Synthesis of Enantiomerically Pure Bay-Region 3,4-Diol 1,2-Epoxide Diastereomers and Other Derivatives of the Potent Carcinogen Dibenz[c,h]acridine

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The four enantiomerically pure bay-region 3,4-diol 1,2-epoxide diastereomers of dibenz[c,h]acridine were synthesized from the corresponding pure *trans*-3,4-dihydroxy-3,4-dihydrodibenz[c,h]acridine enantiomers. Racemic *trans*-3,4-dihydroxy-3,4-dihydrodibenz[c,h]acridine (**7b**) was prepared from *trans*-3,4-bis(benzoyloxy)-1,2,3,4-tetrahydrodibenz[c,h]acridine (**3**) by conventional means. Tetrahydro diester **3** was obtained, along with the corresponding *trans*-1,2-tetrahydro diester **2**, by treatment of the dihydro derivatives resulting from chlorination and dehydrochlorination of 1,2,3,4-tetrahydrodibenz[c,h]acridine with AgOBz and I_2. Racemic **7b** was resolved via conversion to the diastereomeric bis(-)-menthoxy esters, separation of the diastereomers by HPLC, and hydrolysis of the individual diastereomers. Assignment of absolute stereochemistry to the enantiomers was achieved by examination of the exciton chirality interaction bands in the bis *p*-(dimethylamino)benzoate derivative of the tetrahydrodiol obtained by catalytic reduction of one of the enantiomers of **7b**. The bay-region tetrahydro epoxides, 1,2-epoxy-1,2,3,4-tetrahydrodibenz[c,h]acridine, were also obtained in enantiomerically pure form by hydrolysis and cyclization of the individual diastereomeric (-)-(*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl (MPTA) esters derived from the racemic bromohydrins. HPLC and NMR characteristics of the diastereomeric mono and bis esters of the bromohydrins, dihydrodiols, and tetrahydrodiols are discussed. The synthesis of 1,2-dihydrodiol **6b**, K-region oxide **23**, and K-region dihydrodiol **24** derivatives of dibenz[c,h]acridine are also described.

Within the past few years, strong evidence has been obtained that "bay-region"[1] diol epoxides are the major ultimate carcinogenic metabolites of a large number of polycyclic aromatic hydrocarbons (PAH).[2,3] The importance of these molecules has spawned a lively interest in their synthesis and their chemical and biological properties. The metabolic precursors of diol epoxides in mammalian cells are dihydrodiols with trans hydroxyl groups. Consequently, four stereoisomeric bay-region diol epoxides, comprised of two enantiomeric pairs of diastereomers (see Scheme III) are possible in mammalian systems. Selectivity in the metabolism of several PAH to the various bay-region diol epoxide stereoisomers[4] as well as the relative mutagenicity and tumorigenicity of the stereoisomers[2,5] has been determined. Tumor studies of racemic bay-region diol epoxides have revealed that isomer-2 diol epoxides, in which the benzylic hydroxyl group is trans to the oxirane oxygen atom are *generally* much more tumorigenic than the corresponding isomer-1 diol epoxides, in which the benzylic hydroxyl group is cis to the oxirane oxygen atom (Figure 1). Moreover, for benzo[a]pyrene (B[a]P), benz[a]anthracene (BA), and chrysene, the tumorigenic potency of the isomer-2 diol epoxides resides almost entirely in one enantiomer, the benzo ring of which is in all cases superimposable on the benzo[a]pyrene 7-(*R*),8(*S*)-diol 9(*S*),10(*R*)-epoxide-2 shown in Figure 1. The sole exception to the rule of significantly higher tumorigenicity of the isomer-2 diol epoxides at this time is benzo[c]phenanthrene,[6] in which the unusually tumorigenic isomer-1 diol epoxide prefers an uncharacteristic conformation in which the hydroxyl groups are pseudodiequatorial rather than pseudodiaxial. In the absence of unusual steric or electronic factors, bay-region diol epoxide-1 isomers generally prefer the conformation in which the hydroxyl groups are pseudodiaxial and the diol epoxide-2 isomers prefer the conformation in which the hydroxyl groups are pseudodiequatorial.[7]

Azapolycyclic aromatic hydrocarbons (aza-PAH) are also common environmental contaminants, and many have

(1) "Bay regions" exist in PAH when bonds in two nonfused benzene rings are fixed in an *s-cis*-butadiene conformation. Examples are the sterically hindered areas between C-4 and C-5 in phenanthrene, C-10 and C-11 in BaP, and C-1 and C-12 in BA. For the introduction of the term "bay region" to the field of PAH carcinogenesis, see: Jerina, D. M.; Daly, J. W. In "Drug Metabolism–from Microbe to Man"; Parke, D. V., Smith, R. L., Eds.; Taylor and Francis Ltd.: London, 1976; pp 13–32. 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"; de Serres, F. J., Fouts, J. R., Bend, J. R., Philpot, R. M., Eds.; Elsevier/North-Holland Biomedical Press: Amsterdam, 1976; pp 159–177.

(2) For a review of metabolism, tumorgenicity, and mutagenicity of PAH, see: Nordqvist, M.; Thakker, D. R.; Yagi, H.; Lehr, R. E.; Wood, A. W.; Levin, W.; Conney, A. H.; Jerina, D. M. In "Molecular Basis of Environmental Toxicity"; Bhatnagar, R. S., Ed.; Ann Arbor Science Publishers: Ann Arbor, MI, 1980; pp 329–357.

(3) For a recent review of the "bay region theory", with an emphasis on correlation with quantum chemical parameters, see: Lehr, R. E.; Wood, A. W.; Levin, W.; Conney, A. H.; Thakker, D. R.; Yagi, H.; Jerina, D. M. In "Polynuclear Aromatic Hydrocarbons: Physical and Biological Chemistry"; Cooke, M., Dennis, A. J., Fisher, G. L., Eds.; Battelle Press: Columbus, OH, 1982; pp 21–37. Sayer, J. M.; Lehr, R. E.; Whalen, D. L.; Yagi, H.; Jerina, D. M. *Tetrahedron Lett.* **1982**, *23*, 4431–4434.

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(7) See: Yagi, H.; Hernandez, O.; Jerina, D. M. *J. Am. Chem. Soc.* **1975**, *97*, 6881–6883. Whalen, D. L.; Ross, A. M.; Yagi, H.; Karle, J. M.; Jerina, D. M. *J. Am. Chem. Soc.* **1978**, *100*, 5218–5221. Sayer, J. M.; Yagi, H., Croisy-Delcey, M.; Jerina, D. M. *J. Am. Chem. Soc.* **1981**, *103*, 4970–4972.

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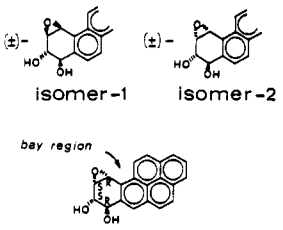


Figure 1. Diastereomeric diol epoxides-1 and -2. Absolute configuration of the most tumorigenic BaP bay-region diol epoxide.

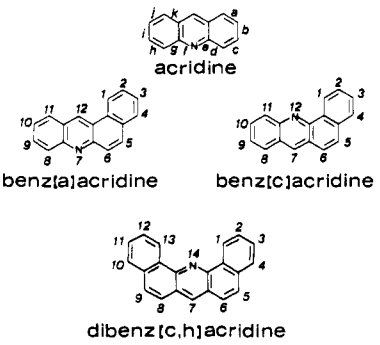
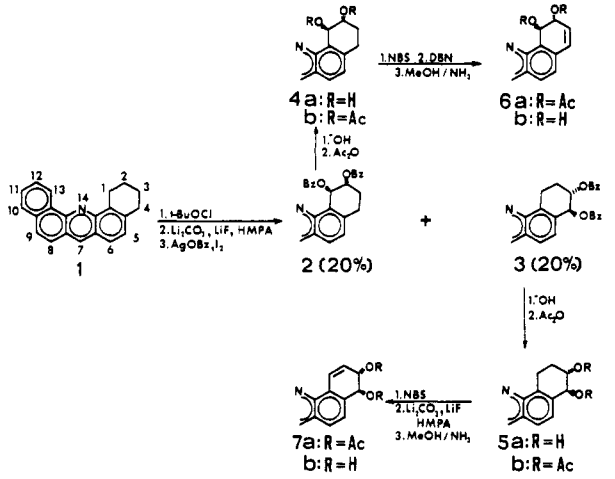


Figure 2. Lettering scheme for annulated acridine derivatives and numbering of the benz[*a*]-, benz[*c*]-, and dibenz[*c,h*]acridine nuclei.

been shown to possess high carcinogenic potency.[8] A large number of these molecules have been tested for carcinogenicity during the past 30 years, but studies designed to determine the nature of the intermediate(s) involved in the metabolic activation of aza-PAH have only recently begun. Early studies of benz[*a*]- and benz[*c*]acridines and their methylated derivatives by Lacassagne and Buu-Hoi[9] showed similarities between their carcinogenic potencies and those of the analogous BA derivatives. At the same time, many benz[*c*]acridine derivatives were considerably more active than the analogous benz[*a*]acridine derivatives (for numbering and lettering of benz- and dibenzacridines, see Figure 2). Recently, syntheses of diol epoxide and other derivatives of benz[*a*]- and benz[*c*]acridine[10] have enabled initial results of structure–activity relationships in the acridine series to be obtained. Thus, epoxides at the bay region of the tetrahydro angular ring of benz[*c*]-acridine (the 1,2-epoxides, Figure 2) are much more mutagenic than other epoxide derivatives of benz[*c*]acridine and greatly exceeded the analogous bay-region benz[*a*]-acridine diol epoxides in mutagenicity.[11] Possible effects of the differences in the position of nitrogen atom substitution relative to the epoxide moiety in these and other heterocycles have been probed by quantum chemical calculations,[12] which predict lower reactivity (conversion to carbocations) for the bay-region benz[*a*]acridine diol epoxides relative to the analogous benz[*c*]acridine diol

Scheme I



epoxides. A study of the tumor-initiating activity of benz[*c*]acridine and 12 of its derivatives has revealed significant tumorigenicity for only those compounds bearing a bay-region epoxide or likely to be metabolized to a molecule bearing a bay-region epoxide.[13]

Metabolism of K-region diols and non-K-region diols has been established for benz[*a*]-,[14] benz[*c*]-[14] and 7-methylbenz[*c*]acridine,[15] but only in the case of benz[*c*]acridine has evidence for metabolism to the dihydrodiol precursor of the bay-region diol epoxide been reported, and in that case very little is found. Interestingly, very little metabolism to bay-region diol epoxides is observed for BA, either,[16] yet a 3,4-diol 1,2-epoxide appears to the responsible for the carcinogenicity of BA.[17]

In contrast to the weak carcinogenicity of benz[*a*]- and benz[*c*]acridine, dibenz[*c,h*]acridine is a potent carcinogen.[8] Its activity is interesting from a structure–activity standpoint as a contrast with the very peak carcinogenicity of the two closely related, isosteric molecules dibenz[*a,j*]-anthracene and dibenz[*a,j*]acridine. In order to further examine factors involved in determining the carcinogenicity of aza-PAH, including absolute stereochemical factors, we have synthesized and characterized the four optically active bay-region 3,4-diol 1,2-epoxides and other derivatives of dibenz[*c,h*]acridine.

