Efficient Syntheses of the *anti*- and *syn*-Diol Epoxide Metabolites of the Carcinogenic Polycyclic Aromatic Hydrocarbon Benzo[*g*]chrysene

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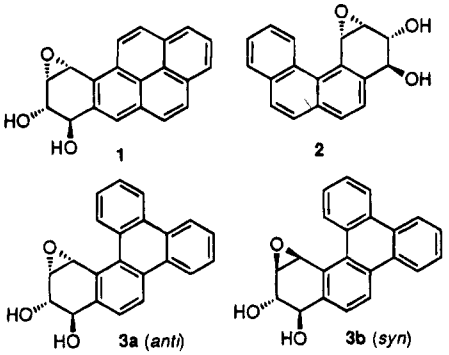
Received May 23, 1995[⊗]

Two new synthetic approaches to the active *fjord* region *anti*- and *syn*-diol epoxide metabolites (**3a** and **3b**) of the potent carcinogenic hydrocarbon benzo[*g*]chrysene are described. The first of these methods entails initial synthesis of the key intermediate 12-hydroxybenzo[*g*]chrysene which is transformed in two steps to *trans*-11,12-dihydroxy-11,12-dihydrobenzo[*g*]chrysene, the synthetic precursor of **3a** and **3b**. The second method involves in the key step oxidative photocyclization of a 1,2-diarylethylene having methoxy groups at appropriate sites for subsequent conversion to the dihydrodiol function. These methods allow efficient preparative scale synthesis of the benzo[*g*]-chrysene diol epoxides required as starting compounds for the synthesis of specifically alkylated benzo[*g*]chrysene–oligonucleotide adducts needed for site-directed mutagenesis and other studies to elucidate molecular mechanisms of carcinogenesis.

Polycyclic aromatic hydrocarbons (PAHs) are widespread environmental contaminants that are produced by combustion processes.[1] Some PAHs are potent carcinogens whose biological action is mediated by oxidative metabolism to diastereomeric *anti*- and *syn*-diol epoxide metabolites that bind covalently to DNA in mammalian tissues.[2,3] The PAH diol epoxide isomers initially found to be most active, such as the *anti*-diol epoxide of benzo[*a*]pyrene (**1**), contain the epoxide function in a bay



molecular region. It was proposed that their activity was due to their exceptional reactivity.[4] However, it was subsequently suggested[2,5] that the role of the bay region was more likely related to steric crowding which serves to protect the epoxide ring from detoxification by the action of the epoxide hydrase enzyme,[6] permitting survival of the epoxide function long enough to attack DNA. This interpretation is consistent with recent findings that *fjord* region diol epoxides, such as the diol epoxides of benzo[*c*]phenanthrene (**2**) and benzo[*g*]chrysene (**3**), which are more sterically crowded, tend to exhibit significantly higher levels of mutagenicity and tumorigenicity.[7–9]

Alkylation by the PAH diol epoxides takes place at numerous sites on the DNA helix. However, only a small fraction of the resulting adducts lead to tumor induction. Identification of these specific target sites is a major objective of current investigations. Emerging evidence suggests that deoxyadenosine adducts in *ras* oncogenes may play the principal role. Thus, 7,12-dimethylbenz[*a*]anthracene (DMBA) and several other potent carcinogenic hydrocarbons induce AT → TA transversion mutations at the second position of the 61st codon of the *ras* oncogene.[10–12] Consistent with this finding, DMBA metabolites exhibit strong affinity for binding to dA sites in DNA,[13] and the *syn*-diol epoxide isomer of DMBA binds selectively to dA residues.[14] The highly tumorigenic diol epoxide metabolites of benzo[*c*]phenanthrene (**2**) and benzo[*g*]chrysene (**3**) also react extensively with dA residues in DNA.[15–17]

⊗ Abstract published in *Advance ACS Abstracts,* September 1, 1995.

(1) Harvey, R. G. *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenicity;* Cambridge University Press: Cambridge, England, 1991.

(2) Reference 1, Chapter 4, pp 50–95.

(3) Harvey, R. G.; Geacintov, N. E. *Acc. Chem. Res.* **1988**, *21*, 66.

(4) Lehr, R. E.; Kumar, S.; Levin, W.; Wood, A. W.; Chang, R. L.; Conney, A. H.; Yagi, H.; Sayer, J. M.; Jerina, D. M. In *Polycyclic Hydrocarbons and Carcinogenesis*; Harvey, R. G., Ed.; ACS Symposium Series 283; American Chemical Society: Washington, DC, 1985; pp 63–84 and references cited therein.

(5) Harvey, R. G. *Acc. Chem. Res.* **1981**, *14*, 218.

(6) The resistance of bay region epoxides to the action of epoxide hydrase is well documented: Oesch, F. In *Enzymatic Basis of Detoxification, II*; Jacoby, W. B., Ed.; Academic Press: New York, 1980; pp 277–290. Gozukara, E. M.; Belvedere, G.; Robinson, R. C.; Deutsch, J.; Coon, M. J.; Guengerich, F. P; Gelboin, H. V. *Mol. Pharmacol.* **1981**, *19*, 153. Wood, A. W.; Levin, W.; Lu, A. Y. H.; Yagi, H.; Hernandez, O.; Jerina, D. M.; Conney, A. H. *J. Biol. Chem.* **1976**, *251*, 4882.

(7) 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.

(8) Glatt, H.; Piée, A.; Pauly, K.; Steinbrecher, T.; Schrode, R.; Oesch, F.; Seidel, A. *Cancer Res.* **1991**, *51*, 1659.

(9) It is also well established that increasing steric hindrance in a bay region by substitution of a methyl group in the nonbenzo ring position tends to markedly enhance carcinogenic activity: *cf.* ref 1, Chapter 3, pp 27–49. For example, 7,12-dimethylbenz[*a*]anthracene and 5-methylchrysene are among the most potent known carcinogens, whereas benz[*a*]anthracene and chrysene exhibit only weak borderline activities: Huggins, C. B.; Pataki, J.; Harvey, R. G. *Proc. Natl. Acad. Sci. U.S.A.* **1967**, *58*, 2253. DiGiovanni, J.; Diamond, L.; Harvey, R. G.; Slaga, T. J. *Carcinogenesis*, **1983**, *4*, 403. Hecht, S. S.; Amin, S.; Huie, K.; Melikian, A. A.; Harvey, R. G. *Cancer Res.* **1987**, *47*, 5310.

(10) Bizub, D.; Wood, A. W.; Skalka, A. M. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 6048.

(11) Dandekar, S.; Sukumar, S.; Zarbl, H.; Young, L.; Cardiff, R. D. *Mol. Cell Biol.* **1986**, 4104.

