CHAPTER III

Synthesis of kigelin
Synthesis of Kigelin

Kigelin, a naturally occurring dihydroisocoumarin, was isolated from *Kigelia pinnata* DC (Family - Bignoniaceae) by Govindachari and coworkers\(^1\). The authors proposed structure 1 for the compound on the basis of spectral data. The structure was later confirmed by synthesis\(^2\) according to Chart I.

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

Two more syntheses, one by Chatterjea and coworkers\(^3\) (cf. Chart II) and another by Narasimhan and coworkers\(^4\) (cf. Chart III) have also been reported.
Synthesis due to Govindachari

Synthesis due to Chatterjea
Synthesis due to Narasimhan

\[ \text{Chart - II} \]

\[ \text{Chart - III} \]

\[ R = -\text{OCH}_3 \]
Conversion of elemicin into kigelin

A retrosynthetic analysis of kigelin is as follows

The striking structural similarity between the acid 3 and elemicin (4), another molecule of natural origin*, lead us to propose the following scheme (Scheme I) for the conversion of elemicin into kigelin (1).

The introduction of the carboxyl group in 3 was sought to be effected via the corresponding aldehyde 5, which in turn was sought to be obtained by formylation of elemicin (4).

*Elemicin, 3,4,5-trimethoxyallylbenzene is the chief constituent of Manila elemi oil.
Vilsmeier-Haack formylation reaction was considered for the formylation of elemicin (4).

It is true that Vilsmeier-Haack reagent can also formylate double bonds, e.g.
However, cases are also known where double bonds survive the Vilsmeier–Haack reaction conditions.
Considering the highly active nature of elemicin aromatic ring it was hoped that conditions could be worked out to achieve formylation of the aromatic ring alone in preference to that of the double bond.

Steric inhibition in the Vilsmeier-Haack reaction was not expected to be serious since 2-acetoxy-1-(3',4',5'-trimethoxyphenyl)-propane underwent smooth formylation in good yield (cf. Chart I). However, an undesirable possibility existed in that of the expected product cyclising to a naphthalene derivative, as reported in some similar cases.
Surprisingly, however, treatment of elemicin (4) with Vilsmeier–Haack complex, prepared from MFA and POCl₃ gave a totally unexpected aldehyde 3,4-dihydro-6,7,8-trimethoxy-2-naphthaldehyde (6)¹³.
The novelty of the reaction was that, not only the Vilsmeier-Haack reaction had occurred, but also reduction. The formation of compound 6 and a mechanism accounting for reduction has been presented in an earlier paper from this laboratory\textsuperscript{13}.

The reaction was found to be a general one and several other allylbenzenes gave corresponding dihydro-naphthaldehydes under similar reaction conditions\textsuperscript{14,15}. Although in other cases studied in this laboratory it was possible to isolate aldehydes corresponding to monoformylation at the aromatic position, in the case of elemicin no such compound could be obtained under the conditions then employed using either DMF/POCl\textsubscript{3} or MFA/POCl\textsubscript{3}.
In order to obtain the monoformylated compound variation of the reaction conditions such as temperature (0-100°C), solvents (DMF, MFA, POCl₃, chloroform), stoichiometry of the reactants was carried out but none of these gave the desired aldehyde 5. Other methods like Gatterman reaction, Friedel-Craft's reaction were also unsuccessful. The synthesis of aldehyde 5 and its conversion to kigelin (1) then remained a challenging problem.

