Chapter III

Synthesis of naphthalenic lignan lactones
Lignans are naturally occurring compounds with very wide occurrence. Several lignans show pronounced antitumor, antifungal and insecticidal activity. Some function as antioxidant for food materials while others are antifertility agents. Lignans, isolated from animals, have been identified as a new class of hormones controlling growth. On account of their broad range of biological activity they have attracted the attention of many organic chemists.

Most of the lignans have two phenylpropanoid units ($C\text{\textsubscript{6}}-C\text{\textsubscript{3}}$ units) linked at the 4\textsuperscript{th} carbon atom of the side chain

![Chemical structure of a lignan](image)

According to the radical theory postulated by Pummerer and Morondel (which is now accepted and confirmed) for the formation of different types of lignans, the substituted 1-(4-hydroxyphenyl)-1-propenes, in their oxidation states may yield radicals which undergo coupling reactions to give the lignan skeleton.
The very large number of 1-phenyl naphthalene and tetralin lignans, occurring in nature, originate this way.

Some examples of lignans along with their known biological properties are mentioned below.

Dibenzylbutane lignans.

\[ R, R = \text{CH}_2 \quad R^1 = \text{H} \quad R^2 = \text{OH} \]

\[ R = \text{Me} \quad R^1 = \text{H} \quad R^2 = \text{OH} \]

(germination inhibitors)
Jatrophan
(*insecticidal activity*)

(+)-Arctigenin

Pregomisin

Aryl tetralin and arylnaphthalide lignans

Galcatin

Cycloolivil
Plicatic acid

Conidendrin
(Polymerization inhibitor)

Podophyllotoxin
(tumor necrotizer)

Collinusin

Justcadin - B

Helioxanthin
$R = H$ Diphyllin
$R = \text{Me}$ Justicidin A

Taiwanin - E

Dehydropodophyllotoxin

Tetrahydrofuranoid lignans

Mangnolenin - C

Nectandrin A
**Furofuranoid Lignans**

Simplexolin

**Dibenzocyclooctadiene Lignans**

Schizandrin

Gomisin 0

\[ R = \text{OAc} \quad R' = \text{H} \quad \text{steganicin} \]
\[ R \quad R' = \text{O} \quad \text{steganone} \]

(Antileukemic activity)
The development of the glycosidic lignan lactones, etopside (2a) and teniposide (2b), into major clinical agents against lung and bladder cancer in recent times has spurred interest for efficient syntheses of aryl naphthalene and tetralin lignan lactones in general and the aglycone of etoposide and teniposide in particular.

Many syntheses of aryl naphthalene and tetralin lignan lactones are known to-date. One can classify them broadly according to the strategies of the key reactions involved. Thus they could be grouped under nine classes, which are as follows.

Syntheses involving -
1) elaboration of alkoxyalted benzophenones
2) condensation reactions involving $\gamma$-lactone intermediates
3) conjugate addition of the thio-acetal carbanion to butenolide
4) addition of aryllithium and intramolecular trapping
5) oxidative coupling of cinnamyl residues
6) electrocyclisation reaction
7) photoreaction
8) cyclisation of acetylenic anhydrides
9) in situ generation of isobenzofurans and their trapping with suitable dienophiles.

Several syntheses of arynaphthalene and tetralin lignan lactones are known. The subject has been extensively reviewed. A representative synthesis from each of the above nine classes is given below.

1) **Elaboration of alkoxylated benzophenones**

*Synthesis due to Gensler et al (1960)*

![Chemical Diagram]

\[
\text{Ar} \quad \text{CO} \quad \text{Et}\quad \text{COOEt} \quad \text{CH}_2\text{COOEt} \quad \text{Na-Hg} \quad \text{HCOOEt/NaOH}
\]
2) **Condensation reaction involving \(\gamma\)-lactone intermediates**

*Synthesis due to Munakata et al (1971)*
Synthesis due to Stevenson and Ganeshpure (1981)
1. reduction
2 KH, then Ca(BH₄)₂

MeO
MeO

LDA
Piperonal

MeO
MeO

TFA
RT

LAH

MeO
MeO

Me

DMSO

MeO
MeO

Me

Lintetralin

MeO
MeO

Me

Isogalcatin
3) **Conjugate addition of thioacetal carbanion to butenolide**

*Synthesis due to Wang and Ripka (1983)*

\[ \text{MeO} \]
\[ n\text{-BuLi,} \]
\[ \text{then piperonal} \]

1. TFA
2. HgO / BF\(_3\)·Et\(_2\)O
3. PyH\(^+\)Br\(_3\) / AcOH
4. MeI / K\(_2\)CO\(_3\)

\[ \text{MeO} \]

1. NBS
2. MeOH

Justicidin P
Synthesis due to Pelter et al (1985)

Deoxyisopodophyllotoxin

Epiisopodophyllotoxin
4) **Addition of aryllithium and intramolecular trapping**

*Synthesis due to Kende et al. (1981)*

- **First Reaction:**
  - 1) $\text{H}_3\text{O}^+$
  - 2) $\text{CrO}_3$
  - 3) $\Theta\text{OH}$
  - 4) $\text{HCHO}$

