CHAPTER IA : SYNTHESIS OF 3,7-DIMETHYL-6-OXO-OCTANOIC ACID
Summary

Isopulegol 25 on heating with lead tetraacetate underwent smooth fragmentation to give 6-acetoxy-3,7-dimethyl-oct-7-en-1-al 32. 32 was transformed to 3,7-dimethyl-6-oxo-octanoic acid 43. 3,7-Dimethyl-6-oxo-octanoic acid 43 is a constituent of geranium oil. Other transformations of 32 confirming its structure will be presented.
INTRODUCTION

Fragmentation reaction can be defined as the one which involves bond breaking process. In general this bond breaking process can be either heterolytic or homolytic. Heterolytic fragmentation involves the regulated cleavage of molecules containing certain combination of atoms such as carbon, oxygen, nitrogen, sulfur, phosphorus, silicon, boron and halogens. Heterolytic fragmentation can be acid or base catalyzed reaction. Carbocation and carbanion are the reactive species in heterolytic fragmentation. This fragmentation reaction has been reviewed by Grob et al.\textsuperscript{1,2}

Homolytic fragmentation involves formation of a new radical and a neutral molecule. In general,

\[ [ABC]^* \rightarrow AB + C^* \text{ or } A^* + BC. \]

Homolytic fragmentation can be initiated thermally or photochemically. This fragmentation involves homolysis of a covalent bond to the radical centre and is hence referred to as \( \beta \)-scission.

Lewis et.al.\textsuperscript{3} observed that in the reaction of butanal with 1,1-dimethyl prop-2-en-1-yl phenyl sulphide \( 1 \), the radical \( 2 \) formed by addition of butyroyl radical to the olefinic double bond undergoes \( \beta \)-scission to afford \( 3 \).
rather than abstract hydrogen from butanal to give
the 1:1 adduct $\frac{1}{2}$ (Chart I, Scheme I).

The loss of an atom $\beta$ to a radical sometimes also
involves the intermediacy of another radical. For e.g.,
the addition of trichloromethyl radicals to 2,3-dimethylbut-2-
enene $\overset{5}{2}$ affords radical $\overset{6}{6}$. Loss of the methyl hydrogen to
the trichloromethyl radical results in the formation of
chloroform and the product of the apparent $\beta$-scission
$4,4,4$-trichloro-2,3,3-trimethylbut-1-ene $\overset{6}{2}$ (Chart I,
Scheme II).

Sometimes, these fragmentation reactions are also
termed as elimination reactions and the above two
reactions are illustrative of this process$^5$. $\beta$-Scission
reaction can also involve the formation of carbon-carbon
double bond as well as carbonyl function. An alkoxy
radical can afford a carbonyl function by fission of
a bond $\beta$ to the radical centre.

$$
\begin{align*}
R-\overset{\cdot}{C}=0 + [H] & \rightarrow H R-\overset{\cdot}{C}-O' \\
& \rightarrow H \overset{\cdot}{C}=0 + [R]
\end{align*}
$$

This is illustrated by the thermolytic decomposition
of t-amyl hypochlorite $\overset{8}{8}$ to afford acetone and ethyl
chloride in a chain reaction$^6$ via $\overset{9}{9}$ (Chart I, Scheme III).
**SCHEME I**

\[
\text{PhSC(Me}_2\text{CH}=\text{CH}_2 + \text{PrCO} \rightarrow \text{PhSC(Me}_2\text{CHCH}_2\text{COPr}}
\]

**SCHEME II**

\[
\text{Cl}_3\text{C} + \text{Me}_2\text{C} = \text{CHCH}_2\text{COPr} \rightarrow \text{Cl}_3\text{C} - \text{C} - \text{Me}_2\text{C} = \text{CHCH}_2\text{COPr} + \text{CHCl}_3
\]

**SCHEME III**

\[
\text{Me}_2\text{(Et) COCl} \rightarrow \text{Me}_2\text{(Et) CO} + \text{Cl}^-
\]

**SCHEME IV**

\[
\text{RCH}_2\text{OR}^1 + \text{Rad}^* (\text{from peroxide}) \rightarrow \left[ \text{RCHO}^1 \right] + \text{Rad} \text{H}
\]

\[
\text{RCHO}^1 \rightarrow \text{R-CHO} + \text{R}^1
\]
When the ether $\text{10}$ is heated with a peroxide
the intermediate $\beta$-alkoxy radical undergoes $\beta$-scission\(^7\)
to give $\text{11}$ (Chart I, Scheme IV).

**Requirement for fragmentation**

Alkoxy radical formed in general can undergo two
different types of reactions, namely (a) abstraction of
hydrogen in intramolecular fashion from $\sigma$-carbon atom
(path a) and (b) fragmentation reactions which are
ergetically favoured\(^8\) in some cases (path b).

![Diagram of alkoxy radical reaction]

The rate $K_b$ of the cleavage reaction increases
with the stability of the product of cleavage, $\text{R-C}$.\(^9,10\)
Besides this other factors must play a part: the stability
of the ketone or aldehyde formed, the decrease in strain
by ejection of bulky groups\(^10\), polar structures in the
transition state stabilized by polarizing group $\text{R}$, entropy
factors in the resonance stabilization of the radical
formed by cleavage and in cyclic compounds (particularly
with small rings), the decrease in strain as a result of
ring opening. All these factors have been exemplified
in the following cases.
CHART II

SCHEME I

12 \[\xrightarrow{\text{Hypoiodite}}\] 13 \[\xrightarrow{\text{Products}}\]

SCHEME II

14 \[\xrightarrow{\text{Pb (OAc)$_4$}}\] 15

SCHEME III

16 \[\xrightarrow{\text{Hypoiodite or Pb (OAc)$_4$}}\] 17

SCHEME IV

18 \[\xrightarrow{\text{Hypoiodite}}\] 19

SCHEME V

20 \[\xrightarrow{\text{Pb (OAc)$_4$}}\] 21

SCHEME VI

22 \[\xrightarrow{\text{Pb (OAc)$_4$}}\] 23 + 24
Fragmentation as a result of resonance stabilization

The steroid alcohol 12 on hypoiodite reaction gave the products derived from the intermediate radical 13\(^\dagger\) (Chart II, Scheme I). Similarly alcohol 14 gave the product 15 on reaction with lead tetraacetate\(^\dagger\) (Chart II, Scheme II). Formation of stable allylic radicals seems to be the driving force for the above reactions.

Fragmentation as a result of loss of bulky substituents

Tertiary 20-hydroxy steroids 16 in contrast to the reaction of secondary 20-hydroxy steroids, the hydrogen abstraction from C-18 is distinctly suppressed in favour of the fragmentation to give 17, although the carbon radical formed is not appreciably stabilized\(^\dagger\) (Chart II, Scheme III). A series of seco steroids were prepared by the fragmentation of alcohol 18 to the product 19\(^\dagger\)\(^\dagger\) (Chart II, Scheme IV).

Fragmentation as a result of decrease in strain

The ease of fragmentation as a result of relief of ring strain is shown by the conversion of 20 to 21\(^\dagger\) (Chart II, Scheme V).

Isoborneol 22 on treatment with lead tetraacetate afforded the products 23 and 24. The driving force for the above two reactions is relief in the strain as a result of ring opening\(^\dagger\) (Chart II, Scheme VI).

