Steven Djuric, and Gilbert Adelstein for helpful suggestions in preparation of the manuscript.

Registry No. (±)-**5**, 59367-20-3; (±)-**6**, 72521-93-8; **12**, 14963-96-3; **13**, 150-78-7; **14**, 52541-76-1; (±)-**16**, 115514-87-9; (±)-**17**, 115514-88-0; **18**, 115514-89-1; **19**, 115514-90-4; **20**, 115514-91-5; **28**, 2961-04-8; **29**, 59326-07-7; **30**, 64831-67-0; **31**, 70071-71-5; (±)-**32**, 115514-92-6; (±)-**33**, 115514-93-7; (±)-**34**, 115514-94-8; (±)-**35**, 115514-95-9; (±)-**36**, 115514-96-0; (±)-**37**, 115514-97-1; (±)-**42**, 71571-58-9; (±)-**45**, 115514-98-2; (±)-**50**, 115533-09-0; (±)-**53**, 115515-02-1; (±)-**54**, 84938-46-5; (±)-**55**, 71571-60-3; (±)-**58**, 115515-06-5; (±)-**59**, 115515-08-7; (±)-**63**, 115515-09-8; (±)-**64**, 115514-99-3; (±)-**65**, 115515-01-0; (±)-**66**, 115515-03-2; (±)-**67**, 115515-04-3; (±)-**68**, 115515-05-4; (±)-**69**, 115515-07-6; (±)-**70**, 115515-10-1; (±)-**71**, 115515-00-9; C_2H_2, 74-86-2.

New Synthetic Approaches to Cyclopenta[*a*]phenanthrenes and Their Carcinogenic Derivatives

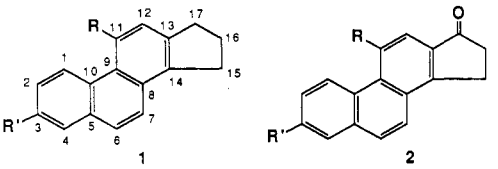
Hongmee Lee and Ronald G. Harvey*

Ben May Institute, University of Chicago, Chicago, Illinois 60637

Received February 24, 1988

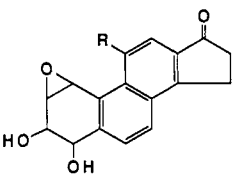
A new general synthetic approach to cyclopenta[*a*]phenanthrenes including their carcinogenic 11-methyl (**1b**) and 17-keto (**2d** and **2b**) derivatives is reported. The simplest example entails alkylation of the bromomagnesium salt of an enamine derivative of cyclopentanone with 2-(1-naphthyl)ethyl iodide followed by acidic hydrolysis, acid-catalyzed cyclization of the alkylated cyclopentanone, and dehydrogenation of the product over a Pd catalyst. Although reaction of the resulting cyclopenta[*a*]phenanthrenes with DDQ in acetic acid affords a mixture of ketones formed by oxidation at both benzylic sites, regiospecific oxidation at the 17-position may be achieved by prior hydrogenation of the 6,7-bond. These synthetic methods provide good overall yields of cyclopenta[*a*]phenanthrenes in relatively few steps. The method is potentially adaptable to the synthesis of the biologically active diol epoxide metabolites.

Although the carcinogenic properties of cyclopenta[*a*]phenanthrene derivatives have been known for many years, compounds in this class have attracted relatively little attention. However, renewed interest has been generated by the finding that cyclopenta[*a*]phenanthrenes are widely distributed in petroleum, mineral oils, coal, lake sediments, and other natural environments[1-4] where they are thought to arise from sterols by microbiological dehydrogenation.[3,4] There is also evidence that cyclopenta[*a*]phenanthrenes may be formed by pyrolysis of the sterols present in edible oils during cooking.[4] The chemistry and biological properties of the cyclopenta[*a*]phenanthrenes have been extensively reviewed in the excellent recent monograph by Coombs and Bhatt.[4] While the parent hydrocarbon 16,17-dihydro-15*H*-cyclopenta[*a*]phenanthrene (**1a**) and its 17-keto analogue **2a** are inactive, the 11-methyl-17-keto derivative **2b** is a relatively potent carcinogen on mouse skin, comparable in activity to benzo[*a*]pyrene.[4-7] There is also now substantial evidence that the active carcinogenic forms of the cyclopenta[*a*]phenanthrenes are diol epoxide metabolites, such as **3**.[4,8,9] However, the synthesis of these active metabolites has not been accomplished.



