Synthesis of a meso-Oxa-Diaminopimelic Acid-Containing Peptidoglycan Pentapeptide and Coupling to the GlcNAc-anhydro-MurNAc Disaccharide

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**General information:**

Reaction were performed using flame dried glassware. All reagents were purchased from Sigma-Aldrich, AK Scientific and Ark pharm. Solvents were distilled under Argon from calcium hydride. All other solvents and reagents were used without further purification. Molecular sieves, Type 3 Å were dried in oven at 150 °C overnight. NMR spectra were recorded on a Bruker AV400 spectrometer or a Bruker AV300 spectrometer at a field strength of 400 MHz or 300 MHz for $^1$H NMR and 101 MHz or 75 MHz for $^{13}$C NMR. Column chromatography was performed using SiliaFlash silica gel F60, 40 - 63 μm purchased from Silicycle. Thin layer chromatography was performed using silica gel 60 F254 purchased from Merck and visualized under short wave UV or KMnO₄ stain. High-resolution mass spectra were recorded on a Waters/Micro mass LCT TOF spectrometer equipped with electrospray (ESI) ionization.

**Synthetic Procedure:**

![Compound 4](image)

**Compound 4:** A solution of 4M HCl in dioxane (20 mL) was cooled to 0 °C. N-Boc-D-Ala-D-Ala-OBn (3.4 g, 9.7 mmol) was added in one portion with stirring. The ice-bath was removed, and the mixture kept stirred for 2 h. The reaction mixture was evaporated to dryness under vacuum. The residue was then triturated with diethyl ether (3x10 mL) and kept under high vacuum for 1 h to give a white foam which was further used without purification. The free
amine was dissolved in DCM (50 mL). PyBOP (5.56 g, 10.7 mmol) and trityl L-serine triethyl ammonium salt (4.78 g, 10.7 mmol) were added to it. DIPEA (2.54 mL, 14.60 mmol) was added to the mixture dropwise at rt. After stirring the mixture for 18 h, it was diluted with DCM (200 mL). The organic layer was washed successively with 10% aq. citric acid (2x100 mL), aq. sodium bicarbonate (2x100 mL) and then with brine (100 mL). The organic layer was dried over sodium sulfate, filtered and evaporated under reduced pressure to give crude product which was purified with silica gel column chromatography (30% ethyl acetate in petroleum ether) to give compound 4 as a white solid (5.1 g, 90%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.86 (d, $J = 7.7$ Hz, 1H), 7.50–7.38 (m, 5H), 7.38–7.16 (m, 15H), 5.15 (dd, $J = 12.2$, 9.8 Hz, 2H), 4.72–4.51 (m, 1H), 4.44–4.28 (m, 1H), 3.72 (d, $J = 10.6$ Hz, 1H), 3.51–3.17 (m, 3H), 2.82–2.67 (m, 1H), 1.39 (d, $J = 7.2$ Hz, 3H), 1.33 (d, $J = 7.1$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 174.3, 173.1, 172.2, 145.6, 135.2, 128.7, 128.7, 128.5, 128.2, 128.2, 126.9, 71.7, 67.3, 63.9, 59.5, 48.9, 48.3, 18.1, 18.0. HRMS (ESI): m/z calcd for C$_{35}$H$_{37}$N$_3$O$_5$ [M+Na]$^+$ 602.2631, found 602.2629

**Compound 5:** Triethylamine (2.16 mL, 15.5 mmol) was added dropwise to a solution of compound 4 (6 g, 10.4 mmol) and methanesulfonyl chloride (0.97 mL, 12.4 mmol) at 0 °C. The resulting solution was stirred at this temperature for 2 h, then diluted with DCM (100 mL) and washed subsequently with 10% aq. citric acid (2x50 mL), aq. sodium bicarbonate (2x50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was dissolved in THF (60 mL), and triethylamine (2.89 mL, 20.7 mmol) was added dropwise. The resulting solution was refluxed at 65 °C and kept stirring for 24 h. The solution was cooled to rt, diluted with DCM (50 mL), and washed subsequently with 10% aq. citric acid (50 mL), saturated aqueous sodium bicarbonate (50 mL), and brine (50 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (5% ethyl acetate in petroleum ether) to give compound 5 as a white solid (5.3 g, 90%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.47 –
7.42 (m, 5H), 7.41 – 7.21 (m, 15H), 6.85 (d, J = 7.3 Hz, 1H), 5.20 (dd, J = 12.6, 10.1 Hz, 2H), 4.70 – 4.53 (m, 2H), 2.07 (dd, J = 2.8, 0.9 Hz, 1H), 2.01 (dd, J = 6.6, 2.7 Hz, 1H), 1.54 – 1.47 (m, 4H), 1.43 (d, J = 7.2 Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 172.4, 171.7, 170.8, 143.2, 135.3, 129.3, 128.6, 128.5, 128.2, 127.8, 127.2, 74.6, 67.2, 48.3, 48.1, 33.9, 29.8, 18.5, 18.0. HRMS (ESI): m/z calcd for C$_{35}$H$_{35}$N$_3$O$_4$ [M+Na]$^+$ 584.2525, found 584.2531