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In the light of above mentioned observations it was decided to study the reaction of lead tetraacetate on (+)-Isopulegol 25. Isopulegol is a naturally occurring monoterpene secondary homo allylic alcohol. (+)-Isopulegol 25 can also be prepared by acid catalyzed cyclization\(^{15}\) of (+)-citronellal \(^5\). Menthol 29 is known to give tetrahydro menthofuran 30 on treatment with lead tetraacetate\(^\text{16}\). The mechanism for this reaction involves the formation of alkoxy radical 29a, which abstracts hydrogen atom from \(\alpha\)-carbon atom to give 29b. The intermediate 29b is then oxidised to 29c, which undergoes ring closure to give 30 (Chart III, Scheme I).

Hence it was anticipated that isopulegol 25 can also react in a similar manner to give ether 27 from alkoxy radical 26. It may be pointed out that this process should be facile, since the alkoxy radical 26, after abstraction of hydrogen atom from \(\alpha\)-carbon can lead to intermediate 26a. 26a - a stable allylic radical can then be oxidised to 26b, which then can undergo ring closure to give 27 (Chart III, Scheme II). It could also be possible to transform 27 to the \(\alpha\)-methylene-\(\gamma\)-butyrolactone 28 by standard reactions. It is well established that \(\alpha\)-methylene-\(\gamma\)-lactone moiety is responsible for biological activity associated with some antitumor compounds\(^{17}\).
CHART III

25 \( R^1 = H, R^2 = \text{OH} \)

31 \( R^1 = \text{CH}_3, R^2 = \text{OH} \)

SCHEME I

\[ \text{MeMe} \]

29 \( \text{OH} \)

29a \( \text{Me} \)

29b \( \text{OH} \)

29c \( \text{Me} \)

30

SCHEME II

25 \( \text{OH} \)

26 \( \text{OH} \)

26a \( \text{Me} \)

26b \( \text{OH} \)

27

SCHEME III

26 \( \text{Me} \)

26c \( \text{Me} \)

32
However when 27 was heated with lead tetraacetate (1:2) in refluxing benzene, the product obtained was not 27. The spectral data obtained for this product was consistent with the structure 32. Compound 32 in IR displayed bands at 2850 cm⁻¹ (aldehyde) and 1230 cm⁻¹ (acetate). NMR spectrum of 32 indicated signals at 9.75 (1H, m, -CHO), 5.04 (1H, t, J = 6Hz, -CHOAc).

A probable mechanism for the formation of 32 is shown (Chart III, Scheme III). The alkoxy radical 26 cleaves at β-position to give a new radical species 26c, which is then transformed to 32. Hence our results shows that the fragmentation reaction to give 32 is favoured other hydrogen abstraction to give 27. No isomerized product 49 could be detected. Saponification of 32 gave alcohol 33, which in its IR showed bands at 3650 cm⁻¹ for OH stretching and 1710 cm⁻¹ for aldehyde carbonyl. Its NMR spectrum displayed an upfield proton shift for proton attached to carbon bearing hydroxyl group i.e. 3.87 (1H, t, J = 6Hz, CHOH). Silver oxide oxidation on 32 in the presence of alkali gave 38. 38 was esterified to methyl ester 39 with diazomethane. Ester 39 being an allylic alcohol, underwent active manganese dioxide oxidation to give 44. The NMR spectrum of 44 showed downfield shift for the olefinic protons i.e. 5.68 and 5.90 s. These experiments show that 32 is an allylic acetate.
It is of interest to note that the aldehyde \( \text{32} \), has the oxygen functions at \( C_1 \) and \( C_6 \) in the dimethyl-octane carbon skeleton and hence is a potential intermediate for the synthesis of naturally occurring ketoacid \( \text{43} \). Keto acid \( \text{43} \) is a constituent of geranium oil\(^{20} \). The ketoacid \( \text{43} \) has the oxygen functions located on the same carbon atoms in the dimethyl-octane skeleton \( \text{32} \). Catalytic hydrogenation of \( \text{32} \) furnishes a mixture of the aldehyde \( \text{34} \) and the hydrogenolysis product \( \text{41} \). This mixture could be fractionally distilled to give \( \text{34} \). Saponification of the aldehyde \( \text{34} \) gave the hydroxy aldehyde \( \text{35} \). Oxidation of \( \text{35} \) with silver oxide\(^{18} \) in the presence of alkali gave the hydroxy acid \( \text{36} \). The acid \( \text{36} \) was characterised as its methyl ester \( \text{37} \). The ester \( \text{37} \) is oxidised with Jones reagent\(^{21} \) and the resulting keto ester \( \text{42} \) on saponification with alkali gave ketoacid \( \text{43} \). The IR and NMR spectra of \( \text{43} \) are identical with those of an authentic sample. Alternatively \( \text{43} \) could also be obtained by the direct oxidation of \( \text{36} \) with Jones reagent\(^{22} \).

Incidentally we have prepared the diol \( \text{45} \) by carrying out sodium borohydride reduction of \( \text{32} \). This route to diol is superior to the reported method\(^{23} \) of preparing it through photosensitized oxidation of citronellol. In the later route the diol \( \text{45} \) is a minor component. The
CHART IV

32 $R^3=H, R^4=\text{OCOCH}_3$
   double bond at $C_7-C_8$
33 $R^3=H, R^4=\text{OH}$
   double bond at $C_7-C_8$
34 $R^3=H, R^4=\text{OCOCH}_3$
35 $R^3=H, R^4=\text{OH}$
36 $R^3=R^4=\text{OH}$
37 $R^3=\text{OCH}_3, R^4=\text{OH}$
38 $R^3=R^4=\text{OH}$
   double bond at $C_7-C_8$
39 $R^3=\text{OCH}_3, R^4=\text{OH}$
   double bond at $C_7-C_8$
40 $R^3=R^4=H, \text{OH at } C_7$
41 $R^3=R^4=H$
47 $R^3=\text{CH}_3, R^4=\text{OCOCH}_3$
   double bond at $C_7-C_8$
48 $R^3=\text{CH}_3, R^4=\text{OH}$
   double bond at $C_7-C_8$
42 $R^5=\text{CH}_3$
43 $R^5=H$
44 $R^5=\text{CH}_3$
   double bond at $C_7-C_8$
45 $R^6=\text{H}$
46 $R^6=\text{COCH}_3$
diol 45 was characterised as diacetate 46.

The reaction of lead tetraacetate on tertiary homoallylic alcohol 31 was also investigated. The alcohol 31 was obtained in two steps by carrying out pyridinium chlorochromate oxidation of isopulegol 25 to isopulegone 50. Reaction of 50 with methyl magnesium iodide gave 31. When 31 was heated with lead tetraacetate and true to our expectation gave the fragmented product 47. NMR spectrum showed signals at 2.03 (3H, s, -CO-CH₃), 4.8 (2H, m, vinyl H), 5.03 (1H, t, J = 6Hz, -CHOAc). 47 on saponification gave 48.

Our work on alcohol 25 and 31 confirms the observation that homoallylic alcohol undergoes fragmentation reaction with lead tetraacetate. Since the yields are good, this reaction could be some preparative values. Another important feature of this reaction was that hydrolysis of 32 gave the hydroxy aldehyde 33, isomeric with widely used perfumeric material 7-hydroxy citronellal 40.
EXPERIMENTAL PROCEDURE

6-Acetoxy-3,7-dimethyl-oct-7-en-1-al (32)

To a boiling mixture of benzene (250 ml), anhydrous calcium carbonate (9 g) and lead tetraacetate (20 g, 0.045 M) was added a solution of isopulegol+ 25 (4.31 g, 0.028 M) in benzene (20 ml). The reaction mixture was heated under reflux for 2 hours, cooled and filtered. The filtrate was washed with 10% potassium iodide solution, 10% sodium thiosulfate solution, water and dried. The residue obtained after the evaporation of benzene was fractionally distilled using a vigreux column (3 inches). The fraction with b.p. 94-95°/1 mm. (Yield 3.55 g; 60%) was composed of entirely acetoxyaldehyde (32).

