Syntheses of Fjord Region Bis-dihydrodiol and Bis-*anti*-diol Epoxide Metabolites of Benzo[*s*]picene

Fang-Jie Zhang and Ronald G. Harvey*

Ben May Institute for Cancer Research, University of Chicago, Chicago, Illinois 60637

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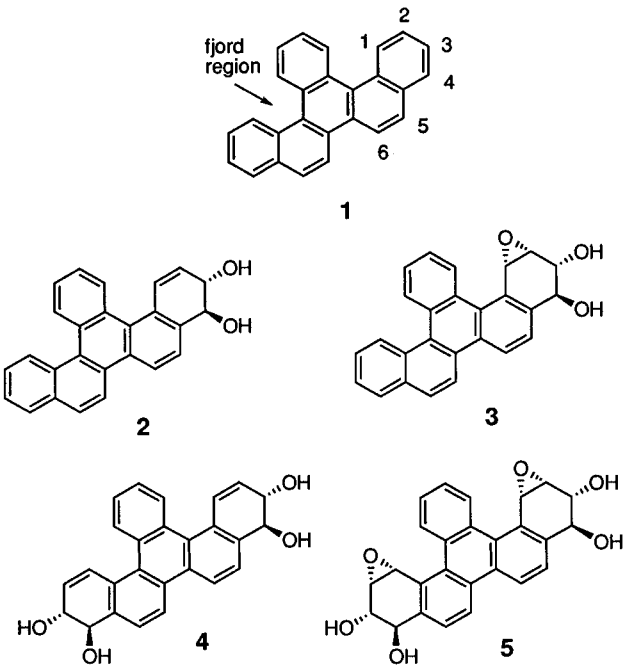
Efficient syntheses of the *trans*-3,4-*trans*-9,10-tetrahydroxy-3,4,9,10-tetrahydro derivatives of benzo[*s*]picene and the corresponding bis-*anti*-diol epoxide derivatives in which the epoxide rings lie in the sterically crowded *fjord* regions are reported. Bis-dihydrodiols and bis-*anti*-diol epoxides of this type are suspected as proximate and ultimate carcinogenic metabolites, respectively, of several polycyclic aromatic hydrocarbons. These are the first examples of this class of molecules to be synthesized. The syntheses entail in the key step double oxidative photocyclization of a tetramethoxy-2,3-distyrylnaphthalene obtained from double Wittig reaction of naphthalene-2,3-dialdehyde. The bis-dihydrodiols were obtained as a mixture of meso and racemic diastereomers separable by HPLC on a reversed-phase ZORBAX ODS column. The bis-*anti*-diol epoxide enantiomers derived from the latter were resolved by HPLC on a chiral column.

Benzo[*s*]picene (**1**) is a symmetrical six-ring polycyclic aromatic hydrocarbon that has only recently become conveniently available via a novel synthetic route.[1] As a consequence of its prior relative unavailability, virtually nothing is known concerning the chemistry of benzo[*s*]-picene.[2] There are no reports of electrophilic substitution or other types of reactions. Our interest was stimulated by the potential carcinogenicity of **1**, since it contains two *fjord* regions, and *fjord* region-containing polyarenes, such as dibenzo[*a,l*]pyrene[3] and benzo[*g*]chrysene,[4] are among the most potent carcinogenic hydrocarbons known. Like these polyarenes, **1** is likely to be distorted from planarity due to steric interference between the *fjord* region hydrogen atoms. Deviation from planarity is associated with carcinogenicity, and it has been proposed that this steric effect on bioactivity may result from increased binding of the active diol epoxide metabolites of **1** to deoxyadenosine sites in DNA.[4−6]

