3.1 Synthesis of di-o-methoxy benzyl ether, a constituent of *Uvaria chamae* and comment on the reactive species formed by heating saligenin in xylene at reflux temperature

Following the attractive suggestion that benzopyranyl sesquiterpenoid tanzanene 1 is formed by a non-enzymatic hetero Diels-Alder reaction of o-benzoquinone methide 2 to the exocyclic double bond of alloaromadendrene 3\(^1\), we reported a simple biomimetic synthesis of (-) tanzanene by refluxing in xylene, a mixture of (-) alloaromadendrene 3, a sesquiterpene with established absolute configuration and saligenin 4\(^2\). This synthesis also defined the absolute configuration of (-) tanzanene as shown.

It was assumed that the o-quinone methide 2 generated *insitu* from saligenin 4 by loss of water reacts with the exocyclic double bond of (-) alloaromadendrene 3 in
a 4+2 cycloaddition process as suggested. Further extension of this work indicated the
generality of the reaction and led to the biomimetic synthesis of lucidene 6* starting
from humulene 5.

The results obtained with other olefins such as (-)-α-phellandrene 7 and
camphene 8 raised doubts about the involvement of 2 as reactive intermediate in the
above thermal reactions. The products 9 and 10 formed from (-)-α-phellandrene 7 and
camphene 8 respectively further suggested that the addition of the C7 unit of 4 takes
place via ionic intermediates. A close look at the methods for the thermal generation 2
or its derivative 11 shows that much higher temperatures are required. Further,
o-benzoquinone methide 2 is known to be highly reactive and at temperatures above
20°C undergoes self Diels-Alder condensation to produce mainly the trimer 12.†

Formation and characterisation of dimer 13 is also reported.*

* Lucidene obtained was found to be optically active as against the racemic nature of
the natural product. Details of this work are presented in chapter-2 (section-1, this
thesis).
In order to probe into the nature of the reactive species generated from saligenin 4 in refluxing xylene it became necessary to look for other products of each reaction, particularly those derived by self condensation of the reactive intermediate obtained from saligenin 4.

It was found that in each reaction, irrespective of the nature of the unsaturated compound used, a crystalline compound, C_{14}H_{14}O_{3} (M^+ 230.0941), m.p.119°C was formed. When saligenin 4 was refluxed alone with xylene, the same product could be isolated. This clearly shows that it is derived from two molecules of 4. The IR
spectrum of compound, m.p. 119°C showed bands due to hydroxyl (3300 cm\(^{-1}\)) and aromatic rings (1497 and 1600 cm\(^{-1}\)). Absence of carbonyl absorption clearly showed that it is not dimer 13, though the molecular formula is as expected for 13. In fact we did not get any fraction having carbonyl absorption in its IR spectrum. This observations clearly established that o-benzoquinone methide 2 is not the reactive intermediate.

Based on the molecular formula, and spectral data (IR, \(^1\)HNMR) two alternative structures 14 and 15 were considered.

![Chemical structures](image)

Compound, m.p. 119°C did not undergo methylation when treated with excess diazomethane at room temperature and led us initially to believe the absence of phenolic hydroxyl groups and structure 15 was therefore preferred over 14. A literature search indicated that bis(2-hydroxy methyl phenyl)ether 15 is known compound and was used recently by Wong and co-workers for the synthesis of dibenzoxepin derivative 16. An authentic sample of 15 was made available for a direct
comparison*. Since $^{13}$CNMR and IR spectra of 15 were not recorded by Wong and co-workers**, we therefore measured the IR and $^{13}$CNMR on the authentic sample made available to us. A direct spectral comparison (IR, $^1$H and $^{13}$C NMR) and co-TLC conclusively established their non identity. Moreover the melting points are also different (lit m.p. 98-99°C).

Having ruled out the possibility of structure 15 for the thermal self condensation product derived from saligenin, we then considered structure 14 for it. Interestingly Ziegler and Lercher* had reported its preparation by heating saligenin in a sealed tube at 120°C. In 1962 Yeddanapalli and Francis* confirmed the findings of Ziegler and Lercher but did not record the spectral data. The IR and $^1$HNMR are consistent with the assigned structure 14 and are reproduced in figures 3.01 and 3.02 respectively. The $^{13}$CNMR showed seven signals and indicated its symmetrical nature. The assignments are given in table-1.

<table>
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<th>Carbon</th>
<th>Chemical shift ($\delta$ ppm)</th>
<th>Multiplicity</th>
</tr>
</thead>
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<td>s</td>
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<tr>
<td>C2 &amp; C2'</td>
<td>122.1</td>
<td>s</td>
</tr>
<tr>
<td>C3 &amp; C3'</td>
<td>129.3</td>
<td>d</td>
</tr>
<tr>
<td>C4 &amp; C4'</td>
<td>120.3</td>
<td>d</td>
</tr>
<tr>
<td>C5 &amp; C5'</td>
<td>129.9</td>
<td>d</td>
</tr>
<tr>
<td>C6 &amp; C6'</td>
<td>116.2</td>
<td>d</td>
</tr>
<tr>
<td>C7 &amp; C7'</td>
<td>70.6</td>
<td>t</td>
</tr>
</tbody>
</table>

* We thank Dr. H. N. C. Wong for the sample of diol 15 and a copy of it $^1$HNMR spectrum.
** Personal communication to Prof. S. K. Paknikar.
Further support for structure 14 was found in mass spectral data. The characteristic feature of EIMS is the fragment ion m/z 212 (M⁻-18), obviously due to loss of water. The genesis of this and other significant peaks is shown in chart-1.

![Diagram of mass spectral fragmentation of 2,2'-dihydroxy bibenzyl ether 14]

On treatment with AC₂O-pyr, 14 gave a liquid diacetate 17, C₁₈H₁₈O₅. The IR spectrum showed bands at 1756 and 1206 cm⁻¹ due to phenolic acetate group. The
\(^1\)HNMR showed a singlet at \(\delta 2.19\) (6H, acetoxy methyls), another singlet at \(\delta 4.44\) (4H, Ar-CH\(_2\)-O-) and a multiplet centered at \(\delta 7.3\) (8H, Ar-H).

![Chemical structure](image1)

![Chemical structure](image2)

Failure of 14 to undergo methylation with diazomethane is most likely due to the hydrogen bonding as shown in 14a. Further 2,2'-Dihydroxy bibenzyl ether slowly dissolved in NaOH as expected.

![Chemical structure](image3)

Interestingly Lasswell and Hufford had reported the isolation of di-o-methoxy bibenzyl ether 18 from *Uvaria chamae*\(^9\). Methylation of 14 would then constitute a simple synthesis of this natural product. Refluxing 14 with dimethyl sulphate and aq. NaOH for 2 hr. and usual workup afforded a mixture (mainly mono and dimethyl ethers) from which only the major compound could be isolated in pure form. In our
hands the major product was obtained as a solid,\textsuperscript{+} C\textsubscript{16}H\textsubscript{18}O\textsubscript{3} (M\textsuperscript{+} 258.1255) confirming it to be the dimethyl ether derivative 18 of 14. The spectral data was found to be completely identical with that reported on the natural product. The \textsuperscript{13}CNMR spectrum (not reported earlier) was fully consistent with the structure. The assignments are shown in table-2.