**Vilsmeier-Haack reaction of elemicin in dichloromethane as the solvent**

Taking a lead from the effective use of dichloromethane as a solvent in the Vilsmeier-Haack reaction of 1-methyl-6-methoxy-3,4-dihydronaphthalene (cf. Chapter I), the Vilsmeier-Haack reaction of elemicin was carried out under similar conditions. The result was gratifying. T.l.c. analysis of the product mixture showed an additional spot (in addition to the dihydronaphthaldehyde 6) giving a positive 2,4-DNP test. The new compound had a Rₚ value very close to that of elemicin. However, its effective separation from the unreacted elemicin could not be achieved easily either by chromatography or by distillation under vacuum.
In general during work-up of a Vilsmeier-Haack reaction aqueous sodium acetate is used to hydrolyse the complex. In the present case, where sodium acetate was not used it was observed that the decomposition of the reaction mixture over crushed ice and then extraction of the products required exhaustive extraction with several portions of ether until the extract gave a negative 2,4-DNP test (at least 15-20 extractions were necessary). Since the products were insoluble in water and readily soluble in ether it was surprising that the extraction should be tedious. The observation was then interpreted to mean that the aldehydes themselves were formed by slow hydrolyses of the corresponding complexes. This was then utilised advantageously to effect the separation. The work-up procedure was modified. Thus, from the reaction mixture, the starting compound, which was not complexed, was just removed by ether extraction. The aqueous layer was then treated with sodium acetate and then again extracted with ether. The product aldehydes were then readily obtained.

(a) Reaction with DMF/POCl₃ complex

Elemicin (1) was treated with preformed Vilsmeier-Haack complex, prepared from DMF/POCl₃, in dichloromethane as the solvent. Decomposition of the reaction mixture over
crushed-ice and extraction of the ice-cold solution with ether provided unreacted elemicin (51% recovery).

The aqueous layer was then treated with sodium acetate. Extraction with ether gave an oil from which two products were separated by flash chromatography over silica gel using 1-3% ethyl acetate in hexane as eluent.

The first product, a pale yellow liquid, C$_{13}$H$_{16}$O$_4$, b.p. 150-155$^0$/0.7 mm (bath temperature), gave a positive 2,4-DNP test. The presence of a carbonyl group was further confirmed by IR spectrum - a band at 1680 cm$^{-1}$. The IR spectrum of the compound also indicated the presence of terminal olefin - bands at 990-910 cm$^{-1}$. The PMR spectrum of the compound was as follows:

PMR (CCl$_4$):

| 3.68  | br.d (J=7 Hz) | 2H  |
| 3.80  | s             | 3H  |
| 3.88  | s             | 3H  |
| 3.96  | s             | 3H  |
| 4.84-5.17 | m       | 2H  |
| 5.67-6.14 | m       | 1H  |
| 6.47  | s             | 1H  |
| 10.26 | s             | 1H  |
On the basis of the above information structure 5 was assigned to the compound.

The second product, a solid, m.p. 85°C, was found to be identical in all respects (t.l.c., m.m.p., superposable IR spectrum) with the dihydronaphthaldehyde 6 isolated earlier.

The recovered elemicin could be recycled. Since large amount of elemicin was recovered under the reaction conditions modifications like using large excess of complex, the reaction at reflux temperature of dichloromethane, keeping reaction mixture for prolonged period of twentyone days were tried. In all cases elemicin was recovered and aromatic aldehyde 5 was obtained in lower yield with increase in the yield of dihydronaphthaldehyde 6.

(b) Reaction with MFA/POCl₃ complex

The Vilsmeier-Haack reaction of elemicin (4) was also performed using complex prepared from MFA/POCl₃ in dichloromethane as the solvent. The reaction was followed by t.l.c. Interestingly enough under this reaction condition the formation of aldehyde 5 could not be detected. However, the reaction was complete after two days and the aldehyde 6
was obtained in higher yield (70.7%) than reported previously \(13\) (56%) where no solvent was used.

**Oxidation of aldehyde 5**

Having obtained aldehyde 5 it was sought to be oxidised to the corresponding acid 3.

In general aldehydes are susceptible to further oxidation to acids not only by oxidising agents but also by air. It was then expected that the oxidation of aldehyde 5 would not pose any problem despite the fact that the aldehyde group was present on an unusually electron rich aromatic nucleus (the rate of oxidation of benzaldehyde with chromic acid is retarded by introduction of methoxy group para to aldehyde \(17\)).

The oxidising agents most commonly employed for the oxidation of aldehydes to acids are potassium dichromate or chromic acid and argentic oxide.

