# Synthesis of Dihydrodiols and Diol Epoxides of Dibenz[a,h]acridine

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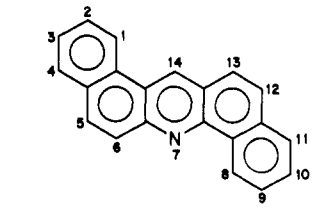
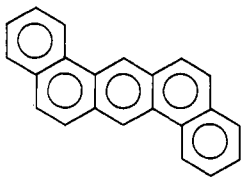
*trans*-1,2-Dihydroxy-1,2-dihydrodibenz[*a*,*h*]acridine (**5**), *trans*-3,4-dihydroxy-3,4-dihydrodibenz[*a*,*h*]acridine (**6**), *trans*-8,9-dihydroxy-8,9-dihydrodibenz[*a*,*h*]acridine (**7**), 3α,4β-dihydroxy-1α,2α-epoxy-1,2,3,4-tetrahydrodibenz[*a*,*h*]acridine (**9**), and 3α,4β-dihydroxy-1β,2β-epoxy-1,2,3,4-tetrahydrodibenz[*a*,*h*]acridine (**10**), which are potentially proximate and ultimate carcinogens of dibenz[*a*,*h*]acridine (**1**), are synthesized from a common intermediate 8,9,10,11-tetrahydrodibenz[*a*,*h*]acridine (**13**). The Birch reduction of **13** produced an intermediate which has been used in preparing **5** and **6**. However, the bromination of **13** followed by dehydrobromination resulted in a mixture of isomeric alkenes which was successfully converted to **7**. $^1$H NMR, UV, and mass spectra of dibenz[*a*,*h*]acridine derivatives are reported.

Dibenz[*a*,*h*]acridine (**1**) is an aza-polynuclear aromatic hydrocarbon (aza-PAH) with significant carcinogenic activity.[2,3] It is structurally analogous to carcinogenic dibenz[*a*,*h*]anthracene (**2**)[2,4] which is believed to be metabolically activated via bay-region diol epoxides (**3** and **4**).[5,6]



**1**



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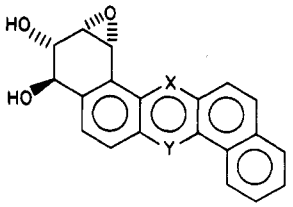
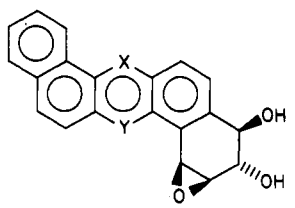


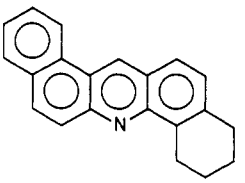
**3**, X = Y = CH
**9**, X = CH; Y = N
**11**, X = N; Y = CH



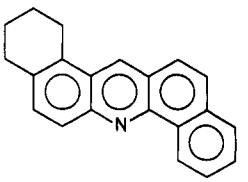
**4**, X = Y = CH
**10**, X = N; Y = CH
**12**, X = CH; Y = N

Since the bay-region diol epoxides of various aza-PAHs are suggested to be involved in the major portion of their carcinogenic activity,[8-11] it is likely that **1** is also metabolically activated via bay-region diol epoxide(s). Interestingly, **1** is an excellent model compound for studying the electronic effect of nitrogen on the mutagenicity/carcinogenicity of bay-region diol epoxides, because it has two bay regions. Most likely, the bay-region diol epoxide derived from the 8,9,10,11-benzo ring of **1** will be more electrophilic and, consequently, more biologically active (based on bay-region theory[22]) than that derived from the 1,2,3,4-benzo ring due to the following electronic reasons: (1) the carbonium ion at C-8 generated by the cleavage of the oxirane ring is not delocalized on nitrogen, whereas the similarly generated positive charge at C-1 is, and (2) the carbonium ion generated C-8 can be stabilized via field effect from nitrogen lone pair, whereas the similarly generated carbonium ion at C-1 cannot be. This prediction also agrees with that made on the basis of the perturbational molecular orbitol calculations.[12] In order to test this hypothesis and to pursue the mechanism by which **1** expresses its mutagenicity/carcinogenicity, we require all metabolically possible non-K-region dihydrodiols **5–8** and diastereomeric bay-region diol epoxides **9–12** of **1**.

In an earlier paper,[12] we reported a highly regiospecific synthesis of *trans*-10,11-dihydroxy-10,11-dihydrodibenz[*a*,*h*]acridine (**8**) and its diastereomeric epoxides **11** and **12** from 8,9,10,11-tetrahydrodibenz[*a*,*h*]acridine (**13**). The present paper reports the synthesis of dihydrodiols **5–7** and diastereomeric diol epoxides **9** and **10** from a common starting material **13**. A quite different approach to the synthesis of dihydrodiols **5** and **6** has been followed due to paucity of the corresponding 1,2,3,4-tetrahydrodibenz[*a*,*h*]acridine (**14**) as a starting intermediate.



**13**



**14**

## Results and Discussion

The methods successfully used to prepare the non-K-region dihyrodiols of benz[*c*]acridine,[13,14] dibenz[*c*,*h*]-acridine,[15] 7-methylbenz[*c*]acridine,[16] and dibenz[*a*,*h*]-acridine[12] employ the corresponding tetrahydro derivatives of these aza-PAHs as starting point. Therefore, 1,2,3,4-tetrahydrodibenz[*a*,*h*]acridine (**14**) was initially selected as a starting material for the synthesis of dihydrodiols **5** and **6**. However, due to the difficulty associated with the synthesis of **14** in large quantity through condensation reactions,[17] an alternate approach for the synthesis of **5**

