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Synthesis of Novel Hydrophenanthrene Derivatives

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Novel hydrophenanthrene lactams (4a, b and 13—16) and hydrophenanthrene derivatives (5a—c and 6a—d) bearing an angular carboxymethyl group were synthesized in good yield *via* the tricyclic compounds (3a, b) readily prepared from the cyanomethyl derivative (2) of Wieland–Miescher ketone and 1-chloro-3-pentanone.

Keywords hydrophenanthrene; lactam; Wieland–Miescher ketone; Robinson annelation; 1-chloro-3-pentanone

In connection with the synthesis of bioactive terpenoids from Wieland–Miescher ketone (**1**), we previously reported a convenient synthesis of the cyanomethyl derivative (**2**),[1] and recently found that the Robinson annelation to **2** with 1-chloro-3-pentanone gave the tricyclic compounds (**3a, b**) in high yields. We now wish to describe a new and facile method for the synthesis of novel hydrophenanthrene lactams (**4a, b** and **13—16**) and hydrophenanthrene derivatives (**5a—c** and **6a—d**) having a carboxymethyl group at the angular position from **2** (Chart 1).

We devised the Robinson annelation to the cyanomethyl derivative (**2**) to obtain hydrophenanthrene derivatives bearing an angular cyanomethyl group. Although treatment of **2** with methyl vinyl ketone or ethyl vinyl ketone was fruitless, refluxing **2** with sodium hydride–dimethyl sulfoxide (DMSO) in tetrahydrofuran (THF) for 4 h followed by addition of 1-chloro-3-pentanone at −10 °C afforded the tricyclic compounds (**3a** and **3b**) in 68% and 25% yields, respectively, along with the uncyclized compound (**7**). Since **7** was converted quantitatively to a mixture of **3a** and **3b** upon treatment with lithium diisopropylamide (LDA), **2** was ultimately converted to the tricyclic compounds (**3a** and **3b**) in 96% yield.[2] Configurations of the hydroxyl groups of **3a** and **3b** were assumed to be as depicted in Chart 2 on the basis of the ^{13}C-nuclear magnetic resonance (^{13}C-NMR) spectral data (**3a**, 81.7 ppm; **3b**, 78.5 ppm; signals for the carbon bearing the hydroxyl group) and examination of a Dreiding model (Chart 2).

Although treatment of **3a** with concentrated sulfuric acid gave only the ketone (**8**), heating **3a** with anhydrous *p*-toluenesulfonic acid (*p*-TsOH) (0.4 eq) in benzene with a Dean–Stark apparatus afforded the tetracyclic compound (**9**) in 55% yield *via* retroaldol–aldol reactions and dehydration,[3] together with a mixture of **3a, b** and **7** in 35% yield. Treatment of **3b** or **7** with anhydrous *p*-TsOH also provided **9** in 55% yield and a mixture of **3a, b** and **7** in 35% yield, resulting in an 85% yield of **9** based on consumed starting material.

As the tetracyclic compound (**9**) was in hand, we examined its reactivity. The tetracyclic system of **9** remained intact on mild acidic treatment or sodium borohydride reduction. On the other hand, regioselective cleavage of the 1,3-dicarbonyl group was observed under basic conditions. Namely, treating **9** with 1 N hydrochloric acid in THF under reflux for 30 min gave the triketone (**10**). Ketalization of **9** with ethylene glycol followed by selective hydrolysis of an intermediary diketal derivative with pyridinium *p*-toluenesulfonate (PPTS) afforded the diketo derivative (**11**) in 93% yield. Sodium borohydride reduction of **9** in methanol at 0 °C afforded stereoselectively the β-hydroxy derivative (**12**) in 85% yield. On the other hand, treatment of **9** with

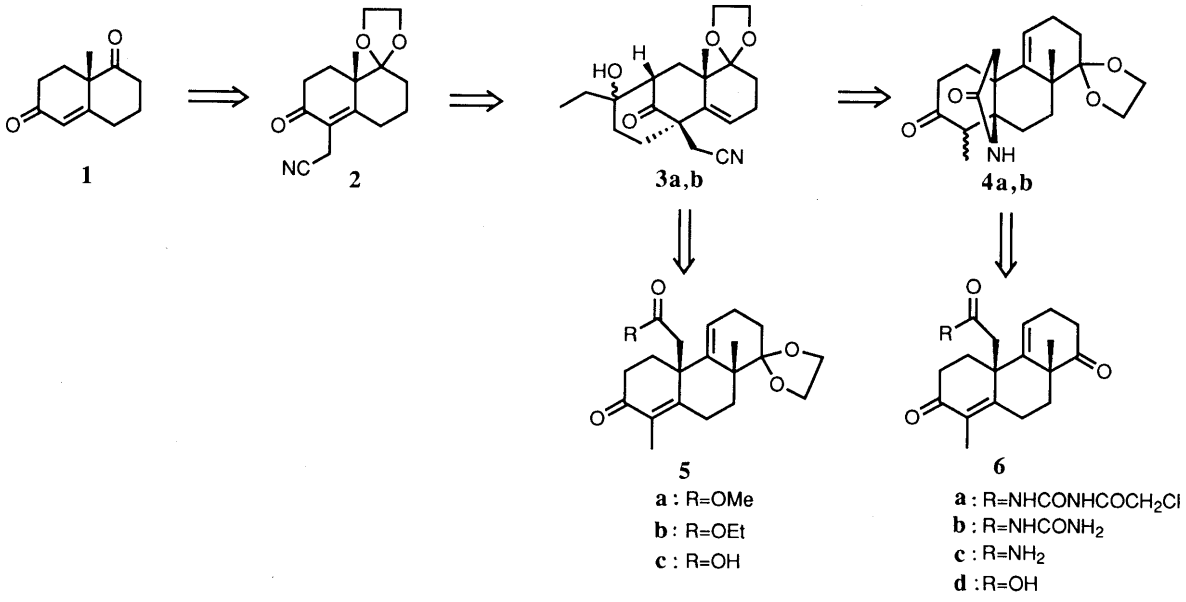
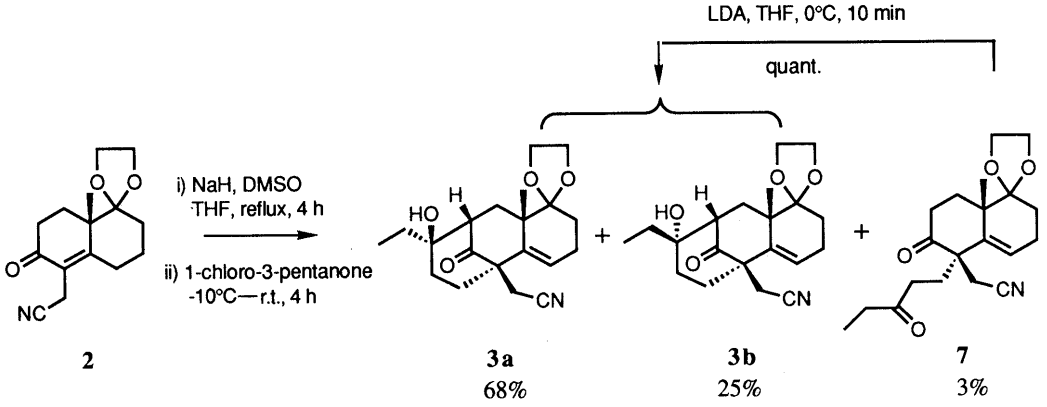


