Synthesis of Ring D Modified Morphinan Systems via Ring Expansion of a Key Codeine Intermediate

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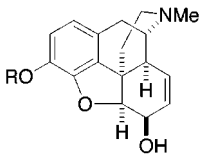
Ring expansion and ring fragmentation products were synthesized from pentacyclic ketones **3** and **4** via Baeyer−Villiger oxidation. Oxidation of **3** with *m*-chloroperbenzoic acid afforded *δ*-lactone **9** which was transformed to enone **12** en route to the C6 inverted ether **14**. Analogous oxidation of **4** gave *δ*-lactone **18**. Opening of the lactone ring of **14** and **18** led to seco structures which, in the case of **19**, underwent reannulation with incorporation of nitrogen to yield the hydroxylactam **21**.

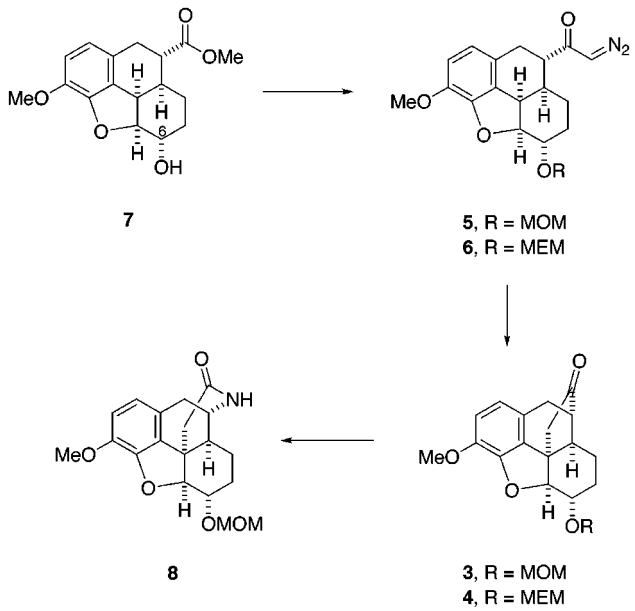
A recent asymmetric synthesis of morphine reported from these laboratories led to the nonnatural (+) enantiomers of **1** and its congener codeine (**2**).[1] The route to **1**



1, R = H
2, R = Me

and **2** employed intramolecular C−H insertion by a rhodium carbenoid to construct a pentacyclic ketone, **3** or **4**, from a diazoketone (**5** or **6**, respectively).[2] The diazoketones were prepared from tetracyclic ester **7**, the choice of MEM or MOM protection of the C6 hydroxyl group being dictated by the need to retain or reverse configuration at the hydroxyl-bearing center. Oxime formation from **3** followed by Beckmann rearrangement afforded *δ*-lactam **8**, from which (+)-codeine (**2**) possessing (6*R*) hydroxyl configuration was obtained.[3]

Initial difficulties with Beckmann rearrangement of the oxime of **3** caused us concern, since it was clear that failure to expand the cyclopentanone ring of this structure would deny access to the morphine skeleton. Baeyer−Villiger oxidation seemed likely to offer an alternative means for ring expansion of **3**, and even though this would necessitate eventual replacement of the lactone oxygen by a nitrogen atom, Baeyer−Villiger oxidation of **3** was expected to be highly regioselective. In the event, exposure of **3** to *m*-chloroperbenzoic acid led smoothly to *δ*-lactone **9** resulting from migration of the more highly substituted carbon to the intermediate oxenium ion.[4] Removal of the MOM protecting group from **9** furnished alcohol **10** which was oxidized with Dess−Martin periodinane[5] to keto lactone **11**. The keto function of **11** afforded an opportunity to introduce the $\Delta^{7,8}$ unsaturation characteristic of morphine alkaloids, and for this transformation α-phenylselenylation followed by periodate oxidation was employed. Acidic conditions for the selenylation[6] ensured that selenium was incorporated exclusively at C7, thereby avoiding complications arising from competing substitution at C5 which occurs under basic conditions. As expected,[1] reduction of **12** with L-Selectride took place with high stereoselectivity from the rear face to yield the 6*β* alcohol **13**.

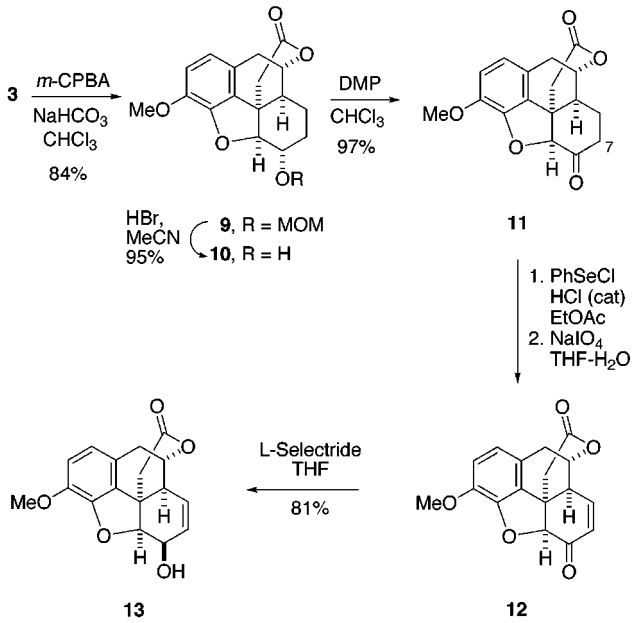


7

5, R = MOM
6, R = MEM

8

3, R = MOM
4, R = MEM



9, R = MOM
10, R = H

11

13

12

(1) White, J. D.; Hrnciar, P.; Stappenbeck, F. *J. Org. Chem.* **1997**, *62*, 5250.
(2) White, J. D.; Hrnciar, P. *J. Org. Chem.* **1999**, *64*, 7271.
(3) White, J. D.; Hrnciar, P.; Stappenbeck, F. *J. Org. Chem.* **1999**, *64*, 7871.
(4) Krow, G. R. *Org. React.* **1993**, *43*, 251.
(5) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(6) Iijima, I.; Rice, K. C.; Silverton, J. V. *Heterocycles* **1977**, *6*, 1157.

