69847-26-3; **6b**, 69847-27-4; **6c**, 4834-35-9; **6d**, 5133-12-0; **7a**, 66240-14-0; **7b**, 66240-30-0; **7c**, 66240-02-6; **7d**, 16277-49-9; **8a**, 66240-13-9; **8b**, 66240-31-1; **8c**, 57266-83-8; **8d**, 14760-53-3; methyl iodide, 74-88-4; aluminum tricyclohexoxide, 1971-69-3.

Supplementary Material Available: Complete proton magnetic resonance spectra, UV data, Infrared spectra, and tables summarizing mass spectra, fluorescence, and phenolate ultraviolet absorption data (21 pages). Ordering information is given on any current masthead page.

References and Notes

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Synthesis of Bromonaphthoquinones from 1,5-Dimethoxynaphthalene

Robert L. Hannan, Randy B. Barber, and Henry Rapoport*

Department of Chemistry, University of California, Berkeley, California 94720

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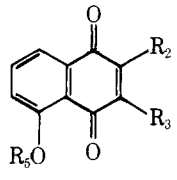
New regiospecific syntheses of 2-bromo-5-methoxy-1,4-naphthoquinone and 3-bromo-5-methoxy-1,4-naphthoquinone have been developed via 4,8-dimethoxy-1-naphthalenecarboxaldehyde, prepared by formylation of 1,5-dimethoxynaphthalene. The naphthaldehyde, on oxidation with *m*-chloroperbenzoic acid and hydrolysis of the intermediate formate, gave 4,8-dimethoxy-1-naphthol. Bromination followed by oxidation of the bromonaphthol gave 3-bromo-5-methoxy-1,4-naphthoquinone in 58% overall yield from 1,5-dimethoxynaphthalene. The naphthol may also be oxidized to 5-methoxy-1,4-naphthoquinone (juglone methyl ether), which was then brominated to give 2-bromo-5-methoxy-1,4-naphthoquinone in 49% overall yield from 1,5-dimethoxynaphthalene. These syntheses offer the advantages of ease of manipulation, increased yields, and purity.

2- and 3-Halo-1,4-naphthoquinones have recently been utilized effectively in the synthesis of naturally occurring anthraquinones because of their regiospecific reaction with ketene acetals.[1-4] The halonaphthoquinones of particular interest are derivatives of 5-hydroxy-1,4-naphthoquinine (**1a**, juglone), a natural product isolated from walnut shells, and include 2-bromo-5-methoxy-1,4-naphthoquinone (**1b**, 2-bromojuglone methyl ether) and 3-bromo-5-methoxy-1,4-naphthoquinone (**1c**, 3-bromojuglone methyl ether) as well as the corresponding hydroxyquinones 2-bromo-5-hydroxy-1,4-naphthoquinone (**1d**, 2-bromojuglone) and 3-bromo-5-hydroxy-1,4-naphthoquinone (**1e**, 3-bromojuglone) which are efficiently methylated to the corresponding ethers. Reported syntheses of the four bromoquinones give poor yields, contamination by the wrong isomer, and/or contamination by compounds containing more than one bromine; these objections led us to seek new syntheses.



1a, $R_5 = H; R_2 = H; R_3 = H$
b, $R_5 = CH_3; R_2 = Br; R_3 = H$
c, $R_5 = CH_3; R_2 = H; R_3 = Br$
d, $R_5 = H; R_2 = Br; R_3 = H$
e, $R_5 = H; R_2 = H; R_3 = Br$
f, $R_5 = CH_3; R_2 = H; R_3 = H$

The reported procedure for the synthesis of 2-bromojuglone methyl ester (**1b**, Scheme I) requires 5-methoxy-1-naphthol (**3**). The production of **3** directly from the cheap and readily available 1,5-dihydroxynaphthalene (**2**) under alkaline[5] or acidic conditions gives a mixture of all three possible products, naphthol, monoether **3**, and 1,5-dimethoxynaphthalene (**4**), with the desired monoether in less than 30% yield. A recently reported[6] synthesis of **3** by total methylation of **2** to **4** followed by monocleavage with sodium thioethoxide in DMF offered a much more attractive route to **3**, and we found that a slight excess of thioethoxide in DMF at 100 °C cleanly demethylated **4** to **3** in 91% yield; neither sodium thiophenoxide nor potassium hydroxide in diethylene glycol was as selective in its cleavage.

