Synthesis of Enantiomerically Pure Bay-Region 10,11-Diol 8,9-Epoxide Diastereomers of the Carcinogen Dibenz[a,h]acridine

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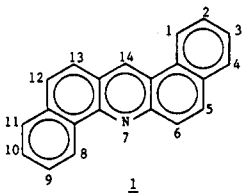
The present study describes the synthesis and configurational assignment of four enantiomerically pure, bay-region 10,11-diol 8,9-epoxide diastereomers 14–17 of dibenz[a,h]acridine (1) from the corresponding optically pure *trans*-10,11-dihydroxy-10,11-dihydrodibenz[a,h]acridine enantiomers 6 and 7. Racemic *trans*-10,11-dihydroxy-10,11-dihydrodibenz[a,h]acridine (3) was resolved via its conversion to the diastereomeric bis((-)-methyloxy) esters, separation of the diastereomers by short bed/continuous developing preparative TLC, and finally saponification of the individual diastereomers. Assignment of (10*R*,11*R*)-absolute configuration to (-)-*trans*-10,11-dihydroxy-10,11-dihydrodibenz[a,h]acridine (6) was achieved through the application of exciton circular dichroism technique to the bis[*p*-(dimethylamino)cinnamic] ester 13 of its tetrahydro analogue 11.

Polycyclic aromatic hydrocarbons (PAHs) derived from the incomplete combustion of organic matter are widespread environmental contaminants found in cigarette smoke, air, water, food, and soil.[1,2] Included in this group are a number of nitrogenous heterocycles (aza-PAHs) which are reported to be carcinogenic in experimental animals.[3-5] Within the past decade, substantial evidence has been obtained suggesting that, like PAHs, their aza analogues (aza-PAHs) are also activated according to the bay-region theory.[6-11] Our recent studies[12,13] with dibenz[a,h]acridine (DB[a,h]ACR, 1), an 7-aza analogue of



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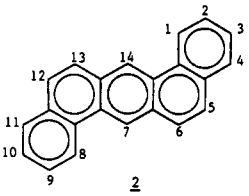

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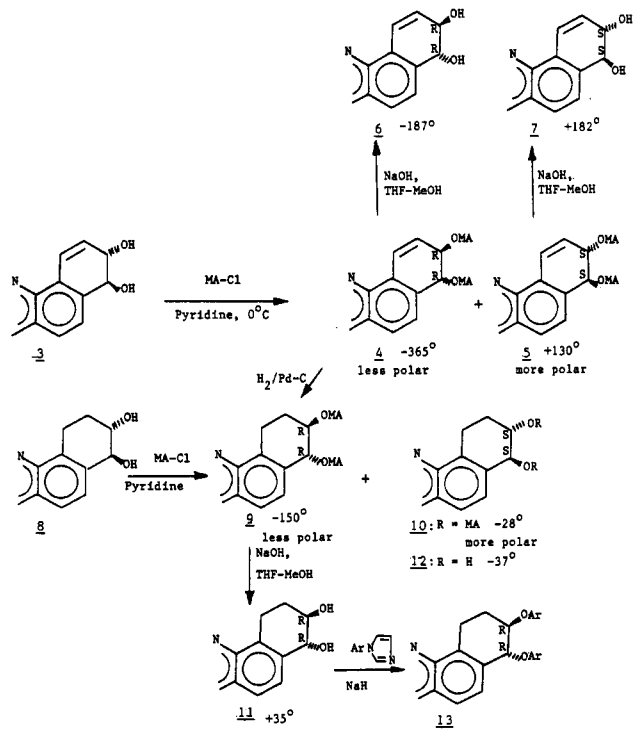
dibenz[a,h]anthracene 2 and a potent carcinogen[3,5] with two asymmetric bay regions, have revealed that DB[a,h]ACR exhibits most of its biological activities via its bay-region 10,11-diol 8,9-epoxide rather than its bay-region 3,4-diol 1,2-epoxide. This result was expected based on qualitative resonance arguments and quantum chemical calculations[14,15] which predict higher electrophilicity for the bay-region 10,11-diol 8,9-epoxide relative to its regioisomer bay-region 3,4-diol 1,2-epoxide. Since each regioisomeric bay-region diol epoxide exists as enantiomers of diastereomer-1 and diastereomer-2 (see Figure 1), the present study was undertaken to synthesize the (+)- and

