Total Syntheses of (±) Laurene, (±) Epilaurene, (±) α-Cuparenone and (±) β-Herbertenol
INTRODUCTION

The protocol developed for cyclopentenone synthesis, discussed in the earlier chapter, has been applied to the synthesis of natural products (±) laurene 1, (±) epilaurene 2, (±) α-cuparenone 3 and (±) β-herbertenol 4.

These natural products have sterically crowded tri and tetra-substituted cyclopentanoid ring in their structures. Application of this protocol has resulted in one of the shortest and efficient syntheses of these natural products.
Total Synthesis of (+) Laurene and (+) Epilaurene
SECTION - A

INTRODUCTION

Laurene was initially isolated\(^1\) from algae *Laurentia glandulifera* and later on was found in many other species.\(^2\) Structure and absolute configuration of laurene was determined to be \((+)^1\) by Irie and co-workers.\(^2\)

\[
\begin{align*}
&(+)^1 \\
&2
\end{align*}
\]

The sesquiterpene laurene has a crowded cyclopentane ring having an exomethylene functionality. There is 1,2 cis relationship between \(\rho\)-tolyl group and tertiary methyl group on the cyclopentane ring. This makes structure 1 thermodynamically less stable as compared to its epimer 2, known as epilaurene. Epilaurene is not naturally occurring and has the \(\rho\)-tolyl group and tertiary methyl group trans to each other. Such a complexity in structure and unusual substitution pattern of laurene has inspired many synthetic organic chemists to take up its synthesis.

Irie and coworkers\(^2\) have attempted a synthesis of laurene (scheme-1). Their approach is based on a strategy invoking a 1,2 transposition of ketone. Methyl lithium was added to racemic cyclopentanone 3\(^3\) to get an epimeric mixture of alcohols 4 which on dehydration gave cyclopentene 5.
Hydroboration of cyclopentene 5 followed by its oxidation gave ketone 6 with required stereochemistry. The fact that hydroboration of cyclopentene 5 would take place from less hindered side accounts for the observed stereochemistry. However, their attempts to convert ketone 6 to laurene by Wittig olefination were unsuccessful as the tertiary methyl group epimerised under the reaction conditions to furnish epilaurene 2. Thus the synthesis of epilaurene was completed in seven steps with 18% overall yield.

McMurry's \(^4\) synthesis of laurene basically follows the same strategy as that of Irie and co-workers for the synthesis of ketone 6. A novel route was adopted to convert compound 6 to laurene which established the exocyclic methylene group without epimerisation (scheme-2). Sequential treatment of cyclopentanone 6 with phenylthiomethyl lithium and benzoic anhydride gave adduct 7 which on reduction with Li/NH\(_3\) gave laurene as the sole product. Thus, the total synthesis is completed in eleven steps with 15.5% overall yield. This constitutes the first total synthesis of (±) laurene.
Posner and co-workers\textsuperscript{5} have shown that in case of β-aryl substituted cyclopentenones, 1,4 addition of dialkyl cuprate followed by alkylation of resulting enolate yields less stable isomer. This methodology has been adopted by these workers in a formal synthesis of laurene (scheme-3).

Cyclopentenone 8, prepared from cyclopentane 1,3 dione, generated the enolate 9 on reaction with lithiumdimethyl cuprate. The enolate 9 was alkylated with methyl iodide to get the ketone 6. According to the authors, the cis stereochemistry is achieved through metal-arene π co-ordination. The cyclopentenone 6 was converted to laurene by using McMurry's method.\textsuperscript{4} Thus, the formal synthesis of laurene was completed in three steps with 33% overall yield.

Taber and co-workers\textsuperscript{6} have reported the total synthesis of laurene in three steps and an overall yield of 37% using catecholborane reduction as a key step (scheme-4). The cyclopentanone 3 was prepared according to Mislow's procedure.\textsuperscript{3} Butylthiomethylation of compound 3 led to compound 10 which on treatment with methyllithium and hydrolysis furnished unsaturated
aldehyde 11. Catecholborane reduction of the tosyl hydrazone of the aldehyde 11 afforded the mixture of laurene and epilaurene in the yields 65% and 35% respectively.

Microbial reduction of racemic 12 effected kinetic resolution giving (+)12 in enantiomerically pure form which was used by Sakai and co-workers\(^7\) in the formal synthesis of laurene (scheme-5). On stereoselective addition of di \(p\)-tolyl zinc to enone (+)12, ketodiester 13 was obtained as a (2:3) mixture of epimers. Decarbomethoxylation of 13 was effected by heating it with NaI in DMSO at 100°C and resulting cyclopentanone was reduced with LAH to triol 14. Carbonyl functionality next to quaternary carbon was established by cleaving the vicinal diol in 14 with sodium metaperiodate to get compound 15. Both the compounds 14 and 15 were obtained as a mixture of epimers (1:1). Mesylation of hydroxy ketone 15 followed by elimination furnished cyclopentenone (+)16. Compound (+)16 was hydrogenated to obtain cyclopentanone (-)3 which has previously been converted to laurene by Taber
and co-workers. Thus, the formal synthesis was completed in eight steps with an overall yield of 33%.

Kametani and coworkers have completed a formal synthesis of Laurene in fourteen steps with an overall yield of 11% using intramolecular carbenoid displacement (ICD) as a key step (scheme-6). Treatment of ketoester 17 with methyl lithium gave benzyl alcohol 18 which on reaction with thiophenol and zinc iodide afforded thioether 19. Thioether 19 on treatment with LDA and ethyl formate gave corresponding α-formyl ester 20 which on reaction with tosyl azide furnished the diazo compound 21. Rhodium acetate catalyzed ICD reaction of the diazo compound 21 furnished a mixture of products from which compound 22 was isolated after the oxidative elimination of the phenyl thio group. Compound 22 was reduced to get allyl alcohol 23.
Mesylation of the allyl alcohol 23 followed by reduction with superhydride afforded the cyclopentene 5. Cyclopentene 5 has previously been converted to laurene.³

Srikrishna and co-worker⁹,¹² have reported two syntheses of laurene, both by radical cyclization approach (scheme-7a). In the first synthesis,⁹

\[
\begin{align*}
\text{p-Tolyl} & \quad \text{COOMe} \\
| & \quad \downarrow \\
\text{24} & \quad \rightarrow \quad \text{p-Tolyl} \\
\text{CHO} & \quad \downarrow \\
\text{26} & \quad \\
\end{align*}
\]

Xanthate 29 was prepared in eight steps starting from p-methyl propiophenone with an overall yield of 15%. Favoraskii reaction of p-methylpropiophenone under Yamauchi¹⁰ conditions and subsequent allylation of the intermediate ester formed gave, the allylated ester 24. Allyl ester 24 through reduction-oxidation sequence, was converted to corresponding aldehyde which was protected as ethylene acetal 25. Allyl group of compound 25 on hydroboration and oxidation gave aldehyde 26. Aldehyde 26 was converted to acetylene moiety 27 by Corey’s¹¹ procedure. The acetylenic acetal 27 was then hydrolyzed and treated with methyl magnesium bromide to get alcohol 28.
which was converted to xanthate 29. Radical cyclization of xanthate 29, using Bu₃SnH and AIBN, furnished a mixture of laurene and epilaurene in (1:1) ratio.

In the second synthesis of laurene, the anion radical cyclization approach was used. Mercuric acetate catalyzed exchange of cinnamyl alcohol 30 with ethyl vinyl ether followed by the Claisen rearrangement generated 4-pentenal 31 (scheme-7b). It was then homologated to 5-hexanal 32 by a two-step sequence. Radical cyclization of 32 using sodium naphthalenide gave alcohol 33. Oxidation of alcohol 33 afforded an epimeric mixture of ketone 6 which is the known precursor of laurene. Thus, the formal synthesis of laurene was completed in six steps with an overall yield of 11%.

Fukumoto and co-workers have reported the first enantioselective total synthesis of (+) laurene in nine steps with an overall yield of 14% (scheme-8). The chiral cyclobutanone 35 was obtained from 2-cyclopropylidene-2-p-tolylethanol 34 by tandem asymmetric epoxidation-enantiospecific ring expansion sequence followed by deoxygenation of resulting hydroxymethyl cyclobutanone. Addition of vinyl magnesium bromide
to chiral cyclobutanone 34 gave a distereomeric mixture of allylic alcohols 36 which was then epoxidised with mCPBA. The mixture of isomeric epoxides was separated and the isomer 37 was subjected to ring expansion with BF₃·Et₂O to get ketone 38. Enone (-)39 was obtained from 38 through mesylation and elimination sequence. Direct catalytic hydrogenation of (-)39 to get (+)6 showed poor selectivity towards cis-trans isomers. So the carbonyl of (-)39 was reduced and was benzyolated. Catalytic hydrogenation of this benzoate, over Rh-alumina offered product (+)40 with high (92%) selectivity. Hydrolysis of the benzoate in (+)40 and oxidation of the alcohol formed with tetrapropylperruthenate furnished ketone (+)6. Ketone (+)6 was easily converted to (+) laurene by employing Lambardo’s olefination conditions.¹⁴

Fadel and co-workers ¹⁵ have reported the total synthesis of (+) epilaurene in eleven steps with an overall yield of 17% (scheme-9).
Enantioselective enzymatic hydrolysis of dimethyl malonate 41 afforded chiral malonic acid monoester (+)42 which was used as a starting material in this synthesis. Compound (+)42 was treated with methyl chloroformate and then with sodium borohydride to get hydroxy ester (+)43. Oxidation of hydroxy ester (+)43 under Swern’s \textsuperscript{16} conditions followed by Wittig olefination with methylenetriphenylphosphorane afforded corresponding unsaturated ester (+)44 which on reduction-oxidation sequence furnished unsaturated aldehyde (+)45. Two carbon homologation of the unsaturated aldehyde to 5-hexenal (+)46 was achieved using routine procedure. Radical cyclization of 5-hexenal (+)46, effected with sodium / naphthalene gave a cis-trans mixture of alcohols 47 in a ratio 8:1. Oxidation of alcohol 47 followed by its olefination with methylenetriphenylphosphorane gave mixture of (+) epilaurene (96%) and (-) laurene (4%).
Meyers, via his famous oxazolidine methodology, has reported the total synthesis of (+) laurene in nine steps with an overall yield of 23% (scheme-10). Condensation of ketoacid 48 and (R) valinol 49 gave the a (1:1) exo/endo mixture of oxazolidine 50. Methylation of this oxazolidine using LDA and methyl iodide gave chiral bicyclic lactam (+)51. The stereospecificity of the reaction can be accounted for by the approach of the electrophile from endo face of the oxazolidine. Compound (+)51 on partial reduction, hydrolysis and intramolecular aldol condensation gave a cyclopentenone (-)52. Monoalkylation of (-)52 gave a mixture of distereomers (-)53a and (-)53b in 1:1 ratio. However, this ratio was improved to 96:4 in favour of less stable isomer (-)53b via deprotonation-reprotonation sequence using LDA as a base and tertiary butanol as a kinetic proton quencher. Catalytic hydrogenation of
cyclopentenone (-)53b followed by methylenation using Tebbe's protocol\textsuperscript{18} completed the total synthesis of (+) lauren.

The most recent synthesis of lauren is reported by Bailey and co-workers (scheme-11).\textsuperscript{19} It involves a distereoselective 5-exotrig cyclization\textsuperscript{20}

\[
\begin{align*}
\text{p-Tolyl} & \quad \text{CN} \quad \text{p-Tolyl} \\
54 & \quad \text{Br} \quad \text{HOC} \\
\end{align*}
\]

\[
\begin{align*}
\text{p-Tolyl} & \quad \text{Br} \quad \text{p-Tolyl} \\
56 & \quad \text{Li} \\
\end{align*}
\]

of vinylic anion 57. 2-aryl propionitrile 54 was alkylated using 2-bromo-4-iodo-1-butene. Partial reduction of the nitrile gave the aldehyde 55. Olefination of aldehyde 55 under Takai conditions\textsuperscript{21} gave 1,6 diene 56. Treatment of the diene 56 with tertiary butyl lithium generated the vinylic anion 57 which cyclized to furnish a mixture of lauren and epilauren in 60% and 17% yield respectively. The authors have explained the observed distereoselectivity on the basis of the chairlike transition state of anion 57 in which p-tolyl group is in pseudoaxial orientation and methyl group is in pseudoequatorial orientation. Thus, the total synthesis of lauren was completed in five steps with an overall yield of 38%.

Many of the synthesis discussed above are elegant and efficient. We discuss, in the following part our efforts towards the total synthesis of (±)
laurene based on the methodology developed for the preparation of allyl vinyl ethers and the protocol developed for cyclopentaannelation.
EXPERIMENTAL DISCUSSION

Application of the methodologies described in chapter 1 and chapter 2 for the generation of allyl vinyl ethers and cyclopentaannellation reactions in natural product synthesis is the logical next step. As laurene 1 has a crowded cyclopentane ring in its structure, its synthesis was planned as shown in scheme.

