Supporting Information

Synthesis of DEFG Ring of Complestatin and Chloropeptin 1: Highly Atropdiastereoselective Macrocyclization by Intramolecular Suzuki-Miyaura Reaction

By Yanxing Jia, Michèle Bois-Choussy, Jieping Zhu*

Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette Cedex, France

General information

Melting points were recorded using Reichert melting point apparatus.

Mass spectra were obtained from an AEI MS-9 using electron spray (ES), or from a MALDI-TOF type of instrument for the high resolution mass spectra (HRMS).

Proton NMR (^{1}H) spectra were recorded at 300 MHz on a Bruker AC-300 spectrometer or at 500 MHz on a Bruker AC-500 spectrometer. Carbon NMR (^{13}C) spectra were similarly recorded at 75 MHz using a broadband decoupled mode with the multiplicities obtained using a JMOD or DEPT sequence.

Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane. NMR experiments were carried out in $CDCl_3$, CD_3OD, acetone-d_6, DMSO-d_6. The following abbreviations are used for the multiplicities: s: singlet, d: doublet, t: triplet, m: multiplet, br s: broad singlet for proton spectra. Coupling constants (J) are reported in Hertz (Hz).

Infrared spectra were recorded on a Peikin Elmer BX spectrometer with ATR diamant.

$[\alpha]_D$ were recorded on a JASCO P-1010 Polarimeter.

Flash chromatography was performed using Kieselgel Si 60, 40-63 μm particle sized silica gel (200-400 mesh). Visualization was achieved under a UVP mineralight UVGL-58 lamp.

All reagents were obtained from commercial suppliers unless otherwise stated.

Experimental procedure and physical data

2-Iodo-5-nitroaniline 5.[1] To a solution of *m*-nitroaniline (6.0 g, 43.5 mmol) and NaOAc (3.74 g, 45.7 mmol) in HOAc (30 mL) was added dropwise a solution of iodine monochloride (7.4 g, 45.7 mmol) in HOAc (20 mL) at 80-82 ºC (6 h). After being stirred at the same temperature for an additional 18 h, the reaction was diluted with H_2O, basified with NaOH to pH 7-8, extracted with EtOAc, washed with water and brine, and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, 5% EtOAc in heptane) and crystallized from EtOAc/heptane to provide 2-iodo-5-nitroaniline (3.5 g, 30%). mp 161-162 ºC; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.80 (d, J = 8.5 Hz, 1H), 7.54 (d, J = 2.3 Hz, 1H), 7.09 (dd, J = 2.3, 8.5 Hz, 1H), 5.88 (br s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 149.8, 148.4, 139.5, 111.1, 106.9, 90.9; HRMS (ESI) *m/z* calcd for $C_6H_4N_2O_2INa$ $(M + Na)^+$ 262.9318; found 262.9310.

Compound 6. Compound **6** was prepared according to a literature procedure.[2] $[\alpha]_D^{23}$ +40.5 (*c* 1.00, $CHCl_3$); IR (neat) 2980, 1792, 1746, 1457, 1368, 1253, 1144, 1118, 1013, 854 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (s, 1H), 4.87 (dd, 1H, J = 4.7, 9.1 Hz), 3.71 (s, 3H), 2.58 (m, 1H), 2.55-2.43 (m, 2H), 2.16 (m, 1H), 1.48 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 170.7, 151.9 (2C), 83.4 (2C), 57.3, 52.2, 40.5, 27.9 (6C), 22.5; MS (EI) *m/z* 345 $(M)^+$.

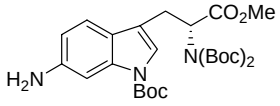
Compound 7. A solution of 2-iodo-5-nitroaniline **5** (2.64 g, 10.0 mmol), aldehyde **6** (3.45 g, 10.0 mmol), DABCO (3.36 g, 30.0 mmol) in dry DMF (50 mL) was degassed for 20 min. $Pd(OAc)_2$ (113 mg, 0.5 mmol) was added to the reaction and the resulting reaction mixture was heated at 85 ºC for 12 h. The reaction mixture was cooled to room temperature and was diluted with water, extracted with EtOAc and the combined organic phases were washed with brine, dried (Na_2SO_4) and evaporated to

1. Fletcher, T. L.; Namkung, M. J.; Pan, H.-L.; Wetzel, W. H. *J. Org. Chem.* **1960,** *25*, 996-1000.
2. Padron, J. M.; Kokotos, G.; Martin, T.; Markidis, T.; Gibbons, W. A.; Martin, V. S. *Tetrahedron Asymmetry* **1998,** 9, 3381-3394.

dryness under reduced pressure. Purification of crude product by flash column chromatography (silica gel, 20-25% EtOAc in heptane, gradient elution) provided the desired product **7** (3.01 g, 65%). mp 75-77 °C; $[\alpha]_D^{23}$ +76.6 (*c* 1.00, $CHCl_3$); IR (neat) 3307, 2979, 1779, 1747, 1696, 1508, 1458, 1369, 1331, 1272, 1143, 1129, 1095, 1059, 851 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.91 (br s, 1H), 8.41 (d, *J* = 1.9 Hz, 1H), 7.99 (dd, *J* = 1.9, 8.8 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.26 (d, *J* = 2.2 Hz, 1H), 5.18 (dd, *J* = 5.0, 10.3 Hz, 1H), 3.79 (s, 3H), 3.62 (dd, *J* = 5.0, 14.9 Hz, 1H), 3.41 (dd, *J* = 10.3, 14.9 Hz, 1H), 1.28 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 151.5 (2C), 143.0, 134.7, 132.0, 129.6, 118.3, 114.6, 111.8, 108.7, 83.6 (2C), 58.6, 52.3, 27.6 (6C), 25.5; HRMS (ESI) *m/z* calcd for $C_{22}H_{29}N_3O_8Na$ $(M + Na)^+$ 486.1852; found 486.1858.

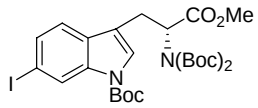
Compound 8. To a solution of tryptophane **7** (5.0 g, 10.8 mmol) in dry MeCN (40 mL) was added DMAP (264 mg, 2.16 mmol) and Boc_2O (3.6 g, 16.2 mmol) at room temperature. After the reaction mixture was stirred at room temperature for 1 h, the volatile was removed by rotary evaporation and the residue was purified by flash column chromatography (silica gel, 12-15% EtOAc in heptane, gradient elution) to afford the desired product (5.78 g, 95%). $[\alpha]_D^{23}$ +72.6 (*c* 2.00, $CHCl_3$); IR (neat) 2980, 1741, 1697, 1519, 1446, 1368, 1338, 1270, 1255, 1144, 1132, 1087, 849 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.10 (dd, *J* = 2.0, 8.7 Hz, 1H), 7.65 (s, 1H), 7.61 (d, *J* = 8.7 Hz, 1H), 5.16 (dd, *J* = 5.3, 9.8 Hz, 1H), 3.75 (s, 3H), 3.52 (dd, *J* = 5.3, 15.0 Hz, 1H), 3.36 (dd, *J* = 9.8, 15.0 Hz, 1H), 1.67 (s, 9H), 1.33 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 151.8 (2C), 148.5, 144.9, 135.2, 134.1, 129.3, 119.0, 117.7, 116.6, 111.6, 85.0, 83.2 (2C), 57.9, 52.3, 28.0 (3C), 27.7 (6C), 25.3; HRMS (ESI) *m/z* calcd for $C_{27}H_{37}N_3O_{10}Na$ $(M + Na)^+$ 586.2377; found 586.2400.