**Compound 6:** Trifluoroacetic acid (3.1 mL, 39.2 mmol) was added dropwise to a solution of compound 5 (4.0 g, 3.1 mmol) in a mixture of chloroform (10 mL) and methanol (5 mL) at 0 °C. The resulting solution was stirred at this temperature for 3 h and then concentrated by rotary evaporation. The residue was partitioned between ethyl acetate (50 mL) and water (30 mL). The organic layer was re-extracted with water (3 x 20 mL). The combined aqueous fractions were neutralized with saturated sodium bicarbonate solution and extracted with DCM (5x50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to afford the free aziridine compound 6 as a white solid (1.48 g, 65%). $^1$H NMR (400 MHz, MeOD) δ 7.42 – 7.27 (m, 5H), 5.16 (dd, J = 12.2, 8.4 Hz, 2H), 4.52 – 4.34 (m, 2H), 2.58 (s, 1H), 1.96 – 1.83 (m, 1H), 1.81 – 1.68 (m, 1H), 1.41 (d, J = 7.3 Hz, 3H), 1.33 (d, J = 7.1 Hz, 3H). $^{13}$C NMR (101 MHz, MeOD) δ 173.4, 172.5, 136.0, 128.3, 128.3, 128.3, 128.3, 128.3, 128.1, 128.0, 66.7, 29.1, 24.8, 17.0, 16.0. HRMS (ESI): m/z calcd for C$_{16}$H$_{21}$N$_3$O$_4$ [M+Na]$^+$ 342.1430, found 342.1429
**Compound 8:** To a solution of N-Boc-d-Glu-1-OBn-5-OH (4.0 g, 11.9 mmol) in DCM (20 mL) at 0 °C under nitrogen was added BF₃·OEt₂ (0.30 mL, 2.37 mmol). Then tert-butyl 2,2,2-trichloroacetimidate (4.25 mL, 23.7 mmol) in cyclohexane (20 mL) was then added dropwise. The reaction was stirred at rt for 18 h. To the crude reaction mixture was added solid NaHCO₃ (1.0 g) and the reaction was filtered. The mother liquors were concentrated in vacuo. The residue was purified by silica gel column chromatography (30% ethyl acetate in petroleum ether) to give the t-butyl ester product as a white solid. The spectroscopic data were identical to reported literature¹. To 20 mL of 4 M HCl in dioxane was added to t-butyl ester acid (1.0 g, 2.54 mmol) at 0 °C and stirred for 2 h. Then the solvent was evaporated under reduced pressure to give oily liquid, which was kept in petroleum ether overnight to give compound 8 as a white solid (0.9 g, quantitative yield).¹ H NMR (400 MHz, MeOD) δ 7.47 – 7.38 (m, 5H), 5.37 – 5.26 (m, 2H), 4.18 (dd, J = 6.6, 4.6 Hz, 1H), 2.58 – 2.34 (m, 2H), 2.25 – 2.11 (m, 2H), 1.45 (s, 9H).¹³C NMR (101 MHz, MeOD) δ 171.4, 168.7, 135.0, 128.5, 128.4, 80.9, 67.9, 52.0, 30.0, 26.9, 25.4. HRMS (ESI): m/z calcd for C₁₆H₂₃NO₄ [M+H]⁺ 294.1705, found 294.1704

**Compound 9:** Compound 8 (2.5 g, 8.52 mmol) and N-Fmoc-L-Ala-NHS ester (3.34 g, 8.52 mmol) was dissolved in mixture of ACN: H₂O (1:1, 100 mL). Then sodium bicarbonate (2.86 g, 34.1 mmol) was added at 0 °C. The reaction mixture was left to stir at rt for 24 h. The solvent was removed under reduced pressure. To the crude product was added H₂O (100 mL) and pH was adjusted to 1 using 1 M HCl. The aqueous layer was extracted with DCM (5x50 mL). Organic layer was collected, dried over sodium sulfate and evaporated under reduced pressure to give a
white foam which was carried on further without purification. The crude product was dissolved in DCM (20 mL) and TFA (20 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. Volatiles were co-evaporated with diethyl ether (4x20 mL) under reduced pressure to give a white precipitate of compound 9 as a white solid (3.6 g, 80 %). 1H NMR (400 MHz, MeOD) δ 7.80 (d, J = 7.5 Hz, 2H), 7.67 (t, J = 7.4 Hz, 2H), 7.43 – 7.27 (m, 9H), 5.20 – 5.10 (m, 2H), 4.50 (dd, J = 9.3, 5.0 Hz, 1H), 4.42 – 4.31 (m, 2H), 4.26 – 4.12 (m, 2H), 2.36 (t, J = 7.5 Hz, 2H), 2.24 – 2.11 (m, 1H), 2.03 – 1.89 (m, 1H), 1.33 (d, J = 7.2 Hz, 3H). 13C NMR (101 MHz, MeOD) δ 174.9, 174.6, 171.5, 144.1, 144.0, 141.3, 135.9, 128.3, 128.0, 127.5, 126.9, 125.0, 124.9, 119.6, 66.8, 52.0, 50.8, 29.6, 26.3, 17.1. HRMS (ESI): m/z calcd for C30H30N2O7 [M+H]+ 531.2131, found 531.2134

