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DIBENZ[*a,c*]ANTHRACENE: ELECTROPHILIC SUBSTITUTION AND SYNTHESIS OF PHENOL ISOMERS

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Abstract: Efficient syntheses of the 3-, 9-, 10-, and 11-phenol isomers of dibenz-[*a,c*]anthracene (DB*a,c*A) and 2,3-dihydroxy-DB*a,c*A are described. Bromination of DB*a,c*A with bromine in CH_2Cl_2 gave 10-bromo-DB*a,c*A and not 9-bromo-DB*a,c*A predicted theoretically. On the other hand, bromination of DB*a,c*A with NBS and $FeCl_3$ furnished 9-bromo-DB*a,c*A. © 1997 Elsevier Science Ltd.

Dibenz[*a,c*]anthracene (DB*a,c*A) is a common atmospheric pollutant and a component of cigarette smoke.[1] It exhibits low activity as a carcinogen on mouse skin, but it shows significant tumor-initiating activity on promotion by a phorbol ester.[2] In connection with studies on activation of DBa,cA by the P-450 microsomal enzymes of mammalian cells, we required several phenol isomers as authentic standards.

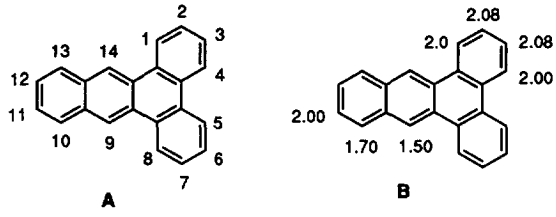

Figure 1. (A) Ring numbering and (B) calculated localization energies in units of ß for dibenz[*a,c*]anthracene (DB*a,c*A).

Electrophilic substitution of DB*a,c*A is predicted by molecular orbital theoretical calculations to take place preferentially in the *meso* region 9,14-positions (Fig. 1A).[3,4] However, this site is in a sterically crowded bay region which may be expected to redirect substitution elsewhere in the molecule. In the prototype hydrocarbon triphenylene, the steric effect is dominant, and substitution occurs predominantly in the less crowded 2-position.[1,5] Nitration of DB*a,c*A is reported to yield 9-nitro-and 10-nitro-DBa,cA as the major and minor products, respectively, based on analysis of the

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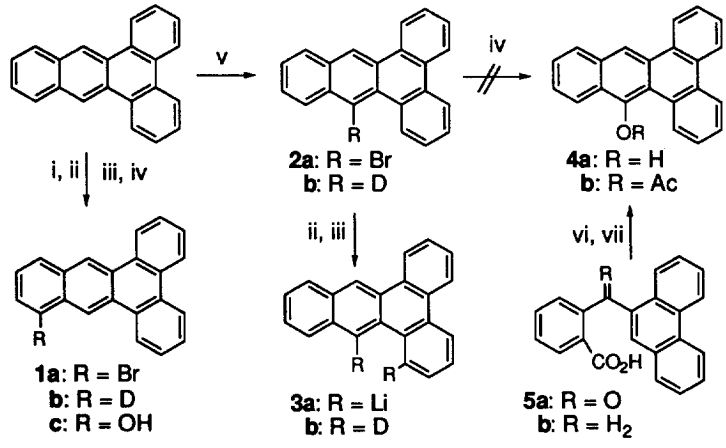
high resolution ^{1}H-NMR spectra.[6] This finding is consistent with theoretical prediction based on the relative localization energies at these sites (Fig. 1B).[3] Apparently, the enhanced reactivity of the meso region overrides the steric factor. This suggests that 9-hydroxy-DB*a,c*A may be synthetically accessible directly from DB*a,c*A by bromination followed by conversion to the Grignard reagent, reaction with trialkyl borate, and oxidation with alkaline peroxide. We now report efficient syntheses of the 9-phenol of DB*a,c*A as well as 3-, 10-, and 11-hydroxy-DB*a,c*A and 2,3-dihydroxyDB*a,c*A.

RESULTS AND DISCUSSION

Bromination of DB*a,c*A with Br_2 in CH_2Cl_2 in the presence of a small amount of $FeCl_3$ gave as the major product a monobromo isomer identified on the basis of its ^{1}H-NMR spectrum and other evidence to be not the predicted 9-bromo-DB*a,c*A isomer, but rather 10-bromo-DB*a,c*A (**1a**) (Scheme 1). The 300 MHz ^{1}H-NMR spectrum showed the presence of singlets at δ 9.40 and 8.96 ppm assigned to the H_9 and H_{14} protons, respectively. The greater downfield shift of the former is due to its location adjacent to the bromine atom. The absence of additional appropriate peaks at relatively low field for bay region protons with an adjacent substituent[7] rules out the ß-substituted monobromo-DB*a,c*A isomers, i.e. 2-, 3-, 6-, 7-, and 11-bromo-DB*a,c*A. Confirmation of the assignment as the 10-bromo-DB*a,c*A isomer was provided by lithium exchange with *n*-BuLi followed by quenching with deuterium oxide to furnish 10-deuterio-DB*a,c*A (**1b**).[8] Its ^{1}H-NMR spectrum matched that of the parent unsubstituted-DB*a,c*A except for a decrease equivalent to one proton in the multiplet signals at δ 8.05 ppm assigned to the $H_{10,13}$ protons.

Scheme 1



i. Br_2; ii. *n*-BuLi; iii. D_2O; iv. $Mg/B(OMe)_3/H_2O_2/NaOH$; v. $NBS/FeCl_3$; vi. Zn/KOH; vii. $ZnCl_2/Ac_2O/AcOH$.