IR spectrum (liquid film) showed bands at 2850 cm⁻¹ (CHO), 1740 cm⁻¹ (carbonyl of acetate and aldehyde), 1660 and 895 cm⁻¹ (C = CH).

NMR spectrum (CCl₄) showed signals at δ 0.98 (3H, d, J = 6 Hz, CH₃-CH), 1.72 (3H, m, CH₃-C=C), 2.03 (3H, s, CH₃-CO-O-), 4.81 (1H, m, vinyl H), 4.88 (1H, m, vinyl H), 5.04 (1H, m, CHOAc).


C₁₂H₂₀O₃ requires C, 67.89; H, 9.50.

+ Since isopulegol is obtained by cyclization of (+)-citronellal, all the compounds prepared in this series were racemic.
6-Hydroxy-3,7-dimethyl-oct-7-en-1-al (33)

A mixture of 32 (1 g, 0.0047 M), methanol (30 ml) and sodium hydroxide (0.92 g, 0.023 M) was heated under reflux for 1 hour, cooled, diluted with water and extracted with ether (2 x 50 ml). The ether extract was washed with water, dried and the solvent evaporated. Distillation of the residue under reduced pressure furnished 33 (0.58 g, 73%), b.p. 120° (bath) / 1 mm.

IR spectrum (liquid film) showed bands at 3200 (OH), 2600 (-CHO), 1710 (carbonyl of aldehyde).

NMR spectrum (CCl₄) showed signals at 0.95 (3H, d, J = 6 Hz, CH₃-CH), 1.66 (3H, m, CH₃-C=C), 3.35 (1H, m, OH exchanges with D₂O), 3.87 (1H, m, -CHOH), 4.65 (1H, m, vinyl H), 4.77 (1H, m, vinyl H), 9.77 (1H, m, -CHO).

Analysis: Found C, 70.17, H, 10.66.

C₁₀H₁₈O₂ requires C, 70.54, H, 10.66.

6-Acetoxy-3,7-dimethyl octanal (34)

A mixture of 32 (3.44 g; 0.016 M), acetone (35 ml) and palladium-charcoal (5%; 0.72 g) was stirred at room temperature in hydrogen atmosphere at atmospheric pressure. After the absorption of 0.02 M of hydrogen the rate of hydrogenation was virtually zero and the hydrogenation was stopped. The reaction mixture was filtered, solvent evaporated from the filtrate and the residue fractionally
distilled. Fraction (i), b.p. 85° (bath)/1 mm was characterised as 3,7-dimethyloctanal 34, since on oxidation furnished 3,7-dimethyloctanoic acid identified by comparison (NMR) with an authentic sample. Fraction (ii), b.p. 110° (bath)/1 mm (yield 2.25 g, 65%) was characterised as 6-acetoxy-3,7-dimethyl octanal 35.

**IR spectrum (liquid film)** showed bands at 2800 cm⁻¹ (-CH₃), 1730 cm⁻¹ (carbonyl of acetate and aldehyde).

**NMR spectrum (CCl₄)** showed signals at δ 0.88 (6H, d, J = 6Hz, CH₃ CH), 0.88 (3H, d, J = 6Hz, CH₃-CH), 2.02 (3H, s, CH₃-CO-0-), 4.82 (1H, m, -CHOAc), 9.07 (1H, m, -CHO).


C₁₂H₂₂O₃ requires C, 67.25; H, 10.35.

**6-Hydroxy-3,7-dimethyl octanal (35)**

A mixture of 34 (1 g, 0.0047 M), methanol (25 ml) and sodium hydroxide (0.92 g, 0.023 M) was heated under reflux for 2 hours, cooled, diluted with water and extracted with ether (2x30 ml). The ether extract was washed with water, dried, evaporated and distilled to give 35 (0.63 g, 78%), b.p. 123° (bath)/1 mm.

**IR spectrum (liquid film)** showed bands at 3580 cm⁻¹ (OH), 2800 and 1720 cm⁻¹ (-CHO).
NMR spectrum (CCl₄) showed signals at ≤ 0.88
[9H, d, J = 6 Hz, (CH₃)₂CH and CH₃-CH], 3.22 [1H, m, -CHOH], 3.62 (1H, m, CH disappears on D₂O exchange), 9.67 (1H, m, -CHO).

**Analysis:** Found C, 69.47; H, 11.43.
C₁₀H₂₀O₂ requires C, 69.72; H, 11.70.

6-Hydroxy-3,7-dimethyl octanoic acid (36)

A mixture of 2₄ (0.785 g, 0.0037 M), ethanol (20 ml), water (10 ml), silver oxide (freshly prepared from 2.26 g of silver nitrate) and sodium hydroxide (0.7 g, 0.017 M) was stirred at room temp. for 48 hours. The filtrate was heated under reflux for 20 minutes, cooled, diluted with water and extracted with ether (1x100 ml). The ether layer was discarded. The aqueous layer was acidified with 10% hydrochloric acid (pH 2) and extracted with ether (2x50 ml). The ether extract washed with water, brine, dried the solvent, distilled off to furnish 36 (0.45 g, 70%).

IR spectrum (liquid film) showed band at 1706 cm⁻¹ (carbonyl of acid).

NMR spectrum (CCl₄) showed signals at ≤ 0.88
[6H, d, J = 6Hz, (CH₃)₂CH], 0.97 (3H, d, J = 6Hz, CH₃-CH⁻), 3.30 (1H, m, -CHOH), 6.73 (2H, bm, OH exchanges with D₂O).

36 was further characterised as methyl 6-hydroxy-
3,7-dimethyloctanoate 37 by esterification with diazomethane in 90% yield, b.p. 153°C (bath)/4 mm.

IR spectrum (liquid film) showed bands at 3620 cm⁻¹ (OH), 1730 cm⁻¹ (carbonyl of ester).

NMR spectrum (CCl₄) showed signals at 0.88 [6H, d, J = 6Hz, (CH₃)₂CH], 0.95 [3H, d, J = 6Hz, CH₃-CH], 3.23 (1H, m, -CHOH), 3.58 (3H, s, -OCH₃).

Analysis: Found C, 65.60; H, 10.98.
C₁₁H₂₂O₃ requires C, 65.31; H, 10.96.

Methyl 3,7-dimethyl-6-oxo-octanoate (42)

To a mixture of 37 (0.195 g, 0.001 M) in acetone (15 ml) was added a Jones reagent at 0°C till the orange colour of reagent was persistent. The reaction mixture stirred for 0.5 hour at the same temperature, poured into water, extracted with ether (2x25 ml). The ethereal solution washed with water, brine, dried and evaporated to give the residue, which on distillation furnished 42 (0.173 g, 92%); b.p. 145°C (bath)/6 mm.

IR spectrum (liquid film) showed bands at 1740 cm⁻¹ (ester carbonyl), 1720 cm⁻¹ (keto carbonyl).

NMR spectrum (CCl₄) showed signals at 0.97 [3H, d, J=6Hz, CH₃-CH], 1.07 [6H, d, J = 6Hz, (CH₃)₂CH], 3.62 (3H, s, OCH₃).

Analysis: Found C, 65.94; H, 10.22.
C₁₁H₂₀O₂ requires C, 65.97; H, 10.07.
3,7-Dimethyl-6-oxo-octanoic acid (43) +

Method (a): A mixture of 42 (0.12 g, 0.00061 M), sodium hydroxide (0.240 g, 0.006 M), methanol (25 ml) and water (1 ml) was heated under reflux for 2 hours, cooled, diluted with water and extracted with ether (2×20 ml). The etheral layer was washed with water, dried and solvent evaporated to give 43 (0.09 g, 82%), identified by comparison (IR, NMR) with an authentic sample.

