Synthesis of the Active Dihydrodiol and Diol Epoxide Metabolites of the Steroid-Related Carcinogen 15,16-Dihydrocyclopenta[a]phenanthrene and Its 11-Methyl Derivative

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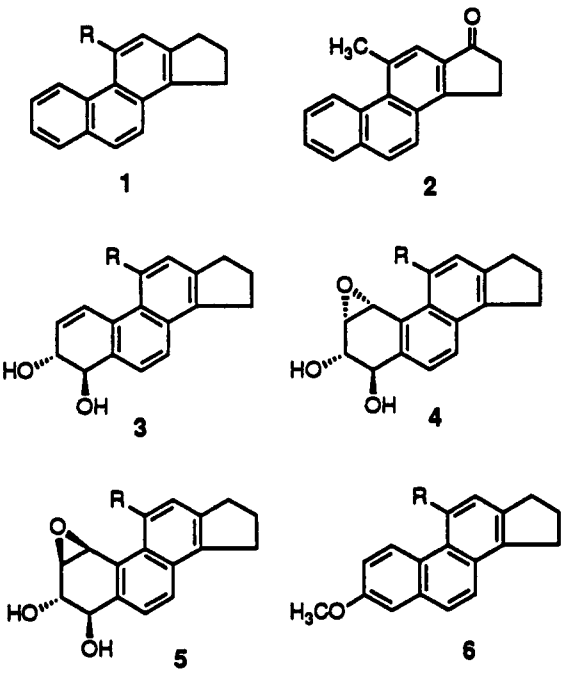
Cyclopenta[a]phenanthrenes are a class of environmentally occurring carcinogens that are structurally related to sterols. While the parent hydrocarbon is biologically inactive, its 11-methyl and 17-keto derivatives are relatively potent carcinogens. Recent research has identified *trans*-3,4-dihydrodiol metabolites as the metabolic precursors of the corresponding *anti*- and/or *syn*-diol epoxides, implicated as the ultimate carcinogenic forms that bind to DNA. We now report the synthesis of the *trans*-3,4-dihydrodiol derivatives of cyclopenta[a]phenanthrene and 11-methylcyclopenta[a]phenanthrene, **3a** and **3b**, respectively, and the corresponding *anti*- and *syn*-diol epoxides of each of these hydrocarbons, **4a**, **4b** and **5a**, **5b**, respectively. Syntheses of the analogous *trans*-3,4-dihydrodiol metabolites of the 17-keto derivatives of cyclopenta[a]phenanthrene and 11-methylcyclopenta[a]-phenanthrene are described in the accompanying paper.

Cyclopenta[a]phenanthrenes are commonly present in petroleum, mineral oils, coal, lake sediments, and other natural environments.[1,2] They are formed from sterols by microbial dehydrogenation and by pyrolysis.[2,3] They also enter into the human diet through the pyrolysis of sterols in edible oils during cooking. Their chemistry and biological properties have been surveyed.[2] While the parent hydrocarbon 15,16-dihydrocyclopenta[a]phenanthrene (**1a**) is noncarcinogenic, its 11-methyl analogue **1b** exhibits significant activity as a carcinogen on mouse skin, and its 11-methyl-17-keto derivative **2** is a relatively potent carcinogen in this assay, comparable in activity to benzo[a]pyrene.[2,4] This latter finding is unexpected, since the keto derivatives of carcinogenic polycyclic aromatic hydrocarbons are generally less active than the parent hydrocarbons.[5] Recent research has identified the *trans*-3,4-dihydrodiol metabolites **3** as the proximate carcinogenic forms that give rise to the corresponding *anti*- and/or *syn*-diol epoxides **4** and **5** implicated as ultimate carcinogenic metabolites.[2,6]

We now wish to report the synthesis of the *trans*-3,4-dihydrodiol derivatives of cyclopenta[a]phenanthrene and 11-methylcyclopenta[a]phenanthrene (**3a** and **3b**) and the corresponding *anti*- and *syn*-diol epoxides of each (**4a**, **4b** and **5a**, **5b**). Syntheses of the analogous series of metabolites of cyclopenta[a]phenanthrene with a 17-carbonyl group are described in the accompanying paper.



a: R = H; **b**: R = CH_3

Results

The synthetic strategy for the preparation of the *trans*-3,4-dihydrodiols **3a** and **3b** entails initial preparation of the key intermediates 15,16-dihydro-3-methoxycyclopenta[a]phenanthrene (**6a**) and its 11-methyl derivative **6b** from the readily available 6-methoxy-1-tetralone via appropriate modification of the route reported earlier for the preparation of the parent hydrocarbon **1a** (Scheme I).[7] Conversion of **6a** and **6b** to the corresponding dihydrodiol derivatives **3a** and **3b**, respectively, can in principle be accomplished via demethylation, oxidation to the corresponding *o*-quinones with Fremy's salt, and reduction with $NaBH_4/O_2$.[8] While this general strategy

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(3) Schmid, L. *Mitt. Geb. Lebensmittelunter Hyg.* **1962**, *53*, 507. Schmid, L.; Waitz, W. *Z. Ernaehungwiss., Suppl.* **1963**, *3*, 45. Hoffelner, K.; Lisbet, H.; Schmid, L. **1964**, *5*, 16.

(4) Coombs, M. M.; Croft, C. J. *Nature (London)* **1966**, *210*, 1281; *Prog. Exper. Tumor Res.* **1969**, *11*, 69-85.

(5) Harvey, R. G. *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenicity*; Cambridge Monographs on Cancer Research; Cambridge University Press: Cambridge, England, 1991.

