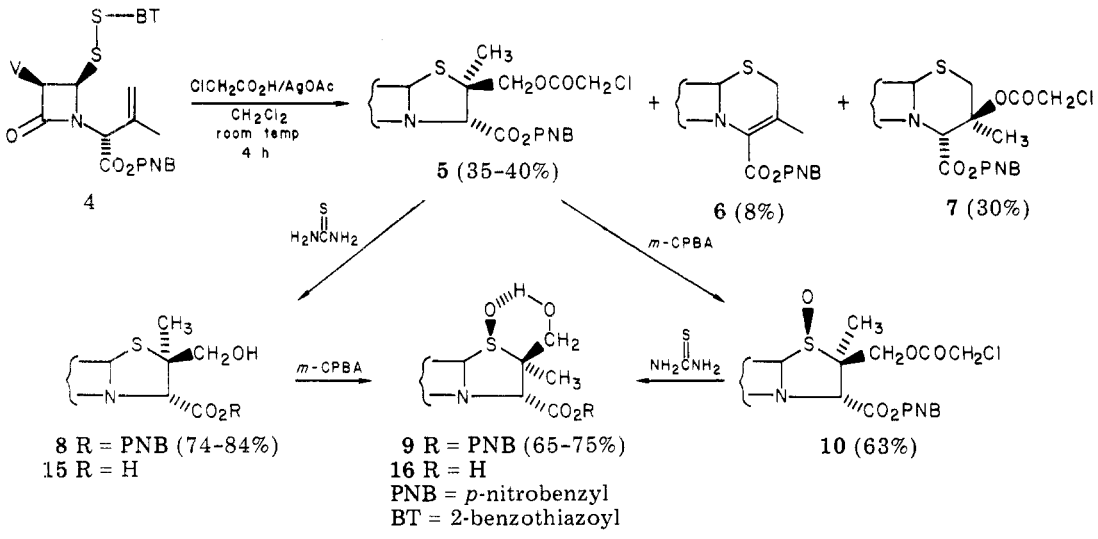
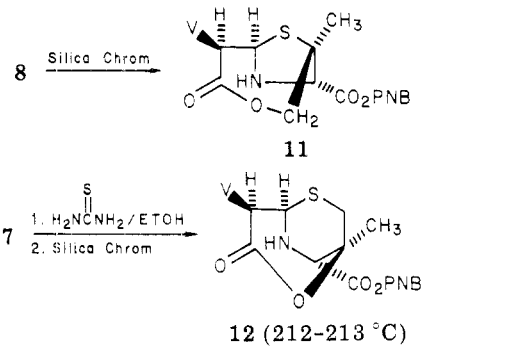
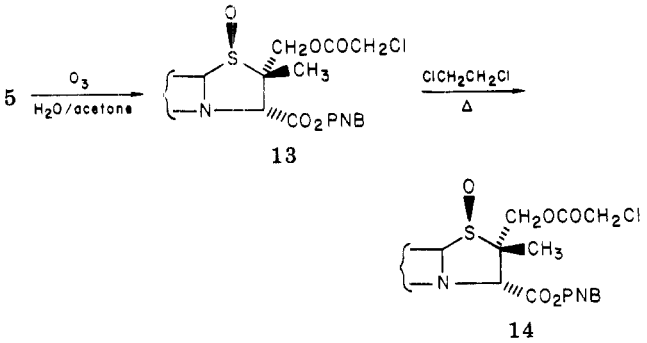
Scheme II



Scheme III



Scheme IV



***p*-Nitrobenzyl 2α-(Chloroacetoxymethyl)-6-(phenoxyacetamido)penicillin 1β-Oxide (14).** Thermal inversion of **13** in refluxing dichloroethane for 1 h gave **14**: NMR ($CDCl_3$) δ 1.76 (s, β-Me), 4.18 (s, CH_2Cl), 4.56 (s, $PhOCH_2$), 4.84 (s, H_3), 5.32 (br, PNB, H_5), 6.15 (q, J = 4, 10 Hz, H_6); IR ($CHCl_3$) 1790 cm^{-1} (β-lactam).

