Highly Efficient Enantiospecific Synthesis of Imidazoline-containing Amino Acids Using Bis(triphenyl)oxodiphosphonium Trifluoromethanesulfonate

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General Methods. Unless stated otherwise, all reactions were carried out in flame-dried glassware under a dry argon atmosphere. All solvents were purchased from Fisher and were dried prior to use. ^{1}H NMR spectra were recorded at 600 MHz on a Bruker DRX spectrometer. ^{13}C NMR spectra were recorded at 150 MHz on a Bruker DRX-600 spectrometer. The chemical shift assignments for major diastereomers, not for minor diastereomers, are reported. Flash chromatography was performed on silica gel 60 (230-400 mesh, E. Merck no. 9385).

Procedure A: Synthesis of *N*-acylated diaminopropionic ester 1a (1a-6a). A solution of *N*-α-Fmoc-*N*-β-4-methyltrityl-L-diaminopropionic acid (0.583 g, 1mmol) in MeOH:Benzene (5 mL; 1:4) was treated with $TMSCHN_2$ (0.6 mL of 2.0 M solution in hexanes, 1.2 mmol) at 25 °C and the reaction progress was monitored by TLC (usually complete after 0.5 h). The resulting mixture was concentrated *in vacuo* and the crude reaction mixture was used in the next step without purification.

Diethylamine (6 mL) was added to a solution of crude methyl ester in CH_3CN (6 mL) and the resulting mixture was stirred at 25 °C for 30 min to ensure complete removal of the Fmoc protecting group. After concentration in *vacuo*, the mixture was azeotroped to dryness with CH_3CN (2 x 6 mL) and the residue was dissolved in CH_2Cl_2 (10 mL). To this solution, benzoyl chloride (0.128 mL, 1.1 mmol) and Et_3N (0.278 mL, 2.1 mmol) were added sequentially. The resulting mixture was stirred at 25 °C for 8 h. The reaction mixture was diluted with CH_2Cl_2, washed with 10% $NaHCO_3$ (aq), water, and brine, the organic layer was dried over anhydrous Na_2SO_4 and then filtered and concentrated under reduced pressure to yield the crude product. Purification by flash chromatography

(EtOAc/hexanes = 1/3) gave *N*-α-benzoyl-*N*-β-4-methyltrityl-L-diaminopropionic ester as a white foam (388 mg, 81%): ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 2.29 (s, 3H), 2.63 (dd, *J* = 4.8, 12.3 Hz, 1H), 2.73 (dd, *J* = 4.8, 12.3 Hz, 1H), 3.78 (s, 3H), 4.90 (dt, *J* = 4.8, 7.5 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 7.15-7.18 (m, 2H), 7.23-7.25 (m, 4H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.42-7.47 (m, 6H), 7.51-7.54 (m, 1H), 7.82 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.9, 45.3, 52.5, 53.0, 70.0, 126.4, 127.1, 127.9, 128.4, 128.6, 128.7, 131.8, 133.8, 136.1, 142.3, 145.5, 167.0, 172.2.

To a solution of *N*-α-benzoyl-*N*-β-4-methyltrityl-L-diaminopropionic ester (388 mg, 0.81 mmol) in CH_2Cl_2 (15 mL) was added TFA (0.5 mL) and PhSH (0.083 mL, 0.81 mmol). The reaction mixture was stirred at 25 °C for 10 min. After concentration *in vacuo*, the mixture was azeotroped to dryness with toluene (2 x 10 mL) and the residue was dissolved in CH_2Cl_2 (10 mL). To this solution, *p*-toluenesulfonyl chloride (172 mg, 0.9 mmol), Et_3N (0.397 mL, 3.0 mmol) and catalytic amount of DMAP were added sequentially. The resulting mixture was stirred at 25 °C for 8 h. The reaction mixture was diluted with CH_2Cl_2, washed with 10% $NaHCO_3$ (aq), water, and brine, the organic layer was dried over anhydrous Na_2SO_4 and then filtered and concentrated under reduced pressure to yield the crude product. Purification by flash chromatography (EtOAc/hexanes = 1/1) gave **1a** as a white foam (259 mg, 85%): $[\alpha]_D^{25}$ = -39.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 2.36 (s, 3H), 3.40-3.51 (m, 2H), 3.69 (s, 3H), 4.86 (ddd, *J* = 3.9, 4.0, 7.5 Hz, 1H), 6.24 (dd, *J* = 6.6, 7.0 Hz, 1H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.36 (dd, *J* = 7.5, 7.9 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.69 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.4, 44.2, 52.8 (2 C), 126.8, 126.9, 127.3, 128.3, 129.7, 131.7, 133.1, 136.4, 143.5,

167.5, 170.4; HRMS (MALDI-FTMS) calcd. for $C_{18}H_{20}N_2O_5S$ ($M+Na^+$) 399.0985, found 399.0981.

Compound 2a: $[\alpha]_D^{25}$ = +38.8 (*c* 1.1, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 2.36 (s, 3H), 3.40-3.51 (m, 2H), 3.69 (s, 3H), 4.86 (ddd, *J* = 3.9, 4.0, 7.5 Hz, 1H), 6.24 (dd, *J* = 6.6, 7.0 Hz, 1H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.36 (dd, *J* = 7.5, 7.9 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.69 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.4, 44.2, 52.8 (2 C), 126.8, 126.9, 127.3, 128.3, 129.7, 131.7, 133.1, 136.4, 143.5, 167.5, 170.4; HRMS (MALDI-FTMS) calcd. for $C_{18}H_{20}N_2O_5S$ ($M+H^+$) 377.1166, found 377.1164.

