of Science of Kagoshima University, for mass spectrometric analyses.

Registry No. 1, 106-51-4; **2a**, 363-03-1; **2b**, 79756-66-4; **2c**, 79756-69-7; **3a**, 844-51-9; **3b**, 79756-68-6; **3c**, 79756-71-1; **3d**, 79756-76-6; **4a**, 2887-97-0; **4b**, 79756-67-5; **4c**, 79756-70-0; **4d**, 79756-75-5; **5**, 130-15-4; **6a**, 2348-77-8; **6b**, 79756-72-2; **6c**, 79756-73-3; **6d**, 99113-62-9; **6e**, 99113-63-0; **6f**, 99113-64-1; **7**, 524-42-5; **8a**, 73671-07-5; **8c**, 79756-74-4; **9**, 99113-71-0; **10**, 99113-72-1; **11**, 99113-73-2; **12**, 99113-74-3; **13**, 99113-65-2; **14**, 99113-66-3; **15**, 99113-67-4; **16**, 99113-68-5; **17**, 99113-69-6; **18**, 99113-70-9; C_6H_6, 71-43-2; 2,5-$Me_2C_6H_4$, 106-42-3; 2,5-$Cl_2C_6H_4$, 106-46-7; 2,5-$F_2C_6H_4$, 540-36-3; 2,4,6-$Me_3C_6H_3$, 108-67-8; 2,3,4,5-$Me_4C_6H_2$, 488-23-3; $Pd(OAc)_2$, 3375-31-3; $Na_2S_2O_8$, 7775-27-1; $K_2S_2O_8$, 7727-21-1; $(NH_4)_2S_2O_8$, 7727-54-0; $Cu(OAc)_2$, 142-71-2; $FeCl_3$, 7705-08-0; $KMnO_4$, 7722-64-7; $K_2Cr_2O_7$, 7778-50-9; furfural, 98-01-1; 2-acetylfuran, 1192-62-7; methyl 2-furoate, 611-13-2; 2-acetylthiophene, 88-15-3; 1-(phenylsulfonyl)pyrrole, 16851-82-4; 1-(phenylsulfonyl)indole, 40899-71-6; 4-pyrone, 108-97-4; 1-methyl-2-pyridone, 694-85-9.

Methoxybenzo[*a*]pyrene 4,5-Oxides Labeled with Carbon-13: Electronic Effects in the NIH Shift

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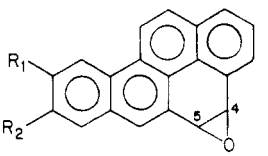
The synthesis of 9-methoxy-4,5-dihydrobenzo[*a*]pyrene-*4*-^{13}C 4,5-oxide and -*5*-^{13}C 4,5-oxide and of 8-methoxy-4,5-dihydrobenzo[*a*]pyrene-*4*-^{13}C 4,5-oxide is reported. The compounds were synthesized in yields of 15% each from unlabeled precursors. ^{13}C NMR analysis of the conversion of the 4,5-oxides to 4-phenols and 5-phenols (NIH shift) revealed a very strong electronic effect of a 9-methoxy substituent, which gave only the 4-phenol, and a significant but weaker effect of an 8-methoxy substituent, which gave both phenols with the 5-phenol predominating.

The environmental carcinogen benzo[*a*]pyrene undergoes microsomal oxidation to form a variety of phenols, quinones, diols, and epoxides.[1] Only a few of these have been shown to bind to DNA, considered by many to be a necessary step in tumor formation.[2] One DNA binding metabolite is 9-hydroxybenzo[*a*]pyrene 4,5-oxide (**1**), which, like the known carcinogenic metabolite 7,8-dihydroxybenzo[*a*]pyrene 9,10-oxide, also causes DNA strand breaks in vitro.[3,4] Despite this similarity, **1** appears to be noncarcinogenic. Why these two compounds show different activities remains an intriguing question whose answer may help elucidate the mechanism of benzo[*a*]pyrene-induced cellular transformation.

The in vitro activity of **1** is also markedly different from that of benzo[*a*]pyrene 4,5-oxide (**2**), which does not bind to DNA,[4] and suggests that the 9-hydroxyl group plays a significant role. Though these differences have been observed in enzymatic systems where the hydroxyl group may affect enzyme binding, another possibility is that the 8-hydroxyl group exerts a through-bond influence within the ring system on epoxide opening.

Using ^{13}C-labeled substrates, Hylarides et al. found that **2** reacted with a variety of nucleophiles, showing no preference for attack at either the 4- or 5-position of the epoxide.[5,6] Likewise, the acid-catalyzed isomerization of **2** to phenol (the NIH shift) produced equal amounts of 4- and 5-phenols. This general lack of regioselectivity was readily determined by the ^{13}C NMR spectra of the crude product mixtures after workup.

As a result of the above study and to compare **1** and **2** under identical experimental conditions, we embarked on the preparation of ^{13}C-labeled 9-hydroxybenzo[*a*]pyrene 4,5-oxide (**1**). Though efforts to synthesize **1** as the free phenol have been unsuccessful, the methyl ether derivative 9-methoxybenzo[*a*]pyrene 4,5-oxide (**3**) has been reported recently[7] and shown to bind to DNA in a manner similar to **1**.[8] The synthesis of **3**, reported by Harvey and Cortez, is not amenable to the incorporation of carbon-13 labels in the epoxide positions. Herein we describe the synthesis of 9-methoxybenzo[*a*]pyrene-*4*-^{13}C 4,5-oxide (**3a**-*4*-^{13}C) and -*5*-^{13}C (**3a**-*5*-^{13}C) and 8-methoxybenzo[*a*]pyrene-*4*-^{13}C 4,5-oxide (**3b**-*4*-^{13}C). These substrates were studied under NIH shift conditions, the results of which are presented below.



1, R_1=OH, R_2=H
2, R_1=R_2=H
3a, R_1=OMe, R_2=H
3b, R_1=H, R_2=OMe

† Taken in part from the Ph.D. Dissertation of I.R.S., submitted to the University of New Mexico in partial fulfillment of the Ph.D. requirements, 1983.

‡ Deceased June 4, 1984.

(1) (a) Selkirk, J. K.; MacLeod, M. C.; Kuroki, T.; Drevon, C.; Piccoli, C.; Montesano, R. *Carcinogenis, (London)* **1982**, 3, 635. (b) Selkirk, J. K. *Nature (London)* **1977**, *270*, 604.

(2) Silverman, I. R. Ph.D. Dissertation, University of New Mexico, 1983.

(3) King, H. W. S.; Thompson, M. H.; Brooker, P. *Int. J. Cancer* **1976**, *18*, 339.

(4) (a) Jernström, B.; Orrenius, S.; Undeman, D.; Gräslund, A.; Ehrenberg, A.; *Cancer Res.* **1978**, *38*, 2600. (b) Nordenskjöld, M.; Sodehall, S.; Moldeus, P.; Jernström, B.; *Biochem. Biophys. Res. Commun.* **1978**, *85*, 1535.

(5) Hylarides, M. D.; Daub, G. H.; Vander Jagt, D. L.; Silverman, I. R.; *J. Labelled Compd. Radiopharm.* **1983**, *20*, 1121.