Scheme I[a]



[a] MA = (-)-(menthyloxy)acetyl- and Ar = *p*-(dimethylamino)-cinnamoyl-

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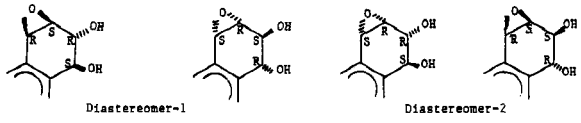

Figure 1. Absolute configuration of four possible enantiomers of diastereomeric diol epoxides.

(−)-enantiomers of the diastereomeric bay-region 10,11-diol 8,9-epoxides of DB[a,h]ACR (*14–17*, see Scheme II) in order to probe whether the stereochemical relationship with tumorigenicity observed for other PAH diol epoxide stereoisomers[16–18] can be extended to their aza analogues. An increased understanding of the factors responsible for subtle differences in tumorigenicity between closely related bay-region diol epoxide stereoisomers of aza-PAHs and PAHs is hoped to shed insight into the mechanism responsible for a cell to become cancerous.

Results and Discussion

Procedures previously used in the synthesis of the bay-region diol epoxide enantiomers of aza-PAHs have employed the corresponding racemic dihydro diols as starting materials.[19,20] Thus, the *trans*-10,11-dihydro diol enantiomers **6** and **7** were resolved as their bis((−)-menthyloxy) esters **4** and **5**, respectively, prepared from (±)-*trans*-10,11-dihydro diol **3**[19,20] and (−)-(menthyloxy)-acetyl chloride (see Scheme I). In view of the poor loadability of the bis((−)-menthyloxy) esters of the racemic dihydro diol **3** or tetrahydro diol **8** on preparative-scale HPLC, we examined alternate chromatographic techniques. The best result was obtained using short bed/continuous developing preparative TLC (Analtech, Newark, DE). We continuously developed preparative TLC plates (20 × 20 cm, 1000 μm) in a 13-cm-high developing chamber using 8% ether in cyclohexane until a clear separation of two bands was observed. By applying this modified technique, we were able to separate 20 mg of the mixture of diastereomers per plate using two plates/chamber (isolated yield of 80–90%). No cross contamination was detected (HPLC) for the separated diastereomers **4** and **5**. The (−)-10,11-dihydro diol *6*, obtained by basic hydrolysis of the less polar bis((−)-menthyloxy) ester **4**, has a broad CD band at 279 nm (Δε −14). The (+)-10,11-dihydro diol **7**, obtained from the more polar bis((−)-menthyloxy) ester *5*, has a CD spectrum symmetric to that of **6** but with Δε +15 at 279 nm.

We have previously pointed out that bis((−)-menthyloxy) esters of the benzo-ring *trans*-dihydro and -tetrahydro diols show several trends in their physical and spectral properties which can be used to predict their absolute configuration.[20–22] Specifically, the (*R,R*) diastereomers (a) elute early (less polar) from silica gel HPLC columns, (b) show

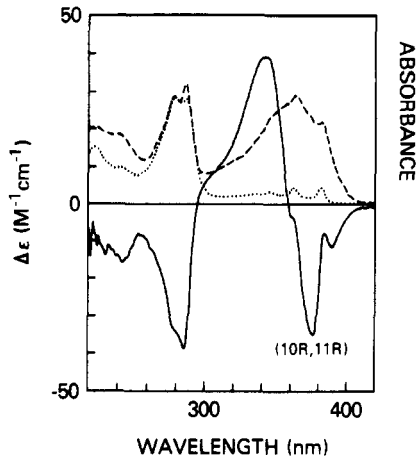

Figure 2. Circular dichroism spectrum (—) and ultraviolet spectrum (---) of the bis[*p*-(dimethylamino)cinnamic]ester **13** of (+)-*trans*-10,11-dihydroxy-8,9,10,11-tetrahydrodibenz[a,h]acridine (**11**) in THF. Concentration of the CD sample was based on λ_{288nm} 81 800 for the corresponding bis(menthyloxy) ester **9** (···, UV).