1 **2**

a: R ◻ R' = H; b: R = CH_3, R' = H; c: R ◻ H, R' = OCH_3



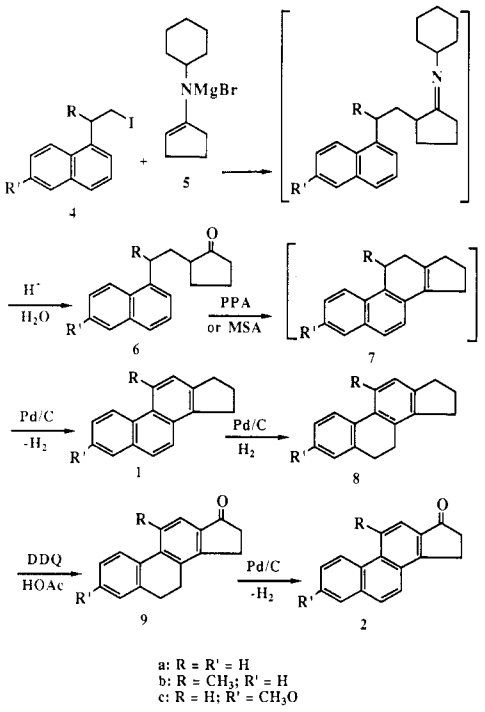
3a: R = H; b: R = CH_3

One of the principal bottlenecks to investigations of the cyclopenta[*a*]phenanthrenes has been their unavailability except through tedious multistep syntheses.[4] Accordingly, we have sought to devise more convenient synthetic approaches in order to make molecules of this class more accessible for studies of their biological properties and mechanism of action. We now report a new general synthesis of cyclopenta[*a*]phenanthrenes which provides good yields in relatively few steps. The method is potentially adaptable to the preparation of the biologically active diol epoxide intermediates.

(1) Ludwig, B.; Hussler, G.; Wehrung, P.; Albrecht, P. *Tetrahedron Lett.* **1981**, *22*, 3313.
(2) Mackenzie, A. S.; Hoffmann, C. F.; Maxwell, J. R. *Geochim. Cosmochim. Acta* **1981**, *45*, 1345.
(3) Wakeharm, S. G.; Schaffner, C.; Giger, W. *Geochim. Cosmochim. Acta* **1980**, *44*, 415.
(4) Coombs, M. M.; Bhatt, T. S. *Cyclopenta[a]phenanthrenes*; Cambridge Monographs on Cancer Research; Cambridge University Press: Cambridge, England, 1987.
(5) Coombs, M. M.; Croft, C. J. *Nature (London)* **1966**, *210*, 1281.
(6) Coombs, M. M.; Bhatt, T. S.; Young, S. *Br. J. Cancer* **1979**, *40*, 914.
(7) The 11-methyl derivative **1b** is intermediate in carcinogenic activity between **1a** and **2b**. Compounds **1b** and **2b** are examples of the *bay region methyl effect*, i.e., enhancement of carcinogenic activity consequent upon introduction of a methyl group into a non-benzo bay region site of a polycyclic aromatic hydrocarbon. DiGiovanni, J.; Diamond, L.; Harvey, R. G.; Slaga, T. J. *Carcinogenesis* **1983**, *4*, 403.
(8) Coombs, M. M.; Kissonerghis, A.-M.; Allen, J. A.; Vose, C. W. *Cancer Res.* **1979**, *39*, 4160.
(9) Coombs, M. M.; Bhatt, T. S. *Carcinogenesis* **1982**, *3*, 449.

0022-3263/88/1953-4253$01.50/0

Scheme I



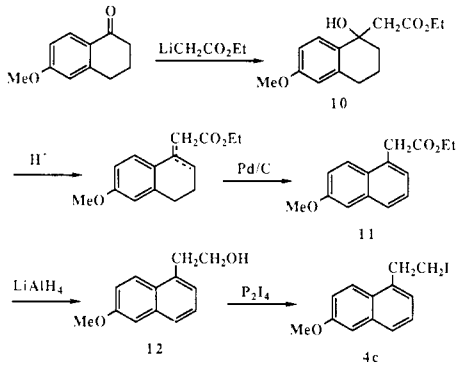
a: R = R' = H
b: R = CH_3; R' = H
c: R = H; R' = CH_3O

