SUPPORTING INFORMATION

Additional Information for References

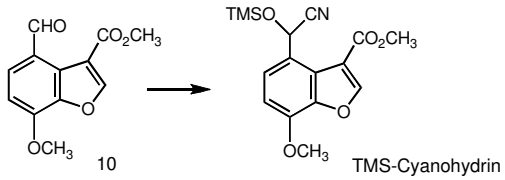
Reference 9: Henke, B.R.; Aquino, C. J.;Birkemo, L. S.; Croom, D. K.; Dougherty, Jr., R. W.; Ervin, G. N.; Grizzle, M. K.; Hirst, G. C.; James, M.K.; Johnson, M. F.; Queen, K. L.; Sherrill, R. G.; Sugg, E. E.; Suh, E.M.; Szewczyk, J. W.; Unwalla, R.J.; Yingling, J.; Willson, T.M., *J. Med. Chem.*, **1997**, *40 (17),* 2706-2725.

Experimental Section

General: ^{1}H NMR spectra were determined with a Bruker DPX-300 and/or DRX-300 spectrometer at 300 MHz or a Bruker DRX-400 at 400 MHz. Chemical shifts δ are reported in parts per million (δ) relative to residual chloroform (7.26 ppm) or TMS (0 ppm), as an internal reference with coupling constants (J) reported in Hertz (Hz). The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad singlet. High Resolution Mass spectra (HRMS, Fab) were recorded on a HX110A Double Focusing Mass Spectrometer (JEOL). ESI-LCMS was recorded on Waters' Q-Tof Premier (Electrospray mass) and Waters' Acquity (LC) using Acquity UPLC BEH C-18 column (1.7 um, size 2.1 x 150 mm). IR spectra were recorded on Nexus 470 FT-IR, Thermo Nicolet Co. Chromatographic purifications were performed by Flash chromatography using Flash silica gel 0.040-0.063 mm of Dynamic Adsorbents, Inc. Thin-layer chromatography (TLC) was performed on EM Chemicals silica gel 60-250 mm plates. The terms "concentrated" and "evaporated" refer to removal of solvents using a rotary evaporator at water aspirator pressure with a bath temperature equal to or less than 60°C. Unless otherwise noted, reagents were obtained from commercial sources and were used without further purification.

Preparation of Dienylcarbinol **5**

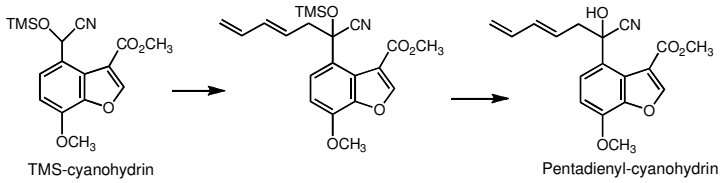
a) TMS-Cyanohydrin



To a stirred solution of aldehyde **10** ((3.0 g, 12.8 mmole. *Vide infra for preparation of* **10**) in CH_2Cl_2 (120 mL) were added KCN (17 mg, 0.256 mmole), TMSCN (1.88 ml, 14.1 mmole) then 18-crown-6 (68 mg, 0.256 mmole) at rt, and the resulting mixture was stirred at rt for 1 h. The organic layer was washed with satd $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*, to give 4.33 g (quantitative yield) of TMS-cyanohydrin as a pale yellow solid. This material was used for the next step without further purification.

NMR δ ($CDCl_3$): 8.39 (1H, s), 7.706 (1H, d, J = 8.2 Hz), 6.951 (1H, d, J = 8.2 Hz), 4.037 (3H, s), 3.992 (3H, s), 3.694 (1H, d, J = 1.2 Hz), 0.254 (9H, s).

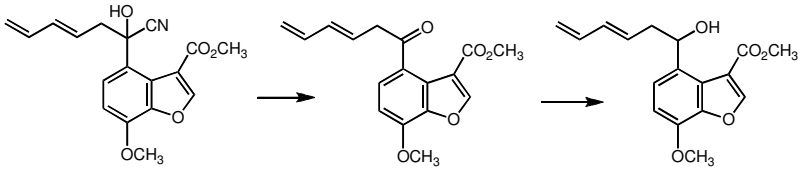
b) Preparation of Pentadienyl Cyanohydrin



To a cooled (-78 ^{o}C, dry ice-acetone bath) solution of TMS cyanohydrin (4.33 g, 12.8 mmole) in anhydrous THF (90 mL) was added LHMDS, prepared from HMDS (4.32 mL, 20 mmole) and n-BuLi (7.7 mL, 19.2 mmole; 2.5 M solution in hexane) in anhydrous THF (15 mL), under argon. The mixture was stirred at -78 ^{o}C for 15 min, and 5-bromo-1,3-pentadiene (3.01 g, 20.5 mmole) prepared from divinylcarbinol and PBr_3 at 0 ^{o}C; (cf Prévost, Ch.; Miginiac, P.; Miginiac-Groizeleau, L. *Bull. Soc. Chim.France* **1964**, 2485.) was added dropwise. The reaction mixture was warmed slowly to 0 ^{o}C, stirred for an additional 2 h, and poured into a mixture of satd NH_4Cl solution, and extracted with ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness to give crude pentadienyl intermediate, which was dissolved in a solution of 100 mL 2/3 CH_2Cl_2 /methanol. Addition of p-toluenesulfonic acid (1.22 g, 6.4 mmole) at rt was followed by stirring at rt for 1 h, concentration *in vacuo*, and dilution with CH_2Cl_2. The organic layer was washed with water, satd $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was loaded on a silica gel Flash column. Elution by CH_2Cl_2 - hexane mixture (5/1, 10/1, finally 1/0) gave 2.58 g (62 %) of pentadienyl cyanohydrin as a pale yellow solid.

NMR δ ($CDCl_3$): 8.430 (1H, s),7.646 (1H, s), 7.521 (1H, d, J = 8.6 Hz), 6.859 (1H, d, J = 8.6 Hz), 6.42-6.20 (2H, m), 5.94-5.86 (1H, m), 5.193 (1H, d, J =15.4 Hz), 5.086 (1H, d, J = 9.8 Hz), 4.033 (3H, s), 3.998 (3H, s), 3.212 (1H, d, J = 6.4 Hz), 3.185 (1H, d, J = 6.8 Hz), 3.093 (1H, d, J = 16.0 Hz), 3.000 (1H, d, J = 7.0 Hz).

c) Preparation of Pentadienyl Carbinol **5**



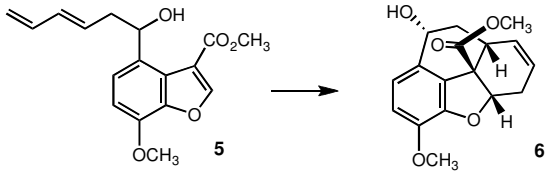
Pentadienyl Cyanohydrin **5**

To a solution of pentadienyl cyanohydrin (2.58 g, 7.89 mmole) in a 3: 1 mixture of ether and CH_2Cl_2 (200 mL) was added a solution of NaOH (631 mg, 15.8 mmole) in water (30 mL) at rt, and the mixture was stirred at rt for 1 hr. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude pentadienylketone was unstable, and was immediately used for the next step without further purification. NMR ***d*** ($CDCl_3$): 8.175 (1H, d, J = 1.6 Hz), 7.489 (1H, d, J = 8.2 Hz), 6.861 (1H, dd, J = 1.2, 8.4 Hz), 6.41-6.10 (2H, m), 6.03-5.90 (1H, m),5.146 (1H, d, J = 16.8 Hz), 5.033 (1H, d, J = 9.6 Hz), 4.057 (3H, s), 3.872 (3H, s), 3.707 (2H, d, J = 7.0 Hz).

To a cooled (0 ^{o}C, ice water bath) solution of the above dienylketone (7.89 mmole) in a 1: 1 mixture of methanol and CH_2Cl_2 (40 mL) was slowly added $NaBH_4$ (596 mg, 15.8 mmole). The resulting mixture was stirred at rt for 1 h, and quenched with brine. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Flash column chromatography (silica gel, elution by CH_2Cl_2 : ethyl acetate = 1/0 to 15/1 mixture) gave 1.78 g (75 % overall from the pentadienyl cyanohydrin) of the desired Diels Alder precursor, pentadienyl cyanohydrin **5** as a colorless solid suitable for the next step.

NMR ***d*** ($CDCl_3$): 8.338 (1H, s), 7.351 (1H, d, J = 8.0 Hz), 6.857 (1H, d, J = 8.0 Hz), 6.37-6.14 (2H, m), 5.84-5.76 (1H, m), 5.40-5.36 (1H, m), 5.111 (1H, d, J =17.0 Hz), 4.095 (1H, d, J = 7.2 Hz), 4.008 (3H, s), 3.928 (3H, s), 2.70-2.62 (2H, m).

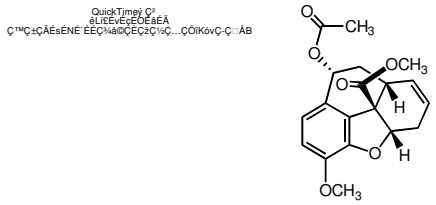
Diels-Alder Cyclization of **5 :** Formation of Phenanthrofuran **6**



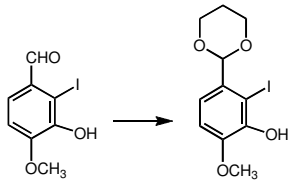
A solution of dienylcarbinol **5** (150 mg, 0.497 mmole), Et_3N (0.69 mL, 4.97 mmole) and 2, 6-di-tert-butyl-4-methylphenol (55 mg, 0.25 mmole) in toluene (50 mL) was placed in a pressure tube, and the solution was degassed by bubbling argon for 1 h. The sealed tube was heated in a sand bath (bath temperature 260 °C) for 16 h. The mixture was cooled to rt, and concentrated *in vacuo.* The residue was loaded on a silica gel Flash column for chromatography. Elution by 4 – 10 % ethyl acetate in CH_2Cl_2 gave 120 mg (80 %) of **6** as a pale yellow oil.

NMR δ ($CDCl_3$): 6.967 (1H, d, J = 8.2 Hz), 6.835 (1H, d, J = 8.2 Hz), 5.90-5.80 (1H, m), 5.70-5.60 (1H, m), 5.421 (1H, t, J = 7.2 Hz), 5.10-4.80 (1H, m), 3.873 (3H, s), 3.668 (3H, s), 3.40-3.10 (1H, m), 2.60-2.30 (2H, m), 2.10-1.90 (2H,m), 1.45-1.30 (1H, m).

The acetate of **6** was prepared (acetic anhydride/pyridine, overnight at rt). It was obtained in 80 % yield, after chromatography on silica gel, as colorless prisma, mp 105 °C. Its structure was established by X-ray analysis.



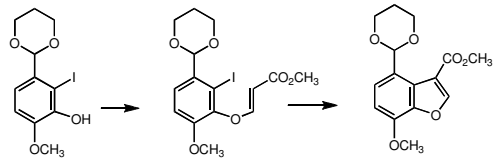
Preparation of Dioxolane **8**



A solution of **7** (20 g, 71.9 mmole), propane-1,3-diol (7.8 mL, 1.02 mole), and *p*-toluenesulfonic acid (684 mg, 3.6 mmole) in toluene (300 mL) was refluxed under a Dean-Stark apparatus. When no more water separated, the mixture was cooled and diluted with ethyl acetate. The organic layer was washed with satd $NaHCO_3$ solution, then with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting dark brown oil was dissolved in a minimum amount of CH_2Cl_2, and treated with a 1:1 mixture of ether and hexanes, to give **8** as a light tan solid (20.45 g, 85 %).

NMR δ ($CDCl_3$): 7.193 (1H, d, J = 8.4 Hz), 6.839 (1H, d, J = 8.4 Hz), 6.203 (1H, s), 5.582 (1H, s), 4.243 (2H, dd, J = 5.1, 10.8 Hz), 4.06-3.98 (2H, m), 3.880 (3H, s), 2.24-2.20 (1H, m), 1.435 (1H, d, J = 13.5 Hz).

Preparation of benzofuran methyl ester **9**



8 9

To a cooled (-20 °C, bath temperature) solution of **8** (16 g, 47.60 mmole) in anhydrous THF (90 mL), under argon, was added Et_3N (7.3 mL, 52.36 mmole), then methyl propiolate (5.51 mL, 61.88 mmole), dropwise, by syringe. The resulting mixture was stirred at a bath temperature between -15 to -10 °C for 1.5 h, then at 0 °C for 2 h. The solvent was concentrated by rotary evaporation, and the residue was diluted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The product was purified by Flash column chromatography (silica gel, elution by 2-5 % ether in CH_2Cl_2), to give the product as a pale yellow oil. The oil was treated with cold ether, and the separated white solid was collected, to give 17.7 g (89 %) of the intermediate phenoxy acrylate.

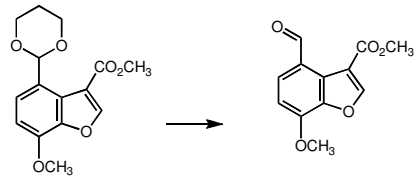
HRMS (FAB) m/z: Calcd for $C_{15}H_{18}IO_6$: 421.0148 [M+H]; Found: 421.0142.

