Synthesis of Potentially Carcinogenic Higher Oxidized Metabolites of Dibenz[*a,j*]anthracene and Benzo[*c*]chrysene

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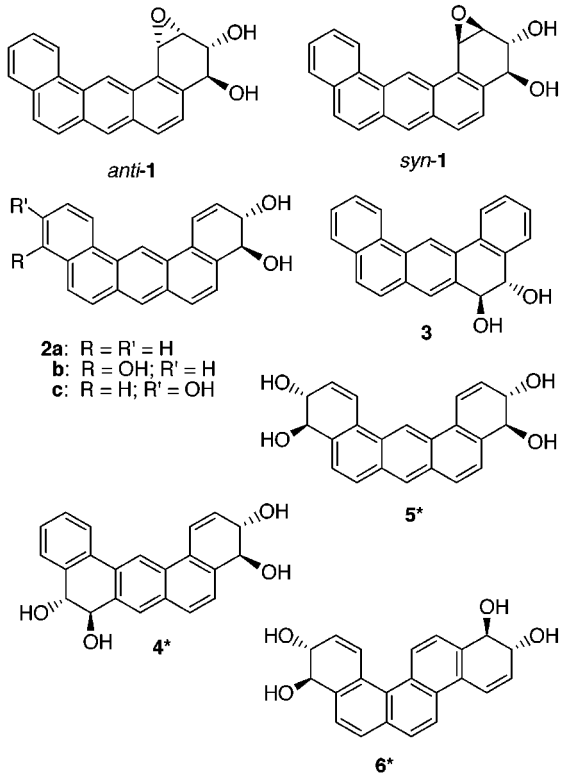
Bis(dihydrodiols) and other higher oxidized metabolites are implicated as active carcinogenic metabolites of polycyclic aromatic hydrocarbons, such as dibenz[*a,j*]anthracene, that possess more than one bay region in the molecule. The bis(dihydrodiol) metabolites may potentially undergo further metabolism to mono- or diepoxides that combine covalently with DNA or undergo conversion to bis(catechols) that enter into a redox cycle with O_2 to form reactive oxygen species that attack DNA. This paper reports convenient syntheses of the terminal ring bis(dihydrodiol) derivatives of dibenz[*a,j*]anthracene (**5**) and benzo[*c*]chrysene (**6**) via routes that involve in the key steps double oxidative photocyclization of tetramethoxy-substituted diolefins. The latter are synthesized via double Wittig reaction of a *bis*(phosphonium) salt with 2,3-dimethoxybenzaldehyde. Demethylation of the bis(catechol) products followed by acetylation and reduction with $NaBH_4$ in the presence of O_2 affords the bis(dihydrodiol) products. Several additional higher oxidized derivatives of dibenz-[*a,j*]anthracene, specifically the 3,11-diphenol (**14a**), the 11-hydroxy-3,4-quinone (**15**), and the 11-hydroxy-*trans*-3,4-dihydrodiol (**2c**), are obtained by an alternative synthesis entailing the reaction of the lithium salt of 1,4-dimethoxy-1,4-cyclohexadiene with 1,3-bis(iodoethyl)benzene to furnish a bis-alkylated diketone which undergoes acid-catalyzed cyclization to 3,11-diketododecahydrodibenz-[*a,j*]anthracene.

Polycyclic aromatic hydrocarbons (PAHs), many of which are carcinogenic in animal assays, are ubiquitous environmental contaminants to which human populations are commonly exposed.[1,2] PAHs are products of incomplete combustion of fossil fuels and organic matter, e.g. in coal and wood burning, and are also major components of tobacco smoke. It is now generally accepted that carcinogenic PAHs are activated by cytochrome P-450 enzymes to form reactive diol epoxide metabolites that bind covalently to DNA resulting in mutations that may lead to tumorigenesis.[1,3]

Metabolism studies suggest that more polar metabolites may also play a role in carcinogenesis particularly for PAHs which have more than one bay or fjord region. Thus, some 85% of the radioactivity associated with the nucleic acid adducts formed by microsomal metabolism of tritium-labeled dibenz[*a,j*]anthracene (DB*a,j*A) was associated with nucleoside adducts more polar than those arising from the bay region *anti*- and *syn*-diol epoxides (*anti*- and *syn*-**1**)[4,5] (see Chart 1). Metabolism of DB*a,j*A in primary cultures of mouse keratinocytes gave the 3,4- and 5,6-dihydrodiols (**2a** and **3**) as the principal identifiable metabolites plus substantial amounts of polar metabolites, the ratio of which increased over time.[6] These unknown polar products were not the tetraols

Chart 1[a]



[a] Asterisk indicates mixtures of bis(*trans*-dihydrodiols).

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

(2) Harvey, R. G. In *The Handbook of Environmental Chemistry*; Volume *PAHs and Related Compounds*, Hutzinger, O., Ed.-in-Chief; Neilson, A., Volume Ed.; Springer: Berlin, Heidelberg, 1977; Chapter 1, pp 1−54.

(3) Harvey, R. G.; Geacintov, N. E. *Acc. Chem. Res.* **1988**, *21*, 66. Harvey, R. G. *Polycyclic Hydrocarbons and Carcinogenesis*; ACS Symposium Series Monograph 283; American Chemical Society: Washington, DC, 1985. Dipple, A.; Moschel, R. C.; Bigger, C. A. H. In *Chemical Carcinogens*, 2nd ed.; Searle, C. E., Ed.; ACS Monograph No. 182; American Chemical Society: Washington, DC, 1984; pp 63−84. Conney, A. H. *Cancer Res.* **1982**, *42*, 4875.

(4) LeCoq, S.; Chalvet, O.; Strapelias, H.; Grover, P. L.; Phillips, D. H.; Duquesne, M. *Chem.-Biol. Interact.* **1991**, *80*, 261.

(5) Syntheses of the *trans*-3,4-dihydrodiol of dibenz[*a,j*]anthracene (**2a**) and the corresponding *anti*-diol epoxide (*anti*-**1**) were reported previously: Harvey, R. G.; Cortez, C.; Sawyer, T. W.; DiGiovanni, J. *J. Med. Chem.* **1988**, *31*, 1308.

