Chapter 3

Tandem Wittig-Claisen-Cope rearrangements
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Introduction:
Since the first report of isolation of a simple coumarin from *coumarouna odorota* by Vogel in 1820, several coumarin derivatives have been isolated from the natural sources. Most of the natural coumarins contain oxygen functions at one or more positions in the benzene ring. A few coumarins are reported to have oxygen function at 3- and 4- positions. The nature of oxygen could be hydroxyl, alkoxy or glycosidic group. A large number of coumarins have oxygen at C-7 position, from which, umbelliferone (7-hydroxy coumarin), a widely distributed coumarin, is regarded as the parent compound. A common feature of most of the naturally occurring coumarins is the presence of isoprenoid chain, either intact or partially degraded or in the oxygenated form. Frequently the unit is a simple 3-methyl-enyl (prenyl) group. This group is present not only as the corresponding epoxide or glycol but also in a variety of oxidized and skeletally rearranged forms. Perhaps coumarins might be the best example of natural products exhibiting the greater number of biogenetic modifications of the simple isoprenoid unit.

Occurrence:
Coumarins are widely distributed in plants especially, those belonging to the *umbelliferae* and the *rutaceae* families. These compounds occur in all parts of the plants from roots to flowers and fruits. Several review articles have been published on natural plant coumarins.

Among different coumarins, 3-allylcoumarins form an important group of plant metabolites. Some of these compounds are mentioned below;
a) 3-allyl coumarin (1)

\[
\begin{align*}
1 & \quad R_1 \quad R_2 \quad R_3 \\
a & \quad H \quad OCH_3 \quad H & \quad Ruta graveolens^{12,13} \\
b & \quad H \quad OCH_3 \quad OCH_3 & \quad Ruta graveolens^{14-17} \\
c & \quad H \quad OH \quad OCH_3 & \quad Ruta graveolens^{14,18} \\
d & \quad OH \quad OCH_3 \quad H & \quad Ruta species^{19,20} \\
e & \quad OCH_3 \quad OCH_3 \quad H & \quad Ruta species^{22} \\
f & \quad H \quad CH_2OH \quad OCH_3 & \quad Ruta pinnata^{11}
\end{align*}
\]

b) Diallyl coumarins (2-5)

\[
\begin{align*}
2 & \quad R_1 \quad R_2 \\
a & \quad H \quad H & \quad Ruta graveolens^{21} \\
b & \quad H \quad CH_3 & \quad Ruta graveolens^{13} \\
c & \quad OCH_3 \quad H & \quad Ruta graveolens^{22}
\end{align*}
\]
3 Plant source: *Amyris balsamifera* \(^{23}\)

4 Plant source: *Ruta graveolens* \(^{22,24}\)

5 Plant source: *Coriaria nepalensis* \(^{25}\)

c) *Linear-dihydrofurocoumarins (6)*

6 Plant source

a R \(\text{H} \) *Ruta chalepensis* \(^{26,27}\)

b COCH\(_3\) *Ruta chalepensis* \(^{27}\)
d) Linear furocoumarin (7)

![Chemical structure of Linear furocoumarin](image)

7. Plant source: *Ruta chalepensis*[^27]

e) Chromeno-coumarins (8-10)

![Chemical structures of Chromeno-coumarins](image)

Plant source

8. *Boenninghausenia albiflora*[^28,29]

9. *Amyris simplicifolia*[^30]

10. *Ruta graveolens*[^22]

f) 4-oxygen substituted-3-allylcoumarins (11-13)

The coumarins 11 and 12 have been isolated from *Bothriocline repensis*[^31] while the coumarin 13 has been isolated from *Ferula communis*[^32]

[^27]: footnote
[^28]: footnote
[^29]: footnote
[^30]: footnote
[^31]: footnote
[^32]: footnote
g) 3-Prenyl coumarin (14)

14, Plant source: *Coriaria nephalensis*
Biogenesis of 3-allylcoumarins:

The similar structural features of many coumarins indicate common biogenesis. Biosynthesis of several coumarins have been studied sufficiently in detail, which indicate mevalonate pathway.\(^{33-36}\) There has been much interest in the biogenesis of coumarins bearing isoprenoid related substituents. Two pathways\(^{37,38}\) which are given below have been considered for 3-allylcoumarins.

Path A: starting from 7-oxygenated coumarin.

Path B: starting from 4-hydroxy coumarin.
Synthesis of 3-allylcoumarins:

Laboratory syntheses of natural coumarins have attracted considerable attention, since in many cases it presents the fascinating challenge of developing methods for the regiospecific introduction of appropriate substituents into the coumarin nucleus. Synthesis of 3-allyl coumarins is quite a formidable task as it involves regiospecific introduction of an allyl group at 3-position. Also their biological activities make them alluring. For example some of the natural derivatives of 3- (1',1'-dimethylallyl) coumarins are known to possess cytostatic and anti-leukemia properties\textsuperscript{39, 40}. Similarly, Chalepensin (7), chalepin (6a) and its acetate, rutamarin (6b) have been reported to exhibit promising spasmodytic activity \textit{in vitro}.\textsuperscript{41, 42}

Though there are several methods known for the syntheses of 3-substituted coumarin, only very few reports are available on the syntheses of 3-allylcoumarins.

Murray \textit{et al.}\textsuperscript{43} have synthesized 3-(1',1'-dimethylallyl)scopolletin from 6,7-dihydroxycoumarin by selective prenylation followed by methylation and Claisen rearrangement (Scheme I).

Kapil and coworkers\textsuperscript{44} have used similar approach for the syntheses of 3-allyl-7-hydroxycoumarin, which they have converted to xanthyletin (Scheme II).

Massanet \textit{et al.}\textsuperscript{45} have synthesized 3-(1',1'-dimethylallyl)coumarins chalepin (6a), rutamarin (6b) and gravelliferone from umbelliferone via Claisen and Cope rearrangement of 3',3'-dimethylallyl ethers of 6-(3',3'-dimethylallyl)umbelliferone with and without an iodine atom as blocking group at C-8.

Treatment of umbelliferone with iodine in ammonia gave 8-iodoumbelliferon, which was alkylated with 3-chloro-3-methyl-1-butyne to give 7-(1',1'-dimethylpropynyl)oxy)-8-iodocoumarin. Partial hydrogenation on BaSO\textsubscript{4}-Pd in toluene, yielded 7-(1',1'-dimethylallyl)oxy)-8-iodocoumarin which on Claisen rearrangement in DMA gave demethylsuberosin and osthelen.

When Claisen rearrangement was carried out in Ac\textsubscript{2}O/AcONa three products were obtained. Treatment of 8-iodo acetyldemethylsuberosin (C) with 3,3-dimethylallylbromide, in the presence of potassium carbonate in acetone, gave 6-(3',3'-dimethylallyl)-7-(3,3-dimethylallyl)oxy)-8-iodocoumarin which when heated
in DMA at 200°C gave gravelliferone (10%), demethylsuberosin (36%) and dihydrofurocoumarin 15 (36%). In this case the yield of gravelliferone obtained was very low therefore they tried different strategy. Thus, demethylsuberosin was subjected to o-prenylation with 3,3-dimethylallyl bromide in acetone to give 6-(3',3'-dimethyl allyl)-7-(dimethylallyloxy)coumarin. This when subjected to Claisen rearrangement in DMA at 200°C, gave gravelliferone (26%), demethylsuberosin (17%), and dihydrofurocoumarin 15 (57%) (Scheme III).

Ahluwalia et al.46 have synthesized few naturally occurring coumarins by making use of biogenetic approach (Scheme IV). Thus, 4-hydroxy coumarin is first prenylated, followed by Claisen rearrangement in acetic anhydride and sodium acetate combination. The 3-allylated-4-acetyl coumarin is then hydrolysed, tosylated which after reductive detosylation gave 3-(1', 1'-dimethylallyl)coumarin.

Cairns et al.47,48 have also synthesized 3-allyl and 6-allyl coumarin. Thus, balsamiferone and gravelliferone have been synthesized from demethylsuberosin using Claisen rearrangement. In their approach the protected 7-hydroxy coumarin is first converted into methyl coumarate, followed by allylation and then Claisen rearrangement to give demethylsuberosin (Scheme V). The balsamiferone was synthesized using 7-benzyloxy-6-prenyl coumarin, which was cleaved to give the methyl coumarate followed by allylation and then Claisen rearrangement in DMA (Scheme VI). Gravelliferone was synthesized (Scheme VII) using similar route described earlier by Massanet et al.45

Collado et al.49 have reported an efficient route for the synthesis of 3-(1',1'-dimethylallyl)coumarin. The key step involved is Ireland-Claisen rearrangement of allyl ester. Later on50 they extended this methodology for the synthesis of furano and pyrano 3-(1',1'-dimethylallyl)coumarin (Scheme VIII, IX).

Mali et al.51,52 have also developed tandem Wittig reaction-Claisen rearrangement and cyclisation route for the synthesis of 8-allyl (Scheme X) and 6-prenyl coumarin (Scheme XI). Using this approach they have accomplished synthesis of naturally occurring coumarins suberosin, toddaculin, o-methylapigravin, o-methylbalsamiferone, nieshoutin. Prior to that, from the same laboratory a
convenient method using Wittig reaction was reported for the synthesis of 3-allyl coumarins (Scheme XII).

Scheme I
Scheme II

A \xrightarrow{\text{Hydrolysis}} \text{Xanthyletin}

B (70%)

(25%)

(11%)

(31%)

C (53%)

\[ \text{Zn} \]

\[ \text{AcO} \]

\[ \text{Ac}_2\text{ONa} \]
Scheme III
Scheme IV

Scheme V
Scheme VI
Scheme IX

Scheme X

Scheme XI

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Present work:
Tandem Wittig reaction, double Claisen rearrangement and cyclisation:
An approach towards the synthesis of Gravelliferone, a naturally occurring 3-allyl coumarin.
Gravelliferone 2a is a naturally occurring coumarin having a 1,1-dimethylallyl group at 3-position & 3,3-dimethylallyl group at 6-position of 7-hydroxy coumarin and it is the precursor for the coumarins 2b, 6, 7, 8 and 10. Most of the reported synthetic methods described above use Claisen rearrangement on the preformed coumarin nucleus. The method reported by Mali et al. (Scheme X) is an attractive method to get allyl substituent at 3-position. But to prepare the corresponding phosphorane so as to get 1’,1’-dimethylallyl group at 3-position of coumarin ring is a difficult task.
We envisaged the use of tandem Wittig reaction double Claisen Cope rearrangement on 2,4-diprenyloxybenzaldehyde 16 for the synthesis of gravelliferone (Scheme XIII). The rational behind this was based on reported synthesis of gravelliferone (Scheme III) and 3-(1’,1’-dimethylallyl)scopolletin (Scheme I), wherein 7-allyloxy coumarin on consecutive Claisen and two Cope rearrangements introduce 1’,1’-dimethylallyl group at 3- position of the coumarin. Thus it was visualized that 2,4-diprenyloxybenzaldehyde 16 on Wittig reaction would give coumarate ester 17 which subsequently would undergo preferentially
Claisen rearrangement of 2-prenyloxy group of 17 to give 7-prenyloxy-6-prenylcoumarin 18, the driving force for this reaction was assumed to be steric decongestion and cyclisation to coumarin nucleus. Further, it was expected to follow the reaction pathway as reported in literature\(^4^8\) (Scheme VII). The plausible mechanism for the proposed route to gravelliferone is shown in Scheme XIV.

Scheme XIII
Plausible mechanism:

A complete array of all possible isomers that could be formed from 17 based on deallylation, abnormal and normal Claisen rearrangement followed by further cyclisation of rearranged products are shown below (Fig I).
Thus the first step was the preparation of resorcialdehyde. This was obtained by Vilsmeier-Haack reaction on resorcinol. Resorcialdehyde was then treated with prenyl bromide (3,3-dimethylallyl bromide) (Prepared from 4-hydroxy-2-methylbut-2-ene by treating with phosphorous tribromide) in refluxing acetone in the presence of potassium carbonate. Usual workup gave a viscous liquid, which was purified by column chromatography over silica gel to get a pure sticky solid. It showed a negative FeCl₃ test.

In its IR spectrum it showed a band at 1675 cm⁻¹ indicating the presence of carbonyl group of aldehyde.

In its ¹H NMR (CDCl₃) spectrum two singlets (6H, each) were seen at δ 1.75 & 1.77 indicating the presence of four methyl groups attached to olefin [2 X =C(CH₃)₂]. A triplet (4H, J = 5.80 Hz) was seen at δ 4.58, which could be assigned to two methylene of two –CH₂CH=CMe₂ groups. A multiplet (2H) at δ 5.5 could
be due to the presence of two olefinic protons of two CH=CH(CH₃)₂ groups. A broad singlet (1H) was seen at δ 6.48. This could be due to the 3-H proton of the aromatic ring. Two doublets (J = 1.8 Hz & 8.7 Hz) at δ 6.55 and δ 7.81 could be assigned to 5-H & 6-H aromatic protons. A singlet at δ 10.3 integrating for a single proton could be due to the presence of the aldehydic proton. Thus on the basis of mode of formation & spectral properties structure 16 was assigned to it.

