Section 3.1
Green Synthesis of 2,3-Disubstituted Indoles
and 1,2,3,4-Tetrahydrocarbazoles

Introduction

Since the first synthesis of indole by Bayer in 1866, more synthetic routes to indoles have probably been published compared to any other heterocyclic or carbocyclic ring system and amongst these routes, the classical Fischer method has been the mainstay of chemists involved in the synthesis of indoles and their derivatives.

![Indole](image)

The first report on indolization of an arylhydrazone was published by Fischer and Jourdan in 1883 and was achieved by the reaction of pyruvic acid 1-methylphenylhydrazone with alcoholic HCl. However, it took almost a year for Fischer and Hess to identify the product of this reaction as 1-methylindole-2-carboxylic acid.

![Reaction](image)

Since this discovery, the reaction has been extensively used for the last more than 120 years and is the most versatile method for the preparation of indoles even today.
There are elaborate review articles reported\(^1\) in the literature on Fischer indole synthesis, its mechanism and applications. Secondly, lots of variations have been reported in the original Fisher indole synthesis.

In its simplest form, the Fischer indole synthesis involves the rearrangement of hydrazones, prepared from arylhydrazines and enolizable ketones, upon heating in acid with loss of ammonia to afford indoles. The use of acid catalyst could be avoided if sufficiently high temperatures are used\(^1\).

The process involves initial tautomerization to an ene-hydrazine that undergoes a [3,3]-sigmatropic rearrangement followed by ring closure and aromatization\(^2\).

![Chemical Reaction](image)

Normally Fischer indole synthesis involves acids as catalysts and acidic workup. Of course, use of acid catalyst is apparently not essential if sufficiently high temperatures are used\(^1\). Several phenylhydrazones were successfully indolized by non-catalytic thermal reaction. Phenylhydrazones have also been thermally rearranged to the corresponding indoles in the presence of NaOH with or without solvent\(^1\).

Our present work is in fact a minor modification of the reported\(^3\) Fischer-indole synthesis so as to make the process green. This method avoids the use of customary higher temperatures and corrosive mineral and Lewis acids as catalysts or during workup. Instead we have used ethanol as the solvent and acetic acid for acidification of the reaction mixture before workup.
temperatures involved are just the refluxing temperature of ethanol which is 77°C. Therefore we would like to consider this method to be a green process which neither makes use of high temperatures nor any toxic or corrosive chemicals.

It involved heating to reflux a mixture phenylhydrazine hydrochloride \(1\) (3.45 mmole), the appropriate ketone (3.28 mmole) in absolute ethanol (25 mL) under \(N_2\) atmosphere for 6 hrs. The \textit{in-situ} generated acid catalyzes the formation of indole nucleus. The workup of the reaction mixture was carried out using acetic acid instead of \(HCl\) affording the indole derivatives in pure form which were further recrystallised using appropriate solvent system.

\[
\begin{align*}
&\text{1} & \text{2 to 5} & \text{6 to 9} \\
\text{NH}_2\cdot\text{HCl} & \text{O} & \text{R} & \text{absolute} \text{ ethanol} \\
& \text{NH}_2 & \text{R} & \text{N}_2 \\
\end{align*}
\]

\textbf{Synthesis of 2,3-disubstituted indoles}

To begin with we used this method to prepare successfully four 2,3-disubstituted indole derivatives (6 to 9) in yields ranging from 70% to quantitative.

\textbf{1) 2,3-Dimethylindole 6}

Heating to reflux a mixture of phenylhydrazine hydrochloride 1 and butanone 2 in absolute ethanol under \(N_2\) atmosphere for 6 hrs followed by neutralisation of the cooled reaction mixture with glacial acetic acid gave 2,3-dimethylindole 6 as pale pink solid in \textbf{85% yield}. Recrystallization from petroleum ether afforded pale pink shiny flakes, m.p. 102°C (Lit.\(^4\) 104-106°C).
2,3-Dimethylindole 6 has been synthesized\(^5\) from phenylhydrazine and 2-methylpropanaldehyde in **50% yield**.

It has also been prepared\(^1\) by \(p\)-toluenesulfonic acid catalyzed indolization of butanone phenylhydrazone in the presence of acetic anhydride followed by treatment with acid or distillation from Zn dust.

Indolization of phenylhydrazones of methyl ketones are known to give exclusively the corresponding 3-substituted-2-methyl indoles\(^1\). However, indolization of butanone phenylhydrazone has been reported\(^6\) to give not only 2,3-dimethylindole 6 but also small amounts of 2-ethyindole.

2) **2-Ethyl-3-methylindole 7**

Similarly reaction of phenylhydrazine hydrochloride 1 with 3-pentanone 3 gave, after workup with glacial acetic acid, 2-ethyl-3-methylindole 7 as a viscous oil which solidified on standing in **quantitative yield**.
Recrystallization from hexane gave 7 as cream coloured flakes having m.p. 66°C (Lit. 4 64-66°C).

3) 3-Butyl-2-methylindole 8

Reaction of 2-heptanone 4 and phenylhydrazine hydrochloride 1 gave dark yellow oil of 3-butyl-2-methylindole 8 in 95% yield.

The indole 8 being a liquid its structure was determined by the analysis of its $^1$H NMR data which agreed well with that reported 2.

3-Butyl-2-methylindole 8 has been synthesized 3 recently (2005) but in only 54% yield from hexanenitrile, methyl lithium and 1. Moreover, this method requires expensive commercially available organolithium reagents or they are to be freshly prepared.
4) 3-Isopropyl-2-methylindole 9

Reaction of 4-methyl-2-pentanone 5 with phenylhydrazine hydrochloride 1 gave 3-isopropyl-2-methylindole 9 as dark yellow oil in only 29% yield. However, we could increase the yield up to 70% using excess of 1 and increasing the reaction time to 24 hrs.

The indole 9 being a liquid its structure was determined by the analysis of its $^1$H NMR data which agreed well with that reported$^7$.

Figure II: Assignments of $^1$H NMR signals for the various protons of 9
3-Isopropyl-2-methylindole 9 has been prepared\(^7\) (1998) along with 2-isopropyl-3-methylindole by the Pd catalyzed reaction of 2-iodoaniline and 4-methylpent-2-yne in DMF at 100°C in only 25% yield.

\[
\text{I} \quad \begin{array}{c}
\text{NH}_2 \\
\text{H}
\end{array}
\quad \text{C}_3 \text{H}_5\text{C} = \text{C} \quad \rightarrow \quad \text{I} \quad \begin{array}{c}
\text{NH}_2 \\
\text{H}
\end{array}
\quad \begin{array}{c}
\text{I} \quad \begin{array}{c}
\text{NH}_2 \\
\text{H}
\end{array}
\quad \begin{array}{c}
\text{I} \quad \begin{array}{c}
\text{NH}_2 \\
\text{H}
\end{array}
\end{array}
\end{array}
\]

We have successfully extended this method for the syntheses of five already reported tetrahydrocarbazole derivatives (10 to 14) and three new (15 to 17) tetrahydrocarbazole derivatives in yields ranging from 67% to quantitative.

**Synthesis of tetrahydrocarbazole derivatives (10 to 14)**

5) 1,2,3,4-Tetrahydrocyclopenta[β]indole 10

Reaction of cyclopentanone 18 with phenylhydrazine hydrochloride 1 gave after workup 1,2,3,4-tetrahydrocyclopenta[β]indole 10 as violet solid in quantitative yield. Recrystallization from petroleum ether gave violet crystals having m.p. 94°C.

Indole 10 has been synthesized\(^8\) (1999) in 75% yield using phenylhydrazine and cyclopentanone using zeolite as catalyst. We could not find...
the m.p. of the indole 10 reported in the literature hence it was characterised by IR and $^1$H NMR spectral data.