Results and Discussion

In order to prepare the stereoisomeric bay-region diol epoxides of dibenz[*c,h*]acridine, an efficient, high-yield synthesis of the precursor *trans*-3,4-dihydroxy-3,4-dihydrodibenz[*c,h*]acridine (**7b**, Scheme I) that would permit isolation of gram quantities of **7b** was required. An existing route[18] to **7b** from 1,2,3,4-tetrahydrodibenz[*c,h*]acridine (1, Scheme I) suffers from a very poor overall yield (0.7%) due mainly to the initial step, lead tetraacetate oxidation, used to introduce functionality into the tetrahydrobenzo ring of 1. This reagent produces a poor conversion of 1

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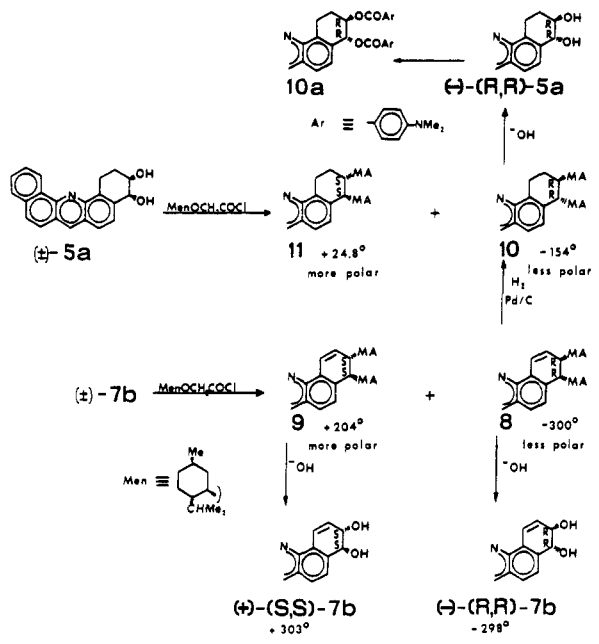
to tetrahydrobenzo ring derivatives *and* yields products indicative of a much higher level of reaction at C-1 relative to C-4 (about 3:1). We examined a number of alternative reactions of **1**, in hope of attaining a higher yield and more selective conversion to C-4 derivatives. Bromination of **1** with *N*-bromosuccinimide gave a similar, unfavorable ratio of derivatives at C-1 and C-4, and the yield of brominated products was only moderate (ca. 50%). Reaction with mercuric acetate was unsuccessful, although it has been shown[10a] to react with the analogous benz[*c*]acridine derivative, 1,2,3,4-tetrahydrobenz[*c*]acridine, exclusively at C-4. It is possible that greater steric hindrance to coordination by mercury with the nitrogen lone pair in **1** is responsible for the unreactivity of **1** with $Hg(OAc)_2$. Much more favorable results were obtained by reacting **1** with *tert*-butyl hypochlorite in CCl_4, which resulted in a high (>85%) conversion to equal amounts of the 1- and 4-chloro derivatives as judged by the relative areas of the peaks at δ 6.9 and 5.5 (H_1 and H_4, respectively, in the 1- and 4-chloro derivatives) in the NMR spectrum of the crude reaction product and by subsequent reactions (vide infra). The selectivity of reaction of this reagent with other tetrahydrobenzo ring derivatives of PAH and aza-PAH is currently under examination. Dehydrochlorination of the crude chlorinated mixture with LiF/Li_2CO_3 in HMPA and reaction of the crude alkene mixture with silver benzoate and iodine yielded a mixture of tetrahydro dibenzoates **2** and **3** (Scheme I). Separation of **2** and **3** was readily achieved by chromatography on silica gel. In this manner, **1** could be converted in three steps without purification of intermediates into an overall 40% yield of trans tetrahydrodibenzoates, consisting of equal amounts of the 1,2 and 3,4 derivatives.

A variety of methods for introducing the double bond into the angular, tetrahydrobenzo ring were explored. The best yield for converting **3** into a 3,4-dihydro derivative was obtained by converting **3** to the analogous diacetoxy derivative, **5b**, followed by bromination with NBS and dehydrobromination. In this manner, **3** was converted to 3,4-diacetoxy-3,4-dihydrodibenz[*c*,*h*]acridine (**7a**) in 53% yield, more than twice that obtained for the analogous dihydrodibenzoyloxy ester by direct bromination/dehydrobromination of **3**.[18] Also, the yield of tetrahydrodiacetate **5b** obtained in this manner is higher than that obtained by Prevost reaction of the crude alkene mixture with silver acetate and iodine, due to the lower yield in the Prevost reaction when AgOAc and I_2 are used. In contrast, a similar, indirect conversion of *trans*-1,2-bis(benzoyloxy)-1,2,3,4-tetrahydrodibenz[*c*,*h*]acridine (**2**) to **6a** proceeded in 27% yield and offers no advantage over the reported conversion[18] of **2** to the analogous bis(benzoyloxy) compound by bromination, dehydrobromination (28%). Dihydrodiol diacetates **6a** and **7a** were converted to dihydrodiols **6b** and **7b** in 51% and 93% yields, respectively. The overall conversion of **1** to pure 3,4 dihydrodiol **7b** was 10%.

Resolution of racemic dihydrodiol **7b** was achieved through conversion to the diastereomeric bis(−)-menthoxy esters with (−)-menthoxyacetyl chloride (Scheme II). Preparative HPLC on a Du Pont Zorbax SIL column (2.12 × 25 cm) using 8% ether in cyclohexane permitted separation of the diastereoisomers into a less polar component (**8**, $k' = 3.7$) and a more polar component (**9**, $k' = 4.5$), with isolated yields of 57% and 60% respectively. The absolute configurations at C-3 and C-4 of **8** and **9** were determined via an exciton chirality[19] experiment on the bis *p*-(dimethylamino)benzoate derivative of the tetrahydrodiol derived from **8**. Thus, reduction of the double bond of bis-(−)-menthoxy ester **8** with H_2 and Pd/C at atmospheric pressure yielded tetrahydro bis (−)-menthoxy ester **10**, identical with **10** that was isolated in quantity as the less polar isomer on preparative HPLC of the diastereomeric tetrahydro bis (−)-menthoxy esters **10** and **11** obtained by reacting racemic tetrahydrodiol **5a** with (−)-menthoxyacetyl chloride. Tetrahydro bis (−)-menthoxy ester **10** (negative $[\alpha]_D$) was hydrolyzed to yield tetrahydrodiol (−)-(*R*,*R*)-**5a**. The absolute configurations at C-3 and C-4 of **5a** were determined by conversion to the bis *p*-(dimethylamino)benzoate **10a**, which was purified by HPLC on a Du Pont Zorbax SIL column, using 30% ethyl acetate in cyclohexane as the eluting solvent. The circular dichroism spectrum of **10a** in MeOH had a symmetric pair of exciton chirality interaction bands at $\Delta\epsilon = -21.1$ (327 nm), 0 (313.5 nm), and +21.9 (297 nm). These Cotton effects result from chiral interaction between the two *p*-(dimethylamino)benzoate chromophores, which residue at least partially in the pseudodiequatorial conformation ($J_{3,4} = 5.8$ Hz). The presence of a negative, long wavelength band allows assignment of 3*R*,4*R* configuration at the chiral carbon atoms in **10**. Consequently, bis (−)-menthoxy ester **8** also has 3*R*,4*R* absolute configuration, and **9** must have 3*S*,4*S* configuration. Both the HPLC behavior and the NMR spectra of these aza-PAH derivatives show striking similarities to those of the analogous angular ring derivatives of B[a]P, chrysene, and BA.[2c] Thus, in all these cases, the (*R*,*R*)-bis (−)-menthoxy ester of the dihydrodiol or tetrahydrodiol elutes earlier in the HPLC profile and has more negative values of $[\alpha]_D$ than the *S*,*S* diastereomer when ether in cyclohexane is used as the eluting solvent (in the present case, **8** prior to **9** and **10** prior to **11**). Similarly, the NMR splitting patterns of the two formally diastereotopic pairs of protons in the $OCOCH_2OMen$ moieties of **8**, **9**, **10**, and **11** show consistencies with the analogous PAH derivatives that are diagnostic of configuration. Thus, the methylene hydrogen atoms in the *S*,*S* bis esters **9** and **11** appear as a pair of AB quartets in each case, whereas for the corresponding

Scheme II



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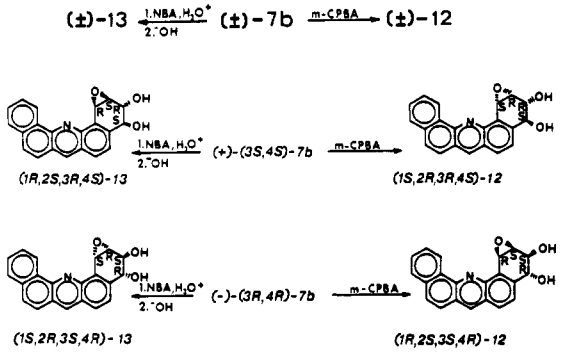
Scheme III



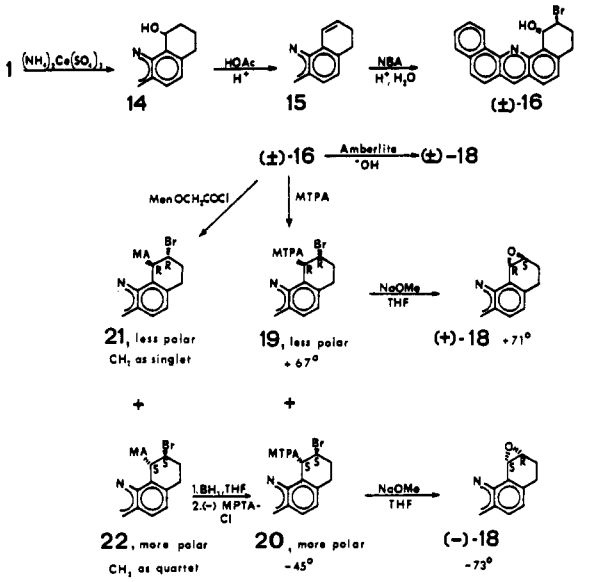
R,R bis esters **8** and **10** either one (as in **11**) or both (as in **9**) of the diastereotopic pairs of protons appear as singlets (cf. ref 21).

