

Synthesis of (±)-*trans*-7,8-Dihydrodiol of 6-Fluoro-benzo[*a*]pyrene via Hydroxyl-Directed Regioselective Functionalization of Substituted Pyrene

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Synthesis of (±)-*trans*-7,8-dihydroxy-6-fluoro-7,8-dihydrobenzo[*a*]pyrene, the metabolite from 6-fluoro-benzo[*a*]pyrene, is described. Position 6 of 7,8,9,10-tetrahydrobenzo[*a*]pyren-7-ol (**1**) was functionalized by bromination with *N*-bromosaccharin. Regioselectivity in the bromination is thought to derive from a substrate–reagent hydrogen bond. NMR evidence is offered to support this model. The 6-bromo derivative **2** was subjected to dehydration followed by bromine–lithium exchange. Quenching the lithio intermediate with NFSi afforded the 6-fluoro derivative **4**. Prévost reaction on the 7,8 double bond resulted in the *trans* dibenzoate **5** (established by comparison to a *cis* derivative prepared by osmium tetroxide *cis* dihydroxylation). Introduction of the 9,10 double bond by a bromination–dehydrobromination procedure, followed by hydrolysis, gave racemic *trans*-7,8-dihydrodiol **7**. Resolution of the enantiomers was achieved by chiral HPLC, and the absolute configurations of the early and late eluting isomers were determined through CD spectroscopy by comparison with the metabolically obtained (7*R*,8*R*)-dihydrodiol.

Introduction

Polycyclic aromatic hydrocarbons (PAHs) are widespread environmental pollutants.¹ These compounds can be metabolized via either a one-electron oxidation to radical cations or a monooxygenase pathway to electrophilic angular-ring diol epoxides. In the first route, the radical cations react with DNA, possibly leading to depurination reactions,^{2,3} whereas in the latter case, the diol epoxides alkylate DNA bases, leading to covalent modification of DNA.³ Formation of diol epoxides occurs via an initial cytochrome P450 mediated oxidation of the angular ring to an arene oxide. This undergoes hydrolysis by epoxide hydrase to a dihydrodiol, which undergoes a second oxidation to a diol epoxide. Two enantiomeric pairs of diastereomeric diol epoxides are produced by such a metabolism (Figure 1). The pair in which the benzylic hydroxyl and epoxide are *cis* are termed *syn* or series 1, whereas in the *anti* or series 2 isomers these groups are *trans*. In benzo[*a*]pyrene (BaP), among the four optically active isomers formed via monooxygenation, the (+)-(7*R*,8*S*)-diol-(9*S*,10*R*)-epoxide predominates and has the most pronounced tumorigenicity.⁴ For most *bay* region containing hydrocarbons studied, this metabolism pattern prevails.⁴ Besides absolute configuration of the diol epoxide, conformation of the tetrahydro ring has also

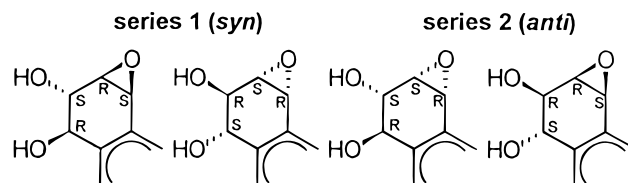


Figure 1. Structures of the four configurational isomers of *bay* region diol epoxides.

been suggested to be at least partially responsible for mutagenic activity. In the absence of unusual structural features, in the series 2 isomers, the vicinal hydroxy moieties normally prefer the quasi-diequatorial orientation. On the other hand, in the series 1 isomers, which are documented to be inactive as tumorigens, the quasi-diaxial arrangement predominates.⁴ Introduction of fluorine at position 6 of BaP diol epoxide, which is *peri* to the benzylic hydroxyl, causes a conformational change of the angular tetrahydro ring. Thus, the preference for the quasi-diaxial orientation of vicinal hydroxyl groups is observed in the (*R*,*S*,*S*,*R*)-diol epoxide isomer of 6-fluoro-benzo[*a*]pyrene (6-F-BaP),⁵ as well as in its metabolic precursor 7,8-dihydroxy-6-fluoro-7,8-dihydrobenzo[*a*]pyrene.⁶ In contrast to the (*R*,*S*,*S*,*R*)-diol epoxide of BaP, the 6-fluoro analogue was reported to have no tumorigenic activity.⁵ The parent hydrocarbon 6-F-BaP, on the other hand, has been shown to be active as a tumorigen, although it is less potent than BaP.^{6,7} The reactivity of 6-F-BaP and 6-F-BaP-7,8-dihydrodiol with DNA has been studied, and the formation of adducts

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largely through the diol epoxide pathway has been suggested.⁸

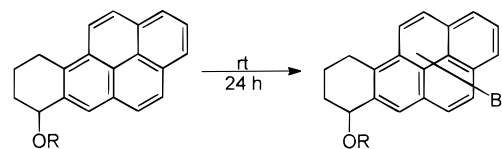
Recent research in PAH-induced carcinogenesis has focused on the correlation between the biochemical process and the solution structures of DNA containing the diol epoxide adducts.⁹ For these studies, site specifically modified oligodeoxyribonucleotides are prepared through multistep synthesis,¹⁰ which requires substantial quantities of diol epoxides. Previously, two of the four possible isomeric diol epoxides of 6-fluoro-benzo[a]pyrene were synthesized from the metabolically formed *trans*-(7*R*,8*R*)-dihydrodiol⁶ by known chemical methods.¹¹ However, for structure–biology studies through DNA binding, a convenient chemical synthesis that provides both the antipodes of the dihydrodiol and all four diol epoxides is required. Herein, an efficient, facile synthesis of (±)-*trans*-7,8-dihydroxy-6-fluoro-7,8-dihydrobenzo[a]pyrene is reported.

Results and Discussion

The key step in the preparation of *trans*-7,8-dihydroxy-6-fluoro-7,8-dihydrobenzo[a]pyrene was the regioselective bromination at C-6 of an appropriately functionalized 7,8,9,10-tetrahydrobenzo[a]pyrene ring. The extremely facile functionalization at the 6 position of benzo[a]pyrene is amply documented, and the preparation of several 6-substituted compounds,¹² including the fluoro derivative,¹³ has been reported. However, these methods cannot be utilized, if the angular ring has to be functionalized for the ultimate preparation of the 7,8-dihydrodiol metabolite.

