Supporting Information

Cinnamoyl Derivatives of 7α-Aminomethyl-6,14-endoethanotetrahydrothebaine and 7α-Aminomethyl-6,14-endoethanotetrahydrooripavine and Related Opioid Ligands.

David Rennison, Adrian P. Neal, Gerta Cami-Kobeci, Mario D. Aceto[#]; Fernando Martinez-Bermejo, John W. Lewis, Stephen M. Husbands.*

Contents: Spectral data (including ^{1}Hnmr, ^{13}Cnmr and mass spec.) for all new compounds.

Experimental

Proton and carbon-13 nuclear magnetic resonance (n.m.r.) spectra were obtained on a JEOL JNM-GX FT 300 MHz spectrometer. Chemical shifts (δ), with tetramethylsilane as a standard, are measured in parts per million (p.p.m.) and coupling constants in Hz. Mass spectra were recorded on Fisons Autospectrometer using electron impac. Infra red (I.R.) spectra were obtained using a Perkin-Elmer 881 spectrometer. Microanalysis were obtained from a Carlo Erba EA 1108 analyser, and the results were within $\pm$0.4% of the theoretical values.

General Procedure A: Preparation of acid chlorides and the *in situ* acylation of 7α-aminomethyl-6,14-endoethanotetrahydrothebaine/oripavine.

A suspension of oxalyl chloride (8.8 eqv) and the corresponding carboxylic acid (1.1 eqv) in anhydrous toluene was heated at reflux for 1 h. The resulting solution was allowed to cool to room temperature and the solvent removed *in vacuo*. The residue was redissolved in anhydrous dichloromethane and added dropwise to a solution of 7α-aminomethyl-6,14-endo-ethanotetrahydrothebaine (1.0 eqv) and triethylamine (1.1 eqv) in anhydrous dichloromethane, and the mixture stirred at room temperature overnight. The solvent was removed *in vacuo* and the crude residue purified by column chromatography (5% CH_3OH in CH_2Cl_2). In the acylation of 7α-aminomethyl-6,14-endoethanotetrahydrooripavine, a second equivalent (2.2 eqv) of the corresponding acid chloride was used to afford the bis-acylated derivative. The crude residue was redissolved in methanol/water (9:1) before adding potassium carbonate (5.0 eqv), and the mixture stirred at room temperature overnight. The solvent was removed *in vacuo* and the crude residue purified by column chromatography (5% CH_3OH in CH_2Cl_2).

General procedure B:

EDC (2.0 eqv) was added to a stirred solution of the appropriate cinnamic acid (1.1 eqv) in dichloromethane (5 mL), followed by HOBt (0.5 eqv). The reaction mixture was stirred for 10 mins and then 7α-aminomethyl-6,14-endo-ethanotetrahydrothebaine (**11**) (1.0 eqv) was added. After 16 h the solvent was removed *in vacuo* and the crude residue purified by column chromatography (CH_2Cl_2:MeOH:NH_4OH, 200:10:1) to afford the desired amides.

General Procedure C: Two-stage reductive amination of 7α-aminomethyl-6,14-endo-ethanotetrahydrothebaine/oripavine.

To a solution of 7α-aminomethyl-6,14-endoethanotetrahydrothebaine/oripavine (1.0 eqv) in anhydrous dichloromethane was added the corresponding cinnamaldehyde (1.0 eqv) and the mixture stirred at room temperature overnight. The solvent was removed *in vacuo* and the crude residue redissolved in methanol, cooled to 0 °C and sodium borohydride (3 eqv) added slowly, with further stirring for 3 h. The reaction was quenched through the addition of hydrochloric acid (1 N), basified with concentrated ammonia and extracted with dichloromethane. The combined organic phases were washed with water, dried over anhydrous magnesium sulfate and the solvent removed *in vacuo*. The crude residue was purified by column chromatography (5% CH_3OH in CH_2Cl_2).

7α-(Aminomethyl)-6,14-endoethenotetrahydrothebaine (10)

A solution of **9** (3.38 g, 9.21 mmol) and hydroxylamine hydrochloride (1.28 g, 18.43 mmol) in ethanol/water (60 mL, 1:1) was heated at reflux for 6 h. The solvent was removed *in vacuo* and the mixture made basic with aqueous ammonia. The aqueous layer was extracted with dichloromethane and the combined organic phases washed with brine, dried over anhydrous magnesium sulfate and the solvent removed *in*

vacuo to afford the oxime intermediate as a solid (quant.), which was used without further purification. A solution of the oxime (0.2 g, 0.52 mmol) in anhydrous tetrahydrofuran (5 mL) was added to a slurry of lithium aluminium hydride (0.06 g, 1.62 mmol) in anhydrous tetrahydrofuran and the mixture heated at reflux under nitrogen overnight. The excess lithium aluminium hydride was decomposed using sodium sulphate decahydrate, the mixture filtered through celite and the solvent removed *in vacuo* to afford **10** as a white solid (1.62 g, 4.4 mmol, 48%). R_f 0.38 (CH_2Cl_2:CH_3OH, 90:10); δ_H ($CDCl_3$) 1.30 (1H, m, H-7), 2.37 (3H, s, NCH_3), 3.21 (1H, d, J = 18.5 Hz, H-10β), 3.59 (3H, s, 6-OCH_3), 3.82 (3H, s, 3-OCH_3), 4.60 (1H, d, J = 1.3 Hz, H-5), 5.44 (1H, d, J = 8.8 Hz, H-19), 5.74 (1H, d, J = 8.8 Hz, H-18), 6.52 (1H, d, J = 8.2 Hz, H-1), 6.62 (1H, d, J = 8.2 Hz, H-2); δ_C ($CDCl_3$) 22.2, 31.0, 33.3, 42.6, 43.5, 44.1, 45.5, 46.9, 52.3, 56.5, 60.0, 81.6, 94.6, 113.2, 119.1, 127.1, 128.1, 134.3, 135.6, 141.8, 148.0; IR ($CHCl_3$) 1656 (s, alkene), 1601 (s, NH) cm^{-1}; EI-MS *m/z* 368 (M+, 100%), *m/z* (High Res.) calc. for $C_{22}H_{28}N_2O_3$ 368.2099, found M+ 368.2099.

7α-(Aminomethyl)-6,14-endoethanotetrahydrothebaine (11)
A solution of **10** (0.16 g, 0.44 mmol) in ethanol (10 mL) was added to a slurry of 10% palladium-on-carbon (40% w/w) in ethanol (10 mL) and subsequently hydrogenated (40 atm) at 50 °C overnight. The mixture was then filtered through celite, the solvent removed *in vacuo* and the crude residue purified by gravity elution chromatography (CH_2Cl_2:CH_3OH:NH_4OH, 83:15:2) to afford **11** as a white foam (100 mg, 0.27 mmol, 61%). R_f 0.34 (CH_2Cl_2:CH_3OH 90:10), 0.47 (CH_2Cl_2:CH_3OH:NH_4OH, 83:15:2); δ_H ($CDCl_3$) 2.31 (3H, s, NCH_3), 3.08 (1H, d, J = 18.7 Hz, H-10β), 3.47 (3H, s, 6-OCH_3), 3.87 (3H, s, 3-OCH_3), 4.50 (1H, s, H-5), 6.58 (1H, d, J = 8.2 Hz, H-1), 6.73 (1H, d, J = 8.3 Hz, H-2), δ_C ($CDCl_3$) 17.3, 22.0, 28.8, 32.6, 34.3, 34.9, 35.6, 41.5, 43.3, 45.2, 51.9, 53.4, 56.7, 61.1, 78.3, 93.8, 114.1, 119.2, 128.2, 132.1, 141.8, 146.7; IR ($CHCl_3$) 1601 (s, NH_2) cm^{-1}; EI-MS *m/z* 370 (M+, 100%), *m/z* (High Res.) calc. for $C_{22}H_{30}N_2O_3$ 370.2256, found M+ 370.2255.

