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OXYGENATED DIHYDROPHENANTHRENES VIA QUINOL ACETALS: A BRIEF SYNTHESIS OF ORCHINOL

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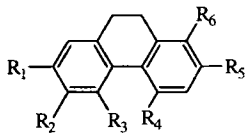
Abstract: *The dihydrophenanthrene phytoalexin Orchinol was synthesized in 5 steps from commercially available 3,5-dimethoxybenzaldehyde. The approach utilized a new synthon, p-benzoquinone dibenzylmonoacetal, which served as a phenol 3,4-dication equivalent in an arylation-cyclization sequence .*

Phenolic dihydrophenanthrene natural products have been of considerable interest to organic chemists not only because of their cytotoxicity and wide range of biological activities, but also due to their deceptively challenging structural architecture.[1] A selected group of these phytoalexins is shown in **Figure 1.**



orchinol: $R_1 = OH, R_2 = H, R_3 = H, R_4 = OCH_3, R_5 = OCH_3, R_6 = H$
effusol: $R_1 = OH, R_2 = H, R_3 = CH{=}CH_2, R_4 = H, R_5 = OH, R_6 = CH_3$
juncusol: $R_1 = OH, R_2 = CH_3, R_3 = CH{=}CH_2, R_4 = H, R_5 = OH, R_6 = CH_3$
juncunol: $R_1 = CH{=}CH_2, R_2 = CH_3, R_3 = H, R_4 = H, R_5 = OH, R_6 = CH_3$
juncunone: $R_1 = CH_3, R_2 = OH, R_3 = COCH_3, R_4 = H, R_5 = OH, R_6 = CH_3$

Figure 1. Selected Dihydrophenanthrene Phytoalexins

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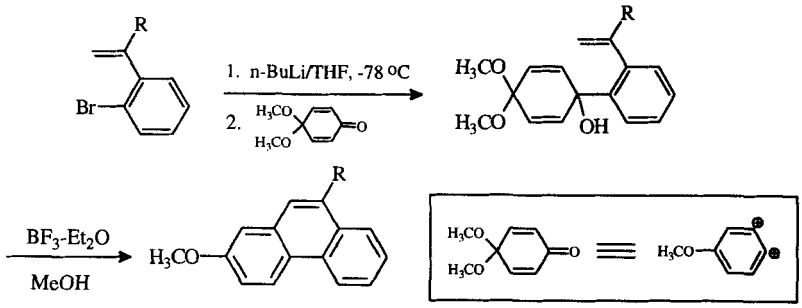


Scheme 1. Phenanthrenes via Quinol Acetal Cyclization

Recently, we reported a regiospecific synthesis of oxygenated phenanthrenes via quinol acetal cyclization as shown in **Scheme 1**, wherein *p*-benzoquinone dimethylmonoacetal formally served as an anisole 3,4-dication equivalent in the addition-cyclization sequence.[2a] In the present report, we describe a useful extension of this work for the synthesis of phenolic phenanthrenes and dihydrophenanthrenes.

Access to simple 2-*hydroxy*phenanthrenes via this methodology would be straightforward using standard methyl ether cleavage protocols. However, for highly oxygenated systems such as *Orchinol* (R^1 = OH, R^4, R^5 = OCH_3), oxygen differentiation would be problematic.[3] Serendipitous cyclization to phenolic phenanthrenes via styrene-substituted quinols has been recently reported,[4] but ketal hydrolysis to such quinols is often complicated by competing cyclization to the methoxylated phenanthrene or by dienone-phenol type rearrangements when the styrene moiety is ring oxygenated.[2a] An alternate quinone monoacetal that would afford oxygenated phenanthrenes subject to selective 2-position ether cleavage would effectively constitute a *phenol* 3,4-dication equivalent for the chemistry outlined above. Since aryl benzyl ethers are readily cleaved in the presence of aryl methyl ethers via hydrogenolysis[5] or dissolving metal reduction,[6] we prepared the previously unreported *p*-benzoquinone dibenzylmonoacetal **2** via

