Experimental Section

Commercially available reagents were used throughout without further purification unless otherwise stated; solvents were dried by standard procedures. Light petroleum refers to the fraction with bp 40 – 60 °C and ether refers to diethyl ether. Reactions were routinely carried out under a nitrogen atmosphere. Fully characterized compounds were chromatographically homogeneous. IR spectra were recorded in the range 4000 – 600 cm^{-1} using a Nicolet Magna FT-550 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded using Bruker 300 and 400 MHz instruments (^{1}H frequencies, corresponding ^{13}C frequencies are 75 and 100 MHz); *J* values are recorded in Hz. In the ^{13}C NMR spectra, signals corresponding to CH, CH_2 or Me groups, as assigned from DEPT, are noted; all others are C. High and low-resolution mass spectra were recorded on a Micromass GCT TOF Spectrometer, or at the EPSRC Mass Spectrometry Service (Swansea).

4-Bromo-*N*,*N'*-di-*tert*-butoxycarbonyltryptamine 12

(a) A solution of 4-bromoindole-3-carboxaldehyde **11**[53] (1.50 g, 6.71 mmol) and ammonium acetate (0.27 g, 3.50 mmol) in nitromethane (45 mL) was heated at reflux under nitrogen for 6 h, then allowed to cool to room temperature overnight. Toluene (30 mL) was added, and the mixture placed in a freezer for 24 h to yield 4-bromo-3-(2-nitrovinyl)indole (1.48 g, 83%) as blood red crystals, mp 200 – 205 °C (nitromethane-toluene) (lit.,[73] mp 200 °C (decomp)); (Found: M^+, 265.9692. $C_{10}H_7{}^{79}BrN_2O_2$ requires 265.9691); ν_{max} (KBr)/cm^{-1} 3275, 3116, 3105, 1605, 1560, 1518, 1489, 1419, 1336, 1294, 1255, 1232, 1182, 1140, 985, 968, 823, 793, 781; δ_H (400 MHz; d_6-DMSO) 12.54 (1H, br s, NH), 9.13 (1H, d, *J* 13.2, C<u>H</u>=CHNO_2), 8.54 (1H, s, 2-H), 8.10 (1H, d, *J* 13.2,

CH=C<u>H</u>NO_2), 7.54 (1H, d, *J* 8.1, 7-H), 7.41 (1H, d, *J* 7.6, 5-H), 7.14 (1H, dd, *J* 8.1, 7.6, 6-H); δ_C (100 MHz; d_6-DMSO) 138.7, 133.7 (CH), 132.6 (CH), 132.2 (CH), 126.5 (CH), 124.5, 124.4 (CH), 113.2 (CH), 113.1, 107.8; *m/z* (EI) 268/266 (M^+, 1%), 236/234 (14), 219 (8), 181 (15), 169 (13), 155 (16), 131 (26), 119 (23), 113 (11), 100 (14), 83 (52), 69 (100), 51 (33).

(b) To a stirred solution of 4-bromo-3-(2-nitrovinyl)indole (1.95 g, 7.31 mmol) in dry THF (50 mL) under nitrogen at -10 °C was added a solution of lithium aluminium hydride (1M in THF; 20.00 mL, 20.00 mmol) dropwise over 20 min, and the reaction mixture allowed to warm to room temperature, and stirred overnight. The mixture was cooled to 0 °C and sodium fluoride (3.4 g) added. Water (1.1 mL) was carefully added over 15 min, and the reaction mixture stirred at 0 °C for 15 min, allowed to warm to room temperature, and stirred for a further 15 min. The reaction mixture was filtered through Celite, and the pad washed with ethyl acetate (250 mL). The organic phase was extracted with HCl (1 M; 4 × 100 mL) and the combined acidic phases were washed with ethyl acetate (100 mL) and basified with NaOH (4 M; 300 mL). The basic aqueous phase was then extracted with ethyl acetate (5 × 100 mL) and these organic phases were combined, washed with brine (100 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield 4-bromotryptamine as a red oil (1.27 g, 73%) that was used in the next step without further purification; (Found: M^+, 238.0098. $C_{10}H_{11}{}^{79}BrN_2$ requires 238.0106); ν_{max} (film)/cm^{-1} 3415, 3209, 2925, 1653, 1560, 1423, 1336, 1186, 1043, 912, 741; δ_H (400 MHz; $CDCl_3$) 8.75 (1H, br s, exch D_2O, NH), 7.28 (1H, dd, *J* 7.8, 0.9, 5-H), 7.26 (1H, dd, *J* 7.8, 0.9, 7-H), 7.03 (1H, s, 2-H), 6.98 (1H, dd, *J* 7.8, 7.8, 6-H), 3.11 (4H,

m, CH_2CH_2), 1.62 (2H, br s, exch D_2O, NH_2); δ_C (75 MHz; $CDCl_3$) 137.9, 125.4, 124.1 (CH), 123.9 (CH), 122.7 (CH), 114.4, 114.3, 110.6 (CH), 43.7 (CH_2), 30.3 (CH_2); *m/z* (EI) 240/238 (M^+, 1%), 211/209 (27), 210/208 (36), 159 (9), 149 (18), 130 (70), 129 (56), 102 (56), 89 (14), 75 (55), 57 (91), 51 (100).

(c) 4-Dimethylaminopyridine (0.06 g, 0.5 mmol) was added to a stirred solution of 4-bromotryptamine (1.20 g, 5.1 mmol) and di-*tert*-butyl dicarbonate (2.30 g, 10.3 mmol) in dry acetonitrile (120 mL) at room temperature. The mixture was stirred overnight, evaporated *in vacuo* and partitioned between water (100 mL) and ether (50 mL). The aqueous phase was further extracted with ether (50 mL) and the organic extracts were combined, washed sequentially with saturated aqueous sodium hydrogen carbonate solution (50 mL) and brine (50 mL), dried (Na_2SO_4), evaporated *in vacuo* and purified by column chromatography on silica, eluting with ethyl acetate-light petroleum (1:6) to give the *title compound* (2.10 g, 92%) as colourless needles, mp 82 – 83 °C (light petroleum); (Found: C, 54.3; H, 6.1; N, 6.2. $C_{20}H_{27}BrN_2O_4$ requires C, 54.6; H, 6.2; N, 6.4%); (Found: M^+, 438.1145. $C_{20}H_{27}{}^{79}BrN_2O_4$ requires 438.1155); ν_{max} ($CHCl_3$)/cm^{-1} 3451, 3161, 3118, 2980, 2936, 1732, 1702, 1556, 1506, 1420, 1368, 1253, 1150, 1099, 1054, 863, 847; δ_H (400 MHz; $CDCl_3$) 8.19 (1H, br d, *J* 8.3, 5-H), 7.44 (1H, s, 2-H), 7.38 (1H, dd, *J* 7.8, 0.9, 7-H), 7.13 (1H, dd, *J* 8.3, 7.8, 6-H), 4.67 (1H, br s, NH), 3.50 (2H, dt, *J* 6.6, 6.8, NCH_2), 3.16 (2H, t, *J* 6.8, CH_2), 1.66 (9H, s, CMe_3), 1.44 (9H, s, CMe_3); δ_C (100 MHz; $CDCl_3$) 155.9, 149.1, 137.2, 128.3, 127.2 (CH), 125.3 (CH), 125.1 (CH), 117.9, 114.5 (CH), 114.1, 84.1, 79.2, 41.2 (CH_2), 28.4 (Me), 28.2 (Me), 26.7 (CH_2); *m/z* (EI)

440/438 (M^+, 1%), 340/338 (2), 284/282 (9), 223/221 (9), 210/208 (30), 129 (9), 128 (7), 85 (32), 83 (53), 57 (100).

3-Allyl-2-methoxybenzeneboronic acid 14

(a) To a stirred solution of 2-bromophenyl allyl ether **13**[74] (5.36 g, 25.2 mmol) in hexane (100 mL) at room temperature under nitrogen was added Et_2AlCl (1 M in hexane; 50 mL, 50.0 mmol). After 2.5 h, the reaction mixture was cooled to 0 °C, followed by careful addition of HCl (2 M; 100 mL). The aqueous phase was then separated and extracted with ethyl acetate (4 × 100 mL), the combined organic phases were washed with brine (2 × 100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield 2-allyl-6-bromophenol (5.49 g, 100%) as a colourless oil (lit.,[75] bp 59 – 60 °C/0.7 torr); (Found: M^+, 211.9832. $C_9H_9{}^{79}BrO$ requires 211.9837); ν_{max} (film)/cm^{-1} 3509, 3076, 2978, 2916, 1638, 1597, 1471, 1450, 1327, 1238, 1195, 1121, 994, 915, 840; δ_H (400 MHz; $CDCl_3$) 7.35 (1H, m, ArH), 7.10 (1H, m, ArH), 6.78 (1H, dd, *J* 7.8, 7.8, 4-H), 6.02 (1H, ddt, *J* 17.7, 9.5, 6.5, C<u>H</u>=CH_2), 5.62 (1H, s, exch D_2O, OH), 5.13 (2H, m, CH=C<u>H</u>$_2$), 3.47 (2H, d, *J* 6.5, CH_2Ar); δ_C (100 MHz; $CDCl_3$) 150.1, 136.1 (CH), 130.0 (CH), 129.7 (CH), 127.8, 121.5 (CH), 116.2 (CH_2), 110.5, 35.0 (CH_2); *m/z* (EI) 213/211 (M^+, 1%), 187/185 (2), 167 (31), 149 (100), 113 (15), 83 (11), 71 (36), 57 (62).

(b) A solution of 2-allyl-6-bromophenol (5.36 g, 25.2 mmol), potassium carbonate (20.00 g, 144.7 mmol) and methyl iodide (20 mL, 321.3 mmol) in acetone (100 mL) was stirred at reflux under nitrogen overnight. The reaction mixture was then allowed to cool to room temperature, filtered and concentrated *in vacuo*. The residue was partitioned

between ethyl acetate (100 mL), and water (100 mL) containing brine (25 mL). The separated aqueous phase was extracted with ethyl acetate (4 × 60 mL), and the combined organic phases were washed with brine (2 × 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the crude product. Flash chromatography eluting with ethyl acetate:light petroleum (1:99) yielded 2-allyl-6-bromomethoxybenzene (5.61 g, 85%) as a colourless oil (lit.,[54] bp 70 °C/0.1 torr); (Found: M^+, 225.9992. $C_{10}H_{11}{}^{79}BrO$ requires 225.9993); ν_{max} (film)/cm^{-1} 3078, 3001, 2977, 2939, 2856, 2824, 1637, 1465, 1420, 1254, 1228, 1074, 1005, 917, 775; δ_H (300 MHz; $CDCl_3$) 7.42 (1H, dd, *J* 7.9, 1.7, 3-H), 7.14 (1H, m, 5-H), 6.94 (1H, dd, *J* 7.9, 7.9, 4-H), 5.98 (1H, ddt, *J* 16.8, 10.3, 6.6, C<u>H</u>=CH_2), 5.10 (2H, m, CH=C<u>H</u>$_2$), 3.84 (3H, s, OMe), 3.47 (2H, d, *J* 6.6, CH_2Ar); δ_C (75 MHz; $CDCl_3$) 155.1, 136.7 (CH), 135.3, 131.6 (CH), 129.7, 125.4 (CH), 117.5, 116.3 (CH_2), 61.0 (Me), 34.4 (CH_2); *m/z* (EI) 228/226 (M^+, 34%), 213/211 (5) 199/197 (9), 171/169 (4), 147 (15), 132 (100), 115 (31), 104 (20), 91 (17), 77 (28), 63 (17), 51 (30).