Compound 3a: $[\alpha]_D^{25}$ = -43.4 (*c* 1.1, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 3.36 (s, 3H), 3.36 (s, 3H), 3.39-3.50 (m, 2H), 3.70 (s, 3H), 4.85 (dt, *J* = 4.0, 7.5 Hz, 1H), 6.19 (t, *J* = 6.6 Hz, 1H), 7.16 (d, *J* = 7.9 Hz, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.52 (d, *J* = 7.0 Hz, 1H), 7.68 (d, *J* = 7.9 Hz, 2H), 7.72 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.3, 21.4, 44.2, 52.8 (2 C), 126.8, 127.3, 129.0, 129.7, 130.2, 136.4, 142.2, 143.5, 167.5, 170.5; HRMS (MALDI-FTMS) calcd. for $C_{19}H_{22}N_2O_5S$ ($M+Na^+$) 413.1142, found 413.1142.

Compound 4a: $[\alpha]_D^{25}$ = -43.4 (*c* 1.4, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 2.36 (s, 3H), 3.38-3.51 (m, 2H), 3.70 (s, 3H), 3.80 (s, 3H), 4.85 (dt, *J* = 4.0, 7.5 Hz, 1H), 6.27 (t, *J* = 6.6 Hz, 1H), 6.84 (d, *J* = 7.9 Hz, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.69 (d, *J* = 7.0 Hz, 2H), 7.79 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR (150 MHz,

$CDCl_3$) δ 21.3, 44.2, 52.7, 52.8, 55.2, 113.5, 125.3, 126.8, 129.1, 129.2, 129.6, 129.7, 136.4, 143.5, 162.3, 167.0, 170.5; HRMS (MALDI-FTMS) calcd. for $C_{19}H_{22}N_2O_6S$ ($M+H^+$) 407.1271, found 407.1267.

Compound 5a: $[\alpha]_D^{25}$ = +12.9 (*c* 0.97, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 2.40 (s, 3H), 3.32 (dd, *J* = 4.4, 7.0 Hz, 2H), 3.62 (s, 2H), 3.72 (s, 3H), 4.68 (dt, *J* = 4.0, 7.9 Hz, 1H), 6.13 (m, 1H), 7.21-7.30 (m, 8H), 7.68 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.4, 42.8, 44.1, 52.4, 52.8, 126.7, 126.9, 128.5, 129.3, 129.7, 134.6, 136.6, 143.5, 170.5, 171.6; HRMS (MALDI-FTMS) calcd. for $C_{19}H_{22}N_2O_5S$ ($M+H^+$) 391.1322, found 391.1308.

Compound 6a: $[\alpha]_D^{25}$ = -33.7 (*c* 1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 2.38 (s, 3H), 3.43-3.54 (m, 2H), 3.77 (s, 3H), 4.90-4.93 (m, 1H), 6.19 (dd, *J* = 6.6, 7.0 Hz, 1H), 7.25 (d, *J* = 8.3 Hz, 2H), 7.50 (dd, *J* = 7.5, 7.9 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.72 (d, *J* = 8.3 Hz, 1H), 7.83 (d, *J* = 7.5 Hz, 1H), 8.07 (d, *J* = 7.9 Hz, 1H), 8.17 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.4, 44.1, 53.0 (2 C), 124.6, 124.7, 126.8, 128.2, 128.3, 129.0, 129.8, 130.5, 130.7, 131.0, 134.1, 136.3, 143.8, 166.2, 170.3; HRMS (MALDI-FTMS) calcd. for $C_{19}H_{19}F_3N_2O_5S$ ($M+H^+$) 445.1039, found 445.1040. HPLC (chiralcel OD-H column, 254 nm, 90/10 hexane/isopropanol to 70/30 hexane/isopropanol gradient over 240 min, flow = 1.0 mL/min) t_R = 80.1 (S), 83.4 (R) min.

Procedure B: Synthesis of diaminopropionic acid-based, fully protected dipeptides (7a-13a). To a solution of 3-(*N*-toluene-4-sulfonyl, *N-tert*-butoxycarbonyl)-2-trityl-

amino)-propionic acid methyl ester[1] (or benzyl ester) (5 mmol) in CH_2Cl_2 (10 mL) was added TFA (3 mL) and PhSH (1.027 mL, 10 mmol). The reaction mixture was stirred at 25 °C for 1 h. After concentration *in vacuo*, the mixture was azeotroped to dryness with toluene (2 x 10 mL) and the residue was dissolved in DMF (20 mL). DIEA was used to adjust the pH to 10 on wet pH paper . Then a solution of the desired protected amino acid (5.5 mmol), HBTU (2.085 g, 5.5 mmol), HOBt•H_2O (0.842 g, 5.5 mmol) and DIEA (1.92 mL, 11 mmol) in DMF (10 mL) was added. The resulting mixture was stirred for 8 h. The reaction mixture was diluted with EtOAc (150 mL), washed with water, 10% $NaHCO_3$ (aq), water, and brine, the organic layer was dried over anhydrous Na_2SO_4 and then filtered and concentrated under reduced pressure to yield the crude product. Purification by flash chromatography (EtOAc/hexanes = 1/1) gave the desired product as a white foam.

Compound 7a (96%): $[\alpha]_D^{25}$ = +7.0 (*c* 0.53, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 2.38 (s, 3H), 3.00 (dd, *J* = 8.3, 14.0 Hz, 1H), 3.17 (dd, *J* = 5.7, 14.0 Hz, 1H), 3.34 (br, 2H), 3.70 (s, 3H), 4.52 (m, 1H), 4.59 (dt, *J* = 4.4, 7.5 Hz, 1H), 4.95 (AB, J_{AB} = 12.3 Hz, 1H), 5.04 (AB, J_{AB} = 12.3 Hz, 1H), 5.57 (d, *J* = 7.5 Hz, 1H), 5.85 (m, 1H), 7.15-7.30 (m, 13H), 7.69 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5, 38.0, 43.8, 52.6, 52.9, 56.2, 67.0, 126.9 (2 C), 127.9, 128.0, 128.4, 128.5, 129.3, 129.7, 136.0, 136.2, 136.7, 143.5, 156.2, 169.9, 171.4; HRMS (MALDI-FTMS) calcd. for $C_{28}H_{31}N_3O_7S$ ($M+Na^+$) 576.1775, found 576.1776.

