Synthesis of the *trans*-3,4-Dihydrodiol Metabolites of the Steroid-Related Carcinogen 15,16-Dihydrocyclopenta[*a*]phenanthren-17-one and Its 11-Methyl Derivative

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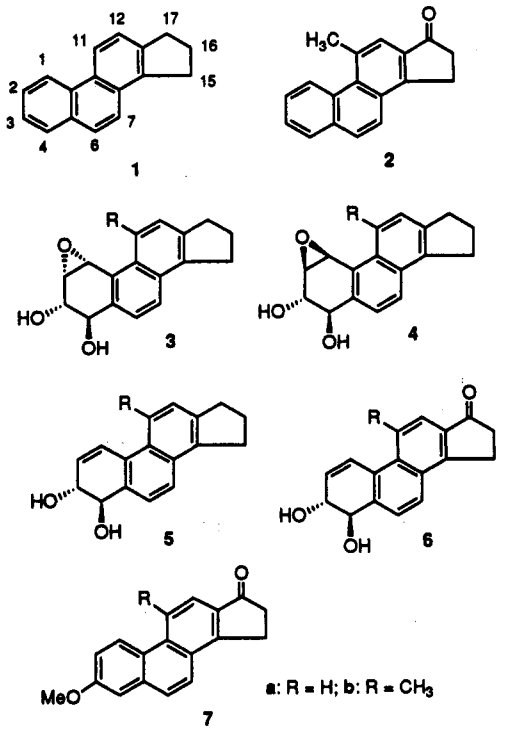
Cyclopenta[*a*]phenanthrenes are a unique class of carcinogenic polycyclic aromatic hydrocarbons that are structurally related to steroids. Optimum tumorigenic activity is associated with a methyl group in the 11-position and a keto group in the 17-position. Syntheses of the putative active *trans*-3,4-dihydrodiol and *anti*- and *syn*-diol epoxide metabolites of cyclopenta[*a*]phenanthrene and its 11-methyl derivative are described in the preceding paper. This paper reports the syntheses of the analogous *trans*-3,4-dihydrodiol derivatives of these same hydrocarbons with a 17-carbonyl function. The related isomeric diol epoxide derivatives were found to be too unstable to isolate in pure state.

Cyclopenta[*a*]phenanthrenes are a steroid-related class of carcinogenic polycyclic aromatic hydrocarbons that are widespread in the environment.[1] Their potential role in human cancer is suggested by their formation by pyrolysis of sterols in foods during cooking.[1,2] Optimum tumorigenic activity is associated with a methyl group in the 11-position and a keto group in the 17-position. 11-Methyl-15,16-dihydrocyclopenta[*a*]phenanthren-17-one (**2**) which possesses both of these structural features is a relatively potent carcinogen, comparable in activity to benzo[*a*]pyrene.[1,3] Activation by a carbonyl group is surprising, since it is contrary to previoius observations for other classes of carcinogenic hydrocarbons.[4a,5] Current evidence indicates that the active carcinogenic metabolites that bind covalently to DNA are the *anti*- and/or *syn*-diol epoxide metabolites, e.g., **3** and **4**.[1,6]

Syntheses of the *anti*- and *syn*-diol epoxide derivatives of cyclopenta[*a*]phenanthrene (**3a** and **4a**) and its 11-methyl derivative (**3b** and **4b**) and their 3,4-dihydrodiol precursors (**5a** and **5b**) are described in the preceding paper. This paper reports syntheses of the related *trans*-3,4-dihydrodiol derivatives of these hydrocarbons with a 17-keto group (**6a** and **6b**). The corresponding isomeric diol epoxide derivatives were found to be too unstable to isolate and obtain in pure state.



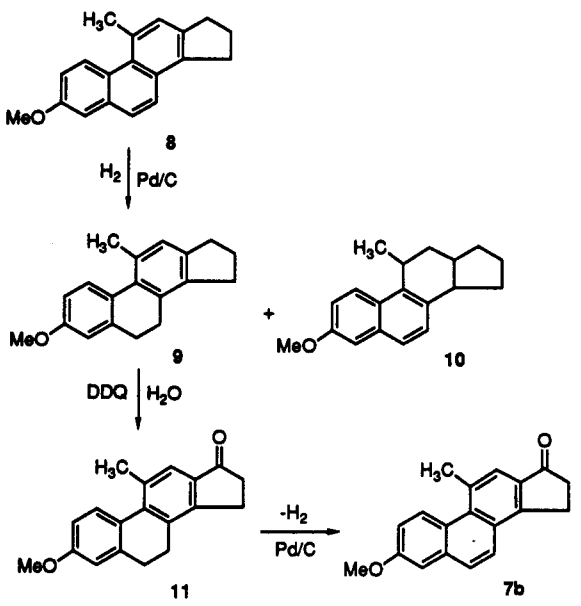
Results and Discussion

The starting points for the syntheses of the active metabolites of the 17-keto series of cyclopenta[*a*]phenanthrene compounds are the 15,16-dihydro-3-methoxycyclopenta[*a*]phenanthren-17-ones with and without an 11-methyl group (**7a** and **7b**). Synthesis of **7a** was described previously,[7] and the same procedure was employed herein for preparation of **7a** on relatively large scale. The starting compound required for the synthesis of the 11-methyl analogue **7b** (Scheme I) is 15,16-dihydro-3-methoxy-11-methylcyclopenta[*a*]phenanthrene (**8**) whose synthesis is described in the accompanying paper. Introduction of the carbonyl group into the 17-position of **8** was accomplished by initial regioselective low-pressure hydrogenation of the 6,7-bond over a 10% palladium–charcoal catalyst under mild conditions.[8] Contrary to the previous observation with the unmethylated derivative,[7] hydrogen addition was not regiospecific affording a significant per-

