Supporting Information

Orvinols with Mixed Kappa/Mu Opioid Receptor Agonist Activity

Greedy, Benjamin M.; Bradbury, Faye.; Thomas, Mark P.; Grivas, Konstantinos; Cami-Kobeci, Gerta; Archambeau, Ashley.; Bosse, Kelly.; Clark, Mary J.; Aceto, Mario; Lewis, John W.; Traynor, John R.; Husbands, Stephen M.

Contents

1: Full details for all final products reported in the manuscript

2: Microanalysis for all tested compounds

Experimental

Reagents and solvents were purchased from Sigma-Aldrich or Alfa Aesar and used as received. ^{1}H and ^{13}C NMR spectra were obtained with a Brucker-400-MHz instrument (^{1}H at 400 MHz, ^{13}C at 100 MHz); δ in ppm, J in Hz with TMS as an internal standard. ESIMS: microTOF (BRUKER). Microanalysis: Perkin-Elmer 240C analyzer. Column Chromatography was performed using pre-packed column in combi flash instrument. Ligands were tested as their hydrochloride salts, prepared by adding 5 equivalents of HCl (1 N solution in diethyl ether) to a solution of compound in anhydrous methanol. All reactions were carried out under an inert atmosphere of nitrogen unless otherwise indicated. All compounds were > 95% pure.

General procedure A: Grignard addition

The Grignard reagents were prepared form the corresponding bromides (5 mmol) by reaction with magnesium (182 mg, 7.5 mmol) in anhydrous THF (5 ml) containing a crystal of iodine). The Grignard reagents were titrated prior to use by adding 1 ml of the Grignard solution to a flask containing 1,10-phenanthroline (~2 mg) in anhydrous THF (2 ml) (purple solution) and titrating with 1M 2-butanol (anhydrous) in THF (end point pale yellow solution)]

A solution of the appropriate Grignard reagent (1 M in THF, 1.2 ml, 1.2 mmol) was treated dropwise at room temperature with a solution of *N*-cyclopropylmethyl-6,14-*endo*-ethanonorthevinone (**8**) (500 mg, 1.18 mmol) or *N*-cyclopropylmethyl-6,14-*endo*-ethanonorthevinal (**10**) (500 mg, 1.22 mmol) in anhydrous toluene (12 ml). After stirring at room temperature for 20 h, the reaction was quenched by addition of saturated aqueous ammonium chloride solution (20 ml). The phases were separated and the aqueous phase extracted with EtOAc. The combined organic phases were washed with saturated aqueous sodium bicarbonate, dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel eluting with a gradient from 10% to 30% ethyl acetate in hexane. R_f values are recorded from TLC eluted with 30:1:69 ethyl acetate/ammonia solution/hexane.

General Procedure B: 3-O-demethylation with propane thiolate and HCl salt formation

A solution of the appropriate thevinol (0.25 mmol) in anhydrous HMPA (1 ml) under an inert atmosphere was treated with sodium hydride (21 mg, 0.875 mmol) followed by 1-propanethiol (79 µl, 0.875 mmol). After the addition was complete, the reaction mixture was heated to 120°C and stirred for 3 h. On cooling to room temperature, NH_4Cl (sat, aq) was added and the mixture extracted with diethyl ether. The organic extracts were washed with water (3×) and brine. The organic phase was dried ($MgSO_4$) filtered and evaporated to dryness. The residue was purified by column chromatography over silica gel.

The HCl salts were prepared by the addition of 2M HCl in diethyl ether (1.2 equiv.) to a solution of the orvinol in diethyl ether. The white precipitate which formed was collected by filtration, washed with ether and dried under high vacuum.

General Procedure D: Reduction with LiAlH4

A solution of the ketone (0.215 mmol) in anhydrous THF (7 ml) was added dropwise to a suspension of $LiAlH_4$ (20.5 mg, 0.54 mmol) in THF at room temperature. The resulting mixture was allowed to stir for 1 hour and then treated carefully with saturated aqueous sodium sulphate sulphate solution until all aluminium salts had precipitated. The aluminium salts were removed by filtration and washed with Et_2O. The filtrate was dried over $MgSO_4$, evaporated to dryness and the residue purified by column chromatography over silica gel (30% ethyl acetate, 0.5% NH_4OH in hexane).

General Procedure E: Swern oxidation

A solution of DMSO (170 µl, 2.4 mmol) in anhydrous DCM (5 ml) was added dropwise to a solution of oxalyl chloride (93 µl, 1.1 mmol) in DCM (2 ml) at -78°C. The resulting solution was stirred at -78°C for 10 min and then treated dropwise with a solution of the alcohol (1 mmol) in DCM (5 ml). The reaction was stirred for a further 15 min before triethylamine (0.7 ml, 5 mmol) was added slowly and the resulting solution allowed to warm to room temperature. Water (10 ml) was added and the resulting mixture stirred for 10 min. The phases were separated and the aqueous phase extracted with DCM. The combined organic extracts were washed with saturated ammonium chloride, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography over silica gel (0.5% NH_4OH, 30% ethyl acetate in hexane) to afford the product.

6,14-*endo*-ethanonorthevinone hydrochloride (7) (Marton, J.; Simon, C.; Hosztafi, S.; Szabó, Z.; Márki, Á.; Borsodi, A.; Makleit, S. New nepenthone and thevinone derivatives. *Bioorg. Med. Chem.*, **1997**, *5*, 369-382)
A solution of 6,14-*endo*-ethanothevinone (**6**: 10 g, 26 mmol) in anhydrous acetonitrile (130 ml) was treated at room temperature with diisopropyl azodicarboxylate (DIAD, 14 ml, 72 mmol) and the resulting mixture brought to reflux and stirred for 3 h. On cooling the acetonitrile was removed under reduced pressure and the resulting red/orange oily residue was dissolved in ethanol (84 ml). Pyridinium hydrochloride (2.7 g, 23 mmol) was then added and the resulting solution stirred at room temperature overnight. The precipitated (**7**) was collected by filtration, washed with ice-cold ethanol and dried under vacuum. A second crop was obtained from the mother liquor after stirring for a further 24h. This afforded 8.11 g (**7**) as a white solid (77%). Mp >300°C (decomp). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.70 (1H, m), 1.38-1.58 (3H, m), 1.87 (1H, dd, *J*= 14.0, 3.0 Hz), 2.00 (1H, dd, *J*=14.0, 5.4 Hz), 2.20-2.32 (1H, m), 2.25 (3H, s), 2.66-2.76 (1H, m), 2.94-3.13 (3H, m), 3.27-3.41 (2H, m), 3.41 (3H, s), 3.62 (1H, d, *J*=6.5 Hz), 3.87 (3H, s), 4.51 (1H, s), 6.66 (1H, d, *J*=8.5 Hz), 6.77 (1H, d, *J*=8.5 Hz), 9.17 (1H, br s), 10.08 (1H, br d, *J*=8.6 Hz). ^{13}C NMR (68 MHz, $CDCl_3$) δ 17.0, 28.2, 29.5, 29.8, 31.0, 34.1, 35.7, 45.2, 48.7, 52.5, 54.0, 56.8, 76.9, 93.9, 115.2, 120.4, 124.6, 130.0, 142.8, 146.9, 209.6. HRMS (ESI^+) calcd for $C_{22}H_{28}NO_4$ (MH^+), 370.2018; found 370.2008.

***N*-cylcopropylmethyl-6,14-*endo*-ethanonorthevinone (8)**

A solution of 6,14-*endo*-ethanonorthevinone hydrochloride **7** (6 g, 14.8 mmol) in anhydrous DMF (36 ml) was treated sequentially at room temperature with sodium bicarbonate (5 g, 60 mmol) and (bromomethyl)cyclopropane (1.87 ml, 19.3 mmol). The resulting suspension was heated to 90°C and stirred for 20 h. On cooling, the DMF was removed *in vacuo* and the residue dissolved in water and rendered basic with 2 M NaOH solution. The product was extracted into chloroform and the organic phases washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The resulting yellow solid was purified by column chromatography over silica gel (50% ethyl acetate in hexane, R_f=0.50) affording 6.15 g **8** as a white solid (98%). Mp 105-106 °C. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.04-0.10 (2H, m), 0.43-0.49 (2H, m), 0.63-0.80 (1H, m), 1.22-1.34 (1H, m), 1.49-1.75 (4H, m), 1.96-2.08 (1H, m), 2.20-2.38 (4H, m), 2.25 (3H, s), 2.58-2.77 (2H, m), 2.93-3.11 (3H, m), 3.42 (3H, s), 3.86 (3H,

s), 4.47 (1H, s), 6.55 (1H, d, *J*=8.0 Hz), 6.63 (1H, d, *J*=8.0 Hz). ^{13}C NMR (68 MHz, $CDCl_3$) δ 3.4, 4.2, 9.6, 17.6, 22.8, 28.8, 30.5, 33.9, 35.4, 35.5, 43.8, 46.6, 49.8, 52.4, 56.8, 58.4, 59.9, 77.8, 94.8, 113.9, 119.2, 128.9, 132.8, 141.8, 146.8, 211.1. HRMS (ESI^+) calcd for $C_{26}H_{34}NO_4$ (MH^+), 424.2488; found 424.2485.

N-Cyclopropylmethylnorthevinal (15)

A mixture of *N*-cyclopropylmethyl-northebaine (1 equivl) and acrolein (1.2 equiv) in anhydrous toluene (4 mL/mmol) was heated at 60°C for 16 h. The solvent and excess acrolein were removed under reduced pressure and the residue subjected to column chromatography over silica gel (R_f=0.17, 20% EtOAc in hexane). This afforded **15** as a pale yellow solid (96%, α/β mixture ~10:1). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.08-0.15 (2H, m), 0.46-0.53 (2H, m), 0.77-0.87 (1H, m), 1.44 (1H, dd, *J*=13.2 and 5.5 Hz), 1.83 (1H, dd, *J*=12.9 and 2.5 Hz), 1.98 (1H, dt, *J*=12.9 and 5.5 Hz), 2.28-2.46 (2H, m), 2.67-2.78 (2H, m), 2.97 (1H, dd, *J*=13.2 and 9.6 Hz), 3.10 (1H, d, *J*=18.4 Hz), 3.56 (1H, d, *J*=6.6 Hz), 3.60 (3H, s), 3.80 (3H, s), 4.62 (1H, d, *J*=1.1 Hz), 5.58 (1H, d, *J*=8.8 Hz), 5.88 (1H, d, 8.8 Hz), 6.51 (1H, d, *J*=8.0 Hz), 6.61 (1H, d, *J*=8.0 Hz), 9.41 (1H, d, *J*=3.9 Hz). ^{13}C NMR (68 MHz, $CDCl_3$) δ 3.5, 4.3, 9.6, 23.3, 26.8, 33.5, 43.0, 44.0, 48.1, 50.0, 56.6, 57.2, 59.9, 81.0, 93.7, 113.4, 119.6, 126.6, 128.2, 134.0, 137.5, 142.0, 148.0, 20202.0. HRMS (ESI^+) calcd for $C_{25}H_{30}NO_4$ (MH^+), 408.2175; found 408.2166.

N-Cyclopropylmethyl-6,14-endoethanonorthevinal (10)

A solution of *N*-cylcopropylmethyl-thevinal (**15,** ~10:1 α:β, 11.5 g, 28.3 mmol) in ethanol (230 ml) containing 10% palladium on carbon (1.15 g) was vigorously stirred under an atmosphere of hydrogen (1 atm) for 3 h. The palladium catalyst was removed by filtration through a plug of celite and the solvent removed *in vacuo*. The residue was subjected to column chromatography over silica gel (R_f=0.50, ethyl acetate) affording **10** as an off-white solid. This solid was recrystallised from hot ethanol to provide **10** as the pure α isomer (single isomer (α), 7.04 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06-0.11 (2H, m), 0.44-0.50 (2H, m), 0.70-0.82 (2H, m), 1.08-1.70 (4H, m), 1.90 (1H, dd, *J*=12.4 and 4.4 Hz), 2.02 (1H, dt, *J*=12.9 and 5.5 Hz), 2.20-2.37 (4H, m), 2.60-2.84 (3H, m), 2.95-3.08 (2H, m), 3.50 (3H, s), 3.86 (3H, s), 4.58 (1H, d, *J*=1.9 Hz), 6.57 (1H, d, *J*=8.0 Hz), 6.70 (1H, d, *J*=8.0 Hz), 9.91 (1H, d, *J*=1.9 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.5, 4.2, 9.6, 20.1, 22.8, 26.8, 28.7, 35.4, 35.5, 43.8, 46.1, 48.8, 56.7, 58.5, 59.9, 77.4, 92.4, 113.8, 119.5, 128.7, 132.4, 141.9, 146.7, 203.5. HRMS (ESI^+) calcd for $C_{25}H_{32}NO_4$ (MH^+), 410.2326; found 410.2309.

(2′R, 5α, 6R, 7R, 14α)-2′-(4,5-epoxy-7,8-dihydro-3,6-dimethoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-3′-methyl-butan-2′-ol (9a)

Using general procedure A, with isopropyl magnesium bromide, **9a** was isolated as a white solid (60 mg, 11%). R_f 0.57. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.07-0.11 (2H, m), 0.44-0.51 (2H, m), 0.69-0.86 (2H, m), 0.98 (6H, dd, *J*=15.7, 6.7 Hz), 1.02-1.12 (1H, m), 1.33 (3H, s), 1.62-2.06 (7H, m), 2.16-2.34 (4H, m), 2.61 (1H, dd, *J*=12.0, 5.0 Hz), 2.89-2.74 (1H, m), 2.91 (2H, dd, *J*=12.4, 6.0 Hz), 3.52 (3H, s), 3.86 (3H, s), 4.41 (1H, s), 5.02 (1H, d, *J*=1.2 Hz), 6.53 (1H, d, *J*=8.1 Hz), 6.69 (1H, d, *J*=8.1 Hz). ^{13}C NMR (68 MHz, $CDCl_3$) δ 3.5, 4.2, 9.6, 16.5, 17.3, 18.0, 21.3, 22.7, 30.1, 31.1, 31.4, 34.4, 35.9, 36.0, 43.6, 44.1, 47.0, 52.8, 56.9, 58.3, 59.8, 80.6, 97.4, 114.0, 119.1, 129.0, 132.8, 141.7, 147.0. HRMS (ESI^+) calcd for $C_{29}H_{42}NO_4$ (MH^+), 468.3108; found 468.3106 (100%).

