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Synthesis of Suspected Carcinogenic Metabolites of 7*H*-Benzo[*c*]fluorene, a Coal Tar Component Implicated in Causation of Lung Tumors

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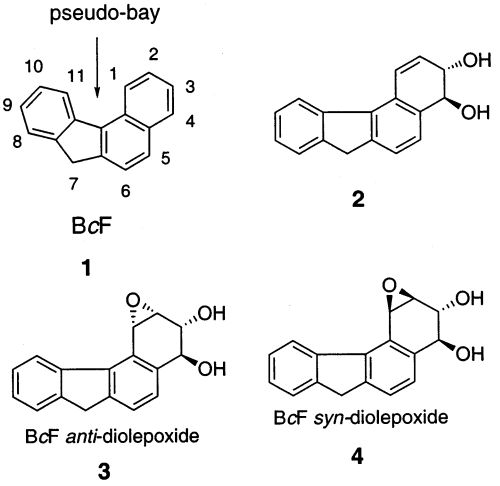
Abstract: High incidences of lung tumors were observed in mice fed coal tar in their diet. The principal component of tar that gives rise to DNA-bound adducts in mouse lung was identified as 7*H*-benzo[*c*]fluorene (B*c*F). We now report the synthesis of suspected active metabolites of B*c*F, specifically the *trans*-3,4-dihydrodiol of B*c*F (**2**), its likely *proximate* carcinogenic metabolite, and the corresponding *anti*- and *syn*-diol epoxides of B*c*F (**3** and **4**) in which the epoxide ring resides in the *pseudobay* region. The diol epoxide derivatives (**3** and **4**) are postulated to be *ultimate* carcinogenic metabolites of B*c*F that bind to DNA in mouse lung.

Weyand and co-workers have recently demonstrated a high incidence of lung tumors in female A/J mice fed coal tar in their diet.[1] Polycyclic aromatic hydrocarbons (PAHs) have been shown by prior studies to be the major carcinogenic components of coal tar.[2−4] Three DNA-bound adducts were detected in the lungs of mice treated with coal tars.[5] The predominant adduct was identified as a derivative of 7*H*-benzo[*c*]fluorene (B*c*F).[6] Subsequently, B*c*F was shown to be a potent inducer of lung tumors in mice fed B*c*F in their diet.[7]

The generally accepted mechanism of PAH carcinogenesis entails activation by P-450 enzymes to diol epoxide metabolites with an epoxide ring in a bay or fjord molecular region. These intermediates react with DNA to form mutagenic adducts.[2,8] B*c*F (**1**) differs from the known PAH carcinogens in that it has neither a bay nor a fjord molecular region but possesses instead a *pseudo*bay region.

In connection with studies to identify metabolites of B*c*F that bind to DNA in mouse lung, we undertook to synthesize the probable active metabolites. We now report the synthesis of the *trans*-3,4-dihydrodiol of B*c*F (**2**) and the corresponding *anti*- and *syn*-diol epoxides (**3** and **4**) (the putative *ultimate* carcinogenic metabolites that bind to DNA in vivo).



The key intermediate in the proposed synthetic route to the 3,4-dihydrodiol of B*c*F (**2**) is 3-hydroxy-7*H*-benzo[*c*]fluorene (**10b**). In principle, **10b** is synthetically accessible via modification of the method for the synthesis of B*c*F itself.[9] This entails alkylation of the enamine of cyclohexanone, pyrrolidino-1-cyclohexene (**6**), by 2-methoxy-6-bromomethylnaphthalene (**5c**), followed by acid-catalyzed cyclization, dehydrogenation, and demethylation (Scheme 1).

2-Methoxy-6-bromomethylnaphthalene (**5c**) was prepared from 6-methoxy-2-naphthaldehyde (**5a**) by reduction with $NaBH_4$ in MeOH to 2-methoxy-6-hydroxymethylnaphthalene (**5b**),[10] followed by reaction with PBr_3. Compound **5c** exhibited a tendency to decompose