(1) Coombs, M. M.; Bhatt, T. S. *Cyclopenta[a]phenanthrenes*; Cambridge Monographs on Cancer Research: Cambridge University Press: Cambridge, England, 1987.
(2) Schmid, L. *Mitt. Geb. Lebensmittelunter Hyg.* **1962**, *53*, 507. Schmid, L.; Waitz, W. *Z. Ernaehungwiss., Suppl.* **1963**, *3*, 45. Hoffelner, K.; Lisbet, H.; Schmid, L. *Ibid.* **1964**, *5*, 16.
(3) Coombs, M. M.; Croft, C. J. *Nature (London)* **1966**, *210*, 1281; *Prog. Exper. Tumor Res.* **1969**, *11*, 69–85.
(4) (a) Harvey, R. G. *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenicity*; Cambridge Monographs on Cancer Research; Cambridge University Press: Cambridge, England, 1991; Chapter 3; (b) Chapter 13; (c) Chapter 14; (d) Chapter 4.
(5) Dipple, A.; Moschel, R. C.; Bigger, C. A. H. In *Chemical Carcinogens*, 2nd ed.; Searle, C. E., Ed.; ACS Monograph 182; American Chemical Society: Washington, D.C., 1984; pp 41–163.
(6) Coombs, M. M.; Kissonerghis, A.-M.; Allen, J. A.; Vose, C. W. *Cancer Res.* **1979**, *39*, 4160. Coombs, M. M.; Bhatt, T. S. *Carcinogenesis* **1982**, *3*, 449.
(7) Lee, H.; Harvey, R. G. *J. Org. Chem.* **1988**, *53*, 4253.
(8) Polycyclic aromatic hydrocarbons are hydrogenated regioselectively in the K-region bonds by palladium catalysts under mild conditions: Fu, P. P.; Lee, H. M.; Harvey, R. G. *J. Org. Chem.* **1980**, *45*, 2797.

0022-3263/93/1958-0361$04.00/0

Scheme I



centage of a product hydrogenated in the ring containing the methyl group (**10**) in addition to the 6,7-dihydro compound **9**. This secondary product proved difficult to remove at this stage, but it was readily separated from the product of the next step in the sequence. Oxidation of **9** with DDQ in moist acetic acid[9] took place regiospecifically in the 17-position to yield the 17-keto derivative **11**. Dehydrogenation of **11** over a 10% palladium–charcoal catalyst provided **7b**. The assignment of **7b** as the 17-keto rather than the 15-keto isomer is supported by the appearance in its 500-MHz proton NMR spectrum of the H_7 aromatic proton peak at δ 7.83, shifted only slightly from the analogous signal of **8** (δ 7.65). The H_7 peak of the 15-keto isomer is expected to be strongly deshielded by the adjacent carbonyl function; this is supported by the earlier observation that the H_7 peak of 15,16-dihydro-11-methylcyclopenta[*a*]phenanthren-15-one appeared as a doublet at δ 9.16.[7]

Conversion of **7a** to the target molecules necessitated appropriate protection of the oxygen functions. A methyl ether group was unsatisfactory for the protection of the 3-hydroxyl function because of the harsh reagents required for its later removal. Initial attempts to protect the 17-keto group as a ketal gave an unstable product that proved unsuitable for this purpose. The successful strategy (Scheme II) involved demethylation of **7a** with BBr_3, formation of a benzoate ester **12a**, reduction of the carbonyl group with $NaBH_4$, and protection of the alcohol function as its *tert*-butyldiphenylsilyl ether derivative **13a**. Debenzoylation of the silylated derivative **13a** by treatment with methanolic KOH gave the free phenol which in turn was oxidized with Fremy's salt to yield the quinone **14a**. Reduction of **14a** by $NaBH_4$ with O_2 bubbling through the solution[4b,7,10] furnished smoothly the *trans*-3,4-dihydrodiol derivative of 17-[(*tert*-butyldiphenylsilyl)oxy]-15,16-dihydrocyclopenta[*a*]phenanthrene (**15a**). This steric assignment is supported by previous findings for similar reactions[4b,10] and by the 500-MHz NMR spectrum of **15a** which showed $J_{3,4}$ = 8.2 Hz consistent with the trans diequatorial conformational assignment of the 3,4-hydroxyl groups.

The dihydrodiol **15a** was transformed to its 17-keto analog **18a** by a four-step sequence. Reaction of **15a** with benzoic anhydride in pyridine afforded the dibenzoate ester **16a** which on treatment with tetrabutylammonium fluoride underwent loss of the silyl protecting group to provide the free alcohol **17a**. The diacetate was used initially instead of the dibenzoate, but it was found that partial deacetylation occurs during the removal of the silyl group, complicating purification considerably. Oxidation of the 17-hydroxyl group of **17a** with DDQ furnished the 17-keto dibenzoate ester which on debenzoylation with NaOMe yielded *trans*-3,4-dihydroxy-17-oxo-3,4,15,16-tetrahydrocyclopenta[*a*]phenanthrene (**18a**). The Dess–Martin "periodinane" reagent[11] was employed as the oxidant in initial studies, but DDQ was found to be more convenient for this purpose.

The 11-methyl derivative of the *trans*-3,4-dihydrodiol 17-ketone **18b** was synthesized from **7b** via an analogous sequence of steps. The structural assignments of all of the synthetic intermediates as well as the dihydrodiols **18a** and **18b** were fully consistent with their 500-MHz proton NMR spectra.

