Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Synthesis of the Cyclic Heptapeptide Core of Callipeltin A

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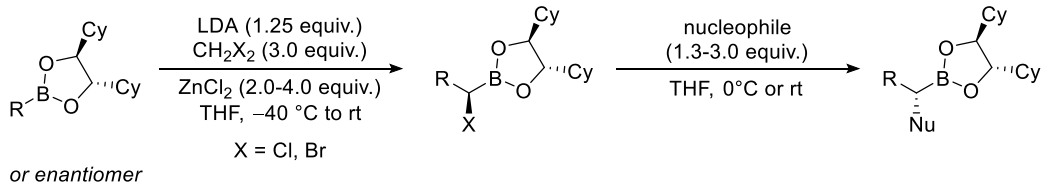
Supporting Information

General Information

All air- or moisture-sensitive reactions were carried out in dried glassware (>100 °C) under an atmosphere of nitrogen. THF was dried over sodium/benzophenone and was distilled before use. Dry DCM, diethylether, DMF, DMSO, toluene and pyridine were purchased from Acros Organics. The products were purified by flash chromatography on silica gel columns (Macherey-Nagel 60, 0.04-0.063 mm) and with a Reveleris® flash chromatography system from Grace with RediSep®-columns from Teledyne Isco. Mixtures of ethyl acetate and petroleum ether (40–60°C fraction), diethyl ether and pentane, dichloromethane and methanol or acetonitrile and water (for reversed phase) were generally used as eluents. Analytical TLC was performed on pre-coated silica gel plates (Macherey-Nagel GmbH & Co. KG, Silica on TLC PET-foils, 4 x 8 cm). Visualization was accomplished with UV-light (254 nm), Cerium-molybdenum solution, $KMnO_4$ solution or with an iodine chamber. Melting points were determined with a MEL-TEMP II melting point apparatus from Laboratory devices and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AV400 [400 MHz (^{1}H) and 100 MHz (^{13}C)], a Bruker AV500 and a Bruker Neo 500 [500 MHz (^{1}H) and 125 MHz (^{13}C)] in $CDCl_3$, or DMSO-d_6. Chemical shifts are reported in ppm relative to TMS ($CDCl_3$) or the residual solvent signal (DMSO-d_6). Peaks were assigned using (^{1}H,^{1}H)-COSY, (^{1}H,^{13}C)-HSQC and (^{1}H,^{13}C)-HMBC spectra. The α-carbon atoms of the alkylboronic esters could not be observed in most ^{13}C NMR spectra. Diastereomeric ratios were determined by NMR and/or HPLC. Mass spectra were recorded with a Finnigan MAT 95 spectrometer (quadrupole) using the CI technique. LCMS analyses were accomplished on a Shimadzu system (LC-10At, autoinjector SCL-6B, mass spectrometer LCMS-2020). A Phenomenex Luna C18(2) column (50x4.6 mm, grain size 3 µm) was used as the column. Optical rotations were measured with a Perkin-Elmer polarimeter (model 341) in a thermostated (20°C ± 1 °C) cuvette, using a sodium vapor lamp (λ = 589 nm) as radiation source. $[\alpha]_D^{20}$ values are given in 10^{-1} deg cm^2 g^{-1}.

General Procedures (GP's)

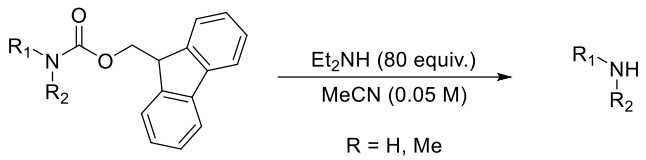
GP-1: Matteson homologation



Preparation of the α-halo-boronic ester: A Schlenk tube was flame dried and DIPA (1.1-2.0 equiv.) was dissolved in dry THF (0.2 mL/mmol). The tube was cooled to –20 °C and *n*-butyllithium (1.0-2.0 equiv.) was added dropwise. After complete addition the mixture was stirred for 20 minutes at room temperature. In a second Schlenk tube zinc chloride (2.0-5.0 equiv.) was dried under high vacuum with a heat gun and after cooling to room temperature dissolved in THF (0.5 mL/mmol). The third Schlenk tube was flame dried and the boronic ester (1.0 equiv.), CH_2Cl_2 or CH_2Br_2 (3.0 equiv.) and THF (1.4 mL/mmol) were added. After cooling to –40 °C the freshly prepared LDA solution was slowly added, and the mixture was stirred for 10–15 minutes at the same temperature. The zinc chloride solution was rapidly added, and the reaction was stirred for 4–16 hours at room temperature.

Reaction with a nucleophile: The mixture was cooled to 0 °C, a solution of the nucleophile was dropwise added, and the reaction was stirred at room temperature until complete consumption of the α-halo-boronic ester was observed (NMR). Then, the reaction was quenched by addition of sat. NH_4Cl and water and extracted thrice with pentane. After drying (Na_2SO_4) of the combined organic layer, the solvent was removed *in vacuo* and the residue was purified by rapid filtration over a short column of silica.

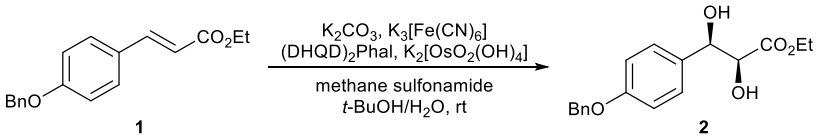
GP-2: Fmoc deprotection



To a solution of Fmoc-protected amino acid or peptide (1.0 equiv.) in MeCN (0.05 M) Et_2NH (80 equiv.) was added and the mixture was stirred at room temperature until complete deprotection was observed by TLC or LC-MS. The volatiles were removed *in vacuo* and the crude amine was used in the next step.

Synthesis of the Compounds

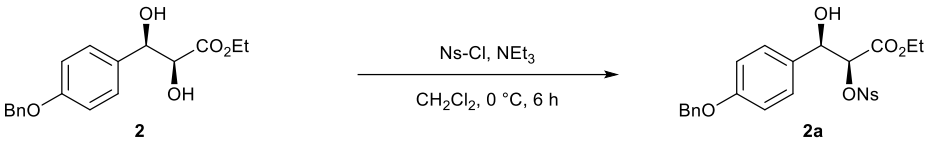
Ethyl (2*S*,3*R*)-3-(4-(benzyloxy)phenyl)-2,3-dihydroxypropanoate (2)[1]



88%, > 98:2 *er*

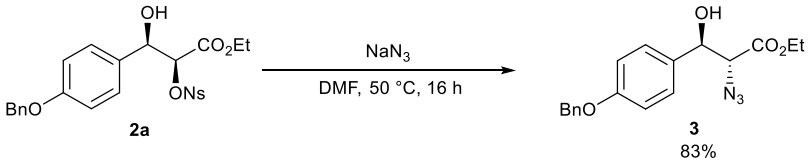
To a well stirred mixture of *t*-BuOH (420 mL) and H_2O (420 mL) were successively added K_2CO_3 (35.1 g, 254 mmol, 3.0 equiv.), $K_3[Fe(CN)_6]$ (84.0 g, 254 mmol, 3.0 equiv.), $(DHQD)_2Phal$ (633 mg, 813 µmol, 9.6 mol%) and $K_2[OsO_2(OH)_4]$ (131 mg, 356 µmol, 4.2 mol%). After addition of methanesulfonamide (8.05 g, 85.0 mmol, 1.0 equiv.) the solution was cooled to 0 °C, stirred for 5 minutes and cinnamyl ester **1**[1] (23.9 g, 85.0 mmol, 1.0 equiv.) was added. The resulting solution was stirred at 0 °C for 2 hours and then at room temperature until complete consumption of the starting material was observed by TLC. The reaction was quenched by addition of sat. $Na_2S_2O_3$ solution and the mixture was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Recrystallization (PE/EtOAc) and flash chromatography (silica, PE/EtOAc 1:1) afforded diol **2** (23.6 g, 74.5 mmol, 88%, >98% *ee*) as white solid, mp 123-125 °C. R_f(**2**) = 0.27 (PE/EtOAc 1:1). $[\alpha]_D^{20}$ = –7.3 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.2 Hz, 3 H), 2.65 (d, *J* = 6.8 Hz, 1 H), 3.09 (d, *J* = 5.9 Hz, 1 H), 4.25 (q, *J* = 7.1 Hz, 2 H), 4.32 (dd, *J* = 5.9 Hz, *J* = 3.2 Hz, 1 H), 4.94 (dd, *J* = 6.6 Hz, *J* = 3.2 Hz, 1 H), 5.07 (s, 2 H), 6.97 (m, 2 H), 7.37 (m, 7 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 62.1, 70.0, 74.2, 74.7, 114.7, 127.4, 127.6, 127.9, 128.5, 132.3, 136.9, 158.6, 172.7. HRMS (CI): m/z calcd for $C_{18}H_{18}O_4$ $[M\text{-}H_2O]^+$: 298.1200, found: 298.1179.

Ethyl (2*S*,3*R*)-3-(4-(benzyloxy)phenyl)-3-hydroxy-2-(((2-nitrophenyl)sulfonyl)oxy)propanoate (2a)[1]



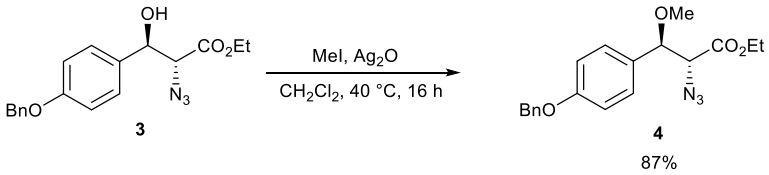
Diol **2** (6.00 g, 19.0 mmol, 1.0 equiv.) was dissolved in anhydrous DCM (150 mL), the solution cooled to 0 °C and 2-nitrobenzenesulfonyl chloride (5.46 g, 24.7 mmol, 1.3 equiv.) was added. After dropwise addition of triethylamine (3.44 mL, 24.7 mmol, 1.3 equiv.) over 5 min. the mixture was stirred for 5.5 hours at 0–3 °C. The reaction was acidified to pH = 2 by addition of aqueous HCl (1 M), the layers were separated, and the aqueous layer extracted twice with DCM. The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated at room temperature under reduced pressure. Rapid flash chromatography (silica, DCM/EtOAc 9:1) afforded nosylate **2a** (9.31 g, 17.8 mmol, 94%, contains 4% EtOAc) as yellow resin which was immediately used in the consecutive step. R_f(**2a**) = 0.40 (DCM/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (t, *J* = 7.1 Hz, 3 H), 2.49 (bs, 1 H), 4.09 (dq, *J* = 10.8 Hz, *J* = 7.3 Hz, 1 H), 4.12 (dq, *J* = 10.8 Hz, *J* = 7.1 Hz, 1 H), 5.02 (s, 2 H), 5.08 (d, *J* = 5.0 Hz, 1 H), 5.14 (d, *J* = 5.0 Hz, 1 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 7.22 (d, *J* = 8.7 Hz, 2 H), 7.36 (m, 5 H), 7.66 (m, 1 H), 7.73 (m, 2 H) 8.00 (d, *J* = 7.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 62.2, 69.9, 73.4, 83.5, 114.8, 124.8, 127.4, 127.8, 128.1, 128.6, 129.3, 129.6, 131.3, 132.3, 134.8, 136.7, 148.0, 159.0, 166.2.

Ethyl (2*R*,3*R*)-2-azido-3-(4-(benzyloxy)phenyl)-3-hydroxypropanoate (3)[1]



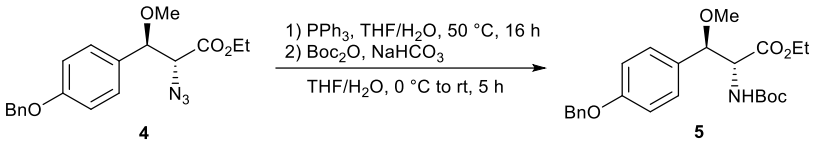
Under an atmosphere of N_2, freshly prepared nosylate **2a** (9.51 g, 19.0 mmol, 1.0 equiv.) was dissolved in anhydrous DMF and sodium azide (2.47 g, 37.9 mmol, 2.0 equiv.) was added. After heating to 50 °C overnight the mixture was diluted with EtOAc, washed three times with water and once with brine. The solvent was evaporated, and the crude product purified by column chromatography (silica, PE/EtOAc 8:2) to obtain azide **3** (5.40 g, 15.8 mmol, 83%) as a yellow solid, mp 95–98 °C (decomposition). R_f(**3**) = 0.33 (PE/EtOAc 4:1). $[\alpha]_D^{20}$ = +8.4 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.2 Hz, 3 H), 2.79 (d, *J* = 4.3 Hz, 1 H), 4.08 (d, *J* = 7.1 Hz, 1 H), 4.25 (q, *J* = 7.1 Hz, 2 H), 4.96 (dd, *J* = 7.0 Hz, *J* = 4.5 Hz, 1 H), 5.07 (s, 2 H), 6.98 (d, *J* = 8.7 Hz, 2 H), 7.31 (d, *J* = 8.7 Hz, 2 H), 7.38 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 62.1, 66.8, 70.0, 73.7, 114.9, 127.4, 127.9, 128.0, 128.6, 131.3, 136.8, 159.1, 168.9. HRMS (CI): m/z calcd for $C_{16}H_{23}N_3O_3$ $[M\text{-}C_2H_5O]^+$: 305.1739, found: 305.1692.

Ethyl (2*R*,3*R*)-2-azido-3-(4-(benzyloxy)phenyl)-3-methoxypropanoate (4)



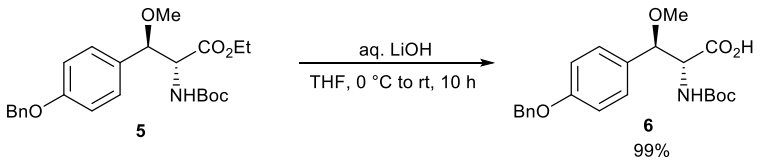
To a solution of azide **3** (7.50 g, 22.0 mmol) in CH_2Cl_2 (440 mL) were added silver oxide (10.2 g, 43.9 mmol, 2.0 equiv.) and methyl iodide (41.2 mL, 659 mmol, 30.0 equiv.). The mixture was stirred at reflux overnight, additional silver oxide (5.09 g, 22.0, 1.0 equiv.) was added, and the reaction stirred for another 8 hours before being filtrated through a pad of celite. The solvent was removed *in vacuo* and the residue purified by flash chromatography (silica, PE/EtOAc 95:5 → 9:1) to afford methyl ether **4** (6.79 g, 19.1 mmol, 87%) as a colorless oil. R_f(**4**) = 0.31 (PE/EtOAc 8:2). $[\alpha]_D^{20}$ = +14.7 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.2 Hz, 3 H), 3.24 (s, 3 H), 4.00 (d, *J* = 7.3 Hz, 1 H), 4.23 (dq, *J* = 10.8 Hz, *J* = 7.2 Hz, 1 H), 4.26 (dq, *J* = 10.8 Hz, *J* = 7.2 Hz, 1 H), 4.49 (d, *J* = 7.3 Hz, 1 H), 5.07 (s, 2 H), 6.99 (d, *J* = 8.7 Hz, 2 H), 7.28 (d, *J* = 8.6 Hz, 2 H), 7.37 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 56.9, 61.8, 66.4, 70.0, 82.7, 114.9, 127.5, 128.0, 128.6, 128.8, 128.8, 136.8, 159.3, 168.5. HRMS (CI): m/z calcd for $C_{19}H_{21}NO_4$ $[M-N_2]^+$: 327.1465, found: 327.1482.

Ethyl (2*R*,3*R*)-3-(4-(benzyloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)-3-methoxy propanoate (5)



Methyl ether **4** (9.06 g, 25.5 mmol) was dissolved in THF/H_2O (255 mL, 25:1), triphenyl-phosphine (20.1 g, 76.0 mmol, 3.0 equiv.) was added and the mixture was heated to 50 °C for 16 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was dissolved in THF/H_2O (350 mL, 2.5:1). Boc_2O (7.10 mL, 30.6 mmol, 1.2 equiv.) and $NaHCO_3$ (4.28 g, 51.0 mmol, 2.0 equiv.) were added and the reaction was stirred for 6 hours at 0 °C. The mixture was acidified with 1 M HCl (pH = 2) and extracted three times with CH_2Cl_2. The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (silica, PE/EtOAc 85:15) afforded Boc-protected amine **5** (10.8 g, 25.2 mmol, 99%) as a colorless resin. R_f(**5**) = 0.24 (PE/EtOAc 85:15). $[\alpha]_D^{20}$ = +21.3 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (t, *J* = 7.2 Hz, 3 H), 1.40 (s, 9 H), 3.30 (s, 3 H), 4.10 (q, *J* = 7.0 Hz, 1 H), 4.48 (d, *J* = 4.5 Hz, 1 H), 4.56 (dd, *J* = 8.7 Hz, *J* = 5.5 Hz, 1 H), 5.06 (s, 2 H), 5.12 (d, *J* = 8.8 Hz, 1 H), 6.96 (d, *J* = 8.7 Hz, 2 H), 7.21 (d, *J* = 8.6 Hz, 2 H), 7.37 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 28.2, 57.4, 58.4, 61.1, 70.0, 79.8, 83.3, 114.7, 127.4, 128.0, 128.2, 128.6, 129.2, 136.9, 155.1, 158.8, 170.3. HRMS (CI): m/z calcd for $C_{24}H_{32}NO_6$ $[M+H]^+$: 430.2224, found: 430.2248.

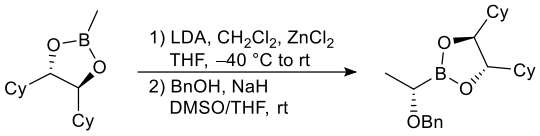
(2*R*,3*R*)-3-(4-(Benzyloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)-3-methoxypropanoic acid (6)



To a solution of ethyl ester **5** (1.66 g, 3.86 mmol) in THF (39 mL) was slowly added a freshly prepared solution of lithium hydroxide (4.25 mL, 4.25 mmol, 1.0 M in H_2O, 1.1 equiv.) at 0 °C. After complete conversion (TLC), the mixture was concentrated, the residue redissolved in water and acidified with 1 M HCl (pH = 2). The aqueous layer was extracted twice with EtOAc, and the combined organic layer washed with brine, dried over Na_2SO_4 and the solvent removed *in vacuo* to afford carboxylic acid **6** (1.53 g, 3.81 mmol, 99%) as a white solid, mp 105–107 °C. R_f(**6**) = 0.09 (PE/EtOAc 7:3). $[\alpha]_D^{20}$ = +35.9 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 9 H), 3.23 (s, 3 H), 4.41 (d, *J* = 4.8 Hz, 1 H), 4.49

(dd, *J* = 8.9 Hz, *J* = 5.1 Hz, 1 H), 4.99 (s, 2 H), 5.06 (d, *J* = 8.9 Hz, 1 H), 6.89 (d, *J* = 8.7 Hz, 2 H), 7.14 (d, *J* = 8.6 Hz, 2 H), 7.25 (m, 1 H), 7.33 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.2, 57.3, 58.2, 70.0, 80.3, 83.0, 114.8, 127.5, 128.0, 128.2, 128.6, 136.8, 126.9, 158.9, 159.0, 174.0. HRMS (CI): m/z calcd for $C_{22}H_{28}NO_6$ $[M+H]^+$: 402.1911, found: 401.1887.

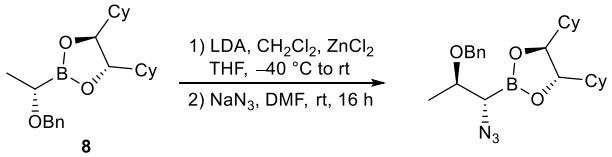
(4*S*,5*S*)-2-((*S*)-1-(Benzyloxy)ethyl)-4,5-dicyclohexyl-1,3,2-dioxaborolane (8)



7 **8** 68%

According to **GP-1**, boronic ester **7**[2] (4.00 g, 16.0 mmol) was reacted with CH_2Cl_2 (3.09 mL, 48.0 mmol, 3.0 equiv.), DIPA (3.08 mL, 21.6 mmol, 1.35 equiv.), *n*-BuLi (7.99 mL, 20.0 mmol, 2.5 M in hexane, 1.25 equiv.) and zinc chloride (4.36 g, 32.0 mmol, 2.0 equiv.) overnight. The nucleophile solution was prepared by suspending sodium hydride (831 mg, 20.8 mmol, 1.3 equiv.) in dry DMSO/THF (42 mL, 3:1) and stirring at room temperature for 6 hours after addition of benzyl alcohol (2.33 mL, 22.4 mmol, 1.4 equiv.). To the solution of the chloro-boronic ester mixture was added the nucleophile solution at 0 °C and the mixture was stirred at room temperature until complete consumption of the starting material was observed (NMR). After aqueous work-up and flash chromatography (silica, pentane/diethyl ether 9:1), benzyl ether **8** (4.01 g, 10.8 mmol, 68%) was obtained as a colorless oil. R_f(**8**) = 0.30 (pentane/diethyl ether 9:1). $[\alpha]_D^{20}$ = –57.3 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (m, 10 H), 1.32 (d, *J* = 7.5 Hz, 3 H), 1.36 (m, 2 H), 1.60 (m, 2 H), 1.68 (m, 2 H), 1.77 (m, 6 H), 3.45 (q, *J* = 7.5 Hz, 1 H), 3.91 (d, *J* = 3.7 Hz, 1 H), 3.93 (d, *J* = 3.6 Hz, 1 H), 4.54 (d, *J* = 12.0 Hz, 1 H), 4.59 (d, *J* = 12.0 Hz, 1 H), 7.25 (m, 1 H), 7.33 (m, 4 H, 13-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.8, 25.9, 26.0, 26.4, 27.3, 28.1, 42.9, 62.8, 71.6, 83.6, 127.3, 127.8, 128.2, 139.1. HRMS (CI): m/z calcd for $C_{23}H_{36}BO_3$ $[M+H]^+$: 371.2752, found: 371.2784.

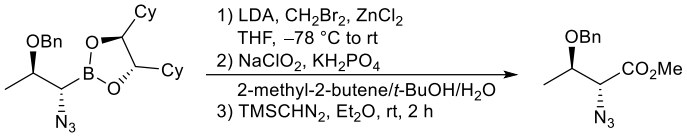
(4*S*,5*S*)-2-((1*S*,2*R*)-1-Azido-2-(benzyloxy)propyl)-4,5-dicyclohexyl-1,3,2-dioxaborolane (9)



8 **9** 79%

According to **GP-1**, benzyl ether **8** (3.80 g, 10.3 mmol) was treated with CH_2Cl_2 (1.98 mL, 30.8 mmol, 3.0 equiv.), DIPA (1.97 mL, 13.9 mmol, 1.35 equiv.), *n*-BuLi (5.13 mL, 12.8 mmol, 2.5 M in hexane, 1.25 equiv.) and zinc chloride (4.20 g, 30.8 mmol, 3.0 equiv.) overnight. After aqueous work up and removal of the solvent, the chloro-boronic ester was dissolved in DMF (103 mL). Sodium azide (6.67 g, 103 mmol, 10.0 equiv.) was added and the mixture was stirred at room temperature for 12 hours. Aqueous work up and flash chromatography (silica, pentane/diethyl ether 95:5) afforded azide **9** (3.43 g, 8.02 mmol, 79%, >98:2 *dr*) as a colorless oil. R_f(**9**) = 0.49 (pentane/diethyl ether 9:1). $[\alpha]_D^{20}$ = –41.6.0 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (m, 10 H), 1.31 (d, *J* = 6.4 Hz, 3 H), 1.33 (m, 2 H), 1.59 (m, 2 H), 1.66 (m, 2 H), 1.74 (m, 6 H), 3.30 (d, *J* = 3.1 Hz, 1 H), 3.91 (qd, *J* = 6.4 Hz, *J* = 3.2 Hz, 1 H), 3.94 (m, 2 H), 4.58 (s, 2 H), 7.25 (m, 1 H), 7.33 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.2, 25.8, 25.9, 26.3, 27.3, 28.3, 42.8, 53.2, 70.7, 77.0, 84.2, 127.4, 127.4, 128.3, 138.4. HRMS (CI): The compound decomposes during the measurements.

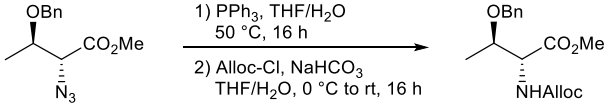
Methyl (2*R*,3*R*)-2-azido-3-(benzyloxy)butanoate (10)



9 **10** 96%

According to **GP-1**, azide **9** (2.00 g, 4.70 mmol) was treated with dibromomethane (985 µL, 14.1 mmol, 3.0 equiv.), DIPA (905 µL, 6.35 mmol, 1.35 equiv.), *n*-BuLi (2.35 mL, 5.88 mmol, 2.5 M in hexane, 1.25 equiv.) and zinc chloride (1.92 g, 14.1 mmol, 3.0 equiv.) at –78 °C and stirred at room temperature for 12 hours. After aqueous work up, the bromo-boronic ester was suspended in *t*-BuOH/H_2O (135 mL, 2:1) and 2-methyl-2-butene (19.9 mL, 188 mmol, 40.0 equiv.), sodium chlorite (5.31 g, 47.0 mmol, 10.0 equiv.) and KH_2PO_4 (6.40 g, 47.0 mmol, 10.0 equiv.) were added. The mixture was stirred at room temperature overnight, acidified with 10% citric acid (pH 4) and extracted three times with diethyl ether. Washing of the combined organic layer with sat. $Na_2S_2O_3$ and drying over Na_2SO_4 was followed by esterification of the cleaved diol with methylboronic acid (338 mg, 5.64 mmol, 1.2 equiv.) in diethyl ether (40 mL) in the presence of $MgSO_4$ (1.13 g, 9.40 mmol, 2.0 equiv.). After filtration of the mixture and evaporation of the solvent, the residue was dissolved in toluene/MeOH (94 mL, 5:1) and TMS-diazomethane (3.53 mL, 7.05 mmol, 1.5 equiv.) was added. After complete consumption of the starting material (TLC), the reaction was diluted with diethyl ether and quenched by addition of 10% acetic acid. The layers were separated, the aqueous layer extracted once with diethyl ether and the combined organic layer was washed with sat. $NaHCO_3$ solution and brine. Drying over Na_2SO_4 and purification via flash chromatography (silica, pentane/diethyl ether 92:8) afforded methyl ester **10** (1.13 g, 4.53 mmol, 96%) as a colorless oil. R_f(**10**) = 0.41 (pentane/diethyl ether 4:1). $[\alpha]_D^{20}$ = –23.9 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (d, *J* = 6.2 Hz, 3 H), 3.78 (s, 3 H), 3.98 (qd, *J* = 6.2 Hz, *J* = 5.3 Hz, 1 H), 4.06 (d, *J* = 5.0 Hz, 1 H), 4.55 (d, *J* = 11.7 Hz, 1 H), 4.62 (d, *J* = 11.7 Hz, 1 H), 7.32 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9, 52.6, 65.5, 71.3, 75.3, 127.6, 127.8, 128.4, 137.6, 169.0. HRMS (CI): m/z calcd for $C_{12}H_{15}NO_3$ $[M\text{-}N_2]^+$: 221.1046, found: 221.1057.