(2′R, 5α, 6R, 7R, 14α)-2′-(4,5-epoxy-7,8-dihydro-3,6-dimethoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-4′-methyl-pentan-2′-ol (9b)

Using general procedure A, with isobutylyl magnesium bromide, **9b** was isolated as a white solid (150 mg, 26%). R_f 0.75. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09-0.11 (2H, m), 0.47-0.50 (2H, m), 0.70-0.84 (2H, m),0.98-1.07 (2H, m), 0.99 (3H, d, *J*=6.7 Hz), 1.03 (3H, d, *J*=6.7 Hz), 1.28-1.43 (1H, m), 1.34 (3H, s), 1.65-1.83 (4H, m), 1.86-2.01 (3H, m), 2.19-2.38 (4H, m), 2.63 (1H, dd, *J*=11.9, 5.0 Hz), 2.78-2.85 (1H, m), 2.97-3.01 (2H, m), 3.54 (3H, s), 3.87 (3H, s), 4.42 (1H, s), 5.10 (1H, s), 6.54 (1H, d, *J*=8.1 Hz),

6.70 (1H, d, *J*=8.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.6, 4.2, 9.6, 18.0, 22.8, 23.7, 23.9, 25.3, 25.5, 30.1, 32.2, 35.9, 36.0, 43.7, 46.7, 47.0, 49.7, 52.9, 57.0, 58.5, 59.9, 76.9, 80.7, 97.2, 114.0, 119.1, 129.0, 132.8, 141.7, 147.1. HRMS (ESI^+) calcd for $C_{30}H_{44}NO_4$ (MH^+), 482.3265; found 482.3271 (100%).

(2′R, 5α, 6R, 7R, 14α)-2′-(4,5-epoxy-7,8-dihydro-3,6-dimethoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-5′-methyl-hexan-2′-ol (9c)

Using general procedure A, with isopentyl magnesium bromide, **9c** was isolated as a white solid (216 mg, 37%). R_f 0.71. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08-0.12 (2H, m), 0.44-0.52 (2H, m), 0.70-0.83 (2H, m), 0.91 (3H, d, *J*=6.4 Hz), 0.93 (3H, d, *J*=6.8 Hz), 1.01-1.08 (2H, m), 1.19-1.56 (5H, m), 1.34 (3H, s), 1.66 (1H, dd, *J*=12.9, 2.4 Hz), 1.74-1.85 (2H, m), 1.90-2.03 (2H, m), 2.19-2.38 (4H, m), 2.64 (1H, dd, *J*=11.9, 4.8 Hz), 2.79-2.86 (1H, m), 2.95-3.01 (2H, m), 3.54 (3H, s), 3.88 (3H, s), 4.42 (1H, s), 5.10 (1H, s), 6.54 (1H, d, *J*=8.1 Hz), 6.70 (1H, d, *J*=8.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.6, 4.1, 9.6, 18.0, 22.7, 22.9, 23.2, 23.8, 28.7, 30.1, 31.8, 31.9, 35.9, 36.0, 39.3, 43.7, 45.8, 47.1, 52.9, 57.0, 58.6, 59.9, 75.8, 80.6, 97.3, 114.1, 119.2, 129.1, 132.8, 141.7, 147.1. HRMS (ESI^+) calcd for $C_{31}H_{46}NO_4$ (MH^+), 496.3421; found 496.3414 (100%).

(1′R, 5α, 6R, 7R, 14α)-1′-cyclopentyl-1′-(4,5-epoxy-7,8-dihydro-3,6-dimethoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-ethan-1′-ol (9d)

Using general procedure A, with cyclopentyl magnesium bromide, **9d** was isolated as a white solid (26 mg, 4.5%). R_f 0.70. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08-0.12 (2H, m), 0.46-0.53 (2H, m), 0.71-0.90 (2H, m), 1.01-1.09 (1H, m), 1.16 (1H, dd, *J*=13.1, 9.5 Hz), 1.36 (3H, s), 1.51-1.83 (11H, m), 1.93-2.00 (3H, m), 2.19-2.39 (4H, m), 2.64 (1H, dd, *J*=11.8, 4.9 Hz), 2.81-2.88 (1H, m), 2.97-3.02 (2H, m), 3.54 (3H, s), 3.88 (3H, s), 4.41 (1H, s), 5.10 (1H, d, *J*=1.3 Hz), 6.55 (1H, d, *J*=8.1 Hz), 6.71 (1H, d, *J*=8.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.6, 4.2, 9.6, 18.1, 22.8, 22.8, 25.7, 25.9, 26.0, 26.1, 30.1, 31.8, 35.9, 36.0, 43.7, 45.4, 47.0, 47.6, 52.9, 57.0, 58.4, 59.9, 76.5, 80.7, 97.3, 114.1, 119.1, 129.1, 132.9, 141.8, 147.1. HRMS (ESI^+) calcd for $C_{31}H_{44}NO_4$ (MH^+), 494.3265; found 494.3258 (100%).

(2′R, 5α, 6R, 7R, 14α)-2′-(4,5-epoxy-7,8-dihydro-3,6-dimethoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-3′-cyclopentyl-propan-2′-ol (9e)

Using general procedure A, with cyclopentylmethyl magnesium bromide, **9e** was isolated as a white solid (260 mg, 43%). R_f 0.70. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08-0.12 (2H, m), 0.47-0.51 (2H, m), 0.70-0.84 (2H, m), 1.00-1.08 (2H, m), 1.10-1.21 (2H, m), 1.35 (3H, s), 1.46-1.68 (9H, m), 1.77-1.82 (2H, m), 1.88-2.03 (4H, m), 2.17-2.30 (3H, m), 2.36-2.40 (1H, m), 2.63 (1H, dd, *J*=12.0, 5.1 Hz), 2.79-2.86 (1H, m), 2.96-3.01 (2H, m), 3.53 (3H, s), 3.87 (3H, s), 4.42 (1H, s), 5.16 (1H, s), 6.54 (1H, d, *J*=8.1 Hz), 6.65 (1H, d, *J*=8.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.5, 4.2, 9.6, 18.1, 22.8, 23.5, 25.1, 25.3, 30.1, 32.2, 35.1, 35.4, 35.9, 36.0, 43.8, 46.9, 47.0, 47.3, 52.9, 57.0, 58.4, 59.9, 76.6, 80.7, 97.2, 114.1, 119.1, 129.0, 132.8, 141.9, 147.1. HRMS (ESI^+) calcd for $C_{32}H_{46}NO_4$ (MH^+), 508.3421; found 508.3422 (100%).

(2′R, 5α, 6R, 7R, 14α)-2′-(4,5-epoxy-7,8-dihydro-3,6-dimethoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-4′-cyclopentyl-butan-2′-ol (9f)

Using general procedure A with 1-bromo-2-cyclopentyl ethane gave **9f** as a white solid (243 mg, 39%) (R_f=0.76; 0.5% NH_4OH, 30% EtOAc in hexane; column ran as a gradient from 10% to 50% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09-0.13 (2H, m), 0.46-0.51 (2H, m), 0.70-0.84 (2H, m), 1.01-1.18 (4H, m), 1.33 (3H, s), 1.33-1.38 (2H, m), 1.45-1.83 (12H, m), 1.90-2.03 (2H, m), 2.20-2.39 (4H, m), 2.64 (1H, dd, *J*=11.5 and 4.5 Hz), 2.79-2.86 (1H, m), 2.96-3.02 (2H, m), 3.54 (3H, s), 3.88 (3H, s), 4.42 (1H, s), 5.10 (1H, s), 6.55 (1H, d, *J*=8.0 Hz), 6.70 (1H, d, *J*=8.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.6, 4.1, 9.6, 18.0, 22.9, 23.7, 25.3, 25.3, 29.2, 30.1, 31.8, 32.8, 33.1, 35.9, 36.0, 40.7, 40.7, 43.7, 45.8, 47.1, 52.9, 57.0, 58.6, 59.9, 75.8, 80.6, 97.2, 114.1, 119.1, 129.0, 132.8, 141.7, 147.1. HRMS (ESI^+) calcd for $C_{33}H_{48}NO_4$ (MH^+), 522.3578; found 522.3587 (100%).

(1′R, 5α, 6R, 7R, 14α)-1′-cyclohexyl-1′-(4,5-epoxy-7,8-dihydro-3,6-dimethoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-ethan-1′-ol (9g)

Using general procedure A, with cyclohexyl magnesium bromide, **9g** was isolated as a white solid (100 mg, 17%). R_f 0.72. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10-0.13 (2H, m), 0.47-0.51 (2H, m), 0.70-0.85 (2H, m), 1.00-1.10 (2H, m), 1.16-1.42 (7H, m), 1.34 (3H, s), 1.64-1.88 (9H, m), 1.94 (1H, td, *J*=12.6, 5.6 Hz), 2.05 (1H, t, *J*=10.2 Hz), 2.21-2.33 (2H, m), 2.64 (1H, dd, *J*=11.9, 5.0 Hz), 2.76-2.83 (1H, m), 2.94-3.02 (2H, m), 3.53 (3H, s), 3.88 (3H, s), 4.41 (1H, d, *J*=1.1 Hz), 5.01 (1H, s), 6.55 (1H, d, *J*=8.1 Hz), 6.71 (1H, d, *J*=8.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.6, 3.9, 9.6, 18.2, 21.0, 22.9, 25.7, 26.6, 26.9, 27.1, 27.2, 30.1, 31.4, 35.9, 36.0, 43.5, 43.6, 44.8, 46.9, 52.8, 56.9, 58.6, 59.7, 77.3, 80.6, 97.4, 114.0, 119.1, 129.0, 132.8, 141.6, 146.9. HRMS (ESI^+) calcd for $C_{32}H_{46}NO_4$ (MH^+), 508.3421; found 508.3430 (100%).

(2′R, 5α, 6R, 7R, 14α)-2′-(4,5-epoxy-7,8-dihydro-3,6-dimethoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-3′-cyclohexyl-propan-2′-ol (9h)

Using general procedure A, with cyclohexylmethyl magnesium bromide, **9h** was isolated as a white solid (190 mg, 31%). R_f 0.77. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10-0.11 (2H, m), 0.48-0.50 (2H, m), 0.70-0.84 (2H, m), 0.95-1.18 (5H, m), 1.25-1.37 (4H, m), 1.34 (3H, s), 1.54-1.69 (5H, m), 1.78-2.04 (6H, m), 2.19-2.41 (4H, m), 2.64 (1H, dd, *J*=12.0, 5.0 Hz), 2.78-2.85 (1H, m), 2.96-3.01 (2H, m), 3.53 (3H, s), 3.88 (3H, s), 4.43 (1H, s), 5.14 (1H, s), 6.54 (1H, d, *J*=8.1 Hz), 6.70 (1H, d, *J*=8.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.6, 4.1, 9.6, 18.0, 22.9, 23.5, 26.6, 26.8, 26.9, 30.1, 32.2, 33.0, 35.9, 36.0, 36.1, 36.1, 43.7, 47.0, 47.2, 48.6, 52.9, 57.0, 58.6, 59.9, 77.0, 80.8, 97.2, 114.0, 119.1, 129.0, 132.8, 141.7, 147.1. HRMS (ESI^+) calcd for $C_{33}H_{48}NO_4$ (MH^+), 522.3578; found 522.3589 (100%).

(2′R, 5α, 6R, 7R, 14α)-2′-(4,5-epoxy-7,8-dihydro-3,6-dimethoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-4′-cyclohexyl-butan-2′-ol (9i)

Using general procedure A, with cyclohexylethyl magnesium bromide, **9i** was isolated as a white solid (223 mg, 35%). R_f 0.74. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09-0.12 (2H, m), 0.47-0.51 (2H, m), 0.71-0.82 (2H, m), 0.87-1.07 (3H, m), 1.13-1.53 (9H, m), 1.32 (3H, s), 1.62-1.82 (8H, m), 1.90-2.03 (2H, m), 2.20-2.39 (4H, m), 2.64 (1H, dd, *J*=11.9 and 4.9 Hz), 2.79-2.86 (1H, m), 2.95-3.01 (2H, m), 3.54 (3H, s), 3.88 (3H, s), 4.41 (1H, s), 5.10 (1H, s), 6.54 (1H, d, *J*=8.1 Hz), 6.70 (1H, d, *J*=8.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.6, 4.1, 9.6, 18.0, 22.9, 23.7, 26.6, 26.6, 26.9, 30.1, 30.3, 31.8, 33.5, 33.9, 35.9, 36.0, 38.4, 38.8, 43.7, 45.9, 47.1, 52.9, 57.0, 58.6, 59.9, 75.9, 80.6, 97.3, 114.1, 119.1, 129.1, 132.8, 141.7, 147.1. HRMS (ESI^+) calcd for $C_{34}H_{50}NO_4$ (MH^+), 536.3734; found 536.3743 (100%).

