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Synthesis in the field of podophyllotoxin and related analogues: Part X—Synthesis of indan analogue of tridemethoxy-β-apopicropodophyllin and ethyl-1-oxo-4-(3′, 4′, 5′-trimethoxyphenyl)-6, 7-trimethylene-1, 2, 3, 4-tetrahydro-3-naphthoate as an intermediate for indan analogue of β-apopicropodophyllin

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The indan analogue **4** of DL-tridemethoxy-β-apopicropodophyllin **3** has been synthesized starting from indan. The synthesis of ethyl 1-oxo-4-(3′, 4′, 5′-trimethoxyphenyl)-6, 7-trimethylene-1, 2, 3, 4-tetrahydro-3-naphthoate as an intermediate for indan analogue **5** of β-apopicropodophyllin **2** has also been reported.

Podophyllotoxin **1**, its derivatives and analogues are antimitotic and anticancer agents[1,2]. Some of the derivatives of **1** have been used as an anticancer agent at clinical level[1]. In earlier parts of the series we have reported the synthesis of analogues of **1** and β-apopicropodophyllin **2** with a view to studying their structure-antimitotic activity relationship[3-6].

β-Apopicropodophyllin **2**, a dehydration product of **1** and its tridemethoxy analogue **3** showed strong antimitotic property[2]. The *o*-xylene analogue of **3** showed almost the same level of antimitotic activity when compared to **2** (ref. 7). We thought it is interesting to see the changes in structure-antimitotic activity relationship, by changing the dioxymethylene moiety in **3** into trimethylene moiety as in **4** and dioxymethylene moiety in **2** into trimethylene moiety as in **5** which might enhance the biological activity towards antimitotic activity and hence we decided to synthesize compounds **4** and **5** starting from indan (Chart I).

The benzophenone **8** was synthesized by Friedel-Crafts acylation of indan with benzoyl chloride **6** using anhydrous aluminium chloride as catalyst. The benzophenone **9** was synthesized in good yield by acylation of indan with 3, 4, 5-trimethoxybenzoic acid **7** using polyphosphoric acid. The products **8** and **9** showed IR absorption bands at 1645 and 1660 cm^{-1} respectively for carbonyl groups. Stobbe condensation of the benzophenones **8** and **9** using diethyl succinate and potassium tertiary butoxide resulted in a mixture of *cis-trans* isomeric (not shown in Chart I) itaconic acid half esters **10** and **11** respectively. Compound **10** on saponification gave *cis-trans* mixture of itaconic acid **12**.

The compound **12** on reduction with sodium amalgam as per the method of Shirvaiker *et al.*[8] yielded the benzhydryl succinic acid **13**. The itaconic acid half ester **10** on reduction by the above method gave a mixture of **13** and **15** which were separated by column chromatography. Compound **11** under same reduction condition also yielded a mixture of benzhydryl succinic acid esters **14** and **16** which were separated by column chromatography.

The tetralone carboxylic acid **18** was obtained by intramolecular Friedel-Crafts acylation of the anhydride **17** (obtained by dehydration of **13** using acetyl chloride) using anhydrous stannic chloride. ^{1}HNMR spectrum of **18** exhibited distinct singlets at δ 6.85 and 7.95 due to aromatic C_5-H and C_8-H respectively, and a doublet at δ 4.7 (J=6 Hz) due to dibenzylic proton C_4-H. The large J value of 6 Hz indicated that C_3-H and C_4-H in **18** were diaxial. Hence, C_3-carbonyl and C_4-phenyl groups should be *trans* to each other, a configuration being thermodynamically stable.

Intramolecular cyclisation of **16** using polyphosphoric acid resulted in tetralone carboxylic ester **20**. Since yield of the required tetralone ester **20** was low we could not proceed further for the target product **5**.

The tetralone ester **19** was prepared by esterification of **18** using dry ethanol and sulphuric acid.