<table>
<thead>
<tr>
<th>Carbons</th>
<th>Chemical shifts $\delta$ (ppm)</th>
<th>Multiplicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_1$ &amp; $C_1'$</td>
<td>156.9</td>
<td>s</td>
</tr>
<tr>
<td>$C_2$ &amp; $C_2'$</td>
<td>127</td>
<td>s</td>
</tr>
<tr>
<td>$C_3$ &amp; $C_3'$</td>
<td>128.3</td>
<td>d</td>
</tr>
<tr>
<td>$C_4$ &amp; $C_4'$</td>
<td>120.3</td>
<td>d</td>
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<td>$C_5$ &amp; $C_5'$</td>
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<tr>
<td>$C_6$ &amp; $C_6'$</td>
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<tr>
<td>$C_7$ &amp; $C_7'$</td>
<td>67.3</td>
<td>t</td>
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</table>

Absence of benzoquinone methide dimer 13 or trimer 12 in the thermal reaction of products of saligenin alone or in the presence of olefins can lead to a safe conclusion that o-benzoquinone methide is not the intermediate. It is now clear that the C7 unit of saligenin is added to the olefinic linkage via ionic intermediates. the reactive intermediate actually involved should be electrophilic and simple.

\textsuperscript{\textsuperscript{+} Lasswell and Hufford had obtained the natural 18 in liquid form. Their synthetic product obtained by a different route was also a liquid.}
dehydroxylation of 4 would generate reactive intermediate 19 which can react with olefinic linkage as shown in scheme-1.

![Scheme 1](image)

Formation of the 2,2'-dihydroxy dibenzyl ether 14 can be also explained in a straightforward manner (scheme-2).

![Scheme 2](image)
The mechanism shown above also explains the formation of 14 by heating saligenin in a sealed tube as reported by Ziegler and Lercher. In view of the several reports on the isolation of o-hydroxy benzylated flavanoids, chalcones, dihydrochalcones from various Uvaria species it was of interest to study the thermal reaction of saligenin in presence of reactive aromatic substrates such as resorcinol, phloroglucinol etc.

The results obtained in the thermal reaction of saligenin and resorcinol 20 are described below.

Reflexing a equimolar mixture of saligenin 7 and resorcinol 20 in dry xylene for 12 hr and removal of xylene by distillation afforded a solid residue. TLC showed the presence of two major components which could be obtained in pure form by column chromatography over silica gel. The two compounds having melting points 202°C and 193°C are designated as compounds A and B respectively.

Compound A, m.p. 202°C analysed for C_{13}H_{12}O_{3}. IR spectrum (KBr) suggested the presence of hydroxyl groups as expected (3220 cm⁻¹). The ^1HNMR (fig3J2⁻) was measured in deuterated acetone because of its poor solubility in other solvents. It showed a singlet at δ 3.82 due to a methylene flanked by aromatic rings. The integration showed the presence of seven aromatic hydrogens. In spite of the complex pattern, it was possible to infer the presence of a 1,2,4-trisubstituted benzene
ring. The upfield positions of two protons at δ 6.30 (1H, dd, J=8.0, 2.8 Hz) and δ 6.40 (1H, d, J=2 Hz) indicated that the resorcinol used has undergone alkylation at the expected site. The chemical shift of the third hydrogen of this ring was observed as a doublet (J=8 Hz) at δ 6.96.

The APT (13CNMR) spectrum showed five singlets (δ 119.5, 129, 155, 156 and 158) and seven doublets (δ 103.5, 108, 116, 120.5, 128, 131 and 132). The signal for the methylene carbon appeared to overlap on the signals of the solvent. The compound A is therefore formulated as 2,2',4'-tri hydroxy diphenyl methane 21.

\[
\begin{align*}
&\text{OH} \\
&\text{HO} \\
&\text{OH}
\end{align*}
\]

21

Compound B, m.p.193°C, analysed for C_{20}H_{18}O_{4}. Its IR spectrum (KBr) showed striking similarity to that of compound A* and hence must be structurally related to it. The most characteristic difference in 1HNMR was the presence of 1,2,4,5-tetrasubstituted benzene ring. Besides, a complex pattern for 8 hydrogens was observed in the region δ 6.7-7.2. A broad single at δ 8.4 integrated for 4 hydrogens and disappeared on addition of D_{2}O. Therefore there are four exchangeable hydrogens in compound B. A four proton singlet at δ 3.8 suggested the presence of two Ar-CH_{2}-

* In both cases a broad band at 2420 cm\(^{-1}\)was present in IR spectrum. This is most probably due to the molecular association caused due to hydrogen bondings.
Ar groupings. These features can be easily accommodated in structure 22 for compound B.

Further confirmation of the structure 22 including its symmetrical nature came from its $^{13}$CNMR spectrum, which showed 4 singlets and 6 doublets all above δ 100. Once again the triplet due to Ar-CH$_2$-Ar overlapped on the signals of the solvent (deuterated acetone).

We plan to use these compounds as starting materials for the preparation of 3-hydroxy xanthone 23 and benzopyrano xanthone 24, which would lend further support to the assigned structures.
3.2 Synthesis of a C\textsubscript{13} - diosphenol, a constituent of \textit{Ipomea pes caprea}

The number of ways in which the enzyme bound isomeric farnesyl pyrophosphate (FPP) precursors gets folded and produce incredibly large numbers of novel sesquiterpene skeletons has attracted the attention of organic chemists all over the world. The observed oxygenation patterns adds further to their novelty and complexity but are rich sources of interesting chemistry. The regular or normal sesquiterpenoids may undergo further transformations e.g. rearrangements which lead to modified or irregular sesquiterpenoids and loss of carbon atoms to produce degraded or \textquote{squib\textprime}enoids. The phenomena is not restricted to sesquiterpenoids and characterisation of \textquote{modified terpenoids} as well as degraded terpenoids has been quite common. In fact steroids (C\textsubscript{27}) and limonoids (C\textsubscript{26}) are the well known examples of degraded terpenoids.

In some cases extra carbons are added at some stage in the biosynthesis and such natural products are also considered as modified terpenoids. The terpenoids which have a mixed biogenetic origin are generally regarded as meroterpenoids.

In the previous chapter, synthesis of meroterpenoids (-)-tanzanene \textbf{1} and lucidene \textbf{6} is described. In this section we report synthesis of a C\textsubscript{13} - diosphenol \textbf{25} and propose that in all probability it is derived biogenetically by the loss of two carbon atoms of the drimane skeleton \textbf{26}.

\footnote{With same number of carbon atoms as present in the bonafied biogenetic precursor}
Bohlin and coworkers\textsuperscript{10} reported that the crude extract of \textit{Ipomea pes caprea} (L) R.Br. (Convolvulaceae) has inhibitory effect on prostaglandin synthesis. Bioactivity guided separation of the extract led to the isolation of four active compounds, \textit{C}_{13} - diosphenol (2-hydroxy-4,4,7-trimethyl-1(4H)-naphthalenone) 25, (-)-mellein 27, eugenol 28, 4-vinyl guaiacol 29.
Isolation of $C_{13}$ - diosphenol 25 attracted our attention because of our continued interest in the biogenesis and synthesis of modified terpenoids and its reported medicinal properties. We have achieved its synthesis from $\beta$-ionone 30 as depicted in scheme-2.

Scheme -2
β-Ionone 30 on distillation in presence of catalytic amount of iodine following the procedure of Bogart and Fourman\textsuperscript{11} gave a hydrocarbon fraction in 85% yield. The product was purified by column chromatography over silica gel and distillation over metallic sodium. The IR spectrum showed bands at 1625, 1510 and 832 cm\textsuperscript{-1} due to aromatic ring and was essentially composed of two components (GLC, carbowax, capillary column, 170\textdegree C) 31 (77.5\%) and 32 (17.1\%) having RT 2.89 and 3.29 respectively. Hydrogenation of the hydrocarbon fraction over Pd/C (10\%) in ethanol gave pure ionene 31 of more than 90\% purity.

