Synthesis of *anti*- and *syn*-Diol Epoxides of *trans*-3,4-Dihydroxy-3,4-dihydrobenzo[*ghi*]fluoranthene: Model Planar Diol Epoxides

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We describe the preparation of *anti*- and *syn*-3,4-dihydroxy-5,5a-epoxy-3,4,5,5a-tetrahydrobenzo-[*ghi*]fluoranthene (**2** and **3**) as model planar diol epoxides. These compounds were synthesized by a dihydroarene method in 10 steps starting from 4*H*-cyclopenta[*def*]phenanthrene. These are the first examples of diol epoxides in which a five-membered ring is fused to the saturated ring bearing an epoxide group, and they are the rigid analogues of the extensively studied benzo[*c*]phenanthrene diol epoxides (**5** and **6**). In accord with expectation, ^{1}H NMR data indicated that the diol conformations of **2** and **3** are locked into diequatorial and diaxial conformations, respectively, and thus are suitable for comparative DNA binding studies.

Introduction

Polycyclic aromatic hydrocarbons (PAHs) are an important class of carcinogens that are found in various environmental, occupational, and food chain settings.[1] In recent years, there has been a renewed interest in structure−activity relationships of PAHs.[2,3] This is due primarily to the findings that PAHs containing a fjord region are exceptionally mutagenic/tumorigenic and their corresponding diol epoxides exhibit a higher DNA adduct formation ability and a greater binding affinity to deoxyadenosine over deoxyguanosine compared to less-hindered bay-region PAH diol epoxides.[4,5] Studies have shown that these features are not limited to fjord-region PAHs but are general to those derived from other nonplanar PAHs, such as 7,12-dimethylbenz[*a*]anthracene[6] and 5,6-dimethylchrysene.[7] The substantial amount of data accumulated thus far supports a trend of increased diol epoxide activities as the molecular deformity of the carcinogen and the population of diequatorial diol conformations increase.

To understand better the role of structural factors in the mechanisms of PAH carcinogenesis, we have focused on the preparation of two model diol epoxides derived from the planar PAH benzo[*ghi*]fluoranthene (**1**, Figure 1): *anti*- and *syn*-3,4-dihydroxy-5,5a-epoxy-3,4,5,5a-tetrahydrobenzo[*ghi*]fluoranthene (**2** and **3**, Figure 1). These are rigid structure analogues of *anti*- and *syn*-3,4-dihydroxy-1,2-epoxy-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene (**5** and **6**, Figure 1), which are derived from the nonplanar PAH benzo[*c*]phenanthrene (**4**). The latter PAH is one of the most mutagenic PAHs known and has been investigated extensively. For instance, all 16 possible purine DNA adducts derived from **5** and **6** have been isolated and characterized.[8] Although **1** and **4** are similar, the linkage between the fjord-region carbons (e.g., C5a−C5e) makes the model molecule **1** planar and rigid (Figure 1). The four sides in the fjord region of **2** and **3** are fused with a phenanthrene ring system, causing their diol conformation to be locked into diequatorial and diaxial orientations, respectively. Thus, the rigid model **2** shares common conformational features with **5** but lacks the steric distortion of the ring aromatic system. An expectation is that **2** would exhibit DNA binding

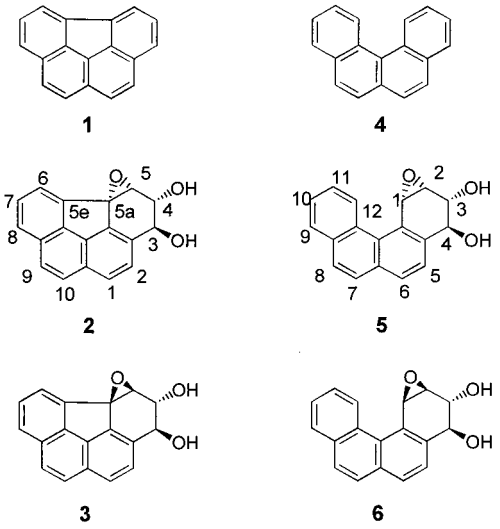

Figure 1. Structures and numberings of benzo[*ghi*]fluoranthene (**1**) and benzo[*c*]phenanthrene (**4**) and the corresponding *anti*- (**2** and **5**) and *syn*- (**3** and **6**) diol epoxides.

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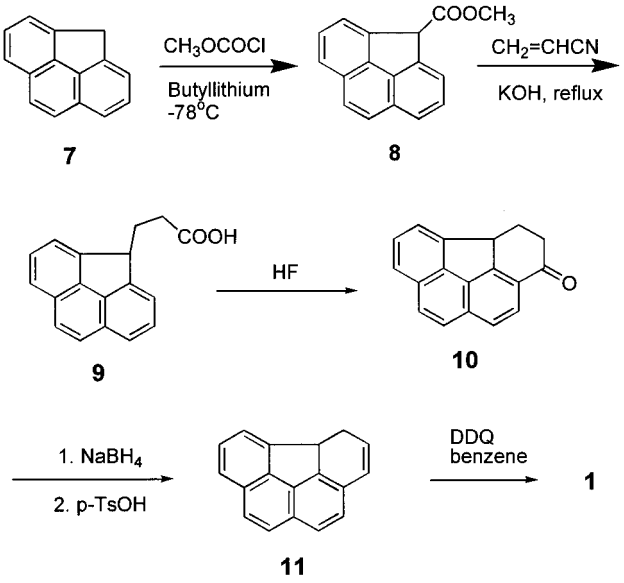
Scheme 1



