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Note

A convenient route for the synthesis of plumbagin[†‡]

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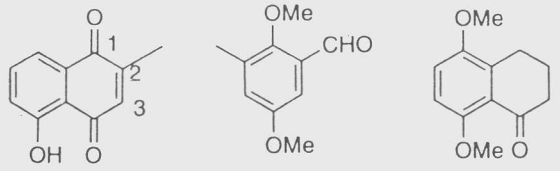
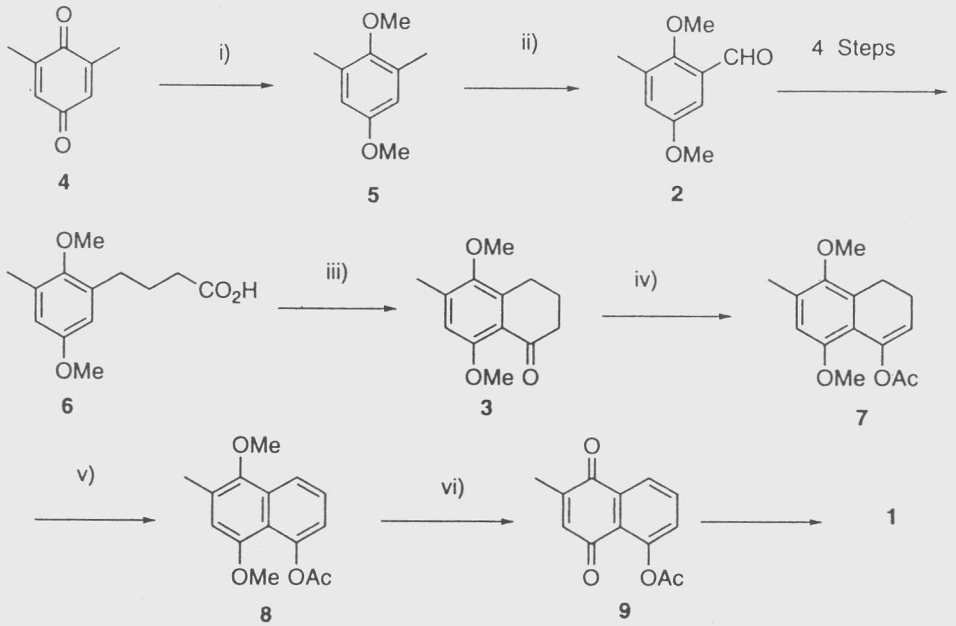
An efficient synthesis of plumbagin **1** has been carried out starting from 2, 6-dimethylbenzoquinone **4**. Two of the key steps are: (I) preparation of aldehyde **2** and (ii) aromatization of **3** via conversion to enol acetate **7** followed by DDQ dehydrogenation to afford **8**.

The naturally occurring quinone, plumbagin **1**[1], which has been isolated in several laboratories including ours shows interesting biological activities and hence it has been synthesized by different groups. We required large quantities of plumbagin for some projects and have developed a convenient route for its synthesis, taking advantage of a literature report that the aldehyde **2** is converted to tetralone **3** in a few steps[2] (Scheme I). The synthesis now reported is more efficient than the syntheses reported in literature[1]. We have employed two recent developments: (a) selective oxidation of methoxylated alkyl aromatic compounds with $Co(OAc)_2$-$Mn(OAc)_2$ in the presence of oxygen[3] and (b) aromatization of α-tetralones by conver-



1 **2** **3**



4 **5** **2** **6** **3** **7** **8** **9**

Reagents: (i) $Na_2S_2O_4$, $(CH_3O)_2SO_2$,K_2CO_3, dry acetone, reflux (ii) $Co(OAc)_2$-$Mn(OAc)_2$, O_2, (iii) Polyphosphate ester, $CHCl_3$, (iv) isopropenyl acetate, PTSA, reflux (v) DDQ, benzene, reflux, (vi) CAN, CH_3CN, H_2O

Scheme I

[†]IICT Communication No. 3419.
[‡]Taken in part from Ph.D. thesis of H Rama Mohan submitted to Osmania Univesity, Hyderabad, 1995.

sion to enol acetates and subsequent oxidation with DDQ[4].

Commercially available **4**[5] is converted to **5** via dithionite reduction and subsequent methylation. Oxidation of **5** with oxygen in the presence of $Co(OAc)_2$-$Mn(OAc)_2$ catalyst furnished the aldehyde **2** which is converted to **6** in four steps in 80% overall yield according to known method[2]. Polyphosphate ester[6] catalyzed cyclization of the acid **6** gave the tetralone **3**. Reaction of **3** with isopropenyl acetate in the presence of PTSA (*p*-toluene sulfonic acid) catalyst furnished the enol acetate **7**[4], which was dehydrogenated to the acetate **8** with DDQ. Ceric ammonium nitrate oxidation of **8** yielded the quinone **9**. Deacetylation of **9** in quantitative yield to give plumbagin **1** on heating with MeOH-HCl is already reported[7].

Since the tetralone ring of the intermediate **3** is prepared from the aldehyde **2** *via* stepwise elongation of carbon chain, the present method allows introduction of labelled carbon at C_1, C_2 and C_3 and the method also allows the preparation of analogues of plumbagin.

Experimental Section

General. Melting points were determined on a Buchi melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian FT 200 spectrometer (200 MHz) using TMS as internal standard. Mass spectra were registered with Finnigan Mat 1210 double focusing spectrometer. Silica gel (60-120 mesh) was used for column chromatography.

1, 4-Dimethoxy-2, 6-dimethylbenzene 5. A mixture of 2, 6-dimethyl benzoquinone **4** (14.0 g, 0.103 mole), sodium dithionite (39.4 g, 0.23 mole), ethyl acetate (220 mL) and water (100 mL) was stirred at 25°C for 1 hr. Work-up afforded the corresponding dihydroxy compound which was methylated with $(CH_3O)_2SO_2$ (32.39 g, 0.26 mole), K_2CO_3 (56.78 g, 0.41 mole) and dry acetone (300 mL) under reflux for 12 hr. Work-up followed by distillation afforded **5** (15.2 g, 89%), b.p. 105°C/10 mm (lit.[8] 103°C/10 mm); ^{1}H NMR ($CDCl_3$); δ 2.25 (s, 6H), 3.66 (s, 3H), 3.71 (s, 3H), 6.49 (s, 2H); Anal. Found: C, 72.18; H, 8.37. Calcd. For $C_{10}H_{14}O_2$: C, 72.26; H, 8.49%.

2, 5-Dimethoxy-3-methylbenzaldehyde 2. To a mixture of **5** (15.0 g, 0.09 mole) in acetic acid (150 mL), cobalt (II) acetate tetrahydrate (3.49 g, 0.014 mole) and $Mn(OAc)_2$ (0.78 g, 4.5 mmole) were added and the reaction contents heated in an autoclave under O_2 (3 atom.) at 110°C for 3 hr. The reaction mixture was cooled, the inorganic salts were filtered and the acetic acid was removed under reduced pressure. The contents were poured into water (200 mL) and extracted into Et_2O (60 mL×3). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography using hexane as eluent to afford **2** (14.96 g, 92%), m.p. 42° (lit.[9] 40-41°); ^{1}H NMR ($CDCl_3$): δ 2.36 (s, 3H), 3.78 (s, 3H), 3.81 (s, 3H), 7.02 (d, *J*=2 Hz, 1H), 7.18 (d, *J*=2 Hz, 1H), 10.38 (s, 1H); Anal. Found: C, 66.64; H, 6.74. Calcd. For $C_{10}H_{12}O_3$: C, 66.65; H, 6.71%.

3, 4-Dihydro-5, 8-dimethoxy-6-methyl-1(2)-naphthalenone 3. A solution of 4-(2, 5-dimethoxy-3-methylphenyl)butyric acid **6** (6.85 g, 0.029 mole), prepared according to known method[2] from **2** in dry $CHCl_3$ (20 mL) was added slowly to the polyphosphate ester (31 mL) and the reaction mixture stirred at 25°C for 6 hr, poured into ice water (100 mL), stirred overnight and extracted into Et_2O (50 mL×3). The combined organic extracts were washed with saturated $NaHCO_3$ solution (20 mL×2), brine, dried and concentrated. The residue was chromatographed using 1:9 mixture of ethyl acetate-hexane as eluent to furnish **3** (5.76 g, 91%); ^{1}H NMR ($CDCl_3$): δ 2.06 (m, *J*=6 Hz, 2H), 2.35 (s, 3H), 2.58 (t, *J*=6 Hz, 2H), 2.94 (t, *J*=6 Hz, 2H), 3.68 (s, 3H), 3.88 (s, 3H), 6.52 (s, 1H), MS(EI): m/z 221 (M+1), 220 (M^+), 205, 191, 177, 91, 44, 32, 28; Anal. Found: C, 70.79; H, 7.27. Calcd. For $C_{13}H_{16}O_3$: C, 70.89; H, 7.32%.

5, 8-Dimethoxy-3, 4-dihydro-6-methylnaphthalene-1-ol acetate 7. A mixture of **3** (5.15 g, 0.023 mole), PTSA monohydrate (0.445 g, 0.002 mole) and isopropenyl acetate (65 mL) was heated at reflux under N_2 for 16 hr. The reaction mixture was cooled, isopropenyl acetate removed under vacuum, and the residue poured into water (20 mL) and extracted with ethyl acetate (20 mL×3). Work-up afforded a residue which was purified by column chromatography using 5% ethyl acetate-hexane as eluent to afford **7** as a viscous oil (5.52 g, 90%); ^{1}H NMR ($CDCl_3$): δ 2.2 (s, 3H), 2.28 (s, 3H), 2.42 (m, 2H), 2.85 (t, *J*=7 Hz, 2H), 3.68 (s,

3H), 3.78 (s, 3H), 5.58 (t, J=5 Hz, 1H), 6.53 (s, 1H); MS(EI): m/z 263 (M+1), 262 (M^+), 220, 205, 189, 85, 43, 32, 28; Anal. Found: C, 68.65; H, 6.88. Calcd. For $C_{15}H_{18}O_{14}$: C, 68.68; H, 6.92%.

5, 8-Dimethoxy-6-methylnaphthalene-1-ol acetate 8. A mixture of **7** | (5.28 g, | 0.02 | mole) in dry benzene (50 mL) and DDQ (13.72 g, 0.06 mole) was heated under reflux for 90 min. The reaction mixture was cooled, the benzene removed under vacuum and the mixture diluted with CH_2Cl_2 (100 mL). The organic layer was washed with 10% NaOH solution, 2 *M* HCl, brine and dried over Na_2SO_4. Removal of solvent furnished a residue which was purified by column chromatography using 10% ethyl acetate-hexane as eluent to afford **8** (4.45 g, 85%), m.p. 107°; ^{1}H NMR ($CDCl_3$): δ 2.36 (s, 3H), 2.42 (s, 3H), 3.84 (s, 3H), 3.89 (s, 3H), 6.62 (s, 1H), 7.0 (dd, J=8 and 2 Hz, 1H), 7.45 (m, 1H), 7.95 (dd, J=8 and 2 Hz, 1H); MS(EI): m/z 260 (M^+), 218, 203, 175, 115, 43; Anal. Found: C, 69.18; H, 6.14. Calcd. For $C_{15}H_{16}O_4$: C, 69.21; H, 6.20%).

2-Methyl-5-acetoxy-1, 4-naphthoquinone 9. To a mixture of **8** (4.25 g, 0.016 mole) in acetonitrile (100 mL), CAN (17.4 g, 0.032 mole) in water (50 ml) was added and the reaction mixture stirred at room temperature for 15 min. The acetonitrile was removed under reduced pressure, the concentrate poured into water (20 mL) and extracted with ethyl acetate (30 mL×2). The organic layer was dried and concentrated to furnish **9** (3.19 g, 85%), m.p. 118°C (lit.[1a] 117-118°C); ^{1}H NMR ($CDCl_3$): 2.17 (s, 3H), 2.39 (s, 3H), 6.67 (s, 1H), 7.30 (dd, J=8 and 1 Hz, 1H), 7.58 (t, J=8 Hz, 1H), 8.03 (dd, J=8 and 1 Hz, 1H), MS(EI): m/z 230 (M^+), 188, 160, 131, 77, 63, 43; Anal. Found: C, 67.88; H, 4.37. Calcd. For $C_{13}H_{10}O_4$: C, 67.82; H, 4.38%.

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