Supporting Information 1

Racemization in Suzuki Couplings: A Quantitative Study Using 4-Hydroxyphenylglycine and Tyrosine Derivatives as Probe Molecules

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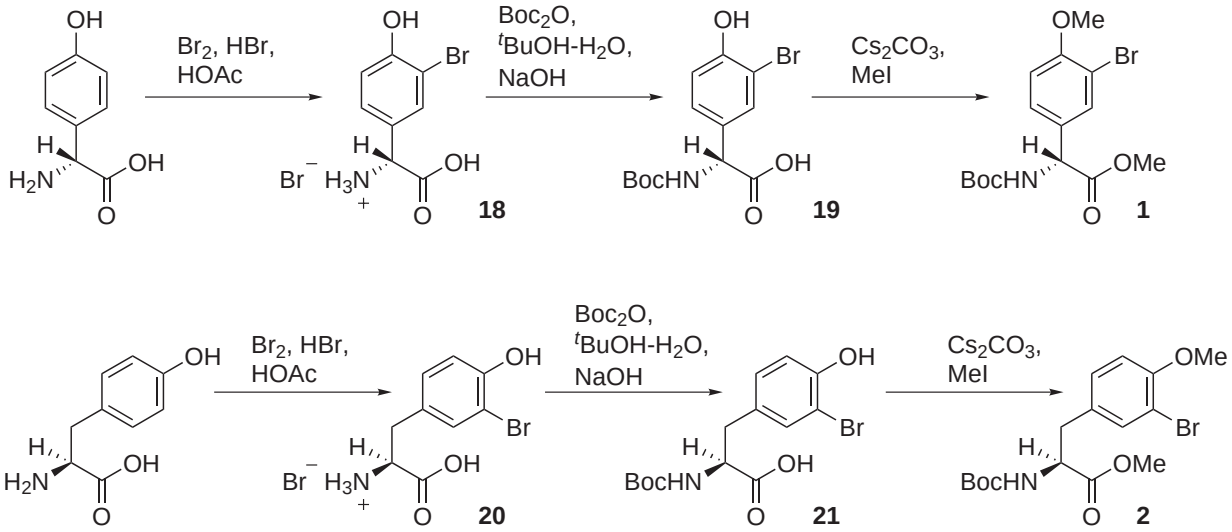
Table of Contents

Reaction Schemes for the Synthesis of Probe Molecules 1 and 2



Scheme 2. Synthesis of probe molecules 1 and 2

General Experimental Methods

All chemicals and reagents used in this study were purchased commercially and used as received. Dichloromethane was distilled from calcium hydride. Toluene was used as received. H_2O refers to deionized water. Organic phases were dried over anhydrous magnesium- or sodium sulfate. Evaporation of solvents was carried out on a rotary evaporator at reduced pressure.

Column chromatography was performed using silica gel 60 (70-230 mesh). Solvent ratios are given as v/v.

HPLC analyses were carried out using a 250x4.6 mm column, containing cellulose tris(3,5-dimethylphenylcarbamate) on silica-gel as stationary phase. Isocratic mixtures of hexane or heptane and isopropanol were used as eluents. UV detection was carried out at 220 nm.

^{1}H-NMR spectra were recorded at 200 MHz, 300 MHz or 400 MHz in $CDCl_3$ with tetramethylsilane as an internal reference. Signals are quoted in ppm as δ downfield from tetramethylsilane (δ 0.00) as internal standard. Coupling constants (*J* values) are given in Hertz. ^{13}C-NMR spectra were recorded at 50 MHz, 75 MHz or 100 MHz, respectively. Chemical shifts were referenced to the deuterated solvent signals.

Melting points are uncorrected.