Oxidation of ionene 31 with CAN \textbackslash acetic acid-water-ether at 35\textdegree C for 30 min followed by usual work up and silica gel chromatography gave yellow a oil of 95\% purity (GLC). IR bands at 1700, 1620 and 1500 cm\textsuperscript{-1} clearly indicated presence of a conjugated carbonyl group. Its \textsuperscript{1}HNMR showed three proton singlets at \textdelta\ 1.44 and 1.45 due to gem dimethyls. Aromatic methyl signal appeared as a singlet at \textdelta\ 2.34 where as two mutually coupled triplets due to two methylene groups were seen at \textdelta\ 2.00 and 2.70. Two aromatic protons were observed in the range of \textdelta\ 7.31-7.34 and third proton at \textdelta\ 7.82. Identity of the CAN oxidation product with 4,4,7-trimethyl tetralone 33 was confirmed by a direct comparison (co-TLC) and comparison of the spectral data (IR and \textsuperscript{1}HNMR) recorded on 33 prepared by an alternate route\textsuperscript{12}.

The spectral data of the CAN oxidation product was also identical with that reported for 4,4,7-trimethyl tetralone whose synthesis was reported by Liu and Browne employing Diels-Alder reaction\textsuperscript{13}.

\* Thanks are due to Dr. V. P. Kamat for the reference sample of tetralone 33.
The present synthesis of tetralone 33 is much shorter and convenient than the previously reported by Kamat and also by Liu.

4,4,7-Trimethyl tetralone 33 on treatment with NaNO₂-HCl at 5°C for 2hr. followed by usual work up afforded a white solid mp 177°C (decomp). Its IR spectrum showed bands at 3218, 1694, 1607 and 1495 cm⁻¹. Its ¹HNMR spectrum revealed two three proton singlets at δ 1.38, aromatic methyl at δ 2.39 and methylene proton singlet at δ 3.00. Aromatic protons were seen at δ 7.34, 7.40 and 7.93 where as hydroxyl proton was observed at δ 11.44. Spectroscopic data supported structure 34 for oximino tetralone. Its mass spectral fragmentation did not show a peak due to the molecular ion but showed characteristic fragments (chart-2) confirming the proposed structure.
Oximino tetralone 34 on refluxing with pyruvic acid in acetic acid for 12 hr, followed by usual work up, recrystallisation from benzene and sublimation under vacuum afforded 25 as a white solid mp 117-118\(^0\)C (lit.\(^1\) 118-118.5\(^0\)C). IR spectrum showed bands at 3380, 1685, 1618, 1498 cm\(^{-1}\). \(^1\)H and \(^{13}\)C NMR spectrums established identity of the synthetic sample with natural as reported by Bohlin and
coworkers\textsuperscript{10}. Comparison of $^1\text{H}$ and $^{13}\text{C}$ NMR are presented in tables 3 and 4 respectively.

Table 3

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### Table-4

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</tr>
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<td>C7-CH3</td>
<td>21.9</td>
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</tr>
</tbody>
</table>

The possible mode of major fragmentation and the likely structures for these fragment ions are shown in Chart-3. The EIMS mass spectrum further established the identity.
Regarding the biogenesis of diosphenol 26, we consider it likely that it is derived by loss of two carbon atoms of a drimane skeleton as shown in scheme-3.
Incidentally, diosphenol 25 was characterised as an oxidation product of 4,4,7-trimethyl-3,4-dihydro 2(1H) naphthalenone 35 by Davis and co-workers\textsuperscript{14} much before its discovery as a natural product. In view of its preparation from $\alpha$-ionone and $\beta$-ionone (present study) it is not easy to rule out its biogenetic origin from a carotenoid precursor. The preparation of 25 reported by Davis and coworkers from $\alpha$-ionone 36 is presented in scheme-4.
Scheme-4

a) tert-butyl chromate oxidation  
b) 80% aq. formic acid  
c) Silver oxide in ethanol
3.3 Synthesis of 7-Hydroxy-4-isopropyl-6-methyl coumarin; a bis norsesquiterpene.

Although a large number of coumarins having different substitution pattern have been found to occur in nature, there are only three coumarins having a C₄-isopropyl substituent (37 and 38) and isopropyl group at C₃ (39) and therefore are regarded as a rare group of natural products.

Satake and coworkers reported the isolation of 37 and 38 from the fronds of Macrothelypteris torresiana CHING var calvata HOLTT. Subsequently pygmaeoherin 39 was isolated from the roots of Pygmaeopremna herbacea.

Biogenetically, it is appropriate to consider the coumarins 37 and 38 as modified sesquiterpenes. Synthesis of 6-hydroxy-4,7-dimethyl-3,4-dihydrocoumarin 40 has been recently reported from our laboratories and shown to be first well characterised tetrano sesquiterpene. In this section we report the synthesis of 37 and also propose its likely biogenetic pathway.
7-Methoxy-6-methylcoumarin 41 has been synthesised from 2,4-dimethoxy toluene in our laboratory\textsuperscript{19} (scheme -5).

The last step i.e., Pechmann condensation in the above scheme was carried on the methyl ether rather than phenol. Based on this observation we envisaged the synthesis of 4-isopropyl-7-methoxy-6-methylcoumarin 42, the methyl ether of a naturally occurring coumarin 37 (scheme-6).
Ethyl isobutyryl acetate 44 required for the synthesis of 37 or its methyl ether 42 was prepared earlier by Kroeker and McElvain as shown in scheme-7.

Scheme-7

The low yield and tedious experimental procedure involved in the above synthesis of 44 made us to look for an alternate simple synthesis. Following the recent synthesis of β-keto esters reported by Yonemitsu and coworkers using Meldrums acid 45, ethyl isobutyryl acetate 44 could be obtained in 56% yield as shown in scheme-8.

Scheme-8

The base catalysed acylation of Meldrums acid 45 with isobutyryl chloride 46 resulted in the formation of 47 in almost quantitative yield, which without further purification was refluxed with ethanol for 3 hr. and usual workup afforded 44 as a colourless oil, whose IR spectrum showed bands at 1745 and 1710 cm\(^{-1}\) for an ester.
and ketone carbonyls respectively. The $^1$H NMR spectrum showed doublets at $\delta$ 1.13 and 1.16 ($J$=7 Hz) and a clean septet at $\delta$ 2.62 ($J$=7 Hz) confirmed the presence of an isopropyl group. A three proton triplet at $\delta$ 1.26 ($J$=8 Hz) and a two proton quartet at $\delta$ 4.17 ($J$=8 Hz) belong to the ester function. The methylene protons appeared as a clean singlet at $\delta$ 3.48. The $^1$H NMR spectrum also showed the presence of the enol tautomer 44a-b.

![Chemical structures](image)

The present synthesis of 44 is superior to that reported by Kroeker and McElvain$^{20}$ because of the simplicity of experimental procedure and better yields.

The Pechmann condensation of ethyl isobutyryl acetate 44 with 2,4-dimethoxy toluene 43 using conc. Sulphuric acid following the standard experimental procedure afforded a complex mixture which on chromatographic separation gave colourless oil as a major product. The spectroscopic analysis of this oil clearly indicated to be an undesired product, the identification of the same is in progress since Pechmann condensation of phenols with $\beta$-keto esters normally produces the corresponding coumarins in good yields, we decided to use 2,4-dihydroxy toluene 48 for the Pechmann condensation. Although synthesis of 48 was reported earlier by Clemanson reduction of $\beta$-resorcyl aldehyde 49$^{22}$; its preparation from commercially available 43 seemed simple.
Demethylation of 43 using BBr₃ at low temperature²³ was found to be most convenient and yielded 48 (40%) a white solid. Recrystallisation from chloroform afforded needles, m.p. 102°C (lit.²² 104°C). Its IR spectrum showed a broad band at 3450 cm⁻¹ due to hydroxyl functionality.¹HNMR spectrum showed a singlet at δ 2.15 due to aromatic methyl where as aromatic protons were seen at δ 6.34 (2H) and δ 6.98 (1H). A two proton singlets at δ 4.8 disappeared on addition of D₂O and was therefore due to exchangeable hydrogens of the phenolic hydroxyl groups. Thus the ¹HNMR spectrum was fully consistent with structure 48 for the demethylated product.