To a solution of nitro-tryptophane (5.5 g, 9.77 mmol) and Zn dust (43.4g) in CH_2Cl_2 (120 mL) was slowly added HOAc (8.8 mL) at 0 ºC. The solution was stirred at room temperature for 30 min and then the solution was filtered through celite. The filtrate was washed with sat. aqueous $NaHCO_3$, H_2O and brine, dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, 25-35% EtOAc in heptane, gradient elution) to provide the desired product **8** (4.79 g, 92%). $[\alpha]_D^{23}$ +70.6 (*c* 1.00, $CHCl_3$); IR (neat) 3374, 2979, 1789, 1731, 1626, 1495, 1450, 1385, 1367, 1306, 1279, 1257, 1149, 1136, 1112, 1084, 853 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.25 (d, *J* = 8.3 Hz, 1H), 7.15 (s, 1H), 6.62 (dd, *J* = 2.1, 8.3 Hz, 1H), 5.17 (dd, *J* = 4.8, 10.1 Hz, 1H), 3.75 (s, 3H), 3.71

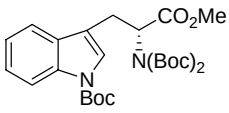


(br s, 2H), 3.44 (dd, *J* = 4.8, 14.9 Hz, 1H), 3.27 (dd, *J* = 10.1, 14.9 Hz, 1H), 1.61 (s, 9H), 1.33 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 151.7 (2C), 149.7, 144.2, 136.9, 123.0, 121.8, 119.4, 116.6, 111.8, 101.5, 82.9, 82.8 (2C), 58.1, 52.2, 28.1 (3C), 27.7 (6C), 25.6; HRMS (ESI) *m/z* calcd for $C_{27}H_{40}N_3O_8$ $(M + H)^+$ 534.2815; found 534.2806.

Compound 9. To a solution of compound **8** (4.63 g, 8.69 mmol) in THF (66 mL), H_2O (40 mL) and 5% HCl (26 mL) was added $NaNO_2$ (1.32 g, 19.1 mmol) at 0 ºC. After being stirred at 0 ºC for 5 min, potassium iodide (3.61 g, 21.73 mmol) was added and the resulting reaction mixture was continued to stir at 0 ºC for 30 min. The reaction mixture was basified to pH 7-8 with sat. aqueous $NaHCO_3$, extracted with EtOAc, and the combined organic phases were washed with H_2O and brine, dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, 10-15% EtOAc in heptane, gradient elution; then CH_2Cl_2 again) to provide the desired product **9** (3.64 g, 65%) and deiodo product (0.9 g, 20%). $[\alpha]_D^{23}$ +60.0 (*c* 1.00, $CHCl_3$); IR (neat) 2979, 1789, 1732, 1697, 1454, 1429, 1366, 1250, 1133, 1082, 842, 808 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.51 (dd, *J* = 1.5, 8.3 Hz, 1H), 7.30 (s, 1H), 7.26 (d, *J* = 8.3 Hz, 1H), 5.15 (dd, *J* = 5.0, 10.0 Hz, 1H), 3.75 (s, 3H), 3.47 (dd, *J* = 5.0, 15.0 Hz, 1H), 3.32 (dd, *J* = 10.0, 15.0 Hz, 1H), 1.63 (s, 9H), 1.33 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 151.8 (2C), 149.1, 136.3, 131.3, 129.8, 124.4, 124.1, 120.4, 116.4, 88.7, 83.9, 83.0 (2C), 58.0, 52.3, 28.0 (3C), 27.7 (6C), 25.4; HRMS (ESI) *m/z* calcd for $C_{27}H_{37}N_2O_8INa$ $(M + Na)^+$ 667.1492; found 667.1488.

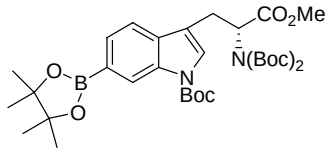


Deiodo Compound: $[\alpha]_D^{23}$ +61.0 (*c* 1.00, $CHCl_3$); IR (neat) 2979, 1790, 1731, 1698, 1454, 1366, 1253, 1223, 1152, 1137, 1082, 853 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.39 (s, 1H), 7.29 (dt, *J* = 1.1, 7.6 Hz, 1H), 7.21 (dt, *J* = 1.1, 7.6 Hz, 1H), 5.20 (dd, *J* = 4.9, 10.2 Hz, 1H), 3.76 (s, 3H), 3.52 (dd, *J* = 4.9, 14.9 Hz, 1H), 3.36 (dd, *J* = 10.2, 14.9 Hz, 1H), 1.64 (s, 9H), 1.32 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 151.7 (2C), 149.5, 135.4, 130.4, 124.3, 124.2, 122.4, 118.8, 116.4, 115.1, 83.3, 82.9 (2C), 58.1, 52.3, 28.1 (3C), 27.6 (6C), 25.5; HRMS (ESI) *m/z* calcd for $C_{27}H_{38}N_2O_8Na$ $(M + Na)^+$ 541.2526; found 541.2511.



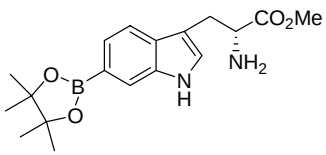
Compound 10. A solution of iodide (2.45 g, 3.80 mmol), bis(pinacolato)diboron (1.06 g, 4.18 mmol), and KOAc (1.12 g, 11.4 mmol) in DMSO (30 mL) was degassed for 20 min.

$PdCl_2(dppf)$**.**CH_2Cl_2 (155 mg, 0.19 mmol) was added to the reaction and the resulting mixture



was stirred at 80 ºC for 3 h. After being cooled to room temperature, the reaction was diluted with EtOAc (40 mL) and 1% HCl (20 mL). The aqueous layers were extracted with EtOAc (40 mL), and the combined organic phases were washed with H_2O and brine, dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, 10-15% EtOAc in heptane, gradient elution) to provide the desired product **10** (2.38 g, 97%). $[\alpha]_D^{23}$ +66.4 (*c* 1.00, $CHCl_3$); IR (neat) 2978, 1792, 1736, 1698, 1481, 1429, 1368, 1354, 1275, 1250, 1145, 1136, 1084 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.42 (s, 1H), 5.20 (dd, *J* = 4.9, 10.1 Hz, 1H), 3.76 (s, 3H), 3.52 (dd, *J* = 4.9, 15.0 Hz, 1H), 3.35 (dd, *J* = 10.1, 15.0 Hz, 1H), 1.65 (s, 9H), 1.34 (s, 12H), 1.33 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 151.7 (2C), 149.4, 135.2, 132.9, 128.5, 125.4, 121.7, 118.2, 116.5, 83.6 (2C), 83.3, 83.0 (2C), 58.2, 52.3, 28.1 (3C), 27.7 (6C), 25.5, 24.9 (4C); HRMS (ESI) *m/z* calcd for $C_{33}H_{49}N_2O_{10}BNa$ $(M + Na)^+$ 667.3378; found 667.3387.