Compound 8a: $[\alpha]_D^{25}$ = +18.8 (*c* 0.26, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 2.41 (s, 3H), 3.04 (dd, *J* = 7.9, 13.6 Hz, 1H), 3.15 (dd, *J* = 6.1, 13.6 Hz, 1H), 3.23 (m, 1H), 3.33-3.34 (m, 1H), 3.70 (s, 3H), 4.51 (m, 1H), 4.59 (dt, *J* = 4.0, 7.5 Hz, 1H), 5.03 (AB, J_{AB} = 12.3 Hz, 1H), 5.07 (AB, J_{AB} = 12.3 Hz, 1H), 5.38 (dd, *J* = 6.1, 7.0 Hz, 1H), 5.52 (d, *J* = 6.6 Hz, 1H), 7.17-7.32 (m, 13H), 7.69 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5, 38.2, 43.8, 52.4, 53.0, 56.4, 67.2, 126.9, 127.1, 128.1, 128.2, 128.4, 128.7, 129.2, 129.8, 135.9, 136.3, 136.7, 143.7, 156.2, 170.0, 171.3; HRMS (MALDI-FTMS) calcd. for $C_{28}H_{31}N_3O_7S$ ($M+Na^+$) 576.1775, found 576.1792.

Compound 9a: $[\alpha]_D^{25}$ = +10.4 (*c* 0.28, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.94 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 7.0 Hz, 3H), 2.11-2.15 (m, 1H), 2.39 (s, 3H), 3.30-3.39 (m, 2H), 3.73 (s, 3H), 4.17 (m, 1H), 4.68 (m, 1H), 4.94 (AB, d, J_{AB} = 12.3 Hz, 1H), 5.07 (AB, d, J_{AB} = 12.3 Hz, 1H), 5.68 (m, 1H), 6.00 (br, 1H), 7.25-7.32 (m, 8H), 7.72 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.7, 19.1, 21.5, 31.3, 44.0, 52.5, 52.9, 60.3, 67.0, 127.0, 128.0, 128.1, 128.4, 129.7, 136.1, 136.6, 143.5, 156.7, 170.1, 171.7; HRMS (MALDI-FTMS) calcd. for $C_{24}H_{31}N_3O_7S$ ($M+Na^+$) 528.1775, found 528.1749.

Compound 10a: $[\alpha]_D^{25}$ = +5.7 (*c* 0.21, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.92 (d, *J* = 6.6 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 2.24 (m, 1H), 2.41 (s, 3H), 3.30-3.41 (m, 2H), 3.74 (s, 3H), 4.14 (dd, *J* = 5.4, 7.6 Hz, 1H), 4.66 (m, 1H), 5.08 (AB, J_{AB} = 11.8 Hz, 1H), 5.15 (AB, J_{AB} = 11.8 Hz, 1H), 5.54 (d, *J* = 7.5 Hz, 1H), 5.83 (dd, *J* = 6.6, 7.0 Hz, 1H), 7.28-7.36 (m, 8H), 7.71 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR (150 MHz,

$CDCl_3$) δ 17.3, 19.3, 21.5, 30.6, 44.0, 52.3, 53.0, 60.5, 67.3, 126.9, 128.2, 128.3, 128.5, 129.8, 136.0, 136.6, 143.7, 156.8, 170.3, 171.6; HRMS (MALDI-FTMS) calcd. for $C_{24}H_{31}N_3O_7S$ ($M+Na^+$) 528.1775, found 528.1771.

Compound 11a: $[\alpha]_D^{25}$ = +10.0 (*c* 0.48, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.89 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 2.07-2.11 (m, 1H), 2.33 (s, 3H), 3.26-3.28 (m, 1H), 3.39-3.41 (m, 1H), 4.19 (m, 1H), 4.72 (m, 1H), 4.87 (AB, d, J_{AB} = 12.3 Hz, 1H), 5.05 (AB, d, J_{AB} = 12.3 Hz, 1H), 5.07 (AB, d, J_{AB} = 12.3 Hz, 1H), 5.17 (AB, d, J_{AB} = 11.8 Hz, 1H), 5.76 (d, *J* = 8.3 Hz, 1H), 6.08 (dd, *J* = 6.1, 6.6 Hz, 1H), 7.20-7.38 (m, 13H), 7.70 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.6, 19.1, 21.4, 31.1, 44.1, 52.5, 60.2, 66.9, 67.8, 126.3, 127.0, 127.9, 128.0, 128.4 (2 C), 128.5 (2 C), 129.5, 129.6, 134.9, 136.1, 136.5, 143.4, 156.8, 169.5, 171.8; HRMS (MALDI-FTMS) calcd. for $C_{30}H_{35}N_3O_7S$ ($M+Na^+$) 604.2088, found 604.2083.

Compound 12a: $[\alpha]_D^{25}$ = +13.8 (*c* 0.65, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.89 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 2.18-2.23 (m, 1H), 2.41 (s, 3H), 3.36-3.40 (m, 2H), 4.06 (dd, *J* = 5.3, 7.5 Hz, 1H), 4.63 (m, 1H), 5.09-5.21 (m, 4H), 5.34 (br, 1H), 7.20 (m, 1H), 7.26-7.37 (m, 12H), 7.70 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.4, 19.3, 21.5, 27.7, 28.2, 30.5, 44.0, 52.5, 60.6, 67.3, 67.9, 126.9, 127.0, 128.0, 128.1, 128.2, 128.3 (2 C), 128.4, 128.5 (2 C), 129.8, 134.8, 136.0, 136.5, 143.6, 156.8, 169.6, 171.6; HRMS (MALDI-FTMS) calcd. for $C_{24}H_{31}N_3O_7S$ ($M+H^+$) 582.2268, found 582.2250.

