Supplementary Material (ESI) for Organic and Biomolecular Chemistry

Suplementary experimental data for

Synthetic approaches to the polycyclic alkaloid stemofoline

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General

Melting points were recorded on a Koffler heated stage microscope. Proton NMR spectra were recorded in deuteriated chloroform, unless otherwise indicated, on Bruker AC300, Varian XL300 and Varian Unity 500 spectrometers; coupling constants are given in Hz and chemical shifts relative to Me_4Si. IR spectra were recorded on a Perkin Elmer 1710FT spectrometer and were run as evaporated films. Mass spectra were measured on a Kratos MS20 and MS25 spectrometers.

Chromatography refers to flash chromatography using Merck silica gel 60H (40 – 63 mm^3, 230-400 mesh). Light petroleum refers to the fraction boiling at 40 – 60 ^oC and ether to diethyl ether. All solvents and reagents were purified by standard techniques before use. All non-aqueous reactions were performed under an atmosphere of dry argon or nitrogen.

_N_-(2-Methylprop-2-yloxycarbonyl)-5-prop-2-enylpyrrolidin-2-one 8

5-Prop-2-enylpyrrolidin-2-one **7** (25.3 g, 202 mmol),[1] di-*tert*-butyl dicarbonate (89.4 g, 404 mmol), 4-(*N*,*N*-dimethylamino)pyridine (2.48 g, 20.2 mmol) and triethylamine (31.0 cm^3, 242 mmol) were stirred in dichloromethane (400 cm^3) at ambient temperature for 12 h. The reaction mixture was concentrated under reduced pressure and the residue suspended in ether. The suspension was filtered through a plug of silica and the product eluted with ether. The filtrate was treated with decolourising charcoal, filtered through celite and concentrated under reduced pressure to give a mobile, pale yellow oil (52.7 g). The oil was taken up in toluene and concentrated under reduced pressure three times, affording the *title compound* **8** as a yellow oil (35.0 g, 76 %) (Found: M^++H, 226.1445. $C_{12}H_{20}NO_3$ requires *M*, 226.1443); υ_{max} (EF) 1787, 1751, 1713, 1600, 1310, 1152 and 1021 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.49 [9 H, s, $C(CH_3)_3$], 1.80 (l H, m, 4-H), 2.05 (l H, m, 4-H'), 2.23-2.62 (4 H, m, 3-H_2 and 1'-CH_2), 4.18 (l H, m, 5-H), 5.12-5.22 (2 H, m, 3'-CH_2) and 5.72 (l H, m, 2'-CH); *m/z* CI(NH_3) 243 (M+18, 7%), 226 (M+1, 15) and 126 (100).

4-[*N*-(2-Methylprop-2-yloxycarbonyl)amino]undec-l-en-7-one 9

Freshly prepared butylmagnesium bromide in tetrahydrofuran (40.0 cm^3, 64.4 mmol) was added via a cannula to a stirred solution of pyrrolidinone **8** (10.0 g, 46 mmol) in tetrahydrofuran (50.0 cm^3) at -20 °C. The reaction mixture was stirred at -20 °C for 2.5 h then warmed to ambient temperature over 1 h. After cooling to 0 °C, saturated aqueous ammonium chloride was added slowly and the organic phase diluted with ether. The aqueous phase was extracted with ether and the combined organic extracts washed with water and dried ($MgSO_4$). 'Amberlite' resin IR-120 (H) acidic ion exchange resin (5.0 g) was added and the suspension stirred for 2 h. The resin was removed by filtration and the filtrate dried ($MgSO_4$). Concentration under reduced pressure afforded the *title compound* **9** as a pale green oil (11.4 g, 91 %). υ_{max} 3357, 1712, 1520,1360 and 1173 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.91 (3 H, t, *J* 7.5, 11-H_3), 1.22-1.39 (2 H, m, 10-H_2), 1.42 [9 H, s, $C(CH_3)_3$], 1.47-1.67 (3 H, m, 9-H_2 and 5-H), 1.78 (1-H, m, 5-H'), 2.12-2.30 (2 H, m, 3-H_2), 2.39 (2 H, t, *J* 7.5, 8-H_2), 2.47 (2 H, t, *J* 7.5, 6-H_2), 3.59 (1 H, m, 4-H), 4.34 (1 H, br d, *J* 12, NH) , 5.05-5.16 (2 H, m, 1-H_2) and 5.78 (1 H, m, 2-H); *m/z* CI(NH_3) 284 (M+1, 9%), 229 (14), 228 (100), 184 (51),166 (80) and 142 (64).

4-[*N*-(2-Methylprop-2-yloxycarbonyl)amino]-7,7-ethylenedioxyundec-l-ene 10

The ketone **9** (36.4 g, 130 mmol), ethylene glycol (40.0 g, 650 mmol) and pyridinium tosylate (3.23 g, 13.0 mmol) were heated under reflux in benzene (400 cm^3) under a Dean Stark trap for 60 h. The reaction mixture was concentrated under reduced pressure and the residue taken up in ether. The resulting solution was washed with saturated aqueous sodium bicarbonate, water and brine then dried ($MgSO_4$). Concentration under reduced pressure and chromatography of the residue using hexane : ether (70 : 30) afforded the *title compound* **10** as a pale yellow oil (25.5 g, 81 %) (Found: M^++H, 328.2482, $C_{18}H_{34}NO_4$ requires *M*, 328.2488); υ_{max} 3252, 1698, 1519, 1366 and 1172 cm^{-1}; δ_H (300 MHz, C_6D_6) 0.95 (3 H, t, *J* 7.5, 11-H_3), 1.27-1.57 (2 H, m, 10-H_2), 1.55 [9 H, s, $C(CH_3)_3$], 1.57-1.88 (8 H, m, 5-H_2, 6-H_2, 8-H_2 and 9-H_2), 1.95-2.23 (2 H, m, 3-H_2), 3.63 (4 H, s, OCH_2CH_2O), 3.87 (l H, m, 4-H), 4.30 (l H, m, NH), 5.00- 5.09 (2 H, m, 1-H_2) and 5.76 (l H, m, 2-H); *m/z* CI(NH_3) 328 (M^++1, 8%), 228 (80), 166 (100) and 129 (44).

