Total synthesis of the cyclic depsipeptide YM-280193, a platelet aggregation inhibitor.

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Supporting Information

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1. General Information

All reagents were used as supplied. Solvents for RP-HPLC were purchased as HPLC grade and used without further purification. L-Proline, glycine, *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU), *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU), *O*-(6-chlorobenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HCTU), 1-hydroxy-7-azabenzotriazole (HOAt), *N*-fluorenylmethoxycarbonyl succinimide (Fmoc-OSu) and di-*tert*-butyl dicarbonate (Boc_2O) were purchased from GL Biochem. *N,N'*-Diisopropylcarbodiimide (DIC), *N,N*-diisopropylethylamine (DIPEA) and piperidine were purchased from Aldrich. D-Phenyllactic acid, H-Ala-OMe·HCl and dithiothreitol (DTT) were purchased from AK Scientific. Fmoc-*N*-MeAla was purchased from Peptides International. Boc-Thr(OH)-COOH and Boc-Thr(Bzl)-COOH were purchased form PolyPeptide Group. H-Cys(S^tBu)-COOH was purchased from Chem Impex International. 2-Chlorotrityl chloride resin was purchased from Novabiochem. TFA was purchased from Scharlau. Unless stated otherwise, all reactions were performed under an atmosphere of nitrogen using standard techniques.

Analytical thin-layer chromatography (TLC) was carried out using Kieselgel F_{254} 200 µm (Merck) silica plates. The compounds were then visualised by ultraviolet fluorescence or by staining with ninhydrin followed by heating of the plate for a few minutes. Column chromatography was performed using Kieselgel F_{254} S 63-100 µm silica gel with the indicated eluent. Melting points, in degrees Celsius (°C), were measured on a Reichert melting point apparatus, equipped with a Reichert microscope and were uncorrected. Infrared spectra were recorded on a Perkin Elmer Spectrum 100 infrared spectrometer and reported in wavenumbers (ν, cm^{-1}). Optical rotations were determined at the sodium D line (589 nm) at 20 °C on a Perkin Elmer 341 instrument. High resolution mass spectra were recorded on a Bruker micrOTOFQ mass spectrometer.

Nuclear magnetic resonance (NMR) spectra were recorded at room temperature on either a Bruker AVANCE 400 spectrometer (^1H, 400 MHz; ^{13}C, 100 MHz) or a Bruker AVANCE HD 500 spectrometer (^1H, 500 MHz; ^{13}C, 125 MHz). All chemical shifts are reported in parts per million (ppm) from tetramethylsilane (δ = 0) and were measured relative to the solvent in which the sample was analysed ($CDCl_3$: δ 7.26 for ^1H NMR, δ 77.0 for ^{13}C NMR; CD_3OD: δ 3.31 for ^1H NMR, δ 49.00 for ^{13}C NMR; D_2O: δ 4.79 for ^1H NMR; CD_3CN: δ 1.94 for ^1H NMR, δ 118.26 for ^{13}C NMR). The ^1H NMR shift values are reported as chemical shift (δ_H), the corresponding integral, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, td = triplet of doublets, qd = quartet of doublets), coupling constant (*J* in Hz) and assignments. ^{13}C NMR values are reported as the chemical shift (δ_C), the degree of hybridisation and assignment. The assignments were made

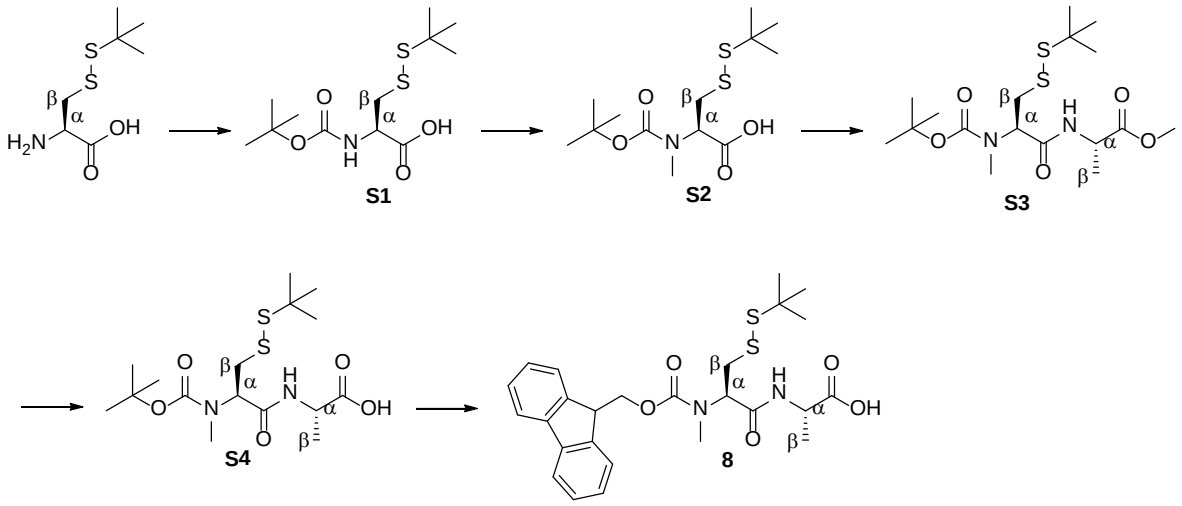
with the aid of HSQC, COSY and HMBC experiments. Where distinct from those due to the major rotamer, resonances due to minor rotamers are denoted by an asterisk.