Enantiomerically pure dihydrodiols (−)-(*R,R*)-**7b** and (+)-(*S,S*)-**7b** were obtained by basic hydrolysis of bis (−)-menthoxy esters **8** and **9**, respectively. For (−)-(*R,R*)-**7b** the yield was 73%, and for (+)-(*S,S*)-**7b** it was 64%. Specific rotations in THF were $[\alpha]^{25}_{D}$ − 298° for the *R,R* isomer and $[\alpha]^{25}_{D}$ +303° for the *S,S* isomer. Notably, all benzo-ring, trans dihydrodiols resolved and assigned thus far have negative values of $[a]_{D}$ (THF) for the *R,R* enantiomers.[22]

Experiments with racemic dihydrodiol (±)-**7b** established that standard methodology[7,23] would be successful in converting **7b** stereospecifically to the isomer-1 and isomer-2 diol epoxides (Scheme III). Thus, (±)-**7b** gave racemic diol epoxide **12** in 70% yield upon reaction with excess *m*-chloroperoxybenzoic acid in dry THF at room temperature. Similarly, (±)-**7b** was converted to a bromo triol in 88% yield upon treatment with *N*-bromoacetamide in aqueous, acidic THF, and the bromo triol was cyclized to racemic diol epoxide **13** with Amberlite/$^{-}$OH in 72% yield. The meso hydrogens (H_7) in **12** and **13** appeared as clean, sharp singlets at δ 9.24 and 9.07, respectively, and no cross-contamination of **12** and **13**, which are readily separated on Eastman Kodak silica gel plates with EtOAc, could be detected. There was no evidence for the presence of an *N*-oxide diol epoxide in either case: the mass spectrum showed a molecular ion only at *m/z* 329 and the expected upfield shift of the meso hydrogen in the NMR spectrum[10d] was not observed.

In like manner, the enantiomeric dihydrodiols were converted to the four stereoisomeric diol epoxides (Scheme III), each of which was pure as shown by comparison of its 300-MHz NMR spectrum with that of the appropriate racemic diol epoxide. Optical rotations of the stereoisomers in THF were too low to permit determinations of valid specific rotations with the limited samples available, so the stereoisomers were characterized by their circular dichroism spectra. For the diol epoxides derived from the dihydrodiol (+)-(3*S*,4*S*)-**7b**, values for $\Delta\epsilon$ at the wavelength of maximum $\Delta\epsilon$ were +4.4 (281 nm) for the isomer-1 epoxide (1*R*,2*S*,3*R*,4*S*)-**13** and +5.3 (282 nm) for the isomer-2 epoxide (1*S*,2*R*,3*R*,4*S*)-**12**. For the diol epoxides derived from the dihydrodiol (−)-(3*R*,4*R*)-**7b**, the corresponding values were −4.4 (279 nm) for the isomer-1 epoxide (1*S*,2*R*,3*S*,4*R*)-**13** and −5.1 (281 nm) for the isomer-2 epoxide (1*R*,2*S*,3*S*,4*R*)-**12**.

Scheme IV



In previous studies of the inherent mutagenic activity in bacteria and in mammalian cells of the optically active bay-region diol epoxides of chrysene[24] and benz[*a*]anthracene,[25] the respective tetrahydro bay-region epoxides were also assessed. Whereas relatively large differences were observed between the four stereoisomers of the bay-region diol epoxides of each hydrocarbon in each of these test systems, only very small differences were found between the enantiomers of the tetrahydro bay-region epoxides, none for chrysene, and less than threefold for benz[*a*]anthracene. As the results were suggestive that the configuration of the hydroxyl groups in the diol epoxides were important determinants of the mutagenic potential of the epoxide portion of these molecules, the enantiomeric 1,2,3,4-tetrahydro 1,2-epoxides of dibenz[*c,h*]acridine (**18**) were synthesized in the present study (Scheme IV). Racemic *trans*-2-bromo-1-hydroxy-1,2,3,4-tetrahydrodibenz[*c,h*]acridine (**16**) was prepared in two ways: by conversion of pure 3,4-dihydrodibenz[*c,h*]acridine (**15**) to the bromohydrin with NBA in aqueous, acidic THF and by chromatographic separation from the isomeric *trans*-3-bromo-4-hydroxy-1,2,3,4-tetrahydrodibenz[*c,h*]acridine on dry column grade silica gel when the mixture of alkenes produced by dehydrochlorination of 1-(and 4-)-chloro-1,2,3,4-tetrahydrodibenzo[*c,h*]acridine (Scheme I) was converted to the mixture of bromohydrins with NBA in aqueous acidic THF. In the former case, 3,4-dihydrodibenz[*c,h*]acridine (**15**) was obtained in 90% yield by dehydration of 1-hydroxy-1,2,3,4-tetrahydrodibenz[*c,h*]acridine (**14**) in glacial HOAc/HCl. The alcohol **14** was obtained in 26% yield from 1,2,3,4-tetrahydrodibenz[*c,h*]acridine by oxidation with ceric ammonium sulfate. The racemic epoxide (±)-**18** was obtained by cyclization of the racemic bromohydrin with Amberlite resin (hydroxide form) in anhydrous THF.[7,23] For the enantiomeric epoxides, the racemic bromohydrin was chosen as the starting material for resolution. Although preparative resolution of the bromohydrin as its menthoxy ester proved impractical due to a low separation factor (α = 1.17) on HPLC, the diastereomeric esters of the bromohydrin with (−)-α-meth-

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Table I. ^{1}H NMR Spectral Data for Dibenz[c,h]acridine Derivatives[a-c]

no.	H_1	H_2	H_3	H_4	H_5	H_6	H_7	H_{13}	aromatic and other
4b	7.28	5.51	2.36 (α), 2.25 (β)	3.15 (α), 3.02 (β)			8.62	9.46	7.3-8.1 (7 H); 2.01, 2.04 (CH_3's)
	($J_{1,2}$ = 2.9; $J_{2\beta,3\alpha} \approx$ 4.0; $J_{2\beta,3\beta} \approx$ 2.3; $J_{3\alpha,3\beta}$ = 14.1; $J_{3\alpha,4\alpha}$ = 3.2; $J_{3\alpha,4\beta}$ = 3.6; $J_{3\beta,4\alpha}$ = 7.4; $J_{3\beta,4\beta}$ = 3.3; $J_{4\alpha,4\beta}$ = 17.1)								
5b	3.85	2.32	5.38	6.30			8.62	9.54	7.4-7.9 (7 H); 2.07, 2.18 (CH_3's)
	($J_{2\alpha,3\beta}$ = 7.5; $J_{2\beta,3\beta}$ = 3.5; $J_{3\beta,4\alpha}$ = 5.4)								
6a		5.60	6.45	6.96			8.62	9.50	7.4-8.1 (7 H, H_1); 2.00, 2.03 (CH_3's)
	($J_{1,2}$ = 1.5; $J_{2,3}$ = 5.4; $J_{3,4}$ = 9.6)								
6b	5.81	4.99	6.32	6.56			8.65	9.11	7.4-8.0 (7 H); 1.60 (O-H)
	($J_{1,2}$ = 11.8; $J_{2,3}$ = 2.0; $J_{2,4}$ = 2.6; $J_{3,4}$ = 9.8)								
7a	8.52	6.35	5.76	6.42			8.63	9.53	7.5-8.0 (7 H); 2.08, 2.15 (CH_3's)
	($J_{1,2}$ = 10.3; $J_{2,3}$ = 4.3; $J_{3,4}$ = 5.5)								
7b	8.13	6.31	4.71	5.10			8.66	9.50	7.8-8.0 (7 H)
	($J_{1,2}$ = 10.1; $J_{1,3}$ = 2.2; $J_{2,3}$ = 1.9; $J_{3,4}$ = 11.4)								
12	5.83	3.91	3.94	4.59			9.24	9.46	7.8-8.3 (7 H)
	($J_{1,2}$ = 4.4; $J_{2,3}$ = 0; $J_{3,4}$ = 8.6)								
13	5.60	3.97	4.23	4.72			9.07	9.48	7.7-8.3 (7 H)
	($J_{1,2}$ = 4.0; $J_{2,3}$ = 2.1; $J_{3,4}$ = 3.7)								
14	5.90		1.8-2.5	2.8-3.2			8.62	9.33	7.3-7.9 (7 H); 6.6 (O-H)
	($J_{1,2}$(cis) = $J_{1,2}$(trans) = 6.4)								
15	8.24	6.37	2.51	3.07			8.57	9.56	7.3-7.9 (7 H)
	($J_{1,2}$ = 9.8; $J_{2,3} \approx$ 4.5; $J_{1,3}$ = 1.8)								
16	6.06	4.72 (β)	2.66 (α), 2.44 (β)	3.18			8.68	9.34	7.3-8.0 (7 H); 6.9 (O-H)
	($J_{1,2}$ = 6.6; $J_{2\beta,3\beta}$ = 4.0; $J_{2\beta,3\alpha}$ = 9.0)								
17	4.02 (α) 3.73 (β)	2.54 (α) 2.75 (β)	4.57	5.15			8.61	9.50	7.7-8.0 (7 H); 2.75 (O-H)
	($J_{1\alpha,1\beta}$ = 18.6; $J_{1\alpha,2\alpha}$ = 5.1; $J_{1\alpha,2\beta}$ = 4.1; $J_{1\beta,2\alpha}$ = 8.1; $J_{1\beta,2\beta} \approx$ 3; $J_{2\alpha,2\beta}$ = 13.6; $J_{2\alpha,3\beta}$ = 10.3; $J_{2\beta,3\beta} \approx$ 3; $J_{3\beta,4\alpha}$ = 7.05; $J_{4\alpha,O\text{-}H}$ = 5.6)								
18	5.95	4.03	2.61 (α), 1.95 (β)	3.08 (α), 2.80 (β)			8.63	9.56	7.3-8.0 (7 H)
	($J_{1,2}$ = 4.2; $J_{2\alpha,3\alpha}$ = 2.4; $J_{2\alpha,3\beta} \approx$ 0; $J_{3\alpha,3\beta}$ = 12.5; $J_{3\alpha,4\alpha}$ = 4.5; $J_{3\alpha,4\beta} \approx$ 0; $J_{3\beta,4\alpha}$ = 12.5; $J_{3\beta,4\beta}$ = 4.4; $J_{4\alpha,4\beta}$ = 16.0)								
23	9.20				4.66	4.78	8.41	9.51	7.5-8.0 (8 H)
					($J_{5,6}$ = 3.9)				
24	8.63				4.70	4.75	8.49	9.36	7.5-8.1 (8 H)
					($J_{5,6} \approx$ 9)				
25	8.67				4.78	4.96	8.46	9.37	7.6-8.2 (8 H)
					($J_{5,6}$ = 3.5)				

[a] Spectra were recorded at 300 MHz; J values are in hertz; Me_4Si was used as internal standard; $CDCl_3$ was used in all cases except 15 and 16, where Me_2SO-d_6 was used; α and β refer to relative stereochemistry. [b] For numbering, see Figure 2. [c] The H_{13} absorption is a multiplet.

oxy-α-(trifluoromethyl)phenylacetic acid (MTPA) were readily separated (α = 1.63). Direct treatment of the separated diastereomers with dry sodium methoxide in THF provided the requisite tetrahydro epoxides (+)-18 and (−)-18. Interestingly, this latter reaction was accompanied by substantial double elimination to produce dibenz[c,h]acridine as a byproduct.

