Approaches to the Quaternary Stereocentre and to the Heterocyclic Core in Diazonamide A using the Heck Reaction and Related Coupling Reactions

Supplementary material

Experimental

2-Bromo-6-(trimethylsilyl)phenol 7. A solution of 2,6-dibromophenol (60.6 g, 0.24 mol) in tetrahydrofuran (60 mL) was added dropwise over 20 min to a stirred suspension of petrol-washed sodium hydride (10.1 g, 0.25 mol) in tetrahydrofuran (60 mL) at 0 °C under a nitrogen atmosphere, and the mixture was then stirred at 0 °C for 1 h. Chlorotrimethylsilane (30.5 mL, 0.24 mol) was added dropwise over 0.5 h and the mixture was stirred at 0 °C for 3 h and then cooled to −78 °C. A solution of *n*-butyllithium (1.6 M) in hexanes (150 mL, 0.24 mol) was added dropwise over 20 min. The mixture was stirred at −78 °C for 5 h, then warmed to room temperature when saturated aqueous ammonium chloride (100 mL) was added. The separated organic phase was diluted with diethyl ether (200 mL), then washed with water (300 mL), dried and concentrated *in vacuo*. The residue was purified by chromatography, eluting with ether in petrol (1:19), to give the *arylsilane* (58.7 g, 99%) as a colourless oil; (Found: C, 44.5; H, 5.5; $C_9H_{13}OBrSi$ requires: C, 44.1; H, 5.3 %); λ_{max}(EtOH)/nm 211 (4000), 283 (2700); ν_{max} (film)/cm^{-1} 3517, 1584; δ_H (270 MHz, $CDCl_3$) 7.42 (1H, dd, *J* 7.9 and 1.3, Ar*H*), 7.27 (1H, d, *J* 6.9, Ar*H*), 6.75 (1H, app t, *J* 7.6, Ar*H*), 5.69 (1H, s, ArO*H*), 0.30 (9H, s, Si(CH_3)$_3$); δ_C (67.8 MHz, $CDCl_3$) 157.2 (s), 135.7 (d), 133.0 (d), 127.0 (s), 121.6 (d), 110.5 (s), −1.2 (q); m/z (EI) Found: 243.9929 (M^+, $C_9H_{13}OBrSi$ requires 243.9920), 229 (100), 215 (7), 149 (73).

2-(2-Bromo-6-(trimethylsilyl)phenoxy)-1-phenylethanone 8a. A solution of 2-bromo-6-(trimethylsilyl)phenol (73.7 g, 0.30 mol), 2-bromoacetophenone (59.8 g, 0.30 mol) and sodium carbonate (38.2 g, 100 mmol) in acetonitrile (1400 mL) was stirred at room temperature under a nitrogen atmosphere for 72 h, and then 2N aqueous hydrochloric acid (1500 mL) was added. The mixture was extracted with ethyl acetate (2 x 1500 mL) and the organic extract was then washed

with 2N aqueous NaOH (150 mL), dried and concentrated *in vacuo*. The residue was purified by chromatography, eluting with ether in petrol (1:99), graduated to 1:9, to give the recovered starting material (16.8 g, 27%) and the *ketone* (70.3 g, 64%) as a colourless oil; (Found: C, 56.4; H, 5.2; Br, 22.2; $C_{17}H_{19}BrO_2Si$ requires: C, 56.2; H, 5.3; Br, 22.0 %); λ_{max}(EtOH)/nm 211 (10200), 242 (7600), 273 (1300), 279 (1300); ν_{max} (film) /cm^{-1} 1705; δ_H (400 MHz, $CDCl_3$) 8.00 (2H, dd, *J* 7.3 and 1.3, Ph*H*), 7.61 (1H, t, *J* 7.9, Ph*H*), 7.59 (1H, dd, *J* 7.9 and 1.6, Ar*H*), 7.50 (2H, app t, *J* 7.9, Ph*H*), 7.40 (1H, dd, *J* 7.2 and 1.6, Ar*H*), 7.04 (1H, app t, *J* 7.9, Ar*H*), 5.36 (2H, s, OCH_2CO), 0.30 (9H, s, Si(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 193.3 (s), 159.6 (s), 135.7 (s), 135.2 (d), 134.6 (d), 133.6 (d), 128.7 (d), 127.8 (d), 125.8 (d), 116.2 (s), 75.1 (t), −0.5 (q); m/z (EI) Found: 362.0328 (M^+, $C_{17}H_{19}O_2BrSi$ requires 362.0338), 347 (11), 283 (52), 105 (76), 75 (100).

2-(2-Bromo-6-iodophenoxy)-1-phenylethanone 8b. Silver tetrafluoroborate (23.8 g, 0.12 mol) was added to a stirred solution of the arylsilane **8a** (40.6 g, 0.11 mol) in dry methanol (1000 mL) at room temperature under a nitrogen atmosphere. The solution was cooled to 0 °C and then iodine (33.9 g, 0.13 mol) was added portionwise over 20 min. The mixture was allowed to warm to room temperature, then stirred for a further 12 h and diluted with diethyl ether (500 mL). The mixture was filtered and the filtrate was then concentrated *in vacuo*. The residue was dissolved in ethyl acetate (500 mL) and the solution was washed successively with water (500 mL), 2N hydrochloric acid (500 mL) and brine (500 mL), then dried and concentrated *in vacuo*. The residue was purified by chromatography, eluting with ethyl acetate in petrol (1:19), to give the *bromoiodo ketone* (43.5 g, 95%) as colourless crystals, m.p. 96-97 °C. (Found: C, 40.6; H, 2.4; I, 30.6; $C_{14}H_{10}O_2IBr$ requires: C, 40.3; H, 2.4; I, 30.4 %); ν_{max} (film) /cm^{-1} 1706; δ_H (250 MHz, $CDCl_3$) 8.03 (2H, dt, *J* 7.0 and 1.5, Ph*H*), 7.76 (1H, dd, *J* 7.9 and 1.5, Ar*H*), 7.63 (1H, tt, *J* 7.3 and 1.4, Ph*H*), 7.57 (1H, dd, *J* 7.9 and 1.5, Ar*H*), 7.51 (2H, tt, *J* 7.3 and 1.4, Ph*H*), 6.79 (1H, t, *J* 7.9, Ar*H*), 5.29 (2H, s, OCH_2CO); δ_C (67.8 MHz, $CDCl_3$) 193.0 (s), 154.8 (s), 138.8 (d), 134.4 (s), 133.9 (d), 133.8 (d), 128.7 (d), 128.1 (d), 127.7 (d), 117.2 (s), 92.3 (s), 74.4 (t); m/z (EI) Found: 415.8925 (M^+, $C_{14}H_{10}O_2IBr$ requires 415.8911), 337 (18), 298 (1), 289 (23).

2-Trimethylsilylethyl *E*-2-(trimethylstannyl)but-2-enoate (10). A solution of trimethylsilylethanol (1.3 g, 10.7 mmol) in dichloromethane (10 mL) was added over 15 min to a

stirred solution of butynoic acid **9a** (0.75 g, 8.9 mmol) in dichloromethane (25 mL) and DCC (2.8 g, 13.4 mmol) at 0 °C. DMAP (75 mg, 10 mol%) was added and the mixture was stirred overnight and then filtered through silica. The filtrate was evaporated *in vacuo* to leave (2-trimethylsilyl)ethyl but-2-ynoate **9b**, as an oil, δ_H (360 MHz, $CDCl_3$) 4.20 (2H, t, *J* 7, CO_2CH_2), 1.91 (3H, s, CH_3), 1.10 (2H, t, *J* 7, CH_2SiMe_3), −0.9 (9H, s, $Si(CH_3)_3$), which was used straightaway.

The but-2-ynoate **9b** (0.4 g, 2.2 mmol) was added to a stirred mixture of $Pd(OAc)_2$ and PPh_3 (45.5 mg, 8 mol%) in benzene (5 mL) and the mixture was stirred at room temperature for 5 min. Bu_3SnH (1.0 g, 0.33 mmol) was added and the mixture was stirred for 20 min and then evaporated to dryness *in vacuo*. The residue was purified by chromatography on silica, eluting with ether in petroleum ether (2:98), to give the *vinyl stannane* (0.9 g, 85%) as a colourless liquid; δ_H (360 MHz, $CDCl_3$) 6.2 (1H, q, *J* 6.6, $=CHCH_3$), 4.2 (2H, m, CO_2CH_2), 2.0 (3H, d, *J* 6.6, $=CHCH_3$), 1.5 (6H, m), 1.3 (6H, m), 1.3 (6H, m), 1.1 (2H, m), 0.9 - 0.5 (18H, m), 0.2 (9H, s, $Si(CH_3)_3$); δ_C (90 MHz, $CDCl_3$) 171.5, 164.6, 147.3, 137.3, 128.5, 62.2, 29.1, 27.4, 22.4, 18.3, 17.5, 13.7, 12.2, 10.3, 9.5, 8.4, −1.4, −1.5; m/z (ESI) Found: 540.2288 ($[M+CH_3CN]^+$, $C_{21}H_{44}O_2SnSi$ requires 540.2290).

(S)-3-(4-Benzyloxy-3-iodo-phenyl)-2-dibutylamino-propionic acid methyl ester (11). Iodotyrosine (0.6 g, 1.95 mmol) was added slowly, over 10 min, to a stirred suspension of NaH (0.37 g, 8 mmol, 50% emulsion) in tetrahydrofuran (50 mL). The mixture was stirred at room temperature for 30 min, and then benzyl bromide (1.6 mL, 9.8 mmol) was added. The mixture was heated under reflux for 30 h, then poured into ice-cold dil. HCl and extracted into ethyl acetate. The ethyl acetate extract was washed with brine, dried and then evaporated to dryness *in vacuo*. The residue was purified by chromatography, eluting with ethyl acetate in petrol (3:97), to give the corresponding benzylated tyrosine (0.83 g, 62%) as a colourless liquid. The benzylated tyrosine was dissolved in dioxane (20 mL), and aqueous LiOH (10%, 6 mL) was added. The mixture was heated at 50 °C for 4 h (monitored by TLC), then cooled and acidified with dil. HCl (pH = 3-4), and extracted into ethyl acetate. The ethyl acetate extract was washed with brine then dried and evaporated *in vacuo* to leave the corresponding carboxylic acid (0.7 g, 93%), as a viscous oil. Diazomethane (1 mL of 0.7 M) in ether was added to a solution of the

carboxylic acid (800 mg, 1.38 mmol) in ether (10 mL) at 0 °C, and the mixture was stirred for 10 min. The solvent was evaporated *in vacuo*, and the residue was crystallised from methanol to give the *methyl ester* (650 mg, 79%) as colourless crystals; (Found: C, 63.0; H, 5.1; N, 2.4; $C_{31}H_{30}O_3NI$ requires: C, 62.95; H, 5.1; N, 2.4 %); $[\alpha]_D^{22}$ −34.4 (c 0.1, $CHCl_3$); δ_H (360 MHz, $CDCl_3$) 7.6 (2H, d, *J* 8, Ar*H*), 7.5 - 7.4 (3H, m, Ar*H*), 7.4 (1H, d, *J* 7, Ar*H*), 7.3 (6H, m, Ar*H*), 7.2 (4H, d, *J* 7, Ar*H*), 6.9 (1H, d, *J* 9, Ar*H*), 6.75 (1H, d, *J* 9, Ar*H*); δ_C (90 MHz, $CDCl_3$) 172.6 (s), 155.7 (s), 140.2 (s), 139.0 (d), 136.6 (s), 132.9 (s), 130.3 (d), 128.6 (s), 128.5 (d), 128.2 (2 x d), 127.8 (d), 126.9 (d), 112.3 (d), 86.5, 70.9 (t), 62.1, 54.3 (q), 51.2 (q), 34.2 (q).

(*E*)-2-[2-Benzyloxy-5-(2-dibenzylamino-2-methoxycarbonyl-ethyl)-phenyl]-but-2-enoic acid 2-trimethylsilanyl ethyl ester (12a). The vinyl stannane **10** (0.64 g, 1.3 mmol) was added to a stirred mixture of the iodotyrosine **11** (0.66 g, 1.2 mmol), triphenylarsine (137 mg, 0.45 mmol) and CuI (42.5 mg, 0.22 mmol) in degassed NMP. The mixture was heated at 80 °C under a nitrogen atmosphere, then Pd/C (66 mg, 10%) was added and the mixture was stirred for 13 h. The cooled mixture was filtered through celite®, then diluted with ether. The ether extracts were washed with 2M NaOH and brine, dried and evaporated *in vacuo*. The residue was purified by chromatography, eluting with ether in petroleum ether (1:1), to give the *substituted styrene* (0.5 g, 55%) as a viscous liquid; δ_H (360 MHz, $CDCl_3$) 7.6 - 7.2 (16H, m, Ar*H*), 6.95 (1H, m, Ar*H*), 6.85 (1H, m, Ar*H*), 6.15 (1H, q, *J* 7, =C*H*CH_3), 5.05 (2H, s, PhCH_2OAr), 4.2 (2H, m), 4.05 (2H, dd, *J* 6 and 14), 3.85 (3H, m), 3.7 (1H, m), 3.6 (2H, dd, *J* 6 and 14), 3.1 (2H, ABq), 2.0 (3H, d, *J* 7, =CHCH_3), 1.2 (2H, m), 0.99 (9H, s); δ_C (90 MHz, $CDCl_3$) 173.0, 168.0, 165.6, 133.2, 131.5, 130.7, 130.2, 129.8, 129.2, 128.8, 128.7, 128.6, 128.5, 128.2, 127.7, 127.3, 127.2, 127.0, 127.0, 126.9, 70.4, 62.4, 61.9, 54.5, 54.4, 51.9, 51.2, 35.0, 26.6, 20.2, 17.4, 15.9, −1.4; m/z (ESI) Found: 672.3133 ($[M+H]^+$, $C_{41}H_{49}NO_5SiNa$ requires 672.3121).

(Z)-2-[2-Benzyloxy-5-((S)-2-dibutylamino-2-methoxycarbonyl-ethyl)-phenyl]-but-2-enoic acid (**12b**). A solution of TBAF (0.5 g, 1.6 mmol) in tetrahydrofuran (5 mL) was added over 10 min to a stirred solution of the silylethyl ester **12a** (340 mg, 0.52 mmol) in tetrahydrofuran (10 mL) at 0-5 °C (ice bath). The mixture was stirred for 15 h at room temperature, then acidified with cold 2M HCl, and extracted with ethyl acetate. The extracts were evaporated and the

residue was purified by chromatography, eluting with ether in petroleum ether (3:7), to give the acid (18 mg, 63%) as an amorphous solid; (Found: C, 76.5; H, 6.4; N, 2.4; $C_{35}H_{35}O_5N$ requires: C, 75.6; H, 6.45; N, 2.5 %); δ_H (360 MHz, $CDCl_3$) 7.5 - 7.15 (16H, m), 6.9 (1H, d, *J* 9, Ar*H*), 6.8 (1H, d, *J* 9, Ar*H*), 6.2 (1H, q, *J* 7, =C*H*CH_3), 5.02 (2H, s), 3.95 (2H, t, *J* 7, CH_2CH_2), 3.8 (3H, s), 3.6 (1H, m), 3.5 (2H, d), 3.05 (2H, ABq), 2.12 (3H, d, *J* 7, =CHCH_3); δ_C (90 MHz, $CDCl_3$) 173.2, 140.8, 134.5, 130.2, 129.0, 128.8, 128.7, 128.4, 127.4, 112.1, 70.7, 62.5, 54.6, 51.4, 35.1, 28.1, 16.3.

(Z)-2-[2-Benzyloxy-5-((S)-2-dibutylamino-2-methoxycarbonyl-ethyl)-phenyl]-but-2-enoic acid 2-bromo-6-iodo-phenyl ester (**13**). EDCI (0.31 g, 1.64 mmol) was added to a stirred solution of the carboxylic acid **12b** (450 mg, 0.82 mmol) in dichloromethane (20 mL) at 0 °C. 2-Bromo-6-iodophenol (293 mg, 0.98 mmol) and DMAP (200.3 mg, 1.64 mmol) were added, and the mixture was stirred at 0 °C for 14 h, then diluted with dichloromethane. The resulting solution was washed successively with water, saturated $NaHCO_3$ and brine, then dried and evaporated *in vacuo*. The residue was purified by chromatography, eluting with ether in petroleum ether (1:9), to give the *ester* (400 mg, 60%) as a colourless solid; (Found: C, 58.7; H, 4.4; N, 1.6; $C_{41}H_{37}O_5NIBr$ requires: C, 59.3; H, 4.5; N, 1.7 %); ν_{max} ($CHCl_3$)/cm^{-1} 1731, 1640, 1561; δ_H (360 MHz, $CDCl_3$) 7.79 (1H, d, *J* 9, Ar*H*), 7.62 (1H, d, *J* 9, Ar*H*), 7.59 (1H, d, *J* 9, Ar*H*), 7.3 (1H, d, *J* 9, Ar*H*), 7.2 (15H, brs), 7.05 (1H, s), 6.99 - 6.8 (2H, m), 5.1 (1H, d), 3.98 (2H, d, *J* 14), 3.8 (3H, s), 3.63 (1H, m), 3.58 (2H, d, *J* 14), 3.1 (2H, ABq), 1.86 (1H, d, *J* 6.5); δ_C (90 MHz, $CDCl_3$) 173.0, 163.0, 160.6, 155.0, 139.4,138.6, 138.4, 137.6, 133.6, 133.4, 132.7, 130.4, 130.2, 128.8, 128.5, 128.4, 128.3, 128.3, 128.0, 127.7, 127.3, 127.2, 127.1, 127.0, 123.6, 117.5, 117.0, 112.8, 112.7, 70.7, 62.5, 54.5, 51.3, 35.0, 16.2.