(12) Quintanella, M.; Brown, K.; Ramsden, M.; Balmain, A. *Nature (London)* **1986**, *322*, 78.

(13) Cheng, S. C.; Prakash, A. S.; Pigott, M. A.; Hilton, B. D.; Lee, H.; Harvey, R. G.; Dipple, A. *Carcinogenesis* **1988**, *9*, 1721.

(14) Cheng, S. C.; Prakash, A. S.; Pigott, M. A.; Hilton, B. D.; Roman, J. M.; Lee, H.; Harvey, R. G.; Dipple, A. *Chem. Res. Toxicol.* **1988**, *1*, 216.

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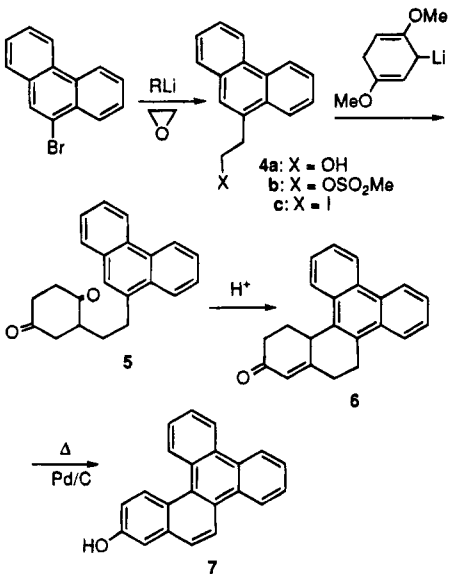
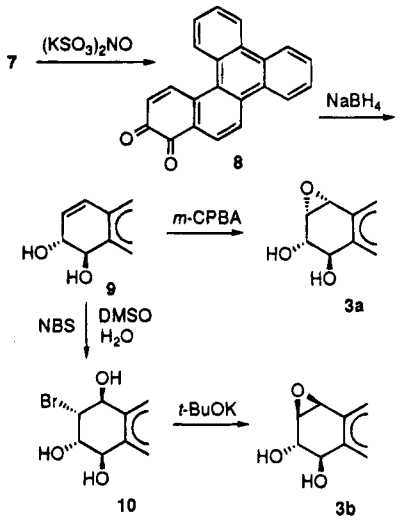
Scheme 1



Scheme 2



In order to further elucidate the mechanisms of PAH carcinogenesis we have undertaken the synthesis of PAH–oligonucleotide adducts having a sterically crowded diol epoxide (e.g., **3**) covalently linked to a specific base site, particularly dA in a *ras* gene sequence. The availability of these adducts will allow correlation between their molecular structures determined by NMR and X-ray crystallographic methods and the types of mutations induced in replication of the adducted oligonucleotides incorporated in DNA. The *anti*- and *syn*-diol epoxides of benzo[*g*]chrysene (**3a** and **3b**) were selected as models because of their relative stabilities and demonstrated preferential binding to dA. Since the syntheses of the benzo[*g*]chrysene–oligonucleotide adducts involves multistep procedures with low yields in one or more steps, relatively large amounts of the starting diol epoxides are required. While syntheses of **3a** and **3b** have been reported,[8,18] the methods entail a large number of steps and are impractical for preparative scale syntheses; in the case of the syntheses reported by Glatt et al.[8] no details of the experimental methods and procedures, yields, or physical or spectral data on the intermediate compounds are presented. We now wish to report efficient synthetic routes to these compounds which are adaptable to relatively large scale preparation. The accompanying paper describes conversion of these diol epoxides to the corresponding amino triols required as key intermediates for the synthesis of benzo[*g*]chrysene–oligonucleotide adducts.

Results

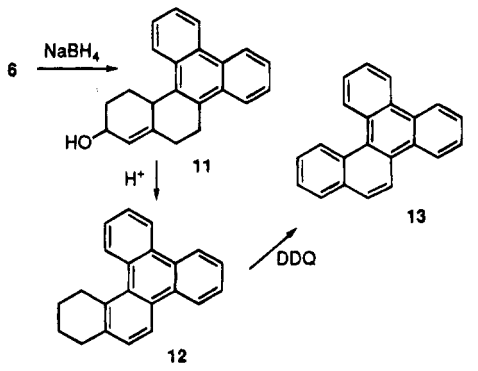
Two synthetic strategies for the construction of the benzo[*g*]chrysene ring system were explored. The first of these methods (Scheme 1) entails initial synthesis of the key intermediate 12-hydroxybenzo[*g*]chrysene (**7**). Chemical transformation of **7** allows easy access to the 11,12-*trans*-dihydrodiol metabolite of benzo[*g*]chrysene (**9**), the precursor for the corresponding *anti*- and *syn*-diol epoxides (**3a** and **3b**). The parent hydrocarbon benzo[*g*]chrysene is also readily accessible through reduction and dehydrogenation of the ketone precursor of **7**. The second method (Scheme 4) involves photochemical cyclization of the appropriately substituted stilbene-type intermediates (**14**) to benzo[*g*]chrysene derivatives.

The synthetic approach to 12-hydroxybenzo[*g*]chrysene (**7**) is based on reaction of ethylene oxide with 9-lithiophenanthrene generated *in situ* from metal exchange of 9-bromophenanthrene with *n*-butyllithium (Scheme 1). Conversion of the alcohol product (**4a**) to its mesylate (**4b**) by treatment with methanesulfonyl chloride followed by reaction of **4b** with NaI furnished 2-(9-phenanthryl)ethyl iodide (**4c**). Reaction of **4c** with the lithium salt of 1,4-dimethoxycyclohexa-1,4-diene, prepared *in situ* from the reaction of the diene with *tert*-butyllithium in ether, gave the diketone adduct **5**. Use of the potassium salt of the diene for analogous reaction in liquid ammonia gave a slightly lower yield of **5**. Cyclodehydration of **5** took place smoothly in methanesulfonic acid at room temperature to provide 12-oxo-9,10,12,13,14,14a-hexahydrobenzo[*g*]chrysene (**6**) essentially quantitatively. Polyphosphoric acid was less satisfactory for this purpose. Dehydrogenation of **6** over a palladium/charcoal catalyst furnished 12-hydroxybenzo[*g*]chrysene (**7**).