***(R)*-3-Bromo-4-hydroxyphenylglycine hydrobromide (18)**

A solution of HBr in glacial acetic acid (33% w/v) (15 ml, 61 mmol) was added to a vigorously stirred suspension of (*R*)-4-hydroxyphenylglycine (5.0 g, 30.6 mmol) in glacial acetic acid (25 ml). A solution of bromine (1.7 ml, 33.2 mmol) in glacial acetic acid (11.3 ml), was added dropwise over 3h and the resulting mixture was stirred at rt for 24h. The precipitate was filtered, washed with glacial acetic acid (3x5 ml) and Et_2O (5x5 ml) giving **18** as a white solid (6.70 g, 67%): mp 210-211 ºC (decomp.) (lit.[1] 210 ºC); IR (NaCl film) 3500-2400, 1737, 1580, 1505, 1476, 1426, 1218, 1184 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ 5.01 (1H, s), 6.97 (1H, d, *J* 8.4), 7.30 (1H, dd, J_1 8.4 J_2 2.2), 7.63 (1H, d, *J* 2.2); ^{13}C NMR (50 MHz, CD_3OD) δ 56.5 (CH), 111.3

(C), 117.6 (CH), 125.8 (C), 129.6 (CH), 134.0 (CH), 156.9 (C), 170.6 (C); MS *m/z* 282 [$(M+N_2H_7)^+$, 21%], 280 [$(M+N_2H_7)^+$, 23%], 265 [$(M+NH_4)^+$, 96%], 263 [$(M+NH_4)^+$, 100%], 248 [$(M+H)^+$, 20%], 246 [$(M+H)^+$, 23%]; HRMS calcd for $C_8H_9BrNO_3$ $(M+H)^+$, 245.976579: found, 245.976322; Anal. Calcd for $C_8H_9Br_2NO_3$: C, 29.39; H, 2.77; N, 4.28; Found: C, 29.21; H, 2.89; N, 4.42; $[\alpha]_D$ -107.2 (MeOH, c 1.00).

***(R)*-*N*-Boc-3-bromo-4-hydroxyphenylglycine (19)**

(R)-3-Bromo-4-hydroxyphenylglycine hydrobromide (2.0 g, 6.12 mmol) was suspended in ^{t}BuOH (18 ml) and H_2O (2 ml) and the pH was adjusted to 9 by adding an aqueous solution of 2M NaOH. Boc_2O (1.59 g, 7.28 mmol) was added and the mixture was stirred for 30 min at rt. The pH was readjusted to 9, Boc_2O (0.79 g, 3.64 mmol) was added and the mixture was stirred for a further 30 min at rt. The pH was increased to 12 by adding 2M NaOH and the mixture was stirred vigorously until the solid had dissolved. The solution was washed with hexanes (2x50 ml) and the aqueous phase was acidified to pH 2-3 by adding 10% HCl. Extraction with AcOEt (3x50 ml) followed by washing of the combined organic phases with H_2O (2x30 ml) and drying over anhydrous $MgSO_4$, filtration and solvent removal gave **19** as a foamy white solid (1.98 g, 94%): mp 78-85 ºC; IR (film NaCl) 3500-2800, 1719, 1698, 1501, 1397, 1162 cm^{-1}; ^{1}H NMR (200 MHz, d_6-acetone) δ 1.40 (9H, s), 5.21 (1H, d, *J* 7.6), 6.63 (1H, d, *J* 5.8), 7.00 (1H, d, *J* 8.6), 7.31 (1H, dd, J_1 8.0 J_2 2.2), 7.62 (1H, d, *J* 2.2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.1 (CH_3), 57.7 (CH), 82.1 (C), 110.0 (C), 115.9 (CH), 128.0 (CH), 130.6 (CH), 131.7 (C), 152.0 (C), 156.8 (C), 173.0 (C); MS *m/z* 348 [$(M+H)^+$, 10%], 346 [$(M+H)^+$, 13%], 292 [$(M-C_4H_8+H)^+$, 45%], 290 [$(M-C_4H_8+H)^+$, 49%], 248 [$(M-C_5H_8O_2+H)^+$, 78%], 246 [$(M-C_5H_8O_2+H)^+$, 70%],

231 [(M-$C_5H_{11}NO_2$+H)$^+$, 99%], 229 [(M-$C_5H_{11}NO_2$+H)$^+$, 100%]; HRMS calcd for $C_{13}H_{17}BrNO_5$ (M+H)$^+$, 346.029009: found, 346.030359; $[\alpha]_D$ -120.6 ($CHCl_3$, c 0.885).