7α-[(Cinnamoyl)-aminomethyl]-6,14-endoethanotetrahydrothebaine (**5a**)
11 was treated with cinnamoyl chloride as in general procedure A to afford **5a** as a white solid (105 mg, 0.21 mmol, 70%). R_f 0.31 (CH_2Cl_2:CH_3OH, 95:5); mp 152-154 °C (oxalate); ^{1}H NMR ($CDCl_3$) δ 2.30 (3H, s, NCH_3), 3.11 (1H, d, J = 18.0 Hz, H-10β), 3.50 (3H, s, 6-OCH_3), 3.88 (3H, s, 3-OCH_3), 4.48 (1H, s, H-5), 6.36 (1H, d, J = 16.0 Hz, C*H*=CHAr), 6.58 (1H, d, J = 8.0 Hz, H-1), 6.72 (1H, d, J = 8.0 Hz, H-2), 7.36-7.49 (5H, m, ArH), 7.59 (1H, d, J = 16.0 Hz, CH=C*H*Ar); ^{13}C NMR ($CDCl_3$) δ 18.7 (CH_2), 22.3 (CH_2), 29.4 (CH_2), 33.6 (CH_2), 35.6 (CH_2), 36.0 (CH), 36.1 (C), 42.1 (CH_2), 43.9 (CH_3), 45.5 (C), 45.6 (CH_2), 51.8 (CH_3), 57.0 (CH_3), 61.7 (CH), 77.8 (C), 93.5 (CH), 113.9 (CH), 119.4 (CH), 121.3 (CH), 128.0 (CH), 128.7 (C), 128.9 (CH), 129.8 (CH), 132.6 (C), 135.1 (C), 140.9 (CH), 141.9 (C), 146.9 (C), 165.9 (C); IR ($CHCl_3$) 1658, 1621 cm^{-1}; FAB-MS *m/z* 501 (MH+, 100%); Anal. (oxalate) ($C_{33}H_{38}N_2O_8.3H_2O$) CHN.

7α-[(2'-Methylcinnamoyl)-aminomethyl]-6,14-endoethanotetrahydrothebaine (**5b**)
11 was treated with 2'-methylcinnamoyl chloride as in general procedure A to afford **5b** as a white solid (95 mg, 0.18 mmol, 51%). R_f 0.36 (CH_2Cl_2:CH_3OH, 95:5); mp 155-157 °C (oxalate); ^{1}H NMR ($CDCl_3$) δ 2.33 (3H, s, NCH_3), 2.46 (3H, s, $ArCH_3$), 3.46 (3H, s, 6-OCH_3), 3.88 (3H, s, 3-OCH_3), 4.59 (1H, s, H-5), 6.56 (1H, d, J = 16.1 Hz, C*H*=CHAr), 6.62 (1H, d, J = 8.0 Hz, H-1), 6.78 (1H, d, J = 8.0 Hz, H-2), 7.20-7.28 (2H, m, ArH), 7.60 (1H, d, J = 8.1 Hz, ArH), 7.86-7.93 (2H, m, CH=C*H*Ar, ArH); ^{13}C NMR ($CDCl_3$) δ 18.7 (CH_2), 20.3 (CH_3), 22.3 (CH_2), 29.4 (CH_2), 33.6 (CH_2), 35.6 (CH_2), 36.0 (CH), 42.1 (CH_2), 43.9 (CH_3), 45.5 (C), 45.6 (CH_2), 51.8 (CH_3), 56.9 (CH_3), 61.7 (CH), 77.8 (C), 93.4 (CH), 113.9 (CH), 199.4 (CH), 122.4 (CH), 126.2 (CH), 126.4 (CH), 128.7 (C), 129.5 (CH), 130.9 (CH), 132.6 (C), 134.1 (C), 137.6 (C),

138.7 (CH), 141.9 (C), 147.0 (C), 165.9 (C); IR ($CHCl_3$) 1657, 1620 cm^{-1}; FAB-MS *m/z* 515 (MH+, 100%); Anal. (HCl) ($C_{32}H_{39}N_2O_4Cl.\ 2H_2O$) CHN.

7α-[(2'-Chlorocinnamoyl)-aminomethyl]-6,14-endoethanotetrahydrothebaine (**5c**)
11 was treated with 2'-chlorocinnamoyl chloride as in general procedure A to afford **5c** as a white solid (168 mg, 0.31 mmol, 87%). R_f 0.33 (CH_2Cl_2:CH_3OH, 95:5); mp 155-157 °C (oxalate); ^{1}H NMR ($CDCl_3$) δ 2.32 (3H, s, NCH_3), 3.52 (3H, s, 6-OCH_3), 3.85 (3H, s, 3-OCH_3), 4.65 (1H, s, H-5), 6.55-6.68 (2H, m, C*H*=CHAr, H-1), 6.80 (1H, d, *J* = 8.0 Hz, H-2), 7.40-7.60 (5H, m, CH=C*H*Ar, ArH); ^{13}C NMR ($CDCl_3$) δ 17.5 (CH_2), 21.5 (CH_2), 28.5 (CH_2), 32.5 (CH_2), 34.5 (CH_2), 35.0 (C), 35.1 (CH), 41.5 (CH_2), 42.9 (CH_3), 44.6 (C), 44.7 (CH_2), 50.9 (CH_3), 56.0 (CH_3), 61.0 (CH), 76.9 (C), 92.7 (CH), 113.5 (CH), 118.6 (CH), 123.5 (CH), 126.4 (CH), 126.9 (C), 127.5 (CH), 129.5 (CH), 129.8 (C), 132.0 (C), 134.0 (C), 135.8 (CH), 141.0 (C), 146.0 (C), 165.0 (C); IR ($CHCl_3$) 1658, 1621 cm^{-1}; FAB-MS *m/z* 535 (MH+, 100%); Anal. (oxalate) ($C_{33}H_{37}N_2ClO_8.2H_2O$) CHN.

7α-[(4'-Methylcinnamoyl)-aminomethyl]-6,14-endoethanotetrahydrothebaine (**5d**)
11 was treated with 4'-methylcinnamoyl chloride as in general procedure A to afford **5d** as a white solid (100 mg, 0.19 mmol, 54%). R_f 0.36 (CH_2Cl_2:CH_3OH, 95:5); mp 156-158 °C (oxalate); ^{1}H NMR ($CDCl_3$) δ 2.32 (3H, s, NCH_3), 2.39 (3H, s, $ArCH_3$), 3.45 (3H, s, 6-OCH_3), 3.86 (3H, s, 3-OCH_3), 4.58 (1H, s, H-5), 6.58-6.62 (2H, m, C*H*=CHAr, H-1), 6.78 (1H, d, *J* = 8.0 Hz, H-2), 7.23 (2H, d, *J* = 8.1 Hz, ArH), 7.47 (2H, d, *J* = 8.1 Hz, ArH), 7.54 (1H, d, *J* = 16.0 Hz, CH=C*H*Ar); ^{13}C NMR ($CDCl_3$) δ 18.7 (CH_2), 21.9 (CH_3), 22.3 (CH_2), 29.4 (CH_2), 33.6 (CH_2), 35.6 (CH_2), 35.9 (CH), 36.0 (C), 42.1 (CH_2), 43.9 (CH_3), 45.5 (C), 45.6 (CH_2), 51.8 (CH_3), 56.9 (CH_3), 61.7 (CH), 77.8 (C), 93.4 (CH), 113.9 (CH), 119.3 (CH), 120.1 (CH), 127.9 (CH), 128.6 (C), 129.7 (CH), 132.3 (C), 132.6 (C), 139.9 (C), 140.8 (CH), 141.9 (C), 146.9 (C), 166.1 (C); IR ($CHCl_3$) 1657, 1620 cm^{-1}; FAB-MS *m/z* 515 (MH+, 100%); Anal. (oxalate) ($C_{34}H_{40}N_2O_8.\ 0.5CH_2Cl_2.H_2O$) CHN.