In connection with studies of the metabolism and carcinogenicity of benzo[*s*]picene, we required samples of its potential active metabolites, specifically the *trans*-3,4-dihydrodiol (**2**) and the *anti*-diol epoxide (**3**) as well as the more highly oxidized *trans*-3,4-*trans*-9,10-tetrahydrotetraol (**4**), referred to herein as the bis-dihydrodiol, and the corresponding bis-*anti*-diol epoxide (**5**). Although bis-dihydrodiols and the derived diol epoxides are implicated as active metabolites of several carcinogenic hydrocarbons, such as dibenz[*a,c*]anthracene, dibenz[*a,h*]-anthracene, dibenz[*a,j*]anthracene, and dibenzo[*b,def*]-chrysene,[7−10] practical methods for their synthesis are lacking. The only bis-dihydrodiols whose syntheses have been described are the 3,4,10,11- and 3,4,12,13-bis-dihydrodiols of dibenz[*a,h*]anthracene; however, the overall yields are low (1.2% and 0.5%, respectively) and minimal experimental details are provided.[7] We now report efficient syntheses of the bis-dihydrodiol and the bis-*anti*-diol epoxide metabolites of benzo[*s*]picene (**4** and **5**).



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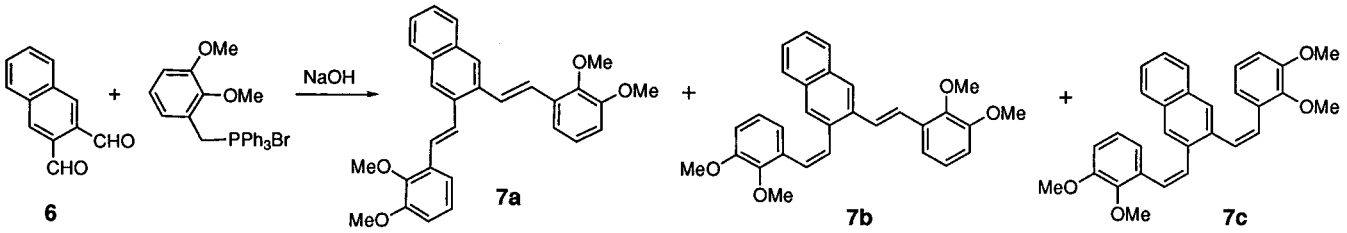
Scheme 1



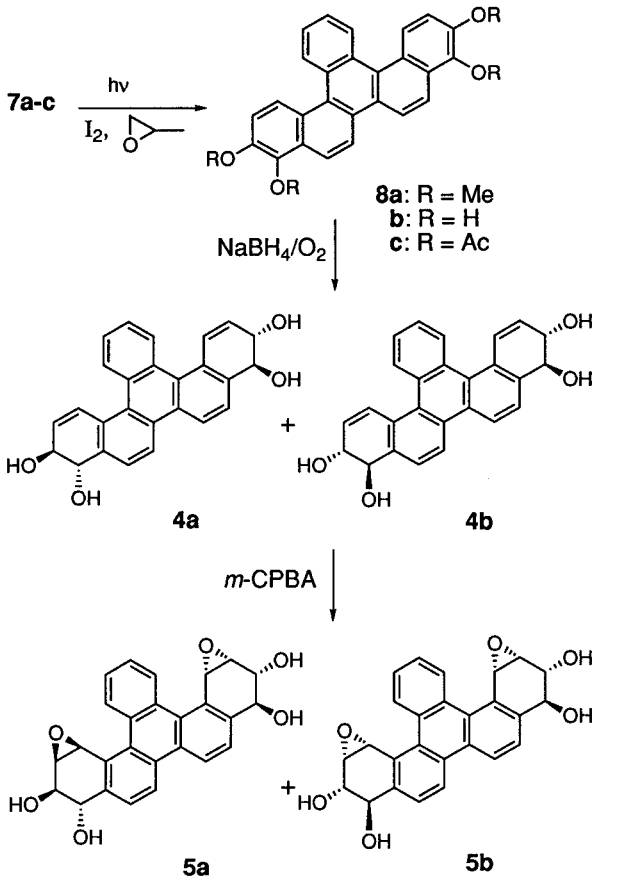
Results and Discussion

Our synthetic approach to the symmetrical terminal ring-oxidized metabolites of benzo[*s*]picene entails in the key step double photocyclization of a tetramethoxy-substituted diolefin (**7a**) (Scheme 1). This intermediate is potentially accessible from double Wittig reaction between an appropriate arylaldehyde and a phosphonium salt, either through reaction of naphthalene-2,3-dialdehyde (**6**) with 2,3-dimethoxybenzyl triphenylphosphonium bromide or via reaction of the bis-benzyl triphenylphosphonium salt of 2,3-bis(bromomethyl)naphthalene with 2,3-dimethoxybenzaldehyde. However, all attempts to obtain **7a** via the latter route failed, possibly due to the highly sterically hindered nature of the dibenzyltriphenylphosphonium salt. Naphthalene-2,3-dialdehyde (**6**) required as the starting compound for the alternative route is readily accessible from naphthalene-2,3-dicarboxylic acid by reduction to the corresponding dialcohol with $LiAlH_4$ followed by oxidation with oxalyl chloride and dimethyl sulfoxide.[11]