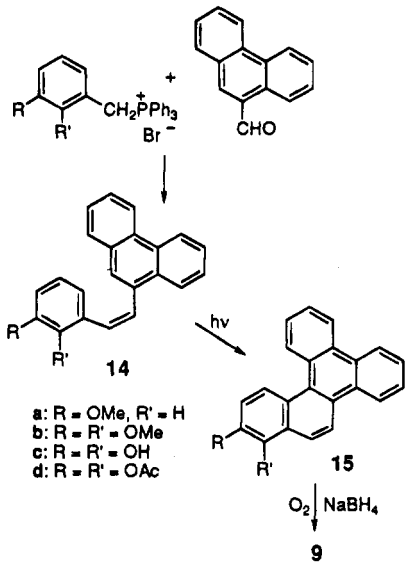
Conversion of **7** to the corresponding dihydrodiol and diol epoxides was carried out by the general method developed in prior studies (Scheme 2).[19] Thus, oxidation of **7** with Fremy's reagent [$(KSO_3)_2NO$] gave benzo[*g*]chrysene-11,12-dione (**8**) whose physical properties were in good agreement with those reported for **8** synthesized by a different route.[18] Reduction of **8** with $NaBH_4$ in EtOH took place stereospecifically to provide *trans*-11,12-dihydroxy-11,12-dihydrobenzo[*g*]chrysene (**9**). The ^1H NMR spectrum of **9** showed a coupling constant for the carbinol protons $J_{11,12}$ = 10.9 Hz, indicating that this dihydrodiol exists in solution in DMSO-d_6 predominantly as the diequatorial conformer.[19a,20] Epoxidation of **9** with

(15) Dipple, A.; Pigott, M. A.; Agarwal, S. K.; Yagi, H.; Sayer, J. M.; Jerina, D. M. *Nature (London)* **1987**, *327*, 535.
(16) Agarwal, S. K.; Sayer, J. M.; Yeh, H. J.; Pannell, L. K.; Hilton, B. D.; Yagi, H.; Jerina, D. M. *J. Am. Chem. Soc.* **1987**, *109*, 2497.
(17) Szeliga, J.; Lee, H.; Harvey, R. G.; Page, J. E.; Ross, H. L.; Routledge, M. N.; Hilton, B. D.; Dipple, A. *Chem. Res. Toxicol.* **1994**, *7*, 420. With the *supF* gene in the pSP189 shuttle vector as a target for the *syn*-diol epoxide of benzo[*g*]chrysene, the principal mutants were AT → TA transversions, accounting for 41% of the mutations.
(18) Bushman, D. R.; Grossman, S. J.; Jerina, D. M.; Lehr, R. E. *J. Org. Chem.* **1989**, *54*, 3533.
(19) (a) Reference 1, Chapter 13, pp 306–329 and references cited therein. (b) Lee, H.; Harvey, R. G. *J. Org. Chem.* **1986**, *51*, 3502. (c) Harvey, R. G.; Pataki, J.; Lee, H. *J. Org. Chem.* **1986**, *51*, 1407.

Scheme 3



Scheme 4



m-chloroperbenzoic acid took place stereospecifically to yield the target *anti*-diol epoxide metabolite, *trans*-11,-12-dihydroxy-*anti*-13,14-epoxy-11,12,13,14-tetrahydrobenzo[*g*]chrysene (**3a**). The *syn*-diol epoxide isomer **3b** was prepared from **9** through reaction with *N*-bromosuccinimide in moist DMSO to form the bromohydrin, 13α-bromo-11β,12α,14β-trihydroxy-11,12,13,14-tetrahydrobenzo[*g*]chrysene (**10**). Treatment of **10** with *t*-BuOK in THF while the extent of reaction was monitored by HPLC on a DuPont Zorbax Sil column gave *trans*-11,12-dihydroxy-*syn*-13,14-epoxy-11,12,13,14-tetrahydrobenzo[*g*]chrysene (**3b**) in good yield. The high-resolution NMR spectra of **3a** and **3b** were fully consistent with the assigned structures and in good agreement with the reported data.[18]

The parent hydrocarbon, benzo[*g*]chrysene, is also conveniently synthetically accessible from the ketone precursor **6** (Scheme 3). Thus, reduction of **6** with $NaBH_4$ in MeOH and THF afforded the corresponding alcohol (**11**) which underwent dehydration on treatment with *p*-toluenesulfonic acid in refluxing toluene to yield 11,-12,13,14-tetrahydrobenzo[*g*]chrysene (**12**). Dehydrogenation of **12** with DDQ provided benzo[*g*]chrysene (**13**) in good overall yield.

An alternative photocyclization route to the oxidized metabolites of benzo[*g*]chrysene (Scheme 4) which is potentially simpler was also investigated. The key intermediates in this approach are 1,2-diarylethylenes (**14**) containing methoxy groups at appropriate sites for later conversion to dihydrodiol functions.[21] These compounds are synthetically accessible via Wittig reactions of 9-phenanthraldehyde. Initial experiments were carried out with a diaryl olefin containing a single methoxy group (**14a**) prepared from reaction of 9-phenanthraldehyde with the Wittig derivative of 2-methoxy-1-(bromomethyl)benzene. Analysis of the high-resolution ^1H NMR spectrum of **14a** showed it to consist of a mixture of *Z*- and *E*-olefins in the ratio of *Z*/*E* = 5:1. Oxidative photocyclization of the mixture in the presence of I_2 and propylene oxide[22] took place smoothly to afford a mixture of the two products arising from ring closure in both directions with only a slight preponderance of the desired 12-methoxybenzo[*g*]chrysene (**15a**). In order to avoid this complication, the diaryl olefin with 2,3-dimethoxy substituents (**14b**) was prepared and subjected to photochemical reaction. 11,12-Dimethoxybenzo[*g*]chrysene (**15b**) was obtained as the sole product. The yield of **15b** was found to be strongly dependent upon reaction conditions. Optimum yields were obtained from photoreactions conducted with dilute solutions of the olefins (3×10^{-3} M) in benzene. Addition of propylene oxide or 1,2-epoxybutane was found to improve the yield dramatically. Combination of these two factors increased the yield of **15b** (and other compounds prepared via this route) to 80–90%. Demethylation of **15b** with BBr_3 furnished 11,-12-dihydroxybenzo[*g*]chrysene (**15c**). Like many other polycyclic catechols, **15c** is susceptible to spontaneous air oxidation. Consequently, it is best preserved and characterized as its diacetate (**15d**) or other appropriate derivative.

Reduction of **15d** to the 11,12-dihydrodiol (**9**) was accomplished by bubbling oxygen through a heterogeneous suspension of **15d** and $NaBH_4$ in moist ethanol. It is likely that the mechanism of this process is complex, involving initial conversion of **15d** to **15c** followed by its oxidation to a quinone and reduction of the latter to the dihydrodiol (**9**).[19a,23] The use of O_2 for reoxidation and recyclizing catechol byproducts to quinones in the reduction of quinones with $NaBH_4$ is well established.[19a] Reductions of this type are highly *trans*-stereoselective. The yield of **9** ranged from 69 to 77%, depending upon the purity of the starting materials and reaction time. Optimum yields were achieved by prior chromatographic purification of **15d**, use of fresh $NaBH_4$, and reaction times of 36–48 h.