- **Second Reaction:**
  - Followed by $\text{LiAlH} (\text{OR})_3$

- **Final Products:**
  - Picropodophyllin
  - Podophyllotoxin
Synthesis due to Meyers and Avila (1981)
(Use of aryllithium and lithiation reaction)

\[ \text{OMe} \quad \overset{n-\text{BuLi}}{\text{CO}_2} \quad \overset{\text{COOH}}{\text{OMe}} \]

\[ \overset{\text{Li}}{\text{OMe}} \quad \overset{s-\text{BuLi-TMEDA}}{\text{DMF}} \quad \overset{\text{OMe}}{\text{NaBH}_4} \]

Similarly,
5) Oxidative coupling of cinnamyl residues

Synthesis due to Pelter et al. (1982)
6) **Electrocyclisation reaction**

*Synthesis due to Homose et al (1978)*

- **Step 1:** LAH
- **Step 2:** p-TSA

**Chemical Equations:**

```
MeO-CH=CH-COOH + LAH → MeO-CH=CH-COOMe
02
DMF, DABCO
```

```
MeO-CH=CH-COOMe + p-TSA → MeO-CH=O
```

**Further Reactions:**

```
MeO-CH=O + K₂But → MeO-CH=O
02
HMPA
```

**Diphyllin**
Synthesis due to Joshi et al (1979)

7) Photoreaction

Synthesis due to Sammes and coworkers (1973)
8) Cyclisation of acetylenic anhydrides

Synthesis due to Holmes et al (1971)

1) $\text{MnO}_2$
2) $\text{NaBH}_4$

Taiwanin E
9) In situ generation of isobenzofurans\textsuperscript{14}

Synthesis due to Rodrigo and coworkers (1980)
Diphyllin, Justicidin A, Taiwanin E, Chinensinaphthol and Dehydropodophyllotoxin were prepared by this route.

Synthesis due to Mann and Piper (1982)
(In situ generation of ortho quinodimethane)
1. MsCl, NEt₃  
2. Na₂S, DMSO, HCl  
3. CH₃COOH

\[ \text{Phyltetralin} \]

\[ \text{Synthesis due to Iwao et al (1984)} \]
Synthesis due to Narasimhan et al (1987)
**Present study:**

In the present study, the naphthalenic lignan lactones have been obtained from the isobenzofurans, specifically 1-aryl isobenzofurans, through a Diels-Alder reaction.
**Isobenzofurans as synthones in Diels-Alder reactions**

Isobenzofurans are versatile synthons in Diels-Alder reactions. Some syntheses using isobenzofurans in Diels-Alder reactions\(^{16}\) are given below.

\[
\begin{align*}
\text{Ph} & \quad + \quad \text{Ph} \\
\text{Ph} & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad }
\[ R = \text{Me, } \text{CH}_2\text{OH, } \text{Br, } \text{SiMe}_3 \]

Ref. 21

Ref. 22
\[ R = \text{COOMe} \]

Ref. 20

Podophyllotoxin

Ref. 15
Isobenzofurans as synthon for lignan lactones

It has been indicated earlier, that the isobenzofurans have been used in Diels-Alder reaction for the synthesis of lignan lactones. Thus Rodrigo and coworkers, Man and Piper and Iwao et al have used isobenzofurans as intermediates in the synthesis of naphthalenic lignan lactones. In our laboratory Dr. S. M. Gokhale has used the isobenzofuran 4.

![Chemical structure](attachment:image.png)

The method for generation of the isobenzofurans by various workers has been described earlier^{14,15}.

In the present study the isobenzofuran 5 was generated as follows.

![Chemical reactions](attachment:image.png)
The same isobenzofuran precursor II, has been obtained by Mr. R. R. Joshi of this laboratory in an alternate way\(^2\), which is shown below.
Synthesis of naphthalenic lignan lactones

Synthesis of lignan lactone 7a

The lignan lactone 7a, a hitherto unknown naphthalenic lignan lactone, was prepared as shown.

\[ \text{R}^1 = \text{OMe} \]
Preparation of bromoacetal 8a

6-Bromoveratraldehyde, m. p. 149° (EtOH) (Lit., m. p. 149-50°), was prepared by bromination of veratraldehyde in acetic acid, in 90% yield.

6-Bromoveratraldehyde, ethylene glycol and p-TSA catalyst were refluxed in benzene, under Dean-Stark water separator for 8 h to provide 6-bromoveratraldehyde ethylene acetal (8a) m.p. 107-08° (C₆H₆) in 95% yield.

Conversion of bromoacetal 8a into hydroxyacetal 9a

Sequential treatment of 6-bromoveratraldehyde ethylene acetal (8a), at -78°, with n-BuLi in ether followed by 4-methoxybenzaldehyde afforded a white crystalline compound, m.p. 106-08° (ether). It analysed for C₁₉H₂₂O₆. The IR spectrum
indicated presence of hydroxyl group (broad band at 3475 cm$^{-1}$). The PMR spectrum was as follows.

**PMR (CDCl$_3$):**

- 3.2 br 1H (exchangeable)
- 3.75, 3.78, 3.88 3s 9H
- 4.05 m 4H
- 5.84 s 1H
- 6.06 brs 1H
- 6.8 d(J=8.5 Hz) 3H
- 7.06 s 1H
- 7.25 d(J=8.5 Hz) 2H

A signal at 6.06 $\delta$(brs, 1H), which became sharp after D$_2$O exchange, was due to Ar-CH$_2$OH group. The signals at 4.05 $\delta$(m, 4H) and 5.84 $\delta$(s, 1H) indicated that the ethylene acetal moiety was intact. Increase in number of methoxyls (by one) and aromatic protons (by four) indicated that the compound obtained was hydroxyacetal 9a$^*$. The yield of hydroxyacetal 9a was 80%.