Results and Discussion

The synthetic route to 16,17-dihydro-15*H*-cyclopenta[*a*]phenanthrene (**1a**) is outlined in Scheme I. Reaction of 2-(1-naphthyl)ethyl iodide (**4a**)[10] with the bromomagnesium salt of *N*-cyclopentenylcyclohexanimine (**5**) followed by acidic hydrolysis of the resulting adduct affords smoothly 2-[2-(1-naphthyl)ethyl]cyclopentanone (**6a**). Cyclization of **6a** in polyphosphoric acid furnishes 11,12,16,17-tetrahydro-15*H*-cyclopenta[*a*]phenanthrene (**7a**) accompanied by the products of acidic disproportionation (shown by NMR and TLC). Disproportionation is commonly observed in acid-catalyzed cyclodehydration reactions, and in some cases the products have been characterized.[11] However, since the secondary products are of no inherent interest and since they all undergo dehydrogenation to the same final product, the mixture was dehydrogenated over a 10% Pd/charcoal catalyst to give **1a** as a crystalline solid, mp 134–135 °C (lit.[12] mp 134–135 °C). The NMR spectrum of **1a** is also fully consistent with this assignment. Excellent yields are obtained in both the initial alkylation and hydrolysis steps (96%) and in the subsequent cyclization and dehydrogenation steps (85%).

The 17-keto derivative of **1a**, 16,17-dihydro-15*H*-cyclopenta[*a*]phenanthren-17-one (**2a**), is apparently not synthetically accessible from direct oxidation of **1a** in view of the report by Butenandt et al.[13] that oxidation of **1a** with chromic acid affords the 15-keto derivative. However, in our hands oxidation of **1a** with DDQ in acetic acid, a reagent recently demonstrated to selectively oxidize benzylic alkyl groups,[14] furnished a mixture of the 15- and 17-keto derivatives in approximately 1:2 ratio (by NMR). The regioselectivity of oxidation is conveniently altered

Scheme II



by hydrogenation of **1a** over a Pd/charcoal catalyst[15] to yield **8a** which contains a biphenyl aromatic ring system. Oxidation of **8a** with DDQ in acetic acid takes place in the 17-position, apparently regiospecifically, to furnish the 17-keto derivative **9a**. It is remarkable that concurrent dehydrogenation of the 6,7-bond does not appear to take place to any significant extent under these conditions.[16] Finally, dehydrogenation of **9a** over a Pd/charcoal catalyst provides pure **2a**, mp 201–202 °C (lit.[17] mp 203–204 °C), in good overall yield.

The assignment of **2a** as the 17-keto derivative is supported by analysis of its 500-MHz ^1H NMR spectrum in comparison with those of **1a** and the 15-keto derivative. Most notably, the H_7 bay region aromatic proton of **2a** appears at δ 7.83, shifted slightly upfield from that of **1a** (δ 7.72), whereas H_7 of the 15-keto derivative is strongly deshielded by the adjacent carbonyl function appearing as a doublet at δ 9.16.

Synthesis of the carcinogenic bay region methyl-substituted analogue of **1a**, 16,17-dihydro-11-methyl-15*H*-cyclopenta[*a*]phenanthrene (**1b**), is accomplished by appropriate modification of the method in Scheme I. Reaction of 1-iodo-2-(1-naphthyl)propane (**4b**) with the bromomagnesium salt of **5** followed by acid hydrolysis furnishes smoothly the ketone intermediate **6b**. Attempted cyclization of the latter in polyphosphoric acid affords a complex mixture of products. However, cyclization takes place smoothly in methanesulfonic acid to yield the hydrocarbon **7b** accompanied by disproportionation products. Catalytic dehydrogenation of this mixture affords **1b**.

Conversion of **1b** to 16,17-dihydro-11-methyl-15*H*-cyclopenta[*a*]phenanthren-17-one (**2b**) is readily accomplished via hydrogenation of **1b** to yield **8b**. Oxidation of **8b** with DDQ in acetic acid gives **9b**, which undergoes dehydrogenation over a Pd/charcoal catalyst to yield **2b** in good overall yield.

The general route in Scheme I is also applicable in principle to the synthesis of the key intermediates required for the synthesis of the biologically active diol epoxide derivatives **3**. In order to demonstrate its feasibility for this purpose, the syntheses of 16,17-dihydro-3-methoxy-15*H*-cyclopenta[*a*]phenanthrene (**1c**) and 16,17-dihydro-3-methoxy-15*H*-cyclopenta[*a*]phenanthren-17-one (**2c**) were carried out. The starting compound 2-[1-(6-methoxynaphthyl)]ethyl iodide (**4c**) was itself synthesized via the route depicted in Scheme II. Lithioethyl acetate was