Compound 13a: $[\alpha]_D^{25}$ = +2.4 (*c* 0.51, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.93 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 2.23 (s, 3H), 3.30 (m, 1H), 3.41 (s, 1H), 4.10 (dd, *J* = 6.6, 15.8 Hz, 1H), 4.13 (dd, *J* = 6.6, 16.7 Hz, 1H), 4.25 (dd, *J* = 7.5, 10.1 Hz, 2H), 4.75 (dd, *J* = 3.5, 4.0 Hz, 1H), 5.07 (AB, d, J_{AB} = 11.8 Hz, 1H), 5.17 (AB, d, J_{AB} = 12.3 Hz, 1H), 5.85 (d, *J* = 8.3 Hz, 1H), 6.04 (dd, *J* = 6.1, 7.0 Hz, 1H), 7.09 (d, *J* = 7.9 Hz, 2H), 7.20-7.25 (m, 2H), 7.31-7.81 (m, 8H), 7.50 (dd, *J* = 7.9, 10.1 Hz, 2H), 7.64 (d, *J* = 7.9 Hz, 2H), 7.71 (dd, *J* = 7.9, 8.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.7, 19.2, 21.3, 31.2, 44.2, 46.9, 52.6, 60.2, 67.2, 68.0, 119.8 (2 C), 125.0, 125.1, 127.0, 127.6, 128.5 (2 C), 128.6, 129.6, 134.9, 136.4, 141.1, 143.5 (2 C), 143.9, 156.8, 169.5, 171.8; HRMS (MALDI-FTMS) calcd. for $C_{37}H_{39}N_3O_7S$ ($M+H^+$) 670.2581, found 670.2589.

Procedure C: Synthesis of thiazolines (1b-13b). To a solution of triphenylphosphine oxide (167 mg, 0.6 mmol) in dry CH_2Cl_2 (2 mL), trifluoromethanesulfonic anhydride (50 µl, 0.3 mmol) was added slowly at 0 °C. The reaction mixture was stirred for 10 min at 0 °C and then adjusted to the desired reaction temperature enabling addition of the fully protected cysteine *N*-amide (0.2 mmol). The reaction progress was monitored by TLC. The reaction mixture was quenched with 10 % aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The resulting crude product was purified by flash chromatography using a mixture of EtOAc/hexanes.

Compound 1b: $[\alpha]_D^{25}$ = +60.9 (*c* 1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 2.41 (s, 3H), 3.67 (s, 3H), 4.20-4.27 (m, 2H), 4.49 (dd, *J* = 8.3, 10.1 Hz, 1H), 7.24 (d, *J* = 8.3 Hz, 2H), 7.38 (dd, *J* = 7.5, 7.9 Hz, 2H), 7.43 (d, *J* = 8.3 Hz, 2H), 7.49 (dd, *J* = 7.5, 8.8 Hz, 2H), 7.66 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 51.3, 52.7, 66.7, 127.5, 127.6, 127.7, 129.5, 129.8 (4 C), 131.4, 134.4, 144.9, 161.5, 170.5; HRMS (MALDI-FTMS) calcd. for $C_{18}H_{18}N_2O_4S$ ($M+Na^+$) 381.0879, found 381.0878. HPLC (chiralcel OD-H column, 254 nm, 98/2 hexane/isopropanol to 90/10 hexane/isopropanol gradient over 240 min, flow = 1.0 mL/min) t_R = 58.9 (S), 63.0 (R) min.

Compound 2b: $[\alpha]_D^{25}$ = -60.9 (*c* 1.1, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 2.41 (s, 3H), 3.67 (s, 3H), 4.20-4.27 (m, 2H), 4.49 (dd, *J* = 8.3, 10.1 Hz, 1H), 7.24 (d, *J* = 8.3 Hz, 2H), 7.38 (dd, *J* = 7.5, 7.9 Hz, 2H), 7.43 (d, *J* = 8.3 Hz, 2H), 7.49 (dd, *J* = 7.5, 8.8 Hz, 2H), 7.66 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 51.3, 52.7, 66.7, 127.5, 127.6, 127.7, 129.5, 129.8 (4 C), 131.4, 134.4, 144.9, 161.5, 170.5; HRMS (MALDI-FTMS) calcd. for $C_{18}H_{18}N_2O_4S$ ($M+H^+$) 359.1060, found 359.1055. HPLC (chiralcel OD-H column, 254 nm, 98/2 hexane/isopropanol to 90/10 hexane/isopropanol gradient over 240 min, flow = 1.0 mL/min) t_R = 58.9 (S), 63.0 (R) min.

Compound 3b: $[\alpha]_D^{25}$ = +45.0 (*c* 1.09, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 2.41 (s, 3H), 2.42 (s, 3H), 3.67 (s, 3H), 4.19-4.26 (m, 2H), 4.44 (dd, *J* = 8.8, 10.1 Hz, 1H), 7.21 (d, *J* = 7.9 Hz, 2H), 7.26 (d, *J* = 7.9 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6 (2 C), 51.3, 52.7, 66.6, 126.6, 127.6, 128.4, 129.7, 129.8 (2 C), 134.3, 141.9, 144.8, 161.6, 170.6; HRMS (MALDI-

FTMS) calcd. for $C_{19}H_{20}N_2O_4S$ ($M+H^+$) 373.1216, found 373.1216. HPLC (chiralcel OD-H column, 254 nm, 98/2 hexane/isopropanol to 90/10 hexane/isopropanol gradient over 240 min, flow = 1.0 mL/min) t_R = 58.0 (S), 75.6 (R) min.

Compound 4b: $[\alpha]_D^{25}$ = +31.9 (*c* 1.2, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 2.42 (s, 3H), 3.67 (s, 3H), 3.86 (s, 3H), 4.21-4.23 (m, 2H), 4.38 (t, *J* = 8.8 Hz, 1H), 6.91 (t, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.69 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 51.4, 52.6, 55.3, 66.5, 113.1, 121.6, 127.5, 129.8, 131.7, 134.3, 144.8, 161.3, 162.2, 170.6; HRMS (MALDI-FTMS) calcd. for $C_{19}H_{20}N_2O_5S$ ($M+H^+$) 389.1166, found 389.1165. HPLC (chiralcel OD-H column, 254 nm, 98/2 hexane/isopropanol to 90/10 hexane/isopropanol gradient over 240 min, flow = 1.0 mL/min) t_R = 100.1 (S), 124.1 (R) min.

