Supporting Information for

Synthesis of Polycyclic Aminal Heterocycles via Decarboxylative Cyclisation of Dipeptide Derivatives

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1. General methods

All reactions were carried out in oven dried glassware under an atmosphere of nitrogen, unless stated otherwise. For flash chromatography, distilled technical grade solvents were used. CH_3CN and CH_2Cl_2 were dried by passage over activated alumina under nitrogen atmosphere (H_2O content < 10 ppm, Karl-Fischer titration). All chemicals were purchased from Acros, Aldrich, Fluka, VWR, TCI, Merck or Bachem and used as such unless stated otherwise. All commercially available dipeptides starting materials were used as received. Chromatographic purification was performed as flash chromatography using Macherey-Nagel silica 40-63, 60 Å, using the solvents indicated as eluent with 0.1-0.5 bar pressure. TLC was performed on Merck silica gel 60 F254 TLC aluminum or glass plates and visualized with UV light and $KMnO_4$ or *para*-anysaldehyde stain. ^{1}H-NMR spectra were recorded on a Brucker DPX-400 400 MHz spectrometer in chloroform-d, methanol-d^4, acetonitrile-d^3 or DMSO-d^6 all signals are reported in ppm with the internal chloroform signal at 7.26 ppm, the internal methanol signal at 3.31 ppm, the internal acetonitrile signal at 1.94 ppm or the internal DMSO signal at 2.50 ppm as standard. The data is being reported as (s = singlet, d = doublet, t= triplet, q = quadruplet, qi = quintet, m = multiplet or unresolved, br = broad signal, app = apparent, coupling constant(s) in Hz, integration, interpretation).^{13}C-NMR spectra were recorded with ^{1}H-decoupling on a Brucker DPX-400 100 MHz spectrometer in chloroform-d, methanol-d^4, acetonitrile-d^3, or DMSO-d^6 all signals are reported in ppm with the internal chloroform signal at 77.0 ppm, the internal methanol signal at 49.0 ppm, the internal acetonitrile signals at 1.32 and 118.26 ppm, or the internal DMSO signal at 39.5 ppm as standard. Infrared spectra were recorded on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prisma and are reported as cm^{-1} (w = weak, m = medium, s = strong, br = broad). Optical rotations were measured on a polarimeter using a 10 cm cell with a Na 589 nm filter. The specific solvents and concentrations (in g/100 mL) are indicated.

High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API. A standard data acquisition and instrument control system was utilized (Thermo Scientific) whereas the ion source was controlled by Chipsoft 8.3.1 software (Advion BioScience). Samples were loaded onto a 96-well plate (Eppendorf, Hamburg, Germany) within an injection volume of 5µl. The experimental condition for the ionization voltage was +1.4kV and the gas pressure was set at 0.30 psi. The temperature of ion transfer capillary was 275 °C, tube voltages. FTMS spectra were obtained in the 80-1000 m/z range in the reduce profile mode with a resolution set to 120,000. In all spectra one microscan was acquired with a maximum injection time value of 1000ms. Typical CID experiments were carried out using Normalized collision energy values of 26-28 and 5 Da of isolation width.

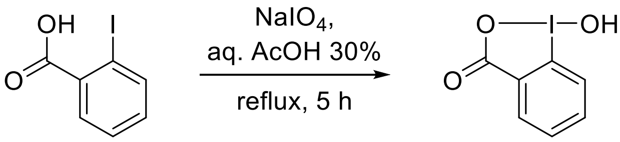
Photoredox catalyzed reactions were performed in test tubes (5 mL), which were hold using a rack for test tubes placed at the center of a crystallization flask. On this flask were attached the blue LEDs (RUBAN LED 5MÈTRES - 60LED/M - 3528 BLEU - IP65 with Transformateur pour Ruban LED 24W/2A/12V, bought directly on RubanLED.com). The distance between the LEDs and the test tubes was approximatively 2 cm. Long irradiation resulted in temperature increasing up to 37 °C during overnight reactions. Light activated reactions were performed in test tubes (5 mL), which were hold with clamps. The tube was placed in between 2 white 40W CFL lamps. The distance between the lamps and the test tubes was approximatively 5 cm. The lamps were aligned and held parallel to the tube.

RP-HPLC-MS measurements were performed on an Agilent 1290 Infinity HPLC system with a G4226a 1290 Autosampler, a G4220A 1290 Bin Pump and a G4212A 1290 DAD detector, connected to a 6130 Quadrupole LC/MS MS, coupled with a Waters XBridge C18 column (250 x 4.6 mm, 5 µm). Water:acetonitrile 95:5 (solvent A) and water:acetonitrile 5:95 (solvent B), each containing 0.1% formic acid, were used as the mobile phase at a flow rate of 0.6 mL/min1. The gradient was programmed as follows: 100% A to 100% B in 20 minutes then isocratic for 5 minutes. The column temperature was set up to 25 °C. Low resolution mass spectrometric measurements were acquired using the following parameters: positive electrospray electrospray ionization (ESI), temperature of drying gas = 350 °C, flow rate of drying gas = 12 L. min-1, pressure of nebulizer gas = 60 psi, capillary voltage = 2500 V and fragmentor voltage = 70 V.

2. Synthesis of reagents

a. Hypervalent Iodine reagents

1-Hydroxy-1,2-benziodoxol-3-(1H)-one (17)

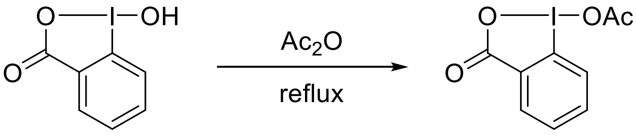


16 **17**

Following a reported procedure,[1] $NaIO_4$ (40.5 g, 189 mmol, 1.05 equiv) and 2-iodobenzoic acid (**16)** (44.8 g, 180 mmol, 1.00 equiv) were suspended in 30% (v:v) aq. AcOH (350 mL). The mixture was vigorously stirred and refluxed for 5 h. The reaction mixture was then diluted with cold water (250 mL) and allowed to cool to RT, protecting it from light. After 1 h, the crude product was collected by filtration, washed on the filter with ice water (3 x 150 mL) and acetone (3 x 150 mL), and air-dried in the dark overnight to afford 1-hydroxy-1,2-benziodoxol-3-(1H)-one (**17**) (44.3 g, 168 mmol, 93%) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (dd, *J* = 7.7, 1.4 Hz, 1H, Ar*H*), 7.97 (m, 1H, Ar*H*), 7.85 (dd, *J* = 8.2, 0.7 Hz, 1H, Ar*H*), 7.71 (td, *J* = 7.6, 1.2 Hz, 1H, Ar*H*). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.7, 134.5, 131.5, 131.1, 130.4, 126.3, 120.4. The values of the NMR spectra are in accordance with reported literature data.[1]

1-Acetoxy-1,2-benziodoxol-3-(1H)-one (AcOBX) (10)



17 **10**

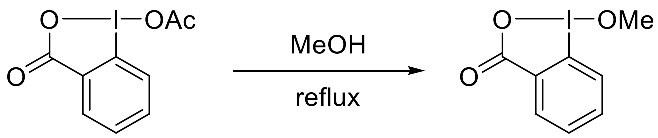
Following a reported procedure,[2] 1-hydroxy-1,2-benziodoxol-3-(1H)-one (**17**) (10.3 g, 39.1 mmol, 1.00 equiv) was suspended in acetic anhydride (35 mL) and heated to reflux for 30 min. The resulting clear, slightly yellow solution was slowly let to warm up to room temperature and

[1] J. P. Brand, C. Chevalley, R. Scopelliti and J. Waser, *Chem. Eur. J.*, 2012, **18**, 5655.
[2] F. L. Vaillant, M. D. Wodrich and J. Waser, *Chem. Sci.*, 2017, **8**, 1790–1800.

then cooled to 0 °C for 30 min. The white suspension was filtered, and the filtrate was again cooled to 0 °C for 30 min. The suspension was once again filtered and the combined two batches of solid product were washed with hexane (2 x 20 mL) and dried under vacuum affording **10** (10.8 g, 35.3 mmol, 90%) as a white solid.

^{1}H NMR (400 MHz, chloroform-*d*) δ 8.24 (dd, 1H, *J* = 7.6, 1.6 Hz, Ar*H*), 8.00 (dd, 1H, *J* = 8.3, 1.0 Hz, Ar*H*), 7.92 (ddd, 1H, *J* = 8.4, 7.2, 1.6 Hz, Ar*H*), 7.71 (td, 1H, *J* = 7.3, 1.1 Hz, Ar*H*), 2.25 (s, 3H, CO*Me*). ^{13}C NMR (100 MHz, chloroform-*d*) δ 176.5, 168.2, 136.2, 133.3, 131.4, 129.4, 129.1, 118.4, 20.4. The values of the NMR spectra are in accordance with reported literature data.[2]

1-Metoxy-1,2-benziodoxol-3-(1H)-one (MeOBX) (18)



10 **18**

Following a reported procedure,[3] AcOBX (**10**) (1.0 g, 3.3 mmol, 1.0 equiv) was refluxed in MeOH (10 mL) for 15 min until a clear, colorless solution was obtained. The mixture was cooled to room temperature and then to -20 °C. The precipitate was filtered, washed with a minimal amount of MeOH, and dried under vacuum. MeOBX (**18**) (0.69 g, 2.5 mmol, 76%) was obtained as a white solid.

^{1}H NMR (400 MHz, chloroform-*d*) δ 8.27 (dd, *J* = 7.6, 1.6 Hz, 1H, Ar*H*), 7.90 (ddd, *J* = 8.5, 7.2, 1.6 Hz, 1H, Ar*H*), 7.76 (dd, *J* = 8.3, 1.0 Hz, 1H, Ar*H*), 7.69 (td, *J* = 7.4, 1.0 Hz, 1H, Ar*H*), 4.27 (s, 3H, O*Me*). ^{13}C NMR (101 MHz, chloroform-*d*) δ 168.1, 135.2, 133.0, 131.1, 130.7, 126.0, 118.6, 62.4. The values of the NMR spectra are in accordance with reported literature data.[3]

b. <u>Synthesis of starting materials</u>

Dipeptides Cbz-Gly-Pro (**8a**), Cbz-Val-Pro (**8h**), Cbz-Phe-Pro (**8i**), and Cbz-Ala-Ala (**8o**) were commercially available.

General procedure A: amide bond coupling using HATU

To a solution of the appropriate carboxylic acid (1.0 equiv), with the corresponding amine (1.5 equiv), and HATU (1.1 equiv) in DMF was added DIPEA (5.0 equiv). The reaction was stirred overnight at RT. The crude mixture was diluted with 20 mL of sat. $NaHCO_3$, extracted with ethyl acetate (3 x 30 mL), washed with brine (20 mL), citric acid (10 %w, 20 mL), LiCl (5 %w, 20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by column chromatography.

General procedure B: amide bond coupling using EDC·HCl and DIPEA

To a solution of the appropriate carboxylic acid (1.1 equiv), with the corresponding amine (1.0 equiv), and EDC·HCl (1.1 equiv) in DCM was added DIPEA (5.0 equiv). The reaction was stirred overnight at RT. The crude mixture was washed with sat. $NaHCO_3$ (20 mL), and brine

[3] J. Hu, T. Lan, Y. Sun, H. Chen, J. Yao and Y. Rao, *Chem. Commun.*, 2015, **51**, 14929.

(20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by column chromatography.

General procedure C: amide bond coupling using EDC·HCl and DMAP

A solution of the appropriate carboxylic acid (1.0 equiv), with the corresponding amine (4.0 equiv), and EDC·HCl (2.0 equiv) and DMAP (0.3 equiv) in DCM was stirred overnight at RT. The crude mixture was washed with water (20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by column chromatography.

General procedure D: saponification using LiOH in water and methanol

To a solution of the appropriate methyl ester (1.0 equiv) in water and methanol was added lithium hydroxide monohydrate (5.0 equiv). The reaction was stirred overnight at RT. The mixture was extracted with ethyl acetate (3 x 20 mL). The pH value of the aqueous layer was adjusted to 1 using HCl (1 M). The mixture was extracted with ethyl acetate (3 x 20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was pure enough for the next step without further purification.

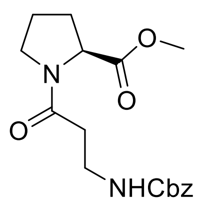
General procedure E: saponification using NaOH in water and THF

To a solution of the appropriate methyl ester (1.0 equiv) in THF and water was added sodium hydroxide (1.0 equiv). The reaction was stirred 2 h at RT. The mixture was extracted with DCM (3 x 20 mL). The pH value of the aqueous layer was adjusted to 1 using HCl (1 M). The mixture was extracted with ethyl acetate (3 x 20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was pure enough for the next step without further purification.

General procedure F: saponification using LiOH in water and THF

To a solution of the appropriate methyl ester (1.0 equiv) in THF and water was added lithium hydroxide monohydrate (5.0 equiv). The reaction was stirred overnight at RT. The mixture was extracted with DCM (3 x 20 mL). The pH value of the aqueous layer was adjusted to 1 using HCl (1 M). The mixture was extracted with ethyl acetate (3 x 20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was pure enough for the next step without further purification.

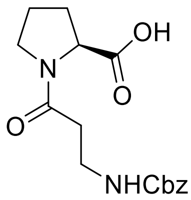
Methyl (3-(((benzyloxy)carbonyl)amino)propanoyl)-L-prolinate (25b)



Following the general procedure A and starting with 3-(benzyloxycarbonylamino)propionic acid (400 mg, 1.79 mmol, 1.00 equiv), (2S)-pyrrolidine-2-carboxylic acid methyl ester hydrochloride (445 mg, 2.69 mmol, 1.50 equiv), HATU (749 mg, 1.97 mmol, 1.10 equiv), DIPEA (1.56 mL, 8.96 mmol, 5.00 equiv), and DMF (10.0 mL), **25b** was obtained after column chromatography (DCM/MeOH 95:5) as a brown oil (132 mg, 0.395 mmol, 22% yield).

Rf(DCM/MeOH 95:5): 0.43. ^{1}H NMR (400 MHz, chloroform-*d*, mixture of rotamers, unresolved mixture) δ 7.39 – 7.28 (m, 5H, Ar*H*), 5.68 (br s, 1H, N*H*Cbz), 5.08 (s, 2H, OC*H₂*Ph), 4.70 – 4.50 (m, 1H, NC*H*), 3.89 – 3.40 (m, 7H, COO*Me* + C(O)CH_2CH_2NHCbz + N$CH_2CH_2CH_2$CH), 2.55 – 2.49 (m, 2H, C(O)CH_2CH_2NHCbz), 2.27 – 1.86 (m, 4H, N$CH_2CH_2CH_2$CH + N$CH_2CH_2CH_2$CH). ^{13}C NMR (101 MHz, chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 172.8, 172.5, 170.6, 156.6, 136.8, 128.5, 128.1, 66.6, 59.3, 58.7, 52.6, 52.4, 47.0, 46.4, 36.7, 34.5, 31.5, 29.3, 24.8, 22.6. IR (ν_{max}, cm^{-1}) 3564 (w), 3325 (m), 2954 (m), 2881 (w), 1712 (s), 1635 (s), 1516 (m), 1442 (s), 1250 (s), 1203 (s), 1003 (m), 733 (s), 914 (m). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{22}N_2NaO_5^+$ 357.1421; Found 357.1420.

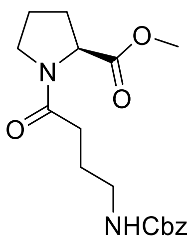
(2S)-1-[3-(Benzyloxycarbonylamino)propanoyl]proline (8b)



Following the general procedure D and starting with **25b** (594 mg, 1.78 mmol, 1.00 equiv), lithium hydroxide monohydrate (373 mg, 8.89 mmol, 5.00 equiv), water (5.0 mL) and methanol (5.0 mL), **8b** was obtained as a brown oil (421 mg, 1.31 mmol, 74% yield).

^{1}H NMR (400 MHz, methanol-*d₄*, 4:1 mixture of rotamers (major/minor)) δ 7.42 – 7.23 (m, 5H, Ar*H* (major+minor)), 5.06 (s, 2H, OCH_2Ph (major+minor)), 4.55 – 4.47 (m, 0.2H, NC*H* (minor)), 4.47 – 4.34 (m, 0.8H, NC*H* (major)), 3.65 – 3.36 (m, 4H, C(O)CH_2CH_2NHCbz + N$CH_2CH_2CH_2$CH (major+minor)), 2.64 – 2.48 (m, 2H, C(O)CH_2CH_2NHCbz (major+minor)), 2.43 – 2.12 (m, 2H, N$CH_2CH_2CH_2$CH + N$CH_2CH_2CH_2$CH (major+minor)), 2.08 – 1.80 (m, 2H, N$CH_2CH_2CH_2$CH + N$CH_2CH_2CH_2$CH (major+minor)). ^{13}C NMR (101 MHz, methanol-*d₄*, mixture of rotamers, signals not fully resolved) δ 175.7, 175.3, 172.7, 172.4, 158.6, 138.3, 129.4, 129.0, 128.8, 67.4, 60.8, 60.1, 47.5, 37.9, 37.7, 35.4, 35.2, 32.1, 30.3, 25.6, 23.5. IR (ν_{max}, cm^{-1}) 3332 (w), 2954 (w), 1716 (s), 1631 (s), 1527 (m), 1454 (m), 1257 (m), 1196 (m), 914 (w), 737 (m). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{20}N_2NaO_5^+$ 343.1264; Found 343.1269. The values of the NMR spectra are in accordance with reported literature data.[4]

Methyl (4-(((benzyloxy)carbonyl)amino)butanoyl)-L-prolinate (25c)



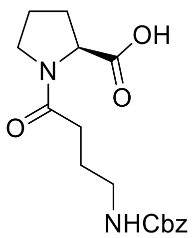
Following the general procedure A and starting with 4-(benzyloxycarbonylamino)butyric acid (600 mg, 2.53 mmol, 1.00 equiv), (2S)-pyrrolidine-2-carboxylic acid methyl ester hydrochloride (628 mg, 3.79 mmol, 1.50 equiv), HATU (1.06 g, 2.78 mmol, 1.10 equiv), DIPEA (2.20 mL,

[4] K. Ha, I. Lebedyeva, S. Hamedzadeh, Z. Li, R. Quiñones, G. G. Pillai, B. Williams, A. Nasajpour, K. Martin, A. M. Asiri and A. R. Katritzky, *Chem. Eur. J.*, 2014, **20**, 4874.

12.6 mmol, 5.00 equiv), and DMF (15.0 mL), **25c** was obtained after column chromatography (DCM/MeOH 95:5) as a brown oil (446 mg, 1.28 mmol, 51% yield).

Rf(DCM/MeOH 95:5): 0.40. ^{1}H NMR (400 MHz, chloroform-*d*, 3:1 mixture of rotamers (major/minor)) δ 7.40 – 7.28 (m, 5H, Ar*H* (major+minor)), 5.10 (s, 2H, OCH_2Ph (major+minor)), 4.50 (dd, *J* = 8.8, 3.5 Hz, 0.75H, NC*H* (major)), 4.44 (dd, *J* = 8.5, 2.6 Hz, 0.15H, NC*H* (minor)), 3.74 (s, 0.5H, COO*Me* (minor)), 3.71 (s, 2.5H, COO*Me* (major)), 3.66 – 3.44 (m, 2H, $NCH_2CH_2CH_2CH$ (major+minor)), 3.32 – 3.17 (m, 2H, $C(O)CH_2CH_2CH_2NHCbz$ (major+minor)), 2.52 – 1.80 (m, 8H, $C(O)CH_2CH_2CH_2NHCbz$ + $C(O)CH_2CH_2CH_2NHCbz$ + $NCH_2CH_2CH_2CH$ + $NCH_2CH_2CH_2CH$ (major+minor)). ^{13}C NMR (101 MHz, chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 172.9, 172.8, 171.4, 156.6, 136.8, 128.5, 128.1, 128.0, 66.5, 59.4, 58.7, 52.7, 52.3, 47.1, 46.5, 40.7, 31.7, 31.5, 29.2, 24.8, 24.5, 22.6. IR (ν_{max}, cm^{-1}) 3321 (m), 2954 (m), 2881 (w), 1716 (s), 1635 (s), 1527 (m), 1442 (s), 1254 (s), 1203 (s), 1018 (m), 741 (m). HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{18}H_{25}N_2O_5^+$ 349.1758; Found 349.1751.

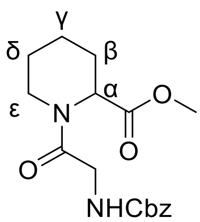
(2S)-1-[4-(Benzyloxycarbonylamino)butanoyl]proline (8c)



Following the general procedure D and starting with **25c** (431 mg, 1.24 mmol, 1.00 equiv), lithium hydroxide monohydrate (79.5 mg, 1.89 mmol, 5.0 equiv), water (3.0 mL) and methanol (3.0 mL), **8c** was obtained as a white sticky solid (116 mg, 0.347 mmol, 92% yield).

^{1}H NMR (400 MHz, methanol-d_4, unresolved mixture of rotamers) δ 7.35 – 7.18 (m, 5H, Ar*H*), 5.03 (s, 2H, OCH_2Ph), 4.57 – 4.33 (m, 1H, NC*H*), 3.79 – 3.42 (m, 2H, $NCH_2CH_2CH_2CH$), 3.18 – 3.03 (m, 2H, $C(O)CH_2CH_2CH_2NHCbz$), 2.39 – 1.68 (m, 8H, $C(O)CH_2CH_2CH_2NHCbz$ + $C(O)CH_2CH_2CH_2NHCbz$ + $NCH_2CH_2CH_2CH$ + $NCH_2CH_2CH_2CH$). ^{13}C NMR (101 MHz, methanol-d_4, unresolved mixture of rotamers) δ 174.4, 174.0, 172.8, 172.4, 157.5, 137.1, 128.1, 127.6, 127.4, 65.9, 58.8, 46.2, 39.8, 30.9, 29.0, 24.9, 24.6, 24.2, 22.1. IR (ν_{max}, cm^{-1}) 3336 (m), 2951 (w), 1716 (s), 1631 (s), 1535 (m), 1450 (s), 1254 (s), 1200 (m), 3062 (w). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{22}N_2NaO_5^+$ 357.1421; Found 357.1420.The values of the NMR spectra are in accordance with reported literature data.[4]

1-[2-(Benzyloxycarbonylamino)acetyl]pipecolinic acid methyl ester (25d)

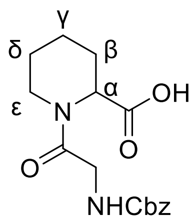


Following the general procedure B and starting with pipecolinic acid methyl ester hydrochloride (472 mg, 2.63 mmol, 1.10 equiv), Cbz-Gly (500 mg, 2.39 mmol, 1.00 equiv), EDC·HCl (504 mg, 2.63 mmol, 1.10 equiv), DIPEA (1.67 mL, 12.0 mmol, 5.00 equiv) and DCM (8.00 mL),

25d was obtained after column chromatography (DCM/MeOH 98.5:1.5) as a white sticky solid (352 mg, 1.05 mmol, 44% yield).

Rf(DCM/MeOH 98:2): 0.43. ^{1}H NMR (400 MHz, chloroform-*d*, 4:1 mixture of rotamers (major/minor)) δ 7.41 – 7.27 (m, 5H, Ar*H* (major+minor)), 5.89 – 5.62 (m, 1H, N*H* (major+minor)), 5.30 (dd, *J* = 6.2, 2.1 Hz, 0.8H, pipHα (major)), 5.10 (s, 2H, OCH_2Ph (major+minor)), 4.54 – 4.46 (m, 0.2H, pipHε (minor)), 4.42 – 4.35 (m, 0.2H, pipHα (minor)), 4.19 – 3.95 (m, 1.8H, C(O)CH_2N (major+minor)), 3.89 – 3.81 (m, 0.2H, C(O)CH_2N (minor)), 3.80 – 3.67 (m, 3H, COO*Me* (major+minor)), 3.62 – 3.50 (m, 0.8H, pipHε (major)), 3.22 (td, *J* = 13.0, 3.1 Hz, 0.8H, pipHε (major)), 2.68 (dt, *J* = 13.5, 6.7 Hz, 0.2H, pipHε (minor)), 2.35 – 2.20 (m, 1H, pipHβ (major+minor)), 1.77 – 1.56 (m, 3H, pipHβ + pipHγ + pipHδ (major+minor)), 1.50 – 1.22 (m, 2H, pipHγ + pipHδ (major+minor)). ^{13}C NMR (101 MHz, chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 171.4, 170.7, 168.2, 167.8, 156.3, 156.2, 136.5, 136.5, 128.5, 128.4, 128.1, 128.0, 66.9, 55.1, 52.5, 52.4, 42.9, 42.7, 42.3, 40.1, 27.1, 26.5, 25.0, 24.4, 20.8. IR (ν_{max}, cm^{-1}) 3406 (w), 3332 (w), 2947 (m), 2866 (w), 1732 (s), 1651 (s), 1508 (m), 1442 (s), 1219 (s), 1165 (m), 1053 (m), 1014 (m), 741 (m). HRMS (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for $C_{17}H_{22}N_2NaO_5^+$ 357.1421; Found 357.1430.

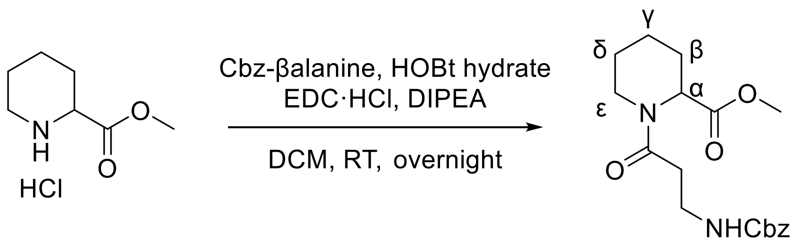
1-[2-(Benzyloxycarbonylamino)acetyl]pipecolinic acid (8d)



Following the general procedure E and starting with **25d** (244 mg, 0.730 mmol, 1.00 equiv), sodium hydroxide (0.73 mL, 0.73 mmol, 1.0M, 1.0 equiv), THF (3.7 mL) and water (3.7 mL), **8d** was obtained as a white sticky solid (225 mg, 0.702 mmol, 96% yield).

^{1}H NMR (400 MHz, chloroform-*d*, 4:1 mixture of rotamers (major/minor)) δ 10.03 (br s, 1H, COO*H* (major+minor)), 7.42 – 7.27 (m, 5H, Ar*H*, (major+minor)), 6.11 (br s, 0.2H, N*H* (minor)), 5.99 (t, *J* = 4.6 Hz, 0.8H, N*H* (major)), 5.31 (dd, *J* = 6.1, 2.1 Hz, 0.8H, pipHα (major)), 5.12 (s, 2H, OCH_2Ph (major+minor)), 4.53 – 4.39 (m, 0.4H, pipHα + pipHε (minor)), 4.27 – 3.90 (m, 2H, NC(O)CH_2 (major+minor)), 3.67 – 3.54 (m, 0.8H, pipHε (major)), 3.33 – 3.14 (m, 0.8H, pipHε (major)), 2.79 – 2.66 (m, 0.2H, pipHε (minor)), 2.39 – 2.19 (m, 1H, pipHβ (major+minor)), 1.83 – 1.54 (m, 3H, pipHβ + pipHγ + pipHδ (major+minor)), 1.53 – 1.30 (m, 2H, pipHγ + pipHδ (major+minor)). ^{13}C NMR (101 MHz, chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 175.1, 173.7, 169.0, 168.5, 156.8, 156.6, 136.3, 128.6, 128.3, 128.2, 128.1, 67.3, 67.1, 55.1, 52.5, 42.9, 42.8, 42.5, 40.3, 27.0, 26.4, 24.9, 24.4, 20.8. IR (ν_{max}, cm^{-1}) 3406 (m), 2943 (m), 2866 (m), 1716 (s), 1647 (s), 1516 (m), 1450 (m), 1227 (s), 1169 (m), 1057 (m), 1014 (m), 910 (m), 733 (s). HRMS (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for $C_{16}H_{20}N_2NaO_5^+$ 343.1264; Found 343.1263.

1-[3-(Benzyloxycarbonylamino)propanoyl]pipecolinic acid methyl ester (25e)

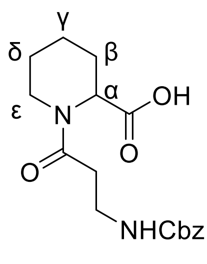


19 **25e**

To a solution of pipecolinic acid methyl ester hydrochloride (**19**) (241 mg, 1.34 mmol, 1.00 equiv), with Cbz-βalanine (300 mg, 1.34 mmol, 1.00 equiv), and EDC·HCl (258 mg, 1.34 mmol, 1.00 equiv), HOBt hydrate (226 mg, 1.48 mmol, 1.10 equiv) in DCM (8.00 mL) was added DIPEA (0.560 mL, 3.16 mmol, 2.35 equiv). The reaction was stirred overnight at RT. The crude mixture was washed with sat. $NaHCO_3$ (20 mL), citric acid (10 %w, 20 mL), brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by column chromatography (DCM/MeOH 98:2) to afford **25e** (283 mg, 0.812 mmol, 60% yield).

Rf(DCM/MeOH 98:2): 0.29. ^{1}H NMR (400 MHz, chloroform-*d*, 4:1 mixture of rotamers (major/minor)) δ 7.39 – 7.28 (m, 5H, Ar*H* (major+minor)), 5.57 (t, *J* = 6.4 Hz, 1H, N*H* (major+minor)), 5.39 – 5.29 (m, 0.8H, pipHα (major)), 5.07 (s, 2H, OC*H₂*Ph (major+minor)), 4.54 – 4.46 (m, 0.4H, pipHα + pipHε (minor)), 3.76 – 3.58 (m, 3.8H, COO*Me* (major+minor) + pipHε (major)), 3.55 – 3.41 (m, 2H, $NC(O)CH_2CH_2$ (major+minor)), 3.18 (td, *J* = 13.0, 3.0 Hz, 0.8H, pipHε (major)), 2.68 – 2.46 (m, 2H, $NC(O)CH_2CH_2$ (major+minor) + pipHβ (minor)), 2.45 – 2.32 (m, 0.2H, $NC(O)CH_2CH_2$ (minor)), 2.32 – 2.18 (m, 1H, pipHβ (major) + pipHε (minor)), 1.76 – 1.54 (m, 3H, pipHβ + pipHγ + pipHδ (major+minor)), 1.49 – 1.22 (m, 2H, pipHγ + pipHδ (major+minor)). ^{13}C NMR (101 MHz, chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 171.8, 171.7, 171.2, 156.6, 136.8, 128.5, 128.1, 66.6, 55.9, 52.6, 52.3, 51.0, 43.3, 39.5, 36.9, 33.4, 33.1, 27.2, 26.6, 25.2, 24.5, 20.9. IR (ν_{max}, cm^{-1}) 3336 (w), 2947 (m), 2866 (w), 1720 (s), 1639 (s), 1516 (m), 1439 (s), 1242 (s), 1149 (m), 1014 (m), 3421 (w). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{24}N_2NaO_5^+$ 371.1577; Found 371.1581.

1-(3-(((Benzyloxy)carbonyl)amino)propanoyl)piperidine-2-carboxylic acid (8e)

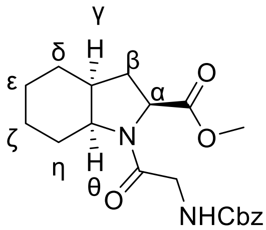


Following the general procedure E and starting with **25e** (240 mg, 0.688 mmol, 1.00 equiv), sodium hydroxide (0.69 mL, 0.69 mmol, 1.0M, 1.0 equiv), THF (3.5 mL) and water (3.5 mL), **8e** was obtained as a whitish oil (215 mg, 0.643 mmol, 93% yield).

^{1}H NMR (400 MHz, chloroform-*d*, 4:1 mixture of rotamers (major/minor)) δ 8.54 (br s, 1H, COO*H* (major+minor)), 7.42 – 7.21 (m, 5H, Ar*H* (major+minor)), 6.02 (br s, 0.2H, N*H* (minor)), 5.87 – 5.66 (m, 0.8H, N*H* (major)), 5.31 (d, *J* = 5.8 Hz, 0.8H, pipHα (major)), 5.07 (s, 2H, OCH_2Ph), 4.63 – 4.36 (m, 0.4H, pipHα + pipHε (minor)), 3.75 – 3.62 (m, 0.8H, pipHε (major)), 3.59 – 3.38 (m, 2H, $NC(O)CH_2CH_2NHCbz$), 3.28 – 3.08 (m, 0.8H, pipHε (major)), 2.72 – 2.37 (m, 2.2H, $NC(O)CH_2CH_2NHCbz$ (major+minor) + pipHε (minor)), 2.27 (d, *J* = 13.3 Hz, 1H, pipHβ (major+minor)), 1.77 – 1.49 (m, 3H, pipHβ + pipHγ + pipHδ (major+minor)), 1.50 – 1.27

(m, 2H, pipHγ + pipHδ (major+minor)). ^{13}C NMR (101 MHz, chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 174.8, 173.9, 172.5, 172.0, 157.0, 156.8, 136.7, 128.5, 128.1, 66.8, 66.7, 55.9, 52.1, 43.5, 39.7, 36.9, 33.5, 33.1, 27.1, 26.5, 25.1, 24.5, 20.8. IR (ν_{max}, cm^{-1}) 3329 (m), 2943 (m), 1709 (s), 1624 (s), 1523 (m), 1446 (m), 1246 (s), 1142 (m), 733 (s), 1014 (m), 910 (m). HRMS (ESI/QTOF) m/z: [M + Na]+ Calcd for $C_{17}H_{22}N_2NaO_5^+$ 357.1421; Found 357.1413.

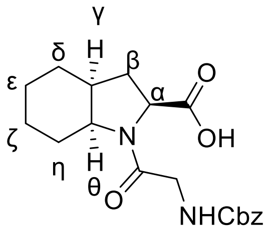
Methyl (2S,3aS,7aS)-1-(((benzyloxy)carbonyl)glycyl)octahydro-1H-indole-2-carboxylate (25f)



Following the general procedure B and starting with (2S,3aS,7aS)-2,3,3a,4,5,6,7,7a-octahydro-1H-indole-2-carboxylic acid methyl ester (385 mg, 2.10 mmol, 1.10 equiv), Cbz-Gly (400 mg, 1.91 mmol, 1.00 equiv), EDC·HCl (403 mg, 2.10 mmol, 1.10 equiv), DIPEA (1.67 mL, 9.56 mmol, 5.00 equiv) and DCM (15.0 mL), **25f** was obtained after column chromatography (DCM/MeOH 98:2) as a yellow oil (330 mg, 0.881 mmol, 46% yield).

Rf(DCM/MeOH 98:2): 0.43. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.38 – 7.27 (m, 5H, Ar*H*), 5.70 (t, *J* = 4.6 Hz, 1H, N*H*), 5.14 – 5.04 (m, 2H, OC*H₂*Ph), 4.40 (dd, *J* = 10.1, 8.0 Hz, 1H, Hα), 4.12 (dd, *J* = 16.9, 4.9 Hz, 1H, C(O)C*H₂*N), 3.94 (dd, *J* = 16.8, 4.0 Hz, 1H, C(O)C*H₂*N), 3.80 – 3.68 (m, 4H, COO*Me* + Hθ), 2.47 – 2.31 (m, 1H, Hγ), 2.19 – 1.89 (m, 3H, 2Hβ + Hδ), 1.78 – 1.43 (m, 5H, Hδ + Hε + Hζ + 2Hη), 1.35 – 1.11 (m, 2H, Hε + Hζ). ^{13}C NMR (101 MHz, chloroform-*d*) δ 172.8, 166.5, 156.3, 136.5, 128.5, 128.1, 128.0, 66.9, 59.0, 57.5, 52.4, 42.9, 37.7, 30.3, 27.7, 25.6, 23.7, 19.9. IR (ν_{max}, cm^{-1}) 3410 (w), 3332 (w), 2931 (m), 2858 (m), 1728 (s), 1651 (s), 1512 (m), 1439 (s), 1250 (s), 1176 (s), 1053 (m), 741 (m), 1361 (m). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{26}N_2NaO_5^+$ 397.1734; Found 397.1737.

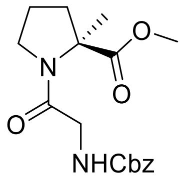
(2S,3aS,7aS)-1-(((Benzyloxy)carbonyl)glycyl)octahydro-1H-indole-2-carboxylic acid (8f)



Following the general procedure E and starting with **25f** (250 mg, 0.668 mmol, 1.00 equiv), sodium hydroxide (0.69 mL, 0.69 mmol, 1.0 M, 1.0 equiv), THF (3.8 mL) and water (3.8 mL), **8f** was obtained as a white sticky solid (168 mg, 0.406 mmol, 87% purity, 61% yield).

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.44 – 7.28 (m, 5H, Ar*H*), 5.55 – 5.19 (m, 1H, COO*H*), 5.82 (t, *J* = 4.8 Hz, 1H, N*H*), 5.11 (s, 2H, OC*H₂*Ph), 4.47 (t, *J* = 9.0 Hz, 1H, Hα), 4.19 (dd, *J* = 17.0, 5.0 Hz, 1H, NC(O)C*H₂*), 3.95 (dd, *J* = 16.9, 3.9 Hz, 1H, NC(O)C*H₂*), 3.84 – 3.74 (m, 1H, Hθ), 2.37 (br s, 1H, Hγ), 2.28 – 2.14 (m, 2H, 2Hβ), 1.94 – 1.40 (m, 6H, 2Hδ + Hε + Hζ + 2Hη), 1.39 – 1.08 (m, 2H, Hε + Hζ). ^{13}C NMR (101 MHz, chloroform-*d*) δ 174.8, 168.0, 156.5, 136.5, 128.6, 128.2, 128.1, 67.1, 59.3, 58.1, 42.9, 37.4, 29.7, 27.7, 25.6, 23.7, 19.9. IR (ν_{max}, cm^{-1}) 3321 (w), 3035 (w), 2931 (m), 2862 (w), 1720 (s), 1643 (s), 1523 (m), 1458 (m), 1250 (m), 1188 (m), 1057 (w), 914 (w), 737 (m). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{24}N_2NaO_5^+$ 383.1577; Found 383.1587.

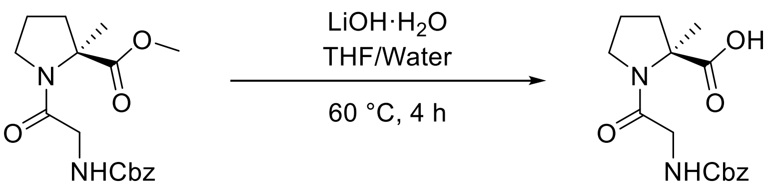
(2S)-1-[2-(Benzyloxycarbonylamino)acetyl]-2-methyl-pyrrolidine-2-carboxylic acid methyl ester (25g)



Following the general procedure B and starting with methyl (2S)-2-methylpyrrolidin-1-ium-2-carboxylate chloride (378 mg, 2.10 mmol, 1.10 equiv), Cbz-Gly (400 mg, 1.91 mmol, 1.00 equiv), EDC·HCl (403 mg, 2.10 mmol, 1.10 equiv), DIPEA (1.67 mL, 9.56 mmol, 5.00 equiv) and DCM (10.0 mL), **25g** was obtained after column chromatography (DCM/MeOH 98:2) as a brown oil (431 mg, 1.29 mmol, 67% yield).

Rf(DCM/MeOH 98:2): 0.40. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.39 – 7.27 (m, 5H, Ar*H*), 5.70 (t, *J* = 4.3 Hz, 1H, N*H*), 5.10 (s, 2H, OCH_2Ph), 4.04 – 3.86 (m, 2H, $C(O)CH_2$), 3.70 (s, 3H, COO*Me*), 3.62 – 3.47 (m, 2H, $NCH_2CH_2CH_2C$), 2.21 – 2.12 (m, 1H, $NCH_2CH_2CH_2C$), 2.12 – 1.96 (m, 2H, $NCH_2CH_2CH_2C$), 1.96 – 1.85 (m, 1H, $NCH_2CH_2CH_2C$), 1.56 (s, 3H, C*Me*). ^{13}C NMR (101 MHz, chloroform-*d*) δ 174.1, 166.3, 156.3, 136.6, 128.6, 128.1, 128.0, 66.9, 66.5, 52.6, 47.0, 43.8, 38.5, 24.0, 21.6. IR (ν_{max}, cm^{-1}) 3410 (w), 3336 (w), 2951 (w), 2881 (w), 1728 (s), 1655 (s), 1512 (m), 1435 (s), 1250 (m), 1219 (m), 1169 (m), 1053 (m), 741 (m). HRMS (ESI/QTOF) m/z: [M + Na]+ Calcd for $C_{17}H_{22}N_2NaO_5^+$ 357.1421; Found 357.1423.

(2S)-1-[2-(Benzyloxycarbonylamino)acetyl]-2-methyl-proline (8g)

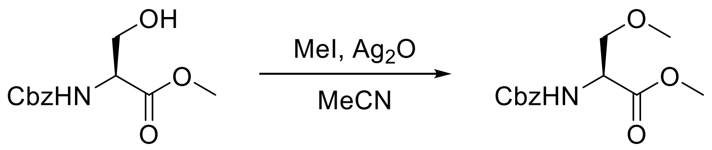


25g **8g**

To a solution of **25g** (371 mg, 1.11 mmol, 1.00 equiv) in THF (5.6 mL) and water (5.6 mL) was added lithium hydroxide monohydrate (46.6 mg, 1.11 mmol, 1.00 equiv). The reaction was stirred 4 h at 60 °C. The mixture was extracted with DCM (3 x 20 mL). The pH value of the aqueous layer was adjusted to 1 using HCl (1M). The mixture was extracted with ethyl acetate (3 x 20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum to give **8g** (325 mg, 1.01 mmol, 91% yield) as a white sticky solid which was pure enough for the next step without further purification.

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.38 – 7.28 (m, 5H, Ar*H*), 5.89 (t, *J* = 4.7 Hz, 1H, N*H*), 5.10 (s, 2H, OCH_2Ph), 4.04 (dd, *J* = 17.2, 5.4 Hz, 1H, $NC(O)CH_2$), 3.88 (dd, *J* = 17.2, 4.0 Hz, 1H, $NC(O)CH_2$), 3.54 (t, 2H, $NCH_2CH_2CH_2$), 2.36 – 2.23 (m, 1H, $NCH_2CH_2CH_2$), 2.11 – 1.92 (m, 2H, $NCH_2CH_2CH_2$), 1.92 – 1.79 (m, 1H, $NCH_2CH_2CH_2$), 1.57 (s, 3H, C*Me*). ^{13}C NMR (101 MHz, chloroform-*d*) δ 176.9, 167.7, 156.6, 136.5, 128.6, 128.2, 128.1, 67.0, 66.9, 47.5, 44.0, 38.3, 24.0, 21.5. IR (ν_{max}, cm^{-1}) 3309 (w), 2951 (w), 1720 (s), 1651 (s), 1523 (w), 1450 (m), 1254 (m), 1176 (m), 1057 (w), 910 (w), 737 (m). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{20}N_2NaO_5^+$ 343.1264; Found 343.1264.

Cbz-Ser(OMe)-OMe (21)

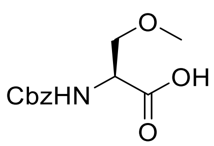


20 **21**

Following a reported procedure,[5] to a solution of MeCN (87.0 mL) and Cbz-Ser-OMe (**20**) (1.00 g, 3.95 mmol, 1.00 equiv) was added successively Ag_2O (4.58 g, 19.7 mmol, 5.00 equiv) and iodomethane (2.46 mL, 39.5 mmol, 10.0 equiv) and the mixture was stirred 24 h at RT. The mixture was filtered, the filtrate was concentrated under vacuum and purified by column chromatography ($CHCl_3$/MeOH 95:5) to obtain Cbz-Ser(OMe)-OMe (**21**) (480 mg, 1.80 mmol, 45% yield) as an oil.

$[\alpha]D^{20}$ = -8.9 (c = 0.66, MeOH). ^1H NMR (400 MHz, chloroform-*d*) δ 7.40-7.28 (m, 5H, Ar*H*), 5.62 (d, *J* = 8.2 Hz, 1H, N*H*), 5.13 (s, 2H, OCH_2Ph), 4.49 (dt, *J* = 8.5, 3.2 Hz, 1H, NHC*H*), 3.82 (dd, *J* = 9.4, 3.1 Hz, 1H, CHCH_2), 3.77 (s, 3H, C(O)O*Me*), 3.61 (dd, *J* = 9.4, 3.3 Hz, 1H, CHCH_2), 3.33 (s, 3H, O*Me*). ^{13}C NMR (101 MHz, chloroform-*d*) δ 170.9, 156.1, 136.4, 128.6, 128.3, 128.2, 72.5, 67.2, 59.4, 54.5, 52.8. The values of the NMR spectra and $[\alpha]D^{20}$ are in accordance with reported literature data.[5]

Z-Ser(OMe)-OH (22)



Following the general procedure D and starting with Z-Ser(OMe)-OMe (**21**) (430 mg, 1.61 mmol, 1.00 equiv) lithium hydroxide monohydrate (338 mg, 8.04 mmol, 5.00 equiv), water (8.6 mL) and THF (8.6 mL), Z-Ser(OMe)-OH (**22**) was obtained as an oil (400 mg, 1.58 mmol, 98% yield).

$[\alpha]D^{20}$ = +8.0 (c = 0.60, MeOH). ^1H NMR (400 MHz, chloroform-*d*) δ 9.48 – 8.55 (br s, 1H, COO*H*), 7.43 – 7.29 (m, 5H, Ar*H*), 5.65 (d, *J* = 8.4 Hz, 1H, N*H*), 5.20 – 5.08 (m, 2H, OCH_2Ph), 4.53 (dt, *J* = 8.0, 3.1 Hz, 1H, NHC*H*), 3.88 (dd, *J* = 9.4, 2.9 Hz, 1H, NHCHCH_2), 3.64 (dd, *J* = 9.4, 3.5 Hz, 1H, NHCHCH_2), 3.36 (s, 3H, O*Me*). ^{13}C NMR (101 MHz, chloroform-*d*) δ 175.2, 156.3, 136.2, 128.7, 128.4, 128.2, 72.1, 67.4, 59.5, 54.2. IR (ν_{max}, cm^{-1}) 2937 (m), 2812 (w), 1716 (s), 1524 (s), 1456 (m), 1414 (m), 1334 (m), 1214 (s), 1117 (s), 1059 (s), 740 (m). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{15}NNaO_5^+$ 276.0842; Found 276.0850. The values of the NMR spectra and $[\alpha]D^{20}$ are in accordance with reported literature data.[5]

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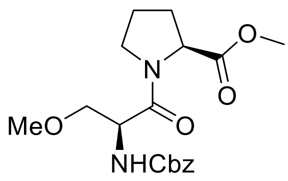
[5] S. V. Andurkar, J. P. Stables and H. Kohn, *Tetrahedron: Asymmetry*, 1998, **9**, 3841.

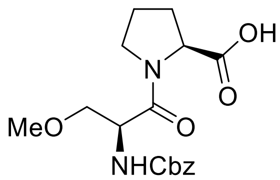
Methyl N-((benzyloxy)carbonyl)-O-methyl-L-seryl-L-prolinate (25j)



Following the general procedure C and starting with Cbz-Ser(OMe)-OH (400 mg, 1.58 mmol, 1.00 equiv), (2S)-pyrrolidine-2-carboxylic acid methyl ester hydrochloride (1.05 g, 6.32 mmol, 4.00 equiv), EDC·HCl (606 mg, 3.16 mmol, 2.00 equiv) and DMAP (57.9 mg, 0.474 mmol, 0.300 equiv) and DCM (29 mL), **25j** was obtained after column chromatography (DCM/MeOH 98:2) as a yellow oil (464 mg, 1.27 mmol, 81% yield).

Rf(DCM/MeOH 98:2): 0.32. $[\alpha]D^{20}$ = -48.4 (c = 0.81, $CHCl_3$). ^1H NMR (400 MHz, chloroform-*d*, 85:15 mixture of rotamers (major+minor)) δ 7.37 – 7.28 (m, 5H, Ar*H* (major+minor)), 5.70 – 5.54 (m, 1H, N*H* (major+minor)), 5.18 – 5.04 (m, 2H, OCH_2Ph (major+minor)), 4.83 – 4.78 (m, 0.15H, NHC*H* (minor)), 4.72 (ddt, *J* = 12.0, 8.2, 4.2 Hz, 0.85H, NHC*H* (major)), 4.59 – 4.43 (m, 1H, $NCH_2CH_2CH_2CH$ (major+minor)), 3.79 – 3.68 (m, 4H, COO*Me* + $NCH_2CH_2CH_2CH$ (major+minor)), 3.67 – 3.41 (m, 3H, $NCH_2CH_2CH_2CH$ + CH_2OMe (major+minor)), 3.40 – 3.28 (m, 3H, CH_2OMe (major+minor)), 2.26 – 2.13 (m, 1H, $NCH_2CH_2CH_2CH$), 2.13 – 1.85 (m, 3H, $NCH_2CH_2CH_2CH$ + $NCH_2CH_2CH_2CH$ (major+minor)). ^{13}C NMR (101 MHz, chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 172.4, 172.3, 169.8, 169.1, 156.1, 155.5, 136.4, 128.6, 128.2, 128.1, 73.8, 72.8, 67.0, 59.4, 59.2, 59.0, 52.9, 52.6, 52.4, 52.0, 47.2, 46.6, 31.1, 29.1, 25.0, 22.4. R (ν_{max}, cm^{-1}) 3313 (w), 2953 (m), 2881 (w), 1742 (s), 1719 (s), 1647 (s), 1529 (m), 1448 (s), 1245 (s), 1198 (s), 1176 (s), 1121 (m), 1046 (m), 753 (m). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{24}N_2NaO_6^+$ 387.1527; Found 387.1532.

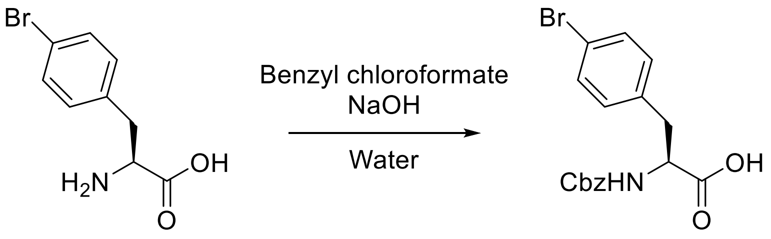
N-((benzyloxy)carbonyl)-O-methyl-L-seryl-L-proline (8j)



Following the general procedure F and starting with **25j** (430 mg, 1.18 mmol, 1.00 equiv) lithium hydroxide monohydrate (248 mg, 5.90 mmol, 5.00 equiv), water (6.3 mL) and THF (6.3 mL), **8j** was obtained as a white sticky solid (410 mg, 1.17 mmol, 99% yield).

$[\alpha]D^{20}$ = -63.4 (c = 0.66, $CHCl_3$). ^1H NMR (400 MHz, chloroform-*d*, 9:1 mixture of rotamers (major/minor)) δ 9.05-8.32 (br s, 1H, COO*H* (major+minor)), 7.38 – 7.28 (m, 5H, Ar*H* (major+minor)), 5.98 (d, *J* = 8.2 Hz, 0.1H, N*H* (minor)), 5.89-5.76 (m, 0.9H, N*H* (major)), 5.15 – 5.04 (m, 2H, OCH_2Ph (major+minor)), 4.75 (m, 1H, NHC*H* (major+minor)), 4.63 – 4.47 (m, 1H, $NCH_2CH_2CH_2CH$ (major+minor)), 3.83-3.66 (m, 2H, $NCH_2CH_2CH_2CH$ (major+minor)), 3.63 – 3.49 (m, 2H, CH_2OMe (major+minor)), 3.38-3.22 (m, 3H, O*Me* (major+minor)), 2.26 – 1.93 (m, 4H, $NCH_2CH_2CH_2CH$ + $NCH_2CH_2CH_2CH$ (major+minor)). ^{13}C NMR (101 MHz, chloroform-*d* mixture of rotamers, signals not fully resolved) δ 174.0, 173.7, 170.8, 170.7, 156.2, 155.9, 136.3, 136.2, 128.6, 128.3, 128.2, 72.8, 72.5, 67.3, 67.2, 59.9, 59.6, 59.4, 52.5, 52.2, 47.8, 47.6, 28.6, 28.4, 24.9, 24.7. IR (ν_{max}, cm^{-1}) 3302 (m), 3066 (m), 2938 (w), 1718 (s), 1638 (s), 1530 (m), 1454 (s), 1192 (s), 1263 (s), 1120 (s), 979 (m), 913 (m), 737 (s). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{22}N_2NaO_6^+$ 373.1370; Found 373.1370.

(2S)-2-(Benzyloxycarbonylamino)-3-(4-bromophenyl)propanoic acid (24)

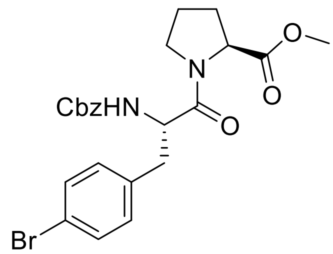


23 **24**

(2S)-2-Amino-3-(4-bromophenyl)propanoic acid (**23**) (1.00 g, 4.10 mmol, 1.00 equiv) and NaOH (328 mg, 8.19 mmol, 2.00 equiv) were dissolved in water (4.00 mL). Benzyl chloroformate (874 µL, 6.15 mmol, 1.50 equiv) was added dropwise at 0 °C. The reaction was stirred at 30 min at 0 °C and 1 h at RT. The reaction mixture was washed with diethyl ether (10.0 mL), acidified with 1 M HCl and extracted with ethyl acetate (3 x 10 mL), the combined organic layer was washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated. (2S)-2-(Benzyloxycarbonylamino)-3-(4-bromophenyl)propanoic acid (**24**) (1.29 g, 3.42 mmol, 83% yield) was obtained as a white solid.

Mp:143-145 °C. $[\alpha]D^{20}$ = +51.8 (c = 0.63, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.04 – 12.67 (br s, 1H, COO*H*), 7.67 (d, *J* = 8.5 Hz, 1H, N*H*), 7.49 – 7.42 (m, 2H, Ar*H*), 7.37 – 7.19 (m, 7H, Ar*H*), 4.97 (s, 2H, OCH_2Ph), 4.18 (ddd, *J* = 10.7, 8.6, 4.4 Hz, 1H, NHC*H*), 3.05 (dd, *J* = 13.4, 4.4 Hz, 1H, NHCHCH_2), 2.80 (dd, *J* = 13.8, 10.7 Hz, 1H, NHCHCH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.1, 156.0, 137.4, 137.0, 131.4, 131.0, 128.3, 127.7, 127.5, 119.6, 65.2, 55.2, 35.8. IR (ν_{max}, cm^{-1}) 3358 (m), 2973 (m), 1713 (s), 1531 (m), 1489 (m), 1455 (m), 1407 (m), 1342 (m), 1260 (s), 1216 (s), 1052 (s), 1012 (m), 740 (m). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{16}{}^{79}BrNNaO_4{}^+$ 400.0155; Found 400.0156.

Methyl ((S)-2-(((benzyloxy)carbonyl)amino)-3-(4-bromophenyl)propanoyl)-L-prolinate (25k)

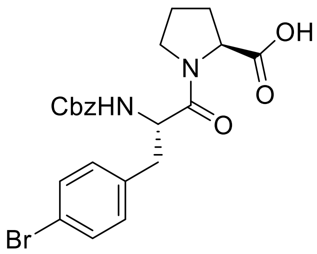


Following the general procedure C and starting with (2S)-2-(benzyloxycarbonylamino)-3-(4-bromophenyl)propanoic acid (500 mg, 1.32 mmol, 1.00 equiv), (2S)-pyrrolidine-2-carboxylic acid methyl ester hydrochloride (876 mg, 5.29 mmol, 4.00 equiv), EDC·HCl (507 mg, 2.64 mmol, 2.00 equiv) and DMAP (48.5 mg, 0.397 mmol, 0.300 equiv) and DCM (24 mL), **25k** was obtained after column chromatography (DCM/MeOH 98:2) as a yellow oil (515 mg, 1.05 mmol, 80% yield).

