CHAPTER VII

PART - I

EXPERIMENTAL RESULTS
7.1 Introduction

Melting points were taken in open capillary tubes using Thomus Hoover melting point apparatus and are uncorrected. The compounds were routinely checked for their purity by TLC using silica gel G. $^1$H NMR spectra were recorded either on Bruker 300 MHz or Bruker 200MHz or Jeol 60 MHZ Hitachi Perkin Elmer spectrometer in CDCl$_3$ solution. Tetramethyl silane was used as internal standard and the chemical shifts are expressed in ppm ($\delta$). The $^{13}$C NMR spectra were measured either on Bruker 500 MHz or 200 MHz or 75 MHz instrument and the values are in parts per million downfield from the tetramethyl silane. Mass spectra were obtained either on Mass spectra MSW 9629 or Finniggen 4021 spectrometer and the important fragments are given with the relative intensities in the bracket.

Thin layer chromatogram were obtained on a precoated silica gel (HF, 254, Merck) on aluminium plates. Visualisation of the spots on the chromatograms was viewed under UV light. Chromatographic separations were carried out on a silica gel (70-320 mesh, Merck.) column. The proportion of the solvents for the chromatography was given as the volume/volume.
7.2 Preparation of Mn(III) acetate dihydrate

A modified procedure of Christensen's was used for the oxidation of manganous acetate. In a 500 mL 3-necked flask fitted with stirrer, condenser and a thermometer, solution of Mn(OAc)$_2$$\cdot$4H$_2$O (42.9 g) in glacial acetic acid (300 mL) was heated to 110°C. To this solution ground potassium permanganate (6.82 g) was added in small portions through the condenser over 20 min period, while the temperature was maintained at 110°C. The reaction mixture was heated for additional 20 min, cooled, poured into water (75 mL) and left to crystallise overnight. The solid was filtered off, washed with ether, and air dried. The yield was 49 g (82%, lit.$^{2b}$ 84%).

7.3 Experiments leading to preparation of analogs of β-Apopicropodophyllin homolactone and its intermediates.

7.3.1 Preparation of γ-phenyl-γ-butyrolactone (73)$^{2a}$

![Chemical Reaction Diagram]

Solution of styrene (2.5 g, 24mmol) in glacial acetic acid (25 mL) was refluxed under nitrogen with Mn(III) acetate dihydrate (12.9 g, 2 equiv.) in the presence of potassium acetate (2.5 g). After 6 hr. of refluxing, disappearance of colour was observed. The
resulting reaction mixture was then cooled and diluted with water (25 mL). It was then extracted with diethyl ether, the ether layer was washed with water (2 x 20 mL), 10% sodium bicarbonate solution (2x20 mL) and finally with water (1x20 mL). Ether layer after drying over anhydrous sodium sulphate was completely evacuated to get thick residue. The pure lactone was isolated by passing through the column packed with 70-320 mesh silica gel and eluting with petroleum ether and ethyl acetate mixture (8:2). Evaporation of the major fraction yields 73 as oily liquid in 1.64 g (42%) yield (lit.2a 60%).

7.3.2 Preparation of α-Hydroxy-(3,4,5-trimethoxyphenyl)-methyl-γ-phenyl-γ-butyrolactone (74a)

\[
\text{Subst. benzaldehyde} \rightarrow \text{NaH} \rightarrow \text{THF}
\]

\[73 \quad 74 \quad (a, b)\]

Solution of γ-phenyl-γ-butyrolactone 732a (1.2 g, 7.4 mmol) in tetrahydrofuran (10 mL) (dried over sodium metal and distilled) was treated with sodium hydride (0.2g) under nitrogen atmosphere. After stirring for 15-20 min at 15-20°C, a solution of 3,4,5-trimethoxybenzaldehyde (1.45 g, 7.4 mmol) in
tetrahydrofuran (10 mL) was added solution slowly over a period of 25-30 min. and it was then stirred at 15-20°C. The progress of the reaction was monitored by TLC using chloroform and acetone mixture (7:1) as eluant. After the reaction, the reaction mixture was poured to water, neutralised with dil. hydrochloric acid and extracted with ether, washed the ether layer to neutral pH and dried over anhydrous sodium sulphate. TLC of this solution showed a single spot having Rf value 0.23. Evaporation of the solvent gave (74a) as a thick paste. The residue was dissolved in chloroform (2mL) and petroleum ether was added drop wise until no more precipitate formed on further addition. The product (74a) after suction drying for 4hr yielded yellowish amorphous powder weighing 1.2 g. (54%), m.p. 87-89°C; IR (Nujol): \( \gamma \) 3500-3300 (OH), 1745 (C=O), 1600 (-C=C-) cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 2.50-2.56 (m, 2H, CH\(_2\)), 2.93-2.97 (m, 1H, CH), 3.87-3.89 (s, 3H, OCH\(_3\)), 3.89-3.92 (s, 6H, OCH\(_3\)), 5.0-5.2 (broad, 1H, OH), 5.24-5.27 (d, 1H, CH), 5.83-5.85 (t, 1H, CH), 6.24-6.28 (s, 2H, Ar'-H), 7.27-7.30 (s, 4H, Ar-H). Anal. Calcd. For C\(_{20}\)H\(_{22}\)O\(_6\): C, 67.03, H, 6.19, O, 21.71; Found: C, 66.88, H, 6.07.

\( \alpha \)-Hydroxy-(3,4-dimethoxyphenyl)-methyl-\( \gamma \)-phenyl-\( \gamma \)-butyrolactone (74b): Obtained from \( \gamma \)-phenyl-\( \gamma \)-butyrolactone 73 (1.2 g, 7.4 mmol) and 3,4-dimethoxy benzaldehyde (1.23 g, 7.4 mmol) as yellowish amorphous powder in 51 % yield (1.23 g) m.p.
80-82°C; IR (Nujol): $\gamma$ 3500-3300 (OH), 1745 (C=O), 1598 (C=C-) cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta$ 2.50-2.53 (m, 2H, CH$_2$), 2.95-2.98 (m, 1H, CH), 3.87-3.91 (bs, 6H, OCH$_3$), 5.0-5.25 (broad, H, OH), 5.27-5.30 (d, 1H, CH), 5.81-5.84 (t, 1H, CH), 6.80-6.83 (m, 3H, Ar'-H), 7.25-7.29 (s, 4H, Ar-H). 

