Z-selective olefin metathesis on peptides: Investigation of side chain influence, preorganization, and guidelines in substrate selection

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Supporting Information

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General Information

All reactions were carried out in dry glassware under an atmosphere of argon using standard Schlenk line techniques. Cyclometalated ruthenium catalysts **1** and **2** were obtained from Materia, Inc. and used as received. All solvents were purified by passage through solvent purification columns and further degassed by bubbling argon. Commercially available reagents were used as received unless otherwise noted. Solid substrates were used after purification by column chromatography (SiO_2; (230-400 mesh)). Thin-layer chromatography utilized EMD Sciences silica gel 60 F254 pre-cast glass plates (Cat. No. 1.05714.0001). Microwave-assisted chemistry utilized a Biotage Initiator 2.5 reactor. Wang resin, MBHA resin, and TentaGel MB RAM resin were purchased from Novabiochem or RAPP Polymere. All Boc-protected or Fmoc-protected amino acids were purchased from ChemImpex or Peptides International. Fmoc-(S)-2-(4-pentenyl)alanine or Fmoc-(R)-2-(7-

octenyl)alanine were synthesized as previously described[1] and confirmed by spectroscopic analysis (NMR). HBTU (N,N,N',N'-tetramethyl-O-(1H-benzotriazol-1-yl)uranium hexafluorophosphate), HATU (1-[Bis(dimethylamino)methylene]-1H-1,2,3,-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate), and HOBt (1-hydroxybenzotriazole) were purchased from NovaBioChem. Piperidine, trifluoroacetic acid (TFA), triisopropylsilane (TIPS), and N,N'-dimethylformamide (DMF) were purchased from Sigma-Aldrich. Triethylamine (TEA) or N,N-diisopropylethylamine (DIEA) were purchased from Sigma-Aldrich and distilled prior to use.

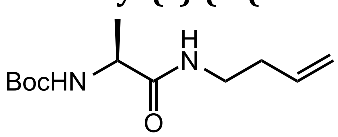
Standard NMR spectroscopy experiments were conducted on a Varian INOVA 500 (^{1}H: 500 MHz, ^{13}C: 125 MHz) or Varian INOVA 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz) spectrometer. NMR spectra are reported as δ values in ppm relative to the reported solvent ($CDCl_3$ referenced to 7.27, CD_3OD referenced to 3.31). Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (b), apparent (app), and combinations thereof. Spectra were analyzed and processed using MestReNova.

High-resolution mass spectra (HRMS) data was obtained on a JEOL JMS-600H high resolution mass spectrometer operating in FAB$^+$ or positive-ion ESI mode. MALDI-TOF spectra were recorded on a Voyager DE-PRO MALDI TOF-MS spectrometer (Applied Biosystems) operating in reflector ion mode using α-cyano-4-hydroxycinnamic acid as the matrix.

Analytical HPLC was performed on an Agilent 1200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), or mixed (MM) ionization mode equipped with an Eclipse Plus C_8 column (1.8 μm, 2.1 x 50 mm). Preparative HPLC was performed with an Agilent 1100 Series HPLC utilizing an Agilent Eclipse XDB-C_{18} column (5 μm, 9.4 x 250 mm) or an Agilent Zorbax RX-SIL column (5 μm, 9.4 x 250 mm) using a gradient of double distilled water and HPLC grade acetonitrile containing 0.1% TFA or 0.1% acetic acid (AcOH). LCMS was performed on an Agilent 1200 Series LCMS equipped with a Quadrupole 6120 MS detector and an Eclipse XDB-C_{18} reverse-phase column (5, 4.6 μm x 150 mm).

General Procedure for Homoallyl Modification of Peptides

tert-butyl (*S*)-(1-(but-3-en-1-ylamino)-1-oxopropan-2-yl)carbamate (3)



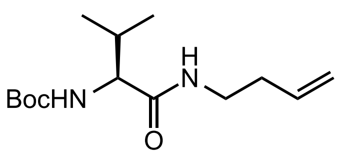
3: $C_{12}H_{22}N_2O_3$
Exact mass: 242.1630

A round-bottom flask was charged with Boc-Ala-OH (1.0 g, 5.3 mmol), HOBt (0.72 g, 5.3 mmol, 1.0 eq) and HBTU (3.0 g, 7.9 mmol, 1.5 eq) under Ar(g). To this was added anhydrous DMF (5 mL) and N,N-diisopropylethylamine (DIEA, 2.7 mL, 15.8 mmol, 3 eq.). The reaction mixture

[1] Bird, G.H.; Crannell, W.C..; Walensky, L.D. *Curr. Protoc. Chem. Biol.* **2011**, *3*, 99.

was allowed to stir at room temperature for 15 min upon which the solution turned to a pale yellow. A solution of 3-butenylamine·HCl (0.85 g, 7.9 mmol, 1.5 eq) in DMF (2 mL) was added and the reaction mixture heated to 50°C and allowed to stir for 1 h. The solution was cooled to room temperature and H_2O (20 mL) was added, followed by CH_2Cl_2 (50 mL). The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (5 x 50 mL). The combined organic layers were washed with brine (5 x 50 mL), and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude residue was purified by flash chromatography (SiO_2 , 0% to 50% EtOAc in hexanes) to provide 1.16 g (91%) of **3** as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.51 (bs, 1H), 5.72 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.22 (d, *J* = 7.7 Hz, 1H), 5.12–4.96 (m, 2H), 4.12 (q, *J* = 7.6 Hz, 1H), 3.38–3.18 (m, 2H), 2.22 (qt, *J* = 6.9, 1.3 Hz, 2H), 1.40 (s, 9H), 1.31 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.71, 155.48, 135.04, 117.09, 79.83, 50.02, 38.41, 33.67, 28.30 (3C), 18.64. HRMS (ESI) m/z calcd for $C_{12}H_{22}N_2O_3$ $[M+H]^+$: 243.1630, found 243.1626

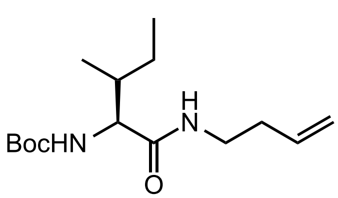
tert-butyl (S)-(1-(but-3-en-1-ylamino)-3-methyl-1-oxobutan-2-yl)carbamate (5a)



5a: $C_{14}H_{26}N_2O_3$
Exact mass: 270.1943

Following the general procedure for the synthesis of **3**, **5a** was synthesized from Boc-Val-OH (1.1 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), and DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine·HCl (0.85 g, 7.9 mmol, 1.5 eq.) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO_2 , 0% to 33% EtOAc in hexanes) to provide 1.17 g (82%) of **5a** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72–6.53 (m, 1H), 5.69 (ddt, *J* = 17.0, 10.1, 6.8 Hz, 1H), 5.32 (d, *J* = 9.3 Hz, 1H), 5.08–4.93 (m, 2H), 3.86 (dd, *J* = 9.1, 6.8 Hz, 1H), 3.36-3.15 (m, 2H), 2.19 (qt, *J* = 6.9, 1.3 Hz, 2H), 2.06-1.95 (m, 1H), 1.37 (s, 9H), 0.87 (dd, *J* = 8.2, 6.7 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.84, 155.94, 135.10, 116.78, 79.34, 59.95, 38.50, 33.71, 30.99, 28.26 (3C), 19.19, 18.10. HRMS (ESI) m/z calcd for $C_{14}H_{26}N_2O_3$ $[M+H]^+$: 271.1943, found 271.1940

tert-butyl ((2S,3R)-1-(but-3-en-1-ylamino)-3-methyl-1-oxopentan-2-yl)carbamate (5b)

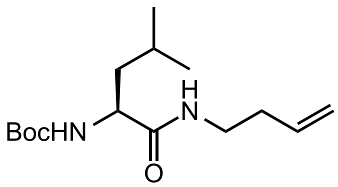


5b: $C_{15}H_{28}N_2O_3$
Exact mass: 284.2100

Following the general procedure for the synthesis of **3**, **5b** was synthesized from Boc-Ile-OH (1.2 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine·HCl (0.85 g, 7.9 mmol, 1.5 eq.) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO_2 , 0% to 33% EtOAc in hexanes) to provide 1.27 g (85%) of **5b** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.26 (d, *J* = 6.1 Hz, 1H), 5.73 (ddt, *J* = 17.1, 10.3, 6.8 Hz, 1H), 5.15 (d, *J* = 8.9

Hz, 1H), 5.11–4.98 (m, 2H), 3.88 (dd, *J* = 8.9, 6.7 Hz, 1H), 3.39-3.21 (m, 2H), 2.23 (qt, *J* = 6.8, 1.3 Hz, 2H), 1.90–1.70 (m, 1H), 1.52-1.44 (m, 1H), 1.41 (s, 9H), 1.18–0.98 (m, 1H), 0.95–0.78 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.83, 155.87, 135.13, 116.87, 79.43, 59.20, 38.48, 37.15, 33.70, 28.27 (3C), 24.76, 15.43, 11.20. HRMS (ESI) m/z calcd for $C_{15}H_{28}N_2O_3$ $[M+H]^+$: 285.2100, found 284.5101

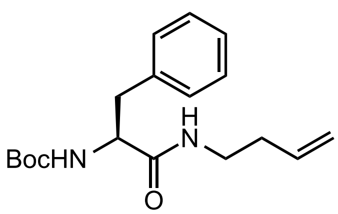
tert-butyl (_S_)-(1-(but-3-en-1-ylamino)-4-methyl-1-oxopentan-2-yl)carbamate (5c)



5c: $C_{15}H_{28}N_2O_3$
Exact mass: 284.2100

Following the general procedure for the synthesis of **3**, **5c** was synthesized from Boc-Leu-OH (1.3 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.) and 3-butenylamine·HCl (0.85 g, 7.9 mmol, 1.5 eq) in DMF at 40°C. The crude product was purified by flash chromatography (SiO_2 , 0% to 33% EtOAc in hexanes) to provide 1.18 g (79%) of **5c** as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 6.34 (bs, 1H), 5.74 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.12–5.02 (m, 2H), 5.00 (d, *J* = 8.5 Hz, 1H), 4.06 (q, *J* = 7.6 Hz, 1H), 3.38–3.20 (m, 2H), 2.24 (qt, *J* = 6.8, 1.4 Hz, 2H), 1.66-1.60 (m, 2H), 1.45-1.40 (m, 1H), 1.42 (s, 9H), 0.96–0.86 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.83, 155.78, 135.10, 116.81, 79.55, 53.02, 41.51, 38.45, 33.66, 28.27 (3C), 24.65, 22.82, 22.00. HRMS (ESI) m/z calcd for $C_{15}H_{28}N_2O_3$ $[M+H]^+$: 285.2100, found 285.2102

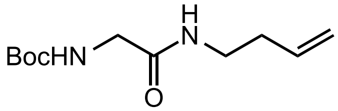
tert-butyl (_S_)-(1-(but-3-en-1-ylamino)-1-oxo-3-phenylpropan-2-yl)carbamate (5d)



5d: $C_{18}H_{26}N_2O_3$
Exact mass: 318.1943

Following the general procedure for the synthesis of **3**, **5d** was synthesized from Boc-Phe-OH (1.4 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine·HCl (0.85 g, 7.9 mmol, 1.5 eq.) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO_2 , 0% to 33% EtOAc in hexanes) to provide 1.53 g (91%) of **5d** as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.26–7.16 (m, 5H), 6.30 (bs, 1H), 5.63-5.57 (m, 1H), 5.38 (d, *J* = 7.9 Hz, 1H), 5.00–4.90 (m, 2H), 4.41–4.26 (m, 1H), 3.26-3.22 (m, 1H), 3.20-3.13 (m, 1H), 3.04–2.95 (m, 2H), 2.13–2.04 (m, 2H), 1.37 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.54, 155.57, 137.05, 135.00 (2C), 129.32 (2C), 128.38, 126.64, 116.85, 79.67, 55.91, 39.02, 38.49, 33.48, 28.28 (3C). HRMS (ESI) m/z calcd for $C_{18}H_{26}N_2O_3$ $[M+H]^+$: 319.1943, found 319.1940

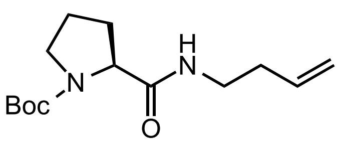
tert-butyl (2-(but-3-en-1-ylamino)-2-oxoethyl)carbamate (5e)



5e: $C_{11}H_{20}N_2O_3$
Exact mass: 228.1474

Following the general procedure for the synthesis of **3**, **5e** was synthesized from Boc-Gly-OH (0.92 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine·HCl (0.85 g, 7.9 mmol, 1.5 eq) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO_2 , 3:1 EtOAc:hexane) to provide 0.84 g (70%) of **5e** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.19 (bs, 1H), 5.75 (ddt, *J* = 17.1, 10.3, 6.8 Hz, 1H), 5.13–5.02 (m, 2H), 3.77 (s, 2H), 3.35 (q, *J* = 6.5 Hz, 2H), 2.27 (qt, *J* = 6.8, 1.4 Hz, 2H), 1.45 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.85, 156.20, 134.92, 117.10, 80.00, 44.22, 38.45, 33.52, 28.25 (3C). HRMS (ESI) m/z calcd for $C_{11}H_{20}N_2O_3$ $[M+H]^+$: 229.1474, found 229.1476

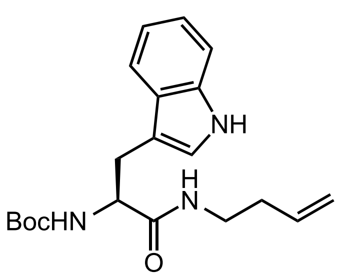
tert-butyl (_S_)-2-(but-3-en-1-ylcarbamoyl)pyrrolidine-1-carboxylate (5f)



5f: $C_{14}H_{24}N_2O_3$
Exact mass: 268.1787

Following the general procedure for the synthesis of **3**, **5f** was synthesized from Boc-Pro-OH (1.1 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine·HCl (0.85 g, 7.9 mmol, 1.5 eq.) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO_2 , 2:1 EtOAc:hexane) to provide 1.02 g (72%) of **5f** as a white solid (mixture of *cis* and *trans* proline isomers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 (bs, 1H), 6.14 (bs, 1H), 5.68-5.61 (m, 1H), 4.99-4.94 (m, 2H), 4.23–3.99 (m, 1H), 3.34–3.19 (m, 4H), 2.14-1.89 (m, 4H), 1.89–1.67 (m, 2H), 1.35 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.42, 171.87, 155.57, 154.57, 135.10, 116.88, 80.15, 61.18, 59.90, 46.94, 38.22, 33.66, 31.01, 28.28 (3C), 24.41, 23.56. HRMS (ESI) m/z calcd for $C_{14}H_{24}N_2O_3$ $[M+H]^+$: 269.1787, found 269.1782

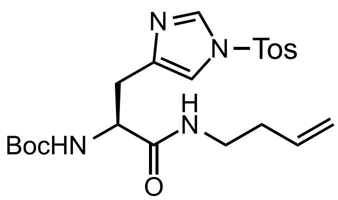
tert-butyl (_S_)-(1-(but-3-en-1-ylamino)-3-(1_H_-indol-3-yl)-1-oxopropan-2-yl)carbamate (5g)



5g: $C_{20}H_{27}N_3O_3$
Exact mass: 357.2052

Following the general procedure for the synthesis of **3**, **5g** was synthesized from Boc-Trp-OH (1.6 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.) A solution of 3-butenylamine·HCl (0.85 g, 7.9 mmol, 1.5 eq.) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO_2 , 0% to 50% EtOAc in hexanes) to provide 1.40 g (74%) of **5g** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (bs, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.37 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.20 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.13 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 5.67 (bs, 1H), 5.58–5.41 (m, 1H), 5.19 (bs, 1H), 4.95–4.75 (m, 2H), 4.39 (q, *J* = 7.2 Hz, 1H), 3.38–3.25 (m, 1H), 3.20-3.11 (m, 3H), 2.05-1.94 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.61, 155.48, 136.28, 134.81, 127.41, 123.17, 122.20, 119.65, 118.87, 117.08, 111.26, 110.63, 80.03, 55.34, 38.35, 33.25, 28.65, 28.32 (3C). HRMS (ESI) m/z calcd for $C_{20}H_{27}N_3O_3$ $[M+H]^+$: 358.2052, found 358.2058

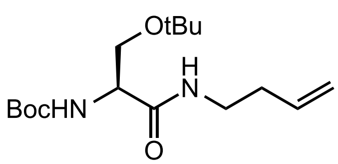
tert-butyl (_S_)-(1-(but-3-en-1-ylamino)-1-oxo-3-(1-tosyl-1_H_-imidazol-4-yl)propan-2-yl)carbamate (5h)



5h: $C_{22}H_{30}N_4O_5S$
Exact mass: 462.1937

Following the general procedure for the synthesis of **3**, **5h** was synthesized from Boc-His(Tos)-OH (2.1 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine·HCl (0.85 g, 7.9 mmol, 1.5 eq.) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO_2 , 3:1 EtOAc:hexanes) to provide 1.73 g (71%) of **5h** as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 8.16 (bs, 1H), 7.94–7.86 (m, 2H), 7.46–7.38 (m, 2H), 7.30 (bs, 1H), 5.70 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.02-4.97 (m, 2H), 4.79 (bs, 1H), 4.28 (dd, *J* = 8.9, 5.3 Hz, 1H), 3.20–3.06 (m, 2H), 2.95 (m, 1H), 2.78 (m, 1H), 2.40 (s, 3H), 2.12 (q, *J* = 6.9 Hz, 2H), 1.34 (s, 9H); ^{13}C NMR (126 MHz, CD_3OD) δ 172.32, 156.06, 146.73, 140.21, 136.73, 135.07, 134.64, 130.33 (2C), 127.29 (2C), 115.80, 115.09, 79.41, 54.14, 38.34, 33.14, 30.23, 27.24 (3C), 20.34. HRMS (ESI) m/z calcd for $C_{22}H_{30}N_4O_5S$ $[M+H]^+$: 462.1937, found 462.1937

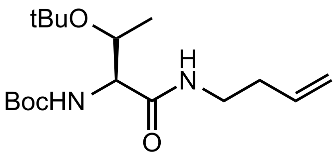
tert-butyl (_S_)-(1-(but-3-en-1-ylamino)-3-(_tert_-butoxy)-1-oxopropan-2-yl)carbamate (5i)



5i: $C_{16}H_{30}N_2O_4$
Exact mass: 314.2206

Following the general procedure for the synthesis of **3**, **5i** was synthesized from Boc-Ser(OtBu)-OH (1.4 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine·HCl (0.85 g, 7.9 mmol, 1.5 eq) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO_2 , 0% to 33% EtOAc in hexanes) to provide 1.46 g (88%) of **5i** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (s, 1H), 5.76–5.65 (m, 1H), 5.39 (bs, 1H), 5.07–4.99 (m, 2H), 4.1–3.99 (m, 1H), 3.74–3.66 (m, 1H), 3.36–3.24 (m, 3H), 2.24–2.15 (m, 2H), 1.39 (m, 9H), 1.12 (m, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.47, 155.42, 135.06, 117.08, 79.74, 73.77, 61.82, 54.24, 38.42, 33.58, 28.25 (3C), 27.37 (3C). HRMS (ESI) m/z calcd for $C_{16}H_{30}N_2O_4$ $[M+H]^+$: 315.2206, found 315.2212

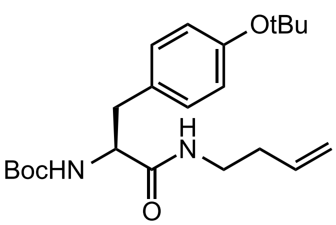
tert-butyl ((2_S_,3_R_)-1-(but-3-en-1-ylamino)-3-(_tert_-butoxy)-1-oxobutan-2-yl)carbamate (5j)



5j: $C_{17}H_{32}N_2O_4$
Exact mass: 328.2362

Following the general procedure for the synthesis of **3**, **5j** was synthesized from Boc-Thr(OtBu)-OH (1.4 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.) A solution of 3-butenylamine·HCl (0.85 g, 7.9 mmol, 1.5 eq.) in DMF (2 mL) was added and the reaction heated to 50ºC and stirred for 1 h. The crude product was purified by flash chromatography (SiO_2 , 0% to 25% EtOAc in hexanes) to provide 1.48 g (85%) of **5j** as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 6.87 (t, *J* = 5.4 Hz, 1H), 5.66 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.55 (d, *J* = 5.6 Hz, 1H), 5.05–4.92 (m, 2H), 3.99 (qd, *J* = 6.4, 3.5 Hz, 1H), 3.93 (m, 1H), 3.29-3.19 (m, 2H), 2.15 (qt, *J* = 6.9, 1.2 Hz, 2H), 1.33 (s, 9H), 1.13 (s, 9H), 0.91 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.46, 155.42, 135.02, 117.10, 79.23, 74.92, 66.80, 58.29, 38.35, 33.54, 28.24 (3C), 28.18 (3C), 17.27. HRMS (ESI) m/z calcd for $C_{17}H_{32}N_2O_4$ $[M+H]^+$: 329.2362, found 329.2366

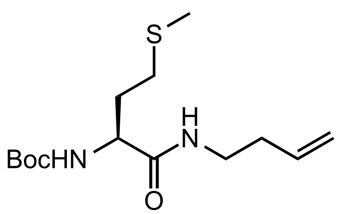
tert-butyl (_S_)-(1-(but-3-en-1-ylamino)-3-(4-(_tert_-butoxy)phenyl)-1-oxopropan-2-yl)carbamate (5k)



5k: $C_{22}H_{34}N_2O_4$
Exact mass: 390.2519

Following the general procedure for the synthesis of **3**, **5k** was synthesized from Boc-Tyr(OtBu)-OH (1.8 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine·HCl (0.85 g, 7.9 mmol, 1.5 eq.) in DMF (2 mL) was added and the reaction heated to 50ºC and stirred for 1 h. The crude product was purified by flash chromatography (SiO_2 , 0% to 33% EtOAc in hexanes) to provide 1.73 g (84%) of **5k** as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.2 Hz, 2H), 6.91 (d, *J* = 8.4, 2H), 5.81 (bs, 1H), 5.63 (ddt, *J* = 17.1, 10.4, 6.9 Hz, 1H), 5.10 (bs, 1H), 5.04–4.89 (m, 2H), 4.23 (q, *J* = 7.5 Hz, 1H), 3.22 (q, *J* = 6.5 Hz, 2H), 3.03-2.93 (m, 2H), 2.15-2.09 (m, 2H), 1.40 (s, 9H), 1.32 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.31, 155.43, 154.15, 134.87, 131.68, 129.69 (2C), 124.15 (2C), 117.06, 79.83, 78.26, 56.00, 38.40, 38.16, 33.47, 28.77 (3C), 28.26 (3C). HRMS (ESI) m/z calcd for $C_{22}H_{34}N_2O_4$ $[M+H]^+$: 391.2519, found 391.2516

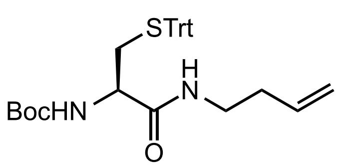
tert-butyl (_S_)-(1-(but-3-en-1-ylamino)-4-(methylthio)-1-oxobutan-2-yl)carbamate (5l)



5l: $C_{14}H_{26}N_2O_3S$
Exact mass: 302.1664

Following the general procedure for the synthesis of **3**, **5l** was synthesized from Boc-Met-OH (1.3 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine·HCl (0.85 g, 7.9 mmol, 1.5 eq) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO_2 , 0% to 33% EtOAc in hexanes) to provide 1.10 g (69%) of **5l** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.60 (bs, 1H), 5.71 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.52–5.35 (m, 1H), 5.11–4.95 (m, 2H), 4.29–4.11 (m, 1H), 3.40–3.13 (m, 2H), 2.59–2.38 (m, 2H), 2.21 (qt, *J* = 6.8, 1.3 Hz, 2H), 2.05 (s, 3H), 2.02-1.98 (m, 1H), 1.96–1.77 (m, 1H), 1.39 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.72, 155.70, 134.98, 117.01, 79.75, 53.46, 38.51, 33.63, 32.05, 30.10, 28.28 (3C), 15.17. HRMS (ESI) m/z calcd for $C_{14}H_{26}N_2O_3S$ $[M+H]^+$: 303.1664, found 303.1668

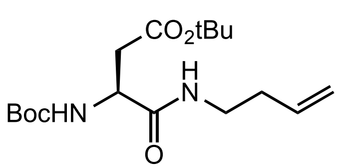
tert-butyl (_R_)-(1-(but-3-en-1-ylamino)-1-oxo-3-(tritylthio)propan-2-yl)carbamate (5m)



5m: $C_{31}H_{36}N_2O_3S$
Exact mass: 516.2447

Following the general procedure for the synthesis of **3**, **5m** was synthesized from Boc-Cys(Trt)-OH (2.5 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine·HCl (0.85 g, 7.9 mmol, 1.5 eq.) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO_2 , 0% to 33% EtOAc in hexanes) to provide 2.04 g (75%) of **5m** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.40 (m, 6H), 7.32–7.27 (m, 6H), 7.25–7.20 (m, 3H), 6.05 (bs, 1H), 5.71 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.10–4.99 (m, 2H), 4.82 (bs, 1H), 3.87-3.84 (m, 1H), 3.32–3.19 (m, 2H), 2.75-2.71 (m, 1H), 2.54-2.50 (m, 1H), 2.21 (qt, *J* = 6.8, 1.3 Hz, 2H), 1.42 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.37, 155.35, 144.47 (3C), 135.01, 129.58 (6C), 128.03 (6C), 126.85 (3C), 117.23, 80.06, 67.13, 53.57, 38.51, 34.05, 33.58, 28.33 (3C). HRMS (ESI) m/z calcd for $C_{31}H_{36}N_2O_3S$ $[M+H]^+$: 517.2447, found 517.2450

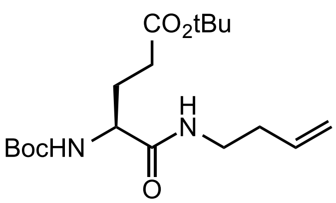
tert-butyl (_S_)-4-(but-3-en-1-ylamino)-3-((_tert_-butoxycarbonyl)amino)-4-oxobutanoate (5n)



5n: $C_{17}H_{30}N_2O_5$
Exact mass: 342.2155

Following the general procedure for the synthesis of **3**, **5n** was synthesized from Boc-Asp(OtBu)-OH (1.5 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine·HCl (0.85 g, 7.9 mmol, 1.5 eq) in DMF (2 mL) was added and the reaction heated to 50^{o}C and stirred for 1 h. The crude product was purified by flash chromatography (SiO_2 , 0% to 50% EtOAc in hexanes) to provide 1.55 g (86%) of **5n** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 (t, *J* = 5.7 Hz, 1H), 5.74–5.67 (m, 2H), 5.11–4.96 (m, 2H), 4.46–4.30 (m, 1H), 3.32–3.23 (m, 2H), 2.80 (dd, *J* = 16.8, 4.9 Hz, 1H), 2.56 (dd, *J* = 16.8, 6.6 Hz, 1H), 2.21 (qt, *J* = 6.7, 1.3 Hz, 2H), 1.41 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.17, 170.71, 155.45, 134.96, 117.15, 81.49, 80.11, 50.69, 38.50, 37.36, 33.55, 28.27 (3C), 27.99 (3C). HRMS (ESI) m/z calcd for $C_{17}H_{30}N_2O_5$ $[M+H]^+$: 343.2155, found 343.2151

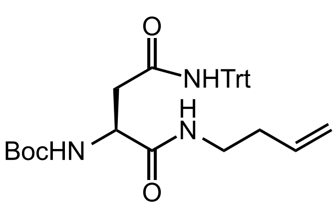
tert-butyl (_S_)-5-(but-3-en-1-ylamino)-4-((_tert_-butoxycarbonyl)amino)-5-oxopentanoate (5o)



5o: $C_{18}H_{32}N_2O_5$
Exact mass: 356.2311

Following the general procedure for the synthesis of **3**, **5o** was synthesized from Boc-Glu(OtBu)-OH (1.6 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), and DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine·HCl (0.85 g, 7.9 mmol, 1.5 eq.) in DMF (2 mL) was added and the reaction heated to 50^{o}C and stirred for 1 h. The crude product was purified by flash chromatography (SiO_2 , 0% to 40% EtOAc in hexanes) to provide 1.53 g (82%) of **5o** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93–6.81 (m, 1H), 5.69–5.57 (m, 2H), 4.99–4.87 (m, 2H), 4.07-4.03 (m, 1H), 3.26-3.21 (m, 1H), 3.14-3.10 (m, 1H), 2.29–2.07 (m, 4H), 1.99–1.87 (m, 1H), 1.84–1.71 (m, 1H), 1.31 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.32, 171.69, 155.62, 134.98, 116.79, 80.32, 79.48, 53.85, 38.47, 33.57, 31.66, 28.21 (3C), 27.93 (3C), 27.90. HRMS (ESI) m/z calcd for $C_{17}H_{30}N_2O_5$ $[M+H]^+$: 357.2311, found 357.2314

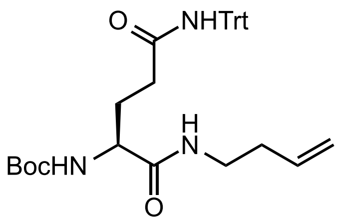
tert-butyl (_S_)-(1-(but-3-en-1-ylamino)-1,4-dioxo-4-(tritylamino)butan-2-yl)carbamate (5p)



5p: $C_{32}H_{37}N_3O_4$
Exact mass: 527.2784

Following the general procedure for the synthesis of **3**, **5p** was synthesized from Boc-Asn(Trt)-OH (2.5 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine·HCl (0.85 g, 7.9 mmol, 1.5 eq) in DMF (2 mL) was added and the reaction heated to 50^{o}C and stirred for 1 h. The crude product was purified by flash chromatography (SiO_2 , 0% to 50% EtOAc in hexanes) to provide 2.17 g (78%) of **5p** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.17 (m, 16H), 6.74 (bs, 1H), 6.29 (bs, 1H), 5.72 (ddt, *J* = 17.1, 10.3, 6.8 Hz, 1H), 5.12–4.99 (m, 2H), 4.43 (dd, *J* = 8.5, 4.6 Hz, 1H), 3.34–3.14 (m, 2H), 3.14–2.99 (m, 1H), 2.54 (dd, *J* = 15.0, 5.8 Hz, 1H), 2.21–

2.17 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.43, 170.49, 155.68, 144.44 (3C), 134.98, 128.73 (6C), 127.88 (6C), 126.93 (3C), 117.20, 79.94, 70.63, 51.76, 38.54, 38.18, 33.45, 28.40 (3C). HRMS (ESI) m/z calcd for $C_{32}H_{37}N_3O_4$ $[M+H]^+$: 528.2784, found 528.2782

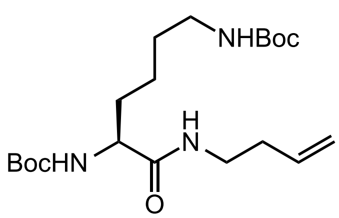


5q: $C_{33}H_{39}N_3O_4$
Exact mass: 541.2941

tert-butyl (_S_)-(1-(but-3-en-1-ylamino)-1,5-dioxo-5-(tritylamino)pentan-2-yl)carbamate (5q)

Following the general procedure for the synthesis of **3**, **5q** was synthesized from Boc-Gln(Trt)-OH (2.5 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine·HCl (0.85 g, 7.9 mmol, 1.5 eq.) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO_2 , 0% to 50% EtOAc in hexanes) to provide 2.37 g (83%) of **5q** as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.12 (m, 17H), 6.41 (bs, 1H), 5.79–5.56 (m, 2H), 5.12–4.91 (m, 2H), 3.00-3.93 (m, 1H), 3.34–3.04 (m, 2H), 2.56–2.24 (m, 2H), 2.25–2.08 (m, 2H), 2.07–1.76 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.86, 171.47, 155.88, 144.59 (3C), 135.05, 128.69 (6C), 127.92 (6C), 126.95 (3C), 117.09, 79.74, 70.57, 53.62, 38.54, 33.73, 33.62, 29.87, 28.36 (3C). HRMS (ESI) m/z calcd for $C_{33}H_{39}N_3O_4$ $[M+H]^+$: 542.2941, found 542.2942

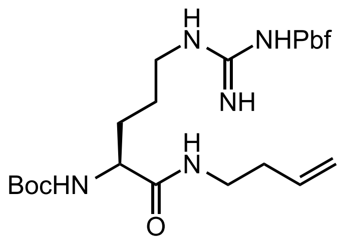
di-_tert_-butyl (6-(but-3-en-1-ylamino)-6-oxohexane-1,5-diyl)(_S_)-dicarbamate (5r)



5r: $C_{20}H_{37}N_3O_5$
Exact mass: 399.2733

Following the general procedure for the synthesis of **3**, **5r** was synthesized from Boc-Lys(Boc)-OH (1.8 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine·HCl (0.85 g, 7.9 mmol, 1.5 eq.) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO_2 , 0% to 50% EtOAc in hexanes) to provide 1.90 g (90%) of **5r** as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 6.60 (bs, 1H), 5.69 (ddt, J = 17.1, 10.2, 6.8 Hz, 1H), 5.43–5.29 (m, 1H), 5.07–4.96 (m, 2H), 4.83–4.70 (m, 1H), 4.02 (m, 1H), 3.35–3.25 (m, 1H), 3.21 (m, 1H), 3.11–2.98 (m, 2H), 2.20 (qt, J = 6.8, 1.3 Hz, 2H), 1.79–1.69 (m, 1H), 1.62–1.51 (m, 1H), 1.49–1.41 (m, 2H), 1.41–1.34 (bs, 18H), 1.35–1.26 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.14, 156.13, 155.76, 135.05, 117.03, 79.75, 78.96, 54.36, 39.92, 38.44, 33.63, 32.15, 29.59, 28.39 (3C), 28.30 (3C), 22.60. HRMS (ESI) m/z calcd for $C_{20}H_{37}N_3O_5$ $[M+H]^+$: 400.2733, found 400.2730

tert-butyl (S)-(1-(but-3-en-1-ylamino)-1-oxo-5-(3-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)guanidino)pentan-2-yl)carbamate (5s)

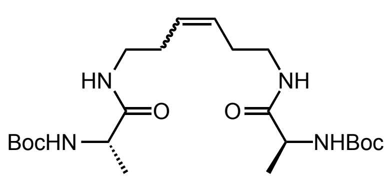


5s: $C_{28}H_{45}N_5O_6S$
Exact mass: 579.3091

Following the general procedure for the synthesis of **3**, **5s** was synthesized from Boc-Arg(Pbf)-OH (2.8 g, 5.3 mmol) in the presence of a stock solution of HOBt (0.72 g, 5.3 mmol, 1.0 eq.), HBTU (3.0 g, 7.9 mmol, 1.5 eq.), DIEA (2.7 mL, 15.8 mmol, 3 eq.). A solution of 3-butenylamine·HCl (0.85 g, 7.9 mmol, 1.5 eq) in DMF (2 mL) was added and the reaction heated to 50°C and stirred for 1 h. The crude product was purified by flash chromatography (SiO_2 , EtOAc) to provide 2.14 g (70%) of **5s** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (bs, 1H), 6.36 (bs, 2H), 5.79–5.60 (m, 2H), 5.09–4.96 (m, 2H), 4.13 (m, 1H), 3.36–3.17 (m, 4H), 2.96 (s, 2H), 2.58 (s, 3H), 2.51 (s, 3H), 2.23 (q, *J* = 6.9 Hz, 2H), 2.10 (s, 3H), 1.80–1.78 (m, 1H), 1.69–1.53 (m, 4H), 1.47 (s, 6H), 1.40 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.36, 158.82, 156.44, 156.00, 138.31, 135.13, 132.71, 132.24, 124.65, 117.55, 116.85, 86.40, 79.92, 64.33, 53.99, 43.25, 40.55, 38.71, 33.56, 30.43, 28.57 (2C), 28.33 (3C), 25.56, 19.26, 17.92, 12.43. HRMS (ESI) m/z calcd for $C_{28}H_{45}N_5O_6S$ $[M+H]^+$: 580.3091, found 580.3096

General Procedure for Homodimerization of Amino Acids

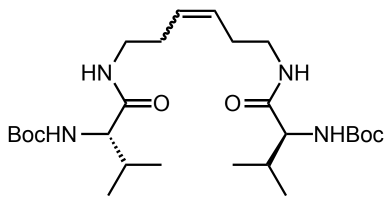
di-tert-butyl ((2S,2'S)-(hex-3-ene-1,6-diylbis(azanediyl))bis(1-oxopropane-1,2-diyl))dicarbamate (4)



4: $C_{22}H_{40}N_4O_6$
Exact mass: 456.2948

The homoallyl-modified alanine **3** (0.20 g, 0.83 mmol) was dissolved in THF (1.4 mL) under a gentle stream of argon. A solution of catalyst **1** or **2** (619 μl of a 0.10 M solution in THF) was added and the reaction heated to 40°C and stirred for 4 h. The solution was allowed to cool to room temperature upon which an excess of ethyl vinyl ether (1.0 mL, 10.4 mmol, 12 eq.) was added to quench the reaction. The solvent was removed *in vacuo* and the residue purified by column chromatography (SiO_2; 0% to 25% EtOAc in hexane) to afford 0.28 g (74%) of product **4** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (bs, 2H), 5.49–5.34 (m, 2H), 5.24 (d, *J* = 8.4 Hz, 2H), 4.31–4.14 (m, 2H), 3.73–3.60 (m, 2H), 3.03–2.86 (m, 2H), 2.26–2.16 (m, 4H), 1.43 (s, 18H), 1.39–1.27 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.34 (2C), 155.73 (2C), 129.23 (2C), 79.91 (2C), 50.08 (2C), 38.65 (2C), 28.35 (3C), 28.32 (3C), 27.97 (2C), 18.53 (2C). HRMS (ESI) m/z calcd for $C_{22}H_{40}N_4O_6$ $[M+H]^+$: 457.2948, found 457.2945

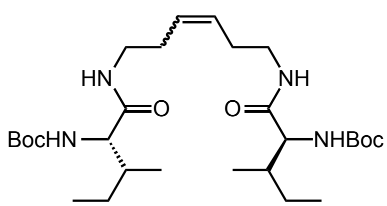
di-*tert*-butyl ((2*S*,2'*S*)-(hex-3-ene-1,6-diylbis(azanediyl))bis(3-methyl-1-oxobutane-1,2-diyl))dicarbamate (6a)



6a: $C_{26}H_{48}N_4O_6$
Exact mass: 512.3574

Following the procedure for **4**, the homodimerization product **6a** was obtained when homoallyl-modified valine **5a** (0.22 g, 0.81 mmol) was reacted with catalyst **1** or **2** (610 µl of a 0.10 M solution in THF) in THF (1.4 mL) under argon for 4 h and quenched with excess ethyl vinyl ether. The residue was purified by column chromatography (SiO_2; 0% to 50% EtOAc in hexane) to afford 0.30 g (71%) of the product **6a** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.36 (m, 2H), 5.42– 5.34 (m, 2H), 5.17 (d, *J* = 9.6 Hz, 2H), 3.95 (dd, *J* = 9.7, 7.7 Hz, 2H), 3.93–3.83 (m, 2H), 2.80-2.76 (m, 2H), 2.25–2.21 (m, 2H), 2.18–2.12 (m, 2H), 1.94–1.90 (m, 2H), 1.67 (bs, 2H), 1.43 (s, 18H), 0.96 (d, *J* = 6.7 Hz, 6H), 0.95 (d, J = 6.6 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.31 (2C), 156.28 (2C), 129.56 (2C), 79.70 (2C), 60.43 (2C), 38.07 (2C), 30.92 (2C), 28.32 (6C), 19.21 (2C), 18.59 (2C). HRMS (ESI) m/z calcd for $C_{26}H_{48}N_4O_6$ $[M+H]^+$: 513.3574, found 513.3570

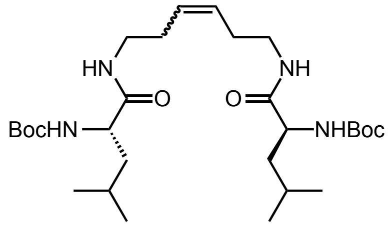
di-*tert*-butyl ((2*S*,2'*S*,3*R*,3'*R*)-(hex-3-ene-1,6-diylbis(azanediyl))bis(3-methyl-1-oxopentan-1,2-diyl))dicarbamate (6b)



6b: $C_{28}H_{52}N_4O_6$
Exact mass: 540.3887

Following the procedure for **4**, the homodimerization product **6b** was obtained when homoallyl-modified isoleucine **5b** (0.21 g, 0.74 mmol) was reacted with catalyst **1** or **2** (553 µl of a 0.10 M solution in THF) in THF (1.3 mL) under argon. The residue was purified by column chromatography (SiO_2; 0% to 50% EtOAc in hexane) to afford 0.27 g (68%) of the product **6b** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52–7.45 (m, 2H), 5.42– 5.33 (m, 2H), 5.14 (d, *J* = 9.7 Hz, 2H), 4.02-3.93 (m, 4H), 2.81–2.70 (m, 2H), 2.27–2.18 (m, 2H), 2.18–2.08 (m, 2H), 1.76–1.63 (m, 2H), 1.58 (m, 2H), 1.42 (s, 18H), 1.21–1.09 (m, 2H), 0.94–0.82 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.46 (2C), 156.14 (2C), 129.59 (2C), 79.64 (2C), 59.02 (2C), 37.95 (2C), 36.86 (2C), 29.69 (2C), 28.33 (6C), 24.90 (2C), 15.31 (2C), 10.60 (2C). HRMS (ESI) m/z calcd for $C_{28}H_{52}N_4O_6$ $[M+H]^+$: 541.3887, found 541.3880

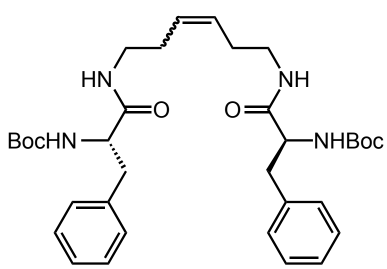
di-*tert*-butyl ((2*S*,2'*S*)-(hex-3-ene-1,6-diylbis(azanediyl))bis(4-methyl-1-oxopentane-1,2-diyl))dicarbamate (6c)



6c: $C_{28}H_{52}N_4O_6$
Exact mass: 540.3887

Following the procedure for **4**, the homodimerization product **6c** was obtained when homoallyl-modified leucine **5c** (0.18 g, 0.63 mmol) was reacted with catalyst **1** or **2** (475 µl of a 0.10 M solution in THF) in THF (1.1 mL) under argon. The residue was purified by column chromatography (SiO_2; 0% to 50% EtOAc in hexane) to afford 0.24 g (70%) of the product **6c** as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.64–7.55 (m, 2H), 5.40–5.38 (m, 2H), 5.06 (d, *J* = 9.1 Hz, 2H), 4.28–4.23 (m, 2H), 3.92–3.90 (m, 2H), 2.77–2.73 (m, 2H), 2.23 (m, 2H), 2.20–2.11 (m, 2H), 1.70–1.64 (m, 4H), 1.56–1.47 (m, 4H), 1.42 (s, 18H), 0.92 (d, *J* = 6.6 Hz, 6H), 0.88 (d, J = 6.6 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.36 (2C), 155.95 (2C), 129.57 (2C), 79.75 (2C), 53.17 (2C), 41.68 (2C), 38.30 (2C), 28.33 (6C), 24.67 (4C), 23.04 (2C), 21.82 (2C). HRMS (ESI) m/z calcd for $C_{28}H_{52}N_4O_6$ $[M+H]^+$: 541.3887, found 541.3879

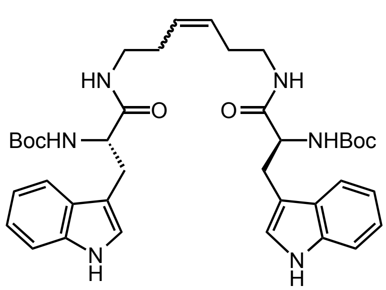
di-*tert*-butyl ((2*S*,2'*S*)-(hex-3-ene-1,6-diylbis(azanediyl))bis(1-oxo-3-phenylpropane-1,2-diyl))dicarbamate (6d)



6d: $C_{34}H_{48}N_4O_6$
Exact mass: 608.3574

Following the procedure for **4**, the homodimerization product **6d** was obtained when homoallyl-modified phenylalanine **5d** (0.23 g, 0.72 mmol) was reacted with catalyst **1** or **2** (542 μl of a 0.10 M solution in THF) in THF (1.2 mL) under argon. The residue was purified by column chromatography (SiO_2; 0% to 50% EtOAc in hexane) to afford 0.32 g (73%) of the product **6d** as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.09 (m, 10H), 7.10–6.91 (m, 2H), 5.36–5.33 (m, 4H), 5.29 (bs, 2H), 4.50–4.30 (m, 2H), 3.62 (m, 2H), 3.12–2.72 (m, 4H), 2.15–2.04 (m, 4H), 1.35 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.98 (2C), 155.80 (2C), 137.01 (2C), 129.21 (4C), 128.46 (4C), 126.63 (2C), 79.94 (2C), 56.03 (2C), 38.92 (2C), 38.61 (2C), 28.28 (6C), 27.91 (2C). HRMS (ESI) m/z calcd for $C_{34}H_{48}N_4O_6$ $[M+H]^+$: 609.3574, found 609.3578

di-*tert*-butyl ((2*S*,2'*S*)-(hex-3-ene-1,6-diylbis(azanediyl))bis(3-(1*H*-indol-3-yl)-1-oxopropane-1,2-diyl))dicarbamate (6g)

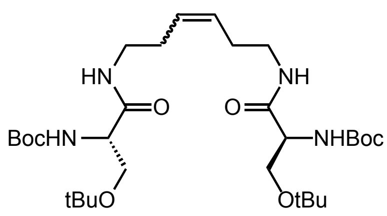


6g: $C_{38}H_{50}N_6O_6$
Exact mass: 686.3792

Following the procedure for **4**, the homodimerization product **6g** was obtained when homoallyl-modified tryptophan **5g** (0.21 g, 0.59 mmol) was reacted with catalyst **1** or **2** (440 μl of a 0.10 M solution in THF) in THF (1.0 mL) under argon. The residue was purified by column chromatography (SiO_2; 3:1 EtOAc:hexanes) to afford 0.26 g (66%) of the product **6g** as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.74 (bs, 2H), 7.59 (d, *J* = 7.9 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.16 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 2H), 7.06 (t, *J* = 7.5 Hz, 2H), 6.94 (bs, 2H), 6.37 (bs, 2H), 5.38 (d, *J* = 8.1 Hz, 2H), 5.14–5.12 (m, 2H), 4.56–4.35 (m, 2H), 3.30–3.11 (m, 6H), 2.98–2.96 (m, 2H), 1.91–1.71 (m, 4H), 1.42 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.14 (2C), 155.71 (2C), 136.28 (2C), 128.53 (2C), 127.43 (2C), 123.38 (2C), 121.97 (2C), 119.47 (2C), 118.74 (2C), 111.34 (2C), 110.39 (2C), 80.08

(2C), 55.39 (2C), 38.77 (2C), 29.71 (2C), 28.34 (6C), 27.30 (2C). HRMS (ESI) m/z calcd for $C_{38}H_{50}N_6O_6$ $[M+H]^+$: 687.3792, found 687.3795

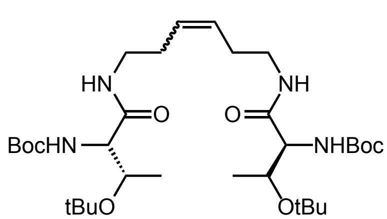
di-*tert*-butyl ((5*S*,16*S*)-2,2,19,19-tetramethyl-6,15-dioxo-3,18-dioxa-7,14-diazaicos-10-ene-5,16-diyl)dicarbamate (6i)



6i: $C_{30}H_{56}N_4O_8$
Exact mass: 600.4098

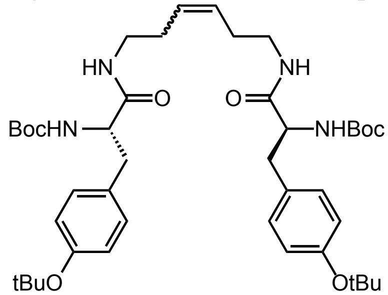
Following the procedure for **4**, the homodimerization product **6i** was obtained when homoallyl-modified serine **5i** (0.20 g, 0.63 mmol) was reacted with catalyst **1** or **2** (477 μl of a 0.10 M solution in THF) in THF (1.1 mL) under argon. The residue was purified by column chromatography (SiO_2; 0% to 50% EtOAc in hexane) to afford 0.27 g (72%) of the product **6i** as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 6.70 (s, 2H), 5.48–5.43 (m, 4H), 4.12 (bs, 2H), 3.76–3.74 (m, 2H), 3.36–3.33 (m, 4H), 3.27-3.24 (m, 2H), 2.32–2.20 (m, 4H), 1.45 (s, 18H), 1.17 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.66 (2C), 155.56 (2C), 128.55 (2C), 79.90 (2C), 73.86 (2C), 61.88 (2C), 54.34 (2C), 39.09 (2C), 28.32 (6C), 27.48 (2C), 27.44 (6C). HRMS (ESI) m/z calcd for $C_{30}H_{56}N_4O_8$ $[M+H]^+$: 601.4098, found 601.4100

di-*tert*-butyl ((4*R*,5*S*,16*R*,17*S*)-2,2,4,17,19,19-hexamethyl-6,15-dioxo-3,18-dioxa-7,14-diazaicos-10-ene-5,16-diyl)dicarbamate (6j)



6j: $C_{32}H_{60}N_4O_8$
Exact mass: 628.4411

Following the procedure for **4**, the homodimerization product **6j** was obtained when homoallyl-modified threonine **5j** (0.19 g, 0.58 mmol) was reacted with catalyst **1** or **2** (433 μl of a 0.10 M solution in THF) in THF (1.0 mL) under argon. The residue was purified by column chromatography (SiO_2; 0% to 40% EtOAc in hexane) to afford 0.26 g (73%) of the product **6j** as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 6.99 (t, J = 5.4 Hz, 2H), 5.65 (d, J = 5.8 Hz, 2H), 5.50 (td, J = 4.4, 2.1 Hz, 2H), 4.11 (qd, J = 6.3, 3.3 Hz, 2H), 4.08–4.00 (m, 2H), 3.40– 3.23 (m, 4H), 2.31–2.25 (m, 4H), 1.45 (s, 18H), 1.25 (s, 18H), 1.03 (d, J = 6.3 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.73 (2C), 155.61 (2C), 128.63 (2C), 79.53 (2C), 75.13 (2C), 66.92 (2C), 58.39 (2C), 39.05 (2C), 28.37 (6C), 28.31 (6C), 27.55 (2C), 17.41 (2C). HRMS (ESI) m/z calcd for $C_{32}H_{60}N_4O_8$ $[M+H]^+$: 629.4411, found 629.4413

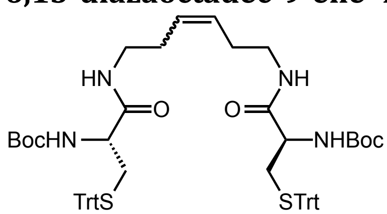


6k: $C_{42}H_{64}N_4O_8$
Exact mass: 752.4724

di-*tert*-butyl ((2*S*,2'*S*)-(hex-3-ene-1,6-diylbis(azanediyl))bis(3-(4-(*tert*-butoxy)phenyl)-1-oxopropane-1,2-diyl))dicarbamate (6k)

Following the procedure for **4**, the homodimerization product **6k** was obtained when homoallyl-modified tyrosine **5k** (0.17 g, 0.44 mmol) was reacted with catalyst **1** or **2** (326 μl of a 0.10 M solution in THF) in THF (0.76 mL) under argon. The residue was purified by column chromatography (SiO_2; 0% to 50% EtOAc in hexane) to afford 0.21 g (64%) of the product **6k** as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.11–7.03 (m, 4H), 6.91–6.85 (m, 4H), 5.34 (dt, *J* = 6,4, 4.8 Hz, 2H), 5.23 (d, *J* = 8.8 Hz, 2H), 4.42-4.35 (m, 2H), 3.59–3.51 (m, 2H), 2.97–2.83 (m, 6H), 2.17-2.05 (m, 6H), 1.36 (s, 18H), 1.31 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.84 (2C), 155.70 (2C), 154.04 (2C), 131.82 (2C), 129.67 (4C), 129.02 (2C), 124.23 (4C), 79.90 (2C), 78.32 (2C), 55.98 (2C), 38.61 (2C), 38.21 (2C), 28.82 (6C), 28.28 (6C), 27.80 (2C). HRMS (ESI) m/z calcd for $C_{42}H_{64}N_4O_8$ $[M+H]^+$: 753.4724, found 753.4719

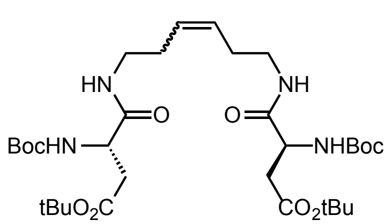
di-*tert*-butyl ((4*R*,15*R*)-5,14-dioxo-1,1,1,18,18,18-hexaphenyl-2,17-dithia-6,13-diazaoctadec-9-ene-4,15-diyl)dicarbamate (6m)



6m: $C_{60}H_{68}N_4O_6S_2$
Exact mass: 1004.4580

Following the procedure for **4**, the homodimerization product **6m** was obtained when homoallyl-modified cysteine **5m** (0.23 g, 0.44 mmol) was reacted with catalyst **1** or **2** (334 μl of a 0.10 M solution in THF) in THF (0.78 mL) under Ar(g). The residue was purified by column chromatography (SiO_2; 0% to 40% EtOAc in hexane) to afford 0.25 g (55%) of the product **6m** as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (m, 12H), 7.31–7.24 (m, 12H), 7.23–7.17 (m, 6H), 6.72 (bs, 1H), 6.11 (bs, 1H), 5.38–5.34 (m, 2H), 5.00–4.86 (m, 2H), 4.06–4.02 (m, 1H), 3.86 (bs, 1H), 3.51–3.48 (m, 1H), 3.19-3.16 (m, 1H), 2.98-2.92 (m, 1H), 2.67 (bs, 1H), 2.53 (m, 4H), 2.23–2.10 (m, 4H), 1.42–1.37 (m, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.67 (2C), 155.52 (2C), 146.86 (2C), 144.46 (3C), 144.43 (3C), 129.57 (2C), 129.56 (6C), 128.92 (2C), 128.02 (2C), 128.00 (6C), 127.95 (2C), 127.91 (2C), 127.23 (2C), 126.84 (2C), 126.77 (2C), 80.14 (2C), 66.95 (2C), 53.58 (2C), 38.82 (2C), 33.98 (2C), 29.69 (2C), 28.32 (3C), 28.29 (3C), 27.66 (2C). HRMS (ESI) m/z calcd for $C_{60}H_{68}N_4O_6S_2$ $[M+H]^+$: 1006.35, found 1006.44

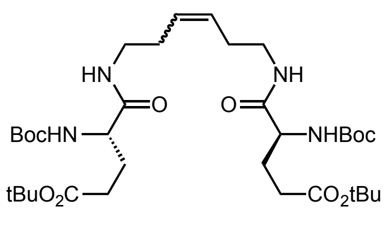
***tert*-butyl (6*S*,17*S*)-6-(2-(*tert*-butoxy)-2-oxoethyl)-17-((*tert*-butoxycarbonyl)amino)-2,2-dimethyl-4,7,16-trioxo-3-oxa-5,8,15-triazanonadec-11-en-19-oate (6n)**



6n: $C_{32}H_{56}N_4O_{10}$
Exact mass: 656.3996

Following the procedure for **4**, the homodimerization product **6n** was obtained when homoallyl-modified aspartate **5n** (0.19 g, 0.55 mmol) was reacted with catalyst **1** or **2** (416 μl of a 0.10 M solution in THF) in THF (1.0 mL) under Ar(g). The residue was purified by column chromatography (SiO_2; 0% to 50% EtOAc in hexane) to afford 0.22 g (61%) of the product **6n** as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 6.74 (bs, 2H), 5.76 (bs, 2H), 5.48–5.38 (m, 2H), 4.47-4.42 (m, 2H), 3.41-3.35 (m, 2H), 3.31-3.29 (m, 2H), 3.23-3.18 (m, 2H), 2.84-2.80 (m, 2H), 2.67–2.57 (m, 2H), 2.26-2.24 (m, 4H), 1.45 (s, 18H), 1.44 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.96 (2C), 155.54 (2C), 128.59 (2C), 81.51 (2C), 80.17 (2C), 50.82 (2C), 39.12 (2C), 37.48 (2C), 29.69 (2C), 28.33 (6C), 28.03 (6C), 27.41 (2C). HRMS (ESI) m/z calcd for $C_{32}H_{56}N_4O_{10}$ [M+H]$^+$: 657.8180, found 657.8177

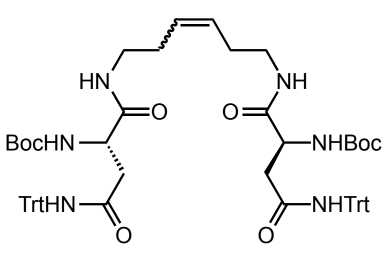
tert-butyl (6*S*,17*S*)-6-(3-(_tert_-butoxy)-3-oxopropyl)-17-((_tert_-butoxycarbonyl)amino)-2,2-dimethyl-4,7,16-trioxo-3-oxa-5,8,15-triazaicos-11-en-20-oate (6o)



6o: $C_{34}H_{60}N_4O_{10}$
Exact mass: 684.4309

Following the procedure for **4**, the homodimerization product **6o** was obtained when homoallyl-modified glutamate **5o** (0.17 g, 0.48 mmol) was reacted with catalyst **1** or **2** (357 μl of a 0.10 M solution in THF) in THF (0.83 mL) under Ar(g). The residue was purified by column chromatography (SiO_2; 0% to 50% EtOAc in hexane) to afford 0.24 g (74%) of the product **6o** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (bs, 2H), 5.46 (d, *J* = 8.3 Hz, 2H), 5.42-5.36 (m, 2H), 4.18-4.14 (m, 2H), 3.70–3.64 (m, 2H), 2.91–2.90 (m, 2H), 2.32-2.29 (m, 4H), 2.25–2.13 (m, 4H), 2.01–1.96 (m, 2H), 1.93–1.83 (m, 2H), 1.41 (s, 36H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.31 (2C), 172.01 (2C), 155.91 (2C), 129.04 (2C), 80.47 (2C), 79.85 (2C), 54.15 (2C), 38.70 (2C), 31.94 (2C), 28.31 (6C), 28.04 (6C), 27.98 (2C), 27.84 (2C). HRMS (ESI) m/z calcd for $C_{32}H_{56}N_4O_{10}$ [M+H]$^+$: 685.4309, found 685.4312

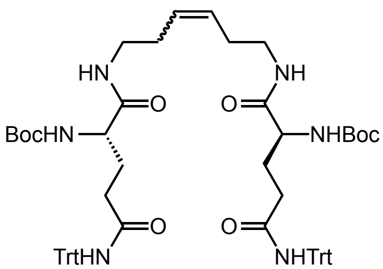
di-_tert_-butyl ((5*S*,16*S*)-3,6,15,18-tetraoxo-1,1,1,20,20,20-hexaphenyl-2,7,14,19-tetraazaicos-10-ene-5,16-diyl)dicarbamate (6p)



6p: $C_{62}H_{70}N_6O_8$
Exact mass: 1026.5255

Following the procedure for **4**, the homodimerization product **6p** was obtained when homoallyl-modified asparagine **5p** (0.18 g, 0.34 mmol) was reacted with catalyst **1** or **2** (255 μl of a 0.10 M solution in THF) in THF (0.60 mL) under Ar(g). The residue was purified by column chromatography (SiO_2; 0% to 66% EtOAc in hexane) to afford 0.24 g (70%) of the product **6p** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.22 (m, 18H), 7.20–7.15 (m, 12H), 7.09 (bs, 2H), 6.84–6.71 (m, 2H), 6.19 (d, *J* = 7.7 Hz, 2H), 5.45–5.31 (m, 2H), 4.40-4.37 (m, 2H), 3.26-3.18 (m, 4H), 2.97-2.94 (m, 2H), 2.57–2.43 (m, 2H), 2.24–2.09 (m, 4H), 1.41 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.20 (2C), 170.37 (2C), 144.31 (6C), 128.64 (12C), 128.61 (2C), 128.43 (2C), 127.99 (2C), 127.93 (12C), 127.90 (2C), 127.04 (6C), 70.68 (2C), 39.21 (2C), 29.70 (2C), 28.32 (6C), 27.29 (2C). HRMS (ESI) m/z calcd for $C_{62}H_{70}N_6O_8$ [M+H]$^+$: 1027.5255, found 1027.5251

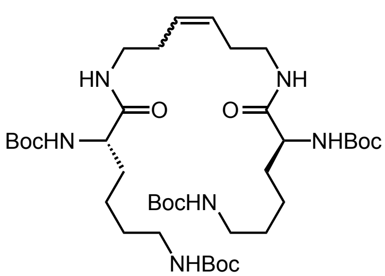
di-*tert*-butyl ((6*S*,17*S*)-3,7,16,20-tetraoxo-1,1,1,22,22,22-hexaphenyl-2,8,15,21-tetraazadocos-11-ene-6,17-diyl)dicarbamate (6q)



6q: $C_{64}H_{74}N_6O_8$
Exact mass: 1054.5568

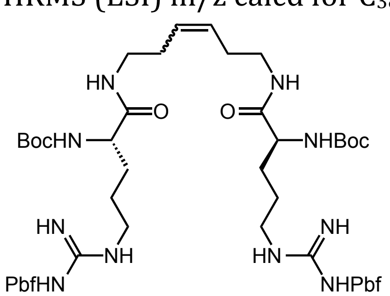
Following the procedure for **4**, the homodimerization product **6q** was obtained when homoallyl-modified glutamine **5q** (0.14 g, 0.26 mmol) was reacted with catalyst **1** or **2** (194 μl of a 0.10 M solution in THF) in THF (0.45 mL) under Ar(g). The residue was purified by column chromatography (SiO_2; 3:1 EtOAc:hexanes) to afford 0.20 g (74%) of the product **6q** as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.26 (m, 12H), 7.25-7.20 (m, 18H), 7.15 (bs, 2H), 6.75–6.64 (m, 2H), 5.62 (d, *J* = 7.7 Hz, 2H), 5.36-5.30 (m, 2H), 4.01-3.97 (m, 2H), 3.25-3.20 (m, 2H), 3.15-3.12 (m, 2H), 2.40-2.27 (m, 4H), 2.18–2.10 (m, 4H), 2.01–1.91 (m, 2H), 1.87-1.82 (m, 3H), 1.42 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.77 (2C), 155.91 (2C), 144.57 (6C), 128.83 (2C), 128.69 (12C), 127.95 (2C), 127.90 (12C), 126.94 (6C), 79.76 (2C), 70.53 (2C), 53.60 (2C), 38.78 (2C), 33.65 (2C), 29.75 (2C), 28.35 (6C), 27.60 (2C). HRMS (ESI) m/z calcd for $C_{64}H_{74}N_6O_8$ $[M+H]^+$: 1055.5568, found 1055.5549

tetra-*tert*-butyl ((5*S*,5'*S*)-(hex-3-ene-1,6-diylbis(azanediyl))bis(6-oxohexane-6,1,5-triyl))tetracarbamate (6r)



6r: $C_{38}H_{70}N_6O_{10}$
Exact mass: 770.5153

Following the procedure for **4**, the homodimerization product **6r** was obtained when homoallyl-modified lysine **5r** (0.21 g, 0.53 mmol) was reacted with catalyst **1** or **2** (394 μl of a 0.10 M solution in THF) in THF (0.92 mL) under Ar(g). The residue was purified by column chromatography (SiO_2; 3:1 EtOAc:hexanes) to afford 0.32 mg (78%) of the product **6r** as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (bs, 1H), 5.43-5.39 (m, 2H), 5.26 (d, *J* = 8.7 Hz, 2H), 4.68 (bs, 2H), 4.17–4.13 (m, 2H), 3.78–3.74 (m, 2H), 3.11–3.07 (m, 4H), 2.89–2.85 (m, 2H), 2.32–2.11 (m, 4H), 1.70 (m, 4H), 1.65–1.54 (m, 4H), 1.48–1.46 (m, 4H) 1.44 (s, 18H), 1.43 (s, 18H), 1.33-1.21 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.67 (2C), 156.04 (4C), 129.32 (2C), 79.89 (4C), 54.45 (2C), 40.15 (2C), 38.47 (2C), 32.34 (2C), 29.69 (2C), 29.63 (2C), 28.44 (6C), 28.34 (6C), 22.86 (2C). HRMS (ESI) m/z calcd for $C_{38}H_{70}N_6O_{10}$ $[M+H]^+$: 771.5153, found 771.5138



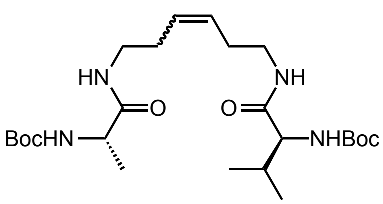
6s: $C_{54}H_{86}N_{10}O_{12}S_2$
Exact mass: 1130.5868

di-*tert*-butyl ((6*S*,17*S*)-1,22-diimino-7,16-dioxo-1,22-bis((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran)-5-sulfonamido)-2,8,15,21-tetraazadocos-11-ene-6,17-diyl)dicarbamate (6s)

Following the procedure for **4**, the homodimerization product **6s** was obtained when homoallyl-modified arginine **5s** (0.14 g, 0.24 mmol) was reacted with catalyst **1** or **2** (181 μl of a 0.10 M solution in THF) in THF (0.42 mL) under Ar(g). The residue was purified by column chromatography (SiO_2; 0% to 2% MeOH in EtOAc) to afford 93 mg (34%) of the product **6s** as a white solid. ^1H NMR (500 MHz, CD_3OD) δ 7.95–7.93 (m, 1H), 7.87–7.85 (m, 1H), 5.44–5.42 (m, 2H), 4.09–3.95 (m, 2H), 3.28–3.07 (m, 8H), 2.99 (s, 4H), 2.57 (s, 6H), 2.51 (s, 6H), 2.30–2.25 (m, 2H), 2.18-2.16 (m, 2H), 2.07 (s, 6H), 1.73–1.69 (m, 2H), 1.63–1.49 (m, 6H), 1.44 (s, 12H) 1.42 (s, 18H); ^{13}C NMR (126 MHz, CD_3OD) δ 176.57 (2C), 173.66 (2C), 158.45 (2C), 156.69 (2C), 156.33 (2C), 137.98 (2C), 132.91 (2C), 132.09 (2C), 124.59 (2C), 117.02 (2C), 86.25 (2C), 79.19 (2C), 54.37 (2C), 42.57 (2C), 39.93 (2C), 38.69 (2C), 32.21 (2C), 29.42 (2C), 27.36 (4C), 27.33 (6C), 25.74 (2C), 18.22 (2C), 17.04 (2C), 11.14 (2C). HRMS (ESI) m/z calcd for $C_{54}H_{86}N_{10}O_{12}S$ $[M+H]^+$: 1131.5868, found 1131.5877

General Procedure for Cross Metathesis of Amino Acids

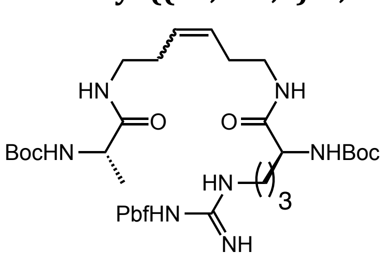
***tert*-butyl ((6*S*,17*S*)-6-isopropyl-2,2-dimethyl-4,7,16-trioxo-3-oxa-5,8,15-triazaoctadec-11-en-17-yl)carbamate (7)**



7: $C_{24}H_{44}N_4O_6$
Exact mass: 484.3261

A round bottom flask was charged with Boc-protected homoallyl alanine **3** (50 mg, 0.20 mmol) and the cross partner homoallyl valine **5a** (223 mg, 0.80 mmol, 4 eq.) under a gentle stream of Ar(g). To this was added anhydrous THF (0.40 mL). A solution of catalyst **1** or **2** (155 μl of a 0.10 M solution in THF) was added and the reaction mixture was heated to 40°C and stirred for 4h. The solution was cooled to room temperature and then quenched with an excess of ethyl vinyl ether (0.50 mL, 5.2 mmol). The solvent was removed *in vacuo* and the residue purified by column chromatography (SiO_2; 0% to 66% EtOAc in hexane) to afford 61 mg (60%) of product **7** as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (bs, 1H), 5.46–5.36 (m, 2H), 5.29-5.24 (m, 2H), 4.34–4.25 (m, 1H), 3.90 (dd, *J* = 9.4, 7.4 Hz, 1H), 3.78-3.73 (m, 2H), 2.94-2.82 (m, 2H), 2.31–2.12 (m, 4H), 1.98-1.89 (m, 2H), 1.43 (s, 18H), 1.33 (d, *J* = 7.0 Hz, 3H), 0.94 (dd, *J* = 6.8, 4.5 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.49, 172.14, 156.21, 155.76, 129.25 (2C), 79.85, 79.72, 60.33, 50.09, 38.63, 38.41, 30.94, 29.67, 28.33 (6C), 28.03, 19.24, 18.51 (2C). HRMS (ESI) m/z calcd for $C_{24}H_{44}N_4O_6$ $[M+H]^+$: 485.3261, found 485.3258

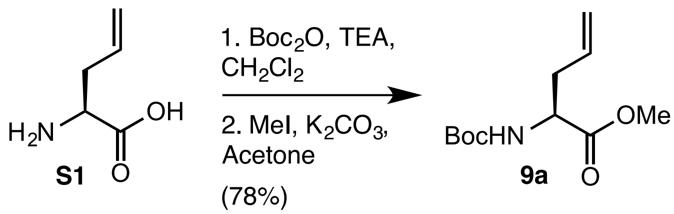
***tert*-butyl ((6*S*,17*S*,*Z*)-2,2-dimethyl-4,7,16-trioxo-6-((3-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)guanidino)methyl)-3-oxa-5,8,15-triazaoctadec-11-en-17-yl)carbamate (8)**



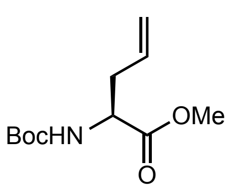
8: $C_{38}H_{63}N_7O_9S$
Exact mass: 793.4408

Following the procedure for **7**, the cross product **8** was obtained when homoallyl-modified arginine **5s** (50 mg, 0.086 mmol) was reacted with alanine **3** (84 mg, 0.35 mmol, 4 eq.) in THF (0.17 mL) in the presence of catalyst **1** or **2** (65 μl of a 0.10 M solution in THF) under Ar(g). The residue was purified by column chromatography (SiO_2; 0% to 2% MeOH in EtOAc) to afford 28 mg (41%) of the product **6s** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (bs, 1H), 6.93 (bs, 1H), 6.35 (bs, 2H), 5.74 (bs, 1H), 5.65 (bs, 1H), 5.45–5.36 (m, 2H), 4.34–4.13 (m, 2H), 3.40–3.16 (m, 6H), 2.95 (s, 2H), 2.59 (s, 3H), 2.52 (s, 3H), 2.24-2.17 (m, 4H), 2.09 (s, 3H), 1.77 (bs, 1H), 1.61–1.53 (m, 3H), 1.46 (s, 6H), 1.41 (s, 18H), 1.33 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.70, 172.70, 158.68, 156.45, 155.77 (2C), 138.29, 133.17, 132.25, 129.77 (2C), 129.26, 124.51, 117.40, 86.27, 79.98 (2C), 53.83, 50.38, 43.29, 40.28, 38.91, 38.60, 32.61, 30.29, 28.54 (2C), 28.36 (3C) 28.35 (3C), 25.51, 19.20, 18.47, 17.86, 12.37. HRMS (ESI) m/z calcd for $C_{24}H_{44}N_4O_6$ $[M+H]^+$: 794.4408, found 794.4411

Synthesis of Allyl-Modified Amino Acids



Methyl (*S*)-2-((tert-butoxycarbonyl)amino)pent-4-enoate (9a)



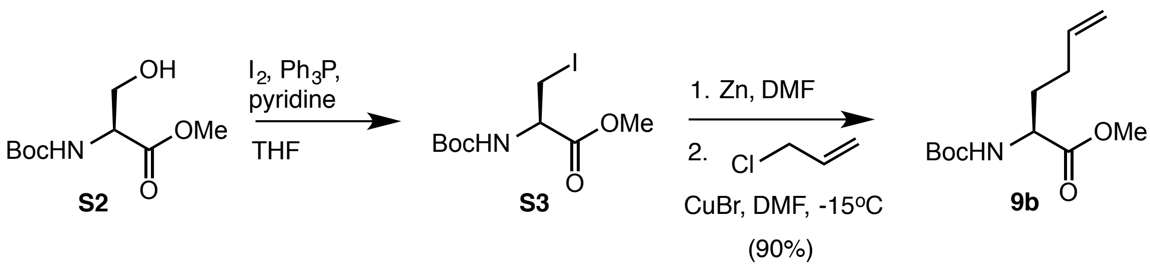
9a: $C_{11}H_{19}NO_4$
Exact mass: 229.1314

The Boc-protected allyl glycine **9a** was synthesized using a two-step procedure starting from allyl glycine. Briefly, to a stirring suspension of (S)-allyl glycine **S1** (2.0 g, 17.3 mmol) in CH_2Cl_2 (25 mL) was added triethylamine (TEA, 1.9 mL, 26.0 mmol, 1.5 eq.) under Ar(g). The solution was cooled to 0°C by immersion in an ice bath. Di-*tert*-butyl dicarbonate (5.6 g, 26.0 mmol, 1.5 eq.) was dissolved in CH_2Cl_2 (10 mL) and added dropwise to the stirring solution. The reaction was removed from the ice bath and allowed to stir at room temperature for 12 h. The crude mixtures was diluted with H_2O (10 mL) and extracted with 1 M HCl (3 x 10 mL), brine (3 x 10 mL), and dried over Na_2SO_4. The solvent was removed *in vacuo* to afford a light yellow oil which was carried on to the next step without further purification.