NMR δ ($CDCl_3$): 7.602 (1H, d, J = 12.3 Hz), 7.508 (1H, d, 8.7 Hz), 6.975 (1H, d, J = 8.7 Hz), 5.562 (1H, s), 5.271 (1H, d, J = 12.3 Hz), 4.263 (2H, dd, J = 5.1, 10.8 Hz), 4.07-3.98 (2H, m), 3.838 (3H, s), 3.694 (3H, s), 2.25-2.21 (1H, m), 1.454 (1H, d, J = 13.8 Hz).

To a mixture of the phenoxy acrylate (16 g, 38.1 mmole), $Pd(OAc)_2$ (0.853 g, 3.8 mmole), triphenylphosphine (1.5 g, 5.72 mmole), sodium acetate (7.8 g, 95.2 mmole) and tetrabutylammonium chloride (11.9 g, 42.8 mmole) was added anhydrous DMF (150 mL) by syringe, under argon. The resulting mixture was vacuumed/filled with argon at least 3 times. Water (1.5 mL, degassed by argon bubbling prior to use) was added to this mixture, which was then heated at 125 °C (bath temperature) under argon for 4 h. The mixture was cooled, poured into a mixture of ice and water, and the aqueous layer was extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The product was purified by Flash column chromatography (silica gel, elution by 2 % ether in CH_2Cl_2), to give 9.30 g (84 %) of **9** as a white solid.

NMR δ ($CDCl_3$): 8.225 (1H, s), 7.647 (1H, d, J = 8.4 Hz), 6.880 (1H, d, J = 8.4 Hz), 6.526 (1H, s), 4.23-4.13 (4H, m), 3.995 (3H, s), 3.899 (3H, s), 2.25-2.20 (1H, m), 1.443 (1H, d, J = 13.2 Hz).

Preparation of Benzofuranaldehyde **10**



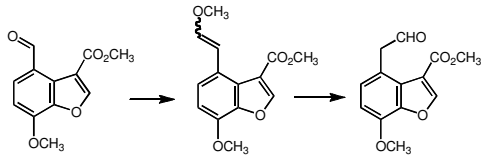
9 10

To a cold solution (ice water bath) of **9** (18 g, 61.6 mmole) in THF (200 mL) was added dropwise concentrated HCl (25 ml). The mixture was stirred at 0 °C for 1.5 h (during this process white solid precipitated), diluted with water and CH_2Cl_2, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, washed with water, satd $NaHCO_3$ solution, then water, dried over $MgSO_4$, filtered, and concentrated to dryness. The resulting white solid (14.15 g, 98 %) was recrystallized from a 1:1 mixture of ether and hexanes, to give 11.5 g (80 %) of **10** as a white solid.

HRMS (FAB) m/z: Calcd for $C_{12}H_{11}O_5$: 235.0606 [M+H]; Found: 235.0618

NMR δ ($CDCl_3$): 11.058 (1H, s), 8.401 (1H, s), 8.058 (1H, d, J = 8.7 Hz), 6.984 (1H, d, J = 8.7 Hz), 4.090 (3H, s), 3.944 (3H, s).

Preparation of Benzofuranacetaldehyde **11**



To a cooled (-40 °C, bath temperature) suspension of methyoxymethyltriphenylphosphonium chloride (9.81 g, 27.8 mmole, 97 % purity) in anhydrous THF (100 mL) was added dropwise a 0.5 M toluene solution of KHMDS (54 ml, 27.0 mmole) by syringe under argon. The resulting deep red mixture was stirred at -30 °C for 30 min. The solution was transferred via cannula to a cooled (-30 °C, bath temperature) suspension of **10** in anhydrous CH_2Cl_2 (200 ml) under argon. The mixture was stirred/warmed slowly to rt, stirred at rt overnight (about 15 h) under argon. The reaction was quenched by addition of a mixture of water and CH_2Cl_2. The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2, and the combined extracts were washed with water, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The product was purified by Flash column chromatography (silica gel, elution by 2 % ether in CH_2Cl_2), to give 5.34 g (95 %) of the intermediate enol ether as a white solid (a mixture of *cis* and *trans* enol ethers; *trans/cis* ratio = ~3.3/1).

Trans: NMR δ ($CDCl_3$): 8.229 (1H, s), 7.177 (1H, d, J = 8.4 Hz), 7.112 (1H, d, J = 12.9 Hz), 6.903 (1H, d, J = 12.9 Hz), 6.782 (1H, d, J = 8.4 Hz), 3.985 (3H, s), 3.879 (3H, s), 3.759 (3H, s).

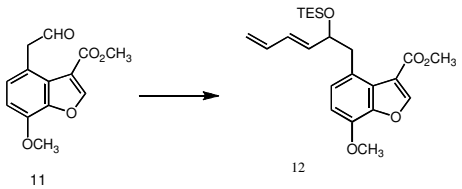
Cis: NMR δ ($CDCl_3$): 8.220 (1H, s), 7.907 (1H, d, J = 8.4 Hz), 7.576 (1H, d, J = 7.2 Hz), 6.835 (1H, d, J = 8.4 Hz), 6.200 (1H, d, J = 7.2 Hz), 3.977 (3H, s), 3.872 (3H, s), 3.780 (3H, s).

To a cooled suspension (ice water bath) of the above cis/trans mixture of the enol ether (18.7 g, 71.3 mmole) in THF (310 ml) was slowly added a cooled solution of concentrated HCl (39 mL) in THF (100 mL). The resulting mixture was stirred at 0 °C for 30 min, the cooling bath was removed, and the solution was stirred at rt for 2 h. Following brine addition, the organic layer was separated. After extraction of the aqueous layer with ethyl acetate, the combined organic layers were washed with brine, satd. $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*, to give **11** (17.6 g, 100 %) as a pale yellow solid. Recrystallization from a mixture of ether and hexanes gave **11**, as a pale yellow solid (15.3 g, 86 %).

HRMS (FAB) m/z: Calcd for $C_{13}H_{13}O_5$: 249.0763 [M+H]; Found: 249.0768.

NMR δ ($CDCl_3$): 9.825 (1H, s), 8.262 (1H, s), 6.994 (1H, d, J = 8.2 Hz), 6.822 (1H, d, J = 8.2 Hz), 4.279 (2H, s), 3.995 (3H, s), 3.845 (3H, s).

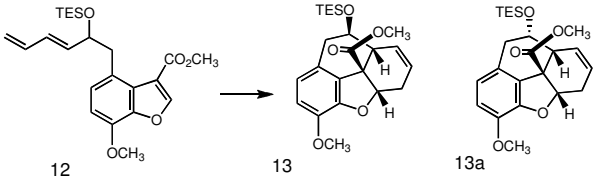
Preparation of Triethylsiloxydiene **12**



To a cooled (-30 °C bath)) suspension of [$ZrCp_2(H)Cl$] (2.0 g, 7.77 mmole) in anhydrous CH_2Cl_2 (13 mL) was added a solution of 3-buten-1-yne (ca 1.25 – 1.5 g, 24 mmole) in anhydrous CH_2Cl_2 (7 mL) all at once, under argon. The resulting suspension was stirred at -10 °C (bath temperature) for 2 h, then at between -10 to -5 °C for an additional 1h. During this process, the solid almost dissolved, to give a bright orange solution to which was added by syringe, a solution of **11** (1.2 g, 4.83 mmole) in anhydrous CH_2Cl_2 (5 mL), followed by silver triflate (130 mg) all at once. The reaction flask was covered with aluminum foil, and the cooling bath was kept at -5 °C. The reaction mixture became dark brown. The mixture was stirred at 0 °C (an ice-water bath) for 2 h under argon. The mixture was then cooled to -78 °C, and imidazole (1.8 g, 26.4 mmole) was added, followed by triethylsilyl chloride (2.8 mL, 16.68 mmole). The resulting mixture was stirred, with gradual warming to rt, and stirred at rt overnight (ca 15 h). The reaction was quenched by addition of satd $NaHCO_3$ solution, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was loaded on a Flash column for chromatography (silica gel, elution by CH_2Cl_2), to give 1.988 g of a mixture of **12** (about 1.848 g, 92 % yield) and Et_3SiCl (0.14 g). Rechromatography of this material gave **12** of >98 % purity.

NMR δ ($CDCl_3$): 8.240 (1H, s), 7.063 (1H, d, J = 8.4 Hz), 6.787 (1H, d, J = 8.4 Hz), 6.38-6.13 (2H, m), 5.813 (1H, dd, J = 5.7, 15.0 Hz), 5.078 (1H, dd, J = 10.2, 16.5), 4.39-4.33 (1H, m), 3.988 (3H, s), 3.878 (3H, s), 3.534 (1H, dd, J = 3.6, 13.2), 3.108 (1H, dd, J = 8.7, 13.2), 0.60-0.80 (9H, m), and 0.20-0.40 (6H, m).

Diels-Alder Cyclization of **12 :** Formation of Tricyclic Adducts **13** and **13a**



A total of 955 mg (2.29 mmole) of **12** was divided in 3 parts, and each part was placed in a 125 mL high pressure tube. Anhydrous decalin (55 mL) and dry Et_3N (1.0 ml, 0.72 mmole) were introduced into each flask, which was then degassed by bubbling argon for at least 2 – 3 min. The tubes were sealed, and heated at 220 – 230 °C (bath temperature) for 5 h. The three reaction mixtures were cooled, combined, and loaded on a silica gel Flash column. Elution with hexanes removed decalin, and elution by 5 % ether in CH_2Cl_2 gave 848 mg (89%) of a mixture of **13** and **13a** (in a ratio of ~ 4: 1 by NMR). Compounds **13** and **13a** could be separated by treatment of the mixture with cold n-pentane, which gave **13** as a white solid and **13a** as a colorless oil. Further transformations of **13a** to (**±**) deoxycodeine (**20**) are shown later sections

13: HRMS (FAB) m/z: Calcd $C_{23}H_{32}O_5Si$: 416.2019 [M^+]; Found: 416.2021.

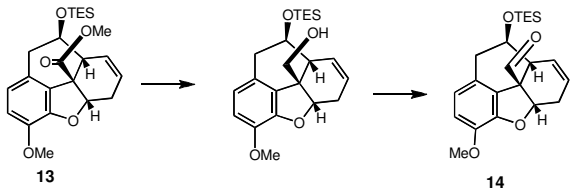
NMR δ ($CDCl_3$): 6.753 (1H, d, J = 8.1 Hz), 6.666 (1H, d, J = 8.1 Hz), 6.020 (1H, ddd, J = 3.3, 5.4,9.0 Hz), 5.746 (1H, ddd, J = 2.7, 6.9, 9.6 Hz), 5.342 (1H, dd, J = 6.6, 9.0 Hz), 3.856 (3H, s), 3.669 (3H, s), 3.435 (1H, dt, J = 3.9, 9.0 Hz), 2.983 (2H, dd, J = 9.6, 14.4 Hz), 2.638 (1H, dd, J = 3.9, 14.4 Hz), 2.517 (1H, dt, J = 6.9, 15.6 Hz), 1.94-1.84 (1H, m), 0.954 (9H, t, J = 7.8 Hz), and 0.60 (6H, q, J = 7.8 Hz).

13a: HRMS (FAB) m/z: Calcd $C_{23}H_{32}O_5Si$: 416.2019 [M^+]; Found: 416.1992

NMR δ ($CDCl_3$): 6.730 (1H, d, J = 8.1 Hz), 6.599 (1H, d, J = 8.1 Hz), 5.86-5.73 (2H, m), 5.326 (1H, dd, J = 4.5, 7.5 Hz), 4.320 (1H, dd, J = 5.1, 9.3 Hz), 3.848 (3H, s), 3.707 (3H, s), 3.14-3.12 (1H, m), 2.973

(1H, dd, J = 5.7, 16.5 Hz), 2.55-2.40 (2H. m), 2.15-2.05 (1H, m), 0.931 (9H, t, J = 7.8 Hz), and 0.578 (6H, q, J = 7.8 Hz).

Preparation of Aldehyde **14**



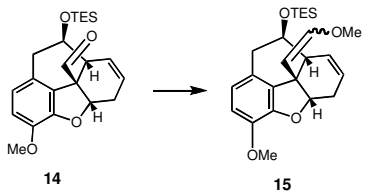
To a cooled (0 °C, ice water bath) solution of **13** (1.6 g, 3.84 mmole) in anhydrous CH_2Cl_2 (40 mL) was added dropwise Super-Hydride (8.45 mL, 8.45 mmole 1.0 M solution in THF) by syringe, under argon. The resulting solution was stirred at 0 °C under argon for an additional 1 h, when TLC analysis indicated the reaction was complete. The mixture was diluted with CH_2Cl_2, and the organic layer was washed with water (2 times), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified by Flash column chromatography (silica gel; elution by 10 % ether in CH_2Cl_2), to give the intermediate alcohol (1.5 g, 100 %) as a colorless oil.

HRMS (FAB) m/z: Calcd for $C_{22}H_{32}O_4Si$: 388.2070 [M^+]; Found: 388.2080.

NMR δ ($CDCl_3$): 6.727 (1H, d, J = 8.1 Hz), 6.647 (1H, d, J = 8.1 Hz), 6.129 (1H, ddd, J = 3.0, 5.4, 9.3), 5.707 (1H, ddd, J = 2.4, 6.9, 9.6), 4.782 (1H, dd, J = 6.3, 9.3 Hz), 3.864 (3H, s), 3.65-3.54 (2H, m), 3.357 (1H, ddd, J = 4.2, 8.7, 10.2 Hz), 2.844 (1H, dd, J =10.5, 14.1 Hz), 2.67-2.60 (2H, m), 2.469 (1H, dd, J = 6.9, 15.3 Hz), 1.97-1.88 (1H, m),1.716 (1H, t, J =6.3 Hz), 0.961 (9H, t, J = 7.8 Hz), and 0.573 (6H, q, J = 7.8 Hz).