***p*-Nitrobenzyl 2β-(Hydroxymethyl)-6-(phenoxyacetamido)penicillinate (8).** The chloroacetoxymethyl sulfide **5** (1.55 g, 1.0 equiv) and 1.02 g (5.0 equiv) of thiourea in 60 mL of EtOH were heated at 60 °C for 30 min. The mixture was then evaporated to dryness, taken up in EtOAc–H_2O, washed with H_2O and brine, dried (Na_2SO_4), and evaporated to 1.11 g of (hydroxymethyl)-penicillin as a froth: NMR ($CDCl_3$) δ 1.38 (s, 3, α-Me), 3.48, 3.76 (AB, J = 10 Hz, 2, CH_2OH), 4.52 (s, 2, $PhOCH_2$), 4.88 (s, 1, H_3), 5.30 (s, 2, PNB), 5.6 (m, 2, H_5, H_6); IR ($CHCl_3$) 1780 cm^{-1} (β-lactam); mass spectrum m/e 501, 483 (M – 18).

***p*-Nitrobenzyl 2β-(Hydroxymethyl)-6-(phenoxyacetamido)penicillin 1β-Oxide (9).** The chloroacetoxymethyl oxide **13** (2.192 g, 1.0 equiv) and 2 equiv (0.560 g) of thiourea were heated at 60 °C for 1 h in 100 mL of EtOH. The mixture was worked up as above in **8** followed by silica gel chromatography using a toluene–ethyl acetate gradient to give 1.405 g of **9** as a white froth. Crystallization from CH_2Cl_2–hexane gave white needles: mp 155–156 °C; NMR ($CDCl_3$) δ 1.16 (s, 3, α-Me), 3.3 (br, 1, OH), 4.13 (s, 2, CH_2OH), 4.50 (s, 2, $PhOCH_2$), 4.95 (s, 1, H_3), 5.02 (d, J = 4 Hz, 1, H_5), 5.30 (s, 2, PNB), 6.10 (q, J = 4, 10 Hz, 1, H_6); IR ($CHCl_3$) 1795 cm^{-1} (β-lactam); mass spectrum m/e 483 (M – 18). Anal. Calcd for $C_{23}H_{23}N_3O_9S$: C, 53.38; H, 4.48; N, 8.12. Found: C, 53.65; H, 4.28; N, 7.97.

***p*-Nitrobenzyl 5-(phenoxyacetamido)-3-oxa-9-thia-7-azabicyclo[4.2.1]nonane-8-carboxylate (11)** was obtained as a white froth from silica gel chromatography of **8**: NMR ($CDCl_3$) δ 1.33 (s, 3, Me), 3.8 (br, 1, NH), 4.20 (s, 1, H_3), 4.23, 4.45 (AB, J = 12 Hz, 2, CH_2O), 4.55 (s, 2, $PhOCH_2$), 5.18 (m, 2, H_5, H_6), 5.32 (s, 2, PNB); IR ($CHCl_3$) 1730 cm^{-1}; mass spectrum m/e 501.

2β-(Hydroxymethyl)-6-(phenoxyacetamido)penicillin 1β-oxide (16): NMR ($CDCl_3$) δ 1.36 (s, 3, α-Me), 4.20 (s, 2, CH_2OH), 4.56 (s, 2, $PhOCH_2$), 4.73 (s, 1, H_3), 5.02 (d, J = 4 Hz, 1, H_5), 6.05 (q, J = 4, 10 Hz, 1, H_6); IR ($CHCl_3$) 1795 cm^{-1} (β-lactam).

2β-(Hydroxymethyl)-6-(phenoxyacetamido)penicillin (15): NMR ($CDCl_3$) δ 1.53 (s, 3, α-Me), 3.50, 3.69 (AB, J = 12 Hz, 2, CH_2OH), 4.60 (s, 2, $PhOCH_2$), 4.75 (s, 1, H_3), 5.7 (m, 2, H_5, H_6); IR ($CHCl_3$) 1775 cm^{-1} (β-lactam).

Registry No. **4**, 70850-41-8; **5**, 70850-42-9; **6**, 28974-31-4; **7**, 70850-43-0; **8**, 70850-44-1; **9**, 70850-45-2; **10**, 70850-46-3; **11**, 70850-47-4; **13**, 70878-66-9; **14**, 70850-48-5; **15**, 70850-49-6; **16**, 70850-50-9.