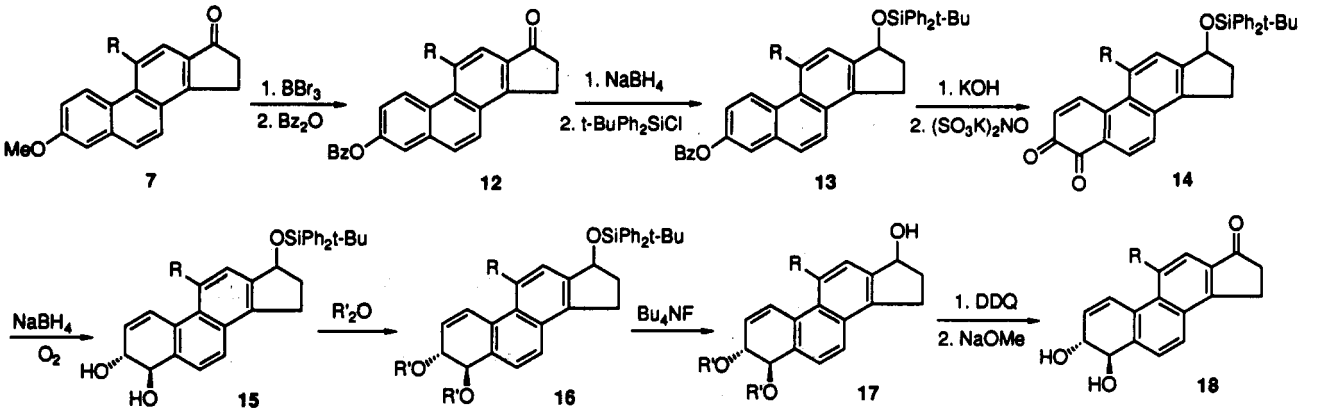
Attempted conversion of the *trans*-3,4-dihydrodiol 17-ketone derivative of 15,16-dihydrocyclopenta[*a*]phenanthrene (**18a**) and its 11-methyl derivative **18b** to the corresponding *anti*-diol epoxide derivatives by reaction with *m*-chloroperbenzoic acid was carried out using the procedure employed previously with other dihydrodiols (Scheme III). While epoxidation took place (shown by NMR analysis), the reaction mixture contained minor secondary products which increased during the course of reaction (shown by TLC and HPLC analysis). These may include products of Baeyer–Villeger oxidation involving the 17-keto group. Precautions to minimize the decomposition during isolation (rapid workup, low temperature, alkaline pH) that were used successfully with other relatively unstable diol epoxides[10c] were observed. However, spontaneous decomposition of the diol epoxide took place with facility as evidenced by the relatively rapid decrease of its HPLC peak (~65% in 1 h on standing at room temperature), preventing its isolation in the pure state necessary for meaningful biological studies.

The instability of the cyclopent[*a*]phenanthrene *anti*-diol epoxides with the 17-keto group contrasts with the relative stability observed for the corresponding *anti*- and *syn*-diol epoxides lacking this functionality. Instability, which may be considered a measure of reactivity, appears to be characteristic of the diol epoxide derivatives of some of the most carcinogenic hydrocarbons, such as the *anti*-diol epoxides of 7,12-dimethylbenz[*a*]anthracene,[10c] 7,-14-dimethyldibenz[*a*,*j*]anthracene,[12] and 12-methylbenz-[*a*]anthracene.[12,13] It is likely that this property is directly related to reactivity with DNA which is assumed to be the primary cellular target for mutation and tumor induction.[4d]

The availability of the oxidized metabolites of cyclopenta[*a*]phenanthrene and its 11-methyl and 17-keto

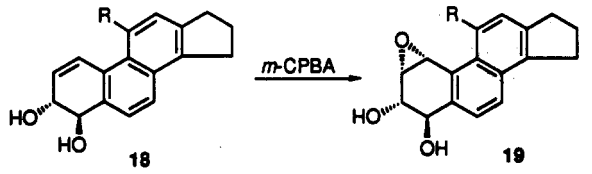
(9) Lee, H.; Harvey, R. G. *J. Org. Chem.* **1988**, *53*, 4587.
(10) (a) Harvey, R. G. *Polycyclic Hydrocarbons and Carcinogenesis*; Harvey, R. G., Ed.; American Chemical Society: Washington, D.C., 1985; pp 35–62. (b) Harvey, R. G. *Synthesis* **1986**, 605–619. (c) Lee, H.; Harvey, R. G. *J. Org. Chem.* **1986**, *51*, 3502. (d) Harvey, R. G.; Pataki, J.; Lee, H. *J. Org. Chem.* **1986**, *51*, 1407.
(11) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(12) Lee, H.; Harvey, R. G. *J. Med. Chem.* **1988**, *31*, 1308.
(13) Our attempts to synthesize the bay region *anti*- and *syn*-diol epoxide metabolites of 12-methylbenz[*a*]anthracene indicate them to be less stable than corresponding metabolites of 7,12-dimethylbenz[*a*]-anthracene.

Scheme II



a: R = H; b: R = CH_3 (R' = Ac or Bz)

Scheme III



a: R = H; b: R = CH_3

derivatives makes possible biological studies to elucidate their mechanism of carcinogenesis. These include mutagenicity and tumorigenicity assays and DNA-binding studies. The synthetic inaccessibility of the diol epoxides with the 17-keto group will only slightly hamper these studies, since the diol epoxides may be generated in situ from the 3,4-dihydrodiols, e.g., by enzymatic oxidation with rat liver microsomes. Preliminary findings from mutagenicity assays conducted with the dihydrodiols and diol epoxides lacking the 17-keto function do not support the hypothesis that the weak tumorigenicity of the parent hydrocarbons is due entirely to the low mutagenicity of their diol epoxide metabolites, since they were found to be relatively potent mutagens.[14,15] Present findings suggest that the high level of tumorigenic activity associated with the 17-keto group may be due partially to the greater reactivity of the corresponding diol epoxide metabolites[16] which results in their greater extent of reaction with DNA or to differences in the types of adducts they form with DNA. However, it cannot be ruled out that enzymatic activation of hydrocarbons lacking the 17-keto group may be relatively inefficient or that they may undergo relatively more facile detoxification. Availability of the oxidized metabolites through synthesis makes it now possible to distinguish these mechanisms.

(14) Young, R. J.; Cortez, C.; Luna, E.; Lee, H.; Harvey, R. G. *J. Org. Chem.*, preceding paper in this issue.

(15) Papaparaskeva-Petrides, C.; Ioannides, C.; Boyd, G. W.; Young, R. J.; Harvey, R. G.; Coombs, M. M. *Mutagenesis* Manuscript submitted for publication.

(16) In previous studies with polyarenediol epoxides it was observed that apparently small differences in structure may dramatically influence relative stabilities and reactivities. For example, while the *anti*- and *syn*-3,4-diol 1,2-epoxides of benz[a]anthracene proved sufficiently stable to allow their isolation in pure state, only the anti isomer of 7-methylbenz[a]anthracene[17] and the syn isomer of 7,12-dimethylbenz[a]anthracene[10c] were relatively stable; the alternative isomers underwent relatively facile decomposition during preparation.

(17) Harvey, R. G.; Cortez, C.; Sugiyama, T.; Ito, Y.; Sawyer, T. W.; DiGiovanni, J. *J. Med. Chem.* 1988, 154.

