but was found to be a mixture containing a large amount of the keto isomer and probably minor amounts of enol isomers as suggested by the IR data: IR (film) 3450 (m, enolic OH), 1760 (s, 2 C=O), 1740 (s, ester C=O), 1695 (m, $\alpha,\beta$-unsaturated C=O), 1610 (m), 1530 and 1350 (s, $NO_2$), 1260–1210 (s, ester) $cm^{-1}$; $^1H$ NMR (acetone-$d_6$) $\delta$ 1.30 (t, 3 H, $CH_3$, $J$ = 6.3 Hz), 4.50 (q, 2 H, $CH_2$, $J$ = 6.3 Hz), 6.62 (d, 1 H, CHF, $J$ = 43.2 Hz), 7.60–8.40 (m, 4 H, aromatic); $^{19}F$ NMR (acetone-$d_6$, from external $CF_3COOH$) $\delta$ −108.8 (d, $J$ = 43.2 Hz); mass spectrum, $m/e$ 255 ($M^+$), 183 ($M^+ - CO_2C_2H_5 + H$), 181 ($M^+ - CO_2C_2H_5 - H$), 155 ($C_7H_5NO_2F$), 154 ($C_7H_4NO_2F$), 108 ($C_7H_5F$), 107 ($C_7H_4F$). Anal. Calcd for $C_{11}H_{10}O_5N$: C, 51.76; H, 3.92; N, 5.49; F, 7.49. Found: C, 51.53; H, 3.80; N, 5.53; F, 7.25.

**Silyl enol ether (4d)** was characterized as follows: bp 120 °C (0.05–0.08 mmHg); IR (oxygen-free $CHCl_3$) 1720 (s, ester C=O), 1520 and 1340 (s, $NO_2$), 1260–1200 (s, ester) $cm^{-1}$; $^{19}F$ NMR (oxygen-free $CDCl_3$) $\delta$ 26.2 (s); mass spectrum, $m/e$ 327 ($M^+$), 312 ($M^+ - CH_3$), 284 ($M^+ - CH_3 - C_2H_4$), 224 ($C_{10}H_7O_4NF$), 220 ($C_{11}H_9NO_4 + H$), 181 ($C_8H_4NO_3F$), 147 ($C_7H_4NO_2F$), 73 ($C_3H_9Si$).

**Ethyl 3-butyryl-3-fluoropyruvate (3e)** was prepared in a yield higher than 70% and characterized as follows: bp 72–78 °C (2 mmHg); IR (oxygen-free $CHCl_3$) 1760–1720 (s, probably three C=O peaks), 1650 (m, C=C of enol isomer), 1260–1200 (s, ester) $cm^{-1}$; mass spectrum, $m/e$ 222 ($M^+$), 174 ($M^+ - CO - HF$), 131 ($M^+ - CO_2C_2H_5$), 71 ($C_4H_7O$), 29 ($C_2H_5$); $^{19}F$ NMR ($CDCl_3$) $\delta$ −34.2 (dt, $J$ = 49.0 Hz, $J$ = 3.0 Hz), 3.0 (t, $J$ = 3.0 Hz), 47.3 (s). Anal. Calcd for $C_9H_{13}O_4F$: C, 52.94; H, 6.42; F, 9.30. Found: C, 52.65; H, 6.28; F, 9.10.

**Conversion of Silyl Enol Ethers 4b–d into Enol-Type 3-Substituted 3-Fluoropyruvates 5b–d.** All the experiments described here were carried out in a nitrogen drybox in order to eliminate oxygen. The silyl enol ether **4b** (200 mg) was hydrolyzed in 4 mL of oxygen-free 75% aqueous methanol at room temperature for 50–30 min, and then water was added to facilitate the precipitation of crystalline product **5b** from the solution. The resultant precipitate was collected by filtration, dried under vacuum, and recrystallized from ether–hexane to afford a pure sample in good yield (50–70%).

**Compound 5b** thus prepared was characterized as follows: mp (under $N_2$) 64–66 °C; IR (oxygen-free $CHCl_3$) 3450 (m, enolic OH), 3030 (w), 2950 (w), 1690 (s, C=O), 1580 (w), 1440 (s), 1380 (s), 1260–1180 (s, ester), 1100 (m, CF) $cm^{-1}$; $^{19}F$ NMR (oxygen-free $CDCl_3$) $\delta$ 22.7 (s), clearly suggesting that no isomer was involved; mass spectrum, $m/e$ 196 ($M^+$), 134 ($M^+ - CO_2CH_3 - H$), 108 ($C_7H_5F$); all the spectroscopic data suggested no contamination by impurities.

**Compound 5c** was similarly prepared and characterized as follows: mp (under $N_2$) 115–120 °C (gradually decomposed from 110 °C); IR (oxygen-free $CHCl_3$) 3440 (m, enolic OH), 3030 (w), 2950 (w), 1685 (s, $\alpha,\beta$-unsaturated ester C=O), 1590 (w), 1490 (m), 1440 (s), 1370 (s), 1100 (m, CF) $cm^{-1}$; $^{19}F$ NMR (oxygen-free $CDCl_3$) $\delta$ 21.6 (s), suggesting that no isomer was involved; mass spectrum, $m/e$ 232 and 230 ($M^+$), 172 and 170 ($M^+ - CO_2CH_3 - H$), 145 and 143 ($C_7H_5FCl$), 144 and 142 ($C_7H_4FCl$), 107 ($C_7H_4F$). Anal. Calcd for $C_{10}H_8O_3FCl$: C, 52.08; H, 3.50; F, 8.24. Found: C, 51.93; H, 3.41; F, 8.54.

**Compound 5d** was similarly prepared and characterized as follows: mp (under $N_2$) 106–108 °C (gradually decomposed from 100 °C); IR (oxygen-free $CHCl_3$) 3430 (m, enolic OH), 3030 (w), 2950 (w), 1690 (s, $\alpha,\beta$-unsaturated ester C=O), 1595 (w), 1520 and 1340 (s, $NO_2$), 1260–1200 (s, ester), 1100 (s, CF) $cm^{-1}$; $^{19}F$ NMR (oxygen-free $CDCl_3$) $\delta$ 19.8 (s), clearly suggesting that no isomer was involved; mass spectrum, $m/e$ 255 ($M^+$), 181 ($M^+ - CO_2C_2H_5 - H$), 155 ($C_7H_5NO_2F$), 154 ($C_7H_4NO_2F$), 153, 107 ($C_7H_4F$).

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**Registry No. 1a**, 6362-56-7; **1b**, 80540-55-2; **1c**, 80540-56-3; **1d**, 80540-57-4; **1e**, 80540-58-5; **3a**, 79547-03-8; **3b**, 76532-83-7; **3c**, 79547-04-9; **3d**, 79547-06-1; **3e**, 79555-08-1; **4b**, 80540-59-6; **4c**, 80540-60-9; **4d**, 80540-61-0; **5b**, 80540-62-1; **5c**, 80540-63-2; **5d**, 80540-64-3; $F_2$, 7782-41-4.

# Synthesis of the Enantiomeric Bay-Region Diol Epoxides of Benz[*a*]anthracene and Chrysene

Haruhiko Yagi, Kamlesh P. Vyas, Masao Tada, Dhiren R. Thakker, and Donald M. Jerina*

*Laboratory of Bioorganic Chemistry, National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20205*