Argentic oxide, prepared in situ by the addition of aqueous sodium hydroxide to aqueous silver nitrate solution was used in first place since, in alkaline medium, it could oxidise aldehydes to acids without affecting the olefinic double bond or allylic and/or benzylic methylenes e.g.
The aldehyde 5, however, remained unaffected for several hours when subjected to the reaction conditions generally employed for such oxidations, i.e. slow addition of sodium hydroxide to a well-stirred mixture of the aldehyde in ethanol and silver nitrate in water at room temperature and further stirring at room temperature. Usually in several other cases three to four hours stirring period was observed to be sufficient. Gently refluxing the reaction mixture was of no help. The aldehyde resisted oxidation even when aqueous
sodium hydroxide was added to a refluxing suspension of the aldehyde in aqueous silver nitrate.

Attention was then turned to chromic acid oxidation. Recently Chakraborty and Chandrasekaran\textsuperscript{21} have reported a facile and high yield conversion of aldehydes to carboxylic acids using (BiPy)\textsubscript{2}CrOCl\textsubscript{5}, a chromium(V) complex with 2,2'-bipyridine, under anhydrous conditions. Thus the following aromatic aldehydes were oxidised in high yields.

\[
\begin{align*}
\text{CHO} & \quad \rightarrow \quad \text{COOH} \\
\begin{array}{c}
\begin{array}{c}
\text{H}_3\text{C} - \quad \text{CHO} \\
\text{CHO}
\end{array}
\end{array} & \quad \rightarrow \quad \begin{array}{c}
\begin{array}{c}
\text{H}_3\text{C} - \quad \text{COOH} \\
\text{COOH}
\end{array}
\end{array} \\
\begin{array}{c}
\begin{array}{c}
\text{CHO}
\end{array}
\end{array} & \quad \rightarrow \quad \begin{array}{c}
\begin{array}{c}
\text{COOH}
\end{array}
\end{array} \\
\begin{array}{c}
\begin{array}{c}
\text{O}_2\text{N} - \quad \text{CHO} \\
\text{CHO}
\end{array}
\end{array} & \quad \rightarrow \quad \begin{array}{c}
\begin{array}{c}
\text{O}_2\text{N} - \quad \text{COOH} \\
\text{COOH}
\end{array}
\end{array}
\end{align*}
\]
The time required for the oxidation was reported to vary from 0.5 to 12 hours. It was disappointing to find that the reagent did not oxidise aldehyde 5, even after prolonged reaction period of thirty to thirtytwo hours.

In the beginning use of CrO₃ (or K₂Cr₂O₇)/acid combination was avoided, for its known reactivity towards activated benzylic methylenes. However, failure in oxidation of 5 with the above reagents and stability of the compound towards air oxidation (the aldehyde was not oxidised even when stored under oxygen atmosphere) made us to consider its use in the present case.

The oxidation of aldehyde with chromic acid is believed to involve the formation and decomposition of the chromate ester of the aldehyde hydrate.$^{22}$

\[
\text{C}_6\text{H}_5\text{CHO} + \text{H}^+ + \text{HCrO}_4^- \rightleftharpoons \text{C}_6\text{H}_5\text{O}^-\text{CrO}_3\text{H}^+\text{H}_2\text{O}^+
\]

\[
\rightarrow \text{C}_6\text{H}_5\text{COOH} + \text{HCrO}_3^- + \text{H}_3\text{O}^+
\]

In the case of aldehyde 5, the intermediate chromate ester could be written as 2.
It was then quite likely that under the acidic conditions lactone 2 might directly be obtained. However, the aldehyde 5 was recovered (70-75%) when molar proportion of the oxidising agent was used along with sulphuric acid or acetic acid (both CrO₃ and K₂Cr₂O₇ were tried with varied concentrations of acid in water). The recovery was lower when either excess of oxidising agent or concentrated solutions of sulphuric acid were used. Interestingly under none of the conditions any other compound could be isolated from the reaction mixture.

**Attempted oxidation of aldehyde 5 with alkaline hydrogen peroxide was also unsuccessful.**

In view of the amazing stability of the aldehyde 5 towards oxidation, the earlier approach to kigelin (Scheme I, p.233) was modified and a new route (Scheme II) to effect the transformation was proposed.
It was envisioned that cyclisation of the benzylic alcohol \(8\) would give isochroman \(2\) which had been oxidised to \(O\)-methyl kigelin \((2)\) by Chatterjea and coworkers\(^3\) (Chart II).