Methyl *N*-((allyloxy)carbonyl)-*O*-benzyl-D-*allo*-threoninate (11)

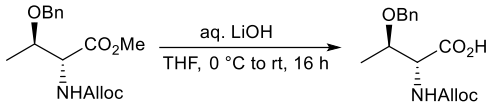


10 **11** 80%

To a solution of azide **10** (900 mg, 3.61 mmol) in THF/H_2O (36 mL, 25:1) was added PPh_3 (2.84 g, 10.8 mmol, 3.0 equiv.) and the mixture was heated to 50 °C for 15 hours. After cooling to room temperature, H_2O (10 mL) and $NaHCO_3$ (607 mg, 7.22 mmol, 2.0 equiv.) were added. The mixture was cooled to 0 °C, allyl chloroformate (578 µL, 5.42 mmol, 1.5 equiv.) was added dropwise and the reaction was stirred overnight. The reaction was quenched with 1 M HCl, the mixture extracted three times with CH_2Cl_2, and the combined organic layer was washed with brine. After drying (Na_2SO_4), evaporation of the solvent under reduced pressure and flash chromatography (silica, pentane/diethyl ether 3:1 → 2:1) the Alloc-protected amine **11** (891 mg, 2.90 mmol, 80%) was obtained as a colorless oil. R_f(**11**) = 0.15 (pentane/diethyl ether 3:1). $[\alpha]_D^{20}$ = –12.7 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 6.5 Hz, 3 H), 3.75 (s, 3 H), 3.87 (m, 1 H), 4.56 (m, 5 H), 5.21 (d, *J* = 10.4 Hz, 1 H), 5.30 (d,

J = 17.1 Hz, 1 H), 5.39 (d, *J* = 8.3 Hz, 1 H), 5.91 (ddt, *J* = 16.8 Hz, *J* = 10.9 Hz, *J* = 5.5 Hz, 1 H), 7.30 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.1, 52.3, 57.2, 65.8, 70.9, 74.9, 117.8, 127.6, 127.7, 128.3, 132.5, 137.8, 155.8, 170.7. HRMS (CI): m/z calcd for $C_{16}H_{22}NO_5$ $[M+H]^+$: 308.1492, found: 308.1486.

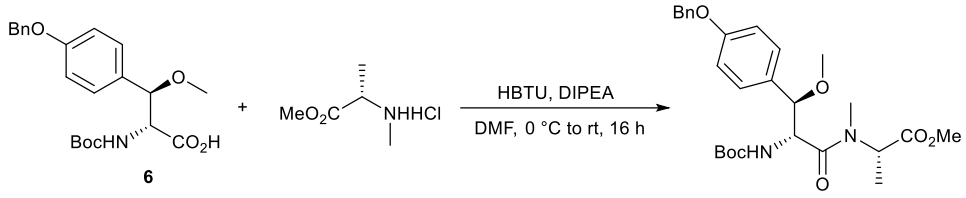
_N_-((Allyloxy)carbonyl)-_O_-benzyl-D-_allo_-threonine (12)



11 **12**
99%

Methyl ester **11** (400 mg, 1.30 mmol) was dissolved in THF (13 mL) and LiOH (1.43 mL, 1.43 mmol, 1.0 M, 1.0 equiv.) was added at 0 °C. After stirring at room temperature until complete conversion was observed by (TLC), the reaction was acidified (pH 2) with 1 M HCl and extracted three times with diethyl ether. The combined organic layer was washed with brine, dried over Na_2SO_4 and the solvent removed *in vacuo* to afford carboxylic acid **12** (377 mg, 1.28 mmol, 99%) as a colorless oil. R_f(**12**) = 0.06 (pentane/diethyl ether 7:3). $[\alpha]_D^{20}$ = –17.4 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (d, *J* = 6.4 Hz, 3 H), 3.93 (m, 1 H), 4.58 (m, 5 H), 5.21 (d, *J* = 10.6 Hz, 1 H), 5.31 (d, *J* = 17.2 Hz, 1 H), 5.49 (d, *J* = 8.1 Hz, 1 H), 5.91 (ddt, *J* = 16.8 Hz, *J* = 10.9 Hz, *J* = 5.4 Hz, 1 H), 7.31 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.1, 56.9, 65.9, 71.0, 74.9, 117.8, 127.8, 127.8, 128.4, 132.6, 137.8, 156.0, 172.8. HRMS (CI): m/z calcd for $C_{15}H_{20}NO_5$ $[M+H]^+$: 294.1336, found: 294.1355.

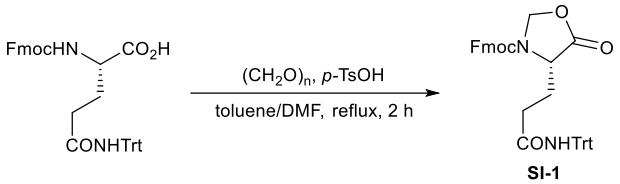
Methyl _N_-((2_R_,3_R_)-3-(4-(benzyloxy)phenyl)-2-((_tert_-butoxycarbonyl)amino)-3-methoxy-propanoyl)-_N_-methyl-L-alaninate (13)



6 **13**
94%

To a solution of tyrosine **6** (7.93 g, 19.8 mmol) in dry DMF (198 mL) were added *N*-methyl-L-alanine methyl ester hydrochloride (6.07 g, 39.5 mmol, 2.0 equiv.), DIPEA (10.4 mL, 59.3 mmol, 3.0 equiv.) and HBTU (7.87 g, 20.7 mmol, 1.05 equiv.) at 0 °C. The mixture was allowed to warm to room temperature overnight, was diluted with EtOAc and successively washed with sat. solution of $NaHCO_3$, 1 M HCl and brine. After drying over Na_2SO_4, the solvent was removed *in vacuo* and the residue purified twice via column chromatography (silica, PE/EtOAc 8:2 → 7:3 → 1:1) to obtain dipeptide **13** (9.29 g, 18.6 mmol, 94%) as a colorless resin. R_f(**13**) = 0.15 (PE/EtOAc 7:3). $[\alpha]_D^{20}$ = +43.2 (c = 1.0, $CHCl_3$). Main rotamer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 9 H), 1.37 (d, *J* = 7.2 Hz, 3 H), 2.91 (s, 3 H), 3.17 (s, 3 H), 3.71 (s, 3 H), 4.23 (d, *J* = 8.1Hz, 1 H), 4.84 (t, *J* = 9.0 Hz, 1 H), 5.06 (s, 2 H), 5.25 (m, 1 H), 6.96 (d, *J* = 8.6 Hz, 2 H), 7.34 (m, 7 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 28.1, 31.7, 52.2, 52.5, 54.2, 57.0, 70.0, 79.4, 85.4, 114.6, 127.4, 127.9, 128.6, 129.0, 129.9, 136.9, 154.5, 158.9, 171.5, 172.0. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (s, 9 H), 1.50 (d, *J* = 7.1 Hz, 3 H), 2.97 (s, 3 H), 3.08 (s, 3 H), 3.76 (s, 3 H), 4.17 (d, *J* = 8.9Hz, 1 H), 5.25 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.2, 28.1, 29.8, 54.0, 56.8, 85.0, 114.5, 127.4, 128.1, 128.6, 129.1, 129.8, 172.0. HRMS (CI): m/z calcd for $C_{27}H_{37}N_2O_7$ $[M+H]^+$: 501.2595, found: 501.2602.

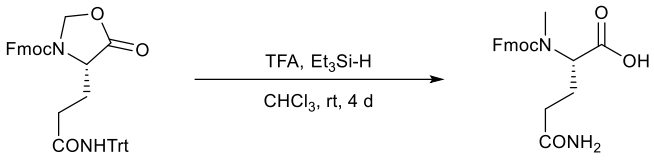
(9H-Fluoren-9-yl)methyl (*S*)-5-oxo-4(3-oxo-3-(tritylamino)propyl)oxazolidine-3-carboxylate (SI-1)[3]



SI-1

In a 500 mL three-neck round-bottom flask fitted with a Dean-Stark apparatus, *p*-formaldehyde (9.83 g, 327 mmol, 20 equiv.) and *p*-TsOH (311 mg, 1.64 mmol, 0.1 equiv.) were suspended in dry toluene (250 mL). After addition of a solution of N_δ-Trityl-N_α-Fmoc-glutamine (10.0 g, 16.4 mmol) in DMF (20 mL) the mixture was heated to reflux for two hours. The resulting clear solution was cooled to room temperature, diluted with EtOAc and successively washed with sat. $NaHCO_3$ (3x), water and brine. The organic layer was dried (Na_2SO_4), concentrated *in vacuo* and the residue purified by flash chromatography (silica, PE/EtOAc 6:4) to afford oxazolidinone **13a** (9.66 g, 15.5 mmol, 95%) as a white solid, mp 100–102 °C. R_f(**13a**) = 0.30 (PE/EtOAc 6:4). $[\alpha]_D^{20}$ = –17.3 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.85 (m, 2 H), 2.18 (m, 1 H), 2.36 (m, 1 H), 4.00 (m, 1 H), 4.30 (t, *J* = 6.3 Hz, 1 H), 4.41 (dd, *J* = 10.3 Hz, *J* = 6.3 Hz, 1 H), 4.47 (dd, *J* = 10.3 Hz, *J* = 6.6 Hz, 1 H), 5.12 (bs, 1 H), 5.32 (m, 1 H), 7.15 (m, 6 H), 7.19 (m, 3 H), 7.25 (m, 6 H), 7.31 (m, 2 H), 7.40 (m, 2 H), 7.64 (dd, *J* = 7.3 Hz, *J* = 3.2 Hz, 2 H), 7.87 (d, *J* = 7.3 Hz, 2 H), 8.59 (bs, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 26.0, 30.8, 46.6, 54.9, 67.2, 77.8, 120.2, 125.2, 126.4, 127.3, 127.5, 127.8, 128.6, 140.8, 143.6, 144.9, 170.8, 172.4. HRMS (CI): m/z calcd for $C_{40}H_{35}N_2O_5$ $[M+H]^+$: 623.2540, found: 623.2562.

N^2-(((9H-Fluoren-9-yl)methoxy)carbonyl)-N^2-methyl-L-glutamine (SI-2)[3]

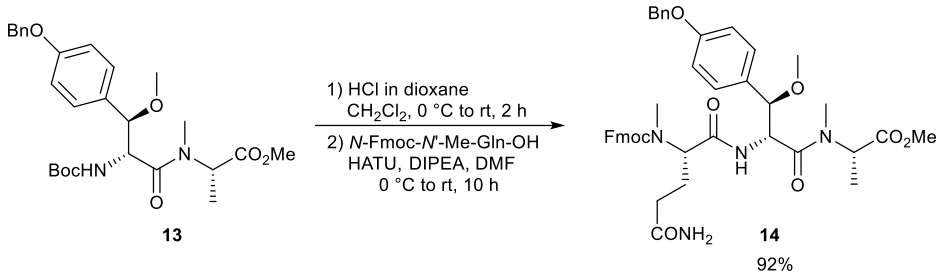


SI-1 **SI-2**

88%

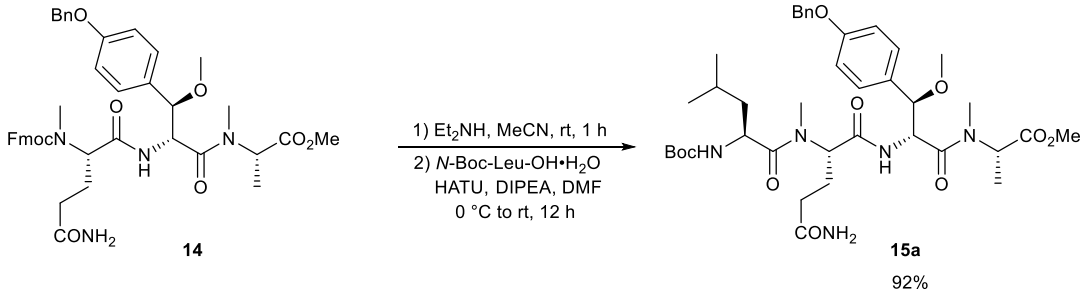
Oxazolidinone **13a** (9.00 g, 14.5 mmol) was dissolved in $CHCl_3$ (115 mL) and trifluoroacetic acid (78.0 mL, 1.01 mol, 70 equiv.) was added which resulted in a dark orange solution. After addition of Et_3Si-H (9.23 mL, 57.8 mmol, 4.0 equiv.) the reaction was sealed and over 4 days the mixture gradually turned colorless again. The solvent was removed *in vacuo* and the residue co-evaporated with toluene twice. Flash chromatography (silica, DCM/MeOH 95:5 → 9:1) yielded glutamine **13b** (4.86 g, 12.7 mmol, 88%) as a white solid, mp 150–151 °C (decomposition). R_f(**13b**) = 0.21 (DCM/MeOH 9:1). $[\alpha]_D^{20}$ = –9.3 (c = 1.0, $CHCl_3$). Major rotamer: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.86 (m, 1 H), 2.09 (m, 3 H), 2.78 (s, 3 H), 4.28 (m, 3 H), 4.51 (m, 1 H), 6.76 (s, 2 H), 7.31 (m, 2 H), 7.42 (t, *J* = 7.0 Hz, 2 H), 7.66 (d, *J* = 7.5 Hz, 2 H), 7.89 (m, 2 H), 12.85 (bs, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.0, 30.6, 31.5, 46.6, 58.2, 66.9, 120.1, 125.1, 127.2, 127.7, 140.7, 143.8, 143.8, 156.1, 172.4, 173.3. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.77 (s, 3 H), 6.80 (s, 1 H), 7.63 (d, *J* = 7.6 Hz, 2 H). HRMS (CI): m/z calcd for $C_{21}H_{24}N_2O_5$ $[M+2H]^+$: 384.1680, found: 384.1668.

Methyl *N*-((2*R*,3*R*)-2-((*S*)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-5-amino-5-oxopentanamido)-3-(4-(benzyloxy)phenyl)-3-methoxypropanoyl)-*N*-methyl-L-alaninate (14)



Dipeptide **13** (3.10 g, 6.19 mmol) was dissolved in DCM (15 mL) and treated with HCl (15.5 mL, 61.9 mmol, 4.0 M in dioxane, 10.0 equiv.) at 0 °C until complete Boc-deprotection was observed by TLC. The mixture was concentrated, dried in high vacuum and redissolved in dry DMF (62 mL). To the hydrochloride solution were added, *N*-Fmoc-*N*-Me-glutamine (2.49 g, 6.50 mmol, 1.05 equiv.), DIPEA (2.27 mL, 13.0 mmol, 2.1 equiv.) and HATU (2.59 g, 6.81 mmol, 1.1 equiv.) at 0 °C and the reaction was stirred overnight. The mixture was diluted with EtOAc and washed with 1 M HCl, sat. $NaHCO_3$ solution and brine. After drying (Na_2SO_4), the solvent was removed under reduced pressure and the residue purified by flash chromatography (silica, DCM/MeOH 98:2 → 97:3) to yield tripeptide **14** (4.37 g, 5.71 mmol, 92%) as a white amorphous solid**.** R_f(**14**) = 0.27 (DCM/MeOH 95:5). $[\alpha]_D^{20}$ = –29.3 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.37 (d, *J* = 7.2 Hz, 3 H), 1.84 (m, 3 H), 2.04 (m, 1 H), 2.66 (s, 3 H), 2.95 (s, 3 H), 3.15 (s, 3 H), 3.63 (s, 3 H), 4.25 (m, 1 H), 4.29 (d, *J* = 7.8 Hz, 1 H), 4.45 (m, 2 H), 5.03 (m, 2 H), 5.19 (m, 2 H), 5.26 (bs, 1 H), 6.74 (m, 1 H), 6.95 (d, *J* = 8.1 Hz, 2 H), 7.25 (m, 1 H), 7.35 (m, 11 H), 7.58 (d, *J* = 7.5 Hz), 7.76 (d, *J* = 7.5 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 23.7, 29.9, 31.8, 47.2, 47.2, 52.2, 52.7, 57.0, 58.3, 70.0, 77.2, 84.5, 114.7, 120.0, 125.0, 127.1, 127.5, 127.7, 127.7, 128.1, 128.6, 129.7, 136.7, 141.3, 141.3, 158.9, 168.7, 170.8, 171.8. HRMS (CI): m/z calcd for $C_{43}H_{49}N_4O_9$ $[M+H]^+$: 765.3494, found: 765.3477.

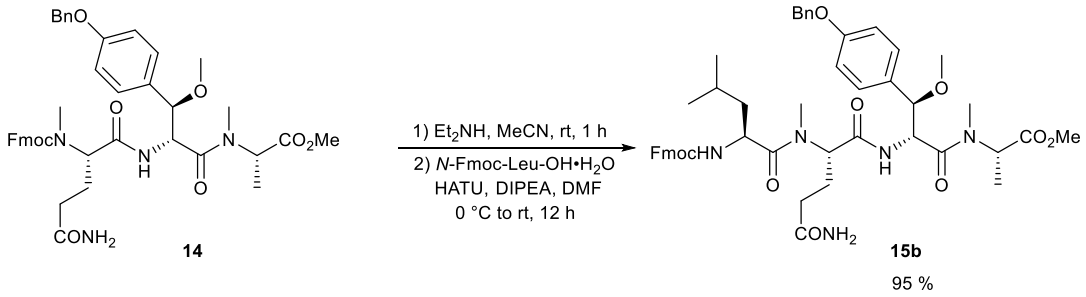
Methyl *N*-((2*R*,3*R*)-2-((*S*)-5-amino-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-*N*,4-dimethyl-pentanamido)-5-oxopentanamido)-3-(4-(benzyloxy)phenyl)-3-methoxypropanoyl)-*N*-methyl-L-alaninate (15a)



To a solution of tripeptide **14** (723 mg, 945 µmol) in MeCN (20 mL) was added diethylamine (7.90 mL, 76.0 mmol, 80.0 equiv.) and the mixture was stirred at room temperature for 30 minutes. The solvent was removed *in vacuo* and the crude product was dried in high vacuum for 4 hours. The amine and Boc-L-leucine hydrate (471 mg, 1.89 mmol, 2.0 equiv.) were dissolved in dry DMF (18 mL) and treated with DIPEA (660 µL, 3.78 mmol, 4.0 equiv.) and HATU (719 mg, 1.89 mmol, 2.0 equiv.) at 0 °C. After warming to room temperature overnight, the reaction was diluted with EtOAc and successively washed with 1 M HCl, sat. $NaHCO_3$ solution and brine. The organic layer was dried (Na_2SO_4), the solvent removed *in vacuo* and the residue purified by flash chromatography (silica, DCM/MeOH 97:3 → 95:5) to afford tetrapeptide **15a** (660 mg, 873 µmol, 92%) as a white foam.

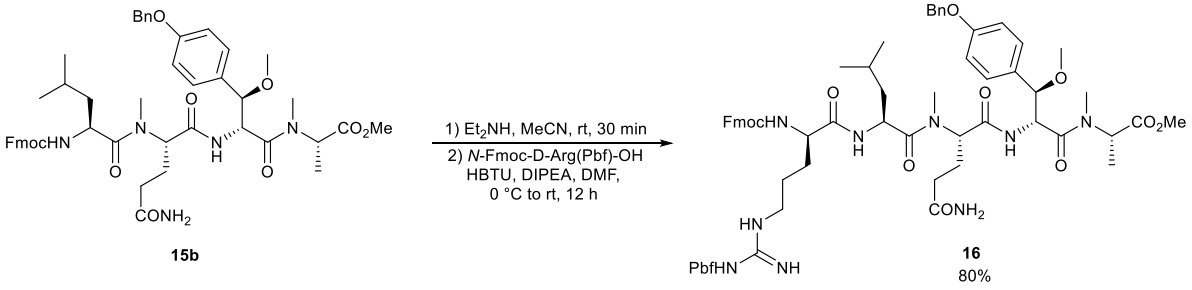
R_f(**15a**) = 0.29 (DCM/MeOH 95:5). $[\alpha]_D^{20}$ = –31.6 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, DMSO-d_6, 373K): δ = 0.89 (d, *J* = 6.6 Hz, 6 H), 1.33 (d, *J* = 6.9 Hz, 3 H), 1.36 (m, 1 H), 1.40 (s, 9 H), 1.43 (m, 1 H), 1.53 (m, 2 H), 1.67 (m, 1 H), 1.80 (m, 2 H), 2.74 (s, 3 H), 2.99 (s, 3 H), 3.10 (s, 3 H), 3.63 (s, 3 H), 4.36 (m, 2 H), 4.77 (m, 1 H), 4.92 (m, 1 H), 5.03 (m, 1 H), 5.10 (s, 2 H), 6.37 (bs, 1 H), 6.53 (bs, 2 H), 6.97 (d, *J* = 8.5 Hz, 2 H), 7.27 (d, *J* = 7.8 Hz, 2 H), 7.32 (m, 1 H), 7.39 (m, 2 H), 7.44 (m, 2 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 13.4, 21.0, 22.1, 23.4, 23.8, 27.7, 29.6, 31.1, 31.4, 40.1, 48.9, 51.1, 52.0, 52.6, 55.4, 56.0, 69.2, 77.8, 82.7, 114.1, 127.0, 127.1, 127.8, 128.5, 129.8, 136.8, 154.7, 158.0, 168.5, 169.7, 170.9, 172.8. HRMS (CI): m/z calcd for $C_{39}H_{58}N_5O_{10}$ $[M+H]^+$: 756.4178, found: 756.4201.

Methyl *N*-((2*R*,3*R*)-2-((*S*)-2-((*S*)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-*N*,4-dimethyl-pentanamido)-5-amino-5-oxopentanamido)-3-(4-(benzyloxy)phenyl)-3-methoxypropanoyl)-*N*-methyl-L-alaninate (15b)



A solution of tripeptide **14** (2.11 mg, 2.76 mmol) in MeCN (55 mL) was treated with diethylamine (23.1 mL, 221 mmol, 80.0 equiv.) at room temperature for 60 minutes. The solvent was removed *in vacuo* and the crude product was dried in high vacuum for 4 hours. The residue was dissolved in dry DMF (55 mL) and Fmoc-L-leucine (1.95 g, 5.52 mmol, 2.0 equiv.), DIPEA (1.93 mL, 11.0 mmol, 4.0 equiv.) as well as HATU (2.10 g, 5.52 mmol, 2.0 equiv.) were added at 0 °C. After 15 hours, the mixture was diluted with EtOAc and washed with 1 M HCl, sat. $NaHCO_3$ solution and brine. The organic layer was dried (Na_2SO_4), the solvent removed *in vacuo* and the crude product purified by flash chromatography (silica, DCM/MeOH 97:3 → 95:5) to afford tetrapeptide **15b** (2.30 g, 2.62 mmol, 95%) as a colorless foam. R_f(**15b**) = 0.36 (DCM/MeOH 95:5). $[\alpha]_D^{20}$ = –61.2 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, DMSO-d_6, 373K): δ = 0.87 (d, *J* = 6.6 Hz, 3 H), 0.89 (d, *J* = 6.9 Hz, 3 H), 1.27 (m, 2 H), 1.32 (d, *J* = 6.0 Hz, 3 H), 1.59 (m, 2 H), 1.80 (m, 3 H), 2.97 (s, 6 H), 3.10 (s, 3 H), 3.58 (dd, *J* = 8.2 Hz, *J* = 5.0 Hz, 1 H), 3.63 (s, 3 H), 4.36 (d, *J* = 7.8 Hz, 1 H), 4.37 (m, 1 H), 4.73 (bs, 1 H), 4.90 (m, 1 H), 5.03 (m, 1 H), 5.10 (s, 2 H), 6.22 (s, 2 H), 6.55 (bs, 2 H), 6.97 (d, *J* = 8.5 Hz, 2 H), 7.27 (m, 2 H), 7.32 (m, 3 H), 7.39 (m, 4 H), 7.44 (m, 2 H), 7.81 (d, *J* = 7.5 Hz, 2 H), 7.86 (d, *J* = 7.2 Hz, 2 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 13.4, 21.3, 22.3, 23.4, 23.7, 28.4, 31.5, 31.5, 44.9, 48.7, 51.1, 52.0, 52.6, 55.0, 56.0, 69.2, 83.0, 108.4, 114.1, 119.3, 120.7, 126.6, 126.8, 126.9, 127.1, 127.8, 128.3, 128.5, 128.8, 136.8, 139.1, 142.3, 158.0, 161.3, 166.1, 169.8, 170.9, 172.8. HRMS (CI): m/z calcd for $C_{39}H_{58}N_5O_{10}$ $[M+H]^+$: 756.4178, found: 756.4201.

Methyl *N*-((2*R*,3*R*)-2-((*S*)-2-((*S*)-2-((*R*)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(3-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)guanidino)pentanamido)-*N*,4-dimethylpentanamido)-5-amino-5-oxopentanamido)-3-(4-(benzyloxy)phenyl)-3-methoxypropan-oyl)-*N*-methyl-L-alaninate (16)



After Fmoc-deprotection of tetrapeptide **15b** (74.0 mg, 84.3 µmol) with diethylamine (704 µL, 6.74 mmol, 80 equiv.) in MeCN (1.7 mL) according to **GP-2**, the amine was dissolved in dry DMF (840 µL) and N_α-Fmoc-N_ω-Pbf-D-arginine (82.0 mg, 126 µmol, 1.5 equiv.) was added. Addition of DIPEA (41.1 µL, 235 µmol, 2.8 equiv.) and HBTU (47.8 mg, 126 µmol, 1.5 equiv.) at 0 °C was followed by stirring for 15 hours and dilution with EtOAc. The mixture was washed with 1 M HCl, sat. $NaHCO_3$ solution and brine, the organic layer dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (silica, DCM/MeOH 95:5 → 9:1) afforded pentapeptide **16** (86.2 mg, 67.0 µmol, 80%) as a colorless foam. R_f(**16**) = 0.08 (DCM/MeOH 95:5). $[\alpha]_D^{20}$ = –49.0 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, DMSO-d_6, 373K): δ = 0.85 (d, *J* = 6.6 Hz, 6 H), 1.32 (m, 3 H), 1.42 (s, 6 H), 1.45 (m, 4 H), 1.58 (m, 2 H), 1.68 (m, 1 H), 1.79 (m, 2 H), 2.02 (s, 3 H), 2.47 (s, 3 H), 2.53 (s, 3 H), 2.74 (bs, 3 H), 2.95 (s, 2 H), 3.00 (m, 3 H), 3.09 (m, 5 H), 3.62 (bs, 3 H), 4.06 (m, 1 H), 4.21 (t, *J* = 6.9 Hz, 1 H), 4.30 (d, *J* = 6.9 Hz, 2 H), 4.37 (m, 1 H), 4.69 (m, 2 H), 4.94 (m, 1 H), 5.04 (m, 1 H), 5.09 (s, 2 H), 6.41 (s, 2 H), 6.55 (m, 2 H), 6.96 (d, *J* = 8.8 Hz, 2 H), 6.98 (m, 1 H), 7.27 (m, 2 H), 7.31 (m, 3 H), 7.38 (m, 4 H), 7.43 (t, *J* = 7.1 Hz, 2 H), 7.68 (dd, *J* = 7.2 Hz, *J* = 4.7 Hz, 2 H), 7.71 (m, 1 H), 7.85 (d, *J* = 7.5 Hz, 2 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 11.4, 13.4, 16.8, 18.1, 21.1, 22.4, 23.8, 25.0, 27.7, 29.1, 29.8, 31.1, 31.4, 39.5, 39.9, 42.2, 46.4, 47.1, 51.1, 51.9, 52.5, 54.1, 55.5, 56.0, 65.5, 69.2, 82.7, 85.6, 114.1, 115.7, 119.4, 123.7, 124.6, 126.5, 126.5, 126.9, 127.0, 127.1, 127.8, 128.5, 129.8, 131.0, 134.2, 136.6, 136.8, 140.3, 143.3, 143.4, 155.2, 155.7, 157.1, 158.0, 168.5, 169.8, 170.8, 172.1, 172.1, 172.8. HRMS (ESI): m/z calcd for $C_{68}H_{88}N_9O_{14}S$ $[M+H]^+$: 1286.6166, found: 1286.6201.