a greater degree of magnetic equivalence between the diastereotopic hydrogens H_A and H_B in the $-OCH_AH_BCO_2-$ moiety of the (menthyloxy)acetyl esters, and (c) have larger negative values of $[\alpha]_D$ than the (*S,S*)-diastereomers. The same pattern has been observed here for the bis(menthyloxy) ester diastereomers **4** and **5** of *trans*-10,11-dihydro diol **3** and tetrahydro diol **8**, as was the case for the related diols of DB[c,h]ACR.[20] The physical correlations, therefore, suggest that early eluting (less polar) bis((−)-menthyloxy) ester diastereomers **4** and **9** and the corresponding free dihydro and tetrahydro diols **6** and **11** have (10*R*,11*R*) absolute configuration. These tentative assignments of absolute configuration have been confirmed by an exciton chirality experiment based on the interaction between two benzoate chromophores.[23] Recently, the use of *p*-(dimethylamino)cinnamic esters (λ_{max} 360 nm) has been introduced[24] for exciton experiments since its bis esters have exciton bands at much higher wavelength thus avoiding overlapping interactions between the aromatic hydrocarbon residue and the ester chromophores. This chromophore has been utilized in the present study to assign absolute configuration to an enantiomer of the *trans*-tetrahydro diol **8**, which was then chemically correlated with an enantiomer of the *trans*-dihydro diol **3** by reduction of the 8,9-double bond.

(+)-*trans*-10,11-Dihydroxy-8,9,10,11-tetrahydrodibenz-[a,h]acridine (**11**) was converted to its bis[*p*-(dimethylamino)cinnamic] ester **13** by the described procedure.[24] The bis ester **13** has a strong UV band at 365 nm (Figure 2). The ^{1}H-NMR spectrum of the bis ester **13** showed a value of $J_{10,11}$ = 6.6 Hz, indicative of a slight preference for the diaxial conformation of the ester groups. This small preference for the diaxial conformation was not expected to preclude an exciton interaction between the ester groups. The CD spectrum (Figure 2) of **13** showed a strong negative band at 377 nm (Δε −35), zero at 358 nm, and a positive band at 344 nm (Δε +40). The negative long wavelength band requires a negative skew-sense for the two ester groups about the C_{10}–C_{11} bond. Thus (10*R*,11*R*) absolute configuration is required for the bis-cinnamoyl ester **13**, the corresponding (+)-tetrahydrodiol **14**, and its less polar bis((−)-menthyloxy) ester **9**. The lack of complete symmetry between the negative and positive portions

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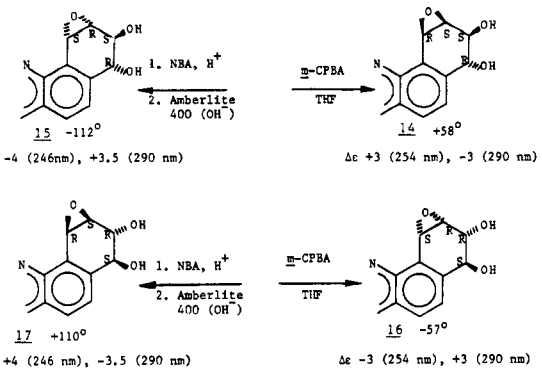
Scheme II