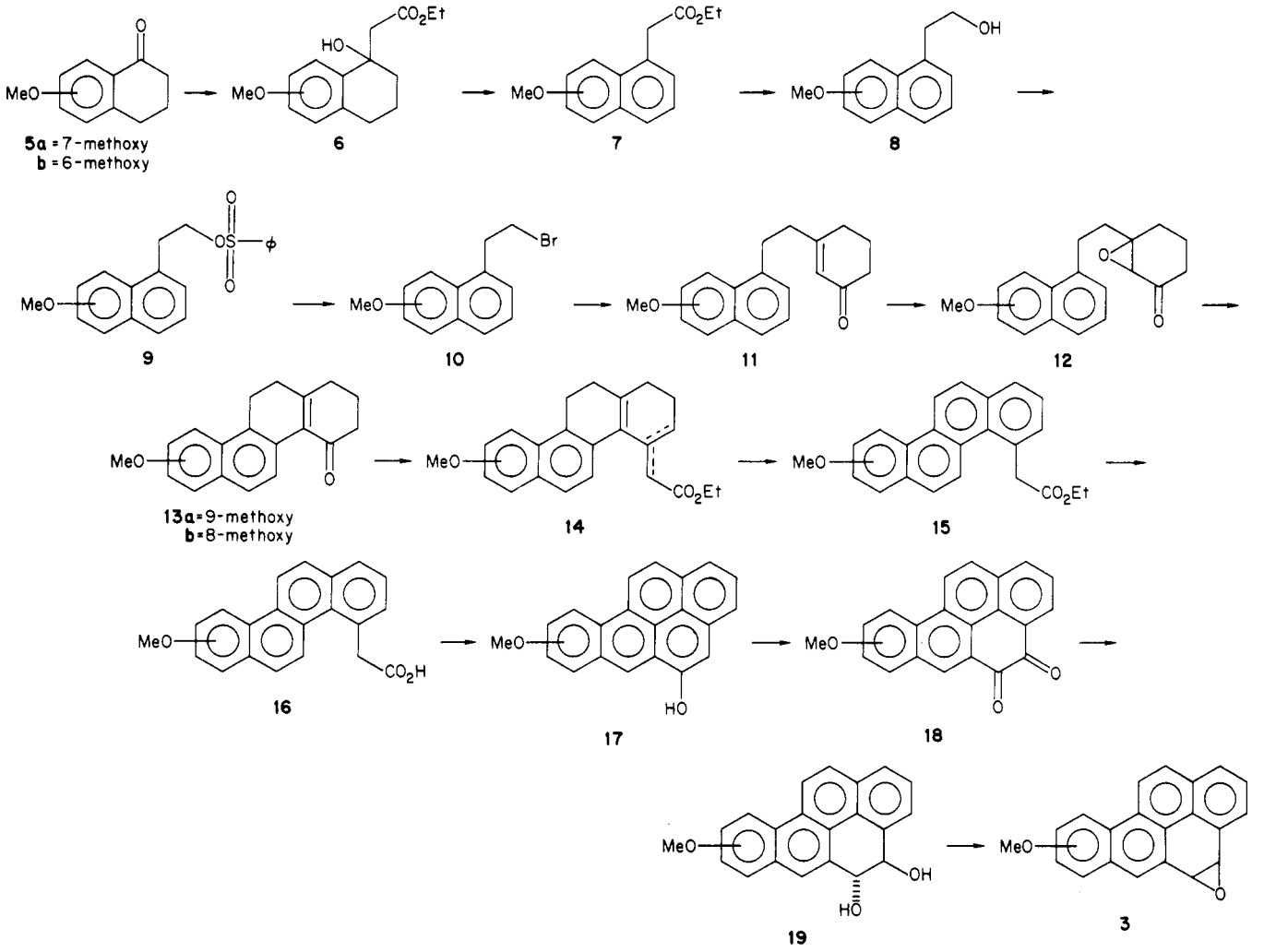
(6) Hylarides, M. D.; Lyle, T. A.; Daub, G. H.; Vander Jagt, D. L.; *J. Org. Chem.* **1979**, *44*, 4652.

(7) Cortez, C. N.; Harvey, R. G. *Carcinogenesis (London)* **1983**, *4*, 941. We thank Dr. Harvey for making the manuscript available to us prior to its publication.

(8) Jeffrey, Alan M., private communication.

0022-3263/85/1950-5550$01.50/0

Scheme I



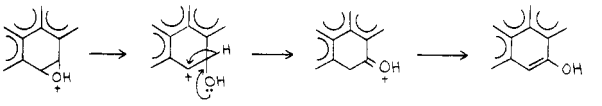
Synthesis

The syntheses of **3a** and **3b** are outlined in Scheme I. Our strategy for incorporating the labeled carbons toward the end of the reaction scheme required initial construction of a chrysene skeleton. Starting with the appropriate methoxytetralone, treatment with ethyl lithioactate[5] followed by dehydration and dehydrogenation (Pd/C, 250 °C) provided ester **7** in 77% yield. Conversion of **7** to bromide **10** was achieved in 76% yield over three steps: reduction by lithium aluminum hydride, formation of the benzenesulfonate ester, and displacement with potassium bromide.

The remaining carbons of the chrysene portion were provided by a Grignard coupling between **10** and 3-ethoxycyclohex-2-enone[9] to give **11** (49% yield). Ring closure (**11** → **13**) was achieved by modification of an epoxidation and cyclization sequence described by Trost.[10]

The carbon-13 labels were introduced by using ethyl acetate having 90% ^{13}C enrichment in either the carbonyl or methyl carbon.[12] Condensation between chrysenone **13** and ethyl lithioacetate (derived from the appropriately enriched ethyl acetate), followed by dehydration and dehydrogenation as above, gave ester **15**. Saponification of **15** to the chryseneacetic acid **16** and cyclization (neat methanesulfonic acid) provided phenol **17**. Without purification, **17** was directly oxidized with Fremy's salt to the quinone **18**. At this point, the preparation of **3** converged with that of the reported unlabeled synthesis.[7] With some modification, the two-step conversion of **18** to **3** followed that of Harvey and Cortez: KBH_4 reduction to the trans-dihydrodiol **19** and treatment with the dimethyl acetal of dimethylformamide to provide the epoxide **3**. The yield of **3** from chrysenone **13** was 10–15% for steps involving ^{13}C-labeled intermediates.

Scheme II



NIH Shift Studies

The acid-catalyzed isomerization of an arene oxide to a phenol is commonly referred to as the NIH shift. The mechanism, shown in Scheme II, involves a 1,2-hydride shift followed by keto–enol tautomerization.[13]

Since a benzylic carbocation is postulated as an intermediate, the direction of oxirane ring opening in epoxides **3a** and **3b** can be used to gauge the influence of the benzo ring methoxy group.

The rearrangement of **3a** and **3b** was performed by adding a catalytic amount of methanesulfonic acid, under

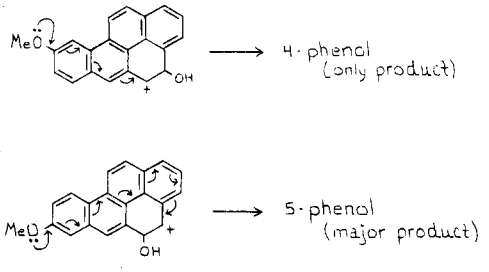
(9) Smith, A. B., III; Dieter, R. K. *J. Am. Chem. Soc.* **1981**, *103*, 2017.
(10) Trost, B. M.; Murayama, E.; Tetrahedron *Lett.* **1982**, *23*, 1047.
(11) Leon, A. A.; Daub, G. H.; Silverman, I. R.; *J. Org. Chem.* **1984**, *49*, 4544.
(12) Provided as a gift by the Los Alamos National Laboratory (Stable Isotope Resources).
(13) Jerina, D. M.; Daly, J. W.; Witkop, B. *J. Am. Chem. Soc.* **1968**, *90*, 6523.

Table I. ^{13}C NMR Shifts in ppm (Acetone-d_6)[a] of Products from the NIH Shift

compd	NMR shifts		
3a-5-^{13}C	105.46		
3a-4-^{13}C	151.96 (major)	150.71 (minor)[b]	
3b-4-^{13}C	152.29 (1.0)	105.39 (2.5)	74.00 (5.0)

[a] Relative intensities in parentheses. [b] The identity of the peak at 150.71 is unknown, and its intensity relative to the one at 151.96 diminishes with shorter reaction times.

Scheme III



nitrogen, to a stirred solution of labeled epoxide in dioxane (1 mg/mL). After 1 h, the solution was partitioned between water and ether. The organic layer was dried (Na_2CO_3) and concentrated to provide the crude phenol which was analyzed directly. Table I shows the ^{13}C NMR shifts for the rearranged epoxides.

As shown in Scheme III, the 9-methoxy group is expected to stabilize carbocation formation at C_5. Indeed, when epoxide **3a** underwent the NIH shift, the 4-phenol was formed exclusively.

Epoxide **3b** containing the 8-methoxy group underwent the NIH shift to give a 2:1 mixture of the 5- and 4-phenols. The predominance of the 5-phenol indicates that the C_8 methoxy group influences oxirane opening as shown in Scheme III. The peaks at 105.39 ppm and at 74.00 ppm compare with those of the synthetically prepared 5-phenol **17b** and trans-dihydrodiol **19b** (presumably formed during workup) in Scheme I.