3-[*N*-(2-Methylprop-2-yloxycarbonyl)amino]-6,6-ethylenedioxydecanal 11

A solution of the undecene **10** (15.0 g, 45.9 mmol) in dry methanol (1500 cm^3) was stirred at -78 °C and ozone passed through the solution until a persistent blue colour was observed. Oxygen was then passed through the solution until the blue colour dispersed. Triphenylphosphine (14.4 g, 486 mmol) was added and the reaction mixture was allowed to warm to ambient temperature over 3 h then concentrated under

reduced pressure. The residue was triturated with hexane and filtered through a plug of celite to remove the solid residue. The filtrate was concentrated under reduced pressure and chromatography of the residue using light petroleum : ethyl acetate (50 : 50) as eluent afforded the *title compound* **11** as a colourless oil (13.7 g, 90 %). (Found: M^++H, 330.2273. $C_{17}H_{32}NO_5$ requires *M*, 330.2280); υ_{max} 3349, 1713,1412, 1252, 1171 and 1076 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.94-1.04 (3 H, t, *J* 7.5,10-H_3), 1.30-1.40 (2 H, m, 9-H_2), 1.40-1.80 (8 H, m, 4-H_2, 5-H_2, 7-H_2 and 8-H_2), 1.45 [9 H, s, $C(CH_3)_3$], 2.55 (2 H, m, 2-H_2), 3.58 (4 H, s, OCH_2CH_2O), 4.06 (l H, m, 3-H), 4.50 (1 H, br d, *J* 9.5, NH) and 9.42 (l H, t, *J* 2, CHO); *m/z* CI(NH_3) 330 (M^++1, 12%), 274 (22), 260 (26), 256 (19), 242 (100), 230 (63), 198 (49),168 (91) and 129 (68).

Methyl 5-[*N*-(2-methylpropyloxycarbonyl)amino]-8,8-ethylenedioxy-3-hydroxydodecanoate 12

Butyllithium (86.5 cm^3,1.6 M in hexanes, 58.3 mmol) was added to a solution of diisopropylamine (8.76 cm^3, 62.5 mmol) in tetrahydrofuran (170 cm^3) at 0 °C via a cannula. The resulting solution was stirred at 0 °C for 15 min and then cooled to -78 °C. Methyl acetate (4.30 cm^3, 54.2 mmol) was added dropwise and the mixture stirred for a further 1 h. A precooled solution of the aldehyde **11** (13.7 g, 41.7 mmol) in tetrahydrofuran (85.0 cm^3) was added via a cannula and the reaction mixture was stirred for 1 h at -78 °C then allowed to warm to ambient temperature over 1 h. Saturated aqueous ammonium chloride was added and the organic phase was washed with water and brine then dried ($MgSO_4$) and concentrated under reduced pressure. The residue was filtered through a silica plug using light petroleum : ethyl acetate (35:65) as eluent and concentration of the filtrate under reduced pressure afforded a 1 : 1 mixture of diastereoisomers of the *title compound* **12** as a yellow oil (15.9 g, 95 %). Chromatography of small portion of the mixture using light petroleum : ethyl acetate (65:35) as eluent separated the two diastereoisomers for characterisation. Less polar diastereoisomer (Found: M^+-MeO, 372.2397. $C_{19}H_{34}NO_6$ requires *M*, 372.2386); υ_{max} 3355br, 1740, 1685, 1526, 1367, 1252, 1170 and 1081 cm^{-1}; δ_H (200 MHz, C_6D_6) 0.98 (3 H, t, *J* 7.5, 12-H_3), 1.19-1.82 (12 H, m, 4-H_2, 6-H_2, 7-H_2, 9-H_2, 10-H_2 and 11-H_2), 1.47 [9 H, s, $C(CH_3)_3$], 2.31 (1 H, dd, *J* 15, 4.5, 2-H), 2.63 (l H, dd, *J* 15, 8, 2-H), 3.41 (3 H, s, OCH_3), 3.60 (4 H, s, OCH_2CH_2O), 3.96 (l H, m, 5-H), 4.29 (l H, m, 3-H), 4.57 (l H, br d, *J* 3.5, OH) and 4.70 (l H, br d, *J* 9, NH); δ_C (50 MHz, C_6D_6) 16.5, 25.3, 28.4, 30.4, 31.8, 36.2, 39.5, 44.0, 46.0, 50.2, 53.2, 67.0, 67.1, 81.2, 113.5, 159.3 and 174.1; *m/z* CI(NH_3) 404 (M^++H, 0.7%), 372 (7.5), 342 (67) and 242 (100). More polar diastereoisomer (Found: M^++H-$(CH_2OH)_2$, 342.2265. $C_{18}H_{32}NO_5$ requires *M*, 342.2280); υ_{max} 3359br, 1745, 1715, 1693, 1524, 1367, 1252 and 1171 cm^{-1}; δ_H (200 MHz, C_6D_6) 0.95 (3 H, t, *J* 7.5, 12-H_3), 1.25-1.86 (12 H, m, 4-H_2, 6-H_2, 7-H_2, 9-H_2, 10-H_2 and 11-H_2), 1.59 [9 H, s,

$C(CH_3)_3$], 2.43 (l H, dd, *J* 15, 9, 2-H), 2.56 (1 H, dd, *J* 15, 5, 2-H), 3.37 (3 H, s, OCH_3), 3.64 (4 H, br s, OCH_2CH_2O), 3.73 (l H, br s, OH), 3.85 (1 H, m, 5-H), 4.23 (1 H, m, 3-H) and 4.72 (1 H, br d, *J* 10, NH); δ_C (50 MHz, C_6D_6) 16.39, 25.43, 28.42, 30.56, 32.11, 35.61, 39.48, 43.67, 44.86, 50.82, 53.16, 66.94, 68.40, 80.71, 113.73, 158.05 and174.76; *m/z* CI(NH_3) 342 (M^+-63, 20%), 268 (16) and 242 (77).