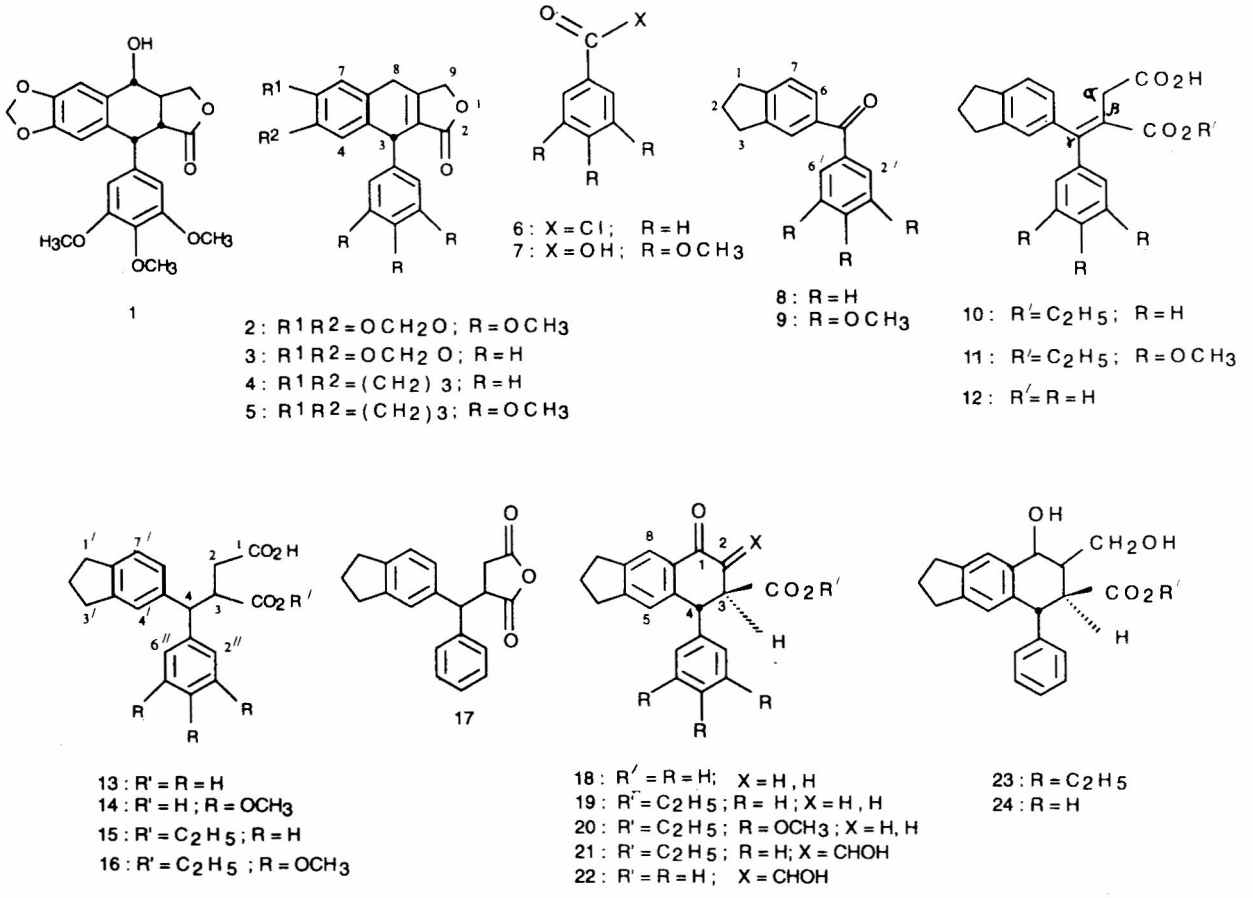

Chart I

Formylation of **19** with ethyl formate and sodium hydride gave hydroxymethylene tetralone ester **21** as the major product and hydroxymethylene tetralone acid **22** as minor product. The IR spectra of **21** showed absorption at 3450-3500 cm^{-1} due to hydroxyl, and absorptions at 1730 and 1685 cm^{-1} due to ester carbonyl and tetralone carbonyl respectively. An IR absorption at 1640 cm^{-1} was attributed to conjugated C=C group. The ^{1}HNMR spectrum of **21** showed two doublets at δ 3.6 and 4.7 (J=6 Hz) due to *trans* C_3-H and C_4-H respectively, a broad singlet at δ 6.0 due to vinylic OH proton and a broad singlet at δ 8.15 due to vinylic proton. In the mass spectra the molecular ion peak was observed at m/z 362 with percent abundance at 20.8. The IR and ^{1}HNMR spectrum of **22** was consistent with the structure assigned.

Reduction of **21** with sodium borohydride in methanol gave **23** whereas **22** on reduction under similar conditions gave **24**. The IR spectrum of **23** showed a broad absorption at 3200-3500 cm^{-1} due to hydroxyl group and at 1735 cm^{-1} due to ester carbonyl group. Saponification of **23** with 2% sodium hydroxide solution gave the corresponding acid **24** in excellent yield. The IR spectrum of **24** showed a broad peak at 3200-3500 cm^{-1} for hydroxyl group and a strong absorption at 1720 cm^{-1} for carboxylic carbonyl group. The compound **24** when treated with *p*-toluenesulphonyl chloride and pyridine in dry benzene at reflux temperature underwent dehydration with concomitant isomerization to the corresponding tridemethoxy-β-apopicropodophyllin analogue **4**. The IR spectrum of **4** showed the absorption at 1775 cm^{-1} due to the presence of unsaturated lactone carbonyl and a shoulder at 1710 cm^{-1} due to tetra substituted C=C[9]. The ^{1}HNMR spectrum of **4** showed a multiplet at δ 3.4-4.0 due to C_1-H and C_9-H, a singlet at δ 4.8