Interestingly, the direction of ring opening in the NIH shift of these epoxides is affected more by the 9-methoxy group than by the 8-methoxy group. That the acid-catalyzed isomerization of **3b** proceeded to give both phenols may be due to the necessity of destroying aromaticity in all four rings of the chrysene aromatic system to achieve the stabilizing resonance hybrid. In the case of **3a**, carbocation stabilization by the 9-methoxy group disrupts only two rings, leaving a naphthalene system intact.

Experimental Section

Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Ruby Ju of the Department of Chemistry, University of New Mexico.

Both ^1H and ^{13}C NMR spectra were determined on a Varian FT-80A spectrometer. The ^1H and ^{13}C chemical shifts are reported as parts per million (ppm) downfield from tetramethylsilane (Me_4Si), and the ^{13}C chemical shifts were referenced to the solvent peaks: $CDCl_3$ (76.9 ppm), Me_2SO-d_6 (39.6 ppm), or acetone-d_6 (29.2 ppm). $CDCl_3$ was passed through basic alumina before use with epoxides or dihydrodiols. Infrared (IR) spectra were taken on a Perkin-Elmer 337 grafting infrared spectrophotometer or a Perkin-Elmer 710 spectrophotometer. The spectra were referenced with the 1601- and 1030-cm^{-1} bands of polystyrene. Mass spectra were taken on solid probe samples with a Finnigan Model 4500 gas chromatograph EI/CI mass spectrometer. UV-vis spectra and absorbances were recorded on a Cary 219 spectrophotometer.

The following adsorbents were used for gravity column chromatography: silica gel 60 (EM reagents, particle size 0.063–0.200 mm, 70–230 mesh ASTM), aluminum oxide Woelm neutral (activity grade 1), and aluminum oxide Woelm basic (activity grades 1 and 4). Medium-pressure chromatography was performed with silica gel Woelm (particle size 32–63 μm) with an FMI lab pump and an Eldex Universal fraction collector. R_f values were measured on glass plates coated with silica gel, 250 μm, containing a 254nm fluorescent indicator with an appropriate solvent.

7-Methoxy-1-tetralone (5a) was prepared by a procedure similar to that described by Snyder and Werber.[14] Molten γ-(*p*-anisyl)butyric acid (22.0 g, 0.113 mol, mp 65–70 °C) was added to 80 g of polyphosphoric acid which had been warmed to 80–85 °C. Under these conditions, a temperature of 90–100 °C is maintained by the reaction. After stirring for 3 min, an additional 70.0 g of polyphosphoric acid was added, and the mixture was heated to 90 °C with stirring for 4 min. The resulting solution was cooled, hydrolyzed, and worked up as previously described.[14] The product, 7-methoxy-1-tetralone (**5a**), was obtained as light yellow plates in 82% yield (16.46 g), mp 60–62 °C, lit.[14] mp 66–67 °C, and was suitable for further use.

Ethyl 1-Hydroxy-7-methoxy-1,2,3,4-tetrahydro-1-naphthaleneacetate (6a). To a mixture of 13.9 g (98.9 mmol) of *N*-isopropylcyclohexylamine in 50 mL of anhydrous THF, cooled to −78 °C, and under an N_2 atmosphere was added 61.8 mL of 1.6 M *n*-butyllithium (98.8 mmol) in hexane. This mixture was recooled to −78 °C, and 8.00 g (90.9 mmol) of ethyl acetate in 50 mL of anhydrous THF was added dropwise at such a rate as to maintain the reaction temperature below −75 °C. After the addition was complete, stirring was continued for 15 min after which time 16.00 g (90.8 mmol) of 7-methoxy-1-tetralone (**5a**), mp 60–62 °C, dissolved in 20 mL of anhydrous THF was added at a rate which maintained the temperature below −75 °C. After the addition was complete, stirring at −78 °C was continued for 1.5 h. The reaction mixture was hydrolyzed by the dropwise addition of 20 mL of concentrated HCl in 50 mL of THF at such a rate as to maintain the reaction mixture at a temperature below −70 °C. The mixture was allowed to warm to room temperature, and 125 mL of water and 125 mL of ether were added. The layers were separated, and the aqueous layer was washed with 60 mL of ether. The combined ether layers were extracted 2 times with 75-mL portions of 5% HCl, once with 75 mL of water, once with 75 mL of 5% $NaHCO_3$, and again with 75 mL of water and dried over anhydrous $MgSO_4$. Removal of the solvent afforded 23.00 g (96% yield) of ethyl 7-methoxy-1-hydroxy-1,2,3,4-tetrahydro-1-naphthaleneacetate (**6a**) as a pale yellow oil. The crude hydroxyester (**6a**) was suitable for further use. A small amount was distilled, bp 140–150 °C (0.06 mm), to obtain an analytical sample; TLC R_f 0.51 (alumina, benzene); IR (KBr) 1720 (C=O), 3470 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.62–7.12 (m, 3 H), 4.11 (q, 2 H, J = 7 Hz), 3.70 (s, 3 H), 2.58–2.73 (m, 4 H), 1.67–2.13 (m, 4 H), 1.19 (t, 3 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 171.92, 157.77, 141.51, 129.41, 128.10, 113.84, 110.41, 70.95, 60.32, 54.85, 45.83, 35.90, 28.21, 19.81 13.77. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.35; H, 7.40.

Ethyl 7-Methoxy-1-naphthaleneacetate (7a). In a dehydrogenation system fitted with a ground-glass cold finger condenser and gas inlet and outlet tubes were placed 20.0 g (75.7 mmol) of (**6a**), bp 140–150 °C (0.06 mm), 2.60 g of 10% Pd–C, 14.73 g (81.74 mmol) of 1,1-diphenylethylene, and 55 mL of 1-methylnaphthalene. The reaction mixture was heated to 250–260 °C (Wood's metal bath) for 3 h while steam was passed through the condenser and a slow flow of N_2 maintained. The cooled reaction mixture was diluted with toluene (200 mL) and filtered through Celite, and the catalyst was washed with an additional 100 mL of toluene. After removal of the toluene on a rotary evaporator, the 1-methylnaphthalene, 1,1-diphenylethane, and unreacted 1,1-diphenylethylene were removed on a Kugelrohr apparatus (50 °C, 0.03 mm).

Upon increasing the temperature of the Kugelrohr apparatus to 110–120 °C (0.03 mm), a yellow oil was obtained. This oil was dissolved in 125 mL of ether, extracted with two 60-mL portions of cold 5% NaOH, and dried over anhydrous $MgSO_4$. Removal of solvent afforded 14.97 g (81% yield) of ethyl 7-methoxy-1-

(14) "Organic Syntheses"; Wiley: New York, 1953; Collect. Vol. 3, p 798.

(15) Available from Aldrich Chemical Company.

naphthaleneacetate (**7a**) as a pale green oil and was suitable for further use: IR (KBr) 1738 (C=O); ^{1}H NMR ($CDCl_3$) δ 6.87–8.02 (m, 6 H), 4.03 (q, 2 H, J = 6 Hz), 3.84 (s, 2 H), 3.77 (s, 3 H), 1.07 (t, 3 H, J = 6 Hz); ^{13}C NMR ($CDCl_3$) δ 171.16, 157.74, 133.01, 129.83, 129.19, 129.01, 128.13, 127.33, 122.83, 117.91, 102.37, 60.46, 54.80, 39.29, 13.81. To obtain an analytical sample, a small amount of **7a** was hydrolyzed to 7-methoxy-1-naphthaleneacetic acid, mp 153–154 °C. Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.06; H, 5.48.

Ethyl 6-Methoxy-1-naphthaleneacetate (7b). In like manner to that described for the synthesis of **7a**, 16.00 g (90.80 mmol) of 6-methoxy-1-tetralone[15] was converted to 20.14 g of ester obtained as an orange oil that was suitable for use in the next step. This ester was unsaturated due to dehydration of **6b** during workup:[16] IR (KBr) 1730 (C=O); ^{1}H NMR ($CDCl_3$) δ 6.61–7.17 (m, 3 H), 5.82 (t, 1 H, J = 5 Hz), 4.10 (q, 2 H, J = 7 Hz), 3.72 (s, 3 H), 3.34 (s, 2 H, 2.72 (t, 2 H, J = 8 Hz), 2.10–2.36 (m, 2 H), 1.18 (t, 3 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 171.34, 158.32, 137.73, 129.54, 127.05, 125.87, 123.48, 113.55, 110.51, 60.15, 54.67, 38.83, 28.14, 22.81, 13.74.