**Reduction of aldehyde \(5\)**

Reduction of aldehyde \(5\) with sodium borohydride was uneventful and proceeded smoothly. The product obtained, a viscous liquid, could not be distilled cleanly. The liquid was homogeneous on t.l.c. and analysed for \(C_{13}H_{18}O_4\). The IR
spectrum of the compound showed presence of hydroxyl group as well as terminal olefin - bands at 3500-3300 cm$^{-1}$ and at 1000 and 900 cm$^{-1}$. The PMR spectrum was in complete agreement with structure 8.

**Cyclisation of 8 to 9**

Cyclisation of the alcohol 8 to isochroman 2 was then attempted using Pd(CH$_3$CN)$_2$Cl$_2$/NaH in THF. However even after repeated attempts no product corresponding to isochroman 2 could be isolated.

Attempts to effect acid catalysed cyclisation were also unsuccessful under a variety of conditions - PPA, H$_2$SO$_4$, HBr/AcOH, HClO$_4$/H$_2$O/benzene. In each case the alcohol was consumed but no characteristic product could be isolated.

Iodocyclisation$^{23}$ of the alcohol 8 by treatment with I$_2$/KI/NaHCO$_3$/H$_2$O/(C$_2$H$_5$)$_2$O was also attempted. The alcohol 8 remained unreacted when the reaction was conducted in dark. However, when the reaction mixture was exposed to daylight, the alcohol reacted giving a complex product mixture.
Ref. 23

\[
\text{R}^1 = H; \quad \text{R}^2 = \text{Bu}^n
\]
\[
\text{R}^1 = \text{SiMe}_2\text{Bu}^t; \quad \text{R}^2 = (\text{CH}_2)_4\text{-CH}_2\text{OH}
\]
\[
\text{R}^1 = \text{SiMe}_2\text{Bu}^t; \quad \text{R}^2 = (\text{CH}_2)_4\text{-COOH}
\]

Having failed in executing schemes I and II a new approach towards solving the problem was considered. In this the olefinic double bond was sought to be hydrated in the desired direction to give alcohol 11, which would indeed exist in the lactol form 12.
The lactol 12 could then be oxidised to kigelin methyl ether (2).

**Hydration of ethylenic double bond in 5**

An efficient and high yield process to bring about hydration of olefin in Markownikoff manner, using mercuric acetate, is now known. Terminal olefins are especially reactive and give product in high yields. The method consisted of treatment of an olefin with mercuric acetate in THF-water, the organomercurial thus formed is then reduced with aqueous alkaline solution of sodium borohydride.

In the present case a problem of concomitant reduction of the aldehyde group and formation of the diol 13, existed on treatment with sodium borohydride.
Reduction of the alkyl organomercurial is known to be a very fast and efficient process. Bordwell and Douglass had studied the reduction process in detail and had observed the stoichiometry of the reduction to be four equivalents of organomercurial to one equivalent of borohydride. It was then thought that by adding calculated amount of sodium borohydride one might avoid the anticipated side reaction. This indeed was found to be the case.

Treatment of the aldehyde 5 with mercuric acetate in tetrahydrofuran-water, followed by reduction of the organomercurial with alkaline solution of sodium borohydride provided a solid $C_{13}H_{18}O_5$, m.p. 129-130°. The IR spectrum of the compound showed presence of hydroxy group - a band at 3410 cm$^{-1}$. The PMR spectrum of the compound had only one exchangeable proton and was as follows:
PMR (CDCl₃) :

