(relative intensity) 178 (M^+, 24), 177 (2), 92 (11), 44 (100); mass spectrum, m/z 178.1578 (M^+, calcd for $C_{12}H_{18}DN$ 178.1579).

11,12-Bis(methoxycarbonyl)-3-azatricyclo[7.4.0.2^{10,13}]pentadeca-8,11,14-triene (11a). A solution of **5a** (380 mg, 2 mmol) and dimethyl acetylenedicarboxylate (570 mg, 4 mmol) in benzene (7 mL) was stirred at 50 °C for 20 h. The mixture was concentrated under reduced pressure. The residue was chromatographed on an alumina column (ether/benzene, 5:95) to give **11a** (417 mg, 63%): mp 118–119 °C; ^{1}H NMR ($CDCl_3$) δ 1.14 (1 H, m), 1.36–1.52 (3 H, m), 1.91 (1 H, m), 2.16 (2 H, m), 2.31 (1 H, m), 2.33 (3 H, s, NMe), 2.44 (2 H, m), 3.13 (1 H, m), 3.78 (6 H, s, COOMe), 3.89 (1 H, m), 4.32 (1 H, dd, J = 1.7 and 6.0 Hz), 5.45 (1 H, dd, J = 6.4 and 11.5 Hz), 6.32 (1 H, m), 6.43 (1 H, m); IR (Nujol) 1705, 1630, 1280, 1070 cm^{-1}; mass spectrum, m/z (relative intensity) 331 (M^+, 37), 300 (15), 272 (45), 137 (82), 136 (79), 84 (85), 57 (100). Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.85; H, 7.62; N, 4.23. Found: C, 68.75; H, 7.68; N, 4.19.

Acknowledgment. This work was supported in part by Grant-in-Aid for General Scientific Research provided by the Ministry of Education, Science, and Culture, Japan (No. 61571012).

Supplementary Material Available: A figure of the H–H COSY for **5a** and full NMR data for **5b–e** (3 pages). Ordering information is given on any current masthead page.

An Efficient Synthesis of the Highly Tumorigenic *anti*-Diol Epoxide Derivative of Benzo[*c*]phenanthrene

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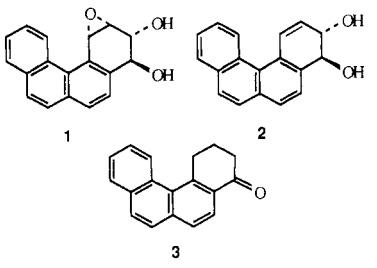
Received July 20, 1988

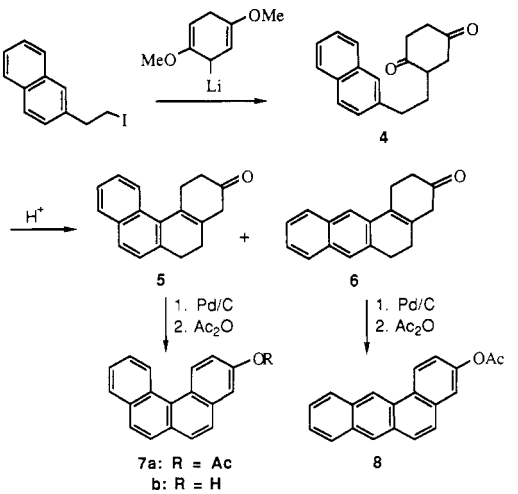
Synthesis of the potent tumorigen *trans*-3,4-dihydroxy-*anti*-1,2-epoxy-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene (**1**) in relatively few steps and superior overall yield is described. The method entails synthesis of the key intermediate 3-hydroxybenzo[*c*]phenanthrene (**7b**) via reaction of the 6-lithio salt of 1,4-dimethoxycyclohexadiene with 2-(2-naphthyl)ethyl iodide followed by cyclodehydration and dehydrogenation. 3-Hydroxybenz[*a*]anthracene is obtained as a minor product of this synthesis. Oxidation of **7b** with $(KSO_3)_2NO$ followed by reduction of the resulting quinone with $NaBH_4$ and peracid oxidation affords **1**. This method is applicable in principle to the synthesis of the substituted derivatives of benzo[*c*]phenanthrene and their oxidized metabolites. Alternative synthetic routes involving $TiCl_4$-catalyzed aldol condensation of the trimethylsilyl enol ethers of cyclohexanone and 6-methoxytetralone with 2-arylacetaldehydes were also examined and shown to afford substantially higher ratios of benz[*a*]anthracene products.

Diol epoxide metabolites are implicated as the active forms of carcinogenic polycyclic aromatic hydrocarbons.[1,2] These intermediates bind covalently to DNA in vivo, leading initially to mutation, and ultimately to tumor induction. The bay region diol epoxide derivative of benzo[*c*]phenanthrene, *trans*-3,4-dihydroxy-*anti*-1,2-epoxy-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene (**1**), is of particular interest because it is reported to exhibit the highest tumor-initiating activity of all the hydrocarbon diol epoxides tested to date.[3] This compound is also distinguished by its exceptionally high level of covalent binding to DNA in vitro and the relatively high ratio of deoxyadenosine–deoxyguanosine adducts it affords.[4,5]



1 2 3

Scheme I



In order to obtain **1** in sufficient quantity for investigations of its mechanism of DNA interaction and other pertinent studies, we required a practical synthetic route to this compound. Although synthesis of the 3,4-di-