Crude unsaturated ester (10.0 g) was directly dehydrogenated as described for the synthesis of **7a**. Subsequent distillation by the Kugelrohr (bp 110–120 °C, 0.05 mm) and aqueous base extraction provided **7b** as a pale green oil (7.93 g, 73% yield from **5b**) which was suitable for further use: IR (KBr) 1738 (C=O); ^{1}H NMR ($CDCl_3$) δ 6.97–7.76 (6 H, m), 3.96 (q, 2 H, J = 7 Hz), 384 (s, 2 H), 3.60 (s, 3 H), 1.01 (t, 3 H, J = 6 Hz); ^{13}C NMR ($CDCl_3$) δ 170.13, 156.59, 134.41, 130.06, 126.73, 126.59, 125.89, 125.08, 124.62, 117.78, 105.82, 59.60, 53.80, 38.00, 12.95. To obtain an analytical sample, a small amount of **7b** was hydrolyzed to 6-methoxy-1-naphthaleneacetic acid, mp 151–152 °C. Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.15; H, 5.48.

7-Methoxy-1-naphthaleneethanol (8a). To a stirred, ice-cold mixture of 12.58 g (0.331 mol) of lithium aluminum hydride in 150 mL of anhydrous ether was added 16.18 g (66.24 mmol) of ethyl 7-methoxy-1-naphthaleneacetate (**7a**) in 125 mL of anhydrous ether dropwise over a 1-h period. After addition of the ester solution, the mixture was warmed, and the mixture was stirred at room temperature overnight. The workup procedure required extreme care. The mixture was recooled in an ice bath, and 12.6 mL of water was added dropwise via syringe. The addition of water to the rapidly stirring mixture required that 1 drop be added only after the reaction caused by the previous drop had subsided. In like manner, 12.6 mL of 15% KOH solution was introduced followed by the addition of 25.2 mL of water. The flocculent mixture was filtered through Celite, and the solvent was removed in vacuo. Recrystallization from benzene afforded 12.59 g (94% yield) of 7-methoxy-1-naphthaleneethanol (**8a**) as a white powder: mp 81–82 °C, lit.[16] mp 83.5–85.5 °C; ^{13}C NMR ($CDCl_3$) δ 157.58, 133.00, 129.99, 129.19, 127.07, 126.57, 122.91, 117.53, 102.57, 62.30, 54.95, 36.00.

6-Methoxy-1-naphthaleneethanol (8b). In like manner to that described for the synthesis of **8a**, 7.33 g (30.04 mmol) of ethyl 6-methoxy-1-naphthaleneacetate (**7b**) was reduced. Subsequent distillation by the Kugelrohr method (bp 126° C, 0.110 mm) afforded 5.65 g (93% yield) of 6-methoxy-1-naphthaleneethanol (**8b**) as a colorless oil: IR (KBr) 3370 (C–OH); TLC R_f 0.49 (50% ethyl acetate in toluene), 0.32 (25% ethyl acetate in toluene); ^{1}H NMR ($CDCl_3$) δ 7.09–7.83 (m, 6 H), 3.86–3.90 (m, 5 H), 3.22 (t, 2 H, J = 6.5 Hz), 1.89–1.99 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 156.84, 134.81, 134.28, 127.16, 125.75, 125.62, 124.91, 124.42, 118.08, 106.35, 62.45, 54.72, 35.76. Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.27; H, 6.79.

1-(2-Bromoethyl)-7-methoxy-1-naphthalene (10a). To a stirred, ice-cold solution of 10.0 g (49.4 mmol) of 7-methoxy-1-naphthaleneethanol (**8a**) in 100 mL of pyridine was added 43.8 g of benzenesulfonyl chloride in 80 mL of pyridine over a 1-h period. After 2 h, the cloudy reaction mixture was poured into 170 g of ice, followed by successive extractions with 85 and 50 mL of toluene. The combined organic layers were washed 3 times with 50 mL of cold 5% HCl, once with 50 mL of water, twice with 50 mL of 5% $NaHCO_3$, and once with 50 mL of water. The toluene layer was dried over $MgSO_4$. Removal of the toluene provided crude sulfonate ester **9a** as a white solid: mp 77–79 °C; ^{1}H NMR ($CDCl_3$) δ 7.10–7.85 (m, 6 H), 4.34 (t, 2 H, J = 5.6 Hz), 3.88 (s, 3 H), 3.38 (t, 2 H, J = 5.6 Hz); ^{13}C NMR ($CDCl_3$) δ 157.96, 135.98, 133.34, 132.78, 130.34, 130.19, 129.13, 128.88, 127.63, 127.41, 127.05, 122.97, 118.14, 101.75, 69.75, 55.22, 32.85.

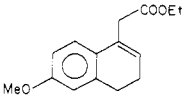
The crude sulfonate ester **9a** was directly dissolved in 80 mL of acetone and added to 8.0 g of 18-crown-6 ether and 16.0 g of KBr. The mixture was refluxed overnight. After removal of the acetone, 60 mL of ether was added to the white residue. The slurry was filtered, and the KBr–crown ether complex was rinsed with an additional 50 mL of ether. The KBr–crown ether complex was saved for future brominations. After removal of the ether, the resultant yellow oil was distilled by the Kugelrohr method to provide 10.67 g (81% yield) of **10a** as a clear oil: bp 132 °C (0.2 mm), lit.[17] bp 169 °C (0.4 mm); TLC R_f 0.47 (50% cyclohexane in toluene).

1-(2-Bromoethyl)-6-methoxy-1-naphthalene (10b). In like manner to that described for the synthesis of **10a**, 6.20 g (30.7 mmol) of 6-methoxy-1-naphthaleneethanol (**8b**) was stirred with benzenesulfonyl chloride in pyridine at room temperature. Crude sulfonate ester **9b** obtained was treated as described above to afford 1-(2-bromoethyl)-6-methoxy-1-naphthalene (5.46 g; 67% yield from **8b**) as white needles: mp 59–60 °C; ^{1}H NMR ($CDCl_3$) δ 6.89–7.62 (m, 6 H), 3.68 (s, 3 H), 3.36 (s, 2 H), 3.36 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 157.25, 135.12, 134.74, 126.42, 125.93, 124.48 (2 carbons), 118.70, 106,78, 55.04, 36.55, 31.80. Anal. Calcd for $C_{13}H_{13}OBr$: C, 58.89; H, 4.94. Found: C, 58.94; H, 5.11.

3-[2-(7-Methoxy-1-naphthyl)ethyl]-2-cyclohexenone (11a). In a 125-mL ground-glass Erlenmeyer flask fitted with a Claisen connecting tube and dropping funnel was placed 1.82 g (75.0 mmol) of magnesium turnings and a stirring bar. After being purged with nitrogen, the magnesium was covered with 10 mL of anhydrous ether. Through the dropping funnel was added about $^1/_4$ of a solution of **10a** (4.00 g, 15.0 mmol) and 1,2-dibromoethane (4.00 g, 21.3 mmol) in 31 mL ether. After a few minutes the reaction set in. The rest of the bromide/dibromoethane solution was added slowly over 1.5 h with stirring at a rate that maintained the reaction. After the addition was complete, the two-phase mixture was stirred for 1 h. The mixture was then cooled in an ice–water bath to 5–9 °C. A solution of 2.80 g (20.0 mmol) of 3-ethoxy-2-cyclohexenone in 23 mL of ether was added over a 0.5-h period to the cooled, stirred mixture. The cooling was maintained for 4 h, after which time the reaction mixture was allowed to warm slowly to room temperature and stir overnight. The Grignard adduct was hydrolyzed by slowly adding 30 mL of 10% HCl to the recooled mixture. The mixture was warmed and stirred for 1 h. After addition of 20 mL of ether and 20 mL of water, the organic layer was separated and washed successively with 30 mL of 5% HCl and 30 mL of water, three times with 30 mL of cold 5% NaOH, and once with 30 mL of saturated NaCl. The ether layer was dried over $MgSO_4$. After removal of solvent, the resultant orange oil was chromatographed through a short silica gel column with toluene and finally purified by medium-pressure chromatography (silica gel, 2% ethyl acetate in toluene). **11a** was obtained as a colorless oil which solidified upon standing: mp 76–77 °C; IR (KBr) 1670 (C=C—C=O); ^{1}H NMR ($CDCl_3$) δ 7.07–7.79 (m, 6 H), 5.96 (s, 1 H), 3.92 (s, 3 H), 3.06–3.25 (m, 2 H), 1.86–2.68 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 199.52, 165.37, 157.71, 135.17, 132.51, 130.34, 126.69, 126.19, 125.84, 123.09, 117.63, 102.16, 55.21, 38.28, 37.17, 30.70, 29.85, 22.54. Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.38; H, 7.19. Found: C, 81.27; H, 7.09.