* For all the compounds studied, detailed assignment of PMR signals is given under experimental.
To a solution of the hydroxyacetal 9a in dry benzene at room temperature DDQ was added in 5-6 portions. After stirring for 3-4 h, the benzene solution was washed with water, aq. NaHCO₃, water and dried, and concentrated to 1/3 of its original volume.

The oxidation product was not isolated, but the benzene solution of the crude oxidation product was stirred with 2N H₂SO₄ for 3 h. This afforded a white crystalline compound, m.p. 146.5-47.5° (C₆H₁₄-EtOAC). It analysed for C₁₇H₁₆O₅. The IR spectrum showed presence of two carbonyls (bands at 1710 and 1660 cm⁻¹). The compound gave a positive 2,4-DNP test. The PMR spectrum was as follows.

PMR (CDCl₃):

<table>
<thead>
<tr>
<th>ppm</th>
<th>J (Hz)</th>
<th>Multiplicity</th>
<th>protons</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.68</td>
<td></td>
<td>3s</td>
<td>9H</td>
</tr>
<tr>
<td>3.93</td>
<td></td>
<td>3s</td>
<td>9H</td>
</tr>
<tr>
<td>4.03</td>
<td></td>
<td>3s</td>
<td>9H</td>
</tr>
<tr>
<td>6.93</td>
<td>9</td>
<td>d(J=9 Hz)</td>
<td>2H</td>
</tr>
<tr>
<td>6.96</td>
<td></td>
<td>s</td>
<td>1H</td>
</tr>
<tr>
<td>7.53</td>
<td></td>
<td>s</td>
<td>1H</td>
</tr>
<tr>
<td>7.78</td>
<td>9</td>
<td>d(J=9 Hz)</td>
<td>2H</td>
</tr>
<tr>
<td>9.83</td>
<td></td>
<td>s</td>
<td>1H</td>
</tr>
</tbody>
</table>

Signals corresponding to -OH, ethylene acetal and benzylic protons were absent in the PMR spectrum. A singlet at 9.83 δ (1H) indicated an aldehyde proton (-CHO). This, along with other signals in the PMR spectrum, indicated that the compound obtained was trimethoxyketonealdehyde 10a.
The yield of trimethoxyketoaldehyde 10a was 65%.

Treatment of trimethoxyketoaldehyde 10a with sodium borohydride

A solution of trimethoxyketoaldehyde 10a in THF-EtOH was treated with NaBH₄ (1:1 equivalent) for 15 min at room temperature. The reaction mixture was concentrated and water added. The resulting precipitate was filtered and crystallised from hexane - ethyl acetate to afford a white, crystalline compound having m.p. 120-21°C. It analysed for C₁₇H₁₈O₅, indicating an increase of two hydrogens. The IR spectrum indicated a -OH group (signal at 3460 cm⁻¹). The IR signal at 1690 cm⁻¹ (CHO group of the starting compound 10a) was absent. The PMR spectrum, besides indicating six aromatic and nine methoxyl protons (i.e. three methoxyl groups) showed a hydroxyl group (a broad peak at 1.7 s which was exchangeable with D₂O) and a Ar-CH₂-O- group (a singlet at 4.53 s, corresponding to two protons). The above data indicated that the compound was 1-hydroxy-1-(4-methoxyphenyl)-5,6-dimethoxyphthalan (11a). The yield was 80%.
The hydroxy phthalan 11a was very unstable to acid and heat. Its color darkened within two hours of keeping. So it was used immediately for further reaction.

The formation of hydroxyphthalan 11a clearly indicated that selective reduction of aldehyde group of ortho-formyl benzophenones indeed was possible.

After having prepared the hydroxyphthalan 11a, it was decided to use it as an isobenzofuran source in a Diels-Alder reaction for the preparation of naphthalenic lignan lactones.

In situ generation of isobenzofuran from hydroxyphthalan 11a and its reaction with dimethyl acetylenedicarboxylate (DMAD)

The hydroxyphthalan 11a and DMAD were dissolved in benzene and heated to reflux for 2 h in presence of a trace of p-TSA. Solvent was evaporated and the residue subjected to flash chromatography on silica gel using hexane-ethyl acetate to yield a crystalline compound having m.p. 189-90°C (EtOAc). It analysed for C_{23}H_{22}O_8. IR spectrum indicated presence of hydroxyl group (a broad band 3300-3000 cm^{-1}) and ester carbonyl groups (bands at 1755 and 1665 cm^{-1}). PMR, in addition to other peaks, indicated five methoxyl groups (indicating that the Diels-Alder reaction
had taken place) and a hydrogen bonded phenolic hydroxyl group (a peak at 12.22 \( \delta \), s, 1H, exchangeable with \( \text{D}_2\text{O} \)). The above data indicated that the compound was dimethyl-4-hydroxy-6,7-dimethoxy-1-(4-methoxyphenyl)-naphthalene-2,3-dicarboxylate (6a).