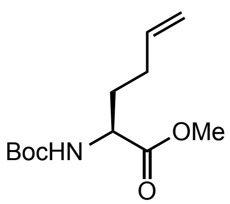
To the oil was added acetone (20 mL) and solid K_2CO_3 (4.8 g, 34.6 mmol, 2 eq.) at room temperature. The reaction was stirred for 10 min, followed by the addition of iodomethane (2.2 mL, 34.6 mmol, 2 eq.) and the mixture stirred for 12 h. The solvent was evaporated and the residue taken up in EtOAc (25 mL) and washed with saturated $Na_2S_2O_3$ (2 x 20 mL), brine (2 x 20 mL), and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude residue was purified by flash chromatography (3:1 Hex:EtOAc) to afford 3.1 g (78%) of **9a** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.64 (ddt, *J* = 16.5, 10.7, 7.2 Hz, 1H), 5.15–4.99 (m, 3H), 4.39– 4.25 (m, 1H), 3.68 (s, 3H), 2.56–2.35 (m, 2H), 1.39 (s, 9H); ^{13}C NMR (126 MHz,

$CDCl_3$) δ 172.47, 155.13, 132.29, 118.95, 79.76, 52.86, 52.14, 36.69, 28.22 (3C). HRMS (ESI) m/z calcd for $C_{11}H_{19}NO_4$ $[M+H]^+$: 230.1314, found 230.1317

Synthesis of homoallyl-modified amino acids



Methyl (*S*)-2-((tert-butoxycarbonyl)amino)hex-5-enoate (9b)



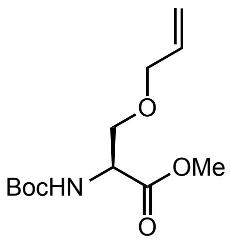
9b: $C_{12}H_{21}NO_4$
Exact mass: 243.1471

Boc-homoallyl glycine **9b** was synthesized using a three-step protocol from commercially available Boc-Ser-OMe (**S2**). In a typical procedure, a flask was charged with Boc-Ser-OMe (2.0 g, 9.1 mmol) and triphenylphosphine (3.6 g, 13.7 mmol, 1.5 eq.) under Ar(g). To this was added THF (20 mL) and the solution cooled to 0°C by immersion in an ice bath. Pyridine (1.5 mL, 18.2 mmol, 2 eq.) was added dropwise, followed by solid iodine (3.5 g, 13.7 mmol, 1.5 eq.) in three portions at 0°C. The ice bath was removed and stirring was continued for 4 h at room temperature. The mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with 1M HCl (3 x 20 mL), 1M $Na_2S_2O_3$ (2 x 20 mL), brine (2 x 20 mL) and dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was of sufficient purity to be used in the next step without further purification.

The iodopropanoate **S3** was dissolved in DMF (5 mL) and added dropwise to a flask containing activated zinc (2.4 g, 36.4 mmol, 4 eq.) at 0°C under Ar(g). The reaction mixture was removed from the ice bath and allowed to stir at room temperature for 3 h, upon which TLC (4:1 petroleum ether: EtOAc) indicated loss of starting material and formation of a lower R_f spot. At this point, the reaction mixture was stopped to let the solid settle to the bottom. The supernatant was then carefully transferred by syringe to a suspension of copper(I) bromide (0.26 g, 1.8 mmol) in DMF (mL) at -15°C that also contained allyl chloride (1.3 mL, 15.5 mmol, 1.7 eq.). After complete addition, the cooling bath was removed and stirring was continued overnight. At this point, EtOAc (20 mL) was added to the reaction mixture and stirring was continued for 15 min. To the mixture was added H_2O (20 mL), the organic layer was removed and successively washed with 1M $Na_2S_2O_3$ (2 x 20 mL), H_2O (2 x 20 mL), brine (2 x 20 mL), and dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (SiO_2, 8:1 petroleum ether:EtOAc) to afford 2.0 g (90%) of **9b** as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 5.72 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.18–5.07 (m, 1H), 5.01–4.90 (m, 2H), 4.26-4.23 (m, 1H), 3.67 (s, 3H), 2.08–2.01 (m, 2H), 1.88–1.79 (m, 1H), 1.70–1.61

(m, 1H), 1.37 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.11, 155.23, 136.87, 115.50, 79.64, 52.09, 51.99, 31.85, 29.39, 28.21 (3C). HRMS (ESI) m/z calcd for $C_{12}H_{21}NO_4$ $[M+H]^+$: 244.1471, found 244.1474

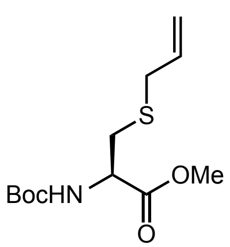
Methyl O-allyl-N-(tert-butoxycarbonyl)-L-serine (9c)



9c: $C_{12}H_{21}NO_5$
Exact mass: 259.1420

A solution of Boc-Ser-OMe **S2** (2.0 g, 9.1 mmol) in anhydrous THF (40 mL) was degassed and treated with allylmethyl carbonate (1.4 mL, 12.7 mmol, 1.4 eq). Tetrakis(triphenylphosphine)palladium (0.21 g, 0.18 mmol, 0.02 eq.) was added and the reaction mixture heated to 60^{o}C for 4 h upon which TLC (2:1 EtOAc:hexanes) indicated loss of starting material. The solvent was removed under reduced pressure and the residue was diluted with EtOAc (30 mL) and washed with $NaHCO_3$ (2 x 30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2; 0% to 66% EtOAc in hexane) to afford 1.6 g (68%) of the product **9c** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 17.3, 10.4, 5.6 Hz, 1H), 5.41–5.31 (m, 1H), 5.25–5.10 (m, 2H), 4.40-4.37 (m, 1H), 3.95-3.92 (m, 2H), 3.80 (dd, *J* = 9.5, 3.3 Hz, 1H), 3.71 (s, 3H), 3.61 (dd, *J* = 9.5, 3.4 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.11, 155.42, 134.01, 117.29, 79.85, 72.14, 69.86, 53.92, 52.37, 28.25 (3C). HRMS (ESI) m/z calcd for $C_{12}H_{21}N_5O_5$ $[M+H]^+$: 260.1420, found 260.1428

Methyl S-allyl-N-(tert-butoxycarbonyl)-L-cysteine (9d)

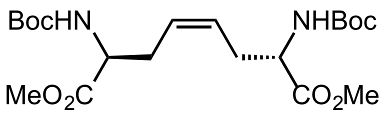


9d: $C_{12}H_{21}NO_4S$
Exact mass: 275.1191

Following the procedure for **9c**, the allyl-protected cysteine **9d** was obtained when Boc-Cys-OMe (1.8 g, 7.6 mmol) was treated with allylmethyl carbonate (1.2 mL, 10.7 mmol, 1.4 eq.) and tetrakis(triphenylphosphine)palladium (0.17 g, 0.15 mmol, 0.02 eq.) in THF (30 mL). The residue was purified by column chromatography (SiO_2; 0% to 25% EtOAc in hexane) to afford 1.4 g (69%) of the product **9d** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (ddt, *J* = 16.9, 9.6, 7.2 Hz, 1H), 5.38–5.29 (m, 1H), 5.12–5.04 (m, 2H), 4.48-4.46 (m, 1H), 3.72 (s, 3H), 3.13–3.03 (m, 2H), 2.88 (dd, *J* = 13.9, 5.0 Hz, 1H), 2.80 (dd, *J* = 13.9, 5.7 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.55, 155.06, 133.62, 117.78, 80.00, 53.10, 52.45, 35.07, 32.76, 28.25 (3C). HRMS (ESI) m/z calcd for $C_{12}H_{21}NO_4S$ $[M+H]^+$: 276.1191, found 276.1188

Procedure for homodimerization of allyl-modified amino acids

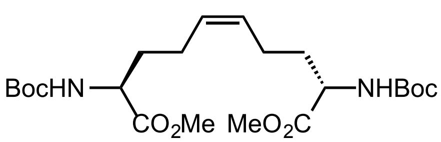
dimethyl (2*S*,7*S*,*Z*)-2,7-bis((*tert*-butoxycarbonyl)amino)oct-4-enedioate (10a)



10a: $C_{20}H_{34}N_2O_8$
Exact mass: 430.2315

Allyl-modified glycine **9a** (0.18 g, 0.79 mmol) was dissolved in THF (1.5 mL) under a gentle stream of Ar(g). A solution of catalyst **1** or **2** in THF (588 μl of a 0.10 M solution in THF) was added and the reaction heated to 40°C and stirred for 4 h. The solution was allowed to cool to room temperature upon which an excess of ethyl vinyl ether (0.5 mL, 5.2 mmol) was added to quench the reaction. The solvent was removed *in vacuo* and the residue purified by column chromatography (SiO_2; 0% to 25% EtOAc in hexane) to afford 0.15 g (45%) of product **10a** as a clear oil. ^1H NMR (500 MHz, $CDCl_3$) δ 5.50–5.46 (m, 2H), 5.17 (d, *J* = 8.3 Hz, 2H), 4.44-4.40 (m, 2H), 3.75 (s, 6H), 2.62–2.54 (m, 2H), 2.47-2.42 (m, 2H), 1.45 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.36 (2C), 155.09 (2C), 127.32 (2C), 109.99 (2C), 80.11 (2C), 52.87 (2C), 52.36 (2C), 30.40 (3C), 28.27 (3C). HRMS (ESI) m/z calcd for $C_{20}H_{34}N_2O_8$ $[M+H]^+$: 431.2315, found 431.2318

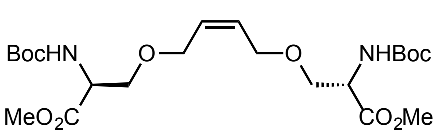
dimethyl (2*S*,9*S*,*Z*)-2,9-bis((*tert*-butoxycarbonyl)amino)dec-5-enedioate (10b)



10b: $C_{22}H_{38}N_2O_8$
Exact mass: 458.2628

Following the procedure for **10a**, the homodimerization product **10b** was obtained when homoallyl-modified glycine **9b** (0.13 g, 0.53 mmol) was reacted with catalyst **1** or **2** (395 μl of a 0.10 M solution in THF) in THF (1.1 mL) under Ar(g). The residue was purified by column chromatography (SiO_2; 3:1 EtOAc:hexanes) to afford 0.14 g (58%) of the product **10b** as a clear oil. ^1H NMR (300 MHz, $CDCl_3$) δ 5.43–5.37 (m, 2H), 5.07 (d, *J* = 8.4 Hz, 2H), 4.32-4.25 (m, 2H), 3.74 (s, 6H), 2.12–2.04 (m, 4H), 1.94–1.76 (m, 2H), 1.74–1.64 (m, 2H), 1.48 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.15 (2C), 155.34 (2C), 129.31 (2C), 79.89 (2C), 63.96 (2C), 52.13 (2C), 32.48 (2C), 28.30 (6C), 23.18 (2C). HRMS (ESI) m/z calcd for $C_{22}H_{38}N_2O_8$ $[M+H]^+$: 459.2628, found 459.2631

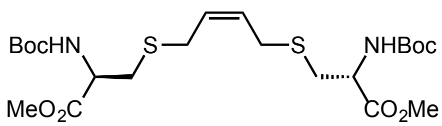
methyl (6S,15S,Z)-15-((tert-butoxycarbonyl)amino)-6-(methoxycarbonyl)-2,2-dimethyl-4-oxo-3,8,13-trioxa-5-azahexadec-10-en-16-oate (10c)



10c: $C_{22}H_{38}N_2O_{10}$
Exact mass: 490.2526

Following the procedure for **10a**, the homodimerization product **10c** was obtained when allyl-modified serine **9c** (0.14 g, 0.54 mmol) was reacted with catalyst **1** or **2** (400 μl of a 0.10 M solution in THF) in THF (1.0 mL) under Ar(g). The residue was purified by column chromatography (SiO_2; 0% to 33% EtOAc in hexanes) to afford 0.17 g (67%) of the product **10c** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.67–5.62 (m, 2H), 5.37 (d, *J* = 8.8 Hz, 2H), 4.46–4.39 (m, 2H), 4.05-3.99 (m, 4H), 3.85-3.81 (m, 2H), 3.76 (s, 6H), 3.66–3.60 (m, 2H), 1.45 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.08 (2C), 155.44 (2C), 129.06 (2C), 80.02 (2C), 70.15 (2C), 66.97 (2C), 53.92 (2C), 52.49 (2C), 28.31 (6C). HRMS (ESI) m/z calcd for $C_{22}H_{38}N_2O_{10}$ $[M+H]^+$: 491.2526, found 491.2533

methyl (6*R*,15*R*,*Z*)-15-((*tert*-butoxycarbonyl)amino)-6-(methoxycarbonyl)-2,2-dimethyl-4-oxo-3-oxa-8,13-dithia-5-azahexadec-10-en-16-oate (10d)

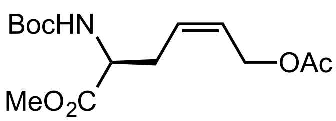


10d: $C_{22}H_{38}N_2O_8S_2$
Exact mass: 522.2070

Following the procedure for **10a**, the homodimerization product **10d** was obtained when allyl-modified cysteine **9d** (0.15 g, 0.54 mmol) was reacted with catalyst **1** or **2** (400 μl of a 0.1 M solution in THF) in THF (1.0 mL) under Ar(g). The residue was purified by column chromatography (SiO_2; 0% to 33% EtOAc in hexanes) to afford 0.20 g (71%) of the product **10d** as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (td, *J* = 5.1, 2.5 Hz, 2H), 5.40 (d, *J* = 8.1 Hz, 2H), 4.60–4.45 (m, 2H), 3.76 (s, 6H), 3.29–3.15 (m, 4H), 2.90 (m, 4H), 1.45 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.54 (2C), 155.16 (2C), 128.31 (2C), 80.17 (2C), 53.31 (2C), 52.57 (2C), 33.95 (2C), 28.76 (2C), 28.31 (6C). HRMS (ESI) m/z calcd for $C_{22}H_{38}N_2O_8S_2$ $[M+H]^+$: 523.3070, found 523.3081

<u>Procedure for cross metathesis of allyl modified amino acids and allyl acetate</u>

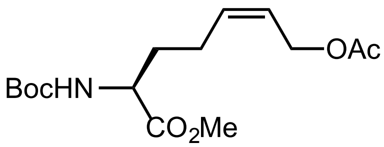
methyl (*S*,*Z*)-6-acetoxy-2-((*tert*-butoxycarbonyl)amino)hex-4-enoate (12a)



12a: $C_{14}H_{23}NO_6$
Exact mass: 301.1525

Boc-protected allyl glycine **9a** (0.15 g, 0.65 mmol) was dissolved in THF (1.1 mL) under a gentle stream of Ar(g). To this was added allyl acetate (0.35 mL, 3.3 mmol, 5 eq.), followed by a solution of catalyst **1** or **2** (490 μl of a 0.10 M solution in THF). The reaction mixture was heated to 40°C and stirred for 4h. The solution was cooled to room temperature and then quenched with an excess of ethyl vinyl ether (0.5 mL, 5.2 mmol). The solvent was removed *in vacuo* and the residue purified by column chromatography (SiO_2; 0% to 25% EtOAc in hexane) to afford 83 mg (42%) of product **12a** as a clear, colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71-5.68 (m, 1H), 5.59-5.53 (m, 1H), 5.20 (d, *J* = 8.4 Hz, 1H), 4.63–4.52 (m, 2H), 4.42–4.32 (m, 1H), 3.73 (s, 3H), 2.69–2.49 (m, 2H), 2.05 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.21, 170.69, 155.17, 128.61, 127.40, 79.90, 59.77, 52.88, 52.26, 30.42, 28.25 (3C), 20.82. HRMS (ESI) m/z calcd for $C_{14}H_{23}NO_6$ $[M+H]^+$: 302.1525, found 302.1588

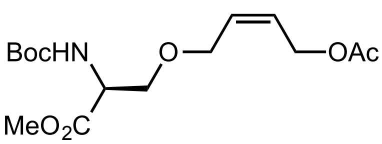
methyl (*S*,*Z*)-7-acetoxy-2-((*tert*-butoxycarbonyl)amino)hept-5-enoate (12b)



12b: $C_{15}H_{25}NO_6$
Exact mass: 315.1682

Following the procedure for **12a**, the cross product **12b** was obtained when homoallyl-modified glycine **9b** (0.14 g, 0.57 mmol) in THF (1.0 mL) was reacted with catalyst **1** or **2** (431 μl of a 0.10 M solution in THF) in the presence of excess allyl acetate (0.31 mL, 2.9 mmol, 5 eq.). The residue was purified by column chromatography (SiO_2; 0% to 20% EtOAc in hexane) to afford 0.10 g (56%) the product **12b** as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65–5.48 (m, 2H), 5.08 (d, *J* = 8.5 Hz, 1H), 4.66–4.51 (m, 2H), 4.32–4.26 (m, 1H), 3.72 (s, 3H), 2.23–2.09 (m, 2H), 2.04 (s, 3H), 1.97–1.80 (m, 1H), 1.78–1.61 (m, 1H), 1.43 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.96, 170.70, 155.28, 133.10, 124.85, 79.90, 60.04, 52.96, 52.16, 32.34, 28.26 (3C), 23.47, 20.82. HRMS (ESI) m/z calcd for $C_{15}H_{25}NO_6$ $[M+H]^+$: 316.1682, found 316.1690

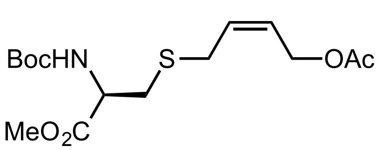
methyl (*Z*)-*O*-(4-acetoxybut-2-en-1-yl)-*N*-(*tert*-butoxycarbonyl)-*L*-serine (12c)



12c: $C_{15}H_{25}NO_7$
Exact mass: 331.1631

Following the procedure for **12a**, the cross product **12c** was obtained when homoallyl-modified serine **9c** (0.13 g, 0.50 mmol) in THF (0.88 mL) was reacted with catalyst **1** or **2** (375 μl of a 0.10 M solution in THF) in the presence of excess allyl acetate (0.27 mL, 2.5 mmol, 5 eq.). The residue was purified by column chromatography (SiO_2; 0% to 33% EtOAc in hexane) to afford 0.11 g (63%) of the product **12c** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74–5.65 (m, 2H), 5.43–5.35 (m, 1H), 4.63-4.58 (m, 2H), 4.46–4.41 (m, 1H), 4.13–4.04 (m, 2H), 3.90-3.85 (m, 1H), 3.77 (s, 3H), 3.68–3.62 (m, 1H), 2.07 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.14, 172.71, 155.24, 136.90, 115.56, 79.77, 53.00, 52.13, 31.97, 29.41, 28.26 (3C), 28.23, 18.56. HRMS (ESI) m/z calcd for $C_{15}H_{25}NO_7$ $[M+H]^+$: 332.1631, found 332.1638

methyl (*Z*)-*S*-(4-acetoxybut-2-en-1-yl)-*N*-(*tert*-butoxycarbonyl)-*L*-cysteine (12d)

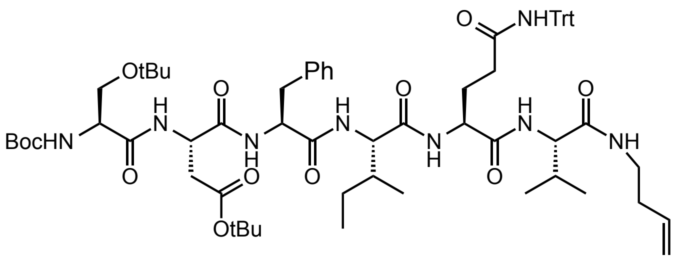


12d: $C_{15}H_{25}NO_6S$
Exact mass: 347.1403

Following the procedure for **12a**, the cross product **12d** was obtained when homoallyl-modified cysteine **9d** (0.14 g, 0.51 mmol) in THF (0.87 mL) was reacted with catalyst **1** or **2** (377 μl of a 0.10 M solution in THF) in the presence of excess allyl acetate (0.27 mL, 2.5 mmol, 5 eq.). The residue was purified by column chromatography (SiO_2; 0% to 33% EtOAc in hexane) to afford 0.11 g (62%) of the product **12d** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73–5.63 (m, 2H), 5.38– 5.30 (m, 1H), 4.68–4.58 (m, 2H), 4.57–4.51 (m, 1H), 3.77 (s, 3H), 3.28–3.21 (m, 2H), 2.95 (dd, *J* = 13.8, 4.9 Hz, 1H), 2.87 (dd, *J* = 13.8, 5.9 Hz, 1H), 2.06 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.41, 170.60, 155.09, 130.09, 126.61, 80.14, 59.55, 53.36, 52.44, 33.97, 29.08, 28.27 (3C), 20.81. HRMS (ESI) m/z calcd for $C_{15}H_{25}NO_6S$ $[M+H]^+$: 348.1403, found 348.1419

General procedure for the synthesis of homoallyl-modified peptides

Boc-Ser(OtBu)-Asp(OtBu)-Phe-Ile-Gln(Trt)-Val homoallyl peptide 13



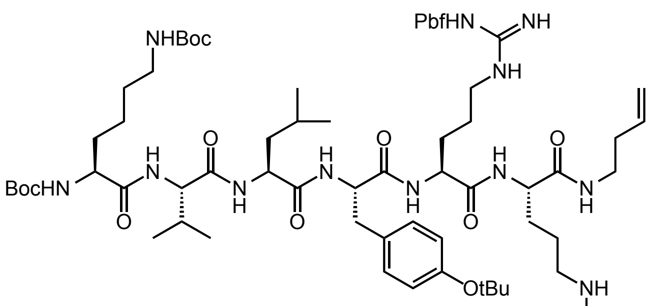
13: $C_{68}H_{94}N_8O_{12}$
Exact Mass: 1214.6991

Peptide **13** was synthesized by solution phase methods using iterative coupling of Fmoc-protected amino acids. Briefly, Boc-protected homoallyl-modified valine **5a** (1.0 g, 3.7 mmol) was dissolved in a mixture of 1:1 TFA:DCM (4 mL) and allowed to stir for 4 h at room temperature upon which TLC (1:1 EtOAc:hexanes) indicated loss of starting material. The solution was diluted with CH_2Cl_2 (30 mL) and the solvent was removed *in vacuo*. The crude residue was dissolved in a mixture of DMF (10 mL) and N,N-diisopropylethylamine (DIEA, 5.3 mL, 30.0 mmol, 8 eq.) and allowed to stir at room temperature for 20 min. At this point, a solution of Fmoc-Gln(Trt)-OH (4.5 g, 7.4 mmol, 2 eq.), HOBt (1.0 g, 7.4 mmol, 2 eq.), HBTU (2.8 g, 7.4 mmol, 2 eq.), and DIEA (2.6 mL, 14.8 mmol, 4 eq.) in DMF (8 mL) was added to the stirring solution. The reaction mixture was heated to 50^{o}C and allowed to stir for 1 h. The solution was cooled to room temperature and quenched with H_2O (20 mL), and to this was added EtOAc (50 mL). The organic layer was removed and washed with H_2O (5 x 20 mL), brine (5 x 20 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to afford the Fmoc-protected dipeptide as a white solid which was found to be of sufficient purity to be used in subsequent reactions.

The Fmoc-protected dipeptide (2.1 g, 2.7 mmol) was dissolved in a mixture of piperidine (3.0 mL, 30 mmol) in DMF (9.0 mL) and allowed to stir at room temperature for 1 h, upon which a white precipitate had formed. The precipitate was filter off, and the filtrate concentrated under reduced pressure. The crude filtrate was dissolved in EtOAc (50 mL) and extracted with H_2O (5 x 30 mL), brine (5 x 30 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to afford a clear oil (1.3 g) which was used in the next step without further purification.

This iterative procedure was used for subsequent amino acid couplings, at each step monitoring the conversion by LC/MS. The termination of the peptide sequence was carried out using the requisite Boc-protected amino acid. After the final coupling, the crude peptide was dissolved in EtOAc (50 mL) and washed with H_2O (5 x 30 mL), brine (5 x 30 mL), and dried over $MgSO_4$. The solvent was removed *in vacuo* and the product purified by column chromatography (SiO_2; 1:1 DCM:EtOAc + 1 to 5% MeOH) to afford a white solid (R_f = 0.45 in 1:1 DCM:EtOAc + 2% MeOH). ^{1}H NMR (500 MHz, $CDCl_3$ + CD_3OD) δ 7.79 (d, *J* = 8.3 Hz, 1H), 7.66 (d, *J* = 8.3 Hz, 1H), 7.44–7.32 (m, 3H), 7.25– 7.09 (m, 17H), 5.75-5.65 (m, 1H), 5.48 (d, J = Hz, 1H), 5.04–4.91 (m, 2H), 4.37-4.35 (m, 1H), 4.33–4.24 (m, 2H), 4.19–4.14 (m, 2H), 4.02–3.97 (m, 2H), 3.79–3.77 (m, 2H), 3.56–3.54 (m, 4H), 3.21–3.19 (m, 4H), 2.57–2.25 (m, 4H), 2.22–2.14 (m, 4H), 2.07-1.92 (m, 3H), 1.85–1.80 (m, 2H), 1.43–1.42 (m, 2H), 1.41 (s, 18H) 1.38–1.35 (m, 6H), 1.13–1.11 (m, 14H), 0.89– 0.79 (m, 9H); ^{13}C NMR (126 MHz, $CDCl_3$ + CD_3OD) δ 172.87, 171.95, 171.93, 171.84, 171.63, 171.18, 170.52, 155.83, 144.50 (3C), 135.36, 129.03, 128.90, 128.70 (3C), 128.67 (3C), 128.57, 128.55, 127.71 (3C), 127.68, 126.77 (3C), 126.74, 126.60, 125.43, 117.87, 116.39, 110.47, 82.01, 80.70, 73.90, 73.53, 61.91, 59.06, 59.03, 58.96, 58.92, 54.02, 38.73, 35.76, 33.36, 33.33, 29.63, 28.22 (3C), 28.13, 27.88 (3C), 27.25, 27.23, 27.22, 27.17 (3C), 25.21, 19.21, 17.59, 17.55, 15.37, 11.03. HRMS (ESI) m/z calcd for $C_{68}H_{94}N_8O_{12}$ $[M+H]^+$: 1215.7016, found 1215.7082

Boc-Lys(Boc)-Val-Leu-Tyr(OtBu)-Arg(Pbf)-Arg(Pbf) homoallyl peptide 14

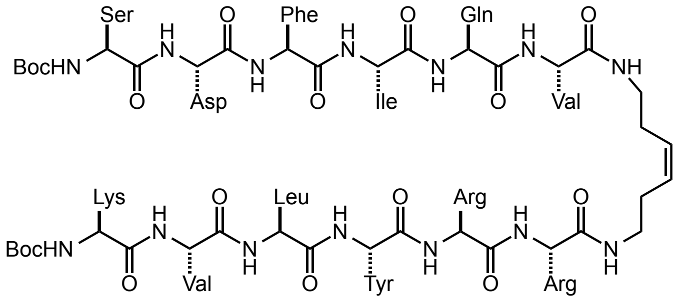


14: $C_{82}H_{130}N_{14}O_{17}S_2$
Exact Mass: 1646.9180

Peptide **14** was synthesized by iterative amino acid coupling in a manner analogous to that of peptide **13**. Purification of the final peptide was achieved by column chromatography (SiO_2; 1:1 DCM:EtOAc + 1 to 5% MeOH) to afford a clear gel. (R_f = 0.55 in 1:1 DCM:EtOAc + 10% MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 6.7 Hz, 1H), 7.54–7.35 (m, 5H), 7.17 (bs, 1H), 7.10–7.07 (m, 2H), 6.79–6.77 (m, 2H), 6.61 (bs, 1H), 6.28 (bs, 4H), 5.72-5.63 (m, 1H), 5.42 (m, 1H), 4.98–4.89 (m, 2H), 4.29–4.15 (m, 3H), 3.19–3.06 (m, 8H), 2.99-2.95 (m, 2H), 2.88–2.84 (m, 8H), 2.78-2.77 (m, 3H), 2.47-2.45 (m, 6H), 2.40-2.39 (m, 6H), 2.20–2.10 (m, 3H), 1.98–1.96 (m, 6H), 1.81-1.50 (m, 12H), 1.38 (s, 9H), 1.36 (s, 9H), 1.34 (s, 9H), 1.20 (m, 12H), 0.93-0.86 (m, 6H), 0.77-0.74 (m, 4H), 0.68-0.66 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$ + CD_3OD) δ 175.42, 174.51, 173.21, 172.91 (2C), 172.32, 162.89 (2C), 158.53, 157.30 (2C), 157.09, 156.43 (2C), 156.36, 153.99, 138.11 (2C), 135.18 (2C), 133.02, 132.06 (2C), 129.26 (2C), 124.45 (2C), 123.94 (2C), 117.32, 116.33, 86.29 (2C), 80.65, 79.30, 78.36, 61.40, 57.09, 56.46, 54.52, 54.31, 53.28, 43.12 (2C), 40.38 (2C), 39.49 (2C), 38.95 (2C), 36.44, 35.82, 33.24 (2C), 31.34, 28.65 (3C), 28.35 (3C), 28.29 (3C), 28.12 (2C), 25.31, 24.52, 22.55 (2C), 20.87 (2C), 18.98 (2C), 18.26 (2C), 17.69 (2C), 12.18 (2C). HRMS (ESI) m/z calcd for $C_{82}H_{130}N_{14}O_{17}S_2$ $[M+H]^+$: 1648.9180, found 1648.9332

Procedure for the synthesis of peptide 15 by cross metathesis

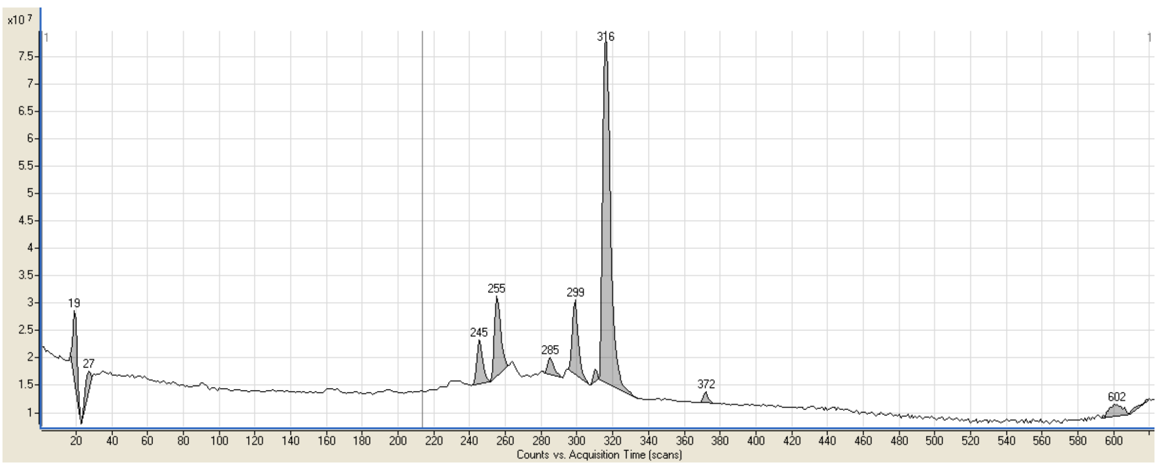
A 1 mL vial was charged with peptides **13** (23 mg, 0.020 mmol) and **14** (33 mg, 0.020 mmol) under a gentle stream of Ar(g). To this was added THF (150 μL), followed by the addition of a solution of catalyst **2** (30 μL of a 0.10 M solution in THF). The reaction mixture was heated to 40°C and stirred for 4h. The solution was cooled to room temperature and then quenched with an excess of ethyl vinyl ether



15: $C_{148}H_{220}N_{22}O_{29}S_2$
Exact mass: 2833.5858

(0.5 mL, 5.2 mmol). The solvent was removed *in vacuo* and the crude mixture analyzed by LC/MS to measure the extent of conversion. (R_f of cross product = 0.32 in 1:1 DCM:EtOAc + 10% MeOH). HRMS (ESI) m/z calcd for $C_{148}H_{220}N_{22}O_{29}S_2$ $[M + 2H]^{2+}$: 1418.7929, found 1418.7948

HPLC of cross metathesis on homoallyl–modified peptides

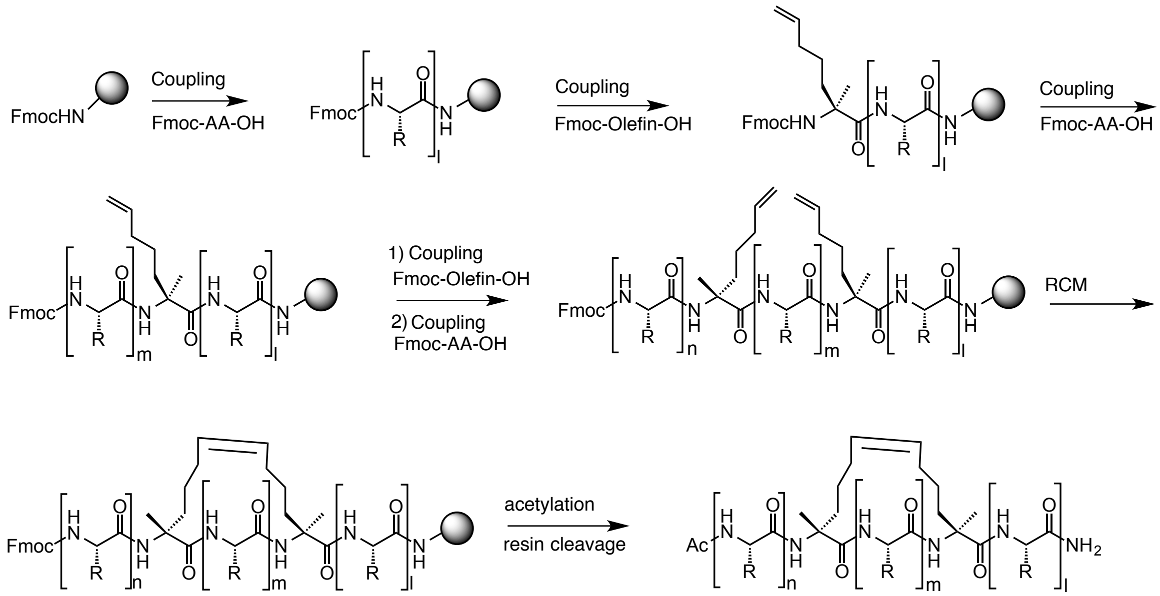


Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	15.9	17.8	20.7	12386573	26460330	8.75
2	21.6	25.5	27.4	3905537	17566003	5.81
3	232.4	235.3	242	8053681	30834550	10.2
4	242	244.9	251.7	14690565	58502397	19.35
5	270.9	273.8	280.5	3084830	11447913	3.79
6	283.4	287.3	295	13667409	51159099	16.92
7	295.9	297.8	299.8	2217449	5490372	1.82
8	299.8	303.6	320.9	64107804	302402244	100
9	354.6	357.5	363.3	1963344	6144511	2.03
10	570.2	578.9	585.6	2176804	18834639	6.23

Figure S1: Analytical HPLC to assess conversion for cross metathesis between peptides **13** and **14**. The percentage conversion was calculated by the ratio of cross product **15** (peak 8) to starting material (peaks 3 corresponding to **13** and peak 5 corresponding to **14**). The homodimers of **13** (peak 4) and **14** (peak 6) are also evident. HPLC conditions: 40-95% acetonitrile:H_2O + 0.1% AcOH.

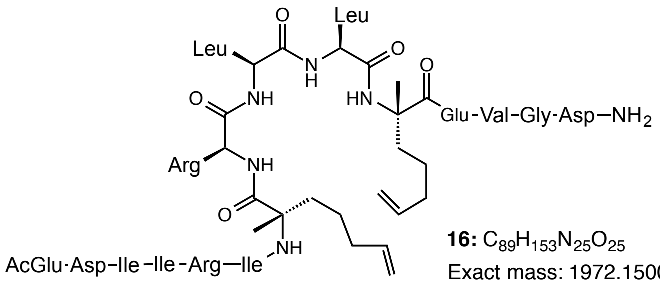
Solid phase synthesis of peptides



Peptides were produced on a Titan 357 (AAPPTec, Louisville, KY) automated peptide synthesizer using Rink Amide MBHA resin (NovaBioChem, 0.4 mmol/g resin), Wang resin (NovaBioChem, 0.5 mmol/g resin), or TentaGel MB RAM resin (RappPolymere, 0.4 mmol/g resin) at 40 μmol scale. The resin was swelled with N-Methyl 2-pyrrolidinone (NMP, 10 mL) for 30 min before use. To load the first amino acid onto the resin, the resin-bound Fmoc-protecting group was removed by treatment with 25% (vol/vol) piperidine in NMP (2 x 10 min). Standard amino acids were coupled for 1 h using HATU as the activating agent (4 eq. based on loading capacity), Fmoc-protected amino acid (5 eq.), and N,N-diisopropylethylamine (DIEA, 10 eq.) in NMP. After each coupling or deprotection reaction, the resin was washed successively with DCM (1 x 1 min), NMP (1 x 1 min), DCM (1 x 1 min) and NMP (1 x 1 min). For the coupling of olefin amino acids, a reaction time of 2 h was used with Fmoc-(S)-2-(4-pentenyl)alanine (3 eq.) or Fmoc-(R)-2-(7-octenyl)alanine (3 eq.), HATU (3 eq.) and DIEA (6 eq.) in NMP. After the final amino acid coupling, the resin was washed with DCM (2 x 1 min) and dried *in vacuo* overnight.

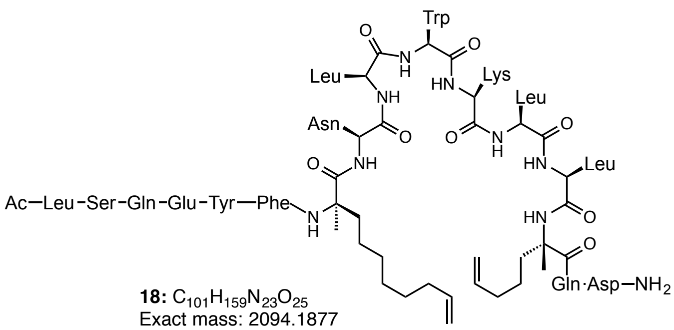
Sequence of peptides used in Z-selective RCM

Peptide **16:** Ac-Glu-Asp-Ile-Ile-Arg-Ile-S5*-Arg-Leu-Leu-S5*-Glu-Val-Gly-Asp



16: $C_{89}H_{153}N_{25}O_{25}$
Exact mass: 1972.1500

Peptide **18**: Ac-Leu-Ser-Gln-Glu-Tyr-Phe-R8*-Asn-Leu-Trp-Lys-Leu-Leu-S5*-Gln-Asp



18: $C_{101}H_{159}N_{23}O_{25}$
Exact mass: 2094.1877

*S5 denotes position of (S)-2-(4-pentenyl)alanine
*R8 denotes position of (R)-2-(7-octenyl)alanine

General procedure for Z-selective RCM on resin-bound olefinic peptides

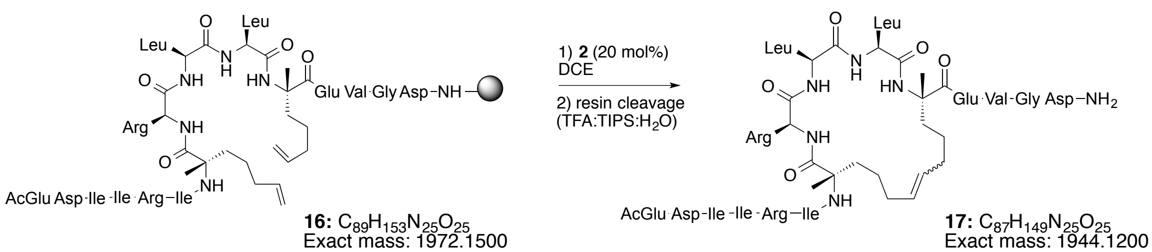
The N-terminal modified peptide on resin (25 mg, 0.01 mmol) was dissolved in degassed dichloroethane (DCE, 2.0 mL). To this was added a stock solution of cyclometalated ruthenium catalyst **2** in degassed DCE (20 μL of a 0.05 M solution in DCE). The reaction was stirred under a gentle stream of Ar(g) for 2 h, the catalyst was filtered off, and the resin washed first with DCE (5 x 2 min) and then with DMF (2 x 2 min). Exposure of the resin bound peptide to an additional round of catalyst stock solution (20 μL) for 2 h ensured nearly quantitative conversion. Upon completion of RCM, the resin bound peptide was washed with DCE (2 x 2 min), DMF (2 x 2 min), and DCM (2 x 2 min) and dried under vacuum.

For N-terminal acetylation of the peptide, the resin was swelled with NMP (1 mL) for 20 min and then washed with NMP (2 x 1 min). The resin was treated with 25% (vol/vol) piperidine in NMP (2 mL), gently agitated for 20 min, and then drained. The resin was washed with DCM (5 x 2 min) and allowed to dry under a gentle stream of argon to afford the amine-terminated peptide. To this was added

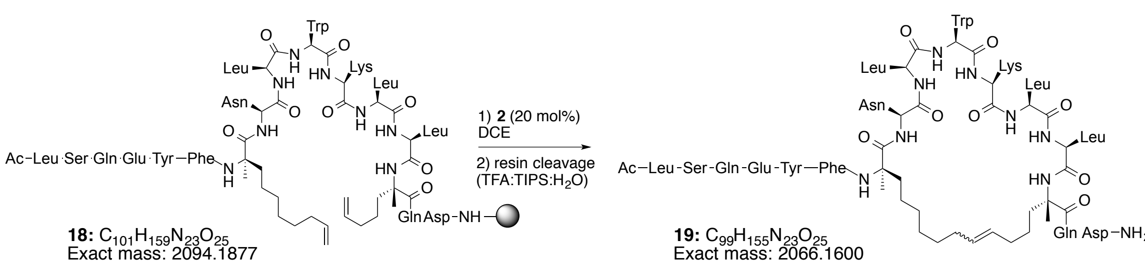
NMP (1 mL), the resin was agitated for 10 min, and the solvent was drained. Acetic anhydride (30 μL, 0.3 mmol, 30 eq.) in NMP (1.0 mL) was added, followed by N,N-diisopropylethylamine (DIEA, 104 μL, 60 eq.) and the resin was agitated for 45 min at room temperature. The resin was washed with DCM (1 x 1 min), NMP (1 x 1 min), and DCM (1 x 1 min) and dried *in vacuo* overnight.

Cleavage of the peptide from the resin and global deprotection were achieved by reacting the resin with 95% TFA, 2.5% triisopropylsilane, 2.5% H_2O (vol/vol/vol) for 2 h. The TFA and other volatiles were removed by evaporation under a stream of argon. The peptides were precipitated with cold diethyl ether (4 mL), vortexed, and collected by centrifugation. The pellet was dried under a gentle stream of argon and subsequently dissolved in a mixture of 50% acetonitrile, 50% H_2O (vol/vol) and the resin was removed by filtration. The cleaved peptides were purified by reverse-phase HPLC using a Zorbax C_8 or C_{18} column (Agilent, 5 μm, 9.4 x 250 mm) and characterized by LC/MS TOF using a Zorbax C_8 column (Agilent, 3.5 μm , 2.1 x 150 mm) or matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF).

Representative Z-selective RCM across one turn of a helix



Representative Z-selective RCM across two helical turns



<u>Monitoring the conversion of RCM on resin-bound olefinic peptides</u>

To measure the percentage conversion of RCM on peptides **16** and **18**, aliquots of the resin suspension (25 μL) were taken from the reaction mixture at the indicated time points, quenched with ethyl vinyl ether (50 μL), filtered, and washed with DCE (300 μL). The resin was dried under a stream of argon and suspended in 100 μL of the cleavage cocktail TFA/TIS/H_2O (95:2.5:2.5) and allowed to stir at room temperature for 1 h. The TFA and other volatiles were removed by evaporation and the crude residue dissolved in diethyl ether (200 μL), vortexed, and centrifuged. The ether was carefully decanted and the pellet was dried under a stream of argon. The pellet was dissolved in 100 μL of 50% (vol/vol) aqueous acetonitrile and filtered to afford the crude peptide. For LC/MS TOF analysis, 5 μL of dissolved peptide was injected onto an analytical column (Eclipse Plus C_8 column (1.8 μm, 2.1 x 50 mm)) operating in positive electrospray ionization (ESI) mode.

*Monitoring ring-closing metathesis on peptide **16***

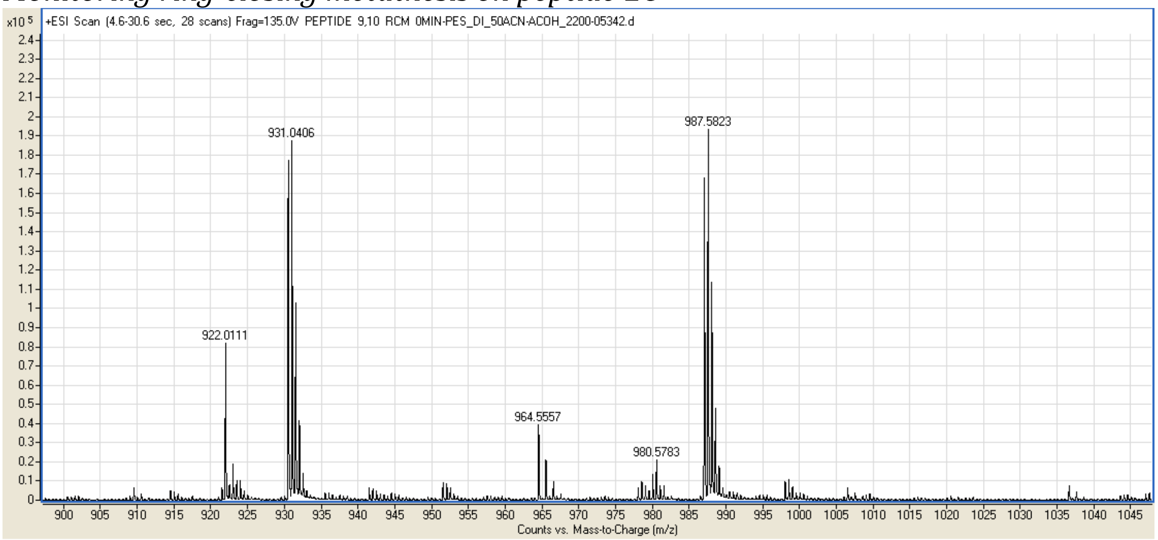


Figure S2: Evaluation of RCM on peptide **16** as a function of time (t = 0 min). The indicated mass corresponding to starting material (987.5823) is observed as the $[M+2H]^{2+}$ ion in ESI and was used to monitor the extent of conversion during the course of the reaction.

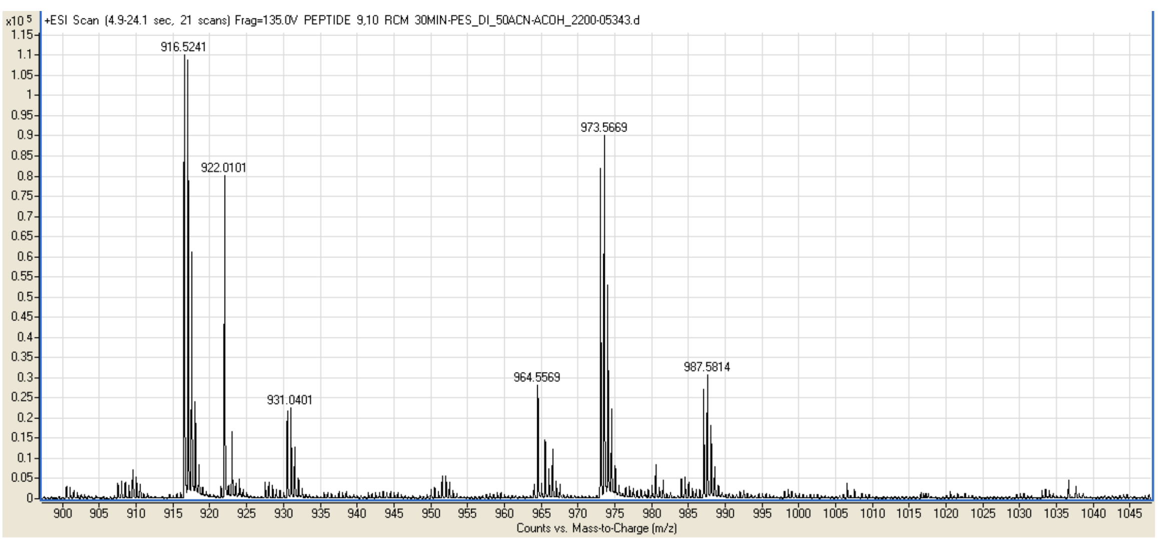


Figure S3: Evaluation of RCM on peptide **16** as a function of time (t = 30 min). Indicated masses correspond to starting material **16** (987.5814) and product **17** (973.5669) as the $[M+2H]^{2+}$ ion as measured by LC/MS TOF.

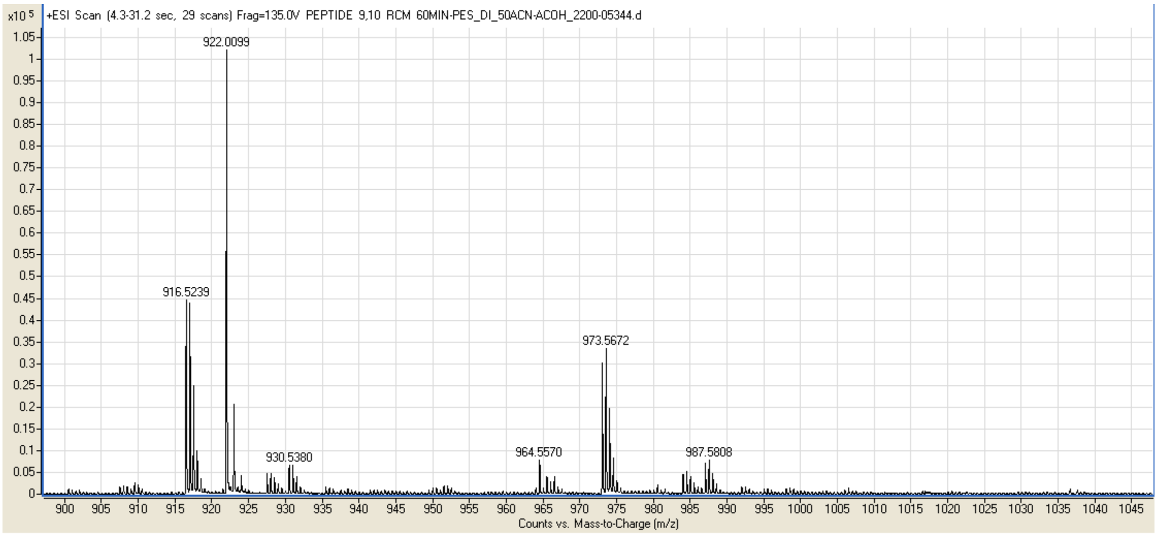


Figure S4: Evaluation of RCM on peptide **16** as a function of time (t = 60 min). Indicated masses correspond to starting material **16** (987.5808) and product **17** (973.5672) as the $[M+2H]^{2+}$ ion as measured by LC/MS TOF.

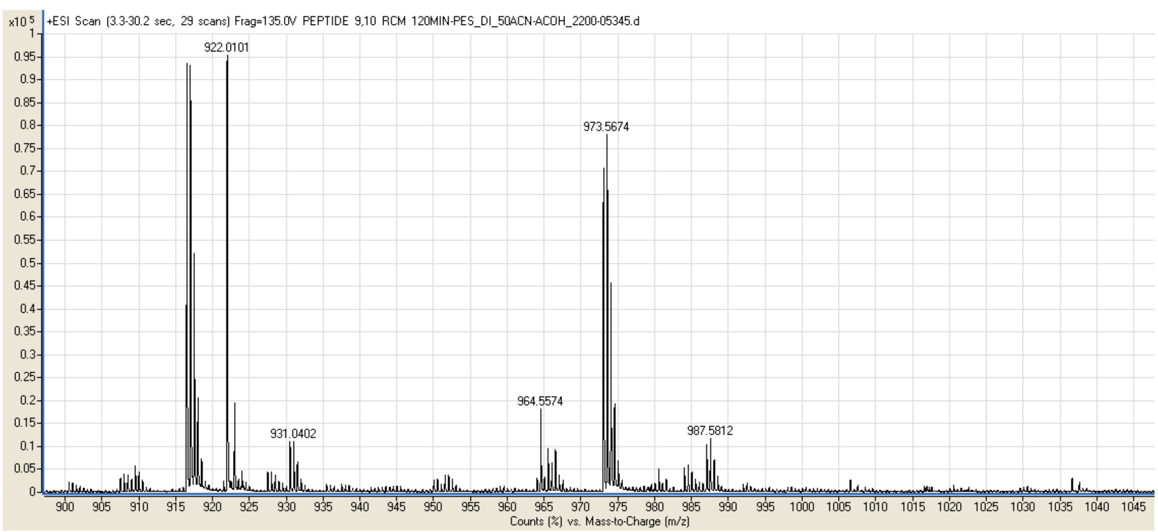


Figure S5: Evaluation of RCM on peptide **16** as a function of time (t = 120 min). Indicated masses correspond to starting material **16** (987.5812) and product **17** (973.5674) as the $[M+2H]^{2+}$ ion as measured by LC/MS TOF.

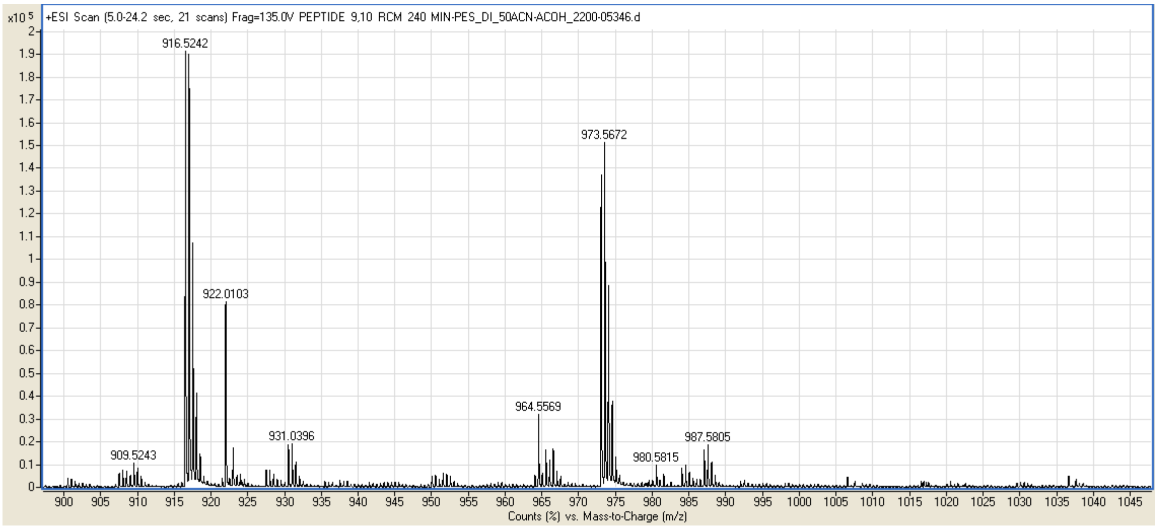


Figure S6: Evaluation of RCM on peptide **16** as a function of time (t = 240 min). Indicated masses correspond to starting material **16** (987.5805) and product **17** (973.5672) as the $[M+2H]^{2+}$ ion as measured by LC/MS TOF.

*HPLC chromatogram of RCM product **17***

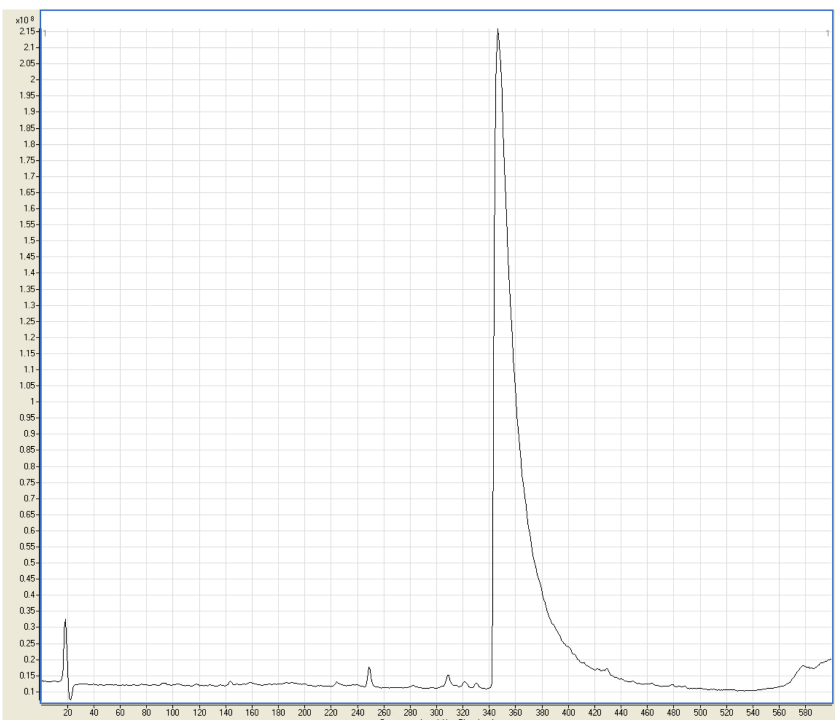


Figure S7. HPLC chromatogram (UV absorbance at 210 nm) of purified peptide **17** (R_t of Z-olefin macrocycle is 348 sec). Column conditions: 5–95% ACN:H_2O + 0.1% AcOH.

*MALDI-TOF spectrum of purified peptide **17**.*

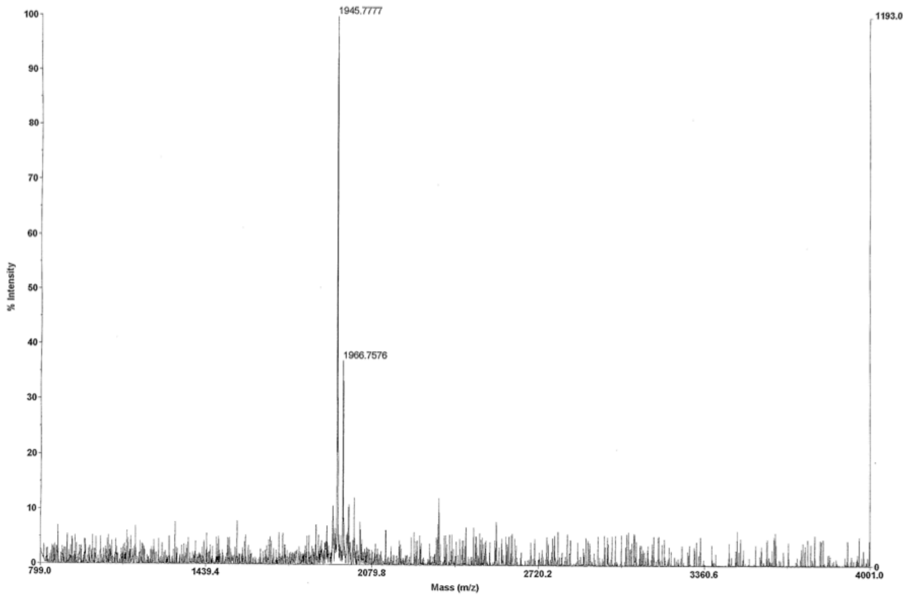


Figure S8: MALDI-TOF of purified peptide **17.** Indicated masses correspond to 1945.7777 $[M+H]^+$ and 1966.7576 $[M+Na]^+$ for the product of Z-selective RCM.

*Monitoring RCM on peptide **18***

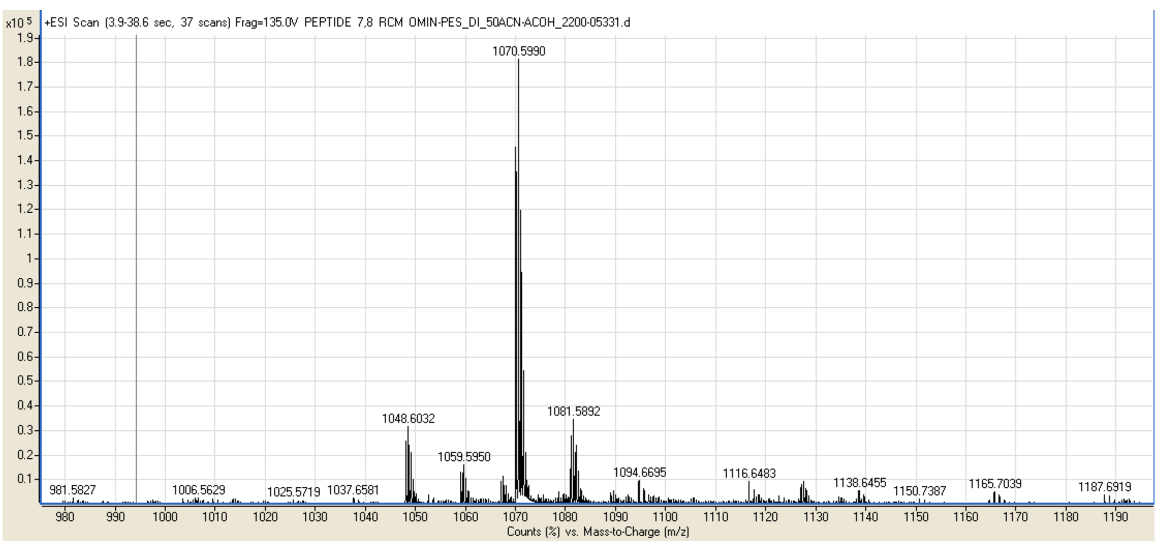


Figure S9: Evaluation of RCM on peptide **18** as a function of time (t = 0 min). The indicated mass corresponding to starting material (1070.5990) is observed as the $[M+2H]^{2+} + Na^+$ ion in ESI and was used to monitor the extent of conversion during the course of the reaction

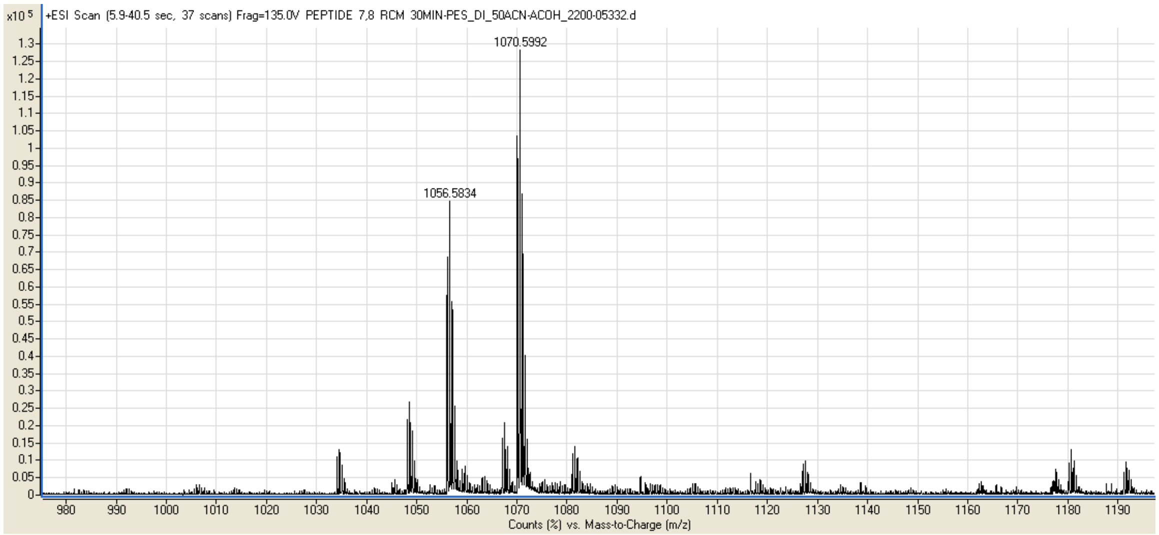


Figure S10: Evaluation of RCM on peptide **18** as a function of time (t = 30 min). Indicated masses correspond to starting material **18** (1070.5992) and product **19** (1056.5834) as the $[M+2H]^{2+}$ ion as measured by LC/MS TOF.

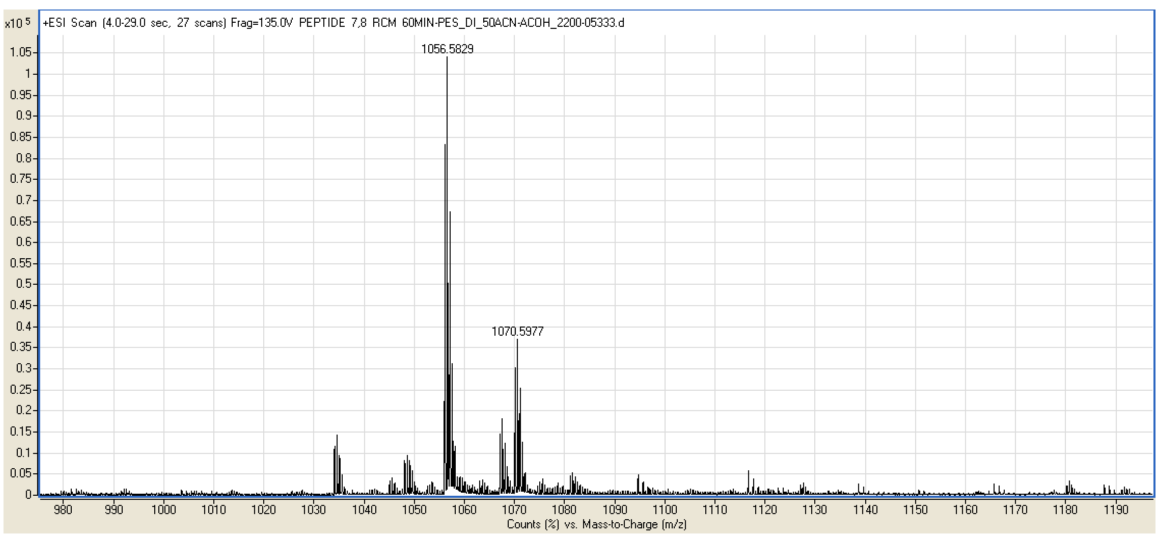


Figure S11: Evaluation of RCM on peptide **18** as a function of time (t = 60 min). Indicated masses correspond to starting material **18** (1070.5977) and product **19** (1056.5829) as the $[M+2H]^{2+}$ ion as measured by LC/MS TOF.

