a cis relationship to each other. These stereochemical features are present in the keto ester (138). The latter could in turn be cyclized to produce the substituted bicyclo[3.2.1]octadione (139).

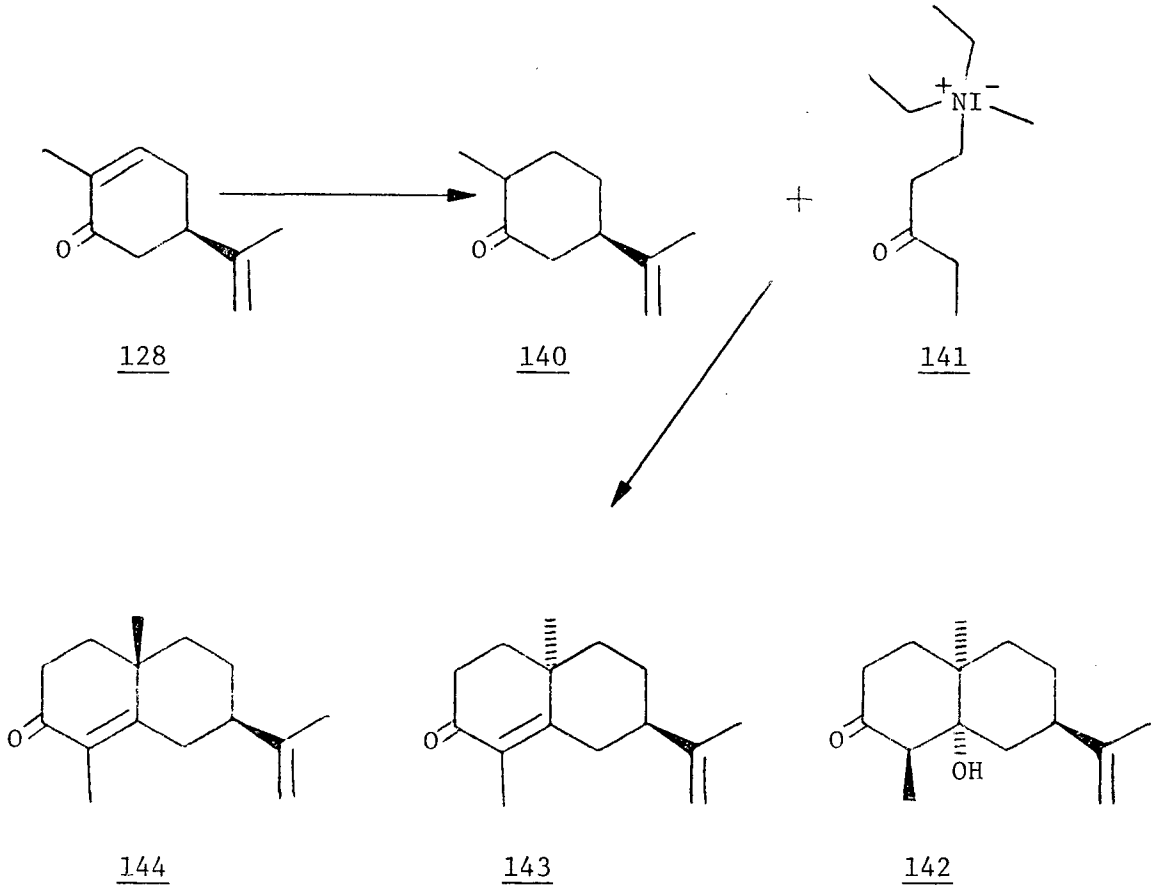


138 139

It was felt that these compounds (138 and 139) would have great synthetic utility. The synthesis of 138 would resolve the stereochemistry at C_1 of diketone 122 (and the corresponding alkylated cyclohexane derivatives 132 and 135). Also, the synthesis of diketone 139 would provide a potentially useful synthetic intermediate to the "ylango"-type sesquiterpenoids. That is, the latter natural products could be obtained from diketone 139 in a manner analogous to that outlined for the conversion of diketone 122 to the "copa"-type sesquiterpenoids (see page 44).

The starting material chosen for this unambiguous synthesis of diketone 139 was, as before, (-)-carvone (128). Birch reduction of (-)-128 with sodium in liquid ammonia in the presence of ethanol,

followed by chromic acid oxidation of the resulting alcohol gave, in 80% yield, (+)-dihydrocarvone (140).[76] It was found that this method was superior to the well known reduction of (-)-carvone with zinc and sodium hydroxide in ethanol,[77] especially in large scale reactions. Condensation of (+)-dihydrocarvone (140) with 1-diethylamino-3-pentanone methiodide (141) in the presence of a sodium amide afforded mainly the (+)-ketol (142), accompanied by an epimeric mixture of (-)-7-epi-α-cyperone (143) and (+)-α-cyperone (144).[78]



128 140 141

144 143 142

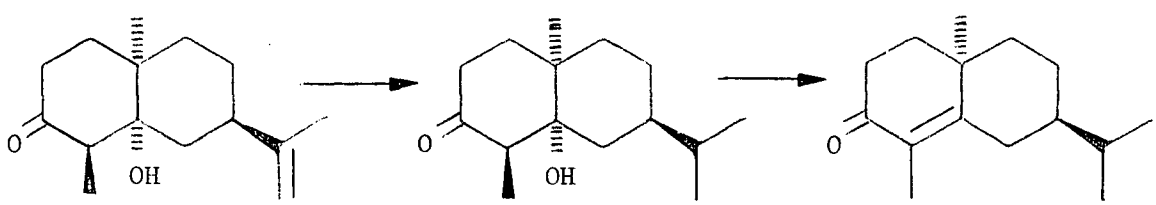
The (+)-ketol (142) was separated from the epimeric cyperones by fractional crystallization. Recrystallization of the ketol, which is of known absolute configuration,[78] afforded a colourless crystalline material which exhibited spectral properties in complete agreement with structure 142 and with the data reported in the literature[78] for this compound. Accordingly, the infrared spectrum showed a hydroxyl absorption at 2.96 μ, a saturated carbonyl absorption at 5.92 μ, and isopropenyl double bond absorptions at 6.14 and 11.28 μ. The n.m.r. spectrum exhibited an unresolved multiplet at τ 5.35 corresponding to the exocyclic methylene group protons, and the vinyl methyl group appeared as a doublet (J = 1.0 Hz) at τ 8.33. The singlet at τ 8.77 was assigned to the tertiary methyl group, whereas the doublet (J = 6.5 Hz) at τ 8.97 was attributed to the protons of the secondary methyl group.

Hydrogenation of the (+)-ketol (142) in ethanol with 10% palladium on charcoal as a catalyst afforded the crystalline (+)-dihydro ketol (145). Of particular note in the infrared spectrum of this material was the absence of any olefinic double bond absorptions. Consistent with this, there were no olefinic protons evident in the n.m.r. spectrum of 145. However, a six-proton doublet (J = 6.0 Hz) at τ 9.16 could be attributed to the newly created isopropyl group. The tertiary methyl group (a singlet at τ 8.75) and secondary methyl group (a doublet at τ 8.94, J = 7.0 Hz) were also evident.

Condensation of the more readily available (+)-carvomenthone (123) with 1-diethylamino-3-pentanone methiodide (141), in a manner analogous

to that reported for (+)-dihydrocarvone, did produce mainly the (+)-dihydro ketol (145), accompanied by the isopropyl analogs of compounds 143 and 144. However, purification of this material was more difficult than the corresponding purification of (+)-ketol 142 owing to the fact that the (+)-dihydro ketol (145) did not crystallize out of the condensation mixture. Thus, extensive column chromatography had to be used in order to obtain the (+)-ketol 145 in a pure form.

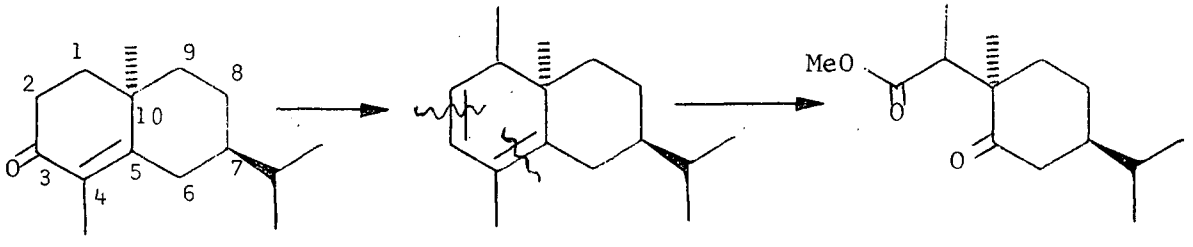
The (+)-dihydro ketol (145) was dehydrated to the corresponding (-)-unsaturated ketone (146) by treatment of the former with refluxing alcoholic potassium hydroxide. The spectral properties of the product were in agreement with structure 146. Of particular pertinence were the ultraviolet spectrum (λ_{max} 250 mμ, ε = 15,800) and infrared spectrum (λ_{max} 6.05 μ), which clearly indicated the presence of the α,β-unsaturated carbonyl group. In the n.m.r. spectrum, the vinyl methyl group appeared as a doublet (J = 1.7 Hz) at τ 8.23. The tertiary methyl group (singlet at τ 8.74) and the isopropyl group (doublet at τ 9.09, J = 6.0 Hz) were also readily evident.



142 145 146

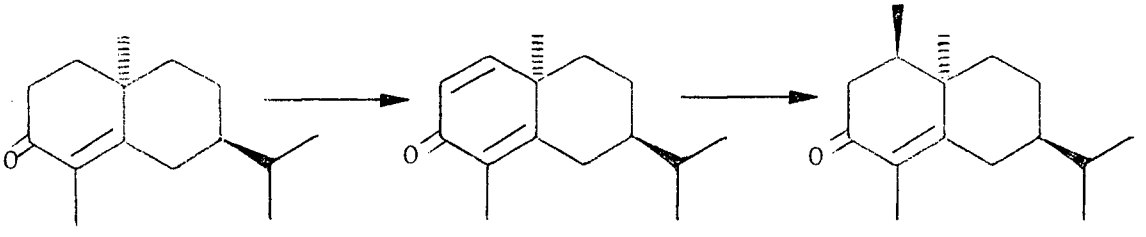
The utility of compound 146 in the stereochemically unambiguous synthesis of dione 139 is now more obvious. Although compound 146 is bicyclic, the saturated ring contains an isopropyl group and a tertiary

methyl group (at asymmetric centres C_7 and C_{10} respectively, see structure 146 for numbering*) of known absolute stereochemistry. Furthermore, the carbon-carbon double bond (of 146) could presumably be converted to a carbonyl group (at C_5) by ozonolysis. In order to obtain a compound such as keto ester 138 in which the isopropyl and propionate groups were in a *cis* orientation to each other, a methyl group would have to be introduced at C_1 of 146, and also oxidative cleavage of the C_2-C_3 and C_4-C_5 would be required.



146 138

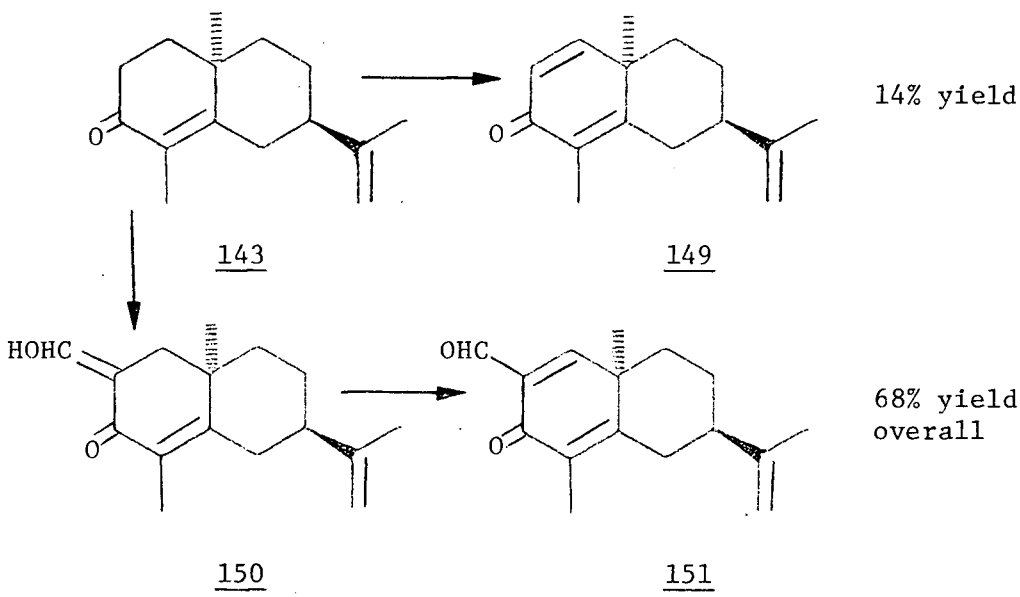
The obvious means of introducing a methyl group at C_1 of 146 would be first to subject this compound to 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[79] oxidation in order to obtain the cross-conjugated dienone (147). The latter (147) could undergo conjugate methylation to produce the alkylated product 148.



146 147 148

* It is now general practice to number eudesmane-type sesquiterpenoids according to the steroid numbering system, as indicated by formula 146.

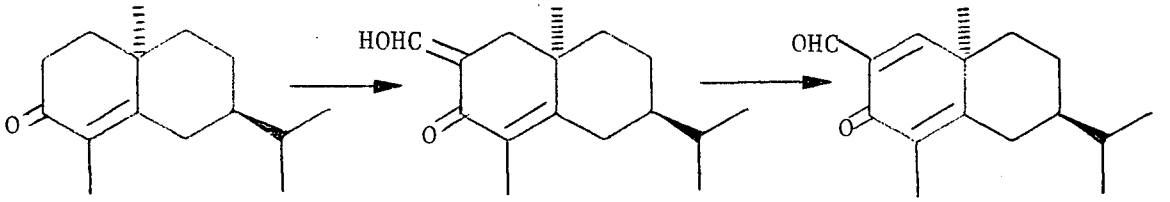
However, in our laboratory, the DDQ oxidation of epi-α-cyperone (143) to the corresponding cross-conjugated dienone (149) was found to be a very poor yielding process.[80] It was subsequently shown that by introducing a hydroxymethylene group at the C_2 position of compound 143, and then performing the DDQ oxidation, a good yield of the corresponding cross-conjugated dienone aldehyde (151) could be obtained.[80]



Accordingly, condensation of (-)-dihydro-epi-α-cyperone (146) with ethyl formate in the presence of sodium methoxide in dry benzene afforded the (-)-2-hydroxymethylene derivative (152) in 96% yield. This crystalline material exhibited the expected spectral properties. Of particular interest was the ultraviolet spectrum (λ_{max} 260 and 311 mμ), characteristically shifting (λ_{max} 256 and 358 mμ) by the addition of sodium hydroxide. In the n.m.r. spectrum, signals at τ-4.17 and 2.61 indicated the presence of the hydroxymethylene protons.

Dehydrogenation of the (-)-hydroxymethylene derivative (152) with

DDQ[79] in dioxan for ten minutes afforded the (+)-2-formyl cross-conjugated dienone (153), in 78% yield, as a pale yellow crystalline material. Again, the spectral data were in complete agreement with the structural assignment of 153. Of note was the appearance in the n.m.r. spectrum of the aldehydic proton as a singlet at τ 1.20. Also present was a singlet at τ 2.45 corresponding to the vinyl proton. Other assignable signals were similar in chemical shift and multiplicity to that of compound 146.



146 152 153

The introduction of the secondary methyl group at C_1 was accomplished by the conjugate addition of lithium dimethylcuprate[81,82] to the cross-conjugated dienone system of compound 153. This reagent was chosen for the conjugate addition since it had been shown to be of greater general utility than the copper-catalyzed methylmagnesium halide reagents.[83] In particular, the lithium dimethylcuprate reagent gives virtually no 1,2-addition products[81] and affords higher yields of the desired product[84] than the Grignard reagents. When there are two conjugate addition sites, (as in compound 153) this reagent will alkylate in a regioselective manner, giving substitution only at the less hindered position. Furthermore, this reagent usually reacts in a

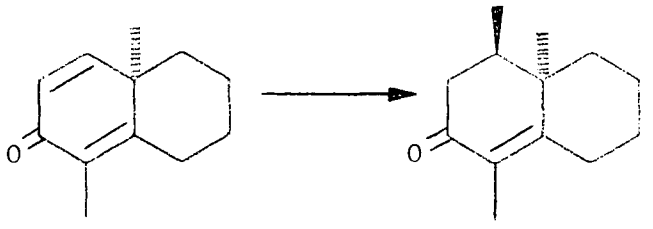
stereoselective manner, a feature that was not essential in this sequence, but is always synthetically pleasing.

Since the conjugate addition of the dimethylcuprate reagent to the cross-conjugated dienone system of 153 would generate a specific enolate anion, it was thought to be desirable to trap this enolate anion with acetyl chloride.[85] It was expected that the resulting enol acetate would be of greater synthetic utility than the corresponding hydroxymethylene derivative which would be obtained by quenching the enolate anion with a proton source.

The lithium dimethylcuprate addition to compound 153 was carried out at 0° and the reaction mixture was quenched with an excess of acetyl chloride. In order to ensure basic work-up conditions, the quenched solution was immediately poured into a rapidly stirred ice-ammonium hydroxide solution, and the organic portion was quickly separated. The enol acetate (154) thus obtained was somewhat unstable and the crude product was used directly in the next reaction. However, an analytical sample was obtained by preparative g.l.c. and the spectral data indicated that the reaction had been completely regioselective and stereoselective. In the infrared spectrum, absorptions at 5.66 and 5.99 μ were characteristic of an enol acetate absorption, while the unsaturated carbonyl group and the olefinic double bond absorptions were recorded at 5.99 and 6.21 μ respectively. That the desired conjugate addition had taken place was quite evident from the n.m.r. spectrum. In addition to the signals of the vinyl methyl group (a broad singlet at τ 8.14), the tertiary methyl group (a singlet at τ 8.83), and the isopropyl methyl groups (poorly resolved multiplets at τ 9.07),

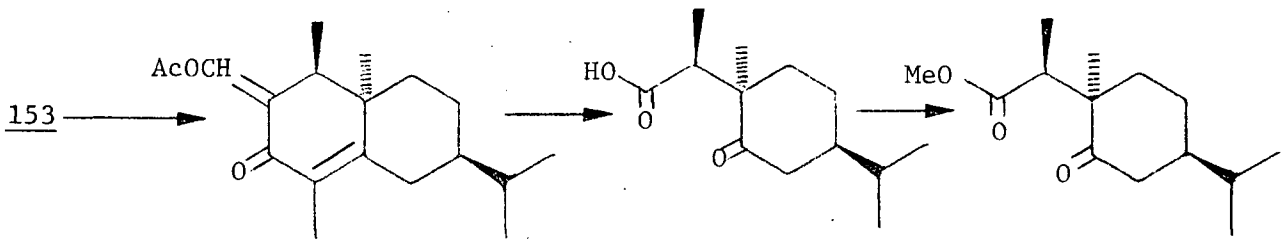
the vinyl proton appeared as a singlet at τ 1.80, the acetyl methyl group appeared as a singlet at τ 7.77 and the newly introduced secondary methyl group was evident as a doublet (J = 7.0 Hz) at τ 8.97.

It is perhaps pertinent to deal briefly with the stereochemistry assigned to compound 154. It has been proposed that in 1,4-conjugate addition reactions of the type employed to produce compound 154, the alkylating agent must attach the β-carbon of the α,β-unsaturated ketone in a manner perpendicular to the π-electron system.[86] Attack on this site may occur from the α-side or the β-side of the molecule. In the particular reaction under discussion, α-attack is not favoured due to the significant steric interactions of the approaching alkylating reagent with the tertiary methyl group. On the other hand, β-approach would be significantly less hindered and alkylation would thus be expected to occur from the side making the secondary methyl group β-oriented. That the conjugated addition of lithium dimethylcuprate to dienones of this type (154) proceeds to give the corresponding trans-vicinal methyl groups has clear literature precedent. This is well illustrated by the conjugate addition of lithium dimethylcuprate to dienone 155, to afford octalone 156 which possesses trans-vicinal methyl groups.[87]



155 156

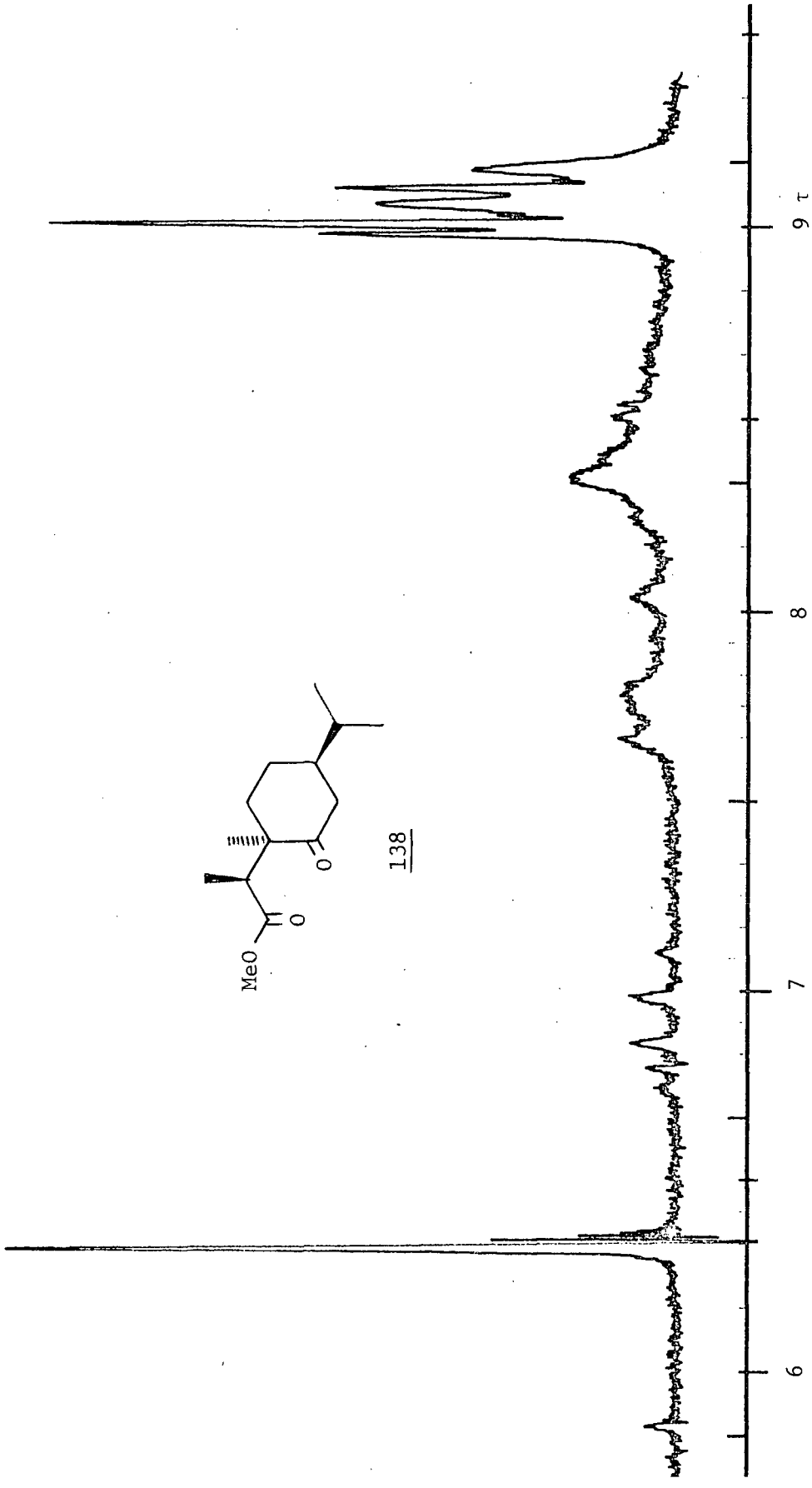
Ozonolysis of the enol acetate (154) in ethyl acetate at -78°, followed by an oxidative workup (aqueous sodium hydroxide and hydrogen peroxide at 90° for approximately one hour)[88] afforded the keto acid 157. This material was esterified by treatment with ethereal diazomethane to produce the (+)-keto ester (138) in 45% yield from the cross-conjugated dienone (153).



154 157 138

The spectral data of the (+)-keto ester (138) were in complete accord with the assigned structure. Accordingly, the infrared spectrum showed ester carbonyl and ketone carbonyl absorptions at 5.76 and 5.85 μ respectively. The n.m.r. spectrum (Figure 3) revealed a singlet at τ 6.34 in accord with the protons of the methyl ester functionality. The proton adjacent to the ester carbonyl group appeared as a quartet (J = 7.2 Hz) at τ 6.93, and the secondary methyl group appeared as a doublet (J = 7.2 Hz) at τ 9.04. The singlet at τ 9.01 and the doublets (J = 6.0 Hz) at τ 9.09 and 9.10 accounted for the tertiary and isopropyl methyl groups, respectively.

Direct comparison of the infrared spectrum of keto esters 135 and 138 was not practical in that the former was an epimeric mixture of diastereomers whereas the latter was completely homogeneous.



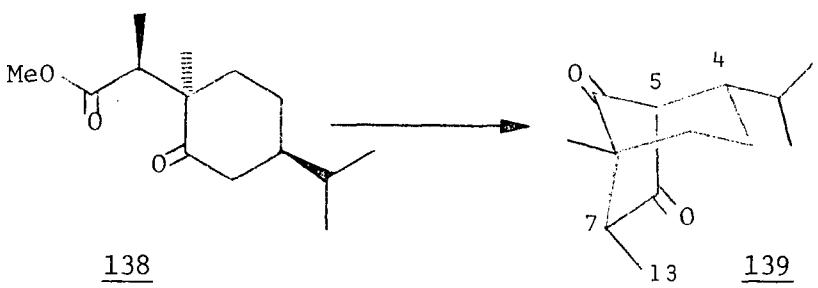
138

Figure 3. N.M.R. Spectrum of the (+)-Keto Ester (138).

However, as mentioned previously, the n.m.r. spectrum of 135 revealed a distinct set of signals for each of the two diastereomers and it was relatively easy to show that the n.m.r. spectrum of the (+)-keto ester (138) was quite different from that of either of the keto ester epimers (135).

Thus, as just described, the (+)-keto ester 138, with the isopropyl group and propionate group in a trans-relationship, had been synthesized unambiguously. Since this compound (138) was different from either of the epimers of keto ester (135), this clearly established that the relationship between the isopropyl group and propionate group of compound 135 was cis, and provided irrefutable proof for the stereochemistry of the alkylated cyclohexanone derivatives 132, 134 and 135.

The difference between the keto esters 135 and 138 was further confirmed by their different chemical behaviour. When the intramolecular cyclization of 138 was attempted, employing the same reaction conditions that were used in the preparation of diketone 122, the desired diketone 139 was obtained, but in very low yield.



138 139

However, by changing the solvent and reaction conditions, better results were obtained. A solution of the (+)-keto ester (138) in dry benzene was added over a period of one hour to a refluxing solution

of sodium bis(trimethylsilyl)amide in benzene, and the reaction mixture was then refluxed for an additional one and one-half hours. The reaction mixture was quenched with aqueous acetic acid in the usual manner to afford the (+)-diketone (139) in 60% yield.

The spectral properties of the crystalline (+)-diketone (139) were in complete accord with the assigned structure, and were similar to, but not identical with, those of its epimer, the (-)-diketone (122). In the infrared spectrum of compound 139, the carbonyl absorptions appeared at 5.66 and 5.80 μ.[74] In the n.m.r. spectrum (Figure 4) a one-proton multiplet at τ 7.10 was assigned to the bridgehead proton (C_5H), whereas the one-proton quartet of doublets (τ 7.71, $J_{C_7H-C_{13}H}$ = 7.3 Hz, $J_{C_5H-C_7H}$ = 1.5 Hz) was attributed to the proton at C_7. The secondary methyl group appeared as a doublet (J = 7.3 Hz) at τ 8.83. The singlet at τ 8.90 and the doublets (J = 6.3 Hz) at τ 9.02 and 9.15 were designated as the tertiary and isopropyl methyl groups respectively. The most distinguishing property between diketones 122 and 139 however, was the rotation (diketone 139, $[\alpha]_D$ + 100°; diketone 122, $[\alpha]_D$ -56°).

The successful synthesis of the (+)-diketone (139), besides corroborating the conclusions previously outlined regarding the stereochemistry of the keto ester 135, also provided a potentially useful synthetic intermediate for the "ylango-"type sesquiterpenoids.

Although, as just outlined, the stereochemistry at C_1 of diketone 122 had been established conclusively, the stereochemistry of the secondary methyl group at C_7 still remained unresolved. In this connection, it is pertinent to point out that the diketone 137 which

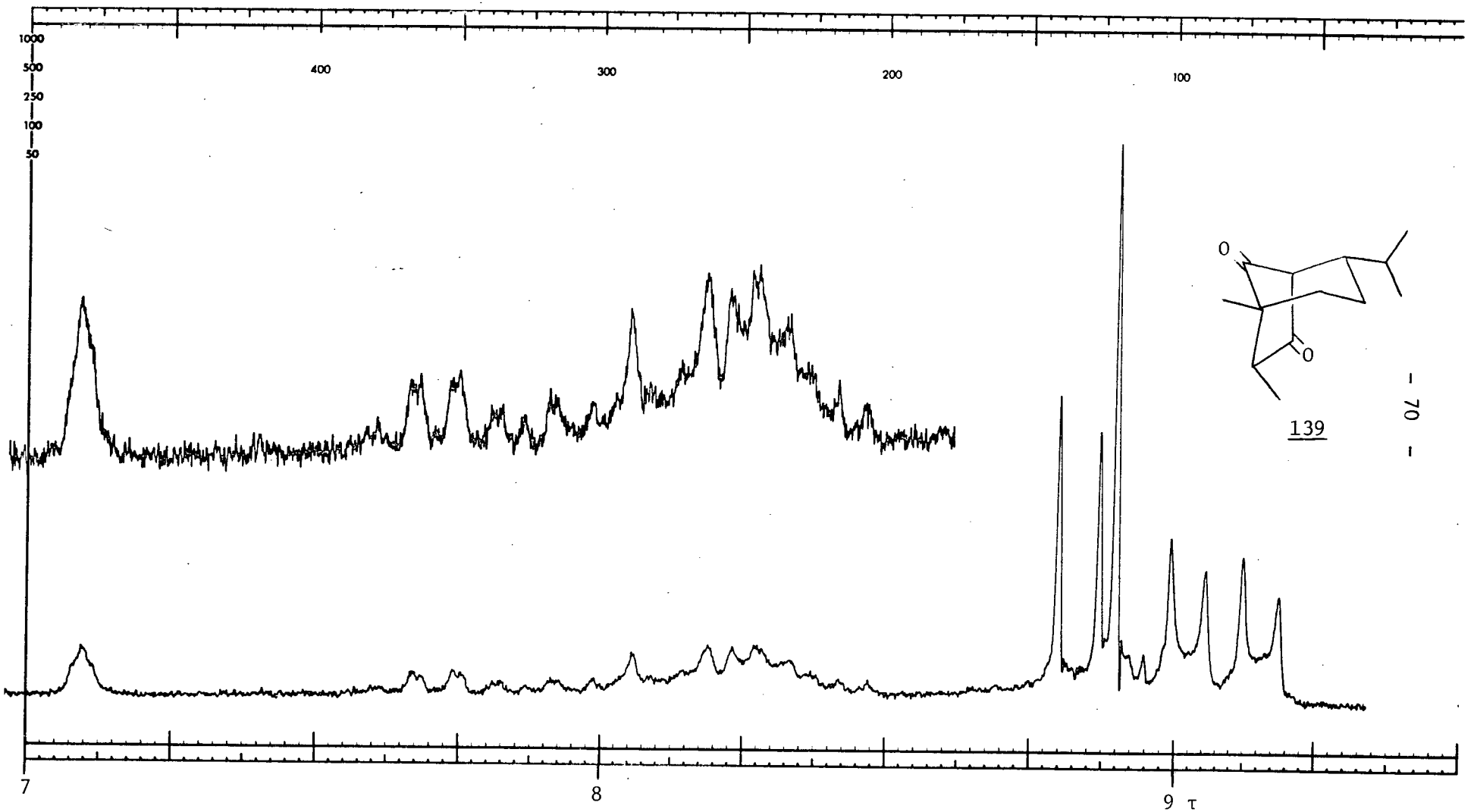
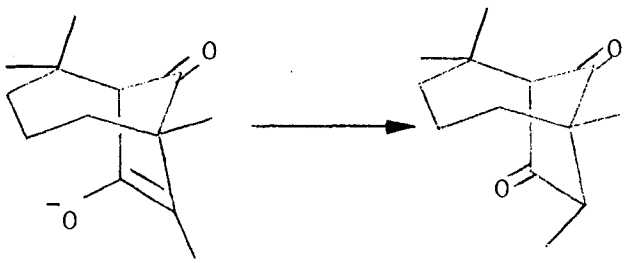


Figure 4. N.M.R. Spectrum of the (+)-Diketone (139).

Roberts and co-workers[74] utilized in their synthesis of culmorin had been assigned the stereochemistry as depicted by 137. Their study of a

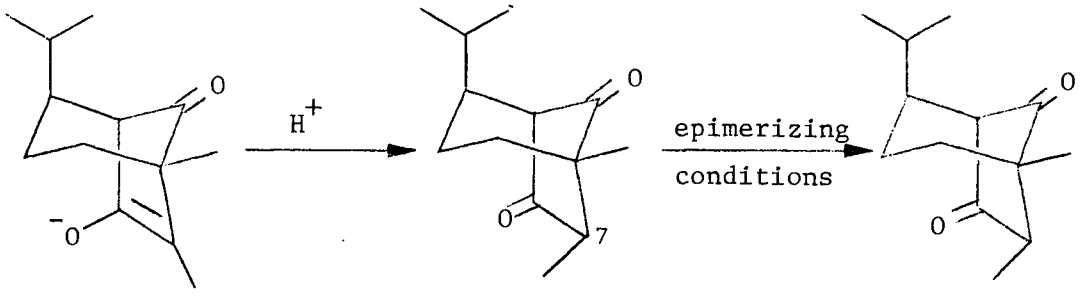


158 137

molecular model of the bicyclo[4.2.1]nonane system revealed that approach of any reagent to the five-membered ring should be strongly directed to the face opposite the four-carbon bridge, due to steric interference by the latter. Accordingly, diketone 137 was envisaged to arise via stereoselective kinetically controlled protonation of enolate 158 from the side opposite the four-carbon bridge.