Synthesis of Some Non-K-Region Derivatives of Dibenz[*a*,*h*]anthracene

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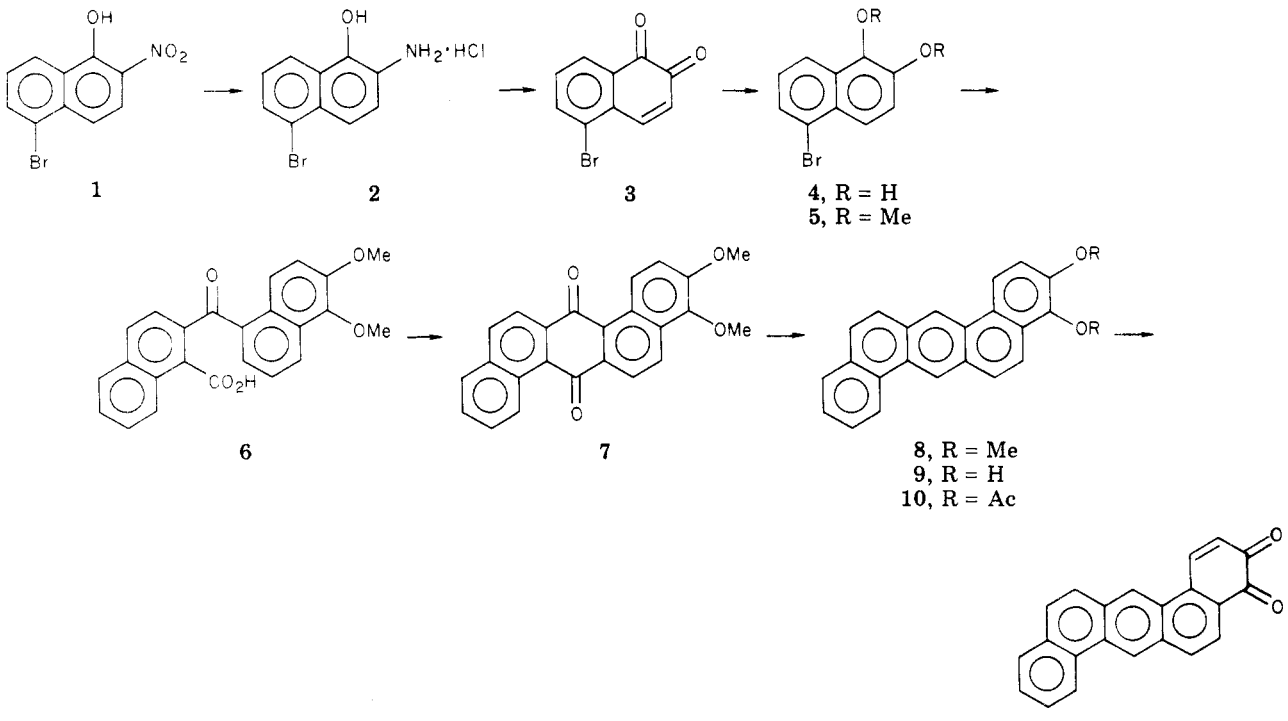
Since polycyclic hydrocarbons have been shown to have carcinogenic activity,[1-5] considerable progress has been made to elucidate the molecular mechanism of chemical carcinogenesis due to these hydrocarbons and related

(1) E. L. Keenaway and I. Hieger, *Brit. Med. J.*, 1, 1044 (1930).
(2) J. W. Cook, I. Hieger, E. L. Keenaway, and W. V. Mayneord, *Proc. R. Soc. London, Ser. B*, 3, 456 (1932).
(3) H. Burrows, I. Hieger, and E. L. Keenaway, *Am. J. Cancer*, 16, 57 (1932).
(4) H. Burrows, *Proc. R. Soc. London, Ser. B*, 3, 238 (1932).
(5) G. Barry and J. W. Cook, *Am. J. Cancer*, 20, 58 (1934).