Even with a convenient preparation of 5-methoxy-1-naphthol in hand, the ultimate conversion to 2-bromojuglone methyl ether (**1b**) is poor. Naphthol **3** has been reported[7] to be brominated in refluxing CCl_4 (18 h) in 33% yield to 2-bromo-5-methoxy-1-naphthol (**5**). In our hands this reaction proceeds rapidly even at 0 °C in 97% yield; care must be taken, however, as excess bromine leads to polybromination and subsequent contamination of the quinone product. Oxidation of **5** with CrO_3–HOAc gives **1b** in 43% yield from **5** according to the report;[7] however, in our experience this oxidation proceeds poorly to give **1b** in an overall yield of about 15%. We

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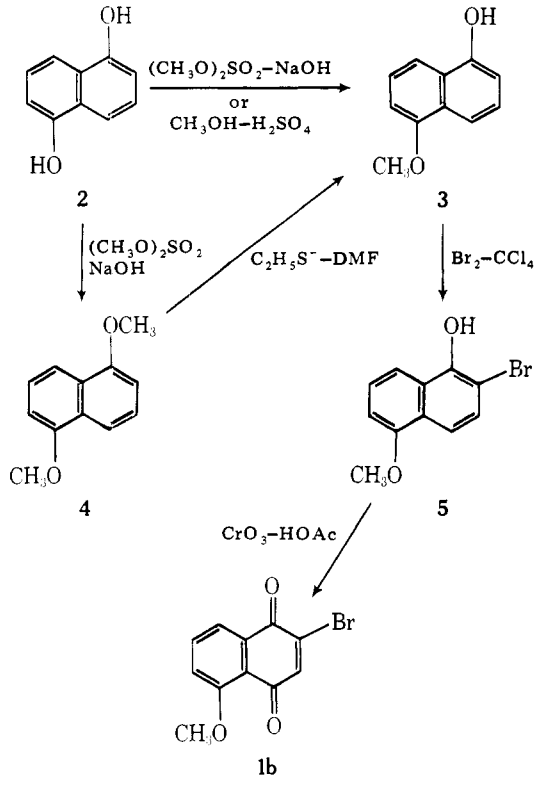
Scheme I. Synthesis of 2-Bromojuglone Methyl Ether (1b) via 5-Methoxy-1-naphthol (3)

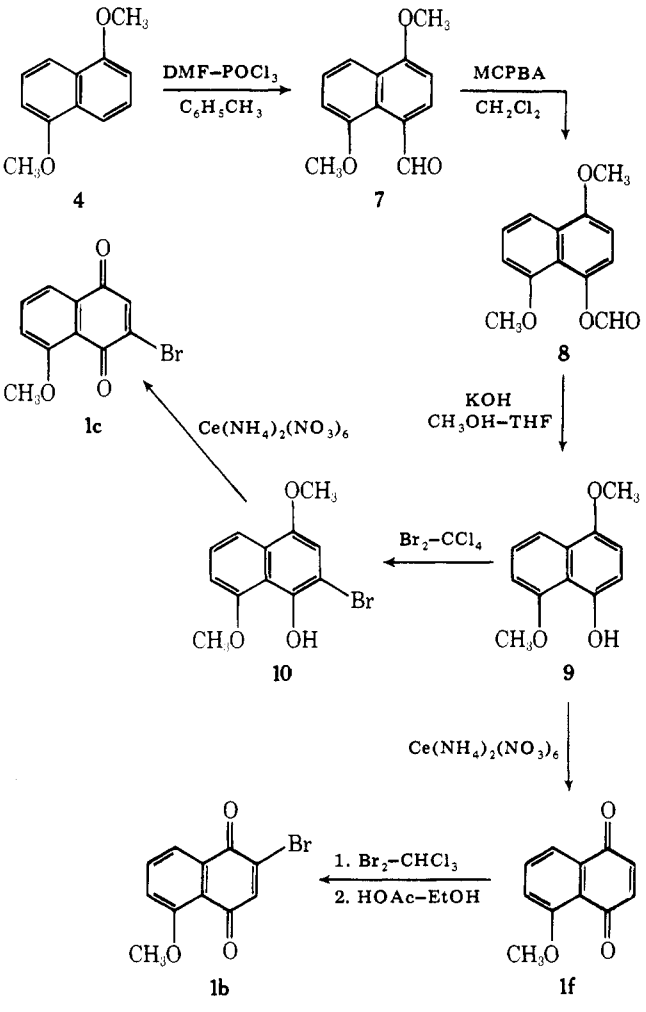


have attempted to improve the oxidation of **5** to **1b** with no success, although the low overall efficiency of this route is somewhat counterbalanced by the relatively high purity of the product bromoquinone **1b**, analyzed by gas chromatography and high pressure liquid chromatography (see Table I).

There is no reported direct synthesis of 3-bromojuglone methyl ether (**1c**); it may be prepared from **1e** by methylation with methyl iodide and silver oxide. Thus, the synthesis of **1e** proceeds from juglone, first by dibromination across the quinoid double bond with bromine in glacial acetic acid, followed by dehydrohalogenation in refluxing ethanol, to give **1e** in 84% yield. This procedure was first reported to give **1d**,[8] but this assignment was shown to be in error.[9] In our hands the overall yield from juglone never exceeded 66% and the bromojuglone produced was invariably contaminated with di- and tribrominated naphthoquinones. Brominating in chloroform at 0 °C followed by a trace of acetic acid and dehydrohalogenating in refluxing ethanol give mostly **1e** in 78% yield; the 3-bromo isomer is free of any polybrominated impurity, but is contaminated by 6–10% of 2-bromo isomer **1d**.