Methyl (*R*)-*N*-Boc-3-bromo-4-methoxyphenylglycinate (1)

(*R*)-Boc-3-bromo-4-hydroxyphenylglycine (1.99 g, 5.75 mmol) was dissolved in MeOH (18 ml) and H_2O (1.2 ml). 20% (w/v) Aqueous Cs_2CO_3 (8.0 ml, 4.89 mmol) was added and the solution was evaporated to dryness. The resulting solid was dried over P_2O_5 under vacuum for 12h. The dry cesium salt was dissolved in DMF (17 ml) and iodomethane (1.5 ml, 23 mmol) was added. The mixture was stirred for 18h at rt. The solvents were evaporated and H_2O (25 ml) was added to the residue. The mixture was extracted with AcOEt (3x50 ml) and the combined organic phases were washed with H_2O (2x25 ml), dried over anhydrous $MgSO_4$ and filtered. The solvent was evaporated and the crude product was purified by column chromatography [silica, hexanes: AcOEt (85:15)] affording **1** as a white solid (1.55 g, 72%): mp 110-111 ºC; IR (film NaCl) 3377, 2979, 1746, 1717, 1497, 1287, 1258, 1165, 1057 cm^{-1}; ^{1}H NMR (200 MHz, d_6-acetone) δ 1.40 (9H, s), 3.68 (3H, s), 3.90 (3H, s), 5.24 (1H, d, *J* 8.0), 6.77 (1H, d, *J* 7.4), 7.07 (1H, d, *J* 8.4), 7.41 (1H, dd, J_1 8.8, J_2 2.2), 7.64 (1H, d, *J* 2.2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.29 (CH_3), 52.85 (CH_3), 56.27 (CH_3), 56.47 (CH), 80.29 (C), 111.9 (CH), 127.4 (CH), 130.5 (C), 131.8 (CH), 155.8 (C), 171.2 (C); MS *m/z* 376 [(M+H)$^+$, 6%], 374 [(M+H)$^+$, 8%], 320 [(M-C_4H_8+H)$^+$, 38%], 318 [(M-C_4H_8+H)$^+$, 38%], 276 [(M-$C_5H_8O_2$+H)$^+$, 11%], 274 [(M-$C_5H_8O_2$+1)$^+$, 13%], 259 [(M-$C_5H_{11}NO_2$+H)$^+$, 99%], 257 [(M-$C_5H_{11}NO_2$+H)$^+$, 100%]; HRMS calcd for $C_{15}H_{20}BrNO_5$ (M+H)$^+$, 374.060309: found, 374.059611; Anal. Calcd for $C_{15}H_{20}BrNO_5$: C, 48.14; H, 5.39; N, 3.74. Found: C, 47.91; H, 5.35; N, 3.5; $[\alpha]_D$ -119.0 ($CHCl_3$, c 0.96).

***(S)*-3-Bromotyrosine hydrobromide (20)**

A solution of HBr in glacial acetic acid (33% w/v) (15 ml, 61 mmol) was added to a vigorously stirred suspension of (*S*)-tyrosine (5.54 g, 30.6 mmol) in glacial acetic acid (25 ml). A solution of bromine (1.7 ml, 33.2 mmol) in glacial acetic acid (11.3 ml) was added dropwise over 3h and the resulting mixture was stirred at rt for 24h. The precipitate was filtered and washed with glacial acetic acid (3x5 ml) and Et_2O (5x5 ml) furnishing **20** as a white solid (10.03 g, 96%); mp 210-215 ºC (decomp.); IR (film NaCl) 3500-2700, 1739, 1505, 1420, 1214 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 3.07 (1H, dd, J_1 14.7 J_2 7.5), 3.21 (1H, dd, J_1 14.5, J_2 5.4), 4.22 (1H, dd, J_1 7.5 J_2 5.4), 6.90 (1H, d, J 8.4), 7.11 (1H, dd, J_1 8.4 J_2 2.1), 7.43 (1H, d, J 2.1); ^{13}C NMR (50 MHz, CD_3OD) δ 36.0 (CH_2), 55.1 (CH), 111.1 (C), 117.6 (CH), 127.7 (C), 130.7 (CH), 135.0 (CH), 155.1 (C), 171.0 (C); MS [CI(NH_3)] *m/z* 262 [$(M+H)^+$, 92%], 260 [$(M+H)^+$, 100%]; HRMS calcd for $C_9H_{11}BrNO_3$ $(M+H)^+$, 261.990183: found, 261.990639; $[\alpha]_D$ +1.27 (MeOH, c 1.03).