Additional confirmation of the assignment of the 10-bromo-DB*a,c*A was provided by its conversion to 10-hydroxy-DB*a,c*A (**1c**) by reaction with magnesium to afford the bromomagnesium salt

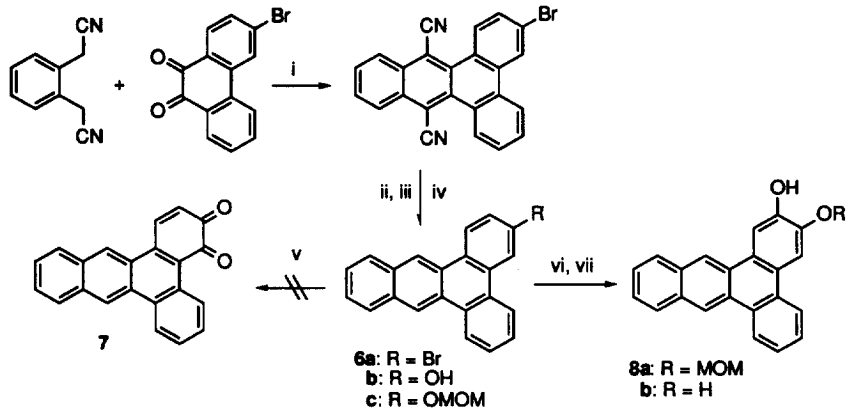
which was reacted with trimethylborate followed by oxidation of the product with alkaline peroxide. The ^{1}H-NMR spectrum and melting point of **1c** were in good agreement with those of authentic **1c** synthesized via a four step route from Friedel-Crafts reaction of succinic anhydride with triphenylene.[9] The overall yield of 10-hydroxy-DB*a*,*c*A was 70% via bromination of DB*a*,*c*A versus 40% via the total synthetic route.

Synthesis of 9-bromo-DB*a*,*c*A (**2a**) was accomplished by bromination of DB*a*,*c*A with NBS and $FeCl_3$. The ^{1}H-NMR spectrum of the major bromination product exhibited a singlet at δ 8.84 ppm corresponding to the H_{14} proton and no additional singlets. The H_8 and H_{10} protons exhibited a marked downfield shift to δ 9.40 and 8.96 ppm, respectively, consistent with their location adjacent to the bromine atom. Reaction of **2a** with one equivalent of *n*-BuLi followed by quenching with D_2O afforded a mixture of deuterated compounds and unreacted **2a**. Similar reaction of **2a** with excess *n*-BuLi (2.5 equivalents) gave dideuterio-DB*a*,*c*A as essentially the sole product. Its ^{1}H-NMR spectrum closely matched that of the parent hydrocarbon except for decreases equivalent to one proton each in the singlet peak at δ 9.05 ppm and the multiplet at δ 8.96 ppm, corresponding to the H_9 and H_8 protons, respectively, indicating it to be 8,9-dideuterio-DB*a*,*c*A (**3b**). The unexpected formation of a dideuterated DB*a*,*c*A derivative is apparently a consequence of the relative acidity of the bay region 8,9-protons of DB*a*,*c*A, resulting in reaction of the 9-lithio intermediate with *n*-BuLi to form 8,9-dilithio-DB*a*,*c*A (**3a**). This is consistent with the previous observation that bay region protons of polyarenes, such as triphenylene, are sufficiently acidic to undergo abstraction with *n*-BuLi to form dilithiated intermediates that may be trapped by reaction with nucleophiles, such as D_2O or I_2.[10] Conversion of 9-bromo-DB*a*,*c*A to 9-deuterio-DB*a*,*c*A (**2b**) was effected by its reaction with magnesium to form the Grignard compound followed by quenching with D_2O. The ^{1}H-NMR spectrum of **2b** closely matched that of DB*a*,*c*A except for a 50% decrease in the singlet at δ 9.05 ppm assigned to the meso region 9,14-protons.

Attempted synthesis of 9-hydroxy-DB*a*,*c*A (**4a**) via reaction of 9-bromomagnesio-DB*a*,*c*A with trimethylborate and oxidation of the product with alkaline peroxide failed to provide the desired phenol, giving instead only DB*a*,*c*A. The failure of the Grignard compound to react with $B(OMe)_3$ is a likely consequence of the steric crowding in the bay region. Synthesis of **4a** was accomplished from 2-(9-phenanthroyl)benzoic acid (**5a**). Prior attempts to convert **5a** to 2-(9-phenanthrylmethyl)-benzoic acid (**5b**) by Clemmensen or Wolff-Kishner reduction were not successful.[11] However, **5a** was smoothly reduced to **5b** with zinc and alkali. Treatment of **5b** with $ZnCl_2$ and Ac_2O in AcOH furnished the cyclized 9-acetoxy-DB*a*,*c*A (**4b**). Alkaline hydrolysis of **4b** gave **4a** whose ^{1}H-NMR spectrum was consistent with this assignment with no indication of the the keto tautomer.

3-Bromo-DB*a*,*c*A (**6a**), the key intermediate in the synthesis of 3-hydroxy-DB*a*,*c*A (**6b**), was synthesized via the reaction sequence in Scheme 2. Condensation of 1,2-phenylenediacetonitrile with 3-bromophenanthrene-9,10-dione[12] in piperidine furnished 3-bromo-9,14-dicyanodibenz[*a*,*c*]-anthracene. Hydrolysis with KOH and decarboxylation of the product by heating in phosphoric acid provided **6a**. Its ^{1}H-NMR spectrum was in good agreement with this assignment. Conversion of **6a** to **6b** was effected by treatment of its bromomagnesium salt with $B(OMe)_3$ and oxidation with alkaline peroxide. The ^{1}H-NMR spectrum of **6b** matched that reported for 3-hydroxy-DB*a*,*c*A.[9a]