The yield of the Diels-Alder adduct 6a was 60%.

Sammes and coworkers\textsuperscript{12a} have smoothly reduced naphthalenic diesters of the type 6a by sodium borohydride in methanol to give good yields of naphthalenic lignan lactones (7).
It was then decided to reduce the naphthalenic diester 6a to the corresponding naphthalenic lignan lactone by sodium borohydride.

Reduction of the adduct 6a with NaBH₄

The adduct 6a in THF-EtOH was treated with portions of NaBH₄ (excess) at room temperature over a period of 18 h. 2N H₂SO₄ was added and the reaction mixture stirred for a further period of 30 min. Removal of solvent under vacuum gave a precipitate which was filtered and recrystallized from acetone to provide a white, crystalline compound having m.p. 280-81°. It analysed for C₂₁H₁₈O₆. The IR spectrum indicated bands at 3150 cm⁻¹ (hydroxyl group) and 1725 cm⁻¹ (lactone carbonyl). PMR of the compound showed three aromatic methoxyl groups. The broad singlet at 9.65S was exchangeable with D₂O and was attributed to a phenolic hydroxyl group. A singlet at 5.37 $\delta$ (2H) was due to Ar-CH₂-O-group. The above data, along with other signals in PMR spectrum, suggested that the compound was 4-hydroxy-6,7-dimethoxy-9-(4-
methoxyphenyl)-naphtho-(2,3,c)-furan-(3H)-one (7a), a hitherto unknown naphthalenic lignan lactone.

The lignan lactone 7a was obtained in 76 % yield.

After the successful synthesis of a new naphthalenic lignan lactone 7a, it was decided to synthesize two naturally occurring lignans viz. tianwanin E25 (7b) and tetrahydrogopodophyllotoxin26 (7c) by using the same strategy.
Synthesis of taiwanin E (7b)

It was carried out as shown below.
Preparation of bromoacetal 8b

6-Bromopiperonal, m.p. 127-28° (EtOH) (Lit.26, m.p. 129°) was refluxed with ethylene glycol and p-TSA in benzene to obtain 6-bromopiperonal ethylene acetal 8b, m.p. 68-90°C (C6H14-C6H6) (Lit.12a, m.p. 68-90°) in 95% yield.

Conversion of bromoacetal 8b into hydroxyacetal 9b

Bromoacetal 8b at -78° was treated with n-BuLi in ether followed by piperonal to obtain the known [α-(1,3-dioxolan-2-yl)-4,5-methylenedioxyphenyl] 3,4-methylenedioxybenzyl alcohol, 9b, a viscous oil in 85% yield.

Preparation of dimethylenedioxyketoaldehyde 10b

Hydroxyacetal 9b was first oxidized with DDQ and then hydrolysed with 2N H2SO4 to furnish a compound C16H10O6, which was characterised as dimethylenedioxyketoaldehyde 10b, m.p. 133-34° (C6H14-EtOAc) in 60% yield.

Adduct 6b

The dimethylenedioxy-ketoaldehyde 10b was reduced with NaBH4. The hydroxyphtalan obtained, was not rigorously purified but was reacted with DMAD/p-TSA to provide dimethyl 4-hydroxy-6,7-methylenedioxy-1-(3,4-methylenedioxyphenyl)-naphthalene-2,3-dicarboxylate 6b, m.p. 191-92° (EtOH) [Lit.12a, m.p. 189-92° (EtOH)] in 60% yield.

The diester 6b has already been converted into
taiwanin E by reduction with sodium borohydride, in 60% yield\textsuperscript{12a}.

The above synthesis of diester 6b thus constitutes a formal synthesis of taiwanin E (7b).

**Synthesis of tetrahydropodophyllotoxin (7c)**

The steps involved in the synthesis were as outlined below.

\[ \text{8b} \xrightarrow{1. NaBH}_4 \xrightarrow{2. DMAD, pTSA} 9c \xrightarrow{} 10c \xrightarrow{} 6c \xrightarrow{} 7c \]
Preparation of hydroxyacetal 9c

Bromoacetal 8b at -78°C, was treated sequentially with n-BuLi in ether and 3,4,5-trimethoxybenzaldehyde to obtain the known [α-(1,3-dioxolan-2-yl)-4,5-methylenedioxyphenyl]-3,4,5-trimethoxybenzyl alcohol 9c, a viscous oil in 78% yield.

Conversion of hydroxyacetal 9c into methylenedioxy-trimethoxy ketoaldehyde 10c

Hydroxyacetal 9c on oxidation with DDO followed by hydrolysis with 2N H2SO4 provided a compound C18H16O7, which was characterised as 2-formyl-4-5-methylenedioxy-3,4,5-trimethoxybenzophenone (10c), m.p. 168.5-69.5°C, in 60% yield.

Adduct 6c

The hydroxyphthalan obtained after reduction of methylenedioxy-trimethoxyketoaldehyde 10c was not rigorously purified but was reacted with DMAD/p-TSA to furnish dimethyl-4-hydroxy-6-7-methylenedioxy-1-(3,4,5-trimethoxyphenyl)naphthalene-2,3-dicarboxylate (6c), m.p. 241-42°C (EtOH-EtOAc) (Lit.12a, m. p. 242-44°C) in 60% yield.

The diester 6c has already been converted into tetradehydropodophyllotoxin by reduction with sodium borohydride, in 67% yield12a.

