extraction allowed recovery of the amino alcohol ligand.

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Registry No. **1a**, 60018-69-1; **1b**, 59983-84-5; **1c**, 72443-71-1; **1d**, 59983-28-7; **1e**, 64704-95-6; **1f**, 72443-72-2; **2a**, 60018-72-6; **2b**, 59983-36-7; **2c**, 72443-73-3; **2d**, 59983-27-6; **2e**, 64765-29-3; **2f**, 72443-74-4; **9a**, 13046-02-1; **9b**, 72443-75-5; **9c**, 72443-76-6; **9d**, 72443-77-7; **9e**, 72443-78-8; **9f**, 72443-79-9; **10**, 38345-66-3; **11**, 72541-03-8; **12**, 72443-80-2; **13**, 72453-30-6; **14**, 72443-81-3; **15**, 72443-82-4; **16**, 72496-14-1; **17**, 72443-83-5; **18**, 72443-84-6; **19**, 72443-85-7; **20**, 72443-86-8; **21**, 72443-87-9; **23**, 59965-12-7; **24**, 59965-11-6; **25**, 98-86-2; **26**, 1517-69-7; **27**, 1445-91-6; dimethylamine, 124-40-3; (*S*)-(−)-*N*,α-dimethylbenzylamine, 19131-99-8.

Synthesis of Biologically Active Metabolites of Dibenz[*a*,*h*]anthracene

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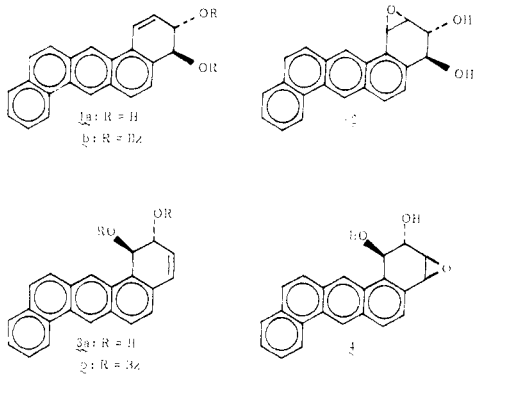
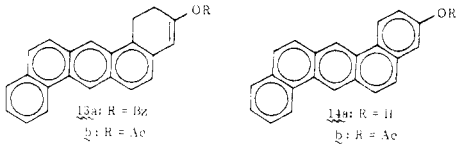
Syntheses are described of the trans 1,2- and 3,4-dihydro diol metabolites (**3a** and **1a**) of dibenz[*a*,*h*]anthracene (DBA) and the corresponding diol epoxide derivatives **4** and **2**, implicated as the ultimate carcinogenic metabolites of DBA. The syntheses of **1a** and **3a** are accomplished from DBA via lithium–ammonia reduction to 1,4,7,8,11,14-hexahydrodibenz[*a*,*h*]anthracene, base-catalyzed isomerization, Prévost reaction, dehydrogenation, and basic methanolysis. This approach involves considerably fewer steps and affords superior overall yields than obtainable by more conventional methods entailing multistep ring construction. Epoxidation of **1a** affords stereospecifically the anti diol epoxide isomer **2**, whereas similar reaction of **3a** furnishes a mixture of the corresponding syn and anti diol epoxide isomers in 3:1 ratio. Biological evidence implicates **1a** and **2** as proximate and ultimate carcinogenic forms, respectively, of DBA. Synthesis of 3-hydroxydibenz[*a*,*h*]anthracene, also known to be a metabolite of DBA, is also described.

Dibenz[*a*,*h*]anthracene (DBA) was the first pure polycyclic aromatic hydrocarbon demonstrated to be carcinogenic.[1] Subsequently, it has been the subject of intensive investigation and has been identified as a widespread environmental contaminant present in the atmosphere, soil, automobile exhaust, cigarette smoke, and foods.[2] Recent evidence indicates that polycyclic aromatic hydrocarbons undergo metabolic activation to highly mutagenic trans dihydro diols which may undergo further metabolic transformation to reactive diol epoxides capable of binding covalently to nucleic acids and inducing tumor formation.[3,4] In the case of DBA, there is evidence for the in vitro metabolic formation of significant amounts of all three possible dihydro diols,[5] and the 3,4-dihydro diol (**1a**) has been demonstrated[6] to undergo cytochrome P-450 catalyzed activation to a mutagenic metabolite presumed to be the corresponding anti diol epoxide derivative (**2**).[7]