Methyl *N*-((2*R*,3*R*)-2-((*S*)-2-((*S*)-2-((*R*)-2-((2*R*,3*R*)-2-(((allyloxy)carbonyl)amino)-3-(benzyl-oxy)-butan-amido)-5-(3-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl) guanidino)-pentanamido)-*N*,4-dimethylpentanamido)-5-amino-5-oxopentanamido)-3-(4-(benzyloxy)-phenyl)-3-methoxy-propanoyl)-*N*-methyl-L-alaninate (17)

According to **GP-2** pentapeptide **16** (1.80 g, 1.40 mmol) was treated with diethylamine (11.7 mL, 112 mmol, 80.0 equiv.) in MeCN (28 mL) for 30 minutes. To a solution of the deprotected amine in dry DMF (14 mL) were added *N*-Alloc-(*O*Bn)-D-*allo*-threonine (605 mg, 1.96 mmol, 1.4 equiv.), DIPEA

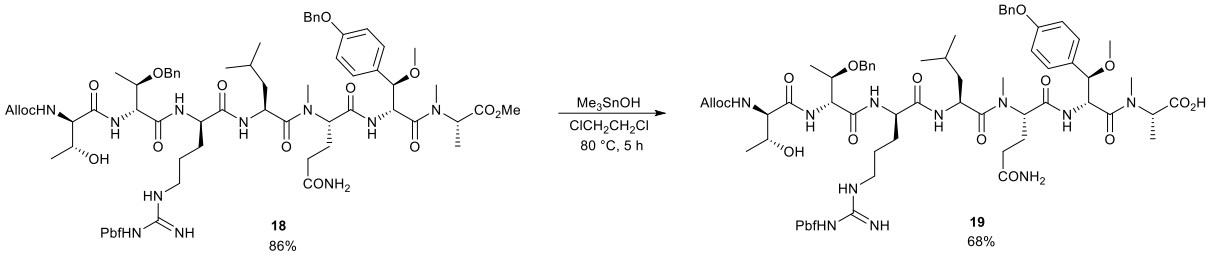
(611 µL, 3.50 mmol, 2.5 equiv.) and HBTU (743 mg, 1.96 mmol, 1.4 equiv.) at 0 °C. After stirring at room temperature overnight, the reaction was diluted with EtOAc and washed with 1 M HCl, sat. $NaHCO_3$ solution and brine. The organic layer was dried (Na_2SO_4), the solvent removed under reduced pressure and the residue purified by flash chromatography (silica, DCM/MeOH 95:5 → 9:1) to afford hexapeptide **17** (1.59 g, 1.19 mmol, 85%) as a white foam. R_f(**17**) = 0.13 (DCM/MeOH 95:5). $[\alpha]_D^{20}$ = –47.2 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, DMSO-d_6, 373K): δ = 0.85 (d, *J* = 6.2 Hz, 3 H), 0.87 (d, *J* = 6.2 Hz, 3 H), 1.10 (d, *J* = 6.3 Hz, 3 H), 1.32 (d, *J* = 6.9 Hz, 3 H), 1.43 (s, 6 H), 1.45 (m, 3 H), 1.58 (m, 3 H), 1.71 (m, 1 H), 1.78 (m, 2 H), 2.03 (s, 3 H), 2.46 (s, 3 H), 2.50 (s, 3 H), 2.52 (s, 3 H), 2.73 (bs, 3 H), 2.96 (bs, 2 H), 3.00 (m, 1 H), 3.05 (m, 2 H), 3.10 (bs, 3 H), 3.63 (bs, 3 H), 3.88 (m, 1 H), 4.06 (m, 1 H), 4.38 (m, 3 H), 4.51 (m, 4 H), 4.68 (m, 1 H), 4.75 (m, 1 H), 4.92 (m, 1 H), 5.03 (m, 1 H), 5.09 (s, 2 H), 5.16 (dq, *J* = 10.7 Hz, *J* = 1.3 Hz, 1 H), 5.29 (dq, *J* = 17.3 Hz, *J* = 1.6 Hz, 1 H), 5.90 (ddt, *J* = 17.2 Hz, *J* = 10.6 Hz, *J* = 5.4 Hz, 1 H), 6.40 (s, 2 H), 6.52 (m, 2 H), 6.81 (d, *J* = 5.3 Hz, 1 H), 6.97 (d, *J* = 8.5 Hz, 2 H), 7.25 (m, 2 H), 7.31 (m, 4 H), 7.38 (m, 2 H), 7.44 (m, 2 H), 7.72 (d, *J* = 7.2 Hz, 2 H), 7.80 (m, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 11.5, 13.4, 15.0, 16.8, 18.1, 21.0, 22.4, 23.7, 24.8, 27.7, 29.2, 29.7, 31.1, 31.5, 39.4, 39.9, 42.2, 47.0, 51.1, 52.0, 52.6, 55.3, 56.0, 57.6, 64.2, 69.2, 69.6, 74.1, 82.7, 85.6, 114.1, 115.7, 116.5, 123.8, 126.6, 126.8, 126.9, 127.1, 127.5, 127.8, 128.5, 129.8, 131.0, 132.9, 134.2, 136.7, 136.8, 138.3, 155.3, 155.7, 157.1, 158.0, 168.9, 169.8, 170.8, 172.0, 172.8. HRMS (ESI): m/z calcd for $C_{68}H_{93}N_{10}O_{16}S$ $[M+H]^+$: 1337.6486, found: 1337.6451.

Methyl *N*-((2*R*,3*R*)-2-((*S*)-2-((*S*)-2-((*R*)-2-((2*R*,3*R*)-2-((2*R*,3*R*)-2-(((allyloxy)carbonyl)amino)-3-hydroxy-butanamido)-3-(benzyloxy)butanamido)-5-(3-((2,2,4,6,7-pentamethyl-2,3-dihydro-benzofuran-5-yl)sulfonyl)guanidino)pentanamido)-*N*,4-dimethylpentanamido)-5-amino-5-oxopentanamido)-3-(4-(benzyloxy)phenyl)-3-methoxypropanoyl)-*N*-methyl-L-alaninate (18)

To a solution of Alloc-protected peptide **17** (1.27 g, 948 µmol) in MeCN/H_2O (19 mL, 1:1) were added diethylamine (495 µL, 4.74 mmol, 5.0 equiv.), TPPTS (22.0 mg, 38.0 µmol, 4mol%) and $Pd(OAc)_2$ (948 µL, 19.0 µmol, 0.02 M in MeCN, 2mol%) and the mixture was stirred for 3 hours at room temperature. After removal of the solvent *in vacuo* and drying in high vacuum, the residue was dissolved in dry DMF (9.5 mL) and cooled to 0 °C. Alloc-*D*-*allo*-threonine (359 mg, 1.66 mmol, 1.75 equiv.), DIPEA (662 µL, 3.79 mmol, 4.0 equiv.) and PyAOP (865 mg, 1.66 mmol,1.75 equiv.) were added and the reaction was stirred overnight. The mixture was diluted with EtOAc, successively washed with 1 M HCl, sat. $NaHCO_3$ solution and brine and the organic layer dried over Na_2SO_4. After removal of the solvent *in vacuo*, flash chromatography (silica, DCM/MeOH 96:4 → 95:5) and lyophilization, heptapeptide **18** (1.17 g, 812 µmol, 86%) was obtained as a white amorphous solid. R_f(**18**) = 0.29 (DCM/MeOH 93:7). $[\alpha]_D^{20}$ = –15.1 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, DMSO-d_6, 373K): δ = 0.85 (d, *J* = 7.2 Hz, 3 H), 0.87 (d, *J* = 6.9 Hz, 3 H), 1.10 (d, *J* = 6.3 Hz, 6 H), 1.32 (d, *J* = 6.9 Hz, 3 H), 1.43 (s, 6 H), 1.45 (m, 4 H), 1.58 (m, 2 H), 1.71 (m, 1 H), 1.78 (m, 4 H), 2.03 (s, 3 H), 2.46 (s, 3 H), 2.52 (s, 3 H), 2.73 (bs, 3 H), 2.99 (m, 5 H), 3.05 (m, 2 H), 3.09 (bs, 3 H), 3.63 (bs, 3 H), 3.91 (m, 2 H), 4.09 (dd, *J* = 8.5 Hz, *J* = 7.2 Hz, 1 H), 4.31 (m, 1 H), 4.37 (m, 1 H), 4.50 (m, 3 H), 4.56 (m, 1 H), 4.63 (dd, *J* = 7.5 Hz, *J* = 5.3 Hz, 1 H), 4.69 (m, 1 H), 4.76 (m, 1 H), 4.93 (m, 1 H), 5.04 (m, 1 H), 5.09 (s, 2 H), 5.16 (dq,

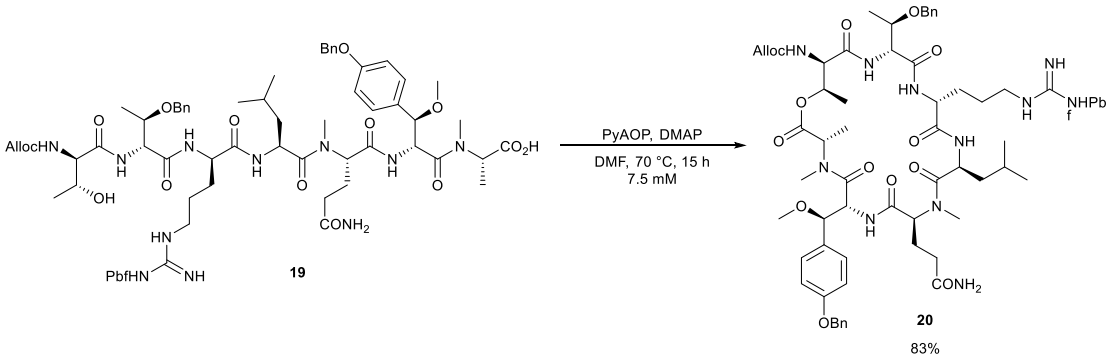
J = 10.5 Hz, *J* = 1.4 Hz, 1 H), 5.29 (dq, *J* = 17.3 Hz, *J* = 1.6 Hz, 1 H), 5.90 (ddt, *J* = 17.3 Hz, *J* = 10.7 Hz, *J* = 5.3 Hz, 1 H), 6.40 (s, 2 H), 6.49 (m, 2 H), 6.76 (d, *J* = 6.0 Hz, 1 H), 6.97 (d, *J* = 8.5 Hz, 2 H), 7.24 (m, 2 H), 7.30 (m, 6 H), 7.38 (m, 2 H), 7.44 (m, 2 H), 7.69 (m, 2 H), 7.74 (m, *J* = 7.8 Hz, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 11.4, 13.4, 15.2, 16.8, 18.1, 19.3, 21.0, 22.4, 23.7, 24.8, 27.7, 28.0, 28.9, 29.6, 31.4, 39.4, 39.9, 42.2, 47.1, 51.1, 51.9, 52.0, 52.6, 55.3, 55.6, 57.6, 60.1, 64.1, 66.8, 69.2, 69.6, 73.9, 82.7, 85.6, 114.1, 115.7, 116.3, 123.7, 126.6, 126.9, 126.9, 127.1, 127.4, 127.8, 128.5, 129.8, 131.0, 133.0, 134.2, 136.6, 136.8, 138.2, 155.2, 155.7, 157.1, 158.0, 168.7, 169.8, 170.3, 170.8, 172.1, 172.9. HRMS (ESI): m/z calcd for $C_{72}H_{100}N_{11}O_{18}S$ $[M+H]^+$: 1438.6963, found: 1438.6937.

_N_-((2_R_,3_R_)-2-((_S_)-2-((_S_)-2-((_R_)-2-((2_R_,3_R_)-2-((2_R_,3_R_)-2-(((Allyloxy)carbonyl)amino)-3-hydroxy-butanamido)-3-(benzyloxy)butanamido)-5-(3-((2,2,4,6,7-pentamethyl-2,3-dihydro-benzofuran-5-yl)sulfonyl)guanidino)pentanamido)-_N_,4-dimethylpentanamido)-5-amino-5-oxopentan-amido)-3-(4-(benzyloxy)phenyl)-3-methoxypropanoyl)-_N_-methyl-L-alanine (19)



To a solution of methyl ester **18** (300 mg, 208 µmol) in 1,2-dichlorethane (2 mL) was added trimethyltin hydroxide (377 mg, 2.08 mmol, 10.0 equiv.) and the reaction was heated to 80 °C for 5 hours. After cooling to room temperature, the mixture was diluted with EtOAc and washed with 1 M $KHSO_4$ solution and brine. The organic layer was dried (Na_2SO_4), the solvent removed *in vacuo* and the residue purified by reversed-phase chromatography (C18, H_2O/MeCN 95:5 → 0:100) to afford carboxylic acid **19** (203 mg, 142 µmol, 68%) as an off-white solid, mp 93–95 °C. R_f(**19**) = 0.18 (DCM/MeOH 9:1). $[\alpha]_D^{20}$ = –33.1 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.85 (m, 6 H), 1.10 (d, *J* = 6.3 Hz 6 H), 1.32 (d, *J* = 7.0 Hz, 3 H), 1.43 (s, 6 H), 1.45 (m, 4 H), 1.59 (m, 2 H), 1.70 (m, 1 H), 1.80 (m, 4 H), 2.03 (s, 3 H), 2.46 (s, 3 H), 2.52 (s, 3 H), 2.73 (bs, 3 H), 2.99 (m, 5 H), 3.04 (m, 2 H), 3.09 (m, 3 H), 3.91 (m, 2 H), 4.09 (dd, *J* = 8.5 Hz, *J* = 7.1 Hz, 1 H), 4.31 (m, 2 H), 4.49 (m, 3 H), 4.56 (m, 1 H), 4.63 (dd, *J* = 7.6 Hz, *J* = 5.0 Hz, 1 H), 4.67 (m, 1 H), 4.77 (m, 1 H), 4.94 (m, 1 H), 5.05 (m, 1 H), 5.09 (s, 2 H), 5.16 (dq, *J* = 10.5 Hz, *J* = 1.4 Hz, 1 H), 5.29 (dq, *J* = 17.3 Hz, *J* = 1.6 Hz, 1 H), 5.90 (ddt, *J* = 17.2 Hz, *J* = 10.6 Hz, *J* = 5.4 Hz, 1 H), 6.41 (s, 2 H), 6.51 (m, 2 H), 6.76 (d, *J* = 7.5 Hz, 1 H), 6.96 (d, *J* = 7.8 Hz, 2 H), 7.24 (m, 3 H), 7.30 (m, 5 H), 7.38 (m, 2 H), 7.44 (m, 2 H), 7.66 (d, *J* = 7.8 Hz, 1 H), 7.74 (m, 2 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 11.5, 13.9, 15.2, 16.8, 18.1, 19.3, 21.0, 22.4, 23.8, 24.8, 27.7, 28.3, 28.9, 29.7, 30.8, 39.4, 39.9, 42.2, 47.1, 51.7, 52.0, 52.1, 55.3, 55.6, 56.0, 60.1, 64.1, 66.8, 69.2, 69.6, 73.9, 83.0, 85.6, 114.1, 115.7, 116.4, 123.8, 126.6, 126.9, 127.1, 127.5, 127.8, 128.5, 129.9, 131.0, 133.0, 134.2, 136.7, 136.8, 138.2, 155.2, 155.7, 157.1, 158.0, 168.7, 169.8, 170.3, 172.2, 172.9. HRMS (ESI): m/z calcd for $C_{71}H_{98}N_{11}O_{18}S$ $[M+H]^+$: 1424.6807, found: 1424.6851.

Allyl ((3*S*,6*R*,9*S*,12*S*,15*R*,18*R*,21*R*,22*R*)-9-(3-amino-3-oxopropyl)-18-((*R*)-1-(benzyloxy)ethyl) -6-((*R*)-(4-(benzyloxy)phenyl)(methoxy)methyl)-12-isobutyl-3,4,10,22-tetramethyl-2,5,8,11,14,17,20-heptaoxo-15-(3-(3-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl) sulfonyl)guanidino)prop-yl)-1-oxa-4,7,10,13,16,19-hexaazacyclodocosan-21-yl)carbamate (20)

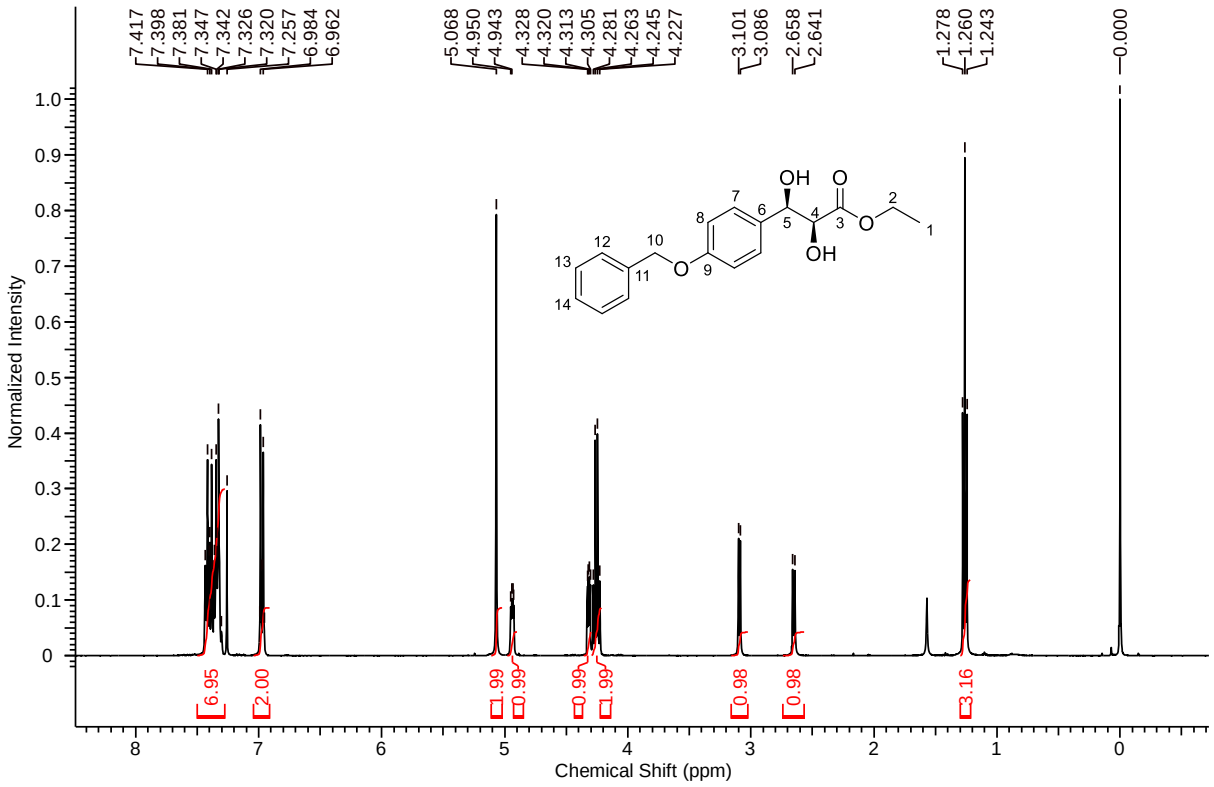


To a solution of linear peptide **19** (180 mg, 126 µmol) in DMF (17 mL) was added DMAP (308 mg, 2.52 mmol, 20.0 equiv.) and PyAOP (79.0 mg, 151 µmol, 1.2 equiv.) and the reaction was heated to 70 °C for 15 hours. After dilution with EtOAc, the mixture was washed with 1 M $KHSO_4$ solution, sat. $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4, concentrated *in vacuo* and the residue purified by column chromatography (silica, DCM/MeOH 97:3 → 95:5) to afford macro lactone **20** (148 mg, 105 µmol, 83%) as a white solid, mp 112–114 °C. R_f(**20**) = 0.14 (DCM/MeOH 95:5). $[\alpha]_D^{20}$ = –51.8 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.5 Hz, 3 H), 0.94 (d, *J* = 6.5 Hz, 3 H), 1.15 (m, 1 H), 1.18 (d, *J* = 6.5 Hz, 3 H), 1.26 (m, 5 H), 1.35 (d, *J* = 7.3 Hz, 3 H), 1.44 (s, 6 H), 1.54 (m, 5 H), 1.67 (m, 3 H), 2.08 (s, 3 H), 2.52 (s, 3 H), 2.58 (s, 3 H), 2.80 (bs, 3 H), 2.93 (bs, 5-H), 3.06 (m, 2 H), 3.16 (bs, 3 H), 4.03 (qd, *J* = 8.5 Hz, *J* = 7.1 Hz, 1 H), 4.32 (t, *J* = 4.6 Hz, 1 H), 4.43 (d, *J* = 11.9 Hz, 1 H), 4.52 (m, 3 H), 4.59 (d, *J* = 11.9 Hz, 1 H), 4.63 (dd, *J* = 13.3 Hz, *J* = 5.8 Hz, 1 H), 4.65 (m, 1 H), 4.69 (dd, *J* = 13.3 Hz, *J* = 5.3 Hz, 1 H), 4.81 (dd, *J* = 8.6 Hz, *J* = 1.9 Hz, 1 H), 5.07 (s, 2 H), 5.09 (t, *J* = 9.5 Hz, 1 H), 5.25 (m, 1 H5.26 (d, *J* = 10.5 Hz, 1 H), 5.33 (m, 1 H), 5.37 (d, *J* = 17.5 Hz, 1 H), 5.55 (d, *J* = 6.6 Hz, 1 H), 5.67 (bs, 1 H), 6.01 (m, 2 H), 6.14 (m, 1 H), 6.24 (bs, 2 H), 6.81 (d, *J* = 7.1 Hz, 1 H), 7.00 (d, *J* = 8.6 Hz, 2 H), 7.24 (m, 3 H), 7.33 (m, 7 H), 7.42 (m, 2 H), 7.54 (m, 2 H), 7.62 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.4, 13.5, 13.8, 15.9, 17.9, 19.1, 21.0, 23.1, 23.9, 24.7, 25.0, 28.6, 29.7, 30.0, 30.2, 31.2, 38.8, 40.7, 43.2, 49.5, 51.4, 51.7, 52.6, 55.3, 56.8, 57.6, 59.3, 66.6, 70.0, 70.7, 70.9, 72.6, 83.3, 86.3, 114.5, 117.3, 118.4, 124.5, 127.5, 127.7, 128.0, 128.0, 128.6, 128.6, 129.7, 130.1, 132.2, 132.4, 133.1, 136.8, 137.4, 138.2, 156.2, 156.5, 158.6, 158.8, 168.8, 169.1, 170.1, 170.2, 170.5, 172.5, 173.9, 174.4. HRMS (ESI): m/z calcd for $C_{71}H_{95}N_{11}O_{17}S$ $[M+H]^+$: 1406.6701, found: 1406.6682.