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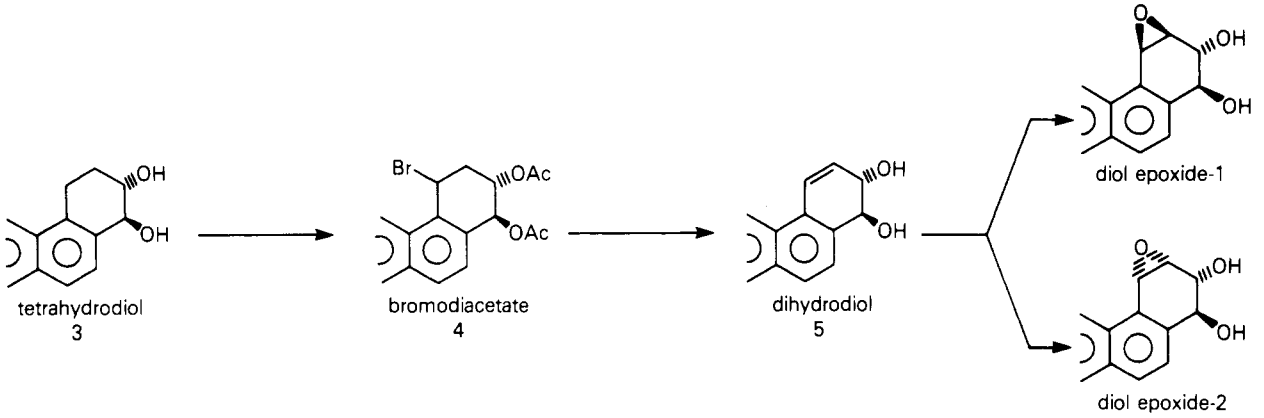
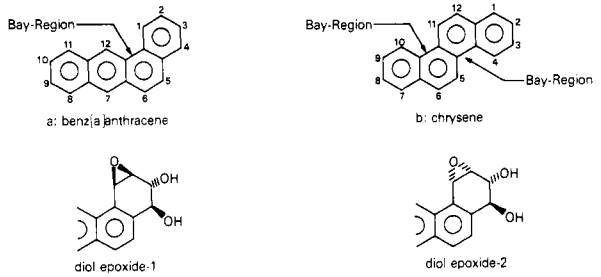
Both *trans*-3,4-dihydroxy-3,4-dihydrobenz[*a*]anthracene and *trans*-1,2-dihydroxy-1,2-dihydrochrysene are known proximate carcinogens of their respective hydrocarbons. The present study describes the synthesis of their (+)- and (−)-enantiomers as well as the diastereomeric pair of bay-region diol epoxides formed from each enantiomer when the double bond of the dihydrodiol ring is epoxidized either cis (isomer-1 series) or trans (isomer-2 series) to the benzylic hydroxyl group. For both hydrocarbons, (i) the tetrahydro analogues of the dihydrodiols were resolved by chromatographic separation of their diastereomeric bis esters with (−)-menthoxyacetic acid, and the resultant tetrahydrodiols were converted to the requisite dihydrodiols, and (ii) the (+)-tetrahydrodiols led to the (−)-dihydrodiols, both with (*R*,*R*) absolute configuration. Assignment of absolute configuration in the chrysene series was achieved through application of the exciton chirality circular dichroism technique to the bis[*p*-(dimethylamino)benzoate] of (−)-*trans*-1,2-dihydroxy-1,2,3,4-tetrahydrochrysene. NMR coupling patterns of the $OCOCH_2O$ hydrogens in the bis[methoxyacetic acid esters] of these vicinal trans diols were found to be diagnostic of their absolute configuration. An interesting correlation was observed upon conversion of the enantiomerically pure dihydrodiols to their diastereomeric pairs of bay-region diol epoxides; as was previously the case for (−)-*trans*-(7*R*,8*R*)-7,8-dihydroxy-7,8-dihydrobenzo[*a*]pyrene, the (−)-(*R*,*R*)-dihydrodiols in the chrysene and benz[*a*]anthracene series led to the (−)-diol epoxide **1** and (+)-diol epoxide **2** isomers. Of the four metabolically possible bay-region diol epoxides for each of the three hydrocarbons, tumor studies now indicate that the (+)-(*R*,*S*)-diol (*S*,*R*)-epoxide **2** isomers (designated from the carbon bearing the benzylic hydroxyl group toward the epoxide) have practically all of the tumorigenic activity.

The polycyclic aromatic hydrocarbons benz[*a*]anthracene (a) and chrysene (b) are weakly carcinogenic environmental contaminants.[1] In accord with predictions of the bay-region theory,[2] their tumorigenic activity is due

Scheme I

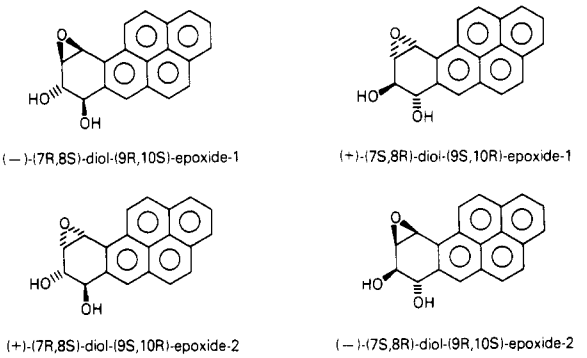



to metabolically formed benzo-ring diol epoxides in which the epoxide group forms part of a bay region of the hydrocarbon.[3] When formed in mammals, the precursor trans dihydrodiols are epoxidized either cis (isomer 1) or trans (isomer 2) to the benzylic hydroxyl group such that a pair of diastereomers are possible. In the absence of




unusual steric factors, isomer 1 diol epoxides prefer the conformation in which the hydroxyl groups are quasi-diaxial and isomer 2 diol epoxides prefer the conformation in which these groups are quasi-diequatorial.[4] With the exception of the bay-region diol epoxides of benzo[c]-phenanthrene where both diastereomers perfer the quasi-diequatorial conformation[5a] and both isomers are tumorigenic,[5b] the diol epoxide 2 diastereomers possess nearly all of the tumorigenic activity.[3]

Each of the diastereomers exists as a pair of enantiomers such that four isomeric bay-region diol epoxides are possible for a given bay region. In the case of benzo[a]pyrene (c), all four of these isomers have been synthesized,[6a] and




their absolute configurations have been deduced by optical[6a,b] and crystallographic[6c] methods. Interestingly, only the (+)-diol epoxide 2 isomer shows high tumorigenic activity.[7] This remarkable concentration of biological activity in one of the four isomers is even more striking when it is recognized that this is the same isomer that is preponderantly formed upon metabolism of the parent hydrocarbon.[8] The present study was undertaken to synthesize the (+)- and (−)-enantiomers of the diastereomeric bay-region 3,4-diol 1,2-epoxides of benz[a]anthracene (a) and 1,2-diol 3,4-epoxides of chrysene (b) in order to establish whether (+)-diol epoxide 2 would also be the tumorigenic isomer of these two hydrocarbons.

## Results and Discussion

Since the 1,2,3,4-tetrahydro trans 3,4-diol (**3a**)[9] of benz[a]anthracene (a) and trans 1,2-diol (**3b**)[10] of chrysene

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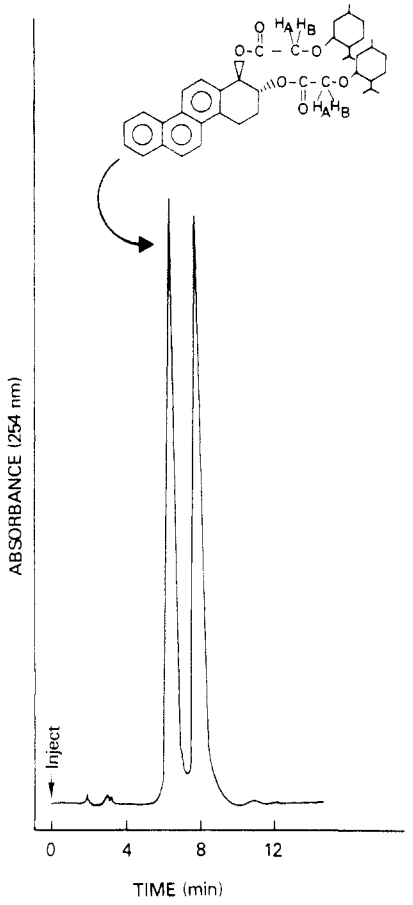


**Figure 1.** Analytical HPLC separation of the diastereomeric bis((−)-menthoxyacetic acid esters) of the (+)- and (−)-1,2,3,4-tetrahydrochrysene 1,2-diols (**3b**); a Waters Associates μ-Porasil column was eluted at 2 mL/min with 8% ether in cyclohexane.

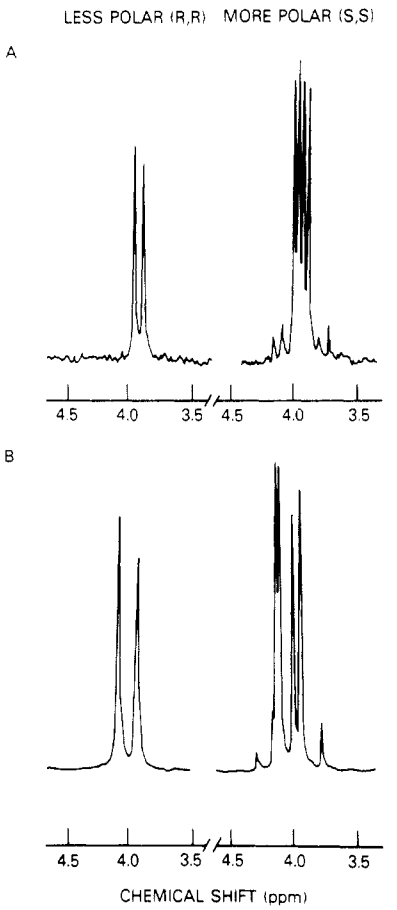


**Figure 2.** Partial NMR spectra (100 MHz, benzene-$d_6$) of the bis((−)-menthoxyacetic acid esters) of the following: (A) the (+)- and (−)-1,2,3,4-tetrahydrobenz[*a*]anthracene 3,4-diol (**3a**) and (B) the (+)- and (−)-benz[*a*]anthracene 3,4-dihydrodiols (**5a**). When the trans hydroxyl groups have (*S,S*) absolute configuration, the methylene hydrogens $H_A$ and $H_B$ (cf. Figure 1) are nonequivalent in each ester and appear as a pair of doublets.