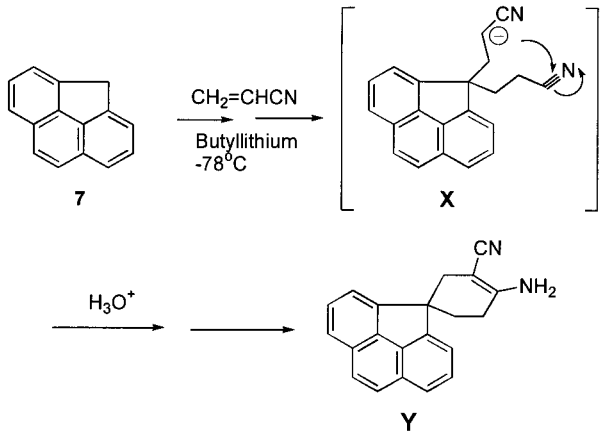
profiles different from those observed for the corresponding nonrigid derivative **5**. The steric crowding in the fjord region of **5** leads to distortion from planarity, which hinders charge localization, thus favoring adduct formation over hydrolysis. In contrast, the gain of planarity in the model diol epoxide **2** will lead to an efficient resonance stabilization of the presumed carbocationic site C5a, disfavoring adduct formation. Sterically, the lack of molecular deformity allows the model molecule ready access to the narrow minor groove of DNA, resulting in a greater deoxyguanosine adduct formation (i.e., a lower deoxyadenosine/deoxyguanosine adduct ratio).[2] Such experiments may provide valuable insight into the mechanisms of fjord-region PAH carcinogenesis. The proposed studies require the preparation of the model diol epoxides **2** and **3**, which is the subject of this report.

Results and Discussion

Syntheses of the two model compounds, **2** and **3**, were achieved from dihydroarene precursors, a general synthetic strategy for bay-region and non-K-region diol epoxides.[1] As shown in Scheme 1, treatment of 4*H*-cyclopenta[*def*]phenanthrene (**7**) with methyl chloroformate in the presence of butyllithium yielded the methyl ester **8**. Michael addition of **8** to acrylonitrile in the presence of KOH, followed by hydrolysis and decarboxylation, afforded **9**. An attractive alternative synthetic route to **9** appeared to be direct Michael addition of 1 equiv of acrylonitrile to the lithiated **7** and subsequent hydrolysis. The procedure, however, resulted in a double addition of acrylonitrile to yield the dinitrile **X**, which underwent an intramolecular Thorpe−Ziegler cyclization,[9] affording **Y** (Scheme 2). Both mass and ^{1}H NMR spectral data are consistent with the cyclized cyanoamine structure of **Y**. The presence of the nitrile and amino groups was also confirmed by characteristic stretching absorption bands at 2185 and 3025 cm^{-1}, respectively, in the IR spectrum of **Y**.

Cyclization of **9** in liquid HF furnished the ketone **10** in nearly quantitative yield. The conversion of **7** to **10** was accomplished in about 30% yield. This represents a major improvement over the existing literature method by Campbell and Reid,[10] which involves multiple steps with low yields and harsh reaction conditions. The ketone **10** was reduced by $NaBH_4$ and dehydrated to give the dihydroarene **11**, which served as the key intermediate for the synthesis of the model compounds **2** and **3** (Scheme 3). Treatment of **11** with DDQ in benzene afforded the parent hydrocarbon benzo[*ghi*]fluoranthene (**1**) in 66% yield.

Scheme 2



Conversion of **11** to the 3,4-quinone **15** was accomplished by a four-step sequence as shown in Scheme 3. Prévost reaction of **11** with silver benzoate and molecular iodine in dry benzene gave exclusively the *trans* tetrahydro dibenzoate **12** in 82% yield. Initially, we aimed at preparing the dihydrodiol **16** through a general two-step procedure, i.e., a selective DDQ dehydrogenation of the C5−C5a bond in **12** and subsequent ester cleavage by $NaOCH_3$. TLC analyses indicated that such dehydrogenation indeed occurred initially but proceeded readily to the fully aromatic **13**. Attempts to increase the formation of the C5−C5a dehydro intermediate by way of controlling the amount of DDQ and variation of the reaction temperature were not successful. Instead, a complete conversion was achieved by employing an excess amount (4 equiv) of DDQ, which provided **13** in 76% yield. Hydrolysis of **13** took place smoothly in methanolic $NaOCH_3$ to yield the catechol **14**. Subsequent oxidation of **14** with Jones' reagent gave the desired quinone **15** in 80% yield. A sharp singlet at 6.92 ppm in the ^{1}H NMR spectrum of **15** is consistent with the presence of an isolated olefinic proton at C5.