Rf(DCM/MeOH 98:2): 0.42. $[\alpha]D^{20}$ = -25.6 (c = 0.50, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*, unresolved mixture of rotamers) δ 7.45 – 7.27 (m, 7H, Ar*H*), 7.16 – 7.05 (m, 2H, Ar*H*), 5.55 (m, 1H, N*H*), 5.12 – 4.98 (m, 2H, OCH_2Ph), 4.74 – 4.65 (m, 1H, NHC*H*), 4.54 – 4.43 (m, 1H, $NCH_2CH_2CH_2CH$), 3.77 – 3.68 (m, 3H, COO*Me*), 3.68 – 3.57 (m, 1H, $NCH_2CH_2CH_2CH$), 3.34

– 3.23 (m, 1H, NCH_2CH$_2$CH$_2$CH), 3.14 – 3.03 (m, 1H, NHCHCH_2), 2.95 – 2.82 (m, 1H, NHCHCH_2), 2.26 – 1.88 (m, 4H, NCH$_2$CH_2CH$_2$CH + NCH$_2$CH$_2$CH_2CH). ^{13}C NMR (101 MHz, chloroform-*d*, unresolved mixture of rotamers) δ 172.3, 170.0, 155.8, 136.4, 135.0, 131.7, 131.6, 128.6, 128.3, 128.1, 121.1, 67.0, 59.0, 53.5, 52.4, 47.1, 38.4, 29.1, 25.0. IR (ν_{max}, cm^{-1}) 3281 (w), 2958 (m), 2884 (w), 1742 (s), 1718 (s), 1645 (s), 1489 (s), 1437 (s), 1250 (s), 1199 (s), 1071 (m), 1027 (m), 910 (m), 735 (s). HRMS (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for $C_{23}H_{25}{}^{79}BrN_2NaO_5{}^+$ 511.0839; Found 511.0847.

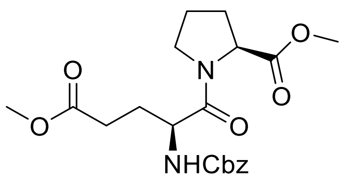
((S)-2-(((benzyloxy)carbonyl)amino)-3-(4-bromophenyl)propanoyl)-L-proline (8k)



Following the general procedure F and starting with **25k** (500 mg, 1.02 mmol, 1.00 equiv) lithium hydroxide monohydrate (214 mg, 5.11 mmol, 5.00 equiv), water (5.5 mL) and THF (5.5 mL), **8k** was obtained as a white sticky solid (200 mg, 0.421 mmol, 41% yield).

[α]D^{20} = -26.1 (c = 0.54, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6, unresolved mixture of rotamers) δ 13.55 – 12.78 (br s, 1H, COO*H*), 7.66 – 7.55 (m, 1H, N*H*), 7.47 – 7.39 (m, 2H, Ar*H*), 7.37 – 7.20 (m, 6H, Ar*H*), 7.19 – 7.11 (m, 1H, Ar*H*), 5.04 – 4.84 (m, 2H, OCH_2Ph), 4.46 – 4.34 (m, 1H, NHC*H*), 4.33 – 4.19 (m, 1H, NCH$_2$CH$_2$CH$_2$C*H*), 3.70 – 3.54 (m, 1H, NCH_2CH$_2$CH$_2$CH), 3.47 – 3.22 (m, 1H, NCH_2CH$_2$CH$_2$CH), 2.98 – 2.82 (m, 1H, NHCHCH_2), 2.82 – 2.65 (m, 1H, NHCHCH_2), 2.19 – 1.59 (m, 4H, NCH$_2$CH_2CH_2CH + NCH$_2$CH$_2$CH_2CH). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.0, 169.3, 155.8, 137.3, 137.0, 131.7, 130.9, 128.3, 127.7, 127.5, 119.5, 65.3, 59.1, 53.9, 46.4, 35.8, 28.7, 24.4. IR (ν_{max}, cm^{-1}) 3302 (w), 3060 (w), 2878 (w), 2955 (w), 1713 (s), 1632 (s), 1489 (m), 1450 (m), 1328 (w), 1264 (m), 1041 (m), 1011 (m), 734 (s). HRMS (ESI/QTOF) m/z: [M + Na]$^+$ Calcd for $C_{22}H_{23}{}^{79}BrN_2NaO_5{}^+$ 497.0683; Found 497.0694.

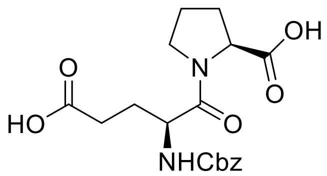
Methyl ((S)-2-(((benzyloxy)carbonyl)amino)-5-methoxy-5-oxopentanoyl)-L-prolinate (25l)



Following the general procedure C and starting with Z-Glu(OMe)-OH (500 mg, 1.69 mmol, 1.00 equiv), (2S)-pyrrolidine-2-carboxylic acid methyl ester hydrochloride (1.12 g, 6.77 mmol, 4.00 equiv), EDC·HCl (649 mg, 3.39 mmol, 2.00 equiv) and DMAP (62.1 mg, 0.508 mmol, 0.300 equiv) and DCM (30 mL), **25l** was obtained after column chromatography (DCM/MeOH 98:2) as a yellow oil (657 mg, 1.62 mmol, 95% yield).

Rf(DCM/MeOH 98:2): 0.31. [α]D^{20} = -50.5 (c = 0.57, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*, unresolved mixture of rotamers) δ 7.38 – 7.28 (m, 5H, Ar*H*), 5.59 (d, *J* = 8.4 Hz, 1H, N*H*), 5.12 – 5.03 (m, 2H, OCH_2Ph), 4.61 (tt, *J* = 8.9, 4.5 Hz, 1H, NHC*H*), 4.53 (dd, *J* = 8.7, 4.3 Hz, 1H, NCH$_2$CH$_2$CH$_2$C*H*), 3.83 – 3.64 (m, 8H, COO*Me* + NCH_2CH$_2$CH$_2$CH), 2.59 – 2.34 (m, 2H, NHCHCH$_2$CH_2), 2.32 – 2.12 (m, 2H, NHCHCH_2 + NCH$_2$CH$_2$CH_2CH), 2.10 – 1.91 (m, 3H, NCH$_2$CH_2CH$_2$CH + NCH$_2$CH$_2$CH_2CH), 1.91 – 1.74 (m, 1H, NHCHCH_2). ^{13}C NMR (101 MHz, chloroform-*d*, unresolved mixture of rotamers) δ 173.6, 172.3, 170.4, 156.3, 136.4, 128.6, 128.3, 128.1, 67.0, 58.9, 52.4, 51.9, 51.6, 47.1, 29.2, 29.1, 27.9, 25.1. IR (ν_{max}, cm^{-1}) 3308 (w), 2952 (w), 1737 (s), 1647 (s), 1525 (m), 1438 (s), 1247 (s), 1199 (s), 1176 (s), 1044 (m), 913 (w), 739 (m). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{26}N_2NaO_7^+$ 429.1632; Found 429.1629.

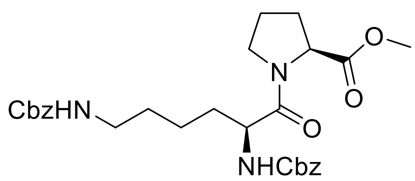
((Benzyloxy)carbonyl)-L-glutamyl-L-proline (8l)



Following the general procedure F and starting with **25l** (600 mg, 1.48 mmol, 1.00 equiv) lithium hydroxide monohydrate (310 mg, 7.38 mmol, 5.00 equiv), water (7.8 mL) and THF (7.8 mL), **8l** was obtained as a white sticky solid (434 mg, 1.15 mmol, 78% yield).

$[\alpha]D^{20}$ = -17.6 (c = 0.95, $CHCl_3$). ^1H NMR (400 MHz, chloroform-*d*, unresolved mixture of rotamers) δ 9.80 – 9.41 (br s, 2H, COO*H*), 7.36 – 7.27 (m, 5H, Ar*H*), 6.36 (d, *J* = 8.5 Hz, 1H, N*H*), 5.06 (s, 2H, OC*H₂*Ph), 4.62 (q, *J* = 7.8 Hz, 1H, NHC*H*), 4.52 (dd, *J* = 8.4, 4.1 Hz, 1H, $NCH_2CH_2CH_2C$*H*), 3.80 – 3.61 (m, 2H, NC*H₂*CH2CH2CH), 2.55 – 2.35 (m, 2H, C*H₂*COOH), 2.28 – 1.81 (m, 6H, NHCHC*H₂* + NCH_2C*H₂*CH_2CH + NCH_2CH_2C*H₂*CH). ^{13}C NMR (101 MHz, chloroform-*d*, unresolved mixture of rotamers) δ 177.4, 175.5, 171.6, 156.6, 136.4, 128.6, 128.2, 128.1, 67.2, 59.2, 51.7, 47.4, 29.3, 28.8, 27.0, 24.9. IR (ν_{max}, cm^{-1}) 3322 (m), 3092 (m), 2947 (w), 1713 (s), 1617 (s), 1532 (m), 1455 (m), 1266 (s), 1191 (s), 913 (s), 737 (s). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{22}N_2NaO_7^+$ 401.1319; Found 401.1318.

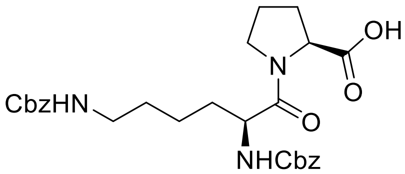
Methyl N^2,N^6-bis((benzyloxy)carbonyl)-L-lysyl-L-prolinate (25m)



Following the general procedure C and starting with Z-Lys(Z)-OH (800 mg, 1.93 mmol, 1.00 equiv), (2S)-pyrrolidine-2-carboxylic acid methyl ester hydrochloride (1.28 g, 7.72 mmol, 4.00 equiv), EDC·HCl (740 mg, 3.86 mmol, 2.00 equiv) and DMAP (70.7 mg, 579 μmol, 0.300 equiv) and DCM (30 mL), **25m** was obtained after column chromatography (DCM/MeOH 98:2) as a yellow sticky oil (881 mg, 1.68 mmol, 87% yield).

Rf(DCM/MeOH 99:1): 0.37. $[\alpha]D^{20}$ = -29.1 (c = 0.62, $CHCl_3$). ^1H NMR (400 MHz, chloroform-*d*) δ 7.41 – 7.28 (m, 10H, Ar*H*), 5.66 (d, *J* = 8.4 Hz, 1H, CHN*H*), 5.27 (d, *J* = 5.5 Hz, 1H, CH_2N*H*), 5.06 (s, 4H, OC*H₂*Ph), 4.56 – 4.45 (m, 2H, $NCH_2CH_2CH_2C$*H* + C*H*NH), 3.79 – 3.66 (m, 2H, NC*H₂*CH_2CH_2CH), 3.63 (s, 3H, COO*Me*), 3.26 – 3.08 (m, 2H, C*H₂*NH), 2.26 – 2.13 (m, 1H, NCH_2CH_2C*H₂*CH), 2.07 – 1.88 (m, 3H, NCH_2C*H₂*CH_2CH + CH_2C*H₂*CH_2CH_2NH), 1.86 – 1.30 (m, 6H, NCH_2CH_2C*H₂*CH + C*H₂*$CH_2CH_2CH_2$NH + CH_2C*H₂*CH_2CH_2NH + CH_2CH_2C*H₂*CH_2NH). ^{13}C NMR (101 MHz, chloroform-*d*) δ 172.6, 170.8, 156.6, 156.1, 136.8, 136.4, 128.6, 128.5, 128.2, 128.1, 128.0, 128.0, 66.9, 66.6, 58.8, 52.4, 52.1, 47.0, 40.5, 32.0, 29.2, 29.0, 25.0, 21.6. IR (ν_{max}, cm^{-1}) 3321 (m), 2951 (m), 1706 (s), 1643 (s), 1526 (s), 1438 (s), 1243 (s), 1219 (s), 1199 (s), 1027 (m), 1176 (m), 735 (s), 698 (s), 752 (s). HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{28}H_{36}N_3O_7^+$ 526.2548; Found 526.2548.

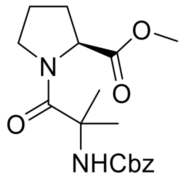
N^2,N^6-bis((benzyloxy)carbonyl)-L-lysyl-L-proline (8m)



Following the general procedure F and starting with **25m** (880 mg, 1.67 mmol, 1.00 equiv) lithium hydroxide monohydrate (351 mg, 8.37 mmol, 5.00 equiv), water (5.0 mL) and THF (5.0 mL), **8m** was obtained as a white sticky solid (724 mg, 1.41 mmol, 84% yield).

$[\alpha]D^{20}$ = -29.0 (c = 0.56, $CHCl_3$). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.25 (s, 1H, COO*H*), 7.38 – 7.09 (m, 10H, Ar*H*), 6.54 – 6.12 (m, 1H, CHN*H*), 5.43 – 5.22 (m, 1H, CH_2NH), 5.20 – 4.89 (m, 4H, OCH_2Ph), 4.59 – 4.31 (m, 2H, $CH_2CH_2CH_2CH$ + CHNH), 3.77 – 3.64 (m, 1H, $NCH_2CH_2CH_2CH$), 3.64 – 3.47 (m, 1H, $NCH_2CH_2CH_2CH$), 3.22 – 3.01 (m, 2H, CH_2NH), 2.18 – 1.54 (m, 6H, $NCH_2CH_2CH_2CH$ + $NCH_2CH_2CH_2CH$ + $CH_2CH_2CH_2CH_2NH$), 1.54 – 1.29 (m, 4H, $CH_2CH_2CH_2CH_2NH$ + $CH_2CH_2CH_2CH_2NH$). ^{13}C NMR (101 MHz, chloroform-*d*, signals not fully resolved) δ 175.0, 172.1, 156.9, 156.5, 136.8, 136.6, 128.6, 128.2, 128.2, 128.1, 66.9, 66.7, 59.6, 52.4, 47.4, 40.8, 31.7, 29.4, 28.7, 25.0, 22.1. IR ($ν_{max}$, cm^{-1}) 3327 (w), 2944 (w), 1702 (s), 1635 (s), 1529 (m), 1454 (m), 1247 (s), 736 (s), 1039 (m), 698 (m), 1028 (m). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{33}N_3NaO_7^+$ 534.2211; Found 534.2214.

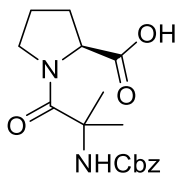
Methyl (2-(((benzyloxy)carbonyl)amino)-2-methylpropanoyl)-L-prolinate (25n)



Following the general procedure C and starting with 1-(phenylmethoxycarbonylamino)cyclopropane-1-carboxylic acid (500 mg, 2.13 mmol, 1.00 equiv), (2S)-pyrrolidine-2-carboxylic acid methyl ester hydrochloride (1.41 g, 8.50 mmol, 4.00 equiv), EDC·HCl (815 mg, 4.25 mmol, 2.00 equiv) and DMAP (77.9 mg, 0.638 mmol, 0.300 equiv) and DCM (10 mL), **25n** was obtained after column chromatography (DCM/MeOH 99.5:0.5) as a yellow oil (262 mg, 0.753 mmol, 36% yield).

Rf(DCM/MeOH 99:1): 0.29. ^{1}H NMR (400 MHz, chloroform-*d*,7:3 mixture of rotamers (major/minor)) δ 7.40 – 7.27 (m, 5H, Ar*H* (major/minor)), 5.60 (s, 0.7H, N*H* (major)), 5.39 (s, 0.3H, N*H* (minor)), 5.20 – 4.84 (m, 2H, OCH_2Ph (major+minor)), 4.53 (s, 0.7H, $NCH_2CH_2CH_2CH$ (major)), 4.23 (s, 0.3H, $NCH_2CH_2CH_2CH$ (minor)), 3.82 – 3.56 (m, 4H, COOMe + $NCH_2CH_2CH_2CH$ (major+minor)), 3.54 – 3.26 (m, 1H, $NCH_2CH_2CH_2CH$ (major+minor)), 2.14 – 1.70 (m, 4H, $NCH_2CH_2CH_2CH$ + $NCH_2CH_2CH_2CH$ (major+minor)), 1.70 – 1.35 (m, 6H, *Me* (major+minor)). ^{13}C NMR (101 MHz, chloroform-*d*) δ 173.1, 172.2, 154.3, 136.6, 128.6, 128.3, 128.2, 66.5, 60.9, 56.9, 52.2, 48.0, 27.8, 25.8, 24.8, 24.4. IR ($ν_{max}$, cm^{-1}) 3304 (w), 2985 (w), 2952 (m), 1717 (s), 1621 (s), 2249 (w), 1524 (m), 1410 (s), 1257 (s), 1168 (s), 1204 (s), 1073 (s), 912 (m), 732 (s), 699 (s). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{24}N_2NaO_5^+$ 371.1577; Found 371.1581.

(2-(((Benzyloxy)carbonyl)amino)-2-methylpropanoyl)-L-proline (8n)



Following the general procedure F and starting with **25n** (262 mg, 0.752 mmol, 1.00 equiv) lithium hydroxide monohydrate (158 mg, 3.76 mmol, 5.00 equiv), water (1.8 mL) and THF (1.8 mL), **8n** was obtained as a white sticky solid (183 mg, 0.548 mmol, 73% yield).

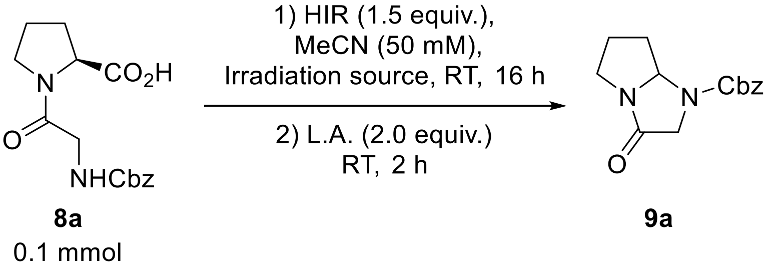
^{1}H NMR (400 MHz, chloroform-*d*, 7:3 mixture of rotamers (major/minor)) δ 7.52 (br s, 1H, COO*H* (major+minor)), 7.41 – 7.29 (m, 5H, Ar*H* (major+minor)), 6.12 (s, 0.3H, N*H* (minor)), 5.54 (s, 0.7H, N*H* (major)), 5.37 (br s, 0.3H, OCH_2Ph (minor)), 5.06 (s, 1.4H, OCH_2Ph (major)), 4.97 – 4.84 (m, 0.3H, OCH_2Ph (minor)), 4.56 (t, *J* = 6.6 Hz, 0.7H, $NCH_2CH_2CH_2C$*H* (major)), 4.23 (br s, 0.3H, $NCH_2CH_2CH_2C$*H* (minor)), 3.67 – 3.22 (m, 2H, NC*H_2*CH_2CH_2CH (major+minor)), 2.16 – 1.62 (m, 4H, NCH_2C*H_2*CH_2CH + NCH_2CH_2C*H_2*CH (major+minor)), 1.61 – 1.36 (m, 6H, *Me* (major+minor)). ^{13}C NMR (101 MHz, chloroform-*d*, mixture of diastereoisomers, signals not fully resolved) δ 174.6, 173.4, 154.9, 136.3, 128.6, 128.5, 67.1, 61.6, 57.1, 48.3, 27.4, 25.9, 25.2, 25.0. IR (ν_{max}, cm^{-1}) 3298 (w), 2984 (w), 1714 (s), 1621 (m), 1527 (m), 1414 (m), 1259 (m), 1177 (m), 1075 (m), 910 (m), 731 (s), 698 (m). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{22}N_2NaO_5^+$ 357.1421; Found 357.1415.

3. Optimisation of the decarboxylative-cyclisation reaction

Photochemistry reactions[a]

Dry MeCN (2 mL) was added in a 5 mL test tube containing Z-Gly-Pro (**8a**) (31 mg, 0.10 mmol, 1.0 equiv), the HIR (0.15 mmol, 1.5 equiv), and the additional reagents under a nitrogen atmosphere. The reaction mixture was irradiated using blue light LEDs or 80 W CFL 16 h at RT. The reaction mixture was cooled to 0 °C and the Lewis acid (2.0 equiv) was added dropwise. The reaction was let stirring for 2 h at RT.

The crude mixture was diluted with 10 mL of sat. $NaHCO_3$ (and 10 mL of $Na_2S_2O_3$ (10 %) when I_2 or NaI were used) then extracted with diethyl ether (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by prep-TLC (DCM/EtOAc 7:3).



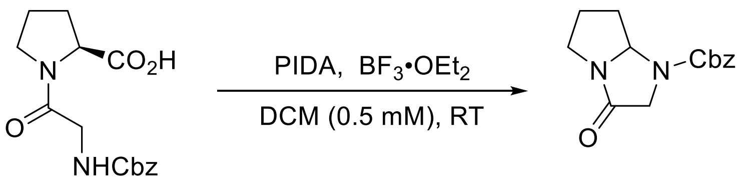
Entry	HIR source	L.A.	Additional reagent	Irradiation source	Conversion[b]	Yield[c]
1[d]	AcOBX	$BF_3{\cdot}Et_2O$	$Ru(bpy)_3Cl_2$ (3 mol%)	Blue LEDs	100%	66%
2[d]	**PIDA**	**$BF_3{\cdot}Et_2O$**	**$Ru(bpy)_3Cl_2$ (3 mol%)**	**Blue LEDs**	**6%**	**76%**
3	MeOBX	$BF_3{\cdot}Et_2O$	$Ru(bpy)_3Cl_2$ (3 mol%)	Blue LEDs	100%	54%
4	MeOBX	TFA	$Ru(bpy)_3Cl_2$ (3 mol%)	Blue LEDs	100%	54%
5	MeOBX	TFA[e]	$Ru(bpy)_3Cl_2$ (3 mol%)	Blue LEDs	100%	76%
6[f]	PIDA	$BF_3{\cdot}Et_2O$	I_2 (0.5 equiv.)	80 W CFL	100%	57%
7	PIDA[g]	$BF_3{\cdot}Et_2O$	NaI (4.0 equiv.)	80 W CFL	100%	78%
8[f]	PIDA	None	I_2 (0.5 equiv.)	None	100%	0%
9[f]	PIDA	$BF_3{\cdot}Et_2O$	None	80 W CFL	54%	92%

[a]Sequential reaction: 16 h for the first step and 2 h after the addition of the Lewis acid. [b]Measured by LCMS after the addition of the Lewis acid. [c]Isolated yield. [d]0.3 mmol scale. [e]10.0 equiv. [f]Reaction performed in DCM. [g]4.0 equiv.

Oxidative reactions

Dry DCM (2 mL) was added in a 5 mL test tube containing Z-Gly-Pro (**8a**) (31 mg, 0.10 mmol, 1.0 equiv) and PIDA under a nitrogen atmosphere. The reaction mixture was cooled to 0 °C and $BF_3{\cdot}OEt_2$ was added dropwise. The reaction was let stirring at RT.

The crude mixture was diluted with 10 mL of sat. $NaHCO_3$ then extracted with diethyl ether (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The resulting mixture was analyzed by ^{1}H NMR (400 MHz, $CDCl_3$) using CH_2Br_2 as an internal standard.



8a 0.1 mmol　　**9a**

Entry	Solvent	PIDA	$BF_3{\cdot}Et_2O$	Time (h)	NMR Yield[a]
1	MeCN	1.5 equiv.	2.0 equiv.	2	88%[b]
2	DCM	1.5 equiv.	2.0 equiv.	2	quant. (97)[b]
4	DCM	1.5 equiv.	1.0 equiv.	2	quant%
5	DCM	1.0 equiv.	1.0 equiv.	2	88%

6	DCM	None	1.0 equiv.	1	0%
7	DCM	1.0 equiv.	None	1	0%
8[c]	DCM	2.0 equiv.	2.0 equiv.	4[d]	96%[b]

[a]^{1}H NMR of the crude mixture with CH_2Br_2 as an internal standard. [b]Isolated yield. [c]0.3 mmol scale. [d]Sequential reaction: the reaction started with PIDA (1.0 equiv) and $BF_3{\cdot}Et_2O$ (1.0 equiv), after 2 h a second equivalent of each is added and the reaction stirred for 2 more h.

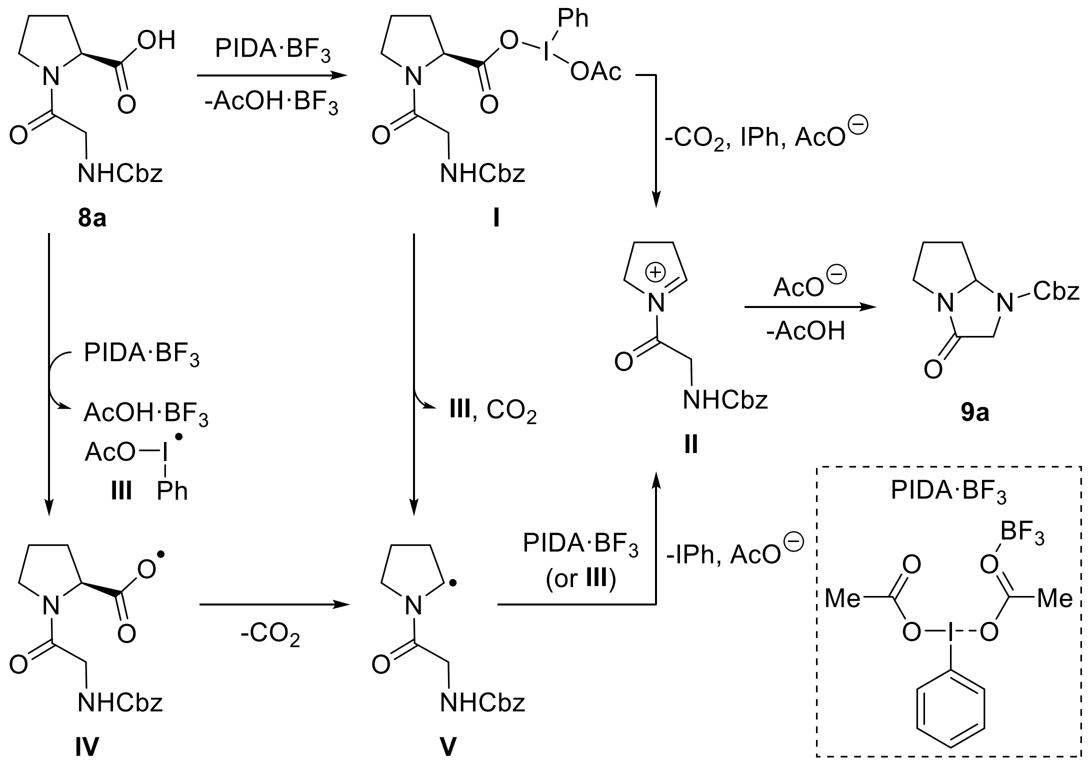
Additionally, other protecting groups than Cbz (Boc or Ac) were not compatible with the decarboxylative cyclisation reaction.

4. Speculative mechanism for the decarboxylative cyclisation

Concerning the mechanism of the reaction, different pathways could be considered. The first one is a polar pathway. A ligand exchange could occur between the starting material and AcO resulting in intermediate **I**,[6] which could undergo a fragmentation cascade, giving **II** along with CO_2, iodobenzene and acetate. Finally, intramolecular attack of the carbamate group would afford compound **9a**. Alternatively, a succession of two single electron transfers (SET) could be considered. The carboxylic acid present on the starting material would be oxidized by the activated $PIDA{\cdot}BF_3$ species,[7] giving the radical AcOIPh (**III**) and intermediate **IV**. Intermediate **IV** would fragment via extrusion of CO_2 to give an alpha aminyl radical intermediate **V**. A second SET between intermediate **V** and the radical AcOIPh (**III**) would lead to *N*-acyliminium **II**. Alternatively, $PIDA{\cdot}BF_3$ could also perform the second SET reaction and AcOIPh (**III**) could accomplish the first SET. Moreover, a radical pathway starting first with the formation of covalently bond intermediate **I** could be also envisaged. Intermediate **I** could then fragment homolytically to give **III** and **V**, which would then be oxidized. The resulting product **9a** has been analyzed on chiral-HPLC and a racemic mixture was observed, supporting the formation in all cases of an *N*-acyliminium intermediate. Further investigation would be needed to discriminate between the proposed pathways.

[6] (*a*) S. Izquierdo, S. Essafi, I. del Rosal, P. Vidossich, R. Pleixats, A. Vallribera, G. Ujaque, A. Lledós and A. Shafir, *J. Am. Chem. Soc.*, 2016, **138**, 12747. (*b*) A. Dasgupta, C. Thiehoff, P. D. Newman, T. Wirth and R. L. Melen, *Org. Biomol. Chem.*, 2021, **19**, 4852.

[7] Selected examples: (*a*) A. Y. Koposov, V. V. Boyarskikh and V. V. Zhdankin, *Org. Lett.*, 2004, **6**, 3613. (*b*) H. Li, D. Gori, C. Kouklovsky and G. Vincent, *Tetrahedron: Asymmetry*, 2010, **21**, 1507. (*c*) J. Kishore Vandavasi, W.-P. Hu, G. Chandru Senadi, H.-T. Chen, H.-Y. Chen, K.-C. Hsieh and J.-J. Wang, *Adv. Synth. Catal.*, 2015, **357**, 2788.



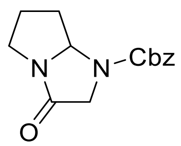
5. Synthesis of aminal heterocycles

General procedure G for the decarboxylative cyclisation of dipeptides derivatives

Dry DCM (6 mL) was added in a 10 mL test tube containing the corresponding dipeptide or small molecule (0.30 mmol, 1.0 equiv) and PIDA (97 mg, 0.30 mmol, 1.0 equiv) under a nitrogen atmosphere. The reaction mixture was cooled to 0 °C and $BF_3 \cdot OEt_2$ (79 µL, 0.30 mmol, 1.0 equiv) was added dropwise. The reaction was let stirring for 2 h at RT. Then, PIDA (97 mg, 0.30 mmol, 1.0 equiv) was added. The mixture was degassed by Ar bubbling, cooled to 0 °C and $BF_3 \cdot OEt_2$ (79 µL, 0.30 mmol, 1.0 equiv) was added dropwise. The reaction was let stirring for 2 h at RT.

The crude mixture was diluted with 15 mL of sat. $NaHCO_3$ then extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel. Compounds **9a** to **9 e, 9g** and **9n** are obtained as a racemic mixture.

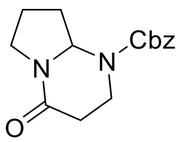
3-Keto-5,6,7,7a-tetrahydro-2H-pyrrol[1,2-a]imidazole-1-carboxylic acid benzyl ester (9a)



Following the general procedure G and starting with Cbz-Gly-Pro (**8a**) (92 mg, 0.30 mmol, 1.0 equiv), **9a** was obtained after column chromatography (DCM/EtOAc 4:1) as a white oil (75 mg, 0.29 mmol, 96% yield).

Rf(DCM/EtOAc 7:3): 0.57. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.41 – 7.29 (m, 5H, Ar*H*), 5.26 – 5.09 (m, 3H, OCH_2Ph + NC*H*), 4.28 – 4.17 (m, 1H, $NC(O)CH_2NCbz$), 4.07 – 3.95 (m, 1H, $NC(O)CH_2NCbz$), 3.77 – 3.65 (m, 1H, $NCH_2CH_2CH_2CHN$), 3.19 – 3.04 (m, 1H, $NCH_2CH_2CH_2CHN$), 2.46 – 1.86 (m, 3H, $NCH_2CH_2CH_2CHN$+ $NCH_2CH_2CH_2CHN$), 1.52 – 1.38 (m, 1H, $NCH_2CH_2CH_2CHN$). ^{13}C NMR (101 MHz, chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 170.4, 170.1, 153.9, 153.5, 136.0, 128.7, 128.4, 128.1, 77.0, 76.6, 67.7, 67.5, 51.3, 51.2, 41.6, 32.2, 31.6, 24.5, 24.4. IR ($ν_{max}$, cm^{-1}) 2951 (w), 2897 (w), 1712 (s), 1408 (m), 1358 (m), 1300 (m), 1122 (m), 1014 (w), 748 (w). HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{14}H_{17}N_2O_3^+$ 261.1234; Found 261.1231.

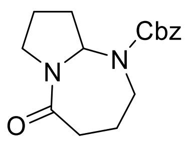
Benzyl 4-oxohexahydropyrrolo[1,2-a]pyrimidine-1(2H)-carboxylate (9b)



Following the general procedure G and starting with **8b** (96 mg, 0.30 mmol, 1.0 equiv), **9b** was obtained after column chromatography (DCM/MeOH 98:2) as a yellow oil (56 mg, 0.21 mmol, 68% yield).

Rf(DCM/MeOH 98:2): 0.34. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.38 – 7.28 (m, 5H, Ar*H*), 5.22 – 5.03 (m, 3H,OCH_2Ph + NC*H*), 4.21 – 4.11 (m, 1H, $NC(O)CH_2CH_2N$), 3.76 – 3.64 (m, 1H, $NCH_2CH_2CH_2CHN$), 3.38 (ddd, *J* = 12.3, 9.4, 3.0 Hz, 1H, $NCH_2CH_2CH_2CHN$), 3.17 (ddd, *J* = 13.1, 10.9, 4.3 Hz, 1H, $NC(O)CH_2CH_2N$), 2.54 – 2.41 (m, 1H, $NCH_2CH_2CH_2CHN$), 2.41 – 2.30 (m, 2H, $NC(O)CH_2CH_2N$), 2.00 – 1.58 (m, 3H, $NCH_2CH_2CH_2CHN$ + $NCH_2CH_2CH_2CHN$). ^{13}C NMR (101 MHz, chloroform-*d*) δ 168.3, 154.4, 136.0, 128.6, 128.4, 128.2, 70.0, 67.7, 43.3, 39.0, 32.9, 32.3, 19.8. IR ($ν_{max}$, cm^{-1}) 3533 (w), 2951 (w), 2889 (w), 1705 (s), 1655 (s), 1450 (s), 1415 (s), 1358 (m), 1200 (s), 1107 (m), 737 (m), 698 (m). HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{19}N_2O_3^+$ 275.1390; Found 275.1394.

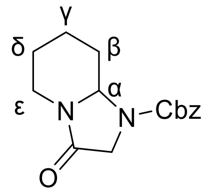
Benzyl 5-oxooctahydro-1H-pyrrolo[1,2-a][1,3]diazepine-1-carboxylate (9c)



Following the general procedure G and starting with **8c** (100 mg, 0.300 mmol, 1.00 equiv), **9c** was obtained after column chromatography (DCM/MeOH 99:1) as a yellow oil (78 mg, 0.27 mmol, 91% yield).

Rf(DCM/MeOH 98:2): 0.37. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.43 – 7.27 (m, 5H, Ar*H*), 5.41 (t, *J* = 6.0 Hz, 1H, NC*H*), 5.22 – 5.09 (m, 2H, OCH_2Ph), 3.84 – 3.70 (m, 1H, $NCH_2CH_2CH_2CHN$), 3.61 – 3.50 (m, 2H, $NC(O)CH_2CH_2CH_2N$), 3.23 – 3.07 (m, 1H, $NCH_2CH_2CH_2CHN$), 2.52 – 2.28 (m, 3H, $NC(O)CH_2CH_2CH_2N$ + $NCH_2CH_2CH_2CHN$), 2.11 – 1.65 (m, 5H, $NCH_2CH_2CH_2CHN$ + $NCH_2CH_2CH_2CHN$ + $NC(O)CH_2CH_2CH_2N$). ^{13}C NMR (101 MHz, chloroform-*d*, one aliphatic signal not resolved) δ 171.7, 154.9, 136.3, 128.7, 128.3, 128.0, 72.2, 67.4, 46.2, 42.3, 33.5, 23.3, 21.9. IR ($ν_{max}$, cm^{-1}) 3537 (w), 2951 (m), 2885 (w), 1701 (s), 1647 (s), 1450 (m), 1412 (s), 1647 (s), 1257 (m), 1180 (m), 1018 (m), 741 (m). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{20}N_2NaO_3^+$ 311.1366; Found 311.1373.

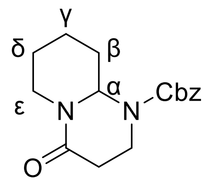
Benzyl 3-oxohexahydroimidazo[1,2-a]pyridine-1(5H)-carboxylate (9d)



Following the general procedure G and starting with **8d** (96 mg, 0.30 mmol, 1.0 equiv), **9d** was obtained after column chromatography (DCM/EtOAc 9:1) as a yellow oil (74 mg, 0.27 mmol, 90% yield).

Rf(DCM/EtOAc 9:1): 0.35. ^{1}H NMR (400 MHz, chloroform-*d*, 3:2 mixture of rotamers (major/minor)) δ 7.42 – 7.28 (m, 5H, Ar*H* (major+minor)), 5.24 – 5.09 (m, 2H, OCH_2Ph (major+minor)), 4.91 (t, *J* = 12.9 Hz, 1H, pipHα (major+minor)), 4.26 (ddt, *J* = 13.4, 5.2, 1.7 Hz, 1H, pipHε (major+minor)), 4.18 – 4.00 (m, 1H, NC(O)CH_2N (major+minor)), 3.97 – 3.84 (m, 1H, NC(O)CH_2N (major+minor)), 2.81 – 2.66 (m, 1H, pipHε (major+minor)), 2.57 – 2.46 (m, 0.6H, pipHβ (major)), 2.38 – 2.24 (m, 0.4H, pipHβ (minor)), 1.97 – 1.84 (m, 1H, pipHγ (major+minor)), 1.74 – 1.60 (m, 1H, pipHδ (major+minor)), 1.60 – 1.43 (m, 1H, pipHγ (major+minor)), 1.43 – 1.28 (m, 1H, pipHδ (major+minor)), 1.28 – 1.13 (m, 1H, pipHβ (major+minor)). ^{13}C NMR (101 MHz, chloroform-*d*, mixture of rotamers, signals not fully resolved) δ 165.6, 153.7, 136.1, 128.7, 128.4, 128.3, 128.1, 72.3, 72.0, 67.7, 67.4, 48.2, 39.9, 32.9, 32.2, 24.4, 22.2, 22.1. IR (ν_{max}, cm^{-1}) 3564 (w), 2943 (w), 2866 (w), 1705 (s), 1450 (m), 1412 (s), 1361 (m), 1304 (m), 1281 (m), 1119 (m), 984 (w), 752 (w). HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{15}H_{19}N_2O_3^+$ 275.1390; Found 275.1397.

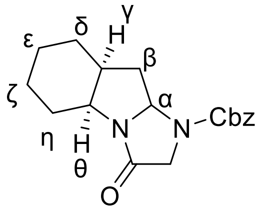
Benzyl 4-oxohexahydro-2H-pyrido[1,2-a]pyrimidine-1(6H)-carboxylate (9e)



Following the general procedure G and starting with **8e** (0.10 g, 0.30 mmol, 1.0 equiv), **9e** was obtained after column chromatography (DCM/EtOAc 9:1) as a white sticky solid (68 mg, 0.24 mmol, 79% yield).

Rf(DCM/EtOAc 9:1): 0.27. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.43 – 7.30 (m, 5H, Ar*H*), 5.37 – 5.23 (m, 1H, pipHα), 5.17 (s, 2H, OCH_2Ph), 4.79 (dd, *J* = 13.3, 1.9 Hz, 1H, pipHε), 4.18 (br s, 1H, NC(O)CH_2CH_2N), 3.27 (s, 1H, NC(O)CH_2CH_2N), 2.61 – 2.44 (m, 2H, pipHε + NC(O)C$H_2$$CH_2$N), 2.42 – 2.32 (m, 1H, NC(O)C$H_2$$CH_2$N), 2.01 – 1.76 (m, 2H, pipHβ + pipHγ), 1.75 – 1.57 (m, 3H, pipHβ + pipHγ + pipHδ), 1.45 – 1.28 (m, 1H, pipHδ). ^{13}C NMR (101 MHz, chloroform-*d*) δ 166.1, 154.0, 136.1, 128.7, 128.5, 128.1, 68.7, 67.9, 43.5, 37.0, 32.6, 31.2, 24.9, 24.2. IR (ν_{max}, cm^{-1}) 2939 (m), 3510 (w), 2862 (w), 1705 (s), 1427 (s), 1200 (s), 1122 (m), 1011 (m), 744 (m), 1315 (m), 1269 (m). HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{21}N_2O_3^+$ 289.1547; Found 289.1547.

Benzyl (4aS,8aS)-3-oxodecahydro-1H-imidazo[1,2-a]indole-1-carboxylate (9f)

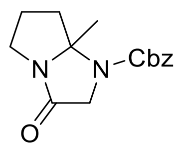


Following the general procedure G and starting with **8f** (108 mg, 0.300 mmol, 1.00 equiv), **9f** was obtained after column chromatography (DCM/EtOAc 97:3) as a yellow oil (29.0 mg, 92.0 µmol, 31% yield, dr 3:2).

The dr ratio was measured from the ^{1}H NMR spectrum of the isolated mixture of diastereoisomers by integrating the NC(O)C*H₂*N proton of each diastereomer. Attributions of protons for each diastereoisomers was supported by 2D experiments.

Rf(DCM/EtOAc 97:3): 0.20. ^{1}H NMR (400 MHz, chloroform-*d*, 3:2 mixture of diastereoisomers (major/minor)) δ 7.46 – 7.29 (m, 5H, Ar*H* (major+minor)), 5.42 (br s, 1H, Hα (major+minor)), 5.25 – 5.09 (m, 2H, OCH_2Ph (major+minor)), 4.21 – 4.10 (m, 1H, $NC(O)CH_2N$ (major+minor)), 4.10 – 4.02 (m, 1H, Hθ (major+minor)), 4.00 – 3.96 (m, 0.6H, $NC(O)CH_2N$ (major)), 3.96 – 3.91 (m, 0.4H, $NC(O)CH_2N$ (minor), 2.39 – 2.03 (m, 2H, Hβ + Hη (major+minor)), 1.95 – 1.60 (m, 3H, Hβ + Hγ + Hη (major+minor)), 1.60 – 1.19 (m, 6H, 2Hδ + 2Hε +2Hζ (major+minor)). ^{13}C NMR (101 MHz, chloroform-*d*, mixture of diastereoisomers, signals not fully resolved) δ 172.1, 154.0, 153.7, 136.1, 128.7, 128.4, 128.2, 75.8, 75.3, 67.5, 56.3, 51.1, 37.7, 36.5, 35.8, 27.5, 26.8, 22.4, 21.2. IR (ν_{max}, cm^{-1}) 2931 (m), 2862 (w), 1709 (s), 1419 (m), 1396 (m), 1354 (m), 1304 (m), 1119 (m), 1007 (w), 741 (m). HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{23}N_2O_3^+$ 315.1703; Found 315.1706.

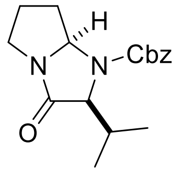
7a-Methyl-3-oxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-carboxylate (9g)



Following the general procedure G and starting with **8g** (96 mg, 0.30 mmol, 1.0 equiv), **9g** was obtained after column chromatography (DCM/EtOAc 4:1) as a yellow oil (38 mg, 0.14 mmol, 47% yield).

Rf(DCM/EtOAc 4:1): 0.27. ^{1}H NMR (400 MHz, chloroform-*d*, 3:2 mixture of rotamers (major/minor)) δ 7.41 – 7.30 (m, 5H, Ar*H* (major+minor)), 5.19 – 5.09 (m, 2H, OCH_2Ph (major+minor)), 4.25 – 4.03 (m, 2H, $NC(O)CH_2N$ (major+minor)), 3.80 – 3.68 (m, 1H, $NCH_2CH_2CH_2C$ (major+minor)), 3.19 – 3.03 (m, 1H, $NCH_2CH_2CH_2C$ (major+minor)), 2.41 – 2.28 (m, 0.6H, $NCH_2CH_2CH_2C$ (major)), 2.24 – 1.97 (m, 2.4H, $NCH_2CH_2CH_2C$ + $NCH_2CH_2CH_2C$ (minor)), 1.92 – 1.73 (m, 1H, $NCH_2CH_2CH_2C$ (major+minor)), 1.59 (s, 1.8H, C*Me* (major)), 1.51 (s, 1.2H, C*Me* (minor)). ^{13}C NMR (101 MHz, chloroform-*d*, mixture of rotamers) δ 168.6, 168.2, 152.8, 152.5, 136.2, 136.0, 128.7, 128.6, 128.4, 128.3, 128.2, 127.9, 84.7, 84.2, 67.7, 67.1, 51.8, 51.3, 40.5, 40.4, 37.4, 36.5, 24.8, 24.7, 24.1, 23.1. IR (ν_{max}, cm^{-1}) 3552 (w), 2970 (w), 1705 (s), 1423 (m), 1392 (m), 1354 (m), 1304 (w), 1215 (w), 1103 (m), 1068 (m), 756 (m). HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{19}N_2O_3^+$ 275.1390; Found 275.1397.

Benzyl 2-isopropyl-3-oxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-carboxylate (9h)

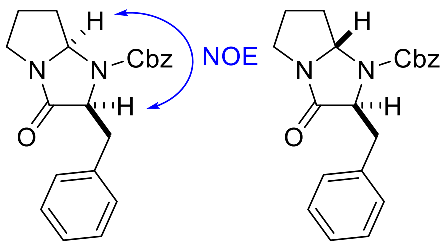


Following the general procedure G and starting with Cbz-Val-Pro (**8h**) (105 mg, 0.300 mmol, 1.00 equiv), **9h** was obtained after column chromatography (DCM/ EtOAc 95:5) as a colorless oil (90 mg, 0.30 mmol, 99% yield, dr 70:30).

The dr ratio was measured from the ^{1}H NMR spectrum of the isolated mixture of diastereoisomers by integrating the NC(O)C*H*N proton of each diastereomer. Attributions of protons for each diastereoisomers was supported by 2D experiments.

Rf(DCM/ EtOAc 95:5): 0.28. $[\alpha]D^{20}$ = +55.8 (c = 0.79, $CHCl_3$, diastereomeric mixture). ^{1}H NMR (400 MHz, acetonitrile-d_3, 7:3 mixture of diastereoisomers (major/minor), complex mixture of rotamers) δ 7.43 – 7.29 (m, 5H, Ar*H* (major+minor)), 5.21 – 5.06 (m, 3H, OCH_2Ph + NC*H* (major+minor)), 4.29 – 4.23 (m, 0.3H, NC(O)C*H*N (minor)), 4.12 – 4.06 (m, 0.7H, NC(O)C*H*N (major)), 3.64 – 3.50 (m, 1H, NCH_2CH$_2$CH$_2$CHN (major+minor)), 3.10 – 2.96 (m, 1H, NCH_2CH$_2$CH$_2$CHN (major+minor)), 2.54 – 1.97 (m, 4H, C*H*iPr + NCH$_2$CH_2CH$_2$CHN + NCH$_2$CH$_2$CH_2CHN (major+minor)), 1.55 – 1.37 (m, 1H, NCH$_2$CH$_2$CH_2CHN (major+minor)), 1.12 – 0.83 (m, 6H, *Me* (major+minor)). ^{13}C NMR (101 MHz, acetonitrile-d_3, mixture of diastereoisomers and rotamers, signals not fully resolved) δ 172.0, 171.8, 154.0, 153.6, 137.9, 137.8, 129.5, 129.0, 128.9, 128.8, 128.7, 128.6, 77.4, 77.1, 67.9, 67.8, 67.7, 67.6, 67.5, 42.2, 42.1, 42.0, 33.2, 32.3, 31.1, 29.8, 24.9, 24.8, 24.8, 18.6, 18.5, 18.3, 17.8, 16.9. IR (ν_{max}, cm^{-1}) 2962 (m), 2893 (w), 1705 (s), 1396 (s), 1119 (m), 1427 (m), 1358 (m), 1331 (m), 1018 (m), 918 (w), 744 (m). HRMS (ESI/QTOF) m/z: [M + H]+ Calcd for $C_{17}H_{23}N_2O_3^+$ 303.1703; Found 303.1707.

Benzyl 2-benzyl-3-oxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-carboxylate (9i)



77 : 23

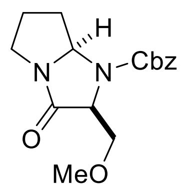
Following the general procedure G and starting with Cbz-Phe-Pro (**8i**) (119 mg, 0.300 mmol, 1.00 equiv), **9i** was obtained after column chromatography (DCM/EtOAc 9:1) as a pale-white oil (99 mg, 0.28 mmol, 94% yield, dr 77:23).

The dr ratio was measured from the ^{1}H NMR spectrum of the isolated mixture of diastereoisomers by integrating the NC*H*N proton of each diastereomer. Attributions of protons for each diastereoisomers was supported by 2D experiments.

Rf(DCM/ethyl acetate 9:1): 0.26. [α]D^{20} = +115.6 (c = 0.64, $CHCl_3$, diastereomeric mixture). ^{1}H NMR (400 MHz, chloroform-*d*, 77:23 mixture of diastereoisomers (major/minor), complex mixture of rotamers) δ 7.53 – 7.31 (m, 5H, Ar*H* (major+minor)), 7.23 – 7.11 (m, 3H, Ar*H* (major+minor)), 7.09 – 6.91 (m, 2H, Ar*H* (major+minor)), 5.42 – 5.08 (m, 2H, OC*H*$_2$Ph (major+minor)), 4.99 (ddd, *J* = 14.1, 8.5, 4.7 Hz, 0.77H, NC*H*N (major)), 4.73 – 4.58 (m, 0.77H, NC(O)C*H*$_2$N (major)), 4.58 – 4.46 (m, 0.23H, NC(O)C*H*$_2$N (minor)), 4.30 – 4.16 (m, 0.23H, NC*H*N (minor)), 3.63 – 3.52 (m, 0.46H, CHC*H*$_2$Ph (minor) + NC*H*$_2$CH$_2$CH$_2$CH (minor)), 3.48 – 3.33 (m, 1.54H, CHC*H*$_2$Ph (major) + NC*H*$_2$CH$_2$CH$_2$CH (major)), 3.32 – 3.23 (m, 0.77H, CHC*H*$_2$Ph (major)), 3.18 (dd, *J* = 13.8, 5.7 Hz, 0.12H, CHC*H*$_2$Ph (minor)), 3.07 (dd, *J* = 9.4, 2.4 Hz, 0.12H, CHC*H*$_2$Ph (minor)), 2.99 – 2.84 (m, 1H, NC*H*$_2$CH$_2$CH$_2$CH (major+minor)), 2.34 (dddd, *J* = 12.5, 7.4, 5.0, 2.2 Hz, 0.12H, NCH$_2$CH$_2$C*H*$_2$CH (minor)), 2.13 (dddd, *J* = 12.2, 7.1, 4.9, 2.1 Hz, 0.12H, NCH$_2$CH$_2$C*H*$_2$CH (minor)), 2.09 – 1.94 (m, 0.23H, NCH$_2$C*H*$_2$CH$_2$CH (minor)), 1.94 – 1.56 (m, 1.77H, NCH$_2$C*H*$_2$CH$_2$CH (major+minor) + NCH$_2$CH$_2$C*H*$_2$CH (major)), 1.56 – 1.43 (m, 0.77H, NCH$_2$C*H*$_2$CH$_2$CH (major), 1.43 – 1.27 (m, 0.23H, NCH$_2$CH$_2$C*H*$_2$CH (minor)), -0.22 – -0.40 (m, 0.77H, NCH$_2$CH$_2$C*H*$_2$CH (major)). ^{13}C NMR (101 MHz, chloroform-*d*, mixture of diastereoisomers and rotamers, signals not fully resolved) δ 171.7, 171.6, 171.1, 170.9, 154.3, 153.5, 153.2, 152.8, 136.7, 136.4, 136.7, 136.0, 135.7, 135.3, 130.5, 129.9, 129.8, 128.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.0, 127.0, 126.9, 76.3, 76.0, 75.9, 75.5, 67.8, 67.6, 67.3, 67.4, 64.3, 64.1, 63.8, 63.6, 41.3, 41.1, 40.9, 36.3, 35.8, 34.6, 32.3, 31.5, 30.4, 29.8, 24.3, 24.2, 23.8, 23.7. IR (ν_{max}, cm^{-1}) 3032 (w), 2951 (w), 2897 (w), 1709 (s), 1427 (m), 1404 (m), 1361 (m), 1300 (w), 1126 (m), 1026 (w), 760 (m), 702 (m). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{22}N_2NaO_3^+$ 373.1523; Found 373.1530.

A gram scale experiment with Cbz-Phe-Pro (**8i**) (1.00 g, 2.52 mmol, 1.00 equiv) was also accomplished using the same procedure and led to **9i** (846 mg, 2.41 mmol, 96%, dr 77:23) with a similar yield and identical dr ratio.

Benzyl 2-(methoxymethyl)-3-oxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-carboxylate (9j)



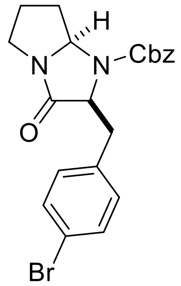
Following the general procedure G and starting with **8j** (105 mg, 0.300 mmol, 1.00 equiv), **9j** was obtained after column chromatography (DCM/EtOAc 9:1) as a yellow oil (79.0 mg, 0.260 mmol, 87% yield, dr 55:45).

The dr ratio was measured from the ^{1}H NMR spectrum of the isolated mixture of diastereoisomers by integrating the NCH$_2$CH$_2$C*H*$_2$CH proton of each diastereomer. Attributions of protons for each diastereoisomers was supported by 2D experiments.

Rf(DCM/EtOAc 9:1): 0.38. [α]D^{20} = +63.2 (c = 0.63, $CHCl_3$, diastereomeric mixture). ^{1}H NMR (400 MHz, chloroform-*d*, 55:45 mixture of diastereoisomers (major/minor)) δ 7.41 – 7.28 (m, 5H, Ar*H* (major+minor)), 5.30 – 5.05 (m, 3H, OC*H*$_2$Ph + NC*H*N (major+minor)), 4.28 (dt, *J* = 2.8, 1.7 Hz, 0.45H, NC(O)C*H*N (minor)), 4.23 – 4.18 (m, 0.55H, NC(O)C*H*N (major)), 4.10 (dd, *J* = 10.0, 2.7 Hz, 0.55H, CHC*H*$_2$OMe (major)), 3.80 (dd, *J* = 10.0, 2.9 Hz, 0.45H, CHC*H*$_2$OMe (minor)), 3.72 – 3.61 (m, 2H, CHC*H*$_2$OMe + NC*H*$_2$CH$_2$CH$_2$CH (major+minor)), 3.33 (s, 1.65H, OMe (major)), 3.23 (s, 1.35H, OMe (minor)), 3.21 – 3.12 (m, 1H, NC*H*$_2$CH$_2$CH$_2$CH (major+minor)), 2.52 (dddd, *J* = 12.3, 7.2, 5.0, 2.2 Hz, 0.45H, NCH$_2$CH$_2$C*H*$_2$CH (minor)), 2.31

(dddd, J = 12.2, 7.1, 4.9, 2.0 Hz, 0.55H, $NCH_2CH_2CH_2CH$ (major)), 2.20 – 1.91 (m, 2H, $NCH_2CH_2CH_2CH$ (major+minor)), 1.54 – 1.37 (m, 1H, $NCH_2CH_2CH_2CH$ (major+minor)). ^{13}C NMR (101 MHz, chloroform-*d*, mixture of diastereoisomers) δ 170.4, 170.2, 153.3, 152.9, 136.2, 136.1, 128.8, 128.7, 128.5, 128.4, 128.3, 128.1, 77.1, 76.6, 70.3, 68.9, 67.4, 67.4, 64.0, 63.8, 59.6, 59.5, 41.6, 41.5, 32.6, 31.8, 24.7, 24.5. IR (v_{max}, cm^{-1}) 3553 (w), 2925 (w), 1706 (s), 1434 (m), 1402 (s), 1361 (m), 1121 (s), 1037 (m), 767 (m), 699 (m). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{20}N_2NaO_4^+$ 327.1315; Found 327.1309.

Benzyl 2-(4-bromobenzyl)-3-oxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-carboxylate (9k)

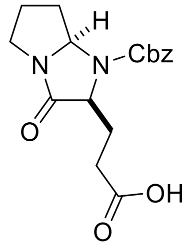


Following the general procedure G and starting with **8k** (0.14 g, 0.30 mmol, 1.0 equiv), **9k** was obtained after column chromatography (DCM/EtOAc 9:1) as a yellow oil (99 mg, 0.23 mmol, 77% yield, dr 75:25).

The dr ratio was measured from the ^1H NMR spectrum of the isolated mixture of diastereoisomers by integrating the NC*H*N proton of each diastereomer. Attributions of protons for each diastereoisomers was supported by 2D experiments.