(2′R, 5α, 6R, 7R, 14α)-2′-(4,5-epoxy-7,8-dihydro-3,6-dimethoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-3′-phenyl-propan-2′-ol (9j)

Using general procedure A, with benzyl magnesium bromide, **9j** was isolated as a white solid (400 mg, 67%). R_f 0.65. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.13-0.17 (2H, m), 0.51-0.56 (2H, m), 0.71-0.79 (1H, m), 0.82-0.89 (1H, m), 1.05-1.21 (2H, m), 1.35 (3H, s), 1.57 (1H, dd, *J*=13.0, 2.5 Hz), 1.73-1.87 (4H, m), 2.21-2.28 (2H, m), 2.34 (2H, dq, *J*=12.4, 6.0 Hz), 2.61 (1H, dd, *J*=11.5, 5.0 Hz), 2.76 (2H, s), 2.97-3.02 (3H, m), 3.51 (3H, s), 3.87 (3H, s), 4.32 (1H, s), 5.33 (1H, s), 6.55 (1H, d, *J*=8.2 Hz), 6.70 (1H, d, *J*=8.2 Hz), 7.21-7.24 (1H, m), 7.28-7.32 (2H, m), 7.38-7.40 (2H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.8, 4.0, 9.7, 18.0, 23.0, 23.1, 30.0, 32.1, 35.7, 36.1, 43.6, 46.2, 47.0, 47.2, 52.9, 56.9, 58.9, 59.9, 76.5, 80.7, 97.0, 114.0, 119.2, 126.2, 127.7, 129.0, 131.3, 132.8, 137.9, 141.7, 147.1. HRMS (ESI^+) calcd for $C_{33}H_{42}NO_4$ (MH^+), 516.3108; found 516.3124 (100%).

(2′R, 5α, 6R, 7R, 14α)-2′-(4,5-epoxy-7,8-dihydro-3,6-dimethoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-4′-phenyl-butan-2′-ol (9k)

Using general procedure A, with phenethyl magnesium bromide, **9k** was isolated as a white solid (275 mg, 44%). R_f 0.63. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09-0.13 (2H, m), 0.47-0.52 (2H, m), 0.73-0.83 (2H, m), 1.03-1.13 (2H, m), 1.40 (3H, s), 1.65-1.73 (2H, m), 1.76-1.90 (3H, m), 1.94-2.03 (2H, m), 2.20-2.36 (4H, m), 2.64 (1H, dd, *J*=12.0 and 4.5 Hz), 2.71-3.02 (5H, m), 3.58 (3H, s), 3.89 (3H, s), 4.44 (1H, d *J*=1.5 Hz), 5.22 (1H, s), 6.56 (1H, d, *J*=8.3 Hz), 6.71 (1H, d, *J*=8.3 Hz), 7.16-7.20 (1H, m), 7.26-7.31 (4H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.7, 4.1, 9.6, 17.9, 22.9, 23.6, 29.6, 30.1, 31.8, 35.9, 36.0, 43.6,

44.0, 46.0, 47.1, 53.0, 57.0, 58.6, 60.0, 75.7, 80.6, 97.3, 114.1, 119.2, 125.7, 128.5, 128.7, 129.0, 132.8, 141.7, 143.5, 147.1. HRMS (ESI^+) calcd for $C_{34}H_{44}NO_4$ (MH^+), 530.3265; found 530.3275 (100%).

(2′R, 5α, 6R, 7R, 14α)-2′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-3′-methyl-butan-2′-ol (1a)

Using general procedure B with **9a** (47 mg) gave **1a** as a white solid (45 mg, 99%) (R_f=0.25; 0.5% NH_4OH, 30% EtOAc in hexane; column ran in 30% EtOAc in hexane ^1H NMR (400 MHz, $CDCl_3$) δ 0.09-0.12 (2H, m), 0,45-0.53 (2H, m), 0.69-0.82 (2H, m), 0.96 (3H, d, *J*=6.5 Hz), 1.02 (3H, d, *J*=7.0 Hz), 1.01-1.12 (2H, m), 1.35 (3H, s), 1.65-2.07 (6H, m), 2.18-2.39 (4H, m), 2.64 (1H, dd, *J*=12.0 and 5.0 Hz), 2.80-2.87 (1H, m), 2.95-3.00 (2H, m), 3.52 (3H, s), 4.44 (1H, d, *J*=1.7 Hz), 4.99 (1H, s), 6.51 (1H, d, *J*=8.0 Hz), 6.69 (1H, d, *J*=8.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.6, 4.2, 9.6, 16.5, 17.3, 18.1, 21.4, 22.9, 30.0, 31.4, 34.5, 35.8, 36.1, 43.7, 44.1, 47.4, 52.8, 58.4, 59.9, 77.2, 80.7, 97.9, 116.4, 119.6, 128.6, 132.5, 137.3, 145.6. HRMS (ESI^+) calcd for $C_{28}H_{40}NO_4$ (MH^+), 454.2952; found 454.2954 (100%). Anal. ($C_{28}H_{39}NO_4$.HCl.1.6H_2O) C, H, N.

(2′R, 5α, 6R, 7R, 14α)-2′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-4′-methyl-pentan-2′-ol (1b)

Using the general procedure B with **9b** (48 mg) gave **1b** as a yellow solid (46 mg, 98%) (R_f=0.30; 0.5% NH_4OH, 30% EtOAc in hexane; column ran in 30% EtOAc in hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 0.06-0.12 (2H, m), 0.45-0.53 (2H, m), 0.69-0.88 (2H, m), 0.98 (3H, d, *J*=6.5 Hz), 1.02 (3H, d, *J*=6.5 Hz), 0.98-1.07 (2H, m), 1.28-1.44 (2H, m), 1.34 (3H, s), 1.66 (1H, dd, *J*=12.5 and 2.0 Hz), 1.76-1.81 (2H, m), 1.87-2.04 (3H, m), 2.18-2.38 (4H, m), 2.64 (1H, dd, *J*=11.5 and 5.0 Hz), 2.79-2.85 (1H, m), 2.95-2.99 (2H, m), 3.52 (3H, s), 4.43 (1H, s), 5.15 (1H, s), 6.50 (1H, d, *J*=8.0 Hz), 6.68 (1H, d, *J*=8.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.6, 4.1, 9.6, 18.0, 22.9, 23.6, 23.9, 25.2, 25.5, 29.9, 32.1, 35.8, 36.1, 43.7, 46.5, 47.3, 49.6, 52.8, 58.5, 59.9, 77.1, 80.8, 97.5, 116.5, 119.6, 128.3, 132.5, 137.4, 145.7. HRMS (ESI^+) calcd for $C_{29}H_{42}NO_4$ (MH^+), 468.3108; found 468.3123 (100%). Anal. ($C_{29}H_{41}NO_4$.HCl.1.5H_2O) C, H, N.

(2′R, 5α, 6R, 7R, 14α)-2′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-5′-methyl-hexan-2′-ol (1c)

Using the general procedure B with **9c** (50 mg) gave **1c** as a yellow solid (47 mg, 98%) (R_f=0.26; 0.5% NH_4OH, 30% EtOAc in hexane; column ran in 30% EtOAc in hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 0.08-0.12 (2H, m), 0.46-0.50 (2H, m), 0.70-0.83 (2H, m), 0.91 (6H, d, *J*=6.0 Hz), 1.00-1.08 (2H, m), 1.19-1.26 (1H, m), 1.34 (3H, s), 1.34-1.54 (4H, m), 1.65-1.69 (1H, m), 1.77-1.81 (2H, m), 1.90-2.03 (2H, m), 2.18-2.38 (4H, m), 2.66 (1H, dd, *J*=12.0 and 5.0 Hz), 2.79-2.86 (1H, m), 2.95-3.00 (2H, m), 3.52 (3H, s), 4.42 (1H, s), 5.16 (1H br s), 6.50 (1H, d, *J*=8.0 Hz), 6.69 (1H, d, *J*=8.0 Hz). ^{13}C NMR (100.6MHz, $CDCl_3$) δ 3.6, 4.1, 9.6, 18.0, 22.7, 23.0, 23.2, 23.8, 28.7, 30.0, 31.8, 31.8, 35.8, 36.1, 39.2, 43.7, 45.7, 47.4, 52.9, 58.6, 59.8, 76.1, 80.7, 97.6, 116.5, 119.6, 128.4, 132.5, 137.5, 145.7. HRMS (ESI^+) calcd for $C_{30}H_{44}NO_4$ (MH^+), 482.3265; found 482.3241 (100%). Anal. ($C_{30}H_{43}NO_4$.HCl.1.5H_2O) C, H, N.

(1′R, 5α, 6R, 7R, 14α)-1′-cyclopentyl-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-ethan-1′-ol (1d)

Using the general procedure above with **9d** (47 mg) gave **1d** as a yellow solid (40 mg, 83%) (R_f=0.24; 0.5% NH_4OH, 30% EtOAc in hexane; column ran in 30% EtOAc in hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 0.08-0.12 (2H, m), 0.45-0.53 (2H, m), 0.69-0.90 (2H, m), 1.00-1.08 (1H, m), 1.16 (1H, dd, *J*=13.0 and 9.5 Hz), 1.36 (3H, s), 1.48-1.85 (11H, m), 1.94-2.01 (3H, m), 2.18-2.38 (4H, m), 2.64 (1H, dd, *J*=12.0 and 5.0 Hz), 2.81-2.88 (1H, m), 2.95-3.00 (2H, m), 3.52 (3H, s), 4.42 (1H, d, *J*=1.2 Hz), 5.07 (1H, s), 6.50 (1H, d, *J*=8.0 Hz), 6.69 (1H, d, *J*=8.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.6, 4.2, 9.6, 18.1, 22.9, 22.9, 25.7, 25.9, 26.0, 26.1, 30.0, 31.8, 35.8, 36.1, 43.7, 45.4, 47.3, 47.7, 52.8, 58.5, 59.9, 76.7, 80.8, 97.7, 116.4, 119.6, 128.6, 132.5, 137.3, 145.7. HRMS (ESI^+) calcd for $C_{30}H_{42}NO_4$ (MH^+), 480.3114; found 480.3097. Anal. ($C_{30}H_{41}NO_4$.HCl.1.5H_2O) C, H, N.

(2′R, 5α, 6R, 7R, 14α)-2′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-3′-cyclopentyl-propan-2′-ol (1e)

Using the general procedure above with **9e** (50 mg) gave **1e** as a yellow solid (46 mg, 93%) (R_f=0.27; 0.5% NH_4OH, 30% EtOAc in hexane; column ran in 30% EtOAc in hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 0.08-0.12 (2H, m), 0.47-0.52 (2H, m), 0.69-0.90 (2H, m), 1.00-1.08 (2H, m), 1.13-1.20 (2H, m), 1.35 (3H, s), 1.46-1.69 (7H, m), 1.76-1.81 (2H, m), 1.85-2.04 (5H, m), 2.18-2.31 (3H, m), 2.36-2.41 (1H, m), 2.64 (1H, dd, *J*=12.0 and 5.0 Hz), 2.79-2.86 (1H, m), 2.95-3.00 (2H, m), 3.52 (3H, s), 4.44 (1H, s), 5.14 (1H, s), 6.50 (1H, d, *J*=8.0 Hz), 6.69 (1H, d, *J*=8.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.6, 4.2, 9.6, 18.1, 22.9, 23.6, 25.1, 25.3, 30.0, 32.2, 35.1, 35.4, 35.8, 36.1, 43.8, 46.8, 47.2, 47.3, 52.8, 58.4, 59.9, 76.7, 80.8, 97.6, 116.4, 119.6, 128.5, 132.5, 137.3, 145.6. HRMS (ESI^+) calcd for $C_{31}H_{44}NO_4$ (MH^+), 494.3265; found 494.3262 (100%). Anal. ($C_{31}H_{43}NO_4.HCl.1.5H_2O$) C, H, N.

(2′R, 5α, 6R, 7R, 14α)-2′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-4′-cyclopentyl-butan-2′-ol (1f)

Using the general procedure B with **9f** (52 mg) gave **1f** as a yellow solid (44 mg, 89%) (R_f=0.27; 0.5% NH_4OH, 30% EtOAc in hexane; column ran in 30% EtOAc in hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 0.08-0.12 (2H, m), 0.44-0.52 (2H, m), 0.69-0.89 (2H, m), 0.99-1.17 (4H, m), 1.33 (3H, s), 1.33-1.41 (2H, m), 1.45-1.81 (12H, m), 1.90-2.04 (2H, m), 2.18-2.38 (4H, m), 2.64 (1H, dd, *J*=11.5 and 5.0 Hz), 2.79-2.86 (1H, m), 2.95-3.00 (2H, m), 3.52 (3H, s), 4.42 (1H, s), 5.14 (1H, s), 6.51 (1H, d, *J*=8.0 Hz), 6.69 (1H, d, *J*=8.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.6, 4.1, 9.6, 18.0, 23.0, 23.7, 25.3, 25.3, 29.2, 30.0, 31.8, 32.8, 33.1, 35.8, 36.1, 40.6, 40.7, 43.7, 45.7, 47.4, 52.8, 58.6, 59.9, 76.0, 80.7, 97.6, 116.5, 119.6, 128.4, 132.5, 137.4, 145.7. HRMS (ESI^+) calcd for $C_{32}H_{46}NO_4$ (MH^+), 508.3421; found 508.3423 (100%). Anal. ($C_{32}H_{45}NO_4.HCl.1.5H_2O$) C, H, N.

(1′R, 5α, 6R, 7R, 14α)-1′-cyclohexyl-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-ethan-1′-ol (1g)

Using the general procedure B with **9g** (50 mg) gave **1g** as a yellow solid (43 mg, 87%) (R_f=0.27; 0.5% NH_4OH, 30% EtOAc in hexane; column ran in 30% EtOAc in hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 0.09-0.13 (2H, m), 0.46-0.51 (2H, m), 0.68-0.88 (2H, m), 0.99-1.11 (2H, m), 1.19-1.42 (7H, m), 1.34 (3H, s), 1.64-1.68 (2H, m), 1.74-1.98 (6H, m), 2.03-2.08 (1H, m), 2.19-2.37 (4H, m), 2.65 (1H, dd, *J*=11.5 and 4.5 Hz), 2.76-2.83 (1H, m), 2.94-3.00 (2H, m), 3.51 (3H, s), 4.42 (1H, s), 5.01 (1H, s), 6.50 (1H, d, *J*=8.0 Hz), 6.69 (1H, d, *J*=8.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.7, 4.0, 9.6, 18.3, 21.1, 23.1, 25.7, 26.7, 26.9, 27.2, 27.3, 30.0, 31.5, 35.9, 36.2, 43.6, 43.6, 44.9, 47.3, 52.8, 58.7, 59.7, 77.6, 80.7, 97.8, 116.5, 119.6, 128.5, 132.6, 137.4, 145.7. HRMS (ESI^+) calcd for $C_{31}H_{44}NO_4$ (MH^+), 494.3265; found 494.3275 (100%). Anal. ($C_{31}H_{43}NO_4.HCl.1.2H_2O$) C, H, N.