(S)-3-[4-Benzyloxy-3-(7-bromo-2-oxo-3-vinyl-2,3-dihydro-benzofuran-3-yl)-phenyl]-2-dibutylamino-propionic acid methyl ester (**14**). A mixture of dppp (23.8 mg, 0.06 mmol), silver phosphate (90 mg, 0.22 mmol) and Bu_4NBr (23.3 mg, 0.072 mmol) in toluene (1 mL) was stirred at room temperature under a nitrogen atmosphere. A solution of the aryl iodide **13** (120 mg, 0.145 mmol) in toluene (1 mL) was added followed by $Pd_2(dba)_3$ (26.5 mg, 20 mol%)/ $Pd_2(dba)_3.CHCl_3$ as a solution in toluene. The mixture was heated at 90 - 95 °C for 26 h under a

nitrogen atmosphere, then cooled and filtered through celite®. The filtrate was evaporated *in vacuo* to leave a residue which was purified by chromatography, eluting with ether in petroleum ether (15:85), to give the *benzofuranone* (50 mg, 49%) as a colourless oil; ν_{max} ($CHCl_3$)/cm^{-1} 1821, 1731; δ_H (360 MHz, $CDCl_3$) 7.49 - 6.9 (21H, m, Ar*H*), 6.2 (1H, dd, *J* 17.3 and 10, C*H*=CH_2), 5.44 (1H, d, *J* 10, =C*H*H), 5.05 (1H, d, *J* 17.3, =C*H*H), 5.0 - 4.8 (2H, m), 4.15 (2H, d, *J* 13.5), 3.85 (3H, m), 3.65 (1H, m), 3.55 (2H, d, *J* 14), 3.1 (2H, ABq); δ_C (90 MHz, $CDCl_3$) 176.1, 172.5, 156.0, 154.1, 144.2, 140.0, 139.2, 139.1, 137.5, 137.1, 136.2, 135.0, 132.1, 132.0, 131.8, 131.5, 130.0, 129.5, 128.6, 128.5, 127.5, 127.2, 127.1, 126.5, 126.4, 126.4, 124.9, 124.8, 123.5, 119.9, 104.5, 70.2, 62.5, 62.4, 60.5, 60.4, 57.3, 54.5, 50.0, 44.9, 44.8, 34.9, 34.7, 16.5; m/z (ESI) Found: 704.29 ($[M+H]^+$, 624.4 ([M−HBr]), 598, 434.47.

2-(2-Benzyloxyphenyl)-3-hydroxybutanoic acid (16a). A solution of *n*-butyllithium (2.5 M) in hexanes (7.44 mL, 18.6 mmol) was added dropwise over 10 min to a stirred solution of di-*iso*-propylamine (2.62 mL, 18.6 mmol) in dry tetrahydrofuran (15 mL) at –10 ºC under a nitrogen atmosphere. The solution of LDA was allowed to warm to 0 ºC and then stirred at 0 ºC for 25 min. The solution was cooled to –78 ºC and a solution of 2-benzyloxyphenylacetic acid **15** (1.79 g, 7.40 mmol) in tetrahydrofuran (20 mL) was added dropwise at –78 ºC over 10 min. The solution was allowed to warm to room temperature over 1 h, then cooled to –50 ºC, and acetaldehyde (0.63 mL, 11.1 mmol) at –10 ºC was added rapidly. The mixture was stirred for a further 20 min then quenched with water (5 mL) and warmed to room temperature. The solvent was removed *in vacuo* and the residue was diluted with ethyl acetate (50 mL) and water (10 mL). The separated aqueous layer was acidified to pH 4 with HCl solution (2 M) and then extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography, eluting with 40% ethyl acetate in petroleum ether, to give the *hydroxy acid* (2.0 g, 92%, 6:5 mixture of diastereomers) as a viscous yellow oil; ν_{max} ($CHCl_3$)/cm^{-1} 3512, 2871 (br), 1732, 1703; δ_H (360 MHz, $CDCl_3$) (*major diastereomer*) 7.44-7.30 (7H, m, Ar*H*), 6.97-6.94 (2H, m, Ar*H*), 5.12-5.03 (2H, m, ArOCH_2), 4.48-4.43 (1H, m, C*H*OH), 3.98 (1H, d, *J* 8.8, C*H*COOH), 0.98 (3H, d, *J* 6.3, CH_3CHOH); *minor diastereomer*: 7.44-7.30 (7H, m, Ar*H*), 6.97-6.94 (2H, m, Ar*H*), 5.12-5.03 (2H, m, ArOCH_2), 4.48-4.43 (1H, m, C*H*OH), 4.25 (1H, d, *J* 5.1, C*H*COOH), 1.18 (3H, d, *J* 6.3,

C*H*$_3$CHOH); δ_C (90.6 MHz) *major diastereomer*: 178.9 (s), 155.8 (s), 136.5 (s), 129.9 (d), 128.4 (d), 127.8 (d), 127.5 (d), 127.0 (d), 125.0 (s), 121.0 (d), 112.2 (d), 70.2 (t), 68.3 (d), 52.3 (d), 20.1 (q); *minor diastereomer*: 178.3 (s), 156.5 (s), 136.6 (s), 130.3 (d), 128.8 (d), 128.5 (d), 127.9 (d), 127.2 (d), 123.3 (s), 121.0 (d), 112.2 (d), 70.3 (t), 67.8 (d), 50.2 (d), 20.1 (q); *m/z* (ESI) Found: 309.1125 ($[M + Na]^+$, $C_{17}H_{18}O_4Na$ requires 309.1103), 251 (8), 223 (7).

Methyl 2-(2-Benzyloxyphenyl)-3-hydroxybutanoate (16b). A solution of the carboxylic acid **16a** (121 mg, 0.42 mmol) in methanol (3 mL) was added dropwise over 2 min to a stirred solution of acetyl chloride (91.0 μL, 1.30 mmol) in methanol (3 mL) at 0 ºC. This solution was stirred at room temperature for 10 min, then heated at reflux for 3 h, and finally cooled to room temperature. Water (5 mL) was added and the solvent was then removed *in vacuo*. Diethyl ether (20 mL) was added and the separated aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution (20 mL) and brine (20 mL), then dried over $MgSO_4$ and concentrated *in vacuo* to leave the *ester* (107 mg, 84% 1.2:1 mixture of diastereomers) as a colourless oil; ν_{max} ($CHCl_3$)/cm^{-1} 3566, 2953, 1716; δ_H (360 MHz, $CDCl_3$) (*major diastereomer*) 7.42-7.32 (5H, m, Ar*H*), 7.27-7.20 (2H, m, Ar*H*), 6.97 (2H, t, *J* 7.2, Ar*H*), 5.14-5.09 (2H, m, PhC*H*$_2$OAr), 4.48-4.38 (1H, m, C*H*OH), 3.97 (1H, d, *J* 8.7, C*H*COOCH$_3$), 3.63 (3H, s, COOC*H*$_3$), 1.03 (3H, d, *J* 6.3, C*H*$_3$CHOH); *minor diastereomer*: 7.42-7.32 (5H, m, Ar*H*), 7.27-7.20 (2H, m, Ar*H*), 6.97 (2H, t, *J* 7.2, Ar*H*), 5.14-5.09 (2H, m, PhC*H*$_2$OAr), 4.48-4.38 (1H, m, C*H*OH), 4.25 (1H, d, *J* 5.2, C*H*COOCH$_3$), 3.65 (3H, s, COOC*H*$_3$), 1.16 (3H, d, *J* 6.3, C*H*$_3$CHOH); δ_C (90.6 MHz, $CDCl_3$) (*major diastereomer*) 175.1 (s), 156.6 (s), 136.8 (s), 129.7 (d), 128.8 (d), 128.6 (d), 128.0 (d), 127.1 (d), 125.6 (s), 121.1 (d), 112.2 (d), 70.2 (t), 68.7 (d), 53.3 (d), 52.1 (q), 20.3 (q); *minor diastereomer*: 174.3 (s), 155.9 (s), 136.8 (s), 130.1 (d), 128.8 (d), 128.6 (d), 128.0 (d), 127.4 (d), 123.8 (s), 121.1 (d), 112.3 (d), 70.5 (t), 68.1 (d), 52.0 (q), 50.1 (d), 20.2 (q); *m/z* (ESI) Found: 323.1232 ($[M + Na]^+$, $C_{18}H_{20}O_4Na$ requires 323.1260), 283 (5), 251 (12), 223 (93), 205 (18).

Methyl (2*E*/*Z*)-2-[2-(benzyloxy)phenyl]but-2-enoate (17). Methane sulfonyl chloride (87.0 μL, 1.10 mmol) was added dropwise over 1 min to a stirred solution of the ester **16b** (107 mg, 0.37 mmol) in dichloromethane (3 mL) at 0 ºC. The solution was allowed to warm to room

temperature and then stirred at this temperature for 1 h. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.56 mL, 3.70 mmol) was added and the mixture was stirred at room temperature for 12 h, then quenched with water (3 mL), and the solvent removed *in vacuo*. Diethyl ether (10 mL) was added to the residue and the separated aqueous layer was then extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography, eluting with 10% ethyl acetate in petroleum ether to give a 2:1 mixture of *E*- and *Z*- isomers of the *alkene* (100 mg, 97%), as a colourless oil; ν_{max} ($CHCl_3$)/cm^{-1} 2951, 1713, 1643; δ_H (360 MHz, $CDCl_3$) (*E isomer*) 7.40-7.25 (7H, m, Ar*H*), 7.17 (1H, q, *J* 7.1, =C*H*CH_3), 7.03-6.96 (2H, m, Ar*H*), 5.08 (2H, s, PhCH_2OAr), 3.68 (3H, s, COOCH_3), 1.74 (3H, d, *J* 7.1, =CHCH_3); *Z isomer*: 7.40-7.25 (6H, m, Ar*H*), 7.13 (1H, dd, *J* 7.4 and 1.8, Ar*H*), 7.03-6.96 (2H, m, Ar*H*), 6.27 (1H, q, *J* 7.3, =C*H*CH_3), 5.08 (2H, s, PhCH_2OAr), 3.57 (3H, s, COOCH_3), 2.12 (3H, d, *J* 7.3, =CHCH_3); δ_C (90.6 MHz, $CDCl_3$) 168.1 (s), 167.9 (s), 156.3 (s), 155.8 (s), 140.1 (d), 138.0 (d), 137.2 (s) 136.9 (s), 132.7 (s), 131.7 (s), 131.3 (d), 130.2 (d), 129.2 (d), 129.2 (d), 128.5 (d), 127.8 (d), 127.6 (d), 127.0 (d), 126.8 (d), 124.8 (s), 121.2 (d), 120.6 (d), 112.5 (d), 112.0 (d), 70.3 (t), 70.0 (t), 51.9 (d), 51.3 (d), 15.9 (d), 15.5 (q); *m/z* (ESI) Found: 282.1246 (M^+, 36%, $C_{18}H_{18}O_3$ requires 282.1256), 192 (32), 190 (35), 160 (27), 159 (24), 131 (39), 119 (33), 92 (54), 91 (100).

Methyl (2*S*)-3-(4-Benzyloxy-3-iodophenyl)-2-[(isopropoxycarbonyl)amino] propanoate (20b). Potassium carbonate (16.4 g, 119 mmol) was added in one portion to a stirred solution of the phenol **20a** (16.7 g, 39.7 mmol)[31] in dimethylformamide (100 mL) at room temperature and the mixture was stirred at room temperature for 10 min. Benzyl bromide (7.30 ml, 59.6 mmol) was added and the solution was stirred for 16 h, then diluted with water (100 mL) and ethyl acetate (100 mL), and stirred for a further 20 min. The separated aqueous layer was extracted with ethyl acetate (3 × 100 mL) and the combined organic extracts were then washed with water (150 mL) and brine (150 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography, eluting with 5% ethyl acetate in petroleum ether, to give the *benzyl ether* (18.2 g, 90%) as colourless crystals; mp 100-102 ºC (from petroleum ether, bp 60-80 °C/acetone); $[\alpha]_D^{22}$ +48.77 (*c* 1.6 in $CHCl_3$) (Found: C, 51.9; H, 5.4; N, 2.7; $C_{22}H_{26}NO_5I$ requires: C, 51.7; H, 5.1; N, 2.7%); ν_{max} ($CHCl_3$)/cm^{-1} 3436, 1742, 1713, 900; δ_H (360 MHz, $CDCl_3$) 7.57

(1H, s, Ar*H*), 7.49 (2H, d, *J* 7.1, OCH_2Ar*H*), 7.40 (2H, t, *J* 7.1, OCH_2Ar*H*), 7.32 (1H, t, *J* 7.1, OCH_2Ar*H*), 7.04 (1H, dd, *J* 8.4 and 2.0, CH_2OAr*H*) 6.78 (1H, d, *J* 8.4, CH_2OAr*H*), 5.12 (2H, s, PhCH_2OAr), 5.03 (1H, d, *J* 7.4, N*H*), 4.53 (1H, m, NHC*H*), 3.73 (3H, s, COOCH_3), 3.04 (1H, dd, *J* 13.8 and 5.7, C*H*HCHNH), 2.94 (1H, dd, *J* 13.8 and 6.1, CH*H*CHNH), 1.44 (9H, s, COOC(CH_3)$_3$); δ_C (90.6 MHz, $CDCl_3$) 172.0 (s), 156.2 (s), 154.9 (s), 140.2 (d), 136.4 (s), 130.5 (s), 130.1 (d), 128.4 (d), 127.8 (d), 126.9 (d), 112.4 (d), 86.6 (s), 79.8 (s), 70.7 (t), 54.4 (d), 52.3 (q), 36.8 (t), 28.2 (q); *m/z* (ESI) Found: 534.0751 ($[M + Na]^+$, $C_{22}H_{26}INO_5Na$ requires 534.0749), 488 (18), 453 (30), 412 (72), 407 (17), 366 (12).

***tert*-Butyl (4*S*)-4-(4-Benzyloxy-3-iodobenzyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (21).** A solution of lithium borohydride (2 M) in tetrahydrofuran (2.4 mL, 4.8 mmol) was added dropwise over 10 min to a stirred solution of the ester **20b** (4.9 g, 9.6 mmol) in tetrahydrofuran (100 mL) at –50 ºC under a nitrogen atmosphere. The mixture was stirred at –50 ºC for 4 h, then allowed to warm to room temperature and stirred for 36 h. The solvent was removed *in vacuo* and then ethyl acetate (100 mL) and water (50 mL) were added slowly to the residue. The resulting solution was stirred at room temperature for 10 min. The separated aqueous layer was extracted with ethyl acetate (3 × 100 mL), and the combined organic extracts were then washed with brine (150 mL), dried over $MgSO_4$ and concentrated *in vacuo* to leave the corresponding *amino alcohol* (4.3 g, 93%) as colourless crystals; mp 117-119 ºC (from chloroform); $[\alpha]_D^{20}$ –16.2 (*c* 1.3 in $CHCl_3$) (Found: C, 51.9; H, 5.3; N, 2.6; $C_{21}H_{26}NO_4I$ requires: C, 52.2; H, 5.4; N, 2.9%); ν_{max} ($CHCl_3$)/ cm^{-1} 3626, 3442, 1705; δ_H (360 MHz, $CDCl_3$) 7.66 (1H, d, *J* 2.0, CIC*H*), 7.50 (2H, d, *J* 7.3, Ar*H*), 7.40 (2H, t, *J* 7.3, Ar*H*), 7.33 (1H, t, *J* 7.3, Ar*H*), 7.12 (1H, dd, *J* 8.4 and 2.0, Ar*H*), 6.79 (1H, *J* 8.4, Ar*H*), 5.14 (2H, s, PhCH_2OAr), 4.72 (1H, br s, N*H*), 3.80 (1H, br, NHC*H*), 3.67 (1H, app d, *J* 11.1, NCHC*H*HOH), 3.56 (1H, dd, *J* 11.1 and 4.3, NCHCH*H*OH), 2.76 (2H, d, *J* 7.2, ArCH_2CH), 2.21 (1H, br s, O*H*), 1.43 (9H, s, COOC(CH_3)$_3$); δ_C (90.6 MHz, $CDCl_3$) 156.0 (s), 140.1 (d), 136.6 (s), 132.5 (s), 130.2 (d), 128.6 (d), 127.9 (d), 127.0 (d), 112.7 (d), 86.9 (s), 79.9 (s), 71.0 (t), 64.1 (t), 53.9 (d), 36.0 (t), 28.4 (q); *m/z* (ESI) Found: 506.0794 ($[M + Na]^+$, 62%, $C_{21}H_{26}NO_4INa$ requires 506.0804), 384 (100), 323 (30), 240 (5).

