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Convenient Syntheses of Dibenzo[*c,p*]chrysene and Its Possible Proximate and Ultimate Carcinogens: In Vitro Metabolism and DNA Adduction Studies

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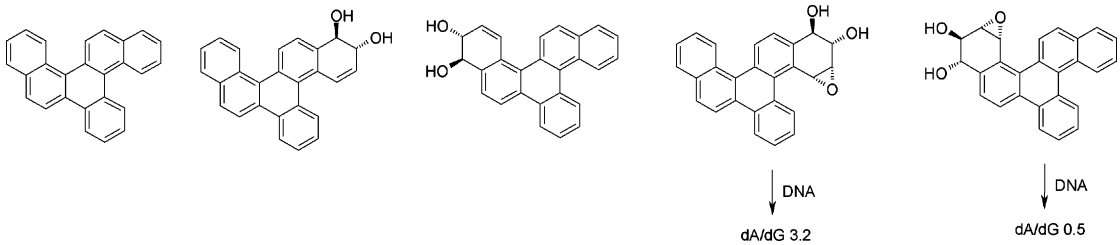
Received December 20, 2004



Dibenzo[*c,p*]chrysene (DB[*c,p*]C) is the only hexacyclic polycyclic aromatic hydrocarbon having two fjord regions, both in different chemical environments. Its environmental presence and relative tumorigenic potency are not known due to the lack of synthetic standards. We report here the synthesis of dibenzo[*c,p*]chrysene (**1**), its proximate carcinogens, i.e., *trans*-1,2-dihydroxy-1,2-dihydro-DB[*c,p*]C (**2**) and *trans*-11,12-dihydroxy-11,12-dihydro-DB[*c,p*]C (**3**), and possible ultimate carcinogens, i.e., *anti-trans*-1,2-dihydroxy-3,4-epoxy-1,2,3,4-tetrahydro-DB[*c,p*]C (**4**) and *anti-trans*-11,12-dihydroxy-13,14-epoxy-11,12,13,14-tetrahydro-DB[*c,p*]C (**5**). The syntheses of **1** and the appropriately methoxy-substituted DB[*c,p*]C (**12** and **27**), key intermediates for the synthesis of its proximate and ultimate metabolites, were tried first using a Suzuki cross-coupling reaction. However, the cyclization of olefins (**10** and **11**) gave poor yields of the desired products. An alternate method was thus developed employing a photochemical approach. The in vitro metabolism of DB[*c,p*]C was established with the *S*9 fraction of liver homogenate from phenobarbital/β-naphthoflavone-induced Sprague−Dawley rats. The major dihydrodiol formed was identified as the fjord region 11,12-dihydroxy-11,12-dihydro-DB[*c,p*]C, while the major and minor phenols were identified as 11-hydroxy-DB[*c,p*]C and 12-hydroxy-DB[*c,p*]C, respectively. Further, the DNA adduction studies with the calf thymus DNA led to a mixture of dA and dG adducts for both fjord region diol epoxides (**4** and **5**). Interestingly, the dA to dG ratio for 1,2-dihydroxy-3,4-epoxide was much higher (3.2) compared to that of 11,12-dihydroxy-13,14-epoxide (0.5).

Introduction

Polycyclic aromatic hydrocarbons (PAHs), the ubiquitous environmental pollutants,[1] require metabolic activation to electrophilic reactive metabolites in order to exert their mutagenic and tumorigenic activity.[2] Structural features have been reported to be the key factor in determining the potency of a PAH as a carcinogen. It has been observed that substituted PAHs with greater steric hindrance are more tumorigenic than their less hindered counterparts, having the same number of rings. For example, 7,12-dimethylbenz[*a*]anthracene, 5-methylchrysene (5-MeC), and 11-methylbenzo[*a*]pyrene, having a methyl group in the bay region, are more carcinogenic than their respective parent PAHs.[3] Further, the fjord region diol epoxides (DEs) derived from benzo[*c*]phenan-

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10.1021/jo040291k CCC: $30.25
Published on Web 05/25/2005

threne (B[*c*]P), benzo[*g*]chrysene (B[*g*]C), and dibenzo[*a,l*]pyrene (DB[*a,l*]P) are more tumorigenic in rodents than the bay region 7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (B[*a*]P-DE).[4] The steric hindrance due to the fjord region causes a deviation from planarity of a molecule, and this stereochemical effect has been associated with carcinogenicity. Dipple et al. have proposed that this effect may be due to an increased number of binding sites of active diol epoxides (DEs) to dexoyadenosine (dA) sites in DNA.[5] For example, the bay region (+)- and (−)-*anti*-B[*a*]P-DE bind predominantly to deoxyguanosine (dG),[6] while the sterically hindered fjord region DEs of B[*c*]P,[7,8] B[*g*]C,[8,9] and DB[*a,l*]P[10] bind more extensively to dA than to the dG residues in DNA to form stable adducts. The fjord PAH diol epoxide−N^6-dA adducts have been reported to be much more resistant to repair by nucleotide excision repair enzymes in human cell extracts than bay region B[*a*]P−DE N^6-dA adducts.[11] This was also supported by greater thermal stability of duplexes with fjord PAH-N^6-dA lesions relative to those with bay region B[*a*]P−DE N^6-dA adducts.[12] Theoretical calculations have attributed the increased activity of sterically hindered PAHs with fjord region to the greater instability of their epoxide ring upon protonation.[13]

The molecules studied so far contained only one fjord region, and little is known about the biological activity of PAHs containing two active sites, e.g., a fjord and a bay region[14] or two fjord regions[15] in the same molecule. Our recent studies on benzo[*c*]chrysene (B[*c*]C), having a bay and fjord region, have shown that the fjord region diol epoxide, i.e., B[*c*]C-9,10-diol-11,12-epoxide, is a much more potent rat mammary gland carcinogen than the bay region B[*c*]C-1,2-diol-3,4-epoxide.[14] In continuation of our pursuits toward the understanding of the structure-carcinogenicity relationship of sterically hindered PAHs, we have chosen to study dibenzo[*c,p*]chrysene (DB[*c,p*]C). It belongs to a class of *cata*-condensed[16] hexacyclic PAHs and attracted our attention because of its unique structure; it contains two fjord regions in the molecule causing it to deviate from planarity which has been shown by theoretical calculations.[17] It incorporates the structures of three potent tumorigenic PAHs, i.e., B[*c*]P, B[*c*]C, and B[*g*]C, in its structure as shown by structures **1a**, **1b**, and **1c**, respectively (Figure 1). In view of all this, we hypothesized that DB[*c,p*]C may be a potent carcinogen. However, its environmental presence, metabolism pattern, and carcinogenicty are not known due to the lack of synthetic standards of DB[*c,p*]C and its potential active metabolites. Thus, as a beginning in this direction, we report here the syntheses of DB[*c,p*]C (**1**); the possible proximate carcinogens *trans*-1,2-dihydroxy-1,2-dihydro-DB[*c,p*]C (**2**) and *trans*-11,12-dihydroxy-11,12-dihydro-DB[*c,p*]C (**3**), required in connection with the metabolism studies; and possible ultimate carcinogens, i.e., *anti-trans*-1,2-dihydroxy-3,4-epoxy-1,2,3,4-tetrahydro-DB[*c,p*]C (**4**) and *anti-trans*-11,12-dihydroxy-13,14-epoxy-11,12,13,14-tetrahydro-DB[*c,p*]C (**5**) (Figure 2) to study the DNA adduct formation pattern.

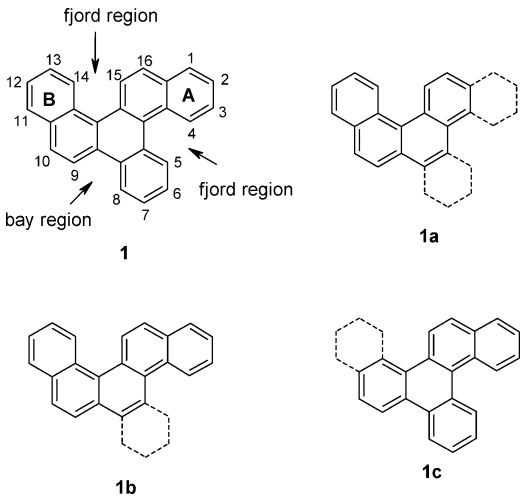

FIGURE 1.