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(6) (a) Koganti, A.; Singh, R.; Rozett, K.; Modi, N.; Goldstein, L. S.; Roy, T. A.; Zhang, F.-J.; Harvey, R. G.; Weyand, E. H. *Carcinogenesis* **2000**, *21*, 1601. (b) The minor adducts were identified as derivatives of benzo[*a*]pyrene and benzo[*a*]fluoranthene.[5a]
(7) Weyand, E. H.; Goldstein, E. S.; Reuhl, K.; Zhang, F.-J.; Harvey, R. G. *The Toxicologists* **2002**, *61*, 909. Mice fed a diet containing 397 mmolB*c*F/kg had a 100% incidence of lung tumors (av 46 tumors/mouse); whereas mice fed a similar diet containing benzo[*a*]pyrene exhibited a 77% tumor incidence (av 1.4 tumors/mouse).
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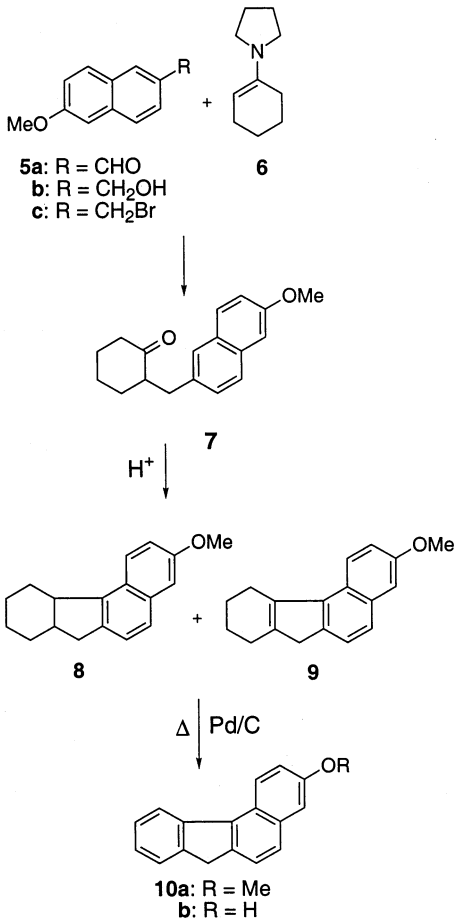
SCHEME 1

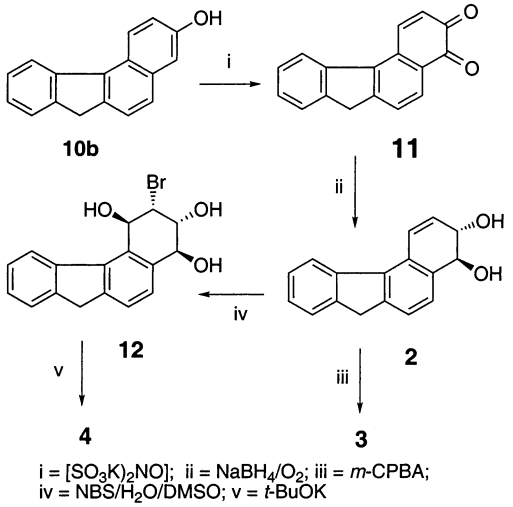


on chromatography, and best results were obtained by its use directly without purification.

Reaction of **5c** with enamine **6** (Scheme 1) by the procedure used for synthesis of B*c*F[9] gave the alkylated cyclohexanone **7** in similar yield (72%). The proton NMR spectrum of **7** was consistent with its assignment. Cyclodehydration of **7** in methanesulfonic acid furnished 7a,8,9,10,11,11a-hexahydro-3-methoxy-B*c*F (**8**) (33%) plus a lesser amount (6%) of the primary product, 8,9,10,11-tetrahydro-3-methoxy-B*c*F (**9**). Although it is likely that **8** is formed from acid-catalyzed disproportionation of **9**, significant amounts of B*c*F, the other expected product, were not detected. Disproportionation was observed in the synthesis of B*c*F,[9] and it commonly occurs in cyclodehydration reactions.[11] Compound **8** was stable, but **9** exhibited a tendency to undergo autoxidation on standing. To minimize secondary processes, the reaction was repeated with minimal reaction time. Dehydrogenation of the crude product over a palladium-charcoal catalyst furnished 3-methoxy-B*c*F (**10a**) in good yield. Compound **10a** was converted to the phenol (**10b**) by heating with 48% HBr in acetic acid.