(10) Harvey, R. G.; Pataki, J.; Lee, H. *J. Org. Chem.* **1986**, *51*, 1407.
(11) Harvey, R. G.; Halonen, M. *Can. J. Chem.* **1967**, *45*, 2630. Cho, B.; Harvey, R. G. *J. Org. Chem.* **1987**, *52*, 5668.
(12) Coombs, M. M. *J. Chem. Soc. C* **1966**, 963.
(13) Butenandt, A.; Dannenberg, D.; von Dresler, D. *Z. Naturforsch.* **1946**, *1*, 222.
(14) Lee, H.; Harvey, R. *J. Org. Chem.*, in press.
(15) Palladium catalysts have been shown to exhibit K-region regiospecificity in the hydrogenation of polycyclic aromatic hydrocarbons under mild conditions: Fu, P. P.; Lee, H. M.; Harvey, R. G. *J. Org. Chem.* **1980**, *45*, 2797.
(16) DDQ is known to efficiently dehydrogenate phenanthrene and other similar dihydro polycyclic aromatic hydrocarbons: Fu, P. P.; Harvey, R. G. *Chem. Rev.* **1978**, *78*, 317.
(17) Coombs, M. M. *J. Chem. Soc. C* **1966**, 955.

prepared from the reaction of lithium bis(trimethylsilyl)amide with ethyl acetate at −78 °C by the method of Rathke[18] and reacted with 6-methoxy-1-tetralone in situ to afford the adduct **10**. Dehydration of **10** with *p*-toluenesulfonic acid in refluxing benzene furnished a mixture of isomeric olefinic products dehydrogenation of which over a 10% Pd/C catalyst gave ethyl 1-(6-methoxynaphthyl) acetate (**11**). Reduction of **11** with $LiAlH_4$ provided the corresponding alcohol **12** which on treatment with P_2I_4 yielded **4c**. Compound **4c** was utilized to synthesize **1c** and **2c** in good overall yields via the same sequence of steps (Scheme I) employed to prepared **1b** and **2b**.

Since methods for the conversion of the β-methoxy derivatives of polyarenes, such as **1c**, to the corresponding diol epoxides have previously been developed,[19] these biologically important molecules are now potentially accessible via the general synthetic approach described herein. Investigations directed toward the synthesis of the active diol epoxide metabolites of the cyclopenta[*a*]phenanthrenes **3a,b** are currently in progress and will be reported in due course.

Experimental Section

Materials and Methods. 2-(1-Naphthyl)ethyl iodide and 1-iodo-2-(1-naphthyl)propane were synthesized by the procedure previously described.[10,20] *N*-Cyclopentenylcyclohexanimine was synthesized by the procedure reported,[21] and its bromomagnesium derivative (**5**) was prepared by the method of Stork and Dowd.[22] 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was recrystallized from benzene. Tetrahydrofuran (THF) was freshly distilled from $LiAlH_4$. Ether was dried over sodium and triglyme was dried over molecular sieves, 4A.

The NMR spectra were obtained on a Varian EM360 spectrometer or the University of Chicago 500-MHz NMR spectrometer in $CDCl_3$ unless stated otherwise with tetramethylsilane as an internal standard. Integration was consistent with all structural assignments. All new compounds gave satisfactory microanalysis for C, H within ±0.3% and/or mass spectra consistent with the assigned structures.

2-[2-(1-Naphthyl)ethyl]cyclopentanone (6a). To a solution of **5** prepared from the reaction of *N*-cyclopentenyl cyclohexanimine (8.5 g, 415 mmol) with ethylmagnesium bromide (60 mmol, 20 mL of a 3 M solution in THF) was added 2-(1-naphthyl)ethyl iodide (12 g, 42 mmol), and the resulting mixture was refluxed for 20 h. Hydrolysis was effected by refluxing with 180 mL of 10% aqueous HCl for 3 h. The product was extracted and further purified by chromatography on a column of Florisil. Elution with benzene afforded **6a** (9.68 g, 96%) as an oil: NMR δ 1.3–2.5 (m, 8, aliphatic), 3.1 (apparent t, 2, benzylic), 7.2–8.2 (m, 7, Ar). Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.72; H, 7.63.