Two possible routes for the selective functionalization of C-6 of 7,8,9,10-tetrahydrobenzo[a]pyren-7-ol (**1**) are direct electrophilic aromatic substitution at C-6 or a *peri* metalation approach using the directing effect of the benzylic 7-hydroxyl group, followed by electrophilic trapping of the C-6 lithio compound. The hydroxyl-directed remote lithiation was unsuccessful, possibly as a result of the low solubility of the initially formed lithium alkoxide.¹⁴ Additionally, we found that a nonenolizable ester-directed *peri* lithiation caused lithiation to occur at C-7 rather than at C-6, leading to an unprecedented O → C acyl migration.¹⁵

Table 1. Regioselectivity of Bromination of **1**



substrate ^a R	reagent ^a	solvent ^b	product ratio ^c	
			6-bromo	other ^d
H	NBS	CH ₂ Cl ₂	37	63
H	NBA	CH ₂ Cl ₂	40	60
H	NBSac	CH ₂ Cl ₂	66	34
H	NBS ^e	PhH	0	0
H	NBSac	PhH	81	19
TBDMS	NBSac	PhH	20	80

^a 0.3 mmol. ^b CH₂Cl₂, 6 mL; PhH, 25 mL. ^c The product ratio was determined by ¹H NMR. ^d Unidentified monobromo regioisomers. ^e 48 h reaction.

Regioselective Bromination of 1. Bromination of phenols with *N*-bromosuccinimide (NBS) has been shown to proceed regioselectively, leading to *ortho* and/or *para* phenols, depending on solvent polarity.¹⁶ The *ortho* selectivity was strongly enhanced in nonpolar solvents such as CS₂, CHCl₃, or CCl₄, possibly as a result of associations caused by hydrogen bonding between the hydroxylic proton of the substrate and the reagent. In our case, the hydroxyl moiety is in the benzylic position; however, with the highly reactive polynuclear aromatic system, nuclear substitution was expected.

Room temperature bromination of **1** with NBS in dichloromethane resulted in a mixture of monobromosubstituted derivatives of **1**, in which the ratio of C-6 substituted product to other, unidentified regioisomers, was 37:63 (Table 1). Although the 6-bromo isomer (**2**, Scheme 1) was obtained in only moderate yield, it was identifiable chromatographically (SiO₂, CH₂Cl₂) by an *R_f* value higher than those of other regioisomers and the starting compound, which all chromatograph together under these conditions. In the ¹H NMR spectrum, the 6-bromo compound was distinguished from **1**, as well as the other product isomers, by a significant downfield shift of approximately 0.34 ppm for the H-7 proton. In the aromatic region of **2**, a singlet signal at 8.23 ppm corresponding to H-6 in **1** disappears, and a doublet signal of H-5 is strongly shifted downfield to 8.52 ppm. Attempted yield improvement by using NBA instead of NBS gave a similar ratio of products. A high increase in the *ortho* selectivity has been reported in the bromination of phenols with NBS upon change of the solvent from CH₂Cl₂ to CS₂, as well as upon higher dilution.^{16a} To possibly enhance the *peri* substitution, less polar benzene was chosen as solvent; however, no reaction was observed with NBS. Therefore, a more powerful, structurally similar electrophilic brominating reagent was needed. The study of relative reactivities of NBS and *N*-bromosaccharin (NBSac) in the bromination reactions of substituted anisoles has shown a higher reactivity of the latter.¹⁷ Moreover, saccharin itself has been shown

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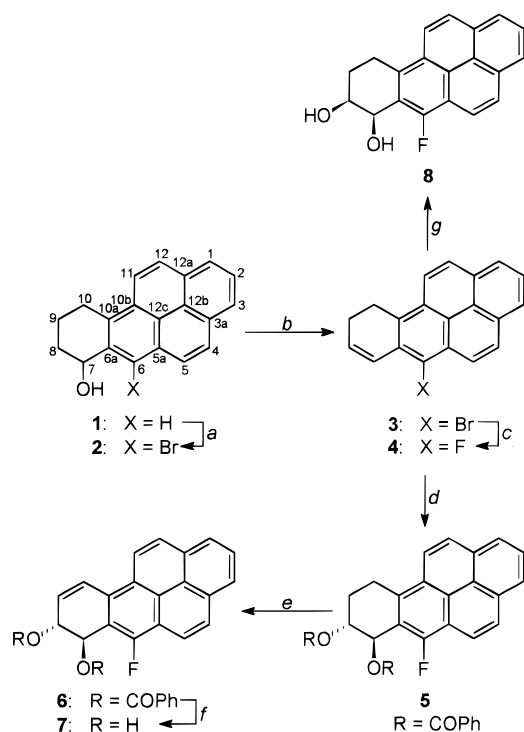
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Scheme 1^a

^a Reagents: (a) NBSac, PhH; (b) *p*-TsOH, PhH; (c) *t*-BuLi, toluene; NFSi; (d) AgOCOPh, I₂, PhH; (e) NBS, AIBN, CCl₄; NEt₃, NaHCO₃, toluene; (f) K₂CO₃, MeOH; (g) OsO₄, pyridine.

to have complex-forming properties with various amides and phenols¹⁸ even in aqueous media. These properties were strongly enhanced in nonaqueous solvents, and were the highest in benzene.¹⁹ Interestingly, bromination of **1** with NBSac in dichloromethane showed an increase in the formation of **2**. When the reaction was carried out in benzene (Table 1), an extremely high yield of the C-6 bromo derivative (81%) was obtained. The observed regioselectivity is probably hydrogen bond dependent, and this analysis is supported by the following two observations. Protection of the 7-hydroxy functionality as the *tert*-butyldimethylsilyl ether caused inversion of the above selectivity, although steric bulk could also affect this ratio. However, more definitive indication of the substrate–reagent hydrogen bond association under the reaction conditions was obtained by proton NMR spectroscopy, in which a downfield shift of the hydroxyl resonance of **1** was observed upon addition of increasing concentrations of H-acceptor. To avoid any complicating features caused by the reaction, *N*-methylsaccharin was used instead of NBSac as a model compound. A 0.01 M solution of **1** in deuterated benzene showed the hydroxyl resonance at 1.32 ppm, which was shifted downfield 0.02–0.1 ppm upon addition of *N*-methylsaccharin in a 0.01–0.04 M concentration range (Figure 2). These results do not exclude other kinds of complexing forces but show a strong indication of H-bonding.