7-[*N*-(2-Methylpropyloxycarbonyl)amino]-4-ethoxycarbonyl-10,10-ethylenedioxy-5-hydroxy-tetradec-1-ene 13

Ethyl pent-4-enoate (2.78 cm^3, 19.5 mmol) was added dropwise to lithium diisopropylamide (13.6 cm^3, 1.5 M in hexanes, 20.4 rnmol) in tetrahydrofuran (40.0 cm^3) at 0 °C and the mixture stirred for 20 min before being cooled to -78 °C and added via a cannula to a precooled (-78 °C) solution of the aldehyde **11** (3.03 g, 9.21 mmol) in tetrahydrofuran (50 cm^3). The reaction mixture was allowed to warm to ambient temperature over a period of 3 h and saturated aqueous ammonium chloride (100 cm^3) was added. The organic phase was washed with water and brine then dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue using toluene : ethyl acetate (60 : 40) as eluent, gave the *title compound* **13** as a mixture of diastereoisomers (3.88 g, 92 %). Further chromatography using eluent toluene : ethyl acetate (80 : 20) as eluent achieved a partial separation of the four diastereoisomers for characterisation; the first isomer of the column (Found: M^++H, 458.3117. $C_{24}H_{44}NO_7$ requires *M*, 458.3118); υ_{max} 3360, 1728, 1715, 1680, 1365, 1250 and 1170 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.84 (3 H, t, *J* 8, 14-H_2), 1.19 (3 H, *t*, *J* 8, OCH_2CH_3), 1.19-1.30 (6 H, m), 1.41 [9 H, s, $C(CH_3)_3$], 1.44-1.69 (6 H, m), 2.30-2.57 (3 H, m, 3-H_2 and 4-H), 3.60-3.76 (2 H, m, 5-H and 7-H), 3.85 (4 H, s, OCH_2CH_2O), 4.06 (2 H, m, OCH_2CH_3), 4.25 (1 H, br d, *J* 5, OH), 4.57 (1 H, br d, *J* 12.5, NH), 4.87-5.02 (2 H, m, 1-H_2) and 5.61-5.79 (l H, m, 2-H); m/z (+FAB) 404 (75%) and 129 (100): the second isomer off the column (Found: M^++H, 458.3111. $C_{24}H_{44}NO_7$ requires *M*, 458.3118); υ_{max} 3348, 1740, 1684, 1365, 1250 and 1170 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.90 (3 H, t, *J* 8, 14-H), 1.26 (3 H, t, *J* 8, OCH_2CH_3),1.27-1.38 (6 H, m), 1.44 [9 H, s, $C(CH_3)_3$], 1.52-1.67 (4 H, m) 1.67-1.78 (2 H, m), 2.30-2.40 (2 H, m, 3-H_2), 2.52 (l H, q, *J* 8, 4-H), 3.68-3.89 (2 H, m, 7-H and 5-H), 3.93 (4 H, s, OCH_2CH_2O), 4.08 (1 H, br d, *J* 5, OH), 4.16 (2 H, q, *J* 8, OCH_2CH_3), 4.63 (1 H, br d, *J* 12.5, NH), 4.96-5.13 (2 H, m, 1-H_2) and 5.65-5.81 (1 H, m, 2-H); *m/z* (+FAB) 404 (16%): the third isomer off the column (Found: M^++H, 458.3125. $C_{24}H_{44}NO_7$, requires *M*, 458.3118); υ_{max} 3364, 1749, 1718, 1685, 1365, 1250 and 1170 cm^{-1}; δ_H (300 MHz, $CDC1_3$) 0.83 (3 H, t, *J* 8, 14-H_3), 1.20 (3 H, t, *J* 8, OCH_2CH_3), 1.16-1.31 (6 H, m), 1.37 [9 H, s, $C(CH_3)_3$], 1.31-1.46 (2 H, m, 6-H_2), 1.46-1.67 (4 H, m), 2.27-2.58 (3 H, m, 3-H_2, 4-H), 3.59 (1 H, m, 7-H), 3.86 (5 H, br s, OCH_2CH_2O and OH), 3.79-3.90 (1 H, m, 5-H), 4.08 (2 H, q, *J* 8, OCH_2CH_3),

4.67 (1 H, br d, *J* 12.5, NH), 4.90-5.07 (2 H, m, 1-H_2) and 5.7 (1 H, m, 2-H); *m/z* (+FAB) 404 (15%) and 129 (34): the fourth isomer off the column (Found: M^++H, 458.3121. $C_{24}H_{44}NO_7$ requires *M*, 458.3118); υ_{max} 3360, 1720, 1695, 1365, 1250 and 1170 cm^{-1}; δ_H (300MHz, $CDCl_3$) 0.87 (3 H, t, *J* 8, 14-H_3), 1.26 (3 H, t, *J* 8, OCH_2CH_3), 1.22-1.37 (6 H, m), 1.42 [9 H, s, $C(CH_3)_3$], 1.47-1.72 (6 H, m), 2.28-2.51 (2 H, m, 3-H_2), 2.60 (1 H, m, 4-H), 3.10 (1 H, br s, OH), 3.66 (1 H, m, 7-H), 3.77 (1 H, m, 5-H), 3.91 (4 H, s, OCH_2CH_2O), 4.13 (2 H, q, *J* 8, OCH_2CH_3), 4.67 (1 H, br d, *J* 12.5, NH), 4.95-5.12 (2 H, m, 1-H_2) and 5.65-5.78 (1 H, m, 2-H); *m/z* (+FAB) 404 (15%) and 296 (7).