due to dibenzylic proton C_4-H. The mass spectrum of the above compound showed the $M^+ + 1$ peak at 303 with 100% abundance.

Experimental Section

Melting points reported are uncorrected. IR spectra in nujol or KBr were recorded on a Perkin-Elmer model 157 or 337 spectrophotometer, ^{1}HNMR spectra on a Hitachi R-600 spectrometer using TMS as internal standard with $CDCl_3$ as solvent unless and otherwise mentioned. The mass spectra were recorded on a Hitachi RMU-61 spectrometer.

5-Indanyl phenyl ketone (8). A mixture of aluminium chloride (28 g, 0.21 mole) and indan (25 g, 0.205 mole) in nitrobenzene (100 mL) were stirred for about 1 hr followed by the dropwise addition of benzoyl chloride (30 g, 0.214 mole) at ~ 5°C for 1 hr. The contents were then stirred at room temperature for 6 hr. The reddish brown reaction mixture was acidified with 5 *N* HCl and extracted with chloroform (200 mL). The organic layer was washed thoroughly with dil. HCl (3 × 25 mL), 10% NaOH (3 × 25 mL) and finally with water (3 × 25 mL). The organic extract was steam-distilled to remove chloroform and nitrobenzene and the dark brown coloured liquid left over after distillation gave a pale yellow oil in 86% yield (40.2 g), b.p. 310-15°C (Found: C, 86.3; H, 6.2. Calcd for $C_{16}H_{14}O$: C, 86.5; H, 6.3%); IR 1645 (C=O); ^{1}HNMR: δ 1.96-2.4 (m, 2H, C_2-H), 3.05 (t, J=7.5 Hz, 4H, C_1-H & C_3-H), 7.25 (d, J=6 Hz, 1H, C_7-H), 7.4-7.85 (m, 7H, Ar−H); mass (m/z, % abundance): 222 (M^+, 48.3).