Even though our ring system was a bicyclo[3.2.1]octane, it was felt that the steric effect of the three-carbon bridge should be similar to that of the four-carbon bridge, so that stereoselective kinetic protonation of enolate 159 should result in the formation of diketone 122. However, diketone 122 was also found to be the thermodynamically more stable diketone. That is, when diketone 122 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 verified by changing the solvent from water to deuterium oxide in the above reaction. In this case, deuterium was incorporated

at C_7, as shown by n.m.r.[89]



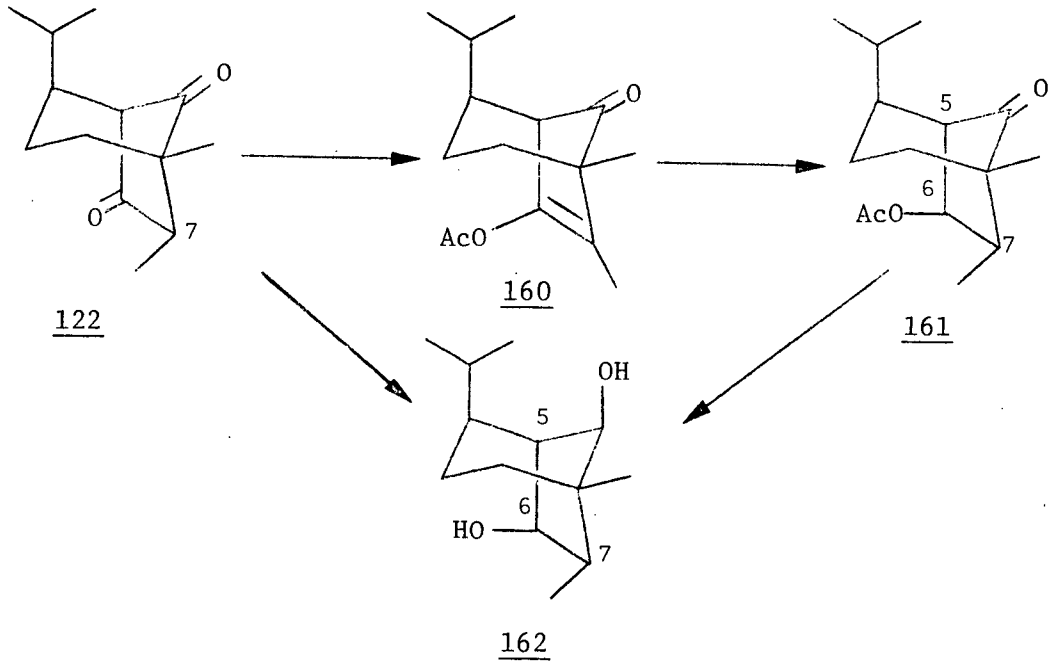
159 122

Because the product from protonation of the enolate anion 159 is the thermodynamically more stable product and not solely the product of kinetic control, the argument for stereoselective kinetic protonation as a stereochemical proof was not valid. Therefore a chemical proof regarding this point was sought and the stereochemistry at C_7 of compound 122 was established conclusively by the following reaction sequence.

The (-)-diketone (122) was treated with sodium bis(trimethylsilyl)-amide in benzene at room temperature and the resulting solution was quenched with acetyl chloride to afford the corresponding keto enol acetate (160). Hydrogenation of the latter with Adams catalyst in ethanol produced the keto acetate (161). It is apparent from the study of a molecular model of 160, that hydrogenation should occur only from the least hindered exo side of the double bond, that is, the side away from the three-carbon bridge. Reduction of compound 161 with lithium aluminum hydride afforded the crystalline diol 162. Again, the approach of the reducing agent to the ketone carbonyl group of compound 161 would be expected to take place from the least hindered side, producing the hydroxyl group at C_8 with stereochemistry as

indicated by structure 162.

When the (-)-diketone (122) was subjected to reduction with either sodium borohydride or lithium aluminum hydride the same crystalline diol (162) was obtained.[89]

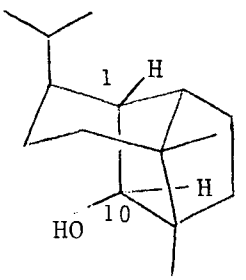


122 160 161 162

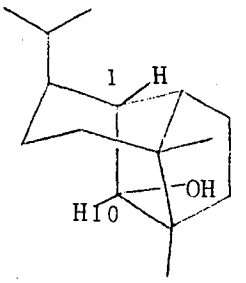
Since the configuration at C_7 of the keto acetate (161) was almost certainly as shown (hydrogenation of 160 from the less hindered side) and since the nonepimerizable reductions of compound 161 and of the diketone 122 produced the same diol (162), therefore the stereochemistry at C_7 of the diketone 122 was as indicated by structure 122.

The n.m.r. spectra of compounds 161 and 162 served to confirm the assigned structures. The proton at C_6 in both compounds appeared as a pair of doublets. That the hydrogenation (160 → 161) had indeed

taken place in a cis manner from the less hindered exo side of the double bond in compound 160 was confirmed by the observed coupling constants, $J_{C_5H-C_6H}$ and $J_{C_6H-C_7H}$. Thus, molecular models indicated that the dihedral angle between the protons in C_6 and C_7 of compounds 161 and 162 was nearly 0°, and, in agreement with the Karplus equation,[90] the observed coupling constants, $J_{C_6H-C_7H}$ was 10.5 Hz in each case. Similarly, in each of compounds 161 and 162, $J_{C_5H-C_6H}$ was found to be approximately 7.5 Hz. Again, this was in agreement with the Karplus equation,[90] since the dihedral angle between the protons on C_5 and C_6 was, on the basis of molecular models, approximately 15-25°. Moreover, copaisoborneol (13) has a similar dihedral angle between protons at C_1 and C_{10} (see below for numbering) and the reported coupling constant $J_{C_1H-C_{10}H}$ was 8.0 Hz.[11] On the other hand, the proton at C_{10} in copaborneol (12) appeared as a broad singlet, because the dihedral angle between protons at C_1 and C_{10} in this compound is approximately 90°.



13



12

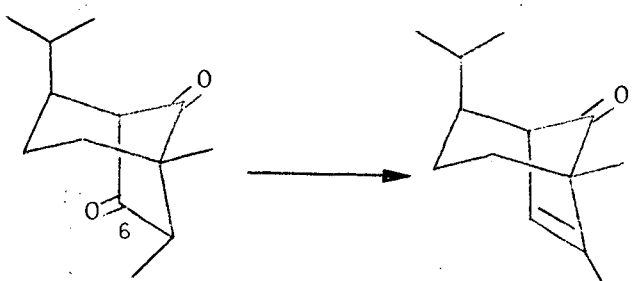
The intermediate (-)-diketone (122) was successfully utilized in the synthesis of (+)-copacamphor (11)* (-)-copacamphene (23) and (-)-cyclocopacamphene (24). The synthesis of (+)-copacamphor[13] which was carried out in a manner similar to the scheme outlined on page 43,

* See the footnote on page 41.

will not be discussed in this thesis, as it represents a portion of the Ph.D. thesis of my co-worker R.J. Keziere.

4. Synthesis of the Substituted Bicyclo[3.2.1]octenone 125

For the synthesis of (-)-copacamphene and of (-)-cyclocopacamphene (as outlined on page 44) it was necessary to introduce an olefinic double bond ($\Delta^{6,7}$) into the diketone (122). As indicated previously, it was planned to use the carbonyl group at C_6 as a "handle" in accomplishing this transformation (diketone 122 → keto olefin 125).

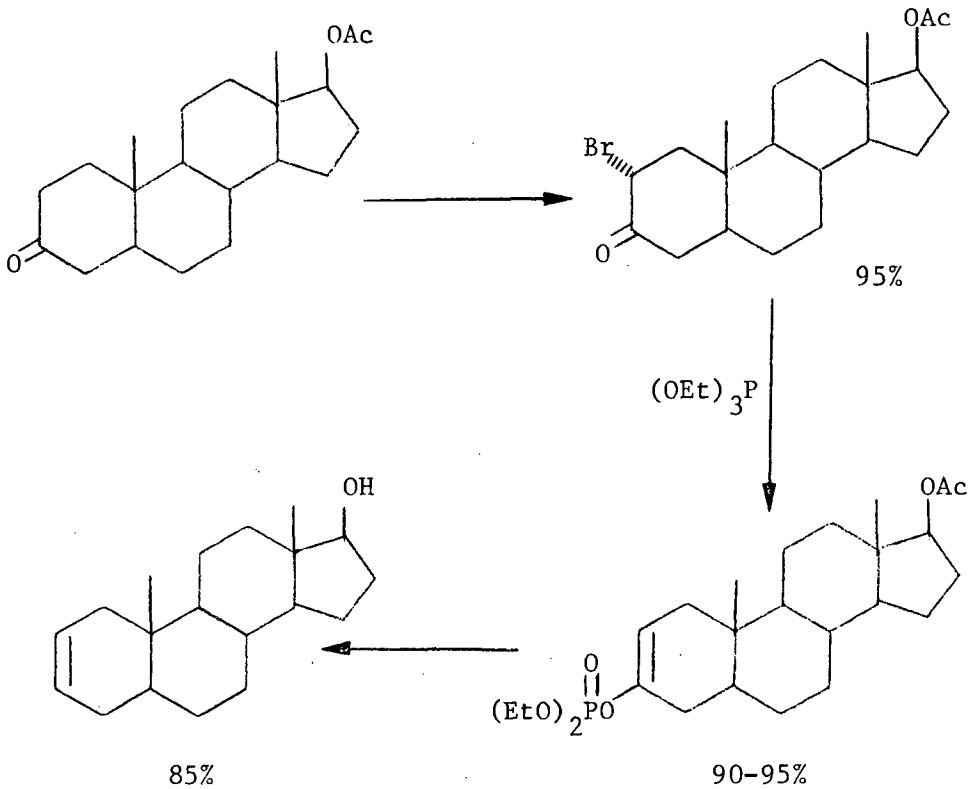


122 125

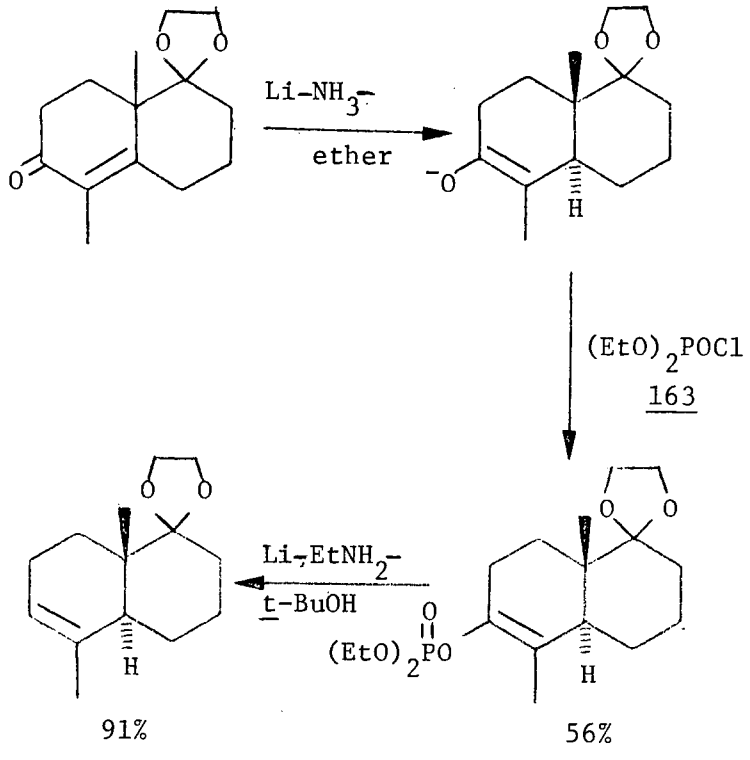
A number of different synthetic routes for obtaining the keto olefin (125) were investigated. Each of these will be discussed in turn.

In 1969, Fetizon and co-workers[91] reported that the reduction of enol diethyl phosphates with sodium or lithium in liquid ammonia gave the corresponding olefin. These enol phosphates were prepared from the corresponding ketones by first making the α-bromoketones, and then reacting the latter with triethylphosphite. The reduction was carried out by adding a solution of the enol phosphate in tetrahydrofuran and t-butyl alcohol to a solution of lithium or sodium in liquid ammonia.

The corresponding desired olefin was thus obtained in good yield. A specific example is given below.



Shortly after this communication by Fetizon and co-workers, Ireland and Pfister[92] reported an alternative method for the synthesis and reduction of enol diethyl phosphates. This synthesis involved reacting an enolate anion of a ketone with diethyl phosphorochlorodate (163), while the reduction involved use of lithium in ethylamine-t-butyl alcohol. One of the exampled cited by Ireland and Pfister[92] is given below.



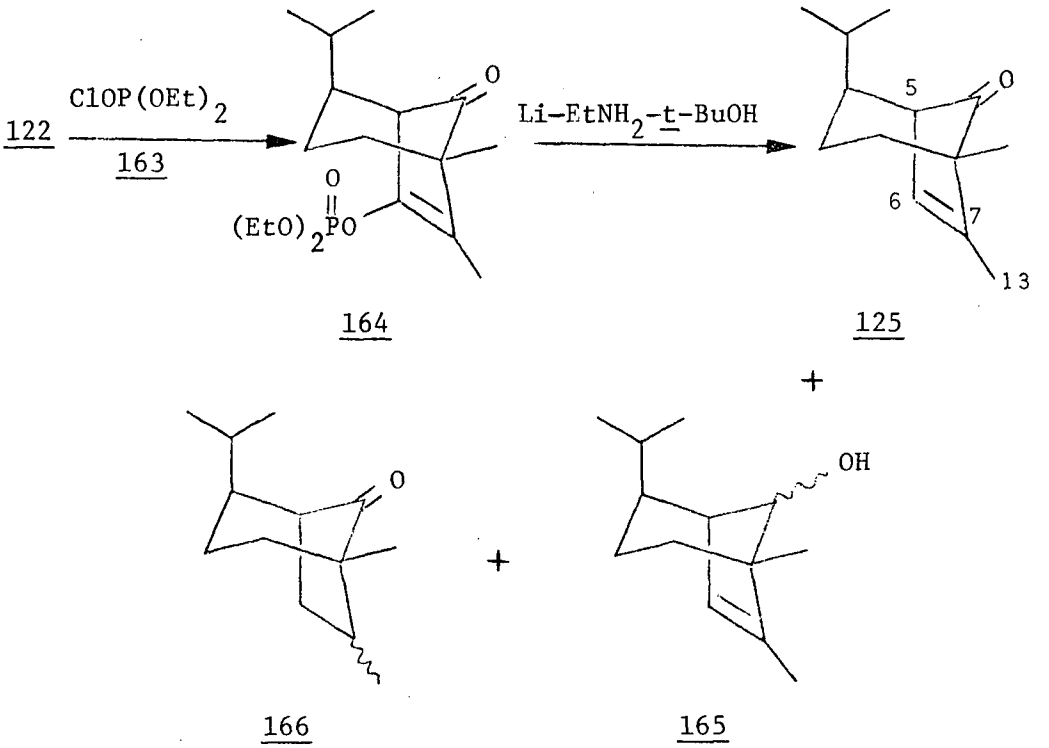
Accordingly, diketone 122 was treated with sodium bis(trimethylsilyl)-amide in tetrahydrofuran to generate the desired enolate (159). The latter was quenched with diethyl phosphorochlorodate (163) in pyridine to afford the (-)-keto enol phosphate (164) in 94% yield.* The infrared absorptions of compound 164 at 5.69 and 5.96 μ clearly showed the presence of the carbonyl and enolic double bond respectively. In the n.m.r. spectrum the protons of the ethoxy groups exhibited in

---

* When the reaction mixture involved in the cyclization of the keto ester (135) to the diketone (122) was quenched directly with diethyl phosphorochlorodate (163) instead of with aqueous acetic acid, the (-)-keto enol phosphate (164) was also formed, but in lower yield.

addition to the coupling normally found in ethyl groups, coupling due to the presence of the phosphorus atom. Thus the methylene protons (of the ethoxy groups) appeared as a pair of quartets (J = 7.0 Hz, J_{H-P} = 1.0 Hz) at τ 4.82, and the methyl protons (of the ethoxy groups) appeared as a pair of triplets (J = 7.0 Hz, J_{H-P} = 1.0 Hz) at τ 8.63. The protons of the vinyl methyl group also exhibited long range coupling with the phosphorus atom, and appeared as a pair of doublets (J = 1.0 Hz, J_{H-P} = 2.2 Hz) at τ 8.30. These phosphorus-proton coupling assignments were verified in a heteronuclear frequency swept decoupling experiment by irradiating the phosphorus atom. The collapse of the signals attributed to the ethoxy groups to the normal triplet and quartet (J = 7.0 Hz) for the methyl and methylene protons respectively was observed, as well as the collapse of the protons of the vinyl methyl group to a doublet (J = 1.0 Hz). The tertiary methyl group (singlet at τ 8.98) and the isopropyl group (doublet at τ 9.08, J = 6.3 Hz) were also evident in the n.m.r. spectrum of compound 164.

Reduction of compound 164 with lithium in ethylamine-t-butyl alcohol gave a mixture of products. The reaction was studied in considerable detail and the effect of varying several different reaction parameters (reactant concentration, reaction temperature, proton source, reaction time and method of quenching) were investigated. However, the maximum yield of the desired keto olefin (125) that was obtained was 26%. Moreover, the product was contaminated with the alcoholic olefin (165), a saturated ketone (166) and unidentified high boiling material. The olefinic alcohol (165) was readily oxidized to the desired product, but the only method that was found for separating



164 125 + 166 + 165

the keto olefin from the unwanted reduction products was preparative g.l.c. The (-)-keto olefin (125) obtained in this fashion gave analytical and spectral data which was in complete agreement with the assigned structure. In the infrared spectrum, absorptions at 3.29 μ and 6.13 μ indicated the presence of an olefinic double bond, whereas the carbonyl absorption appeared at 5.71 μ. The vinyl and allylic protons were now evident in the n.m.r. spectrum (Figure 5), and appeared as unresolved multiplets at τ 4.13 and 7.17 respectively. Also of interest was the appearance of the vinyl methyl group as a pair of doublets at τ 8.25 ($J_{C_5H-C_{13}H}$ = 1.0 Hz, $J_{C_6H-C_{13}H}$ = 1.6 Hz). These coupling constants were assigned after irradiating the vinyl proton (τ 4.13) and the allylic proton (τ 7.17) in separate frequency-swept

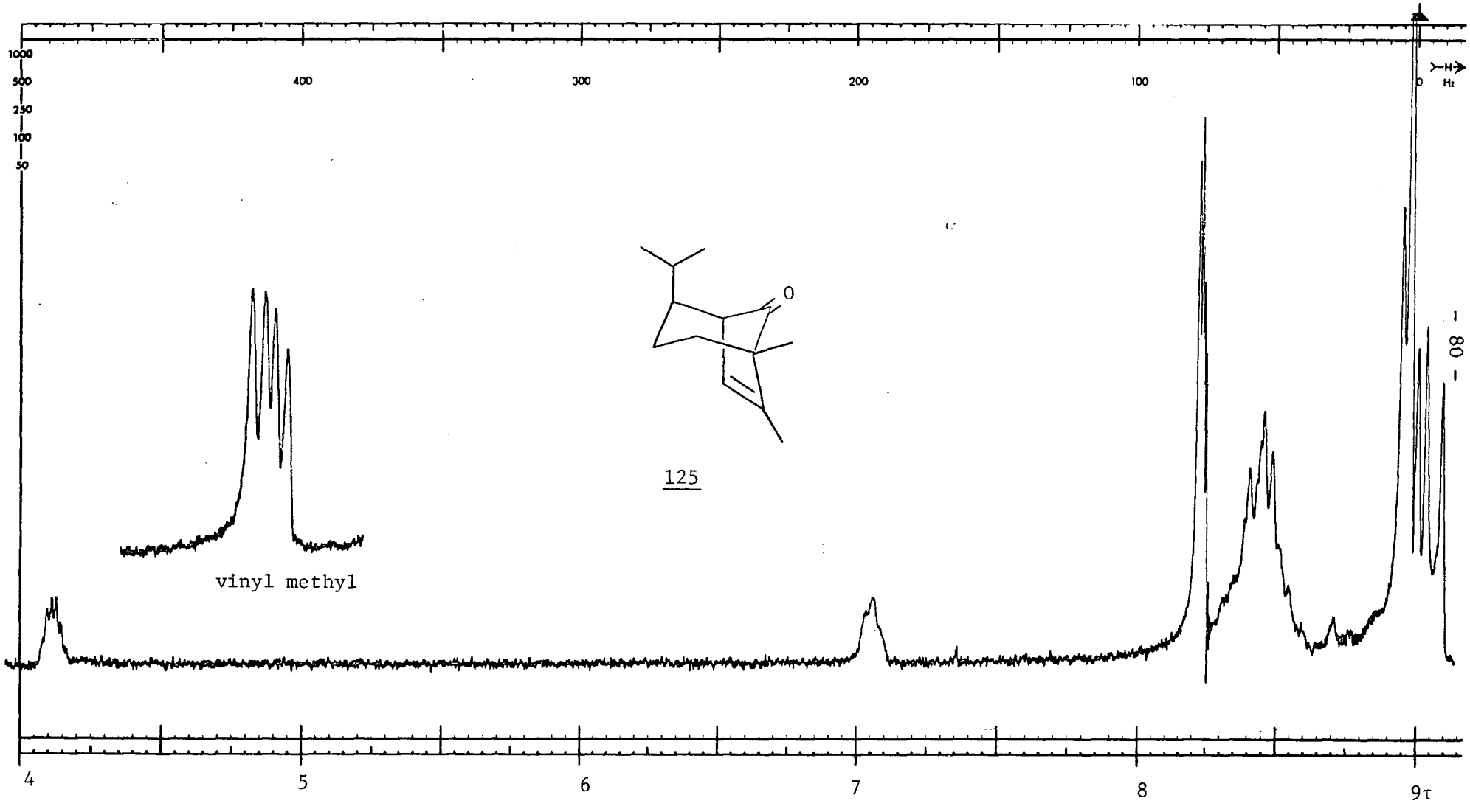


Figure 5. N.M.R. Spectrum of the (-)-Keto Olefin (125).

decoupling experiments and observing the collapse of the pair of doublets to a doublet in each case, with coupling constants of 1.0 Hz and 1.6 Hz respectively. The tertiary methyl group (singlet at τ 9.00) and the isopropyl group (doublets at τ 9.00 and 9.09, J = 6.0 Hz) were also evident in the n.m.r. spectrum of 125.

Since the lithium-ethylamine-t-butyl alcohol reduction of the (-)-keto enol phosphate (164) proved to be a very temperamental reaction, gave only poor yields of the desired product (125), and necessitated the use of rather tedious methods for product purification, alternative routes for the conversion of diketone 122 to keto olefin 125 were investigated.

Another method for the conversion of ketones to olefins is the Bamford-Stevens reaction.[93] In general, this reaction involves the reaction of p-tosylhydrazones of aldehydes and ketones with bases to yield the corresponding salts of the p-tosylhydrazone derivatives. The latter can be heated to give intermediate diazo compounds, which can decompose *in situ* by carbenic mechanisms if aprotic solvents are used, or by cationic processes if a protic media is used. In each case, the corresponding olefins are normally generated.

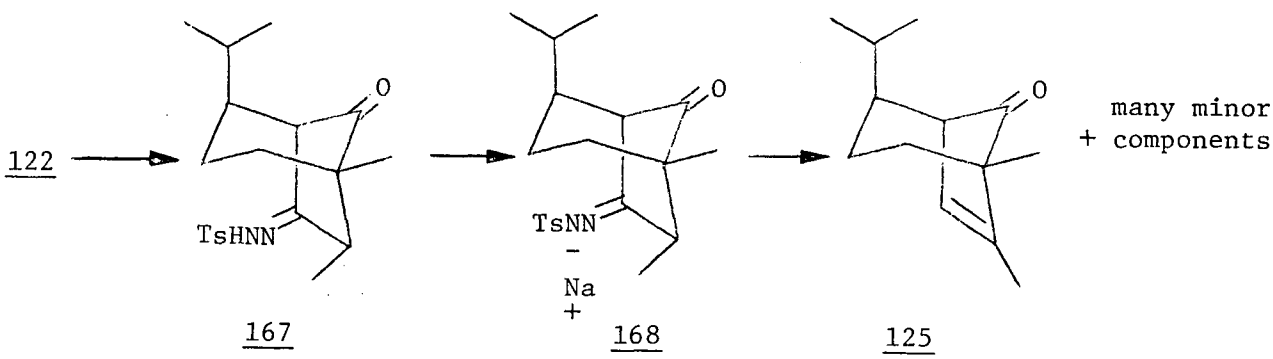
The (-)-diketone (122) was reacted with p-toluenesulfonylhydrazide in methanol in the presence of hydrogen chloride[94] to produce the corresponding p-tosylhydrazone (167). Although the crude product (167) was normally used directly in the Bamford-Stevens reactions, an analytical sample was obtained after purification by column chromatography and recrystallization. The crystalline p-tosylhydrazone (167) thus obtained exhibited spectral data in complete accord with the

assigned structure. In the infrared spectrum, the carbonyl absorption appeared at 5.73 μ, while the carbon-nitrogen double bond, and the aromatic double bonds appeared at 6.05 and 6.25 μ respectively. The n.m.r. spectrum of compound 167 displayed two doublets (J = 9.0 Hz) at τ 2.18 and τ 2.72 attributed to the aromatic protons, and a singlet (τ 7.50) attributed to the aromatic methyl group. The secondary methyl group appeared as a doublet (J = 7.0 Hz) at τ 8.82, while the tertiary methyl group (singlet at τ 9.05) and the isopropyl group (doublets at τ 9.02 and 9.19, J = 6.0 Hz) were also readily evident in this spectrum. The spectral data obtained from compound 167 does not, however, provide conclusive evidence for the regioselectivity of the p-tosylhydrazone formation. That is, if the p-toluenesulfonylhydrazide had reacted preferentially at the C_8 carbonyl group of diketone 122, instead of at the C_6 carbonyl group, the expected spectral properties of the corresponding product would be very similar to those of compound 167. However, theoretical considerations (vide infra), as well as the fact that the (-)-keto olefin (125) was the major product formed from the Bamford-Stevens reaction of compound 167, confirmed the fact that the reaction involved in tosylhydrazone formation was indeed largely regioselective.

In the attempted conversion of the p-tosylhydrazone (167) into the keto olefin (125), it was found that the Bamford-Stevens reaction under protic conditions was only marginally successful. Thus, when compound 167 was pyrolyzed in the presence of sodium ethylene glycolate at temperatures of 190-200°, keto olefin 125 was the major product formed, as determined by gas-liquid chromatographic analysis, but it was

produced in only poor yields (15-20%) and was accompanied by a large number of minor components.

Utilization of the Bamford-Stevens reaction under aprotic conditions proved to be more successful. The p-tosylhydrazone (167) was reacted with sodium bis(trimethylsilyl)amide in dry tetrahydrofuran to form the corresponding sodium salt (168). Although decomposition of 168 could be effected by heating the dry salt, higher yields of the desired keto olefin were obtained by adding approximately 10% (by weight) of high boiling nujol to the reaction mixture. This presumably, allowed for more uniform heating of the salt (168). The reaction mixture was heated slowly to a temperature of 125° under reduced pressure (water aspirator, 10-20 mm). When the reaction mixture had reached this temperature, direct distillation of the product was accomplished by application of a vacuum pump (0.3 mm) to the reaction system.



Unfortunately the (-)-keto olefin (125) was formed in only approximately 40% yield, and was contaminated with a large number of minor components as determined by gas-liquid chromatographic analysis. After careful distillation of the crude product under reduced pressure,

followed by column chromatography of the distillate, the (-)-keto olefin (125) still had to be purified by preparative g.l.c. Therefore, this method of converting the (-)-diketone (122) into the (-)-keto olefin (125) also proved to be quite tedious and inefficient.

Another method of generating an olefin from a tosylhydrazone involves reacting the latter with an alkyllithium reagent.[95,96] Considering p-tosylhydrazone (167), this reaction would not be synthetically useful, in that the alkyllithium in all probability, would also attack the C_8 carbonyl group of 167. However, it was hoped that this problem could be avoided by the selective reduction of the C_8 carbonyl group of the diketone 122.

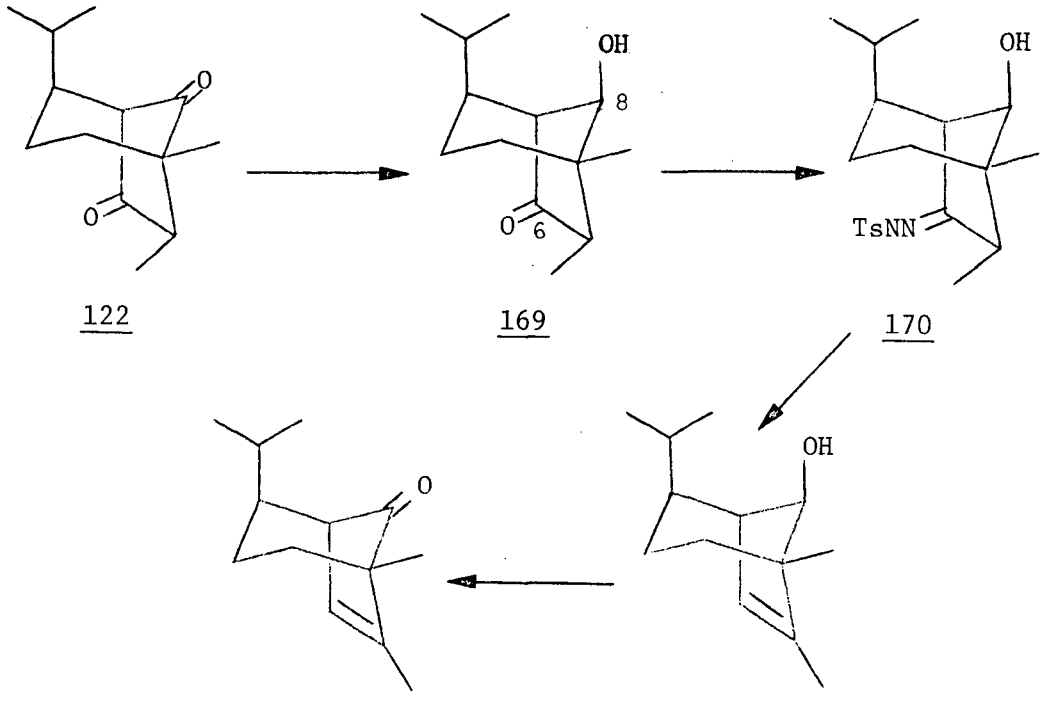
Accordingly, when the (-)-diketone (122) was reacted with one equivalent of hydride (from sodium borohydride) in ethanol at ice temperature for fifteen minutes, the C_8 carbonyl group was preferentially reduced. The reaction was completely regioselective and stereoselective, and afforded the (-)-keto alcohol (169) in 89% yield. A analytical sample of this material exhibited spectral data in complete accord with the assigned structure. Hydroxyl and carbonyl group absorptions (2.93 and 5.80 μ respectively) highlighted the infrared spectrum. The regioselectivity and stereoselectivity of the borohydride reduction was evident from analysis of the n.m.r. spectrum of compound 169. The proton adjacent to the hydroxyl group appeared as a doublet (J = 5.5 Hz) at τ 6.12. Had preferential reduction of the C_6 carbonyl group occurred a pair of doublets (coupling from C_5H and C_7H) would have resulted for the proton adjacent to the hydroxyl group. Stereochemically, hydride

attack on the C_8 carbonyl (of 122) would be expected to take place on the side opposite the bulky isopropyl group. That this was indeed the case was confirmed by the C_5H-C_8H coupling constant (5.5 Hz) which was in good agreement with that predicted by the Karplus equation[90] (5.0-6.0 Hz) for a dihedral angle between 30-40°.

It is interesting to note that the borohydride reduction of the diketone 122 regioselectively produced the keto alcohol 169 (reaction at C_8), while reaction of the diketone 122 with p-toluenesulfonylhydrazide regioselectively afforded the p-tosylhydrazone (167) (reaction at C_6). Although the reasons behind these regioselective reactions are not immediately obvious, it is tempting to speculate that the angle strain (C_1-C_8-C_5 angle less than 120°) associated with the sp^2 centre at C_8 makes this carbonyl group more electrophilic than the C_6 carbonyl group. Transformation of the C_8 carbon from an sp^2 centre to an sp^3 centre would relieve this angle strain and this would thus explain why attack of sodium borohydride on the diketone 122 was completely regioselective.

If one accepts that, due to angle strain, the C_8 carbonyl group of compound 122 is more electrophilic than the C_6 carbonyl group, then p-toluenesulfonylhydrazide would also be expected to preferentially attack the C_8 carbonyl group. However, after the initial nucleophilic attack generates an sp^3 centre (at C_8), p-tosylhydrazone formation requires the elimination of water, which would regenerate an sp^2 centre. It can be readily seen from the above argument that this transformation ($sp^3 \rightarrow sp^2$) would be energetically unfavourable. This would not be the case with the C_6 carbonyl group (of 122). Even though this carbonyl

group might be less electrophilic than the C_8 carbonyl group, once p-toluenesulfonylhydrazide does attack the C_6 position, the resulting α-hydroxy amine would readily lose water to form the corresponding p-tosylhydrazone. Therefore the overall reaction in this case is thermodynamically controlled and one can explain the observed regioselectivity on this basis. The (-)-keto alcohol (169) was reacted with p-toluenesulfonylhydrazide in methanol in the presence of an acid catalyst to afford the corresponding alcoholic p-tosylhydrazone (170) in 98% yield. This crude product (170) was reacted in dry tetrahydrofuran with eight equivalents of ethereal methyllithium at ice temperature.[97] After quenching the reaction mixture with water, followed by appropriate workup, the (-)-olefinic alcohol (171) was obtained in 88% yield. It was essential that tetrahydrofuran was used as the solvent rather than the more normally used ethyl ether, in that lithium salts of polycyclic hydroxy compounds are soluble in the former solvent. The infrared spectrum of the (-)-olefinic alcohol (171) exhibited a hydroxyl absorption at 2.94 μ and olefinic absorptions at 3.28 and 6.17 μ. Of particular interest in the n.m.r. spectrum of compound 171 was the presence of the olefinic proton (a broad singlet at τ 4.60) and the vinyl methyl group (a pair of doublets at τ 8.38, with the coupling constants being identical with those of the vinyl methyl group of the (-)-keto olefin (125), (p. 79). The other assignable signals were similar in chemical shift and multiplicity to those of the (-)-keto olefin (125).



122 169 170 171 125

The oxidation of the (-)-olefinic alcohol (171) was accomplished with either Collins reagent[64,98] of with Jones reagent.[99] Both methods produced good yields (approximately 90% in each case) of the desired keto olefin 125 but the Jones oxidation was preferred as it was more easily applied to larger scale reactions. The (-)-keto olefin (125) thus obtained was identical in every respect with the material prepared previously. Even though this conversion of the (-)-diketone (122) to the (-)-keto olefin (125) involved more synthetic steps than either of the two previously described methods, it was by far the best, not only from the point of view of efficiency (69% overall yield of 125 from 122) but also from the point of view of product purity.