Wittig olefination of $p$-methyl acetophenone with crotyloxymethylene-triphenylphosphorane gave expected allyl vinyl ether 58 in 74% yield. In the IR spectrum of the compound, a weak absorption band at $1638$ cm$^{-1}$ corresponded to the double bond. The $^1$HNMR spectrum showed two sets of signals indicating
that the compound is probably a mixture of geometric isomers. Methyl group on
the enol ether appeared as two singlets at δ2.21 and δ2.62 integrating for one
and half protons each. Hydrogen on the enolic olefin appeared as two singlets
at δ6.45 and δ6.68 integrating for half proton each. This confirmed that the
compound 58 is a 1:1 mixture of E/Z isomers. A doublet at δ1.82 with a
coupling constant of 5.1Hz integrating for three protons was due to the olefinic
methyl group. Aromatic methyl group appeared as a singlet at δ2.25. Multiplet
at δ4.5 integrating for two protons was attributed to the allylic methylene group.
Two olefinic protons appeared as a multiplet at δ5.96. A multiplet between δ7.4
to δ7.91 integrating for four protons was attributed to the aromatic protons.
Elemental analysis supported the molecular formula C_{14}H_{18}O.

Claisen rearrangement of allyl vinyl ether 58 afforded unsaturated
aldehyde 59 in 95% yield. In the IR spectrum of the compound, a weak
absorption band at 1724.3 cm\(^{-1}\) corresponded to an aldehyde carbonyl group.
Weak absorption band at 2710.1 cm\(^{-1}\) confirmed the presence of aldehyde
functionality. A weak absorption band at 1636.9 cm\(^{-1}\) was due to the double
bond. The 1\(^{1}\)HNMR spectrum of the compound, aromatic methyl group appeared
as a singlet at δ2.53. Multiplet at δ3.08 integrating for one proton was attributed
to the methine proton. Multiplets at δ5.1 and δ5.5 integrating for two and one
protons respectively were typical for monosubstituted olefin. Aromatic protons
appeared as a singlet at δ7.23. Singlet at δ9.63 integrating for one proton was
attributed to the aldehydic proton. Methyl group on the allylic carbon showed
two doublets at δ0.76 and δ1.0 with a coupling constant of 7.7Hz integrating for
two and one protons respectively. Methyl group on the quaternary carbon center appeared as two singlets at δ1.34 and δ1.52 integrating for two and one protons respectively. This clearly indicated that the compound 59 is a 2:1 mixture of diastereomers which remain inseparable by gravity column chromatography. Elemental analysis supported the molecular formula C_{14}H_{18}O.

Unsaturated aldehyde 59 on Wacker oxidation furnished ketoaldehyde 60 in 82% yield. In the IR spectrum of the compound, strong absorption bands at 1732 cm^{-1} and 1725 cm^{-1} corresponded to the two carbonyl functionalities in the compound. In the ¹H NMR spectrum, a singlet at δ2.28 integrating for three protons corresponded to the methyl ketone. Aromatic methyl group appeared as a singlet at δ2.35. Methine proton α to carbonyl group appeared as a multiplet at δ3.34. Singlet at δ7.25 integrating for four protons was attributed to the aromatic protons. Aldehydic proton appeared as a singlet at δ9.57. Methyl group β to ketone displayed two doublets at δ0.95 and δ1.14 with a coupling constant of 7.6 Hz integrating for one and half protons. Methyl group on the quaternary carbon center appeared as two singlets at δ1.59 and δ1.64 integrating for one and half protons each. This clearly showed that compound 60 is a 1:1 mixture of diastereomers which remain inseparable by gravity column chromatography. Elemental analysis supported the molecular formula C_{14}H_{18}O_{2}.

Ketoaldehyde 60 on base catalyzed aldol condensation followed by dehydration furnished cyclopentenone 53 in 90% yield. In the IR spectrum of the compound a strong absorption band at 1715.6 cm^{-1} corresponded to the
ketone functionality. A strong absorption band at 1588.8 cm\(^{-1}\) was due to the conjugated double bond. In the \(^1\)H NMR spectrum, Aromatic methyl group appeared as a singlet at \(\delta\)2.32. A multiplet at \(\delta\)2.45 integrating for one proton was attributed to the methine proton \(\alpha\) to the ketone. Aromatic protons appeared as a multiplet at \(\delta\)7.38. Methyl group \(\beta\) to the ketone appeared as two doublets at \(\delta\)0.63 and \(\delta\)1.18 with a coupling constant of 7.2Hz integrating for one and half protons. The isomer in which the methyl group is cis to the aromatic ring shows upfield shift as it comes in the shielding zone of aromatic ring. Methyl group on the quaternary carbon center displayed two singlets at \(\delta\)1.41 and \(\delta\)1.68 integrating for one and half protons each. A triplet at \(\delta\)6.52 with a coupling constant of 5.1Hz integrating for one proton was assigned to the \(\alpha\) proton of the enone functionality. Doublets at \(\delta\)7.8 and \(\delta\)8.0 with a coupling constant of 5.1Hz integrating for half proton each were assigned to the \(\beta\) proton of the enone functionality. This clearly showed that compound 53 is a 1:1 mixture of diastereomers which remain inseparable by gravity column chromatography. Elemental analysis supported the molecular formula C\(_{14}\)H\(_{16}\)O.

Hydrogenation of the cyclopentenone 53 over 5\%Pd/C gave cyclopentanone 6 in 97\% yield. In the IR spectrum of the compound, a strong absorption band at 1740.6 cm\(^{-1}\) corresponded to the five membered cyclic ketone. In the \(^1\)H NMR spectrum of the compound, methylene group \(\beta\) to the ketone appeared as multiplets at \(\delta\)1.28 and \(\delta\)1.71 integrating for one proton each. Methylene group \(\alpha\) to the ketone appeared as a multiplet at \(\delta\)2.08. Aromatic methyl group appeared as a singlet at \(\delta\)2.27. Multiplet at \(\delta\)2.59
integrating for one proton corresponded to the methine proton $\alpha$ to the ketone. Methyl group $\beta$ to the ketone displayed two doublets at $\delta 0.79$ and $\delta 1.07$ with a coupling constant of 6.9Hz integrating for one and half protons each. Methyl group on the quaternary carbon center appeared as a two singlets at $\delta 1.21$ and $\delta 1.43$ integrating for one and half protons each. This clearly indicated that compound 6 is a 1:1 mixture of diastereomers. Elemental analysis supported the molecular formula C$_{14}$H$_{18}$O.

The last step of the synthesis was to convert the ketone functionality to an exomethylene group. Various methods reported for this purpose include Wittig olefination with methylenetriphenylphosphorane, McMurry’s method, Lambardo’s method, and Tebbe’s method. It is reported that when methylenetriphenylphosphorane is employed for methylenation, the ketone 6 undergoes epimerisation during this process to afford exclusively epilaurene 2. In the McMurry’s procedure, anion of thioanisole adds to the ketone and the resulting alkoxide is trapped using benzoic anhydride. The adduct thus formed when exposed to Birch reduction conditions produce laurene 1. No epimerization of asymmetric center is observed in this reaction. Tebbe’s reagent is a versatile methylenation reagent for conversion of ketones and aldehydes to olefins, it offers facile reaction with hindered ketones. It is prepared by reaction of titanocene with trimethyl aluminum at RT.

Methylenation of ketone 6 using Tebbe’s reagent failed at our hands. So it was decided to try Lambardo’s method. Activated zinc and dibromomethane in THF were treated with TiCl$_4$ under argon atmosphere. The brown colour of
$^1$HNMR (200 MHz) of the compounds 1 & 2

1 and 2
the reaction mixture indicated the formation of reagent. Ketone 6 was added to it and the reaction mixture was stirred at RT for 12 hours. After the extractive work up the product was purified by column chromatography using pentane as the eluent. In the IR spectrum of the compound, a weak absorption band at 1654 cm$^{-1}$ corresponded to unconjugated double bond. In the $^1$HNMR spectrum of the compound, doublets at $\delta$0.73 and $\delta$1.02 with a coupling constant of 7.3Hz integrating for one and half protons each corresponded to the methyl group on the tertiary carbon center. Methyl group on the quaternary carbon center appeared as two singlets at $\delta$1.1 and $\delta$1.61 integrating for one and half protons each. Singlet at $\delta$2.39 integrating for three protons was due to the aromatic methyl group. Methine proton and methylene group $\alpha$ to the double bond appeared as a multiplet between $\delta$2.51 to $\delta$2.91. Remaining methylene group appeared as a multiplet between $\delta$1.6 to $\delta$2.05. Protons of the exomethylene group displayed a broad singlet at $\delta$5.0. Multiplet at $\delta$7.35 integrating for four protons was attributed to the aromatic protons. Thus, the methylenation under the Lambardo's conditions furnished a 1:1 mixture of laurene 1 and epilaurene 2 in 80% yield. Elemental analysis supported the molecular formula C$_{15}$H$_{20}$. Spectral values matched well with the reported data.
EXPERIMENTAL SECTION

General: All solvents were distilled before use. Dry THF and toluene were prepared by distilling it over benzophenone and sodium under argon atmosphere and it was stored over sodium wire. All the anhydrous reactions were carried out under argon atmosphere. IR spectra were recorded on Perkin Elmer model 1600 series FTIR instrument. $^1$HNMR [ppm, TMS-internal standard] in CDCl$_3$ were recorded on JEOL FX90Q instrument and Bruker AC-200 instrument, the elemental analysis was obtained on HOSLI semiautomatic C, H analyzer. Silica gel (100-200) mesh was used for column chromatography.

1-Allyloxy-2-(4-methyl phenyl)-2-methyl ethene (58)

Crotyloxyethylene triphenylphosphonium chloride (4.98 gm, 13 mmol) and 4-methylacetophenone (1.34 gm, 10 mmol) were suspended in dry THF (20 ml). Potassium tertiary butoxide (1.5 gm, 13 mmol) in t-butanol (10 ml) was added to it at 0°C in a dropwise manner. The mixture was stirred at 0°C for 1 h. Then the reaction mixture was diluted with water and extracted with ether (3x50ml). Combined ether layer was washed with water, dried over anhyd. Na$_2$SO$_4$ and concentrated. The crude product on purification by column chromatography using hexane as eluent furnished pure 58 ($E/Z$ 1:1) (1.49 gm) in 74% yield as a colourless liquid.

Yield: 74%

IR (Neat): 1638, 1500, 1435, 1371, 950, 795 cm$^{-1}$
\[ ^1 \text{HNMR} 90 \text{ MHz (CDCl}_3) : \delta 1.82 (d, 5.1Hz, 3H, C=C-CH}_3); 2.21, 2.62 (s, 3H, E & Z C=C-CH}_3); 2.25 (s, 3H, Ar-CH}_3); 4.50 (m,2H, -O-CH}_2-CH=); 5.96 (m, 2H, CH=CH); 6.45, 6.68 (s, 1H, E & Z -O-CH=C-); 7.4 to 7.91 (m, 4H, Ar-H) \]

Anal. calc. for C$_{14}$H$_{18}$O : C, 83.12; H 8.97 Found C, 83.04; H, 9.07

2-(4-methyl phenyl)-2,3 dimethyl pene-4-ene-1-al (59)

Allyl vinyl ether 58 (1.0 gm, 4.9 mmol) was taken in dry toluene (5 ml) and was heated to reflux. The reaction was followed by TLC. After 16 hours TLC showed no starting allyl vinyl ether. Toluene was removed under reduced pressure and the crude product was purified by column chromatography to obtain pure 59 (0.95 gm) in 95% yield as a colourless liquid.

B. P. 162°C / 8 Torr.

IR (Neat) : 2710.1, 1724.3, 1636.9, cm$^{-1}$.

\[ ^1 \text{HNMR} 90 \text{ MHz (CDCl}_3) : \delta 0.76 (d, 7.7Hz, 2H,-CH-CH}_3), 1.00 (d, 7.7Hz, 1H, -CH-CH}_3), 1.34 (s, 2H, C-CH}_3), 1.52 (s, 1H, C-CH}_3), 2.53 (s, 3H, Ar-CH}_3), 3.08 (m, 1H, -CH-CH}_3), 5.10 (m, 2H, -CH=CH}_2), 5.29 to 5.95 (m, 1H, -CH=CH}_2), 7.23 (s, 4H, Ar-H), 9.63 (s, 1H, -CHO) \]

Anal. calc. for C$_{14}$H$_{18}$O : C,83.12; H, 8.97 Found C, 83.19; H, 8.85

2-(4-methyl phenyl) 2,3-dimethyl-4-oxo valeraldehyde (60)

In a solution of unsaturated aldehyde 59 (0.8 gm, 4 mmol) in aqueous dimethoxy ethane (10 ml, 1:9) was suspended PdCl$_2$ (0.071 gm, 0.4 mmol) and CuCl$_2$ (0.05 gm, 0.4 mmol). This mixture was stirred at RT under oxygen
atmosphere. On completion of reaction (TLC check, 3 h), the mixture was diluted with water and extracted with ether (3X25 ml). The combined ether layer was washed with water and dried over anhyd. Na$_2$SO$_4$. The ether layer was concentrated and the crude product was purified by column chromatography using hexane-ethyl acetate (20:1) mixture as eluent to obtain pure 60 (0.707 gm) in 82% yield as a colourless oil.

B.P. 97-99°C / 0.2 Torr.