5-Indanyl-3′, 4′, 5′-trimethoxyphenyl ketone (9). A mixture of indan (13.8 g, 0.117 mole), 3, 4, 5-trimethoxybenzoic acid **7** (27.6 g, 0.13 mole) and polyphosphoric acid [prepared by stirring vigorously phosphorous pentoxide (100 g) and *o*-phosphoric acid (d 1.75, 85 mL) at 180°C] was stirred thoroughly for 2 hr at 90-100°C, cooled and poured into ice (250 g). The resultant dark grey coloured precipitate was filtered, stirred with 10% NaOH (100 mL) for 1 hr and filtered again. It was washed repeatedly with water and finally recrystallised from ethanol to give white crystalline solid in 70% yield (25.5 g), m.p. 114-15°C (Found: C, 73.5; H, 6.2. Calcd for $C_{19}H_{20}O_4$: C, 73.1; H, 6.4%); IR: 1660 (C=O), 1595 cm^{-1} (aromatic C=C); ^{1}HNMR: δ 1.95-2.3 (m, 2H, C_2-H), 3.0 (t, J=7.5 Hz, 4H, C_1-H & C_3-H), 3.9 (s, 6H, 3′-OCH_3 and 5′-OCH_3), 3.92 (s, 3H, 4′-OCH_3), 7.1 (s, 2H, 2′-H & 6′-H), 7.3 (d, J=6 Hz, 1H, C_7-H), 7.5-7.7 (m, 2H, C_4-H & C_6-H); mass (m/z, % abundance): 312 (M^+, 100).

γ-(5-Indanyl)-γ-phenylitaconic acid (12). To a freshly prepared potassium *t*-butoxide [prepared from potassium (5 g, 0.13 g.atom) and *t*-butanol (150 mL), the benzophenone **8** (25 g, 0.113 mole) was added quickly under N_2 and refluxed for 1 hr. To this mixture a freshly distilled diethyl succinate (24 g, 0.138 mole) was added at once and refluxed for 24 hr. The excess *t*-butanol was removed by distillation under reduced pressure and the residue acidified with 5 *N* HCl. The precipitated itaconic acid half ester **10** was extracted with 10% $NaHCO_3$ solution and the extract washed with diethyl ether (50 mL). Acidification of the alkaline solution gave semi-solid itaconic acid half ester **10** which was saponified by refluxing in methanol-water (125 mL:100 mL) mixture containing NaOH (9 g) for 12 hr. The pale brown mixture was concentrated to 150 mL and acidified with conc. HCl (40 mL) in ice (400 g). The precipitated solid was recrystallised from benzene-ethanol (2:1) to give white crystalline solid **12** in 70% yield (25.4 g), m.p. 162-64°C; IR: 3100-3500 (OH), 1705 (CH_2−C=O), 1680 (α, β-unsaturated C=O), 1610 cm^{-1} (conjugated C=C); ^{1}HNMR: δ 1.85-2.3 (bm, 2H, C_2-H), 2.65-3.0 (bm, 4H, C_1-H′ & C_3-H), 3.5 (bs, 2H, C_α-H), 6.9-7.4 (bm, 8H, Ar−H), 9.3-9.5 (bs, 2H, COOH); Mass (m/z, % abundance): 322 (M^+, not found), 304 ($M^+ - H_2O$, 100).

γ-(5-Indanyl)-γ-(3′, 4′, 5′-trimethoxyphenyl)itaconic acid half ester 11. It was prepared according to the above procedure using **9** (9 g, 0.029 mole) and diethyl succinate (8 g, 0.046 mole) as pale brownish semi-solid in 83.5% (10.6 g) yield; IR: 1730 (ester C=O), 1705 (acid C=O), 1615 cm^{-1} (conjugated C=C); ^{1}HNMR: δ 1.0 (t, J=6 Hz, 3H, CH_3), 1.9-2.3 (m, 2H, C_2-H), 2.5-3.0 (m, 4H, C_1-H & C_3-H), 3.5 (bs, 2H, C_α-H), 3.7-4.1 [bm, 11H, O-CH_2 and $(OCH_3)_3$], 6.5 (bs, 2H, 2′-H & 6′-H), 7.1-7.3 (bs, 3H, C_4-H, C_6-H & C_7-H), 8.1 (bs, 1H, COOH).