Once we prepared 2,4-diprenyloxybenzaldehyde 16, our next step was to carry out Wittig reaction, double Claisen, and Cope rearrangement and cyclisation in one pot.

Initially we tried one pot reaction by refluxing 2,4-diprenyloxybenzaldehyde with stable phosphorane (Ia) in refluxing DMA for 6 h. Usual work up gave a complex mixture, which was subjected to column chromatography over silica gel. From the complex mixture we could isolate one pure compound 15 (Scheme XV).

The compound 15 in its IR spectrum showed a band at 1725 cm⁻¹ indicating the presence of carbonyl group of coumarin.

In its ¹H NMR (CDCl₃) spectrum (Fig 1a) a doublet (3H, J = 6.6 Hz) at δ 1.42 indicated the presence of a methyl group on a methine carbon. Four singlets (3H each) at δ 1.57, 1.58, 1.71, 1.77 indicated the presence of four methyl groups attached to quaternary carbons of R₂-C-(CH₃)₂ or an olefinic carbon of [-C(CH₃)₂] group. One doublet (2H, J = 7.2 Hz) and one multiplet (1H) were seen at δ 3.29 & 5.29 which could be assigned to =CHCH₂ grouping. One quartet (1H, J = 6.6 Hz) was seen at δ 4.50 which could be assigned to –OCH group flanked by adjacent methyl group. Similarly, the signals at δ 6.17 (1H, d, 9.3 Hz) & 7.60 (1H, d, 9.3
The structure is further confirmed by $^{13}$C NMR and DEPT 135 spectra (Fig1b) peaks at $\delta$ 14.16 (q) & $\delta$ 17.71 (q) could be assigned to two methyl carbons attached to the quaternary carbon observed at $\delta$ 44.38 (s) ((R)$_2$C(CH$_3$)$_2$). Peak at $\delta$ 20.97 (q) could be assigned to methyl carbon attached to a quaternary carbon, which is observed at $\delta$ 90.09 (d). Peaks at 25.33 (q) & 25.68 (q) could be assigned to methyl carbons attached to the quaternary olefinic carbon of =C(CH$_3$)$_2$ group. Peaks at 111.66 (d, CH) & 27.16 (t, CH$_2$) could be assigned to carbons of =CHCH$_2$ grouping. Peaks at 120.99 (d), 127.33 (d), & 144.27 (d) could be assigned to aromatic methine carbons and two olefinic carbons of the lactone ring. The quaternary carbon appearing at 113.09 (s), 121.25 (s), 121.80 (s), 133.58 (s), 150.04 (s) and 160.32 (s) could be attributed to unsaturated carbon of alkene & aromatic carbons respectively.

HRMS of the compound confirmed its elemental composition to be C$_{19}$H$_{22}$O$_3$ (Obsvd, m/z 299.1645 for [M+H]$^+$ Calcd: 299.1647).

Thus on the basis of mode of formation & spectral properties, structure 15 was assigned to it. The spectral properties exhibited by this compound are identical with that of the reported values for 8,9,9-trimethyl-6-(3-methylbut-2-enyl)-8,9-dihydro-2H-furo[2,3-h]chromen-2-one. The structure was further confirmed by
its similarity of the melting point 136-137°C with the lit.* m.p. 136-139°C. The yield of the compound was found to be 30.10%.
The formation of angular dihydrofurocoumarin 15 indicated that indeed as expected Wittig reaction, double Claisen rearrangement and cyclisation did take place in a single step. Also the angular dihydrofurocoumarin being major product of both the reported synthesis by Cairns,48 and Massanet,45 we thought that if we repeat the reaction we may get gravelliferone also. Using DMA as a solvent we repeated the reaction several times, but every time we got only compound 15. The other complex mixture we could not separate properly for any meaningful structural analysis.

So we thought of changing solvent to diphenyl ether as it has got higher boiling point and also it can be separated from reaction mixture in a better way by using column chromatography.

Thus 2,4-prenyloxybenzaldehyde was reacted with stable phosphorane in refluxing diphenyl ether for 6 h. Separation of the reaction mixture by column chromatography over silica gel provided two pure compounds (Scheme XVI). One of these products was angular dihydrofurocoumarin (15) obtained in 53.02% yield.

Based on the mode of formation & spectral properties mentioned below, structure 19 was assigned to the second compound.

IR (v_{max}): 3200 cm\(^{-1}\) (OH), 1725 cm\(^{-1}\) (CO).

\(^1\)H NMR (CDCl\(_3\), 300 MHz): (Fig 2a)
| δ 1.75  | s    | 3H | CH$_3$ |
| δ 1.79  | s    | 3H | CH$_3$ |
| δ 3.38  | d (J = 7.2 Hz) | 2H | CH$_2$-CH= |
| δ 5.31  | t (J = 7.2 Hz) | 1H | CH$_2$-CH= |
| δ 6.24  | d (J = 9.3 Hz) | 1H | CH=CH-CO |
| δ 6.76  | s    | 1H | Ar-OH |
| δ 7.00  | s    | 1H | 5-H |
| δ 7.21  | s    | 1H | 8-H |
| δ 7.67  | d (J = 9.3 Hz) | 1H | CH=CH-CO |

$^{13}$C NMR and DEPT 135 (CDCl$_3$) (Fig 2b): δ 17.83 (q, CH$_3$), 25.80 (q, CH$_3$), 28.03 (t, CH$_2$-CH=), 102.77 (d, CH$_2$-CH=), 111.98 (d, CH=CH-CO), 112.00 (s), 121.25 (d, C$_{ArH}$), 126.39 (s), 128.14 (d, C$_{ArH}$), 134.27 (s), 144.72 (d, CH=CH-CO), 154.02 (s), 158.88 (s), 162.95 (s, CO). HRMS of the compound confirmed its elemental composition to be C$_{14}$H$_{14}$O$_{3}$ (Obsvd, m/z 231.1022 for [M+H]$^+$ Calcd: 231.1021).

Fig 2a

![Chart](image-url)
The spectral properties exhibited by this compound are identical to that of the naturally occurring 6-allyl coumarin (Demethylsuberosin). The structure was further confirmed by its similarity of melting points (observed: 134°C, lit\textsuperscript{48} m.p. 133-134°C). The yield of the product was found to be 12.35%, [combined yield 65.37%]. In the formation of demethylsuberosin, Wittig reaction, Claisen rearrangement of the ortho-prenyloxy coumarate ester (Wittig product), cyclisation and deprenylation of 7-prenyloxy group took place in a tandem manner.

Encouraged by the increased yield of 15 and finding 19 being also formed in the reaction we repeated the reaction several times in search of gravelliferone. But not in a single case we could isolate any other product in pure form. We thought that, this could either be due to the presence\textsuperscript{55} of triphenylphosphine oxide in the reaction mixture which may be preventing conversion of speculated intermediate 18 or 18 was not at all the intermediate.

To check whether triphenylphosphine oxide was affecting the course of reaction, we thought of carrying out the Wittig reaction separately and isolating the intermediate and subjecting it further for Claisen rearrangement conditions.
Thus 2,4-diprenyloxybenzaldehyde was treated with Wittig reagent triphenyl-α-ethoxycarbonyl-methylene phosphorane in refluxing toluene for 8 h (monitored by TLC). Purification by column chromatography gave a sweet smelling viscous oil (Scheme XVII).

Based on the mode of formation & spectral properties mentioned below, structure \textbf{17} was assigned to the compound. Based on the coupling constant ($J = 16.1$ Hz) of the vinylic double bond and the downfield nature of the β-proton indicated that it could be the \textit{trans} ester (Yield = 85%).

IR ($\nu_{\text{max}}$): 1725 cm$^{-1}$ (CO).

$^1$H NMR (CDCl$_3$, 400 MHz): (Fig 3a)

<table>
<thead>
<tr>
<th>$\delta$</th>
<th>$^1$H NMR (CDCl$_3$, 400 MHz)</th>
<th></th>
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<tbody>
<tr>
<td>1.34</td>
<td>t ($J = 7.1$ Hz)</td>
<td>3H</td>
<td>OCH$_2$CH$_3$</td>
</tr>
<tr>
<td>1.76</td>
<td>s</td>
<td>3H</td>
<td>CH$_3$</td>
</tr>
<tr>
<td>1.78</td>
<td>s</td>
<td>3H</td>
<td>CH$_3$</td>
</tr>
<tr>
<td>1.82</td>
<td>s</td>
<td>3H</td>
<td>CH$_3$</td>
</tr>
<tr>
<td>1.84</td>
<td>s</td>
<td>3H</td>
<td>CH$_3$</td>
</tr>
<tr>
<td>4.26</td>
<td>q ($J = 7.1$ Hz)</td>
<td>2H</td>
<td>OCH$_2$CH$_3$</td>
</tr>
<tr>
<td>4.56</td>
<td>2 X d ($J = 6.75$ &amp; 6.4 Hz)</td>
<td>4H</td>
<td>2 X CH$_2$-CH=</td>
</tr>
<tr>
<td>5.50</td>
<td>m</td>
<td>2H</td>
<td>2 X CH$_2$-CH=</td>
</tr>
<tr>
<td>6.48</td>
<td>br s</td>
<td>1H</td>
<td>3-H</td>
</tr>
<tr>
<td>6.55</td>
<td>dd ($J = 8.7$ &amp; 1.8 Hz)</td>
<td>1H</td>
<td>5-H</td>
</tr>
<tr>
<td>7.40</td>
<td>d ($J = 8.7$ Hz)</td>
<td>1H</td>
<td>6-H</td>
</tr>
<tr>
<td>7.44</td>
<td>d ($J = 16.1$ Hz)</td>
<td>1H</td>
<td>CH=CH-CO</td>
</tr>
<tr>
<td>7.97</td>
<td>d ($J = 16.1$ Hz)</td>
<td>1H</td>
<td>CH=CH-CO</td>
</tr>
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</table>
When the trans ester 17 was heated in diphenyl ether or DMA, we were not able to isolate gravelliferone from the reaction mixture though the other two products (15 & 19) could be isolated.

Thus, it was clear that the triphenylphosphine oxide was not affecting the formation of gravelliferone. So, we thought that may be 18 is not an intermediate in the domino sequence. The reaction may be following a different course as shown in scheme XVIII. Wittig reaction, followed by para Claisen rearrangement of the 2'-prenyloxy group, followed by ortho Claisen of the 4'-prenyloxy group, cyclisation of tetrahydrofuran ring and then formation of furan ring. The other possible route was first ortho Claisen rearrangement of the Wittig product, followed by either cyclisation of tetrahydrofuran ring and para Claisen rearrangement or para Claisen rearrangement and then cyclisation of tetrahydrofuran ring and lastly the formation of coumarin nucleus (Scheme XIX).

So, we decided to carry out the reaction for a short duration of time and see whether we could isolate any reaction intermediate in the course of reaction.

Scheme XVIII
Scheme XIX

Fig 3a
Thus 2, 4-diprenyloxybenzaldehyde, upon refluxing with the stable phosphorane in diphenyl ether (20 min) yielded a complex mixture, which was purified by chromatography over silica gel. We could isolate four pure compounds (Scheme XX) from the above crude mixture, including the previously reported three compounds, 15 (10%), 17 (22%), 19 (5.07%) and two new compounds 18 and 20.

The compound 18 (yield: 29.9%) in its IR spectrum showed a band at 1725 cm$^{-1}$ indicating the presence of a carbonyl group of coumarin.

In its $^1$H NMR (CDCl$_3$) spectrum (Fig 4a) two singlets (12H, 6H each) at $\delta$ 1.69 & $\delta$ 1.80 indicated presence of four allylic methyl groups. The mutually coupled signals at $\delta$ 3.3 (2H, d, $J = 7.4$ Hz) & $\delta$ 5.29 (1H, t, $J = 7.4$ Hz) and $\delta$ 4.59 (1H, d, $J = 7.4$ Hz) & $\delta$ 5.46 (1H, t, $J = 7.4$ Hz) could be assigned to $-\text{CH}_2\text{CH}=\text{O}$ and $\text{OCH}_2\text{CH}=\text{O}$ groupings of the side chains. The coumarin ring protons 3-H, 4-H, 5-H and 8-H were seen at $\delta$ 6.30 (1H, d, $J = 9.45$ Hz), 7.6 (1H, d, $J = 9.45$ Hz), 6.76 (1H, s) and 7.17 (1H, s), as expected. The above spectral properties were identical to that of 6-(3-methylbut-2-enyloxy)-7-(3-methylbut-2-enyloxy)coumarin. The structure was further confirmed by comparing their melting points (Observed: 78-79$^0$C, lit$^{48}$: 78-79$^0$C). Thus, on the basis of mode of formation & spectral properties structure 18 was assigned to it.
Isolation of 18 as one of the reaction products indicates that our initial hypothesis of 2’-prenyloxy group undergoing a Claisen rearrangement followed by coumarin ring formation was not entirely wrong. As 18 is a known intermediate in the synthesis of the natural product gravelliferone, the above reaction thus constitutes a formal synthesis of gravelliferone.