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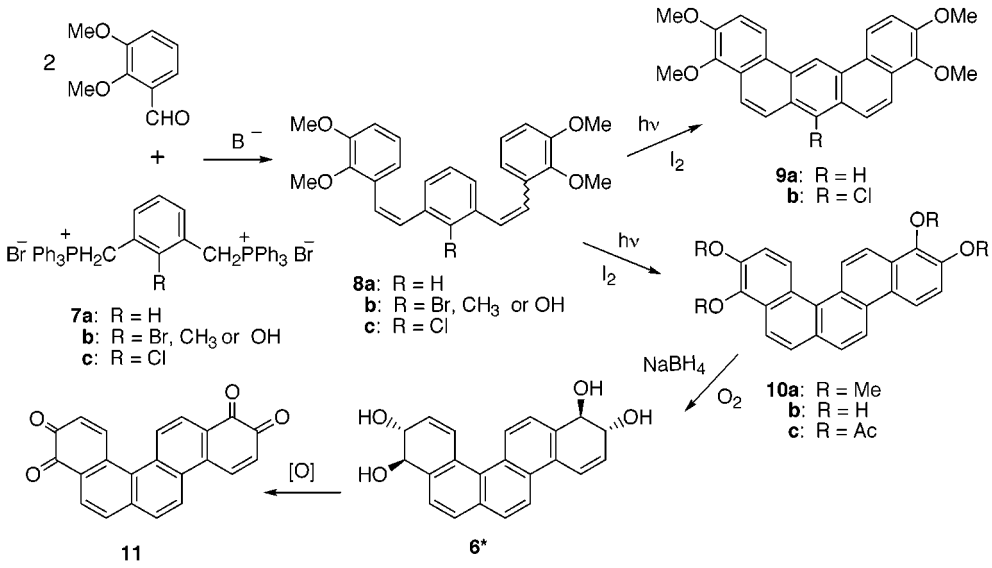
Scheme 1[a]



[a] Asterisk indicates mixtures of bis(*trans*-dihydrodiols).

formed by hydrolysis of the diol epoxides, and it was hypothesized that they were mainly the 3,4,8,9- and 3,4,-10,11-bis(dihydrodiols) (**4** and **5**), plus lesser amounts of phenolic dihydrodiols, such as the 10- and 11-hydroxy-3,4-dihydrodiols (**2b**,**c**). Similar bis(dihydrodiol)s were also tentatively identified as major metabolites of dibenz-[*a*,*c*]anthracene and dibenz[*a*,*h*]anthracene,[4] and evidence has been obtained that the ultimate mutagenic and tumorigenic metabolite of dibenz[*a*,*h*]anthracene is not the bay region diol epoxide, as first suggested,[7] but is instead its higher oxidized derivative 1,2-epoxy-3,4,10,-11-tetrahydroxy-1,2,3,4,10,11-hexahydrodibenz[*a*,*h*]anthracene.[8] The major DNA-bound adduct formed by metabolism of the potent carcinogenic hydrocarbon dibenzo[*b*,*def*]chrysene[9,10] was identified as a bis(diol) epoxide arising from a 1,2,8,9-bis(dihydrodiol) of unspecified stereochemistry. A bis(dihydrodiol), namely 3,4,12,13-tetrahydroxy-3,4,12,13-tetrahydrodibenzo[*a*,*e*]aceanthrylene, has also been identified as the most mutagenic metabolite of dibenzo[*a*,*e*]aceanthrylene.[11,12] Several isomeric phenolic dihydrodiol metabolites were also detected among the metabolites of this hydrocarbon. In the foregoing examples, structural assignments of the higher oxidized metabolites were based almost entirely on spectroscopic evidence, since in most cases syntheses had not been reported and authentic samples were unavailable for comparison.

In view of the potential involvement of bis(dihydrodiol)s and other higher oxidized metabolites in the carcinogenic activities of polycyclic hydrocarbons, we undertook to develop methods for their synthesis. These compounds are urgently required as authentic standards for identification of the active metabolites as well as for investigations of their biological and DNA binding properties. This paper reports efficient syntheses of the terminal ring bis(dihydrodiol) derivatives of dibenz[*a*,*j*]-anthracene (**5**) and benzo[*c*]chrysene (**6**) as well as several higher oxidized derivatives of dibenz[*a*,*j*]anthracene.[13] The accompanying paper reports syntheses of the unsymmetrical bis(dihydrodiol) of dibenz[*a*,*j*]anthracene (**4**) plus the dibenz[*a*,*j*]anthracene phenolic dihydrodiols (**2b**,**c**).

Results

An attractive potential synthetic route to the symmetrical 3,4,10,11-bis(dihydrodiol) of dibenz[*a*,*j*]anthracene (**5**) entails as the key step the double photocyclization of the tetramethoxy-substituted diolefin **8a** to form the corresponding bis(catechol) derivative of DB*a*,*j*A (**9a**) (Scheme 1); it was shown previously that polycyclic aromatic catechols may be reduced to dihydrodiols with $NaBH_4$ and O_2.[14] Diolefin **8a** was synthesized in good yield from double Wittig reaction of the *bis*(phosphonium) salt of 1,3-bis-(bromomethyl)benzene (**7a**) with 2,3-dimethoxybenzaldehyde. Photochemical oxidative cyclodehydrogenation of **8a** in the presence of I_2 and 1,2-epoxybutane[15] took place smoothly to afford a fully aromatic cyclized product. However, its ^{1}H NMR spec-

(6) Nair, R. V.; Nettikumara, A. N.; Cortez, C.; Harvey, R. G.; DiGiovanni, J. *Chem. Res. Toxicol.* **1992**, *5*, 532.
(7) Nordqvist, M.; Thakker, D. R.; Levin, W.; Yagi, H.; Ryan, D. E.; Thomas, P. E.; Conney, A. H.; Jerina, D. M. *Mol. Pharmacol.* **1979**, *16*, 643.
(8) Platt, K. L.; Schollmeier, M. *Chem. Res. Toxicol.* **1994**, *7*, 89. LeCoq, S.; Shé, M. N.; Hewer, A.; Grover, P. L.; Platt, K. L.; Oesch, F.; Phillips, D. H. *Carcinogenesis* **1991**, *12*, 1079. LeCoq, S.; Pfau, W.; Grover, P. L.; Phillips, D. H. *Chem.-Biol. Interact.* **1992**, *85*, 173. Carmichael, P. L.; Platt, K. L.; Shé, M. N.; LeCoq, S.; Oesch, F.; Phillips, D. H.; Grover, P. L. *Cancer Res.* **1993**, *53*, 944.
(9) The older nomenclature for this hydrocarbon was dibenzo[*a, h*]-pyrene; cf.: Harvey, R. G. *Polycyclic Aromatic Hydrocarbons*; Wiley-VCH: New York, 1997.
(10) Marsch, G. A.; Jankowiak, R.; Small, G. J.; Hughes, N. C.; Phillips, D. H. *Chem. Res. Toxicol.* **1992**, *5*, 765.
(11) This hydrocarbon was known as dibenzo[*a*,*e*]fluoranthene in older nomenclature; cf.: Harvey, R. G. *Polycyclic Aromatic Hydrocarbons*, Wiley-VCH: New York, 1997.
(12) Saguem, S.; Mispelter, J.; Perin-Roussel, O.; Lhoste, J. M.; Zajdela, F. *Carcinogenesis* **1983**, *4*, 827. Perin-Roussel, O.; Ekert, B.; Barat, N.; Zajdela, F. *Carcinogenesis* **1984**, *5*, 379.
(13) A preliminary account of these findings was presented without experimental details at the 15th International Symposium on Polycyclic Aromatic Compounds, Belgirate, Italy, Sept 1995: *Polycyclic Aromat. Cmpds* **1996**, *9*, 1.
(14) Dai, W.; Abu-Shqara, E.; Harvey, R. G. *J. Org. Chem.* **1995**, *60*, 4905. Platt, K.; Oesch, F. *Synthesis* **1982**, 459.
(15) The function of 1,2-epoxybutane is to prevent competing reactions by scavenging the HI produced: Liu, L. B.; Yang, B. W.; Katz, T. J.; Poindexter, M. K. *J. Org. Chem.* **1991**, *56*, 3769.