Boron trifluoride diethyl etherate (0.1 mL, 0.7 mmol) was added to a solution of the amino alcohol (4.3 g, 8.9 mmol) in acetone (36 mL) and 2,2-dimethoxypropane (10 mL) at room

temperature under a nitrogen atmosphere. The solution was stirred at room temperature for 18 h and then ethyl acetate (100 mL) and water (50 mL) were added. The separated aqueous layer was extracted with ethyl acetate (3 × 100 mL) and the combined organic extracts were then washed with brine (150 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography, eluting with 10% ethyl acetate in petroleum ether, to give the *acetonide* (4.2 g, 90%) as a colourless viscous oil; $[\alpha]_D^{20}$ –26.7 (*c* 1.7 in $CHCl_3$); (Found: C, 55.4; H, 6.0; N, 2.7; $C_{24}H_{30}INO_4$ requires: C, 55.1; H, 5.8; N, 2.7%); ν_{max} ($CHCl_3$)/ cm^{-1} 1693; δ_H (360 MHz at 318K, $CDCl_3$) 7.68 (1H, br s, Ar*H*), 7.49 (2H, d, *J* 7.3, Ar*H*), 7.41-7.31 (3H, m, Ar*H*), 7.11 (1H, br s, Ar*H*), 6.79 (1H, d, *J* 8.2, Ar*H*), 5.12 (2H, s, PhCH_2OAr), 4.00 (1H, br, NC*H*), 3.83-3.73 (2H, m, NCHCH_2O), 3.06 (1H, br, ArC*H*HCH), 2.61 (1H, app t, *J* 11.2, ArCH*H*CH), 1.59-1.49 (15H, m, COOC(CH_3)$_3$ and C(CH_3)$_2$); δ_C (90.6 MHz at 318K, $CDCl_3$) 156.1 (s), 151.7 (s), 140.3 (d), 136.6 (s), 133.2 (s), 130.2 (d), 128.5 (d), 127.9 (d), 127.0 (d), 112.9 (d), 93.6 (s), 87.0 (s), 79.9 (s), 71.1 (t), 66.1 (t), 59.0 (d), 38.4 (t), 28.6 (q), 27.7 (q), 24.7 (q); *m/z* (EI) Found: 523.1214 (M^+, 18%, $C_{24}H_{30}NO_4I$ requires 523.1220), 450 (6), 200 (52), 144 (42), 100 (71), 91 (71), 57 (100).

***tert*-Butyl (4*S*)-4-[4-Benzyloxy-3-((*Z*)-1-methoxycarbonyl-propenyl)-benzyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (22).** Triphenylarsine (2.4 g, 7.7 mmol) was added in one portion to a stirred suspension of *tris*(dibenzylideneacetone)dipalladium(0) (0.9 g, 1.0 mmol) in 1-methyl-2-pyrrolidinone (10 mL) at room temperature under a nitrogen atmosphere, and the mixture was then stirred at room temperature for 15 min. The acetonide **21** (6.7 g, 13 mmol), followed by a solution of methyl *E*-2-(trimethylstannyl)but-2-enoate (6.2 g, 16 mmol)[32] in 1-methyl-2-pyrrolidinone (30 mL) were added, and the mixture was degassed with nitrogen for 45 min. Copper (I) iodide (4.4 g, 23 mmol) was added and the mixture was then stirred at room temperature for 24 h. Saturated aqueous potassium fluoride solution (5 mL) was added dropwise over 10 min, and the mixture was then stirred at room temperature for 30 min. Water (50 mL) containing concentrated aqueous ammonia solution (15 mL) and diethyl ether (200 mL) were then added. The separated aqueous layer was extracted with diethyl ether (3 × 100 mL) and the combined organic extracts were washed with brine (150 mL), then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography, eluting with 10% ethyl

acetate in petroleum ether, to give the *ester* (4.8 g, 76%) as a colourless oil; $[\alpha]_D^{18}$ –22.9 (*c* 2.2 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 1713, 1692; δ_H (360 MHz at 318K, $CDCl_3$) 7.36-7.27 (5H, m, Ar*H*), 7.10 (2H, br s, Ar*H*), 6.83 (1H, d, *J* 8.1, Ar*H*), 6.24 (1H, q, *J* 6.9, =C*H*CH_3), 5.03 (2H, s, PhCH_2OAr), 4.04 (1H, br, NC*H*), 3.80 (2H, s, NCHCH_2O), 3.56 (3H, s, OCH_3), 3.07 (1H, br, ArC*H*HCH), 2.65 (1H, app t, *J* 12.8, ArCH*H*CH), 2.09 (3H, d, *J* 6.9, =CHCH_3), 1.59-1.50 (15H, m, COOC(CH_3)$_3$ and C(CH_3)$_2$); δ_C (90.6 MHz at 318K, $CDCl_3$) 168.0 (s), 154.7 (s), 152.5 (s), 137.8 (d), 137.1 (s), 132.7 (s), 131.3 (d), 131.2 (s), 129.7 (d), 129.5 (s), 128.4 (d), 127.8 (d), 127.1 (d), 112.4 (d), 94.2 (s), 79.8 (s), 70.6 (t), 66.4 (t), 59.2 (d), 51.2 (q), 38.2 (t), 28.6 (q), 27.7 (q), 24.7 (q), 15.8 (q); *m/z* (EI) Found: 495.2605 (M^+, 16%, $C_{29}H_{37}NO_6$ requires 495.2621), 295 (9), 263 (12), 205 (30), 200 (35), 173 (32), 57 (100).

***tert*-Butyl (4*S*)-4-[4-Benzyloxy-3-((*E*)-1-(2-iodophenylcarbamoyl)prop-1-enyl)- benzyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (23a).** A solution of trimethylaluminium (2 M) in hexane (2.3 mL, 4.6 mmol) was added dropwise over 20 min to a solution of 2-iodoaniline (1.0 g, 4.6 mmol) in dichloromethane (4.5 mL) at 0 °C under an atmosphere of nitrogen, and the mixture was stirred at 0 °C for 1 h. The ester **22** (0.8 g, 1.5 mmol) was added and the mixture was heated under reflux for 36 h and then cooled to 0 °C. Saturated Rochelle's solution (5 mL) was added dropwise over 15 min, and after 20 min, diethyl ether (30 mL) and water (30 mL) were added. The separated aqueous layer was extracted with diethyl ether (3 × 30 mL) and the combined organic extracts were then washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography, eluting with 5-20% ethyl acetate in petroleum ether, to give the *anilide* (0.77 g, 74%) as a yellow oil; $[\alpha]_D^{22}$ –13.6 (*c* 1.0 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3347, 2901, 1794, 1683; δ_H (360 MHz at 333K, C_6D_6) 9.08 (1H, dd, *J* 7.3 and 1.5, Ar*H*), 7.93 (1H, s, N*H*), 7.52 (1H, app. t, *J* 7.9, Ar*H*), 7.50 (1H, q, *J* 7.1, =C*H*CH_3), 7.28-7.26 (2H, m, Ar*H*), 7.21 (1H, br s, Ar*H*), 7.16-7.08 (5H, m, Ar*H*), 6.88 (1H, d, *J* 8.4, Ar*H*), 6.48 (1H, dt, *J* 7.3 and 1.5, Ar*H*), 4.90 (2H, s, PhCH_2OAr), 4.15 (1H, br, C*H*N), 3.85 (1H, dd, *J* 8.9 and 1.5, ArCH$_2$CHC*H*H), 3.74 (1H, *J* 8.9 and 5.7, ArCH$_2$CHCH*H*), 3.30 (1H, br, ArC*H*H), 2.82 (1H, dd, *J* 13.1 and 10.2, ArCH*H*), 1.80 (3H, br s, C(CH_3)$_a$(CH$_3$)$_b$), 1.62 (3H, d, *J* 7.1, =CHCH_3), 1.58 (12H, s, COOC(CH_3)$_3$ and C(CH$_3$)(CH_3)); δ_C (90.6 MHz at 333K, C_6D_6) 164.6 (s), 155.9 (s), 152.0 (s), 140.0 (s), 138.8 (d), 137.6 (d), 137.2 (s), 135.1 (s), 133.3 (d),

132.2 (s), 131.1 (d), 129.5 (d), 128.6 (d), 127.9 (d), 127.3 (d), 125.1 (d), 121.2 (d), 114.0 (d), 94.2 (s), 88.5 (s), 79.5 (s), 70.6 (t), 66.5 (t), 59.7 (d), 39.0 (t), 28.6 (q), 27.7 (q), 24.7 (q), 15.2 (q); *m/z* (ESI) Found: 705.1849 ($[M + Na]^+$, 85%, $C_{34}H_{39}IN_2O_5Na$ requires 705.1801), 627 (100), 592 (33), 518 (13), 440 (20).

***tert*-Butyl (4*S*)-4-[4-Benzyloxy-3-((*E*)-1-(*N*-((2-(trimethylsilyl)ethoxy)methyl)-*N*-(2-iodophenyl) carbamoyl)prop-1-enyl) benzyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (23b).** A solution of sodium hexamethyldisilazide (2 M) in tetrahydrofuran (1.8 mL, 3.6 mmol) was added dropwise over 10 min to a stirred solution of the anilide **23a** (1.9 g, 2.8 mmol) in tetrahydrofuran (15 mL) at 0 °C under an atmosphere of nitrogen. The solution was stirred at 0 °C for 20 min, then 2-trimethylsilyl ethoxymethyl chloride (1.2 g, 1.2 mL, 6.9 mmol) was added dropwise over 10 min, and the mixture was stirred at room temperature for 14 h. Water (15 mL) and diethyl ether (20 mL) were added and the separated aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography, eluting with 10-20% ethyl acetate in petroleum ether, to give the *iodide* (2.0 g, 90%) as a yellow oil; $[\alpha]_D^{17}$ −15.0 (*c* 1.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2987, 1690; δ_H (360 MHz at 368K, $(CD_3)_2SO$) (*the spectrum was complex, with broad peaks due to non-coalescing rotamers*) 7.71, 7.50-7.25, 7.20-6.80, 6.50, 5.30, 5.01, 4.54, 3.84, 3.66, 3.49, 3.01, 2.84, 1.57, 1.50, 0.79, 0.03; δ_C (90.6 MHz, $(CD_3)_2SO$) 154.0 (s), 151.1 (s), 139.3 (s), 137.2 (d), 136.2 (d), 135.8 (d), 131.0 (d), 129.7 (d), 128.8 (d), 128.3 (d), 127.6 (d), 127.1 (d), 112.3 (d), 100.6 (s), 93.3 (s), 79.1 (s), 69.5 (t), 65.9 (t), 65.6 (t), 65.4 (t), 58.6 (d), 38.4 (t), 28.4 (q), 26.8 (q), 23.2 (q), 17.7 (t), 15.1 (q), −1.3 (q); *m/z* (ESI) Found: 835.2601 ($[M + Na]^+$, $C_{40}H_{53}IN_2O_6SiNa$ requires 835.2615), 707 (7), 295 (5).

(±)-7-Bromo-3-Phenyl-2,3-dihydrobenzofuran-3-carboxylic acid (25b). Ozone was bubbled through a solution of the olefin **5** (26.4 g, 88.0 mmol) in dichloromethane (600 mL) containing a crystal of Sudan Red 7B at -78 °C. When the solution had decolourised, after *ca.* 8 h the ozone supply was turned off and the solution was then purged with oxygen for 10 min, followed by nitrogen for 10 min. A solution of triphenylphosphine (25.3 g, 96.8 mmol) in dichloromethane (100 mL) was added over 5 min and the mixture was then allowed to warm to room temperature.

The solution was washed with water (2 × 700 mL) then dried and concentrated *in vacuo*. Diethyl ether (150 mL) was added to the residue, and the mixture was cooled to 0 °C. Pentane (300 mL) was added to the rapidly stirred solution and the mixture was kept at 0 °C for 30 min. The precipitated solid was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with 5% ethyl acetate in petroleum ether, to give the *aldehyde* **25a** (22.3 g, 84%) as a colourless oil; ν_{max} ($CHCl_3$)/cm^{-1} 2821, 1726; δ_H (400 MHz, $CDCl_3$) 9.68 (1H, d, *J* 1.1, C*H*O), 7.49 (1H, d, *J* 7.4, Ar*H*), 7.44-7.37 (3H, m, Ar*H*), 7.24 (1H, d, *J* 7.4, Ar*H*), 7.15 (2H, dd, *J* 7.0 and 1.2, Ar*H*), 6.92 (1H, t, *J* 7.4, Ar*H*), 5.57 (1H, d, *J* 9.2, OCH*H*), 4.41 (1H, dd, *J* 9.2 and 1.1, OC*H*HCCHO); δ_C (100 MHz, $CDCl_3$) 192.7 (d), 158.7 (s), 137.2 (s), 133.5 (d), 129.6 (d), 128.5 (d), 127.4 (d), 125.1 (s), 124.8 (d), 122.5 (d), 104.2 (s), 77.5 (t), 67.5 (s); *m/z* (EI) Found: 301.9944 (M^+, $C_{15}H_{11}O_2Br$ requires 301.9942), 273 (53), 194 (100).

A solution of sodium chlorite (11.1 g, 123 mmol) and potassium dihydrogenphosphate (17.5 g, 128 mmol) in water (190 mL) was added dropwise over 10 min to a stirred solution of the aldehyde **25a** (22.3g, 73.5 mmol) and 2-methyl-2-butene (93 mL, 88.0 mmol) in *t*-butanol (650 mL). The mixture was stirred at room temperature for 24 h and then concentrated *in vacuo*. The aqueous residue was basified to pH 10 with 2M aqueous sodium hydroxide solution, then washed with diethyl ether (2 × 300 mL), acidified to pH 2 with 2M hydrochloric acid and extracted with diethyl ether (2 × 300 mL). The combined ether extracts were dried and concentrated *in vacuo* to leave the *carboxylic acid* (19.6 g, 85%) as a colourless solid, mp 67-68 °C; (Found: C, 56.3; H, 3.7; $C_{15}H_{11}O_3Br$ requires: C, 56.4; H, 3.5%); ν_{max} ($CHCl_3$)/cm^{-1} 3171, 2625, 1713; δ_H (270 MHz, $CDCl_3$) 10.30 (1H, br s, CO_2H), 7.46 (1H, dd, *J* 7.6 and 1.3, Ar*H*), 7.44 (1H, dd, *J* 8.0 and 1.3, Ar*H*), 7.36-7.30 (3H, m, Ar*H*), 7.19 (2H, dd, *J* 7.7 and 1.7, Ar*H*), 6.88 (1H, t, *J* 7.9, Ar*H*), 5.45 (1H, d, *J* 9.2, OCH*H*), 4.54 (1H, d, *J* 9.2, OC*H*H); δ_C (67.8 MHz, $CDCl_3$) 157.6 (s), 140.2 (s), 133.1 (d), 129.0 (d), 128.1 (d), 127.4 (s), 126.4 (d), 126.3 (d), 122.4 (d), 103.4 (s), 80.8 (t), 62.8 (s); *m/z* (EI) Found: 317.9867 (M^+, 14%, $C_{15}H_{11}O_3Br$ requires 317.9892), 274 (31), 240 (4), 194 (98), 164 (8), 77 (18), 75 (4).