The compound 20 (yield = 1.8%), in its IR spectrum showed a band at 1725 cm⁻¹ indicating the presence of carbonyl group of coumarin.

In its ¹H NMR spectrum (Fig 5a) the signals at δ 1.70 (3H, s) & 1.78 (3H, s) and 1.82 (6H, s) indicated presence of four methyl groups, possibly as two –CH₂CH=C(CH₃)₂ groups. The pair of mutually coupled signals at δ 3.24 (2H, d, J = 6.9 Hz) & 5.32 (1H, m) and 4.57 (2H, d, J = 6.9 Hz) & 5.49 (1H, m) could be assigned to methylene and olefinic protons of –CH₂CH= and –OCH₂CH= groups respectively. In addition to this one multiplet (2H) was seen in the aromatic region, which could be attributed to 6-H and 8-H protons of coumarin ring. A doublet at δ 7.33 (J = 9.0 Hz) was seen due to 5-H proton. The 4-H protons appeared at δ 7.40. The absence of 3-H (around δ 6.5) proton of coumarin nucleus and the appearance of 4-H proton as a singlet indicated presence of prenyl group at 3-position of coumarin nucleus.

The structure is further supported by ¹³C NMR and DEPT 135 data (Fig 5b) peaks at 17.82 (q), 18.27 (q), 25.80 (q), could be assigned to the four CH₃ groups of –CH=C(CH₃)₂. Peaks at 101.20 (d), 112.93 (d), & 28.67 (t), 65.33 (t) could be assigned to carbons of =CHCH₂ and =CHCH₂O groups respectively. Peaks at 118.83 (d), 119.48 (d), 128.00 (d), & 138.14 (d) could be assigned to the aromatic methine carbons. The quaternary carbon signals at 100.00 (s), 113.19 (s), 120.00 (s), 125.22 (s), 135.36 (s), and 139.00 (s) could be attributed to unsaturated carbons of alkenes & the benzene ring. The Peak at 162.90 (s) could be assigned to carbonyl carbon of coumarin.

HRMS of the compound confirmed its elemental composition to be C₁₉H₂₂O₃ (Obsvd, m/z 299.1637 for [M+H]⁺ Calcd: 299.1647).

Based on the above spectral data structure 20 was assigned to it.
The plausible mechanism for the formation of 20 is shown in scheme XXI.
As the compound 20 has not been reported earlier, we thought of confirming its structure by an unambiguous synthesis (Scheme XXII). The steps involved are selective monoprenylation of resorcinol followed by treatment with stable phosphorane having prenyl group and then photocyclisation.
Thus, resorcialdehyde was treated with prenyl bromide and potassium carbonate in refluxing acetone, filtration followed by removal of solvent gave crude 21. Further purification of compound 21 by column chromatography using hexanes and ethyl acetate as an eluents (9.5:0.5) gave sweet smelling yellow liquid.

Based on the mode of formation & spectral properties mentioned below, structure 21 was assigned to the compound. The yield was found to be 70.29%.

IR (v max): 1650 cm\(^{-1}\) (CO).

\(^1\)H NMR (CDCl\(_3\), 300 MHz):

| \(\delta\)  |  |  |  |  |
|---|---|---|---|
| 1.71 | s | 3H | CH\(_3\) |
| 1.81 | s | 3H | CH\(_3\) |
| 4.50 | d (J = 7.1 Hz) | 2H | CH\(_2\)-CH= |
| 5.48 | t (J = 7.1 Hz) | 1H | CH\(_2\)-CH= |
| 6.55 | d (J = 8.7 Hz) | 1H | 5-H |
| 7.43 | d (J = 8.7 Hz) | 1H | 6-H |
| 6.43 | s | 1H | 3-H |
| 11.43 | s | 1H | Ar-CHO |
4-prenyloxy-2-hydroxybenzaldehyde, upon heating with Wittig reagent 22, in toluene, for 5 h, followed by purification by column chromatography gave a viscous liquid.

The strong IR (KBr) peak at 1720 cm\(^{-1}\) indicated the presence of the ester group. Its \(^1\)H NMR (CDCl\(_3\)) spectrum showed four singlets (3H, each) at \(\delta\) 1.62, 1.72, 1.76 and 1.81 indicating the presence of four methyl protons of two \(-\text{C(CH}_3\text{)}_2\) groups. One triplet and one quartet at \(\delta\) 1.30 (3H, \(J = 7.2\) Hz) and 4.27 (2H, \(J = 7.2\) Hz) could be attributed to methyl and methylene protons of OCH\(_2\)CH\(_3\) group. Two doublets (\(J = 6.6\) Hz) integrating for two protons each and two multiplets integrating for one proton and two protons were seen at \(\delta\) 3.10, 4.52 and 5.15, 5.52 could be attributed to methylene and olefinic protons of two \(-\text{CH}_2\text{CH}=\) groups and a phenolic \(-\text{OH}\) group. One meta coupled doublet (\(J = 2.1\) Hz) for 6-H proton of the benzene ring was seen at \(\delta\) 6.47. The 4-H appeared as a doublet of a doublet (\(J = 8.7\) & 2.1 Hz) at \(\delta\) 6.52. The ortho coupled doublet (\(J = 8.7\) Hz) appearing at \(\delta\) 7.16 was assigned to 3-H. The downfield singlet at \(\delta\) 7.79 was due to the \(\beta\)-proton of the unsaturated ester. The structure is further supported by \(^{13}\)C NMR and DEPT 135 spectra. Thus, peaks at 17.94 (q), 18.19 (q), 25.76 (q), 25.81 (q) could be attributed to four methyl carbons of two \(-\text{C(CH}_3\text{)}_2\) groups. Peaks at 14.29 (q) and 27.21 (t) could be attributed to carbons of methyl and methylene of OCH\(_2\)CH\(_3\) group. Peak at 60.88 (t), 64.87 (t), 102.14 (d), 107.17 (d) could be attributed to two methylene and two olefinic carbons of two \(-\text{CH}_2\text{CH}=\) group. Peak at 133.50 (d) could be attributed to \(\beta\)-olefinic carbon of the ester. Peaks at 119.35 (d), 121.63 (d), and 130.67 (d) could be attributed to aromatic methine carbons. The quaternary carbons appearing at 115.33 (s), 133.06 (s), 138.46 (s), 155.19 (s), 160.58 (s) could be attributed to unsaturated alkene carbons and aromatic carbons. Peak at 168.60 (s) could be attributed to carbonyl carbon of ester group.

The mode of formation and spectral properties exhibited by the compound suggested that it could be ester having structure 23. The yield was found to be 70.60%.
The compound 23 was photocyclised (sunlight) in benzene for 6 h. Purification by column chromatography gave compound 20 in 80% yield. The physical and spectral properties of the compound were identical with that of the product obtained in tandem studies.

Though isolation of 18 and 20 supported our initial line of thinking that 2-prenyloxy group is undergoing Claisen rearrangement followed by coumarin ring formation yet we could not isolate gravelliferone. Perhaps, it is formed in very less yield and we are not able to isolate it. Isolation of the intermediates shown in scheme XVIII and XIX indicate that the reaction is proceeding through the pathways mentioned therein, at least partly. Here we could do the Wittig reaction, double Claisen rearrangement, double cyclisation in tandem manner.

As we had successfully carried out tandem Wittig reaction double Claisen Cope rearrangement, we thought to check the generality of this sequence (Scheme XXIII).

Thus we initially treated phosphorane (24) with 2, 4-diprenyloxybenzaldehyde (15) in refluxing diphenyl ether for 6 h. The product was purified by column chromatography over silica gel (8:2 hexanes and ethyl acetate). We could isolate only one compound in pure form (Scheme XXIV) from mixture of products.
Based on the mode of formation & spectral properties mentioned below, structure 26 was assigned to the compound (yield = 40%).

IR ($\nu_{\text{max}}$): 1725 cm$^{-1}$ (CO).

$^1$H NMR (CDCl$_3$, 300 MHz): (Fig 6a)

<table>
<thead>
<tr>
<th>$\delta$</th>
<th>$^1$H</th>
<th>$^1$H</th>
<th>$^1$H</th>
</tr>
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<tr>
<td>1.79</td>
<td>s</td>
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<td>3.28</td>
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<td>CH$_2$-CH=</td>
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<td>d ($J = 6.9$ Hz)</td>
<td>2H</td>
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<td>m</td>
<td>1H</td>
<td>CH$_2$-CH=CH$_2$</td>
</tr>
<tr>
<td>5.31</td>
<td>t ($J = 6.9$ Hz)</td>
<td>1H</td>
<td>CH$_2$=CH=</td>
</tr>
<tr>
<td>5.96</td>
<td>m</td>
<td>2H</td>
<td>CH$_2$-CH=CH$_2$</td>
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<tr>
<td>7.47</td>
<td>s</td>
<td>1H</td>
<td>CH=CH-CO</td>
</tr>
</tbody>
</table>

$^{13}$C NMR and DEPT 135 (CDCl$_3$) (Fig 6b): $\delta$ 14.11 (q, CH$_3$), 25.81 (q, CH$_3$), 28.33 (t, CH$_2$-CH=), 34.28 (t, CH$_2$-CH=CH$_2$), 102.72 (d, CH$_2$-CH=), 112.73 (s), 121.23 (d, CH$_2$-CH=CH$_2$), 117.74 (t, CH$_2$-CH=CH$_2$), 123.38 (s), 125.64 (s), 127.64 (d, C$_{Ar}$H), 134.27 (d, C$_{Ar}$H), 134.70 (s), 140.10 (d, C=CH=CH-CO), 153.00 (s), 157.62 (s), 162.99 (s, CO).

HRMS of the compound confirmed its elemental composition to be C$_{17}$H$_{18}$O$_3$ (Obsvd, m/z 309.1104 for [M+K]$^+$ Calcd: 309.0893).

It was interesting to observe that this time the major product isolated was of single Claisen rearrangement with the prenyl group on C-4 oxygen being knocked off during the reaction. Was it due to introduction of one more substituent at 3 positions? To check this we treated 2,4-diprenyloxybenzaldehyde with benzyl phosphorane 27 in refluxing diphenyl ether for 6 h (Scheme XXV). The product
was purified by column chromatography over silica gel, we could isolate one pure compound 28 from mixture of products.

Scheme XXV

The compound 28 (yield = 41%) in its IR spectrum showed a band at 1725 cm\(^{-1}\) indicating the presence of carbonyl group of coumarin.

In its \(^1\)H NMR (CDCl\(_3\)) spectrum (Fig 7a) the signal at δ 1.36 (6H, s) indicated the presence of gem dimethyl group, -C(CH\(_3\))\(_2\). The triplets at δ 1.83 (J = 6.6 Hz), and 2.79 (J = 6.6 Hz) could be assigned to protons of two methylene groups of pyran ring, while the singlet at δ 3.86 (2H) could be attributed to the methylene of benzyl group. In the aromatic region, the signals at δ 7.33 (1H, s), 7.00 (1H, s), 7.16 (1H, s) & 7.36 (5H, m) were assigned to 4-H, 5-H, 8-H & benzene ring respectively.

In its \(^{13}\)C NMR spectrum (Fig 7b) peak at 26.86 (q) could be assigned to two methyl groups. Peaks at 21.9 (t), 32.45 (t) and 36.37 (t) could be assigned to methylene carbons of pyrano and benzylic group respectively. Peaks at 104.16 (d), 126.64 (d), 127.72 (d), 128.67 (d), 129.34 (d), 139.45 (d) could be assigned to aromatic methine carbons. The quaternary carbon appearing at 75.57 (s), 112.72 (s), 118.27 (s), 125.35 (s), 138.28 (s), 152.99 (s), and 156.87 (s) could be attributed to unsaturated carbons of alkene & benzene ring system, while the signal at 162.30 (s) was assigned to carbonyl carbon of coumarin. The multiplicities of carbon signals mentioned were obtained from DEPT 135 experiment.

HRMS of the compound confirmed its elemental composition to be C\(_{21}\)H\(_{20}\)O\(_3\) (Obsvd, m/z 343.1318 for [M+Na]+ Calcd: 343.1310).