**Anal. Calcd. For C$_{19}$H$_{20}$O$_5$:** C, 69.50, H, 6.14, O, 24.36; **Found:** C, 69.41, H, 6.08.

### 7.3.3 Preparation of 1-(3',4',5'-trimethoxyphenyl)-1,2-dihydro-2-naphthoic acid (75a)

Freshly prepared polyphosphoric acid$^{135}$ (4 g) [by treating phosphorous pentoxide with ortho phosphoric acid] was added to 74a (0.96 g, 2.68 mmol) at room temperature and was heated to 65-70°C for 2hr. The reaction mixture was then quenched with water and extracted into ether.

The organic layer was washed with water (2 x 10 mL), 5% sodium bicarbonate solution (2 x 20 mL) and finally with water (1 x 20 mL). Bicarbonate layer was neutralised by addition of 5% hydrochloric acid until precipitation ceases. The precipitated acid was then filtered and thoroughly washed with water (2x20 mL).
was further purified by crystallisation to give 75a as white amorphous solid in 71 % yield, (0.65 g), m.p. 140-144°C; IR (Nujol): \( \gamma \) 3500-3300 (OH), 1710 (C=O), 1590 (C=C) cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 3.79-3.81 (t, 1H, 1-H), \( \delta \) 3.85-3.88 (s, 3H, OCH\(_3\)), 3.89-3.92 (s, 6H, OCH\(_3\)), 4.39-4.42 (d, \( j=12\)Hz, 1H, 1-H), 6.04-6.10 (t, 1H, CH), 6.33-6.34 (s, 2H Ar'-H), 6.82-6.85 (d, 1H, CH), 7.2-7.7 (m, 4H, Ar-H). Anal. Calcd. For C\(_{20}\)H\(_{20}\)O\(_5\): C, 70.57, H, 5.92, O, 23.50; Found: C, 70.48, H, 5.96.

1-(3',4'-dimethoxyphenyl)-1,2-dihydro-2-naphthoic acid (75b):

Obtained from \( \alpha \)-Hydroxy-(3,4-dimethoxyphenyl)-methyl-\( \gamma \)-phenyl-\( \gamma \)-butyrolactone 74b (0.85 g, 2.58 mmol) in yield 69 % (0.55 g), m.p.132-135°C IR (Nujol) : \( \gamma \) 3500-3300 (OH), 1713 (C=O), 1590 (C=C) cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 3.79-3.81 (t, 1H, 2-H), \( \delta \) 3.85-3.88 (s, 3H, OCH\(_3\)), 3.89-3.92 (s, 3H, OCH\(_3\)), 4.39-4.42 (d, \( J=11\)Hz, 1H, 1-H), 6.0-6.10 (t, 1H, CH), 6.82-6.84 (m, 3H Ar'-H), 6.82-6.84 (d, 1H, CH), 7.2-7.7 (m, 4H, Ar-H). Anal. Calcd. For C\(_{19}\)H\(_{18}\)O\(_4\): C, 73.53, H, 5.85, O, 20.62; Found: C, 73.45, H, 5.72.

7.3.4 Preparation of Ethyl-1-(3',4',5'-trimethoxyphenyl)-1,2-dihydro-2-naphthoate (76a)

A Mixture of 75a (1 g, 2.94 mmol) and absolute ethanol (1 mL) in dry dichloromethane (10 mL) was treated with
dicyclohexylcarbodiimide (DCC) (0.65 g, 3.35 mmol) at room temperature and stirred for 10 hr. After the reaction, precipitated urea was filtered and was washed with dichloromethane (2 mL). The organic layer was thoroughly washed with water (2 x 20 mL), 5% sodium hydroxide (2 x 20 mL) and finally with water (2 x 20 mL). The organic phase after drying over anhydrous sodium sulphate was evaporated under vacuum to get thick paste, which was dissolved in chloroform and precipitated by adding petroleum ether. The precipitated solid was filtered and dried under vacuum to give 76a as amorphous powder in 70% yield (0.756 g), mp. 108-112°C; IR (Nujol): $\gamma$ 1745 (C=O), 1600 cm$^{-1}$ (C=C); $^1$H NMR (CDCl$_3$): $\delta$ 1.05-1.10 (t, 3H, CH$_3$), 3.75-3.81 (t, 1H, 2-H), $\delta$ 3.85-3.88 (s, 3H, OCH$_3$), 3.89-3.92 (s, 6H, OCH$_3$), 4.05-4.17 (q, 2H, OCH$_2$), 4.40-4.42 (d, J=12Hz, 1H, 1-H), 6.0-6.10 (t, 1H, 3-H), 6.23-6.24 (s, 2H, Ar'-H), 6.80-6.85 (d, 1H, 4-H), 7.18-7.20 (m, 4H, Ar-H). Anal. Calcd. For C$_{22}$H$_{24}$O$_5$: C, 71.72, H, 6.57, O, 21.71; Found: C, 71.66 H, 6.50.

**Ethyl-1-(3',4'-dimethoxyphenyl)-1,2-dihydro-2-naphthoate (76b):**

Obtained from 1-(3,4-dimethoxyphenyl)-1,2-dihydro-naphthoic acid 75b (0.52 g, 1.67 mmol) as white amorphous solid in yield 65.0% (0.37 g), m.p. 101-103°C; IR (Nujol): $\gamma$ 1739 (C=O), 1600 cm$^{-1}$ (C=C); $^1$H NMR (CDCl$_3$): $\delta$ 1.08-1.17 (t, 3H, CH$_3$), 3.71-3.76 (t, 1H, 2-H), 3.84-3.88 (s, 3H, OCH$_3$), 3.89-3.93 (s, 3H,
OCH₃), 4.08-4.18 (q, 2H, OCH₂), 4.38-4.41 (d, J=10Hz, 1H, 1-H),
6.04-6.12 (t, 1H, CH), 6.70-6.75 (m, 3H Ar'-H), 6.82-6.84 (d, 1H, 
CH), 7.15-7.19 (m, 4H, Ar-H). **Anal. Calcd. For C₂₁H₂₂O₄:** C, 
74.54, H, 6.55, O, 18.91; **Found:** C, 74.58, H, 6.48.