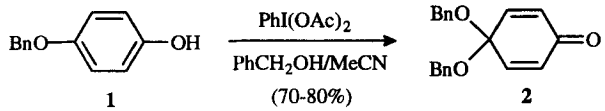
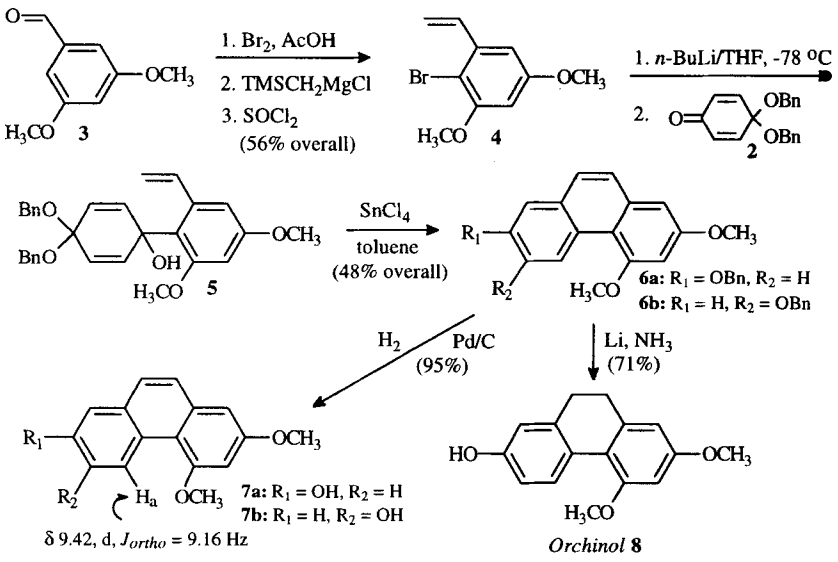


Figure 2. Preparation of *p*-Benzoquinone Dibenzylmonoacetal

hypervalent iodine oxidation of commercially available *p*-benzyloxyphenol **1** as in **Figure 2**.

Interestingly, the **1** → **2** oxidation was found to be sensitive to the order of addition of reagents. Yields of **2** in the 70-80% range were readily obtained, but only via slow addition of an acetonitrile solution of **1** to a stirred solution of iodobenzene diacetate in benzyl alcohol at room temperature. Yields obtained via the more usual method, i.e., addition of the solid oxidant to an alcoholic solution of the phenol,[7] were uniformly poor. The inverse mode of addition reported here may have implications for similar hypervalent iodine oxidations.



Scheme 2. Total Synthesis of *Orchinol* via Quinol Acetal Cyclization

For a concise approach to *Orchinol* via the quinol acetal cyclization method (**Scheme 2**), the requisite 2-bromostyrene **4** was readily prepared by bromination of 3,5-dimethoxybenzaldehyde **3**, followed by Peterson olefination. Metal-halogen exchange on **4** followed by addition of **2** gave the crude quinol ketal **5** which was cyclized via treatment with $SnCl_4$ in toluene to afford 2-benzyloxyphenanthrene **6a** in 48% overall yield from **4**. Although **6a** showed appropriate IR, ^{1}H NMR, ^{13}C NMR and %CH analysis, literature[3a] mp data (227-229 °C, the only analytical data reported) differed markedly from our observed mp of 108-109 °C. We were initially concerned that this discrepancy might be due to an incorrect structural assignment. Indeed, regioisomeric phenanthrene **6b** could quite plausibly be formed via an alternate cyclization mechanism involving acid-catalyzed carbinol ionization of **5**, followed by side-chain ring closure and subsequent 1,2-migration of the electron-rich dimethoxylated aryl ring in a dienone-phenol type rearrengement.[2a,b] However, analysis of the somewhat simplified 270 MHz ^{1}H NMR of the corresponding phenolic phenanthrene **7a** (obtained in 95% yield from **6** via catalytic hydrogenation over 10% Pd/C; see Experimental Section) clearly showed---as expected---the unique, highly deshielded phenanthrene bay-region proton H_a appearing furthest downfield (see **Scheme 2**) as a distinctly *ortho*-coupled doublet at δ 9.42 with J_{ortho} = 9.16 Hz. This rules out the alternate 3-hydroxy regioisomer **7b** (and by inference, **6b**), wherein H_a would appear as a weakly *meta*-coupled singlet with J_{meta} on the order of only 2-3 Hz.

While catalytic hydrogenation of **6a** failed to reduce the 9,10-position, the desired reduction and simultaneous debenzylation was achieved via Birch reduction[8] with Li/NH_3, furnishing *Orchinol* **8** in 71% isolated yield. This was a marked improvement over previously reported reductions of **6** via irradiation in the presence of tri-*n*-butyltin hydride[3a] or by treatment with sodium hydrazide in hydrazine.[3b] Further note that in this scheme, quinone monoacetal **2** served as a phenol 3,4-dication equivalent for the addition-cyclization sequence.

The chemistry reported herein further demonstrates the utility of *p*-aryl quinol acetal cyclization as a useful protocol for the synthesis of oxygenated phenanthrene and dihydrophenanthrene targets. Furthermore, in light of the well-established and wide preparative scope of quinone monoacetal chemistry,[9] ready availability of the previously unreported *p*-benzoquinone dibenzylmonoacetal should be of interest to other synthetic practitioners.