Thus on the basis of mode of formation & spectral properties structure 28 was assigned to it.
Interestingly the above reaction (Scheme XXV) also, the product was a deallylated product, with the rearranged prenyl group undergoing cyclisation to pyrano ring. Having observed that substitution at 3 position of the coumarin may lead to the knocking off of the prenyloxy group at C-7 prompted us to check the feasibility of one step synthesis of balsamiferone 3, a naturally occurring coumarin, isolated\textsuperscript{23} from \textit{Amyris balsamifera}.

As mentioned earlier (Scheme V) Cairns\textsuperscript{48} \textit{et al.} have initially reported difficulty in debenzylation of 7-bezyloxy-3,6-diprenylcoumarin due to formation of a cyclised product. Later on same authors reported successful debenzylation at -50°C using BCl\textsubscript{3} to get balsamiferone. Mali \textit{et al.}\textsuperscript{53} have reported the synthesis of methyl ether of balsamiferone but its conversion to balsamiferone is not reported.
Kapil et al.\(^\text{57}\) have reported synthesis of balsamiferone from 3-(3,3-dimethylallyl)-7-hydroxy coumarin. Condensation of 3-(3,3-dimethylallyl)-7-hydroxy coumarin with 2-chloro-2-methylbut-3-yn in the presence of potassium carbonate and KI gave corresponding propargyl ether which on catalytic hydrogenation afforded I. Claisen rearrangement of I in the presence of butyric anhydride, followed by alkaline hydrolysis gave balsamiferone in 10% overall yield along with two more compounds (Scheme XXVI).

As described earlier Cairns et al.\(^{47,48}\) made use of propynylic ether of umbelliferone to get demethylsuberosin which was subsequently converted to 3,6-diprenyl-7-hydroxycoumarin (Balsameferone) (Scheme V).

Mali et al.\(^{58}\) have synthesized methyl ether of balsamiferone using tandem Wittig and Claisen rearrangement (Scheme XXVII).
HO
H3C—CH3
'. CI
CH3
H3C
H3C
K2CO3, acetone
Nal
H2, Pd/C
BaSO4
H2, Pd/C
BaSO4
reflux
ii) butyric anhydride
ii) hydrolysis

Scheme XXVI

MeO
O
CHO
H2C—CH3
H2C—CH3
Ph3P
COOEi
DMA
H3C
H3C
MeO
O
H3C
H3C
H3C
H3C
H3C

Scheme XXVII
Our strategy for the synthesis of balsamiferone, based on the earlier observation of selective deprenylation during tandem Wittig-Claisen rearrangement, is given in the scheme XXVIII below.

Thus, 2,4-diprenyloxybenzaldehyde was subjected with prenylphosphorane in refluxing diphenyl ether for 6 h. The crude reaction product was purified by chromatography over a silica gel column. We could isolate only one compound in pure form, from the complex reaction mixture.

Based on the mode of formation & spectral properties mentioned below, structure 3 (Balsamiferone) was assigned to the compound (yield = 42%).

IR (v_max): 1725 cm⁻¹ (CO), 3419 cm⁻¹ (-OH).

^1H NMR (CDCl₃, 300 MHz): (Fig 8a)

<table>
<thead>
<tr>
<th>δ</th>
<th>Multiplicity</th>
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<tbody>
<tr>
<td>1.71</td>
<td>s</td>
<td>3H</td>
</tr>
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<td>1.76</td>
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<td>s</td>
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</tr>
<tr>
<td>1.81</td>
<td>s</td>
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<tr>
<td>3.23</td>
<td>d (J = 6.9 Hz)</td>
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<tr>
<td>5.30</td>
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<tr>
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<tr>
<td>7.16</td>
<td>s</td>
<td>1H</td>
</tr>
<tr>
<td>7.41</td>
<td>s</td>
<td>1H</td>
</tr>
</tbody>
</table>
$^1$H NMR and DEPT 135 (CDCl$_3$): δ 17.82 (q, 2 × CH$_3$), 25.82 (q, 2 × CH$_3$), 28.46 (t, CH$_2$-CH=CH$_2$), 28.58 (t, CH$_2$-CH=), 102.75 (d, CH$_2$-CH=), 112.97 (s), 119.53 (d, CH$_2$-CH=), 121.00 (d, C$_{ArH}$), 124.55 (s), 125.39 (s), 127.63 (d, C$_{ArH}$), 134.70 (s), 135.33 (s), 139.00 (d, C=H=CH-CO), 155.82 (s), 157.28 (s), 163.22 (s, CO).

HRMS of the compound confirmed its elemental composition to be C$_{19}$H$_{22}$O$_3$ (Obsvd, m/z 321.1459 for [M+Na]$^+$ Calcd: 321.1467).

The spectral properties exhibited by this compound are identical with that of the reported values for 7-Hydroxy-3,6-bis(3-methylbut-2-enyl) coumarin (Balsamiferone). The structure was further confirmed by its similarity of the melting point 135°C with the lit m.p. 135-137°C.

![Fig 8a](image)

The plausible mechanism for the formation of balsamiferone 3 is given in Schemes XXIX-XXXII. In scheme XXIX the para Claisen rearrangement of 2-prenyloxy group is followed by either deprenylation and cyclisation or cyclisation followed by deprenylation.
According to the scheme XXX, first deprenylation of 4-prenyloxy group takes place, which is then followed by Claisen rearrangement and cyclisation.

In scheme XXXI, Claisen rearrangement at more hindered proton followed by a Cope rearrangement introduces the prenyl group at C-6 position. Subsequent deprenylation followed by cyclisation can then lead to 3.

In Scheme XXXII also, a similar mechanism is shown. The only difference is that here, deprenylation is the first step, which is then followed by subsequent steps leading to the formation of the desired compound 3.
Thus we have successfully synthesized balsamiferone in one step in 42%. The synthesis reported here is the shortest of all the reported methods. Kapil et al. have synthesized balsamiferone in 13 steps. Cairns et al. used eight steps for the synthesis of balsamiferone. In both syntheses the authors have used the preformed coumarin as the starting material. However Mali et al. have synthesized o-methylbalsamiferone but they didn’t convert it to the balsamiferone.
Synthesis of O-methyl ether of 7-hydroxy-6-methoxy-3-(3-methyl-2-buteryl)coumarin using tandem Wittig reaction and Claisen rearrangement.

While working on this tandem methodology we came across a report\(^\text{25}\) regarding the isolation of 7-hydroxy-6-methoxy-3-(3-methyl-2-butenyl)coumarin (14) from the leaves and stems of *coriaria nepalensis* wall. Literature search revealed that o-methyl ether of 7-hydroxy-6-methoxy-3-(3-methyl-2-butenyl) coumarin (3-prenylscoorane) is reported\(^\text{59}\) by Dhars group as a synthetic compound (Scheme XXXIII). Later on in 2006 another report\(^\text{60}\) on the synthesis of 7-hydroxy-6-methoxy-3-(3-methyl-2-butenyl) coumarin by direct prenylation of coumarin nucleus using 2-methyl-3-buten-2-ol in the presence of BF\(_3\)-Et\(_2\)O appeared. The reported yield in this direct prenylation reaction is 25%.

\[ \text{Scheme XXXIII} \]

Mali, *et al.* have used tandem Wittig reaction-Claisen rearrangement for the synthesis of 6-prenylated coumarin. The advantage of this route is that the reaction does not utilize preformed coumarins. The authors have not used this approach for
the synthesis of 3-prenyl coumarin. Hence we thought of evaluating it for the synthesis of methyl ether of the naturally occurring 7-hydroxy-6-methoxy-3-(3-methyl-2-butenyl)coumarin. Besides, we also wanted to know whether the reaction proceeds with initial migration of the 2-prenyloxy group to C-8 or to C-3 position of coumarin ring. If the migration takes place first, it should lead to 1,1-dimethyl allyl group at the respective carbons (C-3 or C-8).

Our strategy visualized for the synthesis of methyl ether of 7-hydroxy-6-methoxy-3-(3-methyl-buteryl)coumarin is shown below (Scheme XXXV) and the probable mechanism for its formation is shown in scheme XXXVI.

![Scheme XXXV](image)

**Mechanism:**

![Scheme XXXVI](image)
Thus, 4,5-dimethoxy-2-hydroxybenzaldehyde was treated with prenyl bromide (3, 3-dimethylallyl bromide) in refluxing acetone in the presence of potassium carbonate. Usual workup, gave a viscous sweet smelling liquid. It showed negative FeCl₃ test.

The compound 29 in its IR spectrum (KBr) showed a band at 1656 cm⁻¹ indicating the presence of carbonyl group of aldehyde. Its ¹H NMR spectrum had signals at δ 1.72 (3H, s) & 1.79 (3H, s) indicating the presence two methyls of -CH=CH(CH₃)₂ group. Similarly, two singlets (3H each) at δ 3.86 and 3.94 could be assigned to two OCH₃ groups. The peaks at δ 4.61 (2H, d, J = 5.6 Hz) and 5.48 (1H, t, J = 5.6 Hz) could be assigned to methylene and olefinic protons of the prenyl group. The aromatic signals were found at δ 6.50 (1H, s, 3-H), 7.30 (1H, s, 6-H) while the aldehyde peak appeared at δ 10.30 (1H, s), as expected.

Thus on the basis of mode of formation & spectral properties structure 29 was assigned to it.

After obtaining 2-prenyloxy-4,5-dimethoxybenzaldehyde in sufficient quantity, our next step was to carry out Wittig reaction, Claisen, Cope rearrangement and cyclisation in one pot.

Thus, 2-prenyloxy-4,5-dimethoxybenzaldehyde (29) was reacted with stable phosphorane in refluxing diphenyl ether for 6 h (Scheme XXXVII). The reaction mixture, upon purification on silica gel column afforded two pure compounds.

![Scheme XXXVII](image)

First fraction (yield = 48.24%) in its IR spectrum showed a band at 1730 cm⁻¹ indicating the presence of carbonyl group of coumarin.
In its $^1$H NMR (CDCl$_3$) spectrum (Fig 9a) two singlets (3H each) were seen at $\delta$ 1.68 & 1.80 indicating the presence of two methyls of prenyl group. Two singlets (3H each) were seen at $\delta$ 3.90 & 3.92 which could be assigned to methyls of two OCH$_3$ groups. One doublet (2H, $J = 7.2$ Hz) and one triplet (2H $J = 7.2$ Hz) were seen at $\delta$ 3.22 and 5.30, which could be assigned to a $-\text{CH}_2\text{CH}=\text{ grouping. In the olefinic region one singlet (1H) was seen at } \delta 7.36 \text{ which could be due to 4-H of coumarin. In addition to this one singlet (2H) was seen in aromatic region at } \delta 6.80 \text{ which could be attributed to 5-H & 8-H.}

Its $^{13}$C NMR spectrum (Fig 9b) peaks at $\delta$ 17.8 (q), 25.80 (q) which could be assigned to the carbons of two methyls of prenyl group. Peaks at 99.63 (d, CH) & 28.65 (t, CH$_2$) could be assigned to $=\text{CH}\text{CH}_2$ grouping. Peaks at $\delta$ 56.29 (q), 56.27 (q) could be assigned to carbons of the two OCH$_3$ groups. Peaks at $\delta$ 107.67 (d), 119.45 (d) and 138.03 (d) could be assigned to aromatic methine carbons. The quaternary carbon appearing at 146.17 (s), 148.57 (s) and 151.71 (s) could be attributed to unsaturated carbon of alkene & benzene respectively. One peak was seen at 162.38 (s), which is attributed to the carbonyl carbon of coumarin. The multiplicities of carbon signal mentioned were obtained from DEPT 135 experiment.

HRMS of the compound confirmed its elemental composition to be C$_{16}$H$_{18}$O$_4$ (Obsvd, m/z 297.1103 for [M+Na]$^+$ Calcd: 297.1091).

Thus on the basis of mode of formation & spectral properties structure 30 was assigned to it. The structure is further confirmed by the similarity of the melting point (Obsvd: 96-97°C, lit$^{59}$ 95-96°C). The spectral properties exhibited by this compound are identical to that of 3-prenylscoporane.$^{59}$

The successful synthesis of methyl ether of natural product 30 showed that the tandem methodology can be extended to synthesis of 3-prenyl coumarin also.

The second fraction (yield = 9.6%) showed in its IR spectrum a band at 1730 cm$^{-1}$ indicating the presence of carbonyl group of coumarin.
In its $^1$H NMR (CDCl$_3$) spectrum two singlets (3H each) at $\delta$ 3.92 & 3.95 which could be assigned to the two methyls of the two OCH$_3$ groups. In the olefinic region two doublets (2H, $J = 9.6$ Hz) were seen at $\delta$ 6.27 & 7.64 which could be due to 3-H & 4-H of coumarin. In addition to these two singlets (1H each) were seen in aromatic region at $\delta$ 6.84 & 6.86 which could be attributed to 5-H & 8-H. The structure was further supported by $^{13}$C NMR and DEPT 135. Thus, peak at 56.36 (q), which could be assigned to the carbons of two -OCH$_3$ groups. Peaks at 108 (d), 113.53 (d) could be assigned to C-5 & C-8 benzene carbons. Peaks at 99.99 (d) and 143.29 (d) could be assigned to unsaturated carbon of pyran ring. The quaternary carbons appearing at 111.43 (s), 146.34 (s), 150.00 (s), and 152.85 (s), could be attributed to aromatic carbons. One peak was seen at 162.38 (s), which is attributed to the carbonyl group of coumarin.