7α-[(4'-Chlorocinnamoyl)-aminomethyl]-6,14-endoethanotetrahydrothebaine (**5e**)
11 was treated with 4'-chlorocinnamoyl chloride as in general procedure A to afford **5e** as a white solid (147 mg, 0.27 mmol, 76%). R_f 0.31 (CH_2Cl_2:CH_3OH, 95:5); mp 154-156 °C (oxalate); ^{1}H NMR ($CDCl_3$) δ 2.35 (3H, s, NCH_3), 3.46 (3H, s, 6-OCH_3), 3.88 (3H, s, 3-OCH_3), 4.58 (1H, s, H-5), 6.62 (1H, d, *J* = 8.1 Hz, H-1), 6.66 (1H, d, *J* = 16.0 Hz, C*H*=CHAr), 6.78 (1H, d, *J* = 8.1 Hz, H-2), 7.42 (2H, d, *J* = 8.1 Hz, ArH), 7.54 (1H, d, *J* = 16.0 Hz, CH=C*H*Ar), 7.58 (2H, d, *J* = 8.1 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 18.6 (CH_2), 22.3 (CH_2), 29.4 (CH_2), 33.6 (CH_2), 35.6 (CH_2), 36.0 (CH), 36.2 (C), 42.1 (CH_2), 43.9 (CH_3), 45.5 (C), 45.6 (CH_2), 51.9 (CH_3), 56.9 (CH_3), 61.6 (CH), 77.8 (C), 93.6 (CH), 113.9 (CH), 119.4 (CH), 121.9 (CH), 128.7 (C), 129.1 (CH), 129.2 (CH), 132.6 (C), 133.6 (C), 135.5 (C), 139.5 (CH), 141.9 (C), 146.9 (C), 165.6 (C); IR ($CHCl_3$) 1659, 1625 cm^{-1}; FAB-MS *m/z* 535 (MH+, 100%); Anal. (oxalate) ($C_{33}H_{37}N_2ClO_8.2H_2O$) CHN.

7α-[(4'-Nitrocinnamoyl)-aminomethyl]-6,14-endoethanotetrahydrothebaine (**5f**)
11 was treated with 4'-nitrocinnamoyl chloride as in general procedure A to afford **5f** as a yellow solid (110 mg, 0.20 mmol, 53%). R_f 0.31 (CH_2Cl_2:CH_3OH, 95:5); mp 158-160 °C (oxalate); ^{1}H NMR ($CDCl_3$) δ 2.29 (3H, s, NCH_3), 3.12 (1H, d, *J* = 18.0 Hz, H-10β), 3.51 (3H, s, 6-OCH_3), 3.88 (3H, s, 3-OCH_3), 4.47 (1H, s, H-5), 6.47 (1H, d, *J* = 16.1 Hz, C*H*=CHAr), 6.60 (1H, d, *J* = 8.1 Hz, H-1), 6.73 (1H, d, *J* = 8.1 Hz, H-2), 7.63-7.69 (3H, m, CH=C*H*Ar, ArH), 8.22 (2H, d, *J* = 8.0 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 17.9 (CH_2), 21.9 (CH_2), 28.9 (CH_2), 33.1 (CH_2), 35.1 (CH_2), 35.6 (C), 35.8 (CH), 41.8 (CH_2), 43.5 (CH_3), 45.2 (CH_2), 51.7 (CH_3), 56.6 (CH_3), 61.3 (CH), 77.4 (C), 93.7 (CH), 113.7 (CH), 119.2 (CH), 124.1 (CH), 125.3 (CH), 128.3 (CH), 128.5 (C), 132.4 (C),

138.1 (CH), 141.2 (C), 141.7 (C), 146.7 (C), 148.0 (C), 164.5 (C); IR ($CHCl_3$) 1658, 1614 cm^{-1}; FAB-MS *m/z* 546 (MH+, 100%); Anal. (HCl) ($C_{31}H_{36}N_3O_6Cl.2H_2O$) CHN.

7α-[(2'-Nitrocinnamoyl)-aminomethyl]-6,14-endoethanotetrahydrothebaine (5g)

11 (133 mg, 0.36 mmol) was treated with 2-nitrocinnamic acid as in general procedure B to afford **5g** as a white solid (161 mg, 0.30 mmol, 82 %). ^{1}H NMR ($CDCl_3$): 2.28 (3H, s, NCH_3), 3.50 (3H, s, 6-OCH_3), 3.87 (3H, s, 3-OCH_3), 4.46 (1H, s, H-5), 6.28 (1H, d, *J* = 15.6 Hz, C*H*=CHAr), 6.58 (1H, d, *J* = 8.2 Hz, H-1), 6.71 (1H, d, *J* = 8.2 Hz, H-2), 7.49-7.62 (3H, m, ArH), 7.93 (1H, d, *J* = 15.6 Hz, CH=C*H*Ar), 8.01 (1H, d, *J* = 7.6 Hz, ArH). ^{13}C NMR: 17.9 (CH_2), 21.9 (CH_2), 28.9 (CH_2), 33.2 (CH_2), 35.1 (CH_2), 35.5 (C), 36.0 (CH), 41.8 (CH_2), 43.5 (CH_3), 45.1 (CH_2), 45.2 (C), 51.7 (CH_3), 56.6 (CH_3), 61.3 (CH), 77.7 (C), 93.7 (CH), 113.7 (CH), 119.1 (CH), 124.8 (CH), 126.6 (CH), 128.5 (C), 129.1 (CH), 130.0 (CH), 131.2 (C), 132.4 (C), 133.4 (CH), 135.6 (CH), 141.8 (C), 146.8 (C), 164.6 (C). FAB-MS *m/z* 546 (MH^+), $C_{31}H_{35}N_3O_6$ requires 545; FAB-HRMS calculated 546.2599 (MH^+), found 546.2575; Anal. (HCl) ($C_{31}H_{36}N_3O_6Cl.3H_2O$) CHN.

7α-[(2'-Methoxycinnamoyl)-aminomethyl]-6,14-endoethanotetrahydrothebaine (5h)

11 (104 mg, 0.28 mmol) was treated with 2-methoxycinnamic acid as in general procedure B to afford **5h** as a white solid (119 mg, 0.22 mmol, 80 %). ^{1}H NMR ($CDCl_3$): 2.27 (3H, s, NCH_3), 3.48 (3H, s, 6-OCH_3), 3.85 (3H, s, 3-OCH_3), 3.86 (3H, s, ArOCH_3), 4.48 (1H, s, H-5), 6.47 (1H, d, *J* = 15.7 Hz, C*H*=CHAr), 6.57 (1H, d, *J* = 8.2 Hz, H-1), 6.70 (1H, d, *J* = 8.2 Hz, H-2), 6.88 (1H, d, *J* = 8.4 Hz, ArH), 6.93 (1H, t, *J* = 7.6 Hz, ArH), 7.29 (1H, t, *J* = 8.4 Hz, ArH), 7.46 (1H, d, *J* = 7.6 Hz, ArH), 7.84 (1H, d, *J* = 15.7 Hz, CH=C*H*Ar). ^{13}C NMR: 18.4 (CH_2), 21.8 (CH_2), 28.9 (CH_2), 33.1 (CH_2), 35.1 (CH_2), 35.3 (CH), 35.5 (C), 41.6 (CH_2), 43.5 (CH_3), 44.9 (C), 45.2 (CH_2), 51.2 (CH_3), 55.3 (CH_3), 56.5 (CH_3), 61.3 (CH), 77.3 (C), 92.8 (CH), 111.0 (CH), 113.6 (CH), 119.1 (CH), 120.6 (CH), 122.0 (CH), 123.8 (C), 128.4 (C), 128.9 (CH), 130.6 (CH), 132.4 (C), 135.9 (CH), 141.7 (C), 146.8 (C), 158.1 (C), 166.4 (C). FAB-MS *m/z* 533 (MH^+), $C_{32}H_{40}N_2O_5$ requires 532; FAB-HRMS calculated 531.2853 (MH^+), found 531.2856; Anal. (HCl) ($C_{32}H_{39}N_2O_5Cl.0.5CH_2Cl_2$) CH, calculated N: 4.65, Found 5.16.