Results and Discussion

A synthesis of DB[*c,p*]C has been reported in the literature starting from self-condensation of tetralone via

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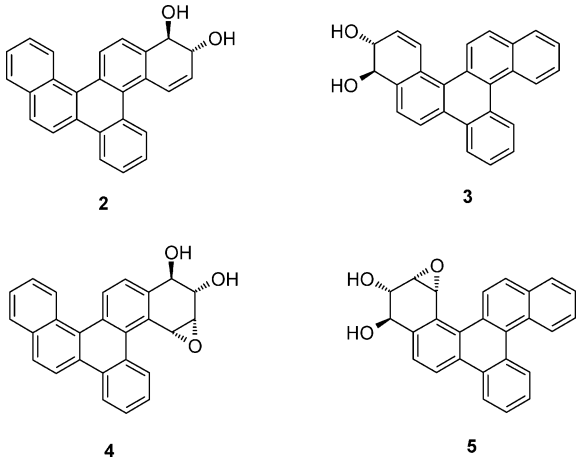

FIGURE 2.

a spiral intermediate.[18] However, this method cannot be applied to the syntheses of fjord region dihydrodiol metabolites of DB[*c,p*]C. We intended to exploit the Suzuki cross-coupling[19] approach for their syntheses. Suzuki coupling has recently been introduced to the PAH synthesis,[20−25] and we also have successfully exploited this approach for the synthesis of N[1,2-*a*]P,[22] N[1,2-*e*]P,[23] B[*c*]C,[24] DMBA,[24] DB[*a,l*]P,[25] and their metabolites. The synthetic sequence of DB[*c,p*]C is depicted in Scheme 1. Chrysene-6-boronic acid (**7**) was obtained by treatment of 6-bromochrysene (**6**) with *n*-BuLi and triisopropyl borate employing a literature method.[21] Suzuki cross-coupling reaction of boronic acid **7** with 2-bromobenzaldehyde in the presence of CsF and a catalytic amount of $Pd(PPh_3)_4$ resulted in the formation of aldehyde **8** in 82% yield. Treatment of **8** with (methoxymethyl)triphenylphosphonium chloride using PhLi as a base afforded the olefin **10**, which cyclized readily on treatment with concentrated sulfuric acid in methylene chloride (at 0 °C) to give DB[*c,p*]C (**1**), but in a very low (∼19%) yield. Various attempts to improve the yield failed. The reactions in the presence of methanesulfonic acid or BF_3-etherate gave even lower yields of the cyclized product. An attempt to cyclize olefin **10** in the presence of PTSA resulted in the formation of aldehyde **13** in quantitative yield. The intermediate for the synthesis of 1,2-dihydroxy-1,2-dihydro-DB[*c,p*]C, i.e., the 2-methoxy-DB[*c,p*]C, was also obtained in a very low yield. Coupling of boronic acid **7** with 2-bromo-5-methoxybenzaldehyde gave a very good (87%) yield of the adduct **9** which on Wittig condensation resulted in high yield of a olefins **11** as a mixture of *cis* and *trans* isomers. However, the cyclization using any of the above methods gave not more than (10−17%) yields of the cyclized product **12**.

We have recently reported the synthesis of various PAHs, e.g., N[1,2-*a*]P,[22] N[1,2-*e*]P,[23] B[*c*]C derivatives,[24] and DMBA derivatives,[24] through a similar approach, and the cyclization with methanesulfonic acid worked very well to give high yields of the cyclized product. The only difference is that in all of the earlier cases, the cyclization occurred to form the K-region of the PAH whereas in the present case we were trying to cyclize the olefins **10** and **11** to form the fjord region. The reaction was extremely quick, perhaps because the K-region (5-position) in compounds **10** and **11** involved in the cyclization is electron rich. However, due to steric reasons the cyclization is not favored to form the desired six-membered ring.

DB[*c,p*]C and 2-methoxy-DB[*c,p*]C thus obtained were characterized on the basis of NMR and high-resolution MS data. Their ^{1}H NMR spectra showed, apart from other protons, the six downfield protons (H4, H5, H8, H9, H14, and H15) characteristic of the bay and fjord regions. Interestingly, the melting point of DB[*c,p*]C (152−153 °C) differed substantially from that reported in the literature (200−202 °C).[18] An alternate synthetic approach was thus necessary to unequivocally confirm the structure as well as to improve the overall yield. For this purpose, we were attracted to the photochemical approach since it has been shown to work better in the case of such sterically hindered molecules.[26] The synthetic approach is shown in Scheme 2. Condensation of 2-naphthaldehyde (**14**) with ethylphenyl acetate in the presence of lithium diisopropylamide (LDA) gave the olefins **16** as a mixture of *cis* and *trans* isomers.[27] Photocyclodehydrogenation of the olefins **16** took place smoothly in the presence of catalytic amount of I_2 to yield 5-ethoxycarbonylbenzo[*c*]-phenantherene (**18**). Reduction of **18** by $LiAlH_4$ yielded the alcohol **20**, which was oxidized to the aldehyde derivative **22** by treatment with pyridinium chlorochromate (PCC). The Wittig condensation of **22** with benzyltriphenylphosphonium chloride resulted in the formation of the olefins **24** as a mixture of *cis* and *trans* isomers in an ∼1:1 ratio, which was easily photocyclized to furnish the desired DB[*c,p*]C in very good (86%) yield. The ^{1}H NMR, MS, and the melting point of DB[*c,p*]C were identical to the those obtained by the Suzuki cross-coupling reaction. This suggested that the compound reported previously in the literature[18] was either not DB-[*c,p*]C but some other rearranged product or the reported melting point was incorrect.

The key intermediates for the synthesis of fjord region dihydrodiols **2** and **3**, i.e., the appropriately substituted methoxy derivatives of DB[*c,p*]C, were also obtained using photochemical methods (Scheme 2). 2-Methoxy-DB-[*c,p*]C was obtained from 6-methoxy-2-naphthaldehyde **15** using a similar reaction sequence. Treatment of **15** with ethylphenyl acetate gave the olefin **17**, which on

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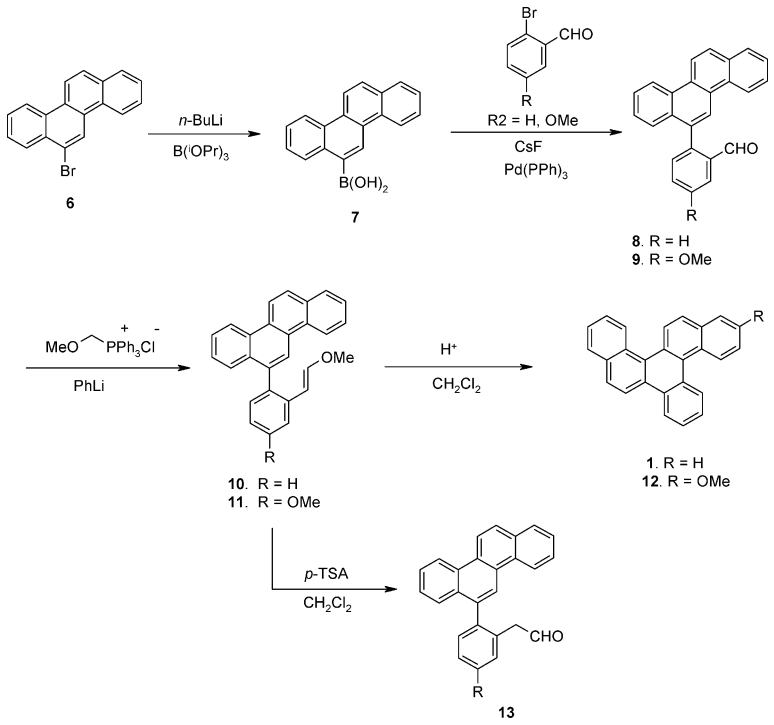
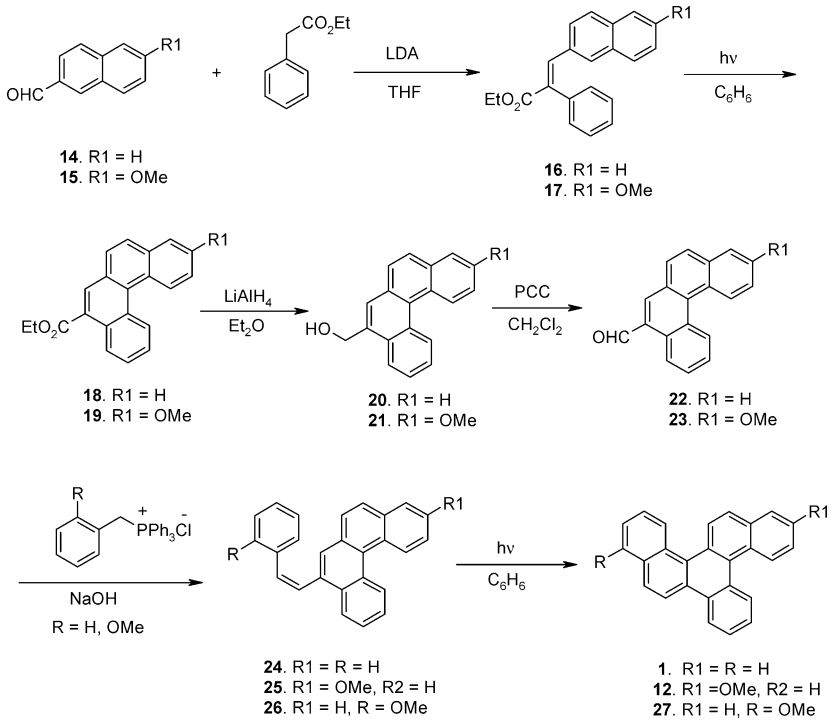
(27) The reaction did not go to completion. However, the olefin mixture was separated easily from the unreacted starting materials by silica gel column chromatography.