0022-3263/79/1944-3086$01.00/0

Scheme I



chemicals.[6,7] Recent extensive work[8-16] has established the non-K-region diol epoxides of benzo[*a*]pyrene and benz[*a*]anthracene as the principal active forms of these carcinogens. Because of its symmetry, we have been particularly interested in the chemistry and biological activities of the polynuclear hydrocarbon dibenz[*a*,*h*]-anthracene. Recently, the synthesis of dibenz[*a*,*h*]-anthracene-3,4-dihydrodiol has been reported.[17] In this connection, we like to report the synthesis of some non-K-region derivatives of dibenz[*a*,*h*]anthracene, which will fill the gap in the knowledge of the chemistry of non-K-region derivatives of this interesting polynuclear and carcinogenic hydrocarbon.

The synthesis of the non-K-region derivatives, which culminated in the synthesis of dibenz[*a*,*h*]anthra-3,4-quinone, was done according to the reaction sequences shown in Scheme I. 5-Bromo-1,2-dimethoxynaphthalene (**5**) was synthesized starting from the known 5-bromo-2-nitro-1-naphthol (**1**).[18] Compound **1** was reduced with stannous chloride and hydrochloric acid in ethanol to the corresponding amine hydrochloride, **2**. Ferric chloride oxidation[19] of **2** led to the formation of the quinone, **3**, as red plates. Sulfur dioxide reduction of **3** and subsequent methylation with methyl iodide in the presence of potassium carbonate in dry acetone led to **5**.

The Grignard reagent prepared from magnesium and compound **5** reacted with 1,2-naphthalic anhydride to yield a single keto acid, **6**, which on polyphosphoric acid cyclization led to a single ketone, **7**. The ketone was smoothly reduced with zinc dust in pyridine and glacial acetic acid to **8**. The product was seen as a single peak on gas–liquid chromatography. Dealkylation of **8** with hydrobromic acid in glacial acetic acid led to **9**. The identity of the compounds as dibenz[*a*,*h*]anthracene derivatives was established by conversion of compound **9** with zinc dust distillation into dibenz[*a*,*h*]anthracene, which was identical with an authentic sample of dibenz[*a*,*h*]-anthracene from mixed melting point, infrared, and ultraviolet spectral comparisons. Compound **9** on oxidation with ferric chloride solution yielded dibenz[*a*,*h*]anthra-3,4-quinone, **11**. The possible importance and role of the synthesized dibenz[*a*,*h*]anthracene derivatives in the carcinogenesis and metabolism of dibenz[*a*,*h*]anthracene are yet to be ascertained.

Experimental Section

Melting points were determined on a Thomas–Hoover melting point apparatus and are uncorrected. The ultraviolet spectra were recorded on a Beckman DB-G, and quantitative measurements were done on a Gilford 2400-S or on a Cary 15 spectrophotometer. Spectra were taken in solvents as indicated. The infrared spectra were taken on a Beckman IR-10 as KBr plates. NMR spectra (reported in δ) were recorded on a Perkin–Elmer R-12 in indicated solvents using tetramethylsilane as internal reference. Mass spectra were obtained with a Varian CH-7 spectrometer (Varian Associates, Palo Alto, Calif.) equipped with a magnet-drive direct-insertion probe (Variset Corp., Madison Wis.). Elemental