Semi-preparative RP-HPLC was performed on a Thermo Scientific Dionex Ultimate 3000 UHPLC equipped with a four channel UV Detector at 210, 225, 254 and 280 nm using either an analytical column (Phenomenex Gemini C_{18}, 110 Å, 250 mm x 4.6 mm, 5 µm) at a flow rate of 1 mL min^{-1} or a semi-preparative column (Phenomenex Gemini C_{18}, 110 Å, 250 mm x 10 mm, 5 µm) at a flow rate of 5 mL min^{-1}. A suitably adjusted gradient of 1% B to 80% B was used, where solvent A was 0.1% TFA in H_2O and B was 0.1% TFA in acetonitrile.

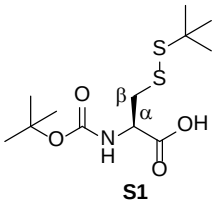
LCMS spectra were acquired on either an Agilent Technologies 1120 Compact LC equipped with a Hewlett-Packard 1100 MSD mass spectrometer or an Agilent Technologies 1260 Infinity LC equipped with an Agilent Technologies 6120 Quadrupole mass spectrometer. An analytical column (Agilent C_3, 150 mm x 3.0 mm, 3.5 µm) was used at a flow rate of 0.3 mL min^{-1} using a linear gradient of 5% B to 95% B over 30 min, where solvent A was 0.1% formic acid in H_2O and B was 0.1% formic acid in acetonitrile.

2. Synthesis of building blocks

2.1 Synthesis of (*S*)-2-((*R*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-3-(*tert*-butyldisulfanyl)propanamido)propanoic acid 8

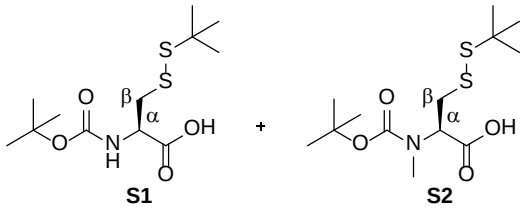


(*R*)-2-((*tert*-butoxycarbonyl)amino)-3-(*tert*-butyldisulfanyl)propanoic acid S1



To a stirring suspension of Cys(S^{t}Bu)-COOH (300 mg, 1.43 mmol) in H_2O (3 mL) and THF (4 mL) was added solid $Na_2CO_3 \cdot H_2O$ (236 mg, 1.9 mmol) and the mixture stirred at room temperature for 10 min until mostly dissolved. To this was added di-*tert*-butyl dicarbonate (415 mg, 1.9 mmol) and the resultant suspension was stirred at room temperature for 18 h. H_2O (3 mL) was added and the aqueous layer was washed with Et_2O (2 x 10 mL), acidified with 1 M HCl (3 mL) to pH 4 and extracted with EtOAc (4 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the *title compound* **S1** as a white solid (423 mg, 96%); **$[\alpha]_D^{20}$** = -145.0 (*c* 1.00, MeOH); **HRMS (EI):** *m/z* $[M + Na]^+$ calculated for $C_{12}H_{23}NNaO_4S_2$: 332.0966, observed: 332.0968; **IR (film) ν_{max}**: 3302, 3103, 2973, 2927, 1718, 1688, 1649. 1404, 1363, 1251, 1163, 1137, 1052, 1025, 840, 770, 654; **mp** 118-119 °C (lit.[1] 119-120 °C); **^{1}H NMR (400 MHz, CD_3OD):** δ 1.34 (9H, s, $SC(CH_3)_3$), 1.46 (9H, s, $OC(CH_3)_3$), 2.99 (1H, dd, *J* = 13.4, 8.7 Hz, Cysβ-H_AH_B), 3.18 (1H, dd, *J* = 13.4, 4.4 Hz, Cysβ-H_AH_B), 4.41 (1H, dd, *J* = 8.5, 4.3 Hz, Cysα-H); **^{13}C NMR (100 MHz, CD_3OD)**: δ 28.7 (CH_3, $OC(CH_3)_3$), 30.2 (CH_3, $SC(CH_3)_3$), 43.1 (CH_2, Cysβ-C), 48.6 (C, $SC(CH_3)_3$), 54.4 (CH, Cysα-C), 80.7 (C, $OC(CH_3)_3$), 157.7 (C, CON), 174.2 (C, COOH).