Wittig reaction of **6** with the phosphonium salt prepared from 2,3-dimethoxybenzyl bromide and triphenylphosphine furnished a mixture of three isomeric diolefins **7a**−**c** (87%) in an approximately equal ratio. Chromatography on a silica gel column eluted with CH_2Cl_2−hexane afforded the individual pure isomers distinguishable by their ^1H NMR spectra. For two of the isomers, the NMR spectra were relatively simple, indicative of the symmetrical *ZZ* and *EE* olefin structures **7a** and **7c**. However, the spectrum of the third isomer was relatively complex, more consistent with the asymmetric *ZE* olefin structure **7b**. The relatively larger coupling constants exhibited by the olefinic protons of **7a** (J_{AB} = 16.2 Hz) than **7c** (J_{AB} = 12.3 Hz) suggest that the former has a trans configuration with the *EE* structure while the latter has a cis configuration with the *ZZ* structure. However, these assignments should be regarded as only tentative. On measurement of the UV spectra of the individual pure isomers, they underwent conversion to an equilibrium mixture of diolefins.

Photochemical cyclodehydrogenation of the mixture of diolefins **7a**−**c** conducted in dilute benzene solution in the presence of iodine and propylene oxide[12] gave a single cyclized product (**8a**) in 91% yield (Scheme 2). The ^1H NMR spectrum of **8a** was consistent with its symmetrical structure, exhibiting a doublet and a multiplet at characteristic low field (δ 8.75 and 8.88, respectively) assigned to the two pairs of *fjord* region protons, three additional doublets at δ 8.63, 8.37, and 7.44 and a multiplet at δ 7.60 assigned to the remaining eight aryl protons, and a pair of singlets at δ 4.09 and 4.10, equivalent to six protons each, for the methoxy protons. Demethylation of **8a** with BBr_3 furnished the bis-catechol, tetrahydroxybenzo[*s*]picene (**8b**), which was isolated as its tetraacetate (**8c**) because of the sensitivity of polycyclic catechols to air oxidation.

Scheme 2



Attempted reduction of **8c** to the bis-dihydrodiol (**4**) by treatment with $NaBH_4$ in EtOH with oxygen bubbling through the solution by the procedure employed previously for reduction of other polycyclic hydroquinones[13] afforded a complex mixture of partially reduced products. Since this apparent resistance to reduction is a likely consequence of the poor solubility of **8b,c** and the partially reduced intermediate products in EtOH, similar reaction was conducted with methylene chloride as cosolvent. Reduction of **8c** with $NaBH_4$ in CH_2Cl_2−EtOH (1:1) took place smoothly and stereospecifically under an oxygen atmosphere to afford a mixture of two diastereomeric *trans*-3,4,9,10-tetrahydrotetraols (**4a** and **4b**)

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separable by HPLC on a reversed-phase ZORBAX ODS column eluted with a linear gradient of 50−100% methanol/water. No trace of the corresponding *cis*-isomers was detected by TLC, HPLC, or NMR analysis, consistent with previous findings of trans-stereospecificity of these types of reductions.[14]

The early- and late-eluting bis-dihydrodiol isomers were assigned structures **4a** and **4b**, respectively, on the basis of their 300 MHz ^{1}H NMR spectra. As a consequence of the asymmetry of **4a**, it is anticipated to exist as a pair of enantiomers, while **4b** is a meso form expected to be optically inactive. The resolution of **4a** was not attempted, but the existence of enantiomers was confirmed indirectly by resolution of the corresponding anti-diol epoxides on a chiral column described in the following paragraph. The coupling constants for the carbinol protons of **4a** were in the range 8.0−8.2 Hz, indicating the dihydrodiol to exist in solution in DMSO-d_6 predominantly as the diequatorial conformer. This is consistent with previous findings for other related dihydrodiols free to adopt this conformation.[14,15]