(6) C. Heidelberger, *Cancer*, **40**, 430 (1977).
(7) C. Heidelberger, *Annu. Rev. Biochem.* **44**, 79 (1975).
(8) H. Yagi, D. R. Thakker, O. Hernandez, M. Koreeda, and D. M. Jerina, *J. Am. Chem. Soc.*, **99**, 1604 (1977).
(9) J. Kapitulnik, W. Levin, H. Yagi, D. M. Jerina, and A. H. Conney, *Nature (London)*, **266**, 378 (1977).
(10) K. Nakanishi, H. Kasai, H. Cho, R. G. Harvey, A. M. Jeffrey, R. W. Jennette, and I. B. Weinstein, *J. Am. Chem. Soc.*, **99**, 258 (1977).
(11) I. B. Weinstein, A. M. Jeffrey, K. W. Jennette, S. H. Blobstein, R. G. Harvey, C. Harris, H. Autrup, H. Kasai, and K. Nakanishi, *Science*, **193**, 592 (1976).
(12) H. W. S. King, M. R. Osborne, F. A. Beland, R. G. Harvey, and P. Brookes, *Proc. Natl. Acad. Sci. U.S.A.*, **73**, 2679 (1976).
(13) R. Mager, E. Huberman, S. K. Yang, H. V. Gelboin, and L. Sachs, *Int. J. Cancer*, **19**, 814 (1977).
(14) A. W. Wood, W. Levin, R. L. Chang, R. E. Lehr, M. Schaefer-Ridder, J. M. Karle, D. M. Jerina, and A. H. Coney, *Proc. Natl. Acad. Sci. U.S.A.*, **74**, 3176 (1977).
(15) A. W. Wood, R. L. Chang, W. Levin, R. E. Lehr, M. Schaefer-Ridder, J. M. Karle, D. M. Jerina, and A. H. Conney, *Proc. Natl. Acad. Sci. U.S.A.*, **74**, 2746 (1977).
(16) P. G. Wislocki, J. Kapitulnik, W. Levin, R. Lehr, M. Schaefer-Ridder, J. M. Karle, D. M. Jerina, and A. H. Conney, *Cancer Res.*, **38**, 693 (1978).
(17) J. M. Karle, H. D. Mah, D. M. Jerina, and H. Yagi, *Tetrahedron Lett.*, 4021 (1977).
(18) K. Fries and E. Kohler, *Ber. Dtsch. Chem. Ges. A*, **57**, 496 (1924).
(19) L. F. Fieser, "Organic Synthesis", Collect. Vol. II, Wiley, New York, 1943, p 430.

analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., or Spang Microanalytical Laboratory, Ann Arbor, Mich. TLC was carried on Eastman Chromagram Sheet 6060 silica gel with fluorescent indicator in the solvents indicated: solvent I, acetone–cyclohexane 1:1; solvent II, chloroform; solvent III, benzene–ethanol 19:1; solvent IV, chloroform–methanol 10:1; and solvent V, benzene–methanol 3:1. Spots were visualized with short- or long-wavelength UV lamps.

5-Bromo-1,2-naphthoquinone (3). To a well-stirred, refluxing suspension of 1 (1.8 g, 6.7 mmol) in absolute ethanol (10 mL), a solution of stannous chloride (6 g) in concentrated hydrochloric acid (6 mL) was added dropwise over 10 min. The mixture was stirred and refluxed for 1.5 h and cooled. The solid was filtered, washed with a little ethanol, and dried to yield 1.5 g (5.5 mmol, 82.1%) of **2**, mp 275–278 °C dec. The hydrochloride can be purified by dissolving it in hot water, filtering the solution, and adding concentrated hydrochloric acid to the filtrate. **2** (500 mg, 1.8 mmol) was dissolved in hot water (100 mL) with addition of a few crystals of stannous chloride and filtered when a practically colorless solution was obtained. To a well-stirred, filtered solution of ferric chloride (11 g) in concentrated hydrochloric acid (4 mL) and water (20 mL) at 45–50 °C, the above solution of the hydrochloride was added dropwise. A yellow voluminous precipitate separated out quickly. It was further stirred for 10 min at 45–50 °C, cooled in an ice bath, and filtered. The residue was washed with ice-water and air dried to yield an orange solid (380 mg, 1.6 mmol, 89%). The material was crystallized from benzene–skelly B to yield red plates of **3**: mp 155–6 °C; IR 1670 cm^{-1} (quinone); R_f 0.82 in solvent I. Anal. Calcd for $C_{10}H_5O_2Br$: C, 50.63; H, 2.11; Br, 33.75. Found: C, 50.80; H, 2.23; Br, 33.94.

5-Bromo-1,2-dimethoxynaphthalene (5). To a hot boiling solution of **3** (250 mg, 1.05 mmol) in ethanol (20 mL) and water (10 mL), sulfur dioxide gas was bubbled in for 15 min. The solution turned much lighter colored (greenish). It was treated with some charcoal and filtered hot, and the filtrate was concentrated with passage of sulfur dioxide. The solution was allowed to crystallize in the refrigerator when slightly pinkish white crystals separated out. These were filtered and dried in a vacuum desiccator overnight to yield 180 mg (0.75 mmol, 71%) of **4**: mp 141–2 °C; R_f 0.58 in solvent I; IR shows a strong absorption at 3420 cm^{-1} (OH), absence of a band at 1670 cm^{-1} (quinone).