A serious limitation of the above synthesis of 3-bromojuglone methyl ether is the requirement for juglone (**1a**). Juglone has been synthesized by oxidation of 1,5-dihydroxynaphthalene (**2**); methods include oxidation with chromic acid,[10,11] peracetic acid,[12] and Fremy's salt,[13] as well as photochemical[14] and anodic oxidation.[15] Chromic acid oxidation is reported to proceed in 16% yield; our own experience and more recent reports[16] indicate that yields of less than 10% are typical. Fremy's salt is reported to oxidize **2** to a 1:1 mixture of 1,4-quinone and 1,2-quinone; large amounts of Fremy's salt are required, and separation of the quinone isomers is necessary. Peracetic acid oxidation inconveniently requires very large amounts of oxidizing agent and gives only moderate yields, while photochemical oxidation gives juglone in 64%, but only at low concentrations; synthetically useful concentrations proceed inefficiently.[15] Anodic oxidation gives juglone in unspecified yield. The overall yield of 3-bromojuglone produced from juglone depends not only on the efficacy of the synthesis of juglone, but also on the efficiency of the separation of the 2-bromo and 3-bromo isomers produced on bromination. Thus, the approaches via juglone are found wanting.

Scheme II. Syntheses of 2- and 3-Bromojuglone Methyl Ethers (1b, 1c) from 4,8-Dimethoxy-1-naphthalenecarboxaldehyde (7)

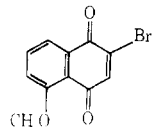
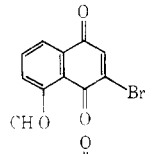
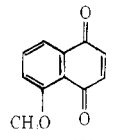
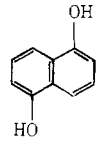
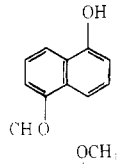
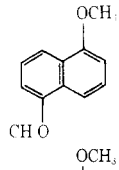
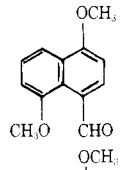
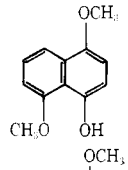
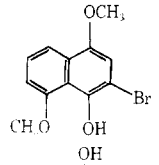
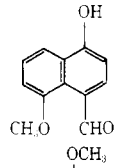
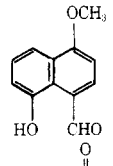
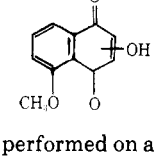


The present syntheses of 2- and 3-bromojuglone methyl ethers rely on 4,8-dimethoxy-1-naphthalenecarboxaldehyde (**7**), prepared from 1,5-dimethoxynaphthalene (**4**, Scheme II).[16] Naphthaldehyde **7** may then be oxidized to 4,8-dimethoxy-1-hydroxynaphthalene (**9**) after hydrolysis of the intermediate formate ester **8**. Dimethoxynaphthol **9** is then either oxidized to 5-methoxy-1,4-naphthoquinone (**1f**, juglone methyl ether) or brominated to give 2-bromo-4,8-dimethoxy-1-naphthol (**10**). Juglone methyl ether (**1f**) is brominated and dehydrohalogenated under conditions identical with those of the bromination of juglone (above) to give the 2-bromo isomer **1b** with greater than 99% purity in 49% overall yield from **4**. Bromonaphthol **10** is oxidized to 3-bromojuglone methyl ether (**1c**), also with greater than 99% purity, in 58% overall yield from **4**.

We ascribe the difference in the bromination products of juglone methyl ether and juglone to the stabilization afforded by their respective enols during dehydrohalogenation of the dibromo adduct. In juglone methyl ether the 4-carbonyl is a vinylogous ester, and therefore the 2-hydrogen is more acidic. In juglone, however, hydrogen bonding between the phenolic hydrogen and the 4-carbonyl makes the 3-hydrogen more acidic and hence the one lost in initiating the dehydrobromination.

The synthesis of naphthaldehyde **7**, using *N*-methyl-

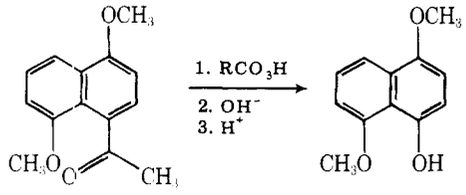
Table I. Gas and Thin-Layer Chromatographic Data for Various 1,5-Hydroxy/Methoxynaphthalenes and 1,4-Naphthoquinones

		GC[a]		TLC	
no.	compd	column[b]	retention time, min	system[c]	R_f
1b		A	2.50	D	0.34[d]
1c		A	2.50	D	0.34[d]
1f		A	2.50	C	0.42
2		A	4.83	C	0.36
3		A	3.75	C	0.47
4		A	3.00	C	0.60
7		A B	8.25 6.50	C D	0.62 0.38
9		A	4.25	D	0.55
10				D	0.65
12		B	7.50	C	0.50
13		B	5.17	C	0.55
14		A B	3.50 1.75	C	0.49