of this Cotton effect may be attributed to weak interactions between one or both ester groups and long wavelength bands of the tetrahydro diol chromophore. To correlate absolute configuration of the bis((-)-menthyloxy) esters of the tetrahydro diol 8 with the bis((-)-menthyloxy) esters of the dihydro diol 3, a diastereomeric mixture of bis-((-)-menthyloxy) esters of the dihydro diol 3 with a 40% excess of the less polar bis((-)-menthyloxy) ester 4 was reduced at the 8,9-double bond to produce a mixture of bis((-)-menthyloxy) esters of 8 enriched in 9 (HPLC). Correlation between 4 and 9 was anticipated from the physical data and is consistent with (10*R*,11*R*)-absolute configuration of **4**, **9**, **11** and **13** (Scheme I). All benzo-ring dihydro diols with (*R*,*R*)-configuration which have been resolved to data have negative value of $[\alpha]_D$ when measured in tetrahydrofuran (THF).[25]

In the manner described earlier for racemic material,[14] the enantiomeric dihydrodiols **6** and **7** were converted to the four stereoisomeric diol epoxides **14**–**17** (Scheme II). Thus, **6** and **7** gave enantiomeric diol epoxides **14** and **16**, respectively, in 85–87% yield upon reaction with an excess of purified *m*-chloroperoxybenzoic acid (*m*-CPBA) in dry THF at rt. Similarly, **6** and **7** were converted to the corresponding bromo triols upon treatment with *N*-bromoacetamide (NBA) in aqueous acidic THF, and the bromo triols were cyclized to enantiomeric diol epoxides **15** and **17**, respectively, with Amberlite-400 (OH^-). Each of the enantiomeric diol epoxides was pure and assigned the relative stereochemistry and, consequently, the absolute configuration by comparing its 270-MHz ^{1}H-NMR spectrum with that of the appropriate racemic diol epoxides.[14] As anticipated,[26] epoxide oxygen from *m*-CPBA and brominium ion (Br^+) from NBA add to the 8,9-double bond on the face of each dihydrodiol enantiomer which bears 10-OH to produce diol epoxide and bromo triol, respectively, with high stereoselectivity. Specific rotations and CD data for the diol epoxide stereoisomers are given in Scheme II. Notably, there is a correlation between sign of rotation and absolute configuration between these and other "bay-region" diol epoxides which differs from that observed for "fjord-region" diol epoxides.[22,27] We are currently evaluating the comparative mutagenicity and tumorigenicity of these four closely related stereoisomers.

Experimental Section

General. ^{1}H-NMR spectra were recorded at 270 or 300 MHz with Me_4Si as internal standard. Optical rotations were measured at a concentration ranging from 0.1 to 0.5 g/100 mL of THF. Chemical ionization (NH_3) mass spectra were obtained with a direct exposure probe. The compounds for microanalysis were dried at rt under vacuum.

(±)-*trans*-10,11-Dihydroxy-10,11-dihydrodibenz[*a*,*h*]acridine (**3**, ϵ_{290nm} 7.5×10^4 in THF) was obtained according to the literature procedure.[14] A value of ϵ_{288nm} 6.6×10^4 in THF was used for the 10,11-diol 8,9-epoxides of dibenz[*a*,*h*]acridine. The ^{1}H-NMR spectrum of the enantiomers **6**, **7**, **14**, **15**, **16**, and **17** was identical to that reported for the corresponding racemic compound.[14]

Diastereomeric Bis((-)-menthyloxy) Esters of *trans*-10,11-Dihydroxy-10,11-dihydrodibenz[*a*,*h*]acridine (4 and 5). To a solution of (±)-*trans*-10,11-dihydroxy-10,11-dihydrodibenz[*a*,*h*]acridine (**3**, 0.8 g) in dry pyridine (40 mL) was added portionwise (-)-(menthyloxy)acetyl chloride (7 mL) under cooling at 0 °C. The mixture was kept at 0–5 °C for 24 h, poured on to HCl–ice, and then extracted with ether (2 × 250 mL). The organic extract was washed with chilled water (2 × 25 mL) and saturated aqueous $NaHCO_3$ (7 × 10 mL), dried (Na_2SO_4), and evaporated under reduced pressure to leave an oily residue. This oily residue was chromatographed over a short column of silica gel using benzene–cyclohexane to produce a yellow semisolid (1.75 g, 97%). Analytical separation of bis((-)-menthyloxy) ester diastereomers **4** and **5** was achieved on a Perkin-Elmer HS-3 silica column using 5% ether in cyclohexane as eluent. This HPLC condition gave an α value of 1.18 with $k' = 7.06$ for **4** and 8.33 for **5**.