(c) *tert*-Butyllithium (1.48 M solution in hexanes; 4.4 mL, 6.5 mmol) was added dropwise over 5 min to a stirred solution of 3-allyl-2-methoxybromobenzene (1.0 g, 4.3 mmol) in dry THF (5 mL) in the absence of oxygen (freeze-thaw technique) at -78 °C. After stirring for 30 min, trimethyl borate (3.0 mL, 26 mmol) was added in one portion. The mixture was warmed rapidly to room temperature, stirred for 1 h, quenched in aqueous hydrochloric acid (0.001 M; 50 mL), and extracted with dichloromethane (50 mL). The aqueous layer was further extracted with dichloromethane (2 × 50 mL) and the organic extracts were combined, dried (Na_2SO_4), evaporated *in vacuo* and purified by column chromatography on silica, eluting with ether-light petroleum (1:4) to give the *title*

compound (0.6 g, 75%) as a colourless solid, mp 97 – 98.5 °C (light petroleum); (Found: M^+, 192.0955. $C_{10}H_{13}BO_3$ requires 192.0958); ν_{max} ($CHCl_3$)/cm^{-1} 3440 (br), 3081, 1061, 2978, 2943, 2905, 2831, 1638, 1592, 1459, 1425, 1351, 1076, 995, 920, 551; δ_H (400 MHz; $CDCl_3$) 7.76 (1H, dd, *J* 7.5, 1.5, 6-H), 7.35 (1H, dd, *J* 7.5, 1.5, 4-H), 7.17 (1H, dd, *J* 7.5, 7.5, 5-H), 6.76 (2H, s, exch D_2O, $B(OH)_2$), 6.01 (1H, m, CH), 5.14 (1H, m, CHC<u>H</u>H), 5.10 (1H, m, CHCH<u>H</u>), 3.82 (3H, s, MeO), 3.46 (2H, d, *J* 6.4, CH_2); δ_C (100 MHz; $CDCl_3$) 163.9, 136.8 (CH), 134.8 (CH), 134.3 (CH), 131.9, 124.8 (CH), 123.2 (br), 116.2 (CH_2), 62.8 (Me), 33.5 (CH_2); δ_B (128 MHz; $CDCl_3$) 29.2 (br s); *m/z* (EI) 192 (M^+, 75%), 133 (65), 119 (15), 115 (100), 105 (10), 91(20), 57 (20), 51 (10).

4-(3-Allyl-2-methoxyphenyl)-*N*,*N'*-di-*tert*-butyloxycarbonyltryptamine 15

Aqueous sodium carbonate solution (2.0 M; 3.30 mL, 6.6 mmol) was added to a stirred solution of the 4-bromotryptamine **12** (1.00 g, 2.2 mmol) in dry DME (40 mL) in the absence of oxygen (freeze-thaw technique) at room temperature. Tetrakis(triphenylphosphine)palladium(0) (0.25 g, 0.2 mmol) and a solution of 3-allyl-2-methoxybenzeneboronic acid **14** (0.54 g, 2.8 mmol) in dry DME (15 mL) were added. The mixture was degassed further (freeze-thaw technique), heated to reflux overnight and partitioned between dichloromethane (70 mL) and water (70 mL). The aqueous phase was further extracted with dichloromethane (70 mL) and the organic extracts were combined, washed sequentially with water (75 mL) and brine (75 mL), dried (Na_2SO_4), evaporated *in vacuo* and purified by column chromatography on silica, eluting with ethyl acetate-light petroleum (1:9) to give the *title compound* (0.95 g, 85%) as a colourless oil; (Found: MH^+, 507.2857. $C_{30}H_{39}N_2O_5$ requires 507.2859); ν_{max} ($CHCl_3$)/cm^{-1} 3448, 2981,

2935, 1725, 1708, 1509, 1462, 1418, 1369, 1284, 1255, 1158, 1099, 923, 854; δ_H (400 MHz; $CDCl_3$) 8.27 (1H, br d, *J* 8.3, 7-H), 7.42 (1H, s, 2-H), 7.35 (1H, dd, *J* 8.3, 7.3, 6-H), 7.26 (1H, dd, *J* 7.2, 2.2, ArH), 7.17 (1H, dd, *J* 7.4, 2.2, ArH), 7.14 (1H, dd, *J* 7.3, 1.0, 5-H), 7.13 (1H, dd, *J* 7.4, 7.2, ArH), 6.05 (1H, ddt, *J* 17.0, 10.0, 6.6, C<u>H</u>=CH_2), 5.15 – 5.09 (2H, m, CH=C<u>H_2</u>), 4.33 (1H, m, CH_2N<u>H</u>), 3.52 (1H, dd, *J* 15.2, 6.3, C<u>H</u>HCH=), 3.44 (1H, dd, *J* 15.2, 6.6, CH<u>H</u>CH=), 3.26 (3H, s, OMe), 2.95 (2H, m, C<u>H_2</u>NH), 2.38 (2H, m, C<u>H_2</u>CH_2NH), 1.68 (9H, s, CMe_3), 1.41 (9H, s, CMe_3); δ_C (100 MHz; $CDCl_3$) 155.9, 155.8, 149.6, 149.3, 137.2 (CH), 134.5, 133.1, 132.0, 130.1 (CH), 130.0 (CH), 128.2, 124.7 (CH), 124.2 (CH), 123.9 (CH), 123.7 (CH), 118.6, 115.8 (CH_2), 114.5 (CH), 83.4, 78.8, 60.5 (Me), 40.2 (CH_2), 34.4 (CH_2), 28.4 (Me), 28.2 (Me), 26.1 (CH_2); *m/z* (CI) 507 (MH^+, 45%), 468 (12), 451 (23), 433 (16), 407 (11), 395 (9), 334 (10), 333 (22), 202 (13), 174 (100) 112 (37), 98 (55), 72 (87).

3-[1-*tert*-Butoxycarbonyl-3-(2-*tert*-butoxycarbonylaminoethyl)indol-4-yl]-2-methoxyphenylacetaldehyde 16

(a) To a stirred solution of osmium(III) chloride (0.019 g, 0.06 mmol), quinuclidine (0.021 g, 0.192 mmol), potassium ferricyanide (1.107 g, 3.36 mmol) and potassium carbonate (0.525 g, 3.80 mmol) in *t*-BuOH/water (1:1, 20 mL) was added a solution of alkene **15** (0.520 g, 1.03 mmol) in *t*-BuOH/water (1:1, 10 mL), the reaction mixture was stirred vigorously under nitrogen for 48 h. Sodium sulfite (1.5 g) was then added, stirred for 1 h, and then partitioned between water (100 mL) and dichloromethane (100 mL). The separated aqueous phase was extracted with dichloromethane (2 × 100 mL), and the combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to

yield the crude product. Flash chromatography eluting with ethyl acetate/MeOH/light petroleum (5:1:14) yielded the intermediate diol (0.466 g, 84%) as a colourless non-crystalline solid, mp 69 – 72 °C (ethyl acetate-light petroleum); (Found: MH^+, 541.2912. $C_{30}H_{41}N_2O_7$ requires 541.2914); ν_{max} (film)/cm^{-1} 3413, 2978, 2933, 1734, 1695, 1686, 1458, 1417, 1369, 1255, 1159, 1099, 1063, 1011, 760; δ_H (400 MHz; $CDCl_3$) 8.25 (1H, d, *J* 8.3, indole 7-H), 7.39 (1H, s, indole 2-H), 7.35 – 7.31 (1H, m, indole 6-H), 7.30 – 7.27 (1H, m, indole 5-H), 7.18 – 7.15 (1H, m, ArH), 7.14 – 7.10 (2H, m, ArH), 4.61 (1H, br s, $CH_2N\underline{H}$), 4.08 – 4.00 (1H, m, C<u>H</u>OH), 3.69 – 3.66 (1H, m, C<u>H</u>HOH), 3.57 – 3.52 (1H, m, CH<u>H</u>OH), 3.29 (3H, s, OMe), 3.06 – 2.95 (3H, m, C<u>H</u>$_2$CHOH, C<u>H</u>HCHH), 2.87 (1H, br s, OH), 2.78 – 2.70 (1H, m, CH<u>H</u>CHH), 2.59 (1H, br s, OH), 2.54 – 2.42 (1H, m, CHHC<u>H</u>H), 2.30 – 2.27 (1H, m, CHHCH<u>H</u>), 1.68 (9H, s, CMe_3), 1.39 (9H, s, CMe_3); δ_C (100 MHz; $CDCl_3$) 156.3, 155.9, 149.5, 136.1, 134.4 (CH), 131.9, 131.5 (CH), 131.2, 130.7 (CH), 128.3, 124.7 (CH), 123.9 (CH), 123.8 (CH), 123.6 (CH), 118.6, 114.6 (CH), 83.5, 79.3, 72.9 (CH), 66.5 (CH_2), 60.5 (Me), 40.5 (CH_2), 34.6 (CH_2), 28.4 (Me), 28.2 (Me), 26.5 (CH_2); *m/z* (CI, NH_3) 541 (MH^+, 28%), 441 (39), 341 (16), 182 (13), 146 (41), 132 (37), 124 (32), 108 (35), 98 (42), 84 (43), 72 (100).

(b) To a stirred solution of the above diol (0.401 g, 0.743 mmol) in THF/water (1:1, 30 mL) was added sodium periodate (0.280 g, 1.308 mmol), and the reaction mixture stirred under nitrogen at room temperature for 2.5 h. The reaction mixture was partitioned between water (50 mL) and dichloromethane (50 mL), and the separated aqueous layer extracted with dichloromethane (2 × 50 mL) and the combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield the crude product. Flash

chromatography eluting with ethyl acetate – light petroleum (3:7) yielded the *title compound* (0.372 g, 99%) as a colourless non-crystalline solid, mp 58 – 60 °C (from ethyl acetate-light petroleum); (Found: MH^+, 509.2627. $C_{29}H_{37}N_2O_6$ requires 509.2652); ν_{max} (film)/cm^{-1} 3415, 2978, 2935, 1728, 1508, 1464, 1419, 1369, 1284, 1255, 1159, 1099, 1063, 1009, 856, 760; δ_H (400 MHz; $CDCl_3$) 9.79 (1H, dd, *J* 1.6, 1.7, CHO), 8.26 (1H, d, *J* 8.3, indole 7-H), 7.41 (1H, s, indole 2-H), 7.34 (1H, dd, *J* 7.5, 8.2, indole 6-H), 7.26 – 7.21 (2H, m, indole 5-H, ArH), 7.17 (1H, d, *J* 7.4, ArH), 7.13 (1H, d, *J* 7.4, ArH), 4.50 (1H, br s, $CH_2N\underline{H}$), 3.82 (1H, dd, *J* 1.7, 16.9, C$\underline{H}$HCHO), 3.72 (1H, dd, *J* 1.6, 16.9, CH$\underline{H}$CHO), 3.18 (3H, s, OMe), 2.96 – 2.87 (2H, m, C$\underline{H_2}$NH), 2.46 – 2.41 (1H, m, C$\underline{H}$HCH_2NH), 2.34 – 2.29 (1H, m, CH$\underline{H}$CH_2NH), 1.67 (9H, s, CMe_3), 1.39 (9H, s, CMe_3); δ_C (100 MHz; $CDCl_3$) 199.1 (CHO), 156.4, 155.8, 149.5, 136.1, 134.2, 131.7 (CH), 131.4, 131.0 (CH), 128.1, 125.8, 124.7 (CH), 124.2 (CH), 123.9 (CH), 123.8 (CH), 118.4, 114.7 (CH), 83.6, 78.9, 60.3 (Me), 45.7 (CH_2), 40.2 (CH_2), 28.4 (Me), 28.2 (Me), 26.2 (CH_2); *m/z* (FAB) 531 (MNa^+, 19%), 509 (MH^+, 30%), 409 (34), 397 (43), 353 (100), 309 (72), 292 (77), 278 (67), 250 (83), 218 (44), 152 (23), 107 (58).