(b) are not considered to be carcinogenic, they represented practical candidates for enantiomeric resolution on a preparative scale prior to the synthesis of the diol epoxides (Scheme I). In earlier synthetic studies,[6a] the diastereomeric pair of 7-monoesters of *trans*-7,8-dihydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (**3c**) with (−)-α-methoxy-α-[(trifluoromethyl)phenyl]acetic acide (MTPA) were separated on HPLC. The 7-monoesters were selected over the 8-mono(MTPA esters) or the 7,8-bis(MTPA esters) since they were most easily separated. For the present studies, the separation factor (α) for bis esters of the tetrahydrodiols (**3**) found to be adequate for preparative work, and (−)-menthoxyacetic acid (MAA) esters proved superior to MTPA esters. Highly efficient chromatographic separations of the diastereomeric bis(MAA esters) of the benz[*a*]anthracene (**3a**) and chrysene (**3b**) tetrahydrodiols were achieved with small amounts of ether in cyclohexane (Figure 1), a solvent combination which we have found particularly useful for the separation of hydrocarbon diastereomers.[6c] For the benz[*a*]anthracene derivatives, as much as 7 g was injected into a Waters Prep LC System 500 equipped with two silica gel cartridges and was completely separated after three recycles (α = 1.36 with 5% ether in cyclohexane). For the chrysene derivatives, 0.5 g of the diastereomer mixture was separated on a 2.5 cm × 120 cm column of 10 μm silica gel (α = 1.32 with 8% ether in cyclohexane). A preliminary indication of the absolute configuration of the diol groups in the separated diastereomers in both series was obtained from their NMR spectra in benzene-$d_6$ (Figure 2, cf. ref 11). For the less polar (early eluting) diastereomers, the $CH_2$ group ($H_AH_B$ in Figure 1) in the acetyl portion of each ester group appears as a singlet. Magnetic equivalence between $H_A$ and $H_B$ in each of the ester groups of the less polar isomers is suggestive of (*R,R*) absolute configuration for the carbinol hydrogens. When $H_A$ and $H_B$ are nonequivalent ($J_{gem}$ ~ 16 Hz), and when they appear as a pair of doublets for each ester in the more polar (late eluting) diastereomers, (*S,S*) absolute configuration is suggested. Subsequent analysis established that the preliminary assignments were correct. Magnetic nonequivalence between $H_A$ and $H_B$ was also noted in the NMR spectrum of the bis(MAA ester) of the benz[*a*]anthracene (+)-(3*S*,4*S*)- but not in the (−)-(3*R*,4*R*)-dihydrodiol (Figure 2). Thus, the splitting of $H_A$ and $H_B$ appears to be as useful a diagnostic tool for predicting the absolute configuration in bis(MAA esters) of vicinal dihydrodiols and tetrahydrodiols as it was for bromohydrins.[11]

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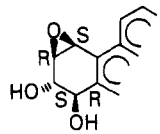
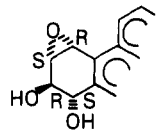
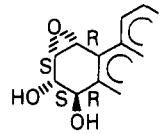
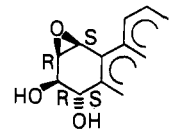
(11) See Kedzierski, B.; Thakker, D. R.; Armstrong, R. N.; Jerina, D. M. *Tetrahedron Lett.* **1980**, *22*, 405–408 and references therein. In some instances, the NMR signal of one of the $OCOCH_2$ groups in the early eluting diastereomer is split. This splitting pattern was first noted by Boyd and co-workers for MAA esters of bromohydrins; Akhtar, M. N.; Boyd, D. R.; Hamilton, J. G. *J. Chem. Soc., Perkins Trans. 1* **1979**, 2437–2440.

Table I. Specific Rotations ($[\alpha]^{23}_D$, deg) of the Enantiomerically Pure Non-Bay-Region Diol Derivatives ($c$ = g/100 mL)

| | benz[a]anthracene enantiomers (a) | | chrysene enantiomers (b) | | benzo[a]pyrene enantiomers (c)[b] | |
|---|---|---|---|---|---|---|
| compd[a] | (3R,4R) | (3S,4S) | (1R,2R) | (1S,2S) | (7R,8R) | (7S,8S) |
| bis((-)-menthoxyacetate) of 3 | -154 (8.00)[c] (less polar) | +31.0 (10.4)[c] (more polar) | -134 (1.00)[d] (less polar) | -32.6 (1.00)[d] (more polar) | | |
| tetrahydrodiol 3 | <+2 (3.85)[d] | <-2 (0.39)[d] | +77.7 (0.57)[d] | -77.2 (0.60)[d] | +83[d] | -80[d] |
| bis acetate of 3 | -183 (1.35)[c] | +186 (1.47)[c] | -112 (0.65)[d] | +104 (0.37)[d] | | +141[c] |
| bis acetate of 5 | -516 (0.49)[d] | +523 (0.47)[d] | -338 (0.60)[d] | +324 (0.45)[d] | -372[c,e] | +385[c,e] |
| dihydrodiol 5 | -363 (0.25)[d] | +365 (0.35)[d,g] | -105 (0.37)[d] | +109 (0.51)[d] | -405[f] | +409[f] |

[a] See Scheme I and Figure 1 for structures. [b] Data taken from ref 6a. [c] Rotations determined in chloroform. [d] Rotations determined in tetrahydrofuran. [e] Determined on the dibenzoate rather than the diacetate. [f] Rotations determined in acetone. [g] The lower rotation previously reported (ref 13) for dihydrodiol 5a is in error due to the presence of a very small amount of a highly colored impurity that severely limited the amount of sample which could be used in the determination. The problem was avoided in the present study by careful exclusion of light from 5a and its diacetate.

Table II. Specific Rotations ($[\alpha]^{23}_D$, deg) of Enantiomerically Pure Bay-Region Diol Epoxides ($c$ = g/100 mL, Tetrahydrofuran)

| | partial structure | | | |
|---|---|---|---|---|
| hydrocarbon |  |  |  |  |
| benz[a]anthracene isomers | (-)-1a<br>-165 (0.54) | (+)-1a<br>+166 (0.32) | (+)-2a<br>+80.9 (0.45) | (-)-2a<br>-81.4 (0.43) |
| chrysene isomers | (-)-1b<br>-25.0 (0.56) | (+)-1b<br>+25.2 (0.54) | (+)-2b<br>+43.9 (0.86) | (-)-2b<br>-42.5 (0.73) |
| benzo[a]pyrene[a] isomers | (-)-1c<br>-127 | (+)-1c<br>+123 | (+)-2c<br>+72 | (-)-2c<br>-68 |

[a] Data taken from ref 6a.

After hydrolysis to remove the bis(MAA ester) groups, the resulting tetrahydrodiols (**3a,b**) were acetylated on the hydroxyl groups, and the diacetates were brominated at their benzylic bay-region methylene groups (**4**) with NBS as previously described for the racemic materials (benz[a]anthracene series,[9] chrysene series[10]). The resulting bromo diacetates in the chrysene series (**4b**) were dehydrobrominated with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and hydrolyzed to the free dihydrodiols as described.[10] The benz[a]anthracene bromo diacetates (**4a**) had been previously dehydrobrominated thermally[9] in modest yield (33%). The yield for this step was doubled in the present study by the use of 1,5-diazabicyclo-[5.4.0]undec-5-ene (DBU). Interestingly, the more rigid reagent DBN failed to effect this dehydrobromination. Specific rotations are presented in Table I.

As we had originally pointed out,[4a] direct epoxidation of benzo-ring, trans dihydrodiols with quasi-equatorial hydroxyl groups[12] stereoselectively produces diol epoxide **2** diastereomers, whereas intermediate bromohydrin formation followed by cyclization results in diol epoxide **1** diastereomers. The optically active 3,4-dihydrodiols of benz[a]anthracene and 1,2-dihydrodiols of chrysene were converted to their diastereomeric diol epoxides as described for the racemic compounds.[4b,c] Specific rotations are presented in Table II.