The $^1$H NMR spectrum of 10 showed three 2H singlets at δ 3.93 (C3-H), 3.86 (C1-H) and 3.79 (C2-H). Further a 1H singlet at δ 6.37 (C7-H), two 1H doublets ($J = 8.7$ Hz) at δ 6.94 (C6-H) & 7.62 (C5-H) and a 1H singlet at δ 7.87 (C9-H) supported the formation of 10.

6) 2,3,4,9-Tetrahydro-1H-carbazole 11 and
7) 5,6,7,8,9,10-Hexahydrocyclohepta[b]indole 12

Similarly the reaction of cyclohexanone 19 and cycloheptanone 20 with phenylhydrazine hydrochloride 1 gave 2,3,4,9-tetrahydro-1H-carbazole 11 and 5,6,7,8,9,10-hexahydrocyclohepta[b]indole 12 as solids in quantitative and 72% yield respectively.

Recrystallization from hexane gave colourless plates of 11 having m.p. 110°C (Lit. 110-114°C).

Hexahydrocarbazole 12 was obtained as pale yellow plates from ethanol having m.p. 134°C.

Compounds 11 and 12 have been synthesized\(^2\) (2006) in 54% and 55% yields by the reaction of phenylhydrazine with cyclopentan aldehyde and cyclohexanaldehyde respectively as shown below.
The m.p. of 12 is not reported and hence it was characterised by comparison of its NMR data which showed a 4H triplet ($J = 2.7$ Hz) at $\delta 1.86$ (C$_{6,7}$-H), a 2H doublet ($J = 5.1$ Hz) at $\delta 1.97$ (C$_5$-H), two 2H triplets ($J = 6.0$ Hz) at $\delta 2.83$ (C$_5$-H) & 2.9 (C$_9$-H), a multiplet between 7.18-7.22 (C$_{2,3}$-H), a 1H doublet ($J = 7.2$ Hz) at $\delta 7.28$ (C$_1$-H) and a 1H doublet ($J = 8.4$ Hz) at $\delta 7.57$ (C$_4$-H) supporting the formation of 12. The data recorded was in accordance with that reported on 12 in the literature.

8) 2-Methyl-2,3,4,9-tetrahydro-1H-carbazole 13

Some conflicting results are reported for the indolization of 3-methylcyclohexanone phenylhydrazone claiming that both the possible isomers 2-methyl-2,3,4,9-tetrahydro-1H-carbazole 13 and 4-methyl-2,3,4,9-tetrahydro-1H-carbazole 13a were formed. According to Grammaticakis the indolization of 3-methylcyclohexanone phenylhydrazone affords only 13, but in two other reports, the 2-methyl isomer 13 was isolated in low and unspecified yield suggesting that the 4-methyl isomer 13a might have been produced but was not isolated.
Interestingly when we carried out this reaction of 3-methylcyclohexanone 21 with phenyldrazine hydrochloride I using our method we got 2-methyl-2,3,4,9-tetrahydro-1H-carbazole 13 as wine red solid in quantitative yield. Recrystallization from petroleum ether afforded 13 as wine red cubes having m.p. 90°C. Neither m.p. nor the spectral data was available on 13 in the literature. Therefore, we characterized it fully by recording its spectral data.

The $^1$H and $^{13}$C NMR assignments for the various protons and carbons of 13 are shown below in figures III & IV.

![Figure III: Assignments of $^1$H NMR signals for the various protons of 13](image)

In the $^{13}$C NMR spectrum of 13, thirteen distinct signals (four quaternary, five methines, three methylenes and a methyl) were observed for all the 13 carbons of 13 as expected.
To confirm the position of the methyl group HMBC and HMQC correlation studies were carried out which fully supported the structure 13.

The $^1$H and $^{13}$C NMR assignments were made on the basis of HMBC correlations. The possibility of formation of 13a was ruled out since in the HMBC correlation spectrum, two methylene groups (C$_1$ & C$_4$) showed correlations to C-4a & C-9a which is possible only if the methyl group is at C-2. This was further supported by the correlation of C$_1$-H to C-2 and C$_2$-CH$_3$. Thus confirming the formation of 13.

9) 5,11-Dihydro-6H-benzo[a]carbazole 14

Reactions of 1-tetralone* 22 with phenylhydrazine hydrochloride 1 gave after workup 5,11-dihydro-6H-benzo[a]carbazole 14 as colourless solid in 76% yield.

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*1-Tetralone 22 was prepared by Jones oxidation of tetralin. We are thankful to Savia P. Torres for a sample of 22.
Recrystallization from petroleum ether-CHCl₃ gave colourless cubes having m.p. 158°C [Lit. ¹³ (1930) m.p. 160-161°C].

Its ESIMS data showed a peak at m/z 242.1 [M + Na]⁺ indicating its molecular formula to be C₁₆H₁₃N as expected.

Synthesis of new tetrahydrocarbazole derivatives (15 to 17)

10) 3-Methyl-2,3,4,9-tetrahydro-1H-carbazole 15

Reaction of 4-methylcyclohexanone 23 with phenylhydrazine hydrochloride 1 gave 3-methyl-2,3,4,9-tetrahydro-1H-carbazole 15 as colourless solid in 93% yield. Recrystallization from hexane gave colourless plates having m.p. 118°C.

The pattern of signals observed in the ¹H NMR spectrum of 15 was similar to that obtained for 2-methyl-2,3,4,9-tetrahydro-1H-carbazole 13 and the assignments of various protons in 15 are shown in figure VI.
Figure VI: Assignments of $^1$H NMR signals for the various protons of 15

The $^{13}$C NMR spectrum of 15 was also similar to that of 13 and showed thirteen distinct signals for all the 13 carbons and their assignments are shown below in figure VII.

Figure VII: Assignments of $^{13}$C NMR signals for the various carbons of 15

The ESIMS data on 15 showed a peak at $m/z$ 185.5 [M$^+$] indicating its molecular formula to be C$_{13}$H$_{13}$N as expected.

11) 2,5,5-Trimethyl-2,3,4,5,6,11-hexahydro-1H-benzo[a]carbazole 16.

Reaction of 4,4,7-trimethyl-1-tetralone$^*$ 24 with phenylhydrazine hydrochloride 1 gave after workup 2,5,5-trimethyl-2,3,4,5,6,11-hexahydro-1H-benzo[a]carbazole 16 as a brown solid in 67% yield.

$^*$ 4,4,7-Trimethyl-1-tetralone 24 was prepared by Jones oxidation of ionene which in turn was prepared from α- & β-ionones. We are thankful to Savia P. Torres for a sample of 24.
Recrystallization from petroleum ether-CHCl₃ gave pale brown flakes, m.p. 190°C. It is a new indole derivative and hence was fully characterized by recording its MS, ¹H, and ¹³C NMR data.

The ESIMS data of 16 showed a peak at m/z 261.5 [M⁺] indicating its molecular formula to be C₁₉H₁₉N as expected.

The ¹H NMR spectrum of 16 showed a 6H singlet at δ 1.4 (gem-dimethyl group at C₃), a 3H singlet at δ 2.5 (Ar-C₂-CH₃), and a 2H singlet at δ 2.9 (-CH₂- at C₆). The ¹³C NMR spectrum of 16 showed 18 signals as expected. The assignments of the ¹H & ¹³C NMR signals are shown below in figures VIII & IX.

Figure VIII: Assignments of ¹H NMR signals for the various protons of 16
Figure IX: Assignments of $^{13}$C NMR signals for the various carbons of 16

12) 1-Methoxy-4-methyl-5,10-dihydro-indeno[1,2-b]indole 17

Reaction of 4-methoxy-7-methyl-1-indanone $^{2}$ with phenylhydrazine hydrochloride 1 gave 1-methoxy-4-methyl-5,10-dihydro-indeno[1,2-b]indole 17 as pale yellow solid in quantitative yield.

Recrystallization from petroleum ether gave pale yellow cotton like threads, m.p. 128-130°C (decomp).

