Synthesis in the field of podophyllotoxin and related analogues: Part XII —
Synthesis of benzodioxan analogue of didemethoxy-β-apopicropodophyllin

S Shashikanth* & Ganesh L Hegde
Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore 570 006, India
Received 2 June 2003; accepted (revised) 27 November 2004

The benzodioxan analogue of didemethoxy-β-apopicropodophyllin 15 has been synthesized starting from 6. On Stobbe condensation of 2,3-dihydro-benzo[1,4]dioxin-6-yl-(4-methoxyphenyl)methanone 6 with diethyl succinate gives 7 which on reduction with sodium amalgam yields 8. Cyclisation of 8 with PPA furnishes tetralone ester 10. Formylation of 10 with ethyl formate and sodium hydride affords 11, which on sodium borohydride reduction followed by alkaline hydrolysis and finally on treatment with p-toluensulphonyl chloride gives 15.

IPC: Int.C7 D 07 D 315/00

Podophyllotoxin 1 and several of its analogues are used as cytotoxic spindle poisons and as antitumor agents, some at clinical level.1 Recently it was discovered that some modified derivatives of podophyllotoxin possess anti-AIDS property.2 Earlier we have reported the synthesis of analogues β-apopicropodophyllin with a view to studying their structure-antimitotic activity relationship.3 Owing to their interest as antineoplastic agents1 and other pharmacological activities,4 considerable works have been done on lignans and other derivatives. An interesting observation from Schrier and his co-workers5 is that tridemethoxy-β-apopicropodophyllin 2, a synthetic product acts as a strong antimitotic agent.

We have synthesized a series of tridemethoxy-β-apopicropodophyllin to study their structural activity relationship and biological activities.6-8 Herein, we report the synthesis of 15, by modifying the structure of 3 with methylenedioxy group into benzodioxan group and 3,4,5-trimethoxy group into 4-methoxy group (Schemes I and II).

Several synthetic routes9 other than Gensler’s10 have been reported for the synthesis of podophyllotoxin 1 via tetralone ester. In the present paper, a similar approach was adopted to construct lignan skeleton using easily available reagents.

According to the Schemes I and II, the starting compound 2,3-dihydrobenzo[1,4]dioxin-6-yl-(4-methoxyphenyl)methanone 6 can be successfully converted into didemethoxy-β-apopicropodophyllin analogue 15 via Stobbe condensation followed by series of reactions like reduction with 10% sodium amalgam, cyclisation with polyphosphoric acid, formylation, reduction with sodium borohydride, hydrolysis with aqueous 2% sodium hydroxide and methanol and dehydration with p-toluene sulfonyl chloride in pyridine.

The first synthetic step, the acylation of 1,4-benzodioxan 4 with 4-methoxybenzoic acid 5 using
polyphosphoric acid yielding 2,3-dihydro-benzo(1,4)-dioxin-6-yl-(4-methoxyphenyl)methanone. In this case, it was found that the acylation had taken place at position 6, which was proved by spectral data of this compound. The IR spectrum of 6 showed absorption at 1630 cm\(^{-1}\) due to carbonyl stretching. \(^1\)H NMR spectrum showed a singlet at \(\delta\) 3.9 ppm assigned to OCH\(_3\) protons, a singlet at \(\delta\) 4.32 ppm assigned to dioxyethylene protons and a multiplet at \(\delta\) 6.8-7.5 ppm assigned to aromatic protons. In the mass spectrum of this compound, the molecular ion peak was found at \(m/z\) 270 and the base peak at \(m/z\) 163. The base peak might have formed by the cleavage of the methoxy phenyl radical from the molecular ion.