SCHEME 1



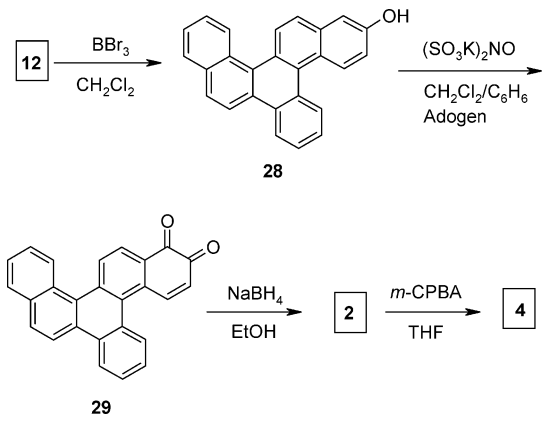
SCHEME 2



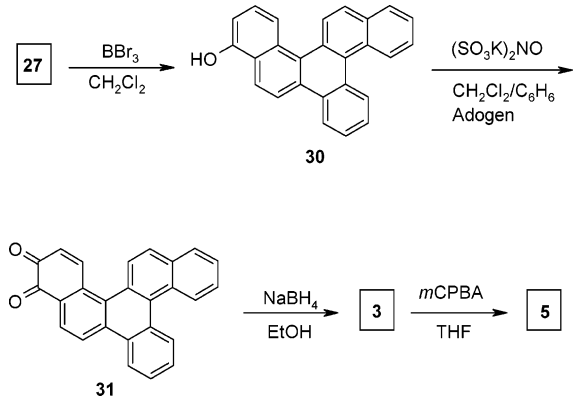
photocyclization afforded 5-ethoxycarbonyl-10-methoxybenzo[*c*]phenanthrene (**19**). $LiAlH_4$ reduction of **19** gave alcohol **21**, which was then oxidized to aldehyde **23** using PCC. The Wittig reaction of **23** with benzyltriphenylphosphonium chloride resulted in the formation of the olefins **25** as a mixture of *cis* and *trans* isomers in an ~1:1 ratio, which was photocyclized to furnish the desired 2-methoxy-DB[*c,p*]C (**12**) in very good (87%) yield. The product was characterized on the basis of its ^{1}H NMR and HRMS.

Demethylation of **12** with BBr_3 in CH_2Cl_2 led to the formation of 2-hydroxy-DB[*c,p*]C (**28**), which was oxidized to DB[*c,p*]C-1,2-dione (**29**) by treatment with Fremy's salt [$(SO_3K)_2NO$] (Scheme 3). Reduction of quinone **29** with $NaBH_4$ furnished the *trans*-1,2-dihydroxy-1,2-dihydro-DB[*c,p*]C (**2**) in excellent yield. The product was characterized on the basis of its ^{1}H NMR and MS. The *trans* stereochemistry of the dihydrodiol **2** was established on the basis of the large coupling constant of 10.5 Hz

SCHEME 3



SCHEME 4



between H1 and H2 in its ^{1}H NMR spectrum seen by resolving the multiplet signal (δ 4.52−4.60) of H1 and H2 through decoupling experiments.

11-Methoxy-DB[*c,p*]C or 12-methoxy-DB[*c,p*]C would be a potential intermediate required for the synthesis of 11,12-dihydroxy-11,12-dihydro-DB[*c,p*]C. However, our synthetic strategy suited the synthesis of 11-methoxy derivative **27** (Scheme 2). The synthesis of 12-methoxy-DB[*c,p*]C by this method would require the reaction of aldehyde **22** with 3-methoxybenzyltriphenylphosphonium chloride, which according to our experience with chrysene derivatives[28] was expected to result in a mixture of 12- and 14-methoxy-DB[*c,p*]C. On the other hand, in the case of the 11-methoxy derivative, there is a probability of formation of a mixture of 11,12-dione and 11,14-dione on the oxidation of 11-hydroxy-DB[*c,p*]C (Scheme 4). However, the chances for such a mixture were minimum in this particular case due to the steric factors.[26]

Thus, the Wittig reaction between aldehyde **22** and 2-methoxybenzyltriphenylphosphonium chloride gave the olefin mixture **26**, which on photocyclization resulted in the formation of 11-methoxy-DB[*c,p*]C (**27**) (Scheme 2). We did not observe the formation of DB[*c,p*]C by elimination of methoxy group as observed by Melory et al. in the photocyclization of stillbenes.[29] Compound **27** was then converted to the 11-hydroxy-DB[*c,p*]C (**30**) using

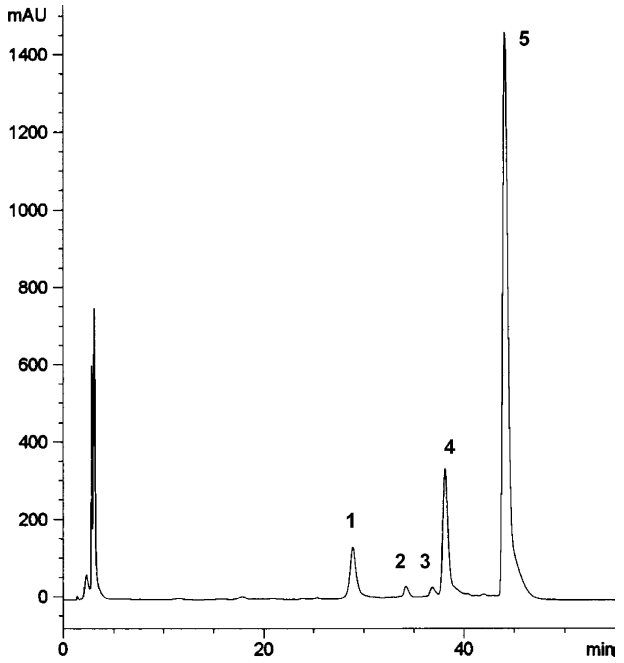


FIGURE 3. HPLC profile of in vitro metabolites of DB[*c,p*]C: peak 1, DB[*c,p*]C-11,12-dihydrodiol; peak 3, 12-hydroxy-DB-[*c,p*]C; peak 4, 11-hydroxy-DB[*c,p*]C; peak 5, DB[*c,p*]C.

BBr_3 (Scheme 4). As expected, 11-hydroxy-DB[*c,p*]C on reaction with Fremy's salt resulted exclusively in the formation of DB[*c,p*]C-11,12-dione **31**. $NaBH_4$ reduction of the dione **31** gave the *trans*-11,12-dihydroxy-11,12-dihydro-DB[*c,p*]C. The structure was confirmed by ^{1}H NMR as well as by MS, and the *trans* stereochemistry of the dihydrodiol was confirmed based on the coupling constant (10.5 Hz) between H-11 and H-12, which was found by resolving the multiplet signal (δ 4.50−4.60) for H11 and H12 through decoupling experiments.