(1) Harvey, R. G. *Polycyclic Hydrocarbons and Carcinogenesis*; ACS Symposium Monograph No. 283; American Chemical Society: Washington, DC, 1985.
(2) Harvey, R. G.; Geacintov, N. E. *Acc. Chem. Res.* **1988**, *21*, 66. Harvey, R. G. *Ibid.* **1981**, *14*, 218.
(3) Levin, W.; Wood, A. W.; Chang, R. L.; Ittah, Y.; Croisy-Delcey, M.; Yagi, H.; Jerina, D. M.; Conney, A. H. *Cancer Res.* **1980**, *40*, 3910.
(4) Dipple, A.; Pigott, M. A.; Agarwal, S. K.; Yagi, H.; Sayer, J. M.; Jerina, D. M. *Nature* **1987**, *327*, 535.
(5) The highly potent carcinogenic hydrocarbon 7,12-dimethylbenz[*a*]anthracene also affords a relatively high ratio of dA/dG adducts: Cheng, S. C.; Prakash, A. S.; Pigott, M. A.; Hilton, B. D.; Lee, H.; Harvey, R. G.; Dipple, A. *Chem. Res. Tox.* **1988**, *1*, 216.

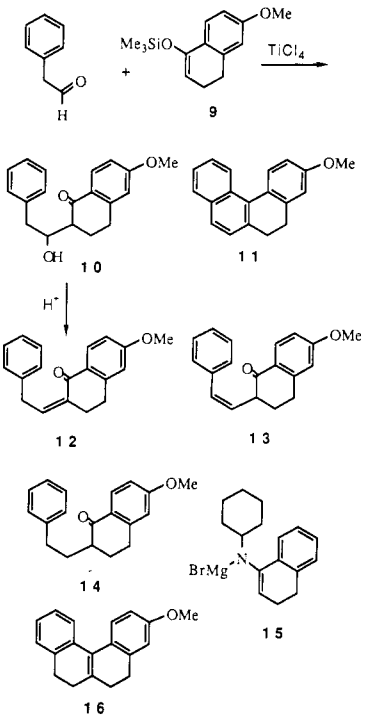
0022-3263/89/1954-0840$01.50/0

hydrodiol precursor of 1 (2) was reported,[6] the synthetic approach entails a large number of steps from readily available compounds and affords 2 in low (2.5%) overall yield. Epoxidation of 2 with *m*-chloroperbenzoic acid furnished 1.[8] Subsequently, we reported a more convenient synthesis of the key intermediate 4-oxo-1,2,3,4-tetrahydrobenzo[c]phenanthrene (3) from reaction of the potassium salt of 1,5-dimethoxy-1,4-cyclohexadiene with 2-(2-naphthyl)ethyl iodide, followed by acid-catalzyed cyclization, and dehydration.[9] This approach entailed fewer steps and provided 3 in superior overall yield. We now report a more efficient alternative synthesis of 1 that does not involve the intermediacy of 3.

Results

Initial investigations were directed toward synthesis of 3-hydroxybenzo[c]phenanthrene (**7b**), the key intermediate in the planned synthesis. The first procedure investigated for this purpose (Scheme I) was a modification of that developed earlier for the preparation of 3 and the corresponding phenol, 4-hydroxybenzo[c]phenanthrene,[9] with the difference that 1,4- rather than 1,3-dimethoxycyclohexadiene was employed. This approach has the advantage that the requisite oxygen atom of the phenol **7b** is present at the appropriate site for subsequent oxidation to the desired *o*-quinone derivative.[10] Reaction of the 6-lithio derivative of 1,4-dimethoxycyclohexadiene with 2-(2-naphthyl)ethyl iodide, followed by hydrolysis, furnished the alkylated 1,4-diketone derivative 4. Compound 4 on treatment with methanesulfonic acid underwent cyclodehydration to yield 5, accompanied by a lesser amount of a second ketonic product identified as the benz[a]anthracene derivative 6, arising from cyclization into the alternative ring position of naphthalene. Dehydrogenation of this mixture over a palladium–charcoal catalyst followed by acetylation and chromatographic separation of the products yielded 3-acetoxybenzo[c]phenanthrene (**7a**) and 3-acetoxybenz[a]anthracene (8) in approximately 3:1 ratio. These assignments are supported by the 500-MHz high-resolution NMR spectra of **7a** and 8. In particular, the spectrum of the former exhibited a pair of low-field doublets at δ 9.09 and 9.04 assigned to protons H_1 and H_{12}. The marked downfield shift of these peaks is characteristic of protons in *fjord regions*, and is a consequence of "edge-deshielding".[11] The low-field part of the NMR spectrum of 8 closely resembled that of the parent hydrocarbon benz[a]anthracene,[12] showing two singlets at δ 9.06 and 8.32 assigned to H_{12} and H_7, respectively, a doublet at δ 8.79 assigned to H_1, and multiplets at δ 8.10 and 8.06 assigned to H_{11} and H_8, respectively. In further support of these assignments, the melting points of 8 (mp 164.5–166.5 °C; lit.[13] 165–166 °C) and 3-hydroxybenzo[c]phenanthrene (**7b**) (mp 106–110 °C; lit.[14] mp 112.0–113.0 °C) were in agreement with the reported values.