[a] Analysis was performed on a Hewlett-Packard Model 402-B gas chromatograph. [b] On a 6-ft column of 5% OV-17 on Chromosorb W, 80–100 mesh, at a column temperature of (A) 210 °C or (B) 255 °C. [c] Thin-layer chromatography on Analtech 250-μm silica gel GF plates in the following solvent systems: (C) ethyl acetate–hexane (1:1), or (D) $CHCl_3$. [d] Compounds **1b** and **1c** were distinguished by LC on a Spectra-Physics Model 3500 liquid chromatograph using a 5-μm LiChrosorb 3.2 mm × 25 cm column at 1600 psi and a flow rate of 1.6 mL/min with hexane–ethyl acetate (19:1) as eluent. The retention time for **1b** was 18 min, and that for **1c** was 13 min.

formanilide and $POCl_3$ in toluene, is reported[16] to give an 84% yield of **7**. In our hands this reaction is difficult to drive to completion and requires the separation of excess *N*-methylformanilide as well as unreacted starting material. Changing stoichiometry did not give complete reaction, but substituting DMF for *N*-methylformanilide increases the yield of naphthaldehyde **7** to 93%.

Baeyer–Villager oxidation to dimethoxynaphthol **9** has been applied to both naphthaldehyde **7** and the corresponding acetonaphthone **11**.[16] The naphthaldehyde reacts readily



11 **9**

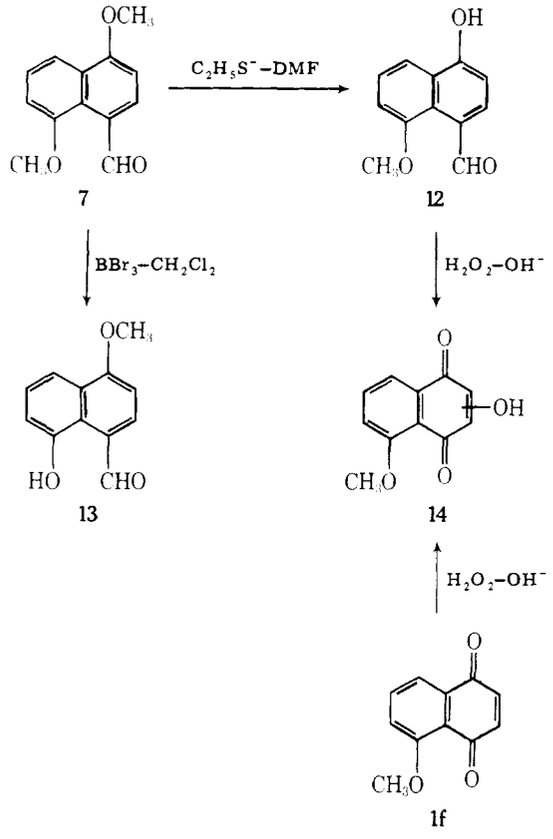
under mild conditions (*m*-chloroperbenzoic acid, MCPBA, in methylene chloride at room temperature); the acetonaphthone is resistant to both MCPBA and trifluoroperacetic acid. Various reaction conditions have been examined in optimizing the conversion of **7** to **9**. Increasing the dilution to 0.1 M greatly increases the purity of the intermediate formate ester **8** in the oxidation step, and cleavage of the formate ester in methanol–THF (1:1) with KOH rather than with just methanol results in complete solubility. Purification of the crude dimethoxynaphthol is most easily accomplished by filtration through silica, giving higher recovery and greater purity than recrystallization. Further changes in stoichiometry and reaction time offered no advantage; the dimethoxynaphthol is produced in 77% yield from the naphthaldehyde. Alternative and inferior preparations of dimethoxynaphthol **9** are reductive methylations of juglone acetate[17] or juglone methyl ether.[18]

The synthetic route from dimethoxynaphthol **9** to 3-bromoquinone **1c** is analogous to the route from 5-methoxy-1-naphthol (**3**) to 2-bromoquinone **1b**. Bromination of **9** with bromine in CCl_4 gives 2-bromo-4,8-dimethoxy-1-naphthol (**10**) in nearly quantitative yield. Oxidation with aqueous ceric ammonium nitrate in acetonitrile gives the quinone **1c** in 83% yield from the bromonaphthol, 58% overall. Gas chromatography and high pressure liquid chromatography show that there is less than 1% polybrominated impurity and no 2-bromo isomer present.