Thus on the basis of mode of formation & spectral properties structure 31 was assigned to it. The structure is further confirmed by the similarity of the melting point 143-144°C with the lit$^5$1 melting point 143-144°C. The spectral properties exhibited by this compound are identical with that of the reported values of 6, 7-dimethoxycoumarin (scoporane).

In this one step experiment, as depicted in strategy scheme XXXVI, Wittig reaction, Claisen rearrangement, Cope rearrangement and cyclisation took place in a domino fashion. However the other possible products of Claisen rearrangement were not observed (scheme XXXVIII).

![Scheme XXXVIII](Image)
Fig 9a

Fig 9b

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we also carried out synthesis in a stepwise manner. Thus, 2-phenyloxy-o,o'-dimethoxybenzaldehyde was treated with 1.2 eq. of stable phosphorane in refluxing toluene for 6 h (monitored by TLC). The compound obtained after column chromatography was a sweet smelling liquid (Scheme XXXIX).

**Scheme XXXIX**

Based on the mode of formation & spectral properties mentioned below, structure 32 was assigned to the compound. The coupling constant (J = 12.84 Hz) of the vinylic double bond and the downfield nature of the β-proton indicated that it could be the trans ester (yield = 79.67%).

IR (v max): 1656 cm⁻¹ (CO).

$^1$H NMR (CDCl₃, 300 MHz):

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<tr>
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<tr>
<td>7.98</td>
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</table>
The ethyl-2(E)-4, 5-dimethoxy-2-prenyloxycinnamate (32) was refluxed in diphenyl ether for 3 h. Purification by column chromatography gave two 30 & 31 in 57.74% and 7.4% yield respectively. Attempted selective demethylation by using either AlCl₃, BBr₃ or pyridinium hydrochloride did not yield the natural product 14 in our hand.

As we were not able to selectively demethylate 30 to get the natural product 14, we thought of synthesizing it by using the methodology we used for the synthesis of balsamiferone 3. Thus, the tandem Wittig reaction-Claisen rearrangement-Cope rearrangement cyclization and deprenylation (Scheme XXXXa) on 5-methoxy-2,4-diprenyloxycinnamaldehyde was planned. Based on our previous experiment it was expected that either we would get 3-prenyl nieshoutin by Wittig reaction double Claisen rearrangement and double cyclization or 7-hydroxy-6-methoxy-3-prenylcoumarin 14 by single Claisen rearrangement, Cope rearrangement and deprenylation. The other possible course for the reaction is depicted in scheme XXXXb. In this one of the prenyl group undergoes Claisen rearrangement and other would get knocked off. This could lead to obliquetin and if it cyclises under the reaction conditions it could give nieshoutin. Thus, 2,4-di-o-(3,3-dimethylallyl)-5-methoxybenzaldehyde was prepared by treating 2,4-dihydroxy-6-methoxybenzaldehyde with prenyl bromide in the presence of potassium carbonate and refluxing acetone (Scheme XXXXI). Workup gave a crude product, which was separated over silica gel column chromatography to yield the pure compound 33.
Scheme XXXXa

Scheme XXXXb

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Liquid 33 (yield = 60.77%) in its IR spectrum showed a band at 1680 cm$^{-1}$ indicating the presence of carbonyl group of aldehyde.

In its $^1$H NMR (CDCl$_3$) spectrum singlets (12H) were seen at $\delta$ 1.76, 1.78, 1.81, indicating the presence of four methyl of two $-\text{C(CH}_3\text{)_2}$ group. One singlet was seen at $\delta$ 3.81 which could be assigned to methyl protons of $-\text{OCH}_3$ group. Two doublets ($J = 6.6\text{Hz}$) were seen at $\delta$ 4.58 and 4.68 which could be assigned to each of two methylene protons of $-\text{CH}_2\text{CH}=\text{C(Me}_3\text{)_2}$ groups. A multiplet at $\delta$ 5.50, integrating for two protons could be due to the presence of two olefinic protons of $\text{CH}=\text{C(Me}_3\text{)_2}$ group. Two singlets were seen at $\delta$ 6.53 and 7.31, this could be due to the 3-H and 6-H protons of the aromatic ring. A singlet at $\delta$ 10.32 integrating for a single proton could be due to the presence of aldehydic proton.

Thus on the basis of mode of formation & spectral properties structure 33 was assigned to it.

Once we had in our hands sufficient quantity of 2,4-di-o-(3,3-dimethylallyl)-5-methoxybenzaldehyde, our next step was to carry out domino Wittig reaction, Claisen, Cope rearrangement and cyclisation in one pot.

Thus, 2, 4-di-o-(3,3-dimethylallyl)-5-methoxybenzaldehyde was heated with stable phosphorane in refluxing diphenyl ether for 6 h. The complex reaction mixture was subjected to column chromatography using ethyl acetate and hexanes as an eluent (XXXXII). We isolated 34 in pure form from the mixture of the products.
Compound 34 (yield = 44.71%) in its IR spectrum showed a band at 1730 cm\(^{-1}\) and 3200 cm\(^{-1}\) indicating the presence of carbonyl group of coumarin and phenolic hydroxyl group respectively.

In its \(^1\)H NMR (CDCl\(_3\)) spectrum (Fig 10a) two singlets (3H each) were seen at \(\delta\) 1.67 & 1.84 indicating the presence of two methyls of prenyl group. One singlet (3H) was seen at \(\delta\) 3.93 which could be assigned to methyl of OCH\(_3\) groups. One doublet (2H, J = 7.2 Hz) and one multiplet (1H) were seen at \(\delta\) 3.57 and 5.28 which could be assigned to \(-\text{CH}_2\text{CH}=\) groupings. In the olefin region two doublets (1H each, J = 9.2 Hz) were seen at \(\delta\) 6.24 and 7.58 which could be due to 3-H & 4-H protons of coumarin respectively. In addition to this one singlet (2H) was seen in aromatic region at \(\delta\) 6.70 which could be attributed to 5-H proton. Peak at \(\delta\) 6.20 could be attributed to \(-\text{OH}\) group.

Its \(^{13}\)C NMR (CDCl\(_3\)) spectrum peak at \(\delta\) 25.74 (q), which could be assigned to two CH\(_3\) groups of CH=C(CH\(_3\))\(_2\). Peaks at 105.05 (d, CH), & 22.15 (t, CH\(_2\)) could be assigned to carbons of =CHCH\(_2\) group. Peak at \(\delta\) 56.30 (q) could be assigned to methyl of OCH\(_3\) group. Peaks at \(\delta\) 113.09 (d), 120.67 (d), 143.6 (d) could be assigned to aromatic methine and olefinic carbons. The quaternary carbon appearing at 147.37 (s), 145.46 (s), 133.15 (s) and 111.18 (s) could be attributed to unsaturated carbon of alkene & benzene ring carbons respectively. One peak was seen at 162.38 (s) which could be attributed to the carbonyl carbon of coumarin. The multiplicities of carbon signals mentioned were obtained from DEPT 135 experiment.

HRMS of the compound confirmed its elemental composition to be C\(_{15}\)H\(_{16}\)O\(_4\) (Obsvd, m/z 283.0933 for [M+Na]\(^+\) Calcd: 283.0946).
Based on the above data it was concluded that there is a prenyl group present in the structure. The position of it could not be at 3-position to give natural product 7-hydroxy-6-methoxy-3-(3-methyl-2-butenyl)coumarin as the data did not match with literature data. Also in the PMR we could see both the olefinic protons (doublets) of the pyran ring indicating that the coumarin ring is unsubstituted at 3 and 4 position. Now, the other possibilities were that the prenyl group could be at 5 or 8 position.

Following 2 structures 34 and 35 with prenyl group at 5 or at 8 were possible for the obtained compounds.
In structure 34 the position of prenyl group is at *ortho* position with respect to starting whereas it is at *meta* position in structure 35. The introduction of prenyl ring in the benzene ring of coumarin can take place either by sigmatropic rearrangement or by direct alkylation (allylation). Considering both these possibilities structure 34 was assigned to the compound.

Plausible mechanism for the formation of 34 is shown in scheme XXXIII.

![Scheme XXXIII](image)

Literature search indicated that compound 34 is a known natural product, cedrelopsin isolated$^{62}$ from the trunk bark of *cedrelopsis grevei*. So, we compared the melting point (172°C) of the compound obtained with that of it reported (170-172°C). The similarity in the melting point concluded that the compound we had assigned the structure 34 was cedrelopsin. Previously Anet *et al.*$^{63}$ in 1949 have synthesized this naturally occurring coumarin 34 for the structural elucidation of another naturally occurring coumarin brayleyanin. Cedrelopsin was synthesized by direct prenylation of sodium salt of 7-hydroxy-6-methoxy coumarin with prenyl bromide in benzene solution (Scheme XXXXIV).
In our synthesis of cedrellopsin Wittig reaction, Clasien rearrangement, double Cope rearrangement, deprenylation and cyclisation took place in a tandem manner.

**Attempted tandem Wittig reaction-triple Claisen rearrangement:**

We were interested to extend the above methodology for triple Claisen rearrangement.

The strategy for the synthesis is depicted in scheme given below (Scheme XXXXV).
Thus pyrroginol was methylated by using dimethyl sulphate, potassium carbonate and acetone as solvent, which was then formylated using Vilsmeier Hack reaction followed by demethylation using AlCl₃. The trihydroxyaldehyde obtained was treated with prenyl bromide (3,3-dimethylallyl bromide) using potassium carbonate & acetone. After usual work up the product was purified by column chromatography using ethyl acetate and hexanes (1:9) to get a sweet smelling viscous liquid (XXXVI).

![Scheme XXXVI](image)

Based on the mode of formation & spectral properties mentioned below, structure 36 was assigned to the compound (yield = 60.10%).

IR (νmax): 1650 cm⁻¹ (CO).

¹H NMR (CDCl₃, 300MHz): (Fig 11a)

| δ 1.76 | 4 s | 18H | 6 × CH₃ |
|δ 4.52 | d (J = 6.6 Hz) | 2H | CH₂-CH= |
|δ 4.62 | d (J = 7.5 Hz) | 2H | CH₂-CH= |
|δ 4.73 | d (J = 7.5 Hz) | 2H | CH₂-CH= |
|δ 5.5 | m | 3H | 3 × CH₂-CH= |
|δ 6.75 | d (J = 8.7 Hz) | 1H | 5-H |
|δ 7.56 | d (J = 8.7 Hz) | 1H | 6-H |
|δ 10.23 | s | 1H | Ar-CHO |
HKMS of the compound confirmed its elemental composition to be C_{22}H_{30}O_4 (Obsvd, m/z 381.2036 for [M+Na]^+ Calcd: 381.2042).

Thus on the basis of mode of formation & spectral properties structure 36 was assigned to it.

Once, we prepared sufficient quantity of 3,4,5-triprenyloxybenzaldehyde, our next step was to carry out Wittig reaction, triple Claisen, Cope rearrangement and cyclisation in one pot.

So we heated aldehyde 36 with stable phosphorane \( \text{Ia} \) in diphenyl ether. It was observed that during heating, the reaction mixture was getting blackish in colour.

The reaction mixture was refluxed for 6 h. The complex mixture (reaction was monitored by TLC), was subjected to column chromatography using ethyl acetate and hexanes (2:8) as an eluent, we were able to isolate one compound in pure form (XXXXXVII).

Based on the mode of formation & spectral properties mentioned below, structure 37 was assigned to the compound. (yield = 16%).

IR (\( \nu_{\text{max}} \)): 1725 cm\(^{-1}\) (CO), 3320 cm\(^{-1}\) (OH).

\(^1\)H NMR (CDCl\(_3\), 300 MHz): (Fig 12a)
The plausible mechanism for the formation of 37 in the reaction is given below (Scheme XXXXVIII).

\[
\begin{array}{|c|c|c|c|}
\hline
\delta & \text{Assignments} & \text{Assignments} \\
\hline
1.40 & s & 2H \\
1.86 & t (J = 6.8 \text{ Hz}) & -\text{CH}_2-\text{CH}_2-\text{Ar} \\
2.82 & t (J = 6.8 \text{ Hz}) & 2H \\
6.21 & d (J = 9.6 \text{ Hz}) & 1H \\
7.57 & d (J = 9.6 \text{ Hz}) & 1H \\
6.75 & s & 1H \\
\hline
\end{array}
\]

$^{13}$C NMR and DEPT (CDCl$_3$): $\delta$ 21.28 (t, CH$_2$), 26.86 (q, CH$_3$), 32.57 (t, CH$_2$), 75.57 (s), 112.27 (s), 113.08 (d, CH$_2$-CH=CO), 118.10 (d, C$_{ArH}$), 118.17 (s), 132.12 (s), 133.24 (s), 143.84 (d, CH$_2$-CH=CO), 144.60 (s), 160.66 (s, CO).