4 (180 mg) was refluxed with stirring in acetone (25 mL) solution under nitrogen atmosphere with methyl iodide (3.0 g) and anhydrous potassium carbonate (250 mg) for 8 h. The acetone was then removed under vacuum, and the residue was treated with water and extracted with ether. The etheral layer was washed with sodium hydroxide solution (2 N), sodium thiosulfate solution (10%), and water and dried. On removal of solvent, a brown oil was obtained which crystallized from ether–skelly B (charcoal treatment) into colorless fine needles of **5**: 120 mg (0.55 mmol, 52%); mp 51 °C; R_f 0.80 in solvent I; NMR ($CDCl_3$) 3.98 (s, 6 H, $-OCH_3$), between 7 and 8.2 (5 H, aromatic). Anal. Calcd for $C_{12}H_{11}O_2Br$: C, 53.93; H, 4.12; Br, 29.96. Found: C, 54.13; H, 4.20; Br, 29.98.

2(1′)-Naphthoyl-5′,6′-dimethoxy-1-naphthoic Acid (6). A mixture of magnesium turnings (180 mg) and **5** (1.3 g, 4.86 mmol) in tetrahydrofuran (20 mL) was refluxed and stirred for 8 h. The brown solution was transferred to a dropping funnel and added dropwise over an hour to a suspension of 1,2-naphthalic anhydride (1.5 g, 7.6 mmol) in benzene (25 mL) and tetrahydrofuran (5 mL) at 10 °C. The mixture was stirred and refluxed for 5 h with continuous distillation and addition of benzene until ca. 25 mL of distillate was collected. At the end of the reaction, a brown complex separated which was filtered hot. The brown complex on decomposition with 5% sulfuric acid yielded **6** as a white solid, 500 mg, mp 203–205 °C. More of the acid was obtained from the benzene solution on decomposition with 5% H_2SO_4 acid and extraction of the benzene layer with 2% sodium bicarbonate solution. A total of 1.15 g (2.97 mmol, 61%) of the acid, **6**, was obtained. The analytical sample obtained as light yellow needles, mp 210 °C, by crystallization from benzene–ethanol mixture: R_f 0.06 in solvent I and 0.44 in solvent V; IR 3320 (OH), 1730 cm^{-1} (C=O); NMR (Me_2SO-d_6) 3.96 (s, 6 H, $-OCH_3$). Anal. Calcd for $C_{24}H_{18}O_5$: C, 74.60; H, 4.70. Found: C, 74.70; H, 4.98.

3,4-Dimethoxydibenz[*a*,*h*]anthra-7,14-quinone (7). A mixture of **6** (100 mg, 0.26 mmol) and poly(phosphoric acid) (10 g) was heated at 100 °C with stirring for 2 h. It was cooled and decomposed with ice and water when red crystals separated. The crystals were filtered, and the aqueous layer was extracted with chloroform to yield more of the quinone. The combined yield of quinone was 54 mg (0.15 mmol, 58%). The product was crystallized from benzene–ethanol to yield orange-red fine needles of **7**: mp 240–1 °C; IR 1660 cm^{-1} (quinone); R_f 0.72 in solvent II and 0.90 in solvent V; mass spectra m/e 368 (M^+); UV (dioxane) λ_{max} (ϵ) 312 (33 052), 385 (5474). Anal. Calcd for $C_{24}H_{16}O_4$: C, 78.25; H, 4.38. Found: C, 78.07; H, 4.44.