7α-[(4'-Methoxycinnamoyl)-aminomethyl]-6,14-endoethanotetrahydrothebaine (5i)

11 (93 mg, 0.25 mmol) was treated with 4-methoxycinnamic acid as in general procedure B to afford **5i** as a white solid (114 mg, 0.22 mmol, 88 %). ^{1}H NMR ($CDCl_3$): 2.25 (3H, s, NCH_3), 3.46 (3H, s, 6-OCH_3), 3.76 (3H, s, ArOCH_3), 3.84 (3H, s, 3-OCH_3), 4.45 (1H, s, H-5), 6.24 (1H, d, *J* = 15.7 Hz, C*H*=CHAr), 6.55 (1H, d, *J* = 8.2 Hz, H-1), 6.68 (1H, d, *J* = 8.2 Hz, H-2), 6.84 (2H, d, *J* = 8.6 Hz, ArH), 7.41 (2H, d, *J* = 8.6 Hz, ArH), 7.54 (1H, d, *J* = 15.7 Hz, CH=C*H*Ar). ^{13}C NMR: 18.3 (CH_2), 21.7 (CH_2), 28.8 (CH_2), 33.0 (CH_2), 35.1 (CH_2), 35.4 (C), 35.5 (CH), 41.5 (CH_2), 43.4 (CH_3), 44.9 (CH), 45.1 (C), 51.2 (CH_3), 55.2 (CH), 56.5 (CH_3), 61.2 (CH), 65.7 (CH_3), 77.2 (C), 92.8 (CH), 113.5 (CH), 114.1 (CH), 118.6 (CH), 119.0 (CH), 127.5 (C), 128.4 (C), 129.2 (CH), 132.3 (C), 132.3 (C), 140.1 (CH), 141.7 (C), 146.7 (C), 160.7 (C), 166.1 (C). FAB-MS *m/z* 533 (MH^+), $C_{32}H_{40}N_2O_5$ requires 532; FAB-HRMS calculated 531.2853(MH^+), found 531.2857; Anal. (HCl) ($C_{32}H_{39}N_2O_5Cl.0.5H_2O$) CHN.

7α-(Aminomethyl)-6,14-endoethanotetrahydrooripavine (12)

To a solution of **11** (0.07 g, 0.20 mmol) in anhydrous dichloromethane (8 mL) was added a solution of boron tribromide (2.6 mL, 2.6 mmol, 1M in CH_2Cl_2) and the mixture stirred at room temperature under nitrogen for 15 min. The reaction was quenched with ice/ammonium hydroxide (1:1) and stirred for a further 30 min. Following extraction with chloroform/methanol (3:1) the organic layer was washed with brine, dried over anhydrous magnesium sulfate and the solvent removed *in*

vacuo. Purification by gravity elution chromatography (CH_2Cl_2:CH_3OH:NH_4OH, 82.5:15:2.5) afforded **12** as a solid (52 mg, 0.14 mmol, 70%). R_f 0.33 (CH_2Cl_2:CH_3OH:NH_4OH, 82.5:15:2.5); δ_H ($CDCl_3$) 1.0 (1H, m, H-8), 1.41 (1H, m, H-7), 2.29 (3H, s, NCH_3), 3.08 (1H, d, J = 18.7 Hz, H-10β), 3.38 (3H, s, 6-OCH_3), 4.46 (1H, s, H-5), 6.51 (1H, d, J = 8.1 Hz, H-1), 6.68 (1H, d, J = 8.1 Hz, H-2), δ_C ($CDCl_3$) 19.1, 21.9, 29.0, 33.4, 35.1, 35.7, 37.3, 43.4, 45.0, 45.4, 50.6, 56.2, 61.4, 91.6, 117.4, 119.5, 126.7, 131.9, 138.5, 145.8; IR ($CHCl_3$) 1604 (s, NH_2) cm^{-1}; EI-MS *m/z* 356 (M+, 45%), *m/z* (High Res.) calc. for $C_{21}H_{28}N_2O_3$ 356.2099, found M+ 356.2095.

7α-[(Cinnamoyl)-aminomethyl]-6,14-endoethanotetrahydrooripavine (6a)

12 was treated with cinnamoyl chloride as in general procedure A to afford **6a** as a white solid (156 mg, 0.32 mmol, 94%). R_f 0.16 (CH_2Cl_2:CH_3OH, 95:5); mp 213-215 °C (oxalate); ^1H NMR ($CDCl_3$) δ 2.35 (3H, s, NCH_3), 3.47 (3H, s, 6-OCH_3), 4.58 (1H, s, H-5), 6.40 (1H, d, J = 16.0 Hz, C*H*=CHAr), 6.50 (1H, d, J = 8.0 Hz, H-1), 6.62 (1H, d, J = 8.0 Hz, H-2), 7.30-7.50 (5H, m, ArH), 7.54 (1H, d, J = 16.0 Hz, CH=C*H*Ar); ^{13}C NMR ($CDCl_3$) δ 18.8 (CH_2), 21.7 (CH_2), 28.6 (CH_2), 32.5 (CH_2), 34.0 (CH), 34.5 (CH_2), 35.3 (C), 40.9 (CH_2), 42.9 (CH_3), 44.6 (CH_2), 45.1 (C), 50.0 (CH_3), 61.3 (CH), 76.6 (C), 90.6 (CH), 116.8 (CH), 119.2 (CH), 120.5 (CH), 126.6 (C), 127.4 (CH), 128.5 (CH), 129.3 (CH), 131.7 (C), 134.6 (C), 137.9 (C), 140.3 (CH), 145.4 (C), 166.9 (C); IR ($CHCl_3$) 3300, 1658, 1613 cm^{-1}; FAB-MS *m/z* 487 (MH+, 100%); Anal. (oxalate) ($C_{32}H_{36}N_2O_8$. $0.5CH_2Cl_2$.H_2O) CHN.