Scheme XXXXVIII
It appears that the triple Claisen rearrangement is difficult and rather deprotonation is a favorable reaction due to steric crowding.

Fig 11a

Fig 12a

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Conclusions:

1. Feasibility of tandem Wittig reaction, double Claisen rearrangement, Cope rearrangement and double cyclisation was demonstrated by the isolation of 8,9,9-trimethyl-6-(3-methylbut-2-eny)-8,9-dihydro-2H-furo[2,3-h]chromen-2-one (15).

2. Completed the formal synthesis of gravelliferone, a naturally occurring coumarin having a 1’,1’-dimethylallyl group at 3-position.

3. Achieved synthesis of demethylsuberosin, a naturally occurring coumarin and also the precursor for the synthesis of gravelliferone by tandem Wittig reaction, deprenylation, Claisen rearrangement, Cope rearrangement and cyclisation.

4. Structure of a new coumarin obtained during tandem Wittig reaction, double Claisen rearrangement, Cope rearrangement and was confirmed by an alternate synthesis.

5. Effect of remote group at 3-position of coumarin nucleus was found to give higher percentage of product by tandem Wittig reaction, deprenylation, Claisen rearrangement, Cope rearrangement and cyclisation. This observation led us to development of one step synthesis of balsamiferone.

6. Synthesis of methyl ether of naturally occurring 7-hydroxy-6-methoxy coumarin was achieved without using preformed coumarin by tandem Wittig reaction, Claisen-Cope rearrangement by taking advantage of steric effects in the Claisen rearrangement.

7. A novel and efficient synthesis of cedrelopsin was achieved by tandem Wittig reaction, Claisen rearrangement, double Cope rearrangement, cyclisation and deprenylation.

8. Tandem Wittig reaction, triple Claisen rearrangement was attempted and product of tandem Wittig, single Claisen rearrangement, double deprenylation and cyclisation was isolated.
Experimental Section:

Expt. 3.1: Preparation of triphenyl-α-ethoxycarbonyl[ methylene] phosphorane (Ia).

\[ \text{PPh}_3 + \text{BrCH}_2\text{COOEt} \xrightarrow{\text{Br}} \text{Ph}_3\text{PCH}_2\text{COOEt} \xrightarrow{\text{NaOH}} \text{Ph}_3\text{P} = \text{CHOOC} \text{Et} \]

Expt. 3.2: Preparation of 2, 4-dihydroxyresorcialdehyde.

Expt. 3.3: Preparation of 1-bromo-3-methyl-but-2-ene/3, 3-dimethyl allylbromide/prenyl bromide.

Expt. 3.4: Preparation of 2, 4-di-o-(3, 3-dimethylallyloxy) benzaldehyde/2,4-o-prenyloxybenzaldehyde (16)
Expt. 3.5: Tandem Wittig reaction, Claisen, Cope rearrangement on 16 in dimethylaniline.

Expt. 3.6: Tandem Wittig reaction, Claisen, Cope rearrangements on 16 in diphenyl ether.

Expt. 3.7a: Preparation of E-ethyl-2, 4-di-o-(3,3-dimethylallyloxy)cinnamate (17).
Expt. 3.7b: Tandem Claisen-Cope rearrangement on 17 in DMA.

Expt. 3.7c: Tandem Claisen-Cope rearrangement on 17 in diphenyl ether.
Expt. 3.6: Tandem Wittig reaction, Cisella, Cope rearrangements of 16 in diphenyl ether.

Expt. 3.9: Preparation of 4-o-(3,3-dimethylallylloxy)-2-hydroxybenzaldehyde (21).

Expt. 3.10: Preparation of triphenyl-α-ethoxycarbonyl-α-(3,3-dimethylallyl)methylene phosphorane (22).
Expt. 3.11: Preparation of \(3-(3,3\text{-dimethylallyloxy})-7-o-(3,3\text{-dimethylallyl})\) coumarin (20).

Expt. 3.12: Preparation of \(3-(3,3\text{-dimethylallyloxy})-7-o-(3,3\text{-dimethylallyl})\) coumarin (20).

Expt. 3.13: Preparation of triphenyl-\(\alpha\)-ethoxycarbonyl-\(\alpha\)-(allyl)-methylene phosphorane (24).

Expt. 3.14: Tandem Wittig reaction, Claisen, Cope rearrangement, deprenylation and cyclisation: Preparation of 3-allyl-6-(3,3-dimethylallyl)-7-hydroxy coumarin (3-allyldemethylsuberosin) (26).
Expt. 3.16: Tandem Wittig reaction, Claisen, Cope rearrangement, deprenylation and cyclisation: Preparation of 3-benzyl dihydroxanthyletin (28).

Expt. 3.17: Tandem Wittig reaction, Claisen, Cope rearrangement, deprenylation and cyclisation: Preparation of 7-Hydroxy-3,6-bis(3-methylbut-2-enyl)coumarin (balsamiferone) 3.

Expt. 3.18: Preparation of 3, 4-dimethoxy phenol
Exp. 3.19: Preparation of 4,5-dimethoxy-2-hydroxybenzaldehyde.

\[
\begin{align*}
\text{H}_3\text{CO} & \quad \text{OH} \\
\text{H}_3\text{CO} & \quad \text{TFA} \\
\text{hexammine} & \quad \text{H}_3\text{CO} \quad \text{OH} \\
\text{CHO} & \quad \text{TFA}
\end{align*}
\]

Exp. 3.20: Alternate method for the preparation of 2-hydroxy-4,5-dimethoxy benzaldehyde.

a) Preparation of hydroquinone.

\[
\begin{align*}
\text{OH} & \quad \text{CrO}_3 \\
\text{OH} & \quad \text{O}
\end{align*}
\]

b) Preparation of 1, 2, 4-triacetoxybenzene.

\[
\begin{align*}
\text{O} & \quad \text{Ac}_2\text{O} \\
\text{O} & \quad \text{H}_2\text{SO}_4 \\
\text{OAc} & \quad \text{OAc} \\
\text{OAc} & \quad \text{OAc}
\end{align*}
\]
c) Preparation of 1, 2, 4-trimethoxybenzene

\[
\begin{align*}
\text{OAc} & \quad \text{DMS/ NaOH} \\
\text{OAc} & \quad \text{OCH}_3 \\
\text{OAc} & \quad \text{OCH}_3 \\
\text{OAc} & \quad \text{OCH}_3
\end{align*}
\]

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e) Preparation of 2-hydroxy-4,5-dimethoxy benzaldehyde.

Expt. 3.21: Preparation of 2-prenyloxy-4,5-dimethoxybenzaldehyde (29).

Expt. 3.22: Tandem Wittig reaction, Claisen, Cope rearrangement and cyclisation: Preparation of o-methyl ether of 7-hydroxy-6-methoxy-3-(3-methyl-2-butenyl) coumarin and scoporane (30 and 31).
Expt. 3.23: Preparation of ethyl-2(\(E\))-4,5-dimethoxy-2-\(O\)-prenyloxycinnamate (32).

Expt. 3.24: Claisen/Cope rearrangement of ethyl-2(\(E\))-4,5-dimethoxy-2-o-(3,3-dimethylallyl) cinnamate: Preparation of \(o\)-methyl ether of 7-hydroxy-6-methoxy-3(3-methyl-2-butenyl)coumarin and scoporane (30 and 31).

Expt. 3.25: Preparation of 5-methoxy-2, 6-diprenyloxy benzaldehyde (33).
Expt. 3.20: Tandem Wittig reaction, Claisen, double Cope rearrangement, deprenylation and cyclisation: Preparation of 8-(3-methyl-2-butenyl)-7-hydroxy-6-methoxycoumarin (cedrelopsin) (34).

Expt. 3.27: Preparation of trimethoxy benzene:

Expt. 3.28: Preparation 2, 3, 4-trimethoxy benzaldehyde

Expt. 3.29: Preparation of 2, 3, 4-trihydroxy benzaldehyde:
Expt. 3.30: Preparation of 2, 3, 4-tri-O-(3,5-dihydroxyphenoxyl) benzaldehyde (36).

Expt. 3.31: Tandem Wittig reaction, Claisen, Cope rearrangement, double deprenylation and cyclisation: Preparation of 8-hydroxydihydroxanthyletin (37).
Expt. 3.1: Preparation of triphenyl-a-ethoxycarbonylmethylene phosphorane (12).

Addition of a solution of triphenylphosphine (10.20 g, 38.97 mmol) in dry benzene (10 mL) to a solution of ethyl bromoacetate (6.50 g, 38.97 mmol) in dry benzene (10 mL) at room temperature resulted in an elevation in temperature to about 70°C and the precipitation of a salt. After allowing the mixture to cool to room temperature, it was shaken & left overnight. The separated solid was filtered, washed with dry benzene and dried. The stirred solution of the salt in water and benzene was neutralized by aqueous sodium hydroxide to a phenolphthalein end point. The benzene layer was separated, dried over sodium sulphate and concentrate to about 1/3 rd volume. Addition of n-hexane resulted in the separation of the crystalline product which was filtered and dried to afford triphenyl-a-ethoxycarbonylmethylene phosphorane (10.9 g, 80.3%) m.p 126°C (lit 63 m.p. 125-127°C).

Expt.3.2: Preparation of 2,4-dihydroxybenzaldehyde.

Phosphorous oxychloride (2.7 g, 17.55 mmol) was added slowly to N, N-dimethylformamide (1.5 g, 20.6 mmol) in acetonitrile (10 mL) at 0°C. Resorcinol (1.68 g, 15.27 mmol) in acetonitrile (5 mL) was added to it with stirring. The reaction mixture was heated on water bath for 3 h and then cooled to 0°C. A saturated solution of sodium acetate (20 mL) was added to it. The white solid thus obtained was filtered, washed with water and dried. It was recrystallized from water to give 2,4-dihydroxybenzaldehyde (1.55 g, 80%) m.p. 134°C (lit 54 m.p. 134-135°C).

Expt.3.3: Preparation of 1-bromo-3-methyl-but-2-ene/3,3-dimethyl allylbromide/prenyl bromide.

To the stirred solution of 4-hydroxy-2-methylbut-2-ene (2 g, 23.3 mmol) and dry pyridine (0.37 g, 0.38 mL, 4.7 mmol) in hexanes (20 mL), solution of phosphorus tribromide (9.3 mmol) in hexanes (10 mL) was added slowly at 0°C. After 30 min, ice water was added and hexanes layer was separated. It was washed first with sodium bicarbonate (20 mL) solution and then with water (20 mL). Drying over anhydrous sodium sulphate and removal of solvent under reduced pressure
afforded liquid which was distilled under reduced pressure to give 1-bromo-3-methyl-but-2-ene as a colourless liquid (1.9 g, 55.90%), b. p. 80°C /90 mm (lit64 b.p. 64-68°C/70 mm).

Expt.3.4: Preparation of 2, 4-diprenyloxybenzaldehyde (16).

To the mixture of 2, 4-dihydroxybenzaldehyde (2 g, 14.50 mmol) and potassium carbonate (5 g, 36.23 mmol) in acetone (40 mL), 3,3-dimethyl allylbromide (5.2 g, 36.23 mmol) was added slowly in portions. The reaction mixture was refluxed for 12 h. It was then cooled, filtered and acetone was removed under vacuum. To this water (20 mL) was added and extracted in diethyl ether (3 X 20 mL). The combined organic layer was washed with 2N sodium hydroxide (2 X15 mL) and then with water (2 X 15 mL). The organic layer was dried over anhydrous sodium sulphate. Evaporation of solvent under reduced pressure gave viscous liquid, which was purified over silica gel column chromatography using hexanes and ethyl acetate (99:1) as an eluent to give a sweet smelling light yellow liquid (3.3 g, 82.5%).

Expt. 3.5: Tandem Wittig reaction, Claisen, Cope rearrangement on 16 in DMA.

A solution of 2,4-o-(3,3-dimethylallyl)benzaldehyde (0.54 g, 1.98 mmol) and phosphorane (Ia) (1.03 g, 2.97 mmol) in DMA (10 mL) was refluxed for 6 h. The reaction mixture was poured into ice-cooled water containing conc. hydrochloric acid and was extracted in ethyl acetate (3 X 25 mL). The combined organic layer was washed with water (2 X 15 mL), dried over sodium sulphate and solvent was removed under vacuum. The residue was subjected to column chromatography using hexanes and ethyl acetate (9:1) as an eluent to give 8,9,9-trimethyl-6-(3-methyl but-2-enyl)-8,9-dihydro-2H-furo[2,3-h]chromen-2-one (15) in 30.10% as a white solid, (0.177 g), m.p. 137°C (lit m.p. 136-139°C)
Expt. 3.6: Tandem Wittig reaction, Claisen, Cope rearrangements on 16 in diphenyl ether.