After preparation of the synthetic standards, e.g., DB-[*c,p*]C, its hydroxy derivatives **28** and **30**, and two critical fjord region dihydrodiols **2** and **3**, we carried out the metabolism of DB[*c,p*]C with phenobarbital/β-naphthoflavone-induced male Sprague−Dawley rat *S9* liver homogenate. The profile of the metabolites by reversed-phase HPLC is shown in Figure 3. Peak 1 was identified as DB-[*c,p*]C-11,12-dihydrodiol (**3**) on the basis of the identical retention time (t_R 28.8 min) and identical UV as the synthetic standard. Similarly, peak 4 was assigned as 11-hydroxy-DB[*c,p*]C (**30**) on the basis of the identical retention time (t_R 38.1 min) and identical UV as the synthetic standard. None of the peaks in the metabolism trace identified with the synthetic standards of DB[*c,p*]C-1,2-dihydrodiol (**2**) or 2-hydroxy-DB[*c,p*]C (**28**). We then carried out the dehydration of 1,2-dihydrodiol by warming in benzene in the presence of *p*-toluenesulfonic acid, which led to the formation of a mixture of 1-hydroxy-DB[*c,p*]C and 2-hydroxy-DB[*c,p*]C. Using this mixture, we did not detect 1-hydroxy-DB[*c,p*]C as a metabolite. Dehydration of DB[*c,p*]C-11,12-dihydrodiol (**3**), under similar conditions, led to a mixture of 11-hydroxy-DB-[*c,p*]C and 12-hydroxy-DB[*c,p*]C. 11-Hydroxy-DB[*c,p*]C (t_R 38.1) in this mixture coeluted with the synthetic standard and peak 4 while the 12-hydroxy-DB[*c,p*]C (t_R 36.8) coeluted with peak 3 in the metabolism trace. Peak 5 coeluted with DB[*c,p*]C, and peak 2 did not match with

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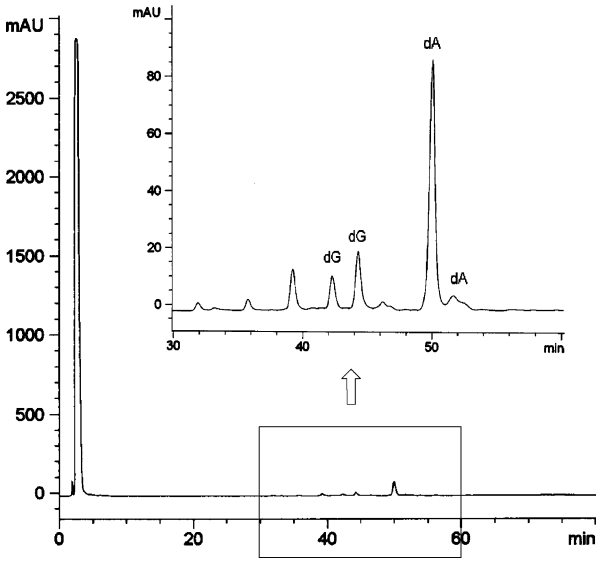

FIGURE 4. DNA adduct pattern of DB[*c,p*]C-1,2-diol-3,4-epoxide.

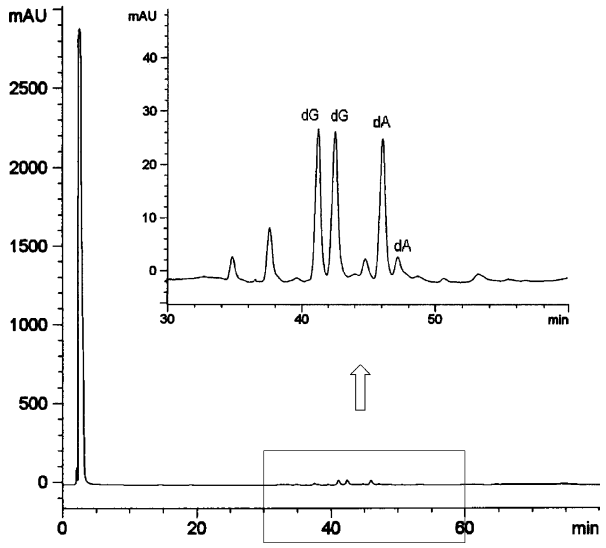

FIGURE 5. DNA adduct pattern of DB[*c,p*]C-11,12-diol-13,-14-epoxide.

any of the synthetic standards and thus was not assigned. The metabolites obtained were thus identified as 11-hydroxy-DB[*c,p*]C, 12-hydroxy-DB[*c,p*]C, and DB[*c,p*]C-11,12-dihydrodiol (Figure 3). This has been an interesting observation because only one terminal ring (ring B, Figure 1) is involved in in vitro metabolism, although both active rings A and B apparently have similar reactive sites to offer.

It is known that diol epoxides derived from more distorted fjord regions give a higher d*A*/d*G* adduct ratio on treatment with calf thymus DNA compared to bay region diol epoxides. This has also been true for B[*c*]C, which possesses both a bay and a fjord region in the same molecule; the d*A*/d*G* adduct ratio for the fjord region DE was ~0.4 compared to ~0.1 for the bay region.[14] DB[*c,p*]C having two fjord regions in different chemical environment, as also indicated by its interesting metabolism pattern, was thus thought to be an interesting candidate to study the DNA adduction pattern with diol epoxides **4** and **5** derived from rings A and B of DB[*c,p*]C, respectively. In view of this we converted dihydrodiols **2** and **3** to the corresponding 1,2-diol-3,4-epoxide **4** and 11,-12-diol-13,14-epoxide **5**, respectively, using *m*-CPBA (Schemes 3 and 4). The reactions were performed under N_2 atmosphere, and the two epoxides were obtained in good yields. These were characterized on the basis of their ^{1}H NMR and MS.

The formation pattern of in vitro adducts with calf-thymus DNA and epoxides **4** and **5** was then examined. First, the nucleoside markers were prepared from epoxides **4** and **5** with 2′-dG-5′-monophosphate and 2′-dA-5′-monophosphate. The modified deoxyribonucleotides were enzymatically hydrolyzed to deoxyribonucleosides, which were analyzed by HPLC. Then, the epoxides **4** and **5** were incubated with calf-thymus DNA and the modified DNA was isolated and digested enzymatically to give nucleoside adducts. The HPLC analysis for 1,2-diol-3,4-epoxide **4** is shown in Figure 4. A pair of dG adduct and a pair of dA adduct peaks were identified by comparison of their retention times to those of the standard markers. The d*A*/d*G* ratio calculated from the peak areas was found to be 3.2, which is comparable to that of DB[*a,l*]P (d*A*/d*G* 3−4), the most potent PAH known. The HPLC analysis for 11,12-diol-13,14-epoxide **5** (Figure 5) also showed a pair of dG adduct and a pair of dA adduct peaks which were identified by comparison of their retention times to those of the standard markers. The d*A*/d*G* ratio in this case was found to be 0.5 which is similar to the d*A*/d*G* ratio for fjord region 3,4-dihydroxy-1,2-epoxy-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene (0.5−0.7); yet it is higher[7] than the d*A*/d*G* ratio of 0.05 for the bay region 7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene.[30] These observations are consistent with the trend that fjord region diol epoxides give enhanced levels of dA adducts.

Conclusion

It is observed that the synthesis of DB[*c,p*]C and its metabolites by Suzuki coupling sequence is indeed possible but the overall yield is low. The photochemical cyclization approach has proved to be a better method in the present case where steric hindrance restricts cyclization by other methods. The method is convenient and gave high overall yields of DB[*c,p*]C and its possible proximate and ultimate carcinogenic metabolites. DB-[*c,p*]C would be a good standard for its identification in the environment and will be useful for the metabolism studies in vivo. The fjord region dihydrodiols **2** and **3** and the hydroxy compounds **28** and **30**, served to identify the metabolites in vitro, and will be useful as standards to identify the products of the metabolism of DB[*c,p*]C in vivo, and for the comparison of their toxicity and tumorigenicity with other known carcinogens. The d*A*/d*G* adduct ratio (0.5) for diol epoxide **5** was similar to B[*c*]C fjord region diol epoxide (0.5−0.7) which is expected from their similar structural features. However, the d*A*/d*G* adduct ratio (3.2) for diol epoxide **4** makes it second only

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to DB[*a,l*]P-11,12-diol-13,14-epoxide to have more than 75% dA adduct. On the basis of these observations, DB-[*c,p*]C may be considered as a carcinogenic PAH.