(*S*)-*N*-Boc-3-bromotyrosine (21)

(S)-3-Bromotyrosine hydrobromide (2.08 g, 6.12 mmol) was suspended in ^{t}BuOH (18 ml) and H_2O (2 ml) and the pH was adjusted to 9 by adding 2M NaOH. Boc_2O (1.59 g, 7.28 mmol) was added and the mixture was stirred for 30 min at rt. The pH was readjusted to 9, Boc_2O (0.79 g, 3.64 mmol) was added and the mixture was stirred for a further 30 min at rt. The solution was washed with hexanes (2x50 ml) and the aqueous phase was acidifed to pH 2-3 by adding 10% HCl. Extraction with AcOEt (3x50 ml) followed by washing of the combined organic phases with H_2O (2x30 ml) and drying over anhydrous $MgSO_4$, filtration and solvent removal gave **21** as a foamy white solid (2.04 g, 93%): mp 76-82 ºC; IR (film NaCl) 3328, 2981, 1719,

1499, 1370, 1291, 1256, 1162 cm^{-1}; ^{1}H NMR (400 MHz, d_6-acetone) δ 1.36 (9H, s), 2.92 (1H, dd, J_1 14.0, J_2 8.8), 3.12 (1H, dd, J_1 14.0 J_2 5.2), 4.36 (1H, m), 6.33 (1H, d, J 8.0), 6.93 (1H, d, J 8.0), 7.12 (1H, d, J_1 8.0 J_2 1.6), 7.41 (1H, d, J 1.6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3 (CH_3), 36.7 (CH_2), 54.3 (CH), 80.5 (C), 110.1 (C), 116.2 (CH), 130.1 (CH), 132.8 (CH), 151.5 (C), 155.4 (C), 175.7 (C); MS [CI(NH_3)] *m/z* 362 [$(M+H)^+$, 3%], 360 [$(M+H)^+$, 5%], 306 [$(M-C_4H_8+H)^+$, 44%], 304 [$(M-C_4H_8+H)^+$, 45%], 262 [$(M-C_5H_8O_2+H)^+$, 85%], 260 [$(M-C_5H_8O_2+H)^+$, 86%], 231 [$(M-C_5H_{11}NO_2+H)^+$, 99%], 229 [$(M-C_5H_{11}NO_2+H)^+$, 100%]; HRMS calcd for $C_{14}H_{19}BrNO_5$ $(M+H)^+$, 360.044659: found, 360.043224; $[\alpha]_D$ +40.1 ($CHCl_3$, c 0.775).

Methyl *(S)*-*N*-Boc-3-bromo-*O*-methyltyrosinate (2)