Experimental Section

Materials and Methods. 15,16-Dihydro-3-methoxycyclopenta[a]phenanthren-17-one (**7a**)[7] and 15,16-dihydro-3-methoxy-11-methylcyclopenta[a]phenanthrene (**8**)[14] were synthesized as previously described. A 10% palladium/charcoal catalyst supplied by Engelhard Industries gave most satisfactory results in the hydrogenations and dehydrogenations; a similar catalyst supplied by Aldrich gave variable results which were not reproducible from batch to batch. *m*-Chloroperbenzoic acid, DDQ, THF, and ether were purified as described in the preceding paper. NMR spectra were obtained on a 500-MHz spectrometer in $CDCl_3$ with tetramethylsilane as internal standard unless stated otherwise. Integration was consistent with all structural assignments. All new compounds gave satisfactory microanalysis for C, H within ±0.4% and/or mass spectra consistent with the assigned structures.

3-Methoxy-11-methyl-6,7,15,16-tetrahydrocyclopenta[a]phenanthrene (9). Hydrogenation of **8** (3.00 g, 1.15 mmol) was conducted over a 10% Pd/C catalyst in ethyl acetate (100 mL) at 32 psi for 16 h. The crude product was filtered through Celite, the Celite cake was washed with ethyl acetate, and the combined filtrate was evaporated to yield an oil (2.8 g) containing **9**, a product hydrogenated in the methyl-substituted ring **10**, plus trace amounts of overreduced products. Careful crystallization from ether furnished pure **9** (1.92 g, 64% isolated yield): NMR δ 2.14 (q, 2, H_{16}), 2.61 (s, 3, CH_3), 2.73 (m, 4, $H_{6,7}$), 2.91 (t, 2, H_{17}), 2.97 (t, 2, H_{15}), 3.88 (s, 3, OMe), 6.83 (d, 1, H_2), 6.84 (s, 1, H_4), 7.08 (s, 1, H_{12}), 7.58 (d, 1, H_1); $J_{1,2}$ = 8.2 Hz; $J_{15,16}$ = 7.4 Hz; *m/z* (EI) 264 (M^+, 100). Anal. Calcd for $C_{19}H_{20}O$; C, 86.32; H, 7.63. Found: C, 86.24; H, 7.55.

It was advantageous to use the crude product directly in the next step and recycle the recovered overhydrogenated products by dehydrogenation over the same catalyst.

3-Methoxy-11-methyl-6,7,15,16-tetrahydrocyclopenta[a]phenanthren-17-one (11). To a stirred solution of **9** (2.74 g, 10.4 mmol) in 250 mL of acetic acid and 25 mL of water was added DDQ (5.0 g, 22 mmol), and the mixture was stirred at room temperature for 24 h under argon. The solvent was evaporated and the residue partitioned between ether and 10% aqueous NaOH. After two further extractions, the combined organics were washed with 10% aqueous NaOH, water, and brine and then dried and evaporated to dryness to yield crude **11** (2.60 g). This was chromatographed on a column of silica gel and eluted with 1:1 ether–hexane to yield pure **11** (2.12 g, 70%) as a pale yellow solid, mp 142–143 °C: NMR δ 2.58 (s, 3, CH_3), 2.65 (t, 2, H_{16}), 2.69 (s, 4, $H_{6,7}$), 2.98 (t, 2 H_{15}), 3.79 (s, 3, OMe), 6.76 (d, 1, H_2), 6.78 (s, 1, H_4), 7.49 (s, 1, H_{12}), 7.55 (d, 1, H_1); $J_{1,2}$ = 8.8 Hz; $J_{15,16}$ = 5.6 Hz; *m/z* (EI) 278 (M^+, 45), 276 (100). Anal. Calcd for $C_{19}H_{18}O_2$; C, 81.99; H, 6.52. Found: C, 82.24; H, 6.65.

15,16-Dihydro-3-methoxy-11-methylcyclopenta[a]phenanthren-17-one (7b). The keto derivative **11** (2.00 g, 7.20 mmol) in 100 mL of triglyme was heated at reflux with 1.0 g of 10% palladium on carbon for 1 h. The solution was allowed to cool, and then water (100 mL) was added and the mixture was heated

in a steam bath for 30 min. This facilitated the workup by breaking up the colloidal product which was otherwise difficult to separate. The precipitate plus catalyst was removed by filtration. The product was dissolved by washing several times with CH_2Cl_2, and then the filtrate was evaporated to dryness and the residue was triturated with ether to yield pure **7b** (1.5 g, 75%) as a white solid, mp 223.5–224.5 °C: NMR δ 2.88 (t, 2, H_{16}), 3.18 (s, 3, CH_3), 3.51 (t, 2, H_{15}), 4.03 (s, 3, OMe), 7.31 (dd, 1, H_2), 7.36 (d, 1, H_4), 7.80 (s, 1, H_{12}), 7.83 (d, 1, $H_{6 \text{ or } 7}$), 7.94 (d, 1, $H_{6 \text{ or } 7}$), 8.91 (d, 1, H_1); $J_{1,2}$ = 9.3; $J_{2,4}$ = 2.8; $J_{6,7}$ = 8.9; $J_{15,16}$ = 4.0 Hz; UV_{max} (Et_{OH}) 218 (5350), 269 (23 800), 281 (23 800) nm; *m/z* (EI) 276 (M^+, 100). Anal. Calcd for $C_{19}H_{16}O_2$; C, 82.58; H, 5.84. Found: C, 82.67; H, 5.87.