The condensation of 4-methyl resorcinol 48 with ethyl isobutyryl acetate 44 using conc. Sulphuric acid at 0°C for 1 hr. and then at room temperature for 16 hr. followed by usual work up afforded yellowish solid which on repeated crystallisation from chloroform-petroleum ether afforded colourless needles of 7-hydroxy-4-isopropyl-6-methylcoumarin 37 in 52% yield, m.p. 197°C (lit.¹⁵ 198°C). Comparison of the spectral data (IR, UV, ¹HNMR, ¹³CNMR and MS) measured on the synthetic compound with those recorded on the natural product established their identity beyond doubt. The base peak at m/z 175 in the mass spectrum appears to be derived by loss of CO followed by CH₃ radical as shown in chart-4.
The biosynthetic origin of 7-hydroxy-4-isopropyl-6-methyl coumarin is interesting. The location of isopropyl, methyl and the hydroxyl substituents suggests that it is derived by loss of two carbon atoms of a sesquiterpene precursor as shown in scheme-9.

Incidentally 1,7-dihydroxy calamenene 50\textsuperscript{24}, 2,7-dihydroxy cadalane,\textsuperscript{51}\textsuperscript{23}, and lancinilene 52\textsuperscript{25}, have been isolated as a natural products tends further support to our hypothetical pathway.
3.4 4-Hydroxy-5-methylcoumarin derivatives from *Diospyros kaki* THUNB and *D. kaki* THUNB var. *sylvesyris* MAKINO; structure and synthesis of 11-methylgerberinol

Till 1978 only few naturally occurring 4-hydroxy-5-methylcoumarins and its derivatives were known, but now number has exceeded hundred and most of them have been isolated from Compositae family\(^{26}\).

Several years ago, Natori and coworkers had isolated naphthaquinones, 7-methyl julgone \(^{53}\), diospyrin \(^{54}\), isodiospyrin \(^{55}\), neodiospyrin \(^{56}\), plumbagin \(^{57}\), mamegakinone \(^{58}\), shinanolone \(^{59}\), binaphthyl-1,1' -quinone \(^{60}\) along with triterpenes lupeol, betulin and betulinic acid from the root extracts of Ebenaceae plants *Diospyros kaki* THUNB and *D. kaki* THUNB var. *sylvesyris* MAKINO\(^{27}\). While compounds 53-60 were characterised, two compounds now designated as A and B, were available in minute quantities and could not be identified. We have now fully characterised these compounds and results are presented in this section.
Characterization of compound A

Compound A (unidentified compound from *D. kaki* thunb var *sylvestris makino*) $C_{21}H_{16}O_6$ mp 267-269°C showed UV ($\lambda_{\text{max}}$ 240, 286, 320 sh nm) and IR bands ($\nu_{\text{max}}$ 3030, 1648, 1599 cm$^{-1}$) typical of a bis-4-hydroxycoumarin$^{28}$. The $^1$HNMR spectrum showed signals at $\delta$ 2.80 (6H, singlet, aromatic methyls), $\delta$ 3.77 (2H, s, CH$_2$ attached to quaternary carbons), $\delta$ 6.9-7.5 (6H, m, typical of a 1,2,3-trisubstituted benzene ring) and two exchangeable protons at $\delta$ 11.7 (-OH).

The high resolution EIMS showed a [M$^+$] peak at m/z 364.094 corresponding to the molecular formula $C_{21}H_{16}O_6$. The base peak at m/z 134 which is due to ion 61a or 61b suggested that compound A is 4-hydroxy coumarin derivative with a methyl substitution either at C$_5$ (62) or C$_8$ (63) position.

Therefore complete structure for compound A must be either 64 or 65.
A survey of the literature indicated that the spectral data and the mp of compound A corresponded exactly to the data reported for gerberinol 64 (mp 263-65°C), previously isolated from *Gerbera lanuginosa* Benth by Sengupta and coworkers. A direct comparison (IR, UV, ^1^HNMR) unambiguously established the identity.

**Characterisation of compound B**

The second compound B (uncharacterised from *D. kaki*), C_{22}H_{18}O_{6}, mp 210-217°C (ethyl acetate), exhibited spectral data UV (\lambda_{max} 246, 295, 305 and 320 nm), IR (\lambda_{max} 1660, 1640, 1595 cm^{-1}) characteristic of a bis-4-hydroxycoumarin. The IR bands at 1383 and 1365 cm^{-1} indicated the presence of a methyl groups. The ^1^HNMR spectrum was strikingly similar to that of compound A (gerberinol 64), the major difference being the replacement of one of the C_{11} hydrogen by a methyl group (\delta 1.85, 3H, d, J= 7 Hz, \delta 4.65, 1H, q, J= 7 Hz) for aromatic region. Structure 66 was therefore assigned to compound B and named 11-methyl gerberinol.

* We thank Prof. S. Natori for the copies of (IR, UV, MS and NMR) spectra measured on uncharacterised compounds of D. Kaki & Prof. P. Sengupta for an authentic sample of gerberinol and the copies of spectra for comparison.
Its high resolution EIMS, showed in addition to the [M+] peak at 378.112 (C\textsubscript{22}H\textsubscript{16}O\textsubscript{6} requires 378.110), significant peaks at m/z 202, 176, 135(100%), 134(96%), and 106. The observed fragment ions are fully consistent with structure 66 and are presented in chart 5.

![Diagram of mass spectral fragmentation of 11-methyl gerberinol 66](chart-5)

**Chart-5**: Mass spectral fragmentation of 11-methyl gerberinol 66
The assigned structure 66 for 11-methyl gerberinol was confirmed by a straightforward synthesis from 4-hydroxy-5-methyl coumarin 62 which was prepared from thymol 67 following a new synthetic route developed by Paknikar and Nadkarni. The 4-hydroxy-5-methyl coumarin 62 was then condensed with acetaldehyde by refluxing in ethanol for 5 min. to afford 11-methyl gerberinol 66 in 59% yield as presented in scheme-10.

\[
\begin{align*}
67 & \quad + \quad \text{HOOC-CH}_2\text{COOH} \quad \xrightarrow{\text{POCl}_3} \quad \text{ZnCl}_2 \\
& \quad \xrightarrow{\text{AlCl}_3, \text{chlorobenzene}} \\
& \quad \xrightarrow{\text{CH}_3\text{CHO, EtOH}} \\
62 & \quad \xrightarrow{\text{IR, UV, }^{1}\text{HNMR}} \\
66 & \quad \text{OH} \\
& \quad \text{OH} \\
& \quad \text{OH} \\
\end{align*}
\]

Scheme-10

The synthetic product 66 was identical in all respects to natural 66 (IR, UV, \(^{1}\text{HNMR}\)). We have now recorded its \(^{13}\text{CNRMR}\) spectrum which is fully consistent with the proposed structure. The \(^{13}\text{CNRMR}\) chemical shifts assignments are shown below.
Natural 11-methyl gerberinol 66 on treatment with acetic anhydride and sulphuric acid gave colourless needles, mp 283-284°C (MeOH-CHCl₃); C₂₂H₁₆O₅, [M⁺] 360.098; UV λmax 277, 300 nm; IR vmax 1715, 1670, 1640, 1605, 1410, 1313 and 1260 cm⁻¹. Its EIMS showed in addition to the [M⁺], a base peak at m/z 345 [M⁺-15] and ¹H NMR did not show any signals due to acetate methyls and the molecular formula suggested the formation of an anhydro compound. Interestingly Sengupta and coworkers²⁹ observed that gerberinol 64 when treated with Ac₂O-pyridine gives an anhydro compound 69 and this structure assignment was based on mechanism and spectral analysis (¹H and ¹³C NMR). Structure 70 was therefore looked likely for anhydro derivative obtained from 11-methyl gerberinol 66. However ¹H NMR and ¹³CNMR data of anhydro 11-methyl gerberinol were not consistent with structure 70.
We have now assigned structure 71 to this product, especially after noting two different types of carbonyl groups (singlets at \( \delta \) 160.4 and 178.7). The assignments of \(^1\)H and \(^{13}\)C NMR spectra are given in the experimental section.