IR spectrum (liquid film) showed band at 1709 cm⁻¹ (acid and keto carbonyl).

NMR spectrum (CDCl₃) showed signals at δ 0.88 (3H, d, J=6 Hz, CH₃-CH), 1.05 (6H, d, J=6 Hz, (CH₃)₂CH), 10.0 (1H, m, CO₂H, exchanges with D₂O).

Method (b): Oxidation of 36 with Jones reagent furnished 42 in 80% yield, identified through its IR, NMR spectrum.

6-Hydroxy-3,7-dimethyl-oct-7-enoic acid (38)

A mixture of 32 (2.14 g, 0.01 M), ethanol (50 ml), water (20 ml), silver oxide (freshly prepared from 7.2 g of silver nitrate) and sodium hydroxide (2.1 g, 0.05 M) was stirred at room temperature for 48 hours. The filtrate was heated under reflux for 20 minutes, cooled, diluted with water and extracted with ether (2×100 ml). The ether

+ For the synthesis of 43 by Bayer-Villiger oxidation of pulegone see reference 26.
extract was rejected. The aqueous layer was acidified with 10% hydrochloric acid (pH 2) and extracted with ether (2x100 ml). The ether layer was washed with water, dried and the solvent evaporated to furnish 38 (1.40 g, 76%).

IR spectra (liquid film) showed band at 1709 cm$^{-1}$ (carbonyl of carboxyl group).

NMR spectra ($\text{CCl}_4$) showed signals at 0.98 (3H, d, J = 6 Hz, $\text{CH}_3$-$\text{CH}_2$), 1.68 (3H, m, $\text{CH}_3$-$\text{C}=$C), 3.98 (1H, m, $\text{CHOH}$), 4.75 (1H, m, vinyl H), 4.87 (1H, m, vinyl H), 7.97 (2H, bm, OH, exchangeable with $\text{D}_2$O).

38 was further characterized as methyl ester 39 with diazomethane in 92% yield b.p. 130°(bath)/1 mm.

IR spectrum (liquid film) showed bands at 3650 cm$^{-1}$ (OH), 1740 cm$^{-1}$ (carbonyl of ester), 1645 and 840 cm$^{-1}$ (=$\text{CH}_2$).

NMR spectra ($\text{CCl}_4$) showed signals at 0.99 (3H, d, J=6Hz, $\text{CH}_3$-$\text{CH}_2$), 1.73 (3H, s, $\text{CH}_3$-$\text{C}=$C), 2.6 (1H, s, OH exchanges with $\text{D}_2$O), 3.6 (3H, s, $\text{OCCH}_3$), 3.96 (1H, t, J = 6 Hz, $\text{CHOH}$), 4.83 (2H, m, =CH$_2$).


$\text{C}_{11}\text{H}_{20}\text{O}_3$ requires C, 65.97; H, 10.07%.

**Methyl-3,7-dimethyl-6-oxo-oct-7-enoate (44)**

A mixture of 39 (0.12 g, 0.0061 M), petroleum ether (20 ml) and active manganese dioxide (1 g) was stirred at room temperature for 2 hours. Evaporation of
petroleum ether gave the residue which when distilled in vacuum gave \( \text{44} \) (0.10 g, 70%), b.p. 150\(^\circ\) (bath)/15 mm. IR spectrum (liquid film) showed bands at 1740 cm\(^{-1}\) (ester carbonyl), 1675 cm\(^{-1}\) (conjugated carbonyl), 1625 cm\(^{-1}\) (carbon-carbon double bond).

NMR spectrum (CCl\(_4\)) showed signals at 0.97 (3H, d, \( J=6 \) Hz, CH\(_3\)-CH), 1.85 (3H, m, CH\(_3\)-C=C), 3.62 (3H, s, OCH\(_3\)), 5.68 (1H, m, vinyl H), 5.90 (1H, m, vinyl H).

Analysis: Found C, 67.01; H, 9.28.

\( \text{C}_{11}\text{H}_{18}\text{O}_3 \) requires C, 66.68; H, 9.15.

3,7-Dimethyl-oct-7-en-1,6-diol (45)

A mixture of 32 (1.5 g, 0.0071 M), ethanol (30 ml), sodium borohydride (0.234 g, 0.0071 M) and water 15 ml was stirred at room temperature for 24 hours and subsequently 10 ml of 5% sodium hydroxide solution was added and the stirring continued for 20 hours. The mixture poured into water and extracted with ether (2x50 ml). The ether layer was washed with water, brine, dried and evaporated to give the residue which after distillation gave \( \text{45} \) (0.90 g, 75%), b.p. 153\(^\circ\) (bath)/2 mm.

IR spectrum (liquid film) showed bands at 3620 cm\(^{-1}\) (OH), 1645 and 890 cm\(^{-1}\) (\( \text{C=CH}_2 \)).

NMR spectrum (CCl\(_4\)) showed signals at 0.90 (3H, d, \( J=6 \) Hz, CH\(_3\)-CH\(_3\)-CH\(_3\)-CH\(_3\)), 1.70 (3H, m, CH\(_3\)-C=C), 3.55 (2H, m, \(-\text{CH}_2\text{OH}\)), 3.90 (1H, m, \(-\text{CHOH}\)), 4.75 (1H, m, vinyl H), 4.85 (1H, m, vinyl H).
3,7-Dimethyl-oct-7-en-1,6-diacetate (46)

A mixture of 45 (1 g, 0.0058 M), pyridine (0.948 g, 0.012 M) and acetic anhydride (1.2 g, 0.012 M) kept at room temperature for 24 hours. The mixture diluted with water and extracted with ether (2x50 ml). The ether extract washed with 5% hydrochloric acid, water, brine, dried and solvent evaporated. The residue was distilled under vacuum to give 46 (1.3 g, 90%), b.p. 150° (bath)/5 mm.

IR spectrum (liquid film) showed bands at 1745 cm⁻¹ (carbonyl of ester), 1645, 890 cm⁻¹ (=CH₂).

NMR spectrum (CCl₄) showed signals at δ 0.92 (3H, d, J=6 Hz, CH₃-CH), 1.70 (3H, m, CH₃-C=C), 1.93 (3H, s, CH₃-C-O-), 1.97 (3H, s, CH₃-C-O-), 3.95 (2H, m, -CH₂-OAc), 4.77 (2H, m, vinyl H), 4.97 (1H, m, -CHOAc).


C₁₄H₂₁O₄ requires C 65.59; H, 9.44.

(+)-Isopulegone (50)

A mixture of isopulegol 25 (4 g, 0.026 M), pyridinium chloro chromate 27 (16.0 g, 0.073 M) and methylene chloride (100 ml) was magnetically stirred at room temperature for 36 hours. The mixture was filtered through celite and the solids were washed thoroughly with methylene chloride. The filtrate was washed with 10% hydrochloric acid (2x50 ml), 10% sodium bicarbonate (2x50 ml), water, dried and evaporated to give residue, which upon distillation under vacuum
furnished (30) (3.8 g, 96%), b.p. 75° (bath)/1.5 mm.

IR spectrum (liquid film) showed bands at 1716 cm\(^{-1}\) (for carbonyl), 1645, 890 cm\(^{-1}\) (=CH\(_2\)).

NMR spectrum (CCl\(_4\)) showed signals at 0.92 (3H, d, J=6 Hz, CH\(_3\)-CH), 1.66 (3H, s, CH\(_3\)-C=C-), 2.9 (1H, q, J = 6 Hz, H-CH-C-), 4.63 (1H, m, vinyl H), 4.8 (1H, m, vinyl H).