Compound 17 is also new and was fully characterized by the study of its spectral data. Its $^1$H NMR spectrum showed 3 characteristic singlets at δ 2.63 (3H, Ar-CH$_3$), δ 3.54 (2H, -C$_{10}$H$_2$) and δ 3.96 (3H, Ar-OCH$_3$). The assignments for the various protons in 17 are shown below in figure X.

$^{2}$ 4-Methoxy-7-methyl-1-indanone 25 was prepared from 6-methylcoumarin in 3 steps. We are thankful to Jose C Menezes for a sample of 25.
Its $^{13}$C NMR spectrum showed seventeen signals for the seventeen carbons and the assignments for the various carbons are shown below in figure XI.

The ESIMS data of 17 showed a peak at $m/z$ 249.5 [$M^+$] indicating it to have the molecular formula $C_{17}H_{15}NO$. 

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Figure X: Assignments of $^1$H NMR signals for the various protons of 17

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Figure XI: Assignments of $^{13}$C NMR signals for the various carbons of 17
2-Methylin dol e 26 and 2-phenylindole 27 have been prepared\textsuperscript{4} by desulfurization of 3-thioalkoxyindoles in 79 and 74\% yield respectively.

Attempts to prepare 26 from acetone and 27 from acetophenone using our above discussed method did not work and instead gave tarry residue after workup.

Similar results were obtained with 2-methylcyclohexanone and menthone.

The formation of dark tarry by-products in some cases during Fischer indolization have been reported\textsuperscript{1}. Camphor when subjected to similar reaction conditions was recovered unchanged.
Synthesis of Salvadoricine, constituent of *Salvadora persica*

**Introduction**

A large number of indole alkaloids have been isolated from a variety of plants and among them 2-acylindole alkaloids form one of the representatives\(^{14}\). Moreover, substituted 2-acylindoles also form a class of pharmacologically active compounds.

The plant *Salvadora Persica* (Salvadoraceae) is known in Pakistan as “Peelu” and is used in folk medicine for the treatment of human ailments. The leaves of this plant are used as a reputed diuretic and also as an odontological remedy (dentifrice to detoxify and strengthen the weakened gums)\(^{15}\).

From the ethanolic extracts of the fresh (not dried) leaves (10 kg) of *Salvadora persica* only 12 mg of the alkaloid salvadoricine (2-acetyl-3-methylindole) \(^{28}\), was isolated\(^{15}\) as a white crystalline solid, m.p. 143-144°C. Its structure was elucidated by spectral analysis and confirmed by synthesis using previously reported method\(^{16}\) and obtained only 32% yield.

![28](image)

**Salvadoricine**

This is the first and the only report on the isolation of \(^{28}\) as a natural product, although the compound 2-acetyl-3-methylindole \(^{28}\) was prepared before\(^{14}\). We have presented below all the available syntheses of 2-acetyl-3-methylindole \(^{28}\) reported before and after it was called salvadoricine so as to make a comparison with our method and also to have them at one place for ready reference.
Reported syntheses of 2-acetyl-3-methylindole 28

Prior to isolation of salvadoricine alkaloid, Jackson et al\textsuperscript{16}, during their studies on the acetylation of 3-methyl indole 29 using BF\textsubscript{3}-etherate obtained 2-acetyl-3-methylindole 28 in quantitative yield. However, the required starting 3-methylindole 29 had to be prepared or purchased.

![Reaction Scheme]

Reported syntheses of salvadoricine 28

1) Salvadoricine was synthesized by Pindur and Abdou\textsuperscript{17} in three steps as shown below. Hydrolysis of methylated pyranoidolone 30 gave 2-acetylindole-3-acetic acid 31 in 76\% yield. Decarboxylation of 31 using bromobenzene gave salvadoricine 28 in 80\% yield. However, the required starting pyranoidolone 30 had to be prepared from indole-3-acetic acid 32 using reported method\textsuperscript{18}.

![Reaction Scheme]

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2) During the synthesis of 3,5-disubstituted-2-acetylindoles, Rajur and coworkers\textsuperscript{19} prepared 2-acetyl-3-methyldindole 28 without knowing that it is salvadoricine in three steps as shown below.

\[
\begin{align*}
\text{PhNH}_2 + \text{HCl} & \xrightarrow{\text{NaNO}_2} \text{PhN} = \text{N} + \text{HCl} \\
\text{BrCO} - \text{CO} & \xrightarrow{\text{HCl}} \text{NH} - \text{N} \text{Cl} + \text{NaOH} \\
\text{boiling HCl} & \rightarrow \text{PhN} - \text{N} - \text{CO} \\
\end{align*}
\]

3) Furstner and Jumbam\textsuperscript{20} have used the titanium on graphite induced reductive coupling of carbonyl compounds (McMurry reaction) to prepare 28 in two steps as shown below.

\[
\begin{align*}
\text{PhNH}_2 + \text{CO} + \text{ClCO} & \xrightarrow{\text{pyridine CH}_2\text{Cl}_2} \text{NH} - \text{N} \text{CO} \\
\text{Ti-Graphite DME} & \rightarrow \text{PhN} - \text{N} - \text{CO} \\
\end{align*}
\]

Our Synthesis of 2-acetyl-3-methyldindole (salvadoricine) 28

The method developed for the synthesis of various 2,3-disubstituted indoles in the preceding part was successfully extended for the synthesis of salvadoricine in two steps as shown below.

\[
\begin{align*}
\text{PhNH}_2\text{HCl} + \text{ absolute ethanol} & \xrightarrow{\text{quantitative yield}} \text{PhN} - \text{N} - \text{CO} \\
\text{HIO}_4 + \text{Na}_2\text{S}_2\text{O}_8 & \rightarrow \text{PhN} - \text{N} - \text{CO} \\
\end{align*}
\]
The first step involving the reaction of phenylhydrazine hydrochloride 1 with 3-pentanone 3 was carried out in the preceding part and we obtained 2-ethyl-3-methylindole 7 in quantitative yield.

The second step involved conversion of 2-ethyl-3-methylindole 7 into 2-acetyl-3-methylindole 28.

Literature survey indicated that periodic acid has been used to selectively oxidize 2,3-disubstituted indoles and also tetrahydrocarbazoles at position 1 to give 2-acylindoles in good yields. Surprisingly oxidation with sodium periodate cleaves the indole double bond to give the corresponding ketoamides as shown below.

Therefore we oxidized 7 with periodic acid and obtained the required 2-acetyl-3-methylindole 26 in 81% yield.

A solution of 2-ethyl-3-methyl indole 7 in methanol was added to excess HIO₄ in methanol-water mixture. Usual workup left a brown residue which was purified by column chromatography. Elution with CHCl₃ gave fine pale yellow needles having m.p. 196-198°C.

In its IR spectrum bands at 3315 (NH) and 1627 (CO) cm⁻¹ were observed.

Its ¹H NMR spectrum showed only five distinct signals instead of the expected six signals. Two 3H singlets at δ 2.50 (C₃-CH₃) and 2.54 (-COCH₃)
was indicative of 2-acetyl-3-methyl grouping. Further a 1H doublet at δ 7.24 (J = 8.7 Hz, Ar-H), a 1H doublet of doublet at δ 7.49 (J = 8.7, 1.5 Hz, Ar-H) and a 1H singlet at δ 8.05 indicated it to be a mono-substituted (on the benzene moiety) 2-acetyl-3-methyl indole.

The 13C NMR spectrum showed 11 signals as expected for the 11 carbons present but one of the sp2 carbon obviously of the benzene moiety is attached to an electronegative atom probably the I atom.

Its ESIMS data showed a peak at m/z 299.9983 [M + H]+ which suggested the molecular formula of this compound to be C11H10INO indicating that iodine is incorporated most probably at the C5-position giving 2-acetyl-5-iodo-3-methyl-indole 33 which could account for the observed NMR data.

![Structure of 33](image)

The formation of the iodo derivative 33 of the required indole 28 was due to excess of HIO4 liberating molecular I2. Hence it was necessary to trap the liberated I2 and this was achieved by the addition of sodium thiosulfate to the reaction mixture.