Chart 1



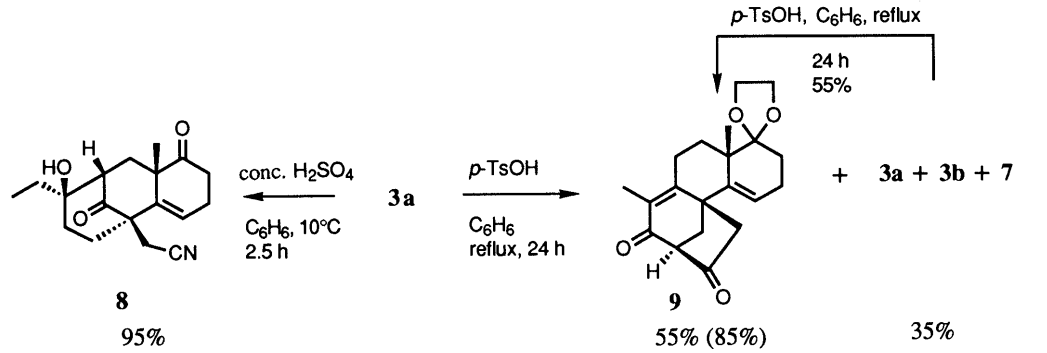


Chart 2

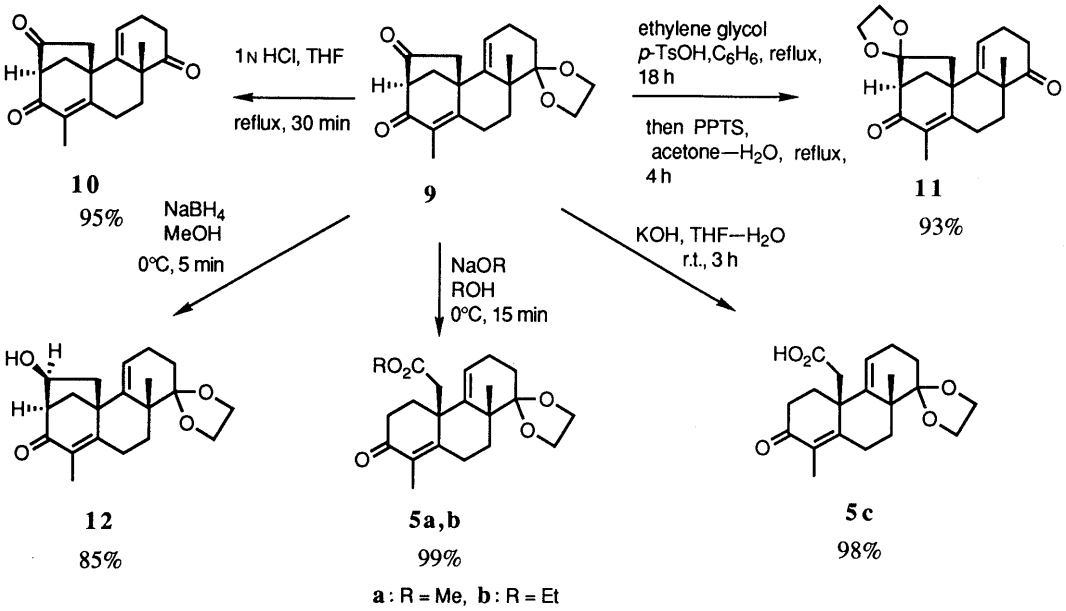


Chart 3

alcoholic sodium methoxide or sodium ethoxide at 0 °C resulted in regioselective alcoholysis of the 1,3-dicarbonyl group, yielding quantitatively new hydrophenanthrene derivatives (**5a, b**) bearing an angular carboalkoxymethyl group. Similarly, **9** was converted to the acid (**5c**) in 98% yield by regioselective hydrolysis of the 1,3-dicarbonyl group when treated with potassium hydroxide (KOH) in aqueous THF at room temperature (Chart 3).

Since novel hydrophenanthrene derivatives (**5a—c**) having an angular carboxymethyl group were obtained in high yield from **3** in two steps (acidic treatment followed by basic treatment), we investigated the reactivity of **3** under basic conditions. Treatment of **3a** with KOH in aqueous methanol under reflux for 30 min gave new hydrophenanthrene lactams (**4a** and **4b**) in 78% and 9% yields, respectively, *via* hydrolysis of the cyano group followed by Michael addition of the resultant amide group to the enone moiety. Compound **3b** was similarly converted to the lactams (**4a** and **4b**) in 78% and 9% yields, respectively. Treatment of either **4a** or **4b** with KOH or lithium hexamethyldisilazide (LHMDS) gave a mixture of **4a** and **4b** in a 6:1 ratio. From these isomer ratios, the stere-

ochemistry of the methyl group of the major lactam (**4a**) was assumed to be equatorial or in β-configuration as a thermodynamically stable option. Also, treatment of **2** with 1-chloro-3-pentanone and KOH in aqueous methanol at $-10\,^{\circ}C$ and subsequent heating under reflux for 1 h gave **4a** and **4b** directly in 72% and 7% yields, respectively.