<table>
<thead>
<tr>
<th>δ</th>
<th>J (Hz)</th>
<th>Multiplicity</th>
<th>J (Hz)</th>
<th>Multiplicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.31</td>
<td></td>
<td>d (J=6 Hz)</td>
<td>3H</td>
<td></td>
</tr>
<tr>
<td>2.56</td>
<td></td>
<td>br.d (J=7 Hz)</td>
<td>2H</td>
<td></td>
</tr>
<tr>
<td>3.50-3.64</td>
<td></td>
<td>bs</td>
<td>1H (exchanges with D₂O)</td>
<td></td>
</tr>
<tr>
<td>3.81</td>
<td></td>
<td>s</td>
<td>6H</td>
<td></td>
</tr>
<tr>
<td>3.91</td>
<td></td>
<td>s</td>
<td>3H</td>
<td></td>
</tr>
<tr>
<td>4.26-4.54</td>
<td></td>
<td>m</td>
<td>1H</td>
<td></td>
</tr>
<tr>
<td>6.01-6.20</td>
<td></td>
<td>bs (sharp singlet after D₂O exchanges)</td>
<td>1H</td>
<td></td>
</tr>
<tr>
<td>6.39</td>
<td></td>
<td>s</td>
<td>1H</td>
<td></td>
</tr>
</tbody>
</table>

On the basis of the above information structure 12 was assigned to the product. The lactol 12 was obtained in 82% yield.

Oxidation of 12 to kigelin methyl ether

The lactol 12 was smoothly oxidised to O-methyl kigelin (2), C₁₃H₁₆O₅, m.p. 104 ° (m.p., mixed m.p., superposable IR and PMR) thus accomplishing a formal synthesis of kigelin from elemicin. Thus oxidation was effected with pyridinium chlorochromate in dichloromethane.
Experimental

Because of the non-availability of elemicin from commercial sources, the compound was synthesised, as had already been reported in literature, according to the following reaction sequence:

The experimental details are not included in the thesis.
Expt. No. 3.1: Vilsmeier-Haack reaction of elemicin

(a) Using complex prepared from DMF/POCl₃ in presence of dichloromethane as a solvent

(b) Using complex prepared from N-MFA/POCl₃ in presence of dichloromethane as a solvent

Expt. No. 3.2: Reduction of aldehyde 5 with sodium borohydride
Expt. No. 3.3 : 1-Hydroxy-3-methyl-6,7,8-trimethoxy isochroman (12)

Expt. No. 3.4 : Kigelin methyl ether (2)
Expt. No. 3.1 : Vilsmeier-Haack reaction of elemicin

(a) Using complex prepared from DMF/POCl\(_3\) in presence of dichloromethane as a solvent

To the Vilsmeier-Haack complex, prepared by mixing DMF (12.7 ml) and POCl\(_3\) (15 ml) in cold (0-5°; cf. Chapter II), elemicin (10 g) in dry dichloromethane (30 ml) was added. The reaction mixture, protected from moisture, was left at room temperature for five days. It was then poured over crushed ice and stirred well. The cold solution was extracted with dichloromethane and then with ether (2 x 30 ml). The combined organic phase was washed with water (2 x 25 ml) (these washings were combined with aqueous layer), aq. sodium bicarbonate, saturated brine and dried over anhydrous sodium sulphate. Evaporation of the solvent gave 6.35 g of liquid, which on distillation under reduced pressure (b.p. 115-118°/1.5 mm) gave the starting compound (5.1 g, 51%). The identity was confirmed by comparison with synthetic material (t.l.c., superposable IR, PMR).

The aqueous layer was treated with sodium acetate trihydrate (20 g) and heated on water-bath for 20-25 minutes. Extraction with ether, followed by washing with water, aq. sodium bicarbonate, water, drying over anhydrous sodium
sulphate and removal of the solvent gave an oil (4.35 g).
Flash chromatography over silica gel using 1-3% ethyl acetate in hexane as eluent gave 5 as a pale yellow liquid (1.9 g, 16.74%), b.p. 150-155°/0.7 mm (bath temperature).

**Analysis:** Found : C, 66.10%; H, 6.77%
Calculated for C_{13}H_{16}O_4 : C, 66.08%; H, 6.83%

**IR (liquid film):** 3070, 2970, 2935, 2850, 1680, 1590, 1560, 1500, 1450, 1380, 1320, 1255, 1195, 1125 (br), 1070, 1030, 990, 910, 835, 780 cm^{-1}.