Synthesis of *trans*-7,8-Dihydroxy-6-fluoro-7,8-dihydrobenzo[*a*]pyrene (7). The key 6-bromo-7,8,9,10-tetrahydrobenzo[*a*]pyren-7-ol (**2**) was isolated in 74% yield after workup and chromatography. Bromine–

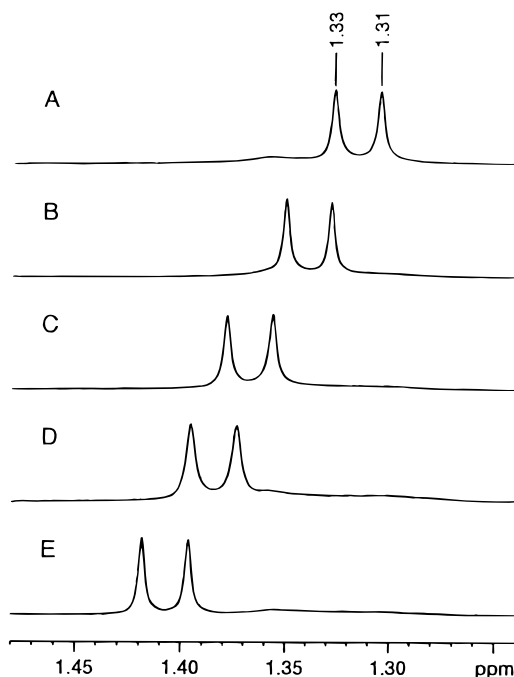


Figure 2. Downfield shift of the OH resonance of **1^a** in C₆D₆ upon addition of *N*-methylsaccharin.^b ^a0.01 M solution. ^bConcentration of *N*-methylsaccharin: A, 0.0 M; B, 0.01 M; C, 0.02 M; D, 0.03 M; E, 0.04 M.

lithium exchange, followed by reaction with electrophilic fluorine, was expected to furnish a substrate ready for derivatization to **7**. Because of the low solubility of **2** it was preferable to prepare the more soluble 6-bromo-9,10-dihydrobenzo[*a*]pyrene (**3**) by dehydration prior to lithiation – fluorination. The critical bromine–lithium exchange of **3** was initially performed with *n*-butyllithium in THF at –78 °C, followed by reaction with *N*-fluorobenzenesulfonimide (NFSi).²⁰ The resulting reaction mixture showed the presence of the protonated 9,10-dihydrobenzo[*a*]pyrene (37%) in addition to the 6-fluoro derivative **4** (63%). The formation of significant amounts of protonated byproduct has been reported in the electrophilic fluorination of a pyrrole derivative via a similar bromine–lithium exchange and reaction with NFSi. This was thought to result from a competing electron-transfer process.²¹ In contrast, when **3** was treated with *tert*-butyllithium in toluene at 0 °C, followed by quenching with NFSi, a remarkable decrease in the formation of the protonated derivative resulted. In several repetitions, this did not exceed 18%. Separation of **4** from the protonated analogue was readily achieved by column chromatography, affording **4** in 75% yield. ¹H NMR spectra of 6-bromo (**3**), 6-fluoro (**4**), and unsubstituted 9,10-dihydrobenzo[*a*]pyrene show that introduction of the halogen atom at position 6 of the aromatic nucleus substantially affects the chemical shift of the vinylic H-7, causing a downfield shift of H-7, and in **4**, a *peri* coupling with the fluorine atom is observed as well (Table 2).

Introduction of a *trans* dibenzoate²² at the 7,8 position of alkene **4** was accomplished by the Prévost reaction with iodine and silver benzoate in refluxing benzene.

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Table 2. ^1H NMR Data of H-7 in Parent 9,10-Dihydrobenzo[a]pyrene and 6-Substituted Derivatives

C-6 substituent	δ/ppm	multiplicity	J/Hz
H	6.85	dt	$J_{7,8}$ 9.5; $J_{7,9}$ 1.8
F (4)	7.13	dtd	$J_{7,8}$ 9.8; $J_{7,9}$ 1.8; $J_{F,H}$ 0.6
Br (3)	7.40	dt	$J_{7,8}$ 9.9; $J_{7,9}$ 1.8

After chromatographic purification, *trans*-7,8-dibenzoyloxy-6-fluoro-7,8,9,10-tetrahydrobenzo[a]pyrene (**5**) was isolated in 46% yield. To unequivocally prove the *trans* relative stereochemistry of the 7,8 substituents in **5**, the *cis* derivative **8** was prepared by osmium tetroxide *cis* dihydroxylation, followed by diacetylation.²³ Dibenzoate **5** was converted to the *trans* diacetate derivative by ester hydrolysis and subsequent diacetylation.²⁴ The NMR spectra of the two 7,8-diacetate derivatives thus obtained confirmed the *trans* stereochemistry of diester substituents in **5**. The H-8 signal appears at 5.38 ppm as a doublet of triplets ($J = 12.6$ and 3.6 Hz) in the *cis* isomer and as a narrow multiplet at 5.42 ppm in the *trans* isomer. The signal for H-7, however, appears as a narrow peak in both cases and is a downfield shifted multiplet at 6.95 ppm in the *cis* isomer and a doublet of multiplets at 6.61 ppm ($J = 3.6$ Hz) in the *trans* isomer.