Preparative separation of the diastereomers **4** and **5** was achieved (>98% diastereomerically pure) on preparative TLC using the short bed/continuous development technique supplied by Analtech with a modification. In the modified procedure, preparative silica gel plates (20 × 20 cm, 1000 μm, Analtech) were developed in a 10- × 20-cm TLC chamber using 6% ether in cyclohexane. The two bands of the diastereomeric esters were separated after continuous development of the plates for 24 h in the fume hood. Evaporation of the extract of the less polar band afforded the bis ester **4** of (-)-(*R*,*R*)-dihydro diol (46% yield): mp 145–147 °C; $[\alpha]_D$ -365° (THF); ^{1}H-NMR (300 MHz, C_6D_6) δ 0.60–3.14 (m, 19 H, menthyl), 3.91 (s, 2 H, $-COCH_AH_B-$), 3.98 (s, 2 H, $-COCH_AH_B-$), 6.06 (t, 1 H, H_{10}), 6.35 (dd, 1 H, H_9), 6.80 (d, 1 H, H_{11}), 7.34–8.23 (m, 9 H, H_8 and Ar*H*), 8.80 (s, 1 H, H_{14}), $J_{1,2}$ = 10 Hz, $J_{8,9}$ = 9.9 Hz, $J_{9,10}$ = 4.4 Hz, $J_{10,11}$ = 5.4 Hz; mass spectrum (CI-NH_3), *m*/*z* 706 ($M^+ + 1$). Anal. Calcd for $C_{45}H_{55}NO_6 \cdot {}^1/_2H_2O$: C, 75.6, H, 7.8. Found: C, 75.5; H, 7.8. Evaporation of the extract of the more polar band afforded the bis ester **5** of the (+)-(*S*,*S*)-dihydro diol (49% yield): mp 76–78 °C; $[\alpha]_D$ +130° (THF); ^{1}H-NMR (300 MHz, C_6D_6) δ 0.60–3.14 (m, 19 H, menthyl), 3.91 (dd, 2 H, $-COCH_AH_B-$, J_{gem} = 16.3 Hz), 3.99 (dd, 2 H, $-COCH_AH_B-$, J_{gem} = 16.3 Hz), 6.07 (t, 1 H, H_{10}), 6.35 (dd, 1 H, H_9), 6.79 (d, 1 H, H_{11}), 7.34–8.23 (m, 9 H, Ar*H* and H_8), 8.69 (d, 1 H, H_1), 8.79 (s, 1 H, H_{14}), $J_{1,2}$ = 10 Hz, $J_{8,9}$ = 9.9 Hz, $J_{9,10}$ = 4.4 Hz, $J_{10,11}$ = 5.7 Hz; mass spectrum (CI-NH_3) *m*/*z* 706 ($M^+ + 1$). Anal. Calcd for $C_{45}H_{55}NO_6 \cdot H_2O$: C, 74.7; H, 7.9. Found: C, 74.7; H, 8.1.

(-)-*trans*-(10*R*,11*R*)-Dihydroxy-10,11-dihydrodibenz[*a*,*h*]acridine (6). To a solution of the less polar diastereomer **4** (0.632 g) in MeOH/THF (1:1, 25 mL) was added 10% aqueous NaOH solution (3.0 mL) with stirring at 0 °C. The reaction mixture was stirred at 0–5 °C for 0.5 h and concentrated under reduced pressure. Ice-cold water (5 mL) was added, and the resulting solid was filtered, washed with water, and dried under vacuum. Trituration of the residual solid with ether produced 0.25 g (89%) of pure **6**: mp 260–262 °C; $[\alpha]_D$ -187° (THF).