Ethyl 4-{3-[1-*tert*-butoxycarbonyl-3-(2-*tert*-butoxycarbonylaminoethyl)indol-4-yl]-2-methoxyphenyl}-3-oxobutanoate 17

To a stirred suspension of $SnCl_2$ (0.021 g, 0.09 mmol) in dry dichloromethane (7 mL) under nitrogen was added ethyl diazoacetate (0.10 mL, 0.95 mmol), followed after 10 min by a solution of aldehyde **16** (0.243 g, 0.48 mmol) in dry dichloromethane (3 mL) added dropwise over 10 min and the reaction mixture stirred under nitrogen at room temperature overnight. The reaction mixture was partitioned between brine (40 mL) and

dichloromethane (25 mL), the separated aqueous layer extracted with dichloromethane (3 × 50 mL) and the combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield the crude product. Flash chromatography eluting with ethyl acetate/MeOH/light petroleum (6:1:33) yielded the *title compound* (0.372 g, 99%) as a pale yellow oil, (Found: MH^+, 595.2998. $C_{29}H_{37}N_2O_6$ requires 595.3019); ν_{max} (film)/cm^{-1} 3412, 2980, 2935, 1728, 1516, 1463, 1419, 1369, 1284, 1255, 1161, 1099, 1063, 1034, 1009, 912, 856, 760, 733; δ_H (400 MHz; $CDCl_3$) 8.26 (1H, d, *J* 8.0, indole 7-H), 7.41 (1H, s, indole 2-H), 7.33 (1H, dd, *J* 7.3, 8.3, indole 6-H), 7.24 – 7.19 (2H, m, indole 5-H, ArH), 7.15 – 7.11 (2H, m, indole 6-H, ArH), 4.68 (1H, br s, $CH_2N\underline{H}$), 4.21 (2H, q, *J* 7.2, $OC\underline{H}_2Me$), 3.99 (1H, d, *J* 16.8, $C\underline{H}HCO$), 3.83 (1H, d, *J* 16.8, $CH\underline{H}CO$), 3.55 (2H, d, *J* 2.1, $COC\underline{H}_2CO$), 3.17 (3H, s, OMe), 2.91 – 3.02 (2H, m, $C\underline{H}_2NH$), 2.47 – 2.39 (1H, m, $C\underline{H}HCH_2NH$), 2.33 – 2.25 (1H, m, $CH\underline{H}CH_2NH$), 1.67 (9H, s, CMe_3), 1.39 (9H, s, CMe_3), 1.28 (3H, t, *J* 7.2, $OCH_2\underline{Me}$); δ_C (100 MHz; $CDCl_3$) 200.4, 167.1, 156.1, 155.9, 149.5, 136.1, 134.0, 131.7 (CH), 131.6, 131.1 (CH), 128.2, 127.1, 124.7 (CH), 124.1 (CH), 123.9 (CH), 123.6 (CH), 118.6, 114.7 (CH), 83.5, 78.7, 61.4 (CH_2), 60.2 (Me), 49.1 (CH_2), 44.8 (CH_2), 40.2 (CH_2), 28.4 (Me), 28.2 (Me), 26.0 (CH_2), 14.1 (Me); *m/z* (FAB) 595 (MH^+, 53%), 556 (10), 539 (29), 509 (19), 495 (31), 453 (12), 148 (38), 134 (11), 52 (100).

Ethyl 4-{3-[1-*tert*-butoxycarbonyl-3-(2-*tert*-butoxycarbonylaminoethyl)indol-4-yl]-2-methoxyphenyl}-2-diazo-3-oxobutanoate 18

To a stirred solution of β-ketoester **17** (0.454 g, 0.765 mmol) in acetonitrile (12 mL) stirred under nitrogen was added 4-acetamidobenzenesulfonyl azide[55] (0.229 g, 1.037

mmol). The reaction mixture was cooled to 0 °C, stirred for 30 min, and triethylamine (0.20 mL, 1.434 mmol) was added dropwise over 10 min and the reaction mixture stirred under nitrogen at room temperature overnight. The reaction mixture was filtered and concentrated *in vacuo* to yield the crude product. Flash chromatography using ethyl acetate – light petroleum (1:4) yielded the *title compound* (0.340 g, 72%) as a yellow oil, (Found: MH^+, 621.2923. $C_{33}H_{41}N_4O_8$ requires 621.2924); ν_{max} (film)/cm^{-1} 3398, 2980, 2935, 2137 (C=N_2), 1716, 1653, 1516, 1464, 1417, 1371, 1298, 1255, 1161, 1099, 1061, 1028, 1009, 912, 856, 760, 733; δ_H (400 MHz; $CDCl_3$) 8.27 (1H, d, *J* 8.0, indole 7-H), 7.39 (1H, s, indole 2-H), 7.33 (1H, dd, *J* 7.6, 8.0, indole 6-H), 7.21 (2H, m, indole 5-H, ArH), 7.14 (1H, d, *J* 7.5, ArH), 7.12 (1H, d, *J* 7.3, ArH), 5.09 (1H, br s, $CH_2N\underline{H}$), 4.48 (1H, d, *J* 17.5, ArC$\underline{H}$H), 4.34 (2H, q, *J* 7.1, OC$\underline{H_2}$Me), 4.04 (1H, d, *J* 17.5, ArCH$\underline{H}$), 3.20 (3H, s, OMe), 3.02 (1H, m, C$\underline{H}$HNH), 2.94 (1H, m, CH$\underline{H}$NH), 2.52 – 2.44 (1H, m, C$\underline{H}$HCH_2NH), 2.36 – 2.28 (1H, m, CH$\underline{H}$CH_2NH), 1.66 (9H, s, CMe_3), 1.40 (9H, s, CMe_3), 1.36 (3H, t, *J* 7.1, OC$H_2\underline{Me}$); δ_C (100 MHz; $CDCl_3$) 190.5, 161.4, 156.3, 156.2, 149.6, 136.0, 134.1, 131.8, 131.4 (CH), 131.2 (CH), 128.3, 127.7, 124.6 (CH), 124.0 (CH), 123.8 (CH), 123.6 (CH), 118.9, 114.6 (CH), 83.4, 78.5, 76.3, 61.5 (CH_2), 60.4 (Me), 41.6 (CH_2), 40.5 (CH_2), 28.4 (Me), 28.2 (Me), 25.7 (CH_2), 14.4 (Me); *m/z* (ES) 643 (M+Na, 100%), 621 (MH^+, 69), 521 (83), 503 (31), 447 (34), 437 (38), 420 (22), 346 (22), 305 (19), 262 (22), 248 (31), 230 (21), 218 (18), 107 (20).

(*S*)-Ethyl 2-(1-benzyloxycarbonylamino-2-methylpropyl)-5-{3-[1-*tert*-butoxycarbonyl-3-(2-*tert*-butoxycarbonylaminoethyl)indol-4-yl]-2-methoxy}benzyloxazole-4-carboxylate 10

(a) To a stirred solution of (*S*)-*N*-Z-valinamide[47] (108.4 mg, 0.434 mmol) and dirhodium tetraacetate (2.4 mg, 0.0054 mmol) in dry chloroform (10 mL) at reflux under nitrogen was added a solution of diazoketoester **18** (65.7 mg, 0.106 mmol) in dry chloroform (5 mL) dropwise over 5 h. Upon complete addition, the reaction mixture was heated at reflux for a further 2 h, then allowed to cool to room temperature, filtered and concentrated *in vacuo* to yield the crude product. Flash chromatography (ethyl acetate/MeOH/light petroleum 4:1:15) yielded (*S*)-ethyl 4-{3-[1-*tert*-butoxycarbonyl-3-(2-*tert*-butoxycarbonylaminoethyl)indol-4-yl]-2-methoxyphenyl}-2-(2-benzyloxycarbonylamino-3-methylbutanoylamino)-3-oxobutanoate **19** (52.9 mg, 59%) as a brown oil that was not characterized, but taken onto the next step directly.

(b) To a stirred solution of triphenylphosphine (99.5 mg, 0.379 mmol) and iodine (93.4 mg, 0.368 mmol) in dry dichloromethane (7 mL) under nitrogen was added triethylamine (0.11 mL, 0.789 mmol) followed by a solution of amide **19** (82.5 mg, 0.098 mmol) in dry dichloromethane (3 mL). The reaction mixture was stirred for 2 h, then partitioned between dichloromethane (10 mL) and saturated $NaHCO_3$ (10 mL). The separated organic phase was washed with water (10 mL), aqueous $CuSO_4$ (10%; 2 × 10 mL), water (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield the crude product. Flash chromatography using ethyl acetate – light petroleum (1:4) yielded the *title compound* (18.2 mg, 22%) as a brown oil, (Found: MH^+, 825.4068.

$C_{46}H_{57}N_4O_{10}$ requires 825.4074); ν_{max} (film)/cm^{-1} 3385, 2976, 2926, 2850, 1734, 1718, 1701, 1647, 1558, 1533, 1521, 1506, 1448, 1419, 1369, 1255, 1159, 1099, 1066, 758, 732; δ_H (400 MHz; $CDCl_3$) 8.25 (1H, d, *J* 8.3, indole 7-H), 7.40 (1H, s, indole 2-H), 7.39 – 7.30 (5H, m, ArH), 7.21 – 7.06 (5H, m, ArH), 5.70 (1H, br s, $CH_2N\underline{H}$), 5.14 – 5.05 (2H, m, $C\underline{H}_2Ph$), 4.77 (1H, m, NHC$\underline{H}$), 4.47 (2H, m, CH_2Ar), 4.42 (2H, q, *J* 7.2, $OC\underline{H}_2Me$), 4.36 (1H, br s, CHN$\underline{H}$), 3.23 (3H, s, OMe), 2.91 – 2.87 (2H, m, $CH_2C\underline{H}_2NH$), 2.39 – 2.21 (2H, m, $C\underline{H}_2CH_2NH$), 2.22 – 2.12 (1H, m, C$\underline{H}Me_2$), 1.68 (9H, s, CMe_3), 1.40 (9H, s, CMe_3), 1.31 – 1.26 (3H, m, $OCH_2\underline{Me}$), 0.95 – 0.88 (6H, m, $CH\underline{Me}_2$); δ_C (100 MHz; $CDCl_3$) 162.1, 157.4, 156.0, 155.8, 149.5, 136.4, 136.2, 134.4, 134.2, 133.3, 131.6, 131.0, 129.6, 129.5, 129.1, 128.4 (CH), 128.2 (CH), 128.0 (CH), 127.9 (CH), 124.7 (CH), 124.3 (CH), 123.8 (CH), 123.6 (CH), 118.5 (CH), 114.6 (CH), 83.5, 79.0, 61.0 (CH_2), 60.3 (Me), 55.4 (CH), 32.6 (CH), 31.5 (CH_2), 29.6 (CH_2), 28.3 (Me), 28.2 (Me), 26.4 (CH_2), 22.5 (CH_2), 18.7 (Me), 14.3 (Me), 13.9 (Me); *m/z* (ES) 847 (M+Na, 49%), 825 (MH^+, 100), 725 (48), 554 (14), 295 (12), 288 (16), 89 (22), 61 (14).

(*S*)-*N*-(Benzyloxycarbonyl)tyrosine *tert*-butyl ester 22

A solution of (*S*)-tyrosine *tert*-butyl ester (10.0 g, 42.1 mmol) in a two-phase mixture of water (215 mL) and ether (172 mL) at 25 °C was treated with sodium carbonate (12.5 g, 126.4 mmol) and benzyl chloroformate (6.1 mL, 42.1 mmol), and the resulting mixture was stirred for 3 h. The ether layer was separated, washed with saturated brine, dried ($MgSO_4$), concentrated *in vacuo* and purified by flash column chromatography using ethyl acetate – hexane (3:17) to give the title compound (14.8 g, 95%) as a yellow oil which solidified to a solid, mp 86 – 88 °C (lit.,[76] mp 86 °C); (Found: M^+, 371.1731.

$C_{21}H_{25}NO_5$ requires 371.1733); ν_{max} (CH_2Cl_2)/cm^{-1} 3365, 1695, 1506, 1224, 1147; δ_H (300 MHz; $CDCl_3$) 7.39 – 7.29 (5H, m, ArH), 6.99 (2H, d, *J* 8.4, ArH), 6.71 (2H, d, *J* 8.4, ArH), 5.26 (1H, d, *J* 8.2, CHNH), 5.09 (2H, d, *J* 3.2, OCH_2Ph), 4.49 (1H, dt, *J* 6.0, 14.1, CHNH), 3.01 – 2.98 (2H, m, CH_2CHNH), 1.41 (9H, s, CMe_3); δ_C (75 MHz; CD_3OD) 173.8, 159.2, 158.2, 139.1, 130.3 (CH), 129.8, 129.6, 129.5 (CH), 117.0 (CH), 83.6, 68.3 (CH_2), 58.7 (CH), 38.8 (CH_2), 29.0 (Me); *m/z* (EI) 371 (M^+, 4%), 270 (35), 220 (100), 107 (98), 91 (98), 77 (79), 57 (90).