Absolute configuration in the benz[a]anthracene series (a) had been previously established[13] via an exciton chirality experiment[14] on the tetrahydro 3,4-diol **3a**. The same approach was used here to assign absolute configuration in the chrysene series (b). The circular dichroism spectrum (Figure 3) of the bis[p-(dimethylamino)benzoate] of (-)-**3b** showed a pair of strong and fairly symmetric Cotton effects centered at 315 nm due to chiral interaction between the two p-(dimethylamino)benzoate chromophores. Since the longest wavelength Cotton effect at 325 nm is positive, (1S,2S) absolute configuration is required for the tetrahydrodiol (-)-**3b**. As can be seen from inspection of Tables I and II, a complete parallel exists between the signs of rotation and the absolute configuration for the diol and diol epoxide derivatives in the benz[a]-anthracene, chrysene, and benzo[a]pyrene series. For non-bay-region diols and derived bay-region diol epoxides, the following relationship obtains: the (+)-(R,R)-tetra-

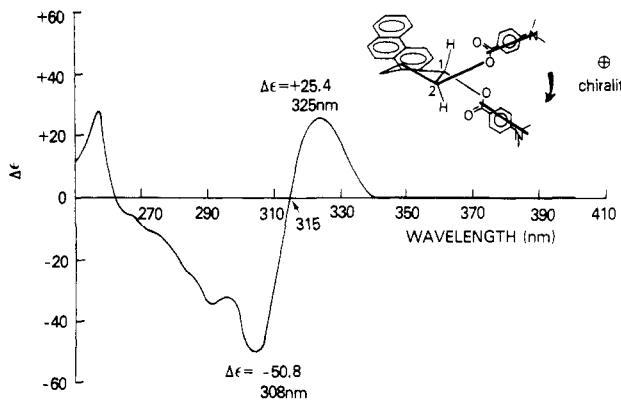
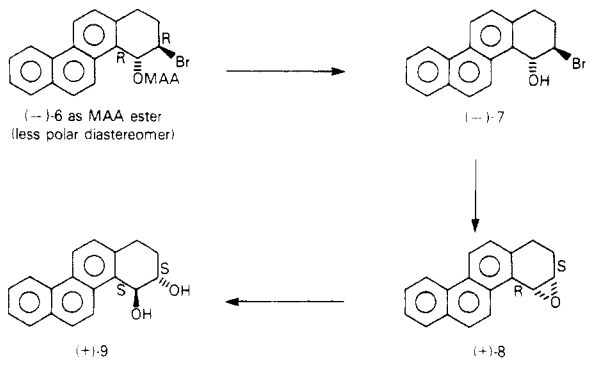



**Figure 3.** Circular dichroism spectrum of the bis(p-(dimethylamino)benzoate) of the (-)-1,2,3,4-tetrahydrochrysene 1,2-diol [(-)-**3b**]. The positive band at 325 nm and the negative band at 308 nm requires (1S,2S) absolute configuration. The spectrum was recorded in methanol.

(12) Jerina, D. M.; Selander, H.; Yagi, H.; Wells, M. C.; Davey, J. F., Mahadevan, V.; Gibson, D. T. *J. Am. Chem. Soc.* **1976**, *98*, 5988–5996.
(13) Levin, W.; Thakker, D. R.; Wood, A. W.; Chang, R. L.; Lehr, R. E.; Jerina, D. M.; Conney, A. H. *Cancer Res.* **1978**, *38*, 1705–1710.
(14) Harada, N.; Takuma, Y.; Uda, H. *J. Am. Chem. Soc.* **1976**, *98*, 5408–5409. Chen, S. L.; Nakanishi, K. *Ibid.* **1975**, *97*, 5345–5352.

Scheme II




hydrodiols **3** ((−)-diacetate) formed (−)-dihydrodiols **5** ((−)-diacetate) which were converted into (−)-diol epoxide **1** and (+)-diol epoxide **2** diastereomers (cf. Tables I and II).

Although previous studies have compared the mutagenic activity of bay-region diol epoxides with their corresponding tetrahydro epoxides,[15] optically active diol epoxides have never been compared to optically active tetrahydro epoxides. For this reason, the enantiomers of 1,2,3,4-tetrahydrochrysene 3,4-epoxide (**8**) were synthesized (Scheme II). Chromatographic separation of the MAA esters of the racemic bromohydrin **6** was achieved on the 10-$\mu$m silica column (2.5 cm × 120 cm) eluted with 3% ether in cyclohexane ($\alpha$ = 1.34). Inspection of the NMR spectra of the two diastereomers established that the $CH_2$ group in the acetyl portion of the ester appeared as a singlet in (−)-**6** and a pair of doublets ($J_{gem}$ ~ 16 Hz) in (+)-**6**. By analogy with related studies,[16] (−)-**6** was anticipated to have (3*R*,4*R*) absolute configuration. Such was found to be the case (Scheme II). Reductive cleavage of the MAA ester in the less polar diastereomer with diborane[17] provided the (−)-enantiomer of bromohydrin **7**, which was cyclized to the (+)-enantiomer of the epoxide **8**. In a separate study,[18] the epoxide (+)-**8** was hydrolyzed to the trans tetrahydrodiol (+)-**9**, which was assigned (3*S*,4*S*) absolute configuration by the exciton chirality technique. Thus, the epoxide group in (+)-**8** has the same absolute configuration (3*S*,4*R*) as is present in the chrysene (+)-1,2-diol 3,4-epoxide **1b** and (+)-1,2-diol 3,4-epoxide **2b** (Table II). A completely parallel situation for both signs of rotation and absolute configuration exists in the benz[*a*]anthracene series where Boyd and co-workers[19] have found that the (+)-1,2-epoxide has (1*R*,2*S*) absolute configuration.

In general, racemic bay-region tetrahydro epoxides are more active as mutagens toward bacterial and mammalian cells than are the corresponding diol epoxides.[15] Interestingly, the (+)- and (−)-enantiomers of the chrysene tetrahydro epoxide **8** have virtually identical mutagenic activity[20] despite large differences in the mutagenic activity of the related diol epoxides. In parallel with studies on benzo[*a*]pyrene derivatives, the (−)-chrysene (1*R*,2*R*)-dihydrodiol (**5b**) is more tumorigenic than the (+)-enantiomer and the related (+)-(1*R*,2*S*)-diol (3*S*,4*R*)-epoxide **2b** is much more tumorigenic[20] than the other three isomers (cf. Table II). The same stereochemical relationships to tumorigenic activity hold true for the benz[*a*]anthracene derivatives. Thus, the active tumorigenic metabolites ((+)-diol epoxide **2**) of three different hydrocarbons are now known to be configurationally superimposable when their bay regions are aligned. One attractive explanation for this phenomenon is that the cellular covalent binding site for these ultimate carcinogens is highly chiral and that only these isomers effectively bind at the site.

## Experimental Section

**General Procedures.** NMR spectra were recorded on a JEOL FX 100. Coupling constants, *J*, are reported in hertz and chemical shifts in parts per million ($\delta$) with tetramethylsilane as internal standard. Only selected signals are reported. Where possible, NMR spectra of optically active compounds were compared with those of previously characterized racemic compounds to ensure structural assignments and purity. UV spectra were recorded on Cary 16 and Beckmann Acta IV spectrophotometers. CD spectra were recorded on a Cary 60 spectrophotometer. Mass spectra were run on Finnigan Model 1015 gas chromatograph/mass spectrometer. Specific rotations (Table I and II) were recorded on Perkin-Elmer 141 and 241 MC automatic polarimeters. Melting points are uncorrected. (−)-Menthoxyacetic acid (MAA; Aldrich, $[\alpha]_D$ −90°) was converted to its (−)-acid chloride as described.[21] Tetrahydrofuran (THF) was purified by distillation from calcium hydride.

**Benz[*a*]anthracene Diols. Preparation of the Diastereoisomeric Mixture of Bis(MAA esters) of (±)-*trans*-3,4-Dihydroxy-1,2,3,4-tetrahydrobenz[*a*]anthracene (3a) and Their Separation by HPLC.** To a solution of (±)-tetrahydrodiol **3a**[9] (1.46 g) in dry pyridine (30 mL) was added the acid chloride of MAA (7.13 g) under cooling at 0 °C over a period of 30 min. The reaction mixture was stirred overnight at room temperature and poured into benzene (200 mL). The benzene was washed with water, 1 N HCl, and water, dried ($K_2CO_3$), and evaporated to give an oil which was eluted through a silica gel column (2.8 cm × 30 cm) with $CHCl_3$ to provide a colorless oil (3.26 g).

Preparative chromatography of the above oil (7 g) was done on a Waters Prep LC System 500 (two silica gel cartridges recycled 3 times) with 5% $Et_2O$ in cyclohexane as eluent at a flow rate of 400 mL/min. Evaporation of the combined (>98% diastereomerically pure) less polar fractions ($k'$ = 6.9) afforded the (−)-bis(MAA ester) of the trans (3*R*,4*R*)-tetrahydrodiol **3a** (2.5 g, 35.8% yield) as colorless needles: mp 147–148 °C (MeOH); NMR (benzene-$d_6$) $\delta$ 3.96 (s, 2 H, $COCH_2O$), 4.11 (s, 2 H, $COCH_2O$), 5.54 (m, 1 H, $H_3$), 6.56 (d, 1 H, $H_4$, $J_{4,3}$ = 6 Hz). Evaporation of combined (>98% diastereomerically pure) more polar fractions ($k'$ = 9.4) afforded the (+) bis MAA ester of the trans (3*S*,4*S*)-tetrahydrodiol **3a** (2.3 g, 32.8% yield) as colorless needles: mp 147–148 °C (MeOH); NMR (benzene-$d_6$) $\delta$ centered at 3.86 and 4.08 (d, d, 2 H, $COCH_2O$, $J_{gem}$ = 16 Hz), centered at 4.04 and 4.12 (d, d, 2 H, $COCH_2O$, $J_{gem}$ = 16 Hz), 5.54 (m, 1 H, $H_3$), 6.56 (d, 1 H, $H_4$, $J$ = 6 Hz). Partial NMR spectra are shown in Figure 2.