Assignment of absolute configuration to the tetrahydro 1,2-epoxides (+)-18 and (−)-18 is based on the NMR spectra of the chiral esters of their bromohydrin precursors. For the less polar (HPLC on silica, ether in cyclohexane) ester of the related, previously studied bromohydrins with (−)-MTPA, *R,R* absolute configuration pertains, and the NMR signal for the hydrogen on the bromine-bearing carbon is at higher field.[26] In the present study, the less polar MTPA ester of the bromohydrin **19** had the signal for H-2 at δ 4.77 whereas this signal was at δ 4.86 for H-2 of the more polar ester **20**, suggestive of 1*R*,2*R* absolute configuration for the less polar bromohydrin ester. Further confirmation of this assignment was sought by chromatographically interrelating the bromohydrin esters with (−)-MTPA to those obtained with (−)-menthoxyacetic acid (MA). The same enantiomer of the bromohydrin formed the more polar member of the diastereomeric pair of esters from either optically active acid. For the less polar (HPLC on silica gel, ether in cyclohexane) ester of the related, previously studied, bromohydrins with (−)-MA, *R,R* absolute configuration pertains and the NMR signal for the methylene group of the $-OCOCH_2-$ appears as a singlet whereas these hydrogens are magnetically nonequivalent in the more polar diastereomer and appear as an AB quartet.[26] In the present study, the NMR signal for these methylene hydrogens appeared as a singlet in the early eluting MA diastereomer **21** and as a quartet in the late eluting diastereomer **22**. The two NMR methods lead to the same conclusion: the less polar ester (either MTPA or MA) of the bromohydrin has 1*R*,2*R* absolute configuration. Thus, tetrahydro 1,2-epoxide (+)-18 must have 1*R*,2*S* absolute configuration (Scheme IV).

The K-region trans diol **24** was prepared as shown in Scheme V. Reaction of dibenz[c,h]acridine with sodium hypochlorite at pH 9 under phase-transfer conditions[22,27] led to isolation of the K-region oxide **23** in 10% yield. Hydrolysis of **23** in aqueous, acidic dioxane gave a mixture of trans and cis diols **24** and **25** in which the trans diol

(26) For a complete discussion of the use of MTPA and menthyloxy acetates in the resolution and assignment of configuration by NMR methods to bromohydrins, see: Balani, S. K.; Boyd, D. R.; Cassidy, E. S.; Devine, G. I.; Malone, J. F.; McCombe, K. M.; Sharma, N. D.; Jennings, W. B. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2751-2756.

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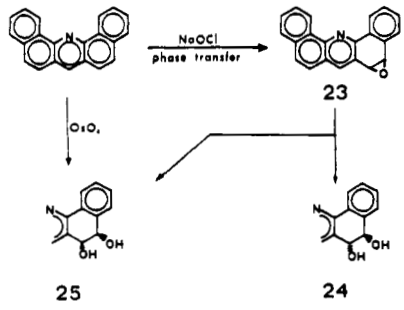
Scheme V



predominated (**23**:**24** > 2). Reaction of this mixture with acetone and anhydrous $CuSO_4$[28] afforded a crude product which after trituration with CH_2Cl_2 to remove the cis acetonide gave trans diol **24** as a pure solid. Unequivocal assignment of structure to the trans and cis diols resulted from independent synthesis of the cis diol **25** in 40% yield through reaction of dibenz[c,h]acridine with OsO_4.

NMR spectral data for the dibenz[c,h]acridine derivatives are listed in Table I. The downfield absorption of the meso proton H_7 (δ 8.4–9.2) is noteworthy, as is the even lower field absorption of H_{13}, the bay-region hydrogen atom on the aromatic benzo ring (δ 9.1–9.6). The bay-region hydrogen atoms at H_1 in alkenes **7a**, **7b**, and **15** also absorb at very low field (δ 8.52, 8.13 and 8.24, respectively). For the di- and tetrahydro derivatives on the angular ring in which a hydroxyl group was present at C_1, there was evidence of intramolecular hydrogen bonding with the nitrogen. For 1-hydroxy- and *trans*-2-bromo-1-hydroxy-1,2,3,4-tetrahydrodibenz[c,h]acridine, **14** and **16**, intramolecular hydrogen bonding was suggested by the unusually low-field absorption of the O–H (δ 6.6 and 6.9, respectively). For the 1,2-dihydrodiol **6b**, the vicinal coupling constant is very large ($J_{1,2}$ = 11.8), as was the case for the analogous benz[c]acridine derivative in $CDCl_3$,[10a] and is consistent with the quasi-diaxial relationship of the carbinol protons that would result if the hydroxyl group at C_1 were pseudoequatorial and hydrogen bonded to nitrogen. The coupling for the carbinol protons of the 3,4-dihydrodiol **7b** is also consistent with a pseudodiequatorial relationship of the hydroxyl groups ($J_{3,4}$ = 11.4) and the *trans*-K-region-5,6-dihydrodiol **24** likewise exhibits a large carbinol proton coupling ($J_{5,6}$ ca. 9), indicative of a preferred pseudodiequatorial conformation for the hydroxyl groups.[29] As is generally observed for bay-region diol epoxides in which unusual steric constraints are absent,[7,23] the coupling constant values were consistent with a predominantly pseudodiaxial conformation of the hydroxyl groups in the diol epoxide-1 isomer, (**13**, $J_{3,4}$ = 3.7) and with a pseudodiequatorial conformation of the hydroxyl groups in the diol-epoxide-2 isomer (**12**, $J_{3,4}$ = 8.6).

Ultraviolet spectra of THF solutions of the 1,2-, 3,4- and 5,6-*trans*-dihydrodiols (**6b**, **7b**, and **24**) and of 1,2,3,4-tetrahydrodibenz[c,h]acridine (**1**) are shown in Figure 3. The bay-region diol epoxides **12** and **13** and the bay-region tetrahydro epoxide **18** exhibit UV spectra virtually identical with that of **1** (data not shown).

Perturbational molecular orbital calculations for the formation of a carbocation at the C-1 position on the tetrahydro ring of 1,2,3,4-tetrahydrodibenz[c,h]acridine

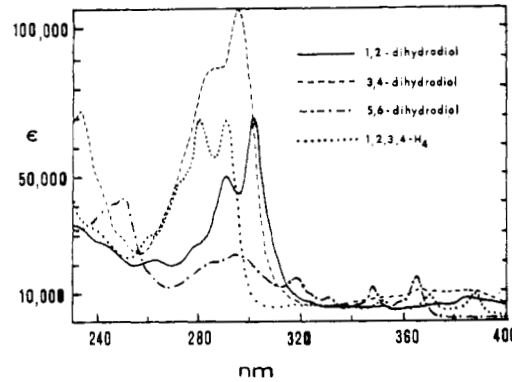


Figure 3. Ultraviolet spectra, in THF, of dihydrodiols **6b**, **7b**, and **24** and of 1,2,3,4-tetrahydrodibenz[c,h]acridine (**1**).

give a value of $\Delta E(\text{deloc})/\beta$ = 0.722.[12] This value is somewhat below that of the corresponding bay-region derivative of benz[c]acridine (0.766). In neither case is the plus charge of the carbocation formally delocalized to the nitrogen atom, so that any deactivating effects due to the electronegativity of the nitrogen atom should be minimal. Studies of the mutagenicity and tumorigenicity of the diol epoxides and other derivatives of dibenz[c,h]acridine are in progress.

Experimental Section

Ultraviolet spectra were recorded on a Hewlett-Packard Model 8450A UV-VIS spectrophotometer. Mass spectra were obtained on a Finnegan 1015D combined gas chromatograph–mass spectrometer. Circular dichroism spectra were recorded on a JASCO J500A circular dichroism spectrophotometer. Nuclear magnetic resonance spectra were recorded on JEOL FX-100 and Varian Associates XL-300 spectrometers. Melting points are uncorrected.

1,2,3,4-Tetrahydrodibenz[c,h]acridine (1). Although this compound has been described in the literature,[18] neither a detailed procedure nor yield information was provided. Accordingly, we include the details of our procedure here. 1-Amino-5,6,7,8-tetrahydronaphthalene (128 g), 1-naphthol (131 g), and paraformaldehyde (30 g) were mixed in a 500-mL round-bottomed flask, which was fitted with a dry ice condenser. The flask was placed in a salt bath maintained at 250 °C. After a few minutes, a vigorous reaction occurred that was controlled by lowering the salt bath. After the reaction had subsided, the reaction mixture was heated at 250 °C for 15 min. Attempted steam distillation of the crude reaction mixture to remove unreacted 1-amino-5,6,7,8-tetrahydronaphthalene was inefficient, so the crude reaction product was extracted with benzene and ether, and these organic phases were combined and extracted with 5% NaOH (4 × 200 mL) to remove unreacted 1-naphthol. After drying the organic phase (Na_2SO_4), most of the solvents were removed under reduced pressure, and the oily residue was distilled at 5–10-mm vacuum from an oil bath maintained at 150–160 °C. A fraction collected at 130–135 °C contained unreacted amine (75 g). The residue was distilled at 1-mm vacuum to give a yellow oil of bp 228–245 °C (28 g) which solidified on standing. Recrystallization from hot EtOAc gave 6.0 g of **1** as yellow crystals (mp 139–140.5 °C) lit.[18] mp 131–132 °C). Additional **1** (6.9 g) was obtained by chromatography of the residue from the mother liquor on dry column grade silica gel using hexane as eluant (total yield: 12.9 g, 13% based on recovered 1-amino-5,6,7,8-tetrahydronaphthalene). This material is sufficiently pure for use in the following experiments, but contains ca. 5–10% of an aromatic ring methylated derivative (CH_3 at δ 2.7) that could not be removed by repeated crystallization from EtOAc or other solvents. In order to obtain highly purified **1** needed for other studies, a sample of **1** (1.0 g) containing ca. 10% of a methyl derivative was reacted with NBA (0.54 g) in glacial HOAc (50 mL) for 5 h at room temperature. HOAc was removed and the crude product was carefully chromatographed on silica gel by using hexane. In this way, it is possible to separate pure **1** from ring-brominated derivatives and bromo acetates. After recrystallization from EtOAc,

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142 mg of 1 containing less than 2% methyl derivative was obtained. UV (THF, λ_{max}, ϵ_{max}, see Figure 3): 280 (68 900), 289 (68 700), 335 (6080), 341 (5650), 350 (6760), 368 (8910), 388 (9270).