To a cooled (0 °C, ice water bath) solution of the alcohol (1.5 g, 3.86 mmole) in anhydrous CH_2Cl_2 (18 mL) was added, portionwise, Dess-Martin reagent (97 % purity, 1.97 g, 4.63 mmole), under argon. The resulting mixture was stirred for 1 h, and the cooling bath was removed. After the mixture had stirred at rt for 3 h, TLC analysis showed that no starting material remained. The reaction was quenched by addition of satd $NaHCO_3$ solution, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated to dryness, to give crude **14**. NMR δ ($CDCl_3$): 9.564 (1H, s), 8.28-7.70 (residue from Dess-Martin reagent), 6.787 (1H, d, J = 8.1 Hz), 6.691 (1H, d, J = 8.1Hz), 5.97-5.91 (1H, m), 5.75-5.67 (1H, m), 5.238 (1H, t, J = 7.5Hz), 3.874 (3H, s), 3.67-3.60 (1H, m), 3.13-3.05 (1H, m), 2.79-2.48 (2H, m), 2.26 (residue from Dess-Martin reagent), 2.05-1.99 (1H, m), 0.955 (9H, t, J = 7.8 Hz), and 0.603 (6H, q, J = 7.8 Hz). This material was used for the next step without further purification.

Preparation of Enol Ether (E/Z mixture) **15** from Aldehyde **14**



Methoxymethylene–triphenylphosphorane [$Ph_3P{=}CHOCH_3$] was generated from the reaction of methoxymethyl triphenylphosphonium chloride (3.97 g, 11.6 mmole, 97 % purity) and KHMDS (22 mL, 11.0 mmole, 0.5 M solution in toluene) in anhydrous THF (25 mL), at -40 °C under argon. The

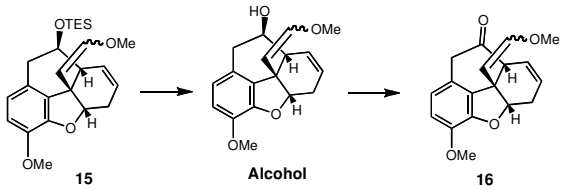
deep red solution was added to a cooled (-50 °C, dry ice acetone bath) solution of **13a** (3.86 mmole) in anhydrous THF (15 mL) via cannula, under argon. The resulting mixture was stirred with slow warming to rt, and stirred at rt overnight (about 15 h). The reaction was quenched with satd $NaHCO_3$ solution, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified by Flash column chromatography (silica gel, elution by 2-3 % ether in CH_2Cl_2), to give 1.37 g (86% overall for the 2 steps from the alcohol) of **15** as a dark yellow oil. Compound **15** was obtained as a mixture of *cis*- and *trans*-enol ethers in ~2.2/1 *cis*-*trans* ratio).

HRMS (FAB) for **15**-*cis/trans* m/z: Calcd for $C_{24}H_{34}O_4Si$: 414.2226 [M^+]; Found: 414.2250.

15-*cis*: NMR δ ($CDCl_3$): 6.678 (1H, d, J = 8.1 Hz), 6.607 (1H, d, J = 8.1 Hz), 6.008 1H, ddd, J = 2.7, 5.1, 9.6 Hz), 5.769 (1H, d, J = 6.6 Hz), 5.70-5.50 (1H, m), 5.081 (1H, dd, J = 6.0, 8.4 Hz), 4.498 (1H, d, J = 6.6 Hz), 3.849 (3H, s), 3.581 (3H, s), 3.41-3.28 (1H, m), 2.86-2.78 (1H, m), 2.45-2.37 (1H, m), 2.00-1.90 (1H, m), 0.960 (9H, t, J = 7.8 Hz), 0.597 (6H, q, J = 7.8 Hz).

15-*trans*: NMR δ ($CDCl_3$): 6.785 (1H, d, J = 8.1 Hz), 6.722 (1H, d, J = 8.1 Hz), 6.105 (1H, ddd, J = 3.3, 5.4, 9.6 Hz), 5.716 (1H, d, J = 12.9 Hz), 5.70-5.50 (1H, m), 4.595 (1H, dd, J = 6.3, 9.6 Hz), 4.917 (1H, d, J = 12.9 Hz), 3.866 (3H, s), 3.432 (3H, s), 3.41-3.28 (1H, m), 2.86-2.78 (1H, m), 2.45-2.37 (1H, m), 2.00-1.90 (1H, m), 0.955 (9H, t, J = 7.8 Hz), 0.589 (6H, q, J = 7.8 Hz).

Preparation of Ketone **16**



To a cooled (-50 °C, dry ice acetone bath) solution of **15** (480 mg, 1.16 mmole) in anhydrous THF (9 mL) was added, dropwise, a solution of TBAF (tetrabutylammonium fluoride, 1.39 mL, 1.39 mmole, 1.0 M solution in THF) by syringe, under argon. The resulting mixture was stirred/warmed to rt, stirred at rt for 2 h until TLC analysis showed no more **15** remained. The reaction was quenched with satd $NaHCO_3$ solution, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was loaded on a Flash column (silica gel) for chromatography. Elution by 10 % ether/CH_2Cl_2 provided 318 mg (92 %) of the secondary alcohol as a mixture of the *cis* and *trans* enol ethers (*cis/trans* ratio = ~2.2/1) as a colorless oil.

HRMS (FAB) the alcohol m/z: Calcd for $C_{18}H_{20}O_4$: 300.1362 [M^+]; Found: 300.1371

Cis: NMR δ ($CDCl_3$): 6.684 (1H, d, J = 8.1 Hz), 6.615 (1H, d, J = 8.1 Hz), 5.853 (1H, d, J = 6.6 Hz), 5.76-5.67 (2H, m), 5.083 (1H, t, J = 6.9 Hz), 4.581 (1H, d, J = 6.6 Hz), 3.848 (3H, s), 3.629 (3H, s), 3.00-2.96 (1H, m), 2.87-2.68 (2H, m), 2.50-2.40 (2H, m), 2.10-1.97 (2H, m).

Trans: NMR δ ($CDCl_3$): 6.731 (1H, d, J = 8.1 Hz), 6.665 (1H, d, J = 8.1 Hz), 5.729 (1H, d, J = 12.6 Hz), 6.11-6.05 (2H, m), 4.954 (1H, d, J = 12.6 Hz), 4.628 (1H, dd, J = 6.3, 9.0 Hz), 3.867 (3H, s), 3.452 (3H, s), 3.00-2.96 (1H, m), 2.87-2.68 (2H, m), 2.50-2.40 (2H, m), 2.10-1.97 (2H, m).

To a cooled (0 °C, ice water bath) solution of the intermediate alcohol (645 mg, 2.15 mmole) in anhydrous CH_2Cl_2 (20 mL) was added Dess-Martin reagent (1.13 g, 2.59 mmole, 97 % purity), portionwise, under argon. The resulting yellow solution was stirred for 4 h at 0 °C, when TLC analysis

showed that the starting material could no longer be detected. The reaction was quenched with satd $NaHCO_3$ solution, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was loaded on a Flash column (silica gel) for chromatography. Elution by 3 % ether in CH_2Cl_2 gave 614 mg (96%) of the ketone **16** as a mixture of the *cis* (**16**-*cis*) and *trans* enol ethers (**16**-*trans*) (*cis/trans* ratio = ~2.2/1).

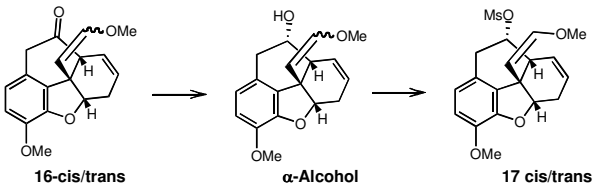
HRMS (FAB) for **16**-*cis*/*trans* m/z: Calcd for $C_{18}H_{18}O_4$: 298.1205 [M^+]; Found: 298.1207.

Compounds, **16**-*cis* and **16**-*trans*, could be separated by further chromatography (silica gel, flash column, 3 % ether in CH_2Cl_2).

16-*cis*: NMR δ ($CDCl_3$): 6.691 (1H,d, J = 8.1 Hz), 6.569 (1H, d, J=8.1 Hz), 5.962 (1H, d, J = 6.3 Hz), 5.88-5.80 (1H, m), 5.432 (1H, dt, J = 2.7, 9.6 Hz), 5.257 (1H, dd, J = 2.4, 5.4 Hz), 4.711 (1H, d, J = 6.3 Hz), 3.852 (3H, s), 3.637 (3H, s), 3.72-3.60 (1H, m), 3.69-3.32 (2H, m), 2.59-2.39 (2H, m).

16-*trans*: NMR δ ($CDCl_3$): 6.739 (1H, d, J = 8.1 Hz), 6.606 (1H, d, J = 8.1 Hz), 6.008 (1H, d, J = 12.6 Hz), 5.88-5.78 (1H, m), 5.48-5.39 (1H, m), 5.002 (1H, dd, J = 2.7, 6.0 Hz), 4.942 (1H, d, J = 12.6 Hz), 3.875 (3H, s), 3.492 (3H, s), 3.65-3.50 (1H, m), 3.45-3.20 (2H, m), 2.55-2.34 (2H, m).

Preparation of α-Mesylate **17**



To a cooled (-50 °C, dry ice-acetone bath) solution of **16** cis/trans mixture (600 mg, 2.0 mmole) in anhydrous THF (10 mL) was treated with L-Selectride (20 mL, 20 mmole, 1.0 M solution in THF), under argon. The resulting mixture was stirred at 0 °C (ice-water bath) for 3.5 h under argon. TLC analysis indicated that **16** was almost completely consumed. The reaction was quenched by careful addition of aqueous satd Rochelle salt solution, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were thoroughly washed with satd Rochelle salt solution, then water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified by Flash column chromatography (silica gel, elution by 10 % ether in CH_2Cl_2), to give 475 mg (79 %) of α-alcohol as a mixture of *cis* and *trans* enol ethers (*cis/trans* ratio = ~2.2/1).

HRMS (FAB) for α-**Alcohol** (*cis*/t*rans enol ethers mixture)* m/z: Calcd for $C_{18}H_{20}O_4$: 300.1362 [M^+]; Found: 300.1378

Cis and trans isomers could be separated by further chromatography (silica gel, Flash column, 10 % ether in CH_2Cl_2).

Cis: NMR δ ($CDCl_3$): 6.691 (1H, d, J = 8.1 Hz), 6.607 (1H, d, J = 8.1 Hz), 5.87-5.78 (3H, m), 5.202 (1H, dd, J = 5.1, 7.5 Hz), 4.499 (1H, d, J = 6.3 Hz), 4.55-4.45 (1H, m), 3.845 (3H, s), 3.640 (3H, s), 3.193 (1H, m), 2.993 (1H, dd, J = 5.1,15.9 Hz), 2.60-2.47 (2H, m), 2.08-1.98 (1H, m), and 1.61 (1H, bs).

Trans: NMR δ ($CDCl_3$): 6.739 (1H, d, J = 8.1 Hz), 6.675 (1H, d, J = 8.1 Hz), 5.93-5.82 (2H, m), 5.700 (1H, d, J = 12.6 Hz), 4.937 (1H, d, J = 12.6 Hz), 4.745 (1H, t, J = 6.9 Hz), 4.46-4.43 (1H, m), 3.861 (3H, s), 3.456 (3H, s), 2.908 (1H, dd, J = 4.2, 15.6 Hz), 2.816 (1H, bs), 2.659 (1H,dd, J = 6.9, 15.6 Hz), 2.54-2.46 (1H, m), 2.03-1.95 (1H, m), and 1.554 (1H, bs).

To a cooled (0 °C, ice-water bath) solution of α-Alcohol (475 mg, 1.58 mmole) in anhydrous CH_2Cl_2 (10 mL) were added, first, Et_3N (0.441 mL, 3.16 mmole), followed by methanesulfonyl chloride (0.184 ml, 2.37 mmole) by syringe, under argon. The resulting mixture was stirred under these conditions for 4 h, when TLC analysis indicated that there was still a very small amount of SM. The reaction was quenched by addition of satd $NaHCO_3$ solution, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was loaded on a Flash column (silica gel) for chromatography. Elution by 5 % ether in CH_2Cl_2 gave 456 mg (76 %) of **17** as a mixture of *cis* and *trans* enol ethers (ratio of cis/*trans* = ~2.2/1).

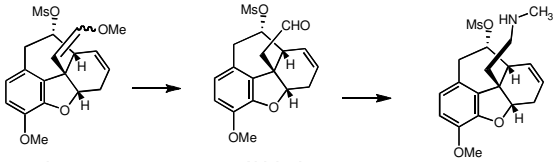
HRMS (FAB) for **17**-*cis/trans* m/z: Calcd for $C_{19}H_{22}O_6S$: 378.1137 [M^+]; Found: 378.1147.

Compounds **17**-cis and **17**-trans, could be separated by further chromatography (silica gel, Flash column, 5% ether in CH_2Cl_2).

17-cis: NMR δ ($CDCl_3$): 6.686 (1H, d, J = 8.1 Hz), 6.559 (1H, d, J = 8.1 Hz), 5.923 (1H, d, J = 6.6 Hz), 5.85-5.82 (1H, m), 5.74-5.69 (1H, m), 5.52-5.44 (1H, m), 5.234 (1H, dd, J = 3.0, 7.8 Hz), 4.539 (1H, d, J = 6.6 Hz), 3.846 (3H, s), 3.675 (3H, s), 3.54-3.49 (1H, m), 3.32-3.21 (1H, m), 3.053 (3H, s), 2.76-2.67 (1H, m), 2.58-2.48 (1H, m), and 2.21-2.18 (1H, m).