Rf(DCM/EtOAc 9:1): 0.39. $[\alpha]D^{20}$ = +123.9 (c = 0.69, $CHCl_3$, diastereomeric mixture). ^1H NMR (400 MHz, chloroform-*d*, 3:1 mixture of diastereoisomers (major/minor), complex mixture of rotamers) δ 7.65 – 7.45 (m, 5H, Ar*H* (major+minor)), 7.45 – 7.36 (m, 2H, Ar*H* (major+minor)), 7.09 – 6.85 (m, 2H, Ar*H* (major+minor)), 5.56 – 5.22 (m, 2H, OCH_2Ph (major+minor)), 5.21 – 5.10 (m, 0.75H, NC*H*N (major)), 4.84 – 4.72 (m, 0.75H, NC(O)C*H*N (major)), 4.69 – 4.59 (m, 0.25H, NC(O)C*H*N (minor)), 4.44 (tdd, J = 8.9, 5.0, 1.8 Hz, 0.25H, NC*H*N (minor)), 3.74 (dtd, J = 11.7, 8.4, 5.2 Hz, 0.25H, $NCH_2CH_2CH_2CH$ (minor)), 3.65 (dd, J = 13.8, 5.5 Hz, 0.25H, $CHCH_2Ar$ (minor)), 3.59 – 3.46 (m, 1.5H, $CHCH_2Ar$ (major) + $NCH_2CH_2CH_2CH$ (major)), 3.40 – 3.31 (m, 0.75H, $CHCH_2Ar$ (major)), 3.31 – 3.22 (m, 0.25H, $CHCH_2Ar$ (minor)), 3.16 – 3.06 (m, 1H, $NCH_2CH_2CH_2CH$ (major+minor)), 2.51 (dddd, J = 12.3, 7.1, 4.9, 2.1 Hz, 0.13H, $NCH_2CH_2CH_2CH$ (minor)), 2.31 (dddd, J = 12.3, 7.2, 5.0, 2.0 Hz, 0.13H, $NCH_2CH_2CH_2CH$ (minor)), 2.23 – 2.12 (m, 0.25H, $NCH_2CH_2CH_2CH$ (minor)), 2.04 – 1.66 (m, 2.25H, $NCH_2CH_2CH_2CH$ (major+minor) + $NCH_2CH_2CH_2CH$ (major)), 1.54 – 1.43 (m, 0.25H, $NCH_2CH_2CH_2CH$ (minor)), 0.00 (br p, J = 9.6 Hz, 0.75H, $NCH_2CH_2CH_2CH$ (major)). ^{13}C NMR (101 MHz, chloroform-*d*, mixture of diastereoisomers and rotamers, signals not fully resolved) δ 171.7, 171.6, 171.1, 171.0, 154.3, 153.5, 153.2, 152.8, 136.7, 136.4, 136.3, 136.0, 135.7, 135.3, 130.5, 129.9, 129.8, 128.8, 128.8, 128.7, 128.4, 128.3, 128.2, 128.0, 127.0, 126.9, 76.3, 76.0, 75.9, 75.5, 67.8, 67.6, 67.3, 67.2, 64.3, 64.1, 63.8, 63.6, 41.3, 41.1, 41.0, 36.3, 35.8, 34.6, 32.3, 31.5, 30.4, 29.8, 24.3, 24.2, 23.8, 23.8. IR (v_{max}, cm^{-1}) 2958 (w), 1709 (s), 1429 (m), 1401 (s), 1123 (m), 755 (m), 1026 (m), 1357 (m), 699 (m), 1487 (m), 1012 (m). HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{22}{}^{79}BrN_2O_3^+$ 429.0808; Found 429.0796.

3-(1-((Benzyloxy)carbonyl)-3-oxohexahydro-1H-pyrrolo[1,2-a]imidazol-2-yl)propanoic acid (9l)



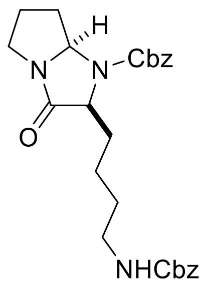
Dry DCM (6 mL) was added in a 10 mL test tube containing **8l** (114 mg, 0.300 mmol, 1.00 equiv) and PIDA (97 mg, 0.30 mmol, 1.0 equiv) under a nitrogen atmosphere. The reaction mixture was cooled to 0 °C and $BF_3·OEt_2$ (79 µL, 0.30 mmol, 1.0 equiv) was added dropwise. The reaction was let stirring for 2 h at RT. Then, PIDA (97 mg, 0.30 mmol, 1.0 equiv) was added. The mixture was degassed by Ar bubbling, cooled to 0 °C and $BF_3·OEt_2$ (79 µL, 0.30 mmol, 1.0 equiv) was added dropwise. The reaction was let stirring for 2 h at RT.

The crude mixture was diluted with 15 mL of sat. $NaHCO_3$ then extracted with diethyl ether (3 x 30 mL), washed with brine (30 mL). The combined aqueous layers were acidified with HCl (1 M) to pH=1 and then extracted with EtOAc (3 x 50 mL). All the organic layers were reunited, dried over $MgSO_4$, filtered, and concentrated under vacuum. **9l** was obtained after prep-TLC (DCM/MeOH 97:3) as a yellow sticky oil (54 mg, 0.16 mmol, 54% yield, dr 67:33).

The dr ratio was measured from the ^{1}H NMR spectrum of the isolated mixture of diastereoisomers by integrating the NC(O)CHN proton of each diastereomer. Attributions of protons for each diastereoisomers was supported by 2D experiments.

Rf(DCM/MeOH 97:3): 0.30. $[\alpha]D^{20}$ = +31.4 (c = 0.40, $CHCl_3$, diastereomeric mixture). ^{1}H NMR (400 MHz, chloroform-*d*, 67:33 mixture of diatereoisomers (major/minor)) δ 7.45 – 7.28 (m, 5H, Ar*H* (major+minor)), 5.27 – 5.05 (m, 3H, OC*H₂*Ph + NC*H*N (major+minor)), 4.48 (s, 0.67H, NC(O)C*H*N (major)), 4.41 – 4.30 (m, 0.33H, NC(O)C*H*N (minor)), 3.77 – 3.59 (m, 1H, $NCH_2CH_2CH_2CH$ (major+minor)), 3.20 – 3.06 (m, 1H, $NCH_2CH_2CH_2CH$ (major+minor)), 2.60 – 1.95 (m, 7H, $NCH_2CH_2CH_2CH$ + $NCH_2CH_2CH_2CH$ + $NCHCH_2CH_2COOH$ + $NCHCH_2CH_2COOH$ (major+minor)), 1.56 – 1.33 (m, 1H, $NCH_2CH_2CH_2CH$ (major+minor)). ^{13}C NMR (101 MHz, chloroform-*d*, mixture of diastereoisomers, signals not fully resolved) δ 177.8, 171.8, 171.6, 155.0, 154.5, 153.3, 152.8, 135.9, 135.8, 128.7, 128.5, 128.8, 128.3, 76.5, 76.1, 67.9, 67.8, 67.7, 61.6, 61.5, 41.5, 41.4, 32.5, 32.0, 31.7, 29.8, 29.4, 26.2, 25.3, 24.4, 24.3. IR (ν_{max}, cm^{-1}) 2952 (w), 1704 (s), 1445 (m), 1401 (s), 1355 (s), 1130 (m), 1029 (w), 911 (m), 729 (s), 698 (m), 3214 (w), 2581 (w). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{20}N_2NaO_5^+$ 355.1264; Found 355.1262.

Benzyl 2-(4-(((benzyloxy)carbonyl)amino)butyl)-3-oxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-carboxylate (9m)

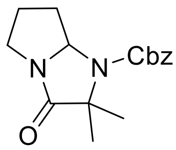


Following the general procedure G and starting with **8m** (153 mg, 0.300 mmol, 1.00 equiv), **9m** was obtained after column chromatography (DCM/MeOH 99:1) as a yellow oil (131 mg, 0.280 mmol, 93% yield, dr 80:20).

The dr ratio was measured from the ^{1}H NMR spectrum of the isolated mixture of diastereoisomers by integrating the $NCH_2CH_2CH_2CH$ proton of each diastereomer. Attributions of protons for each diastereoisomers was supported by 2D experiments.

Rf(DCM/MeOH 99:1):.0.23. $[\alpha]D^{20}$ = +44.8 (c = 0.53, $CHCl_3$, diastereomeric mixture). ^{1}H NMR (400 MHz, chloroform-*d*, 4:1 mixture of diastereoisomers (major+minor)) δ 7.45 – 7.27 (m, 10H, Ar*H* (major+minor)), 5.31 – 5.00 (m, 5.2H, OCH_2Ph (major+minor) + NC*H*N (major+minor) + N*H* (minor)), 4.98 – 4.58 (m, 0.8H, N*H* (major)), 4.51 – 4.21 (m, 1H, $NC(O)CH_2N$ (major+minor)), 3.74 – 3.54 (m, 1H, $NCH_2CH_2CH_2CH$ (major+minor)), 3.26 – 2.97 (m, 3H, $NCH_2CH_2CH_2CH$ + CH_2NH (major+minor)), 2.59 – 2.45 (m, 0.2H, $NCH_2CH_2CH_2CH$ (minor)), 2.39 – 2.20 (m, 0.8H, $NCH_2CH_2CH_2CH$ (major)), 2.20 – 1.78 (m, 4H, $NCH_2CH_2CH_2CH$ + $CHCH_2CH_2CH_2CH_2NH$ (major+minor)), 1.60 – 1.06 (m, 5H, $NCH_2CH_2CH_2CH$ + $CHCH_2CH_2CH_2CH_2NH$ + $CHCH_2CH_2CH_2CH_2NH$ (major+minor)). ^{13}C NMR (101 MHz, chloroform-*d*, mixture of diastereoisomers, signals not fully resolved) δ 172.4, 172.3, 156.5, 153.4, 152.8, 136.8, 136.1, 128.8, 128.6, 128.5, 128.4, 128.3, 128.2, 76.5, 76.2, 67.6, 67.5, 67.4, 66.6, 62.4, 62.3, 41.5, 41.4, 40.9, 40.8, 32.6, 31.8, 30.6, 29.6, 29.5, 24.5, 24.3, 21.6, 21.1, 21.0. IR (ν_{max}, cm^{-1}) 3345 (w), 2936 (w), 1699 (s), 1400 (s), 1245 (m), 1530 (m), 1130 (m), 734 (s), 697 (m), 912 (m), 1356 (m). HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{32}N_3O_5^+$ 466.2336; Found 466.2325.

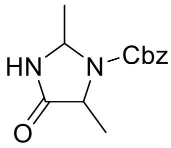
Benzyl 2,2-dimethyl-3-oxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-carboxylate (9n)



Following the general procedure G and starting with **8n** (0.10 g, 0.30 mmol, 1.0 equiv), **9n** was obtained after column chromatography (DCM/EtOAc 9:1) as a yellow oil (85 mg, 0.29 mmol, 98% yield).

Rf(DCM/EtOAc 8:2): 0.35. ^{1}H NMR (400 MHz, chloroform-*d*, 56:44 mixture of rotamers (major/minor)) δ 7.46 – 7.28 (m, 5H, Ar*H* (major+minor)), 5.25 – 5.03 (m, 3H, $NC(O)CH_2$ + NC*H*N(major+minor)), 3.76 – 3.65 (m, 1H, $NCH_2CH_2CH_2CH$ (major+minor)), 3.19 – 3.03 (m, 1H, $NCH_2CH_2CH_2CH$ (major+minor)), 2.54 – 2.44 (m, 0.44H, $NCH_2CH_2CH_2CH$ (major+minor)), 2.37 – 2.24 (m, 0.56H, $NCH_2CH_2CH_2CH$ (major+minor)), 2.18 – 1.90 (m, 2H, $NCH_2CH_2CH_2CH$ (major+minor)), 1.57 (s, 3.36H, Me (major)), 1.48 (d, *J* = 4.9 Hz, 2.64H, Me (minor)), 1.43 – 1.29 (m, 1H, $NCH_2CH_2CH_2CH$ (major+minor)). ^{13}C NMR (101 MHz, chloroform-*d*, mixture of diastereoismers, signals not fully resolved) δ 175.8, 154.4, 152.6, 136.3, 136.0, 128.7, 128.4, 128.3, 128.2, 128.0, 74.7, 74.5, 67.5, 67.0, 64.9, 64.6, 41.6, 41.4, 33.3, 32.6, 25.1, 24.1, 24.0, 22.9. IR (ν_{max}, cm^{-1}) 2979 (w), 1706 (s), 1422 (s), 1397 (s), 1354 (s), 1285 (m), 1091 (s), 999 (m), 769 (m), 753 (m), 698 (m). HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{21}N_2O_3^+$ 289.1547; Found 289.1553.

Benzyl 2,5-dimethyl-4-oxoimidazolidine-1-carboxylate (9o)



Following the general procedure G and starting with Cbz-Ala-Ala (**8o**) (88 mg, 0.30 mmol, 1.0 equiv), **9o** was obtained after column chromatography (DCM/MeOH 97:3) as a white sticky solid (65 mg, 0.26 mmol, 87% yield)**.**

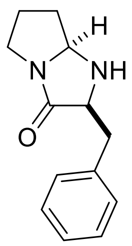
Rf(DCM/MeOH 97:3): 0.47. $[\alpha]D^{20}$ = +24.4 (c = 0.46, $CHCl_3$, diastereomeric mixture). ^{1}H NMR (400 MHz, chloroform-*d*, unresolved mixture of diastereoisomers and rotamers) δ 8.07 – 7.84 (m, 1H, N*H*), 7.41 – 7.28 (m, 5H, Ar*H*), 5.29 – 5.02 (m, 3H, OC*H$_2$*Ph + NC*H*), 4.41 – 4.03 (m, 1H, NC(O)C*H*NCbz), 1.61 – 1.32 (m, 6H, *Me*). ^{13}C NMR (101 MHz, chloroform-*d*, mixture of diastereoisomers and rotamers, signals not fully resolved) δ 174.1, 173.9, 153.9, 153.3, 136.1, 136.0, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 67.4, 66.4, 66.2, 65.9, 54.6, 54.3, 54.1, 24.5, 23.8, 23.0, 21.7, 19.3, 18.6, 17.9, 16.4. IR (ν_{max}, cm^{-1}) 3275 (w), 2935 (w), 1705 (s), 1450 (m), 1408 (m), 1358 (m), 1300 (m), 1107 (m), 1061 (m), 1045 (m), 737 (m), 698 (m). HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{13}H_{17}N_2O_3^+$ 249.1234; Found 249.1230.

6. Product modifications

General procedure H for Cbz deprotection

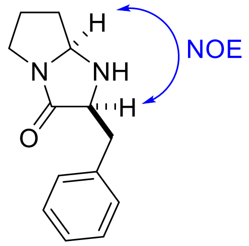
The corresponding carbamate (1.0 equiv) was dissolved in ethanol (30 mM), and $Pd(OH)_2$ (10 mol %) was added. The mixture was stirred overnight at RT under H_2. The catalyst was removed by filtration, the filtrate was concentrated under reduced pressure and purified by prep-TLC.

2-Benzylhexahydro-3H-pyrrolo[1,2-a]imidazol-3-one (11)



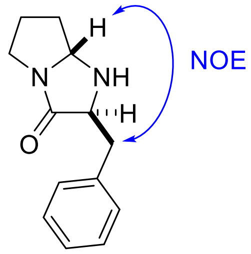
Following the general procedure H and starting with **9i** (35 mg, 0.10 mmol, 1.0 equiv), $Pd(OH)_2$/C (7.0 mg, 10 µmol, 0.10 equiv), and ethanol (3.3 mL), **11** was obtained as an oil (21 mg, 0.10 mmol, 97%, dr 77:23) after prep-TLC (DCM/EtOAc 7:3) allowing the isolation and clean NMR characterization of the major diastereomer. The minor isomer was not obtained as a pure fraction but a ^{1}H and ^{13}C NMR are still provided.

<u>Data for the major cis- diastereoiosmer:</u>



Rf(DCM/EtOAc 7:3): 0.25. ^{1}H NMR (400 MHz, acetonitrile-d_3) δ 7.33 – 7.15 (m, 5H, Ar*H*), 4.76 – 4.67 (m, 1H, NC*H*NH), 4.05 (dd, *J* = 8.6, 3.6 Hz, 1H, NC(O)C*H*NH), 3.45 (dt, *J* = 11.4, 7.3 Hz, 1H, NCH_2CH$_2$CH$_2$CH), 3.06 (dd, *J* = 13.9, 3.9 Hz, 1H, CH_2Ph), 3.00 – 2.90 (m, 1H, NCH_2CH$_2$CH$_2$CH), 2.71 – 2.47 (m, 2H, CH_2Ph + N*H*), 1.92 – 1.81 (m, 3H, NCH$_2$CH_2CH$_2$CH + NCH$_2$CH$_2$CH_2CH), 1.13 – 1.01 (m, 1H, NCH$_2$CH$_2$CH_2CH). ^{13}C NMR (101 MHz, acetonitrile-d_3) δ 176.0, 140.3, 130.4, 129.1, 127.1, 76.7, 64.9, 42.3, 39.9, 33.9, 25.4. IR (ν_{max}, cm^{-1}) 3349 (w), 3524 (w), 2949 (w), 1691 (s), 1496 (m), 1402 (m), 1336 (m), 1132 (w), 1031 (w), 907 (w), 749 (m), 700 (s). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{16}N_2NaO^+$ 239.1155; Found 239.1148.

Data for the minor trans- diastereoiosmer:



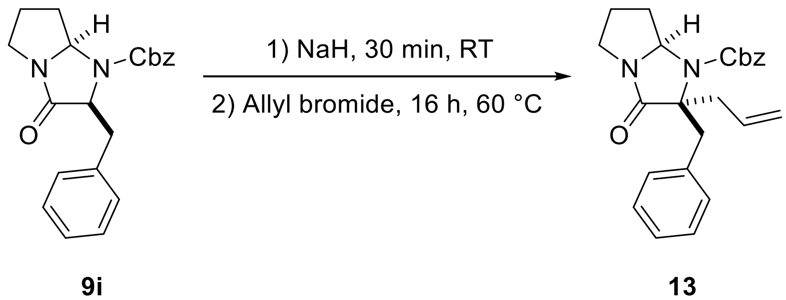
Rf(DCM/EtOAc 7:3): 0.10. ^{1}H NMR (400 MHz, acetonitrile-d_3, 85:15 mixture of diastereomers (trans:cis), only peaks for minor are given) δ 7.35 – 7.16 (m, 5H, Ar*H*), 4.67 – 4.57 (m, 1H, NC*H*NH), 3.70 (ddd, *J* = 8.3, 4.4, 1.2 Hz, 1H, NC(O)C*H*NH), 3.53 – 3.42 (m, 1H, NCH_2CH$_2$CH$_2$CH), 3.02 (dd, *J* = 14.1, 4.4 Hz, 1H, NCH_2CH$_2$CH$_2$CH), 2.99 – 2.91 (m, 1H, CH_2Ph), 2.86 (dd, *J* = 14.0, 8.3 Hz, 1H, CH_2Ph), 2.54 – 2.36 (m, 1H, N*H*), 2.00 – 1.80 (m, 3H, NCH$_2$CH_2CH$_2$CH + NCH$_2$CH$_2$CH_2CH), 1.33 – 1.19 (m, 1H, NCH$_2$CH$_2$CH_2CH). ^{13}C NMR (101 MHz, acetonitrile-d_3, 85:15 mixture of diastereomers (trans:cis), only peaks for trans- are given) δ 178.0, 139.2, 130.2, 129.3, 127.4, 78.0, 64.9, 42.4, 38.8, 32.6, 25.1. IR (ν_{max}, cm^{-1}) 3470 (w), 3332 (w), 2942 (m), 2892 (w), 1692 (s), 1496 (m), 1454 (m), 1397 (m), 1335 (m), 1080 (w), 911 (w), 751 (m), 701 (s). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{16}N_2NaO^+$ 239.1155; Found 239.1148.

Benzyl 2-benzyl-2-methyl-3-oxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-carboxylate (12)

An oven-dried microwave vial was charged with sodium hydride (60% in mineral oil) (40 mg, 1.0 mmol, 10 equiv). After 3 vacuum/N_2 cycles, 1 mL of dry THF was added and the reaction was cooled to 0 °C. A solution of **9i** (35 mg, 0.10 mmol, 1.0 equiv) in 1 mL of dry THF was added dropwise and the reaction mixture was stirred for 30 minutes at RT. Iodomethane (19 μL, 0.30 mmol, 3.0 equiv) was added dropwise and the reaction was stirred overnight at 60 °C. The mixture was then allowed to cool to RT, quenched by addition of saturated aqueous NH_4Cl solution, and extracted with diethyl ether (3 x 15 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification by prep-TLC (DCM/EtOAc 9:1) afforded **12** (19 mg, 52 μmol, 52% yield) as an oil.

Rf(DCM/EtOAc 9:1): 0.5. ^{1}H NMR (400 MHz, chloroform-*d*, unresolved mixture of diastereoisomers and rotamers) δ 7.53 – 7.31 (m, 5H, Ar*H*), 7.19 – 6.93 (m, 5H, Ar*H*), 5.39 – 5.33 (m, 1H, OCH_2Ph), 5.32 – 5.26 (m, 0.4H, OCH_2Ph), 5.04 – 4.99 (m, 0.6H, OCH_2Ph), 4.99 – 4.89 (m, 1H, NC*H*N), 3.47 – 3.35 (m, 1.6H, NCH_2CH$_2$CH$_2$CH + CCH_2Ph), 3.20 – 3.09 (m, 1.4H, CCH_2Ph), 3.00 – 2.89 (m, 1H, NCH_2CH$_2$CH$_2$CH), 1.88 – 1.78 (m, 0.5H, NCH$_2$CH_2CH$_2$CH), 1.71 (s, 2H, Me), 1.69 – 1.64 (m, 1H, NCH$_2$CH$_2$CH_2CH), 1.63 – 1.59 (m, 1.5H, Me + NCH$_2$CH_2CH$_2$CH), 1.50 – 1.39 (m, 1H, NCH$_2$CH_2CH$_2$CH), -0.28 – -0.51 (m, 1H, NCH$_2$CH$_2$CH_2CH). ^{13}C NMR (101 MHz, chloroform-*d*, unresolved mixture of diastereoisomers and rotamers) δ 174.3, 174.2, 153.9, 152.5, 137.8, 137.4, 136.6, 135.9, 130.3, 128.9, 128.7, 128.7, 128.3, 128.2, 127.0, 126.9, 75.0, 74.7, 70.6, 70.2, 67.8, 66.9, 41.7, 41.3, 41.1, 40.6, 31.6, 30.5, 29.7, 24.1, 23.6, 23.5, 22.8. IR (v_{max}, cm^{-1}) 2972 (w), 1707 (s), 1454 (m), 1425 (s), 1398 (s), 1357 (m), 1283 (m), 1116 (m), 1075 (m), 1056 (s), 911 (w), 767 (m), 743 (m), 702 (s). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{24}N_2NaO_3^+$ 387.1679; Found 387.1682.

Benzyl 2-allyl-2-benzyl-3-oxohexahydro-1H-pyrrolo[1,2-a]imidazole-1-carboxylate (13)

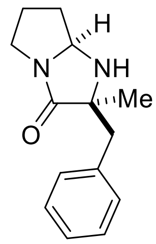


An oven-dried microwave vial was charged with sodium hydride (60% in mineral oil) (40 mg, 1.0 mmol, 10 equiv). After 3 vacuum/N_2 cycles, 1 mL of dry THF was added and the reaction was cooled to 0 °C. A solution of **9i** (35 mg, 0.10 mmol, 1.0 equiv) in 1 mL of dry THF was added dropwise and the reaction mixture was stirred for 30 minutes at RT. Allyl bromide (26 μL, 0.30 mmol, 3.0 equiv) was added dropwise and the reaction was stirred overnight at 60 °C. The mixture was then allowed to cool to RT, quenched by addition of saturated aqueous

NH_4Cl solution, and extracted with diethyl ether (3 x 15 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification by prep-TLC (DCM/EtOAc 9:1) afforded **13** (39 mg, 0.10 mmol, 100% yield) as an oil.

Rf(DCM/EtOAc 9:1): 0.53. ^1H NMR (400 MHz, acetonitrile-d_3, unresolved mixture of diastereoisomers and rotamers) δ 7.58 – 7.53 (m, 0.6H, Ar*H*), 7.49 – 7.33 (m, 4.4H, Ar*H*), 7.22 – 7.12 (m, 3H, Ar*H*), 7.04 – 6.92 (m, 2H, Ar*H*), 5.75 – 5.54 (m, 1H, $CH_2CH{=}CH_2$), 5.35 – 5.24 (m, 1.4H, OCH_2Ph), 5.11 – 4.90 (m, 2.6H, $CH_2CH{=}CH_2$ + OCH_2Ph), 4.87 – 4.74 (m, 1H, NC*H*N), 3.35 – 3.25 (m, 1.6H, CCH_2Ph + $NCH_2CH_2CH_2CH$), 3.13 – 3.04 (m, 2H, CCH_2Ph + $CH_2CH{=}CH_2$), 2.96 – 2.80 (m, 1.4H, $CH_2CH{=}CH_2$ + $NCH_2CH_2CH_2CH$), 2.52 – 2.42 (m, 1H, $CH_2CH{=}CH_2$), 1.77 – 1.55 (m, 2H, $NCH_2CH_2CH_2CH$ + $NCH_2CH_2CH_2CH$), 1.44 – 1.29 (m, 1H, $NCH_2CH_2CH_2CH$), -0.35 – -0.53 (m, 1H, $NCH_2CH_2CH_2CH$). ^{13}C NMR (101 MHz, acetonitrile-d_3, unresolved mixture of diastereoisomers and rotamers) δ 173.4, 173.2, 154.3, 153.3, 138.2, 138.1, 138.0, 137.4, 133.2, 133.0, 131.1, 130.1, 129.6, 129.5, 129.4, 129.1, 129.0, 128.9, 128.8, 127.8, 127.7, 119.8, 76.4, 76.3, 74.7, 74.3, 68.1, 67.3, 42.0, 41.9, 41.2, 40.9, 39.7, 31.3, 30.6, 24.1, 24.0. IR (ν_{max}, cm^{-1}) 3068 (m), 2938 (w), 1706 (s), 1604 (w), 1496 (m), 1441 (s), 1397 (s), 1357 (s), 1288 (m), 1072 (m), 996 (m), 923 (m), 767 (m), 701 (s). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{26}N_2NaO_3^+$ 413.1836; Found 413.1837.

2-Benzyl-2-methylhexahydro-3H-pyrrolo[1,2-a]imidazol-3-one (14)

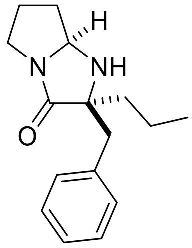


Following the general procedure H and starting with **12** (36 mg, 0.10 mmol, 1.0 equiv), $Pd(OH)_2/C$ (7.0 mg, 10 µmol, 0.10 equiv), and ethanol (3.3 mL), **14** was obtained after prep-TLC (DCM/EtOAc 7:3) as an oil (18 mg, 78 µmol, 78%, dr 93:7).

The dr ratio was measured from the ^1H NMR spectrum of the mixture of diastereoisomers by integrating the NC*H*NH proton of each diastereomer. Attributions of protons for each diastereoisomers was supported by 2D experiments. The dr of the crude mixture was 88:12 whereas the dr of the isolated product was 93:7.

Rf(DCM/EtOAC 9:1): 0.21. ^1H NMR (400 MHz, acetonitrile-d_3, 93:7 mixture of diastereomers (major/minor)) δ 7.30 – 7.15 (m, 5H, Ar*H* (major+minor)), 4.70 (dd, *J* = 8.0, 5.2 Hz, 0.93H, NC*H*NH (major)), 4.37 – 4.30 (m, 0.07H, NC*H*NH (minor)), 3.48 – 3.38 (m, 0.07H, $NCH_2CH_2CH_2CH$ (minor)), 3.32 (dt, *J* = 11.1, 7.7 Hz, 0.93H, $NCH_2CH_2CH_2CH$ (major)), 2.98 – 2.86 (m, 2H, $NCH_2CH_2CH_2CH$ + CCH_2Ph (major+minor)), 2.71 (d, *J* = 13.4 Hz, 0.07H, CCH_2Ph (minor)), 2.62 (d, *J* = 13.2 Hz, 0.93H, CCH_2Ph (major)), 2.23 (br s, 1H, N*H* (major+minor)), 1.83 – 1.59 (m, 3H, $NCH_2CH_2CH_2CH$ + $NCH_2CH_2CH_2CH$ (major+minor)), 1.27 (br s, 3H, Me (major+minor)), 0.61 – 0.46 (m, 1H, $NCH_2CH_2CH_2CH$ (major+minor)). ^{13}C NMR (101 MHz, acetonitrile-d_3, mixture of diastereomers) δ 178.7, 178.3, 139.0, 138.2, 131.8, 131.2, 128.9, 128.6, 127.5, 127.2, 75.5, 75.3, 68.7, 68.5, 45.7, 44.4, 42.2, 42.0, 33.9, 33.4, 26.0, 25.5, 25.1, 25.0. IR (ν_{max}, cm^{-1}) 2929 (m), 1694 (s), 1604 (m), 1482 (m), 1453 (m), 1408 (s), 1304 (m), 1088 (m), 1197 (w), 977 (w), 765 (m), 701 (s). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{18}N_2NaO^+$ 253.1311; Found 253.1311.

2-Benzyl-2-propylhexahydro-3H-pyrrolo[1,2-a]imidazol-3-one (15)



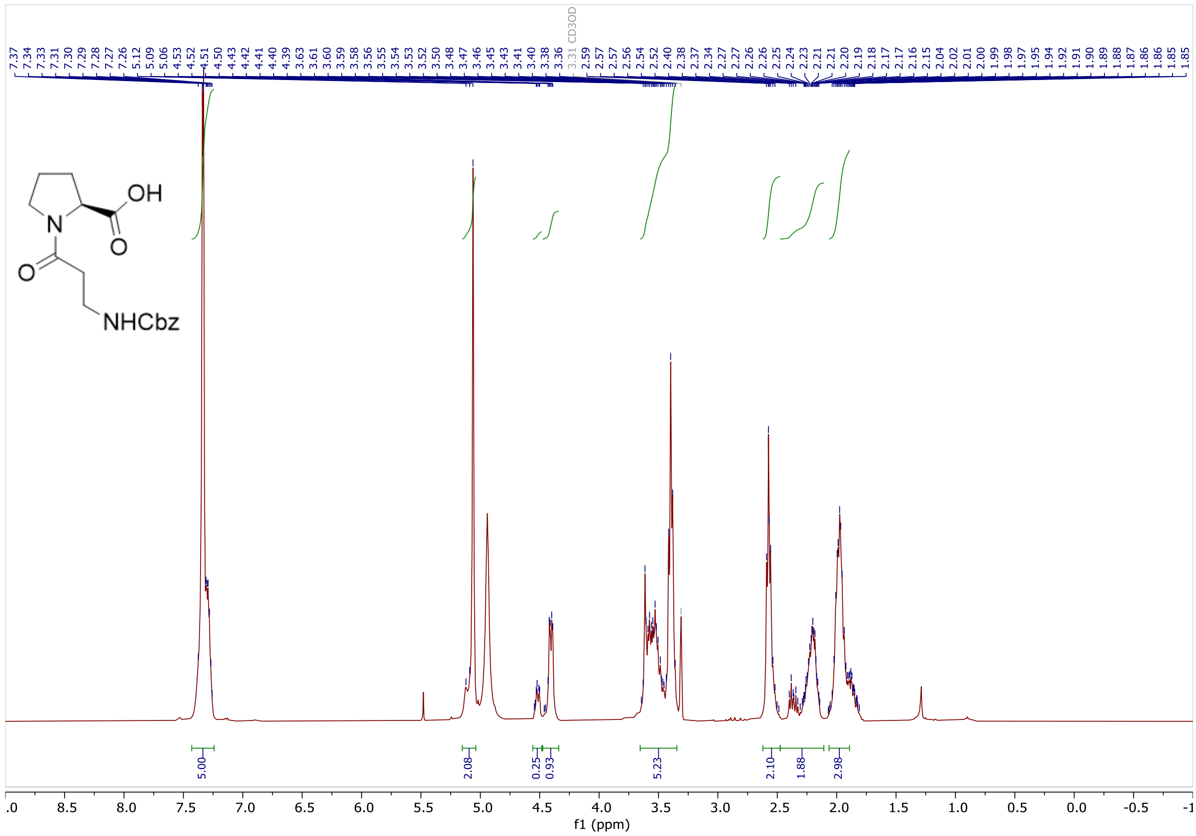
Following the general procedure H and starting with **13** (30 mg, 77 μmol, 1.0 equiv), $Pd(OH)_2/C$ (5.4 mg, 7.7 μmol, 0.10 equiv), and ethanol (2.5 mL), **15** was obtained after prep-TLC (DCM/EtOAc 7:3) as an oil (12 mg, 46 μmol, 60%, dr 15:85).

The dr ratio was measured from the ^1H NMR spectrum of the mixture of diastereoisomers by integrating the NC*H*NH proton of each diastereomer. Attributions of protons for each diastereoisomers was supported by 2D experiments. The dr of the crude mixture was 67:33 whereas the dr of the isolated product was 15:85.

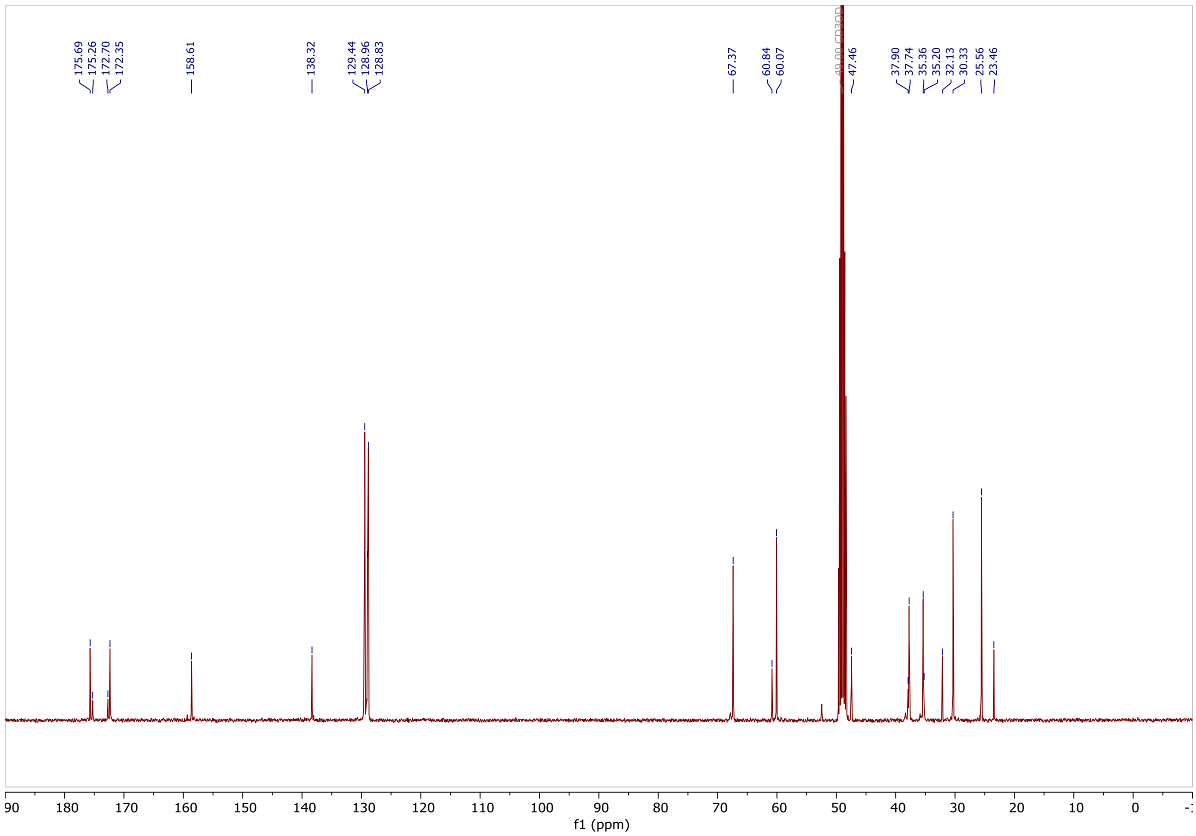
Rf(DCM/EtOAC 7:3): 0.45. ^1H NMR (400 MHz, chloroform-*d*, 15:85 mixture of diastereomers (major/minor)) δ 7.29 – 7.17 (m, 5H, Ar*H* (major+minor)), 4.89 (dd, *J* = 8.5, 5.2 Hz, 0.15H, NC*H*NH (major)), 4.65 (dd, *J* = 8.1, 4.9 Hz, 0.85H, NC*H*NH (minor)), 3.40 (dt, *J* = 11.6, 7.6 Hz, 1H, $CCH_2CH_2CH_3$ (major+minor)), 3.33 (d, *J* = 13.3 Hz, 0.15H, CCH_2Ph (major)), 3.19 (d, *J* = 13.3 Hz, 1H, CCH_2Ph (major+minor)), 2.98 (ddt, *J* = 11.5, 8.7, 3.8 Hz, 1H, $CCH_2CH_2CH_3$ (major+minor)), 2.60 (d, *J* = 13.3 Hz, 0.85H, CCH_2Ph (minor)), 2.42 – 2.32 (m, 0.15H, $CCH_2CH_2CH_3$ (major)), 1.90 – 1.27 (m, 7.85H, N*H* + $CCH_2CH_2CH_3$+ $CCH_2CH_2CH_3$ + $NCH_2CH_2CH_2CH$ + $NCH_2CH_2CH_2CH$ (major+minor)), 0.94 (t, *J* = 7.2 Hz, 3H, CH_3 (major+minor)), 0.25 (qdd, *J* = 12.1, 7.3, 4.5 Hz, 0.85H, $NCH_2CH_2CH_2CH$ (minor)), -0.27 – -0.39 (m, 0.15H, $NCH_2CH_2CH_2CH$ (major)). ^{13}C NMR (101 MHz, chloroform-*d,* mixture of diastereomers) δ 176.8, 173.4, 137.6, 137.5, 130.4, 130.2, 128.4, 128.2, 127.0, 126.8, 75.8, 75.7, 74.8, 72.4, 44.4, 44.0, 41.6, 41.3, 40.8, 37.7, 32.8, 30.0, 29.8, 24.5, 23.6, 17.7, 14.5, 14.0. IR (v_{max}, cm^{-1}) 3343 (w), 2957 (m), 2872 (m), 1687 (s), 1454 (m), 1405 (m), 1284 (w), 1176 (w), 1031 (w), 908 (w), 733 (m), 701 (s). HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{22}N_2NaO^+$ 281.1624; Found 281.1625.

7. ^{1}H and ^{13}C spectra

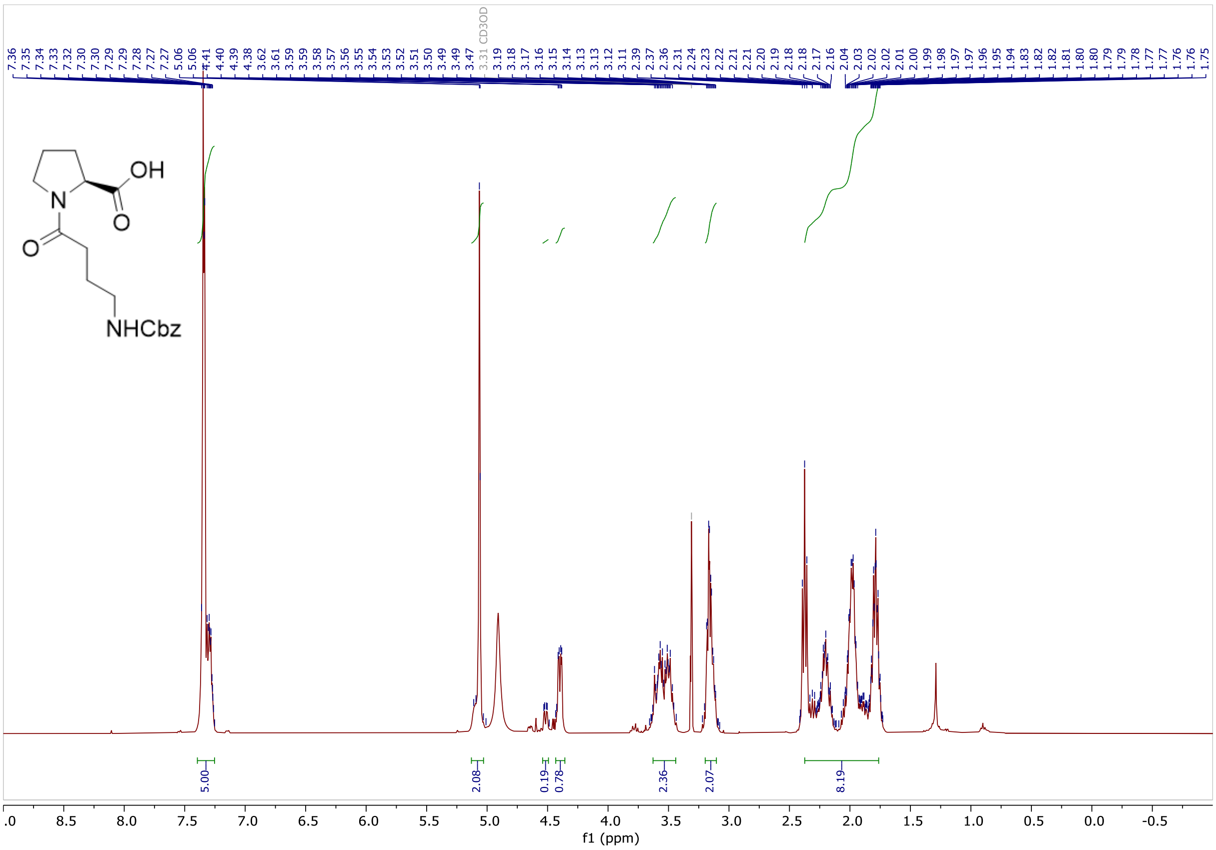
^{1}H-NMR (400 MHz, methanol-*d4*) (8b)



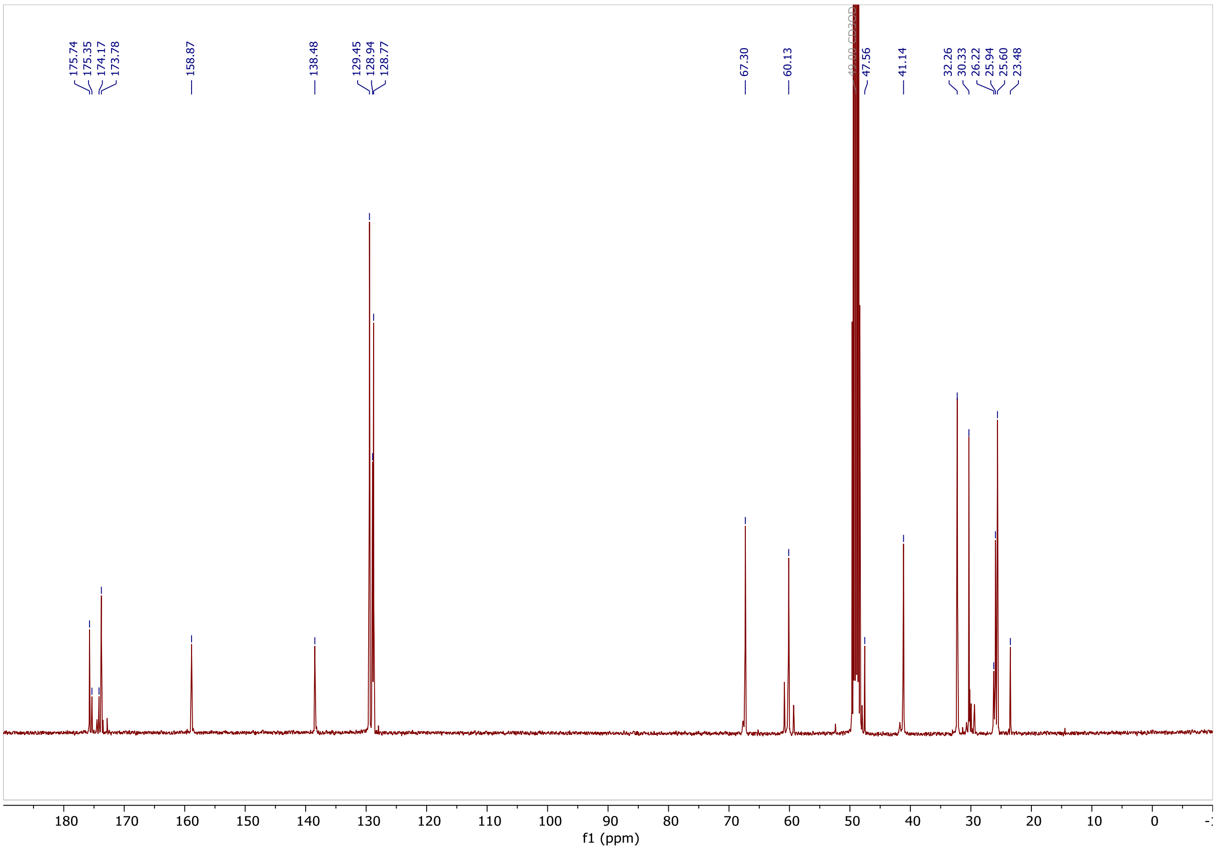
^{13}C-NMR (101 MHz, methanol-*d4*) (8b)



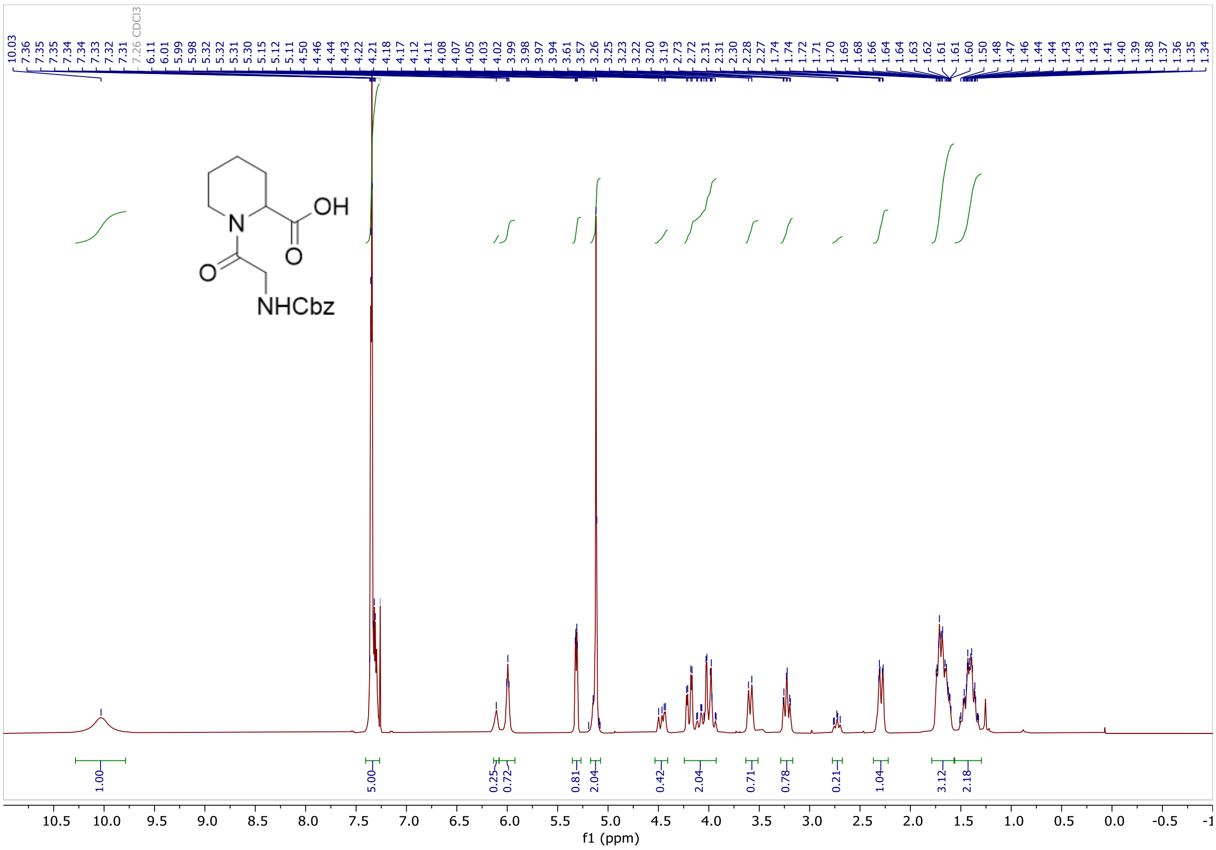
[1]H-NMR (400 MHz, methanol-d_4) (8c)



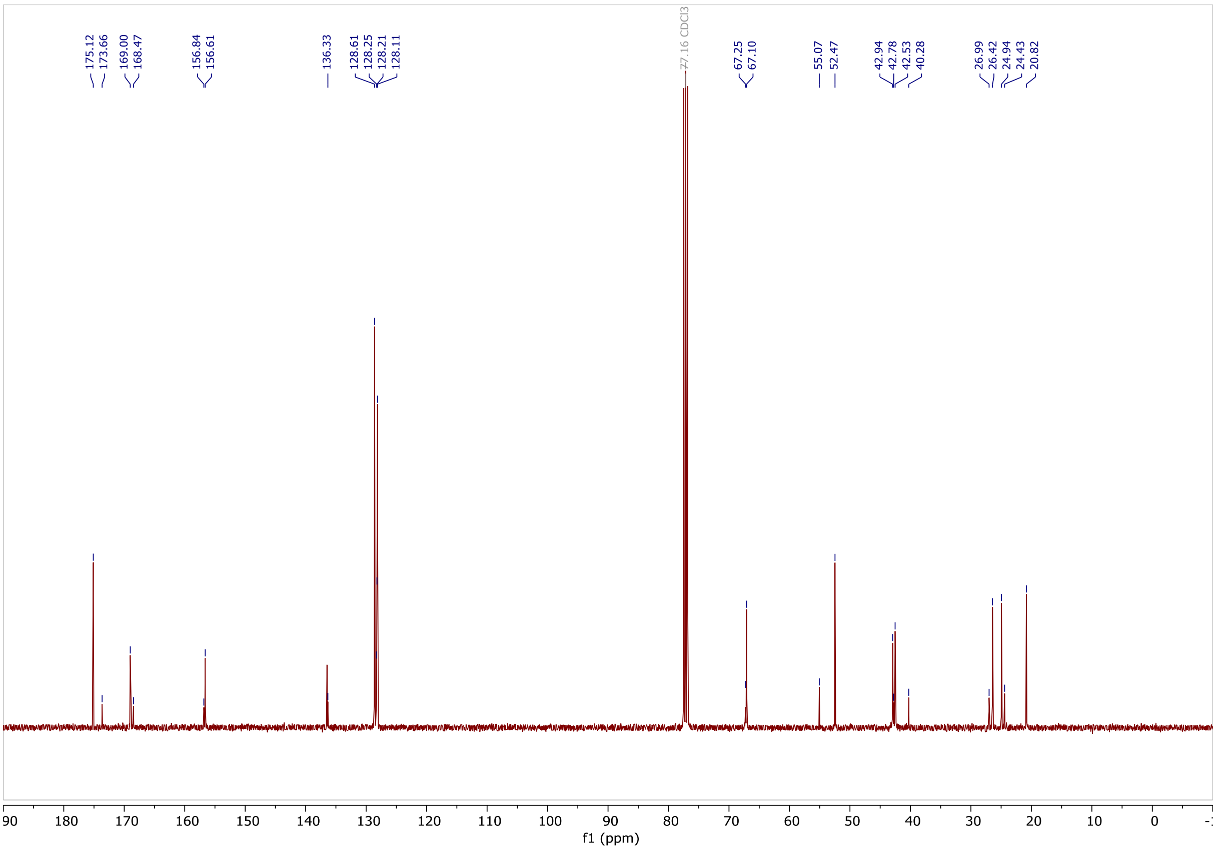
[13]C-NMR (101 MHz, methanol-d_4) (8c)



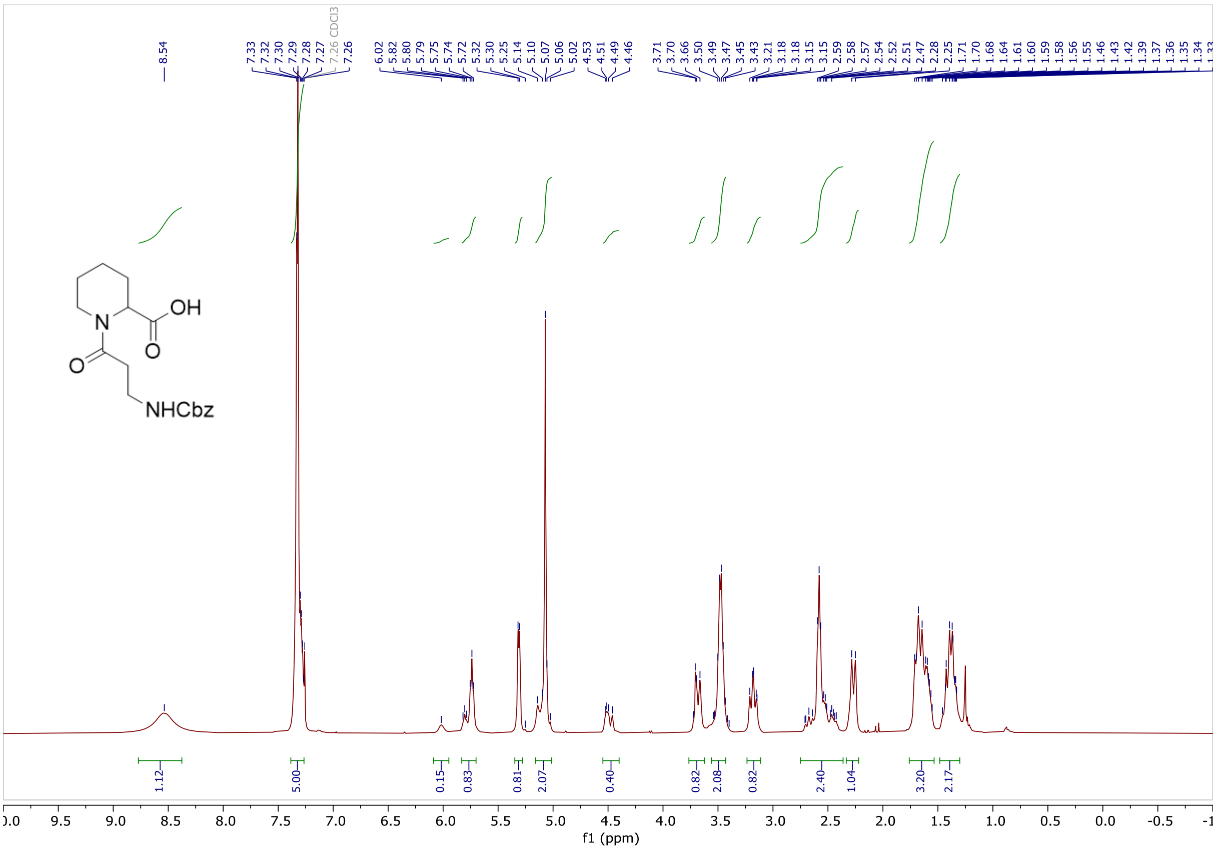
[1]H-NMR (400 MHz, chloroform-*d*) (8d)



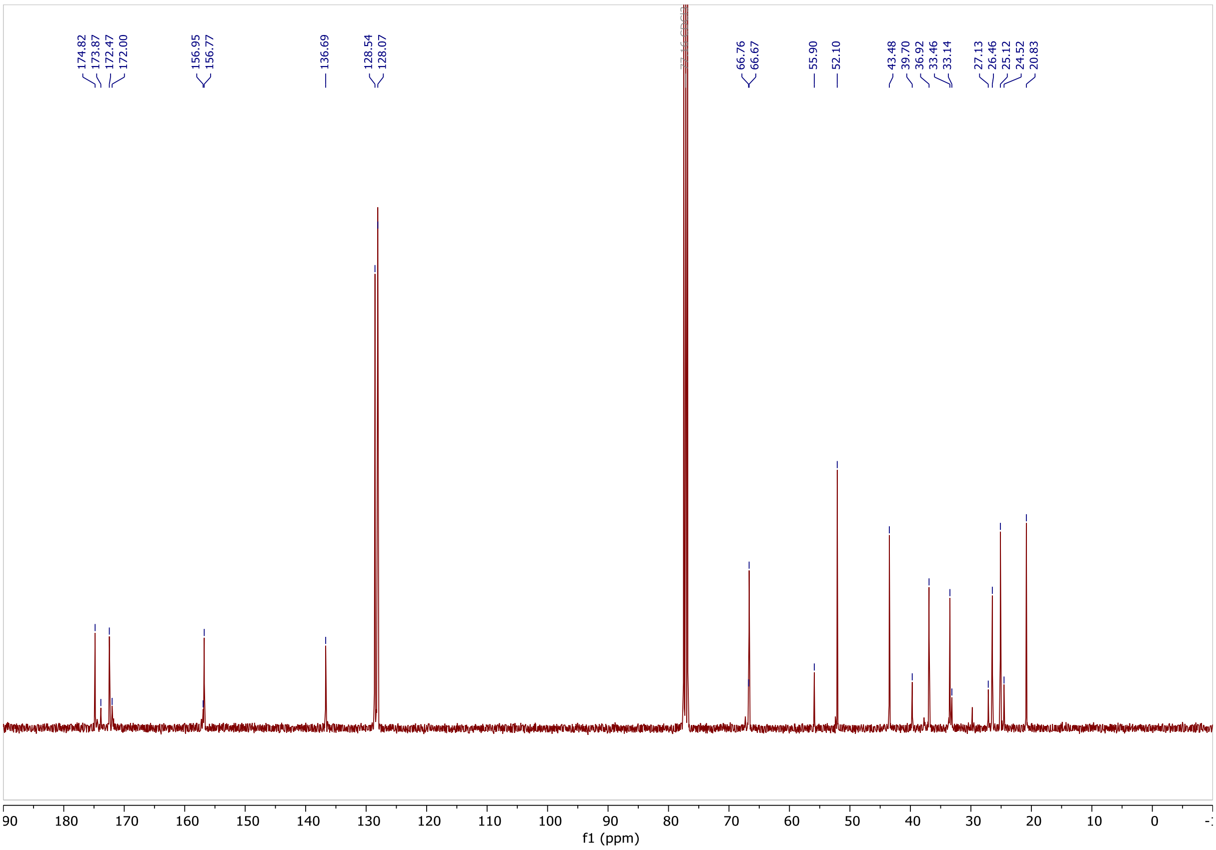
[13]C-NMR (101 MHz, chloroform-*d*) (8d)