Scheme II



Several alternative synthetic approaches to **7b** were also investigated. The first of these (Scheme II) involves $TiCl_4$-catalyzed aldol-type condensation of 2-phenylacetaldehyde with the trimethylsilyl enol ether of 6-methoxytetralone (**9**)[15,16] to yield the adduct **10**. Attempted cyclodehydration of **10** with excess $TiCl_4$ or with methanesulfonic acid failed to afford the expected product **11** but instead provided the olefin **12**, arising from dehydration of **11** as the sole identifiable product. The NMR spectrum of **12** showed a single vinylic proton at δ 6.51 and a doublet at δ 3.57 assigned to the benzylic protons adjacent to the olefinic bond. The alternative structure (**13**) having the olefinic bond conjugated with the phenyl ring was inconsistent with this NMR spectral pattern. Apparently, acid-catalyzed dehydration occurs with greater facility than cyclization. This is most likely due to the steric interference between the aromatic ring protons in the *fjord region* of the cyclization intermediate. Cyclization of the unsaturated compound **12** is expected to be unfavorable due to the relative rigidity of the molecule.

As a potential solution to this difficulty, synthesis of the analogue of **10** lacking a hydroxyl group (**14**) was investigated. However, attempted alkylation of **9** with 2-phenylethyl bromide catalyzed by benzyltrimethylammonium fluoride by the procedure of Kuwajima et al.[17] failed to provide any significant yield of the desired adduct **14**. An alternative potential synthetic route to **14** involving alkylation of the bromomagnesium salt of the enamine derivative of 6-methoxytetralone (**15**) with 2-phenylethyl iodide also failed to provide **14**. However, **14** was obtained in good yield through hydrogenation of **12**. Attempted cyclization of **14** in methanesulfonic acid, polyphosphoric acid, or HF failed to yield the desired 3-methoxy-5,6,7,8-

(6) Croisy-Delcey, M.; Ittah, Y.; Jerina, D. M. *Tetrahedron Lett.* **1979**, 2849. This approach entailed synthesis of the starting compound 4-oxo-1,2,3,4-tetrahydrophenanthrene by the method of Newman[7] (five steps, 60%), conversion of this ketone to 4-oxo-1,2,3,4-tetrahydrobenzo[c]phenanthrene (five steps, 28%, no experimental details), and synthesis of 2 from the latter by established methods (seven steps, 15%).

(7) Newman, M. S.; Zahn, H. V. *J. Am. Chem. Soc.* **1943**, *65*, 1097.

(8) Sayer, J. M.; Yagi, H.; Croisy-Delcey, M.; Jerina, D. M. *J. Am. Chem. Soc.* **1981**, *103*, 4970.

(9) Pataki, J.; Harvey, R. G. *J. Org. Chem.* **1982**, *47*, 20.

(10) The oxidation of β-type phenols with Fremy's reagent is generally preferred to the analogous oxidation of α-type phenols due to the tendency of the latter to afford mainly *p*-quinone products.

(11) Bartle, K. D.; Jones, D. W. *Adv. Org. Chem.* **1972**, *8*, 317.

(12) Thermodynamics Research Center Hydrocarbon Project *Selected Nuclear Magnetic Resonance Spectral Data*, Supplementary Volume F-26; Thermodynamics Research Center, Texas A & M University: College Station, TX, 1982.

(13) Fu, P. P.; Cortez, C.; Sukumaran, K. B.; Harvey, R. G. *J. Org. Chem.* **1979**, *44*, 4265.

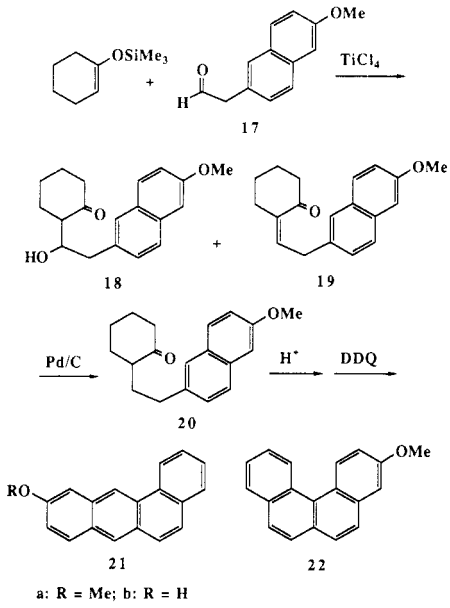
(14) Newman, M. S.; Blum, J. *J. Am. Chem. Soc.* **1964**, *86*, 503.

(15) Mukaiyama, T.; Bano, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503.

(16) Di Raddo, P.; Harvey, R. G. *Tetrahedron Lett.* **1988**, 3885.

(17) Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1982**, *104*, 1025.

Scheme III



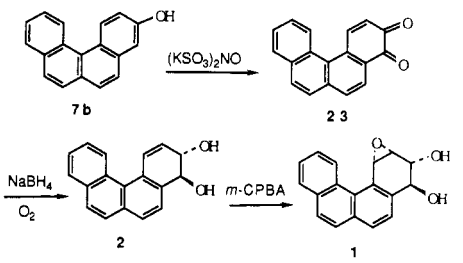
tetrahydrobenzo[*c*]phenanthrene (**16**). In view of the facility of cyclization of **4** under acidic conditions, the failure of **14** to undergo analogous reaction cannot be due solely to the steric crowding in the reaction intermediate. The greater energy barrier for cyclization to a benzene ring in **14** rather than a naphthalene ring as in **1** also contributes importantly to the resistance of **14** to cyclodehydration.