Experimental Section

Caution! *DB[c,p]C and its derivatives described in this paper may be carcinogenic. Therefore, appropriate safety procedures should be followed when working with these compounds.*

Chrysene-6-boronic Acid (7). To a solution of 6-bromochrysene (**6**) (6.14 g, 20 mmol) at −78 °C under N_2 was added *n*-BuLi (2.5 M in hexanes, 17.6 mL, 44 mmol) dropwise, and the reaction mixture was stirred at the same temperature for 1 h. Triisopropylborate (7.52 g, 9.23 mL, 40 mmol) was then added in one portion, and the reaction was stirred at −78 °C for 30 min. It was then warmed to room temperature and stirred for another 1 h. The reaction mixture was then diluted with ether (400 mL) and acidified with 10% HCl (200 mL). The ether extract was washed with water and dried over $MgSO_4$. Removal of solvent gave a white solid which was filtered and washed with hexanes/ether (9/1) to give nearly pure **7** (4.2 g, 77%) which was used as such for further reactions. ^{1}H NMR: δ 7.65−7.79 (m, 4H), 8.09 (d, 1H, J = 7.9 Hz), 8.12 (d, 1H, J = 9.2 Hz), 8.59 (d with fine splitting, 1H, J = 7.6 Hz), 8.62 (br s, 2H), 8.88 (d, 1H, J = 9.2 Hz), 8.94 (d, 1H, J = 7.9 Hz), 8.99 (d, 1H, J = 8.2 Hz), 9.09 (s, 1H, H5).

6-(2-Formylphenyl)chrysene (8). A mixture of chrysene-6-boronic acid (**7**) (1.2 g, 4.4 mmol), 2-bromobenzaldehyde (0.74 g, 0.47 mL, 4.0 mmol), cesium fluoride (1.21 g, 8.0 mmol), and $Pd(PPh_3)_4$ (0.18 g, 0.16 mmol) in anhydrous DME (50 mL) was refluxed for 14 h. The mixture was brought to room temperature, and the reaction was quenched with ice-cold H_2O. The aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL), and the combined organic layers were washed with H_2O and dried over anhydrous $MgSO_4$. Concentration in vacuo provided a residue which was purified by silica gel column chromatography (EtOAc/hexanes 1:99) to give **8** (1.2 g, 82%) as a white crystalline solid. Mp: 184−185 °C. ^{1}H NMR: δ 7.54−7.80 (m, 8H), 8.03 (dd, 1H, J = 7.6 and 2.0 Hz), 8.08 (d, 1H, J = 9.2 Hz), 8.19 (dd, 1H, J = 7.9 and 1.0 Hz), 8.66 (s, 1H), 8.71 (d, 1H, J = 8.9 Hz), 8.78 (d, 1H, J = 9.2 Hz), 8.89 (d, 1H, J = 8.5 Hz), 9.74 (s, 1H). HRMS: *m/z* calcd for $C_{25}H_{16}O$ 332.1196, found 332.1191.

6-(2-Formyl-4-methoxyphenyl)chrysene (9). Yield: 87%. Mp: 165−166 °C. ^{1}H NMR: δ 3.99 (s, 3H), 7.33 (dd, 1H, J = 8.5 and 2.9 Hz), 7.50 (d, 1H, J = 8.5 Hz), 7.55−7.59 (m, 1H), 7.64−7.76 (m, 5H), 8.02 (dd, 1H, J = 6.9 and 1.9 Hz), 8.07 (d, 1H, J = 9.2 Hz), 8.64 (s, 1H), 8.70 (d, 1H, J = 7.5 Hz), 8.77 (d, 1H, J = 9.2 Hz), 8.88 (d, 1H, J = 8.5 Hz), 9.70 (s, 1H). HRMS: *m/z* calcd for $C_{26}H_{18}O_2$ 362.1301, found 362.1304.

6-[2-(β-Methoxyethenyl)phenyl]chrysene (10). A suspension of anhydrous (methoxymethyl)triphenylphosphonium chloride (4.8 g, 14.0 mmol) in freshly distilled Et_2O (110 mL) was cooled to −78 °C under N_2. To this mixture was added PhLi (1.8 M in cyclohexane/ether/70:30, 5.8 mL, 10.5 mmol), dropwise, and the mixture was stirred for 30 min. The reaction mixture was then warmed to −30 °C, stirred for another 30 min, and again cooled to −78 °C. A solution of **8** (0.93 g, 2.8 mmol) in THF (90 mL) was then added dropwise/ and the mixture was left overnight at room temperature. The reaction was quenched with 1 N HCl; the mixture was washed several times with water and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified on a silica gel column chromatography (EtOAc/hexanes 1:99) to yield a mixture of *cis* and *trans* isomers of olefin **10** (0.79 g, 78%) as a clear viscous oil. ^{1}H NMR: δ 3.18 (s, 1.77H, *trans*), 3.71 (s, 1.23H, *cis*), 4.85 (d, 0.41H, J = 7.2 Hz, *cis*), 5.45 (d, 0.59H, J = 12.8 Hz, *trans*), 5.85 (d, 0.41H, J = 7.2 Hz, *cis*), 6.97 (d, 0.59H, J = 12.8 Hz, *trans*), 7.30−7.72 (m, 8.41H), 7.99−8.06 (m, 2H), 8.30 (d, 0.59H, J = 7.9 Hz), 8.61 (s, 0.41H, H5, *cis*), 8.62 (s, 0.59H, H5, *trans*), 8.74 (d, 1H, J = 7.6 Hz), 8.78 (d, 1H, J = 9.2 Hz), 8.86 (d, 1H, J = 8.5 Hz). HRMS: *m/z* calcd for $C_{27}H_{20}O$ 360.1509, found 360.1514.

6-[2-(β-Methoxyethenyl)-4-methoxyphenyl]chrysene (11). Yield: 75%. ^{1}H NMR: δ 3.19 (s, 1.5H), 3.72 (s, 1.5H), 3.95 (s, 1.5H), 3.96 (s, 1.5H), 4.84 (d, 0.5H, J = 7.5 Hz, *cis*), 5.44 (d, 0.5H, J = 13.1 Hz, *trans*), 5.86 (d, 0.5H, J = 7.5 Hz, *cis*), 6.90−6.93 (m, 1H), 6.99 (d, 0.5H, J = 13.1 Hz, *trans*), 7.12 (d, 0.5H, J = 2.6 Hz), 7.31 (d, 0.5H, J = 8.5 Hz), 7.33 (d, 0.5H, J = 8.2 Hz), 7.51−7.56 (m, 1H), 7.61−7.73 (m, 4H), 7.93 (d, 0.5H, J = 2.6 Hz), 7.99−8.05 (m, 2H), 8.61 (s, 0.5H), 8.62 (s, 0.5H), 8.73−8.79 (m, 2H), 8.85 (d, 1H, J = 8.2 Hz). MS: *m/z* 390 (M^+).

Dibenzo[*c,p*]chrysene (1). To a solution of olefin **10** (0.20 g, 0.56 mmol) in anhydrous CH_2Cl_2 (10 mL) was added concd H_2SO_4 (0.05 mL in 0.5 mL of CH_2Cl_2) dropwise under N_2, and the mixture was stirred at room temperature for 10 min. It was then poured into ice-cold H_2O, and the organic layer was separated and washed successively with 10% $NaHCO_3$ solution and with water. The organic layer was dried ($MgSO_4$) and concentrated, and the crude residue was purified via silica gel column chromatography (EtOAc/hexanes 1:99) to give **1** (35 mg, 19%) as a pale yellow crystalline solid. Mp: 152−153 °C (lit.[18] mp 200−202 °C). ^{1}H NMR: δ 7.59−7.77 (m, 6H), 7.95 (d, 1H, J = 8.9 Hz), 8.03−8.07 (m, 3H), 8.69 (d, 1H, J = 8.9 Hz), 8.79 (dd, 1H, J = 7.9 and 1.3 Hz), 8.83 (d, 1H, J = 8.9 Hz), 8.91 (dd, 1H, J = 8.9 and 1.6 Hz), 9.04−9.07 (m, 2H). HRMS: calcd for $C_{26}H_{16}$ 328.1247, found 328.1245.

2-Methoxy-DB[*c,p*]C (12). Yield: 17%. Mp: 116−117 °C. ^{1}H NMR: δ 4.03 (s, 3H), 7.32 (dd, 1H, J = 9.2 and J = 2.6 Hz), 7.38 (d, 1H, J = 2.6 Hz), 7.58−7.76 (m, 4H), 7.86 (d, 1H, J = 8.9 Hz), 8.00−8.04 (m, 2H), 8.65 (d, 1H, J = 8.9 Hz), 8.76 (d, 1H, J = 8.2 Hz), 8.81 (d, 1H, J = 8.9 Hz), 8.89 (dd, 1H, J = 9.2 and 1.6 Hz), 8.95 (d, 1H, J = 9.2 Hz), 8.97 (dd, 1H, J = 7.9 and 1.6 Hz). High-resolution MS: *m/z* calcd for $C_{27}H_{18}O$ 358.1352, found 358.1363.