**Compound 10:** PyBOP (2.65 g, 5.10 mmol) was added to a solution of compound 6 (1.48 g, 4.63 mmol) and compound 9 (2.70 g, 5.10 mmol) in 100 mL DCM. Then DIPEA (2.43 mL, 13.9 mmol) was added to solution dropwise at rt. The reaction mixture was stirred for 18 h and then diluted with DCM (100 mL). The organic layer was successively washed with 10% aq. citric acid (100 mL), aq. sodium bicarbonate (100 mL) and brine (100 mL). Organic layer was collected, dried over sodium sulfate and reduced under pressure to give crude product which was purified by silica gel column chromatography (70 % ethyl acetate in petroleum ether) to give compound 10 as a white solid (1.93 g, 50 %). 1H NMR (400 MHz, MeOD) δ 7.79 (d, J = 7.5 Hz, 2H), 7.66 (t, J = 8.1 Hz, 2H), 7.44 – 7.12 (m, 15H), 5.19 – 5.01 (m, 4H), 4.54 – 4.43 (m, 2H), 4.41 – 4.28 (m, 3H), 4.26 – 4.14 (m, 2H), 3.22 (dd, J = 5.3, 3.1 Hz, 1H), 2.52 – 2.34 (m, 4H), 2.29 – 2.14 (m, 1H), 1.97 – 1.84 (m, 1H), 1.37 – 1.30 (m, 9H). 13C NMR (101 MHz, MeOD) δ 183.8, 174.6, 173.1, 172.6, 171.6, 167.9, 156.9, 144.2, 144.0, 141.3, 141.3, 136.0, 135.9, 128.3, 128.3,
Compound 12: In a flame dried round bottom flask was added oven dried 3Å molecular sieves under an argon atmosphere. Compound 10 (500 mg, 0.60 mmol) and a solution of N-Pht-D-Ser(OH)-OBn (391 mg, 1.20 mmol) in DCM (10 mL) were added sequentially. The mixture was cooled to -78 °C and stirred for 30 min. BF$_3$·OEt$_2$ (190 µl, 1.50 mmol) was added dropwise for 20 min at -78 °C. The reaction was stirred for 3 h, allowed to warm to rt, and then filtered. The volatiles were evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (100% ethyl acetate) to give compound 12 as a white solid (63 mg, 9 % yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.88 – 7.80 (m, 2H), 7.76 (d, $J$ = 7.5 Hz, 2H), 7.72 – 7.65 (m, 2H), 7.59 (d, $J$ = 7.5 Hz, 2H), 7.39 (t, $J$ = 7.5 Hz, 3H), 7.36 – 7.27 (m, 14H), 7.26 – 7.23 (m, 2H), 5.74 (d, $J$ = 7.2 Hz, 1H), 5.23 – 4.89 (m, 8H), 4.62 (d, $J$ = 8.8 Hz, 1H), 4.53 – 4.45 (m, 3H), 4.40 – 4.34 (m, 2H), 4.29 (t, $J$ = 6.9 Hz, 1H), 4.23 – 4.13 (m, 2H), 4.09 (dd, $J$ = 11.0, 5.1 Hz, 1H), 3.97 (d, $J$ = 8.4 Hz, 1H), 3.61 (dd, $J$ = 9.3, 4.9 Hz, 1H), 2.49 – 2.37 (m, 1H), 2.35 – 2.17 (m, 2H), 1.94 – 1.83 (m, 1H), 1.82 – 1.70 (m, 1H), 1.34 – 1.25 (m, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 172.7, 172.4, 172.3, 171.8, 171.6, 169.8, 167.6, 167.3, 156.1, 143.7, 141.3, 135.4, 135.2, 134.8, 134.4, 131.7, 128.6, 128.6, 128.6, 128.5, 128.5, 128.5, 128.3, 128.2, 128.1, 127.8, 127.1, 127.1, 125.1, 123.7, 120.0, 68.4, 67.8, 67.3, 67.2, 67.0, 53.1, 51.5, 50.6, 49.1, 48.2, 47.1, 31.5, 29.7, 28.0, 18.8, 17.9, 17.4. HRMS (ESI): m/z calcd for C$_{64}$H$_{64}$N$_6$O$_{15}$ [M+Na]$^+$ 1179.4327, found 1179.4308
**Compound 14:** N, N-diisopropylethylamine (6.3 mL, 36.2 mmol) was added dropwise to a solution of triethylammonium trityl serine (8.9 g, 19.9 mmol), D-Ala-Oallyl-NH₂·HCl (3.0 g, 18.1 mmol), and PyBOP (10.4 g, 19.9 mmol) in DCM (50 mL) at rt. The resulting solution was stirred for 18 h then diluted with DCM (100 mL). The solution was washed subsequently with 10% aq. citric acid (2x200 mL), aq. sodium bicarbonate (2X200 mL), and brine (200 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20% ethyl acetate in petroleum ether) to afford compound 14 as a white solid (5.98 g, 72%). \(^1\)H NMR (400 MHz, CDCl₃) δ 7.70 (d, J = 7.8 Hz, 1H), 7.48 – 7.38 (m, 5H), 7.34 – 7.20 (m, 10H), 5.99 – 5.83 (m, 1H), 5.35 (dd, J = 17.2, 1.5 Hz, 1H), 5.28 (dd, J = 10.4, 1.6 Hz, 1H), 4.74 – 4.56 (m, 2H), 4.45 (m, 1H), 3.68 (dd, J = 11.2, 2.6 Hz, 1H), 3.34 (dd, J = 4.4, 2.6 Hz, 1H), 2.74 (dd, J = 11.2, 4.4 Hz, 1H), 2.63 ( broad s, 1H), 1.40 (d, J = 7.3 Hz, 3H). \(^{13}\)C NMR (101 MHz, CDCl₃) δ 174.1, 173.2, 145.8, 131.6, 128.8, 128.3, 127.0, 119.1, 71.8, 66.4, 64.5, 59.5, 48.3, 17.6. HRMS (ESI): m/z calcd for C₂₈H₃₀N₂O₄ [M+Na]⁺ 481.2105, found 481.2105

**Compound 15:** Triethylamine (2.64 mL, 18.9 mmol) was added dropwise to a solution of compound 14 (5.8 g, 12.7 mmol) and methanesulfonyl chloride (1.2 mL, 15.2 mmol) in DCM (50 mL) at 0 °C. The resulting solution was stirred at this temperature for 1 h, then diluted with DCM (50 mL) and washed subsequently with 10% aq. citric acid (100 mL) and water (100 mL). The organic layer was dried over sodium sulfate and concentrated under reduced
Pressure. The residue was dissolved in THF (18 mL), and triethylamine (3.5 mL, 25.3 mmol) was added dropwise at rt. The resulting solution was refluxed at 70 °C for 2 h, cooled to rt, then diluted with DCM (100 mL), and washed subsequently with 10% aqueous citric acid (200 mL), saturated aqueous sodium bicarbonate (200 mL), and water (200 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (10% ethyl acetate in petroleum ether) to afford compound 15 as a white solid (5.0 g, 91%). 1H NMR (400 MHz, CDCl3) δ 7.47 – 7.42 (m, 5H), 7.35 – 7.23 (m, 10H), 6.02 – 5.88 (m, 1H), 5.38 (dd, J = 17.2, 1.4 Hz, 1H), 5.30 (dd, J = 10.7, 1.3 Hz, 1H), 4.80 – 4.63 (m, 3H), 2.11 (d, J = 2.2 Hz, 1H), 2.04 (dd, J = 6.6, 2.7 Hz, 1H), 1.58 (d, J = 7.3 Hz, 3H), 1.51 (d, J = 6.8 Hz, 1H). 13C NMR (101 MHz, CDCl3) δ 172.7, 170.5, 143.4, 131.7, 129.5, 127.9, 127.3, 118.9, 74.7, 66.1, 47.6, 34.1, 29.9, 18.9. HRMS (ESI): m/z calcd for C28H28N2O3 [M+H]+ 440.2160, found 440.2177