Compound 5b: $[\alpha]_D^{25}$ = +66.2 (*c* 1.1, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 2.39 (s, 3H), 3.72 (s, 3H), 3.93-4.00 (m, 2H), 4.08 (AB, J_{AB} = 14.9 Hz, 1H), 4.13 (AB, J_{AB} = 15.4 Hz, 1H), 4.64 (dd, *J* = 7.9, 10.5 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 2H), 7.26-7.31 (m, 5H), 7.34 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5, 35.4, 50.1, 52.7, 65.3, 126.9, 127.1, 128.5, 129.1, 129.8, 134.6, 134.8, 144.6, 160.0, 170.8; HRMS (MALDI-FTMS) calcd. for $C_{19}H_{20}N_2O_4S$ ($M+H^+$) 373.1216, found 373.1203. HPLC (chiralcel OD-H column, 254 nm, 98/2 hexane/isopropanol to 90/10 hexane/isopropanol gradient over 240 min, flow = 1.0 mL/min) t_R = 75.5 (S), 79.2 (R) min.

Compound 6b (90%): $[\alpha]_D^{25}$ = +54.1 (*c* 0.93, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 2.43 (s, 3H), 3.72 (s, 3H), 4.25-4.33 (m, 2H), 4.59 (t, *J* = 9.2 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 2H), 7.42 (d, *J* = 7.5 Hz, 2H), 7.56 (t, *J* = 7.9 Hz, 1H), 7.76 (d, *J* = 7.9 Hz, 1H), 7.80 (s, 1H), 7.91 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 51.4, 52.8, 66.8, 126.5 (2 C), 127.4, 127.9 (2 C), 128.3, 130.0, 130.4, 133.2, 134.3, 145.3, 160.2, 170.2; HRMS (MALDI-FTMS) calcd. for $C_{19}H_{17}F_3N_2O_4S$ ($M+H^+$) 427.0934, found 427.0924. HPLC (chiralcel OD-H column, 254 nm, 98/2 hexane/isopropanol to 90/10 hexane/isopropanol gradient over 240 min, flow = 1.0 mL/min) t_R = 65.7 (S), 73.0 (R) min.

Compound 7b: $[\alpha]_D^{25}$ = +77.9 (*c* 0.98, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 2.43 (s, 3H), 3.01 (dd, *J* = 7.5, 14.0 Hz, 1H), 3.40 (dd, *J* = 4.4, 14.0 Hz, 1H), 3.72 (s, 3H), 3.71-3.74 (m, 1H), 4.21 (dd, *J* = 7.0, 10.1 Hz, 1H), 4.42 (m, 1H), 5.01 (AB, J_{AB} = 12.3 Hz, 1H), 5.08 (AB, J_{AB} = 12.3 Hz, 1H), 5.47 (d, *J* = 9.2 Hz, 1H), 5.65 (dd, *J* = 7.9, 12.3 Hz, 1H), 7.20-7.35 (m, 12H), 7.90 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 40.1, 50.4, 50.9, 52.7, 65.4, 66.7, 126.8, 127.7, 127.8, 127.9, 128.3, 128.4, 129.7, 130.2, 133.8, 135.8, 136.3, 145.2, 155.6, 162.1, 170.1; HRMS (MALDI-FTMS) calcd. for $C_{28}H_{29}N_3O_6S$ ($M+Na^+$) 558.1669, found 558.1645. HPLC (chiralcel OD-H column, 254 nm, 90/10 hexane/isopropanol to 70/30 hexane/isopropanol gradient over 240 min, flow = 1.0 mL/min) t_R = 66.8 (S, S), 78.3 (R, R) min.

Compound 8b: $[\alpha]_D^{25}$ = +10.4 (*c* 0.97, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 2.43 (s, 3H), 3.01 (dd, *J* = 7.5, 13.6 Hz, 1H), 3.44 (dd, *J* = 4.0, 13.6 Hz, 1H),

3.56 (s, 3H), 3.85 (dd, J = 8.8, 9.6 Hz, 1H), 4.05 (dd, J = 10.1, 11.0 Hz, 1H), 4.47 (dd, J = 8.8, 10.1 Hz, 1H), 5.02 (AB, J_{AB} = 12.3 Hz, 1H), 5.07 (AB, J_{AB} = 12.3 Hz, 1H), 5.48 (d, J = 9.2 Hz, 1H), 5.63 (dd, J = 8.8, 12.3 Hz, 1H), 7.21-7.34 (m, 12H), 7.88 (d, J = 7.9 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 40.6, 50.3, 51.1, 52.6, 65.4, 66.6, 126.9, 127.8 (2 C), 127.9, 128.3, 128.4, 129.6, 130.2, 133.4, 136.0, 136.4, 145.1, 155.5, 162.0, 169.9; HRMS (MALDI-FTMS) calcd. for $C_{28}H_{29}N_3O_6S$ ($M+Na^+$) 558.1669, found 558.1678. HPLC (chiralcel OD-H column, 254 nm, 90/10 hexane/isopropanol to 70/30 hexane/isopropanol gradient over 240 min, flow = 1.0 mL/min) t_R = 74.4 (R, S), 100.8 (S, R) min.