Introduction of the *bay* region 9,10 double bond was performed via a bromination–dehydrobromination procedure.²² Benzylic bromination with NBS in the presence of AIBN as initiator required careful monitoring for disappearance of the starting material to prevent product decomposition. After workup, the crude product was subjected to dehydrobromination, and after isolation and purification by chromatography, *trans*-7,8-dibenzoyloxy-6-fluoro-7,8-dihydrobenzo[a]pyrene (**6**) was obtained in 50% yield. Removal of the ester functionalities with NaOMe/MeOH afforded **7** in 66% yield, and the yield increased to 87% when the hydrolysis was performed with K_2CO_3 in methanol.²⁵ The overall yield for the conversion of **1** to pure **7** was 10%.

The *trans*-7,8-dihydrodiol **7** shows a 2.2 Hz coupling constant (acetone- d_6 , drop of D_2O , 300 MHz) between the carbinol protons, i.e., H-7 and H-8, as compared to ~ 10 Hz in the unsubstituted analogue.²⁶ The allylic coupling between H-8 and H-10 (W coupling, $J = 2\text{--}3$ Hz)²⁷ is not observed, whereas a coupling between H-8 and H-9 of 5.6 Hz is observed, both of which are indicative

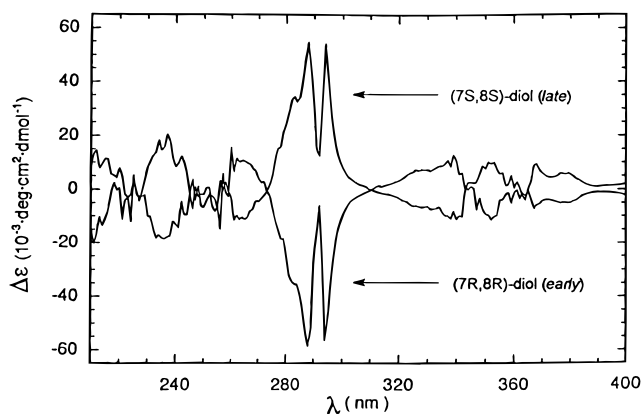
(23) Protection of hydroxy moieties of **8** by acetylation with Ac_2O in pyridine afforded *cis*-7,8-diacetoxy-6-fluoro-7,8,9,10-tetrahydrobenzo[a]pyrene: ^1H NMR (CDCl_3) δ 8.23–7.98 (m, 7 H-aromatic), 6.95 (narrow m, 1 H-7), 5.38 (dt, 1 H-8, $J = 12.6, 3.6$ Hz), 3.87 (ddd, 1 H-10, $J = 17.7, 6.0, 2.3$ Hz), 3.45 (ddd, 1 H-10, $J = 17.7, 11.9, 6.4$ Hz), 2.47 (dq, 1 H-9, $J_{\text{app}} = 12.3, 6.0$ Hz), 2.27 (m, 1 H-9), 2.14 (s, 3 H_{OAc}), 2.13 (s, 3 H_{OAc}); ^{19}F NMR (CDCl_3) δ -127.37 (broad s); HRMS m/e calcd for $\text{C}_{24}\text{H}_{19}\text{O}_4\text{F}$ 390.1267, found 390.1278.

(24) Debenzylation of **5** with $\text{K}_2\text{CO}_3/\text{MeOH}$, followed by acetylation with Ac_2O in pyridine, afforded *trans*-7,8-diacetoxy-6-fluoro-7,8,9,10-tetrahydrobenzo[a]pyrene: ^1H NMR (CDCl_3) δ 8.26–7.99 (m, 7 H-aromatic), 6.61 (dm, 1 H-7, $J = 3.6$ Hz), 5.42 (narrow m, 1 H-8), 3.64 (ddd, 1 H-10, $J = 17.5, 5.9, 3.6$ Hz), 3.43 (ddd, 1 H-10, $J = 17.5, 10.8, 6.2$ Hz), 2.52–2.26 (m, 2 H-9), 2.14 (s, 3 H_{OAc}), 2.02 (s, 3 H_{OAc}); ^{19}F NMR (CDCl_3) δ -127.35 (broad s); HRMS m/e calcd for $\text{C}_{24}\text{H}_{19}\text{O}_4\text{F}$ 390.1267, found 390.1275.

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**Figure 3.** Circular dichroism spectra (in MeOH, unsmoothed) of (7*R*,8*R*)- and (7*S*,8*S*)-**7**.

of the conformation with a pseudoaxial orientation of the allylic C-8 hydroxyl group.²⁷ These observations indicate that **7** prefers the conformation wherein the vicinal hydroxyls are oriented quasi-diaxially. This conforms to findings for the enzymatically obtained *trans*-7,8-dihydroxy-6-fluoro-7,8-dihydrobenzo[a]pyrene.⁶ The ^1H NMR of **7** shows a long-range coupling of 2.0 Hz between fluorine and H-10.

Enantiomeric Resolution of *trans*-7,8-Dihydroxy-6-fluoro-7,8-dihydrobenzo[a]pyrene and Evaluation of the CD Spectra. Racemic **7** was subjected to a chiral HPLC separation on a Daicel Chiralcel OG column. After separation and chromatography to remove traces of the chiral support, the determined enantiomeric purity was 100% and 99.3% for the early- and late-eluting enantiomers, respectively. Figure 3 shows the CD spectra of both synthetic enantiomers. The CD spectrum of the *trans*-(7*R*,8*R*)-dihydroxy-6-fluoro-7,8-dihydrobenzo[a]pyrene (>98% enantiomerically pure),⁶ obtained with liver microsomes from 3-methylcholantrene treated rats, shows a negative sign of the most intense band. This is consistent with that observed for the early eluting isomer in this study. This indicates a (7*R*,8*R*) absolute configuration for the early and a (7*S*,8*S*) configuration for the late eluting synthetic isomer. However, the unsmoothed CD spectrum of the synthetic compound shows certain differences compared to the metabolically obtained product.⁶ Particularly, in the synthetic isomers, the most intense band shows a split that is not seen in the metabolically obtained product. Although we are unable to offer an explanation, it must be pointed out that both antipodes of the synthetic material show identical patterns, indicating that the fine structure is intrinsic to the compounds.