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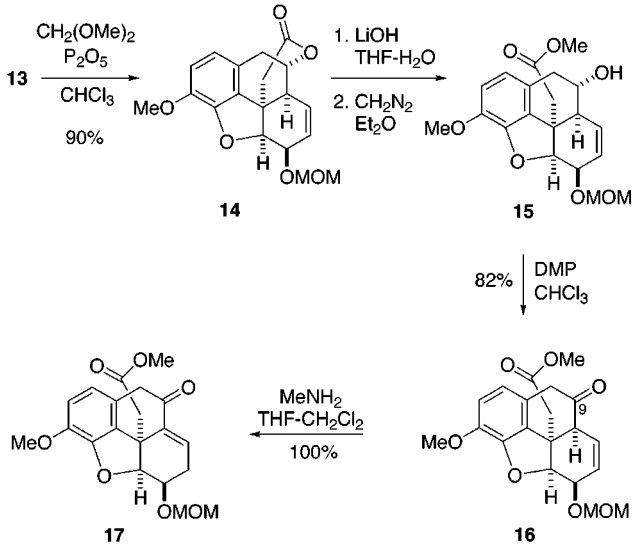
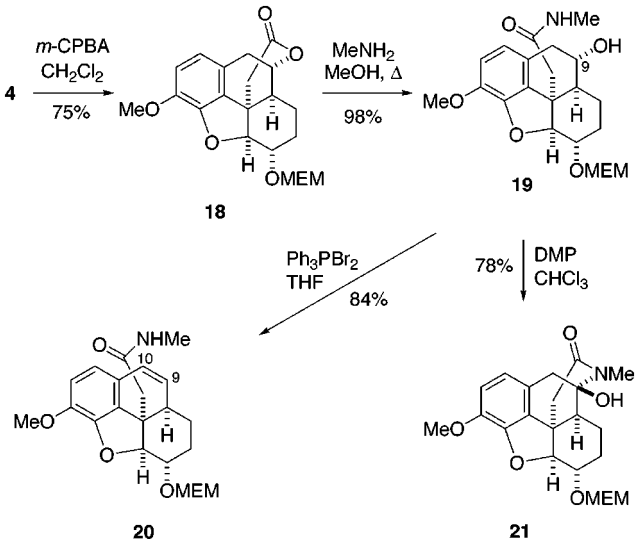
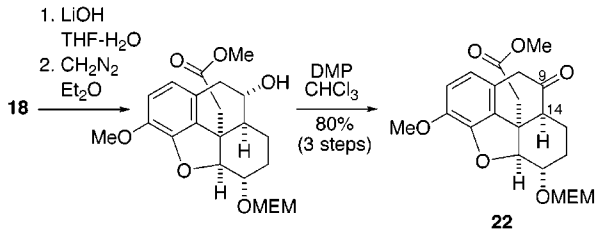
With the goal of replacing the lactone oxygen of **13** by a nitrogen atom, the free hydroxyl group of **13** was first protected as its MOM ether **14**. Basic hydrolysis of lactone **14**, followed by acidification and then treatment of the resultant hydroxy acid with diazomethane, produced methyl ester **15**. The latter was readily oxidized with Dess−Martin periodinane[5] to ketone **16**. Unexpectedly, exposure of β,γ-unsaturated ketone **16** to methylamine led to immediate, quantitative isomerization to α,β-unsaturated isomer **17**. Other attempts to introduce a nitrogen atom into either **16** or **17** were unsuccessful, and it was clear from the uncooperative nature of **17** that a different strategy would be needed if progress toward the morphine skeleton was to advance from a structure such as **16**.



In light of these results, an alternative route was pursued from the MEM protected pentacyclic ketone **4**. As with **3**, Baeyer−Villiger oxidation[4] of **4** proceeded in good yield to give δ-lactone **18**. Exposure of **18** to methylamine in refluxing methanol resulted in nearly quantitative opening of the lactone to afford hydroxy amide **19**. However, attempts to prepare a derivative of the C9 hydroxyl group of **19** for displacement led only to dehydration, giving the $\Delta^{9,10}$ olefin **20** in high yield. By contrast, oxidation of **19** with Dess−Martin periodinane[5] produced (transiently) the C9 ketone, but this compound underwent spontaneous cyclization to yield hydroxy amide **21**. Reductive removal of the hydroxyl substituent from **21** would bring this route from **4** into convergence with our previous synthesis of codeine.[3] Unfortunately, the severe steric hindrance resulting from the bowl-shaped conformation of the carbocyclic portion of **21** precluded access to this *endo*-oriented alcohol, and no method for its reduction could be found.



An attempt was also made to introduce a nitrogen atom into the tetracyclic framework of keto ester **22**. The latter was obtained from **18** by a sequence analogous to that employed in the preparation of **16** from **14**. However, neither the ketone function nor the ester group of **22** were reactive with methylamine. Instead, rapid epimerization occurred at C14 to give a mixture of 14α and 14β stereoisomers of **22**. The unreactive nature of the C9 ketone in **16** and **22** reflects its sterically hindered environment and implies that refunctionalization at this center is more likely to be accomplished through intramolecular processes, as in the formation of **21**.