***trans*-1,2-Bis(benzoyloxy)- and *trans*-3,4-Bis(benzoyloxy)-1,2,3,4-tetrahydrodibenz[*c,h*]acridine (2 and 3).** A solution of 1,2,3,4-tetrahydrodibenz[*c,h*]acridine (10.6 g), *tert*-butyl hypochlorite (5.6 mL), and AIBN (20 mg) in dry CCl_4 (600 mL) was stirred for 8 h at 42–43 °C under a flow of argon. The resulting burgundy solution was filtered and concentrated under reduced pressure to an oil (11.3 g), whose NMR spectrum indicated a 1:1 mixture of 1-chloro-1,2,3,4-tetrahydrodibenz[*c,h*]acridine (H_1 at δ 6.88) and 4-chloro-1,2,3,4-tetrahydrodibenz[*c,h*]acridine (H_4 at δ 5.48). The oil was dissolved in freshly distilled HMPA (50 mL), and a predried mixture of Li_2CO_3 (12 g) and LiF (8 g) was added. The mixture was stirred, under Ar, at 90–92 °C for 6 h, then cooled, diluted with H_2O, and extracted with ether (3 × 100 mL). The ether layer was washed with H_2O (5 × 200 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to an oil (10.4 g). This alkene mixture was dissolved in benzene (100 mL) and added, under Ar, to the complex formed in situ from silver benzoate (17 g) and iodine (9.3g) in dry benzene (500 mL). After a reflux of 4 h, the mixture was filtered hot, and the filtrate was concentrated, under reduced pressure, to a yellow solid. The solid was extracted with EtOAc (3 × 100 mL), and the EtOAc washings were combined, washed with saturated aqueous sodium dithionite and H_2O, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to a dark semisolid. Chromatography of the crude product on dry column grade silica gel using benzene as developing solvent gave first 4.0 g (20%) of *trans*-3,4-bis(benzoyloxy)-1,2,3,4-tetrahydrodibenz[*c,h*]acridine (**3**) (mp 216–218 °C, lit.[18] mp 217–218 °C) and then 3.95 g (20%) of *trans*-1,2-bis(benzoyloxy)-1,2,3,4-tetrahydrodibenz[*c,h*]acridine (**2**) (mp 238–240 °C, lit.[18] mp 239–240 °C).

***trans*-1,2-Diacetoxy-1,2,3,4-tetrahydrodibenz[*c,h*]acridine (4b).** *trans*-1,2-Bis(benzoyloxy)-1,2,3,4-tetrahydrodibenz[*c,h*]-acridine (**2**, 4.8 g) was dissolved in THF (80 mL) and 25% NaOH (16 mL) was added, under Ar. Separation into two layers occurred, and enough MeOH (ca. 40 mL) was added to establish a homogeneous solution at room temperature. The solution was stirred for 24 h, then solvents were removed under reduced pressure, and the residue was diluted with H_2O (50 mL). A solid formed which was collected by filtration, washed with cold H_2O, and dried, leaving 2.9 g (100%) of tetrahydrodiol **4a**, mp 191–194 °C. A suspension of the diol (2.8 g) in Ac_2O (80 mL) and dry pyridine (20 mL) was stirred under Ar and gradually warmed until a clear solution resulted. The solution was stirred at room temperature for 18 h and then was poured onto ice (200 g). The mixture was stirred for 30 min and the light yellow solid that formed was collected by filtration, washed thoroughly with H_2O, and dried to give 3.2 g (92%) of **4b** is a light yellow solid. Recrystallization from acetone and then from CH_2Cl_2–petroleum ether gave **4b** of mp 248–250 °C. Anal. Calcd for $C_{25}H_{21}NO_4$: C, 75.18; H, 5.26; N, 3.51. Found: C, 74.82; H, 5.37; N, 3.39. NMR spectrum: see Table I.

***trans*-1,2-Diacetoxy-1,2-dihydrodibenz[*c,h*]acridine (6a).** A mixture of tetrahydro diacetate **4b** (2.45 g), NBS (1.3 g), and AIBN (15 mg) in dry CCl_4 (150 mL) was stirred under Ar and gradually warmed with a heat lamp. At 55 °C, the mixture became a clear solution, then quickly became cloudy. The mixture was stirred an additional 15 min, then was cooled to 15 °C, and filtered. The filtrate was concentrated under reduced pressure and the residue was triturated with a 1:1 mixture of ether:petroleum ether (50 mL) and stored overnight at ca. −20 °C. The resulting solid was collected by filtration and dried to give the 4-bromo derivative (2.15 g, 73%), which is likely a mixture of stereoisomers, as judged by the complexity of the NMR spectrum. The 4-bromo derivative (1.9 g) was dissolved in dry, freshly distilled THF (100 mL) and the solution was cooled to 0 °C. To this cold solution, under Ar, was added DBN (4 mL) dropwise with occasional shaking. The mixture was kept at 0–5 °C for 48 h, then EtOAc (100 mL) was added, and the liquid phase was decanted from the solid. The EtOAc phase was washed with 0.5% HCl (2 × 100 mL), 5% $NaHCO_3$ (1 × 50 mL), and H_2O (1 × 50 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure to leave a yellow solid, which was recrystallized from EtOAc–CH_2Cl_2 to give **6a** as yellow crystals (0.62 g, 40%) of mp 215–217 °C. Anal. Calcd for $C_{25}H_{19}NO_4 \cdot 8H_2O$: C, 72.91; H, 5.04; N, 3.40. Found: C, 72.79; H, 4.89; N, 3.20. NMR spectrum: see Table I.

***trans*-1,2-Dihydroxy-1,2-dihydrodibenz[*c,h*]acridine (6b).** To a solution of dihydrodiol diacetate **6a** (500 mg) of THF (100 mL) and MeOH (300 mL) was added 40% NaOH (3 mL), and the mixture was stirred at 20 °C, under Ar, for 45 min. The mixture was concentrated to one-third of its original volume under reduced pressure and then was diluted with H_2O (100 mL). A brown solid separated that was collected by filtration, washed with cold H_2O, and dried (desiccator). Recrystallization of the solid from EtOAc/hexane gave **6b** as brown crystals (200 mg, 51%) of mp 180–182 °C. The NMR spectral data (see Table I) agreed with literature[18] values. UV (THF, λ_{max}, ϵ_{max}; see Figure 3): 262 (21 490), 291 (49 710), 302 (70 080), 355 (4980), 386 (7780).

***trans*-3,4-Diacetoxy-1,2,3,4-tetrahydrodibenz[*c,h*]acridine (5b).** To a solution of tetrahydro dibenzoate **3** (2.03 g) in THF (40 mL) and MeOH (65 mL) was added 25% NaOH (5 mL). A dark red solution resulted, which was stirred at room temperature under Ar for 5 h. Solvents were removed under reduced pressure and the residue was dissolved in EtOAc/H_2O (50 mL each). The aqueous phase was removed and the EtOAc phase was washed with H_2O (2 × 50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure until the tetrahydrodiol separated. It was collected as a yellow solid (1.08 g, 88%) of mp 215–218 °C. This solid dissolved in Ac_2O (40 mL) and pyridine (10 mL) upon warming and the solution was stirred for 24 h, under Ar, at room temperature. EtOAc (100 mL) was added, and the mixture was washed with H_2O (3 × 100 mL), saturated $NaHCO_3$ (2 × 100 mL), and H_2O (1 × 100 mL). The EtOAc phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield a light yellow solid which recrystallized from ether as light yellow plates (1.26 g, 92%) of mp 180–182 °C. Anal. Calcd for $C_{25}H_{21}NO_4$: C, 75.18; H, 5.26; N, 3.51. Found: C, 75.07; H, 5.07; N, 3.94. NMR spectrum: see Table I.

***trans*-3,4-Diacetoxy-3,4-dihydrodibenz[*c,h*]acridine (7a).** A mixture of *trans*-3,4-diacetoxy-1,2,3,4-tetrahydrodibenz[*c,h*]-acridine (**5b**) (0.91 g), NBS (0.47 g), and AIBN (3 mg) in dry CCl_4 (90 mL) was stirred and gradually warmed with a heat lamp. The mixture turned cloudy at 60–62 °C and was stirred an additional 15 min at that temperature. The mixture was cooled and filtered, and the filtrate was concentrated to a yellow solid under reduced pressure. Trituration with petroleum ether gave 1-bromo-*trans*-3,4-diacetoxy-1,2,3,4-tetrahydrodibenz[*c,h*]acridine (1.05 g, 96%) as a yellow crystalline solid: mp 137–139 °C dec; ^1H NMR (80 MHz, $CDCl_3$) δ 2.20 (s, 3 H), 2.30 (s, 3 H), 2.52–3.17 (m, 2 H), 5.90–6.35 (m, H_3), 6.58 (d, H_4), 6.9–7.1 (m, H_1), 7.6–8.2 (m, 7 H), 8.65 (s, H_7), 9.50–9.73 (m, H_{13}); $J_{3,4}$ = 12.5 Hz. The bromo diacetate above (1.63 g), Li_2CO_3 (4.0 g) LiF (3.0 g), and freshly distilled HMPA (40 mL) were stirred for 3 h, under Ar, at 85–90 °C. The mixture was cooled, diluted with H_2O (150 mL), and extracted with 1:1 benzene–ether (2 × 100 mL). The organic phase was washed with H_2O (4 × 150 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield a yellow solid (1.28 g) that was recrystallized from EtOAc/hexane to give 0.9 g (66%) of *trans*-3,4-diacetoxy-3,4-dihydrodibenz[*c,h*]acridine as brown-yellow crystals, mp 201–203 °C. NMR: see Table I. Anal. Calcd for $C_{25}H_{19}NO_4$: C, 75.56; H, 4.78; N, 3.52. Found: C, 75.21; H, 5.08; N, 3.58.

***trans*-3,4-Dihydroxy-3,4-dihydrodibenz[*c,h*]acridine (7b).** A solution of dihydro diacetate **7a** (1.7 g) in dry THF (160 mL) and dry MeOH (300 mL) was saturated with NH_3 gas at 0–5 °C, the reaction flask was capped with a balloon, and the solution was stirred an additional 4 h at room temperature. Most of the solvent was removed under reduced pressure and the residue was dissolved in EtOAc/H_2O (100 mL each). The aqueous phase was removed and the organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give 1.25 g (93%) of **7b** as a solid of mp 166–169 °C. The NMR spectrum (see Table I) was in accord with that previously reported.[18] UV (THF, λ_{max}, ϵ_{max}, see Figure 3): 285 (87 000), 294 (104 000), 373 (11 500), 391 (10 700).