The formation of 71 can be accounted by the mechanism shown in scheme-11.
Toyonaga and co-workers have shown that 4-hydroxy-5-methylcoumarins and their derivatives are biosynthetically derived via a polyketide pathway (scheme-12).
Similarly it is known that naphthaquinones are derived via polyketides\textsuperscript{32}. The co-occurrence of gerberinol\textsuperscript{64} and 11-methyl gerberinol\textsuperscript{66} with quinones\textsuperscript{53-60} in \textit{D. kaki} is therefore understandable. In fact, one can anticipate the presence of 4-hydroxy-5-methylcoumarin and its derivatives in any plant and/or marine source which is known to contain the quinone pigments. Isolation of ismailin\textsuperscript{72} and canalicutin\textsuperscript{73} from \textit{Diospyros} species\textsuperscript{33} both resulting from further reaction/s between 4-hydroxy-5-methylcoumarin and naphthaquinones shows the economy and simplicity used by living systems to produce novel natural products.
Fig. 3.01 : IR spectrum of 14
Fig. 3.02: $^1$H NMR spectrum of 14
Fig. 3.03: $^{13}$C NMR spectrum of 14
Fig. 3.04: Mass spectrum of 14
Fig. 3.05: IR spectrum of 15
Fig. 3.06: $^{13}$C NMR spectrum of 15
Fig. 3.07 : IR spectrum of 18
Fig. 3.08: $^1$H NMR spectrum of 18
Fig. 3.09: $^{13}$C NMR spectrum of 18
Fig. 3.10: Mass spectrum of 18
Fig. 3.11 : IR spectrum of 21
Fig. 3.12: $^1$H NMR spectrum of 21
Fig. 3.13: $^{13}$C NMR spectrum of 21
Fig. 3.14: IR spectrum of 22
Fig. 3.15: $^1\text{H}$ NMR spectrum of 22
Fig. 3.16: $^{13}$C NMR spectrum of 22
Fig. 3.17: IR spectrum of 34
Fig. 3.18: $^1$H NMR spectrum of 34
Fig. 3.19: IR spectrum of 25
Fig. 3.20: $^1$H NMR spectrum of 25
Fig. 3.21: IR spectrum of 44
Fig. 3.22: $^1$H NMR spectrum of 44
Fig. 3.23: IR spectrum of 37
Fig. 3.24: $^1$H NMR spectrum of 37
Fig. 3.25: $^{13}$C NMR spectrum of 37
Fig. 3.26 : Mass spectrum of 37
Fig. 3.27: IR spectrum of 64
Fig. 3.28: IR spectrum of 66
Fig. 3.29: $^1$H NMR spectrum of 66
Fig. 3.30: $^{13}$C NMR spectrum of 66
Fig. 3.31: Mass spectrum of 66
Fig. 3.32: UV spectrum of 71
Fig. 3.33: IR spectrum of 71
Fig. 3.34: $^1$H NMR spectrum of 71
Fig. 3.35: $^{13}$C NMR spectrum of 71
Experimental:

2,2'-Dihydroxy bibenzyl ether 14

A solution of o-hydroxy benzyl alcohol 4 (0.300 gm, 2.4 mmole) in dry xylene (5 mL) was refluxed for 10 hr. Xylene was distilled off under reduced pressure, residue chromatographed on silica gel and eluted with ethyl acetate-pet.ether (2:8) to afford 2,2'-dihydroxy bibenzyl ether 14 as a white solid. Recrystallised from benzene-pet.ether (0.117gm, 42%) m.p. 122°C.

IR : v max (KBr) (fig. 3.01) : 3300, 1610, 1600, 1590, 1490, 1455, 1405, 1350, 1270, 1220, 1185, 1110, 1070, 1040, 1015, 980, 930, 850, 760, 750, 740 cm⁻¹.

¹H NMR ( δ ppm,CDCl₃,300 MHz ) (fig. 3.02) : 4.77 (4H, s, -CH₂-), 6.89 (2H, ddd, J=7.5 and 1.2 Hz, C₄-H and C₄-H ), 6.91 (2H, d, J=7.5 Hz, C₃-H and C₃-H), 7.13 (2H, dd, J=7.5 and 1.8 Hz, C₃-H and C₃-H), 7.23 (2H, ddd, J= 9.0, 7.5 and 1.8 Hz, C₃-H and C₃-H ) 7.65 (2H, s, exchanges with D₂O, -OH).

¹³C NMR ( δ ppm,CDCl₃, 75 MHz, APT ) (fig. 3.03): 155.5 (s, C₁ and C₁'), 129.9 (d, C₃ and C₃'), 129.3(d, C₅ and C₅'),122.1 (s, C₆ and C₆'), 120.3 (d, C₄ and C₄'), 116.2 (d, C₂ and C₂), 70.6 (t, C₇ and C₇).

HRMS ( EI ) (fig. 3.04) : m/z 230 (M⁺), 212, 124, 107 (100%), 106, 77.

2,2'-Dimethoxy bibenzyl ether 18:

To a stirred solution of 2,2'-Dihydroxy bibenzyl ether 14 (0.200 gml, 0.87 mmole), NaOH (0.04 gms) in water (2 mL), dimethyl sulphate (0.4 mL) was added over period
of 10 min at 0-5°C. After attaining room temp. the reaction mixture was refluxed for 2
hr., then quenched with ice-water and diluted with EtOAc. The organic phase was
separated, washed with H₂SO₄ (10%), water and dried over anhydrous sodium
sulphate. Removal of solvent yielded yellow oil. Chromatography over silica gel and
elution with ethyl acetate-pet. ether (1:9) yielded 2,2'-Dimethoxy bibenzyl ether 18 as
white solid (0.055 gms, 23%) m.p. 59°C (lit. oil).

IR : v max (KBr) (fig. 3.07): 1590, 1490, 1455, 1438, 1407, 1355, 1300, 1285, 1238,
1125, 1085, 1020, 750, 720 cm⁻¹.

¹H NMR (δ ppm, CDCl₃, 300 MHz) (fig. 3.08): 3.84 (6H, s, -OCH₃), 4.67 (4H, s, -
CH₂-), 5.88 (2H, dd, J=8.0 and 1.0 Hz, C₂-H and C₂-H), 6.98 (2H, ddd, J=7.5, 7.5
and 1.2 Hz, C₄-H and C₄-H), 7.28 (2H, ddd, J=8.2, 7.5 and 1.8 Hz, C₃-H and C₃-H),
7.49 (2H, ddt, J=7.5, 1.8 and 1.0 Hz, C₅-H and C₅-H)

¹³C NMR (δ ppm, CDCl₃, 75 MHz, APT) (fig. 3.09) : 156.9 (s, C₁ and C₁), 128.7
(d, C₃ and C₃), 128.3 (d, C₄ and C₄), 127.0 (s, C₆ and C₆), 120.3 (d, C₄ and C₄), 110
(d, C₂ and C₂), 67.3 (t, C₇ and C₇), 55.3 (q, OCH₃).