Because the lactam rings of **4a, b** underwent no cleavage on alkaline hydrolysis, we attempted to hydrolyze a derivative (**13**) whose amide group was acylated with chloroacetyl isocyanate for activation by an electron withdrawing group.[4] However, treatment of **13** with methanolic sodium methoxide or triethylamine resulted in

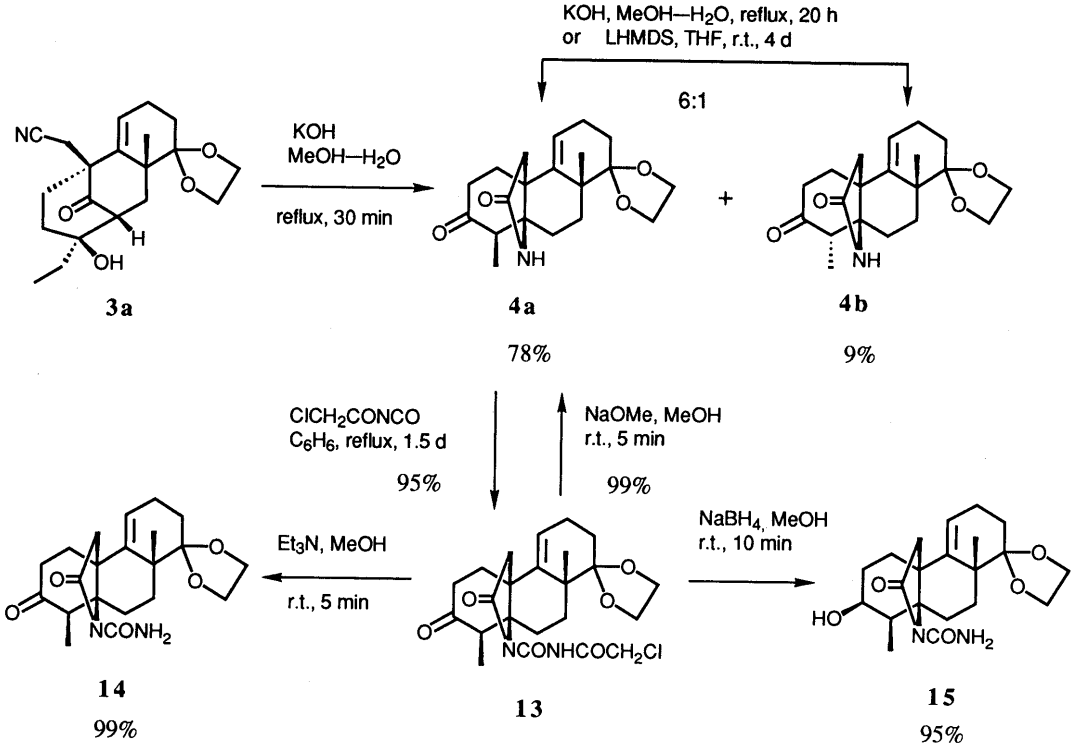


Chart 4

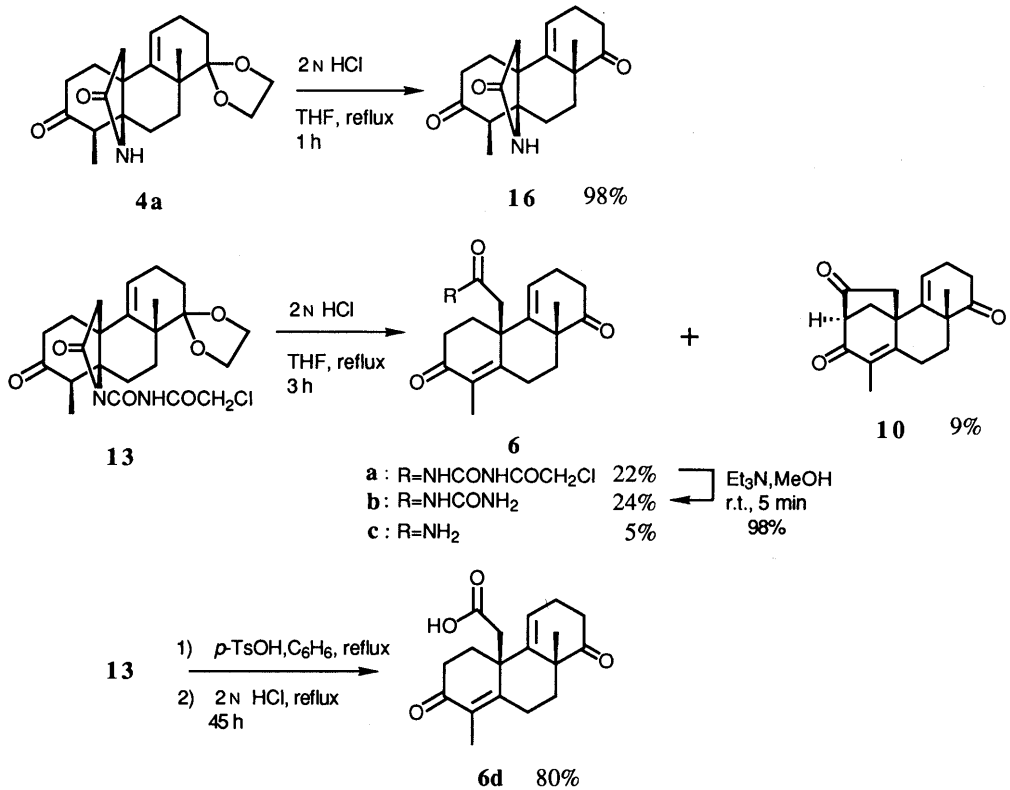


Chart 5

formation of **4a** in 99% yield or the *N*-carbamoyl derivative (**14**) in 99% yield, respectively, and reduction with sodium borohydride in methanol gave only the other *N*-carbamoyl derivative (**15**) in 95% yield (Chart 4).

We therefore examined hydrolysis of the hydrophenanthrene lactams (**4a** and **13**) under acidic conditions. Compound **4a** afforded the diketo-lactam (**16**) in 98% yield when treated with 2 N hydrochloric acid in THF under reflux for 1 h. However, when the *N*-chloroacetylcarbamoyl lactam (**13**) was treated under similar conditions for 3 h, the expected cleavage of the amide linkage was not observed, but instead, a mixture of the hydrophenanthreneacetamides (**6a, b** and **c**) in 22%, 24% and 5% yields, respectively, and the tetracyclic compound (**10**) in 9% yield was obtained as a result of carbon–nitrogen bond cleavage at the angular position. The structures of **6a—c** were determined based on their spectral data and chemical conversion of **6a** into **6b** with Et_3N. Other acidic conditions were examined to prevent hydrolysis of the chloroacetylcarbamoyl group. Treatment of **13** with PPTS in acetone under reflux resulted in recovery of **13**. Refluxing of **13** with *p*-TsOH in benzene for 4 h caused the carbon–nitrogen bond cleavage at the angular position and yielded a mixture including the tetracyclic compounds **9** and **10** as major components *via* formation of **6a**. Addition of 2 N hydrochloric acid to the mixture and subsequent refluxing for 45 h afforded the diketo-acid (**6d**) in 80% yield as the sole final product (Chart 5).

