

First Synthesis of 9,10-Dimethoxy-2-methyl-1,4-anthraquinone: A Naturally Occurring Unusual Anthraquinone

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Keywords: Anthraquinones / Natural products / Radical reactions / Total synthesis

The synthesis of 9,10-dimethoxy-2-methyl-1,4-anthraquinone, an unusual quinone, was achieved in five steps from *p*-benzoquinone. A Kochi–Anderson radical methylation features as the key step in the synthesis. The chemistry of a cyclopropa-1,4-anthracenedione is also described.

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Introduction

Anthraquinones and their derivatives have traditionally received a great deal of attention.^[1a,1b] They are embodied in a variety of natural products, such as anthracyclines,^[1c,1d] dymenins,^[1e] and angucyclines,^[1f] chemotherapeutics, such as mitoxantrones^[1g] and rhein,^[1h] and synthetic dye-stuffs.^[1i] 9,10-Anthraquinones abound in the literature and are extensively studied. In contrast, anthraquinones with other tautomeric forms are infrequently found. However, recently 1,4-anthraquinones have been shown to be useful as tumor-cell-growth inhibitors,^[2] optoelectronic dyes,^[3] and organic conductors.^[4] They are also recognized as building blocks for broad-spectrum anticancer drugs like daunomycin, adriamycin, etc.^[5] Interest in the synthesis and in the evaluation of the bioactivity of 1,4-anthracenediones like **1** and **2** has grown significantly since the publication of the seminal work of Hua et al. (Figure 1).^[6]

In 1989, Singh et al. reported the isolation of 1,4-anthraquinone **3** from the heartwood of *Tectona grandis*,^[7] (commonly known as Sagon)^[8] recorded in traditional medicines, and elucidated its structure by NMR spectroscopic studies. To date, this molecule constitutes the lone example of a natural 1,4-anthraquinone in which both C9 and C10 are occupied by a methoxy group, whereas other derivatives such as **4–7**^[9,10] are substituted only at C10. The substitution pattern of **3** is unique and striking in that its putative biogenetic precursor, 9,10-dihydroxy-1,4-anthraquinone,^[11] has eluded chemical synthesis and characterization owing to its fast tautomerization to the more-stable 1,4-dihydroxy-9,10-anthraquinone. In view of this intriguing substitution pattern, we embarked upon the development of the synthe-

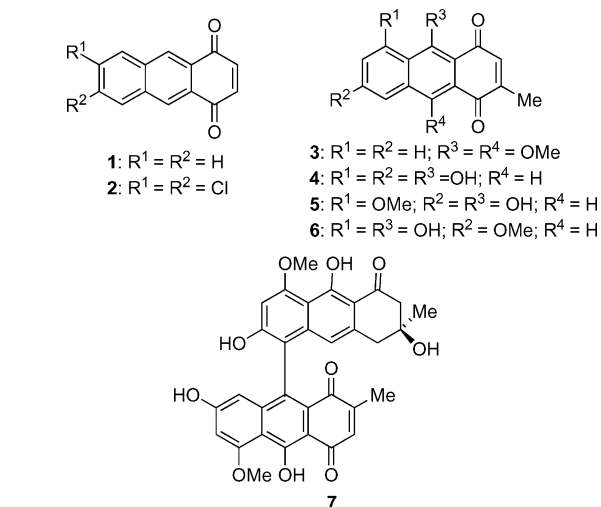


Figure 1. Structures of naturally occurring 1,4-anthraquinones.

sis of 9,10-dioxygenated 1,4-anthraquinones. Herein, we describe a short first synthesis of naturally occurring 1,4-anthraquinone **3**.

Results and Discussion

Very few synthetic methods for 9,10-dioxygenated 1,4-anthraquinones are available in the literature,^[12] and it was concluded that these methods would not qualify for the synthesis of target anthraquinone **3**. Calculations performed by using the Gaussian 03 program^[13] revealed that 2-methyl-9,10-dimethoxy-1,4-anthraquinone (**3**) is 7.84 kcal/mol less stable than isomeric 2-methyl-1,4-dimethoxy-9,10-anthraquinone. Considering its lower stability, we explored the chemistry of cyclopropane-fused anthraquin-

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one **8** and expected that the cyclopropane ring would prevent its tautomerization into **9** and serve as the surrogate of the required C2 CH₃ group.

Commercially available 4-methoxyphenol was converted into bicycloheptenedione **10**^[14] in a three-step reaction sequence that included (i) oxidation with phenyliodonium diacetate (PIDA), (ii) cyclopropanation, and (iii) ketal hydrolysis. Quinone monoketal **11** was prepared in 97% yield from 4-methoxyphenol by oxidation with PIDA (1.2 equiv.)^[15] in methanol. This was then treated with a solution of the sulfur ylide generated in situ by the action of sodium hydride with trimethylsulfoxonium iodide in DMSO. The reaction provided a mixture of bicycloheptenones **10** and **12**. Hydrolysis of the mixture with dilute hydrochloric acid in methanol at room temperature generated **10** in good yield. The Hauser annulation^[16] of compound **10** with 3-phenylsulfanylphthalide **13**^[17] in the presence of lithium *tert*-butoxide at –60 °C provided **8** in 48% yield. The singlet at $\delta = 13.7$ ppm in the ¹H NMR spectrum of **8** indicated the formation of the 9,10-dihydroxyanthracenedione structure. The IR, ¹³C NMR, and MS data were also in agreement with the structure. X-ray crystallographic analysis (Figure 2) further confirmed the structure. Methylation of the two hydroxy groups in **8** with Me₂SO₄–K₂CO₃ afforded **14** in 65% yield. Similar to **8**, compound **14** was fully characterized (Scheme 1).