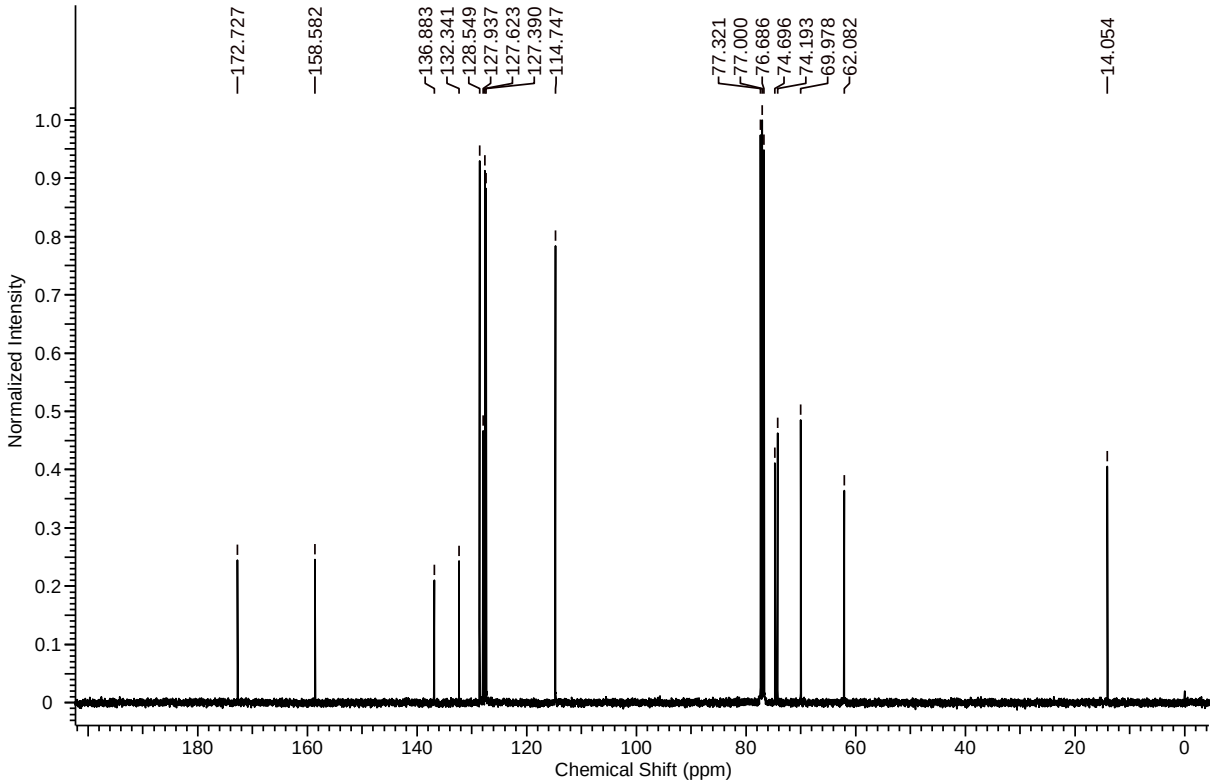
NMR Spectra

Ethyl (2*S*,3*R*)-3-(4-(benzyloxy)phenyl)-2,3-dihydroxypropanoate (2)

^{1}H NMR (400 MHz, $CDCl_3$):

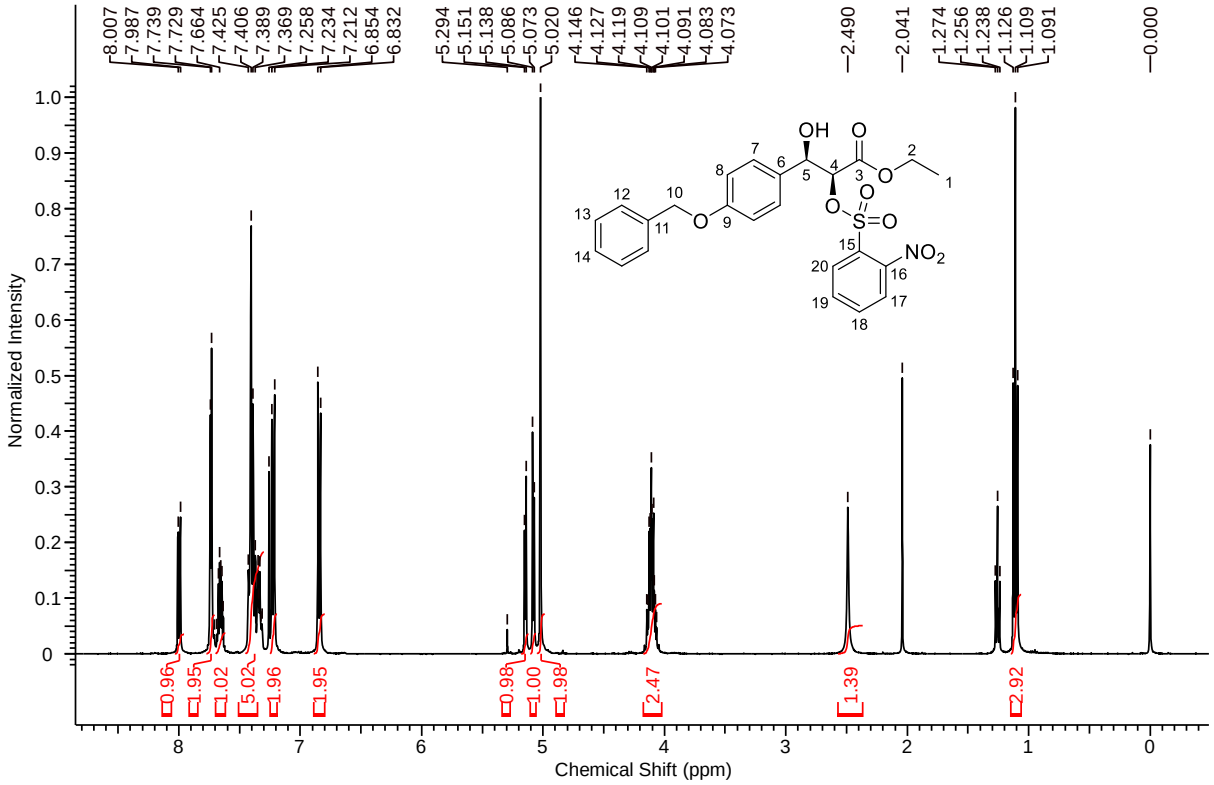


^{13}C NMR (100 MHz, $CDCl_3$):

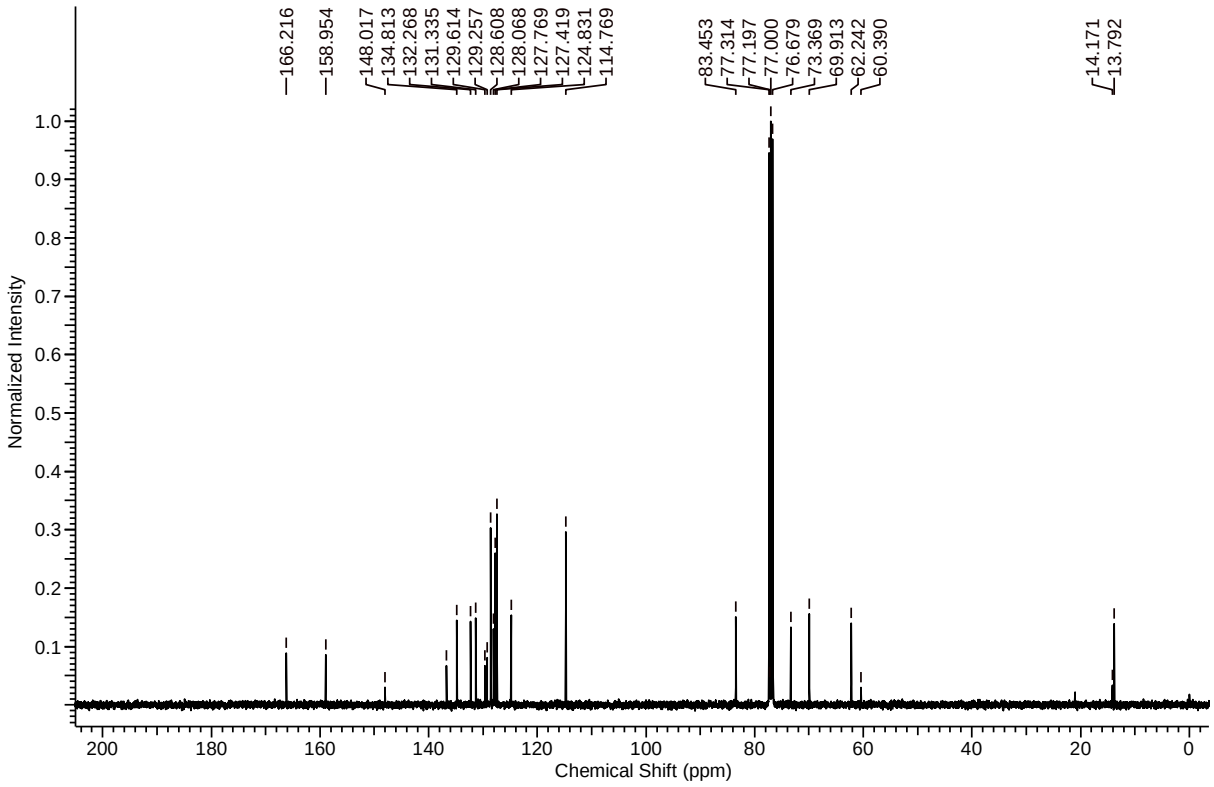


Ethyl (2*S*,3*R*)-3-(4-(benzyloxy)phenyl)-3-hydroxy-2-(((2-nitrophenyl)sulfonyl)oxy)propanoate (2a)

^{1}H NMR (400 MHz, $CDCl_3$):

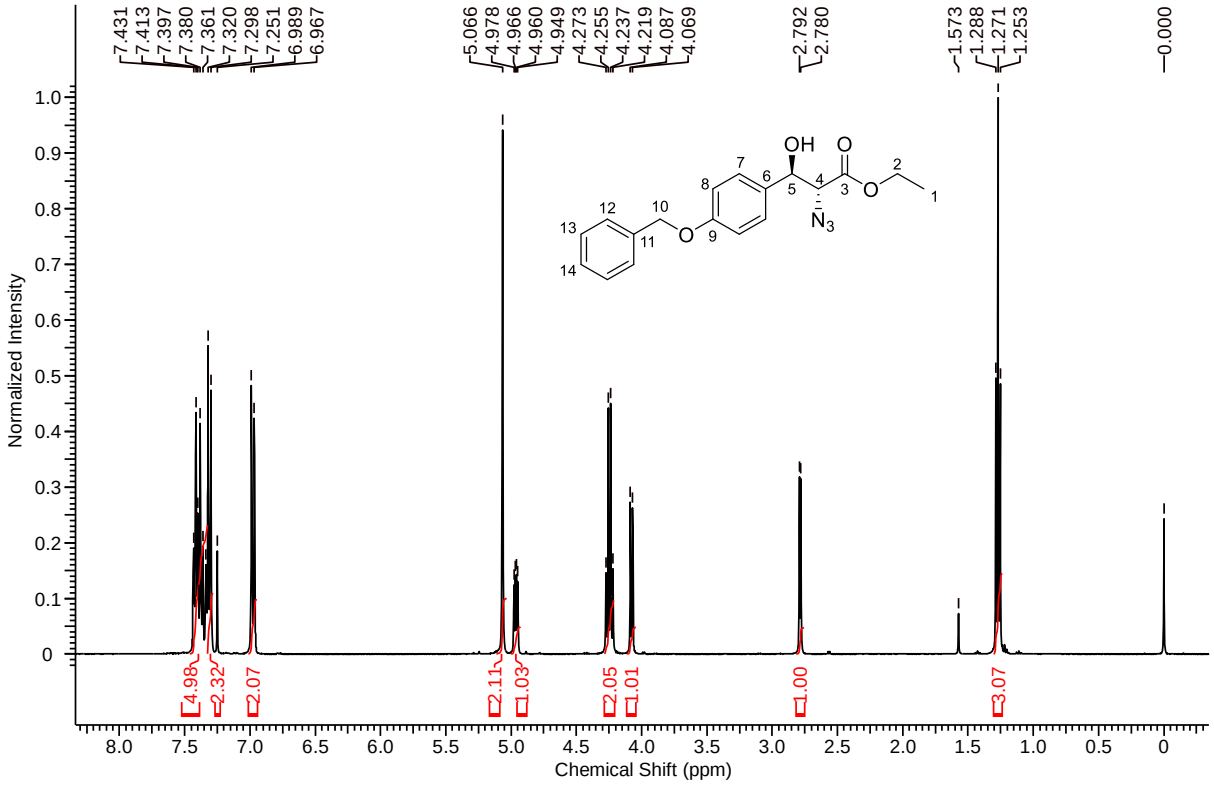


^{13}C NMR (100 MHz, $CDCl_3$):

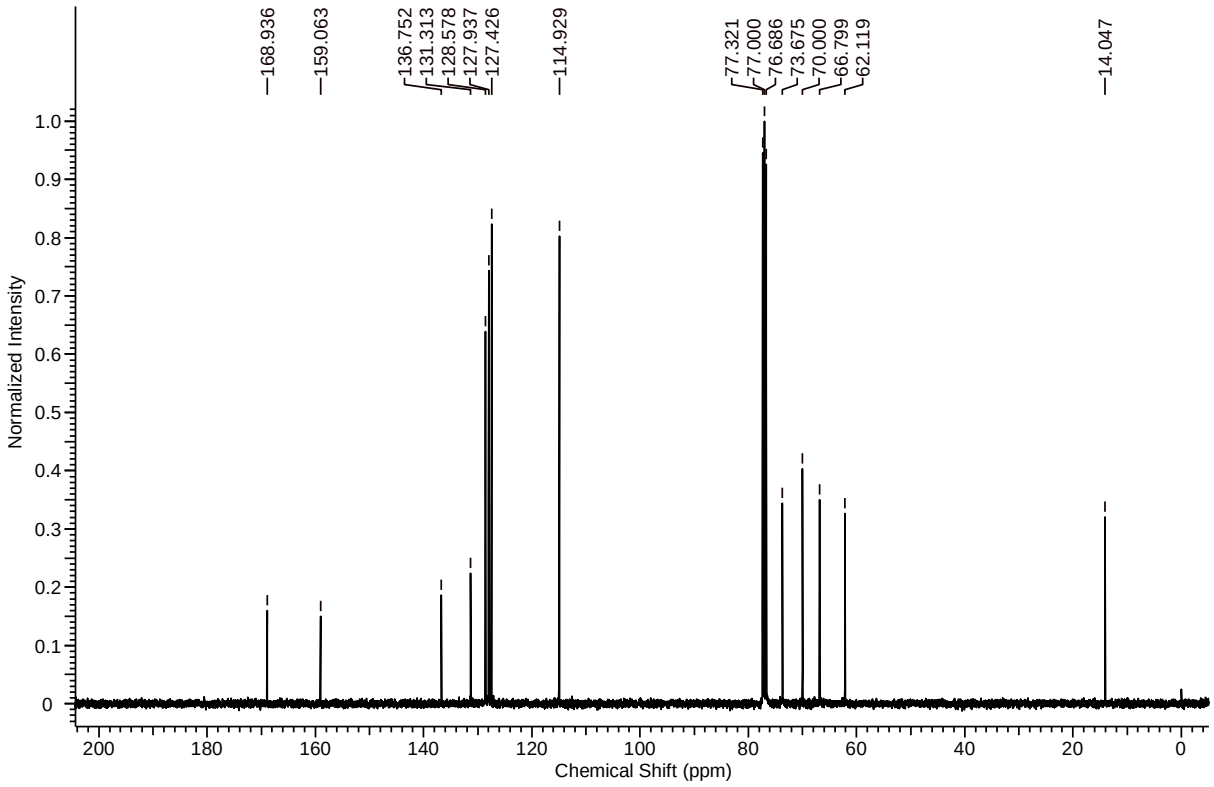


Ethyl (2*R*,3*R*)-2-azido-3-(4-(benzyloxy)phenyl)-3-hydroxypropanoate (3)

^{1}H NMR (400 MHz, $CDCl_3$):

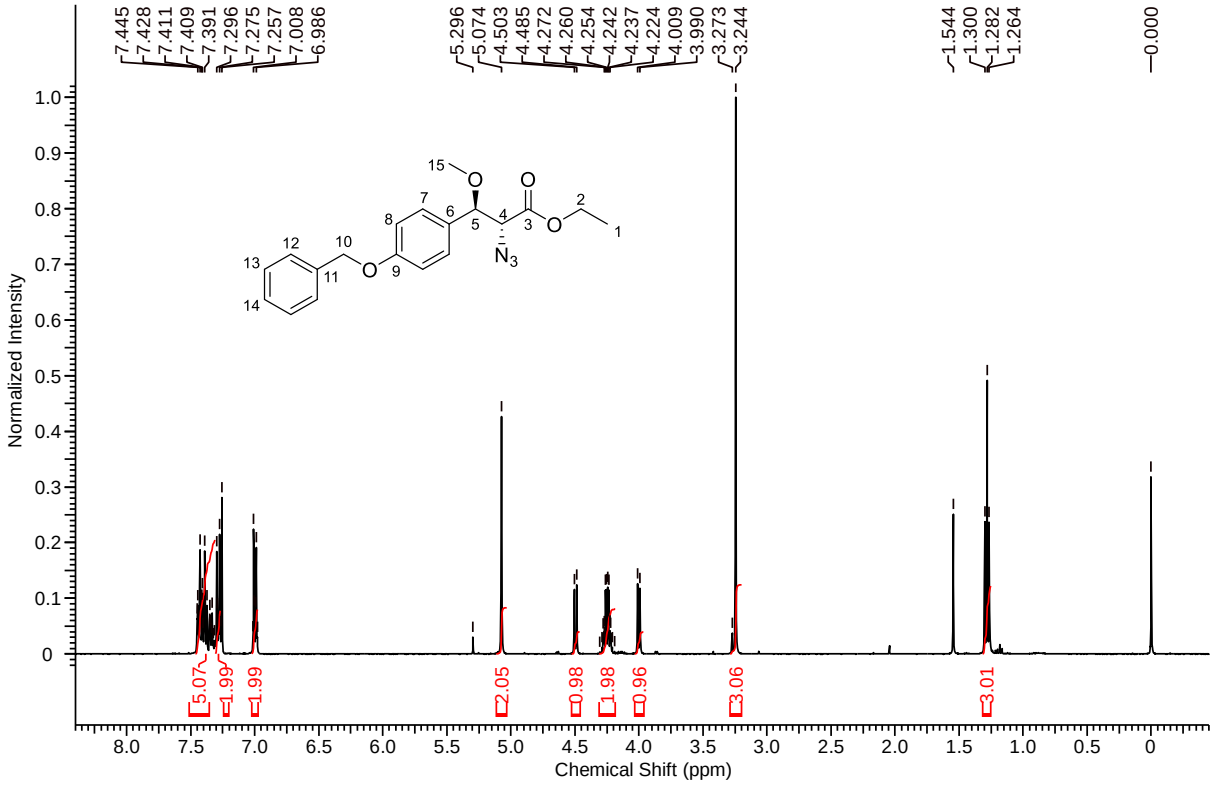


^{13}C NMR (100 MHz, $CDCl_3$):

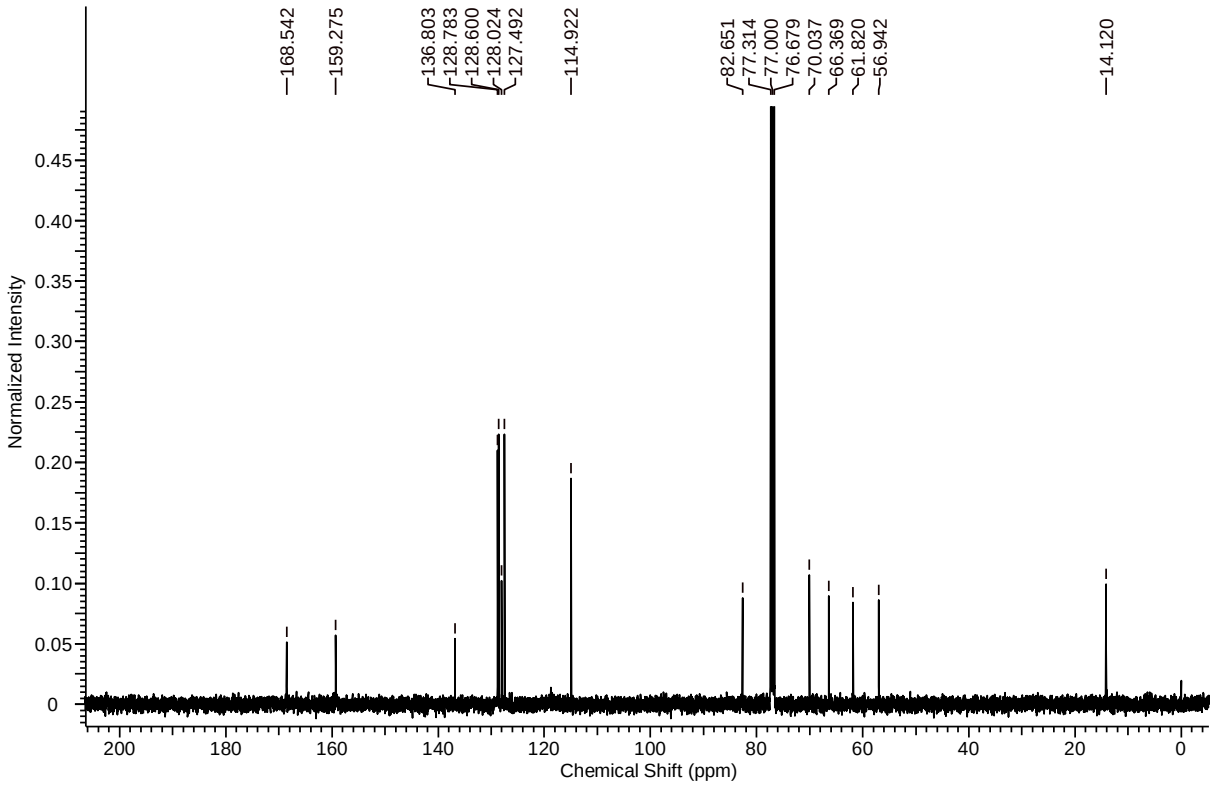


Ethyl (2*R*,3*R*)-2-azido-3-(4-(benzyloxy)phenyl)-3-methoxypropanoate (4)

^{1}H NMR (400 MHz, $CDCl_3$):

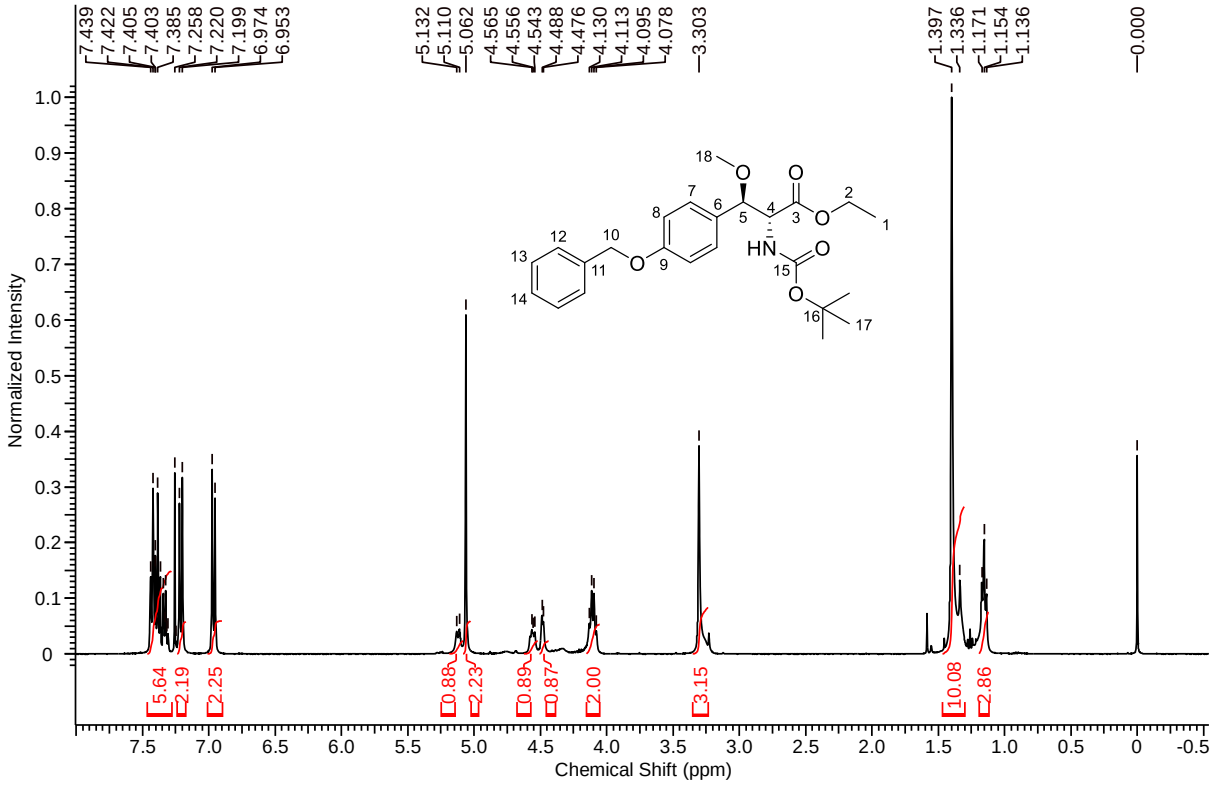


^{13}C NMR (100 MHz, $CDCl_3$):

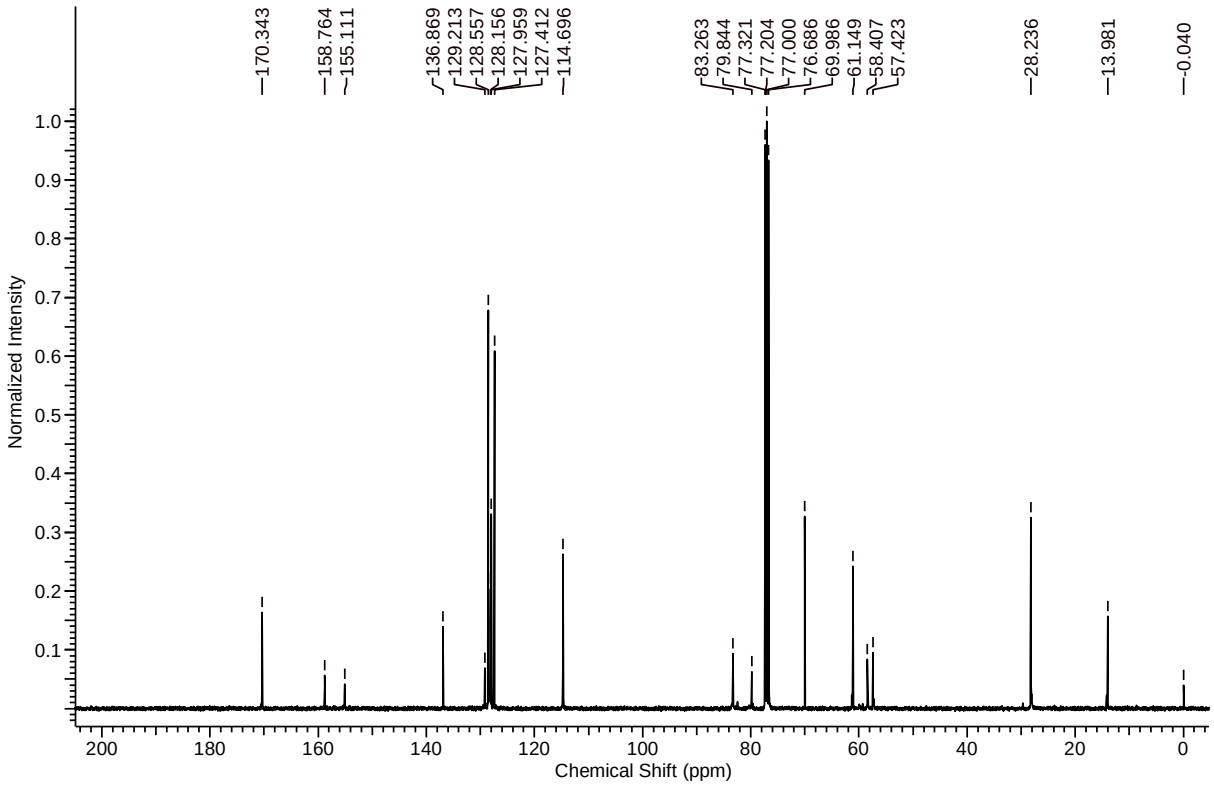


Ethyl (2*R*,3*R*)-3-(4-(benzyloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)-3-methoxy propan-oate (5)

^{1}H NMR (400 MHz, $CDCl_3$):

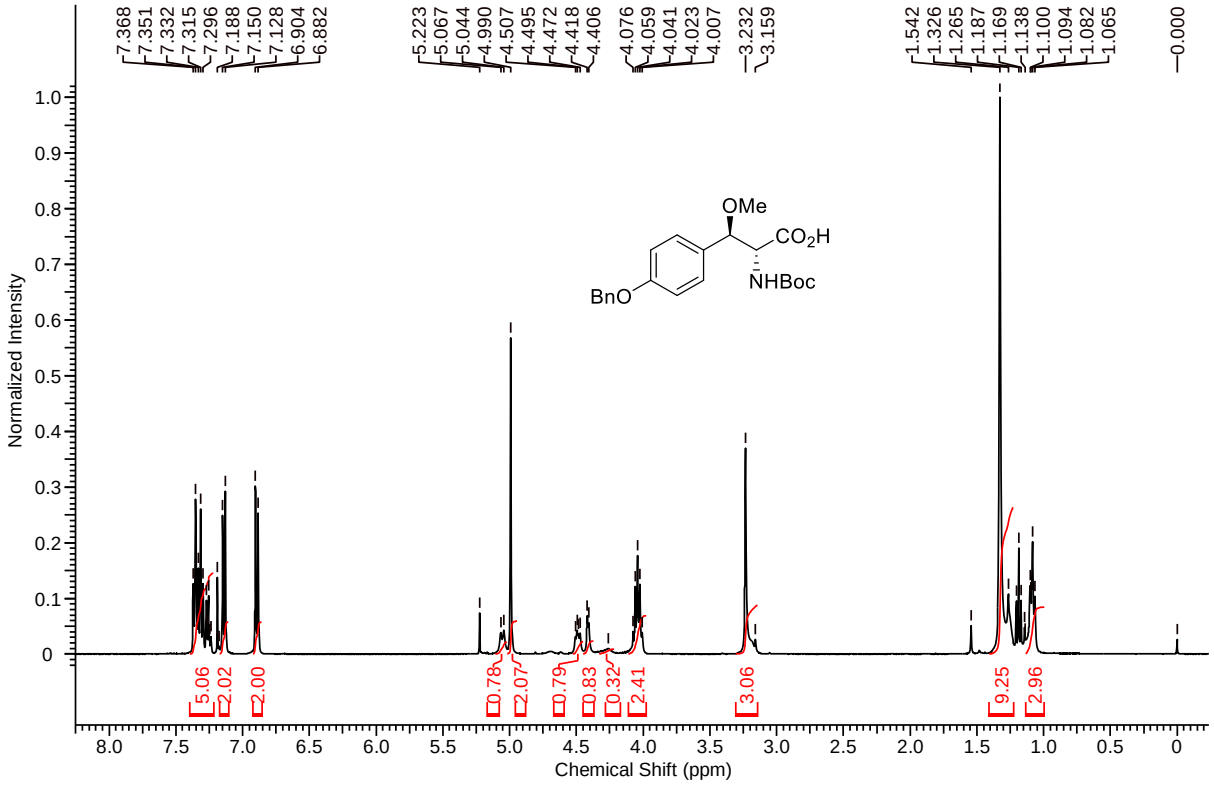


^{13}C NMR (100 MHz, $CDCl_3$):