3-(Benzoyloxy)-15,16-dihydrocyclopenta[*a*]phenanthren-17-one (12a). To a well stirred suspension of the methyl ether **7a** (1.02 g, 4.1 mmol) in 20 mL of dry CH_2Cl_2 at −78 °C under nitrogen was added 3.3 mL of BBr_3 dropwise. After 90 min when HPLC analysis showed completion, the mixture was allowed to warm to room temperature over 20 min and then poured into ice. A yellow solid was collected by filtration, thoroughly washed with CH_2Cl_2 and water, and then dried in vacuo. The phenol product was taken directly to the next step; its NMR spectrum was consistent with its assignment: NMR δ 2.89 (t, 2, $H_{15 \text{ or } 16}$), 3.52 (t, 2, $H_{15 \text{ or } 16}$), 6.50 (br s, 1, OH), 7.27 (d, 1, H_2), 7.34 (d, 1, H_4), 7.78 (d, 1, H_{12}), 7.89 (d, 1, $H_{6 \text{ or } 7}$), 7.98 (d, 1, $H_{6 \text{ or } 7}$), 8.73 (d, 1, H_{11}), 8.76 (d, 1, H_1); $J_{1,2}$ = 9.0; $J_{6,7}$ = 8.8; $J_{11,12}$ = 8.5; $J_{15,16}$ = 4.9 Hz.

To a suspension of the product (4.1 mmol) from the preceding step in 100 mL of dry CH_2Cl_2 under nitrogen was added 4-(*N,N*-dimethylamino)pyridine (750 mg, 6.2 mmol) and benzoic anhydride (1.12 g, 4.9 mmol), and the mixtures was stirred until HPLC analysis showed completion (3 h). Benzoyl chloride and pyridine may also be used in this reaction with similar results. Conventional workup followed by chromatography on a silical gel column and elution with 2% ethanol in chloroform afforded **12a** (880 mg, 61% from **7a**) as a white solid, mp 287–288 °C: NMR δ 2.90 (t, 2, H_{16}), 3.52 (t, 2, H_{15}), 7.53 (t, 2, Ar), 7.57 (dd, 1, H_2), 7.65 (t, 1, Ar), 7.81 (d, 1, H_4), 7.86 (d, 1, $H_{6 \text{ or } 7}$), 7.96 (d, 1, $H_{6 \text{ or } 7}$), 7.97 (d, 1, H_{12}), 8.24 (d, 2, Ar), 8.66 (d, 1, H_{11}), 8.78 (d, 1, H_1); $J_{1,2}$ = 9.0; $J_{2,4}$ = 2.3; $J_{6,7}$ = 9.0; $J_{11,12}$ = 8.6; $J_{15,16}$ = 5.6 Hz; *m/z* (EI) 352 (M^+, 10), 105 ($C_7H_5O^+$, 100). Anal. Calcd for $C_{24}H_{16}O_3$; C, 81.80; H, 4.58. Found: C, 81.77; H, 4.62.

3-(Benzoyloxy)-17-[(*tert*-butyldiphenylsilyl)oxy]-15,16-dihydrocyclopenta[*a*]phenanthrene (13a). To a suspension of **12a** (780 mg, 2.21 mmol) in 200 mL of THF–MeOH (9:1) at 0 °C was added $NaBH_4$ (86 mg, 2.32 mmol) in one portion. After 2 h, during which time the suspension had warmed to ambient temperature, HPLC analysis revealed reaction to be incomplete. Another portion of $NaBH_4$ (100 mg) was added, and stirring was continued for 30 min. The solution was diluted with ether, and solid NH_4Cl and water were added. The layers were separated, the aqueous layer was back-extracted with ether, and the combined organics were washed with brine, dried, and evaporated to yield the alcohol product (650 mg, 83%) as a white solid: NMR δ 1.84–3.19 (m, 4, CH_2), 5.45 (br s, 1, OH), 7.22–7.88 (m, 8, Ar), 8.24 (d, 2, Ar), 8.55 (d, 1, H_{11}), 8.71 (d, 1, H_1); $J_{1,2}$ = 9.0; $J_{11,12}$ = 8.4 Hz. This was used directly in the next step.

To a suspension of the foregoing alcohol (650 mg, 1.84 mmol) in 125 mL of dry CH_2Cl_2 under nitrogen was added 4-(*N,N*-dimethylamino)pyridine (23 mg, 0.18 mmol), imidazole (287 mg, 4.22 mmol), and *tert*-butyldiphenylsilyl chloride (1.08 mL, 4.22 mmol), and the solution was stirred at rt for 2 h (reaction complete by HPLC). The solution was diluted with CH_2Cl_2, washed with iced 1 M HCl (2×), water, and brine, and then dried and evaporated. The resulting caramel was triturated with ether to provide **13a** (875 mg, 81%) as a cream colored solid, mp 181–182 °C: NMR δ 1.05 (s, 9, CMe_3), 2.18–3.39 (m, 4, $H_{15,16}$), 5.52 (t, 1, H_{17}), 7.35–7.75 (m, 18, Ar), 8.23 (d, 2, Ar), 8.46 (d, 1, H_{11}), 8.67 (d, 1, H_1); $J_{1,2}$ = 9.0; $J_{11,12}$ = 8.5; $J_{16,17}$ = 5.6 Hz. Anal. Calcd for $C_{40}H_{36}O_3Si$; C, 81.80; H, 6.12. Found: C, 81.67; H, 6.42.

17-[(*tert*-Butyldiphenylsilyl)oxy]-15,16-dihydrocyclopenta[*a*]phenanthrene-3,4-dione (14a). To a solution of **13a** (425 mg, 0.72 mmol) in 40 mL of THF was added 15 mL of 0.1 M KOH in MeOH. This was stirred at rt under nitrogen for 1 h, and then it was diluted with ether and washed with iced 1 M HCl. The aqueous layer was back-extracted with ether, and the combined organic fractions were washed consecutively with saturated $NaHCO_3$ (3×), water, and brine, dried, concentrated, and passed through a short column of silica gel. Elution with 1:1 ether–hexane gave the free phenol as a colorless glass (350 mg, 100%): NMR δ 1.25 (s, 9, CMe_3), 2.25–3.45 (m, 4, $H_{15,16}$), 5.19 (br s, 1, OH), 5.60 (t, 1, H_{17}), 7.24 (dd, 1, H_2), 7.28 (d, 1, H_4), 7.44–7.51 (m, 7, Ar), 7.66 (d, 1, $H_{6 \text{ or } 7}$), 7.75 (d, 1, $H_{6 \text{ or } 7}$), 7.84 (m, 4, Ar), 8.46 (d, 1, H_{11}), 8.59 (d, 1, H_1); $J_{1,2}$ = 8.8; $J_{6,7}$ = 8.9; $J_{11,12}$ = 8.5; $J_{16,17}$ = 6.4 Hz. Anal. Calcd for $C_{33}H_{32}O_2Si$; C, 81.11; H, 6.60. Found: C, 81.27; H, 6.46.