Conversion of the individual bis-dihydrodiols **4a** and **4b** to the corresponding bis-*anti*-diol epoxides, **5a** and **5b**, took place stereospecifically on treatment with *m*-chloroperbenzoic acid (*m*-CPBA). It was previously demonstrated that epoxidation with *m*-CPBA of *trans*-dihydrodiols that are free to adopt a diequatorial conformation generally takes place with high stereoselectivity to afford the corresponding *anti*-diol epoxide isomers.[14] The HPLC profiles of the bis-*anti*-diol epoxides **5a** and **5b** on a Regis chiral column [PIRKLE Covalent (*R,R*) βGEM] eluted isocratically with EtOH−hexane showed them to be remarkably pure. The bis-*anti*-diol epoxide **5a** was resolved into two peaks on the chiral column, indicative of its existence as a pair of enantiomers and consistent with its assignment as a derivative of the racemic bis-dihydrodiol **4a** with the structure shown in Scheme 2. In isomer **4a**, the hydroxyl groups in both terminal rings are *trans*, and the hydroxyl groups in the 4- and 9-positions are on opposite faces of the molecule as are the hydroxyl groups in the 3- and 10-positions. The bis-*anti*-diol epoxide **5b** exhibited a single sharp peak on the chiral HPLC column, consistent with its origin from the meso bis-dihydrodiol **4b**. In this isomer the hydroxyl groups in the 4- and 9-positions are on the same face of the molecule and trans to the hydroxyl groups in the 3- and 10-positions.

The bis-*anti*-diol epoxides (**5a** and **5b**) of benzo[*s*]picene whose syntheses are reported are the first examples of this class of higher oxidized metabolites of carcinogenic hydrocarbons to be synthesized. Recent biological studies indicate that bis-dihydrodiol and bis-*anti*-diol epoxide metabolites may play a potentially important role in the mechanism of tumorigenesis of some polycyclic aromatic hydrocarbons. The syntheses described are efficient, affording the bis-dihydrodiols (**4a** and **4b**) in 61% overall yield in four steps and the bis-*anti*-diol epoxides (**5a** and **5b**) in 58% overall yield in five steps from readily available precursors. In principle, this synthetic approach may be employed with appropriate modification for the synthesis of analogous oxidized derivatives of other symmetical polycyclic aromatic ring systems. These compounds are urgently required as standards for metabolism studies to identify the more polar metabolites that often accompany the less oxidized metabolites as well as for studies to clarify their role in carcinogenesis.

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Experimental Section

Materials and Methods. Naphthalene-2,3-dialdehyde was synthesized from naphthalene-2,3-dicarboxylic acid (Aldrich) by the published method.[11] (2,3-Dimethoxybenzyl)triphenylphosphonium bromide was prepared by heating an equimolar solution of 2,3-dimethoxybenzyl bromide and PPh_3 in a minimum volume of benzene at reflux for 5 h. The solution was cooled, and the solid precipitate was filtered, dried, and used directly. *m*-Chloroperbenzoic acid (Aldrich) was purified by washing with pH 7.4 phosphate buffer and drying under reduced pressure. THF was distilled from sodium benzophenone ketyl. The ^{1}H NMR spectra were recorded on a QE-300 MHz spectrometer in $CDCl_3$ with tetramethylsilane as internal standard unless stated otherwise. The UV spectra were measured on a Perkin-Elmer Lamda 6 spectrometer. All melting points are uncorrected. ***Caution****: Although benzo[s]picene is not an established carcinogen, it and its dihydrodiol and diol epoxide metabolites are potentially hazardous and should be handled in accordance with "NIH Guidlines for the Laboratory Use of Chemical Carcinogens".*