That is, in this latter conversion, the final product (125) was obtained completely pure, and no laborious separation of products was required.

5. Synthesis of (-)-Copacamphene (23)

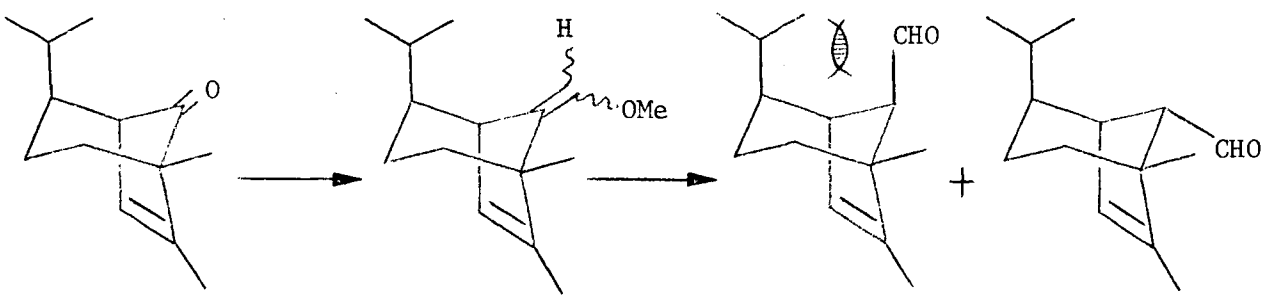
Having achieved an efficient synthesis of the bicyclic keto olefin (125), the remaining synthetic transformations necessary for the synthesis of (-)-copacamphene and (-)-cyclocopacamphene involved the extension of the carbonyl group into a functionalized two carbon side chain, followed by appropriate ring closure reactions.

The carbonyl group of compound 125 was to be used as a "handle" for the introduction of the side chain. To avoid stereochemical problems at C_8, it was felt that it would be more advantageous to introduce the side chain in two stages. The first stage would involve the synthesis of a compound containing a formyl group at C_8. Since there would be a large 1,3-diaxial interaction between an axial substituent at C_8 and the isopropyl group at C_4, subjecting such a compound to epimerizing conditions would then afford the product with the desired equatorial orientation of the formyl group. The second stage of developing the two carbon side chain would be to use this formyl group again as a "handle" for the introduction of the second carbon unit.

The (-)-keto olefin (125) was reacted with methoxymethylenetriphenylphosphorane in dimethyl sulfoxide[62] at 50° for one and one-half hours. This produced a diastereomeric mixture of the corresponding olefinic

enol ethers (172) in 71% yield. In accordance with the assigned structure, 172 exhibited an ultraviolet absorption at 208 mμ (ε = 8,030) and an infrared absorption at 5.88 μ. Both of the absorptions are characteristic of an enol ether functionality. In the n.m.r. spectrum, the vinyl protons of the two isomeric compounds exhibited the same chemical shift and appeared as a singlet at τ 4.43. However, the fact that the product did indeed consist of a mixture of two isomeric compounds was clearly shown by the presence of two singlets (τ 6.51 and 6.54) due to two different $-O-CH_3$ groups. From the integrated area of these two peaks it was estimated that the two isomers were present in the mixture in a ratio of approximately 3:2.

Hydrolysis of the mixture of olefinic enol ethers (172) with 35% perchloric acid in ether at room temperature[100] afforded an epimeric mixture of olefinic aldehydes (173 and 174). Presumably, the presence of 173 in this mixture was due to kinetic protonation of the corresponding intermediate enol, or of the original enol ether 172. Obviously, the hydrolysis conditions did not effect complete epimerization of compound 173 to the more stable epimer (174). G.l.c. and n.m.r. analysis of the hydrolysis product indicated that the two olefinic aldehydes (173 and 174) were present in a ratio of approximately 1:1.



125 172 173 174

As mentioned previously, in olefinic aldehyde 173, there exists a 1,3-diaxial interaction between the formyl group and the isopropyl group, making this compound thermodynamically less stable than the epimeric olefinic aldehyde (174). Because of this rather sizable interaction, when the aldehydes (173 and 174) were subjected to epimerizing conditions (potassium carbonate in aqueous ethanol) olefinic aldehyde 173 was completely converted into the epimeric olefinic aldehyde 174, and the latter was obtained in 86% yield from the enol ethers (172). The (-)-olefinic aldehyde (174) was obtained as a colourless oil, and it exhibited analytical and spectral properties in accord with the assigned structure. Olefinic (3.30 and 6.08 μ) and aldehydic (3.67 and 5.83 μ) absorptions were evident in the infrared spectrum. In the n.m.r. spectrum of compound 174 (Figure 6), the aldehydic proton appeared as a doublet (J = 4.2 Hz) at τ 0.40. The vinyl proton appeared as a broad singlet at τ 4.56, and the allylic proton appeared as an unresolved multiplet at τ 7.53. The proton adjacent to the formyl group, C_8H, was evident as a doublet (J = 4.2 Hz) at τ 7.80. This multiplicity is as anticipated, in that the dihedral angle between C_5H and C_8H is close to 90°, so that no coupling between these two protons was expected. The vinyl methyl group characteristically appeared as a pair of doublets (τ 8.38, $J_{C_6H-C_{14}H}$ = 1.6 Hz, $J_{C_5H-C_{14}H}$ = 1.0 Hz), while the tertiary methyl group (τ 8.97) and isopropyl methyl groups (doublets, τ 9.08 and 9.16, J = 6.2 Hz) were also clearly distinguishable.

Introduction of the second carbon unit into the side chain could again be accomplished in several different ways, depending on the functionality desired in the side chain. For the copacamphene synthesis,

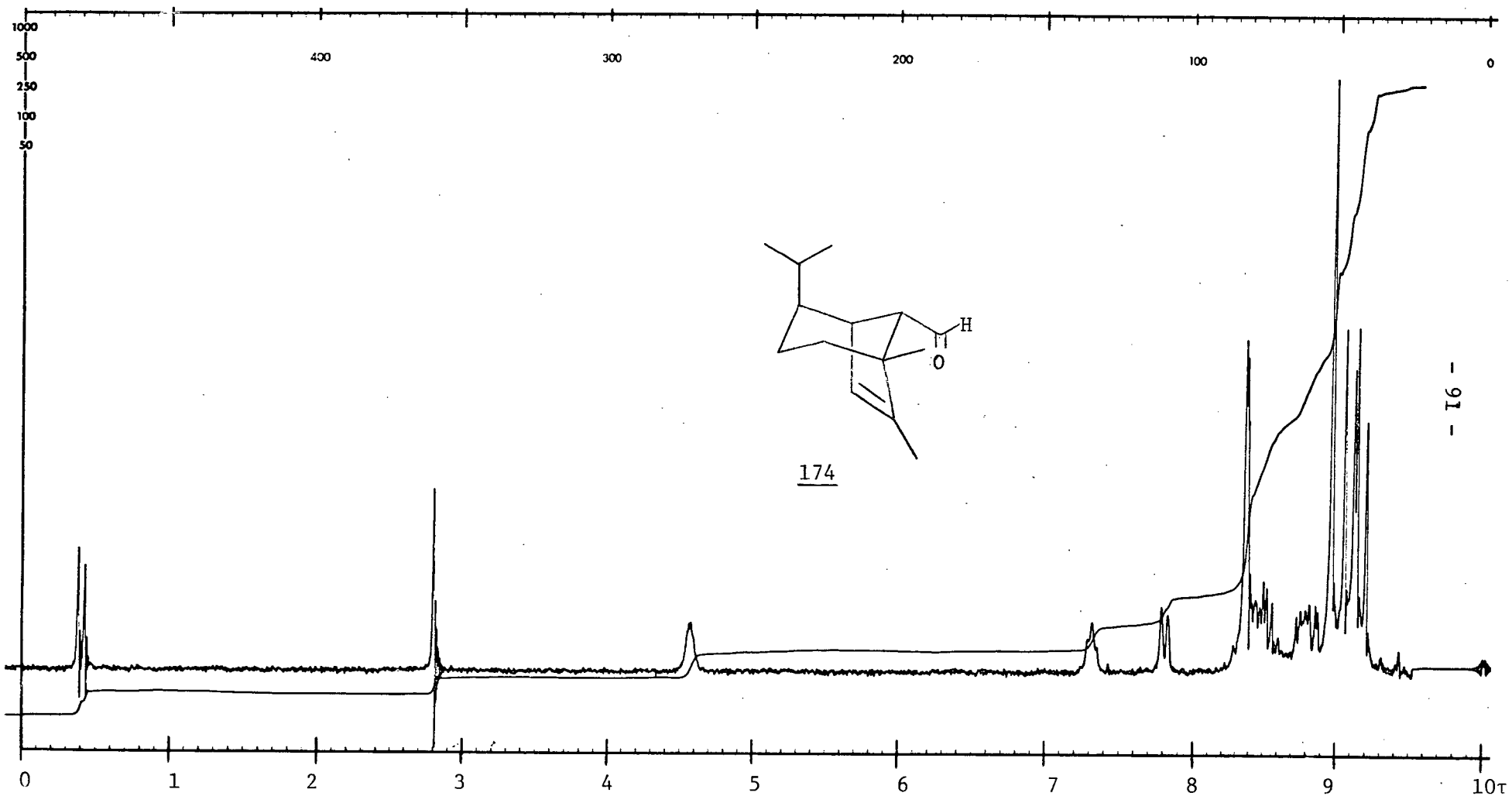
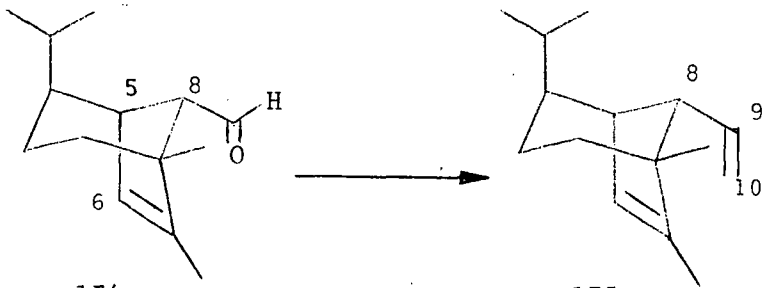


Figure 6. N.M.R. Spectrum of the (-)-Keto Aldehyde (174).

we chose to convert the formyl group of compound 174 into a terminal olefinic double bond.

Reaction of (-)-olefinic aldehyde (174) with methylenetriphenylphosphorane, again following Corey's procedure[62] for the Wittig reaction, afforded the (+)-diene (175) in 83% yield.



174 175

The n.m.r. spectrum of the (+)-diene (175) (Figure 7) was particularly interesting. The C_9 proton (τ 4.22), experiencing coupling with the C_8 proton (J = 9.0 Hz) as well as cis (J = 10.0 Hz) and trans (J = 17.5 Hz) coupling with the terminal olefinic protons at C_{10}, appeared as an eight-line signal. The C_{10} protons each appeared as a pair of doublets as a result of geminal coupling (J = 2.5 Hz) and coupling with the proton on C_9. The C_8 proton appeared as a doublet (J = 9.0 Hz) at τ 7.83. The other assignable signals were similar in chemical shift and multiplicity to the corresponding resonances of the (-)-olefinic aldehyde (174).

In accord with the outline for the planned synthesis of copacamphene (page 44), it was necessary at this stage of the synthesis to selectively functionalize the terminal olefinic double bond of the (+)-diene (175). Conversion of this terminal double bond into a primary alcohol functionality, followed by tosylation of the hydroxyl

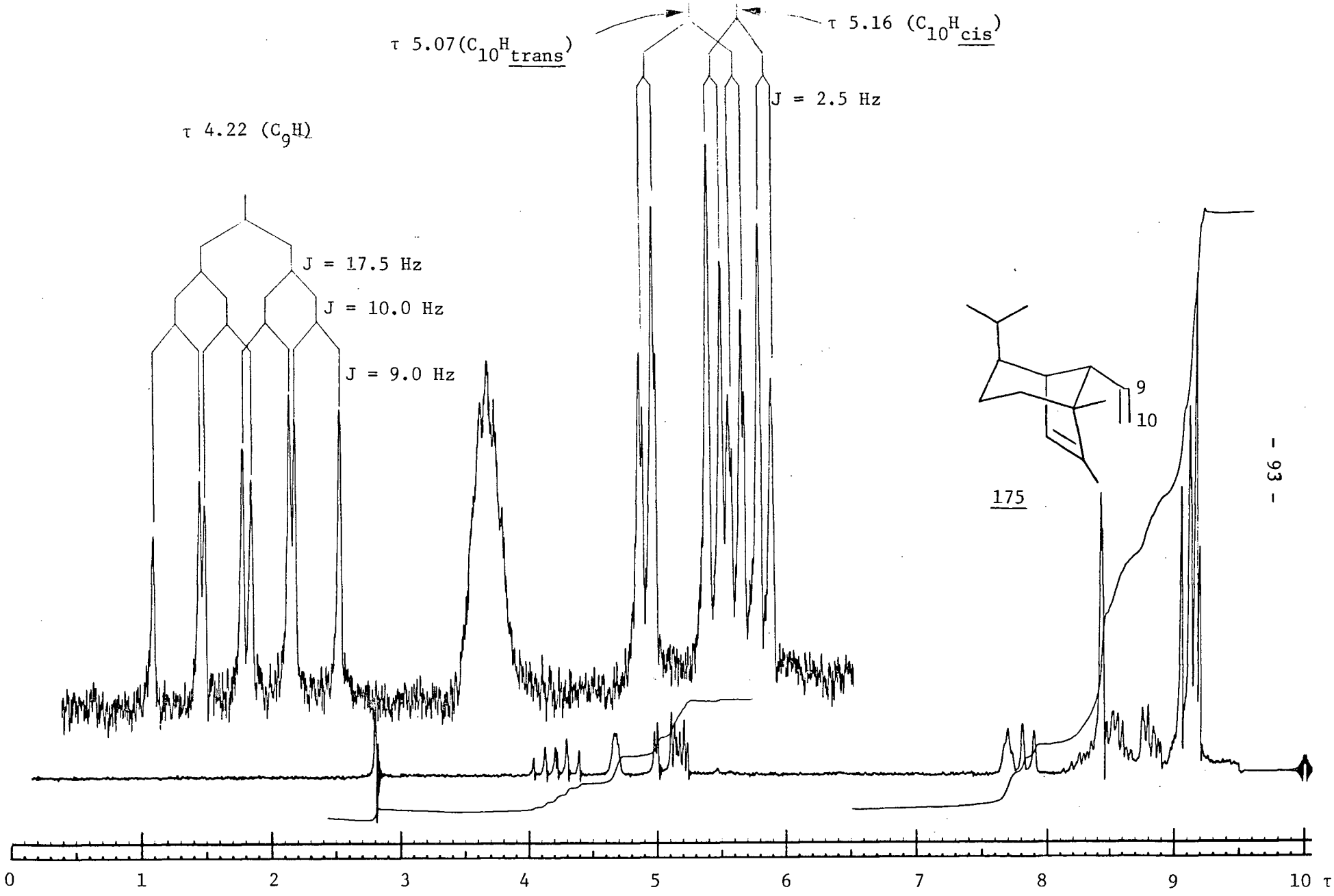
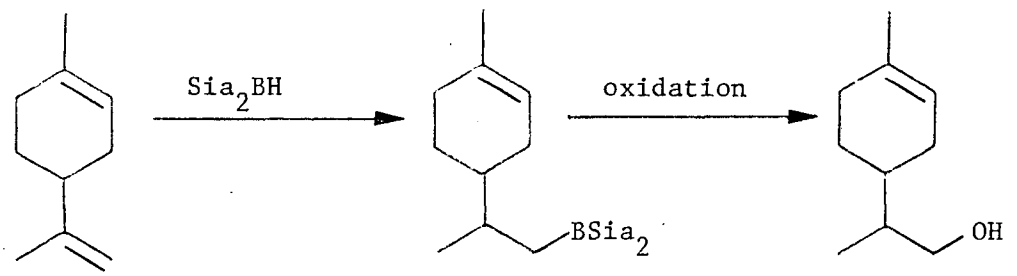


Figure 7. N.M.R. Spectrum of the (+)-Diene (175).

group, would produce an olefinic tosylate appropriately functionalized for eliminative cyclization.

Brown and Zweifel[101] have shown that the selective hydroboration of the less hindered of two double bonds in a diene can readily be carried out by the use of a hindered hydroborating agent, such as disiamylborane* (Sia_2BH). For example, treatment of limonene (176) with disiamylborane, followed by oxidation of the intermediate trialkylborane with alkaline hydrogen peroxide, afforded the primary alcohol 177 in very good yield.



176 177

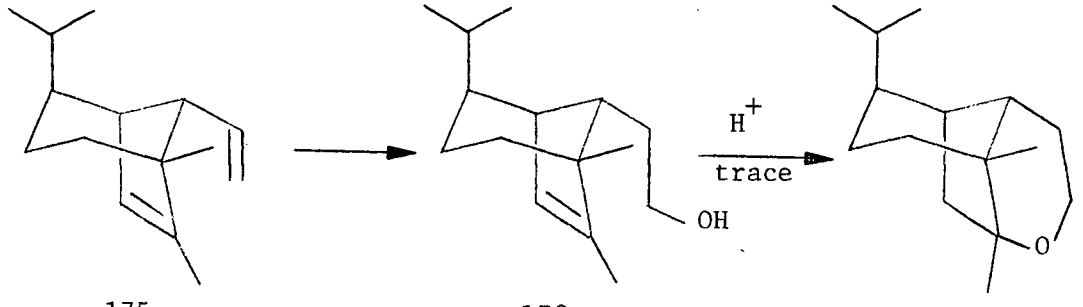
Disiamylborane was prepared by adding a solution of the tetrahydrofuran-borine complex to 2-methyl-2-butene in tetrahydrofuran (1:2.2 molar ratio respectively) at ice temperature. It was desirable to use an excess of the butene to insure that there would be no excess tetrahydrofuran-borine complex present. This procedure would create no undue problems since the butene undergoes rapid hydroboration to the dialkylborane stage, but further reaction to the trialkylborane stage is relatively slow.[101]

Subjection of the (+)-diene (175) to hydroboration with

* This is the common name for bis-3-methyl-2-butylborane.

disiamylborane in tetrahydrofuran, followed by decomposition of the intermediate trialkylborane with alkaline hydrogen peroxide afforded the desired (+)-olefinic alcohol (178) in 91% yield. An analytical sample of this material was obtained by preparative g.l.c. and exhibited spectral data in complete accord with the assigned structure. Most notable in the n.m.r. spectrum of compound 178 was the absence of the terminal olefin protons and the appearance of protons adjacent to the hydroxyl group as a multiplet at τ 6.38. The allylic proton appeared as an unresolved multiplet at τ 7.63, while the pair of doublets (τ 8.44, $J_{C_6H-C_{15}H}$ = 1.6 Hz, $J_{C_5H-C_{15}H}$ = 1.0 Hz) readily accounted for the vinyl methyl group. The tertiary methyl group (τ 9.10) and the isopropyl methyl groups (doublets at τ 9.04 and 9.14, J = 6.0 Hz) were also evident in the n.m.r. spectrum of compound 178.

Care had to be taken to avoid exposure of the (+)-olefinic alcohol (178) to acid, since even trace amounts of acid caused the cyclization of this material to the cyclic ether (179). An analytical sample of this ether 179 was obtained by preparative g.l.c. and exhibited the expected spectral properties. Of particular note in the infrared spectrum was the absence of the absorptions due to the hydroxyl group and olefinic double bond. The n.m.r spectrum exhibited a two-proton multiplet at τ 6.30 corresponding to the protons adjacent to the oxygen atom. The tertiary methyl groups were evident as singlets at τ 8.94 and 9.11 while the isopropyl methyl groups appeared as doublets (J = 6.0 Hz) at τ 9.14 and 9.16.



175 178 179

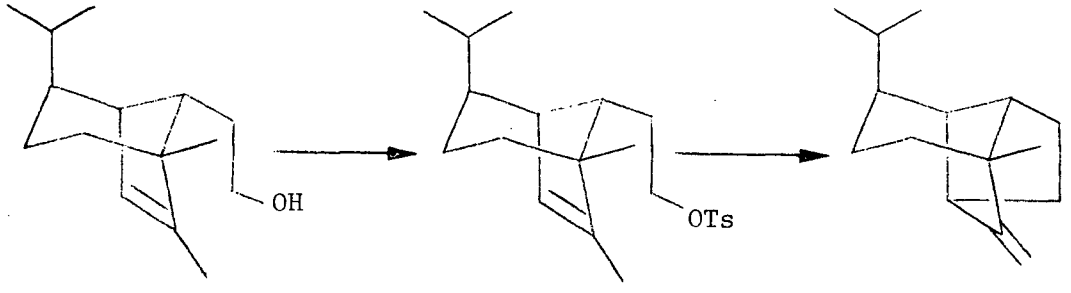
Treatment of the (+)-olefinic alcohol (178) with p-toluenesulfonyl chloride in pyridine at room temperature gave the olefinic tosylate (180) which, presumably largely due to the proximity of the tosylate functionality and the olefinic double bond, exhibited a high propensity towards eliminative cyclization. Thus merely allowing the tosylate (180) to stand at room temperature gave, after filtration of the resultant material through a silica gel column, a 90% yield (from the olefinic alcohol 178) of a mixture consisting largely of (-)-copacamphene (23), accompanied by two other hydrocarbons. The latter comprised approximately 3% and 4% of the mixture, as determined by gas-liquid chromatographic analysis.

Pure synthetic (-)-copacamphene (23) was readily obtained from this mixture by chromatography of the latter over silver nitrate impregnated silica gel and exhibited $[\alpha]_D^{21}$ -159°.* The infrared spectrum (Figure 8) showed absorptions at 3.26, 6.03 and 11.42 μ, due to the exocyclic methylene group. The latter was also clearly evident in the n.m.r. spectrum (Figure 9). Thus, the two olefinic protons appeared as

* See the footnote on p. 18.

singlets at τ 5.21 and 5.49. Furthermore, the broad signal at τ 7.54 could readily be assigned to the allylic proton. Finally, the singlet at τ 9.00 and the doublet (J = 6.0 Hz) at τ 9.10 were readily attributed to the tertiary methyl group and isopropyl methyl groups, respectively.

The (-)-copacamphene thus prepared exhibited g.l.c. retention times and infrared spectrum identical with that of (±)-copacamphene.*

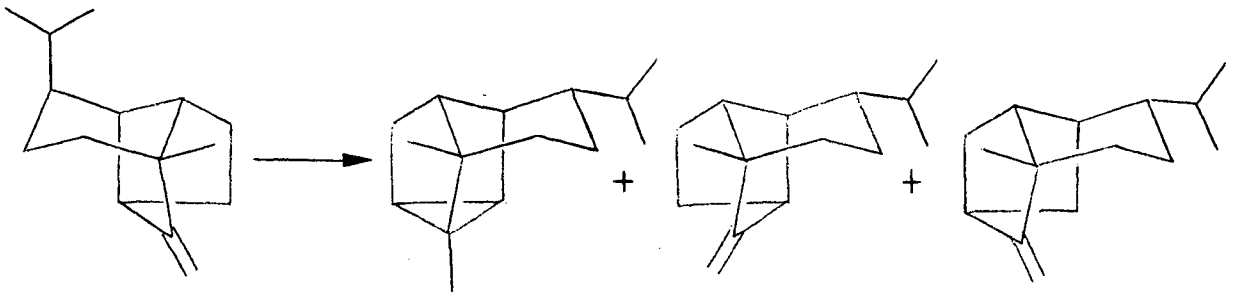


178 180 23

In order to fully determine what the two impurities in this reaction were, we felt it was necessary to obtain samples of some of the compounds of the sativene series, in particular sativene, cyclosativene and isosativene. These were readily obtained by reacting (-)-copacamphene with cupric acetate in refluxing acetic acid for four days[47] (see p. 27). The ratio of products, as determined by gas-liquid chromatographic analysis, was identical with that reported by McMurry[47]: 31% (+)-cyclosativene (27); 7% (+)-sativene (26); and 62% (-)-isosativene (77).

---

* We are very grateful to Professor J.E. McMurry for a small sample of this compound.



23 27 26 77

Purification of this mixture by a combination of column chromatography on silver nitrate impregnated silica gel and preparative g.l.c. allowed the isolation of all three compounds. Thus (+)-cyclosativene (27) exhibited $[\alpha]_D^{25}$ +63°* as well as absorptions at 3.28, 11.62 and 11.87 μ in the infrared spectrum (Figure 19), the latter being characteristic of the tricyclene-type structure.[102] In the n.m.r. spectrum (Figure 20), the tertiary methyl groups appeared as sharp singlets at τ 9.02 and 9.24, while the isopropyl methyl groups were evident as doublets (J = 6.0 Hz) at τ 9.09 and 9.13. The cyclopropyl protons appeared at τ 9.22 (singlet) and 9.33 (doublet, J = 5.5 Hz). This spectral data was in good agreement with that reported in the literature[18,24,47] for (+)-cyclosativene.

(+)-Sativene (26) exhibited a rotation of +174° (lit.[22] +191 ± 3°)** as well as infrared absorptions (Figure 10) at 3.26, 6.04 and

---

* The original rotation for (+)-cyclosativene reported by Zavarin[24] was +94.1°. Our rotation is more in line with that reported by Yoshikoshi (+67.8)[18] and McMurry (+61°).[47]

** The discrepancy is possibly accounted for in part by the errors associated in working with a very small amount of this somewhat volatile hydrocarbon.

11.45 μ, which are characteristic of an exocyclic methylene group. In the n.m.r. spectrum (Figure 11), the olefinic protons of the exocyclic methylene group were clearly evident as singlets at τ 5.26 and 5.58. The allylic proton appeared as a broad signal at τ 7.39, while a singlet at τ 8.96 and doublets (J = 6.0 Hz) at τ 9.10 and 9.13 accounted for the protons of the tertiary methyl group and isopropyl methyl groups, respectively. The spectral data was in good agreement with that reported in the literature[22,23] for (+)-sativene.

The major product from the acetic acid-cupric acetate rearrangement of (-)-copacamphene was (-)-isosativene (77). The latter exhibited the characteristic absorptions of an exocyclic methylene group (3.27, 6.06 and 11.42 μ) in the infrared spectrum (Figure 12). In the n.m.r. spectrum (Figure 13), the exocyclic methylene protons (singlets at τ 5.23 and 5.52), the allylic proton (broad signal at τ 7.39), the tertiary methyl group (singlet at τ 9.03) and the isopropyl methyl groups (doublet at τ 9.12, J = 6.0 Hz) were clearly evident. This spectral data was in good agreement with that reported in the literature[24-26] for (-)-isosativene.

Even though copacamphene, sativene and isosativene are structurally very similar, it was relatively easy to distinguish between these three compounds on the basis of their infrared and n.m.r. spectra (Figures 8-13).

It is appropriate now to return to the discussion regarding the identity of the two hydrocarbon impurities formed during the eliminative cyclization of the olefinic tosylate 180 to (-)-copacamphene. A small

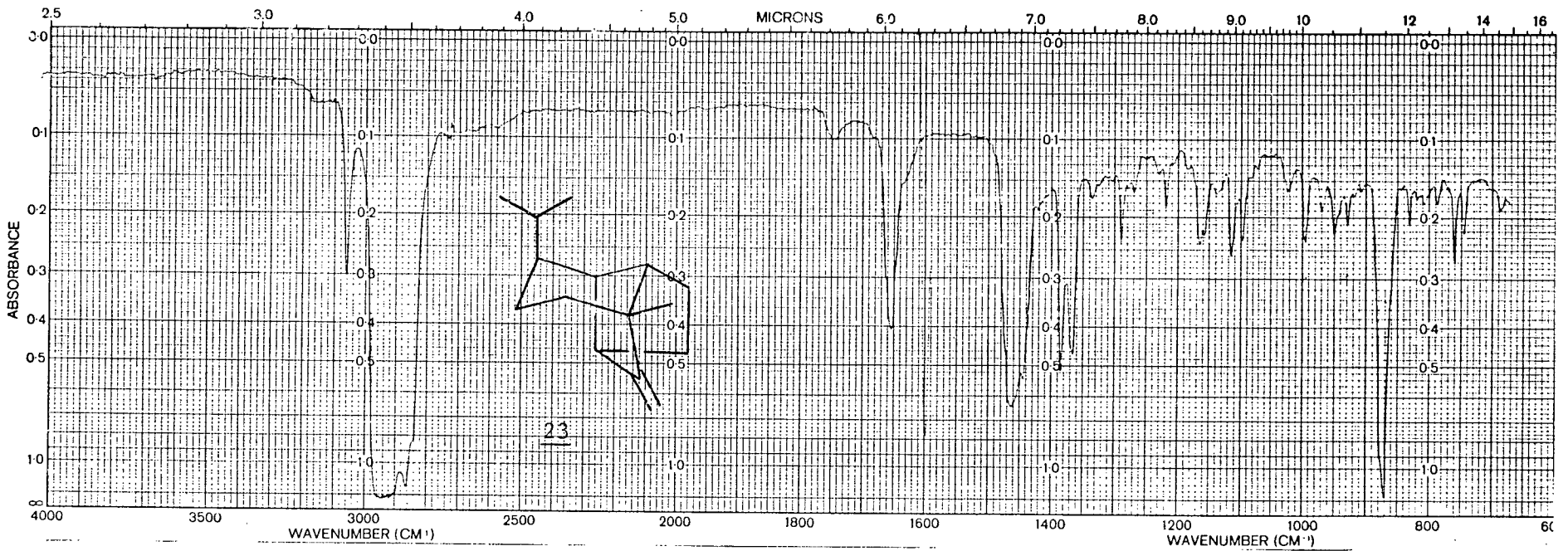
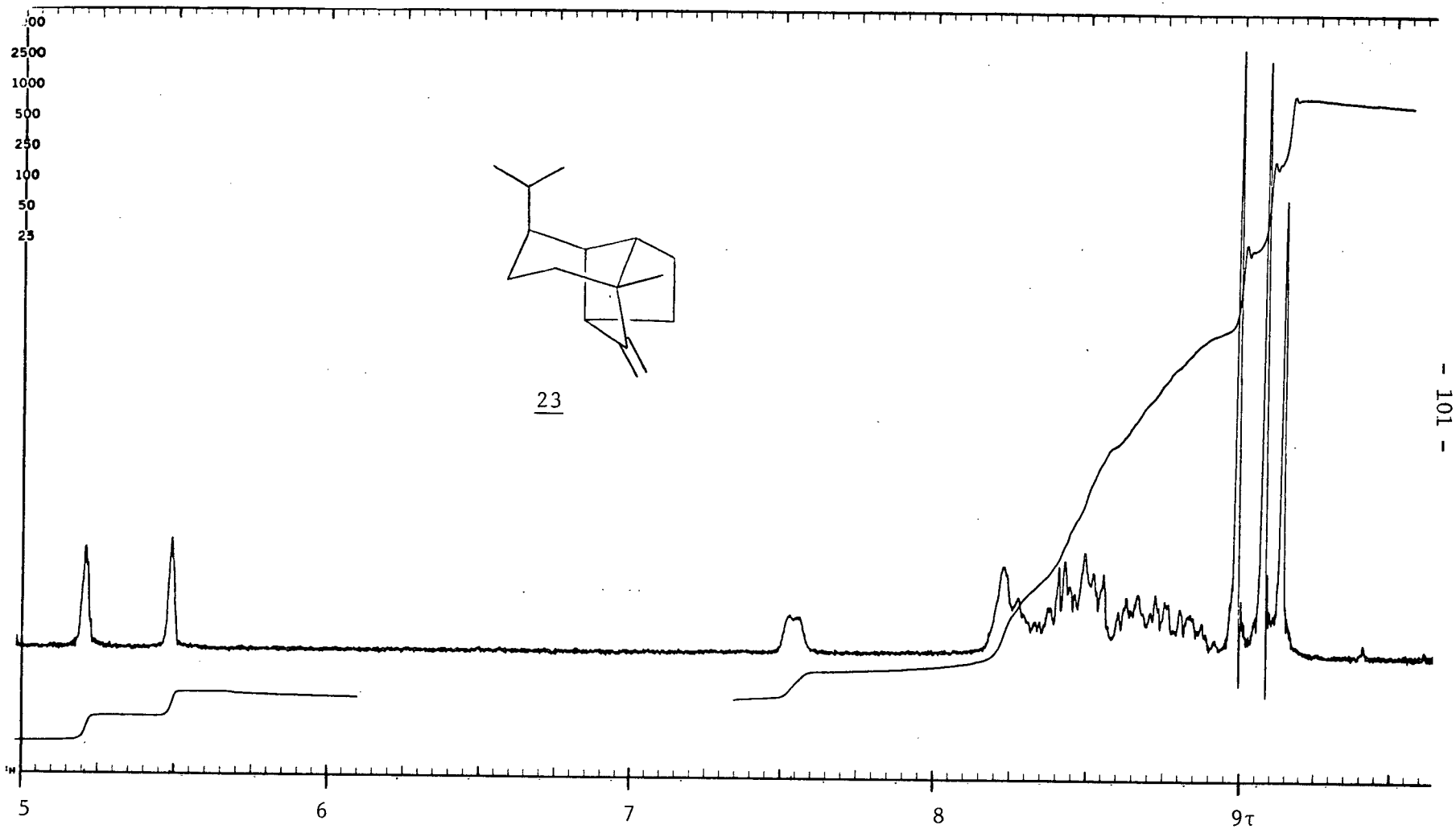


Figure 8. Infrared Spectrum of (-)-Copacamphene (23).



23

Figure 9. N.M.R. Spectrum of (-)-Copacamphene (23).