**Compound 16:** Trifluoroacetic acid (5.3 mL, 68.1 mmol) was added dropwise to a solution of aziridine dipeptide 15 (5.0 g, 11.4 mmol) in a mixture of DCM (15 mL) and methanol (10 mL) at 0 °C. The resulting solution was stirred at this temperature for 3 h then concentrated by rotary evaporation. The residue was partitioned between ethyl acetate (50 mL) and water (30 mL). The organic layer was re-extracted with water (2x30 mL). The combined aqueous fractions were neutralized with sodium bicarbonate (aq) and extracted with DCM (5x50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to afford the free aziridine 16 as a colorless oil (1.57g, 70 %). 1H NMR (400 MHz, MeOD) δ 6.02 – 5.91 (m, 1H), 5.36 (dd, J = 17.3, 1.5 Hz, 1H), 5.25 (dd, J = 10.3, 1.6 Hz, 1H), 4.67 – 4.62 (m, 2H), 4.50 (q, J = 7.3 Hz, 1H), 2.60 (dd, J = 5.7, 3.2 Hz, 1H), 1.90 – 1.82 (m, 2H), 1.44 (d, J = 7.4 Hz, 3H) 13C NMR (101 MHz, MeOD) δ 172.2, 171.2, 132.0, 117.3, 65.4, 48.3, 29.0, 24.8, 16.3. HRMS (ESI): m/z calcd for C9H14N2O3 [M+H]+ 199.1083, found 199.1083
**Compound 18:** N, N-Diisopropylethylamine (578 µL, 3.31 mmol) was added dropwise to a solution of compound 17\textsuperscript{2}(0.95 g, 2.07 mmol), compound 16 (0.33 g, 1.66 mmol), and PyBOP (1.08 g, 2.07 mmol) in DCM (20 mL) at rt. The resulting solution was stirred for 18 h. Then solution was diluted with DCM (50 mL) and washed sequentially with 10% aq. citric acid (100 mL), aq. sodium bicarbonate (100 mL), and brine (100 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (70% ethyl acetate in petroleum ether) to afford the aziridine tripeptide 18 as a white solid (0.66 g, 62%). \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.77 (d, \(J = 7.5\) Hz, 2H), 7.64 – 7.57 (m, 2H), 7.43 – 7.29 (m, 9H), 6.76 (d, \(J = 7.7\) Hz, 1H), 5.92 – 5.78 (m, 1H), 5.56 (d, \(J = 8.2\) Hz, 1H), 5.33 – 5.15 (m, 4H), 4.64 – 4.52 (m, 3H), 4.50 – 4.31 (m, 3H), 4.21 (t, \(J = 7.0\) Hz, 1H), 3.05 (dd, \(J = 6.5, 3.1\) Hz, 1H), 2.58 – 2.41 (m, 3H), 2.38 – 2.23 (m, 2H), 2.11 – 1.99 (m, 1H), 1.44 (d, \(J = 7.2\) Hz, 3H). \(^{13}\)C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) 183.2, 172.3, 171.8, 167.3, 156.3, 143.8, 141.4, 135.2, 131.5, 128.8, 128.1, 128.5, 127.9, 127.2, 125.2, 120.1, 119.0, 67.6, 67.4, 66.2, 53.6, 48.0, 47.2, 36.1, 32.7, 31.2, 27.6, 18.0. HRMS (ESI): m/z calcd for C\textsubscript{36}H\textsubscript{37}N\textsubscript{3}O\textsubscript{8} [M+Na]\textsuperscript{+} 662.2478, found 662.2475
**Compound 19:** In a flame dried round bottom flask was added oven dried 3Å molecular sieves under an argon atmosphere. Aziridine tripeptide 18 (1 g, 1.56 mmol) and a solution of N-Pht-D-Ser(OH)-OBn (1.02 g, 3.13 mmol) in DCM (10 mL) were added sequentially. The mixture was cooled to -78 °C and stirred for 30 min. BF₃·OEt₂ (0.49 mL, 3.91 mmol) was added dropwise for 20 min at -78 °C. The reaction was stirred for 2 h, allowed to warm to rt, and then filtered. The volatiles were evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (90% ethyl acetate in petroleum ether) to give compound 19 as a white solid (0.49 g, 33% yield).

1H NMR (400 MHz, MeOD) δ 7.88 – 7.73 (m, 6H), 7.66 (t, J = 7.2 Hz, 2H), 7.44 – 7.20 (m, 14H), 5.92 – 5.75 (m, 1H), 5.29 – 5.08 (m, 7H), 4.53 (t, J = 4.8 Hz, 1H), 4.48 – 4.35 (m, 3H), 4.33 – 4.08 (m, 6H), 3.77 – 3.67 (m, 2H), 2.37 – 2.16 (m, 3H), 1.94 – 1.80 (m, 1H), 1.25 (d, J = 7.3 Hz, 3H).

13C NMR (101 MHz, MeOD) δ 173.3, 172.0, 171.9, 170.1, 167.6, 167.4, 157.3, 143.9, 143.8, 141.2, 141.2, 135.8, 135.3, 134.3, 131.9, 131.6, 128.2, 128.2, 128.0, 127.9, 127.8, 127.4, 126.8, 125.0, 124.9, 123.1, 119.5, 117.0, 70.2, 67.4, 67.2, 66.8, 66.6, 65.2, 53.5, 53.0, 51.3, 31.3, 27.0, 15.9. HRMS (ESI): m/z calcd for C₅₄H₅₂N₄O₁₃ [M+Na]⁺ 987.3429, found 987.3427