The alternative synthetic route in Scheme III, which involves cyclization onto a naphthalene ring, was also investigated. Reaction of the 6-methoxy derivative of 2-naphthylacetaldehyde (**17**) with the trimethylsilyl enol ether of cyclohexanone in the presence of 1 equiv of $TiCl_4$ afforded the condensation product **18** accompanied by its dehydration product **19**. Hydrogenation of the latter over a 10% Pd–charcoal catalyst furnished the saturated ketone derivative **20**. Cyclodehydration of **20** in polyphosphoric acid furnished a mixture of cyclized products which on dehydrogenation with DDQ gave a 4:1 mixture of 10-methoxybenz[*a*]anthracene (**21a**) and 3-methoxybenzo[*c*]phenanthrene (**22**) separable by fractional crystallization. Analogous reaction of **20** in methanesulfonic acid furnished **21a** as the sole identifiable product. Reaction of **17** with 1-(trimethylsiloxy)cyclohexene in the presence of 3 equiv of $TiCl_4$ gave directly the cyclized product 1,2,3,4-tetrahydro-**21a**. Evidently, condensation, cyclodehydration, and a second dehydration all take place consecutively in the same pot catalyzed by $TiCl_4$. Dehydrogenation of 1,2,3,4-tetrahydro-**21a** with DDQ in refluxing benzene furnished the fully aromatic product **21a**.

In order to confirm the structural assignment of **21a** it was demethylated with HBr in acetic acid to yield the free phenol **21b**. The latter melted at 219–221 °C in good agreement with the melting point reported by Fu et al. (218–222 °C).[13] However, this value differed substantially from the melting point reported earlier by Fieser and Johnson (151.3–151.8 °C).[18] The structural assignments of **21a** and **21b** were confirmed by analysis of their 500-MHz NMR spectra. The latter showed the presence of a low-field singlet (δ 9.01 and 8.95) and a second singlet peak (δ 8.25 and 8.27) assigned to the bay region 12-proton and the 7-proton, respectively. Both spectra also exhibited a characteristic low-field doublet (δ 8.77 and 8.76) assigned

(18) Fieser, L. F.; Johnson, W. S. *J. Am. Chem. Soc.* **1939**, *61*, 1647.

Scheme IV



to the 1-proton in the bay region. Other features of the NMR spectral patterns were also in good agreement with the benz[*a*]anthracene structure and inconsistent with the benzo[*c*]phenanthrene ring system.

3-Hydroxybenzo[*c*]phenanthrene was employed as the starting compound for the preparation of the biologically important diol epoxide derivative **1** (Scheme IV). Oxidation of **7b** with Fremy's salt [$(KSO_3)_2NO$] furnished benzo[*c*]phenanthrene-3,4-dione (**23**). Reduction of this quinone with $NaBH_4$ in the presence of O_2 yielded stereospecifically the desired *trans*-3,4-dihydrodiol **24**. The use of O_2 for the reoxidation of catechol byproducts back to quinone has been previously demonstrated.[19] The dihydrodiol **24** on treatment with *m*-chloroperbenzoic acid was converted, also stereospecifically, to the corresponding *anti*-isomeric bay region diol epoxide **1** in which the epoxide oxygen atom is on the opposite ring face to the benzylic hydroxyl group.[20]

The 500-MHz ^1H NMR spectra and the physical properties of the dihydrodiol **2** and the diol epoxide **1** were consistent with the structural assignments. The NMR data for the chemical shifts and couplings of the protons of **2** in the saturated ring were in good agreement with the literature values.[6] The large coupling between the carbinol protons of **2** ($J_{3,4}$ = 11.1 Hz) indicates that the hydroxy groups exist almost exclusively in the diequatorial conformation.[21,22] The NMR spectrum of the diol epoxide **1** was in good agreement with that reported.[8] The coupling constant for the carbinol protons of **1** was 8.5 Hz, indicating that the conformational equilibrium for **1** in solution favors the diequatorial conformer. These findings are consistent with previous results for other sterically unhindered dihydrodiol and diol epoxide derivatives of polycyclic hydrocarbons.[22] The pattern of the aromatic protons of **2** was also in agreement with the benzo[*c*]phenanthrene ring system (but not with a benz[*a*]anthracene structure).

Discussion

The synthetic routes outlined in Schemes I and IV provides convenient synthetic access to the highly tumorigenic diol epoxide metabolite of benzo[*c*]phenanthrene **1**. This approach entails considerably fewer steps and provides better overall yield than the previous method,[6,8] making this compound readily available for a wide range of chemical and biological studies. The method is also applicable in principle to the synthesis of the analogous

(19) Harvey, R. G. *Synthesis* **1986**, 605. Pataki, J.; Lee, H.; Harvey, R. G. *Carcinogenesis*, **1983**, *4*, 399. Platt, K. L.; Oesch, F. *J. Org. Chem.* **1983**, *48*, 265.

(20) In the corresponding syn isomer these groups are on the same face of the aromatic ring system.