The above synthesis of diester 6c thus constitutes a formal synthesis of tetradehydropodophyllotoxin (7c).
EXPERIMENTAL
EXPERIMENTAL

General Remarks:

1. All melting points (m.p.) and boiling points (b.p.) are uncorrected.

2. All the solvents and reagents were purified and dried using standard procedures.

3. In general all dry reactions were carried out under dry, oxygen-free nitrogen atmosphere.

4. All organic extracts were dried over anhydrous sodium sulphate.

5. Silica gel used for column chromatography was 100-200 mesh, that for flash chromatography finer than 200 mesh and that for preparative high performance liquid chromatography (preparative HPLC) t.l.c. grade.

6. Analysis were carried out using Hosli's rapid carbon-hydrogen analyser.

   Infrared (IR) spectra were recorded on a Perkin-Elmer 337 spectrophotometer.

   Proton magnetic resonance (PMR) spectra were recorded on Perkin-Elmer R-32 (90 MHz) instrument.

   Flash chromatography was done using Eyela Flash Chromatograph EF 10.

   Preparative HPLC was done using Jobin-Yvon high performance liquid chromatograph.

7. PMR data, using standard notations, are presented in the following order- chemical shift (δ) / splitting pattern (J = coupling constant) / relative proton ratio / assignment.
**Expt. no. 3.1 : Hydroxyacetals 9**

8a : \( R^1 = \text{OMe} \)

8b : \( R^1R^1 = \text{OCH}_2\text{O} \)

\( \alpha_a : R^1 = R^3 = \text{OMe} \); \( R^2 = R^4 = \text{H} \)

\( \beta_b : R^1R^1 = R^2R^3 = \text{OCH}_2\text{O} \); \( R^4 = \text{H} \)

\( \gamma_c : R^1R^1 = \text{OCH}_2\text{O} \); \( R^2 = R^3 = R^4 = \text{OMe} \)

**Expt. no. 3.2 : Ketoaldehydes 10**

10a : \( R^1 = R^3 = \text{OMe} \); \( R^2 = R^4 = \text{H} \)

10b : \( R^1R^1 = R^2R^3 = \text{OCH}_2\text{O} \); \( R^4 = \text{H} \)

10c : \( R^1R^1 = \text{OCH}_2\text{O} \); \( R^2 = R^3 = R^4 = \text{OMe} \)
Expt. no. 3.3 : Hydroxyphthalan 11a

\[ \text{Expt. no. 3.3 : Hydroxyphthalan 11a} \]

\[
\begin{align*}
\text{10a} : R^1 &= R^3 = \text{OMe} ; R^2 = R^4 = \text{H} \\
\text{11a} : R^1 &= R^3 = \text{OMe} ; R^2 = R^4 = \text{H}
\end{align*}
\]

Expt. no. 3.4 : Reduction of ketoaldehydes 10 and conversion to naphthalenic diesters 6 by Diels-Alder reaction with DMAD

\[
\begin{align*}
\text{6a} : R^1 &= R^3 = \text{OMe} ; R^2 = R^4 = \text{H} \\
\text{6b} : R^1R^1 &= R^2R^3 = \text{OCH}_2\text{O} ; R^4 = \text{H} \\
\text{6c} : R^1R^1 &= \text{OCH}_2\text{O} ; R^2 = R^3 = R^4 = \text{OMe}
\end{align*}
\]
Expt. no. 3.5: Reduction of naphthalenic diester $6a$ to naphthalenic lignan lactone $7a$

$6a: R^1 = R^3 = OMe; R^2 = R^4 = H$

$7a: R^1 = R^3 = OMe; R^2 = R^4 = H$
Expt. No. 3.1 : Hydroxy acetals 9

General procedure :

To a solution of bromoacetals 8 (10 mmol) in THF (40 ml) was added n-BuLi (11 mmol in ether) at -78°. After 15 min, a solution of an aldehyde (11 mmol) in THF (15 ml) was added. After being stirred for 30 min at -78°, the reaction was decomposed with water and THF was removed under vacuum. The aqueous layer was extracted with ether (4 x 20 ml). Washing of the combined ethereal extract with water, drying and removal of the solvent gave hydroxy acetals 9.

a) Reaction of bromoacetal 8a with n-BuLi followed by p-anisaldehyde :

\[ \text{2-(1,3-Dioxolan-2-yl)-4,5-dimethoxyphenyl-4-methoxybenzyl alcohol, 9a} \]

Yield : 80 %

M.p. : 106-08° (ether)

Analysis : Found : C, 65.75 % ; H, 6.38 %
Calculated for \( \text{C}_{19}\text{H}_{22}\text{O}_{6} \) : C, 65.88 % ; H, 6.40 %

IR (Nujol) : 3475 (br), 1640, 1525, 1475, 1425, 1390, 1240, 1160, 1100, 1030, 995, 880, 860, 810, 770, 730, 610 cm\(^{-1}\).