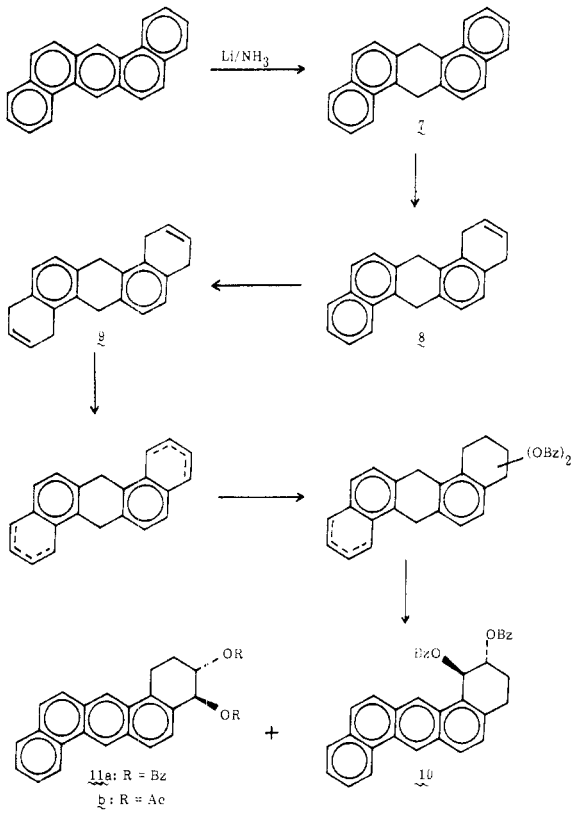


Syntheses of the dihydro diols **1a** and **3a** from the corresponding ketonic intermediate 4-oxo- and 1-oxo-1,2,3,4-tetrahydrodibenz[*a*,*h*]anthracenes (**5** and **6**) in six steps each (in overall yields of 8% and 17%, respectively) are reported in a recent communication by Karle et al.[8] Compounds **5** and **6** were themselves synthesized from

(1) Kenneway, E. L. *Biochem. J.* **1930**, *24*, 497.
(2) International Agency for Research on Cancer: "Monograph on the Evaluation of Carcinogenic Risk of the Chemical to Man: Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds"; World Health Organization: Geneva, Switzerland, 1973; Vol. 3.
(3) Reviews: (a) Harvey, R. G. In "Safe Handling of Chemical Carcinogens, Mutagens, and Teratogens: The Chemist's Viewpoint"; Walters, D. B., Ed.; Ann Arbor Science Publishers, Inc.: Ann Arbor, Mich., in press. (b) Harvey, R. G.; Fu, P. P. In "Polycyclic Hydrocarbons and Cancer: Environment, Chemistry, and Metabolism"; Gelboin, H. V., T'so, P. O. P., Eds.; Academic Press: New York, 1978; Vol. 1, Chapter 6, p 133. (c) Yang, S. K.; Deutsch, J.; Gelboin, H. V., ref 3b, Chapter 10, p 205. (d) Levin, W.; Wood, A. W.; Wislocki, P. G.; Chang, R. L.; Kapitulnik, J.; Mah, H. D.; Yagi, H.; Jerina, D. M.; Conney, A. H., ref 3b, Chapter 9, p 189.
(4) Sukumaran, K. B.; Harvey, R. G. *J. Am. Chem. Soc.* **1979**, *101*, 1353.
(5) Boyland, E.; Sims, P. *Biochem. J.* **1965**, *97*, 7. Sims, P. *Biochem. Pharmacol.* **1970**, *19*, 795.
(6) Wood, A. W.; Levin, W.; Thomas, P. E.; Ryan, D.; Karle, J. M.; Yagi, H.; Jerina, D. M.; Conney, A. H. *Cancer Res.* **1978**, *38*, 1967.
(7) Depicted is the anti isomer in which the epoxide oxygen atom and the benzylic hydroxyl group in the 4-position are on opposite faces of the ring; the syn isomer has these groups on the same face of the molecule.
(8) Karle, J. M.; Mah, H. D.; Jerina, D. M.; Yagi, H. *Tetrahedron Lett.* **1977**, 4021.

0022-3263/80/1945-0588$01.00/0

Scheme I



8-oxo-8,9,10,11-tetrahydrobenz[a]anthracene (five steps and nine steps, respectively) which in turn was prepared from phenanthrene (three steps, 12%) according to published procedures.[9,10] The net overall yields of **1a** and **3a** from phenanthrene via these multistep sequences were <0.5% each.

We now report more convenient syntheses of the isomeric dihydro diols **1a** and **3a** *directly from the parent hydrocarbon DBA* in fewer steps and superior overall yields. Syntheses of the previously unreported anti isomeric diol epoxide derivatives **2** and **4**, urgently required for biological studies, and 3-hydroxydibenz[a,h]anthracene, implicated as a metabolite of DBA,[11] are also described. Preliminary evidence implicates **2** as the ultimate[12] carcinogenic form of DBA.

Results

Initially, an attempt was made to synthesize **1a** via a synthetic approach based on one earlier devised for preparation of the related 3,4-dihydro diol of benz[a]anthracene.[1b,13] However, attempted synthesis of the key intermediate, 1,4,7,14-tetrahydrodibenz[a,h]anthracene (**8**), through two-stage reduction of DBA with lithium in liquid ammonia,[14,15] exhibited a strong propensity to proceed beyond **8** to the 1,4,7,8,11,14-hexahydrodibenz[a,h]anthracene derivative (**9**) (Scheme I). With 4 equiv of lithium metal, reduction of 7,14-dihydrodibenz[a,h]anthracene (**7**) afforded **9** smoothly and essentially quantitatively. The structure of **9** is in accord with molecular orbital theoretical prediction;[15] this assignment was confirmed by NMR analysis which revealed aromatic, vinylic, benzylic, and allylic protons in the anticipated 1:1:1:2 ratio.