The $NaBH_4$ reduction of **14** in absolute ethanol in the presence of oxygen occurred in an expected manner to give the *trans*-dihydrodiol **16**. The coupling constant (6.9 Hz) between H3 and H4 ($J_{3,4}$) in acetone-d_6 implied that the two hydroxyl groups exist as a mixture of diaxial and diequatorial orientations.[11] The $J_{3,4}$ value for **16** is relatively smaller than those (7−11 Hz) observed for other structurally similar dihydrodiols, indicating that the conformational equilibrium is shifted in favor of a diaxial conformer. Molecular modeling indicated that the diol conformation of **16** is distorted by the unique rigidity imposed by a fully substituted five-membered ring in the molecule. The reduction of PAH orthoquinones by metal

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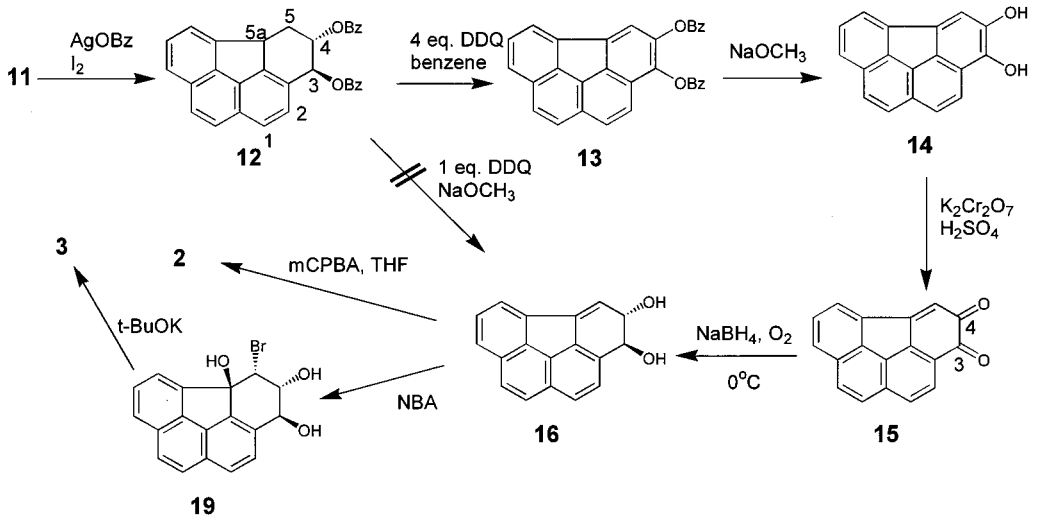
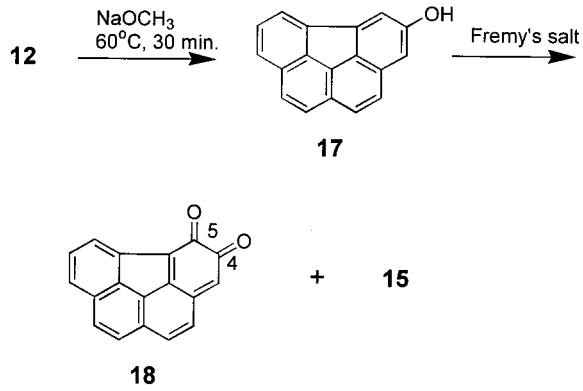
Scheme 3



Scheme 4



hydrides has been widely used for the synthesis of dihydrodiols, but is known to be sensitive to the reaction conditions, such as the presence of oxygen and the temperature.[12] In our case, the reduction of **15** required a strict control of oxygen bubbling and temperature (0 °C); otherwise over-reduced products were formed. These side products were not further characterized.

A potentially interesting alternative to **16** would be the one that involves hydrolysis of the two benzoate groups of **12** followed by DDQ oxidation (Scheme 3). Curiously, however, treatment of **12** with $NaOCH_3$ at 60 °C afforded 4-hydroxybenzo[*ghi*]fluoranthene (**17**) as the sole product (Scheme 4). The mechanism of this phenol formation is not clear, although it should involve a base-catalyzed elimination followed by a dehydrogenative oxidation. Subsequent oxidation of **17** with Fremy's salt proceeded in good yield, resulting in a 5.5:1 mixture of **15** and the isomeric 4,5-quinone (**18**). The two quinones could only be separated by HPLC.

Conversion of **16** to *trans*-3,4-dihydroxy-*anti*-5,5a-epoxy-3,4,5,5a-tetrahydrobenzo[*ghi*]fluoranthene (**2**) was accomplished by treatment with *m*-CPBA in anhydrous THF. The *syn* diastereomer was not detected by ^{1}H NMR spectroscopy. As expected, reaction of **16** with *N*-bromoacetamide in aqueous THF yielded the bromohydrin intermediate **19**, which was subsequently treated with *t*-BuOK to yield the corresponding *syn*-isomer, *trans*-3,4-dihydroxy-*syn*-5,5a-epoxy-3,4,5,5a-tetrahydrobenzo[*ghi*]-fluoranthene (**3**). The NMR data of **2** and **3** were consistent with their assignments. The key starting point was an NOE between H2 and H3, from which subsequent assignments of the H3−H4−H5 proton network were established by using additional NOE, homonuclear decoupling, and COSY experiments. In acetone-d_6, the H3−H4−H5 protons of **2** were well separated over a 1 ppm range. The corresponding signals in the *syn* isomer were severely congested in a narrow range (~0.2 ppm) around 4.8 ppm, which became dispersed by addition of D_2O.