Methyl 5-[*N*-(2-methylpropyloxycarbonyl)amino]-8,8-ethylenedioxy-3-oxododecanoate 14

The diastereomeric alcohols **12** (16.3 g, 40.3 mmol), powdered 4Å molecular sieves (16.3 g) and freshly washed (tetrahydrofuran) pyridinium dichromate (21.1 g, 60.5 mmol) were stirred in dichloromethane (350 cm^3) for 12 h at ambient temperature. Silica gel (16.0 g) was added and the reaction mixture stirred for 30 min then concentrated under reduced pressure. The residue was suspended in ethyl acetate and filtered through a plug of silica with ethyl acetate as eluent. Concentration under reduced pressure and chromatography of the residue using light petroleum : ethyl acetate (60 : 40) afforded the *title compound* **14** as a yellow oil (11.7 g, 73 %) (Found: M^++H, 402.2518. $C_{20}H_{36}NO_7$ requires *M*, 402.2492); υ_{max} 3359,1751, 1713, 1367, 1250 and 1168 cm^{-1}; δ_H (200 MHz, C_6D_6; keto-tautomer) 0.98 (3 H, t, *J* 7.5, 12-H_3), 1.25-1.85 (10 H, m, 6-H_2, 7-H_2, 9-H_2, 10-H_2 and 11-H_2), 1.50 [9 H, s, $C(CH_3)_3$], 2.42 (2 H, d, *J* 7.5, 4-H_2), 3.11 (2 H, s, 2-H_2), 3.32 (3 H, s, OCH_3), 3.51-3.71 (4 H, br s, OCH_2CH_2O), 3.95-4.19 (1 H, m, 5-H) and 4.78 (1 H, br d, NH); δ_C (50 MHz; C_6D_6) 16.37, 25.39, 28.40, 30.49, 31.17, 35.88, 39.41, 49.92, 51.00, 53.68, 66.92, 80.72, 92.98, 113.54, 157.49, 169.31 and 178.29; *m/z* CI(NH_3) 402 (M^++1, 0.5%), 358 (29), 342 (11), 340 (40) and 240 (100).

7-[*N*-(2-methylpropyloxycarbonyl)amino]-4-ethoxycarbonyl-10,10-ethylenedioxytetradec-l-en-5-one 15

The hydroxyester **13** (257 mg, 0.56 mmol, a mixture of diastereoisomers) and Dess-Martin's reagent (594 mg, 1.2 mrnol) were stirred in dichloromethane (20.0 cm^3) at ambient temperature for 12 h. A mixture of saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium thiosulphate (20 cm^3, 50 : 50) was added and the two phase mixture stirred for 30 min. The organic phase was washed with water and brine then dried ($MgSO_4$). After concentration under reduced pressure chromatography of the residue using ether : hexane (60 : 40) as eluent gave the *title compound* **15**, a mixture of diastereoisomers, as a colourless oil (239 mg, 59 %) [Found: $M(^{13}C)^+$+H, 456.2928, $C_{23}{}^{13}CH_{41}NO_7$

requires *M*, 456.2913]; υ_{max} 3485, 1725, 1365, 1250 and 1170 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.93 (3 H, t, *J* 8, 14-H_3), 1.11 (3 H, t, *J* 8, OCH_2CH_3), 1.15-1.35 (6 H, m), 1.40 [9 H, s, $C(CH_3)_3$], 1.44-1.70 (4 H, m), 2.48-2.60 (2 H, m, 3-H_2), 2.70-2.88 (2 H, m, 6-H_2), 3.51 and 3.58 (each 0.5 H, t, *J* 8.5, 4-H), 3.80 (1 H, m, 7-H), 3.86 (4 H, s, OCH_2CH_20), 4.13 (2 H, q, *J* 8, OCH_2CH_3), 4.95-5.06 (3 H, m, NHCH and 1-H_2) and 5.64 (1 H, m, 2-H); *m/z* CI(NH_3) 456 (18%), 394 (100) and 293 (34).

7,7-Ethylenedioxy-2-hydroxy-4-[*N*-(2-methylprop-2-yloxycarbonyl)amino]undecan-1-yl phenyl sulfone 16