3-[2-(6-Methoxy-1-naphthyl)ethyl]-2-cyclohexenone (11b). In like manner to that described for the synthesis of **11a**, **10b** (4.00 g, 15.0 mmol) was converted to the Grignard reagent which was allowed to react with 3-ethoxy-2-cyclohexenone. Workup as previously described provided 2.05 g (49% yield) of 3-2[(6-methoxy-1-naphthyl)ethyl]-2-cyclohexenone (**11b**) as a colorless oil which solidified on standing; mp 63–64 °C; TLC R_f 0.47 (25%

(16) The unsaturated ester has been assigned the structure shown at the side based on the spectroscopic evidence.



(17) Bachmann, W. E.; Horton, W. J. *J. Am. Chem. Soc.* **1947**, *69*, 58.
(18) Sims, P. *J. Chem. Soc.* **1968**, 32.

ethyl acetate in toluene); ^{1}H NMR ($CDCl_3$) δ 7.08–7.94 (m, 6 H), 5.97 (s, 1 H), 3.88 (s, 3 H), 3.05–3.25 (m, 2 H), 1.83–2.62 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 199.09, 164.98, 157.02, 136.48, 134.92, 126.64, 125.81, 125.67, 125.56, 124.51, 123.42, 118.28, 106.60, 54.87, 38.56, 36.96, 30.31, 29.54, 22.33; mass spectrum, *m/e* (relative intensity) 280 (24), 171 (100), 128 (28). Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19. Found: C, 81.36; H, 7.10.

3-[2-(7-Methoxy-1-naphthyl)ethyl]cyclohexanone 2,3-Oxide (12a). To a stirred solution of 3.46 g (12.3 mmol) of **11a** in 130 mL of absolute ethanol was added 5.00 mL (44.2 mmol) of 30% H_2O_2. The mixture was cooled in an ice–water bath to 15–20 °C, and 1.90 mL (11.4 mmol) of 6 N NaOH was added dropwise. The temperature was maintained at about 20 °C, and stirring was continued for 3 h. The mixture was then poured into 200 mL of water and extracted twice with 120 mL of ether. The combined ether extracts were washed twice with 60 mL of water and dried over $MgSO_4$. Removal of solvent in vacuo provided 3.22 g (88% yield) of the oxide **12a** as a pale green oil: IR (KBr) 1720 (C=O); ^{1}H NMR ($CDCl_3$) δ 7.11–7.81 (m, 6 H), 3.93 (s, 3 H), 3.03–3.24 (m, 3 H), 1.56–2.25 (m, 6 H), 1.26 (t, 2 H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 205.96, 157.92, 135.39, 132.64, 130.35, 129.43, 126.75, 126.23, 123.13, 117.78, 102.50, 65.13, 61.09, 55.26, 36.43, 35.81, 27.94, 26.65, 17.55. Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.29; H, 6.90

9-Methoxy-1,2,11,12-tetrahydrochrysen-4(3*H*)-one (13a). To a solution of 3.33 g (11.23 mmol) of the oxide **12a** in 500 mL of dichloromethane was added 50 g of methanesulfonic acid. The deep red mixture was stirred at room temperature for 2 h under a nitrogen atmosphere and then poured over ice. The organic layer was washed with 200-mL portions of water, 5% $NaHCO_3$, and again with water. After drying over $MgSO_4$, the solvent was removed in vacuo. Recrystallization from toluene provided 1.97 g (62% yield) of 9-methoxy-1,2,11,12-tetrahydrochrysen-4(3*H*)-one (**13a**) as white flakes, mp 153–155 °C. The mother liquor which contained approximately 0.29 g (9% yield) of product was saved for purification by medium-pressure chromatography (silica gel, 2% ethyl acetate in toluene): TLC R_f 0.49 (25% ethyl acetate in toluene); IR (KBr) 1660 (C=CC=O); ^{1}H NMR ($CDCl_3$) δ 7.16–8.06 (m, 5 H), 3.92 (s, 3 H), 3.08 (t, 2 H, J = 7 Hz), 2.48–2.71 (m, 6 H), 2.06 (q, 2 H, J = 6 Hz); ^{13}C NMR ($CDCl_3$) δ 196.92, 159.59, 157.54, 131.42, 129.80, 129.67, 128.28, 125.27, 123.23, 117.42, 102.35, 55.11, 39.24, 31.87, 30.39, 22.30, 21.76. Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 81.82; H, 6.40.

8-Methoxy-1,2,11,12-tetrahydrochrysen-4(3*H*)-one (13b). In like manner to that described for the synthesis of **13a**, the ketone **11b** (1.73 g, 6.17 mmol) was converted to the epoxy ketone **12b**. The yellow oil obtained after workup was chromatographed on neutral alumina using toluene to provide 1.32 g of the oxide **12b** as a light green oil. The epoxy ketone **12b** was then directly added to 5% methanesulfonic acid in dichloromethane. TLC analysis after 1 h showed the reaction to be complete. After workup as previously described, the dark green oil was purified by medium-pressure chromatography (silica gel, toluene) to provide 0.76 g (44% yield from **11b**) of 8-methoxy-1,2,11,12-tetrahydrochrysen-4(3*H*)-one (**13b**) as a white powder: mp 131–133 °C; TLC R_f 0.56 (25% ethyl acetate in toluene); ^{1}H NMR ($CDCl_3$) δ 7.07–8.18 (m, 5 H), 3.41 (s, 3 H), 3.12 (t, 2 H, J = 8 Hz), 2.51–2.73 (m, 6 H), 2.15 (q, 2 H, J = 6 Hz); ^{13}C NMR ($CDCl_3$) δ 196.76, 158.78, 156.80, 133.75, 130.94, 130.78, 126.32, 125.94, 125.78, 124.76, 124.04, 117.84, 105.99, 54.81, 38.99, 31.47, 29.99, 21.92, 21.51.

Ethyl 9-Methoxy-4-chryseneacetate (15a). To a stirred mixture of 0.31 g (2.20 mmol) of *N*-isopropylcyclohexylamine in 1.4 mL of anhydrous THF, cooled to −78 °C and under a nitrogen atmosphere, was added 1.37 mL of 1.6 M *n*-butyllithium (2.20 mmol) in hexane. The mixture was recooled to −78 °C and 0.176 g (2.00 mmol) of ethyl acetate in 1.4 mL of THF was added dropwise. After 15 min, 9-methoxy-1,2,11,12-tetrahydrochrysen-4(3*H*)-one (**13a**) (0.55 g, 1.98 mmol) in 10 mL of THF was added as a nonhomogeneous mixture at a rate which maintained the reaction temperature below −75 °C, and stirring was continued for 3 h. The reaction mixture was hydrolyzed by the dropwise addition of 0.4 mL of concentrated HCl in 1.4 mL of THF at such a rate as to maintain the reaction mixture below −70 °C. The mixture was allowed to warm to room temperature and worked up as described in the preparation of **6a**. Crude product, obtained as a yellow oil (690 mg), was dehydrated and dehydrogenated to **15a** directly, according to the procedure described in the preparation of **7a**.