(6) Coombs, M. M.; Kissonerghis, A.-M.; Allen, J. A.; Vose, C. W. *Cancer Res.* **1979**, *39*, 4160. Coombs, M. M.; Bhatt, T. S. *Carcinogenesis* **1982**, *3*, 449.

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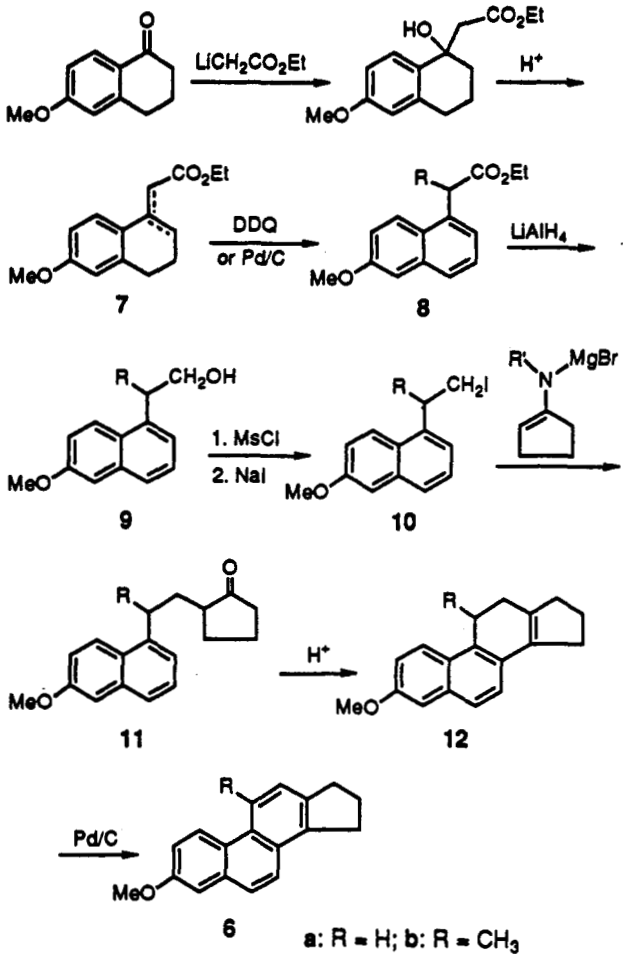
Scheme I

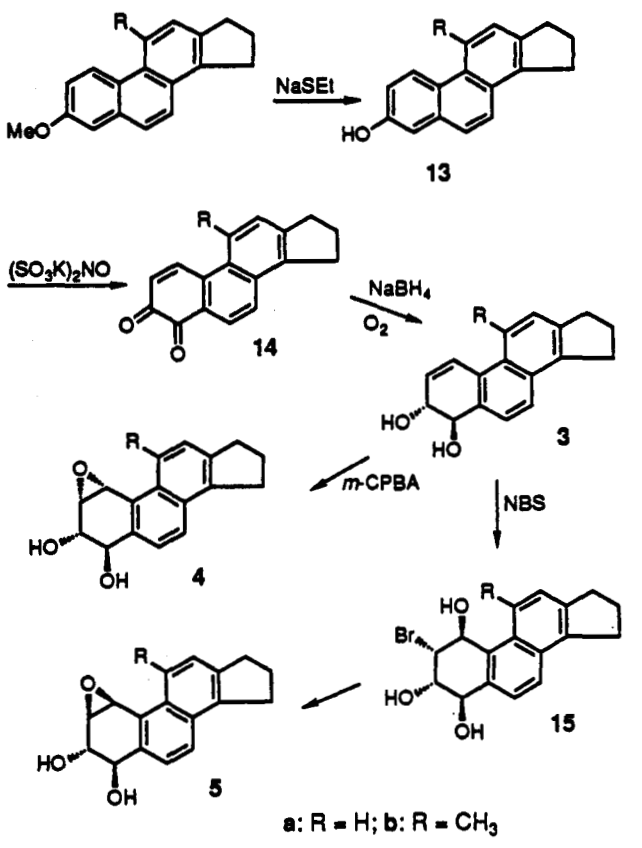


has proven successful, problems were encountered that necessitated modification of the general approach.

2-[1-(6-Methoxynaphthyl)]ethanol (**9a**) was synthesized from 6-methoxy-1-tetralone by the method previously described.[7] Dehydrogenation of the mixture of unsaturated acetate isomers **7** was accomplished equally efficiently by reaction with DDQ in refluxing benzene or by treatment with 10% Pd/C. Conversion of **9a** to the corresponding 2-iodoethyl derivative of 6-methoxynaphthalene (**10a**) was carried out previously by treatment of **9a** with P_2I_4. However, an unidentified secondary product was detected as a contaminant in crude **10a** which made purification difficult and diminished the yield. This problem was solved by conversion of **9a** to its mesylate ester by treatment with methanesulfonyl chloride and triethylamine followed by displacement of the mesylate group with NaI in acetone. The overall yield of pure **10a** is virtually quantitative.

Conversion of **10a** to 15,16-dihydro-3-methoxycyclopenta[a]phenanthrene (**6a**) was accomplished via the sequence previously described, i.e., reaction with the bromomagnesium salt of *N*-cyclohexylcyclopentenylimine, acidic hydrolysis of the adduct to the cyclopentanone derivative **11a**, and cyclodehydration of **11a** in methanesulfonic acid at 0 °C to 3-methoxy-11,12,15,16-tetrahydrocyclopenta[a]phenanthrene (**12a**) accompanied by

Scheme II



products of disproportionation (detected by NMR and TLC). Disproportionation during acidic cyclodehydration is well-known.[9] Variable amounts of an unknown white solid precipitate were removed by filtration. Dehydrogenation of the mixture containing **12a** over a Pd/C catalyst in refluxing triglyme furnished **6a**.