5-Ethoxycarbonylbenzo[*c*]phenanthrene (18). To a solution of ethyl phenylacetate (4.1 g, 25 mmol) in THF (50 mL) at 0 °C was added LDA (2 M solution in THF, heptane, ethylbenzene, 18.75 mL, 37.5 mmol) dropwise, and the mixture was stirred at 0 °C for 2 h. A solution of 2-naphthaldehyde (**14**) (3.9 g, 25 mmol) in THF (50 mL) was then added, and the reaction mixture was refluxed for 2 h. It was then cooled to rt, and ice-cold water was added, acidified with dilute HCl, and extracted with EtOAc. The organic layer was washed with water and dried over anhydrous $MgSO_4$. Concentration in vacuo gave a residue that was purified on a silica gel column chromatography (EtOAc/hexanes 1:99) to yield a mixture of *cis* and *trans* isomers of olefin **16** (4.25 g, 56%). A stirred solution of **16** (1.51 g, 5.0 mmol) and I_2 (cat.) in benzene was irradiated with a Hanovia 450 W medium-pressure lamp, with a Pyrex filter, for 8 h, while the dry air was bubbled through the solution. Removal of solvent gave a residue which was purified by silica gel column chromatography (EtOAc/hexanes 2/98) to give **18** (1.35 g, 89%) as a white crystalline solid. Mp: 96−97 °C. ^{1}H NMR: δ 1.53 (t, 3H, J = 7.2 Hz), 4.56 (q, 2H, J = 7.2 Hz), 7.62−7.74 (m, 4H), 7.86 (d, 1H, J = 8.5 Hz), 7.93 (d, 1H, J = 8.5 Hz), 8.03 (dd, 1H, J = 7.2 and J = 2.0 Hz), 8.53 (s, 1H), 9.01−9.10 (m, 3H). HRMS: *m/z* calcd for $C_{21}H_{16}O_2$ 300.1145, found 300.1146.

5-Ethoxycarbonyl-10-methoxybenzo[*c*]phenanthrene (19). Yield: 83%. Mp: 123−124 °C. ^{1}H NMR: δ 1.51 (t, 3H, J = 7.2 Hz), 4.01 (s, 3H), 4.54 (q, 2H, J = 7.2 Hz), 7.33 (dd, 1H, J = 9.2 and J = 2.6 Hz), 7.36 (d, 1H, J = 2.6 Hz), 7.65−7.72 (m, 2H), 7.83 (s, 2H), 8.51 (s, 1H), 8.95 (d, 1H, J = 9.2 Hz), 8.98−9.03 (m, 2H). HRMS: *m/z* calcd for $C_{22}H_{18}O_3$ 330.1250, found 330.1254.

5-Hydroxymethylbenzo[*c*]phenanthrene (20). To a well-stirred suspension of $LiAlH_4$ (0.76 g, 20 mmol) in anhydrous ether (60 mL) at 0 °C was added a solution of **18** (1.2 g, 4.0 mmol) in ether (50 mL) dropwise. After the addition was complete, the reaction mixture was warmed to rt and stirred

for another 1 h. It was then diluted with ether, poured into ice-cold water, and acidified with 10% HCl. The organic layer was separated, and the aqueous layer was extracted again with ether. The combined ether extracts were washed with water and dried over anhydrous $MgSO_4$. Removal of solvent afforded a crude residue which was purified on a silica gel column chromatography (EtOAc/hexanes 30:70) to give (0.96 g, 93%) of **18** as a white crystalline solid. Mp: 156−157 °C. ^{1}H NMR: δ 5.28 (s, 2H), 7.61−7.71 (m, 4H), 7.81 (d, 1H, J = 8.5 Hz), 7.88 (s, 1H), 7.91 (d, 1H, J = 8.5 Hz), 8.02 (dd, 1H, J = 7.6 and J = 1.3 Hz), 8.27 (dd, 1H, J = 8.2 and J = 2.6 Hz), 9.07 (d, 1H, J = 8.5 Hz), 9.14 (dd, 1H, J = 9.2 and 2.3 Hz). HRMS: *m/z* calcd for $C_{19}H_{14}O$ 258.1039, found 258.1047.

5-Hydroxymethyl-10-methoxybenzo[*c*]phenanthrene (21). Yield: 95%. Mp: 138−139 °C. ^{1}H NMR: δ 4.00 (s, 3H), 5.25 (s, 2H), 7.31 (dd, 1H, J = 9.2 and J = 2.6 Hz), 7.35 (d, 1H, J = 2.6 Hz), 7.64−7.71 (m, 2H), 7.77 (d, 1H, J = 8.5 Hz), 7.81 (d, 1H, J = 8.5 Hz), 7.83 (s, 1H), 8.24−8.27 (m, 1H), 8.96 (d, 1H, J = 9.2 Hz), 9.04−9.07 (m, 1H). HRMS: *m/z* calcd for $C_{20}H_{16}O_2$ 288.1145, found 288.1147.

5-Formylbenzo[*c*]phenanthrene (22). To a stirred suspension of PCC (0.97 g, 4.5 mmol) in CH_2Cl_2 (50 mL) at rt was added a solution of alcohol **20** (0.77 g, 3.0 mmol) in CH_2Cl_2 (80 mL) dropwise. The resulting mixture was stirred for 4 h, diluted with CH_2Cl_2, washed with 10% HCl and water, and dried ($MgSO_4$). Concentration in vacuo provided a residue that was purified on a silica gel column chromatography (EtOAc/hexanes 2:98) to yield 0.70 g (91%) of **22** as a pale yellow crystalline solid. Mp: 133−134 °C. ^{1}H NMR: δ 7.70−7.78 (m, 4H), 7.90 (d, 1H, J = 8.5 Hz), 7.94 (d, 1H, J = 8.5 Hz), 8.03−8.06 (m, 1H), 8.32 (s, 1H), 9.05−9.08 (m, 2H), 9.44 (dd, 1H, J = 8.2 and J = 2.0 Hz), 10.47 (s, 1H). HRMS: *m/z* calcd for $C_{19}H_{12}O$ 256.0883, found 256.0886.

5-Formyl-10-methoxybenzo[*c*]phenanthrene (23). Yield: 89%. Mp: 109−110 °C. ^{1}H NMR: δ 4.02 (s, 3H), 7.34 (dd, 1H, J = 9.2 and J = 2.6 Hz), 7.37 (d, 1H, J = 2.6 Hz), 7.70−7.78 (m, 2H), 7.87 (s, 2H), 8.28 (s, 1H), 8.93−8.99 (m, 2H), 9.43 (dd, 1H, J = 7.9 and J = 2.0 Hz), 10.43 (s, 1H). HRMS: *m/z* calcd for $C_{20}H_{14}O_2$ 286.0988, found 286.0992.

5-(β-Phenylethenyl)benzo[*c*]phenanthrene (24). To a mixture of **22** (0.154 g, 0.6 mmol) and (phenylmethyl)triphenylphosphomium chloride (0.47 g, 1.2 mmol) was added a solution of NaOH (0.06 g, 1.44 mmol) in water (0.5 mL). The resulting mixture was stirred for 15 min, diluted with CH_2Cl_2, washed with 10% HCl and water, and dried ($MgSO_4$). Concentration in vacuo provided a residue that was purified on a silica gel column chromatography (EtOAc/hexanes 1:99) to yield 0.179 g (90%) of **24** as a viscous mass which solidifies as white solid containing a mixture (1:1) of *cis* and *trans* isomers. ^{1}H NMR: δ 6.94 (d, 0.5 H, J = 12.1 Hz), 7.50−7.36 (m, 4H), 7.42−7.47 (m, 1H), 7.61−7.75 (m, 6H), 7.83−8.04 (m, 3H), 8.07 (s, 0.5H), 8.31 (dd, 0.5H, J = 8.2 and 1.3 Hz), 8.42 (dd, 0.5H, J = 7.2 and 2.3 Hz), 9.09 (d, 0.5H, J = 8.5 Hz), 9.13−9.19 (m, 1.5H). HRMS: *m/z* calcd for $C_{26}H_{18}$ 330.1408, found 330.1416.