7.3.5 Preparation of Ethyl-2-oxo-5-(3',4',5'-trimethoxy phenyl)-2,3,3a,4,5-hexahydro-naphtho[1,2-b]furan-4-
carboxylate (77a)

Mixture of carboxylate 76a (0.8 g, 2.17 mmol), Mn(III) 
acetate dihydrate (1.16 g) and potassium acetate (1.5 g) in glacial 
acetic acid (15 mL) were refluxed under nitrogen atmosphere till 
the brown colour disappeared.

The resulting reaction mixture was cooled and diluted with 
water (15 mL). It was then extracted into diethyl ether, washed 
with water (2 x 20 mL), 10% sodium bicarbonate solution (2 x 20 
ml) and finally with water (1 x 20 mL). Ether layer after drying 
over anhydrous sodium sulfate was completely evacuated to get 
thick residue. The pure cis-lactone 77a was isolated by column 
chromatography packed with 70-320 mesh silica gel using
petroleum ether: ethyl acetate mixture (8:2) as eluant. Evaporation of major fraction yields **77a** in 35% (0.32 g) as oily liquid. **IR (Nujol):** $\gamma$ 1760 (ester C=O), 1750 (lactone C=O), 1600 (aromatic C=C) cm$^{-1}$; **$^1$H NMR (CDCl$_3$):** $\delta$ 1.08-1.11 (t, 3H, CH$_3$), 2.45-2.50 (d, 2H, CH$_2$-C=O), 2.78-2.85 (t, 1H, 3-H), 3.41-3.49 (t, J=11Hz, 1H, 2-H), 3.85-3.88 (s, 3H, OCH$_3$), 3.89-3.90 (s, 6H, OCH$_3$), 4.10-4.17 (q, 2H, OCH$_2$), 4.68-4.76 (d, J=12Hz, 1H, 1-H), 5.27-5.30 (d, J=6Hz, 1H, 4-H), 6.38-6.40 (s, 2H, Ar'-H), 7.16-7.19 (m, 4H, Ar-H).

**Anal. Calcd. For C$_{24}$H$_{26}$O$_7$:** C, 67.59, H, 6.15, O, 26.26; **Found:** C, 67.51, H, 6.11.

**Ethyl-2-oxo-5-(3',4'-dimethoxyphenyl)-2,3,3a,4,5,6-hexahydro-naphtho[1,2-b]furan-4-carboxylate (77b):** Obtained from ethyl-1-(3',4'-dimethoxyphenyl)-1,2-dihydro-2-naphthoate **76b** (0.45 g, 1.33 mmol) as oily liquid in 41% yield (0.22 g); **IR (Nujol):** $\gamma$ 1760 (lactone C=O), 1754 (ester C=O), 1600 (aromatic C=C) cm$^{-1}$; **$^1$H NMR (CDCl$_3$):** $\delta$ 1.12-1.14 (t, 3H, CH$_3$), 2.41-2.45 (t, 2H, CH$_2$), 2.80-2.87 (t, 1H, 3-H), 3.44-3.50 (t, J=12Hz, 1H, 2-H), 3.80-3.84 (s, 3H, OCH$_3$), 3.84-3.88 (s, 3H, OCH$_3$), 4.14-4.20 (q, 2H, OCH$_2$), 4.70-4.77 (d, J=12Hz, 1H, 1-H), 5.26-5.29 (d, J=7Hz, 1H, 4-H), 6.80-6.74 (m, 3H, Ar'-H), 7.20-7.22 (m, 4H, Ar-H). **Anal. Calcd. For C$_{23}$H$_{24}$O$_6$:** C, 69.68, H, 6.10, O, 24.22; **Found:** C, 69.55, H, 6.17.

**7.3.6 Preparation of 3-carboxymethyl-4-hydroxy-1-(3',4',5'-trimethoxyphenyl)-1,2,3,4-tetrahydro-2-naphthoic acid (78a):**
Solution of lactone 77a (0.25 g, 0.58 mmol) in alcohol was treated with alcoholic KOH (15 mL, 0.5 g) at room temperature and was refluxed for 5 hr. Progress of the reaction was monitored by TLC using chloroform:acetone (7:1) as eluant. After the reaction, solution was concentrated to approximately 5 mL using boiling water bath. Concentrated mass was cooled to room temperature, diluted with water and finally extracted into ether. The aqueous layer was neutralised with cold hydrochloric acid and the precipitated mass was filtered and dried. TLC of the solid mass showed one spot with $R_f$ value 0.12. Crystallisation of the solid mass yielded 78a as crystalline solid in 64% yield (0.156 g), m.p. 120-123°C; IR (Nujol): ν 3500-3300 (OH), 1715 (COOH), 1600 (C=C) cm$^{-1}$; $^1$H NMR (CDCl$_3$): δ 2.15-2.24 (bd, 2H, CH$_2$), 2.30-2.41 (m, 1H, 3-H), 2.80-2.88 (t, 1H, 2-H), 3.80-3.88 (s, 3H, OCH$_3$), 3.89-3.92 (s, 6H, OCH$_3$), 4.35-4.45 (d, $J$=11 Hz, 1H, 1-H), 4.55-4.62 (d, 1H, 4-H), 6.27-6.30 (s, 2H, Ar'-H), 6.92-7.17, (m, 4H, Ar-H). **Anal. Calcd. For C$_{22}$H$_{24}$O$_8$:** C, 63.45, H, 5.81, O, 30.74; **Found:** C, 63.32, H, 5.69.
3-Carboxymethyl-4-hydroxy-1-(3',4'-dimethoxyphenyl)-1,2,3,4-tetrahydronaphthoic acid (78b): Obtained from ethyl-2-oxo-5-(3',4'-dimethoxyphenyl)-2,3,3a,4,5,6-hexahydronaphtho[1,2-b]furan-4-carboxylate 77b (0.38 g, 0.958 mmol) as amorphous solid 62% in yield (0.30 g), m.p. 115-117°C; IR (Nujol): γ 3500-3300 (OH), 1718 (COOH), 1600 (C=C) cm⁻¹; ¹H NMR (CDCl₃): δ 2.17-2.25 (bd, 2H, CH₃), 2.33-2.42 (m, 1H, 3-H), 2.82-2.89 (t, 1H, 2-H), 3.81-3.87 (s, 3H, OCH₃), 3.87-3.91 (s, 3H, OCH₃), 4.38-4.47 (d, J=12Hz, 1H, 1-H), 4.52-4.60 (d, 1H, 4-H), 6.70-6.79 (m, 3H, Ar¹-H), 6.95-7.17 (m, 4H, Ar-H). Anal. Calcd. For C₂₁H₂₂O₇: C, 65.28, H, 5.74, O, 28.98; Found: C, 65.36, H, 5.67.

