Synthesis of Fluorinated Derivatives of Benzo[k]fluoranthene and Indeno[1,2,3-cd]pyrene and 8,9-Dihydro-8,9-epoxybenzo[k]fluoranthene

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The synthesis of several select fluorinated derivatives of benzo[k]fluoranthene and indeno[1,2,3-cd]pyrene is described. In the benzo[k]fluoranthene series, the 8- and 9-fluoro derivatives have been prepared by Wittig reaction of the 1,2-bis[(triphenylphosphonio)methyl] salt of the appropriate fluorobenzene with acenaphthenequinone under phase-transfer conditions. The synthesis of 2-fluoroindeno[1,2,3-cd]pyrene was achieved by photocyclization of 1-(β,β-difluorovinyl)benzo[b]fluoranthene followed by dehydrofluorination in methanolic sodium methoxide. This represents a new method for the construction of the indeno[1,2,3-cd]pyrene skeleton. 8,9-Difluoroindeno[1,2,3-cd]pyrene was prepared from 1-(2-amino-4,5-difluorophenyl)pyrene by diazotization followed by coupling in the presence of copper–bronze. In addition to these fluorinated derivatives, the synthesis of 8,9-dihydro-8,9-epoxybenzo[k]fluoranthene, a suspect ultimate tumorigenic metabolite of benzo[k]fluoranthene, is reported. This arene oxide was prepared from the trans-8,9-bromo acetate by benzylic bromination and subsequent treatment with sodium methoxide in anhydrous THF.

Introduction

Benzo[k]fluoranthene (1) and indeno[1,2,3-cd]pyrene (2) (Figure 1) are nonalternant polycyclic aromatic hydrocarbons (PAH) which are common environmental pollutants. These compounds, along with other PAH, are formed during incomplete combustion of organic matter. Both of these compounds are active as tumorigenic agents on mouse skin.[1-4] Indeno[1,2,3-cd]pyrene is also active as a complete carcinogen on mouse skin and is a potent carcinogen in rat lungs.[5,6] We have been investigating the mechanism(s) by which these two nonalternant PAH are activated to tumorigenic species. As part of this program we are employing a fluorine-probe approach to assist in identifying those sites on the target molecules which are critically associated with their activation to tumorigenic agents and DNA binding. In this report we discuss the synthesis of specific fluorinated derivatives of 1 and 2. In addition, the synthesis of a suspect ultimate tumorigenic metabolite of 1, 8,9-dihydro-8,9-epoxybenzo[k]fluoranthene is detailed.

Results and Discussion

The synthetic scheme employed for the synthesis of 8- and 9-fluorobenzo[k]fluoranthene is presented in Figure 2. This approach to the benzo[k]fluoranthene skeleton was first employed by Minsky and Rabinovitz and gave 1 in 18% yield in a single reaction step.[7] The key to this sequence is Wittig reaction of fluoro-substituted bis(phosphonium) salt derivatives of *o*-xylene with acenaphthenequinone. The phosphonium salts act both as reagents and as phase-transfer catalysts for the two-phase reaction with lithium hydroxide. Although the yields for the synthesis of 8- and 9-fluorobenzo[k]fluoranthene were low (2% for **6** and 15% for **10**), the reactions can be performed on large scale, and the products are readily isolated with only minimum byproduct formation. The use of the Wittig reaction for the synthesis of these fluorinated derivatives was found to be far superior than an initial approach which utilized either 8- or 9-keto-8,9,10,11-tetrahydrobenzo[k]fluoranthene as starting materials. The ketones were converted to their respective *gem*-difluoro derivatives with (diethylamino)sulfur trifluoride (DAST) and these derivatives were aromatized by heating with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) with the loss of HF. Both reaction steps from the ketone proceeded in poor yield and the DAST reaction gave numerous byproducts which were difficult to separate.

The synthesis of 2-fluoroindeno[1,2,3-cd]pyrene (**14**) outlined in Figure 3 represents a new sequence for the construction of the indeno[1,2,3-cd]pyrene skeleton. 1-Formylbenzo[b]fluoranthene (**11**) was prepared in 43% overall yield from 1-methylbenzo[b]fluoranthene[8] by bromination with *N*-bromosuccinimide followed by treatment with hexamethylenetetramine and acid hydrolysis. This aldehyde underwent conversion to the β,β-difluorovinyl derivative **12** in good yield by reaction with triphenylphosphine and sodium chlorodifluoroacetate in refluxing diglyme.[9] Photocyclization under nitrogen in degassed cyclohexane as described by Lapouyade et al.[9] yielded 2,2-difluoro-1,2-dihydroindeno[1,2,3-cd]pyrene (**13**), which was dehydrofluorinated to **14** in methanolic sodium methoxide. This method is potentially amenable to the synthesis of a wide variety of substituted indeno[1,2,3-cd]pyrene derivatives starting from the appropriate benzo[b]fluoranthene analogues.