Stobbe condensation has been frequently used to construct the basic lignan skeleton. Here we have adopted Genstl's approach to construct the required lignan skeleton. Stobbe condensation of methanone
Scheme II

6 furnished stobbe half ester product 7 as a mixture of cis and trans isomers in good yield (Table I). IR spectrum showed absorption at 3200-3500, 1730, 1710 and 1620 cm\(^{-1}\) which were assigned to carboxylic OH group, \(\alpha,\beta\)-unsaturated carbonyl group, acid carboxyl group and conjugated C=C respectively. \(^1\)H NMR spectrum showed a triplet centered at \(\delta 1.1\) ppm with coupling constant \(J=6\) Hz assigned to methyl protons of ester group, a broad singlet centered at \(\delta 3.6\) ppm due to methylene protons \(\alpha\) to carbonyl group and a quartet centered at \(\delta 4.2\) ppm assigned to methylene protons of ester. A broad singlet centered at \(\delta 8.5\) ppm was due to the carboxylic proton.

Since in our synthesis only benzhydryl succinic acid half ester was required, we have followed the procedure described by Shirvaiker et al.\(^{14}\) to reduce
The mixture of cis and trans isomers 7 to benzhydryl succinic acid half ester 8 and benzhydryl succinic acid 9 using 10% sodium amalgam in 2% aqueous sodium hydroxide as the reducing agent. The two products were separated by column chromatography over silica gel using chloroform-acetone (7:1) as the eluent. The formation of a small fraction of benzhydryl succinic acid 9 may be due to the alkaline hydrolysis of the benzhydryl succinic acid half ester 7 during the reaction. The IR spectrum of acid ester 8 showed absorption at 1750 cm\(^{-1}\) due to carbonyl of acid and at 1710 cm\(^{-1}\) due to carbonyl of ester and at 1710 cm\(^{-1}\) due to carbonyl and conjugated double bond, respectively. Compound 12 showed broad peak at 3400-3500 cm\(^{-1}\) assigned to vinylic hydroxyl, ester carbonyl, tetralone carbonyl and conjugated double bond, respectively. The \(^1\)H NMR spectrum of 10 showed triplet centered at 5.1 ppm with \(J=6\) Hz assigned to ester CH\(_3\) protons, a doublet centered at 5.2 ppm with \(J=6\) Hz assigned to C\(_2\)-H, a multiplet at 5.3 ppm assigned to C\(_3\)-H and triplet centered at 5.9 ppm assigned to ethylene dioxy protons, a singlet at 5.7 ppm assigned to three protons of methoxy group and a quartet centered at 4.2 ppm assigned to methylene protons of ester. The \(^1\)H NMR spectrum showed absorption at 4.6 ppm with \(J=6\) Hz was assigned to the C\(_2\)-H. The large coupling constant indicated that C\(_3\) proton and C\(_4\) proton in 10 were diastereotopic to each other. Hence C\(_3\) ethyl carbonyl and C\(_4\) methoxy phenyl group should lie trans to each other, a configuration being thermodynamically more stable. A singlet at upfield 5.65 ppm was assigned to C\(_4\)-H due to shielding effect of the pendant aromatic ring and a singlet downfield at 7.7 ppm was assigned to C\(_3\)-H due to deshielding effect of the neighbouring carbonyl group. The mass spectrum showed the molecular ion peak at m/z 382.

In our synthetic Scheme II, the formylation of 10 was carried out with ethyl formate and sodium hydride in ethanol as a base, which produced hydroxymethylated ester 11 as major and hydroxymethylated acid 12 as minor reaction products. The compound 11, which was isolated from aqueous sodium hydride, as major and while the compound 12 obtained from sodium bicarbonate solution as minor reaction products. IR, \(^1\)H NMR and mass spectra confirmed the presence of vinylic hydroxyl group and conjugated double bond. The IR spectrum of 11 showed absorption at 3300-3600, 1720, 1680, 1620 cm\(^{-1}\) assigned to vinylic hydroxyl, ester carbonyl, tetralone carbonyl and conjugated double bond, respectively. The \(^1\)H NMR spectrum of 11 showed two doublets, one centered at 5.65 ppm with coupling constant \(J=6\) Hz and the other centered at 5.65 ppm with \(J=6\) Hz, which are assigned to trans C\(_3\)-H and C\(_4\)-H, respectively. A broad singlet at 4.6 ppm was due to vinylic hydroxyl proton and a singlet at 8.2 ppm due to vinylic proton. The IR spectrum of the compound 12 showed broad peak at 3400-3500 cm\(^{-1}\) and a sharp peak at 1640 cm\(^{-1}\) assigned to vinylic hydroxyl as well as carboxylic hydroxyl groups and conjugated double bond, respectively. Compound 12 showed almost similar \(^1\)H NMR absorption in which the signal due to ethyl group was absent and a broad singlet at 9.5 ppm assigned to carboxylic acid proton was present.
The hydroxymethylated ester 11 was converted to dihydroxy ester 13 in one step without affecting ester group. It has been assumed that 1,3 attack on the keto enol system is involved in sodium borohydride reduction of 11 to 13 and the substituents at position C1 and C2 might be assumed to be cis to each other. The absorption spectrum of this compound was consistent with assigned structure. The IR spectrum showed absorbance at 3200-3500 cm⁻¹ assigned to hydroxyl group and the sharp absorption at 1720 cm⁻¹ assigned to the ester carbonyl group. The compound 13 did not show the molecular ion peak but peak of M⁺-H2O was present at m/z 396.