IR (Neat) : 2748, 1732, 1725 cm$^{-1}$

$^1$HNMR 90 MHz (CDCl$_3$) : 8 0.95, 1.14 (d, 7.7 Hz, 3H, -CH-CH$_3$), 1.59, 1.64 (s, 3H, C-CH$_3$), 2.28 (s, 3H, -COCH$_3$), 2.35 (s, 3H, Ar-CH$_3$), 3.34 (m, 1H, -CH-CH$_3$), 7.25 (s, 4H, Ar-H), 9.57 (s, 1H, -CHO).

Anal. calc. for C$_{14}$H$_{18}$O$_2$: C, 77.03 ; H, 8.31 Found C, 77.14 ; H 8.19

4-(4-methyl phenyl)-4,5 dimethyl-2-cyclopentenone (53)

Ketoaldehyde 60 (0.654 gm, 3 mmol) was dissolved in methanol (5 ml) and cooled in an icebath and stirred. An aqueous methanolic solution of KOH (5%, 5 ml) was added to it. The resulting pale yellow colored mixture was stirred at RT. On completion of the reaction (TLC check, 2 h), the methanol was removed under mild vacuum and the crude product was extracted with ether (3 x 30ml). The combined ether layer was dried over anhyd. Na$_2$SO$_4$ and concentrated. The crude product was purified by column chromatography using 1% ethyl acetate in hexane as a eluent to get pure 53 (0.54 gm) in 90% yield as a colourless oil which was found to be thermally labile hence could not be distilled.
IR (Neat): 1715.6, 1588.8, 1513.6, 1453.5 cm\(^{-1}\)

\(^1\)HNMR 90 MHz (CDCl\(_3\)) : \(\delta\) 0.63, 1.18 (d, 7.2Hz, 3H, -CH-CH\(_3\)), 1.41, 1.68 (s, 3H, -C-CH\(_3\)), 2.32 (s, 3H, Ar-H), 2.45 (m, 1H, -CH-CH\(_3\)), 6.52 (t, 5.1Hz, 1H, -COCH=CH-), 7.38 (m, 4H, Ar-H), 7.8, 8.0 (d, 5.1Hz, 1H, -COCH=CH-)

Anal. calc. for C\(_{14}\)H\(_{18}\)O : C, 83.96; H, 8.05 Found C, 83.81; H, 8.13

3-(4-Methyl phenyl)-2,3 dimethyl cyclopentanone (6)

To a solution of cyclopentenone 53 (0.4 gm, 2 mmol) in dry ethyl acetate, Pd/C (5% Pd, 0.05 g) was added. This mixture was shaken under the atmosphere of hydrogen at the atmospheric pressure for 7hours at RT. The reaction mixture was then filtered through a celite pad. The filtrate was concentrated and the crude product was purified by column chromatography using 1% ethyl acetate in hexane as a eluent. The pure product 6 (0.39) was obtained in 97% yield as a colourless oil which was found to be thermally labile hence could not be distilled.

IR (neat) : 1740.6, 1515.0, 1454.9 cm\(^{-1}\)

\(^1\)HNMR 90 MHz (CDCl\(_3\)) : \(\delta\) 0.79, 1.07 (d, 6.92Hz, 3H, -CH-CH\(_3\)), 1.21, 1.43 (s, 3H, C-CH\(_3\)), 1.28 (m, 1H, -CH\(_2\)-), 1.71 (m, 1H, -CH\(_2\)-), 2.08 (m, 2H, -COCH\(_3\)), 2.27 (s, 3H, Ar-CH\(_3\)), 2.59 (m, 1H, -CO-CH-CH\(_3\)), 7.24 (m, 4H, Ar-H).

Anal. calc. for C\(_{14}\)H\(_{18}\)O : C, 83.12; H 8.97 Found C, 83.25; H, 8.91
Laurene and epilaurene (1 and 2)

To a stirred suspension of Zn (5.6 gm, 85.6 mmol) in THF (16 ml) 1M solution of titanium tetrachloride in dichloromethane (14 ml) and dibromomethane (3.2 ml, 45 mmol) at 0°C and the stirring was continued for 15 min. at RT. To this mixture was added a solution of ketone 6 (0.08 gm, 0.4 mmol) in THF (2 ml) and the reaction was stirred at same temperature for 12 hours. It was then diluted with ether (10 ml) and treated with 10% HCl (5 ml). The mixture was extracted with ether and the extract was washed with NaHCO₃ and brine. The ether layer was dried over anhyd. Na₂SO₄ and concentrated. The crude product was purified by column chromatography using pentane as an eluent to get pure 1 and 2 (1:1) in 80% yield (0.063 gm) as a colourless oil.

B. P.: 87 to 89 °C / 10 Torr (lit. 130°C / 30 Torr)

IR (neat): 1654.1, 1519.0, 1447.8 cm⁻¹

¹HNMR 90 MHz (CDCl₃): δ 0.73, 1.02 (d, 7.3 Hz, 3H, -CH-CH₃), 1.1, 1.61 (s, 3H, C-CH₃), 1.6 to 2.05 (m, 2H, -CH₂-C), 2.39 (s, 3H, Ar-CH₃), 2.5 to 2.91 (m, 3H, -CH-CH₃, C=C-CH₂), 5.0 (bs, 2H, C=CH₂), 7.35 (m, 4H, Ar-H).

Anal. Calc. for C₁₅H₂₀: C, 89.94; H, 10.06; Found C, 89.67; H, 10.00.
REFERENCES:

Total Synthesis of (±) α-Cuparenone

SECTION-B
SECTION-B

INTRODUCTION

α-Cuparenone is a sesquiterpene isolated from *Mayurpankhi* tree\(^1\) and liverwort *Mannia fragrans*.\(^2\) Its structure and absolute configuration were determined by Sukhdev and co-workers.\(^1\)

![Structure of α-Cuparenone](image)

The structure of α-cuparenone is quite interesting as it has a five membered ring having two contiguous quaternary centers. This makes α-cuparenone a good synthetic challenge as only a few methods are available for constructing contiguous quaternary centers.\(^3\) Several syntheses of α-cuparenone are reported in the literature employing various strategies. In many cases, the synthesis of α-cuparenone has been used as a demonstration of the novelty and efficiency of new methodology. These several syntheses of α-cuparenone can be broadly classified into the following categories

1. Dieckmann cyclization
2. Via 1,4 dicarbonyl compounds
3. Ring expansion
4. Use of transition metal catalysts
5. Michael addition
6. Miscellaneous

**Dieckmann cyclization approach**

Raphael and co-workers\(^4\) have reported the first total synthesis of \(\alpha\)-cuparenone in seven steps with an overall yield of 18\%(SCHEME-1). The less hindered methylene of ketone 2 was protected via aldol condensation with 2-furaldehyde. The resulting enone was subjected to gem-dimethylation to get enone 3. Ozonolysis of compound 3 afforded substituted adipic acid 4. The acid 4 on esterification followed by Dieckmann cyclization, hydrolysis and decarboxylation afforded \(\alpha\)-cuparenone.

Anand and co-workers\(^5\) have also used Dieckmann cyclization approach for the formal synthesis of \(\alpha\)-cuparenone(Scheme-2). Michael addition of diester 5 to acrolein furnished aldehyde 6 which on acetalization and hydrolysis under basic conditions afforded diacid 7. The diacid 7 on oxidative decarboxylation with lead tetraacetate-pyridine gave gem-diacetate 8. Exposure of compound 8 to base followed by cyclization of resulting ketoaldehyde under mild acidic conditions gave cyclopentenone 9. Compound 9 on sequential hydrogenation, methylation, addition of methylmagnesium...
bromide to the ketone and dehydration furnished cyclopentene 10. Hydroboration of cyclopentene 10 and subsequent oxidation afforded the cyclopentanone 11 which is a known precursor of α-cuparenone. Thus, the formal synthesis was completed in twelve steps with an overall yield of 13%.

Chiral cyclohexenone® (-)12 was used by Asaoka and co-workers7 for the total synthesis of (+) α-cuparenone (SCHEME-3). Addition of lithium dimethyl cuprate to compound (-)12 yielded, by addition-elimination mechanism, a new cyclohexenone which on 1,4 addition with p-tolyl magnesium bromide gave chiral cyclohexanone (+)13. Regiospecific Baeyer-Villiger oxidation of compound (+)13 gave lactone (+)14 which was converted to diester (-)15 via hydrolysis, oxidation and esterification. Dieckmann
cyclization of diester (-)15 afforded cyclopentanone 16. gem-Dimethylation of cyclopentanone (+)16 under Posner's conditions completed the total synthesis of (+) α-cuparenone in ten steps with an overall yield of 4%.

In a formal synthesis of (+) α-cuparenone, Honda and co-workers⁸ have used the approach of "enantioselective deprotonation of meso or prochiral
compounds having a σ-plane using chiral lithium amide bases (SCHEME-4). Base catalyzed Michael addition of aldehyde 17 to MVK followed by intramolecular aldol condensation gave cyclohexenone 18. Compound 18 was hydrogenated and its silyl enol ether was prepared using (S,S') α,α-dimethyl benzyl amide 19 and trimethyl silyl chloride to get compound (-)20. Reaction of compound (-)20 with MoO₂(acac)₂ and t-butylhydroperoxide furnished diester (-)21. Dieckmann cyclization of (-)21 followed by hydrolysis and decarboxylation afforded the cyclopentanone (+)16 which is a known precursor for the synthesis of (+) α-cuparenone. Thus, the formal synthesis was completed in nine steps with an overall yield of 23%.

Rao and co-workers¹⁰ have used chiral succinate¹¹ (-)22a for a formal synthesis of (-)α-cuparenone (SCHEME-5). Chiral diester (-)22b on reduction with LAH gave corresponding diol. Mesylation of this diol followed by treatment with sodium cyanide furnished dinitrile (-)23. Dinitrile (-)23 was hydrolysed to diacid which under mild basic conditions underwent cyclization and decarboxylation affording cyclopentanone (-)24. Selenation of (-)24 followed by oxidative elimination afforded cyclopentenone (+)25 which is a known
precursor of α-cuparenone. Thus, the formal synthesis was completed in eight steps with an overall yield of 9%.

**Via 1,4-dicarbonyl compounds**

Wenkert and co-workers\(^\text{12}\) have used β-oxycyclopropanes in a formal synthesis of α-cuparenone (SCHEME-6). Thermal decomposition of diazoacetone in presence of enol ether 26 generated β-oxycyclopropane 27. Compound 27 on acid hydrolysis underwent ring opening and furnished ketoaldehyde 28. Intramolecular aldol condensation of compound 28 followed by dehydration gave racemic cyclopentenone 29 which has previously been converted to α-cuparenone. Thus, the formal synthesis was completed in six steps with an overall yield of 12%.

Anand and co-workers\(^\text{13}\) have reported another formal synthesis of α-cuparenone starting from α-β unsaturated ketone 30 (SCHEME-7). Cyclopropanation of enone 30 using dimethylsulphoxonium methylide furnished cyclopropylketone 31. Nucleophilic ring opening of 31 by thiophenoxide anion generated thioeter 32 which on oxidation followed by treatment with NCS and HgCl\(_2\) produced 1,4 dicarbonyl compound 33.
Intramolecular aldol condensation of 33 followed by dehydration gave cyclopentenone 34 which is a known precursor of α-cuparenone. Thus, the formal synthesis was completed in five steps with an overall yield of 8%.

In the synthesis of α-cuparenone by Srikrishna and co-workers,\textsuperscript{14} Claisen rearrangement is used as a key step (SCHEME-8). Heating of 2-methoxy propene with cinnamyl alcohol 35 in presence of catalytic amount of propionic acid effected enol ether exchange and Claisen rearrangement to furnish unsaturated ketone 36. Ozonolysis of 36 gave ketoaldehyde 28 which
on intramolecular aldol condensation and dehydration afforded racemic cyclopentenone 29 which has previously been converted to α-cuparenone. Thus, the formal synthesis was completed in five steps with an overall yield of 32%. Mercuric acetate catalysed enol ether exchange followed by Claisen rearrangement is a key step in another formal synthesis reported by Srikrishna and co-workers. Enol ether exchange between cinnamyl alcohol 35 and ethyl vinyl ether mediated by mercuric acetate furnished 4-pentenal 37. Homologation of the aldehyde 37 followed by its radical cyclization using sodium naphthelenide gave cyclopentanol 38. Oxidation of alcohol 38 afforded cyclopentanone 11 which is the known precursor for the synthesis of α-cuparenone. Thus, the formal synthesis was completed in six steps with an overall yield of 11%.

Martin and co-workers have reported a formal synthesis of α-cuparenone using geminal acylation-alkylation at a carbonyl carbon via regiospecifically generated metalloenamines(Scheme-9). Treatment of p-

\[
\begin{align*}
\text{pToly} & \quad \rightarrow \quad \text{pToly} \\
\text{CHO} & \quad \rightarrow \quad \text{CHO} \\
\text{28} & \quad \rightarrow \quad \text{29}
\end{align*}
\]

(Scheme-9)

methyl acetophenone with 39A and its subsequent alkylation with 2,3 dichloro-1-propene followed by hydrolysis furnished chloroolefins 39B. Mercuric acetate catalyzed hydrolysis of 39B gave ketoaldehyde 28 which on intramolecular
aldol condensation yielded cyclopentenone 29 which is a known precursor of α-cuparenone. Thus, the formal synthesis was completed in four steps with an overall yield of 37%.