(*S*)-Boc-3-bromotyrosine (1.40 g, 3.89 mmol) was dissolved in MeOH (11 ml) and H_2O (0.8 ml). 20% (w/v) Aqueous Cs_2CO_3 (5.8 ml, 3.89 mmol) was added and the solution evaporated to dryness. The resulting solid was dried over P_2O_5 under vacuum for 16h. The dry cesium salt was dissolved in DMF (9.5 ml), and iodomethane (0.92 ml, 15.5 mmol) was added. The mixture was stirred vigorously for 18h at rt. The solvent was removed and H_2O (20 ml) was added. The mixture was extracted with AcOEt (3x50 ml) and the combined organic phases were washed with H_2O (2x30 ml), dried over anhydrous $MgSO_4$, filtered and the solvent was removed. The crude product was purified by column chromatography [silica gel, hexanes:AcOEt (80:20)] giving **2** as a white solid (1.07 g, 70%): mp 114-120 ºC; IR (film NaCl) 3371, 2977, 1746, 1715, 1499, 1366, 1281, 1258, 1167, 1055, 1020 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.43 (9H, s), 2.95 (1H, dd, J_1 14.0, J_2 6.0), 3.10 (1H, dd, J_1 13.6 J_2 5.6), 3.73 (3H, s), 3.88 (3H, s), 4.52 (1H, m), 4.99 (1H, d, J 7.4), 6.82 (1H, d, J 8.4), 7.04 (1H, dd, J_1 8.4, J_2 2.2), 7.30 (1H, d, J 2.2); ^{13}C

NMR (50 MHz, $CDCl_3$) δ 28.3 (CH_3), 37.1 (CH_2), 52.3 (CH_3), 54.4 (CH), 56.2 (CH_3), 80.1 (C), 111.8 (CH), 129.2 (CH), 129.6 (C), 134.0 (CH), 154.8 (C), 172.0 (C); MS *m/z* 391 [$(M+H)^+$, 4%], 389 [$(M+H)^+$, 6%], 335 [$(M-C_4H_8+H)^+$, 52%], 333[$(M-C_4H_8+H)^+$, 60%], 291-[$(M-C_5H_8O_2+H)^+$, 90%], 289 [$(M-C_5H_8O_2+H)^+$, 100%], 273 [$(M-C_5H_{11}NO_2+H)^+$, 96%], 271 [$(M-C_5H_{11}NO_2+1)^+$, 80%]; HRMS calcd for $C_{16}H_{22}BrNNaO_5$ $(M+Na)^+$, 410.0579: found, 410.0569; Anal. Calcd for $C_{16}H_{22}BrNO_5$: C, 49.50; H, 5.71; N, 3.61. Found: C, 49.67; H, 5.89; N, 3.67; $[\alpha]_D$ +45.7 ($CHCl_3$, c 0.645).

Methyl *(S)*-*N*-Boc-3-(4'-methoxyphenyl)-O-methyltyrosinate (5)

Solutions of $Pd(PPh_3)_4$ (7 mg, 0.006 mmol) in toluene (0.8 ml) and of 4-methoxyphenylboronic acid (33 mg, 0.21 mmol) in MeOH (0.35 ml) were added to a solution of Na_2CO_3 (41 mg, 0.37 mmol) and methyl (S)-N-Boc-3-bromo-O-methyltyrosinate (100 mg, 0.26 mmol) in toluene (0.8 ml) and H_2O (0.7 ml) under an argon atmosphere. The resulting mixture was stirred at 90 ºC for 1h. The additions of 4-methoxyphenylboronic acid (17 mg, 0.11 mmol) in MeOH (0.35 ml) and $Pd(PPh_3)_4$ (4 mg, 0.003 mmol) in toluene (0.4 ml) were repeated a further three times at 60 min intervals. The mixture was then stirred for a further 5h. After cooling the solvents were evaporated and the resulting crude product was purified by column chromatography [silica gel, AcOEt in hexanes (0-20%)] furnishing 5 as a pale yellow oil (65 mg, 61%): IR (film NaCl) 3369, 2976,1745, 1714, 1516, 1497, 1366, 1246, 1177, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (9H, s), 3.03 (1H, dd, J_1 14.0 J_2 6.0), 3.10 (1H, dd, J_1 14.0 J_2 5.6), 3.72 (3H, s), 3.78 (3H, s), 3.84 (3H, s), 4.55-4.60 (1H, m), 5.00 (1H, d, 7.6), 6.87-6.89 (1H, m), 6.92-6.96 (2H, m), 7.02-7.04 (2H, m), 7.42-7.46 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3 (CH_3), 37.4 (CH_2), 52.2 (CH_3), 54.5 (CH), 55.2 (CH_3), 55.6 (CH_3), 79.8 (C), 111.3 (CH),