In view of the facility of the synthesis of **9**, an attempt to utilize this compound as an alternative to the initially sought **8** in the synthesis of **1a** was made. Sodium methoxide catalyzed isomerization of **9** in Me_2SO furnished a mixture of the four possible conjugated diolefinic intermediates. No attempt to separate this mixture was made. Instead, Prévost reaction with 2 equiv of silver benzoate and I_2 was carried out on the mixture to afford the corresponding mixed trans diol dibenzoates. Dehydrogenation of the latter with DDQ[16] in refluxing benzene furnished a mixture of the dibenzoate esters of *trans*-1,2- and *trans*-3,4-dihydroxy-1,2,3,4-tetrahydrodibenz[a,h]anthracenes (**10** and **11a**) which were readily separable by chromatography and fractional crystallization. The predominant isomer (obtained in a 9:1 ratio) was the less sterically hindered dibenzoate ester **11a**. The related tetrabenzoate esters detected as minor products were readily separated by chromatography.

Dehydrogenation of **11a** to *trans*-3,4-bis(benzoyloxy)-3,4-dihydrodibenz[a,h]anthracene (**1b**) was accomplished through bromination with NBS catalyzed by benzoyl peroxide, followed by dehydrobromination with DBN in tetrahydrofuran.[3b,16] Treatment of **1b** with sodium methoxide in methanol furnished the 3,4-dihydro diol **1a** as a white solid, mp 278–280 °C. Epoxidation of **1a** with *m*-chloroperbenzoic acid provided stereospecifically the corresponding anti diol epoxide **2** in 85% yield. The latter, like diol epoxides generally, proved thermally sensitive; however, it could be crystallized from cool Me_2SO/acetone solutions as white needles, mp 196–197 °C.

The integrated proton NMR spectra (Table I) of the 3,4-dihydro diol and the related anti diol epoxide were in full agreement with the assigned structures. Details of the NMR spectral analysis of **1a**, **1b**, and **2** in comparison with the isomeric 1,2-dihydro diol **3a** and its derivatives **3b** and **4** are discussed in following paragraphs. In further con-

Table I. Proton NMR Data[a] on the Dihydro Diols (1a and 3a), Dibenzoates (1b and 3b), and Anti Diol Epoxides (2 and 4) of Dibenz[a,h]anthracene

	δ				J, Hz		
	H_1	H_2	H_3	H_4	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$
1b		6.51	6.37	6.92	10	4	7
1a	7.5	6.25	4.45	4.85	10	3	11
3b		5.9	6.43	6.98	2	5	10
3a	5.61	4.50	6.30	6.76	2	6	9
2	5.06	3.84	3.94	4.58	4.5	2	9
4	5.27	4.48	3.79	4.05	0		4

[a]Spectra were taken on a Varian T60 or a Bruker HX270 spectrometer in acetone-d_6; chemical shifts are in parts per million relative to Me_4Si. Spectral interpretation was aided by converting the diols to their dideuterio derivatives by addition of D_2O. Further details of the spectra are reported in the Experimental Section.

(9) Haworth, R. D.; Mavin, C. R. *J. Chem. Soc.* **1932**, 1014.
(10) Synthesis of **6** was based on the method of: Cook, J. W.; Schoental, R. *J. Chem. Soc.* **1952**, 9. Since yields are not cited by these authors, yields are estimated from those from the analogous steps in the synthesis of **5**;[9] on this basis, the overall yields of **5** and **6** from 8-oxo-8,9,10,11-tetrahydrobenz[a]anthracene are 27% and 21%, respectively.
(11) Sims, P. *Biochem. Pharmacol.* **1970**, *19*, 795. Boyland, E.; Sims, P. *Biochem. J.* **1965**, *97*, 7.
(12) The *ultimate carcinogen* is in current terminology the metabolically activated form which interacts with the cellular target, generally believed to be DNA, thereby inducing cancer. Metabolically activated intermediate precursors of the ultimate carcinogen, e.g., **1**, are termed *proximate carcinogens*.
(13) Harvey, R. G.; Sukumaran, K. B. *Tetrahedron Lett.* **1977**, 2387.
(14) Harvey, R. G.; Arzadon, L.; Grant, J.; Urberg, K. *J. Am. Chem. Soc.* **1969**, *91*, 4535.
(15) Harvey, R. G. *Synthesis* **1970**, 161. Lindow, D. F.; Cortez, C. N.; Harvey, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 5406. Harvey, R. G.; Lindow, D. F.; Rabideau, P. W. *Tetrahedron* **1972**, *28*, 2909. Harvey, R. G.; Fu, P. P.; Rabideau, P. W. *J. Org. Chem.* **1976**, *41*, 2706.
(16) Fu, P. P.; Harvey, R. G. *Chem. Rev.* **1978**, *78*, 317; *Tetrahedron Lett.* **1977**, 2059.

firmation of the isomeric structural assignments of **1a**, and **3a**, the UV spectrum of **1a** matched that reported[8] for the trans 3,4-dihydro diol of DBA which differed markedly from that of the trans 1,2-dihydro diol of DBA.