17-trans: NMR δ ($CDCl_3$): 6.726 (1H, d, J = 8.1 Hz), 6.609 (1H, d, J = 8.1 Hz), 5.89-5.80 (1H, m), 5.79-5.76 (1H, m), 5.752 (1H, d, J = 12.6 Hz), 5.51-5.44 (1H, m), 4.967 (1H, d, J = 12.6 Hz), 4.846 (1H, dd, J = 4.2, 7.8 Hz), 3.861 (3H, s), 3.496 (3H, s), 3.22-3.13 (1H,m), 3.08-3.03 (1H, m), 3.030 (3H, s), 2.80-2.69 (1H, m), 2.54-2.46 (1H, m), 2.17-2.09 (1H,m).

Preparation of N-Methylaminomesylate **18** from Enol Ether **17**



Concentrated HCl (1.5 mL) was added dropwise to a cooled (0 °C, ice water bath) solution of **17** (300 mg, 0.793 mmole) in THF (20 mL), and the resulting solution was stirred at 0 °C for 3 h. TLC analysis showed the reaction was over at that point. The reaction was quenched by addition of satd $NaHCO_3$ solution, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated to give 271 mg (94%) of the intermediate aldehyde as a yellow oil.

HRMS (FAB) m/z: Calcd for $C_{18}H_{20}O_6S$: 364.0981 [M^+]; Found: 364.0995.

NMR δ ($CDCl_3$): 9.725 (1H, s), 6.759 (1H, d, J = 8.1 Hz), 6.704 (1H, d, J = 8.1 Hz), 5.94-5.89 (1H, m), 5.86-5.81 (1H, m), 5.34-5.30 (1H, m), 4.919 (1H, t, J = 7.2 Hz), 3.877 (3H, s), 3.15-2.94 (3H, m), 2.898 (3H, s), 2.845 (1H dd, J = 1.8, 16.5 Hz), 2.726 (1H, dd, J = 2.1, 16.5 Hz), 2.511 (1H, dt, J = 6.3, 16.5 Hz), 2.00-1.90 (1H, m).

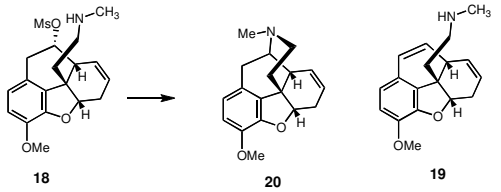
To a cooled (0 °C, ice water bath) solution of the aldehyde (350 mg, 0.961 mmole) and methylamine hydrochloride (130 mg, 1.922 mmole) in anhydrous methanol (10 mL) were added first Et_3N (0.268 ml, 1.922 mmole) dropwise, then titanium *tetra*-iso-propoxide [$Ti(OiPr)_4$] (0.567 mL, 1.922 mmole) by syringe, under argon. After stirring at 0 °C for 5 min, the cooling bath was removed, and the mixture was stirred at rt for 2.5 h, following which the mixture was cooled to 0 °C, and sodium borohydride (54

mg, 1.92 mmole) was added all at once. The cooling bath was removed, and the resulting solution was stirred at rt for 1 h. The solution was poured into a cold mixture of 1N KOH (6 mL) and satd $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with CH_2Cl_2. The extracts were combined, washed with water, dried over Na_2SO_4, filtered and concentrated to dryness, to give 333 mg (92%) of **18** as an amorphous solid. Compound **18** was used for the next step without further purification.

HRMA (FAB) m/z: Calcd for $C_{19}H_{26}NO_5S$: 380.1532 [M+H]; Found: 380.1527.

NMR δ ($CDCl_3$): 6.721 (1H, d, J = 8.1 Hz), 6.618 (1H, d, J = 8.1 Hz), 5.91-5.83 (2H, m), 5.64 (1H, dd, J = 4.2, 9.9 Hz), 4.809 (1H, t, J = 7.2 Hz), 3.869 (3H, s), 3.10-2.93 (3H, m), 2.878 (3H, s), 2.75-2.55 (2H, m), 2.50-2.40 (2H, m), 2.394 (3H, s),2.00-1.75 (3H, m).

Preparation of (±) 6-Deoxycodeine **20**; Cyclization at 50 °C



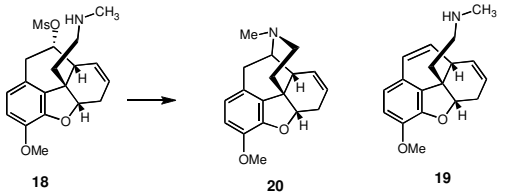
A suspension of **18** (123.5 mg, 0.325 mmole) and potassium carbonate (150 mg, 1.09 mmole) in anhydrous benzene (15 ml) was heated at 50 °C (bath temperature) for 4 days under argon. The mixture was cooled, diluted with CH_2Cl_2, and washed with water until the washings became neutral. The organic layer was dried over Na_2SO_4, filtered and concentrated to dryness. NMR analysis indicated the product was a mixture of the desired cyclized compound, **20**, the eliminated by-product, **19**, and recovered **18**, in the ratio of ~5 : 2 : 1. The mixture was loaded on a silica gel Flash column for chromatography. Elution (CH_2Cl_2 containing of 0.3 % Et_3N, 9 % methanol, and 17 % ether) gave 44.6 mg (44 %) of **20**, and 38.6 mg of a mixture of **20**, **18**, and **19** (in a ratio of ~1: 1 : 1.5, as determined by NMR). Approximate yields of **20**, **18, and 19** were about 55 %, 8 %, and 20 %, respectively. Elimination product **19** was isolated by further chromatography, using the same solvent system.

HRMA (FAB) for **20** m/z: Calcd for $C_{18}H_{21}NO_2$ 284.1651 [M^+]; Found 284.1655.

20: NMR δ ($CDCl_3$): 6.660 (1H, d, J = 8.1 Hz), 6.547 (1H, d, J = 8.1 Hz), 5.76-5.69 (1H, m), 5.365 (1H, t, J = 4.8 Hz), 3.844 (3H, s), 3.356 (1H, dd, J = 3.3, 5.4 Hz), 3.032 (1H, d, J = 18.6 Hz), 2.814 (1H, bs), 2.634 (1H, dd, J = 4.2, 12.0 Hz), 2.477 (3H, s), 2.46-2.31 (4H, m), 2.072 (1H, dt, J = 4.8, 12.3 Hz), 1.827 (1H, dd, J = 1.8, 12.6 Hz).

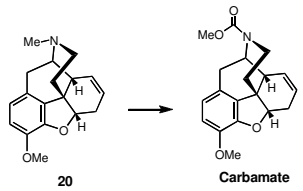
19: NMR δ ($CDCl_3$): 6.724 (1H, d, J = 8.1 Hz), 6.685 (1H, d, J = 8.1 Hz), 6.528 (1H, dd, J = 3.3, 9.6 Hz), 5.904 (1H, d, J = 5.7 Hz), 5.634 (1H, dt, J = 2.4, 8.1 Hz), 4.933 (1H, dd, J = 6.9, 9.9 Hz), 3.864 (3H, s), 3.459 (1H, d, J = 19.8 Hz), 3.239 (1H, dd, J = 6.6, 19.8 Hz), 2.90-2.78 (2H, m), 2.73-2.60 (2H, m), 2.468 (3H, s), 2.10-1.95 (2H, m), 1.92-1.78 (1H, m).

Preparation of **20**; Cyclization at 75 °C



A suspension of **18** (87 mg, 0.2293 mmole) and potassium carbonate (158 mg, 1.146 mmole) in anhydrous benzene (15 ml) was heated at 75 ^{o}C (bath temperature) for 24 h under argon. The mixture was cooled, and diluted with CH_2Cl_2. The white precipitate was removed by filtration through Celite, and the filtrate was concentrated *in vacuo*. The residue was loaded on a silica gel Flash column for chromatography. Elution (CH_2Cl_2 containing of 0.5 % Et_3N, 10 % methanol, and 20 % ether) gave 18 mg (27.7 %) of **20**, and 35.6 mg of a mixture of **20**, and **19** (in a ratio of ~5 : 6, as determined by NMR). Approximate yields of **20**, and **19 (**from NMR) were about 53 %, and 30 %, respectively. Physical properties of **20** and **19** were the same as described above.

Preparation of N-desmethylcarbamate from **20**

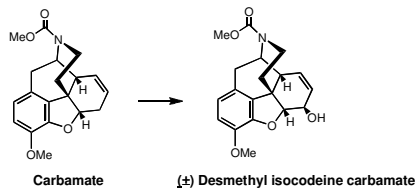


A mixture of **20** (78 mg, 0.275 mmole), $NaHCO_3$ (349 mg, 4.13 mmole), and methyl chloroformate (0.36 mL, 4.68 mmole) in anhydrous $CHCl_3$ was heated at reflux for 17 h under argon. TLC analysis then showed disappearance of the starting material. The mixture was cooled, and diluted with CH_2Cl_2. The organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was loaded on a silica gel Flash column for chromatography. Elution by 5 % ether in CH_2Cl_2 provided 88mg (98 %) of the carbamate as an amorphous solid.

HRMA (FAB) m/z: Calcd for $C_{19}H_{21}NO_4$ 327.1471 [M^+]; Found 327.1488.

NMR δ ($CDCl_3$): 6.683 (1H, d, J = 8.1 Hz), 6.546 (1H, d, J = 8.1 Hz), 5.82-5.70 (1H, m), 5.43-5.30 (1H, m), 4.95-4.85 (1.6H, m), 4.78-4.70 (0.4H, m), 4.10-4.08 (0.4H, m), 4.00-3.92 (0.6H, m), 3.849 (3H, s), 3.752 (0.4 x 3H, s, minor amido rotamer), 3.723 (0.6 x 3H, s, major amido rotamer), 3.05-2.76 (2H, m), 2.75-2.58 (2H, m), 2.42-2.35 (2H, m), 1.92-1.80 (2H, m).

Preparation of (±) N-desmethyl Isocodeinecarbamate



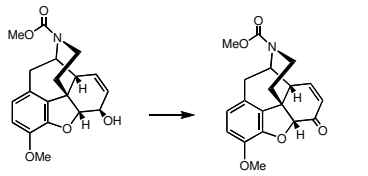
A suspension of 6-deoxycodeine carbamate (88 mg, 0.269 mmole), white sand (200 mg), and finely ground selenium dioxide (299 mg, 2.69 mmole) in anhydrous CH_2Cl_2 (15 mL) was treated with *tert*-butyl hydroperoxide (1.1 ml, 5.38 mmole; 5.0 – 6.0 M solution in decalin) and 3-5 drops of water at rt, under argon. The resulting mixture was heated at reflux under argon for 15 h. The mixture was cooled,

and diluted with CH_2Cl_2. The organic layer was washed with 10 % KOH (3 times) and water until the washings became neutral, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash column chromatography (silica gel; ether/CH_2Cl_2/methanol ~10/10/1) gave 41.2 mg of the crude deoxycarbamate (contaminated with decalin), and 56 mg (61 %) of (**±**) N-desmethylisocodeine carbamate.

HRMA (FAB) m/z: Calcd for $C_{19}H_{21}NO_5$ 343.1420 [M^+]; Found 343.1430.

NMR δ ($CDCl_3$): 6.699 (1H, d, J = 8.1 Hz), 6.561 (1H, d, J = 8.1 Hz), 6.015 (1H, ddd, J = 2.1, 5.1, 9.0 Hz), 5.68-5.60 (1H, m), 4.98-4.90 (0.6H, m), 4.763 (1.4H, bs), 4.256 (1H, d, J = 5.4 Hz), 4.15-4.05 (0.4H, m), 4.02-3.92 (0.6H, m), 3.851 (3H, s), 3.751 (0.4 x 3H, s, minor amide rotamer), 3.722 (0.6 x 3H, s, major amide rotamer), 3.01-2.68 (4H, m), 2.05-1.82 (3H, m).

Preparation of (**±**)N-desmethylcodeinone Carbamate



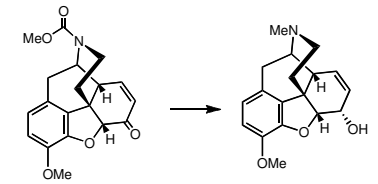
Isocodeine carbamate **(±) Codeinone carbamate**

To a cooled (0 °C, ice water bath) suspension of isocodeine carbamate (56 mg, 0.163 mmole) and molecular sieves (500 mg, 4A powder) in anhydrous CH_2Cl_2 (25 ml) was added pyridinium chlorochromate (PCC, 351 mg, 1.63 mmole), portionwise, under argon. The resulting dark solution was stirred at 0 °C for 10 min, the cooling bath was removed, and the mixture was stirred at rt for 1 h, under argon. TLC analysis then showed absence of SM. The brown reaction mixture was filtered through a cake of silica gel and Celite. The cake was thoroughly rinsed with a mixture of ether and CH_2Cl_2 (1: 1). The extracts were collected, and concentrated *in vacuo*. Flash column chromatography (silica gel; ether: CH_2Cl_2: methanol ~ 10 : 10 : 1) gave 48.3 mg (88 %) of (**±**) N-desmethylcodeinone carbamate.

HRMA (FAB) m/z: Calcd for $C_{19}H_{19}NO_5$ 341.1263 [M^+]; Found 341.1261.