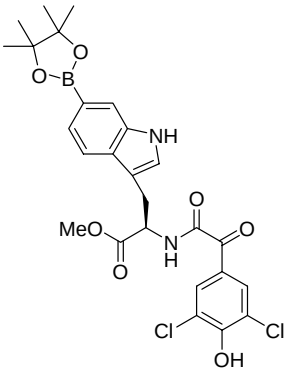
Compound 12. To a solution of boronate **10** (2.38 g, 3.7 mmol) in $CHCl_3$ (18 mL) was added TMSI (4.03 mL, 29.6 mmol) at room temperature. After the reaction was stirred at room temperature for 2 h, MeOH (20 mL) was added to the reaction and the resulting mixture was



allowed to stir for 4 h. The volatiles were removed under reduced pressure and the resulting residue was dissolved in MeOH (20 mL) and the solution neutralized by the addition of triethylamine (10 mL). Volatiles were removed and the resulting residue was dissolved in EtOAc (100 mL), washed with a saturated solution of $NaHCO_3$, brine, dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the desired amine, which was directly used for next reaction. $[\alpha]_D^{23}$ -6.9 (*c* 0.50, $CHCl_3$); IR (neat) 3361, 2976, 2925, 1736, 1504, 1360, 1143 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.34 (br s, 1H), 7.86 (s, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 2.3 Hz, 1H), 3.83 (dd, *J* = 4.9, 7.5 Hz, 1H), 3.70 (s, 3H), 3.27 (dd, *J* = 4.9, 14.4 Hz, 1H), 3.06 (dd, *J* = 7.5, 14.4 Hz, 1H), 1.80 (s, 2H), 1.36 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 136.0, 129.9, 125.3, 124.5, 118.2, 118.0, 111.2, 83.6 (2C), 54.9, 52.0, 30.6, 24.9 (4C); HRMS (ESI) *m/z* calcd for $C_{18}H_{25}N_2O_4BNa$ $(M + Na)^+$ 367.1805; found 367.1780.

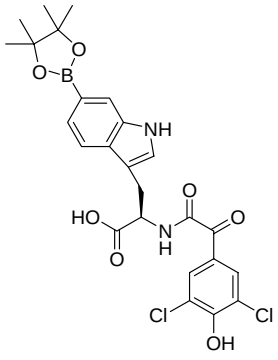
To a solution of the resulting amine and α-ketoacid **11** (952 mg, 4.07 mmol) in THF (30 mL)

was added EDC (1.07 g, 5.55 mmol), HOBt (550 mg, 4.07 mmol), and $NaHCO_3$ (311 mg, 3.7 mmol) at 0 ºC. The resulting solution was allowed to warm to room temperature and stirred for 14 h. The volatile was removed on rotary evaporation and the residue was partitioned by EtOAc and a saturated solution of $NaHCO_3$, extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by silica gel chromatography (silica gel, 2-10% MeOH in CH_2Cl_2, gradient elution) to afford **12** as a yellow solid (1.68 g, 81% overall yield for two steps). $[\alpha]_D^{23}$ -40.0 (*c* 1.00, $CHCl_3$); IR (neat) 3380, 2978, 1737, 1661, 1504, 1361, 1303, 1143 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.57 (br s, 1H), 8.19 (s, 2H), 7.84 (s, 1H), 7.62 (d, *J* = 8.3 Hz, 1H), 7.52 (s, 2H), 7.08 (s, 1H), 4.96 (dt, *J* = 5.8, 8.3 Hz, 1H), 3.71 (s, 3H), 3.39 (d, *J* = 5.8 Hz, 2H), 1.36 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.9, 171.3, 160.9, 153.2, 135.8, 131.5, 129.6, 126.2, 125.5, 124.5, 121.5, 118.4, 117.6, 109.4, 83.6, 52.9, 52.7, 27.6, 24.8; HRMS (ESI) *m/z* calcd for $C_{26}H_{27}BN_2O_7Cl_2Na$ $(M + Na)^+$ 583.1186; found 583.1208.



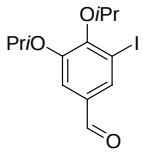
$[\alpha]_D^{23}$ +8.9 (*c* 0.50, MeOH); ^1H NMR (300 MHz, CD_3OD) δ 7.84 (s, 2H), 7.80 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.20 (s, 1H), 4.85 (1H in H_2O), 3.72 (s, 3H), 3.40 (dd, *J* = 5.4, 14.7 Hz, 1H), 3.25 (dd, *J* = 8.2, 14.7 Hz, 1H), 1.34 (s, 12H); ^{13}C NMR (75 MHz, CD_3OD) δ 186.1, 173.0, 165.0, 156.3, 137.5, 132.0, 131.1, 126.6, 126.4, 125.8, 123.3, 119.7, 118.5, 110.7, 84.7, 54.7, 53.0, 28.4, 25.2.

Compound 13. To a solution of **12** (1.7 g, 3.04 mmol) in THF/H_2O (3 : 1, 60 mL) was added LiOH (383 mg, 9.12 mmol) at 0 ºC. The resulting solution was allowed to warm to room temperature and stirred for 2 h. The resulting solution was acidified with 1% HCl to pH 3, and then extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under vacuum to give the desired carboxylic acid **13**, which proved to be of sufficient purity and was therefore used directly without further purification. ^1H NMR (300 MHz, acetone-d_6) δ 8.08 (s, 2H), 7.85 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.37 (s, 1H), 4.94 (dd, *J* = 4.8, 8.0 Hz, 1H), 3.53 (dd, *J* = 4.8, 14.8 Hz, 1H), 3.39 (dd, *J* = 8.0, 14.8 Hz, 1H), 1.32 (s, 12H); ^{13}C NMR (75 MHz, acetone-d_6,) δ 186.1, 173.5, 164.0, 155.9, 138.0, 133.0, 131.8, 128.2, 127.1, 126.6, 123.5, 120.3, 119.4, 111.8, 85.0, 54.8, 28.9, 26.2 (4C); HRMS (ESI) *m/z* calcd for $C_{25}H_{25}BN_2O_7Cl_2Na$ $(M + Na)^+$

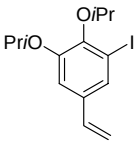


569.1029; found 569.1051.