**Compound 20:** The reaction also gave the Heine rearrangement product 20 (elution with 2% MeOH in ethyl acetate) as a white solid (0.74 g, 37% yield) 1H NMR (400 MHz, MeOD) δ 7.78 (d, J = 7.6 Hz, 2H), 7.64 (m, 2H), 7.39 – 7.34 (m, 3H), 7.32 – 7.24 (m, 6H), 5.98 – 5.73 (m, 1H), 5.32 – 5.08 (m, 4H), 4.65 (dd, J = 10.8, 7.8 Hz, 1H), 4.58 – 4.52 (m, 2H), 4.52 – 4.42 (m, 3H), 4.40 – 4.25 (m, 3H), 4.17 (t, J = 7.1 Hz, 1H), 2.42 (t, J = 7.3 Hz, 2H), 2.32 – 2.21 (m, 1H), 2.06 – 1.93 (m, 1H), 1.40 (d, J = 7.3 Hz, 3H). 13C NMR (101 MHz, MeOD) δ 172.5, 172.1, 172.1, 171.0, 157.4, 144.1, 143.9, 141.3, 135.9, 132.0, 128.3, 128.1, 128.0, 127.6, 126.9, 126.9, 125.0, 125.0, 119.7, 117.3, 70.3, 68.2, 66.8, 65.5, 53.3, 27.1, 23.8, 16.1. HRMS (ESI): m/z calcd for C₃₆H₃₇N₃O₈ [M+H]⁺ 640.2659, found 640.2657
**Compound 21:** Tripeptide 19 (400 mg, 0.42 mmol) was dissolved in THF (5mL) and hydrazine (50 % in water) (30 µl, 0.47 mmol) was added at 0 °C. After 2 h, 1 mL AcOH was added to reaction mixture and the solution was stirred for 10 min at 50 °C. Volatiles were removed under reduced pressure to give the white solid. The solid was triturated with 5 mL ethyl acetate and filtered. The filtrate was evaporated to give an oily crude amine which was used further without purification. Water/ THF (1:1, 10 mL) was added to the crude amine then sodium carbonate (220 mg, 2.1 mmol) was added to it. Cbz-Cl (354 mg, 2.11 mmol) was added dropwise at 0 °C and reaction mixture was stirred for 1 h. Solvent was removed under reduced pressure. The reaction mixture was partitioned between water (30 mL) and DCM (30 mL). The organic layer was separated, and the aq. layer was washed with DCM (2 x10 mL). The combined organic layer was collected, dried over sodium sulfate and filtered and concentrated under reduced pressure. The crude product was purified with silica gel column chromatography (80% ethyl acetate in petroleum ether) to give compound 21 as a white solid (360 mg, 90% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.76 (d, $J = 7.5$ Hz, 2H), 7.59 (m, 2H), 7.43 – 7.27 (m, 19H), 6.51 (d, $J = 7.4$ Hz, 1H), 6.09 (d, $J = 8.4$ Hz, 1H), 5.87 – 5.74 (m, 1H), 5.66 (d, $J = 8.2$ Hz, 1H), 5.33 – 4.98 (m, 8H), 4.64 – 4.32 (m, 8H), 4.13 (t, $J = 7.0$ Hz, 1H), 3.98 – 3.85 (m, 2H), 3.77 (dd, $J = 9.9$, 3.0 Hz, 1H), 3.54 (dd, $J = 9.3$, 5.7 Hz, 1H), 2.39 – 2.27 (m, 1H), 2.27 – 2.18 (m, 1H), 2.18 – 2.07 (m, 1H), 1.87 – 1.75 (m, 1H), 1.35 (d, $J = 7.3$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 172.6, 172.1, 172.0, 170.0, 169.4, 156.4, 156.3, 144.0, 141.4, 136.3, 135.3, 131.8, 128.8, 128.8, 128.7, 128.6, 128.5, 128.5, 128.3, 128.2, 127.9, 127.9, 127.2, 127.1, 125.3, 125.2, 120.1, 118.6, 71.4, 70.5, 67.7, 67.6, 67.2, 66.0, 54.7, 53.2, 52.7, 48.4, 47.4, 31.8, 28.6, 28.6, 17.8. HRMS (ESI): m/z calcd for C$_{54}$H$_{56}$N$_4$O$_{13}$ [M+Na]$^+$ 991.3742, found 991.3743.
**Compound 22:** A solution of 5% piperidine in DMF (2 mL) was added to tripeptide 21 (0.36, 0.37 mmol) and stirred for 5 min at rt. Then volatiles were removed under reduced pressure. The white solid obtained was washed with hexane (3x5 mL) to give crude amine which was used further without purification. N-Boc-Ala (84 mg, 0.45 mmol) was dissolved in 2 mL DCM under an inert atmosphere. Then EDC·HCl (85 mg, 0.45 mmol) and HOBt (68 mg, 0.45 mmol) were added sequentially at 0 °C. The reaction mixture was stirred for 30 min at rt. Then a solution of crude amine and DIPEA (0.130 mL, 0.74 mmol) was added dropwise at 0 °C. The reaction mixture was stirred for 3 h at rt. The reaction mixture was then partitioned between DCM (20 mL) and water (20 mL). The organic layer was separated, washed with water (3x 20 mL), and dried over sodium sulfate and concentrated under reduced pressure to give crude product which was purified by silica gel column chromatography (80 % ethyl acetate in petroleum ether) to give compound 22 as a white foamy solid (212 mg, 62 % yield). ¹H NMR (400 MHz, MeOD) δ 7.51 – 7.12 (m, 15H), 5.98 – 5.79 (m, 1H), 5.33 – 5.00 (m, 8H), 4.63 – 4.36 (m, 6H), 4.15 – 4.00 (m, 1H), 3.90 (dd, J = 9.7, 4.5 Hz, 1H), 3.76 (m, 2H), 3.64 (dd, J = 9.8, 4.5 Hz, 1H), 2.42 – 2.22 (m, 3H), 1.92 – 1.83 (m, 1H), 1.43 (s, 9H), 1.36 (d, J = 7.3 Hz, 3H), 1.26 (d, J = 7.2 Hz, 3H). ¹³C NMR (101 MHz, MeOD) δ 174.9, 173.7, 172.3, 171.4, 170.7, 170.3, 157.4, 156.7, 136.8, 135.9, 135.9, 132.1, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 128.0, 127.8, 127.8, 127.7, 117.3, 79.7, 70.5, 66.9, 66.8, 66.6, 65.5, 54.7, 53.7, 53.5, 51.1, 51.0, 31.1, 27.5, 27.1, 16.8, 16.1. HRMS (ESI): m/z calcd for C₄₇H₅₉N₅O₁₄ [M+H]⁺ 918.4137, found 918.4134
Compound 1: To solution of tetrapeptide 22 (212 mg, 0.23 mmol) in 5 mL DCM was added morpholine (26 µL, 0.30 mmol). Then Pd(PPh₃)₄ (5.3 mg, µmol) was added. The reaction was covered with Al foil and stirred for 1 h. The volatiles were removed under reduced pressure. Water (10 mL) was added to the crude yellow solid and the pH was adjusted to 2-3 using 1M HCl. The aqueous layer was extracted with DCM (3x10 mL). The organic layer was collected, dried over sodium sulfate and evaporated under reduced pressure to give a yellow solid which was used without further purification. To a solution of the crude acid in DCM (5 mL) was added EDC·HCl (66 mg, 0.35 mmol) followed by HOBt (53 mg, 0.35 mmol) at 0 °C. After 30 min, a solution of D-Ala-OBn-tosylate salt (122 mg, 0.35 mmol) and DIPEA (0.121 mL, 0.69 mmol) in DCM (5 mL) was added. The reaction mixture was stirred for 1 h at rt. The reaction mixture was diluted with DCM (10 mL) and then washed with water (3x10 mL). The organic layer was collected, dried over sodium sulfate and concentrated under reduced pressure to give crude product which was purified using silica gel column chromatography (90% ethyl acetate in petroleum ether) to give pentapeptide 1 as a white solid (150 mg, 62% yield). ¹H NMR (400 MHz, MeOD) δ 7.41 – 7.22 (m, 20H), 5.24 – 4.97 (m, 8H), 4.52 – 4.33 (m, 5H), 4.13 – 4.02 (m, 1H), 3.90 (dd, J = 9.7, 4.4 Hz, 1H), 3.76 (m, 2H), 3.65 (dd, J = 9.7, 4.6 Hz, 1H), 2.39 – 2.22 (m, 3H), 2.01 – 1.80 (m, 1H), 1.44 (s, 9H), 1.38 (d, J = 7.3 Hz, 3H), 1.32 (d, J = 7.2 Hz, 3H), 1.23 (d, J = 7.2 Hz, 3H). ¹³C NMR (101 MHz, MeOD) δ 174.9, 173.7, 173.1, 172.4, 171.3, 170.6, 170.2, 157.2, 156.6, 156.6, 136.7, 135.9, 135.8, 128.2, 128.2, 128.2, 128.2, 128.1, 128.0, 128.0, 127.9, 127.9, 127.9, 127.8, 127.8, 127.7, 127.6, 79.5, 70.5, 70.2, 66.8, 66.6, 66.4, 54.6, 54.0, 51.0, 50.8, 49.1, 30.9, 27.4, 26.7, 16.7, 16.6, 15.9. HRMS (ESI): m/z calcd for C₅₄H₆₆N₆O₁₅ [M+Na]⁺ 1061.4484, found 1061.4488
**Compound 25:** To a round bottom flask was added 1.41 g of pulverized flame-dried 3 Å molecular sieves and AgOTf (500 mg, 1.95 mmol, 2.09 eq) under an Argon atmosphere. Subsequently, (1.10 g, 2.14 mmol, 2.29 eq) of the glycosyl donor 24 and (270 mg, 0.934 mmol) of the glycosyl acceptor 23 dissolved in 4 mL of distilled DCM were added. The solution was left to stir under light shielding conditions at rt for 48 h. The crude product mixture was diluted with MeOH and filtered through Celite and a fritted glass funnel with ~60 total mL of MeOH. The light orange solution was concentrated under reduced pressure and the residue was purified by silica gel chromatography with step-wise gradient elution: 70% EtOAc:30% Pet. Ether - 80% EtOAc:20% Pet. Ether - pure EtOAc. Compound 25 was isolated as a light yellow foam (525 mg, 78% yield). $^1$H NMR (600 MHz, MeOD) $\delta$ 5.41 (dd, $J = 10.8, 9.2$ Hz, 1H), 5.19 (s, 1H), 5.06 (t, $J = 9.7$ Hz, 1H), 4.90 (d, $J = 8.5$ Hz, 1H), 4.53 (d, $J = 5.7$ Hz, 1H), 4.32 – 4.27 (m, 2H), 4.18 – 4.13 (m, 2H), 4.05 (d, $J = 9.0$ Hz, 1H), 4.00 (dd, $J = 10.8, 8.4$ Hz, 1H), 3.88 – 3.82 (m, 2H), 3.73 (s, 3H), 3.67 (dd, $J = 7.3$, 5.8 Hz, 1H), 3.50 (s, 1H), 2.07 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H), 1.38 (d, $J = 6.8$ Hz, 3H). $^{13}$C NMR (101 MHz, MeOD) $\delta$ 174.8, 172.7, 172.3, 171.7, 171.2, 165.1, 102.0, 100.7, 78.5, 76.1, 75.5, 74.8, 73.2, 72.9, 70.0, 65.9, 63.1, 57.2, 52.6, 51.5, 22.8, 20.7, 20.6, 20.5, 18.7. HRMS (ESI): m/z calc for C$_{26}$H$_{35}$Cl$_{3}$N$_{2}$O$_{15}$ [M+H]$^+$ 721.1176, found 721.1176.
Compound 26: To compound 25 (56 mg, 0.078 mmol) was added 1 mL of HOAc and 1 mL of Raney Nickel slurry solution in H₂O. The bubbling black mixture was stirred for 30 min at rt. The solution was then diluted with MeOH and filtered through Celite in a fritted glass funnel. The filtrate was concentrated under reduced pressure to give a sticky green film. This material was dry loaded onto 150 mg of silica which was applied to a silica gel column. This column was run with step-wise gradient elution: pure EtOAc - 1% MeOH:99% EtOAc - 2% MeOH:98% EtOAc. Compound 26 of the product was isolated as pure white crystals (35 mg, 73%). NMR and ESI mass spectral data were identical values reported in literature.