Synthesis of the 3,4-dihydrodiol of B*c*F (**2**) from **10b** was carried out by the standard sequence (Scheme 2).[12,13]

SCHEME 2



Oxidation of **10b** with Fremy's salt [$(SO_3K)_2NO$] afforded the quinone, B*c*F-3,4-dione (**11**). Products from competing oxidation in the benzylic position of **10b** were not detected. Reduction of **11** with $NaBH_4$ in ethanol with O_2 bubbling through the solution gave **2**. Formation of the trans isomer is consisent with the known stereospecificity of this reaction and in good agreement with the proton NMR spectrum of **2**.[12,14]

Epoxidation of **2** with *m*-chloroperbenzoic acid furnished *trans*-3,4-dihydroxy-*anti*-1,2-epoxy-1,2,3,4-tetrahydro-B*c*F (**3**) stereospecifically and in good yield (94%). This is consistent with prior findings that epoxidation of PAH dihydrodiols free to adopt the diequatorial conformation takes place trans-stereospecifically to give the *anti*-diol epoxide isomers.[12,13] The *syn*-diol epoxide isomer (**4**) was prepared via reaction of **2** with NBS in moist DMSO to yield the bromohydrin (**12**). Reaction of **12** with potassium *tert*-butoxide in *tert*-butanol took place smoothly to furnish the *syn*-diol epoxide, *trans*-3,4-dihydroxy-*syn*-1,2-epoxy-1,2,3,4-tetrahydro-B*c*F (**4**), in good yield (87%). The stereochemical assignments of **12** and **4** are in good agreement with their proton NMR spectra and with those for analogous compounds from similar reactions.[12,13]

The synthetic accessibility of the BcF derivatives reported herein (**2**, **3**, **4**, **10b**, **11**)[15] permits identification of the active metabolites that bind to DNA in vivo and determination of their biological properties. Preliminary findings from DNA binding studies indicate that topical administration of **2** to the skins of mice affords DNA adducts in skin and lung.[16] The lung adducts are chromatographically identical with those formed by administration of B*c*F. These results suggest that B*c*F is metabolically activated to **2** that is further transformed

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to a diol epoxide that binds to DNA. These findings may be significant for lung cancer in human populations because B*c*F is a widespread environmental pollutant present in tobacco smoke, automobile exhaust, and other sources.[2,3]

Experimental Section

Materials and Methods. 2-Methoxy-6-hydroxymethylnaphthalene (**5b**) was synthesized from 6-methoxy-2-naphthaldehyde (**5a**) by reduction with $NaBH_4$ in MeOH by the published method.[10] 1-Pyrrolidino-1-cyclohexene (**6**), 6-methoxy-2-naphthaldehyde, Fremy's reagent [$(SO_3K)_2NO$], and *m*-chloroperbenzoic acid were purchased from a commerical source. 1,4-Dioxane, triglyme, and THF were freshly distilled from sodium/benzophenone ketal. NBS was recrystallized from water. NMR spectra were recorded on 400 or 500 MHz spectrometers in $CDCl_3$ with tetramethylsilane as internal standard unless stated otherwise. Integration was consistent with all structural assignments. Mass spectra (MS) and HRMS were performed by the University of Illinois at Urbana-Champaign, School of Chemical Sciences. UV spectra were measured with a Perkin-Elmer Lambda 6 spectrometer. Microanalyses were done by Atlantic Microlab, Inc. All melting points are uncorrected.

Caution: Benzo[*c*]fluorene and its *trans*-3,4-dihydrodiol (**2**) and diol epoxide metabolites (**3**, **4**) are potentially hazardous and should be handled with care in accordance with "NIH Guidelines for the Laboratory Use of Chemical Carcinogens".

2-Bromomethyl-6-methoxynaphthalene (5c). A solution of PBr_3 (4.3 mL, 45 mmol) in anhydrous ether (100 mL) was added dropwise to a cold solution of **5b** (7.27 g, 39 mmol) in anhydrous ether (200 mL) at −30 to −40 °C under argon. The solution was allowed to warm to room temperature in a period of 2 h, then the reaction was neutralized by addition of 5% aqueous $NaHCO_3$ solution. The ether layer was washed with water and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave **5c** as a white solid (9.09 g, 94%). Because of the tendency of **5c** to decompose, it was used directly in the next step.