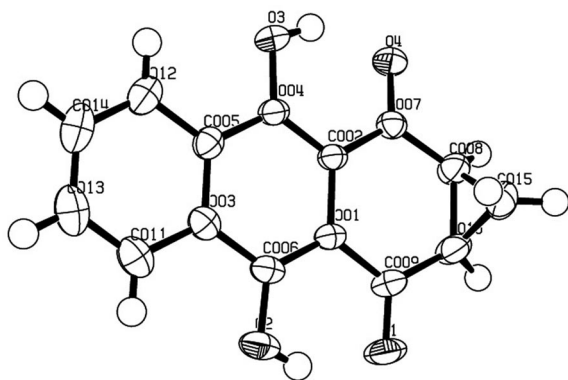
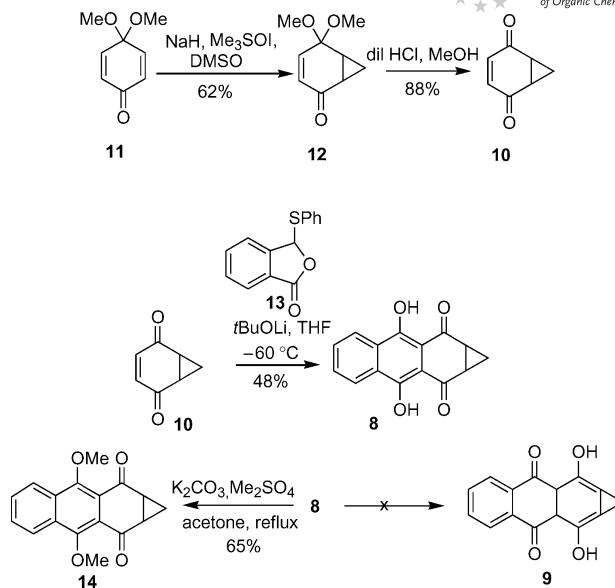


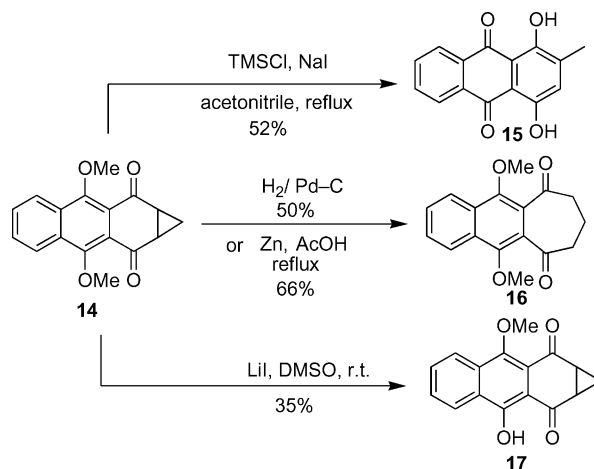
Figure 2. ORTEP diagram of compound **8**.

Cleavage of the cyclopropane ring in **14** (Scheme 2) for the generation of a methyl group was attempted with various reagents, but could not be achieved. With reagents such as PtCl₂/xylene,^[18] Rh₂(OAc)₄,^[19] FeCl₃–TMSCl, etc., quinone **14** remained unchanged. The use of reagents such as ZnI₂, LiI–DMSO, TMSCl–NaBr,^[20] and AcOH–HCl,^[21] which are known to be effective for the ring opening of cyclopropyl ketones, produced demethylated cyclopropa-1,4-anthraquinones **17** and **8**. TMSCl–NaI^[20] furnished 2-methylquinizarin (**15**)^[22] in good yield, which was probably formed through competing ring opening and demethylative tautomerization. Attempted reduction of compound **14** with H₂/Pd–C or Zn/AcOH produced ring-expansion product **16**. The structure of compound **16** was established by

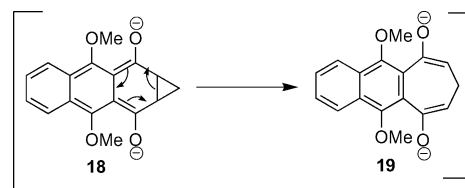


Scheme 1. Preparation of tetracyclic quinone **14**.

its ¹H NMR, ¹³C NMR, and MS data. The facile formation of **16** could be explained in terms of valence isomerism of dianion **18** into intermediate **19** (Scheme 3).



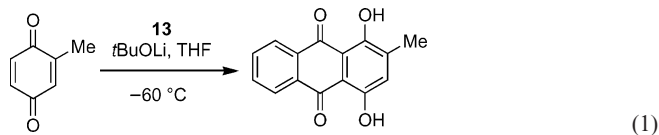
Scheme 2. Attempted ring opening of cyclopropane **14**.