(2′R, 5α, 6R, 7R, 14α)-2′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-3′-cyclohexyl-propan-2′-ol (1h)

Using general procedure B with **9h** (52 mg) gave **1h** as a yellow solid (50 mg, 98%) (R_f=0.27; 0.5% NH_4OH, 30% EtOAc in hexane; column ran in 30% EtOAc in hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 0.08-0.12 (2H, m), 0.45-0.52 (2H, m), 0.68-0.83 (2H, m), 0.94-1.17 (5H, m), 1.24-1.38 (4H, m), 1.34 (3H, s), 1.54-1.68 (5H, m), 1.76-2.06 (6H, m), 2.18-2.40 (4H, m), 2.64 (1H, dd, *J*=12.0 and 5.0 Hz), 2.78-2.85 (1H, m), 2.95-2.99 (2H, m), 3.51 (3H, s), 4.43 (1H, s), 5.19 (1H, s), 6.49 (1H, d, *J*=8.0 Hz), 6.68 (1H, d, *J*=8.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.6, 4.1, 9.6, 18.0, 22.9, 23.5, 26.6, 26.8, 26.9, 29.9, 32.1, 33.0, 35.8, 35.9, 36.0, 36.1, 43.7, 47.0, 47.3, 48.4, 52.8, 58.6, 59.8, 77.2, 80.8, 97.5, 116.5, 119.6, 128.3, 132.5, 137.4, 145.7. HRMS (ESI^+) calcd for $C_{32}H_{46}NO_4$ (MH^+), 508.3421; found 508.3418 (100%). Anal. ($C_{32}H_{45}NO_4.HCl.H_2O$) C, H, N.

(2′R, 5α, 6R, 7R, 14α)-2′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-4′-cyclohexyl-butan-2′-ol (1i)

Using the general procedure B with **9i** (54 mg) gave **1i** as a yellow solid (50 mg, 96%) (R_f=0.26; 0.5% NH_4OH, 30% EtOAc in hexane; column ran in 30% EtOAc in hexane). ^1H NMR (400 MHz, $CDCl_3$) δ

0.08-0.12 (2H, m), 0.46-0.51 (2H, m), 0.69-1.54 (14H, m), 1.33 (3H, s), 1.62-1.81 (9H, m), 1.90-2.02 (2H, m), 2.18-2.38 (4H, m), 2.65 (1H, dd, *J*=12.0 and 5.0 Hz), 2.78-2.85 (1H, m), 2.95-3.00 (2H, m), 3.52 (3H, s), 4.42 (1H, s), 5.17 (1H, s), 6.50 (1H d, *J*=8.0 Hz), 6.68 (1H, d, *J*=8.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.6, 4.1, 9.6, 18.0, 22.9, 23.7, 26.6, 26.6, 26.9, 30.0, 30.3, 31.8, 33.5, 33.8, 35.8, 36.1, 38.3, 38.7, 43.7, 45.7, 47.4, 52.8, 58.6, 59.9, 76.1, 80.7, 97.6, 116.5, 119.6, 128.3, 132.5, 137.5, 145.7. HRMS (ESI^+) calcd for $C_{33}H_{48}NO_4$ (MH^+), 522.3578; found 522.3554 (100%). Anal. ($C_{33}H_{47}NO_4.HCl.1.5H_2O$) C, H, N.

(2′R, 5α, 6R, 7R, 14α)-2′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-3′-phenyl-propan-2′-ol (1j)

Using the general procedure B with **9j** (51 mg) gave **9j** as a yellow solid (49 mg, 98%) (R_f=0.21; 0.5% NH_4OH, 30% EtOAc in hexane; column ran in 30% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.12-0.18 (2H, m), 0.51-0.56 (2H, m), 0.69-0.77 (1H, m), 0.83-0.90 (1H, m), 1.03-1.11 (1H, m), 1.15-1.21 (1H, m), 1.36 (3H, s), 1.56 (1H, dd, *J*=13.0 and 2.5 Hz), 1.71-1.85 (4H, m), 2.20-2.39 (4H, m), 2.62 (1H, dd, *J*=11.5 and 5.0 Hz), 2.71-2.79 (2H, m), 2.96-3.01 (3H, m), 3.48 (3H, s), 4.32 (1H, s), 5.35 (1H, s), 6.50 (1H, d, *J*=8.0 Hz), 6.69 (1H, d, *J*=8.0 Hz), 7.20-7.31 (3H, m), 7.38-7.40 (2H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.8, 3.9, 9.7, 17.9, 23.0, 23.1, 29.8, 32.0, 35.5, 36.2, 43.6, 45.9, 47.1, 47.2, 52.8, 58.9, 59.9, 76.7, 80.7, 97.3, 116.5, 119.6, 126.2, 127.7, 128.3, 131.3, 132.4, 137.4, 137.7, 145.7. HRMS (ESI^+) calcd for $C_{32}H_{40}NO_4$ (MH^+), 502.2952; found 502.2956 (100%). Anal. ($C_{32}H_{39}NO_4.HCl.2H_2O$) C, H, N.

(2′R, 5α, 6R, 7R, 14α)-2′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-4′-phenyl-butan-2′-ol (1k)

Using the general procedure B with **9k** (53 mg) gave **1k** as a yellow solid (45 mg, 88%) (R_f=0.2; 0.5% NH_4OH, 30% EtOAc in hexane; column ran in 30% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06-0.12 (2H, m), 0.46-0.51 (2H, m), 0.70-0.83 (2H, m), 1.01-1.13 (2H, m), 1.40 (3H, s), 1.65-1.83 (5H, m), 1.93-2.03 (2H, m), 2.18-2.35 (4H, m), 2.64 (1H, dd, *J*=11.5 and 5.0 Hz), 2.70-3.00 (5H, m), 3.55 (3H, s), 4.44 (1H, s), 5.25 (1H, s), 6.51 (1H, d, *J*=8.0 Hz), 6.70 (1H, d, *J*=8.0 Hz), 7.15-7.19 (1H, m), 7.24-7.29 (4H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.7, 4.1, 9.6, 17.9, 22.9, 23.6, 29.6, 30.0, 31.8, 35.8, 36.1, 43.6, 44.0, 45.9, 47.5, 52.9, 58.6, 60.0, 75.9, 80.7, 97.7, 116.5, 119.7, 125.7, 128.5, 128.7, 132.5, 137.4, 143.4, 145.7. HRMS (ESI^+) calcd for $C_{33}H_{42}NO_4$ (MH^+), 516.3108; found 516.3113 (100%). Anal. ($C_{33}H_{41}NO_4.HCl.2H_2O$) C, H, N.

(1l) – known compound, ref 19

(2′R, 5α, 6R, 7R, 14α)-2′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-heptan-2′-ol (1m)

Using general procedure B with **9m** (1.00 g) gave **1m** as a white solid (0.63 g, 65%) (Rf 0.55; 10:1 DCM:MeOH). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.10 (2H, m), 0.48 (2H, m), 0.80 (1H, m), 0.90 (3H, t), 1.34 (3H, s), 2.97 (1H, d), 2.98 (1H, d), 3.53 (3H, s), 4.43 (1H, s), 5.14 (1H, s), 6.50 (1H, d), 6.69 (1H, d);). ^{13}C NMR (68 MHz, $CDCl_3$) δ 3.45, 4.01, 9.46, 14.13, 17.90, 22.28, 22.67, 22.78, 23.50, 29.85, 30.93, 31.73, 32.47, 35.67, 35.98, 41.38, 43.61, 45.73, 47.26, 52.69, 58.40, 59.80, 75.93, 80.57, 97.51, 116.39, 119.48, 128.27, 132.39, 137.32, 145.58; HRMS (EI) calcd for $C_{30}H_{43}NO_4$ (M^+) 481.319209; found 481.320221 (100%); Anal. ($C_{30}H_{43}NO_4.HCl.H_2O$) C, H, N.

(1n) – Buprenorphine, supplied by the National Institute on Drug Abuse, Bethesda, Maryland.

Series **2** were prepared by reacting **10** with an appropriate Grignard reagent (General Procedure A), oxidising the resulting alcohol (General Procedure E) and treating the resulting ketone with methyl magnesium bromide (General procedure A). 3-O-demethylation and HCl salt formation were as described in General procedure B. The scheme is illustrated fully for **2e**.

(1′S, 5α, 6R, 7R, 14α)-1′-(4,5-epoxy-7,8-dihydro-3,6-dimethoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)- 2′-cyclohexyl-ethan-1′-ol (11a: R = cyclohexylmethyl)

Using general procedure A on **10** with cyclohexylmethylmagnesium bromide gave **11a**, isolated as a white solid, 89%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09-0.10 (2H, m), 0.46-0.50 (2H, m), 0.68-0.72 (1H, m), 0.78-0.89 (3H, m), 0.95-0.98 (1H, m), 1.13-1.28 (5H, m), 1.47-1.53 (4H, m), 1.63-1.71 (8H, m), 1.83-1.86 (1H, m), 2.00-2.02 (1H, m), 2.21-2.29 (3H, m), 2.58-2.66 (2H, m), 2.95-3.00 (1H, d, *J*=18.1 Hz), 3.06-3.08 (1H, d, *J*=6.3 Hz), 3.41 (1H, s), 3.86 (3H, s), 4.41 (1H, s), 6.53 (1H, d, *J*=8.1 Hz), 6.68 (1H, d, *J*=8.1 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.4, 4.2, 9.3, 20.2, 22.5, 26.1, 26.3, 26.5, 26.7, 29.2, 32.7, 34.2, 34.3, 35.7, 40.7, 43.6, 43.9, 46.0, 51.1, 56.6, 58.3, 59.8, 66.4, 80.0, 93.3, 113.6, 118.8, 128.6, 132.8, 141.6, 147.0; HRMS (ESI^+) calcd for $C_{32}H_{46}NO_4$ (MH^+), 508.34; found 508.34.

(5α, 6R, 7R, 14α)-1′-(4,5-epoxy-7,8-dihydro-3,6-dimethoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-2′-cyclohexylethanone (12, R = cyclohexylmethyl)

Using general procedure D on **11a** (R = cyclohexylmethyl) gave **12** (R = cyclohexylmethyl) as a white solid (80 mg, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07-0.08 (2H, m), 0.45-0.49 (2H, m), 0.68-0.78 (2H, m), 0.84-0.95 (2H, m), 1.12-1.16 (1H, m), 1.22-1.35 (4H, m), 1.50-1.51 (1H, m), 1.54 (3H, s), 1.58-1.68 (5H, m), 1.83-1.85 (1H, m), 1.90-2.00 (1H, m), 2.26-2.35 (3H, m), 2.37-2.38 (1H, d, *J*=6.0, Hz), 2.47-2.53 (1H, dd, *J*=16.2 Hz, J=8.1 Hz), 2.59-2.63 (1H, m), 2.66-2.73 (1H, m), 2.94-2.99 (2H, m), 3.04-3.06 (1H, d, *J*=6.4 Hz), 3.39 (1H, s), 3.86 (3H, s), 4.44 (1H, s), 6.54 (1H, d, *J*=8.1 Hz), 6.69 (1H, d, *J*=8.1Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.2, 4.0, 9.38, 17.2, 22.6. 26.0, 26.1, 26.2, 28.7, 30.5, 33.0, 33.3, 33.5, 35.2, 35.4, 43.7, 46.4, 49.3, 52.1, 54.0, 56.7, 58.3, 59.8. 95.1, 114.0, 119.0, 128.8, 132.7, 141.6, 146.8, 212.7; HRMS (ESI^+) calcd for $C_{32}H_{44}NO_4$ (MH^+), 506.33; found 506.33.

(2′R, 5α, 6R, 7R, 14α)-2′-(4,5-epoxy-7,8-dihydro-3,6-dimethoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-3′-cyclohexyl-propan-2′-ol (13: R = cyclohexylmethyl)

Using procedure A for the addition of methylmagnesium bromide to **12** (R = cyclohexylmethyl), **13** (R = cyclohexylmethyl) was isolated as a white solid (34 mg, 89%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08-0.10 (2H, m), 0.47-0.50 (2H, m), 0.69-0.72 (2H, m), 0.90-0.99 (2H, m), 1.04-1.10 (2H, m), 1.15 (3H, s), 1.20-1.28 (3H, m), 1.56-1-68 (8H, m), 1.74-1.77 (2H, m), 1.85 (1H, m), 1.99-2.03 (2H, m), 2.18-2.24 (2H, m), 2.26-2.36 (1H, m), 2.58-2.63 (1H, m), 2.78-2.86 (1H, m), 2.96-2.99 (1H, d, *J*=12.8 Hz), 2.99-2.03 (1H, d, *J*=6.0 Hz), 3.51 (1H, s), 3.87 (3H, s), 4.38 (1H, s), 4.68 (1H, s), 6.53 (1H, d, *J*=8.1 Hz), 6.69 (1H, d, *J*=8.1 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.2, 4.1, 9.3, 18.1, 22.5, 25.6, 26.4, 29.4, 32.1, 33.5, 35.4, 35.6, 35.8, 35.9, 43.4, 43.6, 46.8, 49.6, 52.5, 56.9, 58.1, 59.8, 80.3, 97.1, 114.2, 118.9, 128.9, 132.7, 141.5, 146.9; HRMS (ESI^+) calcd for $C_{33}H_{48}NO_4$ (MH^+), 522.36; found 522.36.