***N*-(7-Bromo-3-phenyl-2,3-dihydrobenzofuran-3-oyl)-1-amino-1-phenylethane (26)**. Thionyl chloride (15 mL) was added dropwise over 15 min to the carboxylic acid **25b** (280 mg, 0.91

mmol) and the resulting suspension was then heated under reflux for 4 h. The solution was allowed to cool and was then concentrated *in vacuo*. The residue was twice taken up in dry toluene and the combined organic extracts concentrated *in vacuo* to leave the corresponding *acid chloride* (305 mg, 99%) as a colourless solid; ν_{max} ($CHCl_3$)/cm^{-1} 3171, 2625, 1713; δ_H (270 MHz, $CDCl_3$) 7.38 (1H, d, *J* 7.6, Ar*H*), 7.31 (1H, d, *J* 7.9, Ar*H*), 7.21-7.12 (2H, m, Ar*H*), 7.05-6.95 (3H, m, Ar*H*), 6.75 (1H, dd, *J* 7.9 and 7.6, Ar*H*), 5.29 (1H, d, *J* 9.6, OCH*H*), 4.27 (1H, d, *J* 9.6, OC*H*H); δ_C (67.8 MHz, $CDCl_3$) 173.0 (s), 158.2 (s), 137.6 (s), 134.0 (d), 129.4 (d), 128.7 (d), 126.9 (d), 126.5 (d), 124.9 (s), 122.6 (d), 103.9 (s), 80.2 (t), 72.3 (s); which was used without further purification.

A solution of the acid chloride (305 mg, 0.90 mmol) in dichloromethane (5 mL) was added dropwise over 5 min to a stirred solution of (*S*)-(−)-α-methylbenzylamine (0.40 mL, 3.0 mmol) and triethylamine (6 mL) in dichloromethane (5 mL) at 0 °C under a nitrogen atmosphere, and the mixture was then heated under reflux for 16 h. The mixture was cooled to room temperature, then washed with 2 M hydrochloric acid (10 mL), and the separated organic extract was dried and concentrated *in vacuo*. The residue was purified by chromatography, eluting with 10% ethyl acetate in petroleum ether, to give (i) *a less polar amide* **26a** (160 mg, 46%) (eluted first) as a colourless oil; $[\alpha]_D^{25}$ +193.6 (*c* 0.56 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3421, 3030, 2971, 1673, 1599, 1494; δ_H (270 MHz, $CDCl_3$) 7.47 (1H, dd, *J* 7.9 and 1.3, Ar*H*), 7.36-7.14 (10H, m, Ar*H*), 6.91 (1H, t, *J* 7.9, Ar*H*), 5.88 (1H, d, *J* 7.9, CON*H*CH), 5.66 (1H, d, *J* 9.2, OC*H*H), 5.13 (1H, dq, *J* 7.9 and 6.9, NHC*H*CH_3), 4.56 (1H, d, *J* 9.2, OCH*H*), 1.39 (3H, d, *J* 6.9, CHC*H*$_3$); δ_C (67.8 MHz, $CDCl_3$) 170.3 (s), 157.8 (s), 142.6 (s), 140.6 (s), 132.9 (d), 129.6 (s), 128.9 (d), 128.5 (d), 127.9 (d), 127.3 (d), 127.2 (d), 125.8 (d), 123.9 (d), 122.1 (d), 104.0 (s), 82.2 (t), 63.8 (s), 49.4 (d), 21.6 (q); *m/z* (FAB) Found: 421.0654 (M^+, 1%, $C_{23}H_{20}BrNO_2$ requires 421.0677), 273 (38), 194 (43), 105 (53); and (ii) *a more polar amide* **26b** (170 mg, 48%) (eluted second) as a colourless crystalline solid, mp 145-147 °C (from hexane); $[\alpha]_D^{25}$ −158.3 (*c* 1.16 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3421, 3030, 2971, 1673, 1599, 1494; δ_H (270 MHz, $CDCl_3$) 7.43-7.08 (12H, m, Ar*H*), 6.81 (1H, t, *J* 7.7, Ar*H*), 5.76 (1H, d, *J* 7.9, CON*H*CH), 5.66 (1H, d, *J* 8.9, OC*H*H), 5.15 (1H, dq, *J* 7.9 and 6.9, NHC*H*CH_3), 4.58 (1H, d, *J* 8.9, OCH*H*), 1.45 (3H, d, *J* 6.9, CHC*H*$_3$); δ_C (67.8 MHz, $CDCl_3$) 170.5 (s), 157.8 (s), 142.3 (s), 140.7 (s), 132.9 (d), 129.5 (s), 129.1 (d), 128.6 (d), 128.1 (d), 127.4 (d), 127.3 (d), 125.9 (d), 124.0 (d), 122.1 (d), 104.0 (s),

82.2 (t), 63.9 (s), 49.3 (d), 21.1 (q); *m/z* (FAB) Found: 421.0654 (M^+, 1%, $C_{23}H_{20}BrNO_2$ requires 421.0677), 273 (38), 194 (43), 105 (53).

X-ray Crystal Structure of (−)α-Methylbenzylamide 26b

Crystal data. $C_{23}H_{20}BrNO_2$, M = 422.31, orthorhombic, a = 12.865(11), b = 15.761(11), c = 19.557(11) Å, U = 3910.0(5) Å^3, T = 210(2) K, space group $P2_12_12_1$ (No. 19), Z = 8, D_c = 1.415 g cm^{-3}, μ(Mo-$K\alpha$) = 2.090 mm^{-1}, 3102 unique reflections collected and used in all calculations. Final R_1 [1755 $F > 4\sigma(F)$] = 0.112 and wR_2 (all F^2) was 0.240. The absolute structure parameter refined to 0.00(7).

(+)-7-Bromo-3-Phenyl-2,3-dihydrobenzofuran-3-carboxylic acid (27). *p*-Toluenesulfonic acid (300mg, 1.6 mmol) was added to a stirred solution of the less polar α-methyl benzylamide **26a** (160 mg, 0.40 mmol) in toluene (5 mL) under a nitrogen atmosphere, and the mixture was then heated under reflux for 16 h. The solution was concentrated *in vacuo* and the residue was purified by chromatography, eluting with ethyl acetate, to give the corresponding *primary amide* (99mg, 83%) as a colourless oil; $[\alpha]_D^{25}$ +155.9 (*c* 0.98 in EtOH); (Found: C, 55.6; H, 3,8; N, 4.4; $C_{15}H_{12}BrNO_2$ requires: C, 55.6; H, 3.8; N, 4.4%); ν_{max} ($CHCl_3$)/cm^{-1} 3515, 3402, 3032, 2928, 1689, 1580; δ_H (250 MHz, $CDCl_3$) 7.43 (1H, d, *J* 7.9, Ar*H*), 7.39-7.24 (6H, m, Ar*H*), 6.88 (1H, t, *J* 7.7, Ar*H*), 6.40 (2H, bs, CONH_2), 5.58 (1H, d, *J* 9.1, OC*H*H), 4.58 (1H, d, *J* 9.1, OC*H*H); δ_C (67.8 MHz, $CDCl_3$) 174.4 (s), 158.1 (s), 140.7 (s), 133.4 (d), 129.8 (s), 129.5 (d), 128.5 (d), 127.6 (d), 124.6 (d), 122.7 (d), 104.3 (s), 82.5 (t), 64.2 (s); *m/z* (FAB) Found: 317.0056 (M^+, 1%, $C_{15}H_{12}BrNO_2$ requires 317.0052), 273 (57), 194 (100), 165 (47).

3 M Aqueous potassium hydroxide (4 mL) was added to a stirred solution of the amide (80 mg, 0.26 mmol) in ethanol (5 mL), and the mixture was then heated under reflux for 16 h. The mixture was cooled to room temperature and then concentrated *in vacuo* to half volume. The residue was acidified to pH 2 with concentrated hydrochloric acid and the mixture was then extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were dried and concentrated *in vacuo* to leave a residue which was purified by column chromatography, eluting with petrol:ethyl acetate, 1:1, to give the *acid* (67 mg, 84%) as a colourless solid; $[\alpha]_D^{25}$ +230.6 (*c* 0.45 in EtOH).

(−)-7-Bromo-3-Phenyl-2,3-dihydrobenzofuran-3-carboxylic acid (*ent*-27) The more polar α-methylbenzylamide **26** was converted into the carboxylic acid amide, $[\alpha]_D^{25}$ −160.3 (*c* 0.87 in $CHCl_3$) and then into the carboxylic acid $[\alpha]_D^{25}$ –241.2 (*c* 0.55 in EtOH) using an identical procedure to that described for the conversion of the less polar α-methylbenzylamide **26** into the corresponding (+)-carboxylic acid.

Ethyl-3-(7-bromo-3-phenyl-2,3-dihydrobenzofuran-3-yl)-3-oxopropionate (28). A solution of ethyl diazoacetate (1.2 mL, 10.9 mmol) in dichloromethane (8 mL) followed by a solution of the aldehyde **25a** (1.11 g, 3.64 mmol) in dichloromethane (8 mL) were added dropwise over 0.5 h to a stirred solution of zirconium chloride (0.85 g, 3.64 mmol) in dichloromethane (15 mL) at −10 °C under a nitrogen atmosphere. The mixture was warmed to 0 °C and stirred at 0 °C for 2 h, then warmed to room temperature and poured into brine (30 mL). The separated aqueous layer was extracted with dichloromethane (2 x 30 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. The residue was purified by chromatography, eluting with ethyl acetate in petrol (1:9) to give the *β-keto ester* (1.19 g, 84%) as a pale red oil; ν_{max} ($CHCl_3$)/cm^{-1} 1744, 1716; δ_H (360 MHz, $CDCl_3$) 7.46 (1H, d, *J* 8.0, Ar*H*), 7.42 - 7.32 (4H, m, Ar*H*), 7.22 - 7.20 (2H, m, Ar*H*), 6.91 (1H, t, *J* 7.8, Ar*H*), 5.64 (1H, d, *J* 9.1, C*H*HOAr), 4.28 (1H, d, *J* 9.1, CH*H*OAr), 4.05 (2H, dq, *J* 7.1 and 1.9, C*H*$_2$CH$_3$), 3.54 (2H, d, *J* 2.6, C*H*$_2$CO), 1.17 (3H, t, *J* 7.1, C*H*$_3$); δ_C (90 MHz, $CDCl_3$) 197.1(s), 166.3 (s), 158.3 (s), 137.8 (s), 133.2 (d), 129.4 (d), 128.3 (d), 126.7 (d), 126.1 (s), 125.2 (d), 122.2 (d), 104.0 (s), 79.0 (t), 69.3 (s), 61.2 (t), 44.6 (t), 13.8 (q); m/z (EI) Found: 388.0323 ($[M + H]^+$, $C_{19}H_{18}O_4Br$ requires 388.0310).

(E/Z)-Ethyl-3-(7-bromo-3-phenyl-2,3-dihydrobenzofuran-3-yl)-2-hydroxyimino-3-oxopropionate 29a. A solution of sodium nitrite (1.69 g, 23.8 mmol) in water (5 mL) was added dropwise over 3 min to a stirred solution of the β-keto ester **28** (1.16 g, 2.97 mmol) in acetic acid (5 mL) at room temperature. The mixture was stirred at room temperature for 2 h, then diluted with water (20 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed successively with water (70 mL), saturated aqueous sodium hydrogen carbonate (70 mL) and water (70 mL), then dried and concentrated *in vacuo*. The residue was purified by chromatography, eluting with ethyl acetate in petrol (3:7), to give the *oxime* (1.17 g, 94%) as a

yellow oil in a 2:1 mixture of geometrical isomers; ν_{max} ($CHCl_3$)/cm^{-1} 3536, 1630; δ_H (360 MHz, $CDCl_3$) (major isomer) 9.24 (1H, s, O*H*), 7.41 (1H, dd, *J* 6.9 and 1.1, Ar*H*), 7.39 (1H, dd, *J* 7.2 and 1.1, Ar*H*), 7.35 - 7.30 (2H, m, Ar*H*), 7.25 (1H, tt, *J* 7.1 and 2.2, Ph*H*), 7.19 - 7.16 (2H, m, Ar*H*), 6.84 (1H, t, *J* 7.7, Ar*H*), 5.37 (1H, d, *J* 9.7, C*H*HOAr), 4.77 (1H, d, *J* 9.7, CH*H*OAr), 4.34 (2H, q, *J* 7.1, CH_2CH$_3$), 1.33 (3H, t, *J* 7.1, CH_3); δ_C (90 MHz, $CDCl_3$) 190.8(s), 160.8 (s), 157.3 (s), 148.3 (s), 140.8 (s), 133.8 (d), 129.2 (d), 127.6 (d), 127.5 (s), 127.2 (d), 125.6 (d), 122.4 (d), 103.4 (s), 79.4 (t), 67.1 (s), 60.8 (t), 13.9 (q); m/z (EI) Found: 399.0114 ($[M - H_2O]^+$, $C_{19}H_{14}NO_4Br$ requires 399.0106).

Ethyl-2-acetylamino-3-(7-bromo-3-phenyl-2,3-dihydrobenzofuran-3-yl)-3-oxopropionate 29c. Zinc dust (21 mg, 0.32 mmol) was added in a single portion to a stirred solution of the oxime **29a** (68 mg, 0.16 mmol) in 80% aqueous acetic acid (2 mL) at room temperature. The mixture was stirred at room temperature for a total period of 3.5 h, and more zinc dust (21 mg, 0.32 mmol) was added after 2.5 h. The precipitate was removed by filtration and washed with acetic acid. The filtrate was concentrated *in vacuo* to leave the salt of the amine **29b** (74 mg, 100%) as a pale yellow solid, which was used immediately without purification. A solution of acetyl chloride (40 μL, 0.48 mmol) in dichloromethane (2 mL) was added dropwise over 1 min to a stirred solution of the amine salt (74 mg, 0.16 mmol) and triethylamine (70 μL, 0.48 mmol) in dichloromethane (3 mL) at 0 °C under a nitrogen atmosphere. The mixture was warmed to room temperature over 1 h, stirred at room temperature for 9.5 h, then diluted with dichloromethane (15 mL) and washed with water (20 mL). The organic extracts were dried and concentrated *in vacuo*. The residue was purified by chromatography, eluting with ethyl acetate in petrol (1:1), to give the *keto amide* (51 mg, 71%), as a pale yellow oil as a 2:1 mixture of diastereoisomers; ν_{max} ($CHCl_3$)/cm^{-1} 3427, 1749, 1717, 1682; δ_H (360 MHz, $CDCl_3$) 7.79 (1H, dd, *J* 7.6 and 1.1, Ar*H*), 7.58 (1H, dd, *J* 7.6 and 1.1, Ar*H*), 7.49 - 7.44 (2H, m, Ar*H*), 7.40 - 7.30 (6H, m, Ar*H*), 7.23 - 7.19 (4H, m, Ar*H*), 6.97 (1H, t, *J* 7.8, Ar*H*), 6.92 (1H, t, *J* 7.8, Ar*H*), 6.68 (1H, d, *J* 7.2, N*H*), 6.55 (1H, d, *J* 8.8, N*H*), 5.81 (1H, d, *J* 8.8, C*H*N), 5.64 (1H, d, *J* 9.2, C*H*HOAr), 5.61 (1H, d, *J* 7.2, C*H*N), 5.54 (1H, d, *J* 9.4, C*H*HOAr), 4.54 (1H, d, *J* 9.4, CH*H*OAr), 4.29 (1H, d, *J* 9.2, CH*H*OAr), 3.93 - 3.78 (2H, m, CH_2CH$_3$), 3.44 (2H, dq, *J* 10.7 and 7.2, CH_2CH$_3$), 1.92 (3H, s, CH_3CO), 1.89 (3H, s, CH_3CO), 1.03 (3H, t, *J* 7.2, CH$_2$CH_3), 1.03

(3H, t, *J* 7.2, CH_2CH_3); δ_C (90 MHz, $CDCl_3$) 199.4(s), 197.0 (s), 169.5 (s), 169.0 (s), 166.3 (s), 166.1 (s), 158.4 (s), 158.2 (s), 137.2 (s), 137.1 (s), 133.5 (d), 133.2 (d), 129.2 (d), 129.1 (d), 128.4 (d), 128.3 (d), 126.7 (d), 126.6 (d), 126.4 (d), 126.3 (d), 125.6 (s), 122.7 (d), 122.5 (d), 104.1 (s), 103.7 (s), 79.9 (t), 79.2 (t), 69.0 (s), 68.8 (s), 62.4 (t), 62.3 (t), 57.7 (d), 56.6 (d), 22.5 (q), 13.5 (q x 2); m/z (EI) Found: 446.0599 ($[M + H]^+$, $C_{21}H_{21}NO_5Br$ requires 446.0603).