Saponification of dihydroxy ester 13 with 2% NaOH in methanol at reflux temperature gave the corresponding acid 14 in excellent yield. During alkaline hydrolysis, inversion of carbonyl group did not occur which was confirmed by spectral data. The IR spectrum showed absorption at 3200-3500 cm⁻¹ assigned to carboxylic and hydroxyl group of primary and secondary hydroxyl group. The compound did not show the molecular ion peak but an ion peak at m/z 368 due to M⁺-H₂O was found.

Compound 14 when treated with p-toluenesulfonyl chloride and pyridine in dry benzene at reflux temperature underwent dehydration to the corresponding didemethoxy-β-apopicropodophyllin analogue 15 in almost quantitative yield. The IR spectrum of 15 did not show the absorption due to OH group but a strong absorption at 1770 cm⁻¹ due to the presence of α,β-unsaturated lactone carbonyl group and shoulder at 1700 cm⁻¹ due to the tetra substituted C=C were observed. The ¹H NMR spectrum of 15 showed broad multiplet at δ 3.4-4.0 ppm due to C₂-H, C₃-H and O(CH₂)₂O protons and singlet at δ 4.8 ppm due to dibenzylcy C₇-H. The mass spectrum did not show the molecular ion peak but M⁺+1 peak at m/z 351 was observed.

**Experimental Section**

Melting points were determined in open glass capillaries on the Buchi oil-bath melting point apparatus and are uncorrected. Infrared absorption spectra were recorded on a FT-IR Shimadzu 8300 spectrometer; ¹H NMR spectra on a Hitachi R-600 (60MHz) NMR spectrophotometer using CDCl₃ as solvent with TMS as an internal standard; and mass spectra on a Varian Mat CH-7 mass spectrophotometer. The purity of the compounds was checked by TLC using BDH silica gel G-60 on glass slides.

**General procedure for the preparation of 2,3-dihydrobenzo[1,4]dioxin-6-yl-[4′-methoxy phenyl]-methanone 6:** Preparation of polyphosphoric acid (PPA). Orthophosphoric acid (85 mL) was taken in a conical flask and heated for half an hour to remove traces of water present in it. Phosphorous pentoxide (100g) was directly weighed into a 250 mL three-necked flask and then the flask was equipped with a mechanical stirrer, mercury seal tube and guard tube. The hot orthophosphoric acid (75 mL) was added to phosphorous pentoxide and the mixture was vigorously stirred by maintaining the temperature between 170-200°C. The whole mixture became a clear viscous liquid. Any solid lump left over was removed and the liquid was stirred for 1 hr more and cooled to 90-100°C. Benzodioxan 4 (15.0g, 0.1 mole) was added to the above freshly prepared PPA at 80°C in drops and stirred for 15 min followed by the addition of 5 (15.35g, 0.101 mole) at a stretch and stretched vigorously for 3 hr maintaining the temperature of the oil-bath at 90-100°C. The cooled reaction mixture was poured into ice (250g) and the dark grey coloured precipitate was filtered and digested with 10% aqueous sodium hydroxide solution (125 mL) for 30 min using mechanical stirrer. The filtered residue was washed repeatedly with water to free off alkali and finally recrystallised by ethanol to give 6. IR (nujol): 1630 (C=O), 1590 cm⁻¹ (aromatic C=C); ¹H NMR (CDCl₃): δ 3.9 (s, 3H, 4′-OCH₃), 4.32 [s, 4H, O(CH₂)₅O], 6.8-7.5 (bm, 7H, Ar-H); MS (EI): m/z 270 (M⁺, 61.8%), 163 (M⁺-107, 100%), 135 (M⁺-135, 7.0%), 134 (M⁺-136, 11.0%), 107 (M⁺-163, 20.5%).