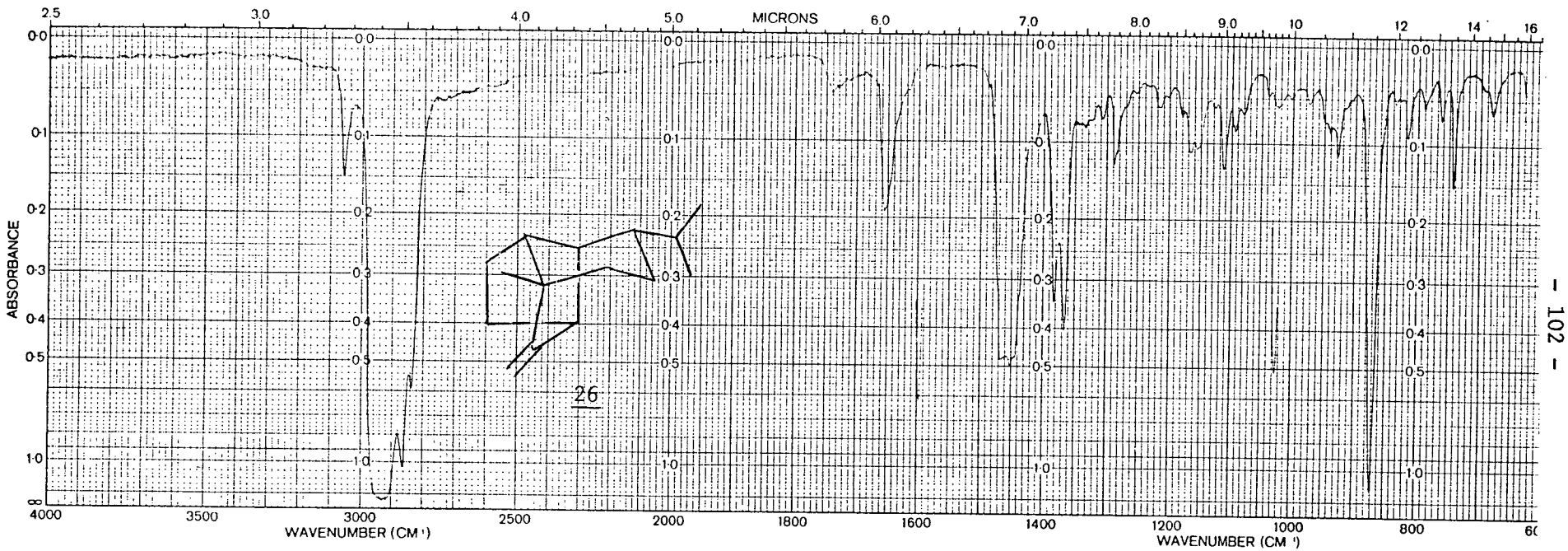
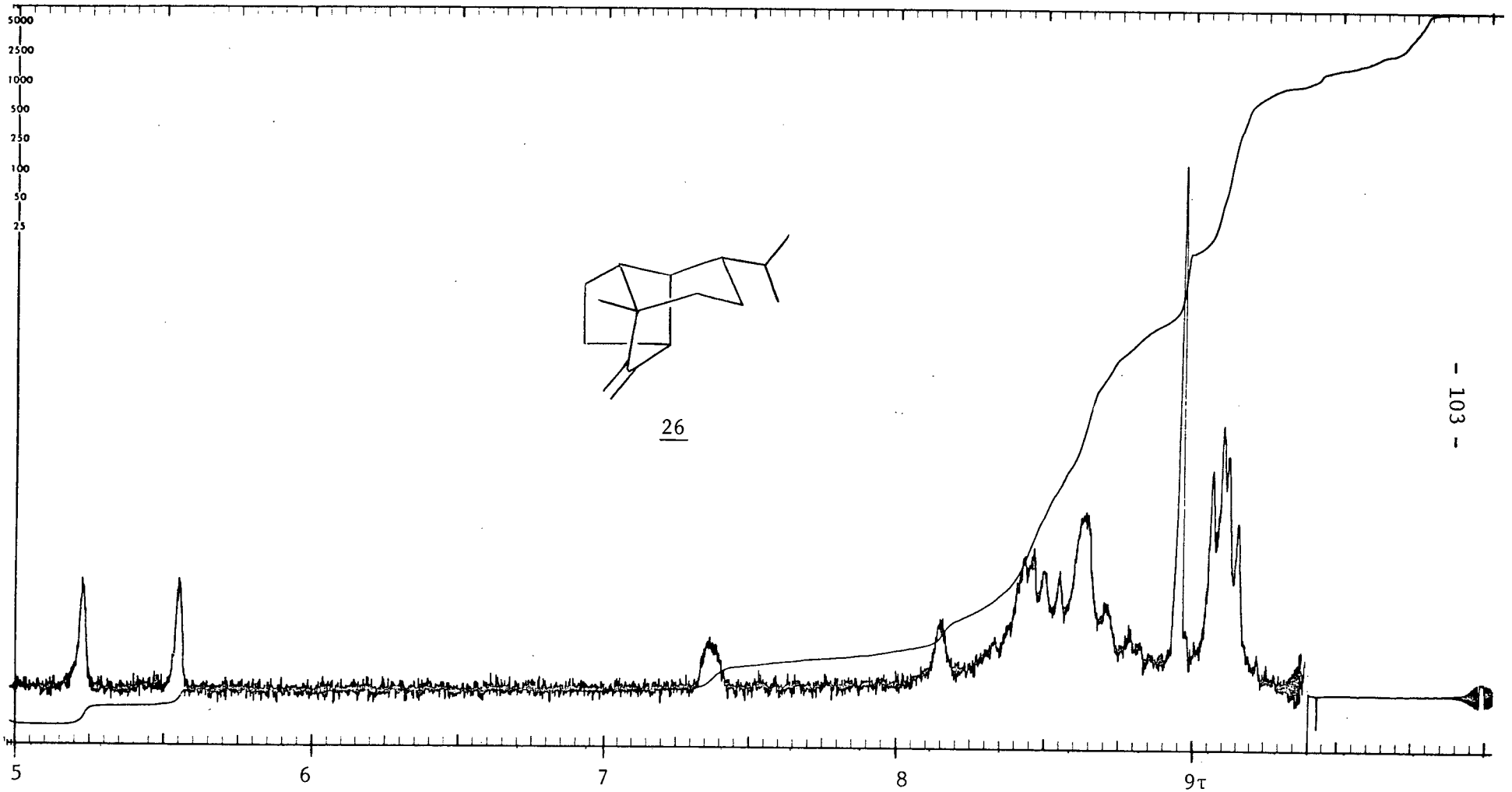


Figure 10. Infrared Spectrum of (+)-Sativene (26).



26

Figure 11. N.M.R. Spectrum of (+)-Sativene (26).

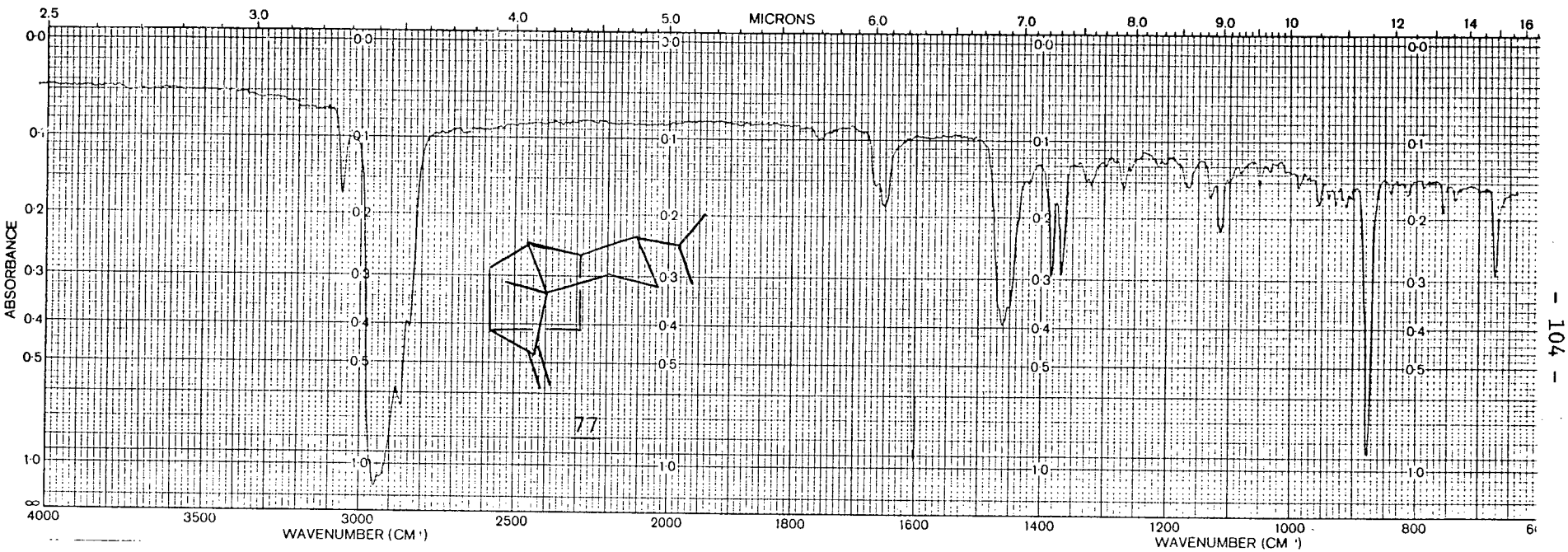
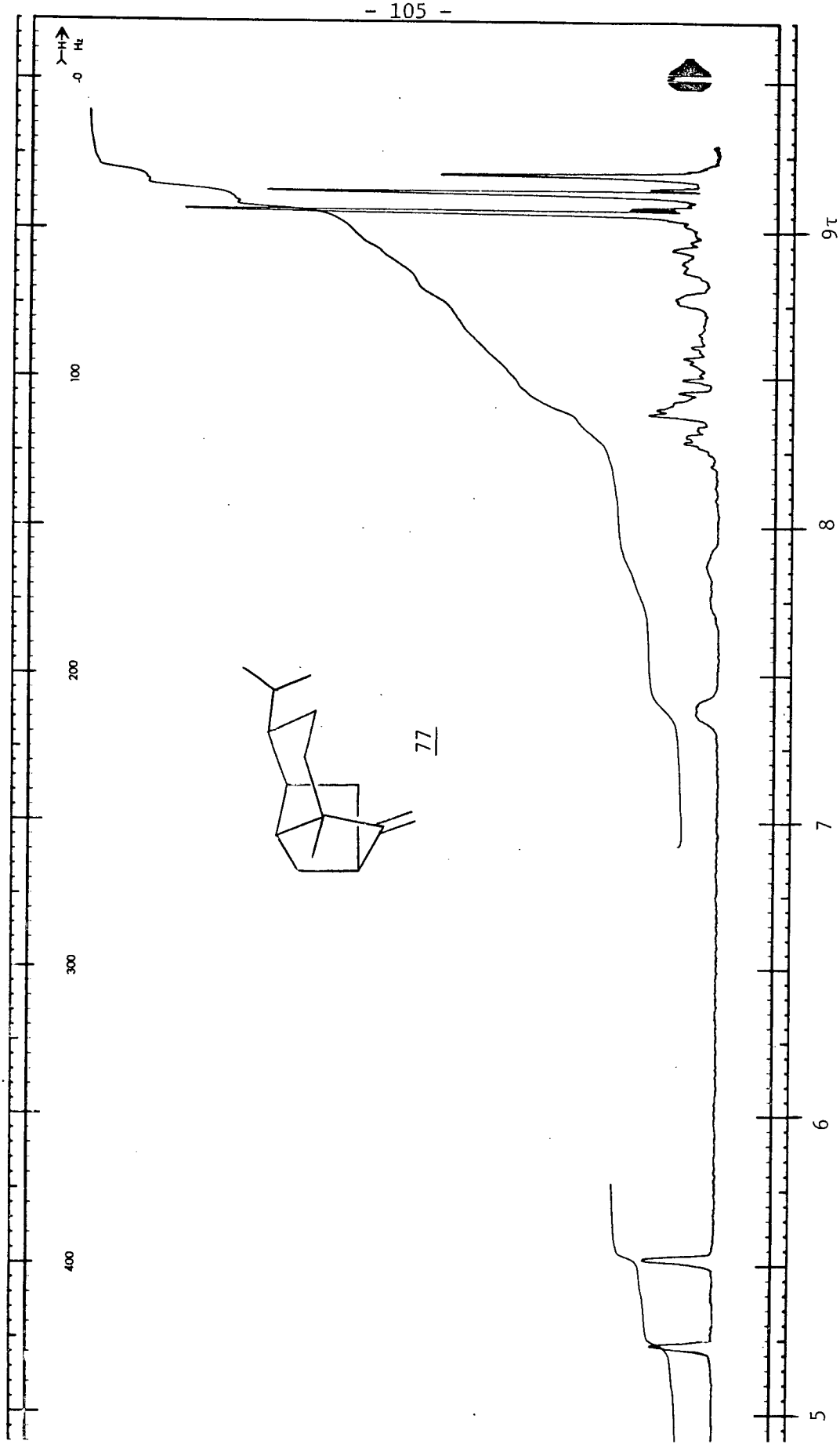


Figure 12. Infrared Spectrum of (-)-Isosativene (77).



77

Figure 13. N.M.R. Spectrum of (-)-Isosativene (77).

sample of each of the two impurities was obtained by preparative g.l.c. These compounds were identified as (+)-cyclosativene (27) and (-)-isosativene (77) by a direct comparison (g.l.c. retention times and infrared spectra) with authentic samples of the two sesquiterpenes.

These impurities were thought to arise from exposure of the initially formed copacamphene to acidic conditions. That is, when the eliminative cyclization of the olefinic tosylate (180) was carried out by allowing the latter compound to stand at room temperature, p-toluenesulfonic acid was produced, thus exposing the initially formed (-)-copacamphene to acidic conditions. This could then cause the partial rearrangement of the first-formed product [(-)-copacamphene] to the two impurities, (+)-cyclosativene and (-)-isosativene.

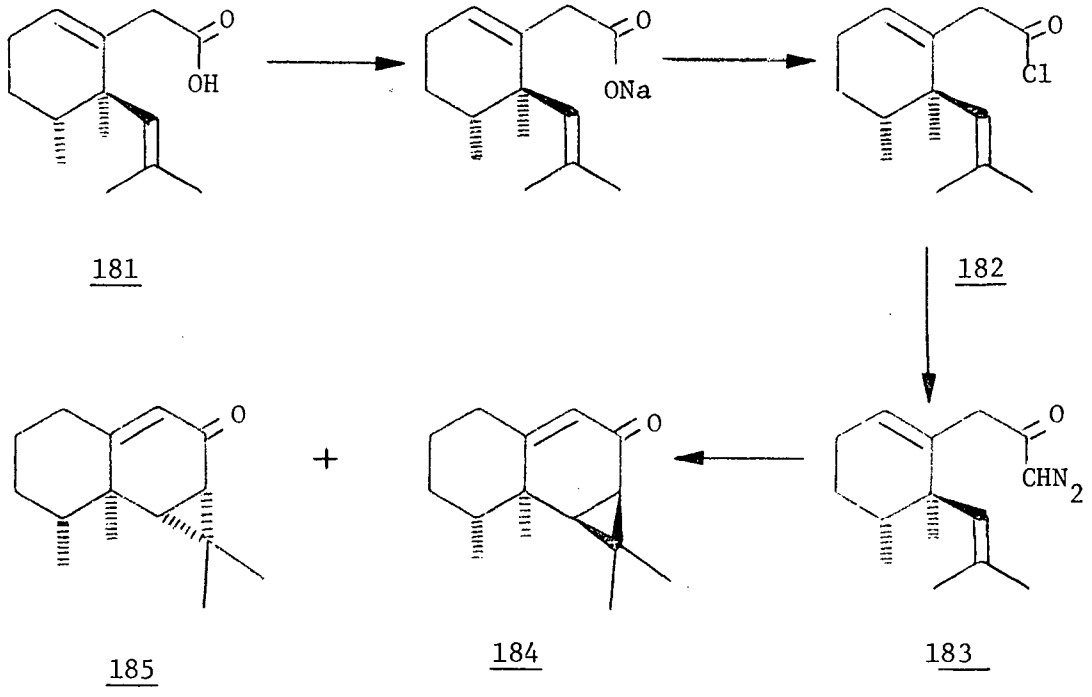
We were interested in testing the validity of this argument by determining whether or not small amounts of p-toluenesulfonic acid would cause rearrangement of (-)-copacamphene. Accordingly, (-)-copacamphene was reacted with a 10 mM solution of p-toluenesulfonic acid in benzene for one hour at room temperature. Complete rearrangement of the starting material was observed, with the formation of the same equilibrium mixture of compounds [(+)-cyclosativene (32%), (+)-sativene (7%) and (-)-isosativene (61%)] that occurred with the acetic acid-cupric acetate rearrangement. The three products were isolated by preparative g.l.c. and in each case, the structure was confirmed by direct comparison (g.l.c. retention times, infrared and n.m.r. spectra) with an authentic sample.

In order to avoid, as much as possible, the formation of the side products during the synthesis of (-)-copacamphene, the procedure

involved in the eliminative cyclization of the olefinic tosylate 180 was modified. That is, in order to avoid prolonged exposure of the initially formed (-)-copacamphene to acid, the crude olefinic tosylate (180) was applied to the top of a silica gel column, and the resulting column was eluted with pentane. From the eluant, could be isolated in high yield, (-)-copacamphene which was now contaminated with only very small amounts (∿ 1-2%) of (+)-cyclosativene and (-)-isosativene.

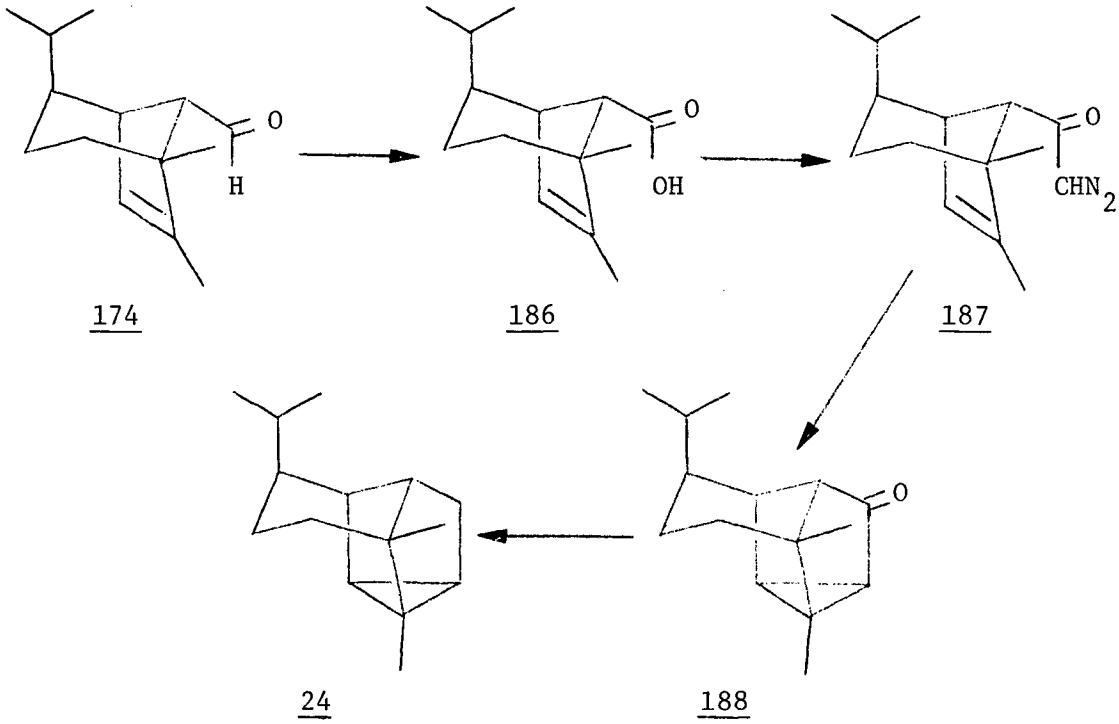
6. Synthesis of (-)-Cyclocopacamphene (24)

Of the number of possible routes which might be employed in the synthesis of cyclocopacamphene, we first chose a reaction sequence involving an intramolecular cyclization of an olefinic diazoketone. This appeared to be a potentially efficient method for the synthesis of the tetracyclic ring system. The use of olefinic diazoketones in intramolecular cyclizations was already well documented,[103] and some successful syntheses in our laboratory had been based upon this type of reaction. For example, this is well illustrated by the synthesis of (±)-aristolone (184).[104] Formation of the sodium salt of acid 181 followed by reaction of the salt with oxalyl chloride produced the acid chloride (182). Reaction of the latter with ethereal diazomethane afforded the olefinic diazoketone (183). Intramolecular cyclization resulted when 183 was refluxed in cyclohexane in the presence of cupric sulfate. (±)-Aristolone (184) and (±)-6,7-epi-aristolone (185) were formed in a ratio of 2:1 respectively.



181 182 183 184 185

For the projected synthesis of (-)-cyclocopacamphene (24), the olefinic acid (186), would be required. Obviously this compound could readily be obtained by oxidation of the previously prepared (-)-olefinic aldehyde (174). Following a reaction sequence similar to that described for the synthesis of aristolone, the olefinic acid (186) would be converted to the corresponding olefinic diazoketone (187), and cyclization of the latter would produce cyclocopacamphenone (188). Wolff-Kishner reduction (or the equivalent) of compound 188 would then afford cyclocopacamphene (24).



174 186 187

24 188

The olefinic acid (186) was readily prepared by a "wet" Sarett oxidation procedure.[105] Thus, treatment of 174 with chromium trioxide in pyridine-water afforded, in 80% yield, the (-)-keto acid (186). This crystalline material exhibited the expected spectral properties. Most notably, the acid proton appeared at τ 0.18 as a broad signal in the n.m.r. spectrum, with the vinyl proton appearing at τ 4.55 as a broad singlet. A one-proton multiplet at τ 7.19 accounted for the allylic proton, while the vinyl methyl group was evident as a pair of doublets ($J_{C_5H-C_{14}H}$ = 1.0 Hz, $J_{C_6H-C_{14}H}$ = 1.6 Hz) at τ 8.40. The tertiary methyl group and the isopropyl methyl groups were clearly evident in the n.m.r. spectrum of compound 186 as a singlet (τ 8.89) and two doublets (τ 9.07 and 9.11, J = 6.0 Hz) respectively.

The sodium salt of the (-)-olefinic acid (186) was treated with oxalyl chloride in anhydrous ether at ice temperature, to afford the corresponding olefinic acid chloride (189) (λ_{max} 5.52 μ). The latter was reacted immediately with a large excess of dry ethereal diazomethane. The progress of the reaction was monitored by infrared, and although weak absorptions due to the diazoketone were noted (λ_{max} 4.70, 6.04 μ), an infrared absorption at 5.73 μ grew in intensity as the acid chloride absorption (λ_{max} 5.52 μ) disappeared. After 2.5 hours at 0°, the acid chloride (189) had completely reacted, as judged by the absence of the corresponding absorptions in the infrared.

Even though the diazoketone (187) was believed to be only a very minor component in the reaction mixture (as judged by the appropriate weak absorptions in the infrared) the carbenoid addition reaction was attempted. Accordingly, a solution of the crude mixture of reaction products in cyclohexane was refluxed in the presence of cupric sulfate[103] for one hour. The crude product thus obtained consisted mainly of the (-)-keto olefin (190), accompanied by a number of minor products. Preparative g.l.c. allowed the isolation of compound 190 in approximately 60% yield from the (-)-olefinic acid (186). The analytical and spectral data exhibited by this compound were in complete accord with the assigned structure. In the infrared spectrum, the five-membered ring carbonyl group appeared characteristically at 5.73 μ, while the terminal olefin absorptions were evident at 3.26, 6.01 and 11.38 μ. In the n.m.r. spectrum of the keto olefin (190) (Figure 14), the signals due to the vinyl protons appeared as singlets at τ 5.03 and 5.27. The signals due to the allylic proton (an unresolved multiplet at τ 7.13),

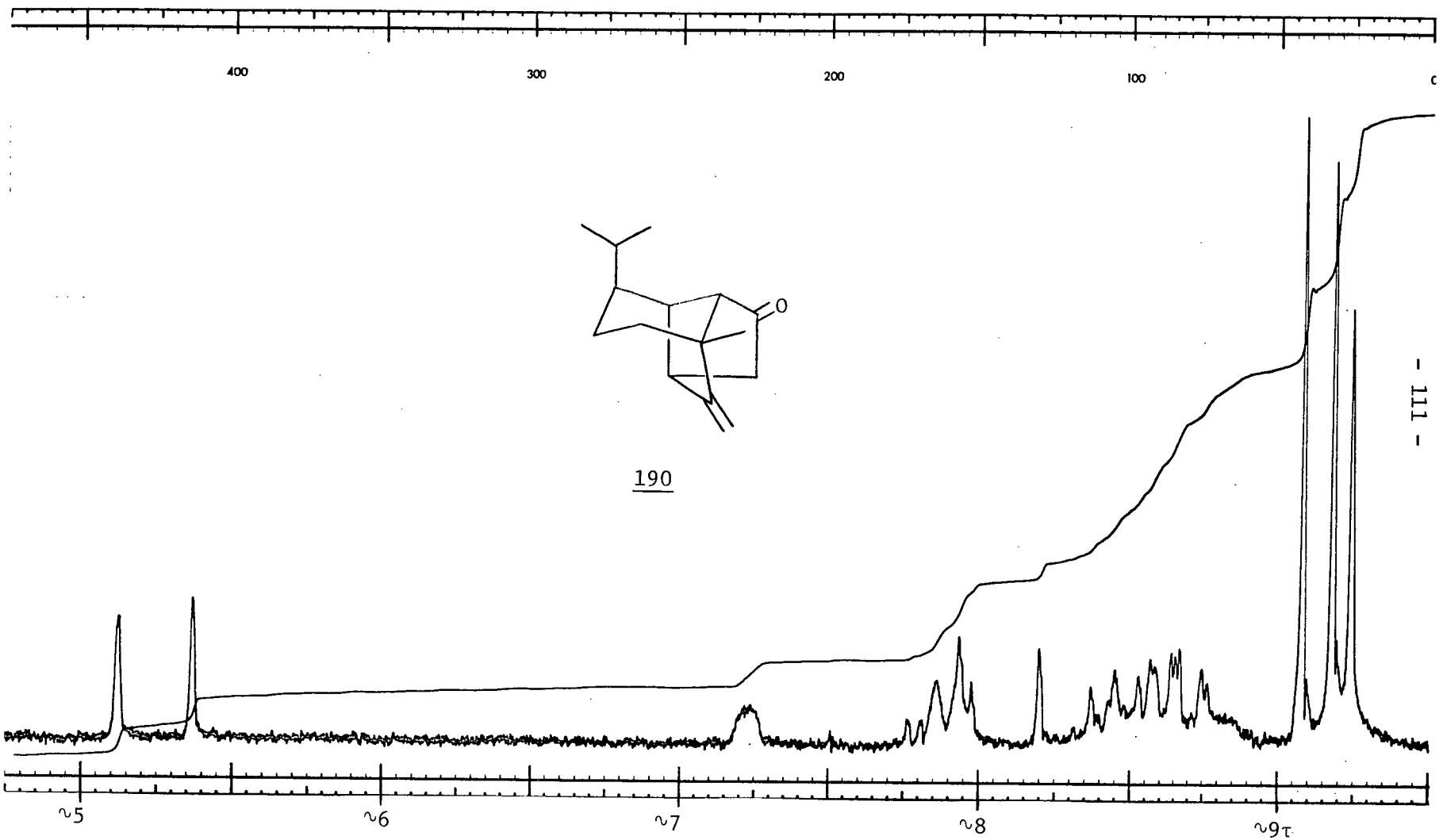
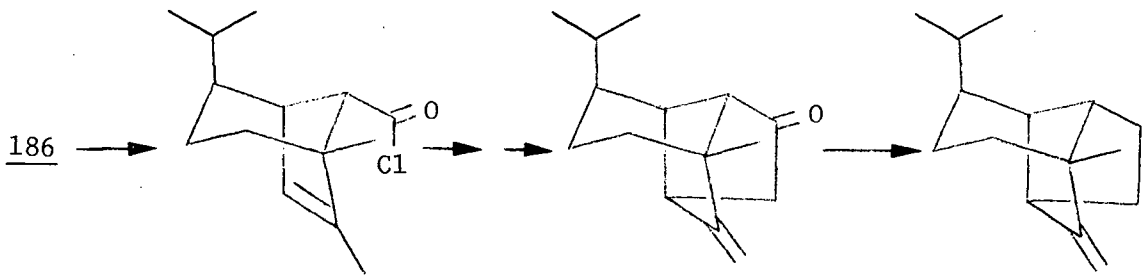


Figure 14. N.M.R. Spectrum of the (-)-Keto Olefin (190).

the tertiary methyl group (a singlet at τ 8.99) and the isopropyl methyl groups (a doublet at τ 9.12, J = 6.0 Hz) were also apparent in this spectrum.

As a further verification of the structure, the (-)-keto olefin (190) was subjected to the Huang-Minlon modified Wolff-Kishner reduction[106] producing (-)-copacamphene (23) in 58% yield. The latter was identified by direct comparison (g.l.c. retention times, infrared and n.m.r. spectra) with authentic material.

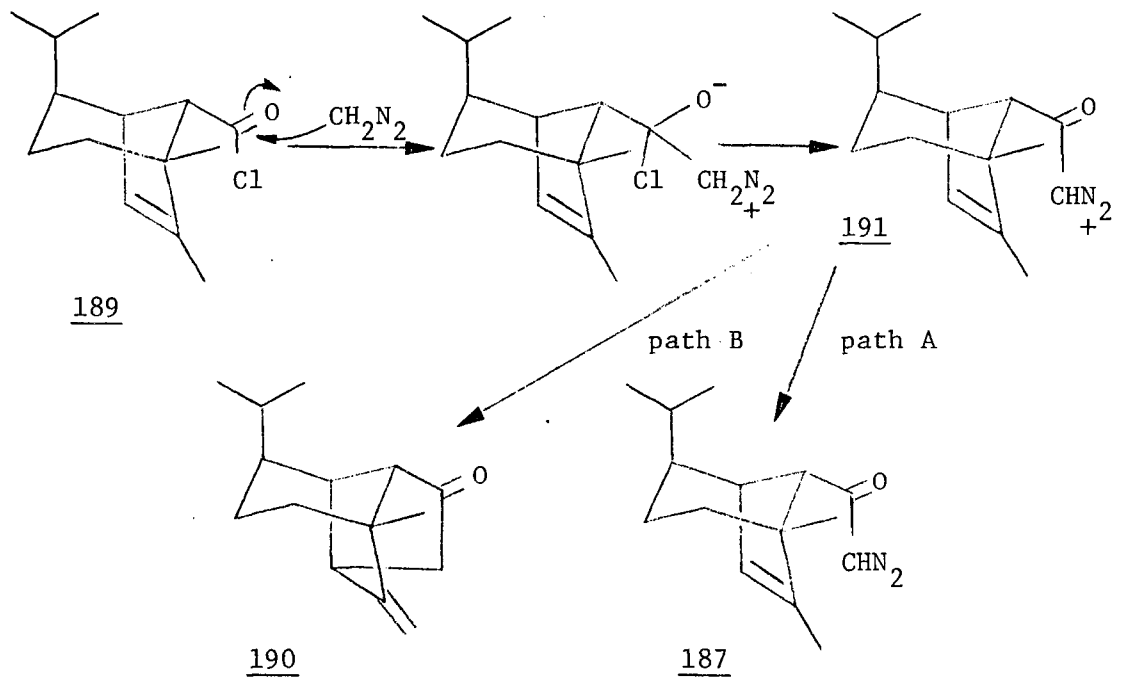


189 190 23

One of the minor components (approximately 5%) that was also isolated by preparative g.l.c. from the cupric sulfate catalyzed cyclization reaction was believed to be cyclocopacamphenone (188). The g.l.c. retention time of this material (188) was similar to that of the (-)-keto olefin (190). Although lack of sufficient material precluded the full characterization of compound 188, the spectral properties that were obtained were in good agreement with the proposed structure. In the infrared spectrum, the carbonyl group absorption appeared at 5.73 μ, while the absorptions at 11.42 and 12.03 μ were characteristic of a tricyclene-type nucleus.[102] The tertiary methyl groups appeared as sharp singlets (τ 8.82 and 9.08) in the n.m.r.

spectrum of 188, while the isopropyl methyl groups were evident as doublets (J = 6.0 Hz) at τ 9.12 and 9.15.

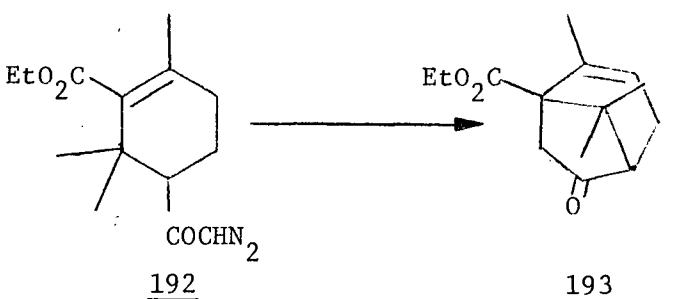
It is appropriate to comment briefly regarding the possible mechanism involved in the formation of the (-)-keto olefin (190). Attack of diazomethane on the carbonyl group of the acid chloride (189), with subsequent expulsion of a chloride ion, would leave the positively charged species 191. Abstraction of a proton from the position α to the carbonyl group (path A) would produce the neutral diazoketone (187)*. However, because of the proximity of the olefinic double bond and the electrophilic carbon (α to the carbonyl and diazo groups) compound 191 could undergo an intramolecular eliminative cyclization (path B) to produce the (-)-keto olefin (190).



* Also produced would be hydrogen chloride which, presumably, would be rapidly destroyed by excess diazomethane.

When the reaction mixture that was obtained from the treatment of the acid chloride (189) with diazomethane was reacted with p-toluenesulfonic acid in benzene, the infrared absorptions corresponding to the diazoketone (187) disappeared almost immediately. The crude product thus obtained again consisted mainly of the (-)-keto olefin (190), as determined by gas-liquid chromatographic analysis and lacked the tetracyclic compound 188. Presumably, the diazoketone (187) was protonated, and the resulting charged species 191 underwent intramolecular cyclization to produce the (-)-keto olefin (190).

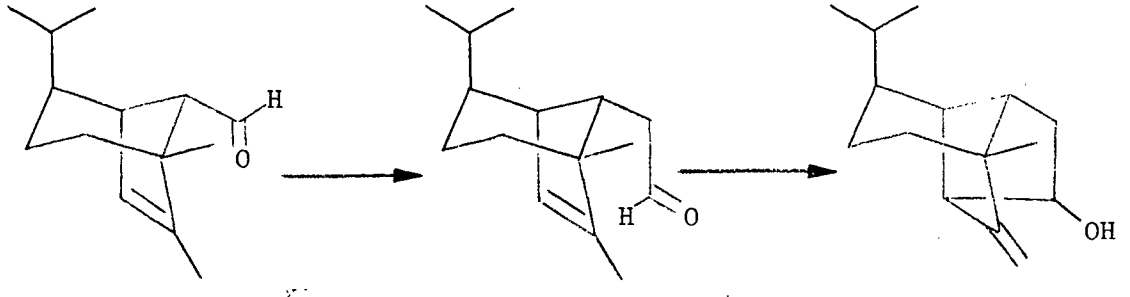
In support of the above conclusion, it should be noted the acid-catalyzed intramolecular cyclization of olefinic diazoketones was recently reported by Erman and Stone.[107] Thus, these workers found, for example, that the olefinic diazoketone (192), when treated with a catalytic amount of a Lewis acid (boron trifluoride etherate), cyclized to the corresponding bicyclic system (193).