(21) Zacharias, D.; Glusker, J. P.; Fu, P. P.; Harvey, R. G. *J. Am. Chem. Soc.* **1979**, *101*, 4043.

(22) Harvey, R. G. In *The Conformational Analysis of Cyclohexanes, Cyclohexadienes and Related Hydroaromatics*; Rabideau, P. W., Ed.; VCH Publishers: New York, in press.

oxidized metabolites of the methyl-substituted and other derivatives of benzo[c]phenanthrene.

The observed difference in the direction of cyclization of the ketonic intermediates **4** and **20** merits comment. It is striking that cyclodehydration of the 1,4-diketonic intermediate **4** takes place preferentially in the 1-position of the naphthalene ring to afford principally the benzo[c]phenanthrene ring system, while the monoketonic intermediate **20** cyclizes mainly into the 3-position to yield predominantly, or exclusively, dependent upon the acid catalyst, the benz[a]anthracene product. The direction of cyclization of **4** is consistent with the previous observation[9] that the 1,3-diketone analogue of **4** undergoes acid-catalyzed cyclization in the same direction as **4** to form a benzo[c]phenanthrene derivative. The unusual direction of cyclization of **20** may be partially due to the electronic effect of the methoxy group. Under the strongly acidic conditions employed this group must be largely protonated; this presumably leads to greater inductive deactivation of the 1-position than the 3-position. Support for this explanation is provided by the independent observation that acidic cyclization of the analogue of **20** lacking the methoxy group afforded benz[a]anthracene and benzo[c]phenanthrene products in the ratio of 2:1.[23] The greater ratio of benzo[c]phenanthrene products obtained from the 1,3- and 1,4-diketonic than from the monoketonic starting compounds indicates that the second carbonyl function also plays a role in determining the direction of cyclization. While the molecular basis of the effect is uncertain, it may be partially a consequence of the flattening of the ring system by the second carbonyl group, thereby decreasing steric hindrance for attack at the 1-position in the reaction intermediate.

The one-pot synthesis of 10-methoxy-1,2,3,4-tetrahydrobenz[a]anthracene by $TiCl_4$-catalyzed aldol-type condensation of a silyl enol ether with 2-naphthylacetaldehyde followed by $TiCl_4$-catalyzed cyclodehydration and dehydration (Scheme III), although it fails to afford the benzo[c]phenanthrene ring system, is of considerable interest in its own right. In addition to providing a practical synthesis of 10-methoxybenz[a]anthracene (**21a**), the method holds promise as a general synthetic route to polycyclic aromatic hydrocarbons.[16] Investigations are in progress to probe its utility for this purpose.

Experimental Section

Materials and Methods. 2-(2-Naphthyl)ethyl iodide[9] and 1,4-dimethoxycyclohexa-1,4-diene[24] were synthesized by the methods reported. The bromomagnesium salt of the enamine derivative of 6-methoxytetralone **13** was prepared by the method of Stork and Dowd.[25] 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was recrystallized from benzene. 6-Methoxytetralone was purchased from Aldrich. Fremy's salt was freshly prepared by the literature method.[26] Tetrahydrofuran (THF) was freshly distilled from $LiAlH_4$. Ether was dried over sodium, and triglyme and dimethylformamide (DMF) were dried over molecular sieves, 4A.

The NMR spectra were obtained on a Varian EM360 spectrometer or the University of Chicago 500-MHz NMR spectrometer in $CDCl_3$ unless stated otherwise with tetramethylsilane as an internal standard. Integration was consistent with all structural assignments. All new compounds gave satisfactory microanalysis for C, H within ±0.3% and/or mass spectra consistent with the assigned structures.

2-[2-(2-Naphthyl)ethyl]cyclohexane-1,4-dione (4). To a solution of 60 mL of 1.7 M *t*-BuLi (0.102 mol) in 430 mL of anhydrous THF was added a solution of 14.8 g (0.105 mol) of 1,4-dimethoxycyclohexa-1,4-diene in 110 mL of anhydrous THF at −78 °C under N_2. The solution was stirred for 1 h, 19.1 mL (19.7 g; 0.11 mol) of HMPA was added, and the red solution was stirred for 10 min. A solution of 27.5 g (97.5 mmol) of 2-(2-naphthyl)ethyl iodide in 200 mL of anhydrous THF was added in 10 min. After the mixture was stirred for 5 min more, 125 mL of saturated brine was added, the organic layer was diluted with hexane, washed twice with 65 mL portions of brine, and dried, and the solvents were removed under reduced pressure. The residue, 37.3 g, was dissolved in 400 mL of acetone, the solution was purged with N_2 for 30 min, and 125 mL of 1 N HCl previously purged with N_2 was added. The solution was stirred for 1 h under N_2. The acetone was removed under reduced pressure, the residue was extracted with CH_2Cl_2, the extract was washed with H_2O and dried, and the solvent was removed. The partly crystalline residue was stirred with 100 mL of Et_2O to give 19.72 g (75.7%) of **4**, mp 101–104 °C. A sample of **4** recrystallized from Et_2O had mp 105–107 °C: NMR δ 2.67 (br s, 9 H), 2.76 (t, 2 H), 7.21–8.87 (m, 7, Ar).