The rigid nature of the aromatic moiety in the model *anti*- and *syn*-diol epoxides causes their diol orientations to be locked into diequatorial and diaxial, respectively. Molecular mechanics calculations indicate that the dihedral angles between H3 and H4 for the *anti* and *syn* isomers are 166° and 67°, respectively. This is consistent with the relatively large $J_{3,4}$ coupling constant (8.1 Hz) observed for the *anti*-diol epoxide **2**, which indicates a preference for the diequatorial diol orientation. This result is also in good agreement with those observed for other structurally similar diol epoxides.[1,11] For instance, the J_{diol} value (9.0 Hz) reported[1] for the nonplanar analogue **5**, in which the epoxide oxygen atom is severely crowded in the fjord region, has also been assumed to be due to a preferred diequatorial diol conformation. On the other hand, the *syn*-isomer **3** exhibited a comparatively lower $J_{3,4}$ value (2.0 Hz), which indicates a markedly higher ratio of the diaxial diol orientation. The ^{1}H NMR spectrum of **3** in acetone-d_6 showed a high-field-shifted, D_2O-exchangeable doublet at 3.30 ppm with a relatively large coupling constant (9.5 Hz), which can be assigned to the benzylic 3-OH hydrogen bonded to the epoxide oxygen. This intramolecular hydrogen bonding may contribute to stabilization of the diaxial diol orientation of the *syn* isomer. A small zigzag coupling ($J_{3,5}$ = 1.3 Hz) between H3 and H5 further defines the unique stereochemistry of the *syn* diol epoxide. A similar long-range coupling was not observed for the *anti* isomer (**2**). Small $J_{4,5}$ coupling constants were observed for the *anti*- (1.1 Hz) and *syn*- (2.0 Hz) isomer, consistent with the molecular modeling structures.

The model diol epoxides (**2** and **3**) described here are the first examples of diol epoxides in which a five-membered ring is fused to the saturated ring bearing an epoxide function. They are rigid analogues of the exten-

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sively studied **5** and **6** with clearly defined diol stereochemistry and molecular deformity and thus are suitable for comparative DNA binding studies. Despite their highly strained ring structure, the newly synthesized diol epoxides are relatively stable, as has been observed with structurally similar diol epoxides derived from fluoranthene,[13] benzo[*j*]fluoranthene,[14] and 4*H*-cyclopenta[*def*]-chrysene.[15]

DNA Binding Studies. Preliminary DNA-binding experiments[16] indicate that, compared to **5**, the model diol epoxide **2** showed a consistently lower extent of DNA−adduct formation, as well as lower affinity to deoxyadenosine over deoxyguanosine. These results confirm the importance of ring deformity for DNA−adduct formation and base selectivity. The DNA binding study results will be reported elsewhere.

Experimental Section

Material and Methods. Tetrahydrofuran (THF) was distilled from $LiAlH_4$, followed by a fresh distillation from sodium/benzophenone prior to use. Benzene was distilled from CaH_2 and stored over molecular sieves prior to use. All reagents including the starting material 4*H*-cyclopenta[*def*]phenanthrene were purchased from Aldrich Co. (Milwaukee, WI). All organic solvents were purchased from Fisher Scientific (Pittsburgh, PA). Melting points were determined on a Büchi 535 melting point apparatus and are uncorrected. Elemental analyses were obtained from M-H-W Laboratories, Phoenix, AZ. High-resolution mass spectra (HRMS) were obtained at the University of Illinois Mass Spectrometry Laboratory, Urbana−Champaign, IL. HPLC separations with a photodiode array detector were conducted using C_{18} columns. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Chemical shifts were expressed in ppm with respect to the internal standard tetramethylsilane (TMS).

Methyl 4*H*-Cyclopenta[*def*]phenanthrene-4-carboxylate (8). Butyllithium (2.8 mL, 1.60 M in hexane, 4.48 mmol) was added to a solution of 4*H*-cyclopenta[*def*]phenanthrene (**7**, 613 mg, 3.23 mmol) in 50 mL of freshly distilled dry THF under a nitrogen atmosphere at −78 °C. The solution turned red immediately. After 20 min of stirring at −78 °C, methyl chloroformate (0.26 mL, 3.20 mmol) was quickly added. After the solution had begun to turn yellow (in minutes), the reaction was quenched by addition of water. The resulting solution was concentrated under reduced pressure to remove THF, and the aqueous solution thus obtained was extracted with ethyl acetate. The combined organic extracts were washed with water and dried over anhydrous $MgSO_4$. Column chromatography on silica gel, using hexane and ethyl acetate (97:3) as the eluent, gave 276 mg of recovered starting material and 379 mg (47%) of **8**. Recrystallization from ethanol gave the product as light-yellow needles: mp 62 °C (lit. 63.5−64.5 °C[17]); ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3, CH_3), 5.41 (s, 1, H_4), 7.74−7.79 (m, 8, aromatic).

4-(2′-Carboxyethyl)-4*H*-cyclopenta[*def*]phenanthrene (9). Acrylonitrile (0.30 mL, 4.56 mmol) was added to a solution of **8** (727 mg, 2.93 mmol) in 3 mL of di(ethylene glycol) ethyl ether and 8 mL of 0.2 M KOH. After 1 h of stirring, 5 mL of 10 M KOH and 2.5 mL of di(ethylene glycol) ethyl ether were added, and the reaction mixture was refluxed for 5 h. The cooled reaction mixture was neutralized with 6 M HCl and extracted with ether. The combined ether extracts were washed several times with water and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography on silica gel using chloroform as the eluent. The product was obtained as brown needles after recrystallization from ethanol: mp 160 °C (lit. 149−153 °C[10]); ^{1}H NMR ($CDCl_3$) δ 2.30 (t, 2, $H_{1'}$, $J_{1,2}$ = 7.2 Hz), 2.53 (m, 2, $H_{2'}$), 4.63 (m, 1, H_4), 7.60−7.90 (m, 8, aromatic).