Preparation of (31)

To a solution of methyl magnesium iodide (5.01 g, 0.03 M, prepared from 0.3 g of methyl iodide and 0.7 g of magnesium) at 0° was added isopulegone (2.5 g, 0.016 M) in 10 ml ether. The mixture stirred at 0° for 1 hour, and then at room temperature for 24 hours. The reaction was quenched with saturated solution of ammonium chloride. The etheral layer was washed with water, brine, dried and evaporated to give liquid which upon distillation under reduced pressure gave (31) (2.16 g, 82%), b.p. 93° (bath)/1.5 mm.

IR spectrum (liquid film) showed bands at 3550 cm\(^{-1}\) (OH), 1660, 890 cm\(^{-1}\) (C=CH\(_2\)).

NMR spectrum (CCl\(_4\)) showed signals at 0.95 (3H, d, J=6 Hz, CH\(_3\)-CH), 1.53 (3H, s, CH\(_3\)-OH), 1.72 (3H, m, CH\(_3\)-C=C), 4.88 (2H, m, vinyl H).

Analysis: Found C, 78.76; H, 11.87.

C\(_{11}\)H\(_{20}\)O requires C, 78.51; H, 11.98.
7-Acetoxy-4,8-dimethyl-non-8-en-2-one (47)

To a boiling mixture of benzene (75 ml) anhydrous calcium carbonate (2.0 g, 0.02 M) and lead tetraacetate (5.1 g, 0.012 M) was added a solution of 3l (1.0 g, 0.006 M) in benzene (5 ml). The reaction mixture was heated under reflux for 2 hours, cooled and filtered. The filtrate was washed with 10% potassium iodide solution, 10% sodium thiosulphate solution, water, dried. The residue obtained after the evaporation of benzene was fractionally distilled. The fraction b.p. 128° (bath)/1.5 mm (0.929 g, 68%) was 47. IR spectrum (liquid film) showed bands at 1782 cm⁻¹ (acetate carbonyl), 1710 cm⁻¹ (keto carbonyl).

NMR spectrum (CCl₄) showed signals at δ 0.83 (3H, d, J=6 Hz, CH₃-CH-), 1.7 (3H, s, CH₃-C=C), 2.0 (3H, s, -C-CH₃), 2.03 (3H, s, -C-CH₃), 4.8 (2H, m, vinyl H), 5.03 (1H, t, J=6 Hz, CHOAc).

Analysis: found C, 68.99; H, 9.80.

C₁₃H₂₂O₃ requires C, 68.81; H, 10.11.

7-Hydroxy-4,8-dimethyl-non-8-en-2-one (48)

To a mixture of 47 (0.226 g, 0.001 M), ethanol (12 ml), sodium hydroxide (0.200 g, 0.005 M) and water (1 ml) heated to reflux for 3 hours. The mixture was cooled, diluted with water and extracted with ether (2x25 ml). The ether was washed with water, brine, dried and evaporated to give residue, which on distillation under vacuum gave 48 (0.156 g, 85%), b.p. 122° (bath)/1 mm.
IR spectrum of (liquid film) showed bands at 3600 cm\(^{-1}\) (OH),
1720 cm\(^{-1}\) (acetate carbonyl), 895 cm\(^{-1}\) (C=CH\(_2\)).
NMR spectrum (CD\(_2\)Cl\(_2\)) showed signals at \(\delta\) 0.83 (3H, d, \(J = 6\) Hz,
CH\(_3\)-CH-), 1.63 (3H, m, CH\(_3\)-CH=CH-), 2.03 (3H, s, -C-CH\(_3\)),
3.06 (1H, m, OH exchangeable with D\(_2\)O), 3.8 (1H, t, \(J = 6\) Hz,
-CHOH), 4.7 (1H, m, vinyl H), 4.8 (1H, m, vinyl H).
Analysis: Found C, 71.69; H, 10.94.

\(\text{C}_{11}\text{H}_{20}\text{O}_2\) requires C, 71.80; H, 10.98.
IR SPECTRUM OF 6-ACETOXY-3,7-DIMETHYL-OCT-7-EN-1-AL. (32)

NMR SPECTRUM OF 6-ACETOXY-3,7-DIMETHYL-OCT-7-EN-1-AL. (32)
NMR SPECTRUM OF 6-HYDROXY-3,7-DIMETHYL-OCT-7-EN-1-AL. (33)

NMR SPECTRUM OF METHYL 6-HYDROXY-3,7-DIMETHYL-OCT-7 ENOATE. (39)
NMR SPECTRUM OF METHYL 3,7-DIMETHYL-6-OXO-OCT-7 ENOATE. (44)

NMR SPECTRUM OF 6-ACETOXY-3,7 DIMETHYLOCTANAL. (34)
NMR SPECTRUM OF METHYL 6-HYDROXY-3,7-DIMETHYL OCTANOATE. (37)

NMR SPECTRUM OF 7-ACETOXY-4,8-DIMETHYL-NON-8-EN-2-ONE. (47)
REFERENCES


CHAPTER IB: SYNTHESIS OF 2,6-DIMETHYL-1,6-HEPTADIENE-3-OL-ACETATE. A POSSIBLE BIOGENESIS OF PHEROMONE-2,6-DIMETHYL-1,5-HEPTADIEN-3-OL-ACETATE INVOLVING 2,6-DIMETHYL-1,6-HEPTADIEN-3-OL-ACETATE AS A PRECURSOR
Summary

6-Acetoxy-3,7-dimethyl-7-en-octanoic acid 22 obtainable easily from isopulegol 20 was transformed to 2,6-dimethyl-1,6-heptadien-3-ol acetate 20 by oxidative decarboxylation. 20 is an analogue of 19. 19 is pheromone isolated from comstock mealybug. The analogue 20 is half as active as 19. Preparation of several other analogues of 20 will be presented. (-)-Menthone 26 was transformed to hydroxy acid 28, which on oxidation gave keto acid 42. The enantiomer of keto acid 42 i.e. 43 is naturally occurring and has been isolated from geranium oil.
INTRODUCTION

The pheromone structural spectrum is perhaps one of the richest in natural product chemistry. It embraces a wide variety of molecules whose number and structural type has grown enormously during the last few years and the trend is certain to continue in view of the continuous development in isolation, structure elucidation technique and synthesis.

That pheromones constitute a growing class of compounds is shown by number of books¹⁻⁶ and reviews⁷⁻¹⁰ that have appeared in last decade. Pheromones are compounds released by the insects used for intraspecific communication and they can be classified according to the response they elicit. These responses may be due to an individual chemical or as is often the case, a mixture of chemicals. For example, male boll weevils (Anthonomus grandis) produce a mixture of alicyclic pheromones 1, 2, 3 and 4 respectively. Here is an instance wherein the total mixture is the pheromone and the individual chemicals that make up the pheromone are termed as pheromone components. In such cases the total effect is greater than the sum of the effects of individual components. This phenomenon is termed as synergism.
Sex pheromones are secreted by one sex to attract the other as an initial part of the mating process. A variety of chemicals have been identified by screening as attractive to one sex. For example, the pheromone of the dried bean beetle (Acanthoscelides obtectus) is shown to have the structure 2. However, there are some instances known particularly among beetles (Coleoptera) where the pheromones may attract both the sexes and therefore serve more than one function. Such compounds are called as aggregation. Some insects use alarm pheromones to alert the members of their species. For example, the alarm pheromone of the Texas leaf cutting ant (Atta texana) is shown to be (S)-(+-4-methyl-3-heptanone 6.