The synthesis of 8,9-difluoroindeno[1,2,3-cd]pyrene (**17**) (Figure 4) was accomplished using a sequence previously described for indenopyrene derivatives substituted at positions 7–10.[10] 1-(4,5-Difluoro-2-nitrophenyl)pyrene (**15**) was prepared by diazotization of 4,5-difluoro-2-nitroaniline with isoamyl nitrite in the presence of pyrene. Catalytic hydrogenation of the nitro group over 10% palladium-on-charcoal did not proceed cleanly and gave several byproducts. Reduction of the nitro group with stannous

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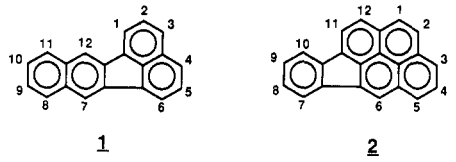
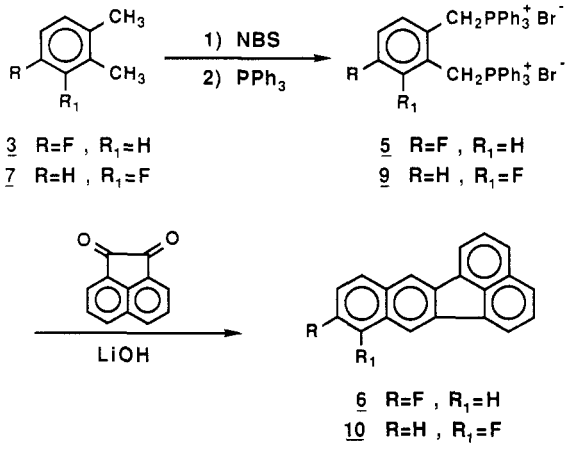


1 2

Figure 1. Structure and numbering of benzo[*k*]fluoranthene (1) and indeno[1,2,3-*cd*]pyrene (2).

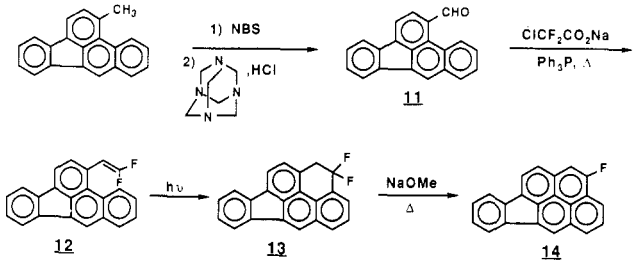


3 R=F , R1=H
7 R=H , R1=F

5 R=F , R1=H
9 R=H , R1=F

6 R=F , R1=H
10 R=H , R1=F

Figure 2. Synthetic scheme for the preparation of 8- and 9-fluorobenzo[*k*]fluoranthene.

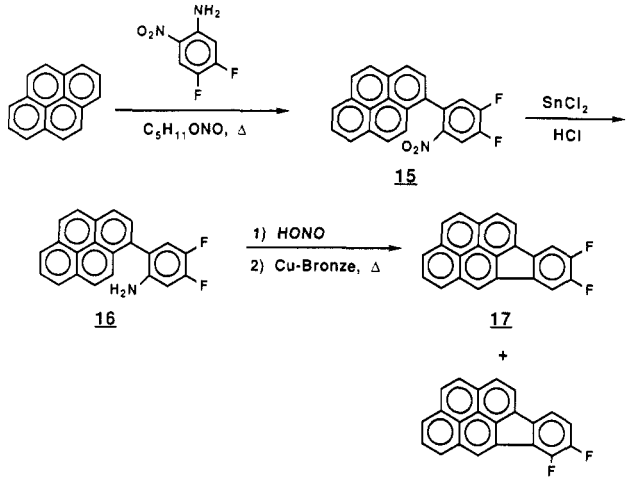


12 13 14

Figure 3. Preparation of 2-fluoroindeno[1,2,3-*cd*]pyrene.

chloride in hydrochloric acid,[11] however, gave the amino derivative **16** in high yield. Diazotization followed by treatment with copper–bronze resulted in formation of 1-(3,4-difluorophenyl)pyrene as the major product (29% yield) accompanied by 8,9-difluoroindeno[1,2,3-*cd*]pyrene (**17**) (2.4% yield) and an isomeric product identified as 7,8-difluoroindeno[1,2,3-*cd*]pyrene (3.6% yield). The formation of 1-(3,4-difluorophenyl)pyrene as the major product indicates that reduction of the diazonium salt is the favored product. Coupling of the diazonium salt with the 4-position on the pyrene ring with formation of a five-membered ring is much less favored. It has been reported by others that cyclization to the 4-position of pyrene generally procedes in low yield.[12-14]

Characterization of the two isomeric difluoroindeno-[1,2,3-*cd*]pyrenes was accomplished primarily on the basis of their 360-MHz NMR spectra. The 8- and 9-protons of **2** are in general the most upfield protons absorbing at approximately 7.5 ppm. In the NMR spectrum of the minor reaction product no such absorptions were observed. The 7- and 10-protons were observed as a pair of doublet of doublets at 8.24 ppm ($J_{7,8}$ = 9.7 Hz, $J_{7,9}$ = 7.5 Hz) and



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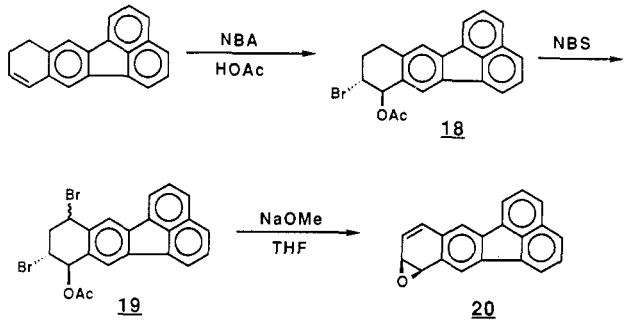
16 17

Figure 4. Preparation of 8,9-difluoroindeno[1,2,3-*cd*]pyrene.