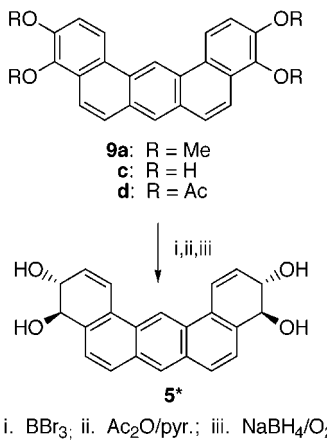
trum was inconsistent with the desired 3,4,10,11-tetramethoxydibenz[*a,j*]anthracene (**9a**) but instead was fully compatible with the structure of 1,2,9,10-tetramethoxybenzo[*c*]chrysene (**10a**), arising from cyclization in the alternative direction. This was evidenced by the absence of the characteristic singlet peaks of the meso region 7,-14-aromatic protons of **9a** and the presence of a pair of low-field doublets at δ 8.90 and 8.73 assigned to the fjord region $H_{12,13}$-protons of **10a** and a second pair of doublets at δ 8.62 and 8.48 assigned to the bay region $H_{4,5}$-protons. This finding was not unexpected, since cyclization of the parent unsubstituted diolefin is known to take place predominantly in the same direction to afford benzo[*c*]-chrysene as the principal product.[16]

1,2,9,10-Tetramethoxybenzo[*c*]chrysene (**10a**) was converted to the corresponding bis(dihydrodiol), *trans*-1,2-*trans*-9,10-tetrahydroxy-1,2,9,10-tetrahydrobenzo[*c*]chrysene (**6**). Treatment of **10a** with BBr_3 furnished the bis(catechol), 1,2,9,10-tetrahydroxybenzo[*c*]chrysene (**10b**). Because of the known sensitivity of polycyclic catechols to air oxidation, **10b** was isolated as its tetraacetate (**10c**). Reduction of **10c** with excess $NaBH_4$ while O_2 was bubbling through the solution took place smoothly and stereospecifically to afford the *trans*,*trans*-bis(dihydrodiol) **6**, consistent with previous findings of *trans*-stereospecificity for reductions of this type.[14] The ^1H and ^{13}C NMR spectra of **6** were fully consistent with its assignment as the racemic bis(dihydrodiol) derivative of benzo[*c*]chrysene existing as two pairs of enantiomers.

It was found recently that polycyclic dihydrodiols are converted by mammalian dihydrodiol dehydrogenase enzymes to polycyclic catechols that are further oxidized to *ortho*-quinones that then enter into a redox cycle with molecular oxygen, resulting in generation of reactive oxygen species (superoxide anion, hydroxyl radicals, and hydrogen peroxide) that cause extensive DNA damage.[17] Therefore, it was of interest to convert the bis(dihydrodiol) **6** into the corresponding bis(*ortho*-quinone) **11**. This was accomplished by oxidation of **6** with *o*-chloranil in THF which furnished **11** quantitatively.

Modification of the synthetic approach in Scheme 1 by the introduction of a blocking group into the central aromatic ring of the diolefin **8a** in order to prevent cyclization in the undesired direction and favor cyclization to form the dibenz[*a,j*]anthracene ring system was also investigated. To this end, two appropriately substituted homologues of 1,3-bis(bromomethyl)benzene were synthesized and converted into the corresponding *bis*-(phosphonium) salts of 1,3-bis(bromomethyl)benzene (**7b,c**). Double Wittig reactions of these *bis*(phosphonium) salts with 2,3-dimethoxybenzaldehyde gave the corresponding substituted distyrylbenzenes (**8b,c**). The ^1H NMR spectra of these diolefins were relatively complex, indicating them to be mixtures of the (*E,E*)-, (*E,Z*)-, and (*Z,Z*)-stereoisomers. Photocyclization of **8b** (R = Br, CH_3 or OH) took place with displacement of the substituent to furnish the benzo[*c*]chrysene derivative (**10a**). However, the chloro group was considerably more effective as a blocking group, cyclization of **8c** taking place to furnish 7-chloro-3,4,10,11-tetramethoxydibenz[*a,j*]anthracene (**9b**) as the principal product isolated. A smaller amount of **10a** was also detected. Several methods for the removal of the chloro substitutent of **9b** were investigated. The most effective of these was reduction with $NiCl_2$ and $LiAlH_4$ which took place smoothly to provide 3,4,10,11-tetramethoxydibenz[*a,j*]anthracene (**9a**) in 92% yield (Scheme 2).[18] Its assignment as a dibenz[*a,j*]-anthracene derivative was confirmed by its ^1H NMR spectra which differed markedly from that of the benzo-[*g*]chrysene derivative **10a**, exhibiting characteristic low-field singlets at δ 8.30 and 9.80 for the meso region protons at C-7 and C-14, respectively, as well as other signals consistent with this structure.

Scheme 2[a]



[a] Asterisk indicates mixtures of bis(*trans*-dihydrodiols).