Butyllithium (2.5 cm^3,1.6 M in hexanes, 4.0 mmol) was added to diisopropylamine (0.596 cm^3, 4.25 mmol) in tetrahydrofuran (10.0 cm^3) at 0 °C. After being stirred at 0 °C for 20 min, the solution was cooled to -78 °C, methyl phenyl sulphone (570 mg, 3.7 mmol) in tetrahydrofuran (3.0 cm^3) was added and the stirring continued for 1 h. Aldehyde **11** (1.0 g, 3.04 mmol) in tetrahydrofuran (2.0 cm^3) was precooled to -78 °C and added *via* cannula to the solution of lithiated methyl phenyl sulphone. The reaction mixture was stirred at -78 °C for 1 h, then allowed to warm to ambient temperature over 2 h. Saturated aqueous ammonium chloride was added and the organic phase diluted with ethyl acetate. The organic phase was washed with water and brine then dried ($MgSO_4$). Concentration under reduced pressure and chromatography of the residue using light petroleum : ether (60 : 40) as eluent gave the title compounds **16**, as a yellow gum, a 50 : 50 mixture of diastereoisomers (855 mg, 58 %). Further chromatography of a small portion of the mixture using light petroleum : ether (75 : 25) as eluent gave the *less polar diastereoisomer* **16** (Found: M^+-$C_2H_5O_2$, 424.2158. $C_{22}H_{34}NO_5S$ requires *M*, 424.2159); υ_{max} 3366, 1680, 1367, 1305, 1250, 1167 and 1084 cm^{-1}; δ_H (300 MHz, $CDC1_3$) 0.90 (3 H, t, *J* 11, 11-H_3), 1.22-1.36 (4 H, m, 9-H_2 and 10-H_2), 1.46 [9 H, s, $C(CH_3)_3$], 1.36-1.80 (8 H, m, 3-H_2, 5-H_2, 6-H_2 and 8-H_2), 3.12 (1 H, dd, *J* 15, 5.5, 1-H), 3.38 (1 H, dd, *J* 15, 9, 1-H'), 3.65 (1-H, m, 4-H), 3.85-3.97 (4 H, m, OCH_2CH_2O), 4.20 (1 H, m, 2-H), 4.60 (1 H, br d, *J* 11, NH), 7.54 (2 H, m, ArH) and 7.64 (1 H, m, Ar-H) and 7.90 (2 H, br d, *J* 11, ArH); *m/z* (+FAB) 508 (M^++23, 1%) and 324 (100). The second product was the *more polar diastereoisomer* **16** (Found: M^+-$C_2H_5O_2$, 424.2182. $C_{22}H_{34}NO_5S$ requires *M*, 424.2159); υ_{max} 3368, 1692, 1367, 1307, 1251, 1170, 1147 and 1085 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.92 (3 H, t, *J* 11, 11-H_3), 1.26-1.38 (4 H, m, 9-H_2 and 10-H_2), 1.43 [9 H, s, $C(CH_3)_3$], 1.50 (2 H, m, 5-H_2), 1.59 (2 H, m, 8-H_2), 1.67 (2 H, m, 6-H_2), 1.75 (2 H, m, 3-H_2), 3.32 (1 H, dd, *J* 16.5, 9, 1-H), 3.41 (1 H, dd, *J* 16.5, 5, 1-H'), 3.60 (1 H, m, 4-H), 3.90-3.98 (4 H, m, OCH_2CH_2O), 4.34 (1 H, m, 2-H), 4.69 (1 H, br d, *J* 16, NH), 7.61 (2 H, m, ArH), 7.68 (l H, m, ArH) and 7.95 (2 H, m, ArH); *m/z* (+FAB) 485 (M^+, 0.7%), 324 (62) and 57 (100).

7-[*N*-(2-Methylprop-2-yloxycarbonyl)amino]-10,10-ethylenedioxy-5-hydroxy-4-phenylsulphonyltetradec-l-ene 17

Butyllithium (2.30 cm^3,1.6 M in hexane, 3.68 mmol) was added dropwise to diisopropylamine (0.55 cm^3, 3.94 mmol) in tetrahydrofuran (5.0 cm^3) at 0 °C and the solution stirred for 20 min at ambient temperature. After cooling to -78 °C, but-3-enyl phenyl sulphone (0.72 mg, 3.42 mmol) in tetrahydrofuran (2.5 cm^3) was added. After 1 h, a cooled (-78 °C) solution of the aldehyde **11** (865 mg, 2.63 mmol) in tetrahydrofuran (2.5 cm^3) was added and the mixture stirred at -78 °C for 1 h then allowed to warm to ambient temperature over 2 h. Saturated aqueous ammonium chloride was added and the two phase mixture stirred for 30 min. The organic phase was washed with water and brine then dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue using light petroleum : ethyl acetate (50 : 50) as eluent, gave the *title compound* **17** (1.10 g, 80 %) as mixture of four diastereoisomers, Repeated chromatography using light petroleum : ethyl acetate (75 : 25) as eluent separated two pairs of diastereoisomers. Data for the less polar mixture (Found: (M^+-$C_7H_{13}O_4$, 364.1945. $C_{20}H_{30}NO_3S$ requires *M*, 364.1946); υ_{max} 3356, 1709, 1685, 1366, 1304, 1170 and 1147 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.91 (3 H, m, 14-H_3), 1.16-1.75 (12 H, m), 1.40 and 1.42 [each 4.5 H, s, $C(CH_3)_3$], 2.48-2.60 (2 H, m, 3-H_2), 3.01 (1 H, m, 4-H), 3.31 (1 H, m), 3.70 (1 H, m), 3.88-4.00 (4 H, m, OCH_2CH_2O), 4.43 (1 H, m), 4.59 (1 H, m), 4.94-5.11 (2 H, m, 1-H_2), 5.73 (1 H, m, 2-H), 7.48-7.70 (3 H, m, ArH) and 7.83-7.97 (2 H, m, ArH); *m/z* (+FAB) 548 (M^++23, 0.5%), 526 (1) and 364 (65). Data for the more polar mixture (Found: M^++Na, 548.2658. $C_{27}H_{43}NO_7SNa$ requires *M*, 548.2663); υ_{max} 3367, 1702, 1367, 1304, 1171 and 1146 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.91 (3 H, m, 14-H_3), 1.18-1.88 (12 H, m), 1.44 and 1.48 [each 4.5 H, s, $C(CH_3)_3$], 2.34-2.72 (2 H, m, 3-H), 3.30 (1 H, m), 3.41-3.69 (2 H, m), 3.88-4.00 (4 H, m, OCH_2CH_2O), 4.15 (1 H, m), 4.54 (1 H, m), 4.89-5.13 (2 H, m, 1-H_2), 5.58 (1 H, m, 2-H), 7.51-7.72 (3 H, ArH) and 7.86- 7.97 (2 H, m, ArH); *m/z* (+FAB) 548 (M^++23, 0.8 %) and 364 (100).