The phenol (350 mg, 0.72 mmol) was dissolved in 30 mL of benzene containing five drops of Adogen 464, and the solution was added to a vigorously stirred solution of Fremy's salt (1.50 g, 5,6 mmol) in 30 mL of M/6 KH_2PO_4. A further two 1.0-g portions of Fremy's salt were added at 30-min intervals. When reaction was complete as shown by loss of color of the aqueous layer, the layers were separated, and the reaction was worked up in the usual manner.[10d] Trituration with ether gave pure **14a** (260 mg, 72%) as a pale red solid, mp 181–182 °C: NMR δ 1.15 (s, 9, CMe_3), 2.23–3.37 (m, 4, $H_{15,16}$), 5.52 (t, 1, H_{17}), 6.57 (d, 1, H_2), 7.40–7.48 (m, 7, Ar), 7.76 (m, 4, Ar), 7.91 (d, 1, H_7), 8.10 (d, 1, H_{11}), 8.17 (d, 1, H_6), 8.31 (d, 1, H_1); $J_{1,2}$ = 10.5; $J_{6,7}$ = 8.6; $J_{11,12}$ = 8.8; $J_{16,17}$ = 6.5 Hz. Anal. Calcd for $C_{33}H_{30}O_3Si$: C, 78.85; H, 6.02. Found: C, 78.84; H, 6.04.

17-[(*tert*-Butyldiphenylsilyl)oxy]-*trans*-3,4-dihydroxy-15,16-dihydrocyclopenta[*a*]phenanthrene (15a). To a solution of **14a** (245 mg, 0.49 mmol) in 125 mL of ethanol was added $NaBH_4$ (370 mg, 10 mmol), and the mixture was stirred with a stream of O_2 bubbling through. After 14 h the red color was still present, so an additional 200 mg of $NaBH_4$ was added, and stirring was continued until the solution became colorless (84 h total) and a single product was evident by HPLC. Reaction was quenched by the addition of solid NH_4Cl, and the solvent was evaporated without heating. The residue was partitioned between ether and the ether phase washed with brine and water, dried, and evaporated. The residue was triturated with ether to furnish **15a** as a white foam (240 mg; 96%): NMR δ 1.10 (s, 9, CMe_3), 2.20–3.35 (m, 4, $H_{15,16}$), 4.59 (m, 1, H_3), 5.01 (m, 1, H_4), 5.50 (br t, 1, H_{17}), 6.22 (d, 1, H_2), 7.22 (d, 1, H_1), 7.35–7.80 (m, 13, Ar), 7.94 (d, 1, H_{11}); $J_{1,2}$ = 10.1; $J_{11,12}$ = 8.4 Hz. Anal. Calcd for $C_{33}H_{34}O_3Si$; C, 78.22; H, 6.76. Found: C, 78.29; H, 6.55.

17-[(*tert*-Butyldiphenylsilyl)oxy]-*trans*-3,4-diacetoxy-15,16-dihydrocyclopenta[*a*]phenanthrene (16a). To a suspension of **15a** (230 mg, 0.45 mmol) in 50 mL of dry CH_2Cl_2 under nitrogen was added 4-(*N,N*-dimethylamino)pyridine (174 mg, 1.42 mmol) and Ac_2O (0.13 mL, 1.42 mmol). The solution was stirred until reaction was complete by HPLC (90 min). The usual workup followed by chromatography on silica gel and elution with 5–20% ether in hexane gave **16a** (145 mg, 54%) as a colorless oil: NMR δ 1.16 (s, 9, CMe_3), 2.08 and 2.15 (pair s, 6, MeCO), 2.20–3.35 (m, 4, $H_{15,16}$), 5.52 (br t, 1 H_{17}), 5.63 (m, 1, H_3), 6.23 (m, 1, H_2), 6.32 (m, 1, H_4), 7.41–7.78 (m, 14, Ar), 8.00 (d, 1, H_{11}); $J_{11,12}$ = 8.7 Hz. Anal. Calcd for $C_{37}H_{38}O_5Si$; C, 75.22; H, 6.48. Found: C, 75.51; H, 6.59. The related dibenzoate ester was synthesized by modification of the same procedure using benzoic anhydride.

***trans*-3,4-Diacetoxy-15,16-dihydrocyclopenta[*a*]phenanthren-17-ol (17a).** The silyl ether **16a** (130 mg, 0.22 mmol) was dissolved in 25 mL of THF to which was added *n*-Bu_4NF (0.33 mmol of 1.0 M solution in THF). This solution was stirred for 4 h until reaction was complete (by HPLC) and then absorbed on the minimal silica gel and evaporated to dryness. The product was placed on a column of silica gel in hexane and eluted with a gradient of 40–80% ether in hexane to provide **17a** (45 mg, 58%) as a white solid: NMR δ 2.08 and 2.15 (pair s, 6, MeCO), 2.16–3.45 (m, 4, $H_{15,16}$), 5.48 (m, 1, H_3), 5.64 (br t, 1, H_{17}), 6.26 (dd, 1, H_2), 6.33 (d, 1, H_4), 7.50 (m, 2, $H_{1,12}$), 7.64 (d, 1, $H_{6 \text{ or } 7}$), 7.81 (d, 1, $H_{6 \text{ or } 7}$), 8.11 (d, 1, H_{11}); $J_{1,2}$ = 10.0; $J_{2,3}$ = 4.1; $J_{3,4}$ = 6.0; $J_{11,12}$ = 8.5 Hz. Anal. Calcd for $C_{21}H_{20}O_5$; C, 71.58; H, 5.72. Found: C, 71.54; H, 5.54.