Experimental Section

General. Acetonitrile was distilled from calcium hydride, benzene was distilled from sodium, toluene was distilled from sodium/potassium alloy, and THF was distilled from lithium aluminum hydride. The NMR spectra were recorded on a 300 MHz spectrometer, with TMS (^1H) and CCl_3F (^{19}F) as internal reference. All melting points are uncorrected. For column chromatography, Fluka Silicagel 60, mesh 220–440 was used. *N*-Bromosaccharin was synthesized as reported.²⁸

6-Bromo-7,8,9,10-tetrahydrobenzo[a]pyren-7-ol (2). To a stirred solution of 7,8,9,10-tetrahydrobenzo[a]pyren-7-ol **1**

(28) Zajc, B. *Synth. Commun.*, in press.

(2.040 g, 7.5 mmol) in benzene (440 mL) at 5 °C was added a solution of *N*-bromosaccharin (1.965 g, 7.5 mmol) in benzene (250 mL), cooled to just above the freezing point, over 30 min. The reaction mixture was stirred for an additional hour at 5 °C and then for 24 h at room temperature. The mixture was diluted with ethyl acetate; washed with aqueous Na₂S₂O₅, aqueous NaHCO₃, and water; dried over anhydrous sodium sulfate; and evaporated. Dry column chromatography (SiO₂, eluted with methylene chloride) gave 6-bromo-7,8,9,10-tetrahydrobenzo[*a*]pyren-7-ol **2** as a pale yellow powder (1.952 g, 74%); mp (THF) 213–215 °C; ¹H NMR (CDCl₃) δ 8.52 (d, 1 H-5, *J* = 9.3 Hz), 8.26 (d, 1 H-11, *J* = 9.3 Hz), 8.22–8.17 (m, 2 H-1, H-3), 8.13 (d, 1 H-12, *J* = 9.3 Hz), 8.09 (d, 1 H-4, *J* = 9.3 Hz), 8.01 (t, 1 H-2, *J* = 7.6 Hz), 5.57 (broad t, 1 H-7, *J*_{app} = 3.0 Hz), 3.70 (ddm, 1 H-10_{eq}, *J* = 17.5, 5.3 Hz), 3.26 (ddd, 1 H-10_{ax}, *J* = 17.7, 12.0, 6.0 Hz), 2.79 (broad s, OH), 2.43 (dm, 1 H-8_{eq}, *J* = 13.7 Hz), 2.31 (qm, 1 H-9_{ax}, *J* = 13.6 Hz), 2.12 (m, 1 H-9_{eq}), 1.97 (tt, 1 H-8_{ax}, *J* = 13.7, 3.4 Hz); ¹³C NMR (CDCl₃) δ 135.20 (C-6a), 133.24 (C-10a), 131.16, 131.09 (C-3a, C-12a), 128.74, 128.71 (C-5a, C-10b), 128.46 (C-4), 127.92 (C-12), 126.54 (C-2, C-5), 125.80 (C-1), 125.60 (C-3), 125.48 (C-12c), 124.29 (C-6), 123.90 (C-12b), 122.86 (C-11), 67.66 (C-7), 30.54 (C-8), 27.16 (C-10), 17.06 (C-9). HRMS *m/e* calcd for C₂₀H₁₅BrO: 350.0306, found 350.0315. Anal. Calcd for C₂₀H₁₅BrO: C, 68.39; H, 4.30. Found: C, 68.91; H, 4.77. IR (5 mM solution in CCl₄): 3601 cm⁻¹ (OH).

6-Bromo-9,10-dihydrobenzo[*a*]pyrene (3). To a stirred suspension of 6-bromo-7,8,9,10-tetrahydrobenzo[*a*]pyren-7-ol **2** (1.769 g, 5.03 mmol) in benzene (120 mL) was added *p*-toluenesulfonic acid monohydrate (190 mg, 1 mmol). The suspension was heated at 70 °C for 2.5 h, cooled, and diluted with ethyl acetate. The mixture was washed with aqueous NaHCO₃ and dried, and the solvent was evaporated. The crude product was purified by dry column chromatography (SiO₂, eluted with benzene). 6-Bromo-9,10-dihydrobenzo[*a*]pyrene **3** was obtained as a yellow powder (1.558 g, 93%); mp (acetone) 187–189 °C; ¹H NMR (CDCl₃) δ 8.50 (d, 1 H-Ar, *J* = 9.3 Hz), 8.19 (d, 1 H-Ar, *J* = 9.3 Hz), 8.11 (m, 2 H-Ar), 8.02 (m, 2 H-Ar), 7.94 (t, 1 H-Ar, *J* = 7.6 Hz), 7.40 (dt, 1 H-7, *J* = 9.9, 1.8 Hz), 6.40 (dt, 1 H-8, *J* = 9.9, 4.5 Hz), 3.46 (t, 2 H-10, *J* = 8.3 Hz), 2.51 (tdd, 2 H-9, *J* = 8.3, 4.5, 1.8 Hz); ¹³C NMR (CDCl₃) δ 131.45, 131.23, 131.04, 130.89, 128.64, 128.42, 128.04, 127.63, 127.32, 126.80, 126.18, 125.42, 125.36, 125.30, 124.25, 122.85, 120.90, 24.30, 22.71; HRMS *m/e* calcd for C₂₀H₁₃Br 332.0201, found 332.0206.