2-(2-Methoxy-6-naphthylmethyl)cyclohexanone (7). Synthesis of **7** was based on the method for the synthesis of B*c*F.[9] Reaction of **5c** (3.88 g, 15.5 mmol) with **6** followed by chromatography of the crude product on a column of silica gel eluted with hexane−EtOAc (9:1) gave **7** (3.02 g, 72%) as a white solid: mp 83−84 °C; ^{1}H NMR ($CDCl_3$) δ 7.64−7.67 (m, 2), 7.51 (s, 1), 7.25 (d, 1), 7.09−7.13 (m, 2), 3.89 (s, 3, CH_3), 3.35 (dd, 1, one benzylic CH_2), 1.35−2.61 (m, 10, 1 benzylic and 9 aliphatic); ^{13}C NMR ($CDCl_3$) δ 212.60, 157.13, 135.40, 132.94, 128.88, 128.82, 127.20, 126.65, 118.66, 105.49, 55.20, 52.42, 42.11, 35.31, 33.32, 27.98, 24.97; FAB MS *m*/*z* 268 (M^+). Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.69; H, 7.69.

Cyclodehydration of 7. Reaction of **7** (7.70 g, 26 mmol) in CH_2Cl_2 (150 mL) and CH_3SO_3H (25 mL) was carried out by the procedure for the preparation of B*c*F[9] (16-h reaction). Chromatography of the crude product on silica gel eluted with hexane−CH_2Cl_2 (6:1) gave 7a,8,9,10,11,11a-hexahydro-3-methoxy-B*c*F (**8**) (1.07 g, 33%) as a white solid: mp 70−71 °C: ^{1}H NMR ($CDCl_3$) δ 7.75 (d, 1, J = 8.83 Hz), 7.54 (d, 1, J = 8.22 Hz), 7.36 (d, 1, J = 8.23 Hz), 7.11−7.16 (m, 2), 3.90 (s, 3, CH_3), 3.35−3.40 (m, 1, benzylic CH), 3.03 (dd, 1, J = 14.96 Hz, benzylic CH_2), 2.80 (dd, 1, J = 15.00 Hz, benzylic CH_2), 2.61−2.71 (m, 1), 1.01−2.11 (m, 8); ^{13}C NMR ($CDCl_3$) 156.55, 145.70, 137.24, 133.67, 125.63, 125.17, 125.02, 124.40, 118.36, 106.49, 55.23, 42.67, 40.07, 35.13, 29.52, 27.24, 24.64, 21.86; FAB MS *m*/*z* 252 (M^+). Anal. Calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.60; H, 7.97. Further elution gave 8,9,10,11-tetrahydro-3-methoxy-B*c*F (**9**) (6.4%) as a white solid: mp 76−77 °C; ^{1}H NMR ($CDCl_3$) δ 8.31 (d, 1, J = 9.23 Hz), 7.51 (s, 2), 7.18 (d, 1, J = 2.68 Hz), 7.11 (d, 1, J = 9.22 Hz), 3.92 (s, 3, CH_3), 3.30 (s, 2, benzylic CH_2), 2.99−3.02 (m, 2), 2.50−2.54 (m, 2), 1.79−1.94 (m, 4); ^{13}C NMR ($CDCl_3$) 156.19, 142.71, 141.18, 138.24, 136.94, 134.47, 125.50, 122.70, 122.67, 117.51, 106.80, 106.48, 55.10, 41.34, 26.78, 26.44, 23.31, 22.55; FAB HRMS calcd for $C_{18}H_{18}O$ *m*/*z* 250.1358, found 250.1357. Anal. Calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.25. Found: C, 86.09; H, 7.27.

3-Methoxybenzo[*c*]fluorene (10a). Dehydrogenation of a mixture of **8** and **9** (130 mg, 0.5 mmol) in 10 mL of triglyme over a 10% palladium−charcoal catalyst (100 mg) at 240 °C (bath) followed by the usual workup gave the crude product. Chromatography on a silica gel column eluted with hexane−CH_2Cl_2 (6:1) furnished pure **10a** (100 mg, 78%) as a white solid: mp 101−102 °C; ^{1}H NMR ($CDCl_3$) δ 8.67 (d, 1, J = 9.17 Hz), 8.34 (d, 1, J = 7.87 Hz), 7.71 (d, 1, J = 8.26 Hz), 7.60−7.65 (m, 2), 7.45−7.51 (m, 1), 7.26−7.37 (m, 3), 3.97 (s, 2, CH_2), 3.95 (s, 3, CH_3); ^{13}C NMR ($CDCl_3$) 156.64, 144.34, 142.70, 140.00, 136.12, 134.67, 126.78, 126.48, 125.67, 125.09, 124.91, 124.82, 123.72, 122.67, 118.73, 107.27, 55.20, 37.46; FAB MS *m*/*z* 246 (M^+). Anal. Calcd for $C_{18}H_{14}O$: C, 87.78; H, 5.73. Found: C, 87.84; H, 5.72.