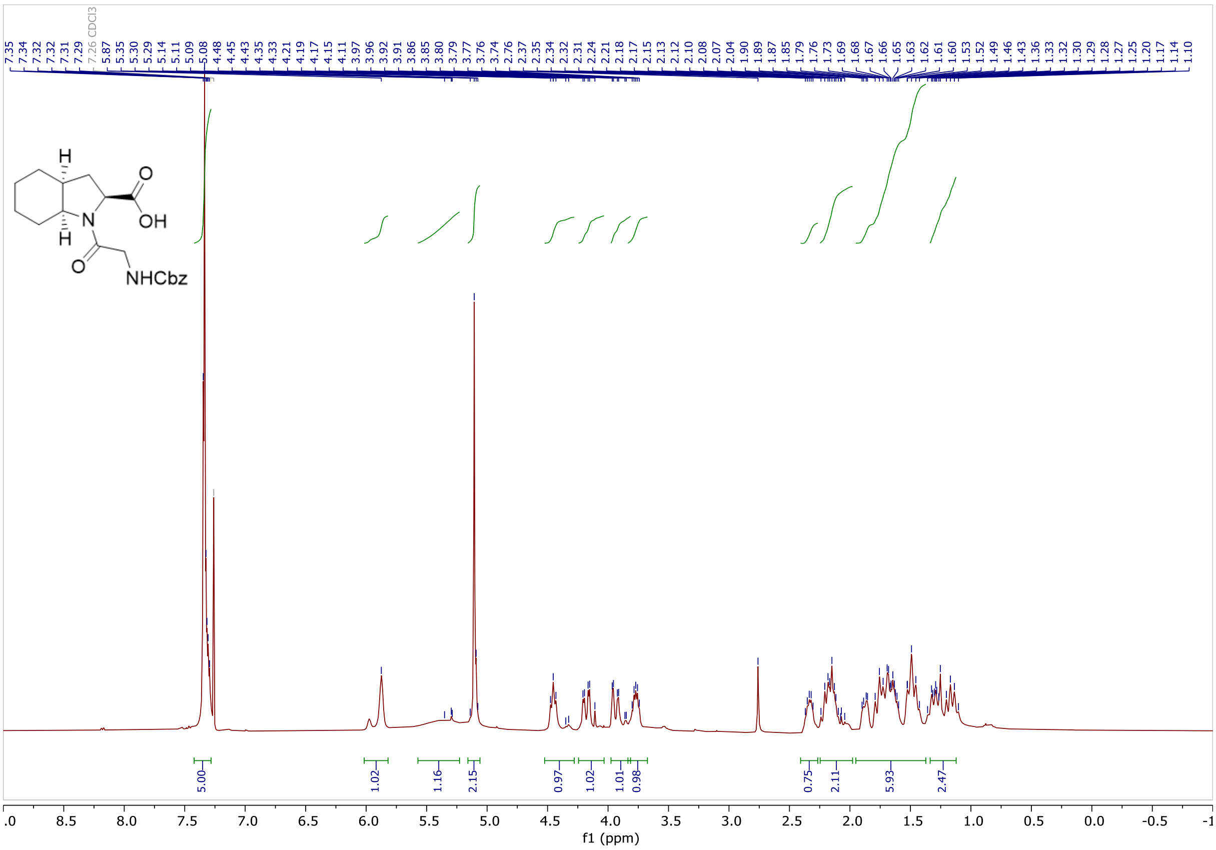
^{1}H-NMR (400 MHz, chloroform-*d*) (8e)



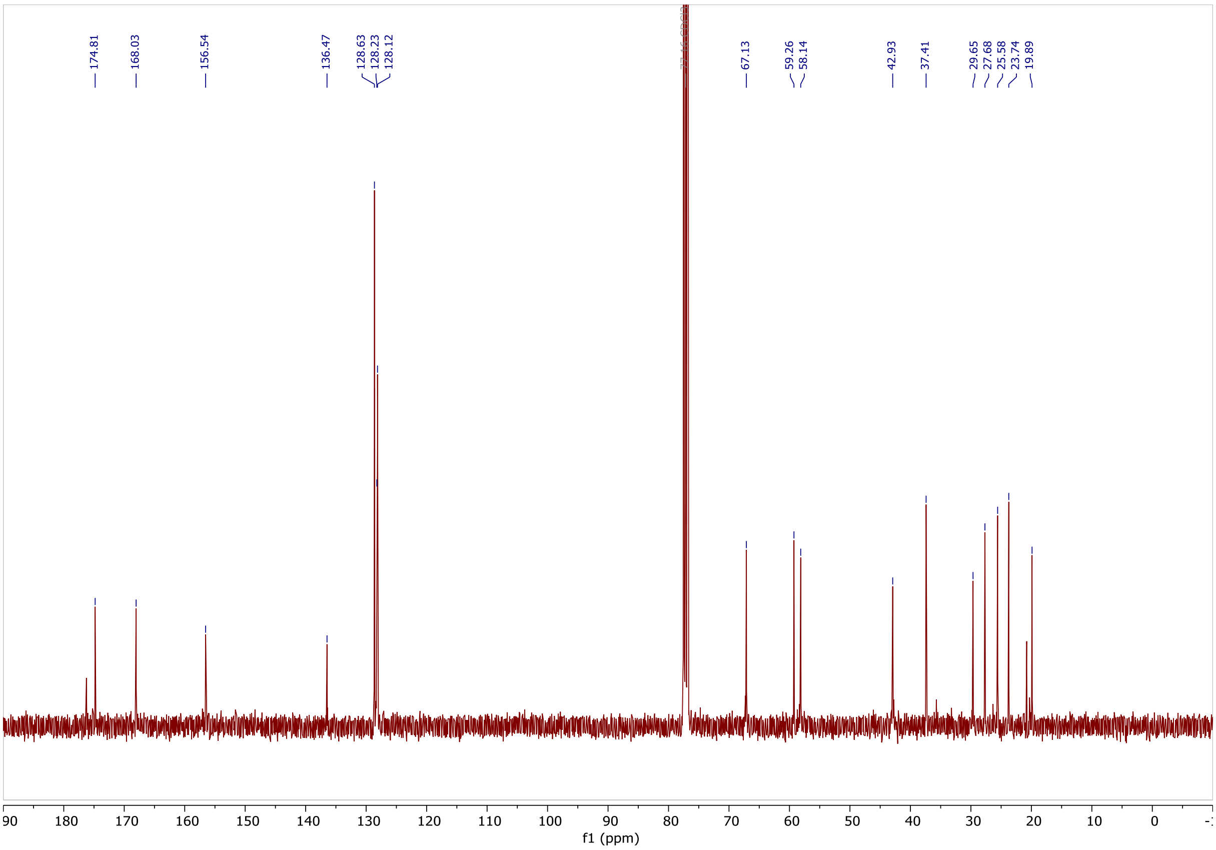
^{13}C-NMR (101 MHz, chloroform-*d*) (8e)



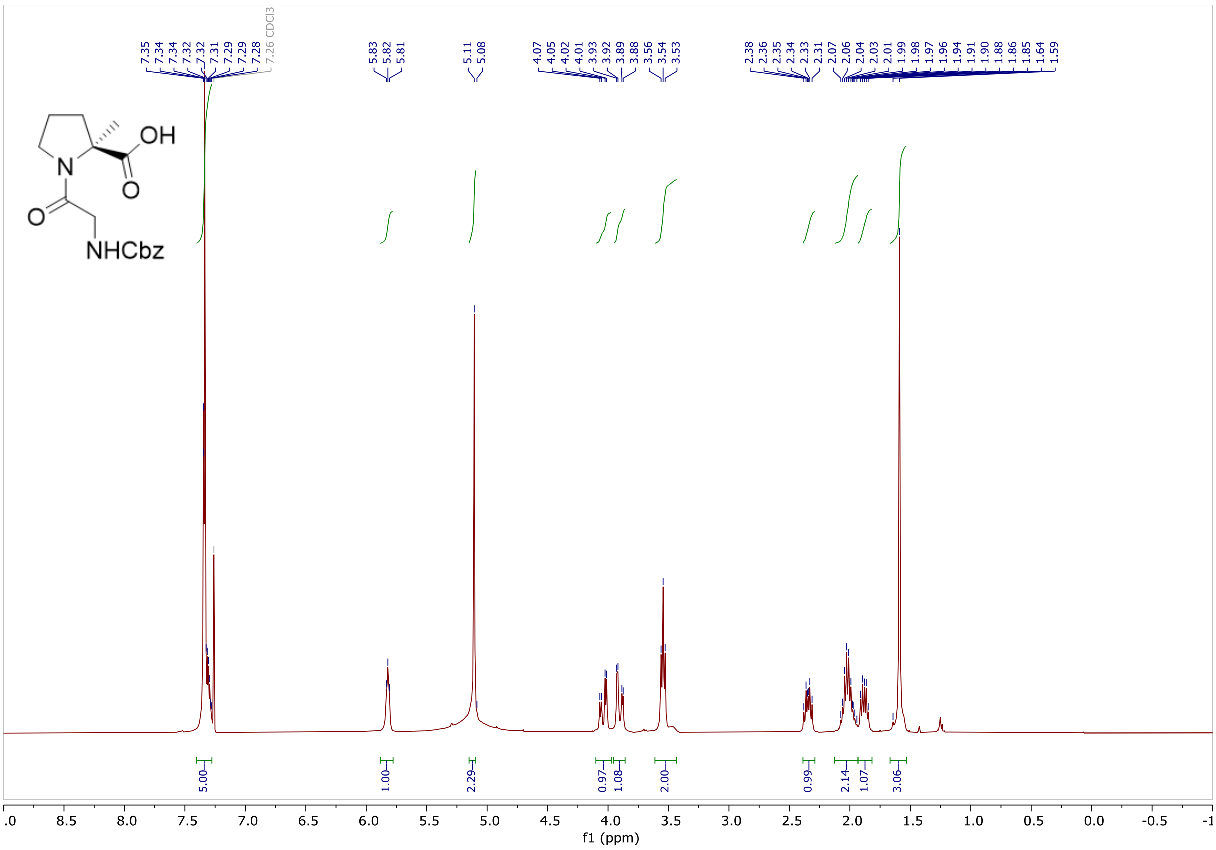
^{1}H-NMR (400 MHz, chloroform-*d*) (8f)



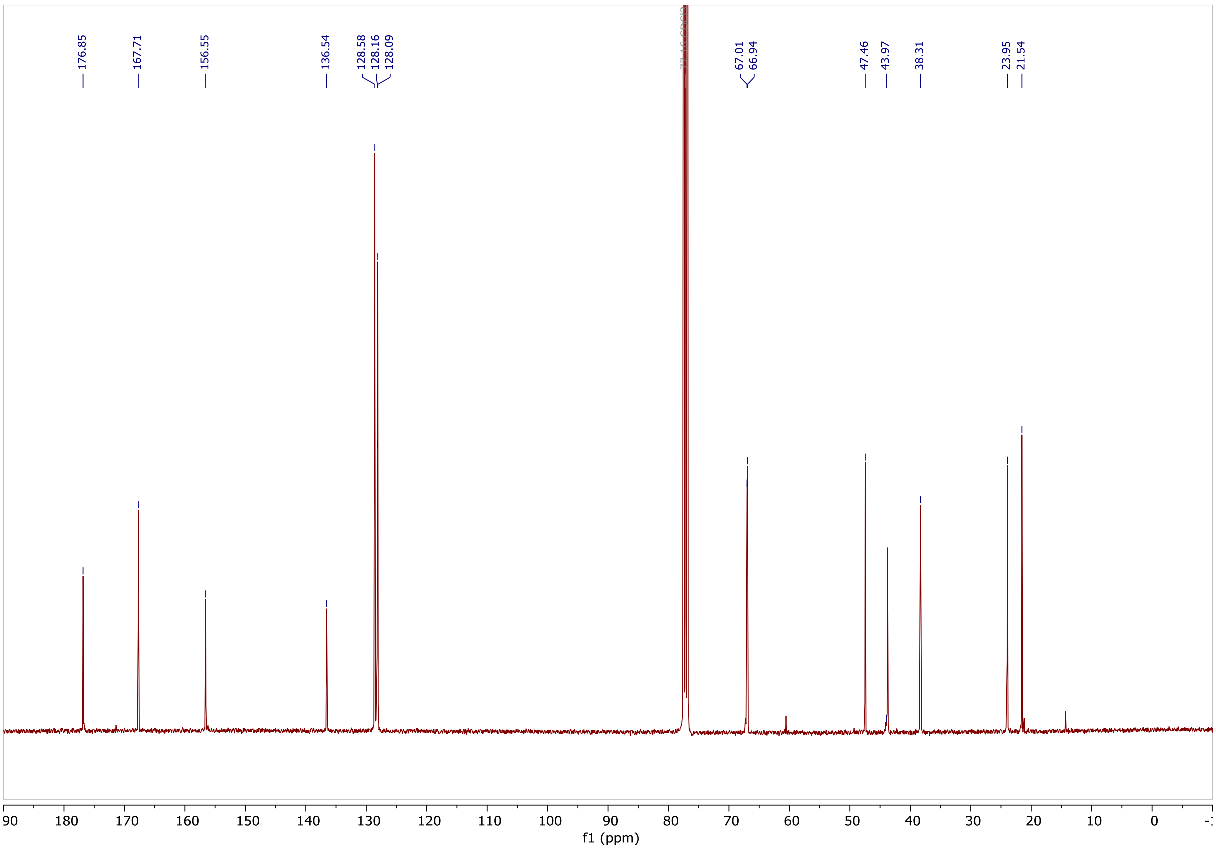
^{13}C-NMR (101 MHz, chloroform-*d*) (8f)



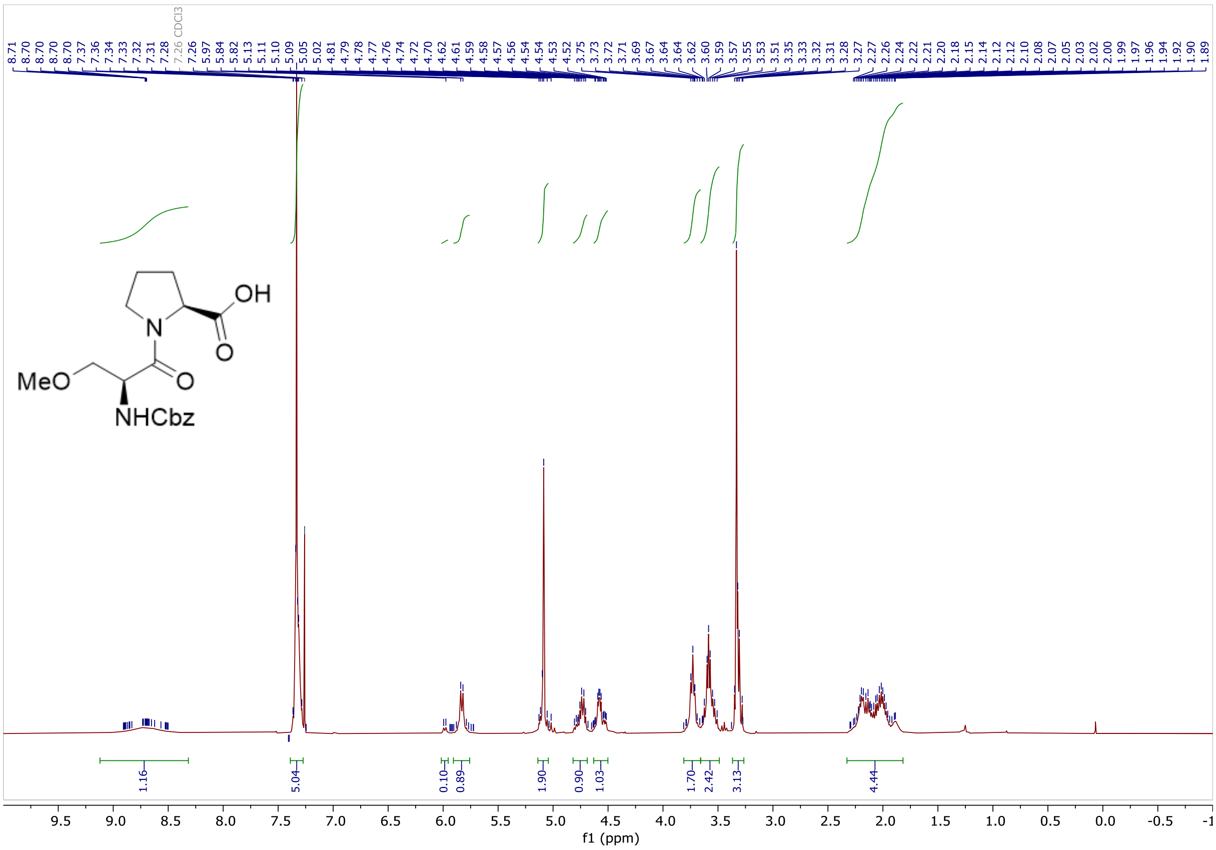
^{1}H-NMR (400 MHz, chloroform-*d*) (8g)



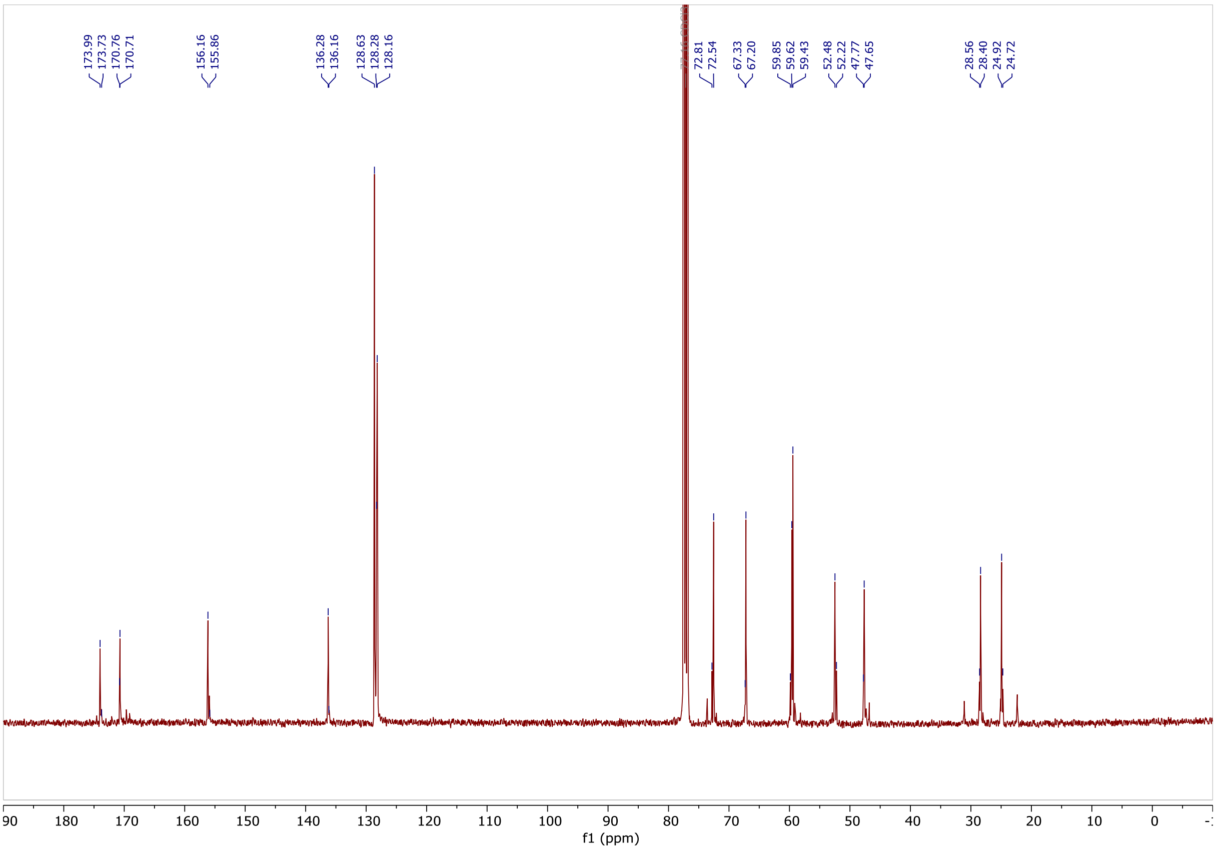
^{13}C-NMR (101 MHz, chloroform-*d*) (8g)



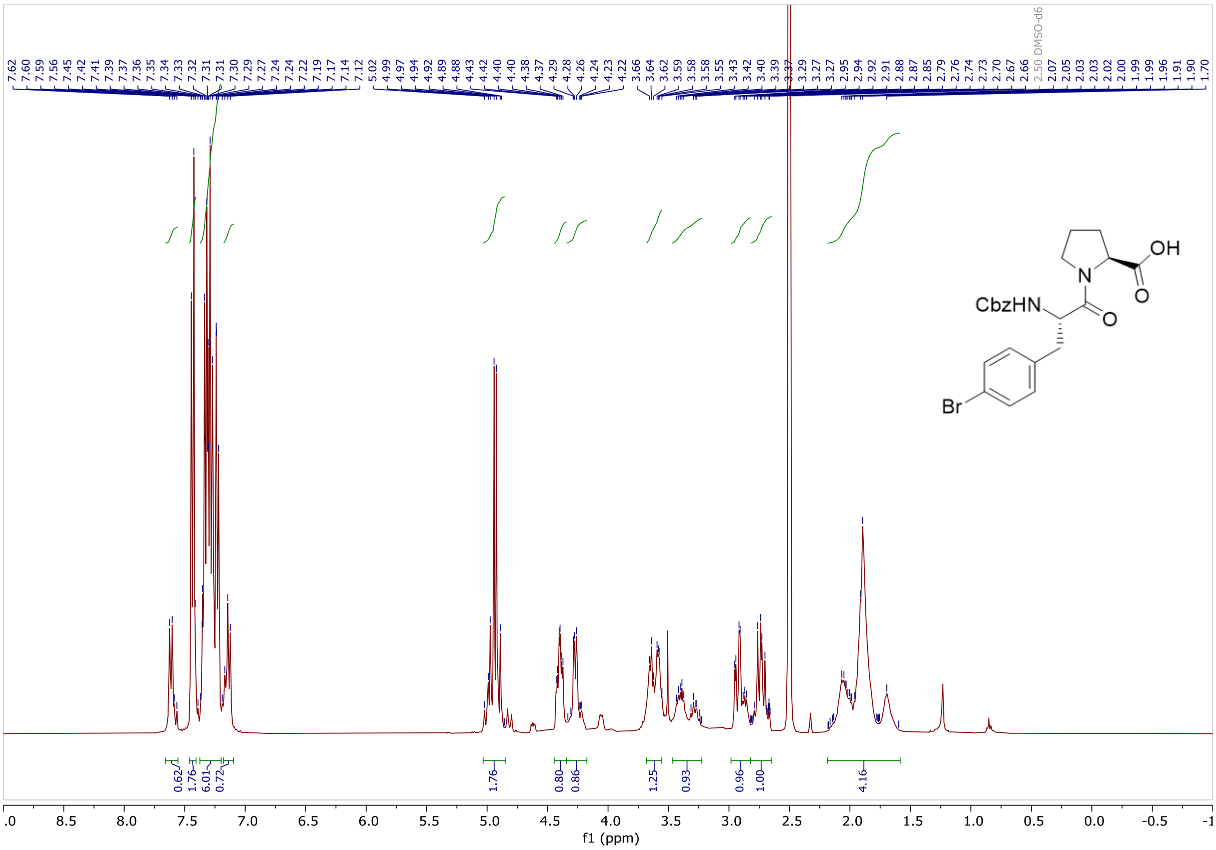
[1]H-NMR (400 MHz, chloroform-*d*) (8j)



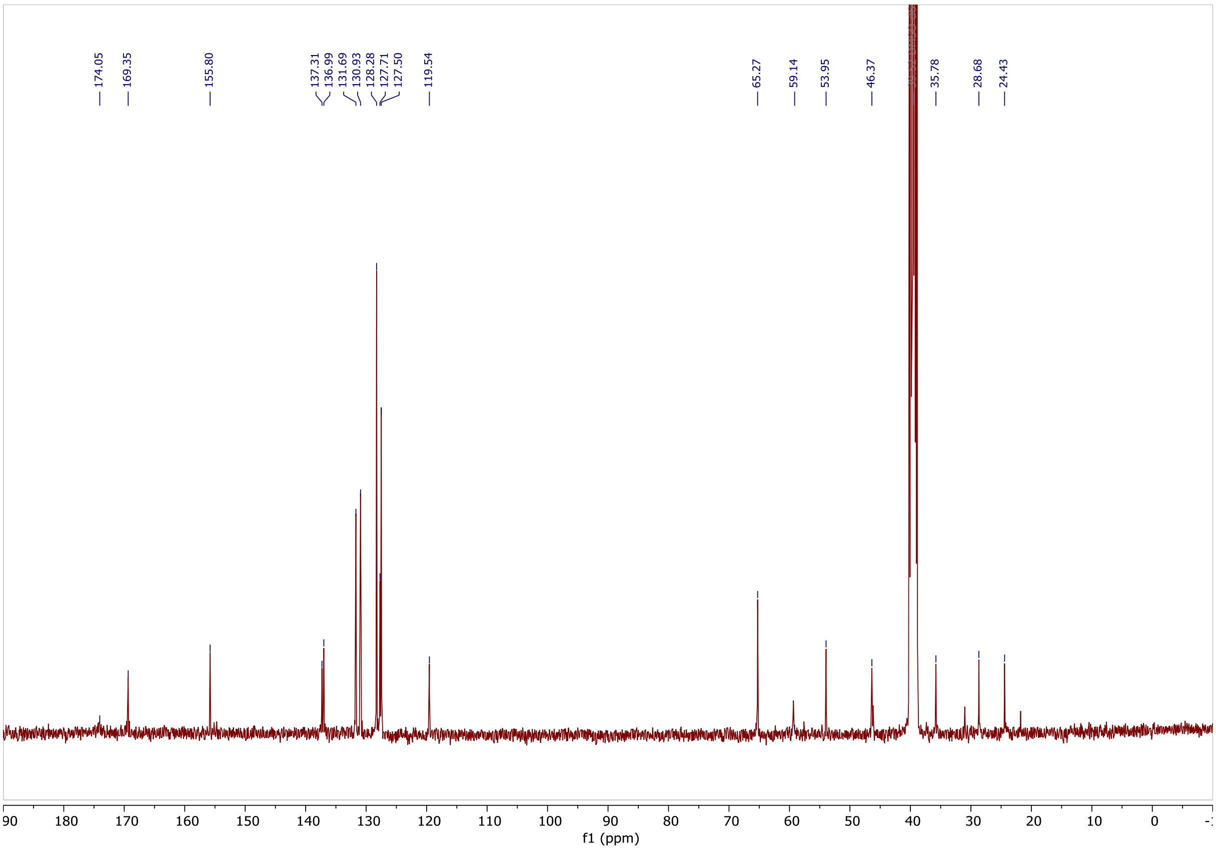
[13]C-NMR (101 MHz, chloroform-*d*) (8j)



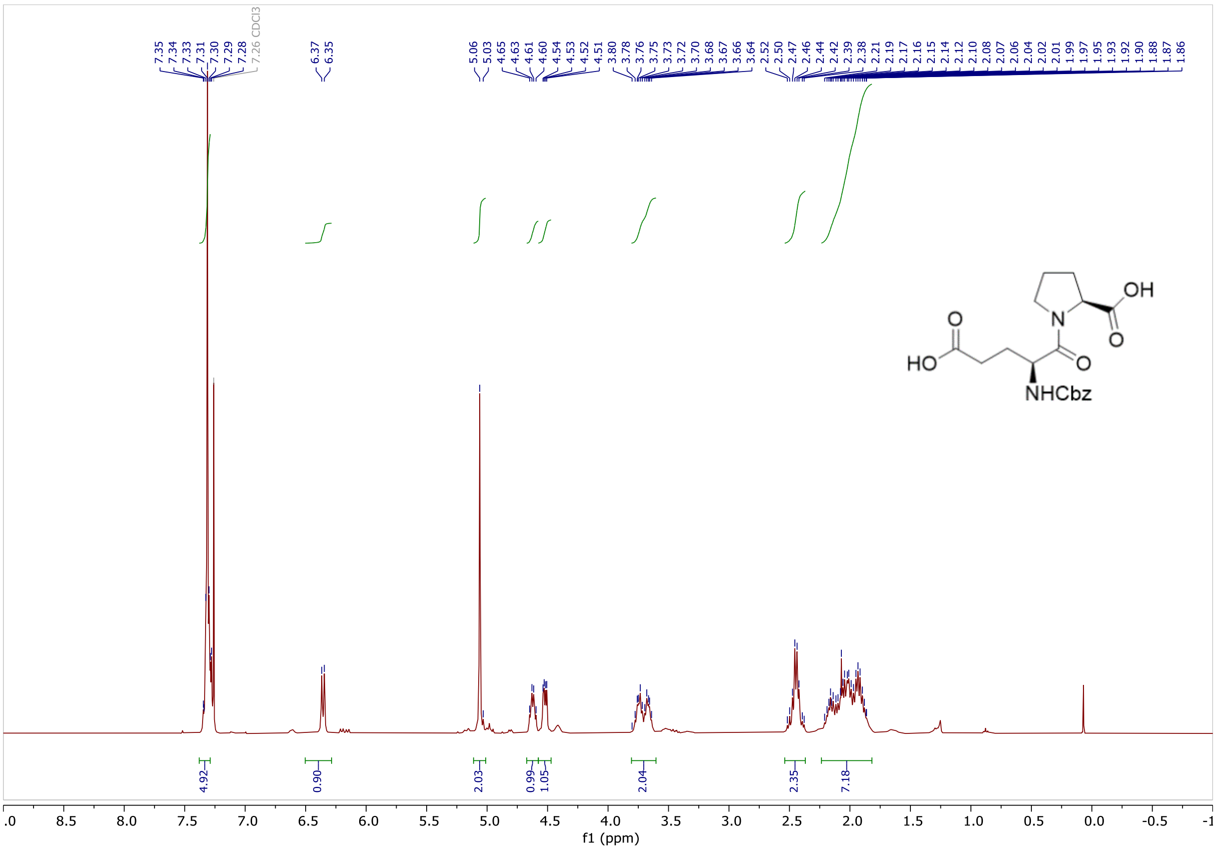
^{1}H-NMR (400 MHz, chloroform-*d*) (8k)



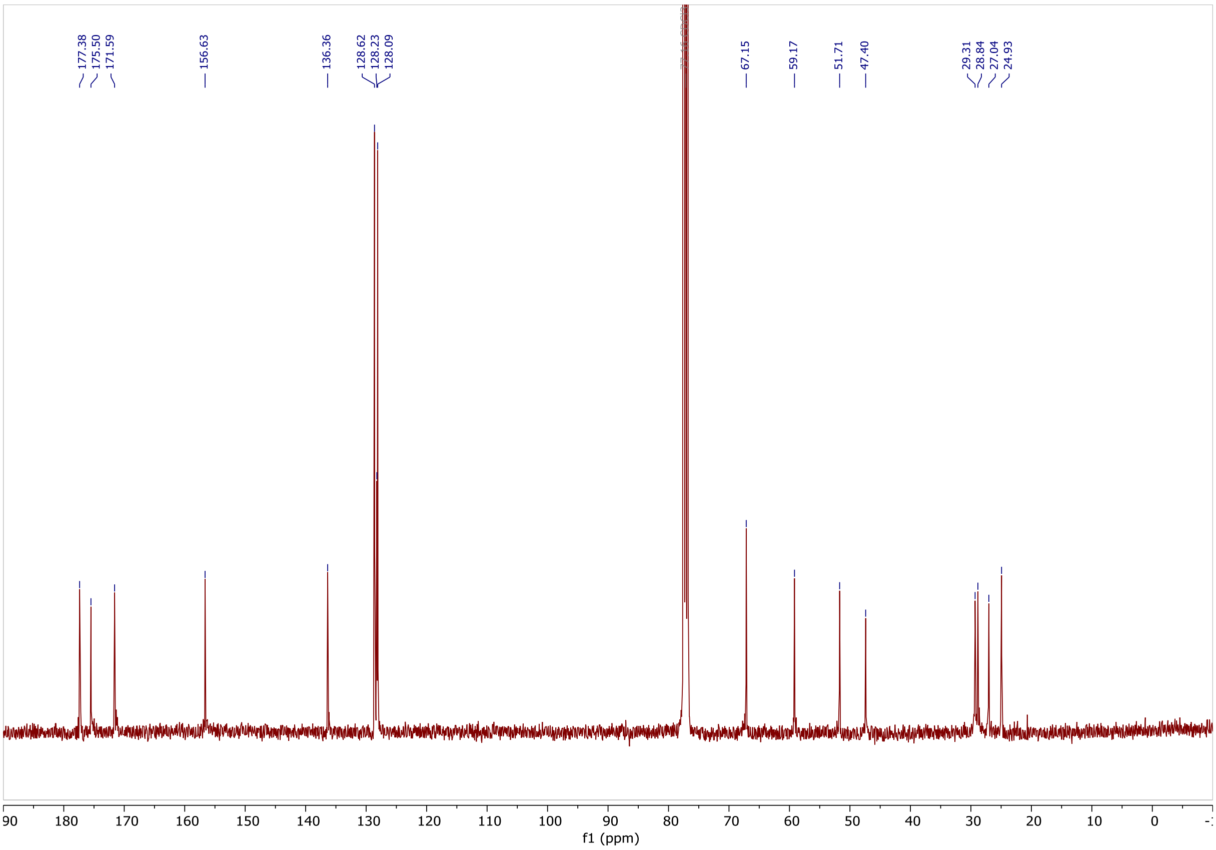
^{13}C-NMR (101 MHz, chloroform-*d*) (8k)



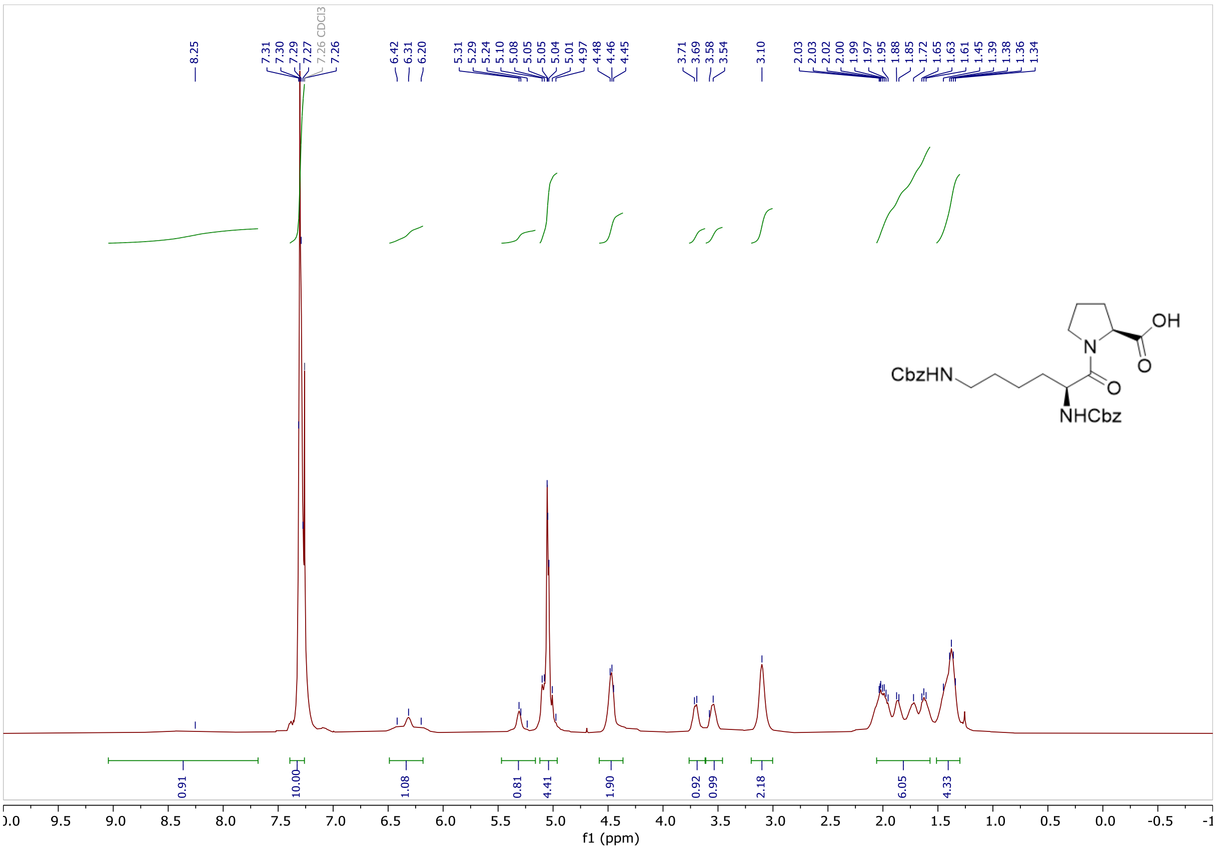
1H-NMR (400 MHz, chloroform-*d*) (8l)



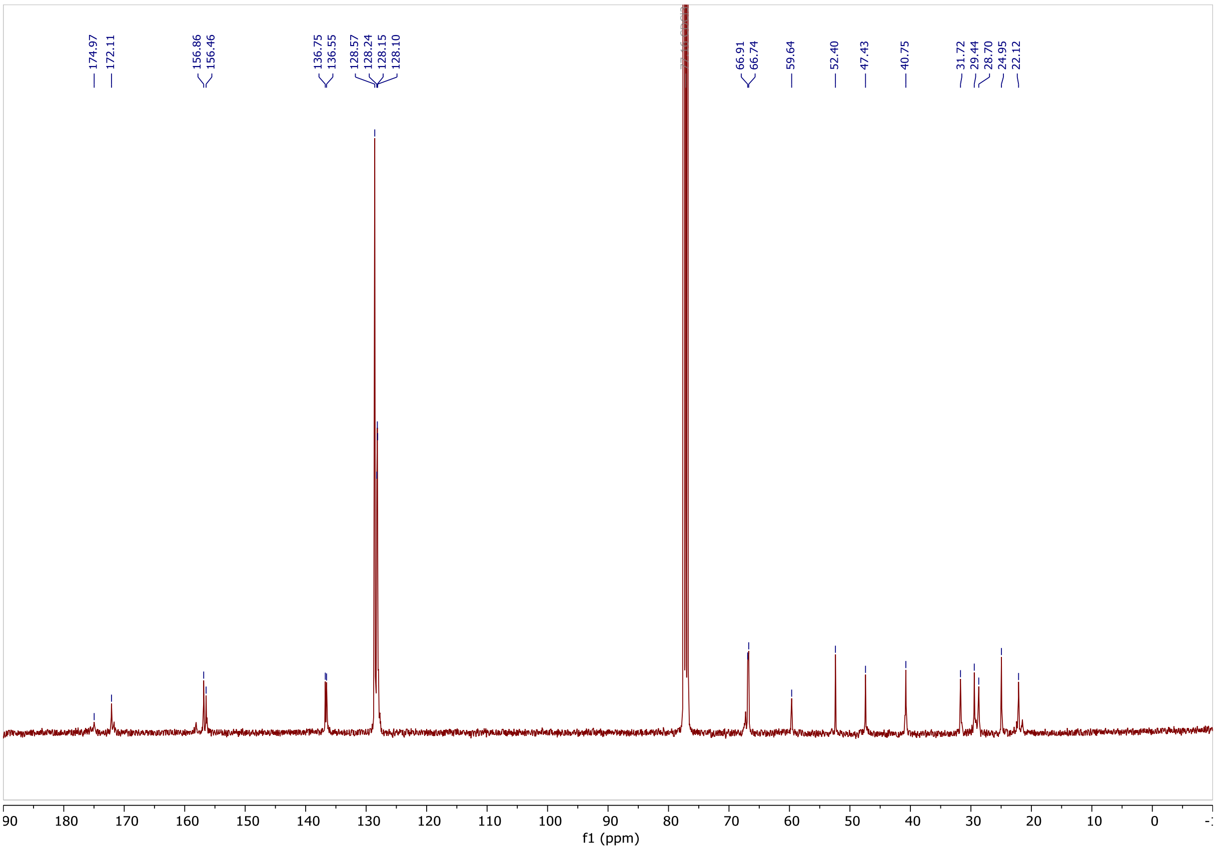
13C-NMR (101 MHz, chloroform-*d*) (8l)



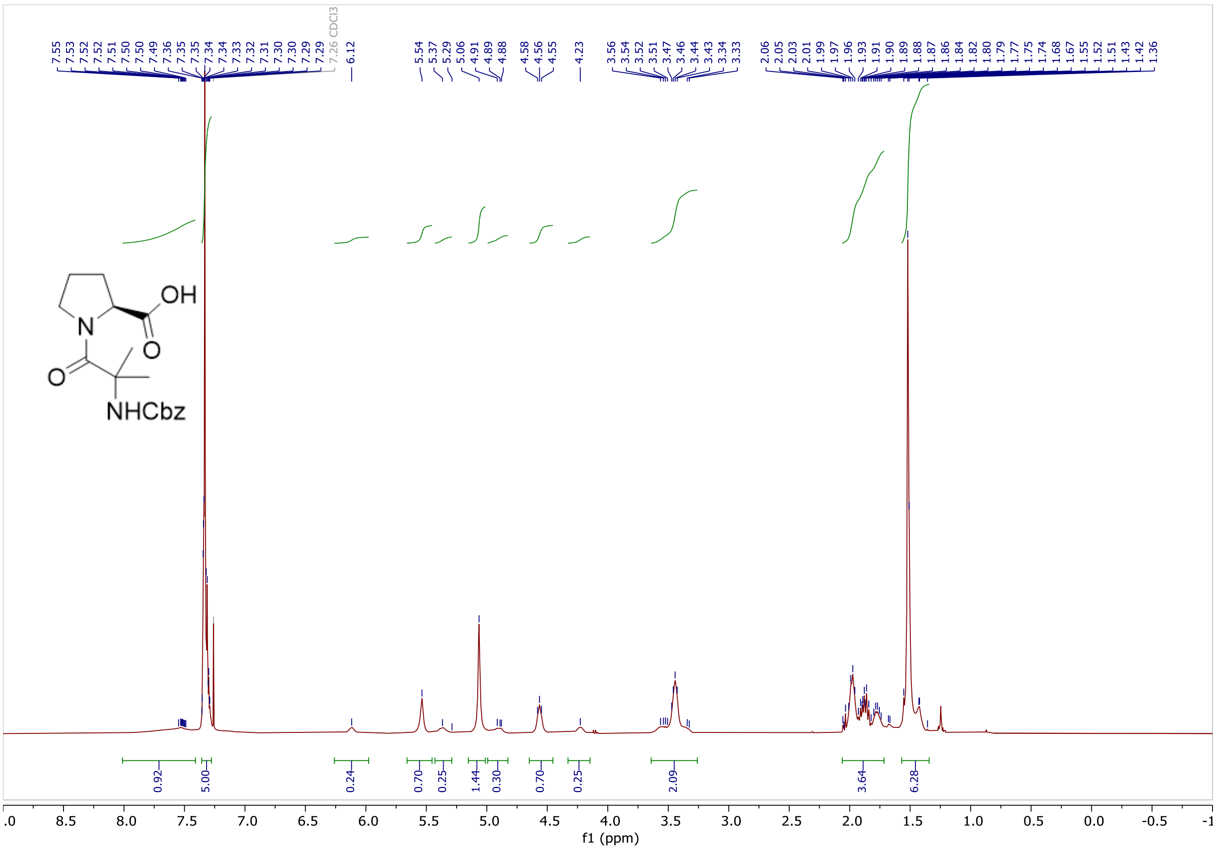
^{1}H-NMR (400 MHz, chloroform-*d*) (8m)



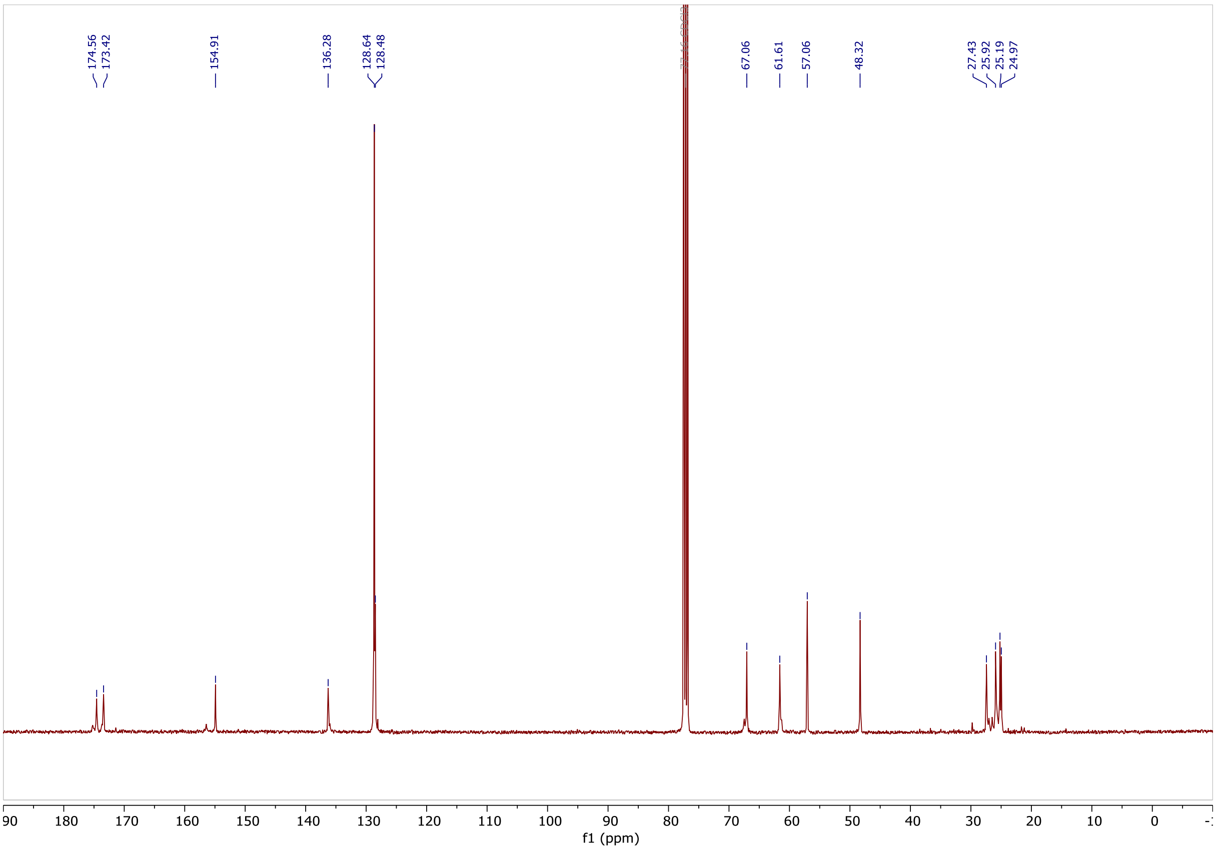
^{13}C-NMR (101 MHz, chloroform-*d*) (8m)



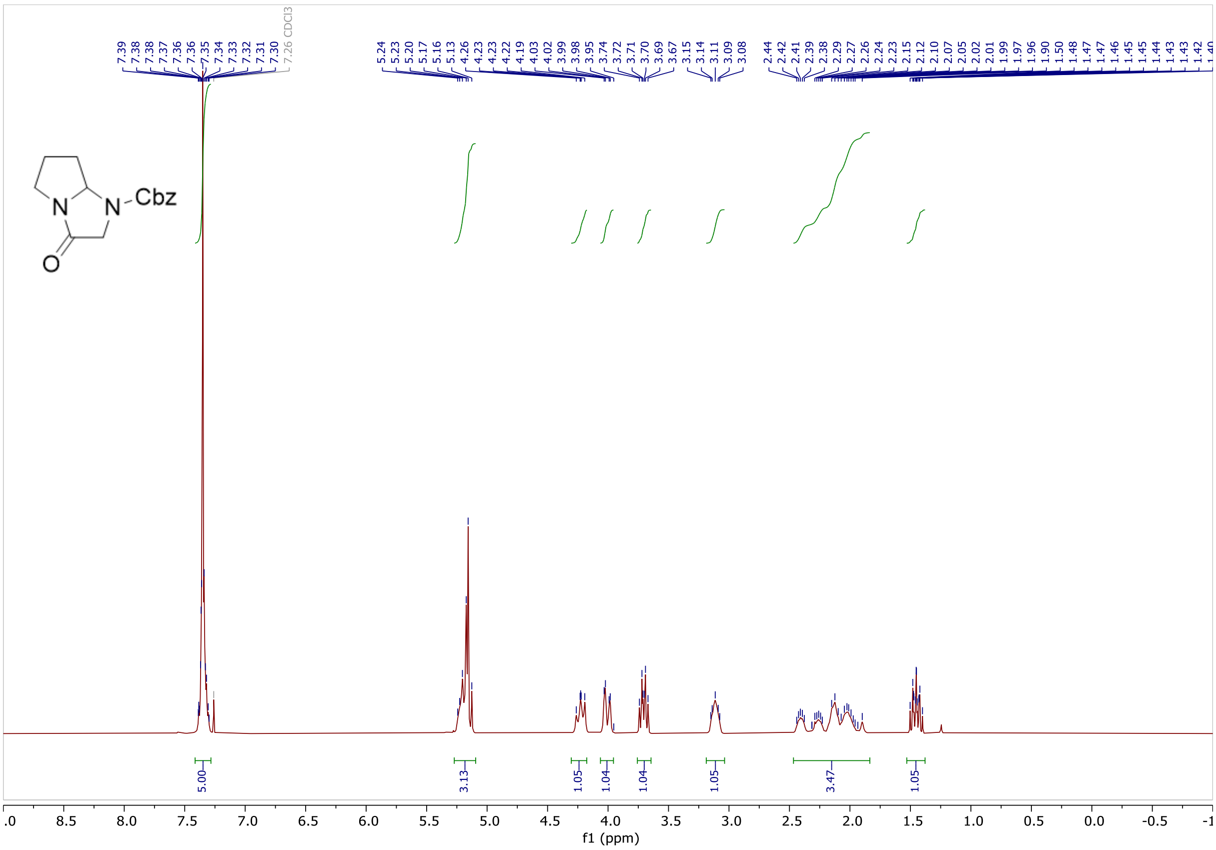
[1]H-NMR (400 MHz, chloroform-*d*) (8n)



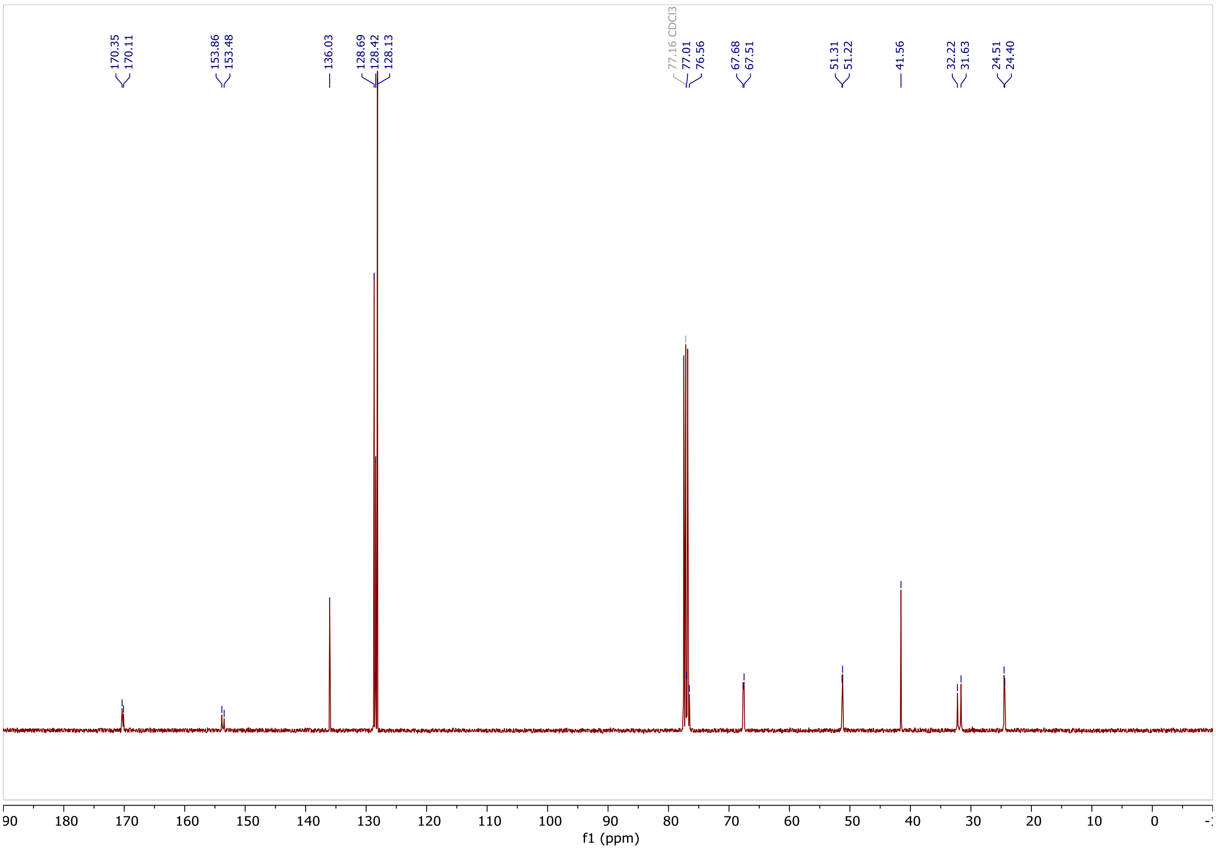
[13]C-NMR (101 MHz, chloroform-*d*) (8n)



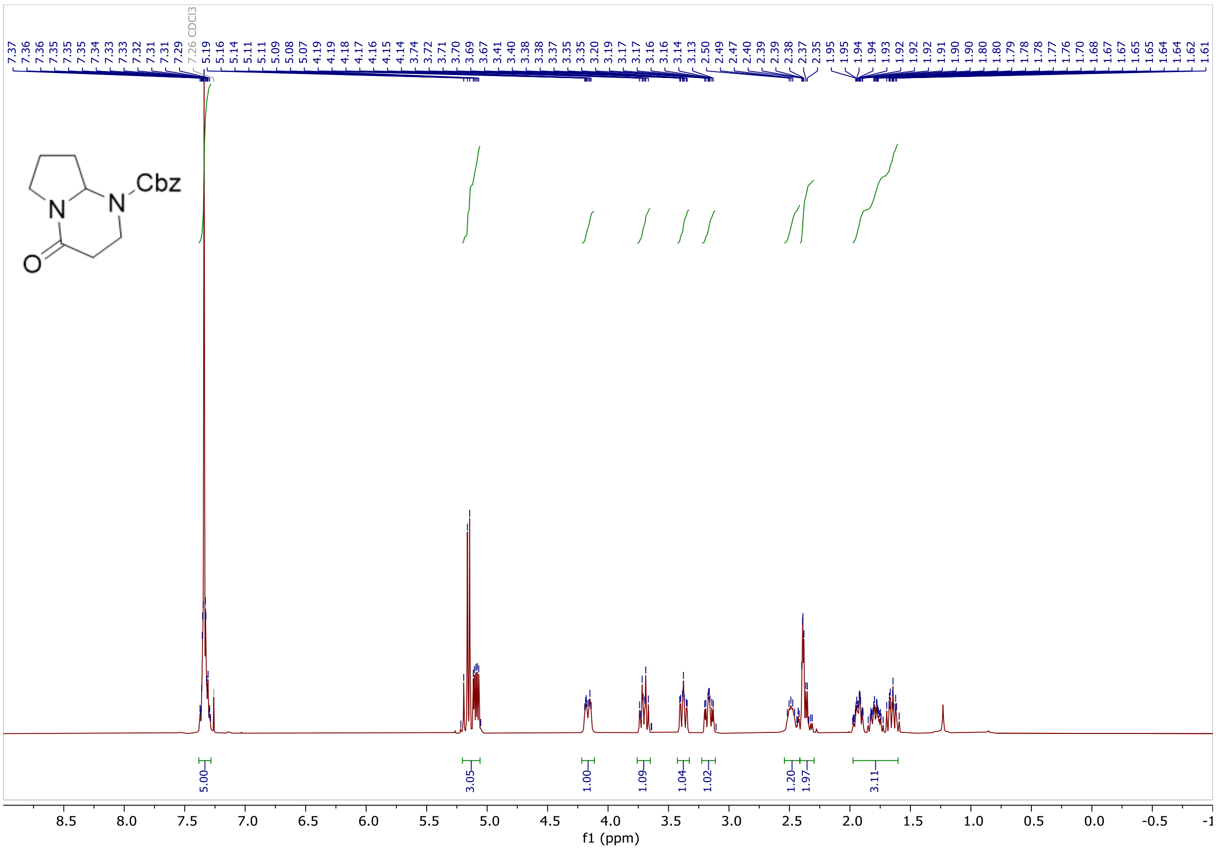
[1]H-NMR (400 MHz, chloroform-*d*) (9a)