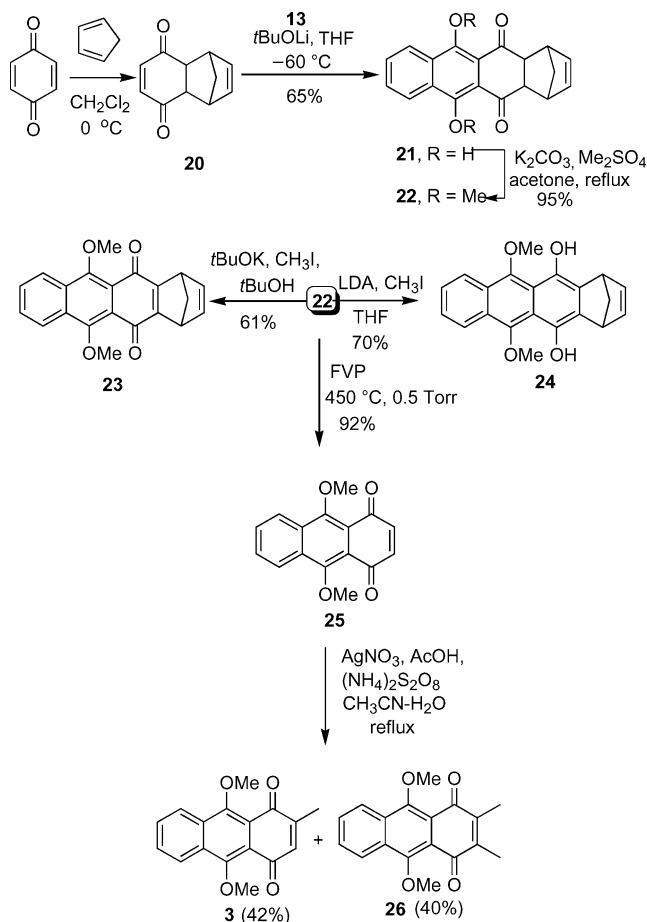
Scheme 3. Mechanism of formation of **16**.

In an alternative pathway, we decided to utilize naphth-acenedione **22**. Incorporation of a methyl group at the annular position of **22** followed by a retro Diels–Alder reaction

by using flash vacuum pyrolysis (FVP) was thought to give target molecule **3**. It may be added that Hauser annulation of 2-methyl-*p*-benzoquinone with **13** gives 2-methyl-9,10-anthraquinone **20** with **13**^[17] [Equation (1)]. The Hauser annulation of compound **20** with **13**^[17] in the presence of lithium *tert*-butoxide at $-60\text{ }^{\circ}\text{C}$ provided naphthacenedione **21**^[24] in 65% yield. *O*-Methylation of the two hydroxy groups in **21** with $\text{Me}_2\text{SO}_4\text{--K}_2\text{CO}_3$ gave pentacyclic quinone **22**^[24] in 95% yield (Scheme 4). The singlet at $\delta = 4.05$ ppm in the ^1H NMR spectrum was indicative of the methoxy groups. Attempted *C*-methylation of **22** with potassium *tert*-butoxide in *tert*-butyl alcohol and methyl iodide was not successful. The reaction gave oxidized naphthacenedione **23** in 53% yield. The absence of signals at $\delta = 3.57$ ppm in the ^1H NMR spectrum and the presence of a peak at $\delta = 132.0$ ppm in ^{13}C NMR spectrum, which corresponds to a quaternary carbon atom, were suggestive of the formation of **23**. Treatment of **22** with lithium diisopropylamide (LDA) in THF and methyl iodide also failed to give the desired *C*-methylation product. Instead, it resulted in naphthacene **24**, which was fully characterized by its spectroscopic data.



Following the failure to introduce the methyl group at the annular position of **22**, we turned to the utilization of anthracenedione **25** (Scheme 4). Compound **25** was obtained by retro [4+2] cycloaddition by flash vacuum pyrolysis (FVP).^[24] Initially the reaction was examined in solution phase under thermal conditions. Heating of **22** in *o*-dichlorobenzene or toluene to effect the retro Diels–Alder reaction was moderately successful ($\approx 30\%$ yield). Direct heating under vacuum (0.1 mm) or atmospheric pressure (760 mm) furnished only 20% of the retro product **25** along with a large amount of decomposed material. Initially 1,4-conjugate addition of $\text{CH}_3\text{MgI/Cu}^{\text{I}}$ salts and Me_2CuLi were attempted for the introduction of a methyl group at C2. However, both attempts failed to give any tractable product corresponding to the methylation. For the direct formation of **3**, we first attempted the recently reported Ghosh protocol involving a sulfur ylide.^[25] Treatment of **25** with the ylide from trimethylsulfonium iodide followed by workup of the mixture provided a mixture of products. The ^1H NMR spectrum of the mixture indicated formation of products other than the desired one. Fortunately, the Kochi–Anderson procedure^[26] for alkylation of quinones worked satisfactorily for **25**. To the best of our knowledge, such radical alkylations have been limited to the chemistry of 1,4-benzoquinones and naphthoquinones.^[27] The behavior of 1,4-anthraquinones, particularly the functionalized ones, to the radical alkylations has not been reported. When treated with silver nitrate, acetic acid, and ammonium persulfate in a 4:3 mixture of acetonitrile and water, compound



Scheme 4. Preparation of 9,10-dimethoxy-2-methyl-1,4-anthraquinone (**3**).