EXPERIMENTAL SECTION

General Procedures: Tetrahydrofuran (THF) was purified by distillation from benzophenone ketyl. Standard work up refers to extraction of crude reaction products into an appropriate solvent (diethyl ether or ethyl acetate), brine extraction, drying through a $CaSO_4$ cone and concentration in vacuo. ^1H and ^{13}C nuclear magnetic resonance spectra (NMR, reported in δ) were recorded at 270 MHz and 69 MHz respectively, using deuterochloroform/TMS, on a JEOL-FX-270 spectrometer. Infrared spectra (IR) were recorded as KBr pellets (solids) or on NaCl plates (oils) on a Perkin-Elmer Model 283B spectrometer. The following abbreviations are used throughout the experimental: diethyl ether (Et_2O), methanol (MeOH), hexane (Hxa), ethyl acetate (EtOAc), *n*-butyllithium (*n*-BuLi), acetic acid (AcOH).

Preparation of *p*-benzoquinone dibenzylmonoacetal (2): *p*-Benzyloxyphenol **1** (2.0 g, 9.99 mmol) was dissolved in acetonitrile (10 mL) with slight heating and was added dropwise to a stirred solution of iodobenzene diacetate (3.45 g, 1.1 equiv) dissolved in benzyl alcohol (25 mL) and acetonitrile (75 mL) at 25 °C. The resulting mixture was stirred for 15 min during which time a change in color from blue to green and finally to amber was observed. After dilution with Et_2O (100 mL), the mixture was slowly poured into sat $NaHCO_3$ solution (2.2 equiv) with stirring. After standard work up, the excess benzyl alcohol was removed via distillation in vacuo (62 °C @ 0.25 mm Hg) after which the residual crude monoacetal solidified upon cooling to room temperature. Recrystallization of the solid from Et_2O/Hxa gave **2** as tan crystals (2.17 g, 71%): mp 93.5-95 °C; IR (KBr pellet, cm $^{-1}$) 3045 (m), 2890 (m), 1680 (s), 1640 (s), 1185 (s), 1090 (s), 1000 (s); ^1H NMR (270 MHz) 7.34 (br s, 10H), 6.62 (AB_q, J = 10.2 Hz, $\Delta\nu$ = 184.6 Hz, 4H), 4.73 (s, 4H); Anal. Calcd for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.28; H, 6.01.

Preparation of 2-bromo-3,5-dimethoxybenzaldehyde (3): Bromine (1.6 mL, 1 equiv) in AcOH (20 ml) was added dropwise over 1h to a solution of 3,5-dimethoxybenzaldehyde (5.0 g) in AcOH (30 mL). The mixture was stirred for 12 h then poured into H_2O (100 mL) to give a thick black suspension that was vacuum filtered, washed with H_2O and air dried. The liquor was re-filtered and the combined solids were chromatographed on silica gel (2:1 Hxa/EtOAc) to give **3** as white crystals (5.6 g, 75%): mp 105-106 °C (lit[10] mp 107 °C).

Preparation of 2-bromo-3,5-dimethoxystyrene (4): Bromoaldehyde **3** from above (5.56 g, 22.7 mmol) was dissolved in THF (30 mL) and chilled to 0 °C under Ar. Next, (trimethylsilyl)methyl magnesium chloride (19.2 mL, 1.3 M, 1.1 equiv) was added dropwise, and the mixture was stirred for 30 min. $SOCl_2$ (1.82 mL, 1.1 equiv) was then slowly added dropwise, the mixture was stirred for 1 h and then quenched with H_2O (30 mL) and diluted with EtOAc (40 mL). Standard work up gave a dark oil which was chromatographed on silica gel (10% EtOAc/Hxa) to give **4** as a water white oil (4.08 g, 74%): IR (NaCl, cm^{-1}) 2960 (m), 1595 (br, s), 1420 (s), 1345 (s), 1335 (s), 1215 (s); ^1H NMR (270 MHz) 7.08 (dd, J = 10.99 Hz, J = 17.58 Hz, 1H), 6.69 (d, J = 2.93 Hz, 1H), 6.42 (d, J = 2.93 Hz, 1H), 5.67 (d, J = 17.58 Hz, 1H), 5.35 (d, J = 10.99 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H); HRMS (EI) calcd for $C_{10}H_{11}O_2Br$ 241.99424 (^{79}Br), found 241.99559.