16,17-Dihydro-15*H*-cyclopenta[*a*]phenanthrene (1a). Cyclization of **6a** (6.4 g, 26 mmol) was carried out in polyphosphoric acid (100 mL) at 110 °C for 2 h under N_2. Ice–water was added, and the mixture was extracted with CH_2Cl_2. The product was worked up conventionally and chromatographed on a column of Florisil to yield a mixture of **7a**, **1a**, and other products of acidic disproportionation. This mixture was dehydrogenated by heating with 10% Pd/C (2.8 g) in triglyme (250 mL) at reflux for 2 h under N_2. The reaction mixture was cooled and filtered, and the filtrate was diluted with ether and washed with water several times to remove triglyme. The ether solution was dried over $MgSO_4$ and evaporated to dryness to afford a white solid, which was triturated with cold hexane to yield pure **1a** (4.9 g, 85%): mp 134–135 °C (lit.[12] mp 134–135 °C); NMR δ 2.27 (m, 2, H_{16}), 3.15 (t, 2, H_{17}), 3.31 (t, 2, H_{15}), 7.53 (t, 1, H_{12}), 7.54 (m, 1, $H_{2\text{ or }3}$), 7.60 (m, 1, $H_{2\text{ or }3}$), 7.72 (s, 2, $H_{6,7}$), 7.85 (m, 1, H_4), 8.50 (d, 1, H_{11}, $J_{11,12}$ = 8.2 Hz), 8.64 (m, 1, H_1).

Oxidation of 1a with DDQ in Acetic Acid. Oxidation of **1a** (35 mg, 0.16 mmol) with DDQ (68 mg, 0.3 mmol) in acetic acid (10 mL) and water (2 mL) under the conditions described below for the preparation of **9a** afforded a mixture of 16,17-dihydro-15*H*-cyclopenta[*a*]phenanthren-15-one and **2a** (30 mg, 81%) in an approximately 1:2 ratio by NMR analysis; the NMR spectrum of the 15-keto compound showed δ 2.84 (t, 2, H_{16}), 3.25 (t, 2, H_{17}), 7.6 (t, 1, H_3), 7.65–7.90 (m, 4, Ar), 8.64 (d, 1, H_1, $J_{1,2}$ = 8.3 Hz), 8.88 (d, 1, H_{11}, $J_{11,12}$ = 8.5 Hz), 9.16 (d, 1, H_7, $J_{6,7}$ = 9.0 Hz); NMR data on **2a** are presented below.

6,7,16,17-Tetrahydro-15*H*-cyclopenta[*a*]phenanthrene (8a). Compound **1a** (4.3 g, 19 mmol) dissolved in ethyl acetate (100 mL) was hydrogenated over a 10% Pd/C catalyst (3.2 g) at 50 psig at ambient temperature for 24 h. Crystallization from hexane gave **8a** as a white solid (2.97 g, 71%): mp 64–65 °C (lit.[23] mp 60 °C); NMR δ 2.2 (m, 2, aliphatic), 2.7–3.2 (m, 8, benzylic), 7.1–7.4 (m, 4, Ar), 7.6 (d, 1, H_{11}), 7.7 (m, 1, H_1).

6,7,16,17-Tetrahydro-15*H*-cyclopenta[*a*]phenanthren-17-one (9a). The hydrocarbon **8a** (48 mg, 0.22 mmol) was dissolved in hot acetic acid (15 mL), and water (5 mL) was added slowly with stirring, maintaining homogeneity of the solution. DDQ (198 mg, 0.88 mmol) was added, changing the color of the solution to dark green. Stirring was continued at reflux for 30 min, during which time the color of the solution changed to dark red. The reaction mixture was cooled and diluted with ether, and the ether layer was washed with water and aqueous NaOH. The solution was dried over $MgSO_4$ and evaporated to provide a white solid, which was chromatographed on a column of Florisil. Elution with ether yielded **9a** (39 mg, 76%): mp 127–128 °C; NMR δ 2.72 (t, 1, $H_{15\text{ or }16}$), 2.85–2.91 (m, 4, $H_{6,7}$), 3.07 (t, 1, $H_{15\text{ or }16}$), 7.24–7.31 (m, 3, $H_{2,3,4}$), 7.67–7.77 (m, 3, $H_{1,11,12}$). Anal. Calcd for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found: C, 87.13; H, 6.03.

16,17-Dihydro-15*H*-cyclopenta[*a*]phenanthren-17-one (2a). A solution of **9a** (147 mg, 0.67 mg, 0.67 mmol) in triglyme (25 mL) was heated at reflux with 10% Pd/C for 30 min. The usual workup followed by crystallization from ethyl acetate afforded **2a** as a white solid (140 mg, 90%): mp 201–202 °C (lit.[17] mp 203–204 °C); NMR δ 2.82 (t, 1, H_{16}), 3.41 (t, 1, H_{15}), 7.64–7.67 (m, 2, $H_{2,3}$), 7.83 (s, 2, $H_{6,7}$), 7.87 (d, 1, H_{12}, $J_{11,12}$ = 8.6 Hz), 7.90 (d of d, 1, H_4), 8.60 (d, 1, H_{11}), 8.66 (d of d, 1, H_1).