NMR δ ($CDCl_3$): 6.717 (1H, d, J = 8.1 Hz), 6.68-6.60 (2H, m), 6.134 (1H, dd, J = 3.0, 10.2 Hz), 5.08-4.82 (1H, m), 4.696 (1H, bs), 4.20-3.90 (1H, m), 3.863 (3H, s), 3.776 (0.4 x 3H, s, minor amido rotamer), 3.743 (0.6 x 3H, s, major amido rotamer), 3.15-3.05 (1H, m), 3.00-2.75 (3H, m), 2.10-1.85 (2H, m).

Preparation of (**±**) codeine (**2**)



(±) Codeinone carbamate **(±) Codeine (2)**

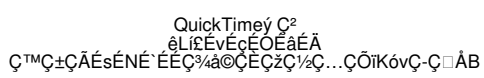
To a cooled (-30 °C, dry ice acetone bath) solution of (**±**) codeinone carbamate (48 mg, 0.14 mmole) in anhydrous ether (20 mL) was added lithium aluminum hydride (1.41 ml, 1.41 mmole, 1.0 M solution

in ether), dropwise, under argon. The resulting mixture was stirred and warmed to rt over a period of 30 – 40 min, and was then heated at reflux for 3 h. The mixture was cooled to 0 ^{o}C (ice-water bath), was treated with a few drops of water, 10 % KOH (a few drops), then water (a few drops), and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was loaded on a silica gel Flash column chromatography. Elution by CH_2Cl_2 containing 0.5 % Et_3N, 10 % methanol, and 20 % ether provided 34 mg (81%) of (**±**)-codeine (**2**) as a white solid, which, after recrystallization from a mixture of ether and hexanes gave a NMR spectrum identical with that of natural codeine.

HRMA (FAB) m/z: Calcd for $C_{18}H_{22}NO_5$ 300.1600 [M+H]; Found 300.1587 .

NMR δ ($CDCl_3$): 6.661 (1H, d, J = 8.1 Hz), 6.567 (1H, d, J = 8.1 Hz), 5.704 (1H, ddd, J = 1.5, 3.0, 9.9 Hz), 5.297 (1H, ddd, J = 2.4, 5.1, 9.9 Hz), 4.889 (1H, dd, J = 1.2, 6.6 Hz), 4.20-4.15 (1H, m), 3.840 (3H, s), 3.349 (1H, dd, J = 3.3, 6.3 Hz), 3.048 (1H, d, J = 18.9 Hz), 2.75-2.65 (1H, m), 2.64-2.55 (1H, m), 2.437 (3H, s), 2.381 (1H, dd, J = 3.6, 12.0 Hz), 2.296 (1H, dd, J = 6.3, 18.6 Hz), 2.066 (1H, dd, J = 5.1, 12.3 Hz), 1.874 (1H, dd, J = 1.8, 12.6 Hz).

Comparisons of (**±**) codeine and (-) codeine using IR, ESI-LCMS, and H-NMR are shown below. a) IR



b) ESI-LCMS: using Acquity UPLC BEH C-18 column (1.7 um, size 2.1 x 150 mm), using a gradient solvent system (Carrier Solvent A: 0.01% formic acid/water, Solvent B: 0.01% formic acid/CH_3CN; gradient system of B 5 % to 40 % in 12 min).

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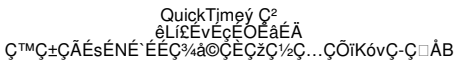
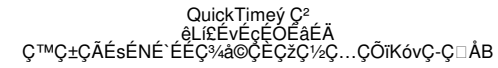
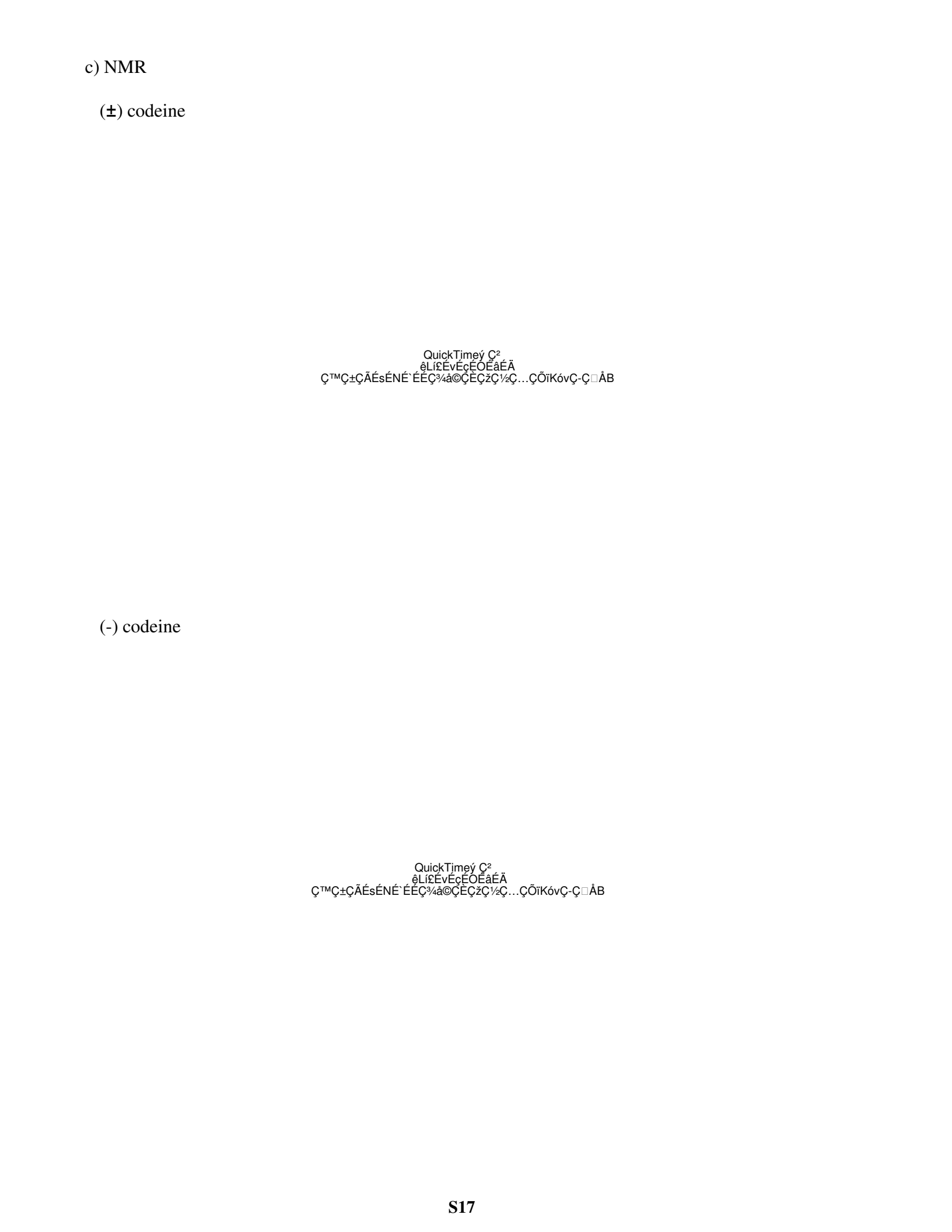


Co injection of synthetic codeine and natural codeine



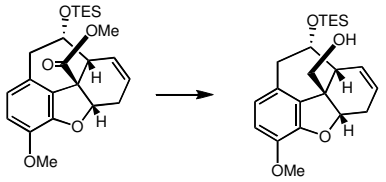
c) NMR

(±) codeine



(-) codeine

Preparation of Alcohol from **13a**

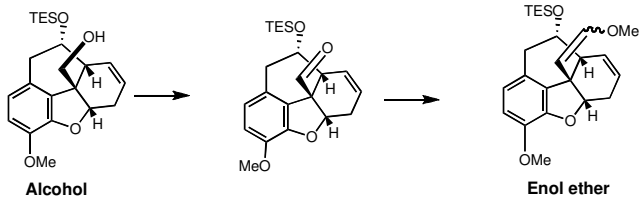


To a cooled (0 ^{o}C, ice water bath) solution of **13a** (341 mg, 0.819 mmole) in anhydrous CH_2Cl_2 (10 mL) was added dropwise Super Hydride (1.8 mL, 1.8 mmole, 1.0 M solution in THF) by syringe, under argon. The resulting solution was stirred at 0 ^{o}C under argon for an additional 1.5 h, when TLC analysis indicated no **13a** remained. The mixture was diluted with CH_2Cl_2, the organic layer was washed with water (3 times), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified by Flash column chromatography (silica gel, elution by 10 % ether in CH_2Cl_2), to give the alcohol (296 mg, 93 %) as a colorless oil.

HRMS (FAB) m/z: Calcd for $C_{22}H_{32}O_4Si$ 388.2070 [M^+]; Found 388.2057.

NMR δ ($CDCl_3$): 6.698 (1H, d, J = 8.1 Hz), 6.601 (1H, d, J = 8.1 Hz), 5.90-5.80 (1H, m), 5.77-5.73 (1H, m), 4.869 (1H, t, J = 7.2 Hz), 4.472 (1H, dt, J = 3.9, 6.9 Hz), 3.853 (3H, s), 3.629 (2H, dd, J = 3.0, 6.3 Hz), 2.89-2.80 (2H, m), 2.551 (1H, dd, J = 6.6, 15.6 Hz), 2.46-2.36 (1H, m), 2.05-1/95 (1H, m), 1.620 (1H, t, J = 5.7 Hz), 0.862 (9H, t, J = 7.8 Hz), 0.512 (6H, q, J = 7.8 Hz).

Preparation of **28-cis/trans** via **27**



To a cooled (0 ^{o}C, ice water bath) solution of the alcohol (300 mg, 0.772 mmole) in anhydrous CH_2Cl_2 (5 ml) was added, portionwise, Dess-Martin reagent (393 mg, 0.926 mmole, 97 % purity) under argon. The resulting mixture was stirred at that temperature for 1h, the cooling bath was removed, and the mixture was stirred at rt for 3 h, when TLC analysis showed that no starting material remained. The reaction was quenched by addition of satd $NaHCO_3$ solution, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated to dryness, to give the crude corresponding aldehyde. NMR δ ($CDCl_3$): 9.671 (1H, s), 8.28-7.70 (residue from Dess-Martin reagent), 6.767 (1H, d, J = 8.1 Hz), 6.656 (1H, d, J = 8.1Hz), 5.89-5.80 (1H, m), 5.77-5.72 (1H, m), 5.186 (1H, t, J = 76.9 Hz), 4.40-4.32 (1H, m), 3.874 (3H, s), 3.23-3.21 (1H, m), 2.740 (1H, dd, J = 4.2, 15.6 Hz), 2.59-2.46 (2H, m), 2.26 (residue from Dess-Martin reagent), 2.15-2.05 (1H, m), 0.955 (9H, t, J = 7.8 Hz), 0.603 (6H, q, J = 7.8 Hz). This material was used for the next step without further purification.

Methoxymethylene–triphenylphosphorane [Ph_3P=$CHOCH_3$] was generated from the reaction of methoxymethyl triphenylphosphonium chloride (794 mg, 2.32 mmole, 97 % purity) and KHMDS (4.63 ml, 2.316 mmole, 0.5 M solution in toluene) in anhydrous THF (10 mL) at -40 ^{o}C under argon. This deep red solution was added to a cooled (-50 ^{o}C, dry ice acetone bath) solution of the aldehyde (0.772 mmole) in anhydrous THF (10 mL) by cannula, under argon. The resulting mixture was stirred with slow warming to rt, and stirred at rt overnight (about 15 h) under argon. The reaction was quenched

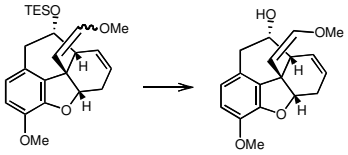
with satd. $NaHCO_3$ solution, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified by Flash column chromatography (silica gel, elution with 2 % ether in CH_2Cl_2), to give 262 mg (82 % overall for the 2 steps from the alcohol SM) of the enol ether as a yellow oil. The product enol ether is obtained as a mixture of cis- and trans-enol ethers in a ~ 10 : 1 ratio**.**

HRMS (FAB) for the enol ether cis/trans m/z: Calcd for $C_{24}H_{34}O_4Si$: 414.2226 [M^+]; Found: 414.2249.

Cis: NMR δ ($CDCl_3$): 6.657 (1H, d, J = 8.1 Hz), 6.515 (1H, d, J = 8.1 Hz), 5.865 (1H, d, J = 6.3 Hz), 5.90-5.67 (2H, m), 5.250 (1H, dd, J = 3.0, 8.1 Hz), 4.532 (1H, d, J = 6.3 Hz), 4.58-4.48 (1H, m), 3.836 (3H, s), 3.657 (3H, s), 3.18-3.12 (1H, m), 2.96-2.85 (1H, m), 2.60-2.47 (2H, m), 2.19-2.12 (1H, m), 0.989 (9H, t, J = 7.8 Hz), 0.631 (6H, q, J = 7.8 Hz).

Trans: NMR δ ($CDCl_3$): 6.767 (1H, d, J = 8.1 Hz), 6.657 (1H, d, J = 8.1 Hz), 5.90-5.67 (2H, m), 5.186 (1H, t, J = 6.6 Hz), 4.952 (1H, d, J = 12.6 Hz), 4.38-4.32 (1H, m), 3.875 (3H, s), 3.845 (3H, s), 3.28-3.18 (1H, m), 2.80-2.71 (1H, m), 2.47-2.34 (2H, m), 2.12-2.06 (1H, m), 0.888 (9H, t, J = 7.8 Hz), 0.545 (6H, q, J = 7.8 Hz).