Scheme 2



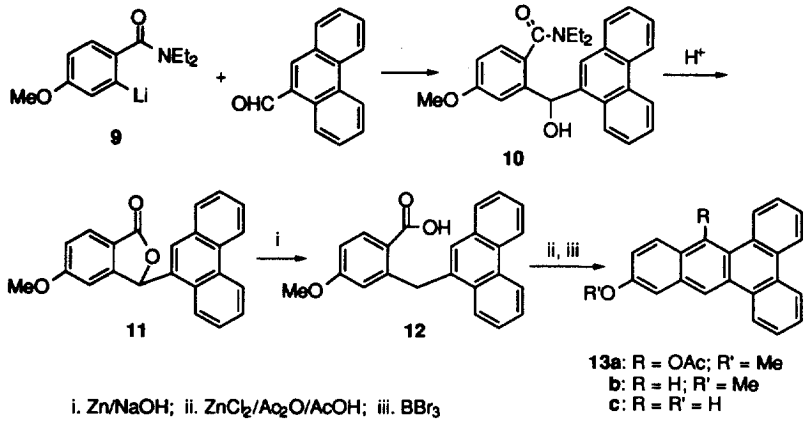
i. piperidine; ii. KOH; iii. H_3PO_4/160°C; iv. Mg/B(OMe)$_3$/H_2O_2/NaOH; v. Fremy's reagent; vi. NaH/$MeOCH_2Cl$; vii. *n*-BuLi/TMEDA; viii. O_2

3-Hydroxy-DB*a,c*A is a potential synthetic precursor of the proximate carcinogenic metabolite of DB*a,c*A, *trans*-3,4-dihydroxy-DB*a,c*A.[9a] Attempted conversion of **6b** to the 3,4-dihydrodiol via oxidation with Fremy's salt [$(SO_3K)_2NO$] to the 3,4-quinone (**7**) by the usual procedure[1,13] failed to yield the desired **7**, affording only recovered **6b**. This resistance to oxidation by Fremy's reagent is most likely due to the steric crowding in the bay region.

Another possible route to the 3,4-dihydrodiol is through the corresponding catechol, 3,4-dihydroxy-DB*a,c*A, which may be potentially obtained by metalation of the methoxymethyl ether of 3-hydroxy-DB*a,c*A followed by oxidation. Treatment of **6b** with NaH and chloromethylmethyl ether gave the 3-methoxymethyl ether derivative (**6c**). This underwent lithiation with *n*-BuLi in THF in the presence of TMEDA to furnish a deep blue solution of the ortho-lithiated anion of **6c**. Bubbling oxygen through the solution, resulted in rapid decolorization with formation of a phenol derivative. However, analysis of the ^{1}H-NMR spectrum indicated that the product was not the 4-phenol, but the 2-phenol derivative (**8a**). This assignment was supported by the presence of four singlet peaks at δ 9.06, 8.92, 8.29, and 8.25 ppm, corresponding to the bay region H_9, H_{14}, H_1, and H_4 protons, respectively. Hydrolysis of **8a** furnished 2,3-dihydroxy-DB*a,c*A (**8b**). Formation of the 2- rather than 4-phenol of 3-methoxymethoxy-DB*a,c*A is surprising in the sense that metalation of ß-substituted phenols usually occurs in the more reactive α-positions, but it provides additional evidence for the important role of the bay region steric effect on reactions that might otherwise be expected to take place in this molecular region.

Synthesis of 11-hydroxy-DB*a,c*A (**13b**) was accomplished via a total synthetic route based on reaction of phenanthrene-9-carboxaldehyde with the ortho-lithiated derivative of *N,N*-diethyl 4-methoxybenzamide (**9**) generated *in situ* by reaction of the benzamide with *sec*-BuLi and TMEDA at -78 °C (Scheme 3).[14] The product of this reaction was not the lactone (**11**) usually obtained from reactions of this type,[14a] but the adduct (**10**). However, on treatment of **10** with *p*-toluenesulfonic acid in refluxing benzene[15] it underwent conversion to **11**. Reductive cleavage of **11** with zinc and

Scheme 3



alkali furnished 4-methoxy-2(9-phenanthrylmethyl)benzoic acid (**12**) which cyclized on treatment with $ZnCl_2$ in Ac_2O/AcOH to yield 9-acetoxy-12-methoxy-DB*a,c*A (**13a**). Reductive deacetoxylation of **13a** with zinc and alkali took place with partial reduction of the meso ring to furnish a mixture of 11-methoxy-DB*a,c*A (**13b**) and 9,14-dihydro-**13b** (not shown). Dehydrogenation of the mixture with *o*-chloranil provided pure **13b**. Demethylation of **13b** with BBr_3 gave 11-hydroxy-DB*a,c*A (**13c**).

Convenient synthetic access to the 3-, 9-, 10-, and 11-phenol isomers of DB*a,c*A and 2,3-dihydroxy-DB*a,c*A, is provided by methods described. Synthesis of 9-hydroxy-DB*a,c*A completes the synthesis of the full set of possible phenol isomers of dibenz[*a,c*]anthracene.[9a] The new syntheses of 3- and 10-hydroxyDB*a,c*A described provide attractive alternatives to older methods in that they entail relatively few steps from readily available starting compounds.

The marked difference in the sites of bromination of DB*a,c*A by Br_2 and NBS in the presence of $FeCl_3$, the former taking place in the 10-position while the latter occurs in the 9-position, merits comment. Since the theoretically predicted site of attack is the 9-position irrespective of the attacking species, bromonium ion or bromine radical, this difference cannot explain the difference in regioselectivity. It is likely that the ionic mechanism entails initial relatively rapid formation of a 9-bromoarenium ion that equilibrates with the more stable 10-bromoarenium ion intermediate which loses a proton to afford the product. The 9-bromoarenium ion is destabilized by the steric crowding in the bay region. The intermediate initially formed from reaction of NBS with DB*a,c*]A apparently goes on to product faster than it isomerizes. The mechanistic basis for this observation is not clear.