**(+)-*trans*-(3*R*,4*R*)-3,4-Dihydroxy-1,2,3,4-tetrahydrobenz[*a*]anthracene [(+)-3a].** A mixture of the above less polar diastereoisomer (785 mg), dry sodium methoxide (160 mg), MeOH (25 mL), and THF (25 mL) was stirred at room temperature for 1 h. Reaction was terminated by addition of 10% $NH_4Cl$ solution (50 mL). The bulk of the solvent was evaporated under reduced

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(19) Dr. D. R. Boyd, Queens Univeristy of Belfast, has kindly provided us with this unpublished information. Also, Boyd, D. R.; Burnett, M. G.; Greene, R. M. E. *J. Chem. Soc., Chem. Commun.* **1981**, 838–839, have independently assigned absolute configuration to the tetrahydrochrysene 3,4-epoxide **8** with a result identical with that of the present study.

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(21) Holmes, D. H.; Adams, R. *J. Am. Chem. Soc.* **1934**, *56*, 2093–2094.

pressure, and the reaction mixture was diluted with water (200 mL) to complete precipitation of the product. The resulting crystals were collected (313 mg, 100% yield) by filtration and were recrystallized from EtOAc/*n*-hexane to give colorless feathers: mp 192–194 °C dec.

**(−)-*trans*-(3*S*,4*S*)-3,4-Dihydroxy-1,2,3,4-tetrahydrobenz[*a*]anthracene [(−)-3a].** The same treatment as above of the more polar diastereoisomer (881 mg) afforded (−)-**3a** (350 mg, 100% yield) as colorless feathers: mp 193–194 °C dec.

**(−)-*trans*-(3*R*,4*R*)-3,4-Diacetoxy-1,2,3,4-tetrahydrobenz[*a*]anthracene.** A mixture of (+)-**3a** (364 mg), acetic anhydride (2.0 mL), and anhydrous pyridine (3.5 mL) was allowed to stand at room temperature overnight. Solvent and excess reagent were evaporated under reduced pressure, and the residue was dissolved in EtOAc. The solution was washed with water (2 × 50 mL), 1 N HCl (2 × 50 mL), saturated $NaHCO_3$ (50 mL), and water (2 × 50 mL). The washed solution was dried ($MgSO_4$) and evaporated to leave crystals which were recrystallized from EtOAc/*n*-hexane to afford colorless needles (460 mg, 95% yield): mp 155–156 °C.

**(+)-*trans*-(3*S*,4*S*)-3,4-Diacetoxy-1,2,3,4-tetrahydrobenz[*a*]anthracene.** Acetylation of (−)-**3a** (3.91 g) with acetic anhydride (25 mL) in pyridine (40 mL) was effected as described above for (+)-**3a**. The acetate was obtained as colorless crystals (5.5 g, 95% yield): mp 156–157 °C.

**(−)-*trans*-(3*R*,4*R*)-3,4-Diacetoxy-3,4-dihydrobenz[*a*]anthracene.** A mixture of (−)-bis(acetate) of **3b** (1.7 g), *N*-bromosuccinimide (NBS, 960 mg), α,α′-azobis(isobutyronitrile) (AIBN, 5 mg), and $CCl_4$ (200 mL) was maintained at 65 °C for 30 min with a heat lamp while a stream of argon gas was passed through the solution. Activated carbon (200 mg) was added to the solution and removed by filtration. The filtrate was evaporated to give the desired 1-bromo diacetate (**4a**; 1.95 g, 94% yield) as yellow needles: mp 121 °C. To a solution of the above 1-bromo diacetate (3.7 g) in THF (20 mL) was added under cooling a solution of DBU (2 g) in THF (10 mL) at 9 °C. The reaction was run under a blanket of argon. During the addition the reaction flask was wrapped in aluminum foil to prevent exposure to light, and all subsequent operations were carried out with similar precautions against direct illumination. The reaction mixture was stirred at room temperature for 2.5 h, by which time all starting material had been consumed as evidenced by HPLC. The THF was evaporated in vacuo, and the residue was dissolved in methylene chloride (250 mL). The methylene chloride was washed with water (3 × 200 mL), dried ($K_2CO_3$), and evaporated to leave a yellow crystalline solid (2.51 g) which was purified by HPLC on a 10-μm silica gel column (2.5 cm × 120 cm) eluted with 0.25% THF in methylene chloride (45 mL/min). Evaporation of the major fraction ($k' = 4.5$) afforded pale yellow crystals which were recrystallized from EtOAc/*n*-hexane (1:1) to afford pale yellow feathers (1.9 g, 65% yield): mp 182–183 °C; $[\alpha]^{23}_D$ −516°, $[\alpha]^{23}_{578}$ −556°, and $[\alpha]^{23}_{546}$ −611° (*c* 0.49, THF). As side products, 4-acetylbenz[*a*]anthracene ($k' = 0.3$, 50 mg) and 4-hydroxybenz[*a*]anthracene ($k' = 1.2$, 40 mg) were also obtained. The reaction should be terminated immediately upon consumption of the starting material, since these side products increase on prolonged exposure of the objective dihydrodiol diacetate to the reaction medium.

**(+)-*trans*-(3*S*,4*S*)-3,4-Diacetoxy-3,4-dihydrobenz[*a*]anthracene.** The reaction of the (+)-bis(acetate) of **3a** (3.18 g), NBS (1.71 g), AIBN (5 mg), and $CCl_4$ (150 mL) was effected as described above. The crude 1-bromo diacetate (3.72 g, 96.5% yield) was treated in THF (50 mL) with DBU (2 g) as described above to give yellow crystals (2.1 g, 63% yield): mp 182–183 °C; $[\alpha]^{23}_D$ +523°, $[\alpha]^{23}_{578}$ +562°, and $[\alpha]^{23}_{546}$ +676° (*c* 0.47, THF).

**(−)-*trans*-(3*R*,4*R*)-3,4-Dihydroxy-3,4-dihydrobenz[*a*]anthracene [(−)-5a].** The (−)-dihydrodiol diacetate (757 mg) was dissolved in THF (40 mL) and saturated $NH_3$–MeOH (150 mL). The reaction vessel was capped and allowed to stand overnight in the dark. After addition of active charcoal (250 mg), the solvent was evaporated under reduced pressure and the residue was triturated with acetone to give pale yellow needles (83.5% yield): mp 213–214 °C.

**(+)-*trans*-(3*S*,4*S*)-3,4-Dihydroxy-3,4-dihydrobenz[*a*]anthracene [(+)-5a].** Ammonolysis of the (+)-dihydrodiol diacetate (1.0 g) in saturated $NH_3$–MeOH (200 mL) and THF (40 mL) was effected as described above to yield yellow needles (610 mg, 90.7% yield): mp 213–214 °C.

**Preparation of Diastereoisomeric Mixture of Bis(MAA esters) of (±)-*trans*-3,4-Dihydroxy-3,4-dihydrobenz[*a*]anthracene (5a) and Their Separation by HPLC.** To a solution of (±)-**5a** (530 mg) in dry pyridine (20 mL) was added portionwise the acid chloride of MAA (2.79 g) under cooling at 0 °C over 30 min. The reaction mixture was stirred overnight at 0–5 °C. After removal of solvent under reduced pressure (5 mmHg) at room temperature, the residue was dissolved in benzene (70 mL) and the solution was washed with saturated $NaHCO_3$ solution (3 × 20 mL) and water (2 × 20 mL). The organic phase was dried ($K_2CO_3$) and evaporated to leave an oil which was subjected to Florisil chromatography, using 10% $Et_2O$ in benzene, to provide a yellowish semisolid (1.15 g, 87%). Preparative separation of the diastereoisomers (~100 mg/injection) was achieved (>98% diastereoisomerically pure) on a 10-μm silica gel column (2.5 cm × 120 cm) eluted with 5% $Et_2O$ in cyclohexane at a flow rate of 45 mL/min ($\alpha = 1.21$). Evaporation of less polar fraction ($k' = 3.0$) afforded the bis(MAA ester) of the (−)-(3*R*,4*R*)-dihydrodiol **5a** (220 mg, 19% yield): mp 139–140 °C ($Et_2O$–MeOH); $[\alpha]^{23}_D$ −181° (*c* 0.29, THF); NMR (benzene-$d_6$) δ 3.91 (s, 2 H, $COCH_2O$), 3.98 (s, 2 H, $COCH_2O$), 6.70 (d, 1 H, $H_4$, $J_{4,3} = 6$ Hz), 6.25 (q, 1 H, $H_2$, $J_{2,1} = 10$, $J_{2,3} = 5$ Hz), 5.96 (distorted t, 1 H, $H_3$). Evaporation of combined more polar fractions ($k' = 3.65$) afforded the bis(MAA ester) of the (+)-(3*S*,4*S*)-dihydrodiol **5a** as an oil (199 mg, 17.2% yield); $[\alpha]^{23}_D$ +85.9° (*c* 0.71, THF); NMR (benzene-$d_6$) δ centered at 3.93 and 4.08 (d, d, 2 H, $COCH_2O$, $J_{gem} = 16$ Hz), 6.70 (d, 1 H, $H_4$, $J_{4,3} = 6$), 6.25 (q, 1 H, $H_2$, $J_{2,1} = 10$, $J_{2,3} = 5$ Hz), 5.96 (distorted t, 1 H, $H_3$). Partial NMR spectra are shown in Figure 2. Hydrolysis of each diastereoisomer was effected with sodium methoxide in MeOH–THF as described above for the bis(menthoxyacetyl esters) of **3a** to give (−)-**5a** and (+)-**5a**, respectively, in 86–95% yield. The somewhat low separation factor ($\alpha = 1.22$) combined with the potential tumorigenicity of these diastereomers mitigated against their use in preparative studies.