The procedures thus developed will be useful for providing a variety of new hydrophenanthrene lactams and hydrophenanthrene derivatives bearing a carboxymethyl group at the angular position,[5] which can be convenient synthons for polycyclic terpenoids and steroids of biological interest that are hardly accessible by other methodology.

Experimental

Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Shimadzu IR-430 spectrophotometer. NMR spectra were determined on JEOL JNM-EX90 and JNM-GX400 spectrometers with tetramethylsilane (δ 0.00) and $CDCl_3$ (center peak δ 77.1) as internal standards. The following abbreviations are used; s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. Low-resolution mass spectra (MS) were determined on a Hitachi RMU-6MG mass spectrometer. Solvents were evaporated under reduced pressure. Flash column chromatography[6] was performed on silica gel (Wako gel C-300, 200—300 mesh).

Reaction of 2 with 1-Chloro-3-pentanone Compound **2** (1307 mg, 5 mmol) was added to a suspension of NaH (60% oil dispersion, 300 mg, 7.5 mmol), dry DMSO (1.4 ml) and MeOH (10 μl) in dry THF (40 ml). The resulting suspension was heated at reflux under nitrogen for 4 h and then cooled to -10 °C. 1-Chloro-3-pentanone (868 μl, 7.5 mmol) was added with vigorous stirring over a 30 min period. The reaction mixture was stirred at -10 °C for 1 h and allowed to warm to room temperature over a 1 h period. The reaction mixture was cooled to 0 °C, neutralized by addition of 1 N HCl and extracted with $CHCl_3$. The organic layer was washed with water and saturated brine, and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by flash column chromatography[6] with hexane–EtOAc (3 : 1) as an eluent to give **3a** (1174 mg, 68%), **3b** (432 mg, 25%) and **7** (52 mg, 3%).

3a: mp 167.5—169.0 °C, colorless needles (EtOAc–Et_2O). ^{1}H-NMR ($CDCl_3$) δ; 0.90 (3H, t, J = 7.0 Hz), 1.18 (3H, d, J = 0.9 Hz), 2.51 (1H, d, J = 16.4 Hz), 2.71 (1H, d, J = 16.4 Hz), 3.99 (4H, m), 5.73 (1H, dd, J = 3.7, 3.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 6.71 (q), 23.87 (t), 25.47 (t), 25.69 (t), 26.05 (q), 28.98 (t), 29.76 (t), 31.85 (t), 39.86 (t), 41.39 (s), 51.28 (d), 51.41 (s), 64.40 (t), 65.18 (t), 81.72 (s), 111.35 (s), 118.15 (s), 122.75 (d), 145.31 (s), 214.78 (s). IR (KBr): 3500, 2900, 2280, 1725 cm^{-1}. MS m/z: 345 (M^+). *Anal.* Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.06. Found: C, 69.44; H, 7.90; N, 3.95.

3b: mp 153.0—154.0 °C, colorless prisms (EtOAc–Et_2O). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J = 6.8 Hz), 1.17 (3H, d, J = 0.9 Hz), 2.57 (2H, s), 4.02 (4H, m), 5.68 (1H, dd, J = 3.7, 3.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 7.04 (q), 24.07 (t), 25.76 (t), 25.82 (t), 26.70 (q), 28.13 (t), 28.98 (t), 30.19 (t), 37.74 (t), 41.45 (s), 50.96 (s), 53.50 (d), 64.73 (t), 65.38 (t), 78.53 (s), 111.61 (s), 118.06 (s), 122.81 (d), 146.15 (s), 213.48 (s). IR (KBr): 3450, 2950, 2250, 1710 cm^{-1}. MS m/z: 345 (M^+), 317. *Anal.* Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.06. Found: C, 69.46; H, 7.90; N, 3.88.

7: Colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, t, J = 7.3 Hz), 1.15 (3H, s), 2.30 (1H, d, J = 16.3 Hz), 2.88 (1H, d, J = 16.3 Hz), 4.00 (4H, m), 5.64 (1H, dd, J = 4.0, 4.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 7.72 (q), 22.83 (q), 23.28 (t), 24.07 (t), 24.62 (t), 25.89 (t), 33.77 (t), 33.96 (t), 36.14 (t), 36.86 (t), 41.87 (s), 54.15 (s), 65.05 (t), 65.18 (t), 111.42 (s), 118.19 (s), 123.23 (d), 143.00 (s), 209.18 (s), 211.04 (s).

Reaction of 7 with LDA A stirred solution of **7** (69 mg, 0.2 mmol) in dry THF (2 ml) was treated with LDA (1.5 M cyclohexane solution, 200 μl, 0.3 mmol) at 0 °C under nitrogen. After 10 min, water was carefully added to the reaction mixture and the solution was extracted with EtOAc. The organic layer was washed with water and saturated brine, and dried over anhydrous $MgSO_4$. After removal of the solvent, a mixture of **3a** and **3b** (69 mg, 100%, 3 : 1 based on ^{1}H-NMR) was obtained as a colorless powder.

Preparation of 8 A solution of **3a** (35 mg, 0.1 mmol) in benzene (1 ml) was treated with concentrated H_2SO_4 (10 μl) at 10 °C. The reaction mixture was stirred for 2.5 h and then extracted with EtOAc. The combined organic solution was washed with water and saturated brine, and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by flash column chromatography with hexane–EtOAc (1 : 1) as an eluent to give **8** (29 mg, 95%) as a colorless powder.

8: mp 170.0—172.0 °C, colorless prisms (EtOAc–Et_2O). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J = 7.0 Hz), 1.26 (3H, s), 2.60 (1H, d, J = 16.6 Hz), 2.78 (1H, d, J = 16.6 Hz), 6.06 (1H, dd, J = 3.7, 3.7 Hz). ^{13}C-NMR ($CDCl_3$) δ: 6.74 (q), 25.73 (t), 25.82 (t), 26.34 (q), 29.24 (t), 31.85 (t), 33.41 (t), 34.65 (t), 39.37 (t), 45.98 (s), 51.48 (s), 51.61 (d), 81.72 (s), 118.09 (s), 123.88 (d), 141.72 (s), 212.31 (s), 213.06 (s). IR ($CHCl_3$): 2990, 2260, 1725, 1720 cm^{-1}.