A solution of 2-ethyl-3-methyl indole 7 in methanol was added to a solution of sodium thiosulfate and excess of HIO4 in methanol-water mixture. Usual workup gave a white solid. Recrystallization from petroleum ether gave white cottony threads having m.p. 142°C (Lit. 143-144°C).

![Structure of 28](image)
Its IR spectrum showed bands at 3325(NH) and 1632(CO) cm$^{-1}$.

In its $^1$H NMR spectrum two 3H singlets at $\delta$ 2.64 (C$_3$-CH$_3$) & 2.64(C$_2$-COCH$_3$) and four signals due to 4 aromatic protons, at $\delta$ 7.14 (dd, $J$ = 6.9, 1.8 Hz, C$_5$-H), 7.37 (d, $J$ = 6.6 Hz, 2H C$_6$,7-H) and 7.69 (d, $J$ = 8.4 Hz, C$_4$-H) supported the formation of salvadoricine 28 and the data was in accordance with that reported$^{15}$ for the natural product.
Fig. 3.01: $^1$H NMR spectrum of 13
Fig. 3.02. $^{13}$C NMR spectrum of 13
Fig. 3.03: $^1$H-$^{13}$C HMBC spectrum of 13
Fig. 3.04: $^1$H-$^{13}$C HMQC spectrum of 13
Fig. 3.05: $^1$H NMR spectrum of 15
Fig. 3.06: $^{13}$C NMR spectrum of 15
Fig. 3.07: $^1$H NMR spectrum of 16
Fig. 3.08: $^{13}$C NMR spectrum of 16
Fig. 3.09: $^1$H NMR spectrum of 17
Fig. 3.10: $^{13}$C NMR spectrum of 17
Fig. 3.11: DEPT spectrum of 17
Fig. 3.12: IR spectrum of 33
Fig. 3.13: $^1$H NMR spectrum of 33
Fig. 3.14: $^{13}$C NMR spectrum of 33
Fig. 3.15: ESIMS spectrum of 33
Experimental

General procedure for the preparation of indoles

A mixture of phenylhydrazine hydrochloride 1 (3.45 mmole) and the appropriate ketone (3.28 mmole) in absolute ethanol (25 mL) was heated to reflux under N₂ atmosphere for 6 hrs. The reaction mixture was cooled to room temperature and poured in glacial acetic acid.

In those cases where the indole derivatives separated out as solids were filtered, washed with 5% Na₂CO₃, water and dried. Pure crystalline indole derivatives were obtained by recrystallization of the solids using appropriate solvents mentioned under respective indole derivative.

In cases where they separated out as oil, the reaction product was extracted with CHCl₃, washed with 5% Na₂CO₃, water, dried over Na₂SO₄ and the solvent evaporated to give the corresponding indole derivatives.

2,3-Dimethylindole 6

\[
\begin{array}{c}
\text{H} \\
6
\end{array}
\]

Reaction of phenylhydrazine hydrochloride 1 (0.5 g, 3.45 mmole) with butanone 2 (0.235 g, 3.28 mmole) gave 2,3-dimethylindole 6 as a pink solid (0.402 g, 85% yield). Recrystallization from petroleum ether gave pink coloured shiny flakes, m.p. 102°C, Lit.¹ 104-106°C.

IR νmax (KBr): 3390 (NH), 1617, 1465, 740 cm⁻¹.
2-Ethyl-3-methylindole 7

![Chemical Structure of 2-Ethyl-3-methylindole](image)

Reaction of phenylhydrazine hydrochloride 1 (0.5 g, 3.45 mmole) with 3-pentanone 3 (0.281 g, 3.28 mmole) gave 2-ethyl-3-methylindole 7 as off-white solid (0.519 g) in quantitative yield. Recrystallization from hexane gave cream coloured flakes, m.p. 66°C, Lit.⁴ 64-66°C.

IR ν max (KBr): 3398 (NH), 2964, 1618, 1462, 744 cm⁻¹.

3-Butyl-2-methylindole 8

![Chemical Structure of 3-Butyl-2-methylindole](image)

Reaction of phenylhydrazine hydrochloride 1 (0.5 g, 3.45 mmole) and 2-heptanone 4 (0.374 g, 3.28 mmole) gave 3-butyl-2-methylindole 8 in the form of dark yellow oil as reported² (0.595 g, 95% yield).

IR ν max (KBr): 3400 (NH), 1617, 1454, 738 cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): For assignments refer Figure I, pg 243.
3-Isopropyl-2-methylindole 9

![Structure](image)

Reaction of phenylhydrazine hydrochloride 1 (0.5 g, 3.45 mmole) with 4-methyl-2-pentanone 5 (0.328 g, 3.28 mmole) for 24 hrs gave 3-isopropyl-2-methylindole 9 in the form of dark yellow oil as reported (0.397 g, 70% yield).

**IR** $v_{\text{max}}$ (KBr): 3404 (NH), 2951, 1469, 734 cm$^{-1}$.

**$^1$H NMR** (CDCl$_3$, 300 MHz): For assignments refer Figure II, pg 244.

1,2,3,4-Tetrahydrocyclopenta[b]indole 10

![Structure](image)

Reaction of phenylhydrazine hydrochloride 1 (0.5 g, 3.45 mmole) with cyclopentanone 18 (0.374 g, 3.28 mmole) gave 1,2,3,4-tetrahydrocyclopenta[b]-indole 10 as a violet coloured solid (0.515 g) in quantitative yield. Recrystallization from petroleum ether gave violet coloured crystals m.p. 94°C.

**IR** $v_{\text{max}}$ (KBr): 3400 (NH), 1617, 1454, 738 cm$^{-1}$.

**$^1$H NMR** (CDCl$_3$, 300 MHz): $\delta$ 3.79 (s, 2H, C$_2$-H), 3.86 (s, 2H, C$_1$-H), 3.93 (s, 2H, C$_3$-H), 6.37 (s, 1H, C$_7$-H), 6.94 (d, $J = 8.7$ Hz, 1H, C$_6$-H), 7.62 (d, $J = 8.7$ Hz, 1H, C$_5$-H), 7.87 (s, 1H, C$_8$-H).
2,3,4,9-Tetrahydro-1H-carbazole 11

\[
\begin{array}{c}
\text{11}
\end{array}
\]

Reaction of phenylhydrazine hydrochloride 1 (0.5 g, 3.45 mmole) with cyclohexanone 19 (0.321 g, 3.28 mmole) gave 2,3,4,9-tetrahydro-1H-carbazole 11 as white solid (0.56 g) in quantitative yield. Recrystallization from hexane gave colourless plates m.p. 110°C, Lit. 110-114°C.

IR \nu_{\text{max}} (KBr): 3390 (NH), 1617, 1468, 742 cm\textsuperscript{-1}.

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz): \delta 1.91 (d, J = 4.5 Hz, 4H, C\textsubscript{2,3-H}), 2.74 (t, J = 6.0 Hz, 4H, C\textsubscript{1,4-H}), 7.1 (d, J = 6.5 Hz, 1H, C\textsubscript{6-H}), 7.15 (d, J = 7.2 Hz, 1H, C\textsubscript{7-H}), 7.28 (d, J = 7.2 Hz, 1H, C\textsubscript{8-H}), 7.5 (dd, J = 6.3, 1.5 Hz, 1H, C\textsubscript{5-H}).

5,6,7,8,9,10-Hexahydrocyclohepta[b]indole 12

\[
\begin{array}{c}
\text{12}
\end{array}
\]

Reaction of phenylhydrazine hydrochloride 1 (0.5 g, 3.45 mmole) with cycloheptanone 20 (0.368 g, 3.28 mmole) gave 5,6,7,8,9,10-hexahydrocyclohepta-[b]indole 12 as light yellow solid (0.597 g, 72% yield). Recrystallization from ethanol gave pale yellow plates of 12, m.p. 134°C.

IR \nu_{\text{max}} (KBr): 3394 (NH), 2912, 1617, 1466, 740 cm\textsuperscript{-1}.