In summary, we have prepared several new morphinan derivatives from the pentacyclic ketones **3** and **4**. These substances will serve as a basis for further efforts directed toward the synthesis of morphine and its analogues.

Experimental Section

Melting points are uncorrected. Chemical ionization (CI) high and low resolution mass spectra (HRMS and MS) were obtained using a source temperature of 120 °C and CH_4 as the ionizing source. Perfluorokerosene was used as a reference.

(1*R,5*S**,13*S**,14*S**,17*S**)-10-Methoxy-14-(methoxymethoxy)-4,12-dioxapentacyclo[9.6.1.0^{1,13}.0^{5,17}.0^{7,18}]octadeca-7(18),8,10-trien-3-one (9).** To a solution of **3** (30 mg, 0.091 mmol) in $CHCl_3$ (10 mL) were added *m*-chloroperbenzoic acid (84%, 37 mg, 0.18 mmol) and $NaHCO_3$ (50 mg), and the mixture was stirred for 5 h at ambient temperature. Methyl sulfide (20 μL) was added to the mixture, and stirring was continued for 20 min. The solution was washed with saturated aqueous Na_2CO_3 and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue (silica gel, EtOAc−hexane, 2:1) gave 26 mg (84%) of **9** as a colorless oil: IR (neat) 1738 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90−1.03 (m, 1H), 1.30−1.43 (m, 1H), 1.77−1.82 (m, 1H), 1.95−2.00 (m, 1H), 2.43 (dt, J = 4, 13 Hz, 1H), 2.67 (d, J = 18 Hz, 1H), 2.83 (dd, J = 18 Hz, 1H), 2.89 (d, J = 18 Hz, 1H), 3.16 (d, J = 18 Hz, 1H), 3.43−3.35 (m, 4H), 3.88 (s, 3H), 4.41 (d, J = 7 Hz, 1H), 4.68 (d, J = 7 Hz, 1H), 4.75 (d, J = 7 Hz, 1H), 4.92−4.94 (m, 1H), 6.67 (d, J = 8 Hz, 1H), 6.79 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 28.0, 30.0, 38.4, 42.1, 43.3, 55.4, 57.5, 76.3, 78.6, 94.4, 95.6, 116.1, 120.3, 121.5, 129.4, 144.5, 144.6, 169.1; MS m/z 346 (M$^+$); HRMS m/z 346.1416 (calcd for $C_{19}H_{22}O_6$: 346.1416).

(1*R,5*S**,13*S**,14*S**,17*S**)-14-Hydroxy-10-methoxy-4,12-dioxapentacyclo[9.6.1.0^{1,13}.0^{5,17}.0^{7,18}]octadeca-7(18),8,10-trien-3-one (10).** To a solution of **9** (36 mg, 0.104 mmol) in acetonitrile (10 mL) was added an aqueous solution of HBr

(36%, 50 μL), and the mixture was stirred for 30 min at ambient temperature. Solid $NaHCO_3$ was added, and stirring was continued for another 30 min. The solution was filtered and concentrated under reduced pressure. Chromatography of the residue (silica gel, EtOAc−hexane, 2:1) afforded 30 mg (95%) of **10** as a colorless oil: IR (neat) 3399, 1733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89−1.03 (m, 1H), 1.39−1.49 (m, 1H), 1.79−1.85 (m, 1H), 1.87−1.94 (m, 1H), 2.45 (dt, J = 4, 13 Hz, 1H), 2.67 (d, J = 18, 1H), 2.84 (dd, J = 4, 18 Hz, 1H), 2.88 (d, J = 18 Hz, 1H), 3.17 (dd, J = 2, 18 Hz, 1H), 3.46−3.39 (m, 1H), 3.88 (s, 3H), 4.35 (d, J = 8 Hz, 1H), 4.93−4.96 (m, 1H), 6.69 (d, J = 8 Hz, 1H), 6.80 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 29.4, 30.0, 38.4, 41.9, 43.4, 56.7, 72.2, 78.7, 96.2, 115.2, 120.3, 121.6, 129.4, 144.3, 144.5, 169.1; MS *m*/*z* 302 (M^+); HRMS *m*/*z* 302.1154 (calcd for $C_{17}H_{18}O_5$: 302.1154).

(1*R,5*S**,13*S**,17*S**)-10-Methoxy-4,12-dioxapentacyclo-[9.6.1.0^{1,13}.0^{5,17}.0^{7,18}]octadeca-7(18),8,10-triene-3,14-dione (11).** A mixture of **10** (35 mg, 0.116 mmol) and Dess−Martin periodinane (52.2 mg, 0.174 mmol) in $CHCl_3$ (25 mL) was stirred for 1 h at ambient temperature. The suspension was treated with an aqueous solution of $Na_2S_2O_3$/$NaHCO_3$ (20 mL, 50 g of $Na_2S_2O_3$ in 200 mL of a saturated solution of $NaHCO_3$), and the $CHCl_3$ layer was separated, washed with a saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue (silica gel, EtOAc− hexane, 2:1) furnished 33 mg (95%) of **11** as a colorless oil: IR (neat) 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20−1.34 (m, 1H), 2.06−2.14 (m, 1H), 2.46−2.54 (m, 2H), 2.83 (dd, J = 4, 18 Hz, 1H), 2.88−2.96 (m, 3H), 3.21 (dd, J = 2, 18 Hz, 1H), 3.92 (s, 3H), 4.72 (s, 1H), 5.00−5.02 (m, 1H), 6.70 (d, J = 8 Hz, 1H), 6.80 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1, 30.0, 38.0, 39.0, 42.8, 45.8, 56.9, 78.0, 90.7, 116.3, 119.9, 122.3, 126.3, 143.9, 145.7, 168.3, 205.5; MS *m*/*z* 300 (M^+); HRMS *m*/*z* 300.0998 (cacld for $C_{17}H_{16}O_5$: 300.0998).