3-Acetoxybenzo[c]phenanthrene (7a) and 3-Acetoxybenz[a]anthracene (8). A. Cyclization. To a stirred solution of 1.0 g of **4** in 25 mL of CH_2Cl_2 was added 2.5 mL of methanesulfonic acid under N_2. The solution was stirred for 6 h. The solution was poured into ice-water, the organic layer was washed with $NaHCO_3$ solution and dried, and the solvent was removed. The residue was dissolved in a small amount of benzene and adsorbed on a column of Florisil. The benzene eluate gave after trituration with Et_2O 573 mg of a mixture of **5** and **6**, mp 97–100 °C.

B. Dehydrogenation. A solution of 540 mg of this mixture in 20 mL of triglyme was heated at reflux with 250 mg of 10% Pd/C catalyst for 1.5 h under N_2. After cooling, the catalyst was filtered off, and the filtrate was diluted with benzene and washed four times with H_2O. After drying, the benzene was removed under reduced pressure. The residue (530 mg) was dissolved in 3 mL of pyridine, 2 mL of Ac_2O was added, and the solution was allowed to stand overnight. After the usual workup, the product (485 mg) was chromatographed on Florisil. The first hexane–benzene (7:3) eluates gave 225 mg of **7a**: mp 125–126 °C (from MeOH) (lit.[9] mp 127–128 °C); NMR δ 2.40 (s, 3, CH_3), 7.40 (dd, 1, H_2), 7.59 (t, 1, $H_{10,11}$), 7.66 (t, 1, $H_{10,11}$), 7.71 (d, 1, H_4), 7.76–8.00 (m, 5, H_{5-9}), 9.05 (d, 1, H_{12}), 9.10 (d, 1, H_1); $J_{1,2}$ = 9.3, $J_{2,4}$ = 2.5, $J_{9,10}$ = 7.4, $J_{10,11}$ = 7.1, and $J_{11,12}$ = 8.4 Hz. From the later hexane–benzene fractions 65 mg of **8** was isolated: mp 164.5–166.5 °C (MeOH) (lit. [13] mp 165–166 °C); NMR δ 2.37 (s, 3, CH_3), 7.20–9.11 (m, 11, Ar).

3-Hydroxybenzo[c]phenanthrene (7b). A solution of 3.0 g of **7a** in 500 mL of MeOH and 10 mL of concentrated HCl was stirred under N_2 for 20 h. NaOAc was added, the NaCl filtered off, and most of the solvent was removed under reduced pressure. To the residue was added H_2O, and the precipitate was filtered off, washed with H_2O, and dried to yield **7b** (2.5 g): mp 107–110 °C (lit.[14] mp 112.0–113.0 °C).

6-Methoxy-1-[(trimethylsilyl)oxy]-3,4-dihydronaphthalene (9). To a solution of 6-methoxy-1-tetralone (22.03 g, 125 mmol) in 50 mL of dry DMF were added chlorotrimethylsilane (16.3 g, 150 mmol) and triethylamine (30.3 g, 300 mmol) under N_2. Some solid separated. The mixture was stirred at reflux for 40 h, cooled, diluted with 150 mL of hexane, and washed with ice-cold $NaHCO_3$ solution (3×) and twice with ice-cold 1 N HCl and again with cold $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$ and evaporated to dryness. The residue was dissolved in hexane and filtered through a column of Florisil to remove some unreacted starting material. The eluted product (28.5 g) was distilled to yield **9** (24.2 g, 77%): bp 99–101 °C (0.25 mm); NMR δ 0.29 (s, 9, $(CH_3)_3Si$), 2.40 (m, 2, CH_2), 2.75 (t, 2, CH_2), 3.83 (s, 3, CH_3), 5.09 (t, 1, H_2), 6.70–7.49 (m, 3, Ar).

2-(1-Hydroxy-2-phenylethyl)-3,4-dihydro-6-methoxy-1-(2*H*)-naphthalenone (10). To a solution of **9** (11.18 g, 45 mmol) and phenylacetaldehyde (5.95 g, 49.5 mmol) in 360 mL of dry CH_2Cl_2 stirred at −78 °C under N_2 was added 60 mL of 1 M $TiCl_4$ in CH_2Cl_2 over 10 min. The solution was stirred for 1 h in an

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(24) Harvey, R. G.; Pataki, J.; Lee, H. *J. Org. Chem.* **1986**, *51*, 1407. Birch, A. J. *J. Chem. Soc.* **1947**, 102.
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ice bath and for 30 min at room temperature. The solution was cooled in an ice bath, and 200 mL of water was added slowly. The organic layer was washed with $NaHCO_3$ solution, dried, and evaporated to dryness. The residue (12.27 g) was chromatographed on Florisil. Elution with benzene and benzene–ether (9:1) gave a material (9.04 g), which on recrystallization from EtOH furnished **10** (8.05 g, 60%): mp 108–11 °C; NMR (DMSO-d_6 + D_2O) δ 2.12–3.03 (m, 7), 3.80 (s, 3, CH_3), 4.58 (m, 1), 6.69–8.05 (m, 8, Ar).

2-(2-Phenylethyl)-3,4-dihydro-6-methoxy-1(2*H*)-naphthalenone (14). A solution of **10** (1.0 g) in 50 mL of benzene was heated at reflux with 125 mg of tosic acid for 1.5 h under N_2. After cooling, the solution was washed with $NaHCO_3$ solution and dried, and the solvent was removed to give **12** (940 mg): NMR δ 2.01–3.10 (m, 4, CH_2), 3.57 (d, 2, CH_2), 3.83 (s, 3, CH_3), 6.51 (t, 1, vinylic), 6.72–8.17 (m, 3, Ar), 7.27 (s, 5, Ar).