Compound 9b: $[\alpha]_D^{25}$ = +139.0 (*c* 0.91, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.88 (d, J = 7.0 Hz, 3H), 1.10 (d, J = 6.6 Hz, 3H), 2.37-2.39 (m, 1H), 2.43 (s, 3H), 3.67 (t, J = 10.5 Hz, 1H), 3.75 (s, 3H), 4.11 (dd, J = 7.0, 10.5 Hz, 1H), 4.46 (dd, J = 6.6, 11.0 Hz, 1H), 5.10 (AB, J_{AB} = 12.3 Hz, 1H), 5.14 (AB, J_{AB} = 12.7 Hz, 1H), 5.37 (dd, J = 3.5, 9.8 Hz, 1H), 5.46 (d, J = 9.7 Hz, 1H), 7.32-7.36 (m, 7H), 7.90 (d, J = 7.9 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.5, 19.8, 21.6, 32.2, 50.8, 52.7, 54.3, 65.3, 66.9, 127.8, 128.0 (2 C), 128.4, 130.2, 133.6, 136.4, 145.1, 156.3, 162.8, 170.6; HRMS (MALDI-FTMS) calcd. for $C_{24}H_{29}N_3O_6S$ ($M+Na^+$) 510.1669, found 510.1669. HPLC (chiralcel OD-H column, 254 nm, 90/10 hexane/isopropanol to 70/30 hexane/isopropanol gradient over 240 min, flow = 1.0 mL/min) t_R = 16.4 (S, S), 26.6 (R, R) min.

Compound 10b: $[\alpha]_D^{25}$ = -19.6 (*c* 1.3, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.87 (d, J = 7.0 Hz, 3H), 1.09 (d, J = 6.6 Hz, 3H), 2.35-2.39 (m, 1H), 2.42 (s,

3H), 3.58 (s, 3H), 3.82 (dd, *J* = 8.8, 10.1 Hz, 1H), 4.03 (t, *J* = 10.5 Hz, 1H), 4.57 (dd, *J* = 8.5, 10.5 Hz, 1H), 5.13 (s, 2H), 5.34 (dd, *J* = 3.5, 9.7 Hz, 1H), 7.30-7.36 (m, 7H), 7.88 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.0, 19.7, 21.6, 32.3, 50.2, 52.6, 54.3, 65.4, 66.7, 127.8, 128.0, 128.4, 130.1, 133.3, 136.5, 145.0, 156.2, 162.3, 170.0; HRMS (MALDI-FTMS) calcd. for $C_{24}H_{29}N_3O_6S$ ($M+Na^+$) 510.1669, found 510.1667. HPLC (chiralcel OD-H column, 254 nm, 90/10 hexane/isopropanol to 70/30 hexane/isopropanol gradient over 240 min, flow = 1.0 mL/min) t_R = 13.8 (R, S), 24.8 (S, R) min.

Compound 11b: $[\alpha]_D^{25}$ = +149.4 (*c* 1.8, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.81 (d, *J* = 6.6 Hz, 3H), 1.07 (d, *J* = 6.6 Hz, 3H), 2.33-2.35 (m, 1H), 2.42 (s, 3H), 3.67 (dd, *J* = 10.5, 11.0 Hz, 1H), 4.09 (dd, *J* = 7.0, 10.5 Hz, 1H), 4.47 (dd, *J* = 6.6, 11.0 Hz, 1H), 5.08-5.18 (m, 4H), 5.36 (m, 1H), 5.46 (d, *J* = 9.7 Hz, 1H), 7.30-7.36 (m, 12H), 7.88 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.9, 22.0, 23.8, 33.9, 51.8, 55.1, 65.9, 67.2, 67.9, 125.7, 125.9, 126.0, 126.4 (2 C), 126.5, 128.1, 131.3, 132.6, 134.0, 142.4, 153.1, 159.4, 166.2; HRMS (MALDI-FTMS) calcd. for $C_{30}H_{33}N_3O_6S$ ($M+Na^+$) 586.1982, found 586.1962. HPLC (chiralcel OD-H column, 254 nm, 90/10 hexane/isopropanol to 70/30 hexane/isopropanol gradient over 240 min, flow = 1.0 mL/min) t_R = 21.7 (S, S), 25.7 (R, R) min.

Compound 12b: $[\alpha]_D^{25}$ = -3.3 (*c* 0.8, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.86 (d, *J* = 7.0 Hz, 3H), 1.09 (d, *J* = 6.6 Hz, 3H), 2.31-2.39 (m, 1H), 2.37 (s, 3H), 3.84 (dd, *J* = 7.9, 10.1 Hz, 1H), 4.03 (t, *J* = 10.5 Hz, 1H), 4.60 (dd, *J* = 7.9, 11.0 Hz, 1H), 4.96 (AB, J_{AB} = 12.3 Hz, 1H), 5.04 (AB, J_{AB} = 12.3 Hz, 1H), 5.08 (AB, J_{AB} = 12.3 Hz, 1H),

5.16 (AB, J_{AB} = 12.7 Hz, 1H), 5.35 (dd, *J* = 3.9, 10.1 Hz, 1H), 5.49 (d, *J* = 10.1 Hz, 1H), 7.18-7.36 (m, 12H), 7.84 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.0, 19.7, 21.6, 32.3, 50.3, 54.4, 65.5, 66.8, 67.0, 127.7 (2 C), 127.9, 128.0, 128.3, 128.4, 128.5, 130.1, 133.3, 135.0, 136.4, 144.9, 156.2, 162.3, 169.3; HRMS (MALDI-FTMS) calcd. for $C_{30}H_{33}N_3O_6S$ ($M+Na^+$) 586.1982, found 586.1966. HPLC (chiralcel OD-H column, 254 nm, 90/10 hexane/isopropanol to 70/30 hexane/isopropanol gradient over 240 min, flow = 1.0 mL/min) t_R = 15.1 (R, S), 19.6 (S, R) min.