2-[2-Methyl-2-(1-naphthyl)ethyl]cyclopentanone (6b). Reaction of 1-iodo-2-(1-naphthyl)propane (12.72 g, 43 mmol) with the bromomagnesium salt **5** by the procedure described for the preparation of **6a** afforded **6b** (8.7 g, 80%) as an oil: NMR δ 1.4 (d, 3, CH_3), 1.5–2.5 (m, 9, aliphatic), 3.8 (m, 1, benzylic), 7.3–8.3 (m, 7, Ar). This compound was used directly in the next step.

11-Methyl-16,17-dihydro-15*H*-cyclopenta[*a*]phenanthrene (1b). Cyclization of **6b** was effected in methanesulfonic acid (200 mL) at room temperature for 2 h under N_2. The usual workup gave a residue that was chromatographed on a column of Florisil to furnish on elution with hexane a mixture of **7b**, **1b**, and other products of acid-catalyzed disproportionation. Dehydrogenation of the mixture over a Pd/C catalyst in refluxing triglyme by the procedure employed for the preparation of **1a** afforded pure **1b** (15.22 g, 87%): mp 80–81 °C (hexane) (lit.[24] mp 81–82 °C); NMR δ 2.2 (m, 2, H_{16}), 3.1 (1, 3, CH_3), 3.1 (m, 4, $H_{15,17}$), 7.3–8.0 (m, 6, Ar), 8.8 (m, 1, H_1).

11-Methyl-6,7,16,17-tetrahydro-15*H*-cyclopenta[*a*]phenanthrene (8b). Hydrogenation of **1b** (1.0 g, 4 mmol) by the procedure employed for the preparation of **8a** afforded **8b** (900 mg, 90%) as an oil: NMR δ 2.1 (m, 2, H_{16}), 2.6 (d, 3, CH_3), 2.8 (m, 8, benzylic), 7.0–7.8 (m, 5, Ar). Anal. Calcd for $C_{18}H_{18}$: C, 92.26; H, 7.74. Found: C, 92.23; H, 7.74.

11-Methyl-6,7,16,17-tetrahydro-15*H*-cyclopenta[*a*]phenanthren-17-one (9b). Oxidation of **8b** (288 mg, 1.2 mmol) with DDQ (615 mg, 2.7 mmol) in acetic acid (90 mL) and H_2O (30 mL) under the conditions utilized for the synthesis of **9a** gave **9b** (305 mg, 76%) as a white solid: mp 160–161 °C; NMR δ 2.75

(18) Rathke, M. W. *J. Am. Chem. Soc.* **1970**, *92*, 3222.
(19) Harvey, R. G. In *Polycyclic Hydrocarbons and Carcinogenesis*; ACS Symposium Series 283; Harvey, R. G., Ed.; American Chemical Society: Washington, DC, 1985; pp 35–62. Harvey, R. G. *Synthesis* **1986**, 605.
(20) Pataki, J.; Harvey, R. G. *J. Org. Chem.* **1982**, *47*, 20.
(21) Whitesell, J. K.; Whitesell, M. A. *Synthesis* **1983**, 517.
(22) Stork, G.; Dowd, S. R. *J. Am. Chem. Soc.* **1963**, *85*, 2178.
(23) Jacob, G.; Cagniant, D.; Cagniant, R. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1971**, *272*, 650.
(24) Coombs, M. M. *J. Chem. Soc. C* **1969**, 2484.

(s, 3, CH_3), 2.85 (s, 4, $H_{6,7}$), 2.69–3.30 (m, 4, $H_{15,16}$), 7.25–7.90 (m, 5, Ar). Anal. Calcd for $C_{18}H_{16}O$: C, 87.06; H, 6.49. Found: C, 87.12; H, 6.51.

11-Methyl-16,17-dihydro-15*H*-cyclopenta[*a*]phenanthren-17-one (2b). Dehydrogenation of **9b** (171 mg, 0.7 mmol) by the procedure employed for the preparation of **2a** provided **2b** (145 mg, 86%) as a white solid: mp 173–174 °C (lit.[17] mp 171–172 °C); NMR δ 2.78 (m, 2, H_{16}), 3.10 (s, 1, CH_3), 3.36 (m, 2, H_{15}), 7.62–7.64 (m, 2, $H_{2,3}$), 7.70 (s, 1, H_{12}), 7.81 (s, 2, $H_{6,7}$), 7.93 (m, 1, H_4), 8.87 (m, 1, H_1).