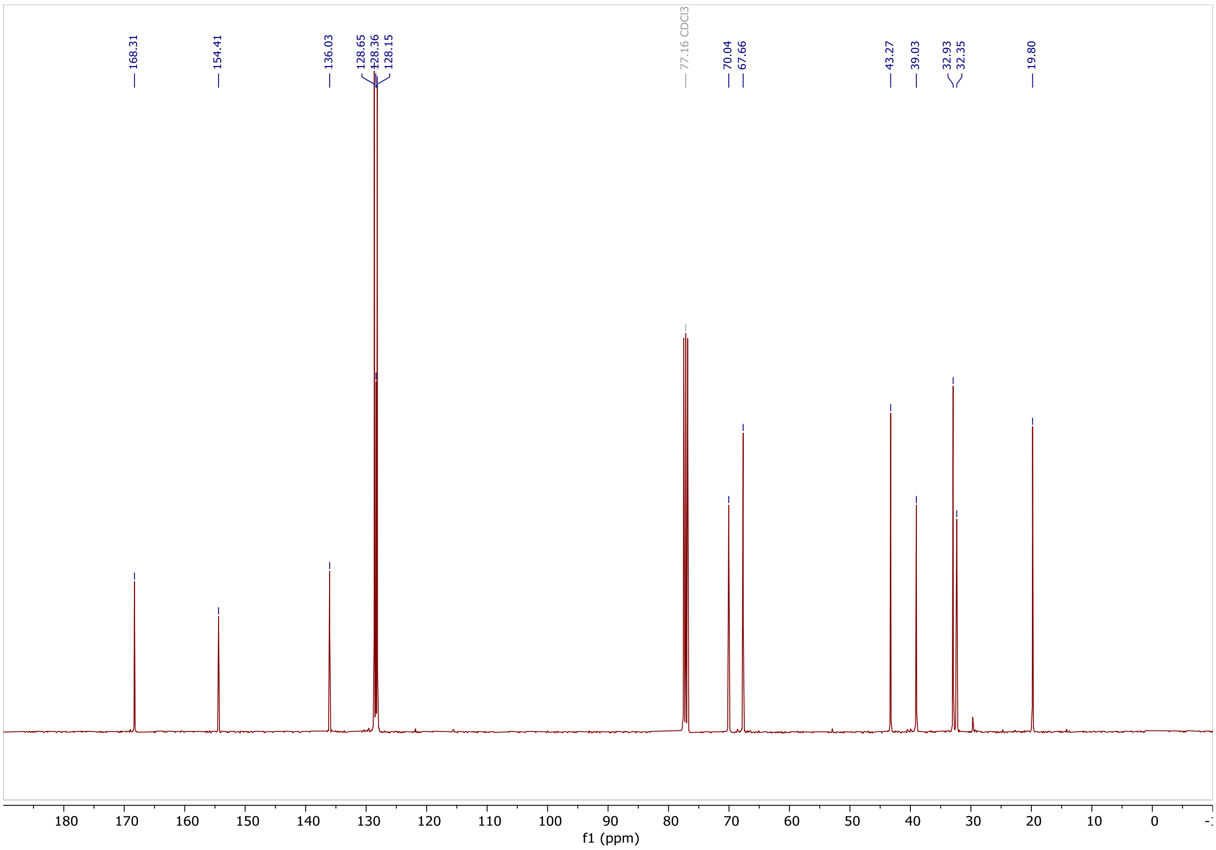
[13]C-NMR (101 MHz, chloroform-*d*) (9a)



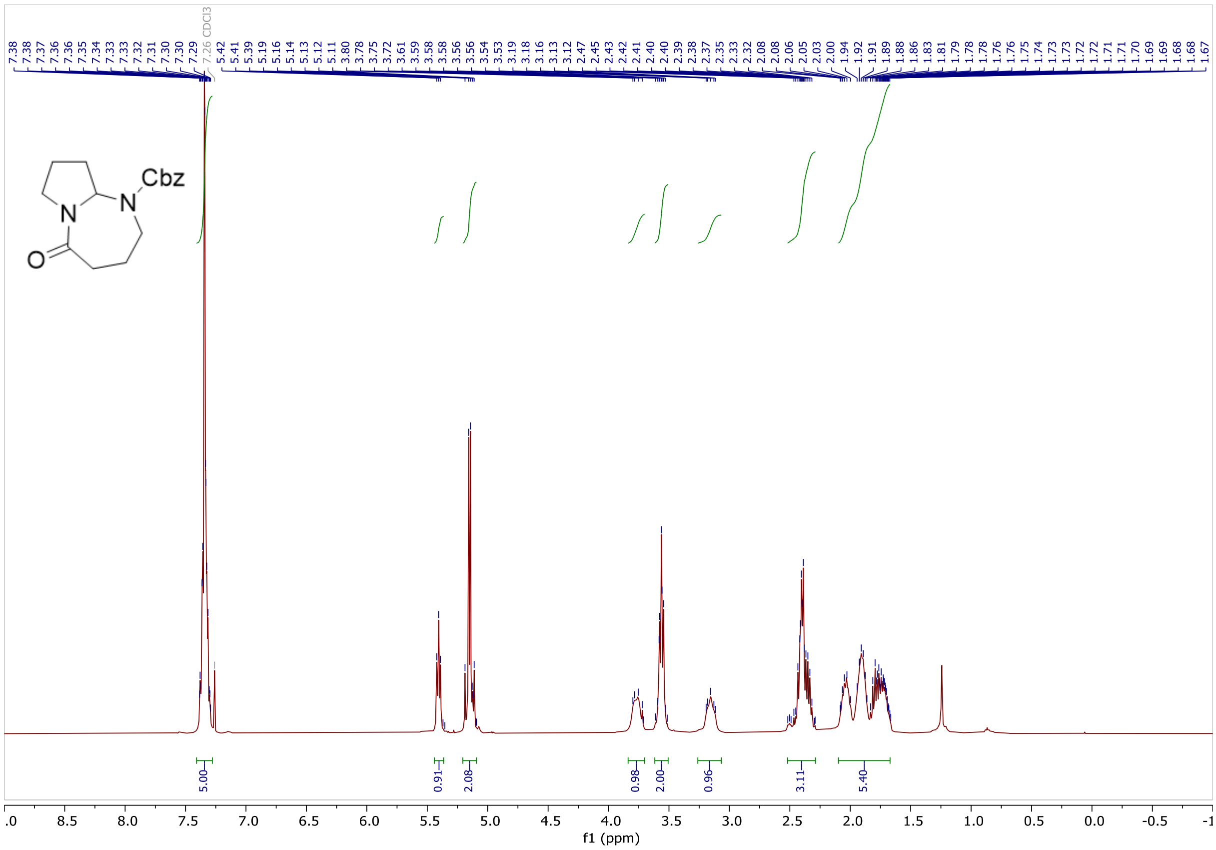
[1]H-NMR (400 MHz, chloroform-*d*) (9b)



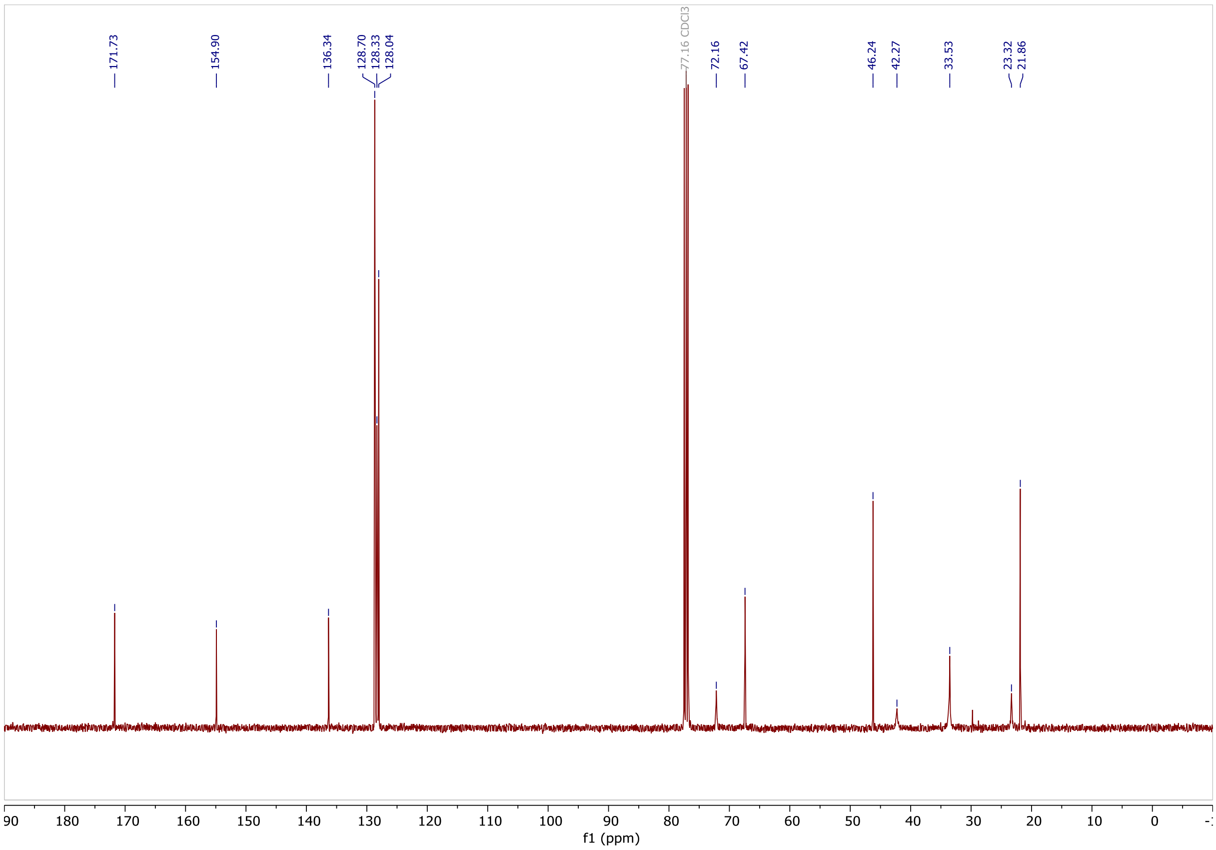
[13]C-NMR (101 MHz, chloroform-*d*) (9b)



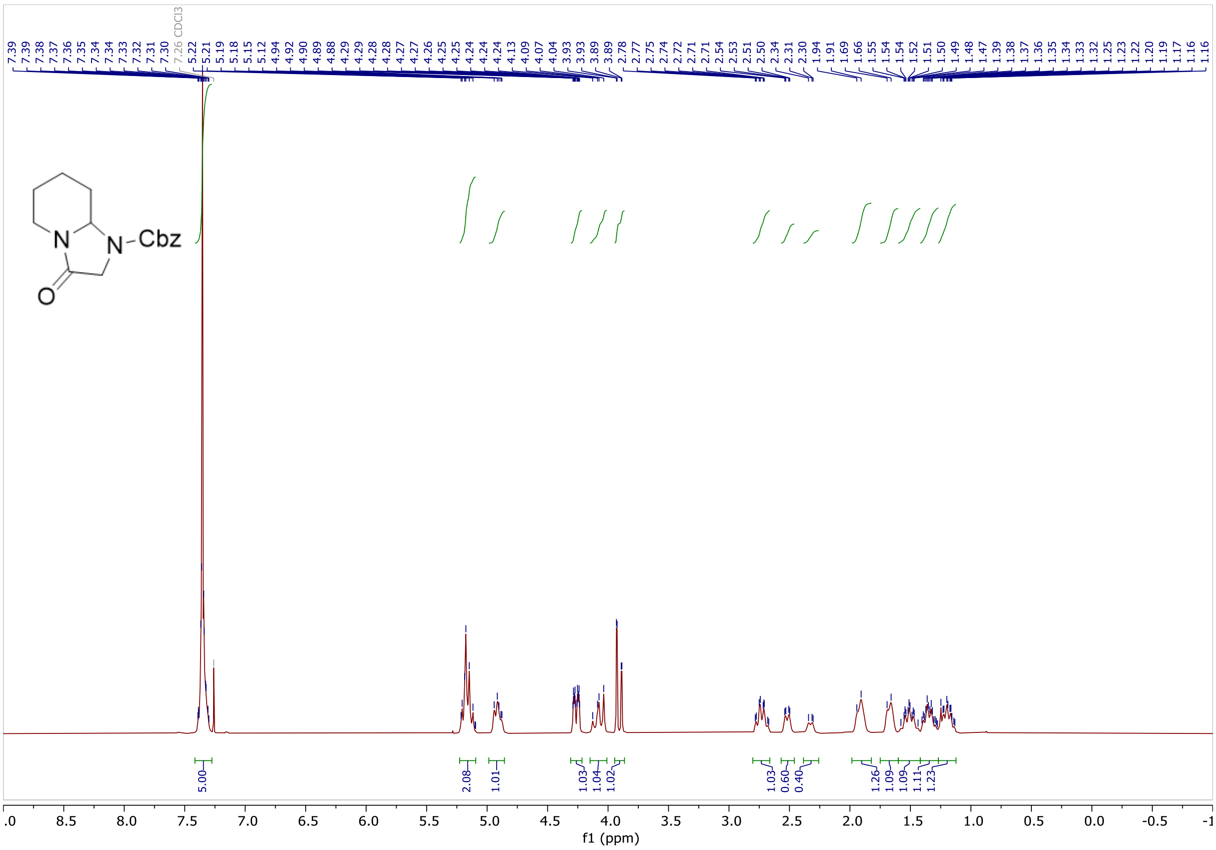
^{1}H-NMR (400 MHz, chloroform-*d*) (9c)



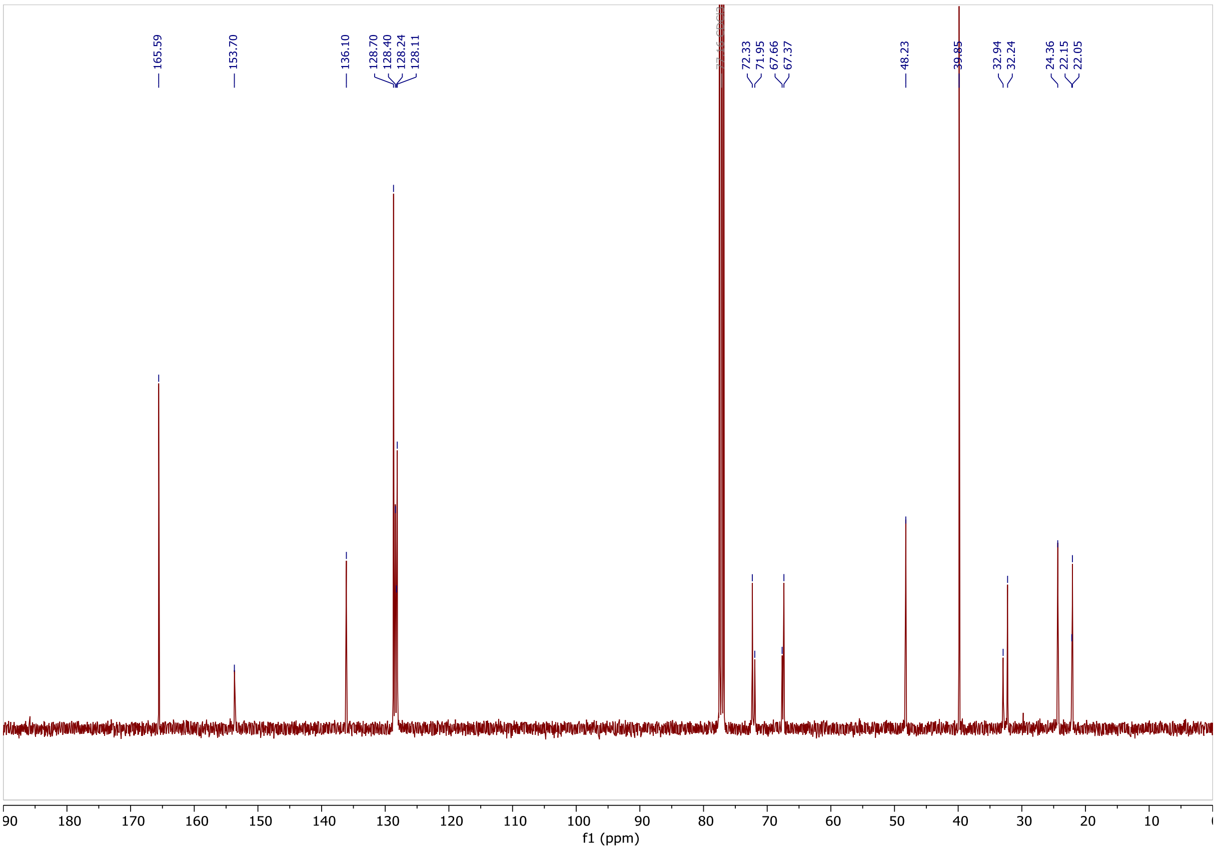
^{13}C-NMR (101 MHz, chloroform-*d*) (9c)



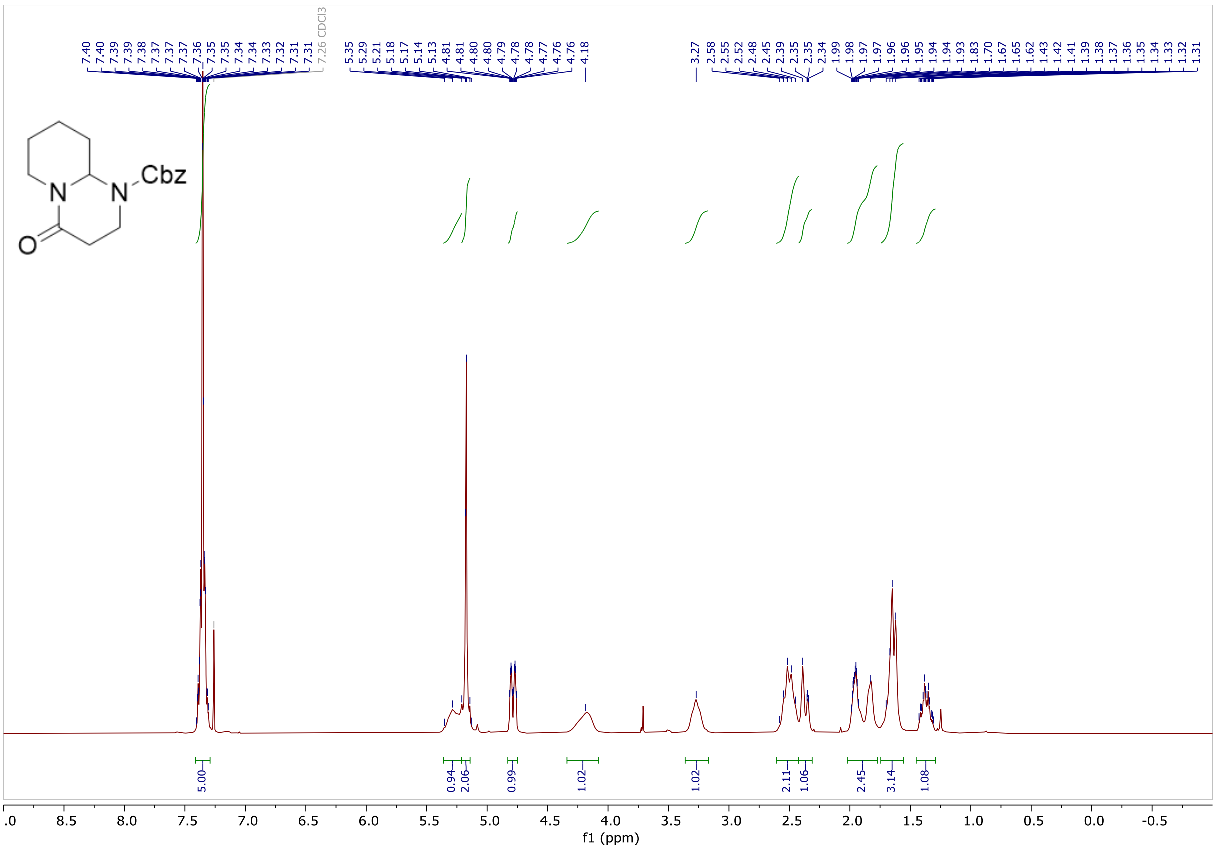
¹H-NMR (400 MHz, chloroform-*d*) (9d)



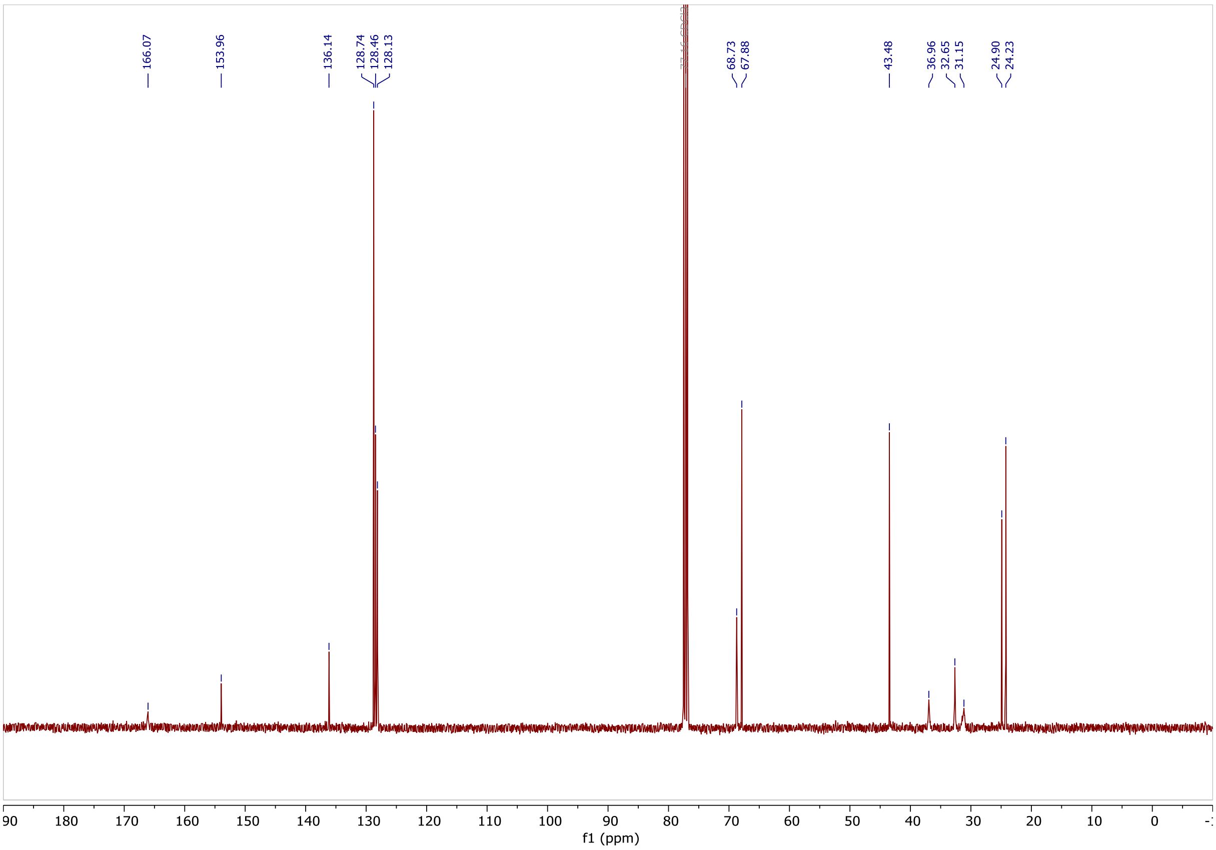
¹³C-NMR (101 MHz, chloroform-*d*) (9d)



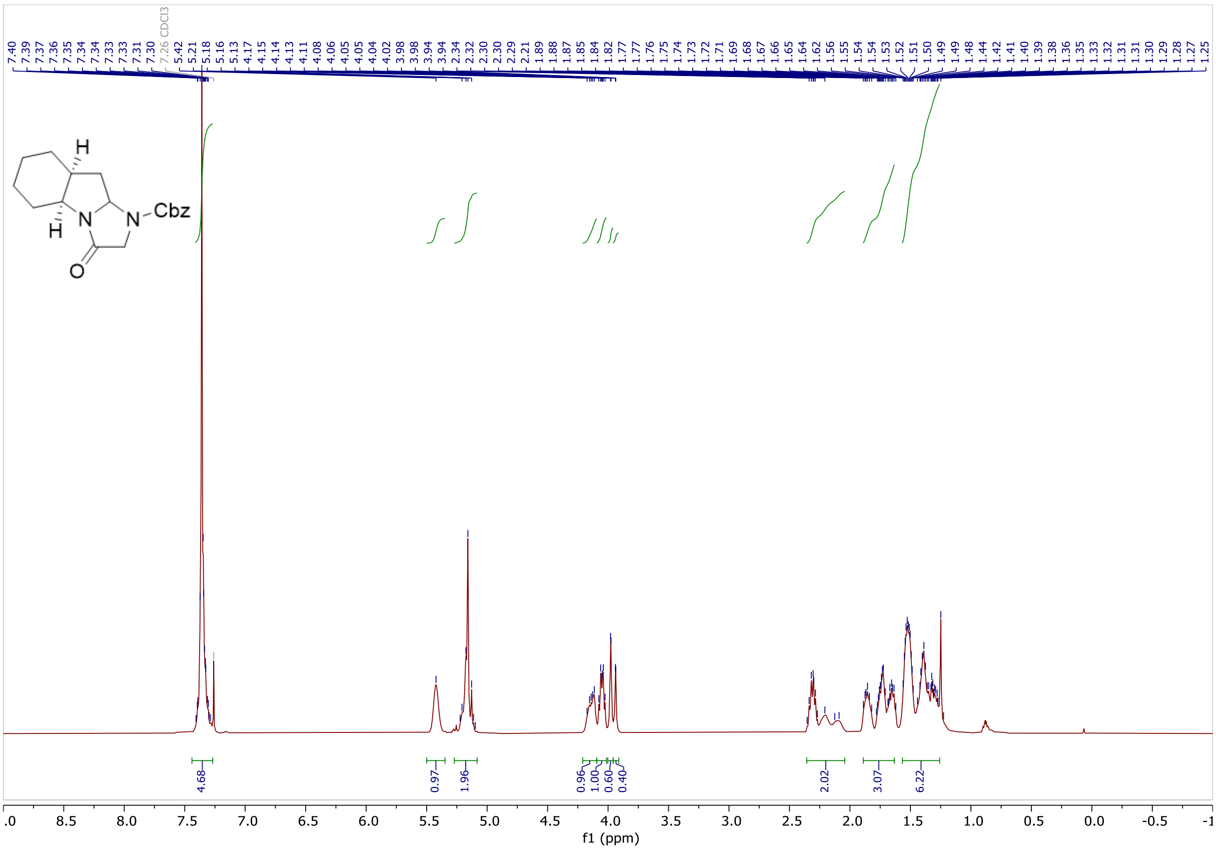
[1]H-NMR (400 MHz, chloroform-*d*) (9e)



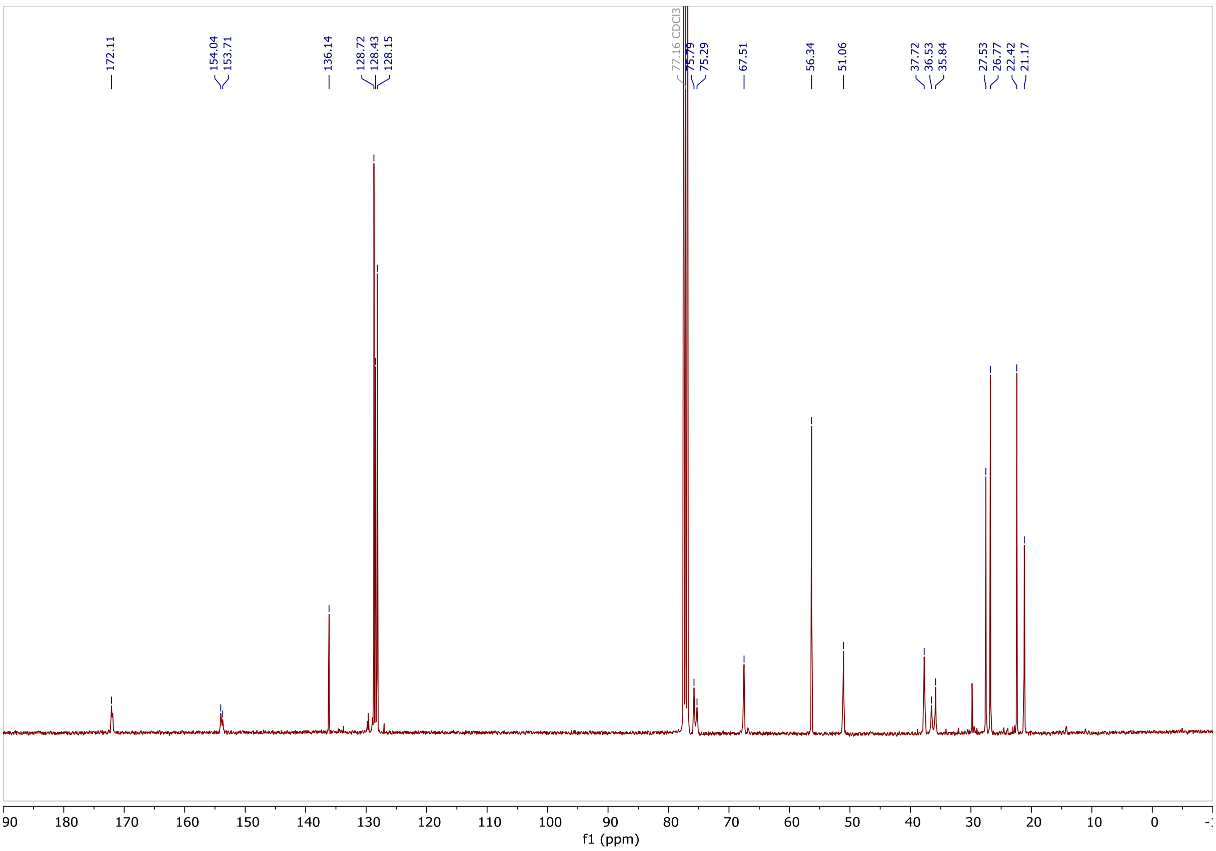
[13]C-NMR (101 MHz, chloroform-*d*) (9e)



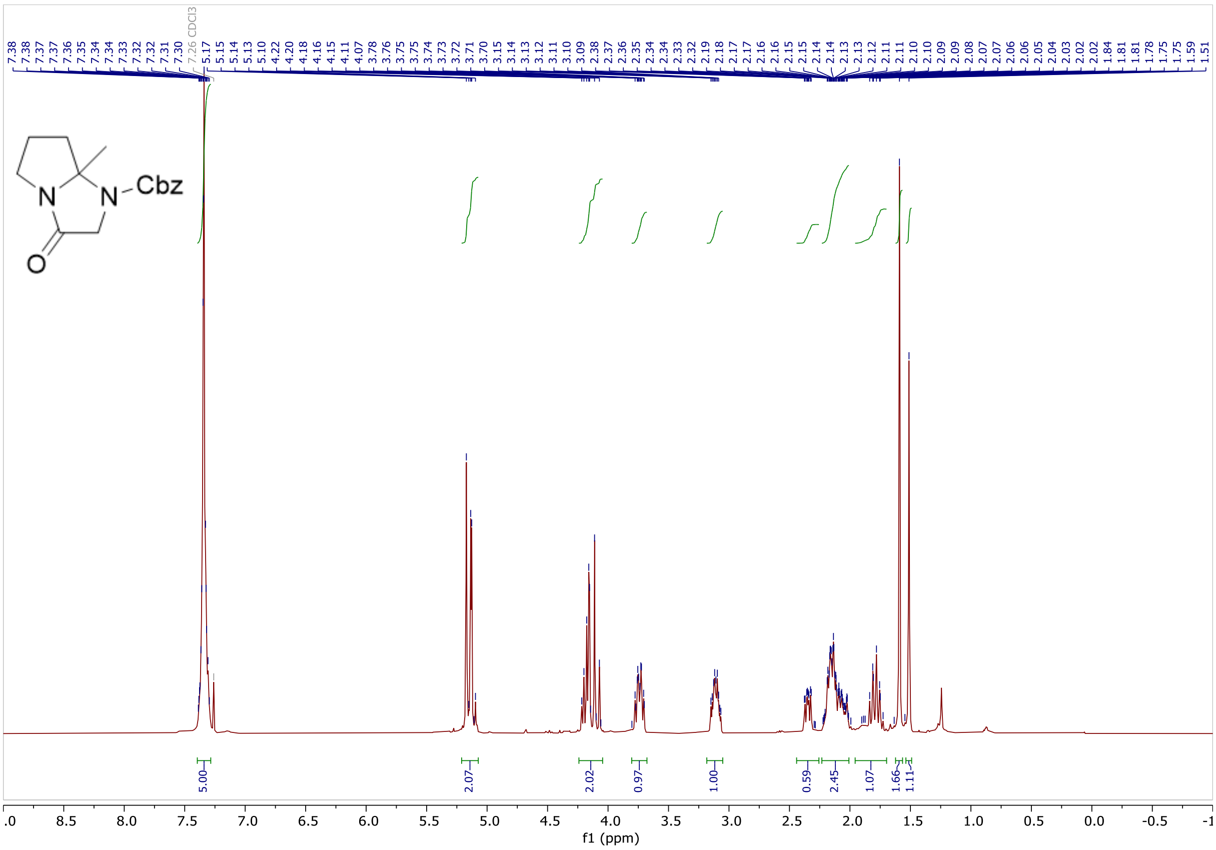
^{1}H-NMR (400 MHz, chloroform-*d*) (9f)



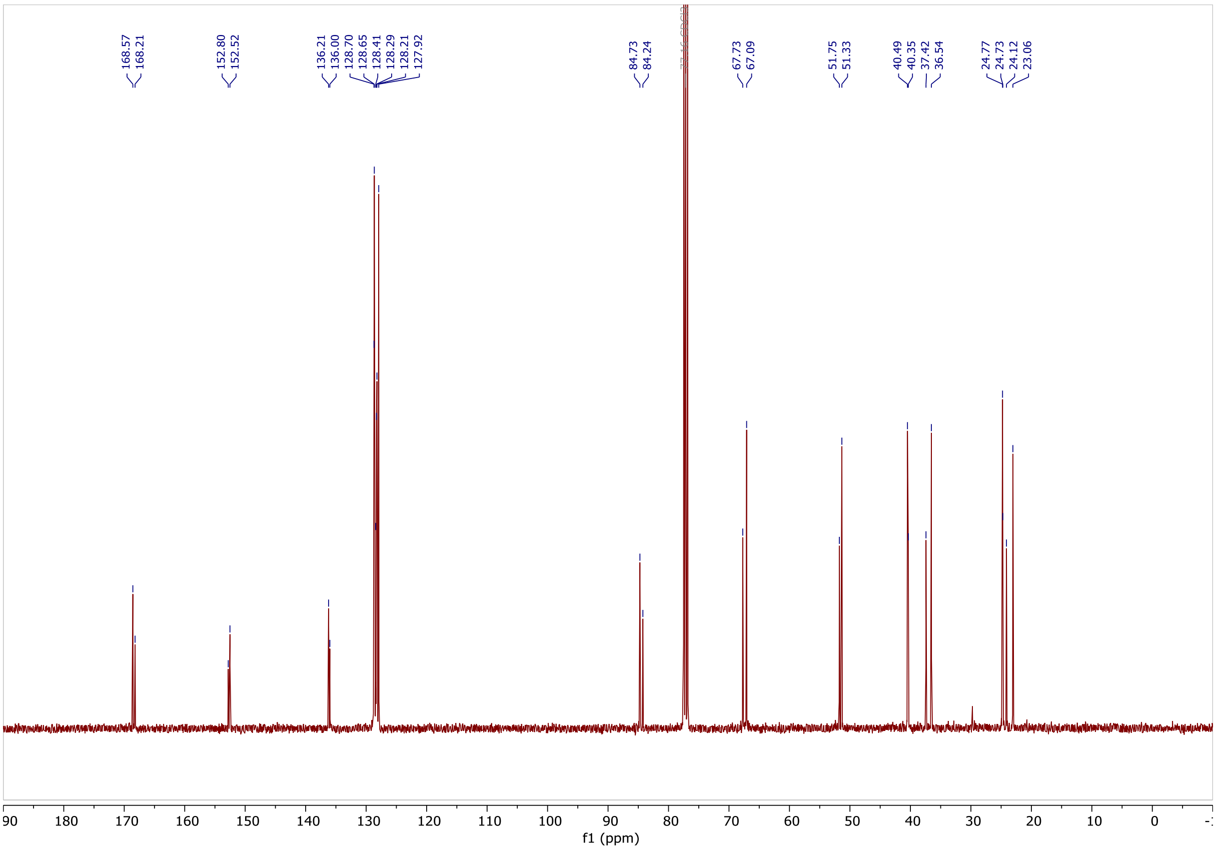
^{13}C-NMR (101 MHz, chloroform-*d*) (9f)



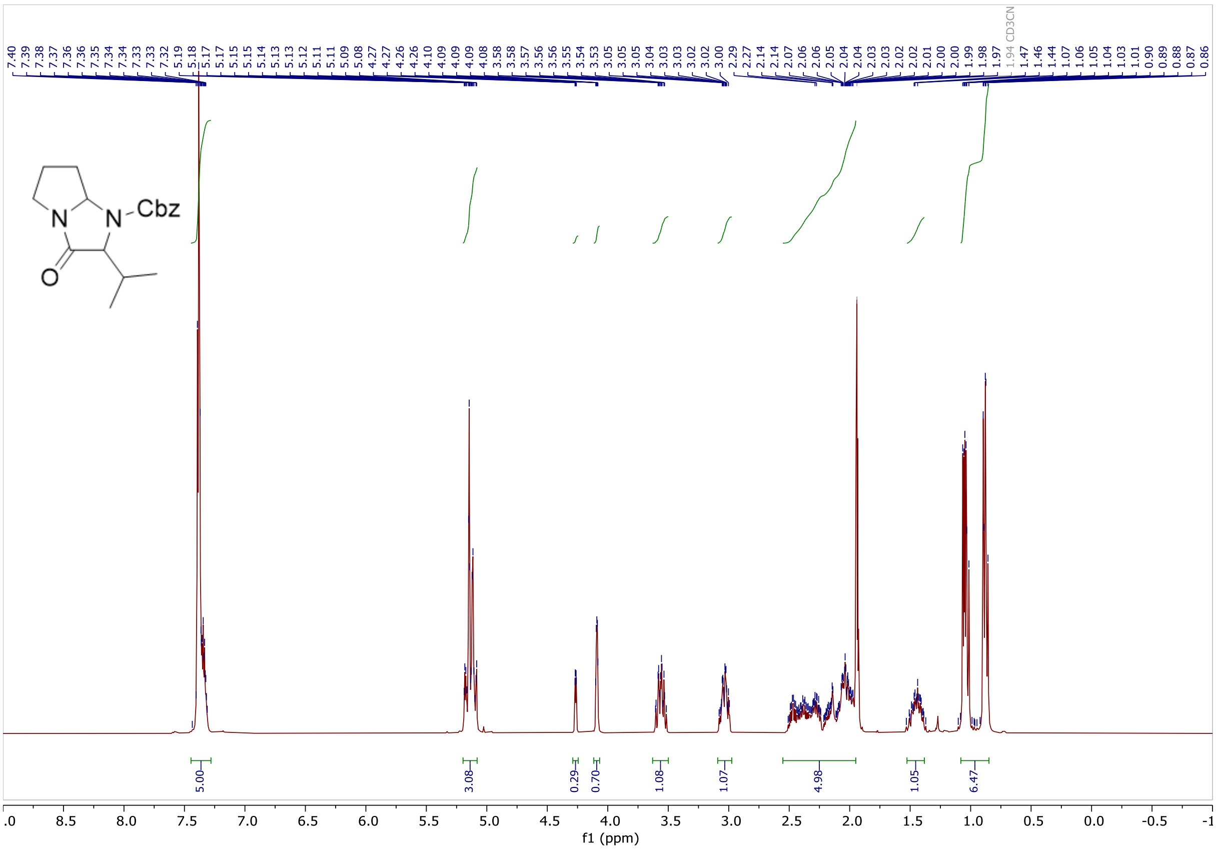
[1]H-NMR (400 MHz, chloroform-*d*) (9g)



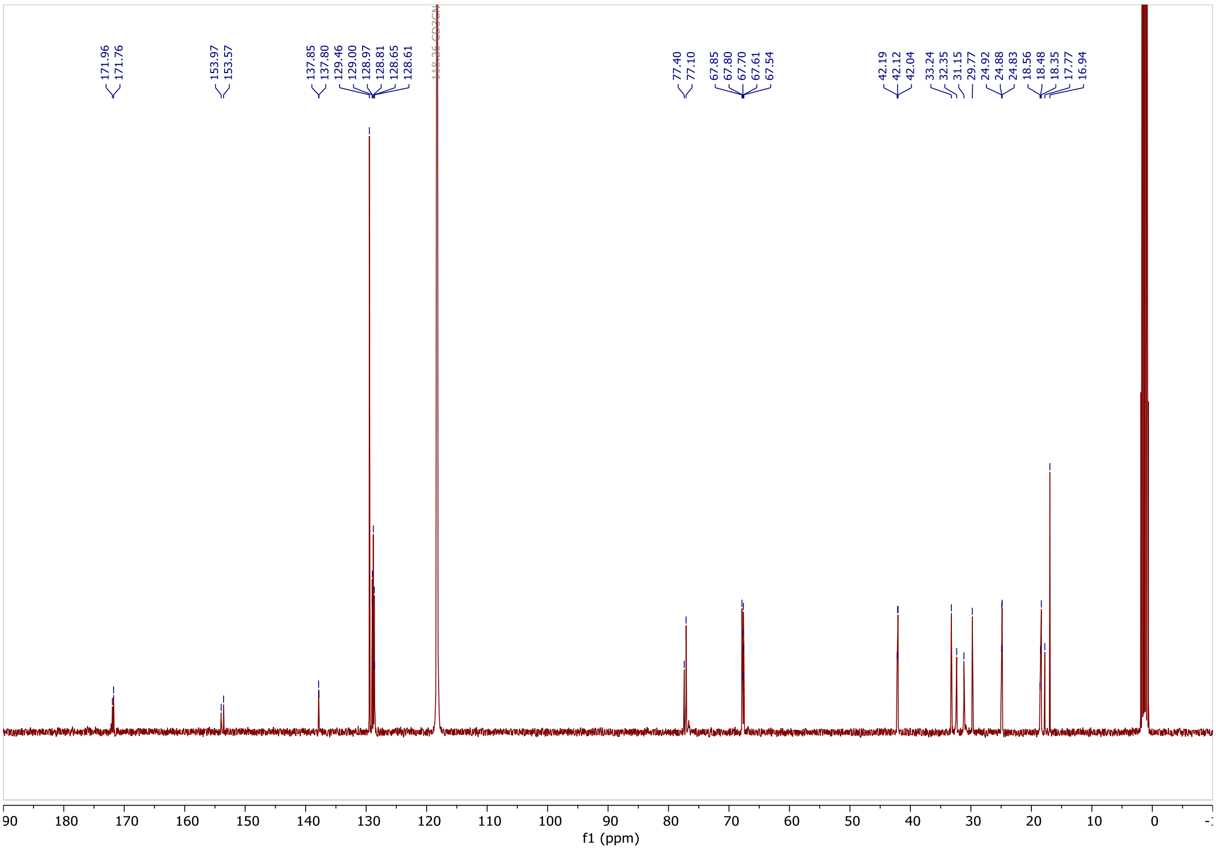
[13]C-NMR (101 MHz, chloroform-*d*) (9g)



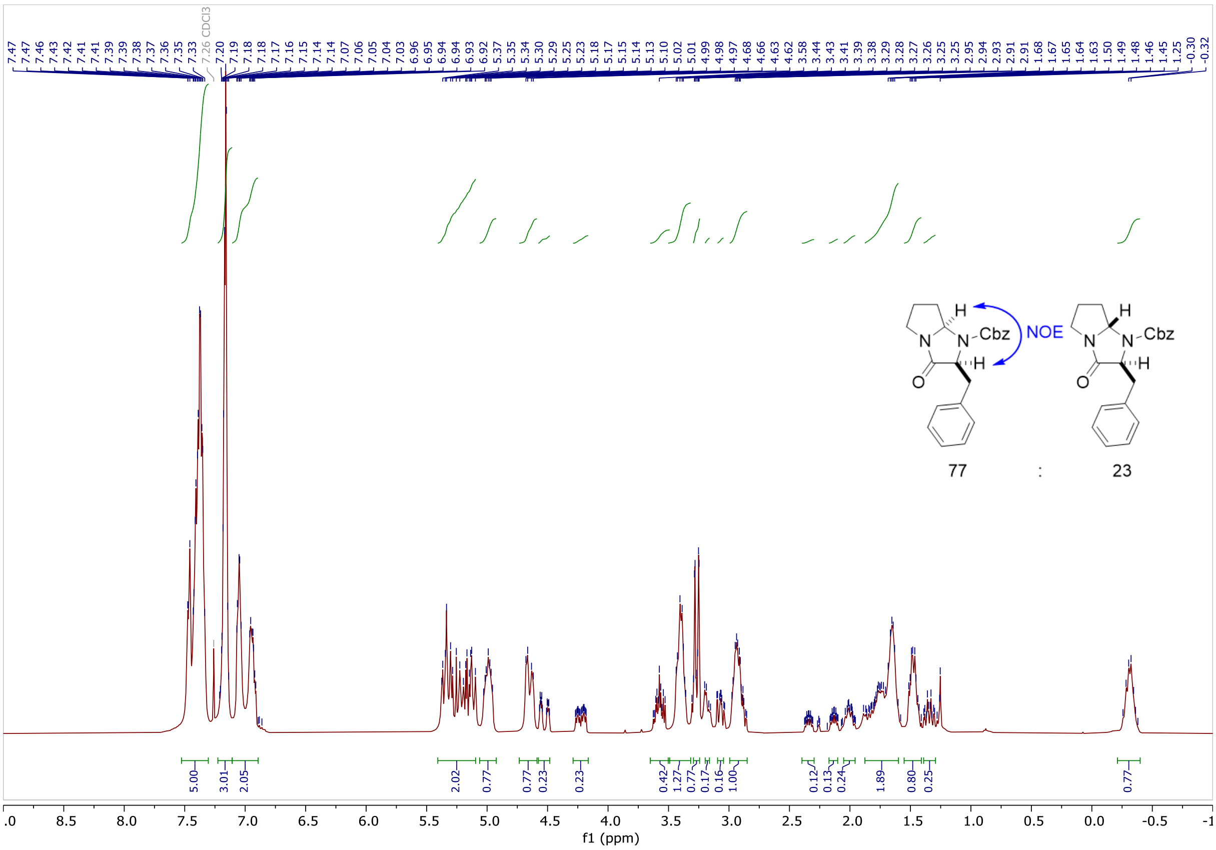
¹H-NMR (400 MHz, acetonitrile-*d*₃) (9h)



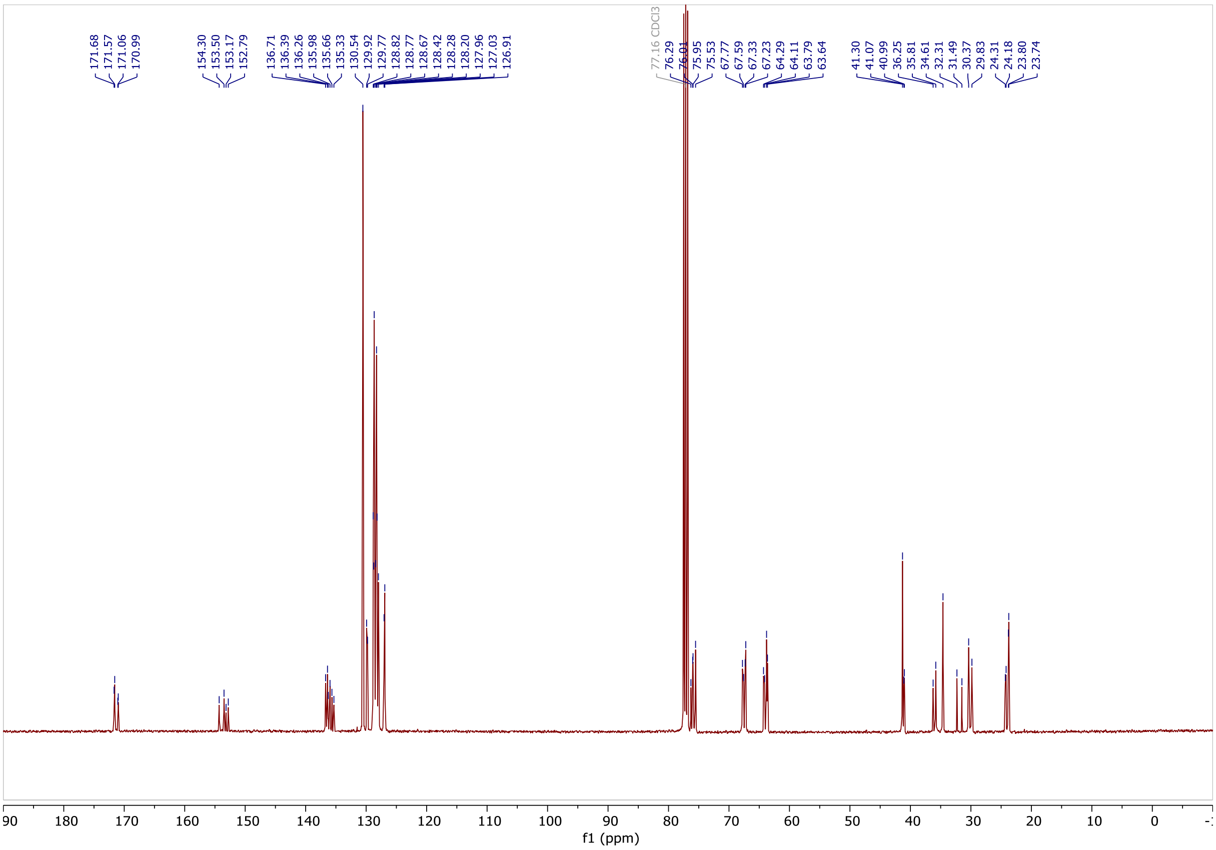
¹³C-NMR (101 MHz, acetonitrile-*d*₃) (9h)



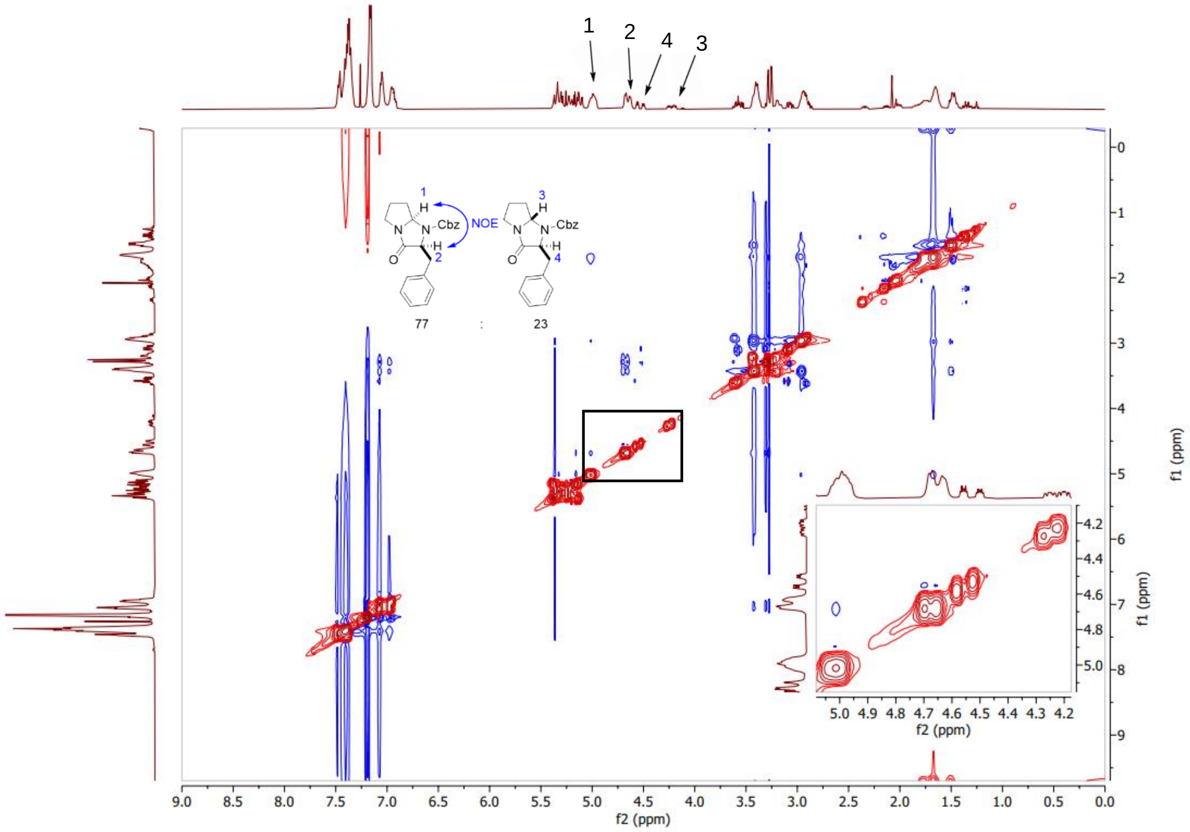
[1]H-NMR (400 MHz, chloroform-*d*) (9i) 77:23 mixture of diastereoisomers



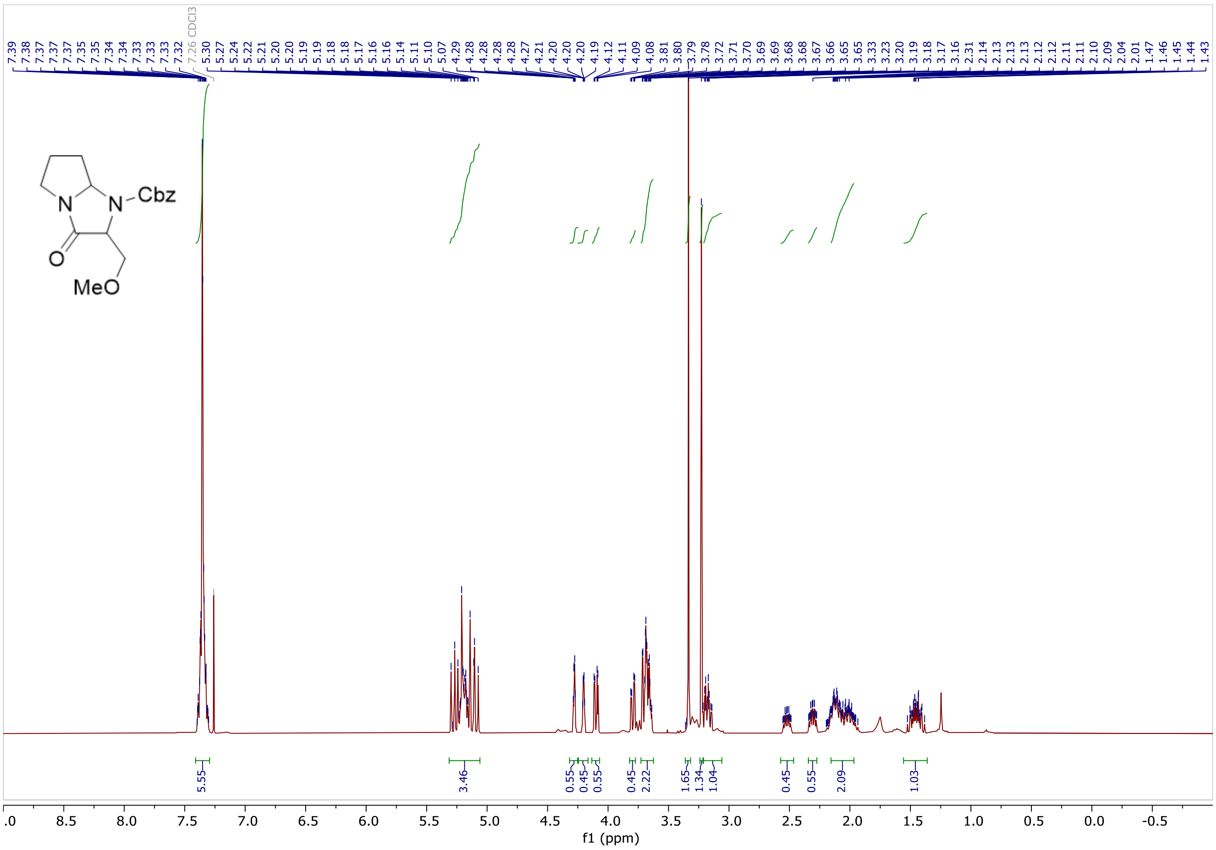
[13]C-NMR (101 MHz, chloroform-*d*) (9i)