(+)-*trans*-(10*S*,11*S*)-10,11-Dihydroxy-10,11-dihydrodibenz[*a*,*h*]acridine (7). Treatment of the more polar bis ester **5** (0.634 g) in the same manner as **4** afforded **7** as a crystalline solid (0.23 g, 80%): mp 260–262 °C; $[\alpha]_D$ +182° (THF). Anal. Calcd for $C_{21}H_{15}O_2 \cdot {}^1/_2H_2O$: C, 78.3; H, 5.0. Found: C, 78.6; H, 4.8.

Diastereomeric Bis((-)-menthyloxy) Esters of *trans*-10,11-Dihydroxy-8,9,10,11-tetrahydrodibenz[*a*,*h*]acridine (9 and 10). To a solution of (±)-*trans*-10,11-dihydroxy-8,9,10,11-dihydrodibenz[*a*,*h*]acridine (**8**) (40 mg)[14] in 2 mL of pyridine was added (-)-(menthyloxy)acetyl chloride, and the mixture was stored at rt for 24 h prior to standard workup as described for **4** and **5**. After preliminary purification on an open silica gel column, the diastereomers were separated on a Rainin Microsorb silica gel

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column (10 × 250 mm) eluted with 6% ether in cyclohexane at flow rate of 2 mL/min (α = 1.16). Evaporation of the less polar fraction (k' = 6.67) afforded the bis ester **9** of the (−)-(*R,R*)-tetrahydro diol: $[\alpha]_D$ −150°; ^{1}H-NMR (300 MHz, C_6D_6) δ 0.81–3.22 (m, 19 H, menthyl), 3.94 (dd, 2 H, $-COCH_AH_B-$, J_{gem} = 16.3 Hz), 4.11 (dd, 2 H, $-COCH_AH_B-$, J_{gem} = 16.3 Hz), 5.65 (m, 1 H, H_{10}), 6.65 (d, 1 H, H_{11}), 7.34–8.28 (m, 9 H, Ar*H*), 8.86 (s, 1 H, H_{14}), $J_{10,11}$ = 5.6 Hz; mass spectrum (CI-NH_3) *m/z* 708 (M^+ + 1); UV spectrum (THF) λ_{max} 288 nm (ϵ 81 800). Evaporation of the more polar fraction (k' = 7.73) afforded bis ester **10** of the (+)-(*S,S*)-tetrahydro diol: $[\alpha]_D$ −28° (THF); ^{1}H-NMR (300 MHz, C_6D_6) δ 0.81–3.22 (m, 19 H, menthyl), 3.95 (dd, 2 H, $-COCH_ACH_B-$, J_{gem} = 16.4 Hz), 4.13 (dd, 2 H, $-COCH_AH_B-$), J_{gem} = 16.4 Hz), 5.65 (m, 1 H, H_{10}), 6.65 (d, 1 H, H_{11}), 7.34–8.28 (m, 8 H, Ar*H*), 8.86 (s, 1 H, H_{14}); $J_{10,11}$ = 5.6 Hz; mass spectrum (CI-NH_3) *m/z* 708 (M^+ + 1); UV spectrum (THF) λ_{max} 288 nm (ϵ 81 800).

(+)-*trans*-(10*R*,11*R*)-Dihydroxy-8,9,10,11-tetrahydrodibenz[*a*,*h*]acridine (11). The bis ester **9** was hydrolyzed with 10% NaOH according to the procedure described in the synthesis of **6**. The product was purified by HPLC on the Rainin Microsorb silica gel column using 5% MeOH and 15% EtOAc in hexane, $[\alpha]_D$ +35° (THF); ^{1}H-NMR (300 MHz, $CDCl_3$ + MeOH-d_4) δ 1.89–2.37 (m, 2 H, H_9), 3.84 (m, 2 H, H_8), 3.93 (m, 1 H, H_{10}), 4.71 (d, 1 H, H_{11}), 7.60–8.02 (m, 7 H, Ar*H*), 8.73 (d, 1 H, H_1), 9.35 (s, 1 H, H_{14}), $J_{1,2}$ = $J_{10,11}$ = 8.1 Hz; mass spectrum *m/z* 316 (M^+ + 1).