***trans*-3,4-Dihydroxy-15,16-dihydrocyclopenta[*a*]phenanthren-17-one (18a).** To a solution of **17a** (30 mg, 0.084 mmol) in THF was added DDQ (38 mg, 0.168 mmol), the mixture was stirred at rt for 5 h and then poured into water, extracted into ether, and the ether phase was washed with 10% NaOH, dried, and evaporated. Trituration of the residue with ether gave the 17-keto product (25 mg, 85%), mp 205–206 °C: NMR δ 2.10 and

2.17 (pair s, 6, MeCO), 2.89 (m, 2, H_{16}), 3.47 (m, 2, H_{15}), 5.68 (dd, 1, H_3), 6.29 (dd, 1, H_2), 6.36 (d, 1, H_4), 7.45 (d, 1, H_1), 7.62 (d, 1, H_6), 7.81 (d, 1, H_{12}), 8.01 (d, 1, H_7), 8.15 (d, 1, H_{11}); $J_{1,2}$ = 10.1; $J_{2,3}$ = 4.0; $J_{3,4}$ = 6.2; $J_{6,7}$ = 8.4; $J_{11,12}$ = 8.9 Hz. Anal. Calcd for $C_{21}H_{18}O_5$; C, 71.99; H, 5.18. Found: C, 71.94; H, 5.39.

A solution of NaOMe (50 mg, 0.9 mmol) in 30 mL of MeOH was heated to reflux, and the keto diacetate product from above dissolved in 20 mL of THF was added. The reaction was heated at reflux for 10 min, cooled, quenched with water, and then extracted with THF, dried, and evaporated to dryness. Trituration of the residue with ether gave pure **18a** (25 mg, 99%) as a white solid, mp 310–312 °C: NMR (DMSO-d_6 + D_2O) δ 2.76 (m, 2, H_{16}), 3.39 (m, 2, H_{15}), 4.32 (br d, 1, H_3), 4.71 (br d, 1, H_4), 6.16 (m, 1, H_2), 7.26 (d, 1, H_1), 7.58 (d, 1, H_6), 7.89 (d, 1, H_{12}), 8.06 (d, 1, H_7), 8.20 (d, 1, H_{11}); $J_{1,2}$ = 10.2; $J_{3,4}$ = 11.0; $J_{6,7}$ = 8.6; $J_{11,12}$ = 8.6 Hz; HRMS calcd for $C_{17}H_{14}O_3$ m/z 266.0943, found m/z 266.0951. Anal. Calcd for $C_{17}H_{14}O_3$; C, 76.68; H, 5.30. Found: C, 76.36; H, 5.59.

3-(Benzoyloxy)-15,16-dihydro-11-methylcyclopenta[a]phenanthren-17-one (12b). Demethylation of **7b** (1.10 g, 3.98 mmol) was carried out by the procedure used for the preparation of **12a** (2 h reaction time). The NMR spectrum of the product was entirely consistent with the phenol structure: NMR δ 2.74 (t, 2, H_{16}), 3.06 (d, 3, CH_3), 3.40 (t, 2, H_{15}), 6.50 (br s, 1, OH), 7.22 (d, 1, H_2), 7.34 (d, 1, H_4), 7.63 (d, 1, H_{12}), 7.84 (d, 1, H_7), 7.93 (d, 1, H_6), 8.83 (d, 1, H_1); $J_{1,2}$ = 9.4; $J_{6,7}$ = 8.9; $J_{15,16}$ = 4.9 Hz.

To a suspension of the phenol (1.0 g, 3.98 mmol) in 15 mL of pyridine was added excess benzoyl chloride (10 mL). The phenol dissolved immediately, the solution was stirred under argon for 5 h, and then water was added to precipitate the product which was filtered off, washed with aqueous $NaHCO_3$ and water, and dried. The crude product was taken up in CH_2Cl_2 and passed through a Florisil column. Elution with 5% ethanol in CH_2Cl_2 furnished **12b** (1.10 g, 76% from **7b**) as a white solid, mp 218–219 °C: NMR δ 2.92 (t, 2, H_{16}), 3.24 (s, 3, CH_3), 3.52 (t, 2, H_{15}), 7.54–7.90 (m, 7, Ar), 8.01 (d, 1, H_7), 8.29 (d, 2, Ar), 9.06 (d, 1, H_1); $J_{1,2}$ = 9.3; $J_{6,7}$ = 8.7; $J_{15,16}$ = 5.4 Hz. Anal. Calcd for $C_{31}H_{22}O_5$; C, 78.47; H, 4.67. Found: C, 78.38; H, 4.60.

3-(Benzoyloxy)-17-[(*tert*-butyldiphenylsilyl)oxy]-15,16-dihydro-11-methylcyclopenta[a]phenanthrene (13b). Reduction of **12b** (850 mg, 2.21 mmol) was carried out by the procedure used for the preparation of **13a**. The alcohol product (815 mg, 95%) has mp 179–181 °C: NMR δ 2.16–3.51 (m, 4, $H_{15,16}$), 3.20 (s, 3, CH_3), 4.73 (br s, 1, OH), 5.50 (br t, 1, H_{17}), 7.51–7.84 (m, 8, Ar), 8.28 (d, 2, Ar), 8.98 (d, 1, H_1); $J_{1,2}$ = 9.3. This alcohol was used directly in the next step.

Conversion of the alcohol (1.01 g, 2.70 mmol) to the silyl ether was carried out by modification of the procedure used for the preparation of **13a**. When the reaction was complete (5 h by TLC), it was worked up similarly except that the crude product was chromatographed on a column of Florisil. Elution with 10% benzene in hexane yielded **13b** (1.40 g, 85%) as a pale yellow solid, mp 92–93 °C: NMR δ 1.18 (s, 9, CMe_3), 2.12–3.48 (m, 4, $H_{15,16}$), 3.09 (s, 3, CH_3), 5.56 (t, 1, H_{17}), 7.35–7.75 (m, 18, Ar), 8.28 (d, 2, Ar), 8.94 (d, 1, H_1); $J_{1,2}$ = 9.3; $J_{16,17}$ = 6.3 Hz. Anal. Calcd for $C_{41}H_{38}O_3Si$; C, 81.15; H, 6.31. Found: C, 81.27; H, 6.44.