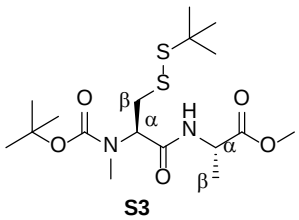
Mixture of (*R*)-2-((*tert*-butoxycarbonyl)amino)-3-(*tert*-butyldisulfanyl)propanoic acid S1 and 2-((*tert*-butoxycarbonyl)(methyl)amino)-3-(*tert*-butyldisulfanyl)propanoic acid S2



S1 **S2**

To a stirring solution of Boc-NH-Cys(S^{t}Bu)-COOH **S1** (299 mg, 0.97 mmol) in anhdyrous THF (3 mL) at 0 °C was added sodium hydride (100 mg, 2.5 mmol, 60% dispersion in mineral oil) in small portions. The resulting suspension was stirred for 5 min after which iodomethane (0.217 mL, 3.5 mmol) was added. The reaction mixture was stirred at room temperature for 21 h, after which H_2O (1 mL) and EtOAc (1 mL) was added. The reaction mixture was concentrated under reduced pressure, acidified with 1 M HCl (0.8 mL) to pH 4 and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash column chromatography (CH_2Cl_2:MeOH:AcOH, 97:2:1) to afford an inseparable mixture of the *title compounds* **S2:S1** (210 mg, 4:1); **^{1}H NMR (400 MHz, $CDCl_3$)** (Boc-*N*-MeCys(S^{t}Bu)-COOH **S2**, 1:1 rotamer ratio, * denotes single rotamer signals)**:** δ 1.34 (9H, s, $SC(CH_3)_3$), 1.46 (9H, s, $OC(CH_3)_3$), 2.93 (3H, s, NCH_3), 2.99 (1H, dd, J = 13.6, 9.8 Hz, Cysβ-H_AH_B*), 3.18 (1H, m, Cysβ-H_AH_B*), 3.30 (1H, dd, J = 13.5, 4.3 Hz, Cysβ-H_AH_B), 4.60 (1H, m, Cysα-H); **^{1}H NMR (400 MHz, $CDCl_3$)** (Boc-NH-Cys(S^{t}Bu)-COOH) **S1:** δ 1.33 (9H, s, $SC(CH_3)_3$), 1.45 (9H, s, $OC(CH_3)_3$), 3.18 (1H, m, Cysβ-H_2), 4.60 (1H, m, Cysα-H), 5.36 (1H, d, J = 6.8 Hz, NH).

(*S*)-methyl 2-((*R*)-2-((*tert*-butoxycarbonyl)(methyl)amino)-3-(*tert*-butyldisulfanyl)propanamido)propanoate S3

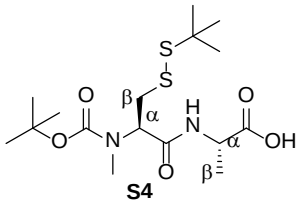


S3

To a stirring mixture of Boc-*N*-MeCys(S^{t}Bu)-COOH:Boc-NH-Cys(S^{t}Bu)-COOH **S2:S1** (279 mg, 4:1), HCTU (457 mg, 1.10 mmol) and H-Ala-OMe·HCl (161 mg, 1.15 mmol) in anhydrous CH_2Cl_2:DMF (9:1, 5mL) at 0 °C was added DIPEA (385 µL, 3.48 mmol) dropwise. The reaction mixture was stirred with slow warming to room temperature for 2 h. To this was added H_2O (5 mL) and CH_2Cl_2 (5 mL). The organic extract was washed successively with 1 M HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue

was purified by flash column chromatography (hexanes:EtOAc, 3.5:1) to afford the *title compound* **S3** as a colourless oil (219 mg, 42% over two steps); **$[\alpha]_D^{20}$** = -126.6 (*c* 0.61, $CHCl_3$); **HRMS (EI):** *m/z* [M + Na]$^+$ calculated for $C_{17}H_{32}N_2NaO_5S_2$: 431.1650; observed: 431.1642; **IR (film) ν_{max}**: 3339, 2960, 2926, 1743, 1678, 1518, 1451, 1365, 1320, 1213, 1155, 757; **^{1}H NMR (400 MHz, $CDCl_3$)** (1:1 rotamer ratio, * denotes single rotamer signals)**:** δ 1.33 (9H, s, $SC(CH_3)_3$), 1.38 (3H, m, Alaβ-H_3), 1.49 (9H, s, $OC(CH_3)_3$), 2.82 (3H, s, NCH_3), 2.91 (1H, m, Cysβ-H_AH_B*), 3.03 (1H, m, Cysβ-H_AH_B*), 3.31 (1H, m, Cysβ-H_AH_B), 3.74 (3H, s, OCH_3), 4.55 (1H, m, Alaα-H), 4.76 (1H, s, Cysα-H), 6.52 (1H, s, NH), 6.79 (1H, s, NH*); **^{13}C NMR (100 MHz, $CDCl_3$)** (1:1 rotamer ratio, * denotes single rotamer signals): δ 18.5 (CH_3, Alaβ-C), 18.7 (CH_3, Alaβ-C*), 28.5 (CH_3, $OC(CH_3)_3$), 30.0 (CH_3, $SC(CH_3)_3$), 31.4 (CH_3, NCH_3), 31.9 (CH_3, NCH_3*), 38.9 (CH_2, Cysβ-C), 48.1 (C, $SC(CH_3)_3$) 48.2 (CH, Alaα-C), 52.6 (CH_3, OCH_3), 58.7 (CH, Cysα-C), 59.5 (CH, Cysα-C*), 81.0 (C, $OC(CH_3)_3$), 81.5 (C, $OC(CH_3)_3$*), 155.4 (C, $CONCH_3$), 156.5 (C, $CONCH_3$*), 169.5 (C, CONH), 173.1 (C, CO_2CH_3).