Thus, 1,1-diphenylethylene (0.80 g, 4.46 mmol) and 10% Pd–C (0.112 g) were added to 690 mg of the above crude product in 8.4 mL of 1-methylnaphthalene and heated to 250–260 °C for 3 h. The cooled reaction mixture was diluted with 10 mL of toluene and filtered through Celite, and the catalyst was washed with an additional 25 mL of toluene. After removal of the toluene on a rotary evaporator, the remaining solvents were removed by the Kugelrohr method as previously described. The brown oily residue was chromatographed on silica gel with toluene and finally purified by medium-pressure chromatography (silica gel, 5% hexanes in toluene) to provide ethyl 9-methoxy-4-chryseneacetate (**15a**) (256 mg, 38% from **13a**) as a white powder: mp 96–97 °C; TLC R_f = 0.55 (10% ethyl acetate in toluene); ^{1}H NMR ($CDCl_3$) δ 7.18–8.65 (m, 10 H), 4.46 (s, 2 H), 4.24 (q, 2 H, J = 7 Hz), 4.05 (s, 3 H), 1.24 (t, 3 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 171.48, 157.86, 133.23, 131.40, 131.21, 130.76, 130.29, 128.96, 128.44, 128.20, 127.89, 127.12, 126.09, 125.13, 124.88, 122.09, 120.73, 116.98, 103.34, 60.43, 54.64, 43.29, 13.67. Anal. Calcd for $C_{23}H_{20}O_3$: C, 80.21; H, 5.85. Found: C, 80.28; H, 6.05.

9-Methoxy-4-chryseneacetic Acid (16a). A stirred mixture of 400 mg (1.27 mmol) of the ester **15a** and 0.40 g (7.1 mmol) of KOH in 35 mL of 95% ethanol and 15 mL of water was refluxed for 2 h. After cooling, 15 mL of 5% NaOH was added, and the reaction mixture was extracted with 2 15-mL portions of ether, filtered through Filter-cel, and acidified to give crude 9-methoxy-4-chryseneacetic acid (**16a**). Recrystallization from toluene afforded 271 mg (74% yield) of **16a** as white flakes: mp 206–207 °C; ^{13}C NMR (Me_2SO-d_6) δ 173.26, 158.51, 133.53, 132.68, 132.31, 131.55, 129.73, 128.62, 128.35, 126.27, 126.12, 125.58, 122.27, 121.87, 118.08, 104.14, 55.68, 43.96.

9-Methoxy-4-chryseneacetic-*carboxy*-^{13}*C* Acid (16a-*carboxy*-^{13}*C*). In like manner to that described for the synthesis of **15a**, 9-methoxy-1,2,11,12-tetrahydrochrysen-4(3*H*)-one (**13a**) (400 mg, 1.44 mmol) was treated with the lithio enolate of ethyl acetate-*carboxy*-^{13}*C* (176 mg, 1.98 mmol). The crude mixture of esters **14a**-*carboxy*-^{13}*C* obtained was directly dehydrated and dehydrogenated. After removal of the solvents by the Kugelrohr method, the dark brown oily residue was chromatographed on silica gel with toluene, providing ethyl 9-methoxy-4-chryseneacetate-*carboxy*-^{13}*C* (**15a**-*carboxy*-^{13}*C*) as a light brown oil which was suitable for use in the next step: ^{13}C NMR of **15a**-*carboxy*-^{13}*C* ($CDCl_3$) δ 171.93 (−*COOEt). Without further purification, **15a**-*carboxy*-^{13}*C* was directly saponified as described in the synthesis of **16a**. Thus, 9-methoxy-4-chryseneacetic-*carboxy*-^{13}*C* acid (**16a**-*carboxy*-^{13}*C*) (240 mg, 53% yield from **13a**) was obtained as light tan flakes: mp 208–208.5 °C; TLC R_f 0.18 (50% ethyl acetate in toluene); ^{1}H NMR (acetone-d_6) δ 7.25–8.78 (m, 10 H), 4.55 (d, 2 H, J = 8 Hz), 4.11 (s, 3 H); ^{13}C NMR (acetone-d_6) δ 172.77 (−*COOH). Anal. Calcd for $C_{20}{}^{13}CH_{16}O_3$ (90%) and $C_{21}H_{16}O_3$ (10%): C, 79.79; H, 5.08. Found: C, 80.08, H, 5.19.

9-Methoxy-4-chryseneacetic-α-^{13}*C* Acid (16a-α-^{13}*C*). In like manner to that described for the synthesis of **15a**-*carboxy*-^{13}*C*, **13a** (1.10 g, 3.95 mmol) was treated with the lithio enolate of ethyl acetate-α-^{13}*C* (0.352 g, 3.95 mmol). Dehydration and dehydrogenation followed by workup as described above provided ethyl 9-methoxy-4-chryseneacetate-α-^{13}*C* (**15a**-α-^{13}*C*) as a light brown oil suitable for use in the next step: ^{13}C NMR ($CDCl_3$) δ 43.99 (−*CH_2COOEt).

Without further purification, **15a**-α-^{13}*C* was directly saponified as described in the synthesis of **16a** except that after acidification, rather than filtering the precipitated product, it was extracted into ether. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo to provide a light brown solid residue. Recrystallization from toluene afforded 9-methoxy-4-chryseneacetic-α-^{13}*C* acid (**16a**-α-^{13}*C*) (320 mg, 26% yield from **13a**) as light tan flakes: mp 206–207 °C; ^{13}C NMR (acetone-Δ_6) δ 43.50 (−*CH_2COOH).

8-Methoxy-4-chryseneacetic-α-^{13}*C* Acid (16b-α-^{13}*C*). In like manner to that described for synthesis of **15a**, 8-methoxy-1,2,11,12-tetrahydrochrysen-4(3*H*)-one (**13b**) (0.48 g, 1.71 mmol) was treated with the lithium enolate of ethyl acetate-α-^{13}*C* (0.176 g, 1.98 mmol). The crude mixture of esters **14b**-α-^{13}*C* obtained was directly dehydrated and dehydrogenated. After removal of

solvents by the Kugelrohr method, the dark brown oily residue was chromatographed on silica gel with toluene. Solvent removal at reduced pressure afforded ethyl 8-methoxy-4-chryseneacetate-α-^{13}C (**15b**-α-^{13}C) which was obtained as a tan, viscous oil and which solidified upon standing: mp 101–102 °C; TLC R_f 0.52 (10% ethyl acetate in toluene); ^{1}H NMR ($CDCl_3$) δ 7.28–8.60 (m, 10 H), 4.45 (d, 2 H, J = 119 Hz), 4.23 (q, 2 H, J = 7 Hz), 3.97 (s, 3 H), 1.23 (t, 3 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 43.82 (–*CH_2COOEt); mass spectrum, m/e 345.3 (M^+), 272.2, 257.2, 240.2, 228.2, 113.6.

Without further purification, **15b**-α-^{13}C was directly saponified as described in the synthesis of **16a**. 8-Methoxy-4-chryseneacetic-α-^{13}C acid (**16b**-α-^{13}C) (185 mg, 34% yield from **13b**) was obtained as white flakes: mp 213–215 °C; TLC R_f 0.17 (50% ethyl acetate in toluene); ^{1}H NMR (acetone-d_6) δ 7.27–8.86 (m, 10 H), 4.54 (d, 2 H, J = 127 Hz), 4.02 (s, 3 H); ^{13}C NMR (acetone-d_6) 43.51 (–*CH_2COOH). Anal. Calcd for $C_{20}{}^{13}CH_{16}O_3$ (90%) and $C_{21}H_{16}O_3$ (10%): C, 79.79; H, 5.08. Found: C, 79.90; H, 5.10.