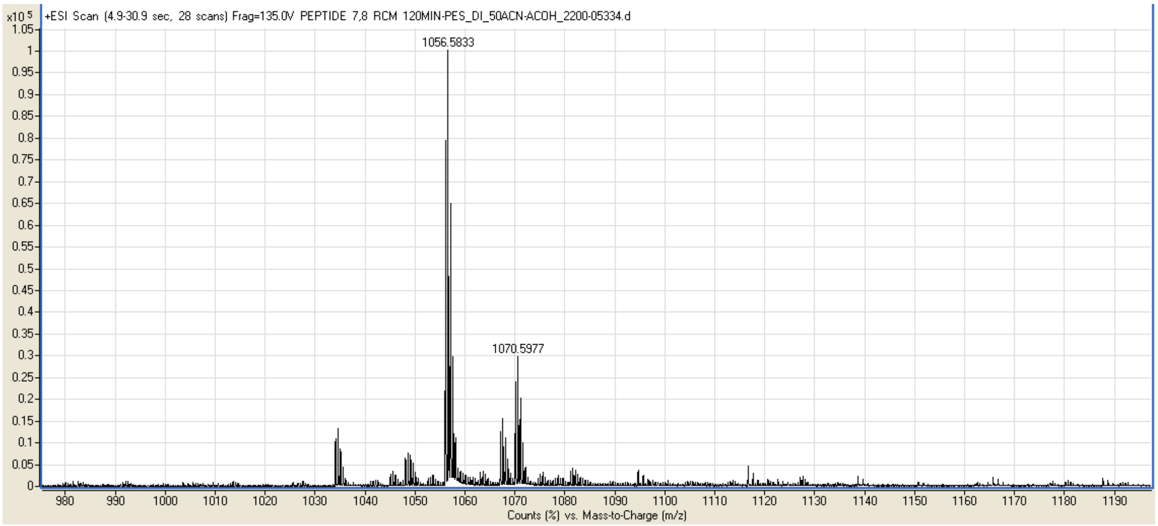


Figure S12: Evaluation of RCM on peptide **18** as a function of time (t = 120 min). Indicated masses correspond to starting material **18** (1070.5977) and product **19** (1056.5833) as the $[M+2H]^{2+}$ ion as measured by LC/MS TOF.

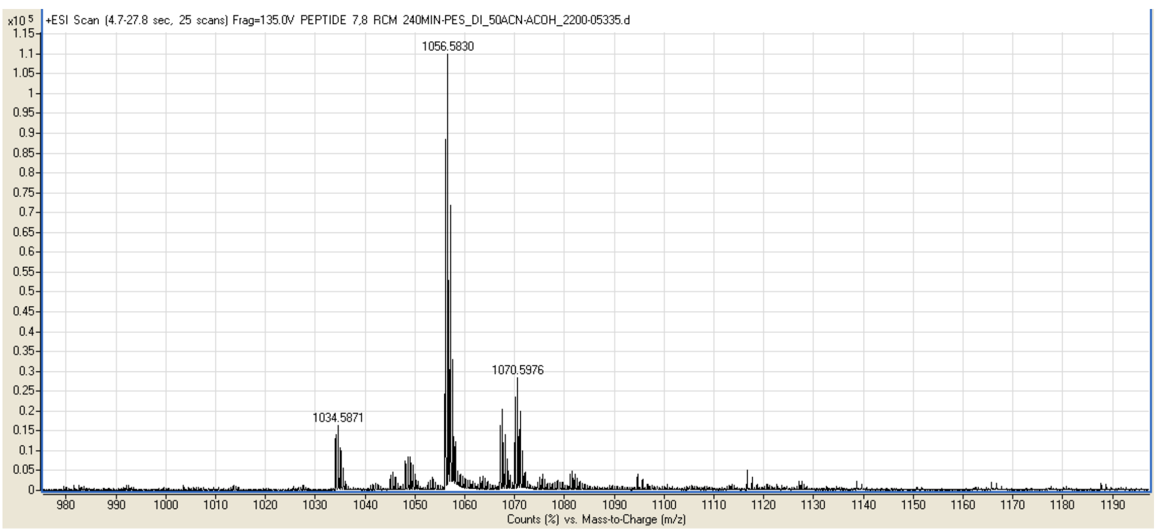


Figure S13: Evaluation of RCM on peptide **18** as a function of time (t = 240 min). Indicated masses correspond to starting material **18** (1070.5976) and product **19** (1056.5830) as the $[M+2H]^{2+}$ ion as measured by LC/MS TOF.

*HPLC chromatogram of RCM product **19***

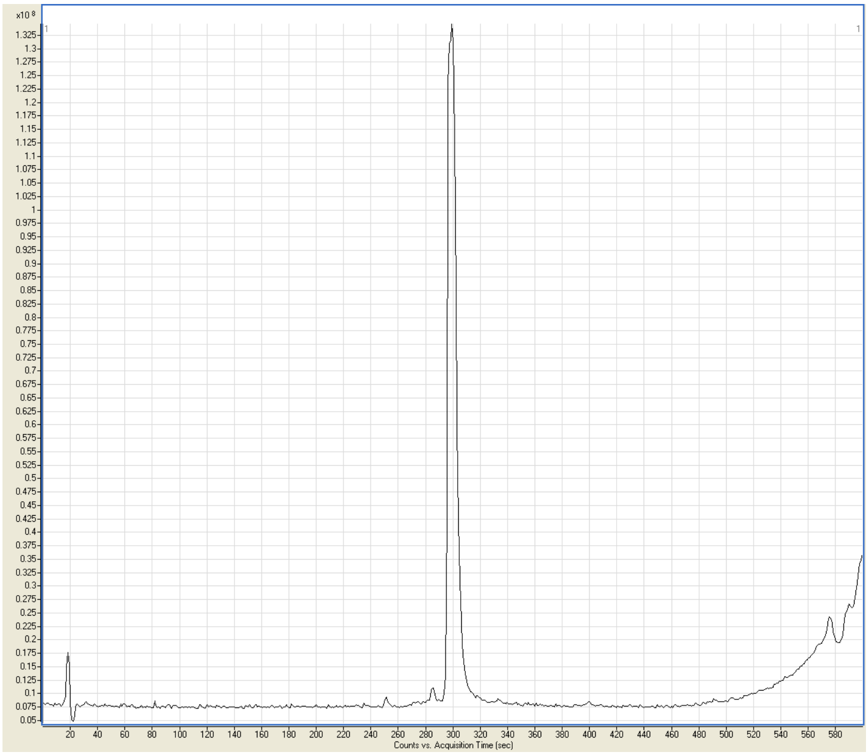


Figure S14: HPLC chromatogram (UV absorbance at 254 nm) of purified peptide **20** (R_t of Z-olefin macrocycle is 302 sec). Column conditions: 5–95% ACN:H_2O + 0.1% AcOH.

*MALDI-TOF spectrum of purified peptide **19**.*

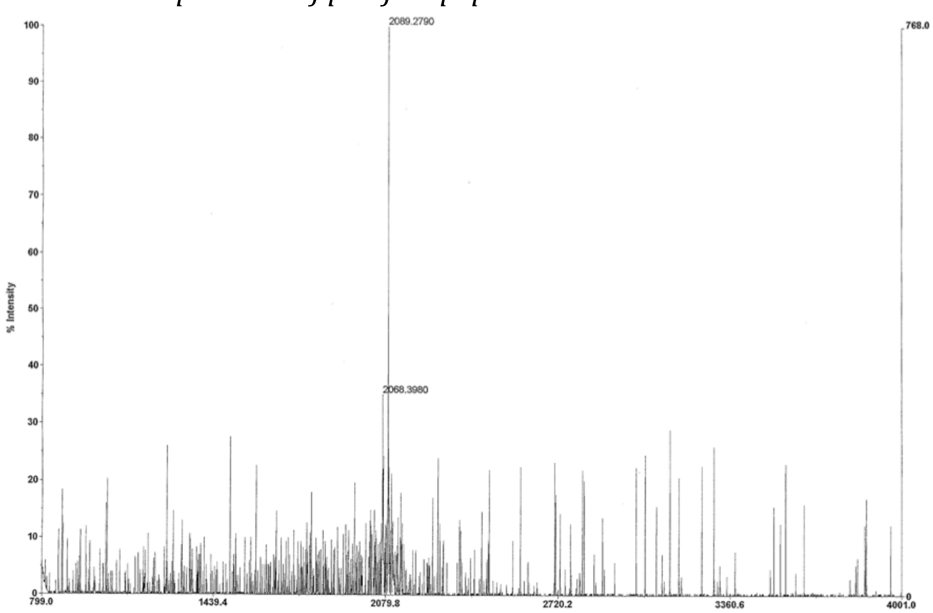
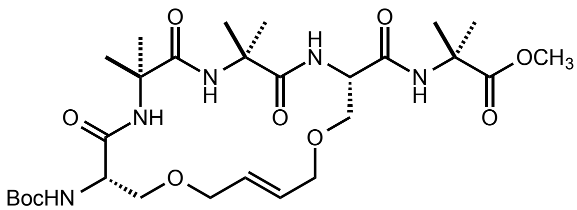


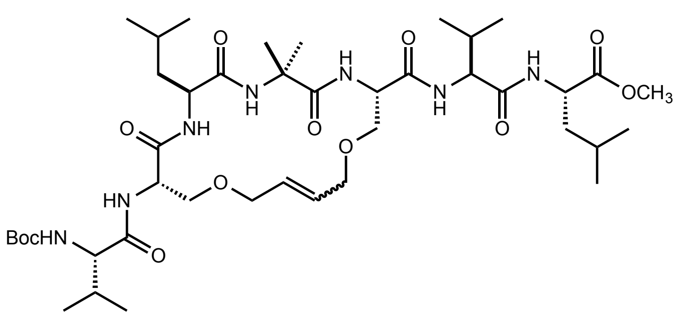
Figure S15: MALDI-TOF of purified peptide **19.** Indicated masses correspond to 2068.3980 $[M+H]^+$ and 2089.2790 $[M+Na]^+$ for the product of Z-selective RCM

General procedure for RCM on Aib-containing peptides bearing i, i+3 crosslinks



21: $C_{28}H_{47}N_5O_{10}$
Exact mass: 613.3323

Boc-Ser(Allyl)-Aib-Aib-Ser(Allyl)-Aib-OMe **20**[2] (20.0 mg, 0.033 mmol) was dissolved in dichloroethane (6.5 mL) in a nitrogen-flushed flask. Second-generation Grubbs catalyst **22** (2.77 mg, 0.0033 mmol), Grubbs-Hoveyda catalyst **23** (2.04 mg, 0.0033 mmol), or cyclometalated ruthenium catalyst **1** (6.11 mg, 0.099 mmol) was added in a single portion and then heated at 40 °C for 4 h. At this point, a 60 μL aliquot was removed and quenched by the addition of H_2O (3 mL) and 30% hydrogen peroxide (3 mL) and the biphasic mixture was vigorously stirred for 8 h. The organic layer was passed through a plug of Na_2SO_4 and an aliquot was removed for LCMS analysis. ^{1}HNMR (400 MHz, CD_2Cl_2): δ 7.48 (1H, d, *J* = 7.4 Hz), 7.47 (1H, s), 6.96 (1H, s), 6.78 (1H, s), 5.74 (2H, m), 5.22 (1H, d, *J* = 7.8), 4.56 (1H, dt, *J* = 2.3, 8.7 Hz), 4.24 (1H, m), 4.16 (2H, m), 3.90 (1H, dd, *J* = 2.9, 9.3 Hz), 3.822 (2H, m), 3.76 (1H, t, *J* = 9.0 Hz), 3.65 (3H, s), 3.48 (1H, dd, *J* = 4.3, 8.7 Hz), 1.55 (3H, s), 1.50 (3H, s), 1.46 (3H, s), 1.44 (15H, s), 1.42 (3H, s). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 175.26, 174.51, 174.46, 171.98, 169.44, 156.31, 132.33, 126.45, 81.17, 70.97, 70.23, 69.29, 66.70, 57.71, 57.45, 56.29, 55.18, 54.73, 52.42, 28.33, 27.78, 26.91, 25.23, 25.08, 23.55, 23.40. HRMS (ESI) m/z calcd for $C_{28}H_{48}N_5O_{10}$ $[M+H]^+$: 614.3521, found 614.3533



25: $C_{42}H_{73}N_7O_{12}$
Exact mass: 867.5300

Following the procedure for RCM on peptide **21**, Boc-Val-L-Ser(Al)-Leu-Aib-L-Ser(Al)-Val-Leu-OMe **24**[2] (9.1 mg, mmol) was dissolved in DCM (1.9 mL) under a stream of nitrogen. To this was added catalysts **22**, **23**, or **1** (10 mol%) and the reaction heated at 40 °C for 4 h. The reaction was diluted with DCM (4 mL) and quenched by addition of water (2 mL) and 30% hydrogen peroxide (2 mL). The biphasic mixture was vigorously stirred for 4 h. An aliquot of the organic layer (60 μL) was removed for LCMS analysis. HRMS (FAB) m/z calcd for $C_{42}H_{48}N_5O_{10}$ $[M+Na]^+$: 890.5209, found 890.5180

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[2] For full characterization of this compound and its ring-closed form, see: Boal, A.K. et al. *J. Am. Chem. Soc.* **2007**, *129*, 6986–6987.

*LCMS chromatogram of RCM product **21** in the presence of catalyst **1***

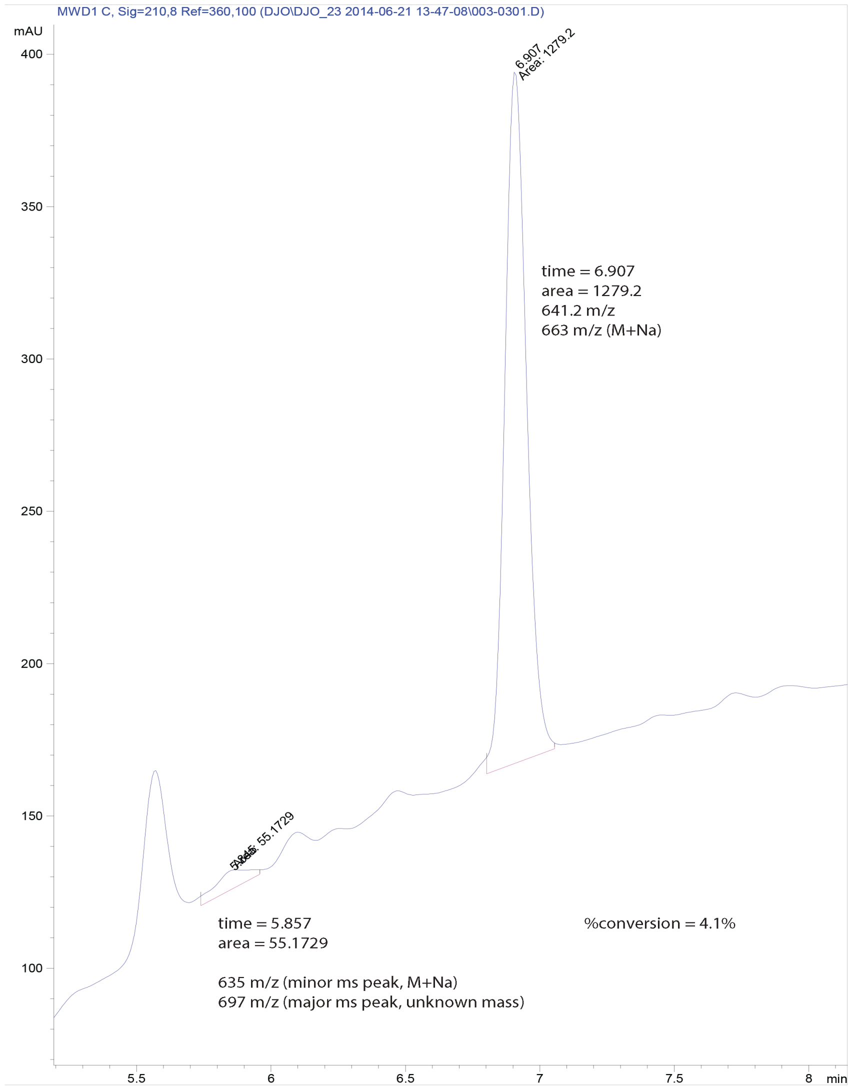


Figure S16: Evaluation of RCM on Boc-Ser(Allyl)-Aib-Aib-Ser(Allyl)-Aib-OMe **20** using catalyst **1.** Indicated masses correspond to starting material (663.2 M + Na) (Rt of starting material is 6.91 min) and product **21** (635 M + Na) (R_t of macrocycle is 5.86 min). Column conditions: 25–100% ACN:H_2O + 0.1% TFA.

*LCMS chromatogram of RCM product **21** in the presence of catalyst **22***

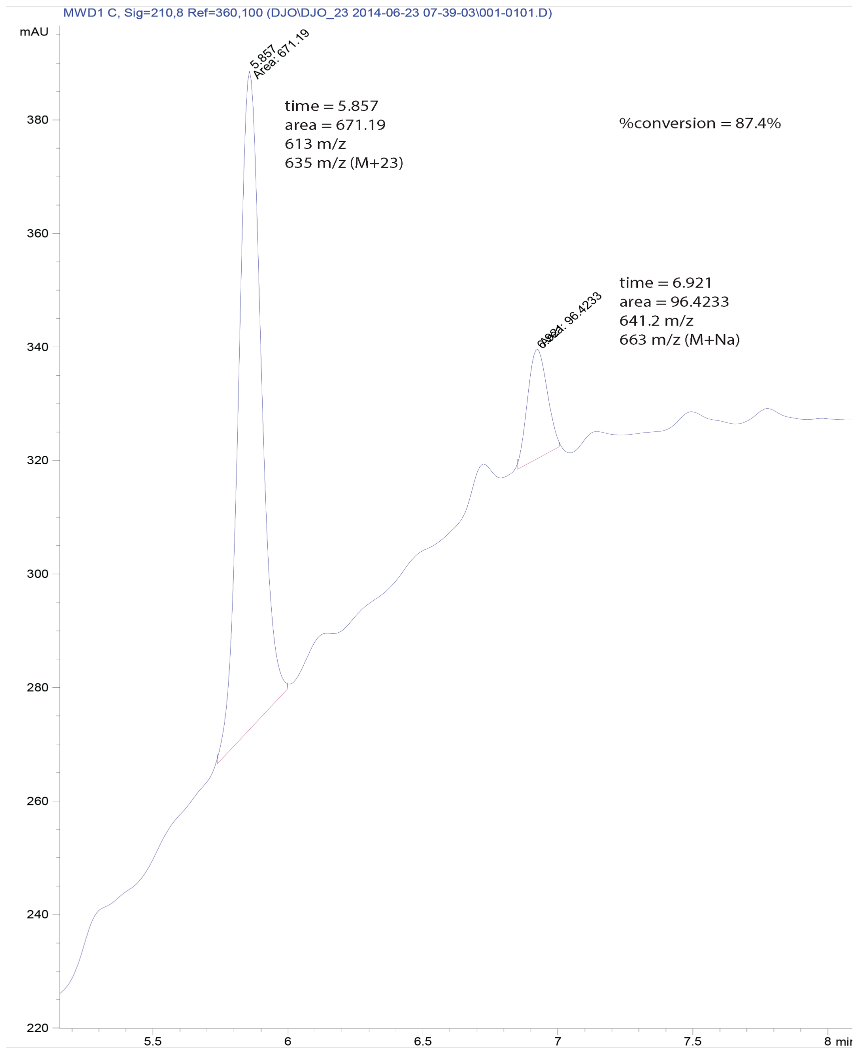


Figure S17: Evaluation of RCM on Boc-Ser(Allyl)-Aib-Aib-Ser(Allyl)-Aib-OMe **20** using catalyst **22.** Indicated masses correspond to starting material (663.2 M + Na) (R_t of starting material is 6.92 min) and product **21** (635 M + Na) (R_t of macrocycle is 5.86 min). Column conditions: 25–100% ACN:H_2O + 0.1% TFA.

*LCMS chromatogram of RCM product **21** in the presence of catalyst **23***

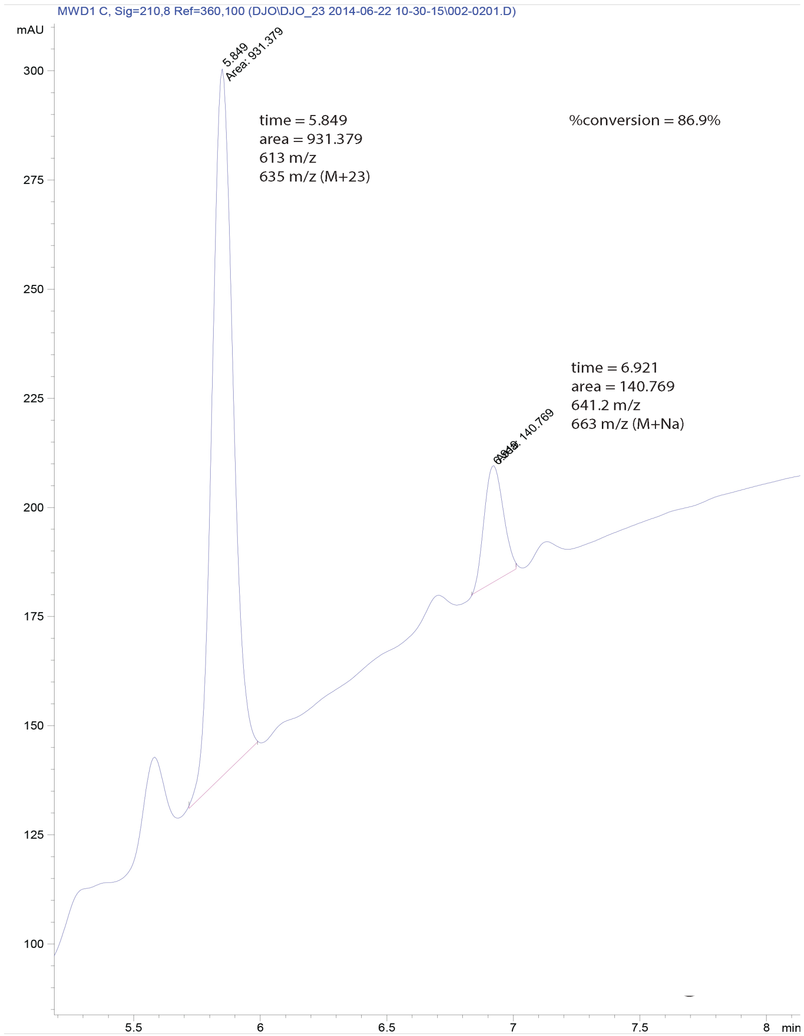


Figure S18: Evaluation of RCM on Boc-Ser(Allyl)-Aib-Aib-Ser(Allyl)-Aib-OMe **20** using catalyst **23.** Indicated masses correspond to starting material (663.2 M + Na) (R_t of starting material is 6.92 min) and product **21** (635 M + Na) (R_t of macrocycle is 5.85 min). Column conditions: 25–100% ACN:H_2O + 0.1% TFA.

*LCMS chromatogram of RCM product **25** in the presence of catalyst **1***

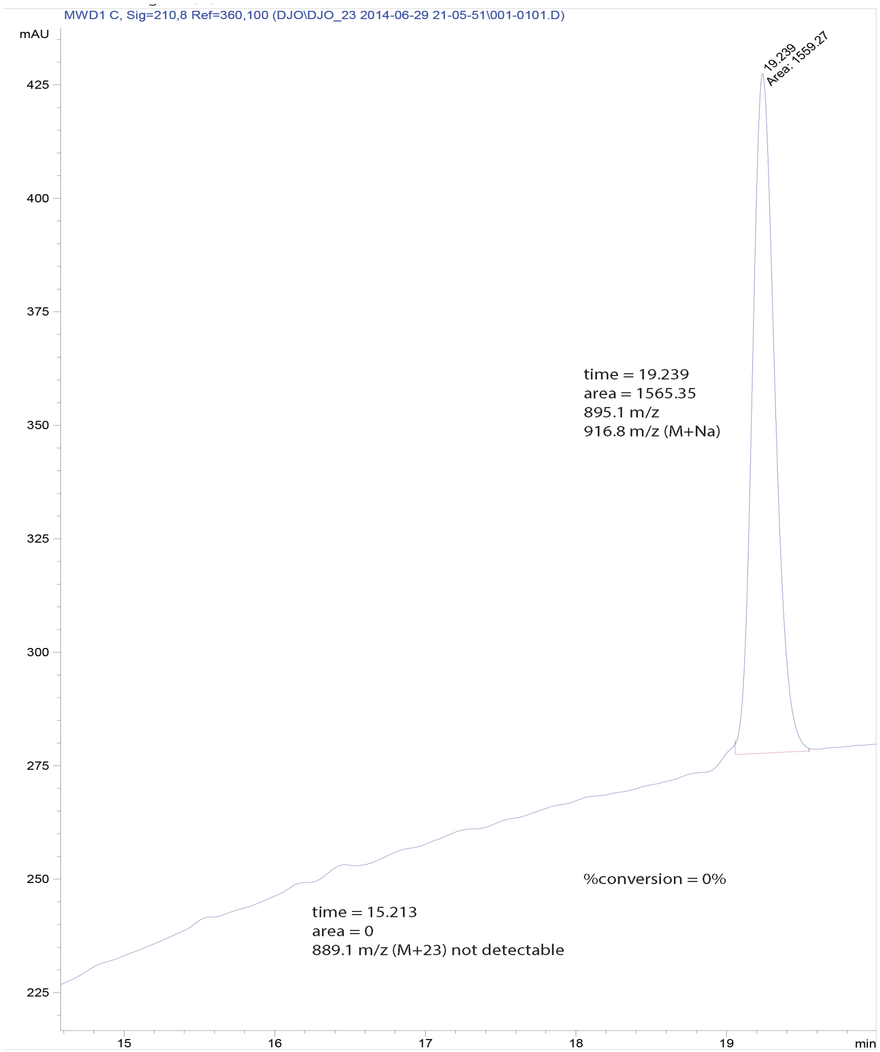


Figure S19: Evaluation of RCM on Boc-Val-Ser(Allyl)-Leu-Aib-Ser(Allyl)-Val-Leu-OMe **24** using catalyst **1.** Indicated masses correspond to starting material (916.8 M + Na) (R_t of starting material is 19.24 min). Column conditions: 25–100% ACN:H_2O + 0.1% TFA.

*LCMS chromatogram of RCM product **25** in the presence of catalyst **22***

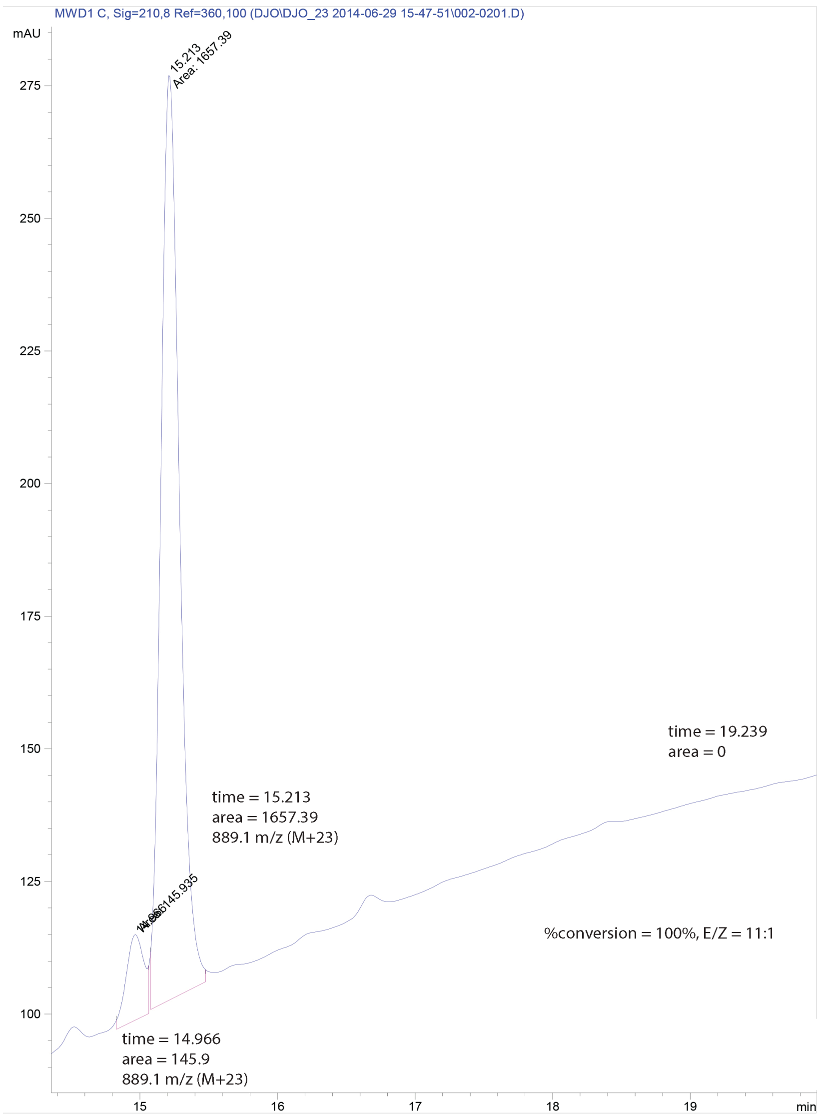


Figure S20: Evaluation of RCM on Boc-Val-Ser(Allyl)-Leu-Aib-Ser(Allyl)-Val-Leu-OMe **24** using catalyst **22.** Indicated masses correspond to starting material (916.8 M + Na) (R_t of starting material is 19.24 min) and product **25** (889.1 M + Na) (R_t of *Z*-olefin macrocyle is 14.96 min and *E*-macrocyle 15.21 min) . Column conditions: 25–100% ACN:H_2O + 0.1% TFA.

*LCMS chromatogram of RCM product **25** in the presence of catalyst **23***

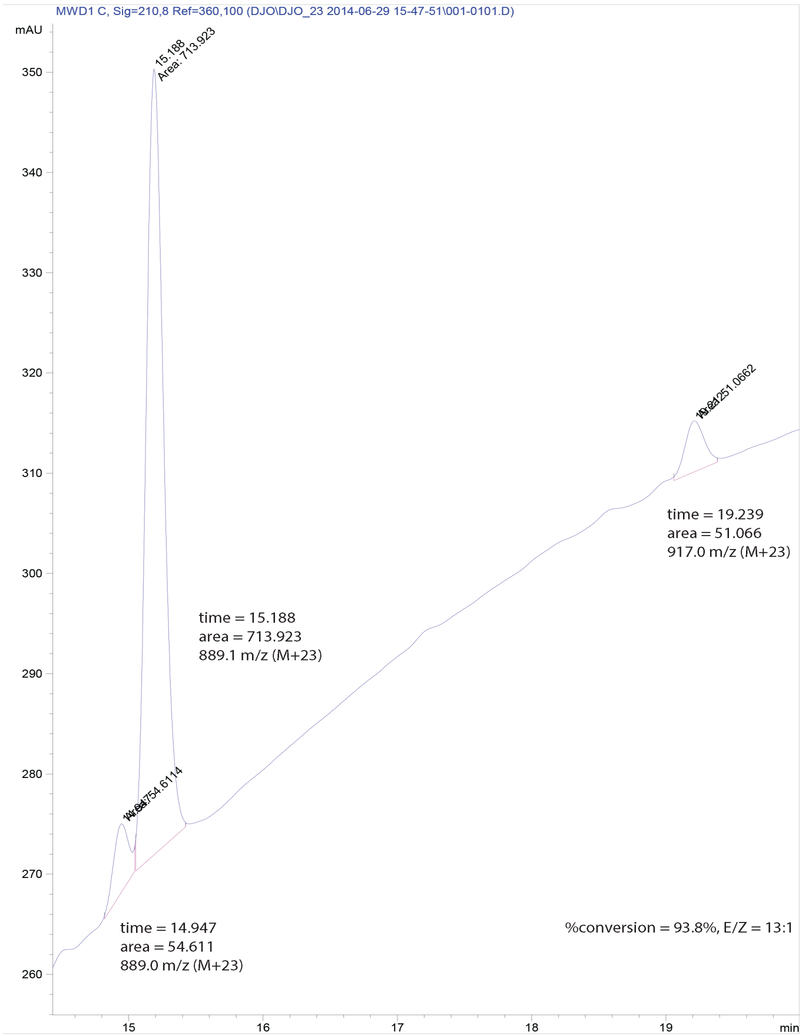
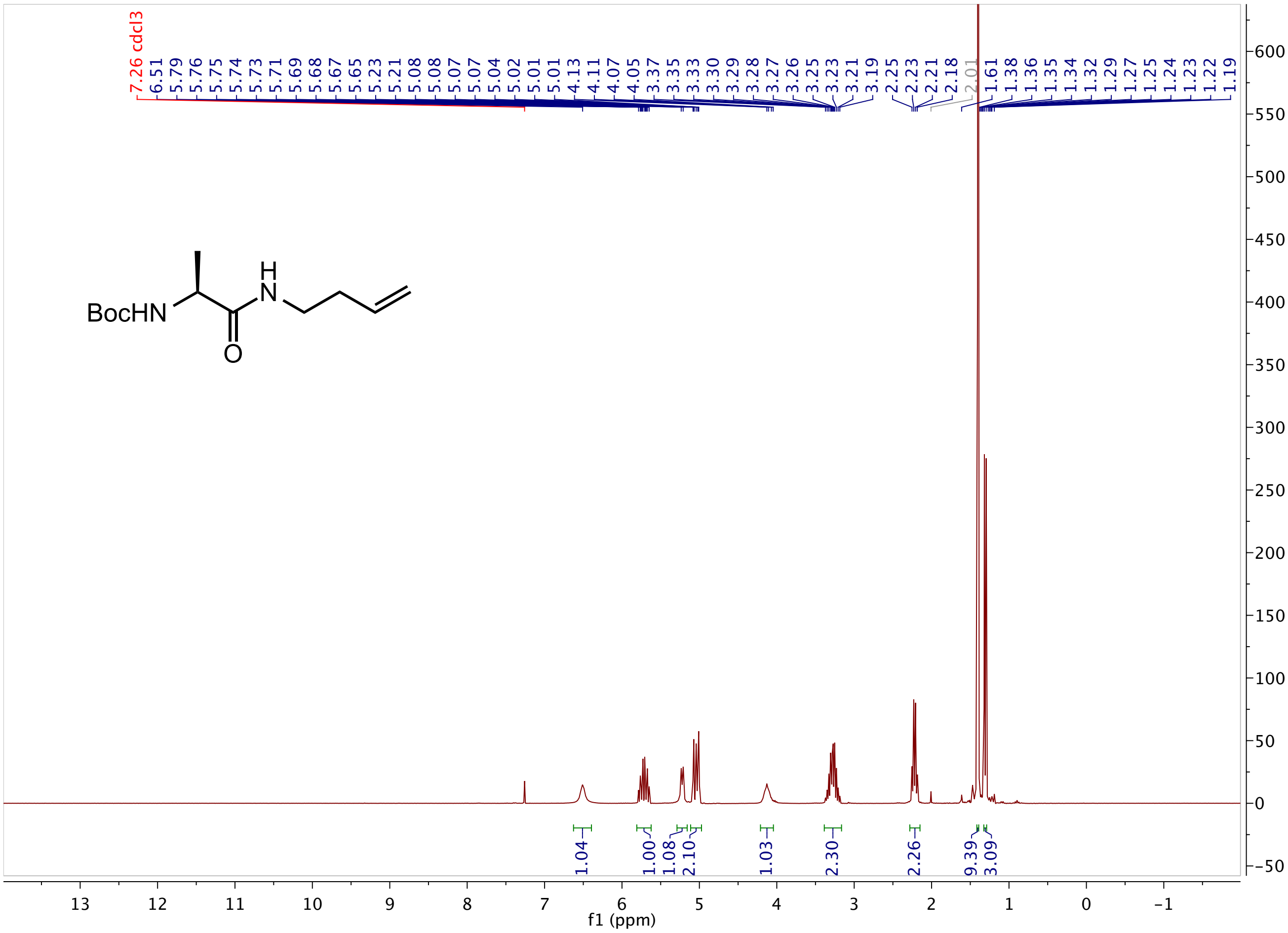
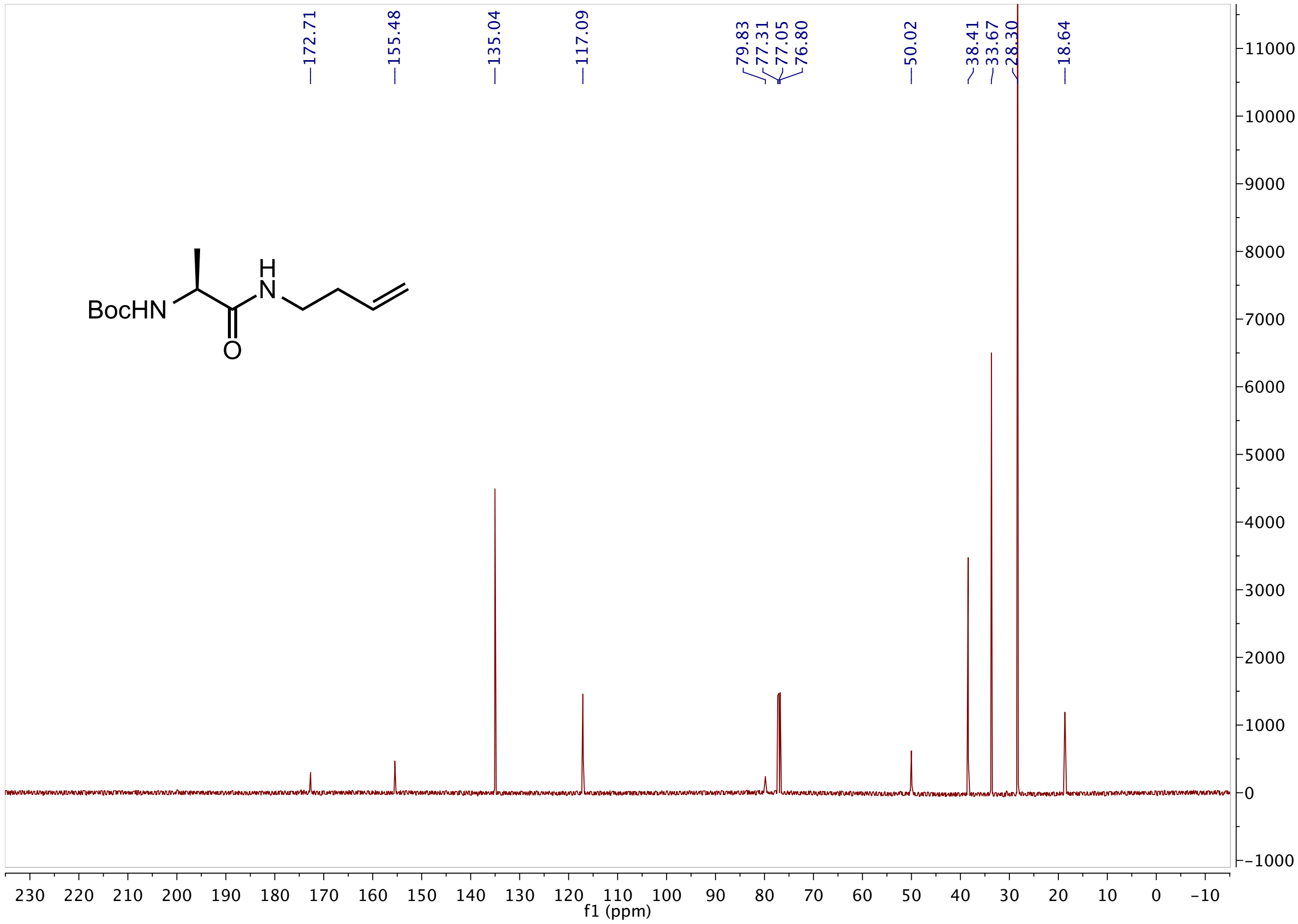


Figure S21: Evaluation of RCM on Boc-Val-Ser(Allyl)-Leu-Aib-Ser(Allyl)-Val-Leu-OMe **24** using catalyst **23.** Indicated masses correspond to starting material (917.0 M + Na) (R_t of starting material is 19.24 min) and product **25** (889.0 M + Na) (R_t of *Z*-olefin macrocyle is 14.95 min and *E*-macrocyle 15.19 min) . Column conditions: 25–100% ACN:H_2O + 0.1% TFA.

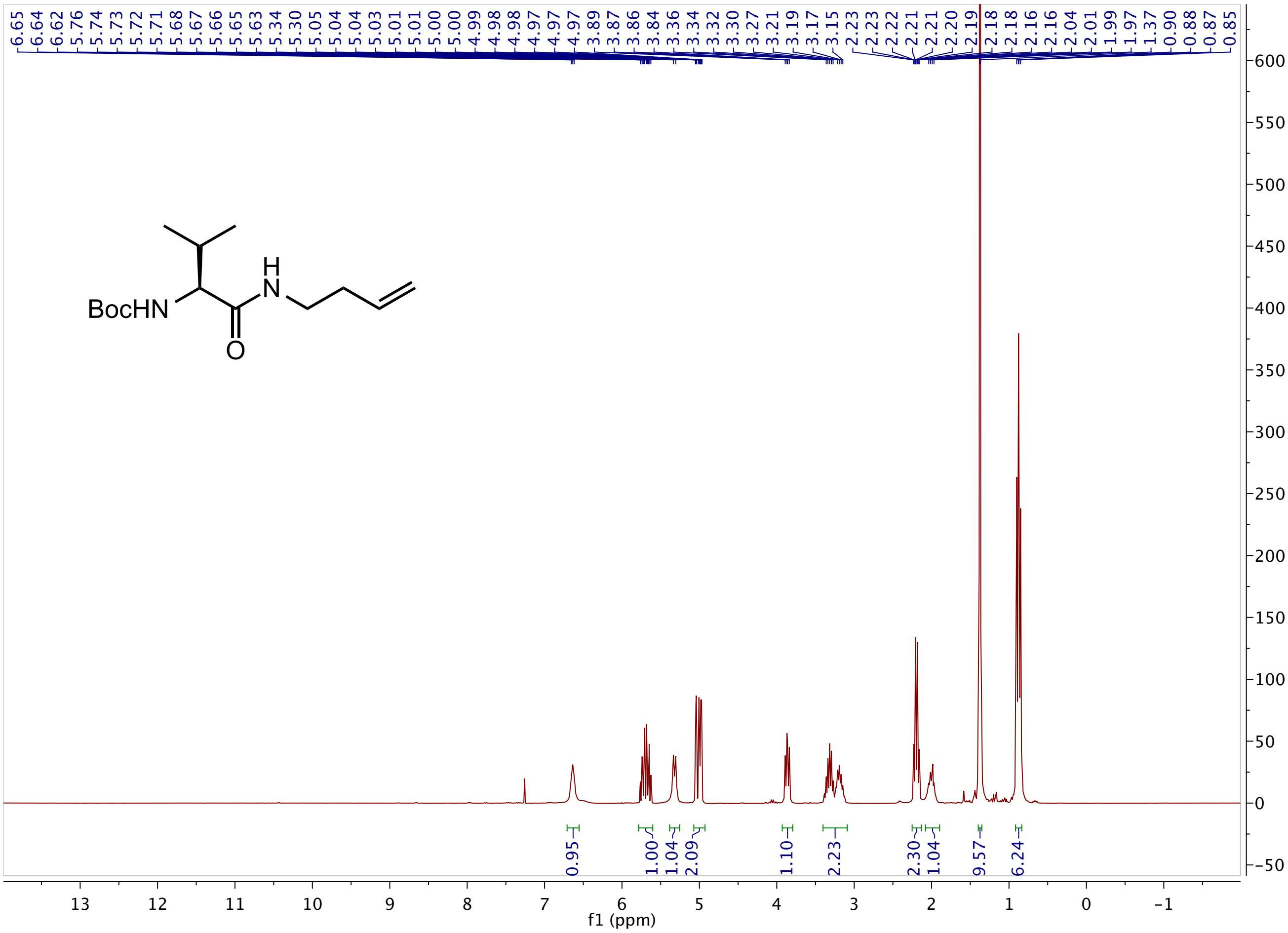
NMR Spectra: ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **3**



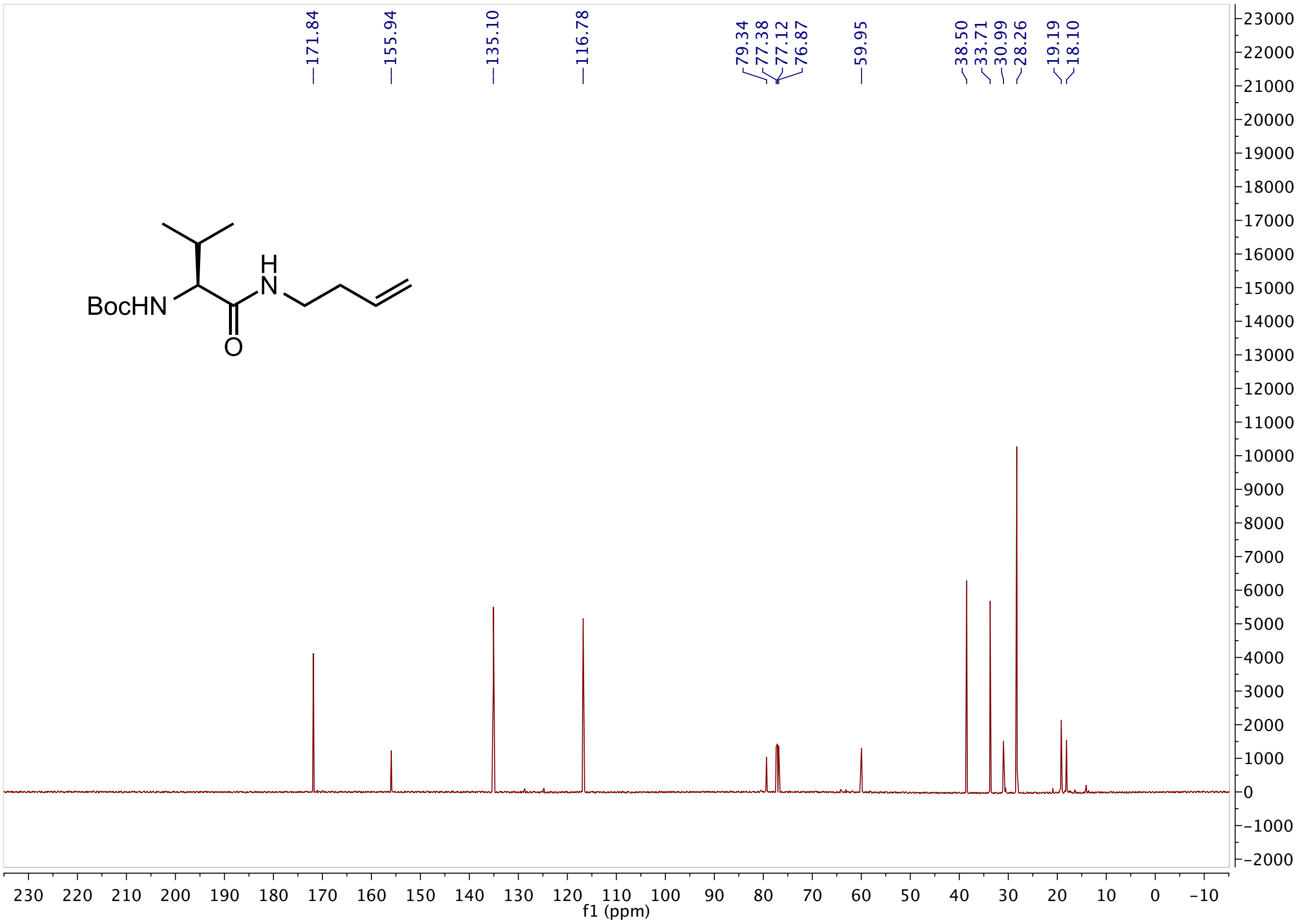
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **3**



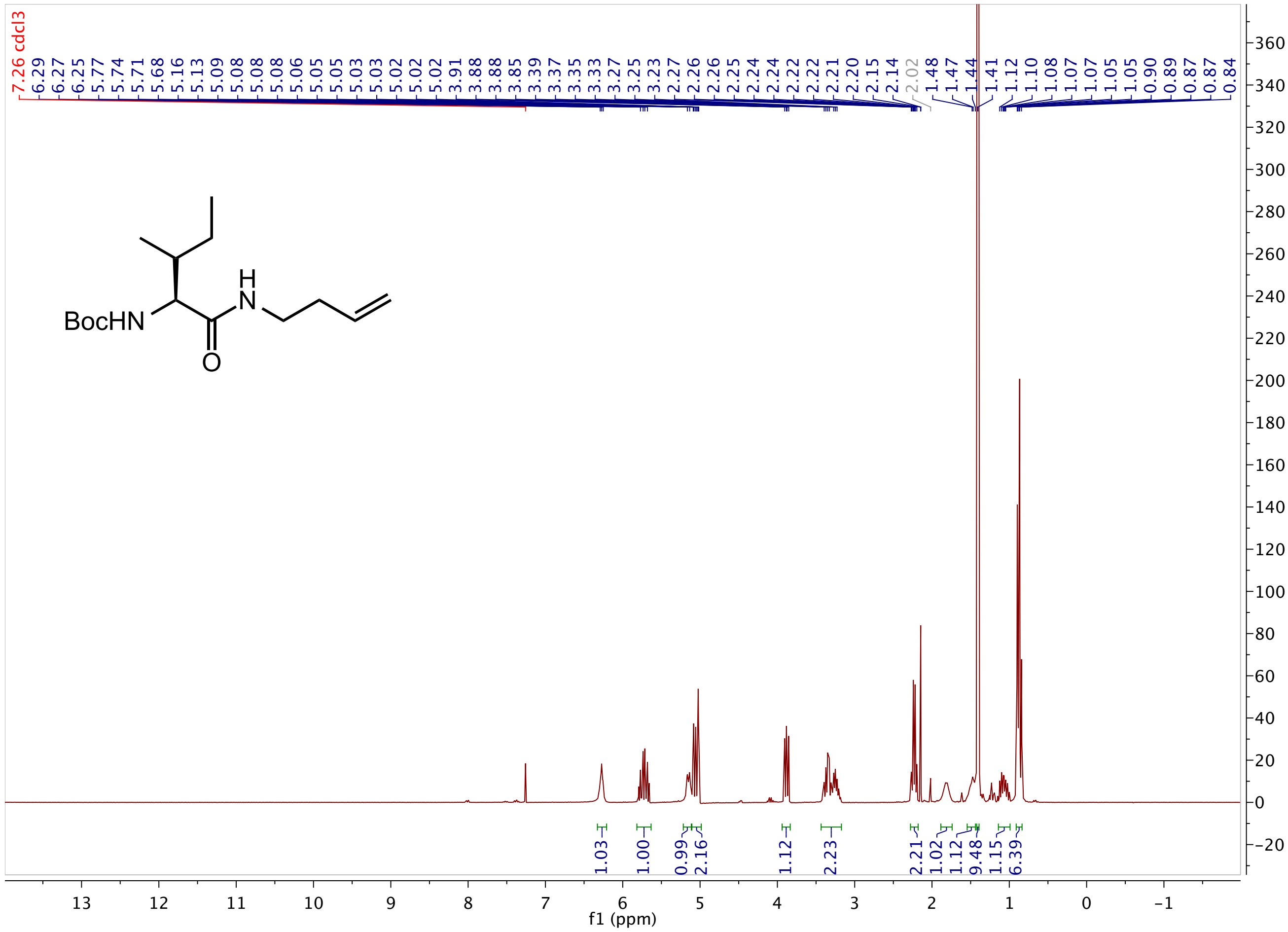
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **5a**



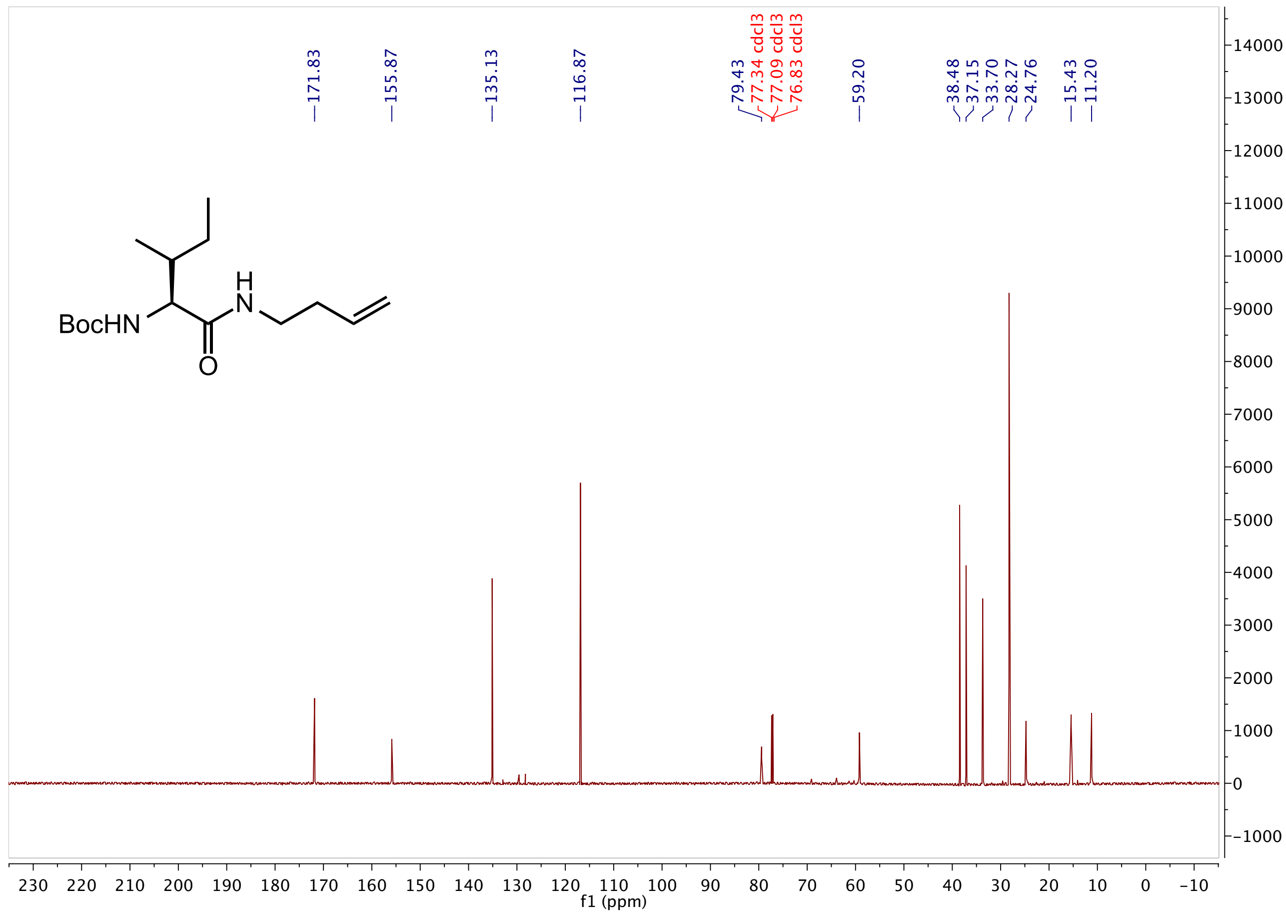
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **5a**



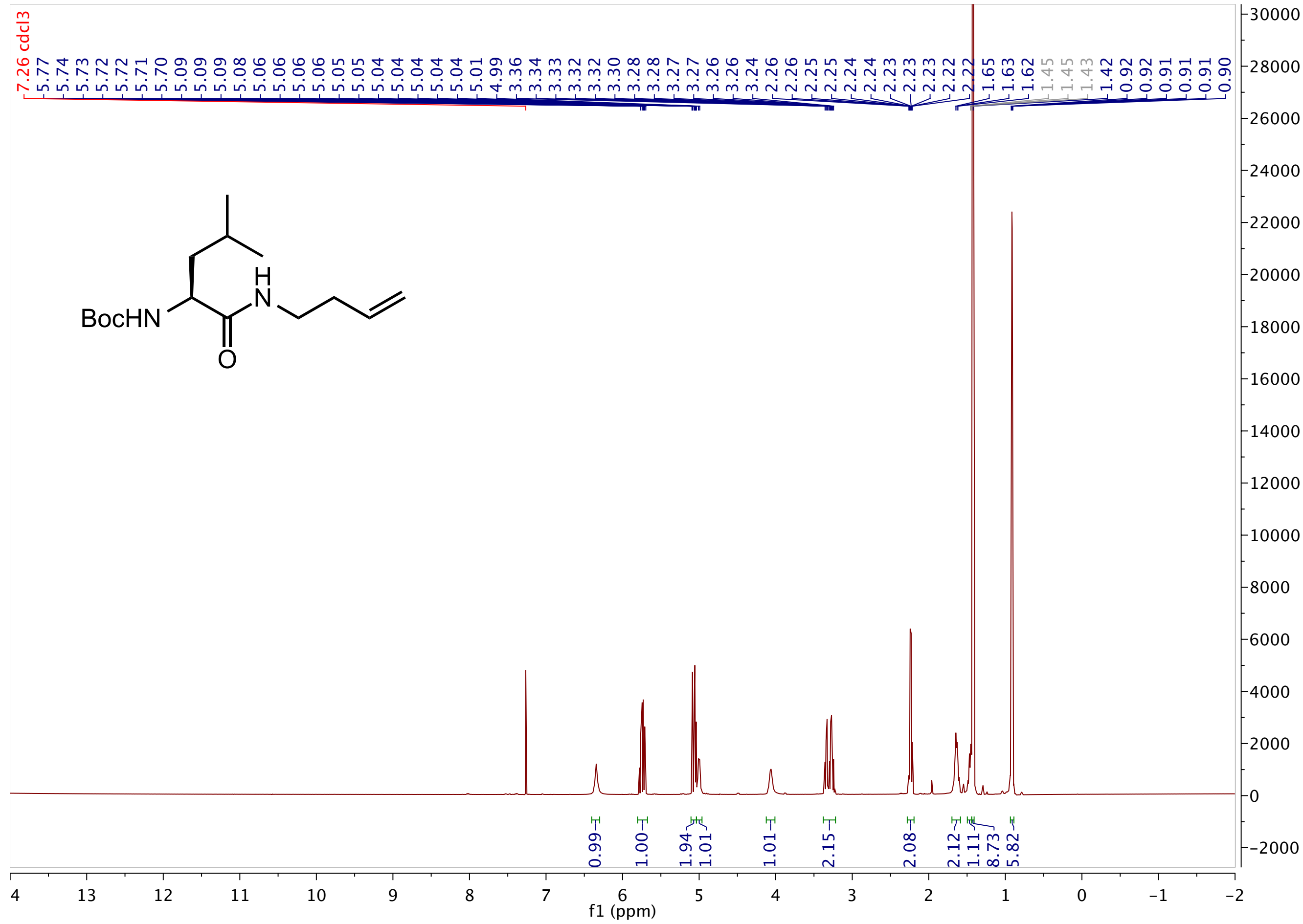
^1H NMR (500 MHz, $CDCl_3$) spectrum of compound **5b**



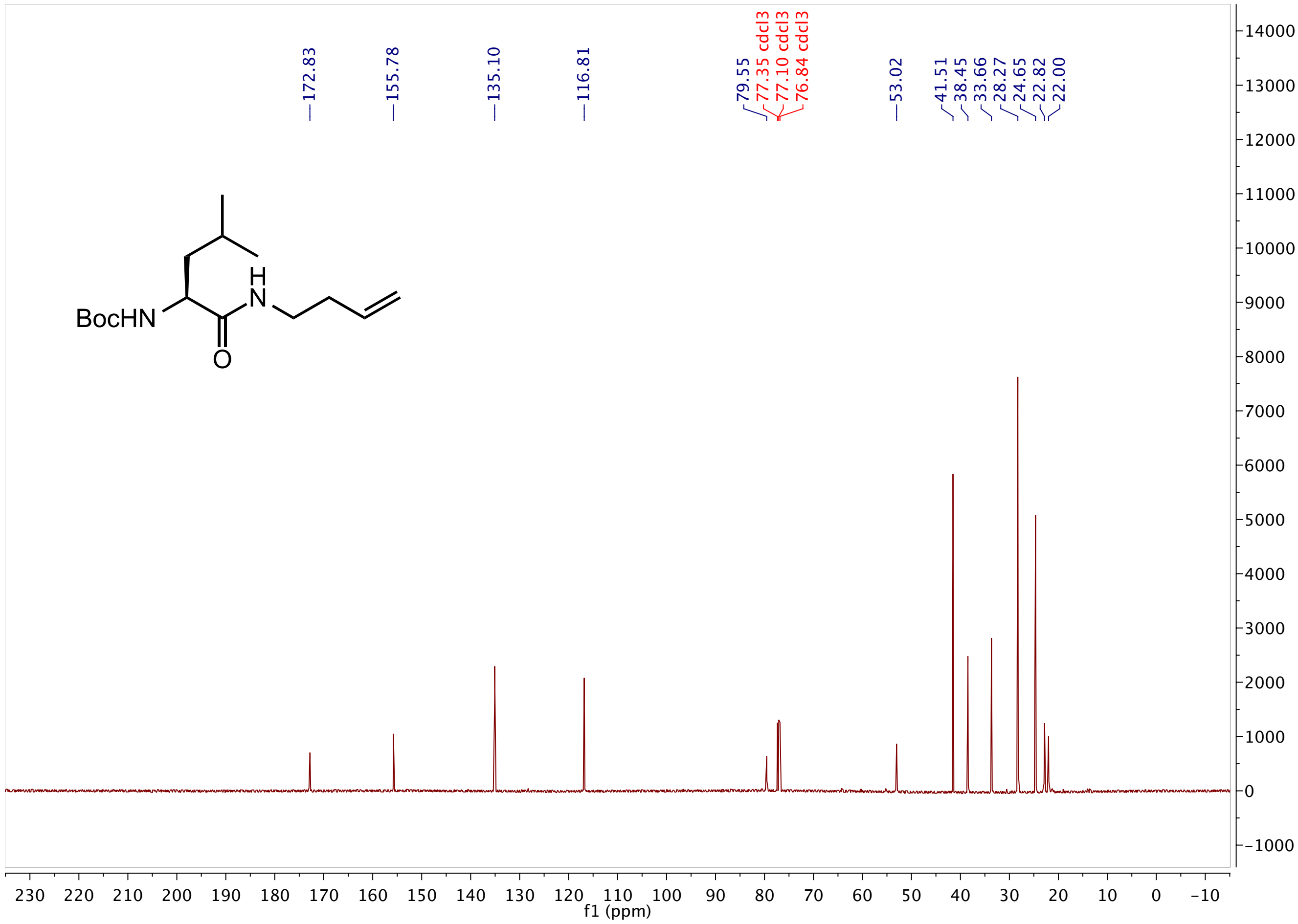
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **5b**



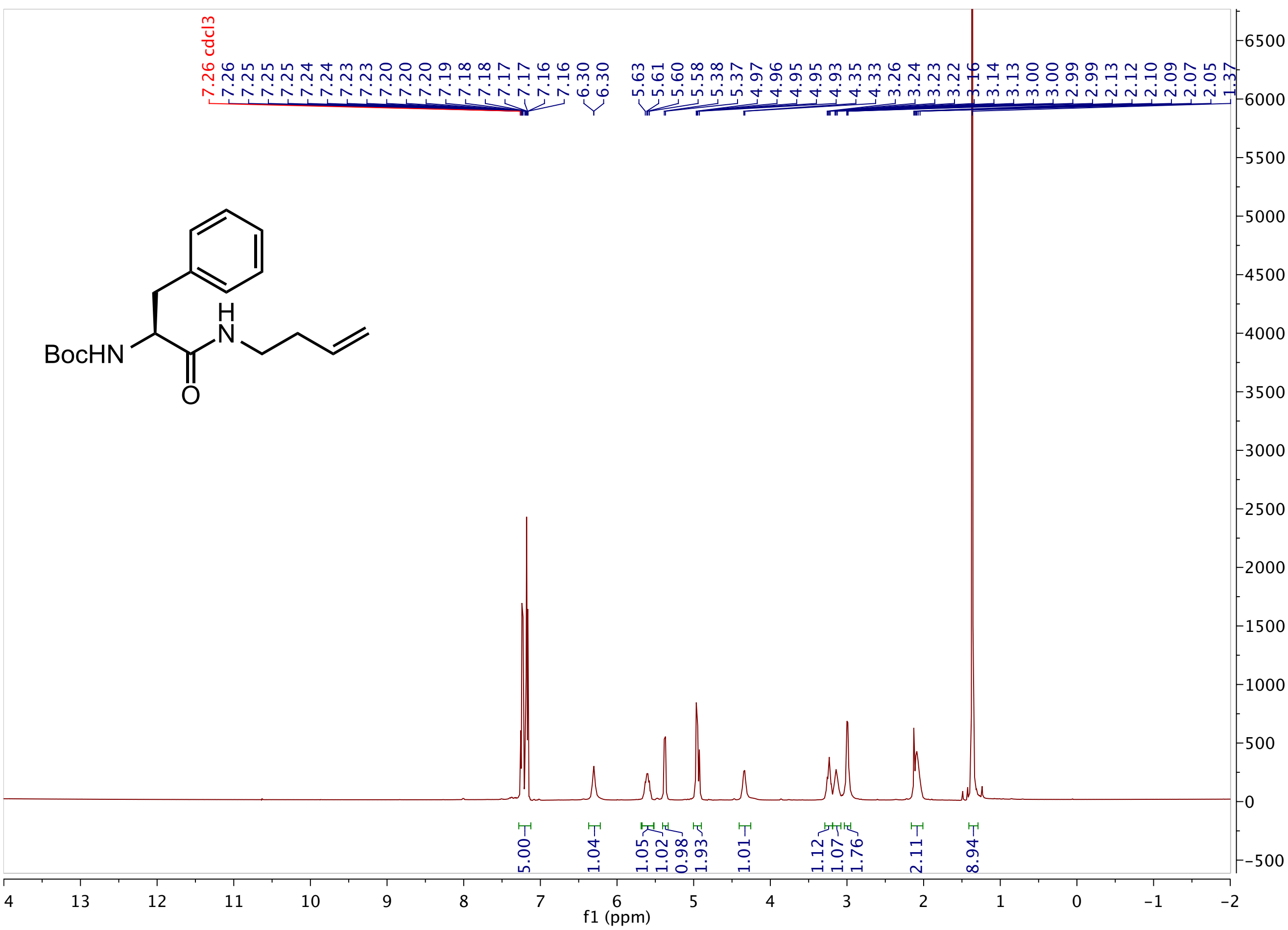
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **5c**



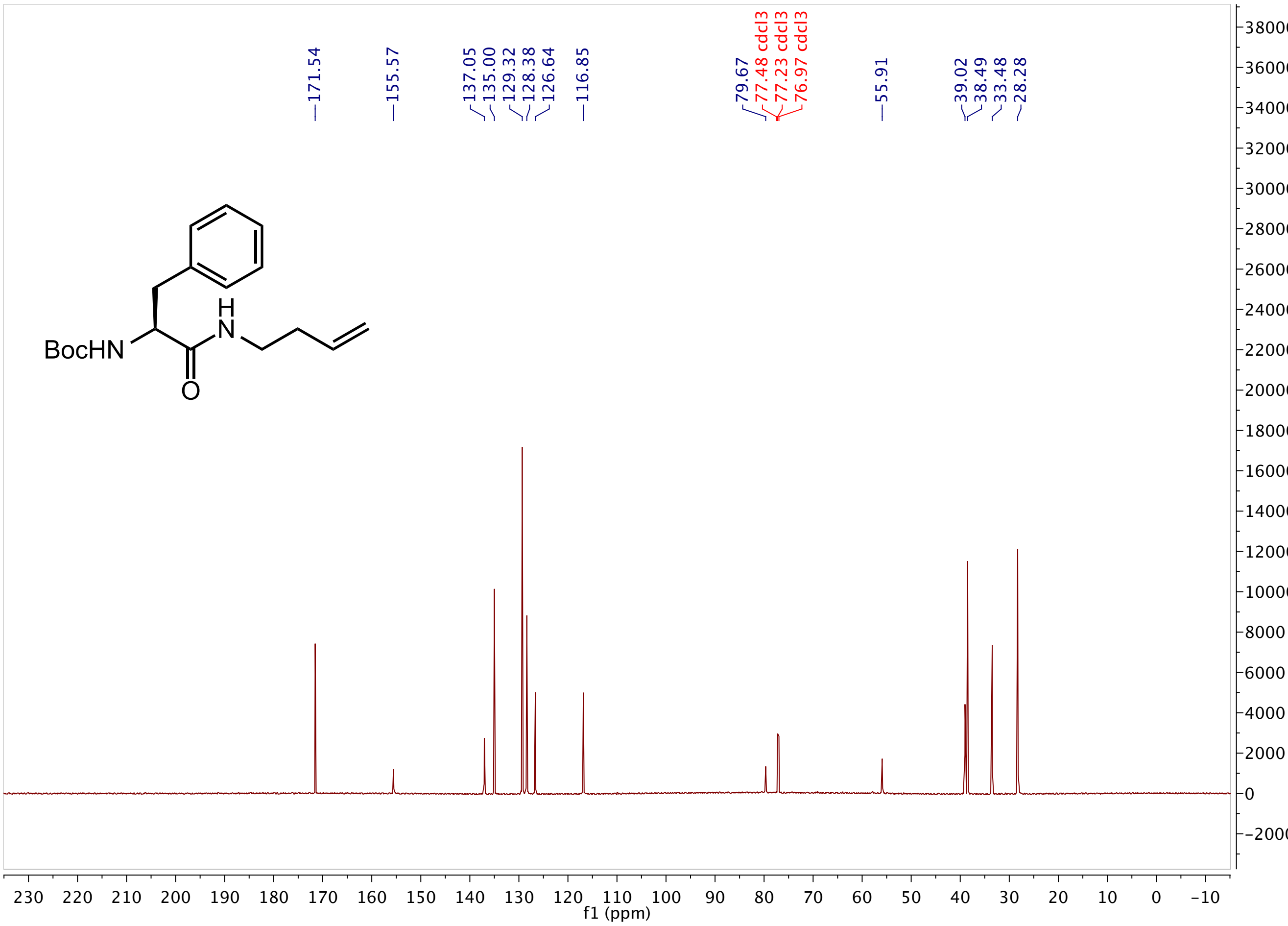
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **5c**