Ethyl [1-(6-Methoxynaphthyl)]acetate (11). To a solution of lithium bis(trimethylsilyl)amide in THF (600 mL of a 1.0 M solution) cooled in a dry ice bath was added ethyl acetate (52.86 g, 0.60 mol) dropwise over 20 min. The clear solution was stirred for an additional 15 min, and then a solution of 6-methoxy-1-tetralone (100 g, 0.57 mol) in 360 mL of anhydrous THF was added over 1 h. Stirring was continued for an additional 10 min, then 200 mL of 20% HCl was added over a 10-min period, and the solution was diluted with water sufficient to redissolve the white precipitate of LiCl. The solution was allowed to warm to room temperature, then extracted with benzene and worked up conventionally to yield the adduct **10** (150 g, 99%) as an oil: NMR δ 1.3 (t, 3, CH_3CH_2O), 2.1 (m, 4, CH_2), 2.8 (m, 4, benzylic and CH_2CO_2Et), 3.85 (s, 3, CH_3O), 4.2 (q, 2, CH_3CH_2O), 6.8-7.6 (m, 3, Ar).

A solution of **10** (150 g, 0.57 mol) and *p*-toluenesulfonic acid (7 g) in benzene (500 mL) was heated at reflux for 1 h, and the water formed was removed azeotropically by using a Dean–Stark apparatus. The usual workup afforded an oil containing a mixture of the isomeric unsaturated acetates. Treatment of this oil with 10% Pd/C (35 g) in refluxing triglyme (800 mL) for 2 h followed by the usual workup provided **11** (130 g, 94%) as an oil: NMR δ 1.2 (t, 3, CH_3CH_2O), 3.9 (s, 3, CH_3O), 4.0 (s, 2, CH_2), 4.1 (q, 2, CH_3CH_2O), 7.0–8.0 (m, 6, Ar).

2-[1-(6-Methoxynaphthyl)]ethanol (12). In a three-neck flask equipped with an addition funnel, a condenser, and a gas inlet were placed $LiAlH_4$ (5.2 g, 136 mmol) in ether (300 mL) under a stream of argon. The mixture was heated at reflux until most of the hydride had dissolved, and then a solution of **11** (45 g, 197 mmol) in 150 mL of dry ether was added with vigorous stirring at a rate to maintain gentle reflux. When addition was complete, the mixture was refluxed for an additional 30 min. The excess $LiAlH_4$ was decomposed by addition of ethyl acetate followed by water. The usual workup gave an oil, which was purified by chromatography on a column of Florisil. Elution with ether afforded **12** (38.23 g, 99%) as an oil: NMR δ 1.7 (br s, 1, OH), 3.3 (t, 3, CH_3O), 3.9 (m, 2, H_1), 7.1–8.1 (m, 3, Ar).

2-[1-(6-Methoxynaphthyl)]ethyl Iodide (4c). To a solution of **12** (37 g, 183 mmol) in CS_2 (800 mL) was added P_2I_4 (28.2 g, 50 mmol), and the reaction mixture was stirred at room temperature for 48 h. The reaction mixture was concentrated to remove CS_2 and then partitioned between ether and water. The organic layer was washed with water and aqueous K_2CO_3 and then dried, and the solvent was evaporated. Chromatography on a column of Florisil eluted with hexane yielded **4c** (30.6 g, 54%) as a white solid: mp 62–63 °C: NMR δ 3.5 (m, 4, CH_2), 4.8 (s, 3, CH_3O), 7.0–7.9 (m, 6, Ar). Anal. Calcd for $C_{13}H_{13}IO$: C, 50.02; H, 4.20; I, 40.65. Found: C, 50.29; H, 4.28; I, 40.37.

2-[2-(1-(6-Methoxynaphthyl))ethyl]cyclopentanone (6c). Alkylation of the bromomagnesium salt prepared from *N*-cyclopentenylcyclohexanimine (18.15 g, 110 mmol) with **4c** by the usual procedure furnished **6c** (23.4 g, 90%) as an oil: NMR δ 1.4–2.3 (m, 9, aliphatic), 3.0 (t, 2, benzylic), 3.75 (s, 3, CH_3O), 7.0–8.0 (m, 6, Ar).