A solution of 2,4-di-o-(3, 3-dimethyl allyl) benzaldehyde (0.50 g, 1.84 mmol) and phosphorane (Ia) (0.96 g, 2.76 mmol) in diphenyl ether (10 mL) was refluxed for 6 h. The reaction mixture was loaded over silica gel column. Using hexanes diphenyl ether was removed first. Further eluted the product with hexanes and ethyl acetate (9:1) as an eluent. Initial fractions gave 8,9,9-trimethyl-6-(3-methyl but-2-enyl)-8,9-dihydro-2H-furo[2,3-h]chromen-2-one (15) (0.29 g, 53.02%) yield and later fractions gave demethylsuberosin (19) (0.05 g, 12.34%).

Expt. 3.7a: Preparation of E-ethyl 2,4-di-o-(3,3-dimethylallyloxy)cinnamate (17).

A solution of 2, 4-di-o-(3, 3-dimethylallyloxy)benzaldehyde (2.50 g, 9.12 mmol) and phosphorane (Ia) (4.76 g, 13.68 mmol) in toluene was refluxed for 12 h. Evaporation of solvent gave a viscous liquid, which was purified over silica gel column chromatography using hexanes and ethyl acetate (95:5) as an eluent to afford E-ethyl 2,4-di-o-(3,3-dimethylallyloxy)cinnamate (17) as a sweet smelling liquid (2.7 g, 85%).

Expt. 3.7b: Tandem Claisen-Cope rearrangement on 17 in DMA.

A solution of E-ethyl-2,4-di-o-(3,3-dimethylallyloxy)cinnamate (17) (0.7 g, 2.03 mmol) in DMA (10 mL) was refluxed for 6 h. The reaction mixture was poured into ice-coiled water containing conc. hydrochloric acid and was extracted in ethyl acetate (3 X 25 mL). The combined organic lauer was washed with water (2 X 15 mL), dried over anhydrous sodium sulphate and solvent was removed under vacuum. The residue was subjected to column chromatography using hexanes and ethyl acetate (9:1) as an eluent to give 8,9,9-trimethyl-6-(3-methyl but-2-enyl)-8,9-dihydro-2H-furo[2,3-h]chromen-2-one (15) in 55% as a white solid (0.33 g), m.p. 137°C (lit\textsuperscript{48} m.p. 136-139°C).
Expt. 3.7c: Tandem Claisen rearrangements on 17 in diphenyl ether.

A solution of E-ethyl-2,4-di-o-(3,3-dimethylallyloxy)cinnamate (0.65 g, 1.9 mmol) in diphenyl ether (10 mL) was refluxed for 6 h. The reaction mixture was subjected to column chromatography using hexanes to remove first diphenyl ether and further elution with hexanes and ethyl acetate (9:1) gave 8,9,9-trimethyl-6-(3-methyl but-2-enyl)-8,9-dihydro-2H-furo[2,3-h]chromen-2-one (15) in 50% (0.28 g) yield, m.p. 137°C (lit m.p. 136-139°C) and later fractions gave demethylsuberosin (19) (0.043 g, 10%).

Expt.3.8: Tandem Wittig reaction, Claisen, Cope rearrangements on 16 in diphenyl ether for 20 min.

A solution of 2, 4-o-(3, 3-dimethylallyl)benzaldehyde (0.8 g, 2.92 mmol) and phosphorane Ia (1.53 g, 4.4 mmol) in diphenyl ether was refluxed for 20 min. The reaction mixture was loaded over silica gel column. Using hexanes, diphenyl ether was removed. Further eluted the product using 10% ethyl acetate and hexanes as an eluent. Initial fractions gave 3-(3-methylbut-2-enyl)-7-(3-methylbut-2-enyloxy)coumarin (20) (0.017 g, 1.8%), second fraction gave E-ethyl 2,4-di-o-(3, 3-dimethylallyloxy)cinnamate (17) (0.28 g, 22%), third fraction gave 8,9,9-trimethyl-6-(3-methyl but-2-enyl)-8,9-dihydro-2H-furo[2,3-h]chromen-2-one (15) (0.087 g, 10%), fourth fraction gave 6-(3-methylbut-2-enyl)-7-(3-methylbut-2-enyloxy)coumarin (18) (0.260 g, 29.9%) and later fraction gave demethylsuberosin (19) (0.03 g, 5.07%).

Expt. 3.9: Preparation of 4-o-(3,3-dimethylallyl)-2-hydroxybenzaldehyde (21).

To the mixture of 2, 4-dihydroxybenzaldehyde (0.20 g, 1.45 mmol) and potassium carbonate (0.24 g, 1.74 mmol) in acetone (10 mL), 3, 3-dimethyl allylbromide (0.26 g, 0.2 ml, 1.74 mmol) was added slowly in portion and was refluxed for 12 h. The reaction mixture was cooled, filtered and solvent was removed under vacuum. To this water (10 mL) was added and the compound was extracted in diethyl ether (2 X 25 mL). The combined organic layer was dried over anhydrous sodium.
suipnate and concentrated under reduced pressure to give a viscous liquid, this was further purified over silica gel column using hexanes and ethyl acetate (99:1) as an eluent to furnish a light yellow colour liquid (0.21 g, 70.29%).

Expt. 3.10: Preparation of triphenyl-α-carboethoxy-α-(3,3-dimethylallyl)methylene phosphorane (22).

A solution of triphenyl-α-carboethoxy methylene phosphorane (IIa) (2.1 g, 6.0 mmol) and prenyl bromide (1.35 g, 9.0 mmol) in dry chloroform (10 mL) was refluxed for 10 h. After allowing reaction mixture to cool to room temperature, chloroform was evaporated under vacuum. It was then stirred in water (10 mL) and benzene (25 mL) and was neutralized by 2N sodium hydroxide to a phenolphthalein end point. The benzene layer was separated, dried over sodium sulphate and evaporation of solvent under vacuum gave triphenyl-α-ethoxycarbonyl-α-(3,3-dimethylallyl)methylene phosphorane as a solid, m.p.122°C (2.5 g, 67.57%).

Expt. 3.11: Preparation of E-ethyl (α-3,3-dimethylallyl)-4-o-(3,3-dimethylallyloxy)-2-hydroxycinnamate (23).

A mixture of 4-o-(3,3-dimethylallyloxy)-2-hydroxy benzaldehyde (0.1 g, 0.48 mmol) and prenyl phosphorane (22) (0.24 g, 0.57 mmol) was heated on water bath for 2 h, after formation of Wittig product (monitored by TLC), the reaction mixture was subjected to column chromatography using hexanes and ethyl acetate (9.9:0.1) as an eluent to give liquid product (23) (0.120 g, 70.60%).

Expt. 3.12: Preparation of 3-(3,3-dimethylallyl)-7-o-(3,3-dimethylallyl) coumarin (20).

E-ethyl (α-3,3-dimethylallyl)-4-o-(3,3-dimethylallyloxy)-2-hydroxycinnamate (23) (0.1 g, 0.29 mmol) was kept in sunlight in benzene solution (5 mL). After concentrating benzene solution the crude mixture was subjected to column chromatography using hexanes and ethyl acetate (9:1) as an eluent to give 3-(3,3-dimethylallyl)-7-o-(3,3-dimethylallyl)coumarin as a liquid (20) (0.07 g, 80%).
Expt. 3.13: Preparation of triphenyl-α-carboethoxy-α-allylmethylene phosphorane (24).

A solution of triphenyl-α-ethoxycarboethoxymethylene phosphorane (5.20 g, 15.03 mmol) and 3,3-dimethyl allylbromide (2.70 g, 22.54 mmol) in dry chloroform (10 mL) was refluxed for 6 h. After allowing the mixture to cool, chloroform was evaporated under vacuum. The salt obtained was stirred in water (10 mL) and benzene (50 mL) mixture and was neutralized by 2N sodium hydroxide to phenolphthalein end point. The benzene layer was separated, dried over sodium sulphate and benzene was removed under vacuum to give triphenyl-α-carboethoxy-α-allylmethylene phosphorane as a white solid, (m.p. 122°C, 4.55 g, 77.87%).

Expt. 3.14: Tandem Wittig reaction, Claisen, Cope rearrangement, deprenylation and cyclisation: Preparation of 3-allyl-6-(3,3-dimethylallyl)-7-hydroxy coumarin (3-allyldemethylsuberosin) (26).

A solution of 2,4-di-o-(3,3-dimethylallyl)benzaldehyde (0.45 g, 1.64 mmol) and triphenyl-α-carboethoxy-α-(allyl)methylene phosphorane (0.96 g, 2.46 mmol) in diphenyl ether (10 mL) was refluxed for 6 h. The reaction mixture was loaded on the silica gel column. Using hexanes, diphenyl ether was removed first. Further elution with 20% ethyl acetate and hexanes as an eluent gave 3-allyldemethylsuberosin as a gummy mass (26) (0.18 g, 40%).

Expt. 3.15: Preparation of triphenyl-α-ethoxycarbonyl-α-benzylmethylene phosphorane (27).

Benzyl bromide (0.64 g, 3.79 mmol) was added to the solution of triphenyl-α-ethoxy carbonylmethylene phosphorane (1.2 g, 3.45 mmol) in dry chloroform (10 mL) and was refluxed for 6 h. Chloroform was evaporated under vacuum, the salt obtained was taken in water (5 mL) and benzene (15 mL) mixture and was neutralized by 2N sodium hydroxide to a phenolphthalein end point. The benzene layer was separated, dried over sodium sulphate and was removed under vacuum to afford triphenyl-α-ethoxycarboethoxy-α-benzylmethylene phosphorane (0.52 g, 64.13%).
Expt. 3.16: Tandem Wittig reaction, Claisen, Cope rearrangement, deprenylation and cyclisation: Preparation of 3-benzyl dihydroxanthyletin (28).

A solution of 2,4-o-(3,3-dimethylallyl)benzaldehyde (0.42 g, 1.54 mmol) and triphenyl-α-ethoxycarbonyl-α-benzyl-methylene phosphorane (1.0 g, 2.30 mmol) in diphenyl ether (10 mL) and was refluxed for 6 h. The reaction mixture was subjected to the silica gel column. Using hexanes, diphenyl ether was removed first and further elution with 20% ethyl acetate and hexanes as an eluent gave 3-benzyl dihydroxanthyletin as a liquid compound (28) (0.20 g, 41%).

Expt. 3.17: Tandem Wittig reaction, Claisen, Cope rearrangement, deprenylation and cyclisation: Preparation of balsamiferone (3).

A solution of 2,4-o-(3,3-dimethylallyl)benzaldehyde (0.45 g, 1.66 mmol) and prenyl phosphorane (1.02 g, 2.46 mmol) in diphenyl ether (10 mL) and was refluxed for 6 h. The reaction mixture was loaded on the silica gel column. Using hexanes, diphenyl ether was removed first. Further elution with 20% ethyl acetate and hexanes as an eluent gave 7-hydroxy-3,6-bis(3-methylbut-2-enyl)coumarin (balsamiferone) 3, m.p.135° C (lit m.p. 134-136° C) (0.19 g, 42%).

Expt. 3.18: Preparation of 3, 4-dimethoxyphenol:

To a rapidly stirred solution of 3,4-dimethoxybenzaldehyde (2.1 g, 12.63 mmol) in dichloromethane (20 mL), m-CPBA (4.70 g, 27.26 mmol) in dichloromethane (10 mL) was added and continued stirring for 2 days. From the reaction mixture dichloromethane was distilled off and the solid separated was dissolved in methanol and THF (1:1) and then sodium hydroxide in methanol (2N, 20 mL) was added and reaction mixture was stirred for 2 h. Methanol and THF was distilled off and the solid was dissolved in water, washed with diethyl ether (recovered 3,4-dimethoxy-2-hydroxybenzaldehyde (500 mg). The aqueous layer was made acidic with 2N HCl under ice-cooling and extracted in diethyl ether (2 X 20 mL). The organic layer was dried over anhyd. sodium sulphate and was evaporated under vacuum. The crude was subjected to column chromatography using hexanes and ethyl acetate (9:1) as an eluent (1.1 g, 47.5%).

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Expt. 3.19: Preparation of 4, 5-dimethoxy-2-hydroxybenzaldehyde.