(−)-*trans*-(10*S*,11*S*)-Dihydroxy-8,9,10,11-tetrahydrodibenz[*a*,*h*]acridine (12). The alkaline hydrolysis of the bis ester **10** as described for the synthesis of **6** and purification of the product by HPLC on the Rainin Microsorb silica gel column gave the tetrahydro diol **12**, $[\alpha]_D$ −37°. ^{1}H-NMR and mass spectra of **12** were identical to those of **11**.

Assignment of Absolute Configuration to the Enantiomeric 10,11-Dihydro Diols. A mixture of bis((−)-menthyloxy) esters **4** and **5** of the dihydro diol (2 mg) with a 40% excess of less polar bis((−)-menthyloxy) ester **4** and 10% Pd–C (12 mg) was stirred in THF (1 mL) under 18 psi of hydrogen for 2 h. After removal of the catalyst, the product was analyzed by HPLC on a Du Pont Zorbax SIL column (6.2 × 80 mm) eluted with 5.5% ether and 0.6% EtOAc in cyclohexane at a flow rate of 1.8 mL/min. Analytical HPLC indicated 30% reduction to a mixture of bis((−)-menthyloxy) esters of the tetrahydro diol, which was enriched in the less polar (−)-(10*R*,11*R*)-isomer **9** by the same percentage as that of the starting (−)-(10*R*,11*R*)-isomer **4** of the dihydro diol **6**. Thus, the less polar bis esters **4** and **9** and their hydrolysis products (−)-dihydrodiol **6** and (+)-tetrahydro diol **11**, respectively, have the same *R,R* absolute configuration.

To a solution of (+)-tetrahydrodiol **11** derived from the less polar bis((−)-menthyloxy) ester **9** (2 mg) in THF (0.5 mL) was added *p*-(dimethylamino)cinnamoylimidazole[23] (6 mg) and NaH (2 mg) under nitrogen. Stirring was continued at rt for 1 day, and reaction was terminated by addition of 20% aqueous NH_4Cl at 0 °C. Usual workup followed by purification on a Rainin Microsorb silica gel column (10 × 250 mm) eluted with 40% EtOAc in hexane at 9 mL/min (k' = 3.2) provided the desired bis[*p*-(dimethylamino)cinnamate] **13**: ^{1}H-NMR ($CDCl_3$) δ 2.43 (m, 2 H, H_9), 2.98 (s, 3 H, NCH_3), 3.01 (s, 3 H, NCH_3), 3.78 (m, 2 H, H_8), 5.55 (m, 1 H, H_{10}), 6.20 (d, 1 H, $-CH{=}CHCO_2-$, J = 15.9 Hz) and 6.30 (d, 1 H, $-CH{=}CHCO_2-$, J = 15.9 Hz), 6.52 (d, 1 H, H_{11}), 6.63–8.00 (m, 15 H, Ar*H*), 8.79 (d, 1 H, H_1), 9.41 (s, 1 H, H_{14}), $J_{1,2}$ = 7.6 Hz, $J_{10,11}$ = 6.6 Hz; mass spectrum (CI-NH_3) 662 (M^+ + 1). The circular dichroism spectrum in THF (see Figure 2) had exciton chirality interaction bands at $\Delta\epsilon$ −35 (377 nm), 0 (358 nm), and +40 (344 nm) consistent with 10*R*,11*R* absolute configuration for **13** and consequently for (+)-tetrahydro diol **11**.