Diastereomeric Bis (−)-Menthoxy Esters of *trans*-3,4-Dihydroxy-3,4-dihydrodibenz[*c,h*]acridine (8 and 9). To a solution of (±)-*trans*-3,4-dihydroxy-3,4-dihydrodibenz[*c,h*]acridine ((±)-**7b**, 498 mg) in dry pyridine (20 mL) was added portionwise (−)-menthoxyacetyl chloride (4 mL) under cooling at 0 °C over

5 min. The reaction mixture was stirred at 0–5 °C for 25 h and was poured into dilute HCl at 0 °C. The suspension was extracted with EtOAc. The extract was washed with water, dried ($MgSO_4$), and concentrated to leave an oil which upon column chromatography on silica gel, using benzene in cyclohexane, yielded a yellowish semisolid (1.02 g, 91%).

Preparative separation of the diastereomers (~90 mg/injection) was achieved (>98% diastereomerically pure) on a Du Pont Zorbax SIL HPLC column (2.12 × 25 cm) eluted with 8% ether in cyclohexane at a flow rate of 24mL/min (α = 1.22). Evaporation of the less polar fraction (k' = 3.70) afforded the bis ester of the (–)-(*R,R*)-dihydrodiol 8 (317 mg, 57% yield): $[\alpha]^{27}_D$ –300° (*c* 2.4, THF); NMR (benzene-d_6) δ 3.94 (s, 2 H, $COCH_2O$) and 4.00 (s, 2 H, $COCH_2O$). Evaporation of the more polar fraction (k' = 4.50) afforded the bis ester of the (+)-(*S,S*)-dihydrodiol **9** (337 mg, 60% yield): $[\alpha]^{25}_D$ +204° (*c* 2.0, THF); NMR (benzene-d_6) two AB quartets with the doublets centered at δ 4.02 and 3.88 (2 H, J_{gem} = 17 Hz, $COCH_2O$) and at 4.08 and 3.95 (2 H, J_{gem} = 16 Hz, $COCH_2O$). Both fractions failed to crystallize.

(–)-*trans*-(3*R*,4*R*)-Dihydroxy-3,4-dihydrodibenz[*c*,*h*]acridine ((–)-(*R,R*)-7b). To a solution of the less polar diastereomer 8 (420 mg) in MeOH/THF (1:1, 24 mL) was added 10% aqueous NaOH solution (2.0 mL) with stirring at 0 °C. The reaction mixture was stirred at room temperature for 1.5 h and was then concentrated under reduced pressure. Water (75 mL) was added and then the mixture was cooled to completely precipitate the product, which was collected by filtration and recrystallized from THF–cyclohexane to yield (–)-(*R,R*)-**7b** as a pale green powder (136 mg, 73%): mp 190–193 °C dec; $[\alpha]^{25}_D$ –298°(*c* 0.60, THF), mass spectrum (CI-NH_3), *m/z* 314 (M^+ + 1), 296 (M^+ + 1 – H_2O) and (CI-NO, N_2), *m/z* 313 (M^+), 295 (M^+ – H_2O).

(+)-*trans*-(3*S*,4*S*)-3,4-Dihydroxy-3,4-dihydrodibenz[*c*,*h*]acridine ((+)-(*S,S*)-7b). Treatment of the more polar diastereomer **9** (530 mg) in the same manner as **8** afforded (+)-(*S,S*)-**7b** as a pale green powder (151 mg, 64%): mp 193–196 °C dec; $[\alpha]^{25}_D$ +303° (*c* 0.70, THF); mass spectrum (CI–NH_3), *m/z* 314 (M^+ + 1), 296 (M^+ + 1 – H_2O); (CI–NO, N_2), *m/z* 313 (M^+), 295 (M^+ – H_2O).

Diastereomeric Bis (–)-Menthoxy Esters of *trans*-3,4-Dihydroxy-1,2,3,4-tetrahydrodibenz[*c*,*h*]acridine (10 and 11). To a solution of (±)-*trans*-3,4-dihydroxy-1,2,3,4-tetrahydrodibenz[*c*,*h*]acridine (8 mg) in dry pyridine (1.5 mL) was added (–)-menthoxyacetyl chloride (0.15 mL) at 0 °C with stirring. The reaction mixture was stirred at 0–5 °C for 22 h and H_2O was added. The mixture was extracted with benzene, and the extract was dried ($MgSO_4$) and concentrated to leave an oil which upon column chromatography on silica gel, using benzene and cyclohexane, yielded a yellowish semisolid. Preparative separation of the diastereomers was achieved (>98% diastereomerically pure) on a Du Pont Zorbax SIL HPLC column (0.94 × 25 cm) eluted with 10% ether in cyclohexane at flow rate of 5.0 mL/min (α = 1.21). Evaporation of the less polar fraction (k' = 1.79) afforded the bis ester **10** (6 mg, 67%) of the (–)-(*R,R*)-tetrahydrodiol: $[\alpha]^{27}_D$ –154° (*c*, 1.7, THF); mp 139–140 °C (ether); NMR (benzene-d_6) an AB quartet with the doublets centered at δ 4.00 and 3.91 (2 H, J_{gem} = 16 Hz, $COCH_2O$) and a singlet at 4.11 (2 H, $COCH_2O$). Evaporation of the more polar fraction (k' = 2.17) afforded the bis ester **11** (6 mg, 67%) of the (+)-(*S,S*)-tetrahydrodiol: $[\alpha]^{27}_D$ + 24.8° (*c* 1.6, THF); mp 125–128 °C (ether–methanol); NMR (benzene-d_6) two AB quartets with the doublets centered at δ 4.05 and 3.89 (2 H, J_{gem} = 16 Hz, $COCH_2O$) and at 4.18 and 4.06 (2 H, J_{gem} = 16.5 Hz). Both bis-esters gave mass spectra (CI-NH_3) with *m/z* = 708 (M^+ + 1).

Assignment of Absolute Configuration to the 3,4-Dihydrodiol. A mixture of **8** (1.4 mg) and 10% palladium on carbon was stirred in THF (3 mL) under 1 atm of hydrogen at room temperature for 10 min. After removal of the catalyst by filtration, the ultraviolet spectrum of the product was found to be identical with that of the tetrahydrodiol. Analysis by HPLC on a Du Pont Zorbax SIL column (0.62 × 25 cm) eluted with 8% ether in cyclohexane at a flow rate of 2.2 mL/min indicated the product was cochromatographic with the less polar bis ester of the tetrahydrodiol **10**. Under these chromatographic conditions, the dihydrodiol bis esters eluted at 12.3 (for **8**) and 14.9 (for **9**) min and the tetrahydrodiol bis esters **10** and **11** eluted at 10.4 and 12.8 min, respectively. Thus, the less polar bis esters of the dihydro- and tetrahydrodiols have the more negative $[\alpha]_D$, the higher degree of magnetic equivalence for the $OCOCH_2$ groups in their NMR spectra, and the same absolute configuration (*R,R*).

Hydrolysis of **10** under conditions similar to those used for hydrolysis of the bis esters of the dihydrodiols provided the negative tetrahydrodiol (–)-(*R,R*)-**5a**: $[\alpha]^{23}_D$ –37.6° (*c* 0.71, THF). Minor impurities were removed by passage through a Waters Associates silica Sep-pak eluted with 50% ethyl acetate in cyclohexane. To a solution of (–)-(*R,R*)-**5a** (4 mg) in THF (1 mL) was added NaH (180 mg in 2 mL of THF) at 0 °C. The suspension was stirred for 30 min before addition of *p*-(dimethylamino)-benzoyl chloride (46 mg in 3 mL of THF) at 0 °C. Stirring was continued at room-temperature for 1 day, and reaction was terminated by addition of 20% aqueous ammonium chloride at 0 °C. Usual workup followed by passage through a silica Sep-pak with 50% ethyl acetate in cyclohexane and HPLC on a Du Pont Zorbax SIL column (0.62 × 25 cm) eluted with 30% ethyl acetate in cyclohexane at a flow rate of 2.0 mL/min (k' = 1.94) provided the desired bis *p*-(dimethylamino)benzoate **10a**: mass spectrum (CI-NH_3), *m/z* 610 (M^+ + 1); NMR (220 MHz, $CDCl_3$) $J_{3,4}$ = 5.8 Hz based on H_3 at δ 5.66 with decoupling from H_2 at 2.5; UV spectrum (MeOH) λ_{max} 278 nm (ϵ 86 800), 287 nm (ϵ 92 700), 312 nm (ϵ 86 700), 365 nm (ϵ 12 400e, and 385 nm (ϵ 11 200). The circular dichroism spectrum (MeOH) had exciton chirality interaction bands at $\Delta\epsilon$ = –21.1 (327 nm), 0 (313.5 nm), and +21.9 (297 nm) consistent with 3*R*,4*R* absolute configuration.

(±)-3α,4β-Dihydroxy-1α,2α-epoxy-1,2,3,4-tetrahydrodibenz[*c*,*h*]acridine (12). To a solution of trans dihydrodiol (±)-**7b** (48 mg) in dry THF (15 mL), under Ar, was added recrystallized *m*-chloroperoxybenzoic acid (400 mg). The clear solution was stirred at room temperature for 3 h and then 30 mL of ether was added. The organic phase was extracted with ice-cold 5% NaOH (2 × 15 mL) and H_2O (2 × 15 mL), dried (Na_2SO_4), and concentrated to a white solid under reduced pressure. Trituration with 10% EtOAc/hexane gave diol epoxide (±)-**12** (35 mg, 70%) as a white crystalline solid: mp 205–207 °C dec; mass spectrum (12 eV), *m/z* (relative intensity) 329 (M^+, 100), 311 (57), 312 (16), 300 (31), 282 (42), 283 (40). NMR spectrum: see Table I.

(±)-3α,4β-Dihydroxy-1β,2β-epoxy-1,2,3,4-tetrahydrodibenz[*c*,*h*]acridine (13). To a solution of trans dihydrodiol (±)-**7b** (100 mg) in THF (30 mL) and H_2O (7 mL) at 0–5 °C, under Ar, was added *N*-bromoacetamide (49 mg). Concentrated HCl (2 drops) was added and the solution was stirred at 0–5 °C for 30 min, then EtOAc (40 mL) was added, and the mixture was extracted with H_2O (2 × 25 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated to a solid under reduced pressure. Trituration with 30% EtOAc/hexane gave 116 mg (88%) of (±)-1β,3α,4β-trihydroxy-2α-bromo-1,2,3,4-tetrahydrodibenz[*c*,*h*]acridine as a greyish yellow solid: NMR (300 MHz, Me_2SO-d_6 + CD_3OD) δ 4.30 (H_3, dd), 4.70 (H_4, d), 4.75 (H_2, dd), 6.36 (H_1, d), 9.00 (H_7, s), 9.47 (H_{13}, m), 7.79–8.21 (7 H, m), $J_{1,2}$ = 3.6, $J_{2,3}$ = 2.7, $J_{3,4}$ = 7.6 Hz.