**Chrysene Diols. Preparation of the Diastereoisomeric Mixture of Bis(MAA esters) of (±)-*trans*-1,2-Dihydroxy-1,2,3,4-tetrahydrochrysene 3b and Their Separation by HPLC.** To a solution of (±)-**3b**[10] (6.66 g) in dry pyridine (70 mL) was added dropwise the acid chloride of MAA (23.41 g) over 10 min at 0 °C with stirring. The mixture was stirred overnight at room temperature and at 65 °C for 0.5 h. After the mixture was cooled, the pyridine was evaporated under reduced pressure, and the residue was dissolved in EtOAc. The solution was washed with water, dilute HCl, water, saturated $NaHCO_3$ solution, and finally with water. The EtOAc was dried ($Na_2SO_4$) and evaporated to provide a light yellow solid (16.4 g, 99.7%) which was purified by HPLC on a 10-μm silica gel column (2.5 cm × 120 cm, ~500 mg/injection), using 8% ether in cyclohexane as a solvent at a flow rate of 50 mL/min ($\alpha = 1.32$). Evaporation of combined less polar fractions ($k' = 2.44$) afforded the (−)-bis(MAA ester) of the (+)-(1*R*,2*R*)-tetrahydrodiol **3b** (5.1 g, 31%) as colorless feathers: mp 108–110 °C; NMR (benzene-$d_6$) δ 3.95 (s, 2 H, $COCH_2O$), 4.12 (s, 2 H, $COCH_2$), 5.52 (m, 1 H, $H_2$), 6.60 (d, 1 H, $H_1$, $J_{1,2} = 6$ Hz). Evaporation of combined more polar fractions ($k' = 3.22$) afforded the (+)-bis(MAA ester) of (−)-(1*S*,2*S*)-tetrahydrodiol **3b** (5.4 g, 33% yield) as colorless feathers: mp 135–138 °C; NMR (benzene-$d_6$) δ centered at 3.84 and 4.07 (d, d, 2 H, $COCH_2O$), centered at 4.08 and 4.21 (d, d, 2 H, $COCH_2O$), 5.52 (m, 1 H, $H_2$), 6.60 (d, 1 H, $H_1$, $J_{1,2} = 6$ Hz). Analytical HPLC showed both of the isomers to be as >98% diastereoisomerically as well as chemically pure.

**(+)-*trans*-(1*R*,2*R*)-1,2-Dihydroxy-1,2,3,4-tetrahydrochrysene [(+)-3b].** To a solution of the less polar diastereoisomer (5.0 g) in MeOH–THF (1:1, 300 mL) was added 10% aqueous NaOH solution (15 mL) with stirring at 0 °C. The reaction mixture was stirred at room temperature under $N_2$ gas for 1 h. The reaction mixture was concentrated to about 50 mL, 150 mL of water was added, and the mixture was cooled to complete the (+)-**3b** precipitation of the product. The resulting precipitate was filtered to give as colorless crystals (2.02 g, 100% yield): mp 236–238 °C dec.

**(−)-*trans*-(1*S*,2*S*)-1,2-Dihydroxy-1,2,3,4-tetrahydrochrysene [(−)-3b].** The same treatment of the more polar diastereoisomer (5.35 g) as above afforded (−)-**3b** (2.17 g, 100% yield)

as colorless crystals: mp 235–236 °C dec.

**(−)-*trans*-(1*R*,2*R*)-1,2-Diacetoxy-1,2,3,4-tetrahydrochrysene.** Acetylation of (+)-**3b** (2.0 g) with acetic anhydride (5 mL) and dry pyridine (30 mL) was effected as described for acetylation of (+)-**3a**. The (−)-bis acetate (2.36 g, 89.6% yield) was obtained as colorless feathers: mp 179–181 °C ($CHCl_3$–petroleum ether).

**(+)-*trans*-(1*S*,2*S*)-1,2-Diacetoxy-1,2,3,4-tetrahydrochrysene.** Acetylation of (−)-**3b** (1.9 g) with acetic anhydride (5 mL) and dry pyridine (30 mL) was effected as described for acetylation of (+)-**3a**. The (+)-bis acetate (2.37 g, 94.8% yield) was obtained as colorless feathers: mp 178–179 °C ($CHCl_3$–petroleum ether).

**(−)-*trans*-(1*R*,2*R*)-1,2-Diacetoxy-1,2-dihydrochrysene.** Benzylic bromination of the (−)-bis(acetate) of (+)-**3b** (2.36 g) was carried out with NBS (1.34 g) and AIBN (5 mg) in $CCl_4$ (175 mL) as described above for the benz[*a*]anthracene derivatives. The crude product was triturated with $Et_2O$ (50 mL) to provide crystals which were collected by filtration and washed with cold ether. The combined filtrate and washing were cooled at −18 °C overnight to give a second crop of product. The combined first and second crops of product afforded the 1-bromo diacetate (**4b**; 2.48 g, 85.8%), which was used for dehydrobromination without further purification. To a solution of the above bromide (2.38 g) in THF (75 mL) was added dropwise DBN (2.5 mL) under cooling at 0 °C with stirring in a current of argon gas. The reaction mixture was stirred for 18 h at room temperature. After evaporation of the solvent at room temperature under reduced pressure, the residue was extracted with EtOAc (3 × 30 mL). The combined organic extract was washed with water, dilute HCl, saturated $NaHCO_3$ solution, and water. The extract was dried ($Na_2SO_4$) and evaporated to leave a slightly greenish solid, which was subjected to silica gel column chromatography, eluting with 0.25% THF in methylene chloride. The product was further purified by HPLC on a 10-μm silica gel column (2.5 cm × 120 cm), using 0.25% THF in methylene chloride at 800 psi ($k' = 2.6$), to afford colorless crystals (450 mg, 23.3% yield): mp 198–200 °C.

**(+)-*trans*-(1*S*,2*S*)-1,2-Diacetoxy-1,2-dihydrochrysene.** The reaction of the (+)-bis(acetate) of (−)-**3a** (2.37 g), NBS (1.34 g), and AIBN (5 mg) in $CCl_4$ (200 mL) was effected as described above to afford the 1-bromo diacetate (2.77 g, 95.4%). A sample of the above 1-bromo diacetate (2.75 g) was subjected for dehydrobromination with DBN (2.5 mL) in THF (100 mL) as described above to afford the (+)-bis(acetate) of (+)-**5b** as colorless crystals (500 mg, 22.4% yield): mp 197–198 °C.

**(−)-*trans*-(1*R*,2*R*)-1,2-Dihydroxy-1,2-dihydrochrysene ((−)-5b).** Ammonolysis of the (−)-bis acetate of (−)-**5b** (434 mg) in saturated $NH_3$–MeOH (100 mL) was effected in the usual manner. The crude product was washed with a mixture of $Et_2O$–MeOH (1:1, 50 mL), and the resulting crystals of (−)-**5b** (296 mg) were collected. The mother liquor was evaporated, and the residue was subjected to silica gel (170 g) chromatography with 30% petroleum ether in EtOAc to provide an additional 15 mg of (−)-**5b** (total yield, 95%): mp 226–228 °C.

**(+)-*trans*-(1*S*,2*S*)-1,2-Dihydroxy-1,2-dihydrochrysene ((+)-5b).** Ammonolysis of the (+)-bis acetate of (+)-**5b** (459 mg) was effected with saturated $NH_3$–MeOH (100 mL) in the same manner as above to give (+)-**5b** as colorless crystals (364 mg, 97% yield): mp 226–228 °C.