113.4 (CH), 128.0 (C), 128.7 (CH), 130.2 (C), 130.5 (CH), 131.7 (CH), 155.0 (C), 155.5 (C), 158.7 (C), 172.4 (C); MS *m/z* 454 [$(M+K)^+$, 37%], 438 [$(M+Na)^+$, 100%]; HRMS calcd for $C_{23}H_{29}NO_6$ ($M^{+\bullet}$), 415.1995: found, 415.1989; $[\alpha]_D$ +38.57 ($CHCl_3$, c 1.00).

Methyl *(R)*-*N*-Boc-3-(indol-6-yl)-4-methoxyphenylglycinate (11)

KH (31 mg, 0.77 mmol) was suspended in anhydrous THF (0.2 ml) under an argon atmosphere at 0 °C. 6-Bromoindole[2-4] (151 mg, 0.77 mmol) in anhydrous THF (1.3 ml) was added and the mixture stirred for 15 min. After cooling to -78 °C, a solution of ^{t}BuLi in pentane (1.53 mmol), previously cooled to -78 ºC, was added dropwise. The mixture was brought to rt and stirred for 10 min and re-cooled to -78 ºC. $B(OMe)_3$ (0.18 ml, 1.53 mmol) was added and stirring was continued for a further 3h at rt. H_2O (5 ml) was added and the mixture was extracted with AcOEt (2x10 ml). The aqueous phase was acidified to pH 1 with 10% HCl and was re-extracted with AcOEt (3x10 ml). The combined organic extracts were dried over anhydrous $MgSO_4$ and filtered. The solvents were evaporated leaving the crude indolylboronic acid **7** as a pale brown oil.

Solutions of $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) in toluene (0.5 ml) and of the crude indolylboronic acid **7** (2/5 of the product prepared above) in MeOH (0.4 ml) were added to a stirred solution of sodium succinate (65 mg, 0.40 mmol) and methyl (R)-N-Boc-3-bromo-4-methoxyphenylglycinate (72 mg, 0.19 mmol) in toluene (0.6 ml) and H_2O (0.4 ml) under an argon atmosphere. The mixture was brought to 90 ºC and stirred for 1h. The additions of indolylboronic acid **7** (1/5 of the crude prepared above) in MeOH (0.2 ml) and $Pd(PPh_3)_4$ (5 mg, 0.005 mmol) in toluene (0.3 ml) were repeated a further three times at 60 min intervals. The mixture was then stirred for a further 5h. The solvents were evaporated and the crude product

was purified by column chromatography [silica gel, AcOEt in hexanes (0-13%)] giving the product as a yellow oil (37 mg, 46%): IR (film NaCl) 3500-2800, 1699, 1499, 1368, 1246, 1163 cm^{-1}; ^{1}H NMR (200 MHz, d_6-acetone) δ 1.41 (9H, s), 3.68 (3H, s), 3.80 (3H, s), 5.29 (1H, d, *J* 7.6), 6.49 (1H, m), 6.74 (1H, d, *J* 7.0), 7.07 (1H, d, *J* 8.6), 7.22 (1H, dd, J_1 8.4 J_2 1.4), 7.33-7.43 (3H, m), 7.44-7.61 (2H, m), 10.26 (1H, s); ^{13}C NMR (50 MHz, d_6-acetone) δ 28.5 (CH_3), 52.5 (CH_3), 55.9 (CH_3), 58.2 (CH), 79.4 (C), 102.1 (CH), 112.4 (CH), 113.0 (CH), 120.2 (CH), 122.0 (CH), 126.0 (CH), 128.0 (CH), 129.9 (C), 130.8 (CH), 132.1 (C), 132.8 (C), 137.0 (C), 157.4 (C), 172.5 (C); MS *m/z* 449 [$(M+K)^+$, 63%], 433 [$(M+Na)^+$, 100%]; HRMS calcd for $C_{23}H_{26}N_2O_5$ ($M^{+\bullet}$), 410.184172: found, 410.184370; $[\alpha]_D$ -71.0 (CH_3Cl, c 1.0).