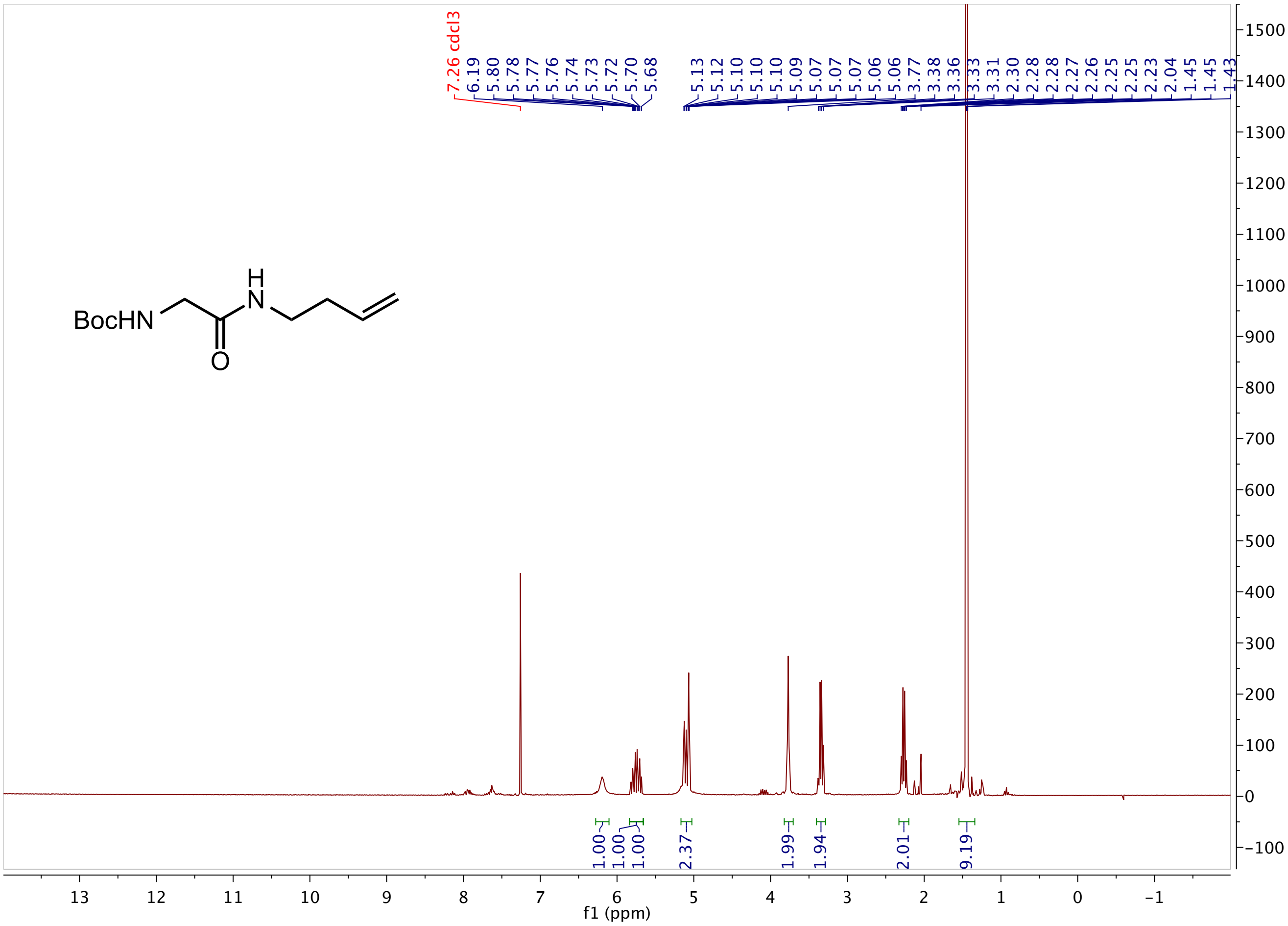
^1H NMR (500 MHz, $CDCl_3$) spectrum of compound **5d**



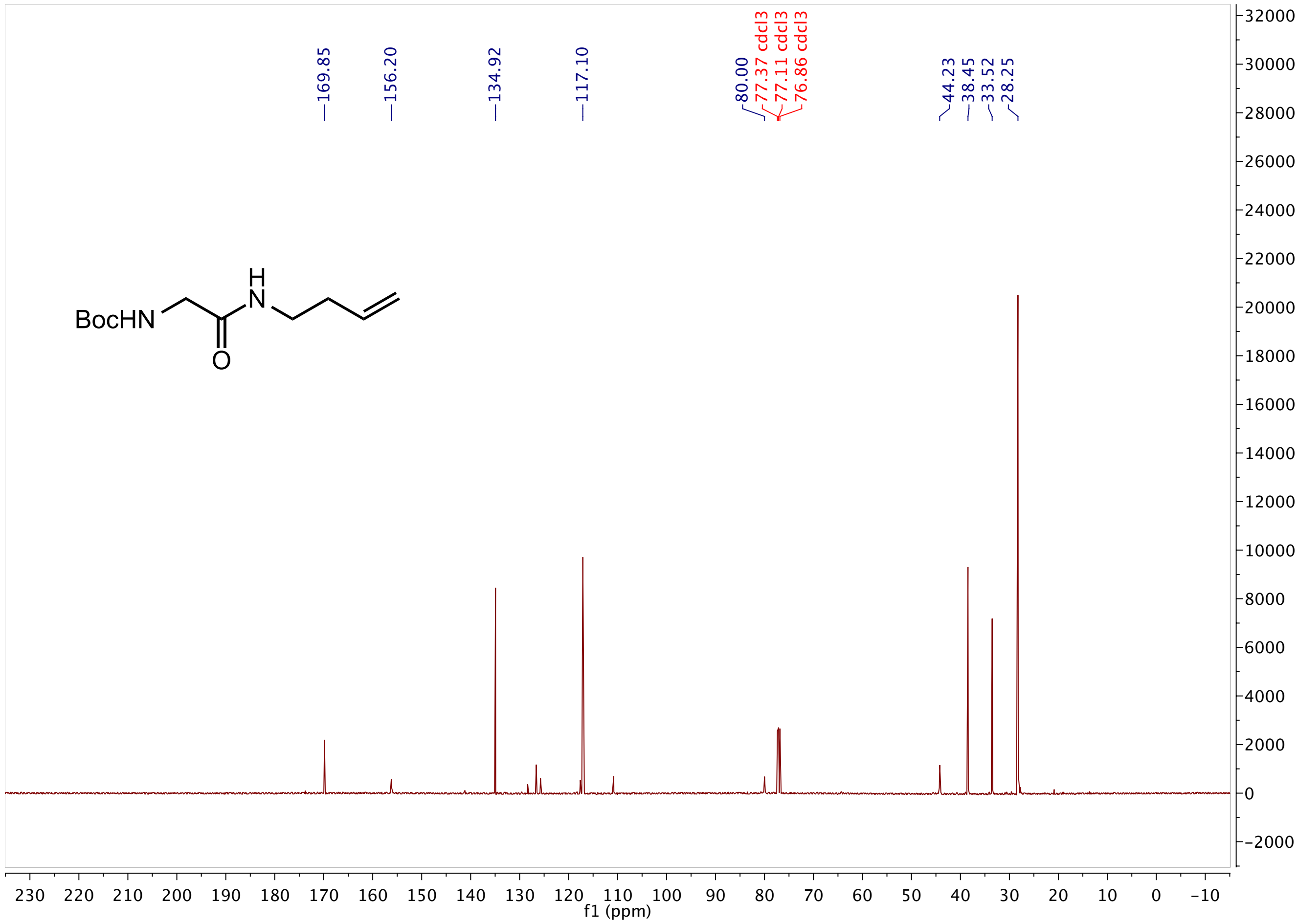
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **5d**



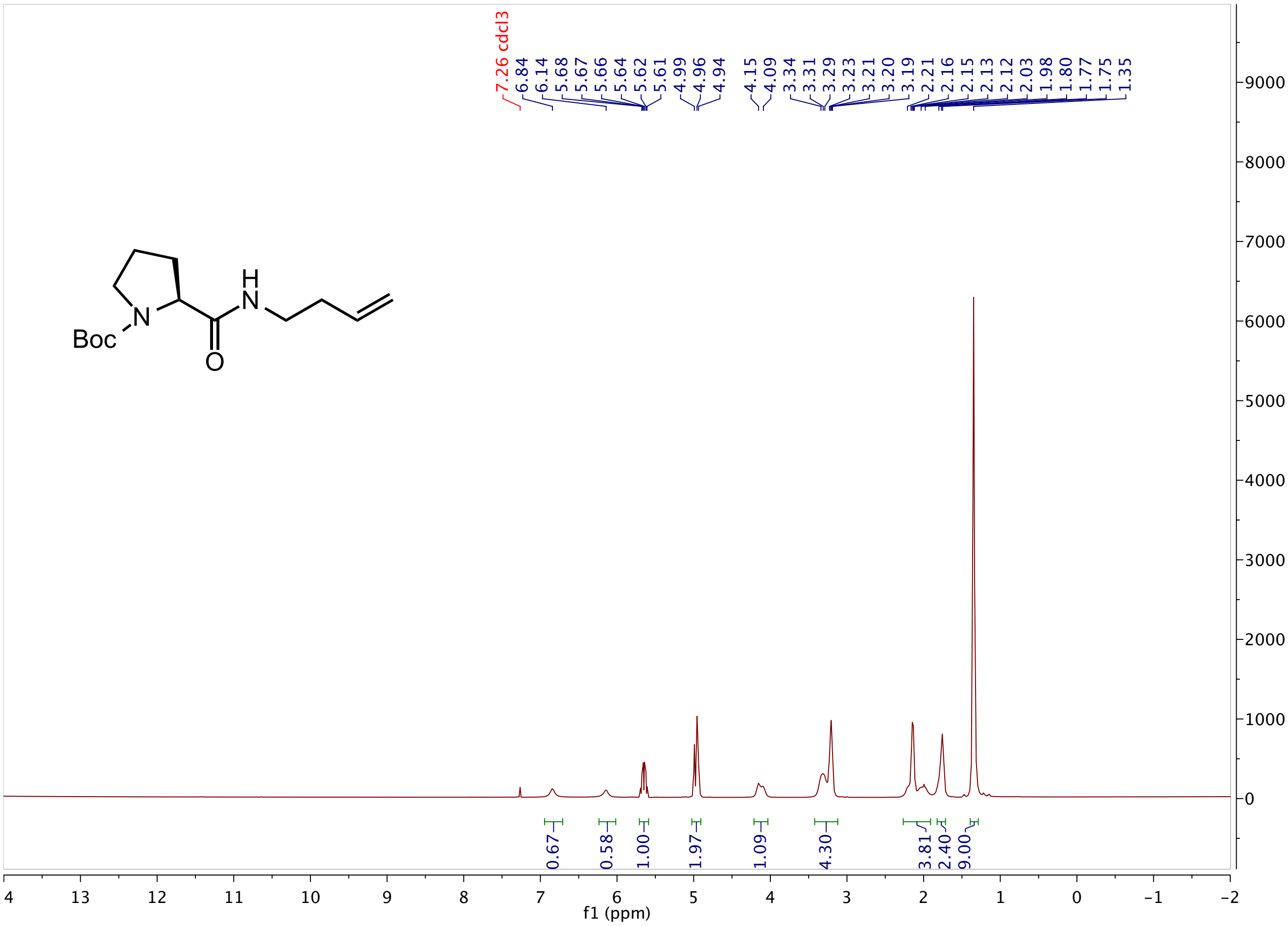
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **5e**



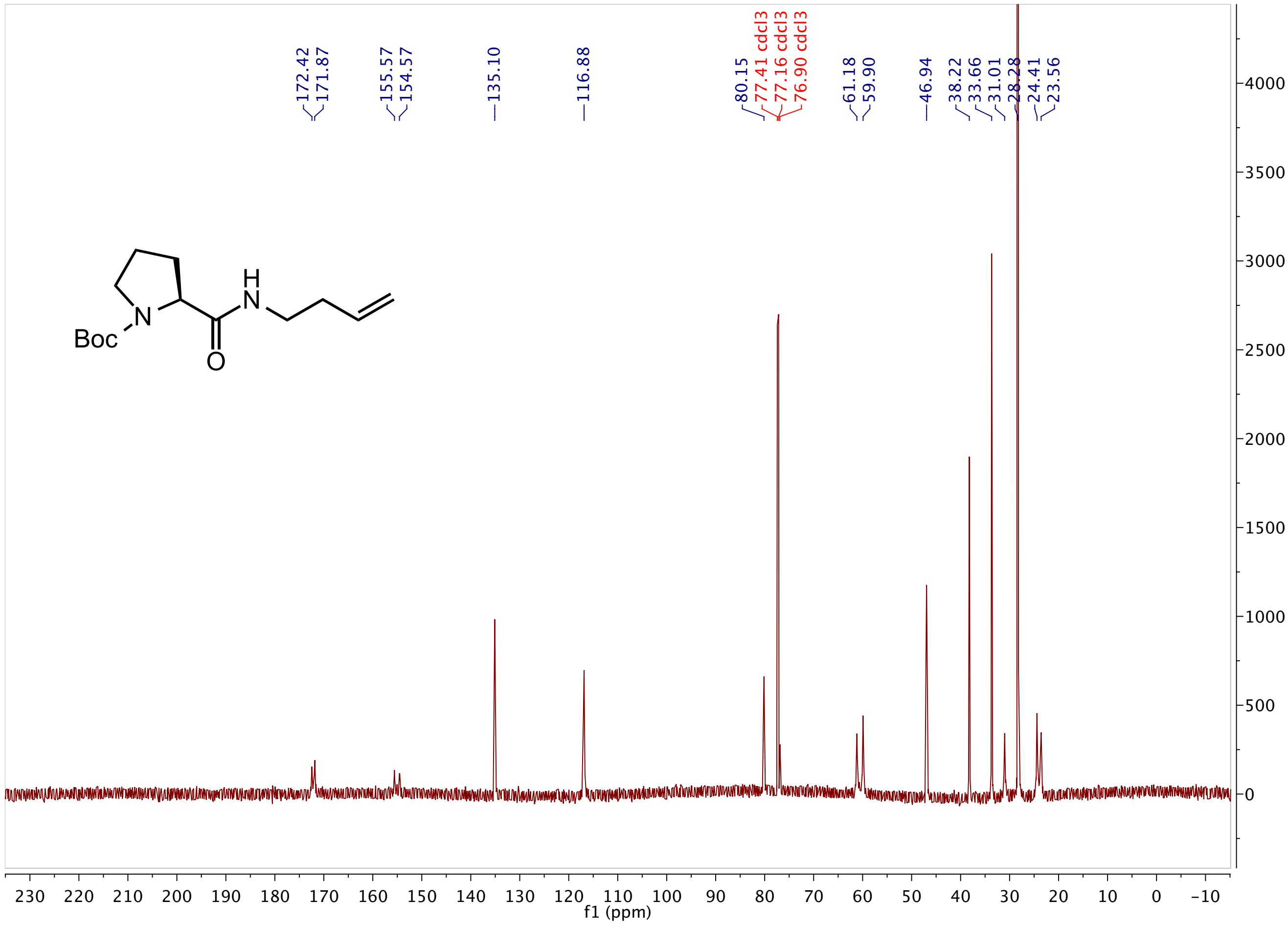
[13]C NMR (126 MHz, CDCl$_3$) spectrum of compound **5e**



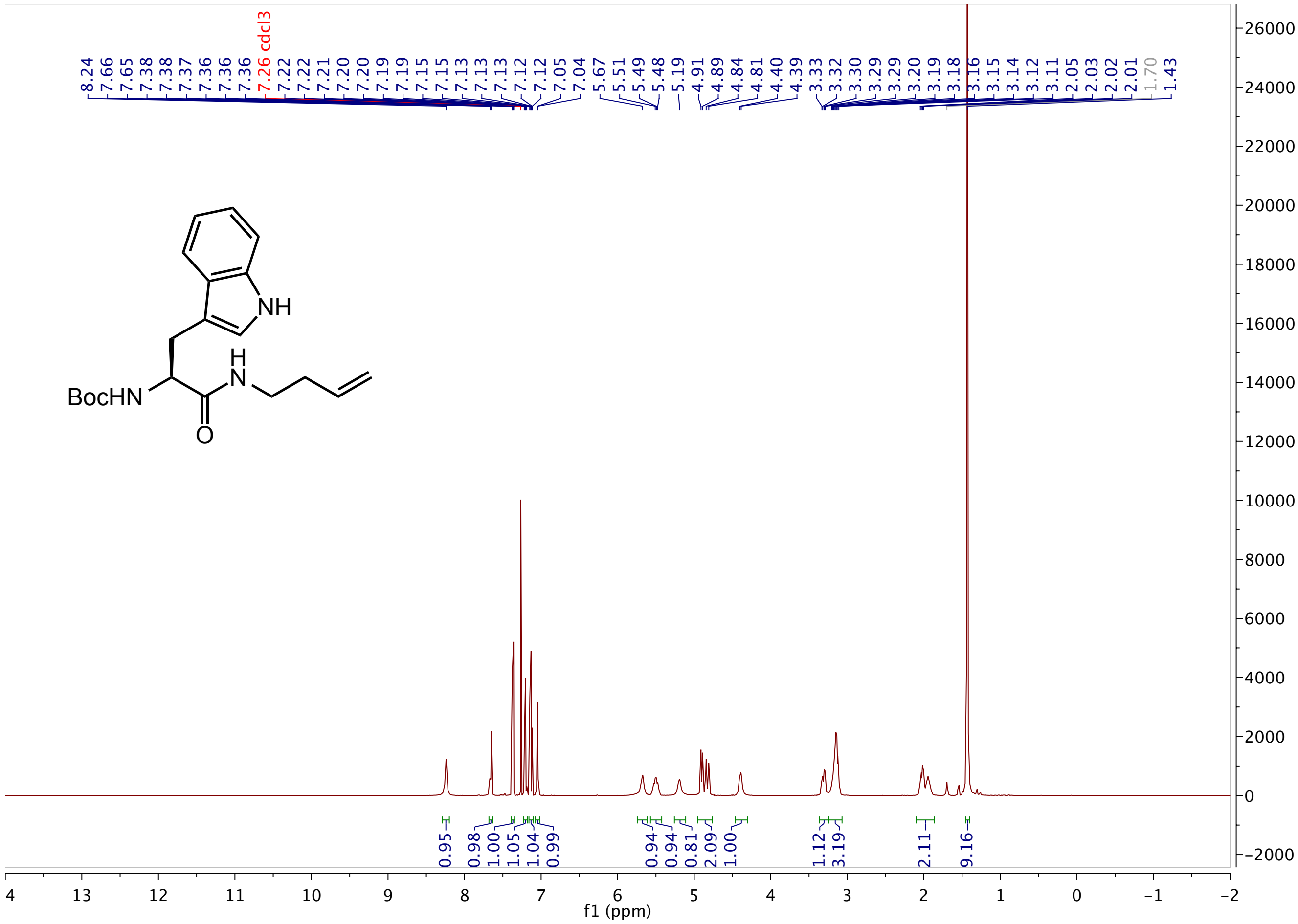
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **5f**



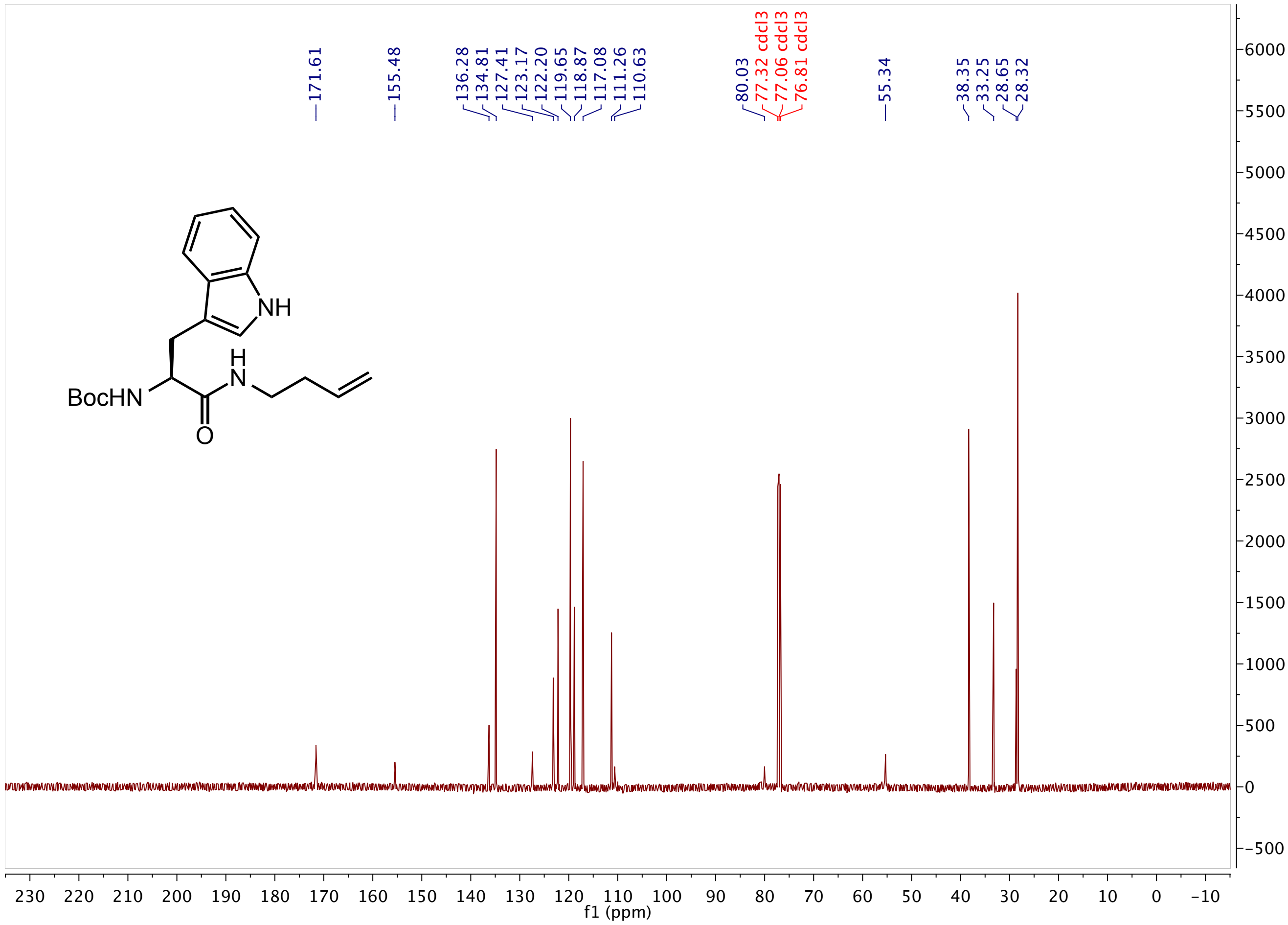
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **5f**



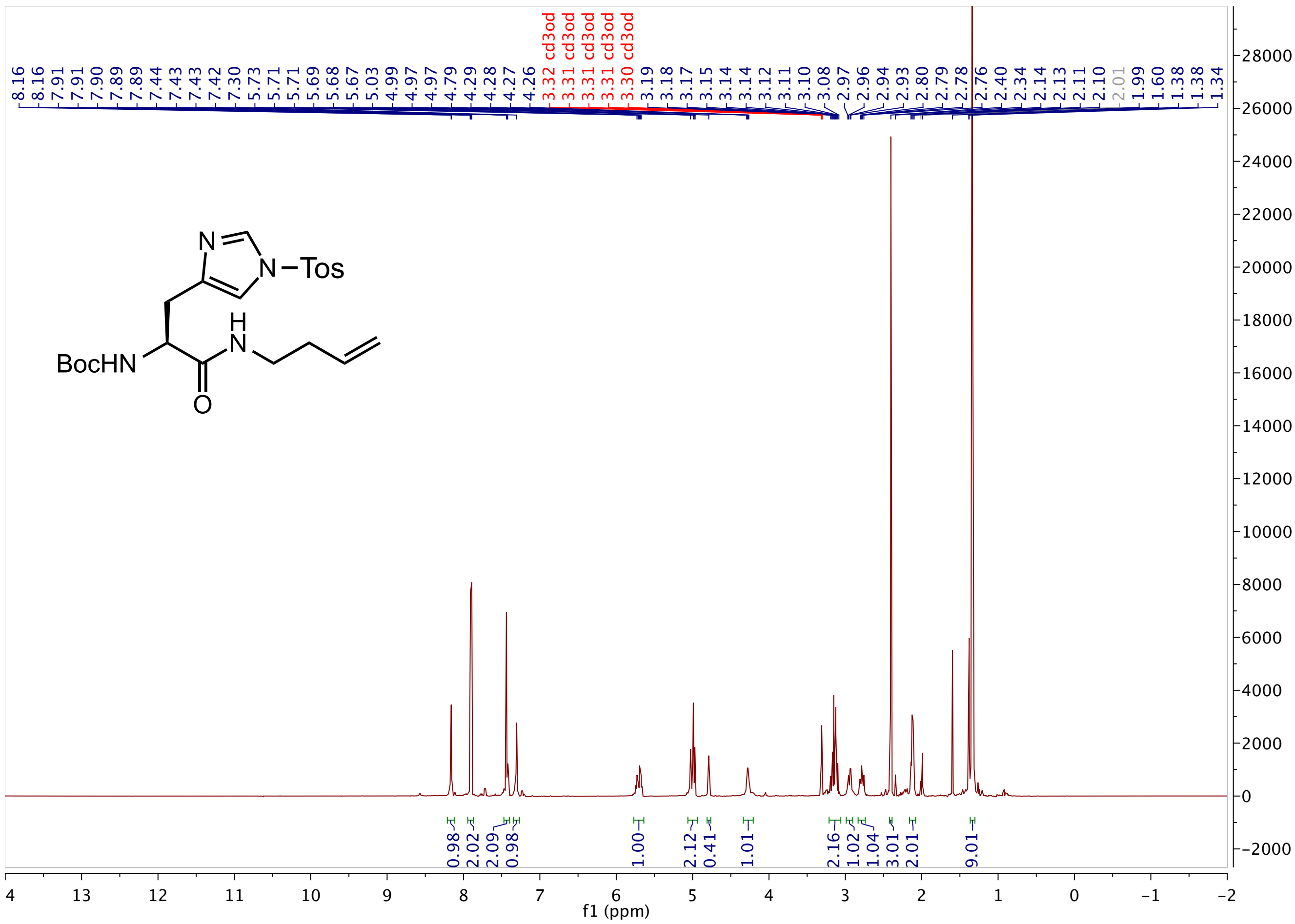
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **5g**



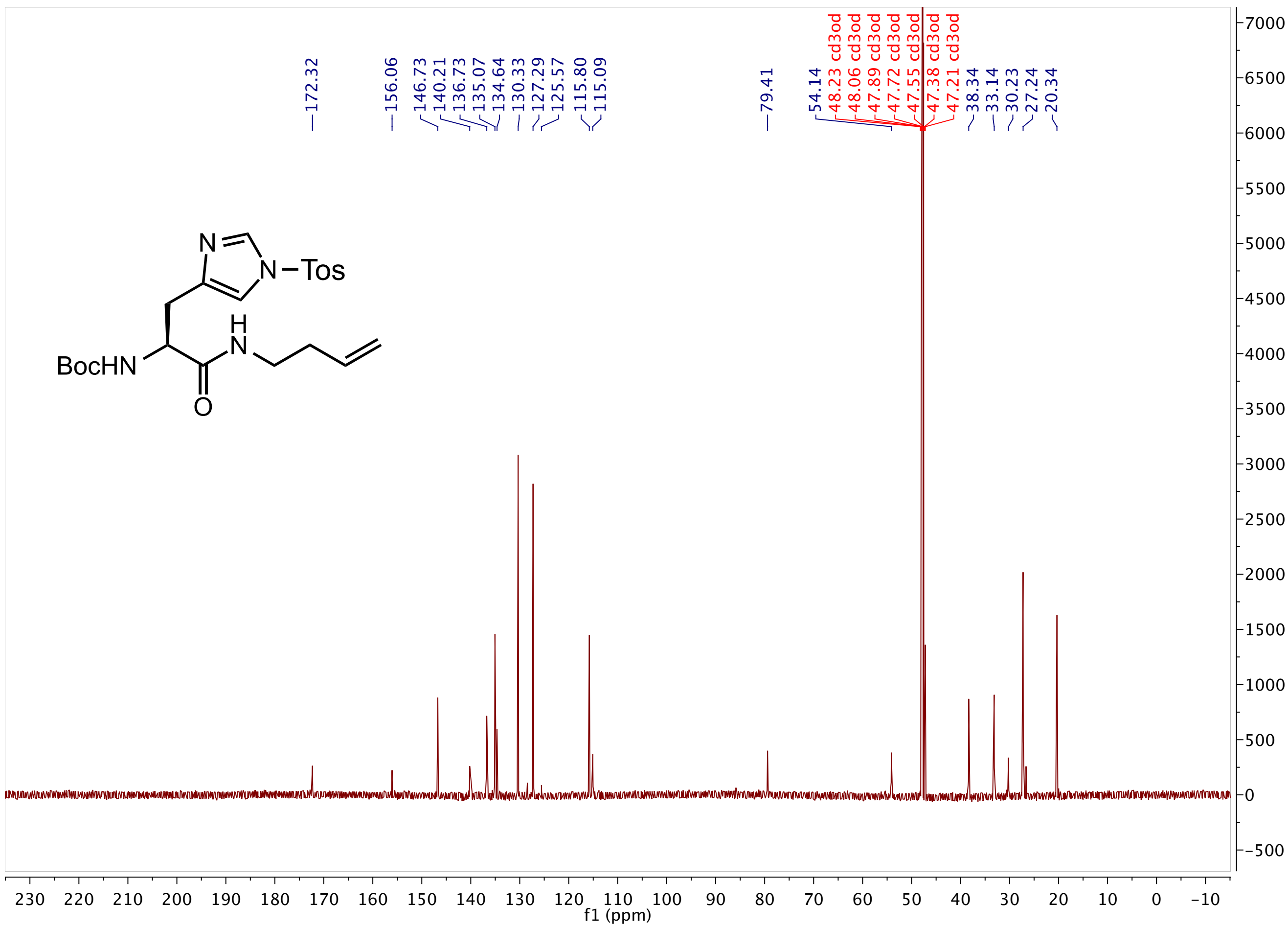
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **5g**



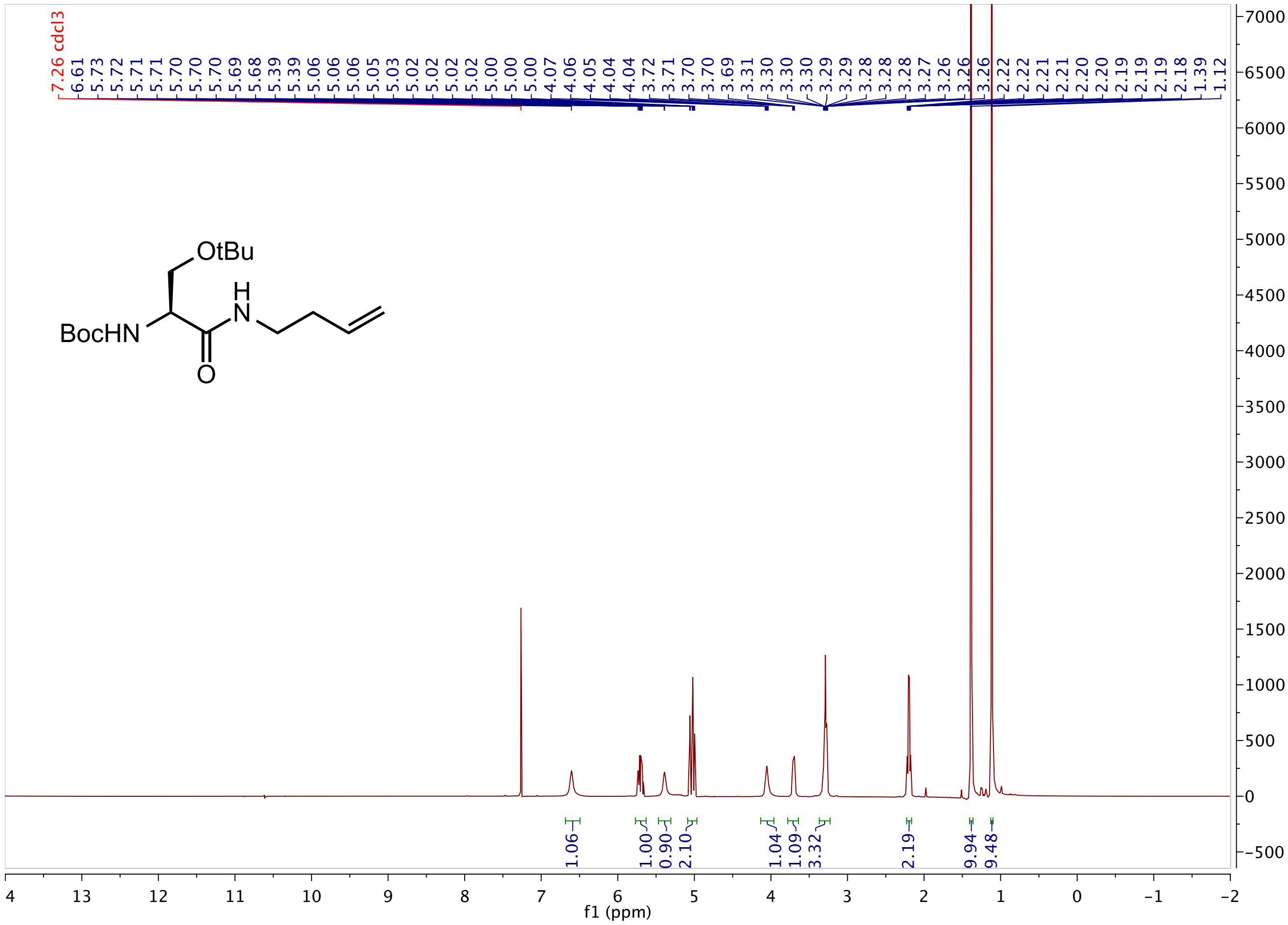
[1]H NMR (500 MHz, CD_3OD) spectrum of compound **5h**



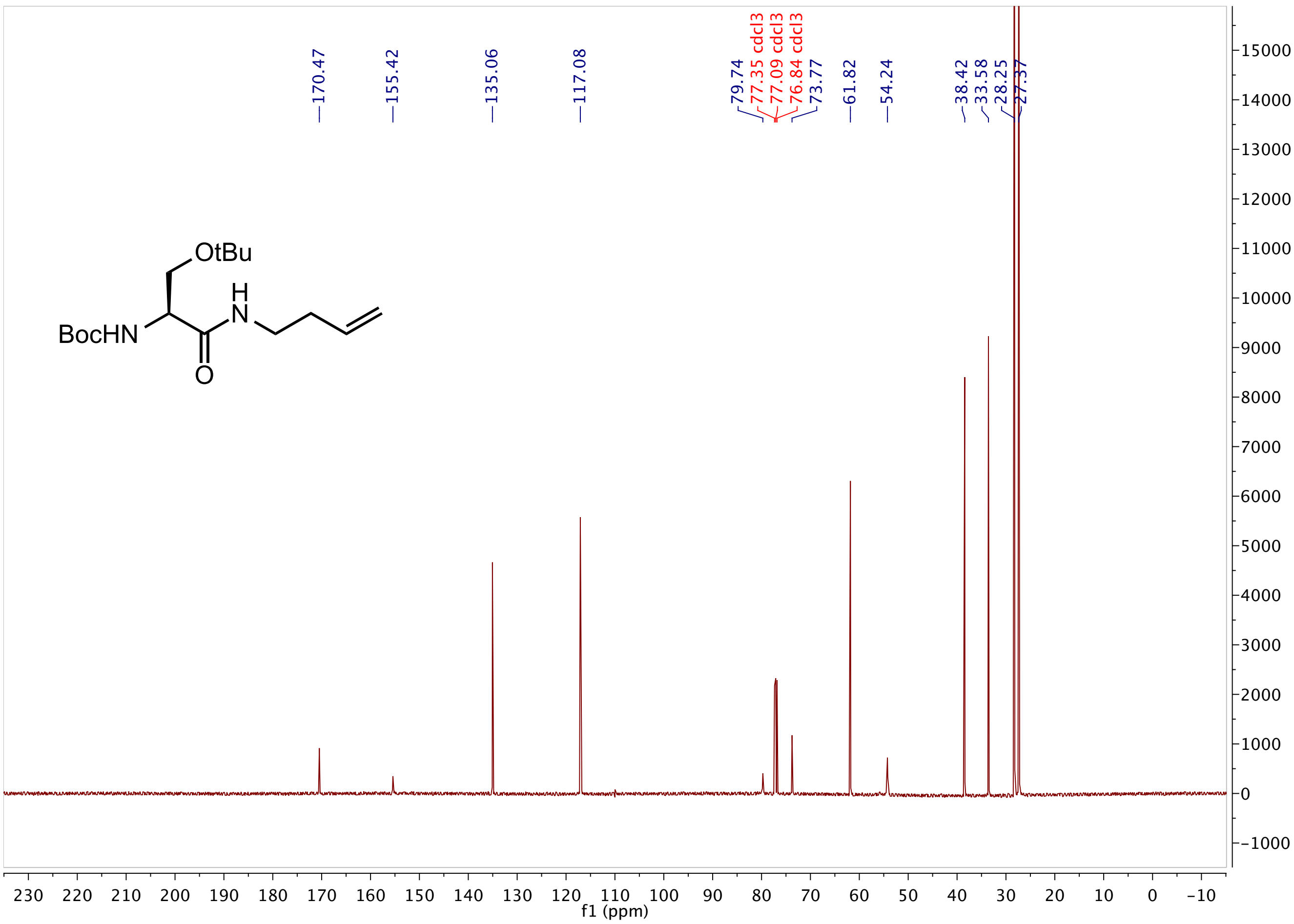
^{13}C NMR (126 MHz, CD_3OD) spectrum of compound **5h**



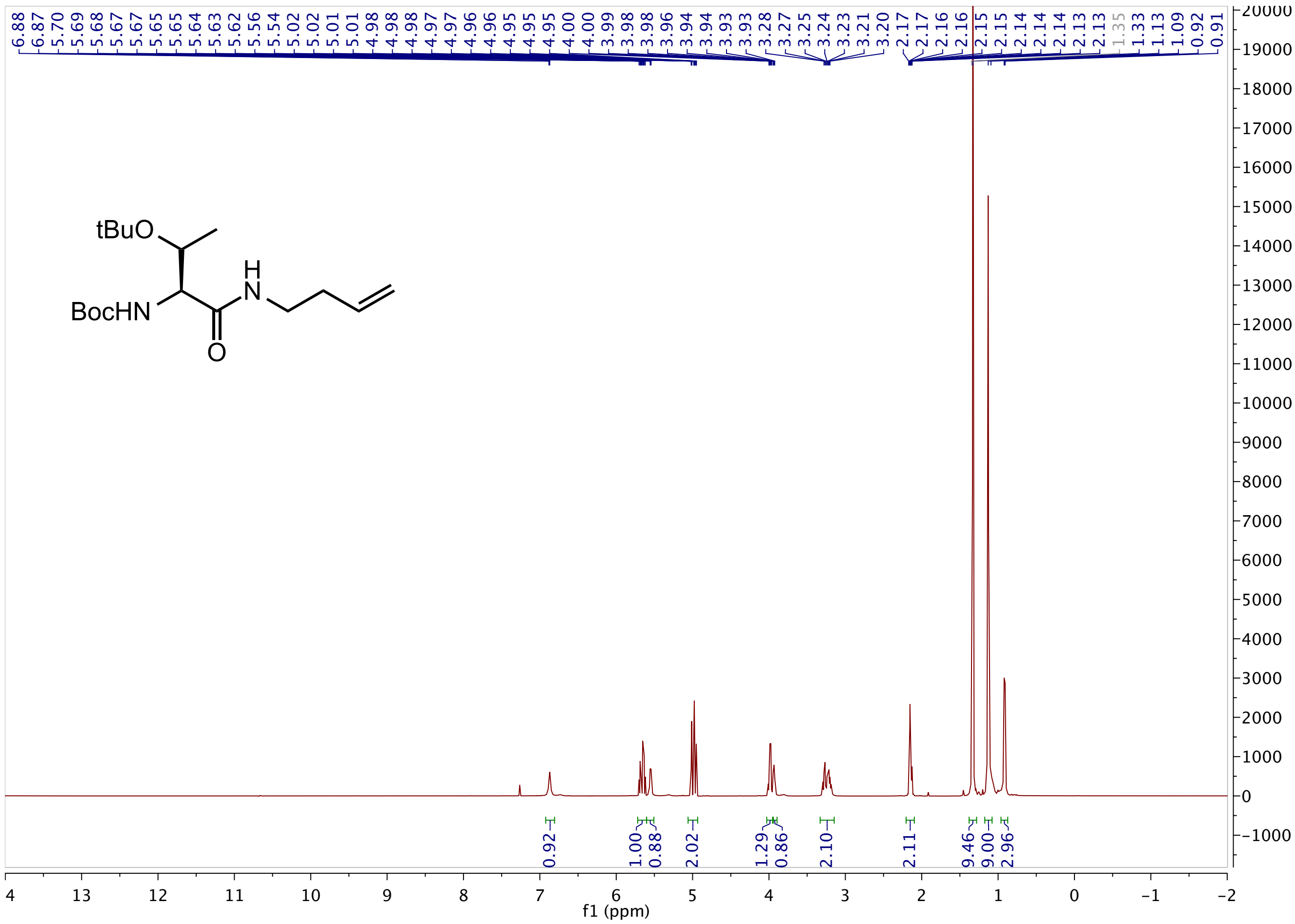
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **5i**



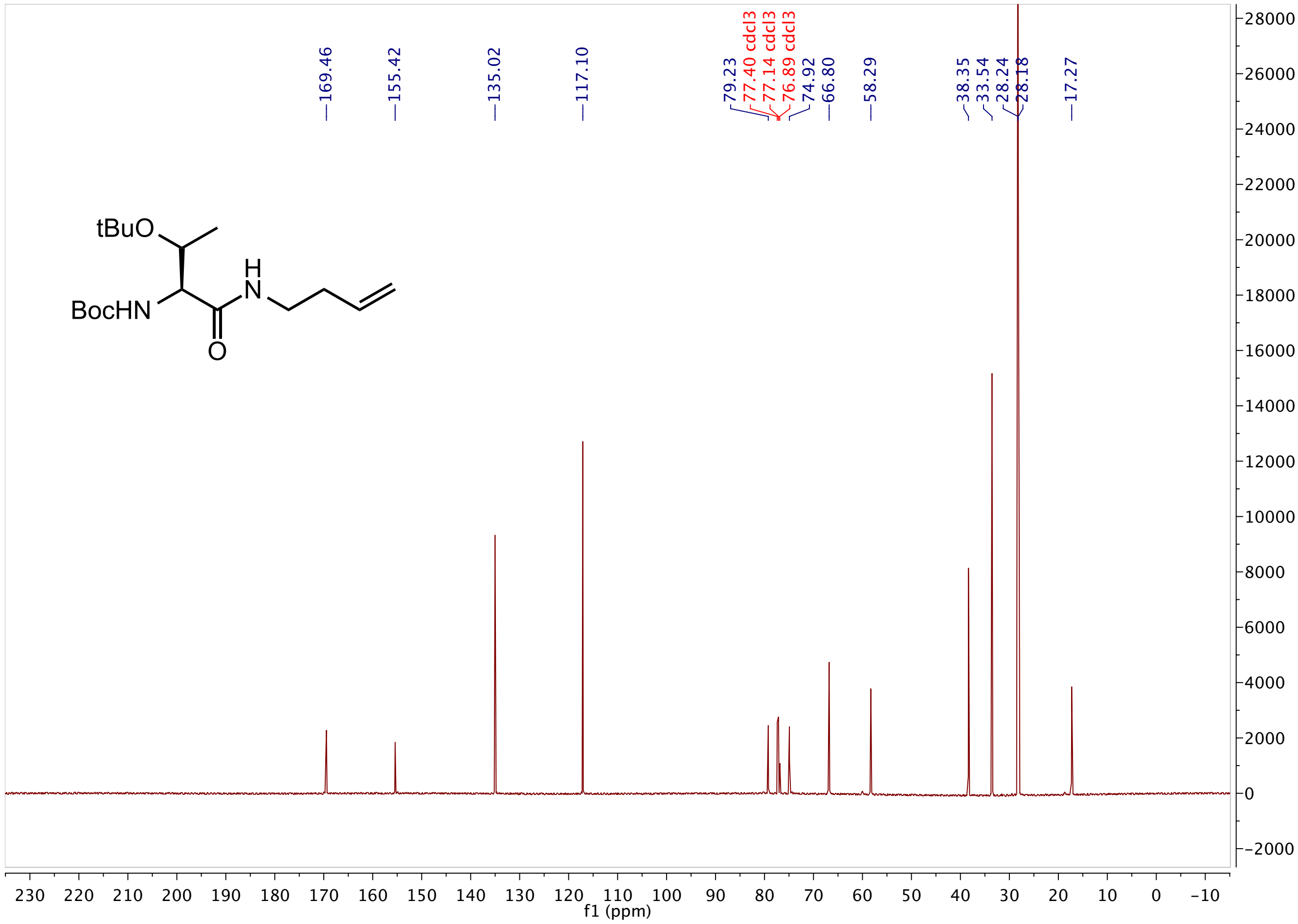
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **5i**



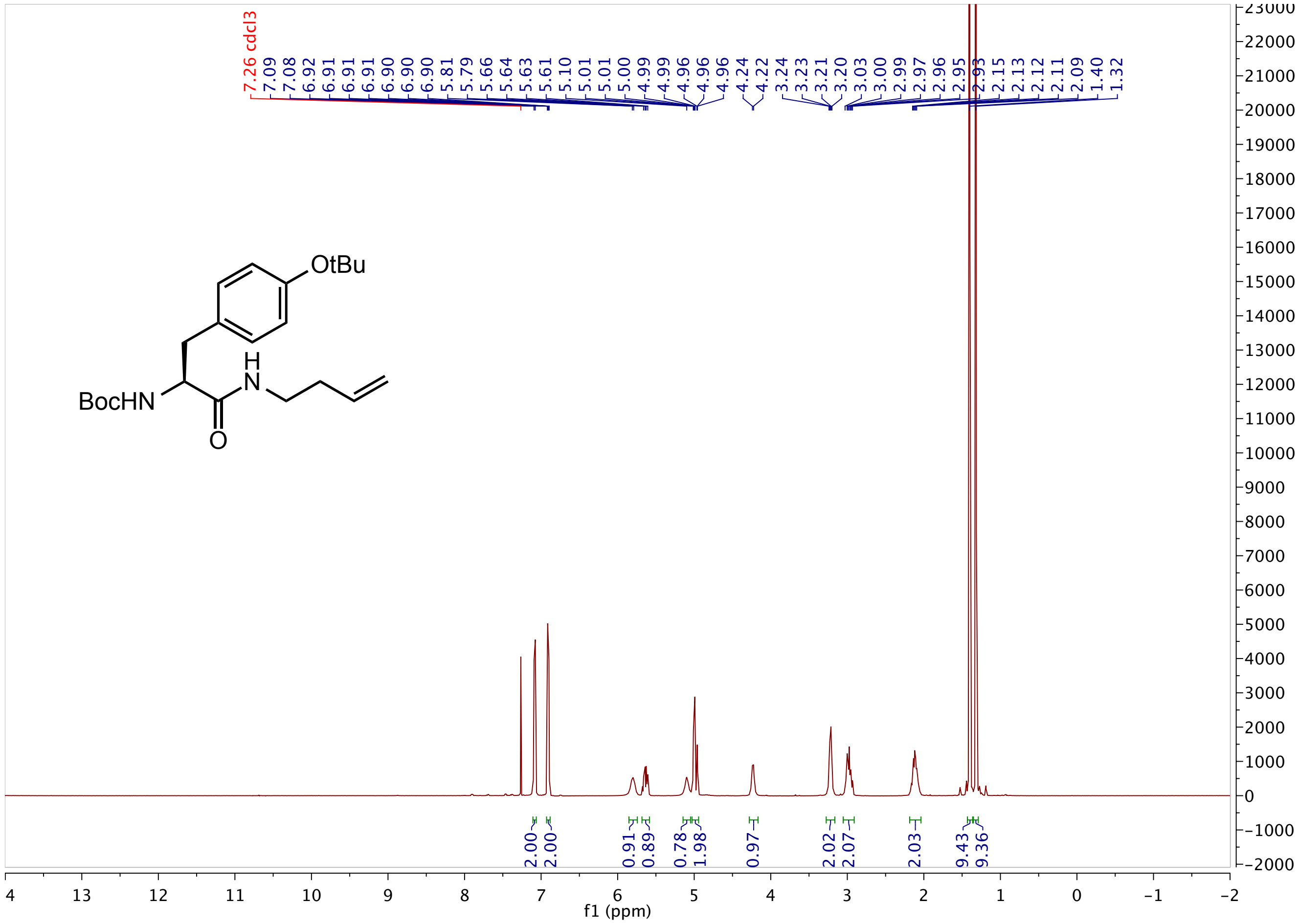
[1]H NMR (500 MHz, $CDCl_3$) spectrum of compound **5j**



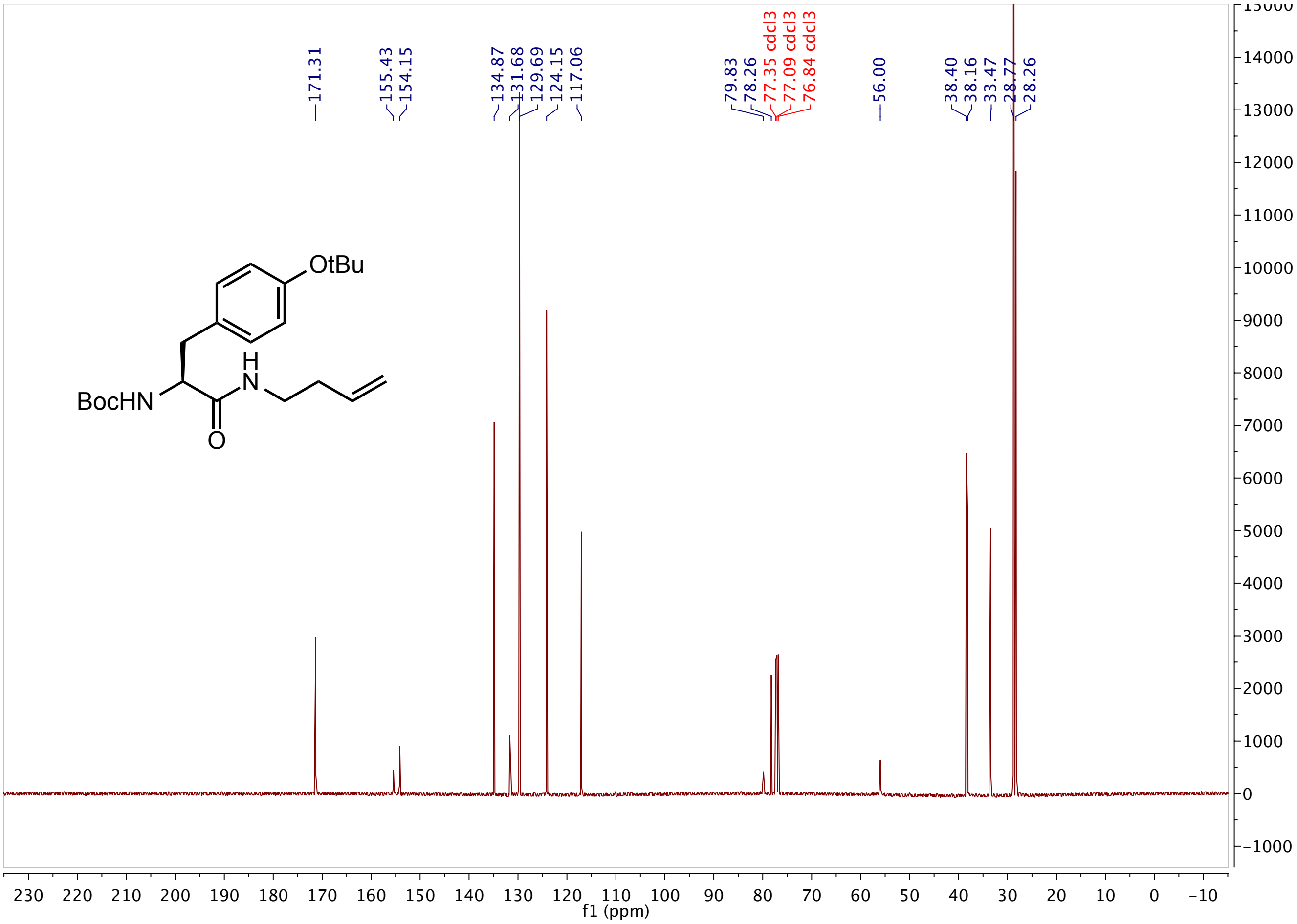
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **5j**



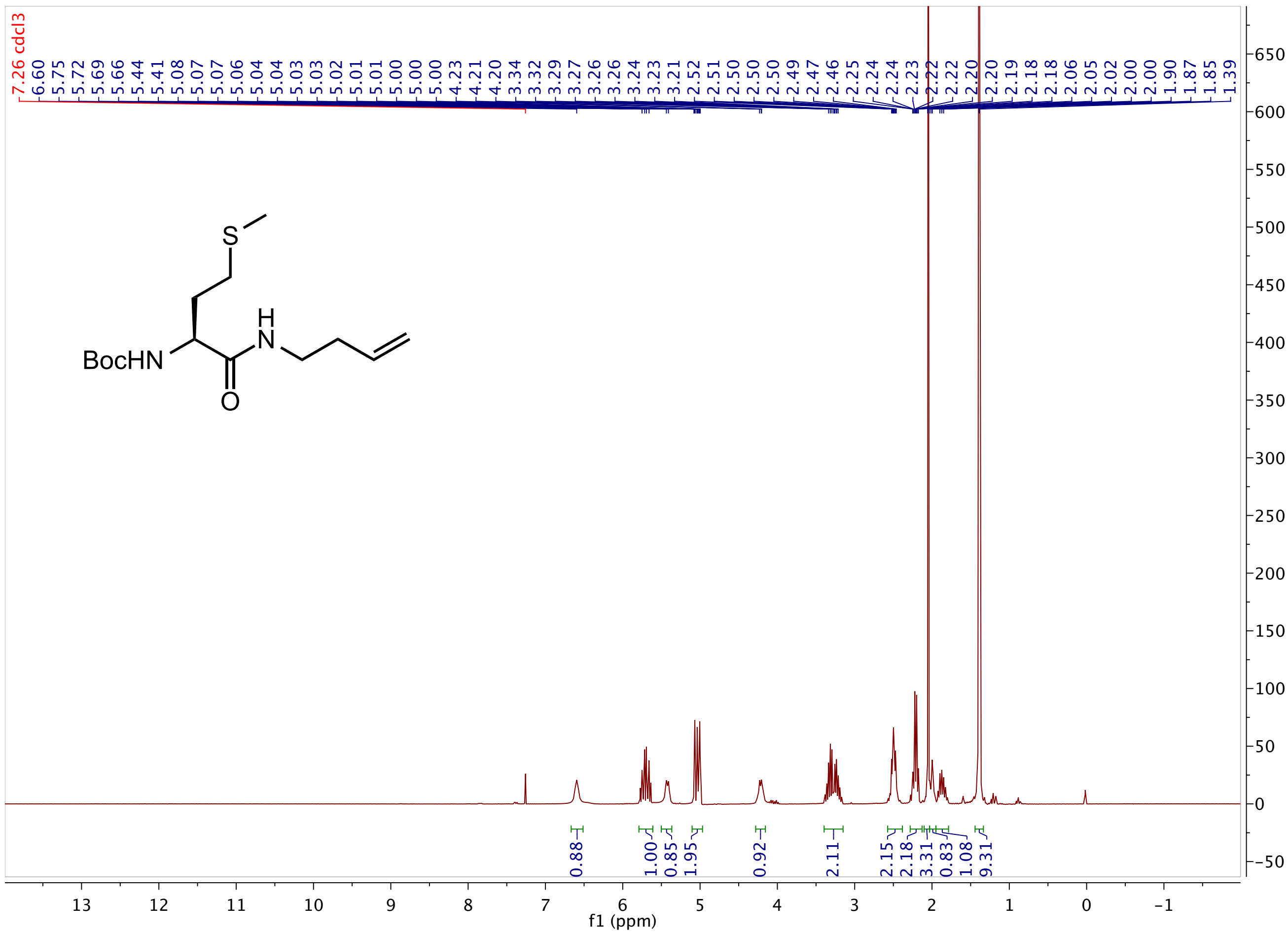
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **5k**



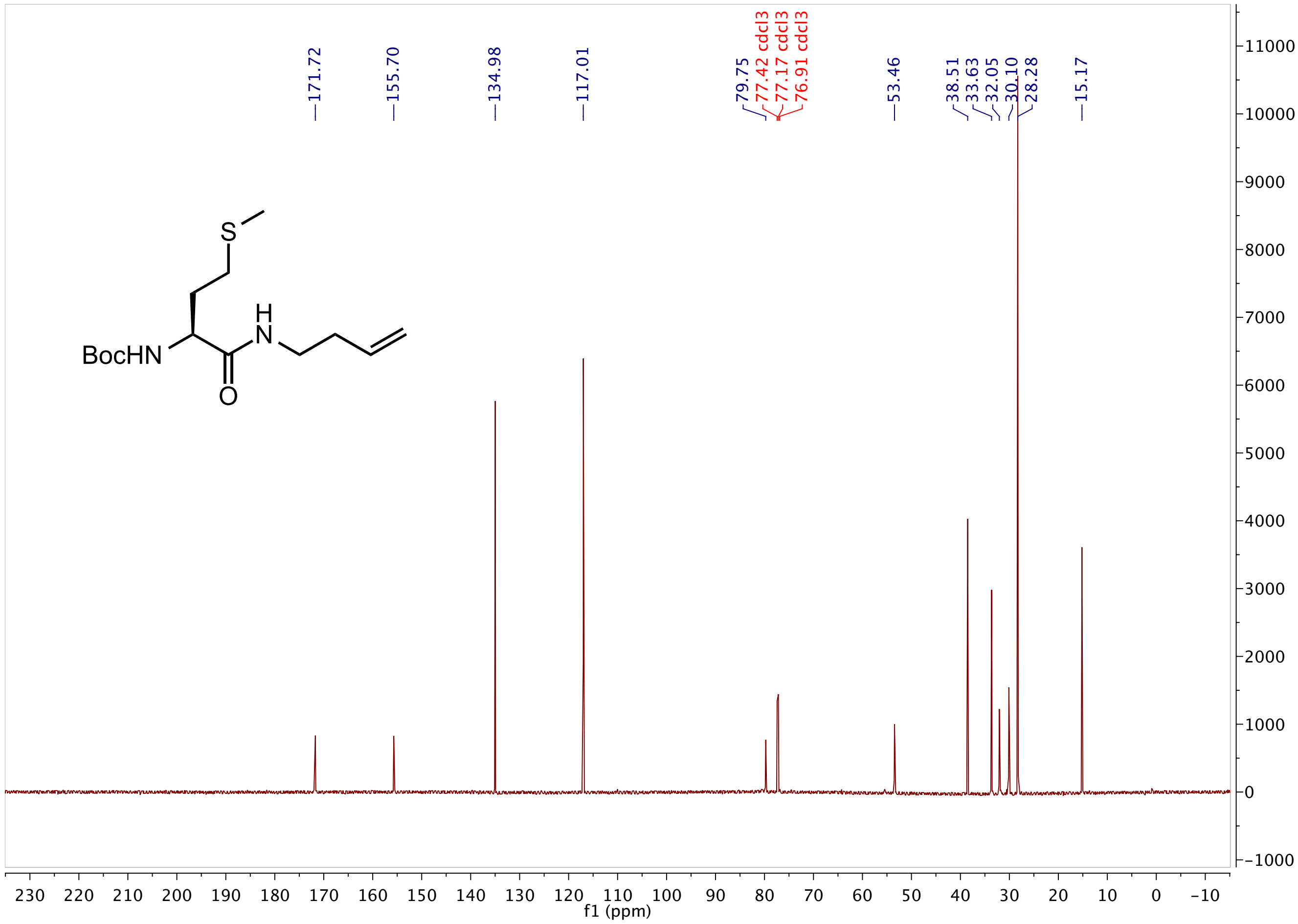
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **5k**



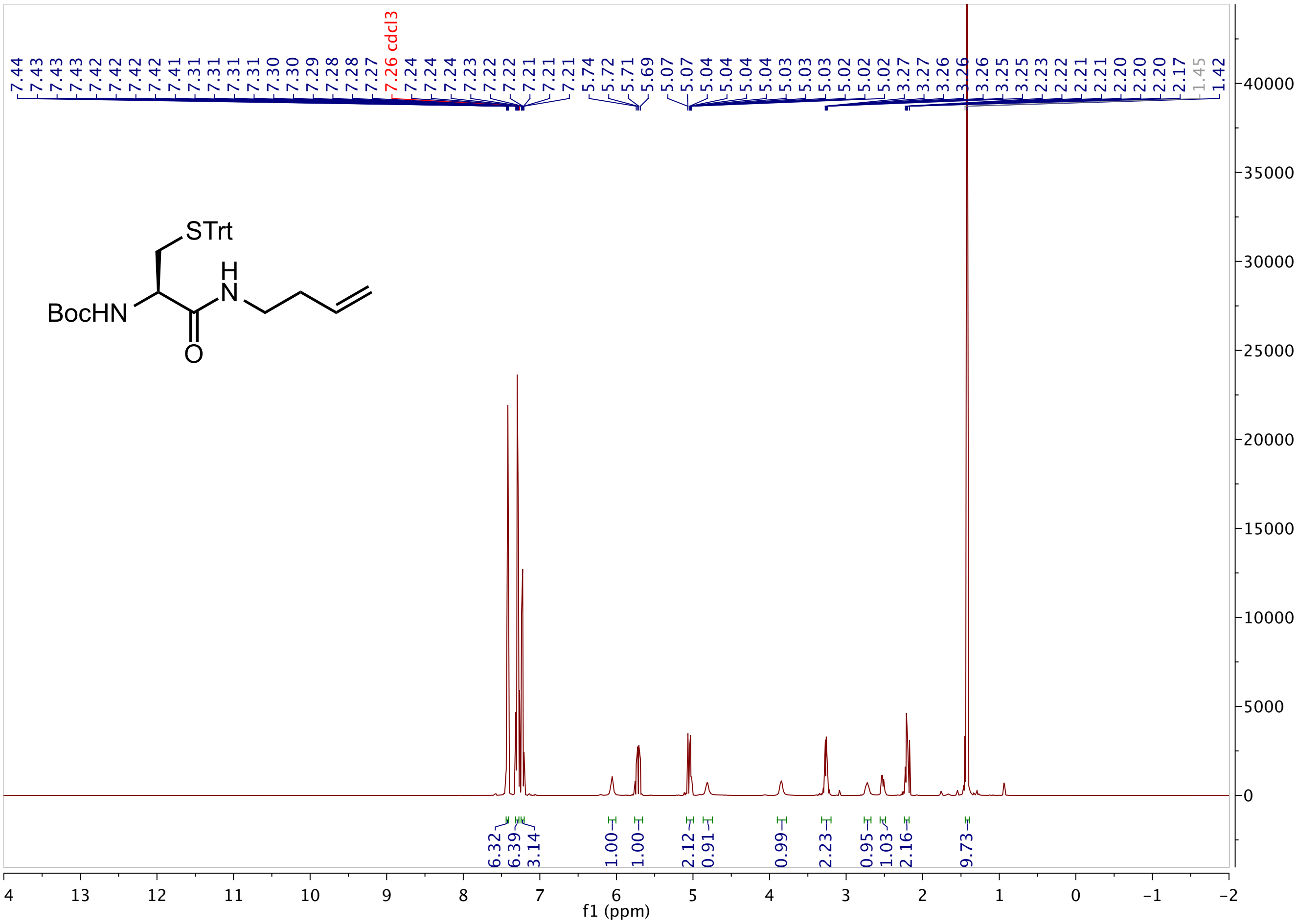
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **5l**



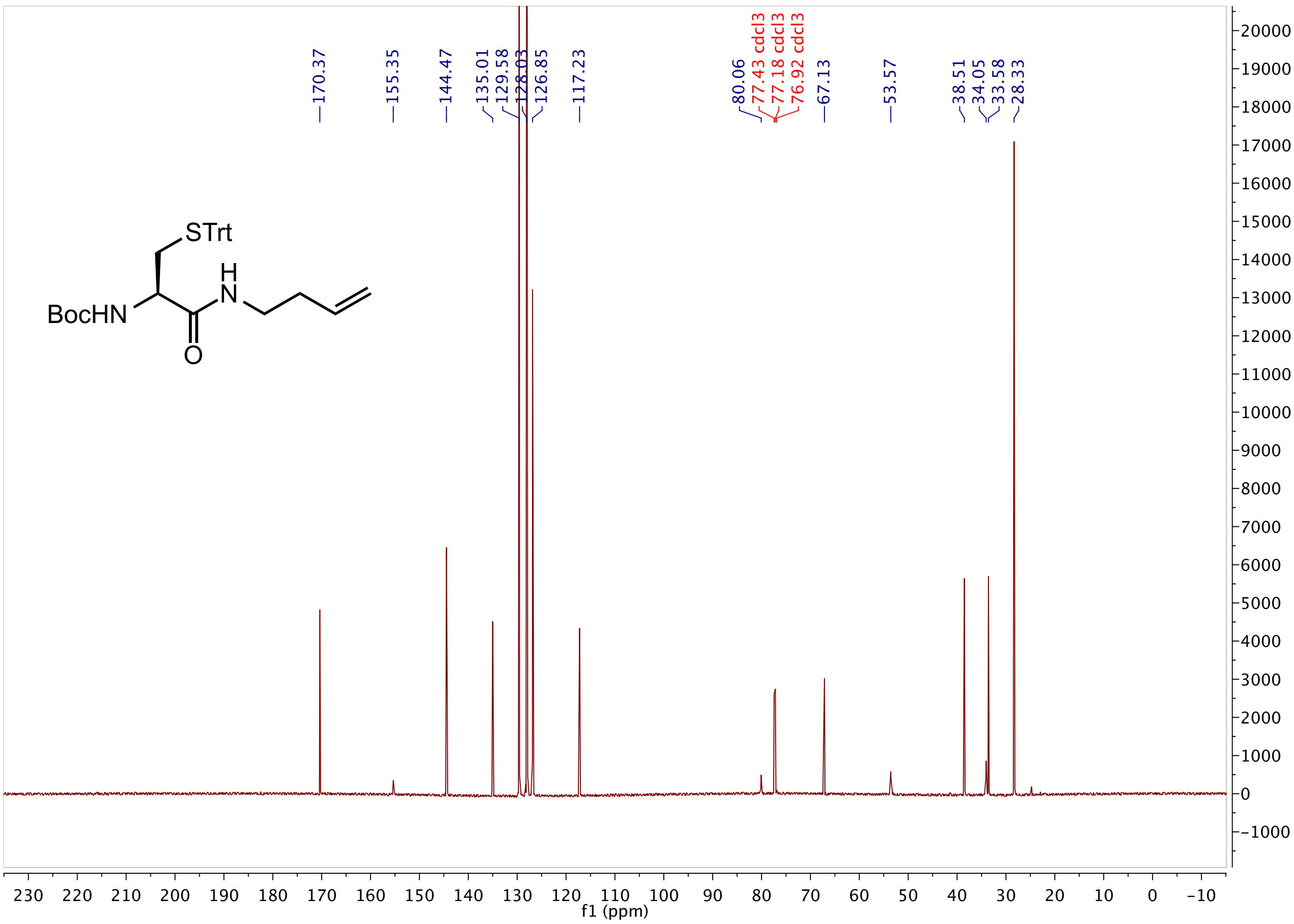
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **5l**



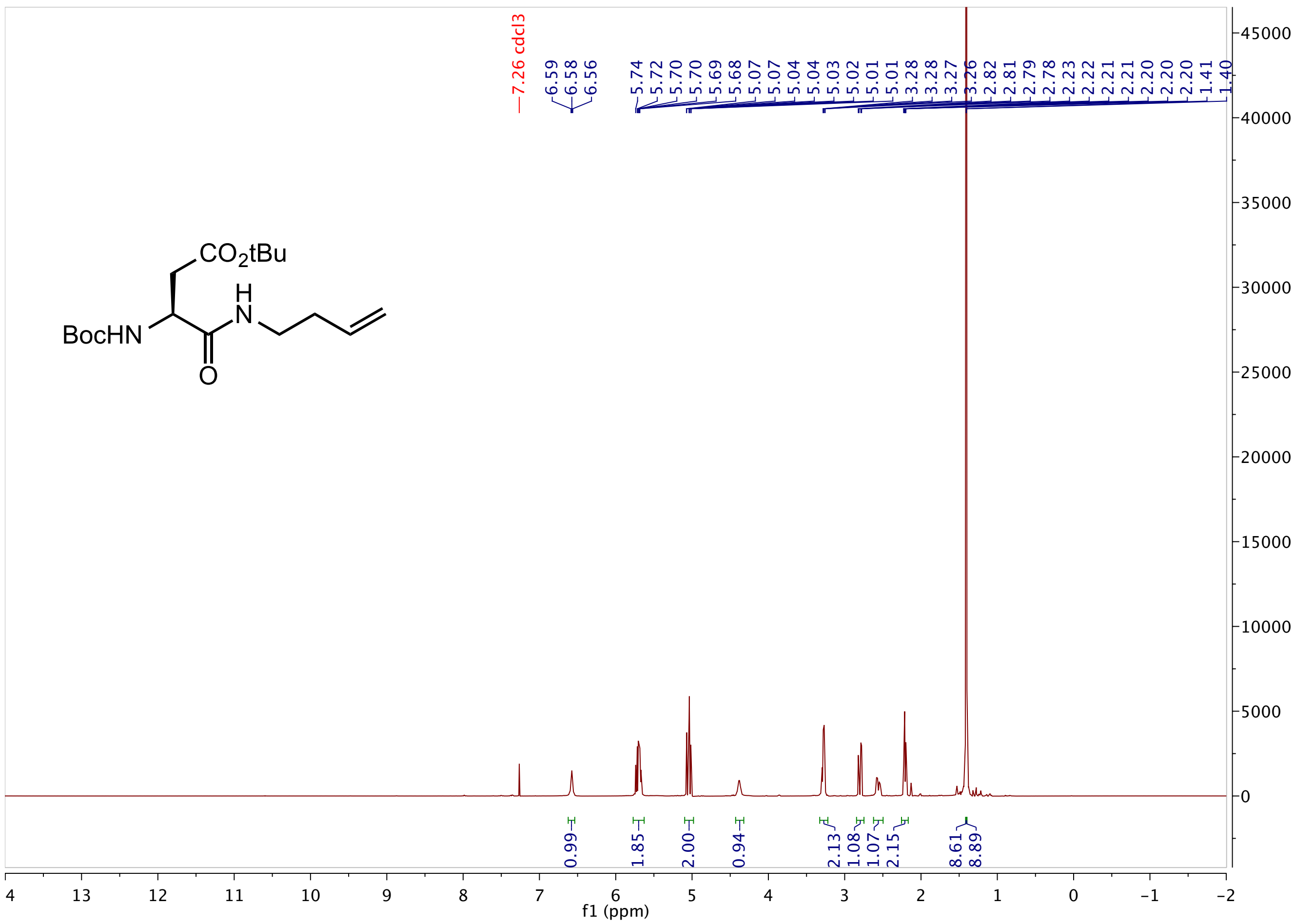
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **5m**