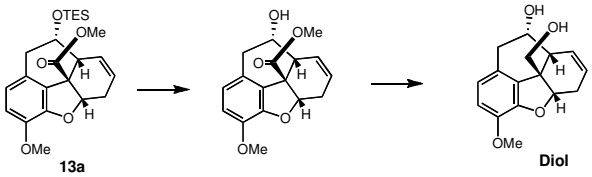
Conversion of Enol Ether-cis/trans to α-Alcohol



Enol ether **α–Alcohol**

To a cooled (-50 ^oC, dry ice acetone bath) solution of the cis-trans enol ether mixture (167 mg, 0.403 mmole) in anhydrous THF (5 mL) a solution of TBAF (0.48 ml, 0.48 mmole, 1.0 M solution in THF) was added dropwise by syringe, under argon. The resulting mixture was stirred/warmed to rt, stirred at rt for 2 h until TLC analysis showed that no more SM remained. The reaction was quenched with satd. $NaHCO_3$ solution, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was chromatographed on a Flash column (silica gel; elution by 10 % ether in CH_2Cl_2) to give 112. mg (92 %) of the α-alcohol as a mixture of the *cis* and *trans* enol ethers (~10 : 1) as a colorless oil. The physical properties of the products were the same as those from the samples described earlier. The ***a***-alcohol (*cis/trans* mixture) was converted to (±)-deoxycodeine (**20**), using the procedures described earlier.

Preparation of Diol for X ray Structure Determination



13a **Diol**

To a cooled (-40 ^oC) solution of **13a** (101 mg, 0.243 mmole) in anhydrous THF (2 mL) was added TBAF (0.267 mL, 0.267 mmole, 1.0 M THF solution) under argon. The resulting solution was warmed

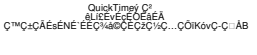
to rt, and stirred at rt for 1.5 h. The reaction was quenched with satd $NaHCO_3$ solution, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified by Flash column chromatography (silica gel, elution by 10 % ether in CH_2Cl_2), to give 52 mg (77%) of the corresponding alcohol as a colorless oil.

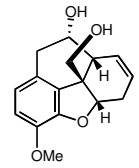
NMR δ ($CDCl_3$): 6.791 (1H, d, J = 8.1 Hz), 6.751 (1H, d, J = 8.1 Hz), 6.003 (1H, dddd, J = 0.9, 1.8, 6.6, 9.9 Hz), 5.902 (1H, ddd, J = 2.7, 5.1, 9.9 Hz), 5.388 (1H, dd, J = 6.9, 8.7 Hz), 4.38-4.32 (1H, m), 3.862 (3H, s), 3.679 (3H, s), 3.30-3.26 (1H, m), 3.069 (1H, dd, J = 2.7, 15.0 Hz), 2.851 (1H, dd, J = 5.1, 15.0 Hz), 2.545 (1H, dt, J = 6.6, 15.9 Hz), 1.96-1.84 (1H, m), 1.496 (1H, bs).

To a cooled (0 °C, ice water bath) solution of the above alcohol (52 mg, 0.172 mmole) in anhydrous CH_2Cl_2 (2 ml) was added a Super Hydride solution (0.4 ml, 0.4 mmole, 1.0 M solution in THF) via a syringe under argon. The resulting solution was stirred at 0 °C under argon for an additional 1.5 h, when TLC analysis indicated that no SM remained. The mixture was diluted in CH_2Cl_2. The organic layer was washed with water (3 times), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified by Flash column chromatography (silica gel, elution by CH_2Cl_2 containing 5 % methanol and 20 % ether), to give the diol (40.8 mg, 86.4 %) as a white solid. Re-crystallization of the diol from a mixture of ether and hexanes gave small needles of the (**±**)diol which were suitable for X-ray structure determination.

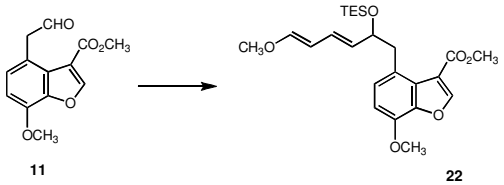
HRMS (FAB) m/z: Calcd for $C_{16}H_{18}O_4$: 274.1205 [M^+]; Found: 274.1209.

NMR δ ($CDCl_3$): 6.715 (1H, d, J = 8.1 Hz), 6.590 (1H, d, J = 8.1 Hz), 5.92-5.84 (1H, m), 5.82-5.72 (1H, m), 4.926 (1H, t, J = 7.2 Hz), 4.437 (1H, d, J = 6.9 Hz), 3.809 (3H, s), 3.479 (2H, q, J = 11.1 Hz), 3.300 (2H, bs), 3.02-2.96 (1H, m), 2.900 (1H, dd, J = 4.5, 15.3 Hz), 2.555 (1H, dd, J = 6.9, 15.3 Hz), 2.47-2.34 (1H, m), 2.00-1.88 (1H, m).





Preparation of **22**



11 **22**

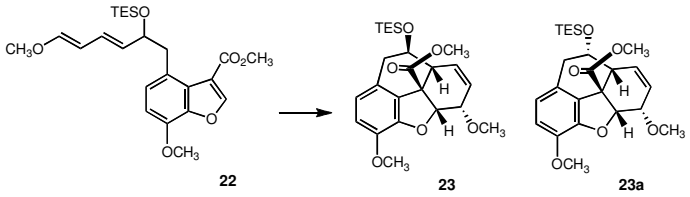
To a cooled (-20 °C bath temperature) suspension of "Zr" reagent [$ZrCp_2(H)Cl$] (1.57 g, 6.10 mmole) in anhydrous CH_2Cl_2 (25 mL) was added 4-methoxy-3-buten-1-yne (largely E; 750 mg, 9.14 mmole) by syringe, all at once under argon. After stirring with gradual warming to 0 °C over a period of 30 min, the suspension was stirred at 0 °C for an additional 30 min. The cooling bath was removed, and the mixture was stirred at rt for 15 min. During this process, the solid was dissolved, and a bright orange solution was obtained. The solution was then cooled to – 20 °C, and was treated with a solution of **11**

(1.1 g, 4.4 mmole) in anhydrous CH_2Cl_2 (10 mL), followed by silver triflate (110 mg) all at once. The reaction flask was covered with aluminum foil to avoid exposure to light. The reaction mixture became dark brown. The mixture was stirred at -20 ^oC for 10 min, the cooling bath was replaced by an ice water bath, and the mixture was stirred at 0 ^oC for 3 h. The mixture was cooled to -78 ^oC, and imidazole (1.4 g, 20.5 mmole) and triethylsilyl chloride (2.41 mL, 14.4 mmole) were added to the solution which was then stirred with gradual warming to rt, and then stirred at rt overnight (ca 15 h) under argon. The reaction was quenched by addition of satd $NaHCO_3$ solution, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was loaded on a Flash column for chromatography (silica gel). Elution by CH_2Cl_2 gave 1.83 g (95 %) **22** as a yellow oil of >98 % purity.

HRMS (FAB) m/z: Calcd for $C_{24}H_{34}O_6Si$: 446.2125 [M^+]; Found: 446.2116.

NMR δ ($CDCl_3$): 8.240 (1H, s), 7.013 (1H, d, J = 8.1 Hz), 6.786 (1H, d, J = 8.1 Hz), 6.551 (1H, d, J = 12.3 Hz), 6.023 (1H, dd, J = 10.8, 15.0 Hz), 5.63-5.46 (2H, m), 4.34-4.27 (1H, m), 3.989 (3H, s), 3.879 (3H, s), 3.585 (3H, s), 3.507 (1H, dd, J = 3.6, 13.2 Hz), 3.097 (1H, dd, J = 9.0, 13.2 Hz), 0.725 (9H, t, J = 7.8 Hz), 0.33-0.23 (6H, m).

Diels-Alder Cyclization of **22 :** Formation of Tetracyclic systems **23** and **23a**



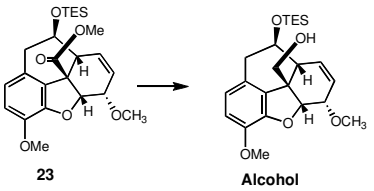
A total of 2.45 g (5.49 mmole) of **22** was divided into 6 portions, and each portion was placed in a 125 mL high pressure tube. Anhydrous decalin (55 mL) and dry Et_3N (1.5 mL, 1.08 mmole) were introduced into each container, which was then degassed by bubbling argon for at least 2–3 min. The containers were sealed, and heated at 235 – 240 ^oC (bath temperature) for 24 h. The reaction mixtures were then cooled, combined, and directly loaded on a silica gel Flash column. Elution with hexanes removed decalin, and elution by 3 % ether in CH_2Cl_2 gave 508 mg (21 %) of recovered **22**, and 1.686 g (69 %) of a mixture of **23** and **23a,** in the approximate ratio of 4: 1 (by NMR). Treatment of this mixture with cold n-pentane, gave a 1: 1 mixture of **23** and **23a,** as white solids. The mother liquor was concentrated *in vacuo*, to give pure **23**, as an oily material. Compound **23a** was not obtained in pure form.

23: HRMS (FAB) m/z: Calcd for $C_{24}H_{34}O_6Si$: 446.2125 [M^+]; Found: 446.2134.

NMR δ ($CDCl_3$): 6.709 (1H, d, J = 8.1 Hz), 6.596 (1H, d, J = 8.1 Hz), 6.03-5.98 (2H, m), 5.364 (1H, d, J = 4.5 Hz), 4.02-3.98 (1H, m), 3.846 (3H, s), 3.681 (3H, s), 3.68-3.63 (1H, m), 3.224 (3H, s), 3.01-2.92 (2H, m), 2.688 (1H, dd, J = 4.5, 14.7 Hz), 0.958 (9H, t, J = 7.8 Hz), 0.592 (6H, q, J = 7.8 Hz).

23a: NMR δ ($CDCl_3$): 6.685 (1H, d, J = 8.4 Hz), 6.520 (1H, d, J = 8.4 Hz), 5.84-5.76 (2H, m), 5.415 (1H, d, J = 6.0 Hz), 4.40-4.32 (1H, m), 3.831 (3H, s), 3.752 (3H, s), 3.68-3.63 (2H, m), 3.527 (3H, s), 3.16-3.03 (2H, m), 2.393 (1H, dd), J = 8.7, 17.4 Hz0, 0.977 (9H, t, J = 7.8 Hz), 0.627 (6H, q, J = 7.8 Hz).

Preparation of Primary Alcohol from **23**

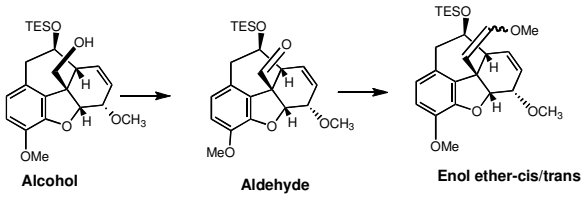


To a cooled (0 ^{o}C, ice-water bath) solution of **23** (2.08 g, 4.66 mmole) in anhydrous CH_2Cl_2 (50 mL) was added, dropwise, Super-Hydride (10.25 mL, 10.25 mmole, 1.0 M solution in THF) by syringe, under argon, and the resulting solution was stirred at 0 ^{o}C for 1.5 h. TLC analysis indicated that no **23** remained. The mixture was diluted with CH_2Cl_2, the organic layer was washed with water (2 times), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified by Flash column chromatography (silica gel, elution by 10 % ether in CH_2Cl_2), to give 97 mg (4.7 %) of recovered **23** and 1.67 g (86%) of the primary alcohol as a colorless oil.

HRMS (FAB) m/z: Calcd for $C_{23}H_{34}O_5Si$: 418.2176 [M^+]; Found: 418.2195.

NMR δ ($CDCl_3$): 6.685 (1H, d, J = 7.8 Hz), 6.576 (1H, d, J = 7.8 Hz), 6.136 (1H, dd, J = 5.4, 9.9 Hz), 5.969 (1H, ddd, J = 1.2, 5.4, 9.9 Hz), 4.792 (1H, d, J = 4.5 Hz), 3.967 (1H, t, J = 4.8 Hz), 3.855 (3H, s), 3.66-3.52 (3H, m), 3.198 (3H, s), 2.827 (1H, dd, J = 9.6, 14.7 Hz), 2.71-2.61 (2H, m), 1.801 (1H, t, J = 6.0 Hz), 0.964 (9H, t, J = 7.8 Hz), 0.607 (6H, q, J = 7.8 Hz).

Preparation of Enol Ethers from Alcohol



To a cooled (0 ^{o}C, ice water bath) solution of the alcohol (1.66 g, 3.97 mmole) in anhydrous CH_2Cl_2 (20 mL) Dess-Martin reagent (97 % purity, 2.02 mg, 4.76 mmole) was added in portions, under argon. The resulting mixture was stirred for 15 min, the cooling bath was then removed, and the mixture was stirred at rt for 3 h. TLC analysis showed that no starting material remained. The reaction was quenched by addition of satd $NaHCO_3$ solution, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated to dryness, to give the crude corresponding aldehyde. NMR δ ($CDCl_3$): 9.483 (1H, s), 8.28-7.70 (residue from Dess-Martin reagent)**,** 6.749 (1H, d, J = 8.1 Hz), 6.633 (1H, d, J = 8.1Hz), 6.085 (1H, dd, J = 5.1, 9.9 Hz), 5.993 (1H, dd, J = 5.1, 9.9 Hz), 5.259 (1H, d, J = 4.8 Hz), 4.03-3.99 (1H, m), 3.86-3.80 (1H, m), 3.868 (3H, s), 3.75-3.65 (1H, m), 3.238 (3H, s), 3.04-2.96 (1H, m), 2.82-2.63 (1H, m), 2.26 (residue from Dess-Martin reagent), 0.955 (9H, t, J = 7.8 Hz), 0.603 (6H, q, J = 7.8 Hz). This material was used for the next step without further purification.