Methyl *(R)*-*N*-Boc-3-(indol-7-yl)-4-methoxyphenylglycinate (12)

KH (31 mg, 0.77 mmol) was suspended in anhydrous THF (0.2 ml) under an argon atmosphere at 0 °C in a flask protected from light. 7-Bromoindole (150 mg, 0.77 mmol) in anhydrous THF (1.3 ml) was added and the mixture stirred for 15 min. After cooling to -78 °C a solution of ^{t}BuLi in pentane (1.53 mmol) , previously cooled to -78 ºC, was added dropwise. The mixture was brought to rt and stirred for 15 min and re-cooled to -78 ºC. $B(OMe)_3$ (0.18 ml, 1.53 mmol) was added and stirring was continued for a further 3h at rt. H_2O (5 ml) was added and the mixture was extracted with AcOEt (2x10 ml). The aqueous phase was acidified to pH 1 with 10% HCl and was re-extracted with AcOEt (3x10 ml). The combined organic extracts were dried over anhydrous $MgSO_4$ and filtered. The solvents were evaporated leaving the crude indolylboronic acid **8** as a pale brown oil.

Solutions of $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) in toluene (0.5 ml) and of the crude indolylboronic acid **8** (2/5 of the product prepared above) in MeOH (0.4 ml) were added to a

stirred solution of sodium succinate (65 mg, 0.40 mmol) and methyl (R)-N-Boc-3-bromo-4-methoxyphenylglycinate (72 mg, 0.19 mmol) in toluene (0.6 ml) and H_2O (0.38 ml) under an argon atmosphere. The mixture was brought to 90 ºC and stirred for 1h. Additions of indolylboronic acid **8** (1/5 of the crude prepared above) in MeOH (0.2 ml) and $Pd(PPh_3)_4$ (5 mg, 0.005 mmol) in toluene (0.3 ml) were repeated a further three times at 60 min intervals. The mixture was then stirred for a further 5h. The solvents were evaporated and the crude product was purified by column chromatography [silica gel, AcOEt in hexanes (0-20%)] giving the product as a colorless oil (33 mg, 42%): IR (film NaCl) 3500-2800, 1740, 1703, 1497, 1366, 1335, 1242, 1161 cm^{-1}; ^1H NMR (200 MHz, d_6-acetone) δ 1.42 (9H, s), 3.67 (3H, s), 3.78 (3H, s), 5.30 (1H, d, *J* 8.0), 6.51 (1H, m), 6.75 (1H, d, *J* 7.0), 7.08-7.13 (3H, m), 7.28 (1H, t, *J* 3.0), 7.44-7.48 (2H, m), 7.56-7.62 (1H, m), 9.89 (1H, s); ^{13}C NMR (50 MHz, d_6-acetone) δ 28.5 (CH_3), 52.5 (CH_3), 55.7 (CH_3), 58.2 (CH), 79.5 (C), 102.2 (CH), 112.0 (CH), 119.8 (CH), 120.4 (CH), 123.4 (CH), 125.3 (C), 125.5 (CH), 128.7 (C), 129.1 (CH), 129.8 (C), 131.2 (CH), 135.2 (C), 157.6 (C), 172.4 (C); MS *m/z* 449 [$(M+K)^+$, 63%], 433 [$(M+Na)^+$, 100%]; HRMS calcd for $C_{23}H_{26}N_2O_5$ ($M^{+\bullet}$), 410.184172: found, 410.184950; $[\alpha]_D$ -75.11 ($CHCl_3$, c 0.90).