(1*R,5*S**,13*S**,17*S**)-10-Methoxy-4,12-dioxapentacyclo-[9.6.1.0^{1,13}.0^{5,17}.0^{7,18}]octadeca-7(18),8,10,15-tetraene-3,14-dione (12).** To a stirred solution of **11** (24 mg, 0.080 mmol) in EtOAc (10 mL) were added PhSeCl (23 mg, 0.12 mmol) and an aqueous solution of HCl (36%, 2 drops), and the mixture was stirred for 5 h at ambient temperature. Solid $NaHCO_3$ (100 mg) was added, and stirring was continued for another 30 min. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in THF−H_2O (1:1.5, 10 mL), and $NaIO_4$ (75.1 mg, 0.35 mmol) was added. The mixture was stirred for 30 h at ambient temperature, after which THF was removed under reduced pressure and the product was extracted with EtOAc. The combined organic extracts were washed with water and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue (silica gel, EtOAc−hexane, 2:1) gave 13 mg (56%) of **12** as a colorless oil: IR (neat) 1738, 1684 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.76 (dd, J = 4, 18 Hz, 1H), 2.95 (d, J = 18 Hz, 1H), 3.08 (d, J = 18 Hz, 1H), 3.31 (d, J = 18 Hz, 1H), 3.52−3.55 (m, 1H), 3.88 (s, 3H), 4.73 (s, 1H), 5.23−5.26 (m, 1H), 6.24 (dd, J = 3, 10 Hz, 1H), 6.68 (dd, J = 2, 10 Hz, 1H), 6.69 (d, J = 8 Hz, 1H), 6.78 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.6, 37.5, 41.7, 42.1, 57.2, 86.9, 116.8, 119.8, 122.6, 128.0, 134.3, 141.2, 142.1, 143.8, 145.1, 167.6, 193.1; MS *m*/*z* 298 (M^+); HRMS *m*/*z* 298.0841 (calcd for $C_{17}H_{14}O_5$: 298.0841).

(1*R,5*S**,13*S**,14*R**,17*S**)-14-Hydroxy-10-methoxy-4,12-dioxapentacyclo-[9.6.1.0^{1,13}.0^{5,17}.0^{7,18}]octadeca-7(18),8,10,15-tetraen-3-one (13).** To a stirred solution of **12** (50 mg, 0.24 mmol) in dry THF (20 mL) at −78 °C under argon was added a 1 M solution of L-Selectride (282 μL, 0.282 mmol), and the mixture was stirred for 2 h at −78 °C. To the solution were added in succession H_2O (200 μL), EtOH (300 μL), 6 M aqueous NaOH (350 μL), and 30% aqueous H_2O_2 (400 μL), and the product was extracted with EtOAc. The solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, EtOAc−hexane, 2:1) to give 41 mg (81%) of **13** as a colorless oil: IR (neat) 3466, 1728 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.79 (dd, J = 5, 19 Hz, 1H), 2.85 (d, J = 18, 1H), 2.97−3.00 (m, 1H), 3.08 (d, J = 18 Hz, 1H), 3.23 (d, J = 19 Hz, 1H), 3.85 (s, 3H), 4.23−4.27 (m, 1H), 4.92 (d, J = 7 Hz, 1H), 5.13−5.16 (m, 1H), 5.33−5.38 (m, 1H), 5.91−5.94 (m, 1H), 6.63 (d, J = 8 Hz, 1H), 6.74 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.9, 36.1, 41.6, 42.3, 56.5, 65.1, 89.7, 114.6, 120.9, 121.8, 122.9, 129.6, 136.3, 143.1, 146.1, 168.7; MS *m*/*z* 300 (M^+); HRMS *m*/*z* 300.0999 (calcd for $C_{17}H_{16}O_5$: 300.0998).

(1*R,5*S**,13*S**,14*S**,17*S**)-10-Methoxy-14-(methoxymethoxy)-4,12-dioxapentacyclo[9.6.1.0^{1,13}.0^{5,17}.0^{7,18}]octadeca-7-(18),8,10-trien-3-one (14).** A mixture of **13** (32 mg, 0.11 mmol), dimethoxymethane (0.28 mL, 4.26 mmol), P_2O_5 (10 mg), and dry $CHCl_3$ (12 mL) was stirred at ambient temperature until TLC analysis indicated complete disappearance of starting material (ca. 3 h). The supernatant was decanted from the solid residue and was neutralized with solid $NaHCO_3$, filtered, and concentrated under reduced pressure. Chromatography of the residue (silica gel, EtOAc−hexane, 1:1) yielded 33 mg (90%) of **14** as a colorless oil: IR (neat) 1733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.81 (d, J = 19 Hz, 1H), 2.82 (d, J = 18 Hz, 1H), 2.97−2.99 (m, 1H), 3.09 (d, J = 18 Hz, 1H), 3.24 (d, J = 18 Hz, 1H), 3.46 (s, 3H), 3.85 (s, 3H), 4.24−4.33 (m, 1H), 4.74 (d, J = 7 Hz, 1H), 4.90 (d, J = 7 Hz, 1H), 4.97 (d, J = 7 Hz, 1H), 5.14−5.16 (m, 1H), 5.40−5.44 (m, 1H), 5.92−5.96 (m, 1H), 6.58 (d, J = 8 Hz, 1H), 6.72 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.1, 36.5, 42.0, 42.3, 56.1, 56.6, 69.5, 89.2, 95.8, 115.0, 120.7, 121.1, 123.9, 129.6, 133.9, 143.1, 147.3, 168.8; MS (CI) *m*/*z* 344(M^+); HRMS (CI) *m*/*z* 344.1259 (calcd for $C_{19}H_{20}O_6$: 314.1260).