The synthetic route in Scheme 4 is readily modified for the preparation of the parent hydrocarbon, benzo[*g*]-chrysene (**13**), or other substituted derivatives. Thus, reaction of 9-phenanthraldehyde with the triphenylphosphonium salt of 1-(bromomethyl)benzene afforded 1-(9-phenanthryl)-2-phenylethylene which underwent oxidative photocyclization to yield **13**.

Finally, an attempt to synthesize benzo[*g*]chrysene via the enamine alkylation route, previously shown to be a

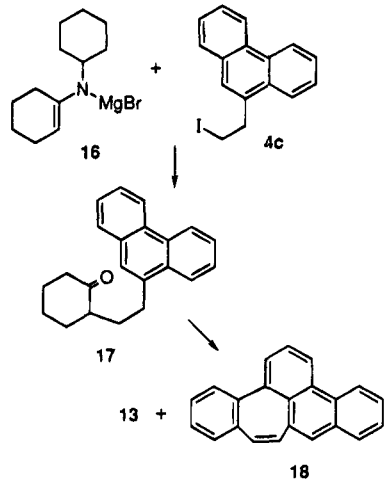
(20) Harvey, R. G. In *The Conformational Analysis of Cyclohexenes, Cyclohexadienes, and Related Hydroaromatic Compounds*; Rabideau, P. W., Ed.; VCH Publishers: New York, 1989; pp 267–298.

(21) Syntheses of other substituted derivatives of benzo[*g*]chrysene via photocyclization routes have recently been reported: Krzeminski, J.; Lin, J.-M.; Amin, S.; Hecht, S. S. *Chem. Res. Toxicol.* **1994**, *7*, 125. Luch, A.; Glatt, H.; Platt, K. L.; Oesch, F.; Seidel, A. *Carcinogenesis* **1994**, *15*, 2507.

(22) Propylene oxide is reported to enhance yields in photocyclizations by scavenging the HI produced: Liu, L. B.; Yang, B. W.; Katz, T. J.; Poindexter, M. K. *J. Org. Chem.* **1991**, *56*, 3769.

(23) (a) Platt, K. L.; Oesch, F. *Synthesis* **1982**, 459. (b) Harvey, R. G. in *Polycyclic Hydrocarbons and Carcinogenesis*; Harvey, R. G., Ed.; American Chemical Society Symposium Series 283; American Chemical Society: Washington, D.C., 1985; pp 35–62.

Scheme 5



general method for the synthesis of polyarenes,[24] afforded a mixture of products (Scheme 5). Reaction of the bromomagnesium salt of *N*-cyclohexenylcyclohexanimine (**16**) with **4c** provided the expected alkylated ketone, 2-[2-(9-phenanthryl)ethyl]cyclohexanone (**17**). However, cyclodehydration of **17** in polyphosphoric acid furnished a mixture of benzo[*g*]chrysene (25%) and a hydrocarbon (mp 195–197 °C) (9%) assigned the structure benzo[4,5]-cyclohept[1,2,3-*jk*]phenanthrene (**18**). This new polyarene is formed by cyclization of **17** to the 1-position of the phenanthrene ring. The high-resolution ^{1}H NMR spectrum of **18** exhibited a singlet peak at δ 8.9 Hz for the former 9-proton of the phenanthrene ring as well as other peaks consistent with this assignment.

Discussion

In summary, two synthetic approaches to the potent carcinogenic hydrocarbon benzo[*g*]chrysene (**13**) and its active *fjord* region *anti*- and *syn*-diol epoxide metabolites (**3a** and **3b**) are described. These syntheses are more efficient than previous methods[8,18] and are readily adaptable to the synthesis of these compounds on a preparative scale. This is of some importance because relatively large amounts of these diol epoxides are required as starting compounds for the synthesis of the corresponding aminotriol derivatives which, in turn, are urgently required as key intermediates for the synthesis of the oligonucleotide adducts of **3a** and **3b** specifically alkylated on deoxyadenosine.

While both synthetic routes use readily available starting compounds and reagents and provide good yields in all steps, they each offer specific advantages. Although the acid-catalyzed cyclization route (Schemes 1 and 2) entails more steps, they are relatively straightforward, and there are no limitations of scale. The photocyclization route (Scheme 4), while it is shorter, is limited in scale by the necessity to conduct the photoreactions in dilute solutions. The use of the 2,3-dimethoxy-substituted precursor (**14b**) in this step ensures that cyclization will occur regiospecifically in the unsubstituted position to form a single isomer. Use of **14b** also has the advantage that it can be converted directly to the desired dihydrodiol without the need for prior oxidation with Fremy's reagent to a poorly soluble quinone intermediate, as required in the established synthetic methodology.[19a]

(24) Harvey, R. G.; Pataki, J.; Cortez, C.; Di Raddo, P.; Yang, C. *J. Org. Chem.* **1991**, *56*, 1210.

Experimental Section

Materials and Methods. 1,4-Dimethoxycyclohexadiene was synthesized by Birch reduction of 1,4-dimethoxybenzene by the procedure described.[19c] *N*-Cyclohexenylcyclohexanimine and its bromomagnesium salt (**16**) were synthesized by published methods.[25] Fremy's salt [$(SO_3K)_2NO$] was prepared by the literature method.[26] *m*-Chloroperbenzoic acid (Aldrich) was purified by washing with pH 7.4 phosphate buffer and dried under reduced pressure. *N*-Bromosuccinimide was crystallized from water prior to use. THF was distilled from sodium benzophenone ketyl. All melting points are uncorrected. The ^{1}H NMR spectra were obtained on the University of Chicago 300- or 500-MHz ^{1}H NMR spectrometers in $CDCl_3$ with tetramethylsilane as internal standard unless stated otherwise.

2-(9-Phenanthryl)ethanol (4a). To a solution of 9-bromophenanthrene (5.14 g, 20 mM) in 300 mL of dry ether at −78 °C was added 32 mL (80 mM) of a 2.5 M solution of *n*-BuLi in hexanes by syringe. The suspension was stirred for 30 min and cooled to −78 °C, and dry ethylene oxide was introduced for 15 min. The cold bath was removed, stirring was continued for 1.5 h, and the solution was decomposed by addition of ice–water. Conventional workup followed by chromatography on a column of Florisil eluted by CH_2Cl_2 gave **4a** as a white solid (3.1 g, 70%), mp 84–86 °C (lit.[27,28] mp 92, 102 °C): ^{1}H NMR δ 1.55 (br s, 1), 3.38 (t, 2, J = 8.0 Hz), 4.05 (q, 2, J = 8.0 Hz), 7.50–8.30 (m, 7), 8.55–8.92 (m, 2). Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.33; H, 6.46.