Lately it has been realized that the activity of these pheromones vary largely depends upon the geometrical and optical isomers of the component. Since the quantity of pheromones isolated from natural resources are less than a milligram, it has been frequently been impossible to establish their structure, optical purity etc. Structure determination rests heavily on information derived from mass spectrum (MS), nuclear magnetic resonance (NMR), infra-red (IR) and ultraviolet (UV). A great deal of information has been recorded with these instruments. Latest method to arrive at the structure conclusion is
based on NMR studies in the presence of optically active lanthanide shift reagents\textsuperscript{11}. The outcome of such a study was structure elucidation of (\textpm)-exo-brevicomin 2, (\textpm)-frontalin 3 and \textpm-(\textpm)-multistriatin 9 respectively\textsuperscript{12}. Whereas enantiomeric composition of alcohol (+)-sucatol 10, (\textpm)-trans-verbenol 11, (\textpm)-ipsdienol 12 were found out by forming the derivatives of \textpm-methoxy-\textpm-trifluoromethyl-phenylacetyl derivatives\textsuperscript{13-15}. At present C-13-NMR has become a powerful tool for structure identification.

C-13-NMR has proved beneficial in identifying the structure and stereochemistry\textsuperscript{15} of endo-brevicomin 13, \textsuperscript{\textpm}-(\textpm)-multistriatin 14 and \textsuperscript{\textpm}-(\textpm)-multistriatin 15. Few instances are known wherein optical rotatory disposition (ORD) measurements have been made to arrive at the structure and enantiomeric forms of related pheromones\textsuperscript{16}.

The ultimate proof for structure is unambiguous synthesis followed by demonstration of equivalent biological activity of synthetic material in the field. These synthesis may not prove all that difficult, since pheromones have comparatively simpler structure as compared to other natural products (This is due to part to the requirement for high volatility and rapid diffusion in the air). However despite all precautions, errors still may occur. For example, it becomes difficult to prove which of the
isomer is active. The principle component of the attractant pheromone produced by the bark beetle (Ips subsp. subsp.) are three optically active component, namely, (+)-cis-verbenol, (+)-Ipsenol and Ipsdienol. None of these compounds are attractive by itself, however in the field the flying beetles respond to the mixture of these three. In or one does not know whether its R or S configuration alcohol shows activity. In such cases both R and S configuration alcohols are synthesised individually assessed for their activity. Thus with S-configuration at alcohol bearing carbon is active, while R-configuration, has been proved to be nearly inactive.

Pheromones have many practical applications. The study of pheromones enhances understanding of insects and their behaviour. The bark beetle in the family of Scolytidae has been the subject of several pheromone studies because of their economic importance. An annual loss of about 5x10^9 bored feet of timber in the USA alone is attributed to them. One of the most important insects pests in the USA, in terms of crop loss economics, is the boll weevil (Anthonomus Grandis). More than three fourths of all insects losses to cotton in this country (USA) have been in fact due to these pests. With the availability of resources, it has now become easy to control them. There are few reports like successful commercial operation against the pink bollworm in cotton fields in 1977 and the full
report on these studies are available. In addition to
crop protection permeation with gossyplure 18 with concomitant
reduction by 50-80% in pesticides use resulted in yield
improvements of as much as 20-50%. This is the first
instance of successful commissioning of a sex pheromone
for protection of a crop. In years to come it is hoped
that many more results will be expected.
PRESENT WORK

Recently, Mori et. al. have shown that 2,6-dimethyl-1,5-heptadien-3-ol acetate is the sex pheromone of Comstock mealybug Pseudococcus comstocki kuwana. Comstock mealybug is one of the most serious pests of apple, peas and other crops. Since the sex pheromone is highly attractive to native males, field trials could be carried out with as little as 0.1 mg of the synthetic (+)-19. Some analogues of 19 were synthesised and analogue 20 was found to be half as active as 19. Considering the dramatic results stated above we have examined convenient routes for the preparation of 20 and many other derivatives of same skeleton. A possible biogenetic route for the formation of 19 involving 20 as an intermediate is suggested.

The two step synthesis of hydroxy acid 21 starting from isopulegol 20a has been reported by us. Acetylation of 21 with acetic anhydride in pyridine furnished the acetoxy acid 22. There are several reports in the literature dealing with the transformation of primary carboxylic acids to alkenes. This process which is known as oxidative decarboxylation can be carried out by using lead tetraacetate in the presence of cupric acetate and pyridine. For example, acid 31 gave an oxidative decarboxylation 32 in good yield (Chart III, Scheme I).
Hence acetoxy acid 22 was subjected to oxidative decarboxylation and as expected the acetoxy alkene 20 was formed. The IR spectrum of 20 showed the absence of carboxyl group and showed bands at 1658 and 897 cm\(^{-1}\) attributable to the presence of exo methylene group (C=CH\(_2\)). The NMR spectrum of 20 showed signals at 1.70 (6H, s, CH\(_3\) on double bond), 1.95 (3H, s, O-CO-CH\(_3\)), 4.5-4.7 (4H, broad singlet, vinylic proton) and 5.1 (1H, t, J=6 Hz, -CHOAc).

Saponification of 20 furnished the hydroxy-alkene 23. IR spectrum of 23 showed absence of band at 1740 cm\(^{-1}\) (carbonyl from acetate) and a new band at 3546 cm\(^{-1}\) (OH stretching). NMR spectrum showed a signal at 4.03 (1H, t, J=6 Hz, -CHOH). 23 was transformed to the propionate 25 through acylation with propionic anhydride in pyridine. The NMR spectrum of 25 showed signals at 1.33 (3H, t, J=6 Hz, CH\(_3\)-CH\(_2\)), 2.33 (2H, q, J=6 Hz, -CH\(_2\)-CH\(_3\)) and 5.2 (1H, t, J=6 Hz -CHOCOCH\(_2\)CH\(_3\)). The IR spectrum of 25 showed reappearance of carbonyl group at 1739 cm\(^{-1}\). Active MnO\(_2\) oxidation of 23 gave 24. The IR spectrum showed band at 1667 cm\(^{-1}\) (conjugated carbonyl) and the NMR spectrum showed downfield shift for vinylic proton i.e. at 5.73 (H, m, vinylic proton) and 5.93 (1H, m, vinyl H).
We next turned our attention to the synthesis of analogue 30, which differs from 20, with respect to the double bond. Baeyer-Villiger oxidation of (-)-menthone 26 with 40% aqueous peracetic acid in the presence of sulfuric acid catalyst and subsequent work-up furnished a mixture of hydroxy acid 28 and acetoxy acid 29 instead of \( \epsilon \)-lactone 27. It was evident that the acids 28 and 29 were formed by acid catalysed ring opening of the initially formed \( \epsilon \)-lactone 27. A probable mechanism involving acylium ion (acyl-oxygen cleavage) is given below.

There are several reports in the literature regarding Baeyer-Villiger oxidation on ketone next to an asymmetric carbon, migrating with the retention of configuration 23. Hence we assume that the oxidation of (-)-menthone also proceeds with retention of configuration. Saponification of the total Baeyer-Villiger oxidation product gave hydroxy acid 28, which upon subsequent acetylation with acetic anhydride-pyridine gave 29. The
IR spectrum of 29 showed bands at 17.45 cm⁻¹ (carbonyl of acetate) and 1718 cm⁻¹ (acid carbonyl). 29 also showed (α)D = +12 (CHCl₃). NMR spectrum of 29 indicated signals at 2.06 (3H, s, -O-CO-CH₃) and 4.73 (1H, m, -CHOAc).