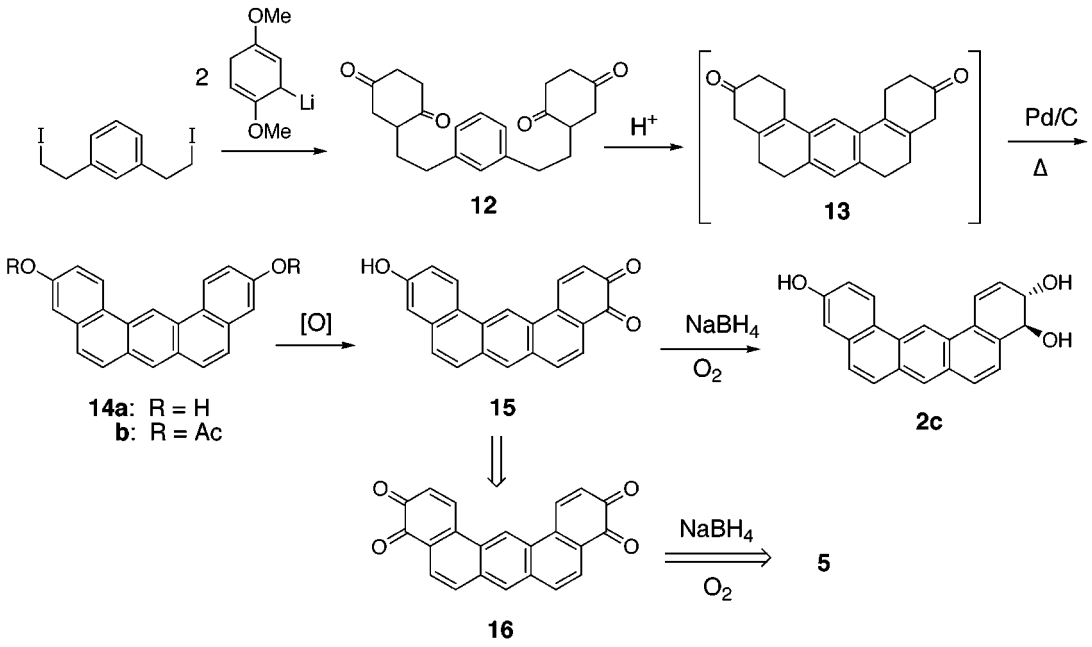
Conversion of **9a** to the corresponding bis(dihydrodiol), *trans*,*trans*-3,4,10,11-tetrahydroxy-3,4,10,11-tetrahydrodibenz[*a,j*]anthracene (**5**), was accomplished, as in the case of the related benzo[*c*]chrysene derivative **10a**, by demethylation with BBr_3, acetylation of the bis(catechol) product (**9c**), and reduction of the tetraacetate (**9d**) with $NaBH_4$ and O_2 (Scheme 2). The high-resolution ^1H NMR spectrum of **5** was consistent with its assignment as the bis(dihydrodiol) derivative of the dibenz[*a,j*]anthracene and showed it to be a mixture of two diastereomers, a meso isomer and a racemic pair of enantiomers. Further confirmation of this structure was provided by the ^{13}C NMR spectrum of **5** which exhibited only 12 peaks, consistent with the symmetry of the dibenz[*a,j*]anthracene ring system. This contrasts with the multiplicity of peaks in the ^{13}C NMR spectrum of the bis-(dihydrodiol) of benzo[*c*]chrysene (**6**) which is lacking in symmetry.

Prior to successful achievement of the synthesis of **5**, an alternative synthetic route was investigated. This method entailed as the key step the reaction of two equivalents of the lithium salt of 1,4-dimethoxy-1,4-cyclohexadiene with 1,3-bis(iodoethyl)benzene (Scheme 3).[19] This furnished a bis-alkylated diketone product (**12**) which underwent smooth acid-catalyzed double cyclodehydration to yield 3,11-diketododecahydrodibenz[*a,j*]an-

(16) Dietz, F.; Scholz, M. *Tetrahedron* **1968**, *24*, 6845.
(17) Burczynski, M. E.; Harvey, R. G.; Penning, T. M. *Biochemistry*, **1998**, *37*, 6781−6790. Flowers, L.; Bleczinski, W.; Burczynski, M. E.; Harvey, R. G.; Penning, T. M. *Biochemistry* **1996**, *35*, 13664. Flowers-Geary, L.; Bleczinski, W.; Harvey, R. G.; Penning, T. M. *Chem.-Biol. Interact.* **1996**, *99*, 55. Jarabak, R.; Harvey, R. G.; Jarabak, J. *Arch. Biochem. Biophys.* **1996**, *327*, 174. Flowers-Geary, L.; Harvey, R. G.; Penning, T. M. *Carcinogenesis* **1995**, *16*, 2707. Flowers-Geary, L.; Harvey, R. G.; Penning, T. M. *Chem. Res. Toxicol.* **1993**, *6*, 252. Smithgall, T. E.; Harvey, R. G.; Penning, T. M. *Cancer. Res.* **1988**, *48*, 1227.

(18) Ashby, E. C.; Lin, J. J. *J. Org. Chem.* **1978**, *43*, 1263.
(19) Pataki, J.; Lee, H.; Harvey, R. G. *Carcinogenesis* **1983**, *4*, 399. Pataki, J., Harvey, R. G. *J. Org. Chem.* **1982**, *47*, 20.

Scheme 3



thracene (**13**). Since acid-catalyzed cyclodehydrations of this type can occur with concomitant disproportionation of the primary products to yield mixtures of more saturated and less saturated polycyclic aromatic products,[20] the crude **13** was dehydrogenated over a palladium charcoal catalyst. The principal product was the diphenol 3,11-dihydroxydibenz[*a*,*j*]anthracene (**14a**) which was isolated as its diacetate. Oxidation of **14a** with Fremy's reagent $[K(SO_3)_2NO]$ by the usual procedure[21] afforded mainly a phenolic quinone arising from oxidation of only one of the two phenolic rings, namely 11-hydroxydibenz[*a*,*j*]anthracene-3,4-dione (**15**). Reduction of **15** with $NaBH_4$ and O_2 afforded stereospecifically the corresponding phenolic *trans*-dihydrodiol (**2c**) in moderate yield. An alternative synthetic route to **2c** is described in the following paper.

The failure of oxidation of **14a** to furnish the bis(quinone) dibenz[*a*,*j*]anthracene-3,4,10,11-dione (**16**) may be partially a consequence of the poor solubility of the phenolic quinone intermediate **15** in the aqueous medium. This synthetic route to the bis(dihydrodiol) **5** was not pursued further because of the success of the synthetic approach outlined above.

Discussion

There is a substantial body of evidence that diol epoxide metabolites in which the epoxide ring resides in a bay or fjord region are the principal carcinogenic metabolites of PAHs with a single bay or fjord region in the molecule, such as benzo[*a*]pyrene and benzo[*g*]chrysene.[1,3] However, recent findings on the metabolic activation and DNA binding of PAHs which contain additional bay or fjord regions, such as dibenz[*a*,*j*]anthracene, suggest that bis(dihydrodiol)s that give rise to the corresponding mono- or diepoxides may also contribute to their carcinogenicity and, in some cases, may be the major active metabolites.[4−11]

The bis(dihydrodiol)s may also potentially serve as substrates for the dihydrodiol dehydrogenase enzymes, forming bis(catechols) and bis(quinones) that participate in a redox cycle that generates reactive oxygen species that cause DNA damage.[17] Although compounds of these classes are urgently required for biological investigations, relatively few are known, and they are not readily accessible through synthesis.[22] This paper reports efficient syntheses of the terminal ring bis(dihydrodiol) derivatives of dibenz[*a*,*j*]anthracene (**5**) and benzo[*c*]chrysene (**6**) along with various additional higher oxidized putative metabolites.