25, prepared by FVP of **22** resulted in a 1:1 mixture of monoalkylated and dialkylated products: 9,10-dimethoxy-2-methyl-1,4-anthraquinone (**3**) and 9,10-dimethoxy-2,3-dimethyl-1,4-anthraquinone (**26**). Both compounds were fully characterized by ^1H NMR, ^{13}C NMR, HRMS, and IR data. All the spectroscopic data of compound **3** were in full agreement with those previously reported^[7] and distinctly different from those of the *O*-methyl derivative^[28] of **15**, prepared by routine methylation with $\text{Me}_2\text{SO}_4\text{--K}_2\text{CO}_3$. A detailed study of radical alkylations of 1,4-anthraquinones is underway for the generation of newer analogues of the title compound.

Conclusions

This work has provided the first short synthesis of naturally occurring 9,10-dimethoxy-2-methyl-1,4-anthraquinone (**3**), confirming its structure. It has illustrated a new avenue for the convenient synthesis of alkyl derivatives of 1,4-anthraquinones by Kochi–Anderson alkylation of a 1,4-anthraquinone.

Experimental Section

General: Melting points are uncorrected. IR spectra were recorded with a Thermo Nicolet Nexus 870 FTIR spectrophotometer by

using KBr pellets. ^1H and ^{13}C NMR spectra of the samples in the indicated solvents were recorded with 200 MHz or 400 MHz spectrometers (Bruker) with residual CHCl_3 as the internal standard. Mass spectra were taken by using a VG Autospec M mass spectrometer. Dry solvents used for reactions were purified before use according to the standard protocols. All solvents for chromatography were distilled prior to use. Columns were prepared with silica gel (60–120 or 230–400 mesh).

Procedure for the Retro Diels–Alder Reaction: A long (40 cm) high-quality glass tube open at both ends was fixed horizontally in a pyrolytic chamber connected in series with a rheostat and an ammeter. One end of the glass tube was closed and a vial containing the substance to be pyrolyzed was pushed inside till it was adjacent to the hot coil. A cotton plug was placed to cover the open end which was then connected to a high-vacuum pump (0.05 Torr). The material in the vial was heated with a spirit lamp till it melted (furnace temperature: 400–500 °C, monitored by a thermo couple). Heating was continued until all the material was collected at the other end of the furnace in the cold zone (most of the materials solidified when the glass tube was cooled by a cotton plug dipped in CH_2Cl_2).

9,10-Dimethoxy-2-methyl-1,4-anthraquinone (3) and 9,10-Dimethoxy-2,3-dimethyl-1,4-anthraquinone (26): A solution of **25** (30 mg, 0.11 mmol), silver nitrate (9.5 mg, 0.06 mmol), and acetic acid (0.02 mL, 0.35 mmol) in a mixture of water (3 mL) and acetonitrile (4 mL) was heated at reflux and ammonium persulfate (40.9 mg, 0.18 mmol) in water (3 mL) was added over 30 min. The reaction mixture was stirred for 30 min. The cooled solution was extracted with dichloromethane (2×20 mL). The combined organic extracts were washed successively with water (10 mL) and brine (5 mL), dried (anhydrous Na_2SO_4), filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel afforded compound **3** (13 mg, 42%) and **26** (13 mg, 40%) as yellow solids. Data for compound **3**: $R_f = 0.55$ (ethyl acetate/petroleum ether, 1:3). M.p. 140–141 °C. UV/Vis (EtOH): $\lambda_{\text{max}} = 210$, 236, 265, 297, 416 nm. IR (KBr): $\tilde{\nu} = 2964$, 1656, 1351, 1250 cm^{-1} . ^1H NMR (200 MHz, CDCl_3 , 25 °C): $\delta = 8.36$ –8.41 (m, 2 H), 7.72–7.77 (m, 2 H), 6.80 (q, $^3J_{\text{H,H}} = 1.6$ Hz, 1 H), 4.07 (s, 3 H), 4.05 (s, 3 H), 2.19 (d, $^3J_{\text{H,H}} = 1.6$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3 , 25 °C): $\delta = 184.8$, 184.0, 155.4, 155.1, 148.7, 137.1, 132.7, 132.5, 129.9, 124.8, 119.61, 119.57, 62.97, 62.92, 16.5 (two CH signals were not resolved) ppm. HRMS (ESI, 70 eV): calcd. for $\text{C}_{17}\text{H}_{15}\text{O}_4$ [$\text{M} + \text{H}$] $^+$ 283.0970; found 283.0961. Data for compound **26**: $R_f = 0.60$ (ethyl acetate/petroleum ether, 1:3). M.p. 110–111 °C. UV/Vis (EtOH): $\lambda_{\text{max}} = 210$, 233, 271, 410 nm. IR (KBr): $\tilde{\nu} = 2933$, 1654, 1347, 1263 cm^{-1} . ^1H NMR (400 MHz, CDCl_3 , 25 °C): $\delta = 8.34$ –8.40 (m, 2 H), 7.68–7.75 (m, 2 H), 4.07 (s, 6 H), 2.18 (s, 6 H) ppm. ^{13}C NMR (100 MHz, CDCl_3 , 25 °C): $\delta = 184.4$, 154.7, 144.5, 132.5, 129.7, 124.8, 119.8, 63.1, 13.2 ppm. HRMS (ESI, 70 eV): calcd. for $\text{C}_{18}\text{H}_{17}\text{O}_4$ [$\text{M} + \text{H}$] $^+$ 297.1127; found 297.1123.