(*S*)-4-Benzyloxy-3-iodo-*N*-(benzyloxycarbonyl)tyrosine *tert*-butyl ester 23

To a solution of (*S*)-*N*-(benzyloxycarbonyl)tyrosine *tert*-butyl ester **22** (14.80 g, 39.8 mmol) in dimethylsulfoxide (102 mL) were added successively sodium iodide (7.16 g, 47.8 mmol) and Chloramine T (10.88 g, 47.8 mmol). The mixture was stirred for 24 h and then diluted with ethyl acetate, washed with hydrochloric acid (5%), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography using ethyl acetate – hexane (1:3) to give a 3:1 mixture of the desired iodo compound along with the starting material **22**. A solution of this crude mixture in dry DMF (115 mL) at 25 °C was treated with benzyl bromide (4.26 mL, 35.8 mmol), potassium carbonate (8.66 g, 62.7 mmol) and tetra-*n*-butylammonium iodide (1.10 g, 2.98 mmol), and the resulting reaction mixture was stirred for 22 h (25 °C). The reaction mixture was diluted with ethyl acetate, washed with 5% hydrochloric acid, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography with ethyl acetate – hexane (1:9) gave the *title compound* (13.9 g, 55% overall) as a colourless solid, mp 98 – 100 °C; $[\alpha]_D^{21}$ 5.9 (*c* 1.08, $CHCl_3$); (Found: $M+NH_4^+$, 605.1508.

$C_{28}H_{34}IN_2O_5$ requires 605.1512); ν_{max} (CH_2Cl_2)/cm^{-1} 3334, 1716, 1485, 1362, 1244, 1147, 727, 697; δ_H (300 MHz; $CDCl_3$) 7.59 (1H, d, *J* 2.2, 2-H), 7.51 – 7.47 (2H, m, ArH), 7.42 – 7.29 (8H, m, ArH), 7.03 (1H, dd, *J* 2.2, 8.6, 6-H), 6.74 (1H, d, *J* 8.6, 5-H), 5.28 (1H, d, *J* 7.9, CHNH), 5.15 – 5.06 (4H, m, 2 × CH_2Ph), 4.51 – 4.44 (1H, m, CHNH), 3.00 – 2.92 (2H, m, CH_2CHNH), 1.41 (9H, s, CMe_3); δ_C (75 MHz; $CDCl_3$) 170.1, 155.9, 155.3, 140.1, 136.3, 136.1, 130.4 (CH), 130.2 (CH), 128.3 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 127.2, 126.7 (CH), 112.2 (CH), 82.2, 70.5 (CH_2), 66.6 (CH_2), 55.0 (CH), 36.7 (CH_2), 27.8 (Me); *m/z* (CI) 605 ($M+NH_4^+$, 42%), 549 (47), 479 (58), 454 (45), 421 (100).

(*S*)-4-Benzyloxy-3-(3-hydroxypropenyl)-*N*-(benzyloxycarbonyl)tyrosine *tert*-butyl ester 25

A mixture of the iodide **23** (13.9 g, 23.6 mmol), E-β-tributylstannyl allyl alcohol **24**[63] (9.0 g, 26.0 mmol), lithium chloride (3.0 g, 71.0 mmol) and dry *N,N*-dimethylformamide (130 mL) was degassed. Bis(triphenylphosphine)palladium dichloride (0.8 g, 1.2 mmol) was added. The solution was further degassed and then stirred for 22 h, under an atmosphere of nitrogen, at 70 °C. After cooling, the catalyst was filtered off. The filtrate was diluted with ethyl acetate, washed with hydrochloric acid (5%), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography using ethyl acetate – hexane (1:3) gave the *title compound* (11.1 g, 91%) as a colourless oil, $[\alpha]_D^{21}$ 5.1 (*c* 0.98, $CHCl_3$); (Found: M^+, 517.2467. $C_{31}H_{35}NO_6$ requires 517.2464); ν_{max} (CH_2Cl_2)/cm^{-1} 3416, 3334, 1726, 1501, 1467, 1250, 1138, 735, 695; δ_H (300 MHz; $CDCl_3$) 7.45 – 7.31 (10H, m, ArH), 7.25 (1H, d, *J* 2.2, 2-H), 6.99 (1H, dd, *J* 8.5, 2.2, 6-

H), 6.95 (1H, dt, *J* 15.9, 1.6, C<u>H</u>=CHCH$_2$), 6.81 (1H, d, *J* 8.5, 5-H), 6.34 (1H, dt, *J* 15.9, 5.7, CH=C<u>H</u>CH$_2$), 5.40 (1H, d, *J* 8.1, CHN<u>H</u>), 5.15 – 5.04 (4H, m, 2 × C<u>H</u>$_2$Ph), 4.51 (1H, dt, *J* 8.1, 6.0, C<u>H</u>NH), 4.25 (2H, d, *J* 5.7, CH=CHC<u>H</u>$_2$), 3.08 – 2.95 (2H, m, C<u>H</u>$_2$CHNH), 2.07 (1H, br s, OH), 1.40 (9H, s, CMe$_3$); δ_C (75 MHz; $CDCl_3$) 170.6, 155.5, 154.7, 136.8, 136.2, 129.4 (CH), 128.4 (CH), 128.3 (CH), 128.2, 128.0 (CH), 127.7 (CH), 127.1 (CH), 125.8, 125.5 (CH), 112.3 (CH), 82.1, 70.1 (CH_2), 66.7 (CH_2), 63.8 (CH_2), 55.1 (CH), 37.4 (CH_2), 27.8 (Me); *m/z* (CI) 535 (M+NH_4^+, 85%), 500 (88), 444 (46), 384 (100).

(*S*)-4-Benzyloxy-3-(3-bromopropenyl)-*N*-(benzyloxycarbonyl)tyrosine *tert*-butyl ester 26

A solution of the allyl alcohol **25** (11.10 g, 21.4 mmol), and dry pyridine (0.95 mL, 11.8 mmol) in anhydrous ether (270 mL) was cooled to -20 °C under an atmosphere of nitrogen. Phosphorus tribromide (1.31 mL, 13.9 mmol) was added dropwise, and the resulting white slurry then allowed to warm to room temperature. After 2 h stirring, the mixture was poured onto ice. The organic layer and ethereal extracts of the aqueous layer were dried ($MgSO_4$) and evaporated to give the title compound (12.00 g, 97%) as an orange oil that was not purified further; ν_{max} (CH_2Cl_2)/cm^{-1} 3332, 1713, 1494, 1251, 1152, 746, 698; δ_H (300 MHz; $CDCl_3$) 7.46 – 7.30 (10H, m, ArH), 7.24 (1H, d, *J* 1.9, 2-H), 7.00 (1H, dd, *J* 8.3, 1.9, 6-H), 6.98 (1H, d, *J* 15.8, C<u>H</u>=CHCH$_2$), 6.84 (1H, d, *J* 8.3, 5-H), 6.40 (1H, dt, *J* 15.8, 7.6, CH=C<u>H</u>CH$_2$), 5.31 (1H, d, *J* 8.0, CHN<u>H</u>), 5.17 – 5.08 (4H, m, 2 × C<u>H</u>$_2$Ph), 4.51 (1H, dt, *J* 8.0, 5.7, C<u>H</u>NH), 4.17 (2H, d, *J* 7.6, CH=CHC<u>H</u>$_2$), 3.07 – 3.01 (2H, m, C<u>H</u>$_2$CHNH), 1.42 (9H, s, CMe$_3$); δ_C (75 MHz; $CDCl_3$) 170.5, 155.5, 155.1, 136.7, 136.2, 130.3 (CH), 129.0 (CH), 128.5 (CH), 128.4 (CH), 128.3, 128.2 (CH), 128.1

(CH), 128.0 (CH), 127.9 (CH), 127.3 (CH), 125.9 (CH), 124.9, 112.4 (CH), 82.3, 70.3 (CH_2), 66.8 (CH_2), 55.1 (CH), 37.5 (CH_2), 34.1 (CH_2), 27.9 (Me).

(*S*)-4-Benzyloxy-3-(3-(2-bromophenoxy)propenyl)-*N*-(benzyloxycarbonyl)tyrosine *tert*-butyl ester 27

The crude allyl bromide **26** (12.0 g, 20.7 mmol) was dissolved in benzene (70 mL). To this solution were added successively aqueous NaOH (50%; 58 mL), tetra-*n*-butylammonium hydrogen sulfate (3.5 g, 10.3 mmol) and 2-bromophenol (2.9 mL, 24.8 mmol). The resulting mixture was stirred vigorously (25 °C) for 40 min. After dilution with dichloromethane, the reaction mixture was washed with hydrochloric acid (5%), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography using ethyl acetate – hexane (3:17) gave the *title compound* (10.2 g, 74%) as a sticky solid, $[\alpha]_D^{21}$ 4.3 (*c* 1.22, $CHCl_3$); (Found: M+NH_4^+, 689.2220. $C_{37}H_{42}{}^{79}BrN_2O_6$ requires 689.2226); ν_{max} (CH_2Cl_2)/cm^{-1} 3339, 1721, 1490, 1244, 1142, 730, 692; δ_H (300 MHz; $CDCl_3$) 7.57 (1H, dd, *J* 7.9, 1.6, ArH); 7.43 – 7.31 (10H, m, ArH), 7.30 (1H, d, *J* 2.2, 2-H), 7.22 (1H, ddd, *J* 7.9, 8.3, 1.6, ArH), 7.16 (1H, dt, *J* 16.2, 1.5, C<u>H</u>=CHCH$_2$), 7.03 (1H, dd, *J* 8.3, 1.4, ArH), 6.93 (1H, dd, *J* 8.6, 2.2, 6-H), 6.86 (1H, d, *J* 8.6, 5-H), 6.85 (1H, dt, *J* 1.4, 7.9, ArH), 6.43 (1H, dt, *J* 16.2, 5.4, CH=C<u>H</u>CH$_2$), 5.38 (1H, d, *J* 8.1, CHN<u>H</u>), 5.15 – 5.07 (4H, m, 2 × C<u>H</u>$_2$Ph), 4.75 (2H, d, *J* 5.4, CH=CHC<u>H</u>$_2$), 4.59 – 4.52 (1H, m, C<u>H</u>NH), 3.07 – 3.01 (2H, m, C<u>H</u>$_2$CHNH), 1.43 (9H, s, CMe_3); δ_C (75 MHz; $CDCl_3$) 170.5, 155.5, 154.9, 154.8, 136.7, 136.2, 133.2 (CH), 129.8 (CH), 128.5 (CH), 128.4 (CH), 128.3, 128.2 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.5 (CH), 127.2 (CH), 125.5, 124.4 (CH), 121.7 (CH), 113.4 (CH), 112.3 (CH), 112.2, 82.1, 70.2 (CH_2), 69.6

(CH_2), 66.7 (CH_2), 55.1 (CH), 37.4 (CH_2), 27.8 (Me); *m/z* (CI) 691/689 ($M+NH_4^+$, 100%), 633 (88).