5-(β-Phenylethenyl)-10-methoxybenzo[*c*]phenanthrene (25). Yield: 95%. ^{1}H NMR: δ 4.01 (s, 1.5H, OCH_3), 4.02 (s, 1.5 H), 6.92 (d, 0.5 H, J = 12.1 Hz), 7.06−7.19 (m, 3H), 7.25−7.37 (m, 3.5H), 7.42−7.46 (m, 1H), 7.60−7.73 (m, 4H), 7.77 (d, 0.5H, J = 8.5 Hz), 7.83 (s, 1H), 7.94 (d, 0.5H, J = 16.1 Hz), 8.28 (dd, 0.5H, J = 8.2 and 1.3 Hz), 8.37−8.40 (m, 0.5H), 8.99 (d, 0.5H, J = 9.2 Hz), 9.02−9.11 (m, 1.5H). HRMS: *m/z* calcd for $C_{27}H_{20}O$ 360.1509, found 360.1514.

5-[β-(2-Methoxyphenyl)ethenyl]benzo[*c*]phenanthrene (26). Yield: 87%. ^{1}H NMR δ 3.83 (s, 1.5H, OCH_3), 3.95 (s, 1.5 H, OCH_3), 6.46 (ddd, 0.5H, J = 7.6, 7.6 and 1.0 Hz), 6.85 (d, 0.5H, J = 8.2 Hz), 6.93 (dd, 0.5H, J = 7.5 and 1.6 Hz), 6.98 (d, 0.5H, J = 8.2 Hz), 7.04−7.11 (m, 1H), 7.17−7.18 (m, 1H), 7.30−7.35 (m, 0.5H), 7.59−8.03 (m, 9H), 8.09 (s, 0.5H), 8.32 (dd, 0.5H, J = 8.2 and 1.6 Hz), 8.43 (dd, 0.5H, J = 7.5 and 2.3 Hz), 9.09 (d, 0.5H, J = 8.5 Hz), 9.12−9.16 (m, 1.5H). HRMS: *m/z* calcd for $C_{27}H_{20}O$ 360.1509, found 360.1513.

Dibenzo[*c,p*]chrysene (1). A stirred solution of **24** (0.15 g, 0.46 mmol) and I_2 (cat.) in dry benzene was irradiated with a Hanovia 450W medium-pressure lamp, with a Pyrex filter, for 3 h, while the dry air was bubbled through the solution. Removal of solvent gave a residue that was purified by chromatography on silica gel (EtOAc/hexanes 1:99) to give pure **1** (0.13 g, 86%) as a pale yellow crystalline solid. Mp: 152−153 °C.

11-Methoxy-DB[*c,p*]C (27). Yield: 95%. Mp: 125−127 °C. ^{1}H NMR: δ 4.10 (s, 3H), 7.00 (d, 1H, J = 7.8 Hz), 7.54 (dd, 1H, J = 8.5 and 7.8 Hz), 7.61−7.76 (m, 4H), 7.92 (d, 1H, J = 8.9 Hz), 8.05 (dd, 1H, J = 7.2 and 2.3 Hz), 8.48 (d, 1H, J = 8.5 Hz), 8.54 (d, 1H, J = 9.2 Hz), 8.68 (d, 1H, J = 9.2 Hz), 8.80 (dd, 1H, J = 7.6 and 1.6 Hz), 8.83 (d, 1H, J = 8.9 Hz), 9.05 (d, 2H, J = 7.9 Hz). HRMS: *m/z* calcd for $C_{27}H_{18}O$ 358.1352, found 358.1361.

2-Hydroxy-DB[*c,p*]C (28). To a stirred solution of 2-methoxy-DB[*c,p*]C (**12**) (0.63 g, 1.75 mmol) in CH_2Cl_2 (35 mL) at room temperature was added dropwise a solution of BBr_3 (1 M solution in CH_2Cl_2, 3.5 mL, 3.5 mmol) under N_2 over 10 min. After continuous stirring for 10 h at room temperature, the reaction was quenched with ice-cold H_2O. The organic layer was washed several times with water and dried over $MgSO_4$. Removal of the solvent gave the crude solid that was purified by silica gel column chromatography (EtOAc/hexanes 8:92) to yield **28** (0.45 g, 75%) as a off-white solid. Mp: 215−216 °C. ^{1}H NMR: δ 7.25 (dd, 1H, J = 9.2 and 2.9 Hz), 7.38 (d, 1H, J = 2.9 Hz), 7.58−7.76 (m, 4H), 7.81 (d, 1H, J = 9.2 Hz), 8.01−8.05 (m, 2H), 8.67 (d, 1H, J = 9.2 Hz), 8.77 (dd, 1H, J = 8.2 and 1.3 Hz), 8.80 (d, 1H, J = 8.9 Hz), 8.89 (dd, 1H, J = 9.2 and 1.9 Hz), 8.95 (d, 1H, H4, J = 9.2 Hz), 8.96 (dd, 1H, J = 8.2 and 1.3 Hz). HRMS: *m/z* calcd for $C_{26}H_{16}O$ 344.1196, found 344.1198.

11-Hydroxy-DB[*c,p*]C (30). Yield: 80%. Mp: 166−167 °C. ^{1}H NMR: δ 6.97 (d, 1H, J = 7.6 Hz), 7.46 (dd, 1H, J = 8.5 and 7.9 Hz), 7.62−7.76 (m, 4H), 7.92 (d, 1H, J = 8.9 Hz), 8.05 (dd, 1H, J = 7.2 and 2.0 Hz), 8.46 (d, 1H, J = 9.2 Hz), 8.49 (d, 1H, J = 8.5 Hz), 8.69 (d, 1H, J = 9.2 Hz), 8.79 (d, 1H, J = 7.6), 8.82 (d, 1H, J = 8.9 Hz), 9.04 (d, 2H, J = 7.9 Hz). HRMS: *m/z* calcd for $C_{26}H_{16}O$ 344.1196, found 344.1199.

DB[*c,p*]C-1,2-dione (29). To a stirred suspension of the hydroxy derivative **28** (0.34 g, 1.0 mmol) in a mixture of CH_2Cl_2/C_6H_6/THF (25:75:3) (103 mL) and Adogen 464 (3 drops) were added an aqueous solution of KH_2PO_4 (0.17 M, 75 mL) and Fremy's salt (0.80 g, 3.0 mmol). The reaction mixture was stirred at room temperature for 1.5 h and then diluted with CH_2Cl_2. The organic layer was separated, washed with water, dried ($MgSO_4$), and filtered. The crude residue obtained after removal of the solvent was washed several times with a mixture of acetone/hexane (1:9) to give **29** (0.30 g, 84%) as a dark red solid. Mp: 222−224 °C. ^{1}H NMR: δ 6.50 (d, 1H, J = 10.5 Hz), 7.61−7.69 (m, 3H), 7.79 (dd, 1H, J = 8.2 and 7.2 Hz), 8.02 (dd, 1H, J = 7.2 and 1.6 Hz), 8.07 (d, 1H, J = 8.9 Hz), 8.12 (d, 1H, J = 7.8 Hz), 8.28 (d, 1H, J = 8.5 Hz), 8.34 (d, 1H, J = 10.5 Hz), 8.49 (d, 1H, J = 8.9 Hz), 8.57 (d, 1H, J = 8.2 Hz), 8.68 (d, 1H, J = 7.9 Hz), 8.85 (d, 1H, J = 8.5 Hz). HRMS: *m/z* calcd for $C_{26}H_{14}O_2$ 358.0988, found 358.1003.

DB[*c,p*]C-11,12-dione (31). Yield: 82%. Mp: 234−236 °C. ^{1}H NMR: δ 6.48 (d, 1H, J =10.5 Hz), 7.66−7.75 (m, 4H), 7.93 (d, 1H, J = 8.9 Hz), 7.98 (d, 1H, J = 8.9 Hz), 8.05 (d, 1H, J = 9.5 Hz), 8.23 (d, 1H, J = 10.5 Hz), 8.33 (d, 1H, J = 8.5 Hz), 8.63 (d, 1H, J = 9.5 Hz), 8.67 (d, 1H, J = 8.5 Hz), 8.88 (unresolved d, 1H, J = 9.5 Hz), 8.95 (unresolved d, 1H, J = 9.2 Hz). HRMS: *m/z* calcd for $C_{26}H_{14}O_2$ 358.0988, found 358.1006.