**General procedure for the preparation of 2-[2,3-dihydro-benzo[1′,4′]dioxin-6-yl]-[4′-methoxyphenyl]-methylenesuccinic acid half ester 7:** To a freshly prepared potassium-t-butoxide [from potassium (5g, 0.13 g atom) and t-butanol (150 mL)], 6 (20.0g, 0.074 mole) was added quickly under nitrogen and refluxed for 1 hr. To this mixture freshly distilled diethyl succinate (15.7g, 0.090 mole) was added at once and refluxed for 25 hr. Then the excess t-butanol was removed by distillation under reduced pressure and the residue was acidified with 5N HCl. The precipitated itaconic acid half ester 7 was extracted into 10% sodium bicarbonate solution and the bicarbonate extract was washed with diethyl ether (3 × 20 mL). Acidification of the alkaline solution gave 7 as a brown semi solid. IR (nujol): 3200-3500 (OH), 1730 (α,β-unsaturated C=O), 1710 (CH=CH=O), 1620 (conjugated C=O), 1580 cm⁻¹ (aromatic C=C); ¹H NMR
4.4 (d, J=6Hz, 1H, CH₃), 3.6 (bs, 2H, CH₂-C=O), 3.76-3.80 (t, J=6Hz, 4H, O(CH₂)₂O), 3.9 (s, 3H, OCH₃), 4.0-4.2 (q, J=6Hz, 2H, O-CH₂), 6.5 (bs, 4H, Ar-H), 6.7 (bs, 3H, Ar-H), 8.5 (bs, 1H, COOH).

General procedure for the preparation of 3-ethyl carboxy-4'-(4',3'-benzodioxan)4-(4-methoxyphenyl)butanoic acid 8. Powdered 10% sodium amalgam (110g) was added in portions to a cooled (5°C) solution of a mixture of cis and trans isomers 7 (110g, 0.025 mole) in 2% aqueous sodium hydroxide solution (30 mL) and kept overnight at room temperature and then filtered. The filtrate was acidified with dil HCl, the solid separated was filtered and then on column chromatographic separation over silica gel (200 x 3 cm) using chloroform-acetone (7:1 as eluent) gave two compounds, acid half ester 8 as the first fraction and diacid 9 as the second fraction. Compound 8 on recrystallisation from benzene gave white crystalline solid.

The compound 9 on recrystallisation from ethanol gave white crystalline needles of 8. IR (nujol): 3200-3600 (OH), 1710 (ester C =O), 3200-3600 (OH), 1750 cm⁻¹ (OH), 1740 cm⁻¹ (ester C =O), 1600 cm⁻¹ (conjugated C=C), 'H NMR (DMSO-d₆): δ 1.0 (t, J=6Hz, 3H, ester CH₃), 2.6 (bs, 2H, CH₂), 3.3-4.2 (brm, 11H, C₅-H, C₄-H, OCH₂, OCH₃, O(CH₂)₂O), 6.6 (s, 4H, 2"",3"",5"",6""-H), 6.8 (s, 3H, 2, 5, 6-H), 8.0-8.4 (bs, 2H, CO₂H); MS (EI): m/z 400 (M⁺, 3.0%), 372 (M⁻-C₃H₄, 4.0%), 354 (M⁺-C₅H₇OH, 16.4%), 256 (M⁺-144, 20.8%), 255 (M⁻-145, 100%).