(1) Post-doctoral Research Associate, 1984.
(2) Dipple, A.; Moschel, R. C.; Bigger, A. H. *Chemical Carcinogens, Second Edition*; Searle, C. E., Ed.; American Chemical Society Monograph 182, American Chemical Society: Washington, D.C., 1984; pp 41–163.
(3) Andervont, B. H.; Shimkin, M. B. *J. Natl. Cancer Inst.* **1940**, *1*, 225.
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(7) Lee, H. M.; Harvey, R. G. *J. Org. Chem.* **1980**, *45*, 588.
(8) Wood, A. W.; Chang, R. L.; Levin, W.; Ryan, D. E.; Thomas, P. E.; Lehr, R. E.; Kumar, S.; Schaefer-Ridder, M.; Engelhardt, U.; Yagi, H.; Jerina, D. M.; Conney, A. H. *Cancer Res.* **1983**, *43*, 1956.
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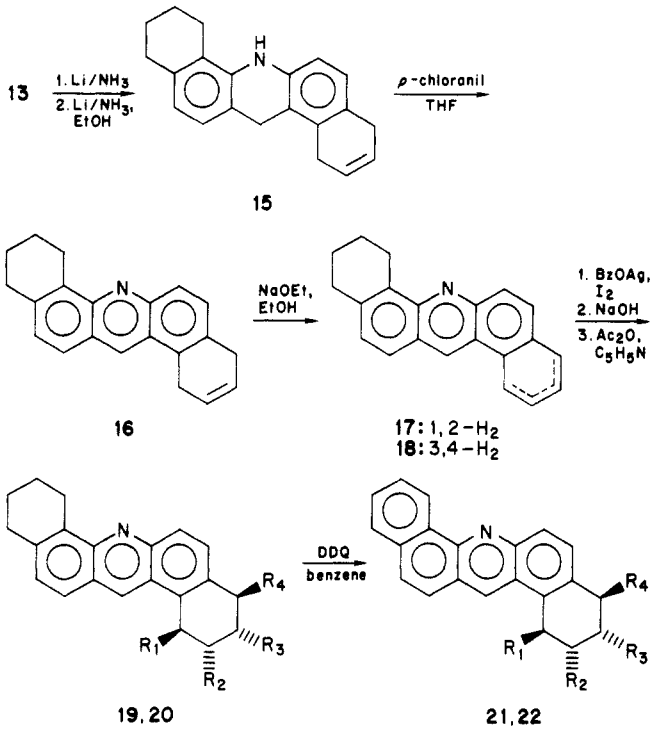
**Scheme I**[a]



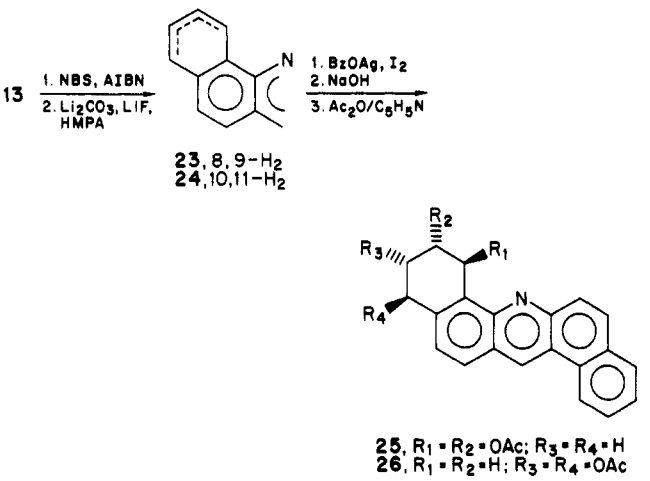

[a] For **19** and **21**: $R_1 = R_2 = H$; $R_3 = R_4 = OAc$. For **20** and **22**: $R_1 = R_2 = OAc$; $R_3 = R_4 = H$.

and **6** was investigated. Recently, Lee and Harvey[7] and Scaefer–Ridder and Engelhardt[18] developed another approach for the synthesis of non-K-region dihydrodiols of PAHs and aza-PAHs using parent compounds as starting point, because partially hydrogenated aromatic systems can be obtained by highly specific and selective Birch reduction. Therefore, the use of **1** as a starting point was investigated. However, this approach was not persued because of the complexicity of the reaction products and the carcinogenicity of the starting material **1** which is then required in relatively large quantities in order to isolate the desired products from the complex reaction mixture in substantial amounts.

During our studies with the Birch reduction of **1**, we also probed the possibility of using 8,9,10,11-tetrahydrodibenz[*a*,*h*]acridine (**13**)[19] as starting material that led to the successful synthesis of dihydrodiols **5** and **6**. Thus, the addition of 2 equiv of lithium to the suspension of **13** in liquid ammonia yielded the 7,8,9,10,11,14-hexahydro derivative **14**. To achieve further reduction in the angular 1,2,3,4-benzo ring, the hexahydro compound **14** was further reduced with $Li/NH_3$ in the presence of absolute EtOH to 1,4,7,8,9,10,11,14-octahydrodibenz[*a*,*h*]acridine (**15**). The purification of **15** by fractional recrystallization was inefficient and produced only a small amount of pure **15**. Therefore, the crude product was treated with an equimolar amount of *p*-chloranil at room temperature and the resulting product was purified via picrate to produce a 50% yield of pure 1,4,8,9,10,11-hexahydrodibenz[*a*,*h*]acridine (**16**) (Scheme I).

Isomerization of the isolated double bond of **16** with sodium ethoxide in absolute EtOH produced a 2.5:1 mixture of 1,2,8,9,10,11-hexahydrodibenz[*a*,*h*]acridine (**17**) and 3,4,8,9,10,11-hexahydrodibenz[*a*,*h*]acridine (**18**) in quantitative yield (Scheme I) as judged by the relative areas

**Scheme II**




of the peaks at $\delta$ 8.78 and 8.85 ($H_{14}$) in **17** and **18**, respectively, in the $^1H$ NMR spectrum of the reaction products. The predominant formation of **17** could conceivably be explained by assuming that the conjugative effect of the nitrogen atom makes the C-1 anion of **17** thermodynamically less stable than the corresponding anion at C-4. Since the separation of **17** and **18** at this stage was difficult to achieve due to their similar chromatographic properties, the mixture of alkenes **17** and **18** was converted to a mixture of *trans*-3,4-diacetoxy-1,2,3,4,8,9,10,11-octahydrodibenz[*a*,*h*]acridine (**19**) and *trans*-1,2-diacetoxy-1,2,3,4,8,9,10,11-octahydrodibenz[*a*,*h*]acridine (**20**) via prevost reaction with silver benzoate and iodine, followed by successive hydrolysis (NaOH/THF–MeOH) and acetylation ($Ac_2O$/pyridine) of the resulting mixture of *trans*-dibenzoates. Separation of **19** and **20** was readily achieved by column chromatography on dry column grade silica gel. In this manner **13** could be converted to **19** and **20** in 26% and 6% yields, respectively.