EXPERIMENTAL

Materials and Methods. Dibenz[*a,c*]anthracene[11] and 3-bromophenanthrene 9,10-dione[12] were synthesized by the methods described previously. NBS was purified by recrystallization from water. THF was freshly distilled from $LiAlH_4$, and TMEDA was distilled over KOH. The ^{1}H-NMR spectra were obtained at 300 MHz in $CDCl_3$. As a standard for comparison, the ^{1}H-NMR spectra of DB*a,c*A had δ 9.05 (s, 2, $H_{9,14}$), 8.74 (m, 2, $H_{1,8}$), 8.57 (m, 2, $H_{4,5}$), 8.05 (m, 2, $H_{10,13}$), 7.36-7.65 (m, 6, Ar).

10-Bromodibenz[*a,c*]anthracene (1a). To a stirred solution of DB*a,c*A (5.56 g, 20 mmol) and $FeCl_3$ (75 mg) in 150 mL of CH_2Cl_2 and 250 mL of CCl_4 a solution of Br_2 (3.52 g, 22 mmol) in 225 ml of CCl_4 was added dropwise over 75 min. Stirring was continued for 1 h. The solution was washed twice with water, dried, and evaporated to dryness. The residue (7.02 g) was dissolved in benzene, filtered through a short column of Florisil, and concentrated to a small volume. Crystallization gave **1a** (3.86 g, 54%), mp 224-228 °C. Recrystallization from benzene raised the mp to 231-232.5 °C: NMR δ 9.40 (s, 1, H_9), 8.96 (s, 1, H_{14}), 8.79 (dd, 1, H_8; $J_{7,8}$ = 9.3 Hz, $J_{6,8}$ = 2.3 Hz), 8.67 (dd, 1, H_1; $J_{1,2}$ = 9.5 Hz, $J_{1,3}$ = 3.3 Hz), 8.55 (dd, 2, $H_{4,5}$; $J_{3,4} = J_{5,6}$ = 9.1 Hz, $J_{2,4} = J_{5,7}$ = 2.3 Hz), 7.98 (d, 1, H_{13}; $J_{12,13}$ = 8.3 Hz), 7.83 (d, 1, H_{11}; $J_{11,12}$ = 7.4 Hz), 7.60-7.81 (m, 4, Ar), 7.35 (t, 1, H_{12}; J = 7.5 Hz). Anal. Calcd for $C_{22}H_{13}Br$: C, 73.94; H, 3.64, Br, 22.40. Found: C, 73.90; H, 3.71, Br, 22.37.

10-Deuteriodibenz[*a,c*]anthracene (1b). To a stirred suspension of **1a** (357 mg, 1 mmol) in 10 mL of dry THF 1 mL of a 2.5M solution of *n*-BuLi in hexane was added under N_2. The dark-colored solution was stirred for 30 min, then the reaction was quenched with 0.5 mL of D_2O. Addition of 50 mL of water precipitated the product which was dissolved in CH_2Cl_2 and dried. Evaporation of the solvent and recrystallization of the residue from benzene gave pure **1b** (279 mg) whose ^{1}H-NMR spectrum matched that of DB*a,c*A except for a decrease in the signal at δ 8.05 equivalent to the loss of one proton (100% D purity).

10-Hydroxydibenz[*a,c*]anthracene (1c). To a mixture of **1a** (1.0 g, 2.8 mmol) in 20 mL of dry THF magnesium turnings (100 mg, 4.1 mmol) and 1 drop of 1,2-dibromoethane were added, and the mixture was heated at reflux for 3 h under Ar. After cooling, the solution was added to a rapidly stirred solution of $B(OMe)_3$ (580 mg, 5.5 mmol) in 2 mL of dry THF at -78 °C over 20 min under Ar. The cold bath was removed and the solution was stirred for 1 h then partitioned between 10% HCl (10 mL) and EtOAc (30 mL). The organic layer was washed with water, dried, and evaporated to dryness. The residue was triturated with 20 mL of warm benzene, then the solid phase was filtered off, dissolved in THF (30 mL) and water (5 mL), and 5 mL of 10% NaOH was added. The stirred solution was cooled in an ice bath, then 5 mL of 14% H_2O_2 was added dropwise over 30 min. The solution was stirred for 1 h at ice bath temperature and for 2 h at room temperature, then 2 mL or AcOH was added, stirring was continued for 3 min, and 100 mL of water was added. The usual workup followed by chromatography of the product on silica gel eluted with CH_2Cl_2 gave **1c** (580 mg, 70%), mp 238-240 °C (lit.[9a] 239-241 °C): NMR δ 9.74 (s, 1, H_9), 9.05 (s, 1, H_{14}), 8.85 (dd, 1, H_8; $J_{7,8}$ = 9.6 Hz, $J_{6,8}$ = 2.8 Hz), 8.71 (dd, 1, H_1; $J_{1,2}$ = 9.4 Hz, $J_{1,3}$ = 3.38 Hz), 8.57-8.60 (m, 2, $H_{4,5}$), 7.62-7.71 (m, 5, Ar), 7.38 (t, 1, H_{12}; J = 7.5 Hz), 6.87 (d, 1, H_{11}; $J_{11,12}$ = 7.3 Hz), 5.50 (s, 1, OH; disappeared on addition of D_2O).