A solution of 3,4-dimethoxyphenol (1 g, 6.5 mmol) in trifluoroacetic acid (10 mL) was cooled to 0°C. To this slowly hexamine (1.1 g, 7.8 mmol) was added and was refluxed for 12 h. The reaction mixture was poured into ice cold saturated solution of sodium carbonate. Acidified it with 2N HCl and then extracted with ethyl acetate (2 X 25 mL). The product after evaporation of ethyl acetate was purified over silica gel column chromatography using ethyl acetate and hexanes (2:8) as an eluent to give 4,5-dimethoxy-2-hydroxybenzaldehyde as a yellow solid (0.54 g, 45.83%) m.p. 104°C (lit. m.p. 105°C).

Expt. 3.20: An alternate method for the preparation of 4,5-dimethoxy-2-hydroxybenzaldehyde.

a) Preparation of p-benzoquinone:

To the solution of chromium oxide (27.90 g, 0.18 mmol) in 40 ml of water, 15 ml of glacial acetic acid was added. This solution was slowly added to the previously cooled solution of hydroquinone (15 g, 0.17 mmol) in 70 ml of glacial acetic acid over a period 2 h. (temperature of reaction mixture was maintained below 10°C) The solid obtained was filtered and washed with ice-cold water to give p-benzoquinone as a yellow crystalline solid, m.p. 115°C (lit. m.p. 116°C) (9.47 g, 63.18%).

b) Preparation of 1, 2, 4-triacetoxy benzene:

p-benzoquinone (10 g, 0.093 mmol) was added in small portions to stirred solution of mixture of acetic anhydride (0.30 mmol) and sulphuric acid (0.25 ml) (temperature of reaction mixture was kept between 40-50°C). The reaction mixture was cooled and poured into 150 ml ice-cold water. Compound was filtered and recrystallized from ethanol to 1, 2, 4-triacetoxy benzene, m.p. 97°C (lit. m.p. 97°C (18.9 g, 81.01%).
c) Preparation of 1, 2, 4-trimethoxy benzene:

Dimethyl sulphate (95.26 g, 72 mL, 0.76 mol) was added to a solution of 1, 2, 4-triacetoxy benzene (9.02 g, 0.04 mol) in methanol (35 mL) with stirring. A solution of sodium hydroxide (2.9 g in 40 mL water) was added dropwise over a period of 1 h at 10°C and was stirred for 2 h at room temperature. To this then water (50 mL) was added and, was extracted in diethyl ether (3 X 50 mL). The combined ether layer was washed with water (50 mL) and dried over sodium sulphate. Evaporation of the solvent gave an oily product which on distillation furnished 1,2,4-trimethoxybenzene b.p. 247°C (lit m.p. 247°C) (9.64 g, 80.20%).

d) Preparation of 2, 4, 5-trimethoxybenzaldehyde:

Phosphorous oxychloride (5.64 g, 36.78 mmol) was added slowly to the cooled N, N-dimethylformamide (2.69 g, 36.78 mmol) at 0°C. The reaction mixture was allowed to attain room temperature. To this 1, 2, 4-trimethoxy benzene (4.12 g, 24.42 mmol) was added and the reaction mixture was heated on water bath for 4 h. The reaction mixture was cooled and to this saturated solution of sodium acetate (20 mL) was added followed by acidification using 2N hydrochloric acid. The white solid thus obtained was filtered, washed with water and dried. It was recrystallized from water to give 2, 4, 5-trimethoxy benzaldehyde, as white needles (m.p. 113°C, 78.75%) (lit m.p. 114°C).

e) Preparation of 2-hydroxy-4, 5-dimethoxybenzaldehyde.

A suspension of anhydrous aluminium chloride (4.35 g, 32.65 mmol) in dry methylene chloride (20 mL) was stirred at room temperature for 15 min. A solution of 2,4,5-trimethoxybenzaldehyde (3.2 g, 16.32 mmol) in methylene chloride (10 mL) was added to it. The reaction mixture was stirred for 6 h and poured over crushed ice containing hydrochloric acid. It was extracted with methylene chloride, dried over anhydrous sodium sulphate. Evaporation of the solvent gave solid which was chromatographed over silica gel using hexanes and ethyl acetate (8:2) as an eluent to give 2-hydroxy-4, 5-dimethoxybenzaldehyde (1.33 g, 44.78%) m.p. 104°C (lit m.p.105°C) and further elution gave 2, 4-dihydroxy-5-methoxybenzaldehyde (0.52 g, 18.97%, m.p. 149°C (lit m.p.152°C).
The mixture of 4, 5-dimethoxy-2-hydroxybenzaldehyde (1.02 g, 5.59 mmol) and potassium carbonate (1.15 g, 8.38 mmol) in acetone (20 mL), 3,3-dimethylallyl bromide (0.97 mL, 8.38 mmol) was added slowly in portions and was refluxed for 12 h. Then crude mixture was cooled, filtered and acetone was removed under vacuum. To this water (25 mL) was added and extracted in diethyl ether (3 X 25 mL). The combined organic layer was washed with water, dried over anhydrous sodium sulphate and evaporation of solvent under reduced pressure resulted in 4, 5-dimethoxy-2-prenyloxybenzaldehyde as yellow liquid (1.03 g, 73.57%).

Expt. 3.22: Tandem Wittig reaction, Claisen, Cope rearrangement and cyclisation: Preparation of 3-(3,3-dimethylallyl)-6,7-dimethoxybenzaldehyde (3-prenyl scoporane) and scoporane.

A solution of 2-o-(3,3-dimethylallyl)-4,5-dimethoxybenzaldehyde (0.53 g, 2.91 mmol) and triphenyl-a-carboethoxy-methylene phosphorane (1.52 g, 4.36 mmol) in diphenyl ether (10 mL) was refluxed for 3 h. The reaction mixture was loaded on the silica gel column. Using hexanes, diphenyl ether was removed first. Further elution with 20% ethyl acetate and hexanes as an eluent gave 3-(3, 3-dimethylallyl)-4, 5-dimethoxy-benzaldehyde (3-prenylscoporane) m.p.96-97°C (lit59 m.p. 95-96°C) and 6,7-dimethoxycoumarin (scoporane) m.p.143-144°C (lit61 m.p. 143-144°C) in (0.39 g, 48.24%) and (0.058 g, 9.6%) respectively.

Expt. 3.23: Preparation of ethyl-2(E)-4, 5-dimethoxy-2-o-(3, 3-dimethylallyl) cinnamate (32).

A solution of 2-o-(3, 3-dimethylallyloxy)-4,5-dimethoxy benzaldehyde (0.9 g, 3.6 mmol) and triphenyl-a-ethoxycarboethoxy-a-methylene phosphorane (1.88 g, 5.4 mmol) in toluene was refluxed for 6 h. Evaporation of solvent gave viscous liquid, which was purified by column chromatography over silica gel using hexanes and ethyl acetate (9:1) as an eluent, to afford E-ethyl 2, 4-di-o-(3,3-dimethylallyloxy) benzaldehyde (32) (0.91 g, 79.67%).
Expt. 3.24: Claisen/Cope rearrangement of ethyl-2(E)-4,5-dimethoxy-2-o-(3,3-dimethylallyl)cinnamate: Preparation of o-methyl ether of 7-hydroxy-6-methoxy-3(3-methyl-2-butenyl)coumarin and scoporane (30 and 31).

A solution of ethyl-2(E)-4,5-dimethoxy-2-o-(3,3-dimethylallyl)cinnamate (0.21 g, 0.65 mmol) in diphenyl ether was refluxed for 3 h. The reaction mixture was loaded on the silica gel column. Using hexanes, diphenyl ether was removed first. Further elution with 20% ethyl acetate and hexanes as an eluent gave 3-prenyl scoporane (30, 0.103 g, 57.74%) and 6, 7-dimethoxy coumarin (31, 10 mg, 7.4%).

Expt. 3.25: Preparation of 2, 4-o-(3,3-dimethylallyl)-6-methoxybenzaldehyde (33).

To the mixture of 2,4-dihydroxy-5-methoxy benzaldehyde (0.20 g, 1.19 mmol) and potassium carbonate (0.41 g, 2.97 mmol) in acetone (30 mL), 3,3-dimethylallyl bromide (0.44 g, 2.97 mmol) was added slowly in portions and was refluxed for 12 h. The crude mixture was then cooled, filtered and solvent was removed under vacuum. To this water (10 mL) was added and was extracted in diethyl ether (2 X 25 mL). The combined organic layer was washed with 2 N NaOH (25 mL) and then with water (25 mL) and was dried over anhydrous sodium sulphate. Evaporation of solvent under reduced pressure resulted in a yellow liquid of 33 (0.22 g, 60.77%).

Expt. 3.26: Tandem Wittig reaction, Claisen, double Cope rearrangement, deprenylation and cyclisation: Preparation of 8-(3-methyl-2-butenyl)-7-hydroxy-6-methoxycoumarin (cedrelopsin) (34).

A solution of 2, 4-o-(3,3-dimethyl)-6-methoxybenzaldehyde (0.10 g, 0.33 mmol) and triphenylcarboethoxy-α-methylene phosphorane (0.17 g, 0.49 mmol) in diphenyl ether (5 mL) was refluxed for 6 h. The reaction mixture was purified by column chromatography using hexanes to remove diphenyl ether first and further elution with 20% ethyl acetate gave 8-(3-methyl-2-butenyl)-7-hydroxy-6-methoxy coumarin, m.p.172°C (lit61 m.p. 170-172°C) (38 mg, 44.71%).
A solution of pyrogallol (4.15 g, 32.90 mmol), dimethylsulphate (12.5 mL, 131.63 mmol,) and potassium carbonate (18.16 g, 131.63 mmol) in acetone (50 mL) was refluxed for 12 h under nitrogen atmosphere. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated in vacuo. The residue obtained was dissolved in diethyl ether (50 mL), washed with 2N sodium hydroxide (20 mL) followed by water (20 mL). The ether layer was dried over anhydrous sodium sulphate and concentrated in vacuo to afford 1, 2, 3,-trimethoxybenzene, m.p. 44°C (lit 70-74°C) (4.41 g, 79.74%).

Expt. 3.28: Preparation of 2,3,4- trimethoxybenzaldehyde.

To the cooled N, N-dimethylformamide (2.13 mL, 27.6 mmol), phosphorous oxychloride (2.60 mL, 27.60 mmol) was added slowly at 0°C. To this 1,2,3-trimethoxybenzene (3.10 g, 28.4 mmol) was added and it was heated on water bath for 10 h. The mixture was poured into ice-cooled water and extracted in diethyl ether (2 X 25 mL). The combined organic layer was dried over sodium sulphate and concentrated in vacuo to give thick oil. It was then distilled under reduced pressure (b.p. 125°C/2 mm) to give 2,3,4-trimethoxybenzaldehyde as yellow coloured liquid (lit 70°C) (2.75 g, 76.40%).

Expt. 3.29: Preparation of 2,3,4-trihydroxy benzaldehyde.

To the solution of 2,3,4-trimethoxybenzaldehyde (2.74 g, 0.014 mol) in dichloromethane (20 mL), aluminium chloride (9.34 g, 0.07 mol) was added and stirred overnight. The mixture was poured into ice-cold water containing hydrochloric acid and was extracted in dichloromethane (2 X 20 mL) and then washed with water (20 mL). The organic layer was dried over sodium sulphate and concentrated in vacuo. The compound was purified by column chromatography using hexanes and ethyl acetate (6:4) as an eluent to give 2,3,4-trihydroxy benzaldehyde as a white solid (1.29 g, 60%).
To the solution of 2,3,4-trihydroxybenzaldehyde (0.2 g, 1.19 mmol) and potassium carbonate (0.57 g, 4.17 mmol) in acetone (20 mL), prenyl bromide (3, 3-dimethylallyl bromide) (0.5 mL, 4.17 mmol) was added slowly in portions and was refluxed for 10 h. The crude mixture was then cooled, filtered and acetone was removed under vacuum. To this water (10 mL) was added and was extracted in diethyl ether (2 X 20 mL). The combined organic layer was washed with 2 N NaOH (15 mL) followed by water (15 mL). The organic layer was dried over anhydrous sodium sulphate and evaporation of solvent gave liquid which was purified by column chromatography using hexanes and ethyl acetate (9:1) to give 2,3,4-triprenyloxybenzaldehyde as a colourless liquid (0.26 g, 60.10%).

Expt. 3.31: Tandem Wittig reaction, Claisen, Cope rearrangement, double deprenylation and cyclisation: Preparation of 8-hydroxydihydroxanthyletin (37).

A solution of 2,3,4-o-tris (3,3-dimethyallyloxy)benzaldehyde (0.11 g, 0.31 mmol) and triphenyl-α-carboethoxy-[methylene] phosphorane (0.16 g, 0.45 mmol) in diphenyl ether (5 mL) was refluxed for 6 h. The reaction mixture was purified by column chromatography using hexanes to remove diphenyl ether first and further elution with 20% ethyl acetate gave 8-hydroxy-dihydroxanthyletin (37) (12 mg, 16.00%).

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