3,8-Dihydroxy-1a,9a-dihydro-1H-cyclopropa[*b*]anthracene-2,9-dione (8): To a stirred solution of lithium *tert*-butoxide (196.7 mg, 2.46 mmol) in THF (10 mL) at –60 °C (chloroform/liquid N_2 bath) under an argon atmosphere was added a solution of **13**^[17] (198.4 mg, 0.82 mmol) in THF (5 mL). The resulting yellowish solution was stirred at –60 °C for 25 min, after which a solution of **10** (100 mg, 0.82 mmol) in THF (5 mL) was slowly added. The cooling bath was removed after about 1 h at –60 °C, and the reaction mixture was brought to room temperature over a period of 1 h and further stirred for 3 h. The reaction was then quenched with 10% aq. NH_4Cl solution (10 mL), and the resulting mixture was concentrated in vacuo. An orange solid appeared, which was dis-

solved in ethyl acetate (50 mL) and washed with water (15 mL). The aqueous layer was extracted with ethyl acetate (2×15 mL). The combined extracts were washed with H_2O (15 mL), brine (15 mL), dried (anhydrous Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to furnish **8** as an orange yellow solid (87 mg, 42%). $R_f = 0.70$ (ethyl acetate/petroleum ether, 1:3). M.p. 160–162 °C. UV/Vis (CHCl_3): $\lambda_{\text{max}} = 253$, 278, 407, 425 nm. IR (KBr): $\tilde{\nu} = 3448$, 1633, 1398, 1251, 1039, 842 cm^{-1} . ^1H NMR (400 MHz, CDCl_3 , 25 °C): $\delta = 13.7$ (s, 2 H), 8.43–8.48 (m, 2 H), 7.74–7.79 (m, 2 H), 2.66–2.71 (m, 2 H), 1.87–1.95 (m, 1 H), 1.47–1.53 (m, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl_3 , 25 °C): $\delta = 198.5$, 156.4, 130.0, 129.0, 124.5, 104.1, 27.8, 19.2 ppm. HRMS: (ESI, 70 eV): calcd. for $\text{C}_{15}\text{H}_{11}\text{O}_4$ [$\text{M} + \text{H}$] $^+$ 255.0657; found 255.0656.

Bicyclo[4.1.0]hept-3-ene-2,5-dione (10):^[14b] Compound **12** (500 mg, 2.98 mmol) was dissolved in methanol (5 mL) containing 10% hydrochloric acid (5 drops). The mixture was then stirred for 45 min. The reaction was quenched by addition of water (10 mL) and extracted with ethyl acetate (2×30 mL). After usual workup, the crude product was subjected to column chromatography to afford compound **10** (320 mg) as a yellow-colored, low-melting solid. Yield: 88%. $R_f = 0.45$ (ethyl acetate/petroleum ether, 1:3). ^1H NMR (400 MHz, CDCl_3 , 25 °C): $\delta = 6.43$ (s, 2 H), 2.50–2.56 (m, 2 H), 1.70–1.78 (m, 1 H), 1.64–1.70 (m, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl_3 , 25 °C): $\delta = 194.7$, 136.8, 27.4, 19.6 ppm.

4,4-Dimethoxycyclohexa-2,5-dienone (11):^[15,29] To a stirred solution of 4-methoxyphenol (100 mg, 0.81 mmol) in dry MeOH (2 mL) at 0 °C under a nitrogen atmosphere was added phenyliodonium diacetate (PIDA; 285.6 mg, 0.89 mmol), and the resulting solution was stirred for 10 min. The reaction was quenched by addition of saturated NaHCO_3 solution (5 mL) and extracted with diethyl ether (2×25 mL). After usual workup, the crude product was subjected to column chromatography to afford compound **11** (120 mg) as a light-yellow-colored liquid. Yield: 97%. $R_f = 0.6$ (ethyl acetate/petroleum ether, 1:3). ^1H NMR (200 MHz, CDCl_3 , 25 °C): $\delta = 6.83$ (dd, $^3J_{\text{H,H}} = 13.2$, 3.2 Hz, 2 H), 6.29 (dd, $^3J_{\text{H,H}} = 13.2$, 3.2 Hz, 2 H), 3.38 (s, 6 H) ppm.

5,5-Dimethoxybicyclo[4.1.0]hept-3-en-2-one (12): To a solution of sodium hydride (374 mg, 15.6 mmol) in DMSO (10 mL) was added trimethylsulfoxonium iodide (3.43 gm, 15.6 mmol), and the solution was stirred for 20 min. To this solution was dropwise added **11** (1.2 g, 7.79 mmol) in DMSO (2 mL) over 10 min. Stirring was continued for 1 h. The reaction was quenched by addition of water (10 mL) and extracted with diethyl ether (2×40 mL). The combined extracts were subjected to usual workup followed by column chromatography to afford compound **12** (800 mg) as a light-yellow-colored liquid. Yield: 61.5%. $R_f = 0.5$ (ethyl acetate/petroleum ether, 1:3). ^1H NMR (400 MHz, CDCl_3 , 25 °C): $\delta = 6.35$ (d, $^3J_{\text{H,H}} = 11.2$ Hz, 1 H), 5.86 (d, $^3J_{\text{H,H}} = 10.8$ Hz, 1 H), 3.43 (s, 3 H), 3.31 (s, 3 H), 2.02–2.07 (m, 2 H), 1.30–1.39 (m, 1 H), 0.94–1.00 (m, 1 H) ppm.