7.3.7 Preparation of homoanhydride (79a):

Dicarboxylic acid 78a (0.15 g, 0.36 mmol) dissolved in freshly distilled acetic anhydride (2mL) was boiled for 2 hr under reflux, protecting against moisture by calcium chloride tube.

The reaction was monitored by TLC with chloroform-acetone (7:1) as eluant. The reaction mixture was cooled to room temperature neutralised with saturated sodium bicarbonate.
solution and finally extracted into chloroform (2 x 20 mL) followed by water wash. The organic layer after drying over anhydrous sodium sulphate was completely evaporated to dryness to get thick residue. The residue was dissolved in chloroform and hexane was added dropwise until no more white solid is formed on further addition. This after suction drying at room temperature for 3-4 hr gave 79a as white amorphous solid in 73% yield (0.1 g), m.p. 94-96°C; IR (Nujol): $\gamma$ 1780 (C=O, anhydride), 1750 (C=O) 1600 (C=C) cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta$ 2.85-2.90 (s, 2H, CH$_2$ -C=O), 3.22-3.25 (s, 2H, 4-H), 3.85-3.87 (s, 3H, OCH$_3$), 3.86-3.90 (s, 6H, OCH$_3$), 4.50-4.56 (s, 1H, 1-H), 6.34-6.37 (s, 2H, Ar'-H), 6.95-7.08 (m, 4H, Ar-H). Anal. Calcd. for C$_{22}$H$_{20}$O$_6$: C, 69.46, H, 5.30, O, 25.23; Found: C, 69.38, H, 5.23.

Preparation of homoanhydride (79b): Obtained from 3-carboxymethyl-4-hydroxy-1-[(3',4'-dimethoxyphenyl)-1,2,3,4-tetrahydronaphthoic acid 78b (0.25 g, 0.65 mmol) as white amorphous powder in 71% yield (0.16 g), m.p. 90-94°C; IR (Nujol): $\gamma$ 1780 (C=O, anhydride), 1750 (C=O), 1598 (C=C) cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta$ 2.90-2.95 (s, 2H, CH$_2$), 3.25-3.28 (s, 2H, CH$_2$), 3.82-3.84 (s, 3H, OCH$_3$), 3.84-3.87 (s, 3H, OCH$_3$), 4.54-4.62 (s, 1H, 1-H), 6.80-6.88 (m, 3H, Ar'-H), 6.95-7.20 (m, 4H, Ar-H). Anal. Calcd. For C$_{21}$H$_{18}$O$_5$: C, 71.99, H, 5.18, O, 22.83; Found: C, 71.90, H, 5.12.
7.3.8 Preparation of analog β-apocicropodophyllin homolactone (80a)

Homoanhydride 79a (0.12 g, 0.3 mmol) dissolved in ethanol (20 mL) was treated with 2% sodium amalgam (0.3 g, 0.005 g atom) and mixture shaken to ensure thorough mixing and was left at room temperature. The progress of the reaction was monitored by TLC using chloroform:actone (7:1) as eluant. An aliquot of the homogeneous reaction mixture was treated with 2N sulphuric acid and extracted into ether layer and ether layer spotted for testing. After a reaction of 18-20 hr homoanhydride completely disappeared and produced new spot on the TLC plate. The reaction mixture was filtered and filtrate was concentrated to small volume by distillation under reduced pressure. The resulting slurry was then extracted into chloroform (25 mL) and the organic phase was successively washed with 2N hydrochloric acid (2 x 20 mL), 5% sodium bicarbonate solution (2 x 20 mL) and finally with water (2 x 20 mL). The organic phase after drying over anhydrous sodium sulphate was completely evacuated to a thick residue. The residue was dissolved in chloroform and hexane was added drop
wise until no more white solid is formed on further addition. The white solid after suction drying at room temperature for 3-4 hr gave \( \text{80a} \) as white amorphous solid in 78% (0.09 g.), m.p. 137-139°C; \( \text{IR (Nujol): } \gamma \ 1748 \text{(C=O), 1590 cm}^{-1} \text{ (aromatic C=C);} \)

\( ^{1}\text{HNMR (CDCl}_3\): \( \delta \ 2.38-2.45 \text{ (t, 2H, CH}_2\), 3.45-3.48 \text{ (s, 2H, 4-H), 3.85-3.88 \text{ (s, 3H, OCH}_3\), 3.89-3.92 \text{ (s, 6H, OCH}_3\), 4.05-4.14 \text{ (t, 2H, OCH}_2\), 4.52-4.54 \text{ (s, 1H, 1-H), 6.28-6.30 \text{ (s, 2H, Ar'-H), 6.86-7.15 \text{ (m, 4H, Ar-H);} } \)