Synthesis of the 11-methyl homolog of **6a** (**6b**) was carried out by a modification of the same synthetic sequence involving α-methylation of the ester intermediate **8a**. Treatment of **8a** with methyl iodide and sodium hydride at 0 °C afforded smoothly the methyl-substituted homolog **8b**. Although the α,α-dimethylated product forms readily at slightly higher temperature, its formation could be prevented by careful control of reaction temperature. Conversion of **8b** to **6b** was readily accomplished via a route analogous to that used for the synthesis of **6a** (Scheme I).

Transformation of the 3-methoxy derivative of 15,16-dihydrocyclopenta[a]phenanthrene (**6a**) to the corresponding 3,4-dihydrodiol derivative, *trans*-3,4-dihydroxy-3,4,15,16-tetrahydrocyclopenta[a]phenanthrene (**3a**) and its further conversion to the corresponding *anti*- and *syn*-diol epoxide derivatives **4a** and **5a** was accomplished via the sequence in Scheme II. Reaction of **6a** with sodium ethylthiolate removed the methyl group to provide the free phenol **13**. Oxidation of **13** with Fremy's salt [$(SO_3K)_2$NO] in a two-phase aqueous methylene chloride system[8a,b,10] furnished the *o*-quinone derivative **14** free of the related *p*-quinone. Reduction of **14** with $NaBH_4$ in ethanol in the presence of O_2 took place smoothly and stereospecifically to yield the *trans*-3,4-dihydrodiol **3a**. This steric assignment is supported by previous findings

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for similar reactions[5,11] and by the 500-MHz NMR spectrum of **3a** which showed $J_{3,4}$ = 8.4 Hz consistent with the assignment of the 3,4-hydroxyl groups as trans diequatorial.[12] The use of O_2 for recycling catechol byproducts back to quinones in reductions with $NaBH_4$ is well-known.[8,13] Oxidation of **3a** with *m*-chloroperbenzoic acid took place stereospecifically to yield the corresponding *anti*-diol epoxide derivative **4a**. This steric preference is consistent with the known stereospecificity of this reaction.[5] The related *syn*-diol epoxide isomer **5a** was synthesized from **3a**, also stereospecifically, by reaction with NBS in moist DMSO to generate the bromohydrin **15a** followed by cyclization with potassium *tert*-butoxide. The assignments of all compounds are consistent with their NMR spectra. Both the *anti*- and *syn*-diol epoxide diastereomers **4a** and **5a** exhibit diequatorial conformational preference as evidenced by the couplings of the 3,4-protons ($J_{3,4}$ = 8.4 and 8.2 Hz, respectively).[5]

Synthesis of the analogous *trans*-3,4-dihydrodiol derivative of 11-methyl-15,16-dihydrocyclopenta[*a*]phenanthrene (**3b**) from **6b** and the further transformation of **3b** to the related *anti* and *syn*-diol epoxide derivatives **4b** and **5b** were carried out by an analogous sequence of steps in good overall yield. Both diol epoxide diastereomers were diequatorial ($J_{3,4}$ = 8.4 and 8.6 Hz, respectively).

Biological Activities. Mutagenicity assays by the Ames method show the dihydrodiols **3a** and **3b** to be more potent mutagens for *Salmonella typimurium* TA 100 bacteria than the parent hydrocarbons.[14] Microsomal activation is required to elicit this activity, supporting the hypothesis that the active mutagenic species are the corresponding *anti*- and/or *syn*-diol epoxide metabolites. In agreement with this expectation, the diol epoxide derivatives **4a,4b** and **5a,5b** show markedly higher initial activity than the precursor dihydrodiols. These findings suggest that the relatively low tumorigenic activity of 15,16-dihydrocyclopenta[*a*]phenanthrene and its 11-methyl derivative relative to their 17-keto analogs may partially due to their low levels of in vivo enzymatic activation to the corresponding dihydrodiols and/or diol epoxides by P-450 microsomal enzymes or more rapid detoxification of these metabolites by conjugation and excretion.

Experimental Section

Material and Methods. Ethyl 2-[1-(6-methoxynaphthyl)]-acetate (**8a**) and 2-[1-(6-methoxynaphthyl)]ethanol (**9a**) were synthesized as previously described.[7] *N*-Cyclohexylcyclopentylidinimine was synthesized by the reported method,[15] and its bromomagnesium derivative was prepared by the method of Stork and Dowd.[16] *m*-Chloroperbenzoic acid (85%) was purified by washing with a phosphate buffer pH 7.42 and drying in vacuo. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was recrystallized from benzene. Tetrahydrofuran was freshly distilled from $LiAlH_4$. Ether was dried over Na, and triglyme was dried over molecular sieves, 4A. The NMR spectra were obtained on a 500-MHz spectrometer in $CDCl_3$ unless stated otherwise with tetramethylsilane as internal standard. Integration was consistent with all structural assignments. All new compounds gave satisfactory microanalysis for C, H within ±0.4% and/or mass spectra consistent with the assigned structures.