Compound 14. To a solution of 3,4-dihydroxy-5-iodobenzaldehyde[3] (5.0 g, 18.9 mmol) in DMF (40 mL) was added K_2CO_3 (10.3 g, 75.8 mmol) and isopropyl bromide (7.1 mL, 75.8 mmol). After being heated at 55 ºC for 5 days, the reaction mixture was quenched with 3N HCl. The mixture was extracted with EtOAc (3 × 50 mL) and the combined organic phase was washed with H_2O (50 mL), brine (3 × 50 mL), dried (Na_2SO_4), and concentrated under vacuum. The residue was purified by flash column chromatography (silica gel, 2% EtOAc in heptanes) to afford the desired 3,4-diisopropoxy-5-iodobenzaldehyde (6.0 g, 91%). IR (neat) 2982, 2934, 2828, 1693, 1582, 1559, 1468, 1422, 1385, 1271, 1175, 1135, 1098, 1022, 925, 857 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.84 (d, J = 1.9 Hz, 1H), 7.37 (d, J = 1.9 Hz, 1H), 4.85 (hept, J = 6.0 Hz, 1H), 4.63 (hept, J = 6.0 Hz, 1H), 1.37 (d, J = 6.0 Hz, 6H), 1.36 (d, J = 6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.8, 153.7, 150.9, 134.8, 133.3, 113.6, 94.2, 76.7, 71.5, 23.0 (2C), 22.0 (2C); MS (EI) *m/z* 346 (M^+), 304, 263, 184; Anal. Calcd for $C_{13}H_{17}IO_3$: C, 44.84; H, 4.92; O, 13.79. Found: C, 44.67; H, 4.92; O, 13.64.



A suspension of methyltriphenylphosphonium bromide (12.6 g, 35.2 mmol) in dry THF (80 mL) at -20 ºC was treated with *n*-BuLi (1.6 M solution in hexanes, 22.0 mL, 35.2 mmol) dropwise over 15 min and the resulting solution was stirred for 30 min. To this reaction mixture was added a solution of aldehyde (8.16 g, 23.4 mmol) in THF (40 mL) over 5 min and the resulting orange suspension was warmed to room temperature, stirred for 2.5 h, quenched by the addition of H_2O (40 mL). The mixture was extracted with EtOAc (3 × 100 mL) and the combined organic phase was washed with H_2O (50 mL), brine (50 mL), dried (Na_2SO_4), and concentrated under vacuum. The residue was purified by flash column chromatography (silica gel, 0.25-0.5% ether in heptane) to afford **14** (6.81 g, 84%). IR (neat) 2974, 2929, 1585, 1544, 1469, 1411, 1381, 1371, 1264, 1229, 1174, 1136, 1100, 986, 928, 906, 854, 840 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 1.9 Hz, 1H), 6.83 (d, J = 1.9 Hz, 1H), 6.46 (dd, J = 10.9, 17.3 Hz, 1H), 5.53 (d, J = 17.3 Hz, 1H), 5.11 (d, J = 10.9 Hz, 1H), 4.59 (hept, J = 6.0 Hz, 1H), 4.47 (hept, J = 6.0 Hz, 1H), 1.26 (d, J = 6.0

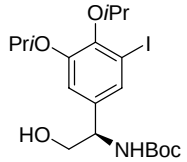


3. (a) Shiba, T.; Cahnmann, H. J.; Matsuura, T.; Nishinaga, A.; Sakamoto, H. *J. Org. Chem.* **1964**, *29*, 3061-3063. (b) Nishinaga, A.; Matsuura, T.; *J. Org. Chem.* **1964**, *29*, 1812-1817. (c) Anhoury, M.-L.; Crooy, P.; De Neys, R.; Eliaers, J. *J. Chem. Soc., Perkin Trans 1*. **1974**, 1015-1017.

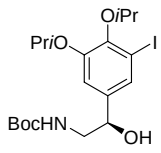
Hz, 6H), 1.25 (d, J = 6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 135.2, 133.6, 129.3, 128.5, 114.3, 113.8, 94.7, 75.8, 71.4, 22.8 (2C), 22.1 (2C); HRMS (ESI) *m/z* calcd for $C_{14}H_{19}IO_2Na$ $(M + Na)^+$ 369.0328; found 369.0313.

Compounds 15 and 16. A solution of *tert*-butyl carbamate (10.72 g, 91.5 mmol, 3.05 eq) in *n*-PrOH (120 mL) was sequentially treated with NaOH (3.66 g, 91.5 mmol in 225 mL water) and *t*-BuOCl (10.5 mL, 9.9 g, 91.5 mmol). After 5 min of stirring, the solution was cooled to 0 ºC and a solution of $(DHQD)_2PHAL$ (1.44 g, 1.8 mmol, 6 mol % dissolved in 120 mL of *n*-PrOH) was added; the reaction mixture should be homogeneous at this point. A solution of styrene (10.38 g, 30.0 mmol dissolved in 210 mL of *n*-PrOH) was then added followed by $K_2OsO_2(OH)_4$ (441 mg, 1.2 mmol, 4 mol %). The reaction mixture was stirred for 1 h at 0 ºC, the light green solution turned light yellow, and the reaction was quenched with saturated aqueous sodium sulfite (300 mL). *n*-PrOH (about 400 mL) was removed by rotary evaporation and the resulting solution was extracted with ethyl acetate (2 × 200 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. Flash column chromatography of the residue (silica gel, 10-30% EtOAc in heptane, gradient elution) afforded **15** (4.74 g, 33%) and **16** (8.2 g, 49%).

Compound 15. %ee = 76%: Chiral HPLC: chiralcell OD column, 5% *i*-PrOH/hexane, 1.0 mL min^{-1}, 230 nm, retention time = 6.54 (major enantiomer), retention time = 7.97 (minor enantiomer). $[\alpha]_D^{23}$ –23.4 (*c* 1.0, $CHCl_3$); IR (neat) 3359 (br s), 2975, 2358, 1692, 1469, 1367, 1271, 1168, 1104 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 7.26 (d, J = 1.9 Hz, 1H), 6.80 (d, J = 1.9 Hz, 1H), 5.24 (br s, 1H), 4.62 (hept, J = 6.0 Hz, 1H), 4.62 (m, 1H), 4.52 (hept, J = 6.0 Hz, 1H), 3.78 (m, 2H), 2.43 (br s, 1H), 1.42 (s, 9H), 1.33 (d, J = 6.0 Hz, 6H), 1.32 (d, J = 6.0 Hz, 3H), 1.31 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 150.6, 147.8, 136.5, 128.7, 114.9, 94.6, 80.1, 75.8, 71.3, 66.5, 55.9, 28.3 (3C), 22.8 (2C), 22.1, 22.0; HRMS (ESI) *m/z* calcd for $C_{19}H_{30}INO_5Na$ $(M + Na)^+$ 502.1066; found 502.1054.