3-Carboxy-4- (5′-indanyl) -4-phenylbutanoic-acid 13. Powdered 10% sodium amalgam (150 g) was added to a cooled solution (5°C) of **12** (15.5 g, 0.048 mole) in 2% aq. NaOH (100 mL). The reaction mixture was kept overnight at room temperature and filtered. The filtrate was acidified with 5 *N* HCl and the solid obtained was recrystallised from benzene-ethanol (2:1) to furnish **13** in 90% yield (14 g), m.p. 222-23°C (Found: C, 73.6; H, 6.3. Calcd for $C_{20}H_{20}O_4$: C, 74.1; H, 6.2%); IR: 3400-3500 (OH), 1725 cm^{-1} (C=O); ^{1}HNMR (DMSO-d_6): δ 1.85-2.3 (bm, 2H, C_2-H), 2.35-2.45 (bs, 2H, C_2-H), 2.6-2.95 (bm, 4H, C_1-H & C_3-H), 3.2-3.65 (m, 1H, C_3-H), 4.0 (d,

J=10 Hz, 1H, C_4-H), 6.9-7.3 (m, 8H, Ar−H), 8.6 (bs, 2H, COOH); Mass (m/z, % abundance): 324 (M^+, 2.9).

General procedure for the synthesis of the benzhydryl succinic acid esters 14 and 16

3-Carboethyl-4-(5′-indanyl)-4-(3″, 4″, 5″-trimethoxyphenyl)butanoic acid 16. A typical procedure. Powdered 10% sodium amalgam (110 g) was added to a cooled solution of **11** (5.7 g, 0.013 mole) in 2% aq. NaOH (100 mL) solution. The reaction mixture was stirred and kept overnight at room temperature and then filtered. The filtrate was acidified with dil. HCl. The solid thus separated was filtered and dried. The product on column chromatographic separation over silica gel (60×3 cm column) using chloroform-acetone (7:1) as eluant gave two compounds, **16** as the first fraction and **14** as second fraction. **16** on recrystallisation from benzene gave white crystalline solid in 54% yield (3.1 g), m.p. 146-48°C (Found: C, 67.5; H, 6.5. Calcd for $C_{25}H_{30}O_7$: C, 67.9; H, 6.8%); IR: 3200-3300 (OH), 1750 (ester C=O), 1720 cm^{-1} (acid C=O); ^{1}HNMR: δ 0.95 (t, J=6 Hz, 3H, ester CH_3), 1.8-2.3 (bm, 2H, $C_{2'}$-H), 2.4-3.1 (bm, 7H, $C_{1'}$-H, $C_{3'}$-H, C_2-H & C_3-H), 3.5-4.1 [bm, 12H, C_4-H, O-CH_2 and $(OCH_3)_3$], 6.8 (s, 2H, $C_{2''}$-H, $C_{6''}$-H), 7.1 (bs, 3H, $C_{4'}$-H, $C_{6'}$-H & $C_{7'}$-H), 9.3 (bs, 1H, COOH); mass (m/z, % abundance): 442 (M^+, 1.2).

Compound **14** on recrystallisation with benzene-ethanol (2:1) gave white crystalline solid in 25% yield (1.4 g), m.p. 190-91°C (Found: C, 66.8 H, 6.2%. Calcd for $C_{23}H_{26}O_7$: C, 66.7; H, 6.3%); IR: 3200-3500 (OH), 1720 cm^{-1} (C=O); ^{1}HNMR (DMSO-d_6): δ 1.8-2.0 (bm, 2H, $C_{2'}$-H), 2.2-2.8 [bm, 7H, ($C_{1'}$-H, $C_{3'}$-H, C_2-H, C_3-H), 3.8 [bs, 10H, C_4-H & $(OCH_3)_3$], 6.5 (s, 2H, $C_{2''}$-H & $C_{6''}$-H), 7.0 (bs, 3H, $C_{4'}$-H, $C_{6'}$-H & $C_{7'}$-H), 8.4 (bs, 2H, COOH); mass (m/z, % abundance): 414 (M^+, 4.9).