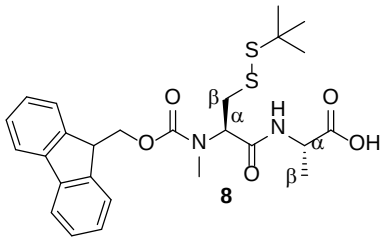
(*S*)-2-((*R*)-2-((*tert*-butoxycarbonyl)(methyl)amino)-3-(*tert*-butyldisulfanyl)propanamido)propanoic acid S4



S4

To a stirring solution of Boc-*N*-MeCys(S^{t}Bu)-Ala-CO_2Me **S3** (77 mg, 0.189 mmol) in THF:MeOH (3:1, 0.8 mL) was added an aqueous solution of LiOH·H_2O (8.3 mg, 2.0 mmol, 0.2 mL). The reaction mixture was stirred at room temperature for 1 h after which H_2O (4 mL) was added. The resultant mixture was acidified with 1 M HCl (0.3 mL) to pH 4 and extracted with CH_2Cl_2 (3 x 6 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash column chromatography (hexanes:EtOAc, 1:3) to afford the *title compound* **S4** as a white solid (66 mg, 89%); **$[\alpha]_D^{20}$** = -136.2 (*c* 0.68, $CHCl_3$); **HRMS (EI):** *m/z* [M + Na]$^+$ calculated for $C_{16}H_{30}N_2NaO_5S_2$: 417.1494; observed: 417.1476; **IR (film) ν_{max}**: 3346, 2961, 2926, 1734, 1668, 1520, 1452, 1391, 1366, 1156, 736; **mp** 130-132 °C; **^{1}H NMR (400 MHz, CD_3OD):** δ 1.36 (9H, s, $SC(CH_3)_3$), 1.42 (3H, m, Alaβ-H_3), 1.50 (9H, s, $OC(CH_3)_3$), 2.88 (3H, s, NCH_3), 3.03 (1H, m, Cysβ-H_AH_B), 3.33 (1H, m, Cysβ-H_AH_B), 4.41 (1H, m, Alaα-H), 4.75 (1H, m, Cysα-H); **^{13}C NMR (100 MHz, CD_3OD)** (1:1 rotamer ratio, * denotes single rotamer signals): δ 17.6 (CH_3, Alaβ-C), 28.7 (CH_3, $OC(CH_3)_3$), 30.2 (CH_3, $SC(CH_3)_3$), 32.2 (CH_3, NCH_3), 40.6 (CH_2, Cysβ-C), 40.8 (CH_2, Cysβ-C*), 49.5 (CH, Alaα-C), 59.6 (CH, Cysα-C), 60.8 (CH, Cysα-C*), 81.8 (C, $OC(CH_3)_3$), 82.3 (C, $OC(CH_3)_3$*), 157.2 (C, $CONCH_3$), 157.9 (C, $CONCH_3$*), 171.8 (C, CONH), 175.7 (C, COOH).

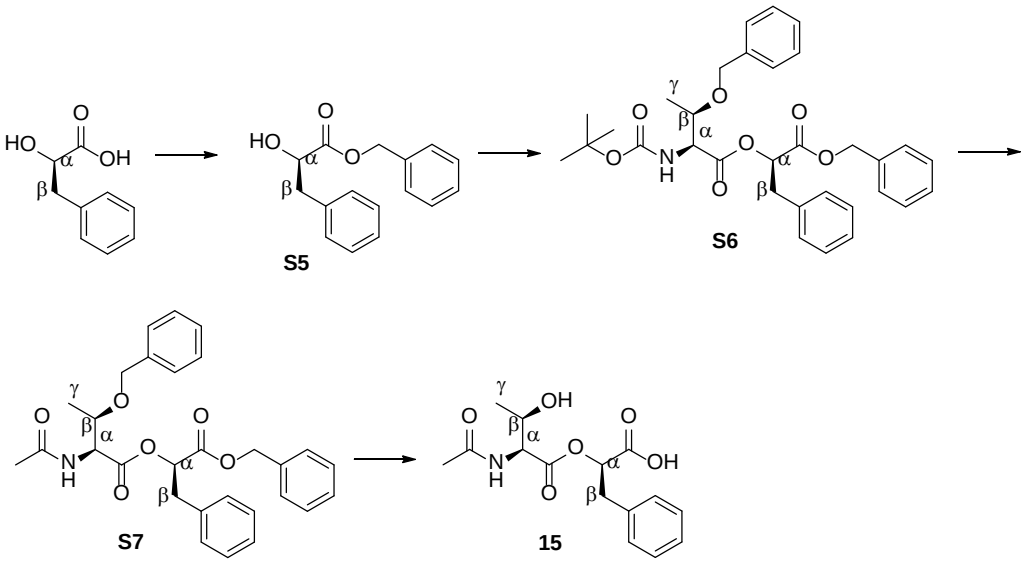
(*S*)-2-((*R*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-3-(*tert*-butyldisulfanyl)propanamido)propanoic acid 8