Compound 13b: $[\alpha]_D^{25}$ = +120.9 (*c* 0.35, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.87 (d, *J* = 7.0 Hz, 3H), 1.08 (d, *J* = 6.6 Hz, 3H), 2.36-2.38 (m, 1H), 2.37 (s, 3H), 3.69 (dd, *J* = 10.5, 11.0 Hz, 1H), 4.11 (dd, *J* = 7.9, 10.1 Hz, 1H), 4.23 (t, *J* = 7.0 Hz, 1H), 4.33 (dd, *J* = 7.5, 10.5 Hz, 1H), 4.45 (dd, *J* = 7.9, 10.1 Hz, 1H), 4.50 (dd, *J* = 7.0, 11.0 Hz, 1H), 5.19 (m, 2H), 5.36 (d, *J* = 9.7 Hz, 1H), 5.48 (d, *J* = 9.7 Hz, 1H), 7.24-7.40 (m, 11H), 7.60 (dd, *J* = 6.1, 7.0 Hz, 2H), 7.76 (d, *J* = 7.5 Hz, 2H), 7.88 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.6, 19.8, 21.5, 32.2, 47.1, 50.9, 54.3, 65.4, 67.0, 67.6, 119.9 (2 C), 125.1, 125.2, 127.0, 127.6 (2 C), 127.7, 128.5, 128.6, 130.2, 133.6, 134.9, 141.2, 143.8, 145.1, 156.3, 163.0, 170.0; HRMS (MALDI-FTMS) calcd. for $C_{37}H_{37}N_3O_6S$ ($M+H^+$) 654.2476, found 652.2486. HPLC (chiralcel OD-H column, 254 nm, 90/10 hexane/isopropanol to 70/30 hexane/isopropanol gradient over 240 min, flow = 1.0 mL/min) t_R = 39.5 (S, S), 55.8 (R, R) min.

Synthesis of imidazole-based amino ester 14. To a solution of **11b** (338, 0.6 mmol) in CH_2Cl_2 (25 mL) at 0 °C, DBU (99 μL, 0.66 mmol) and $BrCCl_3$ (71 μL, 0.72 mmol) were

added separately. The reaction mixture was stirred overnight at 25 °C. After dilution with CH_2Cl_2 (25 mL), the reaction mixture solution was washed with saturated NH_4Cl (2 x 25 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL), and the combined organic layer was dried, filtered and concentrated. The resulting crude product was purified by flash chromatography (EtOAc/hexanes = 1/3) yielding **14** (289 mg, 86%) as a white foam: $[\alpha]_D^{25}$ = -13.3 (*c* 0.48, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.90 (d, *J* = 6.1 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 2.19 (m, 1H), 2.38 (s, 3H), 5.06 (s, 2H), 5.28 (AB, d, J_{AB} = 12.3 Hz, 1H), 5.34 (AB, d, J_{AB} = 12.3 Hz, 1H), 5.38-5.41 (m, 1H), 5.63 (m, 1H), 7.26-7.42 (m, 12H), 7.93-7.96 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.4, 19.4, 21.7, 34.8, 66.7 (2 C), 124.5, 127.8, 128.0, 128.4, 128.5, 128.6, 130.5, 132.5, 134.1, 135.5, 136.4, 150.6, 155.9, 161.4; HRMS (MALDI-FTMS) calcd. for $C_{30}H_{31}N_3O_6S$ ($M+H^+$) 562.2006, found 562.2013. HPLC (chiralcel OD-H column, 254 nm, 90/10 hexane/isopropanol to 70/30 hexane/isopropanol gradient over 240 min, flow = 1.0 mL/min) t_R = 11.5 (S), 16.8 (R) min.

Synthesis of imidazole-based amino ester 15. To a solution of **13b** (326 mg, 0.5 mmol) in CH_2Cl_2 (5 mL), activated MnO_2 (<5 micron, 85%, 0.51 g, 5 mmol) was added. The reaction mixture was stirred 2 d at 25 °C, then activated MnO_2 (<5 micron, 85%, 0.51 g, 5 mmol) was added again. The reaction mixture was stirred another 2d at 25 °C, then filtered through a short silica gel and celite column and washed with EtOAc. The organic solution was concentrated. The resulting crude product was purified by flash chromatography (EtOAc/hexanes = 1/4) yielding **15** (205 mg, 63%) as a white foam: $[\alpha]_D^{25}$ = -31.1 (*c* 0.27, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.91 (d, *J* =

6.6 Hz, 3H), 0.99 (d, J = 6.6 Hz, 3H), 2.21 (m, 1H), 2.29 (s, 3H), 4.16 (dd, J = 7.0, 7.5 Hz, 1H), 4.23 (dd, J = 7.5, 10.5 Hz, 1H), 4.38 (dd, J = 7.0, 10.1 Hz, 1H), 5.30 (AB, d, J_{AB} = 11.8 Hz, 1H), 5.36 (AB, d, J_{AB} = 11.8 Hz, 1H), 5.38 (dd, J = 7.0, 10.1 Hz, 1H), 5.66 (d, J = 10.1 Hz, 1H), 7.24-7.29 (m, 4H), 7.34-7.43 (m, 7H), 7.52 (d, J = 7.5 Hz, 1H), 7.56 (d, J = 7.5 Hz, 1H), 7.75 (d, J = 7.5 Hz, 2H), 7.95 (d, J = 7.5 Hz, 2H), 7.97 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.5, 19.4, 21.6, 34.8, 47.0, 53.3, 66.7, 67.0, 119.9 (2 C), 124.5, 125.0, 125.1, 127.0, 127.6 (2 C), 128.0, 128.4, 128.5, 128.6, 130.5, 132.5, 134.1, 135.5, 141.2, 143.7 (2 C), 146.9, 150.6, 155.9, 161.4; HRMS (MALDI-FTMS) calcd. for $C_{37}H_{35}N_3O_6S$ ($M+H^+$) 650.2139, found 650.2339. HPLC (chiralcel OD-H column, 254 nm, 90/10 hexane/isopropanol to 70/30 hexane/isopropanol gradient over 240 min, flow = 1.0 mL/min) t_R = 18.1 (S), 38.3 (R) min.