192 193

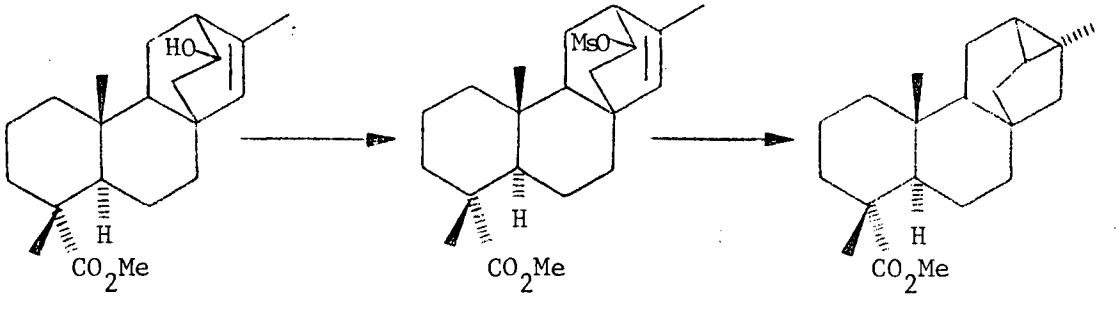
Although the work just described resulted in an interesting alternative synthesis of (-)-copacamphene, the sequence was clearly unsatisfactory for the synthesis of (-)-cyclocopacamphene. Therefore, alternative routes were considered. One possibility which was

investigated, for example, involved the proposed conversion of the (-)-olefinic aldehyde (174) into the next higher homolog, the olefinic aldehyde (194). Subsequent acid catalyzed cyclization of the latter would presumably afford the olefinic alcohol (195), possibly a potentially useful intermediate for the synthesis of (-)-cyclocopacamphene.



174 194 195

Recently, Herz and co-workers[108] reported a synthesis of methyl trachylobanate (see below) in which the key synthetic step involved the formation of the cyclopropane ring by reduction of the olefinic mesylate with sodium borohydride. It was thus felt that a similar reduction of the mesylate corresponding to the olefinic alcohol (195) could result in the formation of (-)-cyclocopacamphene.



Reaction of the (-)-olefinic aldehyde (174) with methoxymethylene-triphenylphosphorane in dimethyl sulfoxide[62] afforded, in 55% yield, a mixture of the cis-and trans-olefinic enol ethers (196 and 197) in a 1:6 ratio, respectively, as determined by gas-liquid chromatographic analysis. An analytical sample of the trans-olefinic enol ether (197) was obtained by preparative g.l.c., and exhibited spectral properties in complete accord with the assigned structure. In the n.m.r. spectrum, the doublet (J = 15 Hz) at τ 3.62 was assigned to the C_{10} proton (see compound 197 for numbering), while the pair of doublets(J=15Hz,J=10Hz) at τ 5.23 was attributed to the C_9 proton. The other vinyl proton appeared at τ 4.64 as a broad singlet, while the protons of the methoxy group were evident as a sharp singlet at τ 6.54. The vinyl methyl group appeared as a pair of doublets ($J_{C_5H-C_{16}H}$ = 1.0 Hz, $J_{C_6H-C_{16}H}$ = 1.6 Hz) at τ 8.38, while the tertiary methyl group (a singlet at τ 9.16) and the isopropyl methyl groups (doublets at τ 9.08 and 9.14 J = 6.0 Hz) were also readily evident in the n.m.r. spectrum of 197.

When the mixture of enol ethers (196 and 197) was subjected to hydrolysis with 35% perchloric acid in ether at room temperature,[100] the corresponding olefinic aldehyde 194 was not obtained. Rather, the resultant product was the tricyclic olefinic alcohol 195, undoubtedly formed by an acid catalyzed internal Prins reaction of the intermediate olefinic aldehyde 194. The olefinic alcohol was somewhat unstable, and for this reason, it was not fully characterized. However, the spectral data that was obtained was in complete agreement with the assigned structure. In the infrared spectrum, the hydroxyl absorption

appeared at 2.96 μ, while the absorptions at 3.25, 6.03 and 11.38 μ were characteristic of an exocyclic methylene group. N.m.r. evidence indicated that this material was an epimeric mixture of diasteriomers, presumably with respect to the centre (C_8) bearing the hydroxyl group. The vinyl protons were evident as a broad singlet (width at half-height = 7.0 Hz) at τ 5.05, while the proton adjacent to the hydroxyl group appeared as multiplet at τ 5.94. Because of the epimeric nature of this material, the other signals were difficult to assign.

Due to the fact that the olefinic alcohol (195) consisted of a mixture of epimeric compounds and somewhat unstable, this material was subjected directly to Collins oxidation.[98] It was felt that the (-)-keto olefin (198) thus obtained would also be a potentially useful intermediate (*vide infra*) for the synthesis of (-)-cyclocopacamphene. An analytical sample of compound 198 was obtained by preparative g.l.c., and exhibited the expected spectral properties. In the infrared spectrum, the carbonyl group absorption was evident at 5.69 μ, while the terminal methylene group absorptions appeared at 3.25, 6.03 and 11.28 μ. In the n.m.r. spectrum (Figure 15) the signals corresponding to the olefinic protons appeared as triplets (J = 0.8 Hz) at τ 4.82 and 5.18. The allylic proton appeared as a broad singlet at τ 7.04, while the three-proton singlet at τ 8.90, and the six-proton doublet (J = 6.3 Hz) at 9.07 accounted for the presence of the tertiary methyl group and isopropyl methyl groups respectively.

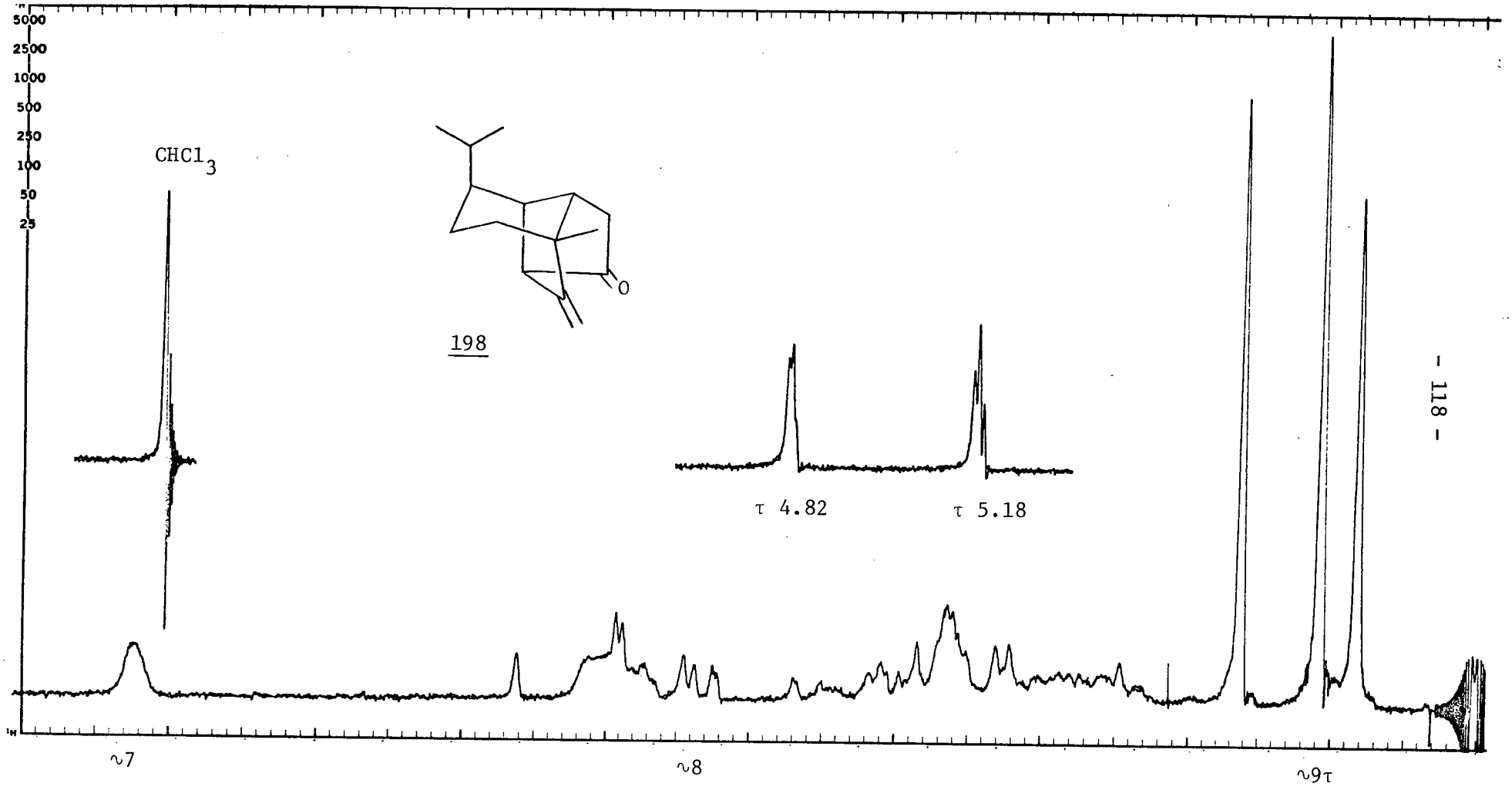
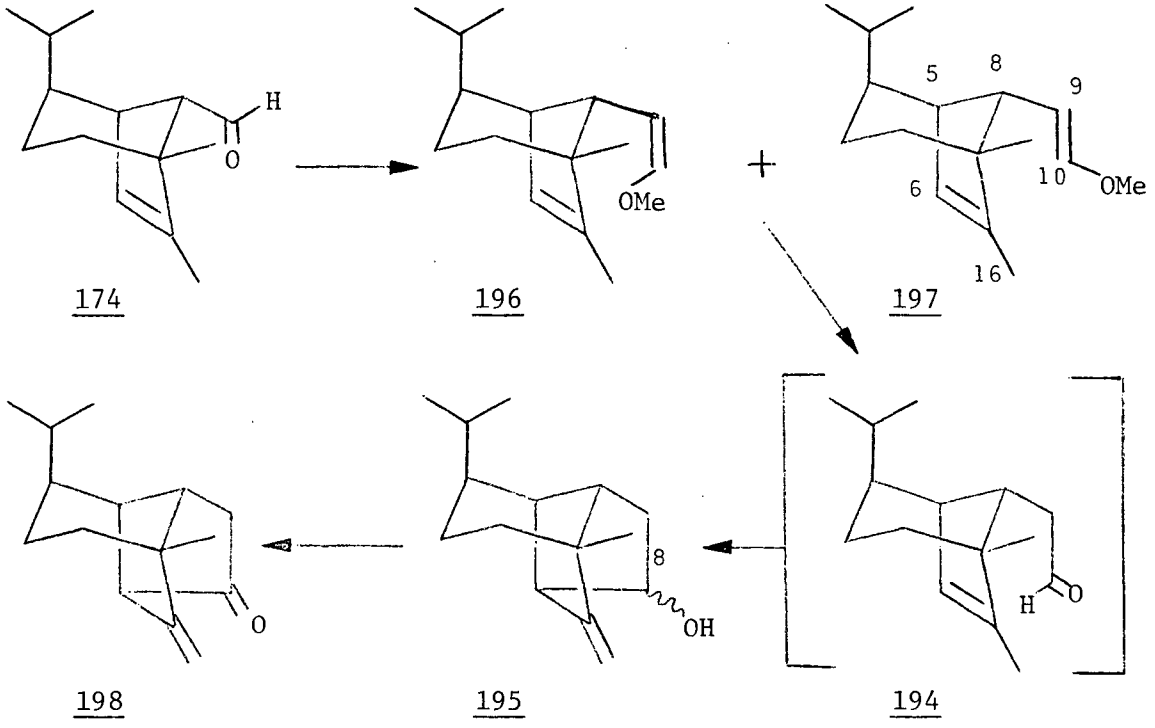


Figure 15. N.M.R. Spectrum of the (-)-Keto Olefin (198).



174 196 197

198 195 194

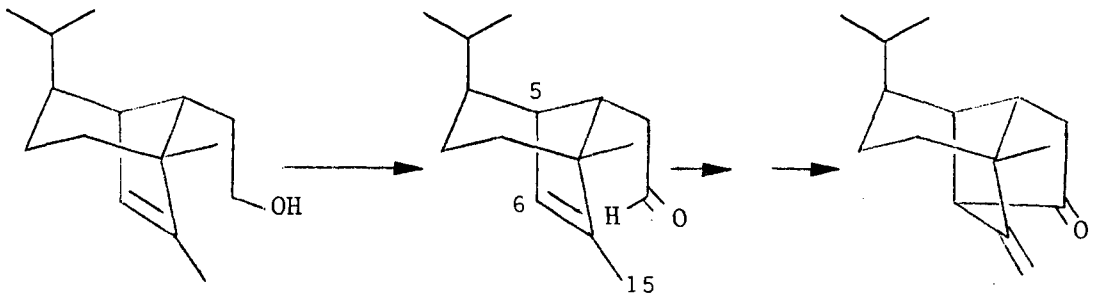
Due to the fact that the overall yield of the above reaction sequence was quite poor (10-15% from 174 → 198), other means of synthesizing the (-)-keto olefin (198) were investigated. In particular, it was decided to oxidize the previously prepared (+)-olefinic alcohol (178) under basic or neutral conditions, and then to cyclize the resultant olefinic aldehyde (194) under carefully controlled conditions.

Utilizing the modified Collins oxidation procedure,[98] the (+)-olefinic alcohol (178) was converted into the (-)-olefinic aldehyde (194) in 91% yield. The analytical and spectral data of this material was in complete accord with the assigned structure. In the infrared spectrum of compound 194, the aldehydic absorptions appeared at 3.68 and

5.80 μ, while the olefinic double bond absorptions appeared at 3.29 and 5.96 μ. The aldehydic proton appeared as a triplet (J = 2.5 Hz) at τ 0.20 in the n.m.r. spectrum. The vinyl proton appeared as a broad singlet at τ 4.60, while the vinyl methyl group appeared at τ 8.42 as a pair of doublets ($J_{C_5H-C_{15}H}$ = 1.0 Hz, $J_{C_6H-C_{15}H}$ = 1.6 Hz). The isopropyl methyl groups were evident as doublets (J = 6.5 Hz) at τ 9.07 and 9.13, while the tertiary methyl group was evident as a singlet at τ 9.10.

The intramolecular Prins reaction was accomplished by reacting the (-)-olefinic aldehyde (194) with a 0.05 mM solution of p-toluenesulfonic acid in benzene at room temperature for thirty minutes. The reaction mixture was then quenched by addition of pyridine. The crude cyclization product was immediately oxidized with Collins reagent[98] to produce a mixture of the (-)-keto olefin (198) and the starting material (194) in a ratio of 5:2 respectively. The (-)-keto olefin (198) purified by preparative g.l.c., was obtained in 65% yield (based on unrecovered olefinic aldehyde 194). Considerable effort was expended in an attempt to find optimum reaction conditions for the internal Prins reaction. It was found that the use of reaction times longer than thirty minutes, or of more concentrated solutions of p-toluenesulfonic acid, produced, after Collins oxidation of the crude product, primarily the desired keto olefin (198) but in much lower yield. Use of shorter reaction times resulted in the isolation of considerable amounts of starting material (194).

As a further verification of the structure of the (-)-keto olefin (198), this material was subjected to the Huang-Minlon modification[106] of the Wolff-Kishner reduction. The reaction produced, in poor yield

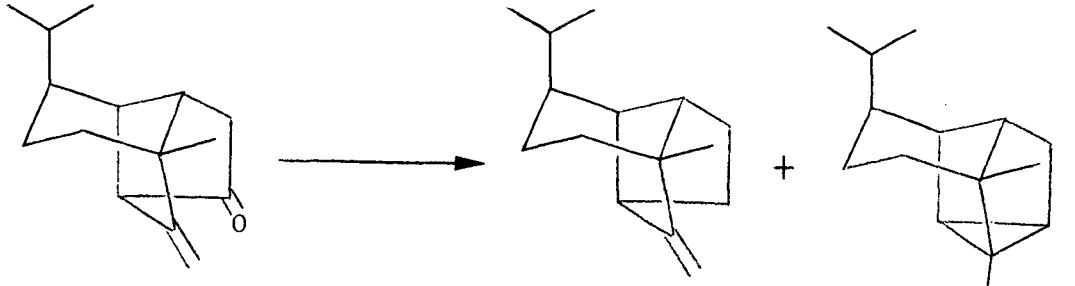


178 194 198

(25%), two hydrocarbon in a ratio of 4:1, as determined by gas-liquid chromatographic analysis. These compounds were separated by column chromatography on silver nitrate impregnated silica gel and the major component was identified as (-)-copacamphene by direct comparison (g.l.c. retention times, infrared and n.m.r. spectra) with authentic material. The minor component was identified as (-)-cyclocopacamphene (24), and exhibited $[\alpha]_D^{21}$ -42°. The infrared spectrum (Figure 17) showed absorptions at 3.29, 11.60, 11.80, and 12.10 μ which are characteristic of the tricyclene-type skeleton.[102] In the n.m.r. spectrum (Figure 18), the tertiary methyl groups appeared as singlets at τ 8.99 and 9.26, while the isopropyl methyl groups were evident as doublets (J = 6.5 Hz) at τ 9.10 and 9.13. Two broad signals at τ 9.32 and 9.37 could be attributed to the presence of the cyclopropyl protons. The infrared and n.m.r. spectra of this material were identical* with those of authentic (+)-cyclocopacamphene (24).[18]

---

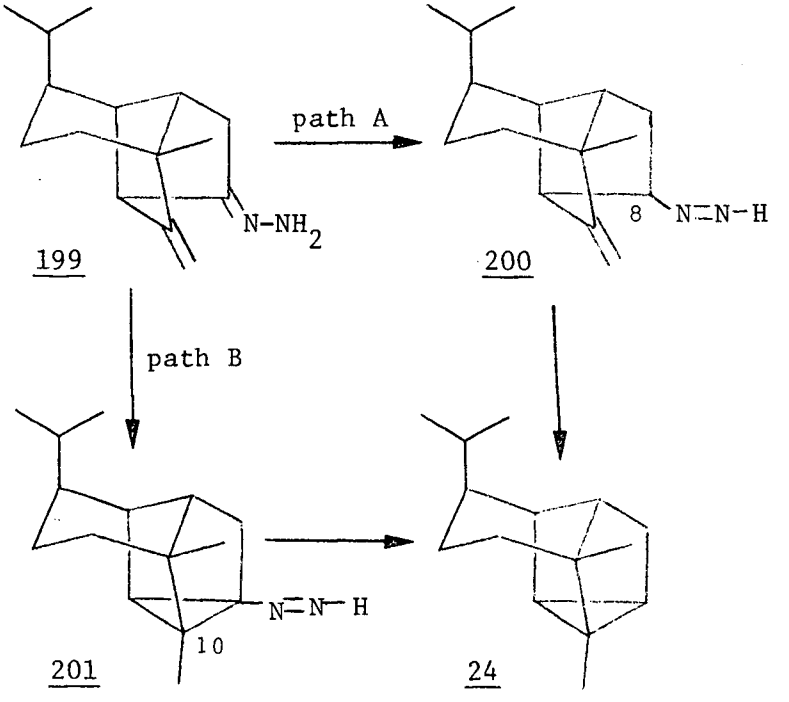
* F. Kido, Ph.D. Thesis, Tohoku University, Sendai, Japan (1970). We are grateful to Dr. Kido for his help in carrying out this comparison.



198 23 24

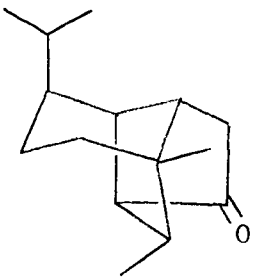
The formation of (-)-cyclocopacamphene (24) in the Huang-Minlon reduction of the (-)-keto olefin (198) was somewhat surprising. Speculatively, the former compound could be thought to arise via one or both of two different pathways involving decomposition of the intermediate hydrazone (199). Firstly, abstraction by base of one of the amine protons of compound 199, followed by normal protonation of the resulting intermediate on C_8 (path A), would produce the tricyclic azo intermediate (200). Abstraction of a second proton from the nitrogen atom of 200, followed by concomitant elimination of nitrogen, closure of the cyclopropane ring and protonation of the terminal carbon of the exocyclic methylene group, would produce the tetracyclic structure of cyclocopacamphene (24). Another possible mechanism to account for the formation of compound 24 (path B) would simply involve reversal of the order of the two steps obtained above. Thus, proton abstraction from compound 199, followed by concomitant ring closure and protonation at C_{10}, would produce the tetracyclic azo compound (201). Abstraction of the second amine proton, followed by elimination of nitrogen and normal protonation of the resulting carbanion would

also account for the production of (-)-cyclocopacamphene (24).

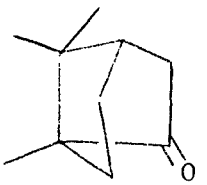


Although the work just described represented a total synthesis of (-)-cyclocopacamphene, an alternate, more efficient reaction sequence was sought.

There are several examples in the literature of reactions involving the cyclization of camphor or camphor-like substances into compounds containing cyclopropane rings.[109,110] These reactions were of particular interest, since the hydrogenated form of the (-)-keto olefin (198), ketone 202, has incorporated into it the same structural unit (substituted bicyclo[2.2.1]heptanone system) present in camphor (5).

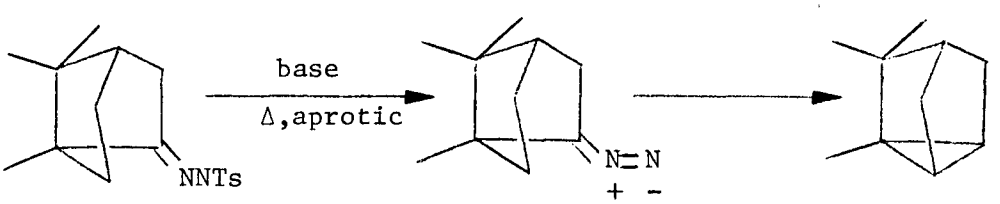


202



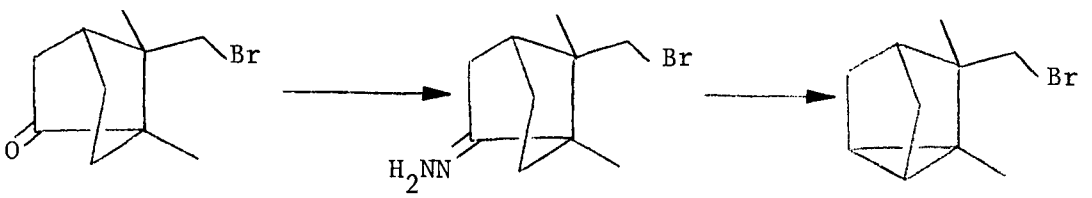
5

When camphor tosylhydrazone (203) was reacted with more than one equivalent of base in an aprotic solvent, tricyclene (21) was the only product formed, in yields of between 90-95%.[109] The intermediate diazocamphane (204) loses nitrogen to give a carbene or carbenoid intermediate which undergoes an intramolecular carbon-hydrogen insertion reaction.



203 204 21

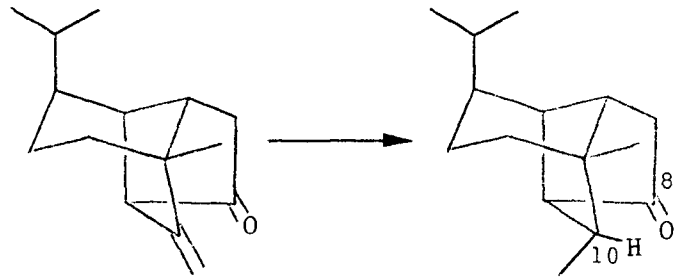
In their total synthesis of α-santalene, Corey and co-workers[110] utilized another procedure for the formation of a cyclopropane ring. The bromocamphor (205) was converted into the corresponding hydrazone (206), and the latter was oxidized with mercuric oxide in methanol to produce bromotricyclene (207). Presumably, an intermediate carbenoid was also involved in this reaction.



205 206 207

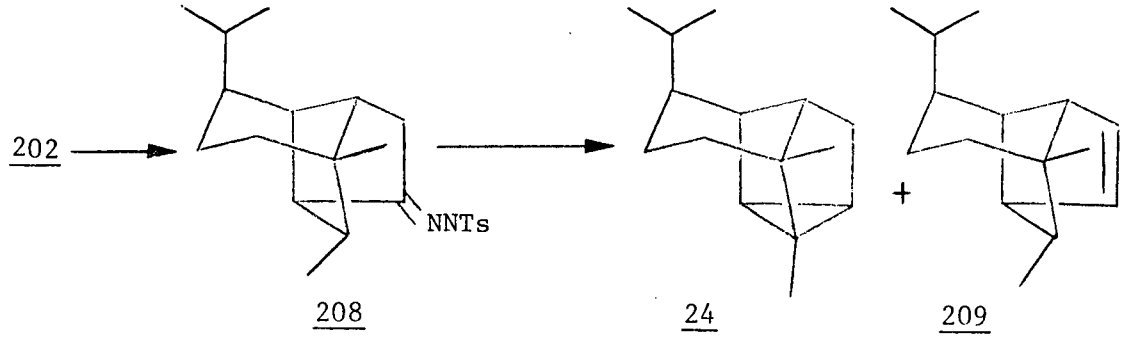
Hydrogenation of the (-)-keto olefin (198) in ethanol over 5% palladium on charcoal afforded the (-)-tricyclic ketone (202). The stereochemistry at the newly created asymmetric centre (C_{10}) was of some importance. That is, if one wishes to achieve cyclopropane ring formation by insertion of a carbene (generated at C_8) into the C_{10}-H bond, then the latter bond would have to be endo to the bicyclo[2.2.1]heptanone system present in compound 202. In other words, hydrogenation of compound 198 would have to afford compound 202 with stereochemistry at C_{10} as shown. A study of a molecular model of the (-)-keto olefin (198) revealed that hydrogenation of this compound should indeed occur in the desired sense and one could be reasonably certain that the hydrogenation product possessed the desired stereochemistry. The spectral properties of the hydrogenated product (202) were in complete accord with the assigned structure. The carbonyl group absorption appeared at 5.73 μ in the infrared spectrum. Of particular interest in the n.m.r. spectrum was the absence of any signals corresponding to the vinyl protons, and the appearance of a doublet (J = 7.0 Hz) at τ 9.19 which was attributed to the newly created secondary methyl group.

The tertiary methyl group (a singlet at τ 9.08) and the isopropyl methyl groups (a doublet at τ 9.11, J = 6.3 Hz) were also clearly evident in the n.m.r. spectrum of compound 202.



198 202

Reaction of the (-)-tricyclic ketone (202) with p-toluenesulfonylhydrazide in refluxing methanol in the presence of an acid catalyst afforded the corresponding p-tosylhydrazone (208). The latter was converted into the corresponding carbene intermediate in two different ways. Firstly, compound 208 was added to a suspension of sodium hydride in diglyme, and after formation of the p-tosylhydrazone salt, the reaction mixture was heated at 140° for one hour. In the second procedure, one equivalent of n-butyllithium in hexane was added to a solution of compound 208 in tetrahydrofuran. The solvents were removed under reduced pressure, and the remaining dry tosylhydrazone salt was pyrolyzed in the absence of a solvent. In each case, gas-liquid chromatographic analysis of the product indicated that approximately only 10% of (-)-cyclocopacamphene was formed. Furthermore, the major product (approximately 65%) was the (+)-tricyclic olefin (209). Also present were a number of minor unidentified hydrocarbons.



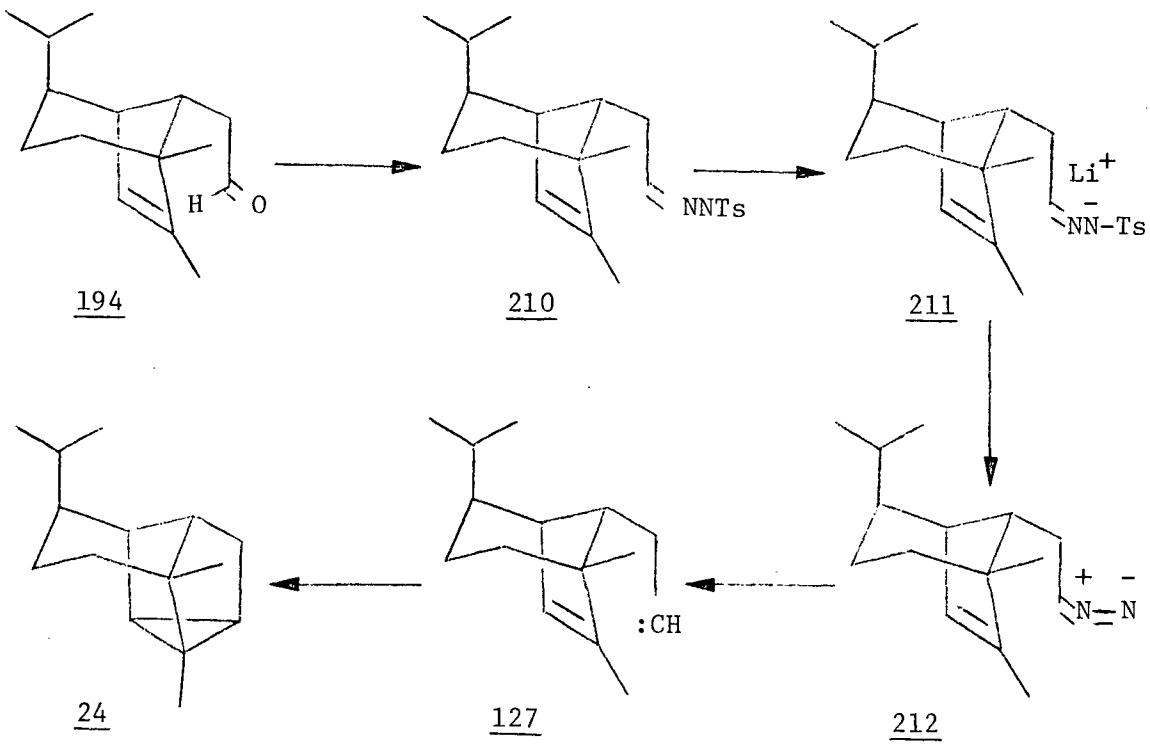
208 24 209

In each case, (-)-cyclocopacamphene (24) was isolated by preparative g.l.c. and identified by direct comparison (g.l.c. retention time and infrared spectrum) with the authentic material. The (+)-tricyclic olefin (209) was also isolated by preparative g.l.c. and exhibited spectral properties in accord with the assigned structure. The olefinic double bond absorptions appeared at 3.26, 6.03 and 13.90 μ in the infrared spectrum. In the n.m.r. spectrum of 209, the vinyl protons appeared as an overlapped pair of doublets at τ 3.80. The isopropyl methyl groups appeared as doublets (J = 6.0 Hz) at τ 9.16 and 9.17, while the sharp singlet of the tertiary methyl group (τ 9.28) and the doublet (J = 7.0 Hz) of the secondary methyl group (τ 9.30) were also clearly evident.

In a related attempt at the synthesis of (-)-cyclocopacamphene, the hydrazone of the ketone 202 was prepared. When this hydrazone was reacted with yellow mercuric oxide in refluxing methanol,[110] (-)-cyclocopacamphene was obtained in approximately 30% yield, although the tricyclic olefin (209) was again the major product (55%)

of the reaction. These attempts to prepare (-)-cyclocopacamphene via a carbene insertion reaction were not persued further because, while this research was in progress, another more efficient synthetic route to (-)-cyclocopacamphene was developed.

The synthetic route which finally resulted in an efficient synthesis of (-)-cyclocopacamphene was originally based on a proposed intramolecular addition of a carbenoid to a carbon-carbon double bond. Thus, it was planned to convert the previously prepared (-)-olefinic aldehyde (194) into the corresponding p-tosylhydrazone (210). Pyrolysis of the lithium salt (211) of the latter would, hopefully, product the corresponding diazo compound (212) which would, presumably, be a direct precursor of the required carbenoid-olefin (127). Intramolecular addition of the latter would then produce (-)-cyclocopacamphene (24).

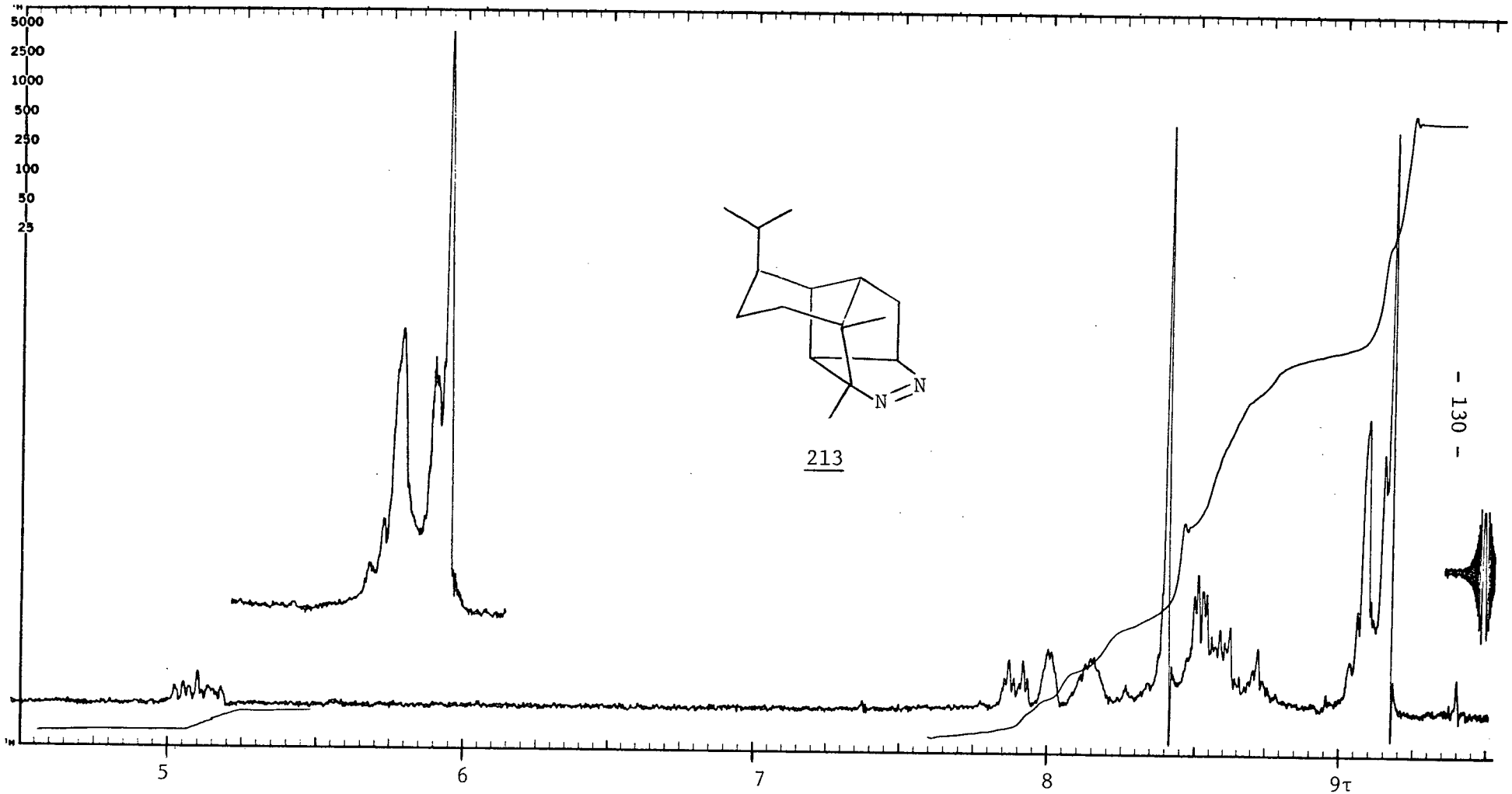


194 210 211

24 127 212

Preparation of the p-tosylhydrazone 210 was readily accomplished by reacting the (-)-olefinic aldehyde (194) with p-toluenesulfonylhydrazide in refluxing benzene for five minutes. Compound 210 was unstable, so it was reacted immediately with one equivalent of n-butyllithium to form the corresponding salt (211). Pyrolysis (120-140°) of compound 211 under reduced pressure (0.25 mm) with direct distillation of the product afforded, not the diazo compound (212), or cyclocopacamphene, but the (+)-pyrazoline (213) in 81% yield from 194. Obviously, the (+)-pyrazoline (213) was formed by a facile intramolecular 1,3-dipolar cycloaddition of the intermediate diazoalkene (212). The facility with which this reaction took place was presumably a function of the proximity of the two reacting functional groups and of the fairly strained nature of the olefinic double bond.[111] The (+)-pyrazoline (213) exhibited the expected spectral properties with characteristic pyrazoline absorptions at 334 mμ (ε = 232) in the ultraviolet spectrum, and at 6.45 μ in the infrared spectrum. The regioselectivity of the reaction (212 → 213) was demonstrated by the n.m.r. spectrum (Figure 16) of compound 213. Thus, the one-proton multiplet at τ 5.11 was assigned to the proton adjacent to the -N=N-moeity.[112] Furthermore, the tertiary methyl groups (singlets at τ 8.42 and 9.18) and the isopropyl methyl groups (a doublet at τ 9.14, J = 6.0 Hz) were readily distinguishable.