**(+)-*trans*-(1*S*,2*S*)-1,2-Bis[(*p*-(dimethylamino)benzyl)oxy]-1,2,3,4-tetrahydrochrysene [Bis[*p*-(dimethylamino)benzoate] of (−)-3b].** To a solution of (−)-**3b** (20 mg) in ~5 drops of dry pyridine was added *p*-(dimethylamino)benzoyl chloride (55 mg) and *p*-(dimethylamino)pyridine (3 mg). The reaction mixture was heated at 75 °C for 16 h. After the mixture was cooled, the product was extracted into $CHCl_3$ (3 × 2 mL). The combined chloroform extract was washed with water, dried ($Na_2SO_4$), and evaporated prior to preparative TLC on silica gel G (Analtech, 250 μm) eluted with $CHCl_3$. The product was further purified by HPLC on a Du Pont Zorbax sil column (6.2 mm × 25 cm) eluted with 0.25% THF in methylene chloride at a flow rate of 6.0 mL/min ($k' = 4.0$). Evaporation of the mobile phase afforded colorless crystals (10 mg, 23.6% yield): mp 199–203 °C; $[\alpha]^{23}_D$ +69.0° (*c* 0.17, THF); UV (MeOH) $\lambda_{max}$ 256 nm (ε 68 300), 312 (ε 59 860), $\Delta\epsilon$ = +25.4 ($\lambda^{MeOH}$ 325 nm); mass spectrum (C-I-$NH_3$), *m/e* 559 ($M^+ + 1$), 515 [$M^+ + 1 - N(CH_3)_2$], 344 ($M^+$ – (dimethylamino)benzoate); NMR ($CDCl_3$) δ 2.50 (m, 2 H, $H_3$ equatorial and $H_3$ axial), 2.94 (s, 12 H, $(CH_3)_2N$), 3.43 (distorted t, 2 H, $H_4$ and $H_{4'}$), 5.55 (0, 1 H, $H_2$, $J_{2,3}$(a) = 11.2, $J_{2,1}$ = 8.8, $J_{2,3}$(e) = 4.8 Hz), 6.60 (d, 1 H, $H_1$, $J_{1,2}$ = 8.8). Coupling constants were confirmed by decoupling.

**Diol Epoxides. (−)-(1*S*,2*R*,3*S*,4*R*)-3,4-Dihydroxy-1,2-epoxy-1,2,3,4-tetrahydrobenz[*a*]anthracene [(−)-1a].** A mixture of (−)-**5a** (150 mg), *N*-bromoacetamide (90 mg), THF (30 mL), and water (10 mL) was stirred at room temperature for 48 h under argon in the dark. After 10% $NaHSO_3$ solution (5 mL) was added, the solvent THF was evaporated and the aqueous mixture was extracted with EtOAc (3 × 80 mL). The combined organic extract was washed with water (2 × 10 mL), dried ($MgSO_4$), and evaporated to leave crystals which were recrystallized from $CH_2Cl_2$/petroleum ether to give the corresponding bromo triol as colorless prisms (186 mg, 95.5% yield): mp 145–150 °C dec; $[\alpha]^{23}_D$ +26.7° (*c* 0.24, THF).

A mixture of the above bromo triol (170 mg), the hydroxide form of dry Amberlite IRA-400 (2 g), and THF (10 mL) was stirred under argon for 20 h. After completion of the reaction, the mixture was filtered to remove the resin. The filtrate was evaporated to leave solid (−)-diol epoxide **1a**, which was recrystallized from THF–benzene to give a pale yellow crystalline powder of diol epoxide **1a** (113 mg, 85.5% yield): mp 173–174 °C dec.

**(+)-(1*R*,2*S*,3*R*,4*S*)-3,4-Dihydroxy-1,2-epoxy-1,2,3,4-tetrahydrobenz[*a*]anthracene [(+)-1a].** The same treatment of (+)-**5a** (150 mg) as above afforded the corresponding bromo triol (185 mg, 90.5% yield): mp 149–150 °C dec; $[\alpha]^{23}_D$ −26.4° (*c* 0.37, THF). Successive dehydrobromination of the bromo triol (145 mg) was carried out as described above to give (+)-**1a** as a pale yellow crystalline powder (95.5 mg, 85% yield): mp 173–174 °C dec.

**(−)-(1*R*,2*S*,3*R*,4*S*)-1,2-Dihydroxy-3,4-epoxy-1,2,3,4-tetrahydrochrysene [(−)-1b].** A mixture of (−)-**5b** (97.5 mg), *N*-bromoacetamide (57 mg), THF (12 mL), and water (4 mL) was stirred at room temperature for 21 h under argon gas. After 10% $NaHSO_3$ solution (5 mL) was added, the solvent THF was evaporated, and the aqueous mixture was extracted with EtOAc (3 × 60 mL). The combined organic extract was washed with water (2 × 10 mL), dried ($MgSO_4$), and evaporated to leave crystals which were triturated with $Et_2O$ to give the desired bromo triol (115 mg), mp 160–162 °C dec, which was used for the following reaction without further purification. To a solution of the above bromo triol (115 mg) in THF (10 mL) was added the hydroxide form of dry Amberlite IRA-400 (1 g). The reaction mixture was stirred under argon gas for 24 h. Reaction was monitored by TLC on an Eastman 13181 silica gel chromatogram sheets, using $CHCl_3$/THF (3:1) as solvent (starting dihydrodiol and product had $R_f$ values of ~0.25 and ~0.5, respectively). After completion of the reaction, the mixture was filtered to remove the resin. The filtrate was evaporated to leave solid (−)-**1b**, which was triturated with $Et_2O$ to give a colorless crystalline powder (61.5 mg, 57.8% overall yield for the above two steps): mp 172–175 °C dec.

**(+)-(1*S*,2*R*,3*S*,4*R*)-1,2-Dihydroxy-3,4-epoxy-1,2,3,4-tetrahydrochrysene [(+)-1b].** Formation of the bromo triol from (+)-**5b** (100 mg) and successive dehydrobromination were carried out as described above for its enantiomer to give (+)-**1b** as a colorless crystalline powder (65.4 mg, 61.6% for the two steps): mp 172–174 °C dec.

**(+)-(1*R*,2*S*,3*S*,4*R*)-3,4-Dihydroxy-1,2-epoxy-1,2,3,4-tetrahydrobenz[*a*]anthracene [(+)-2a].** To a solution of (−)-**5a** (87 mg) in THF (15 mL) was added *m*-chloroperoxybenzoic acid (870 mg) under cooling at 0 °C in the dark. The reaction mixture was allowed to stand at room temperature for 15 min in dark by which time its UV spectrum showed only the 1,2,3,4-tetrahydro BA chromophore. Cold ethyl acetate (200 mL) was added to the reaction mixture, which was then washed with cold NaOH solution (3 × 40 mL) and water and dried ($MgSO_4$). Evaporation of the solvent gave (+)-**2a** as a slightly yellowish solid which was triturated with $Et_2O$ to give a pale yellow crystalline powder (72 mg, 78.5% yield): mp 188–189 °C dec.

**(−)-(1*S*,2*R*,3*R*,4*S*)-3,4-Dihydroxy-1,2-epoxy-1,2,3,4-tetrahydrobenz[*a*]anthracene [(−)-2a].** Direct epoxidation of (+)-**5a** (87 mg) was effected by the same way as described above for its enantiomer to give (−)-**2a** (89 mg, 80.5% yield) as a crystalline powder: mp 188–189 °C dec.

**(+)-(1*R*,2*S*,3*S*,4*R*)-1,2-Dihydroxy-3,4-epoxy-1,2,3,4-tetrahydrochrysene [(+)-2b].** Direct epoxidation of (-)-**5b** (98 mg) was effected with *m*-chloroperoxybenzoic acid (1 g) in THF (10 mL) for 2 h as described above for the synthesis of (+)-**2a** to give (+)-**2b** as a colorless crystalline powder (80.6 mg, 77.5% yield): mp 233 °C dec.

**(-)-(1*S*,2*R*,3*R*,4*S*)-1,2-Dihydroxy-3,4-epoxy-1,2,3,4-tetrahydrochrysene [(-)-2b].** Direct epoxidation of (+)-**5b** (100 mg) was effected as described above to give (-)-**2b** as a colorless crystalline powder (89 mg, 83.9% yield) mp 233 °C dec.

**Tetrahydrochrysene 3,4-Epoxide. Preparation of Diastereoisomeric MAA Esters of (±)-*trans*-3-Bromo-4-hydroxy-1,2,3,4-tetrahydrochrysene and Their Separation by HPLC.** To a solution of (±)-3-bromo-4-hydroxy-1,2,3,4-tetrahydrochrysene[4c] (642 mg) in dry pyridine (10 mL) was added (-)-menthoxyacetyl chloride (1 g) under cooling at 0 °C within 30 min. The reaction mixture was stirred overnight at room temperature and poured into $CHCl_3$ (200 mL). The $CHCl_3$ solution was washed with water, dilute HCl, and water, dried ($MgSO_4$), and evaporated to give crystals (1.2 g).