6-Fluoro-9,10-dihydrobenzo[*a*]pyrene (4). A stirred solution of 6-bromo-9,10-dihydrobenzo[*a*]pyrene **3** (225 mg, 0.676 mmol) in dry toluene (15 mL) under argon was cooled in an ice bath, and *tert*-butyllithium (1.351 mL, 1.5 M in pentane, 2.03 mmol) was added. Stirring was continued for 2.5 h, and *N*-fluorobenzenesulfonimide (467 mg, 1.481 mmol) in dry toluene (8.6 mL) was added to the reaction mixture. After addition, the ice bath was removed, and the reaction was allowed to proceed at room temperature for 1.5 h. Subsequently, saturated aqueous NH₄Cl was added, and the reaction mixture was diluted with ethyl acetate. The ethyl acetate layer was washed three times with saturated aqueous sodium carbonate and dried over anhydrous sodium sulfate. After evaporation of the solvent and purification on a SiO₂ column using hexane/benzene (96:4), the product 6-fluoro-9,10-dihydrobenzo[*a*]pyrene **4** (138 mg, 75%) was obtained as an off-white powder: mp (*i*-PrOH) 128–129 °C; ¹H NMR (CDCl₃) δ 8.18 (d, 1 H-5, *J* = 9.1 Hz), 8.11 (d, 1 H-11, *J* = 9.3 Hz), 8.06 (d, 2 H-1, H-3, *J* = 7.6 Hz), 7.96 (d, 1 H-4, *J* = 9.1 Hz), 7.94–7.88 (m, 2 H-12, H-2), 7.13 (dt, 1 H-7, *J* = 9.8, 1.8, 0.6 Hz), 6.31 (dt, 1 H-8, *J* = 9.8, 4.4 Hz), 3.43 (t, 2 H-10, *J* = 8.3 Hz), 2.55 (tdd, 2 H-9, *J* = 8.3, 4.4, 1.8 Hz); ¹³C NMR (CDCl₃) δ 152.40 (d, C-6, *J* = 252.6 Hz), 131.30 (d, C-3a, *J* = 1.1 Hz), 130.99 (s, C-12a), 130.84 (d, C-10a, *J* = 4.1 Hz), 129.82 (d, C-8, *J* = 2.5 Hz), 126.85 (d, C-4, *J* = 2.6 Hz), 126.27 (d, C-12, *J* = 2.7 Hz), 126.08 (d, C-2, *J* = 1.0 Hz), 125.13 (d, C-12c, *J* = 5.9 Hz), 124.97–124.85 (two d, 2 C-1, C-3), 124.80 (d, C-12b, *J* = 3.9 Hz), 124.37 (d, C-10b, *J* = 3.1 Hz), 122.67 (d, C-11, *J* = 2.2 Hz), 120.59 (d, C-7, *J* = 7.1 Hz), 119.44 (d, C-5, *J* = 5.5 Hz), 119.23 (d, C-6a, *J* = 14.3 Hz), 117.23 (d, C-5a, *J* = 15.7 Hz),

23.29 (d, C-10, *J* = 3.0 Hz), 22.85 (s, C-9); ¹⁹F NMR (CDCl₃) δ –133.23 (broad s); HRMS *m/e* calcd for C₂₀H₁₃F 272.1001, found 272.1010. Anal. Calcd for C₂₀H₁₃F: C, 88.21; H, 4.81. Found: C, 87.96; H, 4.65.

trans-7,8-Dibenzoyloxy-6-fluoro-7,8,9,10-tetrahydrobenzo[*a*]pyrene (5). Silver benzoate (138.9 mg, 0.607 mmol) was suspended in dry benzene (5 mL) and finely powdered iodine (77 mg, 0.303 mmol) was added. The reaction mixture was protected from light and stirred at room temperature for 2 h. 6-Fluoro-9,10-dihydrobenzo[*a*]pyrene **4** (75 mg, 0.276 mmol) was added with 1 mL of benzene. The stirring was continued for 22 h at room temperature and then under reflux for another 10 h. The reaction mixture was filtered hot through Celite, the Celite was washed with hot benzene, and the filtrate was evaporated. The crude product was purified by preparative TLC (SiO₂, 2 mm, 20 cm × 20 cm, using 20% *n*-hexane in benzene) to yield white crystalline *trans*-7,8-dibenzoyloxy-6-fluoro-7,8,9,10-tetrahydrobenzo[*a*]pyrene **5** (65 mg, 46%); mp (benzene) at 148 °C, a gradual transformation of original crystals into needlelike crystals started, along with the formation of liquid droplets; the transformation was complete at approximately 200 °C, and the needles melted at 207–210 °C; ¹H NMR (CDCl₃) (': C-7 benzoyloxy; '': C-8 benzoyloxy) δ 8.27 (d, 1 H-11, *J* = 9.3 Hz), 8.21 (d, 1 H-5, *J* = 9.1 Hz), 8.20 (broad d, 1 H-1, *J* = 7.5 Hz), 8.16 (broad d, 1 H-3, *J* = 7.2 Hz), 8.12 (d, 1 H-12, *J* = 9.3 Hz), 8.09–7.99 (m, 4 H-2', H-6', H-4, H-2), 7.93–7.88 (m, 2 H-2'', H-6''), 7.53 (tt, 1 H-4', *J* = 7.4, 1.3 Hz), 7.47 (tt, 1 H-4'', *J* = 7.4, 1.3 Hz), 7.39 (tm, 2 H-3', H-5', *J* = 7.4 Hz), 7.31 (tm, 2 H-3'', H-5'', *J* = 7.4 Hz), 7.04 (d, 1 H-7, *J* = 3.5 Hz), 5.84–5.79 (m, 1 H-8), 3.76 (ddd, 1 H-10, *J* = 17.6, 5.6, 4.0 Hz), 3.57 (ddd, 1 H-10, *J* = 17.6, 10.2, 6.1 Hz), 2.70–2.50 (m, 2 H-9); ¹³C NMR (CDCl₃) δ 165.51 (s, CO'), 165.11 (s, CO'), 155.77 (d, C-6, *J* = 254.7 Hz), 133.18 (s, C-4'), 133.13 (s, C-4''), 132.42 (d, C-10a, *J* = 3.2 Hz), 131.58 (s, C-3a), 131.24 (s, C-12a), 129.94 (s, 2 C-2', C-6'), 129.86 (s, C-1'), 129.81 (s, C-1''), 129.73 (s, 2 C-2'', C-6''), 128.39 (s, 2 C-3', C-5'), 128.36 (s, 2 C-3'', C-5''), 127.45 (d, C-4, *J* = 2.6 Hz), 126.88 (d, C-12, *J* = 2.8 Hz), 126.81 (s, C-2), 125.91 (d, C-12c, *J* = 6.4 Hz), 125.55 (d, C-1, *J* = 2.3 Hz), 125.37 (d, C-3, *J* = 1.8 Hz), 125.06 (d, C-10b, *J* = 3.3 Hz), 124.43 (d, C-12b, *J* = 3.8 Hz), 122.58 (d, C-11, *J* = 2.1 Hz), 119.37 (d, C-5, *J* = 5.2 Hz), 117.51 (d, C-6a, *J* = 15.4 Hz), 117.34 (d, C-5a, *J* = 15.4 Hz), 69.64 (s, C-8), 65.72 (d, C-7, *J* = 4.7 Hz), 23.12 (s, C-9), 21.87 (d, C-10, *J* = 2.1 Hz); ¹⁹F NMR (CDCl₃) δ –127.36 (broad s); HRMS *m/e* calcd for C₃₄H₂₃O₄F 514.1580, found 514.1588.