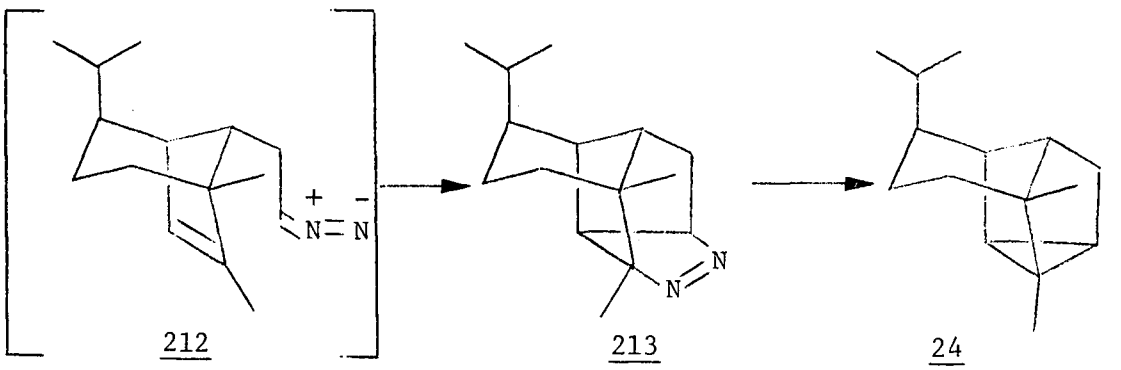
The (+)-pyrazoline (213) was irradiated in ether at room temperature for approximately one hour, using a Rayonet reactor equipped with 3500 Å lamps and a pyrex filter. Removal of the solvent, and reduced



213

Figure 16. N.M.R. Spectrum of the (+)-Pyrazoline (213).

pressure distillation of the resulting oil afforded pure (-)-cyclocopacamphene (24) in 93% yield. This material was identical [g.l.c. retention times, specific rotation, infrared and n.m.r. spectra (Figures 17 and 18)] with the (-)cyclocopacamphene prepared previously.



212 213 24

Thus, in conclusion, the structure and absolute stereochemistry of (-)-copacamphene and of (-)-cyclocopacamphene have been fully corroborated by the described stereoselective synthesis of these compounds.

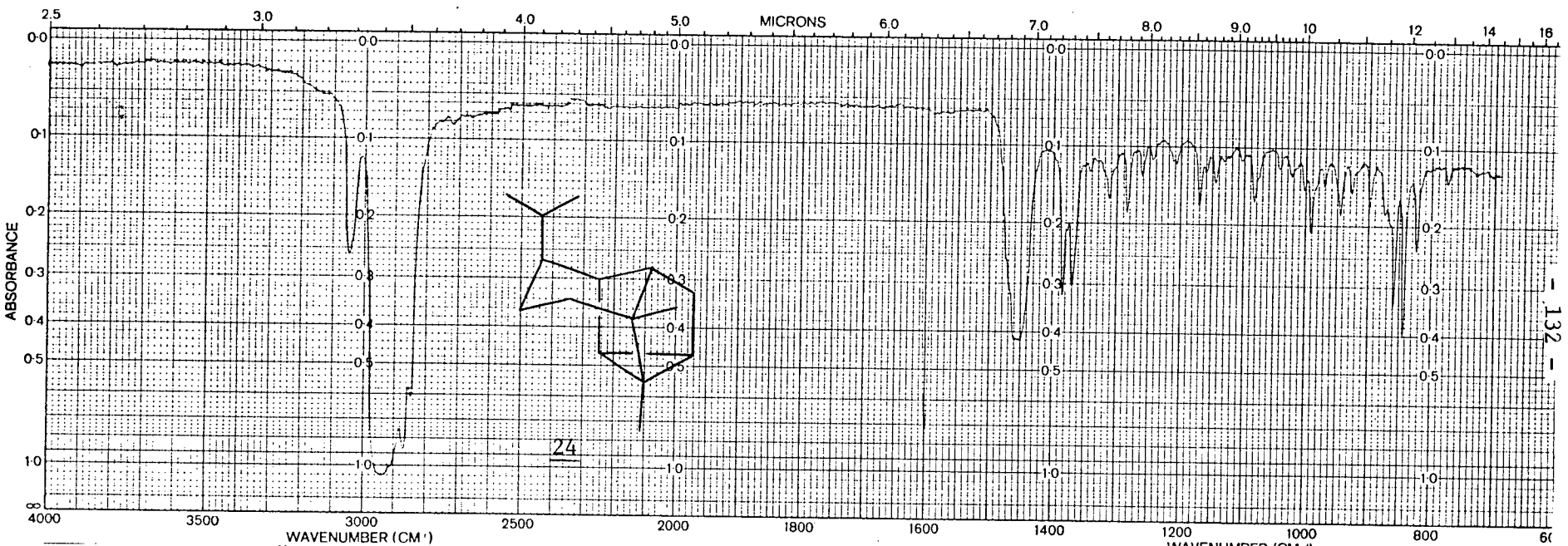


Figure 17. Infrared Spectrum of (-)-Cyclocopacamphene (24).

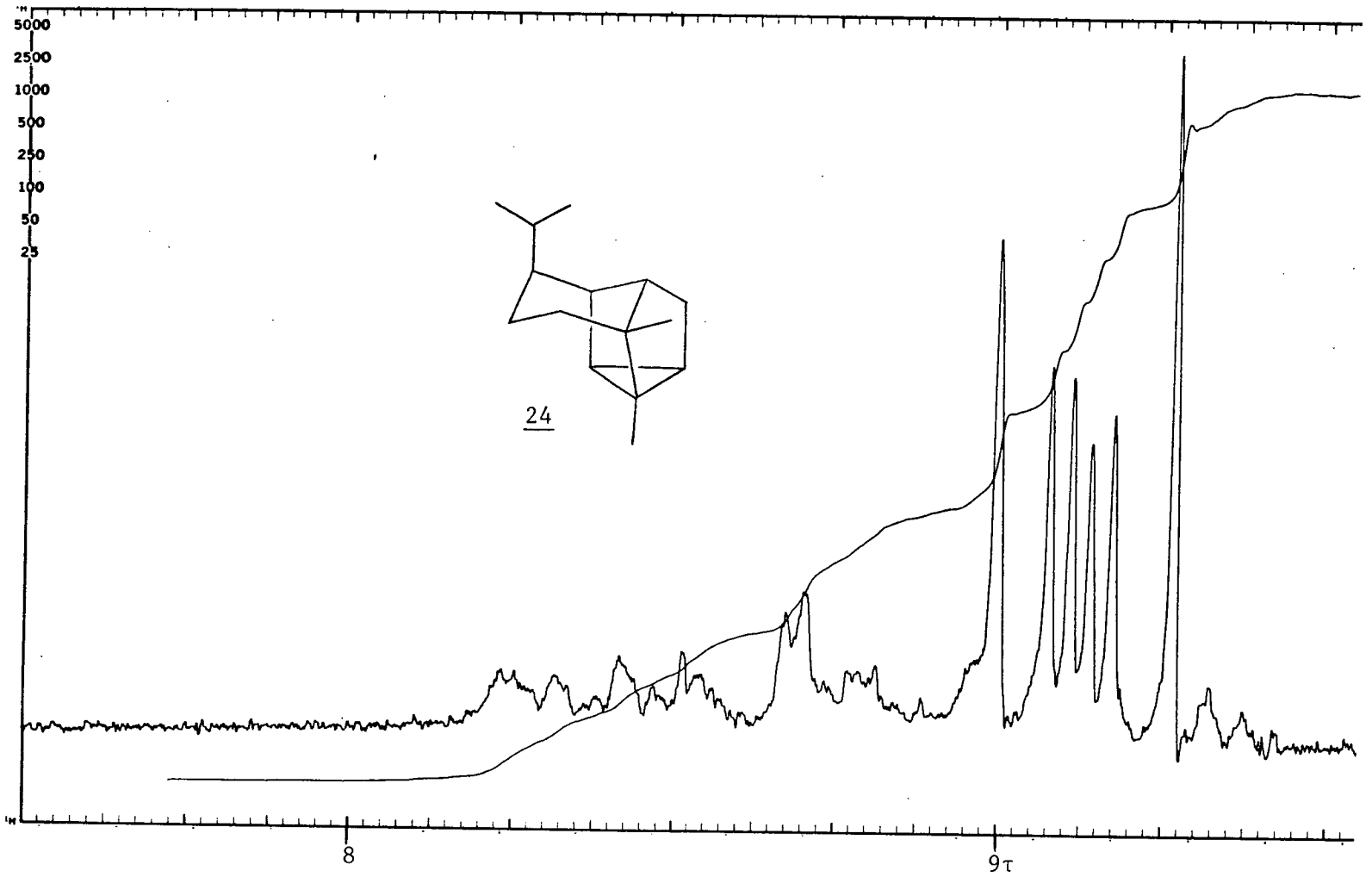


Figure 18. N.M.R. Spectrum of (-)-Cyclocopacamphene (24).

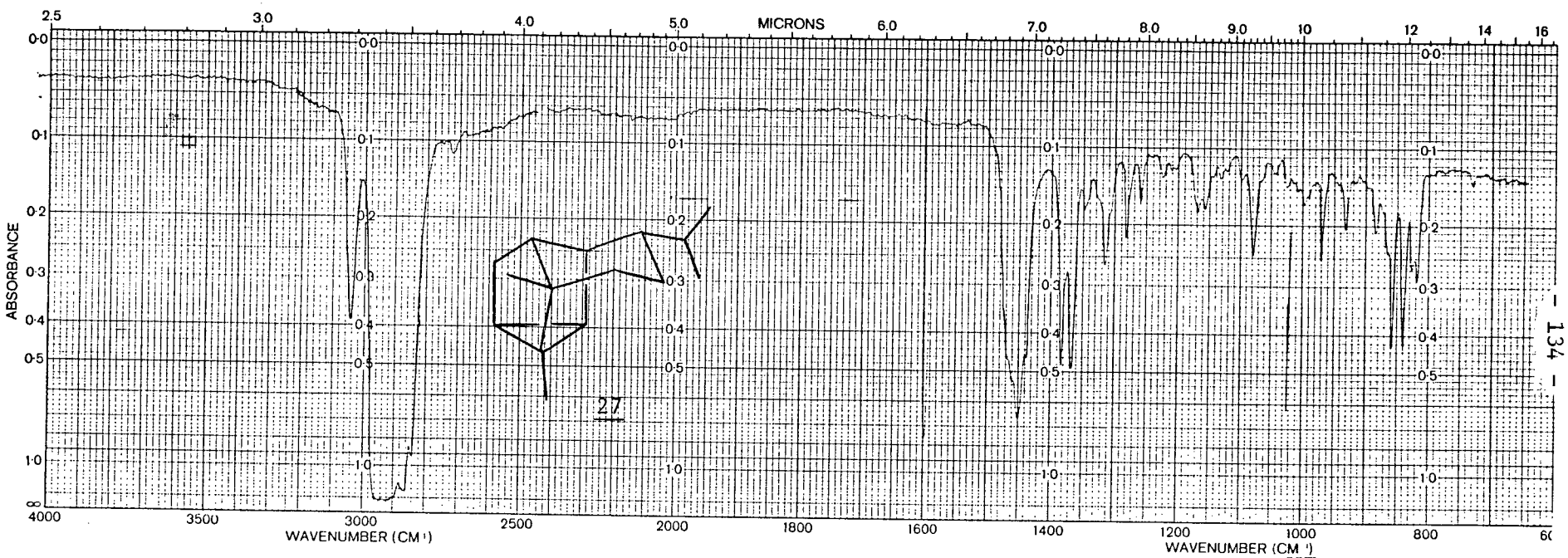


Figure 19. Infrared Spectrum of (+)-Cyclosativene (27).

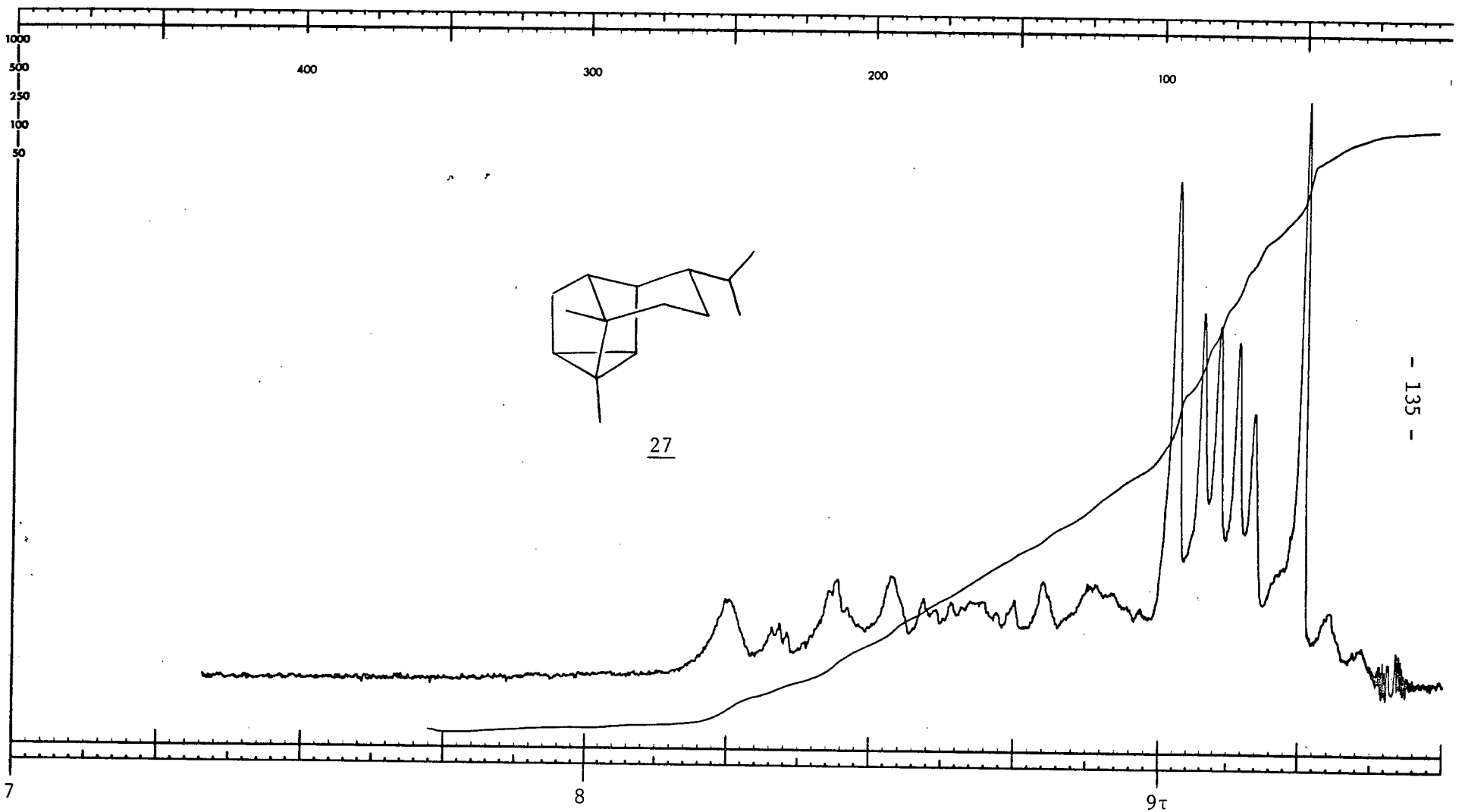


Figure 20. N.M.R. Spectrum of (+)-Cyclosativene (27).

EXPERIMENTAL

General

Melting points, which were determined on a Kofler block, and boiling points are uncorrected. Optical rotations were obtained at the sodium D line, using a Rudolph Polarimeter, model 219, a Bendix ETL-NPL Automatic Polarimeter Type 143A, or Perkin-Elmer Model 141 Automatic Polarimeter. Ultraviolet spectra were, unless otherwise noted, measured in methanol solution on either a Cary, model 14, or a Unicam, model SP 800, spectrophotometer. Routine infrared spectra were recorded on a Perkin-Elmer Infracord model 137 or a Perkin-Elmer Model 710 spectrophotometer while comparison spectra were recorded on a Perkin-Elmer spectrophotometer, model 457. N.m.r. spectra were, unless otherwise noted, recorded in deuterochloroform solution on Varian Associates spectrometers models A-60, T-60 and/or HA-100, XL-100. Line positions are given in the Tiers τ scale, with tetramethylsilane as internal standard; the multiplicity, integrated peak areas and proton assignments are indicated in parentheses. Gas-liquid chromatography (g.l.c.) was carried out on either an Aerograph Autoprep model 700 or a Varian Aerograph, model 90-P. The following columns (10 ft x 1/4 in, unless otherwise noted) were employed, with the inert supporting material being, in each case, 60/80 mesh Chromosorb W (unless otherwise noted): column A (5 ft x 1/4 in),

20% SE 30; column B, 20% SE 30; column C (20ft x 3/8 in), 30% SE 30; column D, 20% Apiezon J; column E (10 ft x 3/8 in), 8% FFAP (60/80 mesh Chromosorb G); column F, 8% FFAP (60/80 mesh Chromosorb G); column G (10 ft x 3/8 in) 30% Apiezon J. The specific column used, along with the column temperature and carrier gas (helium) flow-rate (in ml/min), are indicated in parentheses. Microanalyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia, Vancouver. High resolution mass spectra were recorded on a AEI type MS-9 mass spectrometer.

Preparation of the Hydroxymethylene Derivative (130)

To an ice-cooled, stirred suspension of powdered sodium methoxide (81.5 g, 1.51 moles) in 300 ml of dry benzene, kept under an atmosphere of dry nitrogen, was added a solution of 77.2 g (.502 mole) of (-)-carvomethone (123) in 300 ml of dry benzene. The resulting mixture was stirred for 10 min, and then a solution of 112 g (1.51 moles) of ethyl formate in 60 ml of dry benzene was added. The mixture was warmed to room temperature and allowed to stir overnight. Water was added, the mixture was thoroughly shaken 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 cooled, acidified with concentrated hydrochloric acid and thoroughly extracted with ether. The combined ethereal extracts were washed with water and brine, and dried over anhydrous magnesium sulfate. Removal of solvent, followed by distillation of the residual oil under

reduced pressure, gave 75.3 g (83%) of the hydroxymethylene derivative (130) (mixture of epimers) as a pale yellow oil, b.p. 89-93° at 1.0 mm; n_D^{21} 1.4936; ultraviolet, λ_{max} 291 mμ (ε = 6,570), $\lambda_{max}^{NaOH\ added}$ 317 mμ (ε = 17,000); infrared (film), λ_{max} 5.78, 5.88, 6.14, 6.32, 6.88, 7.35 μ.

Preparation of the 2-n-Butylthiomethylene Derivative (131)

A solution of the hydroxymethylene derivative (130) (62.0 g , .341 mole), n-butanethiol (36.8 g, .408 mole), and p-toluenesulfonic acid (40 mg) in 400 ml of dry benzene was refluxed in a nitrogen atmosphere under a Dean Stark water separator overnight, at which time 6 ml of water had been collected. The cooled solution was washed with saturated aqueous sodium bicarbonate, then with water, and finally dried over anhydrous magnesium sulfate. Removal of the solvent gave an oil, which, upon distillation under reduced pressure, afforded 72.1 g (83%) of the n-butylthiomethylene derivative (131) (mixture of epimers), b.p. 120-126° at 0.2 mm; n_D^{21} 1.5252; ultraviolet, λ_{max} 302 mμ (ε = 11,700); infrared (film), λ_{max} 6.00, 6.51, 6.89, 8.58, 12.51 μ.

Anal. Calcd. for $C_{15}H_{26}OS$: C, 70.82; H, 10.30; S, 12.58. Found: C, 70.57; H, 10.42; S, 12.40.

Preparation of the Alkylated n-Butylthiomethylene Derivative (132)

The n-butylthiomethylene derivative (131) (101.6 g, 0.40 mole) was added to 1 ℓ of dry t-butanol containing 46.0 g (0.46 mole) of potassium t-butoxide and the resulting solution was stirred at room temperature for 10 min and then cooled to 0°. Ethyl 2-iodiopropionate

[prepared from reaction of 181.9 g (1.0 moles) of ethyl 2-bromopropionate and 165 g (1.1 moles) of sodium iodide in 1 ℓ of acetone, followed by appropriate workup] was added slowly, and the reaction mixture was stirred at room temperature under an atmosphere of dry nitrogen overnight. Most of the solvent was removed under reduced pressure and the residue was diluted with water. The resulting mixture was extracted with ether, and the organic layer was 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 103.2 g (73%) of the desired alkylated product (132) (mixture of epimers), b.p. 172-180° at 0.8 mm; n_D^{24} 1.5181; ultraviolet, λ_{max} 301 mμ (ε = 10,300); infrared (film), λ_{max} 5.79, 6.00, 6.51, 6.88, 8.50 μ.

Anal. Calcd. for $C_{20}H_{34}O_3S$: C, 67.76; H, 9.67; S, 9.03. Found: C, 67.74; H, 9.49; S, 9.00.

Preparation of Keto Ester (135)

To a solution of the alkylated n-butylthiomethylene derivative (132) (103 g) in 450 ml of diethylene glycol was added 450 ml of 25% aqueous potassium hydroxide and the resulting solution was refluxed under nitrogen for 22 h. The reaction mixture was cooled and acidified with concentrated hydrochloric acid and then thoroughly extracted with ether. The ethereal layer was dried over anhydrous magnesium sulfate and then concentrated. The crude acid (134) thus obtained was reacted with excess ethereal diazomethane, then the excess diazomethane was destroyed by the addition of acetic acid. The ethereal

layer was washed with water, a 10% sodium carbonate solution and brine, then dried over anhydrous magnesium sulfate. Removal of the solvent followed by distillation of the residual oil gave 61.2 g (85%) of the desired keto ester (135) (epimeric mixture of diastereomers), b.p. 120-126° at 0.2 mm; n_D^{21} 1.4722; infrared (film), λ_{max} 5.77, 5.89, 6.87, 8.38 μ; n.m.r., τ 6.34, 6.36 (singlets, 3H, methyl ester protons), 7.00, 7.13 (quartets, 1H, protons adjacent to the ester carbonyls, $J_{\tau 7.00}$ = 7.5 Hz, $J_{\tau 7.13}$ = 7.0 Hz), 8.76, 8.87 (singlets, 3H, tertiary methyls), 8.84, 8.89 (doublets, 3H, secondary methyls, $J_{\tau 8.84}$ = 7.5 Hz, $J_{\tau 8.89}$ = 7.0 Hz), 9.09 (doublet, 6H, isopropyl methyls, J = 6.0 Hz).

Anal. Calcd. for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.84; H, 9.90.

Preparation of Sodium Bis(trimethylsilyl)amide

To a solution of 89.0 g (.553 mole) of 1,1,1,3,3,3-hexamethyldisilazane in 200 ml of dry benzene was added 20.0 g (.513 mole) of sodium amide. The mixture was refluxed for 4 h at which time the evolution of ammonia had ceased. The hot solution was filtered through celite, then the solvent and the excess hexamethyldisilazane were removed under water aspirator pressure. The resulting crystalline material was recrystallized from dry benzene, and the last traces of the solvent were removed by placing the crystals under vacuum overnight, to afford 57.5 g (57%) of the desired sodium bis(trimethylsilyl)amide.

Preparation of the (-)-Diketone (122)

To a solution of 80.6 g (0.44 mole) of sodium bis(trimethylsilyl)-amide in 900 ml of dry dimethoxyethane was added a solution of 48.0 g (0.20 mole) of the keto ester (135) in 100 ml of dry dimethoxyethane, and the resulting mixture was refluxed under an atmosphere of dry nitrogen for 1.0 h. The reaction was then cooled, and quenched by pouring the cooled reaction mixture into a rapidly stirred solution of 27.0 g (0.45 mole) of glacial acetic acid in 300 ml of ice water. The reaction mixture was concentrated, and the residue was dissolved in ether. The ethereal layer was washed with water, a 10% sodium bicarbonate solution, and brine, and then dried over anhydrous magnesium sulfate. Removal of the solvent afforded a crystalline material which was recrystallized from petroleum ether (b.p. 60-110°) to yield 37.4 g (90%) of the desired diketone (122), m.p. 76-77°; $[\alpha]_D^{20}$ -56° (c, 4.0 in $CHCl_3$); infrared ($CHCl_3$), λ_{max} 5.66, 5.79, 6.88, 8.46 μ; n.m.r., τ 7.08 (broadened doublet, 1H, bridgehead proton, J = 4.8 Hz), 7.66 (quartet of doublets, C_7H, $J_{C_7H-C_{13}H}$ = 7.0 Hz, $J_{C_5H-C_7H}$ = 1.5 Hz), 8.75 (doublet, 3H, secondary methyl, J = 7.0 Hz), 8.90 (singlet, 3H, tertiary methyl), 9.00, 9.10 (doublets, 6H, isopropyl methyls, J = 6.3 Hz).

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.80; H, 9.75.

Mol. Wt. Calcd. for $C_{13}H_{20}O_2$: 208.146. Found (high resolution mass spectrometry): 208.143.

Preparation of (+)-Dihydrocarvone (140)

To approximately 2 ℓ of liquid ammonia was added 35 g (5.00 moles) of lithium metal, and the resulting blue solution was stirred for 30 min. A solution of (-)-carvone (128) (150 g, 1.00 moles) in 250 ml of anhydrous ether was added over a period of one hour, and the resulting solution was stirred for an additional hour. After the reaction had been quenched with 150 ml of methanol, the ammonia was allowed to evaporate and the residual material was diluted with water. The aqueous layer was saturated with salt and thoroughly extracted with ether. The combined extracts were dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure afforded 132 g of the crude alcohol.

Standard chromic acid solution[99] was added to a solution of the crude alcohol (132 g) in 750 ml of acetone at 0° until an orange colour persisted. Isopropyl alcohol was added to destroy the excess oxidizing reagent and the solution was evaporated under reduced pressure. The residual material was diluted with water and then extracted thoroughly with ether. The ethereal extracts were dried over anhydrous magnesium sulfate and the ether was removed at aspirator pressure. Distillation of the residual oil gave 116 g (78%) of (+)-dihydrocarvone (140) as a colourless oil, b.p. 67-68° at 2.0 mm, lit.[77] b.p. 100-104° at 12.0 mm; infrared (film), λ_{max} 5.85, 6.10, 11.20 μ; n.m.r., τ 5.30 (unresolved multiplet, 2H, vinyl protons), 8.26 (singlet, 3H, vinyl methyl), 8.95 (doublet, 3H, secondary methyl, J = 6.5 Hz).

Preparation of the (+)-Ketol(142)

To a solution of (+)-dihydrocarvone (140) (100 g, 0.657 mole) in 1 ℓ of anhydrous ether was added sodium amide (29 g, 0.725 mole). To this mixture was added slowly a solution of 1-diethylamino-3-pentanone methiodide (141) (206 g, 0.690 mole), [prepared by reaction of 1-diethylamino-3-pentanone (110 g, 0.690 mole) with methyl iodide (96 g, 0.690 mole)] in 200 ml of dry pyridine. The reaction mixture was stirred at 0° for 6 h and then refluxed for 6 h. Water was then added and the resulting mixture was extracted with ether. The combined ether extracts were washed with water and brine, then dried over anhydrous magnesium sulfate. Removal of the solvent, afforded a yellow oil which was subjected to fractional distillation under reduced pressure. The initial fractions (22 g, b.p. 75-110° at .8 mm) consisted mainly of the starting material, (+)-dihydrocarvone (140). The later fractions (98 g, b.p. 144-174° at 0.8 mm) consisted of an oil which solidified on standing.

Recrystallization of the above solidified material from hexane gave 42.3 g of the pure ketol (142) (52% based on unrecovered (+)-dihydrocarvone) m.p. 108°, lit.[78] m.p. 106°; infrared ($CHCl_3$), λ_{max} 2.96, 5.92, 6.14, 11.28 μ; n.m.r., τ 5.35 (multiplet, 2H, vinyl protons), 8.33 (doublet, 3H, vinyl methyl, J = 1.0 Hz), 8.77 (singlet, 3H, tertiary methyl), 8.97 (doublet, 3H, secondary methyl, J = 6.5 Hz).

Preparation of the (+)-Ketol (145)

The ketol (142) (42.0 g) in 250 ml of ethanol was hydrogenated over 4.0 g of 10% palladium on charcoal at room temperature until the

uptake of hydrogen was complete (approximately 1 h). Removal of catalyst and solvent yielded the (+)-ketol (145) (41.6 g) as colourless crystals, m.p. 65°, lit.[78] m.p. 64-65°; $[\alpha]_D^{20}$ +49.4° (c, 1.5 in MeOH); infrared ($CHCl_3$), λ_{max} 2.85, 5.87, 6.90, 9.65 μ; n.m.r., τ 7.10 (quartet, 1H, C_4H, J = 7.0 Hz), 8.75 (singlet, 3H, tertiary methyl), 8.94 (doublet, 3H, secondary methyl, J = 7.0 Hz), 9.16 (doublet, 6H, isopropyl methyls, J = 6.0 Hz).

Anal. Calcd. for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.40; H, 10.83.

Preparation of (-)-11,12-Dihydro-7-epi-α-cyperone (146)

The (+)-ketol (145) (41.0 g) was dissolved in 425 ml of 10% ethanolic potassium hydroxide and the resulting solution was heated under reflux in an atmosphere of nitrogen for 10 h. The cooled solution was diluted with water and neutralized with concentrated hydrochloric acid. The resulting mixture was extracted with petroleum ether (b.p. 30-60°). The organic extracts were dried over anhydrous magnesium sulfate. Removal of the solvent, followed by distillation of the residual oil under reduced pressure afforded 32.9 g (87%) of the desired octalone (146), b.p. 114-120° at 0.5 mm; n_D^{23} 1.5178, lit.[78] n^{20} 1.5190; $[\alpha]_D^{20}$ -170° (c, 1.3 in MeOH); ultraviolet, λ_{max} 250 mμ (ε = 15,800); infrared (film), λ_{max} 6.01, 6.22, 6.90, 8.36, 9.85 μ; n.m.r., τ 8.23 (doublet, 3H, vinyl methyl, J = 1.7 Hz), 8.74 (singlet, 3H, tertiary methyl), 9.08 (doublet, 6H, isopropyl methyls, J = 6.0 Hz).

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.59; H, 10.97.

Preparation of (-)-2-Hydroxymethylene-11,12-dihydro-7-epi-α-cyperone (152)

To an ice-cooled, stirred suspension of powdered sodium methoxide (10.8 g, 0.20 mole) in 60 ml of dry benzene, kept under an atmosphere of dry nitrogen, was added a solution of 14.5 g (.0659 mole) of the (-)-octalone (146) in 120 ml of dry benzene. The resulting mixture was stirred for 10 min, and then a solution of 14.8 g (0.20 mole) of ethyl formate in 60 ml of dry benzene was added. The mixture was warmed to room temperature and allowed to stir for 4 days. Water was added, the mixture was thoroughly shaken, and the layers separated. The organic layer was extracted with two portions of 10% aqueous sodium hydroxide. The combined aqueous layer and alkaline extracts were cooled, acidified with concentrated hydrochloric acid and thoroughly extracted with ether. The combined ethereal extracts were washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent, followed by distillation of the residual oil under reduced pressure, gave 15.7 g (96%) of the (-)-hydroxymethylene derivative (152) as a pale yellow oil, which then solidified, m.p. 45-48°; $[\alpha]_D^{20}$ -16.4 (c, 1.3 in MeOH); ultraviolet, λ_{max} 260 mμ (ε 9,350), 311 mμ (ε 4,760); $\lambda_{max}^{NaOH\ added}$ 256 mμ (ε = 9,620), 358 mμ (ε = 8,620); infrared ($CHCl_3$), λ_{max} 6.12, 6.40, 6.88, 8.25 μ; n.m.r., τ -4.17 (broad signal, 1H, =CHOH), 2.61 (singlet, 1H, =CHOH, width at half-height = 7.0 Hz), 8.14 (doublet, 3H, vinyl methyl, J = 1.6 Hz), 8.93 (singlet, 3H, tertiary methyl), 9.07 (doublet, 6H, isopropyl methyls, J = 6.0 Hz).

Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.20; H, 9.64.