3,4,5,5a-Tetrahydrobenzo[*ghi*]fluoranthen-3-one (10). The acid **9** (2.73 g, 10.4 mmol) was placed in a gastight Teflon delivery system containing ∼15 mL of HF. The dark reaction mixture was stirred overnight under a nitrogen atmosphere in a closed system at room temperature. The residual HF was removed with the aid of a combination of reduced pressure and flushed nitrogen. The resulting solid was dissolved in methylene chloride, and the solution washed with dilute KOH and water and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography on silica gel, using hexane/ethyl acetate (95:5). Recrystallization from ethanol furnished pure **10** (2.5 g, 97%): mp 161 °C (lit.159−161 °C[10]); ^{1}H NMR ($CDCl_3$) δ 1.70−1.85 (m, 1), 2.85−3.15 (m, 1), 2.95 (m, 1), 3.05 (m, 1), 4.65 (dd, 1, H_{5a}, $J_{5,5a}$ = 5.0 Hz, $J_{5',5a}$ = 12.8 Hz), 7.60−8.00 (m, 7, aromatic); ^{13}C NMR ($CDCl_3$) δ 28.3, 40.4, 46.8, 121.6, 122.8, 123.7, 124.4, 125.2, 126.8, 127.7, 128.6, 130.9, 135.7, 138.7, 145.2, 154.4, 196.6 (C=O).

5,5a-Dihydrobenzo[*ghi*]fluoranthene (11). To a solution of **10** (694 mg, 2.84 mmol) in 200 mL of absolute ethanol was added $NaBH_4$ (1.80 g, 47.6 mmol). After stirring at room temperature for 2 h, the reaction was quenched by addition of water, and the solvent was removed under reduced pressure. The residue was extracted with ether. The organic phase was washed with water and dried over anhydrous $MgSO_4$. After removal of the solvent under reduced pressure, the solid residue was refluxed for 5 h in 200 mL of dry benzene containing a catalytic amount of *p*-TsOH. The cooled reaction mixture was successively washed with 5% $NaHCO_3$, H_2O, and saturated NaCl. The organic phase was dried over $MgSO_4$ and concentrated to give a residue, which was purified by column chromatography on silica gel using hexane/ethyl acetate (95:5) to furnish **11** as plates (596 mg, 92%): mp 113 °C (ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$) δ 2.07 (tt, 1, H_5, $J_{5,5'} \sim J_{5,5a}$ = 16.1 Hz, $J_{4,5}$ = 2.4 Hz, $J_{3,5}$ = 3.0 Hz), 3.00 (ddd 1, $H_{5'}$, $J_{5,5'}$ = 16.1 Hz, $J_{5',5a}$ = 8.6 Hz, $J_{4,5'}$ = 6.4 Hz), 4.45 (dd, 1, H_{5a}, $J_{5,5a}$ = 16.1 Hz, $J_{5',5a}$ = 8.6 Hz), 6.04 (td, 1, H_4, $J_{3,4}$ = 9.3 Hz, $J_{4,5}$ = 2.4 Hz, $J_{4,5'}$ = 6.4 Hz), 6.74 (dd, 1, H_3, $J_{3,4}$ = 9.3 Hz, $J_{3,5}$ = 3.0 Hz), 7.24 (d, 1, H_6 or H_8, J = 8.0 Hz), 7.47 (t, 1, H_7, J = 7.4 Hz), 7.54 (d, 1, H_6 or H_8, J = 7.1 Hz), 7.62 (d, 1, H_1 or H_2, $J_{1,2}$ = 7.5 Hz), 7.66 (d, 2, H_9 and H_{10}, $J_{9,10}$ = 7.8 Hz), 7.69 (d, 1, H_1 or H_2, $J_{1,2}$ = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 26.6, 43.0, 121.6, 123.2, 123.3, 123.5, 125.0, 125.4, 126.9, 127.1, 127.3, 128.7, 128.9, 129.4, 133.8, 139.9, 141.8 (olefinic), 146.73 (olefinic). Anal. Calcd for $C_{18}H_{12}$: C, 94.70; H, 5.30. Found: C, 94.56; H, 5.45.

Benzo[*ghi*]fluoranthene (1). Dihydroarene **13** (46 mg, 0.20 mmol) was heated at reflux for 6 h in 10 mL of benzene containing DDQ (137 mg, 0.60 mmol). The reaction mixture was poured onto a short column containing neutral (activity I) aluminum oxide. Elution with benzene furnished a solid residue, which after recrystallization from benzene gave pure **1** as yellow needles (30 mg, 66%): mp 140 °C (lit. 145−148 °C[10]); ^{1}H NMR ($CDCl_3$) δ 7.66 (dd, $H_{4,7}$, J = 7.5 Hz), 7.85−8.00 (m, 6), 8.09 (d, 2, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 123.3, 125.0, 126.4, 126.6, 126.7, 127.7, 128.3, 133.1, 133.3, 137.4. Anal. Calcd for $C_{18}H_{10}$: C, 95.55; H, 4.46. Found: C, 95.60; H, 4.48.