Reaction of 3a with Anhydrous *p*-TsOH Anhydrous *p*-TsOH (62 mg, 0.4 mmol) was added to a solution of **3a** (345 mg, 1 mmol) in dry benzene (30 ml). The mixture was refluxed under nitrogen for 24 h with a Dean–Stark condenser, then cooled and extracted with EtOAc. The combined organic solution was washed with water and saturated brine, and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography with hexane–EtOAc (3 : 1) as an eluent to give **9** (181 mg, 55%) and with hexane–EtOAc (2 : 1) as an eluent to give a mixture of **3a**, **3b** and **7** (121 mg, 35%).

9: mp 145.0—147.0 °C, colorless needles (EtOAc). ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, s), 1.65 (3H, br s), 3.50 (1H, ddd, J = 4.2, 1.1, 0.9 Hz), 4.06 (4H, m), 5.65 (1H, dd, J = 3.7, 3.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 10.49 (q), 23.97 (t), 25.63 (t), 27.26 (t), 27.87 (t), 28.49 (q), 41.71 (s), 42.52 (t), 48.45 (s), 49.39 (t), 64.63 (d), 64.89 (t), 65.09 (t), 113.30 (s), 121.51 (d), 127.34 (s), 142.02 (s), 165.98 (s), 191.31 (s), 209.97 (s). IR (KBr): 2950, 1760, 1670 cm^{-1}.

Preparation of 10 A mixture of **9** (66 mg, 0.2 mmol) in THF (3 ml) and 1 N HCl solution (150 μl) was refluxed for 30 min, then cooled and extracted with EtOAc. The combined organic solution was washed with saturated $NaHCO_3$ solution, water and saturated brine, and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by flash column chromatography with hexane–EtOAc (2 : 1) as an eluent to give **10** (54 mg, 95%) as a colorless oil.

10: ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, s), 1.67 (3H, d, J = 1.3 Hz), 3.54 (1H, dd, J = 4.8, 1.3 Hz), 6.01 (1H, dd, J = 5.5, 4.3 Hz). ^{13}C-NMR ($CDCl_3$) δ: 10.55 (q), 22.57 (t), 24.65 (q), 26.90 (t), 27.42 (t), 34.16 (t), 42.20 (t), 48.09 (s), 48.97 (t), 49.03 (s), 64.47 (d), 123.36 (d), 127.79 (s), 142.74 (s), 162.89 (s), 190.92 (s), 208.96 (s), 212.44 (s). IR ($CHCl_3$): 2950, 1750, 1715, 1670 cm^{-1}. MS m/z: 284 (M^+), 268, 256.

Transformation of 9 into 11 A mixture of **9** (66 mg, 0.2 mmol), ethylene glycol (100 μl, 1.8 mmol) and *p*-TsOH·H_2O (2 mg, 0.01 mmol) in dry benzene (5 ml) was refluxed for 18 h with a Dean–Stark condenser. The reaction mixture was cooled and extracted with EtOAc. The combined organic solution was washed with water and saturated brine, and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was dissolved in acetone–water (5 ml, 9 : 1). PPTS (51 mg, 0.2 mmol) was added to the mixture, and the whole was refluxed for 4 h, then cooled and extracted with EtOAc. The combined organic solution was washed with water and saturated brine, and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by flash column chromatography with

hexane–EtOAc (3 : 1) as an eluent to give **11** (61 mg, 93%) as a colorless oil.

11: ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, s), 1.69 (3H, d, J=1.3 Hz), 2.95 (1H, br d, J=4.6 Hz), 3.94 (4H, m), 5.90 (1H, dd, J=5.3, 3.1 Hz). ^{13}C-NMR ($CDCl_3$) δ: 10.29 (q), 22.53 (t), 24.52 (q), 26.83 (t), 27.58 (t), 34.49 (t), 42.33 (t), 49.13 (s), 49.36 (s), 50.08 (t), 57.66 (d), 63.82 (t), 65.28 (t), 116.46 (s), 122.32 (d), 127.43 (s), 143.39 (s), 162.50 (s), 196.98 (s), 213.19 (s). IR ($CHCl_3$): 2960, 1715, 1670 cm^{-1}.

Reduction of 9 with $NaBH_4$ $NaBH_4$ (2 mg, 0.05 mmol) was added to a stirred solution of **9** (33 mg, 0.1 mmol) in dry MeOH (1 ml) at 0 °C. After 5 min, a drop of AcOH was added to the mixture and MeOH was removed by evaporation. The residue was diluted with EtOAc, washed with water and saturated brine, and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by flash column chromatography with hexane–EtOAc (1 : 1) as an eluent to give **5a** (4 mg, 11%) and **12** (28 mg, 85%) as a colorless oil.

5a: ^{1}H-NMR ($CDCl_3$) δ: 1.46 (3H, s), 1.79 (3H, br s), 2.82 (1H, d, J=14.5 Hz), 3.62 (3H, s), 3.95 (4H, m), 5.56 (1H, dd, J=3.5, 3.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 11.43 (q), 24.16 (t), 24.88 (t), 25.89 (t), 26.28 (q), 28.40 (t), 31.13 (t), 33.80 (t), 41.84 (t), 42.39 (s), 43.47 (s), 51.41 (q), 65.02 (t), 65.28 (t), 112.82 (s), 123.01 (d), 129.88 (s), 142.96 (s), 160.61 (s), 170.60 (s), 198.15 (s). IR ($CHCl_3$): 2950, 1720, 1660 cm^{-1}.

12: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.32 (3H, s), 1.70 (3H, br s), 3.18 (1H, m), 4.04 (4H, m), 4.79 (1H, ddd, J=9.5, 6.1, 2.7 Hz), 5.46 (1H, dd, J=3.7, 3.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 10.23 (q), 23.84 (t), 25.66 (t), 27.45 (t), 27.87 (t), 28.43 (q), 41.74 (s), 42.20 (t), 47.38 (t), 50.96 (s), 55.45 (d), 64.86 (t), 65.02 (t), 72.05 (d), 113.40 (s), 119.95 (d), 128.21 (s), 143.19 (s), 168.06 (s), 200.36 (s). IR ($CHCl_3$): 3400, 2960, 2900, 1660 cm^{-1}.