3-Phenylthiophthalide (13): To a stirred solution of phthalaldehydic acid (200 mg, 1.33 mmol) and *p*-toluenesulfonic acid (10 mg) in dry benzene (5 mL) was added thiophenol (0.3 mL, 1.6 mmol). The mixture was heated at reflux for 2 h with a Dean-stark apparatus. The reaction mixture was then cooled and benzene was removed to obtain a crude solid. The crude product was recrystallized from ethyl acetate/petroleum ether to give the pure crystalline product (290 mg, 90%). ^1H NMR (200 MHz, CDCl_3 , 25 °C): $\delta = 7.81$ –7.46 (m, 9 H), 6.72 (s, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl_3 , 25 °C): $\delta = 169.2$, 146.1, 134.4, 133.7, 130.3, 130.1, 129.1, 129.0, 126.2, 125.4, 123.5, 86.5 ppm.

3,8-Dimethoxy-1a,9a-dihydro-1H-cyclopropa[b]anthracene-2,9-dione (14): Compound **8** (100 mg, 0.39 mmol) was dissolved in dry acetone (5 mL) under a nitrogen atmosphere. To this solution was added dry K_2CO_3 (269 mg, 1.95 mmol) and Me_2SO_4 (98 mg, 0.07 mL, 0.78 mmol; freshly washed with cold water, saturated $NaHCO_3$ solution, brine, and dried with anhydrous K_2CO_3). After 2 h at reflux, on completion of the reaction, the inorganic salts were filtered and the filtrate concentrated. The residue was diluted with ethyl acetate (5 mL), stirred with Et_3N (2 mL) at room temperature, and stirred for 30 min. The reaction mixture was then diluted with ethyl acetate (50 mL), washed with 5% aq. HCl solution (5 mL) and water (15 mL), dried with anhydrous Na_2SO_4 , and concentrated under reduced pressure to obtain a yellow residue. This was purified by column chromatography on silica gel to give **14** as a pure-yellow solid (73 mg, 66%). R_f = 0.6 (ethyl acetate/petroleum ether, 1:3). M.p. 166–168 °C. UV/Vis ($CHCl_3$) λ_{max} = 254, 345 nm. IR (KBr): $\tilde{\nu}$ = 3081, 2931, 1681, 1347, 1261, 1093, 804, 744 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.28–8.33 (m, 2 H), 7.67–7.72 (m, 2 H), 4.06 (s, 6 H), 2.67–2.73 (m, 2 H), 1.67–1.76 (m, 1 H), 1.56–1.63 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 193.6, 153.2, 132.1, 129.1, 124.2, 119.7, 64.0, 27.4, 18.4 ppm. HRMS: (ESI, 70 eV): calcd. for $C_{17}H_{15}O_4$ [$M + H$]⁺ 283.0970; found 283.0962.

1,4-Dihydroxy-2-methylanthraquinone (15):^[22] To a solution of compound **14** (30 mg, 0.11 mmol) in acetonitrile (2 mL) was added sodium iodide (24 mg, 0.16 mmol) and trimethylsilyl chloride (0.02 mL, 0.16 mmol). The solution was heated at reflux for 2 h. The reaction mixture was then diluted at room temperature with water and extracted with ethyl acetate (2 × 20 mL). The combined extracts were washed successively with water (10 mL), saturated aqueous solution of sodium thiosulfate (5 mL), and brine (5 mL). The organic layer was dried (anhydrous Na_2SO_4), filtered, and concentrated under reduced pressure. Column chromatography of the residue afforded compound **15** as an orange solid (18 mg, 66%). R_f = 0.70 (ethyl acetate/petroleum ether, 1:5). 1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 13.35 (s, 1 H), 12.96 (s, 1 H), 8.30–8.38 (m, 2 H), 7.78–7.86 (m, 2 H), 7.16 (s, 1 H), 2.37 (d, $^3J_{H,H}$ = 0.7 Hz, 3 H) ppm.

5,11-Dimethoxy-8,9-dihydro-7H-cyclohepta[b]naphthalene-6,10-dione (16)

Method A: To a stirred solution of **14** (30 mg, 0.11 mmol) in dry methanol (2 mL) was added 10% Pd–C (50 mg). The resulting stirred mixture was exposed to a balloon of hydrogen gas for 6 h. The mixture was then filtered through Celite. The filtrate was concentrated, and column chromatography of the crude product gave compound **16** as a white solid (15 mg, 50%). R_f = 0.50 (ethyl acetate/petroleum ether, 1:3).

Method B: To a stirred solution of compound **14** (30 mg, 0.11 mmol) in acetic acid (5 mL) was added Zn dust (21.6 mg, 0.33 mmol), and the mixture was heated at reflux for 1.5 h. The reaction mixture was cooled, diluted with water, and extracted with ethyl acetate (2 × 20 mL). The organic layer was washed successively with water (10 mL), saturated aqueous solution of sodium hydrogen carbonate (5 mL), and brine (5 mL), dried (anhydrous Na_2SO_4), filtered, and concentrated under reduced pressure. Column chromatography of the residue afforded compound **16** as a white solid (20 mg, 66%). R_f = 0.50 (ethyl acetate/petroleum ether, 1:3). M.p. 85–86 °C. IR (KBr): $\tilde{\nu}$ = 2925, 1693, 1457, 1353, 1085 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.17–8.23 (m, 2 H), 7.59–7.67 (m, 2 H), 4.02 (s, 6 H), 2.84 (t, $^3J_{H,H}$ = 6.4 Hz, 4 H), 2.04–2.10 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C):

δ = 203.2, 149.7, 130.4, 128.2, 127.1, 123.7, 65.0, 43.5, 19.1 ppm. HRMS: (ESI, 70 eV): calcd. for $C_{17}H_{17}O_4$ [$M + H$]⁺ 285.1127; found 285.1124.