Synthesis of the isomeric trans 1,2-dihydro diol **3a** was accomplished from **10** via an analogous sequence of transformations. Dehydrogenation of **10** by the bromination–dehydrobromination method gave the dibenzoate ester **3b** in 94% yield as a crystalline solid, mp 143–145 °C; the latter was isolated previously as a glass.[8] The integrated proton NMR spectrum of **3b** (Table I) was in close agreement with that reported for **3b** obtained from total synthesis,[8] confirming the structural assignment. Methanolysis of **3b** with sodium methoxide in methanol furnished the free trans 1,2-dihydro diol **3a**, mp 257–259 °C (73%).

Epoxidation of the trans 1,2-dihydro diol with *m*-chlorobenzoic acid by the same general procedure employed for synthesis of **2** gave a mixture of the isomeric anti and syn diol epoxides [*trans*-1,2-dihydroxy-*anti*(and *syn*)-1,2-epoxy-1,2,3,4-tetrahydrodibenz[*a,h*]anthracenes (**4** and **12**)] in a 3:1 ratio separated by high-pressure LC on a Zorbax SIL column and identified by NMR (270 MHz) analysis.

Metabolic studies of DBA[11] have tentatively identified the 1,2-, 3,4-, and 5,6-dihydro diols and the 3- and 4-phenols as principal metabolites of DBA on the basis of TLC and UV evidence. Confirmation of these structural assignments requires the authentic phenolic and dihydro diol derivatives of DBA. Since 3-hydroxydibenz[*a,h*]-anthracene (**14a**) remains the only major probable metabolite of DBA still unavailable synthetically, its synthesis was made a goal of this investigation.[17]

Synthesis of 3-hydroxydibenz[*a,h*]anthracene was achieved from the tetrahydrodibenz[*a,h*]anthracene dibenzoate intermediate **11a**. Treatment of **11a** with *p*-toluenesulfonic acid in refluxing benzene furnished a mixture of the corresponding enol benzoate (**13a**) and 3-oxo-1,2,3,4-tetrahydrodibenz[*a,h*]anthracene. This difficulty was avoided by converting **11a** to the corresponding diacetate ester **11b** through basic methanolysis followed by acetylation with acetic anhydride and pyridine. Acid-catalyzed elimination of **11b** followed by treatment of the crude product with isopropenyl acetate and acetic anhydride afforded the pure enol acetate, 3-acetoxy-1,2-dihydrodibenz[*a,h*]anthracene (**13b**), as a white solid, mp 232–233 °C (79%). Dehydrogenation with DDQ provided 3-acetoxydibenz[*a,h*]anthracene (**14b**). Treatment of the latter with *n*-butyllithium in refluxing ether afforded cleanly 3-hydroxydibenz[*a,h*]anthracene (**14a**), mp 288–290 °C.

Discussion

The syntheses of the 1,2- and 3,4-dihydro diols (**3a** and **1a**) and the corresponding diol epoxides (**4** and **2**) reported provide relatively convenient methods for preparation of these biologically important derivatives of DBA. Thus, **2** is obtained from DBA in nine steps in 19% overall yield, and **3a** is obtained in only three additional steps from the 1,2-dibenzoate ester intermediate **10** in 69% yield, affording a net overall yield of **3a** of 11% from DBA.

The structural assignments of the dihydro diols and the related diol epoxide derivatives are supported by their proton NMR spectra (Table I). Comparison of the spectra of the 1,2- and 3,4-dihydro diols reveals the anticipated downfield shift of the bay-region benzylic and vinylic protons of **3a** and **1a**, respectively, due to steric interaction with the H_{14} aromatic protons. Thus, the H_4 benzylic signal of **1a** is found at δ 5.61 and the H_4 vinylic proton of **3a** is found at δ 6.76, while the analogous H_1 vinylic signal of **1a** is displaced downfield to δ 7.5. A similar effect was evident in the spectra of the corresponding dibenzoate esters, the H_1 protons of which were shifted into the aromatic region, preventing their accurate assignment. In further confirmation of the assignments, the spectrum of **3b** agreed with that reported by Karle et al.[8] for this diester; the spectra of all other compounds in Table I were not previously reported. The observed coupling patterns of the vinylic, allylic, and benzylic protons were also consistent with these assignments.

Previous NMR[23-26] and X-ray crystallographic[27] studies support the existence of bay-region trans dihydro diols of polycyclic arenes in the exclusive diaxial conformation. $J_{1,2}$ values of **3a** and **3b** are 2 Hz, in good agreement with the experimentally determined and theoretically calculated couplings for the diequatorial protons of a diaxial conformer.[27] The notably larger values for $J_{3,4}$ of **1a** and **1b** (11 and 7 Hz, respectively) indicate existence of these isomers as an equilibrium mixture predominantly in the diequatorial conformation. The observed stereoselectivity of epoxidation of **3a** is consistent with previous findings that anti-stereospecific epoxidation only occurs on vicinal trans dihydro diols free to adopt the diequatorial conformation.[3b,23-26]