Compound 27: Compound 26 (87 mg, 0.14 mmol) was dissolved in 3.5 mL of DMA (previously degassed under high vacuum). Subsequently, 142 mg (1.13 mmol, 8.07 eq) of 4-aminothiophenol and 120 mg of Cs₂CO₃ (0.368 mmol, 2.63 eq) were added. The light yellow solution was heated to 110 °C under an Argon atmosphere for 30 min; after which the solution became dark orange. The mixture was quenched by the addition of 1 mL of formic acid and thereafter concentrated under reduced pressure to give a sticky light brown film. This film was purified by silica gel chromatography. The column was run with step-wise gradient elution: pure EtOAc - 2% MeOH:1% formic acid:97% EtOAc - 4% MeOH:1% formic acid:95% EtOAc. Compound 27 was isolated as a light yellow foam (67 mg, 85%).
NMR (600 MHz, MeOD) δ 5.26 – 5.21 (m, 2H), 5.01 (dd, $J = 10.2, 9.3$ Hz, 1H), 4.77 (d, $J = 8.4$ Hz, 1H), 4.51 (d, $J = 5.3$ Hz, 1H), 4.32 (dd, $J = 12.4, 4.4$ Hz, 1H), 4.21 (m, 1H), 4.16 (d, $J = 7.3$ Hz, 2H), 4.12 (dd, $J = 12.4, 2.3$ Hz, 1H), 3.99 (s, 1H), 3.96 (dd, $J = 10.7, 8.4$ Hz, 1H), 3.86 – 3.81 (m, 2H), 3.68 (dd, $J = 7.3, 5.8$ Hz, 1H), 3.54 (s, 1H), 2.06 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.96 (s, 3H), 1.37 (d, $J = 6.6$ Hz, 3H). $^{13}$C NMR (101 MHz, MeOD) δ 174.3, 172.3, 171.8, 171.3, 102.1, 101.3, 77.4, 77.0, 75.3, 73.5, 73.0, 70.0, 66.1, 63.1, 55.4, 52.3, 23.1, 22.7, 20.7, 20.6, 20.6. HRMS (ESI): m/z calc for C$_{25}$H$_{36}$N$_{2}$O$_{15}$ [M+H]$^+$ 605.2188, found 605.2195.