2-(9-Phenanthryl)ethyl Iodide (4c). Methanesulfonyl chloride (1,76 g, 15.4 mM) was added to a stirred solution of **4a** (3.1 g, 14 mM) and Et_3N (2,12 g, 21 mM) in 50 mL of CH_2Cl_2 at −10 °C over a period of 10 min. The mixture was stirred at ambient temperature for 2 h and water was added, the solution was extracted with 2 × 25 mL of CH_2Cl_2, and the extract was washed with 10% HCl solution, aqueous $NaHCO_3$ solution, and brine. The organic layer was dried over $MgSO_4$ and evaporated to dryness to furnish **4b** (4.22 g, 100%) as a white solid, mp 124–125 °C: ^{1}H NMR δ 2.82 (s, 3), 3.63 (t, 2, J = 8.0 Hz), 4.65 (t, 2, J = 8.0 Hz), 7.60–9.00 (m, 9), 8.55–8.92 (m, 2); **4b** was employed directly in the next step.

A solution of **4b** (4.20 g, 14 mM) and NaI (6.3 g, 42 mM) in 100 mL of acetone was stirred at reflux for 16 h. The solution was cooled, poured into ice–water, and extracted with ether. The organic layer was dried over $MgSO_4$, concentrated, and purified by chromatography on a column of Florisil. Elution with hexanes provided **4c** as a white solid (4.53 g, 97%), mp 86–88 °C: ^{1}H NMR δ 1.43 (t, 2, J = 8.0 Hz), 3.15 (q, 2, J = 8.0 Hz), 7.43–7.63 (m, 5), 7.79 (d, 1, J = 7.5 Hz), 8.05 (d, 1, J = 7.5 Hz), 8.60 (d, 1, J = 7.5 Hz), 8.67 (d, 1, J = 7.5 Hz). Anal. Calcd for $C_{16}H_{13}O$: C, 57.85; H, 3.94; I, 38.20. Found: C, 57.84; H, 3.99; I, 38.12.

2-[2-(9-Phenanthryl)ethyl]cyclohexane-1,4-dione (5). A solution of 1,4-dimethoxycyclohexa-1,4-diene (1.48 g, 10.5 mM) in 11 mL of dry THF was added slowly to a vigorously stirred solution of *t*-BuLi (10.5 mM) in dry THF (45 mL) at −78 °C under argon. The mixture was stirred for 1 h at this temperature, HMPA (1.91 mL, 1.97 g, 11 mM) was added, the resulting red solution was stirred for an additional 10 min, and a solution of **4c** (3.24 g, 9.75 mM) in 20 mL of dry THF was added by syringe over a period of 10 min. The solution was allowed to stir for an additional 5 min until TLC (silica gel, eluted with ether–hexane, 2:1) indicated no **4c** remaining. The reaction mixture was treated with 2 × 50 mL of brine, the organic layer was separated and concentrated, and the residue was dissolved in 40 mL of acetone. The resulting solution was purged for 30 min with N_2, treated with 50 mL of 10% HCl (purged with N_2), and stirred at room temperature for 1 h. Solvent was removed under reduced pressure, the solution was extracted with 2 × 25 mL of CH_2Cl_2, and the

(25) Stork, G.; Dowd, S. R. *J. Am. Chem. Soc.* **1963**, *85*, 2178.
(26) Wehrli, P. A.; Pigott, F. *Org. Synth.* **1972**, *52*, 83.
(27) Castellan, A.; Kessab, L.; Grelier, S.; Nourmamode, A.; Cotrait, M.; Marsau, P. *J. Chem. Soc., Perkin Trans. 2* **1993**, 953.
(28) Bergmann, E.; Blum-Bergman, O. *J. Am. Chem. Soc.* **1936**, *58*, 1678.

extract was washed with water, dried over $MgSO_4$, and evaporated to dryness. The crystalline residue was washed with 3 × 15 mL of ether and purified by chromatography on a column of Florisil. Elution with CH_2Cl_2 afforded **5** (50%), mp 140–141 °C: ^1H NMR δ 1.86–2.31 (m, 4), 2.54–3.45 (m, 7), 7.51–7.62 (m, 4), 7.53 (s, 1), 7.77–8.10 (m, 2), 8.60–8.68 (m, 2). Anal. Calcd for $C_{22}H_{20}O_2$: C, 83.52; H, 6.37. Found: C, 83.32; H, 6.43.

12-Oxo-9,10,12,13,14,14a-hexahydrobenzo[*g*]chrysene (6). The diketone **5** (500 mg, 1.6 mM) and methanesulfonic acid (5 mL) in 20 mL of dry CH_2Cl_2 were stirred overnight. The solution was concentrated, and the residue was dissolved in ether, washed with water and brine, dried over $MgSO_4$, and evaporated to dryness. Crystallization of the residue from benzene furnished **6** (463 mg, 98%) as a white solid, mp 167–168 °C: ^1H NMR δ 1.68 (m, 2), 2.62 (m, 3), 2.80–3.15 (m, 2), 3.62–4.46 (m, 2), 6.14 (s, 1), 7.50–7.62 (m, 4), 8.00–8.06 (m, 2), 8.72 (m, 2). Anal. Calcd for $C_{22}H_{18}O$: C, 88.56; H, 6.08. Found: C, 88.42; H, 6.15.

12-Hydroxybenzo[*g*]chrysene (7). A solution of the ketone **6** (440 mg, 1.49 mM) in triglyme (40 mL) was heated with 10% Pd/C (220 mg) at reflux for 2.5 h under argon. The catalyst was separated by filtration, and the solution was diluted with 50 mL of ether, washed with 5 × 30 mL of water, dried over $MgSO_4$, and concentrated to dryness. Purification by chromatography on a column of Florisil eluted with benzene–ether 7:3 gave **7** (381 mg, 88%) as a white solid, mp 220–221 °C: ^1H NMR (500 MHz, $CDCl_3$) δ 5.42 (br s, 1), 7.16 (dd, 1, J = 9.0, 3.0 Hz), 7.28 (d, 1, J = 9.0 Hz), 7.56 (m, 4), 7.79 (d, 1, J = 9.0 Hz), 8.51 (d, 1, J = 9.0 Hz), 8.55–8.68 (m, 3), 8.76–8.79 (m, 2). Anal. Calcd for $C_{22}H_{14}O$: C, 89.76; H, 4.80. Found: C, 89.54; H, 4.91.