3,4-Dimethoxydibenz[*a*,*h*]anthracene (8). **7** (2 g, 5.4 mmol) was dissolved in hot pyridine (200 mL) and glacial acetic acid (20 mL). To the well-stirred solution, zinc dust (90 g) was added portionwise over 1 h, followed by dropwise addition of 80% (v/v acetic acid (80 mL) to the refluxing solution. The mixture was refluxed with stirring for a total of 3 h and filtered hot, and the residue was washed with pyridine (50 mL). The combined filtrates were acidified with 6 N hydrochloric acid to pH 1 and extracted with chloroform. The chloroform extract was washed with dilute HCl and water and dried, and the solvent was removed to yield a solid, **8**, 0.95 g (2.8 mmol, 52%), which crystallized from chloroform into glistening white plates, mp 268–269 °C. The product on GLC (1.5% OV-1 column, T = 270 °C) was seen as a single peak substance: R_f 0.66, 0.40, 0.77, and 0.69 in solvents II, III, IV, and V respectively; IR shows the absence of the 1660 cm^{-1} (quinone) band; NMR ($CDCl_3$) 4.06 (s, 6H, OCH_3); mass spectrum m/e 338 (M^+); UV (95% EtOH) λ_{max} (ϵ) 225 (28 893), 278 (20 847), 291 (43 898), 302 (73 475), 324 (17 966), 338 (11 864), 351 (5763). Anal. Calcd for $C_{24}H_{18}O_2$: C, 85.18; H, 5.36. Found C, 85.29; H, 5.35.

3,4-Dihydroxydibenz[*a*,*h*]anthracene (9). A mixture of **8** (1.3 g, 3.8 mmol), 48% hydrobromic acid (100 mL), and glacial acetic acid (30 mL) was refluxed under nitrogen atmosphere with stirring for 5 days. At the end of the reaction, the mixture was evaporated to dryness and crystallized from dioxane to yield **9** (1.1 g, 3.5 mmol, 92%) as silvery small plates: mp 317–319 °C; R_f 0.00, 0.07, and 0.2 in solvents II, III, and IV, respectively; UV (dioxane) λ_{max} (ϵ) 293 (29 839), 302 (48 629), 330 (14 315), 342 (12 419), 354 (7766), 383 (2016), 405 (2508). Anal. Calcd for $C_{22}H_{14}O_2$: C, 85.14; H, 4.55. Found: C, 85.09; H, 4.54.

3,4-Diacetoxydibenz[*a*,*h*]anthracene (10). Pyridine (2.5 mL) and acetic anhydride (25 mL) were refluxed for 1 h. To the cooled solution, **9** (100 mg, 0.32 mmol) was added, and the mixture was stirred overnight (20 h) and then refluxed for 1 h. It was cooled and filtered to yield **10** (100 mg, 0.25 mmol, 78%) which was crystallized from benzene: mp 277–8 °C; R_f 0.46 and 0.39 in solvents II and III, respectively; IR 1770 cm^{-1} (acetoxy); mass spectra m/e 394 (M^+); UV (dioxane) λ_{max} (ϵ) 282 (50 648), 290 (98 704), 301 (150 766), 323 (22 803), 337 (18 410), 352 (15 406), 374 (1166), 394 (966). Anal. Calcd for $C_{26}H_{18}O_4$: C, 79.17; H, 4.60. Found: C, 79.28; H, 4.67.

Dibenz[*a*,*h*]anthra-3,4-quinone (11). **9** (80 mg, 0.26 mmol) in dioxane (15 mL) was added to a ferric chloride (22 g) solution in concentrated hydrochloric acid (8 mL) and water (20 mL) at 45–50 °C over 15 min. The mixture was further stirred for 15 min, diluted with ice to 100 mL, filtered, and dried. A brown solid (75 mg, 0.24 mmol, 92%) was obtained which was crystallized from chloroform into deep purple fine needles of 11: mp 301–2 °C; R_f 0.00 and 0.83 in solvents III and V, respectively; IR 1660 cm^{-1} (quinone); UV (dioxane) λ_{max} (ϵ) 228 (43 900), 280 (47 430), 290 (54 950), 332 (28 500), 420 (4105), 505 (1288). Anal. Calcd for $C_{22}H_{12}O_2$: C, 85.70; H, 3.92. Found: C, 85.84; H, 4.28.

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Registry No. 1, 70644-27-8; 2, 70644-28-9; 3, 62784-49-0; 4, 70644-29-0; 5, 70644-30-3; 6, 70644-31-4; 7, 70644-32-5; 8, 70644-33-6; 9, 64414-77-3; 10, 70644-34-7; 11, 70644-35-8; 1,2-naphthalic anhydride, 5343-99-7.