Dimethoxynaphthol **9** is oxidized to juglone methyl ether (**1f**) in 85% yield with aqueous ceric ammonium nitrate in acetonitrile; the quinone is then brominated and dehydrohalogenated (Br_2–$CHCl_3$; HOAc, EtOH at reflux) to give **1b** in 80% recrystallized yield from **1f** with less than 1% of the 3-bromo isomer present by LC. Other routes to the preparation of juglone methyl ether are via oxidation of 5-methoxy-1-naphthol (**3**) with chromic acid in 42% yield,[19] via nitration of **4** followed by reduction and oxidation (48% yield),[20] via anoidic oxidation of 1,5-dimethoxynaphthalene (65% yield),[21] and via photochemical oxidation at low concentrations (43% yield).[14]

Naphthaldehyde **7** may be selectively demethylated at either the 4 or 8 position to give 4-hydroxy-8-methoxy-1-naphthalenecarboxaldehyde (**12**) and 8-hydroxy-4-methoxy-1-naphthalenecarboxaldehyde (**13**, Scheme III). Thus, treatment of **7** with sodium thioethoxide in refluxing DMF gives **12** in 84% yield; basic conditions yield the more stable para anion which is conjugated with the aldehyde.[22] Conversely, treatment of **7** with boron tribromide in methylene chloride at −60 °C gives **13** in 82% yield; coordination of the Lewis acid with the carbonyl effects selective cleavage of the peri methoxy.[23,24] The *p*-hydroxy isomer **12** may be oxidized

Scheme III. Regioselective Demethylation of 4,8-Dimethoxy-1-naphthalenecarboxaldehyde (7)



1f

with alkaline hydrogen peroxide to a hydroxyjuglone methyl ether (**14**), identical with the hydroxyquinone obtained when juglone methyl ether (**1f**) is subjected to similar conditions. Confusion in the literature prevents the absolute assignment of the structure of quinone **14**,[25] but identity of the hydroxyquinone obtained from **12** and **1f** establishes that the free phenol in **12** is para (not peri) to the aldehyde. Further support is found in the recently reported[26] formylation of 1-acetoxy-5-methoxynaphthalene, in which substitution is reasonably assumed to occur in the methoxylated ring. Hydrolysis gives a compound to which structure **13** has been assigned and which has the same physical properties as **13**.

Experimental Section[27]

5-Methoxy-1-naphthol (3). Sodium hydride (550 mg, 11.5 mmol, 50% oil dispersion) was washed with hexane (20 mL) and slurried in DMF (10 mL), and ethanethiol (0.83 mL, 11 mmol) in DMF (10 mL) was added. The slurry was stirred for 10 min, and an additional 20 mL of DMF was added followed by 1,5-dimethoxynaphthalene (**4**; 1.88 g, 10 mmol). The mixture was heated at 100 °C for 6 h, cooled, acidified with 5% aqueous HCl (50 mL), and poured into 500 mL of water. Extraction with $CHCl_3$ (3 × 100 mL), washing, and drying of the organic phase and evaporation of the solvent gave 1.74 g (9.1 mmol, 91%) of naphthol **3**, mp 140–141 °C (lit.[9] mp 140–142 °C), that was identical with authentic material and contained less than 1% of either starting material or 1,5-dihydroxynaphthalene (**2**) by gas chromatography (Table I).

4,8-Dimethoxy-1-naphthalenecarboxaldehyde (7). 1,5-Dimethoxynaphthalene (**4**; 18.8 g, 0.1 mol), DMF (11.5 mL), and toluene (19 mL) were slurried together and cooled in an ice bath, after which $POCl_3$ (11.4 mL) was added and the mixture was stirred in the ice bath for 30 minutes and then heated to reflux to give a red solution. After 2 h, the reaction mixture was poured into aqueous NaOH (300 mL of 10% NaOH–100 mL of ice) with stirring, the mixture was extracted with benzene (3 × 100 mL), and the organic phases were washed sequentially with 5% aqueous HCl (2 × 100 mL), water (2 × 100 mL), and brine (100 mL), dried, combined, and evaporated to give 20.2 g (0.093 mol, 93%) of naphthaldehyde **7**. The initial product contained no starting material by gas chromatography (Table I), mp 125–126 °C (lit.[16] mp 124–126 °C.)

4,8-Dimethoxy-1-naphthol (9). A solution of 4,8-dimethoxy-1-naphthalenecarboxaldehyde (**7**; 6.48 g, 30 mmol) and MCPBA (12.2 g, 0.061 mol, 86% by iodometric titration) in CH_2Cl_2 (325 mL) was rapidly stirred for 2 h and 20 min. Aqueous sodium thiosulfate (100 mL, 10% solution) was introduced, and after being stirred for 30 min the mixture was poured into an additional 250 mL of aqueous thiosulfate and vigorously shaken. The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL), and the organic phases were washed successively with aqueous thiosulfate (2 × 200 mL) and brine (200 mL), dried, combined, and evaporated to give 6.87 g (29.7 mmol, 99%) of crude formate **8.** The crude formate was dissolved in degassed THF–CH_3OH (1:1, 200 mL) and cooled in an ice bath, KOH (4.25 g) in ice-cold degassed CH_3OH (40 mL) was added, and after 15 min 5% aqueous HCl was added to pH 1 and the reaction mixture was poured into water (1 L) and extracted with CH_2Cl_2 (3 × 150 mL). The organic phases were washed sequentially with water (2 × 200 mL) and brine (200 mL), dried, combined, and evaporated to give 5.88 g of crude material which was taken up in a minimum amount of CH_2Cl_2 and filtered through 15 g of silica (EM silica gel G, Type 60) on a sintered glass funnel to give, after evaporation, 4.71 g (23.1 mmol, 77%) of crystalline dimethoxynaphthol **9**, mp 155–156 °C (lit.[18] mp 155–156 °C). The product contained less than 1% starting material and unhydrolyzed ester by gas chromatography (Table I).