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz): \delta 1.86 (t, J = 2.7 Hz, 4H, C\textsubscript{6,7-H}), 1.97 (d, J = 5.1 Hz, 2H, C\textsubscript{8-H}), 2.83 (t, J = 6.0 Hz, 2H, C\textsubscript{5-H}), 2.9 (t, J = 5.7 Hz, 2H, C\textsubscript{9-H}), 7.18-
7.22 (m, 2H, C_{2,3}-H), 7.28 (d, J = 7.2 Hz, 1H, C_{1}-H), 7.57 (d, J = 8.4 Hz, 1H, C_{4}-H).

2-Methyl-2,3,4,9-tetrahydro-1H-carbazole 13

Reaction of phenylhydrazine hydrochloride 1 (0.5 g, 3.45 mmole) with 3-methylcyclohexanone 21 (0.367 g, 3.28 mmole) gave 2-methyl-2,3,4,9-tetrahydro-1H-carbazole 13 as wine red coloured solid (0.606 g) in quantitative yield. Recrystalization from petroleum ether gave wine red coloured cubes m.p. 90°C.

IR \nu_{\text{max}} (KBr): 3404 (NH), 2949, 1487, 1300, 740 cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\), 300 MHz, Fig. 3.01): For assignments refer Figure III, pg 248.

\(^{13}\)C NMR (CDCl\(_3\), 75 MHz, Fig. 3.02): For assignments refer Figure IV, pg 249.

5,11-Dihydro-6H-benzo[\(a\)]carbazole 14

Reaction of phenylhydrazine hydrochloride 1 (0.5 g, 3.45 mmole) and 1-tetralone 22 (0.475 g, 3.28 mmole) gave 5,11-dihydro-6H-benzo[\(a\)]carbazole 14 as white solid (0.507 g, 76% yield). Recrystalization from petroleum ether and CHCl\(_3\) mixture gave colourless cubes m.p. 158°C, Lit.\(^\text{13}\) 160-161°C.
IR \( \nu_{\text{max}} \) (KBr): 3427 (NH), 1462, 1303, 741 cm\(^{-1}\).

ESIMS: \( m/z \) [M + Na]\(^+\) calcd for C\(_{16}\)H\(_{13}\)NNa 242.0940, Found 242.1.

3-Methyl-2,3,4,9-tetrahydro-1H-carbazole 15

![Structure 15]

Reaction of phenylhydrazine hydrochloride 1 (0.5 g, 3.45 mmole) with 4-methylcyclohexanone 23 (0.367 g, 3.28 mmole) gave 3-methyl-2,3,4,9-tetrahydro-1H-carbazole 15 as white solid (0.564 g, 93% yield). Recrystallization from hexane gave colourless plates m.p. 118°C.

IR \( \nu_{\text{max}} \) (KBr): 3400 (NH), 2920, 1480, 740 cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\), 300 MHz, Fig. 3.05): For assignments refer Figure VI, pg 251.

\(^13\)C NMR (CDCl\(_3\), 75 MHz, Fig. 3.06): For assignments refer Figure VII, pg 251.

ESIMS: \( m/z \) [M]\(^+\) calcd for C\(_{13}\)H\(_{15}\)N 185.1205, Found 185.5.

2,5,5-Trimethyl-5,11-Dihydro-6H-benzo[a]carbazole 16

![Structure 16]

Reaction of phenylhydrazine hydrochloride 1 (0.5 g, 3.45 mmole) with 4,4,7-trimethyl-1-tetralone 24 (0.544 g, 3.28 mmole) gave 16 as brown solid (0.502 g, 282
66.5% yield). Recrystallization from petroleum ether and CHCl₃ mixture gave pale brown flakes m.p. 190°C.

IR νmax (KBr): 3402 (NH), 1515, 1466, 746 cm⁻¹.

¹H NMR (CDCl₃, 300 MHz, Fig. 3.07): For assignments refer Figure VIII, pg 252.

¹³C NMR (CDCl₃, 75 MHz, Fig. 3.08): For assignments refer Figure IX, pg 253.

ESIMS: m/z [M]⁺ calculated for C₁₀H₁₉N 261.1517, Found 261.5.

1-Methoxy-4-methyl-5,10-dihydro-indeno[1,2-b]indole 17

Reaction of phenylhydrazine hydrochloride 1 (0.5 g, 3.45 mmole) and 4-methoxy-7-methyl-1-indanone 25 (0.577 g, 3.28 mmole) gave 17 as yellow solid (0.816 g) in quantitative yield. Recrystallization from petroleum ether gave pale yellow crystals like cotton threads, m.p. 128-130°C (decomp.).

IR νmax (KBr): 3400 (NH), 1590, 1458, 737 cm⁻¹.

¹H NMR (CDCl₃, 300 MHz, Fig. 3.09): For assignments refer Figure X, pg 254.

¹³C NMR-DEPT (CDCl₃, 75 MHz, Fig. 3.10 & Fig. 3.11): For assignments refer Figure XI, pg 254.

ESIMS: m/z [M]⁺ calcd for C₁₇H₁₉NO 249.1153, Found 249.5.
To a solution of HIO₄ (1.434 g, 6.58 mmol) in 1:1 methanol:water mixture (15 mL) was added drop by drop 2-ethyl-3-methylindole 7 (0.5 g, 3.14 mmol) in methanol (4 mL) at 0°C. The reaction mixture was stirred at 0°C for 1 hr and then at room temperature for 1 hr. The dark coloured reaction mixture was decanted and the aqueous portion was extracted with CHCl₃ (3 × 10 mL). The organic extracts were then washed with saturated Na₂CO₃ (3 × 10 mL), dilute sodium bisulfite solution (3 × 10 mL), water (3 × 10 mL), dried over Na₂SO₄ and evaporated to leave a crude brown residue (0.7 g). The residue was purified by column chromatography using silica gel (200-400 mesh) and elution with CHCl₃ gave 2-acetyl-5-iodo-3-methylindole 33 (0.327 g, 60%) as fine pale yellow needles m.p. 196-198°C.

**IR** νmax (KBr, Fig. 3.12): 3315(NH), 1627(CO) cm⁻¹.

**¹H NMR** (DMSO-d₆, 300 MHz, Fig. 3.13): δ 2.50 (s, 3H, C₃-CH₃), 2.54 (s, 3H, C₂-COCH₃), 7.24 (d, J = 8.7 Hz, 1H, C₆-H), 7.49 (dd, J = 8.7, 1.5 Hz, 1H, C₇-H), 8.05 (s, 1H, C₄-H).

**¹³C NMR** (DMSO-d₆, 75 MHz, Fig. 3.14): δ 10.82 (C₃-CH₃), 29.49 (C₂-COCH₃), 83.5 (C-5), 115.34 (C-3), 117.19 (C-7), 129.81 (C-6), 131.08 (C-4), 133.19 (C-3a), 133.72 (C-2), 135.54 (C-7a), 191.18 (CO).

**ESIMS** (Fig. 3.15): m/z [M + H]+ calcd for C₁₁H₁₁INO 299.987975, Found 299.9983.
2-Acetyl-3-methylindole 28 (salvadoricine)

To a solution of HIO₄ (1.434 g, 6.58 mmol) & sodium thiosulfate (50 mg) in methanol:water (1:1, 15 mL) was added drop by drop 2-ethyl-3-methylindole 7 (0.5 g, 3.14 mmol) in methanol (4 mL) at 0°C. The reaction mixture was stirred at 0°C for 1 hr and then at room temperature for 1 hr. The dark coloured reaction mixture was decanted and the aqueous portion was extracted with diethyl ether (3 × 10 mL). The organic extracts were then successively washed with saturated Na₂CO₃ (3 × 10 mL), dilute sodium bisulfite (3 × 10 mL), water (3 × 10 mL), dried over Na₂SO₄ and evaporated to leave 2-acetyl-3-methyl-indole 28 as white solid (0.442 g, 81% yield). Recrystallization from petroleum ether gave white crystals like cotton threads, m.p. 142°C (Lit.¹⁵ 143-144°C).