3-Hydroxy-8-methoxy-1a,9a-dihydro-1H-cyclopropa[b]anthracene-2,9-dione (17): To a stirred solution of **14** (30 mg, 0.11 mmol) in dry dimethyl sulfoxide (2 mL) was added lithium iodide (21.4 mg, 0.16 mmol). The resulting mixture was stirred at room temperature for 3 h. The reaction mixture was then diluted with water and extracted with ethyl acetate (2 × 20 mL). The organic layer was washed successively with water (10 mL) and brine (5 mL), then dried (anhydrous Na_2SO_4), filtered, and concentrated under reduced pressure. Column chromatography of the residue afforded compound **17** as a light-yellow solid (10 mg, 35%). R_f = 0.40 (ethyl acetate/petroleum ether, 1:3). M.p. 125–126 °C. IR (KBr): $\tilde{\nu}$ = 3450, 2927, 1683, 1612, 1434, 1380, 1259, 1099, 1039 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 13.7 (s, 1 H), 8.48 (d, $^3J_{H,H}$ = 8 Hz, 1 H), 8.28 (d, $^3J_{H,H}$ = 8 Hz, 1 H), 7.72–7.78 (m, 1 H), 7.65–7.72 (m, 1 H), 4.05 (s, 3 H), 2.65–2.77 (m, 2 H), 1.81–1.87 (m, 1 H), 1.58–1.64 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 200.1, 193.3, 158.7, 150.9, 133.2, 130.9, 128.9, 128.4, 124.7, 124.2, 116.4, 106.7, 63.3, 29.5, 29.1, 19.7 ppm. HRMS: (ESI, 70 eV): calcd. for $C_{16}H_{13}O_4$ [$M + H$]⁺ 269.0814; found 269.0810.

1,4,4a,8a-Tetrahydro-1,4-methanonaphthalene-5,8-dione (20):^[30] To a solution of *p*-benzoquinone (10.8 g, 0.1 mol) in dichloromethane (30 mL) at 0 °C was added freshly distilled cyclopentadiene (6.82 g, 0.104 mol) over 45 min. Stirring was continued for 1 h at 0 °C and for 0.5 h at room temperature. The resulting mixture was concentrated and then diluted with petroleum ether (50 mL), cooling of which in an ice bath yielded pale-yellow crystals. These were collected by filtration, washed with petroleum ether, and air dried to afford Diels–Alder adduct **20** (15 g). Concentration of the filtrate to about half the volume and cooling afforded a second crop of **20** (1.5 g). The combined yield of **20** was 16.5 g, 97%. 1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.57 (s, 2 H), 6.06 (s, 2 H), 3.55 (s, 2 H), 3.22 (s, 2 H), 1.54 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H), 1.43 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H) ppm.

6,11-Dihydroxy-1,4,4a,12a-tetrahydro-1,4-methanonaphthacene-5,12-dione (21):^[31] This compound was prepared as a yellow solid in 65% yield by condensation of **20** with **13** according to the procedure of annulation described for the preparation of **8**. The crude product was purified by column chromatography on silica gel (R_f = 0.70; ethyl acetate/petroleum ether, 1:3) to furnish **21**. M.p. 143–144 °C. IR (KBr): $\tilde{\nu}$ = 3421, 3068, 2995, 1719, 1609, 1495, 1460, 1397, 1242, 1043, 856, 781, 706 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 14.48 (s, 2 H), 8.41–8.47 (m, 2 H), 7.72–7.79 (m, 2 H), 6.06 (s, 2 H), 3.72 (s, 2 H), 3.48 (s, 2 H), 1.53–1.61 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 202.8, 156.5, 135.5, 130.5, 129.4, 124.6, 107.5, 50.1, 49.3, 48.7 ppm. HRMS: (ESI, 70 eV): calcd. for $C_{14}H_9O_4$ [$M - C_5H_5$]⁺ 241.0501; found 241.0484.

6,11-Dimethoxy-1,4,4a,12a-tetrahydro-1,4-methanonaphthacene-5,12-dione (22):^[24] This compound was prepared as a yellow solid in 95% yield from **21** by following the procedure of methylation described for the preparation of **14**. The crude product was purified by column chromatography on silica gel (R_f = 0.50; ethyl acetate/petroleum ether, 1:3) to furnish **22**. M.p. 160–162 °C. UV/Vis ($CHCl_3$) λ_{max} = 255, 405, 425 nm. IR (KBr): $\tilde{\nu}$ = 3468, 2998, 1685, 1613, 1564, 1392, 1346, 1239, 1162, 1075, 971, 780, 704 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.26–8.32 (m, 2 H), 7.65–7.71 (m, 2 H), 6.11 (s, 2 H), 4.05 (s, 6 H), 3.54 (s, 2 H), 3.49 (s, 2 H), 1.60 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H), 1.48 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 197.5, 152.1, 136.3, 131.7,

129.1, 125.0, 124.3, 64.0, 52.9, 48.4, 46.3 ppm. HRMS: (ESI, 70 eV): calcd. for $C_{16}H_{13}O_4 [M - C_5H_5]^+$ 269.0814; found 269.0791.