Compound 29: Compound 27 (17 mg, 0.028 mmol) was dissolved in 0.3 mL of distilled DCM and treated with HOBt hydrate powder (19 mg, 0.12 mmol, 4.4 eq), EDCI (21 mg, 0.11 mmol, 3.9 eq), and 0.05 mL (0.3 mmol, 10 eq) of Hunig’s base at rt and light shielding for 4 h. Meanwhile, compound 1 (35 mg, 0.033 mmol, 1.2 eq) was stirred with 2 mL of 4M HCl in dioxane at rt for 2 hr. This pentapeptide solution was then concentrated, re-diluted several times with diethyl ether, and subsequently re-concentrated to give 28 as a white solid to which was transferred the activated ester solution. This reaction mixture was stirred at rt with light shielding for 36 h. The solution was diluted with 50 mL of DCM, washed with 2x30 mL of 0.2 M aqueous NaH$_2$PO$_4$, then washed with 2x30 mL of sat. aqueous NaHCO$_3$. The organic layer was dried over Na$_2$SO$_4$. This organic extract was concentrated under reduced pressure.
to give a light brown sticky film. The crude product was purified by silica gel chromatography using high-purity Davisil Grade 633 silica gel with 60 Å pore size and 200-425 mesh particle size. This column was run with step-wise gradient elution: pure EtOAc - 1% MeOH:99% EtOAc - 2% MeOH:98% EtOAc - 3% MeOH:97% EtOAc - 4% MeOH:96% EtOAc. Compound 29 was attained as a clear colourless wax (11 mg, 26%).$^1$H NMR (600 MHz, MeOD) δ 7.38 – 7.24 (m, 20H), 5.31 (s, 1H), 5.21 (dd, $J = 10.8, 9.2$ Hz, 1H), 5.18 – 5.04 (m, 8H), 5.01 (t, $J = 9.7$ Hz, 1H), 4.71 (d, $J = 8.4$ Hz, 1H), 4.62 – 4.57 (m, 2H), 4.47 (t, $J = 4.1$ Hz, 1H), 4.45 – 4.32 (m, 4H), 4.33 – 4.26 (m, 2H), 4.15 – 4.09 (m, 2H), 4.02 (dd, $J = 10.8, 8.4$ Hz, 1H), 3.94 (s, 1H), 3.87 (dd, $J = 9.8, 4.6$ Hz, 1H), 3.84 – 3.79 (m, 2H), 3.77 – 3.70 (m, 3H), 3.64 (dd, $J = 9.8, 4.7$ Hz, 1H), 3.55 (s, 1H), 2.48 – 2.14 (m, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 2.01 (s, 3H), 2.02 - 1.99 (m, 1H), 1.98 (s, 3H), 1.40 – 1.25 (m, 12H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 173.4, 172.9, 172.9, 172.2, 171.9, 171.9, 171.8, 171.2, 170.8, 170.3, 170.2, 169.3, 156.5, 136.5, 135.6, 135.4, 128.8, 128.7, 128.7, 128.6, 128.6, 128.6, 128.4, 128.4, 128.3, 128.2, 128.2, 101.4, 100.2, 77.8, 75.7, 74.3, 72.7, 72.3, 72.0, 71.4, 70.6, 68.2, 67.6, 67.3, 67.2, 67.1, 64.6, 62.0, 54.6, 54.3, 53.4, 51.1, 49.6, 48.5, 47.0, 31.4, 29.8, 28.0, 23.8, 22.8, 20.9, 20.8, 20.7, 17.9, 17.7, 17.6, 17.4. HRMS (ESI): m/z calc for C$_{74}$H$_{92}$N$_8$O$_{27}$ [M+Na]$^+$ 1547.5964, found 1547.5946.
**Compound 2:** To compound 29 (4.2 mg, 0.0028 mmol) dissolved in 2 mL of 1:1 MeOH:distilled H₂O was added 5.8 mg of 10% Pd/C (1.4 wt eq). This solution was stirred under a H₂ atmosphere at rt for 3 h. This solution was then filtered through a fine fritted glass funnel with distilled H₂O eluent and subsequently concentrated under reduced pressure to give a clear colourless film. This resultant material was dissolved in 2 mL of 1:1 MeOH:distilled H₂O and 15 mg of K₂CO₃ (0.11 mmol, 39 eq) was added. This basic solution was stirred for 3 h at rt; after which it was quenched with 50WX8 hydrogen form Dowex resin until the solution’s pH became 4-5. Finally, the mildly acidic solution was filtered through a fine fritted glass funnel with distilled H₂O eluent and subsequently concentrated under reduced pressure to give compound 2 as a clear colourless film (1.7 mg, 62%).