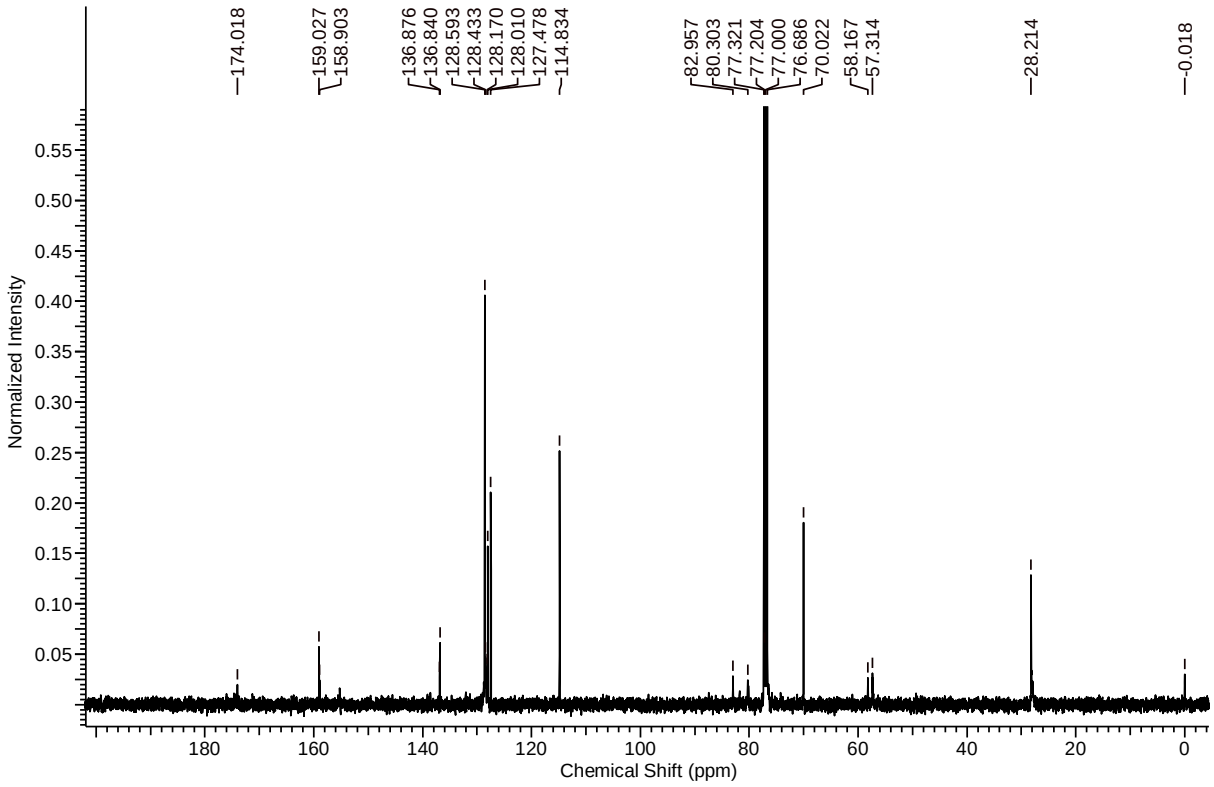


(2*R*,3*R*)-3-(4-(Benzyloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)-3-methoxypropanoic acid (6)

^{1}H NMR (400 MHz, $CDCl_3$):

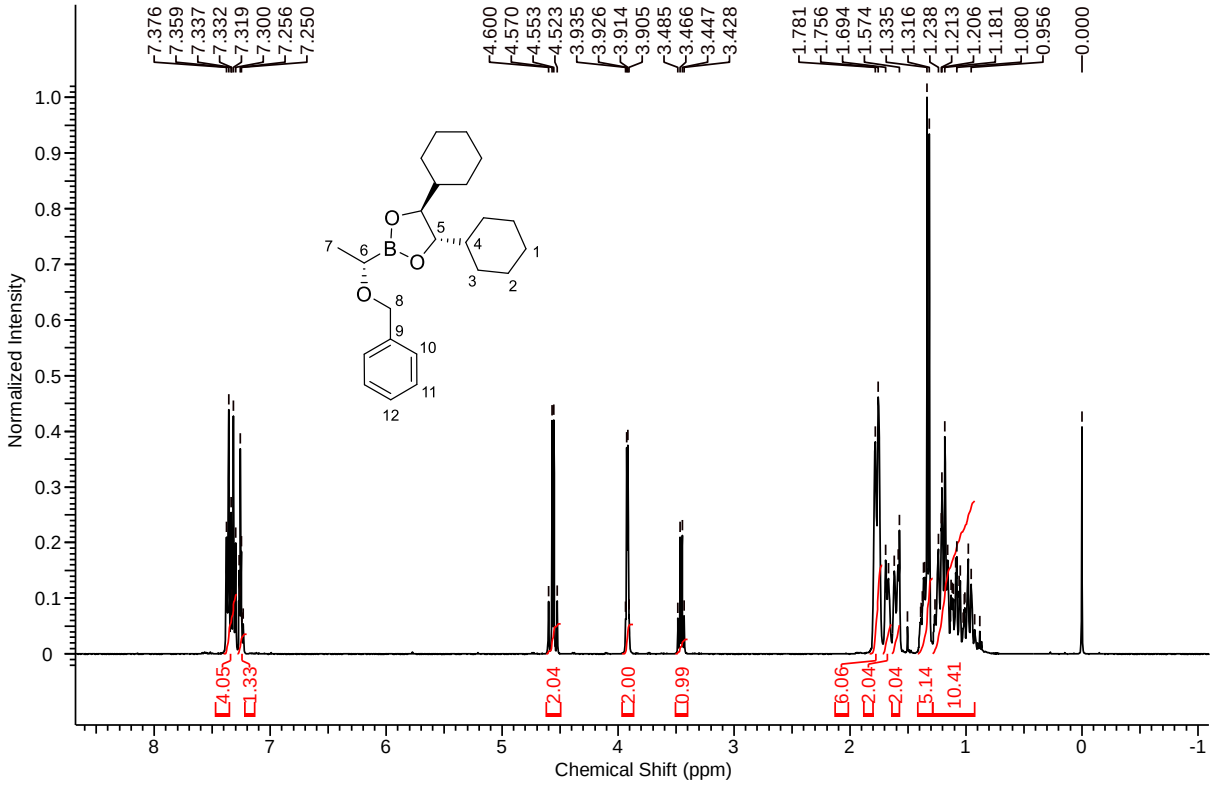


^{13}C NMR (100 MHz, $CDCl_3$):

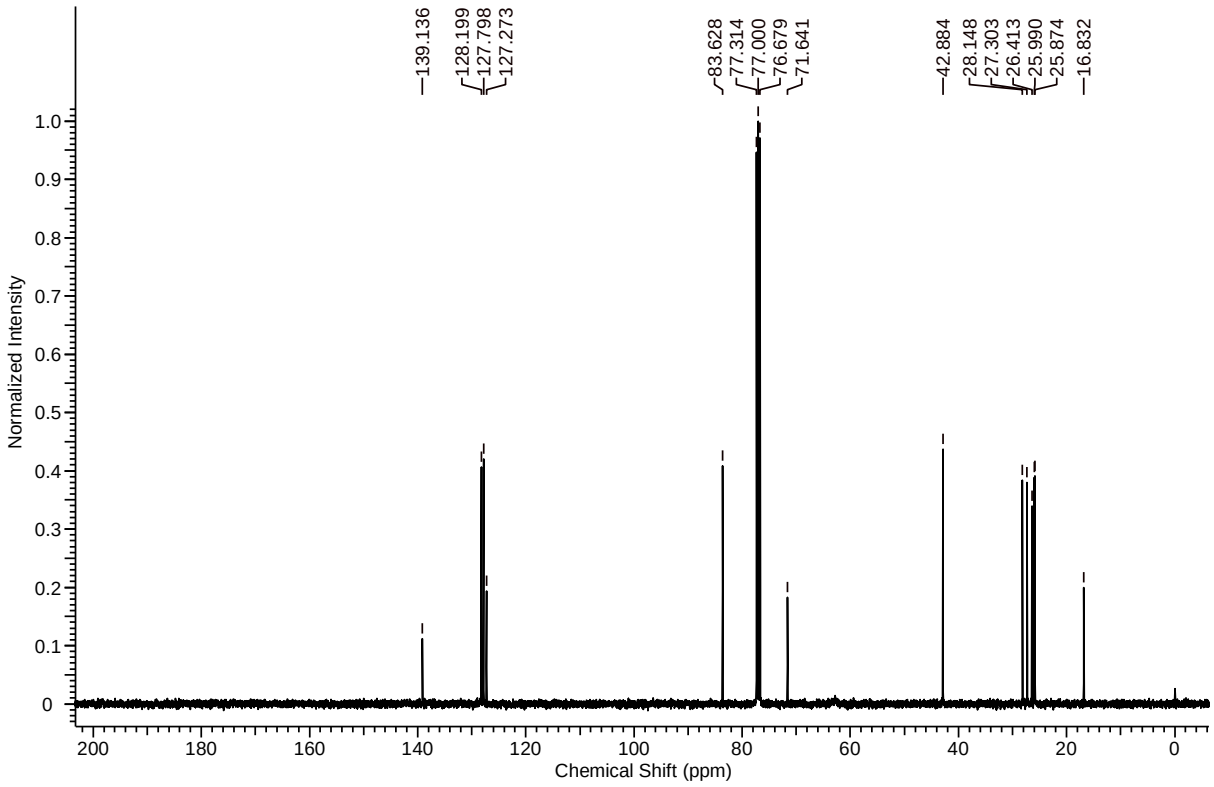


(4*S*,5*S*)-2-((*S*)-1-(Benzyloxy)ethyl)-4,5-dicyclohexyl-1,3,2-dioxaborolane (8)

^{1}H NMR (400 MHz, $CDCl_3$):

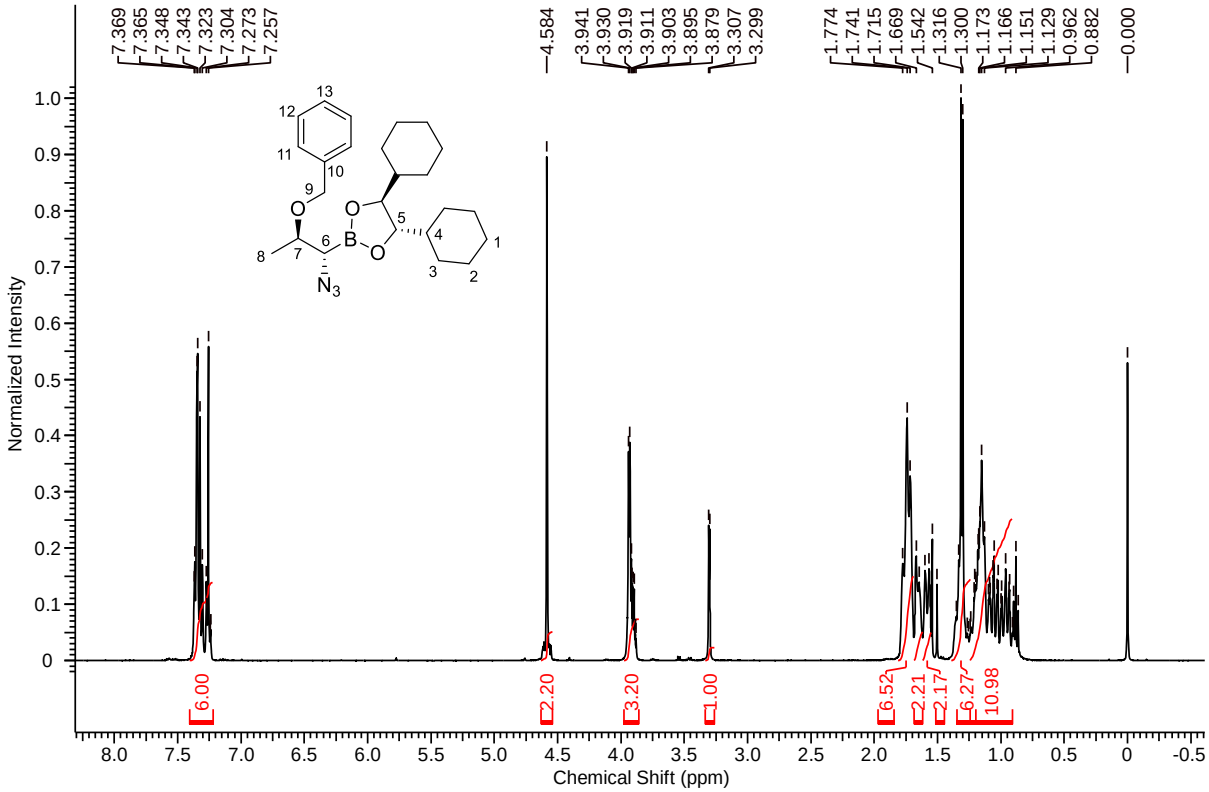


^{13}C NMR (100 MHz, $CDCl_3$):

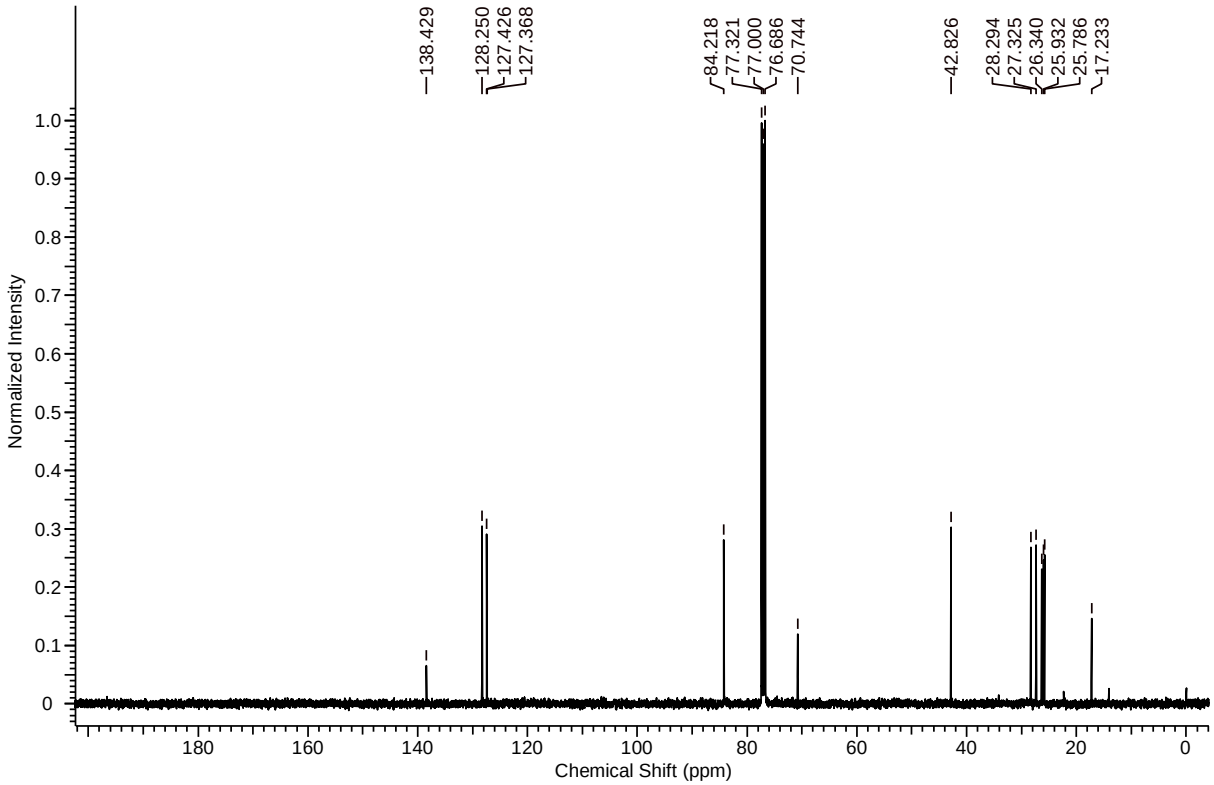


(4*S*,5*S*)-2-((1*S*,2*R*)-1-Azido-2-(benzyloxy)propyl)-4,5-dicyclohexyl-1,3,2-dioxaborolane (9)

^{1}H NMR (400 MHz, $CDCl_3$):

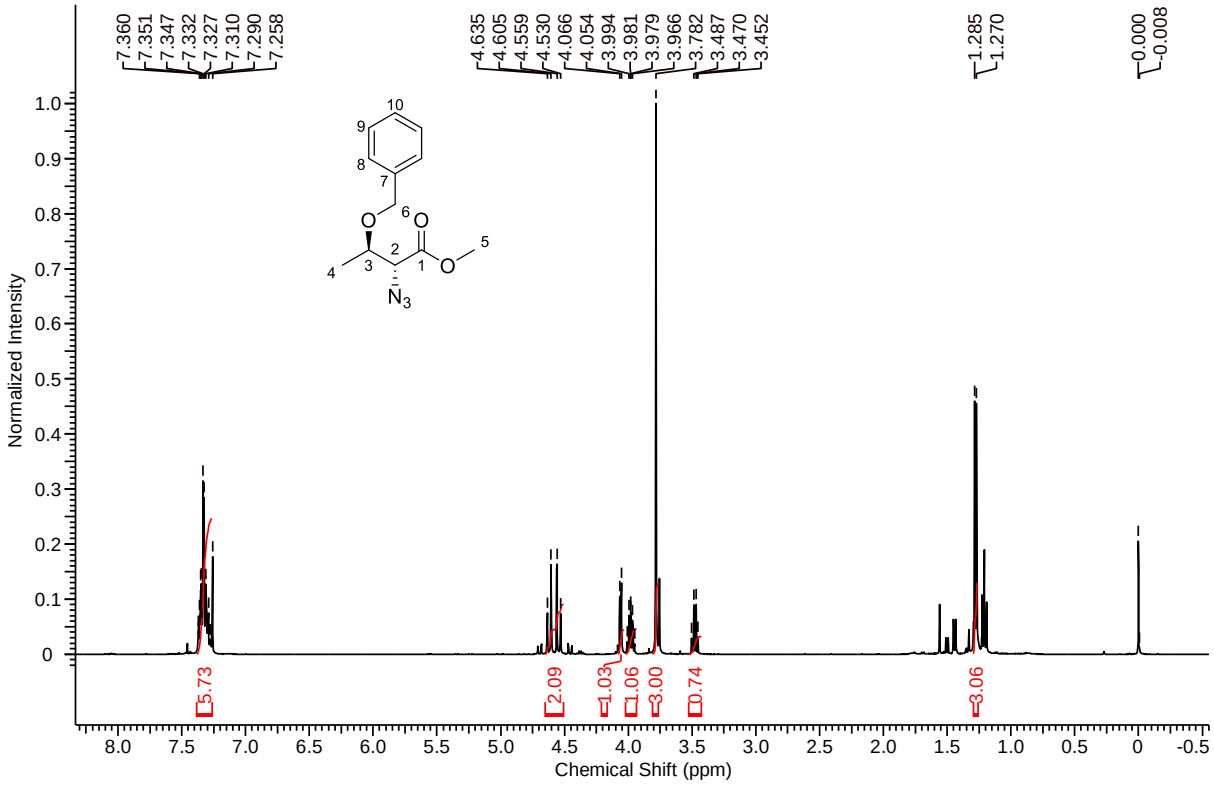


^{13}C NMR (100 MHz, $CDCl_3$):

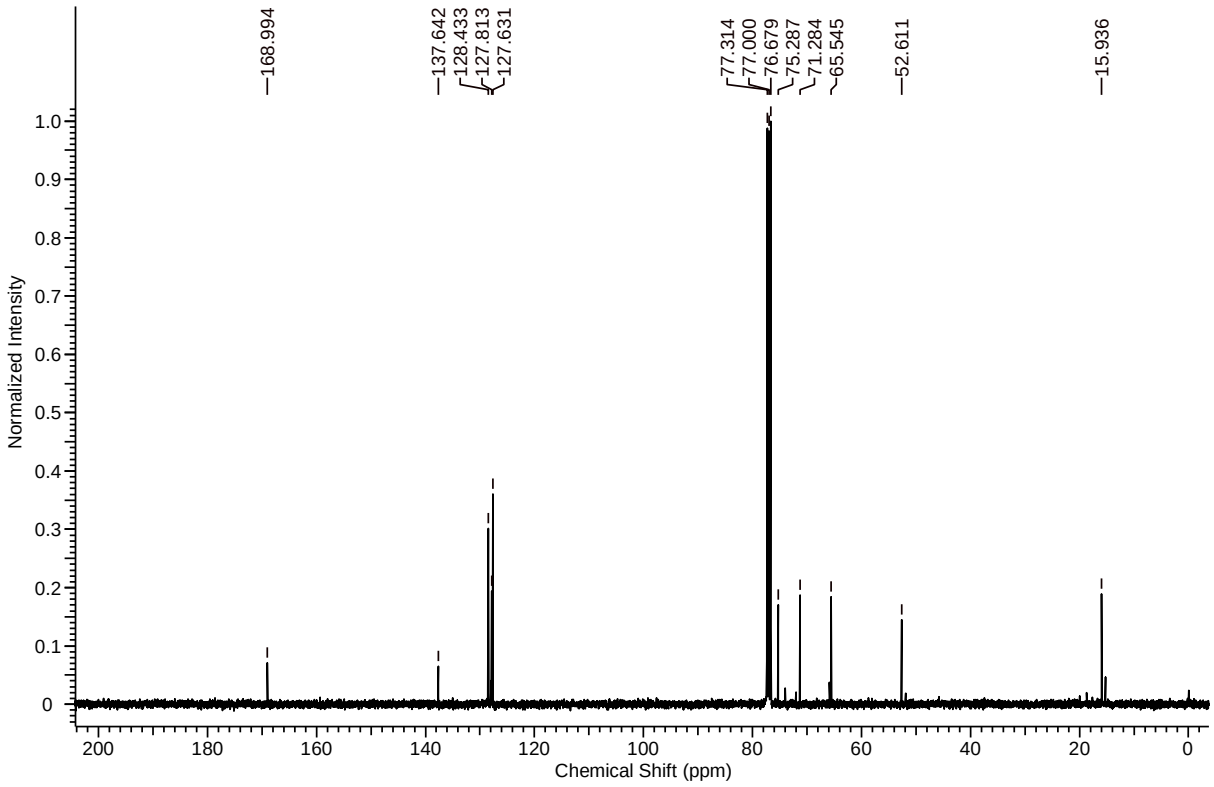


Methyl (2*R*,3*R*)-2-azido-3-(benzyloxy)butanoate (10)

^{1}H NMR (400 MHz, $CDCl_3$):

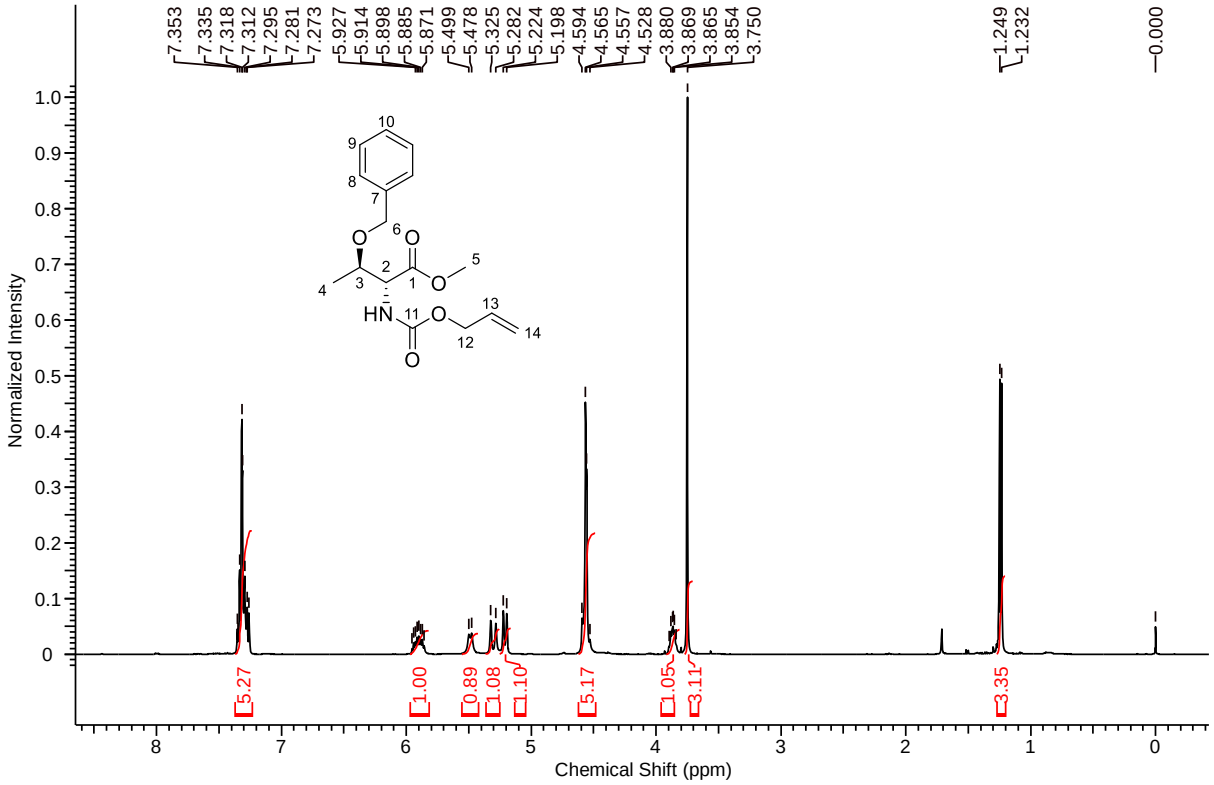


^{13}C NMR (100 MHz, $CDCl_3$):