9: IR (nujol): 3200-3600 (OH), 1710 cm⁻¹ (acid C=O); 'H NMR (DMSO-d₆): δ 2.4-2.8 (brm, 3H, C₃-H and C₄-H), 3.8 (s, 3H, OCH₃), 4.20 (s, 4H, O(CH₂)₂O) 4.4 (d, J=8Hz, 1H, C₆-H), 6.8 (bs, 4H, 2"",3"",5"",6""-H), 7.0 (m, 3H, 2",5",6"",6""-H), 8.6 (bs, 2H, COOH).

General procedure for the preparation of 3-ethylcarboxy-4-(4'-methoxyphenyl)-6,7-ethyleneedioxy-1-tetralone 10. Compound 8 (6g, 0.015 mole) was added to a freshly prepared PPA [from P₂O₅ (60g) and orthophosphoric acid (70 mL) at 180°C] at 90-100°C and stirred vigorously for 2 hr. The pale cream-coloured reaction mixture was poured into crushed ice (250g), the solid was filtered and washed with water, dried, dissolved in diethyl ether (60 mL) and washed with saturated sodium bicarbonate solution (3 x 30 mL), water (3 x 30 mL) and dried over anhydrous sodium sulphate. The pasty residue obtained after evaporation of the solvent was recrystallised from ethanol to give white crystalline needles of 10. IR (nujol): 1720 (ester C=O), 1670 (tetralone C=O), 1580 cm⁻¹ (aromatic C=O); 'H NMR (CDCl₃): δ 1.1 (t, J=6Hz, 3H, ester CH₃), 2.8 (d, J=6Hz, 2H, C₂-H), 3.2-3.6 (m, 1H, C₃-H), 3.72-3.76 (t, J=6Hz, 4H, O(CH₂)₂O), 3.9 (s, 3H, OCH₃), 4.1-4.4 (q, J=6Hz, 2H, O-CH₂), 4.6 (d, J=6Hz, 1H, C₅-H), 6.45 (s, 1H, C₆-H), 7.2-7.4 (m, 4H, Ar-H), 7.6 (s, 1H, C₇-H).

General procedure for the preparation of 4-(4'-methoxyphenyl)-1-oxo-2-methylenedioxy-3-ethylcarboxy-6,7-ethyleneedioxy-1,2,3,4-tetrahydronaphthalene 11 and 4-(4'-methoxyphenyl)-1-oxo-2-methylenedioxy-3-carboxy-6,7-ethyleneedioxy-1,2,3,4-tetrahydronaphthalene 12. Sodium hydride(0.504g, 0.021 mole) was added to a solution of absolute ethanol (10 mL) in dry benzene (150 mL) and stirred well under dry nitrogen at 0°C. Ethyl formate (5 mL) was added dropwise to the reaction mixture and stirred for 1 hr followed by dropwise addition of 10 (3g, 7.8 mmole) in dry benzene (100 mL) over a period of 1 hr. The reaction mixture was then stirred at room temperature for 12 hr and the rusty red mixture obtained was poured into 2N H₂SO₄ (100 mL) in ice (100g). The organic layer separated was washed with water (3 x 50 mL) and extracted into saturated sodium bicarbonate solution (3 x 30 mL), followed by 1% sodium hydroxide solution (3 x 30 mL).

The sodium hydroxide extract on acidification with 2N H₂SO₄ furnished dark pink coloured precipitate, which was chromatographed over silica gel column (40 x 1 cm) using chloroform as the eluent. The TLC monitored eluents were combined and on evaporation gave pale yellow solid 11. The bicarbonate extract was acidified with 2N H₂SO₄ and the yellow solid on recrystallisation with benzene-ethanol (2:1) gave 12 as pale yellow crystalline solid.