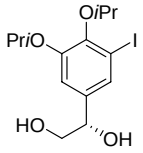


Compound 16. White solid. mp 127-128 ºC; $[\alpha]_D^{23}$ -16.8 (*c* 1.00, $CHCl_3$); IR (neat) 3399 (br s), 2975, 2930, 1691, 1512, 1468, 1419, 1367, 1270, 1171, 1105, 1008, 929, 855 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, J = 1.9 Hz, 1H), 6.87 (d, J = 1.9 Hz, 1H), 4.98 (br s, 1H), 4.69 (m, 1H), 4.63 (hept, J = 6.4 Hz, 1H), 4.54 (hept, J = 6.0 Hz, 1H), 3.43 (m, 1H), 3.39 (br s, 1H), 3.19 (m, 1H), 1.44 (s, 9H), 1.33 (d, J = 6.4 Hz, 6H), 1.32 (d, J = 6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 150.5, 147.5,



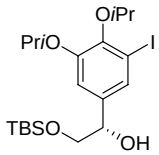
138.8, 128.2, 113.7, 94.3, 80.0, 75.8, 73.0, 71.1, 48.3, 28.3 (3C), 22.8 (2C), 22.1, 22.0; HRMS (ESI) *m/z* calcd for $C_{19}H_{30}INO_5Na$ $(M + Na)^+$ 502.1066; found 502.1068.

Compound 17. To a stirred suspension of AD-mix-α (16.2 g, 1.4 gmmol^{-1}) in *t*-BuOH/H_2O (1:1, 116 mL) was added styrene (4.0 g, 11.56 mmol) at 25 ºC. The reaction mixture was stirred at ambient temperature for 6 h before sodium sulfite (17.3 g, 1.5 gmmol^{-1}) was added. The resulting mixture was stirred for 0.5 h and then it was extracted with EtOAc (3 × 80 mL). The combined organic phases were washed with H_2O (50 mL), brine (50 mL), dried (Na_2SO_4), and concentrated under vacuum. Flash column chromatography of the residue (silica gel, 25-40% EtOAc in hexanes, gradient elution) afforded **17** (4.3 g, 95% ee, 98%).



Chiral HPLC: chiralcell OD-H column (0.46 × 25 cm, 3% EtOH/hexane, 1.0 mL min^{-1}). Retention time = 25.04 (major enantiomer). Retention time = 21.69 (minor enantiomer). $[\alpha]_D^{23}$ +27.5 (*c* 1.00, $CHCl_3$); IR (neat) 3380 (br s), 2974, 2929, 1559, 1468, 1417, 1382, 1268, 1135, 1104, 1004, 928, 854 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 1.9 Hz, 1H), 6.85 (d, *J* = 1.9 Hz, 1H), 4.66 (m, 1H), 4.62 (hept, *J* = 6.2 Hz, 1H), 4.54 (hept, *J* = 6.0 Hz, 1H), 3.71-3.55 (m, 2H), 3.10 (br s, 1H), 2.57 (br s, 1H), 1.33 (d, *J* = 6.2 Hz, 6H), 1.32 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 147.6, 137.6, 128.4, 113.9, 94.3, 75.9, 73.6, 71.2, 67.9, 22.8 (2C), 22.0 (2C); HRMS (ESI) *m/z* calcd for $C_{14}H_{21}IO_4Na$ $(M + Na)^+$ 403.0382; found 403.0391. Anal. Calcd for $C_{14}H_{21}IO_4$: C, 44.22; H, 5.57; O, 16.83. Found: C, 44.13; H, 5.62; O, 16.88.

Compound 18. To a solution of diol **17** (4.70 g, 12.4 mmol) in DMF (40 mL) at 0 ºC were added sequentially TBSCl (2.25 g, 14.8 mmol) and imidazole (1.26 g, 18.6 mmol). The resulting solution was stirred at that temperature for 5 h before H_2O (60 mL) was added. The reaction mixture was extracted with EtOAc (3 × 50 mL) and the combined organic phases were washed with H_2O (80 mL), brine (4 × 30 mL), dried (Na_2SO_4), and concentrated under vacuum. Flash column chromatography (silica gel, 3-10% EtOAc in hexanes, gradient elution) afforded desired product (6.0 g, 98%). $[\alpha]_D^{23}$ +20.8 (*c* 1.00, $CHCl_3$); IR (neat) 2928, 2856, 1561, 1469, 1418, 1383, 1267, 1105, 1006, 930, 836 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 2.1 Hz, 1H), 6.91 (d, *J* = 2.1 Hz, 1H), 4.65 (hept, *J* = 6.2 Hz, 1H), 4.61 (m, 1H), 4.55 (hept, *J* = 6.0 Hz, 1H), 3.73 (dd, *J* = 3.8, 10.2 Hz, 1H), 3.51 (dd, *J* = 8.3, 10.2 Hz, 1H), 2.92 (d, *J* = 2.6 Hz, 1H), 1.33 (d, *J* = 6.2 Hz, 6H),

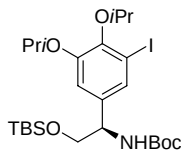


1.32 (d, *J* = 6.0 Hz, 6H), 0.90 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 147.8, 137.3, 128.8, 114.5, 94.2, 75.7, 73.2, 71.3, 68.7, 25.8 (3C), 22.8 (2C), 22.1 (2C), 18.3, -5.4 (2C); HRMS (ESI) *m/z* calcd for $C_{20}H_{35}ISiO_4Na$ $(M + Na)^+$ 517.1247; found 517.1258. Anal. Calcd for $C_{13}H_{17}IO_3$: C, 48.58; H, 7.13. Found: C, 48.66; H, 7.11.

To a solution of above alcohol (5.93 g, 12.0 mmol) in THF (50 mL) at 0 ºC were added sequentially triphenylphosphane (7.86 g, 30 mmol), diisopropyl azodicarboxylate (DIAD, 6.09 mL, 30 mmol), and diphenylphosphoryl azide (DPPA, 6.66 mL, 30 mmol). The reaction mixture was stirred at 0 ºC for 2 h and then it was concentrated under vacuum. Flash column chromatography of the residue (silica gel, 1% EtOAc in hexanes, gradient elution) afforded azide product (4.60 g, 79%). $[\alpha]_D^{23}$ -19.6 (*c* 1.00, $CHCl_3$); IR (neat) 2975, 2929, 2857, 2100, 1559, 1469, 1418, 1382, 1258, 1104, 1004, 930, 836 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 2.1 Hz, 1H), 6.82 (d, *J* = 2.1 Hz, 1H), 4.66 (hept, *J* = 6.2 Hz, 1H), 4.54 (hept, *J* = 6.0 Hz, 1H), 4.45 (dd, *J* = 4.7, 7.7 Hz, 1H), 3.79 (dd, *J* = 4.7, 10.6 Hz, 1H), 3.73 (dd, *J* = 7.7, 10.6 Hz, 1H), 1.34 (d, *J* = 6.2 Hz, 6H), 1.33 (d, *J* = 6.0 Hz, 6H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 148.2, 133.9, 129.6, 115.1, 94.3, 75.8, 71.4, 68.0, 66.1, 25.8 (3C), 22.8 (2C), 22.1, 22.0, 18.2, -5.5, -5.6; HRMS (ESI) *m/z* calcd for $C_{20}H_{34}IN_3O_3SiNa$ $(M + Na)^+$ 542.1322; found 542.1322.