Methyl (±)-*cis*-2′,3′,4′,4′a,6′,8′a,9′,10′-Octahydro-1′,8′a-dimethyl-2′-oxospiro[1,3-dioxolane-2,8′(7′*H*)-phenanthrene]-4′a-acetate (5a) A stirred solution of **9** (33 mg, 0.1 mmol) in dry MeOH (1 ml) was treated with 28% NaOMe–MeOH solution (19 μl, 0.1 mmol) at 0 °C under nitrogen. After 15 min, MeOH was removed by evaporation. The residue was diluted with EtOAc, washed with water and saturated brine, and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by flash column chromatography with hexane–EtOAc (2 : 1) as an eluent to give **5a** (36 mg, 99%) as a colorless oil.

Ethyl (±)-*cis*-2′,3′,4′,4′a,6′,8′a,9′,10′-Octahydro-1′,8′a-dimethyl-2′-oxospiro[1,3-dioxolane-2,8′(7′*H*)-phenanthrene]-4′a-acetate (5b) Compound **9** (33 mg, 0.1 mmol) was reacted with NaOEt (7 mg, 0.1 mmol) as described in the case of NaOMe to give **5b** (37 mg, 99%) as a colorless oil.

5b: ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.0 Hz), 1.79 (3H, d, J=0.9 Hz), 2.81 (1H, d, J=13.8 Hz), 3.96 (4H, m), 4.09 (2H, q, J=7.0 Hz), 5.56 (1H, dd, J=3.7, 3.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 11.37 (q), 14.33 (q), 24.13 (t), 24.81 (t), 25.89 (t), 26.25 (q), 28.40 (t), 31.10 (t), 33.80 (t), 41.97 (t), 42.36 (s), 43.50 (s), 60.30 (t), 64.96 (t), 65.25 (t), 112.78 (s), 122.94 (d), 129.78 (s), 142.96 (s), 160.67 (s), 170.15 (s), 198.15 (s). IR ($CHCl_3$): 2980, 1720, 1660 cm^{-1}.

(±)-*cis*-2′,3′,4′,4′a,6′,8′a,9′,10′-Octahydro-1′,8′a-dimethyl-2′-oxospiro-[1,3-dioxolane-2,8′(7′*H*)-phenanthrene]-4′a-acetic Acid (5c) A stirred solution of **9** (33 mg, 0.1 mmol) in THF (1 ml) was treated with 10% KOH solution (240 μl, 0.5 mmol) at 0 °C under nitrogen. The mixture was stirred for 3 h at room temperature, then cooled to 0 °C, neutralized with 1 N HCl solution, and extracted with EtOAc. The combined organic solution was washed with water and saturated brine, and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by flash column chromatography with hexane–EtOAc–MeOH (10 : 30 : 1) as an eluent to give **5c** (34 mg, 98%) as a colorless oil.

5c: ^{1}H-NMR ($CDCl_3$) δ: 1.47 (3H, s), 1.79 (3H, s), 2.40 (1H, d, J=14.1 Hz), 2.83 (1H, d, J=14.1 Hz), 3.95 (4H, s), 5.61 (1H, dd, J=3.5, 3.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 11.43 (q), 24.13 (t), 24.91 (t), 25.89 (t), 26.34 (q), 28.40 (t), 30.97 (t), 33.77 (t), 41.74 (t), 42.36 (s), 43.40 (s), 65.02 (t), 65.25 (t), 112.82 (s), 123.73 (d), 129.97 (s), 142.67 (s), 160.74 (s), 175.16 (s), 198.31 (s).

Preparation of the Hydrophenanthrene Lactams (4a and 4b) A stirred solution of **3a** (345 mg, 1 mmol) in MeOH (10 ml) was treated with 10% KOH solution (2.4 ml). The mixture was heated under reflux for 30 min, and cooled to room temperature. After removal of MeOH, the residue was diluted with water and extracted with $CHCl_3$. The combined organic solution was washed with water and saturated brine, and dried over anhydrous $MgSO_4$. The solution was evaporated and the residue was purified by flash column chromatography with hexane–EtOAc–MeOH (10 : 30 : 1) as an eluent to give **4a** (269 mg, 78%) and **4b** (31 mg, 9%) as a colorless powder.

4a: mp 199.5—200.0 °C, colorless prisms (EtOAc–Et_2O). ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, d, J=6.8 Hz), 1.43 (3H, s), 2.15 (1H, d, J=17.8 Hz), 2.67 (1H, q, J=6.8 Hz), 3.00 (1H, d, J=17.8 Hz), 3.98 (4H, m), 5.74 (1H, dd, J=3.7, 3.5 Hz), 6.16 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: 8.08 (q), 23.58 (t), 24.65 (t), 25.53 (t), 29.53 (q), 31.85 (t), 32.40 (t), 35.10 (t), 41.74 (s), 44.54 (s), 45.19 (t), 47.02 (d), 64.73 (t × 2), 67.17 (s), 112.95 (s), 122.81 (d), 141.04 (s), 176.50 (s), 210.94 (s). IR (KBr): 3200, 3100, 2980, 2900, 1730, 1690 cm^{-1}. MS *m/z*: 345 (M^+), 301, 273. *Anal.* Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.06. Found: C, 69.80; H, 7.90; N, 3.86.

4b: mp 230.5—232.0 °C, colorless prisms (EtOAc–Et_2O). ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, d, J=6.8 Hz), 1.31 (3H, s), 2.36 (1H, d, J=18.0 Hz), 2.83 (1H, d, J=18.0 Hz), 2.91 (1H, q, J=6.8 Hz), 3.90 (4H, br s), 5.59 (1H, dd, J=3.7, 3.7 Hz). ^{13}C-NMR ($CDCl_3$) δ: 9.12 (q), 23.58 (t), 24.26 (t), 25.82 (t), 28.95 (t), 29.05 (q), 31.75 (t), 36.08 (t), 41.52 (s), 44.93 (s), 47.73 (t), 51.71 (d), 64.83 (t), 65.25 (t, s), 113.08 (s), 122.97 (d), 140.59 (s), 175.81 (s), 211.89 (s). IR (KBr): 3200, 3100, 2990, 1720, 1700 cm^{-1}. MS *m/z*: 345 (M^+). *Anal.* Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.06. Found: C, 69.25; H, 7.87; N, 3.79.