HRMS (EI) (fig. 3.10): m/z 258 (M⁺), 150, 137, 122, 91(100%), 77, 69.

2,2'-Diacetyl bibenzyl ether 17:

Acetic anhydride (2 mL) was added to a solution of 2,2'-dihydroxy bibenzyl ether 2
(0.100 gm, 6.43 mmole) in dry pyridine (2 mL). After stirring for 16 hr at room
temp., the reaction mixture was diluted with CH₂Cl₂, washed with HCl (10%), and
dried over anhydrous sodium sulphate. Concentration followed by column
chromatography using EtOAc- pet.ether (1:1) yielded 2,2'-diacetyl bibenzyl ether 4 (0.063 gm, 52% ) as colourless oil.

IR : $\nu_{\text{max}}$ (film):1756, 1610, 1586, 1489, 1453, 1369, 1206, 1112, 1079, 1011, 754 cm$^{-1}$.

$^1$H NMR ( $\delta$ ppm,CDCl$_3$,60 MHz ) : 2.19 (6H, s, OCOCH$_3$), 4.44 (4H, s, -CH$_2$-), 7.0-7.6 (8H,m, Ar-H).

Reaction of resorcinol 20 with saligenin 4 :

An equimolar mixture saligenin 4 (0.44 gms, 4.0 mmole) and resorcinol 20 (0.496 gms, 4.0 mmole) in dry xylene (5 mL) was refluxed for 14 hrs. At the end of this period the TLC pattern remained unchanged. Solvent was removed under reduced pressure, residue chromatographed over silica gel and eluted with EtOAc- pet.ether (2:8) to afforded 2,2',4'-trihydroxy diphenyl methane 21 as a white solid which was recrystallised from EtOAc, m.p. 202°C (84 mgs,33 %).

IR : $\nu_{\text{max}}$ (KBr) (fig. 3.11): 3220, 2420, 1605, 1500, 1300,1245,1070,1015, 745 cm$^{-1}$.

$^1$H NMR ( $\delta$ ppm,d$_6$-acetone,300 MHz ) (fig. 3.12): 3.82 (2H, s, Ar-CH$_2$-Ar), 6.30 (1H, dd, J=8.0,2.8 Hz, C$_6$-H), 6.40 (1H, d, J=2.0 Hz, C$_3$-H), 6.74 (1H, d, J=8.0 Hz, C$_5$-H), 7.01 (1H, ddd, J=8.0, 8.0, 2.0 Hz, C$_3$-H), 8.0-8.4 (3H, br.d, exchanges with D$_2$O, -OH).

$^{13}$C NMR ( $\delta$ ppm, d$_6$-acetone, 75 MHz, APT ) (fig. 3.13): 158 (s, C$_2$), 156 (s, C$_2'$), 155 (s, C$_4$), 132 (d, C$_6$), 131 (d, C$_4$), 129 (s, C$_1$), 128 (d, C$_6$), 120.5 (d, C$_3$), 119.5 (s,
Further elution with the same solvent afforded 3,5-di(o-hydroxy benzyl) resorcinol 22 as a white solid recrystallised from benzene m.p.193°C (81 mgs,11 %).

IR : $\nu_{\text{max}}$ (KBr) (fig. 3.14): 3200, 2420, 1595, 1490, 1295, 1250, 740 cm$^{-1}$.

$^1$H NMR ( $\delta$ ppm, $d_6$-acetone,300 MHz ) (fig. 3.15): 3.8 (4H, s), 6.44 (1H, s), 6.72 (1H, ddd, J=8.0, 8.0, 1.5 Hz), 6.80 (1H, dd, J=8.0, 1.5 Hz), 6.98 (1H, ddd, J=8.0, 8.0, 2.0 Hz), 7.04 (1H, s), 7.09 (1H, dd, J=8.0, 2.0 Hz), 8.4 (4H, br.s, exchanges with D$_2$O).

$^{13}$C NMR ( $\delta$ ppm, $d_6$-acetone, 75 MHz, APT ) (fig. 3.16): 153 (s), 152 (s), 133 (d), 131 (d), 129 (s), 128 (d), 120.5 (d), 119 (s), 118 (d), 103 (d), 30 (t).

Cyclodehydration of $\beta$-ionone : Preparation of a mixture of 31 and 32

$\beta$-Ionone 30(19.2 gms, 0.1 mole) was distilled over catalytic amount of iodine using magnetically stirred oil bath. To the distillate, powdered sodium thiosulphate was added, filtered through silica gel column and eluted with pet.ether to yield hydrocarbon fraction (15.8 gms, 91%) which was further purified by distilling over metallic sodium to give mixture of 31(77%) and 32(17%) by GLC.

Catalytic hydrogenation of 31 and 32 :

Hydrocarbon fraction (2.4 gms) was hydrogenated over 10% Pd-C (0.200 gms) in ethanol (15 mL) for 3 hr. The reaction product was filtered, residue washed with ethanol, concentrated and purified by column chromatography using pet.ether as eluent to yield 31(89% purity by GLC).
4,4,7-Trimethyl - 1- tetralone 33:
To a stirred solution of CAN (28.6 gms, 51.6 mmole) in (1:1:1) mixture of glacial acetic acid, ether and water (525 mL) was added ionene 31(1.5 gms, 8.6 mmole). After heating at 35°C on a water bath for 30 min., reaction mixture was allowed to cool and extracted with ether (3 x 100 mL). The combined organic extracts were washed with sat. NaHCO₃ solution, water and dried over anhydrous sodium sulphate. Evaporation of the solvent yielded yellow oil which was purified by column chromatography using benzene - pet. ether (3:7) to give 4,4,7-trimethyl - 1- tetralone 33(0.575 gms, 36%) as colourless oil.

IR : vₒₘₜ (film) : 2970, 1700, 1620, 1500, 1290, 1190, 820 cm⁻¹.

NMR (δ ppm,CDCl₃,300 MHz) : 1.44 (3H, s, C₄ - CH₃), 1.45 (3H, s, C₄ - CH₃), 2.00 (2H, t, J=7.0 Hz, C₃ - H), 2.34 (3H, s, Ar - CH₃), 2.70 (2H, t, J=7.0 Hz, C₂ - H), 7.31 - 7.34 (2H, m, C₅ - H and C₆ - H), 7.82 (1H, s, C₈ - H).

4,4,7-Trimethyl - 2 - oximino - 1- tetralone 34:
To a well cooled solution of 4,4,7-trimethyl - 1- tetralone 33(0.328 gms, 2 mmole) in ethanol (20 mL) was added conc. HCl (2 mL) and a solution of NaNO₂ (1 gms) in water (5 mL). After stirring at 5°C for 2 hr., ethanol was distilled off and reaction mixture was diluted with water, neutralised with saturated solution of NaHCO₃ and extracted with ether (3 x 50 mL). The combined organic extracts were washed with
water, dried over anhydrous sodium sulphate and concentrated to yield yellow oil. Chromatography over silica gel using benzene gave unreacted 4,4,7-trimethyl-1-tetralone 33 (0.137 gms). Further elution with EtOAc - benzene (1:4) yielded white solid which was recrystallised from benzene - pet. ether to afford 4,4,7-trimethyl-2-oximino-1-tetralone 34 (60 mgs, 48% based on recovered 33 m.p. 177°C (dec). IR $\nu_{\text{max}}$(KBr) (fig. 3.17): 3218, 1694, 1607, 1495, 1307, 947, 840 cm$^{-1}$.