9-Bromodibenz[*a,c*]anthracene (2a). A mixture of DB*a,c*A (11.13 g, 40 mmol), NBS (8.90 g, 50 mmol), and $FeCl_3 \cdot H_2O$ (50 mg) in 250 mL of CCl_4 was heated at reflux for 6 h. After cooling, the succinimide was filtered off, and the filtrate was evaporated to dryness. The residue was dissolved in hot benzene, filtered through a short Florisil column, and again evaporated. Recrystallization of the product from acetone gave **2a** (9.95 g, 70%), mp 134-136 °C: NMR δ 9.25 (d, 1, H_8; $J_{7,8}$ = 8.3 Hz), 8.84 (s, 1, H_{14}), 8.59 (d, 1, H_1; $J_{1,2}$ = 8.6 Hz), 8.49 (dd, 1, H_{10}; $J_{10,11}$ = 9.4 Hz, $J_{10,12}$ = 3.4 Hz), 8.40-8.37 (m, 2, $H_{4,5}$), 7.95 (d, 1, H_{13}; $J_{12,13}$ = 8.1 Hz), 7.65-7.47 (m, 16, Ar). Anal. Calcd for $C_{22}H_{13}Br$: C, 73.94; H, 3.64, Br, 22.40. Found: C, 74.04; H, 3.69. Br. 22.27.

9-Deuteriodibenz[*a,c*]anthracene (2b). A solution of **2a** (500 mg, 1.4 mmol) and one drop of methyl iodide in 10 mL of THF and 50 mg of Mg turnings were heated at reflux under Ar for 1 h, then the reaction mixture was cooled in an icebath and reaction was quenched with D_2O. The usual workup and by chromatography on a silica gel column gave **2b** (341 mg, 87%) whose ^{1}H-NMR spectrum matched that of DB*a,c*A except for a decrease in the singlet peak at δ 9.05 equivalent to the loss of one proton (~90% D purity).

8,9-Dideuteriodibenz[*a,c*]anthracene (3b). To a stirred solution of **2a** (357 mg, 1 mmol) in 10 mL of dry THF was added 1 mL of *n*-BuLi (2.5M in hexane), and the solution was stirred for 30 min under Ar. Reaction was quenched with D_2O (0.5 mL) followed after 5 min with 50 mL of water. The precipitated product was filtered off, dissolved in CH_2Cl_2 dried, and evaporated to dryness. Recrystallization of the residue from benzene afforded **3b** (263 mg, 94%) whose ^{1}H-NMR spectrum closely matched that of DB*a,c*A except for the decrease in the singlet at δ 9.05 and the doublet of doublets at δ 8.74 equivalent to the loss of one proton for each (100% D purity).

2-(9-Phenanthryl)benzoic acid (5b). A mixture of 2-(9-phenanthroyl)benzoic acid[11] (**5a**) (5 g, 15 mol), NaOH (15 g), zinc (60 g activated by 2 g of $CuSO_4$), and 300 mL of water were heated at reflux overnight. The mixture was cooled to ambient temperature, the Zn was filtered off and washed with 10% NaOH solution. The solution was acidified with HCl, and the solid precipitate was filtered, washed with warm water, and dried. Recrystallization from benzene gave **5b** (3.82 g, 82%) as white crystals, mp 194-196 °C: NMR (DMSO-d_6+D_2O) δ 8.74 (d, 1, J = 8.3 Hz), 8.68 (d, 1, J = 7.9 Hz), 8.18 (dd, 1, J = 9.0 Hz, J = 2.5 Hz), 7.96 (d, 1, J = 8.0 Hz), 7.79 (d, 1, J = 7.5 Hz), 7.52-7.76 (m, 4, Ar), 7.43 (s, 1, Ar), 7.02-7.37 (m, 3, Ar), 4.96 (s, 2, CH_2). Anal. Calcd for $C_{22}H_{16}O_2$: C, 84.61; H, 5.12. Found: C, 84.44; H, 5.16.

9-Hydroxydibenz[*a,c*]anthracene (4a). A mixture of **5b** (1.5 g, 4.8 mmol), 300 mg of $ZnCl_2$, 19 mL of Ac_2O, and 40 mL of AcOH was heated at reflux and stirring for 2 h. The solution was cooled in an icebath and then poured into icewater. The precipitate was filtered, washed with H_2O, and dried. Chromatography on a silica gel column eluted with hexane-CH_2Cl_2 (2:3) gave 9-acetoxydibenz[*a,c*]anthracene (**4b**) (1.29 g, 80%) as a white solid, mp 150-152 °C: NMR δ 9.13 (dd, 1, H_8; $J_{7,8}$ = 7.8 Hz, $J_{6,8}$ = 1.3 Hz), 8.99 (s, 1, H_{14}), 8.68 (dd, 1, H_1; $J_{1,2}$ = 7.7 Hz, $J_{1,3}$ = 3.0 Hz), 8.48-8.56 (m, 2, $H_{4,5}$), 8.07 (dd, 1, H_{10}; $J_{10,11}$ = 8.5 Hz, $J_{10,12}$ = 2.4 Hz), 8.02 (dd, 1, H_{13}; $J_{12,13}$ = 8.7 Hz, $J_{11,13}$ = 2.3 Hz), 7.54-7.65 (m, 6, Ar). Anal. Calcd for $C_{24}H_{16}O_2$: C, 85.71; H, 4.76. Found: C, 85.64; H, 4.82.

To a stirred solution of **4b** (5 g, 1.5 mmol) in 50 mL of EtOH was added 2 g of KOH. The mixture was heated at reflux for 0.5 h, then cooled, acidified with cold HCl. The precipitate was filtered, washed with water, dried, and chromatographed on a silica gel column. Elution with CH_2Cl_2 and recrystallization of the product from benzene afforded **4a** (380 mg, 87%), mp 170-172 °C: NMR (DMSO-d_6) δ 10.44 (s, 1, OH, disappeared with D_2O), 9.88 (dd, 1, H_8; $J_{7,8}$ = 8,2 Hz, $J_{6,8}$ = 1.5 Hz), 8.93 (s, 1, H_{14}), 8.85 (dd, 1, H_1; $J_{1,2}$ = 7.8 Hz, $J_{1,3}$ = 2.4 Hz), 8.65-8.70 (m, 2, $H_{4,5}$), 8.52 (dd, 1, H_{10}; $J_{10,11}$ = 9.6Hz, $J_{10,12}$ = 1.6 Hz), 8.16 (dd, 1, H_{13}; $J_{12,13}$ = 9.4 Hz, $J_{11,13}$ = 2.5 Hz), 7.58-7.70 (m, 6, Ar). Anal. Calcd for $C_{22}H_{14}O$: C, 89.79; H, 4.76. Found: C, 89.55; H, 4.80.