2-Bromo-4,8-dimethoxy-1-naphthol (10). 4,8-Dimethoxy-1-naphthol (**9**; 960 mg, 4.7 mmol) was suspended in CCl_4 (40 mL), and bromine (768 mg, 4.8 mmol) in CCl_4 (15 mL) was added dropwise. After being stirred for 30 min, aqueous sodium thiosulfate (50 mL, 10% solution) was added, stirring was continued for 10 min, and the mixture was poured into 150 mL of thiosulfate solution and extracted with CH_2Cl_2 (3 × 100 mL). The organic phases were washed sequentially with thiosulfate solution (100 mL), water (2 × 200 mL), and brine (200 mL), dried, combined, and evaporated to give 1.30 g (4.6 mmol, 98%) of naphthol **10.** The crude material was of adequate purity for further steps. A small amount was recrystallized twice from CH_3OH–H_2O to give pale brown red needles: mp 141–142 °C dec; NMR δ 9.56 (1 H, s), 7.95–6.75 (4 H, m), 4.03 (3 H, s), 3.93 (3 H, s); IR 3380, 1410 cm^{-1}. Anal. Calcd for $C_{12}H_{11}O_3Br$: C, 50.9; H, 3.9. Found: C, 51.0; H, 4.1.

3-Bromo-5-methoxy-1,4-naphthoquinone (1c). A solution of ceric ammonium nitrate (5.8 g, 10.7 mmol) in water (15 mL) was added dropwise over 5 min to a suspension of 2-bromo-4,8-dimethoxy-1-naphthol (**10**; 1.2 g, 4.3 mmol). The mixture was stirred for 5 min after the addition was complete and then poured into 500 mL of water. The aqueous suspension was extracted with CH_2Cl_2 (3 × 100 mL); the organic phases were washed sequentially with water (100 mL), aqueous bicarbonate (2 × 100 mL), water (100 mL), and brine (100 mL), dried, combined, and evaporated to give 1.04 g of crude material which was sublimed at 100 °C (0.01 mm) to give 946 mg (3.57 mmol, 83%) of 3-bromojuglone methyl ether: mp 154–155 °C; NMR δ 7.70–7.15 (4 H, m), 4.01 (3 H, s); chromatography data are in Table I. A small amount of sublimed material was recrystallized from CH_2Cl_2 (mp unchanged) for combustion analysis. Anal. Calcd for $C_{11}H_7O_3Br$: C, 49.5; H, 2.6. Found: C, 49.5; H, 2.8.

5-Methoxy-1,4-naphthoquinone (1f). A solution of ceric ammonium nitrate (8.1 g, 14.7 mmol) in water was added dropwise over 5 min to a solution of 4,8-dimethoxy-1-naphthol (**9**; 1.2 g, 5.9 mmol) in acetonitrile (100 mL). The reaction mixture was stirred for an additional 5 min, poured into water (1 L), and extracted with CH_2Cl_2 (4 × 100 mL). The organic phases were washed sequentially with water (100 mL), aqueous bicarbonate (2 × 100 mL), water (100 mL), and brine (100 mL), dried, combined, and evaporated to give 1.03 g of crude quinone which was sublimed at 130 °C (0.01 mm) to give 935 mg (5.02 mmol, 85%) of bright orange quinone, mp 180–185 °C (lit.[20] mp 182–185 °C).

2-Bromo-5-methoxy-1,4-naphthoquinone (1b). A solution of bromine (835 mg, 5.2 mmol) in $CHCl_3$ (100 mL) was added to an ice-cold solution of 5-methoxy-1,4-naphthoquinone (**1f**; 890 mg, 4.75 mmol) in $CHCl_3$ (50 mL). The reaction mixture was stirred for 15 min with cooling in an ice bath, and solvent and unreacted bromine were then evaporated until only a few milliliters of $CHCl_3$ remained; then 10% aqueous HOAc (3 mL) was added via syringe. The mixture was evaporated to a moist residue, EtOH (50 mL, 95%) was added, and the mixture was heated to reflux (15 min), after which it was allowed to cool for 30 min, poured into water (500 mL), and extracted with CH_2Cl_2 (4 × 100 mL). The organic phases were washed sequentially with aqueous bicarbonate (2 × 200 mL), water (2 × 200 mL), and brine (200 mL), dried, combined, and evaporated to give 1.23 g of orange quinone. Recrystallization from EtOH (95%, 12 mL/1.2 g) gave 1.02 g (3.83 mmol, 80%) of quinone **1b,** mp 132–133 °C (lit.[7] mp 134 °C), that contained less than 1% of the 3 isomer by LC (Table I).