To a solution of the bromo triol (40 mg) in dry THF (10 mL) was added Amberlite-400 (10 g) that had been converted to the hydroxide form. The mixture was stirred at room temperature, under Ar, for 5 h, and was quickly filtered, and the filtrate was concentrated under reduced pressure. Trituration of the solid with petroleum ether gave diol epoxide (±)-**13** (23 mg, 72%) as a light grey solid: mp 193–196 °C dec; mass spectrum (12 eV), *m/z* (relative intensity) 329 (M^+, 6), 311 (100), 312 (28), 295 (25). NMR spectrum: see Table I.

(1*R*,2*S*,3*S*,4*R*)-3,4-Dihydroxy-1,2-epoxy-1,2,3,4-tetrahydrodibenz[*c*,*h*]acridine (12). In the manner described for (±)-**12**, (–)-(3*R*,4*R*)-**7b** (60 mg) and *m*-ClPBA (500 mg) in dry THF (25 mL) were reacted to yield 49 mg (78%) of (1*R*,2*S*,3*S*,4*R*)-3,4-dihydroxy-1,2-epoxy-1,2,3,4-tetrahydrodibenz[*c*,*h*]acridine (**12**) as white crystals of mp 208–210 °C dec. NMR spectrum (as for (±)-**12** in Table I).

(1*S*,2*R*,3*R*,4*S*)-3,4-Dihydroxy-1,2-epoxy-1,2,3,4-tetrahydrodibenz[*c*,*h*]acridine (12). Direct epoxidation of (+)-(3*S*,4*S*)-3,4-dihydrodiol **7b** (55 mg) as described above for the enantiomer gave 41 mg (71%) of (1*S*,2*R*,3*R*,4*S*)-3,4-dihydroxy-1,2-epoxy-1,2,3,4-tetrahydrodibenz[*c*,*h*]acridine (**12**) as a white crystalline solid of mp 208–210 °C dec. NMR spectrum (as for (±)-**12** in Table I).

(1*S*,2*R*,3*S*,4*R*)-3,4-Dihydroxy-1,2-epoxy-1,2,3,4-tetrahydrodibenz[*c*,*h*]acridine (13). In the manner described for the preparation of (±)-**13** (-)-(3*R*,4*R*)-dihydrodiol **7b** (63 mg) and *N*-bromoacetamide (31 mg) in THF (12 mL) and H_2O (3 mL) with a drop of concentrated HCl were converted to the bromo triol (71 mg, 90%) of mp 154–157 °C dec. Cyclization of the bromo triol (65 mg) in THF (7 mL) with Amberlite-IRA 400 (5 g) gave 38 mg (70%) of diol epoxide (1*S*,2*R*,3*S*,4*R*)-3,4-dihydroxy-1,2-epoxy-1,2,3,4-tetrahydrodibenz[*c*,*h*]acridine (**13**) as a white crystalline solid of mp 198–200 °C dec. NMR spectrum (as for (±)-**13** in Table I).

(1*R*,2*S*,3*R*,4*S*)-3,4-Dihydroxy-1,2-epoxy-1,2,3,4-tetrahydrodibenz[*c*,*h*]acridine (13). In the same manner described above for the enantiomer (+)-(3*S*,4*S*)-dihydrodiol **7b** (63 mg) was converted to the bromo triol (69 mg, 79%) of mp 152–154 °C dec. Cyclization of the bromo triol (58 mg) gave 22 mg (45%) of diol epoxide (1*R*,2*S*,3*R*,4*S*)-3,4-dihydroxy-1,2-epoxy-1,2,3,4-tetrahydrodibenz[*c*,*h*]acridine (**13**) as a white crystalline solid of mp 189–191 °C dec. NMR spectrum (as for (±)-**13** in Table I).

1-Hydroxy-1,2,3,4-tetrahydrodibenz[*c*,*h*]acridine (14). 1,2,3,4-Tetrahydrodibenz[*c*,*h*]acridine (3.7 g) was dissolved in benzene (150 mL) and HOAc (300 mL), and a solution of ceric ammonium sulfate (8.5g) in H_2O (40 mL) was added. The clear solution was stirred at 40–45 °C for 96 h. Most of this solvent was removed under reduced pressure at 45–50 °C and the remaining residue was neutralized with ice-cold 20% NaOH. The mixture was extracted with EtOAc (3 × 100 mL) and the organic phase was washed with H_2O (2 × 100 mL), dried over Na_2SO_4, and evaporated to yield 2.6 g of crude product, which was chromatographed over dry column grade silica gel using CH_2Cl_2–CCl_4 (1:1) as developing solvent. Initially, 0.7 g of 1,2,3,4-tetrahydrodibenz[*c*,*h*]acridine was eluted, followed by 1.0 g (26%) of 1-hydroxy-1,2,3,4-tetrahydrodibenz[*c*,*h*]acridine (**14**) mp 138–140 °C (lit.[18] mp 143–144 °C). NMR spectrum (see Table I).

3,4-Dihydrodibenz[*c*,*h*]acridine (15). 1-Hydroxy-1,2,3,4-tetrahydrodibenz[*c*,*h*]acridine (0.5 g) was suspended in a solution of HOAc (25 mL) and concentrated HCl (4 drops). The mixture was stirred at ca. 65 °C for 2.5 h under Ar. The reaction mixture was cooled in ice and basified with saturated Na_2CO_3. The basic solution was extracted with EtOAc (2 × 100 mL). The organic phase was washed with H_2O (2 × 75 mL) and dried (Na_2SO_4), and solvents were removed to leave a yellow solid, which was purified by chromatography on a small column of silica gel, using benzene–hexane (1:1). The 3,4-dihydrodibenz[*c*,*h*]acridine thus obtained (0.42 g, 90%) as a yellow crystalline solid had mp 128–130 °C (lit.[18] mp 132–133 °C). NMR spectrum (see Table I).

***trans*-2-Bromo-1-hydroxy-1,2,3,4-tetrahydrodibenz[*c*,*h*]acridine (16).** To an ice-cooled solution of 3,4-dihydrodibenz[*c*,*h*]acridine (**15**) in THF (20 mL) and H_2O (4 mL) were added NBA (0.17 g) and concentrated HCl (2 drops). The solution was stirred at 0–5 °C, under Ar, for 1 h. EtOAc (50 mL) was added, and the organic phase was extracted with 5% $NaHCO_3$ (1 × 25 mL) and H_2O (1 × 25 mL), dried (Na_2SO_4), and evaporated under reduced pressure to yield a solid, which was triturated with EtOAc–hexane (1:5), leaving *trans*-2-bromo-1-hydroxy-1,2,3,4-tetrahydrodibenz[*c*,*h*]acridine (**16**) as a yellow powder (360 mg, 79%) of mp 151–153 °C after recrystallization from EtOAc–hexane. NMR spectrum (see Table I). The same bromohydrin was also obtained by reaction of a mixture of 1,2- and 3,4-dihydrodibenz[*c*,*h*]acridine (1.7 g, see experimental for **2** and **3**) in THF (100 mL) and H_2O (25 mL) with NBA (0.84) and 0.1 N HCl (2 drops) for 18 h at 0–5 °C. Workup as described above followed by chromatography of the mixture on dry column grade silica gel using 10% EtOAc–hexane gave first 303 mg (13%) of **16**, followed by 320 mg (14%) of *trans*-3-bromo-4-hydroxy-1,2,3,4-tetrahydrodibenz[*c*,*h*]acridine (**17**), mp 184–186.5 °C (needles from EtOAc/hexane). NMR spectra (see Table I).

(±)-1,2-Epoxy-1,2,3,4-tetrahydrodibenz[*c*,*h*]acridine ((±)-18). 2-Bromo-1-hydroxy-1,2,3,4-tetrahydrodibenz[*c*,*h*]-acridine (82 mg) was stirred with 5.0 g of Amberlite-400 ($^-$OH form)[7,23] in dry THF, under Ar, at room temperature. After 1 h, the mixture was filtered, the resin was washed with dry THF, and the solvent was evaporated, leaving a yellow solid which after recrystallization from ether/petroleum ether gave (±)-**18** (43.5 mg, 67%) as a solid of mp 134–135 °C (lit.[18] mp 135.5–136.5 °C).

Diastereomeric (-)-(*S*)-α-(Trifluoromethyl)phenylacetyl (MTPA) Esters 19 and 20 of *trans*-1-Hydroxy-2-bromo-1,2,3,4-tetrahydrodibenz[*c*,*h*]acridine. To a solution of (±)-*trans*-1-hydroxy-2-bromo-1,2,3,4-tetrahydrodibenz[*c*,*h*]acridine (350 mg) in dry pyridine (12 mL) was added portionwise (-)-(*S*)-MTPA chloride (3.5 mL) under cooling at 0 °C over 5 min. The reaction mixture was stirred at 0–5 °C for 16 h and was diluted with EtOAc. The solution was washed with 1 N HCl to remove pyridine. Then the organic layer was washed with 5% $NaHCO_3$ and H_2O, dried ($MgSO_4$), and evaporated to leave crude MTPA ester which was subjected to silica gel column chromatography, using EtOAc in cyclohexane.

Preparative separation of the diastereomers was achieved (100% diastereomerically pure) on a Du Pont Zorbax SIL HPLC column (2.12 × 25 cm) eluted with 5% EtOAc in cyclohexane at a flow rate of 20 mL/min (α = 1.63). Evaporation of the less polar fraction (k' = 2.37) afforded **19**, the (+)-ester of the (*R*,*R*)-bromohydrin (258 mg, 94%): $[\alpha]^{20}_D$ +67° (*c* 1.75, THF); NMR ($CDCl_3$, 220 MHz) δ 7.84 (d, 1 H, J = 2.9 Hz, H_1), 4.77 (q, 1 H, J = 3 Hz, H_2); mp 188–190 °C (EtOAc–MeOH). Evaporation of the more polar fraction (k' = 3.87) afforded **20**, the (-)-ester of the (*S*,*S*)-bromohydrin (217 mg, 79%): $[\alpha]^{20}_D$ -45° (*c* 1.60 THF); NMR ($CDCl_3$, 220 MHz) δ 7.93 (d, 1 H, J = 2.9 Hz, H_1), 4.86 (q, 1 H, J = 3 Hz, H_2); this fraction failed to crystallize. Both esters gave mass spectra (CI-NH_3) with m/z 596 (M^+ + 3), 594 (M^+ + 1), 362 (M^+ + 3 - $C_{10}H_9O_3F_3$), 360 (M^+ + 1 - $C_{10}H_9O_3F_3$), 282 (base peak), 252 ($C_{10}H_9O_3F_3$ + NH_3 + 1).