7,7-Ethylenedioxy-4-[*N*-(2-methylprop-2-yloxycarbonyl)amino]-2-oxoundecan-1-yl phenyl sulfone 18

A mixture of the diastereoisomeric hydroxysulphones **16** (498 mg, 1.0 mmol) and the Dess-Martin periodinane (950 mg, 2.00 mmol) was stirred in dichloromethane (15.0 cm^3) at ambient temperature for 2 h. Saturated aqueous sodium bicarbonate (20.0 cm^3) and saturated aqueous sodium thiosulphate (20.0 cm^3) were added and the two-phase mixture stirred until the solid material dissolved. The organic phase

was washed with water and brine then dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue using light petroleum : ethyl acetate (70 : 30) as eluent gave the *title compound* **18** as a white amorphous, hygroscopic solid (356 mg, 72 %) (Found: C, 63.6; H, 7.85; N, 3.2; S, 6.8%. $C_{24}H_{37}NO_7S$ requires C, 63.85; H, 7.75; N, 3.1; S, 7.1%); υ_{max} 3368, 1708, 1367, 1323 and 1157 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.89 (3 H, m, 11-H_3), 1.10-1.35 (4 H, m, 9-H_2 and 10-H_2), 1.40 [9 H, s, $C(CH_3)_3$], 1.56-1.68 (4 H, m, 8-H_2 and 6-H_2), 1.68-1.84 (2 H, m, 5-H_2), 2.78 (1 H, dd, *J* 12.5, 7.5, 3-H), 2.96 (1 H, dd, *J* 12.5, 6.5, 3-H'), 3.88 (1 H, m, 4-H), 3.94 (4 H, s, OCH_2CH_2O), 4.08 and 4.31 (each 1 H, d, *J* 15, 1-H), 4.74 (1 H, br d, *J* 10, NH), 7.58 (2 H, m, ArH), 7.69 (1 H, m, ArH) and 7.88 (2 H, m, ArH); *m/z* CI(NH_3) 484 (M^++1, 0.1%), 282 (76) and 182 (100).

7-[*N*-(2-Methylprop-2-yloxycarbonyl)amino]-10,10-ethylenedioxy-4-phenylsulphonyltetradec-1-en-5-one 19

The diastereoisomeric hydroxysulphones **17** (1.10 g, 2.08 mmol), 4Å powdered molecular sieves (1.20 g) and pyridinium dichromate (l.l1 g, 3.12 mmol) in dichloromethane (10.0 cm^3) were stirred at ambient temperature for 12 h. Silica gel (2.0 g) was added and the mixture was stirred for 30 min then concentrated under reduced pressure. The residue was suspended in ethyl acetate, filtered through a plug of silica and eluted with ethyl acetate. The filtrate was concentrated under reduced pressure and chromatography of the residue using light petroleum : ethyl acetate (50 : 50) as eluent gave the *title compound* **19** (730 mg, 66%), a colourless oil, as a mixture of diastereoisomers (Found: (M^+-$C_7H_{13}O_4$, 362.1799. $C_{20}H_{28}NO_3S$ requires *M*, 362.1790); υ_{max} 3369, 1711, 1367, 1310 and 1152 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.88 (3 H, t, *J* 8, 14-H_3), 1.21-1.37 (4 H, m), 1.42 [9 H, s, $C(CH_3)_3$], 1.48-1.68 (4 H, m), 1.68-1.81 (2 H, m), 2.34-2.43 (2 H, m, 3-H_2), 2.43-2.53 (2 H, m, 6-H_2), 3.72 (4 H, s, OCH_2CH_2O), 3.90 (1 H, m, 4-H), 4.14 (1 H, m, 7-H), 4.83 (1 H, m, NH), 4.96-5.07 (2 H, m, 1-H_2), 5.53 (1 H, m, 2-H), 7.52-7.61 (2 H, m, ArH), 7.65-7.72 (1 H, m, ArH) and 7.73-7.81 (2 H, m, ArH); *m/z* (+FAB) 546 (M^++23, 0.7%),462 (5) and 362 (100).

Dimethyl (1*RS*,2*RS*,5*SR*)-1-butyl-3,3-ethylenedioxy-8-azabicyclo[3.2.1]octane-2,8-dicarboxylate 50

Toluene *p*-sulphonic acid monohydrate (270 mg, 1.42 mmol) and 2-methoxy-1,3-dioxolane (0.9 cm^3, 9.440 mmol) were added to the keto ester **21** (230 mg, 0.774 mmol) in methanol (6 cm^3) and toluene (0.5 cm^3). The mixture was heated at 50 ^oC for 4 h, then allowed to cool and aqueous sodium hydroxide (1 M) added until basic. The mixture was extracted with dichloromethane, dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue, using ethyl acetate: hexane (20 :

80) as eluent, gave the *title compound* **50** (230 mg, 87%) as a yellow oil (Found: M^+, 341.1842. $C_{17}H_{27}NO_6$ requires *M*, 341.1838); ν_{max} 1750, 1730, 1714, 1700, 1445, 1380, 1368 and 1104 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.90 (3 H, t, *J* 6.9, 4'-H_3), 1.20-1.47 (4 H, m, 2'-H_2 and 3'-H_2), 1.62 (1 H, br d, *J* 13.5, 4-H_{eq}), 1.73-1.95 (4 H, m), 2.07-2.22 (2 H, m), 2.49 (1 H, dd, *J* 13.5, 3, 4-H_{ax}), 2.78 (1 H, s, 2-H), 3.63 and 3.65 (each 3 H, s, OCH_3), 3.80-3.86, (2 H, m), 3.94-4.01 (2 H, m) and 4.46 (1 H, br s, 5-H); *m/z* CI(NH_3) 342 (M^++1, 77%) and 341 (M^+, 11).