Several features of these syntheses are deserving of comment. The observed propensity of 7,14-dihydrodibenz[*a,h*]anthracene to undergo reduction to the hexahydro stage is readily understood as a consequence of the poor solubility of the hydrocarbon in THF–ammonia at −33 °C coupled with the tendency of the two naphthalene ring components of 7,14-dihydrodibenz[*a,h*]anthracene to undergo reduction independently of one another. It is predicted that structurally analogous hydrocarbons, such as dibenz[*a,j*]anthracene, should exhibit a similar facility of multiple-stage reduction. Preferential formation of **11a** over **10** from base-catalyzed isomerization of 1,4,7,8,11,14-hexahydrodibenz[*a,h*]anthracene followed by Prévost reaction is interpreted as primarily a consequence of steric interference in the bay region of the hydrocarbon to proton abstraction at the 1-position. As a consequence, proton abstraction is preferentially favored in the 4-position, leading to formation of the conjugated olefin in the nonbay region. A similar effect was noted earlier in the analogous reactions of 1,4,7,12-tetrahydrobenz[*a*]-anthracene.[1b,13]

Bioactivity

Biological evidence supports the bay-region diol epoxide **2** as the ultimate carcinogenic metabolite of DBA. The

(17) Syntheses of all the monohydroxy derivatives of DBA except **14a** have been described.[18-22]

(18) Cook, J. W. *J. Chem. Soc.* **1931**, 3273.
(19) Cook, J. W.; Schoental, R. *J. Chem. Soc.* **1952**, 9.
(20) LaBudde, J. A.; Heidelberger, C. *J. Am. Chem. Soc.* **1958**, *80*, 1225.
(21) Boyland, E.; Sims, P. *Biochem. J.* **1965**, *97*, 7.
(22) Fu, P. P.; Harvey, R. G.; Beland, F. *Tetrahedron* **1978**, *34*, 857.
(23) Harvey, R. G.; Lee, H. M.; Shyamasundar, N. *J. Org. Chem.* **1979**, *44*, 78. Although stereospecific epoxidation of the benzo[*e*]pyrene 9,10-trans dihydro diol was reported initially, subsequent studies in our laboratory have led to detection of variable amounts of the syn isomer as a coproduct.
(24) Lehr, R. E.; Taylor, C. W.; Kumar, S.; Mah, H. D.; Jerina, D. M. *J. Org. Chem.* **1978**, *43*, 3462.
(25) Lehr, R. E.; Schaefer-Ridder, M.; Jerina, D. M. *J. Org. Chem.* **1977**, *42*, 736.
(26) Fu, P. P.; Harvey, R. G. *J. Chem. Soc., Chem. Commun.* **1978**, 585.
(27) Zacharias, D.; Glusker, J. P.; Fu, P. P.; Harvey, R. G. *J. Am. Chem. Soc.* **1979**, *101*, 4043.

anti diol epoxide **2** is found to strongly inhibit infectious ϕX174 viral DNA replication in *E. coli* spheroplasts,[28] while the isomeric syn and anti diol epoxide derivatives (**4**) exhibit only weak borderline activity. Under the standard experimental conditions, **2** gave 66% inhibition of viral replication; in comparison, the analogous bay-region anti diol epoxide of benzo[a]pyrene, the most active compound tested to date, showed >99% inhibitory activity.[28,29] Buening et al.[30] and Slaga et al.[31] report the 3,4-dihydro diol of DBA to be somewhat less tumorigenic than DBA on mouse skin and in newborn mice, while the 1,2- and 5,6-dihydro diols exhibit weak or no activity. The related diol epoxide derivative **2** is found to be only weakly carcinogenic on mouse skin.[31] The only bay-region diol epoxide tested so far that exhibits greater activity than the parent hydrocarbon is derived from benz[a]anthracene.[32,33] The relatively weak activity of the diol epoxides in animal experiments is very likely a consequence of indiscriminant interaction of these reactive molecules with water, proteins, and other nucleophiles before they can reach the critical cellular target (presumably DNA).[31]

Experimental Section

General Procedures. Dibenz[a,h]anthracene (DBA) was purchased from Eastman Kodak Co. 7,14-Dihydrodibenz[a,h]-anthracene (**7**) was synthesized through lithium–ammonia reduction of DBA.[13] *N*-Bromosuccinimide (NBS) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) were supplied by Arapahoe Chemical Co.; NBS was crystallized from water prior to use. *m*-Chloroperbenzoic acid was obtained from Aldrich Chemical Co. and was purified by washing with a phosphate buffer of pH 7.5 and drying under reduced pressure.

Reductions in liquid ammonia were conducted by utilizing standard procedures and conditions developed in earlier metal–ammonia reduction studies.[13,14] Precautions for the exclusion of moisture and atmospheric oxygen were scrupulously followed; ammonia was distilled into the reaction vessel through a column of barium oxide (10–20 mesh); reductions were carried out under helium. Tetrahydrofuran (THF) was freshly distilled from $LiAlH_4$.

The NMR spectra were obtained on a Varian T60 or a Bruker HX270 spectrometer with tetramethylsilane as an internal standard in $CDCl_3$ unless specified otherwise. Melting points are uncorrected. All new compounds gave satisfactory microanalyses for C and H (within ±0.3%) and/or mass spectra consistent with the assigned structure.