4-Hydroxy-8-methoxy-1-naphthalenecarboxaldehyde (12). Sodium hydride (550 mg, 11.5 mmol, 50% oil dispersion) was washed with hexane (20 mL) and slurried in DMF (10 mL). Ethanethiol (0.83 mL, 11 mmol) in DMF (10 mL) was then added, and the mixture was stirred in an ice bath 5 min. 4,8-Dimethoxy-1-naphthalenecarboxaldehyde (**7**; 2.16 g, 10 mmol) in DMF (20 mL) was added, and the mixture was heated at 160 °C. After 2 h and 15 min the mixture was allowed to cool, HCl (20 mL of 5%) was introduced, and the mixture was poured into water (100 mL) and extracted with EtOAc (2 × 500 mL). The organic phases were washed sequentially with water (3 × 400 mL) and brine (400 mL), dried, combined, and evaporated to give 2.15 g of crude hydroxynaphthaldehyde which was extracted into alkali. The alkaline aqueous phases were acidified and extracted with EtOAc, and the organic phases were washed in the usual fashion to give 1.64 g (8.1 mmol, 81%) of hydroxynaphthaldehyde **12.** A portion of this material was recrystallized twice from methanol to give light brown prisms: mp 221–221.5 °C dec; NMR (Me_2SO-d_6) δ 11.12 (1 H, br s, exchanges with D_2O), 11.00 (1 H, S), 8.15–7.1 (6 H, m), 4.03 (3 H, s); IR 3005, 1640 cm^{-1}; UV (0.075 N HCl) 232 nm ($\log_{10}$ ε 4.28), 251 (4.20, 348 (3.78); UV (0.75 N NaOH) 257 nm ($\log_{10}$ ε 4.19), 332 (3.35), 394 (4.26); chromatographic data are in Table I. Anal. Calcd for $C_{12}H_{10}O_3$: C, 71.3; H, 5.0. Found: C, 71.1; H, 5.1

8-Hydroxy-4-methoxy-1-naphthalenecarboxaldehyde (13). Boron tribromide (1.0 mL, 2.64 g, 10.5 mmol) was added to 4,8-dimethoxy-1-naphthalenecarboxaldehyde (**7**; 2.16 g, 10 mmol) in CH_2Cl_2 (50 mL) cooled in a CO_2/acetone bath. The reaction mixture was allowed to warm to room temperature; after 75 min it was poured into saturated aqueous bicarbonate (250 mL), shaken for 30 min, and extracted with CH_2Cl_2 (3 × 50 mL). The organic phases were washed sequentially with saturated aqueous bicarbonate (2 × 100 mL), water (2 × 100 mL), and brine (100 mL), dried, combined, and evaporated to give 1.73 g of crude hydroxynaphthaldehyde. The crude was taken up in a minimum amount of CH_2Cl_2, filtered through silica (5 g, slurried on a sintered glass funnel), and evaporated to give a bright yellow solid, 1.65 g (8.2 mmol, 82%) of hydroxynaphthaldehyde: mp 91–92 °C (lit.[26] mp 91–93 °C); NMR (Me_2SO-d_6) δ 10.66 (1 H, s), 9.5 (1 H, s, exchanges with D_2O), 8.2–7.05 (5 H, m), 4.07 (3 H, s); NMR ($CDCl_3$) δ 12.06 (1 H, s, exchanges with D_2O), 11.16 (1 H, s), 7.90–6.55 (5 H, m), 4.06 (3 H, s); IR 2750, 1650, 1505 cm^{-1}; UV (0.75 N HCl) 234 nm ($\log_{10}$ ε 4.01), 263 (4.03), 365 (3.87); UV 0.075 N NaOH) 216 nm ($\log_{10}$ ε 4.43), 269 (4.21), 344 (3.94); chromatographic data are in Table I. Anal. Calcd for $C_{12}H_{10}O_3$: C, 71.3; H, 5.0. Found: C, 71.1; H, 5.1.

Hydroxyjuglone Methyl Ether (14).[25] 4-Hydroxy-8-methoxy-1-naphthalenecarboxaldehyde (**12:** 606 mg, 3 mmol) was added to a solution of KOH (420 mg, 7.5 mmol) in water (20 mL), and hydrogen peroxide (260 mg, 7.5 mmol, 30% H_2O_2) in water (10 mL) was added. After 30 min, the reaction mixture was extracted with $CHCl_3$ (3 × 100 mL) and the organic phases were washed sequentially with water (2 × 100 mL) and brine (100 mL), combined, dried, filtered, and evaporated to give 526 mg of brown solid which was filtered through silica gel (3 g on a sintered glass funnel) to give 447 mg (2.2 mmol, 73%) of hydroxyjuglone methyl ether **14:** mp 160–165 °C dec; NMR δ 7.85–6.60 (5 H, m), 4.00 (3 H, s); chromatographic data are in Table I; MS *m/e* (rel intensity) 206 (12), 205 (11), 204 (M^+, 88), 186 (13). An identical product was obtained when these oxidation conditions were applied to juglone methyl ether (**1f**).