7α-[(2'-methylcinnamoyl)-aminomethyl]-6,14-endoethanotetrahydrooripavine (6b)

12 was treated with 2'-methylcinnamoyl chloride as in general procedure A to afford **6b** as a white solid (42%). mp 208-215 °C (HCl); R_f 0.45 (CH_2Cl_2:CH_3OH:NH_4OH, 89:10:1); δ_H ($CDCl_3$) 1.15 (1H, m, H-8), 1.50 (1H, m, H-7), 2.29 (3H, s, $ArCH_3$), 2.42 (3H, s, NCH_3), 3.07 (1H, d, J = 18.9 Hz, H-10β), 3.47 (3H, s, 6-OCH_3), 4.50 (1H, s, H-5), 6.25 (1H, d, J = 15.6 Hz, C*H*=CHAr), 6.38 (1H, m, H-5'), 6.54 (1H, d, J = 8.1 Hz, H-1), 6.73 (1H, d, J = 8.1 Hz, H-2), 7.20 (2H, m, H-3'/H-4'), 7.50 (1H, m, H-6'), 7.90 (1H, d, J = 15.6 Hz, CH=C*H*Ar); δ_C ($CDCl_3$) 18.6, 19.8, 22.0, 28.9, 33.1, 34.9, 35.0, 35.7, 41.7, 43.4, 45.2, 45.3, 51.0, 61.3, 92.5, 116.7, 119.6, 121.9, 126.0, 126.1, 127.6, 129.4, 130.7, 132.1, 133.9, 137.5, 137.8, 138.7, 145.4, 166.0; IR ($CHCl_3$) 3584 (s, NH), 1654 (s, carbonyl), 1614 (s, alkene) cm^{-1}; CI-MS *m/z* 500 (MH+, 60%), *m/z* (High Res.) calc. for $C_{31}H_{36}N_2O_4$ 500.2675, found M+ 500.2662; Anal. (HCl) ($C_{31}H_{37}N_2O_4Cl.CH_3OH.0.5\ CHCl_3$) CHN

7α-[(2'-Chlorocinnamoyl)-aminomethyl]-6,14-endoethanotetrahydrooripavine (6c)

12 was treated with 2'-chlorocinnamoyl chloride as in general procedure A to afford **6c** as a white solid (68 mg, 0.13 mmol, 39%). R_f 0.22 (CH_2Cl_2:CH_3OH, 95:5); mp 188-190 °C (oxalate); ^1H NMR ($CDCl_3$) δ 2.30 (3H, s, NCH_3), 3.49 (3H, s, 6-OCH_3), 4.63 (1H, s, H-5), 6.58-6.66 (2H, m, C*H*=CHAr, H-1), 6.79 (1H, d, J = 8.0 Hz, H-2), 7.39-7.56 (5H, m, CH=C*H*Ar, ArH); ^{13}C NMR ($CDCl_3$) δ 18.3 (CH_2), 21.8 (CH_2), 28.7 (CH_2), 32.9 (CH_2), 34.8 (C), 35.0 (CH_2), 35.5 (CH), 41.5 (CH_2), 43.2 (CH_3), 48.1 (CH_2), 50.9 (CH_3), 61.1 (CH), 76.9 (C), 92.6 (CH), 116.5 (CH), 119.5 (CH), 123.7 (CH), 126.7 (CH), 127.3 (CH), 127.6 (C), 129.9 (CH), 130.2 (CH), 131.9 (C), 133.0 (C), 134.5 (C), 136.4 (C), 137.3 (CH), 145.2 (C), 165.2 (C); IR ($CHCl_3$) 3304, 1657, 1614 cm^{-1}; EI-MS *m/z* 535 (M+, 100%); Anal. (oxalate) ($C_{32}H_{35}N_2ClO_8$. $0.7CH_2Cl_2$) CHN.

7α-[(4'-Methylcinnamoyl)-aminomethyl]-6,14-endoethanotetrahydrooripavine (6d)

12 was treated with 4'-methylcinnamoyl chloride as in general procedure A to afford **6d** as a white solid (63%). mp 215-220 °C (HCl); R_f 0.44 (CH_2Cl_2:CH_3OH:NH_4OH,

89:10:1); δ_H ($CDCl_3$) 1.32 (2H, m, H-8), 1.50 (1H, m, H-7), 2.38 (3H, s, $ArCH_3$), 2.53 (3H, s, NCH_3), 3.15 (1H, d, *J* = 18.9 Hz, H-10), 3.46 (3H, s, 6-OCH_3), 4.56 (1H, s, H-5), 6.52 (1H, d, *J* = 15.8 Hz, C*H*=CHAr), 6.58 (1H, d, *J* = 8.1 Hz, H-1), 6.73 (1H, d, *J* = 8.1 Hz, H-2), 7.19 (2H, d, *J* = 8.0 Hz, H-3'/H-5'), 7.43 (2H, d, J = 8.0 Hz, H-2'/H-6'), 7.55 (1H, d, *J* = 15.8 Hz, CH=C*H*Ar); δ_C ($CDCl_3$) 19.1, 21.2, 23.0, 28.8, 32.5, 33.8, 34.1, 35.8, 41.0, 42.9, 44.4, 45.9, 50.2, 62.4, 90.3, 117.6, 119.7, 119.9, 125.2, 127.8, 129.5, 131.2, 132.2, 138.8, 140.0, 140.7, 145.9, 167.8; IR ($CHCl_3$) 3577 (w, NH), 1664 (s, carbonyl) cm^{-1}; EI-MS *m/z* 500 (M+, 100%), *m/z* (High Res.) calc. for $C_{31}H_{36}N_2O_4$ 500.2675, found M+ 500.2669. Anal. (HCl) ($C_{31}H_{37}N_2O_4Cl$.0.7 $CHCl_3$.H_2O) CHN.

7α-[(4'-Chlorocinnamoyl)-aminomethyl]-6,14-endoethanotetrahydrooripavine (**6e**)
12 was treated with 4'-chlorocinnamoyl chloride as in general procedure A to afford **6e** as a white solid (76 mg, 0.15 mmol, 43%). R_f 0.27 (CH_2Cl_2:CH_3OH, 95:5); mp 194-196 °C (oxalate); ^{1}H NMR ($CDCl_3$) δ 2.26 (3H, s, NCH_3), 3.41 (3H, s, 6-OCH_3), 4.43 (1H, s, H-5), 6.25 (1H, d, *J* = 16.0 Hz, C*H*=CHAr), 6.46 (1H, d, *J* = 8.1 Hz, H-1), 6.62 (1H, d, *J* = 8.1 Hz, H-2), 7.25 (2H, d, *J* = 8.1 Hz, ArH), 7.34 (2H, d, *J* = 8.1 Hz, ArH), 7.48 (1H, d, *J* = 16.0 Hz, CH=C*H*Ar); ^{13}C NMR ($CDCl_3$) δ 18.9 (CH_2), 22.5 (CH_2), 29.4 (CH_2), 33.6 (CH_2), 35.4 (CH_2), 35.6 (CH), 36.1 (C), 42.1 (CH_2), 43.8 (CH_3), 45.7 (CH_2), 51.5 (CH_3), 61.7 (CH), 77.7 (C), 93.0 (CH), 116.9 (CH), 119.9 (CH), 121.6 (CH), 127.9 (C), 129.1 (CH), 129.2 (CH), 132.3 (C), 133.5 (C), 135.6 (C), 137.8 (C), 139.7 (CH), 145.5 (C), 165.7 (C); IR ($CHCl_3$) 3307, 1658, 1620 cm^{-1}; EI-MS *m/z* 520 (M+, 100%); Anal. (oxalate) ($C_{32}H_{35}N_2ClO_8$.2H_2O) CHN.