(*S*)-4-Benzyloxy-3-(1-(3-bromo-2-hydroxyphenyl)prop-2-enyl)-*N*-(benzyloxycarbonyl)tyrosine *tert*-butyl ester 28

A solution of the allyl ether **27** (10.2 g, 15.2 mmol) in dry *N,N*-dimethylformamide (140 mL) was heated to reflux under an nitrogen atmosphere for 11 h. After cooling, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography with ethyl acetate – hexane (1:9) to afford recovered starting material (15%) and the *title compound* (5.1 g, 50%) as a colourless foam (mixture of two diastereoisomers), $[\alpha]_D^{21}$ 2.2 (*c* 1.15, $CHCl_3$); (Found: $M+NH_4^+$, 689.2220. $C_{37}H_{42}{}^{79}BrN_2O_6$ requires 689.2226); ν_{max} (CH_2Cl_2)/cm^{-1} 3598, 3416, 1710, 1495, 1449, 1244, 1147, 727, 681; δ_H (300 MHz; $CDCl_3$) 7.35 – 7.26 (9H, m, ArH), 7.24 – 7.13 (2H, m, ArH), 7.05 – 6.86 (3H, m, ArH), 6.80 (1H, d, *J* 8.3, 5-H), 6.69 (0.5H, t, *J* 7.7, ArH), 6.68 (0.5H, t, *J* 7.7, ArH), 6.30 – 6.18 (1H, m, =CH), 5.72 (0.5H, s, OH), 5.70 (0.5H, s, OH), 5.43 (1H, d, *J* 5.9, CHN<u>H</u>), 5.27 – 5.15 (2H, m, OC<u>H</u>$_2$Ph), 5.13 – 5.06 (2H, m, OC<u>H</u>$_2$Ph), 5.02 – 4.86 (3H, m, =CH_2, Ar_2C<u>H</u>), 4.53 – 4.47 (1H, m, C<u>H</u>NH), 3.04 – 2.95 (2H, m, C<u>H</u>$_2$CHNH), 1.39 (9H, s, CMe_3); δ_C (100 MHz; $CDCl_3$) 170.6, 155.5, 154.9, 149.9, 138.5, 136.9, 136.8, 136.3, 130.8, 130.7, 130.6 (CH), 130.4 (CH), 130.0 (CH), 129.9 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 128.1 (CH), 128.0 (CH), 127.8, 127.7 (CH), 127.2 (CH), 127.1 (CH), 121.2 (CH), 116.6 (CH_2), 116.5 (CH_2), 112.0 (CH), 110.6, 82.2, 70.2 (CH_2), 70.1 (CH_2), 66.8 (CH_2), 55.1

(CH), 42.4 (CH), 37.5 (CH_2), 28.0 (Me); *m/z* (CI) 691/689 ($M+NH_4^+$, 56%), 636 (37), 633 (100).

(*S*)-4-Benzyloxy-3-(7-bromo-2-hydroxy-1,2-dihydrobenzo[*b*]furan-3-yl)-*N*-(benzyloxycarbonyl)tyrosine *tert*-butyl ester 29

A solution of the alkene **28** (5.10 g, 7.58 mmol) in 72 mL of the tertiary solvent system of MeOH/ethyl acetate/water (3:2:1) was treated with potassium periodate (8.57 g, 37.00 mmol) and an etheral solution (9.4 mL) of osmium tetroxide (37 mg, 0.14 mmol). The reaction was stirred vigorously at 25 °C for 8 h and was then partitioned between water and dichloromethane. The organic extracts were combined, dried over $MgSO_4$ and evaporated. Purification by flash column chromatography eluting with ethyl acetate – hexane (1:4) gave the *title compound* (4.49 g, 88%) as a colourless foam (mixture of four diastereoisomers), $[\alpha]_D^{21}$ 3.1 (*c* 1.08, $CHCl_3$); (Found: $M+NH_4^+$, 691.2018. $C_{36}H_{40}{}^{79}BrN_2O_7$ requires 691.2019); ν_{max} (CH_2Cl_2)/cm^{-1} 3400, 1716, 1495, 1460, 1239, 1147, 737, 697; δ_H (300 MHz; $CDCl_3$) 7.35 – 7.21 (10H, m, ArH), 7.12 – 6.86 (4H, m, ArH), 6.80 – 6.65 (2H, m, ArH), 6.14 (0.34H, br s), 6.02 (0.33H, br s), 5.96 (0.33H, br s), 5.24 – 5.13 (1H, m, CHN<u>H</u>), 5.09 – 4.92 (4.34H, m), 4.82 (0.66H, m), 4.49 – 4.40 (1H, m), 3.71 (1H, br s, OH), 3.13 – 2.81 (2H, m, C<u>H</u>$_2$CHNH), 1.42 (9H, s, CMe_3); δ_C (75 MHz; $CDCl_3$) 170.6, 170.5, 170.4, 155.8, 155.7, 155.6, 155.5, 155.3, 155.1, 136.6, 136.4, 136.2, 136.1, 131.6 (CH), 131.5 (CH), 131.4 (CH), 130.5 (CH), 130.4 (CH), 130.1 (CH), 130.0 (CH), 129.9 (CH), 129.8 (CH), 129.7 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.3 (CH), 127.2 (CH), 127.1 (CH), 124.4 (CH), 124.2 (CH), 124.1 (CH), 122.6 (CH), 122.4 (CH), 122.3 (CH), 112.3 (CH), 112.1 (CH),

112.0 (CH), 107.2 (CH), 107.1 (CH), 103.3, 103.2, 103.1, 103.0, 102.6 (CH), 102.3 (CH), 82.6, 82.4, 82.3, 82.2, 70.6 (CH_2), 70.2 (CH_2), 66.9 (CH_2), 55.2 (CH), 55.1 (CH), 54.9 (CH), 52.0 (CH), 38.1 (CH_2), 37.5 (CH_2), 37.3 (CH_2), 28.0 (Me), 27.9 (Me); *m/z* (CI) 693/691 ($M+NH_4^+$, 100%), 619 (58), 600 (43), 539 (38).

(*S*)-4-Benzyloxy-3-(7-bromo-2-oxo-1,2-dihydrobenzo[*b*]furan-3-yl)-*N*-(benzyloxycarbonyl)tyrosine *tert*-butyl ester 31

A solution of the lactol **7** (4.49 g, 6.65 mmol) in 400 mL of dichloromethane at 25 °C was treated with 1-hydroxy-1,3-dihydro-3,3-bis(trifluoromethyl)-1,2-benziodoxole-1-oxide **30** (8.00 g, 19.9 mmol) and stirred for 2 h. After adding further oxidant (1.40 g) and stirring for another 90 min, the mixture was filtered through a pad of Celite, washed with dichloromethane and concentrated under reduced pressure. Purification by flash column chromatography (ethyl acetate-hexane 1:4) gave the *title compound* (3.71 g, 83%) as a white foam (mixture of two diastereoisomers); $[\alpha]_D^{21}$ 2.1 (*c* 0.59, $CHCl_3$); (Found: $M+NH_4^+$, 689.1865. $C_{36}H_{38}{}^{79}BrN_2O_7$ requires 689.1862); ν_{max} (CH_2Cl_2)/cm^{-1} 3411, 1823, 1716, 1506, 1444, 1250, 1219, 1081, 732, 691; δ_H (300 MHz; $CDCl_3$) 7.43 – 7.27 (9H, m, ArH), 7.11 – 7.02 (4H, m, ArH), 6.93 – 6.87 (2H, m, ArH), 6.82 (1H, dd, *J* 2.0, 7.9, ArH), 5.30 – 5.22 (1H, m, CHN<u>H</u>), 5.18 – 5.03 (2H, m, OC<u>H</u>$_2$Ph), 4.93 (1H, d, *J* 11.4, OC<u>H</u>HPh), 4.86 (1H, s, benzofuran 3-H), 4.84 (1H, d, *J* 11.4, OCH<u>H</u>Ph), 4.49 (1H, m, C<u>H</u>NH), 3.13 – 2.97 (2H, m, C<u>H</u>$_2$CHNH), 1.41 (9H, s, CMe_3); δ_C (75 MHz; $CDCl_3$) 173.6, 173.5, 170.5, 170.4, 154.9, 154.8, 151.7, 151.6, 136.4, 136.3, 135.6, 132.3 (CH), 132.1 (CH), 131.9 (CH), 131.8 (CH), 131.0 (CH), 130.9 (CH), 129.2, 129.1, 128.8, 128.7, 128.6 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 127.3 (CH), 125.0 (CH), 123.8,

123.7, 122.9 (CH), 122.8 (CH), 112.4 (CH), 112.3 (CH), 103.3, 103.2, 82.5, 82.4, 70.5 (CH_2), 70.4 (CH_2), 66.9 (CH_2), 55.2 (CH), 55.1 (CH), 48.1 (CH), 48.0 (CH), 37.4 (CH_2), 28.0 (Me), 27.9 (Me); *m/z* (CI) 691/689 ($M+NH_4^+$, 91%), 633 (36), 611 (100), 555 (35).

(*S*)-*N*-Benzyloxycarbonyl-*O*-(3-phenylprop-2-enyl)tyrosine methyl ester 37

To an unwashed emulsion of NaH (60% in mineral oil; 70 mg, 1.7 mmol) in dry THF (1.5 mL) at 0 °C, was added a cooled solution of *N*-benzyloxycarbonyl-(*S*)-tyrosine methyl ester **36** (500 mg, 1.5 mmol) in dry THF (3 mL) over approximately 45 min. The reaction mixture was maintained at 0 °C for 1 h prior to the dropwise addition of cinnamyl bromide (450 mg, 2.3 mmol) in dry THF (2.5 mL). After an additional 1 h stirring, the THF was removed under reduced pressure and ethyl acetate (20 mL) was added to the residue. This solution was washed with brine and water, dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by chromatography using light petroleum – ethyl acetate (5:2) to give the *title compound* (204 mg, 30%) as a pale yellow solid, mp 96 – 97 °C; (Found: C, 72.8; H, 6.2; N, 2.8. $C_{27}H_{27}NO_5$ requires C, 72.8; H, 6.1; N, 3.1%); (Found: MH^+, 446.1985. $C_{27}H_{28}NO_5$ requires 446.1967); ν_{max} (film)/cm^{-1} 3031, 2952, 1724, 1611, 1511, 1449, 1242, 1214, 1178, 1059, 1017, 967, 737, 695; δ_H (400 MHz; $CDCl_3$) 7.42 – 7.23 (10H, m, ArH), 7.01 (2H, d, *J* 8.6, ArH), 6.86 (2H, d, *J* 8.6, ArH), 6.72 (1H, bd, *J* 16.1, PhC<u>H</u>=CHCH$_2$), 6.40 (1H, dt, *J* 16.1, 5.8, PhCH=C<u>H</u>CH$_2$), 5.21 (1H, bd, *J* 8.0, CHN<u>H</u>), 5.13 – 5.06 (2H, m, OC<u>H</u>$_2$Ph), 4.66 (2H, dd, *J* 1.4, 5.8, CH=CHC<u>H</u>$_2$O), 4.66 – 4.60 (1H, m, C<u>H</u>NH), 3.71 (3H, s, OMe), 3.08 (1H, dd, *J* 6.1, 14.5, C<u>H</u>HCHNH), 3.03 (1H, dd, *J* 6.2, 14.4, CH<u>H</u>CHNH); δ_C (100 MHz; $CDCl_3$) 172.0, 157.8, 155.6, 136.4, 136.3, 133.0 (CH), 130.3 (CH), 128.6 (CH), 128.5

(CH), 128.2 (CH), 128.1 (CH), 127.91 (CH), 127.87 (CH), 126.6 (CH), 124.4 (CH), 114.9 (CH), 68.7 (CH_2), 67.0 (CH_2), 54.9 (CH), 52.3 (Me), 37.4 (CH_2); *m/z* (CI) 446 (MH^+, 12%), 430 (5), 402 (100), 385 (3).