***trans*-1,2-Dihydroxy-1,2-dihydro-DB[*c,p*]C (2).** To a suspension of dione **29** (0.11 g, 0.3 mmol) in ethanol (400 mL) was added $NaBH_4$ (0.34 g, 9.0 mmol) in several portions over 10 min. The mixture was stirred for 24 h at room temperature while a stream of oxygen was bubbled through the solution. The solution was then concentrated under reduced pressure to one-fourth of its original volume. This concentrate was

diluted with ice-cold water and extracted with EtOAc (3 × 40 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated, and the resulting residue was washed with a mixture of ether/hexanes (1:9) to give dihydrodiol **2** (0.081 g, 74%). Silica gel column chromatography (EtOAc/CH_2Cl_2/Et_3N 30:70:0.5) gave pure dihydrodiol **2**. Mp: 197−199 °C. ^{1}H NMR (DMSO-d_6): δ 4.52−4.60 (m, 2H, H1, H2), 5.40 (d, 1H, OH, $J_{OH,2}$ = 4.2 Hz), 5.75 (d, 1H, OH, $J_{OH,1}$ = 4.6 Hz), 6.23 (d, 1H, H3, $J_{3,4}$ = 10.2 Hz), 7.11 (d, 1H, H4, $J_{4,3}$ =10.2 Hz), 7.65−7.77 (m, 4H), 7.93 (d, 1H, J = 8.2 Hz), 8.01−8.14 (m, 2H), 8.38 (d, 1H, J = 8.2 Hz), 8.71−8.77 (m, 3H), 8.82 (d, 1H, J = 8.2 Hz). HRMS: *m/z* calcd for $C_{26}H_{18}O_2$ 362.1301, found 362.1293.

***trans*-11,12-Dihydroxy-11,12-dihydro-DB[*c,p*]C (3).** Yield: 90%. Mp: 200−202 °C. ^{1}H NMR (DMSO-d_6): δ 4.50−4.60 (m, 2H), 5.36 (d, 1H, J = 4.6 Hz), 5.70 (d, 1H, J = 5.3 Hz), 6.20 (dd, 1H, J = 10.2 and 1.6 Hz), 7.00 (d, 1H, J =10.2 Hz), 7.64−7.73 (m, 4H), 7.94 (d, 1H, J = 8.2 Hz), 7.99 (d, 1H, J = 8.9 Hz), 8.10 (d, 1H, J = 7.9 Hz), 8.30 (d, 1H, J = 8.9 Hz), 8.75 (d, 1H, J = 8.5 Hz), 8.81 (br d, 2H, J = 7.9 Hz), 8.89 (d, 1H, J = 7.9 Hz). HRMS: *m/z* calcd for $C_{26}H_{18}O_2$, 362.1301, found 362.1291.

***anti-trans*-1,2-Dihydroxy-3,4-epoxy-1,2,3,4-tetrahydro-DB[*c,p*]C (4).** A solution of dihydrodiol **2** (54 mg, 0.15 mmol) and *m*-CPBA (0.26 g, 1.5 mmol) in freshly distilled THF (30 mL) was stirred at room temperature under N_2 and monitored by normal-phase HPLC using analytical Licrosorb Si60 column (5 μm) (E. Merck, Darmstadt, Germany) with hexane/THF (75:25) in isocratic program at a flow rate of 1.0 mL/min. After 2 h of stirring, the mixture was diluted with 150 mL of ether, washed with cold 2% NaOH (2 × 100 mL) and water (3 × 150 mL), and then dried (K_2CO_3), filtered, and concentrated at room temperature. The concentrate was washed with a mixture of hexane/ether (3:1, 50 mL) and dried in vacuo to yield diol epoxide **4** (0.041 g, 72%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6): δ 3.77 (dd, 1H, H3, J = 4.3 and 1.5 Hz), 3.95 (dd, 1H, H2, J = 8.5 and 1.5 Hz), 4.68 (d, 1H, H4, J = 4.3 Hz), 4.95 (d, 1H, H1, J = 8.5 Hz), 7.62−7.69 (m, 4H), 7.75−7.79 (m, 1H), 8.06−8.09 (m, 2H), 8.61 (d, 1H, J = 7.9 Hz), 8.66 (d, 1H, J = 8.9 Hz), 8.71 (d, 1H, J = 7.9 Hz), 8.85 (d, 1H, J = 8.9 Hz), 8.87 (d, 1H, J = 9.8 Hz). HRMS: *m/z* calcd for $C_{26}H_{18}O_3$ 378.1250, found 378.1232.

***anti-trans*-11,12-Dihydroxy-13,14-epoxy-11,12,13,14-tetrahydro-DB[*c,p*]C (5).** Yield: 77%. ^{1}H NMR (DMSO-d_6): δ 3.79 (dd, 1H, H13, J = 4.3 and 1.3 Hz), 3.93 (dd, 1H, J = 8.9 and 1.3 Hz), 4.69 (d, 1H, J = 4.3 Hz), 4.94 (d, 1H, J = 8.9 Hz), 7.65−7.78 (m, 4H), 8.07 (d, 1H, J = 8.9 Hz), 8.11 (d, 1H, J = 8.5 Hz), 8.15 (d, 1H, J = 7.9 Hz), 8.58 (d, 1H, J = 8.9 Hz), 8.81−8.87 (m, 2H), 8.93 (d with fine splitting, 1H, J = 7.9 Hz), 9.01 (d, 1H, J = 8.2 Hz). HRMS: *m/z* calcd for $C_{26}H_{18}O_3$ 378.1250, found 378.1239.

In Vitro Metabolism of DB[*c,p*]C with Phenobarbital/β-Naphthoflavone-Induced Male Sprague−Dawley Rat *S9* Liver Homogenate. DB[*c,p*]C (2 mg in 200 μL DMSO) was incubated at 37 °C for 20 min, in the presence of cofactors and 8 mL of the 9000 g supernatant from livers of phenobarbital/β-naphthoflavone-induced male Sprague−Dawley rats.[31] The mixture was extracted with EtOAc (3 × 30 mL), dried ($MgSO_4$), filtered, and concentrated at reduced pressure to give a residue that was dissolved in methanol. The metabolites of DB[*c,p*]C were analyzed by HPLC on a 4.6 × 250 mm (5 μm) Vydac C18 reversed-phase column (Separation Group, Hesperia, CA) with solvent A, H_2O, or solvent B, methanol, using a gradient program from A/B (50:50) to A/B (0:100) over 40 min.

Preparation of DNA Adducts. *anti*-DB[*c,p*]CDE (**4/5**) (1 mg) in 1.0 mL of THF was added to a solution of calf thymus DNA (10 mg) in 10 mL of 10 mM Tris-HCl buffer, pH 7. This mixture was incubated at 37 °C. The DNA was isolated and enzymatically hydrolyzed to deoxyribonucleosides as described in the literature.[30] Modified deoxyribonucleosides were analyzed by HPLC.

Preparation of the Standard 2′-dGuo or 2′-dAdo Adducts from Diol Epoxide. Approximately 100 mg each of 2′-dGuo-5′-monophosphate or 2′-dAdo-5′-monophosphate were dissolved in 10 mL of 10 mM Tris-HCl buffer (pH 7.0). Then *anti*-DB[*c,p*]CDE (**4/5**) (1 mg) in 1.0 mL of acetone/THF (50/50) was added, and the solution was incubated overnight at 37 °C. The modified deoxyribonucleotides were separated from unmodified deoxyribonucleotides on Sep-Pak C_{18} cartridges. They were then enzymatically hydrolyzed to the corresponding deoxyribonucleosides,[32] and analyzed by HPLC with a Beckman Ultrasphere ODS 5-μm column (4.6 × 250 mm; reversed-phase) using the following solvent system: 46% MeOH in H_2O for 10 min, followed by a linear gradient from 46 to 60% MeOH in H_2O over 20 min, then 90% MeOH in H_2O for 30 min at a flow rate of 1 mL/min.

Acknowledgment. This study was supported by NCI Contract No. NO2-CB-37025-48 and Cancer Center Support Grant No. CA-17613. Further support has been provided by the Penn State Cancer Institute of the Penn State College of Medicine.

Supporting Information Available: Experimental procedures for compounds **3**, **5**, **9**, **11**, **12**, **19**, **21**, **23**, **25**−**27**, **30**, and **31** and copies of the ^{1}H NMR spectra for compounds **1**−**3**, **5**, **8**−**12**, and **18**−**31**. Also includes the HPLC traces for incubation of diol epoxides **4** and **5** with dA, dG, and DNA. This material is available free of charge via the Internet at http://pubs.acs.org.

JO040291K

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