3-Bromodibenz[*a,c*]anthracene (6a). To a stirred solution of 3-bromophenanthrene 9,10-dione (28.55 g, 100 mmol) and 1,2-phenylenediacetonitrile (17.20 g, 110 mmol) in 150 mL of piperidine was added 25 mL of water. An exothermic reaction ensued and the flask contents solidified. The mixture was allowed to stand for 18 h at room temperature, then the solid was filtered off, washed with methanol, and dried to yield 3-bromo-9,14-dicyanodibenz[*a,c*]anthracene which was used directly in the next step.

A mixture of the dinitrile (17.5 g, 43 mmol) and 165 g of KOH in 1.65 L of EtOH were heated at reflux for 165 h. The solution was poured into 5L of water and the yellow precipitate was filtered off, washed with water, and dried. A mixture of the crude 3-bromodibenz[*a,c*]anthracene 9,14-dicarboxamide (15.34 g) and crystalline H_3PO_4 at 80 °C was gradually heated to 155 °C. Evolution of CO_2 began at about 125 °C. Stirring was continued at this temperature for 30 min, then the mixture was allowed to cool. Water (400 mL) was added, and the solid was filtered off, washed with water, dried, and extracted twice with 250 mL portions of boiling benzene. The combined extracts were concentrated and adsorbed on a column of Florisil. Elution with benzene provided **6a** (7.92 g, 50% from the dinitrile), mp 196-198 °C: NMR δ 8.92 (s, 1, H_{14}), 8.86 (s, 1, H_9), 8.67 (dd, 1, H_8; $J_{7,8}$ = 9.1 Hz, $J_{6,8}$ = 2.2 Hz), 8.57 (d, 1, H_4; $J_{2,4}$ = 1.9 Hz), 8.45 (d, 1, H_1; $J_{1,2}$ = 8.8 Hz), 8.37 (dd, 1, H_5; $J_{5,6}$ = 9.1 Hz, $J_{5,7}$ = 1.9 Hz), 7.98-8.03 (m, 2, $H_{10,13}$), 7.53-7.68 (m, 5, Ar). Anal. Calcd for $C_{22}H_{13}Br$: C, 73.96; H, 3.67; Br, 22.37. Found: C, 74.11; H, 3.49; Br, 22.14.

3-Hydroxydibenz[*a,c*]anthracene (6b). The procedure used to synthesize **1c** from **1a** was employed to convert **6a** (5.0 g, 14 mmol) to **6b** (2.40 g, 58%), mp 244-246 °C (lit.[16] 247 °C, lit.[9a] 252-253 °C): NMR δ 10.03 (s, 1, OH, disappeared with D_2O), 9.33 (s, 1, H_9), 9.29 (s, 1, H_{14}), 8.94 (dd, 1, H_8; $J_{7,8}$ = 9.6 Hz, $J_{6,8}$ = 1.8 Hz), 8.79 (d, 1, H_1; $J_{1,2}$ = 9.0 Hz), 8.57 (dd, 1, H_5; $J_{5,6}$ = 9.5 Hz, $J_{5,7}$ = 1.8 Hz), 8.15-8.20 (m, 2, $H_{10,13}$), 8.03 (d, 1, H_4; $J_{2,4}$ = 2.2 Hz), 7.56-7.72 (m, 4, Ar), 7.24 (dd, 1, H_2; $J_{1,2}$ = 9.0 Hz, $J_{2,4}$ = 2.2 Hz).

3-Methoxymethoxydibenz[*a,c*]anthracene (6c). To a stirred solution of **6b** (2.15 g, 7.3 mmol) in 60 mL of dry THF cooled in an ice bath was added NaH (720 mg, 30 mmol) as a 60% oil dispersion under N_2. After 5 min, the ice bath was removed and stirring was continued for 30 min at room temperature. Then chloromethyl methyl ether (3.22 g, 40 mmol) was added and stirring was continued for 3 h. Reaction was quenched by dropwise addition of water, then ether was added and the reaction was worked up conventionally. The crude solid product was triturated twice with hexane, dissolved in benzene, and the solution filtered through a short column of Florisil. The solid was recrystallized from acetone-hexane to give **6c** (1.68 g, 68%), mp 140-142 °C: NMR δ 9.02 (s, 1, H_9), 8.92 (s, 1, H_{14}), 8.73 (dd, 1, H_8; $J_{7,8}$ = 9.4 Hz, $J_{6,8}$ = 2.6 Hz), 8.65 (d, 1, H_1; $J_{1,2}$ = 9.0 Hz), 8.48 (dd, 1, H_5; $J_{5,6}$ = 9.4 Hz, $J_{5,7}$ = 2.7 Hz), 8.17 (d, 1, H_4; $J_{2,4}$ = 2.5 Hz), 8.02-8.06 (m, 2, $H_{10,13}$), 7.52-7.65 (m, 4, Ar), 7.35 (dd, 1, H_2; $J_{1,2}$ = 9.0 Hz, $J_{2,4}$ = 2.5 Hz), 5.36 (s, 2, CH_2), 3.59 (s, 3, OCH_3). Anal. Calcd for $C_{24}H_{18}O_2$: C, 85.18; H, 5.36. Found: C, 85.31; H, 5.29.