11: IR (KBr): 3300-3600 (OH), 1720 (ester C=O), 1680 (tetralone C=O), 1620 (conjugated C=C), 1580 cm⁻¹ (tetralone C=O); 'H NMR (DMSO-d₆): δ 1.1 (t, J=6Hz, 3H, ester CH₃), 3.6 (d, J=4Hz, 1H, C₃-H), 3.85 (s, 3H, 4'-OCH₃), 3.9-4.2 (m, 6H, O(CH₂)₂O, O-CH₂), 4.5 (d, J=6Hz, 1H, C₄-H), 6.05 (bs, 1H, vinylic OH), 6.6 (s, 1H, C₆-H), 7.1-7.4 (m, 4H, Ar-H), 7.7 (s, 1H, C₇-H), 8.2 (s, 1H, vinylic); MS (EI): m/z 410 (M⁺, 49.1%), 382 (M⁺-C₃H₆, 7.6%), 380 (M⁺-H₂CO, 24.5%), 352 (35.3%), 336 (100), 335 (29.5%), 337 (28.2%), 308 (7.9%).

12: IR (KBr): 3400-3500 (OH), 1725 (carboxyl C=O), 1680 (tetralone C=O), 1640 (conjugated C=C), 1580 cm⁻¹ (aromatic C=C); 'H NMR (DMSO-d₆): δ 3.5 (d, J=6Hz, 1H, C₅-H), 3.85 (s, 3H, 4'-OCH₃), 4.0 (s, 4H, O(CH₂)₂O), 4.6 (d, J=6Hz, 1H, C₆-H), 5.9-
SHASHIKANTH et al.: SYNTHESIS OF PODOPHYLLOTOXIN AND RELATED ANALOGUES 1719

6.25 (bs, 1H, vinylic OH), 6.7 (s, 1H, C₆-H), 7.2-7.4 (m, 4H, Ar-H), 7.8 (s, 1H, C₇-H), 8.1 (s, 1H, vinylic) 9.5 (bs, 1H, COOH).

General procedure for the preparation of 1-hydroxy-2-methylhydroxy-3-ethyl carboxy-4-(4'-methoxyphenyl)-6,7-ethylenedioxy-1,2,3,4-tetrahydrodronaphthalene 13. To a solution of 11 (2g, 4.8 mmol), sodium borohydride (0.44g, 15 mmol) in sodium hydroxide solution (2 x 15 mL), water (2 x 15 mL) was added during 1 hr at room temperature. At hourly interval, a solution of sodium borohydride (0.44g, 15 mmol) in methanol (10 mL) was added three times. The reaction mixture after stirring at room temperature for 12 hr was concentrated to 30 mL, acidified with 2N HCl and then the pH of the solution was adjusted to 8 by adding 1% aqueous ammonium hydroxide solution. The solid was extracted into diethyl ether (2 x 30 mL), the ether layer was washed with cold 1% sodium hydroxide solution (2 x 15 mL), water (2 x 15 mL) and then dried over anhydrous sodium sulphate. Evaporation of the solvent yielded a pasty mass, which was dissolved in minimum quantity of chloroform and poured into petroleum ether (20 mL). The solid was filtered and recrystallized from ethanol to afford 13 as a white 10 mL solid. IR (nujol): 3200-3500 (OH), 1720 (C=O), 1680 (tetralone C=O); 1580 cm⁻¹ (aromatic C=C); 1H NMR (DMSO-δ₆): \( \delta \) 1.0-1.3 (t, \( J=5\)Hz, 3H, ester CH₃), 1.35-1.5 (m, 2H, C₆-H), 3.0-3.3 (bs, 1H, OH), 3.4-3.65 (m, 3H, OCH₃, C₇-H), 4.0 (m, 9H, ester OCH₂, OCH₃, O(CH₂)₂O), 4.3-4.5 (d, \( J=8\)Hz, 1H, C₁-H), 6.9-7.3 (m, 6H, Ar-H); MS (EI): m/z 396 (M⁺H₂O, 2.8%), 378 (M⁺H₂O, 1.4%), 368 (M⁺C₆H₄OH, 61.0%), 350 (M⁺C₆H₄OH & H₂O, 30%), 336 (100%), 308 (1.0%), 306 (18.0%), 290 (16.0%).