A variety of methods for aromatizing the 8,9,10,11-tetrahydrobenzo ring without affecting 1,2,3,4-tetrahydrobenzo ring of **19** and **20** were explored. The best yield of **21** and **22** (50%) was achieved by treating the corresponding octahydro derivatives **19** and **20** with an excess of DDQ in refluxing benzene.[20] Most likely, the steric hindrance caused by acetoxy groups prevents the aromatization of the substituted 1,2,3,4-tetrahydrobenzo ring of **19** and **20**. The use of DDQ in the selective dehydrogenation of other similarly substituted octahydro PAHs and aza-PAHs is, currently, under investigation.

The routes employed for the synthesis of *trans*-8,9-diacetoxy-8,9,10,11-tetrahydrodibenz[*a*,*h*]acridine (**25**) and *trans*-10,11-diacetoxy-8,9,10,11-tetrahydrodibenz[*a*,*h*]-acridine (**26**) were similar to those previously described for the analogous derivatives of benz[*c*]acridine[13] using **13** as the starting material (Scheme II). Bromination of **13** with NBS followed by dehydrobromination with $Li_2CO_3$, LiF/HMPA resulted in a 2:1 mixture of alkenes **23** and **24** with a conversion of 68% as judged by the relative areas of the peaks at $\delta$ 3.08 and 3.75 ($H_8$ and $H_{11}$, respectively, in alkenes **23** and **24**) in the $^1H$ NMR spectrum of the crude product. The conversion of the alkene mixture to a mixture of **25** and **26** was achieved in a similar manner as described for **19** and **20**. The separation of **25** and **26** by column chromatography on dry column grade silica gel was not effective because one of the compounds **25** slowly decomposed on the column to *trans*-8-hydroxy-9-acet-

(17) Buu-Hoi, N. P.; Jacquignon, P. *J. Chem. Soc.* **1951**, 2964.
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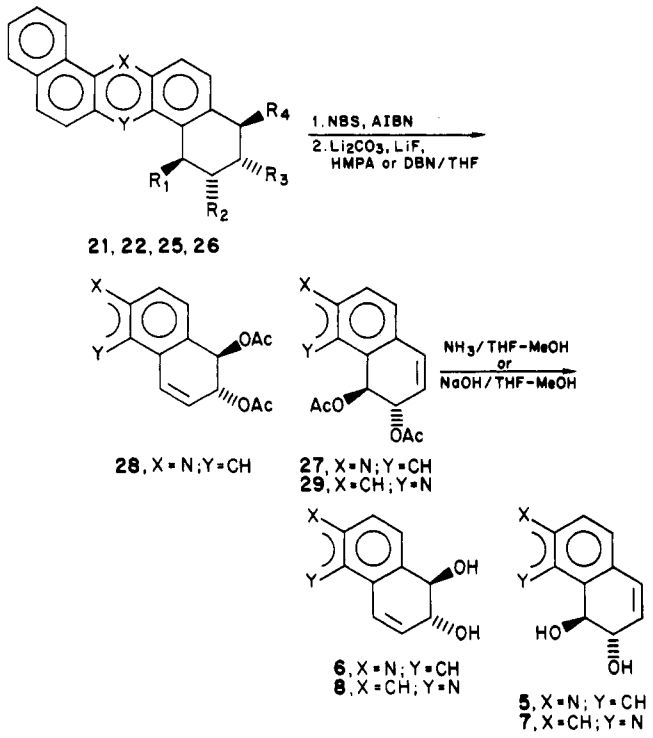
(19) Buu-Hoi, N. P. *J. Chem. Soc.* **1956**, 2593.
(20) Kumar, S. *Tetrahedron Lett.* **1985**, *26*, 6417.

**Scheme III**



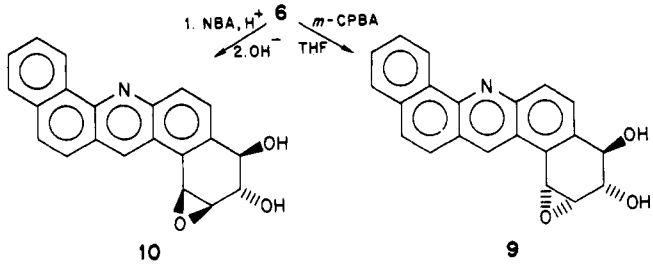

oxy-8,9,10,11-tetrahydrodibenz[a,h]acridine. However, this problem was resolved by replacing dry column grade silica gel with dry column grade neutral alumina. The overall yield of **25** and **26** based on **13** was 20% and 12.5%, respectively. The *trans*-tetrahydro diacetate **26** was found identical in all respects with that obtained by alternate procedures.[12]

As usual, the NBS treatment of **21**, **22**, and **25** was followed by dehydrobromination to yield *trans*-1,2-deacetoxy-1,2-dihydro-, *trans*-3,4-diacetoxy-3,4-dihyro-, and *trans*-8,9-diacetoxy-8,9-dihydrodibenz[a,h]acridines **27–29**, respectively (Scheme III). A better yield of **27** was obtained by using $Li_2CO_3$,LiF/HMPA in the dehydrobromination step; however, DBN was the most appripriate reagent in the preparation of **27** and **29**. Hydrolysis of **27–29** afforded the dihydro diols **5–7**, respectively, in moderate yields.