18 19 20

Figure 5. Synthesis of 8,9-dihydro-8,9-epoxybenzo[*k*]fluoranthene.

8.13 ppm ($J_{9,10}$ = 10.4 Hz, $J_{8,10}$ = 7.7 Hz). The large coupling constants for these protons indicate that the fluorine atoms are oriented ortho to these protons. On this basis the minor product was identified as **17**. In the spectrum of the isomeric difluoro compound, the 9-proton was observed as a multiplet at 7.47 ppm with coupling constants of 11.1, 7.9, and 7.9 Hz. The large coupling constant most likely arises from an ortho fluorine atom while the other two constants result from an ortho H–H and a meta H–F coupling. In this spectrum the 10-proton absorbs as a multiplet at 7.99 ppm with coupling constants of 7.9, 3.8, and 0.7 Hz. In acetone-d_6 solution the singlet for H_6 absorbs at 8.89 ppm which is consistent with the chemical shift observed for H_6 of **2** (8.84 ppm) and **17** (8.87 ppm). In $CDCl_3$ solution, however, H_6 appears as a singlet at 8.71 ppm as compared to 8.45 ppm for **2** and 8.53 ppm for **17**. In a previous study of oxygenated derivatives of **2**, H_6 consistently absorbed between 8.48 and 8.51 ppm in $CDCl_3$ solution except when a substituent was placed at the 7-position.[10] In the spectrum of 7-methoxyindeno-[1,2,3-*cd*]pyrene for example, H_6 absorbs at 8.70 ppm. These results are most consistent with the this difluoro compound being 7,8-difluoroindeno[1,2,3-*cd*]pyrene. The mechanism by which this isomeric product forms under these reaction conditions is not known. No such similar rearrangements have been observed previously during the preparation of indeno[1,2,3-*cd*]pyrene derivatives using this method.[10]

The synthesis of 8,9-dihydro-8,9-epoxybenzo[*k*]-fluoroanthene (**20**) was accomplished by using the general method of Yagi and Jerina for non-K-region arene oxides[15] (Figure 5). 8,9-Dihydrobenzo[*k*]fluoranthene[16] was con-

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verted into the trans-8-acetoxy-9-bromo derivative **18** in high yield by treatment with *N*-bromoacetamide in acetic acid. The coupling constants and chemical shifts observed in the NMR spectrum of this bromo acetate are in close agreement with those previously reported for *trans*-1-acetoxy-2-bromo-1,2,3,4-tetrahydronaphthalene.[15] Bromination at the remaining unsubstituted benzylic position with *N*-bromosuccinimide gave the 8-acetoxy-9,11-dibromo derivative **19**, which was purified by repeated recrystallization from ether–petroleum ether. Treatment of this dibromo acetate with sodium methoxide in anhydrous THF gave the 8,9-oxide. The success of this reaction was found to depend greatly on the purity of the dibromo acetate precursor. The 8,9-oxide was found to be stable when isolated in a pure state and stored at −20 °C in the dark. A sample stored in deuteriated acetone for 1 month did not undergo isomerization to the phenol or hydrolysis to the dihydrodiol.

Bioassays are currently in progress to evaluate the activity of each of these fluorinated derivatives of **1** and **2** and the 8,9-oxide of **1** as tumor initiators on mouse skin.

Experimental Section

Melting points were measured on a Thomas-Hoover Uni Melt apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ unless otherwise specified on a JEOL 90-FXQ spectrometer or a Bruker AM 360 spectrometer and are reported as ppm downfield from internal tetramethylsilane. UV spectra were measured on a Hewlett-Packard Model 8452A diode array spectrophotometer. Mass spectra were run on a Hewlett-Packard Model 5982A instrument. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. High-resolution mass spectral analyses were performed by Shrader Analytical and Consulting Laboratories, Detroit, MI, and by the Rockefeller University Mass Spectrometric Biotechnology Resource Center, New York, NY.

4-Fluoro-1,2-xylene (3). A solution of sodium nitrite (13.8 g, 0.2 mol) in 30 mL of H_2O was added slowly at 0 °C to a solution of 3,4-dimethylaniline (24.2 g, 0.2 mol) in 100 mL of 60% fluoroboric acid. After the addition was complete, the solution was stirred for an additional 20 min at 0 °C, and then the diazonium salt was filtered and washed with cold water, methanol, and then ether. The air-dried diazonium salt weighed 22.8 g (52%). A 500-mL round-bottom flask was charged with 30 g (0.14 mol) of the diazonium salt and a distillation head with a Vigreux column was attached to the flask. The flask was slowly heated to 80 °C in an oil bath until nitrogen evolution commenced. After the decomposition began, the oil bath was removed, and the reaction was self-sustaining. The reaction was complete after 45 min and the product isolated by distillation at atmospheric pressure at 147–148 °C. The yield of 4-fluoro-1,2-xylene (**3**) was 8.7 g, 51% yield: NMR δ 7.37–6.58 (m, 3), 2.23 (s, 6); mass spectrum, *m/e* (relative intensity) 124 (M^+, 40), 123 (22), 109 (100).