PMR (CDCl\(_3\)) :

<table>
<thead>
<tr>
<th>3.2</th>
<th>br</th>
<th>1H</th>
<th>OH (exchanges with D(_2)O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.75</td>
<td>s</td>
<td>3H</td>
<td>OCH(_3)</td>
</tr>
</tbody>
</table>
3.78  s  
3H OCH$_3$

3.88  s  
3H OCH$_3$

4.05  m  
4H -O-CH$_2$-CH$_2$-O-

5.84  s  
1H -O-CH-O-

6.06  brs  
1H Ar-CH-OH

6.8  d($J=8.5$ Hz)  
3H ArH ($H_3$, $H_5$, $H_6$,)

7.06  s  
1H ArH ($H_3$)

7.25  d($J=8.5$ Hz)  
2H ArH ($H_2$, $H_6$)

b) Reaction of bromoacetal 8b with n-BuLi followed by piperonal:

$\alpha\beta$-[2-(1,3-Dioxolan-2-yl)-4,5-methylenedioxyphenyl]-3,4-
methylenedioxybenzyl alcohol, 9b

Nature: Viscous liquid, single & homogeneous on t.l.c. plate.

Yield: 85% 

IR (CHC$_3$): 3400 (br), 1500, 1480, 1440, 1380, 1330, 1240(br), 1090, 1040, 1000, 930, 860, 810, 755 cm$^{-1}$.

PMR (CDC$_3$):

3.07  d($J=4$ Hz)  
1H OH (exchanges with D$_2$O)

4.08  m  
4H -O-CH$_2$-CH$_2$-O-

5.92  s  
3H -O-CH$_2$-O- and -O-CH-O-

6.08  d($J=4$ Hz)  
1H Ar-CH-OH

6.71  s  
1H Ar-H ($H_6$)

6.84  m  
3H Ar-H ($H_2$, $H_5$, $H_6$)

7.05  s  
1H Ar-H ($H_3$)
C) Reaction of bromoacetal 8b with n-BuLi followed by 3,4,5-
trimethoxybenzaldehyde:

\[ \text{-[2-(1,3-Dioxolan-2-yl)-4,5-methylenedioxyphenyl]-3,4,5-} \]
\[ \text{trimethoxybenzyl alcohol}, 9\text{c} \]

**Nature**: Viscous liquid, single and homogeneous on t.l.c. plate.

**Yield**: 78%

**IR (neat)**: 3440(br), 1610, 1475, 1425, 1330, 1225, 1120, 1080,
1030, 930, 875, 790, 740, 720 cm\(^{-1}\).

**PMR (CDCl\(_3\))**:  
3.4 d(J=3 Hz) 1H OH (exchanges with D\(_2\)O)  
3.85 s 3H OCH\(_3\)  
3.86 s 3H OCH\(_3\)  
3.87 s 3H OCH\(_3\)  
4.11 m 4H -O-CH\(_2\)-CH\(_2\)-O-  
5.95 s 2H -O-CH\(_2\)-O-  
6.0 s 1H -O-CH-O-  
6.1 d(J=3 Hz) 1H Ar-CH-OH  
6.97 \{ 2s 3H Ar-H (H\(_2\) , H\(_6\) , H\(_6\)' )  
6.99 \}  
7.08 s 1H Ar-H (H\(_3\) ,)

**Expt. No. 3.2**: *Ketoaldehydes 10*

**General procedure**:  
To a solution of the hydroxyacetals 9 (1 eq) in dry
benzene at room temperature was added DDO (1.1 eq) in 5 - 6 portions. The black - green coloured mixture was stirred for 3-4 h, during which time the colour of the reaction mixture turned to buff. The benzene solution was washed with water, satd. aq. NaHCO₃, water and dried. The benzene solution was concentrated to 1/3 of its original volume (approx. 20 ml )

The above solution was vigorously stirred at room temperature with 2N H₂SO₄ for 3 h. Filtration of the resulting precipitate and recrystallization from hexane - ethyl acetate afforded the ketoaldehydes 10.

a) Oxidation and hydrolysis of hydroxvacetal 9a :

2'-Formyl-4,4',5'-trimethoxybenzophenone, 10a

Yield : 65 %

M.p. : 146.5-47.5⁰

Analysis : Found : C, 67.94 % ; H, 5.26 %
Calculated for C₁₇H₁₆O₅ : C, 67.99 % ; H, 5.37 %

IR (Nujol) : 1710, 1660, 1625, 1605, 1530, 1475, 1360, 1290, 1260, 1240, 1200, 1150, 1090, 1028, 938, 885, 850, 780, 750, 625 cm⁻¹.

PMR (CDCl₃) :
3.88 s 3H OCH₃
3.93 s 3H OCH₃
4.00 s 3H OCH₃
6.93 \quad d(J=9 \text{ Hz}) \quad 2H \quad \text{Ar-H (H}_3, H_5\text{)}

6.96 \quad s \quad 1H \quad \text{Ar'-H (H}_{6'}\text{)}

7.53 \quad s \quad 1H \quad \text{Ar'-H (H}_3', \text{)}

7.78 \quad d(J=9 \text{ Hz}) \quad 2H \quad \text{Ar-H (H}_2, H_6\text{)}

9.83 \quad s \quad 1H \quad \text{Ar'-CHO}

b) **Oxidation and hydrolysis of hydroxyacetel 9b:**

2'-Formyl-3,4-4',5'-dimethylenedioxybenzophenone, 10b

**Yield** : 60%

**M.p.** : 133-34°C

**Analysis:**

Found: C, 64.33%; H, 3.42%

Calculated for C_{16}H_{10}O_6: C, 64.43%; H, 3.38%.