IR νₘₚₓ (KBr): 3325 (NH), 1632 (CO) cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): δ 2.64 (s, 3H, C₃-H₃), 2.64 (s, 3H, COCH₃), 7.14 (dt, J = 6.9, 1.8 Hz, 1H, C₅-H), 7.37 (d, J = 6.6 Hz, 2H, C₆,7-H), 7.69 (d, J = 8.4 Hz, 1H, C₄-H).
References

Section 3.2

Studies towards the Synthesis of Grandifloracin, a Constituent of *Uvaria grandiflora*

Characterization of Two New Compounds Similar to Grandifloracin

**Introduction**

The genus *Uvaria* of the family *Annonaceae* has been known to be a rich source of bioactive compounds. Several compounds with novel carbon framework have been isolated by the elegant studies of various groups.

Yong-Hong and coworkers\(^1\) carried out a systematic chemical investigation of the CH\(_2\)Cl\(_2\) extract of *Uvaria grandiflora* and isolated a crystalline biscyclohexene oxide grandifloracin 1 (m.p. 161-163°C) in addition to two cyclohexene oxides zeylenone and grandiflorone. The structure 1 including the relative stereochemistry assigned to it was based on the detailed spectral analysis (UV, IR, \(^1^H, \(^1^3^C \text{ NMR}, \text{ COSY, HMBC, MS}).

\(\text{BzO} \quad \text{HO} \quad \text{O} \quad \text{OBz} \quad \text{OH} \quad \text{O} \quad \text{1}\)

**Results and discussion**

The carbon framework of 1 attracted our attention and it was proposed\(^*\) that 1 is derived from two molecules of 2 by Diels-Alder self-dimerization. Due to our continued interest in the synthesis of naturally occurring compounds derived from Diels-Alder self-dimerization it was suggested\(^2\) that the ideal route

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*We are grateful to Prof. S. K. Paknikar for his interest & contribution in proposing biogenesis and biogenetic type synthesis of natural products and making useful suggestions during this work.*
towards the synthesis of 1 could be saligenin 3 which is known to dimerize upon oxidation with sodium metaperiodate (NaIO₄) to the corresponding dimer 4.

This work involving biogenetic type synthesis of 1, starting with saligenin 3 was initiated in our Laboratory by Dr. Asha D’Souza in 1999. However, all her attempts to prepare 5, the monobenzoate of 3 did not yield to. Of course, she did succeed in preparing 6, the monoacetate of 3 but unfortunately, NaIO₄ as well as HIO₄ oxidation of 6 did not yield the expected dimer 7 but resulted in the total recovery of the starting material. For details please refer to her thesis².
The dimer 4 is also reported to give a crystalline compound 8, when treated with HBr, by the nucleophilic oxirane ring opening. The structural features of 4 and 8 are ideally suitable for their conversion into 1 either by opening of the oxirane rings or by displacement of the bromide by the benzoate nucleophile.

These reactions were also carried out but with partial success i.e the reaction of 8 with sodium benzoate in the presence of TBAB did give an impure product (mixture of two compounds) having NMR data close to that of 1.

Therefore we decided to retry the synthesis of grandifloracin 1 by making necessary modifications in the previously used reaction conditions, reagents etc. mainly because until then (2004) the synthesis of 1 was not reported.

Moreover, we came across a regioselective ring opening reaction of epoxides with benzoic acid and its derivatives in the presence of catalytic amount of tetrabutylammonium bromide (TBAB) in anhydrous acetonitrile to give benzyolated 1,2-diols from terminal epoxides.
Simple reaction conditions and good yields encouraged us to try the above reaction on the saligenin dimer 4 which also being a substituted terminal diepoxide should give the required grandifloracin 1 in single step.

Thus a solution of 4 and excess of benzoic acid in anhydrous CH$_3$CN was refluxed for 8 hrs. Usual workup of the reaction mixture gave a brown viscous residue. Purification by column chromatography and elution with CHCl$_3$:MeOH (9.8:0.2) gave a white solid having m.p. 164-66°C. Although the m.p. of the white solid obtained was close to that of natural grandifloracin 1 (161-163°C), it got raised to 182°C on recrystallization from acetonitrile.

Although its IR spectrum showed the presence of two OH groups as expected for 1, their frequencies at 3570 & 3400 cm$^{-1}$ did not match with those reported for 1. Moreover, only two carbonyl bands at 1726 cm$^{-1}$ (ester CO) and at 1687 cm$^{-1}$ (probably the conjugated CO) were observed. The third carbonyl band seen at around 1700 cm$^{-1}$ in the IR of 1 was missing.

Therefore, we determined its molecular formula to be C$_{21}$H$_{18}$O$_6$ on the basis of its ESIMS data which showed a peak at m/z 367.1499 [M + H]$^+$. This clearly indicated that one out of the two expected benzoate groups (C$_7$H$_5$O$_2$) present in 1 was missing.

The $^1$H NMR spectrum of the white solid having m.p. 182°C showed the presence of three OH groups, one monosubstituted benzene ring, two additional aromatic protons, only two olefinic protons and two methylene groups attached to oxygen atom.

Its $^{13}$C NMR spectrum showed 19 signals, out of which eight were quaternary (including two of carbonyl carbons at $\delta$ 201.05 & 165.03), two
methylenes (δ 67.94 & 53.65) and nine methines as indicated by its $^{13}$C NMR DEPT spectrum.

On the basis of the above spectroscopic information and also by comparison of the IR, $^1$H and $^{13}$C NMR data reported for 1, and that of the white solid, we could arrive at the following structure 9 which can account for all the signals observed in the NMR data and their assignments are shown below in figures I and II.

**Figure I:** Assignments of $^1$H NMR signals for the various protons of 9

**Figure II:** Assignments of $^{13}$C NMR signals for the various carbons of 9

The structure 9 was further supported by HMBC experiments. In the HMBC the tertiary hydroxyl proton correlated to C-1, C-10 & C-1' indicating that
the tertiary hydroxyl is at C-9; correlation of C_1-H to C-9, C-10 & C-2' indicated that the -CH_2-COOPh is attached to C-9. Further correlation of C_4-H and C_3-H to C-5 established the position of the phenolic OH at C-5.

**Figure III:** Selected HMBC of 9

The EIMS fragmentation pattern also supports structure 9. In addition to the peak at m/z 367 [M + H]^+ its mass spectrum showed significant peaks at m/z 349 (100%), 321 and 199. The possible mode of fragmentation and the likely structures for the major fragment ions are shown in chart-1.

**Chart-1:** Mass spectral fragmentation pattern of 9
The probable mechanism for the formation of 9 from the dimer 4 is rationalised below in scheme 1:

It appears that the reaction is initiated by protonation of the conjugated carbonyl with H⁺ in the presence of benzoic acid leading to dienol epoxide which immediately undergoes aromatization as shown below in scheme 1. The other epoxide is opened up by the nucleophilic attack of the benzoate anion.

Scheme 1: Probable mechanism for the formation of 9 from 4

Meanwhile we came across another literature report for the synthesis of esters of benzoic acid wherein bromide is displaced by the benzoate anion. The method involved heating a mixture of potassium salt of benzoic acid with appropriate bromo-compound in either DMF or DMSO as solvents.

Thus a mixture of dibromide 8 and potassium benzoate in dry DMF was heated to 85°C for 2 hrs. Workup of the reaction mixture gave dark yellow viscous oil. Purification by silica gel column chromatography using CHCl₃:MeOH (9.8:0.2) as eluent afforded white solid having m.p. 164-66°C. Recrystallization from CH₃CN gave white crystals (m.p. 182°C) identical with 9 (m.p., co-TLC and IR).