16,17-Dihydro-3-methoxy-15*H*-cyclopenta[*a*]phenanthrene (1c). To a solution of methanesulfonic acid (10 mL) in CH_2Cl_2 (100 mL) was added a solution of **6c** (543 mg, 2 mmol) in CH_2Cl_2 (5 mL). The solution was stirred at ambient temperature for 1 h, then ice–water was added, and the reaction was worked up in the usual manner. Chromatography of the residue on a column of Florisil gave on elution with benzene a mixture of **7c**, **1c**, and other products of disproportionation. Dehydrogenation of the mixture over a Pd/C catalyst in refluxing triglyme as described for the preparation of **1a** afforded **1c**, which was crystallized from ether giving pure **1c** (300 mg, 60%): mp 139–140 °C (lit.[25] mp 134.5–136 °C); NMR δ 2.2 (q, 2, H_{16}), 3.2 (apparent q, 4, $H_{15,17}$), 3.9 (s, 3, CH_3O), 7.2–7.7 (m, 5, Ar), 8.3 (m, 2, $H_{1,11}$).

3-Methoxy-6,7,16,17-tetrahydro-15*H*-cyclopenta[*a*]phenanthrene (8c). Hydrogenation of **1c** (4 g, 16 mmol) by the procedure employed for the preparation of **8a** (40 h) furnished **8c** (2.9 g, 73%) as a white solid: mp 104–105 °C (ether–hexane) (lit.[26] mp 101–102 °C); NMR δ 2.1 (t, 2, H_{16}), 2.85 (m, 8, benzylic), 3.85 (s, 3, CH_3O), 6.75–7.75 (m, 5, Ar).

3-Methoxy-6,7,16,17-tetrahydro-15*H*-cyclopenta[*a*]phenanthren-17-one (9c). A solution of **8c** (880 mg, 3.5 mmol) and DDQ (1.76 g, 7.7 mmol) in acetic acid (350 mL) and water (45 mL) was stirred for 24 h at ambient temperature. The usual workup followed by chromatography on a column of Florisil eluted with CH_2Cl_2 gave **9c** (781 mg, 83%): mp 141–142 °C; NMR δ 2.8 (m, 8, CH_2), 3.8 (s, 3, CH_3O), 6.7–7.8 (m, 5, Ar). Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.85; H, 6.14.

3-Methoxy-16,17-dihydro-15*H*-cyclopenta[*a*]phenanthren-17-one (2c). Dehydrogenation of **9c** (781 mg, 2.95 mmol) in refluxing triglyme over a Pd/C catalyst (400 mg) for 30 min afforded **2c** (702 mg, 90%) as a white solid: mp 212–213 °C (THF/EtOAc) (lit.[17] mp 209 and 230 °C); NMR (500 MHz) δ 2.83 (m, 2, H_{16}), 3.43 (m, 2, H_{15}), 3.97 (s, 3, CH_3O), 7.26 (d, 1, H_4, $J_{2,4}$ = 2.6 Hz), 7.30 (d of d, 1, H_2, $J_{1,2}$ = 8.6 Hz), 7.77 (d, 1, H_{12}, $J_{11,12}$ = 9.1 Hz), 7.85 (d, 1, $H_{6\text{ or }7}$, $J_{6,7}$ = 6.5 Hz), 7.80 (d, 1, $H_{6\text{ or }7}$), 8.52 (d, 1, H_1), 8.58 (d, 1, H_{11}).

Acknowledgment. This research was supported by grants from the National Cancer Institute, DHHS (CA 36097, CA 14599) and the National Institute of Environmental Health Sciences (ES 04266) as well as by the American Cancer Society (BC 132).

Registry No. **1a**, 482-66-6; **1b**, 24684-41-1; **1c**, 98656-35-0; **2a**, 786-66-3; **2b**, 892-17-1; **2c**, 792-07-4; **4a**, 75325-81-4; **4b**, 101349-61-5; **4c**, 115338-40-4; **6a**, 115338-35-7; **6b**, 115338-37-9; **6c**, 115338-41-5; **8a**, 31301-55-0; **8b**, 115338-38-0; **8c**, 115338-42-6; **9a**, 115338-36-8; **9b**, 115338-39-1; **9c**, 17521-83-4; **10**, 92508-62-8; **11**, 99416-98-5; **12**, 63469-50-1; *N*-cyclopentenylcyclohexanimine, 115338-34-6; 16,17-dihydro-15*H*-cyclopenta[*a*]phenanthren-15-one, 32425-83-5; ethyl acetate, 141-78-6; 6-methoxy-1-tetralone, 1078-19-9.

(25) Cook, J. W.; Girard, A. *Nature (London)* **1934**, *133*, 377.
(26) Robinson, R.; Slater, S. N. *J. Chem. Soc.* **1941**, 376.