Treatment of the dihydro diol **6** with an excess of *m*-chloroperoxybenzoic acid in dry THF at room temperature produced the diastereomeric *anti*-diol epoxide **9** in 67% yield. In another two-step sequence, **5** was converted to bromo triol **30** in 80% yield upon treatment with *N*-bromoacetamide (NBA) in aqueous acidic THF, and the bromo triol **30** was then cyclized to diastereomeric *syn*-diol epoxide **10** in 67% yield (Scheme IV). The meso hydrogen ($H_{14}$) in **9** and **10** appeared as a clean sharp singlet at $\delta$ 9.66 and 9.53, respectively, and no cross contamination of **9** and **10**, which are readily separated on Analtech silica gel uniplates with EtOAc, could be detected. There was no evidence for the presence of *N*-oxide diol epoxide in either case as the high resolution mass spectra showed a molecular ion only at *m/e* 329, and the expected downfield shift of the bay hydrogen ($H_8$) in the $^1H$ NMR was not noticed.

$^1H$ NMR spectral data for the dibenz[a,h]acridine derivatives are given in the Experimental Section. The downfield absorption of the meso proton $H_{14}$ ($\delta$ 8.61–9.94) is noteworthy. The bay-region hydrogen atom $H_8$ on the aromatic benzo ring absorbs at very low field due to the presence of nitrogen in the same bay region. As noticed with the analogous dihydrodiols of benzo[c]acridine[13] and dibenz[c,h]acridine,[15] for dihydrodiol **7** the vicinal coupling

**Scheme IV**




constant is very large ($J_{8,9}$ = 12.3) and is consistent with the quasi-diaxial conformation of the carbinol protons that would occur if the hydroxyl group at C-8 is quasi-equaterial and hydrogen bonded to nitrogen atom. The $^1H$ NMR spectral data of the other derivatives of **1** were consistent with the analogous derivatives of aza-PAHs reported in the literature.[12-16]

UV spectra and EtOH solution (containing 5% THF) of various dihydro diols **5–7** are given in the Experimental Section.

Preliminary studies[21] in our laboratory have indicated that the dihydrodiols **5** and **7** are the major metabolites produced in ca. 1:1 ratio when **1** is incubated with rat liver microsomes. In a separate study, the preliminary results indicate that the bay-region diol epoxides **11** and **12** are 25- to 50-fold more active than **9** and **10** toward mutant strains TA-98 and TA-100 of *Salmonella typhimurium*.[23] The studies on the metabolism of **1** and the biological activity of the diol epoxides and other derivatives of **1** are, currently, in progress and the results will be reported elsewhere.

## Experimental Section

Ultraviolet spectra were recorded on Perkin-Elmer Model Lambda-3 UV–vis spectrophotometer. $^1H$ NMR spectra were recorded on JOEL-270 FX and Bruker WF-360 spectrometers. The State University of New York at Buffalo and the Syracuse University high field NMR facilities were used for 270-MHz and 360-MHz spectra, respectively. Unless noted otherwise, $CDCl_3$ was used as the solvent. Coupling constants (*J*) are recorded in hertz (Hz) and chemical shifts in parts per million ($\delta$) with $Me_4Si$ as an internal standard. Mass spectra were obtained on KRATOS MS80RFA spectrometer at the Department of Biophysics, State University of New York, Buffalo. Elemental microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Dry column grade silica gel and neutral alumina were purchased from ICN Pharmaceuticals. Melting points are uncorrected. The designations $\alpha$ and $\beta$ are used to indicate relative stereochemistry.

**1,4,8,9,10,11-Hexahydrodibenz[a,h]acridine (16).** A solution of 8,9,10,11-tetrahydrobenz[a,h]acridine (**13**) (4.5 g, 0.016 mol)[19] in anhydrous THF (60 mL) was added dropwise to vigorously stirred liquid ammonia (800 mL). Lithium (225 mg, 0.032 mol) was added in small portions and the mixture was refluxed for 20 min. Ethanol (7 mL) was added followed by lithium (500 mg, 0.071 mol) in pieces. After adding each portion of lithium, a blue color appeared. After final addition of lithium, the mixture was refluxed until the blue color disappeared. After evaporation of ammonia, the residue was treated with water (300 mL) and the aqueous phase was extracted with ether (2 × 200 mL). The combined organic phase was washed with water (2 × 100 mL), dried ($Na_2SO_4$), filtered, and concentrated. A small portion of the resulting semisolid was recrystallized from $CH_2Cl_2$–petroleum

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(22) Jerina, D. M.; Lehr, R. E.; Yagi, H.; Hernandez, O.; Dansette, P. M.; Wislocki, P. G.; Wood, A. W.; Chang, R. L.; Levin, W.; Conney, A. H. In *In Vitro Metabolic Activation in Mutagenesis Testing*; deSerres, F. J., Fouts, J. R., Bend, J. R., Philpot, R. M., Eds.; Elsevier/North Holland Biomedical Press: Amsterdam, 1976; pp 159–177.

(23) Experiments performed by A. W. Wood, Hoffmann-LaRoche, Inc.

ether to yield pure **15**: 209–210 °C: $^1$H NMR (270 MHz) δ 1.77 ($H_{10}$, m), 1.88 ($H_9$, m), 2.52 ($H_8$, t), 2.71 ($H_{11}$, t), 3.33 ($H_{1,4}$, m), 3.98 ($H_{14}$, s), 5.74 ($H_7$, s), 5.89 ($H_{2,3}$, bs), 6.55 ($H_{12,13}$, m), 6.85 ($H_{5,6}$, m), $J_{8,9}$ = 6.6, $J_{10,11}$ = 6.0; mass spectrum, *m/e* 287 ($M^+$, base peak).

The major portion of the above semisolid (4.5 g) was dissolved in anhdrous THF (300 mL) and powdered *o*-chloranil (4.3 g) was added portionwise while the solution was stirred under Ar. After 45 min of stirring at room temperature, EtOAc (200 mL) was added, and the mixture was washed with 5% NaOH (3 × 100 mL) and water (2 × 100 mL), successively. The organic layer was dried ($Na_2SO_4$) and evaporated to dryness. The crude residue was purified via picrate to yield **16** (2.3 g, 51%) as a pale yellow crystalline solid of mp 210–212 °C: $^1$H NMR (270 MHz) δ 1.98 ($H_{9,10}$, m), 2.96 ($H_{11}$ m), 3.46 ($H_8$, m), 3.57 ($H_4$, m), 3.82 ($H_1$, m), 6.06 ($H_{2,3}$, m), 7.21–8.07 (4 H, m), 8.64 ($H_{14}$, s); mass spectrum, *m/e* 285 ($M^+$, base peak). Anal. Calcd for $C_{21}H_{19}N$: C, 88.42; H, 6.66; N, 4.91. Found: C, 88.64; H, 6.84; N, 4.72.