trans-7,8-Dibenzoyloxy-6-fluoro-7,8,9,10-tetrahydrobenzo[*a*]pyrene (6). *trans*-7,8-Dibenzoyloxy-6-fluoro-7,8,9,10-tetrahydrobenzo[*a*]pyrene **5** (115 mg, 0.224 mmol) was placed into a three-neck round-bottom flask equipped with a thermometer, water condenser, and argon inlet. CCl₄ (33.6 mL) was added, the mixture was stirred and carefully heated with a tungsten halogen lamp (50 W), while argon was bubbled through the solution. When the temperature of the solution reached 60 °C, NBS (47 mg, 0.264 mmol) and AIBN (1.5 mg) were simultaneously added to the reaction mixture. The reaction was carefully monitored every few minutes by TLC (SiO₂, 25% ethyl acetate in *n*-hexane), and after 10 min, only trace amounts of the starting compound were left. The heating was therefore discontinued after 13 min, and the flask quickly immersed into ice–water. After cooling, a small amount of decolorizing carbon was added to the mixture, and the suspension filtered through Celite. The Celite was washed thoroughly with CCl₄, and the filtrate was carefully evaporated at room temperature. Finally, the reaction mixture was dried in vacuo. The crude product was dissolved in dry toluene (25.8 mL), NEt₃ (168 μL) and NaHCO₃ (674 mg) were added, and the reaction mixture was refluxed under a small flux of argon. The reaction was monitored by TLC (SiO₂, benzene). After 7 h, the heating was discontinued, and the reaction mixture was cooled and filtered through Celite. After evaporation of the filtrate, the product was purified by preparative TLC (SiO₂, 2 mm, 20 cm × 20 cm, using benzene (30%)/*n*-hexane (65%)/ethyl acetate (4%)/NEt₃ (1%), developed twice). Pure *trans*-7,8-dibenzoyloxy-6-fluoro-7,8-dihydrobenzo[*a*]pyrene **6** (57 mg, 50%) was isolated as a yellow solid: ¹H NMR (CDCl₃) (': C-7 benzoyloxy; '': C-8

benzoyloxy): δ 8.39 (d, 1 H-11, $J = 9.4$ Hz), 8.30 (d, 1 H-5, $J = 9.1$ Hz), 8.18 (d, 2 H-1, H-3, $J = 7.6$ Hz), 8.11 (d, 1 H-4, $J = 9.1$ Hz), 8.09 (d, 1 H-12, $J = 9.4$ Hz), 8.06–7.97 (m, 3 H-2, H-2', H-6'), 7.95–7.90 (m, 3 H-10, H-2'', H-6''), 7.51 (tt, 1 H-4', $J = 7.4$, 1.3 Hz), 7.46 (tt, 1 H-4'', $J = 7.4$, 1.3 Hz), 7.36 (tm, 2 H-3', H-5', $J = 7.8$ Hz), 7.31 (tm, 2 H-3'', H-5'', $J = 7.7$ Hz), 7.19 (m, 1 H-7), 6.65 (ddd, 1 H-9, $J = 9.9$, 5.4, 0.7 Hz), 5.94 (dd, 1 H-8, $J = 5.4$, 2.4 Hz); ^{13}C NMR (CDCl_3) δ 165.55 (s, CO'), 165.33 (s, CO'), 154.97 (d, C-6, $J = 254.4$ Hz), 133.23 (s, C-4'), 133.14 (s, C-4''), 131.64 (s, C-3a), 131.16 (s, C-12a), 129.97 (s, 2 C-2', C-6'), 129.86 (s, 2 C-2'', C-6''), 129.67 (s, C-1), 129.62 (s, C-1'), 128.44–128.21 (m, 5 C-4, C-3', C-5', C-3'', C-5''), 127.53 (d, C-12, $J = 2.5$ Hz), 127.34 (d, C-10, $J = 3.8$ Hz), 127.03 (s, C-2), 126.79 (d, C-12c, $J = 6.2$ Hz), 126.62 (d, C-10a, $J = 3.7$ Hz), 125.89 (d, C-3, $J = 1.5$ Hz), 125.79 (d, C-1, $J = 2.0$ Hz), 124.68 (s, C-9), 124.61 (d, C-12b, $J = 3.8$ Hz), 123.97 (d, C-10b, $J = 2.9$ Hz), 121.88 (d, C-11, $J = 1.7$ Hz), 119.58 (d, C-5, $J = 5.3$ Hz), 119.55 (d, C-5a, $J = 16.0$ Hz), 114.78 (d, C-6a, $J = 15.6$ Hz), 66.72 (s, C-8), 64.84 (d, C-7, $J = 4.9$ Hz); ^{19}F NMR (CDCl_3) δ -128.1 (broad s); HRMS m/e calcd for $\text{C}_{34}\text{H}_{21}\text{O}_4\text{F}$ 512.1424, found 512.1434.