1-Oxo-4-phenyl-6, 7-trimethylene-1, 2, 3, 4-tetrahydro-3-naphthoic acid 18. A mixture of **17** (3.7 g, 0.012 mole) [prepared from **13** (6.8 g, 0.021 mole) and acetyl chloride (20 mL)] and stannic chloride (11.5 g, 0.044 mole) in nitrobenzene (40 mL) was stirred initially for 2 hr at ~ 0°C and then for 10 hr at room temperature. 5 *N* HCl (100 mL) was then added, the organic phase extracted into diethyl ether (100 mL) and the ether layer washed with 5 *N* HCl (2×30 mL) and repeatedly extracted with 5% sodium bicarbonate. The bicarbonate extract was acidified and the resulting yellow solid filtered and recrystallised from ethanol to give **18** as white crystalline solid, yield 65% (2.4 g), m.p. 194-95°C (Found: C, 78.3; H, 5.5%. Calcd for $C_{20}H_{18}O_3$: C, 78.4; H, 5.9%); IR: 3200-3600 (OH), 1710 (carboxy C=O), 1680 cm^{-1} (tetralone C=O); ^{1}HNMR: δ 1.9-2.3 (bm, 2H, CH_2), 2.5-3.1 [bm, 6H, $(Ar-CH_2)_2$, C_2-H], 3.2-3.5 (m, 1H, C_3-H), 4.7 (d, J=6 Hz, 1H, C_4-H), 6.85 (s, 1H, C_5-H), 7.0-7.5 (bm, 5H, Ar−H), 7.95 (s, 1H, C_8-H), 9.2 (s, 1H, COOH); mass (m/z, % abundance): 306 (M^+, 10.5).

Ethyl 1-oxo-4-phenyl-6, 7-trimethylene-1, 2, 3, 4-tetrahydro-3-naphthoate 19. A solution of keto acid **18** (2 g, 6.5 mmole) in absolute ethanol (50 mL) containing conc. H_2SO_4 (0.6 mL) was refluxed under anhydrous condition for 6 hr. Excess ethanol was removed under reduced pressure and the concentrate poured into ice (100 g). The precipitated solid on recrystallisation from ethanol gave white needles, yield 83% (1.8 g), m.p. 105-6°C, IR: 1735 (ester C=O), 1690 cm^{-1} (tetralone C=O); ^{1}HNMR: δ 1.0 (t, J=6 Hz, 3H, CH_3), 1.9-2.4 (bm, 2H, CH_2), 2.7-3.1 [m, 6H, $(Ar-CH_2)_2$, C_2-H], 3.25-3.55 (m, 1H, C_3-H), 4.0 (q, J=6 Hz, 2H, ester CH_2), 4.6 (d, J=6 Hz, 1H, C_4-H), 6.8 (s, 1H, C_5-H), 7.05-7.4 (bm, 5H, Ar−H), 7.95 (s, 1H, C_8-H).