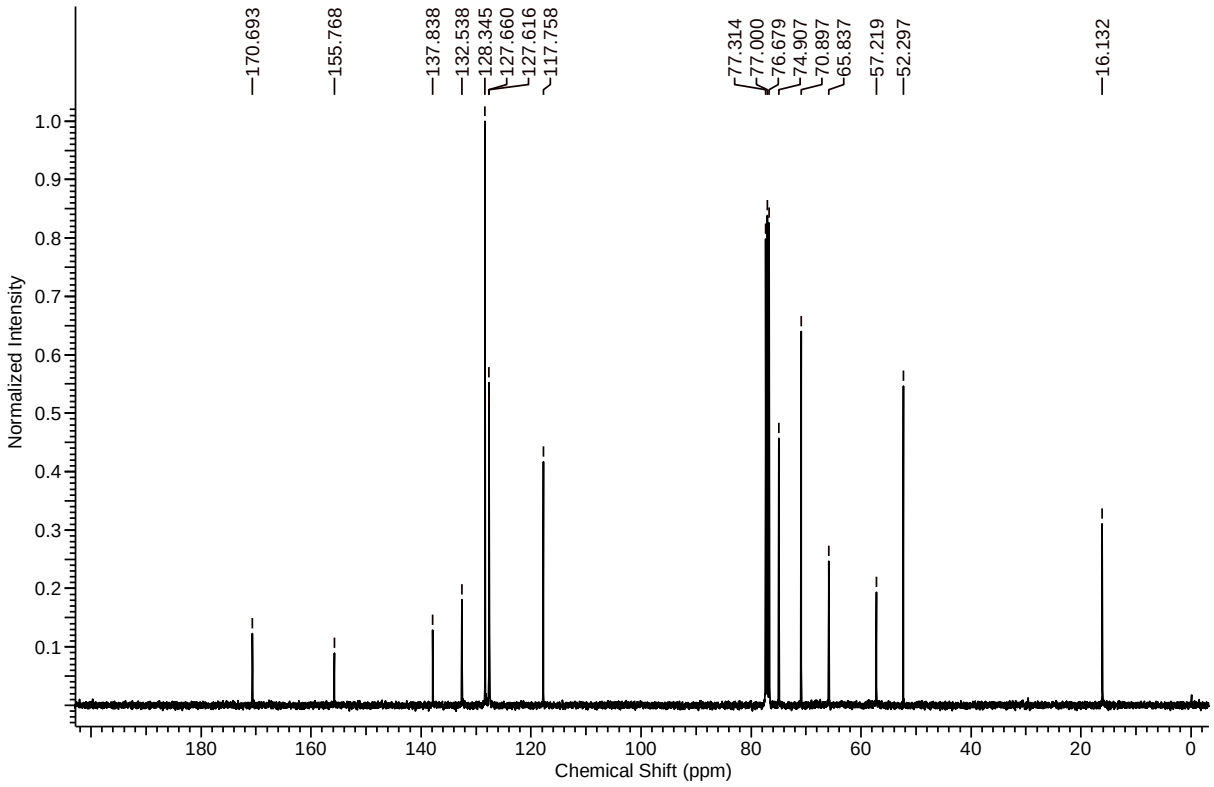


Methyl *N*-((allyloxy)carbonyl)-*O*-benzyl-D-*allo*-threoninate (11)

^{1}H NMR (400 MHz, $CDCl_3$):

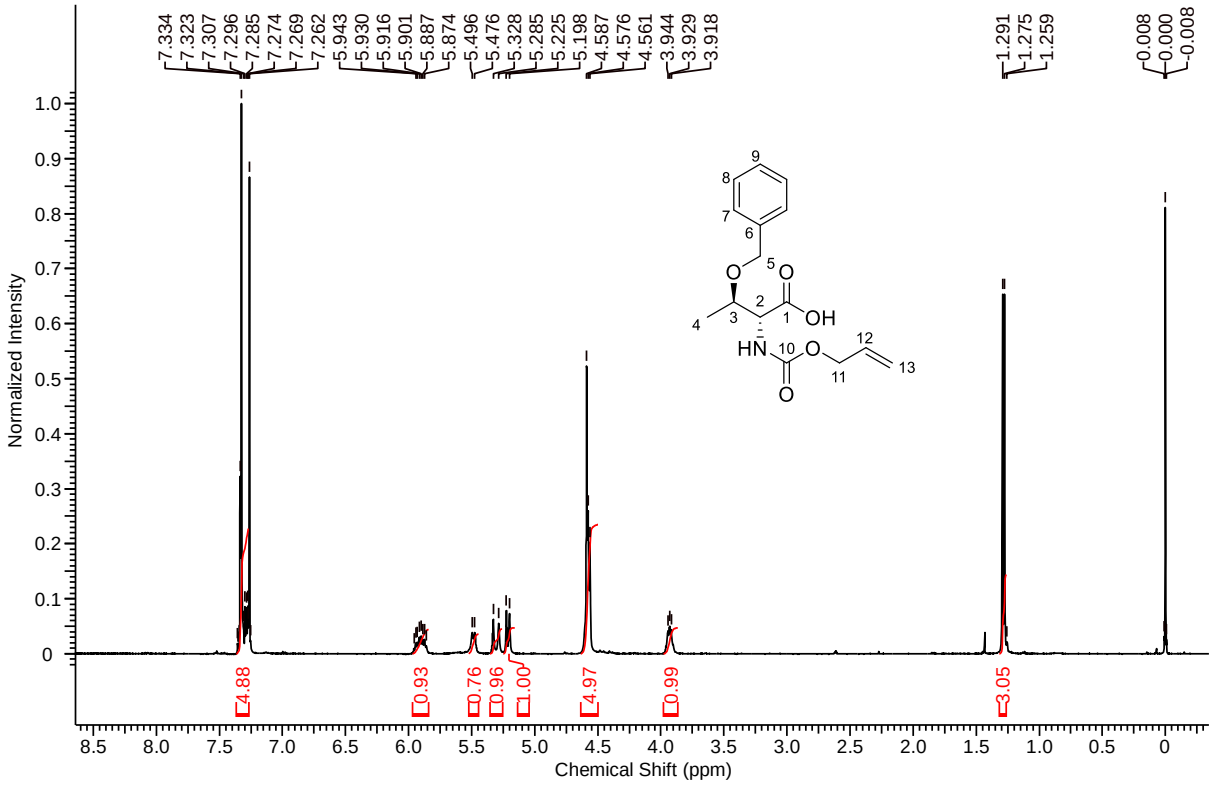


^{13}C NMR (100 MHz, $CDCl_3$):

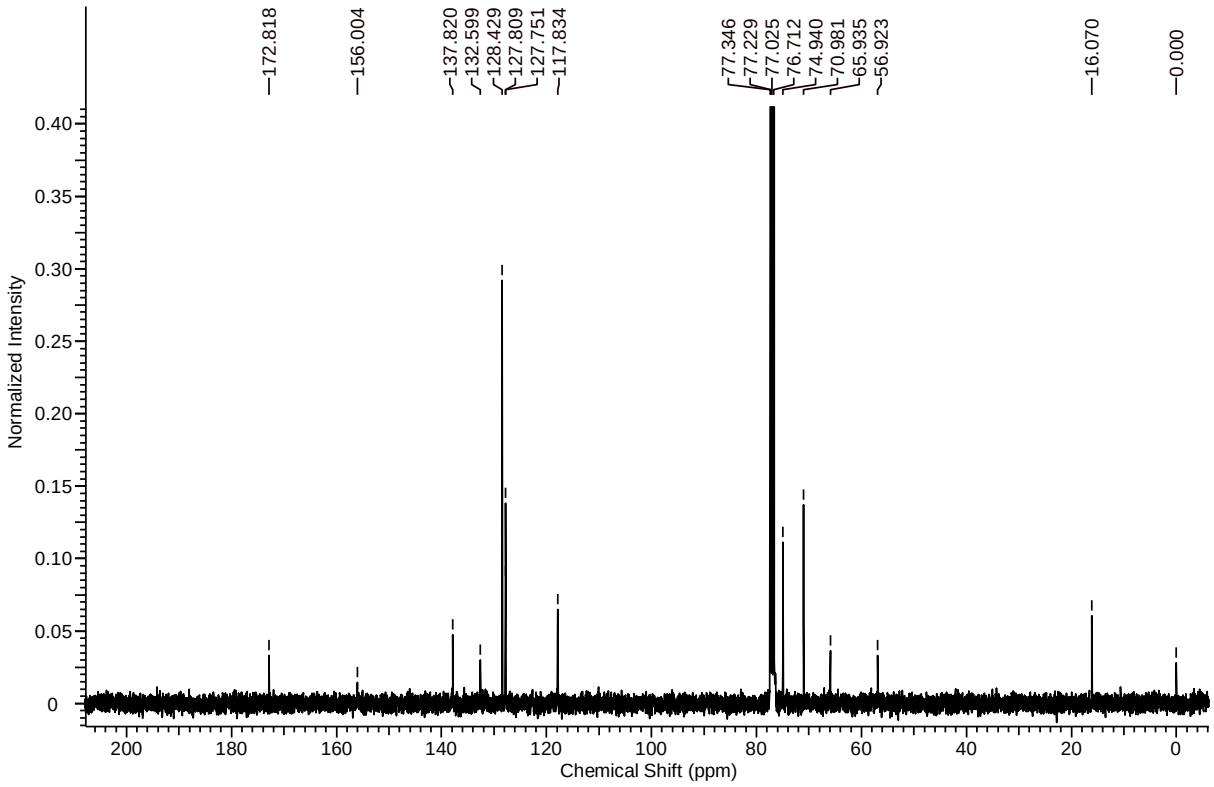


_N_-((Allyloxy)carbonyl)-_O_-benzyl-D-_allo_-threonine (12)

^{1}H NMR (400 MHz, $CDCl_3$):

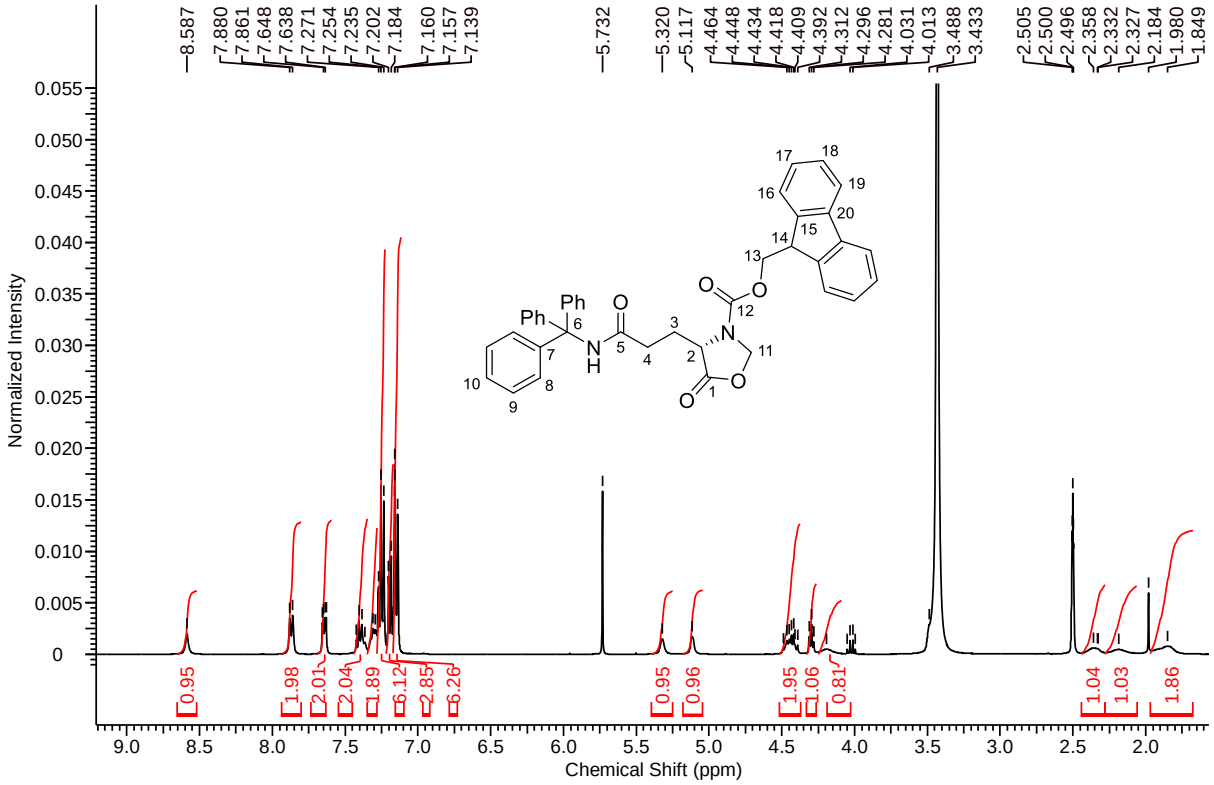


^{13}C NMR (100 MHz, $CDCl_3$):

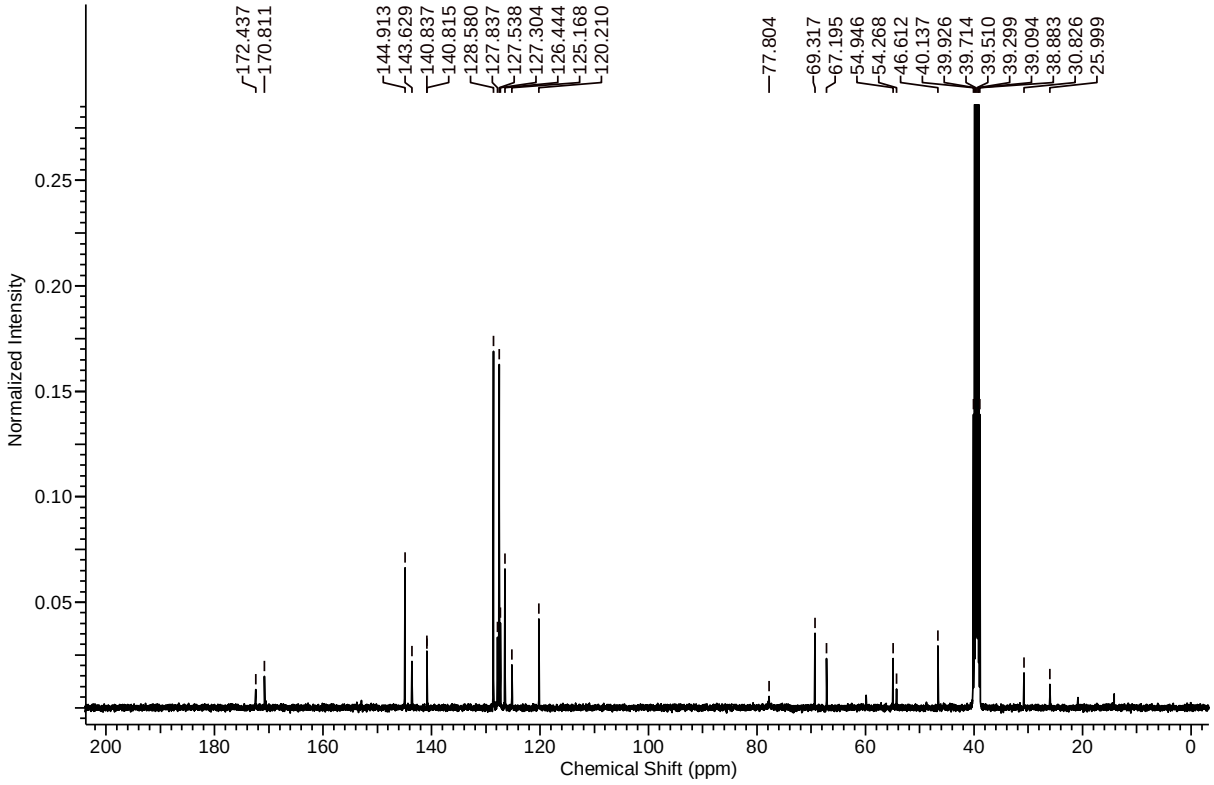


(9H-Fluoren-9-yl)methyl (*S*)-5-oxo-4(3-oxo-3-(tritylamino)propyl)oxazolidine-3-carboxylate (SI-1)

^{1}H NMR (400 MHz, DMSO-d_6):

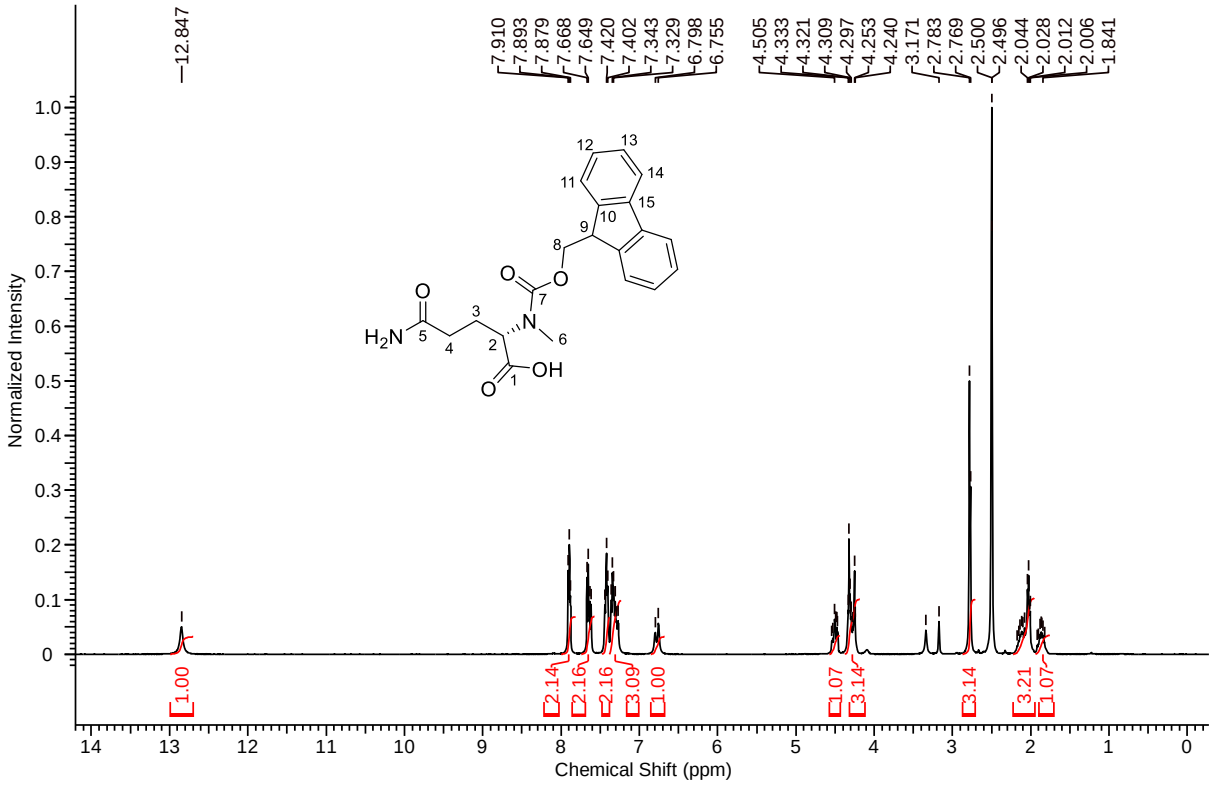


^{13}C NMR (100 MHz, DMSO-d_6):

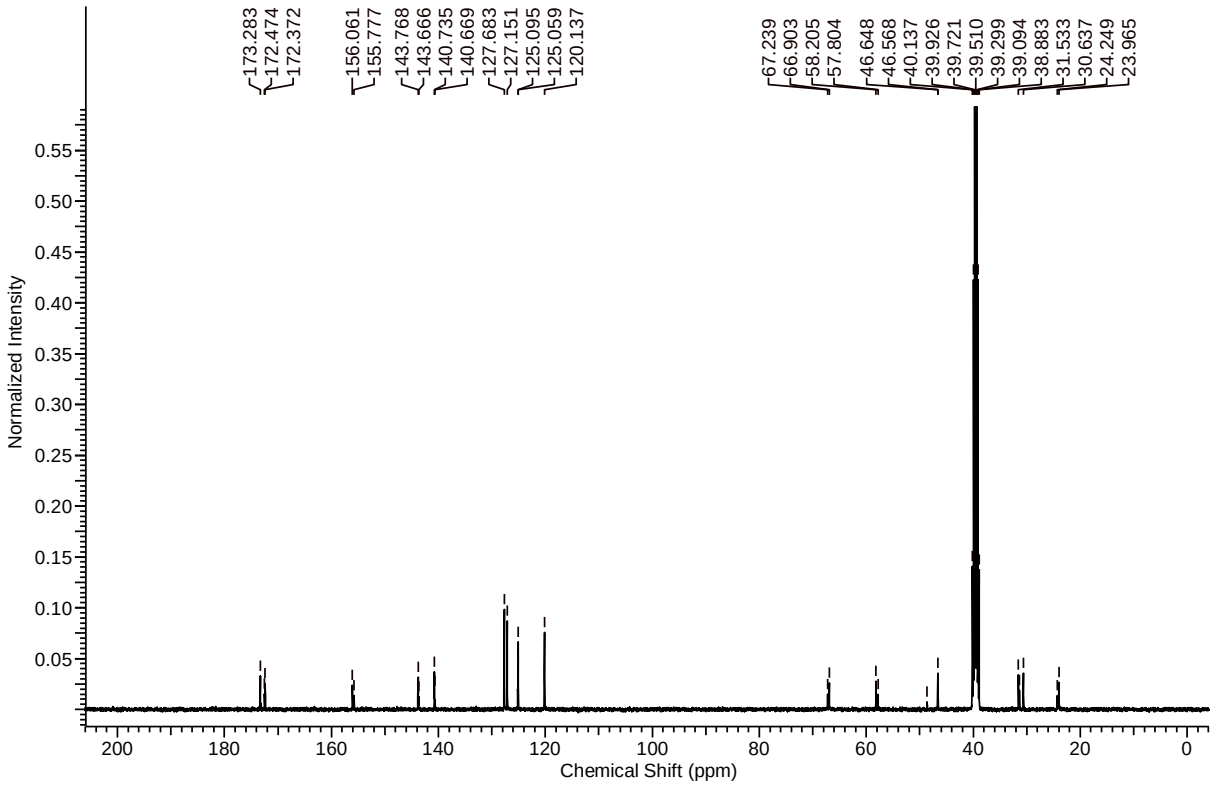


N^2-(((9H-Fluoren-9-yl)methoxy)carbonyl)-N^2-methyl-L-glutamine (SI-2)

^{1}H NMR (400 MHz, DMSO-d_6):

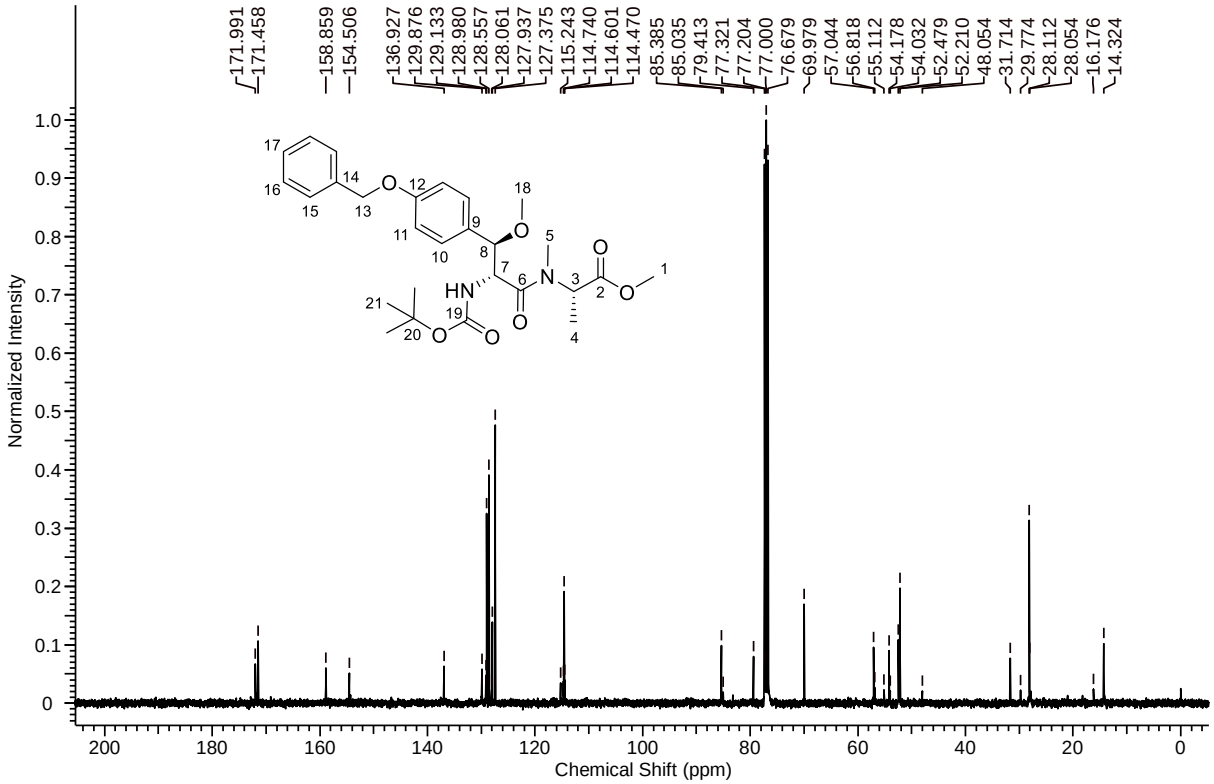


^{13}C NMR (100 MHz, DMSO-d_6):

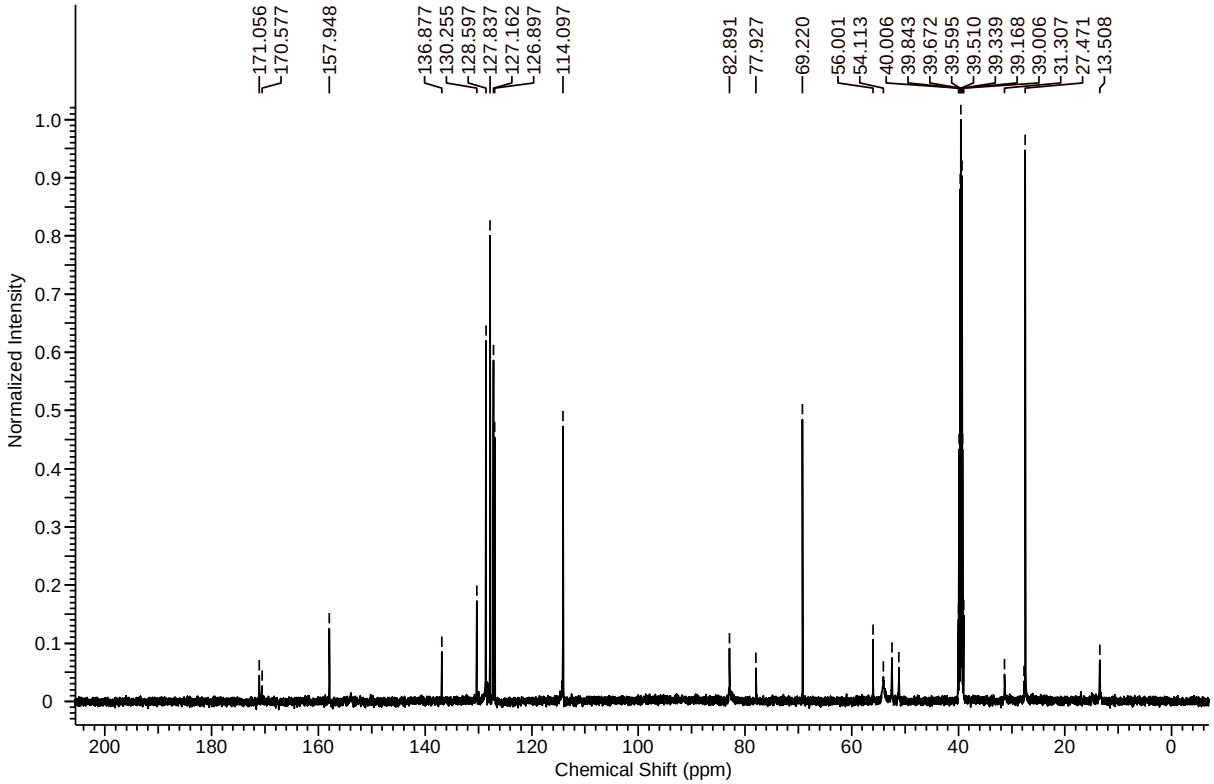


Methyl *N*-((2*R*,3*R*)-3-(4-(benzyloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)-3-methoxy-propanoyl)-*N*-methyl-L-alaninate (13)