A solution of **12** (1.10 g) in 40 mL of EtOAc was hydrogenated over a 10% Pd/C catalyst (550 mg) at 40 psig for 6 h. The catalyst was removed by filtration, and the solvent was evaporated to afford **14**: NMR δ 1.23–3.00 (m, 9), 3.82 (s, 3, CH_3), 6.71–8.13 (m, 3, Ar), 7.29 (s, 5, Ar).

Attempts to cyclize **14** with methanesulfonic acid (neat or 10% in CH_2Cl_2) at room temperature or at 100 °C or in polyphosphoric acid at 115 °C all led to recovery of the starting material.

2-(6-Methoxynaphthyl)acetaldehyde (17). 2-Bromo-6-methoxynaphthalene (11.86 g, 50 mmol) was added to a solution of 66 mL of 1.6 M *n*-butyllithium (0.1 mol) in 500 mL of dry ether under N_2 and cooled in an ice bath. The solution was stirred for 30 min, and then 0.15 mol of ethylene oxide in ether was added over 25 min. A copious white precipitate separated. The suspension was stirred for 1 h more, and then water (125 mL) was added slowly. The usual workup gave a residue, which was crystallized from acetone–hexane to yield 2-(6-methoxynaphthyl)ethanol (8.78 g, 87%): mp 111.5–113.5 °C; NMR δ 1.60 (s, 1, OH), 2.96 (t, 2, CH_2), 3.72 (t, 2, CH_2), 3.89 (s, 3, CH_3), 7.05–7.78 (m, 6, Ar).

A solution of 2-(6-methoxynaphthyl)ethanol (5.05 g, 25 mmol) in 200 mL of CH_2Cl_2 was added to a solution of periodane[27] (12.5 g, 29.5 mmol) in 250 mL of CH_2Cl_2 under N_2. The solution was stirred for 2 h at room temperature, diluted with 450 mL of ether, and stirred with 175 mL of saturated $NaHCO_3$ solution containing 31 g of $Na_2S_2O_3$ for 10 min. The usual workup gave a residue (5.22 g), which was dissolved in benzene and filtered through a column of silica gel. The product crystallized to yield **17** (4.97 g, 99%): mp 70–72 °C; NMR δ 3.67 (d, 2, CH_2), 3.81 (s, 3, CH_3), 7.10–7.83 (m, 6, Ar), 9.85 (t, 1, CHO).

Condensation of 17 with 1-[(Trimethylsilyl)oxy]cyclohexene. To a stirred solution of **17** (5.0 g, 25 mmol) and 1-[(trimethylsilyl)oxy]cyclohexene (4.7 g, 27.5 mmol) in 200 mL of dry CH_2Cl_2 at −78 °C under N_2 was added 25 mL of 1 M $TiCl_4$ in CH_2Cl_2 over 15 min. Stirring was continued for 1.5 h, water (100 mL) was added over 10 min, and the mixture was stirred for an additional 30 min. The usual workup gave a residue (8.49 g), which was chromatographed on Florisil. Elution with hexane–benzene (1:1) furnished **18** (1.62 g, 23%): mp 110–13 °C (acetone–hexane); NMR δ 1.30–3.47 (m, 11), 3.86 (s, 3, CH_3), 4.44 (m, 1), 7.07–7.78 (m, 6, Ar). Further elution with benzene–ether (4:1) gave **19** (4.02 g, 54%): mp 93–95 °C (EtOH); NMR δ 1.79–2.67 (m, 8), 3.56 (d, 2, benzylic), 3.93 (s, 3, CH_3), 6.55 (t, 1, vinylic), 7.15–7.84 (m, 6, Ar).

Hydrogenation of 19. A solution of **19** (1.30 g) in EtOAc (60 mL) was hydrogenated over a 10% Pd/C catalyst (650 mg) at 40 psig for 6 h. Following the usual workup, **20** (1.30 g) was obtained as a white crystalline solid: mp 104–106 °C; NMR δ 0.12–2.90 (m, 13), 3.88 (s, 3, CH_3), 7.11–7.78 (m, 6, Ar).

Cyclodehydration and Dehydrogenation of 20. A. Polyphosphoric Acid. A mixture of **20** (200 mg) in PPA (20 g) was stirred at 110–14 °C for 1 h and then poured into ice water. Conventional workup gave a residue, which was dissolved in benzene and filtered through a short column of Florisil. The product (149 mg) was dissolved in dry benzene (10 mL) and heated at reflux with DDQ (423 mg, 1.86 mmol) under N_2 for 1 h. After cooling, the solution was filtered, and the filtrate was concentrated to a small volume and passed through a short column of Florisil. Elution with benzene gave a crystalline product whose NMR spectrum indicated it to be a 4:1 mixture of **21a** and **22**.