Methyl (2*S)-2-[13*R**,3a*S**,9a*S**)-5-Methoxy-3-(methoxymethoxy)-9-oxo-3,8,9,9a-tetrahydrophenanthro[4,5-*bcd*]furan-9(3a*H*)-yl]acetone (16).** To a solution of **14** (28 mg, 0.081 mmol) in a THF−H_2O mixture (1:1, 10 mL) was added LiOH−H_2O (32 mg, 0.77 mmol), and the mixture was stirred for 20 h at ambient temperature. The solution was cooled to 4 °C and neutralized with aqueous HCl (5%). The product was extracted with CH_2Cl_2, and the combined organic extracts were washed with saturated aqueous NaCl and dried over anhydrous Na_2SO_4. To the dried solution was added 0.6 M diazomethane in diethyl ether (20 mL), and the mixture was stirred for 15 min at 0 °C. Excess diazomethane was decomposed with AcOH, and the resultant solution was washed with H_2O and saturated aqueous NaCl and dried over anhydrous Na_2SO_4. Volatile materials were removed under reduced pressure, the residue was dissolved in $CHCl_3$ (5 mL), and Dess−Martin periodinane (49 mg, 0.12 mmol) was added to the solution. The mixture was stirred for 1 h at ambient temperature and treated with a solution of $Na_2S_2O_3$/$NaHCO_3$ (5 mL, 50 g of $Na_2S_2O_3$ in 200 mL of saturated aqueous $NaHCO_3$). The organic layer was separated, washed with a saturated solution of NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue (silica gel, EtOAc−hexane, 1:2) gave 25 mg (82%) of **16** as a colorless oil: IR (neat) 1737, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.80 (d, J = 17 Hz, 1H), 2.95 (d, J = 17 Hz, 1H), 3.37−3.39 (m, 1H), 3.43 (d, J = 21 Hz, 1H), 3.68 (d, J = 20 Hz, 1H), 3.47 (s, 3H), 3.71 (s, 3H), 3.84 (s, 3H), 4.46−4.50 (m, 1H), 4.80 (d, J = 7 Hz, 1H), 4.88 (d, J = 7 Hz, 1H), 5.34 (dt, J = 3, 10 Hz, 1H), 5.38 (d, J = 5 Hz, 1H), 5.90−5.94 (m, 1H), 6.57 (d, J = 8 Hz, 1H), 6.71 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.6, 41.4, 47.1, 51.9, 52.1, 55.6, 56.1, 72.0, 89.8, 85.7, 113.7, 119.7, 121.1, 125.8, 129.2, 131.4, 143.2, 147.9, 170.0, 210.2; MS *m*/*z* 374 (M^+); HRMS *m*/*z* 374.1365 (calcd for $C_{20}H_{22}O_7$: 374.1365).

Methyl (2*S)-2-[(3*R**,3a*S**)-5-Methoxy-3-(methoxymethoxy)-9-oxo-3,3a,8,9-tetrahydrophenanthro[4,5-*bcd*]furan-9(2*H*)-yl]acetate (17).** To a solution of **16** (10 mg, 0.028 mmol) in CH_2Cl_2 (2 mL) was added 1 M methylamine in THF (50 μL, 0.050 mmol), and the mixture was stirred for 2 h at ambient temperature. The solution was washed with aqueous HCl (5%) and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 10 mg (100%) of pure **17** as a colorless oil: IR (neat) 1738, 1689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.51−2.57 (m, 2H), 2.66 (d, J = 16 Hz, 1H), 2.88 (d, J = 16 Hz, 1H), 3.19 (s, 3H), 3.51 (d, J = 21 Hz, 1H), 3.63 (s, 3H), 3.75 (d, J = 21 Hz, 1H), 3.88 (s, 3H),

4.29 (d, J = 7 Hz, 1H), 4.36−4.32 (m, 1H), 4.67 (d, J = 7 Hz, 1H), 5.45 (d, J = 5 Hz, 1H), 6.65 (d, J = 8 Hz, 1H), 6.73−6.79 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.9, 41.4, 46.4, 51.6, 55.2, 56.5, 72.5, 88.6, 96.2, 113.8, 119.8, 121.2, 130.8, 133.4, 138.4, 142.9, 145.7, 170.5, 197.6; MS m/z 374 (M^+); HRMS m/z 374.1365 (calcd for $C_{20}H_{22}O_7$: 374.1366).