Chavan and co-workers have used azaClaisen rearrangement as a key step in the synthesis of α-cuparenone (SCHEME-10). α-p-Tolyl propionic acid was converted to allyl amide 40. AzaClaisen rearrangement of compound 40 mediated by triphenyl phosphine furnished unsaturated nitrile 41 which on partial reduction and hydrolysis afforded 4-pentenal 42. Wacker oxidation of compound 42 followed by intramolecular aldol condensation and dehydration gave cyclopentenone 29. gem-Dimethylation of compound 11 followed by hydrogenation completed the total synthesis of α-cuparenone. Thus, the total synthesis was completed in eight steps with an overall yield of 14%.
Fadel and co-workers\textsuperscript{16} have reported a formal synthesis of (+) \(\alpha\)-cuparenone starting from malonate 43 (SCHEME-11). Diester 43 on partial enzymatic hydrolysis using PLE enzyme gave chiral ester acid (+)44 which on treatment with methyl chloroformate and sodium borohydride gave hydroxy ester (+)45. The alcohol in the compound (+)45 was protected as a TBDMS ether and the ester was converted to the aldehyde (-)46. Homologation of compound (-)46 afforded lactol 47 which on treatment with methyl magnesium bromide gave diol 48. Oxidation of 48 furnished the corresponding ketoaldehyde which on intramolecular aldol condensation followed by dehydration afforded cyclopentenone (-)29, the known precursor of \(\alpha\)-cuparenone. Thus, the formal synthesis was completed in eight steps with an overall yield of 32%.
Kametani and co-workers\textsuperscript{20} have reported a synthesis of (-) $\alpha$-cuparenone (SCHEME-12). Compound (-)49, obtained from O-protected prolinol, was converted to corresponding quaternary salt 50 by cyanomethyl benzyl sulphonate. The salt 50 underwent [2,3] sigmatropic rearrangement, with total chirality transfer, to afford enantiomerically pure aminonitrile (+)51 as a single distereomer. Hydrolysis of (+)51 gave unsaturated aldehyde (+)52 which was easily converted to (-)$\alpha$-cuparenone using routine steps.

Meyers and co-workers\textsuperscript{21} have completed the total synthesis of (-) $\alpha$cuparenone via his famous oxazolidine methodology\textsuperscript{22} (SCHEME-13). Condensation of ketoacid 53 and (S)-valinol 54 furnished bicyclic lactam 55. Methylation of lactam 55 gave the product (+)56 with 93/7 distereoselectivity as a result of approach of electrophile from the less hindered $\alpha$-face of the lactam 55. Partial reduction of (+)56 followed by hydrolysis afforded ketoaldehyde 57.
which was converted to \( \alpha \)-cuparenone through a series of routine steps. Thus, the total synthesis was completed in ten steps with an overall yield of 26%.

**Ring expansion approach**

Gadwood\(^{23} \) has used ring expansion methodology for the synthesis of \( \alpha \)-cuparenone (SCHEME-14). Addition of lithium isopropylphenyl selenoxide to cyclobutanol 59. The salt 59 when refluxed in THF underwent pinacol type rearrangement to furnish \( \alpha \)-cuparenone. Thus, the total synthesis was completed in two steps starting from 58 with an overall yield of 39%.
Krief and co-workers\textsuperscript{24} have also used ring expansion approach for the total synthesis of \( \alpha \)-cuparenone (SCHEME-15). Addition of \( \alpha \)-bromocyclopropyl lithium to \( p \)-methyl acetophenone gave alcohol 60 which on treatment with potassium tertiary butoxide suffered ring expansion furnishing cyclobutanone 58. Addition of lithium isopropylmethyl selenide to cyclobutanone 58 afforded cyclobutanol 61. Dichlorocarbene, generated from thallium ethoxide and chloroform, reacted with 61 to yield 62 which \textit{in situ} underwent ring expansion, as shown, to provide \( \alpha \)-cuparenone. Thus, the total synthesis was completed in five steps with an overall yield of 38%.

Leriverend\textsuperscript{25} in his approach employs a thermal (2+2) cycloaddition reaction-ring expansion sequence for the total synthesis of \( \alpha \)-cuparenone (SCHEME-16). Compound 63 when heated with 2-\( p \)-tolyl-1-propene in presence of potassium carbonate suffered a thermal (2+2) cycloaddition reaction furnishing cyclobutanone 64 which has two contiguous quaternary centers. Such a cyclobutanone on ring expansion would furnish \( \alpha \)-cuparenone.
Compound 64 was epoxidised using dimethyl sulphonium methyldide to get spiroepoxide 65 which on treatment with sodamide gave amine 66. This β-amino alcohol on subsequent treatment with nitrous acid gave a mixture of α and β cuparenones in (2:1) ratio. Thus, the total synthesis was completed in four steps with an overall yield of 12%.

Diastereofacially selective (2+2) cycloaddition of a chiral olefin with dichloroketene is a key step in the total synthesis of (-) α-cuparenone reported by Green (SCHEME-17). Chiral cyclohexanol (+)67 and allylic chloride 68 gave corresponding allyl ether which was isomerised by tertiary butoxide to the enol ether (-)69. A (2+2) cycloaddition of compound (-)69 with dichloroketene gave cyclobutanone (-)70 with 90% e.e. The approach of the ketene is favoured only from the re face of the double bond resulting in the observed stereochemistry. Cyclobutanone (-) 70 on ring expansion with diazomethane afforded ring expanded product which on reductive elimination
with chromous perchlorate gave cyclopentenone (+)71. gem-Dimethylation and hydrogenation/hydrogenolysis of cyclopentenone (+)71 completed the total synthesis of (-) α-cuparenone. Thus, the total synthesis was completed in eight steps with an overall yield of 27%.

Tandem Katsuki-Sharpless epoxidation and enantiospecific ring expansion is a key step in the formal synthesis of (+) and (-) α-cuparenone reported by Fukumoto27 (SCHEME-18). Cyclopropylidene alcohol 72 on Sharpless-epoxidation using (-) DET followed by 1,2 rearrangement of the epoxide gave corresponding cyclobutanone (+)73 which was deoxygenated to (R) cyclobutanone 74. Similarly, use of (+) DET gave (S) cyclobutanone.
These cyclobutanones in racemic form have previously been converted to α-cuparenone. Thus, the formal synthesis was completed in seven steps with an overall yield of 15%.

**Transition metal catalyst**

Eilbracht and coworkers\(^{28}\) have reported the total synthesis of α-cuparenone, using hydrocarbonylation of a 1,4 diene catalyzed by Co\(_2\) (CO)\(_6\) complex as a key step (SCHEME-19). The 1,4 diene 76 was prepared from diacid 75 via reduction, tosylation and elimination sequence.

Hydrocarbonylation of diene 76 in water with Co\(_2\)(CO)\(_6\) under CO atmosphere furnished cyclopentanone 11 which on methylation afforded α-cuparenone. Thus, the total synthesis was completed in six steps with an overall yield of 17%

Noyori and co-workers\(^{29}\) have reported a one step total synthesis of α-cuparenone (SCHEME-20). Dibromoketone 77 when treated with 2-p-tolyl-1-

\[ \text{(SCHEME-19)} \]

\[ \text{(SCHEME-20)} \]
propene in presence of Fe(CO)₉ directly afforded the α-cuparenone, though in very low yield (18%).

**Michael addition**

Takano and co-workers³⁰ have reported the formal synthesis of (+) α-cuparenone starting from dicyclopentadiene (SCHEME-21). SeO₂ oxidation of dicyclopentadiene gave allylic alcohol 78. The acetates of these racemic alcohols on hydrolysis with lipase selectively gave (+) enantiomer, while the acetate of (-) enantiomer remained unhydrolysed. Oxidation of (+) antipode 78 with PCC gave enone (+)79. Addition of methyl lithium to enone (+)79 followed by oxidation with PCC gave new enone 80. Michael addition of di p-tolylmagnesium cuprate to enone 80 gave ketone 81 which on heating suffered retro Diels-Alder reaction to give cyclopentanone (-) 29 which is the known precursor of α-cuparenone. Thus, the total synthesis was completed in ten steps with an overall yield of 9%.
Posner and co-workers have used 2-(arylsulfinyl) cyclopentene as a chiral starting material for the formal synthesis of (+) α-cuparenone (SCHEME-22). Compound when treated with ditolyl lithium cuprate gave the cyclopentanone. Oxidation of sulfoxide with mCPBA followed by methylation gave sulfone. Treatment of sulfone with lithium dimethyl cuprate and methyl iodide gave (+) α-cuparenone. Thus, the formal synthesis was completed in four steps with an overall yield of 7%. Optically pure cyclopentenone (+) obtained by microbial kinetic resolution of the racemic compound was used by Sakai and co-workers for the formal synthesis of (-) α-cuparenone (SCHEME-23). Stereoselective addition of di p-tolyl zinc to enone gave ketodiester which was reduced to triol using LAH. Carbonyl functionality next to quaternary carbon center was established by cleaving the vicinal diol with sodium metaperiodate to get compound. Hydroxy group of compound was protected as THP.
ether and the ketone was reduced. Mesylation of the resulting alcohol followed by elimination afforded the olefin 89. Jone's oxidation of compound 89 gave cyclopentenone (+)29 which is the known precursor of α-cuparenone. Thus, the formal synthesis was completed in eleven steps with an overall yield of 31%.

Miscellaneous

Rhodium catalyzed intramolecular C-H insertion of a carbene is the key step in the total synthesis of (+) α-cuparenone reported by Taber and co-workers33 (SCHEME-24). Ketoester (-)90 on successive treatment with tosylazide and rhodium acetate effected an intramolecular carbene insertion to provide cyclopentanone 92 as an epimeric mixture. The reaction proceeds via
the corresponding diazo compound 91. The epimeric mixture of ketoester 92 was easily converted to (+) α-cuparenone using routine functional group transformations. Thus, the total synthesis was completed in eleven steps with an overall yield of 2%.

Ishibashi and co-workers\textsuperscript{34} have reported a formal synthesis of α-cuparenone starting from thiochroman 93 (SCHEME-25). Thiochroman 93,
obtained from m-tolyl thiomethyl chloride and 1-methyl cyclopentene, on oxidation with mCPBA and then on exposure to trifluoroacetic anhydride gave thiochromene 94 via Pummer rearrangement. Thiochromene 94 was oxidised to corresponding sulfoxide and then it was deconjugated to 95 using LDA. Deoxygenation of 95 with TiCl$_3$ followed by hydroboration produced alcohol 96. Raney Nickel desulfurisation and oxidation of alcohol completed the synthesis of $\alpha$-cuparenone. Thus, the total synthesis was completed in nine steps with an overall yield of 12%.

Sakurai and co-workers$^{35}$ have completed the total synthesis of $\alpha$-cuparenone in two steps with an overall yield of 20% (SCHEME-26). Treatment

```
O
CH$_3$CC(CH$_3$)$_2$Br ----► CH$_2$=CC(CH$_3$)$_2$Br
97
```

(SCHME-26)

of bromoketone 97 with LDA and TMSCl gave silyl enol ether 98. Reaction of 98 with 2-p-tolyl-1-propene furnished $\alpha$-cuparenone.

Most of the syntheses discussed above are result of demonstration of efficiency of methodologies developed by various workers. We have applied the protocol for cyclopentenone construction, discussed above, to the $\alpha$-cuparenone synthesis. These efforts are presented in the following part.
EXPERIMENTAL DISCUSSION

The structural similarity between (±) laurene and (±) α-cuparenone obviously calls for the application of the same strategy, used in the synthesis of former, for the synthesis of α-cuparenone.

For this purpose allyl vinyl ether 99, the key intermediate, is required. The Wittig olefination methodology discussed in chapter-1 could, in principle, furnish the allyl vinyl ether 99. However, as discussed in the same chapter, we could not prepare the required chloro compound 100 namely, chloromethyl prenyl ether. The nonavailability of prenyloxymethylenetriphenylphosphonium chloride made us to explore other possibilities of preparing the required chloro compound 100.

\[
\text{Diisopropyl amine} + \text{OH} + \text{Cl}^+\text{O}^+\text{Me} \rightarrow \text{OMe} \\
\]

It has been reported\(^{36}\) that methoxymethyl ethers of alcohols on treatment with boron trichloride at RT furnish the corresponding chloroethers in moderate yields. For adopting this methodology, methoxymethyl ether of prenyl alcohol 101 was prepared from chloromethyl methyl ether and prenyl alcohol using diisopropyl amine as a base, following the reported\(^{36a}\) procedure. The crude product was purified (73%) by column chromatography using hexane as an eluent. In the \(^1\)HNMR spectrum, singlets at δ1.56 and δ1.62 integrating for three protons each
corresponded to two vinylic methyl groups. A doublet at δ3.95 with a coupling constant of 6.4Hz integrating for two protons was attributed to methylene group flanked by double bond and oxygen. Methylene group in between two oxygens appeared as a doublet at δ4.55 with a coupling constant of 5.4Hz. Multiplet at δ5.34 integrating for one proton was attributed to vinylic proton. Methoxy group appeared as a singlet at δ3.28 but, instead of integrating for three protons, it integrated for one and half protons only. It was interesting to observe the methoxy group consistently integrating for one and half protons rather than three protons even after the repeated purification of the sample. The mass spectrum of the compound showed the M⁺ peak at m/z 130 confirming the molecular formula C₇H₁₄O₂. The formation of daughter ion peaks at m/z 115, 99, 85, and 69 further confirmed the above molecular formula. The origin of the daughter ion peaks is shown in the scheme-1.