**Isomerization of 1,4,8,9,10,11-Hexahydrodibenz[*a*,*h*]acridine (16).** Sodium (3.0 g) was dissolved in absolute ethanol (350 mL) under Ar. Compound **16** (2.0 g) in anhydrous THF (50 mL) was added, and the solution was refluxed for 28 h. After evaporation of the most of the solvent, the residue was partitioned between EtOAc (250 mL) and water (250 mL). After removing the organic layer, the aqueous layer was extracted once with ethyl acetate (150 mL). The combined EtOAc extracts were washed with water (2 × 100 mL) and brine (1 × 100 mL), successively. After drying ($Na_2SO_4$), the EtOAc solution was concentrated in vacuo leaving a mixture of isomers **17** and **18** (2.0 g, 100%; ratio 2.5:1).

***trans*-1,2-Diacetoxy-1,2,3,4,8,9,10,11-octahydrodibenz[*a*,*h*]acridine (20) and *trans*-3,4-Diacetoxy-1,2,3,4,8,9,10,11-octahydrodibenz[*a*,*h*]acridine (19).** Silver benzoate (5.05 g, 0.022 mol) and iodine (2.9 g, 0.011 mol) were added to dry benzene (200 mL). As soon as the iodine color disappeared, the isomeric mixture of alkenes **17** and **18** (3.0 g, 0.01 mol) was added, and the mixture was gradually heated to reflux under Ar. After continuous refluxing for 6 h, the reaction mixture was cooled to room temperature and filtered. The benzene solution was concentrated to dryness to yield a mixture of dibenzoates as aerosol. The crude mixture of dibenzoates (3.80 g) was dissolved in THF (150 mL), MeOH (150 mL), and 20% NaOH (25 mL), and the dark solution was stirred at room temperature for 2 h under Ar. Most of the solvent was distilled in vacuo, and the residue was treated with water (250 mL). The solid which separated out was filtered, washed with water, and dried. The mixture of tetrahydrodiols thus obtained was added to a mixture of acetic anhydride (100 mL) and pyridine (25 mL). The solution was stirred at room temperature for 15 h under Ar. The reaction mixture was poured on to crushed ice (500 g) and stirred. The solid which separated out was filtered, washed with water, and dissolved in EtOAc (250 mL). The EtOAc solution was washed with saturated $NaHCO_3$ (2 × 100 mL) and water (1 × 100 mL). The organic layer was dried ($Na_2SO_4$), filtered, and concentrated to give a yellow solid. Chromatography of the crude product on dry column grade silica gel using 15% EtOAc–hexane as the developing solvent gave first 0.51 g (12%) of **20** [mp 207–209 °C (EtOAc): $^1$H NMR (270 MHz) δ 2.02 (3 H, s), 2.08 (3 H, s), 1.75–2.4 (6 H, m), 2.30–2.65 (4 H, m), 3.45 ($H_8$, m), 5.37 ($H_2$, dd), 6.65 ($H_1$, d), 7.23–8.19 (4 H, m), 8.61 ($H_{14}$, s), $J_{1,2}$ = 2.6, $J_{2,3}$ = 6.5; mass spectrum, *m/e* 403 ($M^+$, base peak), 343 ($M^+ - CH_3COOH$). Anal. Calcd for $C_{25}H_{25}NO_4$: C, 74.26; H, 6.31; N, 3.41. Found: C, 74.44; H, 6.20; N, 3.47.] and then 2.15 g (50.7%) of **19** [mp 193–194 °C (EtOAc): $^1$H NMR (270 MHz) δ 2.06 (3 H, s), 2.17 (3 H, s), 1.80–2.40 (6 H, m), 2.96 ($H_{11}$, m), 3.35 ($H_1$ m), 3.45 ($H_8$, m), 5.31 ($H_3$, m) 6.22 ($H_4$, d), 7.23–8.11 (4 H, m), 8.75 ($H_{14}$, s), $J_{3,4}$ = 5.30; mass spectrum, *m/e* 403 ($M^+$), 343 ($M^+ - CH_3COOH$). Anal. Calcd for $C_{25}H_{25}NO_4$: C, 74.79; H, 6.05; N, 3.48. Found: C, 74.44; H, 6.20; N, 3.47.].

***trans*-1,2-Diacetoxy-1,2,3,4-tetrahydrodibenz[*a*,*h*]acridine (22).** A mixture of octahydro diacetate **20** (0.29 g) and DDQ (0.6 g) in anhydrous benzene (60 mL) was refluxed with stirring under Ar for 3 h. More DDQ (0.2 g) was added, and the mixture was allowed to reflux for an additional 1 h. The mixture was cooled to room temperature and poured onto a small column of neutral alumina. The compound was eluted with EtOAc to give 0.133 g (46%) of colorless crystalline solid of mp 229–230 °C (EtOAc): $^1$H NMR (270 MHz) δ 2.03 (3 H, s), 2.10 (3 H, s), 2.10–2.40 ($H_3$, s), 2.90–3.33 ($H_4$, m), 5.39 ($H_2$, dd), 6.70 ($H_1$, d), 7.55–8.35 (7 H, m), 8.65 ($H_{14}$, s) 9.48 ($H_8$, m), $J_{1,2}$ = 3.0, $J_{2,3}$ = 6.5; mass spectrum, *m/e* 399 ($M^+$), 339 ($M^+ - CH_3COOH$), 297 (base peak). Anal. Calcd for $C_{25}H_{21}NO_4$: C, 75.18; H, 5.26; N, 3.50. Found: C, 74.75; H, 5.17; N, 3.43.