1,2-Bis(bromomethyl)-4-fluorobenzene (4). A solution of **3** (5.0 g, 40 mmol), *N*-bromosuccinimide (15.84 g, 88 mmol), and benzoyl peroxide (10 mg) in carbon tetrachloride (60 mL) was heated at reflux for 45 min. After cooling to room temperature, the reaction mixture was filtered and the solvent removed under reduced pressure. The dibromide was precipitated with cold methanol, washed several times with hexane, and dried under vacuum to give pure **4** as a white solid: 4.2 g, 37% yield. An analytical sample was recrystallized from ether/petroleum ether, giving **4** as colorless plates: mp 47–48.5 °C; NMR δ 7.45–6.85 (m, 3), 4.62 (s, 3), 4.60 (s, 3); mass spectrum, *m/e* (relative intensity) 284 (M + 4, 4), 282 (M + 2, 9), 280 (5, M^+), 203 (97), 201 (100), 122 (85).

1,2-Bis[(triphenylphosphonio)methyl]-4-fluorobenzene Dibromide (5). A solution of **4** (4.2 g, 15 mmol) and triphenylphosphine (9.3 g, 35 mmol) in dry *N,N*-dimethylformamide (60 mL) was heated at reflux for 9 h. The solution was allowed to cool to room temperature, and the precipitate was filtered and washed several times with ether. The bis Wittig salt was recrystallized from $CHCl_3$ to give **5** as a white crystalline solid, 9.8 g, 81% yield: NMR δ 8.02–7.60 (m, 30), 7.12–6.58 (m, 3), 5.66 (d, 2, $J_{P,H}$ = 9.8 Hz), 5.47 (d, 2, $J_{P,H}$ = 7.1 Hz).

9-Fluorobenzo[*k*]fluoranthene (6). A solution of **5** (9.8 g, 12.2 mmol) and acenaphthenequinone (1.52 g, 8.2 mmol) in CH_2Cl_2 (125 mL) was stirred vigorously at room temperature for 48 h with 40 mL of 5 N aqueous lithium hydroxide. The mixture was then poured into H_2O (250 mL) and extracted with CH_2Cl_2 (2 × 150 mL). The organic layer was separated and dried over sodium sulfate. After removal of the solvent under reduced pressure the residue was purified by column chromatography on basic alumina eluting with 2:1 hexane/benzene. 9-Fluorobenzo[*k*]fluoranthene was further purified by recrystallization from MeOH as yellow needles: 50 mg, 2% yield; mp 206–207 °C; NMR (360 MHz) δ 8.29 (s, 1, H_7), 8.25 (s, 1, H_{12}), 8.02 (d, 1, H_1, $J_{1,2}$ = 7.4 Hz), 8.00 (d, 1, H_6, $J_{5,6}$ = 7.6 Hz), 7.91 (dd, 1, H_{11}, $J_{10,11}$ = 8.9 Hz, $J_{F,11}$ = 5.7 Hz), 7.86 (d, 1, H_3, $J_{2,3}$ = 8.1 Hz), 7.85 (d, 1, H_4, $J_{4,5}$ = 8.2 Hz), 7.65 (dd, 2, $H_{2,5}$), 7.55 (dd, 1, H_8, $J_{F,8}$ = 9.9 Hz, $J_{8,10}$ = 2.6 Hz), 7.24 (m, 1, H_{10}, $J_{F,10}$ = 8.6 Hz); UV (MeOH) λ_{max} (ϵ) 398 nm (8700), 376 (8100), 358 (4500), 307 (45 500), 295 (32 900), 280 (16 400), 268 (15 800); mass spectrum, *m/e* (relative intensity) 270 (M^+, 100), 268 (19), 135 (29). Anal. Calcd for $C_{20}H_{11}F$: C, 88.87; H, 4.10; F, 7.03; Found: C, 88.43; H, 3.97; F, 6.72.

1,2-Bis(bromomethyl)-3-fluorobenzene (8). Reaction of 2.5 g (20 mmol) of 3-fluoro-1,2-xylene as described above for **4** afforded the bis(bromomethyl) compound **8** as a white solid, 3.0 g (53% yield). An analytical sample was recrystallized from ether/petroleum ether to give **8** as colorless plates: mp 41–42.5 °C; NMR δ 7.45–6.83 (m, 3), 4.78 (s, 2), 4.61 (s, 2); mass spectrum, *m/e* (relative intensity) 284 (M + 4, 3), 282 (M + 2, 6), 280 (M^+, 3), 203 (50), 201 (53), 122 (100).

1,2-Bis[(triphenylphosphonio)methyl]-3-fluorobenzene Dibromide (9). The bis(triphenylphosphonium) salt **9** was prepared from **8** (2.9 g, 10 mmol) as described above for **5**. The yield of **9** was 6.61 g (82% yield): NMR δ 8.05–7.50 (m, 30), 7.38–6.5 (m, 3), 5.41 (d, 2, $J_{P,H}$ = 15.2 Hz), 5.14 (d, 2, $J_{P,H}$ = 16.2 Hz).