trans-7,8-Dihydroxy-6-fluoro-7,8-dihydrobenzo[a]pyrene (7). *trans*-7,8-Dibenzoyloxy-6-fluoro-7,8-dihydrobenzo[a]pyrene **6** (33 mg, 0.064 mmol) was suspended in methanol (3.3 mL), and solid K_2CO_3 (29.1 mg, 0.211 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, diluted with ethyl acetate, and washed with water. The water layer was back-extracted with ethyl acetate three times, the organic layers were combined and dried, and the solvent was evaporated. The product was purified by column chromatography (SiO_2 , using benzene (90%)/methanol (9.5%)/ NEt_3 (0.5%)) and *trans*-7,8-dihydroxy-6-fluoro-7,8-dihydrobenzo[a]pyrene **7** (17 mg, 87%) was isolated as a white solid (in solution, this compound rapidly turns yellow): ^1H NMR ($\text{CD}_3\text{COCD}_3/\text{drop of D}_2\text{O}$) δ 8.52 (d, 1 H-11, $J_{11,12} = 9.4$ Hz), 8.28 (d, 1 H-5, $J_{4,5} = 9.2$ Hz), 8.29–8.25 (m, 2 H-1, H-3), 8.20 (d, 1 H-4, $J_{4,5} = 9.2$ Hz), 8.15 (d, 1 H-12, $J_{11,12} = 9.4$ Hz), 8.06 (t, 1 H-2, $J_{1,2} = J_{2,3} = 7.7$ Hz), 7.76 (dd, 1 H-10, $J_{9,10} = 10.0$; $J_{10,\text{F}} = 2.0$ Hz), 6.52 (ddd, 1 H-9, $J_{9,10} = 10.0$; $J_{8,9} = 5.6$; $J_{7,9} = 1.1$ Hz), 5.43 (broad s, 1 H-7), 4.46 (dd, 1 H-8, $J_{8,9} = 5.6$; $J_{7,8} = 2.2$ Hz); ^{13}C NMR ($\text{CD}_3\text{COCD}_3/\text{drop of D}_2\text{O}$) δ 156.95 (d, C-6, $J = 249.95$ Hz), 133.15 (d, C-3a, $J = 0.7$ Hz), 132.83 (s, C-12a), 132.04 (s, C-9), 129.42 (d, C-4, $J = 2.5$ Hz), 128.76 (d, C-10a, $J = 5.1$ Hz), 128.45 (d, C-12, $J = 2.8$ Hz), 128.43 (s, C-2), 127.29 (d, C-12c, $J = 5.8$ Hz), 127.12–127.05 (m, 2 C-1, C-3), 126.15 (d, C-12b, $J = 4.0$ Hz), 125.12 (d, C-10, $J = 3.9$ Hz), 125.0 (d, C-10b, $J = 3.1$ Hz), 123.92 (d, C-11, $J = 2.1$ Hz), 122.19 (d, C-6a, $J = 16.3$ Hz), 120.61 (d, C-5, $J = 5.6$ Hz), 120.10 (d, C-5a, $J = 16.7$ Hz), 68.67 (s, C-8), 67.08 (d, C-7, $J = 4.4$ Hz); ^{19}F NMR ($\text{CD}_3\text{COCD}_3/\text{drop of D}_2\text{O}$) δ -131.90 (broad s); MS (rel int) 304 (M^+ , 23), 287 (24), 286 (100), 270 (17), 259 (18), 258 (88), 257 (73), 238 (20), 237 (21); HRMS m/e calcd for $\text{C}_{20}\text{H}_{13}\text{O}_2\text{F}$ 304.0900, found 304.0901.

cis-7,8-Dihydroxy-6-fluoro-7,8,9,10-tetrahydrobenzo[a]pyrene (8). To 6-fluoro-9,10-dihydrobenzo[a]pyrene **4** (31.5 mg, 0.116 mmol) in pyridine (1 mL) was added a 0.44 M

solution of osmium tetroxide in pyridine (0.29 mL, 0.127 mmol) at 0 °C. The stirring was continued at 0 °C for 1 h and at room temperature for 18 h, aqueous $\text{Na}_2\text{S}_2\text{O}_5$ was added to the reaction mixture (484 mg, 2.548 mmol in 4.5 mL of water), and the stirring was continued for 6 h. The reaction mixture was diluted with ethyl acetate and washed with 10% aqueous HCl, which was saturated with NaCl; the aqueous layer was reextracted with ethyl acetate (three times); the organic layers were combined, washed with saturated NaHCO_3 , and dried over anhydrous sodium sulfate; and the solvent was evaporated. The crude product was purified by preparative TLC (SiO_2 , 2 mm, 20 cm \times 20 cm, using CH_2Cl_2 (90%)/ CH_3OH (10%), and *cis*-7,8-dihydroxy-6-fluoro-7,8,9,10-tetrahydrobenzo[a]pyrene (**8**) (25 mg, 70%) was isolated as an off white solid compound, mp (*i*-PrOH) 226–229 °C; ^1H NMR ($\text{CD}_3\text{COCD}_3/\text{drop of D}_2\text{O}$) δ 8.32–8.02 (m, 7 H-aromatic), 5.36 (narrow m, 1 H-7), 4.04 (dt, 1 H-8, $J = 12.1$; 3.6 Hz), 3.79 (ddd, 1 H-10, $J = 17.9$, 6.0, 2.2 Hz), 1 H-10: partially buried under water signal), 2.35 (dq, 1 H-9, $J_{\text{app}} = 12.2$, 6.0 Hz), 1 H-9: partially buried under acetone signal; ^{19}F NMR (CD_3COCD_3) δ -128.87 (broad s); HRMS m/e calcd for $\text{C}_{20}\text{H}_{15}\text{O}_2\text{F}$ 306.1056, found 306.1065.

Chiral HPLC Separation of (+)- and (-)-trans-7,8-Dihydroxy-6-fluoro-7,8-dihydrobenzo[a]pyrene. Racemic **7** (7 mg) was separated on a Daicel Chiralcel OG column (0.46 cm \times 25 cm) with a precolumn (0.46 cm \times 5 cm), eluting with 30% *i*-propanol in *n*-hexane at a flow rate of 0.9 mL/min. Column effluent was monitored at $\lambda = 390$ nm. The early and late isomers eluted at 18 and 26 min, respectively, and 2.2 mg of each was isolated. After separation, their enantiomeric purity was determined by reinjection into the above chiral column and was found to be 100% for the early and 99.3% for the late isomer. Each of the enantiomers was subsequently repurified by column chromatography (SiO_2 , packed and eluted by 9.5% MeOH and 0.5% NEt_3 in benzene) to remove any traces of the chiral support that may have leached from the column, and 1.7 mg of the early isomer and 1.8 mg of the late isomer were isolated.

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Supporting Information Available: 300 MHz ^1H NMR spectra of compounds **2–8** and UV spectra of the (*7R,8R*) and (*7S,8S*) isomer of **7**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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