$^1$HNMR (δ ppm, CDCl$_3$, 300MHz) (fig. 3.18): 1.38 (6H, s, C$_4$-CH$_3$), 2.39 (3H, s, Ar-CH$_3$), 3.00 (2H, s, C$_3$-H), 7.34 (1H, d, J=8Hz, C$_5$-CH$_3$), 7.40 (1H, dd, J=8.0, 2.44 Hz, C$_6$-H), 7.93 (1H, d, J=2.44 Hz, C$_8$-H), 11.44 (1H, -OH).

GCMS: m/z 201, 186 (100%), 159, 158, 143 and 115.

2-Hydroxy-4,4,7-trimethyl-1-(4H)-naphthalene 25:

A mixture of 4,4,7-trimethyl-2-oximino-1-tetralone 34 (30 mg, 0.14 mmole), glacial acetic acid (2mL), pyruvic acid (0.1 mL) and water (0.5 mL) was refluxed for 12 hr. The reaction mixture was then decomposed on ice and extracted with ether (3x10 mL). The combined organic extracts were washed with sat. NaHCO$_3$ soln., water and dried over anhydrous MgSO$_4$. Evaporation of the solvent yielded crude 25 which on recrystallisation (benzene) followed by sublimation afforded white needles of 2-hydroxy-4,4,7-trimethyl-1-(4H)-naphthalene 25 (15 mg, 54%), m.p. 117-118°C (lit.$^9$ 118°C).

IR $\nu_{\text{max}}$(KBr) (fig. 3.19): 3380, 2965, 1685, 1645, 1618, 1498, 1312, 1271, 1288, 829 cm$^{-1}$. 
$^1$HNMR (δ ppm, CDCl$_3$, 300MHz) (fig. 3.20): 1.48 (6H, s, C$_4$-CH$_3$), 2.42 (3H, s, Ar-CH$_3$), 6.18 (1H, s, C$_3$-H), 6.41 (1H, br.s, C$_2$-OH), 7.40 (1H, dd, J=8.2, 2.1 Hz, C$_6$-H), 7.46 (1H, J=8.1 Hz, C$_5$-H), 8.01 (1H, d, J=2.0Hz, C$_8$-H).

$^{13}$C NMR (δ ppm, CDCl$_3$, 75 MHz): 181.5 (C$_1$), 148.6 (C$_{10}$), 145.0 (C$_2$), 136.6 (C$_7$), 134.2 (C$_6$), 128.4 (C$_9$), 127.0 (C$_8$), 126.6 (C$_3$), 126.5 (C$_5$), 36.8 (C$_4$), 30.4 (C$_4$-CH$_3$), 30.4 (C$_4$-CH$_3$), 20.9 (C$_7$-CH$_3$).

GCMS: m/z 202 (M+), 187, 174, 173, 159 (100%), 115, 91.

2-Isobutyryl-Meldrums acid 47:

To a stirred solution of Meldrums acid 45 (1.44 gms, 0.01 mole) in dry CH$_2$Cl$_2$ (10mL) at 0°C, dry pyridine (1.6 mL, 0.02 mole) was added under nitrogen atmosphere, followed by addition of isobutyryl chloride 46 (1.2 mL, 0.011 mole). After stirring the reaction mixture for 1 hr at 0°C and 2 hr at room temp, it was decomposed on ice containing 2N HCl and diluted with CH$_2$Cl$_2$ (30 mL). The organic layer was then separated, washed with dil HCl (2 x 20 mL), water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave 2-isobutyryl-Meldrums acid 47 as yellow oil in quantitative yield which was used in the following experiment without further purification.

Isobutyryl acetic ester 44:

A solution of 2-isobutyryl Meldrums acid 47 (1.93 gms, 0.01 mole) in ethanol (20 mL) was refluxed for 3 hr and then ethanol was distilled out under reduced pressure.
Concentrated product was chromatographed over silica gel and eluted with EtOAc-pet ether (1:9) to yield isobutyryl acetic ester 44 (0.880 gms, 56%) as colourless oil.

**IR** : $\nu_{\text{max}}$ (film) (fig. 3.21): 2990, 1745, 1710,1620, 1470, 1310, 1220, 1055 cm$^{-1}$.

$^1$H NMR ( $\delta$ ppm, CDCl$_3$,300 MHz ) (fig. 3.22) : 1.13 (3H, d, $J$=7.0 Hz, C$_2$ - CH$_3$), 1.16 (3H, d, $J$=7.0 Hz, C$_2$ - CH$_3$), 1.26 (3H, t, $J$= 8 Hz, C$_7$ - CH$_3$), 2.62 (1H, s, C$_2$ - H), 3.48 (2H, septet, C$_5$ - H), 4.17 (2H, d, $J$= 8 Hz, C$_7$ - H).

2,4-Dihydroxy toluene 48 :

To a stirred solution of 2,4-dimethoxy toluene 43 (1.0 gm, 6.5 mmole) under nitrogen atmosphere in dry CH$_2$Cl$_2$ (25 mL) was added BBr$_3$ (4 mL, 26 mmole) in dry CH$_2$Cl$_2$ (45 mL) over a period of 45 minutes. After stirring for 15 hr at room temp, the reaction mixture was refluxed for 30 min, decomposed with moist EtOAc, ice and extracted with 2N NaOH. The aqueous layer was neutralised with dil HCl and extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were washed with brine, water and dried over anhydrous sodium sulphate. Removal of the solvent yielded dark oil which was chromatographed over silica gel and eluted with EtOAc-pet ether (4:6) to give white solid. Recrystallisation from CHC$_3$ afforded 2,4-dihydroxy toluene 48 (0.325 gms, 40%), m.p. 102 °C (lit 22 . 104 °C).

**IR** : $\nu_{\text{max}}$ (KBr): 3420, 1620, 1520, 1470, 1300, 1245, 1150, 1110, 1000, 960, 840, 790 and 620 cm$^{-1}$.

$^1$H NMR ( $\delta$ ppm, CDCl$_3$,300 MHz ) : 2.15 (3H, s, C, - CH$_3$), 4.75 (2H, br s, both -OH), 6.37 (2H, m, C$_3$- H and C$_6$ - H), 6.88 (1H, d, $J$= 6 Hz, C$_5$ - H).
7-Hydroxy-4-isopropyl-8-methylcoumarin 37:

To vigorously stirred conc. H$_2$SO$_4$ (1.0 mL) at 0°C, solution of 2,4-dihydroxy toluene 48 (0.124 gms, 0.1 mmole) and isobutyryl acetic ester 44 (0.158 gms, 0.1 mmole) was added slowly. After stirring for 1 hr at room temperature, the reaction mixture was diluted with cold water and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with sat. NaHCO$_3$ solution, brine, water and dried over anhydrous sodium sulphate. Evaporation of the solvent yielded crude yellow solid which was recrystallised from CHCl$_3$ - pet ether to give colourless needles of 7-hydroxy-4-isopropyl-8-methylcoumarin 37 (0.113 gms, 52%), m.p. 194°C (lit 16. 198°C).

UV : $\lambda_{max}$ (CH$_3$OH) : 330, 220, 204 nm.,

UV : $\lambda_{max}$ (CH$_3$OH + NaOAc) : 375, 220 nm.

IR : $\nu_{max}$ (KBr) (fig. 3.23) : 3120, 1680, 1608, 1530, 1400, 1390, 1315, 1285, 1270, 1155, 1105 cm$^{-1}$.