Similar results were obtained when the reaction was carried out using anhydrous DMSO as solvent at 100-105°C.
Having failed to obtain the required compound 1 we thought of repeating the reaction of the dibromide 8 and sodium benzoate in the presence of TBAB as catalyst. As mentioned before, this reaction was carried out previously in our laboratory\(^2\) and the product obtained had striking similarities in its NMR data with that of natural grandifloracin 1.

Reaction of the dibromide 8 with potassium benzoate in refluxing benzene and water mixture in the presence of TBAB after usual workup gave a pale brown residue. TLC (\(C_6H_6:Et_2O; 95:5\)) indicated it to be a mixture of two compounds, dimer 4 and a more polar component. Purification by column chromatography using \(C_6H_6\) as eluent gave dimer 4 (co-TLC, m.p. and IR).

Further elution with \(C_6H_6:Et_2O\) (8:2) gave a white solid. Careful observation of TLC (\(C_6H_6:Et_2O; 6:4\)) indicated it to be a mixture of two closely spaced spots which could be resolved using \(CHCl_3:EtOAc\) (9:1) as solvent system. The white solid was reloaded on silica gel column and purified by using \(CHCl_3:EtOAc\) (98:2) as eluent to give a white solid. Recrystallization from the same solvent gave white shiny flakes having m.p. 180°C. Although the m.p. of the solid obtained was very close to that of 9 (m.p. 182°C), its TLC and IR clearly indicated its non-identity with 9 and it was given number 10.

IR spectrum of 10 showed the presence of three carbonyls (1736, 1708 & 1691 \(cm^{-1}\)) as reported\(^1\) for grandifloracin 1 but showed a band at 3500 \(cm^{-1}\) indicating the presence of only one OH group in 10.

The ESIMS spectrum of 10 showed two molecular ion peaks at \(m/z\) 389.1416 \([M + Na]^+\) and 367.3094 \([M + H]^+\). Thus its molecular formula was determined to be \(C_{21}H_{18}O_6\) same as that of the compound 9.

The \(^1H\) NMR spectrum of 10 showed striking similarities to 1, however the aromatic region showed signals accounting for only nine protons (five of the benzene ring and four olefinic protons) indicating the presence of only one monosubstituted benzene ring. Further two doublets at \(\delta\) 2.94 and 3.1 \((J = 6\ \text{Hz})\) integrated for 1H each indicated the presence of an oxirane ring.
The $^{13}$C NMR and DEPT spectra of 10 showed in all 19 signals of six quaternary carbons (including three of carbonyl carbons), two methylenes and eleven methines for 21 carbons present in 10.

Thus on the basis of the above IR, NMR & MS data, the compound 10 was assigned the following structure which can account for all the signals observed in the $^1$H and $^{13}$C NMR spectra of 10 and their assignments for the various protons and carbons of 10 are shown below in figures IV and V.

Figure IV: Assignments of the $^1$H NMR signals for the various protons of 10

Figure V: Assignments of the $^{13}$C NMR signals for the various carbons of 10
The structure was further supported by HMBC experiments (figure VI). In the HMBC spectrum, the C1-H correlated to C-2' and C-4 indicating that the \(-\text{CH}_2\)-COOPh is attached to C-3. The C5-H correlated to C-7 & C-3 and the C6-H correlated to C-4, C-2 & C-8. Further correlation of C1-H to C-9 & C-9' indicated oxirane ring at C-10.

![Figure VI: HMBC of 10](image)

Thus the compound 10 of which NMR data appeared very close to that of 1 is in fact having all the structural features of 1, except one benzoate unit and a tertiary OH group. Instead there is an oxirane ring. Although 10 is formed from dibromide 8 and not from the dimer 4, it appears as if the structure 10 is derived by opening of one of the two oxirane rings of the dimer 4 and not both the rings to give 1. Therefore we may name it as semi-grandifloracin.

During its formation from dibromide 8 only one bromine got displaced by the external benzoate nucleophile, while the other bromine was displaced by the internal tertiary OH nucleophile. And this was always observed whenever the dibromide 8 was used; we obtained invariably some amount of the dimer 4 as the side product by intramolecular nucleophilic displacement of the bromide.

Iodine being a better leaving group than bromine we thought of preparing the di-iodo compound 11 so that the nucleophilic displacement of iodine by benzoate may facilitate the formation of 1. Moreover, we came across a report wherein oxirane ring was opened up using I2 in dioxane.
Thus the reaction of the dimer 4 with two equivalents of I$_2$ in dioxane using reported conditions should give the di-iodo compound 11. However, when this reaction was carried out we could neither isolate the product nor recover the starting dimer 4.

Literature survey revealed that there are only two reports for the preparation of 2-hydroxybenzyl benzoate 5. The first report was on its preparation from the azide of saligenin 3 and the second by selective monobenzoylation of 3 using diethylbenzoyl phosphonate 12.

We thought of preparing 5 as per the second report using diethylbenzoyl phosphonate 12.
The required diethylbenzoyl phosphonate 12 was prepared by the reaction of benzoyl chloride with triethyl phosphite* at 0°C followed by reduced pressure distillation to give yellow oil (b.p. 140-142°C at 3 mm) as reported9.

The reaction of saligenin 3 with 12 in the presence of 1,5-diazabicyclo[5,4,0]undec-5-ene (DBU) after usual workup gave sticky residue insoluble in common organic solvents and was not investigated.

Meanwhile we came across a report10 wherein saligenin 3 was oxidised to diacetoxy cyclohexadienone 13 using NaIO4 in Ac2O. Therefore, we decided to prepare grandifloracin 1 as per the scheme 2 in which the acetylative oxidation of 3 would give the dieneone diacetate 13. Protection of the carbonyl followed by base catalyzed hydrolysis would give the protected diene diol 14. Selective benzoylation of the primary alcohol with simultaneous deprotection of the carbonyl would give in-situ the required o-quinol 2 that would immediately dimerize to 1.

Scheme 2

* We are thankful to Dr. S. G. Tilve, Goa University, for providing triethyl phosphite and DBU
However, after several attempts even with different hands, oxidation of 3 gave the diacetate 15 as yellow oil but we never got even a trace of the reported product 13 indicating that the reported reaction\textsuperscript{10} was not reproducible.

Thus in conclusion, although we did not succeed in synthesizing the targeted molecule grandifloracin 1, we could obtain and fully characterize two compounds 9 \& 10, both having the same molecular formula $\text{C}_{21111806}$ and especially the compound 10 is in fact semi-grandifloracin.

It may be noted that the work towards the synthesis of grandiflarcin 1 was initiated in our laboratory in 1999 soon after its isolation report in 1997 in the right direction i.e. by self Diels-Alder dimerization of o-quinol 2. However, we did not succeed mainly because we could not prepare 2-hydroxybenzyl benzoate 5 in our laboratory. The synthesis of grandiflarcin 1 has been recently (2007) reported\textsuperscript{11} that too by self Diels-Alder dimerization of 2-hydroxybenzyl benzoate 5 via SIBX-mediated hydroxylative phenol dearomatization in 30\% yield.
Fig. 3.16: IR spectrum of 9
Fig 3.17: $^1$H NMR spectrum of 9
Fig 3.18: $^{13}$C NMR spectrum of 9
Fig. 3.19: $^1$H-$^1$H COSY spectrum of 9
Fig. 3.20: $^1$H-$^{13}$C HMBC spectrum of 9
Fig 3.21: ESIMS spectrum of 9
Fig 3.22: IR spectrum of 10
Fig 3.23: $^1$H NMR spectrum of 10
Fig 3.24: $^{13}$C NMR spectrum of 10
Fig. 3.25: $^1$H-$^{13}$C HMBC spectrum of 10
Fig. 3.26: $^1$H-$^{13}$C HMBC spectrum (expansion) of 10
Fig. 3.27: $^1$H-$^{13}$C HMBC spectrum (expansion) of 10
Fig 3.28: ESIMS spectrum of 10
Experimental

1,3,4,4a,5,8a-Hexahydro-1,4-ethenonaphthalene-3,5-bisspirooxirane-2,6-dione 4 and 1,3,4,4a,5,8a-Hexahydro-3,5-bis(bromomethyl)-3,5-dihydroxy-1,4-ethenonaphthalene-2,6-dione 8

Prepared according to the reported literature procedure.