17-[(*tert*-Butyldiphenylsilyl)oxy]-15,16-dihydro-11-methylcyclopenta[a]phenanthrene-3,4-dione (14b). Debenzoylation of **13b** (680 mg, 1.12 mmol) with KOH was carried out by the method used for the preparation of **13a** (3 h reaction time). The phenol was obtained as a white foam (540 mg, 96%): NMR δ 1.17 (s, 9, CMe_3), 2.20–3.40 (m, 4, $H_{15,16}$), 3.04 (s, 3, CH_3), 4.99 (br s, 1, OH), 5.54 (t, 1, H_{17}), 7.16 (dd, 1, H_2), 7.28 (d, 1, H_4), 7.40–7.47 (m, 7, Ar), 7.61 (d, 1, H_6), 7.72 (d, 1, H_7), 7.78 (m, 4, Ar), 8.79 (d, 1, H_1); $J_{1,2}$ = 9.2; $J_{2,4}$ = 2.8; $J_{6,7}$ = 8.8; $J_{16,17}$ = 6.3 Hz. Oxidation of the phenol (540 mg, 1.07 mmol) to the quinone was carried out by the procedure used for the Fremy's salt oxidation of **14a** (reaction time 3 h). Pure **14b** was a dark red solid (260 mg, 47%; yields as high as 82% were obtained in some runs), mp 194–195 °C: NMR δ 1.17 (s, 9, CMe_3), 2.20–3.35 (m, 4, $H_{15,16}$), 2.86 (s, 3, CH_3), 5.47 (t, 1, H_{17}), 6.41 (d, 1, H_2), 7.37 (s, 1, H_{12}), 7.40–7.47 (m, 6, Ar), 7.77 (m, 4, Ar), 7.87 (d, 1, H_6), 8.12 (d, 1, H_7), 8.56 (d, 1, H_1); $J_{1,2}$ = 10.9; $J_{6,7}$ = 8.4; $J_{16,17}$ = 6.5 Hz. Anal. Calcd for $C_{34}H_{32}O_3Si$: C, 79.03; H, 6.24. Found: C, 79.30; H, 6.19.

17-[(*tert*-Butyldiphenylsilyl)oxy]-*trans*-3,4-dihydroxy-15,16-dihydro-11-methylcyclopenta[a]phenanthrene (15b). Reduction of **14b** (168 mg, 0.33 mmol) by the method used for the preparation of **15a** (48 h required for completion) gave **15b** (170 mg, 99%) as a white foam: NMR δ 1.20 (s, 9, CMe_3), 2.15–3.25 (m, 4, $H_{15,16}$), 2.80 (2 s, 3, CH_3), 4.55 (m, 1, H_3), 4.80 (m, 1, H_4), 5.50 (br t, 1, H_{17}), 6.10 (d, 1, H_2), 7.22 (d, 1, H_1), 7.35–7.80 (m, 14, Ar); $J_{1,2}$ = 10.2 Hz. Anal. Calcd for $C_{34}H_{36}O_3Si$: C, 78.42; H, 6.97. Found: C, 78.29; H, 6.75.

17-[(*tert*-Butyldiphenylsilyl)oxy]-*trans*-3,4-bis(benzoyloxy)-15,16-dihydro-11-methylcyclopenta[a]phenanthrene (16b). Conversion of **15b** (170 mg, 0.33 mmol) to its dibenzoate ester was carried out by the procedure used for the preparation of the diacetate **15a** (2 h reaction time). The dibenzoate ester **16b** was obtained as an oil (100%): NMR δ 1.20 (s, 9, CMe_3), 2.12–3.26 (m, 4, $H_{15,16}$), 2.81 (s, 3, CH_3), 5.40 (br t, 1, H_{17}), 5.60 (br t, 1, H_3), 6.02 (m, 1, H_2), 6.21 (m, 1, H_4), 6.74 (m, 1, Ar), 7.04 (2 s, 1, H_{12}), 7.30–8.12 (m, 22, Ar); $J_{3,4}$ = 7.0 Hz. Anal. Calcd for $C_{48}H_{44}O_5Si$; C, 79.09; H, 6.08. Found: C, 79.28; H, 6.15.

***trans*-3,4-Bis(benzoyloxy)-15,16-dihydro-11-methylcyclopenta[a]phenanthren-17-ol (17b).** Desilylation of **16b** (130 mg, 0.22 mmol) was carried out in the same manner as for **17a**. Reaction was stopped after 16 h while still incomplete because longer reaction time or larger excess of n-Bu_4F resulted in formation of multiple secondary products (by TLC). The crude product was dissolved in minimum benzene and passed through a short column of silica gel. Unreacted starting material was eluted with CH_2Cl_2, and **17b** was eluted with 1:1 ether–CH_2Cl_2. Attempted further purification of **17b** (45 mg) led to its decomposition; it was, therefore, used directly in the next step.

***trans*-3,4-Dihydroxy-15,16-dihydro-11-methylcyclopenta[a]phenanthren-17-one (18b).** Oxidation of the crude **17b** with DDQ was carried out by the method for preparation of **18a** (reaction time 15 h). The usual workup gave the 17-keto compound (43 mg, 56% from **16b**) as a white solid, mp 186–187 °C: NMR δ 2.81 (m, 2, H_{16}), 2.93 (s, 3, CH_3), 3.36 (t, 2, H_{15}), 6.10 (dd, 1, H_3), 6.28 (dd, 1, H_2), 6.78 (d, 1, H_4), 7.33–8.05 (m, 14, Ar); $J_{1,2}$ = 10.3 Hz. Anal. Calcd for $C_{32}H_{24}O_5$; C, 78.67; H, 4.95. Found: C, 78.41; H, 5.00. Debenzoylation was accomplished by treatment with NaOMe as for **18a**. Trituration of the crude product with ether yielded pure **18b** (19 mg, 76%) as a white solid, mp 220 °C dec: NMR (DMSO-d_6 + D_2O) δ 2.73 (t, 2, H_{16}), 2.82 (s, 3, CH_3), 3.33 (m, 2, H_{15}), 4.29 (br d, 1, H_3), 4.57 (d, 1, H_4), 6.10 (dd, 1, H_2), 7.28 (dd, 1, H_1), 7.37 (s, 1 H_{12}), 7.88 (d, 1, H_6), 8.03 (d, 1, H_7); $J_{1,2}$ = 10.4; $J_{6,7}$ = 8.4; HRMS calcd for $C_{18}H_{16}O_3$ m/z 280.1099, found m/z 280.1097.

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