The m/z at 115 arises by loss of the methyl group following a cleavage of O-CH₃ bond (cleavage-a). The peak at m/z 99 arises following the cleavage of the
-OCH$_3$ group (cleavage-b). The peak at m/z 85 results from the cleavage of the O-C bond following cleavage-c. The loss of -O-CH$_2$OCH$_3$ group gives rise to a peak at m/z 65 (cleavage-d). The detection of M$^+$ ion and fragmentation pattern soundly supports the formation of compound 101. According to the reported procedure, compound 101 was treated with boron trichloride at RT. However, the starting material was recovered unchanged. The failure to prepare chloro ether 100 unfortunately prevented us from applying our methodology of Wittig olefination for the preparation of allyl vinyl ether 99.

![Reaction of phenols with dichloromethane](image)

Reaction of phenols with dichloromethane under certain conditions is known to provide chloromethyl aryl ethers. Logically, replacement of phenol with prenyl alcohol in the above reaction should, in principle, yield the chloromethyl ether 100. Reaction of the alkoxide, generated from prenyl alcohol and sodium hydride, with dichloromethane at reflux temperature produced a compound which was found to be diprenyl formal 102, instead of chloromethyl ether 100, from its spectral characteristics. In the $^1$HNMR spectrum of the compound 102, a singlet at 81.62 integrating for twelve protons corresponded to the four vinylic methyl groups. A doublet at 84.03 with a coupling constant of 7.7Hz was due to the allylic methylene group. Methylene group flanked by two oxygens appeared as a singlet at 84.7. A triplet at 85.4 with a coupling constant of 7.7Hz was attributed to the vinylic proton. Though it was surprising to get compound 102, in the light of the reported work, it made us look for alternatives to prepare allyl vinyl ether 99.
It was considered that if we can prepare a keto ether of type-1, then by effecting appropriate Grignard addition to this ketone followed by dehydration of the tertiary alcohol would lead to the key intermediate 99.

Ethyl prenyloxy acetate 103 could be a probable source for the preparation of keto ether of type-1. For this purpose alkoxide generated from prenyl alcohol and sodium hydride was stirred with ethyl bromoacetate at RT for three hours. The spectral investigation of the product showed it to be prenyl bromoacetate 104. In the $^1$HNMR spectrum of the compound 104, a broad singlet at $\delta$1.81 was attributed to two vinylic methyl groups. A singlet at $\delta$4.18 was due to the methylene group flanked by bromine and carbonyl group. Allylic methylene group appeared as a doublet at $\delta$4.8 with a coupling constant of 7.4Hz. Vinylic proton appeared as a triplet at $\delta$5.53 with a coupling constant of 7.4Hz. Apparently, an ester exchange reaction was faster than SN$^2$ displacement of bromide. It was discovered that the reaction of prenyl alcohol with ethyl bromoacetate in refluxing dry acetone using anhydrous K$_2$CO$_3$ as a base yielded the sought after compound namely, ethyl prenyloxy acetate 103 in 69% yield. In the $^1$HNMR spectrum of the compound, ethyl group appeared as a triplet at $\delta$1.21 with a coupling constant of
5.5 Hz integrating for three protons and a quartet at $\delta$4.1 with a coupling constant 5.5Hz integrating for two protons. Broad singlet at $\delta$1.75 integrating for six protons was attributed to two vinylic methyl groups. Singlet at $\delta$4.21 integrating for two protons was due to the methylene group in between carbonyl group and oxygen. Allylic methylene group appeared as a doublet at $\delta$4.8 with a coupling constant of 7.6Hz. Vinylic proton appeared as a multiplet at $\delta$5.59. Though we could prepare the compound 103 which is equivalent to the ketoether of type-I, it was doubtful whether one could effect the controlled Grignard additions to arrive at the ketoether of type-I.

$$\begin{align*}
\text{OH} & \quad \text{Br} \\
& \quad \text{MeO} \quad \text{OMe} \\
\end{align*}$$

To avoid this complication, bromoacetone dimethyl ketal was reacted with prenyl alcohol using sodium hydride as a base at RT. The compound 105 was obtained though in a low yield of in less than 10%. In the $^1$HNMR spectrum, a singlet at $\delta$1.44 integrating for three protons was attributed to methyl group on the quaternary center. Two vinylic methyl groups appeared as singlets at $\delta$1.71 and $\delta$1.82. Singlet at $\delta$3.31 integrating for six protons was due to two methoxy groups. Methylene group flanked by double bond and oxygen appeared as a multiplet at $\delta$4.2. The remaining methylene group appeared as a singlet at $\delta$3.45. Vinylic proton appeared as a multiplet at $\delta$5.53. Mild acid hydrolysis of the compound 105 would furnish the keto ether 106. Such a hydrolysis was effected by exposing the ketal 105 to 10% aqueous oxalic acid solution for five hours at RT. The keto ether
106 was obtained in a pathetically low yield of 3% over two steps. This prevented us from adopting the same approach for the preparation of allyl vinyl ether 99. The formation of ketoether of 106 was substantiated by its spectral data.

\[
\begin{align*}
&\text{106} \\
\end{align*}
\]

In the IR spectrum of the compound a strong absorption peak at 1724 cm\(^{-1}\) corresponded to the ketone carbonyl group. In the \(^1\)HNMR spectrum, singlet at \(\delta 1.78\) integrating for six protons was attributed to two vinylic methyl groups. Methyl group \(\alpha\) to the ketone appeared as a singlet at \(\delta 2.2\). A doublet at \(\delta 4.1\) with a coupling constant of 7.2Hz integrating for two protons corresponded to the allylic methylene group. Methylene group in between carbonyl group and oxygen appeared as a singlet at \(\delta 4.21\). Vinylic proton showed a multiplet at \(\delta 5.5\).

A direct preparation of the keto ether 106 from hydroxy acetone and prenyl transfer reagents like prenyl halides or prenyl tosylates was attempted but failed at our hands.

\[
\begin{align*}
&\text{107} \\
\end{align*}
\]

As an alternative strategy for the preparation of keto ether of type-I it was thought that an SN\(^2\) displacement on \(\omega\)-halo acetophenone by prenyl alcohol should serve the purpose. Reaction of \(\omega\)-chloroacetophenone 107 with prenyl alcohol in refluxing acetone using \(\text{K}_2\text{CO}_3\) as a base afforded a compound as a
white crystalline material. However, with the limited facilities at hand we were not able to characterize the compound. It was clear from the $^1$HNMR spectrum of the compound that it certainly was not the keto ether of type-1. It is reported that the outcome of such reactions of $\omega$-chloroacetophenones with alkoxide is variable depending upon the substrate structure and reaction conditions and one isolates various compound except the expected product.

With these failures, we had to go back and chalk out a different strategy for the preparation of allyl vinyl ether 99. One effective strategy that was contemplated was to effect an enol ether exchange between enol ether 108 and prenyl alcohol. For this purpose, the required enol ether 108 was prepared by Wittig olefination of $p$-methyl acetophenone with methoxymethyleneetriphenylphosphonium chloride using potassium tertiary butoxide as a base. The enol ether 108 was purified by column chromatography to get 83% of pure product. In the IR spectrum, a weak absorption band at 1655cm$^{-1}$ corresponded to unconjugated olefin. The $^1$HNMR spectrum showed two sets of signals rather than one indicating that the product is possibly a mixture of geometric isomers. Singlets at $\delta$1.93 and $\delta$2.0 integrating for one and half proton each were attributed to vinylic methyl group. Aromatic methyl group appeared as a singlet at $\delta$2.33. Methoxy group also showed two singlets at $\delta$3.72 and $\delta$3.78. Two broad singlets at $\delta$6.24 and $\delta$6.54
integrating for half proton each corresponded to vinylic protons. Aromatic protons appeared as a multiplet at δ7.20 to δ7.76.

With the enol ether in hand, we proceeded to effect the exchange of enol ether 108 with prenyl alcohol. Enol ether exchange was first attempted using mercuric acetate,\(^{39}\) a well known catalyst for such exchanges. Expecting an enol ether exchange reaction, an equimolar mixture of enol ether 108 and prenyl alcohol was heated at 190°C for 18 hours in presence of 10 mol% mercuric acetate. But the reaction gave some untractable products. It is well-documented\(^{40}\) that one can effect enol ether exchange reaction using protic acids like propionic acid, PTSA etc. To our dismay, conducting the intended enol ether exchange between enol ether 108 and prenyl alcohol under these conditions gave back unchanged starting material quantitatively.

Our attempts to effect O-prenylation of α-β-tolyl propionaldehyde 109, obtained by acid hydrolysis of enol ether 108 at 80°C, under different conditions to get allyl vinyl ether 99 failed miserably.
While scanning the literature, for methods to effect enol ether exchange we came across a very recent report by Nakai.41 He has reported that enol ether exchange can be readily effected by using trifluoroacetic acid (TFA) as a catalyst. He has further stated that method works more efficiently for cyclic enol ethers rather than acyclic enol ethers.

An equimolar mixture of enol ether 108 and prenyl alcohol was heated in refluxing toluene in presence of 10% TFA. Reaction was followed by TLC. After 18 hours reaction showed no starting enol ether. Volatile material was removed under mild vacuum and residue as such was chromatographed on silica gel column using hexane as an eluent. The IR spectrum showed a strong absorption peak at 1724.3 cm$^{-1}$ indicating carbonyl group and an absorption band at 2703 cm$^{-1}$ showed it to be an aldehyde functionality. Peak at 1682.8 cm$^{-1}$ indicated presence of unconjugated olefin and a strong absorption band at 814.7 cm$^{-1}$ corresponded to mono substituted olefin. The $^1$HNMR spectrum of the product showed four singlets at $\delta$ 1.05, 1.08, 1.45 and 2.34 integrating for three protons each indicating presence of four methyl groups in the compound. Typical vinylic pattern was observed in the olefinic region as a multiplet at $\delta$ 5.00 integrating for two protons and another multiplet at $\delta$ 5.95 integrating for one proton. A singlet at $\delta$ 7.15 integrating for four protons indicated the presence of disubstituted benzene ring. The singlet at $\delta$ 9.88 integrating for one proton indicated the presence of aldehyde functionality. In the $^{13}$C NMR spectrum, peaks at 17.04, 21.13, 23.54 and 23.66 confirmed the presence of four methyl groups. Small peaks at 41.76 and 57.58 indicated the presence of two quaternary carbon centers. Aldehyde carbon
appeared as a small peak at 204.15. All the spectral information showed that the product formed has four methyl groups, an aldehyde functionality, two aliphatic quaternary carbon centers, a unconjugated terminal olefin and a disubstituted benzene ring. It can be very easily inferred that the enol ether exchange reaction has occurred and the allyl vinyl ether 99 so generated has in situ undergone a Claisen rearrangement, under the reaction conditions, to furnish 4-pentanal 110. Elemental analysis also supported the molecular formula C_{15}H_{20}O.

These results were certainly delightful for us. However, the isolation of 4-pentenal 110 in low yield of 29% forced us to investigate reaction more critically. After some experimentation, it was found that besides the initial addition of 10mol% amount of TFA it was necessary to add same amount of TFA every after four hours. Probably, TFA being low boiling may be escaping the reaction mixture necessitating the addition of TFA. The yield of the reaction was improved to 69%.

After the successful preparation of 4-pentenal 110, the total synthesis of α-cuparenone was completed using Wacker oxidation, aldol condensation and hydrogenation reaction sequence as shown in scheme-2.

The 4-pentenal 110 was subjected to Wacker oxidation using PdCl$_2$ (10 mol%), CuCl$_2$ (10 mol%) in (9:1) DME:H$_2$O mixture under oxygen atmosphere. The reaction was followed by TLC. After three hours, the TLC showed no staring.
The expected ketoaldehyde 111 was obtained in 81% yield after extractive work up and purification by column chromatography using 2% ethyl acetate in hexane as an eluent.

The IR spectrum of the compound 111 showed strong absorption peaks at 1718.3 cm\(^{-1}\) and 1700.1 cm\(^{-1}\) corresponding to two carbonyl functionalities. In the \(^1\)HNMR spectrum, singlets at \(\delta 1.13\) and \(\delta 1.20\) integrating for three protons each were due to the gem-dimethyl group. Singlet at \(\delta 1.53\) integrating for three protons corresponded to methyl group on the quaternary carbon center. Singlet at \(\delta 2.06\) integrating for three protons was attributed to methyl group \(\alpha\) to the ketone. Aromatic methyl group appeared as a singlet at \(\delta 2.32\). Singlet at \(\delta 7.13\) with integration of four protons was attributed to aromatic protons. Singlet at \(\delta 9.95\) integrating for one proton was due to aldehydic proton. \(^{13}\)CNMR spectrum of the product confirmed the presence of five methyl groups by the peaks at 17.49, 21.10, 22.62, 23.07 and 27.97. Two small peaks at 53.92 and 57.32 indicated the presence of two aliphatic quaternary carbon centers. Aromatic carbons appeared
$^{13}$C NMR (125 MHz) of the compound 112
Expecting an intramolecular aldol condensation reaction followed by dehydration, the ketoaldehyde 111 was treated with aqueous methanolic KOH. TLC after two hours showed no starting ketoaldehyde. After extractive workup and purification by column chromatography using 2% ethylacetate in hexane as an eluent, the pure product 112 was obtained in 87% yield.