***trans*-1,2-Diacetoxy-1,2-dihydrodibenz[*a*,*h*]acridine (27).** A mixture of tetrahydro diacetate **22** (101 mg), NBS (49 mg), and AIBN (5 mg) in dry $CCl_4$ (20 mL) was refluxed for 15 min under Ar. The solution was cooled to 5 °C and filtered. The filtrate was concentrated under reduced pressure and the residue was triturated with a 1:1 mixture of ether–petroleum ether (5 mL). The resulting solid was collected by filtration and dried to give 97 mg (80%) of the 4-bromo derivative: mp 288–292 °C dec, which is likely to be a mixture of stereoisomers, as judged by complexity of the NMR spectrum. The 4-bromo derivative (90 mg) was dissolved in dry freshly distilled THF (10 mL) and the solution was cooled to 0 °C. DBN (0.25 mL) was added dropwise under Ar to this cold solution with occasional shaking. The mixture was kept at 5 °C for 30 h and then diluted with EtOAc (50 mL). The EtOAc layer was washed with cold water (3 × 25 mL), dried ($Na_2SO_4$), filtered, and evaporated under reduced pressure to yield a yellow solid which was recrystallized from EtOAc–hexane to give **27** as yellow crystals (55 mg, 73%) of mp 192–193 °C dec: $^1$H NMR (270 MHz) δ 2.02 (3 H, s), 2.06 (3 H, s), 5.48 ($H_2$, dd), 6.35 ($H_3$, dd), 6.95 ($H_1$, bs), 6.96 ($H_4$, dd), 7.60–7.95 (6 H, m), 8.42 (1 H, d), 9.45 ($H_{14}$, s), 9.48 ($H_8$, m), $J_{1,2}$ = 1.6, $J_{1,3}$ = $J_{2,4}$ = 2, $J_{2,3}$ = 5.5, $J_{3,4}$ = 9.6; high resolution mass spectrum, obsd 397.1325, calcd mass 397.1314.

***trans*-1,2-Dihydroxy-1,2-dihydrodibenz[*a*,*h*]acridine (5).** To a solution of dihydrodiol diacetate **27** (45 mg) in THF (10 mL) and MeOH (10 mL) was added 20% NaOH (0.5 mL), and the mixture was stirred at room temperature for 30 min under Ar. Most of the solvent was distilled under reduced pressure and then diluted with water (15 mL). A brown solid separated that was extracted with EtOAc (50 mL), and the EtOAc layer was washed with water (2 × 20 mL), dried ($Na_2SO_4$), and distilled under reduced pressure to give a yellow crystalline solid. The trituration of this solid with cold ether gave 26 mg (73%) of **5**: mp 246–248 °C dec; $^1$H NMR (270 MHz, $Me_2SO$-$d_6$–$CD_3OD$) δ 4.28 ($H_2$, m), 5.38 ($H_1$, bs), 6.29 ($H_3$, dd), 6.81 ($H_4$, d), 7.70–8.30 (7 H, m), 9.29 ($H_{14}$, s), 9.35 ($H_8$, m), $J_{1,2}$ = $J_{2,4}$ = 1.0, $J_{2,3}$ = 5.5, $J_{3,4}$ = 10; high resolution mass spectrum, obsd 313.1087, calcd mass 313.1103; UV (5% THF–EtOH) $\delta_{max}$ (ε) 225 (21 200), 243 (16 300), 282 (36 400, sh), 289 (52 500), 301 (36 900, sh), 348 (4800), 361 (5800), 366 (5600), 380 (8300), 411 (9000).

***trans*-3,4-Diacetoxy-1,2,3,4-tetrahydrodibenz[*a*,*h*]acridine (21).** A mixture of octahydrodiacetate **19** (0.30 g) and DDQ (0.6 g) in anhydrous benzene (60 mL) was refluxed with stirring, under Ar, for 3 h. More DDQ (0.2 g) was added, and the mixture was allowed to reflux for an additional 1 h. The reaction mixture was worked up as described for the preparation of **20**. The crude product was recrystallized from EtOAc to afford **21** as a light yelow crystalline solid of mp 229–230 °C: $^1$H NMR (270 MHz) δ 2.07 (3 H, s), 2.19 (3 H, s), 2.20–2.45 ($H_2$, m), 3.41 ($H_1$, m), 5.34 ($H_3$, m), 6.27 ($H_4$, d), 7.60–8.30 (7 H, m), 8.79 ($H_{14}$, s), 9.50 ($H_8$, m), $J_{3,4}$ = 5.3; high resolution mass spectrum, obsd 399.1371, calcd mass 399.1471.

**1-Bromo-3α,4β-diacetoxy-1,2,3,4-tetrahydrodibenz[*a*,*h*]acridine (31).** A mixture of tetrahydro diacetate **21** (185 mg), NBS (95 mg), and α,α′-azobis(isobutyronitrile) (AIBN, 5 mg), and dry $CCl_4$ (30 mL) was heated for 30 min at ca. 60–70 °C under a stream of Ar. The mixture was cooled and filtered and the filtrate was distilled under reduced pressure. The yellow solid thus obtained was triturated with ether–petroleum ether (1:1) to give 221 mg (99%) of yellow crystalline solid of mp 171–175 °C dec as a ca. 1:1 stereoisomeric mixture; β-bromo isomer [$^1$H NMR (270 MHz) δ 2.55–3.25 ($H_2$ m), 5.98 ($H_3$, m), 6.20 ($H_1$, m), 6.55 ($H_4$, d), $J_{2α,2β}$ = 13, $J_{2α,3β}$ = 8, $J_{2β,3β}$ = 4, $J_{3,4}$ = 9]; α-bromo isomer [$^1$H NMR (270 MHz) δ 2.55–3.25 ($H_2$, m), 5.36 ($H_3$, m), 6.20 ($H_1$, m) 6.28 ($H_4$, d), $J_{2α,3β}$ = $J_{2β,3β}$ = $J_{3β,4α}$ = 2.5].