$^1$H NMR ($\delta$ ppm, CDCl$_3$, 300 MHz) (fig. 3.24) : 1.27 (6H, d, J=7 Hz, both C$_9$ - CH$_3$), 2.27 (3H, s, C$_6$ - CH$_3$), 2.45 (1H, br s, exchanges with D$_2$O, C$_7$ - OH), 3.25 (1H, septet, C$_9$ - H), 6.10 (1H, s, C$_3$ - H), 6.90 (1H, s, C$_8$ - H), 7.38 (1H, s, C$_5$ - H),

$^{13}$C NMR ($\delta$ ppm, CDCl$_3$, 75 MHz, APT) (fig. 3.25) : 16.0 (q, C$_6$ - CH$_3$), 21.9 (s each, both C$_9$ - CH$_3$), 28.6 (d, C$_9$), 102.3 (d, C$_8$), 106.4 (d, C$_3$), 111.1 (s, C$_{4a}$), 122.6 (s, C$_5$), 125.2 (d, C$_2$), 153.5 (s, C$_{4a}$), 158.9 (s, C$_4$), 163.5 (s, C$_7$), 163.5 (s, C$_2$).

HRMS : m/z 218 (M$^+$), 190, 175(100%).
4-Hydroxy-8-isopropyl-5-methylcoumarin (68):

A mixture of thymol (25 gms, 0.17 mole), malonic acid (17 gms, 0.17 mole), anhydrous ZnCl₂ (68 gms, 0.5 mole) and POCl₃ (45 mL, 3.5 mole) was stirred at 60-65°C for 35 hr. The reaction mixture was cooled to room temp. and decomposed on ice. The solid obtained was filtered and dissolved in 10% Na₂CO₃ solution, acidified with dil. HCl and extracted with ethyl acetate (3x 100 mL). The combined organic extracts were washed with brine, water and dried over anhydrous sodium sulphate. Evaporation of the solvent yielded a black solid which was chromatographed on silica gel and eluted with ethyl acetate -pet.ether (1:1) to yield a solid. Recrystallisation from EtOH afforded 4-hydroxy-8-isopropyl-5-methylcoumarin (68) (11.4 gms, 32%), m.p. 223°C (lit. 223-224°C).

4-Hydroxy-5-methylcoumarin (62):

To a stirred solution of 4-hydroxy-8-isopropyl-5-methylcoumarin (0.400 gms, 0.92 mmole) in chlorobenzene (13 mL), finely powdered anhydrous AlCl₃ (1.3 gms, 10 mmole) was added in portions over a period of 30 min. After heating at 95°C for 1 hr, the reaction mixture was cooled, poured on crushed ice containing some dil HCl and diluted with EtOAc. The organic layer was separated and extracted with saturated solution of NaHCO₃ (3x50 mL). Aqueous layer was then neutralised with dil HCl to give white gelatinous precipitate, which was filtered, washed with water and dried to yield 4-hydroxy-5-methylcoumarin (62) (0.210 gms, 65%) m.p. 235°C (lit. 233-234°C).
11-Methyl gerberinol 66:

Acetaldehyde (5mL) was added to a boiling solution of 4-hydroxy-5-methylcoumarin 62 (75 mgs, 0.43 mmole) in aqueous ethanol (3 mL). After refluxing the reaction mixture for 5 min excess of acetaldehyde and ethanol was distilled off to afford a solid which on repeated crystallisation from methanol gave white crystalline 11-methyl gerberinol 66 (48 mgs, 59%) m.p. 218°C (lit. 210-217°C).

IR : ν max (KBr) (fig. 3.28): 3009, 1686, 1655, 1599, 1560, 1409, 1383, 1365, 1331, 1280, 1232, 1134, 981, 866, 790 cm⁻¹.

¹H NMR (δ ppm, CDCl₃, 400 MHz) (fig. 3.29) : 1.85 (3H, d, J=7.55 Hz, C₁₁- CH₃), 2.80 (3H, s, C₅- CH₃), 2.81 (3H, s, C₅,- CH₃), 4.70 (1H, q, J=7.55 Hz, C₁₁-H), 7.10 (1H, dd, J=8.3 and 2.0 Hz, C₈-H), 7.12 (1H, dd, J=7.6 and 1.99 Hz, C₉-H), 7.20 (1H, d, J=8.3 Hz, C₆-H), 7.22 (1H, d, J=7.95 Hz, C₉-H), 7.39 (1H, dd, J=7.95 and 4.37 Hz, C₇-H), 7.43 (1H, dd, J=7.94 and 4.37 Hz, C₇-H), 11.86 (1H, br.s, exchanges with D₂O, -OH), 12.58 (1H, br.s, exchanges with D₂O, -OH).

¹³C NMR (δ ppm, CDCl₃, 100 MHz, DEPT) (fig. 3.30) : 15.1 (q, C₁₁- CH₃), 23.5 and 23.6 (q, C₅- CH₃ and q, C₅,- CH₃), 26.9(d, C₁₁), 106.5 and 106.8 (s, C₃ and s, C₇), 114.9 (d, C₈ and d, C₉), 116.0 (s, C₁₀ and s, C₁₀), 128.2 (d, C₆ and d, C₆), 131.5 and 131.7(d, C₇ and d, C₇), 138.5 (s, C₈ and s, C₉), 153.4 and 153.6 (s, C₅ and s, C₅), 167.2 and 167.6 (s, C₄ and s, C₄), 168.1 and 168.8 (s, C₂ and s, C₂).

HRMS : m/z 378(M⁺), 202, 176, 135(100%), 134, 106.
Anhydro-11-methyl gerberinol 71:

To a solution of 11-methyl gerberinol 66 (50 mgs, 0.13 mmole) in acetic anhydride (4 mL), a few drops of conc H₂SO₄ were added and warmed to give a clear solution, it was then left aside at room temperature for 24 hr. The white solid separated, was filtered and crystallised from CH₃OH-CHCl₃ (46 mgs, 98%), m.p. 283°C.

UV: λ max (CH₃OH) (fig. 3.32): 277, 300, 333 nm.

IR: ν max (KBr) (fig. 3.33): 1795, 1680, 1640, 1610, 1480, 1415, 1375, 1320, 1265, 1170, 1080, 1025, 790 and 780 cm⁻¹.

¹H NMR (δ ppm, CDCl₃, 400 MHz) (fig. 3.34): 1.49 (3H, d, J= 6.4 Hz, C₁₁-CH₃), 2.87 (3H, s, C₅-CH₃), 2.89 (3H, s, C₁₆-CH₃), 4.26 (1H, q, J=6.8 Hz, C₁₁-H), 7.14 (1H, d, J=7.6 Hz, C₈-H), 7.18 (1H, d, J=7.6 Hz, C₁₉-H), 7.24 (1H, d, J=8.4 Hz, C₆-H), 7.33 (1H, d, J=8.4 Hz, C₁₇-H), 7.44 (1H, dd, J=8.0 and 8.0 Hz, C₇-H), 7.52 (1H, dd, J=8.0 and 8.0 Hz, C₁₈-H).

¹³C NMR (δ ppm, CDCl₃, 100 MHz, DEPT) (fig. 3.35): 20.8 (q, C₁₁'-CH₃), 22.6 (q, C₅'-CH₃), 23.3 (q, C₁₆'-CH₃), 24.5 (d, C₁₁), 100.9 (s, C₁₄), 108.4 (s, C₉), 112.1 (s, C₂₁), 115.3 (d, C₈), 115.6 (d, C₁₉), 128.1 (d, C₆), 128.5 (d, C₁₇), 131.7 (d, C₇), 132.6 (d, C₁₈), 136.3 (s, C₅), 141.4 (s, C₁₆), 153.7 (s, C₉), 154.5 (s, C₂₀), 156.2 (s, C₄), 157.5 (s, C₁₃), 160.4 (s, C₂), 178.7 (s, C₁₅).
References: