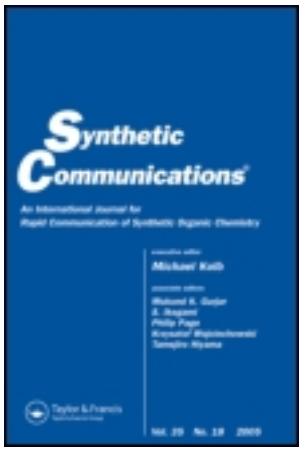

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Synthesis of Methoxy-2-hydroxy-1,4-naphthoquinones and Reaction of One Isomer with Aldehydes Under Basic Conditions

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ABSTRACT

Two protocols for the synthesis of methoxy-2-hydroxy-1,4-naphthoquinones were investigated in order to evaluate their behavior towards aldehydes under amine-basic conditions. Both the nature of the quinone and aliphatic aldehyde contribute to the viability of this condensation as well as further transformations.

Key Words: Methoxy-2-hydroxy-1,4-naphthoquinones; Methoxy-naphtho[2,3-*b*]pyran-5,10-diones; Aldehydes; Isomer.

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INTRODUCTION

Erythrostominone **1**, isolated from *Gnomonia erythrostoma*, belongs to the broad class of naphtho[2,3-*b*]pyranquinone antibiotics and has a demonstrated in vitro activity against both Gram positive and Gram negative bacteria.[1,2] In seeking out routes for constructing the naphtho[2,3-*b*]pyran nucleus, the earlier work of Hooker regarding condensation of 2-hydroxy-1,4-naphthoquinone with aldehydes under acid conditions[3] and later developed by Giles et al.[4] who employed DDQ for intramolecular cyclizations of these intermediates into the naphtho[2,3-*b*]pyran nucleus, was considered to offer good prospects. Since the aldehydes envisaged to be used were acid labile, we developed a protocol employing an amine base to facilitate condensation with 2-hydroxy-1,4-naphthoquinone.[5,6]

Thus far, we[7,8] and others[9] have concentrated efforts on the reactions of nor-methoxy-2-hydroxy-1,4-naphthoquinones in the expectation that should good protocols be developed, then application to mompain trimethyl ether **2**, which has the correct oxygenation pattern, would lead to a synthesis of erythrostominone **1** (Fig. 1). This article describes our best syntheses of some methoxy-2-hydroxy-1,4-napthoquinones and the condensation of the 8-methoxy isomer with two hexanals under amine-base conditions.

In searching for the most appropriate synthetic protocol to our target molecules, it was clear that a route providing regiospecific control would be a Friedel Crafts acylation between a methoxylated benzene **3** and succinic anhydride **4** affording the corresponding ketobutyric acids **5**. Clemmenson reduction of the keto moiety followed by acid-assisted intramolecular cyclization of the derived 4-arylbutyric acid would produce the corresponding α-tetralones **6**. Finally, regiospecific oxidation of tetralones **6** would afford the corresponding 2-hydroxynaphthoquinones **7**. (Sch. 1).

In order to investigate and establish a viable route to be adopted for the synthesis of mompain trimethyl ether **2**, anisole **3a** (1-MeO) was transformed

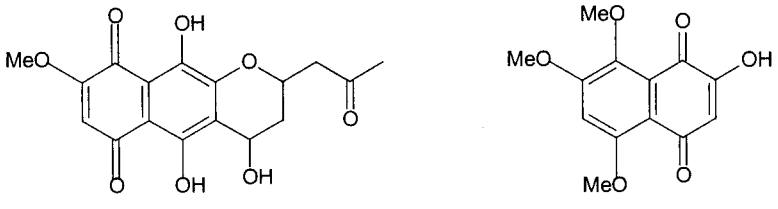

Figure 1. Structures of compounds **1** and **2**.

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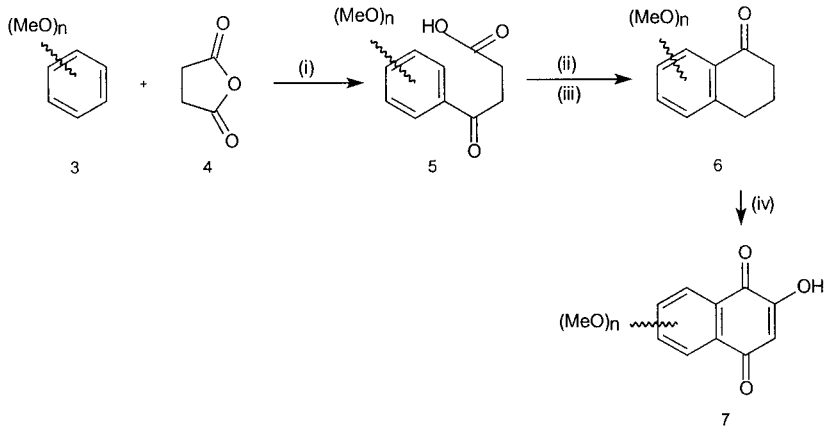

Scheme 1. (i) Lewis acid/solvent; (ii) Clemmensen reduction of benzilic carbonyl group with Zn/HCL/toluene; (iii) ring closure with PPA; and (iv) regiospecific autoxidation.

into the 7-methoxy α-tetralone **6a** (7-MeO) by the methodology of Yang et al.[10] in an overall yield of 53% for the three steps. Similarly 1,4-dimethoxy benzene **3b** (1,4-dimethoxy) was transformed into the α-tetralone **6b** (5,8-dimethoxy) in an overall yield of 60% while the trimethoxybenzene **3c** (1,2,4-trimethoxy) was efficiently transformed into α-tetralone **6c** (5,7,8-trimethoxy) in 45% yield. Use of a recently proposed Lewis acid to catalyze the intramolecular cyclization of 4-arylbutyric acids to α-tetralones viz., $Bi(NTf_2)_3$[11] was discounted due to scale-up difficulties and neither was the recent report describing the oxidation of alkoxy-1,2,3,4-tetrahydronaphthalenes to α-tetralones using DDQ[12] considered due to the inherent difficulties in synthesizing the precursor molecules.

Methods which were investigated for the oxidative conversion of tetralones **6** into the corresponding 2-hydroxy-1,4-naphthoquinones **7** include the following, reaction with *N*,*N*-dimethyl-4-nitrosoaniline,[13] potassium superoxide in 18-crown-6,[14] potassium superoxide in toluene/pyridine and toluene/THF,[15] selenium dioxide in acetic acid followed by potassium superoxide in dichloromethane,[16] and the method by Malinovskaya et al.[17] using the harsh conditions of MnO_2 in concentrated H_2SO_4 at 55°C seemed unappealing. Of the forgoing methods, those of Bekaert et al.[16] and Anderson et al.[13] gave at best yields of 10–20% in our hands. We thus turned our attention to the methods published contiguously by Baillie and Thomson[18] and by Kasturi and Arunachalam[19] in spite of the poor yield quoted by Thomson[18] for trimethoxy mompain **7c** (5,7,8-trimethoxy).

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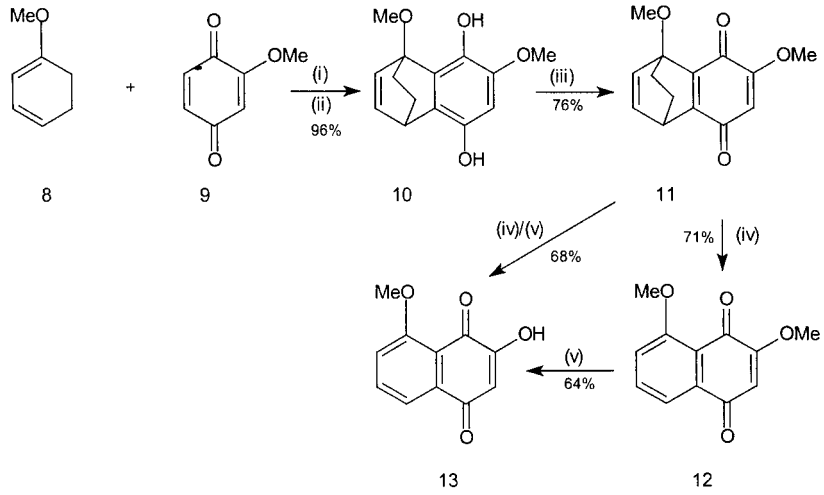
Thus, treatment of α-tetralone **6a** (7-methoxy) in *t*-butanol in the presence of 5 mol equivalents of potassium *t*-butoxide under vigorous oxygen bubbling at 25°C afforded the expected 2-hydroxy-1,4-naphthoquinone **7a** (7-methoxy) in 75% yield, while treatment of α-tetralone **6b** (5,8-dimethoxy) under these conditions afforded the corresponding 2-hydroxynaphthoquinone **7b** (5,8-dimethoxy) in a lower yield of 60%. These two examples represent oxygenation patterns bearing similarities to trimethoxy mompain **7c** (5,7,8-trimethoxy). Applying the above autoxidative protocol to α-tetralone **6c** (5,7,8-trimethoxy) afforded the mompain trimethyl ether **7c** (5,7,8-trimethoxy) in 58% yield. A major drawback of our findings was the scale of the autoxidation ranging from 500 mg for **6a** to 200 mg for **6c**. Thus, in order to test the influence of a methoxy group on the condensation between methoxy-2-hydroxynaphthoquinones with aldehydes under amine-base conditions, the Diels Alder approach used by Giles et al.[4,20] was adopted and modified to obtain large quantities of quinone **13**, a further precursor to an analogue of erythrostominone **1**.

Thus, condensation between 1-methoxycyclohexadiene **8** and 2-methoxybenzoquinone **9** afforded quinol **10** in 96% yield after passage through a silica gel column. Oxidation of quinol **10** to quinone **11** was accomplished in 76% yield with aqueous acetonitrile containing cerium(IV) ammonium nitrate, and after pyrolysis of the bridged quinone **11** at 140°C, the crude product **12** was hydrolyzed under basic conditions to give the target molecule **13** in 68% yield for the last two steps (Sch. 2).



Scheme 2. (i) Reflux/benzene; (ii) column chromatography; (iii) CAN oxidation; (iv) pyrolysis; and (v) $NaOH/H_2O$.

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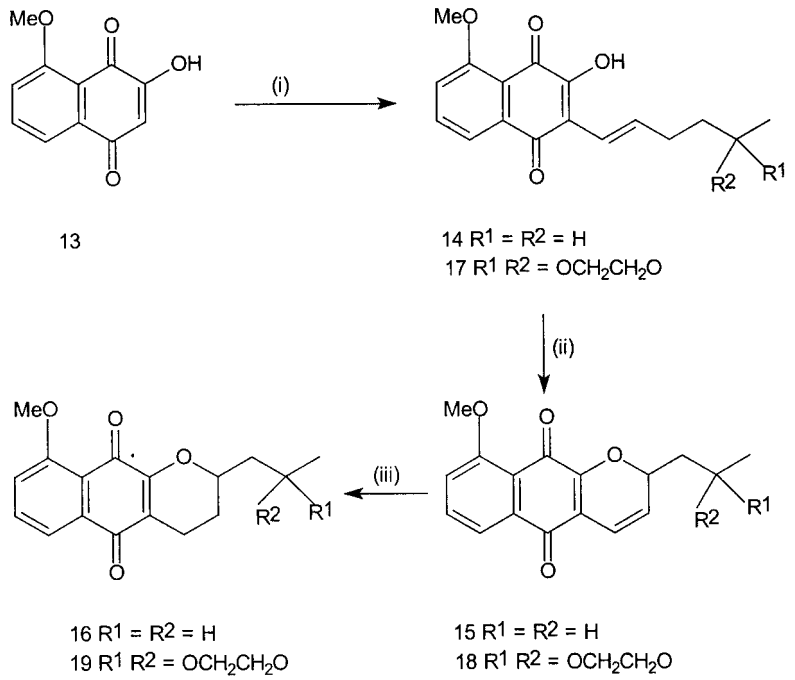
With quinone **13** in hand, its condensation with two hexanals pertinent to the planned synthetic protocol of erythrostominone and its analogs was investigated. Thus, condensation between **13** and caproaldehyde in acetonitrile containing 1 equiv. of triethylamine[6] afforded the trans olefin **14** in 78% yield. Clear evidence of the trans nature of the double bond was provided by the ^{1}H NMR spectrum in which the signal assigned to 1′-H appeared as a dt at 6.56 ppm (*J* 16.6 and 1.4) while that assigned to 2′-H appeared as a dt at 7.02 ppm (*J* 16.6 and 7.0). Intramolecular cyclization of quinone **14** to the corresponding naphtho[2,3-*b*]pyrenequinone **15** was effected using DDQ in hot benzene[8] in 83% yield. Evidence for the cyclization was provided by the ^{1}H NMR spectrum viz., a dd at 5.74 ppm (*J* 10.0 and 3.8) assigned to 3-H and a dd at 7.64 ppm (*J* 10.0 and 1.6) assigned to 4-H of the pyrene ring. Finally, reduction of the double bond of the pyrene **15** under catalytic hydrogenation afforded the naphtho[2,3-*b*]pyranquinone **16** in 99% yield (Sch. 3).



Scheme 3. (i) Aldehyde/triethylamine/acetonitrile; (ii) DDQ/benzene; and (iii) H_2/Pd/C/EtOAc.

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Attention was then focussed on the condensation between quinone **13** and the acid sensitive aldehyde, 5-dioxolanohexanal which had earlier been condensed with Lawsone in a moderate yield of 56%.[8] After numerous attempts, including variations of temperature, base, ratio of base to quinone, we were able to isolate the desired product **17** in a best yield of 16%. Sharp bands at 3468, 1670, and 1645 cm^{-1} in the infrared spectrum attest to the functionalities while the ^1H NMR spectrum confirmed the trans nature of the C-1′, C-2′ double bond. Intramolecular cyclization of quinone **17** to the corresponding naphtho[2,3-*b*]pyrenequinone **18** gave a best yield of 15% under similar conditions of DDQ used earlier. Finally catalytic hydrogenation of naphthopyrenequinone **18** afforded the expected quinone **19** in 80% isolated yield.

In conclusion we have found that the most convenient transformation of methoxy-α-tetralones **6** into 2-hydroxy-1,4-naphthoquinones **7** is by employing potassium *t*-butoxide in *t*-butanol under vigorous passage of oxygen. Whereas, amine-base-catalysed condensation between 2-hydroxy-8-methoxy-1,4-naphthoquinone **13** with hexanal occurs in good yield, similar condensation with the acid-sensitive aldehyde, 5-dioxolanohexanal is not viable. In addition, whereas, methoxy-2-hydroxy-3-(1′-hexenyl)-1,4-naphthoquinone **14** undergoes intramolecular cyclization to the pyrene **15** in good yield, similar cyclization of an acid-sensitive system **17** is nonviable.

Ways of improving yields of both condensation and cyclization are being sought.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded using a Varian 200 MHz spectrometer at 20°C in deuterochloroform and *J* values are given in Hz. Infrared spectra were measured as Nujol mulls on a Perkin Elmer FT-IR 1000 PC spectrometer. Melting points were determined on a Fischer–Johns melting point stage and are uncorrected. Mass spectra were recorded on a Finnigan–Matt GCQ instrument. Column chromatography was carried out using Merck Kieselgel 60 (70–230 mesh) as dry columns. The residue obtained upon workup refers to material obtained from the dried (magnesium sulphate) organic extract after filtration and solvent removal. Hexane refers to that fraction of b.p. 70–75°C. In ^{13}C-spectra, assignments with the same superscript may be interchanged.

General Protocol for Autoxidation of α-Tetralones

To a stirred solution of the tetralone (1 mmol) in dry *t*-butanol (10 mL) at 25°C saturated with oxygen for 15 min was added at once, potassium

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t-butoxide (5 mmol), and stirring was continued under a stream of oxygen for 45 min after which time the reaction mixture was acidified with dilute aqueous hydrogen chloride (0.5 M) and extracted with methylene dichloride. The combined organic extracts were washed with aqueous sodium hydrogen carbonate (0.5 M) and this basic extract was then acidified with dilute sulphuric acid (0.5 M) and finally extracted with methylene dichloride. The residue obtained upon workup was chromatographed using EtOAc as eluent to yield the product.

2-Hydroxy-7-methoxy-1,4-naphthoquinone (7a). Tetralone **6a**[21] (500 mg, 2.84 mmol) afforded quinone **7a** (435 mg, 75%) as an orange solid, m.p. 212–214°C (from hexane), lit.[19] m.p. 214–215°C. ν_{max} 3200–2700 cm^{-1} (broad) OH, 1672 and 1640 cm^{-1} (C═O), δ_H 3.95 (3H, s, OCH_3), 6.29 (1H, s, 3-H), 7.25 (1H, dd, *J* 8.4 and 3.0, 6-H), 7.55 (1H, d, *J* 3.0, 8-H), and 8.05 (1H, d, *J* 8.4, 5-H). δ_C 56.1 (OCH_3), 110.4 (C-5)[a], 110.7 (C-6)[a], 118.9 (C-8a)[b], 121.3 (C-8)[b], 129.1 (C-3)[b], 131.3 (C-4a)[b], 138.2 (C-2), 156.1 (C-7), 184.1 and 188.9 (C═O). [Found: C, 64.8%; H, 3.9%; M^+ 204 (10), 176 (60), 135 (70). Calc. for $C_{11}H_8O_4$: C, 64.7%; H, 3.9%; M 204].

2-Hydroxy-5,8-dimethoxy-1,4-naphthoquinone (7b). Tetralone **6b**[10] (320 mg, 155 mmol) afforded quinone **7b** (218 mg, 60%) as orange crystals, m.p. > 300°C (decomp.) (from ethanol). ν_{max} 3220–2800 cm^{-1} (OH), 1668 and 1660 cm^{-1} (C═O), δ_H 3.96 and 4.00 (each 3H, s, OCH_3), 6.21 (1H, s, 3-H), 7.27 (1H, d, *J* 9.4, 7-H) and 7.42 (1H, d, *J* 9.4, 6-H). δ_C 56.8 and 57.3 (OCH_3), 110.7 (C-6)[a], 119.0 (C-7)[a], 123.6 (C-3), 132.6 (C-4a)[b], 138.2 (C-8a)[b], 147.8 (C-2), 151.8 (C-8)[c], 153.9 (C-5)[c], 181.3 and 184.1 (C-1 and C-4). [Found: C, 61.8%; H, 4.3%; M^+ 234. Calc. for $C_{12}H_{10}O_5$: C, 61.5%; H, 4.1%; M 234].

2-Hydroxy-5,7,8-trimethoxy-1,4-naphthoquinone (7c). Tetralone **6c**[13] (200 mg, 0.847 mmol) afforded mompain trimethyl ether **7c** (130 mg, 58%) as light brown crystals (from methanol–water), m.p. 173–174°C, (lit.[18] m.p. 174°C). ν_{max} 3300–2700 cm^{-1} (broad) OH, 1679 and 1635 cm^{-1} (C═O); δ_H 3.88 and 3.99 (×2) (each 3H, s, OCH_3), 6.18 (1H, s, 6-H), 6.82 (1H, s, 3-H). δ_C 56.4, 57.2, and 61.3 (OCH_3), 104.0 (C-6), 123.7 (C-3), 133.6 (C-4a)[a], 134.6 (C-8a)[a], 154.7 (C-2)[b], 158.8 (C-5)[b], 162.8 (×2) (C-8 and C-7)[b], 181.5 and 186.5 (C═O). [Found: C, 58.9%; H, 4.7%; M^+ 264. Calc. for $C_{13}H_{12}O_6$: C, 59.2%; H, 4.5%; M 264].

1,4-Dihydro-1,7-dimethoxy-1,4-ethanonaphthalene-5,8-diol (10). 1-Methyoxycyclohex-1,3-diene **8** (6.4 g, 58.2 mmol) was heated under reflux in benzene (100 mL), containing quinone **9**[4] (3.0 g, 21.7 mmol) for 1.5 hr, at which stage all the quinone was consumed. The solvent was evaporated off and the residue chromatographed using EtOAc : hexane (3 : 7) as eluent to give the product **10**, as white crystals (2.8 g, 96%), m.p. 108–110°C. ν_{max} 3400–2500 cm^{-1} (broad) OH; δ_H 1.59 (4H, m, $-CH_2CH_2-$), 3.67 and 3.77

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(each 3H, s, OCH_3), 4.10 (1H, m, 4-H), 4.48 (1H, D_2O exchangeable, 5-OH), 6.22 (1H, s, 6-H), 6.49 (1H, dd, *J* 8.4 and 5.8, 3-H), 6.65 (1H, dd, *J* 8.4 and 1.2, 2-H), and 8.69 (1H, s, D_2O exchangeable, 8-OH). δ_C 26.0 (CH_2)[a], 28.3 (CH_2)[a], 32.3 (C-4), 52.2 and 56.5 (OCH_3), 86.3 (C-1), 99.2 (C-6), 120.4 (C-4a)[b], 127.7 (C-8a)[b], 134.3 (C-2)[c], 134.8 (C-3)[c], 136.8 (C-8)[d], 141.1 (C-5)[d], and 146.2 (C-7)[d]. [Found: C, 68.0%; H, 6.1%; M^+ 248 (2), 220 (100), 205 (70). Calc. for $C_{14}H_{16}O_4$: C, 67.7%; H, 6.5%; M 248].

1,4-Dihydro-1,7-dimethoxy-1,4-ethanonaphthalene-5,8-dione (11). To a stirred solution of adduct **10** (2.48 g, 10 mmol) in acetonitrile (60 mL) and water (10 mL), was added dropwise a solution of cerium(IV) ammonium nitrate (10.96 g, 20 mmol) in water (10 mL). Stirring was continued for an additional 30 min, followed by the addition of water (400 mL) and then extraction with dichloromethane. The residue obtained upon workup afforded quinone **11** (1.87 g, 76%), as an olive-green solid, m.p. 116–117°C (from ethanol); (lit.[4] 118–118.5°C). ν_{max} 1668 and 1645 cm^{-1} (C═O), δ_H 1.60 (4H, m, $-CH_2CH_2-$), 3.67 and 3.78 (each 3H, s, OCH_3, 4.30 (1H, m, 4-H), 5.77 (1H, s, 6-H), 6.35 (1H, dd, *J* 8.2 and 5.8, 3-H) and 6.55 (1H, dd, *J* 8.2 and 1.0, 2-H). [Found: C, 68.3%; H, 5.3%; M^+ 246 (60). Calc. for $C_{14}H_{14}O_4$: C, 68.5%; H, 5.7%; M 246].

2,8-Dimethoxy-1,4-naphthoquinone (12). The crude quinone **11** (1.8 g, 7.6 mmol), was pyrolyzed at 140°C under an atmosphere of nitrogen for 30 min to afford the naphthoquinone **12** (1.18 g, 71%) as green crystals; m.p. 198–201°C (from ethanol), (lit.[4] 202–202.5°C). ν_{max} 1670 and 1665 cm^{-1} (C═O), δ_H 3.86 and 3.99 (each 3H, s, OCH_3), 6.08 (1H, s, 3-H), 7.25 (1H, dd, *J* 8.0 and 1.8, 7-H), 7.66 (1H, t, *J*, 8.0, 6-H), and 7.73 (1H, dd, *J* 8.0 and 1.8, 5-H). δ_C 56.5 and 56.6 (OCH_3), 108.0 (C-7), 117.5 (C-3)[a], 119.0 (C-6)[a], 119.1 (C-8a)[b], 134.5 (C-4a)[b], 135.4 (C-5)[a], 160.3 (C-2)[c], 161.2 (C-8)[c], 178.6 and 184.8 (C═O). [Found: C, 59.3%; H, 3.9%; M^+ 218 (80), 203 (100). Calc. for $C_{12}H_{10}O_4$: C, 59.5%; H, 4.1%; M 218].

2-Hydroxy-8-methoxy-1,4-naphthoquinone (13). The naphthoquinone **12** (1.0 g, 4.6 mmol) in aqueous 4% sodium hydroxide (20 mL) was stirred until it had dissolved. The solution was washed with ether and then acidified with 5 M hydrochloric acid. The resulting solution was extracted with dichloromethane, and the residue afforded the quinone **13** (0.6 g, 64%) as yellow crystals; m.p. 211–214°C (decomp.), (from ethanol); [lit.[4] 209–211°C (decomp.)]. ν_{max} 3200–2700 cm^{-1} (broad) OH, 1670 and 1667 cm^{-1} (C═O). δ_H 4.05 (3H, s, OCH_3), 6.29 (1H, s, 3-H), 7.27 (1H, dd, *J* 7.2 and 2.2, 7-H), 7.73 (1H, t, *J* 7.2, 6-H), 7.70 (1H, s, D_2O exchangeable, 2-OH), and 7.79 (1H, dd, *J* 7.2 and 2.2, 5-H). δ_C 56.6 (OCH_3), 108.6 (C-7), 117.0 (C-3)[a], 117.1 (C-4a)[b], 119.7 (C-5)[a], 135.4 (C-8a)[b], 136.9 (C-6)[a], 156.9 (C-2)[c], 160.5 (C-8)[c], 180.2 and 184.7 (C═O). [Found: C, 65.0%; H, 3.9%; M^+ 204 (60), 186 (30). Calc. for $C_{11}H_8O_4$: C, 64.7%; H, 3.95%; M 204].

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In a subsequent experiment, naphthoquinone **11** (1.45 g, 6 mmol) was pyrolyzed at 140°C under nitrogen for 30 min and the crude product hydrolyzed with aqueous sodium hydroxide (25 mL of the 4% solution) and worked up as described earlier to afford quinone **13** (835 mg, 68%) identical with the material synthesized earlier vide infra.

2-Hydroxy-8-methoxy-3-(1′-hexenyl)-1,4-naphthoquinone (14). Caproaldehyde (1.0 g, 0.7 mL; 10 mmol) was added to a stirred mixture of quinone **13** (1.0 g, 4.9 mmol) in acetonitrile (25 mL) over 3 min after which triethylamine (1.0 g, 1.4 mL; 10 mmol) was added dropwise and the reaction mixture was allowed to stir for 6 hr under reflux in an atmosphere of nitrogen. After 12 hr stirring at 25°C the solvent was removed to leave a dark red oil, which was taken up in acetonitrile (20 mL) and ether (200 mL) and washed with 0.5 M sulphuric acid (50 mL). The residue obtained upon workup was purified using column chromatography with EtOAc : hexane (3 : 7) as eluent to yield the quinone **14** (1.10 g, 78%) as a dark red solid; m.p. 153–155°C (from hexane–ethyl acetate). ν_{max} 3200–2500 cm^{-1} (broad) OH, 1685 and 1635 cm^{-1} (C═O). δ_H 0.92 (3H, t, *J* 7.0, 6′-H), 1.42 (4H, m, 4′- and 5′-H), 2.30 (2H, m, 3′-H), 4.03 (3H, s, OCH_3), 6.56 (1H, dt, *J* 16.6 and 1.4, 1′-H), 7.02 (1H, dt, *J* 16.6 and 7.0, 2′-H), 7.23 (1H, dd, *J* 7.6 and 1.4, 7-H), 7.73 (1H, t, *J* 7.6, 6-H), 7.80 (1H, dd, *J* 7.6 and 1.4, 5-H), and 8.17 (1H, s, 2-OH), δ_C 14.0 (C-6′), 22.4 (C-5′), 31.4 (C-4′), 34.7 (C-3′), 56.6 (OCH_3), 116.8 (C-7)[a], 116.9 (C-3)[a], 118.5 (C-2′)[a], 120.0 (C-6)[a], 135.2 (C-4a)[b], 136.4 (×2) (C-8a)[b] and (C-1′)[b], 143.1 (C-5)[b], 151.9 (C-2), 159.9 (C-8), 180.0 and 184.2 (C═O). [Found: C, 71.3%; H, 6.3%; M^+ 286 (38), 229 (100). Calc. for $C_{17}H_{18}O_4$: C, 71.0%; H, 6.2%; M 286].

8-Methoxy-2-(1′-propyl)-3,4-dehydronaphtho[2,3-*b*]pyran-5,10-dione (15). To a solution of quinone **14** (0.227 g, 0.794 mmol) in benzene (3 mL), 1.2 equiv. of dichlorodicyanobenzoquinone (0.216 g, 0.951 mmol) in benzene (3 mL) were added and stirred at 65°C for 2 hr; filtered and evaporated to obtain a residue which was purified by column chromatography using EtOAc : hexane (3 : 7) as eluent, to afford the pyranquinone **15** (0.187 g, 83%) as an orange-brown solid; m.p. 45–48°C (from hexane). ν_{max} 1667 cm^{-1}; δ_H 0.94 (3H, t, *J* 7.0, 3′-H), 1.50 (2H, m, 2′-H), 1.65 (2H, m, 1′-H), 3.99 (3H, s, OCH_3), 5.15 (1H, m, 2-H), 5.74 (1H, dd, *J* 10.0 and 3.8, 3-H), 6.66 (1H, dd, *J* 10.0 and 1.6, 4-H), 7.24 (1H, dd, *J* 7.5 and 1.4, 8-H), 7.64 (1H, t, *J* 7.5, 7-H), and 7.75 (1H, dd, *J* 7.5 and 1.4, 6-H). δ_C 13.9 (C-3′), 17.6 (C-2′), 37.8 (C-1′), 56.6 (OCH_3), 77.9 (C-2), 116.9 (×2) (C-8 and C-4a)[a], 117.6 (C-6)[a], 119.2 (C-3)[a], 125.4 (×2), (C-7 and C-5a)[a], 134.0 (C-9a)[a], 135.2 (C-4)[a], 153.9 (C-10a)[a], 159.9 (C-9)[a], 178.6 and 181.7 (C═O). [Found: C, 71.8%; H, 5.3%; M^+ 284. Calc. for $C_{17}H_{15}O_4$: C, 71.5%; H, 5.6%; M 284].

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8-Methoxy-3,4-dihydro-2-(1′-propyl)-naphtho[2,3-*b*]pyran-5,10-dione (16). Quinone **15** (30 mg, 0.106 mmol) in ethyl acetate (20 mL) and palladium–charcoal (5%) (10 mg), was hydrogenated until 2 mol of hydrogen were absorbed. The solution was filtered and the solvent removed. The residue obtained upon workup was purified by flash chromatography using EtOAc : hexane (3 : 7) as eluent to afford the pyranquinone **16** (30 mg, 99%); yellow crystals m.p. 78–81°C (from hexane). ν_{max} 1672 cm^{-1}; δ_H 0.96 (3H, t, *J* 7.0, 3′-H), 1.64 (2H, m, 2′-H), 2.04 (2H, m, 1′-H), 2.42 (1H, ddd, ^2J 18.8, ^3J 9.6 and 5.8, 3-Ha), 2.49 (1H, ddd, ^2J 18.8, ^3J 5.8 and 4.4, 3-He), 2.63 (1H, ddd, ^2J 18.4, ^3J 9.6 and 4.4, 4-Ha), 2.68 (1H, ddd, ^2J 18.2, ^3J 5.8 and 4.4, 4-He), 3.97 (3H, s, OCH_3), 4.08 (1H, m, 2-H), 7.21 (1H, dd, *J* 8.2 and 1.4, 8-H), 7.61 (1H, t, *J* 8.4, 7-H), and 7.73 (1H, dd, *J* 8.2 and 1.4, 6-H). δ_C 14.0 (C-3′), 18.0 (C-2′), 18.6 (C-1′), 25.5 (C-3), 36.5 (C-4), 55.6 (OCH_3), 77.9 (C-2), 117.3 (C-8), 119.0 (C-7)[a], 119.2 (× 2), (C-5a and C-4a)[a], 134.6 (C-9a)[a], 134.9 (C-6)[a], 156.3 (C-10a). 159.9 (C-9), 178.6 and 184.4 (C═O). [Found: C, 71.7%; H, 6.3%; M^+ 286 (25), 216 (100). Calc. for $C_{17}H_{18}O_4$: C, 71.3%; H, 6.5%; M 286].

2-Hydroxy-8-methoxy-3-(5′-dioxolano-1′-hexenyl)-1,4-naphthoquinone (17). Quinone **13** (1.0 g, 6.4 mmol) in acetonitrile (30 mL) containing 5-dioxolanohexanal[8] (1.82 g, 11.5 mmol) was treated with triethylamine (5.0 g, 49.5 mmol), and the red solution was stirred under nitrogen at 60°C for 8 hr. After cooling the solution, water (150 mL) was added and the resultant solution was extracted with ether (4 × 60 mL). The ether extract was washed with sulphuric acid (40 mL of a 0.5 M solution) and the residue obtained upon workup was flash chromatographed using EtOAc : hexane (2 : 3) as eluent to afford quinone **17** (346 mg, 16%) as a red oil. ν_{max} 3468, 1670, and 1645 cm^{-1}; δ_H 1.36 (3H, s, 6′-H), 1.84 (2H, m, 4′-H), 2.39 (2H, m, 3′-H), 3.96 (4H, sharp, m, OCH_2CH_2O), 4.03 (3H, s, OCH_3), 6.64 (1H, dt, *J* 16.0 and 1.0, 1′-H), 7.03 (1H, dt, *J* 16.0 and 6.8, 2′-H), 7.23 (1H, dd, *J* 7.6 and 1.0, 7-H), 7.69 (1H, t, *J* 7.6, 6-H), 7.80 (1H, dd, *J* 7.6 and 1.0, 5-H), and 8.16 (1H, s, D_2O exchangeable, 2-OH). δ_C 24.1 (C-6′), 29.6 (C-4′), 38.5 (C-3′), 56.6 (OCH_3), 64.8 (×2) (OCH_2CH_2O), 109.9 (×2) (C-5′ and C-7), 116.8 (C-2′)[a], 116.9 (C-3)[a], 118.6 (C-6)[a], 120.1 (C-5)[a], 135.2 (C-4a)[b], 136.4 (C-8a)[b], 142.2 (C-1′)[a], 152.0 (C-2), 160.0 (C-8), 180.0 and 184.1 (C═O). [Found: C, 66.7%; H, 6.1%; M^+ 344. Calc. for $C_{19}H_{20}O_6$: C, 66.3%; H, 5.8%; M 344].

9-Methoxy-2-(2′-dioxolanopropyl)-3,4-dehydronaphtho[2,3-*b*]pyran-5,10-dione (18). To a solution of quinone **17** (200 mg, 0.58 mmol) in benzene (15 mL), was added a solution of dichlorodicyanobenzoquinone (158 mg, 0.70 mmol) in benzene (15 mL) and the resulting solution was stirred at 25°C under nitrogen for 12 hr; filtered and the residue was chromatographed by preparative layer chromatography using EtOAc : hexane (3 : 7) as eluent

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to afford the pyranquinone **18** (30 mg, 15%) as a thick red oil. ν_{max} 1690 and 1670 cm^{-1}; δ_H 1.26 (3H, s, 3′-H), 2.17 (1H, m, 1′-H), 2.38 (1H, m, 1′-H), 3.98 (7H, sharp m, OCH_2CH_2O and CH_3O), 5.35 (1H, m, 2-Ha), 5.81 (1H, dd, *J* 9.8 and 3.6, 3-H), 6.65 (1H, dd, *J* 9.8 and 1.8, 4-H), 7.24 (1H, dd, *J* 8.0 and 1.2, 8-H), 7.64 (1H, t, *J* 8.0, 7-H), and 7.76 (1H, dd, *J* 8.0 and 1.2, 6-H). δ_C 25.1 (C-3′), 44.3 (C-1′), 55.8 (OCH_3), 64.9 and 65.3 (OCH_2CH_2O), 74.8 (C-2), 108.8 (C-1′), 116.8 (×2), (C-3 and C-2′)[a], 117.4 (C-8)[a], 119.8 (C-6)[a], 124.2 (C-4a)[a], 125.6 (C-7)[a], 126.0 (C-8a)[a], 134.2 (C-9a)[a], 136.2 (C-4)[a], 153.9 (C-10a), 159.8 (C-9), 181.3 and 185.2 (C═O). [Found: C, 67.1%; H, 4.8%; M^+ 341. Calc. for $C_{19}H_{20}O_6$: C, 66.9%; H, 5.0%; M 341].

9-Methoxy-2-(2′-dioxolanopropyl)-3,4-dihydronaphtho[2,3-*b*]pyran-5,10-dione (19). The quinone **18** (10 mg, 0.03 mmol) was hydrogenated as described earlier to afford after PLC using EtOAc : hexane (3 : 7) as eluent the product quinone **19** (8 mg, 80%) as a thick red oil. ν_{max} 1674 cm^{-1}; δ_H 1.28 (3H, s, 3′-H), 2.21 (1H, m, 1′-H), 2.28 (1H, m, 1′-H), 2.45 (1H, m, 3-Ha), 2.47 (1H, m, 3-He), 2.64 (1H, m, 4-Ha), 2.70 (1H, m, 4-He), 3.98 (4H, m, OCH_2CH_2O), 3.99 (3H, s, OCH_3), 4.11 (1H, m, 2-H), 7.22 (1H, dd, *J* 8.2 and 1.4, 8-H), 7.60 (1H, t, *J* 8.2, 7-H), 7.74 (1H, dd, *J* 8.2 and 1.4, 6-H). δ_C 24.1 (C-3′), 26.7 (C-3), 36.8 (C-4), 39.8 (C-1′), 55.8 (OCH_3), 64.6 and 65.0 (OCH_2CH_2O), 78.1 (C-2), 115.7 (C-2′), 118.6 (C-8)[a], 120.1 (C-7)[a], 120.4 (C-5a)[a], 120.6 (C-4a)[a], 134.7 (C-9a)[a], 135.2 (C-6)[a], 156.3 (C-10a)[b], 156.4 (C-9)[b], 177.8 and 185.2 (C═O). HRMS: Calc. for $C_{19}H_{20}O_6$: 344.12499. Found: 344.12584.

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