(*S*)-*N*-Benzyloxycarbonyl-3-(1-phenylprop-2-enyl)tyrosine methyl ester 38

A solution of the allyl ether **37** (60 mg, 0.13 mmol) in 1,2-dichlorobenzene (1.5 mL) was submerged in a preheated oil bath at *ca*. 200 °C. The reaction mixture was allowed to stir for 15 h. The dichlorobenzene solution was added directly to a silica column using light petroleum – ethyl acetate (5:2) as eluant and purified to give the *title compound* (mixture of diastereomers) as an oil (27 mg, 45%); (Found: MH^+, 446.1972. $C_{27}H_{28}NO_5$ requires 446.1967); ν_{max} (film)/cm^{-1} 3361, 1717, 1701, 1610, 1508, 1262, 1061, 734; δ_H (400 MHz; $CDCl_3$) 7.35 – 7.17 (11H, m, ArH), 6.82 – 6.78 (1H, m, ArH), 6.68 – 6.66 (1H m, ArH), 6.30 – 6.21 (1H, m, C<u>H</u>=CH_2), 5.42 (1H, d, *J* 6.1, CHN<u>H</u>), 5.26 – 5.23 (1H, m, CH=CH<u>H</u>), 5.09 (2H, s, OC<u>H_2</u>Ph), 4.97 – 4.96 (1H, m, C<u>H</u>CH=CH_2), 4.97 – 4.90 (1H, m, CH=C<u>H</u>H), 4.61 – 4.59 (1H, m, C<u>H</u>NH), 3.67/3.57 (3H, 2 × s, OMe), 3.01 (2H, m, C<u>H_2</u>CHNH), 1.75 (1H, bs, OH); δ_C (100 MHz; $CDCl_3$) 173.4, 157.0, 154.1 (CH), 143.0, 140.9 (CH), 137.5, 131.7, 130.6, 130.0, 129.89, 129.87, 129.5, 129.4, 128.8, 128.0, 118.3 (CH_2), 117.6 (CH), 61.8 (CH_2), 56.2 (CH), 53.6 (Me), 49.9 (CH), 38.8 (CH_2); *m/z* (CI) 446 (MH^+, 9%), 430 (17), 428 (5), 402 (100), 385 (10), 338 (44), 223 (23).

5-[2-(Benzyloxycarbonyl)amino-2-methoxycarbonyl]ethyl-3-phenyldihydrobenzo[*b*]furan-2-ol 40

A solution of the above alkene **38** (280 mg, 0.62 mmol) in MeOH (13 mL) was cooled to -78 °C and ozone was bubbled through the solution until a persistent blue colouration was observed (*ca*. 1 h). The reaction mixture was flushed with nitrogen for 5 min after which no blue colouration remained. Dimethyl sulfide (0.2 mL) was added and the mixture was allowed to stir overnight with warming to room temperature. Concentration of the reaction mixture under reduced pressure and purification of the residue by chromatography with light petroleum – ethyl acetate (2:1) gave the *title compound* (96 mg, 35%) as a yellow oil, as a complex mixture of diastereomers that could not be fully characterized; δ_H (400 MHz; $CDCl_3$) 7.50 – 7.29 (13H, m, ArH), 6.45 (1H, bd, *J* 7.5, 2-H), 5.79/5.77 (1H, 2 × d, *J* 7.3/7.4, CHNH), 5.12 – 4.87 (3H, m, OCH_2Ph and 3-H), 4.61 – 4.55 (1H, m, CHNH), 3.73/3.69 (3H, 2 × s, OMe), 3.45 – 3.13 (2H, m, CH_2CHNH); δ_C (100 MHz; $CDCl_3$) 171.2, 156.1, 131.0 (CH), 130.9 (CH), 129.7, 129.22 (CH), 129.18 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 128.24 (CH), 128.16 (CH), 128.1 (CH), 122.3, 98.1 (CH), 67.3 (CH_2), 53.0/52.9 (Me), 50.00/49.98 (CH), 44.5/44.1 (CH), 39.0/38.7 (CH_2).

(*S*)-*N*-Benzyloxycarbonyl-3-iodotyrosine-*tert*-butyl ester 43

(a) 3-Iodotyrosine **41** (1.50 g, 4.95 mmol) was added to a biphasic mixture of ether (25 mL) and water (25 mL) at room temperature. The tyrosine gradually dissolved following the addition of Na_2CO_3 (1.47 g, 14.82 mmol). The solution was then treated with benzyl chloroformate (0.72 mL, 14.95 mmol) and the reaction mixture was allowed to stir for 8 h. The aqueous phase was washed with ether (2 × 20 mL) prior to acidification to pH 1 with HCl (2 M). Extraction of the aqueous phase with ether (3 × 25 mL) was followed by

washing the organics with brine, drying ($MgSO_4$) and concentration *in vacuo* to give *N*-benzyloxycarbonyl-3-iodo-(*S*)-tyrosine **42** (1.60 g, 75%) as a colourless oil,(lit.,[77] no data) used without further purification.

(b) The above iodotyrosine (1.60 g, 3.6 mmol) was dissolved in THF (79 mL) and treated with benzyltriethylammonium chloride (BTEAC, 0.78 g, 8.6 mmol) followed by water (2 – 4 drops). K_2CO_3 (12.25 g, 89 mmol) and 2-bromo-2-methylpropane (18.9 mL, 165.0 mmol) were added sequentially and the reaction mixture was heated to *ca*. 60 °C with vigorous stirring overnight. The mixture was filtered through Celite and concentrated under vacuum. Ethyl acetate (20 mL) and water (20 mL) were added followed by further extraction of the aqueous layer with ethyl acetate (2 × 30 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography using light petroleum – ethyl acetate (2:1) to give the *title compound* (1.18 g, 66%) as an oil; $[\alpha]_D^{24}$ 23.0 (*c* 1.0, CH_2Cl_2); (Found: MH^+, 498.0764. $C_{21}H_{25}INO_5$ requires 498.0777); ν_{max} (film)/cm^{-1} 3344, 1717, 1700, 1604, 1506, 1456, 1153; δ_H (300 MHz; $CDCl_3$) 7.44 – 7.29 (7H, m, ArH), 7.00 (1H, d, *J* 8.2, ArH), 6.86 (1H, d, *J* 8.2, ArH), 5.39 (1H, s, OH), 5.28 (1H, bd, *J* 7.8, CHN<u>H</u>), 5.16 – 5.06 (2H, m, OC<u>H</u>$_2$Ph), 4.48 – 4.44 (1H, m, C<u>H</u>NH), 2.98 (2H, bd, *J* 5.7, C<u>H</u>$_2$CHNH), 1.42 (9H, s, CMe_3); δ_C (75 MHz; $CDCl_3$) 170.3, 155.6, 153.9, 138.9 (CH), 136.5, 131.3 (CH), 130.2, 128.6 (CH), 128.2 (CH), 128.1 (CH), 114.9 (CH), 85.4, 82.7, 66.9 (CH_2), 55.2 (CH), 37.0 (CH_2), 28.0 (Me); *m/z* (CI) 498 (MH^+, 2%), 488 (8), 442 (29), 398 (53), 346 (18), 91 (100).

Ethyl 2-tri-*n*-butylstannylbut-2-enoate 45

A degassed solution of tri-*n*-butyltin hydride (18.60 g, 17.20 mL, 63.9 mmol) in dry THF (80 mL) was added dropwise to a solution of ethyl 2-butynoate **44** (7.16 g, 7.45 mL, 63.9 mmol) and $Pd(PPh_3)_4$ (1.48 g, 1.29 mmol) in dry THF (80 mL) over *ca*. 1 h. The mixture was allowed to stir at room temperature overnight. The THF was removed under reduced pressure and light petroleum (200 mL) was added prior to filtration through Celite and concentration *in vacuo*. Column chromatography eluting with light petroleum – ethyl acetate (10:1) gave a mixture of the *title compound* (22.56 g, 88%) as a colourless oil, contaminated with its regioisomer (*ca*. 3:1 mixture used without further purification); (Found: MH^+, 405.1815. $C_{18}H_{37}O_2{}^{120}Sn$ requires 405.1821); ν_{max} (film)/cm^{-1} 2957, 2927, 2872, 2854, 1709, 1607, 1464, 1376, 1179, 1036; δ_H (400 MHz; $CDCl_3$) (major regioisomer) 6.18 (1H, q, *J* 6.8, =C<u>H</u>Me), 4.16 (2H, q, *J* 7.2, OC<u>H</u>$_2$Me), 2.01 (3H, d, *J* 6.8, =CH<u>Me</u>), 1.51 – 1.47 (6H, m, 3 × C<u>H</u>$_2$), 1.33 – 1.27 (9H, m, OCH$_2$<u>Me</u> + 3 × C<u>H</u>$_2$), 0.93 – 0.87 (15H, m, 3 × C<u>H</u>$_2$, 3 × C<u>H</u>$_3$); (minor regioisomer) 5.96 (1H, q, *J* 1.9, C<u>H</u>CCO$_2$Et), 4.15 (2H, q, *J* 7.2, OC<u>H</u>$_2$Me), 2.40 (3H, d, *J* 1.8, =C<u>Me</u>SnBu$_3$); *m/z* (EI) 405 (MH^+, 5%), 347 (100).

(*E*)-Ethyl 2-phenylbut-2-enoate 46

A solution of iodobenzene (2.8 mL, 25 mmol) in dry DMF (230 mL) was degassed and sequentially treated with impure ethyl 2-tri-*n*-butylstannylbut-2-enoate **45** (10.0 g, 25 mmol), $Pd(PPh_3)_4$ (2.5 g, 2 mmol) and CuI (3.5 g, 19 mmol). The reaction mixture was allowed to stir at room temperature. The mixture was diluted with with ethyl acetate (100 mL) and filtered through Celite. The filtrate was then stirred for 1 h with saturated aqueous NH_4Cl after which the organic layer was separated, washed with brine and

concentrated *in vacuo*. Ethyl acetate (1 L) and aqueous KF solution (50%; 500 mL) were added and the biphasic mixture was stirred vigorously for 3 h. The emulsion was filtered through Celite prior to extraction of the aqueous phase with ethyl acetate (2 × 250 mL). The combined organic layers were washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography using light petroleum – ethyl acetate (10:1) gave an inseparable mixture of regioisomers (*ca.* 7:1) with the *title compound* as the major isomer (3.2 g, 63%); (Found: MH^+, 191.1066. $C_{12}H_{14}O_2$ requires 191.1072); ν_{max} (film)/cm^{-1} 2981, 1718, 1448, 1396, 1346, 1271, 1198, 1027; δ_H (400 MHz; $CDCl_3$) (major regioisomer) 7.39 – 7.05 (5H, m, ArH), 6.28 (1H, q, *J* 7.2, =C<u>H</u>Me), 4.32 (2H, q, *J* 7.1, OC<u>H</u>$_2$Me), 2.06 (3H, d, *J* 7.2, =CH<u>Me</u>), 1.33 (3H, t, *J* 7.1, OCH$_2$<u>Me</u>); (minor regioisomer) 7.39 – 7.05 (5H, m, ArH), 6.16 (1H, d, *J* 0.8, =C<u>H</u>CO$_2$Et), 4.24 (2H, q, *J* 7.1, OC<u>H</u>$_2$Me), 2.61 (3H, d, *J* 0.8, =C<u>Me</u>Ph), 1.31 (3H, t, *J* 7.1, OCH$_2$<u>Me</u>); *m/z* (CI) 191 (MH^+, 79%), 190 (M^+, 69), 145 (100), 117 (35).

(*E*)-2-Phenylbut-2-enoic acid 47

A solution of mostly ethyl 2-phenylbut-2-enoate **46** (3.17 g, 16.7 mmol), KOH (1.46 g, 25.8 mmol) in ethanol (108 mL) was heated under reflux for 24 h. The ethanol was removed under reduced pressure and water (40 mL) was added followed by washing with dichloromethane (50 mL). The aqueous phase was acidified with HCl (2 M) to *ca*. pH 1 and extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under vacuum. Recrystallization of the residue with light petroleum:ethyl acetate gave the title compound (1.63 g, 60%) as fine pale yellow crystals, mp 139 – 140 °C (ethyl acetate/light petroleum) (lit.,[78] mp 136

– 138 °C; (*Z*)-isomer mp 96 – 98 °C); (Found: MH^+, 163.0740. $C_{10}H_{11}O_2$ requires 163.0759); ν_{max} ($CHCl_3$)/cm^{-1} 3061, 2254, 1688, 1635, 1276; δ_H (300 MHz; $CDCl_3$) 7.38 – 7.18 (6H, m, ArH + =C<u>H</u>Me), 1.78 (3H, d, *J* 7.2, =CH<u>Me</u>), OH not observed; δ_C (75 MHz; $CDCl_3$) 172.3, 142.8 (CH), 134.4, 134.1, 129.8 (CH), 128.1 (CH), 127.6 (CH), 15.8 (Me); *m/z* (CI) 163 (MH^+, 100%), 145 (77), 117 (16).