1,4,7,8,11,14-Hexahydrodibenz[a,h]anthracene (9). Lithium metal (1.68 g, 240 mmol) was added to a solution of **7** (13.56 g, 48 mmol) in THF (800 mL) and ammonia (800 mL), and the resulting purple solution was stirred at reflux for 1 h. The color was discharged by addition of excess solid NH_4Cl followed by water. Partition of the solution between ether and water and conventional workup afforded **9** as a white solid (13.5 g, 99%). Crystallization from benzene–hexane gave pure **9** as white needles: mp 227–228 °C; NMR δ 3.35 (s, 8, $H_{1,4,8,11}$), 3.83 (s, 4, $H_{7,14}$), 5.85 (s, 4, $H_{2,3,9,10}$), 6.95 (app d, 4, $H_{5,6,12,13}$).

Isomerization of 9. To a solution of **9** (14 g, 50 mmol) in degassed Me_2SO (1 L) was added NaOMe (3.61 g, 68 mmol). The solution was stirred at ambient temperature under N_2 for 16 h; then ice water was added and the product extracted with ether. The ether fraction was washed with water (4×), dried, and evaporated to afford mixed hexahydrodibenz[a,h]anthracene isomers (13.5 g, 96%): NMR δ 2.3 (broad signal, 4, allylic), 2.72 (app t, 4, benzylic), 3.9 (app s, 4, $H_{7,14}$), 5.7–6.8 (m, 4, vinylic), 6.8–7.2 (m, 4, aromatic). This product was used directly in the next step.

Prévost Reaction of Hexahydrodibenz[a,h]anthracene Isomers. A mixture of silver benzoate (20.61 g, 90 mmol) and I_2 (11.43 g, 45 mmol) in dry benzene (1.5 L) was stirred under reflux until the red color disappeared. A solution of the above mixed hexahydrodibenz[a,h]anthracene isomers (13.5 g, 48 mmol) in dry benzene (100 mL) was added, and the resulting suspension was stirred at reflux for 16 h. The product was filtered hot and the precipitate washed with hot ethyl acetate. The combined filtrate was evaporated, and the residue was dissolved in benzene and chromatographed on Florisil. Elution with hexane gave unreacted hexahydrodibenz[a,h]anthracene (0.8 g). Further elution with benzene afforded the crude mixed trans diol dibenzoates of octahydrodibenz[a,h]anthracene (24.4 g, 94%): NMR δ 2.0–3.2 (m, 2, aliphatic), 3.9 (s, 4, $H_{7,14}$), 5.4–7.2 (m, 4, vinylic and carbinol), 7.0–7.5 (m, 10, aromatic), 7.75–8.1 (m, 4, aromatic).

***trans*-1,2- and -3,4-Bis(benzoyloxy)-1,2,3,4-tetrahydrodibenz[a,h]anthracenes (10 and 11a).** To a solution of the mixed dibenzoate esters from the previous reaction (6.34 g, 12 mmol) in dry benzene (0.5 L) under N_2 was added DDQ (6.0 g, 26 mmol) with stirring, and the resulting solution was heated at reflux for 1 h. The hot solution was filtered through Celite and washed in with hot benzene. The combined filtrate was evaporated, and the residue was chromatographed on Florisil. Elution with benzene afforded pure **11a** (4.1 g). Further elution with benzene–ether (9:1) furnished a mixture of **10** and **11a** (1.55 g) which were separated by fractional crystallization. The predominant isomer **11a** crystallized from ether as pale yellow leaflets, mp 199–200 °C, while the minor isomer **10** was obtained from ether as pale yellow flakes, mp 202–203 °C (lit.[8] mp 164–166 °C). Yields of pure **11a** and **10** were 71% and 18%, respectively. NMR of **11a**: δ (acetone-d_6) 2.55 (m, 2, H_2), 3.55 (app t, 2, H_1), 5.75 (m, 1, H_3), 6.65 (d, 1, H_4, $J_{3,4}$ = 5.8 Hz), 7.2–8.2 (m, 7, aromatic), 8.41 (s, 1, H_{14}), 8.8 (m, 1, H_8), 9.12 (s, 1, H_7). NMR of **10**: δ (acetone-d_6) 2.5 (m, 2, H_3), 3.2 (m, 2, H_4), 5.8 (m, 1, H_2), 7.0–8.15 (m, 8, H_1 and aromatic), 8.4 (s, 1, H_{14}), 8.63 (m, 1, H_8), 9.15 (s, 1, H_7).

***trans*-3,4-Bis(benzoyloxy)-3,4-dihydrodibenz[a,h]-anthracene (1b).** A suspension of NBS (1.17 g, 6.6 mmol) in a solution of **11a** (2.86 g, 5.5 mmol) and benzoyl peroxide (10 mg) in CCl_4 (250 mL) was heated at reflux under N_2 and a heat lamp (10 min) for 1 h. Conventional workup gave the crude 1-bromo derivative of **11a** (3.2 g) as a yellow solid: NMR δ 2.7–3.3 (m, 2, H_2), 5.6–6.3 (m, 2, $H_{3,4}$), 6.8–8.1 (m, 21, H_1 and aromatic). This compound was dissolved in THF (300 mL) and chilled to 0 °C, and DBN (9 mL) was added dropwise with stirring. The resulting solution was stirred at 4 °C for 3.5 h; then ethyl acetate (400 mL) and ether (200 mL) were added, and the solution was extracted successively with water, 5% aqueous acetic acid, water, dilute $NaHCO_3$ solution, and water, dried, and concentrated. Trituration with ether provided **1b** (1.95 g, 68%) as a white solid, mp 239–240 °C; NMR data in Table I.