Oxidative decarboxylation of 29 furnished the acetoxy alkene 30. The IR spectrum of 30 showed bands at 1739 cm⁻¹ (acetate carbonyl), 1664 and 885 cm⁻¹ (C=CH₂). The NMR spectrum showed signals at 2.02 (3H, s, -O-CO-CH₃), 4.66 (2H, m, vinyl hydrogen) and 4.83 (1H, t, J=6 Hz, -CHOAc).

A possible biogenesis of 19 involving 20 is reported here-in as outlined in Scheme II, Chart III. In view of the similarity of the carbon skeleton with monoterpenes such as citral 44 (Chart II), the two differ by only one carbon atom, it is tempting to assume that the pheromone 19 is of terpenic origin. Many pheromones like Verbenol 11 and 16, Ipsenol 17 and Ipsdienol 12 are derived from monoterpene precursor α-pinene 24 or β-pinene 32 and myrcene 30 36. The first step may be the formation of allylic alcohol 32a from acid 31a. In this connection it is of interest to note that compounds having allylic alcohol functionality of the type present in 32a are known to occur in nature. For example, a number of compounds have been isolated from lavandin oil, one of them was 37.

The allylic alcohol 32a can undergo a very facile intramolecular michael addition to give 33, which may
**Chart III**

**Scheme I**

![Chemical Structure](chart)

Pb(OAc)$_4$/Cu$^{+2}$/Pyridine

**Scheme II**

![Chemical Structure](chart)

**Scheme III**

![Chemical Structure](chart)

**Scheme IV**

![Chemical Structure](chart)
undergo β-elimination to give hydroxy alkene 23. 23 on acetylation gives 20. Conversion of 20 to 19 involves double bond migration and requires the presence of an enzyme.

During the course of biogenesis of terpenoids, Bloch et al. isolated a metabolic product to which the structure Δ3-isopentenol pyrophosphate (IPP) 38 (Chart I) was assigned. This phosphate ester 38 was shown to be a bio-genetic precursor of many of the terpenes. During the course of these investigations a preparation derived from Baker's yeast has been found to catalyze the migration of the unsaturated bond of IPP 38 to yield γ,γ-dimethylallyl pyrophosphate (DMAPP) 39. Subsequently it was also realized that 39 also was incorporated in terpene biogenesis. It was found that this enzyme had sulfhydryl groups, which led Lynen et al. to conclude that a simple addition of enzyme and IPP to give enzyme substrate complex 40, which then undergoes elimination to give 39 and enzyme. This transformation can be written in the manner given in Scheme III, Chart III.

Precedent for the sulfide catalyzed migration of an olefinic double bond is found in the Willgerodt reaction, in which a saturated intermediate state also has been postulated.

On the basis of above mentioned arguments, we
assume that similar type of enzyme might be involved in the transformation of 20 to 19 via 41. A simple addition - elimination mechanism is given in Chart III, Scheme IV.

Incidentally we have also effected the synthesis of keto acid 42 from 28. The enantiomer of 42 i.e. 43 is naturally occurring. 28 on oxidation with Jones reagent gave 42 in good yield. Compounds 21, 22, 23 and 25 were prepared from racemic isopulegol and hence are racemates. Compounds 28, 29 and 30 are prepared from (-)-menthone have the S-configuration at the acetoxy (or hydroxy) bearing carbon, since Baeyer-Villiger oxidation is known to proceed with retention of configuration.
EXPERIMENTAL PROCEDURE

3,7-Dimethyl-6-acetoxy-oct-7-enoic acid (22)

A mixture of hydroxy acid\textsuperscript{24} \(21\) (3.0 g, 0.016 M), pyridine (2.5 g, 0.032 M) and acetic anhydride (3.2 g, 0.032 M) kept at room temperature for 24 hours. The mixture was diluted with water (100 ml), warmed up to 55-60° for 0.5 hour, cooled and extracted with ether (2x100 ml). The ether layer was washed with water, 10% solution of hydrochloric acid, 10% solution of sodium bicarbonate, water, brine, dried and evaporated to give residue, which on distillation under vacuum furnished \(\text{22}\) (2.9 g, 81%); b.p. 175° (bath)/0.3 mm.

IR spectrum (liquid film) showed bands at 1748 cm\(^{-1}\) (ester carbonyl), 1724 cm\(^{-1}\) (acid carbonyl).

NMR spectrum (CCl\(_4\)) showed signals at \(\delta\) 0.93 (3H, d, \(J = 6\) Hz, CH\(_3\)-CH\(-\)), 1.7 (3H, s, -CH\(_3\)-C=C), 2.0 (3H, s, -C-C\(_3\)), 4.86 (1H, m, vinyl H), 4.9 (1H, m, vinyl H), 5.03 (1H, t, \(J = 6\) Hz, -CHOAc), 9.7 (1H, broad singlet, OH exchangeable with D\(_2\)O).

Analysis: Found: C, 63.06; H, 8.88.

\(\text{C}_{12}\text{H}_{20}\text{O}_4\) requires C, 63.13; H, 8.83.

2,6-Dimethyl-1,6-heptadien-3-ol-acetate (20)

A mixture of \(\text{22}\) (2.9 g, 0.01 M), cupric acetate (0.468 g, 0.0025 M), pyridine (0.300 g, 0.038 M), lead tetraacetate (12 g, 0.027 M) and benzene (75 ml) was stirred under nitrogen for 0.5 hour at room temperature
and under reflux for 2 hours. Excess of lead tetraacetate was destroyed with ethylene glycol. The product was separated into acidic and neutral positions with 10% aqueous sodium carbonate solution. Acidic part on work-up yielded compound 22 (1.1 g). Neutral part after work-up and on vacuum distillation furnishes 20 (0.825 g, 58% on the basis of 22 actually consumed), b.p. 135° (bath)/16 mm, (Lit. 22 b.p. 105-110°/13 mm).

IR spectrum (liquid film) showed bands at 1745 cm⁻¹ (ester carbonyl), 1658, 897 cm⁻¹ (C=C).

NMR spectrum (CCl₄) showed signals at δ 1.7 (6H, s, CH₃-C=C), 2.0 (3H, s, -O-CO-CH₃), 4.73 (2H, bm, C=CH₂), 5.0 (2H, m, C=CH₂), 5.2 (1H, t, J=6 Hz, -CHOAc).

2,6-Dimethyl-1,6-heptadien-3-ol (23)

A mixture of 20 (0.430 g, 0.026 M), ethanol (10 ml) and sodium hydroxide (0.100 g, 0.025 M) was heated under reflux for 3 hours, cooled, diluted with water and extracted with ether (2x50 ml). The ether extract was washed with water, brine, dried and the solvent evaporated. Distillation of the residue in vacuum furnished 23 (0.257 g, 70%), b.p. 132° (bath)/15 mm (Lit. 22 reports b.p. 120-150°/13 mm).

IR spectrum (liquid film) showed band at 3546 cm⁻¹ (OH stretching).

NMR spectrum (CCl₄) showed signals at δ 1.7 (6H, s, CH₃-C=C-), 4.0 (1H, t, J=6 Hz, -CHOH), 4.6 (2H, bm, C=CH₂), 4.9 (2H, m, C=CH₂).
2,6-Dimethyl-1,6-heptadien-3-one-propionate (25)

A mixture of 23 (0.250 g, 0.0178 M), pyridine (1.58 g, 0.02 M), propionic anhydride (0.520 g, 0.02 M) was kept at room temperature for 48 hours. The mixture was poured into water and extracted with ether (2x50 ml). The etheral solution was washed with water, 10% hydrochloric acid solution, 10% sodium carbonate solution, brine, dried and evaporated to give the residue. The residue was vacuum distilled to give 25 (0.302 g, 84%), b.p. 121\(^{\circ}\) (bath)/18 mm. IR spectrum (liquid film) showed bands at 1739 cm\(^{-1}\) (ester carbonyl), 1653 and 880 cm\(^{-1}\) (exo methylene). NMR spectrum (CCl\(_4\)) showed signals at \(\delta\) 1.33 (3H, t, J=6 Hz, CH\(_3\)-CH\(_2\)), 1.73 (6H, s, CH\(_3\)-C=C), 2.33 (2H, q, J=6 Hz, -C-CH\(_2\)-CH\(_3\)), 4.76 (2H, m, -C=CH\(_2\)), 4.96 (2H, m, -C=CH\(_2\)), 5.2 (1H, t, J=6 Hz, -CHOPr).