Assignment of Absolute Configuration to the Bromohydrins. To a solution of the (±) bromohydrin **16** (5 mg) in dry pyridine (1 mL) was added (-)-menthoxyacetyl (MA) chloride (0.2 mL) under cooling at 0 °C. The reaction mixture was stirred at 0–5 °C for 3 h and was diluted with EtOAc. The solution was washed with 1 N HCl, 5% $NaHCO_3$, and H_2O. The organic layer was dried ($MgSO_4$) and evaporated to leave crude MA ester which was subjected to silica gel column chromatography using 3% EtOAc in cyclohexane.

Preparation separation of the diastereomers was achieved (>98% diastereomerically pure) on a Du Pont Zorbax SIL HPLC column (0.94 × 25 cm) eluted with 5% EtOAc in cyclohexane at a flow rate of 3.92 mL/min (α = 1.17). Evaporation of the less polar fraction (k' = 1.88) afforded **21**, the ester of the (*R*,*R*)-bromohydrin (3 mg, 79%): NMR (C_6D_6, 100 MHz) δ 4.69 (q, 1 H, J = 3Hz, H_2), 4.04 (s, 2 H, $COCH_2O$). Evaporation of the more polar fraction (k' = 2.19) afforded **22**, the ester of the (*S*,*S*)-bromohydrin (2 mg, 53%): NMR (C_6D_6, 100 MHz) δ 4.64 (q, 1 H, J = 3 Hz, H_2), an AB quartet with the doublets centered at 4.04 and 3.84 (2 H, J_{gem} = 16.5 Hz, $COCH_2O$). Both esters gave mass spectra (CI-NH_3) with m/z 576 (M^+ + 3), 574 (M^+ + 1), 362 (M^+ + 3 - $C_{12}H_{22}O_3$), 360 (M^+ + 1 - $C_{12}H_{22}O_3$), 282 (base peak), 232 ($C_{12}H_{22}O_3$ + NH_3 + 1).

To the MA ester of the more polar (*S*,*S*)-bromohydrin **22** (2 mg) was added a 1 M solution of borane–tetrahydrofuran complex (1 mL) under cooling at 0 °C. The reaction mixture was stirred at 0–5 °C for 55 h and was poured into 1 mL of MeOH/H_2O (9:1). The solution was diluted with EtOAc, washed with 5% $NaHCO_3$, dried ($MgSO_4$), and evaporated. The bromohydrin was purified on a Du Pont Zorbax SIL HPLC column (0.62 × 25 cm) eluted with 10% EtOAc in cyclohexane at a flow rate of 2.8 mL/min (k' = 2.14); mass spectrum (CI-NH_3) m/z 380 (M^+ + 3), 378 (M^+ + 1), 298 (M^+ - Br, base peak).

To a solution of the (*S*,*S*)-bromohydrin in dry pyridine (0.5 mL) was added (-)-MTPA chloride (50 μL) under cooling at 0 °C. The reaction mixture was stirred at 0–5 °C for 4 h and was diluted with EtOAc. The solution was washed with 1 N HCl, 5% $NaHCO_3$, and H_2O, and was dried ($MgSO_4$). The extract was analyzed on a Du Pont Zorbax SIL HPLC column (0.62 × 25 cm) eluted with 10% EtOAc in cyclohexane at a flow rate of 2.8 mL/min and found to be cochromatographed with **20**, the more polar (-)-(*S*,*S*)-MTPA ester of the bromohydrin (k' = 1.89) which was well separated from the less polar (+)-(*R*,*R*-MTPA ester (k' = 1.33).

Preparation of (-)-(1*S*,2*R*)-1,2-Epoxy-1,2,3,4-tetrahydrodibenz[*c*,*h*]acridine ((-)-18). To a solution of **20**, the more polar (-)-(*S*,*S*)-MTPA ester of the bromohydrin (170 mg) in freshly distilled THF (10 mL) was added sodium methoxide (200 mg). The reaction mixture was stirred at 0–5 °C for 45 h. The reaction

mixture was diluted with ether and washed with water and 10% Na_2CO_3. The ether solution was dried (Na_2CO_3) and evaporated to leave crude epoxide. The crude epoxide was purified by a Du Pont Zorbax SIL HPLC column (0.94 × 25 cm) eluted with 5% EtOAc in cyclohexane at a flow rate of 3.92 mL/min to provide 30 mg (35%) of pure epoxide ($k' = 2.85$): mp 149–150 °C (ether–petroleum ether) $[\alpha]^{20}_D$ –73° (c 0.81, THF). NMR (as for (±)-18 in Table I). Dibenz[c,h]acridine ($k' = 0.96$, 1 mg, 1%) and unreacted (–)-(S,S)-MTPA ester ($k' = 3.34$, 5 mg, 3%) were also obtained.

Preparation of (+)-(1*R*,2*S*)-1,2-Epoxy-1,2,3,4-tetrahydrodibenz[*c*,*h*]acridine ((+)-18). To a solution of the less polar (+)-(R,R)-MTPA ester of the bromohydrin (210 mg) in freshly distilled THF (10 mL) was added sodium methoxide (200 mg). Every 4 days, fresh sodium methoxide (200 mg) was added to the reaction mixture which was stirred at 0–5 °C for 13 days. The reaction mixture was diluted with ether and washed with water and 10% Na_2SO_3. The ether solution was dried (Na_2CO_3) and evaporated to leave crude epoxide. The crude epoxide was purified by a Du Pont Zorbax SIL HPLC column (0.94 × 25 cm) eluted with 5% EtOAc in cyclohexane at a flow rate of 3.92 mL/min to provide 56 mg (53%) of pure epoxide ($k' = 2.92$): mp 149–151 °C (ether–petroleum ether) $[\alpha]^{20}_D$ +71° (1.01, THF). NMR (as for (±)-18 in Table I). Dibenz[c,h]acridine ($k' = 0.98$, 11 mg, 11%) and unreacted (+)-(R,R)-MTPA ester ($k' = 2.26$, 26 mg, 12%) were also obtained. Both enantiomers of the tetrahydro 1,2-epoxide gave mass spectra (CI-NH_3) with m/z 298 ($M^+ + 1$). UV (THF): λ_{max} 279 nm (ε 70 200), 290 nm (ε 71 900), 338 (ε 5960), 344 (ε 5790), 353 (ε 7250), 371 (ε 9480), 382 (ε 9710).

Dibenz[*c*,*h*]acridine 5,6-Oxide (23). A mixture of dibenz[c,h]acridine (2.6 g), obtained by dehydrogenation of 1,2,3,4-tetrahydrodibenz[c,h]acridine with 10% Pd/C at 330–350 °C for 3 h under Ar, Chlorox (160 mL), pH 9 buffer (80 mL), tetrabutylammonium hydrogen sulfate (1.8 g), and $CHCl_3$ (100 mL) was stirred vigorously at room temperature under Ar for 5 h. The mixture was extracted with ether (500 mL) and the ether layer was washed with H_2O (6 × 150 mL), dried (Na_2SO_4), and concentrated under reduced pressure to a yellow solid (2.6 g) that was a ca. 3:2 mixture of dibenz[c,h]acridine and its 5,6-oxide, as judged by NMR analysis. A small portion (100 mg) of this solid was chromatographed on Florisil using benzene as eluant. Following an initial fraction containing mostly dibenz[c,h]acridine, dibenz[c,h]acridine 5,6-oxide contaminated with very small amounts of phenol(s) was obtained. Further chromatography of this material on a column of dry column grade neutral alumina using benzene as eluant gave **23** (11 mg, 10%) as a colorless, flaky solid of mp 172–175 °C (lit.[30] mp 179–180 °C). NMR spectrum: see Table I. UV (THF, λ_{max}, ϵ_{max}): 251 (26 140), 294 (18 730), 312 (8700), 320 (8600), 326 (8800), 349 (8160), 358 (3400), 367 (10 100).

***trans*-5,6-Dihydroxy-5,6-dihydrodibenz[*c*,*h*]acridine (24).** The major portion (2.5 g) of the crude reaction product in the synthesis of K-region oxide **23** was dissolved in dioxane (250 mL) that had been filtered through a column of activated alumina to remove peroxides, HOAc (16 mL), and H_2O (65 mL). The solution was stirred at 38–40 °C, under Ar, for 88 h. EtOAc (300 mL) was added, and the organic phase was washed with H_2O (4 × 150 mL), 10% Na_2CO_3 (1 × 150 mL), and H_2O (1 × 150 mL), dried (Na_2SO_4), and concentrated under reduced pressure to a reddish yellow solid (2.5 g). Chromatography of this material on dry column grade silica gel (400 g) using benzene gave first 1.7 g of dibenz[c,h]acridine, which was recrystallized from CCl_4 to give 1.2 g of highly pure dibenz[c,h]acridine, mp 188–189.5 °C. This procedure removes small quantites (ca. 5%) of ring-methylated dibenz[c,h]acridine that contaminates the dibenz[c,h]acridine obtained by dehydrogenation of incompletely purified 1,2,3,4-tetrahydrodibenz[c,h]acridine. Further elution with 1:1 EtOAc:hexane gave 78 mg of a mixture of cis and trans 5,6-dihydrodiols, which was refluxed for 4 h in acetone containing anhydrous $CuSO_4$. Filtration, followed by removal of the acetone under reduced pressure, left a solid that was triturated with CH_2Cl_2 to yield 53 mg (6%) of trans-K-region dihydrodiol **24** as a pale yellow crystalline solid, mp 205–207 °C. NMR (see Table I). UV (THF) (λ_{max}, ϵ_{max} see Figure 3): 249 (42 400), 295 (23 000), 318 (14 500), 331 (8110), 348 (12 600), 365 (15 800).

***cis*-5,6-Dihydroxy-5,6-dihydrodibenz[*c*,*h*]acridine (25).** A solution of dibenz[c,h]acridine (57 mg), OsO_4 (57 mg), and anhydrous pyridine (2.5 mL) was stirred for 4 days under Ar. A saturated solution of sodium bisulfite (10 mL) was then added and the mixture was stirred for 3 h and extracted with EtOAc (2 × 25 mL). The EtOAc layer was extracted with 0.5% HCl (2 × 50 mL) and H_2O, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue (43 mg), was chromatographed on dry column grade silica gel using EtOAc as eluent. The solid obtained in this manner was triturated with Et_2O/CH_2Cl_2 and recrystallized from EtOAc/hexane to give cis-K-region diol **25** as pale yellow crystals (25 mg, 40%) of mp 202–204 °C. NMR spectrum (see Table I).

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