***trans*-3,4-Dihydroxy-3,4-dihydrodibenz[a,h]anthracene (1a).** Sodium methoxide (675 mg, 12.5 mmol) was added to a solution of **1b** (1.35 g, 2.51 mmol) in THF (100 mL) and methanol (50 mL) under N_2, and the solution was heated at reflux for 15 min, cooled, and partitioned between ether and water. The combined ether extracts were dried, evaporated to dryness, and triturated with ether to afford **1a** (415, 53%): mp 278–280 °C; NMR (Me_2SO-d_6/D_2O) δ 7.6–8.3 (m, 7, aromatic), 8.9 (s, 1, H_{14}), 9.0 (m, 1, H_8), 9.4 (s, 1, H_7) (cf. Table I for other NMR data).

***trans*-3,4-Dihydroxy-*anti*-1,2-epoxy-1,2,3,4-tetrahydrodibenz[a,h]anthracene (2).** A solution of **1a** (55 mg, 0.18 mmol) and *m*-chloroperbenzoic acid (550 mg) in 25 mL of dry THF was stirred under N_2 at room temperature for 1.5 h. The solution was diluted with ether, washed with 10% aqueous NaOH and with water, and dried. Evaporation of the solvent (avoiding heat) followed by trituration with ether gave **2** (50 mg, 85%) as a white

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(29) In this assay, the hydrocarbon derivatives are incubated initially with the infectious viral nucleic acid; then unreacted hydrocarbon is washed out and infectivity of the treated DNA is assayed by incubation with *E. coli* spheroplasts and counting viral plaque formation on agar plates. While the parent hydrocarbons are generally inactive, arene oxides, diol epoxides, and other hydrocarbon derivatives capable of alkylation of nucleic acids exhibit significant inhibitory activity.

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solid which crystallized from dry Me_2SO/acetone (avoiding heat) as needles: mp 196–197 °C; NMR (Me_2SO-d_6/acetone-d_6) 270 MHz δ 7.47–8.19 (m, 7, aromatic), 8.82 (d, 1, H_8), 8.94 (s, 1, H_{14}), 9.27 (s, 1, H_7) (cf. Table I for other NMR data).

***trans*-1,2-Bis(benzoyloxy)-1,2-dihydrodibenz[*a*,*h*]anthracene (3b).** Dehydrogenation of **10** (323 mg, 0.62 mmol), through bromination with NBS, and dehydrobromination with DBN were carried out by the procedures employed for the analogous reactions of **11a**; the only modifications were omission of the heat lamp and an increase in the reaction time of the second stage to 16 h. Similar workup furnished **3b** (300 mg, 94%): mp 143–145 °C; NMR data in Table I.

***trans*-1,2-Dihydroxy-1,2-dihydrodibenz[*a*,*h*]anthracene (3a).** Methanolysis of **3b** (274 mg, 0.53 mmol) by the procedure employed for preparation of **1a** gave crude **3a**. Chromatography on Florisil and elution with benzene–ethyl acetate (4:1) gave pure **3a** (123 mg, 72%): mp 257–259 °C; NMR (acetone-d_6/D_2O) δ 7.28–8.18 (m, 7, aromatic), 8.91 (m, 2, $H_{8,14}$), 9.31 (s, 1, H_7) (cf. Table I for other NMR data).

***trans*-1,2-Dihydroxy-*anti*-(and *syn*)-3,4-epoxy-1,2,3,4-tetrahydrodibenz[*a*,*h*]anthracenes (4).** Epoxidation of **3a** by the procedure employed (trituration omitted) for **2** gave a product (72%) shown by NMR and high-pressure LC analysis to be a 3:1 mixture of the syn and anti isomers (cf. Table I for NMR data). Separation was accomplished on a Du Pont Zorbax SIL column (0.6 × 25 cm) eluted with 40% THF in heptane.

***trans*-3,4-Diacetoxy-1,2,3,4-tetrahydrodibenz[*a*,*h*]anthracene (11b).** A solution of **11a** (990 mg, 1.93 mmol) in 1 N NaOH (30 mL), THF (45 mL), and methanol (85 mL) was stirred at ambient temperature for 3 h. Solvent was stripped off, cold water was added, and the precipitate of crude tetrahydro diol (590 mg) was removed by filtration and dried. Acetylation with acetic anhydride (50 mL) and pyridine (12 mL) at room temperature overnight gave **11b** (763 mg, 98%) as a pale yellow solid: mp 216–217 °C (lit.[8] mp 195–196 °C); NMR δ 2.03 (s, 3, CH_3), 2.15 (s, 3, CH_3), 2.33 (m, 2, H_2), 3.36 (t, 2, H_1), 5.12 (q, 1, H_3), 6.17 (d, 1, H_4, $J_{3,4}$ = 6 Hz), 7.4–8.04 (m, 7, aromatic), 8.36 (s, 1, H_{14}), 8.75 (m, 1, H_8), 9.05 (s, 1, H_7).