Methyl *(R)*-*N*-Boc-3-(2',4'-dimethoxy-6'-*N*'-Cbz-aminomethylphenyl)-4-methoxyphenyglycinate (17)

Triethylamine (0.031 ml, 0.22 mmol) was added to a a solution of methyl (R)-N-Boc-3-(2',4'-dimethoxy-6'-hydroxymethylphenyl)-4-methoxyphenylglycinate (68 mg, 0.15 mmol) in CH_2Cl_2 (0.3 ml). The mixture was cooled to 0 ºC and mesyl chloride (0.18 ml, 0.22 mmol) was added dropwise over 10 min. The mixture was then stirred at 0 ºC for 30 min and at rt for a further 30 min. The resulting solution was diluted with CH_2Cl_2 (25 ml) and washed with 1M aqueous

$KHSO_4$ (5 ml), 5% $NaHCO_3$ (5 ml) and brine (5 ml). The organic phase was dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated leaving the crude mesylate **14** which was used without further purification.

A solution of **14** (80 mg, 0.22 mmol) and sodium azide (20 mg, 0.30 mmol) in DMF (1.45 ml) was stirred at 60 ºC for 6h. After cooling to rt the solvent was evaporated and the resulting solid was suspended in H_2O (10 ml) and extracted with AcOEt (3x25 ml). The combined organic extracts were dried over anhydrous $MgSO_4$ and filtered. Solvent removal gave the crude azide **15** as a yellow oil that was used without further purification.

Azide **15** (72 mg, 0.22 mmol) and 10% Pd/C (8 mg) in MeOH (1.5 ml) were vigorously stirred under a hydrogen atmosphere for 20h. After filtration through Celite and rotatory evaporation the crude amine **16** was obtained as a yellow oil and was used directly without further purification.

A solution of **16** (68 mg, 0.15 mmol) in THF (1.5 ml) was stirred with benzyloxycarbonyl chloride (0.064 ml, 0.45 mmol) and triethylamine (0.17 ml, 1.2 mmol) for 24h at rt. The solvent was removed and the resulting brown oil was dissolved in CH_2Cl_2 (30 ml). This solution was washed with saturated aqueous sodium bicarbonate $NaHCO_3$ (10 ml) and brine (10 ml). The solution was dried over anhydrous Na_2SO_4 and filtered and the solvent removed. The crude product was purified by column chromatography [silica gel, AcOEt in hexanes (0-35%)] giving the product as a pale yellow oil (26 mg, 29%): IR (film NaCl) 3354, 2956, 2838, 1717, 1605, 1507, 1324, 1260, 1160, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (9H), 1.42 (9H, s), 3.66 (3H, s), 3.67 (3H, s), 3.69 (3H, s), 3.70 (3H, s), 3.71 (6H, s), 3.81 (6H, s), 3.98-4.05 (4H, m), 4.92 (1H, t, *J* 5.2), 5.06 (5H, s), 5.26 (2H, d, *J* 4.8), 5.49 (1H, d, *J* 6.4), 5.64 (1H, d, *J* 6.8), 6.45-6.47 (2H, m), 6.57 (1H, sa), 6.62 (1H, sa), 6.91 (2H, d, *J* 8.8), 7.08 (2H, sa), 7.29-7.35 (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.3 (CH_3), 43.4 (CH_2), 52.5 (CH_3), 55.4 (CH_3), 55.7 (CH_3), 55.8

(CH_3), 57.0 (CH), 66.5 (CH_2), 98.1 (CH), 104.6 (CH), 111.2 (CH), 118.8 (CH), 125.5 (C), 127.7 (CH), 127.9 (CH), 128.3 (CH), 128.6 (C), 130.9 (CH), 138.8 (C), 157.1 (C), 158.1 (C), 160.2 (C), 171.7 (C); MS *m/z* 633 [$(M+K)^+$, 47%], 617 [$(M+Na)^+$, 100%]; HRMS calcd for $C_{27}H_{31}N_2O_7$: $(M-C_4H_8-CO_2+H)^+$, 495.213127: found: 495.211118; $[\alpha]_D$ -45.3 (CH_2Cl_2, c 0.32).

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