General procedure for the preparation of 1-hydroxy-2-methylhydroxy-3-carboxy-4-(4'-methoxyphenyl)-6,7-ethylenedioxy-1,2,3,4-tetrahydrodronaphthalene 14. A solution of 13 (1.2g, 2.8 mmol) in methanol (25 mL) and 2% sodium hydroxide (25 mL) were refluxed for 3 hr. After removing the methanol under reduced pressure, the alkaline solution was acidified with 2N HCl. The solid was extracted into diethyl ether (3 x 20 mL) and washed with water (2 x 25 mL) and then it was extracted with saturated sodium bicarbonate solution (2 x 25 mL). The bicarbonate extract on acidification with dil HCl gave pale yellow precipitate, which on recrystallisation from methanol gave white crystals of 14. IR (KBr): 3290-3500 (OH), 1710 (C=O), 1600 cm⁻¹ (aromatic C=C); 1H NMR (DMSO-δ₆): \( \delta \) 1.5-1.75 (m, 1H, C₁-H), 2.8-3.0 (m, 1H, C₂-H), 3.05-3.2 (bs, 2H, OH), 3.4-3.7 (m, 3H, OCH₃, C₃-H), 3.85 (s, 3H, OCH₃, 3.9-4.2 [m, 4H, O(CH₂)₂O]; 4.35-4.5 (d, \( J=6\)Hz, 1H, C₁-H), 6.9 (s, 1H, C₂-H), 7.0-7.2 (m, 4H, Ar-H), 7.45 (s, 1H, C₆-H); MS (EI): m/z 368 (M⁺H₂O, 100%), 354 (M⁺-OCH₃OH, 20.5%), 353 (M⁺-C₆H₄OH, -H, 28.5%), 350 (M⁺-2H₂O, 35.5%), 309 (2.5%), 305 (20.5%), 308 (32.5%).

General procedure for the preparation of 3-(4-methoxyphenyl)-3H-6,7,10,11-tetrahydro-1,5,8-trioxa-cyclopantha[b]anthracene-2-one 15. A mixture of 14 (0.8g, 2.7 mmol), p-toluene sulphonyl chloride (3.59g, 179 mmol) and pyridine (22 mL) in dry benzene (50 mL) was refluxed for 3 hr. The reaction mixture was cooled to room temperature, washed with 2N HCl (2 x 25 mL) and then with water (2 x 30 mL). The organic layer was dried and evaporated at 50°C on a rotary evaporator to a thick residue. The crude product was column chromatographed over silica gel column (15 x 1 cm) using chloroform as the eluent. The TLC monitored eluents were combined and on evaporation under reduced pressure gave 15 as a white powder. IR (nujol): 1770 (laconite C=O), 1700 (shoulder, tetrasubstituted C=C), 1600cm⁻¹ (aromatic C=C); 1H NMR (CDCl₃): \( \delta \) 3.4-4.0 [bm, 11H, C₁-H, C₆-H, O(CH₂)₂O, OCH₃], 4.8 (s, 1H, C₁-H), 6.5 (s, 1H, C₆-H), 7.05 (s, 1H, C₁-H), 7.1-7.4 (bm, 4H, Ar-H); 13C NMR (CDCl₃): \( \delta \) 35.6 (d), 39.2 (t), 56.0 (q), 72.2 (t), 75.2 (t), 116.0 (s), 114.6 (d), 124.2 (s), 129.4 (d), 129.8 (s), 135.3 (s), 135.9 (s), 141.9 (s), 142.0 (s), 145.0 (s), 159.5 (s), 171.0 (s). Anal. Caled for C₂₁H₁₃NO₂: C, 76.92; H, 5.70; N, 5.28. Found: C, 76.92; H, 5.60; N, 5.25%. MS (EI): m/z 351 (M⁺+1, 100%), 349 (15.5%), 348 (2.9%), 320 (9.5%), 307 (28.5%), 306 (48.5%), 305 (12.5%), 272 (15.6%).

Acknowledgement
Authors wish to thank the University of Mysore, Mysore for providing facilities to carry out research work at the Department of Studies in Chemistry.

References