3-Acetoxy-1,2-dihydrodibenz[*a*,*h*]anthracene (13b). A solution of **11b** (1.15 g, 2.9 mmol) and *p*-tosic acid (220 mg) in benzene (200 mL) was refluxed for 1.5 h. The solvent was then evaporated, isopropenyl acetate (200 mL) and acetic anhydride (15 mL) were added, and the solution was refluxed overnight. Conventional workup, followed by chromatography on Florisil and elution with benzene, gave **13b** as a white solid (745 mg, 79%): mp 232–233 °C (benzene); NMR δ 2.2 (s, 3, CH_3), 2.68 (t, 2, H_2), 2.55 (t, 2, H_1), 6.34 (s, 1, H_4), 7.08–8.0 (m, 7, aromatic), 8.37 (s, 1, H_{14}), 8.7 (m, 1, H_8), 9.0 (s, 1, H_7).

3-Acetoxydibenz[*a*,*h*]anthracene (14b). A solution of **13b** (745 mg, 2.2 mmol) and DDQ (522 mg, 2.3 mmol) in benzene (100 mL) was refluxed for 1.5 h. The hot solution was filtered, and the filtrate was concentrated and crystallized, affording **14b** (581 mg, 74%) as a white solid: mp 247–248 °C; NMR δ 2.36 (s, 3, CH_3), 7.16–8.08 (m, 9, aromatic), 8.68–8.91 (m, 2, $H_{1,8}$), 9.01 and 9.08 (2 s, 1, $H_{7,14}$).

3-Hydroxydibenz[*a*,*h*]anthracene (14a). A suspension of **14b** (467 mg, 1.57 mmol) in a solution of *n*-butyllithium (2.3 mmol) in ether (50 mL) was heated at reflux for 1 h. The usual workup followed by chromatography on Florisil (elution with benzene) afforded crude **14a**. Crystallization from THF–benzene gave pure **14a** (450 mg, 98%): mp 288–290 °C; NMR (acetone-d_6/D_2O) δ 7.16–8.15 (m, 9, aromatic), 8.7–9.05 (m, 2, $H_{1,8}$), 9.16 and 9.22 (2 s, 2, $H_{7,14}$).

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Registry No. 1a, 66267-19-4; **1b**, 72378-81-5; **2**, 70951-81-4; **3a**, 66267-18-3; **3b**, 66302-72-5; **4**, isomer 1, 72378-82-6; **4**, isomer 2, 72402-37-0; **9**, 72378-83-7; **10**, 66267-13-8; **11a**, 72378-84-8; **11a**, 1-bromo derivative, 72378-85-9; **11b**, 66267-14-9; **13b**, 72378-86-0; **14a**, 1421-80-3; **14b**, 72378-87-1; hexahydrodibenz[*a*,*h*]anthracene isomers, 72390-47-7; octahydrodibenz[*a*,*h*]anthracene mixed trans diol benzoates, 72390-49-9.

Expedient Synthesis of Racemic and Optically Active *N*-Norreticuline and N-Substituted and 6′-Bromo-*N*-norreticulines[1]

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Practical methodology, utilizing unprotected diphenolic intermediates, is described for the synthesis of crystalline (±)-*N*-norreticuline, and a number of *N*-substituted and 6′-bromo congeners, which are versatile starting materials for alkaloidal syntheses. This sequence includes a simple high-yielding optical resolution of the key intermediate, (±)-*N*-norreticuline, and is readily amenable to synthesis of large quantities of these 1-benzyl-1,2,3,4-tetrahydroisoquinolines in racemic and chiral form. Thermal condensation of the readily available (from vanillin) 2-(4-hydroxy-3-methoxyphenyl)ethylamine with (3-hydroxy-4-methoxyphenyl)acetic acid afforded the amide (90%) which was transformed to (±)-*N*-norreticuline–*p*-toluenesulfonic acid–1-water (80%) via 1,2-dehydro-*N*-norreticuline generated in situ. Direct conversion of (±)-*N*-norreticuline to the *N*-carbethoxy and *N*-formyl derivatives in >90% yield is reported as is direct regioselective bromination of these compounds to the corresponding 6′-bromo compounds. Rotomers of these *N*-acyl derivatives were detected by NMR, and in the case of the *N*-formyl compounds the rotomers were separable by TLC. Direct bromination of (±)-*N*-norreticuline afforded the 6′-bromo base in 93% yield. The racemate and optical isomers of reticuline and the racemate of the 6′-bromo compound were readily obtained in >90% yield by borane reduction of the corresponding diphenolic *N*-formyl-*N*-nor derivatives. The racemate of tetrahydropapaveroline–hydrogen bromide and the 6′-bromo compound was obtained (>90%), in addition to the optical isomers of the former, by O-demethylation of the corresponding *N*-norreticuline derivatives.

The 1-benzyl-1,2,3,4-tetrahydroisoquinolines (BTIQ) *N*-norreticuline (**1**), reticuline (**2**), and their congeners are valuable intermediates for biomimetic and other syntheses of a large number of isoquinoline alkaloids and related