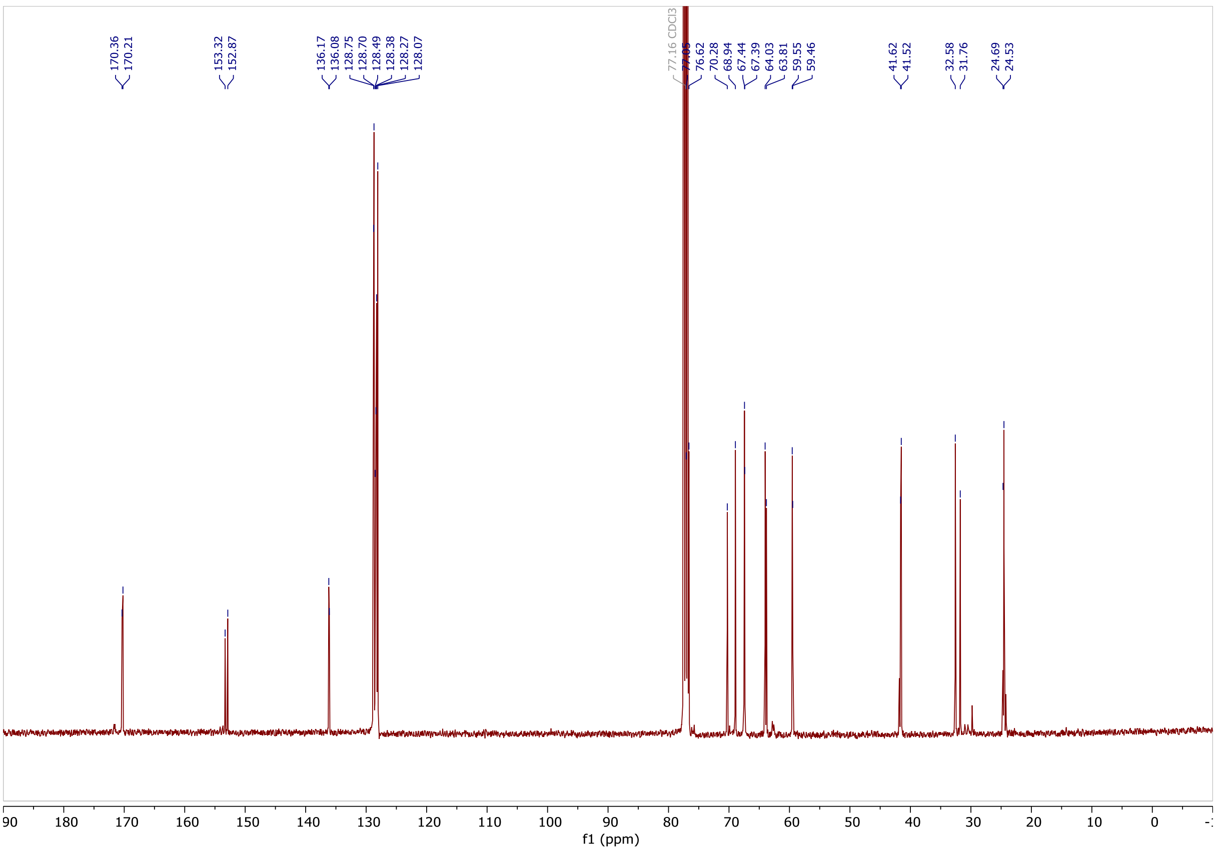
2D-NOESY (400 MHz, chloroform-*d*) (9i) 77:23 mixture of diastereoisomers



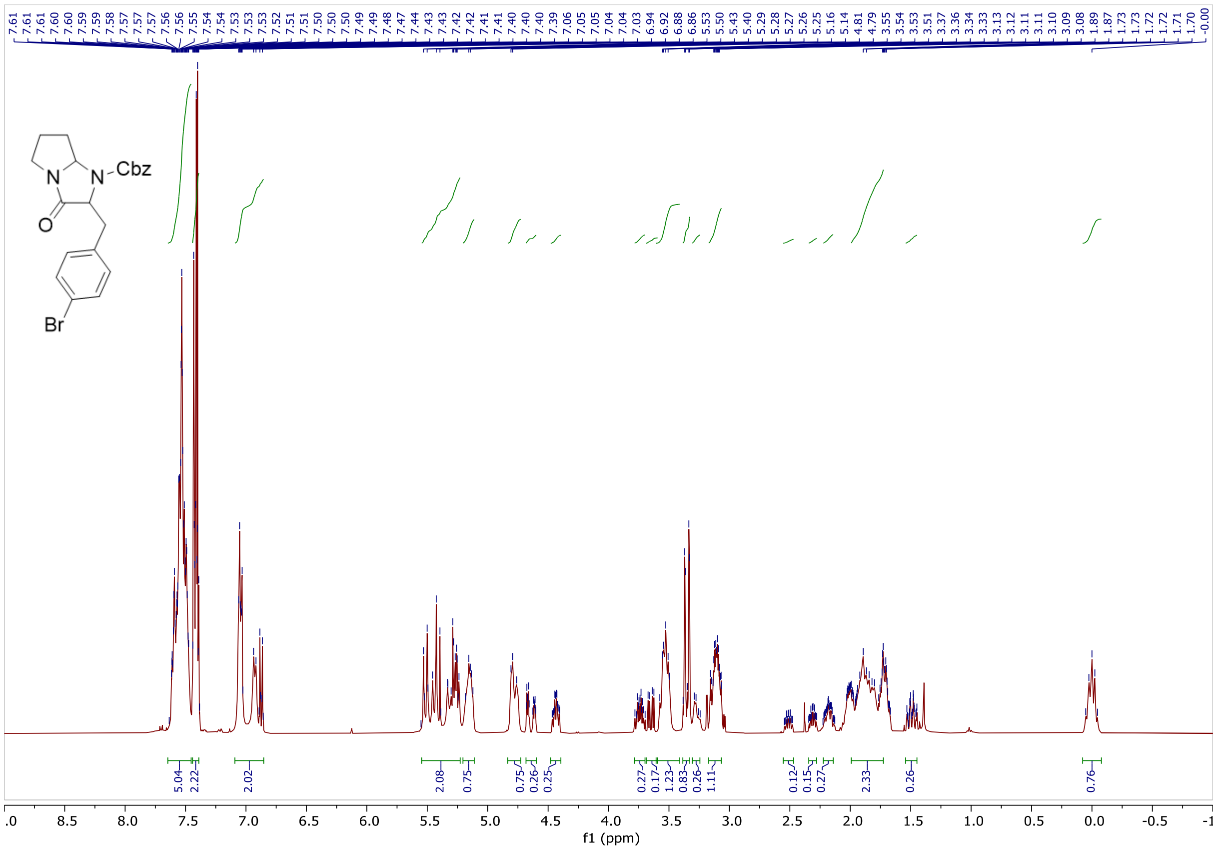
[1]H-NMR (400 MHz, chloroform-*d*) (9j)



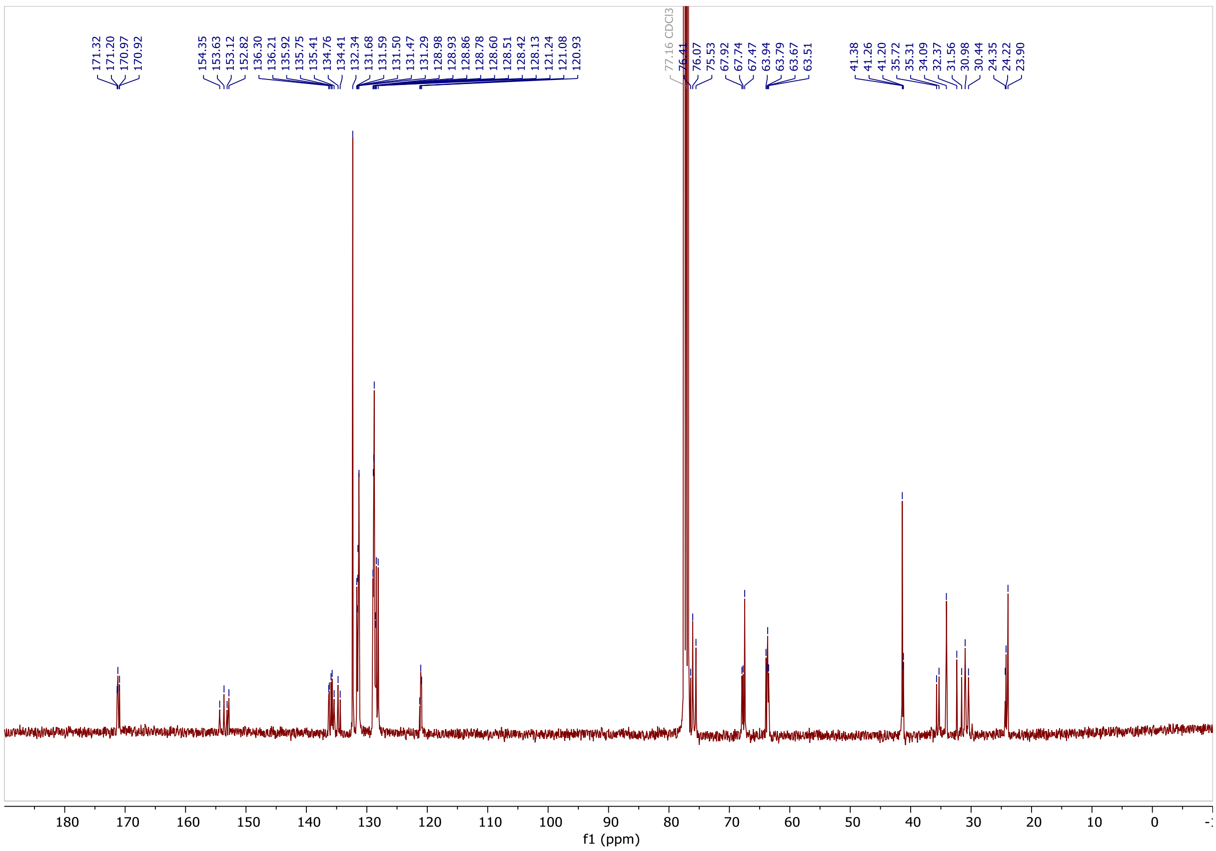
[13]C-NMR (101 MHz, chloroform-*d*) (9j)



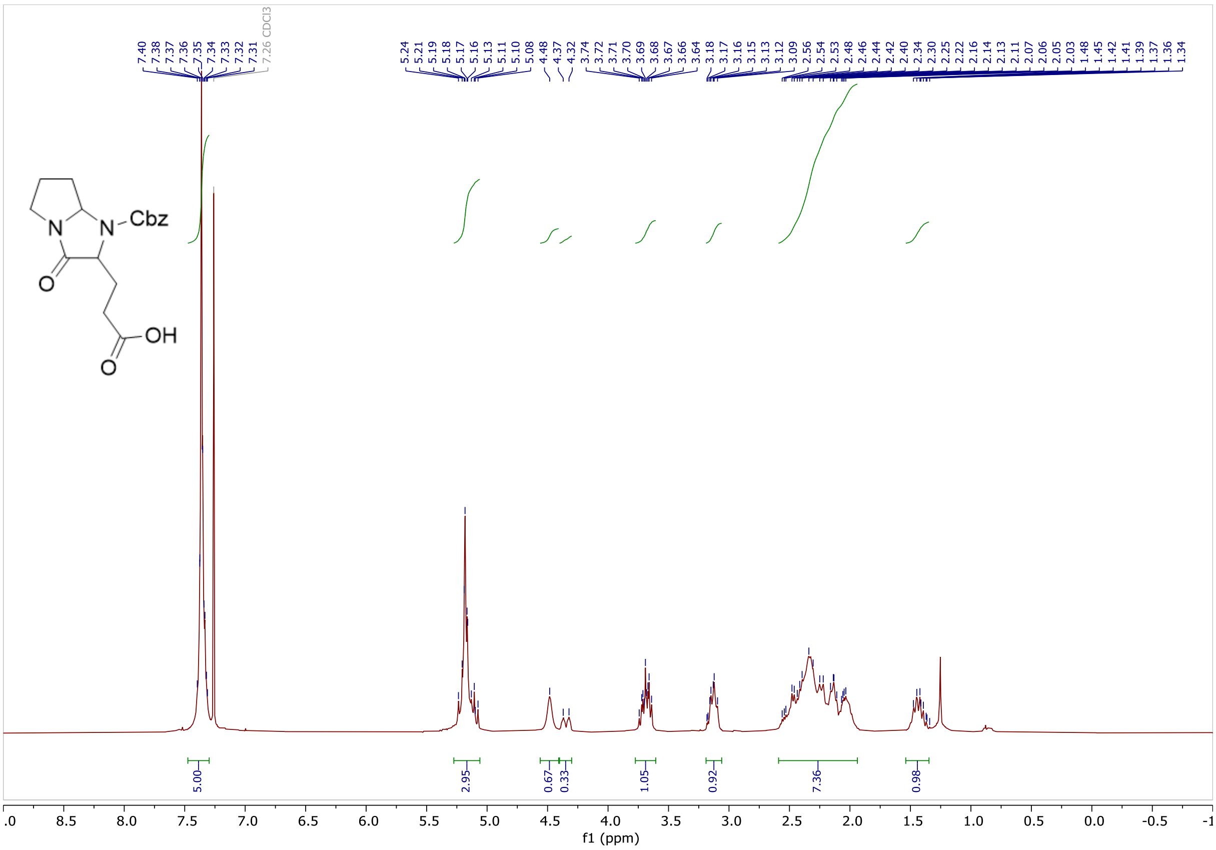
^{1}H-NMR (400 MHz, chloroform-*d*) (9k)



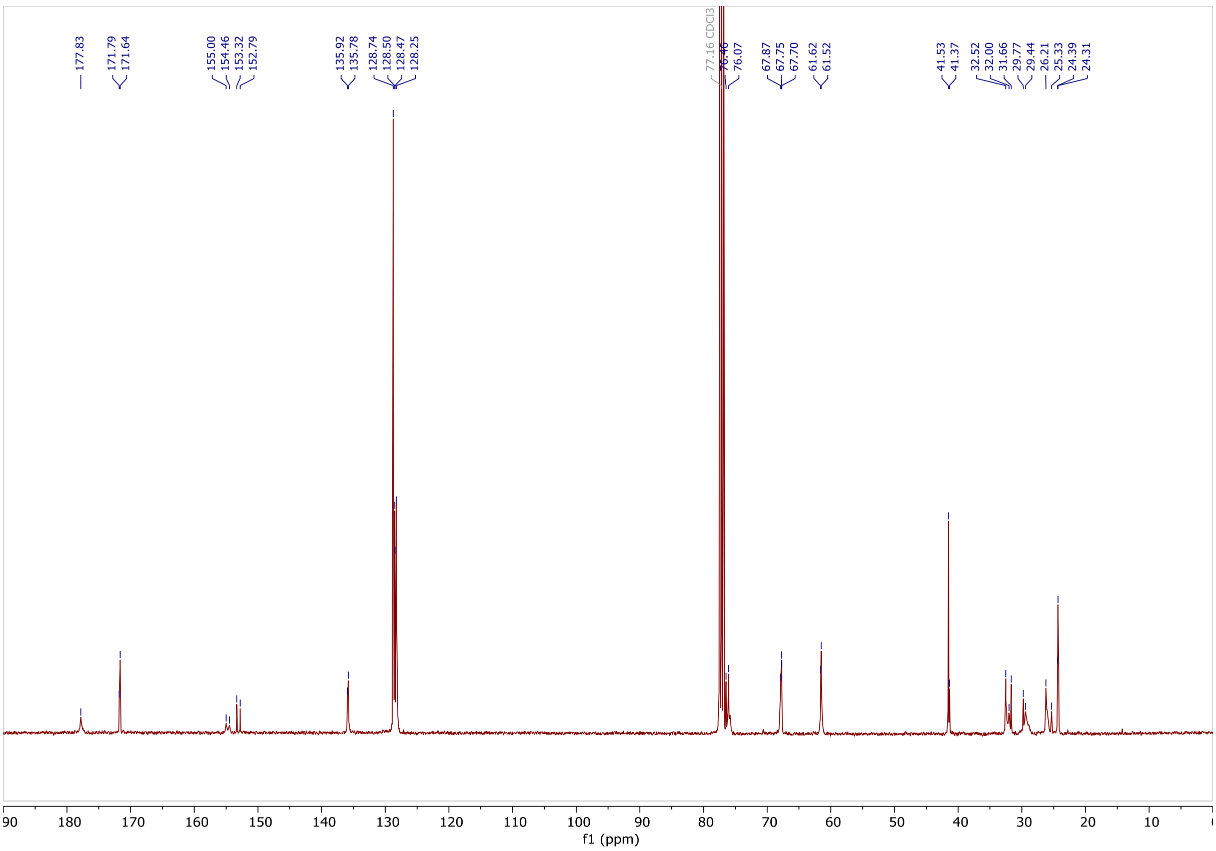
^{13}C-NMR (101 MHz, chloroform-*d*) (9k)



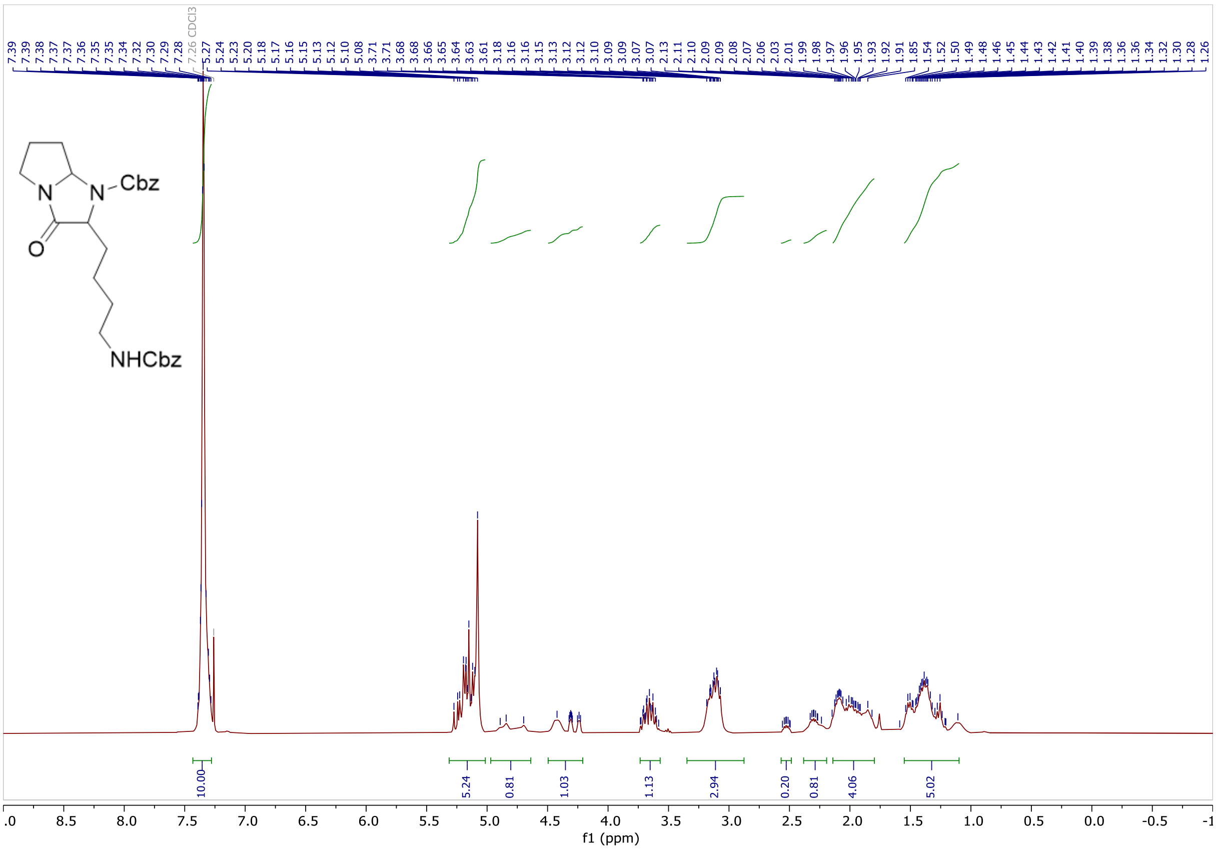
[1]H-NMR (400 MHz, chloroform-*d*) (9l)



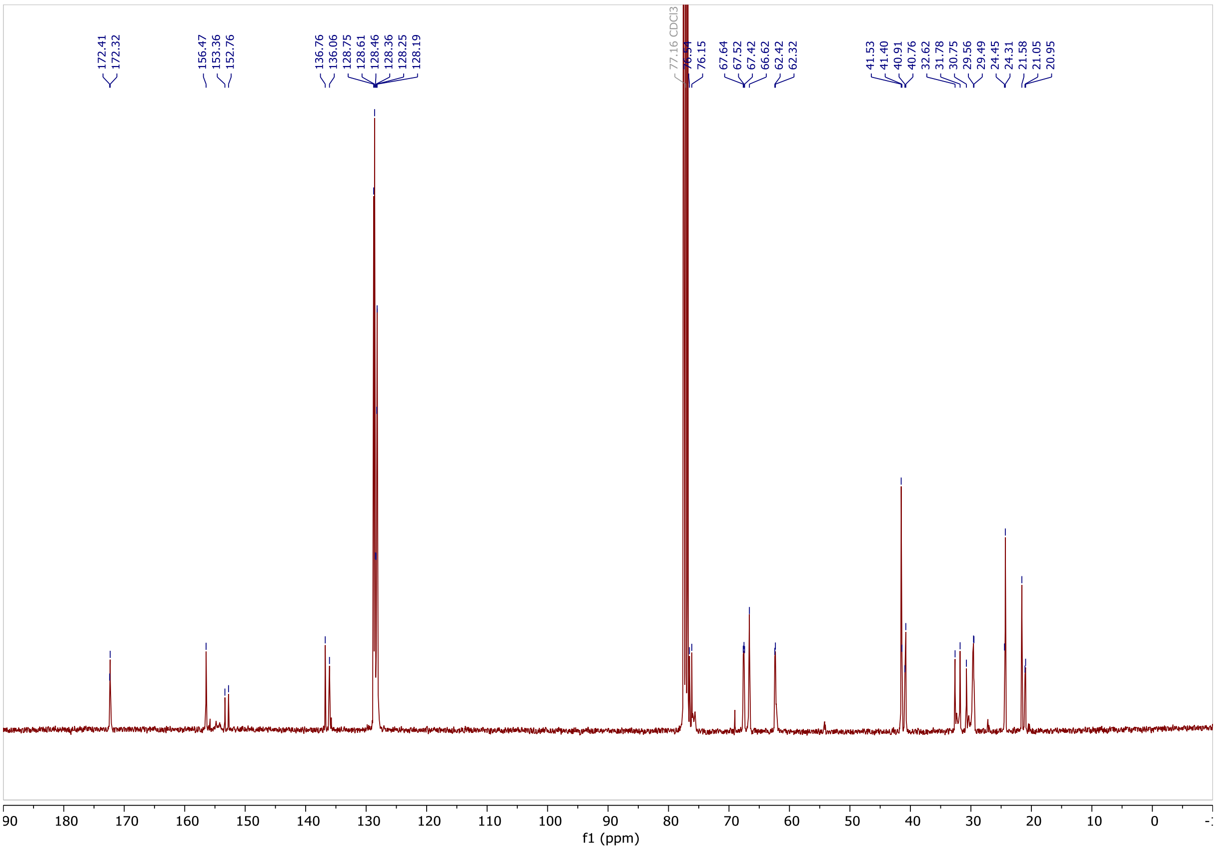
[13]C-NMR (101 MHz, chloroform-*d*) (9l)



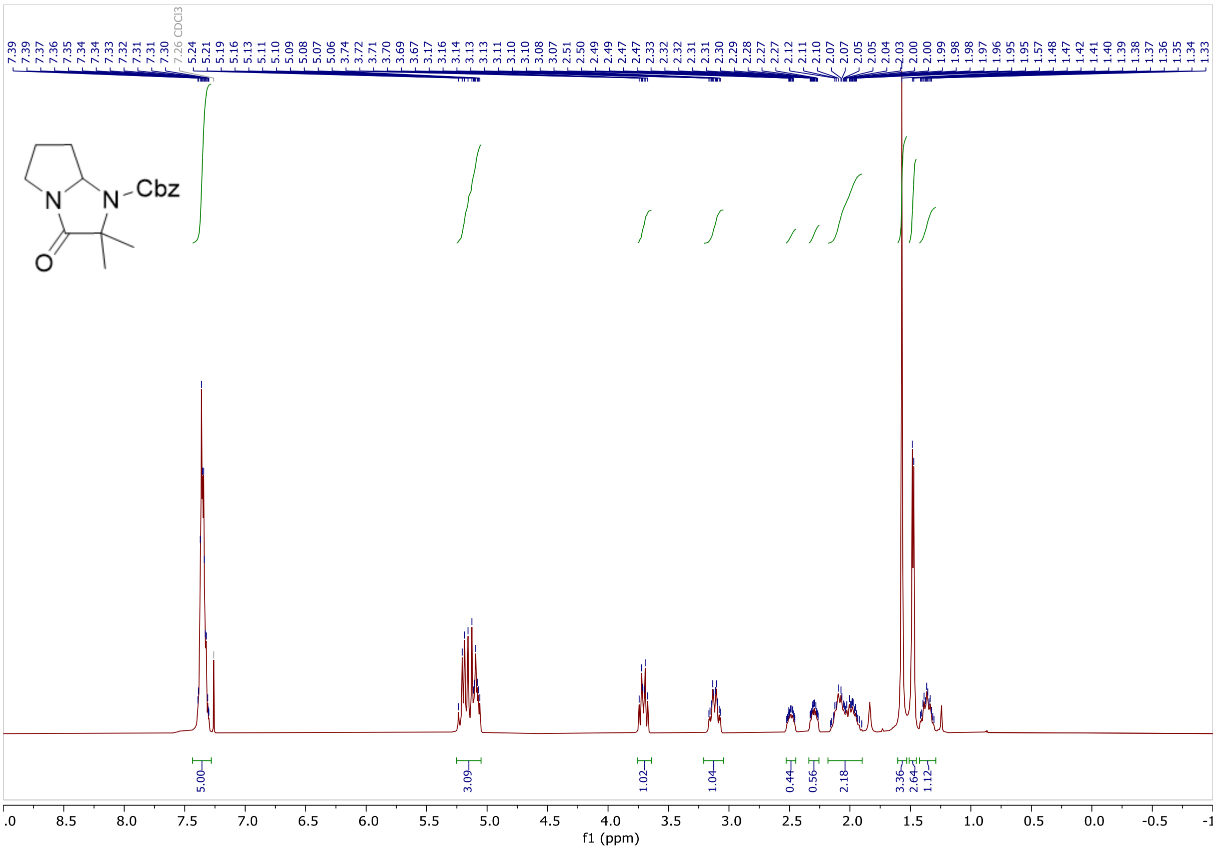
[1]H-NMR (400 MHz, chloroform-*d*) (9m)



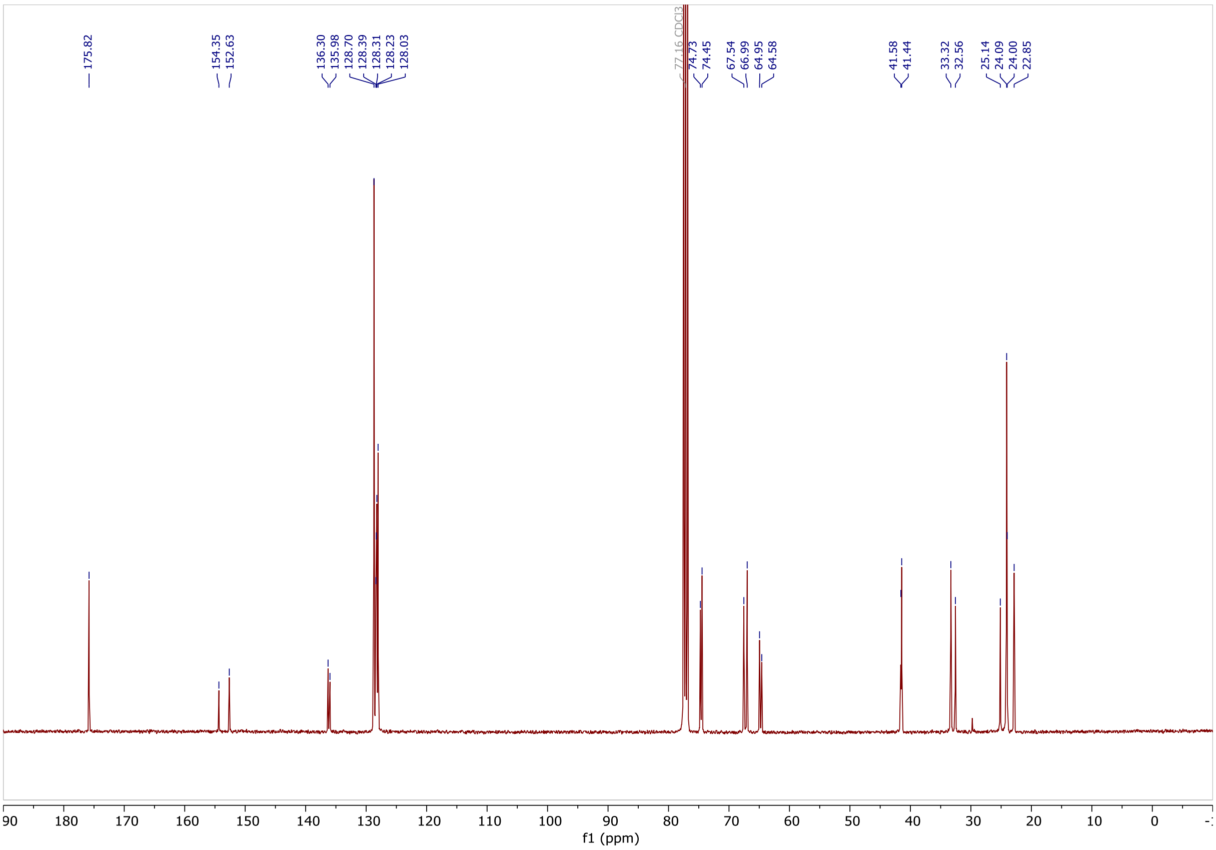
[13]C-NMR (101 MHz, chloroform-*d*) (9m)



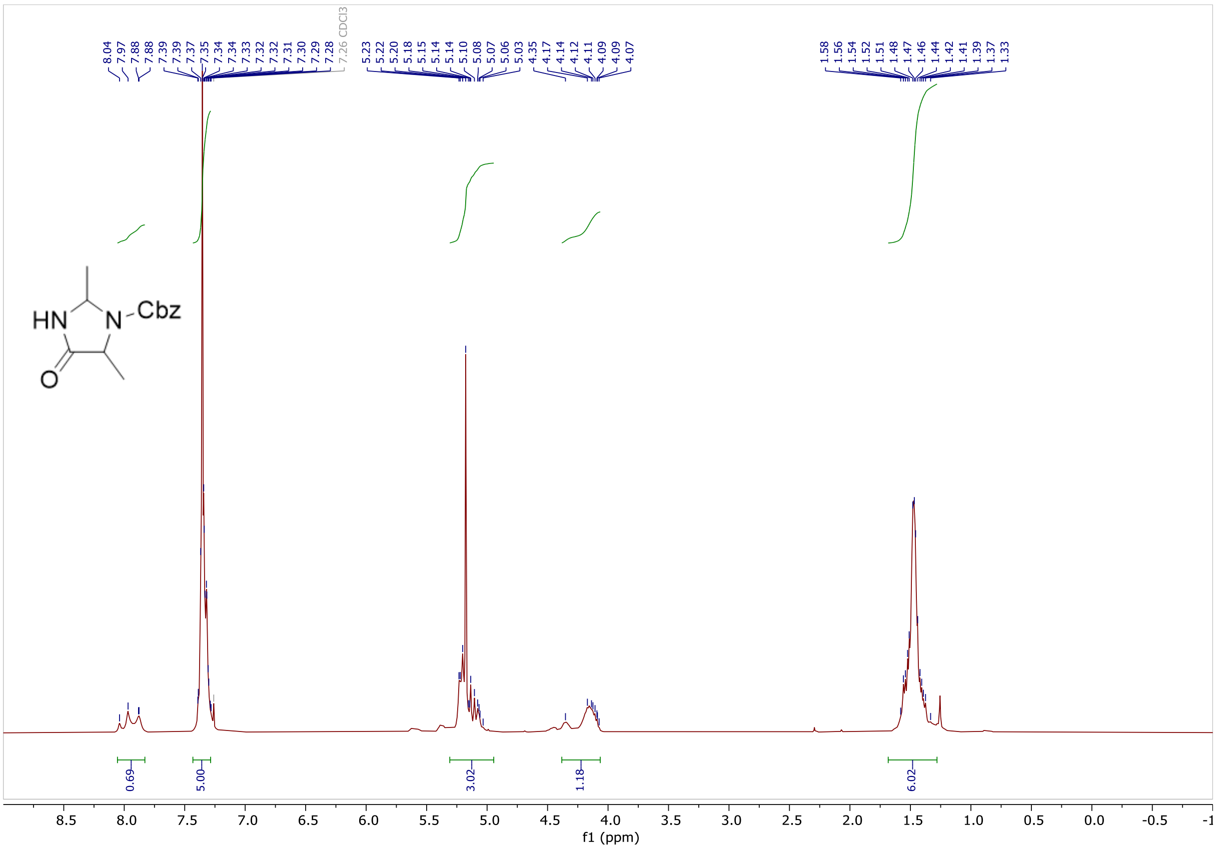
^{1}H-NMR (400 MHz, chloroform-*d*) (9n)



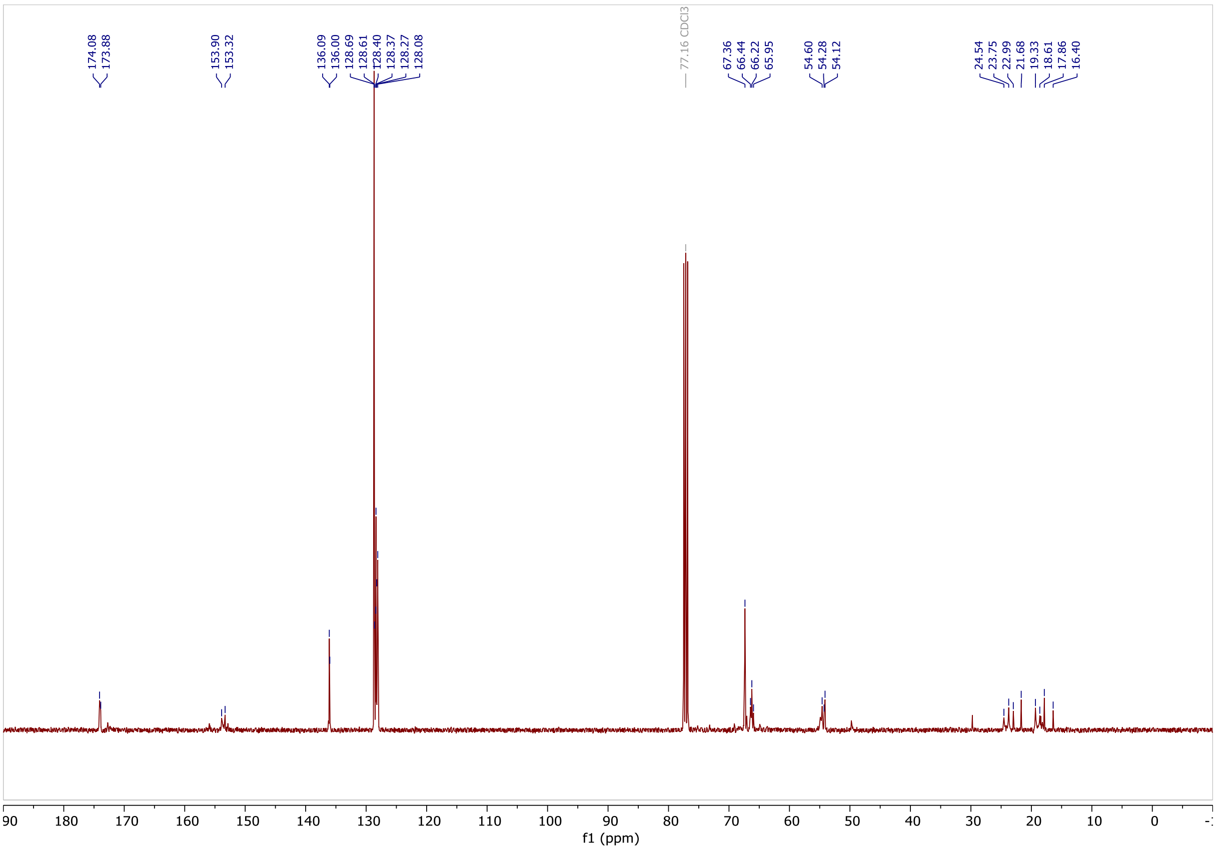
^{13}C-NMR (101 MHz, chloroform-*d*) (9n)



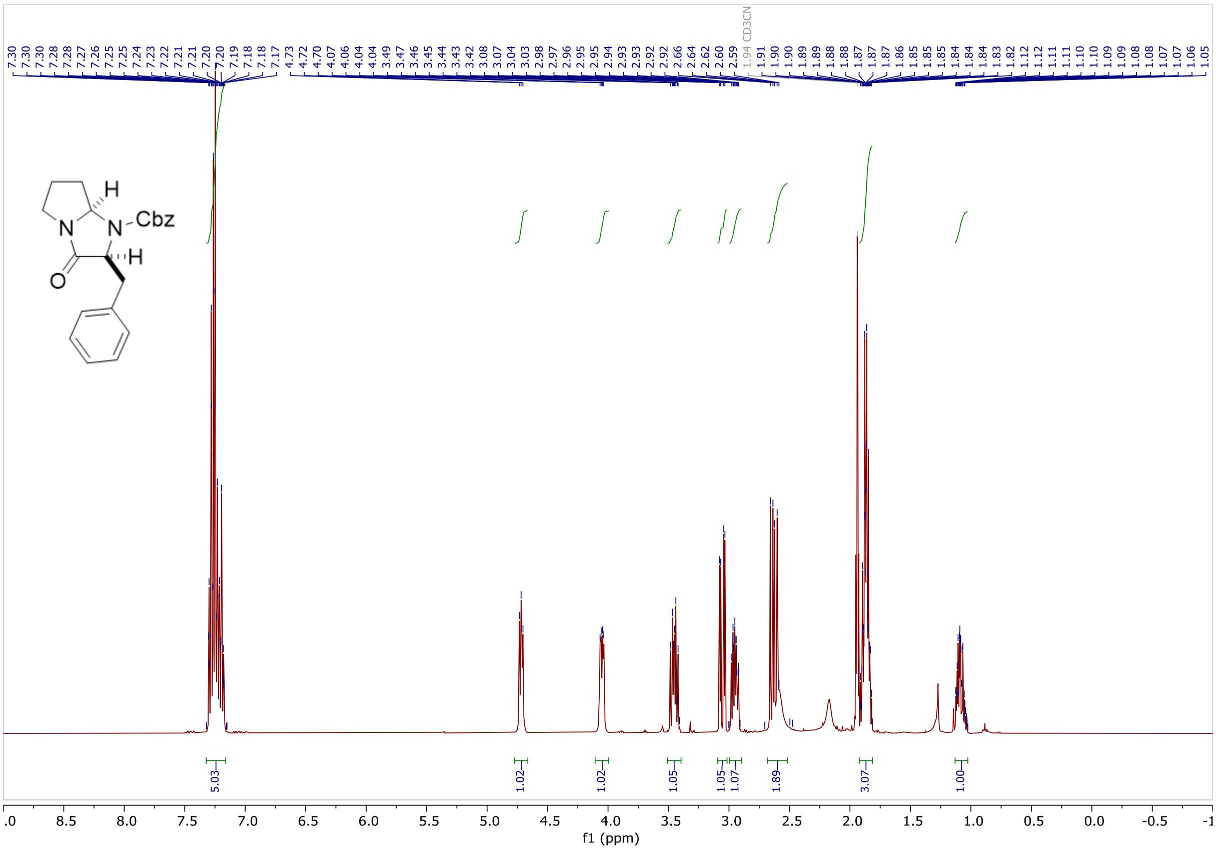
[1]H-NMR (400 MHz, chloroform-*d*) (9o)



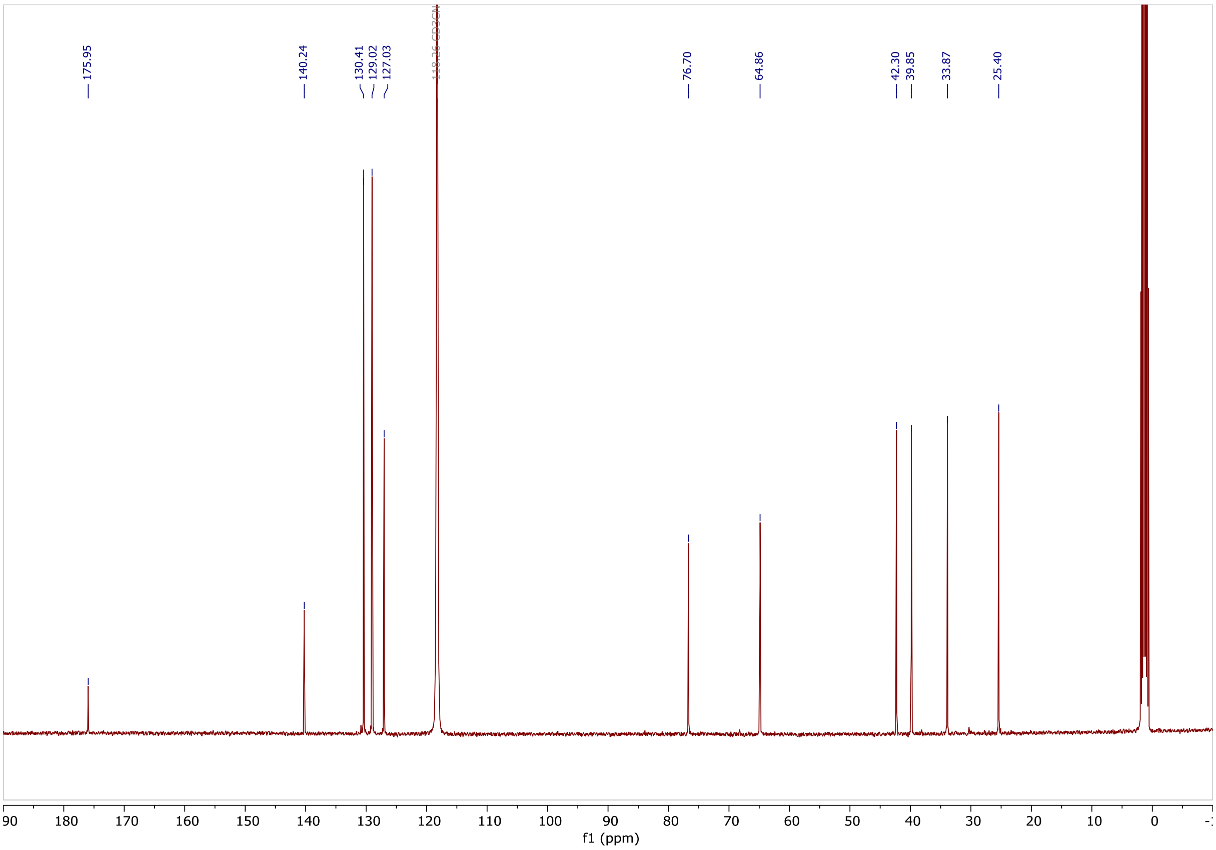
[13]C-NMR (101 MHz, chloroform-*d*) (9o)



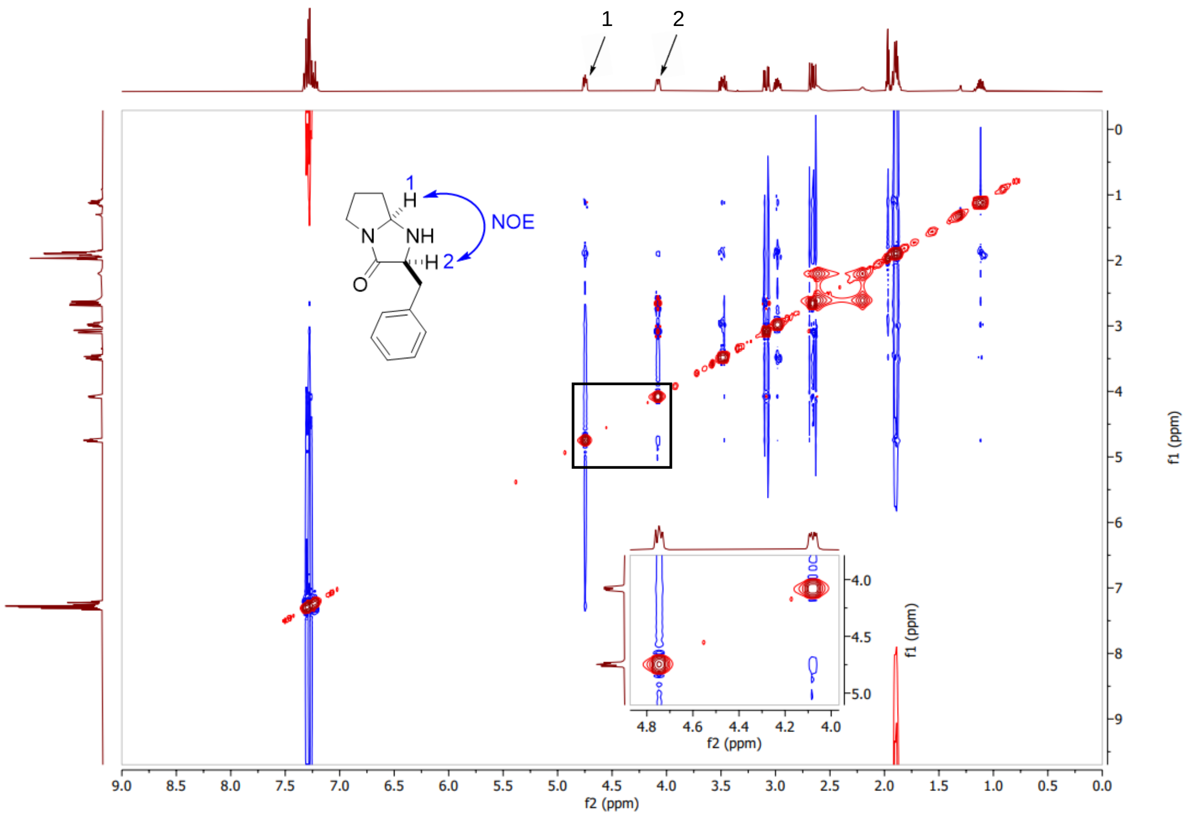
[1]H-NMR (400 MHz, acteonitrile-*d₃*) (11) Major cis- diastereoisomer



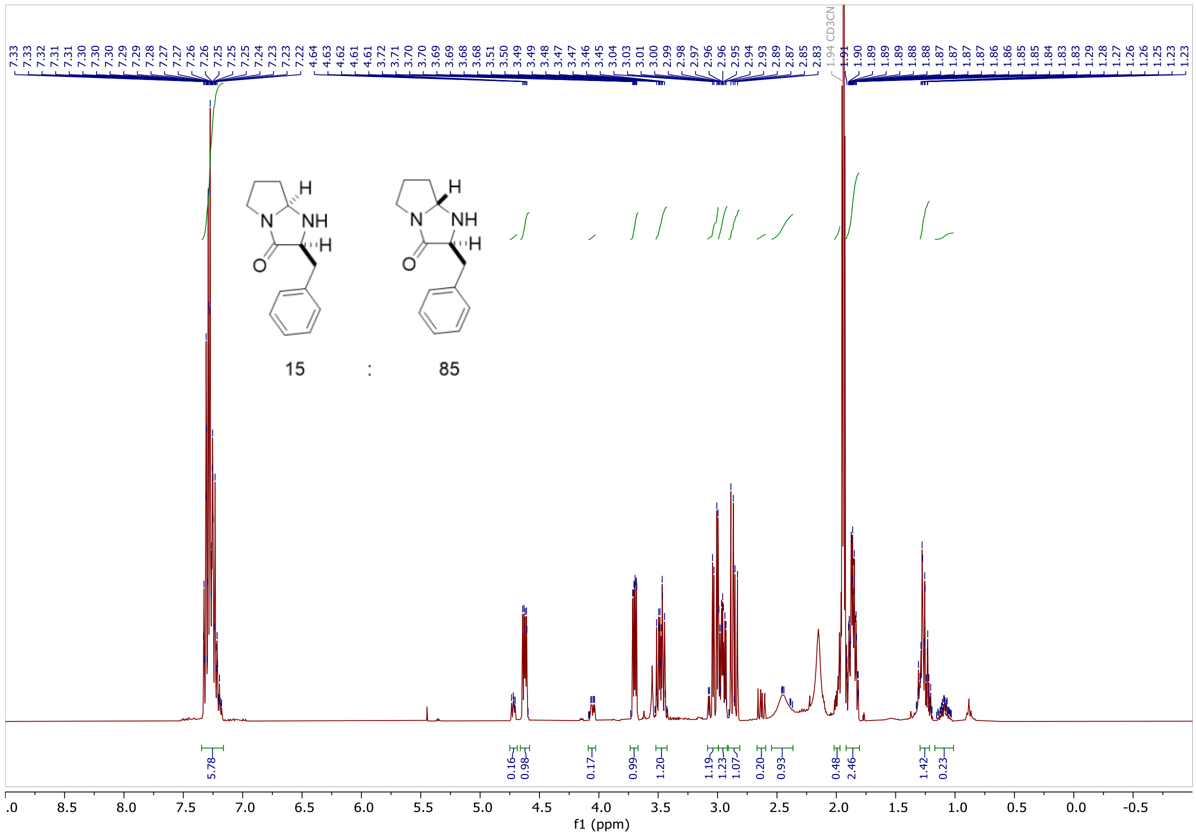
[13]C-NMR (101 MHz, acteonitrile-*d₃*) (11) Major cis- diastereoisomer



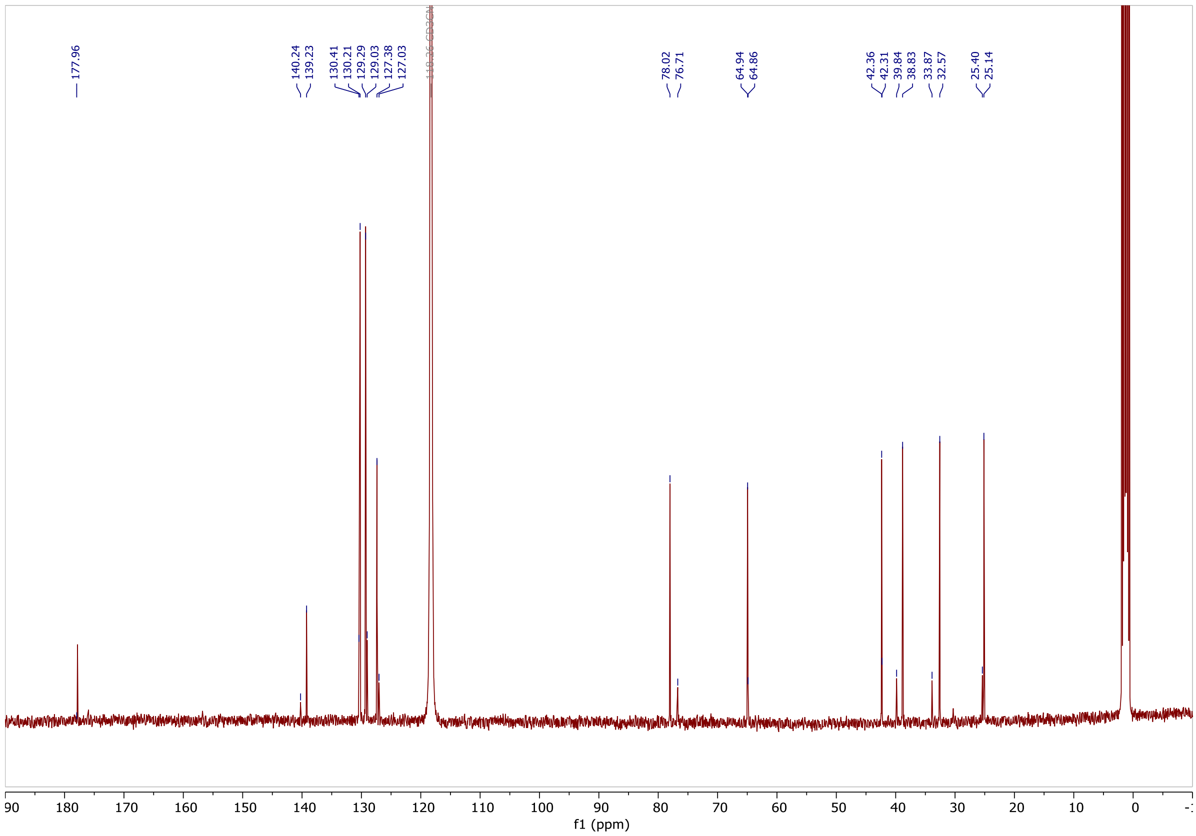
2D-NOESY (400 MHz, acteonitrile-*d₃*) (11) Major cis- diastereoisomer



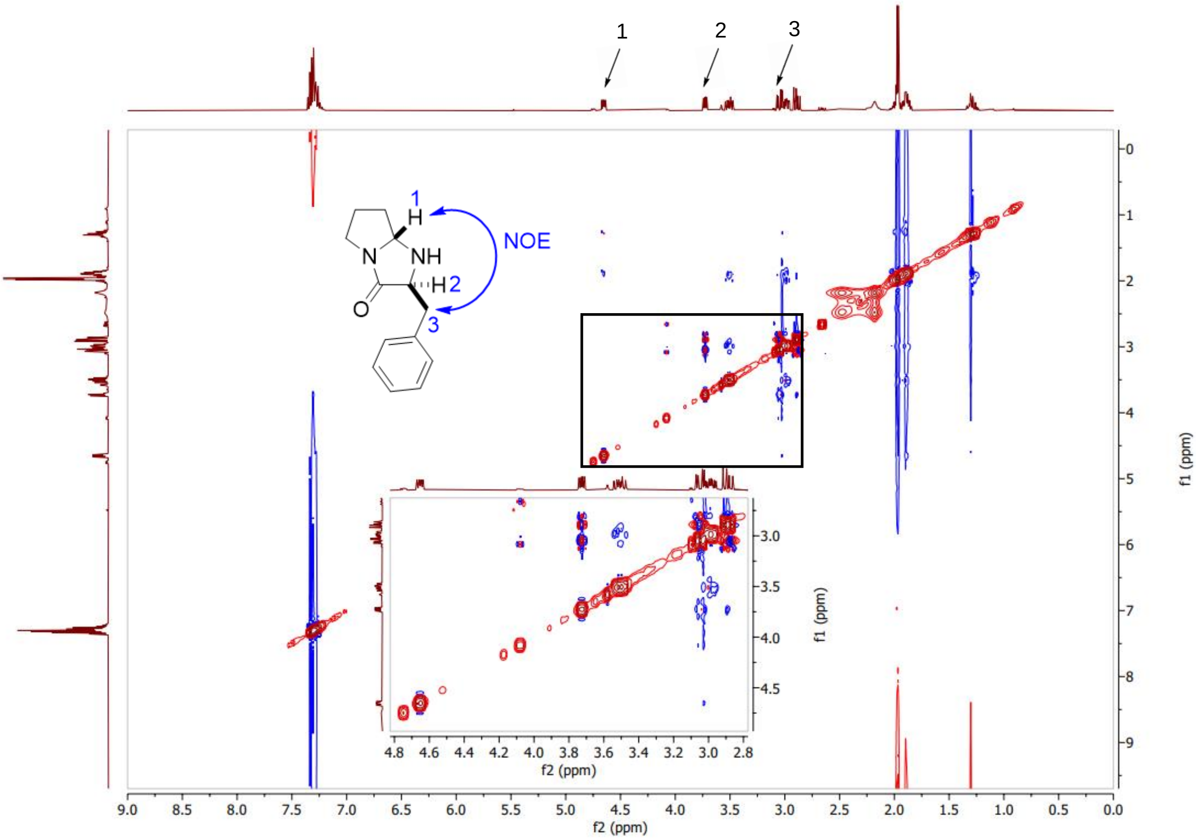
^{1}H-NMR (400 MHz, acteonitrile-d_3) (11) 85:15 mixture of diastereoisomers (trans:cis)