^{1}H NMR (400 MHz, $CDCl_3$):

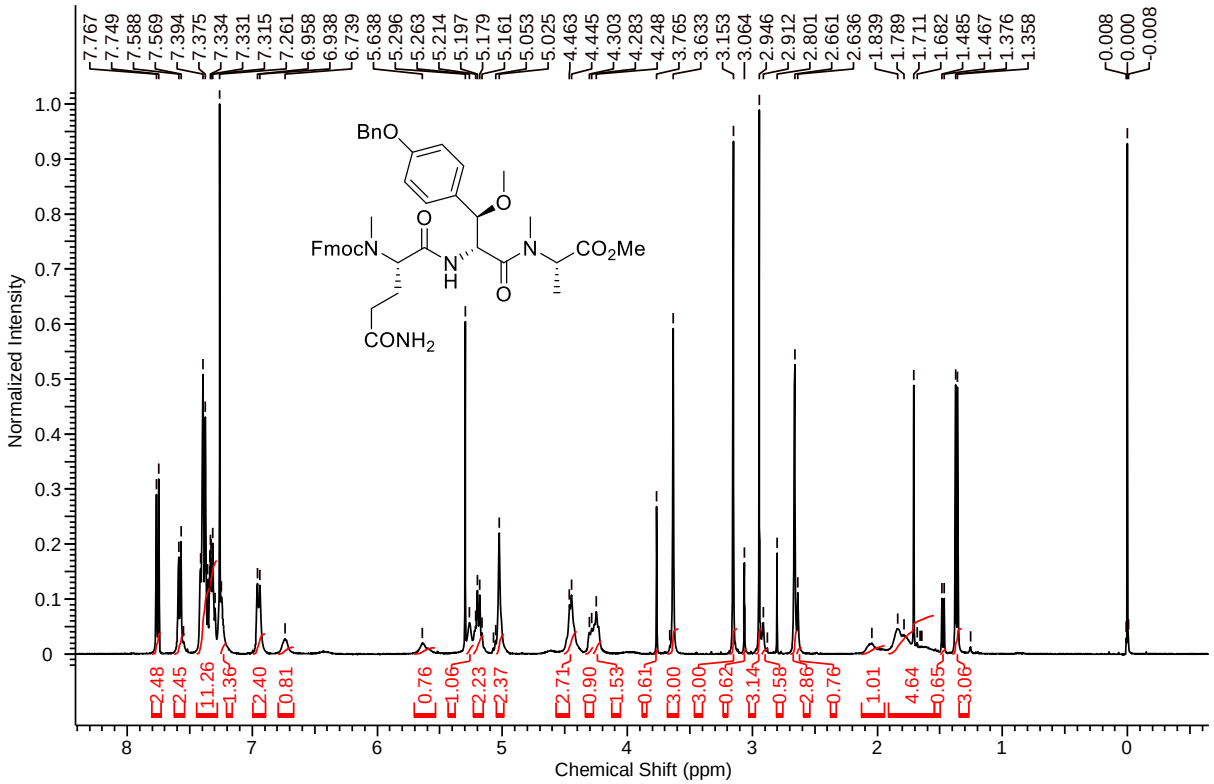


^{13}C NMR (100 MHz, $CDCl_3$):

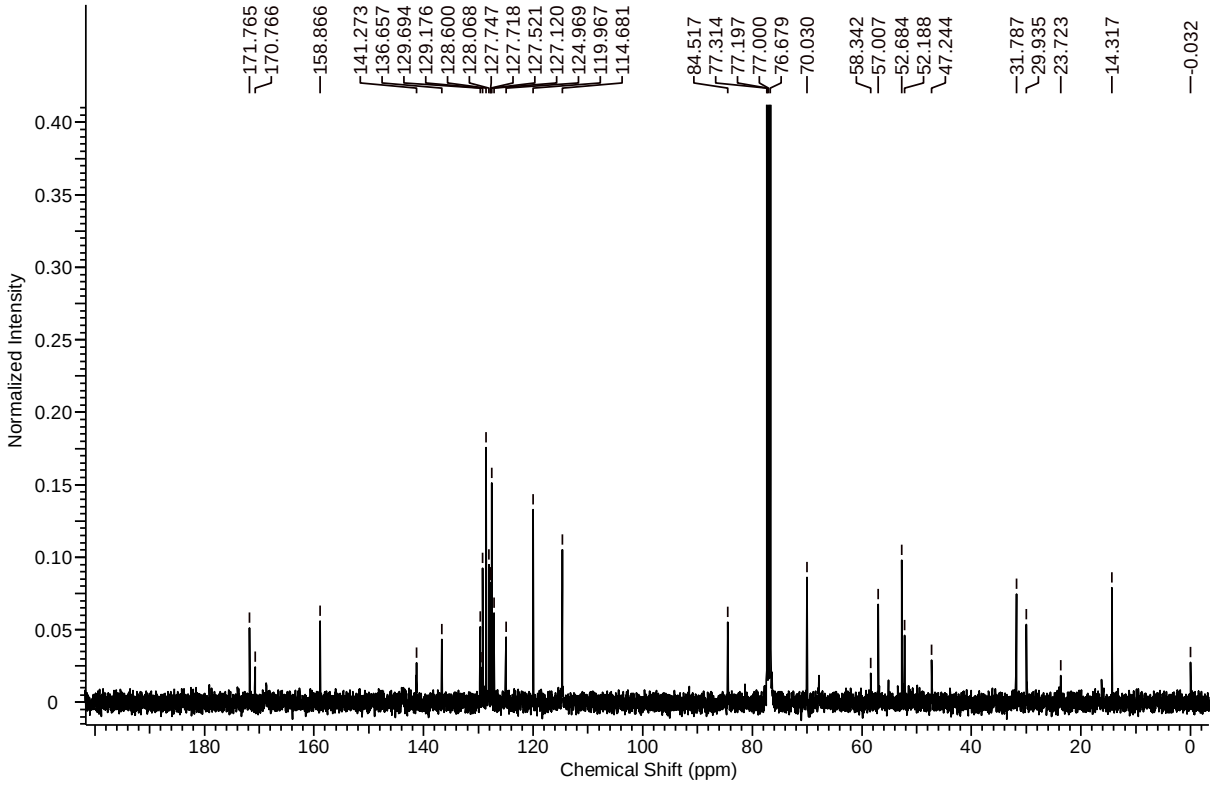


Methyl *N*-((2*R*,3*R*)-2-((*S*)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-5-amino-5-oxopentanamido)-3-(4-(benzyloxy)phenyl)-3-methoxypropanoyl)-*N*-methyl-L-alaninate (14)

^{1}H NMR (400 MHz, $CDCl_3$):

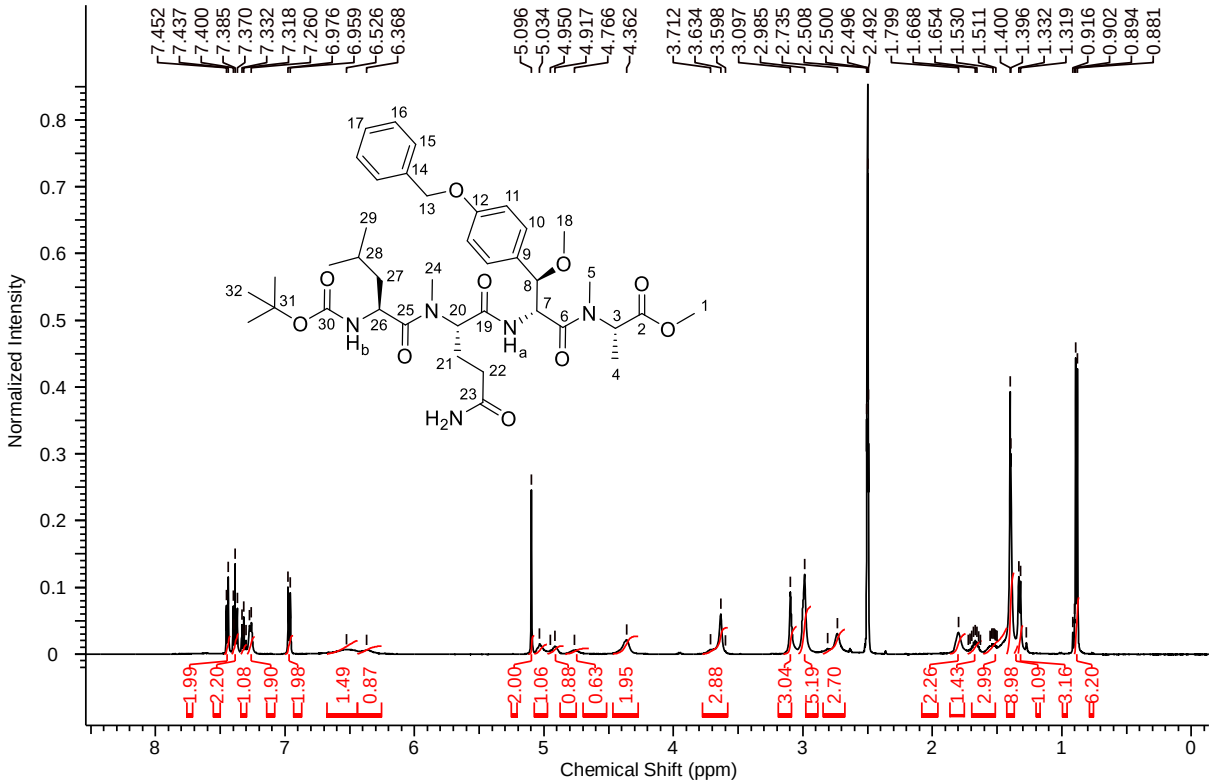


^{13}C NMR (100 MHz, $CDCl_3$):

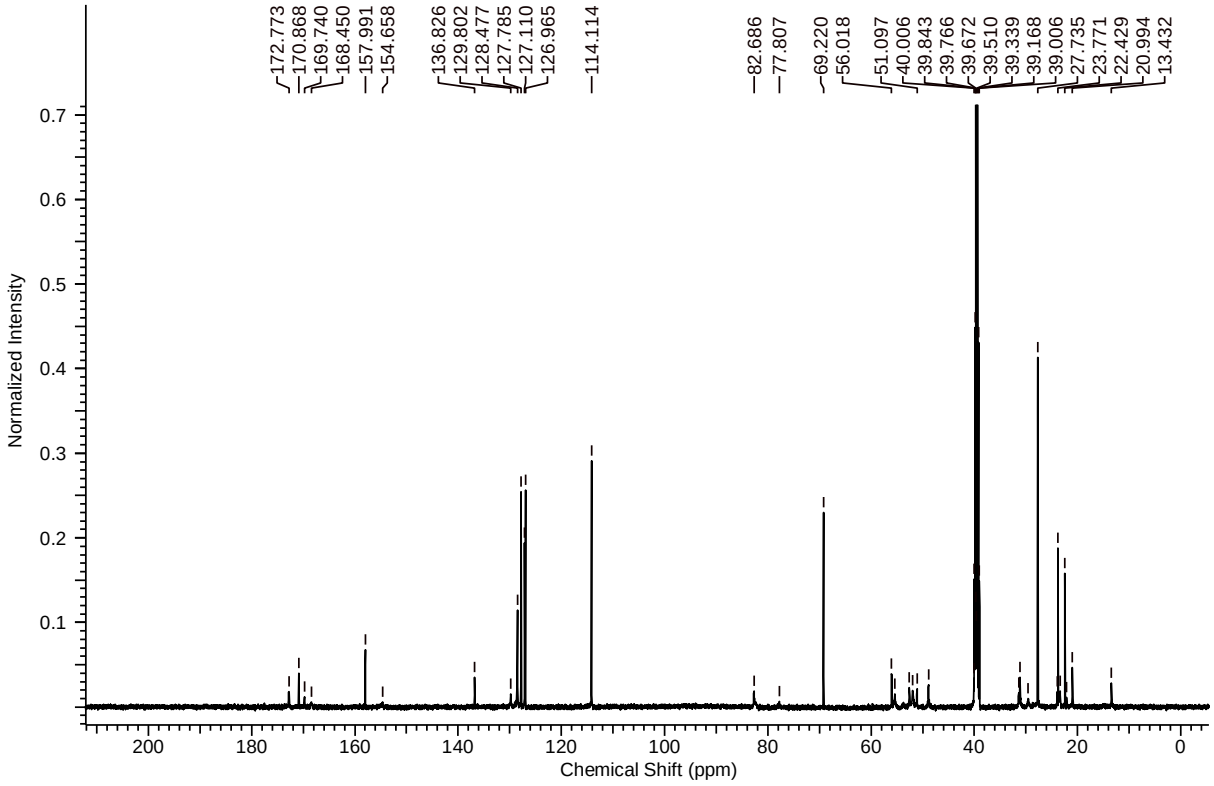


Methyl *N*-((2*R*,3*R*)-2-((*S*)-5-amino-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-*N*,4-dimethyl-pentanamido)-5-oxopentanamido)-3-(4-(benzyloxy)phenyl)-3-methoxypropanoyl)-*N*-methyl-L-alaninate (15a)

^{1}H NMR (500 MHz, DMSO-d_6, 373 K):

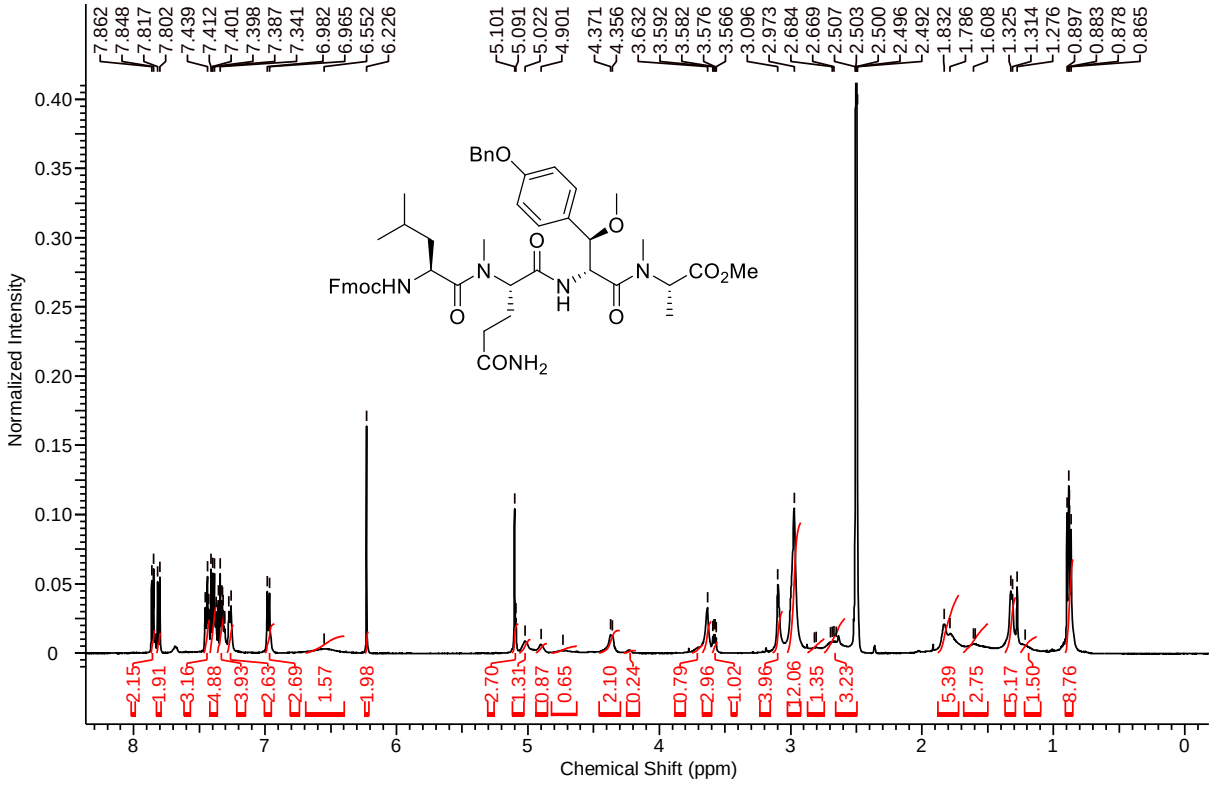


^{13}C NMR (100 MHz, DMSO-d_6, 373 K):

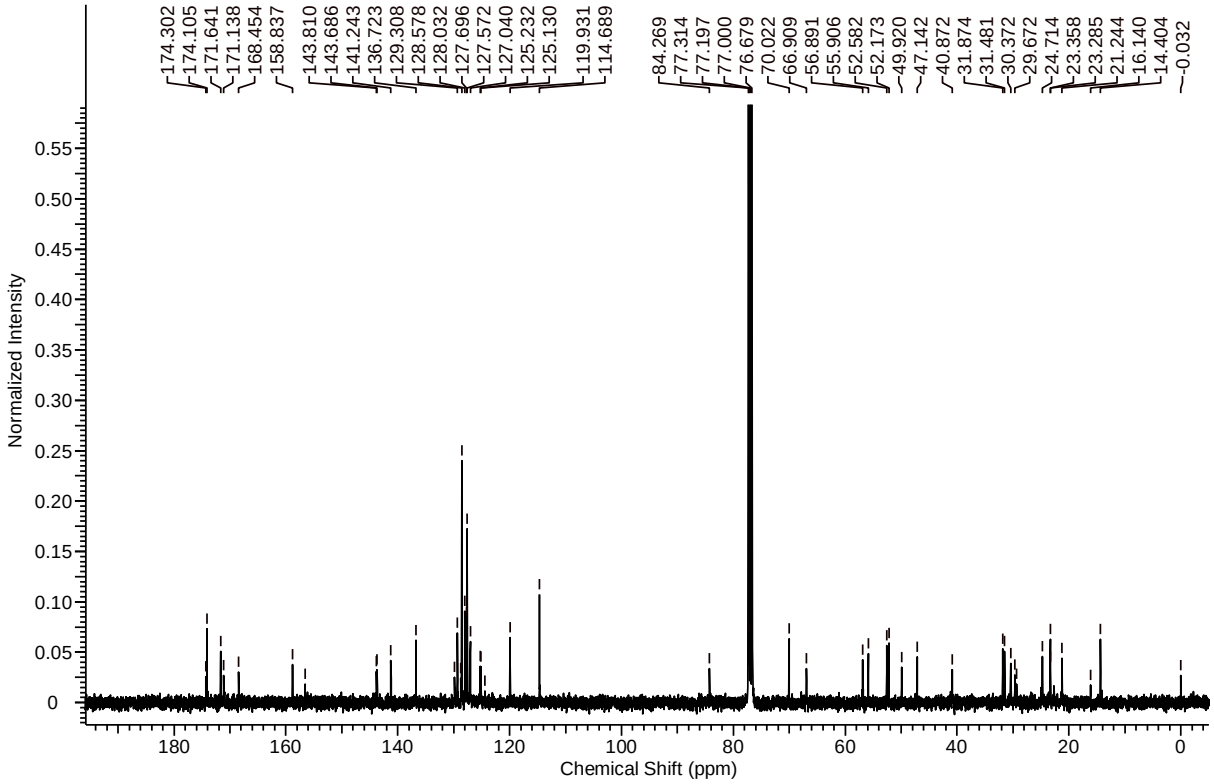


Methyl *N*-((2*R*,3*R*)-2-((*S*)-2-((*S*)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-*N*,4-dimethyl-pentanamido)-5-amino-5-oxopentanamido)-3-(4-(benzyloxy)phenyl)-3-methoxypropanoyl)-*N*-methyl-L-alaninate (15b)

^{1}H NMR (500 MHz, DMSO-d_6, 373 K):

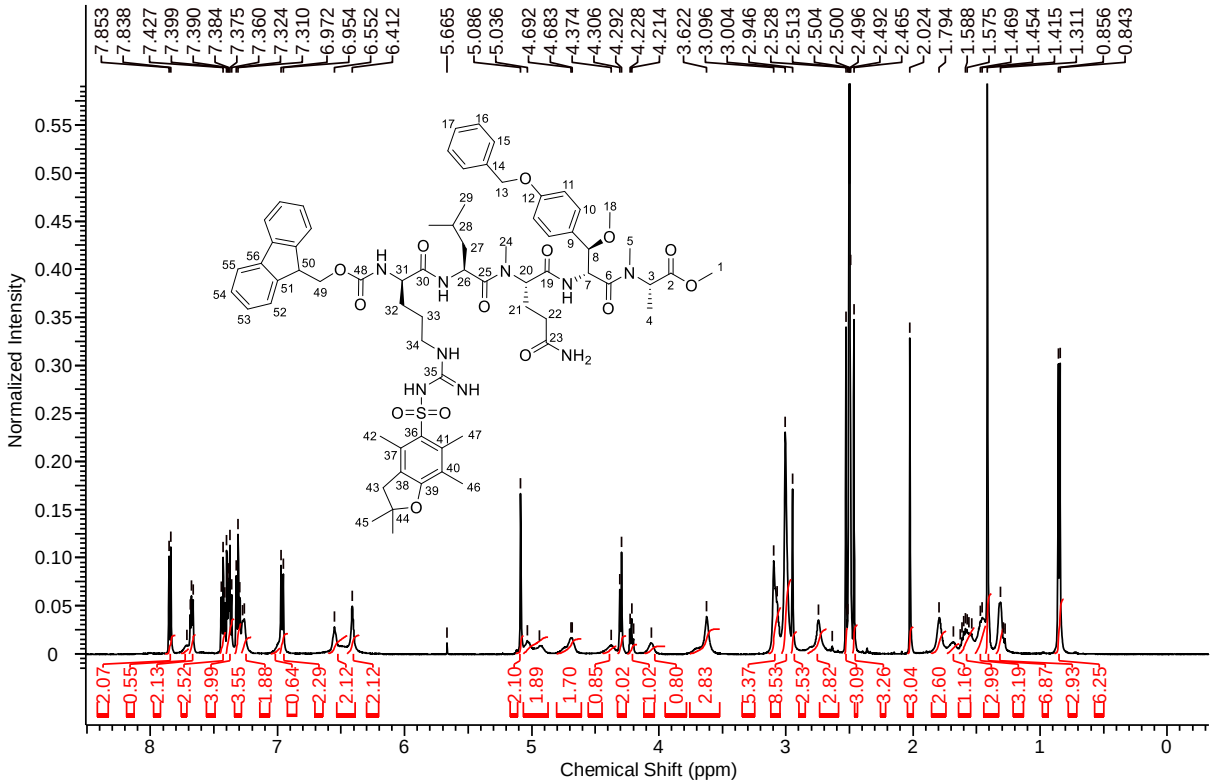


^{13}C NMR (100 MHz, DMSO-d_6, 373 K):

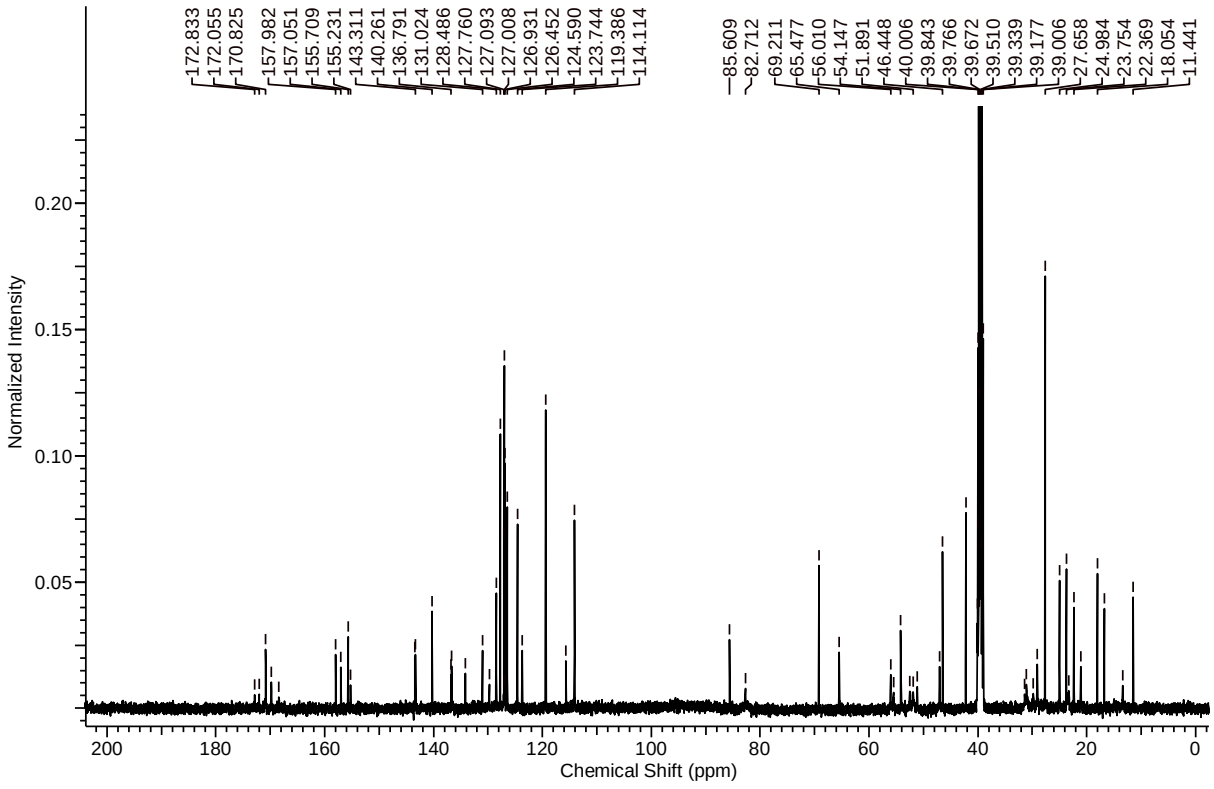


Methyl *N*-((2*R*,3*R*)-2-((*S*)-2-((*S*)-2-((*R*)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(3-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)guanidino)pentanamido)-*N*,4-dimethylpentanamido)-5-amino-5-oxopentanamido)-3-(4-(benzyloxy)phenyl)-3-methoxypropan-oyl)-*N*-methyl-L-alaninate (16)

^{1}H NMR (500 MHz, DMSO-d_6, 373 K):