In the IR spectrum, the strong absorption bands at 1709.0 cm\(^{-1}\) and 1654.3 cm\(^{-1}\) corresponded to the carbonyl group and the conjugated double bond respectively. Decrease in carbonyl frequency than its normal value is due to the conjugated enone functionality. The \(^1\)HNMR spectrum of the product showed singlets at \(\delta\) 0.53 and \(\delta\)1.19 integrating for three protons each for gem-dimethyl group. Upfield shift of one of the methyls of gem-dimethyl group is due to its cis relationship with aromatic ring. It comes in the shielding zone of aromatic ring. Singlet at \(\delta\) 1.45 corresponded to the methyl group on the quaternary carbon center. Aromatic methyl group appeared as a singlet at \(\delta\)2.33. Doublets at \(\delta\) 6.22 and 7.74 integrating for one proton each with a coupling constant of 5.9 Hz were due to the \(\alpha\) and \(\beta\) protons of the enone functionality respectively. Quartet at \(\delta\) 7.1 with a coupling constant of 7.6 Hz integrating for four protons corresponded to the aromatic protons. In the \(^{13}\)CNMR spectrum, peaks at 20.21, 21.17, 26.03 and 26.59 confirmed the presence of four methyl groups and peaks at 51.80 and 54.76 indicated the presence of two quaternary carbon centers. Peak at 215.07
represents the ketone carbon. Elemental analysis supported the molecular formula C_{15}H_{20}O.

The cyclopentenone 112 was subjected to hydrogenation at atmospheric pressure using Pd/C as a catalyst. Completion of the reaction was confirmed by TLC. The catalyst was removed from the mixture by filtration and the product was purified by column chromatography using 1% ethylacetate in hexane as an eluent. The reaction gave the product 1 in 94% yield.

In the ^1^H NMR spectrum of the compound, singlets at δ0.62 and δ1.18 integrating for three protons each corresponded to the gem-dimethyl group. Methyl group on the quaternary carbon center appeared as a singlet at δ1.18. Singlet at δ2.35 integrating for three protons was due to the aromatic methyl group. Multiplet δ 2.44 integrating for two protons indicated the presence of methylene α to ketone. Aromatic protons appeared as a quartet at δ7.23 with a coupling constant of 7.6Hz. In the IR spectrum a strong absorption band at 1739.3 cm\(^{-1}\) corresponded to the five membered cyclic ketone.

Elemental analysis supported the molecular formula C_{15}H_{20}O. The spectral properties of compound 1 matched well with the reported values.

Thus, the total synthesis of α-cuparenone was completed in four steps, starting from enol ether 108 with an overall yield of 47%.
EXPERIMENTAL SECTION

General: All solvents were distilled before use. Dry toluene and THF was prepared by distilling over benzophenone and sodium, under argon atmosphere and it was stored over sodium wire. Methoxymethylene triphenylphosphonium chloride was prepared from freshly distilled chloromethyl methyl ether and triphenyl phosphine and used immediately. Melting points are uncorrected and boiling points represent the bath temperature. IR spectra were recorded on Perkin Elmer model 1600 series FT-IR instrument. $^1$HNMR and $^{13}$CNMR [ ppm, TMS-internal standard ] in CDCl$_3$ were recorded on JEOL FX90Q and and Bruker AMX500 instrument. Mass spectrum was recorded at an ionisation energy of 70ev on Finnigan MAT-1020 automated GC/MA instrument and mass values are expressed as m/e. The elemental analysis was obtained on HOSLI semiautomatic C, H analyzer. Silica gel (100-200) mesh was used for column chromatography.

5,7-oxa-2-methyl-2-octene (101)

A mixture prenyl alcohol (0.86 gm, 10 mmol) and diisopropylamine (2.02 gm, 20 mmol) in THF (15 ml) was stirred at 0°C. Methoxymethylene chloride (1.6 gm, 20 mmol) was added to it in a dropwise manner. The reaction was followed by TLC. After the completion of the reaction, the reaction mixture was diluted with water and extracted with ether. The ether layer was dried over anhyd. Na$_2$SO$_4$ and concentrated. The crude product was purified by column chromatography using hexane as an eluent to obtain pure 101 (0.94 gm) in 73% yield.
$^1$HNMR 90 MHz (CDCl$_3$): $\delta$ 1.56 (s, 3H, C=C-CH$_3$); 1.62 (s, 3H, C=C-CH$_3$); 3.28 (s, 1.5H, -OCH$_3$); 3.95 (d, 6.4Hz, 2H, O-CH$_2$-C=C); 4.55 (d, 5.4Hz, 2H, O-CH$_2$-O); 5.34 (m, 1H, C=CH-)

5,7-oxa-2,10 dimethyl 2-9 undecadiene (102)

To the stirred suspension of sodium hydride (0.264 gm, 11 mmol) in THF (15 ml) at 0°C was added prenyl alcohol (86 gm, 10 mmol) in dropwise manner. Dichloromethane (5 ml) was added to the reaction mixture and it was heated to reflux. The reaction was followed by TLC. After completion of the reaction (30 hours), the reaction mixture was diluted with water and extracted with ether. The ether layer was dried over anhyd. Na$_2$SO$_4$ and concentrated. The crude product was purified by column chromatography using hexane as an eluent to obtain pure 102 (0.69 gm) in 76% yield.

$^1$HNMR 90 MHz (CDCl$_3$): $\delta$ 1.62 (s, 12H, 4x C=C-CH$_3$), 4.03(d, 7.7Hz, 4H, 2x O-CH$_2$-C=C); 4.7 (s, 2H, O-CH$_2$-O); 5.4 (t, 7.7Hz, 2H, 2x C=CH-)

5,8-oxa-7-oxo-2-methyl-2-decene (103)

To the stirred suspension of potassium carbonate (2.76 gm, 20 mmol) in acetone (20 ml) was added prenyl alcohol (86 gm, 10 mmol) in dropwise manner. Ethyl bromoacetate (1.67 gm, 10 mmol) was added to the reaction mixture and it was heated to reflux. The reaction was followed by TLC. After completion of the reaction (8 hours), the acetone was removed by distillation and reaction mixture
was diluted with water and extracted with ether. The ether layer was dried over anhyd. Na₂SO₄ and concentrated. The crude product was purified by column chromatography using 1% ethyl acetate in hexane as an eluent to obtain pure 103 (1.18 gm) in 69% yield.

\[ ^1H NMR \text{ } 90 \text{ } MHz \text{ } (CDCl}_3): \delta \ 1.21 \text{ } (t, 5.5Hz, 3H, -CH}_2CH}_3); \ 1.75 \text{ } (bs, 6H, 2x C=C-CH}_3); \ 4.1 \text{ } (q, 5.5Hz, 2H, -CH}_2CH}_3); \ 4.21 \text{ } (s, 2H, O-CH}_2-CO); \ 4.8 \text{ } (d, 7.8Hz, 2H, O-CH}_2-C=C); \ 5.59 \text{ } (m, 1H, C=CH-) \]

7-bromo-5-oxa-6-oxo-2-heptene (104)

To the stirred suspension of sodium hydride (0.264 gm, 11 mmol) in THF (15 ml) at 0°C was added prenyl alcohol (86 gm, 10 mmol) in dropwise manner. Ethyl bromoacetate (1.67 gm, 10 mmol) was added to the reaction mixture and it was stirred at RT. The reaction was followed by TLC. After completion of the reaction (3 hours), the reaction mixture was diluted with water and extracted with ether. The ether layer was dried over anhyd. Na₂SO₄ and concentrated. The crude product was purified by column chromatography using hexane as an eluent to obtain pure 104 67% yield.

\[ ^1H NMR \text{ } 90 \text{ } MHz \text{ } (CDCl}_3): \delta \ 1.81 \text{ } (bs, 6H, 2x C=C-CH}_3); \ 4.18 \text{ } (s, 2H, Br-CH}_2-CO); \ 4.8 \text{ } (d, 7.4Hz, 2H, O-CH}_2-C=C); \ 5.53 \text{ } (t, 7.4Hz, 1H, C=CH-) \]

5-oxa-7,7-dimethoxy-2-methyl-2-octene (105)

To the stirred suspension of sodium hydride (0.264 gm, 11 mmol) in THF (15 ml) at 0°C was added prenyl alcohol (86 gm, 10 mmol) in dropwise manner.
Bromoacetone dimethyl ketal (1.86 gm, 10 mmol) was added to the reaction mixture and it was stirred at RT. The reaction was followed by TLC. Even after 20 hours the reaction was found to be incomplete so, the reaction mixture was diluted with water and extracted with ether. The ether layer was dried over anhyd. Na$_2$SO$_4$ and concentrated. The crude product was purified by column chromatography using 1%ethyl acetate in hexane as an eluent to obtain pure 105 in 10% yield.

$^1$HNMR 90 MHz (CDCl$_3$): $\delta$ 1.44 (s, 3H, C-CH$_3$); 1.71 (s, 3H, C=C-CH$_3$); 1.82 (s, 3H, C=C-CH$_3$); 3.31 (s, 6H, 2x OCH$_3$); 3.45 (s, 2H, OCH$_2$-); 4.2 (m, 2H, O-CH$_2$-C=C); 5.53 (m, 1H, C=CH-)

*E & Z -2 (4-methyl phenyl) 1- methoxy 1- propene (108)*

Methoxymethylenetriphenylphosphonium chloride (8.2 gm, 24 mmol) was suspended in dry THF (15 ml). Potassium tertiary butoxide in t-butanol (30 mmol in 20 ml of t-butanol) was added to it at 0°C in a dropwise manner. The mixture was stirred at 0°C for 1 h and then 4-methyl acetophenone (2.69 g, 20mmol) was added to it. On further stirring for 1 h at RT the reaction mixture was diluted with water and extracted with ether (3x50ml). Combined ether layer was washed with water, dried over anhyd. Na$_2$SO$_4$ and concentrated. The crude product on purification by column chromatography using hexane as eluent furnished pure 108 (E/Z 1:1) (2.68 g) in 83% yield as a colourless liquid.

B.P. 68-70°C/0.2 Torr

IR (Neat) : 1655 cm$^{-1}$. 

$^1$HNMR 90 MHz (CDCl$_3$): $\delta$ 1.93, 2.00 (s, 3H, E C-CH$_3$, Z C-CH$_3$), 2.33 (s, 3H, Ar-CH$_3$), 3.72, 3.78 (s, 3H, E =C-OCH$_3$ Z =C-OCH$_3$), 6.24, 6.54 (bs, 1H, E CH=C, Z CH=C), 7.20 to 7.76 (m, 4H, Ar-H).

2-(4-Methyl phenyl) 2,3,3-trimethyl-pent-1-ene 4-ene (110):

To the solution of the enol ether 108 (1.62 g, 10 mmol) and prenyl alcohol (1.18g, 13 mmol) in dry toluene was added trifluoroacetic acid (0.114 g, 1mmol). This reaction mixture was heated to reflux and the reaction was followed by TLC. At the end of 18 h TLC showed no starting enol ether. The reaction mixture was then cooled and concentrated under vacuum to remove the volatile materials. The crude product so obtained was purified by column chromatography using hexane as the eluent to get pure 110 (1.49 g.) in 69% yield as a colourless oil.

B.P. 72-74°C/0.4 Torr.

IR (Neat): 2703.1, 1724.3, 1682.8, 1607.1, 1514.0, 1455.8, 814.7 cm$^{-1}$.

$^1$HNMR 500 MHz (CDCl$_3$): $\delta$ 1.05 (s, 3H, C-CH$_3$), 1.08 (s, 3H, C-CH$_3$), 1.45 (s, 3H, C-CH$_3$), 2.34 (s, 3H, Ar-CH$_3$), 5.00 (m, 2H, C=CH$_2$), 5.95 (m, 1H, -CH=C ), 7.15 (s, 4H, Ar-H), 9.88 (s, 1H, -CHO).

$^{13}$CNMR 125 MHz (CDCl$_3$): $\delta$ 17.04, 21.15, 23.54, 23.66, 41.76, 57.58, 113.23, 128.68, 129.18, 136.18, 136.87, 145.06, 204.15.