2-[1-(6-Methoxynaphthyl)]ethyl Methanesulfonate. To a solution of **9a** (20.2 g, 100 mmol) in 500 mL of CH_2Cl_2 containing 20.7 mL (150 mmol) of Et_3N at 0 to −10 °C was added 10% excess MsCl (13.7 g, 120 mmol) over 10 min. The reaction mixture was stirred at this temperature for 2 h and then worked up by addition of water and extraction into CH_2Cl_2. The organic layer was washed consecutively with dilute HCl, saturated $NaHCO_3$ solution, brine, and water to yield the methanesulfonate ester (28.5 g, 99%), mp 56–57 °C: NMR δ 2.78 (s, 3, CH_3), 3.49 (t, 2, CH_2), 3.92 (s, 3, OCH_3), 4.51 (t, 2, CH_2), 7.14–7.23 (m, 3, Ar), 7.34 (d, 1, Ar), 7.65 (d, 1, Ar), 7.89 (d, 1, Ar). Anal. Calcd for $C_{14}H_{16}O_4S$; C, 59.98; H, 5.75. Found: C, 60.06; H, 5.77.

2-[1-(6-Methoxynaphthyl)]ethyl Iodide (10a). To a solution of the mesylate ester (29.0 g, 100 mmol) in 300 mL of acetone was added NaI (28.4 g), and the mixture was heated at reflux overnight. The mixture was concentrated and then partitioned between ether and water, dried, and evaporated to yield **10a** (32.0 g, 99%) as a white solid, mp 62–63 °C (lit.[7] mp 62–63 °C): NMR spectrum matched that of an authentic sample.

3-Hydroxy-15,16-dihydrocyclopenta[*a*]phenanthrene (13a). A solution of ethanethiol (7.4 mL, 100 mmol) in 50 mL of DMF was added dropwise to a suspension of NaH (4.0 g, 100 mmol) in 30 mL of DMF. This was stirred for 5 min, and then a solution of the methoxy ether **6a** (2.48 g, 10.0 mmol) in 75 mL of DMF was added, the mixture was heated at reflux for 3 h, and then it was poured into ice water, acidified, and extracted twice with ether. The organic phase was washed (4×) with water and brine, dried, and evaporated. Purification by flash chromatography gave **13a** (2.05 g, 88%) as white prisms, mp 198–199 °C: NMR δ 2.30 (q, 2, H_{16}), 3.17 (t, 2, $H_{15\text{ or }17}$), 3.33 (t, 2, $H_{15\text{ or }17}$), 4.95 (s, 1, OH), 7.21 (dd, 1, H_2), 7.24 (d, 1, H_4), 7.53 (d, 1, H_{12}), 7.62 (d, 1, $H_{6\text{ or }7}$), 7.74 (d, 1, $H_{6\text{ or }7}$), 8.42 (d, 1, H_{11}), 8.57 (d, 1, H_1); $J_{1,2}$ = 8.8, $J_{2,4}$ = 2.3, $J_{6,7}$ = 8.9, $J_{11,12}$ = 8.3, $J_{15,16,17}$ = 7.5 Hz; UV λ_{max} (EtOH) 209 (25 100), 237 (18 300), 261 (48 500), 303 (6840) nm. Anal. Calcd for $C_{17}H_{14}O$; C, 87.15; H, 6.02. Found: C, 86.96; H, 5.87.

15,16-Dihydrocyclopenta[*a*]phenanthrene-3,4-dione (14a). The phenol **13a** (1.90 g, 8.1 mmol) was dissolved in 150 mL of benzene, and 10 drops of Adogen 464 was added. To this vigorously stirred solution was added a solution of Fremy's salt (8.6 g, 32 mmol) in 150 mL of M/6 KH_2PO_4 diluted with 100 mL of water. After 5 h, the reaction was worked up in the usual manner,[17] but NMR analysis showed only 70% completion. The crude product was treated again with Fremy's salt by the same procedure until TLC showed reaction to be complete (5 h). The organic layer was washed with water twice and brine (3×), dried, and evaporated. Trituration with ether gave a burgundy solid (1,64 g, 81%), mp 176–177 °C: NMR δ 2.34 (q, 2, H_{16}), 3.19 (t, 2, $H_{15\text{ or }17}$), 3.32 (t, 2, $H_{15\text{ or }17}$), 6.55 (d, 1, H_2), 7.59 (d, 1, H_{12}), 7.90 (d, 1, $H_{6\text{ or }7}$), 8.15 (d, 1, $H_{6\text{ or }7}$), 8.09 (d, 1, H_{11}), 8.31 (d, 1, H_1); $J_{1,2}$ = 10.5, $J_{6,7}$ = 8.6, $J_{11,12}$ = 8.7, $J_{15,16,17}$ = 7.5 Hz; UV λ_{max} (EtOH) 218 (7840), 235 (7090), 304 (7760), 390 (1990) nm. Anal. Calcd for $C_{17}H_{12}O_2$; C, 82.24; H, 4.87. Found: C, 82.38; H, 4.78.

***trans*-3,4-Dihydroxy-3,4,15,16-tetrahydrocyclopenta[*a*]phenanthrene (3a).** A suspension of **14a** (1.0 g, 4.0 mmol) and $NaBH_4$ (1.49 g, 40 mmol) in 250 mL of EtOH was stirred with a stream of O_2 bubbling through for 72 h. Then solid NH_4Cl was added to quench the reaction, and the solvent was evaporated without heating. The residue was partitioned between ether and water, washed by brine, dried, and evaporated. Trituration of the residue with ether gave **3a** (405 mg, 40%) as a white solid, mp 202–204 °C: NMR (DMSO-d_6) δ 2.20 (q, 2, H_{16}), 3.10 (t, 2 $H_{15\text{ or }17}$), 3.25 (t, 2, $H_{15\text{ or }17}$), 4.34 (m, 1, H_3), 4.71 (dd, 1, H_4), 5.23 (d, 1, OH), 5.56 (d, 1, OH), 6.12 (dd, 1, H_2), 7.23 (d, 1, H_{12}), 7.45 (dd, 1, H_1), 7.73 (m, 2, $H_{6,7}$), 8.03 (d, 1, H_{11}); $J_{1,2}$ = 8.7, $J_{2,3}$ = 2.0, $J_{3,4}$ = 8.4, $J_{11,12}$ = 9.1, J_{OH} = 5.5, 5.2, $J_{15,16,17}$ = 7.3 Hz; UV λ_{max} (EtOH) 204 (17 100), 237 (39 800), 321 (2700), 348 (2500) nm. Anal. Calcd for $C_{17}H_{16}O_2$; C, 80.93; H, 6.39. Found: C, 80.68; H, 6.58.