Ethyl 2-bromo-3-oxo-3-(7-bromo-3-phenyl-2,3-dihydrobenzofur-3-yl)-propanoate 29d. A solution of the β-keto ester **28** (3.00 g, 7.71 mmol) in tetrahydrofuran (30 mL) was added dropwise over 15 min to a stirred suspension of petrol-washed sodium hydride (308 mg, 7.71 mmol) in tetrahydrofuran (60 mL) at 0 °C under a nitrogen atmosphere and the mixture was stirred at 0 °C for 20 min. Bromine (0.397 mL, 7.71 mmol) was added over 5 min, and the solution was stirred at 0 °C for 20 min. The solution was diluted with water (80 mL) and then solid sodium thiosulphate was added until the solution decolourised. The mixture was extracted with diethyl ether (3 x 60 mL) and the combined extracts were dried and concentrated *in vacuo*. The residue was purified by chromatography, eluting with ethyl acetate in petrol (1:4), to give the *bromide* (3.67 g, 99%) as an oil and as a 2:1 mixture of diasteromers; ν_{max} ($CHCl_3$)/cm^{-1} 2941, 1754, 1731, 1598; δ_H (400 MHz, $CDCl_3$) 7.34 - 7.52 (10H, m, Ph*H*), 7.23 - 7.27 (4H, m, Ar*H*), 6.97 (1H, t, *J* 7.8, Ar*H*), 6.91 (1H, t, *J* 7.8, Ar*H*), 5.65 (1H, d, *J* 9.2, OCH*H*C), 5.63 (1H, d, *J* 9.4, OCH*H*C), 5.13 (1H, s, COC*H*$BrCO_2$), 5.11 (1H, s, COC*H*$BrCO_2$), 4.42 (1H, d, *J* 9.4, OC*H*HC), 4.34 (1H, d, *J* 9.2, OC*H*HC), 4.01 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 3.91 (1H, dq, *J* 10.7 and 7.1, CO_2CHHCH_3), 3.81 (1H, dq, *J* 10.7 and 7.1, CO_2CHHCH_3), 1.15 (3H, t, *J* 7.1, OCH_2CH_3), 1.05 (3H, t, *J* 7.1, OCH_2CH_3); δ_C (67.8 MHz, $CDCl_3$) 193.8 (s), 193.5 (s), 164.4 (s), 164.2 (s), 158.7 (s), 158.3 (s), 136.8 (s), 136.5 (s), 133.8 (d), 129.6 (d), 129.3 (d), 128.8 (d), 128.7 (d), 127.2 (d), 127.1 (d), 125.8 (d), 125.6 (s), 125.5 (s), 125.4 (d), 122.6 (d), 122.4 (d), 104.3 (s), 104.2 (s), 80.0 (t), 79.9 (t), 69.3 (s), 69.2 (s), 63.2 (t), 63.1 (t), 45.6 (d), 43.8 (d), 13.7 (q), 13.5 (q); m/z (EI) Found: 465.9415 (M^+, $C_{19}H_{16}O_4Br_2$ requires 465.9416), 273 (2), 164 (11).

Ethyl 2-azido-3-hydroxy-3-(7-bromo-3-phenyl-2,3-dihydrobenzofur-3-yl)-prop-2-enoate 29e. Sodium azide (139 mg, 2.14 mmol) was added to a solution of the bromide **29d** (1.00 g, 2.14 mmol) in dimethylformamide (25 mL) at 0 °C under a nitrogen atmosphere and the mixture was then stirred at 0 °C for 1.5 h. Water (120 mL) was added, and the mixture was then extracted

with diethyl ether (2 x 100 mL). The combined extracts were dried and then concentrated *in vacuo* to leave the *azide* (730 mg, 79%) as a colourless oil; ν_{max} ($CHCl_3$)/cm^{-1} 2940, 2133, 1744, 1731, 1673; δ_H (400 MHz, $CDCl_3$) 11.61 (1H, s, C=CO*H*), 7.42 (1H, d, *J* 7.7, Ar*H*), 7.26 - 7.38 (6H, m, Ar*H*), 6.84 (1H, t, *J* 7.7, Ar*H*), 5.69 (1H, d, *J* 9.4, OCH*H*C), 4.61 (1H, d, *J* 9.4, OC*H*HC), 4.11 (1H, dq, *J* 10.7 and 7.1, CO_2CH*H*CH_3), 4.04 (1H, dq, *J* 10.7 and 7.1, CO_2C*H*HCH_3), 1.15 (3H, t, *J* 7.1, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 196.8 (s), 165.4 (s), 158.4 (s), 158.3 (s), 138.3 (s), 133.2 (d), 129.1 (d), 128.2 (d), 126.8 (d), 126.5 (d), 122.4 (s), 122.3 (d), 103.6 (s), 80.0 (t), 67.9 (s), 63.1 (t), 13.6 (q), which was used immediately without further purification.

Ethyl 2-amino-3-oxo-3-(7-bromo-3-phenyl-2,3-dihydrobenzofur-3-yl)-propanoate 29b. A solution of triphenylphosphine (750 mg, 2.86 mmol) in tetrahydrofuran (5 mL) was added portionwise to a mixture of the azide **29e** (1.17 g, 2.72 mmol) and water (0.10 mL) in tetrahydrofuran (20 mL) at room temperature under a nitrogen atmosphere. The mixture was heated at reflux temperature for 24 h, then cooled to room temperature, diluted with diethyl ether (30 mL) and extracted with 1N hydrochloric acid (40 mL). The separated aqueous extract was basified to pH 8 with saturated aqueous sodium bicarbonate and the resulting emulsion was extracted with diethyl ether (2 x 30 mL). The separated organic extract was dried and concentrated *in vacuo* to leave the *amine* (870 mg, 79%) as an oil and as a 2:1 mixture of diastereomers; ν_{max} ($CHCl_3$)/cm^{-1} 3671, 3395, 3327, 2991, 1744, 1716, 1598; δ_H (400 MHz, $CDCl_3$) 7.67 (1H, dd, *J* 7.6 and 1.3, Ar*H*), 7.47 (1H, dd, *J* 7.9 and 1.3, Ar*H*), 7.44 (1H, dd, *J* 7.6 and 1.3, Ar*H*), 7.31 - 7.41 (7H, m, Ph*H*), 7.19 - 7.26 (4H, m, Ph*H*), 6.95 (1H, dd, *J* 7.9 and 7.6, Ar*H*), 6.88 (1H, dd, *J* 7.9 and 7.6, Ar*H*), 5.64 (1H, d, *J* 9.2, OC*H*HC), 5.63 (1H, d, *J* 9.2, OC*H*HC), 4.60 (1H, s, COC*H*(NH_2)CO_2), 4.49 (1H, s, COC*H*(NH_2)CO_2), 4.45 (1H, d, *J* 9.2, OC*H*HC), 4.38 (1H, d, *J* 9.2, OC*H*HC), 3.74 - 3.90 (2H + 1H, m, $CO_2CH_2CH_3$, CO_2C*H*HCH_3), 3.63 (1H, dq, *J* 10.9 and 7.3, CO_2C*H*HCH_3), 1.09 (3H, t, *J* 7.3, OCH_2CH_3), 1.04 (3H, t, *J* 7.3, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 201.7 (s), 200.9 (s), 169.8 (s), 169.3 (s), 158.5 (s), 138.0 (s), 137.8 (s), 133.4 (d), 133.3 (d), 129.3 (d), 129.2 (d), 128.7 (s), 128.6 (s), 128.3 (d), 128.2 (d), 127.0 (d), 126.8 (d), 126.4 (d), 126.1 (d), 122.5 (d), 122.3 (d), 104.2 (s), 103.8 (s), 80.2 (t), 79.9

(t), 69.1 (s), 68.9 (s), 62.0 (t), 61.9 (t), 60.1 (d), 60.0 (d), 13.7 (q); m/z (EI) Found: 403.0415 (M^+, $C_{19}H_{18}NO_4Br$ requires 403.0420), 273 (61), 259 (1), 164 (55), 77(6).

Ethyl-5-(7-bromo-3-phenyl-2,3-dihydrobenzofuran-3-yl)-2-methyloxazole-4-carboxylate 30a. Method a: Triethylamine (0.17 mL, 1.20 mmol), followed by a solution of the amide **29e** (0.13 g, 0.30 mmol) in dichloromethane (3 mL) were added dropwise over 10 min to a stirred solution of triphenylphosphine (0.16 g, 0.60 mmol) and iodine (0.15 g, 0.60 mmol) in dichloromethane (6 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred at room temperature for 12 h, then concentrated *in vacuo*. The residue was purified by chromatography, eluting with ethyl acetate in petrol (1:1), to give the *oxazole* (0.11 g, 86%) as a pale yellow oil; ν_{max} ($CHCl_3$)/cm^{-1} 1722; δ_H (360 MHz, $CDCl_3$) 7.40 (1H, dd, *J* 8.0 and 1.1, Ar*H*), 7.38 (1H, dd, *J* 7.6 and 1.1, Ar*H*), 7.31 - 7.24 (3H, m, Ar*H*), 7.14 - 7.11 (2H, m, Ar*H*), 6.83 (1H, t, *J* 7.7, Ar*H*), 5.29 (1H, d, *J* 9.9, C*H*HOAr), 5.19 (1H, d, *J* 9.9, CH*H*OAr), 4.24 (1H, dq, *J* 10.9 and 7.2, C*H*$_2$CH$_3$), 4.17 (1H, dq, *J* 10.9 and 7.2, C*H*$_2$CH$_3$), 2.50 (3H, s, OC(C*H*$_3$)N), 1.20 (3H, t, *J* 7.2, CH$_2$C*H*$_3$); δ_C (90 MHz, $CDCl_3$) 161.2 (s), 159.9 (s), 158.5 (s), 156.8 (s), 143.0 (s), 132.5 (d), 131.2 (s), 128.7 (d), 128.2 (s), 127.4 (d), 126.2 (d), 125.7 (d), 122.5 (d), 103.4 (s), 83.7 (t), 61.3 (t), 56.5 (s), 14.0 (q); m/z (EI) Found: 428.0493 ($[M + H]^+$, $C_{21}H_{19}NO_4Br$ requires 428.0497).

Method b: A solution of acetyl chloride (0.41 mL, 5.73 mmol) in dichloromethane (5 mL) was added dropwise over 10 min to a stirred solution of the amine **29b** (0.77 g, 1.91 mmol) and triethylamine (0.80 mL, 5.73 mmol) in dichloromethane (25 mL) at 0 °C under a nitrogen atmosphere. The mixture was warmed to room temperature over 2 h, and then stirred at this temperature for 16 h. Dichloromethane (25 mL) was added, the mixture was washed with water (50 mL). The separated organic extract was dried and concentrated *in vacuo*. The residue was purified by chromatography, eluting with ethyl acetate in petrol (1:4), to give the *oxazole* (0.51 g, 63%) as a colourless oil whose spectroscopic data were identical with those recorded under method (a).

5-(7-Bromo-3-phenyl-2,3-dihydrobenzofuran-3-yl)-2-methyloxazole-4-carboxylic acid 30b. Lithium hydroxide (29 mg, 0.70 mmol) was added in a single portion to a stirred solution of the oxazole **30a** (30 mg, 70 μmol) in methanol (1.5 mL) and water (0.5 mL) at room temperature. The mixture was stirred at room temperature for 8 h, then acidified with 10% aqueous citric acid (2 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were dried

and concentrated *in vacuo* to leave the carboxylic acid (28 mg, 98 %) as a colourless solid; m.p. 194 -196 °C (hexane), λ_{max} (EtOH) 291 (1.85 x 10^4), 284 (1.80 x 10^4), 291 nm (1.08 x 10^5); ν_{max} ($CHCl_3$)/cm^{-1} 3494, 3241 (br), 1762, 1702, 1077; δ_H (360 MHz, $CDCl_3$) 7.44 - 7.41 (2H, m, Ar*H*), 7.31 - 7.24 (3H, m, Ar*H*), 7.13 - 7.10 (2H, m, Ar*H*), 6.86 (1H, t, *J* 7.8, Ar*H*), 5.41 (1H, d, *J* 10.0, C*H*HOAr), 5.14 (1H, d, *J* 10.0, CH*H*OAr), 2.53 (3H, s, OC(CH_3)N); δ_C (90 MHz, $CDCl_3$) 162.9 (s), 160.3 (s), 159.3 (s), 157.0 (s), 142.3 (s), 132.7 (d), 130.7 (s), 128.8 (d), 127.6 (d), 126.3 (d), 125.9 (d), 122.5 (d), 103.5 (s), 83.3 (t), 56.5 (s), 13.7 (q); m/z (ESI) Found: 463.0269 ($[MNaMeCN]^+$, $C_{21}H_{17}N_2O_4BrNa$ requires 463.0309).

2-(4-Iodo-1*H*-indol-3-yl)-2-oxoethylammonium bromide 31.

Benzyl-[2-(1H)-indol-3-yl]-2-oxoethylcarbamate (20 mg, 60 μmol)[33] was added, in a single portion, to a stirred solution of thallium trifluoroacetate (44 mg, 80 μmol) in trifluoroacetic acid (0.1 mL) at room temperature under a nitrogen atmosphere. The mixture was heated at 30 °C for 2 h, then cooled to room temperature and concentrated *in vacuo*. Iodine (48 mg, 0.19 mmol), copper iodide (50 mg, 0.26 mmol), and then DMF (0.44 mL), were added to the residue at room temperature under a nitrogen atmosphere. The mixture was heated at 25 °C for 2 h, then cooled to room temperature and diluted with a solution of methanol (2 mL) in dichloromethane (40 mL). The mixture was filtered through celite® and the filtrate was then washed with brine (40 mL) and water (40 mL), dried and concentrated *in vacuo*. The residue was purified by chromatography, eluting with ethyl acetate in petrol (2:1), to give benzyl-[2-(4-iodo-1H-indol-3-yl)-2-oxoethylcarbamate (15 mg, 58%) as a yellow oil which solidified on standing; m.p. 170 - 172 °C; (Found: C, 49.7; H, 3.4; N, 6.1; I, 29.1; $C_{18}H_{15}IN_2O_3$ requires: C, 49.8; H, 3.5; N, 6.5; I, 29.2 %); λ_{max} (MeOH) 257 (1.46 x 10^4), 217 (3.88 x 10^4), 194 nm (3.99 x 10^4); ν_{max} ($CHCl_3$)/cm^{-1} 3454, 1716, 1673, 1048; δ_H (360 MHz, $CDCl_3$) 9.25 (1H, br s, indole N*H*), 7.83 (1H, d, *J* 7.6, Ar*H*), 7.80 (1H, m, Ar*H*), 7.42 - 7.32 (6H, m, Ar*H*), 6.96 (1H, app. t, *J* 7.9, Ar*H*), 5.93 (1H, s, N*H*CO), 5.17 (2H, s, CH_2Ar), 4.52 (2H, d, *J* 4.7, CH_2N); δ_C (90 MHz, $CDCl_3$) 193.0 (s), 160.0 (s), 140.3 (s), 139.1 (s), 136.9 (d), 135.5 (d), 130.7 (s), 130.3 (d), 129.8 (d), 129.7 (d), 126.4 (d), 118.0 (s), 114.0 (d), 86.4 (s), 68.6 (t), 51.2 (t); m/z (ESI) Found: 457.0055 ($[M + Na]^+$, $C_{18}H_{15}N_2O_3INa$ requires 457.0025).

The above iodide (19 mg, 40 μmmol) was added in a single portion to a stirred solution of hydrogen bromide in acetic acid (1.2 ml, 30 wt%) at room temperature under a nitrogen atmosphere. The mixture was stirred at room temperature for 1.5 h, then diluted with diethyl ether (5 mL). The precipitate was filtered and dried *in vacuo* (1 mm Hg) to leave the *salt* (17 mg, 99%) as a pale brown solid; m.p. 210 - 212 °C (MeOH); λ_{max} (H_2O) 305 (6.3 x 10^3), 253 (9.2 x 10^3), 216 nm (2.09 x 10^4); ν_{max} ($CHCl_3$)/cm^{-1} 3407, 3103, 2924, 1654; δ_H (360 MHz, D_2O) 7.94 (1H, s, indole *H*), 7.61 (1H, d, *J* 7.4, Ar*H*), 7.30 (1H, d, *J* 8.1, Ar*H*), 6.80 (1H, app. t, *J* 7.7, Ar*H*), 4.25 (2H, s, CH_2); δ_C (90 MHz, D_2O) 186.5 (s), 137.7 (s), 136.0 (d), 135.4 (d), 127.4 (s), 125.1 (d), 113.2 (s), 112.6 (d), 83.5 (s), 45.6 (t); m/z (ESI) Found: 342.0106 ([MHMeCN − HBr]$^+$, $C_{11}H_{13}N_3OI$ requires 342.0103).