2,3-Bis(2,3-dimethoxystyryl)naphthalene (7). Naphthalene-2,3-dialdehyde (552 mg, 3 mmol) and (2,3-dimethoxybenzyl)triphenylphosphonium bromide (4.43 g, 9 mmol) were dissolved in CH_2Cl_2 (70 mL), and to this solution was added 50% NaOH (14 g). The mixture was stirred under argon at room temperature for 15 h and then diluted with ice-water. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The extracts were combined, washed with water, dried (Na_2SO_4), and evaporated to dryness, and the residue was chromatographed on a silica gel column. Elution with EtOAc−hexane (1:4) afforded a mixture of **7a**−**c** (1.18 g, 87%) in approximately equal ratio as a semisolid. TLC of the mixture on silica gel with CH_2Cl_2 gave R_f values for **7a**−**c** of 0.65, 0.52, and 0.38, respectively. Chromatography on a silica gel column using CH_2Cl_2−hexane (1:1) to CH_2Cl_2 as the eluting solvent gave the pure isomers. **7a**: mp 138−139 °C (MeOH); ^{1}H NMR δ 3.86 (s, 6), 3.90 (s, 6), 6.86 (dd, 2, J = 8.0, 1.0 Hz), 7.08 (t, 2, J = 8.0 Hz), 7.29 (br d, 2, J = 7.9 Hz), 7.40−7.50 (m, 2), 7.45 (d, 2, J = 16.2 Hz), 7.60 (d, 2, J = 16.2 Hz), 7.82−7.90 (m, 2), 8.06 (s, 2); FAB MS m/z 453 ([M + H]$^+$); UV λ_{max} 303 (ϵ 94 260) nm. Anal. Calcd for $C_{30}H_{28}O_4$: C, 79.62; H, 6.24. Found: C, 79.35; H, 6.28. **7b**: mp 125−126 °C (MeOH); ^{1}H NMR δ 3.82 (s, 3), 3.85 (s, 3), 3.89 (s, 3), 3.90 (s, 3), 6.55−6.72 (m, 3), 6.85 (dd, 1, J = 8.1, 0.9 Hz), 6.90−7.10 (m, 3), 7.23 (dd, 1, J = 7.1, 1.0 Hz), 7.32−7.48 (m, 2), 7.49 (s, 1), 7.50 (s, 1), 7.60 (d, 1, J = 7.1 Hz), 7.61 (s, 1), 7.86 (d, 1, J = 8.1 Hz), 8.13 (s, 1); FAB MS m/z 453 ([M + H]$^+$); UV λ_{max} 292 (ϵ 58 290) nm. Anal. Calcd for $C_{30}H_{28}O_4$: C, 79.62; H, 6.24. Found: C, 79.46; H, 6.31. **7c**: mp 167−168 °C (MeOH); ^{1}H NMR δ 3.85 (s, 6), 3.92 (s, 6), 6.59 (dd, 2, J = 7.6, 1.7 Hz), 6.66 (t, 2, J = 7.8 Hz), 6.72 (dd, 2, J = 8.0, 1.8 Hz), 6.84 (d, 2, J = 12.3 Hz), 6.90 (d, 2, J = 12.3 Hz), 7.28−7.38 (m, 2), 7.53−7.60 (m, 2), 7.67 (s, 2); FAB MS m/z 453 ([M + H]$^+$); UV λ_{max} 303 (ϵ 94 260) nm. Anal. Calcd for $C_{30}H_{28}O_4$: C, 79.62; H, 6.24. Found: C, 79.67; H, 6.26.

3,4,9,10-Tetramethoxybenzo[*s*]picene (8a). Argon was bubbled through a solution of the mixture of diolefins **7a**−**c** (1.2 g, 2.65 mmol) and I_2 (3.57 g, 5.3 mmol) in benzene (1.5 L) for 15 min, and then propylene oxide (15 mL) was added. The mixture was irradiated with a Hanovia 450 W medium-pressure mercury lamp through a Pyrex filter for 5 h. TLC showed the reaction to be complete. The solvent was removed, the residue was dissolved in $CHCl_3$, and the solution was washed with 10% $Na_2S_2O_3$ and H_2O and dried over $MgSO_4$. Evaporation of the solvent followed by recrystallization of the solid residue from $CHCl_3$ gave **8a** (1.08 g, 91%) as a white

solid: mp 303−304 °C dec; ^{1}H NMR δ 4.09 (s, 6), 4.10 (s, 6), 7.44 (d, 2, J = 9.2 Hz), 7.58−7.65 (m, 2), 8.37 (d, 2, J = 9.2 Hz), 8.63 (d, 2, J = 9.2 Hz), 8.88−8.95 (m, 2), 8.75 (d, 2, J = 9.3 Hz); FAB MS m/z 448 (M^+); UV (THF) λ_{max} 320 (ϵ 83 630), 285 (137 390) nm. Anal. Calcd for $C_{30}H_{24}O_4$: C, 80.34; H, 5.39. Found: C, 80.26; H, 5.42.