B. Methanesulfonic Acid. Cyclodehydration of **20** (200 mg) in a solution of MSA (2 mL) in CH_2Cl_2 (20 mL) for 2 h followed by the usual workup furnished the cyclized product (166 mg). The latter was dehydrogenated with DDQ (470 mg, 2.07 mmol) by the foregoing procedure to yield **21a** (145 mg): mp 169.5–170.5 °C (EtOH); NMR δ 3.99 (s, 3, CH_3), 7.2–7.9 (m, 8, Ar), 8.26 (s, 1, H_{11}), 8.77 (d, 1, H_1, $J_{1,2}$ = 8.1 Hz), 9.01 (s, 1, H_{12}).

Condensation of 16 with 1-[(Trimethylsilyl)oxy]cyclohexene Using 3 Equiv of $TiCl_4$. This reaction was carried out as previously described with **17** (2.50 g, 12.5 mmol) with the difference that a higher ratio of $TiCl_4$ (37.5 mL of a 1 M solution) was employed and reaction time was extended to 2 h at −78 °C followed by 4 h at room temperature. There was obtained 1,2,3,4-tetrahydro-**20a** (2.21 g, 67%): NMR δ 1.92–3.14 (m, 8), 3.89 (s, 3, CH_3), 7.12–7.90 (m, 5, Ar), 8.19 (s, 1, H_7), 8.25 (s, 1, H_{12}).

Dehydrogenation of 1,2,3,4-Tetrahydro-21a. A solution of tetrahydro-**21a** (2.21 g, 8.41 mmol) and DDQ (4.2 g, 18.5 mmol) in 60 mL of dry benzene was heated at reflux under N_2 for 45 min. The usual workup followed by chromatography on Florisil furnished on elution with benzene **21a** (1.74 g, 79%): mp 167–70 °C (EtOH); the NMR spectrum matched that of an authentic sample.

10-Hydroxybenz[*a*]anthracene (21b). A solution of **21a** (300 mg) in 30 mL of glacial acetic acid and 15 mL of 48% HBr solution was heated at reflux for 20 h under N_2. The product was worked up conventionally and filtered through a short column of Florisil eluted with benzene to yield **21b** (237 mg): mp 219–21 °C dec (benzene) (lit.[14] mp 218–22 °C).

Benzo[*c*]phenanthrene-3,4-dione (23). To a vigorously stirred solution of 2.50 g of **7b** in 300 mL of benzene and 10 drops of Adogen 464 was added a solution of 10 g of Fremy's salt in 500 mL of 6 M KH_2PO_4. Stirring was continued for 1 h. The layers were separated, and the aqueous solution was extracted with benzene. The organic solutions were washed with H_2O, combined, and dried, and the solvent was removed. The residue was triturated with MeOH and recrystallized from benzene to yield **23** (2.19 g): mp 178–180 °C; NMR (500 MHz) δ 6.55 (d, 1, vinylic, $J_{1,2}$ = 10.6 Hz), 7.7–8.0 (m, 6, H_{6-11}), 8.23 (apparent t, 2, $H_{5,12}$), 8.48 (d, 1, vinylic, $J_{1,2}$ = 10.6 Hz).

***trans*-3,4-Dihydroxy-3,4-dihydrobenzo[*c*]phenanthrene (24).** A 2.10-g portion of **22** was stirred in 260 mL of EtOH with 7 g of $NaBH_4$ for 126 h, while O_2 was bubbled into the solution. The green solution became colorless. It was partitioned between CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2; the extracts were washed with H_2O, combined, dried, and evaporated to dryness under reduced pressure. The residue (2.04 g) was triturated with Et_2O to yield **2** (1.64 g): mp 190–192 °C; NMR (500 MHz, Me_2SO-d_6) δ 4.55 (m, 1, H_3, $J_{3,4}$ = 11.1 Hz), 4.57 (d, 1, H_4), 5.64 (d, 1, OH, J = 6.0 Hz), 5.32 (d, 1, OH, J = 5.0 Hz), 6.23 (dd, 1, H_2, $J_{2,3}$ = 2.1 Hz), 7.18 (dd, 1, H_1, $J_{1,2}$ = 10.1, $J_{1,3}$ = 2.1 Hz), 7.60 (m, 2, $H_{10,11}$), 7.73 (m, 2, $H_{5,6}$), 7.85 (apparent s, 2, $H_{7,8}$), 7.95 (m, 1, H_9), 8.50 (m, 1, H_{12}).

***trans*-3,4-Dihydroxy-*anti*-1,2-epoxy-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene (1).** A solution of 50 mg (0.19 mmol) of **2** in 10 mL of anhydrous THF was stirred with 328 mg (1.9 mmol) of *m*-chloroperbenzoic acid for 2 h under N_2. After being diluted with Et_2O, the solution was washed twice with ice-cold 10% NaOH solution and once with H_2O and dried, and the solvents were removed under reduced pressure at 30 °C. The residue (43 mg) was triturated with Et_2O to yield **1** (33 mg): mp 182–185 °C dec; NMR (500 MHz, Me_2SO-d_6) δ 3.70 (dd, 1, H_2), 3.79 (m, 1, H_3), 4.61 (dd, 1, H_4), 4.72 (d, 1, H_1), 5.59 (d, 1, OH), 5.78 (d, 1, OH), 7.6–8.1 (m, 7, Ar), 8.62 (m, 1, H_{12}), $J_{3,4}$ = 8.5 Hz; UV_{max} (EtOH) 255.4 (50 700) nm.

Acknowledgment. This research was made possible by grants from the National Institutes of Health, DHHS (CA 36097, CA 14599, and ES 04266).

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