**IR (Nujol):** 1700, 1650, 1600, 1500, 1450, 1360, 1260, 1090, 1035, 930, 900, 870, 830, 770, 620 cm^{-1}.

**PMR (CDCl₃):**

6.06 \quad s \quad 2H \quad -O-CH₂-O-

6.14 \quad s \quad 2H \quad -O-CH₂-O-

6.82 \quad d(J=9 \text{ Hz}) \quad 1H \quad \text{Ar-H (H}_5\text{)}

6.9 \quad s \quad 1H \quad \text{Ar'-H(H}_{6'}\text{)}

7.3 \quad d d(J=9,2 \text{ Hz}) \quad 1H \quad \text{Ar-H (H}_6\text{)}

7.37 \quad d(J=2 \text{ Hz}) \quad 1H \quad \text{Ar-H (H}_7\text{)}

7.45 \quad s \quad 1H \quad \text{Ar'-H(H}_3', \text{)}

9.77 \quad s \quad 1H \quad \text{Ar'-CHO}
c) **Oxidation and hydrolysis of hydroxracetal 9c:**

2'-Formyl-4',5'-methylenedioxy-3,4,5-trimethoxybenzophenone, 10c

Yield: 60%

M.p.: 168.5-69.5°C

**Analysis:**

Found: C, 62.56% ; H, 4.68%

Calculated for C18H16O7: C, 62.79% ; H, 4.68%

**IR (Nujol):** 1690, 1650, 1575, 1450, 1400, 1340, 1310, 1260, 1218, 1120, 1066, 1035, 1005, 935, 870, 785, 745 cm⁻¹.

**PMR (CDCl₃):**

<table>
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<th>Assignment</th>
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<td>3.86</td>
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<td>6.94</td>
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<td>s</td>
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<tr>
<td>7.46</td>
<td>s</td>
<td>1H</td>
</tr>
<tr>
<td>9.78</td>
<td>s</td>
<td>1H</td>
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</tbody>
</table>

**Expt. No. 3.3: Hydroxyphthalan 11a**

To a solution of ketoaldehyde 10a (0.6 g, 2 mmol) in THF-ethanol (40:60, 20 ml) at 0°C was added NaBH₄ (0.019 g, 0.5 mmol). The resulting mixture was stirred for 15 min at room temperature. Solvent was removed under vacuum at room temperature. To the thick residue water was added. Filtration of
the resulting precipitate, followed by crystallisation from hexane–ethyl acetate afforded needles of 1,3-dihydro-5,6-dimethoxy-3-(4'-methoxyphenyl)-isobenzofuran-3-ol, 11a (0.52 g, 86%), m.p. 120–21°.

Analysis: Found: C, 67.63%; H, 6.06%
Calculated for C_{17}H_{18}O_5: C, 67.54%; H, 6.0%

IR (Nujol): 3440, 1640, 1610, 1560, 1520, 1460 (br), 1350, 1250, 1210, 1160, 1100, 1030, 1010, 880, 860, 800, 780, 765, 675, 630 cm⁻¹.

PMR (CDCl₃):

| 1.7 | br | 1H | OH (exchanges with D₂O) |
| 3.81 | s | 3H | OCH₃ |
| 3.90 | s | 3H | OCH₃ |
| 3.99 | s | 3H | OCH₃ |
| 4.53 | s | 2H | Ar-CH₂-O- |
| 6.9–7.05 | m | 4H | Ar-H (H₄, H₇, H₃, H₅) |
| 7.78 | d(J=9 Hz) | 2H | Ar-H (H₂, H₆) |

Expt. No. 3.4: Reduction of Ketoaldehydes 10 and conversion to naphthalenic diesters 6 by Diels–Alder reaction with DMAD

General procedure:

The ketoaldehyde 10 was reduced with NaBH₄ as in the above experiment. The precipitate obtained was dissolved in
ether. Ether layer was washed with water and dried. Ether was removed under reduced pressure at room temperature.

The residue obtained and dimethyl acetylene dicarboxylate (1.5 eq) were heated in refluxing benzene containing a trace of toluene-p-sulphonic acid for 2 h. Benzene was evaporated and the residue subjected to flash chromatography on silica gel using hexane - 20 % ethyl acetate as eluent to yield the naphthalenic diesters 6.

a) Reaction of ketoaldehyde 10a with NaBH₄ followed by DMAD:

Dimethyl-4-hydroxy-6,7-dimethoxy-1-(4'-methoxyphenyl)-naphthalene-2,3-dicarboxylate, 6a

Yield : 60 %

M.p. : 189-90° (EtOAc)

Analysis:

Found : C, 64.75 %; H, 5.11 %

Calculated for C₂₉H₂₅O₈ : C, 64.78 %; H, 5.20 %

IR (Nujol): 3300-3000, 1755, 1665, 1615, 1505, 1440, 1360, 1310, 1250, 1230, 1200, 1165, 1130, 1100, 1020, 1000, 890, 865, 820, 790, 750 cm⁻¹.