Benzo[*g*]chrysene-11,12-dione (8). To a vigorously stirred solution of **7** (164 mg, 0.5 mM) in 120 mL of benzene were added Adogen 464 (1 mL) and a solution of Fremy's salt (604 mg, 2.25 mM) in a solution of 30 mL of water and 30 mL of 0.16 M KH_2PO_4. Stirring was continued for 1 h, and then the bright orange organic layer was separated and washed with water. The organic layer was dried over $MgSO_4$ concentrated, and the residue was triturated with 10 mL of cold MeOH to furnish **8** (150 mg, 88%) as a bright orange solid, mp 213–214 °C (lit.[18] mp 179–182 °C).

***trans*-11,12-Dihydroxy-11,12-dihydrobenzo[*g*]chrysene (9).** O_2 was bubbled through a stirred suspension of **8** (600 mg, 1.97 mM) and $NaBH_4$ (2.1 g) in 600 mL of absolute ethanol for 2 days. The resulting solution was concentrated under vacuum to 100 mL, diluted with 200 mL of ether, and washed with water, and the aqueous layer was extracted with 3 × 20 mL of ether. The combined ether fraction was washed with 3 × 50 mL of water, dried over $MgSO_4$, and concentrated, and the pale yellow residue was washed with 10 mL of cold Et_2O to provide **9** (506 mg, 83%) as a white solid, mp 188–190 °C (lit.[18] mp 150–153 °C, lit.[18] *R,R* enantiomer mp 164–167 °C). The ^1H NMR spectrum of **9** showed good agreement with the data presented below for **9** synthesized via reduction of diacetoxybenzo[*g*]chrysene, but some minor discrepancies with the data reported by Bushman et al.[18] were found; this may partially reflect differences in the solvents employed ($CDCl_3$ vs C_6D_6).

***trans*-11,12-Dihydroxy-*anti*-13,14-epoxy-11,12,13,14-tetrahydrobenzo[*g*]chrysene (3a).** A solution of **9** (62 mg, 0.2 mM) in 30 mL of anhydrous THF was stirred with *m*-chloroperbenzoic acid (620 mg) for 1.5 h under argon. The solution was diluted with ether (50 mL) and washed with 2 × 30 mL of ice-cold 10% NaOH and 50 mL of ice-cold water, and the organic layer was separated, dried over $MgSO_4$, and concentrated to dryness at 0 °C. These operations were carried out as rapidly as possible to minimize hydrolysis and thermal decomposition of the sensitive diol epoxide. The residue was triturated with cold ether (10 mL) to afford **3a** (55 mg, 85%) as a white solid, mp 160 °C dec (lit.[18] mp 151–153 °C): ^1H NMR (400 MHz, $CDCl_3$) δ 3.71 (dd, 1, J = 4.0, 2.0 Hz), 3.79 (dd, 1, J = 8.4, 2.0 Hz), 4.54 (d, 1, J = 4.0 Hz), 4.69 (d, 1, J = 8.4 Hz), 7.63–7.74 (m, 4), 7.96 (d, 1, J = 8.4 Hz), 8.48 (dd, 1, J = 8.0, 0.8 Hz), 8.70–8.78 (m, 4); this data shows some minor discrepancies with the reported data;[18] MS *m/z* 329 (6), 328 (M^+, 24), 311 (24), 310 (100); HRMS (EI) calcd for $C_{22}H_{16}O_3$ 328.1099, found 328.1107; UV (MeOH) λ_{max} 201 (ε = 13 900), 261 (43 400).

13α-Bromo-11β,12α,14β-trihydroxy-11,12,13,14-tetrahydrobenzo[*g*]chrysene (10). A solution of *N*-bromosuccinimide (70 mg, 0.39 mM) in 0.5 mL of DMSO was added to a solution of **9** (111 mg, 0.36 mM) in 15 mL of DMSO and 0.4 mL of water. The resulting dark yellow solution was stirred at ambient temperature for 1 h, diluted with 50 mL of EtOAc, and washed with 3 × 20 mL of ice-cold water, and the organic layer was separated, dried over $MgSO_4$, and concentrated to dryness at 0 °C. The residue was triturated with 2 × 5 mL of cold ether to furnish **10** (113 mg, 78%) as a white solid, mp 125–126 °C (lit.[18] mp 90–93 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 4.61 (d, 2, J = 8.0 Hz), 4.72 (dd, 1, J = 4.0, 2.4 Hz), 5.44 (d, 1, J = 4.0 Hz), 7.61–7.73 (m, 4), 7.96 (d, 1, J = 8.8 Hz), 8.71–8.75 (m, 2), 8.78 (d, 1, J = 8.4 Hz), 8.84 (d, 1, J = 8.8 Hz), 9.42 (d, 1, J = 8.4 Hz); there are some minor discrepancies with the ^1H NMR data reported by Bushman et al.;[18] MS (FAB) *m/z* 410 (18, M^+ ^{81}Br), 408 (19, M^+ ^{79}Br), 393 (18), 391 (20); UV (MeOH) λ_{max} 200 (ε = 43 400), *255* (48 500).

***trans*-11,12-Dihydroxy-*syn*-13,14-epoxy-11,12,13,14-tetrahydrobenzo[*g*]chrysene (3b).** A solution of *t*-BuOK (14.5 mg, 0.13 mM) in 5 mL of dry THF was added slowly by syringe to a stirred solution of **10** (35 mg, 0.086 mM) in 10 mL of dry THF under argon. The resulting solution was stirred for 1 h, diluted with 30 mL of ether, washed with 2 × 30 mL of ice-cold water, dried over Na_2SO_4, and concentrated at 0 °C to dryness. The solid residue was triturated with 2 × 5 mL of cold ether to furnish **3b** (27 mg, 96%) as a white solid, mp 158–160 °C dec (lit.[18] mp 153–156 °C). Compound **3b** was also prepared in 97% yield by treating **10** with Amberlyst IRA-400 (~10-fold weight excess) in dry THF for 24 h. Data for **3b**: ^1H NMR (400 MHz, $CDCl_3$) δ 3.81 (dd, 1, J = 8.8, 2.0 Hz), 3.89 (dd, 1, J = 4.0, 2.0 Hz), 4.17 (d, 1, J = 4.0 Hz), 4.65 (d, 1, J = 8.8 Hz), 7.63–7.75 (m, 4), 7.94 (d, 1, J = 8.8 Hz), 8.72–8.75 (m, 2), 8.83 (dd, 1, J = 7.2, 0.8 Hz), 8.85 (d, 1, J = 8.8 Hz), 8.94 (dd, 1, J = 8.0, 0.4 Hz); there are some minor discrepancies with the data reported by Bushman et al.;[18] MS *m/z* 329 (6), 328 (M^+, 24), 311 (24), 310 (100); HRMS (EI) calcd for $C_{22}H_{16}O_3$ 328.1099, found 328.1107; UV (MeOH) λ_{max} 201 (ε = 13 900), 261 (43 400).