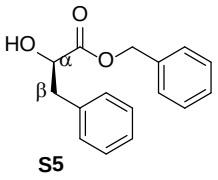
8

To a stirring solution of Boc-*N*-MeCys(S^{t}Bu)-Ala-COOH **S4** (58 mg, 0.147 mmol) in anhydrous CH_2Cl_2 (3.0 mL) was added trifluoroacetic acid (0.3 mL) dropwise. The reaction mixture was stirred at room temperature for 30 minutes, after which it was concentrated under reduced pressure. The resultant residue was dissolved in 1,4-dioxane (1.5 mL) and 10% aqueous $NaHCO_3$ solution (3 mL) was added, followed by a solution of *N*-fluorenylmethoxycarbonyl succinimide (59.4 mg, 0.176 mmol) in 1,4-dioxane (1.5 mL) dropwise. The resulting suspension was stirred at room temperature for 22 h after which H_2O (5 mL) was added. The aqueous layer was washed with Et_2O (2 x 5 mL), acidified with 1 M HCl (4 mL) to pH 4 and extracted with EtOAc (4 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash column chromatography (hexanes:EtOAc, 1:1) to afford the *title compound* **8** as a colourless foam (67 mg, 88%); **$[\alpha]_D^{20}$** = -86.8 (*c* 0.95, $CHCl_3$); **HRMS (EI):** *m/z* $[M + Na]^+$ calculated for $C_{26}H_{32}N_2NaO_5S_2$: 539.1650; observed: 539.1637; **IR (film) ν_{max}**: 3324, 2952, 2931, 1678, 1527, 1478, 1451, 1400, 1317, 1213, 1170, 758, 741; **^{1}H NMR (400 MHz, $CDCl_3$)** (2:1 rotamer ratio, * denotes minor rotamer signals)**:** δ 1.32 (9H, s, $SC(CH_3)_3$), 1.41 (3H, d, *J* = 6.5 Hz, Alaβ-H_3), 2.88 (3H, s, NCH_3*), 2.90 (3H, s, NCH_3), 2.99 (1H, dd, *J* = 13.9, 9.6 Hz, Cysβ-H_AH_B), 3.22 (1H, dd, *J* = 13.9, 5.8 Hz, Cysβ-H_AH_B), 3.32 (1H, dd, *J* = 14.0, 4.0 Hz, Cysβ-H_AH_B*), 4.28 (1H, t, *J* = 6.9, OCH_2CH), 4.39 (1H, m, OCH_2), 4.53 (2H, m, OCH_2, Alaα-H), 4.77 (1H, m, Cysα-H*), 4.99 (1H, dd, *J* = 5.8, 9.5, Cysα-H), 6.73 (1H, d, *J* = 7.4 Hz, NH*), 7.09 (1H, d, *J* = 6.9 Hz, NH), 7.32 (2H, td, *J* = 7.4, 0.9 Hz, Ar-H), 7.40 (2H, t, *J* = 7.4, 0.9 Hz, Ar-H), 7.59 (2H, dd, *J* = 7.2, 3.1 Hz, Ar-H), 7.77 (2H, dd, *J* = 7.5 Hz, Ar-H); **^{13}C NMR (100 MHz, $CDCl_3$)** (2:1 rotamer ratio, * denotes minor rotamer signals): δ 18.2 (CH_3, Alaβ-C), 30.0 (CH_3, $SC(CH_3)_3$), 30.9 (CH_3, NCH_3), 38.9 (CH_2, Cysβ-C), 47.2 (CH, OCH_2CH), 48.2 (C, $C(CH_3)_3$), 48.4 (CH, Alaα-C), 58.6 (CH, Cysα-C), 68.5 (CH_2, OCH_2), 120.2 (CH, 2 x Ar-CH), 125.1 (CH, Ar-CH), 125.2 (CH, Ar-CH), 127.3 (CH, 2 x Ar-CH), 128.0 (CH, 2 x Ar-CH), 141.5 (C, 2 x Ar-C), 143.7 (C, Ar-C), 143.9 (C, Ar-C), 157.7 (C, $CONCH_3$*), 169.2 (C, CONH), 175.5 (C, COOH).