9-Methoxy-4,5-dihydrobenzo[*a*]pyrene-4,5-dione-*5*-^{13}C (18a-*5*-^{13}C). A solution of 9-methoxy-4-chryseneacetic-*carboxy*-^{13}C acid (**16a**-*carboxy*-^{13}C) (200 mg, 0.63 mmol) in 13 mL of methanesulfonic acid under a nitrogen atmosphere was stirred for 30 min at 50 °C. The deep red complex was hydrolyzed by pouring it into 100 g of ice water, and the brown precipitate of 9-methoxybenzo[a]pyren-5-ol-*5*-^{13}C (**17a**-*5*-^{13}C) which was collected was directly dissolved in 32 mL of acetone and added to a solution of 0.42 g (1.55 mmol) dipotassium nitrosodisulfonate (Fremy's salt) in 25 mL of water buffered with 6.3 mL 0.167 M KH_2PO_4. The yellow-brown solution was shaken for 2 h. To ensure complete oxidation 5 mL of acetone was added followed by addition of a fresh solution of 0.14 g of Fremy's salt in 4 mL of water buffered with 1.0 mL of 0.167 M KH_2PO_4. After shaking for another 2 h, the red-brown precipitate which formed was collected and heated with 75 mL of 5% aqueous Na_2CO_3 for 30 min at 70–80 °C. After filtering, the red precipitate was dried and chromatographed on silica gel with warm $CHCl_3$. The fractions containing product appeared bright red. These were combined and reduced in volume to about 6 mL, and ethyl acetate (4 mL) was added to facilitate crystallization. A second crop obtained provided a total of 150 mg (76% yield from **16a**-*1*-^{13}C) of 9-methoxy-4,5-dihydroxybenzo[a]pyrene-4,5-dione-*5*-^{13}C (**18a**-*5*-^{13}C) as red-orange crystals: mp >265 °C (lit.[17] mp >265 °C). **17a**-*5*-^{13}C: ^{13}C NMR ($CDCl_3$) 151.06 (*C_5); UV–vis (CH_2Cl_2) absorption maxima in nm (log ϵ) are 258 (5.27), 264 (5.27), 280 (4.80), 291 (4.62), 315 (4.18). **18a**-*5*-^{13}C: ^{13}C NMR ($CDCl_3$) δ 180.11 (–*COCO–) (C_5); mass spectrum, m/e 313, 285, 284, 242, 241, 213, 142, 106.

9-Methoxy-4,5-dihydrobenzo[*a*]pyrene-4,5-dione-*4*-^{13}C (18a-*4*-^{13}C). In like manner to that described for the synthesis of **18a**-*5*-^{13}C, 9-methoxy-4-chryseneacetic-2-^{13}C acid (**16a**-α-^{13}C) (250 mg, 079 mmol) was converted to 9-methoxy-4,5-dihydrobenzo[a]pyrene-4,5-dione-*4*-^{13}C (**18a**-*4*-^{13}C) (165 mg, 65% yield): mp >265 °C; ^{13}C NMR ($CDCl_3$) 180.83 (*C_4).

8-Methoxy-4,5-dihydrobenzo[*a*]pyrene-4,5-dione-*4*-^{13}C (18b-*4*-^{13}C). In like manner to that described for the synthesis of **18a**-*5*-^{13}C, 8-methoxy-4-chryseneacetic-α-^{13}C (**16b**-α-^{13}C) (100 mg, 0.32 mmol) was dissolved in methanesulfonic acid resulting in the gradual formation of a deep purple solution. After hydrolysis in ice water, 8-methoxybenzo[a]pyrene-5-ol-*4*-^{13}C (**17b**-*4*-^{13}C) was collected as a yellow-green precipitate. Fremy's salt oxidation as described above provided 8-methoxy-4,5-dihydroxybenzo[a]pyrene-4,5-dione-*4*-^{13}C (**18b**-*4*-^{13}C) (59 mg, 63% yield from **16b**-α-^{13}C) as an orange-red powder, mp >270 °C. **17b**-*4*-^{13}C: ^{13}C NMR (acetone-d_6) δ 105.28 (*C_4). ^{13}C NMR of **18b**-*4*-^{13}C ($CDCl_3$) δ 180.55 (*C_4).

9-Methoxy-4,5-dihydrobenzo[*a*]pyrene-*5*-^{13}C 4,5-Oxide (3a-*5*-^{13}C). A suspension of 55 mg (0.18 mmol) of 9-methoxy-4,5-dihydrobenzo[a]pyrene-4,5-dione-*5*-^{13}C (**18a**-*5*-^{13}C) in 15 mL of freshly distilled 2-propanol was placed in a vibrasonic bath for 2 min. The resultant fine suspension of quinone **18a**-*5*-^{13}C was stirred, during the addition of 0.92 g (17 mmol) of KBH_4 as a fine powder. The reaction mixture was then stirred for 30 h at reflux. The yellow solution was cooled to 0 °C and hydrolyzed by the dropwise addition of 2 N HCl (approximately 18 mL) without allowing allowing the pH to become acidic. Cold ether (35 mL) and water (15 mL) were then added to the hydrolysate. The organic layer was washed with 15-mL portions of water, 5% $NaHCO_3$, and again with water and dried over $MgSO_4$. After filtration to remove the drying agent, the ether was removed in vacuo. The dark brown solid obtained was triturated with warm $CHCl_3$ (pretreated with basic alumina), cooled, and filtered to provide 39 mg (70% yield) of *trans*-9-methoxy-4,5-dihydrobenzo[a]pyrene-4,5-diol-*5*-^{13}C (**19a**-*5*-^{13}C) as a light tan solid: mp 195–196 °C, lit.[7] mp for **19a** 201–202 °C; TLC R_f 0.19 (25% ethyl acetate in toluene); ^{13}C NMR(Me_2SO-d_6) δ 72.83 (–*CH–OH)(*C_5).

The dehydration of **19a**-*5*-^{13}C to **3a**-*5*-^{13}C was performed with freshly distilled tetrahydrofuran (THF) and dimethylformamide (DMF) and dimethylformamide dimethyl acetal (DMA–DMF) that had been passed through a short basic alumina column prior to use. DMA–DMF (0.171 mL, 1.60 mmol) was added to a stirred solution of the trans-dihydrodiol **19a**-*5*-^{13}C prepared above in THF (3.0 mL) and DMF (1.0 mL), and the yellow solution was stirred at reflux in the dark overnight. After cooling, 15 mL of ether was added, and the organic layer was washed with 3 10-mL portions of cold water and dried over Na_2CO_3. Separation of dessicant and solvent provided 22 mg (42% yield from **18a**-*5*-^{13}C) of 9-methoxy-4,5-dihydrobenzo[a]pyrene-*5*-^{13}C 4,5-oxide (**3a**-*5*-^{13}C) as a pale yellow solid: mp 146–149 °C dec, lit.[7] mp 155–156 °C dec; ^{13}C NMR ($CDCl_3$) δ 56.85 (C*$_5$); mass spectrum, m/e: 299 (M^+), 284, 256, 227, 111, 97, 83, 69, 55.

9-Methoxy-4,5-dihydrobenzo[*a*]pyrene-*4*-^{13}C 4,5-Oxide (3a-*4*-^{13}C). In like manner to that described for the synthesis of **3a**-*5*-^{13}C, quinone **18a**-*4*-^{13}C (36 mg, 0.115 mmol) was reduced to the trans-dihydrodiol **19a**-*4*-^{13}C (22 mg), mp 191–192 °C. ^{13}C NMR (acetone-d_6) of **16a**-*4*-^{13}C δ 74.01 (*C_4). ^{13}C NMR (Me_2SO-d_6) of **19a**-*4*-^{13}C δ 72.61 (*C_4); UV–vis (EtOH) absorption maxima in nm (log ϵ) are 271 (4.70), 308 (3.97), 326 (3.82); mass spectrum, m/e 317 (M^+).

Dehydration of **19a**-*4*-^{13}C to **3a**-*4*-^{13}C as described above provided 9-methoxybenzo[a]pyrene-*4*-^{13}C 4,5-oxide (**3a**-*4*-^{13}C) (11 mg, 32% yield from **18a**-*4*-^{13}C) as a pale yellow solid: mp 145–157 °C dec; ^{13}C NMR ($CDCl_3$) δ 56.16 (*C_4).

8-Methoxy-4,5-dihydrobenzo[*a*]pyrene-*4*-^{13}C 4,5-Oxide (3b-*4*-^{13}C). In like manner to that described for the synthesis of **3a**-*5*-^{13}C, quinone **18b**-*4*-^{13}C (44 mg, 0.140 mmol) was reduced to provide *trans*-8-methoxy-4,5-dihydrobenzo[a]pyrene-4,5-diol-*4*-^{13}C (**19b**-*4*-^{13}C) (38 mg) as a light tan solid: mp 195–198 °C; TLC R_f 0.15 (25% ethyl acetate in toluene); ^{13}C NMR (acetone-d_6) δ 74.02 (*C_4).