To a solution of above azide (4.60 g, 8.86 mmol) in THF (50 mL) was added triphenylphosphane (6.97 g, 26.6 mmol) and H_2O (1.6 mL, 88.6 mmol) at 25 ºC. The resulting solution was heated to 60 ºC for 3 h before it was cooled to 25 ºC. The solvent was removed under vacuum and the residue was purified by flash column chromatography (silica gel, 10-30% EtOAc in hexanes, gradient elution) to afford amine **18** (3.3 g, 76%). $[\alpha]_D^{23}$ -12.3 (*c* 1.00, $CHCl_3$); IR (neat) 2928, 2856, 1558, 1469, 1416, 1381, 1258, 1104, 1004, 932, 835 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 1.9 Hz, 1H), 6.91 (d, *J* = 1.9 Hz, 1H), 4.63 (hept, *J* = 6.2 Hz, 1H), 4.54 (hept, *J* = 6.0 Hz, 1H), 3.94 (dd, *J* = 4.1, 7.9 Hz, 1H), 3.66 (dd, *J* = 4.1, 9.8 Hz, 1H), 3.47 (dd, *J* = 7.9, 9.8 Hz, 1H), 1.68 (br s, 2H), 1.33 (d, *J* = 6.2 Hz, 6H), 1.31 (d, *J* = 6.0 Hz, 6H), 0.88 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.4, 147.4, 139.9, 129.5, 115.3, 94.2, 75.6, 71.3, 69.3, 56.7, 25.9 (3C), 22.8 (2C), 22.1 (2C), 18.2, -5.4 (2C); HRMS (ESI) *m/z* calcd for $C_{20}H_{37}INO_3Si$ $(M + H)^+$ 494.1587; found 494.1599. Anal. Calcd for $C_{20}H_{36}INO_3Si$: C, 48.68; H, 7.35; N, 2.84. Found: C, 48.65; H, 7.57; O, 2.84.

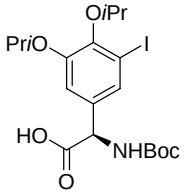
Compound 15. To a solution of amine **18** (3.27 g, 6.6 mmol) in CH_2Cl_2 (50 mL) at room temperature were added Et_3N (2.8 mL, 19.8 mmol) and Boc_2O (2.2 g, 9.9 mmol). The resulting solution was stirred for overnight before it was concentrated under vacuum. The residue was purified by flash column chromatography (silica gel, 3-5% EtOAc in hexanes, gradient elution) to afford Boc derivative (3.83 g, 97%). $[\alpha]_D^{23}$ -19.4 (*c* 1.00, $CHCl_3$); IR (neat) 2975, 2929, 1703, 1470, 1366, 1257, 1171, 1105, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 2.1 Hz, 1H), 6.80 (d, *J* = 2.1 Hz, 1H), 5.21 (d, *J* = 6.0 Hz, 1H), 4.62 (hept, *J* = 6.0 Hz, 1H), 4.58 (m, 1H), 4.50 (hept, *J* = 6.0 Hz, 1H), 3.83 (dd, *J* = 4.1, 10.2 Hz, 1H), 3.68 (dd, *J* = 3.6, 10.2 Hz, 1H), 1.42 (s, 9H), 1.33 (d, *J* = 6.0 Hz, 3H), 1.32 (d, *J* = 6.0 Hz, 3H), 1.31 (d, *J* = 6.0 Hz, 3H), 1.30 (d, *J* = 6.0 Hz, 3H), 0.83 (s, 9H), -0.06 (s, 3H), -0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 150.3, 147.4, 137.8, 129.4, 115.5, 94.2, 79.7, 75.6, 71.4, 66.4, 55.1, 28.3 (3C), 25.8 (3C), 22.7 (2C), 22.2, 22.0, 18.2, -5.6 (2C); HRMS (ESI) *m/z* calcd for $C_{25}H_{44}INO_5SiNa$ $(M + Na)^+$ 616.1931; found 616.1944.



To a solution of above product (3.79 g, 6.38 mmol) in THF (50 mL) at 0 ºC was added *n*Bu_4NF (1.0 M solution in THF, 7.70 mL, 7.70 mmol). The resulting solution was stirred at that temperature for 2 h before it was quenched by the addition of saturated aqueous NH_4Cl (10 mL). The mixture was extracted with EtOAc (3 × 50 mL), and the combined organic extracts were washed with H_2O (40 mL), brine (40 mL), dried (Na_2SO_4), and concentrated under vacuum. The residue was purified by flash column chromatography (silica gel, 20-25% EtOAc in hexanes, gradient elution) to afford alcohol **15** (2.2 g, 72%).

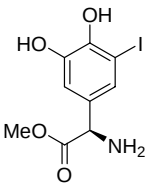
%ee = 92%: Chiral HPLC: chiralcell OD column, 5% *i*-PrOH/hexane, 1.0 mL min^{-1}, 230 nm, retention time = 6.54 (major enantiomer), retention time = 7.92 (minor enantiomer). $[\alpha]_D^{23}$ -25.6 (*c* 1.00, $CHCl_3$).

Compound 19. To a solution of alcohol **15** (2.4 g, 5.0 mmol) in acetone (25 mL) at 0 ºC was added 5% aqueous $NaHCO_3$ (25 mL). The resulting suspension was stirred vigorously before the addition of KBr (60 mg, 0.5 mmol) and TEMPO (860 mg, 5.5 mmol). Sodium hypochlorite (5% aqueous solution, 20 mL) was added dropwise over 0.5 h and the resulting mixture was stirred at 0 ºC for 1 h before the addition of 1% HCl (50 mL) and EtOAc (50 mL). The aqueous phase was extracted with EtOAc (3 × 50 mL) and the combined organic extracts were washed with H_2O, brine, dried (Na_2SO_4), and concentrated under vacuum. Flash column chromatography of the residue

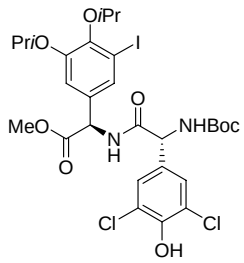


(silica gel, 1-10% MeOH in CH_2Cl_2, gradient elution) afforded acid **19** (1.6 g, 65%). mp 70-72 ºC; $[\alpha]_D^{23}$ -81.5 (*c* 1.00, $CHCl_3$); IR (neat) 2976, 1721, 1658, 1470, 1420, 1384, 1369, 1270, 1160, 1104, 1055, 1012, 929, 855 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.60 (br s, 1H), 7.96 (s, 1H), 7.41 (s, 1H), 6.93 (s, 1H), 4.99 (d, *J* = 4.5 Hz, 1H), 4.65 (hept, *J* = 6.0 Hz, 1H), 4.53 (hept, *J* = 6.0 Hz, 1H), 1.33 (d, *J* = 6.0 Hz, 6H), 1.31 (d, *J* = 6.0 Hz, 3H), 1.28 (d, *J* = 6.0 Hz, 3H), 1.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 157.0, 150.5, 148.0, 134.9, 130.0, 114.6, 94.0, 82.1, 75.7, 71.3, 57.9, 28.0 (3C), 22.8 (2C), 21.9 (2C); HRMS (ESI) *m/z* calcd for $C_{19}H_{28}INO_6Na$ $(M + Na)^+$ 516.0859; found 516.0873. Anal. Calcd for $C_{19}H_{28}INO_6$: C, 46.26; H, 5.72; N, 2.84; O, 19.46. Found: C, 46.46; H, 5.57; N, 2.78; O, 19.58.