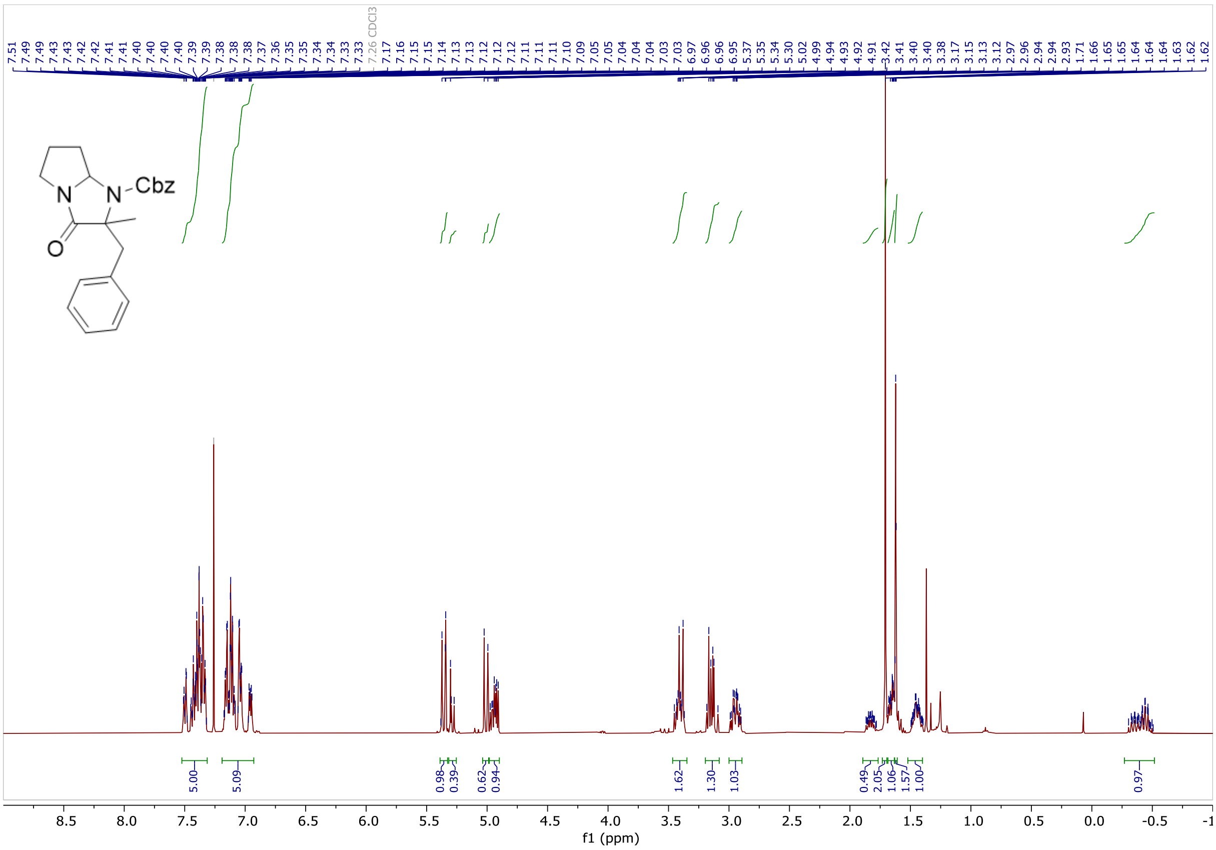
^{13}C-NMR (101 MHz, acteonitrile-d_3) (11) 85:15 mixture of diastereoisomers



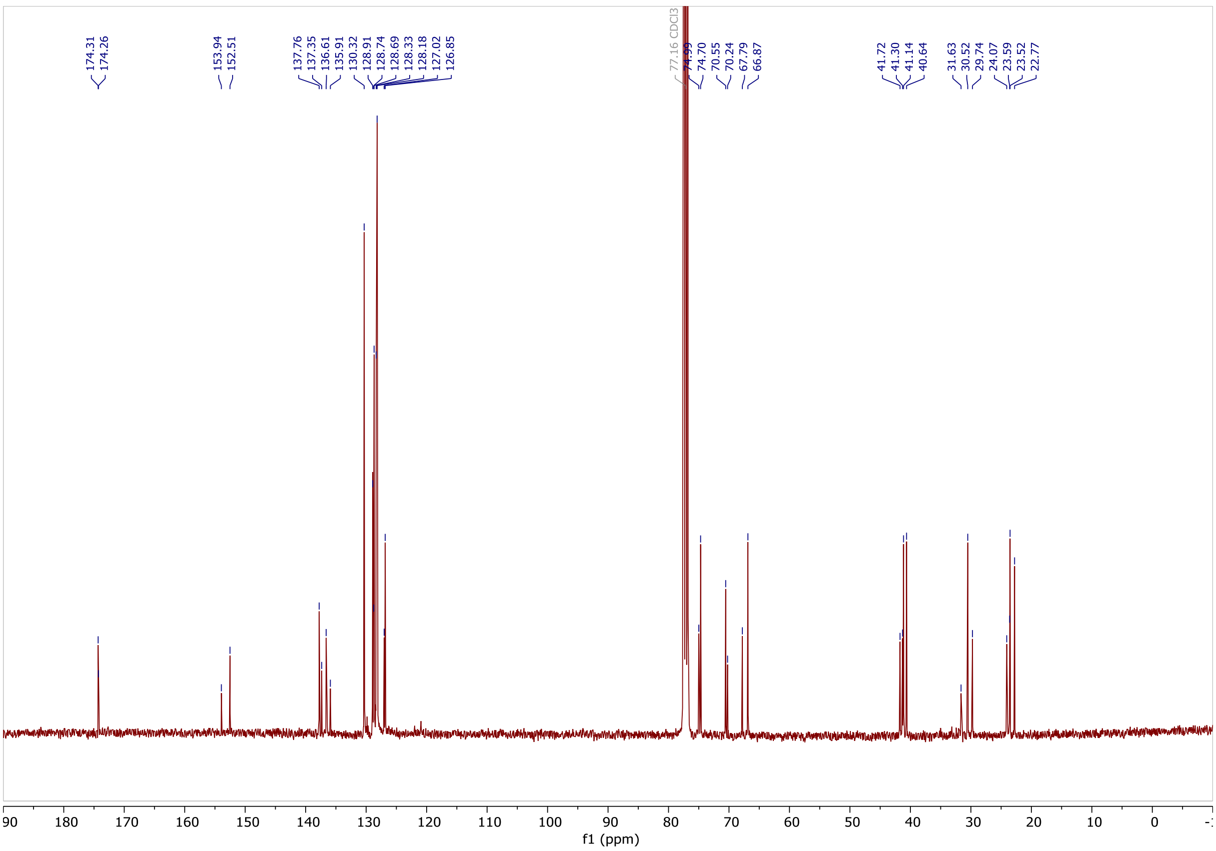
2D-NOESY (400 MHz, acteonitrile-d_3) (11) 85:15 mixture of diastereoisomers (trans:cis)



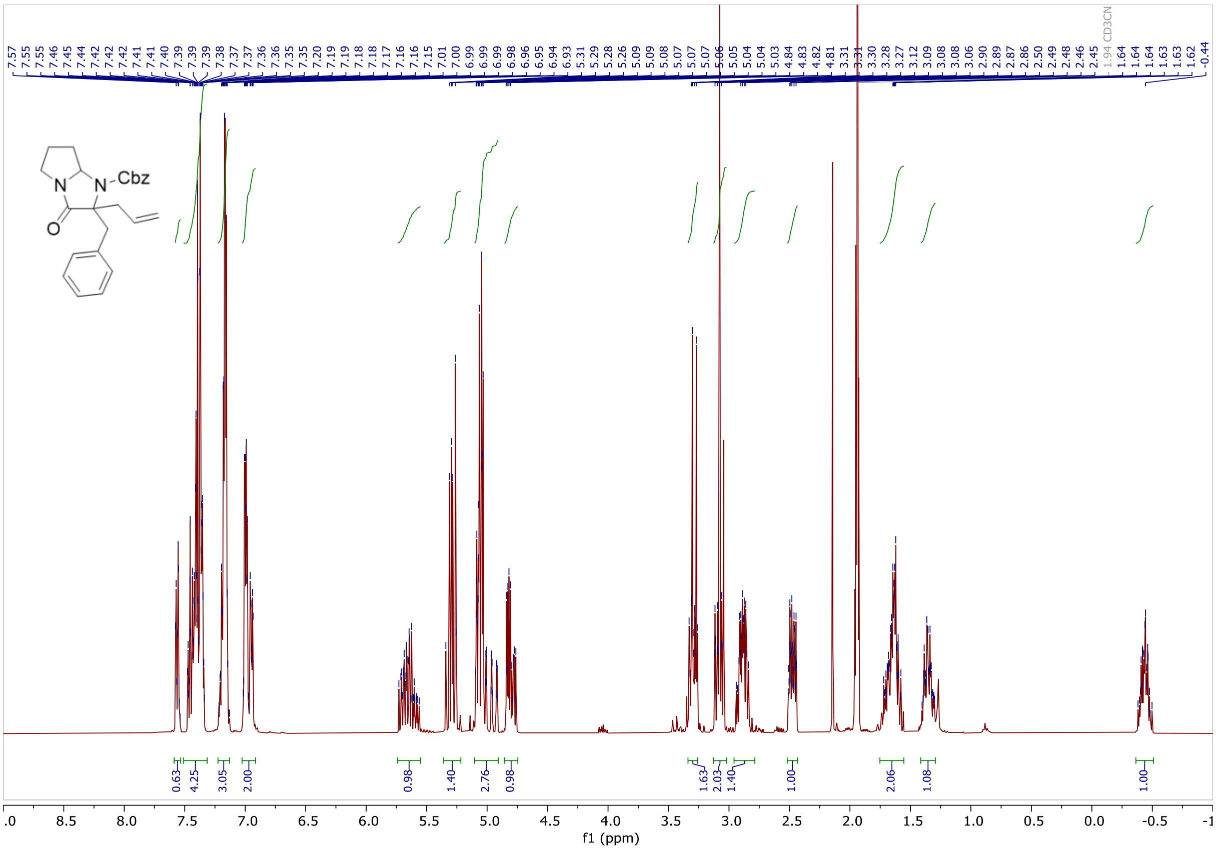
[1]H-NMR (400 MHz, chloroform-*d*) (12)



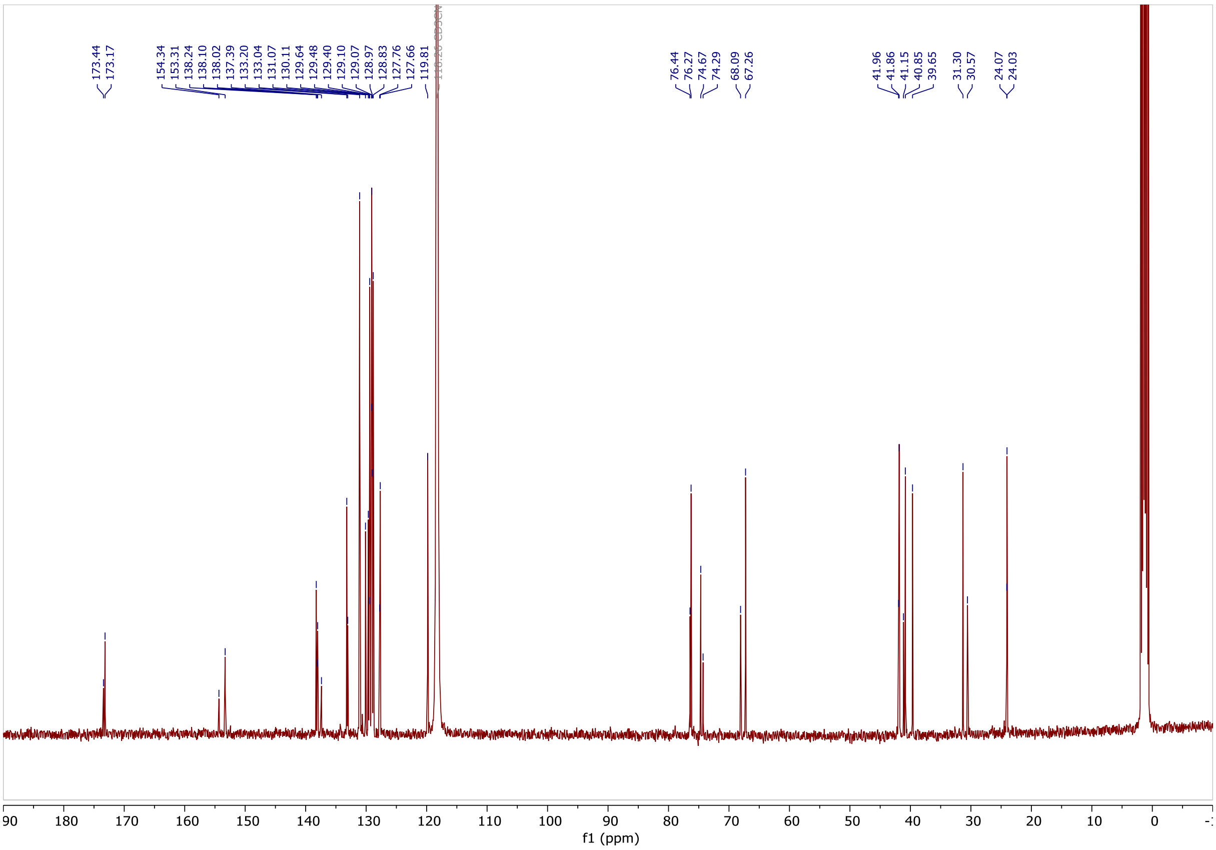
[13]C-NMR (101 MHz, chloroform-*d*) (12)



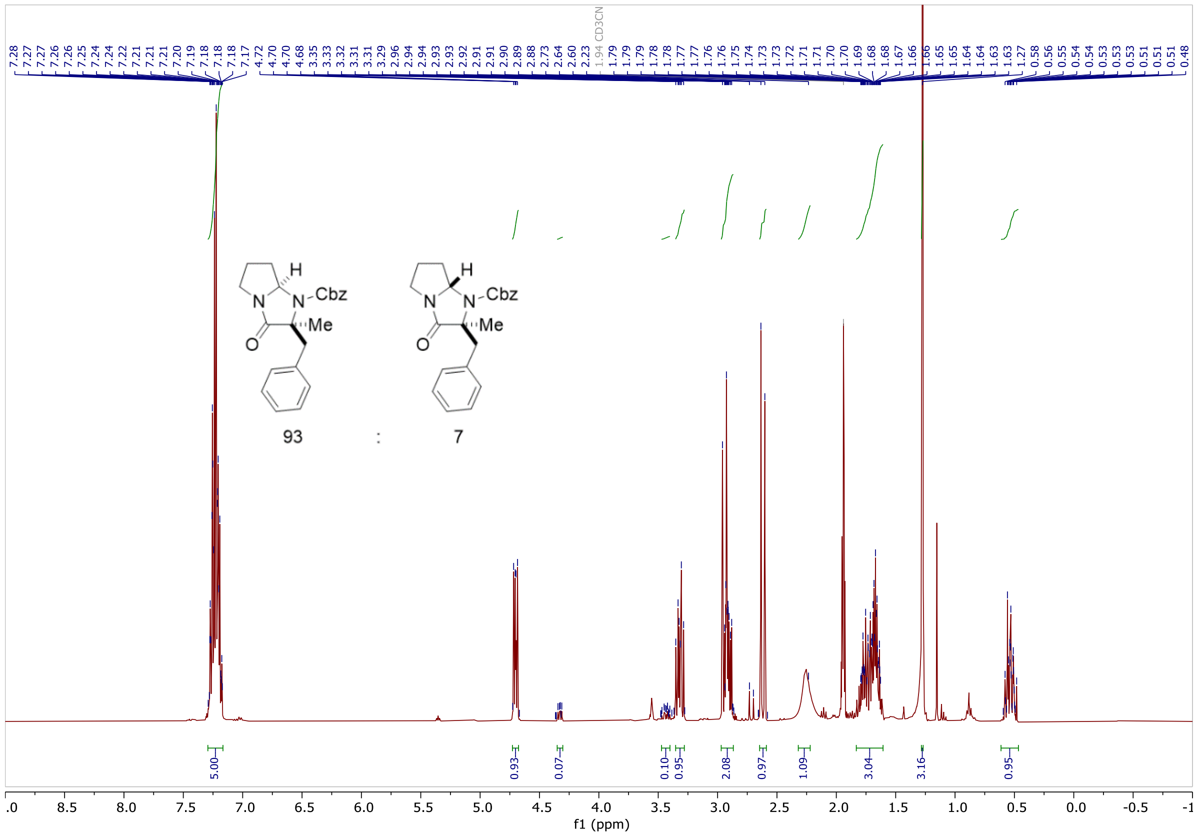
^{1}H-NMR (400 MHz, acteonitrile-d_3) (13)



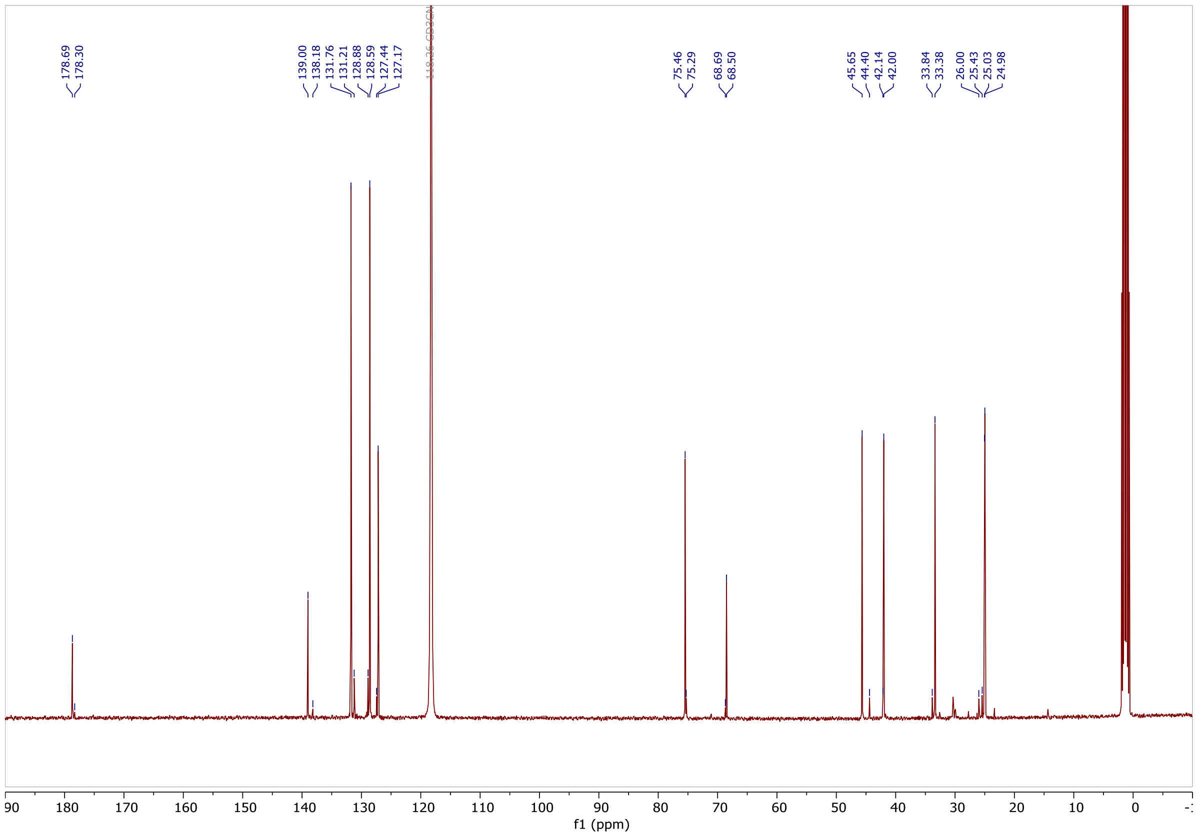
^{13}C-NMR (101 MHz, acteonitrile-d_3) (13)



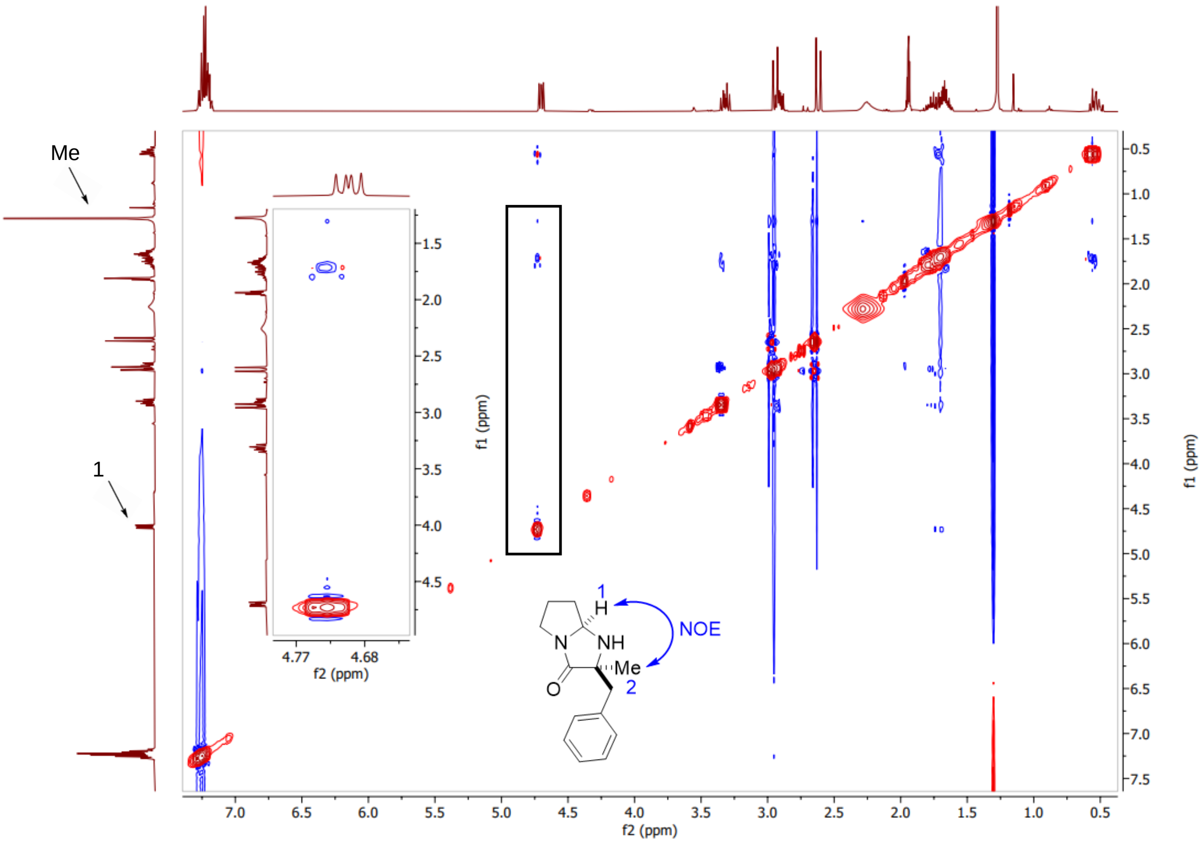
^{1}H-NMR (400 MHz, acteonitrile-d_3) (14) 93:7 mixture of diastereoisomers (cis:trans)



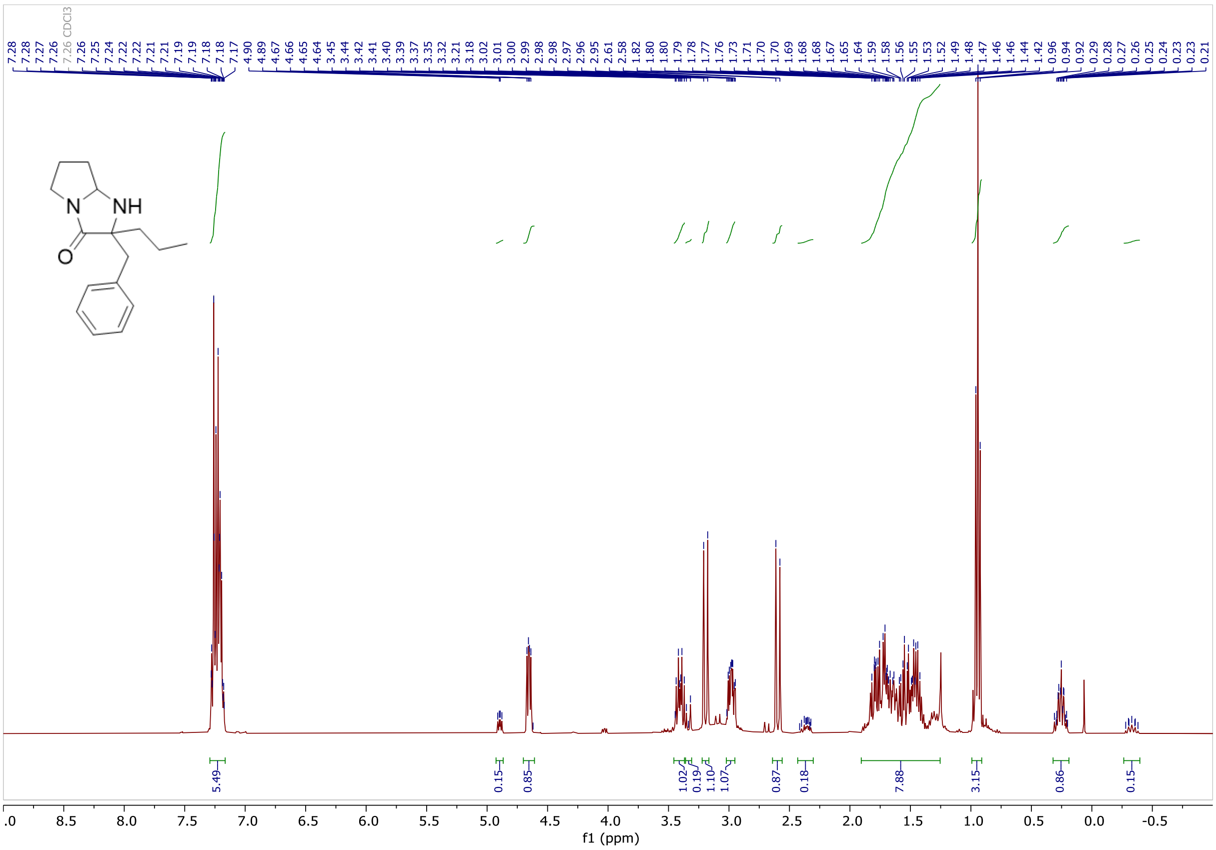
^{13}C-NMR (101 MHz, acteonitrile-d_3) (14) 93:7 mixture of diastereoisomers



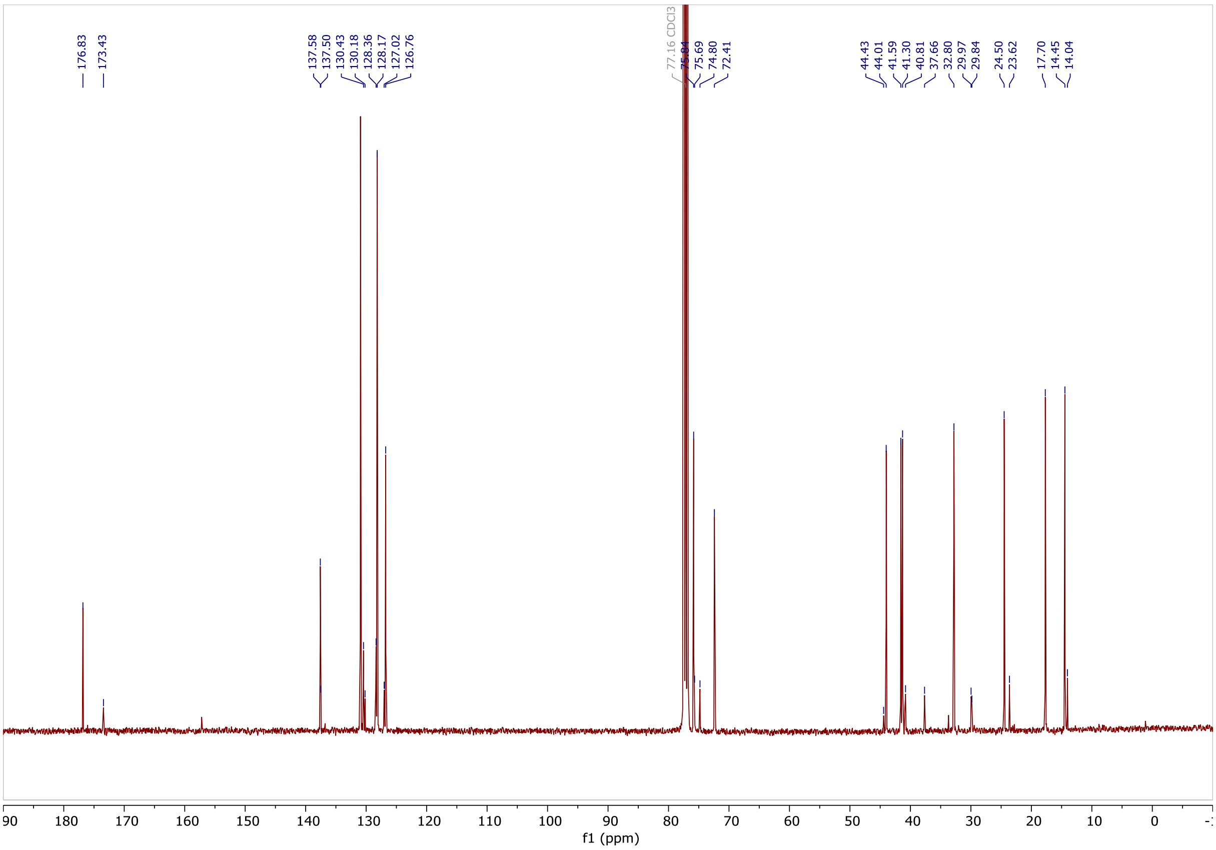
2D-NOESY (400 MHz, acteonitrile-*d*$_3$) (14) 93:7 mixture of diastereoisomers (cis:trans)



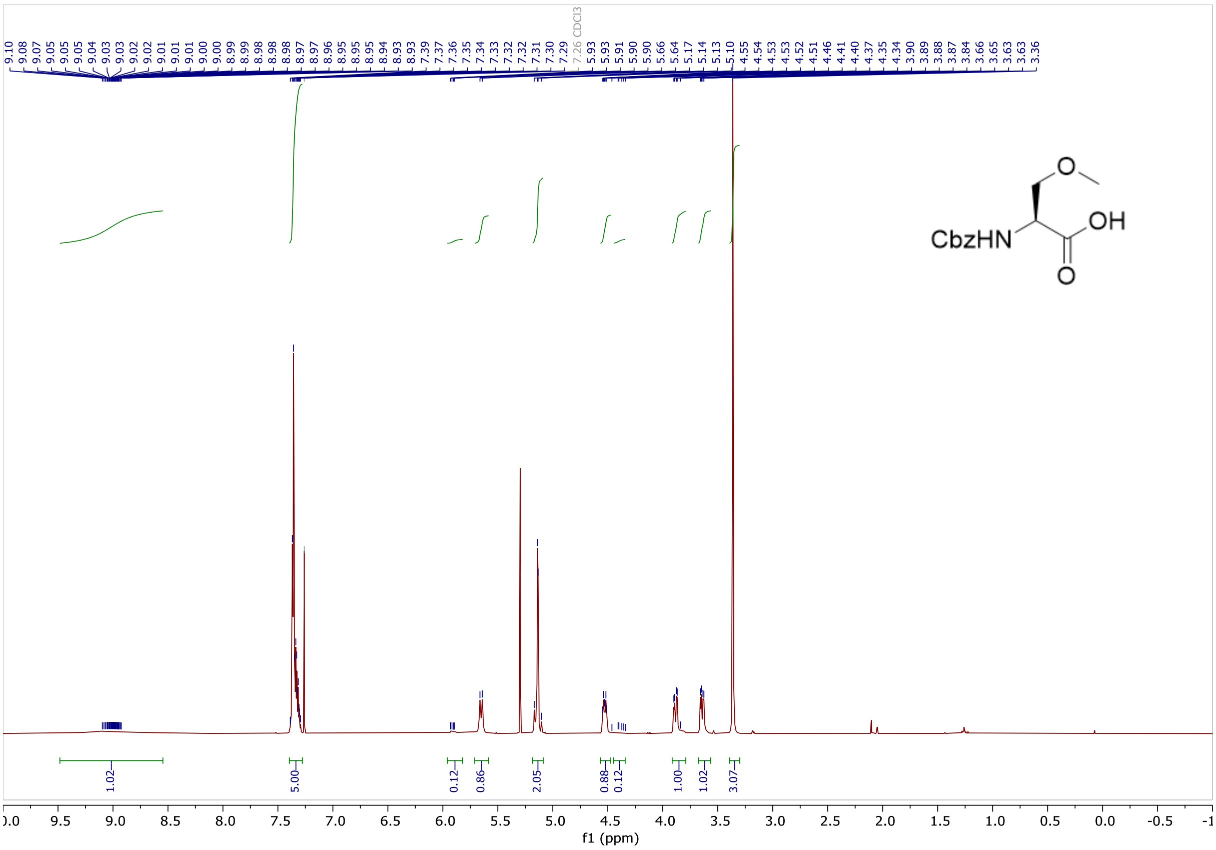
^{1}H-NMR (400 MHz, chloroform-*d*) (15)



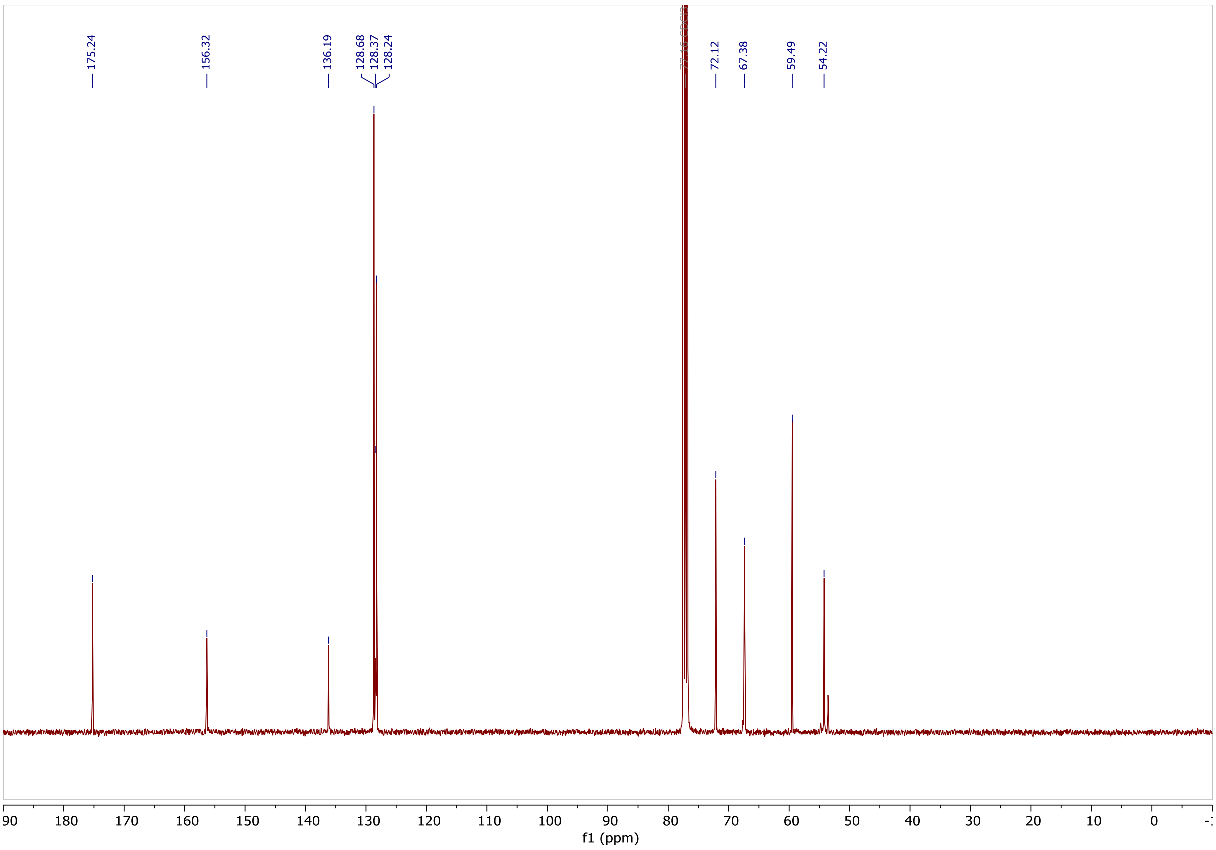
^{13}C-NMR (101 MHz, chloroform-*d*) (15)



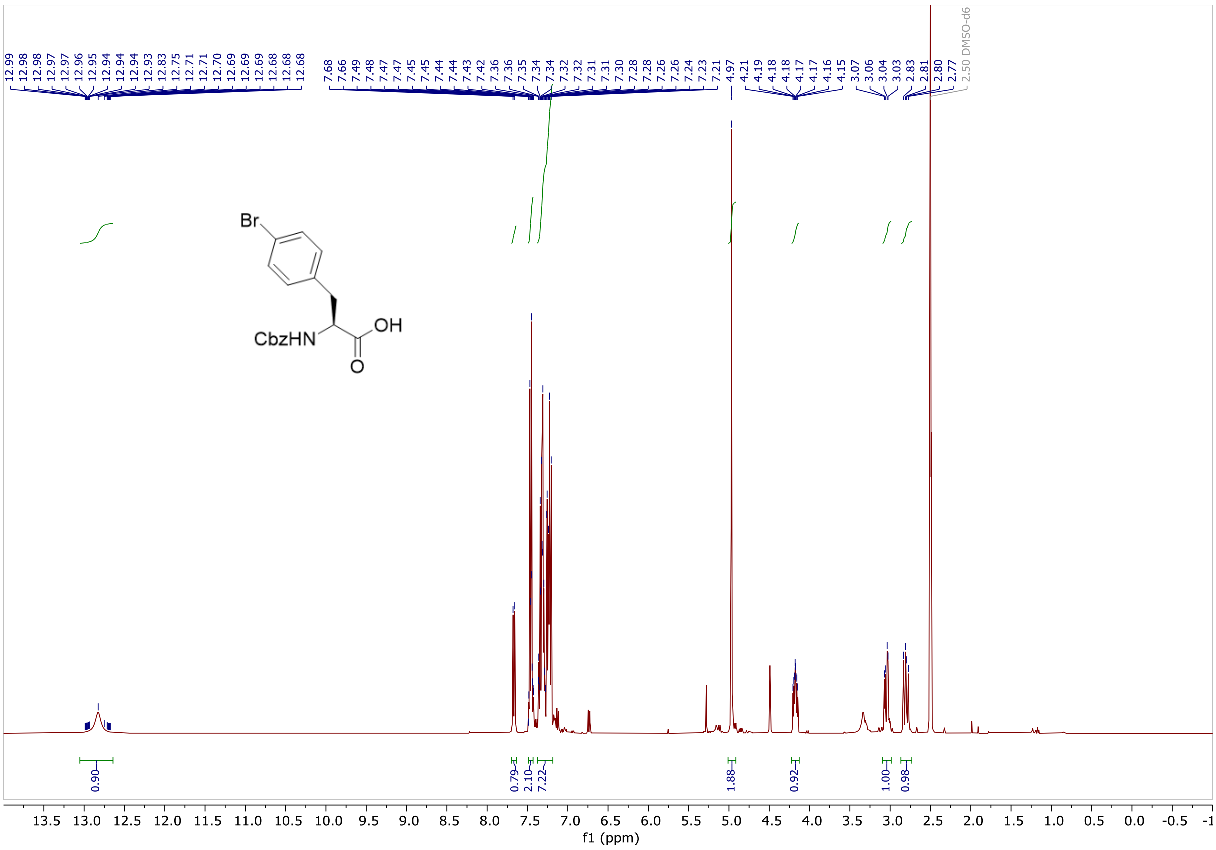
[1]H-NMR (400 MHz, chloroform-*d*) (22)



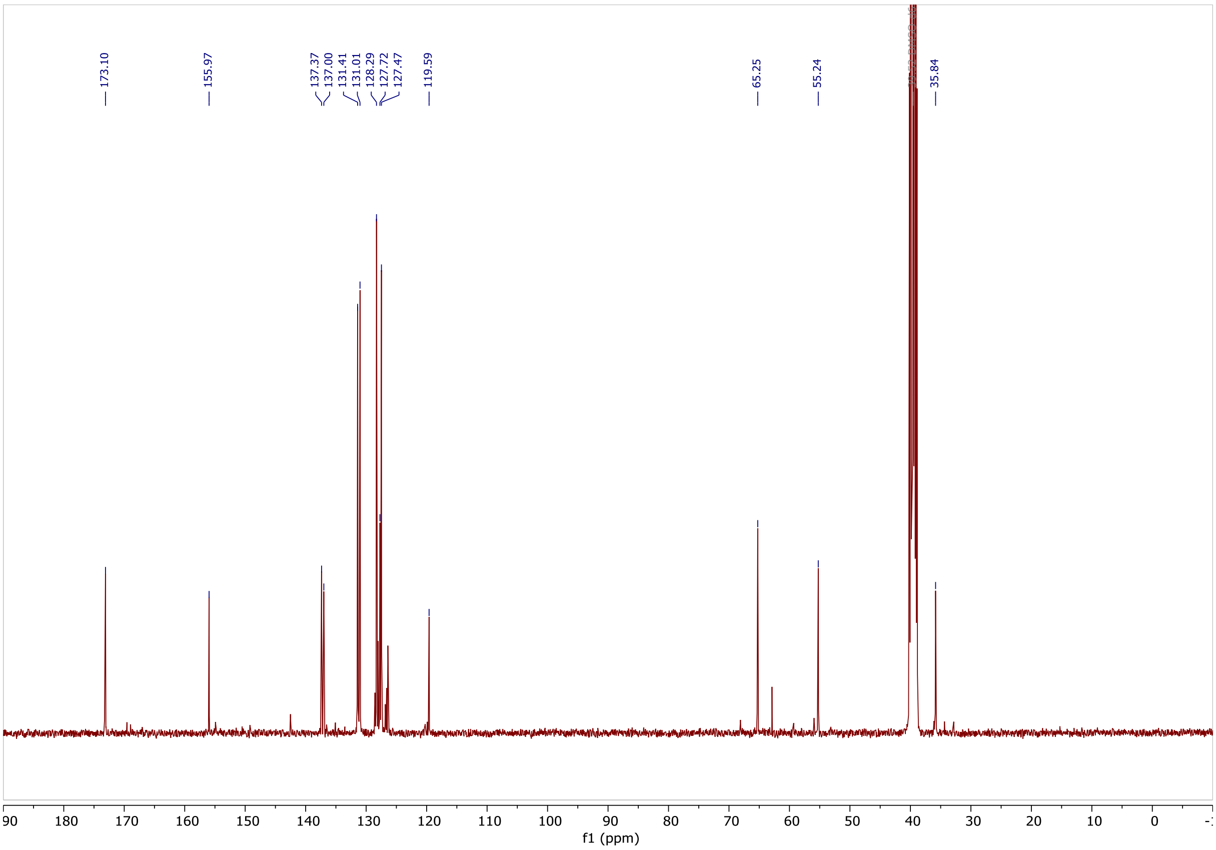
[13]C-NMR (101 MHz, chloroform-*d*) (22)



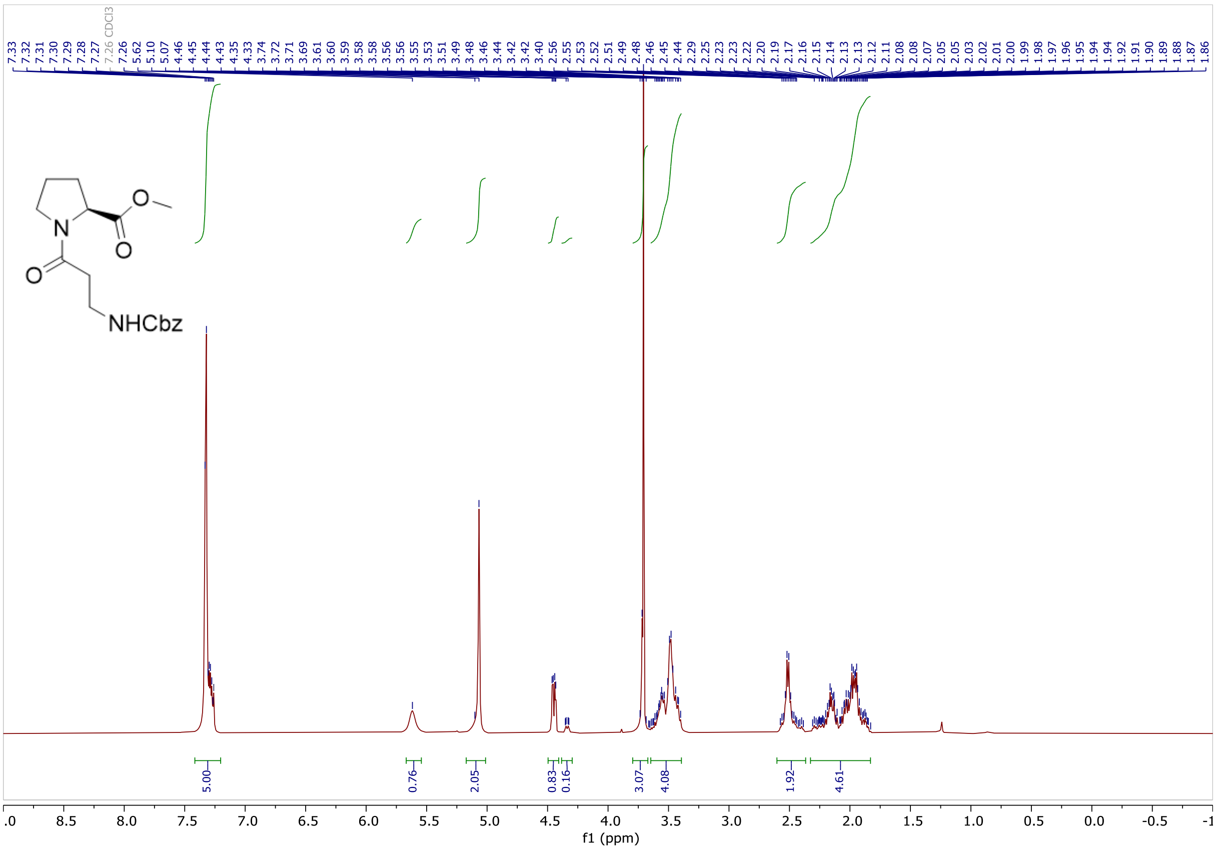
^{1}H-NMR (400 MHz, chloroform-*d*) (24)



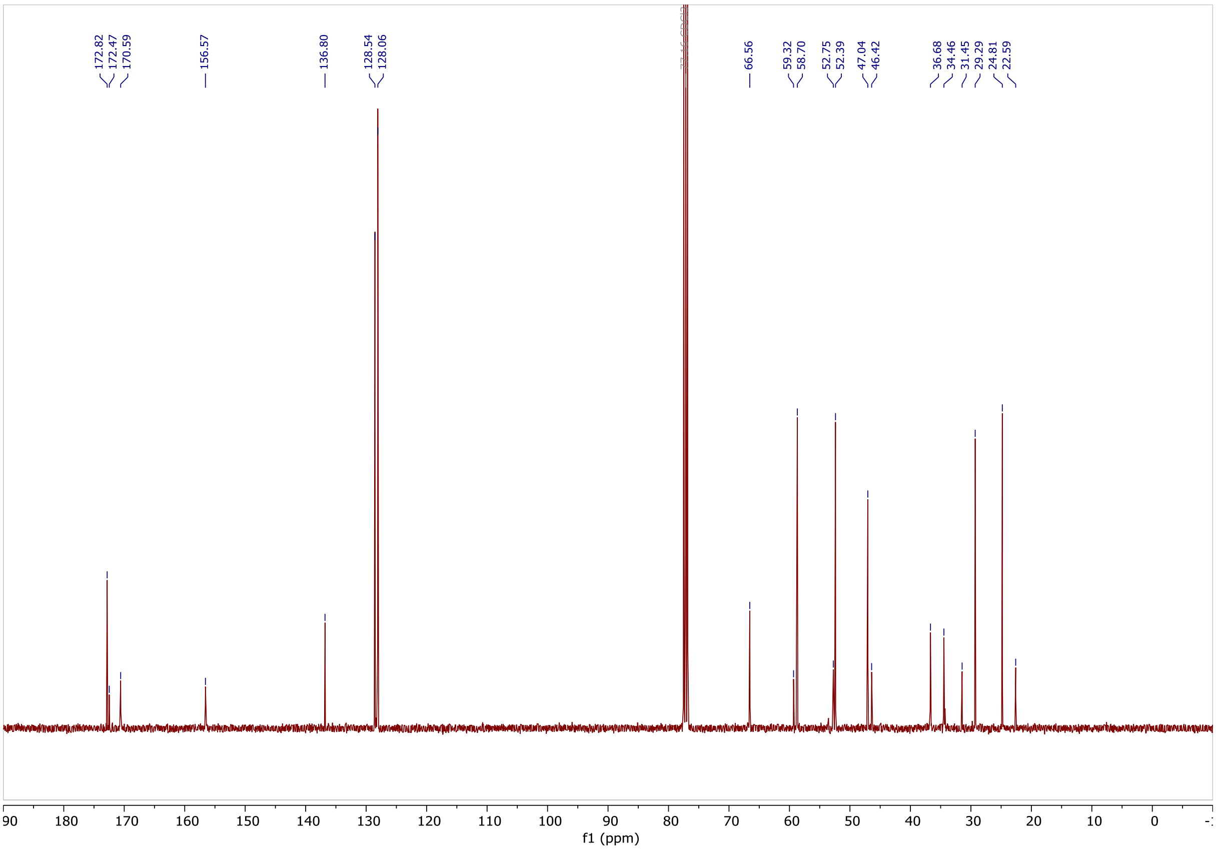
^{13}C-NMR (101 MHz, chloroform-*d*) (24)



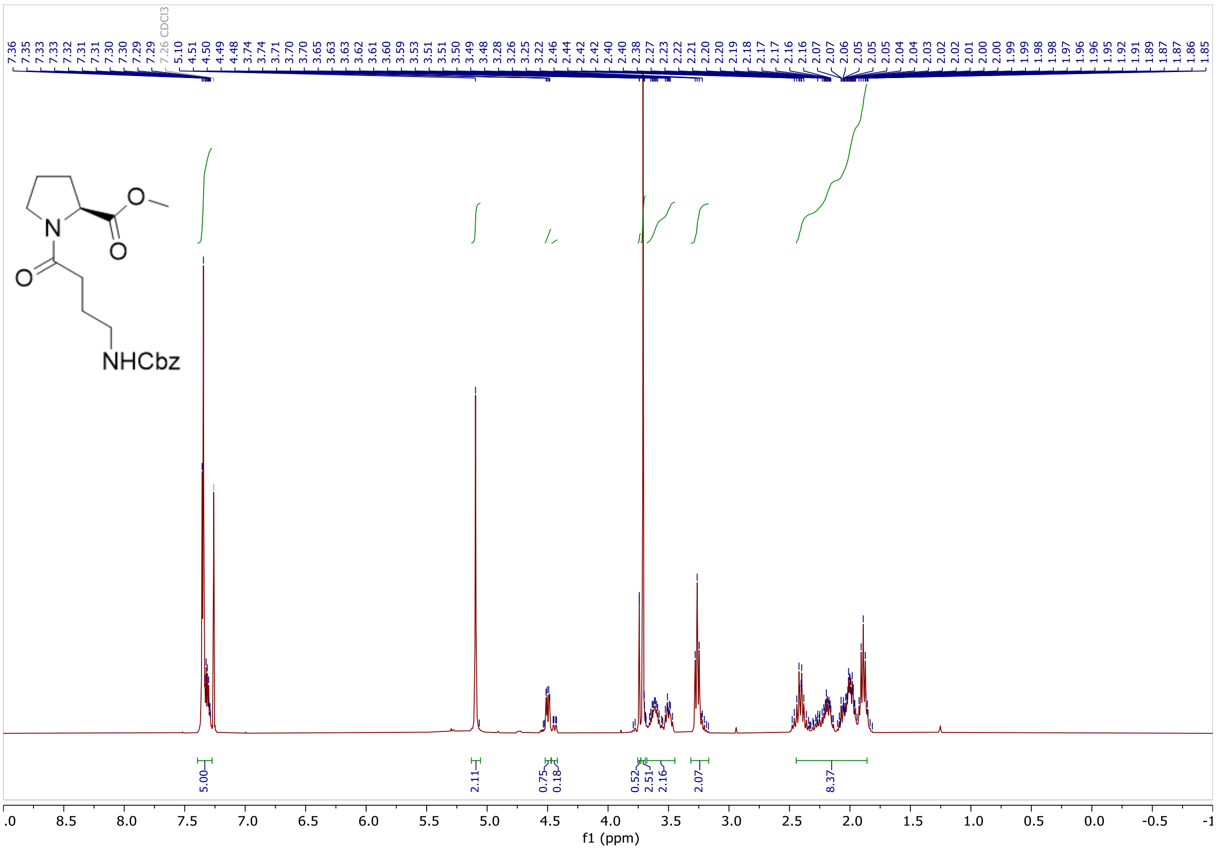
^{1}H-NMR (400 MHz, chloroform-*d*) (25b)



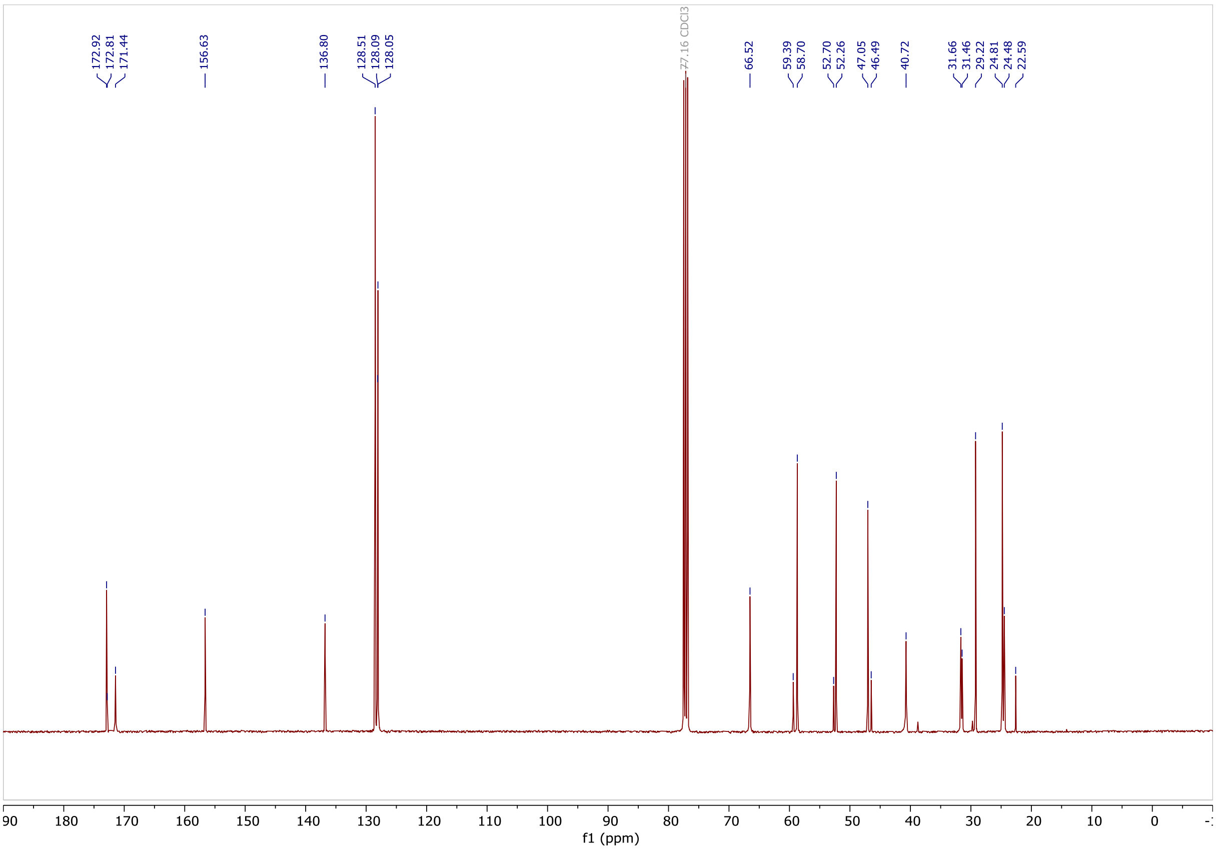
^{13}C-NMR (101 MHz, chloroform-*d*) (25b)