3,4,9,10-Tetraacetoxybenzo[*s*]picene (8c). To a solution of **8a** (1.0 g, 2.23 mmol) in dry CH_2Cl_2 (150 mL) at −20 °C was added a solution of BBr_3 in CH_2Cl_2 (1 M, 30 mL). The resulting yellowish solution was stirred at the same temperature for 30 min and then at room temperature for 3 h. Ice was added, and the CH_2Cl_2 was removed at reduced pressure. The aqueous suspension was extracted with EtOAc, and the combined EtOAc solution was washed with brine, dried over Na_2SO_4, and evaporated to dryness. The solid thus obtained was dissolved in pyridine (60 mL) and Ac_2O (42 mL) and stirred at ambient temperature for 48 h. The mixture was poured into ice−water and extracted with $CHCl_3$. The organic layer was washed with 1 N HCl and brine in turn and dried over Na_2SO_4. After removal of the solvent, the residue was recrystallized from CH_2Cl_2−MeOH to afford **8c** (1.15 g, 92%) as a white solid: mp 314−316 °C dec; ^{1}H NMR δ 2.43 (s, 6), 2.57 (s, 6), 7.55 (d, 2, J = 9.2 Hz), 7.65−7.75 (m, 2), 8.07 (d, 2, J = 9.0 Hz), 8.65 (d, 2, J = 9.2 Hz), 8.82−8.90 (m, 2), 8.91 (d, 2, J = 9.0 Hz); FAB MS m/z 560 (M^+); UV (THF) λ_{max} 309 (ϵ 96 140), 289 (67 580), 280 (126 760) nm. Anal. Calcd for $C_{34}H_{24}O_8$: C, 72.85; H, 4.32. Found: C, 72.97; H, 4.32.

***trans*-3,4-*trans*-9,10-Tetrahydroxy-3,4,9,10-tetrahydrobenzo[*s*]picene (4a and 4b).** A mixture of **8c** (840 mg, 1.5 mmol) and $NaBH_4$ (2.27 g, 60 mmol) in 200 mL of EtOH−CH_2Cl_2 (1:1) was stirred under an oxygen atmosphere at room temperature for 16 h. The solvent was removed under reduced pressure without heating, 200 mL of cold water was added, and the suspension was extracted with EtOAc. The organic layer was washed with brine, 1 N HCl, and brine in turn and dried over Na_2SO_4. The solvent was removed *in vacuo*, and the residue was recrystallized from EtOAc to afford a mixture of **4a** and **4b** (540 mg, 91%) as a white solid, mp 192−195 °C. Anal. Calcd for $C_{26}H_{20}O_4$: C, 78.77; H, 5.09. Found: C, 78.50; H, 5.20. The isomers **4a** and **4b** were separated by HPLC on a ZORBAX ODS column (9.4 mm × 25 cm) eluted with a linear gradient of 50−100% MeOH/H_2O with a flow rate of 4 mL/min. Retention times of **4a** and **4b** were 7.0 and 8.0 min, respectively. The early-eluting isomer **4a** was a white solid that softened at 205 °C and melted at 250 °C (THF−hexane): ^{1}H NMR (DMSO-d_6) δ 4.28−4.40 (m, 2) [after addition of D_2O changed to 4.35 (br d, 2, J = 8.0 Hz)], 4.56−4.70 (m, 2) [after addition of D_2O changed to 4.61 (br d, 2, J = 8.2 Hz)], 5.29 (d, 2, J = 5.0 Hz, exchangeable with D_2O), 5.54 (d, 2, J = 5.6 Hz, exchangeable with D_2O), 6.17 (dd, 2, J = 10.1 and 3.2 Hz), 7.14 (d, 2, J = 10.1 Hz), 7.50−7.62 (m, 2), 7.77 (d, 2, J = 8.4 Hz), 8.15−8.28 (m, 2), 8.51 (d, 2, J = 8.4 Hz); UV (THF) λ_{max} 283 (ϵ 64 150) nm; FAB MS m/z 396 (M^+); HRMS calcd for $C_{26}H_{20}O_4$ 396.1362, found 396.1363. The late-eluting isomer **4b** was a white solid: mp 252−255 °C (THF−hexane); ^{1}H NMR (DMSO-d_6) δ 4.51 (br s, 4), 5.38 (br s, 2, exchangeable with D_2O), 5.72 (br s, 2, exchangeable with D_2O), 6.18 (d, 2, J = 10.1 Hz), 6.98 (d, 2, J = 10.1 Hz), 7.50−7.60 (m, 2), 7.83 (d, 2, J = 8.3 Hz), 8.15−8.25 (m, 2), 8.53 (d, 2, J = 8.4 Hz); UV (THF) λ_{max} 282 (ϵ 67 240) nm; FAB MS m/z 396 (M^+); HRMS calcd for $C_{26}H_{20}O_4$ 396.1362, found 396.1363.