***trans*-3,4-Bis(benzyoyloxy)-3,4,5,5a-tetrahydrobenzo-[*ghi*]fluoranthene (12).** A suspension of silver benzoate (1.15 g, 5.0 mmol) and iodine (0.64 g, 2.5 mmol) in 75 mL of dry benzene was stirred under reflux until all iodine was consumed as indicated by a color change from red to yellow. A solution of **11** (250 mg, 1.10 mmol) in 50 mL of dry benzene was added to the suspension, and the reaction mixture was refluxed for another 2 h. After cooling to room temperature, the reaction mixture was filtered through Celite, and the solvent was

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evaporated. Column chromatography on Florisil using hexane/ethyl acetate (first 97:3 and then 90:10) provided a solid product. Dibenzoate **12** (420 mg, 82%) was obtained as a white solid after recrystallization from hexane: mp 192 °C; ^{1}H NMR ($CDCl_3$) δ 1.86 (AB quartet, 1, H_5), 3.27 (m, 1, $H_{5'}$), 4.81 (dd, 1, H_{5a}, $J_{5,5a}$ = 12.6 Hz, $J_{5',5a}$ = 4.70 Hz), 6.25−6.40 (m, 1, H_4), 6.79 (d, 1, H_3, $J_{3,4}$ = 6.9 Hz), 7.30−8.30 (m, 17, aromatic); ^{13}C NMR ($CDCl_3$) δ 33.4, 44.6, 74.6, 77.1, 121.1, 123.6, 124.8, 125.2, 126.4, 127.1, 127.4, 128.1, 128.4, 128.5, 128.6, 129.8, 129.9, 130.0, 133.1, 136.2, 138.5, 145.2, 145.8, 166.2 (C=O), 166.9 (C=O). Anal. Calcd for $C_{32}H_{22}O_4$: C, 81.69; H, 4.71. Found: C, 81.67; H, 4.51.

3,4-Bis(benzoyloxy)benzo[*ghi*]fluoranthene (13). A solution of tetrahydrodibenzoate **12** (1.50 g, 3.2 mmol) and DDQ (2.91 g, 12.8 mmol) in 300 mL of dry benzene was heated at reflux for 18 h. After cooling, the reaction mixture was filtered through Celite and washed successively with 5% $Na_2S_2O_5$, water, 5% NaOH, and saturated NaCl solution. The organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The solid residue was subjected to column chromatography on Florisil first with hexane/ethyl acetate (97:3) and then with chloroform. Recrystallization from benzene afforded pure **13** (1.13 g, 76%): mp 226−227 °C; ^{1}H NMR ($CDCl_3$) δ 7.39 (s, 1, H_5), 7.4−7.5 (4), 7.55−7.72 (m, 4), 7.90−8.00 (m, 4), 8.07 (d, 1, J = 8.2 Hz), 8.12−8.30 (m, 4); ^{13}C NMR ($CDCl_3$) δ 120.6, 121.9, 122.1, 123.8, 125.0, 126.2, 126.8, 126.8, 127.1, 128.0, 128.4, 128.5, 128.6, 128.7, 128.8, 129.1, 130.3, 130.5, 132.1, 132.7, 133.7, 133.8, 135.5, 136.6, 139.2, 142.6, 164.5 (C=O), 164.9 (C=O); MS *m*/*z* (relative abundance) 466.1 (M^+, 15), 105.0 (100); HRMS calcd for $C_{32}H_{18}O_4$ 466.1205, found 466.1206. Anal. Calcd for $C_{32}H_{18}O_4$: C, 82.39; H, 3.89. Found: C, 82.56; H, 3.95.

Benzo[*ghi*]fluoranthene-3,4-dione (15). Sodium methoxide (3.96 mL, 0.5 M, 1.98 mmol) in methanol was added to a solution of **16** (421 mg, 0.90 mmol) in 40 mL of dry THF, and the reaction mixture was stirred under N_2 at room temperature. After 10 min, the reaction was quenched by addition of water, and the solvent was removed under reduced pressure. The resulting aqueous mixture was extracted with methylene chloride, and the organic phase was dried over anhydrous $MgSO_4$. Evaporation of the solvent furnished the catechol **14**, which was used for the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 6.96 (s, 1, H_5), 7.68 (dd, 1, H_7, J = 8.0, 7.3 Hz), 7.77 (d, 1, J = 8.8 Hz), 7.80 (d, 1, J = 8.3 Hz), 7.87 (m, 2), 7.94 (m, 2); ^{13}C NMR ($CDCl_3$) δ 123.8, 124.0, 125.2, 125.5, 125.8, 126.7, 128.3, 128.6, 129.2, 129.5, 130.7, 133.1, 140.1, 141.5, 150.7, 175.8 (C−OH), 182.2 (C−OH). To a solution of $K_2Cr_2O_7$ (702 mg, 2.4 mmol) in 25 mL of 50% sulfuric acid was added **14**, and the mixture was stirred at room temperature for 2 h. The reaction mixture was extracted with benzene, and the organic layer was dried over anhydrous $MgSO_4$. Silica gel chromatography with dichloromethane/hexane (6:4) as an eluent, followed by a recrystalization (dichloromethane/hexane) gave the 3,4-dione **15** (184 mg, 80%) as red crystals: mp ∼285 °C; ^{1}H NMR ($CDCl_3$) δ 6.92 (s, 1, H_5), 7.68 (dd, 1, H7, $J_{6,7}$ = 7.3 Hz, $J_{7,8}$ = 8.2 Hz), 7.76 (d, 1, H_{10}, $J_{9,10}$ = 8.4 Hz), 7.77 (d, 1, H_1, $J_{1,2}$ = 9.1 Hz), 7.85 (d, 1, H_9, $J_{9,10}$ = 8.4 Hz), 7.85 (d, 1, H_8, $J_{7,8}$ = 8.2 Hz), 7.93 (d, 1, H_2, $J_{1,2}$ = 9.1 Hz), 7.94 (d, 1, H_6, $J_{6,7}$ = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 123.7, 124.0, 125.2, 125.5, 125.6, 126.6, 128.3, 128.6, 129.2, 129.4, 130.7, 133.0, 140.0, 140.5, 150.6, 176.5 (C=O), 182.1 (C=O); MS *m*/*z* (relative abundance) 256.0 (M^+, 42), 200.1 (100); HRMS calcd for $C_{18}H_8O_2$ 256.0524, found 256.0536. Anal. Calcd for $C_{18}H_8O_2$: C, 87.79; H, 3.27. Found: C, 87.84; H, 3.33.