***trans*-3,4-Dihydroxy-*anti*-1,2-epoxy-1,2,3,4,15,16-hexahydrocyclopenta[*a*]phenanthrene (4a).** A solution of **3a** (10 mg)

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(12) Reference 5, Chapter 13.
(13) Platt, K. L.; Oesch, F. *J. Org. Chem.* **1983**, *48*, 265.
(14) Papaparaskeva-Petrides, C.; Ioannides, C.; Boyd, G. W.; Young, R. J.; Harvey, R. G.; Coombs, M. M. *Mutagenesis* Manuscript submitted for publication.
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(17) Harvey, R. G.; Pataki, J.; Lee, H. *J. Org. Chem.* **1986**, *51*, 1407.

in dry THF was stirred under nitrogen with 100 mg of *m*-chloroperbenzoic acid. The reaction was monitored by HPLC (on a 15-cm × 6.4-mm Zorbax Sil column with 30% THF/hexane, 3 mL/min); completion was evident after 75 min. The mixture was partitioned between ether and water, and the organic phase was washed with water, 10% NaOH (2×), and water. All washes were prechilled to minimize hydrolysis of the sensitive product. The solvent was evaporated rapidly under vacuum using a dry ice condenser. Trituration of the residue with ether yielded **4a** (8.4 mg) as a white solid, mp 173–175 °C dec: NMR (DMSO-d_6) δ 2.20 (q, 2, H_{16}), 3.15 (t, 2, $H_{15\text{ or }17}$), 3.30 (t, 2, $H_{15\text{ or }17}$), 3.76 (d, 1, H_2), 3.85 (dd, 1, H_3), 4.49 (dd, 1, H_4), 4.96 (d, 1 H_1), 5.64 (d, 1, OH), 5.77 (d, 1, OH), 7.56 (d, 1, H_{12}), 7.87 (s, 2, $H_{6,7}$), 8.34 (d, 1, H_{11}); $J_{1,2}$ = 4.5, $J_{3,4}$ = 8.4, $J_{11,12}$ = 8.4, J_{OH} = 5.0, 6.6, $J_{15,16,17}$ = 7.2 Hz; UV λ_{max} (EtOH) 235 (36 900), 275 (14 800), 285 (19 900) nm. Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 75.88; H, 6.18.

2α-Bromo-1,2,3,4,15,16-hexahydro-1β,3α,4β-trihydroxycyclopenta[a]phenanthrene (15a). A solution of **3a** (40 mg, 0.16 mmol) and NBS (31 mg, 0.17 mmol) in 4.0 mL of DMSO/H_2O (9:1) was stirred under nitrogen, and the reaction was monitored by HPLC as before. When reaction was complete (15 min), the product was partitioned between ether and water, and the organic phase was washed with water (5×) and brine, dried, and evaporated. The residue was triturated with ether to yield **15a** (38 mg, 69%) as a white solid, mp 168–170 °C dec: NMR (DMSO-d_6) δ 2.17 (q, 2, H_{16}), 3.02 (t, 2, $H_{15\text{ or }17}$), 3.17 (t, 2, $H_{15\text{ or }17}$), 4.07 (m, 1, H_3), 4.58 (m, 2, $H_{2,4}$), 5.47 (dd, 1, H_1), 5.59 (d, 1, OH), 5.76 (d, 1, OH), 6.20 (d, 1, OH), 7.45 (d, 1, H_{12}), 7.66 (d, 1, H_{6or7}), 7.78 (d, 1, H_{6or7}), 7.95 (d, 1, H_{11}); $J_{1,2}$ = 3.1, $J_{2,3}$ = 3.8, $J_{3,4}$ = 7.8, $J_{11,12}$ = 8.8, J_{OH} = 4.4, 6.1, 6.6, $J_{15,16,17}$ = 7.4 Hz. Anal. Calcd for $C_{17}H_{17}O_3Br$; C, 58.47; H, 4.91. Found: C, 58.68; H, 5.19.

***trans*-3,4-Dihydroxy-*syn*-1,2-epoxy-1,2,3,4,15,16-hexahydrocyclopenta[a]phenanthrene (5a).** To a solution of **15a** (25.1 mg, 0.072 mmol) in dry THF under N_2 was added a solution of *t*-BuOK (13 mg, 0.11 mmol) in 0.15 mL of *t*-BuOH. When reaction was complete (10 min by HPLC), the product was partitioned between cold ether and water (20 mL) and evaporated rapidly in vacuo using a dry ice condenser without heating. Trituration of the residue with ether yielded **5a** (15.6 mg, 81%) as a white solid, mp 149–151 °C dec: NMR (DMSO-d_6 + D_2O) δ 2.24 (q, 2, H_{16}), 3.12 (t, 2, H_{15or17}), 3.27 (t, 2, H_{15or17}), 3.72–3.82 (m, 2, $H_{2,3}$), 4.70 (m, 2, $H_{1,4}$), 5.11 (br d, 1, OH), 5.64 (br d, 1, OH), 7.53 (d, 1, H_{12}), 7.67 (d, 1, H_{6or7}), 7.88 (d, 1, H_{6or7}), 8.20 (d, 1, H_{11}); $J_{1,2}$ = 4.5, $J_{3,4}$ = 8.6, $J_{6,7}$ = 8.5, $J_{15,16,17}$ = 7.4 Hz. Anal. Calcd for $C_{17}H_{16}O_3$; C, 76.10; H, 6.01. Found: C, 76.38; H, 6.24.