2.2 Synthesis of (*R*)-2-(((2*S*,3*R*)-2-Acetamido-3-hydroxybutanoyl)oxy)-3-phenylpropanoic acid 15

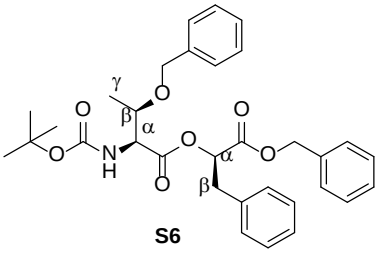


(*R*)-Benzyl 2-hydroxy-3-phenylpropanoate S5



To a stirring solution of D-phenyllactic acid (1.00 g, 6.0 mmol) in anhydrous DMF (4 mL) was added Cs_2CO_3 (2.16 g, 6.6 mmol), and the resulting suspension stirred at room temperature for 40 min. To this was added benzyl bromide (0.72 mL, 6.1 mmol) at 0 °C and the reaction mixture stirred for 1 h at 0 °C and a further 18 h at room temperature. The suspension was diluted with EtOAc (45 mL) and washed successively with saturated aqueous $NaHCO_3$ (40 mL), water (40 mL) and brine (20 mL). The organic extract was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (hexanes:EtOAc, 6:1) to afford the *title compound* **S5** as a colourless gum (1.40 g, 91%); $\mathbf{[\alpha]_D^{20}}$ = +54.5 (*c* 1.30, CH_2Cl_2) (lit.[2] +55.2 (*c* 1.88, CH_2Cl_2)) (lit.[3] +54.9 (*c* 1.50, CH_2Cl_2)); **HRMS (EI):** *m/z* $[M + Na]^+$ calculated for $C_{16}H_{16}NaO_3$: 279.0997, observed: 279.0997; **IR (film)** $\boldsymbol{\nu_{max}}$: 3450, 3031, 2933, 1733, 1497, 1455, 1262, 1187, 1091, 742, 697; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.01 (1H, dd, *J* = 13.9, 6.6 Hz, D-Plaβ-H_AH_B), 3.15 (1H, dd, *J* = 13.9, 4.6 Hz, D-Plaβ-H_AH_B), 4.52 (1H, dd, *J* = 6.6, 4.6 Hz, D-Plaα-H), 5.21 (2H, d, *J* = 1.5 Hz, OCH_2), 7.16–7.41 (10H, m, Ar-H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 40.6 (CH_2, D-Plaβ-C), 67.5 (CH_2, OCH_2), 71.4 (CH, D-Plaα-C), 127.0 (CH, Ar-CH), 128.5 (CH, 2 x Ar-CH), 128.7 (CH, 2 x Ar-CH), 128.8 (CH, 3 x Ar-CH), 129.7 (CH, 2 x Ar-CH), 135.1 (C, Ar-C), 136.2 (C, Ar-CH), 174.1 (C, COO). The spectroscopic data[3] and optical rotation[2,3] were in agreement with that reported in the literature.

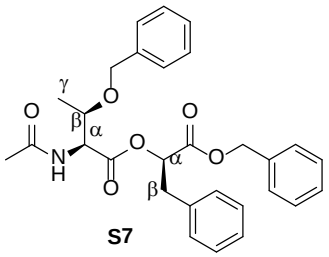
(2*S*,3*R*)-(*R*)-1-(Benzyloxy)-1-oxo-3-phenylpropan-2-yl 3-(benzyloxy)-2-((*tert*-butoxycarbonyl)aminobutanoate S6



S6

To a stirring solution of D-phenyllactic acid benzyl ester **S5** (1.30 g, 5.1 mmol) in anhydrous CH_2Cl_2 (25 mL) was added Boc-L-Thr(Bzl)-COOH (2.42 g, 7.8 mmol), DMAP (0.15 g, 1.2 mmol) and DCC (1.61 g, 7.8 mmol). The resulting suspension was stirred at room temperature for 18 h, filtered and the filtrate concentrated under reduced pressure. The crude residue was purified by flash column chromatography (hexanes:EtOAc, 4:1) to afford the *title compound* **S6** as a colourless oil (2.60 g, 95%); $[\alpha]_D^{20}$ = +83.0 (*c* 1.00, $CHCl_3$); **HRMS (EI):** *m/z* $[M + H]^+$ calculated for $C_{32}H_{38}NO_7$: 548.2648, observed: 548.2645; **IR (film)** ν_{max}: 3448, 3033, 2978, 2934, 1751, 1715, 1497, 1455, 1366, 1158, 1070, 910, 732, 695; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.20 (3H, d, *J* = 6.2 Hz, Thrγ-H_3), 1.46 (9H, s, $C(CH_3)_3$), 3.06 (1H, dd, *J* = 14.2, 8.4 Hz, D-Plaβ-H_AH_B), 3.14 (1H, dd, *J* = 14.2, 4.8 Hz, D-Plaβ-H_AH_B), 3.91 (1H, d, *J* = 11.5 Hz, CHOCH_2), 3.97 (1H, qd, *J* = 6.2, 2.2 Hz, Thrβ-H), 4.24 (1H, d, *J* = 11.5 Hz, CHOCH_2), 4.43 (1H, dd, *J* = 9.7, 2.2 Hz, Thrα-H), 5.14 (2H, s, CO_2CH_2), 5.24 (1H, dd, *J* = 8.5, 4.9 Hz, D-Plaα-H), 5.28 (1H, d, *J* = 9.8 Hz, NH), 7.11–7.35 (15H, m, Ar-H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 16.5 (CH_3, Thrγ-C), 28.5 (CH_3, OC(CH_3)$_3$), 37.4 (CH_2, D-Plaβ-C), 58.2 (CH, Thrα-C), 67.3 (CH_2, CO_2CH_2), 70.9 (CH_2, CHOCH_2), 74.1 (CH, D-Plaα-C), 75.2 (CH, Thrβ-C), 79.9 (C, $C(CH_3)_3$), 127.2 (CH, Ar-CH), 127.6 (CH, 2 x Ar-CH), 127.7 (CH, Ar-CH), 128.3 (CH, 2 x Ar-CH), 128.4 (CH, 2 x Ar-CH), 128.5 (CH, Ar-CH), 128.7 (CH, 4 x Ar-CH), 129.4 (CH, 2 x Ar-CH), 135.2 (C, Ar-C), 135.7 (C, Ar-C), 138.2 (C, Ar-C), 155.9 (C, CONH), 169.1 (C, CO_2CH_2), 170.8 (C, NHCHCO).