8-Fluorobenzo[*k*]fluoranthene (10). A solution of acenaphthenequinone (1.0 g, 5.5 mmol) and **9** (6.61 g, 8.2 mmol) in CH_2Cl_2 (80 mL) was stirred with 5 N LiOH (30 mL) for 48 h as described above for **6**. After column chromatography on basic alumina (hexane) and recrystallization from benzene–ethanol pure **10** was obtained as pale yellow needles, 230 mg (15% yield): mp 168–169 °C; NMR (360 MHz) δ 8.58 (s, 1, H_7), 8.33 (s, 1, H_{12}), 8.07 (d, 1, H_6, $J_{5,6}$ = 7.0 Hz), 8.04 (d, 1, H_1, $J_{1,2}$ = 7.0 Hz), 7.88 (d, 2, $H_{3,4}$, $J_{2,3}$ = $J_{4,5}$ = 8.3 Hz), 7.72 (d, 1, H_{11}, $J_{10,11}$ = 7.9 Hz), 7.69 (dd, 2, $H_{2,5}$), 7.40 (m, 1, H_{10}, $J_{9,10}$ = 7.8 Hz, $J_{F,10}$ = 5.5 Hz), 7.16 (m, 1, H_9, $J_{F,9}$ = 10.7 Hz, $J_{9,11}$ = 1.0 Hz); UV (MeOH) λ_{max} (ϵ) 401 nm (15 600), 379 (14 700), 360 (7800), 306 (52 800), 295 (45 200), 283 (29 300), 267 (27 600); mass spectrum, *m/e* (relative intensity) 270 (M^+, 100), 268 (17). Anal. Calcd for $C_{20}H_{11}F$: C, 88.87; H, 4.10; F, 7.03; Found: C, 88.59; H, 4.05; F, 7.29.

1-Formylbenzo[*b*]fluoranthene (11). A solution of 1-methylbenzo[*b*]fluoranthene[8] (520 mg, 1.9 mmol), *N*-bromosuccinimide (480 mg, 2.6 mmol), and benzoyl peroxide (2 mg) in carbon tetrachloride (50 mL) was heated at reflux under nitrogen for 2 h. The solution was allowed to cool to room temperature and was then filtered. Solvent was removed under reduced pressure giving 1-(bromomethyl)benzo[*b*]fluoranthene as a yellow solid; 650 mg (92%): mass spectrum, *m/e* (relative intensity) 346 (M + 2, 7), 344 (M^+, 7), 265 (100). Hexamethylenetetramine (3.0 g, 21 mmol) was added in one portion to a suspension of 1-(bromomethyl)benzo[*b*]fluoranthene (650 mg, 1.9 mmol) in EtOH (45 mL) and H_2O (10 mL). The mixture was heated at reflux for 12 h and then cooled to 5 °C as concentrated HCl (10 mL) was added slowly. The solution turned yellow and was then heated at reflux for 1 h and then poured into H_2O (150 mL). The solution was extracted with EtOAc (3 × 50 mL), and the combined organic layers were washed with H_2O and brine and then dried over sodium sulfate. The crude aldehyde was purified by flash column chromatography on silica gel, eluting with 30% CH_2Cl_2/hexane. Upon evaporation of the solvents **11** was obtained as light yellow crystals: 250 mg (47%); mp 154–156 °C; NMR δ 11.00 (s, 1, CHO),

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8.51–8.40 (m, 2, $H_{2,12}$), 8.19 (d, 1, H_3), 8.15 (s, 1, H_8), 8.02–7.85 (m, 3, $H_{4,7,9}$), 7.69–7.62 (m, 2, $H_{10,11}$), 7.49–7.40 (m, 2, $H_{5,6}$); mass spectrum, m/e (relative intensity) 280 (M^+, 100), 252 (73).

1-(β,β-Difluorovinyl)benzo[*b*]fluoranthene (12). A solution of **11** (510 mg, 1.8 mmol) and triphenylphosphine (785 mg, 3 mmol) in diglyme (10 mL) was heated in an oil bath to 160 °C. To this was added a warm (50 °C) solution of sodium chlorodifluoroacetate in diglyme (15 mL) over a 30-min period. After about 10 min the reaction mixture became dark in color, and CO_2 evolution was observed. The reaction was heated at 160 °C for 4 h, cooled to room temperature, and then filtered through Celite. Diglyme was removed by Kugelrohr distillation, and the residue was purified by flash chromatography through silica gel, eluting with hexane. Unreacted **11** (260 mg) was recovered by gradually increasing the percentage of CH_2Cl_2 up to 20%. The yield of **12** was 230 mg (41%; 82% based upon unreacted **11**). An analytical sample was recrystallized from benzene/hexane as colorless needles: mp 165–168 °C; NMR δ 8.25 (s, 1, H_8), 8.05–7.3 (m, 10), 6.16 (d, 1, CH=CF_2, J = 25.3 Hz); mass spectrum, m/e (relative intensity) 314 (M^+, 55), 294 (100). Anal. Calcd for $C_{22}H_{12}F_2$: C, 84.06; H, 3.85; Found: C, 83.83; H, 3.81.

2-Fluoroindeno[1,2,3-*cd*]pyrene (14). A solution of **12** (320 mg, 1.0 mmol) in freshly degassed cyclohexane (750 mL) was irradiated for 6 h with a Hanovia 450-W medium-pressure mercury vapor lamp contained inside a Vycor filter within a quartz well. Nitrogen was bubbled through the solution during the irradiation. Solvent was removed under reduced pressure, giving crude 2,2-difluoro-1,2-dihydroindeno[1,2,3-*cd*]pyrene (**13**) as a yellow oil. Crude **13** (1.0 mmol) was dissolved in 50 mL methanolic sodium methoxide (prepared by dissolving 150 mg sodium in 50 mL MeOH), and the solution was heated at reflux for 4 h. After cooling to room temperature, the mixture was poured into 150 mL of H_2O and extracted with EtOAc (3 × 60 mL). The combined extracts were washed with H_2O and brine and dried over sodium sulfate. After evaporation, the crude product was purified by column chromatography on activated neutral alumina eluting with 20% CH_2Cl_2/hexane. The product was obtained as a yellow crystalline solid, which was recrystallized from EtOH/benzene as yellow needles: 80 mg, (27%); mp 178–180 °C; NMR δ 8.55 (s, 1, H_6), 8.52–8.40 (m, 2), 8.31–7.95 (m, 5), 7.74 (d, 1, H_1, $J_{1,F}$ = 12.5 Hz), 7.56–7.39 (m, 4, H_{7-10}); UV (MeOH) λ_{max} (ε) 375 nm (5700), 356 (6600), 313 (13 000), 303 (16 600), 291 (11 300), 249 (27 500); mass spectrum, m/e (relative intensity) 294 (M^+, 100), 274 (4); high-resolution mass spectrum, calcd for $C_{22}H_{11}F$ 294.0842, found 294.0845.