5-(7-Bromo-3-phenyl-2,3-dihydrobenzofuran-3-yl)-2-methyloxazole-4-carboxylic acid [2-(4-Iodo-1*H*-indol-3-yl)-2-oxoethyl]amide 32. A solution of the carboxylic acid **30b** (0.13 g, 0.32 mmol) in oxalyl chloride (4 mL) was stirred at room temperature for 3 h. The solution was concentrated *in vacuo* to leave the crude acid chloride (0.13 g, 100%) as a yellow oil, which was used immediately without characterisation. Triethylamine (0.45 mL, 3.20 mmol) was added dropwise over 1 min to a stirred suspension of the salt **31** (0.46 g, 1.22 mmol) in dichloromethane (6 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred at 0 °C for 15 min, and then a solution of the acid chloride (0.13 g, 0.32 mmol) in dichloromethane (3 mL) was added dropwise over 1 min. The mixture was warmed to room temperature for 16 h, then diluted with dichloromethane (10 mL) and washed with water (10 mL). The separated aqueous phase was extracted with dichloromethane (2 x 10 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. The residue was purified by chromatography, eluting with ethyl acetate in petrol (2:1), to give the *amide* (0.13 g, 60%) as a yellow solid; m.p. 139 - 142 °C; λ_{max} (EtOH) 290 (1.55 x 10^4), 203 nm (6.35 x 10^4); ν_{max} ($CHCl_3$)/cm^{-1} 3454, 3391, 2926, 2855, 1659, 1610; δ_H (360 MHz, $CDCl_3$) 9.59 (1H, br s, indole N*H*), 8.14 (1H, t, *J* 4.9, N*H*CO), 7.78 (1H, d, *J* 7.0, Ar*H*), 7.73 (1H, d, *J* 3.0, indole *H*), 7.44 (1H, dd, *J* 7.6 and 1.1, Ar*H*), 7.41 (1H, dd, *J* 8.0 and 1.1, Ar*H*), 7.28 - 7.14 (6H, m, Ar*H*), 6.89 (1H, app. t, *J* 7.8, Ar*H*), 6.85 (1H, app. t, *J* 7.8, Ar*H*), 5.56 (1H, d, *J* 10.0, C*H*HOAr), 5.22 (1H, d, *J* 10.0, CH*H*OAr), 4.61 (2H, d, *J* 4.9, CH_2N), 2.47 (3H, s, CH_3); δ_C (90 MHz, $CDCl_3$) 187.7 (s),

161.2 (s), 159.2 (s), 157.0 (s), 155.5 (s), 143.3 (s), 137.6 (s), 135.5 (d), 132.5 (d), 132.3 (d), 131.4 (s), 129.9 (s), 128.7 (s), 128.2 (s), 127.4 (d), 126.5 (d), 126.0 (d), 124.9 (d), 122.4 (d), 115.9 (s), 112.1 (d), 103.3 (s), 84.3 (s), 84.1 (t), 56.3 (s), 47.7 (t), 13.8 (q); m/z (ESI) Found: 703.9727 ($[M + Na]^+$, $C_{29}H_{21}N_3O_4BrINa$ requires 703.9658).

3-[5′-(7-Bromo-3-phenyl-2,3-dihydrobenzofuran-3-yl)-2′-methyl-[2,4′]-bisoxazolyl-5-yl]-4-iodo-1*H*-indole 33. Triethylamine (30 μL, 0.23 mmol), followed by a solution of the amide **32** (40 mg, 30 μmmol) in dichloromethane (1 mL) were added dropwise over 10 min to a stirred solution of triphenylphosphine (31 mg, 0.12 mmol) and hexachloroethane (28 mg, 0.12 mmol) in dichloromethane (1 mL) at 0 °C under a nitrogen atmosphere. The mixture was warmed to room temperature and stirred for 3 h, then more triphenylphosphine (31 mg, 0.12 mmol), hexachloroethane (28 mg, 0.12 mmol) and triethylamine (30 μL, 0.23 mmol) were added. The mixture was stirred for a further 2 h, then diluted with dichloromethane (10 mL), and washed with water (10 mL). The separated aqueous phase was extracted with dichloromethane (2 x 10 mL), and the combined organic extracts were then dried and concentrated *in vacuo*. The residue was purified by chromatography, eluting with ethyl acetate in petrol (2:1), to give the *bis-oxazole* (32 mg, 81%) as a yellow oil; λ_{max} (EtOH) 284 (2.51 x 10^4), 202 nm (7.71 x 10^4); ν_{max} ($CHCl_3$)/cm^{-1} 3467, 1640, 1595; δ_H (360 MHz, $CDCl_3$) 9.18 (1H, br s, indole N*H*), 7.58 (1H, d, *J* 7.5, Ar*H*), 7.53 (1H, dd, *J* 7.6 and 1.1, Ar*H*), 7.41 (1H, dd, *J* 6.7 and 1.1, Ar*H*), 7.39 (1H, dd, *J* 6.0 and 1.1, Ar*H*), 7.28 - 7.20 (6H, m, Ar*H*), 7.14 (1H, s, oxazole *H*), 6.90 (1H, app. t, *J* 7.9, Ar*H*), 6.87 (1H, app. t, *J* 7.9, Ar*H*), 5.69 (1H, d, *J* 9.9, C*H*HOAr), 5.12 (1H, d, *J* 9.9, CH*H*OAr), 2.53 (3H, s, CH_3); δ_C (90 MHz, $CDCl_3$) 160.7 (s), 157.1 (s), 154.3 (s), 151.8 (s), 144.1 (s), 142.6 (s), 135.7 (s), 132.7 (d), 132.0 (d), 131.4 (s), 129.2 (d), 128.7 (d), 128.5 (s), 127.9 (d), 127.4 (d), 126.6 (d), 126.4 (d), 126.3 (s), 123.9 (d), 122.5 (d), 111.6 (d), 105.0 (s), 103.4 (s), 84.9 (s), 83.3 (t), 56.4 (s), 13.9 (q); m/z (ESI) Found: 663.9786 ($[M + H]^+$, $C_{29}H_{20}N_3O_3BrI$ requires 663.9734).

3-Phenyl-3-triisopropylsilanyloxy-2,3-dihydro-benzofuran-7-boronic acid 35. Ozone (50 mL/min, 1.5A) was bubbled through a solution of the alkene **5** (6.54 g, 21.7 mmol) in dichloromethane (260 mL) at −78 °C for 2 hours and then oxygen and nitrogen were bubbled

through the solution for 10 minutes. Methanol (50 mL) was added and the solution was then warmed to 0 °C. Sodium borohydride (4.23 g, 108.5 mmol) was cautiously added and the resulting mixture was then stirred at this temperature for 2 hours. Ammonium chloride (100 mL) was added dropwise and the mixture was then concentrated *in vacuo*. The residue was partitioned between water (100 mL) and ether (100 mL) and the separated aqueous phase was then extracted with ether (2 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried and concentrated *in vacuo*. The residue was purified by chromatography, eluting with ether in petrol (1:2 to 1:1), to give 3-phenyl-2,3-dihydrobenzofuran-3-methanol (4.40 g, 61%) as a colourless oil; ν_{max} ($CHCl_3$)/cm^{-1} 3385, 3058, 3025, 1598, 1582; δ_H (360 MHz, $CDCl_3$) 7.28 - 7.42 (6H, m, Ar*H*), 7.14 (1H, dd, *J* 7.6 and 1.1, Ar*H*), 6.85 (1H, t, *J* 7.6, Ar*H*), 4.87 (1H, d, *J* 9.1, C*H*HOAr), 4.70 (1H, d, *J* 9.1, CH*H*OAr), 4.13 (1H, d, *J* 11.3, C*H*HOH), 4.04 (1H, d, *J* 11.3, CH*H*OH), 1.74 (1H, s, O*H*); δ_C (90 MHz, $CDCl_3$) 157.8 (s), 142.0 (s), 132.2 (d), 131.7 (d), 128.8 (d), 127.3 (d), 126.8 (s), 124.4 (d), 122.1 (d), 103.3 (s), 81.4 (t), 67.4 (s), 57.3 (t); m/z (ESI) Found: 304.0085 (M^+, $C_{15}H_{13}O_2Br$ requires 304.0099), 306 (5), 304 (5), 273 (52), 194 (100), 127 (12), 107 (13).

Triisopropylsilyl chloride (4.6 mL, 21.6 mmol) was added to a stirred solution of imidazole (1.96 g, 28.8 mmol) and the benzofuranmethanol (4.40 g, 14.4 mmol) in *N*, *N*-dimethylformamide (14 mL), and the mixture was stirred at room temperature for 17 hours. Ammonium chloride (10 mL) was added and the mixture was then partitioned between ether (100 mL) and water (100 mL). The organic extracts were washed with water (3 x 100 mL), and the combined aqueous extracts were then extracted with ether (2 x 100 mL). The combined organic phases were then washed with brine (100 mL), dried, concentrated *in vacuo*. The residue was purified by chromatography, eluting with ether in petrol (1:40), to give the corresponding silyl ether (5.34 g, 83%) as a colourless oil; ν_{max} ($CHCl_3$)/cm^{-1} 1600, 1584; δ_H (360 MHz, $CDCl_3$) 7.30 - 7.37 (6H, m, Ar*H*), 7.00 (1H, dd, *J* 7.6 and 1.2, Ar*H*), 6.79 (1H, t, *J* 7.6, Ar*H*), 4.95 (1H, d, *J* 9.0, C*H*HOAr), 4.67 (1H, d, *J* 9.0, CH*H*OAr), 4.20 (1H, d, *J* 9.7, C*H*HOSi), 4.15 (1H, d, *J* 9.7, CH*H*OSi), 0.97 (21H, m, [(CH_3)$_2$C*H*]$_3$Si); δ_C (90 MHz, $CDCl_3$) 157.8 (s), 142.9 (s), 132.9 (d), 131.6 (d), 128.4 (d), 127.2 (d), 126.9 (s), 124.6 (d), 121.7 (d), 102.8 (s), 81.6 (t), 68.4 (s), 57.5 (t), 17.6 (s), 12.0 (q); m/z (ESI) Found: 381.2233 ([M- Br]$^+$, $C_{24}H_{33}O_2BrSi$ requires 381.2250), 417 (17), 381 (12), 273 (12), 145 (76), 91 (100).

Butyllithium (3.69 mL of a 1.6 M solution in hexanes, 5.89 mmol) was added dropwise over 0.5 h to a solution of the above bromobenzofuran (1.29 g, 2.80 mmol) in tetrahydrofuran (60 mL) at −78 °C. The mixture was stirred at −78 °C for 1 h, and then trimethyl borate (1.55 mL, 13.83 mmol) was added dropwise over 10 min and the resulting solution was allowed to warm slowly to room temperature over 17 h. The mixture was concentrated *in vacuo*, and the residual boronic acid (~1.2 g) was used directly without purification, in the Suzuki coupling reaction with the 5-bromoindole **36**..

{2-[4-(3-Phenyl-3-triisopropylsilanyloxymethyl-2,3-dihydro-benzofuran-7-yl)-1*H*-indol-3-yl]-ethyl}-carbamic acid *tert*-butyl ester 37a. The crude boronic acid **35** (~1.2g) was dissolved in degassed dimethoxyethane (60 mL), and sufficient degassed water (~ 8 mL) was then added to obtain a clear solution. The solution was stirred for 2 h, and then a solution of the 5-bromoindole **36** (1.34 g, 3.96 mmol)[21] in degassed DME (31 mL) was added dropwise *via* a cannula over 1 h. Tetrakis(triphenylphosphine)palladium (333 mg, 0.28 mmol) was introduced, and then a solution of potassium carbonate (6.65 g, 48.2 mmol) in degassed water (9.3 mL) was added. The mixture was heated under reflux for 17 h, then cooled and partitioned between brine (20 mL) and dichloromethane (100 mL). The separated organic phase was washed with brine (3 x 20 mL) and the combined aqueous extracts were then extracted with dichloromethane (30 mL). The organic extracts were dried, and then concentrated *in vacuo*. The residue was purified by chromatography, eluting with ethyl acetate in petrol (1:3 to 1:1), to give the *bis-aryl* (1.41 g, 80%) as an almost colourless solid as a 3:1 mixture of stereoisomers; δ_H (360 MHz, $CDCl_3$) 8.27 (0.75H, br s, N*H*), 8.14 (0.25H, br s, N*H*), 6.87 - 7.49 (12H, m, Ar*H*), 4.86 (0.25H, d, *J* 9.0, C*H*HOAr), 4.80 (0.75H, d, *J* 9.0, CH*H*OAr), 4.63 (0.75H, d, *J* 9.0, C*H*HOAr), 4.56 (0.25H, d, *J* 9.0, CH*H*OAr), 4.26 (1H, d, *J* 10.0, C*H*HOSi), 4.22 (1H, d, *J* 10.0, CH*H*OSi), 4.09 (0.25H, br s, N*H*), 3.49 (0.75H, br s, N*H*), 2.84 - 3.12 (2.5H, m, CH_2CH_2N), 2.42 - 2.61 (1.5H, m, CH_2CH_2N), 1.63 - 1.71 (3H, m, $[(CH_3)_2CH]_3Si$), 1.48 (2.25H, s, *^{t}Bu*), 1.41 (6.75H, s, *^{t}Bu*), 1.03 (4.5H, d, *J* 6.2, $[(CH_3)_2CH]_3Si$), 0.97 (13.5H, d, *J* 6.2, $[(CH_3)_2CH]_3Si$); δ_C (90 MHz, $CDCl_3$) 158.2, 155.8, 143.7, 136.8, 130.8, 130.5, 130.1, 128.4, 128.2, 127.5, 127.2, 126.8, 126.5, 124.9, 124.5, 123.1, 121.6, 121.4, 120.3, 110.9, 109.6, 81.2, 80.8, 78.8, 68.4, 67.9, 56.6, 40.9, 28.4, 17.9, 11.9; m/z

(ESI) Found: 640.3724 (M^+, $C_{39}H_{52}N_2O_4Si$ requires 640.3696), 640 (70), 541 (61), 397 (60), 350 (72), 336 (100), 322 (17), 91 (26).

(*Z*)-3-{7-[3-(2-*tert*-Butoxycarbonylamino-ethyl)-1*H*-indol-4-yl]-3-phenyl-2,3-dihydro-benzofuran-3-yl}-acrylic acid methyl ester 38. TBAF (867 mg, 2.76 mmol) was added, in one portion, to a stirred solution of the silyl ether **37a** (1.35 g, 2.12 mmol) in tetrahydrofuran (40 mL) at room temperature. The mixture was stirred at room temperature for 17 h and then more TBAF (867 mg, 2.76 mmol) was added, followed by another portion (300 mg, 0.96 mmol) after a further 5 h. The mixture was heated at 60 °C for 5 h, then cooled and aqueous ammonium chloride (10 mL) was added. The separated aqueous phase was extracted with ether (3 x 50 mL) and the combined organic extracts were then washed with brine (100 mL), dried, and concentrated *in vacuo*. The residue was purified by chromatography, eluting with ethyl acetate in petrol (1:2 to 1:1), to give the alcohol **37b** (933 mg, 91%) as an almost colourless solid as a 3:1 mixture of diastereomers; ν_{max} ($CHCl_3$)/cm^{-1} 3415, 3056, 1693, 1508; δ_H (360 MHz, $CDCl_3$) 8.35 (1H, br s, N*H*), 7.22 - 7.42 (10H, m, Ar*H*), 6.93 - 7.10 (2H, m, Ar*H*), 4.83 (0.66H, d, *J* 9.0, C*H*HOAr), 4.74 (0.33H, d, *J* 9.0, CH*H*OAr), 4.65 (0.33H, d, *J* 9.0, C*H*HOAr), 4.56 (0.66H, d, *J* 9.0, CH*H*OAr), 4.09 - 4.24 (2H, m, CH_2OH), 2.45 - 2.98 (4H, m, CH_2CH_2N), 1.42 (10H, s, ^{t}*Bu*, O*H*); δ_C (90 MHz, $CDCl_3$) 158.3, 158.2, 143.3, 142.9, 137.0, 136.7, 130.8, 128.8, 127.2, 127.1, 127.0, 126.9, 125.0, 124.6, 124.5, 123.3, 121.6, 121.3, 120.7, 120.4, 113.1, 112.9, 111.0, 81.0, 80.9, 79.2, 78.9, 67.2, 60.4, 56.5, 53.4, 41.2, 40.9, 28.3; m/z (ESI) Found: 485.2441 (M^+, $C_{30}H_{32}N_2O_4$ requires 485.2440), 485(7), 429 (17), 398 (32), 135 (100), 91 (39), 57 (31).