Anal. calc. for C$_{15}$H$_{20}$O : C, 83.28; H, 9.32. Found C, 83.42; H, 9.21.
2,3,3-trimethyl 2- (p-tolyl) 4-oxo valeraldehyde (111):

In a solution of unsaturated aldehyde 110 (1.72 gm, 8 mmol) in aqueous dimethoxy ethane (10 ml, 1:9) was suspended PdCl₂ (0.141 gm, 0.8 mmol) and CuCl₂ (0.11 gm, 0.8 mmol). This mixture was stirred at RT under oxygen atmosphere. On completion of reaction (TLC check, 3 h), the mixture was diluted with water and extracted with ether (3X25 ml). The combined ether layer was washed with water and dried over anhyd. Na₂SO₄. The ether layer was concentrated and the crude product was purified by column chromatography using hexane-ethyl acetate (20:1) mixture as eluent to obtain pure 111 (1.49 gm) in 81% yield as a colourless oil.

B.P. 87-90°C/0.1 Torr.

IR (Neat) : 1718.3, 1700.1 cm⁻¹.

¹HNMR 500 MHz (CDCl₃) : δ 1.13 (s, 3H, C-CH₃), 1.20 (s, 3H, C-CH₃), 1.53 (s, 3H, C-CH₃), 2.06 (s, 3H, -CO-CH₃), 2.32 (s, 3H, Ar-CH₃), 7.13 (s, 4H, Ar-H), 9.95 (s, 1H, -CHO).

¹³CNMR 125 MHz (CDCl₃) : δ 17.49, 21.10, 22.62, 23.07, 27.97, 53.92, 57.32, 125.35, 129.00, 129.09, 136.15, 137.17, 202.37, 214.51.

Anal. calc. for C₁₅H₂₀O₂: C, 77.55; H, 8.68. Found C, 77.46; H, 8.81.
4- (4-methyl phenyl) 4,5,5- trimethyl 2-Cyclopentenone (112):

Ketoaldehyde 111 (1.62 gm, 7 mmol) was dissolved in methanol (5 ml) and cooled in an icebath and stirred. An aqueous methanolic solution of 5% KOH (5 ml) was added to it. The resulting pale yellow colored mixture was stirred at RT. On completion of the reaction (TLC check, 2 h), the methanol was removed under vacuum and the crude product was extracted with ether (3 x 30ml). The combined ether layer was dried over anhyd. Na$_2$SO$_4$ and concentrated. The crude product was purified by column chromatography using 1% ethyl acetate in hexane as an eluent to get pure 112 (1.29 gm) in 87% yield as a low melting solid.

M.P. 36-38 °C

IR (Neat): 1709.0, 1654.3, 816.3 cm$^{-1}$.

$^1$HNMR 500 MHz (CDCl$_3$) : $\delta$ 0.53 (s, 3H, C-CH$_3$), 1.19 (s, 3H, C-CH$_3$), 1.45 (s, 3H, C-CH$_3$), 2.33 (s, 3H, Ar-CH$_3$), 6.22 (d, 1H, 5.9 Hz, HC=CH-CO), 7.10 (q, 7.6Hz, 4H, Ar-H), 7.74 (d, 1H, 5.9 Hz, COCH=CH).

$^{13}$CNMR 125 MHz (CDCl$_3$) : 20.26, 21.17, 26.03, 26.59, 51.80, 54.76, 126.94, 129.26, 129.48, 136.60, 140.50, 169.08, 215.07.

Anal. calc. for C$_{15}$H$_{16}$O: C, 84.07; H, 8.47. Found C, 84.21; H, 8.25.

$\alpha$ - Cuparenone (1):

To a solution of cyclopentenone 112 (0.642 gm, 3 mmol) in dry ethyl acetate, Pd/C (5% Pd, 0.05 g) was added. This mixture was shaken under the atmosphere of hydrogen at the atmospheric pressure for 8 hours at RT. The
reaction mixture was then filtered through a celite pad. The filtrate was concentrated and the crude product was purified by column chromatography using 1% ethyl acetate in hexane as a eluent. The pure product 1 (0.611 gm) was obtained in 94% yield as a low melting solid. M.P. 46-48°C

(lit. M.P. 52°C)

IR (neat) : 1739.3 cm⁻¹

¹HNMR 500 MHz (CDCl₃) : δ 0.62 (s, 3H, C-CH₃), 1.18 (s, 3H, C-CH₃), 1.26 (s, 3H, C-CH₃), 1.91 (m, 1H, CH-H) 2.35 (s, 3H, Ar-CH₃), 2.44 (m, 2H, -CH₂), 2.53 (m, 1H, CH-H), 7.23 (q, 7.6Hz, 4H, Ar-H).

¹³CNMR 125 MHz (CDCl₃) : 18.67, 21.11, 22.38, 25.59, 29.91, 34.03, 48.57, 53.45, 126.64, 129.17, 136.04, 142.15, 222.84.

REFERENCES:

Total Synthesis of (±) β-Herbertenol

SECTION-C
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\text{INTRODUCTION}

\(\beta\)-Herbertenol 1 and its congeners is a group of sesquiterpenes isolated from Liverwort \textit{Herberta adunsa} by Matsuo and co-workers.\(^1\)

Their structure is very much similar to cuparene group of sesquiterpenes. Both the groups of sesquiterpenes have aryl substituted cyclopentane ring with two vicinal quaternary carbon centers, thereby creating a rather crowded cyclopentane ring. The parent hydrocarbon Herbertene 2 which is isomeric to cuparene 3 has been synthesized previously.\(^2\)

Eicher and co-workers\(^3\) have successfully completed the first and the only synthesis of \(\beta\)-Herbertenol (scheme). The \(\beta\)-ketoester 4 was prepared by

\[
\text{(scheme)}
\]
Sato's procedure. Addition of 4-methoxy-3-methyl phenyl magnesium bromide to cyclic β-ketoester 4 followed by dehydration of intermediate alcohol formed gave unsaturated ester 5. Cyclopentene ester 5 was converted to aldehyde 6 through reduction and oxidation sequence. Aldehyde group was then reduced by Wolff-Kishner reaction to get new cyclopentene 7. Hydroboration of 7 followed by oxidation gave cyclopentanone 8. Methylolation at benzylic position of 8 followed by Wolff-Kishner reduction completed the total synthesis of β-herbertenol 1. In this manner the total synthesis was completed in 12 steps, with an overall yield of 11%.

This, being the only synthesis of β-herbertenol, the synthesis of β-herbertenol, reported in the following section assumes importance.
EXPERIMENTAL DISCUSSION

As stated earlier, β-herbertenol is structurally very much similar to cuparene group of sesquiterpenes so it was logical for us to plan its synthesis on the same lines as that of α-cuparenone. The synthesis of β-herbertenol was planned as shown in the scheme.

The required starting material 9 was obtained by benzylolation of corresponding hydroxy acetophenone which in turn was prepared by Frie's migration of 2-methyl phenyl benzoate. In the IR spectrum of the compound 9 a
strong absorption band at 1703.2 cm\(^{-1}\) corresponded to the ketone carbonyl group. In the \(^1\)HNMR spectrum, singlet at \(\delta 2.38\) integrating for three protons was due to methyl group \(\alpha\) to the ketone carbonyl group. Aromatic methyl group appeared as a singlet at \(\delta 2.54\). Singlet at \(\delta 5.26\) integrating for two protons corresponded to benzylic methylene group. Doublet at \(\delta 7.00\) with coupling constant 7.71 Hz integrating for one proton was due to aromatic proton ortho to benzyloxy group. Monosubstituted phenyl ring appeared as a singlet at \(\delta 7.52\). Remaining two aromatic protons appeared as a multiplet at \(\delta 7.91\).

Wittig olefination of acetophenone 9 with methoxymethylenetriphenylphosphonium chloride using tertiary butoxide as a base gave enol ether 10 in 78% yield. In the IR spectrum, a weak absorption band at 1661 cm\(^{-1}\) was due to unconjugated olefin. In the \(^1\)HNMR spectrum, two sets of signals indicated the product to be a mixture of geometric isomers. Singlets at \(\delta 1.85\) and \(\delta 1.98\) integrating for one and half protons each were due to the vinylic methyl group. Aromatic methyl group appeared as a singlet at \(\delta 2.27\) Singlets at \(\delta 3.68\) and \(\delta 3.74\) integrating for one and half protons each corresponded to the vinylic methoxy group. Singlet at \(\delta 5.12\) integrating for two protons was attributed to benzylic methylene group. Broad singlets at \(\delta 6.08\) and \(\delta 6.37\) integrating for one proton were due to vinylic proton. Two aromatic protons appeared as multiplets at \(\delta 6.92\) and \(\delta 7.12\). Broad singlet at \(\delta 7.41\) integrating for six protons was due to remaining aromatic protons. All the spectral information confirmed the compound 10 to be the 1:1 mixture of geometric isomers. Elemental analysis supported the molecular formula \(\text{C}_{18}\text{H}_{20}\text{O}_2\).
Enol ether exchange reaction was effected to the extent of 64% by heating the mixture of enol ether 10, prenyl alcohol and trifluoroacetic acid (10 mol%). The reaction was followed by TLC. The reaction was over in 17 hours. The volatile material was removed under reduced pressure and the reaction mixture as such was chromatographed to get pure product. In the IR spectrum, a strong absorption band at 1722.4 cm\(^{-1}\) was attributed to aldehyde carbonyl group which was confirmed by weak absorption band at 2724.4 cm\(^{-1}\). Weak absorption band at 1605.6 cm\(^{-1}\) was due to unconjugated olefin and an absorption band at 810.4 cm\(^{-1}\) confirmed it to be monosubstituted olefin. In the \(^1\)HNMR spectrum, singlets at \(\delta 1.07\) and \(\delta 1.12\) integrating for three protons each were attributed to gem-dimethyl group. Singlet at \(\delta 1.45\) was due to methyl group on the quaternary carbon center. Aromatic methyl group appeared as a singlet at \(\delta 2.33\). Multiplets at \(\delta 5.01\) and \(\delta 6.00\) integrating for two and one protons each were typical for monosubstituted olefin. Benzylic methylene group appeared as a singlet at \(\delta 5.18\). Multiplet at \(\delta 7.52\) integrating for three protons was attributed to aromatic protons. Protons on the monosubstituted phenyl ring appeared as a singlet at \(\delta 7.52\). Singlet at \(\delta 9.95\) integrating for one proton was due to aldehydic proton. All the spectral information given above supported the formation of expected 4-pentenal 11. Compound 11 analyzed for the molecular formula \(\text{C}_{22}\text{H}_{26}\text{O}_2\).

To obtain ketoaldehyde 12, 4-pentenal 11 was subjected to Wacker oxidation conditions employed previously. The crude product was purified (79%) by column chromatography using ethyl acetate-hexane as eluent. In the IR spectrum, strong absorption bands at 1718.1 cm\(^{-1}\) and 1700.8 cm\(^{-1}\) were due to two
carbonyl functionalities in the compound. In the $^1$HNMR spectrum, singlets at $\delta 1.07$ and $\delta 1.12$ integrating for three protons each were due to gem-dimethyl group. Singlet at $\delta 1.45$ integrating for three protons was attributed to methyl group on the quaternary carbon center. Singlet at $\delta 1.92$ integrating for three protons corresponded to methyl group $\alpha$ to ketone. Aromatic methyl group appeared as a singlet at $\delta 2.22$. Singlet at $\delta 5.03$ integrating for two protons was due to benzylic methylene group. Aromatic protons showed two sets of signals. Multiplet at $\delta 6.91$ corresponded to three aromatic protons. Remaining five protons appeared as a multiplet at $\delta 7.33$. Singlet at $\delta 9.91$ integrating for one proton was attributed to aldehydic proton. Elemental analysis corresponded to the molecular formula $C_{22}H_{26}O_3$.

Ketoaldehyde 12 on treatment with 5% aqueous methanolic KOH gave cyclopentenone 13 in 86% yield. In the IR spectrum of the compound, an absorption band at 1701.9 cm$^{-1}$ was due to ketone carbonyl and strong absorption band at 1592.4 cm$^{-1}$ was attributed to the conjugated olefin. In the $^1$HNMR spectrum, singlets at $\delta 0.57$ and $\delta 1.22$ integrating for three protons each were due to gem-dimethyl group. Upfield shift of one of the methyl groups was attributed to the fact that after cyclization it comes in the shielding zone of the aromatic ring. Singlet at $\delta 1.48$ integrating for three protons corresponded to methyl group on the quaternary carbon center. Aromatic methyl group appeared as a singlet at $\delta 2.32$. Singlet at $\delta 5.15$ integrating for two protons was attributed to benzylic methylene group. Doublet at $\delta 6.31$ with coupling constant 5.65 Hz integrating for one proton corresponded to $\alpha$ proton of the enone. Similarly, doublet at $\delta 7.82$ with coupling
constant 5.65 integrating for one proton was attributed to β proton of the enone. Multiplet at δ7.01 integrating for three protons was due to aromatic protons. Monosubstituted phenyl ring appeared as a singlet at δ7.48. Elemental analysis supported to the molecular formula C_{22}H_{24}O_{2}.