_N_-Benzyloxycarbonyl-3-iodo-_O_-(2-phenylbut-2-enoyl)tyrosine _tert_-butyl ester 48

2-Phenylbut-2-enoic acid **47** (0.18 g, 1.08 mmol) and the iodotyrosine derivative **43** (1.12 g, 2.26 mmol) were dissolved in dry dichloromethane (3 mL) under a nitrogen atmosphere. A second solution of DCC (0.51 g, 2.47 mmol) in dry dichloromethane (5 mL) was prepared and both solutions were cooled to 0 °C. The DCC solution was added to the first solution slowly over 30 min, and the mixture was stirred at 0 °C for 2 h. Dichloromethane (10 mL) was added to the suspension which was then filtered through Celite and washed with brine and water, then dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by chromatography using light petroleum – ethyl acetate (5:2) to give (i) the excess iodotyrosine derivative **43** (0.33 g, 83%) and (ii) the *title compound* as a colourless oil (513 mg, 74%) ; (Found: MH^+, 642.1353. $C_{31}H_{33}INO_6$ requires 642.1352); $[\alpha]_D^{25}$ 40.0 (*c* 2.0, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3348, 2978, 1734, 1637, 1497, 1483, 1252, 1217, 1158, 734; δ_H (400 MHz; $CDCl_3$) 7.61 (1H, d, *J* 1.3, 2-H), 7.54 (1H, q, *J* 7.2, =C<u>H</u>Me), 7.42 – 7.32 (10H, m, ArH), 7.12 (1H, d, *J* 8.0, ArH), 7.02 (1H, d, *J* 8.2, ArH), 5.31 (1H, bd, *J* 7.8, CHN<u>H</u>), 5.14 – 5.07 (2H, m, OC<u>H</u>$_2$Ph), 4.50 (1H, dd, *J* 5.9, 13.6, C<u>H</u>NH), 3.03 (2H, d, *J* 5.9, C<u>H</u>$_2$CHNH), 1.86 (3H, d, *J* 7.2, =CH<u>Me</u>), 1.41 (9H, s, CMe_3); δ_C (100 MHz; $CDCl_3$) 170.1, 164.6, 155.5, 150.5, 143.2 (CH), 140.1 (CH),

136.3, 135.7, 134.3, 133.9, 130.5 (CH), 130.1 (CH), 128.6 (CH), 128.1 (CH, 2 masked signals), 127.7 (CH), 122.8 (CH), 90.3, 82.9, 66.9 (CH_2), 55.0 (CH), 37.3 (CH_2), 28.0 (Me), 15.9 (Me); *m/z* (CI) 642 (MH^+, 5%), 586 (39), 542 (67), 496 (5), 145 (50), 91 (100).

5-[2-(Benzyloxycarbonyl)amino-2-*tert*-butoxycarbonyl]ethyl-3-phenyl-3-vinyldihydrobenzo[*b*]furan-2-one 49

A solution of *N*-benzyloxycarbonyl-3-iodo-*O*-(2-phenylbut-2-enoyl)tyrosine *tert*-butyl ester **48** (2.04 g, 3.20 mmol), $Pd_2(dba)_3$•$CHCl_3$ (0.31 g, 0.32 mmol, 10 mol%), Ag_3PO_4 (1.57 g, 3.76 mmol), *S*-BINAP (0.43 g, 0.72 mmol, 23 mol%) in dry dimethylacetamide (39 mL) was prepared under nitrogen and degassed twice. The reaction mixture was then heated to 100 °C with stirring for 48 h. Ethyl acetate (50 mL) was added and the mixture was filtered through Celite before washing with HCl (1 M; 100 mL) and water (50 mL). The organics were dried ($MgSO_4$) and concentrated under pressure to give a brown oil purified by chromatography using light petroleum – ethyl acetate (5:2). The *title compound* was obtained as a colourless oil (1.04 g, 63%) as a mixture of diastereomers in the ratio 1:1.5 as determined from CMe_3 signals in the ^1H NMR; (Found: MH^+, 514.2213. $C_{31}H_{32}NO_6$ requires 514.2229); ν_{max} (film)/cm^{-1} 3344, 2979, 1805, 1719, 1485, 1255, 1230, 1154, 1054; δ_H (400 MHz; $CDCl_3$) 7.34 – 7.25 (10H, m, ArH), 7.11 – 7.09 (2H, m, ArH), 6.98 (1H, s, ArH), 6.27/6.25 (1H, 2 × dd, *J* 10.3/10.4, 17.3/17.2, C<u>H</u>=CH_2), 5.40 (1H, dd, *J* 1.9, 10.3, CH=CH<u>H</u>), 5.27 – 5.24 (1H, m, CHN<u>H</u>), 5.22 (1H, dd, *J* 6.3, 17.2, CH=C<u>H</u>H), 5.12 – 5.03 (2H, m, OC<u>H</u>$_2$Ph), 4.54 – 4.47 (1H, m, C<u>H</u>NH), 3.14/3.07 (1H, 2 × dd, *J* 6.2/6.2, 14.0/14.0, CH<u>H</u>CHNH), 3.09 – 3.02 (1H, m, C<u>H</u>HCHNH), 1.37/1.32

(9H, 2 × s, CMe_3): δ_C (100 MHz; $CDCl_3$) 175.8, 170.4/170.2, 155.5, 151.83/151.80, 138.4/138.3, 136.2, 135.9/135.8 (CH), 132.54/132.51, 130.5 (CH), 129.8/129.7, 129.0 (CH), 128.5 (CH), 128.3/128.2 (CH), 128.1 (CH), 127.21 (CH), 127.16 (CH), 126.7 (CH), 118.4 (CH_2), 110.94/110.89 (CH), 82.62/82.61, 66.9 (CH_2), 59.1/59.0, 55.3/55.1 (CH), 38.3/38.0 (CH_2), 28.0/27.9 (Me); *m/z* (CI) 514 (MH^+, 16%), 458 (58), 414 (100), 362 (73), 322 (17).

5-[2-(Benzyloxycarbonyl)amino-2-*tert*-butoxycarbonyl]ethyl-3-phenyl-3-vinyldihydrobenzo[*b*]furan-2-ol 51

5-[2-(Benzyloxycarbonyl)amino-2-*tert*-butoxycarbonyl]ethyl-3-phenyl-3-vinyldihydrobenzo[*b*]furan-2-one **49** (110 mg, 0.22 mmol) was dissolved in THF (3.6 mL) and the solution cooled on an ice-bath. Approximately half of the $NaBH_4$ (21 mg, 0.55 mmol, total) was added to the mixture with stirring and after 15 min the remaining $NaBH_4$ was added. Water (10 mL) was added to the reaction mixture after a total of 30 min stirring and the mixture extracted with ethyl acetate (3 × 15 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography with light petroleum – ethyl acetate (5:2) gave the *title compound* (35 mg, 32%) as a colourless oil as a mixture of diastereomers; (Found: MH^+, 516.2380. $C_{31}H_{34}NO_6$ requires 516.2386); ν_{max} (film)/cm^{-1} 3365, 2978, 2361, 1117, 1701, 1488, 1363, 1250, 1154; δ_H (400 MHz; $CDCl_3$) 7.32 – 6.80 (13H, m, ArH), 6.45 – 6.30 (1H, m, C<u>H</u>=CH_2), 6.00 – 5.94 (1H, m, C<u>H</u>OH), 5.45 (0.5H, dd, *J* 6.6, 10.6, CH=C<u>H</u>H), 5.31 (0.5H, dd, *J* 2.9, 10.7, CH=C<u>H</u>H), 5.24 – 5.20 (1H, m, CHN<u>H</u>), 5.17 – 5.01 (3H, m, O<u>CH_2</u>Ph + CH=CH<u>H</u>), 4.49 – 4.48 (1H, m, C<u>H</u>NH), 3.39 (0.5H, d, *J* 9.2, CHO<u>H</u>), 3.10 –

2.93 (2H, m, C<u>H</u>$_2$CHNH), 2.69 (0.5H, dd, *J* 4.3, 10.8, CHO<u>H</u>), 1.39/1.35 (9H, 2 × s, CMe_3); δ_C (100 MHz; $CDCl_3$) 170.6, 156.9/156.8, 156.2, 155.5, 142.9, 139.8 (CH), 137.20/137.16 (CH), 130.6/130.5, 129.5, 129.2, 129.14 (CH), 129.11 (CH), 128.9, 128.8, 128.73/127.72 (CH), 128.63/128.62 (CH), 128.5 (CH), 128.12 (CH), 128.06 (CH), 128.0 (CH), 127.96 (CH), 127.92 (CH), 127.3 (CH), 127.16/127.14 (CH), 126.84/126.75 (CH), 119.5 (CH_2), 116.04/115.96 (CH_2), 110.4/110.3 (CH), 108.6/108.5 (CH), 106.7 (CH), 82.4/82.3, 66.8 (CH_2), 61.75/61.70, 60.7, 55.3 (CH), 37.9/37.8 (CH_2), 28.0 (Me),; *m/z* (CI) 516 (MH^+, 22%), 498 (17), 460 (12), 416 (61), 91 (12).

5-[2-(Benzyloxycarbonyl)amino-2-*tert*-butoxycarbonyl]ethyl-3-phenyl-3-vinyldihydrobenzo[*b*]furan-2-yl acetate 52

The lactol **51** (30 mg, 0.06 mmol) was dissolved in dichloromethane (1 mL) and the solution was treated with pyridine (0.2 mL) and acetic anhydride (0.1 mL). TLC analysis of the reaction mixture following 4 h stirring showed complete consumption of the starting material and the reaction was quenched with saturated aqueous ammonium chloride (10 mL). Additional dichloromethane (5 mL) allowed for separation of the organic layer that was washed with HCl (2 M; 3 × 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The *title compound* (17 mg, 52%) was isolated following column chromatography using light petroleum – ethyl acetate (5:2) as a colourless oil; (Found: M^+-OAc, 498.2303. $C_{31}H_{32}NO_5$ requires 498.2280); ν_{max} (film)/cm^{-1} 2979, 1724, 1486, 1370, 1225, 1155, 1016; δ_H (300 MHz; $CDCl_3$) 7.61 – 6.64 (13H, m, ArH), 6.23 (0.5H, dd, *J* 10.7, 17.3, C<u>H</u>=CH_2), 6.21 (0.5H, dd, *J* 10.6, 17.3, C<u>H</u>=CH_2), 5.36 – 4.90 (5H, m, OC<u>H</u>$_2$Ph, CHN<u>H</u>, CH=C<u>H</u>$_2$), 4.55 – 4.49 (1H, m,

$CH_2C\underline{H}NH$), 3.12 – 3.05 (2H, m, $C\underline{H}_2CHNH$), 2.15 (3H, s, Me), 1.14/1.38 (9H, 2 × s, CMe_3); δ_C (75 MHz; $CDCl_3$) 170.6, 169.7, 157.3, 155.5, 141.2, 136.80/136.75 (CH), 130.7 (CH), 129 – 127 (several overlapping signals), 119.1/119.0 (CH_2), 110.6 (CH), 105.9/105.8 (CH), 82.43/82.40, 66.9 (CH_2),61.7/61.3, 55.4/55.2 (CH), 37.9 (CH_2), 28.0 (CH), 21.1 (Me); *m/z* (CI) 498 (M-OAc, 40%), 442 (100), 398 (92), 91 (7).