Preparative separation (>99.5% diastereomerically pure) of the above diastereomeric mixture (1.2 g) by HPLC was achieved on a 10-μm silica gel column (2.5 cm × 120 cm) elauted with 3% $Et_2O$ in cyclohexane at a flow rate of 44 mL/min ($\alpha$ = 1.34). Evaporation of combined less polar fraction ($k'$ = 2.6) afforded the MAA ester of *trans*-(3*R*,4*R*)-3-bromo-4-hydroxy-1,2,3,4-tetrahydrochrysene (-)-**6** (0.5 g, 39%), as colorless feathers: mp 102-103 °C (petroleum ether); $[\alpha]^{23}_D$ -134° (*c* 1.43, $CHCl_3$); NMR (benzene-$d_6$) $\delta$ 3.90 (s, 2 H, $COCH_2O$), 4.56 (q, 1 H, $H_3$, $J_{3,4}$ = 6, $J_{3,2}$ = $J_{3,2'}$ = 2.2 Hz). Evaporation of combined more polar fractoin ($k'$ = 3.4) afforded the MAA ester of *trans*-(3*S*,4*S*)-3-bromo-4-hydroxy-1,2,3,4-tetrahydrochrysene (+)-**6** (0.5 g, 39%) as colorless feathers: mp 103-104 °C (MeOH) $[\alpha]^{23}_D$ +57.2° (*c* 1.01, $CHCl_3$); NMR (benzene-$d_6$) $\delta$ centered at 3.78 and 3.96 (d, 5, 2 H, $COCH_2O$, $J_{gem}$ = 16 Hz), 4.56 (q, 1 H, $H_3$, $J_{3,4}$ = 6, $J_{3,2}$ = $J_{3,2'}$ = 2.2 Hz.

**(-)-*trans*-(3*R*,4*R*)-3-Bromo-4-hydroxy-1,2,3,4-tetrahydrochrysene [(-)-7].** A mixture of the above less polar MAA ester (-)-**6** (315 mg) and 1 M $B_2H_6$-THF solution (50 mL) was allowed to stand at room termperature for 1 week. After decomposition of excess $B_2H_6$ with ice water, the solvent was evaporated to leave crystals (120 mg), which were washed with cold MeOH. Recrystallization from MeOH afforded colorless needles of (-)-**7**: mp 183-184 °C; $[\alpha]^{23}_D$ -62.5° (*c* 0.59, THF).

**(+)-*trans*-(3*S*,4*S*)-3-Bromo-4-hydroxy-1,2,3,4-tetrahydrochrysene [(+)-7].** The reaction of the more polar diastereoisomer (+)-**6** (300 mg) with 1 M $B_2H_6$-THF solution (50 mL) was effected as described above for its diastereomer to afford (+)-**7** as colorless needles: mp 183-184 °C (MeOH); $[\alpha]^{23}_D$ +61.5° (*c* 0.60).

**(+)-(3*S*,4*R*)-3,4-Epoxy-1,2,3,4-tetrahydrochrysene [(+)-8].** A mixture of (-)-**7** (90 mg), the hydroxide form of dry amberlite IRA-400 (1 g), and THF (5 mL) was stirred under argon gas for 18 h. After filtration to remove the resin, the filtrate was evaporated to leave crystals of (+)-**8** which were recrystallized from $Et_2O$ to give colorless prisms (60 mg): mp 188-189 °C; $[\alpha]^{23}_D$ +89.6° (*c* 0.40, THF); NMR ($CDCl_3$) $\delta$ 3.88 (t, 1 H, $H_3$, $J_{3,4}$ = 4.3, $J_{3,2}$ = $J_{3,2'}$ = 2.5 Hz), 4.75 (d, 1 H, $H_4$, $J_{4,3}$ = 4.3 Hz); mass spectrum (NO-$N_2$, EI), *m/e* 246 ($m^+$).

**(-)-(3*R*,4*S*)-3,4-Epoxy-1,2,3,4-tetrahydrochrysene [(-)-8].** The reaction of (+)-**7** (98 mg) with the hydroxide form of dry Amberlite IRA-400 (1 g) in THF (5 mL) was affected as described above for its enantiomer to afford (-)-**8** as colorless prisms (62 mg): mp 188-189 °C; $[\alpha]^{23}_D$ -89.9° (*c* 0.46, THF); NMR ($CDCl_3$), superimposable with that of (+)-**8**; mass spectrum (NO-$N_2$, EI), *m/e* 246 ($M^+$).

**Registry No.** (-)-(1*S*,2*R*,3*S*,4R)-**1a**, 80433-78-9; (+)-(1*R*,2*S*,3*R*,4*S*)-**1a**, 80433-79-0; (-)-(1*R*,2*S*,3*R*,4*S*)-**1b**, 77123-24-1; (+)-(1*S*,2*R*,3*S*,4*R*)-**1b**, 80433-80-3; (+)-(1*R*,2*S*,3*S*,4*R*)-**2a**, 80446-23-7; (-)-(1*S*,2*R*,3*R*,4*S*)-**2a**, 80433-81-4; (+)-(1*R*,2*S*,3*S*,4*R*)-**2b**, 77123-23-0; (-)-(1*S*,2*R*,3*R*,4*S*)-**2b**, 80433-82-5; (±)-*trans*-**3a**, 80399-21-9; (+)-(3*R*,4*R*)-**3a**, 80433-83-6; (-)-(3*S*,4*S*)-**3a**, 80433-84-7; (-)-(3*R*,4*R*)-**3a** bis(MAA) ester, 80399-22-0; (+)-(3*S*,4*S*)-**3a** bis(MAA) ester, 80433-85-8; (-)-(3*R*,4*R*)-**3a** diacetate, 80433-86-9; (+)-(3*S*,4*S*)-**3a** diacetate, 80433-87-0; (±)-*trans*-**3b**, 67175-75-1; (+)-(1*R*,2*R*)-**3b**, 80433-88-1; (-)-(1*S*,2*S*)-**3b**, 80433-89-2; (+)-(1*R*,2*R*)-**3b** bis(MAA ester, 80399-23-1; (-)-(1*S*,2*S*)-**3h** bis(MAA) ester, 80446-24-8; (-)-(1*R*,2*R*)-**3b** diacetate, 80433-90-5; (+)-(1*S*,2*S*)-**3b** diacetate, 80433-91-6; (-)-(1*S*,2*S*)-**3b** bis[(*p*-dimethylamino)benzoate], 80399-24-2; **4a**, 80399-25-3; **4b**, 80409-34-3; (±)-**5a**, 64501-86-6; (-)-(3*R*,4*R*)-**5a**, 67335-42-6; (+)-(3*S*,4*S*)-**5a**, 67335-43-7; (-)-(3*R*,4*R*)-**5a** diacetate, 80433-92-7; (+)-(3*S*,4*S*)-**5a** diacetate, 80433-93-8; (-)-(3*R*,4*R*)-**5a** bis(MAA) ester, 80399-26-4; (+)-(3*S*,4*S*)-**5a** bis(MAA) ester, 80433-94-9; (-)-(1*R*,2*R*)-**5b**, 77123-18-3; (+)-(1*S*,2*S*)-**5b**, 80433-95-0; (-)-(1*R*,2*R*)-**5b** diacetate, 80433-96-1; (+)-(1*S*,2*S*)-**5b** diacetate, 80433-97-2; (±)-**6**, 80124-65-8; (-)-(3*R*,4*R*)-**6** MAA ester, 80056-88-8; (+)-(3*S*,4*S*)-**6** MAA ester, 80124-35-2; (-)-(3*R*,4*R*)-**7**, 80056-91-3; (+)-(3*S*,4*R*)-**7**, 80433-98-3; (+)-(3*S*,4*R*)-**8**, 80433-99-4; (-)-(3*R*),4*S*)-**8**, 80434-00-0; (*p*-dimethylamino)benzoyl chloride, 4755-50-4; (-)-menthoxyacetyl chloride, 15356-62-4.

# Isolation and Characterization of the Trichoverroids and New Roridins and Verrucarins

Bruce B. Jarvis,* G. Patrick Stahly, Gowsala Pavanasasivam, Jacob O. Midiwo, Tuley DeSilva, and Chester E. Holmlund

*Department of Chemistry, University of Maryland, College Park, Maryland 20742*

Eugene P. Mazzola

*Division of Chemistry and Physics, Food and Drug Administration, Washington, DC 20204*

Richard F. Geoghegan, Jr.

*Frederick Cancer Research Facility, Frederick, Maryland 21701*

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*Myrothecium verrucaria* grown on a large scale (760 L) has yielded a variety of new trichothecenes including the nonmacrocyclic trichoverroids **13-19**, which contain a pendant C4 cis,trans-dienic ester side chain normally common only to the macrocyclic roridins and verrucarins. Several novel macrocyclic trichothecenes (roridins J and K acetate) and verrucarins L and L acetate also were isolated and characterized.

The trichothecene complex of antibiotics has generated a great deal of interest during the past 10 years, principally due to the wide spectrum of biological activity exhibited by these sesquiterpene mycotoxins.[1] Our interest in this

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