\( ^{13}\text{C NMR (CDCl}_3\): \( \delta \ 31.3 \text{ (t, -CH}_2\), 37.5 \text{ (d, 1-Ç), 37.4 \text{ (t, 4-Ç), 55.4 \text{ (q, 4'-OCH}_3\), 56.1 \text{ (q, 3',5'-OCH}_3\), 67.8 \text{ (t, -OCH}_2\), 107.7 \text{ (d, 2',6'-CH}, 121.4 \text{ (d, 2,6-Ç), 126.6 \text{ (d, 7-Ç), 128.5 \text{ (d, 8Ç), 129.0 \text{ (d, 5-Ç), 130.4 \text{ (s, 4'-Ç), 136.6 \text{ (s, 1'-Ç), 137.1 \text{ (s, 4a-Ç), 143.2 \text{ (s, 8a-Ç), 147.0 \text{ (s, 3-Ç), 150.6 \text{ (s, 3',5'-Ç) 170.2 \text{ (s, -C=O ); MS (relative intensity, %): m/z for C}_{22}\text{H}_{22}\text{O}_{5}, 366 (M}^{+} 100), 351 (10), 350 (30), 294 (55), 199 (20), 168 (50), 153 (12), 127 (60), 125 (19). \text{Anal. Calcd.: } C, 72.12, H, 6.05, O, 21.83; \text{Found: } C, 72.03, H, 5.92. \)

\textbf{Preparation of } \beta\text{-apopicrocrophyllin homolactone (80b):}

Obtained from \( \text{79b} \) (0.15 g, 0.428 mmol) as white amorphous solid in yield 71% (0.1 g), m.p. 136-138°C; \( \text{IR (Nujol): } \gamma \ 1755 \text{(lactone -C=O stretch), 1750 (C=O), 1590 cm}^{-1} \text{ (aromatic C=C);} \)

\( ^{1}\text{H NMR (CDCl}_3\): \( \delta \ 2.30-2.34 \text{ (t, 2H, CH}_2\), 3.40-3.44 \text{ (s, 2H, 4-H), 3.85-3.87 \text{ (s, 3H, OCH}_3\), 3.87-3.89 \text{ (s, 3H, OCH}_3\), 4.05-4.12 \text{ (t, 2H, OCH}_2\), 4.52-4.54 \text{ (s, 1H, 1-H), 6.80-6.82 \text{ (m, 2H Ar'-H), 6.86-7.18 \text{ (m, 4H, Ar-H);} } \)

\( ^{13}\text{C NMR (CDCl}_3\): \( \delta \ 31.9 \text{ (t, -CH}_2\), 37.2 \text{ (d, 1-Ç), 38.0 \text{ (t, 4-} \)
56.6 (q, 3'-OCH$_3$), 56.8 (q, 4'-OCH$_3$), 66.8 (t, -OCH$_2$), 115.7 (d, 2', 5'-C), 121.9 (d, 6'-C), 122.8 (s, 2-C), 125.5 (d, 6-C), 126.5 (d, 7-C), 128.4 (d, 8-C), 130.1 (d, 5-C), 136.2 (s, 1'-C), 138.2 (s, 4a-C), 144.2 (s, 8a-C), 144.6 (s, 4'-C), 146.7 (s, 3-C), 148.3 (s, 3'-C), 171.2 (s, -C=O); **MS** (relative intensity, %): m/z for C$_{21}$H$_{20}$O$_4$, 336 (M$^+$ 100), 321 (09), 320 (31), 264 (53), 199 (22), 138 (52), 127 (59), 123 (11), 95 (20). **Anal. Calcd.** : C, 74.98, H, 5.99, O, 19.03; **Found**: C, 74.89, H, 5.91.
7.4 General procedure for the acetylation of the alcohols.

\[
\text{R—OH} \xrightarrow{\text{Mn(OAc)}_2\text{H}_{2}\text{O}, \text{CH}_3\text{COOH, Reflux}} \text{R—OAc}
\]

**Preparation of Phenethyl Acetate:**

In a typical experiment, a catalytic amount of Mn(III) acetate dihydrate (0.011 g, 0.04 mmol) was added to a stirred solution of phenethyl alcohol (1.2 g, 10 mmol) in acetic acid (10 mL). Reaction was refluxed for 2 hr during this period there will be disappearance of the colour occurs. After the reaction, it was cooled to room temperature, diluted with water (10 mL) and extracted into ether (20 mL). Organic layer after washing with water (2x20 mL), 5% sodium bicarbonate solution (2x20 mL) and finally with water (1x20 mL) was dried over anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure gave phenethyl acetate as colourless liquid in 99% yield (1.6 g), bp. 236-238°C. (Lit. bp. 238-239°C).\textsuperscript{113c} **IR (Nujol):** \(\gamma 1750 \text{ cm}^{-1} \) (ester C=O), 1600 (aromatic C=C) cm\(^{-1}\); \textsuperscript{1H NMR(CDC\textsubscript{3})}: \(\delta 2.25-2.26 \) (s, 3H, CH\textsubscript{3}), 2.88-2.90 (t, 2H, CH\textsubscript{2}), 4.44-4.47 (t, 2H, OCH\textsubscript{2}), 7.12-7.20 (m, 5H, Ar-H).

**1-Methylbenzyl acetate:** Obtained from methylbenzyl alcohol (1.2 g, 10 mmol) and Mn(III) acetate dihydrate (0.011 g, 0.04 mmol) as colourless oil in 99% yield (1.62 g). bp 93-95°C. (Lit. bp. 94-95°C).\textsuperscript{113a} **IR (Nujol):** \(\gamma 1748 \text{ cm}^{-1} \) (ester C=O), 1600 (aromatic
C=C) cm⁻¹; \(^1H\) NMR (CDCl₃): δ 1.70-1.72 (d, 3H, CH₃), 2.28-2.30 (s, 3H, CH₃), 5.44-5.50 (m, 1H, CH), 7.18-7.22 (m, 5H, Ar-H).