2-Hydroxy-3-Methoxymethoxydibenz[*a,c*]anthracene (8a). To a solution of **6c** (300 mg, 0.89 mmol) and TMEDA (0.15 mL, 0.9 mmol) in 10 mL of dry THF at 0 °C was added *n*-BuLi (0.42 mL of a 2.5M solution in hexanes) under Ar. The solution turned deep blue. After stirring for 30 min at 0 °C, O_2 was bubbled through the solution for 2 h and the resulting yellow solution was poured onto ice. Ether was added and the ether layer was washed with 2N HCl. The usual workup followed by chromatography on a silica gel column afforded recovered **6c** (65 mg) and **8a** (205 mg, 65%), mp 137-139 °C: NMR δ 9.06 (s, 1, H_9), 8.92

(s, 1, H_{14}), 8.75 (dd, 1, H_8; $J_{7,8}$ = 9.5 Hz, $J_{6,8}$ = 2.1 Hz), 8.40 (dd, 1, H_5; $J_{5,6}$ = 9.5 Hz, $J_{5,7}$ = 2.0 Hz), 8.29 (s, 1, H_1), 8.25 (s, 1, H_4), 8.05-8.08 (m, 2, $H_{10,13}$), 7.54-7.63 (m, 4, Ar), 6.19 (s, 1, OH, disappeared with D_2O), 5.44 (s, 2, CH_2), 3.65 (s, 3, OCH_3). Anal. Calcd for $C_{24}H_{18}O_3$: C, 81.35; H, 5.08. Found: C, 80.98; H, 5.12.

2,3-Dihydroxydibenz[*a,c*]anthracene (8b). To a solution of **8a** (100 mg, 0.28 mmol) in 15 mL of MeOH was added 05 mL of conc. HCl. The solution was heated at reflux for 30 min, then cooled, and water was added. The solid product was extracted with EtOAc and chromatographed on a column of silica gel eluted with ether to furnish **8b** (71 mg, 81%), mp 183-185 °C: NMR (DMSO-d_6) δ 9.76 (s, 2, OH, disappeared with D_2O), 9.39 (s, 1, H_9), 9.05 (s, 1, H_{14}), 8.96 (d, 1, H_8; $J_{7,8}$ = 7.4 Hz), 8.46 (d, 1, H_5; $J_{5,6}$ = 7.3 Hz), 8.20-8.26 (m+s, 3, $H_{1,10,13}$), 8.05 (s, 1, H_4), 7.54-7.73 (m, 4, Ar); HRMS (EI) calcd for $C_{22}H_{14}O_2$ 310.09937, found 310.09949.

Reaction of phenanthrene-9-carboxaldehyde with N,N-diethyl 2-lithio-4-methoxybenzamide (9) Compound **9** was generated *in situ* by reaction of the *N,N*-diethyl 4-methoxybenzamide (20.7 g, 100 mmol) with *sec*-BuLi (120 mmol) and TMEDA (120 mmol) in anhydrous ether (800 mL) and THF (200 mL) at -78 °C by the reported procedure.[14a] Reaction of **9** with phenanthrene-9-carboxaldehyde (20.6 g, 100 mmol) at -78 °C by the usual procedure[14a] (reaction time 3 h) gave the adduct **10** (40.0 g) which was dissolved in dry benzene (500 mL) and heated with *p*-TsOH (4g) at reflux for 2 h. The solution was cooled to room temperature, concentrated to ~100 mL, and passed through a silica gel column eluted with benzene-hexane to provide the lactone **11** (15.48 g, 48%), mp 166-167 °C: NMR δ 8.78 (dd, 1, Ar), 8.67 (d, 1, Ar, J = 8.3 Hz), 8.25 (m, 1, Ar), 7.94 (d, 1, Ar, J = 8.5 Hz), 7.57-7.80 (m, 6, Ar), 7.14 (s, 1, Ar), 7.09 (dd, 1, Ar, J = 8.5 Hz, J = 1.9 Hz), 6.89 (s, 1, CH), 3.79 (s, 1, CH_3). Anal. Calcd for $C_{23}H_{16}O_3$: C, 81.16; H, 4.74. Found: C, 80.95; H, 4.70.

Reduction of the lactone 11 to 4-methoxy-2-(9-phenanthrylmethyl)benzoic acid (12). To a solution of **11** (11.75 g, 36.3 mol) in pyridine (50 mL) was added 800 mL of 10% NaOH and 90 g of activated zinc, and the mixture was heated at reflux overnight. The reaction was worked up as for **5b** to furnish **12** (9.0 g, 76%), mp 209-210 °C: NMR δ 8.73 (d, 1, Ar, J = 7.8 Hz), 8.68 (d, 1, Ar, J = 8.1 Hz), 8.19 (d, 1, Ar, J = 8.8 Hz), 7.95 (d, 1, J = 8.2 Hz), 7.78 (d, 1, J = 7.8 Hz), 7.54-7.66 (m, 5, Ar), 7.44 (s, 1, Ar), 6.80 (dd, 1, J = 8.8 Hz, J = 2.6 Hz), 6.52 (s, 1, OH,), 4.95 (s, 2, CH_2), 3.62 (s, 3, CH_3). Anal. Calcd for $C_{23}H_{18}O_3$: C, 80.68; H, 5.30. Found: C, 80.64; H, 5.16.