Methoxymethylene–triphenylphosphorane [Ph_3P=$CHOCH_3$] was generated from the reaction of methoxymethyl triphenylphosphonium chloride (3.51 g, 9.92 mmole, 97 % purity) and KHMDS (19.83 ml, 9.92 mmole, 0.5 M solution in toluene) in anhydrous THF (40 mL) at -40 ^{o}C, under argon. The deep red solution was transferred by cannula to a cooled (-50 ^{o}C, dry ice-acetone bath) solution of the aldehyde (3.97 mmole) in anhydrous THF (25 mL). The resulting mixture was stirred, with slow warming, to rt, and stirred at rt overnight (about 15 h). The reaction was quenched with satd $NaHCO_3$ solution, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified by Flash column chromatography (silica gel, elution by 3 % ether in CH_2Cl_2), to

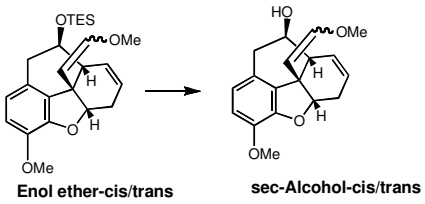
give 1.30 g of the enol ether (74 % overall for 2 steps from the alcohol) as a yellow oil. The product was obtained as a mixture of cis- and trans-enol ethers in an approximate ratio of 2.5/1 (by NMR). Further elution by 10 % ether in CH_2Cl_2 gave 222 mg (*ca* 8 %) of the recovered crude aldehyde.

HRMS (FAB) Enol ether-cis/trans mixture m/z: Calcd for $C_{25}H_{36}O_5Si$: 444.2332 [M^+]; Found: 444.2332.

Cis: NMR δ ($CDCl_3$): 6.612 (1H, d, J = 8.1 Hz), 6.526 (1H, d, J = 8.1 Hz), 5.881 (1H, d, J = 6.3 Hz), 5.85-5.75 (1H, m), 5.55-5.45 (1H, m), 5.289 (1H, d, J = 4.2 Hz), 4.758 (1H, d, J = 6.3 Hz), 3.806 (3H, s), 3.598 (3H, s), 3.453 (3H, s), 2.90-2.75 (3H, m), 2.70-2.50 (1H, m), 0.969 (9H, t, J = 7.8 Hz), 0.603 (6H, q, J = 7.8 Hz).

Trans: NMR δ ($CDCl_3$): 6.666 (1H, d, J = 8.1 Hz), 6.564 (1H, d, J = 8.1 Hz), 6.00-5.90 (2H, m), 5.942 (1H, d, J = 12.9 Hz), 4.950 (1H, d, J = 12.9 Hz), 4.715 (1H, d, J = 4.2 Hz), 3.98-3.90 (1H, bs), 3.846 (3H, s), 3.453 (3H, s), 3.251 (3H, s), 3.21-3.10 (1H, m), 2.90-2.75 (3H, m), 0.969 (9H, t, J = 7.8 Hz), 0.603 (6H, q, J = 7.8 Hz).

Detesylation to Secondary Alcohol



Enol ether-cis/trans **sec-Alcohol-cis/trans**

To a cooled (-50 °C, dry ice-acetone bath) solution of the enol ethers (cis/trans, 1.3 g, 2.92 mmole) in anhydrous THF (18 mL) under argon was added, dropwise, a solution of TBAF (3.8 mL, 3.8 mmole, 1.0 M solution in THF) via syringe. The resulting mixture was stirred/warmed to rt, stirred at rt for 2 h, when TLC analysis showed no more starting material**.** The reaction was quenched with satd $NaHCO_3$ solution, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was loaded on a Flash column (silica gel) for chromatography. Elution by 10 % ether in CH_2Cl_2 provided 65 mg (5 %) of recovered starting material. Further elution gave 849 mg (88 %) of the corresponding alcohol as a colorless oil, a mixture of the *cis* and *trans* enol ethers (~2.5/1).

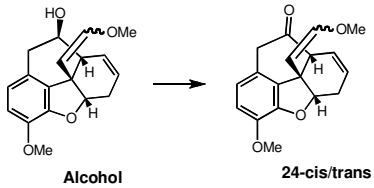
HRMS (FAB) **Alcohol**-cis/trans m/z: Calcd for $C_{19}H_{22}O_5$: 330.1467 [M^+]; Found: 330.1478.

Further chromatography (flash column, silica gel, 10 % ether in CH_2Cl_2) separated cis and trans.

Cis: NMR δ ($CDCl_3$): 6.625 (1H, d, J = 8.1 Hz), 6.544 (1H, d, J = 8.1 Hz), 5.974 (1H, d, J = 6.3 Hz), 5.776 (1H, d, J = 9.9 Hz), 5.387 (1H, dt, J = 2.7, 9.9 Hz), 5.298 (1H, d, J = 3.6 Hz), 4.775 (1H, d, J = 6.3 Hz), 4.10-4.07 (1H, m), 4.05-3.95 (1H, m), 3.805 (3H, s), 3.673 (3H, s), 3.493 (3H, s), 3.23-3.08 (1H, m), 2.93-2.91 (1H, m), 2.736 (1H, dd. J = 7.8, 14.7 Hz), 2.115 (1H, bs).

Trans: NMR δ ($CDCl_3$): 6.680 (1H, d, J = 8.1 Hz), 6.584 (1H, d, J = 8.1 Hz), 5.93-5.91 (2H, m), 5.889 (1H, d, J = 12.6 Hz), 4.977 (1H, d, J = 12.6 Hz), 4.760 (1H, d, J = 4.5 Hz), 3.97-3.88 (1H, m), 3.848 (3H, s), 3.73-3.69 (1H, m), 3.474 (3H, s), 3.295 (3H, s), 2.87-2.74 (2H, m), 2.65-2.61 (1H, m), 2.095 (1H. bs).

Preparation of Ketone **24**



Alcohol **24-cis/trans**

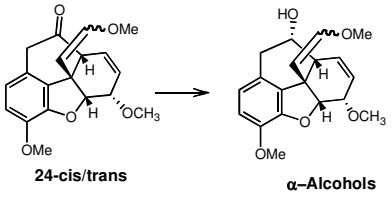
To a cooled (0 °C, ice water bath) solution of the alcohol (769 mg, 2.328 mmole) in anhydrous CH_2Cl_2 (15 mL) was added Dess-Martin reagent (1.22 g, 2.793 mmole, 97 % purity) all at once under argon. The resulting yellow solution was stirred at 0 °C until TLC analysis no longer detected the starting material (about 4.5 h). The reaction was quenched with satd $NaHCO_3$ solution, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was loaded on a Flash column (silica gel) for chromatography. Elution by 5 % ether in CH_2Cl_2 gave 689 mg (90%) of **24** as a mixture (ratio ~2.5/1) of the *cis* and *trans* enol ethers.

HRMS (FAB) for **24**-cis/trans m/z: Calcd for $C_{19}H_{20}O_5$: 328.1311 [M^+]; Found: 328.1300.

24-cis: NMR δ ($CDCl_3$): 6.675 (1H, d, J = 8.1 Hz), 6.562 (1H, d, J = 8.1 Hz), 6.005 (1H, d, J = 6.3 Hz), 5.92-5.85 (1H, m), 5.392 (1H, dd, J = 1.2, 4.2 Hz), 5.35-5.28 (1H, m), 4.788 (1H, d, J = 6.3 Hz), 4.09-4.04 (1H, m), 3.825 (3H, s), 3.74 (1H, bs), 3.674 (3H, s), 3.560 (3H, s), 3.45-3.42 (1H, m), 3.38-3.30 (1H, m).

24-trans: NMR δ ($CDCl_3$): 6.709 (1H, d, J = 8.1 Hz), 6.558 (1H, d, J = 8.1 Hz), 6.148 (1H, d, J = 12.9 Hz), 5.92-5.85 (1H, m), 5.177 (1H, dd, J = 1.2, 4.5 Hz), 5.35-5.28 (1H, m), 4.938 (1H, d, J = 12.9 Hz), 3.88-3.84 (1H, m), 3.846 (3H, s), 3.60 (1H, bs), 3.544 (3H, s), 3.521 (3H, s), 3.38-3.30 (1H, m), 3.15-3.11 (1H, m).

Preparation of **α-Alcohol**



24-cis/trans **α–Alcohols**

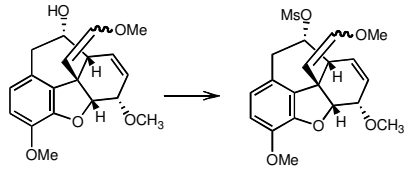
A cooled (-20 °C, dry ice-acetone bath) solution of **24**-cis/trans (680 mg, 2.07 mmole) in anhydrous THF (10 mL) under argon was treated with L-Selectride (20.7 mL, 20.7 mmole, 1.0 M solution in THF). The resulting mixture was stirred with gradual warming to rt, and stirred at rt for 6 h. The reaction mixture was cooled to 0 °C (ice-water bath), and was quenched by careful addition of satd Rochelle salt solution. The aqueous layer was extracted with CH_2Cl_2, and the combined extracts were thoroughly washed with satd Rochelle salt solution, with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was loaded on a Flash column for chromatography (silica gel). Elution by 6 % ether in CH_2Cl_2 gave 161 mg (24 %) of recovered **24**. Further elution by 10 % ether in CH_2Cl_2 gave 359 mg (53 %) of the corresponding α-alcohol as a mixture (ratio ~ 2.5/1) of *cis* and *trans* enol ethers.

HRMS (FAB) for **α-Alcohol**-cis/trans m/z: Calcd for $C_{19}H_{22}O_5$: 330.1467 [M^+]; Found: 330.1488.

Cis: NMR δ ($CDCl_3$): 7.734 (1H, d, J = 8.1 Hz), 6.668 (1H, d, J = 8.1 Hz), 6.12-6.07 (2H, m), 5.780 (1H, d, J= 6.3 Hz), 5.068 (1H, d, J = 4.5 Hz), 4.480 (1H, d, J = 6.6 Hz), 4.38-4.28 (1H, m), 4.02-3.96 (1H, m), 3.864 (3H, s), 3.599 (3H, s), 3.229 (3H, s), 3.86-3.80 (1H, m), 2.99-2.70 (1H, m).

Trans: NMR δ ($CDCl_3$): 6.752 (1H, d, J = 8.1 Hz), 6.710 (1H, d, J = 8.1 Hz), 6.20-6.17 (2H, m), 5.723 (1H, d, J = 12.6 Hz), 4.884 (1H, d, J = 12.3 Hz), 4.586 (1H, d, J = 4.2 Hz), 4.38-4.28 (1H, m), 4.02-3.96 (1H, m), 3.883 (3H, s), 3.433 (3H, s), 3.190 (3H, s), 3.86-3.80 (1H, m), 2.99-2.70 (1H, m).

Preparation of Mesylate **25**



α-Alcohol-cis/trans **25-cis/trans**

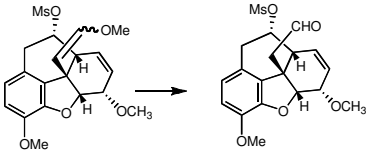
To a cooled (0 °C, ice water bath) solution of the **α-Alcohol**-cis/trans (300 mg, 0.9081 mmole) in anhydrous CH_2Cl_2 (12 mL) were added Et_3N (0.19 mL, 1.36 mmole), then methanesulfonyl chloride (0.085 mL, 1.09 mmole) by syringe, under argon. The resulting mixture was stirred at 0 °C for 6 h. The reaction was quenched by addition of satd $NaHCO_3$ solution, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was loaded on a Flash column (silica gel) for chromatography. Elution by 5 % ether in CH_2Cl_2 gave 275 mg (74 %) of **25** as a mixture (~ 2.5/1) of *cis* (**25**-cis) and *trans* (**25**-trans) enol ethers and 54.1 mg (18 %) of recovered **α-Alcohol**.

HRMS (FAB) for **25**-cis/trans m/z**:** Calcd for $C_{20}H_{24}O_7S$: 408.1234 [M^+]; Found: 408.1254.

25-cis: NMR δ ($CDCl_3$): 6.641 (1H, d, J = 8.1 Hz), 6.504 (1H, d, J = 8.1 Hz), 5.969 (1H, d, J = 6.3 Hz), 5.90-5.85 (1H, m), 5.69-5.53 (2H, m), 5.383 (1H, d, J = 5.7 Hz), 4.655 (1H, d, J = 6.0 Hz), 4.00-3.95 (1H, m), 3.822 (3H, s), 3.714 (3H, s), 3.530 (3H, s), 3.35-3.23 (2H, m), 3.067 (3H, s), 2.73-2.62 (1H, m).