Ethyl 1-oxo-4-(3′, 4′, 5′-trimethoxyphenyl)-6, 7-trimethylene-1, 2, 3, 4-tetrahydro-3-naphthoate 20. Compound **16** (1.8 g, 0.004 mole) was added to polyphosphoric acid at 90-100°C and the mixture stirred for 2 hr. The pale cream coloured reaction mixture was poured onto crushed ice (200 g) and the precipitated solid filtered and washed with water. It was dissolved in diethyl ether (60 mL) and washed with saturated sodium bicarbonate solution (3×30 mL). After drying and evaporating the ether layer, the pasty residue was recrystallised from ethanol to give white crystalline needles in 46% yield (0.8 g), m.p. 151-52°C. IR: 1720 (ester C=O), 1670 cm^{-1} (tetralone C=O); ^{1}HNMR: δ 1.05 (t, J=6 Hz, 3H, CH_3), 1.9-2.3 (bm, 2H, CH_2), 2.7-3.0 [bm, 6H, $(Ar-CH_2)_2$, C_2-H], 3.2-3.6 (bm, 1H, C_3-H), 3.7-4.2 ([bm, 11H, O=C-O-CH_2 and $(OCH_3)_3$], 4.5 (d, J=8 Hz, 1H, C_4-H), 6.3 (s, 2H, $C_{2'}$-H & $C_{6'}$-H), 6.85 (s, 1H, C_5-H), 7.9 (s, 1H, C_8-H).

3 - Carboxyethyl-2-hydroxymethylene-1-oxo-4-phenyl-6, 7-trimethylene-1, 2, 3, 4-tetrahydronaphthalene (21) and 3-carboxy-2-hydroxymethylene-1-oxo-4-phenyl-6, 7-trimethylene-1, 2, 3, 4-tetrahydronaphthalene (22). Sodium hydride (1. 2 g, 0.05 mole) was added to a solution of dry ethanol (10 mL) and dry benzene (150 mL)

and the mixture stirred well in the presence of dry N_2. Ethyl formate (10 mL) was added dropwise to it and the mixture stirred for 1 hr. A solution of **19** (6 g, 0.0185 mole) in dry benzene (100 mL) was then added dropwise to the stirred mixture over a period of 1 hr. After stirring the rusty red mixture at room temperature for 12 hr, it was poured into 2 *N* H_2SO_4 (100 mL) in ice (100 g). The organic layer was separated and washed with water and extracted first with saturated sodium bicarbonate solution (3 × 30 mL) and then with 1% sodium hydroxide solution (3 × 30 mL). The bicarbonate extract was acidified with 2 *N* H_2SO_4 and the precipitated yellow solid recrystallised from benzene-ethanol (2:1) to give **22** as crystalline solid, yield 13% (0.8 g), m.p. 200-5°C; IR(KBr): 3200-3400 (OH), 1740 (carboxyl C=O), 1700 (tetralone C=O), 1625 (conjugated C=C), 1600 cm^{-1} (aromatic C=C); ^{1}HNMR: δ 1.9-2.3 (bm, 2H, CH_2), 2.7-3.1 [bm, 4H, $(Ar-CH_2)_2$], 3.6 (bs, 1H, C_3-H), 4.7 (d, *J*=6 Hz, 1H, C_4-H), 5.1 (bs, 1H, vinylic OH), 6.9-7.4 (bm, 6H, Ar−H & C_5-H), 7.9 (s, 1H, C_8-H), 8.2 (s, 1H, vinylic), 9.3 (bs, 1H, COOH); Mass (m/z, % abundance): 334 (M^+, 30.8).

The sodium hydroxide extract on acidification with 2 *N* H_2SO_4 furnished a dark pink coloured precipitate which was chromatographed over silica gel column (40 × 1 cm) using chloroform as eluant. The TLC monitored eluates were combined and on evaporation under reduced pressure, the product **21** was obtained as a pale yellow solid, yield 61% (4 g), m.p. 132-34°C; IR: 3450-3500 (OH), 1730 (ester C=O), 1685 (tetralone C=O), 1640 cm^{-1} (conjugated C=C); ^{1}HNMR: δ 1.1 (t, *J*=8 Hz, 3H, ester CH_3), 2.05 (t, 2H, CH_2), 2.7-3.1 [m, 4H, $(Ar-CH_2)_2$], 3.6 (d, *J*=6 Hz, 1H, C_3-H), 4.1 (q, 2H, O-CH_2), 4.7 (d, *J*=6 Hz, 1H, C_4-H), 6.0 (bs, 1H, vinylic OH), 7.0-7.3 (bm, 6H, Ar−H and C_5-H), 7.9 (s, 1H, C_8-H), 8.15 (s, 1H, vinylic); Mass (m/z, % abundance): 362 (M^+, 20.8).