2-Octyl acetate: Obtained from 2-octyl alcohol (1.3 g, 10 mmol) and Mn(III) acetate dihydrate (0.011 g, 0.04 mmol) as colourless oil in 99% yield (1.72 g); IR (Nujol): γ 1750 cm⁻¹ (ester C=O); \(^1H\) NMR (CDCl₃): δ 1.04-1.06 (t, 3H, CH₃), 1.30-1.36 (m, 10H, CH₂), 1.59-1.62 (m, 3H, CH₃), 2.24-2.26 (s, 3H, CH₃), 3.96-4.02 (m, 1H, OCH),

Phenyl acetate: Obtained from phenol (0.94 g, 10 mmol) and Mn(III) acetate dihydrate (0.011 g, 0.04 mmol) as colourless liquid in 99% yield (1.36 g), bp 194-195°C. (Lit. bp. 195-196°C). IR (Nujol): γ 1750 cm⁻¹ (ester C=O); \(^1H\) NMR (CDCl₃): δ 2.12-2.13 (s, 3H, CH₃), 7.15-7.22 (m, 5H, Ar-H).

t-Butyl acetate: Obtained from t-butyl alcohol (1.3 g, 10 mmol) and Mn(III) acetate dihydrate (0.011 g, 0.04 mmol) as colourless liquid in 99% yield (1.16 g), bp 96-97°C. (Lit. bp. 98°C). IR (Nujol): γ 1745 cm⁻¹ (ester C=O); \(^1H\) NMR (CDCl₃): δ 1.46-1.47 (s, 9H, CH₃), 2.18-2.20 (s, 3H, CH₃).

n-Hexyl acetate: Obtained from n-hexyl alcohol (1.02 g, 10 mmol) and Mn(III) acetate dihydrate (0.011 g, 0.04 mmol) as colourless liquid in 99% yield (1.42 g), bp 166-168°C. (Lit. bp. 168-170°C). IR (Nujol): γ 1749 cm⁻¹ (ester C=O)
$^1$H NMR (CDCl$_3$): $\delta$ 1.02-1.03 (t, 3H, CH$_3$), 1.30-1.36 (m, 6H, CH$_2$), 1.54-1.56 (m, 2H, CH$_2$), 2.20-2.22 (s, 3H, CH$_3$), 3.96-4.02, (t, 2H, OCH$_2$).

Cyclohexyl acetate: Obtained from cyclohexyl alcohol (1.0 g, 10 mmol) and Mn(III) acetate dihydrate (0.011 g, 0.04 mmol) in yield 1.42 g. (99%). bp 170-170°C. (Lit. bp. 172-173°C). IR (Nujol): $\gamma$ 1748 cm$^{-1}$ (ester C=O); $^1$H NMR (CDCl$_3$): $\delta$ 1.20-1.40 (bm, 10H, CH$_2$), 2.20-2.22 (s, 3H, CH$_3$), 4.01-4.03 (m, 1H, CH).

Menthy1 acetate: Obtained from menthyl alcohol (1.56 g, 10 mmol) and Mn(III) acetate dihydrate (0.011 g, 0.04 mmol) in 99% yield (1.92 g), bp 228-232°C. (Lit. bp. 228-229°C). IR (Nujol): $\gamma$ 1750 cm$^{-1}$ (ester C=O); $^1$H NMR (CDCl$_3$): $\delta$ 1.07-1.10 (dd, 6H, CH$_3$), 1.13-1.15 (d, 3H, CH$_3$), 1.31-1.35 (m, 4H, CH$_2$), 1.52-1.54 (m, 2H, CH), 1.63-1.67 (m, 1H, CH), 1.84-1.88 (m, 1H, CH), 2.12-2.14 (s, 3H, COCH$_3$), 2.22-2.26 (m, 1H, CH), 4.01-4.03 (m, 1H, CH).
7.5 General Procedure for the Preparation of Acetoacetanilides

\[
\begin{align*}
97a-f & \quad + \quad \begin{array}{c}
\text{o-Xylene} \\
\text{Reflux}
\end{array} \\
\rightarrow \\
98a-f
\end{align*}
\]

a: \(R_1=\text{Cl}, R_2=R_3=\text{H}\)
b: \(R_1=\text{H}, R_2=\text{Cl}, R_3=\text{H}\)
c: \(R_1=R_2=\text{H}, R_3=\text{Cl}\)
d: \(R_1=R_2=\text{Cl}, R_3=\text{H}\)
e: \(R_1=\text{H}, R_2=R_3=\text{Cl}\)
f: \(R_1=\text{OCH}_3, R_2=R_3=\text{H}\)

In a typical reaction, solution of ethyl acetoacetate (3.6 g) in \(\text{o-xylene (10 mL)}\) containing catalytic quantity of triethanolamine (0.02 g) was heated to reflux. To this solution of 4-chloroaniline [97a, 3.0 g, 25.3 mmol] in \(\text{o-xylene (10 mL)}\) was added slowly with simultaneous distillation of \(\text{o-xylene (60-65\% by volume taken for reaction and dissolution)}\). Once the addition was completed the remaining \(\text{o-xylene}\) was distilled off. It was then maintained at 135-140\(^\circ\)C for 1hr and the progress of the reaction was monitored by TLC using toluene : ethyl acetate (9 :1) as eluant. The reaction mixture was cooled to 60-65\(^\circ\)C diluted with \(n\)-hexane (10 mL), cooled to 0-5\(^\circ\)C, filtered and washed with cold \(n\)-hexane (10 mL), dried in oven at 60-65\(^\circ\)C gave \(N\)-(4-chlorophenyl)acetoacetanilide [98a] in 80 \% yield (4.0 g), m.p. 130-134\(^\circ\)C.
The other acetoacetanilides are also prepared using similar procedure. The results are tabulated below.