1,4-Dihydro-6,11-dimethoxy-1,4-methanonaphthacene-5,12-dione (23): Compound **22** (50 mg, 0.15 mmol) was dissolved in *tert*-butyl alcohol (5 mL) containing potassium *tert*-butoxide (25 mg, 0.22 mmol). To this mixture was added iodomethane (0.02 mL, 0.30 mmol), and the resulting mixture was stirred at room temperature for 2 h. The mixture was then diluted with water and extracted with ethyl acetate (2×20 mL). The combined extracts were washed successively with water (10 mL), dilute hydrochloric acid (5 mL), and brine (5 mL). The organic layer was then dried with anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. Column chromatography of the residue afforded compound **23** as a light-yellow solid (30 mg, 61%). $R_f = 0.60$ (ethyl acetate/petroleum ether, 1:3). M.p. 150–151 °C. IR (KBr): $\tilde{\nu} = 2933, 1693, 1349, 1267, 1025\text{ cm}^{-1}$. 1H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 8.26\text{--}8.32$ (m, 2 H), 7.67–7.72 (m, 2 H), 6.65 (s, 2 H), 4.06 (s, 6 H), 3.57 (s, 2 H), 1.65 (d, $^3J_{H,H} = 8.8\text{ Hz}$, 1 H), 1.60 (d, $^3J_{H,H} = 8.8\text{ Hz}$, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 191.4, 153.7, 141.4, 133.5, 132.0, 129.3, 124.3, 121.5, 64.4, 42.4, 41.6\text{ ppm}$. HRMS: (ESI, 70 eV): calcd. for $C_{21}H_{17}O_5 [M + OH]^+$ 349.1076; found 349.1073.

1,4-Dihydro-5,12-dihydroxy-6,12-dimethoxy-1,4-methanonaphthacene (24): To a stirred solution of diisopropylamine (0.01 mL, 0.18 mmol) in THF (3 mL) cooled to -78°C was added *n*-butyllithium (0.15 mL, 0.18 mmol), and the reaction mixture was stirred for 15 min. Compound **22** (50 mg, 0.15 mmol) was added to this mixture. After 20 min at -78°C , iodomethane (0.05 mL, 0.75 mmol) was added, and then the mixture was stirred for 1 h. The mixture was brought to room temperature over 1 h and further stirred for 1–2 h. The reaction mixture was then diluted with water (10 mL) and extracted with ethyl acetate (2×20 mL). The combined extracts were washed successively with water (10 mL), dilute hydrochloric acid (5 mL), and brine (5 mL). The organic layer was dried with anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel afforded compound **24** as an orange solid (35 mg, 70%). $R_f = 0.55$ (ethyl acetate/petroleum ether, 1:3). M.p. 140–141 °C. IR (KBr): $\tilde{\nu} = 3448, 2942, 1648, 1346, 1276\text{ cm}^{-1}$. 1H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 8.32\text{--}8.37$ (m, 2 H), 7.65–7.75 (m, 2 H), 6.92 (s, 2 H), 4.25 (s, 2 H), 4.06 (s, 6 H), 2.33 (d, $^3J_{H,H} = 6.8\text{ Hz}$, 1 H), 2.29 (d, $^3J_{H,H} = 6.8\text{ Hz}$, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 181.0, 163.4, 155.4, 142.5, 132.7, 129.8, 124.9, 120.8, 72.0, 63.0, 48.8\text{ ppm}$. HRMS: (ESI, 70 eV): calcd. for $C_{16}H_{13}O_4 [M - H]^+$ 333.1127; found 333.1120.

9,10-Dimethoxyanthracene-1,4-dione (25):^[32] This compound was prepared as a yellow solid in 92% yield from **22** by following the flash vacuum pyrolytic procedure described above. The product was purified by column chromatography on silica gel ($R_f = 0.50$; ethyl acetate/petroleum ether, 1:3) to furnish **25**. M.p. 189–192 °C. IR (KBr): $\tilde{\nu} = 3442, 2933, 1658, 1610, 1561, 1397, 1344, 1079, 998\text{ cm}^{-1}$. 1H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 8.38\text{--}8.43$ (m, 2 H), 7.74–7.79 (m, 2 H), 6.91 (s, 2 H), 4.06 (s, 6 H) ppm.

Supporting Information (see footnote on the first page of this article): Copies of NMR spectra of all new compounds and comparative table for physical data of synthetic and natural **3**.

Acknowledgments

This research was supported by the Department of Science and Technology (DST), New Delhi. We are thankful to Dr. A. Patra and Dr. P. Pahari for helpful discussions and to Mr. L. Rajput for

the crystallographic data. S. R. is thankful to the Council of Science and Industrial Research, New Delhi, for her research fellowship. The 400 MHz NMR instrument and the CCD X-ray diffractometer were purchased under FIST program of the DST, New Delhi.

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Received: February 26, 2008
Published Online: April 29, 2008