Bis-*anti*-diol Epoxides of Benzo[*s*]picene (5a and 5b). To a solution of **4a** (50 mg, 0.13 mmol) in 10 mL of dry THF was added freshly recrystallized *m*-CPBA (434 mg, 2.52 mmol). The solution was stirred at room temperature under argon for 2 h and then concentrated under vacuum without heating, and the residue was dissolved in 6 mL of THF. Addition of 24 mL of hexane gave a precipitate that was collected by filtration and washed twice with a mixture of THF (3 mL) and hexane (12 mL). Pure **5a** (47.5 mg, 88%) was a gray solid: mp 223−225 °C; ^{1}H NMR δ 3.81 (d, 2, J = 4.5 Hz), 3.85−3.97 (m, 2) [after addition of D_2O changed to 3.90 (d, 2, J = 8.7 Hz)], 4.40−4.52 (m, 2) [after addition of D_2O changed to 4.49 (d, 2, J = 8.7 Hz)], 4.82 (d, 2, J = 4.4 Hz), 5.65 (d, 2, J = 5.2 Hz, exchangeable with D_2O), 5.78 (d, 2, J = 6.7 Hz, exchangeable with D_2O), 7.55−7.70 (m, 2), 7.84 (d, 2, J = 8.3 Hz), 8.15−8.25 (m, 2), 8.58 (d, 2, J = 8.6 Hz); UV (THF) λ_{max} 273 (ϵ 74 700) nm; FAB MS m/z 427 ($M - H^+$); HRMS calcd for $C_{26}H_{19}O_6$ 427.1182, found 427.1182. Pure **5b** (48 mg, 89%) was a gray solid: mp 225−227 °C; ^{1}H NMR δ 3.70−3.82 (m, 4), 4.50−4.70 (m, 4), 5.68 (d, 2, J = 5.1 Hz, exchangeable with D_2O), 5.84 (d, 2, J = 6.5 Hz, exchangeable with D_2O), 7.64−7.75 (m, 2), 7.88 (d, 2, J = 8.4 Hz), 8.30−8.45 (m, 2), 8.64 (d, 2, J = 8.6 Hz); UV (THF) λ_{max} 274 (ϵ 80 200) nm; FAB MS m/z 429 ($M + H^+$); HRMS calcd for $C_{26}H_{21}O_6$ 429.1338, found 429.1336.

HPLC of the bis-*anti*-diol epoxides **5a** and **5b** on a Regis chiral column [PIRKLE Covalent (R,R) βGEM, 250 × 4.6 mm, 5 μm] eluted isocratically with EtOH-hexane (40:60) at a flow rate of 1 mL/min confirmed their purity. The **5a** isomer showed two peaks on the chiral column (retention times 7.5 and 8.5 min), indicative of its existence as a racemate and consistent with origin from the racemic bis-dihydrodiol **4a**. The **5b** isomer appeared as a single sharp peak eluted at 7.0 min on the chiral column, consistent with its origin from the meso bis-dihydrodiol **4b**.

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