9-Acetoxy-12-methoxydibenz[a,c]anthracene (13a). A solution of **12** (540 mg, 1.65 mmol), $ZnCl_2$ in 10 mL of Ac_2O and 20 mL of AcOH was heated at reflux for 1 h, then cooled and poured over ice. The solid product was filtered and dried, then dissolved in a small volume of benzene and passed through a silica gel column. Elution with benzene-ether gave **13a** (490 mg, 81%), mp 209-210 °C: NMR δ 9.07 (dd, 1, H_8; $J_{7,8}$ = 8.0 Hz, $J_{6,8}$ = 2.3 Hz), 8.87 (s, 1, H_{14}), 8.65 (m, 1, H_1), 8.48-8.55 (m, 2, $H_{4,5}$), 7.90 (dd, 1, H_{10} ; $J_{10,11}$ = 9.2 Hz,), 7.55-7.62 (m, 4, Ar), 7.23-7.32 (m, 2, Ar), 3.98 (s, 3, CH_3), 2.57 (s, 3, CH_3). Anal. Calcd for $C_{25}H_{18}O_2$: C, 81.95; H, 4.95. Found: C, 82.03; H, 4.96.

11-Methoxydibenz[a,c]anthracene (13b). To a solution of **13a** (300 mg, 0.82 mmol) in 15 mL of pyridine was added zinc metal activated with $CuSO_4$ (20 g) and 75 mL of 10% NaOH, and the mixture was heated at reflux overnight. The usual workup and extraction with ether gave 100 mg of a mixture of **13b** and

its 9,14-dihydro derivative (by NMR). The mixture was dehydrogenated to **13b** by heating with *o*-chloranil in refluxing benzene for 5 h. The product was passed through a short column of silica gel eluted with benzene-hexane to yield pure **13b** (90 mg, 38%), mp 220-221 °C: NMR δ 8.99 (s, 1, Ar), 8.95 (s, 1, Ar), 8.71-8.77 (m, 2, Ar), 8.56-8.60 (m, 2, Ar), 7.96 (d, 1, H_{13}; $J_{12,13}$ = 9.0 Hz), 7.61-7.68 (m, 4, Ar), 7.33 (d, 1, H_{10}, J = 2.3 Hz), 7.25 (dd, 1, Ar), 4.01 (s, 3, CH_3). Anal. Calcd for $C_{23}H_{16}O$: C, 89.53; H, 5.23. Found: C, 89.36; H, 5.31.

11-Hydroxydibenz[a,c]anthracene (13c). A solution of **13b** (70 mg, 0.23 mmol) and 2.3 mL of BBr_3 (2.3 mmol) in 30 mL of CH_2Cl_2 was stirred at room temperature under Ar for 3 h, then poured over ice. The precipitate was filtered, washed with water, dried, and passed through a short column of silica gel. Elution with benzene-ether furnished **13c** (40 mg, 61%), mp 222-223 °C: NMR (acetone-d_6) δ 9.15 (s, 1, Ar), 9.02 (s, 1, Ar), 8.79-8.83 (m, 2, Ar), 8.25 (m, 2, Ar), 8.04 (d, 1, H_{13}; $J_{12,13}$ = 8.9 Hz), 7.57-7.64 (m, 4, Ar), 7.45 (s, 1, Ar), 7.25 (dd, 1, Ar). Anal. Calcd for $C_{22}H_{14}O$: C, 89.77; H, 4.79. Found: C, 89.86; H, 4.60.

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REFERENCES AND NOTES

1. Harvey, R. G. *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenesis*, Cambridge University Press: Cambridge, England, 1991, pp. 191-193.
2. Slaga, T. J.; Gleason, G. L.; Mills, G.; Ewald, L.; Fu, P. P.; Lee, H. M.; Harvey, R. G. *Cancer Res.* **1980**, *40*, 1981.
3. Dewar, M. J. S. *J. Am. Chem. Soc.* **1952**, *74*, 3357.
4. Hites, R. A.; Simonsick, W. J., Jr. *Calculated Molecular Properties of Polycyclic Aromatic Hydrocarbons*, Elsevier: Amsterdam, 1987.
5. Harvey, R. G. *Polycyclic Aromatic Hydrocarbons* Wiley-VCH: New York, NY, 1997, pp. 140-144.
6. Iverson, B.; Sydnes, K. L.; Greibrokk, T. *Acta Chem. Scand.* **1985**, B39, 837.
7. Bay region protons with an adjacent substituent generally appear as a singlet or a doublet with small meta coupling at relatively low field.
8. The technique of deuterium substitution coupled with NMR analysis to determine the site of bromine substitution was reported earlier: Minabe, M.; Cho, B.; Harvey, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 3809.
9. (a) Kole, P. L.; Dubey, S. K.; Kumar, S. *J. Org. Chem.* **1989**, *54*, 845. (b) Lee, H.; Harvey, R. G.; *J. Org. Chem.* **1983**, *48*, 749. (c) Harvey, R. G.; Fu, P. P. *J. Org. Chem.* **1980**, *45*, 169.
10. Ashe III, A. J.; Kampf, J. W.; Savla, P. M. *J. Org. Chem.* **1990**, *55*, 5558.
11. Harvey, R. G.; Leyba, C.; Konieczny, M.; Fu, P. P.; Sukumaran, K. B. *J. Org. Chem.* **1978**, *43*, 3423.
12. Bhatt, M. V. *Tetrahedron* **1964**, *20*, 803. Schmidt, J.; Eitel, M. *J. Prakt. Chem.* **1932**, *134*, 167.
13. Sukumaran, K. B.; Harvey, R. G. *J. Org. Chem.* **1980**, *45*, 4407.
14. (a) Harvey, R. G.; Cortez, C.; Jacobs, S. A. *J. Org. Chem.* **1982**, *47*, 2120. (b) Beak, P.; Brown, R. A. *J. Org. Chem.* **1977**, *42*, 1823.
15. Methanesulfonic acid in refluxing CH_2Cl_2 provides equally satisfactory results.
16. Harvey, R. G.; Ray, K. J.; Sukumaran, K. B. *Org. Prep. Proc. Internat.* **1983**, *15*, 335.

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