Compound 20. To a solution of compound **19** (986 mg, 2.0 mml) in MeOH (10 mL) was added $SOCl_2$ (3 mL). After being stirred for 12 h, the volatiles were removed under vacuum to provide compound **20**, which was directly used for next reaction.

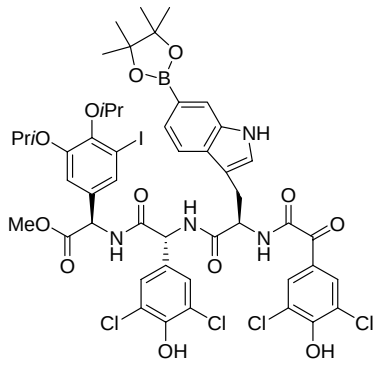


Compound 22. To a solution of the amine **20** (244 mg, 0.6 mmol) and α-amido acid **21** (221 mg, 0.66 mmol) in THF/CH_2Cl_2 (2/1, 3 mL) at 0 ºC were added 2,5-lutidine (209 µL, 1.8 mmol) and HATU (342 mg, 0.9 mmol). The resulting reaction mixture was stirred at 5 ºC for 12 h. After this time, CH_2Cl_2 was added and the organic phase was washed with a solution of 1N HCl (2 × 5 mL) and brine, dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash column chromatography (silica gel, 50% EtOAc in hexane) to afford compound **22** (348 mg, 80%). mp 119-120 ºC; $[\alpha]_D^{23}$ -62 (*c* 0.20, MeOH); IR (neat) 3250, 1720, 1686, 1644, 1426, 1281, 1165 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.35 (s, 2H), 7.30 (s, 1H), 7.00 (s, 1H), 5.39 (s, 1H), 5.17 (s, 1H), 4.69 (hept, *J* = 6.2 Hz, 1H), 4.58 (hept, *J* = 6.0 Hz, 1H), 3.68 (s, 3H), 1.42 (s, 9H), 1.31 (d, *J* = 6.2 Hz, 3H), 1.30 (d, *J* = 6.2 Hz, 3H), 1.29 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 171.9, 171.8, 157.2, 151.9, 150.5, 149.4, 134.2, 131.6, 130.9, 128.7, 123.3, 116.3, 95.0, 81.1, 76.9, 72.4, 68.8, 57.2, 53.3, 28.7 (3C), 23.2 (2C), 22.4, 22.3; HRMS (MALDI) *m/z* calcd for $C_{28}H_{35}N_2O_8Cl_2INa$ $(M + Na)^+$ 747.1209; found 747.1219.

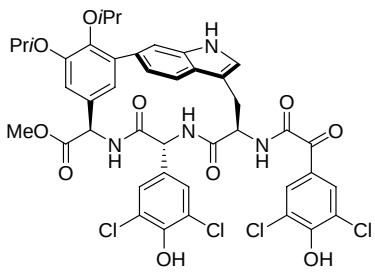


Compound 23. A solution of above dipeptide **22** (348 mg, 0.48 mmol) and TFA (9 mL) in anhydrous CH_2Cl_2 (18 mL) was stirred at 0 ºC for 1 h, after which volatiles were removed

under vacumm. To this residue was added EtOAc and drops of saturated solution of $NaHCO_3$ (with stirring) until the solution pH 7-8. The aqueous solution was washed with EtOAc (3 times) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum to afford the desired neutral amine. This material was used for next reaction without further purification. To a solution of the amine and α-amido acid (284 mg, 0.52 mmol) in THF/CH_2Cl_2 (2/1, 15 mL) at 0 ºC were added 2,5-lutidine (226 µL, 1.9 mmol) and HATU (273 mg, 0.72 mmol). The resulting reaction mixture was stirred at 5 ºC for 12 h. After this time, CH_2Cl_2 was added and the organic phase was washed with a solution of 1N HCl (2 × 5 mL) and brine, dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash column chromatography to afford compound **23** (430 mg, 78%). mp 168-170 ºC; $[\alpha]_D^{23}$ -28 (*c* 0.60, MeOH); IR (neat) 3300, 1745, 1648, 1490, 1360, 1270, 1140 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.83 (s, 2H), 7.79 (s, 1H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.37 (d, *J* = 1.8 Hz, 1H), 7.31 (s, 2H), 7.22 (s, 1H), 7.01 (d, *J* = 1.8 Hz, 1H), 5.43 (s, 1H), 5.34 (s, 1H), 4.84 (m, 1H in water), 4.69 (hept, *J* = 6.2 Hz, 1H), 4.59 (hept, *J* = 5.9 Hz, 1H), 3.70 (s, 3H), 3.30 (m, 1H in CD_3OD), 3.21 (dd, *J* = 8.2, 14.8 Hz, 1H), 1.35 (s, 12H), 1.30-1.28 (m, 12H); ^{13}C NMR (75 MHz, CD_3OD) δ 185.6, 173.0, 171.9, 171.2, 167.5, 155.9, 152.0, 150.6, 149.5, 149.0, 139.7, 137.7, 134.0, 132.3, 131.3, 131.0, 130.7, 129.0, 126.7, 125.8, 124.7, 123.4, 122.3, 119.7, 118.8, 116.5, 110.8, 94.9, 84.7 (2C), 77.0, 72.5, 57.5, 56.9, 55.3, 53.3, 28.9, 25.3 (3C), 25.1, 23.2 (2C), 22.4, 22.2; HRMS (MALDI) *m/z* calcd for $C_{48}H_{50}N_4O_{12}BCl_4INa$ $(M + Na)^+$ 1175.1209; found 1175.1213.