**Table 4: Acetoacetanilides prepared using corresponding anilines.**

<table>
<thead>
<tr>
<th>Aniline</th>
<th>Acetoacetanilide</th>
<th>Yield (%)</th>
<th>m.p. (°C)</th>
<th>Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>97b</td>
<td>98b</td>
<td>80</td>
<td>102-104</td>
<td>Pale yellow coloured powder</td>
</tr>
<tr>
<td>97c</td>
<td>98c</td>
<td>81.5</td>
<td>104-106</td>
<td>White coloured powder</td>
</tr>
<tr>
<td>97d</td>
<td>98d</td>
<td>75</td>
<td>88-90</td>
<td>Pale yellow coloured powder</td>
</tr>
<tr>
<td>97e</td>
<td>98e</td>
<td>78</td>
<td>86-88</td>
<td>Light brown coloured powder</td>
</tr>
<tr>
<td>97f</td>
<td>98f</td>
<td>81</td>
<td>107-110</td>
<td>Pale yellow coloured powder</td>
</tr>
</tbody>
</table>


![Diagram of the reaction](image)

- a: \(R_1=\text{Cl}, R_2=R_3=\text{H}\)
- b: \(R_1=\text{H}, R_2=\text{Cl}, R_3=\text{H}\)
- c: \(R_1=R_2=\text{H}, R_3=\text{Cl}\)
- d: \(R_1=R_2=\text{Cl}, R_3=\text{H}\)
- e: \(R_1=\text{H}, R_2=R_3=\text{Cl}\)
- f: \(R_1=\text{OCH}_3, R_2=R_3=\text{H}\)
Typical procedure for the synthesis of 7-Chloro-9-methyl-3H-furo[3,2-b] quinolin-2-one (99a):

Mixture of \( N \)-4-chlorophenyl]acetoacetanilide (98a, 0.5 g, 2.36 mmol) and Mn(III) acetate dihydrate (1.27 g) in toluene (10 mL) containing small quantity of acetic acid were heated to 65-70°C until the disappearance of Mn(III) acetate colour occurs. It was then stirred for 3-4 hr at 65-70°C. The progress of the reaction was monitored by TLC using chloroform : acetone (7:1) as eluant. After the reaction, reaction mixture was cooled to room temperature, filtered over celite bed to remove unreacted Mn(III) acetate dihydrate and the filtrate was concentrated under vacuum. The resultant oily mass was then extracted into ether (20 mL), washed with water (2x20 mL), 5% sodium bicarbonate solution (2x20 mL) and finally with water (2x20 mL). The TLC of the organic layer showed a major spot with Rf value 0.54 and one minor spot with Rf value 0.72. The organic layer after drying over anhydrous sodium sulphate was concentrated under vacuum to get a thick oily mass. It was then subjected to column chromatography using chloroform as eluant. The major fraction was then evaporated under vacuum gave 99a as light brown coloured solid in 46% yield (0.25 g). m.p. 140-145°C; IR (Nujol) : \( \gamma 
1748 \text{ (C=O)}, 1600 \text{ (C=C) cm}^{-1}

\(^1\text{H NMR: (CDCl}_3): \delta 2.43 \text{ (s, 3H, CH}_3\text{), 3.80 (s, 2H CH}_2\text{), 7.46 (s, 1H, ArH), 7.89-7.91 (s, 1H, ArH), 7.94-7.96 (s, 1H, ArH); ^13\text{C NMR} \)
5-Chloro-9-methyl-3H-furo[3,2-b] quinolin-2-one (99b):

Obtained from N-(3-chlorophenyl)acetoacetanilide (98b) 0.5 g, 2.36 mmol) and Mn(III) acetate dihydrate (1.27 g) in 40% yield as white coloured powder (0.22 g), m.p. 118-120°C; IR (Nujol): \( \gamma \) 1744 cm\(^{-1}\)(C=O); \(^1\)H NMR: (CDCl\(_3\)): \( \delta \) 2.41 (s, 3H, CH\(_3\)), 3.79 (s, 2H, CH\(_2\)), \( \delta \) 7.49 (s, 1H, Ar-H), 7.88-8.00 (bs, 2H, ArH); \(^{13}\)C NMR (CDCl\(_3\)): \( \delta \) 12.3 (q, -CH\(_3\)), 38.1 (t, 3-CH\(_2\)), 124.3 (s, 8-\( \mathrm{C}\)), 126.0 (s, 7-\( \mathrm{C}\)), 127.6 (d, 5-\( \mathrm{C}\)), 131.8 (s, 9-\( \mathrm{C}\)), 132.5 (d, 6-\( \mathrm{C}\)), 145.7 (s, 4a-\( \mathrm{C}\)), 146.2 (s, 9a-\( \mathrm{C}\)), 156.3 (s, 3a-\( \mathrm{C}\)), 168.4 (s, 2-C=O); MS (relative intensity, %) m/z for C\(_{12}\)H\(_8\)ClNO\(_2\), 236 (04), 234 (M+1, 11), 205 (08), 189 (10), 188 (51), 179 (30), 177 (100), 78 (31); Anal. Calcd.: C, 61.69; H, 3.45; N, 5.99; Cl, 15.17; O, 13.7%; Found: C, 61.60; H, 3.38; N, 6.05; Cl, 15.20.

5-Chloro-9-methyl-3H-furo [3,2-b] quinolin-2-one (99c):