(2′S, 5α, 6R, 7R, 14α)-2′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-3′-cyclohexyl-propan-2′-ol (2e)

Using General Procedure B on **13** (R = cyclohexylmethyl) gave **2e** as a white solid. ^{1}H NMR, 270 MHz ($CDCl_3$) δ 0.07-0.11 (2H, m), 0.46-0.50 (2H, m), 0.67-0.81 (2H, m), 0.86-1.30 (10H, m), 1.55-1.89 (12H, m), 1.94-2.08 (2H, m), 2.14-2.26 (3H, m), 2.34-2.41 (1H, m), 2.55 (1H, dd, *J*=20.50 Hz), 2.76-2.86 (1H, m), 2.92 (1H, d, *J*=18.44 Hz), 2.99 (1H, d, *J*=6.59 Hz), 3.50 (3H, s), 4.40 (1H, s), 4.71 (1H, s), 6.48 (1H, d, *J*=7.99 Hz), 6.66 (1H, d, *J*=7.99 Hz); ^{13}C NMR, ($CDCl_3$) δ 3.3, 4.2, 9.3, 18.1, 22.6, 25.5, 26.4, 26.5, 26.6, 29.9, 32.1, 33.5, 35.4, 35.5, 35.9, 35.9, 43.4, 43.7, 47.2, 49.6, 52.6, 58.1, 59.8, 77.7, 80.5, 97.5, 116.5, 119.3, 127.9, 132.3, 137.5, 145.6. HRMS, m/z for ($C_{32}H_{46}NO_4$) $[MH]^+$, calcd- 508.3427, found- 508.3424. Anal. ($C_{32}H_{45}NO_4 \cdot HCl \cdot 1.5H_2O$) C, H, N.

(2′S, 5α, 6R, 7R, 14α)-2′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-3′-methyl-butan-2′-ol (2a)

^{1}H NMR, 270 MHz ($CDCl_3$) δ 0.05-0.09 (2H, m), 0.46-0.49 (2H, m), 0.64-0.81 (2H, m), 0.96 (3H, d, *J*=6.88 Hz), 1.00 (3H, d, *J=6.88 Hz*), 1.11-1.21 (5H, m), 1.45 (1H, m), 1.62 (4H, m), 1.93-2.08 (2H, m), 2.12-2.41 (4H, m), 2.58 (1H, dd, *J*=4.97 and 11.56 Hz), 2.72-2.81 (1H, m), 2.92 (1H, d, *J*=17.06 Hz), 2.99 (1H, d, *J*=5.78 Hz), 3.48 (3H, s), 3.65-3.72 (1H, bd), 4.42 (1H, s), 6.48 (1H, d, *J*=7.99 Hz), 6.66 (1H, d, *J*=7.99 Hz); ^{13}C NMR, ($CDCl_3$) δ 3.4, 4.1, 9.4, 18.4, 19.6, 20.3, 22.6, 29.5, 30.6, 34.8, 35.4, 36.1, 43.7, 46.7, 47.3, 52.2, 58.3, 59.9, 60.4, 78.2, 79.5, 97.1, 116.4, 119.4, 128.2, 132.4, 137.3, 145.6. HRMS, m/z for ($C_{28}H_{40}NO_4$) $[MH]^+$, calcd- 454.2957, found- 454.2944. Anal. ($C_{28}H_{39}NO_4 \cdot HCl \cdot 3H_2O$) C, H, N.

(2′S, 5α, 6R, 7R, 14α)-2′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-4′-methyl-pentan-2′-ol (2b)

^{1}H NMR, 270 MHz ($CDCl_3$) δ 0.07-0.09 (2H, m), 0.46-0.49 (2H, m), 0.68-0.81 (2H, m), 0.91 (3H, d, *J*=6.88 Hz), 0.98-1.08 (6H, m), 1.16 (3H, s), 1.57-1.68 (4H, m), 1.71-1.88 (3H, m), 1.96-2.07 (1H, m), 2.15-2.29 (3H, m), 2.34-2.41 (1H, m), 2.58 (1H, dd, *J*=4.67 Hz *and* 11.56 Hz), 2.75-2.87 (1H, m), 2.93 (1H, d, *J*=18.71 Hz), 2.99 (1H, d, *J*=6.61 Hz), 3.51 (3H, s), 4.40 (1H, s), 4.78 (1H, s), 6.48 (1H, d, *J=7.99 Hz*), 6.67 (1H, d, *J=7.99 Hz*); ^{13}C NMR, ($CDCl_3$) δ 3.3, 4.2, 9.3, 18.1, 22.5, 24.1, 24.6, 25.1, 25.4, 29.8, 32.1, 35.5, 35.6, 43.7, 44.6, 47.1, 49.7, 52.6, 58.1, 59.8, 77.6, 80.5, 97.4, 116.4, 119.4, 128.1, 132.3, 137.4, 145.6. HRMS, m/z for ($C_{29}H_{42}NO_4$) $[MH]^+$, calcd- 468.3114, found- 468.3105. Anal. ($C_{29}H_{41}NO_4 \cdot HCl \cdot 3H_2O$) C, H, N.

(2′S, 5α, 6R, 7R, 14α)-2′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-5′-methyl-hexan-2′-ol (2c)

^{1}H NMR, 270 MHz ($CDCl_3$) δ 0.07-0.09 (2H, m), 0.46-0.50 (2H, m), 0.72-0.81 (2H, m), 0.86-0.94 (6H, m), 1.02-1.22 (6H, m), 1.42-1.80 (8H, m), 1.89-2.06 (2H, m), 2.13-2.28 (3H, m), 2.35-2.42 (1H, m), 2.58 (1H, dd, *J*=4.94 Hz *and* 11.56 Hz), 2.76-2.86 (1H, m), 2.93 (1H, d, *J*=18.71 Hz), 3.00 (1H, d, *J*=6.88 Hz), 3.50 (3H, s), 4.42 (1H, s), 4.67 (1H, s), 6.48 (1H, d, *J*=8.26 Hz), 6.67 (1H, d, *J*=8.26 Hz); ^{13}C NMR, ($CDCl_3$) δ 3.3, 4.2, 9.3, 18.1, 22.5, 23.1, 25.2, 28.8, 29.9, 31.9, 32.5, 34.2, 35.5, 35.9, 43.7, 47.2, 49.1, 52.6, 58.1, 59.8, 77.4, 80.5, 97.4, 116.5, 119.3, 127.9, 132.3, 137.5, 145.6. HRMS, m/z for ($C_{30}H_{44}NO_4$) $[MH]^+$, calcd- 482.3270, found- 482.3268. Anal. ($C_{30}H_{43}NO_4 \cdot HCl \cdot 2H_2O$) C, H, N.

(1′S, 5α, 6R, 7R, 14α)-1′-cyclopentyl-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-ethan-1′-ol (2d)

^{1}H NMR 400 MHz ($CDCl_3$) δ 0.07-0.08 (2H, m), 0.44-0.51 (2H, m), 0.70-0.78 (1H, m), 0.79-0.86 (1H, m), 1.06-1.20 (5H, m), 1.35-1.58 (6H, m), 1.63-1.81 (6H, m), 1.96-2.03 (2H, m), 2.14-2.47 (4H, m), 2.60-2.62 (1H, m), 2.73-2.78 (1H, m), 2.94-2.99 (2H, m), 3.51 (3H, s), 4.41 (2H, s), 6.48 (1H, d, *J*=8.00 Hz), 6.68 (1H, d, *J*=8.00 Hz); ^{13}C NMR, ($CDCl_3$) δ 3.4, 4.1, 9.3, 17.8, 21.5, 22.6, 24.3, 26.4, 28.6, 29.4, 29.7, 30.5, 35.5, 36.1, 43.7, 46.9, 47.4, 48.8, 52.5, 58.3, 59.9, 77.9, 79.9, 97.5, 116.4, 119.4, 128.1, 132.4, 137.4, 145.6. HRMS, m/z for ($C_{30}H_{42}NO_4$) $[MH]^+$, calcd- 480.3114, found- 480.3106. Anal. ($C_{30}H_{41}NO_4 \cdot HCl \cdot 3H_2O$) C, H, N.

(2′S, 5α, 6R, 7R, 14α)-2′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-4′-cyclohexyl-butan-2′-ol (2f)

^{1}H NMR 270 MHz ($CDCl_3$) δ 0.07-0.09 (2H, m), 0.46-0.50 (2H, m), 0.72-0.93 (4H, m), 1.02-1.28 (10H, m), 1.52-1.81 (12H, m), 1.89-2.04 (2H, m), 2.12-2.29 (3H, m), 2.34-2.41 (1H, m), 2.55 (1H, dd, *J*=20.50 Hz), 2.77-2.86 (1H, m), 2.93 (1H, d, *J*=18.71 Hz), 3.00 (1H, d, *J*=6.59 Hz), 3.49 (3H, s), 4.42 (1H, s), 4.65 (1H, s), 6.48 (1H, d, *J*=8.26 Hz), 6.67 (1H, d, *J*=8.26 Hz); ^{13}C NMR, ($CDCl_3$) δ 3.3, 4.2, 9.4, 18.1, 22.6, 25.3, 26.4, 26.7, 29.9, 31.2, 31.9, 33.4, 33.7, 33.7, 35.5, 35.9, 38.5, 43.7, 47.2, 49.1, 52.6, 58.1, 59.8, 76.8, 80.5, 97.5, 116.4, 119.4, 128.1, 132.3, 137.4, 145.6. HRMS, m/z for ($C_{33}H_{48}NO_4$) $[MH]^+$, calcd- 522.3583, found- 522.3590. Anal. ($C_{33}H_{47}NO_4 \cdot HCl \cdot 1.5H_2O$) C, H, N.

(1′S, 5α, 6R, 7R, 14α)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-pentan-2′-ol (2g)

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08-0.09 (2H, m), 0.45-0.47 (2H, m), 0.69-0.89 (3H, m), 0.94-0.97 (3H, m), 1.1-1.16 (2H, m), 1.24 (2H, s), 1.35-1.46 (2H, m), 1.67-1.71 (4H, m), 1.79-1.88 (2H, m), 2.02-2.07 (2H, m), 2.16-2.33 (3H, m), 2.46-2.53 (1H, m), 2.61-2.67 (1H, m), 2.84-3.04 (2H, m), 3.33 (3H, s), 4.51 (1H, s), 5.29 (1H, s), 6.50 (1H, d, *J*=8.1 Hz), 6.68 (1H, d, *J*=8.1 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 4.0, 9.4, 14.7, 16.9, 18.6, 21.2, 25.9, 29.4, 32.6, 35.6, 36.1, 43.4, 45.2, 46.0, 50.5, 52.4, 59.8, 67.0, 70.7, 88.7, 98.2, 119.4, 120.8, 127.1, 132.3, 137.2, 145.5; HRMS (ESI$^+$) calcd for $C_{28}H_{40}NO_4$ (MH^+), 454.30; found 454.31. Anal. ($C_{28}H_{39}NO_4$.HCl.H_2O) C, H, N.

(1′S, 5α, 6R, 7R, 14α)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-heptan-2′-ol (2h)

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08-0.09 (2H, d, *J*=4.8 Hz), 0.45-4.48 (2H, m), 0.70-0.79 (2H, m), 0.87-0.93 (3H, m), 1.06-1.12 (1H, m), 1.31-1.44 (8H, m), 1.67-1.70 (3H, d, *J*=12.7 Hz), 1.75 (3H, s), 2.02-2.13 (3H, m), 2.16-2.43 (3H, m), 2.48-2.52 (1H, m), 2.62-2.67 (1H, m), 2.82-2.89 (1H, m), 2.94-2.99 (1H, d, *J*=18.4 Hz), 3.00-3.03 (1H, m), 3.33 (3H, s), 3.52 (1H, t, *J*=12.8 Hz), 4.51 (1H, s), 5.29 (1H, s), 6.50 (1H, d, *J*=8.1 Hz), 6.68 (1H, d, *J*=8.1 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.3, 9.4, 14.0, 20.4, 22.3, 29.5, 31.8, 35.9, 43.8, 46.2, 50.5, 59.8, 67.0, 71.2, 88.7, 98.2, 118.0, 120.8, 127.1, 132.3, 139.0, 145.9; HRMS (ESI$^+$) calcd for $C_{30}H_{44}NO_4$ (MH^+), 482.33; found 482.35. Anal. ($C_{30}H_{43}NO_4$ HCl.H_2O) C, H, N.

(1′S, 5α, 6R, 7R, 14α)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-3′-dimethylbutan-2′-ol (2i)

^{1}H NMR (400 MHz, MeOD) δ 0.54-0.59 (2H, d, *J*=4.8 Hz), 0.82-0.84 (2H, m), 0.87-0.89 (1H, m), 1.10 (9H, s), 1.15-1.18 (1H, m), 1.34-1.42 (1H, m), 1.52 (3H, s), 1.61-1.69 (1H, m), 1.91-2.02 (2H, m), 2.43-2.56 (4H, m), 2.96-3.02 (1H, m), 3.07-3.17 (2H, m), 3.32-3.37 (1H, d, *J*=18.2 Hz), 3.37-3.41 (4H, m), 3.45 (3H, s), 4.02 (1H, s), 4.71 (1H, s), 6.69 (1H, d, *J*=8.1 Hz), 6.78 (1H, d, *J*=8.1 Hz); ^{13}C NMR (100.6 MHz, MeOD) δ 3.6, 6.0, 6.9, 20.6, 23.5, 25.5, 27.7, 28.9, 30.9, 32.7, 36.3, 38.7, 41.9, 44.6, 46.8, 59.9, 61.2, 78.9, 79.1, 92.3, 119.2, 121.1, 132.2, 140.7, 147.4; HRMS (ESI$^+$) calcd for $C_{29}H_{42}NO_4$ (MH^+), 468.31; found 468.32. Anal. ($C_{29}H_{41}NO_4$.HCl) C, H, N.

Series **3** were prepared by reacting **10** with an appropriate Grignard reagent (General Procedure A), oxidising the resulting alcohol (General Procedure E) and treating the resulting ketone with $LiAlH_4$ (General procedure D). 3-O-demethylation and HCl salt formation were as described in General procedure C. This is illustrated in full for R = phenethyl.