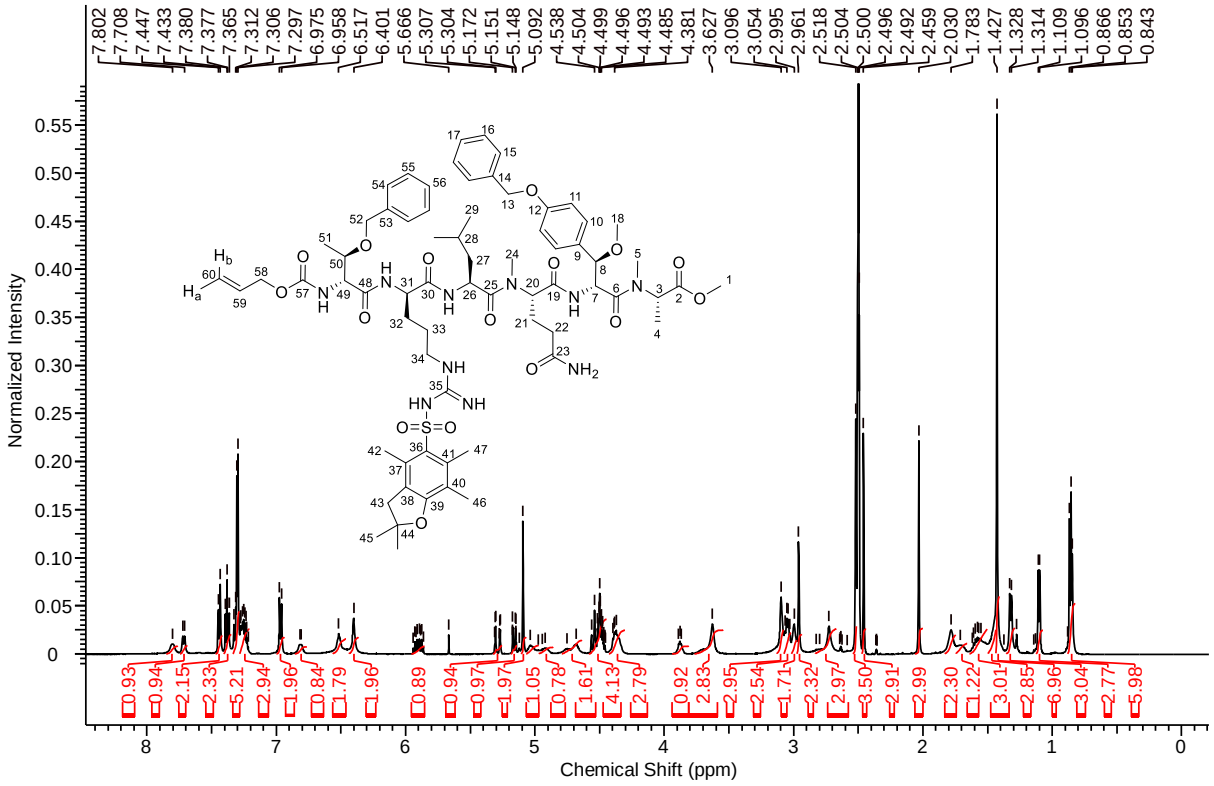


^{13}C NMR (100 MHz, DMSO-d_6, 373 K):

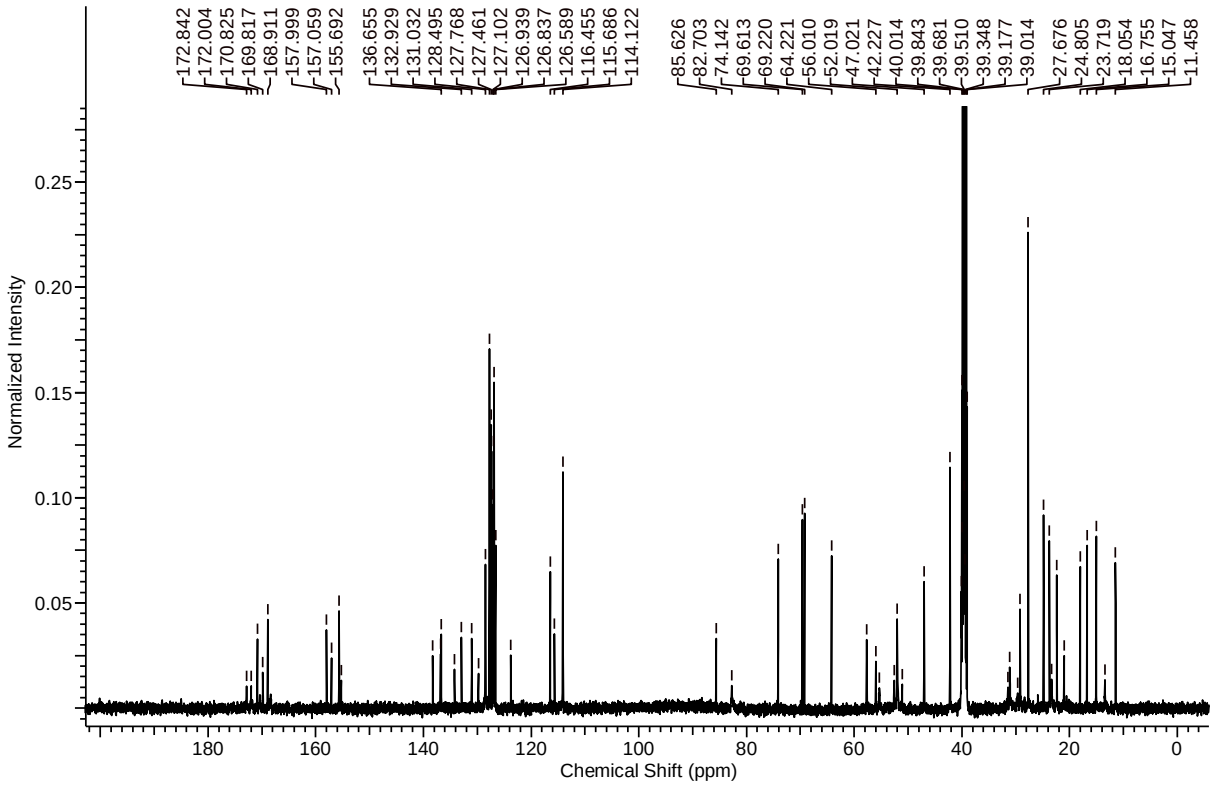


Methyl *N*-((2*R*,3*R*)-2-((*S*)-2-((*S*)-2-((*R*)-2-((2*R*,3*R*)-2-(((allyloxy)carbonyl)amino)-3-(benzyl-oxy)-butanamido)-5-(3-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl) guanidino)-pentanamido)-*N*,4-dimethylpentanamido)-5-amino-5-oxopentanamido)-3-(4-(benzyloxy)-phenyl)-3-methoxypropanoyl)-*N*-methyl-L-alaninate (17)

^{1}H NMR (500 MHz, DMSO-d_6, 373 K):

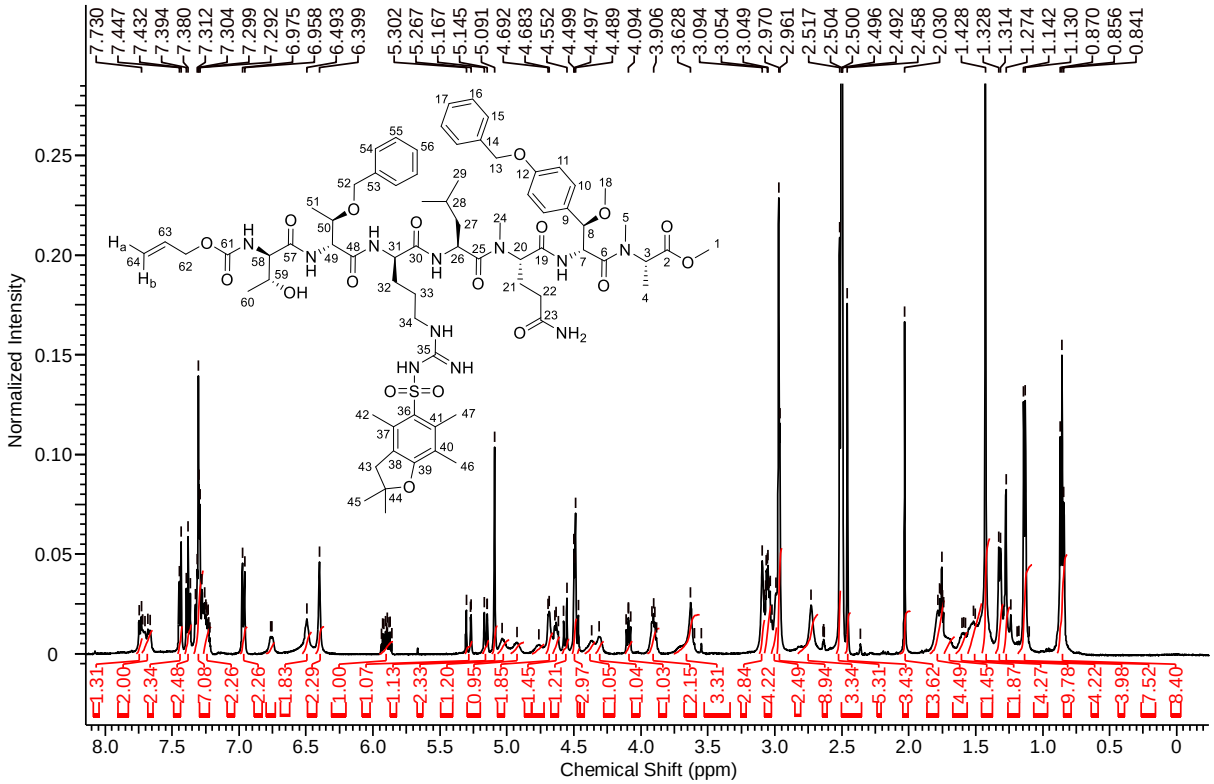


^{13}C NMR (100 MHz, DMSO-d_6, 373 K):

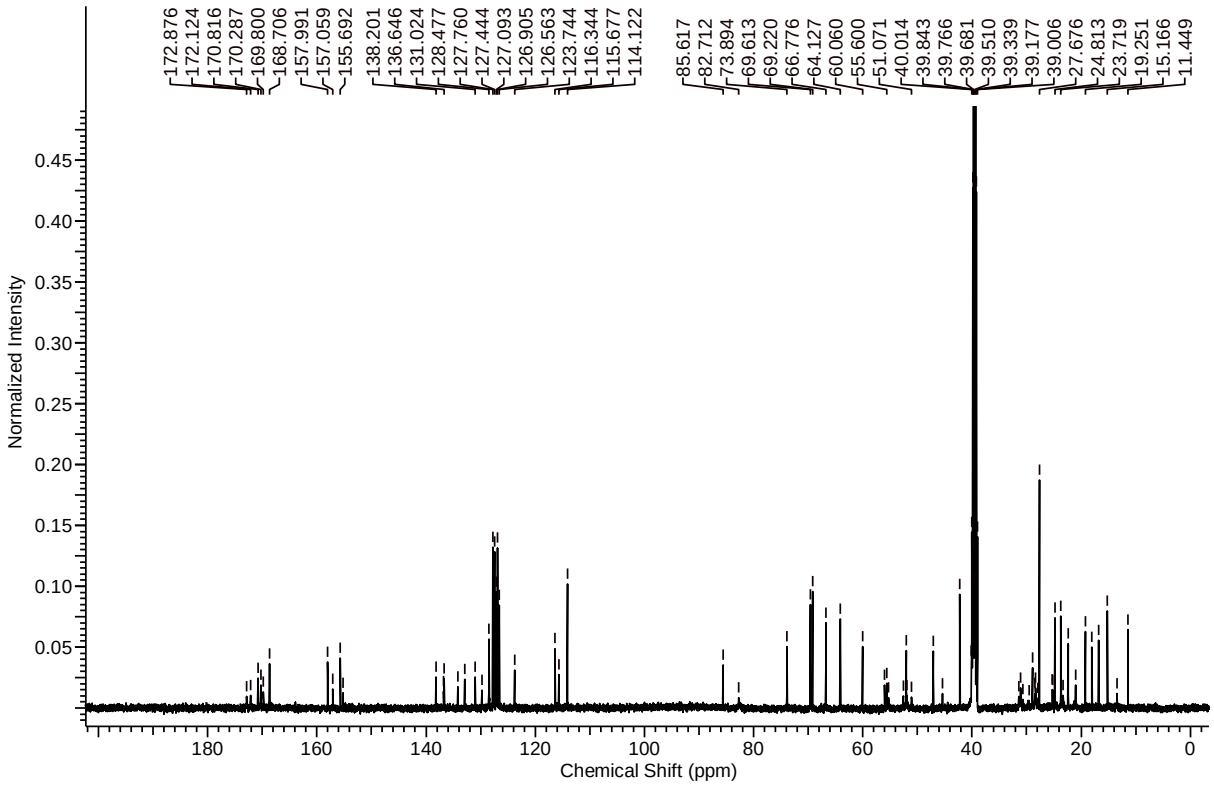


Methyl *N*-((2*R*,3*R*)-2-((*S*)-2-((*S*)-2-((*R*)-2-((2*R*,3*R*)-2-((2*R*,3*R*)-2-(((allyloxy)carbonyl)amino)-3-hydroxy-butanamido)-3-(benzyloxy)butanamido)-5-(3-((2,2,4,6,7-pentamethyl-2,3-dihydro-benzofuran-5-yl)sulfonyl)guanidino)pentanamido)-*N*,4-dimethylpentanamido)-5-amino-5-oxopentanamido)-3-(4-(benzyloxy)phenyl)-3-methoxypropanoyl)-*N*-methyl-L-alaninate (18)

^{1}H NMR (500 MHz, DMSO-d_6, 373 K):

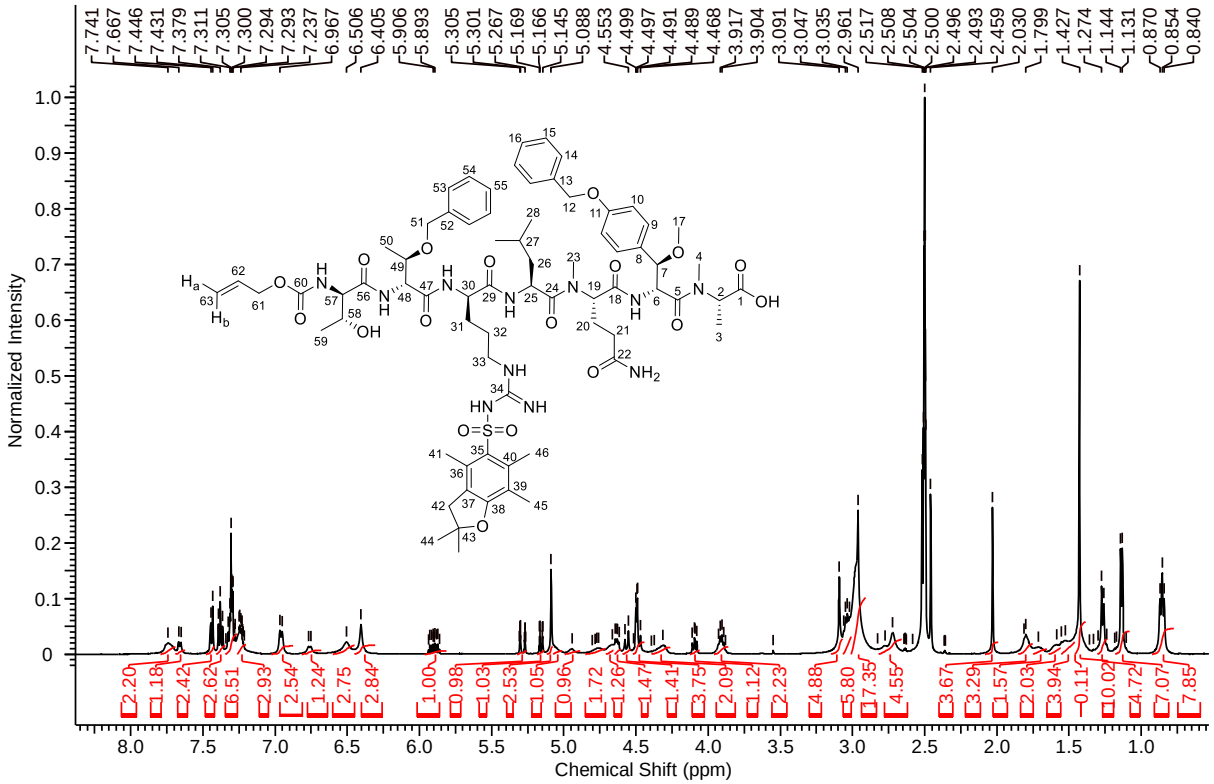


^{13}C NMR (100 MHz, DMSO-d_6, 373 K):

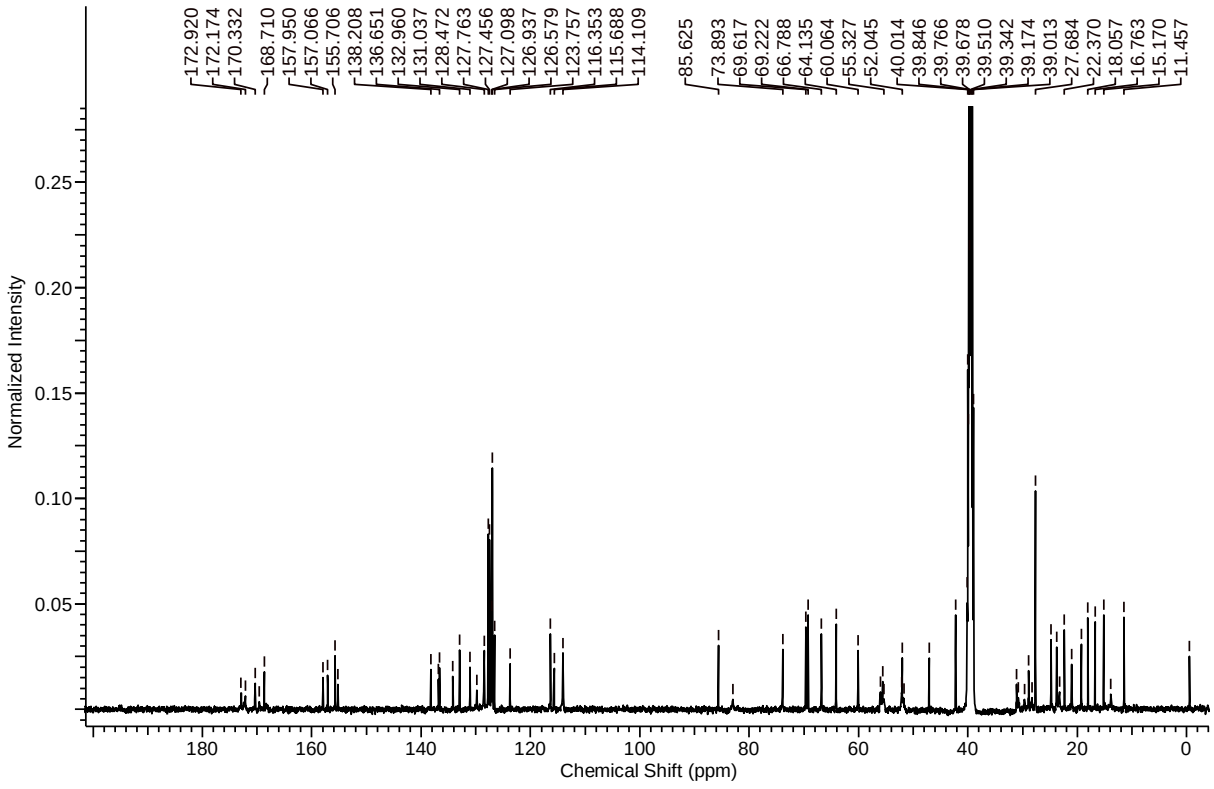


_N_-((2_R_,3_R_)-2-((_S_)-2-((_S_)-2-((_R_)-2-((2_R_,3_R_)-2-((2_R_,3_R_)-2-(((Allyloxy)carbonyl)amino)-3-hydroxy-butanamido)-3-(benzyloxy)butanamido)-5-(3-((2,2,4,6,7-pentamethyl-2,3-dihydro-benzofuran-5-yl)sulfonyl)guanidino)pentanamido)-_N_,4-dimethylpentanamido)-5-amino-5-oxopentan-amido)-3-(4-(benzyloxy)phenyl)-3-methoxypropanoyl)-_N_-methyl-L-alanine (19)

^{1}H NMR (500 MHz, DMSO-d$_6$):

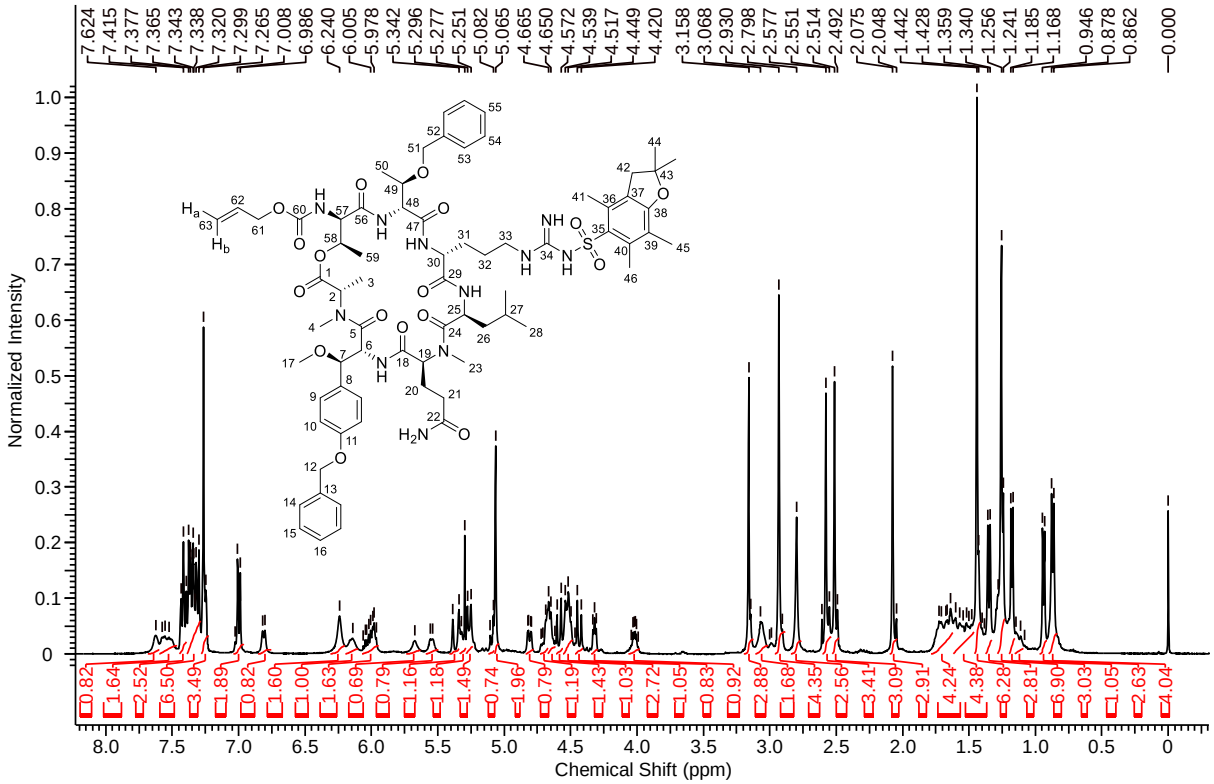


^{13}C NMR (100 MHz, DMSO-d$_6$):

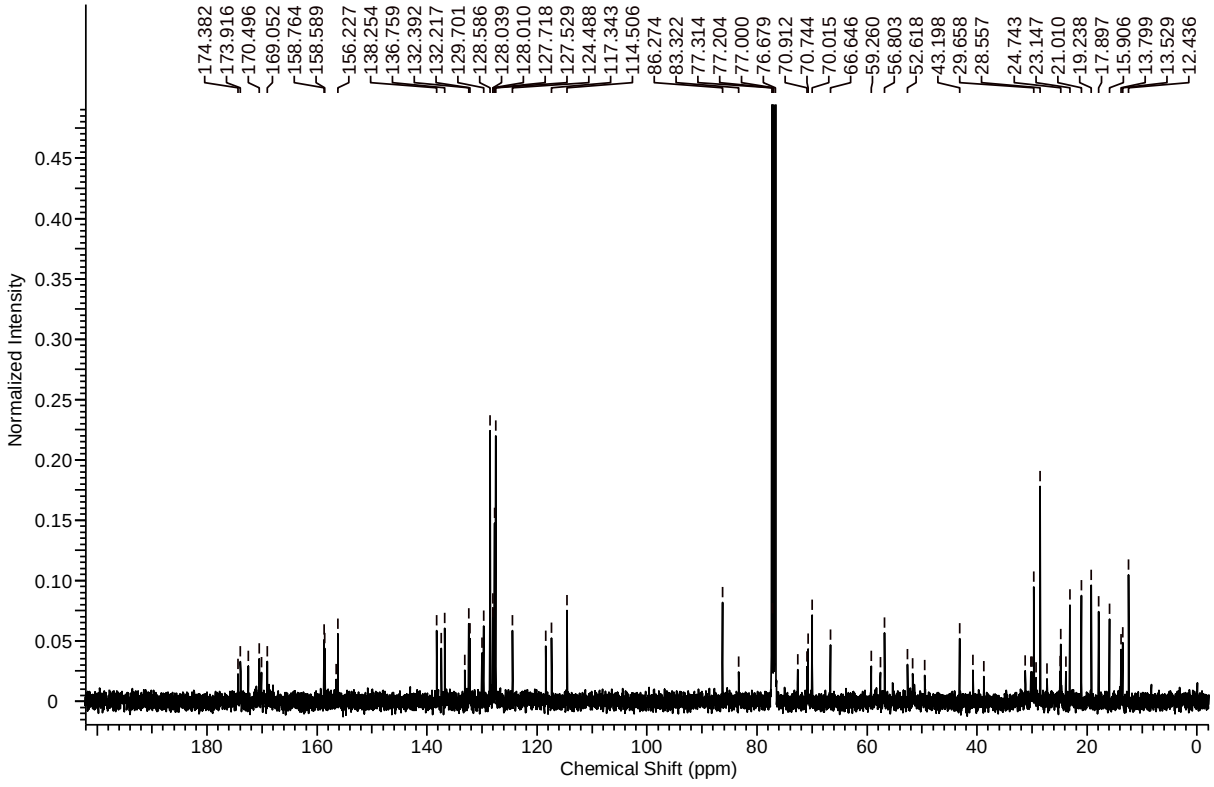


Allyl ((3*S*,6*R*,9*S*,12*S*,15*R*,18*R*,21*R*,22*R*)-9-(3-amino-3-oxopropyl)-18-((*R*)-1-(benzyloxy)ethyl)-6-((*R*)-(4-(benzyloxy)phenyl)(methoxy)methyl)-12-isobutyl-3,4,10,22-tetramethyl-2,5,8,11,14,17,20-heptaoxo-15-(3-(3-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl) sulfonyl)guanidino)propyl)-1-oxa-4,7,10,13,16,19-hexaazacyclodocosan-21-yl)carbamate (20)

^{1}H NMR (500 MHz, $CDCl_3$):



^{13}C NMR (100 MHz, $CDCl_3$):



Literature

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