***trans*-3,4-Diacetoxy-3,4-dihydrodibenz[*a*,*h*]acridine (28).** A mixture of **31** (220 mg), anhydrous $Li_2CO_3$ (0.72 g), and anhydrous LiF (0.5 g) in freshly distilled HMPA (15 mL) was stirred, under Ar, at 80–85 °C for 3 h. The mixture was cooled, diluted with ether (100 mL), and poured into a separatory funnel leaving most of the salt behind. The organic layer was washed with water

(4 × 75 mL), dried ($Na_2SO_4$), and distilled in vacuo to give a solid residue. Recrystallization from ethyl acetate gave **28** as a yellow crystalline solid: 130 mg (71%); mp 215–216 °C dec; $^1H$ NMR (270 MHz) $\delta$ 2.08 (3 H, s), 2.16 (3 H, s), 5.71 ($H_3$, dd), 6.36 ($H_2$, dd), 6.41 ($H_4$, d), 7.60 ($H_1$, d), 7.62–8.38 (7 H, m), 8.95 ($H_{14}$, s), 9.48 ($H_8$, d), $J_{1,2}$ = 9.8, $J_{2,3}$ = 4.3, $J_{3,4}$ = 6, $J_{8,9}$ = 7; high resolution mass spectrum, obsd 397.1304, calcd mass 397.1314.

***trans*-3,4-Dihydroxy-3,4-dihydrodibenz[*a*,*h*]acridine (6).** To a solution of dihydrodiol diacetate **28** (125 mg) in THF (20 mL) and MeOH (20 mL) was added 20% NaOH (1.2 mL), and the mixture was stirred at room temperature for 30 min under Ar. Most of the solvent was removed under reduced pressure and the residue was extracted with EtOAc–$H_2O$, 50 mL:30 mL). The EtOAc layer was separated, washed with water (1 × 20 mL), dried ($Na_2SO_4$), and concentrated under vacuum to give 70 mg (71%) of pure **6** of mp 264–266 °C dec: $^1H$ NMR (270 MHz, $Me_2SO$-$d_6$) $\delta$ 4.46 ($H_3$, m), 4.82 ($H_4$, d), 5.38 ($OH_4$, d), 5.78 ($OH_3$, d), 6.30 ($H_2$, dd), 7.47 ($H_1$, dd), 7.70–8.30 (7 H, m), 9.33 ($H_8$, m), 9.38 ($H_{14}$, s), $J_{1,2}$ = 10, $J_{1,3}$ = 1.6, $J_{2,3}$ = 2.3, $J_{3,4}$ = 11, $J_{3,OH}$ = 5.9, $J_{4,OH}$ = 5.3; mass spectrum, *m/e* 313 ($M^+$), 295 ($M^+ - H_2O$, base peak); UV (5% THF–EtOH) $\delta_{max}$ ($\epsilon$) 222 (24600, sh), 228 (30100), 280 (50200, sh), 289 (60300), 358 (5000), 369 (6100), 393 (5900).

**3$\alpha$,4$\beta$-Dihydroxy-1$\alpha$,2$\alpha$-epoxy-1,2,3,4-tetrahydrodibenz[*a*,*h*]acridine (9).** A mixture of **6** (24 mg) and purified *m*-CPBA (210 mg) in anhydrous THF (10 mL) was stirred at room temperature for 90 min under Ar. The mixture was diluted with ether, extracted with ice-cold 2% NaOH and water, dried ($Na_2SO_4$), and concentrated in vacuo to give diol epoxide **9** (17 mg, 67%) as a pale yellow solid of mp 199–201 °C dec: $^1H$ NMR (270 MHz, $Me_2SO$-$d_6$ + $CD_3OD$) $\delta$ 3.85 ($H_2$, d), 3.93 ($H_3$, d), 4.54 ($H_4$, d), 5.14 ($H_1$, d), 7.65–8.50 (7 H, m), 9.35 ($H_8$, m), 9.66 ($H_{14}$, s), $J_{1,2}$ = 4.5, $J_{2,3}$ = 0, $J_{3,4}$ = 9; high resolution mass spectrum, obsd 329.1073, calcd mass 329.1052.

**3$\alpha$,4$\beta$-Dihydroxy-1$\beta$,2$\beta$-epoxy-1,2,3,4-tetrahydrodibenz[*a*,*h*]acridine (10).** To a stirred solution of dihydrodiol **6** (95 mg) in THF (25 mL) at 0 °C was added $H_2O$ (5 mL), *N*-bromoacetamide (45 mg), and 1 drop of 4 N HCl under Ar. The solution was stirred at 0–5 °C for 30 min. EtOAc (50 mL) was added, and the organic layer was washed with water (2 × 15 mL), dried ($Na_2SO_4$), and then concentrated in vacuo to give bromo triol, 2$\alpha$-bromo-1$\beta$,3$\alpha$,4$\beta$-trihydroxy-1,2,3,4-tetrahydrodibenz[*a*,*h*]-acridine (**30**) as a colorless crystalline solid: 100 mg (80%); mp 211–212 °C dec; $^1H$ NMR (270 MHz, $Me_2SO$-$d_6$ + $CD_3OD$) $\delta$ 4.18 ($H_3$, dd), 4.66–4.82 ($H_{2,4}$, m), 5.72 ($H_1$, bs), 7.72–8.36 (7 H, m), 9.22 ($H_{14}$, s), 9.36 ($H_8$, m), $J_{1,2}$ = 1.5, $J_{2,3}$ = 2, $J_{3,4}$ = 8; high resolution mass spectrum, obsd 409.0327 and 411.0311, calcd mass 409.0313 and 411.0293.

To a stirred solution of bromo triol **30** (50 mg) in anhydrous THF (20 mL) was added Amberlite-400 (4 g) that had been converted to the hydroxide form. The mixture was stirred at room temperature, under Ar, for 2 h and quickly filtered, and the filtrate was concentrated under reduced pressure. The trituration of the colorless solid with 10% EtOAc–hexane gave diol epoxide **10** (27 mg, 67%) as a colorless solid of mp 233–235 °C dec: $^1H$ NMR (270 MHz, $Me_2SO$-$d_6$ + $CD_3OD$) $\delta$ 3.85 ($H_2$ m), 3.97 ($H_3$, dd), 4.75 ($H_4$, dd), 4.89 ($H_1$, d), 5.23 ($OH_4$, d), 5.69 ($OH_3$, d), 7.60–8.40 (7 H, m), 9.35 ($H_8$, m), 9.53 ($H_{14}$, s), $J_{1,2}$ = 4.3, $J_{2,3}$ = 2.0, $J_{3,4}$ = 6, $J_{3,OH}$ = 5, $J_{4,OH}$ = 7; high resolution mass spectrum, obsd 329.1071, calcd mass 329.1052.