(1′R, 5α, 6R, 7R, 14α)-1′-(4,5-epoxy-7,8-dihydro-3,6-dimethoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-3′-phenyl-propan-1′-ol (11a, R = phenethyl)

Isolated as a white solid 218 mg, 58%). R_f 0.48: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08-0.10 (2H, m), 0.46-0.49 (2H, m), 0.72-0.96 (2H, m), 1.15-1.25 (3H, m), 1.51-1.66 (2H, m), 1.72-1.79 (4H, m), 1.90-2.03 (2H, m), 2.21-2.35 (4H, m), 2.62-2.69 (3H, m), 2.95-3.06 (2H ,dd, *J*=18.3 Hz, *J*=6.4 Hz)), 3.38 (3H, s), 3.86 (3H, s), 4.18 (1H, m), 4.40 (1H, s), 6.53 (1H, d, *J*=8.0 Hz), 6.68 (1H, d, *J*=8.0 Hz), 7.16-7.30 (5H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.3, 4.0, 9.3, 14.1, 17.8, 21.4, 22.7, 28.5, 31.3, 31.7, 33.4, 35.2, 37.0, 43.5, 44.1, 45.5, 51.9, 56.9, 56.9, 58.8, 59.8, 93.0, 114.3, 119.0, 125.7, 128.5, 128.6, 133.1, 141.8, 142.7, 171.0; HRMS (ESI$^+$) calcd for $C_{33}H_{42}NO_4$ (MH^+), 516.31; found 516.31.

(5α, 6R, 7R, 14α)-(4,5-epoxy-7,8-dihydro-3,6-dimethoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-3-phenyl-propanone (12: R = phenethyl)

11a, R = phenethyl (0.36 mmmol) was treated as described in general procedure E. The residue was purified by column chromatography using combi flash machine (30% ethyl acetate in hexane) to afford **12** (R = phenethyl). Isolated as a uncoloured solid (100 mg, 54%) Rf 0.55: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07-0.09 (2H, d, *J*=4.9 Hz), 0.44-0.49 (2H, m), 0.73-0.76 (1H, m), 1.15-1.32 (2H, m), 1.53-1.57 (1H, m), 1.56-1.71 (2H, m), 1.99-2.03 (2H, m), 2.23-2.32 (4H, m), 2.59-2.60 (1H, m), 2.70-2.78 (2H, m), 2.89-3.08 (5H, m), 3.37 (3H, s), 3.86 (3H, s), 4.43 (1H, s), 6.54 (1H, d, *J*=8.0 Hz), 6.68 (1H, d, *J*=8.0 Hz), 7.14-7.24 (5H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.3, 9.4, 17.2, 22.7, 28.6, 29.5, 30.0, 35.2, 35.4, 43.6, 46.4, 47.7, 49.5, 52.2, 56.7, 58.3, 59.7, 95.1, 114.0, 119.0, 125.7, 128.2, 141.3, 141.7, 146.7, 211.9; HRMS (ESI^+) calcd for $C_{33}H_{40}NO_4$ (MH^+), 514.30; found 514.30.

(1′R, 5α, 6R, 7R, 14α)-1′-(4,5-epoxy-7,8-dihydro-3,6-dimethoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-3′-phenyl-propan-1′-ol (11b: R = phenethyl)

12, R = phenethyl (100.0 mg, 0.19 mmol), was treated as described in general procedure D to give **11b: R = phenethyl**. Isolated as a white solid (86 mg, 86%). R_f 0.51. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07-0.09 (2H, m), 0.47-0.49 (2H, m), 0.72-0.80 (2H, m), 0.87-0.99 (2H, m), 1.59-1.82 (5H, m), 1.96-2.04 (2H, m), 2.18-2.34 (5H, m), 2.61-2.72 (2H, m), 2.74-2.82 (1H, m), 2.92-2.99 (3H, m), 3.54 (3H, s), 3.87 (3H, s), 4.47-4.48 (1H, d, *J*=1.8 Hz), 5.46 (1H, s), 6.54 (1H, d, *J*=8.0 Hz), 6.70 (1H, d, *J*=8.0 Hz), 7.15-7.18 (1H, m), 7.24-7.28 (4H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.5, 3.9, 9.4, 14.1, 17.8, 20.9, 22.6, 29.2, 31.6, 32.1, 35.1, 36.6, 41.0, 43.4, 45.7, 52.2, 56.7, 58.5, 59.9, 60.2, 73.2, 80.0, 94.4, 114.1, 119.1, 125.2, 128.2, 128.4, 132.7, 141.7, 142.8, 146.7, 211.905; HRMS (ESI^+) calcd for $C_{33}H_{42}NO_4$ (MH^+), 516.31; found 516.31.

(1′R, 5α, 6R, 7R, 14α)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-3′-phenyl-propan-1′-ol (3i)

11b: R = phenethyl (54 .0 mg, 0.10 mmol) was treated as described in general procedure B to give **3i**. Isolated as a white solid (48 mg, 96%). R_f 0.14; ^{1}H NMR, 270 MHz ($CDCl_3$) 0.06-0.09 (2H, m), 0.45-0.50 (2H, m), 0.64-0.80 (2H, m), 0.82-0.98 (2H, m), 1.58-1.86 (5H, m), 1.91-2.08 (2H, m), 2.13-2.32 (4H, m), 2.60-2.84 (3H, m), 2.91-3.03 (3H, m), 3.50 (3H, s), 3.81 (1H, t, *J*=9.07 Hz), 4.49 (1H, s), 5.45 (1H, s), 6.48 (1H, d, *J*=7.99 Hz), 6.67 (1H, d, *J*=7.99 Hz), 7.13-7.32 (5H, m); ^{13}C NMR, ($CDCl_3$) δ 3.6, 4.1, 9.5, 18.2, 22.8, 29.2, 31.7, 32.2, 35.2, 35.4, 36.7, 40.7, 43.7, 46.1, 52.2, 58.5, 60.0, 73.5, 76.6, 80.3, 94.6, 116.7, 119.8, 125.7, 128.4, 128.6, 128.7, 132.5, 137.1, 142.90. HRMS, m/z for ($C_{32}H_{40}NO_4$) $[MH]^+$, calcd- 502.2957, found- 502.2956. Anal. ($C_{32}H_{39}NO_4 \cdot HCl \cdot 1.5H_2O$) C, H, N.

(1′R, 5α, 6R, 7R, 14α)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-2′-methyl-propan-1′-ol (3a)

^{1}H NMR, 270 MHz ($CDCl_3$) δ 0.05- 0.09 (2H, m), 0.46-0.50 (2H, m), 0.71-0.82 (2H, m), 0.88-0.94 (3H, d, *J=6.59 Hz*), 0.96-1.08 (5H, m), 1.17-1.24 (1H, m), 1.60-1.67 (3H, m), 1.84-1.93 (2H, m), 2.01-2.08 (1H, m), 2.14-2.27 (3H, m), 2.29-2.42 (1H, m), 2.63-2.79 (2H, m), 2.92 (1H, d, *J=18.44 Hz*), 3.49 (3H, s), 3.69 (1H, d, *J=9.91 Hz*), 4.51 (1H, s), 5.25 (1H, s), 6.49 (1H, d, *J=7.96 Hz*), 6.67 (1H, d, *J=7.96 Hz*); ^{13}C NMR (MeOD) δ 3.9, 5.9, 6.8, 14.5, 18.6, 21.1, 25.4, 29.9, 30.3, 31.0, 32.9, 36.7, 38.5, 45.6, 46.8, 52.8, 60.3 60.7, 78.5, 80.4, 93.7, 119.5, 121.4, 124.3, 131.4, 140.9, 147.4. HRMS, m/z for ($C_{27}H_{38}NO_4$) $[MH]^+$, calcd- 440.2801, found- 440.2783. Anal. ($C_{27}H_{37}NO_4 \cdot HCl \cdot 2H_2O$) C, H, N.

(1′R, 5α, 6R, 7R, 14α)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-3′-methyl-butan-1′-ol (3b)

^{1}H NMR, 270 MHz ($CDCl_3$) δ 0.07-0.09 (2H, m), 0.45-0.50 (2H, m), 0.72-1.03 (10H, m), 1.31-1.38 (2H, m), 1.5-1.80 (4H, m), 1.92-2.08 (2H, m), 2.13-2.36 (4H, m), 2.61 (1H, dd, *J=4.97 and 11.55 Hz*), 2.72-2.82 (1H, m), 2.92-2.99 (2H, m) 3.48 (3H, s), 3.82-3.87 (1H, m), 4.49 (1H, s), 5.34 (1H, s), 6.48 (1H, d, *J=7.96 Hz*), 6.66 (1H, d, *J=7.96 Hz*); ^{13}C NMR (MeOD) δ 3.9, 5.8, 6.8, 19.3, 21.7, 24.6, 25.3, 30.0, 31.2, 33.1, 36.8, 41.6, 44.8, 45.7, 46.8, 52.5, 60.3, 60.9, 72.4, 79.8, 93.0, 119.5, 121.3, 124.3, 131.3, 140.9,

147.5. HRMS, m/z for ($C_{28}H_{40}NO_4$) $[MH]^+$, calcd- 454.2957, found- 454.2941. Anal. ($C_{28}H_{39}NO_4 \cdot HCl \cdot 2H_2O$) C, H, N.

(1′R, 5α, 6R, 7R, 14α)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-4′-methyl-pentan-1′-ol (3c)

^{1}H NMR, 270 MHz ($CDCl_3$) δ 0.07-0.09 (2H, m), 0.46-0.50 (2H, m), 0.64-0.72 (2H, m), 0.78-0.84 (6H, m), 1.24-1.84 (10H, m), 1.99-2.10 (2H, m), 2.16-2.40 (4H, m), 2.61 (1H, dd, *J=5.04 and 11.93 Hz*), 2.72-2.85 (1H, m), 2.92-2.99 (2H, m) 3.48 (3H, s), 3.74 (1H, t, *J=7.69 Hz*), 4.49 (1H, s), 5.37 (1H, s), 6.48 (1H, d, *J=7.96 Hz*), 6.66 (1H, d, *J=7.96 Hz*); ^{13}C NMR, ($CDCl_3$) δ 3.5, 4.4, 9.5, 18.4, 22.5, 22.7, 23.1, 28.3, 29.3, 32.5, 34.5, 35.2, 35.4, 40.4, 43.8, 46.0, 52.1, 58.4, 60.0, 74.4, 76.6, 80.2, 94.3, 116.7, 119.7, 128.1, 132.5, 137.5, 145.4. HRMS, m/z for ($C_{29}H_{42}NO_4$) $[MH]^+$, calcd- 468.3114, found- 468.3105. Anal. ($C_{29}H_{41}NO_4 \cdot HCl \cdot 3H_2O$) C, H, N.

(1′R, 5α, 6R, 7R, 14α)-1′-cyclopentyl-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-methanol (3d)

^{1}H NMR, 270 MHz ($CDCl_3$) δ 0.07-0.09 (2H, m), 0.46-0.49 (2H, m), 0.68-0.79 (2H, m), 0.96-1.06 (2H, m), 1.46-1.80 (12H, m), 1.78-1.90 (1H, m), 1.96-2.04 (1H, m), 2.12-2.25 (4H, m), 2.33-2.41 (1H, m), 2.60 (1H, dd, *J=4.94 and 11.82 Hz*), 2.72-2.83 (1H, m), 2.92 (1H, d, *J=18.14 Hz*), 2.99 (1H, d, *J=6.61 Hz*), 3.48 (3H, s), 3.88 (1H, d, *J=9.91 Hz*), 4.50 (1H, s), 5.28 (1H, s), 6.48 (1H, d, *J=7.96 Hz*), 6.66 (1H, d, *J=7.96 Hz*); ^{13}C NMR, ($CDCl_3$) δ 3.3, 4.2, 9.2, 18.3, 22.7, 23.9, 26.2, 29.4, 32.2, 33.1, 35.4, 39.2, 41.3, 43.7, 45.8, 52.2, 58.3, 59.8, 75.5, 80.5, 94.6, 116.5, 119.3, 128.1, 132.3, 137.8, 145.6. HRMS, m/z for ($C_{29}H_{40}NO_4$) $[MH]^+$, calcd- 466.2957, found- 466.2941. Anal. ($C_{29}H_{39}NO_4 \cdot HCl \cdot 2H_2O$) C, H, N.

(1′R, 5α, 6R, 7R, 14α)-1′-cyclohexyl-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-methanol (3e)

^{1}H NMR, 270 MHz ($CDCl_3$) δ 0.05-0.10 (2H, m), 0.47-0.51 (2H, m), 0.66-0.83 (2H, m), 0.92-1.08 (2H, m), 1.13-1.33 (4H, m), 1.46-1.69 (7H, m), 1.74-1.83 (2H, m), 1.89-2.10 (3H, m), 2.13-2.30 (3H, m), 2.35-2.42 (1H, m), 2.61-2.80 (2H, m), 2.92 (1H, d, *J=18.71 Hz*), 3.00 (1H, d, *J=6.61 Hz*), 3.47 (3H, s), 3.64 (1H, d, *J=9.91 Hz*), 4.51 (1H, s), 5.25 (1H, s), 6.49 (1H, d, *J=7.96 Hz*), 6.67 (1H, d, *J=7.96 Hz*); ^{13}C NMR (MeOD) δ 3.9, 5.8, 6.8, 18.6, 25.4, 25.7, 27.6, 27.8, 28.0, 30.0, 31.0, 32.1, 32.9, 36.7, 37.6, 39.1, 40.7, 45.6, 46.8, 52.8, 60.3, 60.8, 78.7, 80.3, 93.6, 119.5, 121.3, 124.3, 131.4, 140.8, 147.4. HRMS, m/z for ($C_{30}H_{42}NO_4$) $[MH]^+$, calcd- 480.3114, found- 480.3096. Anal. ($C_{30}H_{41}NO_4 \cdot HCl \cdot 1.5H_2O$) C, H, N.