Obtained from N-(2-chlorophenyl)acetoacetanilide (98c) 0.5 g, 2.36 mmol) and Mn(III) acetate dihydrate (1.27 g) in 42% yield as light brown coloured powder (0.23 g), m.p. 114-115°C; IR (Nujol)
: \gamma 1750 \text{ cm}^{-1}(\text{C}=\text{O}); ^1\text{H NMR: } (\text{CDCl}_3): \delta 2.41 (s, 3\text{H}, \text{CH}_3), 3.78 (s, 2\text{H}, \text{CH}_2), 7.51 (bs, 1\text{H}, \text{ArH}), 7.88-8.00 (bs, 2\text{H}, \text{ArH}); ^{13}\text{C NMR (CDCl}_3): \delta 12.9 (q, -\text{CH}_3), 37.8 (t, 3-\text{CH}_2), 121.6 (s, 8-\text{C }), 125.7 (s, 7-\text{C}), 126.8 (s, 8a-\text{C}), 128.6 (d, 6-\text{C}), 131.6 (s, 9-\text{C}), 132.2 (d, 5-\text{C}), 142.8 (s, 4a-\text{C}), 148.5 (s, 9a-\text{C}), 155.2 (s, 3a-\text{C}), 168.1 (s, 2-\text{C}=\text{O}); MS (relative intensity, \%) m/z for C_{12}\text{H}_8\text{ClNO}_2, 236 (03), 234 (M+1, 09), 205 (09), 189 (12), 188 (48), 179 (31), 177 (100), 78 (29); Anal. Calcd. : C, 53.76; H, 2.63; N, 5.22; Cl, 26.45; O, 11.94%; Found: C, 53.71; H, 2.67; N, 5.25; Cl, 26.49.

6,7-Dichloro-9-methyl-3H-furo [3,2-b] quinolin-2-one (99d):

Obtained from N-(3,4-dichlorophenyl)acetoacetanilide (0.5 g, 2.03 mmol) and Mn(III) acetate dihydrate (1.09 g) in 48 \% yield as white coloured powder (0.26 g), m.p. 107-109°C; IR (Nujol) : \gamma 1748 \text{ cm}^{-1}(\text{C}=\text{O}); ^1\text{H NMR: } (\text{CDCl}_3): \delta 2.42-2.44 (s, 3\text{H}, \text{CH}_3), 3.78-3.80 (s, 2\text{H}, \text{CH}_2), 7.64-7.78 (m, 2\text{H}, \text{Ar-H}); ^{13}\text{C NMR (CDCl}_3): \delta 12.7 (q, -\text{CH}_3), 38.0 (t, 3-\text{CH}_2), 123.7 (s, 8a-\text{C}), 124.6 (s, 8-\text{C }), 128.3 (d, 5-\text{C}), 130.5 (s, 9-\text{C}), 131.5 (s, 7-\text{C}), 134.4 (d, 6-\text{C}), 144.4 (s, 4a-\text{C}), 147.6 (s, 9a-\text{C}), 156.5 (s, 3a-\text{C}), 168.3 (s, 2-\text{C}=\text{O}); MS (relative intensity, \%) m/z for C_{12}\text{H}_7\text{Cl}_2\text{NO}_2, 271 (01), 270 (03), 268 (M+1, 09), 239 (07), 223 (10), 222 (51), 215 (10), 213 (62), 211 (100), 78 (30); Anal. Calcd. for C_{12}\text{H}_7\text{Cl}_2\text{O}_2 C, 53.76; H, 2.63; N, 5.22; Cl, 26.45; O, 11.94%. Found: C, 53.69; H, 2.57; N, 5.27; Cl, 26.49.
5,6-Dichloro-9-methyl-3H-furo [3,2-b] quinolin-2-one (99e):

Obtained from 7-(2,3-dichlorophenyl)acetoacetanilide (98e, 0.5 g, 2.03 mmol) and Mn(III) acetate dihydrate (1.09 g) in 48% yield as white coloured powder (0.25 g), m.p. 110-112°C; IR (Nujol) : γ 1747 cm⁻¹(C=O); ¹H NMR: (CDCl₃): δ 2.42-2.44 (s 3H, CH₃), 3.73-3.77 (s, 2H CH₂), 7.66-8.0 (m, 2H ArH); ¹³C NMR (CDCl₃): δ 12.8 (q, -CH₃), 38.2 (t, 3-CH₂), 123.5 (s, 8-C), 124.9 (s, 8a-C), 125.8 (s, 7-C), 131.2 (d, 5-C), 131.5 (s, 9-C), 133.4 (d, 6-C), 143.5 (s, 4a-C), 149.7 (s, 9a-C), 157.6 (s, 3a-C), 168.4 (s, 2-C=O); MS (relative intensity, %) m/z for C₁₂H₇Cl₂NO₂, 271 (01), 270 (03), 268 (M+1, 08), 239 (08), 223 (11), 222 (52), 215 (9), 213 (60), 211 (100), 78 (31); Anal. Calcd. for C₁₂H₇Cl₂NO₂: C, 53.76; H, 2.63; N, 5.22; Cl, 26.45; O, 11.94%. Found: C, 53.65; H, 2.61; N, 5.24; Cl, 26.54.

7-Methoxy-9-methyl-3H-furo [3,2-b] quinolin-2-one (99f):

Obtained from N-(p-methoxyphenyl)acetoacetanilide (98f, 0.5 g, 2.41 mmol) and Mn(III) acetate dihydrate (1.29 g) in 47% yield as white coloured powder (0.26 g), m.p. 120-121°C; IR (Nujol) : γ 1751 cm⁻¹(C=O); ¹H NMR: (CDCl₃): δ 2.38-2.40 (s, 3H, CH₃), 3.78-3.82 (s, 2H CH₂), 3.82-3.84 (s, 3H, OCH₃) 7.47-7.48 (s, 1H, ArH), 7.80-8.0 (bs, 2H, ArH); ¹³C NMR (CDCl₃): δ 12.6 (q, -CH₃), 38.6 (t, 3-CH₂), 103.5 (s, 8-C), 122.5 (d, 6-C), 126.7 (s, 8a-C), 130.2 (d, 5-C), 130.6 (s, 9-C), 141.8 (s, 4a-C), 146.7 (s, 9a-C), 152.4 (s, 3a-C), 157.4 (s, 7-C), 168.0 (s, 2-C=O); MS (relative
intensity, %) m/z for C_{13}H_{11}NO_3: 230 (M+1, 11), 214 (65), 201 (09), 186 (10), 158 (21), 173 (100), 185 (09), 184 (49), 78 (31); Anal. Calcd. for C_{13}H_{11}NO_3: C, 68.11; H, 4.84; N, 6.11; O, 20.94%; Found: C, 68.18; H, 4.75; N, 6.10.