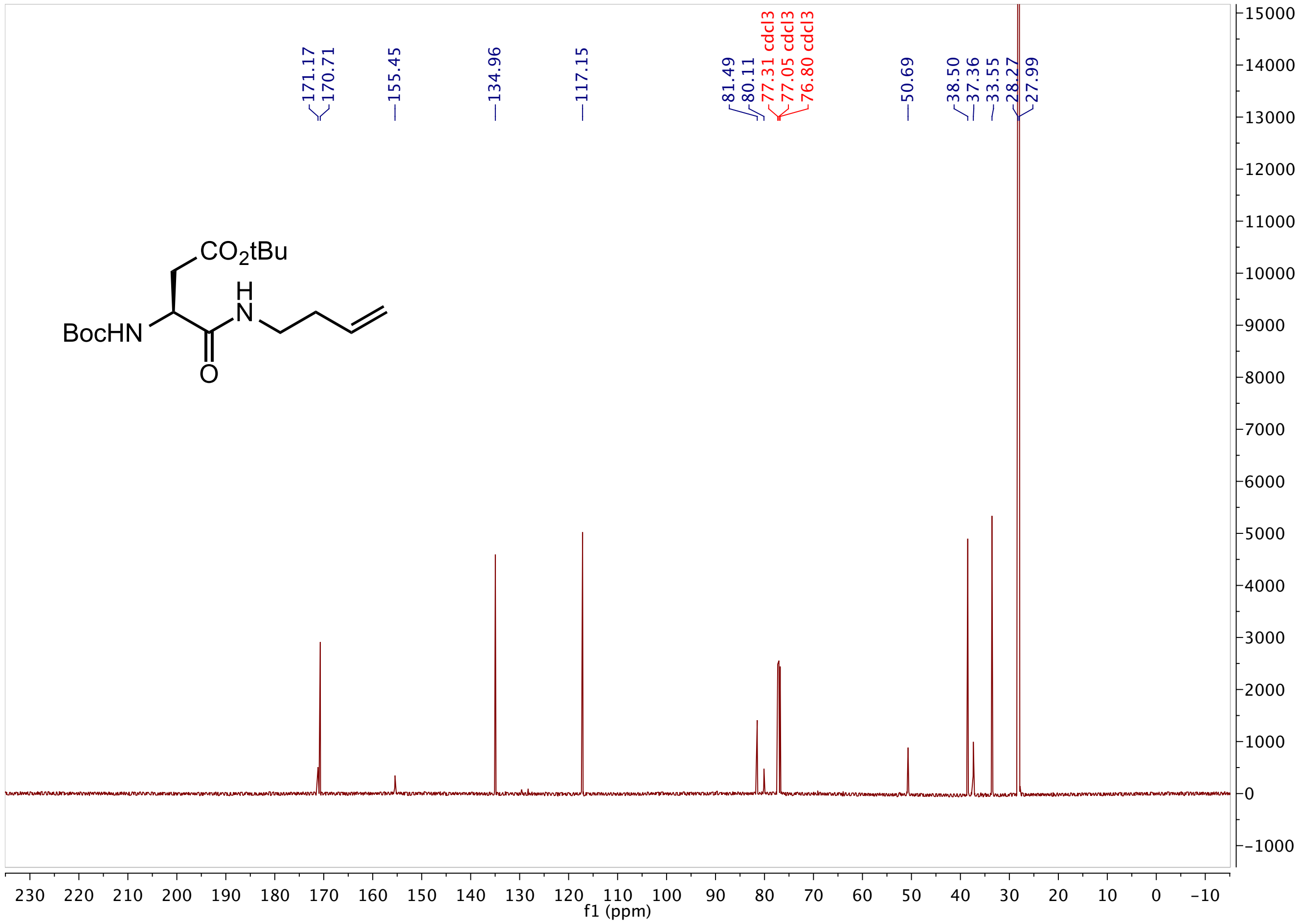
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **5m**



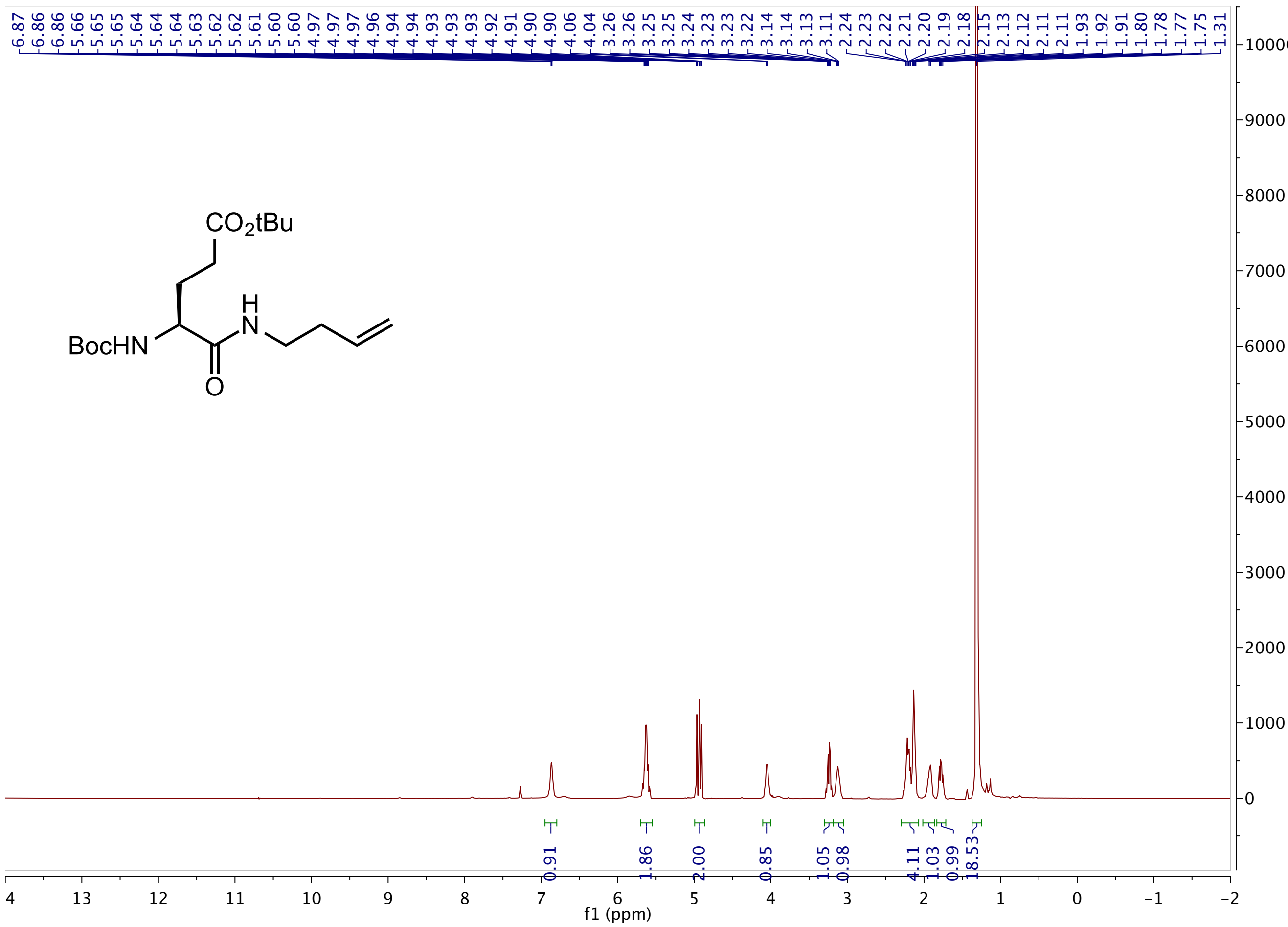
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **5n**



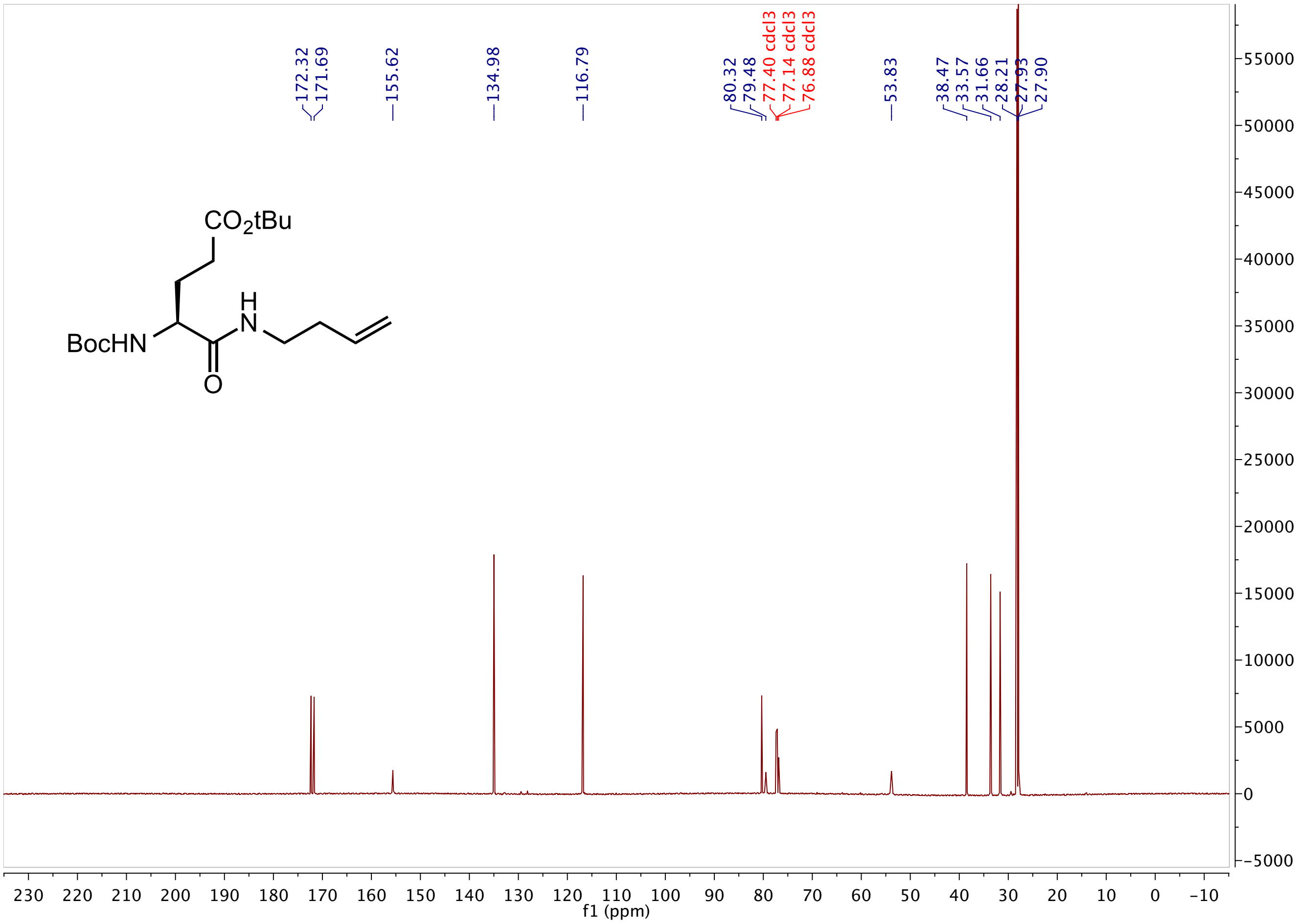
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **5n**



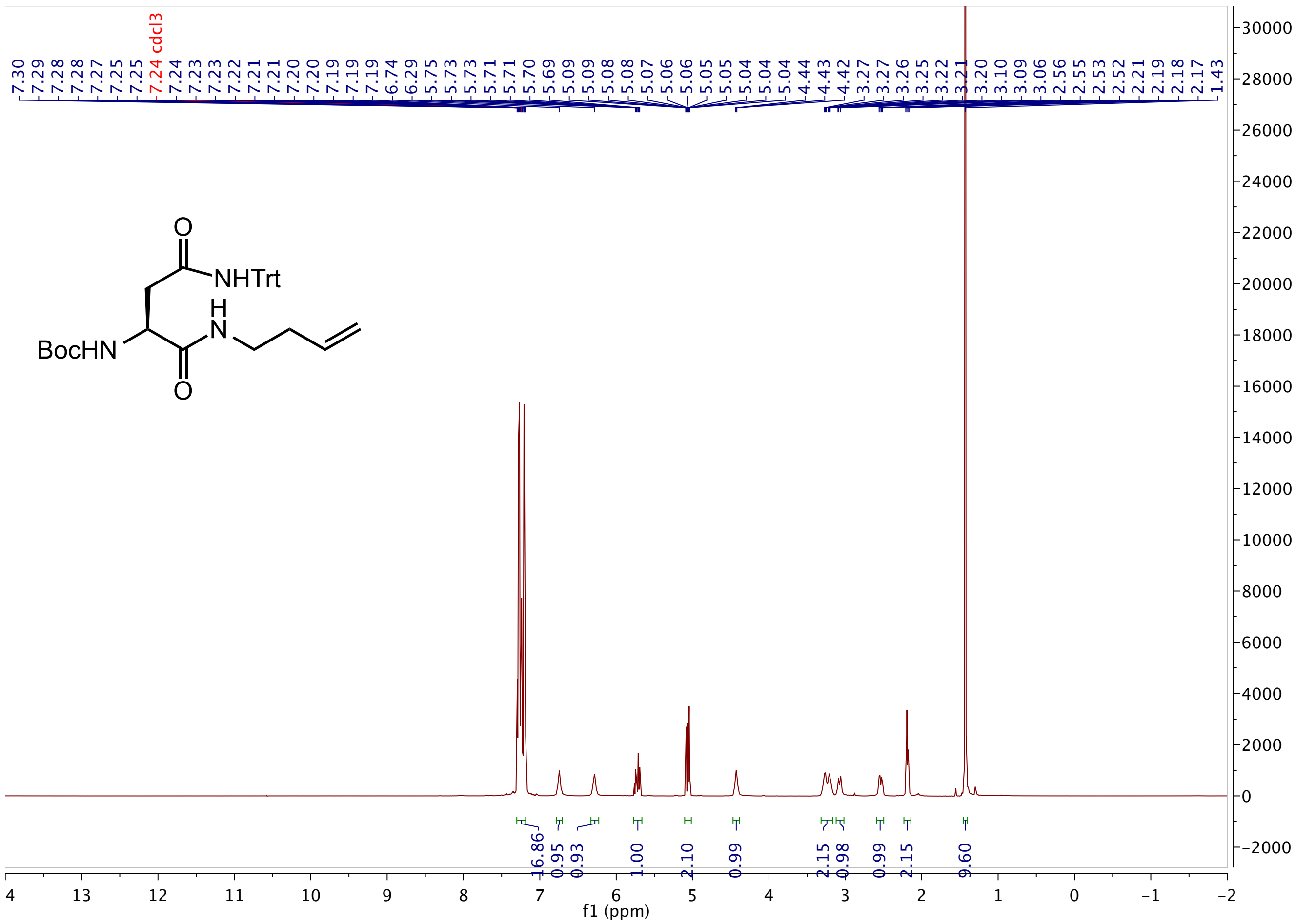
^1H NMR (500 MHz, $CDCl_3$) spectrum of compound **5o**



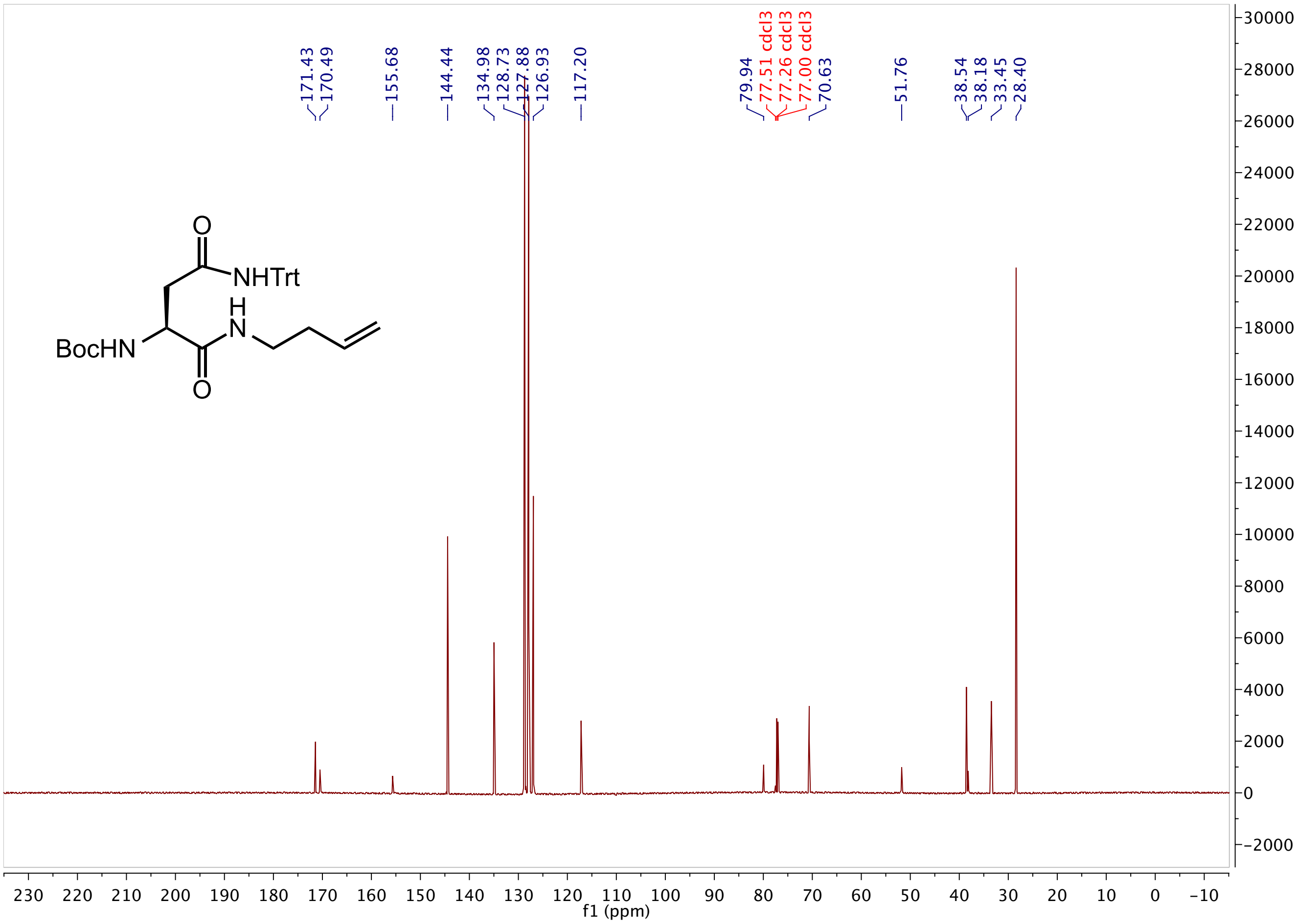
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **5o**



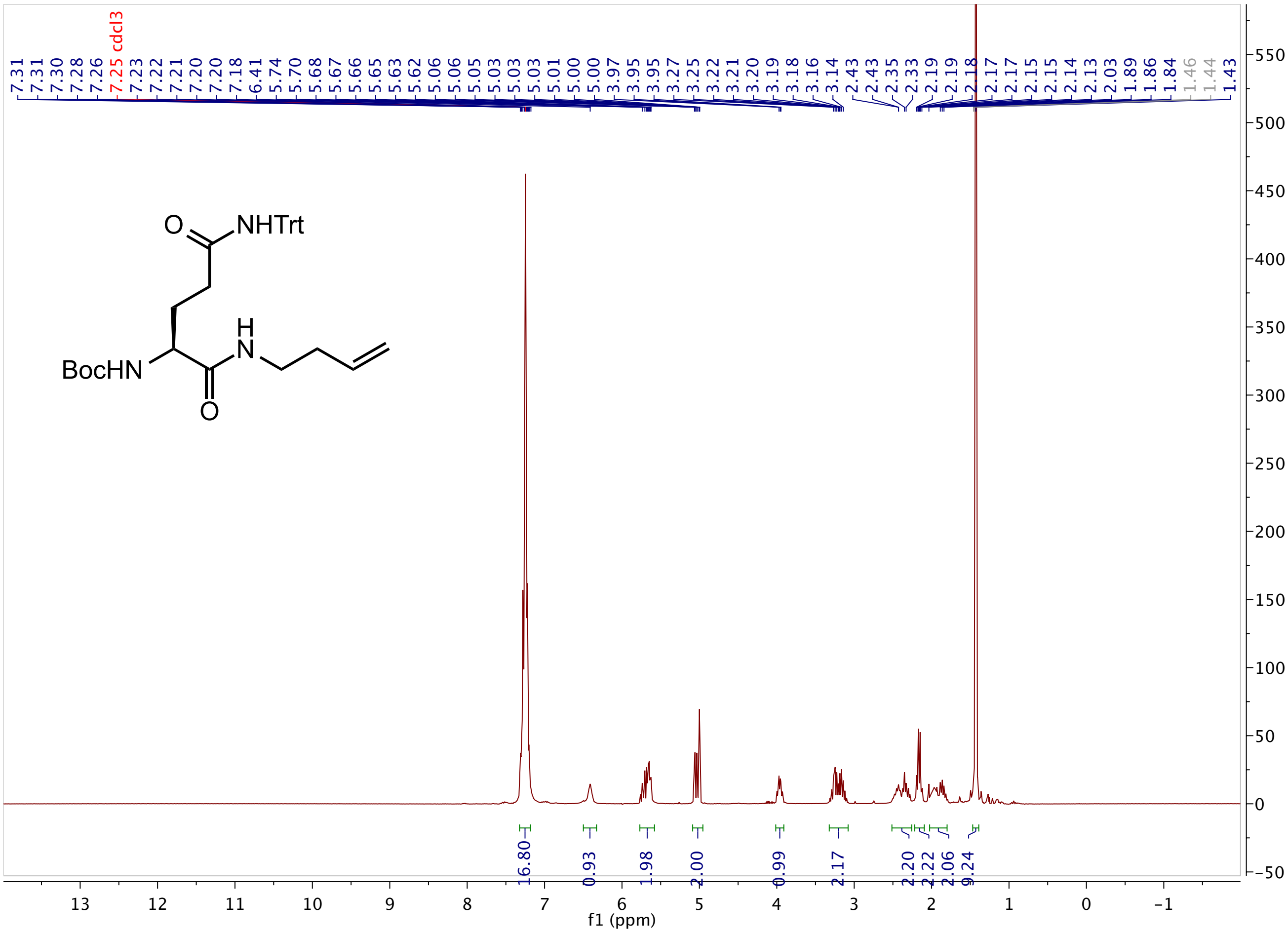
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **5p**



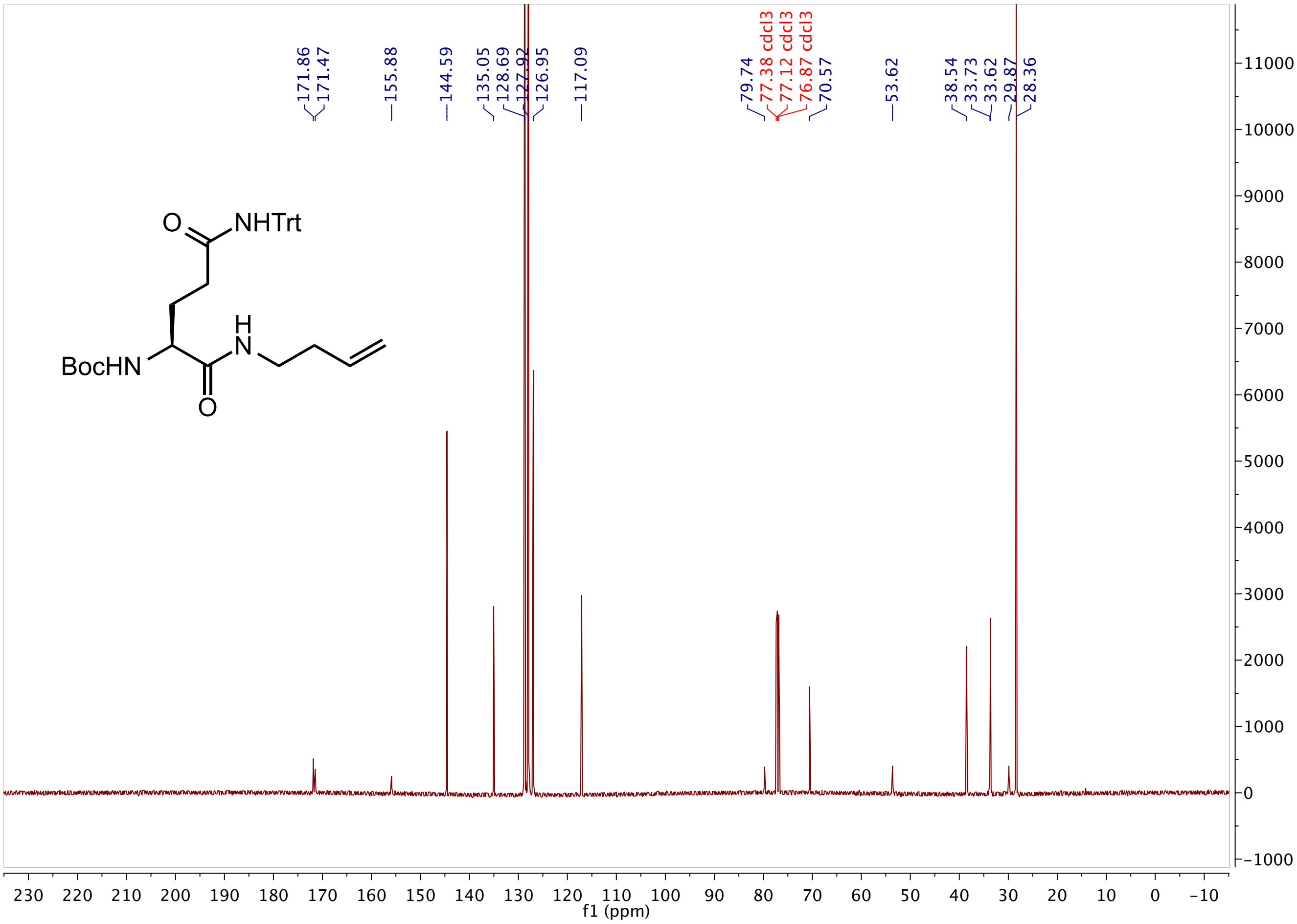
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **5p**



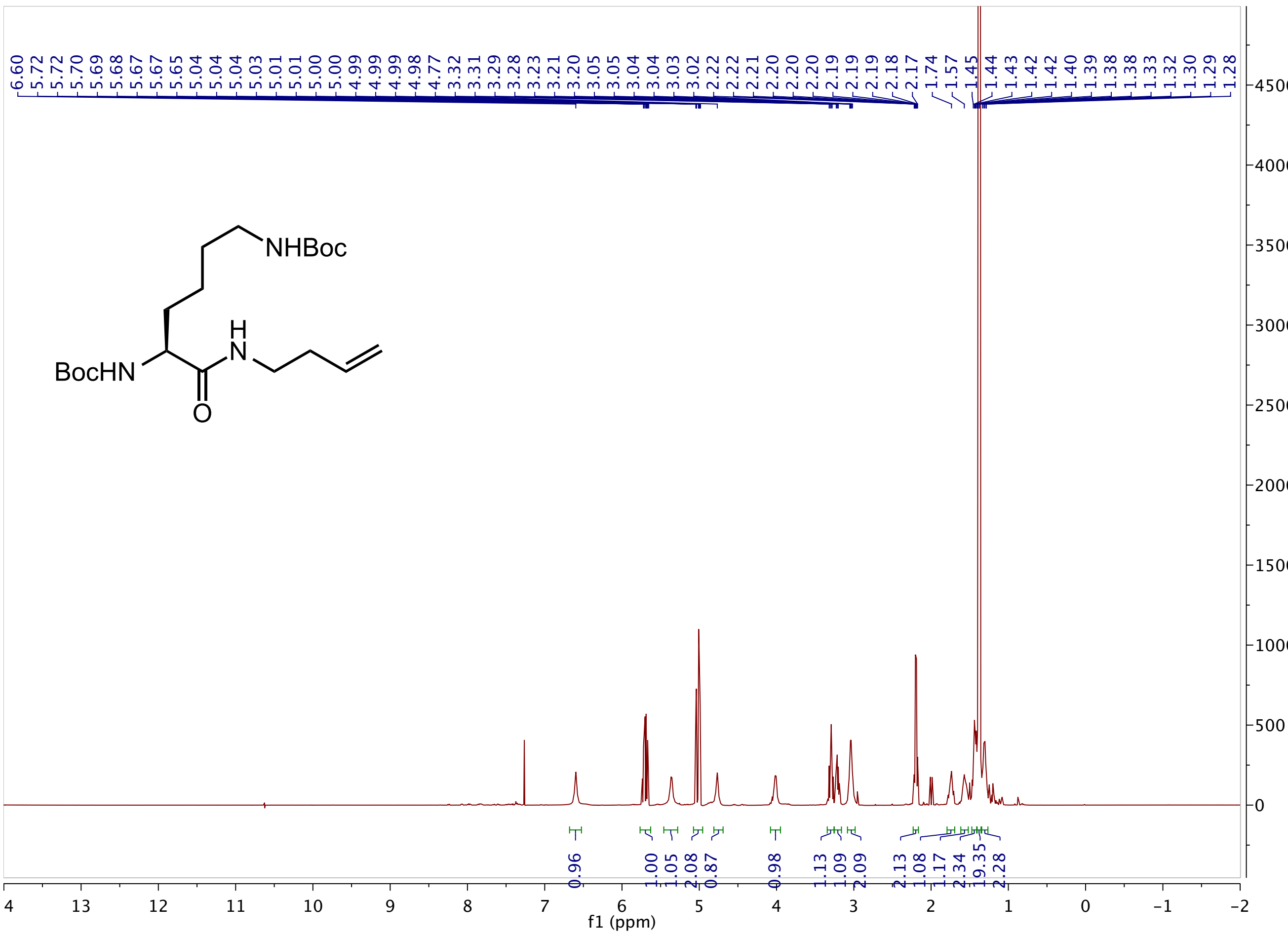
[1]H NMR (500 MHz, $CDCl_3$) spectrum of compound **5q**



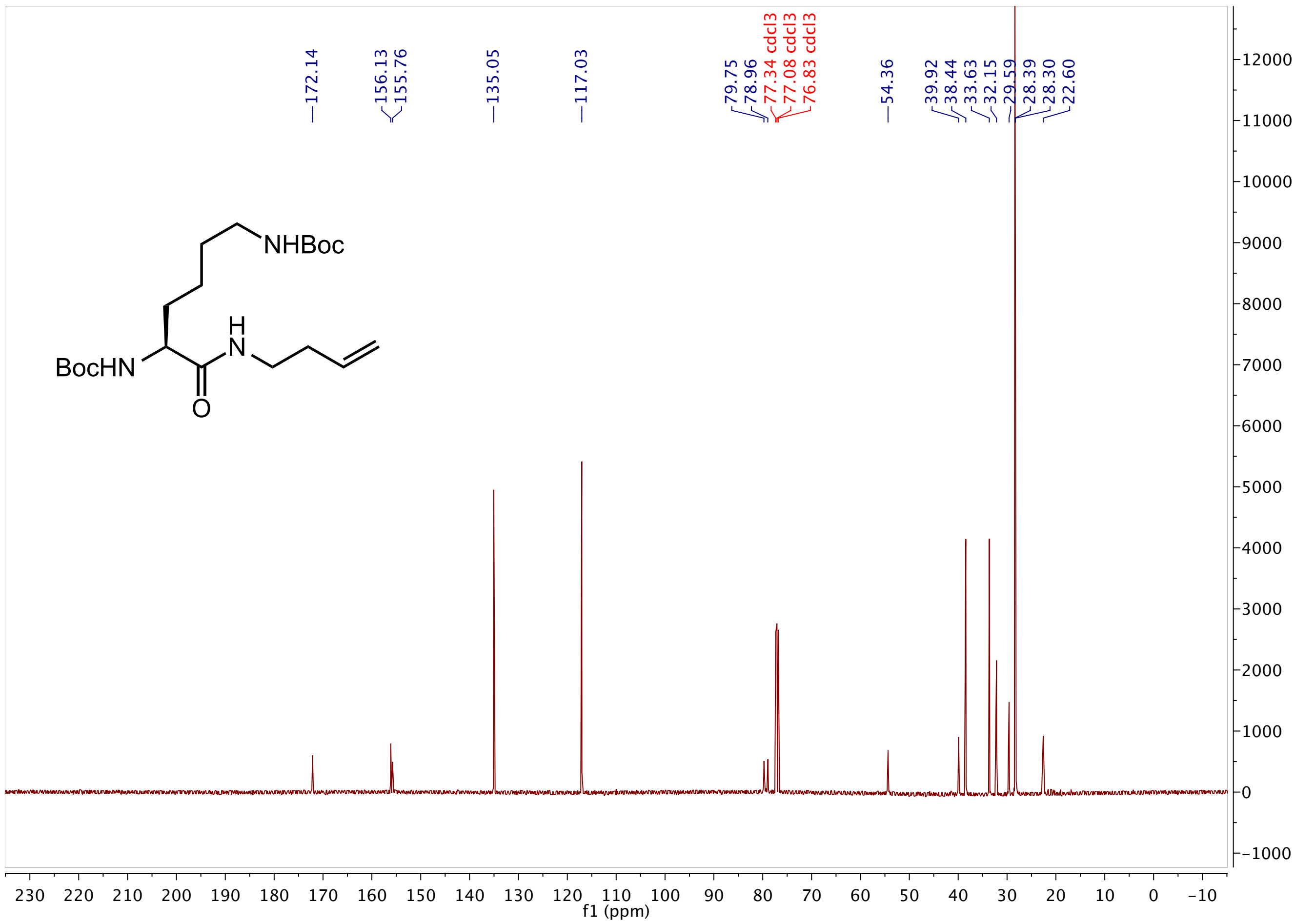
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **5q**



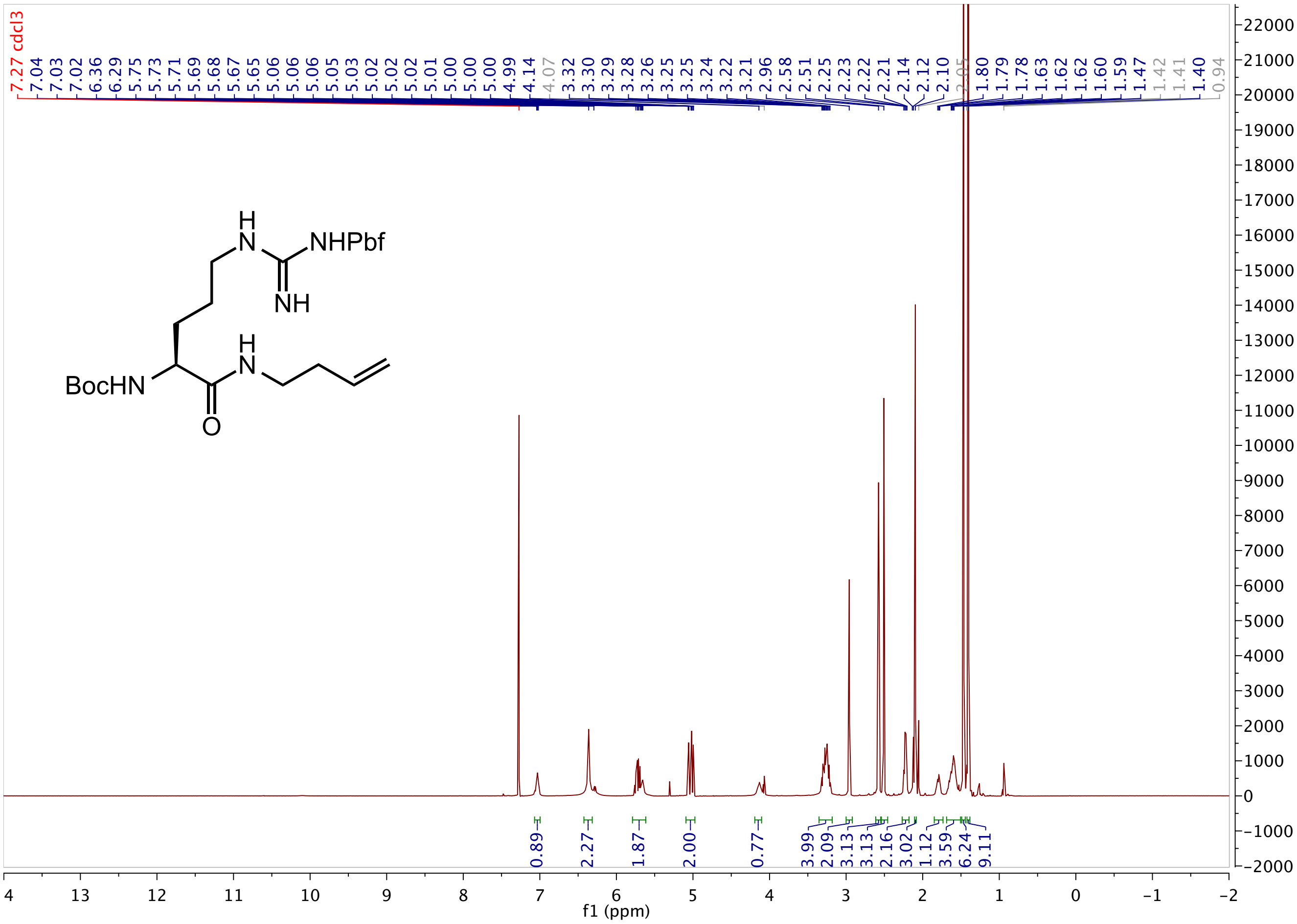
[1]H NMR (500 MHz, $CDCl_3$) spectrum of compound **5r**



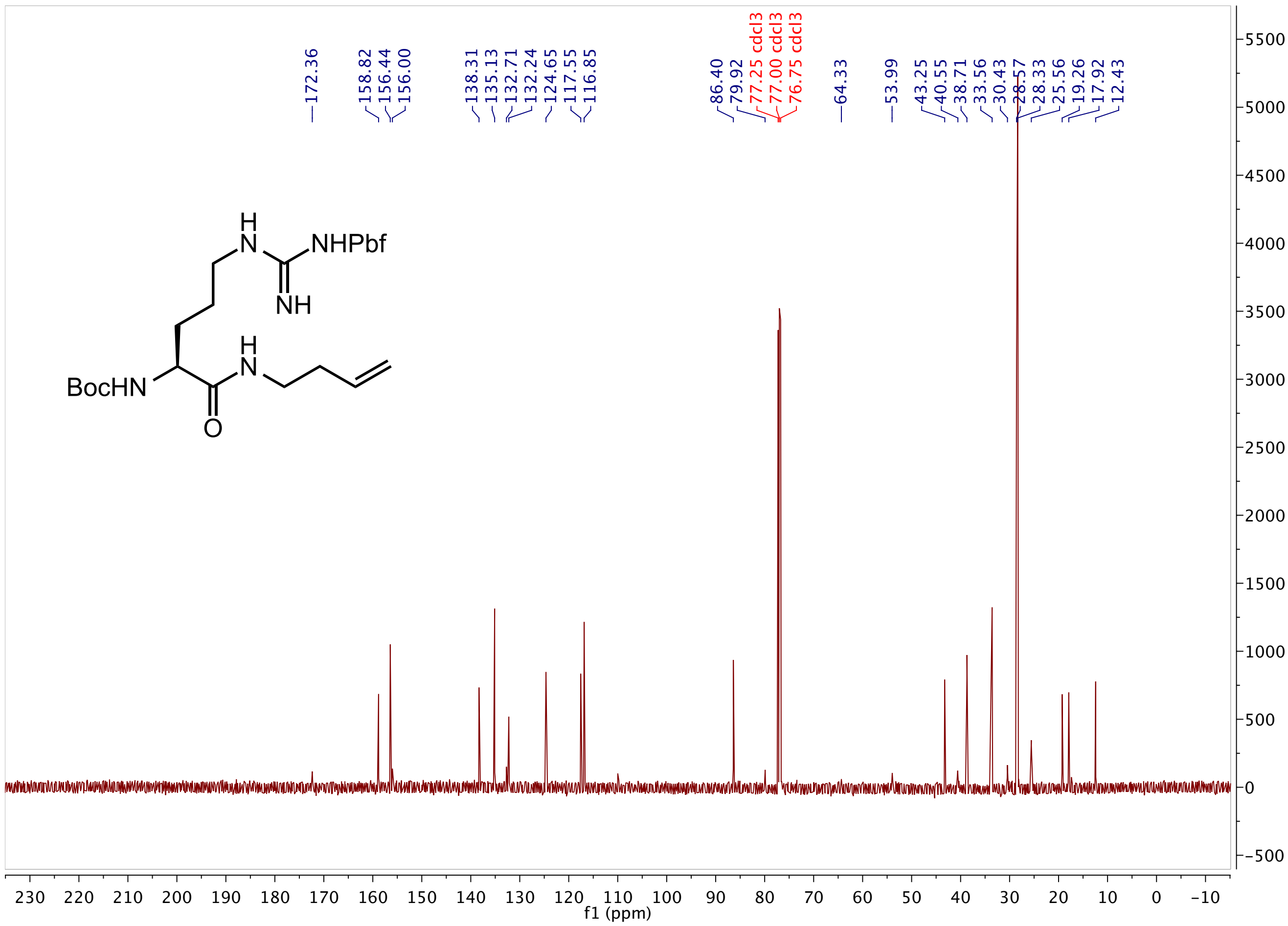
[13]C NMR (126 MHz, $CDCl_3$) spectrum of compound **5r**



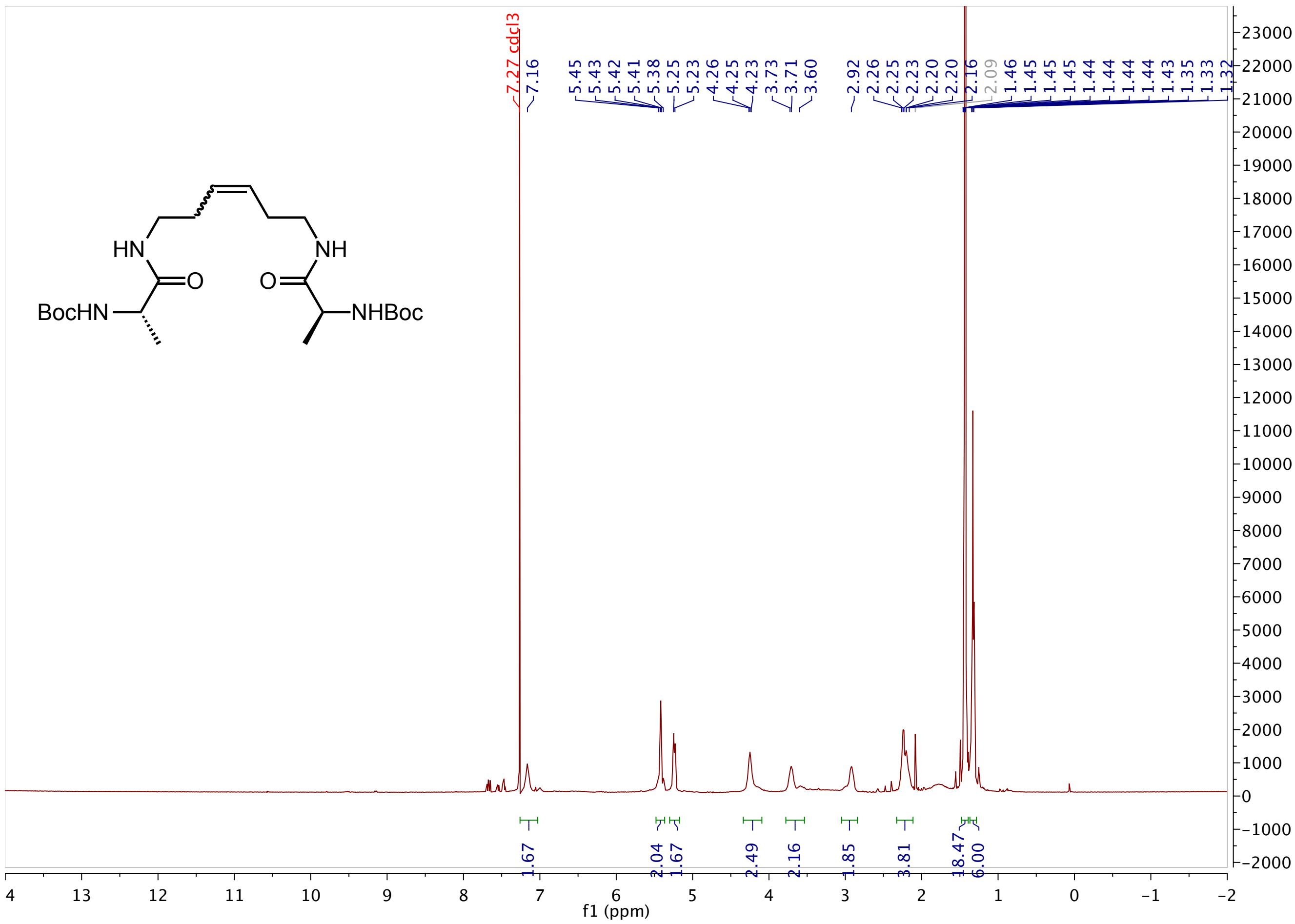
^1H NMR (500 MHz, $CDCl_3$) spectrum of compound **5s**



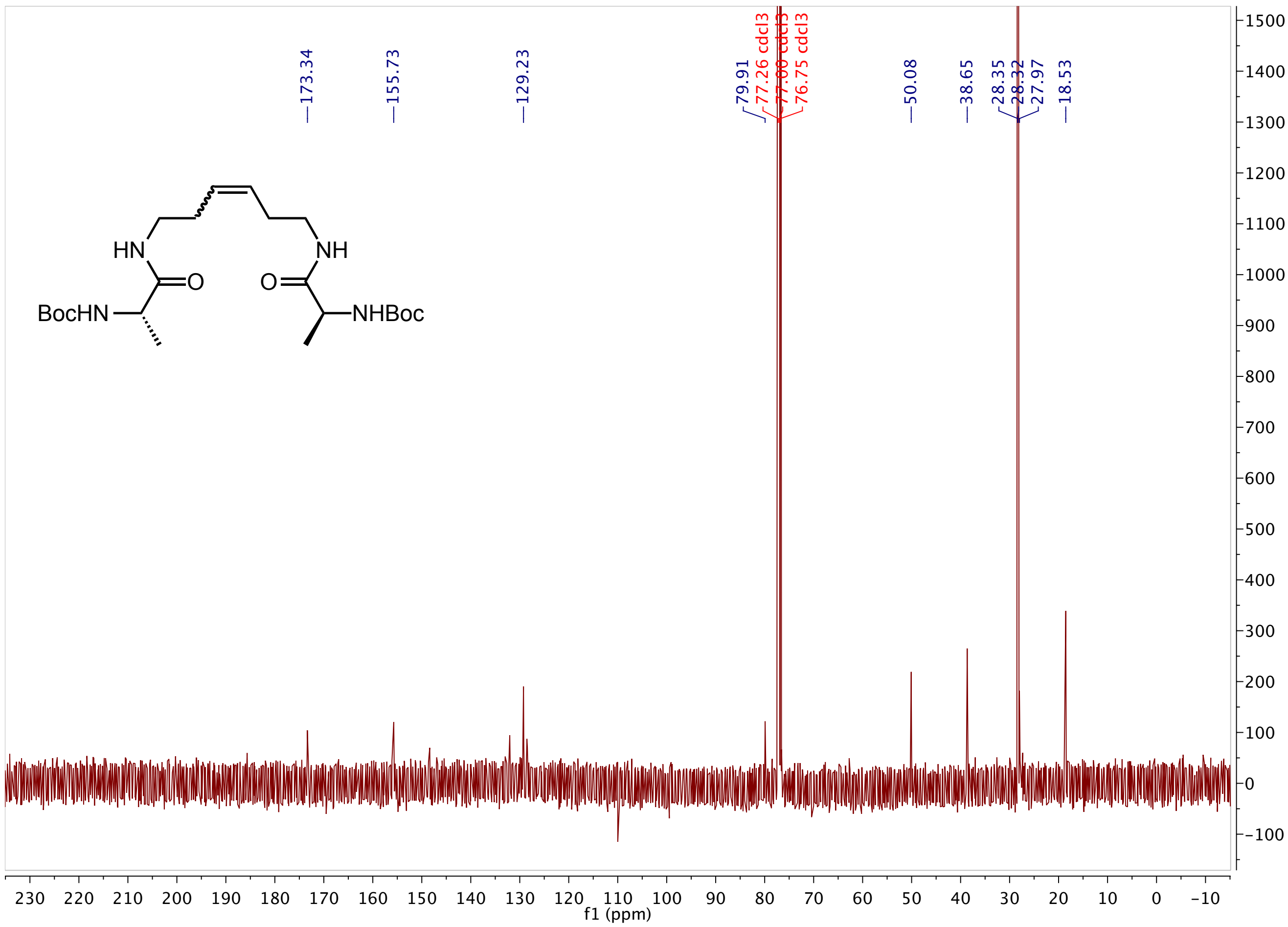
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **5s**



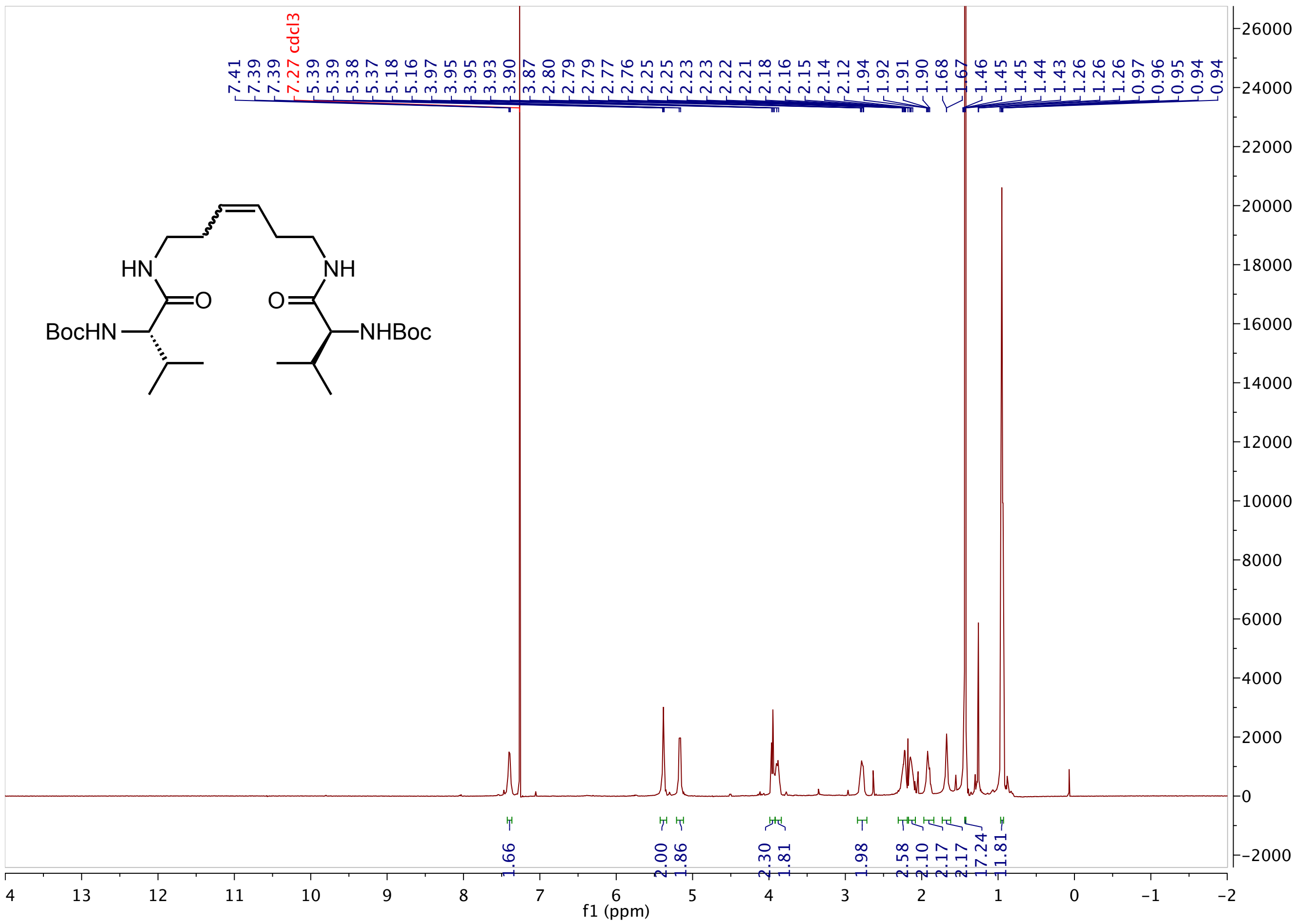
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **4**



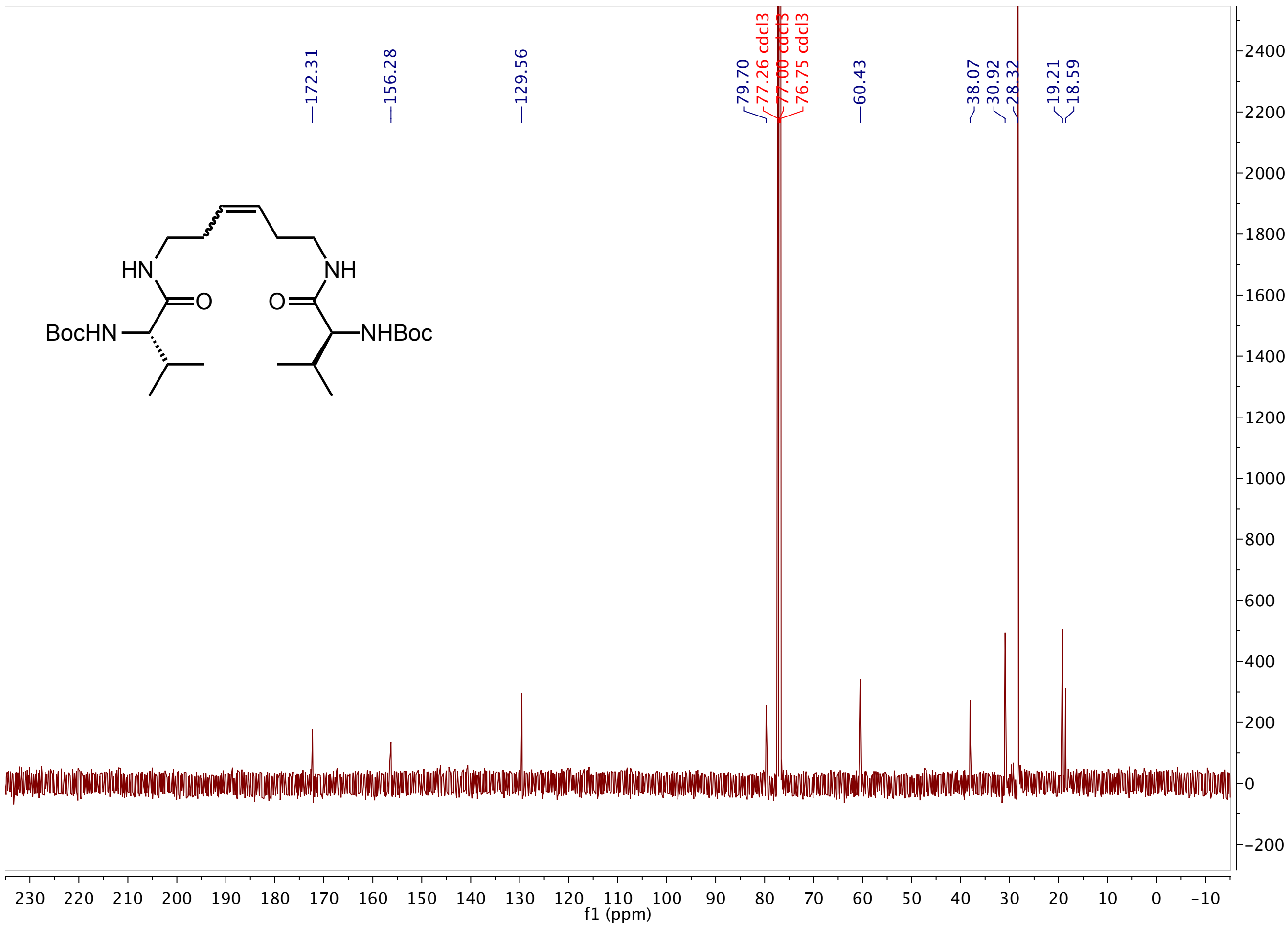
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **4**



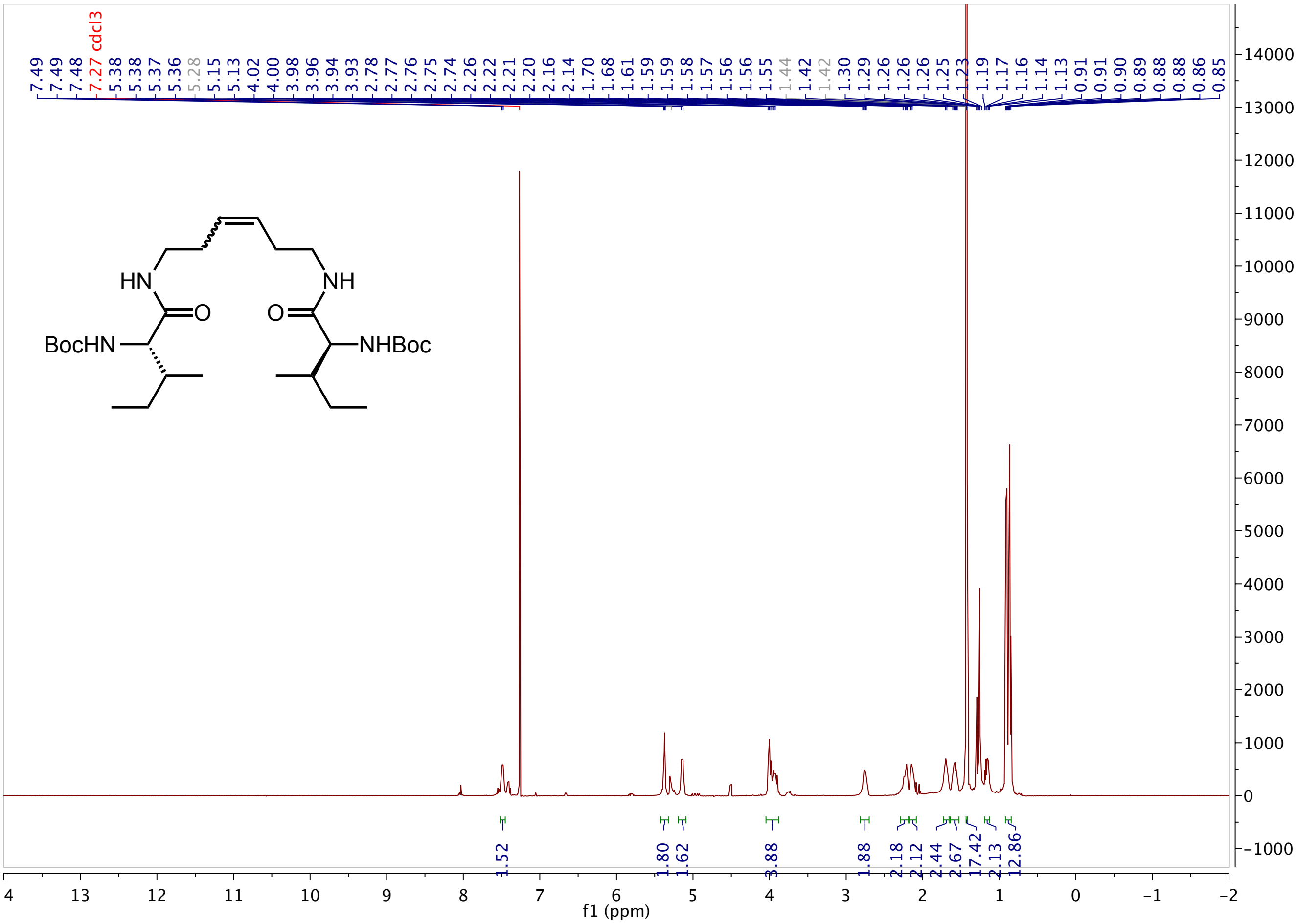
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **6a**



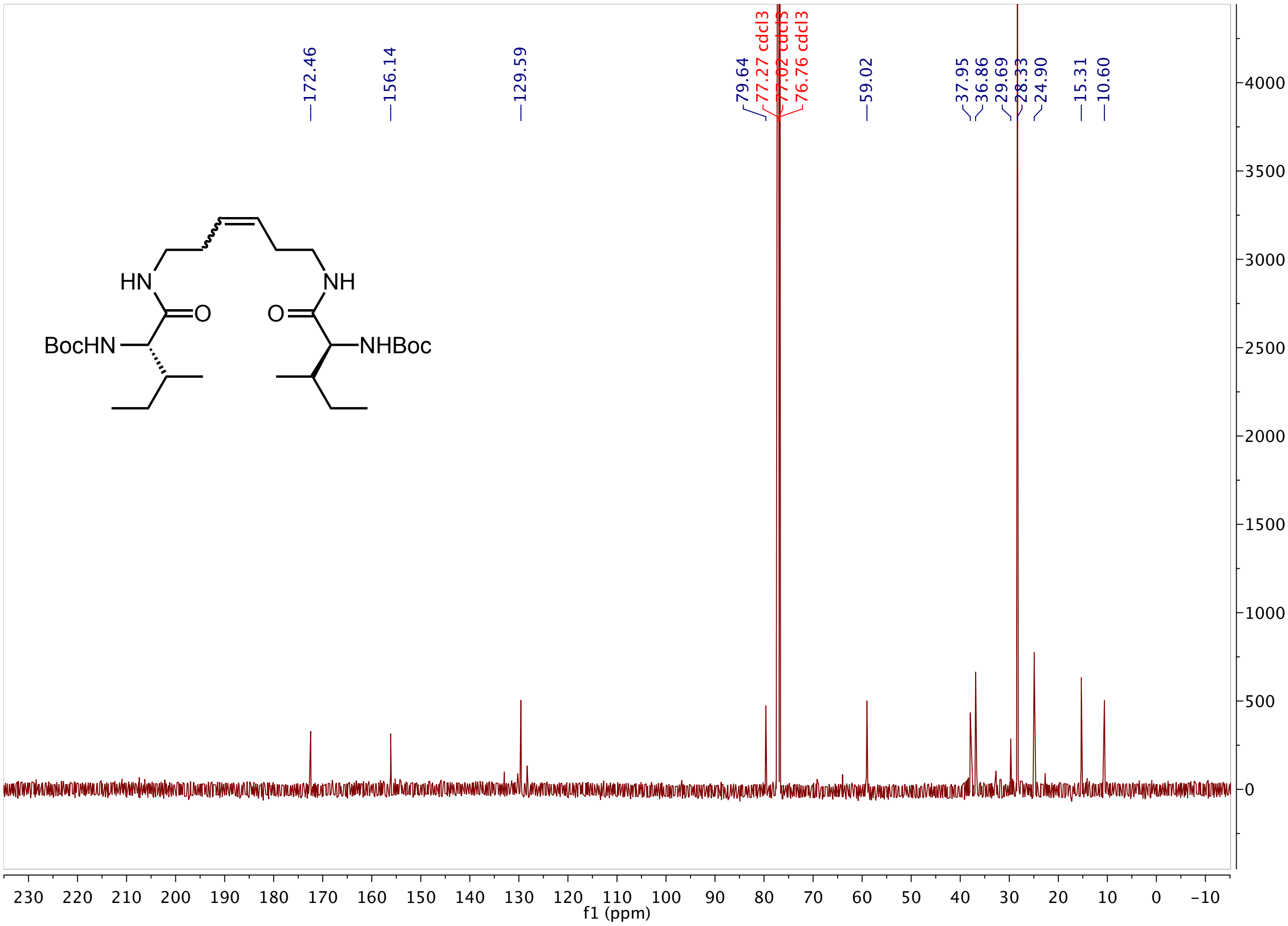
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **6a**



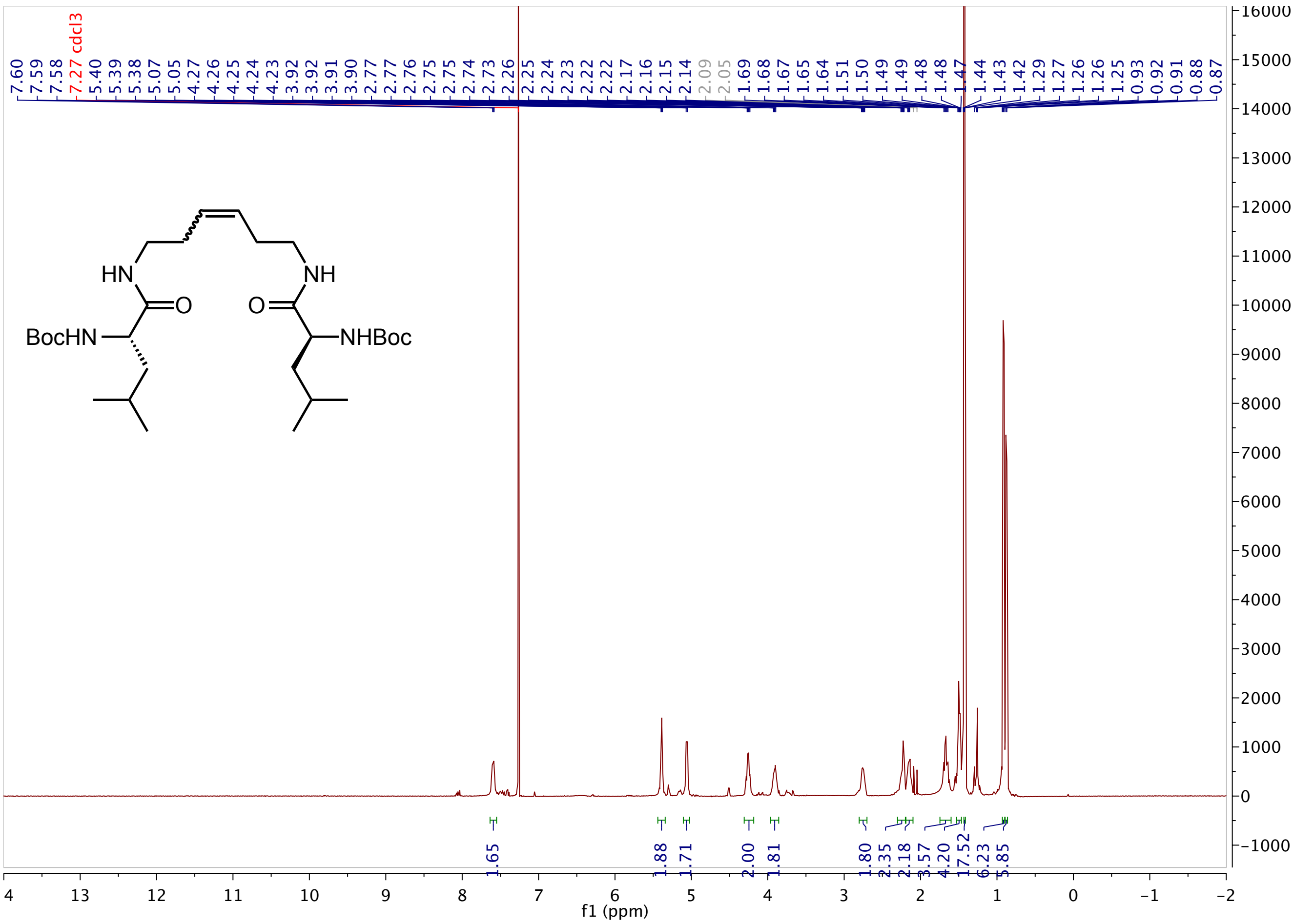
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **6b**