Reaction of 4a or 4b with Base i) A solution of **4a** (17 mg, 0.05 mmol) in MeOH (1 ml) was treated with 10% KOH solution (200 μl). The mixture was heated under reflux for 20 h and worked up as described above to give a mixture of **4a** and **4b** (17 mg, **4a** : **4b** = 6 : 1, based on ^{1}H-NMR) as a colorless powder. ii) **4b** was reacted with KOH as described in i). **4a** : **4b** = 6 : 1, based on ^{1}H-NMR. iii) A solution of **4a** (17 mg, 0.05 mmol) in dry THF (1 ml) was treated with 1 M THF solution of LHMDS (100 μl, 0.1 mmol). The mixture was stirred for 4 d at room temperature under nitrogen, and extracted with EtOAc. The combined organic solution was washed with water and saturated brine, and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded a mixture of **4a** and **4b** (17 mg, **4a** : **4b** = 6 : 1, based on ^{1}H-NMR) as a colorless powder. iv) **4b** was reacted with LHMDS as described in iii). **4a** : **4b** = 6 : 1, based on ^{1}H-NMR.

Reaction of 4a with Chloroacetyl Isocyanate Chloroacetyl isocyanate (85 μl, 1.0 mmol) was added to a suspension of **4a** (173 mg, 0.5 mmol) in dry benzene (3 ml). The mixture was heated under reflux for 30 h, then cooled to room temperature, and extracted with EtOAc. The combined organic solution was washed with water and saturated brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by flash column chromatography with hexane–EtOAc (1 : 1) as an eluent to give **13** (221 mg, 95%) as a colorless powder.

13: mp 190.0—191.0 °C, colorless prisms (EtOAc–$CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, d, J=7.0 Hz), 1.32 (3H, s), 2.55 (1H, d, J=18.7 Hz), 3.07 (1H, d, J=18.7 Hz), 3.09 (1H, q, J=7.0 Hz), 3.97 (4H, m), 4.41 (2H, s), 5.71 (1H, dd, J=3.7, 3.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 14.10 (q), 24.00 (t), 24.39 (t), 25.66 (t), 28.20 (q), 30.84 (t), 32.82 (t), 34.52 (t), 41.65 (s), 42.33 (s), 44.51 (t), 48.35 (t), 51.74 (d), 65.18 (t), 65.25 (t), 73.39 (s), 112.52 (s), 124.83 (d), 140.49 (s), 148.79 (s), 166.83 (s), 177.41 (s), 211.30 (s). IR (KBr): 3450, 2950, 1715, 1705 cm^{-1}.

Preparation of the *N*-Carbamoyl Derivative (14) Et_3N (46 μl, 0.3 mmol) was added dropwise to a stirred suspension of **13** (46 mg, 0.1 mmol) in dry MeOH (4 ml) at room temperature under nitrogen. After 5 min, the mixture was concentrated. The residue was diluted with water and extracted with EtOAc. The combined organic solution was washed with water and saturated brine, and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by flash column chromatography with hexane–EtOAc (1 : 2) as an eluent to give **14** (38 mg, 99%) as a colorless powder.

14: mp 189.1—190.0 °C, colorless prisms (EtOAc–Et_2O). ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, d, J=7.5 Hz), 1.31 (3H, s), 2.49 (1H, d, J=18.2 Hz), 3.00 (1H, d, J=18.2 Hz), 3.09 (1H, q, J=7.5 Hz), 3.96 (4H, m), 5.44 (1H, br s), 5.68 (1H, dd, J=3.7, 3.7 Hz), 8.51 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: 14.46 (q), 23.93 (t), 24.52 (t), 25.66 (t), 28.33 (q), 31.72 (t), 32.66 (t), 34.45 (t), 41.58 (s), 42.20 (s), 48.65 (t), 52.49 (d), 65.12 (t), 65.18 (t), 72.02 (s), 112.72 (s), 123.95 (d), 141.24 (s), 153.64 (s), 176.72 (s), 212.54 (s). IR (KBr): 3400, 2950, 1730, 1720, 1710 cm^{-1}.

Reaction of 13 with NaOMe A stirred suspension of **13** (46 mg, 0.1 mmol) in dry MeOH (4 ml) was treated with 28% NaOMe–MeOH solution (67 μl, 0.3 mmol) at room temperature under nitrogen. After 5 min, the mixture was worked up as described for **14** to give **4a** (34 mg, 99%) as a colorless powder.

Preparation of the *N*-Carbamoyl Derivative (15) A stirred suspension of **13** (46 mg, 0.1 mmol) in dry MeOH (5 ml) was treated with $NaBH_4$ (7 mg, 0.2 mmol) at room temperature under nitrogen. After 5 min, the mixture was worked up as described for **14** to give **15** (37 mg, 95%) as a colorless oil.

15: ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, d, J=7.0 Hz), 1.27 (3H, s), 2.35

(1H, d, J=17.6 Hz), 2.84 (1H, d, J=17.6 Hz), 3.97 (5H, m), 5.64 (1H, dd, J=2.9, 2.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 11.79 (q), 23.77 (t), 24.85 (t), 25.76 (t), 26.54 (t), 28.53 (q), 30.12 (t), 31.03 (t), 41.39 (s), 42.20 (d), 43.40 (s), 47.12 (t), 65.12 (t×2), 68.83 (d), 71.37 (s), 113.08 (s), 123.17 (d), 142.51 (s), 154.81 (s), 177.70 (s).

Preparation of the Diketo Lactam (16) A 2 N HCl solution (200 μl) was added to a solution of **4a** (35 mg, 0.1 mmol) in THF (2 ml). The mixture was heated under reflux for 1 h, cooled to room temperature, and extracted with EtOAc. The combined organic solution was washed with water and saturated brine, and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by flash column chromatography with hexane–EtOAc–MeOH (10 : 30 : 1) as an eluent to give **16** (30 mg, 98%) as a colorless powder.

16: mp 216.0—217.5 °C, colorless prisms (EtOAc). ^{1}H-NMR ($CDCl_3$) δ: 1.05 (3H, d, J=6.8 Hz), 1.39 (3H, s), 2.28 (1H, d, J=18.5 Hz), 2.75 (1H, q, J=6.8 Hz), 2.97 (1H, d, J=18.5 Hz), 6.10 (1H, dd, J=3.6, 3.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 8.08 (q), 22.01 (t), 24.39 (q), 24.72 (t), 32.63 (t), 33.54 (t×2), 33.60 (t), 44.09 (s), 44.35 (t), 48.65 (d), 49.98 (s), 65.38 (s), 126.13 (d), 143.26 (s), 176.04 (s), 210.04 (s), 212.24 (s). IR (KBr): 3180, 3090, 2950, 1725, 1710, 1690 cm^{-1}.