Pyridine-sulfur trioxide complex (140 mg, 0.88 mmol) was added to a stirred solution of the alcohol **37b** (71 mg, 0.15 mmol) in dimethylsulfoxide/dichloromethane (0.7 mL/3 mL) containing triethylamine (128 μL, 1 mmol) at room temperature. The mixture was stirred at room temperature for 23 h, and then the dichloromethane was removed *in vacuo*. The residue was partitioned between ether (10 mL) and ammonium chloride (10 mL) and the separated organic extract was subsequently washed with ammonium chloride (10 mL) and copper sulfate (2 x 10 mL). The aqueous phase was extracted with ether (4 x 10 mL) and the combined organic extracts were then washed with brine (20 mL), dried and concentrated *in vacuo*. The residue was purified by chromatography, eluting with ethyl acetate in petrol (2:3 containing 1% triethylamine), to

give the corresponding aldehyde (58 mg, 82%) as a colourless oil as a 3:1 mixture of diastereomers; ν_{max} ($CHCl_3$)/cm^{-1} 1721, 1697; δ_H (360 MHz, $CDCl_3$) 9.80 (0.33H, s, C*H*O), 9.77 (0.66H, s, C*H*O), 8.35 (1H, s, N*H*), 7.34 - 7.47 (6H, m, Ar*H*), 7.21 - 7.25 (3H, m, Ar*H*), 7.14 (1H, t, *J* 7.4, Ar*H*), 7.01 (2H, t, *J* 7.4, Ar*H*), 5.43 (1H, d, *J* 9.0, C*H*HOAr), 4.46 (0.33H, br, N*H*), 4.35 (0.66H, d, *J* 9.5, N*H*), 4.25 (1H, d, *J* 9.0, CH*H*OAr), 3.02 (2H, br s, CH_2CH_2N), 2.48 - 2.56 (1.33H, m, CH_2CH_2N), 2.35 - 2.41 (0.66H, m, CH_2CH_2N), 1.42 (9H, s, ^tBu); δ_C (90 MHz, $CDCl_3$) 193.7, 193.1, 158.6, 156.0, 138.4, 136.8, 132.2, 129.6, 129.3, 128.3, 127.7, 127.5, 125.7, 125.6, 124.9, 123.1, 122.9, 121.9, 121.7, 121.4, 121.1, 113.6, 113.2, 78.9, 66.8, 66.6, 60.4, 53.4, 40.8, 28.4; m/z (FAB) Found: 482.2245 (M^+, $C_{30}H_{30}N_2O_4$ requires 482.2206), 482 (74), 454 (8), 427 (43), 409 (11), 398 (47), 336 (45), 324 (31), 307 (26), 154 (100), 136 (67), 107 (23), 57 (36).

Potassium *bis*(trimethylsilyl)amide (5.9 mL of a 0.5 M solution in toluene, 2.95 mmol) was added dropwise over 15 min to a stirred solution of *bis*-(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate (938 mg, 2.95 mmol) and 18-crown-6 (1.32 g, 5.04 mmol) in tetrahydrofuran (28 mL) at −78 °C under a nitrogen atmosphere. The mixture was stirred at −78 °C for 0.5 h, and then a solution of the above aldehyde (406 mg, 0.84 mmol) in tetrahydrofuran (14 mL) was added *via* a cannula. The solution was stirred at −78 °C for a further hour and then ammonium chloride (8 mL) was added. The mixture was warmed to room temperature and then partitioned between ether (30 mL) and ammonium chloride (30 mL). The organic phase was washed with ammonium chloride (2 x 30 mL) and the separated aqueous phase was then extracted with ether (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), then dried and concentrated *in vacuo*. The residue was purified by chromatography, eluting with acetone in benzene (1:5), to give a 3:1 mixture of isomers of the *Z*-α,β-unsaturated ester (433 mg, 96%) as a colourless oil; ν_{max} ($CHCl_3$)/cm^{-1} 3416, 2976, 2949, 1712, 1697, 1642, 1508, 1472, 1438, 1366, 1250, 1203, 1174; δ_H (360 MHz, $CDCl_3$) 8.38 (1H, br s, N*H*), 7.23 - 7.38 (9H, m, Ar*H*), 6.97 - 7.05 (3H, m, Ar*H*), 6.81 (1H, d, *J* 12.2, =C*H*), 6.13 (0.66H, d, *J* 12.2, =C*H*), 6.09 (0.33H, d, *J* 12.2, =C*H*), 5.17 (0.66H, d, *J* 9.1, C*H*HOAr), 5.03 (0.33H, d, *J* 9.1, CH*H*OAr), 4.79 (0.33H, d, *J* 9.1, C*H*HOAr), 4.75 (0.66H, d, *J* 9.1, CH*H*OAr), 4.48 (0.33H, br s, N*H*), 4.37 (0.66H, br s, N*H*), 3.47 (0.9H, s, OCH_3), 3.42 (2.1H, s, OCH_3), 2.95 (2H, br, CH_2CH_2N), 2.47 - 2.63 (2H, m, CH_2CH_2N), 1.42 (9H, s, ^tBu); δ_C (90 MHz, $CDCl_3$) 165.7, 156.9, 155.8, 149.8, 149.0, 144.9, 144.6, 136.9, 133.3, 133.0, 130.7, 129.8, 128.6, 126.9,

126.7, 125.9, 124.9, 123.8, 121.8, 121.7, 121.6, 121.0, 84.4, 84.1, 78.8, 56.6, 53.4, 53.0, 51.3, 40.8, 28.4, 26.5, 26.1; m/z (FAB) Found: 538.2485 (M^+, $C_{33}H_{34}N_2O_5$ requires 538.2468), 538 (61), 439 (27), 307 (16), 154 (100), 136 (82), 107 (36), 95 (42), 81 (48), 69 (92), 57 (94).

Macrolactam 39. Lithium hydroxide (23 mg, 0.56 mmol) was added to a stirred solution of the ester **38** (60 mg, 0.11 mmol) in dimethoxyethane/water (0.9 mL/0.3 mL) and the mixture was stirred at room temperature for 7 h. A further portion of lithium hydroxide was added (9 mg, 0.22 mmol), and after 24 h the DME was removed *in vacuo*. Water (5 mL) and 0.1 M HCl (3 mL) were added to the residue and the mixture was then extracted with ether (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried and concentrated *in vacuo* to leave the crude carboxylic acid which was used directly.

Trifluoroacetic acid (2.4 mL) was added to a stirred solution of the crude carboxylic acid in dichloromethane (2.4 mL). The mixture was stirred at room temperature for 30 min and then concentrated *in vacuo*. The residue was azeotroped with ether (3 x 8 mL) and then benzene (3 x 10 mL) to leave the amino acid as a colourless solid which was used directly in the next reaction.

Diphenylphosphoryl azide (122 μL, 0.55 mmol) was added to a stirred solution of the crude amino acid and diisopropylethylamine (70 μL, 0.39 mmol) in dichloromethane (24 mL). After 18 h more diphenylphosphoryl azide (122 μL, 0.55 mmol) was added, and after a further 72 h a final portion (122 μL, 0.55 mmol) was added. The mixture was stirred at room temperature for 16 h, then ammonium chloride (15 mL) was added and the mixture was extracted with dichloromethane (3 x 40 mL). The combined organic extracts were washed with brine (30 mL), dried concentrated *in vacuo*. The residue was purified by chromatography, eluting with ethyl acetate in petrol (1:10 to 1:1), to give the *macrolactam* (22 mg, 49%) as a colourless oil; ν_{max} ($CHCl_3$)/cm^{-1} 3404, 3056, 2924, 1634, 1513; δ_H (360 MHz, $CDCl_3$) 8.29 (1H, s, N*H*), 7.22 - 7.42 (9H, m, Ar*H*), 7.08 (2H, dd, *J* 7.5 and 2.6, Ar*H*), 7.00 (1H, d, *J* 2.3, Ar*H*), 6.48 (1H, d, *J* 12.7, =C*H*), 6.11 (1H, d, *J* 12.7, =C*H*), 4.93 (1H, d, *J* 4.9, N*H*), 4.84 (1H, d, *J* 9.5, C*H*HOAr), 4.70 (1H, d, *J* 9.5, CH*H*OAr), 3.72 (1H, m, CH_2CH_2N), 2.89 (1H, ddd, *J* 14.7, 8.4 and 5.8, CH_2CH_2N), 2.78 (1H, m, CH_2CH_2N), 2.20 (1H, dt, *J* 14.7 and 5.1, CH_2CH_2N); m/z (ESI) Found: 406.1658 (M^+, $C_{27}H_{22}N_2O_2$ requires 406.1681), 407 (4), 154 (11), 123 (11), 109 (21), 95 (38), 81 (44), 69 (76), 55 (100).

1-(Benzyloxy)-2-prop-1-yn-1-ylbenzene (41). Bis(triphenylphosphine)palladium(II)chloride (2.30 g, 3.15 mmol) and copper (I) iodide (1.20 g, 6.32 mmol) were added to a stirred solution of the benzylether of 2-iodophenol (20.0 g, 63.5 mmol) in diethylamine (300 mL) and the mixture was cooled to 0 ^{o}C. An excess of propyne was bubbled steadily through the slurry for 30 min and the mixture was then allowed to slowly warm to room temperature over 30-45 min. Propyne was introduced for a further 2 hr at room temperature and the mixture was then left to stir overnight under an atmosphere of propyne. The mixture was concentrated *in vacuo* to leave a black viscous oil which was purified by chromatography, eluting with diethyl ether : pentane (3 : 97), to give the *alkyne* (12.8 g, 91%) as a yellow oil; υ_{max}/cm^{-1} ($CDCl_3$) 2240, 1599, 1574 and 1502; δ_H (360 MHz, $CDCl_3$, 298 K) 7.56-7.54 (2H, m, Ar*H*), 7.50 (1H, dd, *J* 7.6 and 1.7, Ar*H*), 7.47-7.42 (2H, m, Ar*H*), 7.40-7.35 (1H, m, Ar*H*), 7.27-7.23 (1H, m, Ar*H*), 6.98-6.92 (2H, m, Ar*H*), 5.23 (2H, s, ArCH_2O), 2.18 (3H, s, ≡CCH_3); δ_C (90 MHz, $CDCl_3$, 298 K) 159.1 (s), 137.1 (s), 133.5 (d), 128.7 (d), 128.4 (d), 127.6 (d), 126.9 (d), 120.8 (d), 114.0 (s), 112.9 (d), 90.1 (s), 76.0 (s), 70.4 (t), 4.6 (q); *m/z* (FAB) Found: 222.1045 ([M]$^+$, $C_{16}H_{14}O$ requires 222.1029), 222 ([M]$^+$, 42%), 199 (37), 176 (15), 154 (35), 136 (33), 91 (100) and 73 (41).

{(1*E*)-1-[2-(Benzyloxy)phenyl]prop-1-en-1-yl}(tributyl)stannane (42). Bis(triphenylphosphine)palladium(II)chloride (0.33 g, 0.45 mmol) was added to a stirred solution of the alkyne **41** (1.00 g, 4.50 mmol) in tetrahydrofuran (20 mL) at 0 ^{o}C. An excess of tributyltin hydride (1.50 g, 1.4 mL, 5.15 mmol) was added dropwise over 3 hr and the mixture was then concentrated *in vacuo*. The residue was purified by chromatography on basic alumina, eluting with diethyl ether : pentane (5 : 95), to give the *stannane* (1.69 g, 73%) as a colourless oil; υ_{max}/cm^{-1} (film) 3066, 2955, 2926, 1591, 1574, 867, 748, 696 and 667; δ_H (360 MHz, $CDCl_3$, 298 K) 7.41-7.27 (5H, m, Ar*H*), 7.09-7.07 (1H, m, Ar*H*), 6.90 (2H, br m, Ar*H*), 6.87 (1H, app d, *J* 8.2, Ar*H*), 5.91 (1H, q, *J* 6.5, =C*H*), 5.04 (2H, s, ArCH_2O), 1.66 (3H, d, *J* 6.5, =HCH_3), 1.41-1.35 (6H, m, SnCH_2CH_2), 1.22 (6H, sx, *J* 7.3, $CH_2CH_2CH_3$), 0.83 (9H, t, *J* 7.3, CH_2CH_3), 0.85-0.75 (6H, m, SnCH_2CH_2); δ_C (90 MHz, $CDCl_3$, 298 K) 154.7 (s), 142.7 (s), 137.7 (s), 136.0 (d), 134.1 (s), 128.7 (d), 128.4 (d), 127.6 (d), 127.2 (d), 126.2 (d), 120.7 (d), 112.1 (d), 70.1 (t), 29.0 (t), 27.4 (t), 16.5 (q), 13.8 (q), 10.3 (t); *m/z* (EI) Found: 457.1537 ([M –Bu]$^+$, $C_{24}H_{33}O^{120}Sn$

requires 457.1553), 515 ([M + H]$^+$, 2%), 457 (100), 366 (30), 343 (17), 309 (15), 291 (10), 251 (12), 179 (25) and 91 (50).

1-(Benzyloxy)-2-[(1*E*)-1-iodoprop-1-en-1-yl]benzene (53). Iodine (1.48 g, 5.80 mmol) was added portionwise over 0.5 hr to a stirred solution of the vinylstannane **42** (2.38 g, 4.64 mmol) in tetrahydrofuran (25 mL) at 0 ^{o}C and the mixture was then allowed to warm to room temperature and stirred for 1 hr. The mixture was concentrated *in vacuo* and the residue was diluted with diethyl ether (100 mL) and stirred vigorously overnight with sat. aqueous potassium fluoride (150 mL). The ether extracts were washed successively with sat. aqueous sodium metabisulfite (100 mL), sat. aqueous sodium bicarbonate solution (100 mL) and brine (100 mL), then dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with diethyl ether : pentane (5 : 95) to give the *vinyl iodide* (1.4 g, 81%) as a pale yellow oil; (Found: C, 55.2; H, 4.2; $C_{16}H_{15}OI$ requires: C, 54.9; H, 4.3 %); υ_{max}/cm^{-1} (film) 3029, 1638, 1593, 1579, 859, 750 and 696; δ_H (360 MHz, $CDCl_3$, 298 K) 7.53-7.50 (2H, m, Ar*H*), 7.43-7.38 (2H, m, Ar*H*), 7.35-7.31 (1H, m, Ar*H*), 7.27-7.22 (1H, m, Ar*H*), 7.20 (1H, app dd, *J* 7.6 and 1.7, Ar*H*), 6.97-6.91 (2H, m, Ar*H*), 6.59 (1H, q, *J* 7.0, =C*H*), 5.18 (2H, s, ArCH_2O), 1.53 (3H, d, *J* 7.0, =CHCH_3); δ_C (90 MHz, $CDCl_3$, 298 K) 154.9 (s), 139.0 (d), 137.0 (s), 130.6 (s), 130.1 (d), 129.4 (d), 128.4 (d), 127.6 (d), 126.9 (d), 120.7 (d), 112.9 (d), 90.0 (s), 70.0 (t), 17.8 (q); *m/z* (FAB$^+$Ve): 350.0164 ([M]$^+$, $C_{16}H_{15}OI$ requires 350.0169), 350 ([M]$^+$, 2%), 259 (7), 223 (30), 207 (10), 145 (8), 133 (13), 105 (35) and 91 (100).

[(*E*)-(1*S*,2*R*)-2-Benzyloxy-3-(2-benzyloxy-phenyl)-1-hydroxymethyl-pent-3-enyl]-carbamic acid *tert*-butyl ester (55). Sodium hydride (60% dispersion in oil, 27.5 mg, 0.688 mmol) was added portionwise over 10 min to a cold solution of the *anti*-allylic alcohol **54b** (155 mg, 0.342 mmol) in tetrahydrofuran (4 mL) at 0 ^{o}C, and the mixture was then stirred at 0 ^{o}C for 15 min. Benzyl bromide (0.25ml, 175 mg, 1.02 mmol) was added in one portion and the mixture was heated to 65 ^{o}C for 6 hr and then concentrated *in vacuo*. The residue was quenched with sat. aqueous ammonium chloride (5 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic extracts were washed with sat. aqueous sodium bicarbonate solution (5 mL) and brine (5 mL), then and concentrated *in vacuo*. The residue was purified by chromatography, eluting with

ethyl acetate in petrol (5 : 95 to 20 : 80), to give the corresponding *benzyl ether* (170 mg, 92%) as a colourless viscous oil; $[\alpha]_D^{18}$ –8.9 (*c* 1.67 in $CDCl_3$); υ_{max}/cm^{-1} ($CDCl_3$ soln.) 2975, 2935, 1689, 1238 and 1059; δ_H (360MHz, C_6D_6, 343K) 7.50 (2H, d, *J* 7.6, Ar*H*), 7.40-7.38 (2H, m, Ar*H*), 7.35-7.15 (7H, m, Ar*H*), 7.10-7.03 (1H, m, Ar*H*), 6.96 (1H, dt, *J* 7.4 and 1.0, Ar*H*), 6.86 (1H, d, *J* 8.2, Ar*H*), 6.18 (1H, q, *J* 6.8, [rotamer 1 + rotamer 2] =C*H*CH_3), 5.45-4.87 (1H, br s, C*H*O), 4.88-4.81 (3H, m, ArC*H*HOAr and ArCH_2O), 4.62 (1H, d, *J* 12.1, ArCH*H*OAr), 4.42 (1H, dd, *J* 8.7 and 4.5, C*H*HO), 4.18 (1H, app br s, C*H*N), 3.89 (1H, dd, *J* 8.7 and 7.6, CH*H*O), 1.85 (3H, br s, C(CH_3)(CH_3)), 1.68 (3H, br s, C(CH_3) (CH_3)), 1.59 (3H, d, *J* 6.8, [rotamer 1 + rotamer 2] =CHCH_3), 1.43 (9H, br s, C(CH_3)$_3$); δ_C (90MHz, C_6D_6, 343K) 156.3 (s), 151.7 (s), 139.3 (s), 137.1 (s), 136.65 (s), 130.9 (d), 128.2-126.85 ((7 × d) and (s)), 123.1 (d), 120.8 (d), 112.4 (d), 94.5 (s), 80.3 (d), 78.55 (s), 71.65 (t), 70.3 (t), 62.9 (t), 59.2 (d), 28.0 (q), 25.7 (q), 24.9 (q), 13.7 (q); *m/z* (ESI) Found: 566.2881 ($[M + Na]^+$, $C_{34}H_{41}NO_5Na$ requires 566.2882), 566 ($[M + Na]^+$, 100%), 322 (50).