12-Hydroxy-9,10,12,13,14,14a-hexahydrobenzo[*g*]chrysene (11). $NaBH_4$ (250 mg) was added to a stirred solution of the ketone **6** (500 mg, 1.7 mM) in 30 mL of methanol. Stirring was continued for 2.5 h, the solution was concentrated in vacuo, the residue was treated with water, and the precipitate was collected and dried in a vacuum oven to provide **11** (450 mg, 89%), mp 109–111 °C: ^1H NMR δ 1.22–4.48 (m, 10), 5.70 (s, 1), 7.60–7.66 (m, 4), 8.05 (m, 2), 8.72 (m, 2). Anal. Calcd for $C_{22}H_{20}O$: C, 87.96; H, 6.71. Found: C, 88.12; H, 6.75.

11,12,13,14-Tetrahydrobenzo[*g*]chrysene (12). A solution of **11** (282 mg, 0.94 mM) and *p*-toluenesulfonic acid (28 mg) in 50 mL of benzene in a flask equipped with a Dean–Stark trap was refluxed for 1 h under argon. The solution was passed through a Florisil column and evaporated to dryness to afford **12** (233 mg, 83%). Compound **12** was further purified by crystallization from ether to give pure **12** as a white solid, mp 101–102 °C: ^1H NMR δ 1.70–1.95 (m, 4), 3.05 (m, 2), 3.43 (m, 2), 7.35 (d, 1, J = 8.5 Hz), 7.47–7.58 (m, 4), 8.37 (d, 1, J = 8.5 Hz), 8.45–8.57 (m, 4). Anal. Calcd for $C_{22}H_{18}$: C, 93.58; H, 6.42. Found: C, 93.47; H, 6.48.

Benzo[*g*]chrysene (13). A solution of **12** (88 mg, 0.31 mM) and DDQ (231 mg, 0.94 mM) in 15 mL of benzene was refluxed for 4 h. The solution was filtered through a short Florisil column eluted with benzene. Evaporation of the solvent afford **13** (75 mg, 87%) which was recrystallized from benzene to furnish pure **13** as a white solid, mp 116–117 °C (lit.[1] mp 114.5 °C) whose ^1H NMR spectrum was identical with that reported.[29]

2-[2-(9-Phenanthryl)ethyl]cyclohexanone (17). A solution of **4c** (1.06 g, 3.84 mM) in 5 mL of THF was added by syringe to a vigorously stirred solution of the bromomagnesium

(29) Bax, A.; Ferretti, J. A.; Nashed, N.; Jerina, D. *J. Org. Chem.* **1985**, *50*, 3029.

salt of *N*-cyclohexenylcyclohexanimine (**16**) prepared from the imine (687 mg, 3.84 mM) and EtMgBr (4.61 mM, 4.61 mL of a 1 M solution in THF). The resulting solution was heated at reflux for 20 h, treated with 15 mL of 10% HCl, refluxed for an additional 3 h. The product was extracted with ether and further purified by chromatography on a column of Florisil eluted with benzene to yield **17** (960 mg, 99%) as a white solid: ^{1}H NMR δ 1.42–2.43 (m, 4), 3.02–3.22 (m, 9), 7.43–7.62 (m, 4), 7.57 (s, 1), 7.75–8.12 (m, 2), 8.60–8.66 (m, 2). Anal. Calcd for $C_{22}H_{22}O$: C, 87.38; H, 7.33. Found: C, 87.10; H, 7.35.

Cyclization of 17 with Polyphosphoric Acid. A suspension of **17** (120 mg, 0.4 mM) in 30 mL of PPA was heated at 120 °C for 14 h. The usual workup afforded a residue which was heated with DDQ (272 mg, 1.2 mM) in refluxing benzene for 2 h. The benzene solution was passed through a short column of Florisil eluted with benzene, and the resulting solution was concentrated and purified further by chromatography on a Florisil. Elution with hexanes furnished benzo[4,5]cyclohept[1,2,3-*jk*]phenanthrene (**18**) (30 mg), mp 195–197 °C, and **13** (10 mg) whose ^{1}H NMR spectrum was identical with that of an authentic sample. Physical data for **18**: ^{1}H NMR δ 7.46–7.62 (m, 5), 7.89–7.97 (m, 2), 8.49–8.54 (m, 2), 8.58–8.65 (m, 2), 8.81–8.85 (m, 2), 8.94 (s, 1). Anal. Calcd for $C_{22}H_{14}$: C, 94.93; H, 5.07. Found: C, 94.88; H, 5.09.

1-(9-Phenanthryl)-2-(2,3-dimethoxyphenyl)ethylene (14b). Phenanthrene-9-carboxaldehyde (14.4 g, 79 mM) and the phosphonium salt (31.5 g, 70 mM) prepared from (2,3-dimethoxy)methyl bromide and triphenylphosphine were dissolved in 400 mL of CH_2Cl_2, and the resulting solution was treated with 46 g of 50% NaOH. The reaction mixture was stirred at room temperature for 2 h by which time TLC indicated the absence of the starting aldehyde. The solution was diluted by the addition of water (200 mL) and the organic layer separated. The aqueous layer was extracted with 2 × 50 mL of CH_2Cl_2, and the extracts were combined, washed with brine, dried over $MgSO_4$, and evaporated to dryness. Chromatography on a column of silica gel eluted with hexanes afforded a mixture of the *Z*- and *E*-isomers of **14b** (18.3 g, 80% overall), *Z*/*E* = 5.0. The mixture of olefins was used for photocyclization. *Z*-Isomer: mp 95 °C; ^{1}H NMR δ 3.60 (s, 3), 3.65 (s, 3), 6.57–6.65 (m, 5), 7.10–7.65 (m, 7), 8.21–8.52 (m, 2); MS *m*/*z* = 341 (M^+, 100), 325 (15), 259 (24); UV (EtOH) λ_{max} 209 (ϵ = 38 100), 219 (51 200), 301 (11 500). Anal. Calcd for $C_{24}H_{20}O_2$: C, 84.68; H, 5.92. Found: C, 84.77; H, 6.12. *E*-Isomer: mp 124 °C; ^{1}H NMR δ 3.85 (s, 3), 4.01 (s, 3), 6.65–8.00 (m, 12), 8.51–8.75 (m, 2); MS *m*/*z* = 341 (M^++1, 34), 340 (M^+, 100), 325 (12), 259 (41); UV (EtOH) λ_{max} 209 (ϵ = 37 200), 219 (37 700), 251 (43 600), 324 (22 700). Anal. Calcd for $C_{24}H_{20}O_2$: C, 84.68; H, 5.92. Found: C, 84.73; H, 6.02.