(2*S*,3*R*)-(*R*)-1-(Benzyloxy)-1-oxo-3-phenylpropan-2-yl 2-acetamido-3-(benzyloxy)butanoate S7

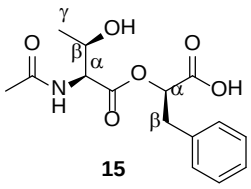


S7

To a stirring solution of Boc-L-Thr(Bzl)-Pla-CO_2Bn **S6** (2.60 g, 4.75 mmol) in anhydrous CH_2Cl_2 (50 mL) was added trifluoroacetic acid (5 mL, 65.3 mmol) dropwise. The resultant mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the

resultant residue was re-dissolved in Et_2O (20 mL) and saturated aqueous $NaHCO_3$ (40 mL). To this was added acetic anhydride (1.2 mL, 12.7 mmol) and the reaction mixture stirred at room temperature for 2 h. The reaction mixture was extracted with EtOAc (4 x 25 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (hexanes:EtOAc, 1:1) to afford the *title compound* **S7** as a colourless oil (2.19 g, 95%); **$[\alpha]_D^{20}$** = +27.9 (*c* 1.00, $CHCl_3$); **HRMS (EI):** *m/z* $[M + Na]^+$ calculated for $C_{29}H_{31}NNaO_6$: 512.2049; observed: 512.2019; **IR (film) ν_{max}**: 3442, 3032, 2935, 1748, 1708, 1672, 1498, 1455, 1378, 1273, 1185, 1155, 1091, 1028, 908, 728, 696; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.15 (3H, d, *J* = 6.2 Hz, Thrγ-H_3), 2.00 (3H, s, $COCH_3$), 3.04 (1H, dd, *J* = 14.3, 8.7 Hz, D-Plaβ-H_AH_B), 3.12 (1H, dd, *J* = 14.3, 4.7 Hz, D-Plaβ-H_AH_B), 3.88 (1H, d, *J* = 11.4 Hz, $CHOCH_2$), 3.96 (1H, qd, *J* = 6.2, 2.2 Hz, Thrβ-H), 4.23 (1H, d, *J* = 11.4 Hz, $CHOCH_2$), 4.78 (1H, dd, *J* = 9.3, 2.2 Hz, Thrα-H), 5.13 (2H, s, CO_2CH_2), 5.22 (1H, dd, *J* = 8.7, 4.7 Hz, D-Plaα-H), 6.12 (1H, d, *J* = 9.3 Hz, NH), 7.09–7.34 (15H, m, Ar-H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 16.6 (CH_3, Thrγ-C), 23.2 (CH_3, $COCH_3$), 37.3 (CH_2, D-Plaβ-C), 56.5 (CH, Thrα-C), 67.3 (CH_2, CO_2CH_2), 71.0 (CH_2, $CHOCH_2$), 74.1 (CH, D-Plaα-C), 75.0 (CH, Thrβ-C), 127.2 (CH, Ar-CH), 127.7 (CH, 2 x Ar-CH), 127.8 (CH, Ar-CH), 128.4 (CH, 2 x Ar-CH), 128.5 (CH, 2 x Ar-CH), 128.6 (CH, Ar-CH), 128.7 (CH, 4 x Ar-CH), 129.4 (CH, 2 x Ar-CH), 135.2 (C, Ar-C), 135.6 (C, Ar-C), 138.0 (C, Ar-C), 168.9 (C, CO_2CH_2), 170.3 (C, CONH), 170.4 (C, NHCHCO).