At this stage subjecting the compound 13 to hydrogenation conditions would effect two operations at the same time. It would hydrogenate the olefin and simultaneously bring about hydrogenolysis of the benzyl ether. So, the compound 13 was shaken with catalytic amount of Pd/C in hydrogen atmosphere under 80 psi pressure. Reaction was complete in eight hours and gave the expected compound 14 in 93% yield. In the IR spectrum of the compound, absorption band at 3327.8 cm⁻¹ corresponding to hydroxy group confirmed the hydrogenolysis of the benzyl ether. Ketone gave a strong absorption band at 1720.5 cm⁻¹. In the HNMR spectrum, singlets at δ0.61 and δ1.18 were due to gem-dimethyl group. Methyl group on the quaternary carbon center appeared as a singlet at δ1.22. Multiplet between δ1.41 and δ1.92 integrating for two protons was corresponded to methylene group β to the ketone. Aromatic methyl group appeared as a multiplet at δ2.28. Multiplet between δ2.39 and δ2.73 was due to methylene group α to the ketone. Aromatic protons appeared as a multiplet between δ6.6 to δ7.3. Compound 14 analyzed for the molecular formula C_{15}H_{20}O_{2}.

Last step of the synthesis was to reduce the ketone carbonyl of the compound 14 to corresponding methylene group. Methods for direct reduction of ketone group to methylene group include Wolff-Kishner reduction⁵ and Clemmensen reduction.⁶ Wolff-Kishner reduction employs strong basic
conditions while Clemmensen reduction employs strong acidic conditions. Another commonly used method to effect the reduction involves the formation of a thioketal followed by desulphurization with Raney nickel. Reduction of ketone carbonyl to methylene group could be effected indirectly by deoxygenation of the corresponding alcohol. Various methods for deoxygenation are reported in the literature. Mesylates and tosylates of simple alcohols can be reduced to corresponding hydrocarbons using lithium aluminium hydride, sodium cyanoborohydride and lithium triethyl borohydride. For the reduction of sterically hindered mesylates, transition metal salts such as nickel chloride, cobalt chloride and copper chloride are employed along with the above mentioned reagents. Heating of mesylate with zinc powder and sodium iodide in presence of polar solvent cleaves the carbon-oxygen bond. Electrolysis of the mesylate also effect the carbon-oxygen bond cleavage. Xanthates on treatment with tributyltinhydride yield corresponding hydrocarbons. It was further demonstrated that thionobenzoates, thiocarbonyl immidazolides, thioformates and phenoxy thiocarbonates also undergo above transformation. Photolysis of acetate in aqueous HMPA is reported to cleave the carbon-oxygen bond. However, we preferred Wolff-Kishner reduction as it is a one step reaction and our compound can tolerate stronger basic conditions.

Cyclopentanone 14 on Wolf-kishner reduction gave β-herbertenol 1 in 29% yield. In the IR spectrum of the compound, a strong absorption band at 3383.5 cm⁻¹ was attributed to phenolic hydroxy group. In the ¹HNMR spectrum of the compound, singlets at δ0.58 and δ1.06 integrating for three protons each were attributed to gem-dimethyl group. Multiplet between δ1.42 and δ1.93 integrating
for five protons was due to aliphatic protons. Aromatic methyl group appeared as a singlet at $\delta 2.34$. One aliphatic proton appeared as a multiplet between $\delta 2.45$ and $\delta 2.81$. Aromatic protons appeared as a multiplet between $\delta 7.05$ and $\delta 7.51$. All this spectral data matched well with the reported values. Thus the total synthesis was completed in six steps with an overall yield of 10%.

The syntheses of (±) laurene, (±) $\alpha$-cuparenone and (±) herbertenol demonstrate the efficiency of the protocol for the syntheses of sterically crowded cyclopentanoids. In principle, this protocol can be extended to more complex polycyclic cyclopentanoid natural products.
EXPERIMENTAL SECTION

**General:** All solvents were distilled before use. Dry toluene was prepared by distilling over benzophenone and sodium, under argon atmosphere and it was stored over sodium wire. Methoxymethylenetriphenylphosphonium chloride was prepared from freshly distilled chloromethyl methyl ether and triphenyl phosphine and used immediately. Melting points are uncorrected and boiling points represent the bath temperature. IR spectra were recorded on Perkin Elmer model 1600 series FT-IR instrument. $^1$HNMR and $^{13}$CNMR [ ppm, TMS-internal standard ] in CDCl$_3$ were recorded on JEOL FX90Q. The elemental analysis was obtained on HOSLI semiautomatic C, H analyzer. Silica gel (100-200) mesh was used for column chromatography.

$E \& Z\text{-}2$-(4-benzyloxy-3-methyl phenyl)-1-methoxy-1-propene (10):

Methoxymethylenetriphenylphosphonium chloride (8.2 gm, 24 mmol) was suspended in dry THF (15 ml). Potassium tertiary butoxide in t-butanol (30 mmol in 20 ml of t-butanol) was added to it at 0°C in a dropwise manner. The mixture was stirred at 0°C for 1 h and then 4-benzyloxy-3-methyl acetophenone ( 4.8g, 20mmol) was added to it. On further stirring for 1 h at RT the reaction mixture was diluted with water and extracted with ether (3x50ml). Combined ether layers were washed with water, dried over anhyd. Na$_2$SO$_4$ and concentrated. The crude product on purification by column chromatography using hexane as eluent furnished pure 10 ($E/Z$ 1:1) ( 4.18 g) in 78% yield as solid.
IR (Neat) : 1661 cm⁻¹.

¹H-NMR 90 MHz (CDCl₃) : δ 1.85, 1.98 (s, 3H, E-C-CH₃, Z-C-CH₃), 2.27 (s, 3H, Ar-CH₃), 3.68, 3.74 (s, 3H, E-C-OCH₃, Z-C-OCH₃), 5.12 (s, 2H, Ph-CH₂-O), 6.08, 6.37 (bs, 1H, E-CH=C, Z-CH=C), 6.92 (m, 1H, Ar-H), 7.12 (m, 1H, Ar-H), 7.41 (brs, 6H, Ar-H)

2-(4-benzyloxy-3-methyl phenyl) 2,3,3-trimethyl pent-4-ene 1-al (11):

To the solution of the enol ether 10 (2.68g, 10 mmol) and prenyl alcohol (1.18g, 13 mmol) in dry toluene was added trifluoroacetic acid (0.114 g, 1mmol). This reaction mixture was heated to reflux and the reaction was followed by TLC. At the end of 16 h TLC showed no starting enol ether. The reaction mixture was then cooled and concentrated under vacuum to remove the volatile materials. The crude product so obtained was purified by column chromatography using hexane as the eluent to get pure 11 (2.06 g) in 64% yield as a thick colourless undistillable liquid.

IR (Neat) : 2724.4, 1722.4, 1605.6, 1504.6, 1454.3, 1378.3, 914.6, 810.4 cm⁻¹.

¹H-NMR 90 MHz (CDCl₃) : δ 1.07 (s, 3H, C-CH₃), 1.12 (s, 3H, C-CH₃), 1.45 (s, 3H, C-CH₃), 2.33 (s, 3H, Ar-CH₃), 5.01 (m, 2H, C=CH₂), 5.18 (s, 2H, Ar-CH₂-O), 6.00 (m, 1H, -CH=CH₂), 7.08 (m, 3H, Ar-H), 7.52 (s, 5H, Ar-H), 9.95 (s, 1H, -CHO).

Analysis : calculated for C₂₂H₂₆O₂ : C, 89.95; H, 8.13, Found C, 81.84; H, 8.19.
2-(4-benzyloxy-3-methyl phenyl )-2,3,3- trimethyl-4-oxo valeraldehyde (12):

In a solution of unsaturated aldehyde 11 (1.28 gm, 4 mmol) in aqueous dimethoxy ethane (10 ml, 1:9) was suspended PdCl₂ (0.071 gm, 0.4 mmol) and CuCl₂ (0.055 gm, 0.4 mmol). This mixture was stirred at RT under oxygen atmosphere. On completion of reaction (TLC check, 3 h), the mixture was diluted with water and extracted with ether (3X25 ml). The combined ether layers were washed with water and dried over anhyd. Na₂SO₄. The ether layer was concentrated and the crude product was purified by column chromatography using hexane-ethyl acetate (20:1) mixture as eluent to obtain pure 12 (1.05 gm) in 79% yield as a low melting solid.

M. P. 41-43°C.

IR (Neat) : 2754.3, 1718.1, 1700.8, 1607.0, 1560.0, 1542.0, 1507.6, 1458.5 cm⁻¹.

¹HNMR 90 MHz (CDCl₃) : δ 1.07 (s, 3H, C-CH₃), 1.12 (s, 3H, C-CH₃), 1.45 (s, 3H, C-CH₃), 1.92 (s, 3H, -CO-CH₃), 2.22 (s, 3H, Ar-CH₃), 5.03, (s, 2H, Ph-CH₂-O) 6.91(m, 3H, Ar-H), 7.33 (m, 5H, Ar-H), 9.91 (s, 1H, -CHO).

Analysis : calculated for C₂₂H₂₆O₃: C,78.08; H, 7.74, Found C,78.11; H, 7.8.

4- (4-benzyloxy-3-methyl phenyl )-4,5,5- trimethyl-2-Cyclopentenone (13):

Ketoaldehyde 12 (0.845 gm, 2.5 mmol) was dissolved in methanol (4 ml) and cooled in an icebath and stirred. An aqueous methanolic solution of KOH (5%, 4 ml) was added to it. The resulting pale yellow colored mixture was stirred at RT. On completion of the reaction (TLC check, 2 h), the methanol was removed under vacuum and the crude product was extracted in ether (3 x 30ml). The
combined ether layers were dried over anhyd. Na$_2$SO$_4$ and concentrated. The crude product was purified by column chromatography using 3% ethyl acetate in hexane as a eluent to get pure 13 (0.68 gm) in 86% yield as a solid.

M.P. 92-93°C.

IR (Neat): 1701.9, 1592.4, 1506.4, 1456.8, 816.3 cm$^{-1}$.

$^1$HNMR 90 MHz (CDCl$_3$) : 0.57 (s, 3H, C-CH$_3$), 1.22 (s, 3H, C-CH$_3$), 1.48 (s, 3H, C-CH$_3$), 2.32 (s, 3H, Ar-CH$_3$), 5.15 (s, 2H, Ar-CH$_2$-O), 6.31 (d, 1H, 5.6Hz, COCH=CH), 7.01 (m, 3H, Ar-H), 7.48 (m, 5H, Ar-H) 7.82 (d, 1H, 5.6Hz, CO-CH =CH).

$^{13}$CNMR 22.5MHz (CDCl$_3$) : 816.48, 20.00, 25.58, 26.67, 51.41, 53.97, 69.68, 110.91, 124.89, 126.89, 127.59, 128.30, 129.06, 135.12, 137.18, 155.44, 168.66, 214.44.

Analysis : calculated for C$_{22}$H$_{24}$O$_2$: C,82.46; H, 7.55, Found C, 82.55; H, 7.48.

2,2,3-trimethyl-3-(4-hydroxy-3-methyl phenyl) cyclopentanone(14).

To a solution of cyclopentenone 13 (0.32 gm, 1 mmol) in dry ethyl acetate, Pd/C (10% Pd, 0.05 g) was added. This mixture was shaken under the atmosphere of hydrogen at the atmospheric pressure for 8 hours at RT. The reaction mixture was then filtered through a celite pad. The filtrate was concentrated and the crude product was purified by column chromatography using 2% ethyl acetate in hexane as a eluent. The pure product 14 (0.297 gm) was obtained in 93% yield as a solid.
M.P 120-121°C.

IR (Neat) : 3327.8, 1720.5, 1610.3, 1515.9, 1460.4, 1409.3, cm⁻¹

¹HNMR 90 MHz (CDCl₃) : δ 0.61 (s, 3H, C-CH₃), 1.18 (s, 3H, C-CH₃), 1.22 (s, 3H, C-CH₃), 1.41 to 1.92 (m, 2H, -CO-CH₂-CH₂-), 2.28 (s, 3H, Ar-CH₃), 2.39 to 2.73 (m, 2H, -CO-CH₃), 6.6 to 7.3 (m, 3H, Ar-H).


β-Herbertenol(1)

A mixture of 14 (100mg, 0.32 mmol), N₂H₄·H₂O (0.5 gm, 10 mmol), NaOH (0.4 gm, 10 mmol) and diethylene glycol (4 ml) was heated to 220°C for 72 hours. Then the reaction mixture was diluted with water and neutralized with dil HCl. Aqueous layer was extracted in ether. Ether layer was dried and concentrated. The crude product was purified by column chromatography using 3% ethyl acetate in hexane as an eluent. The pure product 1 was obtained in 32 % yield as a colourless solid.

M. P. 76-78°C (lit.³ M.P. 84°C)

IR (Neat) : 3383.5, 1513.4, 1461.4 cm⁻¹

¹HNMR 90 MHz (CDCl₃) : δ 0.58 (s, 3H, C-CH₃), 1.06 (s, 3H, C-CH₃), 1.23 (s, 3H, C-CH₃), 1.42 to 1.93 (m, 5H, aliphatic H), 2.34 (s, 3H, Ar-CH₃), 2.45 to 2.81 (m, 1H, aliphatic H), 7.05 to 7.51 (m, 3H, Ar-H).
REFERENCES

   Wolff, L. Ann. 1912, 394, 86.
   Huang Minlon J. Am. Chem. Soc. 1946, 68, 2487.
6. a) Clemmensen, E. Ber. 1913, 46, 1837.