1-(2-Nitro-4,5-difluorophenyl)pyrene (15). A mixture of 4,5-difluoro-2-nitroaniline (1.74 g, 10 mmol), pyrene (2.02 g, 10 mmol), and isoamyl nitrite (2 mL) was heated in a large test tube at 90 °C for 10 min. This reaction was repeated one more time, and then the two reaction mixtures were combined and applied in a minimum of benzene to a silica column. The column was eluted with hexane and then 25% CH_2Cl_2/hexane. The first three 250-mL fractions (with the mixed elution solvent) were concentrated and applied to a second silica gel flash chromatography column and eluted with hexane. The product **15** eluted as a yellow solution, which was evaporated and recrystallized from aqueous acetone as yellow plates, mp 155.5–157 °C: 947 mg (13%); NMR δ 8.27–8.00 (m, 8), 7.82 (d, 1, H_2, $J_{2,3}$ = 7.7 Hz), 7.65 (d, 1, H_{10}, $J_{9,10}$ = 9.0 Hz), 7.42 (dd, 1, $H_{6'}$, $J_{6',F4}$ = 7.9 Hz, $J_{6',F5}$ = 10 Hz); mass spectrum, m/e (relative intensity) 359 (M^+, 91), 314 (20), 313 (33), 312 (100), 156 (43). Anal. Calcd for $C_{22}H_{11}F_2NO_2$: C, 73.53; H, 3.09; F, 10.57; N, 3.90; Found: C, 73.39; H, 3.07; F, 10.64; N, 3.87.

1-(2-Amino-4,5-difluorophenyl)pyrene (16). A suspension of **15** (422 mg, 1.2 mmol) in 10 mL of EtOH and 40 mL of glacial acetic acid was added in one portion to tin(II) chloride (890 mg, 4.8 mmol) in concentrated HCl (5 mL). After heating at 50 °C for 5 h the solution was poured into 150 mL of H_2O and made basic with 10 N NaOH. The product was extracted into ethyl acetate, washed with water and brine, and dried over sodium sulfate. After evaporation of the solvent, the product was purified by flash chromatography on silica gel, eluting with 25% CH_2Cl_2/hexane. Product **16** was obtained as a pale yellow oil: 327 mg, 83% yield. An analytical sample was recrystallized from CH_2Cl_2 as pale yellow prisms: mp 169.0–169.5 °C; NMR δ 8.29–8.02 (m, 7), 7.90 (d, 1, H_2, $J_{2,3}$ = 7.9 Hz), 7.85 (d, 1, H_{10}, $J_{9,10}$ = 8.4 Hz), 7.10 (dd, 1, $H_{6'}$, $J_{6',F5}$ = 9.9 Hz, $J_{6',F4}$ = 8.0 Hz), 6.68 (dd, 1, $H_{3'}$, $J_{3',F4}$ = 11.9 Hz, $J_{3',F5}$ = 7.0 Hz), 3.46 (br s, 2, NH_2); mass spectrum, m/e (relative intensity) 329 (M^+, 100), 328 (57), 327 (55), 326 (23), 308 (9).