The syntheses of **5** and **6** involve in the key steps photocyclization of appropriately substituted distyrylbenzenes (**8a**,**c**) (Scheme 1). The use of a chloro substituent to direct cyclization to the less favored site is novel in that its effectiveness is contrary to prior observations that chloro groups tend to undergo relatively facile displacement in these types of photoreactions.[23] Whether cyclization occurs with or without displacement is dependent, in principle, on the difference between the activation energies for cyclization in either direction. This, in turn, is likely to depend on the structure of the polycyclic aromatic ring system. The present finding suggests that simple rules regarding the susceptibility of various groups to undergo displacement during photocyclization should be treated with caution.

The syntheses of the bis(dihydrodiol)s **5** and **6** described herein are relatively efficient, entailing relatively few steps and providing good overall yields. In principle, this synthetic approach may be utilized with appropriate modification for the synthesis of the bis(dihydrodiol) metabolites of numerous other PAHs. The principle limitation is the photocyclization step. It is often necessary to conduct these types of reactions in relatively

(20) (a) Cho, B.; Harvey, R. G. *J. Org. Chem.* **1987**, *52*, 5668. (b) Harvey, R. G.; Halonen, M. *Can. J. Chem.* **1967**, *45*, 2630. (c) Harvey, R. G.; Pataki, J.; Cortez, C.; Di Raddo, P.; Yang, C. *J. Org. Chem.* **1991**, *56*, 1210.

(21) Sukumaran, K. B.; Harvey, R. G. *J. Org. Chem.* **1980**, *45*, 4407.

(22) Synthesis of bis(dihydrodiol) derivatives of benzo[*s*]picene has recently been described: Zhang, F.-J.; Harvey, R. G. *J. Org. Chem.* **1998**, *63*, 1168.

(23) Mallory, F. B.; Mallory, C. W. *Org. React.* **1984**, *30*, 1.

dilute solutions, severely limiting the amount of olefin that may be employed. This has not proven to be a serious problem in the examples studied to date. Good yields of cyclized products were obtained from photoreactions conducted on a 1−2 g scale, and only milligram amounts of the ultimate synthetic targets, the bis(dihydrodiol)s, suffice for most biological studies.

Although the bis(dihydrodiol) **5** could not be obtained via the alternative synthetic method outlined in Scheme 3, this approach provides convenient synthetic access to other previously unknown higher oxidized metabolites of dibenz[*a*,*j*]anthracene, specifically the diphenol (**14a**), the phenolic quinone (**15**), and the phenolic dihydrodiol (**2c**). It is interesting that the second stage acid-catalyzed cyclization of the intermediate **12** takes place exclusively in one direction to favor formation of the partially saturated dibenz[*a*,*j*]anthracene ring system. This is consistent with the previous observation that similar cyclodehydration of the diketone analogue of **12**, lacking the additional keto groups which are not involved in cyclization, also takes place in the same direction.[20c]

The bis(dihydrodiol)s **5** and **6** and the other higher oxidized derivatives of dibenz[*a*,*j*]anthracene (**14a**, **15**, and **2c**) have been submitted as standards for metabolism and for other biological studies to determine their role in the mechanism of carcinogenesis of the parent PAHs.

Experimental Section

Materials and Methods. *m*-Chloroperbenzoic acid (Aldrich) was purified by washing with pH 7.4 phosphate buffer and drying under reduced pressure. THF was distilled from sodium benzophenone ketyl. The ^{1}H NMR spectra were recorded on 300 and 500 MHz spectrometers in $CDCl_3$ with tetramethylsilane as internal standard unless stated otherwise; the ^{13}C NMR spectra were recorded on a 125 MHz spectrometer in THF-d_8. All melting points are uncorrected.

Caution! *Dibenz[a,j]anthracene is a weak carcinogen in animal assays. It and its dihydrodiol and diol epoxide derivatives, as well as the bis(dihydrodiol)s of dibenz[a,j]-anthracene and benzo[c]*chrysene, *are potentially hazardous and should be handled with care in accordance with "NIH Guidelines for the Laboratory Use of Chemical Carcinogens*".

1,3-Bis(bromomethyl)-2-chlorobenzene. A solution of 2-chloro-1,3-dimethylbenzene (10 g, 71.1 mmol), NBS (31.6 g, 178 mmol), and a few crystals of benzoyl peroxide in CCl_4 was heated at reflux for 24 h. The mixture was cooled to room temperature, and the precipitate of succinimide was removed by filtration. The filtrate was passed through a short column of silica gel and then evaporated to dryness, and the solid residue was crystallized from hexane to yield 1,3-bis(bromomethyl)-2-chlorobenzene (6 g, 28%) as a white solid, mp 89−90 °C: ^{1}H NMR δ 4.58 (s, 4), 7.20 (t, 1, J = 7.6 Hz), 7.36 (d, 2, J = 7.7 Hz). Anal. Calcd for $C_8H_7Br_2Cl$: C, 32.20; H, 2.36. Found: 32.24; H, 2.32.

1,3-Bis((triphenylphosphono)methyl)benzene bromide (7a). A solution of 1,3-bis(bromomethyl)benzene (25.0 g, 95 mmol) and PPh_3 (50.0 g, 190 mmol) in 150 mL of dimethylformamide was heated at reflux for 48 h. The solution was cooled and concentrated under vacuum to a small volume. The resulting precipitate was filtered out, washed thoroughly with ether, and then dried under vacuum to yield **7a** (64.4 g, 85%) as a white solid, mp 298−299 °C: ^{1}H NMR δ 5.20 (d, 4, J = 14.5 Hz), 6.83 (s, 3), 7.36 (s, 1), 7.63−7.73 (m, 30). Anal. Calcd for $C_{44}H_{38}P_2Br_2$: C, 67.02; H, 4.86. Found: C, 66.96; H, 4.82.

1,3-Bis((triphenylphosphono)methyl)-2-chlorobenzene bromide (7c). A solution of 1,3-bis(bromomethyl)-2-chlorobenzene (7.0 g, 23.4 mmol) and PPh_3 (12.3 g, 46.8 mmol) in 500 mL of toluene was heated at reflux for 24 h. The reaction was worked up as in the preceding example to afford **7c** (19.0 g, 100%) as an off white solid, mp > 290 °C: ^{1}H NMR δ 5.52 (d, 4, J = 11.6 Hz), 6.96 (t, 1, J = 7.9 Hz), 7.40 (d, 2, J = 7.8 Hz), 7.59−7.82 (m, 30). Anal. Calcd for $C_{44}H_{37}P_2Br_2Cl$: C, 64.22; H, 4.53. Found: C, 64.36; H, 4.52.