**PMR (CCl₄):**

<table>
<thead>
<tr>
<th>Chemical Shift</th>
<th>Multiplicity</th>
<th>Assignments</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.68</td>
<td>bd (J=7 Hz)</td>
<td>2H Ar-CH₂⁻</td>
</tr>
<tr>
<td>3.80</td>
<td>s</td>
<td>3H OCH₃</td>
</tr>
<tr>
<td>3.88</td>
<td>s</td>
<td>3H OCH₃</td>
</tr>
<tr>
<td>3.96</td>
<td>s</td>
<td>3H OCH₃</td>
</tr>
<tr>
<td>4.84-5.17</td>
<td>m</td>
<td>2H CH=CH₂</td>
</tr>
<tr>
<td>5.67-6.14</td>
<td>m</td>
<td>1H CH₂-CH=CH₂</td>
</tr>
<tr>
<td>6.47</td>
<td>s</td>
<td>1H Ar⁻H</td>
</tr>
<tr>
<td>10.26</td>
<td>s</td>
<td>1H CHO</td>
</tr>
</tbody>
</table>

Further elution with 5% ethyl acetate hexane gave 6 (2.0 g, 17%), m.p. 85° (from hexane). This was identical in all respects with authentic sample^{13} (t.l.c., m.p., m.m.p., superposable IR spectrum).
(b) Using complex prepared from N-MFA/POCl₃ in presence of dichloromethane as a solvent

To the Vilsmeier-Haack complex, prepared by mixing N-MFA (4.8 ml) and POCl₃ (3.5 ml) in cold (5-10°C), elemicin (2.5 g) in dry dichloromethane (20 ml) was added. The reaction mixture, protected from moisture, was left at room temperature for two days. It was then decomposed by pouring over crushed ice with vigorous stirring. The decomposed reaction mixture was treated with sodium acetate trihydrate (3 g) and heated on water-bath for 15-20 minutes with stirring. After cooling to room temperature it was extracted with ether (5 x 20 ml). Combined organic phase was washed with water, aq. sodium bicarbonate, water and dried over anhydrous sodium sulphate. Removal of solvent gave an oil which upon drying under vacuum for a longer period was set into a semi solid mass. Crystallisation of the material from hot hexane furnished aldehyde 6 (2.1 g) which was slightly contaminated with unidentified impurities (t.l.c. analysis). This was combined with the solid (0.4 g of same Rf value) obtained by chromatography of the mother liquor and then purified again by flash chromatography over silica gel using 3-5% ethyl acetate in hexane as eluent. Crystallisation from hexane gave 6 as a pale yellow
crystalline solid (2.1 g, 70.7%), m.p. 85°C. The identity of the product was established by comparison with an authentic sample (t.l.c., m.p., m.m.p., superposable IR).

Expt.No. 3.2 : Reduction of aldehyde 5 with sodium borohydride

To a solution of aldehyde 5 (0.4 g) in tetrahydrofuran (2 ml), sodium borohydride (200 mg) in water (0.4 ml) was added. The reaction mixture was stirred for one hour and then decomposed with saturated solution of ammonium chloride (2 ml). It was then extracted with ether (4 x 10 ml), ether extract was washed once with water and then dried over anhydrous sodium sulphate. Evaporation of the solvent furnished 8 as a viscous liquid (0.38 g, 94%). The liquid could not be distilled cleanly, however it was homogeneous on t.l.c.

Analysis : Found : C, 65.76%; H, 7.69%
Calculated for C₁₃H₁₈O₄ : C, 65.53%; H, 7.61%

IR (nujol) : 3500-3300, 1600, 1500, 1410, 1370, 1340, 1240, 1190, 1120, 1045, 1000, 910, 830 cm⁻¹.