8,9-Difluoroindeno[1,2,3-*cd*]pyrene (17). Amine **16** (360 mg, 1.1 mmol) was dissolved in glacial acetic acid (30 mL) and concentrated sulfuric acid added (2 mL). The solution was cooled to 5–10 °C, and sodium nitrite (98 mg, 1.4 mmol) in H_2O (5 mL) was added dropwise. The dark red solution was stirred at 5–10 °C for 20 min, and then a solution of urea (33 mg, 0.5 mmol) in H_2O (3 mL) was added in one portion. The solution was stirred for 20 min and then added dropwise over 10 min to a well-stirred warm (90 °C) suspension of copper–bronze (20 g) in glacial acetic acid (50 mL). The suspension was stirred for an additional 10 min at 90 °C and was filtered hot. The filter was washed with hot toluene, and the filtrate was then placed in a separatory funnel. The toluene layer was separated, and the aqueous layer was extracted with toluene. The toluene layers were combined, washed with water and brine, and dried over sodium sulfate. After removal of the solvents in vacuo the residue was applied to a flash chromatography column packed with silica. The column was eluted with hexane, and the first fractions were evaporated and purified further on preparative TLC plates (0.5 mm) by eluting with hexane (two developments). Pure **17** was obtained as a yellow solid, 8.3 mg (2.4%); this was crystallized from CH_2Cl_2 as yellow needles, mp 211–212 °C: NMR (360 MHz, acetone-d_6) δ 8.87 (s, 1, H_6), 8.59 (d, 1, H_5, $J_{4,5}$ = 8.2 Hz), 8.55 (d, 1, H_{12}, $J_{11,12}$ = 7.8 Hz), 8.45 (d, 1, H_3, $J_{3,4}$ = 6.8 Hz), 8.38 (d, 1, H_{11}), 8.27 (d, 1, H_2, $J_{1,2}$ = 9.0 Hz), 8.24 (dd, 1, H_7, $J_{7,F8}$ = 9.7 Hz, $J_{7,F9}$ = 7.5 Hz), 8.23 (d, 1, H_1), 8.17 (dd, 1, H_4), 8.13 (dd, 1, H_{10}, $J_{10,F9}$ = 10.4 Hz, $J_{10,F8}$ = 7.7 Hz); UV (EtOH) λ_{max} (ε) 383 (3400), 375 (4600), 357 (4900), 317 (10 700), 304 (9700), 299 (9500), 293 (8600), 288 (8000), 278 (8400), 250 (19 800), 242 (14 900); mass spectrum, m/e (relative intensity) 312 (M^+, 100), 292 (6), 156 (20); high-resolution mass spectrum, calcd for $C_{22}H_{10}F_2$ 312.0748, found 312.0751. A second yellow-green fluorescent band which was slightly less polar than **17** was isolated from preparative TLC. This compound was obtained as a yellow solid, 12.3 mg (3.6%), which crystallized from CH_2Cl_2 as yellow needles, mp 177–178 °C: NMR (360 MHz, acetone-d_6) δ 8.89 (s, 1, H_6), 8.68 (dd, 1, H_5, $J_{4,5}$ = 7.8 Hz, $J_{3,5}$ = 0.7 Hz), 8.57 (d, 1, H_{12}, $J_{11,12}$ = 7.9 Hz), 8.48 (dd, 1, H_3, $J_{3,4}$ = 7.7 Hz), 8.40 (d, 1, H_{11}), 8.29 (d, 1, H_2, $J_{1,2}$ = 9.0 Hz), 8.25 (d, 1, H_1), 8.20 (dd, 1, H_4), 7.99 (m, 1, H_{10}, $J_{9,10}$ = 7.9 Hz, $J_{10,F8}$ = 3.8 Hz, $J_{10,F7}$ = 0.7 Hz), 7.47 (m, 1, H_9, $J_{9,F8}$ = 11.1 Hz, $J_{9,F7}$ = 7.9 Hz); UV (EtOH) λ_{max} (ε) 388 nm (3100), 380 (2650), 374 (2700), 357 (3700), 342 (2600), 314 (6300), 302 (9600), 293 (7250), 267 (5200), 248 (19 300); mass spectrum, m/e (relative intensity) 312 (M^+, 100), 292 (5), 156 (25); high-resolution mass spectrum, calcd for $C_{22}H_{10}F_2$ 312.0748, found 312.0751. A band of blue fluorescence which was the least polar product isolated from TLC was evaporated to a colorless oil, 102 mg, 29%. This was crystallized from aqueous acetone as colorless needles, mp 79–81 °C: NMR δ 8.27–7.86 (m, 9), 7.57–7.25 (m, 3); UV (EtOH) λ_{max} (ε) 340 nm (27 500), 326 (19 700), 313 (9400), 277 (35 800), 267 (22 600), 243 (46 800), 235 (37 100); mass spectrum, m/e (relative intensity) 314 (M^+, 100), 313 (33), 312 (43), 294 (11), 156 (7). Anal. Calcd for $C_{22}H_{12}F_2$: C, 84.05; H, 3.85; Found: C, 83.60; H, 3.89.

***trans*-8-Acetoxy-9-bromo-8,9,10,11-tetrahydrobenzo[*k*]fluoranthene (18).** A solution of 8,9-dihydrobenzo[*k*]fluoranthene[16] (250 mg, 1 mmol) and lithium acetate (0.5 g) in glacial acetic acid (50 mL) was stirred in the dark under N_2 at room temperature as solid N-bromoacetamide (140 mg, 1 mmol) was added in three portions. The mixture was stirred overnight at room temperature and then was poured into water and the precipitate filtered. The solid was washed with water and air-dried. The product was crystallized from benzene–hexane giving pure **18** as pale yellow needles: 400 mg (80%); mp 144–145 °C; NMR δ 7.95–7.52 (m, 8), 6.30 (d, 1, H_8, $J_{8,9}$ = 4.1 Hz), 4.55 (m, 1, H_9), 3.09 (m, 2, H_{11}), 2.58–2.25 (m, 2, H_{10}), 2.15 (s, 3, CH_3CO_2); mass spectrum, m/e (relative intensity) 394 (M + 2, 9), 392 (M^+, 9), 334 (34), 332 (36), 270 (62), 254 (36), 253 (100). Anal. Calcd for $C_{22}H_{17}BrO_2$: C, 67.17; H, 4.36. Found: C, 67.05; H, 4.44.

***trans*-8-Acetoxy-9,11-dibromo-8,9,10,11-tetrahydrobenzo-[*k*]fluoranthene (19).** A solution of **18** (200 mg, 0.5 mmol), *N*-bromosuccinimide (100 mg, 0.5 mmol), and benzoyl peroxide (10 mg) in carbon tetrachloride (35 mL) was heated at reflux under

nitrogen for 90 min. After cooling to room temperature, the solution was filtered and the solvent removed under reduced pressure. The brown residue was washed with a small volume of hexane–carbon tetrachloride (1:1) and then crystallized from carbon tetrachloride to give **19** as a yellow amorphous solid: 112 mg (48%); mp 96–97 °C; NMR δ 8.16–7.56 (m, 8), 6.45 (d, 1, H_8, $J_{8,9}$ = 8.2 Hz), 5.69 (dd, 1, H_{11}, $J_{10a,11e}$ = 4.4 Hz, $J_{10e,11e}$ = 4.4 Hz), 4.82 (m, 1, H_9, $J_{9a,10a}$ = 8.0 Hz, $J_{9a,10e}$ = 3.7 Hz), 3.17–2.56 (m, 2, $H_{10a,e}$), 2.30 (s, 3, CH_3CO_2); chemical ionization mass spectrum (methane), *m/e* (relative intensity) 391 (2), 389 (2), 361 (20), 359 (20), 333 (97), 331 (100), 311 (38), 252 (80), 57 (78).