(1′R, 5α, 6R, 7R, 14α)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-2′-cyclohexyl-ethan-1′-ol (3f)

^{1}H NMR, 270 MHz ($CDCl_3$) δ 0.07-0.09 (2H, m), 0.47-0.50 (2H, m), 0.74-1.08 (6H, m), 1.12-1.45 (6H, m), 1.58-1.78 (8H, m), 1.87-2.08 (2H, m), 2.14-2.38 (4H, m), 2.61 (1H, dd, *J=4.67 and 11.96 Hz*), 2.72-2.87 (1H, m), 2.92-2.99 (2H, m) 3.48 (3H, s), 3.85 (1H, t, *J=9.64 Hz*), 4.49 (1H, s), 5.36 (1H, s), 6.48 (1H, d, *J=7.96 Hz*), 6.66 (1H, d, *J=7.96 Hz*); ^{13}C NMR, ($CDCl_3$) δ 3.2, 5.8, 6.1, 18.3, 25.0, 26.3, 26.5, 26.6, 29.5, 31.5, 32.1, 32.3, 33.6, 34.6, 35.7, 39.5, 42.4, 44.2, 45.9, 51.9, 57.9, 58.9, 71.6, 78.9, 92.0, 118.5, 120.1, 122.3, 130.2, 139.1, 145.7. HRMS, m/z for ($C_{31}H_{44}NO_4$) $[MH]^+$, calcd- 494.3270, found- 494.3253. Anal. ($C_{31}H_{43}NO_4 \cdot HCl \cdot 2H_2O$) C, H, N.

(1′R, 5α, 6R, 7R, 14α)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-3′-cyclohexyl-propan-1′-ol (3g)

^{1}H NMR, 270 MHz ($CDCl_3$) δ 0.06-0.09 (2H, m), 0.46-0.49 (2H, m), 0.64-1.06 (6H, m), 1.12-1.51 (7H, m), 1.60-1.80 (10H, m), 1.97-2.08 (1H, m), 2.14-2.39 (4H, m), 2.61 (1H, dd, *J=4.94 and 11.56 Hz*), 2.74-2.87 (1H, m), 2.92-2.99 (2H, m) 3.48 (3H, s), 3.69 (1H, t, *J=7.96 Hz*), 4.49 (1H, s), 5.33 (1H, bd), 6.48 (1H, d, *J=8.26 Hz*), 6.66 (1H, d, *J=8.26 Hz*); ^{13}C NMR, ($CDCl_3$) δ 3.4, 5.7, 6.2, 18.1, 25.1, 26.4, 26.5, 26.7, 29.6, 31.7, 31.9, 33.1, 33.8, 35.6, 37.5, 39.3, 42.5, 44.3, 46.1, 46.3, 51.7, 52.1, 58.0, 74.3, 78.9,

92.3, 118.6, 120.2, 122.2, 130.2, 139.2, 145.7. HRMS, m/z for ($C_{32}H_{46}NO_4$) $[MH]^+$, calcd- 508.3427, found- 508.3433. Anal. ($C_{32}H_{45}NO_4 \cdot HCl \cdot 3H_2O$) C, H, N.

(1′R, 5α, 6R, 7R, 14α)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-2′-phenyl-ethan-1′-ol (3h)

^{1}H NMR, 270 MHz ($CDCl_3$) δ 0.09-0.13 (2H, m), 0.48-0.53 (2H, m), 0.73-0.82 (2H, m), 1.02-1.11 (2H, m), 1.59-1.66 (3H, m), 1.82-1.88 (1H, m), 1.97-2.09 (1H, m), 2.15-2.41 (4H, m), 2.55-2.69 (2H, m), 2.90-3.08 (4H, m), 3.44 (3H, s), 4.01 (1H, t, *J=7.42 Hz*), 4.92 (1H, s), 5.41 (1H, s), 6.50 (1H, d, *J=7.99 Hz*), 6.66 (1H, d, *J=7.99 Hz*), 7.18-7.32 (5H, m); ^{13}C NMR (MeOD) δ 3.9, 5.9, 6.8, 19.4, 25.4, 30.0, 31.6, 33.0, 36.9, 40.5, 41.7, 45.6, 46.8, 52.4, 60.2, 60.7, 76.0, 79.9, 92.9, 119.5, 121.4, 124.4, 127.2, 129.2, 130.8, 131.4, 140.4, 140.8, 147.5. HRMS, m/z for ($C_{31}H_{38}NO_4$) $[MH]^+$, calcd- 488.2801, found- 488.2807. Anal. ($C_{31}H_{37}NO_4 \cdot HCl \cdot 3H_2O$) C, H, N.

Series 4 were prepared by 3-O-demethylation (General procedure C) of the products from Grignard addition to **10**.

(1′S, 5α, 6R, 7R, 14α)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-2′-methyl-propan-1′-ol (4a)

^{1}H NMR, 270 MHz ($CDCl_3$) δ 0.05- 0.09 (2H, m), 0.45-0.49 (2H, m), 0.63-0.65 (1H, m), 0.76-0.82 (1H, m), 0.91 (3H, d, *J=6.59 Hz*), 0.99 (3H, d, *J=6.59 Hz*), 1.15-1.23 (2H, m), 1.31-1.35 (1H, m), 1.58-1.82 (4H, m), 1.96-2.08 (2H, m), 2.17-2.29 (3H, m), 2.38-2.47 (1H, m), 2.57-2.62 (2H, m), 2.91 (1H, d, *J=18.44 Hz*), 3.09 (1H, d, *J=6.34 Hz*), 3.37 (3H, s), 3.66 (1H, d, *J=8.83 Hz*), 4.47 (1H, d, *J=1.64 Hz*), 6.47 (1H, d, *J=8.26 Hz*), 6.65 (1H, d, *J=8.26 Hz*); ^{13}C NMR (MeOD) δ 3.8, 6.0, 6.9, 20.1, 20.2, 20.8, 25.4, 26.1, 29.9, 33.3, 34.2, 37.3, 37.3, 45.8, 46.9, 51.1, 60.1, 61.1, 74.0, 77.2, 91.9, 119.3, 121.1, 124.5, 131.6, 140.7, 147.8. HRMS, m/z for ($C_{27}H_{38}NO_4$) $[MH]^+$, calcd- 440.2801, found- 440.2786. Anal. ($C_{27}H_{37}NO_4 \cdot HCl \cdot 1.5H_2O$) C, H, N.

(1′S, 5α, 6R, 7R, 14α)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopr opylmethyl-6,14-ethano-morphinan-7-yl)-3′-methyl-butan-1′-ol (4b)

^{1}H NMR, 270 MHz ($CDCl_3$) δ 0.08- 0.11 (2H, m), 0.47-0.51 (2H, m), 0.63-0.66 (1H, m), 0.78-0.83 (1H, m), 0.91-0.95 (6H, m), 1.09-1.22 (2H, m), 1.35-1.42 (1H, m), 1.51-1.58 (2H, m), 1.69-1.78 (4H, m), 1.98-2.05 (2H, m), 2.19-2.28 (3H, m), 2.37-2.43 (1H, m), 2.60-2.65 (2H, m), 2.91 (1H, d, *J=18.18 Hz*), 3.08 (1H, d, *J=6.34 Hz*), 3.40 (3H, s), 4.17-4.21 (1H, m), 4.43 (1H, d, *J=2.21 Hz*), 6.47 (1H, d, *J=7.96 Hz*), 6.65 (1H, d, *J=7.96 Hz*); ^{13}C NMR, ($CDCl_3$) δ 3.3, 4.6, 9.4, 20.8, 22.2, 22.7, 23.7, 24.8, 26.7, 29.3, 35.6, 36.0, 40.0, 44.1, 45.1, 46.3, 50.8, 58.4, 60.0, 66.9, 77.6, 92.5, 116.9, 119.6, 128.1, 132.6, , 137.5, 145.7. HRMS, m/z for ($C_{28}H_{40}NO_4$) $[MH]^+$, calcd- 454.2957, found- 454.2931. Anal. ($C_{28}H_{39}NO_4 \cdot HCl \cdot 2H_2O$) C, H, N.

(1′S, 5α, 6R, 7R, 14α)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-4′-methyl-pentan-1′-ol (4c)

^{1}H NMR, 270 MHz ($CDCl_3$) δ 0.05- 0.09 (2H, m), 0.47-0.51 (2H, m), 0.64-0.67 (1H, m), 0.78-0.83 (1H, m), 0.88-0.91 (6H, m), 1.13-1.24 (2H, m), 1.28-1.38 (4H, m), 1.48-1.82 (6H, m), 1.98-2.05 (1H, m), 2.18-2.30 (3H, m), 2.39-2.47 (1H, m), 2.59-2.65 (2H, m), 2.92 (1H, d, *J=18.18 Hz*), 3.09 (1H, d, *J=6.34 Hz*), 3.39 (3H, s), 4.06 (1H, bd), 4.45 (1H, s), 6.49 (1H, d, *J=7.99 Hz*), 6.66 (1H, d, *J=7.99 Hz*); ^{13}C NMR, ($CDCl_3$) δ 3.3, 4.5, 9.5, 20.8, 22.7, 22.8, 26.6, 28.2, 29.3, 33.9, 35.6, 35.8, 35.9, 39.6, 44.1, 46.3, 50.8, 52.1, 58.4, 60.0, 69.4, 76.7, 92.5, 116.8, 119.5, 128.1, 132.6, 137.5, 145.7. HRMS, m/z for ($C_{29}H_{42}NO_4$) $[MH]^+$, calcd- 468.3114, found- 468.3096. Anal. ($C_{29}H_{41}NO_4 \cdot HCl \cdot 2H_2O$) C, H, N.

(1′S, 5α, 6R, 7R, 14α)-1′-cyclopentyl-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-methanol (4d)

^{1}H NMR, 270 MHz ($CDCl_3$) δ 0.05-0.10 (2H, m), 0.45-0.49 (2H, m), 0.61-0.69 (1H, m), 0.76-0.82 (1H, m), 1.06-1.22 (3H, m), 1.28-1.43 (2H, m), 1.54-1.78 (7H, m), 1.81-1.91 (3H, m), 1.94-2.05 (2H, m), 2.12-2.33 (3H, m), 2.41-2.47 (1H, m), 2.44-2.56 (2H, m), 2.92 (1H, d, *J=18.44 Hz*), 3.13 (1H, bd), 3.38 (3H, s), 3.79 (1H, d, *J=9.91 Hz*), 4.46 (1H, d, *J=1.65 Hz*), 6.48 (1H, d, *J=7.99 Hz*), 6.66 (1H, d, *J=7.99 Hz*); ^{13}C NMR, ($CDCl_3$) δ 3.2, 4.4, 9.4, 21.1, 23.2, 25.4, 25.5, 26.3, 29.3, 29.9, 30.5, 35.7, 35.9, 38.5, 44.2, 44.9, 46.2, 50.5, 58.2, 59.9, 73.8, 76.8, 92.0, 116.8, 119.5, 128.1, 132.6, 137.5, 145.7. HRMS, m/z for ($C_{29}H_{40}NO_4$) $[MH]^+$, calcd- 466.2957, found- 466.2939. Anal. ($C_{29}H_{39}NO_4 \cdot HCl \cdot 0.5H_2O$) C, H, N.

(1′S, 5α, 6R, 7R, 14α)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-2′-cyclopentyl-ethan-1′-ol (4e)

^{1}H NMR, 270 MHz ($CDCl_3$) δ 0.05-0.10 (2H, m), 0.45-0.49 (2H, m), 0.62-0.68 (1H, m), 0.78-0.86 (1H, m), 1.06-1.21 (3H, m), 1.31-1.41 (2H, m), 1.45-1.66 (6H, m), 1.72-2.08 (8H, m), 2.18-2.27 (3H, m), 2.33-2.45 (1H, m), 2.58-2.69 (2H, m), 2.92 (1H, d, *J=18.17 Hz*), 3.09 (1H, bd), 3.40 (3H, s), 4.13-4.16 (1H, m), 4.45 (1H, s), 6.48 (1H, d, *J=8.26 Hz*), 6.66 (1H, d, *J=8.26 Hz*); ^{13}C NMR, ($CDCl_3$) δ 3.3, 4.4, 9.4, 20.8, 24.0, 25.1, 25.3, 26.7, 29.4, 32.6, 33.3, 36.0, 36.9, 39.7, 42.4, 44.1, 46.3, 48.4, 50.7, 58.4, 59.9, 68.3, 76.7, 92.4, 116.8, 119.5, 128.1, 132.6, 137.5, 145.7. HRMS, m/z for ($C_{30}H_{42}NO_4$) $[MH]^+$, calcd- 480.3114, found- 480.3086. Anal. ($C_{30}H_{41}NO_4 \cdot HCl \cdot 2H_2O$) C, H, N.

(1′S, 5α, 6R, 7R, 14α)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-3′-cyclopentyl-propan-1′-ol (4f)

^{1}H NMR, 270 MHz ($CDCl_3$) δ 0.08-0.10 (2H, m), 0.49-0.52 (2H, m), 0.62-0.68 (1H, m), 0.75-0.86 (1H, m), 1.08-1.21 (3H, m), 1.25-1.54 (9H, m), 1.59-1.73 (7H, m), 1.94-2.08 (2H, m), 2.15-2.31 (3H, m), 2.35-2.47 (1H, m), 2.57-2.69 (2H, m), 2.92 (1H, d, *J=18.17 Hz*), 3.09 (1H, bd), 3.39 (3H, s), 4.04-4.07 (1H, m), 4.45 (1H, m), 6.48 (1H, d, *J=7.99 Hz*), 6.66 (1H, d, *J=7.99 Hz*); ^{13}C NMR, ($CDCl_3$) δ 3.3, 4.2, 9.4, 20.7, 21.8, 23.3, 25.3, 25.4, 26.6, 29.3, 31.0, 32.7, 32.9, 33.1, 35.3, 39.7, 40.2, 43.8, 46.3, 50.8, 58.4, 59.9, 69.4, 77.6, 92.6, 116.8, 119.5, 128.1, 132.6, 137.5, 145.7. HRMS, m/z for ($C_{31}H_{44}NO_4$) $[MH]^+$, calcd- 494.3270, found- 494.3253. Anal. ($C_{31}H_{43}NO_4 \cdot HCl \cdot 1.5H_2O$) C, H, N.