3 - Carboxyethyl-1-hydroxy-2-methylenehydroxy-4-phenyl-1, 6, 7-trimethylene-1, 2, 3, 4-tetrahydronaphthalene (23). To a solution of **21** (2.2 g, 6.0 mmole) in abs. methanol (50 mL), sodium borohydride (3 g, 0.079 mole) in abs. methanol (30 mL) was added during 1 hr at room temperature. At every hourly interval a solution of sodium borohydride (0.6 g, 0.016 mole) in methanol (10 mL) was added three times. The reaction mixture after stirring at room temperature for 10 hr was concentrated to 10 mL and acidified with 2 *N* HCl and the *p*H of the solution adjusted to 8 by adding 1% ammonium hydroxide solution. The precipitated solid was extracted with diethyl ether (2 × 25 mL). To the dried ether extract pet. ether (40-60°C) was added until the precipitation was complete to give the white solid in 67% yield (1.5 g), m.p. 139-42°C (Found: C, 74.8; H, 7.2. Calcd for $C_{23}H_{26}O_4$: C, 75.4; H, 7.1%); IR: 3200-3500 (OH), 1735 (ester C=O), 1590 cm^{-1} (aromatic C=C); Mass (m/z, % abundance): 366 (M^+ ion not found), 348 ($M^+ - H_2O$, 15.4).

3 - Carboxy-1-hydroxy-2-methylenehydroxy-4-phenyl-6, 7-trimethylene-1, 2, 3, 4-tetrahydronaphthalene (24). A solution of **23** (0.47 g, 1.4 mmole) in methanol (20 mL) and 2% aq. sodium hydroxide (20 mL) was refluxed for 2 hr. After removing methanol under reduced pressure, the alkaline solution was acidified with 2 *N* HCl, the precipitated solid extracted into diethyl ether (50 mL) and washed with water (2 × 20 mL) and then extracted with saturated sodium bicarbonate solution (2 × 20 mL). The bicarbonate extract on acidification gave a pale yellow precipitate which on recrystallisation from methanol gave white feathery crystalline solid in 85% yield (0.4 g), m.p. 161-65°C (Found: C, 74.8; H, 6.3. Calcd for $C_{21}H_{22}O_4$: C, 74.6; H, 6.5%); IR: 3200-3500 (OH), 1720 (acid C=O), 1600 cm^{-1} (aromatic C=C).

DL-Tridemethoxy-β-apopicropodophyllin analogue (4). A mixture of **24** (0.2 g, 0.6 mmole), *p*-toluenesulphonyl chloride (0.8 g, 4.0 mmole) and pyridine (5 mL) in dry benzene (25 mL) were refluxed for 2 hr. The reaction mixture was cooled to room temperature and washed with 2 *N* HCl (2 × 20 mL) and then with water (2 × 20 mL). The organic layer was dried and evacuated at 50°C on a rotary evaporator to a thick residue. The crude product was chromatographed over silica gel column (15 × 1 cm) using chloroform as eluant. The TLC monitored eluants were combined and on evaporation under reduced pressure gave **4** as a white powder, yield 78% (0.18 g), m.p. 159-60°C; IR: 1775 (lactone C=O), 1710 (shoulder, tetrasubstituted C=C), 1600 cm^{-1} (aromatic C=C): ^{1}HNMR: δ 1.9-2.3 (bm, 2H, CH_2), 2.8-3.1 (t, 4H, benzylic), 3.4-4.0 (bm, 4H, C_8-H & C_9-H), 4.8 (s, 1H, C_3-H), 6.5 (s, 1H, C_4-H), 7.2 (s, 1H, C_7-H), 7.3-7.6 (bs, 5H, Ar−H); Mass (m/z, % abundance), 303 ($M^+ + 1$, 100).

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