Ethyl 2-[1-(6-Methoxynaphthyl)]propionate (8b). To a stirred suspension of NaH (4.93 g, 200 mmol) in 90 mL of dry 1,2-dimethoxyethane at rt under nitrogen was added dropwise a solution of **8a** (50.04 g, 200 mmol) and methyl iodide (58.22 g, 400 mmol) in 60 mL of the same solvent. The rate of addition was controlled to prevent the temperature from rising above 25 °C in order to prevent formation of the dimethylated product. Stirring was continued for 3 h until reaction was complete (by TLC), and then reaction was quenched by addition of a saturated solution of NH_4Cl and worked up by partition between ether and water. The organic layer was washed with water and brine and dried over $MgSO_4$ and the solvent evaporated. Chromatography of the residue on a silica gel column gave on elution with hexanes and then a hexanes–ether gradient pure **8b** (45.00 g, 87%) as a clear oil: NMR δ 1.16 (t, 3, CH_3CH_2O), 1.62 (d, 3, CH_3), 3.91 (s, 3, CH_3O), 4.12 (dq, 2, CH_3CH_2O), 4.23 (q, 1, CH), 7.15–7.40 (m, 4, Ar), 7.65 (d, 1, Ar), 8.00 (d, 1, Ar). Anal. Calcd for $C_{16}H_{18}O_3$; C, 74.40; H, 7.02. Found: C, 74.43; H, 7.05.

4-[1-(6-Methoxynaphthyl)]-1-propanol (9b). A suspension of $LiAlH_4$ (3.88 g, 1.2 mmol) in 150 mL of dry ether was refluxed for 30 min under nitrogen. Then a solution of **8b** (37.90 g, 147 mmol) in 150 mL of dry ether was added dropwise over a 40-min period, and heating was continued for an additional 30 min. The solution was allowed to cool to rt, and 40 mL of ethyl acetate was added carefully. To the resulting gel was added 30 mL of water dropwise with good stirring. This was followed by 20 mL of aqueous 15% NaOH solution, and then the mixture was diluted with 80 mL of water and filtered through Celite. The layers were separated, the aqueous phase was extracted back with ethyl ether, and the organic fractions were combined, washed with water, and dried over $MgSO_4$. Evaporation of the solvent and purification by flash chromatography through a silica gel column eluted initially with hexanes followed by hexane–ether (1:1) afforded pure **9b** (23.73 g, 75%) as a viscous syrup: NMR δ 1.34 (d, 3, CH_3), 2.16 (br s, 1, OH), 3.69 (m, 2, CH_2), 3.82 (m, 1, CH), 3.85 (s, 3, CH_3O), 7.10–7.39 (m, 4, Ar), 7.58 (d, 1, Ar), 7.98 (d, 1, Ar). Anal. Calcd for $C_{14}H_{16}O_2$; C, 77.75; H, 7.46. Found: C, 77.50; H, 7.51.

1-Iodo-2-[1-(6-methoxynaphthyl)]propane (10b). Reaction of **9b** (23.78 g, 110 mmol) with MsCl (13.78 g, 123 mmol) was conducted by the procedure described for preparation of the mesylate of **10a** (reaction time 2.5 h). Chromatography on silica gel eluted with a hexanes–CH_2Cl_2 gradient furnished the mesylate ester of **9b** as a clear oil (30.97 g, 96%): NMR δ 1.51 (d, 3, CH_3), 2.79 (s, 3, OSO_2CH_3), 3.93 (s, 3, CH_3), 4.04 (m, 2, CH_2), 7.16–7.45 (m, 4, Ar), 7.66 (d, 1, Ar), 8.01 (d, 1, Ar).

A solution of the mesylate (30.97 g, 100 mmol) and NaI (70.03 g, 200 mmol) in 650 mL of dry acetone was stirred at reflux under nitrogen for 24 h. Then it was poured onto ice, extracted with CH_2Cl_2, dried over $MgSO_4$, and evaporated to dryness. Passage of the residue through a Florisil column eluted with hexanes gave **10b** (29.22 g, 81%) as a colorless oil: NMR δ 1.53 (d, 3, CH_3), 3.31 (apparent t, 1, CH_2), 3.54 (dd, 1, CH_2), 3.80 (m, 1, CH), 3.89 (s, 3, CH_3O), 7.14–7.41 (m, 4, Ar), 7.63 (d, 1, Ar), 7.91 (d, 1, Ar). Anal. Calcd for $C_{14}H_{15}IO$; C, 51.55; H, 4.64; I, 38.91. Found: C, 51.50; H, 4.57.