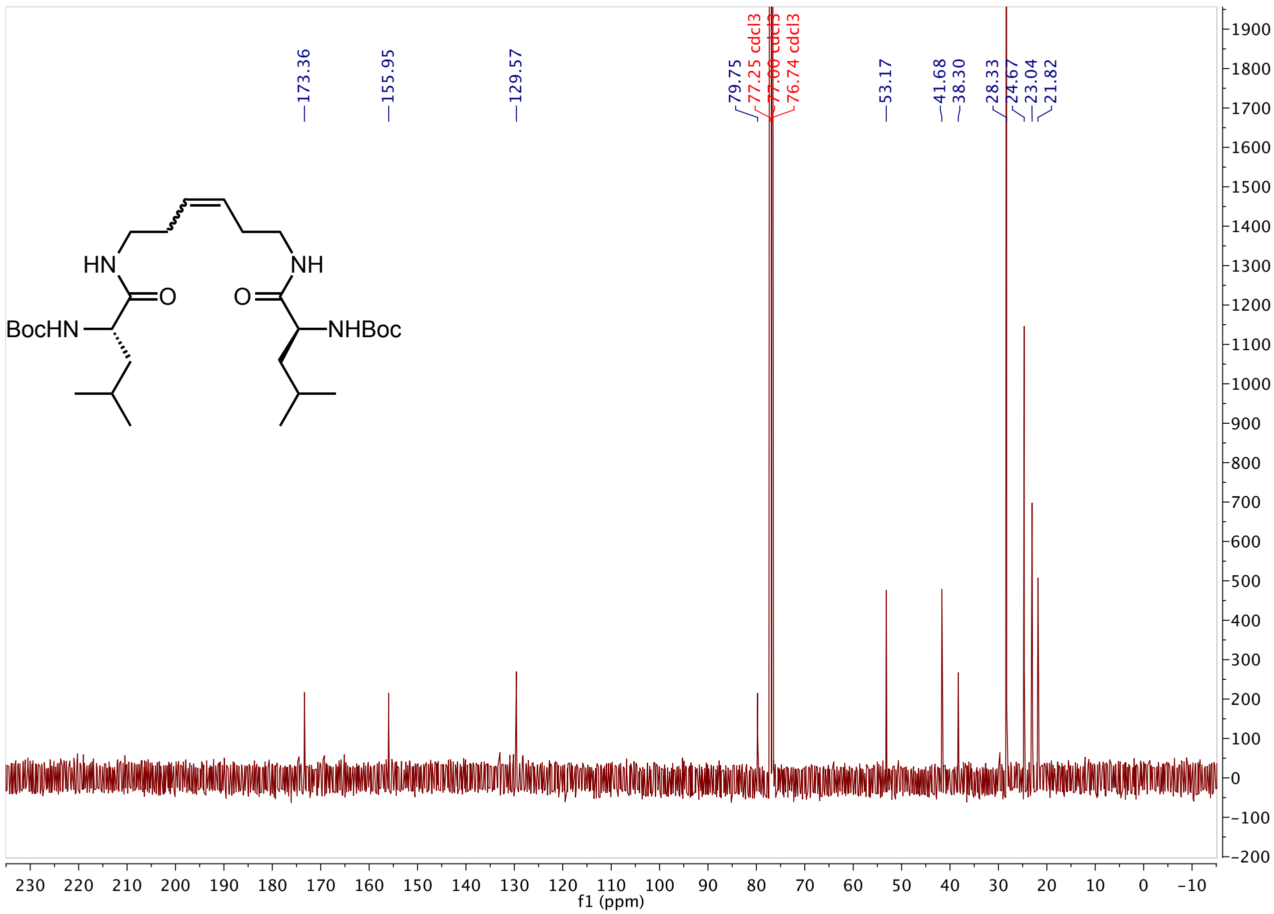
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **6b**



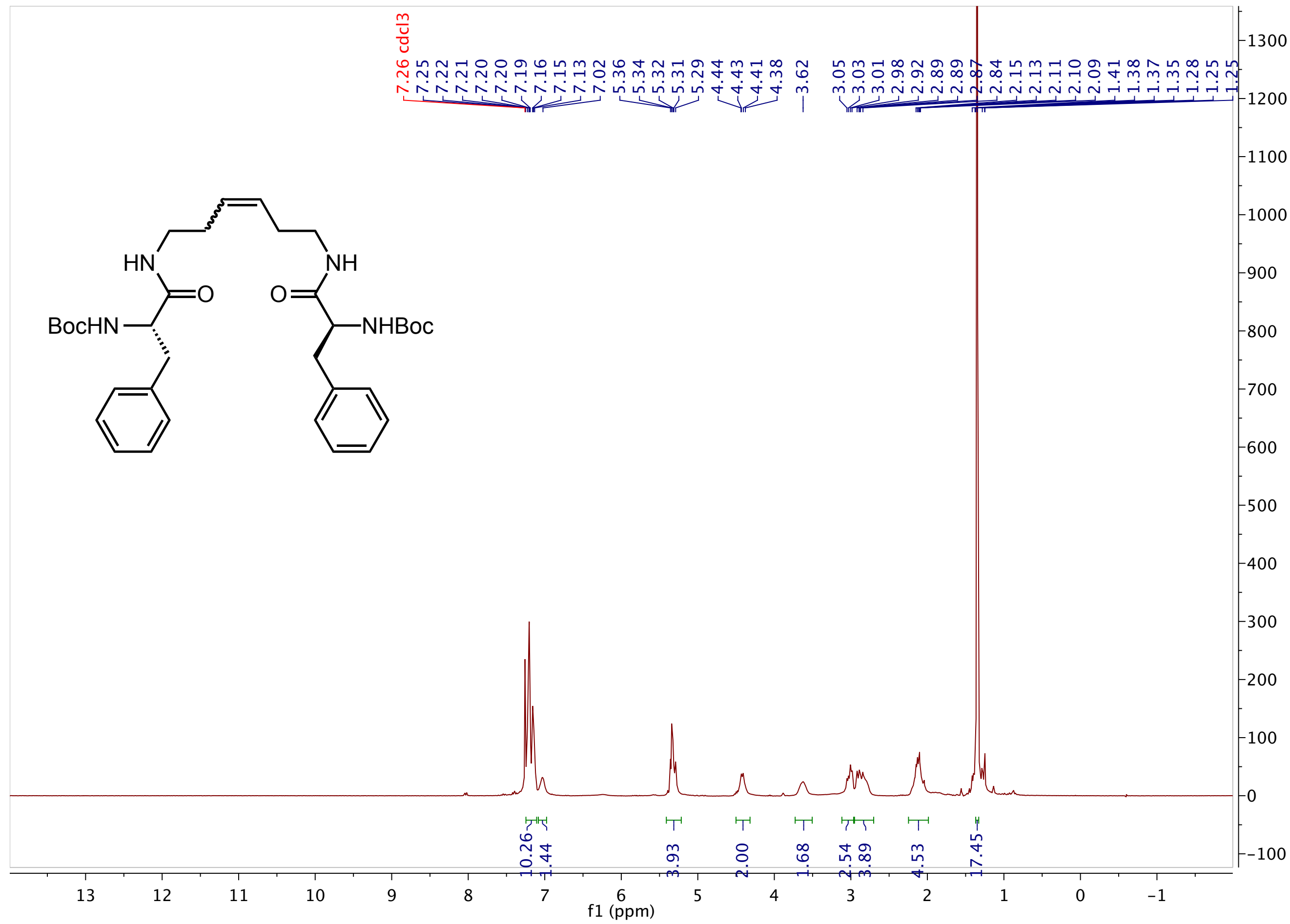
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **6c**



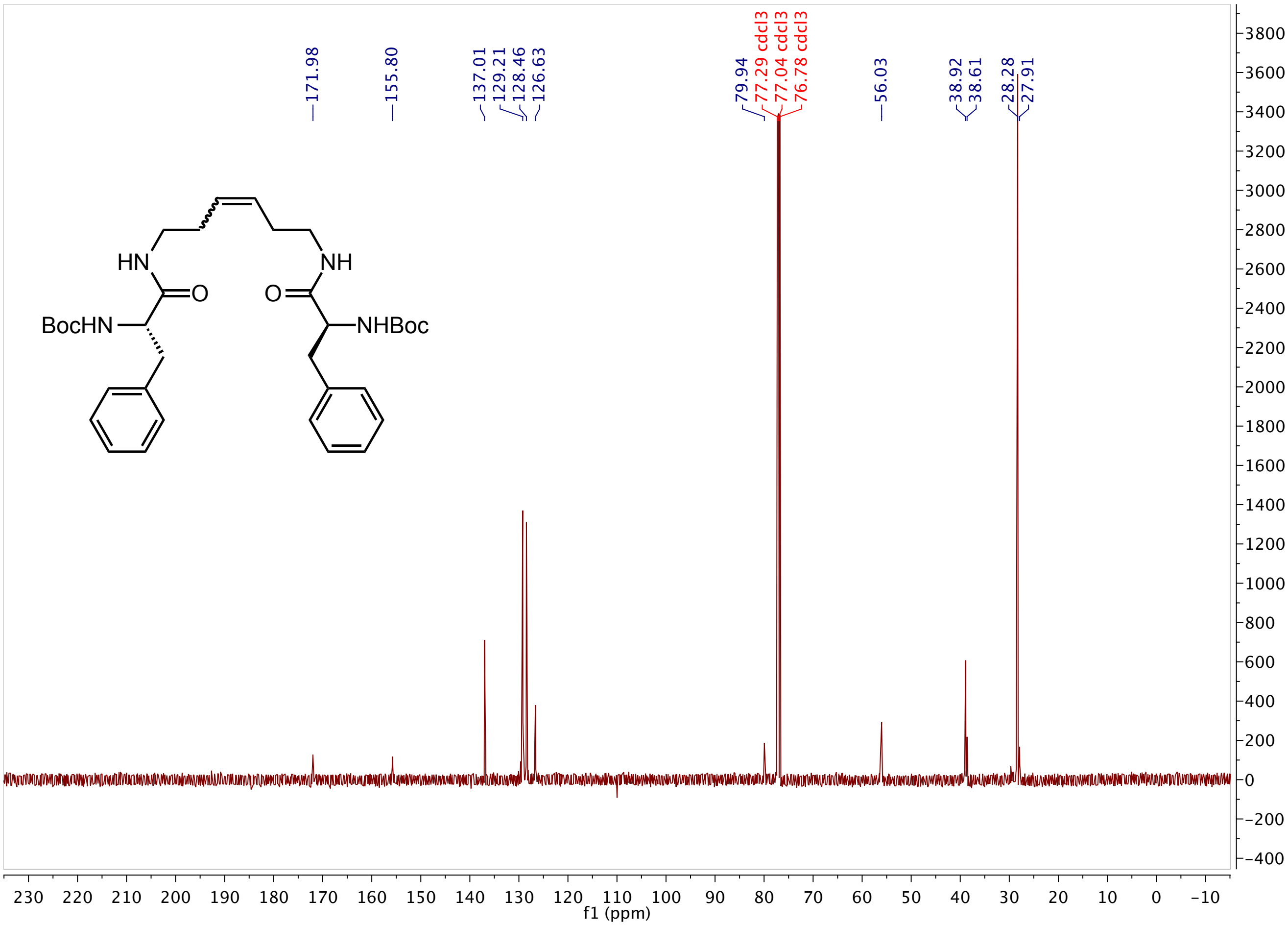
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **6c**



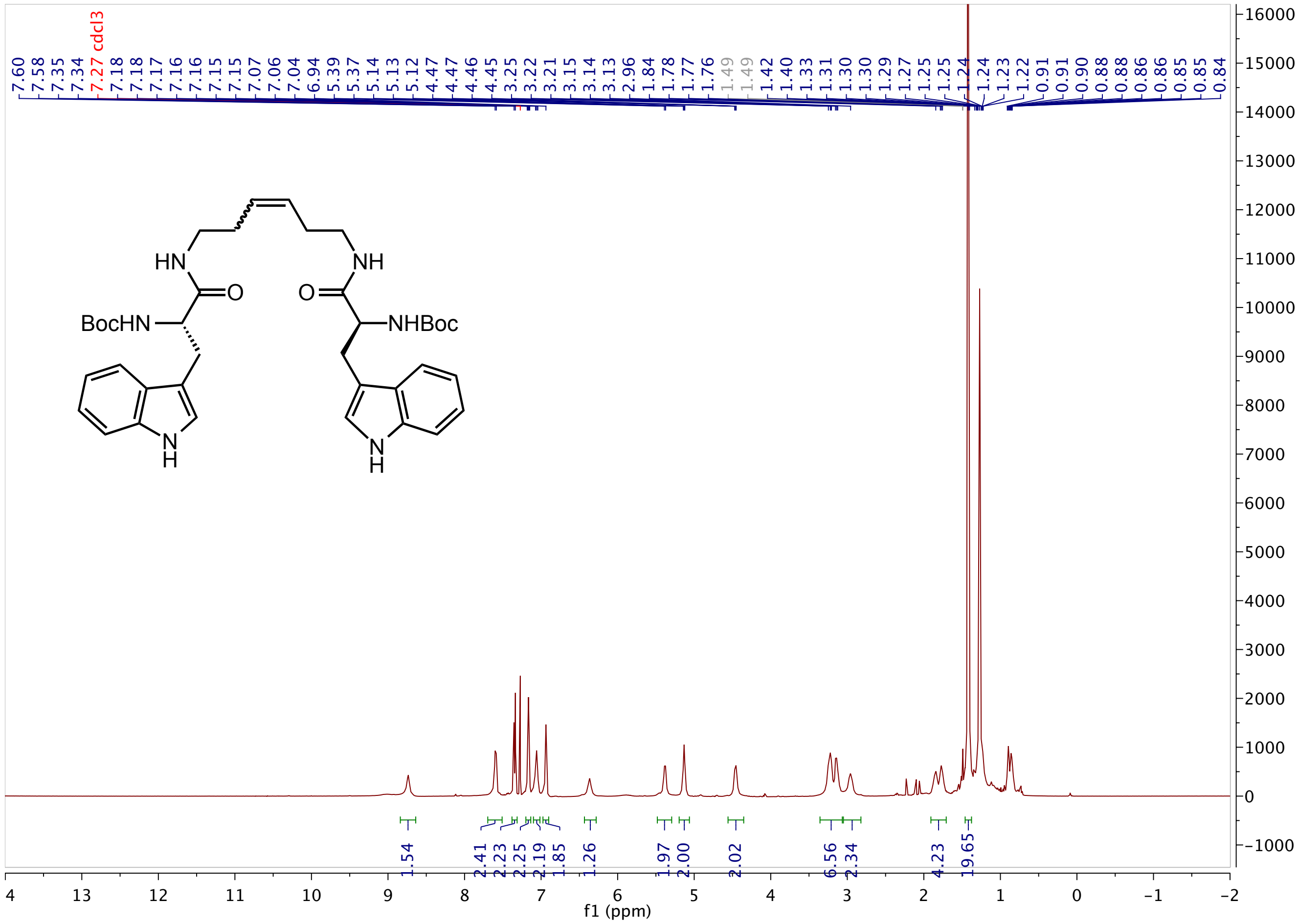
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **6d**



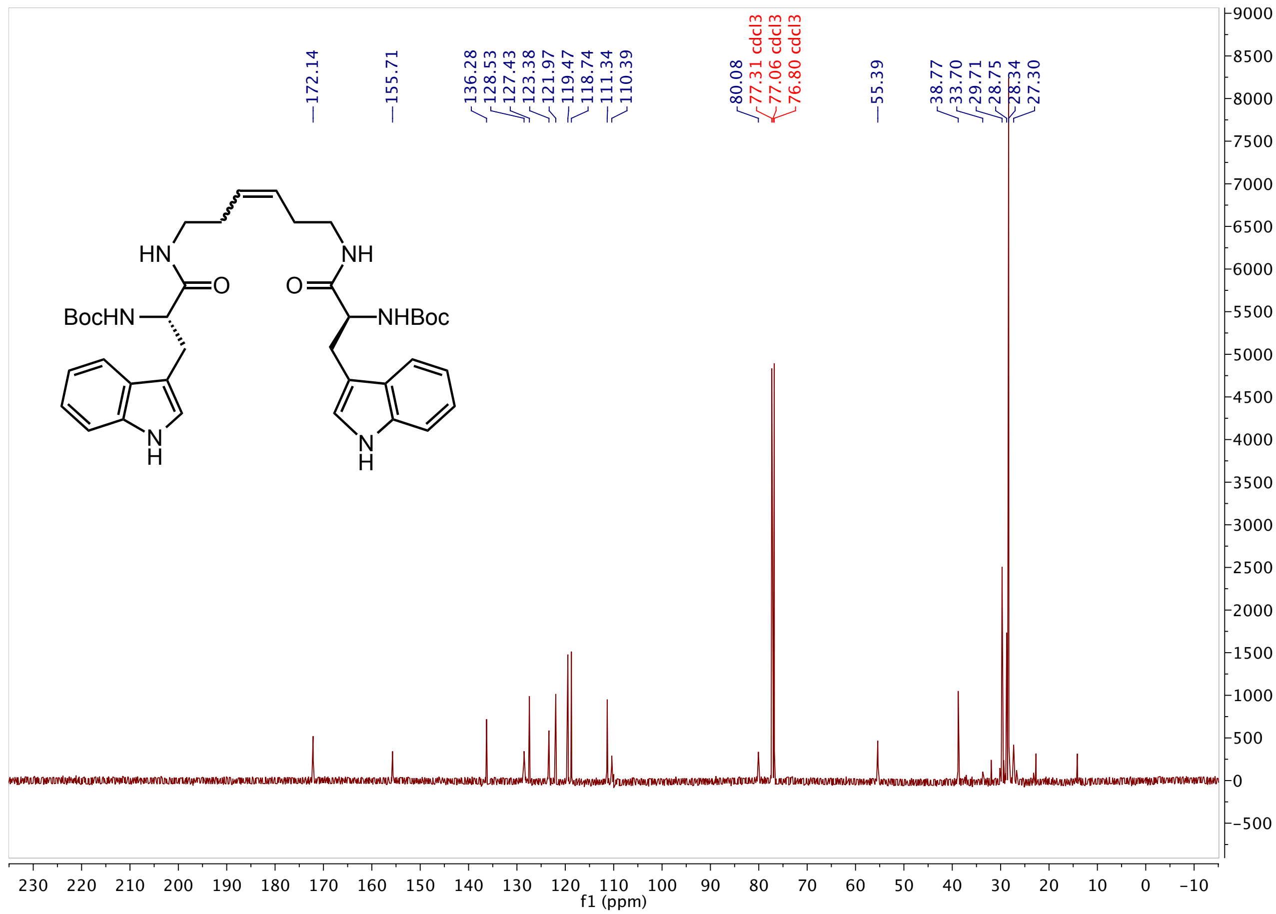
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **6d**



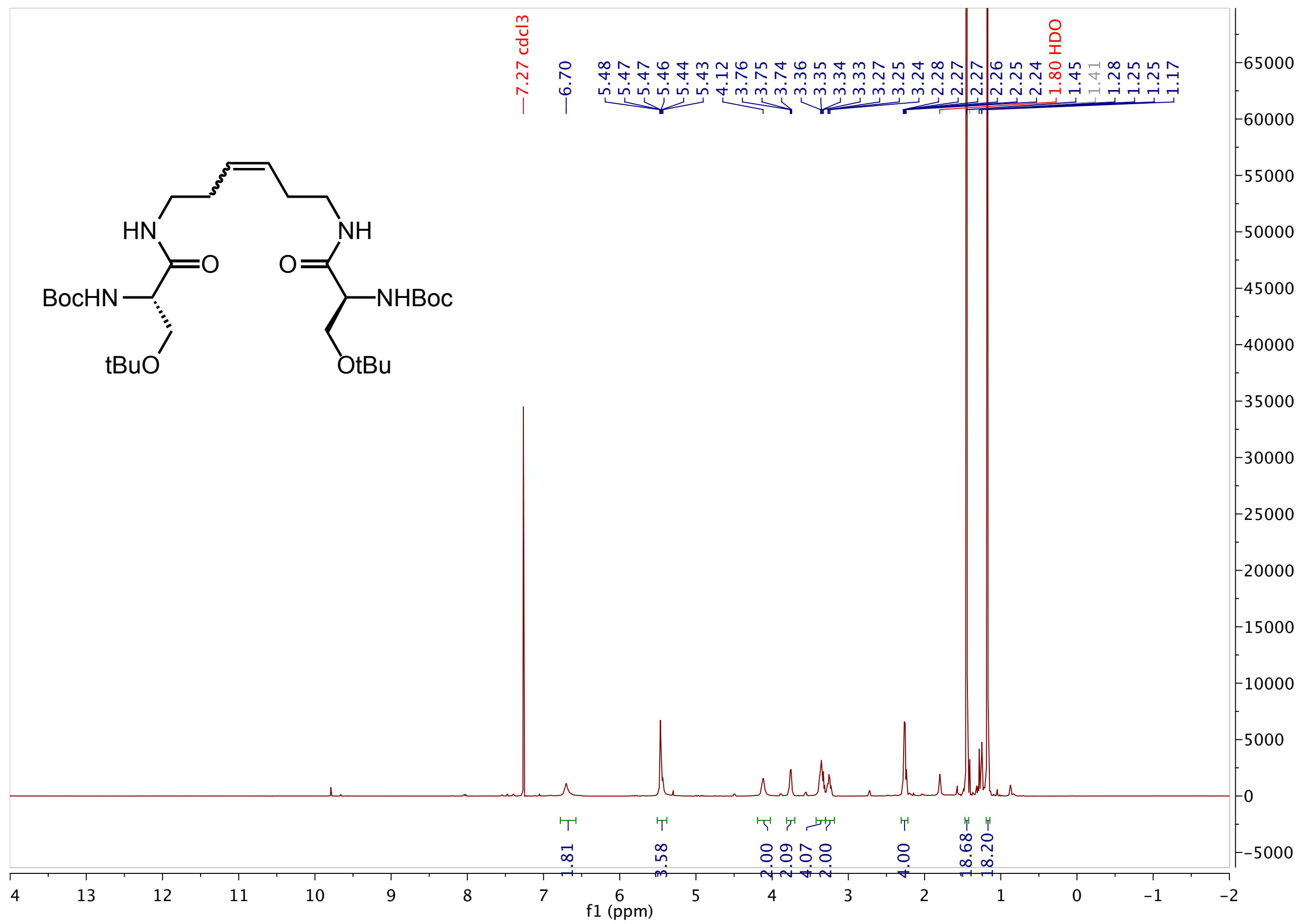
^1H NMR (500 MHz, $CDCl_3$) spectrum of compound **6g**



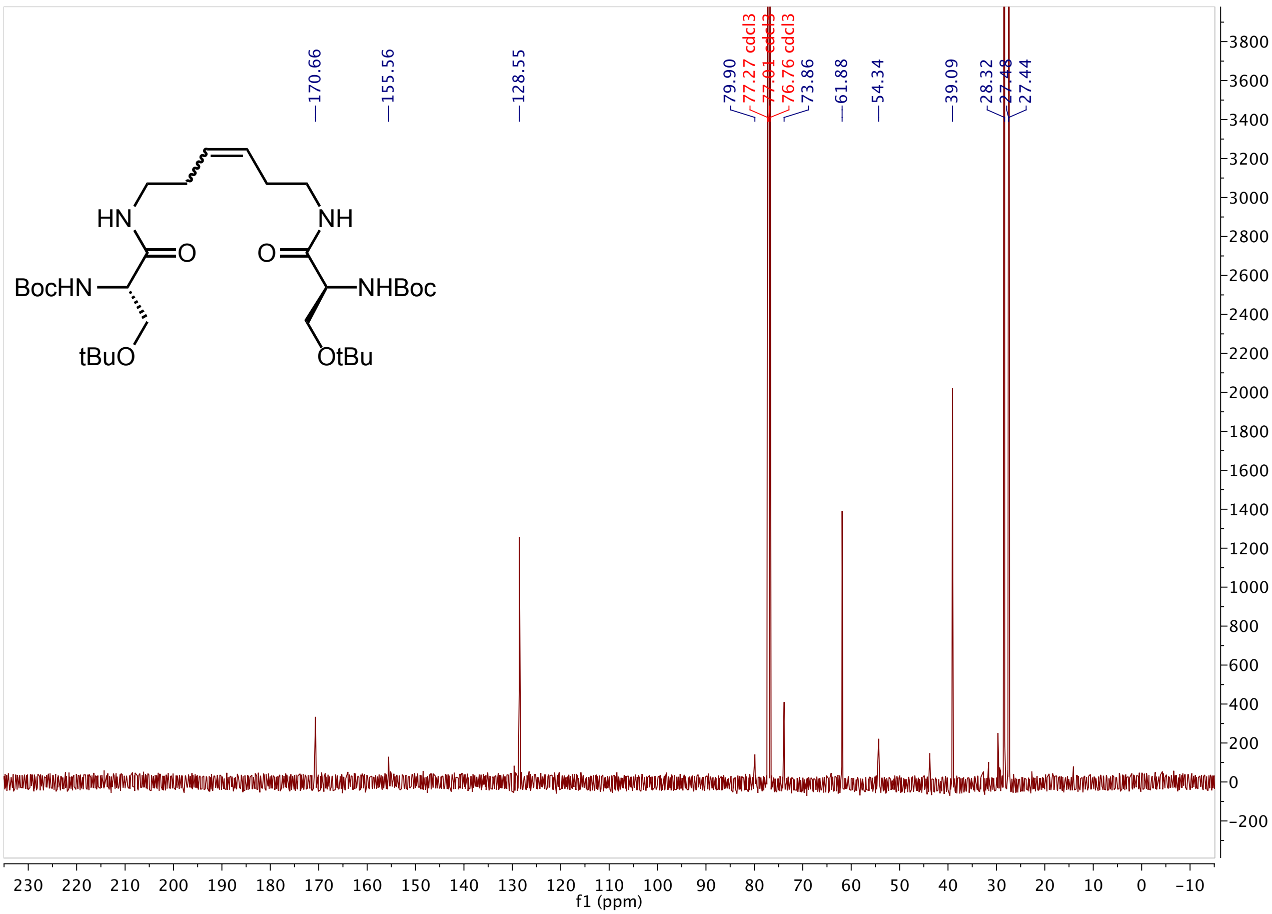
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **6g**



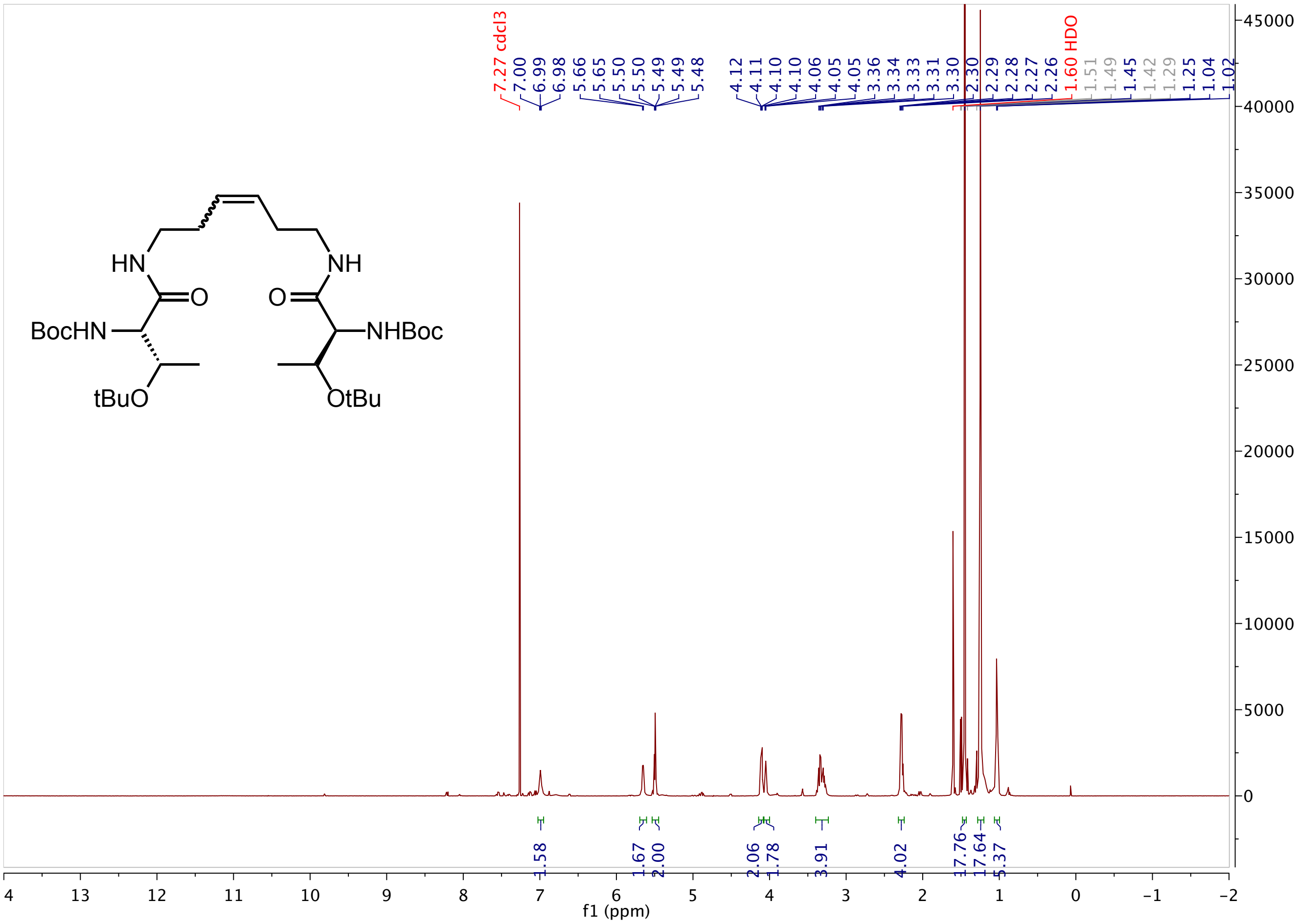
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **6i**



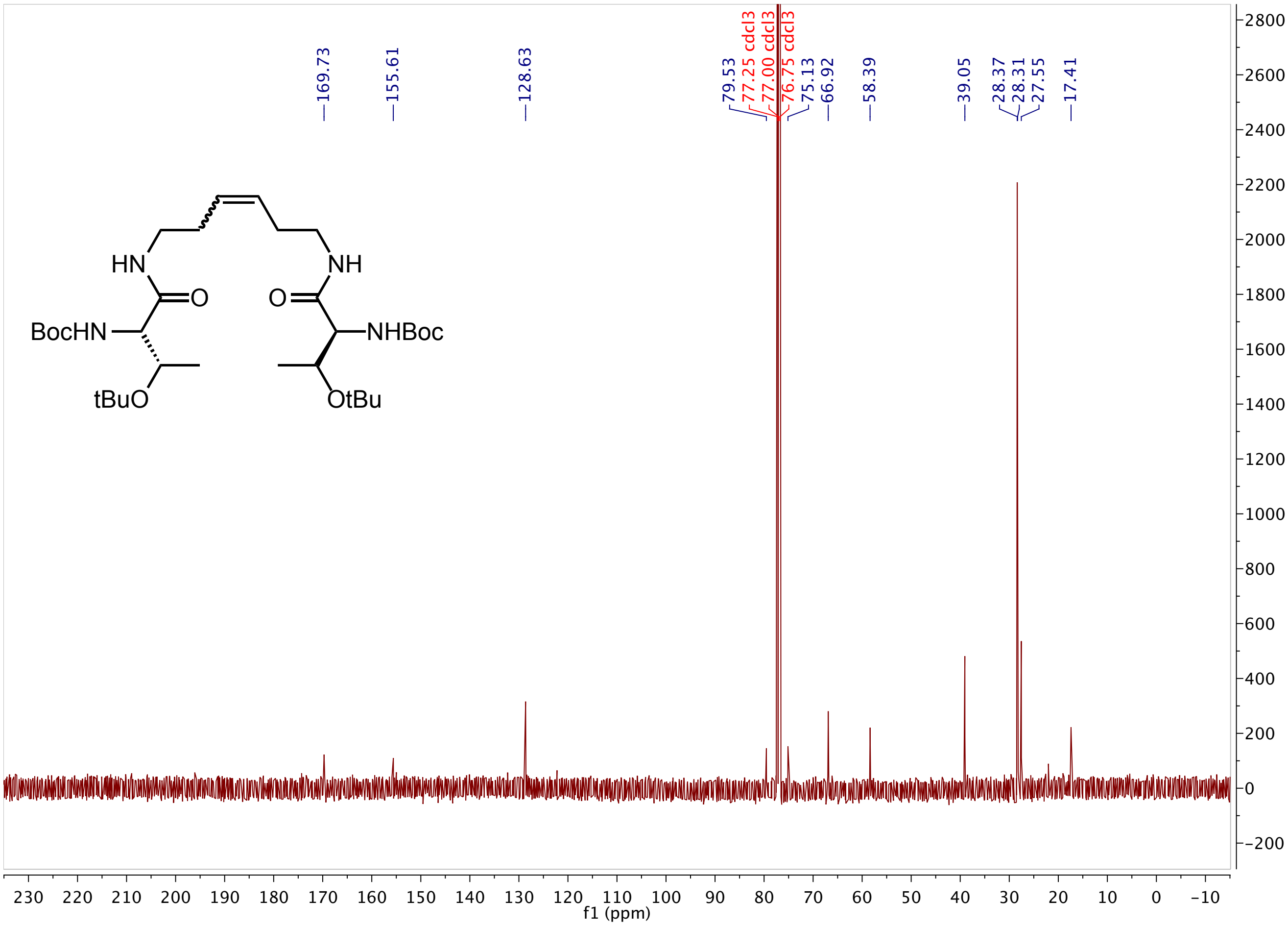
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **6i**



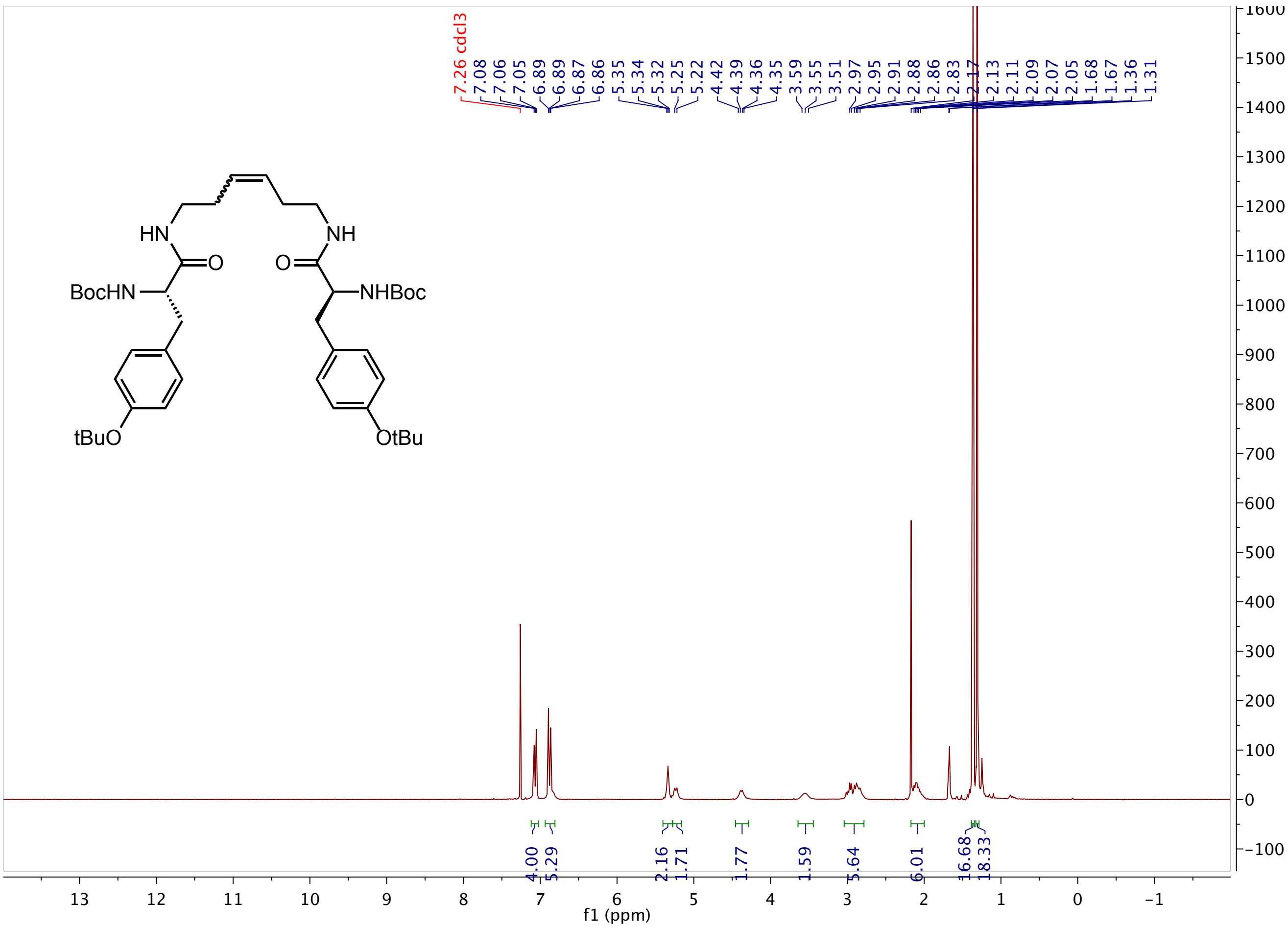
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **6j**



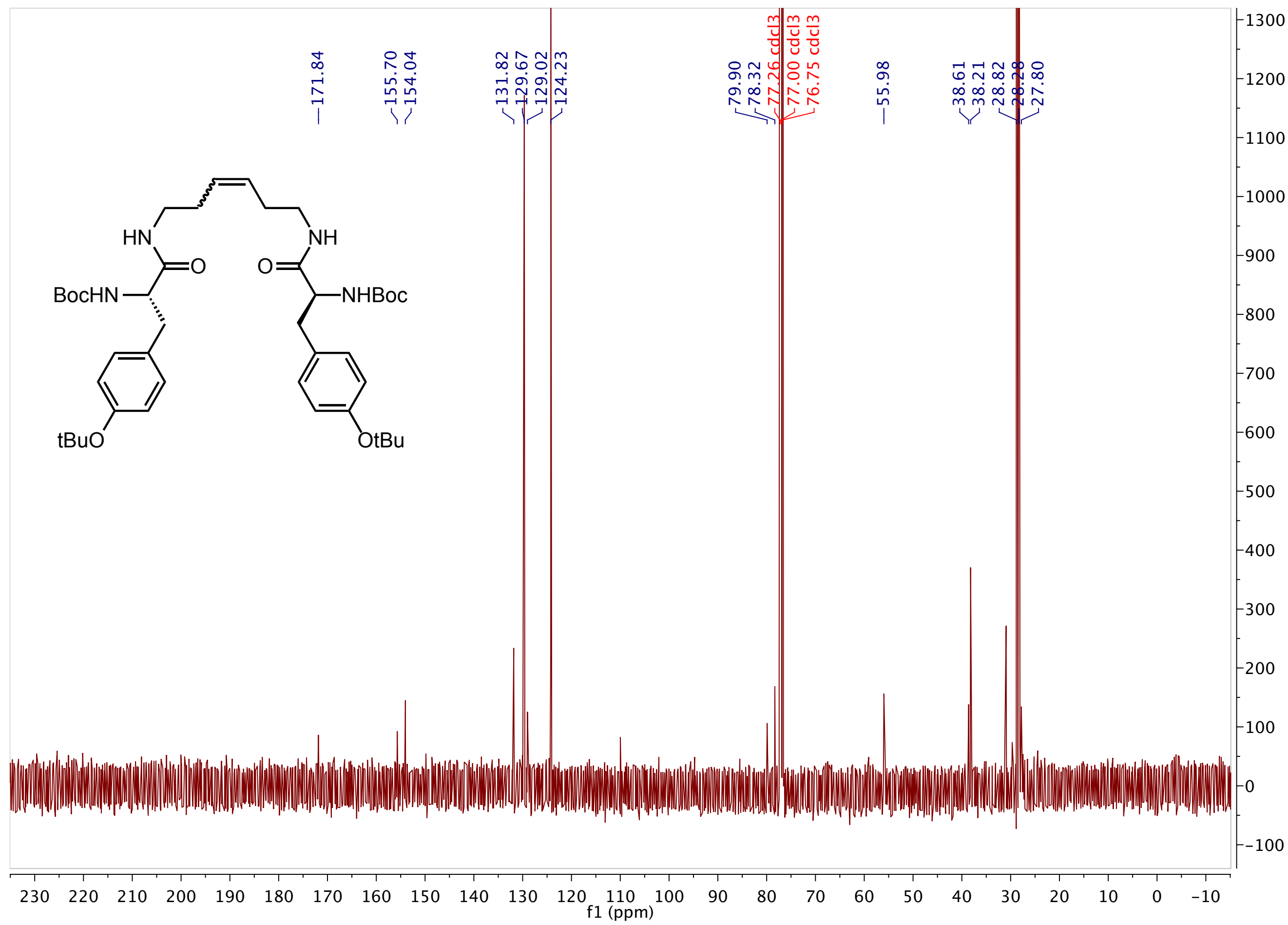
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **6j**



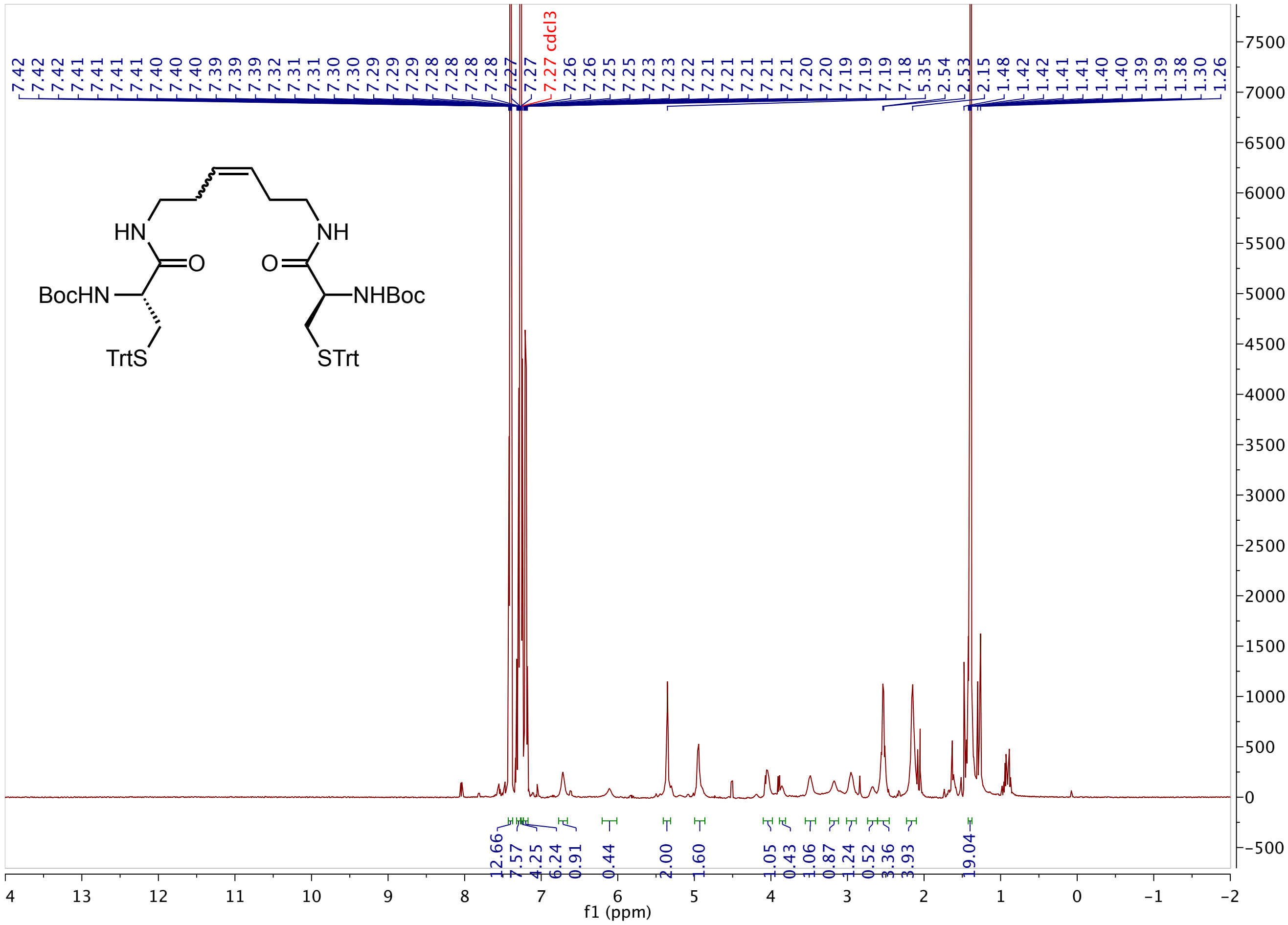
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **6k**



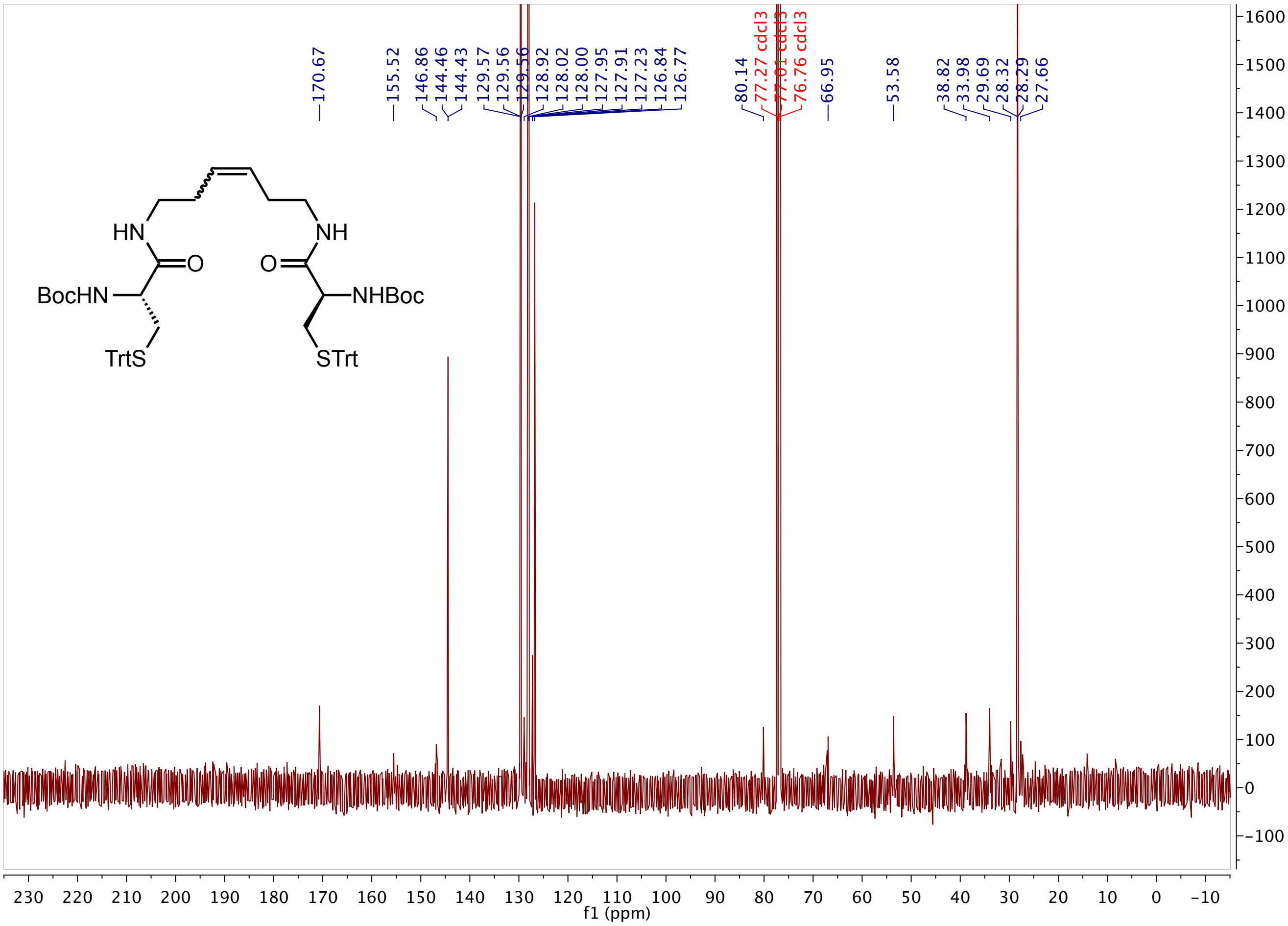
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **6k**



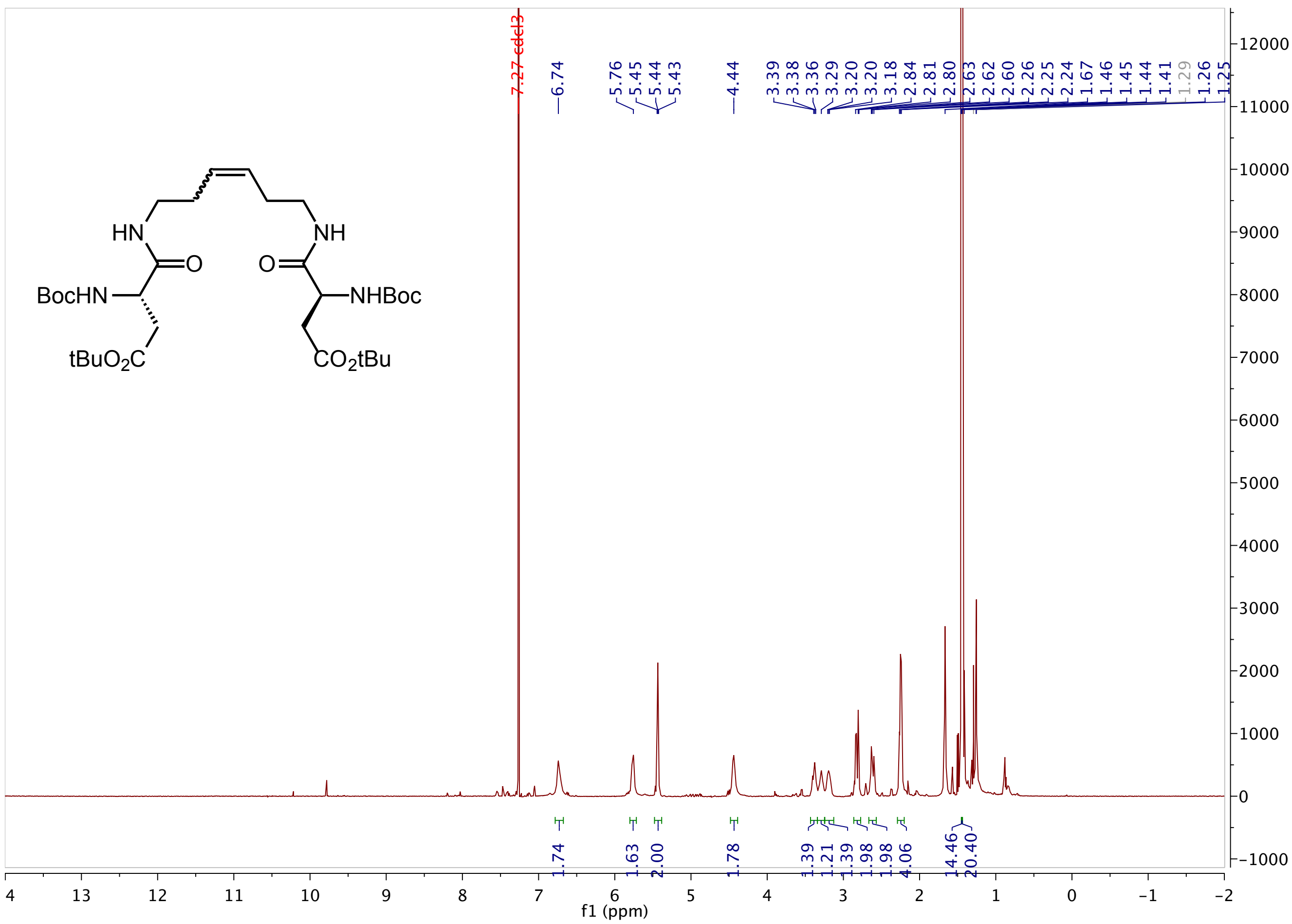
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **6m**



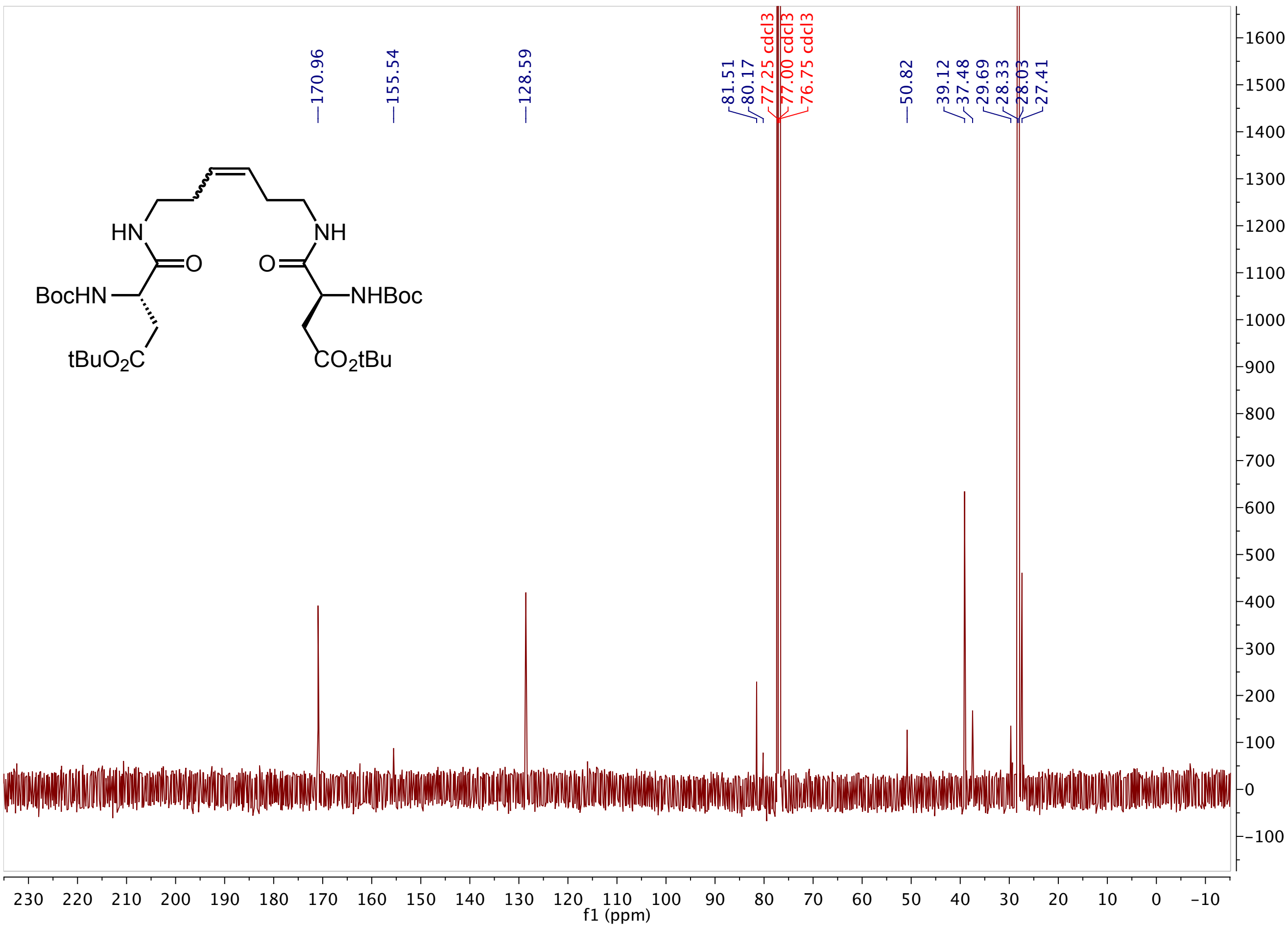
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **6m**



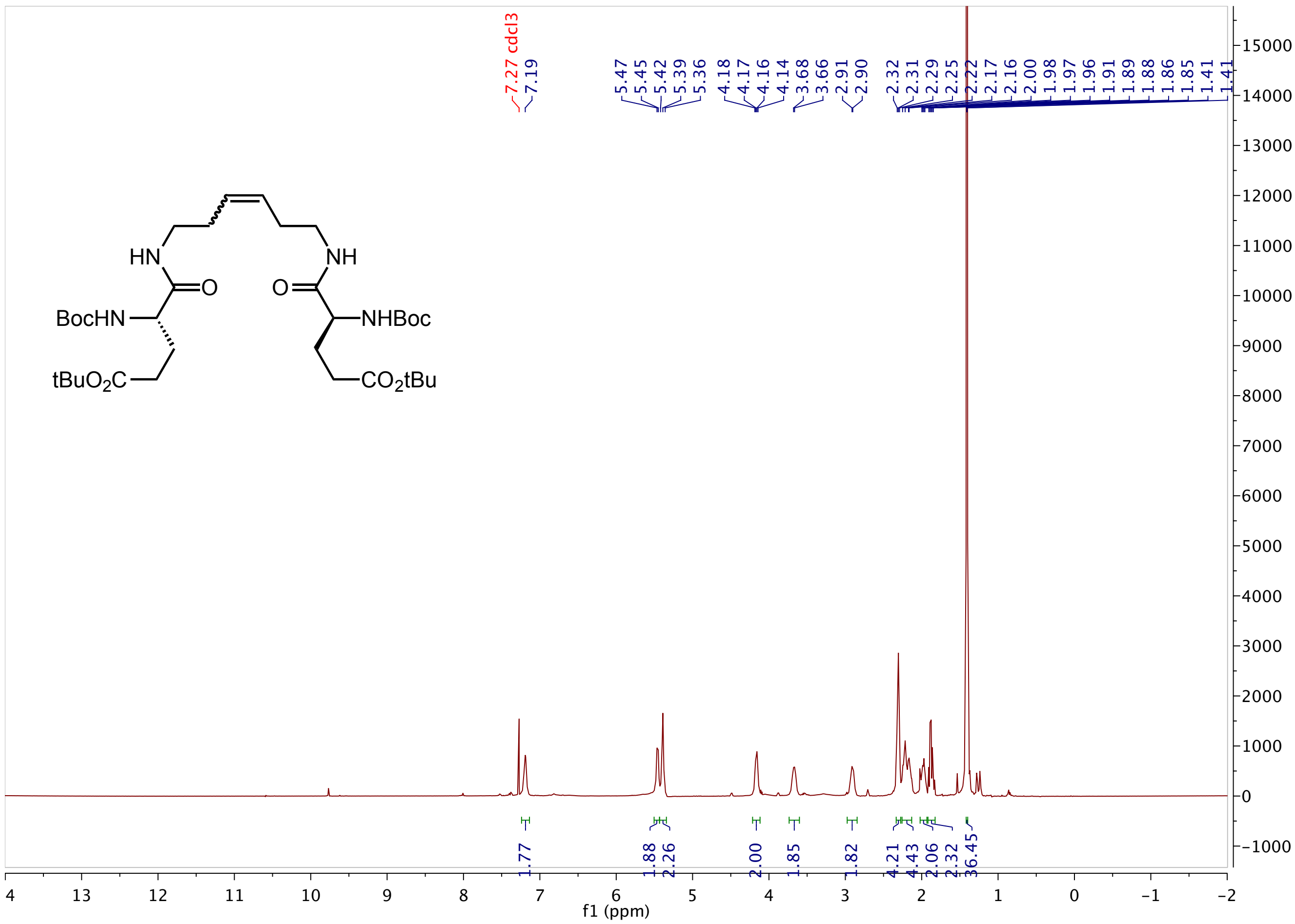
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **6n**



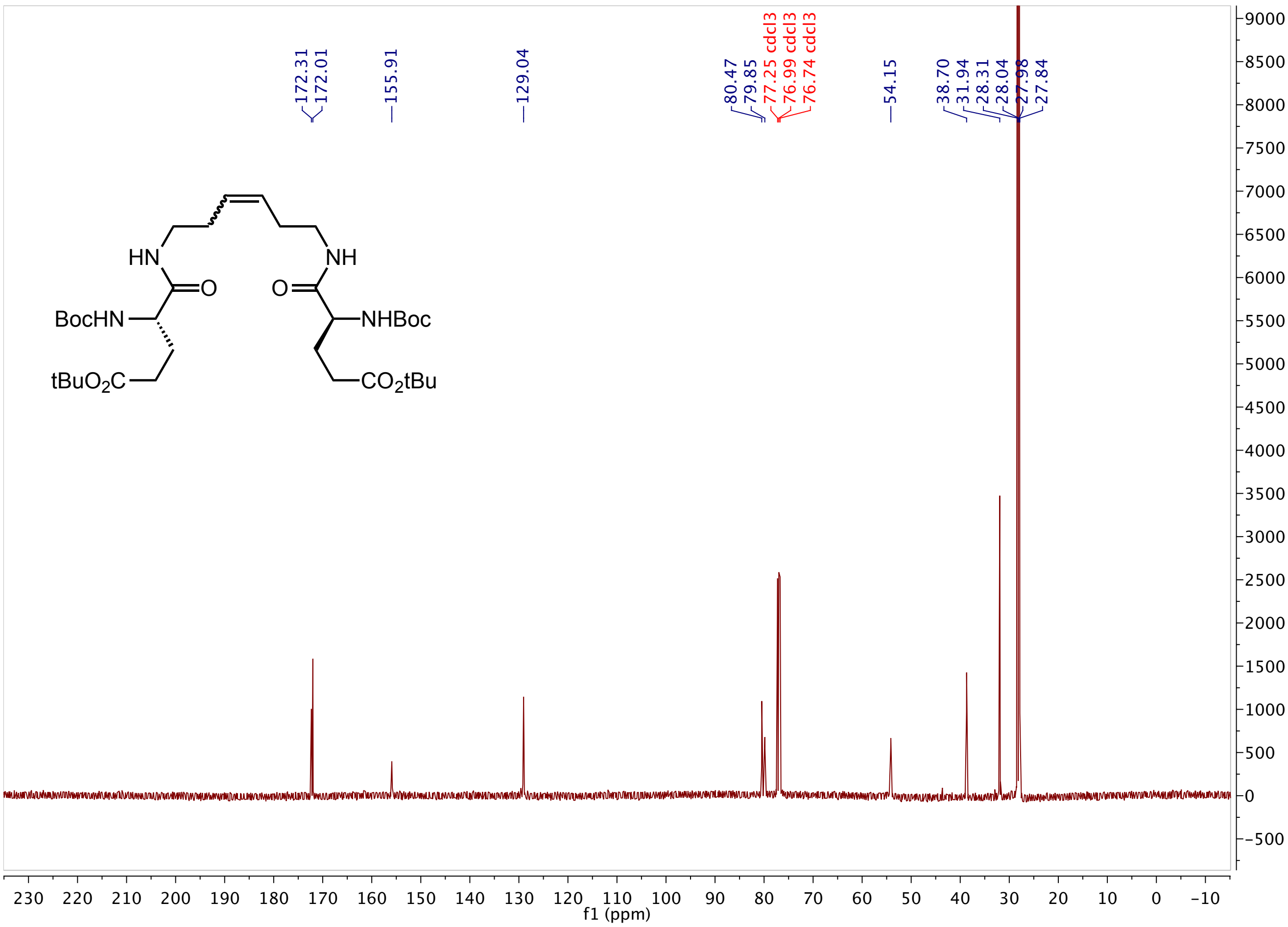
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **6n**



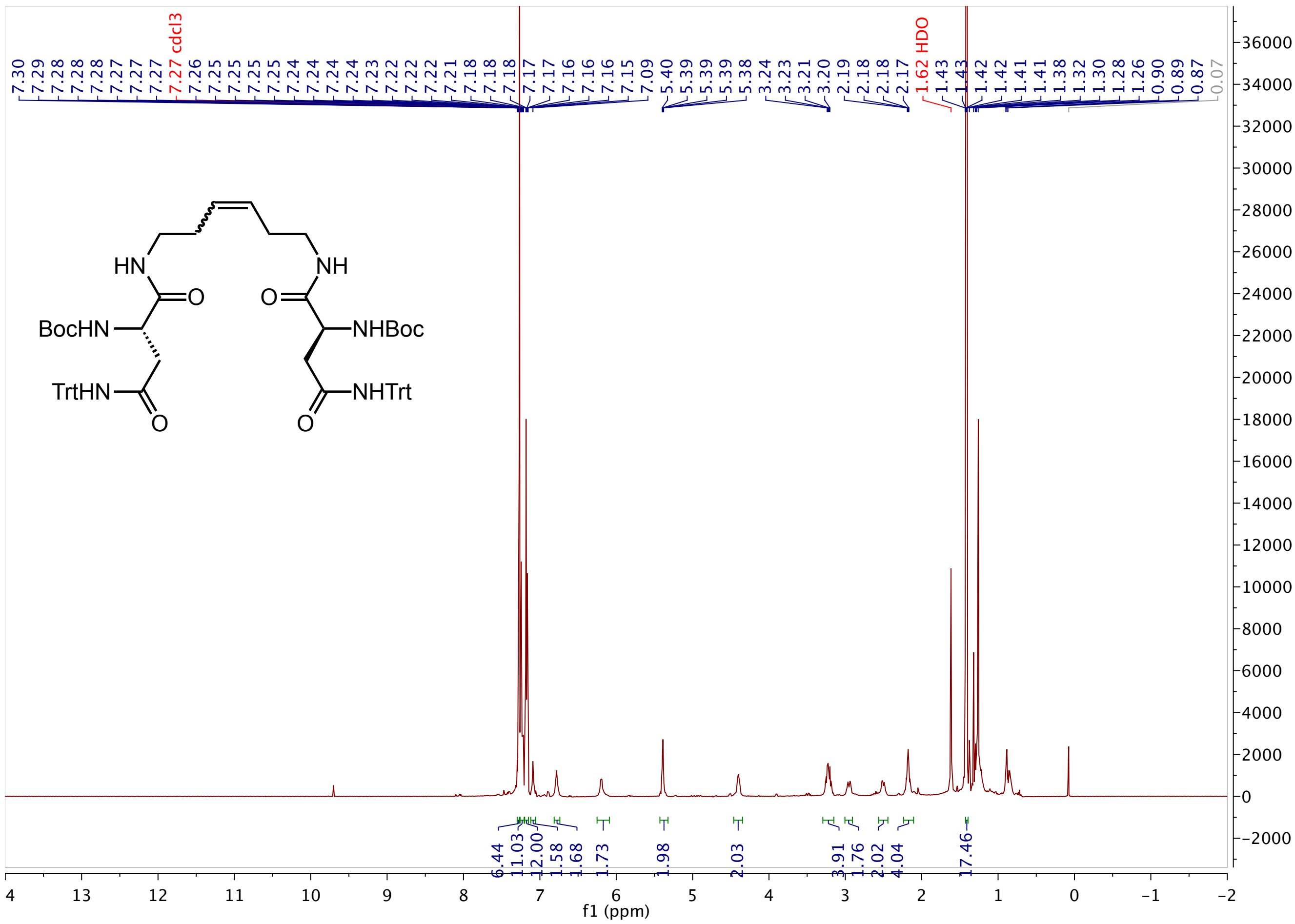
[1]H NMR (500 MHz, $CDCl_3$) spectrum of compound **6o**



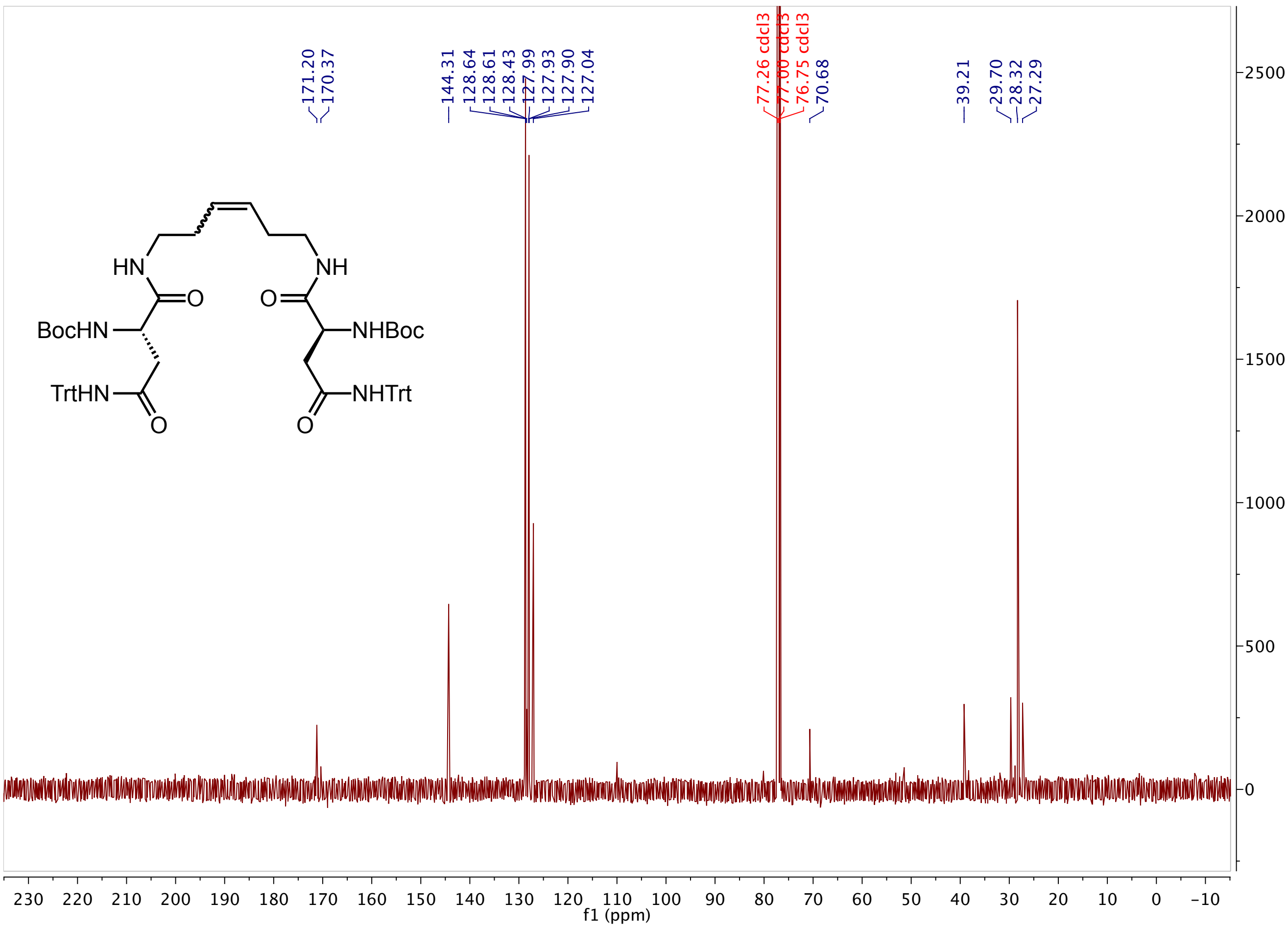
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **6o**