Methyl (1*RS*,2*SR*,5*SR*)-1-butyl-3,3-ethylenedioxy-2-formyl-8-azabicyclo[3.2.1]octane-8-carboxylate 51 and methyl (1*RS*,2*SR*,5*SR*)-1-butyl-3,3-ethylenedioxy-2-hydroxymethyl-8-azabicyclo[3.2.1]octane-8-carboxylate 52

Diisobutylaluminium hydride (60 cm^3, 1 M in dichloromethane, 60 mmol) was added to the ester **50** (1.80 g, 5.28 mmol) in dichloromethane (40 cm^3) at –78 °C. The mixture was stirred for 2 h at this temperature then allowed to warm to ambient temperature over 2 h. Celite (2.0 g) and water (2.5 cm^3) were added and stirring continued for 2 h. Magnesium sulphate was added until the solid material became granular and the solid was removed by filtration being washed with ethyl acetate. The combined organic extracts were concentrated under reduced pressure. Chromatography of the residue, using light petroleum : ethyl acetate (80 : 20) as eluent gave the *title compound* **51** (150 mg, 9%), as a colourless oil; ν_{max} 1720, 1447, 1368 and 1104 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.88 (3 H, t, *J* 7, 4'-H_3), 1.15-1.43 (4 H, m), 1.78-2.10 (6 H, m), 2.16 (1 H, m), 2.27 (1 H, dd, *J* 14.5, 3.5, 4-H_{ax}), 2.60 (1 H, d, *J* 6.5, 2-H), 3.66 (3 H, s, OCH_3), 3.74 and 3.84 (each 1 H, m), 3.94-4.01 (2 H, m), 4.56 (1 H, m, 5-H) and 9.35 (1 H, d, *J* 6, CHO); δ_C (75 MHz, $CDCl_3$) 13.90, 22.97, 24.47, 25.80, 34.46, 35.77, 40.52, 52.09, 55.55, 62.82, 64.40, 64.53, 66.51, 106.17, 154.47 and 198.30. The second eluted product was the *title compound* **52** (905 mg, 55%), a colourless oil (Found: M^+, 313.1887. $C_{16}H_{27}NO_5$ requires *M*, 313.1889); ν_{max} 3500, 1706, 1447, 1378, 1139 and 1103 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.91 (3 H, t, *J* 7, 4'-H_3), 1.16-1.43 (4 H, m, 2'-H_2 and 3'-H_2), 1.63-1.90 (5 H, m, 1'-H, 4-H_{eq}, 6-CH_2 and 7-H), 1.93 (1 H, d, *J* 8, OH), 2.08 (1 H, dd, *J* 14, 3.5, 4-H_{ax}), 2.37 (1 H, m, 7-H), 2.55 (1 H, m, 1'-H'), 3.14 (1 H, dd, *J* 11, 2.5, 2-H), 3.62 (1 H, m, 2-CH), 3.63 (3 H, s, OCH_3), 3.83-3.90 (2 H, m), 3.90-4.05 (3 H, m) and 4.33-4.41 (1 H, m, 5-H); δ_C

(75 MHz, $CDCl_3$) 14.00, 23.27, 25.02, 26.68, 35.91, 36.00, 38.17, 51.82, 54.80, 55.57, 60.85, 63.27, 64.26, 65.12, 111.07 and 154.58; *m/z* (EI) 313 (M^+, 7%), 270 (19), 196 (36), 182 (83) and 181 (100).

Methyl (1*RS*,2*RS*,5*SR*)-1-butyl-2-iodomethyl-3,3-ethylenedioxy-8-azabicyclo[3.2.1]octane-8-carboxylate 53

Following the procedure outlined for the synthesis of iodide **38**, the alcohol **52** (851 mg, 2.72 mmol) gave, after chromatography using ethyl acetate: hexane (5 : 95) as eluent, the *title compound* **53** (895 mg, 78 %) as a white solid, m.p. 61-63 ºC (Found: C, 45.7; H, 6.2; N, 3.4. $C_{16}H_{26}INO_4$ requires C, 45.4; H, 6.2; N, 3.3%) (Found: M^++H, 424.1002, $C_{16}H_{27}INO_4$ requires *M*, 424.0987); ν_{max} 1702, 1445, 1381 and 1101 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.95 (3 H, t, *J* 7, 4'-H_3), 1.26 (1 H, m, 2'-H), 1.32-1.50 (3 H, m, 2'-H' and 3'-H_2), 1.57 (1 H, br d, *J* 14, 4-H_{eq}), 1.64-1.92 (4 H, m, 6-CH_2, 7-H, 1'-H), 2.01 (1 H, dd, *J* 14, 3.5, 4-H_{ax}), 2.30 (1 H, m, 7-H), 2.41 (1 H, m, 2-CH), 2.56 (1 H, td, *J* 13, 3, 1'-H'), 3.13 (1 H, dd, *J* 10.5, 5.5, 2-H), 3.63 (1 H, m, 2-CH'), 3.63 (3 H, s, OCH_3), 3.86 (1 H, m), 3.90-4.05 (3 H, m) and 4.38 (1 H, m, 5-H); δ_C (75 MHz, $CDCl_3$) -0.62, 14.09, 23.16, 25.09, 27.23, 35.39, 36.06, 38.70, 51.88, 55.17, 56.92, 63.95, 64.85, 67.95, 109.03 and 154.80; *m/z* (CI) 425 (20%) and 424 (M^++1,100).