7α-[(4'-Nitrocinnamoyl)-aminomethyl]-6,14-endoethanotetrahydrooripavine (**6f**)
12 was treated with 4'-nitrocinnamoyl chloride as in general procedure A to afford **6f** as a yellow solid (92 mg, 0.17 mmol, 51%). R_f 0.19 (CH_2Cl_2:CH_3OH, 95:5); mp 185-187 °C (oxalate); ^{1}H NMR ($CDCl_3$) δ 2.24 (3H, s, NCH_3), 3.05 (1H, d, *J* = 18.0 H-10β), 3.46 (3H, s, 6-OCH_3), 4.45 (1H, s, H-5), 6.45-6.53 (2H, m, C*H*=CHAr, H-1), 6.68 (1H, d, *J* = 8.0 Hz, H-2), 7.58-7.64 (3H, m, CH=C*H*Ar, ArH), 8.17 (2H, d, *J* = 8.0 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 18.5 (CH_2), 22.0 (CH_2), 29.0 (CH_2), 33.0 (CH_2), 34.1 (CH_2), 35.8 (CH), 41.3 (CH_2), 43.4 (CH_3), 45.3 (CH_2), 45.7 (C), 50.8 (CH_3), 61.5 (CH), 92.0 (CH), 117.0 (CH), 120.0 (CH), 124.1 (CH), 125.0 (CH), 127.0 (C), 128.3 (CH), 132.0 (C), 138.0 (C), 138.2 (CH), 141.0 (C), 145.5 (C), 148.0 (C), 165.0 (C); IR ($CHCl_3$) 3303, 1655, 1610 cm^{-1}; EI-MS *m/z* 500 (MH+, 100%); Anal. (HCl) ($C_{30}H_{34}N_3O_4Cl$. CH_2Cl_2) CHN.

7α-[(Cinnamyl)-aminomethyl]-6,14-endoethanotetrahydrothebaine oxalate (**7a**)
11 was treated with cinnamyl bromide as in general procedure C to afford **7a** as a white solid (107 mg, 0.22 mmol, 65%). mp 110-112 °C (oxalate); ^{1}H NMR ($CDCl_3$) δ 2.30 (3H, s, NCH_3), 3.41 (3H, s, 6-OCH_3), 3.44 (2H, m, CH_2CH=CHAr), 3.87 (3H, s, 3-OCH_3), 4.53 (1H, s, H-5), 6.32 (1H, m, CH_2C*H*=CHAr), 6.56 (1H, d, *J* = 16.1 Hz, CH_2CH=C*H*Ar), 6.58 (1H, d, *J* = 8.0 Hz, H-1), 6.71 (1H, d, *J* = 8.0 Hz, H-2), 7.19-7.39 (5H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 19.1 (CH_2), 21.8 (CH_2), 29.0 (CH_2), 33.8 (CH_2), 35.0 (CH), 35.2 (CH_2), 35.6 (C), 43.5 (CH_3), 44.8 (C), 45.2 (CH_2), 50.8 (CH_3), 51.1 (CH_2), 51.9 (CH_2), 56.5 (CH_3), 61.3 (CH), 76.7 (C), 92.1 (CH), 113.6 (CH), 118.9 (CH), 126.2 (CH), 127.3 (CH), 127.7 (CH), 128.5 (CH), 131.6 (CH), 132.4 (C), 136.9 (C), 141.7 (C), 146.9 (C); EI-MS *m/z* 486 (M+, 30%), 117 (100); Anal. (oxalate) ($C_{33}H_{40}N_2O_7$. CH_2Cl_2.H_2O) CHN.

7α-[(Cinnamyl)-aminomethyl]-6,14-endoethanotetrahydrooripavine (**8a**)
12 was treated with cinnamyl bromide as in general procedure C to afford **8a** as a white solid (109 mg, 0.23 mmol, 61%). mp 190-192 °C (oxalate); ^{1}H NMR ($CDCl_3$) δ 2.25 (3H, s, NCH_3), 3.36 (3H, s, 6-OCH_3), 3.48 (2H, m, CH_2CH=CHAr), 4.45 (1H, s,

H-5), 5.46 (1H, br s, OH), 6.29 (1H, m, CH_2CH=CHAr), 6.50 (1H, d, *J* = 16.1 Hz, CH_2CH=C*H*Ar), 6.53 (1H, d, *J* = 8.0 Hz, H-1), 6.69 (1H, d, *J* = 8.0 Hz, H-2), 7.20-7.40 (5H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 19.4 (CH_2), 21.9 (CH_2), 29.0 (CH_2), 33.8 (CH_2), 34.0 (CH), 35.1 (CH_2), 35.7 (C), 43.4 (CH_3), 44.9 (C), 45.2 (CH_2), 50.4 (CH_3), 50.5 (CH_2), 51.4 (CH_2), 61.3 (CH), 76.9 (C), 92.1 (CH), 117.4 (CH), 119.4 (CH), 126.3 (CH), 126.8 (CH), 127.0 (CH), 127.4 (C), 128.4 (CH), 131.0 (C), 132.1 (CH), 136.7 (C), 138.4 (C), 145.9 (C); EI-MS *m/z* 472 (M+, 40%), 117 (110); Anal. (oxalate) ($C_{32}H_{38}N_2O_7$. CH_2Cl_2.H_2O) CHN.

7α-[(4'-Chlorocinnamyl)-aminomethyl]-6,14-endoethanotetrahydrothebaine (**7b**)
11 was treated with 4'-chlorocinnamyl bromide as in general procedure C to afford **7b** as a white solid (94 mg, 0.18 mmol, 64%). mp 110-112 °C (oxalate); ^{1}H NMR ($CDCl_3$) δ 2.30 (3H, s, NCH_3), 3.41 (3H, s, 6-OCH_3), 3.44 (2H, m, CH_2CH=CHAr), 3.87 (3H, s, 3-OCH_3), 4.52 (1H, s, H-5), 6.30 (1H, m, CH_2CH=CHAr), 6.50 (1H, d, *J* = 16.1 Hz, CH_2CH=C*H*Ar), 6.58 (1H, d, *J* = 8.0 Hz, H-1), 6.71 (1H, d, *J* = 8.0 Hz, H-2), 7.26-7.29 (4H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 19.8 (CH_2), 22.3 (CH_2), 29.6 (CH_2), 34.4 (CH_2), 35.6 (CH), 35.7 (CH_2), 36.0 (C), 43.9 (CH_3), 45.2 (C), 45.7 (CH_2), 51.1 (CH_3), 51.8 (CH_2), 52.4 (CH_2), 56.9 (CH_3), 61.8 (CH), 77.1 (C), 92.3 (CH), 113.7 (CH), 119.2 (CH), 127.6 (CH), 128.8 (C), 128.9 (CH), 129.3 (CH), 130.1 (CH), 132.8 (C), 133.1 (C), 135.9 (C), 142.0 (C), 147.1 (C); EI-MS *m/z* 520 (M+, 60%), 151 (100); Anal. (oxalate) ($C_{33}H_{39}N_2ClO_7$. CH_2Cl_2.0.5H_2O) CHN

7α-[(4'-Chlorocinnamyl)-aminomethyl]-6,14-endoethanotetrahydrooripavine (**8b**)
12 was treated with 4'-chlorocinnamyl bromide as in general procedure C to afford **8b** as a white solid (111 mg, 0.22 mmol, 62%). mp 195-196 °C (oxalate); ^{1}H NMR ($CDCl_3$) δ ^{1}H NMR ($CDCl_3$) δ 2.23 (3H, s, NCH_3), 3.35 (3H, s, 6-OCH_3), 3.46 (2H, m, CH_2CH=CHAr), 4.47 (1H, s, H-5), 4.53 (1H, br s, OH), 6.28 (1H, m, CH_2CH=CHAr), 6.47 (1H, d, *J* = 16.1 Hz, CH_2CH=C*H*Ar), 6.51 (1H, d, *J* = 8.0 Hz, H-1), 6.69 (1H, d, *J* = 8.0 Hz, H-2), 7.24-7.27 (4H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 19.9 (CH_2), 22.4 (CH_2), 29.5 (CH_2), 34.4 (CH_2), 34.6 (CH), 35.6 (CH_2) 36.2 (C), 43.8 (CH_3), 45.4 (CH_2), 45.7 (C), 50.8 (CH_3), 51.3 (CH_2), 52.0 (CH_2), 61.7 (CH), 77.3 (C), 91.6 (CH), 117.6 (CH), 117.8 (CH), 127.2 (C), 127.7 (CH), 128.3 (CH), 128.9 (CH), 131.0 (CH), 132.3 (C), 133.2 (C), 135.6 (C), 138.5 (C), 146.0 (C); EI-MS *m/z* 506 (M+, 50%), 151 (100); Anal. (oxalate) ($C_{32}H_{37}N_2ClO_7$. CH_2Cl_2.0.5H_2O) CHN.