Preparation of 2-Benzyloxy-5,7-dimethoxyphenanthrene (6a): Bromostyrene **4** (1.0 g, 4.10 mmol) was dissolved in THF (20 mL) under Ar and chilled to -78 °C. Next, *n*-BuLi (2.26 mL, 1.1 equiv, 2.0 M in hexanes) was added dropwise and the mixture was stirred for 1 h. Quinone monoacetal **2** (1.26 g, 1.0 equiv) in THF (10 mL) was then added dropwise. After warming to room temperature, the reaction mixture was quenched with H_2O (10 mL), and diluted with Et_2O (75 mL). Standard work up afforded the crude, highly labile quinol acetal **5** which was cyclized directly without further purification as follows: crude **5** was dissolved in toluene (40 mL), chilled to 0 °C and treated with neat $SnCl_4$ (0.96 ml, 2.0 equiv) which was added over 5 min, after which the reaction was allowed to stir for 15 min and then was quenched with H_2O (10 mL) and diluted with Et_2O (50 mL). Standard workup gave a dark oil which was chromatographed on silica gel (CH_2Cl_2) to give a water-white oil that slowly solidified. Recrystallization from CH_2Cl_2/ethanol gave the title compound **6a** as white crystals (0.67 g, 48% overall): mp 108-109 °C (lit[3a] mp 227-229 °C, see also note 11); IR (KBr, cm^{-1}) 1622 (s), 1465 (m), 1279 (m), 1232 (m), 1223 (m), 1177 (m), 1167 (m); ^1H NMR,

9.46 (d, J = 10.62 Hz, 1H), 7.61-7.30 (m, 9H), 6.88 (d, J = 2.19 Hz, 1H), 6.77 (d, J = 2.19 Hz, 1H), 5.22 (s, 2H), 4.09 (s, 3H), 3.95 (s, 3H); ^{13}C NMR, 159.27 (1C), 157.43 (1C), 155.82 (1C), 137.07 (1C), 134.34 (1C), 133.18 (1C), 129.27 (1C), 128.58 (1C), 127.91 (2C), 127.77 (1C), 127.57 (2C), 127.34 (1C), 125.01 (1C), 116.88 (1C), 115.85 (1C), 109.86 (1C), 101.22 (1C), 99.35 (1C), 69.95 (1C), 55.63 (1C), 55.34 (1C); Anal. Calcd for $C_{23}H_{20}O_3$: C, 80.21; H, 5.89. Found: C, 79.72; H, 5.85.

Preparation of 2-hydroxy-5,7-dimethoxyphenanthrene, *Dehydroorchinol* (7a): Benzyloxyphenanthrene **6a** from above (0.150 g) was dissolved in ethyl acetate (25 mL) and hydrogenated at atmospheric pressure over 10% Pd/C (0.015 g) for 72 h. Filtration and concentration afforded phenolic phenanthrene **7a** (0.105 g, 95%) as a white solid: mp 168-170°C (lit[3a] mp 165-166 °C); IR (KBr, cm^{-1}) 3350 (br) 1620 (s), 1220 (m), 1200 (m), 1170 (m), 1158 (m), 1061 (m); ^{1}H NMR (270 MHz) 9.44 (d, J = 9.16 Hz, 1H), 7.59 (s, 2H), 7.21 (d, J = 2.93 Hz, 1H), 7.16 (dd, J = 9.16 Hz, J = 2.93 Hz, 1H), 6.88 (d, J = 2.19 Hz, 1H), 6.77 (d, J = 2.19 Hz, 1H), 5.08 (s, 1H), 4.09 (s, 3H), 3.95 (s, 3H).

Preparation of 2-hydroxy-5,7-dimethoxy-9,10-dihydrophenanthrene, *Orchinol* (8): Benzyloxyphenanthrene **6a** (0.15 g, 0.44 mmol) was dissolved in THF (15 mL) and added dropwise to a flask containing liquid NH_3 (50 mL) under Ar. A piece of Li metal (21.2 mg, 7.0 equiv) was then added with stirring whereupon the solution turned from green to blue before fading to red and then to a pale yellow. After 15 min, the reaction was quenched with solid NH_4Cl (8.0 equiv) followed by H_2O (1.0 mL). The NH_3 was evaporated under a stream of Ar and the residue was acidified with 5% HCl (50 mL) to below pH 6 and extracted with EtOAc (2 X 25 mL). Standard workup gave a brown oil which was chromatographed on silica gel (20% EtOAc/Hxa) to give a light tan oil that slowly crystallized to give the title compound (79.8 mg, 71% yield) as an off-white solid, mp 125-127 °C (lit[3b] mp 126-127 °C). Spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR) were in excellent agreement with literature values.[3c,d]

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11. We noted coincidentally that our mp for **6a** was essentially in agreement with the literature (ref 3a) when converted from °C to °F.

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