1-{(4a*S,5*S**,7a*S**,8*S**,9c*R**)-3-Methoxy-5-[(2-methoxyethoxy)methoxy]-4a,5,6,7,7a,9,9c-octahydrophenanthro-[4,5-*bcd*]furan-8-yl}-2-diazo-1-ethanone (6).** To a stirred solution of **7** (35.2 mg, 0.12 mmol) in CH_2Cl_2 (5 mL) were added MEMCl (53.0 mL, 0.46 mmol) and *N*,*N*-diisopropylethylamine (90.6 mL, 0.52 mmol), and the mixture was stirred for 3 h at ambient temperature. The mixture was washed with H_2O and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue (silica gel, EtOAc−hexane, 1:1) gave 43 mg (95%) of the MEM ether of **7** as a colorless oil: IR (neat) 1733 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03−1.32 (m, 2H), 1.61−1.65 (m, 1H), 1.81−1.91 (m, 1H), 2.63−2.71 (m, 2H), 2.87−2.89 (m, 1H), 3.15 (d, J = 17 Hz, 1H), 3.34−3.58 (m, 7H), 3.64−3.71 (m, 4H), 3.84−3.78 (m, 4H), 4.71−4.77 (m, 3H), 6.62 (d, J = 8 Hz, 1H), 6.69 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4, 24.8, 28.0, 34.1, 38.5, 43.6, 56.7, 59.0, 66.6, 71.8, 75.6, 77.4, 91.0, 93.9, 114.3, 120.1, 124.0, 127.0, 143.5, 145.5, 175.0; MS m/z 392 (M^+); HRMS m/z 392.1835 (calcd for $C_{21}H_{28}O_7$ 392.1835).

To a solution of the MEM ether obtained above (26.0 mg, 0.066 mmol) in THF−H_2O (2:1, 6 mL) was added LiOH·H_2O (13.9 mg, 0.331 mmol), and the mixture was stirred at ambient temperature for 20 h. The mixture was acidified with aqueous HCl (5%), and the product was extracted with EtOAc. The combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford 24.8 mg (99%) of the carboxylic acid as a colorless oil: IR (neat) 3162, 1730, 1709 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05−1.36 (m, 2H), 1.64−1.68 (m, 1H), 1.88−1.91 (m, 1H), 2.63−2.73 (m, 2H), 2.90−2.93 (m, 1H), 3.15 (d, J = 18 Hz, 1H), 3.36 (s, 3H), 3.37−3.60 (m, 4H), 3.65−3.72 (1H, m), 3.80−3.84 (m, 4H), 4.73−4.78 (m, 3H), 6.63 (d, J = 8 Hz, 1H), 6.70 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 24.8, 28.0, 34.0, 38.5, 43.5, 56.8, 59.1, 66.7, 71.9, 75.6, 91.0, 94.0, 114.4, 120.2, 123.8, 126.9, 143.6, 145.6, 180.5; MS m/z 378 (M^+); HRMS m/z 378.1678 (calcd for $C_{20}H_{26}O_7$ 378.1678).

To a solution of the carboxylic acid obtained above (50 mg, 0.13 mmol) in dry benzene (2 mL) was added oxalyl chloride (46.5 mL, 0.53 mmol), and the mixture was stirred for 18 h at ambient temperature.The solvent and excess oxalyl chloride were removed under reduced pressure, and the residue was dissolved in benzene (2 mL) and treated with 0.6 M diazomethane in diethyl ether (5 mL). The solution was purged with nitrogen to remove excess diazomethane, and the mixture was concentrated under reduced pressure. Chromatography of the residue (silica gel, EtOAc−hexane 2:1) produced 37 mg (71%) of **6** as a colorless oil: IR (neat) 2107, 1634 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05−1.28 (m, 2H), 1.64−1.70 (m,1H), 1.87−1.92 (m,1H), 2.04−2.56 (m, 1H), 2.69−2.79 (m, 2H), 2.93 (d, J = 17 Hz, 1H), 3.35 (s, 3H), 3.37−3.57 (m, 4H), 3.65−3.72 (m, 1H), 3.79−3.87 (m, 1H), 3.83 (s, 3H), 4.72−4.89 (m, 3H), 5.31 (s, 1H), 6.65 (d, J = 8 Hz, 1H), 6.72 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5, 25.3, 28.1, 35.3, 38.4, 54.3, 56.8, 59.1, 66.7, 71.9, 75.7, 91.1, 94.0, 114.5, 120.2, 123.5, 127.5, 143.8, 145.8, 197.2.

(1*R,4*S**,12*S**,13*S**,16*R**)-9-Methoxy-13-[(2-methoxyethoxy)methoxy]-11-oxapentacyclo[8.6.1.0^{1,12}.0^{4,16}.0^{6,17}]-heptadeca-6(17),7,9-trien-3-one (4).** To a solution of **6** (50 mg, 0.124 mmol) in CH_2Cl_2 (100 mL) under argon was added $Rh_2(OAc)_4$ (ca 2 mg), and the mixture was stirred for 30 min at ambient temperature. The solution was concentrated under reduced pressure, and the residue was chromatographed (silica gel, EtOAc−hexane, 1:1) to furnish 21 mg (46%) of **4** as a colorless oil: IR (neat) 1756 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21−1.34 (m, 1H), 1.41−1.54 (m, 1H), 1.76−1.82 (m, 1H), 1.88−1.97 (m, 1H), 2.49 (s, 2H), 2.73−2.76 (m, 1H), 2.86−2.88 (m, 2H), 3.38 (s, 3H), 3.52−3.76 (m, 3H), 3.80−3.84 (m, 1H), 3.86 (s, 3H), 4.75 (d, J = 6 Hz, 1H), 4.81−4.87 (m, 2H), 6.59 (d, J = 8 Hz, 1H), 6.71 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7, 27.5, 28.2, 42.3, 49.2, 50.1, 53.9, 56.7, 59.2, 67.0, 71.9, 90.9, 94.5, 114.7, 120.7(x2), 122.3, 133.0, 144.0, 218.0; MS m/z 374 (M^+); HRMS m/z 374.1729 (calcd for $C_{21}H_{24}O_6$: 374.1729).