Compound 16. Pd on activated carbon (30 mg) was added to a flask containing **15** (260 mg, 0.4 mmol) in MeOH (10 mL). The reaction flask was filled with H_2 using a balloon, and evacuated and purged with H_2 three times. The reaction progress was monitored by LCMS and was complete in 2 h. After removing the solvent, the residue was passed through a short silica gel column and eluted with MeOH. The solvent was removed under pressure. Typically we use this form of **16** (without further purification) for the coupling reaction with **17**. The resulting crude product can be purified by flash chromatography ($CHCl_3$/MeOH: 1/1), yielding **16** as a white foam (150 mg, 92%): ^{1}H NMR (600 MHz, CD_3OD, 25 °C) δ 0.75-1.28 (m, 6H), 2.50 (br, 1H), 4.16 (br, 1H), 4.39 (br, 1H), 4.86-4.90 (m, 2H), 7.15 (d, J = 7.5 Hz, 1H), 7.20 (d, J = 7.9 Hz, 2H), 7.34 (br, 1H), 7.46 (d, J

= 7.9 Hz, 1H), 7.58 (br, 1H), 7.68 (d, *J* = 7.9 Hz, 2H), 7.75 (br, 1H); HRMS (MALDI-FTMS) calcd. for $C_{23}H_{23}N_3O_4$ ($M+H^+$) 406.1761, found 406.1765.

Compound 18. Deprotecting the Fmoc group in **17** (193 mg, 0.3 mmol)[2] used diethylamine as described in the procedure A. The residue was dissolved in DMF (4 mL). In another flask, a solution of **16** (134 mg, 0.3 mmol) in DMF (4 mL) was treated with HBTU (125 mg, 0.33 mmol) and HOBt•H_2O (50 mg, 0.33 mmol). After 10 min, this mixture and DIEA (3.65 mL, 21 mmol) were sequentially added to the above free amino ester. The reaction was stirred at 25 °C for 8 h. After regular workup, the resulting crude product was purified by flash chromatography (EtOAc/hexanes = 2/1) to afford compound **18** as a white foam (226 mg, 93%): $[\alpha]_D^{25}$ = -30.7 (*c* 0.41, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.87 (d, *J* = 5.7 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.99 (d, *J* = 6.6 Hz, 3H), 1.00-1.03 (m, 6H), 2.31 (m, 1H), 2.56-2.60 (m, 2H), 3.0 (br, 1H), 4.15 (m, 1H), 4.35-4.39 (m, 2H), 4.60 (m, 1H), 4.80-4.82 (m, 2H), 5.26 (d, *J* = 10.1 Hz, 1H), 5.33 (t, *J* = 7.9 Hz, 1H), 5.34-5.38 (m, 2H), 5.96-6.03 (m, 2H), 7.18-7.22 (m, 2H), 7.32-7.36 (m, 2H), 7.51 (dd, *J* = 7.9, 9.2 Hz, 2H), 7.58 (br, 1H), 7.71 (d, *J* = 7.5 Hz, 2H), 7.78 (d, *J* = 7.9 Hz, 1H), 8.01 (s, 1H), 8.06 (s, 1H), 8.10 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.8, 17.9, 18.6, 19.3, 19.4, 19.6, 29.6, 32.0, 33.0, 36.5, 47.1, 55.4, 55.9, 56.5, 65.9, 66.8, 118.8, 119.4, 119.9, 123.6, 124.8, 126.9, 127.0, 127.3, 127.7, 131.7, 135.1, 141.1, 141.2, 143.5 (2 C), 146.9, 148.5, 149.2, 156.5, 160.9, 163.0, 172.0 (2 C); HRMS (MALDI-FTMS) calcd. for $C_{42}H_{47}N_7O_6S_2$ ($M+H^+$) 810.3102, found 810.3096.

Compound 19. Deprotecting the Fmoc group in **18** (81 mg, 0.1 mmol) used diethylamine as described in the Procedure A. The resulting amino ester was dissolved in CH_2Cl_2 (5 mL). To this solution, $Pd(OAc)_2$ (0.9 mg, 0.004 mmol) and styrene polymer bound-triphenylphosphine (20.2 mg, 1.59 mol/g, 0.032 mmol) were added. After stirring for 10 min, $PhSiH_3$ (0.024 mL, 0.2 mmol) was added. The reaction progress was monitored by TLC and the reaction was complete in 15 min. After removal of the solvent, the residue was passed through a short silica gel column and washed with $CHCl_3$/EtOH (1/1). The carboxylic acid was used in the next step without further purification. The resulting amino acid was dissovled in CH_2Cl_2/DMF (10 mL, v/v: 2/1) as a 0.01 M solution. This solution was added to a flask containing PyBOP (104 mg, 0.2 mmol) and DMAP (24.4 mg, 0.2 mmol) in CH_2Cl_2/DMF (20 mL, v/v: 2/1) over 8 h using a syringe pump. After the addition was complete, the mixture was stirred for 2 h. Regular workup and purification by flash chromatography (EtOAc/Hexanes: 4/1) gave **1** as a white foam (34 mg, 64%): $[\alpha]_D^{25}$ = -142.8 (*c* 0.54, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 1.03 (d, *J* = 6.6 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H), 1.08 (d, *J* = 6.6 Hz, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.12 (d, *J* = 6.6 Hz, 3H), 2.27-2.32 (m, 4H), 5.24 (dd, *J* = 6.1, 8.3 Hz, 1H), 5.37 (dd, *J* = 5.7, 9.2 Hz, 1H), 5.43 (dd, *J* = 6.1, 9.2 Hz, 1H), 7.56 (s, 1H), 8.07 (s, 1H), 8.08 (s, 1H), 8.46 (d, *J* = 9.7 Hz, 1H), 8.52 (d, *J* = 8.8 Hz, 1H), 8.70 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.2, 18.5, 18.6, 18.8, 19.0 (2 C), 34.7, 35.3, 35.5, 52.8, 55.4 (2 C), 118.9, 123.2, 123.6, 135.4, 147.3, 148.8, 149.2, 159.9, 160.4, 162.1, 168.7, 169.1; HRMS (MALDI-FTMS) calcd. for $C_{24}H_{31}N_7O_3S_2$ ($M+H^+$) 530.2002, found 530.2005.

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