1,3-Bis(2,3-dimethoxystyryl)benzene (8a). 2,3-Dimethoxybenzaldehyde (3.30 g, 20 mmol) and **7a** (7.90 g, 10 mmol) were dissolved in CH_2Cl_2 (250 mL), and to this solution was added 25 mL of a 50% aqueous NaOH solution. The mixture was heated at reflux under argon for 72 h, and the reaction was monitored by TLC. The product was extracted into CH_2Cl_2, and then the solution was washed with water, dried, and evaporated to dryness. The crude product was redissolved in a small amount of CH_2Cl_2 and chromatographed on a column of Florisil. Elution with CH_2Cl_2−hexane gave **8a** (2.48 g, 62%) as white crystals, mp 94−95 °C: ^{1}H NMR δ 3.76 (s, 6), 3.84 (s, 6), 6.49 (d, 2, J = 12.2 Hz), 6.62−6.77 (m, 8), 6.97 (m, 3), 7.08 (s, 1). Anal. Calcd for $C_{26}H_{26}O_4$: C, 77.59; H, 6.51. Found: C, 77.77; H, 6.60.

1,3-Bis(2,3-dimethoxystyryl)-2-chlorobenzene (8c). Reaction of 2,3-dimethoxybenzaldehyde (6.60 g, 40 mmol) with **7c** (16.40 g, 20 mmol) and NaOH (100 mL of 50% aqueous solution) was carried out by the procedure employed for the preparation of **8a**. The crude product was further purified by chromatography on a column of silica gel. Elution with CH_2Cl_2−hexane furnished **8c** (3.00 g, 35%) as white crystals, mp 125−126 °C: ^{1}H NMR δ 3.78−3.88 (m, 4), 6.53−7.20 (m, 9); the complexity of the spectrum indicated a mixture of the (*E*,*E*)-, (*E*,*Z*)-, and (*Z*,*Z*)-isomers. Anal. Calcd for $C_{26}H_{25}O_4$-Cl: C, 71.47; H, 5.77; Cl, 8.11. Found: C, 71.40; H, 5.78; Cl, 8.18.

1,2,9,10-Tetramethoxybenzo[*c*]chrysene (10a). Argon was bubbled through a solution of **8a** (1.30 g, 3.2 mmol) in 500 mL of benzene for 30 min. Then iodine (1.63 g, 6.4 mmol) and 1,2-epoxybutane (30 mL) were added, and the mixture was irradiated with a Hanovia 450 W medium-pressure lamp through a Pyrex filter for 12 h. The solvent was concentrated under vacuum to a small volume and purified by chromatography on a Florisil column. Elution with benzene−hexane afforded after trituration with ether−hexane **10a** (470 mg, 37%) as a white solid, mp 189−190 °C: ^{1}H NMR δ 4.05 (m, 12), 7.36 (d, 1, J = 9.3 Hz), 7.39 (d, 1, J = 9.3 Hz), 7.80 (d, 1, J = 8.9 Hz), 7.93 (d, 1, J = 8.6 Hz), 8.18 (d, 2, J = 9.1 Hz), 8.48 (d, 1, J = 9.1 Hz), 8.63 (d, 1, J = 8.6 Hz), 8.73 (d, 1, J = 9.2 Hz), 8.89 (d, 1, J = 9.4 Hz). Anal. Calcd for $C_{26}H_{22}O_4$: C, 78.37; H, 5.57. Found: C, 78.27; H, 5.59.

1,2,9,10-Tetrahydroxy- and 1,2,9,10-tetraacetoxybenzo[*c*]chrysene (10b,c). To a solution of **10a** (300 mg, 0.75 mmol) in 10 mL of dry CH_2Cl_2 was added 30 mL of a 1 M BBr_3 solution in CH_2Cl_2. The resulting solution was stirred at room temperature under argon for 3 h. The product was precipitated by addition of ice−water, filtered, and dried to furnish **10b** (200 mg, 78%) as a white solid that was used directly in the next step.

A solution of **10b** (200 mg, 0.58 mmol), 9 mL of Ac_2O, and 1 mL of pyridine was stirred at room temperature under argon for 16 h. Then the product was precipitated by addition of ice−water and filtered out, and the crude **10c** was further purified by passage through a Florisil column. Elution with benzene−ether gave pure **10c** (250 mg, 84%) as white solid, mp 193−194 °C: ^{1}H NMR δ 2.38 (s, 6), 2.51 (d, 6, J = 4.8 Hz), 7.48 (d, 1, J = 9.0 Hz), 7.54 (d, 1, J = 9.1 Hz), 7.90 (m, 3), 8.00 (d, 1, J = 8.7 Hz), 8.66 (d, 1, J = 9.1 Hz), 8.71 (d, 1, J = 8.8 Hz), 8.82 (d, 1, J = 9.2 Hz), 8.93 (d, 1, J = 9.4 Hz). Anal. Calcd for $C_{30}H_{22}O_8$: C, 70.58; H, 4.34. Found: C, 70.68; H, 4.39.

***trans*-1,2-*trans*-9,10-Tetrahydroxy-1,2,9,10-tetrahydrobenzo[*c*]chrysene (6).** A solution of **10c** (245 mg, 0.48 mmol) and $NaBH_4$ (726 mg, 19.2 mmol) in 100 mL of EtOH with O_2 slowly bubbling through the solution was stirred at room temperature for 16 h, and then the solvent was removed under vacuum without heating. The solid precipitate was filtered out, washed with water, and dried to yield **6** (151 mg, 90%) as white solid, mp 255−256 °C: ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.31−4.71 (m,4), 5.23 (m, 2, OH, exchangeable with D_2O), 5.57 (m, 2, OH, exchangeable with D_2O), 6.11 (d,

1, J = 9.0 Hz), 6.16 (d, 1, J = 10.1 Hz), 7.08 (d, 1, J = 10.7 Hz), 7.27 (d, 1, J = 10.2 Hz), 7.68−7.86 (m, 4), 8.07 (br d, 1, J = 9.0 Hz), 8.31 (br d, 1, J = 8.3 Hz); ^{13}C NMR δ 73.17, 73.26, 73.95, 74.30, 76.29, 76.31, 76.54, 76.61, 121.88, 122.20, 122.30, 122.78, 123.02, 123.07, 124.47, 124.56, 127.63, 127.72, 127.80, 128.01, 128.20, 128.24, 128.51, 128.98, 129.09, 129.96, 130.03, 130.08, 130.12, 130.54, 130.59, 132.74, 132.79, 132.85, 133.01, 134.75, 135.28, 137.76, 139.28; UV (EtOH) λ_{max} (ϵ) 273 (4.6 × 10^4), 287 (3.1 × 10^4), 297 (3.5 × 10^4), 310 (2.4 × 10^4), 334 (1.3 × 10^4) nm; MS *m*/*e* 346 (M^+, 7), 310 (100); HRMS calcd for $C_{22}H_{18}O_4$ 346.1205, found 346.1221.