4-Hydroxybenzo[*ghi*]fluoranthene (17). To a solution of **12** (60 mg, 0.13 mmol) in 6 mL of dry THF was added $NaOCH_3$ (0.8 mL, 0.5 M, 20 mmol) in methanol, and the reaction mixture was heated at 60 °C under nitrogen for 10 min. The reaction was quenched by the addition of H_2O and concentrated under reduced pressure. The residue was neutralized by adding 6 M HCl, and the resulting aqueous solution was extracted with ether (3 × 30 mL). The combined ether extracts were washed with water and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography on silica gel using hexane/ethyl acetate (9:1) and then chloroform as an eluent provided pure **17** (23 mg, 75%): ^{1}H NMR (acetone-d_6) δ 7.40 (d, 1, H_3, $J_{3,5}$ = 1.4 Hz), 7.73 (dd, 1, H_7, $J_{6,7}$ = 7.0 Hz, $J_{7,8}$ = 8.1 Hz), 7.89 (d, 1, H_1 or H_2, $J_{1,2}$ = 8.7 Hz), 7.90 (d, 1, H_5, $J_{3,5}$ = 1.4 Hz), 7.88−7.98 (m, 3, $H_{9,10}$, H_1 or H_2), 8.00 (d, 1, H_8, $J_{7,8}$ = 8.1 Hz), 8.22 (d. 1, H_6, $J_{6,7}$ = 7.0 Hz), 8.96 (s, 1, OH); ^{13}C NMR (acetone-d_6) δ 110.1, 117.1, 124.5, 126.1, 126.2, 126.26, 126.30, 127.0, 127.7, 128.5, 128.9, 129.4, 129.4, 134.0, 134.6, 138.1, 139.7, 160.3 (C−OH); MS *m*/*z* (relative abundance) 242.1 (M^+, 100); HRMS calcd for $C_{18}H_{10}O$ 242.0732, found 242.0739.

Fremy's salt (89 mg, 0.33 mol), dissolved in 2.5 mL of 0.17 M potassium hydrogen phosphate (KH_2PO_4), was poured into a solution of **17** (20 mg, 0.083 mmol) in 10 mL of dry benzene. To the reaction mixture were added one drop of Adogen 464 and 2.5 mL of water, and then the mixture was stirred vigorously for 30 min. The benzene layer was separated from the water layer, and the water layer was back extracted with benzene three times. The combined benzene layers were dried over anhydrous $MgSO_4$, and the benzene was evaporated under reduced pressure. The ^{1}H NMR spectrum of the residue (13 mg) in $CDCl_3$ showed two singlets at 6.9 and 7.3 ppm in a ratio of 5.5 to 1, which correspond to the olefinic protons of the desired 3,4-dione (**15**) and the 4,5-dione (**18**) isomer, respectively.

***trans*-3,4-Dihydroxy-3,4-dihydrobenzo[*ghi*]fluoranthene (16).** To a solution of **15** (184 mg, 0.72 mmol) in 125 mL of absolute ethanol was added $NaBH_4$ (571 mg, 15.0 mmol), and the mixture was bubbled with O_2 at 0 °C in the dark. The reaction progress was monitored by HPLC [C_{18} column (4.6 mm × 25 cm), with 60% methanol at the rate of 1.0 mL/min]. The retention time of the dihydrodiol product was 10.3 min. The reduction was completed within 8−10 h. The excess hydride was decomposed by adding water, and the solvent was evaporated under reduced pressure using a dry ice/acetone cooler. The solid residue was treated with ice water and extracted with cold ether and ethyl acetate (1:1) several times. The combined organic phase was dried over anhydrous $MgSO_4$ and evaporated under diminished pressure to give about 115 mg of a solid residue. Chromatographically pure **16** (∼40 mg) was obtained by HPLC separation on a semiprep C_{18} column (10 mm × 250 mm) at 2.0 mL/min using a 30-min gradient of 20% to 45% acetronitrile/water: ^{1}H NMR (acetone-d_6) δ 5.08 (dd, 1, H_4, $J_{3,4}$ = 6.9 Hz, $J_{4,5}$ = 3.3 Hz), 5.25 (d, 1, H_3, $J_{3,4}$ = 6.9 Hz), 6.97 (d, 1, H_5; $J_{4,5}$ = 3.3 Hz), 7.58 (dd, 1, H_7, J = 7.1, 7.9 Hz), 7.74 (dd, 1, H_2, $J_{1,2}$ = 8.6 Hz, $J_{2,3}$ = 1.2 Hz), 7.83 (d, 1, J = 8.1 Hz), 7.88 (s, 2, $H_{9,10}$), 7.91 (d, 1, J = 8.1 Hz), 7.96 (d, 1, J = 7.1 Hz).