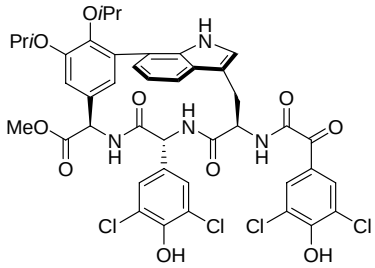


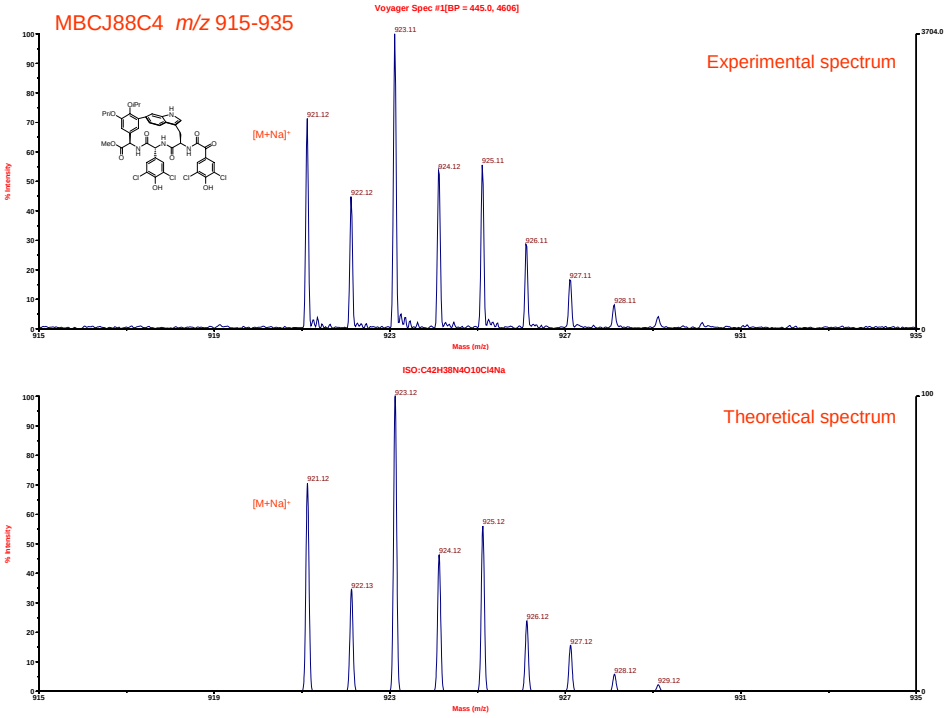
Compound 3. A solution of tripeptide **23** (46 mg, 0.04 mmol), and K_2CO_3 (55 mg, 0.4 mmol) in 1,4-dioxane/H_2O (40:3, 86 mL) was degassed for 30 min. $PdCl_2(dppf).CH_2Cl_2$ (32 mg, 0.04 mmol) was added to the solution and the resulting mixture was stirred at 90 ºC for 1 h. After being cooled to room temperature, 1% HCl was added to pH 6 and the solvent was passed through celite to remove palladium. The filtrate was evaporated and the residue was partitioned with EtOAc and 1% HCl, and the organic phase was washed with H_2O and brine, dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue



was purified by flash column chromatography (silica gel, from 4:5:1 heptane:EtOAc:MeOH to 10% MeOH in CH_2Cl_2, gradient elution) to provide the desired product **3** (24 mg, 66%). ^{1}H NMR (500 MHz, CD_3OD) δ 7.90 (s, 2H), 7.60 (d, J = 8.2 Hz, 1H), 7.29 (s, 1H), 7.25 (s, 2H), 7.23 (s, 1H), 7.06 (d, J = 8.2 Hz, 1H), 6.80 (d, J = 2.0 Hz, 1H), 5.71 (d, J = 2.0 Hz, 1H), 5.57 (s, 1H), 5.35 (s, 1H), 4.58 (m, 2H), 4.20 (dd, J = 3.0, 10.7 Hz, 1H), 3.81 (s, 3H), 3.62 (dd, J = 10.7, 14.0 Hz, 1H), 2.98 (dd, J = 3.0, 14.0 Hz, 1H), 1.38 (d, J = 6.1 Hz, 3H), 1.35 (d, J = 6.1 Hz, 3H), 1.32 (t, J = 6.1 Hz, 6H); HRMS (MALDI) *m/z* calcd for $C_{42}H_{38}N_4O_{10}Cl_4Na$ $(M + Na)^+$ 921.1240; found 921.1256. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.79 (s, 1H), 8.51 (d, J = 9.0 Hz, 1H), 7.98 (d, J = 8.9 Hz, 1H), 7.92 (br s, 2H), 7.72 (d, J = 7.8 Hz, 1H), 7.52 (d, J = 8.3 Hz, 1H), 7.21 (s, 2H), 6.98 (d, J = 8.3 Hz, 1H), 6.89 (s, 2H), 6.70 (s, 1H), 5.62 (s, 1H), 5.47 (d, J = 9.0 Hz, 1H), 5.22 (d, J = 8.9 Hz, 1H), 4.64 (hept, J = 6.1 Hz, 1H), 4.53 (hept, J = 6.1 Hz, 1H), 4.09 (t, J = 8.7 Hz, 1H), 3.73 (s, 3H), 3.31 (m, 1H in water), 2.88 (d, J = 11.5 Hz, 1H), 1.33 (d, J = 6.1 Hz, 3H), 1.28 (d, J = 6.1 Hz, 6H), 1.27 (d, J = 6.1 Hz, 3H).

Compound 4. Compound **3** (4 mg, 4.4 × 10^{-3} mmol) was dissolved in TFA (500 µL) and allowed to stir at 60 ºC for 30 min. TFA was removed under vacuum and the resulted product was directly analysed by NMR. IR (neat) 3390, 3280, 1733, 1660, 1634, 1558, 1489, 1369, 1212 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 9.42 (s, 1H), 8.24 (s, 2H), 8.08 (d, J = 7.1 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.71 (s, 1H), 7.45 (s, 2H), 7.40 (d, J = 7.6 Hz, 1H), 7.06 (d, J = 6.4 Hz, 1H), 7.02 (t, J = 7.4 Hz, 1H), 7.02 (s, 1H), 5.90 (d, J = 2.0 Hz, 1H), 5.49 (m, 1H), 5.40 (d, J = 8.4 Hz, 1H), 5.14 (m, 1H), 4.68-4.61 (m, 2H), 3.79 (s, 3H), 3.38 (dd, J = 6.3, 14.0 Hz, 1H), 3.20 (dd, J = 12.0, 14.0 Hz, 1H), 1.39 (t, J = 6.0 Hz, 6H), 1.32 (d, J = 6.1 Hz, 3H), 1.18 (d, J = 6.1 Hz, 3H).




MBCJ88C4 m/z 915-935
Voyager Spec #1[BP = 445.0, 4606]
Experimental spectrum
[M+Na]+
923.11
921.12
924.12
925.11
922.12
926.11
927.11
928.11
3704.0
% Intensity
Mass (m/z)
ISO:C42H38N4O10Cl4Na
Theoretical spectrum
[M+Na]+
923.12
921.12
925.12
924.12
922.13
926.12
927.12
928.12
929.12
100