Benzo[*c*]chrysene-1,2,9,10-tetraone (11). A solution of **6** (200 mg, 0.58 mmol) and *o*-chloranil (720 mg, 2.92 mmol) in 50 mL of anhydrous THF was stirred at room temperature under argon for 72 h. The red precipitate was removed by filtration, washed with ether and then with acetone, and dried to yield **11** (200 mg, 99%) as a red solid, mp 330−331 °C: ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.51 (d, 1, J = 10.7 Hz), 6.56 (d, 1, J = 10.5 Hz), 8.02 (d, 1, J = 8.9 Hz), 8.13−8.22 (m, 3), 8.28 (d, 1, J = 10.1 Hz), 8.43 (d, 1, J = 9.0 Hz), 8.58−8.63 (m, 2). Anal. Calcd for $C_{22}H_{10}O_4$: C, 78.10; H, 2.18. Found: 78.24; H, 2.32.

7-Chloro-3,4,10,11-tetramethoxydibenz[*a*,*j*]anthracene (9b). Argon was bubbled through a solution of **8c** (570 mg, 1.3 mmol), iodine (1.0 g, 3.9 mmol), and 1,2-epoxypropane (50 mL) in 500 mL of ether, while the mixture was irradiated with a Hanovia 450 W medium-pressure lamp through a Vycor filter for 2 h. The reaction was monitored by TLC, and then most of the solvent was removed under vacuum and the product was purified by chromatography on a Florisil column. Elution with CH_2Cl_2−hexane afforded **9b** (120 mg, 21.4%) as a white solid, mp 248−250 °C: ^{1}H NMR δ 4.06 (s, 6), 4.08 (s, 6), 7.43 (d, 2, J = 9.0 Hz), 8.18 (d, 2, J = 9.6 Hz), 8.40 (d, 2, J = 9.6 Hz), 8.68 (d, 2, J = 9.0 Hz), 9.76 (s, 1). Anal. Calcd for $C_{26}H_{21}O_4Cl$: C, 72.14; H, 4.89; Cl, 8.19. Found: C, 72.13; H, 4.91; Cl, 8.27.

3,4,10,11-Tetramethoxydibenz[*a*,*j*]anthracene (9a). To a suspension of **9b** (120 mg, 0.28 mmol) in THF under argon was added $NiCl_2$ (181 mg, 1.4 mmol), and the mixture was stirred at ambient temperature for 20 min. To this was added 2.8 mL of a 1 M solution of $LiAlH_4$ in THF (2.8 mmol). Gas was evolved, and the solution turned black. The reaction was monitored by TLC. After it was complete (∼1 h), the mixture was quenched by addition of a small amount of distilled water and stirred for an additional 20 min, and then the solution was dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was dissolved in a small amount of CH_2Cl_2 and chromatographed on a silica gel column. Elution with 1:1 CH_2Cl_2−hexane yielded **9a** (100 mg, 91%) as a white solid, mp 255−256 °C: ^{1}H NMR δ 4.05 (s, 6), 4.07 (s, 6), 7.42 (d, 2, J = 9.0 Hz), 7.85 (d, 2, J = 9.3 Hz), 8.07 (d, 2, J = 9.2 Hz), 8.30 (s, 1), 8.70 (d, 2, J = 9.0 Hz), 9.80 (s, 1). Anal. Calcd for $C_{26}H_{22}O_4$: C, 78.37; H, 5.57. Found: C, 78.27; H, 5.61.

3,4,10,11-Tetrahydroxy- and 3,4,10,11-Tetraacetoxydibenz[*a*,*j*]anthracene (9c,d). To a stirred solution of **9a** (120 mg, 0.3 mmol) in 100 mL of CH_2Cl_2 was added 6 mL of a 1 M solution of BBr_3 in CH_2Cl_2. When TLC showed the reaction to be complete (1 h), it was quenched by the addition of water. The solvent was removed by evaporation, and the precipitate was dried to furnish **9c** (100 mg, 97%) which, because of its air sensitivity, was used directly in the next step.

A solution of **9c** (100 mg, 0.30 mmol) in 4.5 mL of Ac_2O and 0.5 mL of pyridine was stirred at room temperature under argon for 16 h, and then **9d** (150 mg) was precipitated by the addition of ice−water, filtered out, and chromatographed on a Florisil column eluted with CH_2Cl_2. Trituration with 1% CH_2Cl_2 in ether gave pure **9d** (102 mg, 65%), mp 289−290 °C: ^{1}H NMR (500 MHz) δ 2.37 (s, 6), 2.48 (s, 6), 7.53 (d, 2, J = 8.9 Hz), 7.67 (d, 2, J = 9.1 Hz), 7.81 (d, 2, J = 9.3 Hz), 8.25 (s, 1), 8.76 (d, 2, J = 9.0 Hz), 9.74 (s, 1). Anal. Calcd for $C_{30}H_{22}O_8$: C, 70.58; H, 4.34. Found: C, 70.49; H, 4.37.

***trans*-3,4-*trans*-10,11-Tetrahydroxy-3,4,10,11-tetrahydrodibenz[*a*,*j*]anthracene (5).** Reduction of **9d** (90 mg, 0.18 mmol) with $NaBH_4$ (800 mg) was carried out by the procedure employed for the reduction of **10c**. When TLC showed reaction to be incomplete after 3 days, additional $NaBH_4$ (800 mg) was added, and stirring was continued for 2 days. The usual workup provided **5** (34 mg, 54%) as a white solid, mp 204−206 °C: ^{1}H NMR (DMSO-d_6 + D_2O) (data is for the major isomer; the minor isomer showed slightly different chemical shifts) δ 4.39 (d, 2, J = 10.9 Hz), 4.75 (d, 2, J = 10.9 Hz), 6.19 (d, 2, J = 6.2 Hz), 7.47 (d, 1, J = 9.9 Hz), 7.50 (d, 1, J = 9.9 Hz), 7.70 (d, 2, J = 8.5 Hz), 7.93 (d, 2, J = 8.5 Hz), 8.44 (s, 1), 8.91 (s, 1); ^{13}C NMR δ 74.48, 76.58, 117.24, 122.66, 124.03, 127.89, 128.12, 128.33, 129.06, 131.97, 134.64, 136.53; UV (EtOH) λ_{max} (ϵ) 223 (1.95 × 10^4), 271.5 (1.21 × 10^4), 294.6 (1.03 × 10^4), 307 (0.8 × 10^4), 384.6 (0.3 × 10^4), 405 (0.5 × 10^4), 429 (0.38 × 10^4) nm. Anal. Calcd for $C_{22}H_{18}O_8$: C, 70.58; H, 4.34. Found: C, 70.49; H, 4.37. Acetylation of **5** by the procedure employed for the preparation of **9d** gave the tetraacetate as a white solid, mp 230−231 °C (ether−hexane): ^{1}H NMR δ 2.07 (s, 6), 2.15 (s, 6), 5.69 (m, 2), 6.35 (m, 4), 7.47 (d, 2, J = 8.7 Hz), 7.67 (d, 2, J = 10.1 Hz), 7.97 (d, 2, J = 8.7 Hz), 8.44 (s, 1), 9.03 (s, 1).