The crude trans-dihydrodiol **19b**-*4*-^{13}C was directly cyclized as previously described to provide 23 mg (55% yield from **18b**-*4*-^{13}C) of 8-methoxybenzo[a]pyrene-*4*-^{13}C 4,5-oxide (3b-*4*-^{13}C) as a tan solid: mp 151–153 °C dec, shrinkage 134 °C; TLC R_f 0.35 (toluene); ^{13}C NMR ($CDCl_3$) δ 56.20 (*C_4).

8-Methoxybenzo[*a*]pyrene. A solution of 0.200 g (0.581 mmol) of ethyl 8-methoxy-4-chryseneacetate (**15b**), prepared from 8-methoxy-1,2,11,12-tetrahydrochrysen-4(3*H*)-one (**13b**) as previously described, was dissolved in 9 mL of dry toluene and cooled to –78 °C under a nitrogen atmosphere. To the stirred solution was added 0.92 mL (0.60 mmol) of diisobutylaluminum hydride (0.65 M in hexane). After 45 min, the reaction was quenched by the addition of 0.25 mL of concentrated HCl in 2.5 mL of THF. Upon warming to room temperature, 10 mL of ether was added to the pale yellow solution, and the organic layer was washed with 10-mL portions of 5% HCl and twice with water. After drying over $MgSO_4$, removal of the solvent provided 150 mg of the aldehyde as a yellow oil.

The crude aldehyde was directly dissolved in 15 mL of dichloromethane. Upon addition of 1.60 g of methanesulfonic acid, the solution turned dark blue and was allowed to stir under a nitrogen atmosphere overnight at room temperature. The reaction mixture was hydrolyzed by pouring into ice–water. The organic layer, including an additional 15 mL of dichloromethane for rinsing, was washed with water, 5% $NaCHO_3$, and again with water. After drying over $MgSO_4$ and removing the solvent, the residue was dissolved in toluene and chromatographed on neutral alumina with toluene. 8-Methoxybenzo[a]pyrene (90 mg, 54% yield from **15b**) was obtained as light green crystals: mp 185–186 °C, lit.[18] mp 188 °C; TLC R_f 0.73 (25% ethyl acetate in toluene); ^{13}C NMR ($CDCl_3$) δ 157.66, 130.76, 127.70, 127.35, 125.32, 124.65, 124.46, 123.54, 123.34, 121.79, 118.41, 106.51, 55.27; mass spectrum, m/e 282 (M^+).

9-Methoxybenzo[*a*]pyrene-*5*-^{13}C. In like manner to that

described for the synthesis of 8-methoxybenzo[a]pyrene, 50 mg (0.145 mmol) of ethyl 9-methoxy-4-chryseneacetate-*1*-^{13}C (**15a**-*carboxy*-^{13}C) was converted to 9-methoxybenzo[a]pyrene-*5*-^{13}C by initial treatment with diisobutylaluminum hydride followed by diluted methanesulfonic acid. Workup and chromatography as described provided 9-methoxybenzo[a]pyrene-*5*-^{13}C (26 mg, 64% yield from **15a**-*carboxy*-^{13}C) as bright greenish yellow flakes: mp 144.5–147 °C, lit.[18] mp 150 °C; TLC R_f 0.71 (toluene); ^{13}C NMR ($CDCl_3$) δ 128.06 (*C_5).

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Synthesis, Rapid Resolution, and Determination of Absolute Configuration of Racemic 2,2′-Binaphthyldiyl Crown Ethers and Analogues via β-Cyclodextrin Complexation

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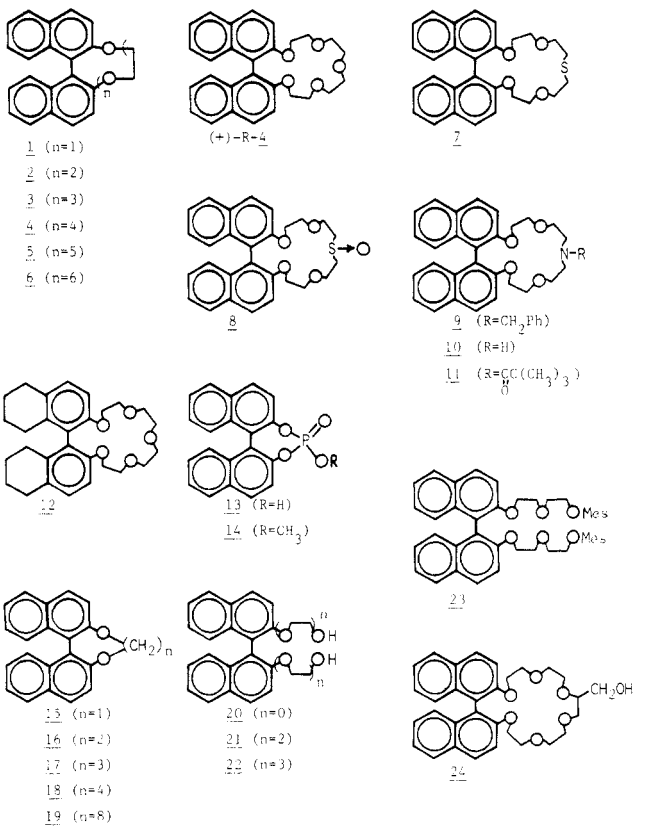
Twenty racemic and four diastereomeric 2,2′-binaphthyldiyl crown ethers and analogues were synthesized. Chiral interactions between these compounds and immobilized β-cyclodextrin were examined. Thirteen of the enantiomeric pairs and two of the diastereomers were successfully resolved. It was found that relatively small changes in the structure of these compounds could have large effects on chiral recognition. In general, the (−)-*S* enantiomers formed stronger inclusion complexes with β-cyclodextrin than did the (+)-*R* enantiomers.

It is well-known that cyclodextrins can catalyze certain hydrolyses and transacylation reactions of racemic substrates with some degree of stereospecificity.[1-11] More recently, properly immobilized cyclodextrins have been shown to produce highly efficient separations of some enantiomers.[12-18] Previously, in somewhat analogous studies, Cram and co-workers studied the chiral interaction and separation of organoamines with chiral crown ethers.[19-22] Despite extensive bodies of work on both cyclodextrins and crown ethers, little has been done to study the interactions and complexes between these compounds. In one of the few studies in this area, Vögtle and Müller have reported that small symmetrical crown ethers and cryptands will crystallize with γ-cyclodextrin as 1:1 and 2:1 complexes.[23]

In the present work several racemic and diastereomeric 2,2′-binaphthyldiyl crown ethers and analogues have been synthesized. Chiral interaction and separation of these species via complexation by immobilized β-cyclodextrin were studied. As a result of the high degree of chiral recognition in this system, β-cyclodextrin bonded phases offer a convenient means to separate optical isomers of many 2,2′-binaphthyldiyl derivatives, in addition to evaluating the optical purity of syntheses involving such compounds and determining the absolute configuration of structurally related compounds.

Results and Discussion

Synthesis. Racemic 2,2′-binaphthyldiyl-11-crown-3 **2**, 2,2′-binaphthyldiyl-14-crown-4 **3**, and 2,2′-binaphthyldiyl-20-crown-6 **5** were prepared by condensation of racemic 1,1′-bi-2-naphthol (**20**) with the appropriate ditosylates in a CsF–CH_3CN reaction mixture.[24,25] Isolated yields of **2**, **3**, and **5** were 73%, 18%, and 55%, respectively. Optically active (+)-(*R*)-2,2′-binaphthyldiyl-17-crown-5 **4**



was also obtained by the cesium-assisted cyclization of (+)-(*R*)-1,1′-bi-2-naphthol with tetraethylene glycol dito-

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(1) Van Etten, R. L.; Sebastian, J. F.; Clowes, G. A.; Bender, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 3242.
(2) Van Hooidonk, C. *Recl. Trav. Chim. Pays-Bos* **1972**, *91*, 1103.
(3) Daffe, V.; Fastrez, J. *J. Am. Chem. Soc.* **1980**, *102*, 3601.
(4) Cooper, A. MacNicol, D. D. *J. Chem. Soc., Perkin Trans. 2* **1978**, 760.

0022-3263/85/1950-5556$01.50/0