***trans*-8,9-Diacetoxy-8,9,10,11-tetrahydrodibenz[*a*,*h*]-acridine (25).** A mixture of purified 8,9,10,11-tetrahydrodibenz[*a*,*h*]acridine (**13**) (2.83 g, 0.01 mol), NBS (1.95 g, 0.011 mol), and $\alpha$,$\alpha'$-azobis(isobutyronitrile) (AIBN, 20 mg) in dry $CCl_4$ (200 mL) was stirred for 30 min at 65–72 °C while bubbling Ar. The reaction mixture was cooled to 10 °C and filtered, the filtrate was evaporated to dryness in vacuo to give a mixture of 11-bromo-8,9,10,11-tetrahydrodibenz[*a*,*h*]acridine, and 8-bromo-8,9,10,11-tetrahydrodibenz[*a*,*h*]acridine as a pale yellow solid (3.25 g). The mixture of isomeric bromo derivatives (3.20 g) was dissolved in freshly distilled HMPA (25 mL) and an anhydrous mixture of $Li_2CO_3$ (6 g) and LiF (4 g) was added. The mixture was stirred at 80–85 °C for 3 h under Ar, cooled, diluted with water (200 mL), and extracted with ether (3 × 100 mL). The combined ether extracts were washed with water (5 × 100 mL), dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure to give 2.08 g of a 1:2 mixture of alkenes **23** and **24**. The alkene mixture (2 g) was dissolved in dry benzene (25 mL) and added, under Ar, to the reagent formed in situ from silver benzoate (3.1 g) and iodine (1.7 g) in dry benzene (150 mL). The reaction mixture was refluxed for 17 h, cooled to room temperature, and filtered. The evaporation of the benzene solution under reduced pressure gave a dark oil (3.23 g). This crude mixture of *trans*-8,9-bis(benzoyloxy)- and *trans*-10,11-bis(benzoyloxy)-8,9,10,11-tetrahydrodibenz[*a*,*h*]acridines was converted to a mixture of *trans*-8,9-diacetoxy- and *trans*-10,11-diacetoxy-8,9,10,11-tetrahydrodibenz-[*a*,*h*]acridines (**25** and **26**) in the same manner as described above for the preparation of the mixture of **19** and **20**. Chromatography of the resulting crude mixture of diacetates (1.4 g) on dry column grade neutral alumina using benzene as the developing solvent gave first 0.5 g (12.5%) of **26** (mp 210–212 °C, lit.[12] mp 211–212 °C) and then 0.8 g (20%) of **25** as pale yellow crystalline solid of mp 255–257 °C: $^1H$ NMR (360 MHz) $\delta$ 2.12–2.43 (2 H, m), 2.96–3.25 (2 H, m), 5.46 ($H_9$, m), 7.06 ($H_8$, d), 7.34–8.10 (7H, m), 8.75 ($H_1$, d), 9.37 ($H_{14}$, s), $J_{1,2}$ = 9, $J_{8,9}$ = 3. Anal. Calcd for $C_{25}H_{21}NO_4$: C, 75.18; H, 5.26; N, 3.50. Found: C, 74.80; H, 5.24; N, 3.25.

***trans*-8,9-Diacetoxy-8,9-dihydrodibenz[*a*,*h*]acridine (29).** The reaction of tetrahydro diacetate **25** (0.322 g, 0.008 mol), NBS (0.177 g, 0.01 mol), and AIBN (15 mg) was effected as described for **31**. Trituration of the crude product from ether (0 °C) gave 11-bromo derivative (0.48 g, 100%), which was probably a mixture of stereoisomers, as judged by the complexity of the $^1H$ NMR. The 11-bromo derivatives (0.48 g) was then dehydrobrominated by DBN (1 mL) in THF (50 mL) at 0–5 °C as described for the preparation of **27**. The crude product was recrystallized from EtOAc–hexane to give **29** (0.18 g, 67%) as a yellow crystalline solid of mp 212–213 °C dec: $^1H$ NMR (360 MHz) $\delta$ 1.99 (6 H, s), 5.56 ($H_9$, dd), 6.40 ($H_{10}$, dd), 6.91 ($H_{11}$, d), 7.34–8.14 (7 H, $H_1$, m), 8.72 ($H_1$, d), 9.35 ($H_{14}$, s), $J_{1,2}$ = 8.2, $J_{8,9}$ = 1.5, $J_{9,10}$ = 5.6, $J_{10,11}$ = 9.7; high resolution mass spectrum, obsd 397.1328, calcd mass 397.1314.

***trans*-8,9-Dihydroxy-8,9-dihydrodibenz[*a*,*h*]acridine (7).** Hydrolysis of dihydrodiol diacetate **29** (0.256 g) in THF (10 mL), MeOH (40 mL), and 20% NaOH (1 mL) was effected under Ar as described for **5**. The isolated product was triturated with ether to afford **7** as a yellow solid (0.169 g, 84%) of mp 150–152 °C dec. The product was found to be pure on the basis of TLC (EtOAc, $R_f$ 0.55): $^1H$ NMR (360 MHz, $CDCl_3$ + $CD_3OD$) $\delta$ 4.93 ($H_9$, dd), 5.70 ($H_8$, d), 6.28 ($H_{10}$, dd), 6.41 ($H_{11}$, d), 7.35–8.03 (7 H, m), 8.72 ($H_1$, d), 9.39 ($H_{14}$, s), $J_{1,2}$ = 7.7, $J_{8,9}$ = 12.3, $J_{9,10}$ = 1.5, $J_{9,11}$ = 2.7, $J_{10,11}$ = 10.0; UV (5% THF–EtOH) $\lambda_{max}$ ($\epsilon$) 222 (29200), 241 (24200), 288 (57700), 291 (57700), 346 (5800), 3671 (6600), 378 (8900), 398 (9800).

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