1,3-Bis[2-(2,5-diketocyclohexyl)ethyl]benzene (12). To 50 mL of anhydrous THF in a flame-dried two-neck flask cooled to −78 °C was added *tert*-BuLi (29.4 mL, 1.7 M in pentane, 50 mmol) and 1,4-dimethylcyclohexa-1,4-diene (7.0 g, 50 mmol) in 8.5 mL of dry THF. The solution was stirred for 1 h under argon, and then HMPA (8.7 mL) was added and the red solution was stirred for 10 min. A solution of 1,3-bis-(iodoethyl)benzene (7.72 g, 20 mmol) in 50 mL of THF was added dropwise over 30 min. The reddish solution was stirred for 10 min. Then the reaction was quenched with brine, ether was added, and the organic layer was washed with brine, dried over Na_2SO_4, and evaporated to dryness.

The crude product was dissolved in 100 mL of acetone, and 20 mL of 1 N HCl was added (both acetone and hydrochloric acid were purged with argon for 30 min before use). The solution was stirred at room temperature under argon for 1 h. Acetone was evaporated under reduced pressure, and the residue was extracted with CH_2Cl_2. The usual workup and chromatography on Florisil elution with hexane−CH_2Cl_2 afforded pure **12** as a white solid (2.5 g, 36%): ^{1}H NMR δ 1.64−1.72 (m, 2), 2.14−2.24 (m, 2), 2.41−2.90 (m, 12), 6.99 (s, 1), 7.01 (d, 2, J = 7.5 Hz), 7.20 (t, 1, J = 7.5 Hz). Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.55; H, 7.42.

3,11-Dihydroxydibenz[*a*,*j*]anthracene (14a). A mixture of **12** (2.51 g, 7.08 mmol) in 4.5 mL of methanesulfonic acid and 50 mL of CH_2Cl_2 was stirred for 24 h. The usual workup followed by chromatography on a silica gel column eluted with hexane−CH_2Cl_2 gave **13** as a pale yellow solid (220 mg): ^{1}H NMR δ 2.20 (t, 4, J = 7.5 Hz), 2.64 (t, 4, J = 7.0 Hz), 2.78 (t, 4, J = 8.0 Hz), 2.87 (t, 4, J = 6.5 Hz), 3.02 (s, 4), 6.90 (s, 1), 7.00 (s, 1H). Compound **13** was used directly in the next step.

A mixture of **13**, Pd/C (250 mg, 10%), and 50 mL of triglyme was refluxed for 5 h, and then the reaction mixture was cooled to room temperature and poured onto ice. The usual workup and chromatography on silica gel eluted with CH_2Cl_2/EtOAc gave **14a** (154 mg, 70% for the two steps) as white solid, mp 281−283 °C: ^{1}H NMR (acetone-d_6) δ 7.31 (dd, 2, J = 2.5, 8.8 Hz), 7.34 (d, 2, J = 2.5 Hz), 7.64 (d, 2, J = 9.0 Hz), 7.86 (d, 2, J = 9.0 Hz), 8.38 (s, 1H), 8.78 (s, 1.2, exchangeable with D_2O), 9.09 (d, 2, J = 8.8 Hz), 9.97 (s, 1).

Compound **14a** was further characterized by conversion to its diacetate **14b**, white solid, mp 252−254 °C: ^{1}H NMR δ 2.41 (s, 6), 7.49 (dd, 2, J = 2.4, 8.9 Hz), 7.65 (d, 2, J = 2.3 Hz), 7.69 (d, 2, J = 9.0 Hz), 7.88 (d, 2, J = 9.0 Hz), 8.35 (s, 1), 8.97 (d, 2, J = 8.9 Hz), 9.88 (s, 1); MS *m*/*e* 394 (M^+, 45), 310 (100); HRMS calcd for $C_{26}H_{18}O_4$ 394.1205, found 394.1198.

11-Hydroxydibenz[*a*,*j*]anthracene-3,4-dione (15). A solution of **14a** (45.0 mg, 0.15 mmol) in 10 mL of benzene was added with 2 drops of Adogen 464 and Fremy's salt (374 mg, 1.45 mmol in 10 mL of 0.167 M KH_2PO_4 buffer). The reaction mixture was stirred with O_2 bubbled through for 2 h. The precipitate was collected, washed with water and Et_2O, and dried. Compound **15** (40 mg, 85%) was obtained as a black solid, mp 218−220 °C: ^{1}H NMR (DMSO-d_6) δ 6.57 (d, 1, J = 10.5 Hz), 7.20 (d, 1, J = 8.5 Hz), 7.22 (s, 1), 7.68 (d, 1, J = 9.0 Hz), 7.79 (d, 1, J = 9.0 Hz), 7.94 (d, 1, J = 8.6 Hz), 8.17 (d, 1,

J = 8.8 Hz), 8.50 (s, 1), 9.09 (d, 1, J = 10.5 Hz), 9.10 (d, 1, J = 8.7 Hz), 9.69 (s, 1); MS *m/e* 326 ($M^+ + 2$, 30), 310 (65), 156 (100); HRMS calcd for $C_{22}H_{14}O_3$ 326.0943, found 326.0942.

***trans*-3,4,11-Trihydroxy-3,4-dihydrodibenz[*a,j*]anthracene (2c).** To a suspension of **15** (35 mg, 0.108 mmol) in 100 mL of EtOH was added $NaBH_4$ (267 mg, 7.14 mmol). The solution was stirred with O_2 bubbling through for 2.5 h. The usual workup gave **2c** (27 mg, 77%) as yellow solid; its physical and spectral properties were essentially identical with those of an aunthentic sample of **2c** reported in the following paper.

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