Reaction of dimer 4 with benzoic acid in acetonitrile; formation of [(9R)-5,9-dihydroxy-6-(hydroxymethyl)-10-oxotricyclo[6.2.2.0\(^{2.7}\)]dodeca-2,4,6,11-tetraen-9-yl]methylbenzoate 9

A mixture of dimer 4 (0.244 g, 1 mmole), benzoic acid (0.366 g, 3 mmole) and TBAB (10 mg) was heated to reflux in dry acetonitrile (10 mL) for 8 hrs. The reaction mixture was cooled to room temperature and extracted with CHCl\(_3\). The organic extracts were washed with saturated NaHCO\(_3\), water, dried over Na\(_2\)SO\(_4\) and the solvent evaporated to leave a brown viscous residue (0.402 g). Purification using column chromatography by eluting with CHCl\(_3\):MeOH (9.8:0.2) gave 9 as white solid, m.p. 164-66°C. Recrystallization from CH\(_3\)CN gave colourless crystals, m.p. 182°C.
IR $\nu_{\text{max}}$ (KBr, Fig. 3.16): 3570 (OH), 3400 (OH), 1726 (ester C=O), 1687 (C=O), 1597, 1292, 983 cm$^{-1}$.

$^1$H NMR (CDCl$_3$, 300 MHz, Fig. 3.17): For assignments refer Figure I, pg 291.

$^{13}$C NMR (CDCl$_3$, 75 MHz, Fig. 3.18): For assignments refer Figure II, pg 291.

ESIMS (Fig. 3.21): $m/z [M + H]^+$ calcd for C$_{21}$H$_{19}$O$_6$ 367.1176, Found 367.1499.

Reaction of dibromide 8 with potassium benzoate in DMF; formation of 9

A mixture of the dibromide 8 (0.244 g, 1 mmole) and potassium benzoate (0.48 g, 3 mmole) was heated to 85°C in dry DMF (10 mL) for 2 hrs. The reaction mixture was cooled to room temperature and extracted with CHCl$_3$. The organic extracts were washed with saturated NaHCO$_3$, water, dried over Na$_2$SO$_4$ and the solvent evaporated to leave dark yellow viscous oil (0.1288 g). Purification by silica gel column chromatography and elution with CHCl$_3$:MeOH (9.8:0.2) gave 9 as white solid having m.p. 164-66°C. Recrystallization from CH$_3$CN gave colourless crystals having m.p. 182°C.

Reaction of dibromide 8 with potassium benzoate in DMSO; formation of 9

A mixture of dibromide 8 (0.244 g, 1 mmole) and potassium benzoate (0.48 g, 3 mmole) was heated to 100-105°C in dry DMSO (10 mL) for 2 hrs. The reaction mixture was cooled to room temperature and extracted with CHCl$_3$. The organic extracts were washed with saturated NaHCO$_3$, water, dried over Na$_2$SO$_4$ and the solvent evaporated to leave dark yellow viscous oil (0.158 g). Purification by silica gel column chromatography and elution with CHCl$_3$:MeOH (9.8:0.2) gave 9 as white solid having m.p. 164-66°C. Recrystallization from CH$_3$CN gave colourless crystals having m.p. 182°C.
Reaction of dibromide 8 with potassium benzoate in benzene-water mixture using TBAB as catalyst; formation of (3R)-Hydroxy-4,9-dioxo-10,10-epoxymethyltricyclo[6.2.2.02,7]dodeca-5,11-dien-3-ylmethylbenzoate 10

A mixture of dibromide 8 (0.244 g, 1 mmole), potassium benzoate (0.48 g, 3 mmole) and TBAB (10 mg) was refluxed in water (0.5 mL) and benzene (15 mL) mixture for 15 hrs. The reaction mixture was cooled to room temperature, the organic layer was separated and washed with saturated NaHCO₃, water and dried over Na₂SO₄. Evaporation of the solvent afforded a pale brown residue. Purification by silica gel column chromatography using C₆H₆ as eluent gave dimer 4. Further elution with C₆H₆:Et₂O (8:2) gave white solid. Careful TLC observation of the white solid (C₆H₆:Et₂O; 6:4) indicated it to be a mixture of two closely spaced spots which could be resolved (TLC) using CHCl₃:EtOAc (9:1) as solvent system. Further purification of the white solid by silica gel column chromatography using CHCl₃:EtOAc (9:2) as eluent gave 10 as white solid. Recrystallization from the same solvent gave white shiny flakes having m.p. 180°C.

IR ν max (KBr, Fig. 3.22): 3500 (OH), 1736 (ester C=O), 1708 (C=O), 1691 (-HC=CH-CO-), 1600, 1480, 1277, 1100, 760, 711 cm⁻¹.

¹H NMR (CDCl₃, 300 MHz, Fig. 3.23): For assignments refer Figure IV, pg 295.

¹³C NMR (CDCl₃, 75 MHz, Fig. 3.24): For assignments refer Figure V, pg 295.

ESIMS (Fig. 3.28): m/z [M + H]⁺ calcd for C₂₁H₁₉O₆ 367.1176, Found 367.3094; [M + Na]⁺ cald for C₂₁H₁₈O₆Na 389.09956, Found 389.1416
Reaction of saligenin dimer 4 with I₂ in dioxane

To a solution of the saligenin dimer 4 (0.5 g, 2.05 mmole) in dioxane (60 mL) was added iodine (1.07 g, 4.1 mmole). The reaction mixture was stirred for 24 hrs at room temperature followed by addition of saturated solution of sodium thiosulfate (50 mL). The mixture was stirred vigorously for 1 hr. The organic phase was separated, washed with water (2 × 15 mL), dried over Na₂SO₄ and concentrated under reduced pressure. No appreciable amount of residue was left in the flask after total removal of the solvent.

Diethylbenzoyl phosphonate 12

Triethyl phosphite (9.1 g, 0.05 mole) was added drop by drop over a period of 30 mins to benzoyl chloride (7.02 g, 0.05 mole) at 0°C. The mixture was stirred at room temperature for 30 mins and then distilled under reduced pressure to give pure diethylbenzoyl phosphonate 12 (8.54 g, 54.5%) as yellow oil, b.p. 140-42°C at 3 mm.

Reaction of saligenin 3 with diethylbenzoyl phosphonate 12

To a solution of saligenin 3 (0.198 g, 1.6 mmole) in dry CH₂Cl₂ (10 mL) was added diethylbenzoyl phosphonate 12 (0.4065 g, 1.68 mmole) and DBU (1 equiv) and the mixture was refluxed for 5 hrs. The organic portion was separated and concentrated under reduced pressure to give pale brown sticky residue insoluble in common organic solvents.
Acetylation of saligenin 3, formation of 2-(acetyloxy)benzyl acetate 15

To a stirred solution of 3 (0.661 g, 5.3 mmole) in Ac$_2$O (3 mL) was added NaIO$_4$ (1.395 g, 6.4 mmole) in portions over a period of 1 hr. Stirring was further continued for 5 hrs at room temperature. The reaction mixture was then poured into a saturated solution of NaHCO$_3$ and stirred vigorously to neutralise excess acetic acid. The aqueous layer was extracted with ethyl acetate (3 x 5 mL) and combined organic extracts were washed successively with saturated NaHCO$_3$ (10 mL), water (10 mL) and brine (10 mL), followed by drying over Na$_2$SO$_4$. Removal of the solvent furnished a residue. Purification by silica gel column chromatography using petroleum ether:ethyl acetate (8:2) as eluent gave 2-(acetyloxy)benzyl acetate 15 (0.753 g, 73%) as yellow oil.

IR $\nu_{\text{max}}$ (KBr): 1766, 1737, 1228, 1176, 754 cm$^{-1}$. 

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References