2-[2-[1-(6-Methoxynaphthyl)]propyl]cyclopentanone (11b). A solution of the bromomagnesium salt of *N*-cyclohexyl-*N*-cyclopentenylamine was prepared by heating *N*-cyclohexylcyclopentylidinimine (33 g, 200 mmol) with a 1 M solution of ethyl magnesium bromide (200 mmol) in THF at reflux for 3 h.[14] It was then cooled to rt, a solution of **10b** (32.6 g, 100 mmol) in 100 mL of THF was added, and reflux was continued for 15 h. The reaction mixture was again cooled to rt, 10% HCl solution was added cautiously, and reflux was resumed for 3 h. The product was worked up by partition between ether and water, and the organic layer was washed with a saturated solution of $NaHCO_3$, dried, and evaporated to dryness. Chromatography of the crude product on a column of silica gel eluted with 40% CH_2Cl_2 in hexanes gave **11b** (25.34 g, 90%) as an oil: NMR δ 1.00–2.80 (m, 10, aliphatic), 1.44 (d, 3, CH_3), 3.94 (s, 3, CH_3O), 6.90–8.40 (m, 6, Ar). Anal. Calcd for $C_{19}H_{22}O_2$; C, 80.82; H, 7.85. Found: C, 80.68; H, 7.97.

15,16-Dihydro-3-methoxy-11-methylcyclopenta[a]phenanthrene (6b). The ketone **11b** (13.8 g, 49 mmol) was dissolved in 250 mL of CH_2Cl_2 and added dropwise to a solution of methanesulfonic acid (30 mL) in 600 mL of CH_2Cl_2 at 0 °C. The reaction was stirred at this temperature for 1 h, it was quenched by addition of ice–water, and the organic layer was separated, washed with water, $NaHCO_3$ solution (2×), and brine, dried, and evaporated. The residue was passed through a Florisil column eluted with 20% CH_2Cl_2 in hexanes to afford a mixture of cyclized and disproportionated products. This was dissolved in 600 mL of triglyme and heated at reflux with 4 g of 10% Pd/C for 3–14 h; required reaction time was dependent upon whether the catalyst was Engelhart (3 h) or Aldrich (14 h or more). The resulting suspension was cooled, passed through a Celite plug, and washed with ether. This was extracted with water, and after a back extraction with ether, the combined organics were washed with water and brine, dried, and evaporated. The crude product mixture was purified by flash chromatography eluted with hexane to yield **6b** (8.97 g, 70%) as fine white needles, mp 98–99 °C (EtOH): NMR δ 2.30 (q, 2, H_{16}), 3.10 (s, 3, CH_3), 3.15 (t, 2, $H_{15\text{ or }17}$), 3.30 (t, 2, $H_{15\text{ or }17}$), 3.90 (s, 3, OMe), 7.25 (dd, 1, H_2), 7.35 (d, 1, H_4), 7.40 (s, 1, H_{12}), 7.65 (d, 1, H_{6or7}), 7.75 (d, 1, H_{6or7}), 8.75 (d, 1, H_1); $J_{1,2}$ = 9.1, $J_{2,4}$ = 2.8, $J_{6,7}$ = 8.7, $J_{15,16,17}$ = 7.3 Hz; UV λ_{max} (EtOH) 209 (11 800), 262 (44 300), 307 (6930) nm; *m/z* (EI) 262 (M^+, 100). Anal. Calcd for $C_{19}H_{18}O$; C, 86.99; H, 6.91. Found: C, 87.07; H, 6.95.

15,16-Dihydro-3-hydroxy-11-methylcyclopenta[a]phenanthrene (13b). Demethylation of **6b** (1.44 g, 5.5 mmol) was carried out by the procedure described for the preparation of **13a**. Purification by flash chromatography furnished pure **13b** (1,29 g, 95%) as white needles, mp 168–169 °C: NMR δ 2.29 (q, 2, H_{16}), 3.11 (s, 3, CH_3), 3.15 (t, 2, $H_{15\text{ or }17}$), 3.33 (t, 2, $H_{15\text{ or }17}$), 4.93 (s, 1, OH), 7.17 (dd, 1, H_2), 7.28 (d, 1, H_4), 7.40 (s, 1, H_{12}), 7.61 (d,

1, H_{6or7}), 7.74 (d, 1, H_{6or7}), 8.79 (d, 1, H_1); $J_{1,2}$ = 9.2, $J_{2,4}$ = 2.8, $J_{6,7}$ = 8.8, $J_{15,16,17}$ = 7.4 Hz; UV λ_{max} (EtOH) 207 (24 500), 262 (62 900), 285 (1400), 295 (10 700), 308 (12 300) nm; *m/z* (EI) 248 (M^+, 100). Anal. Calcd for $C_{18}H_{16}O$; C, 87.06; H, 6.49. Found: C, 87.14; H, 6.55.

15,16-Dihydro-11-methylcyclopenta[*a*]phenanthrene-3,4-dione (14b). Oxidation of **13b** (1.20 g, 4.8 mmol) by Fremy's salt was carried out by the procedure described for the preparation of **14a**. Reaction was complete in 4 h (by TLC). The usual workup followed by trituration with ether provided **14b** (1.07 g, 84%) as a red-brown solid, mp 180–182 °C: NMR δ 2.30 (q, 2, H_{16}), 2.96 (s, 3, CH_3), 3.12 (t, 2, $H_{15\text{ or }17}$), 3.27 (t, 2, $H_{15\text{ or }17}$), 6.40 (d, 1, H_2), 7.39 (s, 1, H_{12}), 7.87 (d, 1, H_{6or7}), 8.12 (d, 1, H_{6or7}), 8.58 (d, 1, H_1); $J_{1,2}$ = 10.8, $J_{6,7}$ = 8.8, $J_{15,16,17}$ = 8.5 Hz; UV λ_{max} (EtOH) 218 (10 800), 236 (12 000), 309 (11 600), 395 (3300) nm. Anal. Calcd for $C_{18}H_{14}O_2$; C, 82.42; H, 5.38. Found: C, 82.44; H, 5.45.