8,9-Dihydro-8,9-epoxybenzo[*k*]fluoranthene (20). Sodium methoxide (250 mg, 5 mmol) was prepared by dissolving a sphere of sodium in dry methanol and evaporating under reduced pressure. Benzene was added, and the solvents were again evaporated. The dry sodium methoxide was suspended in dry THF (10 mL) under nitrogen at 0 °C. A solution of **19** (110 mg, 0.23 mmol) in THF (1 mL) was added to the methoxide and the reaction mixture was stirred at 0 °C overnight. Dry ether (20 mL) was added, and the solution was quickly washed with ice-cold water and then dried over potassium carbonate. The flask was wrapped with foil to keep the contents in the dark, and the solvents were removed under reduced pressure below 35 °C. The residue was dissolved in ether and precipitated by the addition of hexane, giving **20** as a yellow solid: 54 mg (84%); NMR δ 8.12 (s, 1, H_7), 8.0–7.55 (m, 7), 6.90 (d, 1, H_{11}, $J_{10,11}$ = 11.2 Hz), 6.46 (dd, 1, H_{10}, $J_{9,10}$ = 3.9 Hz), 4.61 (d, 1, H_8, $J_{8,9}$ = 3.7 Hz), 4.17 (m, 1, H_9); mass spectrum, *m/e* (relative intensity) 268 (M^+, 100), 239 (54), 213 (8); UV (THF) λ_{max} (ϵ) 418 nm (6700), 397 (7500), 380 (6800), 340 (6400), 302 (35 200), 272 (17 300), 240 (39 600); high-resolution mass spectrum, calcd for $C_{20}H_{12}O$ 268.0888, found 268.0874.

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Asymmetric Electrophilic Substitution on Phenols. 2. Enantio- and Diastereoselective Synthesis of *o*-Hydroxyatrolactic Esters[1]

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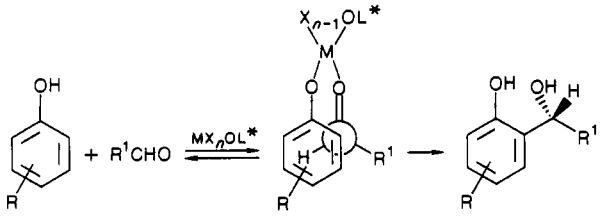
Both 2*R* and 2*S* stereoisomers of *o*-hydroxyatrolactic acid esters **3–5** are available with respective absolute configuration from phenols **1** and pyruvic acid esters **2** by using menthol only as a chiral inductor. Three asymmetric approaches were designed based on (a) single induction by chiral metal alkoxides, (b) single induction by chiral pyruvic esters, and (c) double induction by chiral pyruvic esters and chiral metal alkoxides. Route a furnished optically enriched enantiomers **3** with ee's ranging from 13% to 46%; route b furnished diastereomeric compounds **4** and **5** with 46–52% de; route c furnished diastereomeric compounds **4** and **5** with 36–88% de. The results have been incorporated into a mechanistic rationale involving a chelate transition state of the sort depicted in Figure 2.

The synthetic value of electrophilic aromatic substitution is widely recognized as a means of carbon–carbon bond construction leading to a variety of arylated compounds. Aiming at developing asymmetric versions of this reaction we have recently shown that chiral modified aluminum reagents promote enantioselective electrophilic substitution on phenols when reacted with prochiral carbonyl compounds.[2] In this special case the substitution reaction utilizes the chirality attached to the metal center to direct the carbonyl compound probably via a chelation-controlled transition state (Scheme 1), ultimately producing α-chiral nonracemic *o*-hydroxybenzyl alcohol derivatives.

In principle, according to this scheme, a second chiral procedure can be designed based on diastereoselective carbon–carbon bond formation by using carbonyl compounds incorporating suitable chiral centers, and, in addition, a double asymmetric approach can be developed which takes advantage from the combined use of the

Scheme I



chiralities in the reactant and promoter. In the present paper we describe a regio- and stereocontrolled entry to *o*-hydroxyatrolactic esters of either 2*R* or 2*S* configuration **3–5** by reaction of phenols **1** with pyruvic esters **2** by using three asymmetric techniques: (a) enantioselection using chiral metal alkoxides; (b) diastereoselection using chiral pyruvic esters; (c) double asymmetric induction using chiral metal alkoxides and chiral pyruvic esters.

Results and Discussion

Enantioselection by Chiral Metal Alkoxides. First we investigated the reactions between 3-*tert*-butylphenol (**1a**) and ethyl pyruvate (**2a**) in the presence of chiral

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(2) Bigi, F.; Casiraghi, G.; Casnati, G.; Sartori, G.; Gasparri Fava, G.; Ferrari Belicchi, M. *J. Org. Chem.* **1985**, *50*, 5018.

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