(1*R,5*S**,13*S**,14*S**,17*S**)-10-Methoxy-14-[(2-methoxyethoxy)methoxy]-4,12-dioxapentacyclo[9.6.1.0^{1,13}.0^{5,17}.0^{7,18}]-octadeca-7-(18),8,10-trien-3-one (18).** To a solution of **4** (8 mg, 0.021 mmol) in CH_2Cl_2 (3 mL) were added $NaHCO_3$ (20 mg, 0.24 mmol) and *m*-chloroperbenzoic acid (86 wt %, 8.7 mg, 0.043 mmol), and the mixture was stirred for 6 h at ambient temperature. The solution was washed with saturated aqueous Na_2CO_3 and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue (silica gel, EtOAc−hexane, 2:1) gave 6 mg (75%) of **18** as a colorless oil: IR (neat) 1737 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88−1.02 (m, 1H), 1.25−1.39 (m, 1H), 1.74−1.86 (m, 1H), 1.94−2.02 (m, 1H), 2.42 (dt, J = 4, 12 Hz, 1H), 2.65 (d, J = 18 Hz, 1H), 2.82 (dd, J = 4, 18 Hz, 1H), 2.87 (d, J = 18 Hz, 1H), 3.15 (dd, J = 2, 18 Hz, 1H), 3.35 (s, 3H), 3.39−3.48 (m, 1H), 3.52−3.56 (m, 2H), 3.66−3.73 (m, 1H), 3.79−3.84 (m, 1H), 3.86 (s, 3H), 4.38 (d, J = 7 Hz, 1H), 4.76−4.80 (m, 2H), 4.90−4.93 (m, 1H), 6.66 (d, J = 8 Hz, 1H), 6.77 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 27.5, 29.9, 38.4, 42.0, 43.3, 56.6, 59.1, 66.8, 71.8, 75.9, 78.6, 94.1, 94.2, 115.5, 120.2, 121.4, 129.3, 144.4, 144.5, 169.5; MS m/z 390 (M^+); HRMS m/z 390.1680 (calcd for $C_{21}H_{26}O_7$ 390.1678).

(2*S)-2-[(3*S**,3a*S**,9*S**,9a*S**)-9-Hydroxy-5-methoxy-3-[(2-methoxyethoxy)methoxy]-1,3,3a,8,9,9a-hexahydrophenanthro[4,5-*bcd*]furan-9(2*H*)-yl]-*N*-methylacetamide (19).** A mixture of **18** (17 mg, 0.043 mmol) and 1 M $MeNH_2$ in MeOH (5 mL) was placed in a sealed tube and was stirred for 10 h at 70 °C. Volatile materials were removed under reduced pressure, and the residue was chromatographed (silica gel, EtOAc−MeOH, 96:4) to give 18 mg (98%) of **19** as a colorless oil: IR (neat) 3379, 1658, 1644 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75−0.88 (m, 1H), 1.22−1.30 (m, 1H), 1.60−1.65 (m, 2H), 1.81−1.85 (m, 1H), 2.47 (d, J = 13 Hz, 1H), 2.57−2.63 (m, 1H), 2.73−2.86 (m, 6H), 2.88−3.34 (m, 1H), 3.36 (s, 3H), 3.52−3.55 (m, 2H), 3.66−3.75 (m, 1H), 3.79−3.82 (m, 1H), 3.86 (s, 3H), 4.26 (m, 1H), 4.76 (d, J = 7 Hz, 1H), 4.78 (s, 2H), 6.11−6.13 (m, 1H), 6.65 (d, J = 8 Hz, 1H), 6.74 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.5, 26.6, 27.4, 30.0, 31.4, 39.7, 43.6, 45.4, 56.6, 59.1, 66.7, 71.0, 71.9, 94.1, 95.0, 114.5, 121.3, 123.1, 130.8, 143.8, 144.7, 172.5; MS m/z 421 (M^+); HRMS m/z 421.2100 (calcd for $C_{22}H_{31}NO_7$: 421.2100).

(2*S)-2-[(3*S**,3a*S**,9a*S**)-5-Methoxy-3-[(2-methoxyethoxy)methoxy]-1,3,3a,9a-tetrahydrophenanthro[4,5-*bcd*]furan-9(2*H*)-yl]-*N*-methylacetamide (20).** To a solution of triphenylphosphine (10 mg, 0.0372 mmol) in THF (1 mL) maintained at −78 °C was added 1 M Br_2 in CCl_4 (347 mL, 0.0347 mmol), and the mixture was stirred for 30 min at −78 °C. To the mixture was added a solution of **19** (10 mg, 0.0248 mmol) in THF (0.5 mL), and the resulting mixture was stirred for 1 h at −78 °C and for 16 h at ambient temperature. MeOH (0.5 mL) was added, and the mixture was filtered through a short column of silica gel. The filtrate was concentrated under reduced pressure, and the residue was chromatographed (silica gel, EtOAc−hexane, 6:1) to yield 9 g (84%) of **20** as a colorless oil: IR (neat) 3355, 1660 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88−0.99 (m, 1H), 1.31−1.41 (m, 1H), 1.75−1.83 (m, 2H), 2.22 (d, J = 14 Hz, 1H), 2.35 (d, J = 14 Hz, 1H), 2.76 (d, J = 4 Hz, 3H), 2.85−2.91 (m, 1H), 3.37 (s, 3H), 3.47−3.61 (m, 3H), 3.70−3.75 (m, 1H), 3.84−3.89 (m, 1H), 3.87 (s, 3H), 4.81−4.85 (m, 2H), 5.10 (d, J = 7.4 Hz, 1H), 5.33 (br s, 1H), 5.82 (dd, J = 5, 9 Hz, 1H), 6.38 (d, J = 9 Hz, 1H), 6.62 (d, J = 8 Hz, 1H), 6.69 (d, J = 8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1, 26.4, 26.9, 37.9, 40.9, 45.7, 56.4, 59.1, 66.7, 71.9, 94.1, 94.9, 113.3, 117.7, 123.0, 123.4, 128.9, 130.6, 133.2, 144.6, 145.4, 171.3.