(1′S, 5α, 6R, 7R, 14α)-1′-cyclohexyl-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-methanol (4g)

^{1}H NMR, 270 MHz ($CDCl_3$) δ 0.05-0.11 (2H, m), 0.45-0.49 (2H, m), 0.60-0.65 (1H, m), 0.72-0.82 (1H, m), 0.85-0.97 (2H, m), 1.05-1.42 (6H, m), 1.53-1.81 (7H, m), 1.92-2.07 (4H, m), 2.13-2.31 (3H, m), 2.39-2.46 (1H, m), 2.53-2.67 (2H, m), 2.90 (1H, d, *J=18.17 Hz*), 3.10 (1H, d, *J=6.05 Hz*), 3.35 (3H, s), 3.69 (1H, d, *J=8.80 Hz*), 4.45 (1H, s), 6.45 (1H, d, *J=7.99 Hz*), 6.64 (1H, d, *J=7.99 Hz*); ^{13}C NMR, ($CDCl_3$) δ 3.2, 4.1, 9.4, 20.4, 21.4, 26.1, 26.2, 26.3, 26.4, 29.3, 29.8, 29.8, 35.6, 35.9, 41.7, 43.9, 44.2, 46.1, 50.3, 58.2, 59.9, 73.0, 77.1, 91.8, 116.8, 119.5, 128.1, 132.6, 137.5, 145.7. HRMS, m/z for ($C_{30}H_{42}NO_4$) $[MH]^+$, calcd- 480.3114, found- 480.3093. Anal. ($C_{30}H_{41}NO_4 \cdot HCl \cdot 1.5H_2O$) C, H, N.

(1′S, 5α, 6R, 7R, 14α)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-2′-cyclohexyl-ethan-1′-ol (4h)

^{1}H NMR, 270 MHz ($CDCl_3$) δ 0.05-0.11 (2H, m), 0.45-0.49 (2H, m), 0.61-0.72 (1H, m), 0.74-1.02 (3H, m), 1.11-1.29 (5H, m), 1.33-1.56 (4H, m), 1.61-1.88 (8H, m), 1.96-2.07 (2H, m), 2.15-2.33 (3H, m), 2.38-2.46 (1H, m), 2.57-2.70 (2H, m), 2.92 (1H, d, *J=18.17 Hz*), 3.09 (1H, d, *J=6.31 Hz*), 3.39 (3H, s), 4.21-4.25 (1H, m), 4.44 (1H, s), 6.48 (1H, d, *J=7.96 Hz*), 6.66 (1H, d, *J=7.96 Hz*); ^{13}C NMR, ($CDCl_3$) δ 3.3, 4.4, 9.4, 20.7, 22.7, 26.3, 26.5, 26.7, 29.3, 29.8, 32.9, 34.2, 34.4, 35.9, 35.9, 40.1, 43.8, 44.1, 46.3, 50.8, 58.4, 59.9, 66.2, 77.3, 92.6, 116.8, 119.5, 128.1, 132.6, 137.5, 145.7. HRMS, m/z for ($C_{31}H_{44}NO_4$) $[MH]^+$, calcd- 494.3270, found- 494.3257. Anal. ($C_{31}H_{43}NO_4 \cdot HCl \cdot 2H_2O$) C, H, N.

(1′S, 5α, 6R, 7R, 14α)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-3′-cyclohexyl-propan-1′-ol (4i)

^{1}H NMR, 400 MHz ($CDCl_3$) δ 0.08-0.11 (2H, m), 0.46-0.51 (2H, m), 0.64-0.68 (1H, m), 0.77-0.82 (1H, m), 0.89-0.92 (2H, m), 1.13-1.28 (6H, m), 1.34-1.46 (3H, m), 1.51-1.57 (2H, m), 1.61-1.81 (10H, m), 2.00 (1H, dt, *J=7.04 and 12.64 Hz*), 2.20-2.34 (3H, m), 2.37-2.42 (1H, m), 2.61-2.68 (2H, m), 2.94 (1H, d, *J=18.24 Hz*), 3.09 (1H, d, *J=6.36 Hz*), 3.40 (3H, s), 4.02-4.04 (1H, m), 4.44 (1H, s), 6.49 (1H, d, *J=8.04 Hz*), 6.66 (1H, d, *J=8.04 Hz*); ^{13}C NMR (MeOD) δ 3.8, 5.9, 6.9, 20.6, 25.4, 26.1, 27.5, 27.6, 27.8, 30.0, 33.3, 34.5, 34.8, 35.0, 35.2, 37.2, 39.1, 40.3, 45.8, 46.9, 51.2, 60.2, 61.2, 68.8, 77.2, 92.0, 119.4, 121.1, 124.5, 131.6, 140.7, 147.8. HRMS, m/z for ($C_{32}H_{46}NO_4$) $[MH]^+$, calcd- 508.3427, found- 508.3445. Anal. ($C_{32}H_{45}NO_4$·HCl·2H_2O) C, H, N.

(1′S, 5α, 6R, 7R, 14α)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-2′-phenyl-ethan-1′-ol (4j)

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.11-0.13 (2H, d, *J*=4.8 Hz), 0.49-0.53 (2H, t, *J*=13.5 Hz), 0.64-0.70 (1H, m), 0.76-0.89 (1H, m), 1-14-1.17 (1H, m), 1.22 (1H, s), 1.29-1.43(2H, m), 1.65-1.66 (3H, m), 1.75-1.85 (3H, m), 1.98-2.05 (1H, m), 2.26-2.33 (2H, m), 2.40-2.45 (1H, dd, *J*=18.1, 5.4 Hz), 2.63-2.74 (2H, m), 2.77-2.84 (2H, m), 2.95-3.00 (1H, d, *J*=18.2 Hz), 3.12-3.13 (1H, d, *J*=6.4 Hz), 3.28 (1H, s), 4.32-4.34 (1H, m), 4.40 (1H, s), 6.50 (1H, d, *J*=8.1 Hz), 6.67 (1H, d, *J*=8.1 Hz), 7.30 (3H, m), 7.32 (2H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.2, 4.3, 9.4, 20.3, 22.5, 26.1, 29.0, 35.4, 35.8, 38.9, 42.8, 43.9, 46.1, 50.5, 58.3, 59.8, 69.9, 92.7, 116.3, 119.4, 126.5, 128.6, 129.3, 132.4, 137.1, 138.6, 145.4; HRMS (ESI^+) calcd for $C_{31}H_{38}NO_4$ (MH^+), 488.28; found 488.29. Anal. ($C_{31}H_{37}NO_4$·HCl·1.5H_2O) C, H, N.

(1′S, 5α, 6R, 7R, 14α)-1′-(4,5-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-17-cyclopropylmethyl-6,14-ethano-morphinan-7-yl)-3′-phenyl-propan-1′-ol (4k)

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08-0.09 (2H, m), 0.45-0.50 (2H, m), 0.66 (1H, m), 079 (1H, m), 1.12-1.13 (1H, m), 1.39-1.48 (1H, m), 1.52-1.57 (2H, m), 1.63-1.67 (1H, d, J= 8.0 Hz), 1.70-1.80 (4H, m), 1.90-1.99 (3H, m), 2.19-2.38 (5H, m), 2.60-2.70 (3H, m), 2.85 (1H, m), 2.93-2.98 (1H, d, *J*=18.2 Hz), 3.04-3.05 (1H, d, *J*=6.3 Hz), 3.35 (3H, s), 4.41 (1H, s), 6.49 (1H, d, *J*=8.0 Hz), 6.67 (1H, d, *J*=8.0 Hz),
7.16 (1H, m), 7.16-7.30 (4H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.2, 4.1, 9.3, 20.4, 22.6, 26.7, 29.2, 32.8, 35.5, 35.9, 37.4, 40.2, 43.8, 46.3, 50.8, 58.4, 59.8, 68.9, 93.0, 116.4, 119.4, 125.7,128.3, 132.4, 137.2, 141.9, 145.5; HRMS (ESI^+) calcd for $C_{32}H_{40}NO_4$ (MH^+), 502.30; found 502.30. Anal. ($C_{32}H_{39}NO_4$·HCl·0.5H_2O) C, H, N.

Microanalysis

Cpd	Expected			Found		
	C	H	N	C	H	N
1a: $C_{28}H_{39}NO_4$.HCl.1.6H_2O	64.8	8.30	2.70	64.5	7.96	2.60
1b: $C_{29}H_{41}NO_4$.HCl.1.5H_2O	65.5	8.47	2.63	65.0	8.22	2.55
1c: $C_{30}H_{43}NO_4$.HCl.1.5H_2O	66.0	8.62	2.57	66.0	8.40	2.53
1d: $C_{30}H_{41}NO_4$.HCl.1.5H_2O	66.3	8.28	2.58	66.1	7.98	2.50
1e:$C_{31}H_{43}NO_4$.HCl.1.5H_2O	66.7	8.43	2.51	66.2	8.19	2.42
1f: $C_{32}H_{45}NO_4$.HCl.1.5H_2O	67.2	8.58	2.45	67.2	8.38	2.37
1g: $C_{31}H_{43}NO_4$.HCl.2H_2O	65.8	8.54	2.47	65.6	8.32	2.45
1h:$C_{32}H_{45}NO_4$.HCl.H_2O	68.3	8.61	2.49	67.9	8.32	2.40
1i: $C_{33}H_{47}NO_4$.HCl.1.5H_2O	67.6	8.71	2.39	67.3	8.49	2.35
1j: $C_{32}H_{39}NO_4$.HCl.2H_2O	66.9	7.72	2.44	67.1	7.34	2.42
1k: $C_{33}H_{41}NO_4$.HCl.2H_2O	67.4	7.88	2.38	66.9	7.47	2.35
1m: $C_{30}H_{43}NO_4$.HCl.H_2O	67.2	8.65	2.61	67.5	8.70	2.37
2a: $C_{28}H_{39}NO_4$·HCl·3H_2O	61.8	8.52	2.57	61.3	8.16	2.32
2b: $C_{29}H_{41}NO_4$·HCl·3H_2O	62.4	8.67	2.51	61.9	8.23	2.28
2c: $C_{30}H_{43}NO_4$·HCl·2H_2O	65.0	8.67	2.53	64.5	8.26	2.47
2d: $C_{30}H_{41}NO_4$·HCl·3H_2O	63.2	8.49	2.46	63.7	8.01	2.28
2e: $C_{32}H_{45}NO_4$·HCl·1.5H_2O	67.2	8.58	2.45	66.7	8.41	2.36
2f: $C_{33}H_{47}NO_4$·HCl·1.5H_2O	67.7	8.71	2.39	67.3	8.60	2.27
2g: $C_{28}H_{39}NO_4$.HCl.H_2O	66.2	8.33	2.76	66.4	8.51	2.67
2h: $C_{30}H_{43}NO_4$·HCl·H_2O	67.7	8.65	2.61	67.5	8.72	2.33
2i: $C_{29}H_{41}NO_4$.HCl	69.1	8.40	2.78	69.0	8.48	2.53
3a: $C_{27}H_{37}NO_4$·HCl·2H_2O	63.3	8.27	2.74	63.6	8.07	2.35
3b: $C_{28}H_{39}NO_4$·HCl·2H_2O	63.9	8.43	2.66	63.9	8.38	2.53
3c: $C_{29}H_{41}NO_4$·HCl·3H_2O	62.4	8.11	2.47	61.9	8.11	2.47
3d: $C_{29}H_{39}NO_4$·HCl·2H_2O	64.7	8.24	2.36	64.6	7.99	2.36
3e: $C_{30}H_{41}NO_4$·HCl·1.5H_2O	66.2	8.29	2.58	65.7	8.29	2.58
3f: $C_{31}H_{43}NO_4$·HCl·2H_2O	65.8	8.55	2.47	65.6	8.51	2.25
3g: $C_{32}H_{45}NO_4$·HCl·3H_2O	64.2	8.76	2.34	63.8	8.30	2.20
3h: $C_{31}H_{37}NO_4$·HCl·3H_2O	64.4	7.67	2.42	64.0	7.35	2.19
3i: $C_{32}H_{39}NO_4$·HCl·1.5H_2O	68.0	7.61	2.48	68.2	7.47	2.28
4a: $C_{27}H_{37}NO_4$·HCl·1.5H_2O	64.4	8.15	2.78	64.2	8.10	2.75
4b: $C_{28}H_{39}NO_4$·HCl·2H_2O	63.9	8.43	2.66	63.4	8.03	2.52
4c: $C_{29}H_{41}NO_4$·HCl·2H_2O	64.5	8.58	2.59	64.5	8.27	2.57
4d: $C_{29}H_{39}NO_4$·HCl·0.5H_2O	68.1	8.02	2.74	67.7	7.91	2.68
4e: $C_{30}H_{41}NO_4$·HCl·2H_2O	65.3	8.40	2.54	64.8	8.10	2.38
4f: $C_{31}H_{43}NO_4$·HCl·1.5H_2O	66.8	8.50	2.51	66.4	8.21	2.44
4g: $C_{30}H_{41}NO_4$·HCl·1.5H_2O	65.3	8.40	2.54	65.4	7.95	2.41
4h: $C_{31}H_{43}NO_4$·HCl·2H_2O	65.7	8.55	2.47	65.4	8.22	2.28
4i: $C_{32}H_{45}NO_4$·HCl·2H_2O	66.2	8.69	2.41	65.8	8.17	2.30
4j: $C_{31}H_{37}NO_4$·HCl ·1.5H2O	67.5	7.44	2.54	67.1	7.29	2.40
4k: $C_{32}H_{39}NO_4$·HCl ·0.5H2O	70.2	7.49	2.56	70.6	7.40	2.37