Preparation of the (+)-Dienone Aldehyde (153)

A solution of 15.6 g (62.9 mmoles) of the hydroxymethylene derivative (152) and 15.3 g (67.3 mmoles) of 2,3-dichloro-5,6-dicyano-benzoquinone in 500 ml of dry dioxan was stirred for 10 min under a dry nitrogen atmosphere. This solution was then filtered through a sintered glass funnel, and the solvent was removed under reduced pressure. The resulting oil was taken into ether and washed with a 1% solution of sodium hydroxide, and water, then dried over anhydrous magnesium sulfate. The solvent was removed, and the resulting yellow oil was distilled (b.p. 143° at 0.23 mm). The distillate solidifed on standing and was recrystallized from hexane-ether to afford 12.0 g (78%) of the desired dienone aldehyde (153), m.p. 54°; $[\alpha]_D^{20}$ +139° (c, 1.0 in MeOH); ultraviolet, λ_{max} 262 mμ (ε = 11,600); infrared ($CHCl_3$), λ_{max} 3.67, 5.88, 6.07, 6.14, 6.24, 6.88, 8.03, 12.11 μ; n.m.r., τ -1.20 (singlet, 1H, aldehydic proton), 2.45 (singlet, 1H, vinyl proton), 8.00 (doublet, 3H, vinyl methyl, J = 1.0 Hz), 8.63 (singlet, 3H, tertiary methyl), 9.03, 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, 78.12; H, 8.95.

Preparation of the (+)-Keto Ester (138)

To a stirred suspension of cuprous iodide (2.8 g, 20.0 mmoles) in 90 ml of anhydrous ether at 0° and under an atmosphere of dry nitrogen, was added 18.5 ml of 2.16 M ethereal methyllithium. A small

amount of cuprous iodide was added until a noticeable amount of yellow precipitate was clearly visible, thus ensuring that no excess methyllithium was present. To the resulting lithium dimethylcuprate solution was added a solution of the (+)-dienone aldehyde (153) (2.46 g, 10.0 mmoles) in 90 ml of anhydrous ether, over a period of 10 min. The reaction was stirred at 0° for an additional 2 h. A solution of acetyl chloride (1.57 g, 20.0 mmoles) in 40 ml of anhydrous ether was added over a period of 5 min. The resulting solution was poured into a rapidly stirred mixture of concentrated ammonium hydroxide and crushed ice, in a ratio of approximately 1:2. The ether layer was quickly separated from the aqueous layer and washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. This material was somewhat unstable, and was used without further purification in the next reaction. However, an analytical sample of the keto acetate (154) was obtained by preparative g.l.c. (column A, 210°, 90) and exhibited infrared (film), λ_{max} 5.66, 5.99, 6.21, 7.33, 8.42, 8.77 μ; n.m.r., τ 1.80 (singlet, 1H, vinyl proton), 7.77 (singlet, 3H, acetate methyl), 8.14 (broad singlet, 3H, vinyl methyl), 8.83 (singlet, 3H, tertiary methyl), 8.97 (doublet, 3H, secondary methyl, J = 7.0 Hz), 9.07 (poorly resolved multiplets, 6H, isopropyl methyls).

A solution of the crude keto acetate (154) (2.5 g) in 80 ml of ethyl acetate was cooled to -78° by means of a dry ice-acetone bath. Ozone was bubbled through the solution until a permanent blue colour persisted, and then continued for an additional 20 min. The solution was allowed to warm to room temperature, and then concentrated, with the last traces of solvent being removed by vacuum pump. To the crude

ozinide was added 80 ml of 5% NaOH, and the reaction mixture was stirred at room temperature. To this mixture was added 16.5 ml of 30% hydrogen peroxide, in 1 ml portions over the period of 1 h. During this hour, the reaction was heated to 90°, and then maintained at this temperature for an additional hour. The reaction was then cooled, neutralized with concentrated hydrochloric acid, and extracted thoroughly with ether. The ethereal layer was dried over anhydrous magnesium sulfate, and concentrated. The crude acid (157) thus obtained was treated with excess ethereal diazomethane, then the excess diazomethane was destroyed by the addition of acetic acid. The ethereal layer was washed with water, 10% sodium bicarbonate solution and brine, then dried over anhydrous magnesium sulfate. Removal of the solvent and distillation of the residual oil, gave 1.09 g (45% from the dienone aldehyde) of the desired keto ester (138), b.p. 120° at 0.15 mm; n_D^{22} 1.4744; $[\alpha]_D^{22}$ +147° (c, 1.4 in $CHCl_3$); infrared (film), λ_{max} 5.76, 5.85, 6.89, 8.47 μ; n.m.r., τ 6.34 (singlet, 3H, methyl ester protons), 6.93 (quartet, 1H, proton adjacent to the carbonyl ester, J = 7.2 Hz), 9.01 (singlet, 3H, tertiary methyl), 9.04 (doublet, 3H, secondary methyl, J = 7.2 Hz), 9.09, 9.10 (doublets, 6H, isopropyl methyls, J = 6.0 Hz).

Anal. Calcd. for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.86; H, 9.97.

Preparation of the (+)-Diketone (139)

To a refluxing solution of 8.97 g (49.0 mmoles) of sodium bis-(trimethylsilyl)amide in 165 ml of dry benzene under an atmosphere of

dry nitrogen gas was added, over a period of 1 h, a solution of 3.36 g (14.0 mmoles) of the (+)-keto ester (138) in 30 ml of dry benzene. The reaction mixture was refluxed for an additional hour, then cooled to ice temperature and quenched by pouring this cooled solution into a rapidly stirred solution of 10 ml of acetic acid and 30 ml of water. The organic layer was washed with water, a saturated sodium carbonate solution, and brine, then dried over anhydrous magnesium sulfate. Removal of the solvent afforded a crystalline material which was recrystallized from pentane to yield 1.75 g (60%) of the desired diketone (139), m.p. 77-78°; $[\alpha]_D^{20}$ +100° (c, 2.8 in $CHCl_3$); infrared ($CHCl_3$), λ_{max} 5.66, 5.80, 6.87, 8.50, 9.95 μ; n.m.r., τ 7.10 (multiplet, 1H, C_5H), 7.71 (quartet of doublets, C_7H, $J_{C_7H-C_{13}H}$ = 7.3 Hz, $J_{C_5H-C_7H}$ = 1.5 Hz), 8.38 (doublet, 3H, secondary methyl, J = 7.3 Hz), 8.90 (singlet, 3H, tertiary methyl),9.02,9.15(doublets,6H,isopropyl methyls,J=6.3Hz).

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.65; H, 9.48.

Preparation of the (-)-Keto Enol Phosphate (164)

To a solution of 6.6 g (36 mmoles) of sodium bis(trimethylsilyl)-amide in 90 ml of dry tetrahydrofuran was added a solution of 5.0 g (24 mmoles) of the (-)-diketone (122) in 10 ml of dry tetrahydrofuran. The reaction mixture was stirred at room temperature under an atmosphere of dry nitrogen for 20 min, then quenched by the addition of a solution of 10.7 g (62 mmoles) of diethyl phosphorochlorodate (163) dissolved in 30 ml of dry pyridine. After stirring at room temperature for 30 min, the reaction mixture was concentrated under

water aspirator pressure. The residual material was diluted with water then thoroughly extracted with ether. The combined ethereal extracts were washed with water and saturated brine, then dried over anhydrous magnesium sulfate. Removal of the solvent, followed by distillation of the residual oil under reduced pressure afforded 7.8 g (94%) of the desired keto enol phosphate (164), b.p. 135-145° at 0.25 mm; n_D^{21} 1.4722; $[\alpha]_D^{25}$ -5.8° (c, 1.4 in $CHCl_3$); infrared (film), λ_{max} 5.69, 5.96, 7.87, 9.14, 9.77, 10.42, 11.42, 12.01 μ; n.m.r., τ 4.82 (pair of quartets, 4H, $-OC\underline{H}_2CH_3$, J = 7.0 Hz, J_{H-P} = 1.0 Hz), 8.30 (pair of doublets, 3H, vinyl methyl, $J_{C_5H-C_{13}H}$ = 1.0 Hz, J_{H-P} = 2.2 Hz), 8.63 (pair of triplets, 6H, $-O-CH_2C\underline{H}_3$, J = 7.0 Hz, J_{H-P} = 1.0 Hz), 8.98 (singlet, 3H, tertiary methyl), 9.08 (doublet, 6H, isopropyl methyls, J = 6.3 Hz).

Anal. Calcd. for $C_{17}H_{29}O_5P$: C, 59.29; H, 8.49. Found: C, 59.18; H, 8.45.

Preparation of the (-)-Keto Alcohol (169)

A solution of the (-)-diketone (122) (14.0 g, 67.3 mmoles) in 170 ml of ethanol was cooled to 0° and a solution of 825 mg (21.8 mmoles) of sodium borohydride dissolved in 30 ml of ethanol was added. The solution was stirred at 0° for 15 min and then the excess hydride was destroyed by addition of 4.4 g (74.0 mmoles) of acetic acid. The reaction mixture was concentrated under reduced pressure then the residue was diluted with water, and thoroughly extracted with ether. The combined ethereal extracts were washed with a saturated sodium carbonate solution and brine, and then dried over anhydrous magnesium

sulfate. Removal of the solvent followed by distillation of the residual oil under reduced pressure afforded 12.5 g (89%) of the desired keto alcohol (169), b.p. 125-130° at 0.4 mm; n_D^{25} 1.4916; $[\alpha]_D^{25}$ -69° (c, 1.0 in $CHCl_3$); infrared (film), λ_{max} 2.93, 5.80, 6.85, 9.00, 9.10 μ; n.m.r., τ 6.12 (doublet, 1H, C_8H, J = 5.5 Hz), 7.30 (multiplet, 1H, C_5H), 8.92 (doublet, 3H, secondary methyl, J = 7.0 Hz), 8.97 (singlet, 3H, tertiary methyl), 9.02, 9.13 (doublets, 6H, isopropyl methyls, J = 6.5 Hz).

Anal. Calcd. for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.12; H, 10.50.

Preparation of the (-)-Olefinic Alcohol (171)

A mixture of the (-)-keto alcohol (169) (12.0 g, 57.2 mmoles), p-toluenesulfonylhydrazide (11.7 g, 62.8 mmoles) and 9.0 ml of methanol were heated and stirred until a homogeneous solution was obtained. Then 300 μℓ of acetyl chloride was added to the solution, and the reaction mixture was stirred under an atmosphere of dry nitrogen at 90-100° for 3 h. The reaction was diluted with water and thoroughly extracted with ether. The combined etheral extracts were washed with a 10% solution of sodium bicarbonate, then with brine, and finally dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure yielded 21.2 g (98%) of the p-tosylhydrazone alcohol (170) as a viscous yellow oil [infrared (film), λ_{max} 2.76, 2.98, 3.01, 6.03, 6.25, 8.55 μ]. This material was used without further purification.

To an ice-cooled solution of the p-tosylhydrazone alcohol (170) (21.2 g, 56.2 mmoles) dissolved in 1100 ml of dry tetrahydrofuran was added 214 ml of 2.1 M ethereal methyllithium over a period of 30 min.

The reaction was allowed to warm to room temperature and was stirred under an atmosphere of dry nitrogen for an additional 3 h. The solution was then cooled to 0°, and the excess methyllithium was destroyed by the careful addition of water. The reaction mixture was concentrated, then the residue was diluted with water and thoroughly extracted with ether. The combined etheral extracts were washed with brine and dried over anhydrous magnesium sulfate. Removal of the solvent followed by distillation of the residual oil under reduced pressure afforded 9.57 g (88%) of the desired olefinic alcohol (171) as a colourless oil, b.p. 80° at 0.25 mm; n_D^{25} 1.4898; $[\alpha]_D^{25}$ -61° (c, 0.7 in $CHCl_3$); infrared (film), λ_{max} 2.94, 3.28, 6.17, 6.90, 9.18, 9.38, 12.43 μ; n.m.r., τ 4.60 (broad singlet, 1H, vinyl proton), 5.57 (singlet, 1H, hydroxyl proton), 6.36 (doublet, 1H, C_8H, J = 5.5 Hz), 7.34 (multiplet, 1H, allylic proton), 8.38 (pair of doublets, 3H, vinyl methyl, $J_{C_6H-C_{13}H}$ = 1.6 Hz, $J_{C_5H-C_{13}H}$ = 1.0 Hz), 9.10 (singlet, 3H, tertiary methyl), 9.03, 9.13 (doublets, 6H, isopropyl methyls, J = 6.5 Hz).

Anal. Calcd. for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.16; H, 11.27.

Preparation of the (-)-Keto Olefin (125)

(a) from lithium-ethylamine reduction of the (-)-keto enol phosphate (164)

A solution of 1.38 g (200 mmoles) of lithium metal in approximately 70 ml of dry ethylamine was stirred at room temperature for 20 min. To this solution was added dropwise over a period of 10 min a solution of the (-)-keto enol phosphate (164) (3.43 g, 10.0 mmoles), and t-butyl

alcohol (1.48 g, 20.0 mmoles) in 10 ml of dry ether and then the reaction was allowed to proceed for an additional 5 min. The solution was filtered through a small glass wool plug to remove the excess lithium, and the filtrate was added to a rapidly stirred ether-water mixture. The solution was extracted twice with ether, then the combined ethereal extracts were washed with water and brine, and dried over anhydrous magnesium sulfate. The ether was removed at aspirator pressure and the crude product was distilled under reduced pressure (b.p. 65-75° at 0.5 mm) to afford 900 mg of a yellow oil. Gas-liquid chromatographic analysis (column B, 170°, 95) of the distilled product indicated that it consisted of a mixture of approximately 50% of the keto olefin (125), 20% of the corresponding alcoholic olefin (165), 10% of the saturated ketone (166) and several minor, unidentified components.

Standard chromic acid solution[99] was added to a solution of the distilled reduction product (900 mg) in acetone (25 ml) at 0° until the orange colour persisted. Isopropyl alcohol was added to destroy the excess oxidizing reagent, and the solution was evaporated under reduced pressure. The residual material was diluted with water and thoroughly extracted with ether. The combined ethereal extracts were dried over anhydrous magnesium sulfate and the ether was removed at aspirator pressure. Purification of the keto olefin was achieved by preparative g.l.c. (column C, 230°, 200). The (-)-keto olefin (125) thus obtained (500 mg, 26%) was a colourless oil and exhibited n_D^{23} 1.4789; $[\alpha]_D^{23}$ -29° (c, 1.3 in $CHCl_3$); infrared (film), λ_{max} 3.29, 5.71, 6.13, 9.44, 12.22 μ; n.m.r., τ 4.13 (unresolved multiplet, 1H, vinyl proton), 7.17 (unresolved multiplet, 1H, allylic proton), 8.25 (pair

of doublets, 3H, vinyl methyl, $J_{C_6H-C_{13}H}$ = 1.6 Hz, $J_{C_5H-C_{13}H}$ = 1.0 Hz), 9.00 (singlet, 3H, tertiary methyl), 9.00, 9.09 (doublets, 6H, isopropyl methyls, J = 6.0 Hz).

Anal. Calcd. for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.30; H, 10.59.

(b) from the Bamford-Stevens reaction of the p-tosylhydrazone (167)

A mixture of the (-)-diketone (122) (11.6 g, 56.0 mmoles), p-toluenesulfonylhydrazide (13.0 g, 70.0 mmoles) and 10 ml of methanol was heated and stirred under an atmosphere of dry nitrogen until a homogeneous solution was obtained. Then 100 μℓ acetyl chloride was added to the solution and the reaction mixture was stirred at room temperature for 3 h. The methanol was removed under reduced pressure, and the residue was diluted with water and thoroughly extracted with ether. The ethereal extracts were washed with a 10% solution of sodium bicarbonate and brine, and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure yielded 21.1 g (100%) of the p-tosylhydrazone (167). In general, this material was used for the next reaction without further purification. However an analytical sample was obtained by recrystallization of compound (167) and exhibited m.p. 77-80°; infrared ($CHCl_3$), λ_{max} 2.84, 3.12, 5.73, 6.05, 6.25, 8.59 μ; n.m.r., τ 2.18, 2.72 (doublets, 4H, aromatic protons, J = 9.0 Hz), 7.50 (singlet, 3H, aromatic methyl), 8.82 (doublet, 3H, secondary methyl, J = 7.0 Hz), 9.05 (singlet, 3H, tertiary methyl), 9.02, 9.19 (doublets, 6H, isopropyl methyls, J = 6.0 Hz).

To a solution of the p-tosylhydrazone (167) (21.1 g, 56.0 mmoles)

dissolved in 150 ml of dry tetrahydrofuran was added a solution of 10.7 g (58.7 mmoles) of sodium bis(trimethylsilyl)amide and 2.2 ml of high boiling nujol (> 210° at 0.2 mm) dissolved in 50 ml of dry tetrahydrofuran, and the reaction was stirred under an atmosphere of dry nitrogen for 1 h. The reaction mixture was then concentrated under reduced pressure. The remaining mixture of nujol and the sodium salt of the p-tosylhydrazone was heated slowly to 125° under reduced pressure (water aspirator, 10-20 mm) at which temperature decomposition of the salt was observed to take place. At this temperature, direct distillation of the product was accomplished by application of a vacuum pump (0.3 mm) to the reaction system. The product thus obtained was redistilled (75-80° at 0.5 mm) and those distillation fractions containing significant amounts of keto olefin (gas-liquid chromatographic analysis, column B, 170°, 95) were chromatographed on silica gel. Elution with 10:1 petroleum ether (b.p. 30-60°)-ether afforded fractions containing significant amounts of keto olefin (gas-liquid chromatographic analysis, column B, 170°, 95). These fractions were then subjected to preparative g.l.c. (column C, 230°, 150) and (4.0 g, 38%) of the pure (-)-keto olefin (125) was obtained in this manner. This material was identical (g.l.c. retention time, infrared and n.m.r. spectra) with the keto olefin prepared previously.

(c) from Jones oxidation of (-)-olefinic alcohol (171)

Standard chromic acid solution[99] was added to a solution of the (-)-olefinic alcohol (171) (1.94 g, 10 mmoles) in acetone (50 ml) at 0°, until the orange colour persisted. Isopropyl alcohol was added

to destroy the excess oxidizing agent, and the solution was evaporated under reduced pressure. The residual material was diluted with water and thoroughly extracted with ether. The combined ethereal extracts were washed with brine and dried over anhydrous magnesium sulfate. Removal of the solvent, followed by distillation of the residual oil under reduced pressure (b.p. 70° at 0.5 mm) afforded 1.71 g (89%) of the (-)-keto olefin (125). This material was identical (g.l.c. retention time, infrared and n.m.r. spectra) with the (-)-keto olefin (125) prepared previously.

Preparation of the Olefinic Enol Ethers (172)

A stirred suspension of sodium hydride (200 mg, 8.35 mmoles) in dry dimethyl sulfoxide (9 ml) was slowly heated, under an atmosphere of dry nitrogen, to 75° and kept at this temperature until frothing had ceased (approximately 30 min). The solution was cooled to room temperature and a solution of methoxymethyltriphenylphosphonium chloride (3.07 g, 10 mmoles) in 12 ml of dry dimethyl sulfoxide was added. The resulting solution was stirred for 10 min, and then a solution of the (-)-keto olefin (125) (320 mg, 1.67 mmoles) in 9 ml of dimethyl sulfoxide was added. The reaction mixture was heated at 40-50° for 1.5 h, then cooled, diluted with water and thoroughly extracted with petroleum ether (b.p. 30-60°). The combined extracts were washed twice with water, once with saturated brine and then dried over anhydrous magnesium sulfate. Removal of the solvent, followed by careful hot box distillation of the residual oil under reduced pressure yielded 262 mg (71%) of the olefinic enol ethers (172) as a colourless

oil, b.p. 76° at 0.5 mm; n_D^{21} 1.4927; ultraviolet, λ_{max} 208 mμ (ε = 8,030); infrared (film), λ_{max} 3.30, 5.88, 6.90, 8.09, 8.23, 8.99 μ; n.m.r., τ 4.43 (singlet, 2H, vinyl protons), 6.51, 6.54 (singlets, 3H, $-OCH_3$), 7.23 (broad singlet, 1H, C_5H).

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 82.00; H, 11.11.

Mol. Wt. Calcd. for $C_{15}H_{24}O$: 220.183. Found (high resolution mass spectrometry): 220.183.

Preparation of the (-)-Olefinic Aldehyde (174)

To a solution of 10 ml of 35% perchloric acid dissolved in 45 ml of ether was added 250 mg of the olefinic enol ethers (172) in 5 ml of ether. The reaction mixture was stirred for 1 h at room temperature, and then neutralized by the slow addition of solid sodium carbonate to the stirred solution. The ethereal layer was then concentrated, and the residue was dissolved in 5 ml of methanol and added to a stirred solution of 0.5 g potassium carbonate dissolved in 2.5 ml water and 25 ml of methanol. The resulting solution was stirred for 2 h and then concentrated. The residue was diluted with water, then thoroughly extracted with ether. The combined ethereal extracts were washed with brine, and dried over anhydrous magnesium sulfate. Removal of the solvent, followed by distillation of the residual oil under reduced pressure yielded 202 mg (86%) of the (-)-olefinic aldehyde (174) as a colourless oil, b.p. 105° at .3 mm (bath temperature); n_D^{21} 1.4931; $[\alpha]_D^{22}$ -20° (c, 1.7 in $CHCl_3$); infrared (film), λ_{max} 3.30, 3.67, 5.83, 6.08, 6.90, 7.24, 12.38; n.m.r., τ 0.40 (doublet, 1H, aldehydic proton,

J = 4.2 Hz), 4.56 (broad singlet, 1H, vinyl proton, width at half-height = 6.0 Hz), 7.53 (unresolved multiplet, 1H, allylic proton), 7.80 (doublet, 1H, C_8H, J = 4.2 Hz), 8.38 (pair of doublets, 3H, vinyl methyl, $J_{C_6H-C_{14}H}$ = 1.6 Hz, $J_{C_5H-C_{14}H}$ = 1.0 Hz), 8.97 (singlet, 3H, tertiary methyl), 9.08, 9.16 (doublets, 6H, isopropyl methyls, J = 6.2 Hz).

Mol. Wt. Calcd. for $C_{14}H_{22}O$: 206.167. Found (high resolution mass spectrometry): 206.166.

Preparation of the (+)-Diene (175)

A stirred suspension of sodium hydride (540 mg, 22.5 mmoles) in dry dimethyl sulfoxide (27 ml) was heated slowly, under an atmosphere of dry nitrogen, to 75° and kept at this temperature until the frothing had ceased (approximately 45 min). The solution was cooled to room temperature and a solution of methyltriphenylphosphonium bromide (9.65 g, 27.0 mmoles) in 36 ml of dimethyl sulfoxide was added. The solution was stirred for 10 min and then a solution of the (-)-olefinic aldehyde (174) (900 mg, 4.5 mmoles) in 27 ml of dimethyl sulfoxide was added. The reaction mixture was heated at 40-50° for 1 h, then cooled, diluted with water and thoroughly extracted with petroleum ether (b.p. 30-60°). The combined petroleum ether extracts were washed twice with water, once with saturated brine and then dried over anhydrous magnesium sulfate. Removal of the solvent, followed by distillation of the residual oil under reduced pressure afforded 740 mg (83%) of the desired diene (175), b.p. 90° at 0.30 mm (bath temperature); n_D^{26} 1.4820; $[\alpha]_D^{21}$ +4.3° (c, 1.5 in $CHCl_3$); infrared (film), λ_{max} 3.30,

6.10, 6.90, 10.03, 11.04, 11.87, 12.41 μ; n.m.r., τ 4.22 (doublet of a doublet of a doublet, 1H, C_9H, $J_{C_8H-C_9H}$ = 9.0 Hz, $J_{C_9H-C_{10}H_{trans}}$ = 17.5 Hz, $J_{C_9H,C_{10}H_{cis}}$ = 10.0 Hz), 4.67 (broad singlet, 1H, C_6H, width at half-height = 4.0 Hz), 5.07 (pair of doublets, 1H, $C_{10}H_{trans}$, $J_{C_{10}H-C_{10}H}$ = 2.5 Hz, $J_{C_9H-C_{10}H_{trans}}$ = 17.5 Hz), 5.16 (pair of doublets, 1H, $C_{10}H_{cis}$, $J_{C_{10}H-C_{10}H}$ = 2.5 Hz, $J_{C_9H-C_{10}H_{cis}}$ = 10.0 Hz), 7.67 (unresolved multiplet, 1H, C_5H), 7.83 (doublet, 1H, C_8H, J = 9.0 Hz), 8.42 (pair of doublets, 3H, vinyl methyl, $J_{C_6H-C_{15}H}$ = 1.6 Hz, $J_{C_5H-C_{15}H}$ = 1.0 Hz), 9.07, 9.15 (doublets, 6H, isopropyl methyls, J = 6.5 Hz), 9.16 (singlet, 3H, tertiary methyl).

Anal. Calcd. for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.08; H, 12.00.

Mol. Wt. Calcd. for $C_{15}H_{24}$: 204.188. Found (high resolution mass spectrometry): 204.188.

Preparation of the (+)-Olefinic Alcohol (178)

To a solution of 630 mg (9.0 mmoles) of 2-methyl-2-butene in 6 ml of dry tetrahydrofuran at 0° and under an atmosphere of dry nitrogen was added 1.37 ml of 3.4 M borane in tetrahydrofuran. After this solution had been stirred for 30 min at 0°, a solution of 306 mg (1.5 mmoles) of the (+)-diene (175) in 6 ml of tetrahydrofuran was added, and the reaction mixture was then stirred at room temperature for 1.5 h. The reaction mixture was again cooled to ice temperature, and 2 ml of 3 N NaOH was added slowly, followed by addition of 2 ml of 30% hydrogen peroxide. The reaction mixture was warmed to room

temperature and stirred for 1 h, then concentrated. The resulting material was diluted with water then thoroughly extracted with ether. Then combined ether extracts were washed with a saturated brine solution, and dried over anhydrous magnesium sulfate. Removal of the solvent, followed by distillation of the residual material under reduced pressure [b.p. 120° at 0.2 mm (bath temperature)] afforded 300 mg (91%) of the desired olefinic alcohol (178) as a colourless oil. An analytical sample was obtained by preparative g.l.c. (column B, 210°, 100) and exhibited n_D^{24} 1.4936; $[\alpha]_D^{20}$ +8.5° (c, 5.6 in $CHCl_3$); infrared (film), λ_{max} 3.05, 3.31, 6.09, 6.90, 7.26, 9.50 μ; n.m.r., τ 4.68 (broad singlet, 1H, vinyl proton, width at half-height = 4.2 Hz), 6.38 (multiplet, 2H, protons adjacent to the hydroxyl), 7.63 (unresolved multiplet, 1H, allylic proton), 8.44 (pair of doublets, 3H, vinyl methyl, $J_{C_6H-C_{15}H}$ = 1.6 Hz, $J_{C_5H-C_{15}H}$ = 1.0 Hz), 9.08, 9.14 (doublets, 6H, isopropyl methyls, J = 6.0 Hz), 9.10 (singlet, 3H, tertiary methyl).

Anal. Calcd. for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.78; H, 11.78.

Mol. Wt. Calcd. for $C_{15}H_{26}O$: 222.198. Found (high resolution mass spectrometry): 222.198.

Preparation of the (+)-Cyclic Ether (179)

A solution of the (+)-olefinic alcohol (178) (50 mg) and p-toluenesulfonic acid (10 mg) in 25 ml of dry benzene was stirred under nitrogen for 5 h. The solution was then washed with saturated aqueous sodium bicarbonate and brine, and dried over anhydrous magnesium sulfate. The organic layer was concentrated and distilled under reduced pressure. Gas-liquid chromatographic analysis (column D, 210°, 95) of the

resultant oil indicated that the major product was the (+)-cyclic ether (179) accompanied by a small amount (∿ 5%) of starting material (178) and several unidentified components. An analytical sample of compound 179 was obtained by preparative g.l.c. (column D, 210°, 95) and exhibited n_D^{26} 1.4908; $[\alpha]_D^{21}$ +13.5° (c, 1.1 in $CHCl_3$); infrared (film), λ_{max} 6.89, 9.22, 9.42 μ; n.m.r, τ 6.30 (multiplet, 2H, protons adjacent to the oxygen), 8.94, 9.11 (singlets, 6H, tertiary methyls), 9.14, 9.16 (doublets, 6H, isopropyl methyls, J = 6.0 Hz).

Mol. Wt. Calcd. for $C_{15}H_{26}O$: 222.198. Found (high resolution mass spectrometry): 222.198.

Preparation of (+)-Cyclosativene (27), (+)-Sativene (26), and (-)-Isosativene (77)

(a) from the acetic acid-cupric acetate rearrangement of (-)-copacamphene (23)

A solution of 102 mg (0.50 mmole) of (-)-copacamphene and 25 mg (.125 mmole) of cupric acetate in 5 ml of glacial acetic acid was refluxed for 4 days. The solution was cooled and diluted with water, then thoroughly extracted with petroleum ether (b.p. 30-60°). The combined petroleum ether extracts were washed with water, 10% sodium bicarbonate solution, and dried over anhydrous magnesium sulfate. The material obtained after removal of the solvent was chromatographed on 5 g of 10% silver nitrate impregnated silica gel. Elution with 10 ml of pentane produced 25 mg of (+)-cyclosativene (27), b.p. 80° at .25 mm (bath temperature); $[\alpha]_D^{25}$ +63° (c, 1.1 in $CHCl_3$),

lit.[18] $[\alpha]_D^{20}$ +67.8°(c, 1.15 in $CHCl_3$); infrared (film), λ_{max} 3.28, 6.88, 7.21, 7.29, 11.62, 11.87, 12.05, 12.19 μ; n.m.r., τ 9.02, 9.24 (singlets, 6H, tertiary methyls), 9.09, 9.13 (doublets, 6H, J = 6.0 Hz), 9.22 (singlet, 1H, cyclopropyl proton), 9.33(doublet, 1H, cyclopropyl proton, J = 5.5 Hz).

Mol. Wt. Calcd. for $C_{15}H_{24}$: 204.188. Found (high resolution mass spectrometry): 204.188.

Further elution of the column with ether afforded a mixture of (+)-sativene and (-)-isosativene. These compounds were separated by preparative g.l.c. (column E, 145°, 120). The minor component, (+)-sativene (26) (4 mg, 4%), exhibited $[\alpha]_D^{24}$ +174° (c, 0.3 in $CHCl_3$); lit.[22] $[\alpha]_D$ + 191°; infrared (film), λ_{max} 3.26, 6.04, 7.22, 7.30, 11.45 μ; n.m.r., τ 5.26, 5.58 (singlets, 2H, vinyl protons), 7.39 (broad signal, 1H, allylic proton), 8.96 (singlet, 3H, tertiary methyl), 9.10, 9.13 (doublets, 6H, isopropyl methyls, J = 6.0 Hz).

Mol. Wt. Calcd. for $C_{15}H_{24}$: 204.188. Found (high resolution mass spectrometry): 204.188.

The major component isolated by preparative g.l.c. was (-)-isosativene (77) (45 mg, 44%) and exhibited $[\alpha]_D^{24}$ -23° (c, 0.9 in $CHCl_3$); infrared (film), λ_{max} 3.27, 6.06, 6.85, 7.23, 7.42, 11.42 μ; n.m.r., τ 5.23, 5.52 (singlets, 2H, vinyl protons), 7.39 (broad signal, 1H, allylic proton), 9.03 (singlet, 3H, tertiary methyl), 9.12 (doublet, 6H, isopropyl methyls, J = 6.0 Hz).

Mol. Wt. Calcd. for $C_{15}H_{24}$: 204.188. Found (high resolution mass spectrometry): 204.187.

(b) from the p-toluenesulfonic acid rearrangement of (-)-copacamphene (23).

To 20 ml of a 10 mM solution of p-toluenesulfonic acid in dry benzene was added a solution of 100 mg of (-)-copacamphene in 1 ml of dry benzene. The reaction mixture was stirred under an atmosphere of dry nitrogen at room temperature for 1 h, then washed with a 10% sodium bicarbonate solution, and brine. The organic layer was dried over anhydrous magnesium sulfate, and then concentrated, to afford 85 mg of a colourless oil. Gas-liquid chromatographic analysis (column F, 135°, 90) indicated that this oil consisted of approximately 32% (+)-cyclosativene (27), 7% (+)-sativene (26) and 61% (-)-isosativene (77). These three products were isolated by preparative g.l.c. (column E, 145°, 120) and in each case, the structure was confirmed by direct comparison (g.l.c. retention time, infrared and n.m.r. spectra) with an authentic sample.

Preparation of the (-)-Olefinic Acid (186)

A solution of 206 mg (10.0 mmoles) of the (-)-olefinic aldehyde (174) in 1.5 ml of pyridine was added to the Sarett reagent prepared from 1.2 g of chromium trioxide and 12 ml of pyridine; then 5 drops of water was added, and the dark mixture was stirred for 18 h at room temperature.[105] The reaction mixture was then diluted with water, and extracted with ether. The combined ethereal extracts were washed first with water and then with a dilute hydrochloric acid solution. The organic layer was extracted with 10% aqueous sodium hydroxide. The

alkaline extracts were cooled, acidified with 6 N hydrochloric acid and thoroughly extracted with ether. The combined ethereal extracts were washed with water, and dried over anhydrous magnesium sulfate. Removal of the solvent afforded 174 mg (82%) of the crystalline (-)-olefinic acid (186), m.p. 138-139.5°; $[\alpha]_D^{26}$ -16.7° (c, 1.2 in $CHCl_3$); infrared ($CHCl_3$), λ_{max} 5.87 μ; n.m.r., τ 0.18 (very broad signal, 1H, acid proton), 4.55 (broad singlet, 1H, vinyl proton, width at half-height = 6.0 Hz), 7.19 (unresolved multiplet, 1H, allylic proton), 7.50 (singlet, 1H, C_8H), 8.40 (pair of doublets, 3H, vinyl methyl, $J_{C_6H-C_{14}H}$ = 1.6 Hz, $J_{C_5H-C_{14}H}$ = 1.0 Hz), 8.89 (singlet, 3H, tertiary methyl), 9.07, 9.11 (doublets, 6H, isopropyl methyls, J = 6.0 Hz).

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.33; H, 9.98.