(1*R,5*R**,13*S**,14*S**,17*S**)-5-Hydroxy-10-methoxy-14-[(2-methoxyethoxy)methoxy]-4-methyl-12-oxa-4-azapentacyclo[9.6.1.0^{1,13}.0^{5,17}.0^{7,18}]octadeca-7(18),8,10-trien-3-one (21).** A solution of **19** (10 mg, 0.024 mmol) and Dess−Martin periodinane (13 mg, 0.31 mmol) in $CHCl_3$ (5 mL) was stirred for 5 h at ambient temperature. To the mixture was

added a solution of $Na_2S_2O_3$/$NaHCO_3$ (5 mL, 50 g of $Na_2S_2O_3$ in 200 mL of saturated aqueous $NaHCO_3$), and stirring was continued for 15 min. The organic layer was separated, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue (silica gel, EtOAc−MeOH, 96:4) gave 8 mg (78%) of **21** as a colorless oil: IR (neat) 3327, 1637 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92−1.05 (m, 1H), 1.18−1.33 (m, 1H), 1.97−2.02 (m, 2H), 2.10 (dd, J = 4, 12 Hz, 1H), 2.59 (d, J = 17 Hz, 1H), 2.67 (d, J = 17 Hz, 1H), 2.75 (d, J = 17 Hz, 1H), 2.95 (s, 3H), 3.08 (d, J = 17 Hz, 1H), 3.24 (s, 1H), 3.37 (s, 3H), 3.38−3.49 (m, 1H), 3.53−3.56 (m, 2H), 3.66−3.72 (m, 1H), 3.83−3.85 (m, 1H), 3.86 (s, 3H), 4.37 (d, J = 7 Hz, 1H), 4.79 (s, 2H), 6.60 (d, J = 8 Hz, 1H), 6.74 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 26.8, 27.2, 33.1, 44.3, 44.9, 47.0, 56.8, 59.1, 66.8, 71.9, 76.1, 88.7, 94.1, 94.6, 115.3, 120.9, 122.3, 129.6, 144.7, 144.9, 168.5; MS *m*/*z* 419 (M^+); HRMS *m*/*z* 419.1944 (calcd for $C_{22}H_{29}NO_7$: 419.1944).

Methyl (2*S)-2-[(3*S**,3a*S**,9a*S**)-5-Methoxy-3-[(2-methoxyethoxy)methoxy]-9-oxo-1,3,3a,8,9,9a-hexahydrophenanthro[4,5-*bcd*]furan-9(2*H*)-yl]acetate (22).** To a solution of **18** (30 mg, 0.077 mmol) in THF−H_2O (1:1, 10 mL) was added LiOH·H_2O (32 mg, 0.77 mmol), and the mixture was stirred for 20 h at ambient temperature. The solution was cooled to 4 °C and neutralized with aqueous HCl (5%), and the product was extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O and saturated aqueous NaCl and dried over anhydrous Na_2SO_4. To the dried solution maintained at 4 °C was added 0.6 M diazomethane in diethyl ether (5 mL), and the mixture was stirred for 15 min. Nitrogen was passed through the solution to remove excess diazomethane, and volatile materials were then removed under reduced pressure. To a solution of the residue in $CHCl_3$ (10 mL) was added Dess−Martin periodinane (49 mg, 0.12 mmol), and the mixture was stirred for 1 h at ambient temperature. A solution of $Na_2S_2O_3$/$NaHCO_3$ (10 mL, 50 g of $Na_2S_2O_3$ in 200 mL of saturated aqueous $NaHCO_3$) was added, and stirring was continued for 20 min. The organic layer was separated, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue (silica gel, EtOAc−hexane, 1:2) produced 26 mg (80%) of **22** as a colorless oil: IR (neat) 1735, 1704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16−1.29 (m, 1H), 1.38−1.50 (m, 1H), 1.86−1.95 (m, 1H), 2.34 (d, J = 16 Hz, 1H), 2.71 (d, J = 16 Hz, 1H), 3.00 (dd, J = 6, 13 Hz, 1H), 3.37 (s, 3H), 3.51 (s, 2H), 3.46−3.58 (m, 4H), 3.67−3.77 (m, 4H), 3.81−3.87 (m, 1H), 3.89 (s, 3H), 4.80−4.85 (m, 2H), 4.90 (d, J = 7 Hz, 1H), 6.66 (d, J = 8 Hz, 1H), 6.80 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7, 26.9, 38.4, 41.7, 47.7, 52.0, 52.4, 56.6, 59.1, 66.9, 71.9, 93.6, 94.3, 114.9, 120.3, 121.9, 128.7, 144.6, 145.2, 170.8, 210.9; MS *m*/*z* 420 (M+), 89; HRMS *m*/*z* 420.1782 (calcd for $C_{22}H_{28}O_8$: 420.1784).

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Supporting Information Available: ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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