(4*RS*,7*SR*,10*RS*)-10-Butyl-5,5-ethylenedioxy-1-azatricyclo[5.3.0.0^{4,10}]decan-2-one 54 and methyl (1*RS*,2*RS*,5*SR*)-1-butyl-3,3-ethylenedioxy-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate 55

Following the procedure outlined for the preparation of lactam **39**, iodide **53** (190 mg, 0.448 mmol), after chromatography using ethyl acetate: light petroleum (15 : 85) as eluent, gave first the *title compound* **54** (88 mg, 74 %) as a yellow oil (Found: M^+, 265.1675. $C_{15}H_{23}NO_3$ requires *M*, 265.1678); ν_{max} 1749, 1132 and 1096 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.89 (3 H, t, *J* 7, 4'-H_3), 1.21-1.48 (5 H, m 1'-H, 2'-H_2 and 3'-H_2), 1.52-1.73 (3 H, m), 1.82 (1 H, ddd, *J* 12, 9.5, 2.5), 2.04-2.21 (2 H, m, 8-H and 6-H_{ax}), 2.37 (1 H, d, *J* 5.5, 4-H), 2.49 (1 H, d, *J* 18.5, 3-H), 2.74-2.84 (1 H, m, 9-H), 2.86 (1 H, dd, *J* 18, 5.5, 3-H') and 3.70-4.07 (5 H, m OCH_2CH_2O, 7-H); δ_C (75 MHz, C_6D_6) 14.20, 23.44, 27.15, 30.42, 38.30, 38.82, 41.12, 50.58, 61.95, 62.85, 64.99, 71.23, 110.15 and 194.05; *m/z* (EI) 266 (M^++1, 23%), 265 (5), 124 (20) and 112 (100). Further elution gave the *title compound* **55** (5 mg, 4 %) as a colourless oil: δ_H (300 MHz, $CDCl_3$) 0.92 (3 H, t, *J* 7, 4'-H_3), 0.97 (3 H, d, *J* 7.5, 2-CH_3), 1.15-1.44 (4 H, m, 2'-H_2 and 3'-

H_2), 1.57 (1 H, br d, *J* 13.5, 4-H_{ax}), 1.68-1.82 (3 H, m), 1.82-1.93 (2 H, m), 2.03 (1 H, dd, *J* 13.5, 3.5, 4-H_{eq}), 2.31-2.41 (1 H, m, 7-H), 2.47 (1 H, m, 1'-H), 3.63 (3 H, s, OCH_3), 3.71-4.00 (4 H, m, OCH_2CH_2O) and 4.34-4.40 (1 H, m, 5-H).

(4*RS*,7*SR*,10*RS*)-10-Butyl-5,5-ethylenedioxy-1-azatricyclo[5.3.0.0^{4,10}]decan-2-ol 56

Following the procedure used to prepare the aminol **44**, lactam **54** (250 mg, 0.943 mmol) was reduced to give the *title compound* **56** (208 mg, 83%) as a white solid, m.p. 155 – 166 ^{o}C (Found: M^+, 267.1837. $C_{15}H_{25}NO_3$ requires *M*, 267.1834); ν_{max} 3154, 1112, 1075 and 1033 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.88 (3 H, t, *J* 6.5, 4'-H_3), 1.05-1.52 (5 H, m, 1'-H, 2'-H_2 and 3'-H_2), 1.47 (1 H, d, *J* 14.5, 6-H_{eq}), 1.55-1.83 (3 H, m, 6-H_{ax}, 9-H and 8-H), 1.83-2.20 (4 H, m), 2.34 (1 H, m, 3-H), 2.62 (1 H, ddd, *J* 13.5, 10, 6.5, 9-H), 3.33 (1 H, t, *J* 5.5, 7-H), 3.69-4.03 (4 H, m, OCH_2CH_2O), 5.00 (1 H, br s, 2-H) and 5.75 (1 H, br s, OH); *m/z* (EI) 268 (M^++1, 4%), 225 (24), 195 (27), 140 (31) and 139 (100).

(4*RS*,7*SR*,10*RS*)-10-Butyl-5,5-ethylenedioxy-1-azatricyclo[5.3.0.0^{4,10}]decane 57

Thionyl chloride (0.35 cm^3, 4.80 mmol) was added dropwise to the aminol **56** (255 mg, 0.955 mmol) in ether (9 cm^3) and dichloromethane (2 cm^3). After 90 min, the solvent was removed under reduced pressure. The residue was dissolved in tetrahydrofuran (10 cm^3), and the solution added to lithium aluminium hydride (260 mg, 6.87 mmol) in tetrahydrofuran (2 cm^3) at 0 ^{o}C. The reaction mixture was stirred at ambient temperature for 3 h, then cooled to 0 ^{o}C and water (1.5 cm^3) and celite (300 mg) were added. After stirring for 30 min, portions of magnesium sulphate were added until the solid material became granular. Filtration and concentration under reduced pressure followed by chromatography of the residue, using light petroleum : ether: ethyl acetate: methanol: diethylamine (63 : 20 : 20 : 1 : 1) as eluent, gave the *title compound* **57** (180 mg, 75%) as a pale yellow oil; ν_{max} 1463, 1338, 1120 and 1091 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.89 (3 H, t, *J* 7, 4'-H_3), 1.19-1.39 (5 H, m, 1'-H, 2'-H_2 and 3'-H_2), 1.45 (2 H, m, 1'-H' and 6-H_{eq}), 1.61 (1 H, td, *J* 12.5, 3), 1.74 (1 H, ddd, *J* 12.5, 10, 3), 1.84 (1 H, ddd, *J* 14, 5, 1.5, 6-H_{ax}), 1.89-2.09 (4 H, m, 3-CH_2, 4-H and 8-H), 2.61 (1 H, ddd, *J* 16.5, 10, 6, 9-H), 2.82-3.03 (2 H, m, 2-CH_2), 3.30 (1 H, t, *J* 5.5, 7-H) and 3.71-4.05 (4 H, m, OCH_2CH_2O); *m/z* (CI) 269, (M^++18, 7%), 268 (39), 253 (24) and 252 (100).

Sulphuric acid (1% aqueous solution, 7.0 cm^3) was added to the acetal **57** (160 mg, 0.637 mmol) and the mixture heated at 75 ^oC for 17 h before being allowed to cool. Solid potassium carbonate was added until basic, then the mixture was extracted with dichloromethane. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ethyl acetate : ether : methanol : diethylamine (98 : 20 : 20 : 1 : 1) as eluent, gave the ketone **49** (119 mg, 90%) as a pale yellow oil.

Reference

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