Preparation of (-)-Keto Olefin (190)

The (-)-olefinic carboxylic acid (186) (111 mg, 0.5 mmole) was dissolved in aqueous sodium hydroxide (.55 mmole), the water was evaporated under reduced pressure, and the residue was dried in a vacuum oven at 70°. A stirred suspension of the resulting dry sodium salt in 10 ml of anhydrous ether containing 20 μℓ of dry pyridine was cooled to 0° and 640 mg (5.0 mmoles) of oxalyl chloride was added. The reaction mixture was stirred at 0° for 15 min under an atmosphere of dry nitrogen, then filtered, and concentrated under reduced pressure (vacuum pump). The solution was kept at 0° during this process. The crude acid chloride (189) [infrared (film), λ_{max} 5.52 μ] thus obtained was dissolved in 15 ml of anhydrous ether and the resulting solution

was added to excess alcohol-free ethereal diazomethane which had been dried over potassium hydroxide. This reaction mixture was stirred at 0° for 2.5 h, then the excess diazomethane and solvent was removed under reduced pressure. The resulting crude reaction mixture [infrared (film), λ_{max} 5.73 μ (strong), 4.70, 6.04 μ (weak)] was dissolved in 15 ml of dry cyclohexane, and cupric sulfate (400 mg) was added. The resulting suspension was refluxed, with stirring, for 3 h. The cooled reaction mixture was filtered, and the filtrate was washed with saturated aqueous sodium bicarbonate, water, and brine, and then dried over anhydrous magnesium sulfate. Removal of the solvent, followed by distillation of the residual material under reduced pressure, yielded 66 mg (60%) of a colourless oil, b.p. 115° at 0.25 mm (bath temperature). This material was shown by gas-liquid chromatographic analysis (column D, 200°, 95) to consist mainly (∿ 80%) of the keto olefin (190). In addition, the tetracyclic ketone (188) (∿ 5%) and a number of minor unidentified compounds were also present. Compounds 188 and 190 were isolated by preparative g.l.c. (column G, 240°, 200). The tetracyclic ketone 188, thus obtained, exhibited infrared (film), λ_{max} 3.27, 5.73, 11.42, 12.03 μ; n.m.r., τ 8.82, 9.08 (singlets, 6H, tertiary methyls), 9.12, 9.15 (doublets, 6H, isopropyl methyls, J = 6.0 Hz).

The (-)-keto olefin (190) thus obtained, exhibited n_D^{24} 1.5036; $[\alpha]_D^{26}$ -100° (c, 1.0 in $CHCl_3$); infrared (film), λ_{max} 3.26, 5.73, 6.01, 6.84, 8.55, 11.38 μ; n.m.r., τ 5.03, 5.27 (singlets, 2H, vinyl protons), 7.13 (unresolved multiplet, 1H, allylic proton), 8.99 (singlet, 3H, tertiary methyl), 9.12 (doublet, 6H, isopropyl methyls, J = 6.0 Hz).

Mol. Wt. Calcd. for $C_{15}H_{22}O$: 218.167. Found (high resolution mass spectrometry): 218.165.

The attempted diazoketone formation reaction was repeated employing a reaction procedure identical with that just described. The crude product obtained by reaction of the acid chloride (189) with diazomethane [infrared (film), λ_{max} 5.73 μ (strong), 4.70, 6.04 μ (weak)] was dissolved in approximately 1 ml of dry benzene, and added to 25 ml of a 5.0 mM solution of p-toluenesulfonic acid in benzene. The reaction mixture was stirred for 30 min at room temperature under an atmosphere of dry nitrogen. The solution was then washed with saturated aqueous sodium bicarbonate, water and brine, and then dried over anhydrous magnesium sulfate. Removal of the solvent, followed by distillation of the reduced material under reduced pressure yielded 65 mg (60%) of a colourless oil. The major product (∿ 80%) was the (-)-keto olefin (190), with no trace of the tetracyclic ketone 188 being present as determined by gas-liquid chromatographic analysis (column D, 200°, 95). The (-)-keto olefin (190) was obtained by preparative g.l.c. (column G, 240°, 200) and was identical (g.l.c. retention time, infrared and n.m.r. spectra) to the material prepared previously.

Preparation of the (-)-Olefinic Aldehyde (194)

To a solution of 286 mg (3.6 mmoles) of dry pyridine dissolved in 4.0 ml of dry methylene chloride was added 180 mg (1.8 mmoles) of dry chromium trioxide. The reaction was stirred under an atmosphere of dry nitrogen at room temperature for 15 min, during which time the

dark red colour of the chromium trioxide-pyridine complex developed.[98] To this mixture was added a solution of 64 mg (.301 mmole) of the (+)-olefinic alcohol (178) dissolved in .5 ml of methylene chloride. The reaction was allowed to proceed for 15 min, then approximately 10 ml of ether was added, and the organic layer was washed with a saturated sodium carbonate solution. After the organic layer had been washed with water and dried over anhydrous magnesium sulfate, the solvent was removed, and the remaining oil was distilled under reduced pressure to yield 58 mg (91%) of the desired olefinic aldehyde (194) as a colourless oil, b.p. 85° at 0.25 mm (bath temperature); n_D^{24} 1.4906; $[\alpha]_D^{21}$ -39° (c, 1.6 in $CHCl_3$); infrared (film), λ_{max} 3.29, 3.68, 5.80, 5.96, 6.86, 7.22 μ; n.m.r., τ 0.20 (triplet, 1H, aldehydic proton, J = 2.5 Hz), 4.60 (singlet, 1H, vinyl proton), 8.42 (pair of doublets, 3H, vinyl methyl, $J_{C_6H-C_{15}H}$ = 1.6 Hz, $J_{C_5H-C_{15}H}$ = 1.0 Hz), 9.07, 9.13 (doublets, 6H, isopropyl methyls, J = 6.5 Hz), 9.10 (singlet, 3H, tertiary methyl).

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.45; H, 10.98.

Preparation of (-)-Copacamphene (23)

(a) from the (+)-olefinic alcohol (178)

To a solution of 200 mg (.902 mmole) of the (+)-olefinic alcohol (178) in 4 ml of dry pyridine was added a solution of 342 mg (1.80 mmoles) of p-toluenesulfonyl chloride in 1 ml of dry pyridine. The reaction mixture was stirred under an atmosphere of dry nitrogen for 2.5 h. The solution was then diluted with hexane and the organic layer was washed first with a sodium bicarbonate solution, and then

water and brine, and dried over anhydrous magnesium sulfate. The solvent was removed first at aspirator pressure, and finally the last traces of pyridine were removed by application of a vacuum pump. The residual oil was transferred to the top of a silica gel column (5.0 g) and the column was eluted with approximately 50 ml of pentane. Removal of the solvent from the eluant, followed by reduced pressure distillation of the residual oil (80° at 0.25 mm, bath temperature) afforded 164 mg (89%) of a colourless oil. Gas-liquid chromatographic analysis (column F, 135°, 85) of this material indicated that it consisted of a major component (98%) accompanied by two minor components (in a ratio of approximately 1:1) that comprised 1-2% of the total mixture. Final purification was effected by column chromatography on 10% silver nitrate impregnated silica gel. Elution with 25:1 pentane-ether afforded pure (-)-copacamphene (23), $[\alpha]_D^{21}$ -159° (c, 2.2 in $CHCl_3$); infrared (film), λ_{max} 3.26, 6.03, 7.20, 7.30, 11.42 μ; n.m.r., τ 5.21, 5.49 (singlets, 2H, vinyl protons), 7.54 (broad signal, 1H, allylic proton), 9.00 (singlet, 3H, tertiary methyl), 9.10 (doublet, 6H, isopropyl methyls, J = 6.0 Hz). This material was found to be identical (g.l.c. retention time, infrared) with authentic (±)-copacamphene (23) (see the footnote on page 97).

Mol. Wt. Calcd. for $C_{15}H_{24}$: 204.188. Found (high resolution mass spectrometry): 204.188.

The minor components were collected by preparative g.l.c. (column E, 145°, 120) and were identified as (+)-cyclosativene (27) and (-)-isosativene (77) by direct comparison, in each case, (g.l.c. retention times, infrared spectra) with an authentic sample.

(b) from reduction of the (-)-keto olefin (190)

A solution of 50 mg of the (-)-keto olefin (190) in 2.0 ml of ethylene glycol containing 0.1 ml of 85% hydrazine hydrate and 100 mg of potassium hydroxide was refluxed for 2 h. The reflux condensor was removed and replaced by a distillation head and the temperature of the reaction mixture was slowly raised to 200° and maintained at this temperature for 3 h. The distillate was collected in a dry ice-acetone cooled receiver and combined with the cooled reaction mixture. This solution was diluted with water and thoroughly extracted with petroleum ether (b.p. 30-60°). The combined petroleum ether extracts were washed with water and brine and dried over anhydrous magnesium sulfate. The dried petroleum ether extracts were filtered through 2 g of silica gel, and the column was further eluted with petroleum ether. Removal of the solvent followed by distillation of the residual oil produced 27 mg (58%) (-)-copacamphene (23). This material was identical (g.l.c. retention time, specific rotation, infrared and n.m.r. spectra) with the (-)-copacamphene prepared previously.

Preparation of the Olefinic Enol Ethers (196 and 197)

The procedure utilized was similar to that employed for the preparation of the olefinic enol ethers (172) (see p. 156). The crude product was distilled under reduced pressure [100° at 0.25 mm, (bath temperature)] to afford a colourless oil (55% from olefinic aldehyde 174). Gas-liquid chromatographic analysis (column B, 200°, 100) indicated that this material consisted of a mixture of the cis- and trans-olefinic enol ethers, in a ratio of approximately 1:6, respectively.

An analytical sample of each of the cis-(196) and trans-(197) products was obtained by preparative g.l.c. (column B, 200°, 100). The cis-olefinic enol ether (196) exhibited infrared (film), λ_{max} 3.28, 5.97, 6.88, 8.30, 8.82 μ. The trans-olefinic enol ether (197) exhibited n_D^{25} 1.4926; $[\alpha]_D^{25}$ -22° (c, 0.6 in $CHCl_3$); infrared (film), λ_{max} 3.27, 6.08, 6.90, 8.29, 8.76 μ; n.m.r., τ 3.62 (doublet, 1H, $C_{10}H$, J = 15.0 Hz), 4.64 (broad singlet, 1H, C_6H), 5.23 (pair of doublets, 1H, C_9H, $J_{C_8H-C_9H}$ = 10.0 Hz, $J_{C_9H-C_{10}H}$ = 15.0 Hz), 6.54 (singlet, 3H, $-OCH_3$), 8.38 (pair of doublets, 3H, vinyl methyl, $J_{C_6H-C_{16}H}$ = 1.6 Hz, $J_{C_5H-C_{16}H}$ = 1.0 Hz), 9.08, 9.14 (doublets, 6H, isopropyl methyls, J = 6.0 Hz), 9.16 (singlet, 3H, tertiary methyl).

Mol. Wt. Calcd. for $C_{16}H_{26}O$: 234.198. Found (high resolution mass spectrometry): 234.198.

Preparation of the (-)-Keto Olefin (198)

(a) from the olefinic enol ethers (196 and 197)

To a solution of 10 ml of 35% perchloric acid dissolved in 40 ml of ether was added 200 mg of the mixture of olefinic enol ethers (196 and 197) in 5 ml of ether. The reaction mixture was stirred at room temperature for 1 h, then neutralized by the slow addition of sodium carbonate to the stirred solution. The ethereal layer was separated, then dried over anhydrous magnesium sulfate and concentrated. The residual oil (∿ 90 mg) was identified as an epimeric mixture of the olefinic alcohols (195), infrared (film), λ_{max} 2.96, 3.25, 6.03, 11.38 μ; n.m.r., τ 5.05 (broad singlet, 2H, olefinic protons, width at half-height = 7.0 Hz), 5.94 (multiplet, 1H, proton adjacent to the hydroxyl).

To a solution of 400 mg (5.05 mmoles) of dry pyridine dissolved in 5.5 ml of dry methylene chloride was added 253 mg (2.53 mmoles) of dry chromium trioxide. The reaction mixture was stirred at room temperature under an atmosphere of dry nitrogen for 15 min. To this mixture was added a solution of 90 mg (.422 mmole) of the crude olefinic alcohol (195) dissolved in 0.5 ml of methylene chloride. The reaction was allowed to proceed for 15 min, then 15 ml of ether was added to the reaction mixture, and the organic layer was washed with a saturated sodium carbonate solution. After the organic layer had been washed with water, and dried over anhydrous magnesium sulfate, the solvent was removed and the residual material was distilled under reduced pressure. The desired keto olefin (198) was separated from a number of minor components by means of preparative g.l.c. (column E, 220°, 120). Compound 198 thus obtained (43 mg, 23% yield from 196 and 197) exhibited b.p. 110° at 0.2 mm (bath temperature); n_D^{23} 1.5120; $[\alpha]_D^{22}$ -183° (c, 1.2 in $CHCl_3$); infrared (film), λ_{max} 3.25, 5.69, 6.03, 6.82, 8.81, 11.28 μ; n.m.r., τ 4.82, 5.18 (triplets, 2H, olefinic protons, J = 0.8 Hz), 7.04 (broad singlet, 1H, allylic proton, width at half-height = 4.0 Hz), 8.90 (singlet, 3H, tertiary methyl), 9.07 (doublet, 6H, isopropyl methyls, J = 6.3 Hz).

Anal. Calcd. for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.19; H, 10.38.

(b) from the (-)-olefinic aldehyde (194)

To 20 ml of a 0.05 mM solution of p-toluenesulfonic acid in dry benzene was added 110 mg (0.5 mmole) of the (-)-olefinic aldehyde (194),

and the reaction mixture was stirred at room temperature for 30 min. The reaction was then quenched by adding 1 ml of dry pyridine, and the solvent was removed under reduced pressure. The residual material was dissolved in 1 ml of dry methylene chloride and the resulting solution was added to a pre-formed solution of Collin reagent[98] [360 mg (3.6 mmoles) of chromium trioxide, 572 mg (7.2 mmoles) of pyridine in 8 ml of methylene chloride]. The reaction mixture was stirred for 15 min, then approximately 20 ml of ether was added. The organic layer was then washed with a saturated sodium carbonate solution, water, saturated brine, and then dried over anhydrous magnesium sulfate. The organic layer was then concentrated and the residual material was distilled under reduced pressure. Gas-liquid chromatographic analysis (column B, 200°, 100) of the distillate indicated that it consisted of a mixture of the (-)-keto olefin (198) and the (-)-olefinic aldehyde (194) in a ratio of approximately 5:2. Separation of this mixture was effected by preparative g.l.c. (column E, 220°, 120) to yield 58 mg [65% based on recovered starting material (194), 12 mg] of the (-)-olefinic ketone (194). This material was identical (g.l.c. retention time, infrared and n.m.r. spectra) with the (-)-keto olefin (198) prepared as described previously.

Preparation of the (-)-Ketone (202)

The (-)-keto olefin (198) (58 mg) in 10 ml of ethanol was hydrogenated over 29 mg of 5% palladium on charcoal at room temperature overnight. Removal of the catalyst and solvent yielded 55 mg of the (-)-ketone (202) as a colourless oil, b.p. 110° at .2 mm (bath

temperature), n_D 1.4968; $[\alpha]_D^{26}$ -53.5° (c, 0.9 in $CHCl_3$); infrared (film), λ_{max} 5.73, 6.81, 8.62 μ; n.m.r., τ 9.08 (singlet, 3H, tertiary methyl), 9.11 (doublet, 6H, isopropyl methyls, J = 6.3 Hz), 9.19 (doublet, 3H, secondary methyl, J = 7.0 Hz).

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.47; H, 11.07.

Preparation of the (+)-Pyrazoline (213)

In a 5 ml flask equipped with a Dean Stark water separator there was placed 58 mg (0.263 mmoles) of the (-)-olefinic aldehyde (194) and 49 mg (0.263 mmole) of p-toluenesulfonylhydrazide in 2.5 ml of dry benzene. The reaction mixture was refluxed in an atmosphere of dry nitrogen for 5 min. The solvent was then removed, and replaced with 2.5 ml of dry tetrahydrofuran. To this stirred solution was added 0.131 ml of 2 M n-butyllithium in hexane. After 30 min, the solvent was removed, and the residual lithium salt of the p-tosylhydrazone was heated slowly under reduced pressure (.25 mm). Between the temperatures of 120° and 140°, 50 mg of the (+)-pyrazoline (213) (81% yield from the aldehyde) was collected as a colourless oil, n_D^{24} 1.5042; $[\alpha]_D^{22}$ +95° (c, 1.0 in $CHCl_3$); ultraviolet, λ_{max} 334 mμ (ε = 232); infrared (film), λ_{max} 6.45, 6.87, 7.26, 8.91 μ; n.m.r., τ 5.11 (multiplet, 1H, proton adjacent to the -N=N- moiety), 8.42, 9.18 (singlets, 6H, tertiary methyls), 9.14 (doublet, 6H, isopropyl methyls, J = 6.0 Hz).

The instability of this material precluded satisfactory elemental analysis.

Preparation of (-)-Cyclocopacamphene (24)

(a) from reduction of the (-)-keto olefin (198)

The Huang-Minlon modified Wolff Kishner reduction of the (-)-keto olefin (198) was carried out under conditions very similar to those employed for the conversion of the (-)-keto olefin (190) to (-)-copacamphene (23) (see p. 169). The crude product obtained from reaction of 218 mg of the (-)-keto olefin (198) was 50 mg (25%) of a colourless oil, which was composed of two components in a ratio of 4:1, as determined by gas-liquid chromatographic analysis (column F, 140°, 85). This material was chromatographed on 3.5 g of 10% silver nitrate impregnated silica gel. Elution with 10 ml of pentane gave 10 mg of pure (-)-cyclocopacamphene, b.p. 80° at 0.25 mm (bath temperature); $[\alpha]_D^{21}$ -42° (c, 1.1 in $CHCl_3$); infrared (film), λ_{max} 3.29, 6.85, 7.21, 11.60, 11.80, 12.10 μ; n.m.r., τ 8.99, 9.26 (singlets, 6H, tertiary methyls), 9.10, 9.13 (doublets, 6H, isopropyl methyls, J = 6.5 Hz), 9.32, 9.37 (broad signals, 2H, cyclopropyl protons). The infrared and n.m.r. spectra of this material were identical with those of authentic (+)-cyclocopacamphene (24) (see the footnote on page 121).

Anal. Calcd. for $C_{15}H_{24}$: C, 88.14; H, 11.84. Found: C, 88.35; H, 11.90.

Elution with 10 ml of ether afforded 38 mg of (-)-copacamphene which was identical with the material prepared previously.

(b) from the p-tosylhydrazone (208) of the (-)-ketone (202)

To a solution of the (-)-ketone (202) (50 mg,.228 mmole) and p-toluenesulfonylhydrazide (47 mg, .250 mmole) in 3 ml of methanol was added 10 μℓ acetyl chloride, and the reaction mixture was refluxed for 2 h. The methanol was then removed under reduced pressure, and the residue was diluted with water, and then thoroughly extracted with ether. The ethereal extracts were washed with a 10% solution of sodium bicarbonate, with brine, and then dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure yielded 64 mg (97%) of the p-tosylhydrazone (208), infrared ($CHCl_3$), λ_{max} 2.87, 6.05, 6.25, 8.63 μ. This material was used without further purification.

To a solution of 30 mg (.104 mmole) of the p-tosylhydrazone (208) in 2 ml of dry diglyme was added 7 mg (.310 mmole) of sodium hydride, and the reaction mixture was stirred under an atmosphere of dry nitrogen until the evolution of hydrogen had ceased (approximately 5 min). The reaction mixture was heated to 140° for 1 h, then cooled and diluted with water. The reaction mixture was thoroughly extracted with petroleum ether (b.p. 30-60°) and the combined petroleum ether extracts were dried over anhydrous magnesium sulfate. This organic layer was then filtered through 3 g of silica gel, and the solvent was removed under reduced pressure. Gas-liquid chromatographic analysis (column F, 140°, 85) of the residual oil (16 mg) indicated that (-)-cyclocopacamphene (24) comprised only 10% of the mixture. This material (24) was identified by direct comparison (g.l.c. retention time and infrared spectrum) with an authentic sample. The major component (65%), obtained by preparative g.l.c. (column E, 140°,120),

was identified as the tricyclic olefin (209) and exhibited $[\alpha]_D^{24}$ +9.3° (c, 0.4 in $CHCl_3$); infrared (film), λ_{max} 3.26, 6.03, 6.89, 13.90 μ; n.m.r., τ 3.80 (overlapped pair of doublets, 2H, olefinic protons), 9.16, 9.17 (doublets, 6H, isopropyl methyls, J = 6.0 Hz), 9.28 (singlet, 3H, tertiary methyl), 9.30 (doublet, 3H, secondary methyl, J = 7.0 Hz).

Mol. Wt. Calcd. for $C_{15}H_{24}$: 204.188. Found (high resolution mass spectrometry): 204.188.

To a solution of 30 mg (.104 mmole) of p-tosylhydrazone (208) in 2 ml of dry tetrahydrofuran was added 76 μℓ of 2 M n-butyllithium in hexane. The reaction mixture was allowed to stand for 15 min, and then the solvent was removed, and the residue was heated slowly under reduced pressure (0.3 mm). Between temperatures of 120° and 140°, 15 mg of a colourless oil was collected. Gas-liquid chromatographic analysis (column F, 135°, 85) of this oil revealed that (-)-cyclocopacamphene (24) again only comprised 10% of the mixture, while the (+)-tricyclic olefin (209) accounted for 65%. These products were isolated by preparative g.l.c. (column E, 145°, 120) and were identified in each case by direct comparison (g.l.c. retention time and infrared spectra) with the authentic samples.

(c) from hydrazone of the (-)-ketone (202)

A solution of 30 mg (.136 mmole) of the (-)-ketone (202), 48 μℓ of 95% hydrazine, 9 μℓ of glacial acetic acid and 1.0 ml of ethanol was refluxed for 4 h. The reaction mixture was then cooled and the ethanol was removed under reduced pressure. The residue was diluted with

water, and the resultant mixture was thoroughly extracted with ether. The combined ethereal extracts were washed with a 10% solution of sodium bicarbonate, with brine, and then dried over anhydrous magnesium sulfate. Removal of the ether at aspirator pressure gave the crude hydrazone [infrared (film), λ_{max} 3.01, 6.14, 6.88 μ] which was used without further purification.

To a solution of the crude hydrazone (32 mg) in 1 ml of methanol was added 100 mg of yellow mercuric oxide, and the reaction mixture was refluxed overnight. The reaction mixture was then cooled and diluted with petroleum ether (b.p. 30-60°) and filtered through celite. The resulting filtrate was concentrated, and the residue was dissolved in petroleum ether (b.p. 30-60°) and filtered through 3 g of silica gel. The solvent was again removed under reduced pressure to afford 18 mg (65%) of a colourless oil. Gas-liquid chromatographic analysis (column F, 135°, 85) of the reaction product indicated that (-)-cyclocopacamphene (24) comprised 30% of the mixture, while the major product (55%) was again the (+)-tricyclic olefin (209). These products were isolated by preparative g.l.c. (column E, 140°, 120) and were identified, in each case, by direct comparison (g.l.c. retention time and infrared spectra) with authentic samples.

(d) from the (+)-pyrazoline (213)

A solution of 35 mg of the (+)-pyrazoline (213) in 35 ml of dry ether was irradiated in a Rayonet Reactor, using 3500 Å lamps and a pyrex filter, for 1 h. Removal of the solvent, followed by distillation of the residual oil under reduced pressure [b.p. 80° at

0.3 mm (bath temperature)] afforded 30 mg (93%) of the desired (-)-cyclocopacamphene (24) which was identical (g.l.c. retention time, rotation, infrared and n.m.r. spectra) with the material prepared previously.

BIBLIOGRAPHY

1. L. Ruzicka, A. Eschenmoser, and H. Heusser. Experimentia, 9, 357 (1953).

2. L. Ruzicka, A. Eschenmoser, O. Jeger, and A. Arigoni. Helv. Chem. Acta, 38, 1890 (1955).

3. G. Ourisson, S. Munaralli, and C. Ehret. International Tables of Selected Constants. Vol. 15, Data Relative to Sesquiterpenoids, Pergamon Press, New York, 1966.

4. K. Nahanishi, M. Ohashi, M. Tada, and Y. Yamada. Tetrahedron, 21, 1231 (1965).

5. F. Sorm and V. Herout. Coll. Czech. Chem. Commun., 13, 177 (1948).

6. F. Sorm, V. Herout, A. Reiser and V.V. Sykora. ibid., 23, 1306 (1958).

7. K.S. Baalsrud, D. Holme, M. Nestrold, J. Pliva, J.S. Sorensen and N.A. Sorensen. Acta Chem. Scand., 6, 883 (1952).

8. H. Hikino, N. Suzuki and T. Takemoto. Tetrahedron Letters, 1196 (1969).

9. H. Hikino, N. Suzuki and T. Takemoto. Chem. Pharm. Bull. (Tokyo), 19, 87 (1971).

10. G.L. Hodgson, D.F. MacSweeney and T. Money. Chem. Commun., 766 (1971).

11. M. Kolbe and L. Westfelt. Acta Chem. Scand., 21, 585 (1967).

12. M. Kolbe-Haugwitz and L. Westfelt. ibid., 24, 1623 (1970).

13. E. Piers, R.W. Britton, R.J. Keziere and R.D. Smillie. Can. J. Chem., 49, 2620 (1971).

14. S.C. Bisarya and S. Dev. Tetrahedron Letters, 3761 (1964).

15. J.E. McMurry. ibid., 3731 (1970).

16. J.E. McMurry. J. Org. Chem., 36, 2826 (1971).

17. E. Piers, R.W. Britton, R.J. Keziere and R.D. Smillie. Can. J. Chem., 49, 2623 (1971).

18. F. Kido, R. Sakuma, H. Uda and A. Yoshikoshi. Tetrahedron Letters, 3169 (1969).

19. Schimmel and Co. Ber. Schimmel, 48 (1914).

20. V.H. Kapadia, B.A. Nagasampagi, V.E. Naik and S. Dev. Tetrahedron, 21, 607 (1965).

21. P. de Mayo and R.E. Williams. Tetrahedron, 21, 619 (1965).

22. P. de Mayo and R.E. Williams. J. Amer. Chem. Soc., 87, 3275 (1965).

23. J.E. McMurry. J. Amer. Chem. Soc., 90, 6821 (1968).

24. L.A. Smedman and E. Zavarin. Tetrahedron Letters, 3833 (1968).

25. L.A. Smedman, E. Zavarin and R. Teranishi. Phytochemistry, 8, 1457 (1969).

26. J.E. McMurry. Tetrahedron Letters, 55 (1969).

27. V. Herout and D.I. Dimitrov. Chem. Listy, 46, 432 (1952).

28. O. Motl, V. Herout and F. Sorm. Tetrahedron Letters, 451 (1965).

29. G.L.K. Hunter and W.B. Brogden. J. Org. Chem., 29, 2100 (1964).

30. Y. Ohta and Y. Hirose. Tetrahedron Letters, 1601 (1969).

31. J.L. Simonsen. J. Chem. Soc., 117, 578 (1920).

32. A.E. Bradfield, E.M. Francis and J.L. Simonsen. J. Chem. Soc., 188 (1934).

33. R.H. Moffett and D. Rogers. Chem. Ind. (London), 916 (1953).

34. P. Naffa and G. Ourisson. ibid., 917 (1953).

35. G. Ourisson. ibid., 918 (1953).

36. U.R. Nayak and S. Dev. Tetrahedron Letters, 243 (1963).

37. L. Westfelt. Acta Chem. Scand., 21, 159 (1967).

38. H. Erdtman and L. Westfelt. ibid., 17, 2351 (1963).

39. J.B. Henderson. Tetrahedron, 7, 82 (1959).

40. W. Parker, J.S. Roberts and R. Ramage. Quart. Rev., 21, 331 (1967).

41. D.E. Wolf, C.H. Hoffman, P.E. Aldrich, H.R. Skeggs, L.D. Wright and K. Folkers. J. Amer. Chem. Soc., 78, 4499 (1956).

42. R.B. Clayton. Quart. Rev., 19, 201 (1965).

43. B.W. Agranoff, H. Eggerer, U. Henning, and F. Lynen. J. Amer. Chem. Soc., 81, 1254 (1959).

44. A.J. Birch. Fortschritte d. Chem. Org. Nature, 14, 1186 (1957).

45. A.J. Birch. Proc. Chem. Soc., 3 (1962).

46. J.H. Richards and J.B. Hendrickson. The Biosynthesis of Steroids, Terpenes and Acetogenins. W.A. Benjamin, Inc., New York (1964).

47. J.E. McMurry. Tetrahedron Letters, 3735 (1970).

48. T. Money. Can. Inst. Chem.-Am. Chem. Soc. Conference, Toronto, May 1970.

49. T.S. Patterson and W.F. Erman. J. Amer. Chem. Soc., 50, 2464 (1928).

50. G. Brieger. Tetrahedron Letters, 2132 (1963).

51. A. Homma, M. Kato, Ming-Der Wu and A. Yoshikoshi. Tetrahedron Letters, 231 (1970).

52. U.R. Nayak and S. Dev. Tetrahedron, 8, 42 (1960).

53. J.R. Prahlad, R. Ranganathan, U.R. Nayak, T.S. Santhanakrishnan and S. Dev. Tetrahedron Letters, 417 (1964).

54. U.R. Nayak and S. Dev. Tetrahedron, 24, 4099 (1968).

55. G. Ourisson. Proc. Chem. Soc., 274 (1964).

56. U.R. Nayak and S. Dev. Tetrahedron, 24, 4102 (1968).

57. P. Naffa and G. Ourisson. Bull. Soc. Chim. France, 1410 (1954).

58. D.H.R. Barton and P. de Mayo. J. Chem. Soc., 887 (1953).

59. P. Wieland and K. Miescher. Helv. Chim. Acta, 33, 2215 (1950).

60. J.E. McMurry. Chem. Commun., 433 (1968).

61. G.A. Fleisher and E.C. Kendall. J. Org. Chem., 16, 556 (1951).

62. E.J. Corey and M. Chaykovsky. J. Amer. Chem. Soc., 87, 1345 (1965), and references therein.

63. C.H. Heathcock, R.A. Badger and J.W. Patterson. J. Amer. Chem. Soc., 89, 4133 (1967).

64. J.C. Collins, W.W. Hess and F.J. Frank. Tetrahedron Letters, 3363 (1968).

65. E.J. Corey, M. Ohno, R.B. Mitra and P.A. Vatakencherry. J. Amer. Chem. Soc., 86, 478 (1964).

66. E.J. Corey and N. Nozoe. J. Amer. Chem. Soc., 87, 5728 (1965), and references therein.

67. R.E. Ireland and J.A. Marshall. J. Org. Chem., 27, 1615 (1962), and references therein.

68. W.J. LeNoble. Synthesis, 1 (1970), and references therein.

69. R.G. Pearson. Science, 151, 172 (1966).

70. R.G. Pearson and J. Songstad. J. Amer. Chem. Soc., 89, 1827 (1967).

71. S.K. Malhotra and F. Johnson. Chem. Commun., 1149 (1968), and references therein.

72. H.O. House, B.A. Tefertiller and H.O. Olmstead. J. Org. Chem., 33, 935 (1968).

73. E.J. Corey and R.A. Snen. J. Amer. Chem. Soc., 78, 6269 (1956).

74. B.W. Roberts, M.S. Poonian and S.C. Welch. J. Amer. Chem. Soc., 91, 3400 (1969).

75. M. Tanabe and D.F. Crow. Chem. Commun., 1498 (1969), and references therein.

76. W. Cocker, D.P. Hanna and P.V.R. Shannon. J. Chem. Soc., 489 (1968).

77. M. Yoshida. Chem. Pharm. Bull. (Tokyo), 3, 215 (1955).

78. R. Howe and J.F. McQuillin. J. Chem. Soc., 2423 (1955), 2672 (1956).

79. D. Walker and J.D. Hiebert. Chem. Rev., 67, 153 (1967).

80. Kin-Fai Cheng, Ph.D. Thesis, University of British Columbia, July 1969.

81. H.O. House, W.L. Respess, and G.M. Whitesides. J. Org. Chem., 31, 3128 (1966).

82. H.O. House and W.F. Fishers. J. Org. Chem., 33, 949 (1968).

83. E. Piers and R.J. Keziere. Can. J. Chem., 47, 137 (1969).

84. J.A. Marshall and H. Roebke. J. Org. Chem., 33, 840 (1968).

85. J.A. Marshall and A.R. Hochstetler. J. Amer. Chem. Soc., 91, 648 (1969).

86. N.L. Allinger and C.K. Riew. Tetrahedron Letters, 1269 (1966), and references therein.

87. W.M. Phillips, Ph.D. Thesis, University of British Columbia, August, 1971.

88. R.E. Ireland and R.C. Kierstead. J. Org. Chem., 31, 2543 (1966).

89. R.J. Keziere, Ph.D. Thesis, University of British Columbia (incomplete).

90. M. Karplus. J. Amer. Chem. Soc., 85, 2870 (1963).

91. M. Fetizon, M. Jurion and N.T. Anh. Chem. Commun., 112 (1969).

92. R.E. Ireland and G. Pfister. Tetrahedron Letters, 2145 (1969).

93. W.R. Bamford and T.S. Stevens. J. Chem. Soc., 4735 (1952).

94. M. Fischer, Z. Pelah, D.H. Williams and C. Djerassi. Chem. Ber., 98, 3236 (1965).

95. R.H. Shapiro and M.J. Heath. J. Amer. Chem. Soc., 89, 5734 (1967).

96. G. Kaufman, F. Cook, H. Shechter, J. Bayless, L. Friedman. J. Amer. Chem. Soc., 89, 5736 (1967).

97. A.K. Bose and N.G. Steinberg. Synthesis, 595 (1970) and references therein.

98. R. Ratcliffe and R. Rodehorst. J. Org. Chem., 35, 4000 (1970).

99. K. Bowden, I.M. Heilbron, E.R.H. Jones and B.C.L. Weedon. J. Chem. Soc., 39 (1946).

100. H.O. House, T.M. Bare, W.E. Hanner. J. Org. Chem., 34, 2209 (1969).

101. H.C. Brown and G. Zweifel. J. Amer. Chem. Soc., 83, 1241 (1961).

102. M. Hanack and H. Effensperger. Justus Liebigs Ann. Chem., 648, 1 (1961).

103. M.M. Fawzi and C.D. Gutsche. J. Org. Chem., 31, 1390 (1966), and references therein.

104. E. Piers, R.W. Britton, and W. de Waal. Can. J. Chem., 47, 831 (1969).

105. W.S. Johnson, J.C. Collins, R. Pappo, M.B. Rubin, P.J. Kropp, W.F. Johns, J.E. Pike and W. Bartmann. J. Amer. Chem. Soc., 85, 1409 (1963).

106. Huang-Minlon. J. Amer. Chem. Soc., 68, 2487 (1946).

107. W.F. Erman and L.C. Stone. J. Amer. Chem. Soc., 93, 2822 (1971).

108. W. Herz, R.N. Mirrington and H. Young. Tetrahedron Letters, 405 (1968).

109. R.H. Shapiro, J.H. Duncan and J.C. Clopton. J. Amer. Chem. Soc., 89, 1442 (1967).

110. E.J. Corey, S.W. Chow and R.A. Scherrer. J. Amer. Chem. Soc., 79, 5773 (1957).

111. C.W. Cowell and A. Ledwith. Quart. Rev., 24, 119 (1970), and references therein.

112. R.J. Crawford, A. Mishra and R.J. Dummel. J. Amer. Chem. Soc., 88, 3959 (1966).