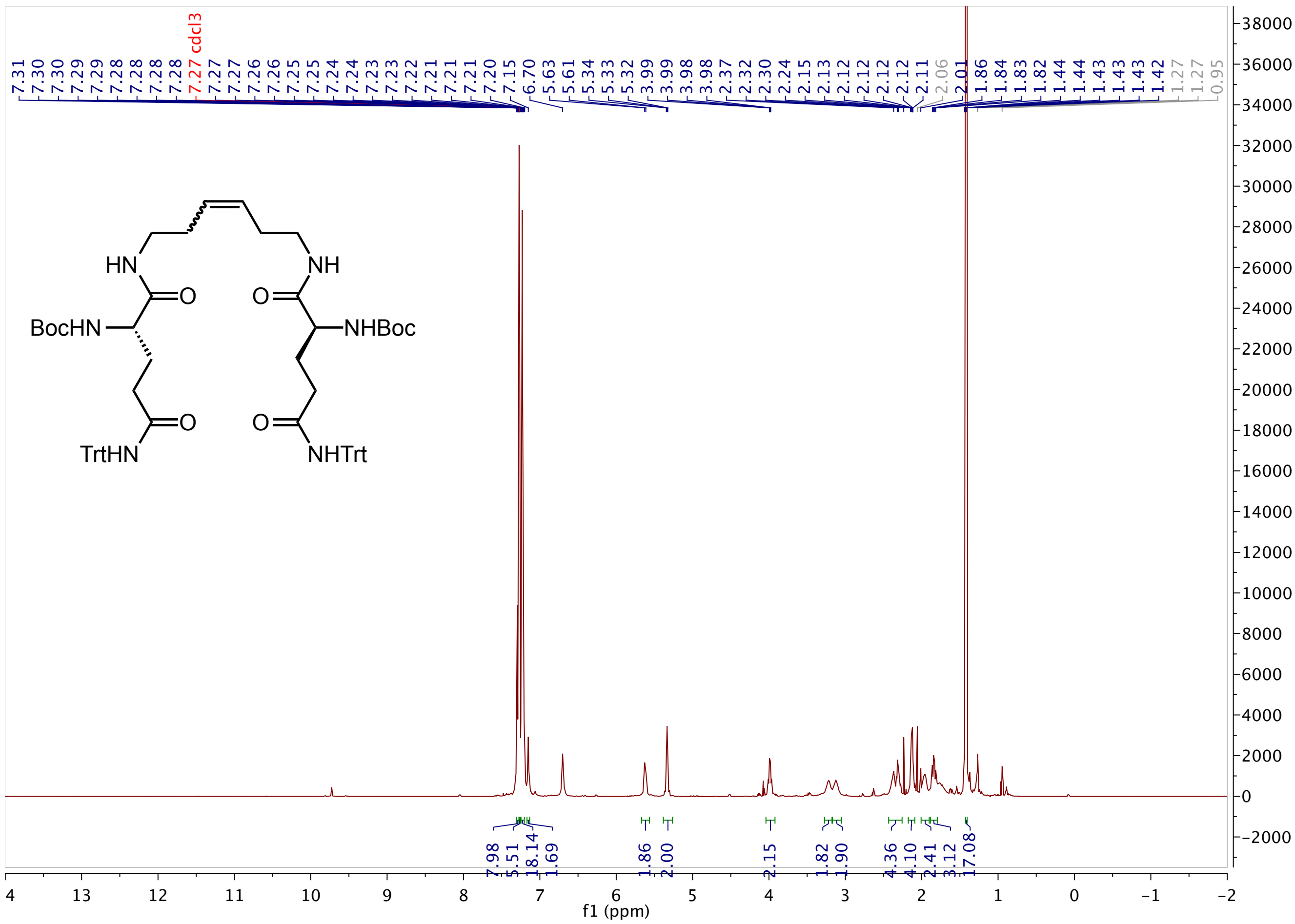
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **6p**



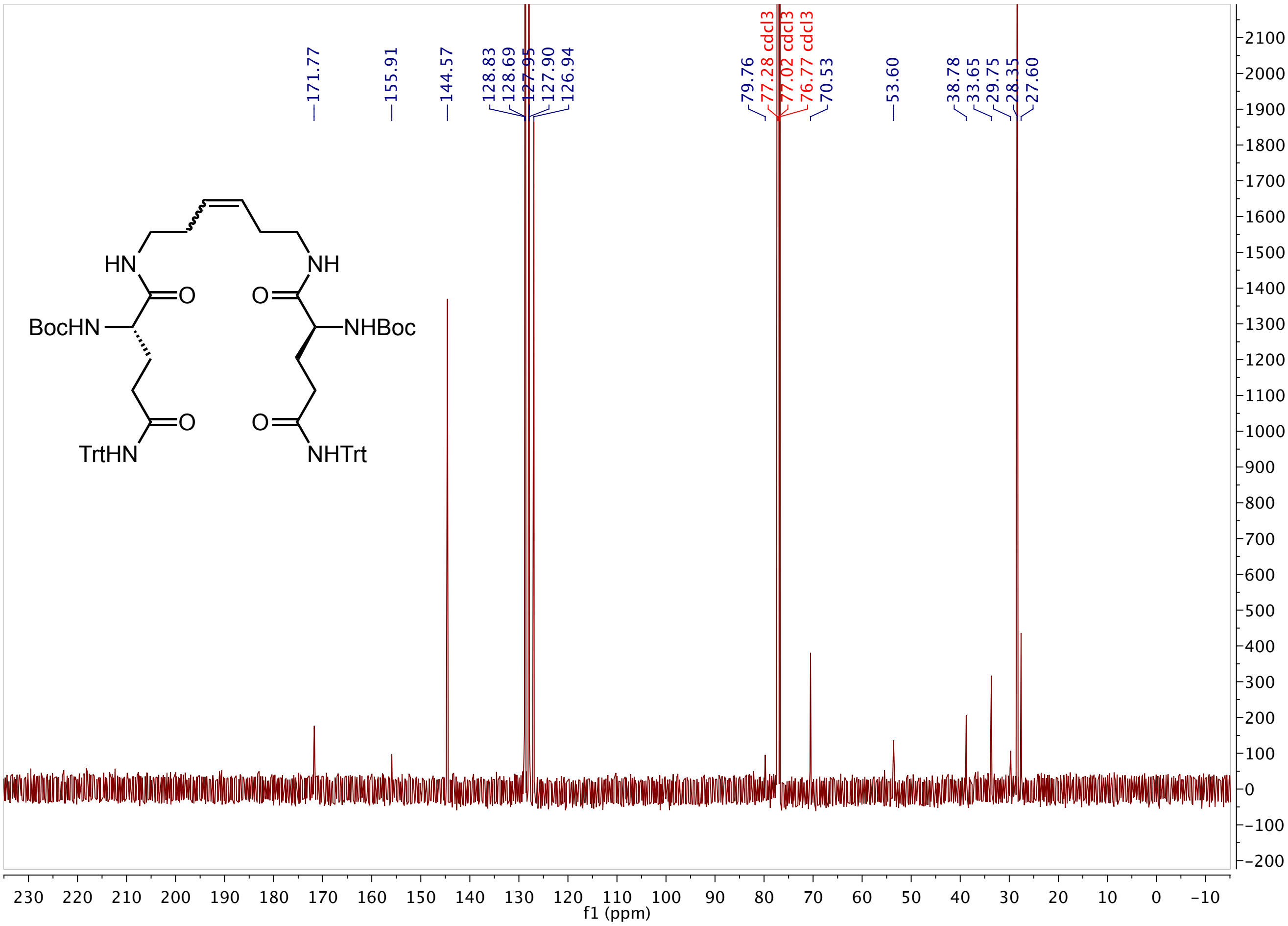
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **6p**



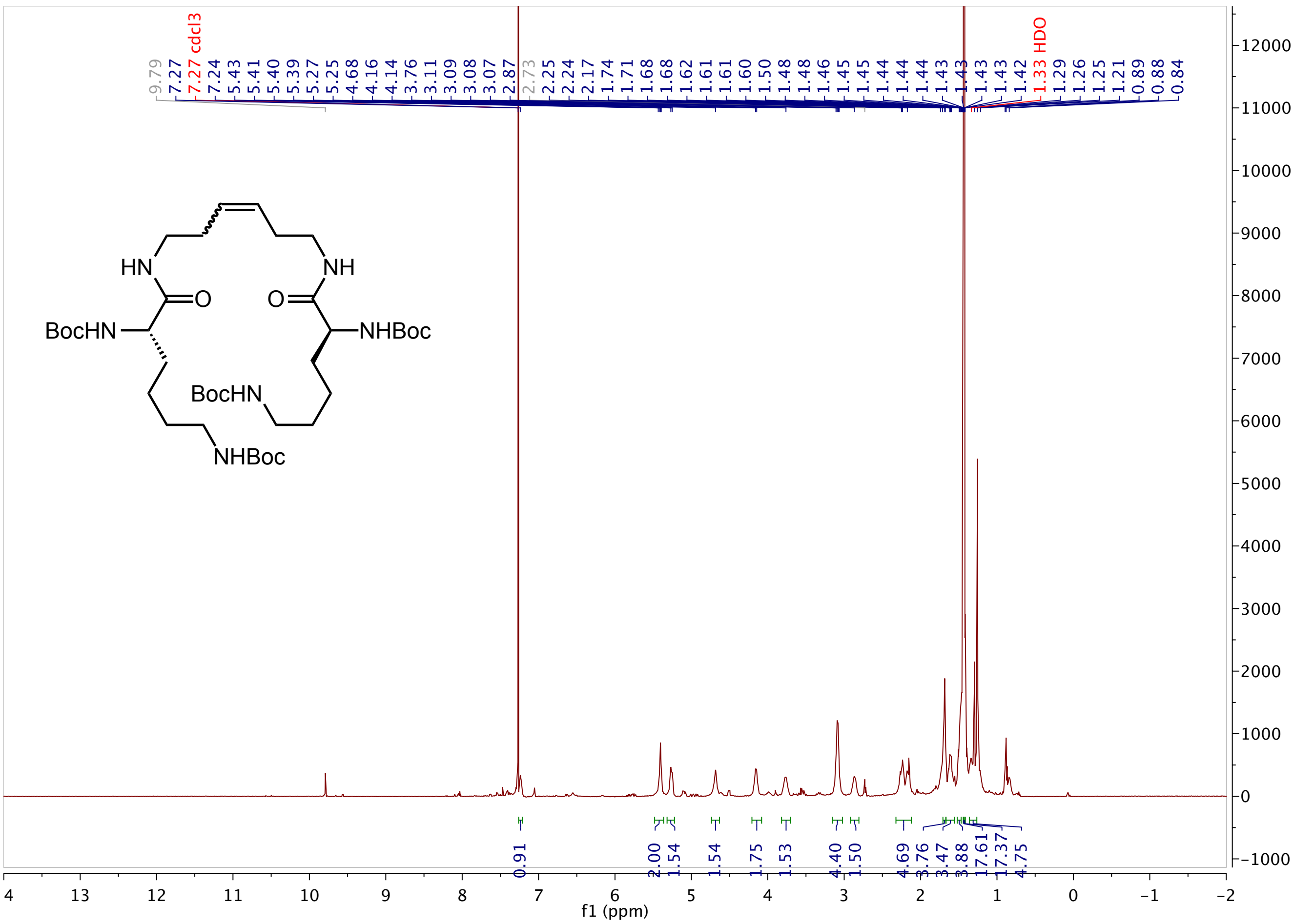
^1H NMR (500 MHz, $CDCl_3$) spectrum of compound **6q**



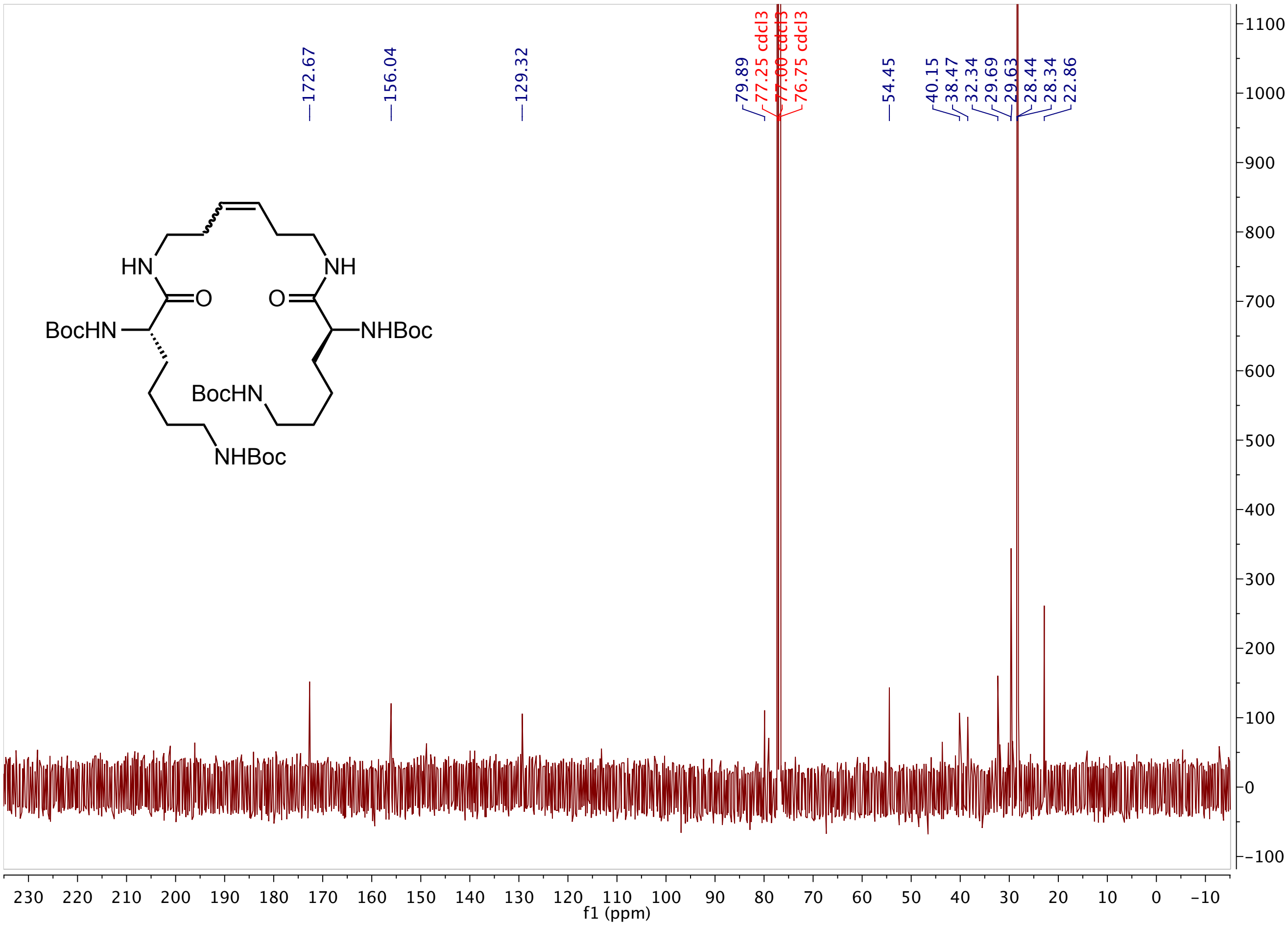
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **6q**



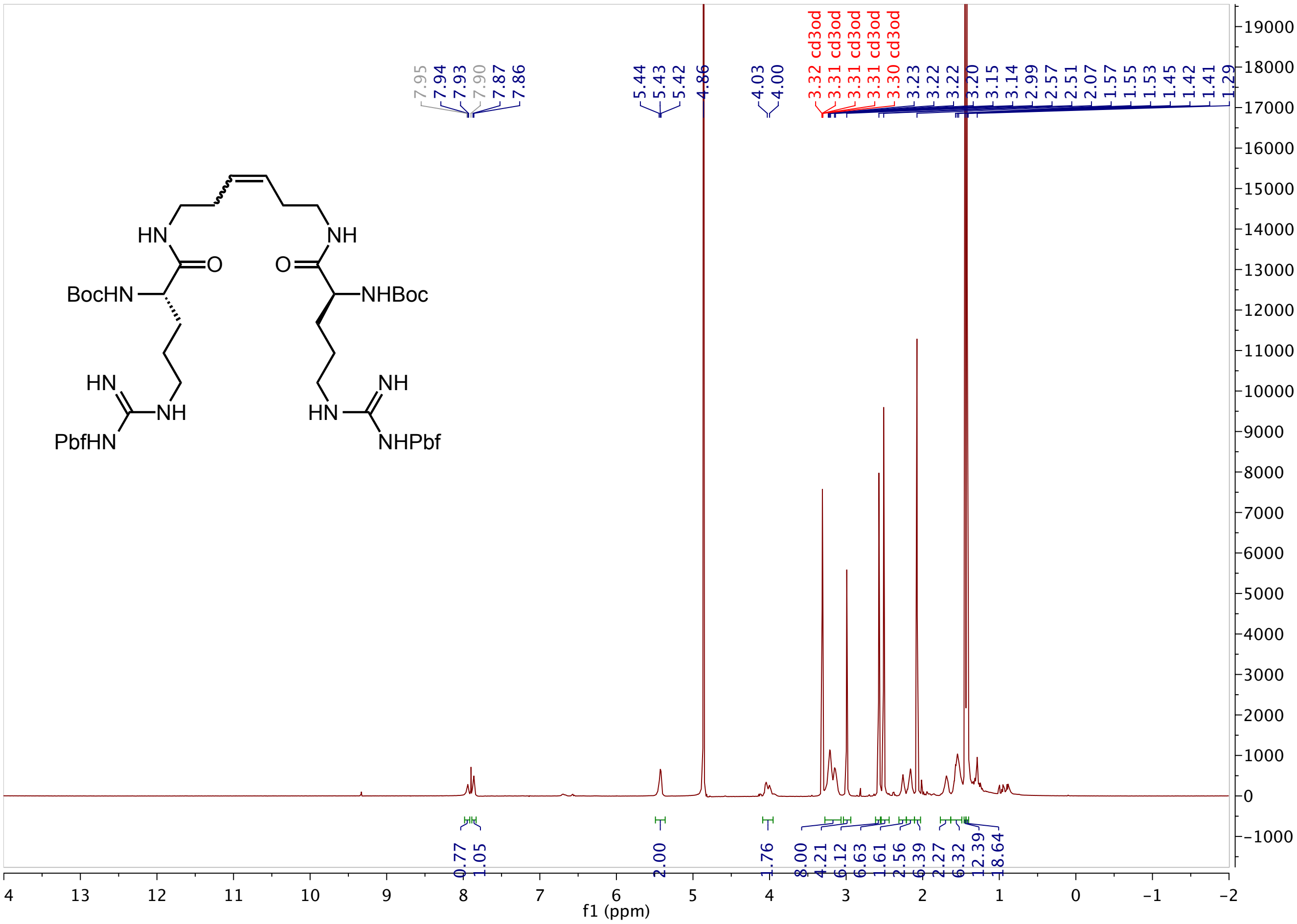
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **6r**



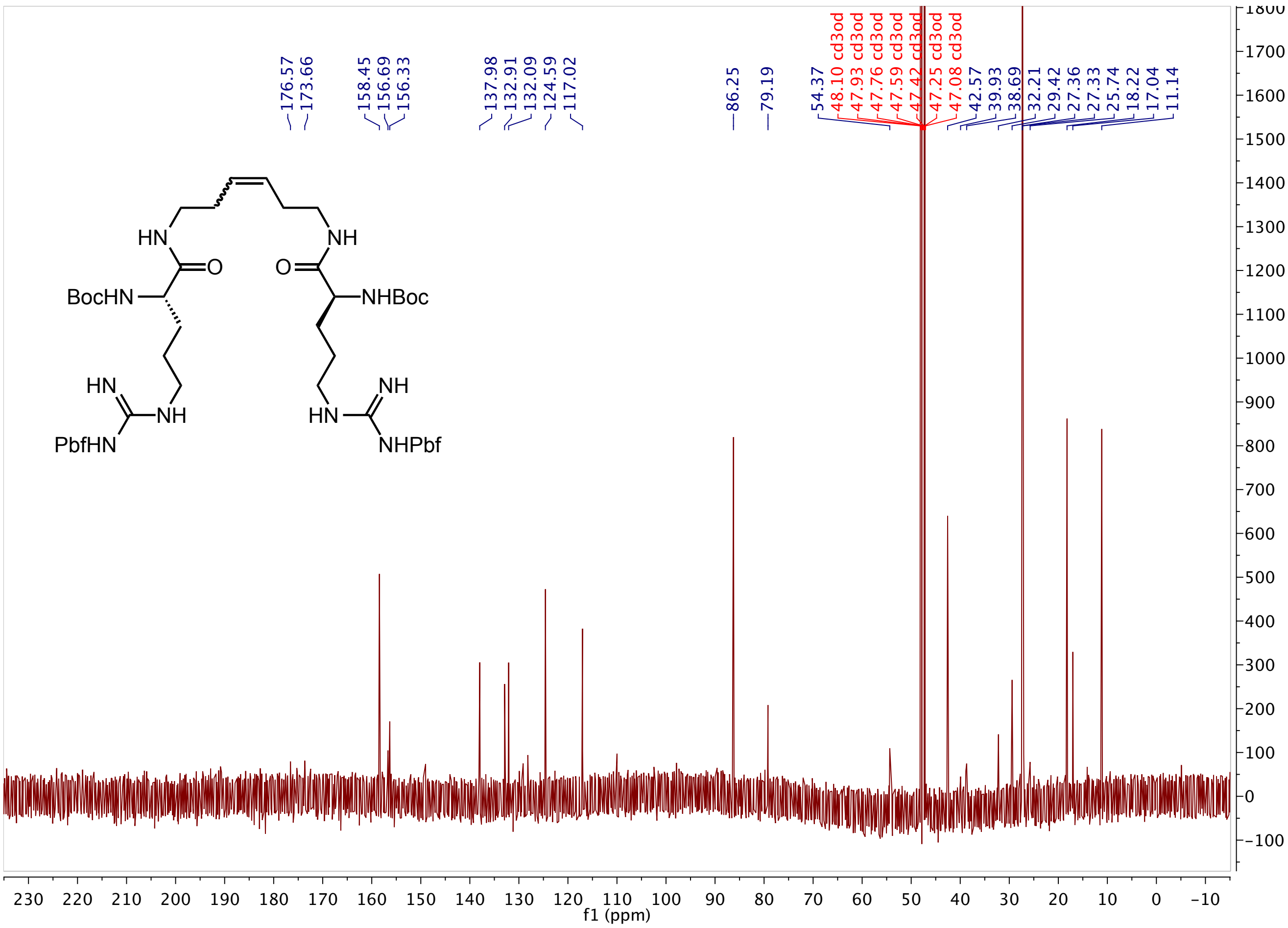
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **6r**



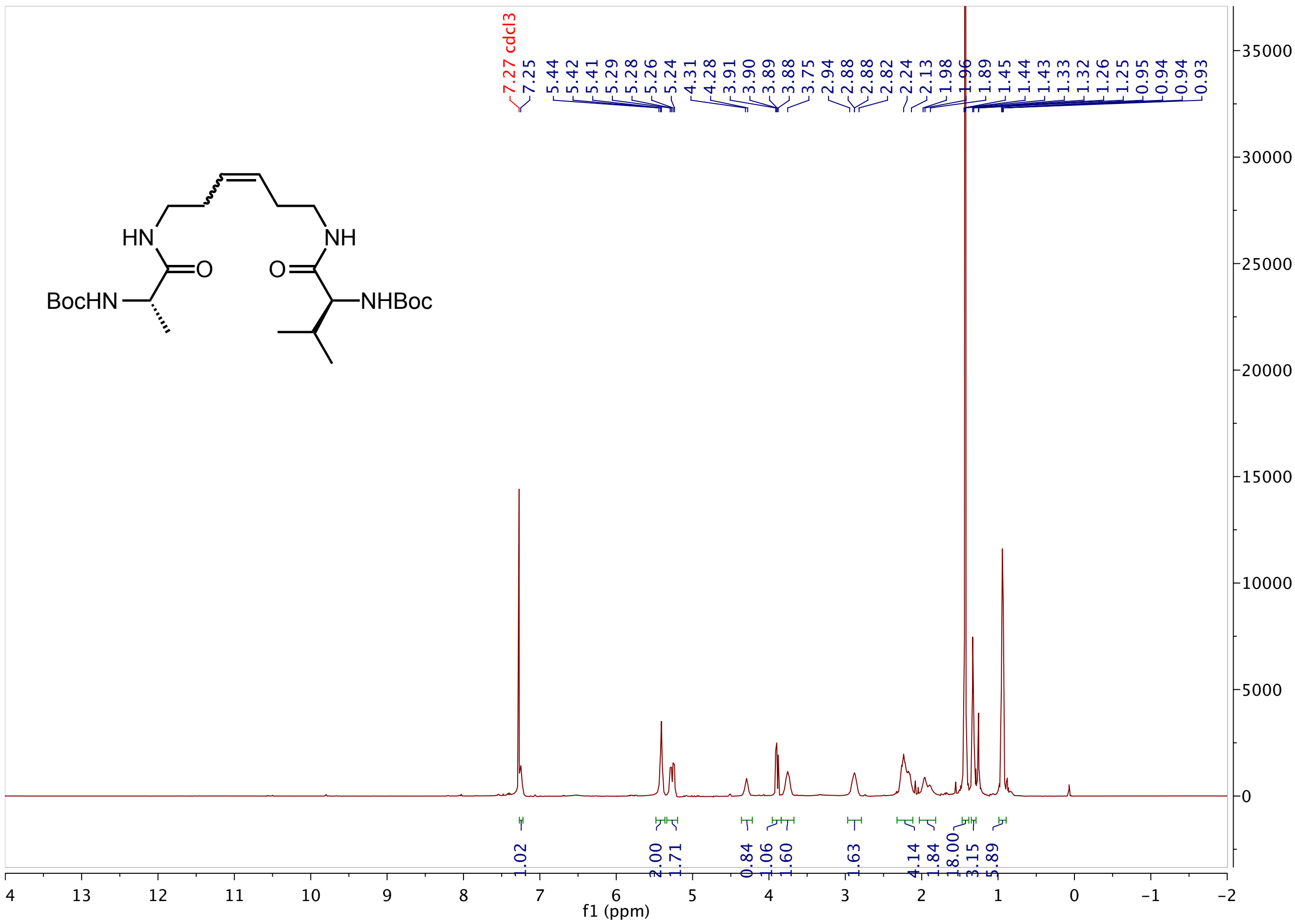
^1H NMR (500 MHz, CD_3OD) spectrum of compound **6s**



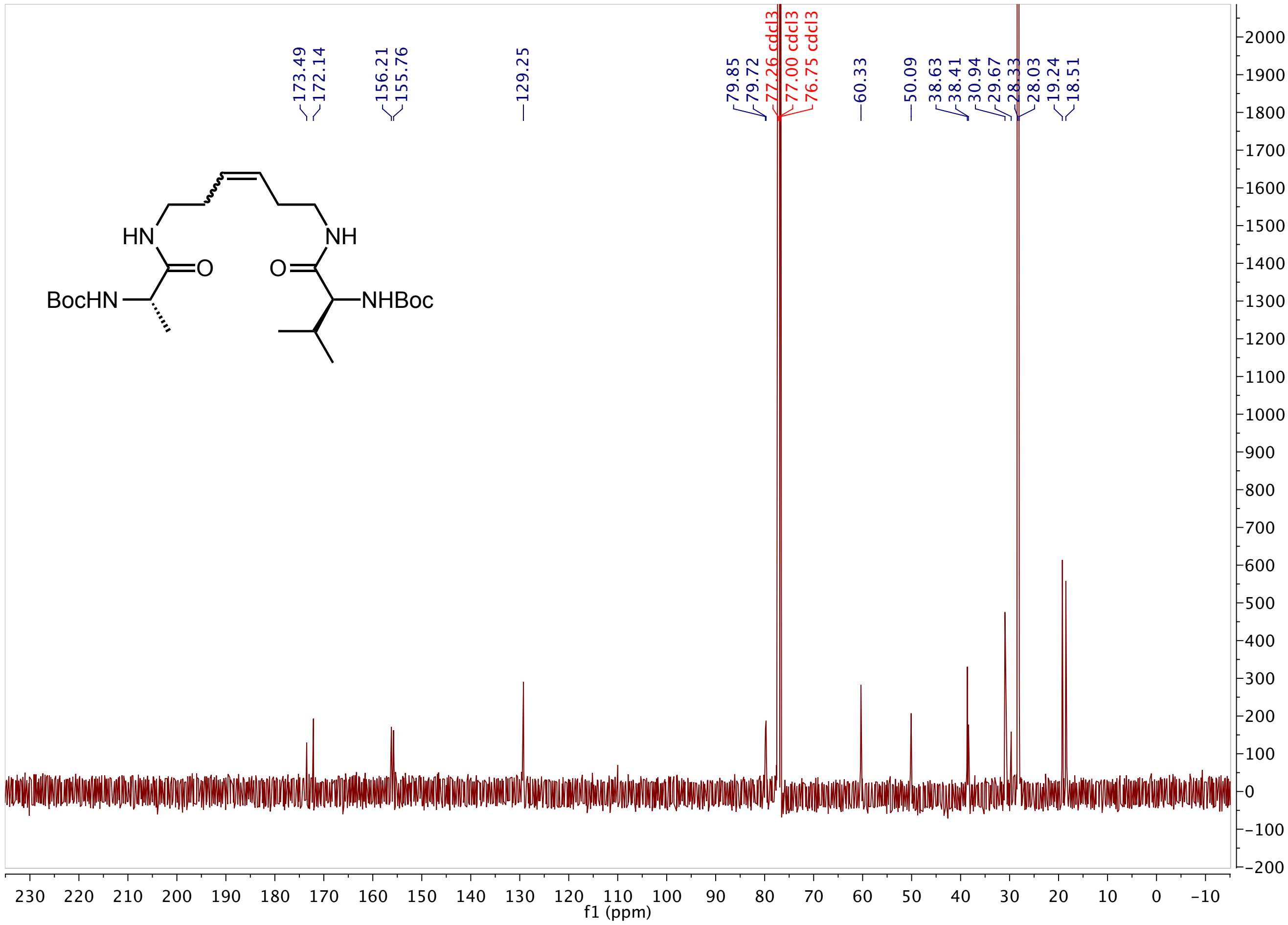
^{13}C NMR (126 MHz, CD_3OD) spectrum of compound **6s**



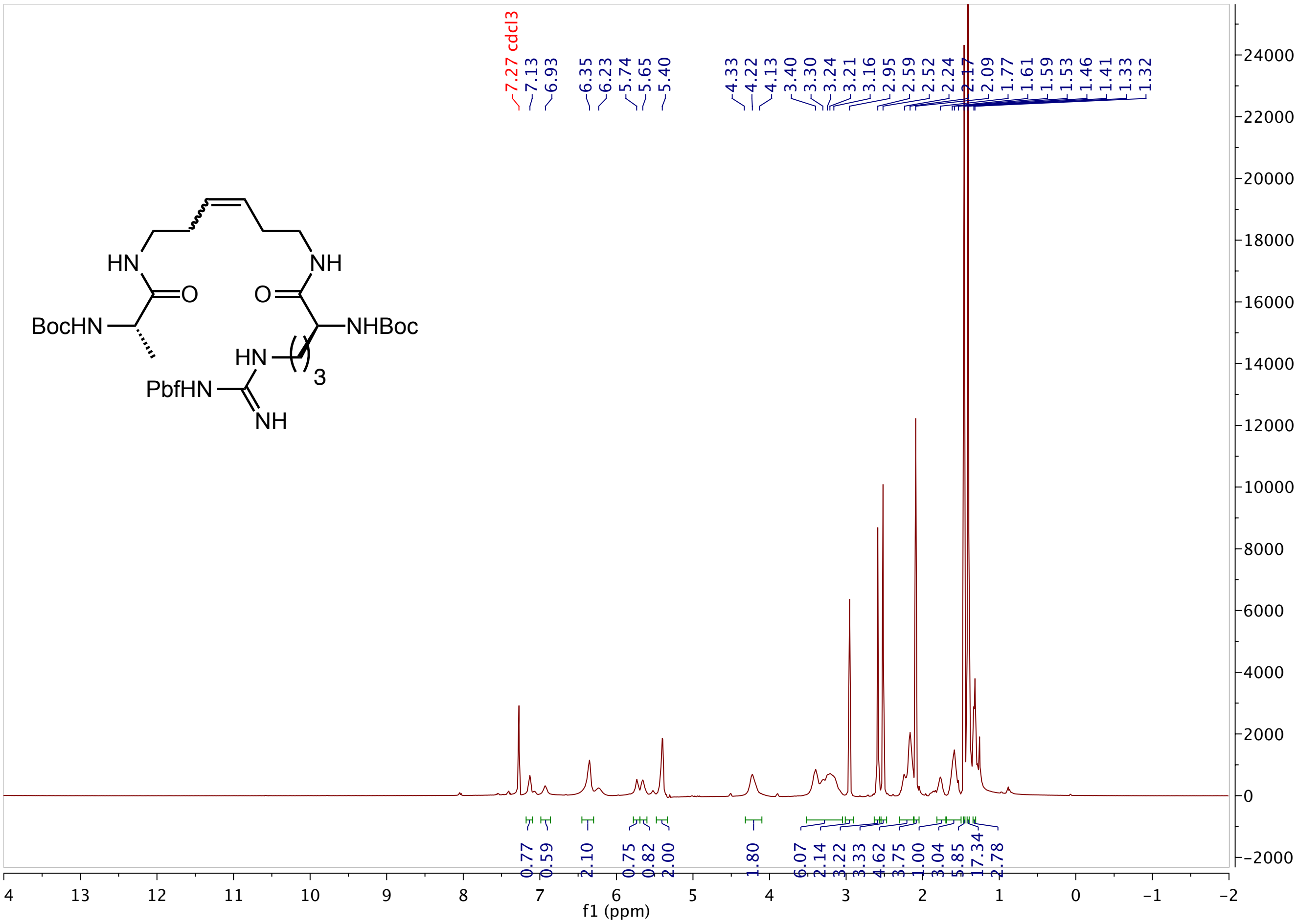
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **7**



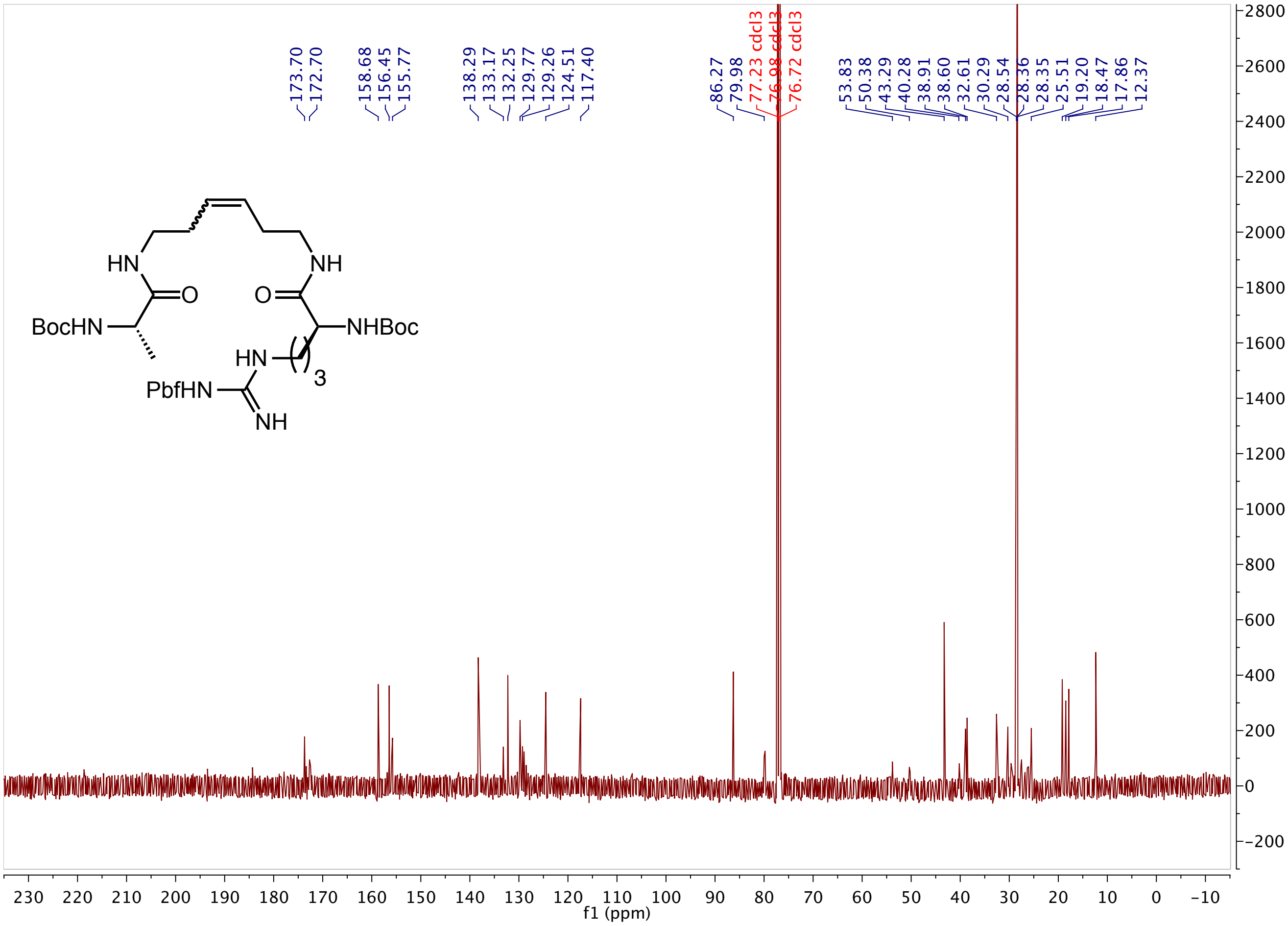
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **7**



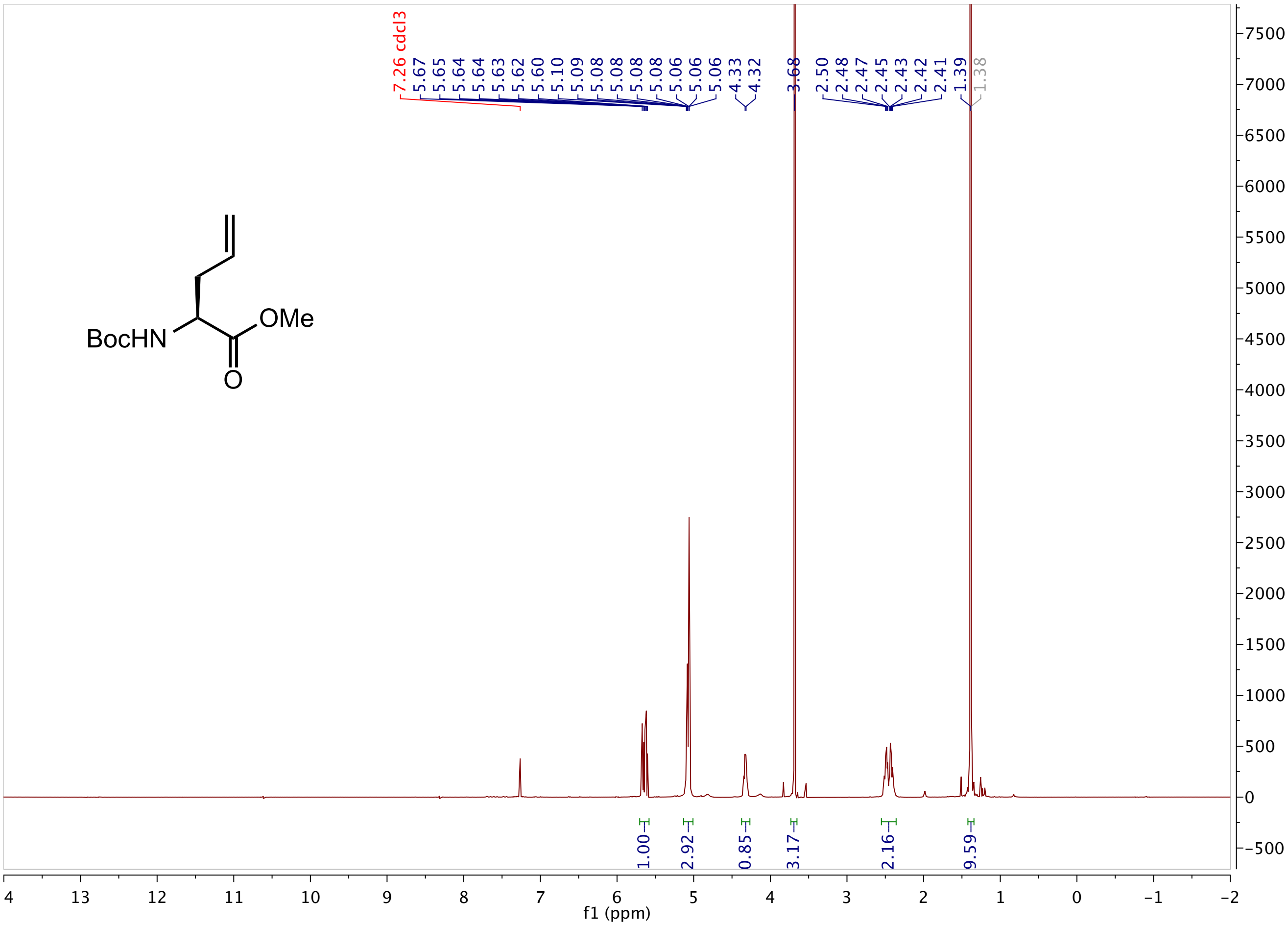
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **8**



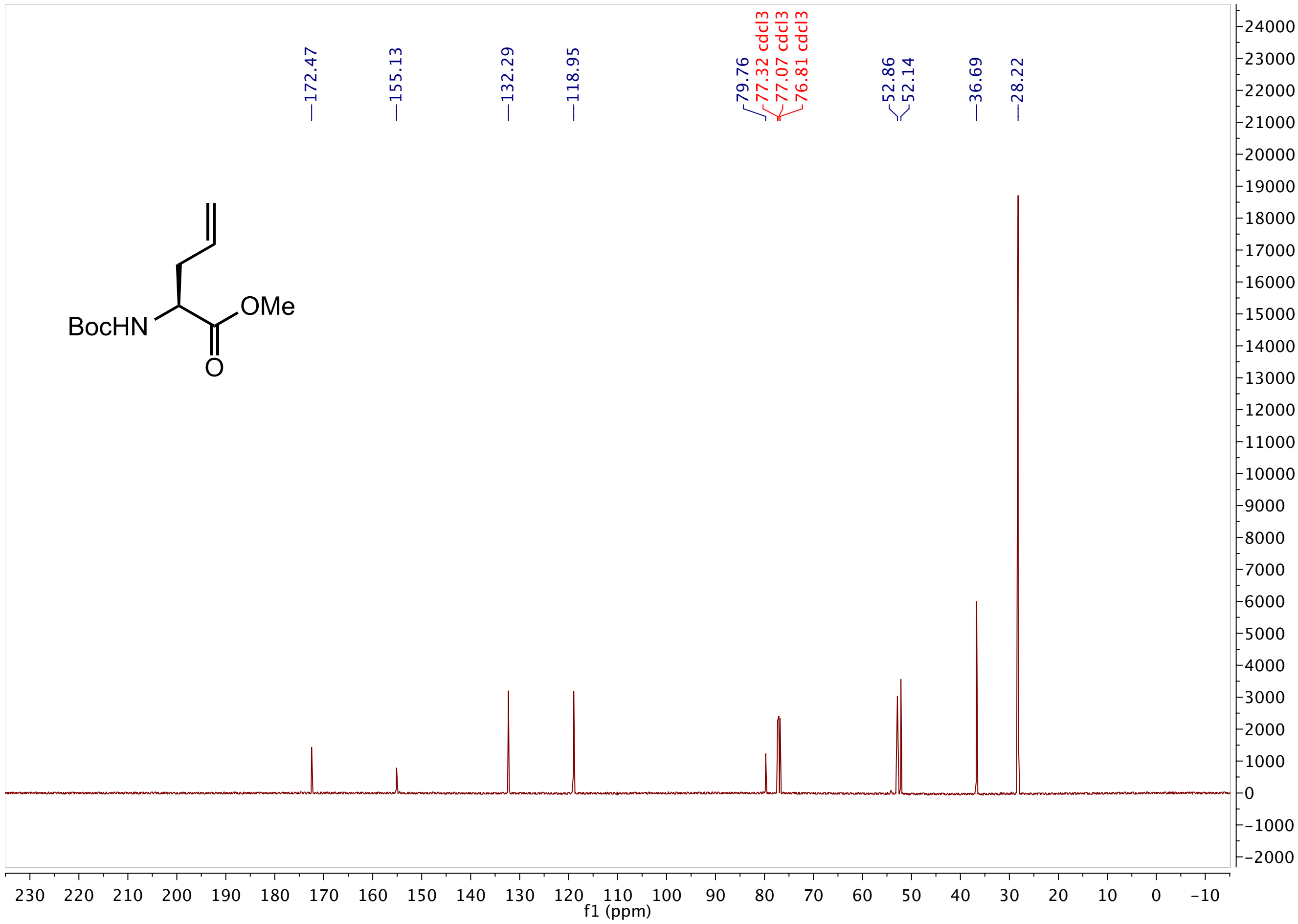
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **8**



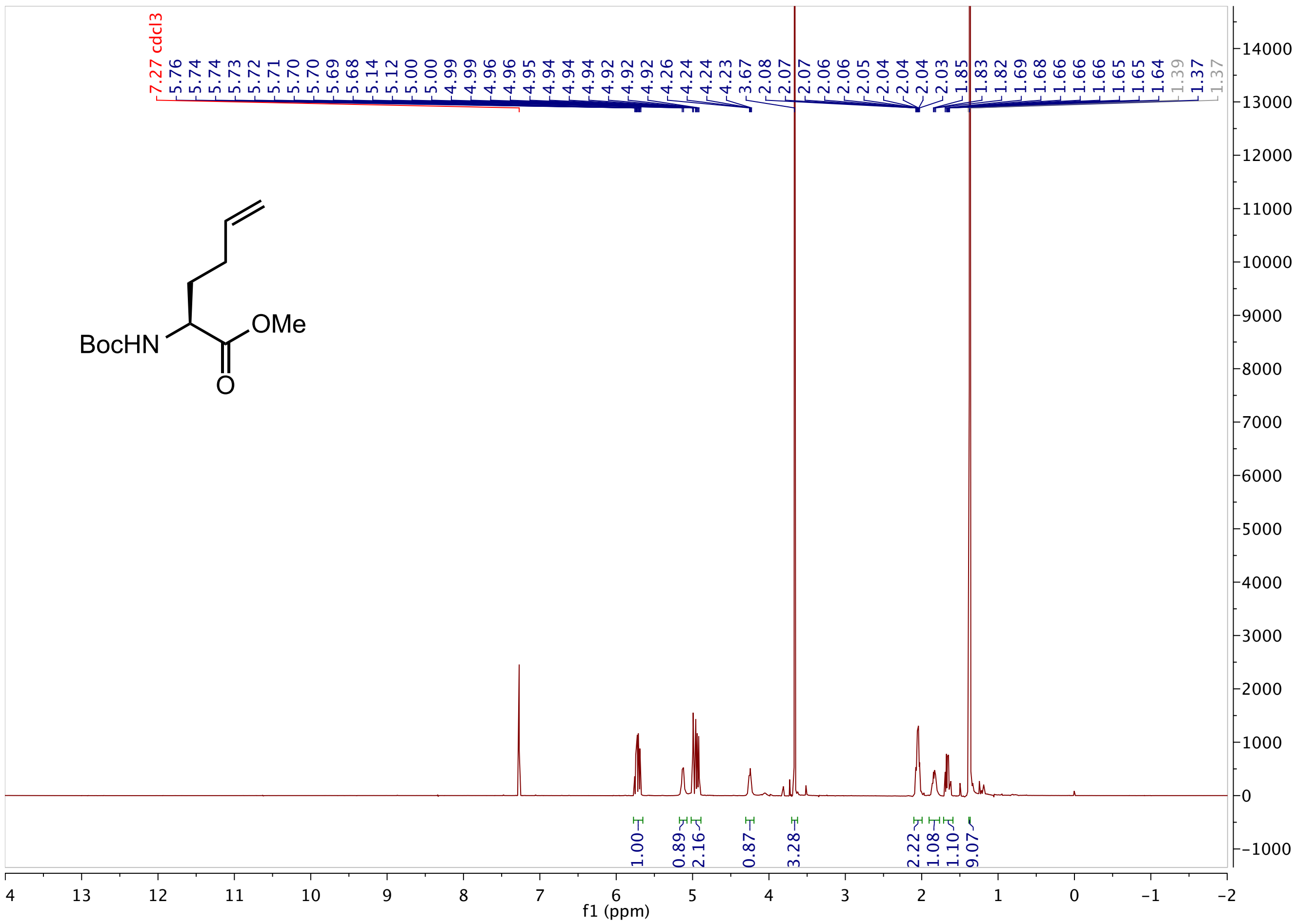
^1H NMR (500 MHz, $CDCl_3$) spectrum of compound **9a**



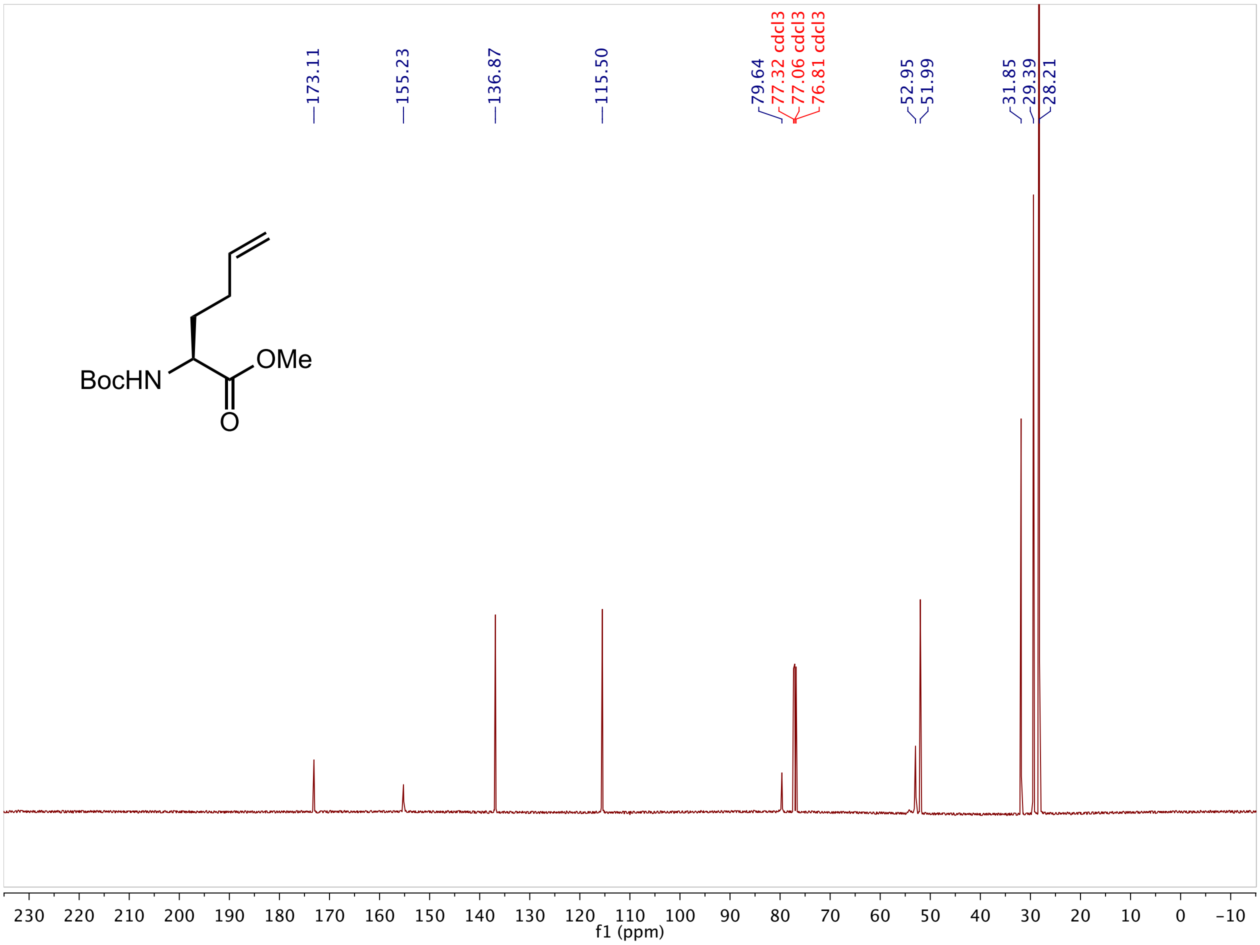
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **9a**



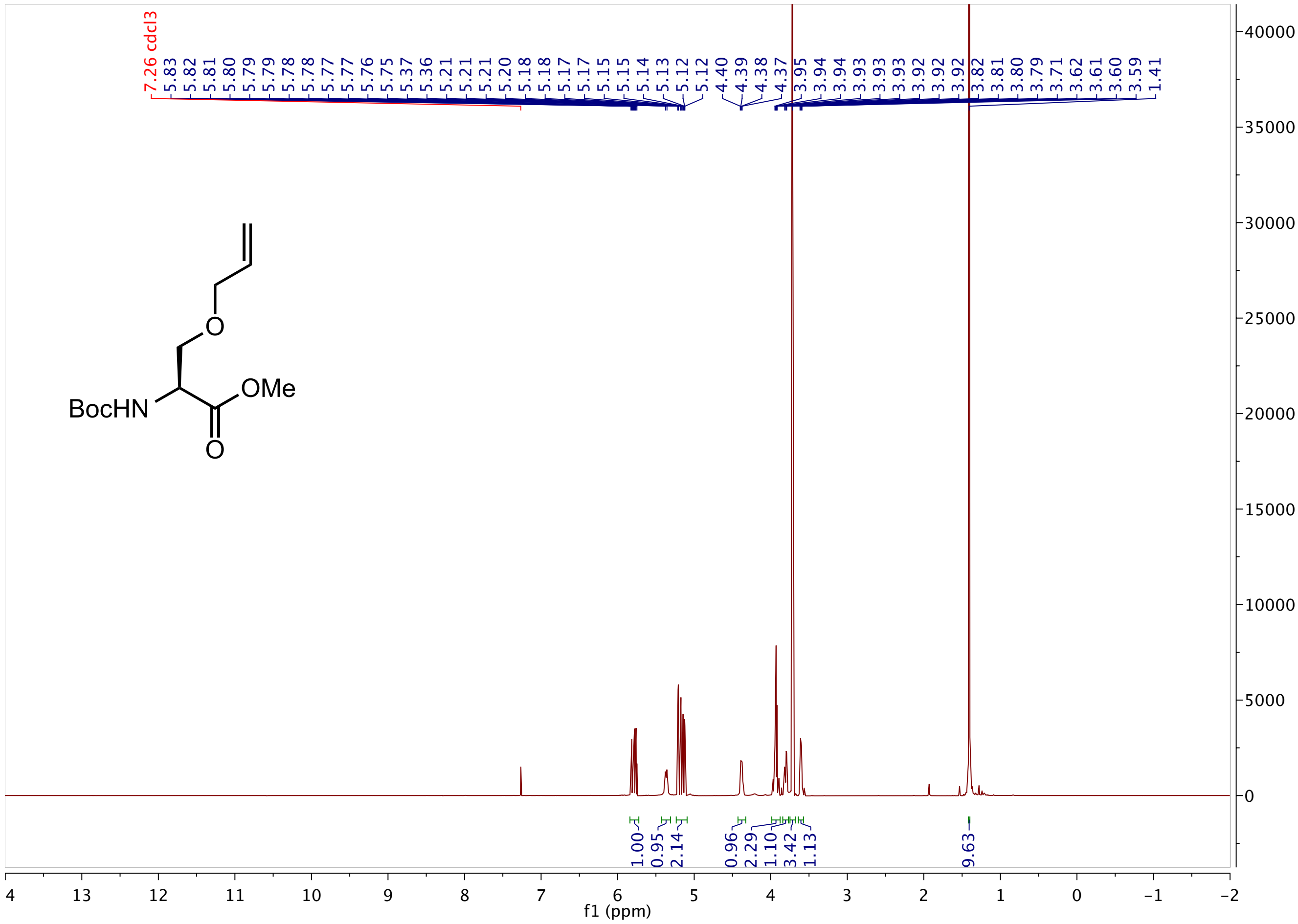
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **9b**



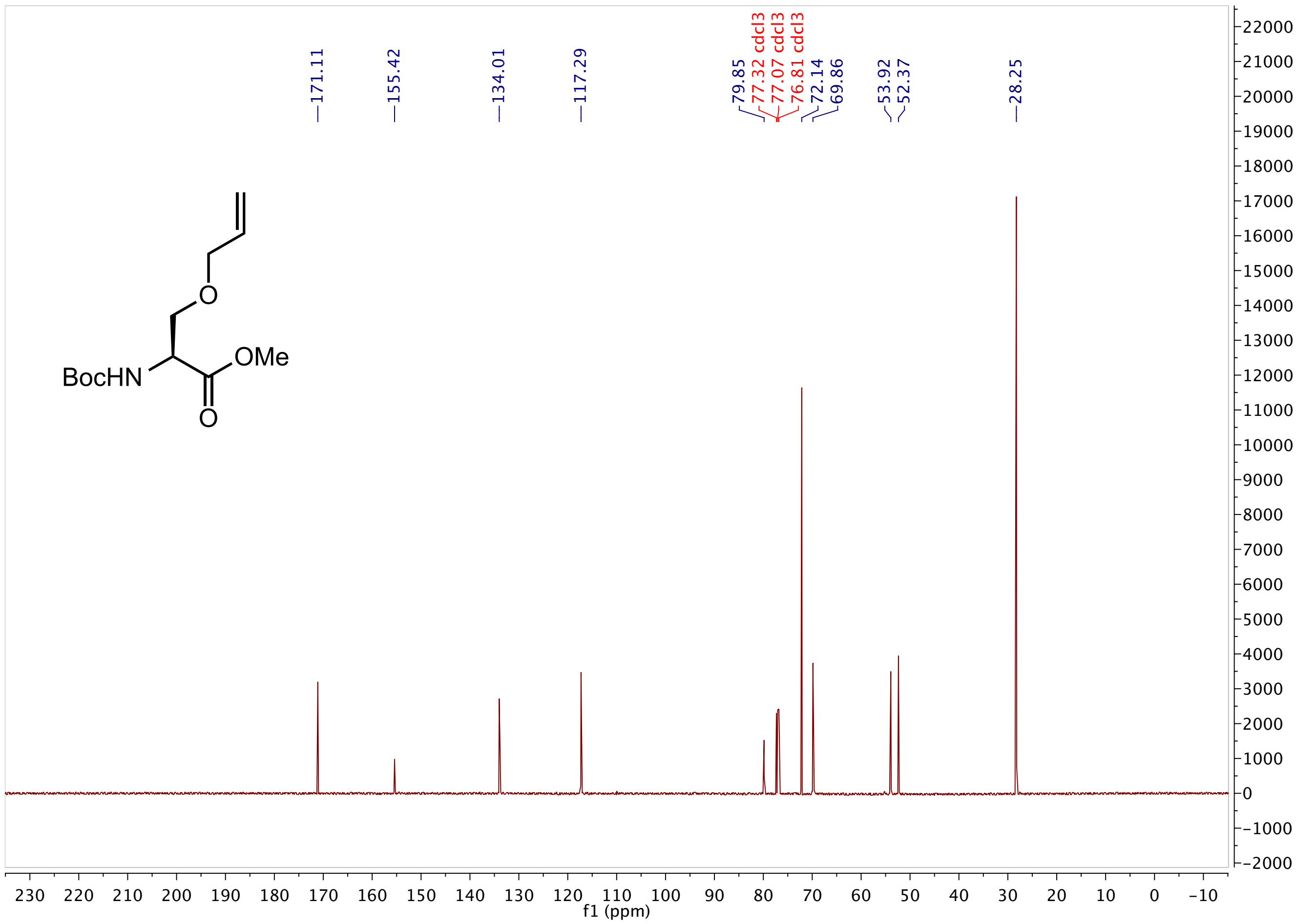
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **9b**



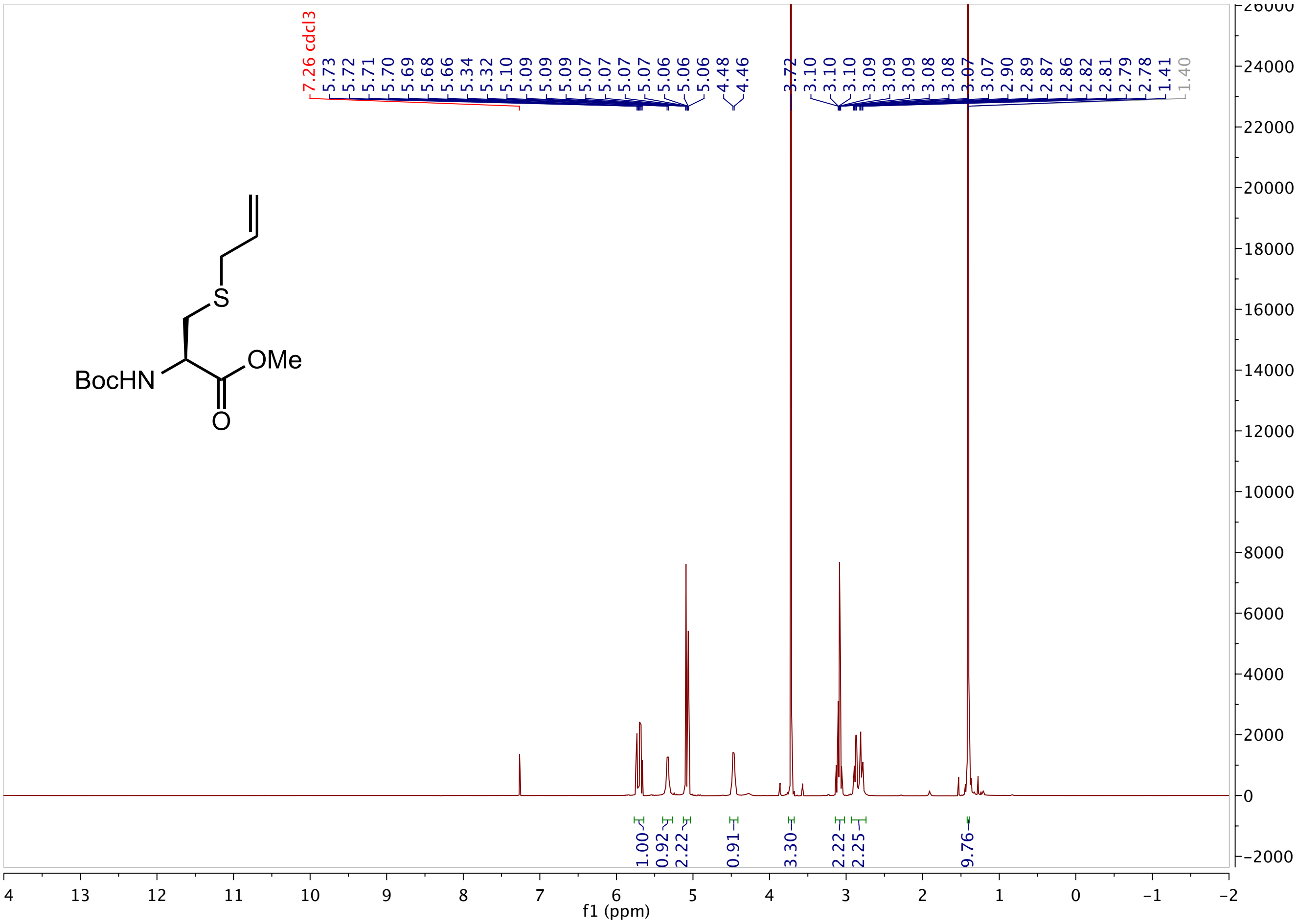
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **9c**



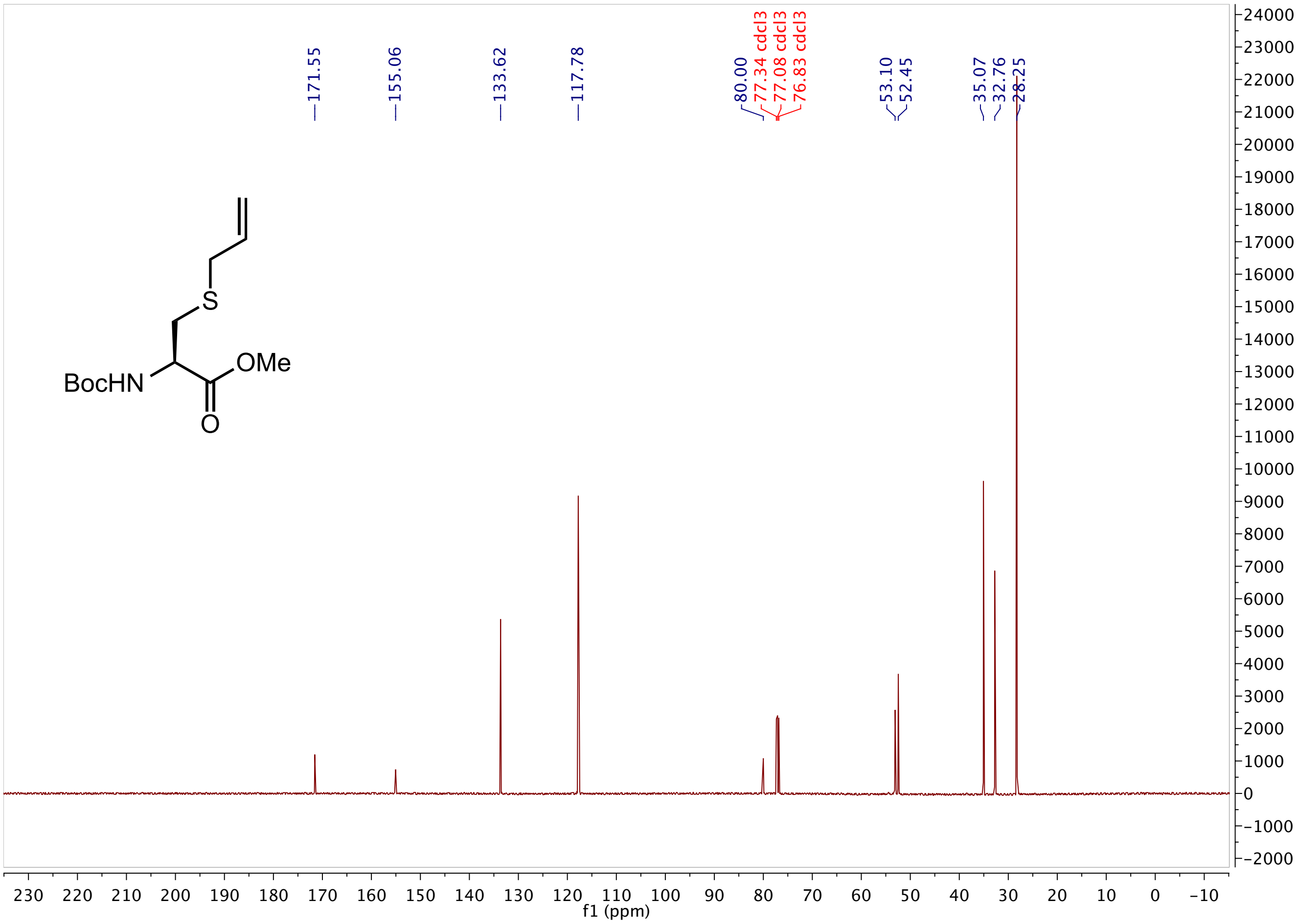
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **9c**