NMR samples were doped with CH₃OH as an internal standard for ¹³C NMR. ¹H NMR (600 MHz, D₂O with an internal standard of CH₃OH) δ 5.44 (s, 1H), 4.69 (d, J = 5.5 Hz, 1H), 4.65 (d, J = 8.4 Hz, 1H), 4.48 (t, J = 4.3 Hz, 1H), 4.37 (q, J = 6.1, 4.9 Hz, 1H), 4.35 – 4.31 (m, 1H), 4.27 (d, J = 7.9 Hz, 1H), 4.20 – 4.15 (m, 2H), 4.11 (q, J = 7.3 Hz, 1H), 3.99 (s, 1H), 3.97 (s, 1H), 3.96 – 3.84 (m, 4H), 3.82 – 3.72 (m, 6H), 3.60 (s, 1H), 3.56 (dd, J = 9.9, 8.1 Hz, 1H), 3.48 – 3.44 (m, 2H), 2.34 (t, J = 7.7 Hz, 2H), 2.15 (tt, J = 13.8, 6.7 Hz, 1H), 2.06 (s, 3H), 2.04 (s, 3H), 1.90 (dd, J = 14.6, 7.3 Hz, 1H), 1.42 (d, J = 7.2 Hz, 3H), 1.39 – 1.35 (m, 6H), 1.33 (d, J = 7.3 Hz, 3H). ¹³C NMR (151 MHz, D₂O with an internal standard of CH₃OH) δ 180.3, 178.2, 176.5, 176.2, 176.0, 174.5, 174.3, 174.3, 172.3, 172.3, 101.3, 100.5, 77.8, 76.7, 76.6, 75.2,
74.3, 74.0, 70.6, 70.4, 69.7, 65.5, 61.2, 56.2, 54.8, 54.7, 51.5, 50.3, 49.4, 32.3, 28.5, 23.0, 22.6, 18.7, 17.8, 17.7, 17.3. HRMS (ESI): m/z calc for C_{39}H_{62}N_{8}O_{22} [M+H]^+ 995.4051, found 995.4061.

References:


NMR Spectra

$^1$H NMR (300 MHz, CDCl$_3$) of Compound 4
$^{13}$C NMR (75 MHz, CDCl$_3$) of Compound 4
$^1$H NMR (300 MHz, CDCl$_3$) of Compound 5
$^{13}$C NMR (75 MHz, CDCl$_3$) of Compound 5
$^1$H NMR (400 MHz, MeOD) of Compound 6
\(^{13}\)C NMR (101 MHz, MeOD) of Compound 6
$^1$H NMR (400 MHz, MeOD) of Compound 8
$^{13}$C NMR (101 MHz, MeOD) of Compound 8
$^1$H NMR (400 MHz, MeOD) of Compound 9
$^{13}$C NMR (101 MHz, MeOD) of Compound 9
$^1$H NMR (400 MHz, MeOD) of Compound 10
$^{13}$C NMR (101 MHz, MeOD) of Compound 10
$^1$H NMR (400 MHz, CDCl$_3$) of Compound 12
$^{13}$C NMR (101 MHz, CDCl$_3$) of Compound 12

![Chemical structure of Compound 12](image)
\(^1\)H NMR (400 MHz, CDCl\(_3\)) of Compound 14
$^{13}$C NMR (101 MHz, CDCl$_3$) of Compound 14
$^1$H NMR (400 MHz, CDCl$_3$) of Compound 15
$^{13}$C NMR (101 MHz, CDCl$_3$) of Compound 15
$^1$H NMR (400 MHz, MeOD) of Compound 16

![NMR Spectrum](image-url)
$^{13}$C NMR (101 MHz, MeOD) of Compound 16
$^1$H NMR (400 MHz, CDCl$_3$) of Compound 18

![Chemical Structure]

$\text{FmocHN} = \text{CO}_2\text{Bn}$
$^{13}$C NMR (101 MHz, CDCl$_3$) of Compound 18
$^1$H NMR (400 MHz, MeOD) of Compound 19
$^{13}$C NMR (101 MHz, MeOD) of Compound 19
$^1$H NMR (400 MHz, MeOD) of Compound 20
$^{13}$C NMR (101 MHz, MeOD) of Compound 20
$^1$H NMR (400 MHz, CDCl$_3$) of Compound 21
$^{13}$C NMR (101 MHz, CDCl$_3$) of Compound 21
$^1$H NMR (400 MHz, MeOD) of Compound 22
$^{13}$C NMR (101 MHz, MeOD) of compound 22
$^1$H NMR (400 MHz, MeOD) of compound 1
$^{13}$C NMR (101 MHz, MeOD) of compound 1
$^1$H NMR (600 MHz, MeOD) of compound 25
$^{13}$C NMR (101 MHz, MeOD) of Compound 25
$^{1}$H NMR (600 MHz, MeOD) of Compound 27
\(^{13}\)C NMR (101MHz, MeOD) of Compound 27
\(^1\)H NMR (600 MHz, MeOD) of Compound 29
$^{13}$C NMR (101 MHz, MeOD) of Compound 29
$^1$H NMR (600 MHz, MeOD) of Compound 2
$^{13}$C NMR (151 MHz, D$_2$O with an internal standard of CH$_3$OH) of Compound 2