1'-Benzyl-2',5'-dioxo-[7α,8α:3',4']-pyrrolidino-6,14-endoethenotetrahydrothebaine (14)
A mixture of thebaine (**13**) (1.6 g, 5.1 mmol) and *N*-benzylmaleimide (1.4 g, 7.7 mmol) in toluene (30 mL) was heated at reflux for 18 h. The solvent was removed *in vacuo* to afford **14** as an orange solid (quant.), which was used without further purification. R_f 0.75 (CH_2Cl_2:CH_3OH, 90:10); δ_H ($CDCl_3$) 2.48 (3H, s, NCH_3), 3.10 (1H, d, *J* = 7.7 Hz, H-7), 3.25 (1H, d, *J* = 18.7 Hz, H-10β), 3.69 (3H, s, 6-OCH_3), 3.81 (3H, s, 3-OCH_3), 4.03 (1H, d, *J* = 6.4 Hz, H-9), 4.30 (1H, d, *J* = 7.7 Hz, H-8), 4.50 (1H, d, *J* = 14.2 Hz, CH_2Ph), 4.57 (1H, d, *J* = 14.2 Hz, CH_2Ph), 4.67 (1H, d, *J* = 1.4 Hz, H-5), 5.28 (1H, d, *J* = 8.5 Hz, H-19), 5.66 (1H, d, *J* = 8.5 Hz, H-18), 6.56 (1H, d, *J* = 8.3 Hz, H-1), 6.64 (1H, d, *J* = 8.3 Hz, H-2), 7.25 (5H, m, Ph); IR ($CHCl_3$) 1710, 1771 (s, C-20, -22 carbonyls), 1633 (alkene) cm^{-1}; δ_C ($CDCl_3$) 22.5, 33.3, 41.3, 41.5, 42.6, 43.1, 44.9, 45.2, 47.7, 51.5, 56.3, 57.1, 80.6, 90.5, 113.6, 119.9, 127.6, 127.8, 128.3, 129.1, 132.4, 133.1, 134.1, 135.6, 142.1, 147.8, 173.7, 176.9; EI-MS *m/z* 498 (M+, 50%).

1'-Benzyl-[7α,8α:3',4']-pyrrolidino-6,14-endoethenotetrahydrothebaine (15)
To a slurry of lithium aluminium hydride (0.58 g, 15.43 mmol) in anhydrous tetrahydrofuran (10 mL) at room temperature under nitrogen was added **14** (2.16 g,

4.34 mmol) in anhydrous tetrahydrofuran (20 mL), and the suspension heated at reflux for 16 h. The mixture was then filtered through celite and the solvent removed *in vacuo*. The residue was then purified by gravity elution chromatography (CH_2Cl_2:CH_3OH, 97:3) to afford **15** as a white foam (1.52 g, 3.23 mmol, 74%). R_f 0.57 (CH_2Cl_2:CH_3OH, 90:10) 0.78 (CH_2Cl_2:CH_3OH:NH_3, 82.5:15:2.5); δ_H ($CDCl_3$) 2.32 (3H, s, NCH_3), 3.0 (2H, m, H-16), 3.07 (1H, d, *J* = 6.3 Hz, H-9), 3.19 (1H, d, *J* = 18.7 Hz, H-10β), 3.49 (3H, s, 6-OCH_3), 3.65 (2H, m, CH_2Ph), 3.82 (3H, s, 3-OCH_3), 4.62 (1H, d, *J* = 1.3 Hz, H-5), 5.33 (1H, dd, *J* = 8.6 and 1.0 Hz, H-19), 5.76 (1H, d, *J* = 8.6 Hz, H-18), 6.52 (1H, d, *J* = 8.2 Hz, H-1), 6.62 (1H, d, *J* = 8.2 Hz, H-2), 7.28 (5H, m, PhH); δ_C ($CDCl_3$) 20.1, 32.8, 41.3, 42.3, 43.6, 44.5, 45.3, 48.4, 51.4, 56.4, 56.6, 58.8, 60.4, 81.7, 93.1, 112.9, 119.1, 126.9, 127.8, 128.2, 128.7, 130.3, 134.3, 135.4, 139.0, 141.9, 147.9; IR ($CHCl_3$) 1633 (C=C) cm^{-1}; EI-MS *m/z* 470 (M+, 85%), *m/z* (High Res.) calc. for $C_{30}H_{34}N_2O_3$ 470.2569, found 470.2578.

[7α,8α:3',4']-Pyrrolidino-6,14-endoethenotetrahydrothebaine (16)
To a solution of **15** (1.41 g, 3.0 mmol) in ethanol (10 mL) was added concentrated hydrochloric acid (0.62 mL, 7.52 mmol) and 10% palladium-on-carbon (40% w/w) and the mixture hydrogenated (40 psi) at room temperature for 5 d. The mixture was then filtered through celite and the solvent removed *in vacuo* to afford **16** as a white solid (0.24 g, 0.64 mmol, 22%); with 63% recovery of starting material. R_f 0.44 (CH_2Cl_2:CH_3OH:NH_4OH, 82.5:15:2.5); δ_H ($CDCl_3$) 1.85 (1H, m, H-8), 2.12 (1H, m, H-7), 2.36 (3H, s, NCH_3), 3.53 (3H, s, 6-OCH_3), 3.82 (3H, s, 3-OCH_3), 4.60 (1H, d, *J* = 1.3 Hz, H-5), 5.37 (1H, d, *J* = 8.8 Hz, H-19), 5.84 (1H, d, *J* = 8.8 Hz, H-18), 6.53 (1H, d, *J* = 8.2 Hz, H-1), 6.63 (1H, d, *J* = 8.2 Hz, H-2); δ_C ($CDCl_3$) 22.2, 32.8, 42.1, 43.6, 43.8, 44.8, 45.3, 48.5, 48.8, 49.2, 51.8, 56.4, 58.9, 81.3, 93.2, 113.2, 119.3, 127.7, 130.7, 133.7, 134.8, 142.0, 147.9; IR ($CHCl_3$) 3602 (s, NH), 1602 (s, alkene) cm^{-1}; EI-MS *m/z* 380 (M+, 100%), m/z (High Res.) calc. for $C_{23}H_{28}N_2O_3$ 380.2099, found 380.2100.