5-[2-(Benzyloxycarbonyl)amino-2-*tert*-butoxycarbonyl]ethyl-3-formyl-3-phenyl-3-dihydrobenzo[*b*]furan-2-yl acetate 53

5-[2-(Benzyloxycarbonyl)amino-2-*tert*-butoxycarbonyl]ethyl-3-phenyl-3-vinyldihydrobenzo[*b*]furan-2-yl acetate **52** (10 mg, 0.02 mmol) in a solution of dichloromethane (2 mL) and methanol (0.4 mL) was cooled to -78 °C and treated with ozone until the solution appeared blue. Nitrogen was bubbled through the solution until the blue colour dissipated. Dimethylsulfide (0.05 mL) was added and the cold-bath was removed allowing the reaction mixture to warm to room temperature overnight. Concentration of the solution under vacuum provided an oil which was purified by column chromatography using light petroleum – ethyl acetate (5:2) to yield the *title compound* (12 mg, 100%); δ_H (400 MHz; $CDCl_3$) 9.88 (1H, d, *J* 7.2, CHO), 7.35 – 7.20 (10H, m, ArH), 7.19 (1H, d, *J* 1.2, ArH), 7.11 (1H, s, $C\underline{H}OAc$), 6.92 (1H, d, *J* 8.2, ArH), 5.30 (1H, t, *J* 8.3, $CHN\underline{H}$), 5.11 – 5.07 (2H, m, $OC\underline{H}_2Ph$), 4.58 – 4.53 (1H, m, $C\underline{H}NH$), 3.19 – 3.08 (2H, m, $C\underline{H}_2CHNH$), 2.14 (3H, s, Me), 1.41/1.37 (9H, 2 × s, CMe_3); δ_C (100 MHz; $CDCl_3$) 193.5/193.4 (CH), 170.5/170.4, 169.49/169.48, 157.9/157.8, 155.6, 136.3 (CH), 135.75/135.71, 131.7/131.6 (CH), 130.4/130.3, 129.2 (CH), 129.1/129.0, 128.5 (CH), 128.4/128.3 (CH), 128.2 (CH), 128.15/128.13 (CH), 127.6 (CH), 124.19/124.16,

110.9/110.8 (CH), 82.6/82.5, 68.23/68.16, 66.9 (CH_2), 55.3/55.2 (CH), 37.9/37.8 (CH_2), 28.0 (Me), 20.9 (Me); *m/z* (CI) no molecular ion observed.

Methyl (2-nitrophenyl)acetate 54

Sulfuric acid (5.4 g, 55 mmol) was added to a solution of (2-nitrophenyl)acetic acid (5.1 g, 28 mmol) in methanol (80 mL) and the resulting mixture was stirred for 20 h at room temperature. The solvent was removed *in vacuo*. The residue was taken up in dichloromethane (40 mL) and washed with a concentrated solution of sodium hydroxide and water (2 × 100 mL). The organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a pale yellow oil (5.1 g, 94%) (lit.,[79] bp 112 – 115 °C/2 mmHg); (Found: M^+, 195.0540. $C_9H_9NO_4$ requires 195.0532); ν_{max} (film)/cm^{-1} 3071, 3003, 2954, 2848, 1740, 1613, 1579, 1526, 1436, 1414, 1348, 1219, 1171, 1001, 864, 789, 712; δ_H (300 MHz; $CDCl_3$) 8.12 (1H, d, *J* 8.1, ArH), 7.61 (1H, t, *J* 7.5, ArH), 7.49 (1H, t, *J* 8.4, ArH), 7.36 (1H, d, *J* 7.5, ArH), 4.04 (2H, s, CH_2), 3.72 (3H, s, OMe); δ_C (75 MHz; $CDCl_3$) 170.9, 149.1, 134.1 (CH), 133.5 (CH), 130.1, 128.7 (CH), 125.8 (CH), 52.5 (Me), 39.8 (CH_2); *m/z* (FI) 195 (M^+, 100%).

(*E*)-Methyl 2-(2-nitrophenyl)but-2-enoate 55

Methyl (2-nitrophenyl)acetate **54** (2.0 g, 10.2 mmol) and 18-crown-6 (0.7 g, 2.6 mmol) were dissolved in dry and degassed THF (40 mL), under a nitrogen atmosphere. The resulting solution was cooled to -78 °C and potassium *tert*-butoxide (1.2 g, 10.7 mmol) was added dropwise over 5 min. Acetaldehyde (2.9 mL, 51.0 mmol) was then added to the blue solution and stirred for 40 min at -78 °C. The solution was then stirred for 15

min at room temperature until the blue colour disappeared. The mixture was finally cooled again to -78 °C and quenched by rapid addition of saturated ammonium chloride solution. The mixture was then allowed to warm to room temperature and the product was extracted with dichloromethane (4 × 50 mL). The organic layers were washed once with water (100 mL) and once with aqueous saturated sodium chloride (150 mL). The combined extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo* and purified by column chromatography on silica, eluting with dichloromethane to afford the *title compound* as a pale yellow oil (0.6 g, 28 %); (Found: MH^+, 222.0772. $C_{11}H_{11}NO_4$ + H requires 222.0766); ν_{max} (film)/cm^{-1} 3069, 2991, 2952, 2855, 2360, 2340, 1716, 1647, 1610, 1573, 1526, 1436, 1349, 1271, 1248, 1199, 1047, 1035, 855, 790, 765, 751, 710; δ_H (400 MHz; $CDCl_3$) 8.14 (1H, d, *J* 8.1, ArH), 7.65 (1H, t, *J* 7.5, ArH), 7.52 (1H, t, *J* 7.5, ArH), 7.22 (1H, q, *J* 7.2, =C<u>H</u>Me), 7.25 (1H, d, *J* 7.4, ArH), 3.69 (3H, s, OMe), 1.72 (3H, d, *J* 7.2, =CH<u>Me</u>); δ_C (100 MHz; $CDCl_3$) 165.9, 148.5, 139.8 (CH), 133.2 (CH), 132.6 (CH), 132.1, 130.9, 128.9 (CH), 124.8 (CH), 52.1 (Me), 15.4 (Me); *m/z* (FI) 222 (MH^+, 3%), 190 (100), 162 (7).

(*E*) 2-(2-Nitrophenyl)but-2-enoic acid 56

Caesium carbonate (6.5 g, 19.95 mmol) in 40 mL of water was added to a solution of the ester **55** (1.1 g, 4.98 mmol) in methanol (10 mL). The resulting mixture was stirred at 50 °C for 48 h then acidified to pH 1 with aqueous hydrochloric acid (2 M). The solvent was removed *in vacuo* to a volume of 15 mL and the product was extracted with dichloromethane. The combined extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo* and purified by column chromatography on silica, eluting with

dichloromethane – methanol (10:0 to 8:2) to give the *title compound* as a colourless solid (0.5 g, 50 %), mp 153 – 156 °C (ethyl acetate – light petroleum); (Found: C, 57.7; H, 4.2; N, 6.6. $C_{10}H_9NO_4$ requires C, 58.0; H, 4.4; N, 6.7%); (Found: MH^+, 208.0618. $C_{10}H_{10}NO_4$ requires 208.0610); ν_{max} (KBr)/cm^{-1} 3100 – 2536, 1676, 1632, 1529, 1479, 1425, 1354, 1289, 1198, 1001, 944, 924, 853, 795, 747, 707; δ_H (300 MHz; $CDCl_3$) 7.96 (1H, d, *J* 8.1, ArH), 7.44 (1H, t, *J* 7.5, ArH), 7.33 (1H, t, *J* 6.6, ArH), 7.11 – 7.06 (2H, m, =C<u>H</u>Me and ArH), 1.54 (3H, d, *J* 7.2, Me), OH signal not observed; δ_C (75 MHz; $CDCl_3$) 170.8, 148.3, 142.1 (CH), 133.3 (CH), 132.6 (CH), 131.8, 130.3, 129.1 (CH); 124.8 (CH), 15.7 (Me); *m/z* (CI) 208 (MH^+, 3%), 190 (100), 146 (16).

_N_-Benzyloxycarbonyl-3-iodo-_O_-[2-(2-nitrophenyl)but-2-enoyl]tyrosine _tert_-butyl ester 57

(*E*) 2-(2-Nitrophenyl)but-2-enoic acid **56** (125 mg, 0.60 mmol) and *N*-benzyloxycarbonyl-3-iodo-L-tyrosine-*tert*-butyl ester **43** (330 mg, 0.66 mmol) were dissolved in dry dichloromethane (15 mL) under a nitrogen atmosphere. A second solution of DCC (162 mg, 0.78 mmol) in dry dichloromethane (3 mL) was prepared and both solutions were cooled to 0 °C. The DCC solution was added to the first solution dropwise over 40 min. The resulting mixture was stirred at 0 °C for 3.5 h until the reaction was complete. Dichloromethane (10 mL) was added to the suspension, which was filtered through Celite and washed with brine and water, then dried ($MgSO_4$) and concentrated *in vacuo*. The title compound was purified by column chromatography on silica, eluting with dichloromethane – ether (100:0 to 96:4) to give the *title compound* as a colourless solid (320 mg, 70%), mp 46 – 51 °C (light petroleum); (Found: C, 54.1; H,

4.7; N, 4.0. $C_{31}H_{31}IN_2O_8$ requires C, 54.2; H, 4.5; N, 4.1%); (Found: M+NH_4^+, 704.1470. $C_{31}H_{35}IN_3O_8$ requires 704.1463); $[\alpha]_D^{30}$ 28.0 (*c* 0.5, CH_2Cl_2) ν_{max} (KBr)/cm^{-1} 3369, 3064, 3033, 2361, 2341, 2976, 2930, 2856, 1732, 1643, 1572, 1526, 1482, 1346, 1253, 1217, 1169, 1039, 987, 845, 790, 742, 698; δ_H (300 MHz; $CDCl_3$) 8.14 (1H, d, *J* 8.2, ArH), 7.64 (1H, t, *J* 7.5, ArH), 7.52 – 7.20 (9H, m,=CHMe and ArH), 6.96 (2H, t, *J* 7.5, ArH) 5.23 (1H, br d, *J* 7.9, CHNH), 5.02 (2H, m, OCH_2Ph), 4.41 (1H, td, *J* 7.8, 5.8, CHNH), 2.95 (2H, br d, *J* 5.7, CH_2CHNH), 1.71 (3H, d, *J* 7.2, =CHMe), 1.32 (9H, s, CMe_3); δ_C (100 MHz; $CDCl_3$) 170.0, 163.1, 155.5, 150.1, 148.3, 142.2 (CH), 139.9 (CH), 136.2, 135.9, 133.6 (CH), 133 (CH), 131.7, 130.6 (CH), 130.4, 129.4 (CH), 128.6 (CH), 128.2 (CH), 128.1 (CH), 125.1 (CH), 122.7 (CH), 89.8, 82.9, 66.9 (CH_2), 55.0 (CH), 37.2 (CH_2), 29.7 (Me), 15.9 (Me); *m/z* (ESI) 704 (M+NH_4^+, 76%), 631 (32), 587 (100).

(*E*) 2-(2-Nitrophenyl)but-2-enoic acid 56: Crystal data

Empirical formula	$C_{10}H_9NO_4$	
Formula weight	207.18	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 10.244(2) Å	α= 90°.
	b = 13.920(3) Å	β= 92.4243(17)°.
	c = 13.155(3) Å	γ = 90°.
Volume	1874.1(7) $Å^3$	
Z	8	
Density (calculated)	1.469 Mg/m^3	
Absorption coefficient	0.115 mm^{-1}	
F(000)	864	
Crystal size	0.1000 x 0.1000 x 0.0500 mm^3	

Theta range for data collection	2.13 to 25.35°
Index ranges	-11<=h<=12, -16<=k<=14, -15<=l<=9
Reflections collected	11668
Independent reflections	3344 [R(int) = 0.0314]
Completeness to theta = 25.35°	97.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.0000 and 0.8375
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3344 / 2 / 282
Goodness-of-fit on F^2	1.010
Final R indices [I>2sigma(I)]	R1 = 0.0367, wR2 = 0.0886
R indices (all data)	R1 = 0.0471, wR2 = 0.0937
Extinction coefficient	0.0005(6)

The authors have deposited atomic coordinates with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from The Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

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