25-trans: NMR δ ($CDCl_3$): 6.673 (1H, d, J = 8.1 Hz), 6.531 (1H, d, J = 8.1 Hz), 5.823 (1H, d, J = 12.6 Hz), 5.90-5.85 (1H, m), 5.69-5.53 (2H, m), 5.073 (1H, d, J = 6.0 Hz), 4.986 (1H, d, J = 12.6 Hz), 3.90-3.84 (1H, m), 3.843 (3H, s), 3.530 (3H, s), 3.511 (3H, s), 3.35-3.23 (2H, m), 3.087 (3H, s), 2.73-2.62 (1H, m).

Hydrolysis of Enol Ether



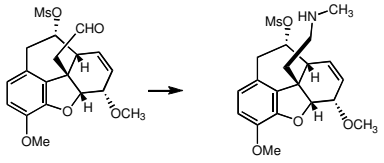
25-cis/trans **Aldehyde**

Concentrated HCl (2.0 ml) was added dropwise to a cooled (0 °C, an ice-water bath) solution of **25** (260 mg, 0.637 mmole) in THF (20 mL), and the resulting solution was stirred at 0 °C for 5 h. The reaction was quenched by addition of satd $NaHCO_3$ solution, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated to dryness, to give 280 mg of the crude aldehyde. Flash column chromatography (silica gel, elution by 10 % ether in CH_2Cl_2) gave 32 mg (12 %) of recovered **25** and 216 mg (86 %) of the corresponding aldehyde as a colorless amorphous solid.

HRMS (FAB) m/z: Calcd for $C_{19}H_{22}O_7S$: 394.1086 [M^+]; Found: 394.1090

NMR δ ($CDCl_3$): 9.814 (1H, s), 6.682 (1H, d, J = 8.1 Hz), 6.558 (1H, d, J = 8.1 Hz), 5.939 (1H, d, J = 10.2 Hz), 5.700 (1H, dt, J = 2.4, 10.2 Hz), 5.46-5.39 (1H, m), 5.158 (1H, d, J = 6.0 Hz), 4.07-4.01 (1H, m), 3.838 (3H, s), 3.479 (3H, s), 3.340 (1H, dd, J = 7.5, 17.1 Hz), 3.27-3.24 (1H, m), 3.035 (3H, s), 3.09-2.98 (2H, m), 2.792 (1H, dd, J = 7.8, 17.1 Hz).

Preparation of Methylamine **26**



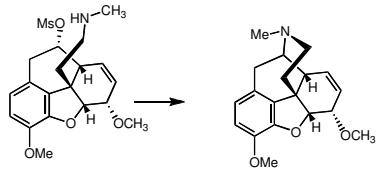
Aldehyde **26**

To a cooled (0 °C, ice water bath) solution of the aldehyde (94.7 mg, 0.240 mmole) and methylamine hydrochloride (33 mg, 0.480 mmole) in anhydrous methanol (3 mL) were added, first, Et_3N (0.067 ml, 0.480 mmole), dropwise, then titanium *tetra*-isopropoxide [Ti(*Oi*P*r*)$_4$] (0.147 mL, 0.480 mmole) by syringe, under argon. After stirring at 0 °C for 30 min, the cooling bath was removed, and the mixture was stirred at rt for 2.5 h. The mixture was cooled to 0 °C, sodium borohydride (14 mg, 0.480 mmole) was added all at once, and the mixture was stirred at 0 °C for 15 min. The cooling bath was removed, and the resulting solution was stirred at rt for 45 min. The solution was poured into a cold mixture of 1N KOH solution (3 mL) and satd $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with CH_2Cl_2. The extracts were combined, washed with water until washings became neutral, dried over Na_2SO_4, filtered, and concentrated to dryness, to give 91.3 mg (93 %) of **26** as an amorphous solid. Compound **26** was used for the next step without further purification.

HRMS (FAB) m/z: Calcd for $C_{20}H_{28}NO_6S$: 410.1637 [M+H]; Found: 410.1634.

NMR δ ($CDCl_3$): 6.650 (1H, d, J = 8.1 Hz), 6.530 (1H, d, J = 8.1 Hz), 5.885 (1H, d, J = 10.2 Hz), 5.682 (1H, dt, J = 2.7, 10.2 Hz), 5.62-5.56 (1H, m), 5.152 (1H, dd, J = 0.9, 5.7 Hz), 3.829 (3H, s), 3.86-3.78 (1H, m), 3.495 (3H, s), 3.385 (1H, dd, J = 7.5, 17.1 Hz), 3.11-3.05 (1H, m), 3.069 (3H, s), 2.89-2.61 (3H, m), 2.433 (3H, s), 2.06-1.96 (1H, m), 1.91-1.81 (1H, m), 1.520 (1H, bs).

(±)**Codeine Methyl Ether** (**27**)



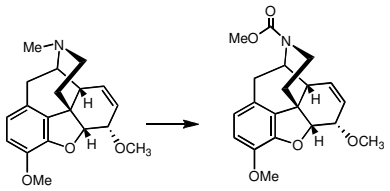
26 **27**

A suspension of **26** (70 mg, 0.171 mmole) and potassium carbonate (118 mg, 0.855 mmole) in anhydrous benzene (15 mL) was heated at 75 °C (bath temperature) for 24 h under argon. The mixture was cooled, diluted with CH_2Cl_2, and the white solid was removed through a celite pad. The cake was washed with CH_2Cl_2, and the organic layers were collected and concentrated *in vacuo*. The residue was loaded on a silica gel Flash column for chromatography. Elution by CH_2Cl_2, containing of 0.6 % Et_3N, 5 % methanol, and 20 % ether, gave 39 mg (73 %) of (±) codeine methyl ether (**27**) as a white solid. The NMR spectrum of **27** was superimposable on that of the methyl ether from natural codeine.

HRMS (FAB) m/z: Calcd for $C_{19}H_{24}NO_3$: 314.1756 [M+H]; Found: 314.1765.

NMR δ ($CDCl_3$): 6.631 (1H, d, J = 8.1 Hz), 6.535 (1H, d, J = 8.1 Hz), 5.725 (1H, dtd, J = 2.1, 2.4, 9.9 Hz), 5.321 (1H, dt, J = 2.7, 9.9 Hz), 4.990 (1H, dd, J = 1.2, 6.0 Hz), 3.827 (3H, s), 3.81-3.76 (1H, m), 3.533 (3H, s), 3.366 (1H, dd, J = 3.3, 6.0 Hz), 3.045 (1H, d, J = 18.6 Hz), 2.68-2.65 (1H, m), 2.590 (1H, dd, J = 3.9, 12.3 Hz), 2.446 (3H, s), 2.44-2.38 (1H, m), 2.314 (1H, dd, J = 6.3, 18.6 Hz), 2.049 (1H, dt, J = 5.1, 12.3 Hz), 1.904 (1H, dt, J = 1.5, 12.6 Hz).

Preparation of the Carbamate from **27**



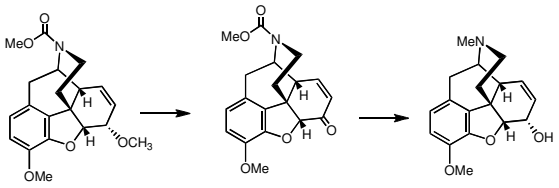
27 Carbamate from **27**

A mixture of **27** (60 mg, 0.192 mmole), $NaHCO_3$ (242 mg, 2.873 mmole), and methyl chloroformate (0.25 mL, 3.26 mmole) in anhydrous $CHCl_3$ (7 mL) was heated at reflux for 17 h, under argon. The mixture was cooled, and diluted with CH_2Cl_2. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated in *vacuo*. The residue (88 mg) was loaded on a silica gel Flash column for chromatography. Elution by 10 % ether in CH_2Cl_2 provided 61.9 mg (90.5 %) of the carbamate from **27** as an amorphous solid.

HRMS (FAB) m/z: Calcd for $C_{20}H_{23}NO_5$: 357.1576 [M^+]; Found: 357.1591.

NMR δ ($CDCl_3$): 6.665 (1H, d, J = 8.1 Hz), 6.518 (1H, d, J = 8.1 Hz), 5.788 (1H, d, J = 9.6 Hz), 5.35-5.30 (1H, m), 4.989 (1H, d, J = 6.0 Hz), 4.95 (0.55H, bs), 4.81 (0.45H, bs), 4.16-3.97 (1H, m), 3.837 (3H, s), 3.66-3.62 (4H = 3.650 for 3H x 0.45, s, minor amid rotamer; 3.627 for 3H x 0.55, s, major amid rotamer; also 1H, m), 3.531 (3H, s), 3.10-2.70 (3H, m), 2.519 (1H, bs), 2.046 (2H, bs).

Conversion of **28** to **(±) Codeine** (**2**)

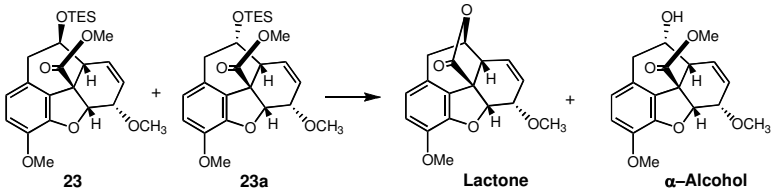


Carbamate from **27** **28** **2**

To a suspension of the carbamate from **27** (60 mg, 0.168 mmole), white sand (150 mg), and finely ground selenium dioxide (186 mg, 1.68 mmole) in CH_2Cl_2 (9 mL) was added *tert*-butyl-hydroperoxide (0.67 mL, *ca* 3.358 mmole; 5.0–6.0 M solution in decalin) and 4 drops of water at rt under argon. The resulting mixture was heated at reflux under argon for 15 h. The mixture was cooled, diluted with CH_2Cl_2, and the organic layer was washed with cold 10 % KOH solution, then with water until washings became neutral, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was loaded on a silica gel Flash column for chromatography. Elution by 10 % ether in CH_2Cl_2 gave 11.6 mg (19 %) of recovered SM. Further elution by a 1: 1 mixture of ether/CH_2Cl_2 gave 41 mg (72 %) of the ketone **28.** The HRMS and H-NMR of the product were identical with those for **28** described earlier in this document**.**

To a cooled (-30 °C, dry ice acetone bath) solution of **28** (40 mg, 0.117 mmole) in anhydrous ether (15 mL), under argon, was added lithium aluminum hydride (1 M solution in ether, 1.2 mL, 1.2 mmole,) dropwise. The resulting mixture was stirred with warming to rt over a period of 30 min, and the mixture was then heated at reflux for 3h under argon. The mixture was cooled to 0 °C (ice water bath), a few drops of water were added, followed by a few drops of 10 % KOH, and again a few drops of water, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was loaded on a silica gel Flash column for chromatography. Elution by CH_2Cl_2 containing 0.6 % Et_3N, 6 % methanol, and 25 % ether provided 28.7 mg (82 %) of (**±**) codeine (**2**). The HRMS and NMR of **2** were identical with those of (±) codeine described earlier in this document.

Structure Determination of 23 and **23a**



To a cooled (-40 °C) solution of a mixture of **23** and **23a** (186 mg, 0.417 mmole) in anhydrous THF (7 mL) was added TBAF (0.625 ml, 0.625 mmole, 1.0 M THF solution), under argon. The resulting solution was stirred at rt for 2 h. The reaction was quenched with satd $NaHCO_3$ solution, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue (182 mg) was loaded on a silica gel Flash column for chromatography. Elution by 3 % ether in CH_2Cl_2 gave 14 mg (11 %) of **lactone** as a white solid. Further elution by 10 % ether in CH_2Cl_2 gave 76.0 mg (55 %) of **α-Alcohol** as a white solid.

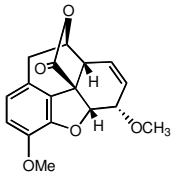
Lactone was recrystallized from a mixture of ether and n-pentane (1:1), to give crystals suitable for X ray analysis.

NMR δ ($CDCl_3$): 6.728 (1H, d, J = 8.1 Hz), 6.611 (1H, d, J = 8.1 Hz), 5.890 (1H, d, J = 9.6 Hz), 5.712 (1H, d, J = 5.4 Hz), 5.533 (1H, dt, J = 2.7, 9.9 Hz), 5.178 (1H, dt, J = 2.7, 5.4 Hz), 3.88-3.82 (1H, m), 3.844 (3H, s), 3.571 (3H, s), 3.23-3.15 (2H, m), 2.817 (1H, dd, J = 2.7, 18 Hz).

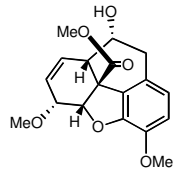
The **α–Alcohol** was recrystallized from a 1: 1 mixture of ether and n-pentane, to give prisms suitable for X-ray analysis.

HRMS (FAB) m/z: Calcd for $C_{18}H_{20}O_6$: 332.1260 [M^+]; Found: 332.1268.

NMR δ ($CDCl_3$): 6.796 (1H, d, J = 8.1 Hz), 6.756 (1H, d, J = 8.1 Hz), 6.236 (1H, dd, J = 6.0, 9.9 Hz), 6.177 (1H, dd, J = 6.0, 9.9 Hz), 5.404 (1H, d, J = 4.2 Hz), 4.40-4.32 (1H, m), 4.094 (1H, dd, J = 4.5, 6.3 Hz), 3.879 (3H, s), 3.671 (3H, s), 3.375 (1H, t, J = 5.1 Hz), 3.254 (1H, d, J = 9.9 Hz), 3.192 (3H, s), 2.987 (1H, d, J = 14.7 Hz), 2.898 (1H, dd, J = 3.6, 14.7 Hz).



Lactone



α–Alcohol