Registry No.—**1b,** 69833-08-6; **1c,** 69833-10-9; **1f,** 4923-61-9; **2,** 83-56-7; **3,** 3588-80-5; **4,** 10075-63-5; **7,** 69833-11-0; **8,** 69833-12-1; **9,** 3843-55-8; **10,** 69833-13-2; **12,** 69833-14-3; **13,** 67243-03-2; **14,** 69832-57-1.

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Synthesis of Cyclopenta[*cd*]pyrene

Maria Konieczny and Ronald G. Harvey*

Ben May Laboratory for Cancer Research, University of Chicago, Chicago, Illinois 60637

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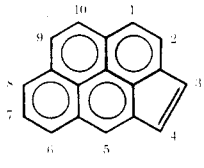
A novel and efficient synthesis of the recently discovered environmental carcinogen cyclopenta[*cd*]pyrene (1) from 1,2,3,6,7,8-hexahydropyrene (6) is described. This synthesis affords 1 in good overall yield (38%) and provides a convenient synthetic route to 1 on a practical scale.

Cyclopenta[*cd*]pyrene (1) has recently been identified as a component of carbon black[1,2] and automobile exhaust[3] and has been reported to be carcinogenic to mice[4] and a potent bacterial mutagen.[5] Eisenstadt and Gold suggest[5] that the 3,4-oxide (2) may be the ultimate carcinogenic and mutagenic metabolite. In view of the potential importance of 1 in human cancer, relatively larger amounts of 1 are required for biological studies than are conveniently available through isolation from carbon black or through synthesis.[6] We, therefore, undertook development of a more convenient synthesis of 1. Following completion of these studies, alternative syntheses of 1 were reported from two laboratories.[7,8] However, the method described herein provides higher overall yield and is more convenient in certain respects than either approach.



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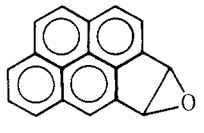

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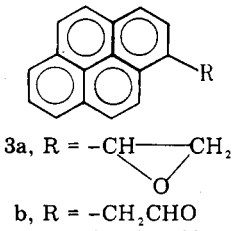
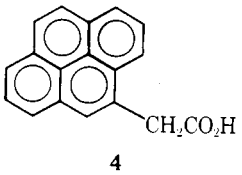
Results

In view of the synthetic accessibility of 1-oxiranylpyrene[9] (**3a**), we initially attempted to utilize this compound as a synthetic precursor of **1**. On treatment with boron trifluoride etherate, **3a** underwent rearrangement quantitatively to 1-pyrenylacetaldehyde (**3b**), while reaction of **3a** with $NaBH_4$ in methanol furnished 1-pyrenylethanol (**3c**) in 95% yield. Attempted cyclization of **3a, 3b,** or **3c** in liquid HF afforded only dimeric and oligomeric products from which no trace of 1 or 3,4-dihydro-1 could be isolated. Treatment of **3b** and **3c** with polyphosphoric acid furnished similar intractable polymeric products. Evidently, intramolecular cyclization to the 4 position of pyrene is considerably less facile than intermolecular condensation. This observation is in accord with the recently reported failure of cyclization of 1-pyrenylacetic acid under similar conditions.[7,8]



3a, R = –CH—CH$_2$ (with O)
b, R = $-CH_2CHO$
c, R = CH_2CH_2OH

Since pyrene itself readily undergoes Friedel–Crafts acylation in the 1 position,[10] it was reasoned that 4-pyrenylacetic acid (**4**) might readily cyclize to this position to furnish the ketone, 3-oxo-3,4-dihydrocyclopenta[*cd*]pyrene (**5**). Synthesis of **4** was achieved from 1,2,3,6,7,8-hexahydropyrene[11] (**6**) via the sequence depicted in Scheme I. Bromination of **6** by a modification of the published procedure[12] smoothly afforded 4-bromo-1,2,3,6,7,8-hexahydropyrene (**7**), mp 128–130 °C (lit.[12] mp 130–131 °C), in 96% yield. On treatment with DDQ in refluxing benzene for 3 h, **7** underwent dehydrogenation to 4-bromopyrene (**8a**), mp 147–149 °C (lit.[12] mp 148.2–150.2 °C), in 80% yield. This result contrasts with the earlier report by Streitweiser et al.[12] that attempted dehydrogenation of **7** with *o*-chloranil in refluxing toluene for 19 h failed to afford **8a**, while prolonged reaction (76 h) with this reagent in refluxing benzene gave **8a** in only moderate yield. Reaction of **8a** with *n*-butyllithium in ether followed by treatment with methyl iodide furnished 4-methylpyrene (**8b**), mp 144–146 °C (lit.[13,14] mp 146–147 °C; 149 °C), in 88% yield. Bromination of **8b** with NBS furnished crude 4-bromomethylpyrene (**8c**),



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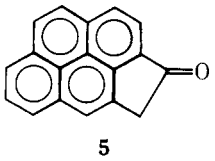

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