Boron trifluoride-acetic acid complex (0.27 mL, 1.90 mmol) was added in one portion to a solution of the above oxazolidine (170 mg, 0.319 mmol) in methanol (4 mL) and the mixture was stirred at room temperature for 3 hr, then quenched with sat. aqueous sodium bicarbonate solution (5 mL) and concentrated *in vacuo*. The residue was diluted with water (5 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), then dried and concentrated *in vacuo*. The residue was purified by chromatography, eluting with ethyl acetate : petrol (25 : 75), to give the *alcohol* (156 mg, 98%) as a colourless viscous oil; $[\alpha]_D^{17}$ +2.3 (*c* 1.0 in $CDCl_3$); υ_{max}/cm^{-1} ($CDCl_3$ soln.) 3522, 3441, 1704 and 1500; δ_H (360MHz, C_6D_6, 343K) 7.37 (2H, m, Ar*H*), 7.32-7.25 (5H, br m, Ar*H*), 7.24 (1H, app br s, Ar*H*), 7.21-7.14 (4H, m, Ar*H*), 6.95 (1H, dt, *J* 7.4 and 1.0, Ar*H*), 6.86-6.84 (1H, m, Ar*H*), 6.07 (1H, q, *J* 6.8, [rotamer 1 + rotamer 2] =C*H*), 5.32 (1H, br d, *J* 6.8, N*H*), 4.86 (2H, s, ArCH_2OAr), 4.72 (1H, d, *J* 11.9, ArC*H*HOCH), 4.67 (1H, br s, C*H*O), 4.36 (1H, d, *J* 11.9, ArCH*H*OCH), 4.12 (1H, dd, *J* 11.5 and 4.2, C*H*HOH), 3.94 (1H, m, C*H*N), 3.82 (1H, br d, *J* 11.5, CH*H*OH), 2.49 (1H, br s, OH), 1.61 (3H, d, *J* 6.8, [rotamer 1 + rotamer 2] =CHCH_3), 1.45 (9H, s, C(CH_3)$_3$); δ_C (90MHz, C_6D_6, 343K) 156.3 (s), 155.4 (s), 138.7 (s), 137.15 (s), 135.8 (s), 131.0 (d), 128.4 (d), 128.2 (d), 128.1 (d), 127.8 (d), 127.6 (d), 127.3 (s), 127.2 (d), 126.8 (d),

124.5 (d), 120.8 (d), 112.45 (d), 84.7 (d), 78.3 (s), 71.85 (t), 70.35 (t), 61.7 (t), 54.1 (d), 28.0 (q), 13.9 (q); *m/z* (ESI) Found: 526.2540 ($[M + Na]^+$, $C_{31}H_{37}NO_5Na$ requires 526.2569), 526 ($[M + Na]^+$, 100%), 404 (18), 296 (70).

(*E*)-(2*R*,3*R*)-3-Benzyloxy-4-(2-benzyloxy-phenyl)-2-*tert*-butoxycarbonylamino-hex-4-enoic acid (56). Sodium bicarbonate (435 mg, 3.10 mmol) and Dess-Martin periodinane (447 mg, 1.03 mmol) were added to a stirred solution of the alcohol **55** (130 mg, 0.258 mmol) in dichloromethane (3 mL) and the mixture was then stirred at room temperature for 2 hr. The solution was washed with water (3 × 4 mL), and the seperated aqueous extracts were then extracted with dichloromethane (3 × 4 mL). The combined organic extracts were washed with brine (10 mL), dried and concentrated *in vacuo*. The residue was purified by chromatography, eluting with ethyl acetate : petrol (30 : 70), to give the corresponding *aldehyde* (70 mg, 54%) as a colourless viscous oil; $[\alpha]_D^{18}$ –49.5 (*c* 0.767 in $CDCl_3$); υ_{max}/cm^{-1} ($CDCl_3$) 3435, 1707 and 1499; δ_H (360MHz, $CDCl_3$, 333K) 9.56 (1H, s, C*H*O), 7.40-7.25 (9H, m, Ar*H*), 7.24-7.21 (2H, m, Ar*H*), 7.11 (1H, dd, *J* 7.4 and 1.7, Ar*H*), 7.03-6.99 (2H, m, Ar*H*), 6.04 (1H, q, *J* 6.9, [rotamer 1 + rotamer 2] =C*H*), 5.15 (1H, br s, N*H*), 5.09 (2H, s, ArCH_2OAr), 4.69 (1H, d, *J* 12.1, ArC*H*HOCH), 4.52 (1H, m, C*H*N), 4.32 (1H, d, *J* 12.1, ArCH*H*OCH), 4.26-4.21 (1H, m, C*H*OBn), 1.58 (3H, d, *J* 6.9, [rotamer 1 + rotamer 2] =CHCH_3), 1.37 (9H, s, C(CH_3)$_3$); δ_C (90MHz, $CDCl_3$, 333K) 198.85 (d), 156.55 (s), 155.35 (s), 138.4 (s), 137.1 (s), 134.1 (s), 131.45 (d), 129.3 (d), 128.75 (d), 128.45 (d), 128.25 (d), 127.85 (d), 127.7 (d), 127.6 (d), 126.9 (s), 126.3 (d), 121.45 (d), 112.7 (d), 82.9 (d), 79.8 (s), 71.7 (t), 70.9 (t), 61.7 (d), 28.4 (q), 14.4 (q); *m/z* (ESI) Found: 524.2421 (M^+ + Na, $C_{31}H_{35}NO_5Na$ requires 524.2413), 524 ($[M + Na]^+$, 100%).

An aliquot (3.5 mL) of a solution of $NaClO_2$ (119 mg, 1.32 mmol) and KH_2PO_4 (131 mg, 0.961 mmol) in water (4.2 mL) was added in one portion to a rapidly stirred solution of the above aldehyde (70 mg, 0.14 mmol) in *t*-BuOH (6.5 mL) and 2-methyl-2-butene (3.0 mL) at room temperature. The mixture was stirred at room temperature for 4 h and then concentrated *in vacuo*. Water (5 mL) was added and the separated aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried, and concentrated *in vacuo* to leave the *carboxylic acid* (52 mg, 72%) as a colourless

viscous oil; $[\alpha]_D^{20}$ –16.6 (*c* 0.43 in $CDCl_3$); υ_{max}/cm^{-1} ($CDCl_3$) 3500-2500, 3435, 1760, 1713 and 1500; δ_H (360MHz, $CDCl_3$, 332K) 7.42-7.20 (11H, m, Ar*H*), 7.15 (1H, d, *J* 7.5, Ar*H*), 7.00 (2H, d, *J* 7.9, Ar*H*), 6.07 (1H, q, *J* 6.8, =C*H*CH_3), 5.21 (1H, br d, *J* 7.5, N*H*), 5.10 (2H, s, ArCH_2OAr), 4.70 (1H, d, *J* 12.0, ArC*H*HOCH), 4.50 (1H, app d, *J* 3.8, C*H*N), 4.38 (1H, d, *J* 12.0, ArCH*H*OCH), 4.29 (1H, dd, *J* 8.0 and 4.6 C*H*OBn), 1.57 (3H, d, *J* 6.8, =CHCH_3), 1.37 (9H, s, C(CH_3)$_3$); δ_C (90MHz, $CDCl_3$, 333K) 171.5 (s), 156.2 (s), 155.4 (s), 138.2 (s), 136.8 (s), 133.4 (s), 131.7 (d), 129.25 (d), 128.8 (d), 128.5 (d), 128.3 (d), 127.9 (d), 127.65 (d), 127.45 (d), 126.55 (s), 121.5 (d), 112.6 (d), 82.1 (d), 80.15 (s), 71.6 (t), 70.95 (t), 57.0 (d), 28.4 (q), 14.4 (q); *m/z* (ESI) Found: 540.2387 ($[M + Na]^+$, $C_{31}H_{35}NO_6Na$ requires 540.2362), 540 ($[M + Na]^+$, 100%), 321 (80).

(*E*)-(2*R*,3*R*)-3-Benzyloxy-4-(2-benzyloxy-phenyl)-2-*tert*-butoxycarbonylamino-hex-4-enoic acid 2-bromo-6-iodo-phenyl ester (57). A solution of the carboxylic acid **56** (36 mg, 0.069 mmol) in dichloromethane (0.5 mL) together with EDC (21 mg, 0.10 mmol) and DMAP (20 mg, 0.15 mmol) were added sequentially to a stirred solution of 2-iodo-6-bromophenol (24 mg, 0.077 mmol) in dichloromethane (0.5 mL) at room temperature. The mixture was stirred at room temperature for 24 hours then diluted with dichloromethane (5 mL) and washed successively with water (5 × 5 mL), sat. aqueous sodium bicarbonate solution (5 mL) and brine (5 mL). Evaporation of the dried extract *in vacuo* left a colourless viscous oil which was purified by chromatography, eluting with ethyl acetate : petrol (5 : 95 to 20 : 80), to give the *ester* (30 mg, 55%) as a colourless viscous oil; $[\alpha]_D^{20}$ +35.3 (*c* 0.63 in $CDCl_3$); υ_{max}/cm^{-1} ($CDCl_3$) 3692, 3440, 1770 and 1713; δ_H (360MHz, $CDCl_3$, 334K) 7.74 (1H, dd, *J* 7.9 and 1.5, Ar*H*), 7.54 (1H, dd, *J* 8.0 and 1.4, Ar*H*), 7.42 (2H, m, Ar*H*), 7.35-7.20 (9H, br m, Ar*H*), 7.01 (2H, m, Ar*H*), 6.79 (1H, app t, *J* 7.9, Ar*H*), 6.23 (1H, q, *J* 6.8, [rotamer 1 + rotamer 2] =C*H*CH_3), 5.28 (1H, br s, N*H*), 5.10 (2H, s, ArCH_2OAr), 4.76 (1H, br s, C*H*NH), 4.74 (1H, d, *J* 11.9, CHOC*H*HAr), 4.69-6.64 (1H, m, C*H*O), 4.32 (1H, d, *J* 11.9, CHOCH*H*Ar), 1.60 (3H, d, *J* 6.8, [rotamer 1 + rotamer 2] =CHCH_3), 1.40 (9H, s, C(CH_3)$_3$); δ_C (90MHz, $CDCl_3$, 334K) 166.6 (s), 156.7 (s), 154.7 (s), 149.6 (s), 138.9 (d), 137.3 (s), 133.9 (s), 133.7 (d), 132.4 (d), 128.9 (d), 128.7 (d), 128.25 (d),

128.1 (d), 128.0 (d), 127.9 (d), 127.7 (d), 127.35 (d), 127.3 (s), 121.3 (d), 116.8 (s), 112.7 (d), 91.6 (s), 82.7 (d), 79.8 (s), 71.6 (t), 70.8 (t), 57.5 (d), 28.6 (q), 14.5 (q).

(*S*)-4-[(*E*)-(*R*)-2-(2-Benzyloxy-phenyl)-1-(2-iodo-benzyloxy)-but-2-enyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (59b). Sodium hydride (60% dispersion in oil, 53 mg, 1.3 mmol) was added portionwise over 10 min to a stirred solution of the *anti*-allylic alcohol **54b** (500 mg, 1.10 mmol) in tetrahydrofuran (5 mL) at 0 ^{o}C, and the mixture was stirred at 0 °C for 15 min. 2-Iodobenzyl bromide (448 mg, 1.43 mmol) was added and the mixture was heated to 55 ^{o}C for 20 hr and then concentrated *in vacuo*. The residue was quenched with sat. aqueous ammonium chloride (5 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic extracts were washed with sat. aqueous sodium bicarbonate solution (5 mL) and brine (5 mL), then dried and concentrated *in vacuo*. The residue was purified by chromatography, eluting with ethyl acetate : petrol (5 : 95 to 20 : 80), to give the corresponding *benzyl ether* (582 mg, 79%) as an oil; $[\alpha]_D^{24}$ +5.0 (*c* 0.93 in CH_2Cl_2); υ_{max}/cm^{-1} ($CDCl_3$) 2935 and 1694; δ_H (360 MHz, DMSO, 353 K) 7.83 (1H, app d, *J* 7.3, Ar*H*), 7.56 (1H, app d, *J* 7.5, Ar*H*), 7.45-7.25 (7H, m, Ar*H*), 7.15 (1H, app d, *J* 8.0, Ar*H*), 7.10-6.95 (3H, m, Ar*H*), 5.98 (1H, d, *J* 6.7, =C*H*CH_3), 5.20-5.10 (1H, m, ArCH_2O), 4.78 (1H, br s, C*H*O), 4.68 (1H, d, *J* 13.2, ArC*H*HO), 4.42 (1H, d, *J* 13.2, ArC*H*HO), 4.01-3.99 (1H, m, CH*H*O), 3.85 (1H, br s, CH*H*O), 3.70 (1H, br s, C*H*N), 1.49 (3H, d, *J* 6.7, =CHCH_3), 1.42 (3H, s, C(CH_3)(CH_3)), 1.37 (3H, s, C(CH_3)(CH_3)), 1.29 (9H, br s, C(CH_3)$_3$); δ_C (90 MHz, DMSO, 353 K) 156.2 (s), 151.7 (s), 141.2 (s), 139.1 (d), 137.6 (s), 131.0 (d), 129.6 (d), 129.1 (d), 129.0 (d), 128.7 (d), 128.5 (d), 128.1 (d), 127.9 (d), 127.7 (s), 123.4 (d), 121.1 (d), 113.3 (d), 97.6 (s), 94.3 (s), 81.1 (d), 79.4 (s), 75.7 (t), 70.4 (t), 62.6 (t), 59.0 (d), 28.5 (q), 26.0 (q), 24.8 (q), 14.3 (q); *m/z* (ESI) Found: 692.1794 (M^+ + Na, $C_{34}H_{40}NO_5INa$ requires 692.1849), 692 ([M + Na]$^+$, 100%), 576 (22); (1*R*,7a*S*)-1-{(1*E*)-1-[2-(Benzyloxy)phenyl]prop-1-en-1-yl}-5,5-dimethyldihydro-1*H*-[1,3]oxazolo [3,4-*c*][1,3]oxazol-3-one (50 mg, 12%) was also obtained as an oil; υ_{max}/cm^{-1} ($CDCl_3$) 2937, 1754 and 1692; δ_H (360 MHz, $CDCl_3$, 318 K) 7.40-7.28 (6H, m, Ar*H*), 7.07 (1H, dd, *J* 7.45 and 1.8, Ar*H*), 7.02 (1H, app d, *J* 8.4, Ar*H*), 6.99 (1H, dt, *J* 7.4 and 1.0, Ar*H*) 6.09 (1H, q, *J* 6.9, [rotamer 1 + rotamer 2] =C*H*CH_3), 5.52 (1H, dt, *J* 8.1 and 1.5, C*H*O), 5.08 (2H, s, ArCH_2O), 4.10 (1H, ddd, *J* 9.0, 8.2 and 6.4 C*H*N), 3.63 (1H, dd, *J* 9.0 and 8.6, C*H*HO), 3.54 (1H, dd, *J* 8.6 and 6.4, CH*H*O), 1.68 (3H, s, C(CH_3)(CH_3)), 1.61 (3H,

d, *J* 6.9, [rotamer 1 + rotamer 2] =CHCH_3), 1.36 (3H, s, C(CH_3)(CH_3)); δ_C (90 MHz, $CDCl_3$, 318 K) 157.0 (s), 156.3 (s), 136.7 (s), 132.0 (s), 131.5 (d) 129.6 (d), 128.8 (d), 128.3 (d), 127.4 (d), 125.8 (d), 125.5 (s), 121.3 (d) 113.1 (d), 94.8 (s), 75.6 (d), 70.7 (t), 65.1 (t), 61.7 (d), 28.4 (q), 23.5 (q), 14.5 (q); *m/z* (ESI) Found: 402.1719 ($[M + Na]^+$, $C_{23}H_{25}NO_4Na$ requires 402.1681), 402 ($[M + Na]^+$, 100%).

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