[7α,8α:3',4']-Pyrrolidino-6,14-endoethenotetrahydrooripavine (17)
To a solution of **16** (0.07 g, 0.15 mmol) in anhydrous dichloromethane (6 mL) at room temperature under nitrogen was added a solution of boron tribromide (2.0 mL, 2.0 mmol, 1M in CH_2Cl_2) and the mixture stirred for 15 min. The mixture was then quenched with ice/ammonia (50:50) and stirred for further 30 min. The organic layer was extracted with dichloromethane/methanol (3:1), the combined organic phases washed with brine, dried over anhydrous magnesium sulphate and the solvent removed *in vacuo*. The crude residue was then purified by gravity elution chromatography (CH_2Cl_2:CH_3OH:NH_4OH, 82.5:15:2.5) to afford **17** as a light brown foam (40 mg, 0.11 mmol, 72%). R_f 0.30 (CH_2Cl_2:CH_3OH:NH_4OH, 82.5:15:2.5); δ_H ($CDCl_3$) 1.85 (1H, m, H-8), 2.12 (1H, m, H-7), 2.38 (3H, s, NCH_3), 3.24 (1H, d, *J* = 18.9 Hz, H-10β), 3.52 (3H, s, 6-OCH_3), 3.82 (3H, s, 3-OCH_3), 4.60 (1H, d, *J* = 1.3 Hz, H-5), 5.37 (1H, d, *J* = 8.8 Hz, H-19), 5.75 (1H, d, *J* = 8.8 Hz, H-18), 6.53 (1H, d, *J* = 8.2 Hz, H-1), 6.59 (1H, d, *J* = 8.2 Hz, H-2); δ_C ($CDCl_3$) 22.3, 32.6, 42.6, 43.4, 44.0, 44.9, 45.5, 49.3, 51.2, 54.2, 59.1, 81.5, 92.3, 116.8, 119.7, 126.4, 129.2, 133.5, 135.0, 138.5, 146.8; IR ($CHCl_3$) 3573 (s, NH), 1604 (s, alkene) cm^{-1}; EI-MS *m/z* 366 (M+, 100%), *m/z* (High Res.) calc. for $C_{22}H_{26}N_2O_3$ 366.1943, found 366.1936.

1'-(o-Methylcinnamoyl)-[7α,8α:3',4']-pyrrolidino-6,14-endoethenotetrahydrooripavine (18a)
17 was treated as in general procedure A with purification by gravity elution chromatography (CH_2Cl_2:CH_3OH:NH_4OH, 94:5:1) and preparative thin layer chromatography (EtOAc:NH_4OH 99:1) affording **18a** as a white solid (160 mg, 0.31 mmol, 47%). mp >250 °C (HCl); R_f 0.47 (CH_2Cl_2:CH_3OH:NH_4OH, 89:10:1); δ_H ($CDCl_3$) 1.85 (1H, m, H-8), 2.25 (1H, m, H-7), 2.36 (3H, s, ArCH_3), 2.40 (3H, s,

NCH_3), 3.55 (3H, s, 6-OCH_3), 4.60 (1H, d, *J* = 1.3 Hz, H-5), 5.35 (1H, d, *J* = 8.8 Hz, H-19), 5.75 (1H, d, *J* = 8.8 Hz, H-18), 6.38 (1H, d, *J* = 15.5 Hz, C*H*=CHAr), 6.48 (1H, d, *J* = 8.1 Hz, H-1), 6.64 (1H, d, *J* = 8.1 Hz, H-2), 7.20 (3H, m, H-3'/H-4'/H-5'), 7.50 (1H, m, H-6'), 7.95 (1H, d, *J* = 15.5 Hz, CH=C*H*Ar); δ_C ($CDCl_3$) 19.8, 22.4, 32.8, 38.7, 41.0, 43.5, 45.4, 48.1, 48.7, 51.5, 52.0, 58.8, 81.1, 93.0, 116.6, 119.7, 120.6, 126.0, 127.0, 128.1, 129.4, 130.6, 133.5, 134.0, 135.0, 137.6, 138.1, 139.9, 140.3, 146.4, 164.5; IR ($CHCl_3$) 1645 (s, carbonyl), 1602 (s, alkene) cm^{-1}; CI-MS *m/z* 511 (MH+, 50%). Anal. (HCl) ($C_{32}H_{35}N_2O_4Cl.0.3\ CHCl_3.3\ H_2O$) CHN.

1'-(p-Methylcinnamoyl)-[7α,8α:3',4']-pyrrolidino-6,14-endoethenotetrahydrooripavine (18b)

17 was treated as in general procedure A with purification by gravity elution chromatography (CH_2Cl_2:CH_3OH:NH_4OH, 94:5:1) and preparative thin layer chromatography (CH_2Cl_2:CH_3OH:NH_4OH, 94:5:1) affording **18b** as a white solid (90 mg, 0.18 mmol, 43%). mp >250 °C (HCl); R_f 0.45 (CH_3OH:CH_2Cl_2:NH_4OH, 10:89:1); δ_H ($CDCl_3$) 1.85 (1H, m, H-8), 2.25 (1H, m, H-7), 2.35 (3H, s, $ArCH_3$), 2.41 (3H, s, NCH_3), 3.55 (3H, s, 6-OCH_3), 4.61 (1H, s, H-5), 5.35 (1H, d, *J* = 9.0 Hz, H-19), 5.75 (1H, d, *J* = 9.0 Hz, H-18), 6.48 (1H, d, *J* = 8.1 Hz, H-1), 6.64 (2H, m, C*H*=CHAr, H-2), 7.15 (2H, d, *J* = 8.0 Hz, H-3'/H-5'), 7.41 (2H, d, *J* = 8.0 Hz, H-2'/H-6'), 7.60 (1H, d, *J* = 15.6 Hz, CH=C*H*Ar); δ_C ($CDCl_3$) 21.3, 22.4, 30.8, 38.7, 43.4, 45.5, 48.1, 48.7, 52.0, 58.7, 81.1, 92.5, 116.6, 117.1, 119.8, 127.8, 128.1, 129.4, 132.3, 137.9, 139.8, 142.0, 164.5; IR ($CHCl_3$) 1646 (s, carbonyl), 1603 (s, alkene) cm^{-1}; CI-MS *m/z* 511 (MH+, 100%). Anal. (HCl) ($C_{32}H_{35}N_2O_4Cl.\cdot CHCl_3\cdot 0.25\ H_2O$) CHN.

Microanalysis

C'pd	Calculated C	H	N	Found C	H	N
5a.oxalate.3H_2O	61.5	6.8	4.3	61.4	6.9	4.1
5b.HCl.2H_2O	65.4	7.15	4.77	65.0	7.05	4.89
5c.oxalate.2H_2O	60.0	6.2	4.2	59.8	5.8	4.1
5d.oxalate.0.5CH_2Cl_2.H_2O	62.3	6.47	4.21	62.4	6.32	4.09
5e.oxalate.2H_2O	60.0	6.2	4.2	60.2	5.8	4.2
5f.HCl.2H_2O	59.6	6.13	6.95	59.3	6.35	7.05
5g.HCl.3H_2O	58.5	6.60	6.60	58.2	6.34	6.76
5h.HCl.0.5CH_2Cl_2	63.4	6.50	4.65	63.1	6.67	5.16
5i.HCl.0.5H_2O	66.7	6.77	4.86	66.5	6.97	4.70
6a.oxalate.0.5CH_2Cl_2.H_2O	61.2	6.12	4.40	61.2	5.97	4.24
6b.HCl.H_2O	67.0	6.85	5.04	66.8	7.01	5.18
6c.oxalate.0.7CH_2Cl_2	58.6	5.43	4.18	58.8	5.61	4.16
6d.HCl.0.75CH_2Cl_2.0.25H_2O	62.9	6.44	4.63	63.3	6.24	4.28
6e.oxalate.2H_2O	59.3	6.03	4.33	59.7	5.87	4.43
6f.HCl.CH_2Cl_2	57.0	5.51	6.43	57.4	5.49	6.32
7a.oxalate.CH_2Cl_2.H_2O	60.1	6.48	4.12	60.5	6.21	4.12
7b.oxalate.CH_2Cl_2.0.5H_2O	57.9	5.96	3.97	57.8	5.85	3.97
8a.oxalate.CH_2Cl_2.H_2O	59.5	6.32	4.21	59.7	6.12	4.21
8b.oxalate.CH_2Cl_2.0.5H_2O	57.3	5.79	4.06	57.5	5.74	4.07
18a.HCl.0.5CH_2Cl_2.2H_2O	62.1	6.90	4.60	61.9	6.84	4.28
18b.HCl.0.75CH_2Cl_2	59.9	6.68	4.40	60.1	6.51	4.11