11,12-Dimethoxybenzo[*g*]chrysene (15b). A solution of **14b** (5 L, 3 × 10^{-3}M), I_2 (317 mg), and 1,2-epoxybutane (2 g) in benzene was irradiated by UV (Hanovia lamp). When TLC indicated absence of the starting olefins (6–8 h), the solution was concentrated to 500 mL and washed with $Na_2S_2O_3$ and the solvent removed under vacuum. Purification by chromatography on a silica gel column eluted with hexanes afforded pure **15b** (97%) as bright yellow crystals, mp 95 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05 (s, 3), 4.06 (s, 3), 7.24 (d, 1, *J* = 9.6 Hz), 7.63–7.75 (m, 4), 8.33 (d, 1, *J* = 9.6 Hz), 8.63 (d, 1, *J* = 9.6 Hz), 8.69 (d, 1, *J* = 9.6 Hz), 8.66–8.76 (m, 3), 8.89 (d, 1, *J* = 8.0 Hz); MS *m*/*z* = 338 (M^+, 100), 322 (17), 295 (22), 280 (18); UV (MeOH) λ_{max} 207 (ϵ = 50 200), 263 (59 600), 280 (68 300), 290 (61 000). Anal. Calcd for $C_{24}H_{18}O_2$: C, 85.18; H, 5.36. Found: C, 85.05; H, 5.38.

11,12-Dihydroxybenzo[*g*]chrysene (15c). A solution of **15b** (1 g, 3 mM) in 100 mL of dry CH_2Cl_2 was stirred with BBr_3 (10.5 mL of a 1 M solution in CH_2Cl_2) at −10 °C under argon until TLC indicated absence of **15b** (12 h). The resulting solution was diluted with ice–water (300 mL) and EtOAc (200 mL), and the organic layer was separated, washed with brine, dried over Na_2SO_4, and evaporated to dryness. In view of the air sensitivity of **15b**, it was isolated and characterized as its diacetate.

11,12-Diacetoxybenzo[*g*]chrysene (15d). Acetylation of **15c** with Ac_2O in pyridine gave **15d** as a white solid, mp 172–173 °C dec: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3), 2.54 (s, 3), 7.48 (d, 1, *J* = 9.2 Hz), 7.63–7.73 (m, 4), 8.02 (d, 1, *J* = 9.2 Hz), 8.60–8.72 (m, 4), 8.79 (d, 1, *J* = 8.0 Hz), 8.83 (d, 1, *J* = 9.2 Hz); MS *m*/*z* = 394 (M^+, 15), 352 (18), 311 (24), 310 (100); UV (MeOH) λ_{max} 211 (ϵ = 64 100), 267 (77 500), 276 (79 000), 309 (18 200), 323 (18 300). Anal. Calcd for $C_{26}H_{18}O_4$: C, 79.24; H, 4.60. Found: C, 79.11; H, 4.43.

Reduction of 11,12-Diacetoxybenzo[*g*]chrysene (15d) to 11,12-Dihydroxy-11,12-dihydrobenzo[*g*]chrysene (9). A suspension of **15d** (394 mg, 1 mM) and $NaBH_4$ (378 mg, 10 mM) in 60 mL of an EtOH/H_2O solution (10:1) with O_2 bubbling through the solution was stirred at ambient temperature for 48 h until TLC (silica gel eluted with Et_2O) indicated conversion of **15d** to be complete. The mixture was filtered through sand and concentrated under reduced pressure at 0 °C to ~5–6 mL, and 40 mL of H_2O was added. The aqueous suspension was extracted with 5 × 50 mL of CH_2Cl_2, and the organic extracts were combined, washed with 2 × 50 mL of brine, dried over Na_2SO_4, and evaporated to dryness to give **9** (243 mg, 78%). This material, which contains only minor impurities (5–7% by NMR), may be used directly for the preparation of the *anti*- and *syn*-diol epoxides. This procedure may be scaled up 2.5–3.0-fold without significant decrease in yield. Pure **9** may be obtained via its diacetate derivative. A solution of crude **9** (312 mg, 1 mM) in 20 mL of a mixture of pyridine/Ac_2O (2:1) was stirred under argon for 24 h. The dark red solution was evaporated to dryness under reduced pressure avoiding heating, and the residue was dissolved in minimal EtOAc and chromatographed on a column of Florisil (100–220 mesh) eluted with hexanes–EtOAc, 2:1) to give analytically pure *trans*-11,12-diacetoxy-11,12-dihydrobenzo[*g*]chrysene (396 mg), mp 181–182 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.11 (s, 3), 2.61 (s, 3), 5.74 (dd, 1, *J* = 7.2, 4.0 Hz), 6.21 (dd, 1, *J* = 9.6, 4.0 Hz), 6.31 (d, 1, *J* = 7.2 Hz), 7.39 (d, 1, *J* = 9.6 Hz), 7.56–7.71 (m, 5), 8.31 (dd, 1, *J* = 8.0, 1.2 Hz), 8.52–8.61 (m, 4); MS *m*/*z* = 396 (3), 295 (30), 294 (100); UV (MeOH) λ_{max} 205 (ϵ = 37 900), 271 (64 000). Anal. Calcd for $C_{26}H_{20}O_4$: C, 78.77; H, 5.09. Found: C, 78.82; H, 4.87.

To a solution of the dihydrodiol diacetate (396 mg) in 10 mL of dry THF at 0 °C under argon was added a solution of NaOMe (115 mg, 2.1 mM in 7 mL of MeOH). When reaction was complete (4 h) by TLC, the solution was evaporated to dryness under reduced pressure at low temperature, 10 mL of water was added, and the pH was adjusted to ~6 with 1 N HCl. The mixture was extracted with 3 × 20 mL of EtOAc/THF (5:1), and the combined extracts were washed with 2 × 20 mL of brine, dried over Na_2SO_4, and evaporated to give pure **9** (286 mg, 92% from **15d**), 188–190 °C dec: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.51–4.55 (m, 1), 4.59 (dd, 1, *J* = 10.9 Hz), 5.31 (d, 1), 5.67 (d, 1), 6.21 (dd, 1, *J* = 10.2, 2.0 Hz), 7.03 (d, 1, *J* = 10.2, 2.0 Hz), 7.59–7.70 (m, 4), 7.85 (d, 1, *J* = 8.4 Hz), 8.35 (dd, 1, *J* = 8.0, 1.2 Hz), 8.68 (m, 4); MS *m*/*z* = 313 (16), 312 (66), 295 (12), 294 (37), 266 (100); HRMS (EI) calcd for $C_{22}H_{16}O_2$: 312.1150. Found: 312.1154; UV (MeOH) λ_{max} 205 (ϵ = 39 300), 271 (63 000).

Acknowledgment. This research was supported by grants from the National Institute for Environmental Health Sciences (ES 04266) and the American Cancer Society (CN-22).

JO950939G