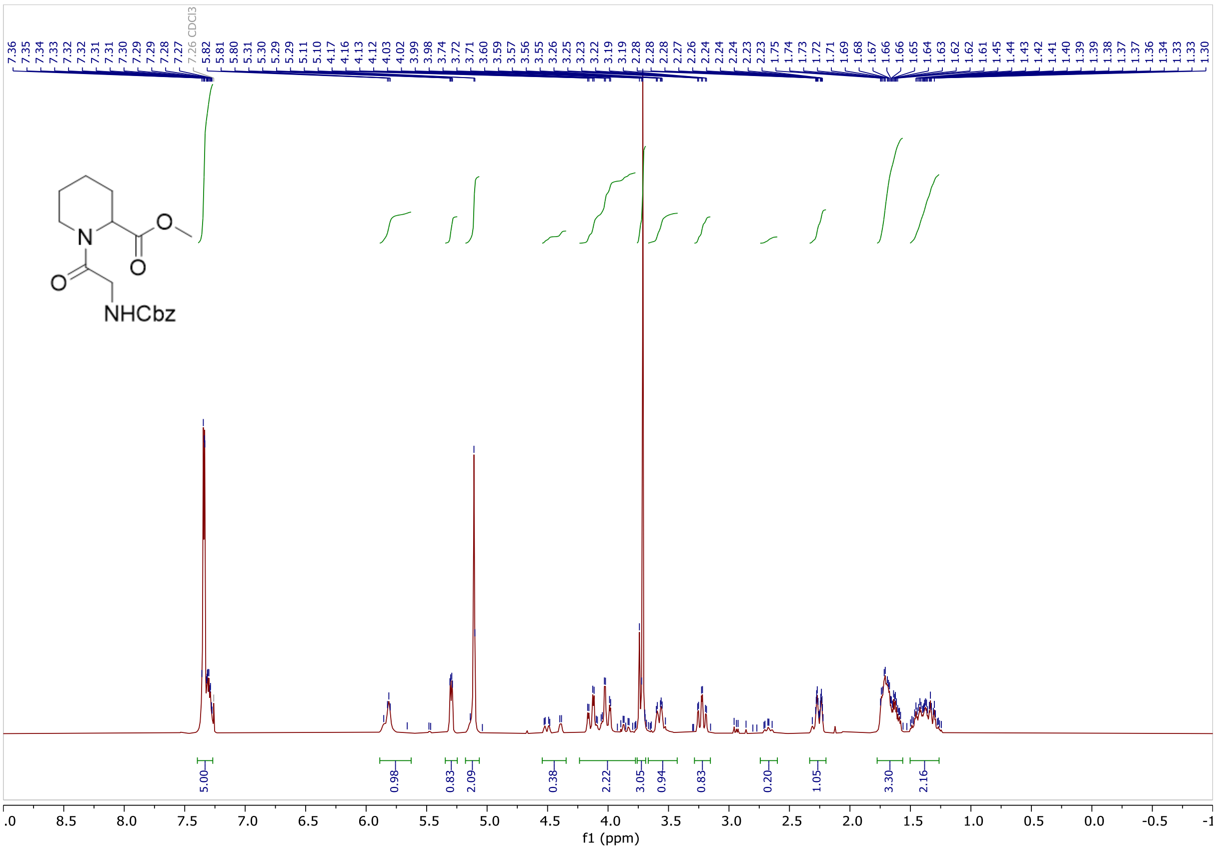
^{1}H-NMR (400 MHz, chloroform-*d*) (25c)



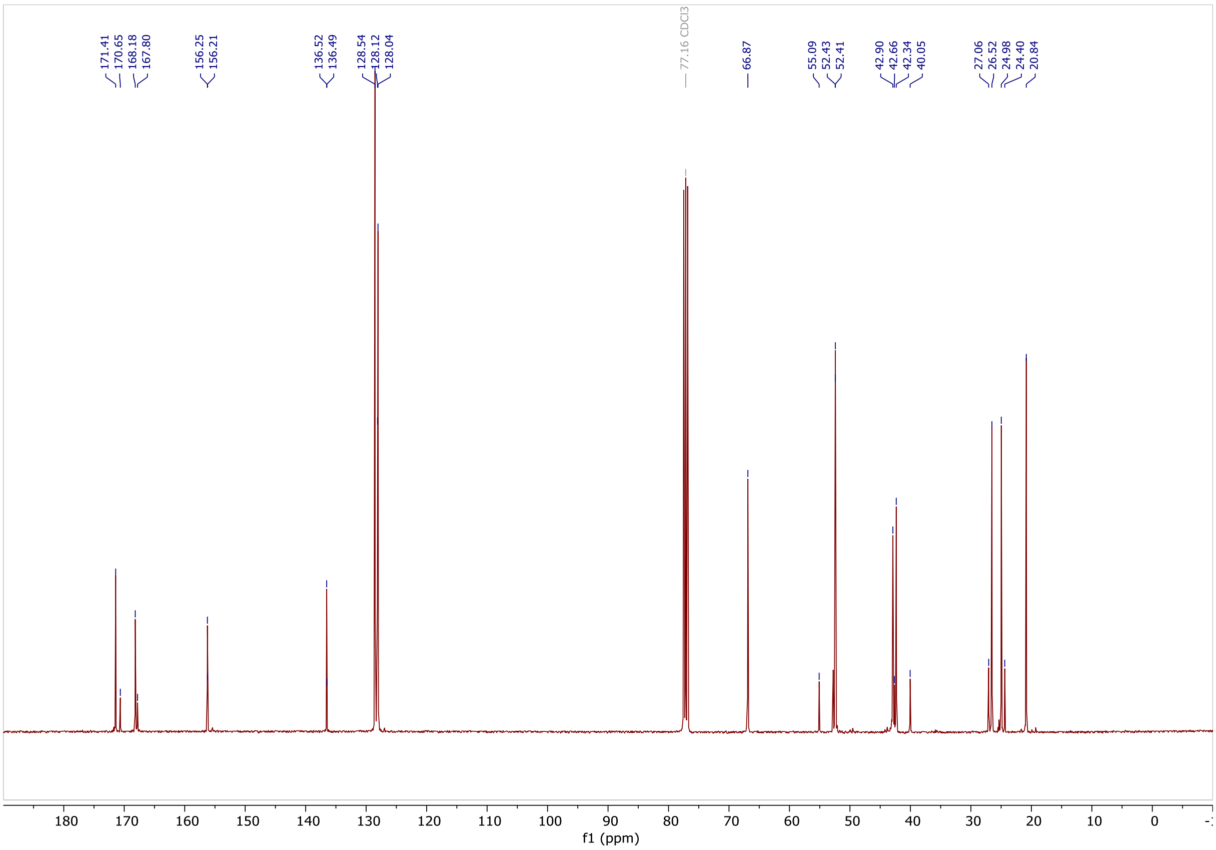
^{13}C-NMR (101 MHz, chloroform-*d*) (25c)



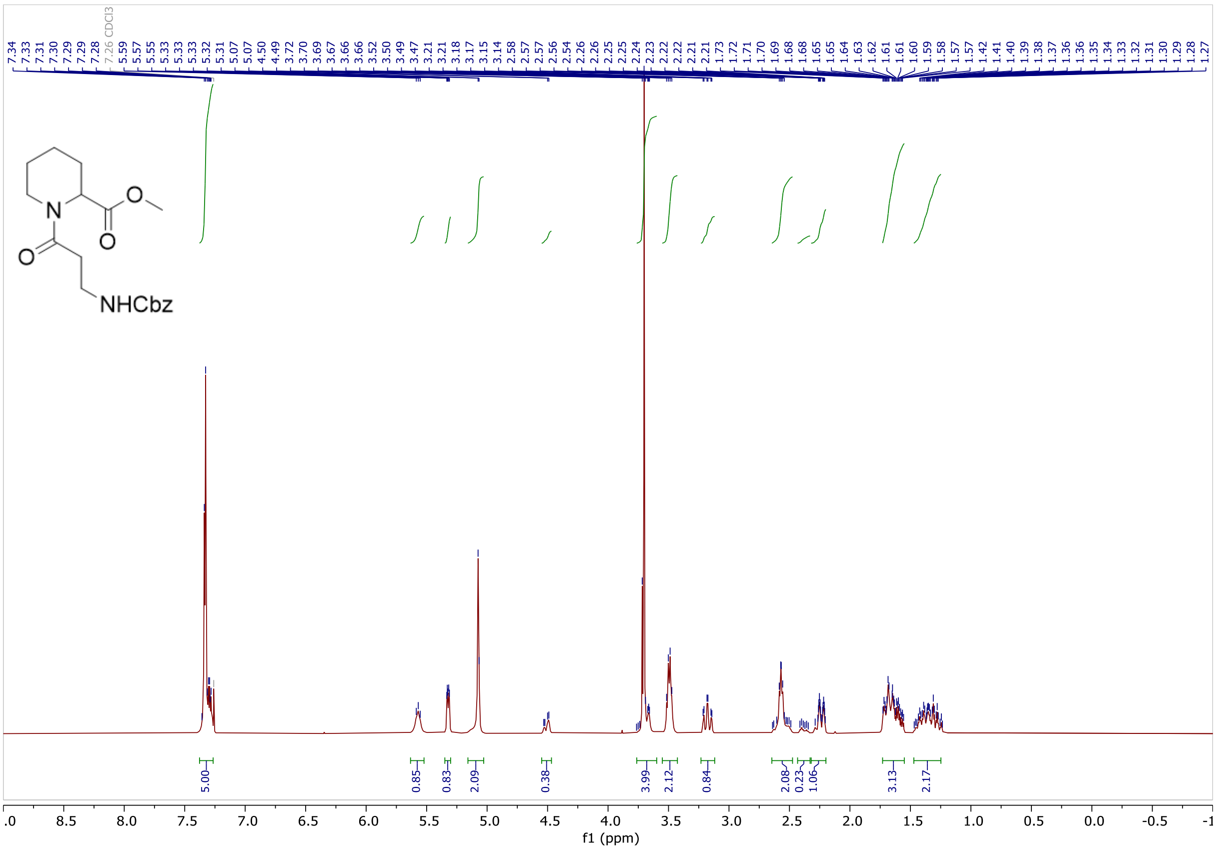
^{1}H-NMR (400 MHz, chloroform-*d*) (25d)



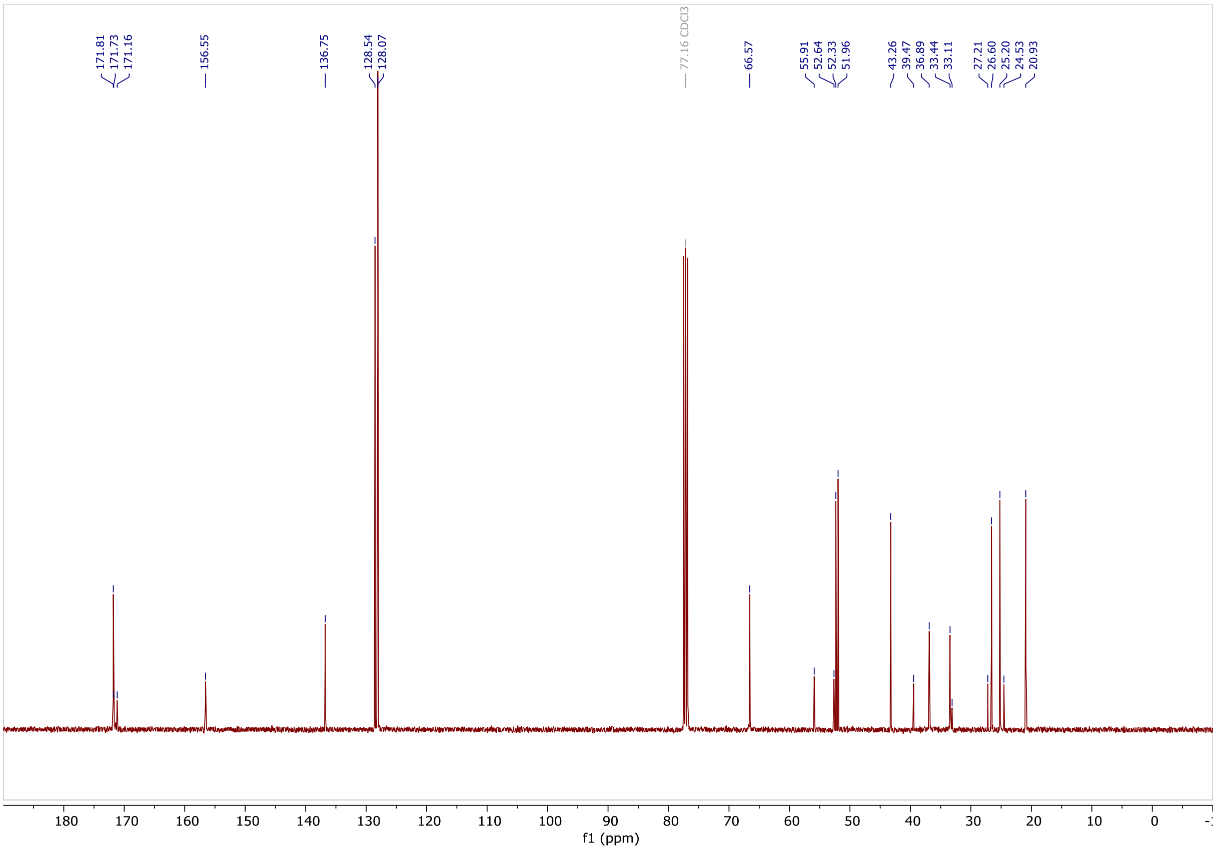
^{13}C-NMR (101 MHz, chloroform-*d*) (25d)



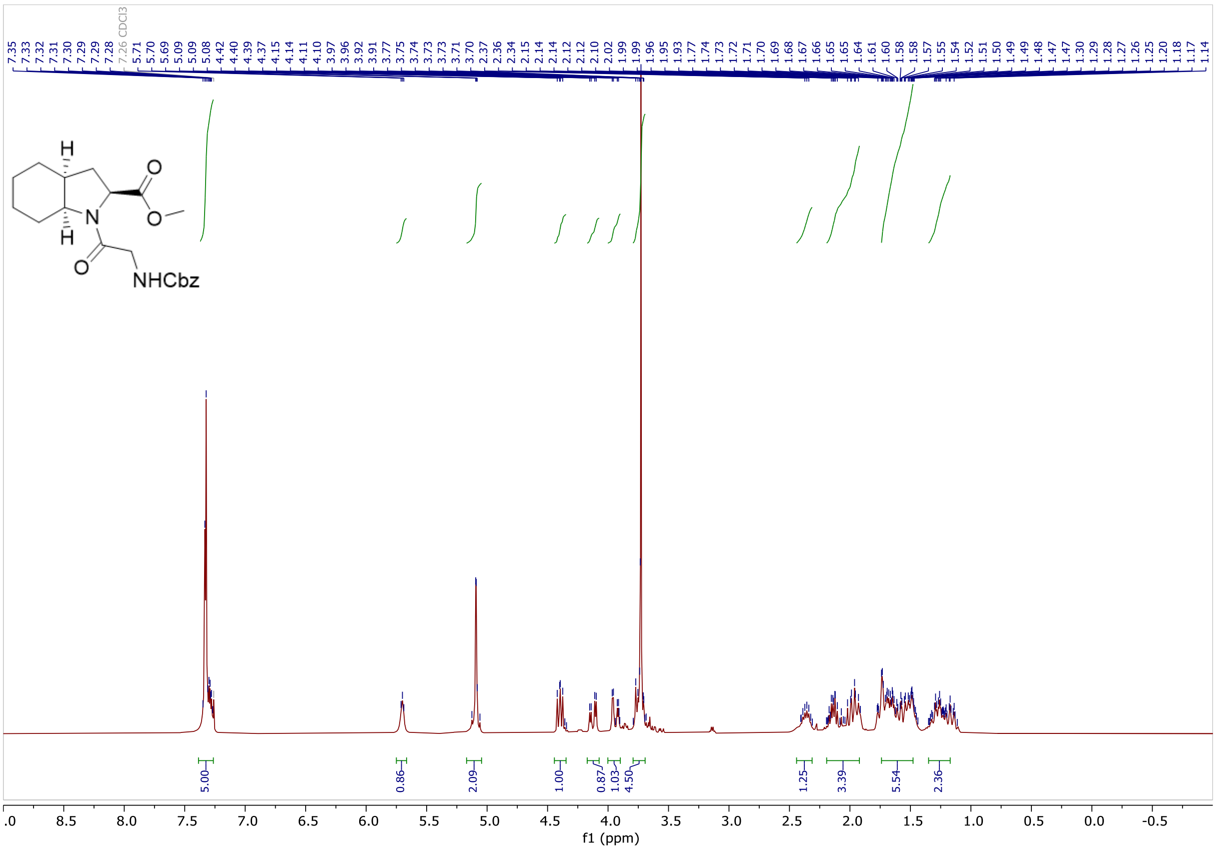
^{1}H-NMR (400 MHz, chloroform-*d*) (25e)



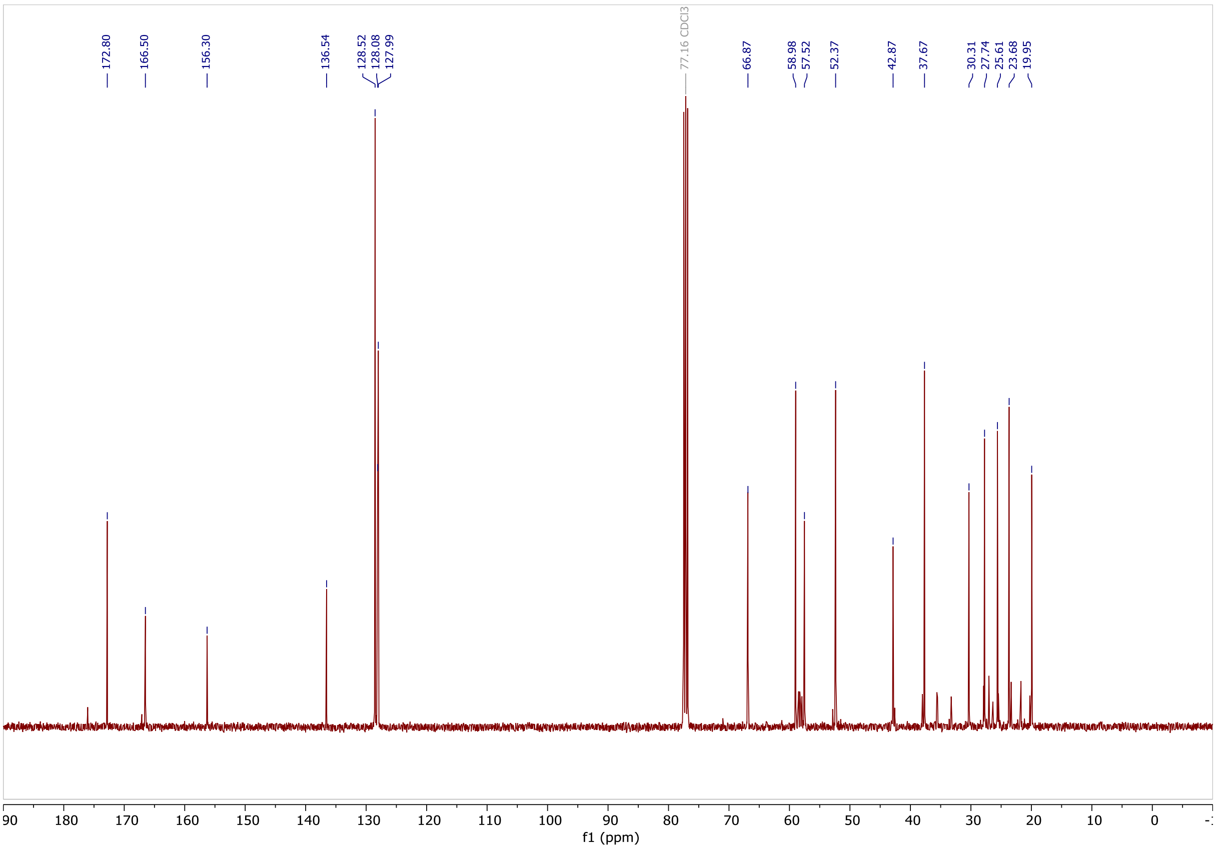
^{13}C-NMR (101 MHz, chloroform-*d*) (25e)



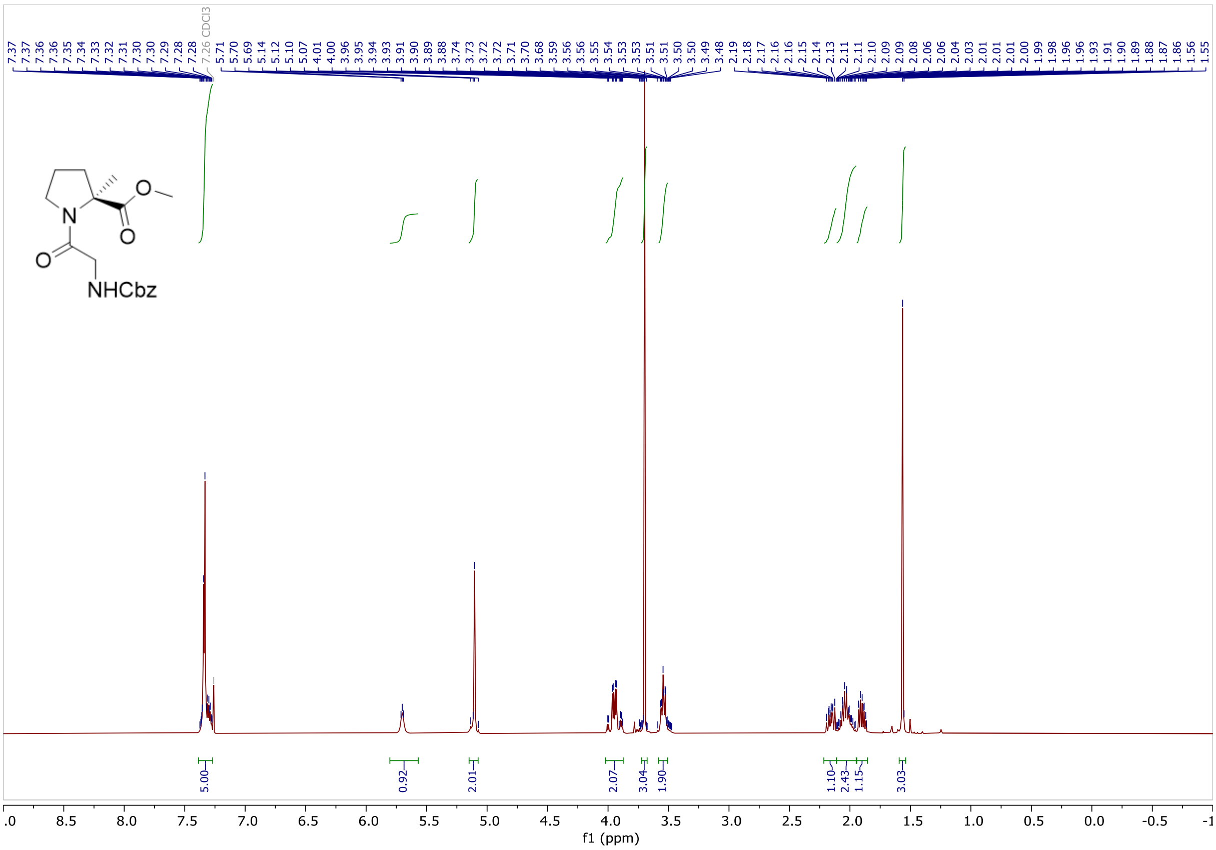
^{1}H-NMR (400 MHz, chloroform-*d*) (25f)



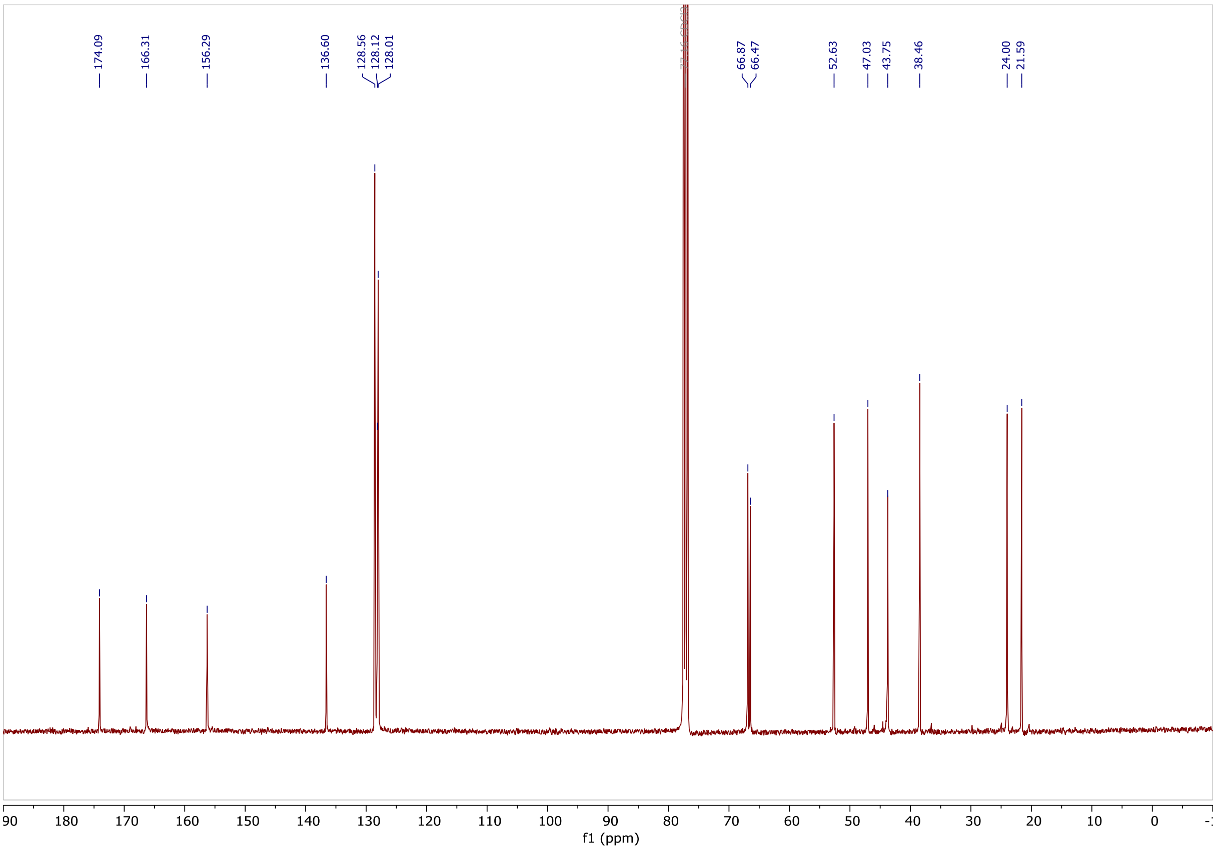
^{13}C-NMR (101 MHz, chloroform-*d*) (25f)



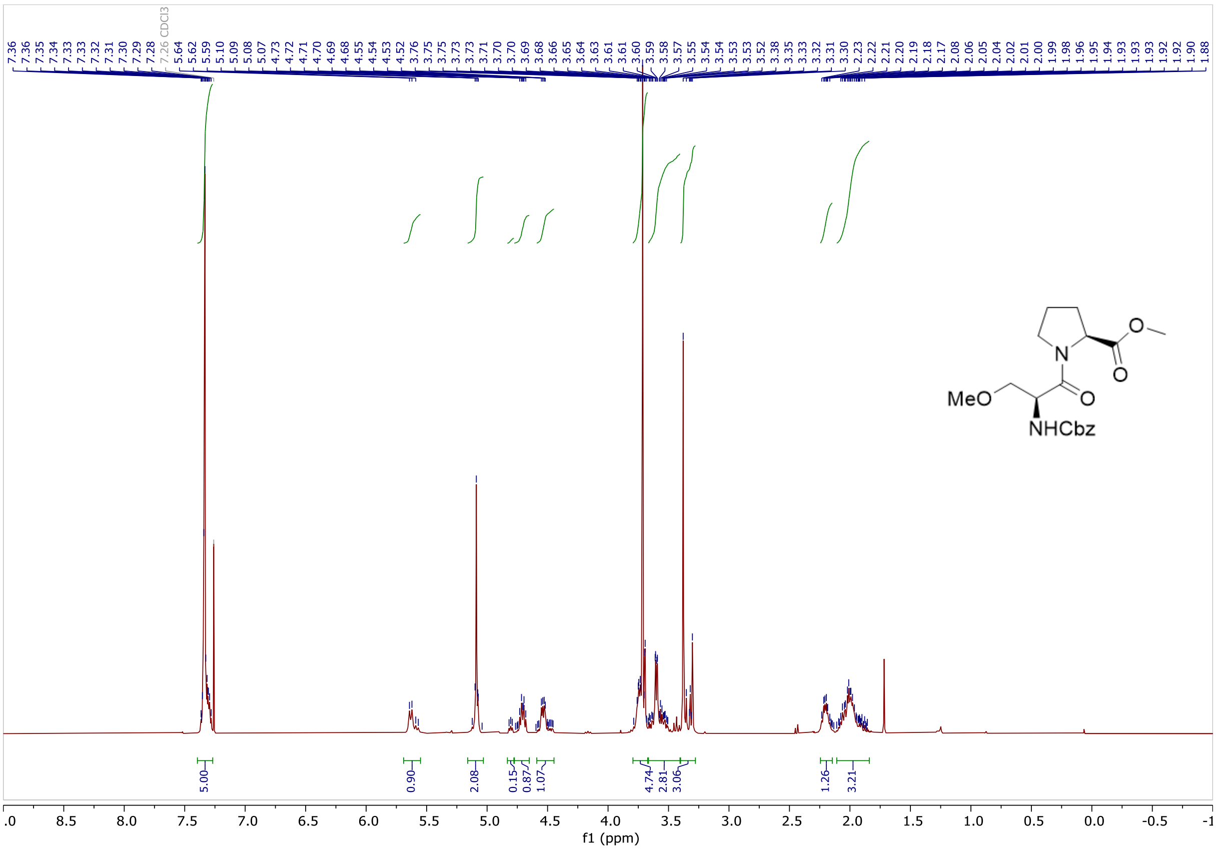
[1]H-NMR (400 MHz, chloroform-*d*) (25g)



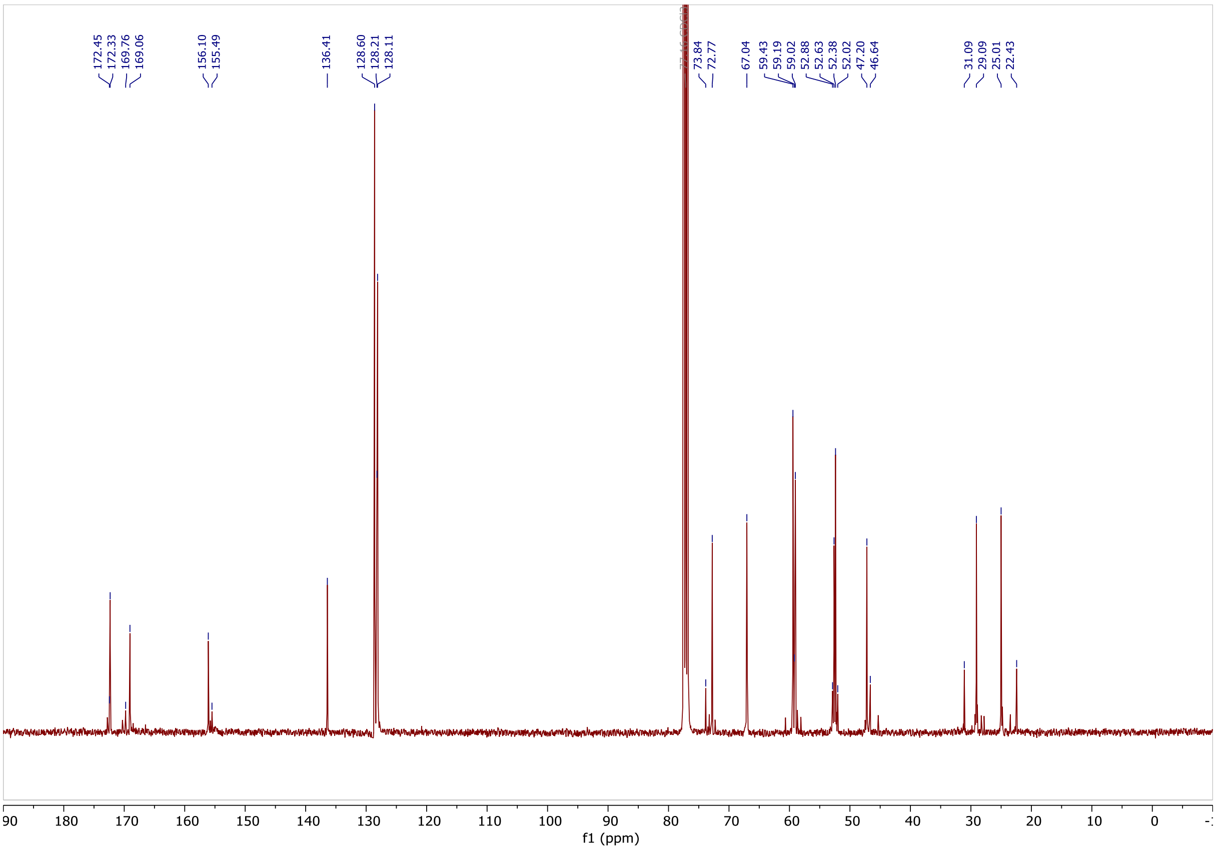
[13]C-NMR (101 MHz, chloroform-*d*) (25g)



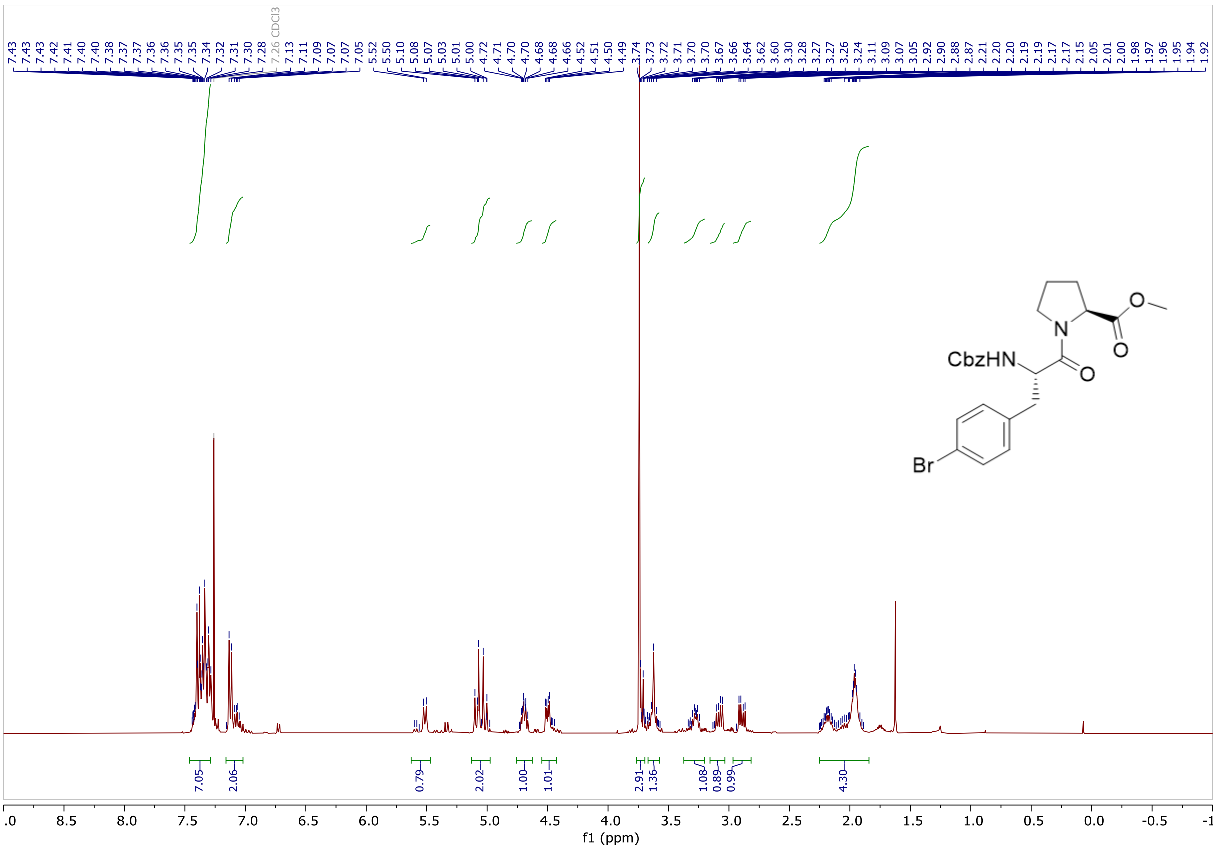
^{1}H-NMR (400 MHz, chloroform-*d*) (25j)



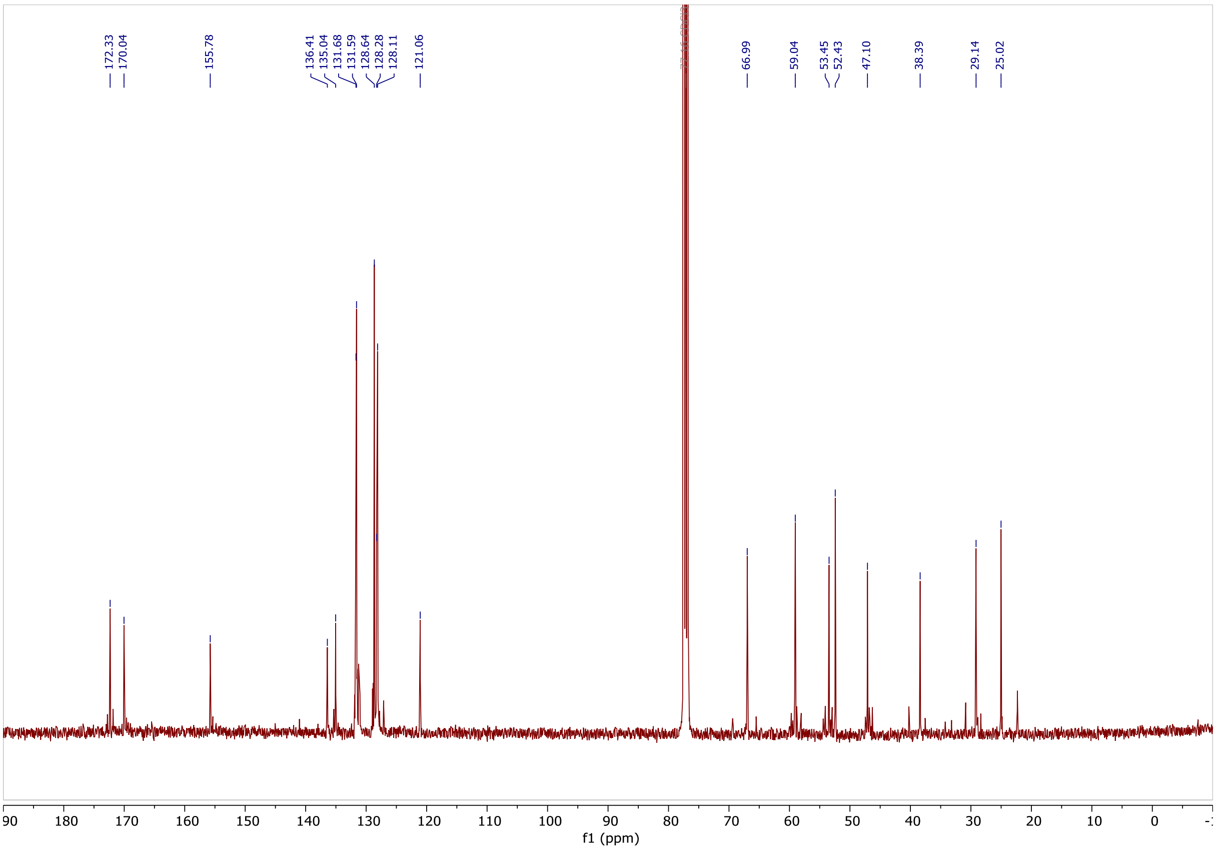
^{13}C-NMR (101 MHz, chloroform-*d*) (25j)



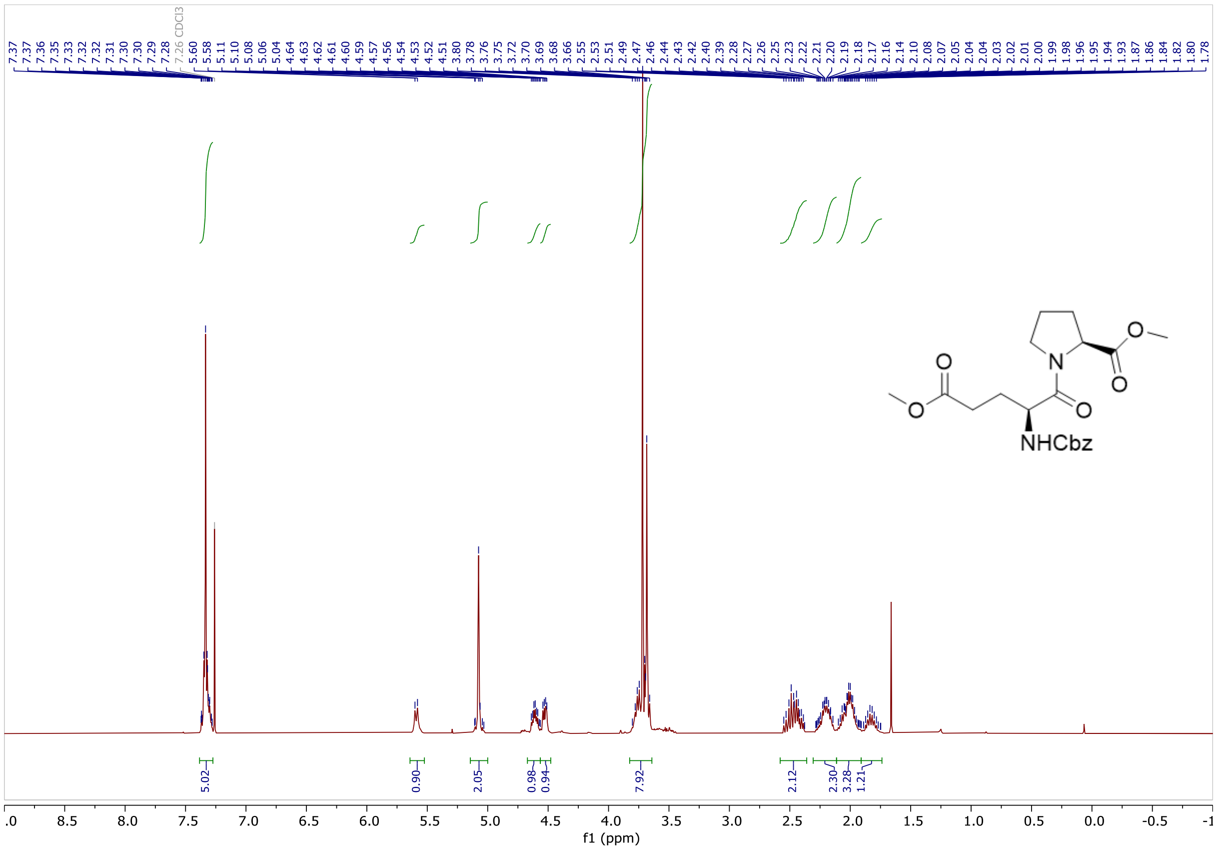
^{1}H-NMR (400 MHz, chloroform-*d*) (25k)



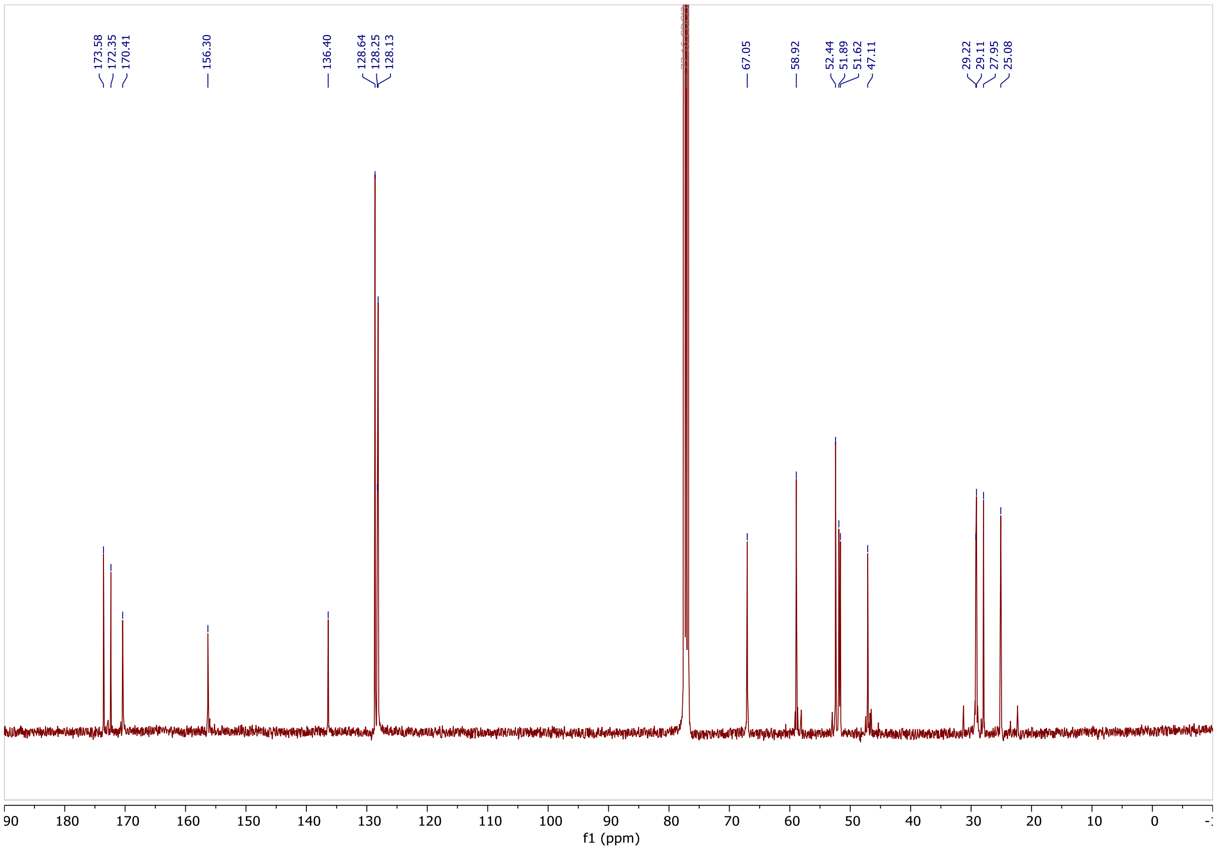
^{13}C-NMR (101 MHz, chloroform-*d*) (25k)



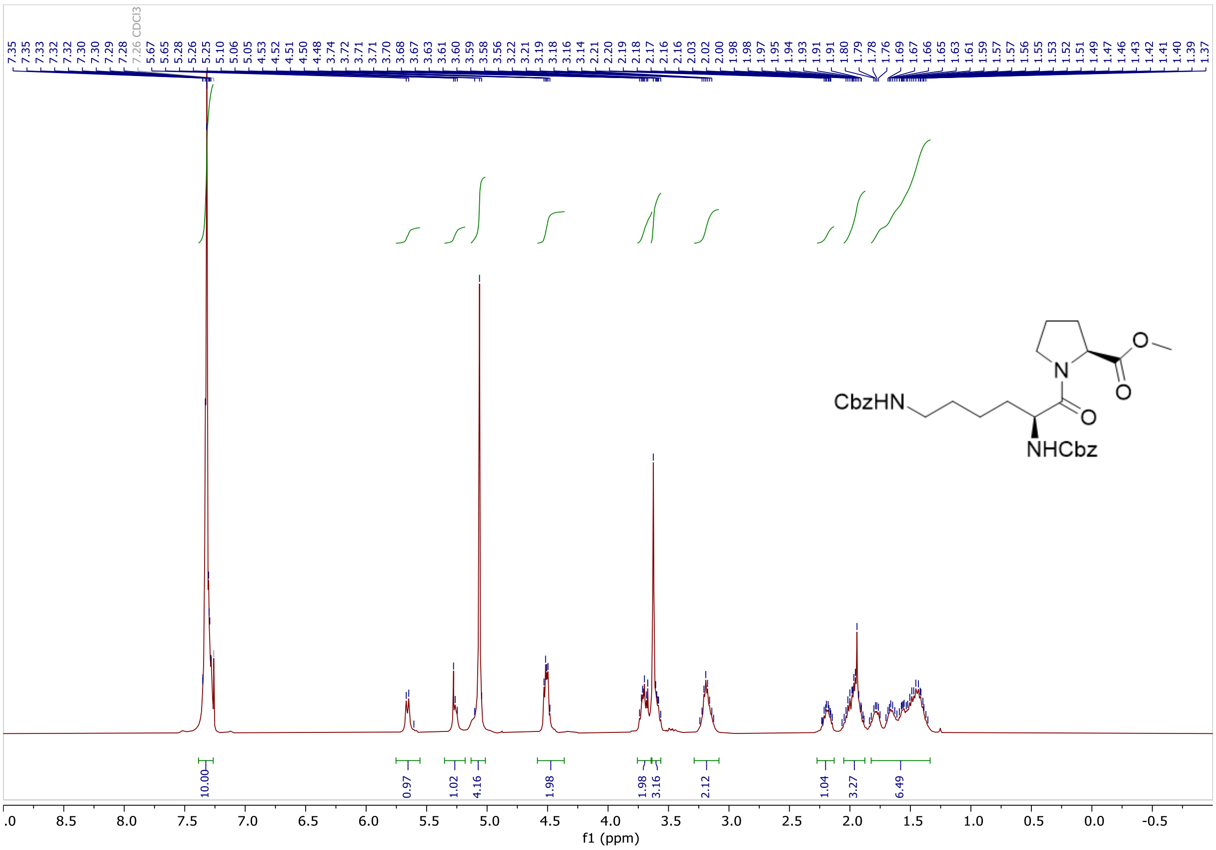
^{1}H-NMR (400 MHz, chloroform-*d*) (25l)



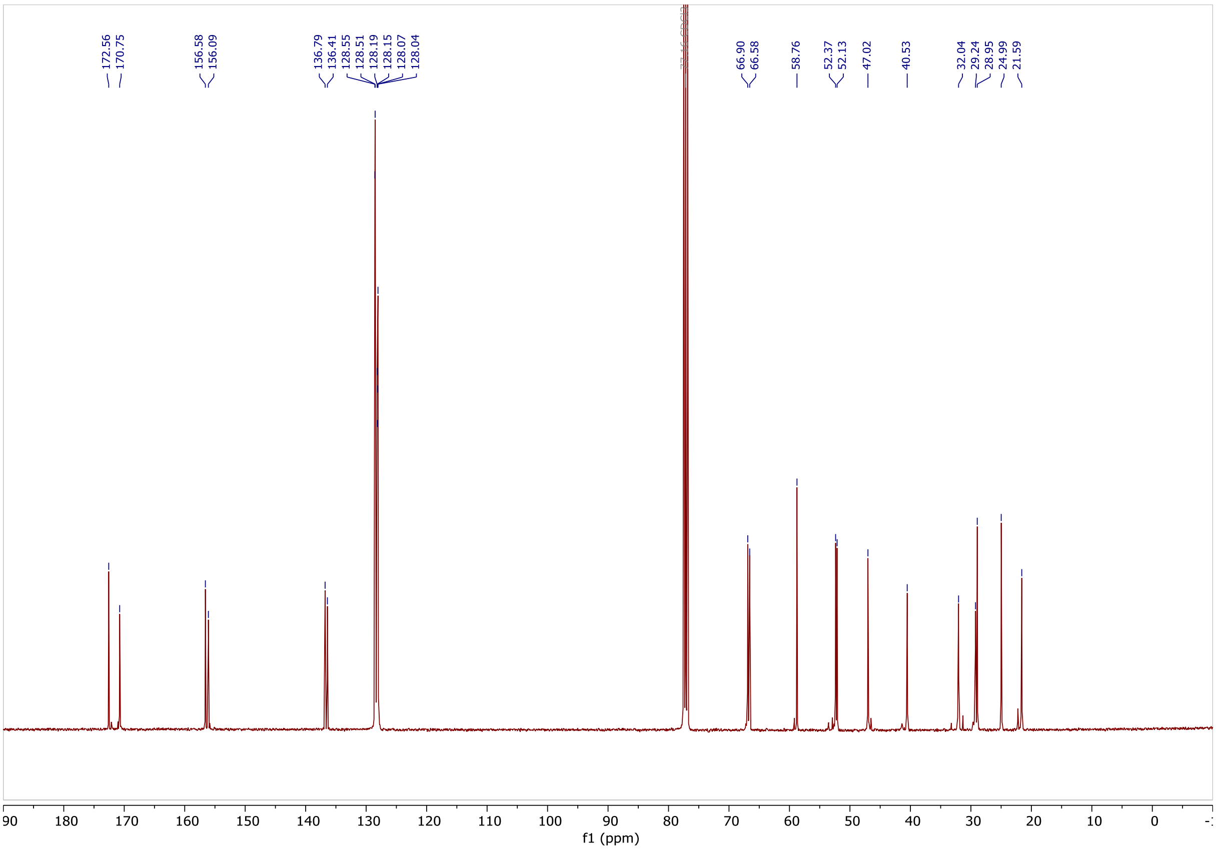
^{13}C-NMR (101 MHz, chloroform-*d*) (25l)



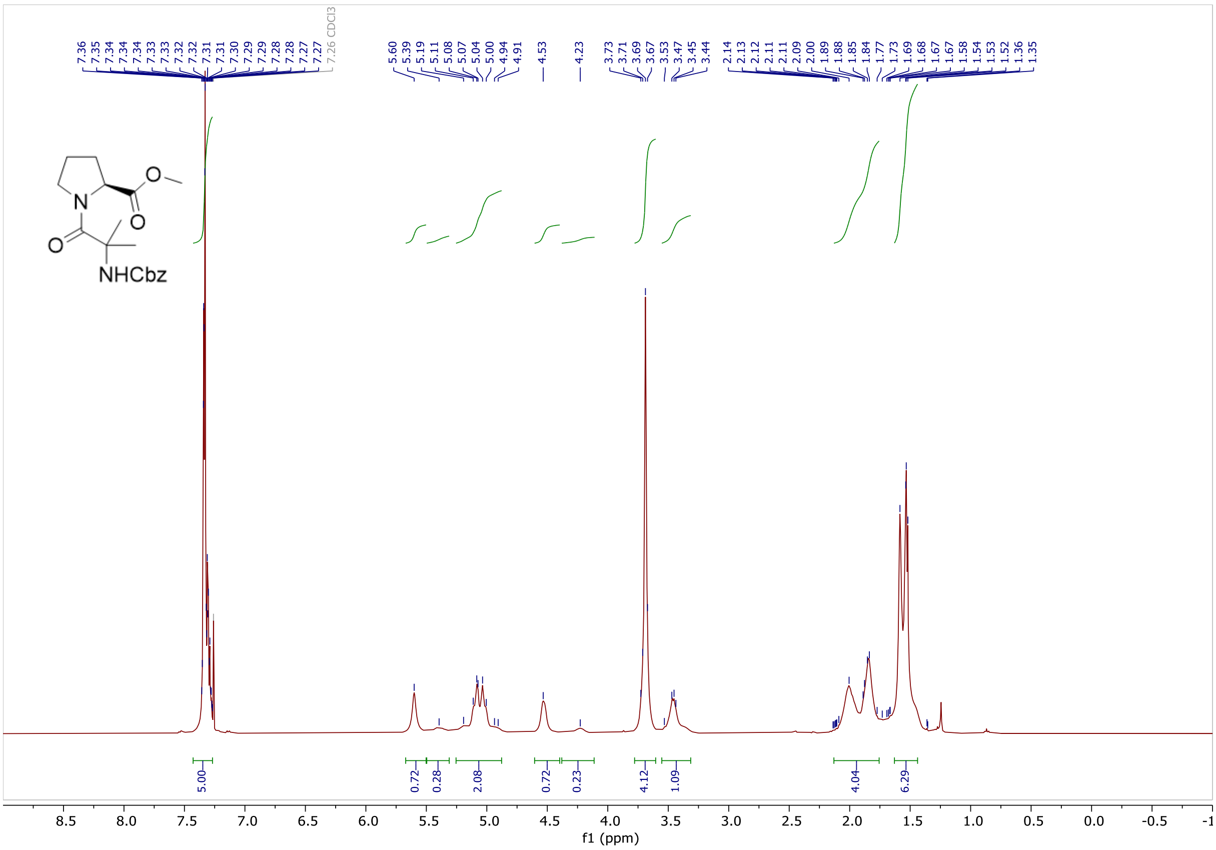
^{1}H-NMR (400 MHz, chloroform-*d*) (25m)



^{13}C-NMR (101 MHz, chloroform-*d*) (25m)



^{1}H-NMR (400 MHz, chloroform-*d*) (25n)



^{13}C-NMR (101 MHz, chloroform-*d*) (25n)