***trans*-3,4-Dihydroxy-11-methyl-3,4,15,16-tetrahydrocyclopenta[*a*]phenanthrene (3b).** Reduction of **14b** (855 mg, 3.26 mmol) with a large excess of $NaBH_4$ (4.5 g) in ethanol (500 mL) was carried out by the procedure for the preparation of **3a** (96 h). Trituration of the crude product with ether gave **3b** (615 mg, 71%) as a white solid, mp 188–190 °C: NMR (DMSO-d_6) δ 2.12 (q, 2, H_{16}), 2.94 (t, 2, $H_{15\text{ or }17}$), 3.10 (t, 2, $H_{15\text{ or }17}$), 3.24 (s, 3, CH_3), 4.22 (m, 1, H_3), 4.47 (dd, 1, H_4), 5.08 (d, 1, OH), 5.43 (d, 1, OH), 5.96 (dd, 1, H_2), 7.15 (s, 1, H_{12}), 7.22 (dd, 1, H_1), 7.61 (br s, 1, H_{6or7}), 7.67 (br s, 1, H_{6or7}); $J_{1,2}$ = 10.4, $J_{2,3}$ = 2.0, $J_{3,4}$ = 8.4, $J_{6,7}$ = 8.5, $J_{15,16,17}$ = 7.3 Hz; UV λ_{max} (EtOH) 204 (12 300), 221 (10 800), 244 (28 200), 333 (4030), 356 (3830) nm; *m/z* (EI) 266 (M^+, 70), 248 (100). Anal. Calcd for $C_{18}H_{18}O_2$; C, 81.17; H, 6.81. Found: C, 81.11; H, 6.75.

***trans*-3,4-Dihydroxy-*anti*-1,2-epoxy-1,2,3,4,15,16-hexahydro-11-methylcyclopenta[*a*]phenanthrene (4b).** Epoxidation of **3b** (10 mg) was carried out by the procedure for preparation of **4a**. Trituration of the crude product with ether gave **4b** (8.2 mg, 76%) as a white solid, mp 165–167 °C dec: NMR (DMSO-d_6) δ 2.20 (q, 2, H_{16}), 2.90 (s, 3, CH_3), 3.05 (t, 2, $H_{15\text{ or }17}$), 3.20 (t, 2, $H_{15\text{ or }17}$), 3.67 (dd, 1, H_2), 3.80 (m, 1, H_3), 4.46 (dd, 1, H_4), 4.88 (dd, 1, H_1), 5.52 (d, 1, OH), 5.72 (d, 1, OH), 7.35 (s, 1, H_{12}), 7.82 (s, 2, $H_{6,7}$); $J_{1,2}$ = 4.5, $J_{2,3}$ = 1.7, $J_{3,4}$ = 8.5, $J_{15,16,17}$ = 7.2 Hz; UV λ_{max} (EtOH) 222 (7800), 244 (18 700), 307 (1250) nm. Anal. Calcd for $C_{18}H_{18}O_3$; C, 76.57; H, 6.43. Found: C, 76.75; H, 6.55.

2α-Bromo-1,2,3,4,15,16-hexahydro-11-methyl-1β,3α,4β-trihydroxycyclopenta[*a*]phenanthrene (15b). Conversion of **3b** (50 mg, 0.19 mmol) to **15b** was carried out by the procedure used for the preparation of **15a**. Reaction was complete in 25 min. Trituration of the crude product with ether gave **15b** (45 mg, 65%) as a white solid, mp 136–137 °C dec: NMR (DMSO-d_6 + D_2O) δ 2.19 (q, 2, H_{16}), 2.94 (s, 3, CH_3), 2.96 (t, 2, $H_{15\text{ or }17}$), 3.10 (t, 2, $H_{15\text{ or }17}$), 4.21 (dd, 1 H_3), 4.61 (m, 2, $H_{2,4}$), 5,82 (dd, 1, H_1), 7.28 (s, 1, H_{12}), 7.70 (d, 1, H_{6or7}) 7.79 (d, 1, H_{6or7}); $J_{1,2}$ = 4.5, $J_{2,3}$ = 2.7, $J_{3,4}$ = 7.9, $J_{6,7}$ = 8.6, $J_{15,16,17}$ = 7.3 Hz. Anal. Calcd for $C_{18}H_{19}BrO_3$; C, 59.52; H, 5.27. Found: C, 59.40; H, 5.03.

***trans*-3,4-Dihydroxy-*syn*-1,2-epoxy-1,2,3,4,15,16-hexahydro-11-methylcyclopenta[*a*]phenanthrene (5b).** The synthesis of **5b** from **15b** (7.5 mg, 0.02 mmol) was conducted by the method used for preparation of **5a** (reaction time 40 min). The product was triturated with ether to yield **5b** (4.2 mg, 72%) as a white solid, mp 141–143 °C dec: NMR (DMSO-d_6 + D_2O) δ 2.15 (q, 2, H_{16}), 2.90 (s, 3, CH_3), 3.05 (t, 2, $H_{15\text{ or }17}$), 3.20 (t, 2, $H_{15\text{ or }17}$), 4.10 (m, 2, $H_{2,3}$), 4.45 (d, 1, H_1), 4.62 (m, 1, H_4), 7.30 (s, 1, H_{12}), 7.69 (d, 1, H_{6or7}) 7.82 (d, 1, H_{6or7}); $J_{1,2}$ = 4.5, $J_{3,4}$ = 8.2, $J_{6,7}$ = 8.5, $J_{15,16,17}$ = 7.2 Hz. Anal. Calcd for $C_{18}H_{18}O_3$; C, 76.57; H, 6.43. Found: C, 76.43; H, 6.58.

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