3-Hydroxybenzo[*c*]fluorene (10b). A mixture of **10a** (1.38 g, 5.6 mmol) in 35 mL of HOAc and 45 mL of 48% hydrobromic acid was heated at reflux for 2 h under argon. Conventional workup and chromatography of the product on a silica gel column eluted with CH_2Cl_2 gave **10b** (1.21 g, 93%) as an off-white solid: mp 178−179 °C; ^{1}H NMR ($CDCl_3$) δ 8.67 (d, 1, J = 8.87 Hz), 8.32 (d, 1, J = 7.82 Hz), 7.60−7.67 (m, 3), 7.47 (t, 1, J = 7.54 Hz), 7.33 (t, 1, J = 7.43 Hz), 7.22−7.28 (m, 2), 4.95 (br s, 1, OH), 3.97 (s, 2, CH_2); ^{13}C NMR ($CDCl_3$) 152.51, 144.36, 142.66, 137.53, 136.17, 134.74, 126.82, 126.14, 125.74, 125.52, 124.97, 124.87, 122.67, 117.89, 111.00, 37.53; FAB MS *m*/*z* 232 (M^+). Anal. Calcd for $C_{17}H_{12}O$: C, 87.90; H, 5.21. Found: C, 87.76; H, 5.23.

Benzo[*c*]fluorene-3,4-dione (11). Oxidation of **10b** (100 mg, 0.43 mmol) in acetone (20 mL) and 12 mL of 1.6 M aqueous KH_2PO_4 by Fremy's salt (340 mg, 1.3 mmol) in 36 mL of water was carried out overnight at room temperature under argon.[2,13] The usual workup followed by chromatography on silica gel eluted with CH_2Cl_2 gave **11** (100 mg, 94%) as an orange solid: mp 175 °C dec; ^{1}H NMR ($CDCl_3$) δ 8.39 (d, 1, J = 10.48 Hz), 8.02 (d, 1, J = 7.69 Hz), 7.94−7.98 (m, 1), 7.52−7.59 (m, 2), 7.36−7.45 (m, 2), 6.45 (d, 1, J = 10.49 Hz), 3.91 (s, 2, CH_2); ^{13}C NMR ($CDCl_3$) 181.18, 179.21, 152.53, 144.31, 141.28, 140.44, 139.46, 131.43, 129.27, 129.13, 128.39, 127.59, 127.39, 126.86, 125.66, 123.79, 37.30. Anal. Calcd for $C_{17}H_{10}O_2$: C, 82.91; H, 4.09. Found: C, 82.92; H, 4.14.

***trans*-3,4-Dihydroxy-3,4-dihydrobenzo[*c*]fluorene (2).** To a solution of **11** (70 mg, 0.28 mmol) in THF (40 mL) and ethanol (150 mL) was added $NaBH_4$ (1.0 g). The orange color disappeared, and the solution was stirred overnight with O_2 bubbling through it. The usual workup followed by chromatography on a silica gel column eluted with EtOAc−hexane (1:1) gave **2** (50 mg, 70%) as a white solid: mp 132−134 °C; ^{1}H NMR (DMSO-d_6) δ 8.02 (d, 1, J = 7.70 Hz), 7.57 (d, 1, J = 7.28 Hz), 7.49 (d, 1, J = 7.62 Hz), 7.21−7.44 (m, 4), 6.11 (d, 1, J = 10.01 Hz), 5.47 (d, 1, J = 5.59 Hz, OH), 5.20 (d, 1, J = 4.98 Hz, OH), 4.50−4.60 (m, 1, CH), 4.20−4.30 (m, 1, CH), 3.87 (s, 2, CH_2); ^{13}C NMR (DMSO-d_6) δ 143.93, 142.63, 141.10, 137.29, 135.75, 134.42, 127.36, 126.88, 126.30, 125.17, 123.95, 123.49, 123.01, 122.76, 73.81, 71.36, 36.03. Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.30; H, 5.77.