***trans*-3,4-Dihydroxy-*syn*-5,5a-epoxy-3,4,5,5a-tetrahydrobenzo[*ghi*]fluoranthene (3).** Compound **16** (115 mg, 0.44 mmol) and *N*-bromoacetamide (NBA, 62 mg, 0.45 mmol) were dissolved in 45 mL of a 3:1 mixture of THF and H_2O, and the solution was stirred at 0 °C in the dark. The reaction progress was monitored by HPLC [C_{18} column (4.6 mm × 25 cm), at 1.0 mL/min, 60% methanol/water]. The retention time of the product was 4.45 min. After 4 h, it was necessary to add an additional batch of NBA (30.8 mg, 0.23 mmol). After 6 h, the solvent was removed under reduced pressure, and the residue was partitioned between ice water and ethyl acetate (3 × 30 mL). The combined organic extracts were washed with saturated $NaHCO_3$ and saturated NaCl and dried with $MgSO_4$. Evaporation of the solvent under reduced pressure gave **19**, which was used for the next step without further purification (∼140 mg). Chromatographically pure **19** was obtained by HPLC on a C_{18} column (10 mm × 250 mm) at 2.0 mL/min using 50% methanol/water: ^{1}H NMR (acetone-d_6 with 3 drops of D_2O) δ 3.64 (dd, 1, H_4, $J_{3,4}$ = 2.4 Hz, $J_{4,5}$ = 3.5 Hz), 4.15 (dd, 1, H_5, $J_{4,5}$ = 3.5 Hz, $J_{3,5}$ = 0.6 Hz), 5.10 (d, 1, H_3, $J_{3,4}$ = 2.4 Hz), 7.50 (d, 1, H_2, $J_{1,2}$ = 8.2 Hz), 7.56 (dd, 1, H_7, J = 7.8, 7.3 Hz), 7.75−7.85 (m, 5, aromatic). To crude **19** (130 mg) in 100 mL of dry THF was added potassium *tert*-butoxide (1.5 mL, 1 M in THF, 1.5 mmol). The reaction was kept at 0 °C under nitrogen in the dark. The color of the solution turned immediately from yellow to blue−green upon the addition of the base. The reaction progress was monitored by HPLC on a C_{18} column

(4.6 mm × 250 mm) eluted at 1.0 mL/min with 60% methanol. The retention time of the product was 5.4 min. After 2 h, the reaction was quenched with water and concentrated under reduced pressure. The residue was then partitioned between ice water and ethyl acetate. The organic extracts were dried over anhydrous $MgSO_4$ and evaporated to furnish a solid product, which was purified by HPLC to give pure **3** (42 mg): ^{1}H NMR (acetone-d_6 with 3 drops of D_2O) δ 4.68 (dd, 1, H_5, $J_{4,5}$ = 2.0 Hz, $J_{3,5}$ = 1.3 Hz), 4.75 (dd, 1, H_4, $J_{3,4}$ = 2.1 Hz, $J_{4,5}$ = 2.0 Hz), 4.83 (apparent t, 1, H_3, $J_{3,4}$ = 2.1 Hz), 7.62 (d, 1, H_2, $J_{1,2}$ = 8.1 Hz), 7.62−7.65 (m, 2, $H_{6,8}$), 7.88 (s, 2, $H_{9,10}$), 7.93 (dd, 1, H_7, J = 5.5, 3.1 Hz); MS *m*/*z* (relative abundance) 276.1 (M^+, 35), 189.1 (100); HRMS calcd for $C_{18}H_{12}O_3$ 276.0786, found 276.0796.

***trans*-3,4-Dihydroxy-*anti*-5,5a-epoxy-3,4,5,5a-tetrahydrobenzo[*ghi*]fluoranthene (2).** To a solution of **16** (21 mg, 0.08 mmol) in 12 mL of dry THF was added excess *m*-CPBA (140 mg, 0.81 mmol). The reaction mixture was kept at 0 °C under a nitrogen atmosphere in the dark. The reaction was monitored by HPLC on a C_{18} column (4.6 mm × 25 cm) at 1.0 mL/min using 60% methanol/water. The retention time was 8.3 min. The epoxidation was completed in 20 min. The reaction mixture was diluted with the addition of 100 mL of ether. The organic layer was then washed successively with 10% NaOH, H_2O, and saturated NaCl and dried over anhydrous $MgSO_4$. Evaporation of the solvent furnished the *anti*-diol epoxide **2** as a beige solid. Pure **2** (∼15 mg) was obtained by HPLC separation on a C_{18} column (1.0 mL/min, 50% methanol/water): ^{1}H NMR (acetone-d_6 with 3 drops of D_2O) δ 3.95 (dd, 1, H_4, $J_{3,4}$ = 8.0 Hz, $J_{4,5}$ = 1.2 Hz), 4.53 (d, 1, H_5, $J_{4,5}$ = 1.2 Hz), 5.12 (d, 1, H_3, $J_{3,4}$ = 8.1 Hz), 7.6−8.0 (m, 7, aromatic); MS *m*/*z* (relative abundance) 276.1 (M^+, 24), 149.0 (100); HRMS calcd for $C_{18}H_{12}O_3$ 276.0786, found 276.0786.

Supporting Information Available: NMR Spectra (^{1}H and ^{13}C NMR, COSY, 1D NOE) of compounds **1**−**3**, **8**−**17**, and **19** and online HPLC profiles of compounds **2** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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