Analysis: Found C, 73.55; H, 10.35. C\(_{12}\)H\(_{20}\)O\(_2\) requires C, 73.43; H, 10.27.

2,6-Dimethyl-1,6-heptadien-3-one (24)

A mixture of 23 (0.175 g, 0.0013 M), petroleum ether (25 ml) and active manganese oxide was stirred at room temperature for 3 hours. The petroleum ether filtrate obtained after filtration was concentrated to give the residue, which on distillation under vacuum gave 24 (0.167 g, 93%), b.p. 105\(^{\circ}\) (bath)/20 mm.
IR spectrum (liquid film) showed bands at 1667 cm\(^{-1}\) (conjugated carbonyl), 1639 cm\(^{-1}\) (C=CH\(_2\)).

N\(_{19}\)H spectrum (CD\(_3\)J showed signals at 81.76 (3H, s, CH\(_3\)-C=C), 1.86 (3H, s, CH\(_3\) on double bond conjugated to carbonyl), 4.66 (2H, m, C=CH\(_2\) ), 5.73 (1H, m, vinyl H), 5.93 (1H, m, vinyl H).

Analysis: Found C, 78.81; H, 10.30

C\(_9\)H\(_{14}\)O requires C, 78.21; H, 10.20.

3R-7-Dimethyl-6S-hydroxy-octanoic acid (28)

A mixture of (-)-menthone\(^{27}\) \(\text{26 (6.0 g, 0.038 M)}\), glacial acetic acid (12 ml), peroxy acetic acid (10 ml, 40%) and concentrated sulfuric acid (0.250 g) was kept at room temperature for 18 hours and then heated at 50\(^{\circ}\)C for 0.5 hour. The mixture was cooled, diluted with water and extracted with ether (2x75 ml). The etheral layer was washed with water and 10% sodium bicarbonate solution. Removal of ether led to the recovery of unreacted menthone. Aqueous portion after acidification with 10% hydrochloric acid solution and extracted with ether (1x100 ml). The ether was washed with water, brine, dried and evaporated to give a mixture of 28 and 29 (5.9 g). The above mixture was saponified with ethanolic sodium hydroxide and refluxed for 2 hours. The mixture was acidified with 10% hydrochloric acid solution and extracted with ether (2x100 ml). The ether layer was washed with water, brine, dried and evaporated to give 28 (5.1 g) identified by comparison of IR and N\(_{19}\)H with authentic sample\(^{24}\) reported by us.
3R-7-Dimethyl-6B-acetoxy-octanoic acid (29)

A mixture of 28 (2.5 g, 0.013 M), pyridine (1.97 g, 0.025 M) and acetic anhydride (2.55 g, 0.025 M) was kept at room temperature for 24 hours. The mixture was diluted with water and extracted with ether (2x50 ml). The etheral layer was washed with water, 10% hydrochloric acid solution, brine and evaporated to give residue, which after distillation gave 29 (1.8 g, 62%), b.p. 168° (bath)/0.3 mm. (α)D = +12 (c, 40).

IR spectrum (liquid film) showed bands at 1755 cm⁻¹ (ester carbonyl), 1718 cm⁻¹ (acid carbonyl).

NMR spectrum (CCl₄) showed signals at: 0.83 (6H, d, J = 6 Hz, (CH₃)₂CH), 1.03 (3H, d, J=6 Hz, CH₃-CH), 2.06 (3H, s, O-C-CH₃), 4.73 (1H, m, CHOAc).


2,6-Dimethyl-hept-6-en-3-ol acetate (30)

A mixture of 29 (1.0 g, 0.0043 M), cupric acetate (0.158 g, 0.00087 M), pyridine (0.100 g, 0.0012 M), lead tetraacetate (3.9 g, 0.0087 M) and benzene (25 ml) was stirred under nitrogen atmosphere for 0.5 hours at room temperature and under reflux for 2 hours. Excess of lead tetraacetate destroyed with ethylene glycol. The benzene layer was washed with water, 10% sodium carbonate solution, brine, dried and evaporated to give residue, which after distillation under vacuum gave 30 (0.265 g, 33%), b.p. 130-5° (bath)/16 mm. (α)D = +3.3 (c, 12).
IR spectrum (liquid film) showed bands at 1739 cm$^{-1}$ (carbonyl of ester), 1664 and 885 cm$^{-1}$ (C=CH$\_2$).

NMR spectrum ($\text{CCL}_4$) showed signals at $\delta$ 0.88 (6H, d, J=6 Hz, (CH$_3$)$_2$CH, 1.7 (3H, s, -CH$_3$-C=O), 2.0 (3H, s, 6-CH$_3$), 4.66 (2H, m, C=CH$_2$), 4.83 (1H, t, J=6 Hz, -CH$_2$Ac).

Analysis: Found C, 71.69; H, 10.94.

$\text{C}_{11}^\text{H}_{20}^\text{O}_2$ requires C, 72.08; H, 10.84.

3R,7-Dimethyl-6-oxo-octanoic acid (42)

To a mixture of hydroxy acid 28 (2.0 g, 0.011 M) in acetone (30 ml) at 0° was added Jones reagent till the orange colour of reagent was persistent. The mixture stirred for 1 hour at room temperature, diluted with water and extracted with ether (2x50 ml). The ethereal layer was washed with water, brine, dried and evaporated to give a liquid, which on distillation under vacuum gave 42 (1.9 g, 93%), b.p. 148° (bath)/0.6 mm. ($\rho$)$_D$ = +7.8 (c, 40).

IR spectrum (liquid film) showed band at 1712 cm$^{-1}$ (for keto and acid carbonyl).

NMR spectrum ($\text{CCL}_4$) showed signals at $\delta$ 0.87 (3H, d, J=6 Hz, CH$_3$-CH), 1.1 (6H, d, J=6 Hz, (CH$_3$)$_2$CH), 2.2-2.7 (5H, m, -CH$_2$ and -CH adjacent to carbonyl), 10.8 (1H, bs, -COOH exchanges on addition of $\text{D}_2$O).
NMR SPECTRUM OF 3,7-DIMETHYL-6-ACETOXY-OCT-7 ENOIC ACID. (22)

NMR SPECTRUM OF 2,6-DIMETHYL-1,6-HEPTADIEN-3-OL-ACETATE. (20)
IR SPECTRUM OF 2,6-DIMETHYL-1,6-HEPTADIENE-3-OL-PROPIONATE (25)

NMR SPECTRUM OF 2,6-DIMETHYL-1,6-HEPTADIENE-3-OL-PROPIONATE (25)
NMR SPECTRUM OF 3R,7-DIMETHYL-6S-ACETOXY-OCTANOIC ACID. (29)

NMR SPECTRUM OF 2,6-DIMETHYL-HEPT-6-EN-3S-OL-ACETATE. (30)
NMR SPECTRUM OF 2,6-DIMETHYL-1,6-HEPTADIEN-3-ONE. (24)

NMR SPECTRUM OF 3R,7-DIMETHYL-6-OXO-OCTANOIC ACID. (42)
REFERENCES