***trans*-3,4-Dihydroxy-*anti*-1,2-epoxy-1,2,3,4-tetrahydrobenzo[*c*]fluorene (3).** A solution of **3** (50 mg, 0.20 mmol) and *m*-CPBA (350 mg) in anhydrous THF (40 mL) was stirred under argon for 3 h. Then it was diluted with EtOAc and washed with cold 10% NaOH solution (4 × 25 mL) and cold water (2 × 25 mL). The organic layer was dried over anhydrous Na_2CO_3, and the solvent was removed under reduced pressure. *All operations were carried out rapidly and heating was avoided to minimize hydrolysis and decomposition of the relatively sensitive diol epoxide product.* Trituration of the crude product with cold pure EtOAc gave **3** (50 mg, 94%) as a white solid: mp 89 °C dec; ^{1}H NMR (DMSO-d_6) δ 8.16 (d, 1, J = 7.64 Hz), 7.61 (d, 1, J = 7.09 Hz), 7.52−7.60 (m, 2), 7.32−7.42 (m, 2), 5.62 (d, 1, J = 6.48 Hz, OH), 5.56 (d, 1, J = 4.92 Hz, OH), 4.92 (d, 1, J = 4.45 Hz, CH), 4.35−4.43 (m, 1, CH), 3.91 (s, 2, CH_2), 3.73−3.79 (m, 1, CH), 3.67 (d, 1, J = 4.40 Hz, CH); ^{13}C NMR (DMSO-d_6) δ 144.18,

142.55, 140.44, 139.97, 139.92, 126.97, 126.77, 126.29, 125.48, 124.68, 124.00, 123.08, 71.16, 69.64, 55.93, 50.12, 36.15. Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30. Found: C, 76.38; H, 5.40.

2-*β*-Bromo-1α,3*β*,4α-trihydroxy-1,2,3,4-tetrahydrobenzo[*c*]fluorene (12). A solution of **2** (50 mg, 0.20 mmol) and NBS (200 mg, 1.12 mmol) in DMSO (10 mL) and water (0.3 mL) was stirred at 30 °C for 6 h under argon. The usual workup followed by chromatography on a silica gel column eluted with EtOAc−hexane (2:1) afforded **12** (50 mg, 72%) as a, white solid: mp 149 °C dec; ^{1}H NMR (DMSO-d_6) δ 8.02 (d, 1, J = 7.71 Hz), 7.50−7.62 (m, 3), 7.28−7.43 (m, 2), 6.25 (d, 1, J = 5.72 Hz, OH), 5.72 (d, 1, J = 6.49 Hz, OH), 5.59 (d, 1, J = 4.18 Hz, OH), 5.42−5.56 (m, 1, CH), 4.50−4.60 (m, 2, CH), 4.05−4.10 (m, 1, CH), 3.89 (s, 2, CH_2); ^{13}C NMR (DMSO-d_6) δ 143.90, 142.84, 140.64, 139.75, 137.95, 128.44, 126.71, 126.35, 126.32, 124.84, 124.69, 124.08, 71.19, 70.19, 67.99, 61.22, 36.30. Anal. Calcd for $C_{17}H_{15}BrO_3$: C, 58.81; H, 4.35. Found: C, 58.59; H, 4.38.

***trans*-3,4-Dihydroxy-*syn*-1,2-epoxy-1,2,3,4-tetrahydrobenzo[*c*]fluorene (4).** To a solution of **12** (30 mg, 0.086 mmol) in anhydrous THF (10 mL) was added a solution of *t*-BuOK (15 mg) in *t*-BuOH (1 mL). The solution was stirred at room temperature under argon for 25 min (reaction complete by TLC). The solution was transferred to a separatory funnel, diluted with cold EtOAc, and washed three times with cold water. The organic layer was filtered and evaporated to dryness under reduced pressure without heating. *All operations were carried out rapidly avoiding heating in order to minimize decomposition*. Trituration with cold pure EtOAc gave **4** (20 mg, 87%) as an off-white solid: mp 177 °C dec; ^{1}H NMR (DMSO-d_6) δ 8.03 (d, 1, J = 7.56 Hz), 7.57−7.67 (m, 2), 7.33−7.49 (m, 3), 5.70 (d, 1, J = 4.85 Hz, OH), 5.35 (d, 1, J = 6.40 Hz, OH), 4.53−4.59 (m, 1, CH), 4.49 (d, 1, J = 4.24 Hz, CH), 3.95 (d, 1, J = 22.0 Hz, CH_2), 3.89 (d, 1, J = 22.0 Hz, CH_2), 3.60−3.64 (m, 1, CH), 3.52−3.60 (m, 1, CH); ^{13}C NMR (DMSO-d_6) δ 143.95, 142.40, 140.72, 140.41, 138.98, 126.94, 126.90, 125.74, 125.41, 125.32, 125.11, 122.69, 71.33, 71.06, 58.78, 47.43, 36.20.

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