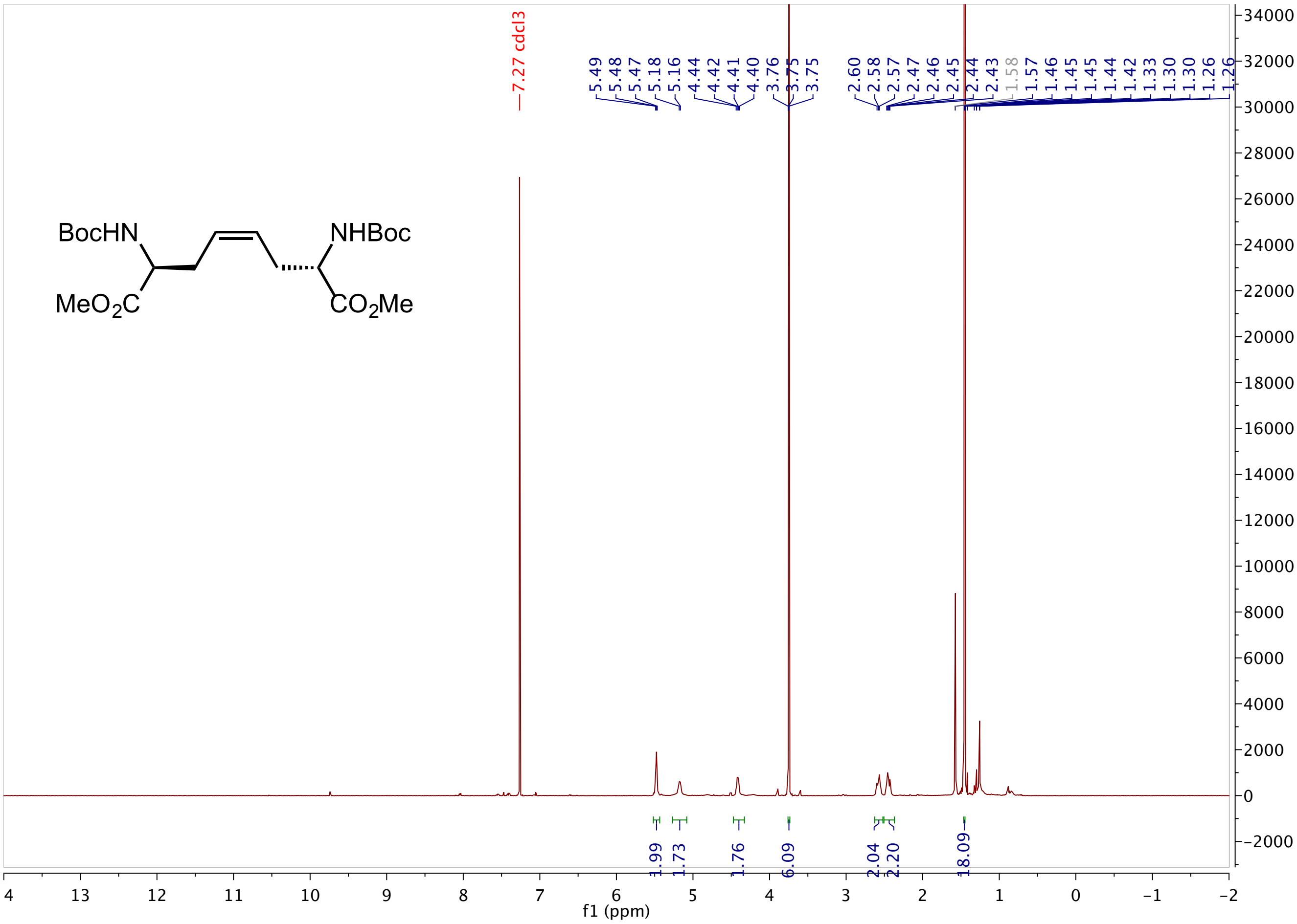
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **9d**



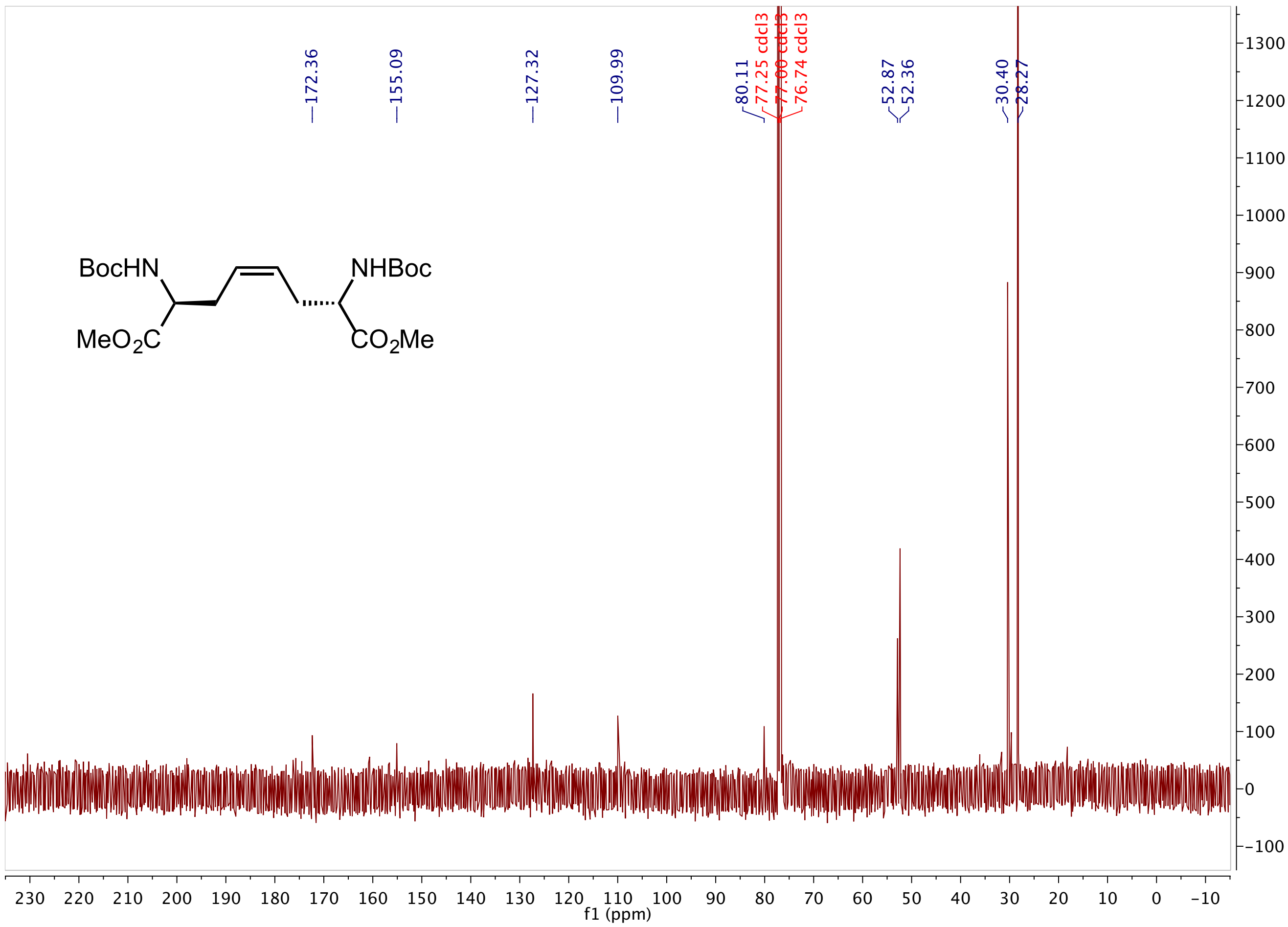
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **9d**



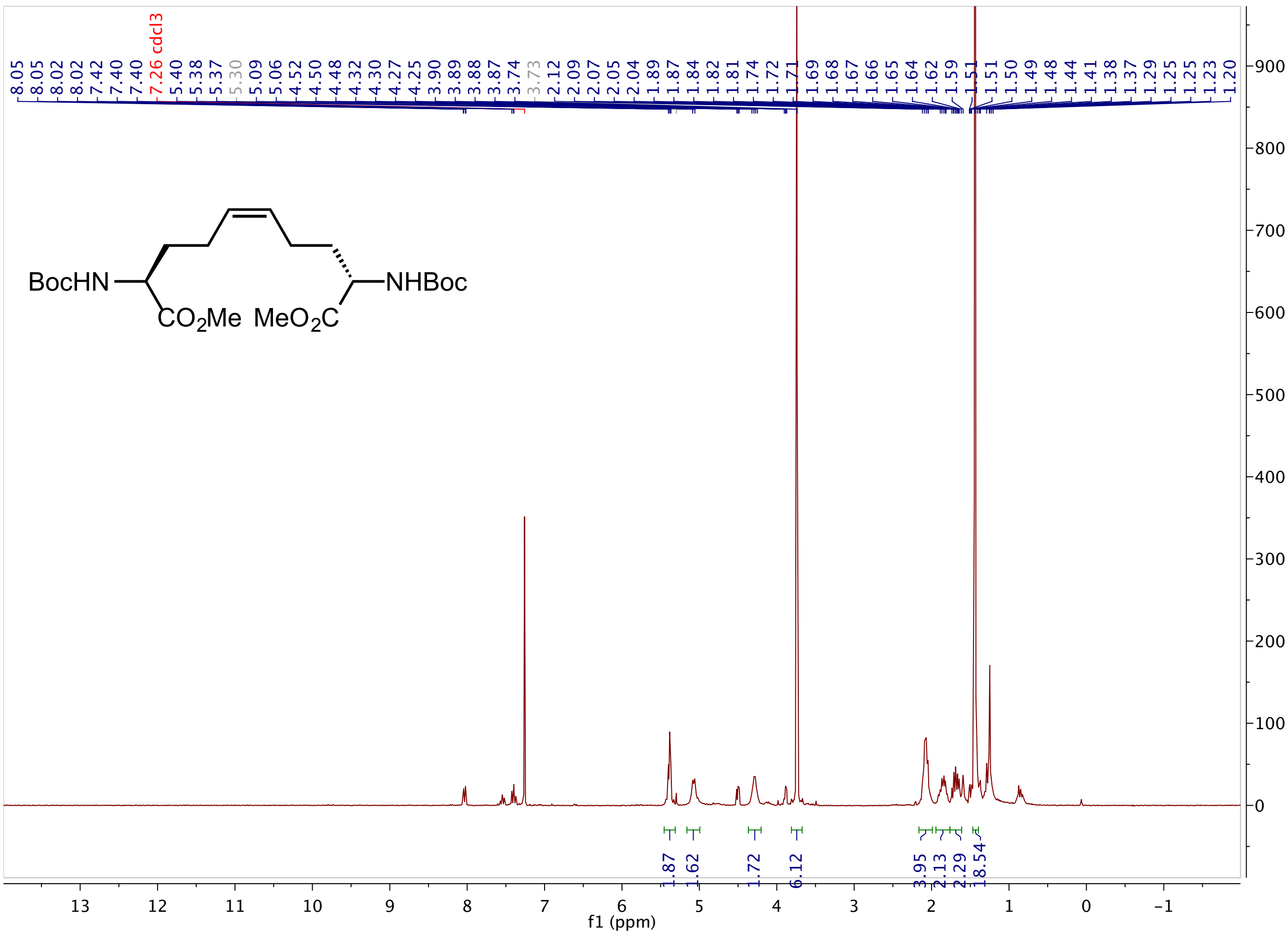
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **10a**



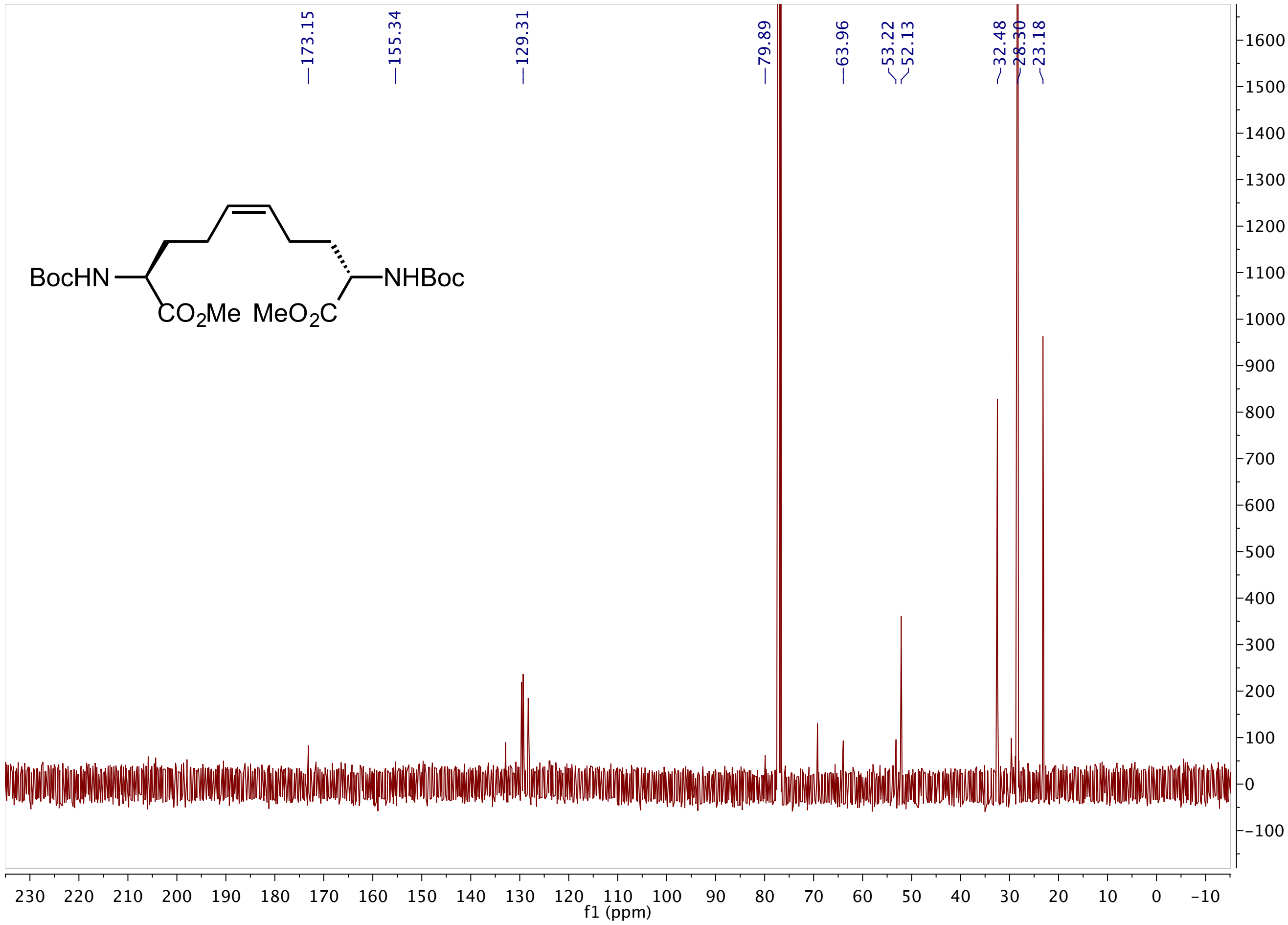
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **10a**



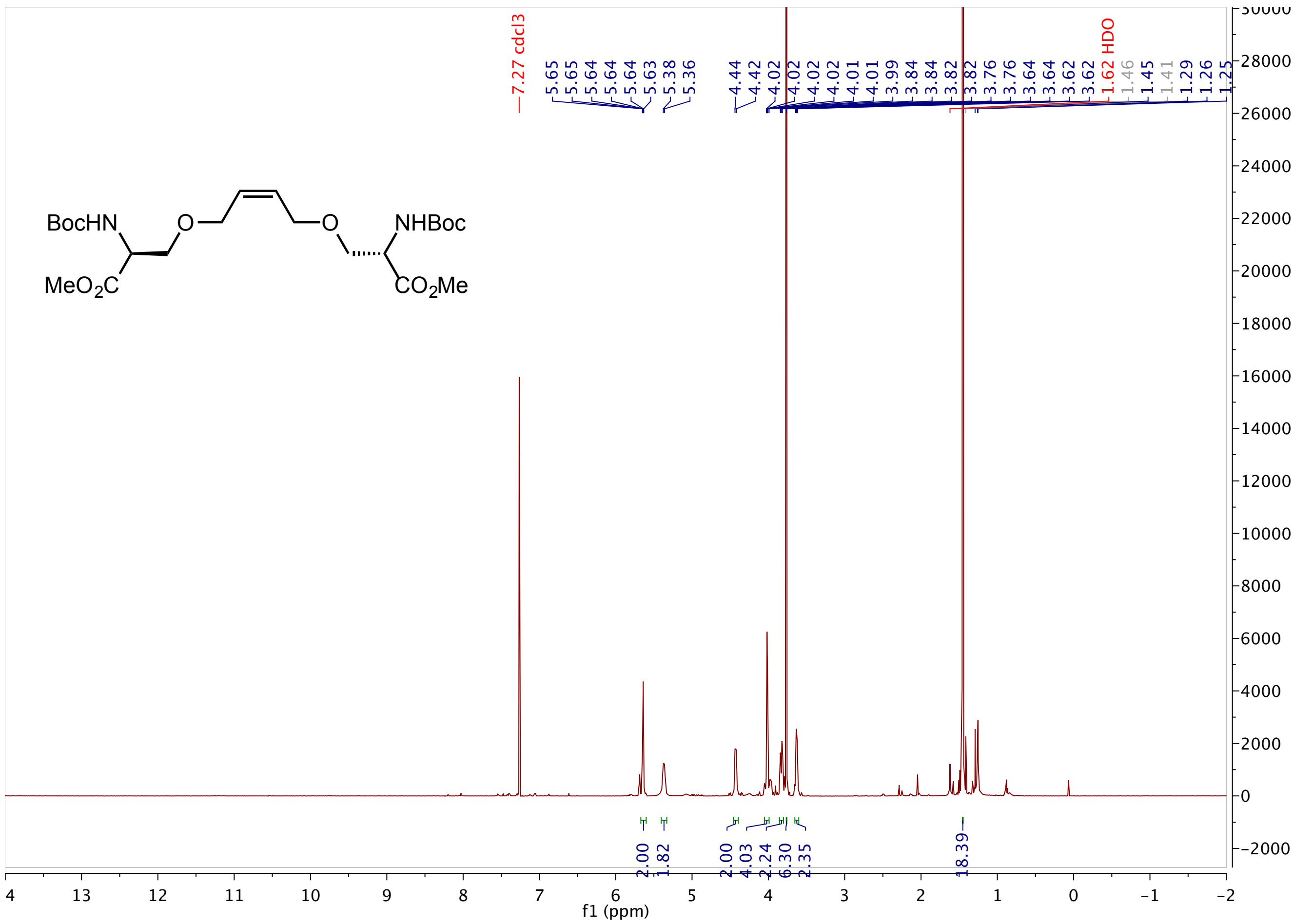
^1H NMR (500 MHz, $CDCl_3$) spectrum of compound **10b**



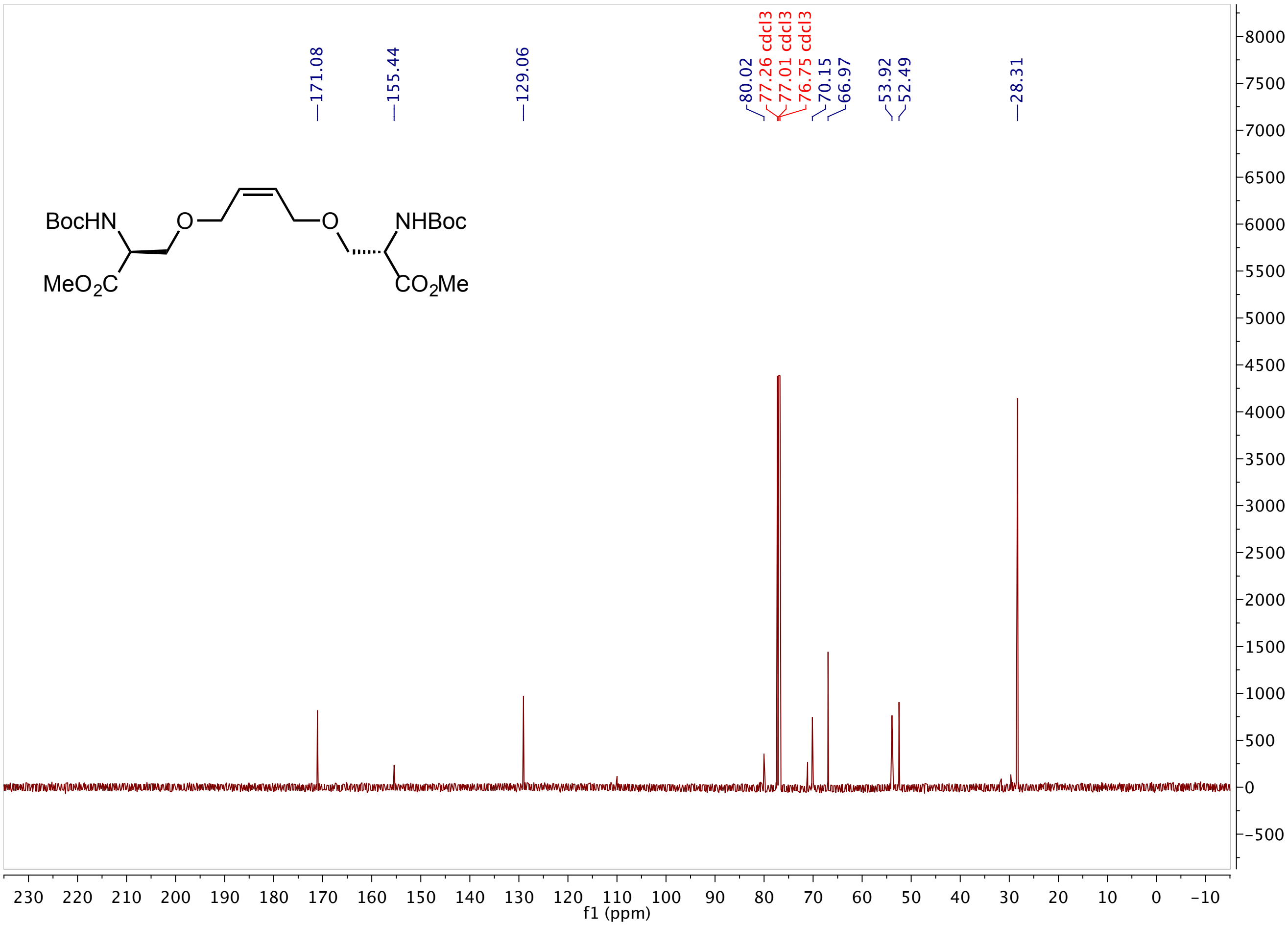
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **10b**



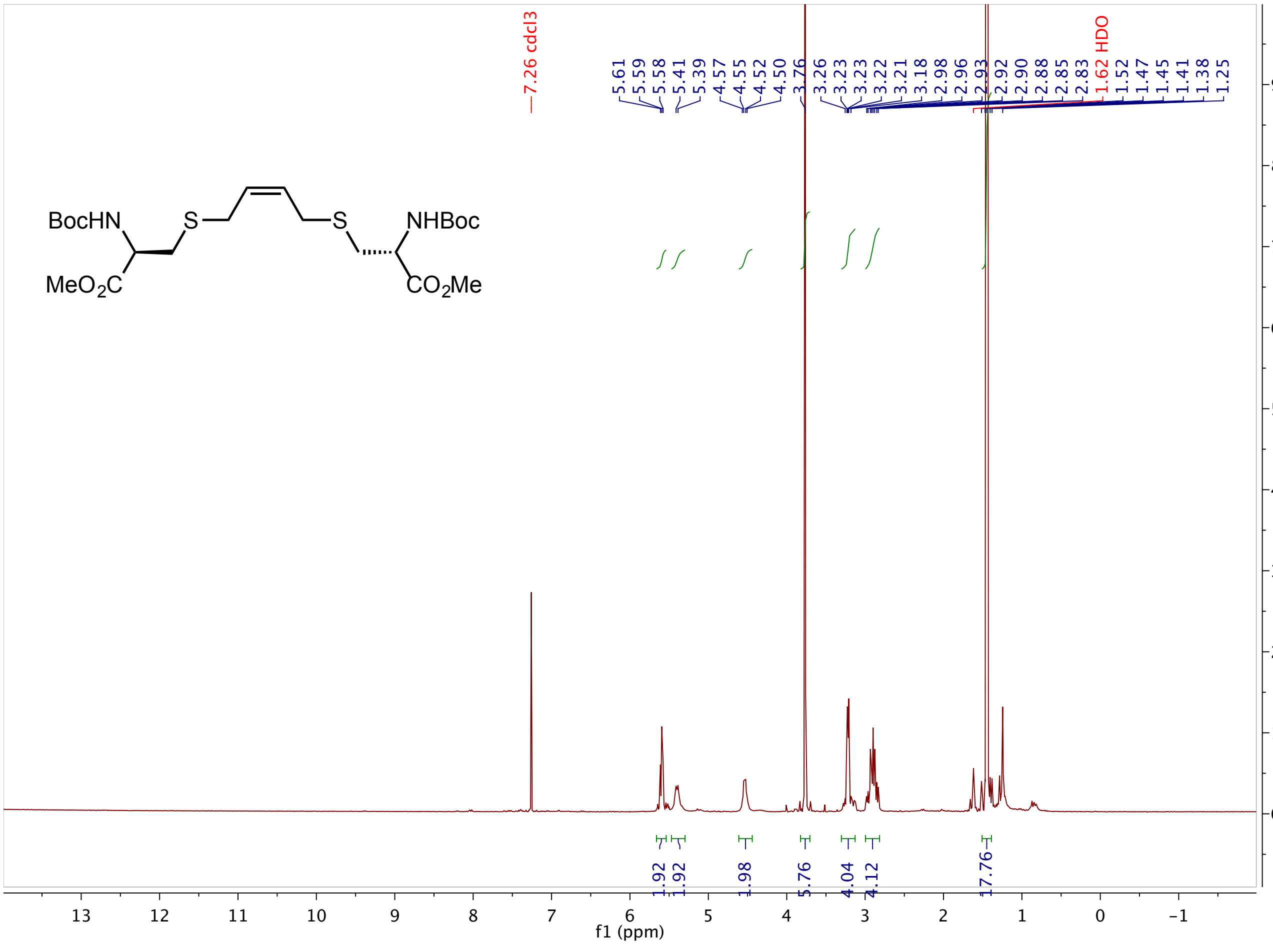
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **10c**



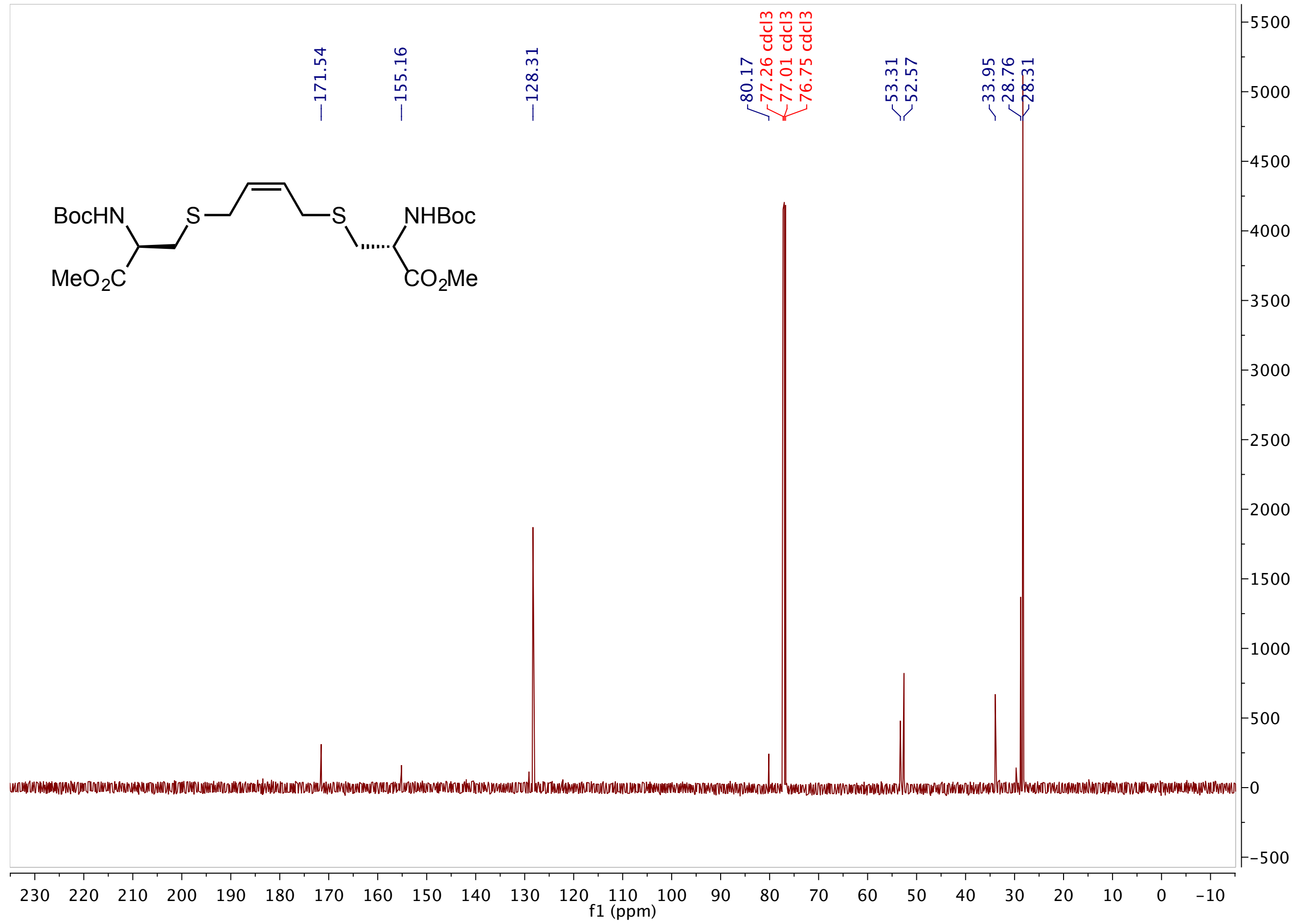
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **10c**



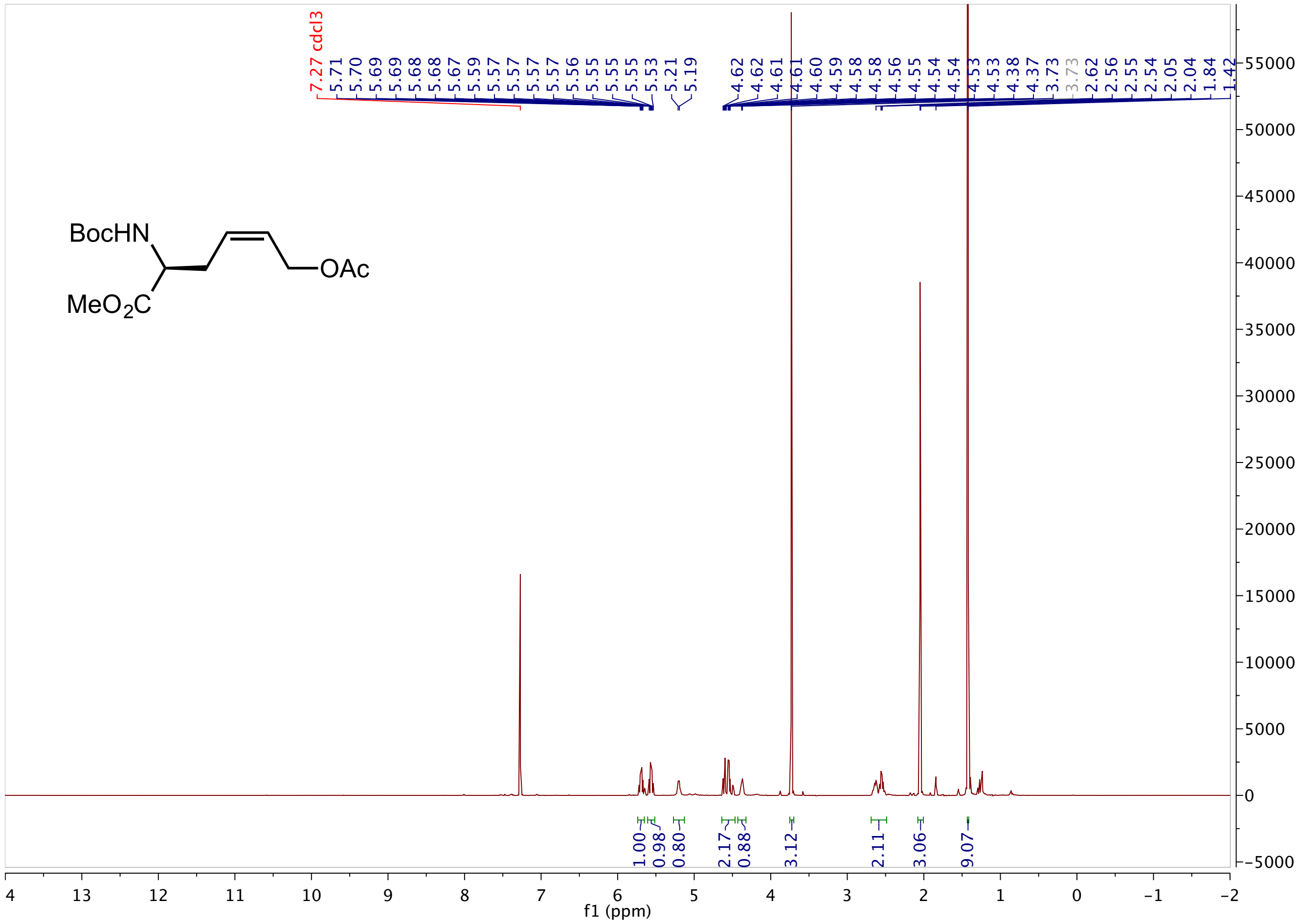
^1H NMR (500 MHz, $CDCl_3$) spectrum of compound **10d**



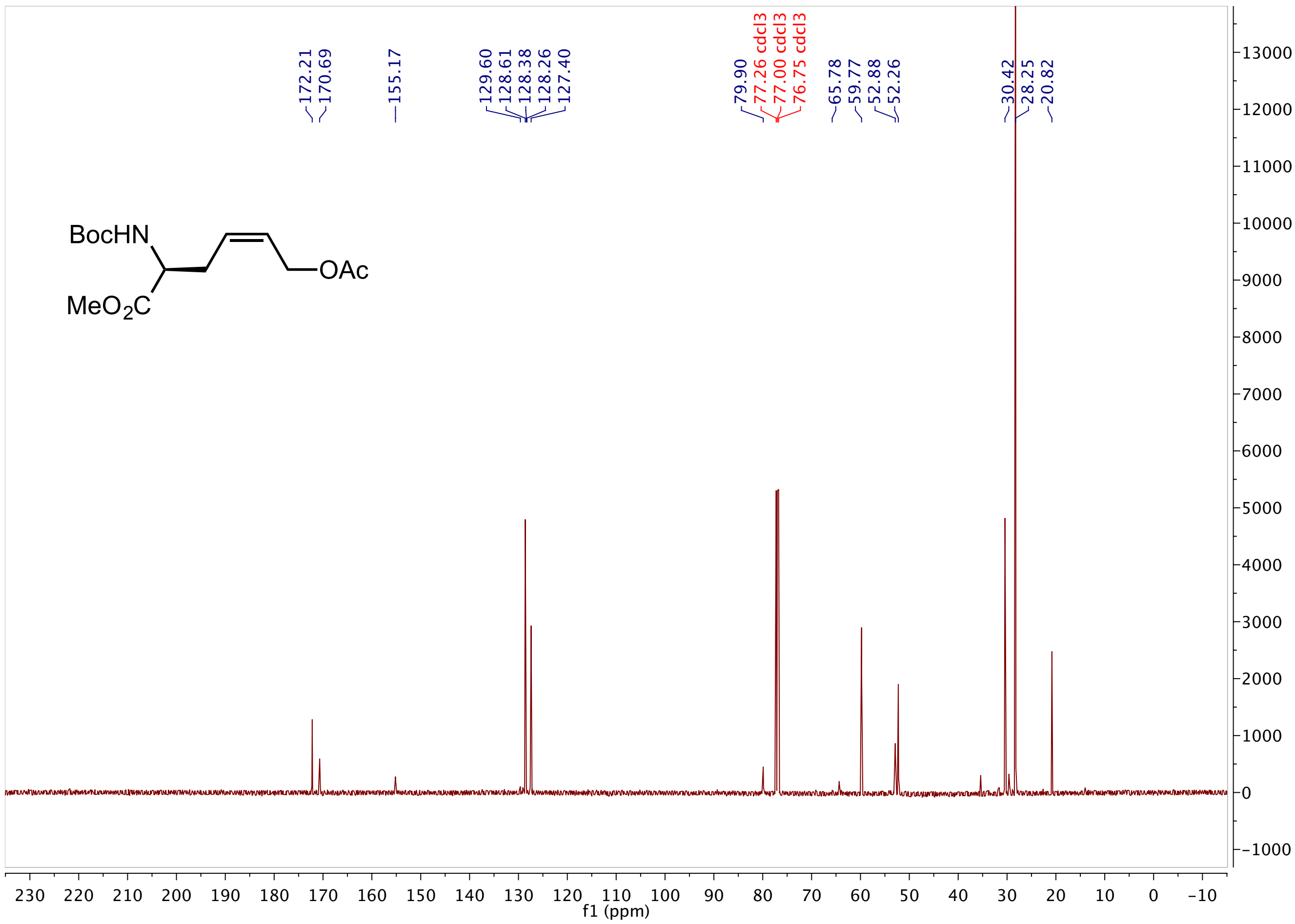
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **10d**



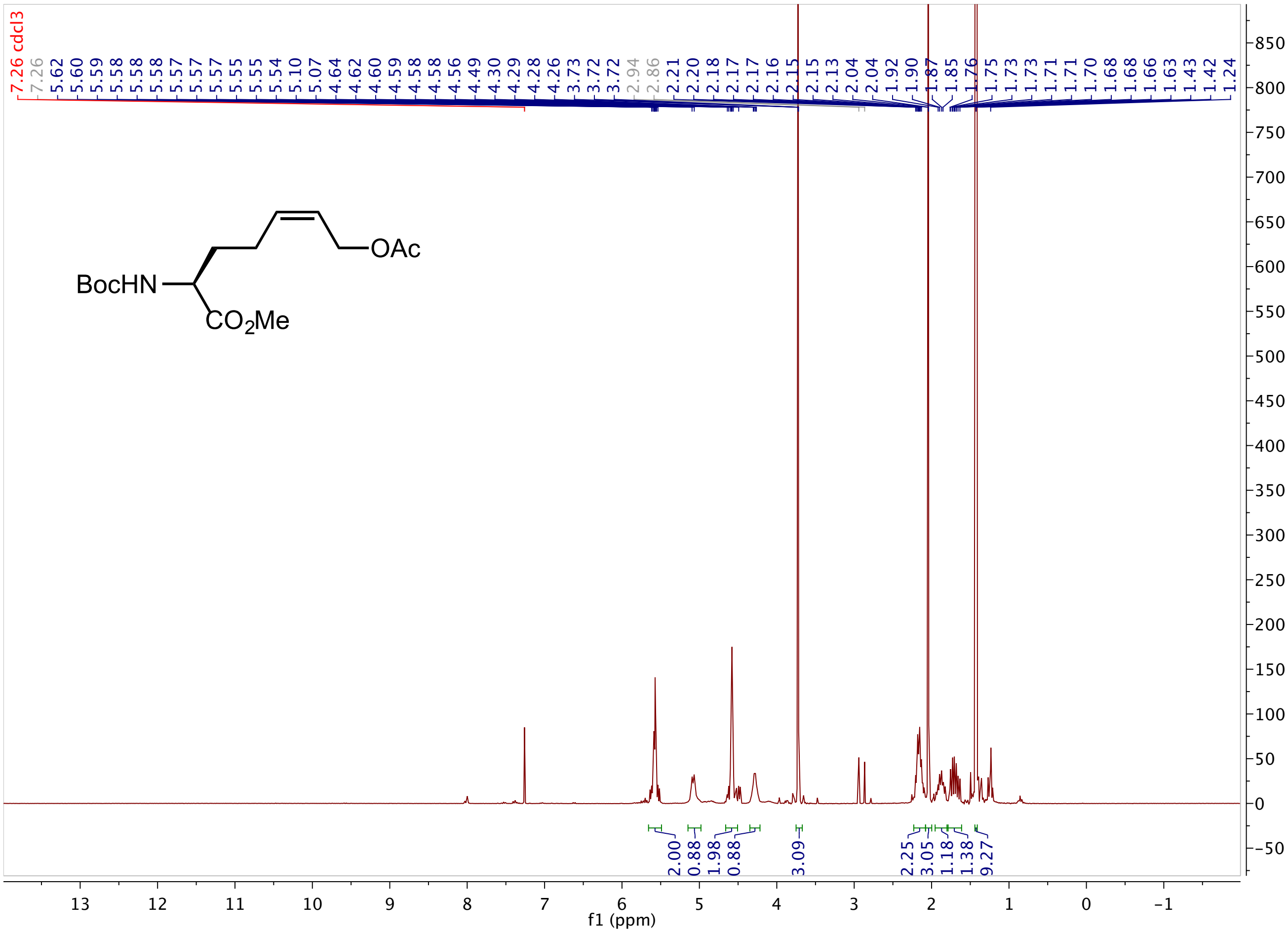
^1H NMR (500 MHz, $CDCl_3$) spectrum of compound **12a**



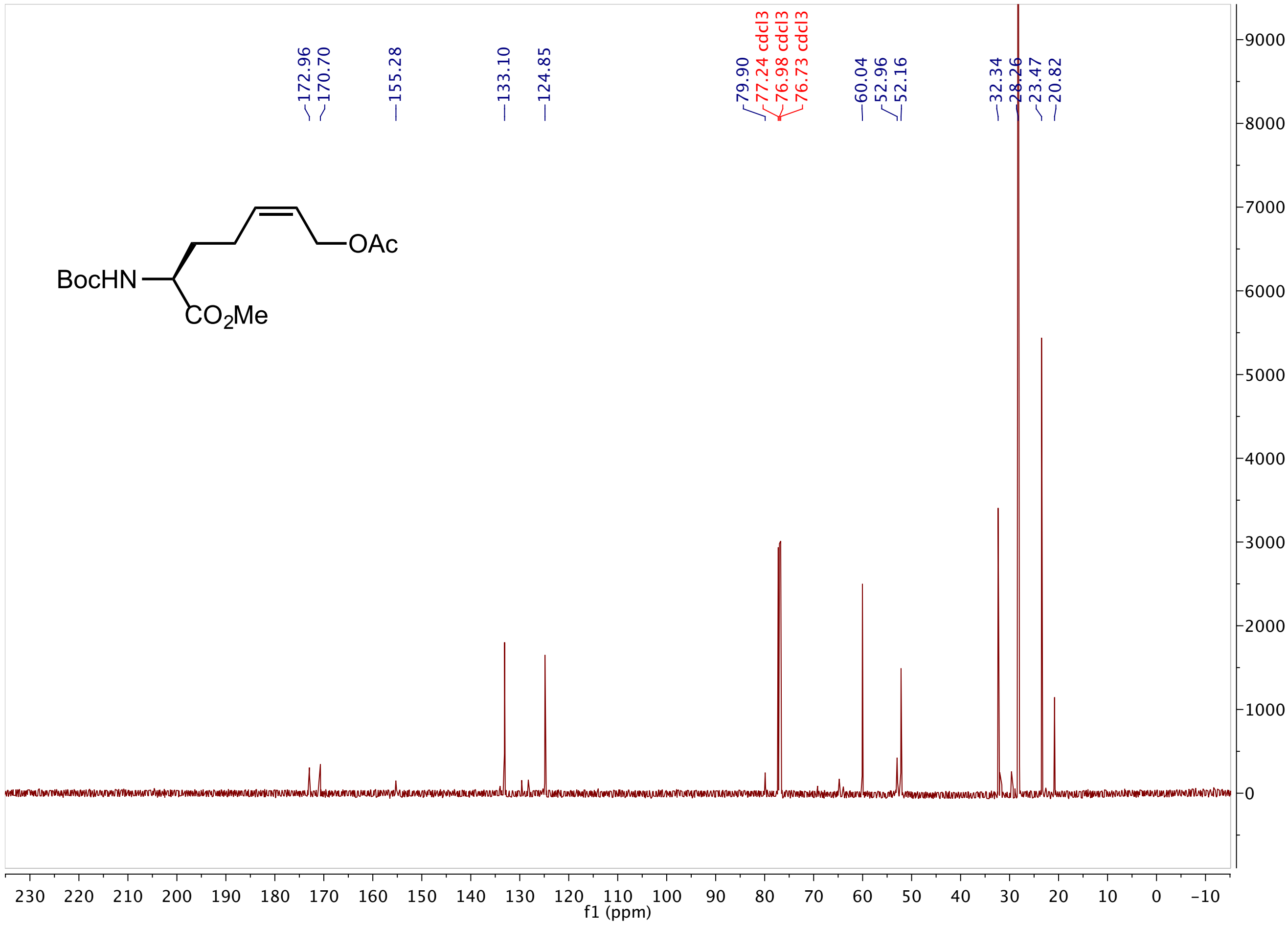
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **12a**



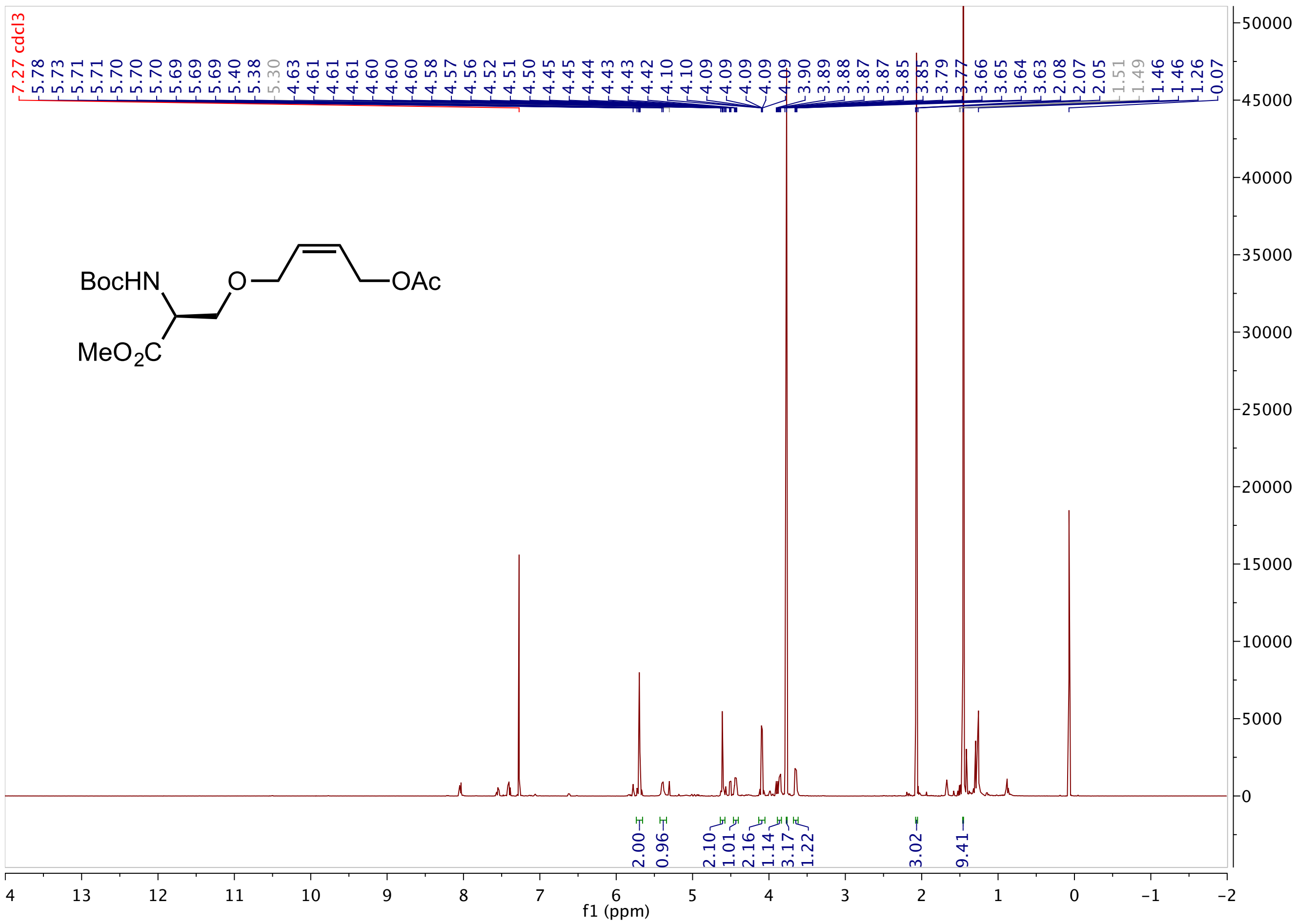
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **12b**



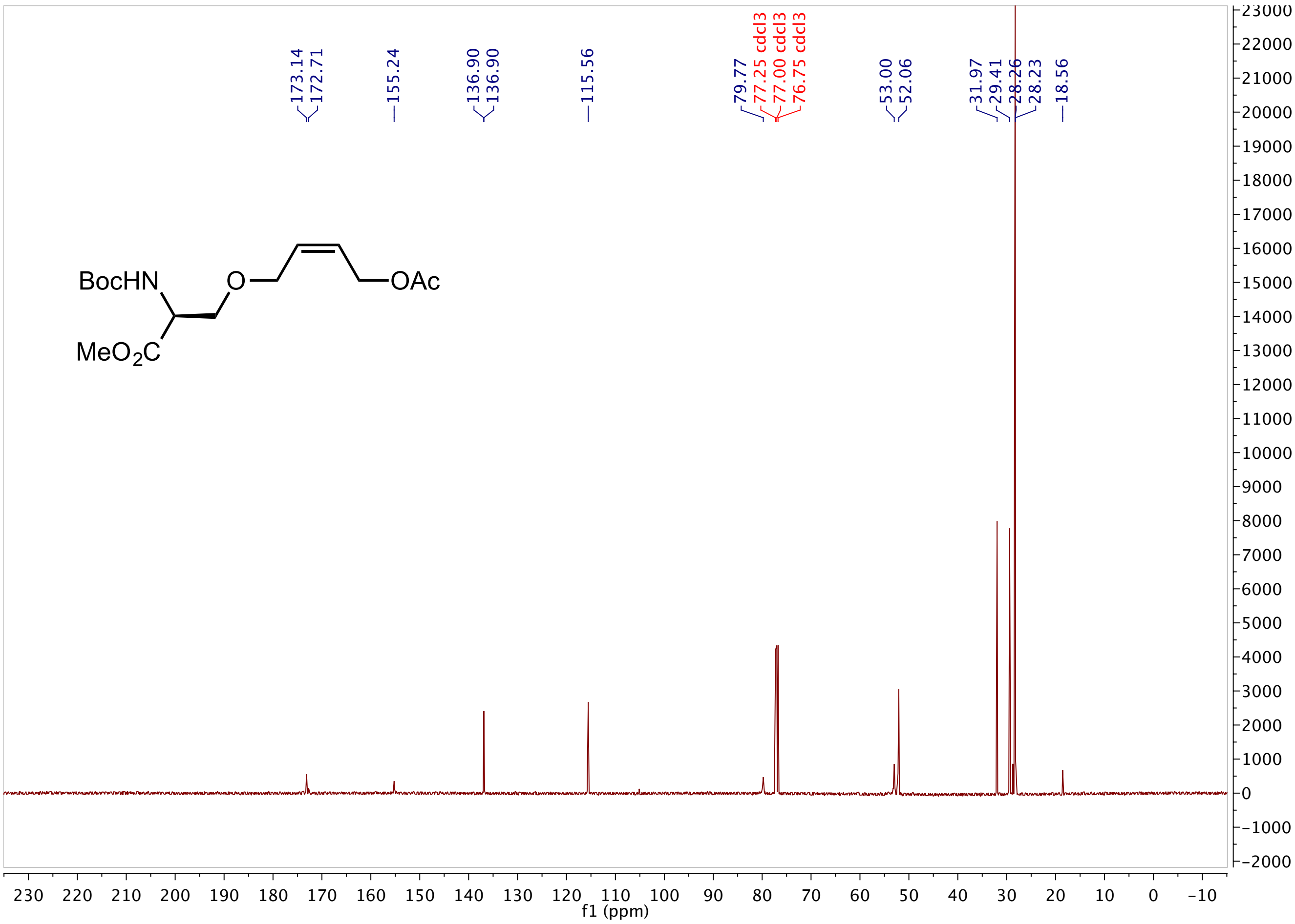
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **12b**



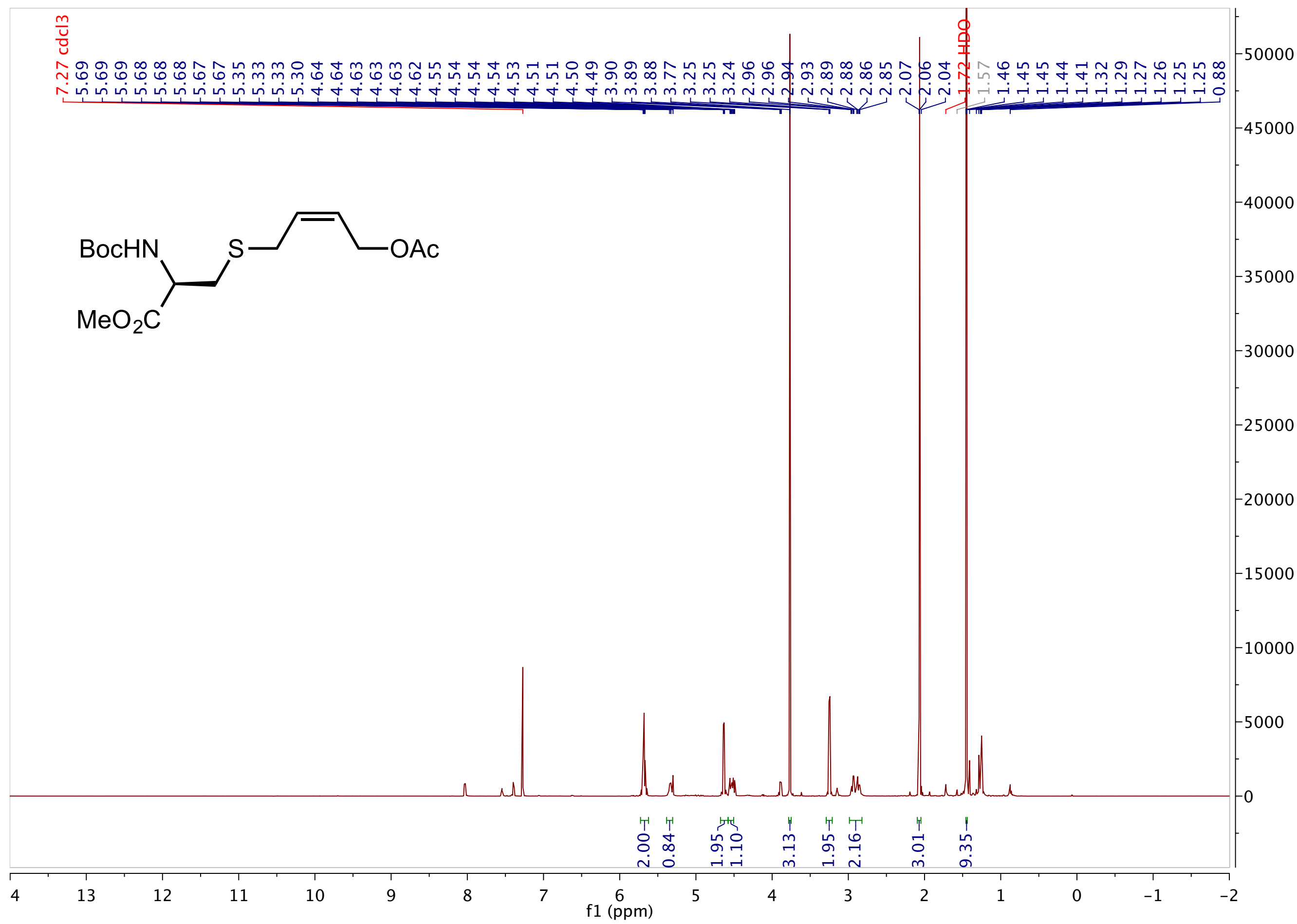
^1H NMR (500 MHz, $CDCl_3$) spectrum of compound **12c**



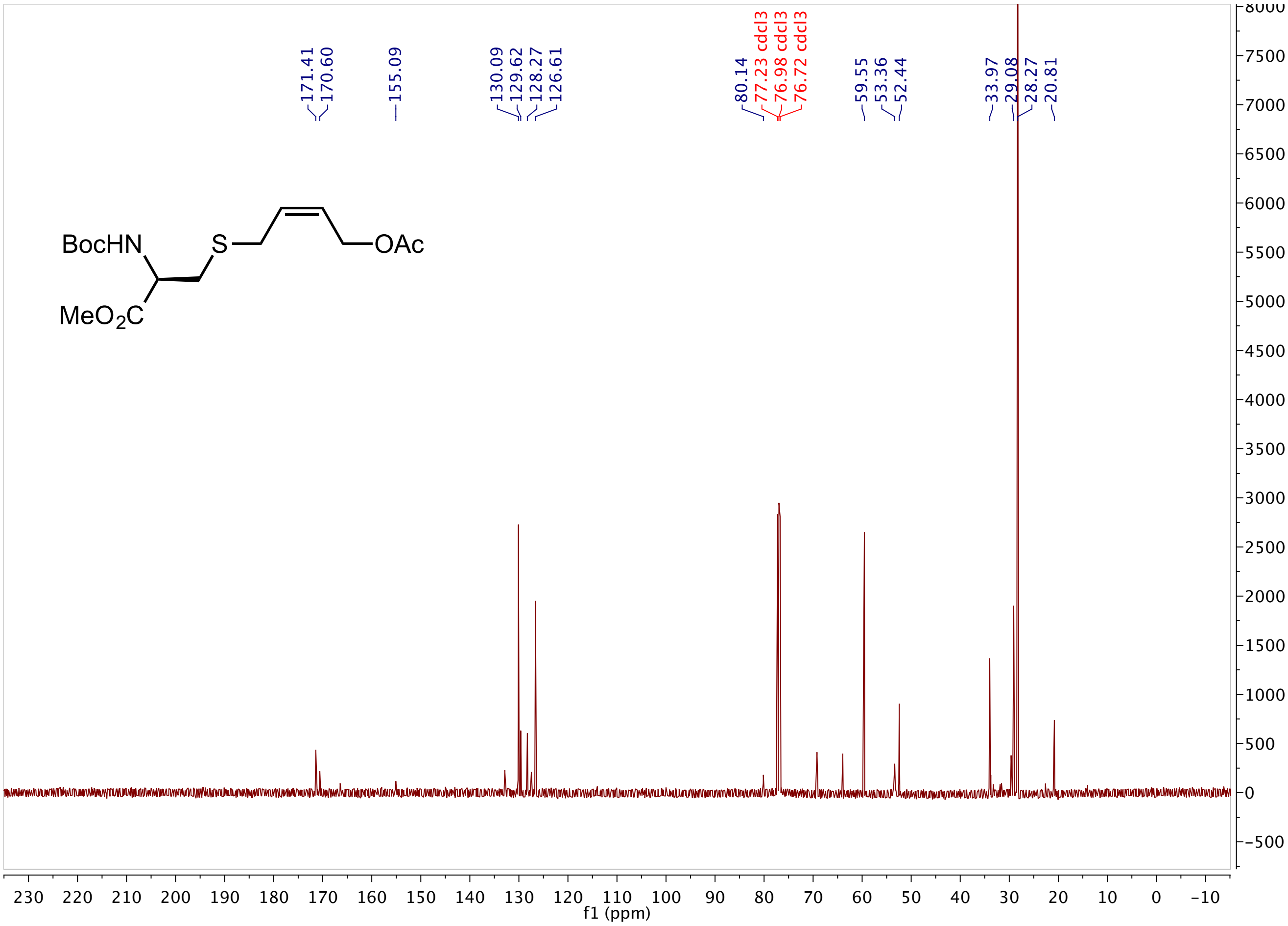
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **12c**



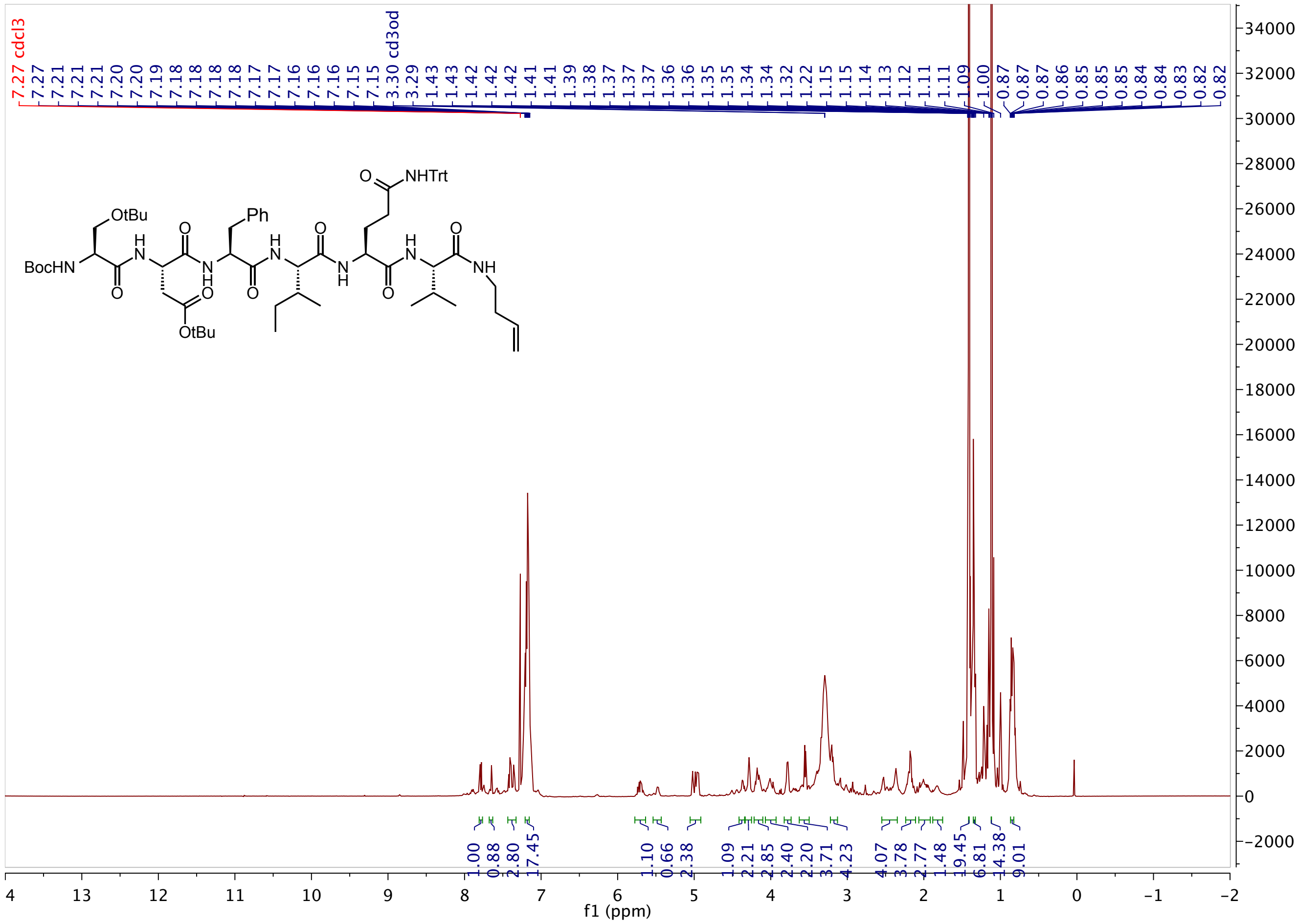
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **12d**



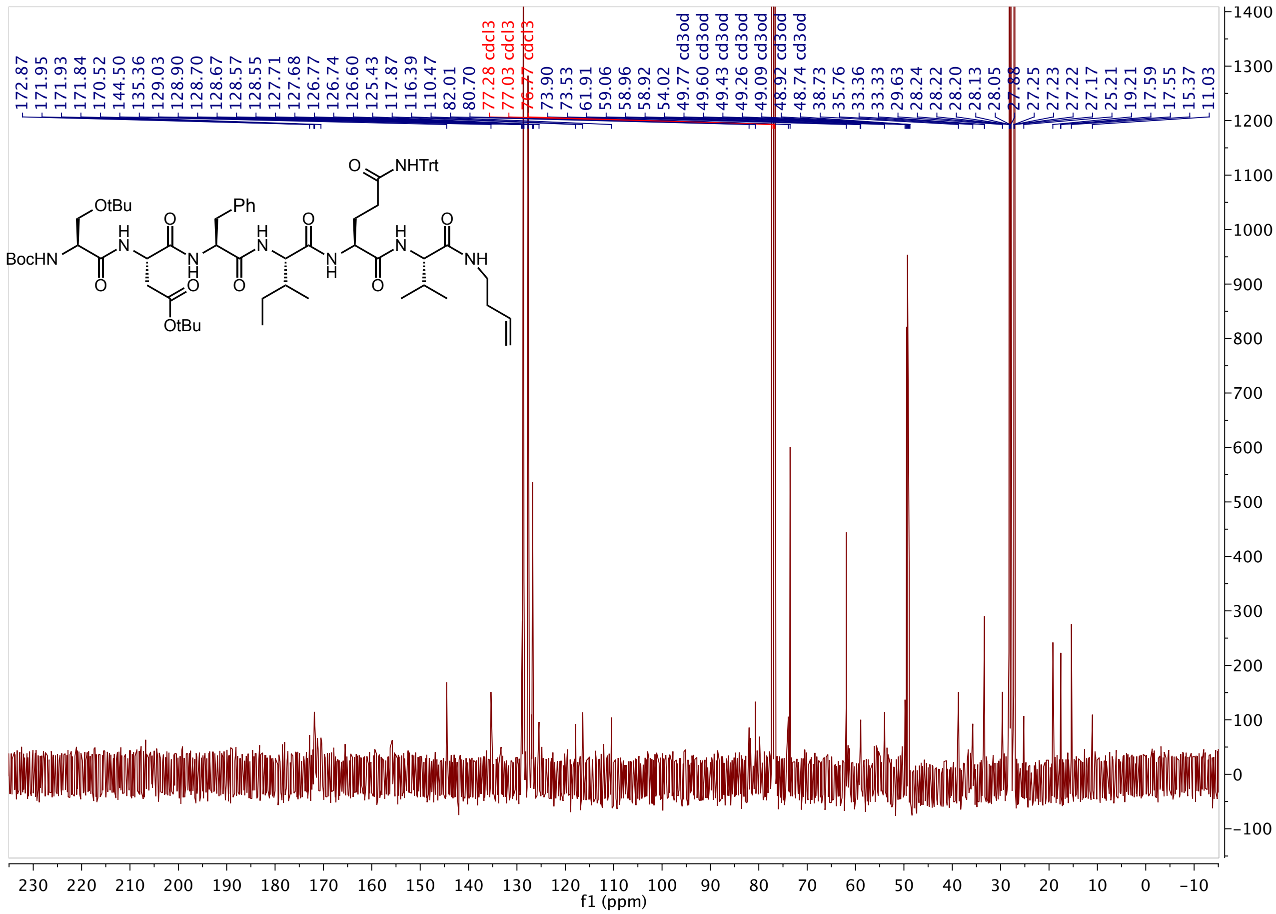
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of compound **12d**



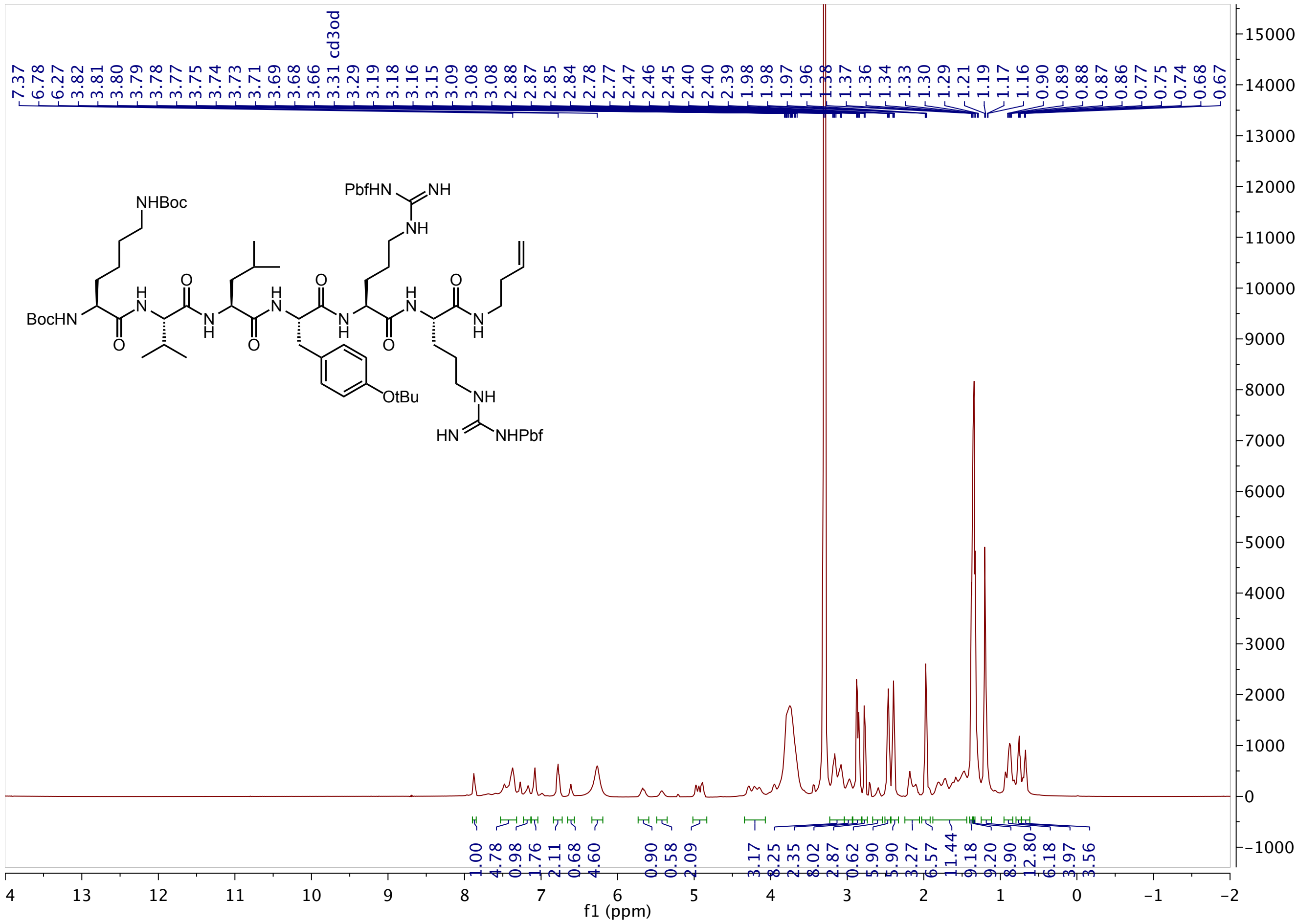
^1H NMR (500 MHz, $CDCl_3$ + CD_3OD) spectrum of compound **13**



^{13}C NMR (126 MHz, $CDCl_3$ + CD_3OD) spectrum of compound **13**



^{1}H NMR (500 MHz, $CDCl_3 + CD_3OD$) spectrum of compound **14**



^{13}C NMR (126 MHz, $CDCl_3$ + CD_3OD) spectrum of compound **14**