PMR (CDCl₃) :

1.8-2.0 br 1H OH (exchanges with D₂O)
3.4 bd (J=7 Hz) 2H Ar-CH₂-CH=CH₂
| 3.78 s | 6H | OCH₃ |
| 3.80 s | 3H | OCH₃ |
| 3.88 s | 2H | Ar-CH₂-OH |
| 4.52 s | 2H | CH₂=CHCH₂ |
| 4.84-5.16 m | 1H | CH₂=CHCH₂ |
| 5.72-6.20 m | 1H | Ar-H |

**Expt. No. 3.3 : 1-Hydroxy-3-methyl-6,7,8-trimethoxy isochroman (12)**

Mercuric acetate (638 mg) was dissolved in water (2 ml) by stirring. Tetrahydrofuran (2 ml) was then introduced, when a yellow precipitate was obtained. To the vigorously stirred mixture of the above at room temperature, aldehyde 5 (425 mg) in tetrahydrofuran (2 ml) was added over two minutes, by which time the yellow colour was completely discharged. Stirring was continued for further twenty minutes and 3 M aq. sodium hydroxide (2 ml) was added rapidly followed by a solution of sodium borohydride (19 mg) in 3 M aq. sodium hydroxide (2 ml). The reaction mixture was stirred until most of the mercury was coagulated. The supernatant tetrahydrofuran layer was separated and aqueous layer was further saturated with sodium chloride and extracted first with
tetrahydrofuran (2 x 3 ml) and finally with ether (2 x 15 ml). The combined organic phase, which retained some of the mercury, was evaporated, the residue redissolved in tetrahydrofuran and passed through a short pad of neutral alumina. Removal of the solvent gave 12 as a solid (375 mg, 82%), m.p. 129-130° (from ethyl acetate-hexane).

Analysis: Found: C, 61.59%; H, 7.12%
Calculated for C$_{13}$H$_{18}$O$_5$: C, 61.40%; H, 7.14%

IR (nujol): 3410, 1620, 1600, 1500, 1380, 1350, 1300, 1270, 1245, 1220, 1190, 1125, 1090, 1070, 1050, 1020, 990, 935, 865, 835, 820, 790 cm$^{-1}$.

PMR (CDCl$_3$):

1.31 d (J=6 Hz) 3H CH-CH$_3$
2.56 bd (J=7 Hz) 2H Ar-CH$_2$-CH
3.50-3.64 br 1H OH (exchanges with D$_2$O)
3.81 s 6H 2 x OCH$_3$
3.91 s 3H OCH$_3$
4.26-4.54 m 1H OCH(CH$_3$)CH$_2$-
6.01-6.20 bs 1H Ar-CH(OH)-O-
6.39 s 1H Ar-$H$

Expt. No. 3.4: Kigelin methyl ether (2)

To a well stirred suspension of pyridinium chlorochromate (324 mg) in dry dichloromethane (3 ml) lactol 12
(230 mg) in dry dichloromethane (2 ml) was added in one portion. The mixture was stirred further for 16 hours and diluted with dry ether (10 ml). The organic phase was decanted and the precipitate washed with dry ether (2 x 5 ml). The combined organic layer was washed with 1 N HCl, water and brine. Drying over sodium sulphate and evaporation of the solvent gave a brown mass. This was then triturated with benzene, and the benzene extract chromatographed over neutral alumina using benzene as eluent to get a solid, which crystallised from hexane to give 2 (175 mg, 77%), m.p. 104° (lit. 2 m.p. 105°).

Analysis: Found: C, 62.30%; H, 6.44%
Calculated for C_{13}H_{16}O_5: C, 61.89%; H, 6.39%

IR (nujol): 1710, 1600, 1580, 1420, 1380, 1370, 1345, 1325, 1255, 1220, 1210, 1190, 1180, 1165, 1130, 1115, 1100, 1070, 1045, 1010, 980, 945, 930, 910, 840, 825, 800, 755, 715 cm⁻¹.

PMR (CDCl₃):

- 1.43 d (J=7 Hz) 3H CH-CH₃
- 2.81 d (J=6 Hz) 2H Ar-CH₂-
- 3.85 s 3H OCH₃
- 3.90 s 3H OCH₃
- 3.95 s 3H OCH₃
- 4.32-4.73 m 1H O-CH(CH₃)CH₂-
- 6.50 s 1H Ar-H
References

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