(+)-(8*R*,9*S*,10*S*,11*R*)-10,11-Dihydroxy-8,9-epoxy-8,9,10,11-tetrahydrodibenz[*a*,*h*]acridine (14). To a solution of (−)-(10*R*,11*R*)-10,11-dihydro diol **6** (55 mg) in dry THF (20 mL) under Ar was added purified *m*-CPBA (0.5 g). The clear solution was stirred at rt for 2.5 h, and then ether (40 mL) was added. The organic phase was extracted with ice-cold 5% NaOH (3 × 5 mL) and water (2 × 5 mL), dried (Na_2SO_4), and concentrated to a white solid under reduced pressure. Trituration with ether gave 49 mg (84.7%) of the diol epoxide **14** as white crystals of mp >200 °C dec; $[\alpha]_D$ +58°. Anal. Calcd for $C_{21}H_{15}NO_3 \cdot {}^1/_4H_2O$: C, 73.6; H, 4.8. Found: C, 73.8; H, 4.6.

(−)-(8*S*,9*R*,10*R*,11*S*)-10,11-Dihydroxy-8,9-epoxy-8,9,10,11-tetrahydrodibenz[*a*,*h*]acridine (16). Direct epoxidation of (+)-(10*S*,11*S*)-10,11-dihydro diol **7** (55 mg) as described above for the enantiomer **6** gave 50 mg (87%) of **16** as a crystalline solid of mp >200 °C dec; $[\alpha]_D$ −57°. Anal. Calcd for $C_{21}H_{15}NO_3 \cdot {}^3/_4H_2O$: C, 73.6; H, 4.8. Found: C, 73.9; H, 4.7.

(−)-(8*S*,9*R*,10*S*,11*R*)-10,11-Dihydroxy-8,9-epoxy-8,9,10,11-tetrahydrodibenz[*a*,*h*]acridine (15). To a solution of (−)-(10*R*,11*R*)-10,11-dihydro diol **6** (62.6 mg) in THF (20 mL) and water (5 mL) at 0–5 °C was added NBA (29 mg) under Ar. HCl (5 N, 1 drop) was added, and the solution was stirred at 0–5 °C for 15 min. After a drop of saturated $NaHCO_3$ was added, most of the solvent was removed under reduced pressure without external heating. The residue was diluted with 1 mL of ice-cold water to produce a solid that was filtered and washed with cold water. After being dried in vacuum, the solid was triturated with ether to produce 80 mg (97%) of bromo triol as a grayish yellow crystalline solid.

To a solution of the above bromo triol (54.6 mg) in dry THF (5 mL) was added 10 g of Amberlite-400 (OH^-). The reaction mixture was stirred at rt for 5 h under Ar and was quickly filtered. The filtrate was concentrated under reduced pressure. Trituration of the solid with ether gave 30 mg (68%) of the diol epoxide **15** as a white crystalline solid of mp >200 °C dec; $[\alpha]_D$ −112°. Anal. Calcd for $C_{21}H_{15}NO_3 \cdot 1.5H_2O$: C, 70.8; H, 5.0. Found: C, 70.3; H, 4.7.

(+)-(8*R*,9*S*,10*R*,11*S*)-10,11-Dihydroxy-8,9-epoxy-8,9,10,11-tetrahydrodibenz[*a*,*h*]acridine (17). In the same manner described above, the enantiomer (+)-(10*S*,11*S*)-10,11-dihydro diol **7** (45.8 mg) was converted to the bromo triol (56 mg, 93%). Cyclization of the bromo triol (23.5 mg) with 5 g of Amberlite-400 (OH^-) in dry THF (3 mL) gave 16.6 mg (70%) of the diol epoxide **17** as a white crystalline solid of mp >200 °C; $[\alpha]_D$ +110°. Anal. Calcd. for $C_{21}H_{15}NO_3 \cdot 1.5H_2O$: C, 70.8; H, 5.0. Found: C, 71.1; H, 4.7.

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Supplementary Material Available: ^{1}H-NMR for **6**, **9**, **10**, **12**, and **13** (5 pages). Ordering information is given on any current masthead page.