***N*-(*N'*-Chloroacetylcarbamoyl)-(±)-*cis*-2,3,4,4a,6,7,8,8a,9,10-decahydro-1,8a-dimethyl-2,8-dioxo-4a-phenanthreneacetamide (6a), *N*-Carbamoyl-(±)-*cis*-2,3,4,4a,6,7,8,8a,9,10-decahydro-1,8a-dimethyl-2,8-dioxo-4a-phenanthreneacetamide (6b), (±)-*cis*-2,3,4,4a,6,7,8,8a,9,10-Decahydro-1,8a-dimethyl-2,8-dioxo-4a-phenanthreneacetamide (6c) and 10** A solution of **13** (465 mg, 1 mmol) in THF (10 ml) was treated with 2 N HCl (1 ml), 2 mmol), and the mixture was heated under reflux for 3 h. After cooling, the mixture was extracted with EtOAc. The combined organic solution was washed with 10% Na_2CO_3 solution, water and saturated brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by flash column chromatography with hexane–EtOAc (1 : 1) as an eluent to give **10** (26 mg, 9%) and **6a** (93 mg, 22%) with hexane–EtOAc (1 : 5) as an eluent to give **6b** (83 mg, 24%) as a colorless powder, respectively, and with hexane–EtOAc–MeOH (10 : 50 : 1) as an eluent to give **6c** (15 mg, 5%) as a colorless oil.

6a: mp 182.0—183.0 °C, colorless prisms (EtOAc–$CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, s), 1.73 (3H, br s), 2.85 (1H, d, J=16.0 Hz), 3.20 (1H, d, J=16.0 Hz), 4.35 (2H, s), 6.08 (1H, br t). ^{13}C-NMR ($CDCl_3$) δ: 11.37 (q), 22.60 (t), 24.26 (q), 26.64 (t), 28.30 (t), 31.16 (t), 33.44 (t), 33.67 (t), 42.92 (t), 43.24 (s), 43.73 (t), 48.52 (s), 127.50 (d), 131.01 (s), 141.69 (s), 149.08 (s), 159.73 (s), 167.28 (s), 170.77 (s), 197.53 (s), 212.51 (s). IR (KBr): 3400, 3280, 3200, 2950, 1725, 1710, 1685, 1640 cm^{-1}. MS m/z: 386 (M^+ − Cl), 385 (M^+ − HCl).

6b: mp 204.0—206.3 °C, colorless prisms (EtOAc–$CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, s), 1.73 (3H, br s), 2.67 (1H, d, J=15.8 Hz), 2.97 (1H, d, J=15.8 Hz), 5.44 (1H, br s), 6.03 (1H, br t), 6.09 (1H, br s), 8.17 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: 11.34 (q), 22.57 (t), 24.07 (q), 26.54 (t), 28.33 (t), 31.46 (t), 33.44 (t), 33.73 (t), 42.72 (t), 43.31 (s), 48.55 (s), 126.98 (d), 130.85 (s), 142.31 (s), 155.04 (s), 159.60 (s), 171.22 (s), 197.50 (s), 212.73 (s). IR (KBr): 3450, 3300, 3180, 3100, 2990, 1725, 1710, 1665 cm^{-1}.

6c: Colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, s), 1.73 (3H, br s), 6.02 (1H, dd, J=3.6, 3.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 11.27 (q), 22.60 (t), 23.90 (q), 26.51 (t), 28.30 (t), 31.46 (t), 33.54 (t), 33.80 (t), 41.19 (t), 43.08 (s), 48.55 (s), 126.20 (d), 130.69 (s), 143.21 (s), 160.58 (s), 173.40 (s), 197.79 (s), 213.09 (s). IR ($CHCl_3$): 3400, 2950, 1720, 1670 cm^{-1}.

***N*-Carbamoyl-(±)-*cis*-2,3,4,4a,6,7,8,8a,9,10-decahydro-1,8a-dimethyl-2,8-dioxo-4a-phenanthreneacetamide (6b)** Et_3N (46 μl, 0.3 mmol) was added dropwise to a stirred suspension of **6a** (46 mg, 0.1 mmol) in dry MeOH (4 ml) at room temperature under nitrogen. After 5 min, the mixture was concentrated. The residue was dissolved in water and $CHCl_3$. The organic solution was washed with water and saturated brine, and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by flash column chromatography with hexane–EtOAc (1 : 5) as an eluent to give **6b** (34 mg, 98%) as a colorless powder.

(±)-*cis*-2,3,4,4a,6,7,8,8a,9,10-Decahydro-1,8a-dimethyl-2,8-dioxo-4a-phenanthreneacetic Acid (6d) *p*-TsOH·H_2O (10 mg, 0.05 mmol) was added to a suspension of **13** (93 mg, 0.2 mmol) in benzene (10 ml), and the mixture was heated under reflux for 4 h. Then 2 N HCl (1 ml) and THF (2 ml) were added to the mixture and heating was continued for 45 h. After cooling, the mixture was diluted with EtOAc and extracted with 1 N $NaHCO_3$ solution. The $NaHCO_3$ solution was acidified with 2 N HCl solution and extracted with EtOAc. The combined organic solution was washed with water and saturated brine, and dried over anhydrous $MgSO_4$. The solution was evaporated and the residue was purified by flash column chromatography with hexane–EtOAc–MeOH (10 : 30 : 1) as an eluent to give **6d** (48 mg, 80%) as a colorless oil.

6d: ^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, s), 1.73 (3H, br s), 2.70 (1H, d, J=14.3 Hz), 2.96 (1H, d, J=14.3 Hz), 6.00 (1H, br t). ^{13}C-NMR ($CDCl_3$) δ: 11.27 (q), 22.57 (t), 23.93 (q), 26.44 (t), 28.33 (t), 31.36 (t), 33.44 (t), 33.73 (t), 41.12 (s), 43.08 (t), 48.52 (s), 126.29 (d), 130.85 (s), 142.38 (s), 159.86 (s), 174.64 (s), 197.85 (s), 213.03 (s). IR ($CHCl_3$): 2950, 1720, 1710, 1660 cm^{-1}.

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References and Notes

1) T. Shimizu, S. Hiranuma, H. Yoshioka, *Synlett*, **1991**, 833.
2) When the corresponding enones having a substituted methyl group, such as CH_2CO_2Me, CH_2CO_2H, CH_2CH_2OMEM and CH_2OMe, were treated in the same manner as described for **2**, a complex mixture was obtained or the starting material was recovered.
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5) Starting from the benzoate derivative of the ketal (**2**), the corresponding hydrophenanthrene derivatives were also synthesized *via* a similar route.
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