PMR (CDCl₃):

<table>
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<tr>
<th>Chemical Shift</th>
<th>Multiplicity</th>
<th>Integration</th>
<th>Assignments</th>
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</thead>
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<tr>
<td>3.52</td>
<td>s</td>
<td>3H</td>
<td>COOCH₃ (at C₃)</td>
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<tr>
<td>3.75</td>
<td>s</td>
<td>3H</td>
<td>COOCH₃ (at C₂)</td>
</tr>
<tr>
<td>3.90</td>
<td>s</td>
<td>3H</td>
<td>Ar-OCH₃</td>
</tr>
<tr>
<td>3.95</td>
<td>s</td>
<td>3H</td>
<td>Ar-OCH₃</td>
</tr>
<tr>
<td>4.05</td>
<td>s</td>
<td>3H</td>
<td>Ar-OCH₃</td>
</tr>
</tbody>
</table>
6.68 \ s \ 1H \ Ar-H (H_8) \\
6.94 \ d(J=9\ Hz) \ 2H \ Ar'-H (H_3, H_5) \\
7.2 \ d(J=9\ Hz) \ 2H \ Ar'-H (H_2, H_6) \\
7.7 \ s \ 1H \ Ar-H (H_5) \\
12.22 \ s \ 1H \ OH (exchanges with D_2O)

b) Reaction of ketoaldehyde 10b with NaBH_4 followed by DMAD:

Dimethyl-1-hydroxy-6,7-methylenedioxy-4-(3',4'-methylenedioxyphenyl)naphthalene-2,3-dicarboxylate, 6b

Yield: 60 \%

M.p.: 191-92° (EtOH) (Lit.^{12a}, m.p. 189-92°)

Analysis: Found: C, 62.26 \%; H, 4.05 \%
Calculated for C_{22}H_{16}O_9: C, 62.26 \%; H, 3.80 \%

IR (Nujol): 3300-3000, 1745, 1670, 1620, 1500, 1450, 1360, 1320, 1300, 1215, 1080, 1040, 940, 890, 870, 815, 770, 730 cm^{-1}.

PMR (CDCl_3):

3.58 \ s \ 3H \ COOCH_3 (at C_3) \\
3.92 \ s \ 3H \ COOCH_3 (at C_2) \\
6.02 \ s \ 4H \ 2 \times -O-CH_2-O- \\
6.7-6.9 \ m \ 4H \ Ar-H (H_8, H_2, H_5, H_6) \\
7.7 \ s \ 1H \ Ar-H (H_5) \\
12.14 \ s \ 1H \ OH (exchanges with D_2O)
c) Reaction of ketoaldehyde 10c with NaBH₄ followed by DMAD:

Dimethyl-1-hydroxy-6,7-methylenedioxy-4-(3',4',5'-trimethoxy-phenyl)naphthalene-2,3-dicarboxylate, 6c

Yield: 60%  
M.p.: 241-42° (EtOH-EtOAc) (Lit.12a, m.p. 242-44°)

Analysis:  
Found: C, 61.18%; H, 4.71%  
Calculated for C₁₄H₁₁O₁₀: C, 61.27%; H, 4.72%.

IR (Nujol): 3200-2900, 1740, 1665, 1600, 1450(br), 1375, 1310, 1220 (br), 1120, 1030, 1000, 940, 860, 810, 780, 730, 690, 670 cm⁻¹.

PMR (CDCl₃):

3.63  s  3H  COOCH₃ (at C₃)
3.90  s  6H  COOCH₃ (at C₂) & Ar-OCH₃
4.0   s  6H  2 x ArOCH₃
6.1   s  2H  -O-CH₂-O-
6.56  s  2H  Ar'-H (H₂', H₆')
6.84  s  1H  Ar-H (H₃)
7.77  s  1H  Ar-H (H₅)
12.21 s  1H  OH (exchanges with D₂O)

Expt. No. 3.5: Reduction of naphthalenic diester 6a to naphthalenic lignan lactone 7a

The naphthalenic diester 6a (0.1 g) in THF - ethanol (20 ml) was treated with portions of NaBH₄ (3 x 0.5 g) at room
temperature over 18 h. 2N H₂SO₄ was then added and the mixture stirred for a further period of 30 min. Removal of solvent under vacuum, gave a precipitate, which was filtered. Recrystallization from acetone provided 4-hydroxy-6,7-dimethoxy-9-(4'-methoxyphenyl)-naphtho-(2,3,c)-furan-(3H)-one, 7a (0.065 g, 76%), m. p. 280-81°.

Analysis:  Found: C, 68.65%; H, 5.00%
Calculated for C₂₁H₁₈O₆: C, 68.84%; H, 4.95%

IR (Nujol): 3150(br), 1725, 1630, 1475, 1360, 1245, 1205, 1170, 1100, 1035, 1010, 880, 850, 810, 770 cm⁻¹.

PMR (CDCl₃-DMSO-d₆):

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<td>OCH₃</td>
</tr>
<tr>
<td>4.07</td>
<td>s</td>
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<td>OCH₃</td>
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<tr>
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<td>Ar-CH₂-O-</td>
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<tr>
<td>7.0</td>
<td>m</td>
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<td>Ar'-H &amp; Ar-H (H₃', H₅', &amp; H₈)</td>
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<td>7.26</td>
<td>d(J=9 Hz)</td>
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<td>Ar'-H (H₂', H₆')</td>
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<td>Ar-H (H₅)</td>
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<td>9.65</td>
<td>brs</td>
<td>1H</td>
<td>OH (exchanges with D₂O)</td>
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</table>
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