(*R*)-2-(((2*S*,3*R*)-2-Acetamido-3-hydroxybutanoyl)oxy)-3-phenylpropanoic acid 15

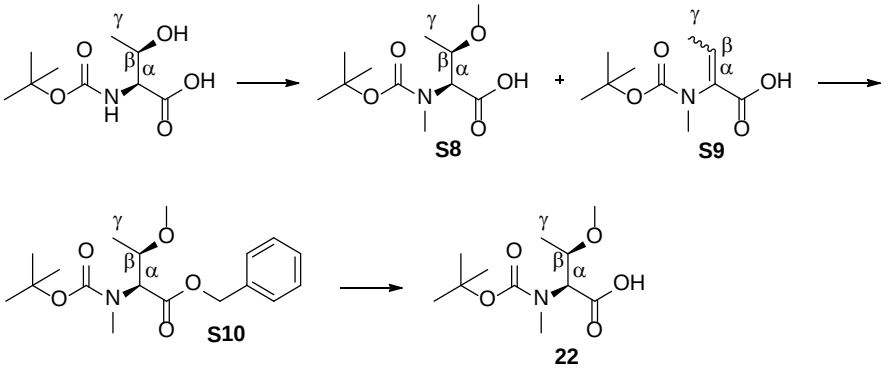


15

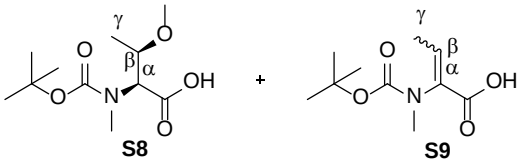
To a stirring solution of Ac-L-Thr(Bzl)-Pla-CO_2Bn **S7** (2.20 g, 4.5 mmol) in MeOH (50 mL) was added palladium on activated carbon (10%, 200 mg, 1.7 mmol). The resulting mixture was stirred under an atmosphere of H_2 (balloon) at room temperature for 6 h. The reaction mixture was filtered through a pad of Celite® and the filtrate concentrated under reduced pressure to afford the *title compound* **15** as a white solid (1.30 g, 94%); **$[\alpha]_D^{20}$** = -10.7 (*c* 1.10, MeOH); **HRMS (EI):** *m/z* $[M + Na]^+$ calculated for $C_{15}H_{19}NNaO_6$: 332.1110; observed: 332.1113; **IR (film) ν_{max}**: 3502, 3311, 2904, 1736, 1712, 1564, 1498, 1443, 1413, 1294, 1230, 1147, 1112, 1057, 1019, 705, 654; **mp** 152-155 °C; **^{1}H NMR (400 MHz, CD_3OD):** δ 1.13 (3H, d, *J* = 6.4, Thrγ-H_3), 2.00 (3H, s, $COCH_3$), 3.14 (1H, dd, *J* = 14.4, 8.2 Hz, D-Plaβ-H_AH_B), 3.22 (1H, dd, *J* = 14.4, 4.4 Hz, D-Plaβ-H_AH_B), 4.17 (1H, qd, *J* = 6.4, 3.6 Hz, Thrβ-H), 4.46 (1H, d, 3.6, Thrα-H), 5.24 (1H, dd, *J* =8.1, 4.4 Hz, D-Plaα-H), 7.22–7.31 (5H, m, Ar-H); **^{13}C NMR (100 MHz, CD_3OD)**: δ 20.1 (CH_3, Thrγ-C), 22.4 (CH_3, $COCH_3$), 38.1 (CH_2, D-Plaβ-C), 59.6 (CH, Thrα-C), 68.3 (CH,

Thrβ-C), 75.0 (CH, D-Plaα-C), 128.0 (CH, Ar-CH), 129.4 (CH, 2 x Ar-CH), 130.5 (CH, 2 x Ar-CH), 137.5 (C, Ar-C), 171.4 (C, NHCH*C*O), 172.7 (C, COOH), 173.5 (C, CH_3*C*O).

2.3 Synthesis of (2*S*,3*R*)-2-((*tert*-butoxycarbonyl)(methyl)amino)-3-methoxybutanoic acid 22

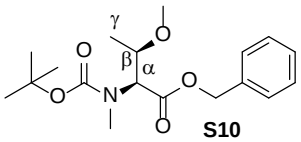


Mixture of (2*S*,3*R*)-2-((*tert*-butoxycarbonyl)(methyl)amino)-3-methoxybutanoic acid S8 and 2-((*tert*-butoxycarbonyl)(methyl)amino)but-2-enoic acid S9



To a stirring solution of Boc-L-Thr(OH)-COOH (1.50 g, 6.8 mmol) and iodomethane (4.26 mL, 68.4 mmol) in anhydrous THF (40 mL) at 0 °C was added sodium hydride (1.37 g, 34.2 mmol, 60% dispersion in mineral oil). The resulting suspension was stirred at 0 °C for 1 h and a further 17 h at room temperature. The reaction mixture was diluted with water (10 mL) and EtOAc (10 mL), concentrated under reduced pressure and acidified with 10% citric acid to pH 4. The aqueous layer was extracted with EtOAc (4 x 25 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash column chromatography (hexanes:EtOAc, 3:1) to afford an inseparable mixture of the *title compounds* **S8:S9** (1.5 g, 3:1); **^{1}H NMR (400 MHz, $CDCl_3$)** (Boc-*N*-MeThr(OMe)-COOH **S8**, 2:1 rotamer ratio, * denotes minor rotamer signals)**:** δ 1.17 (3H, d, *J* = 6.3 Hz, Thrγ-H_3), 1.19 (3H, d, *J* = 5.8 Hz, Thrγ-H_3*), 1.44 (9H, s, $C(CH_3)_3$*), 1.46 (9H, s, $C(CH_3)_3$), 2.95 (3H, s, NCH_3), 2.97 (3H, s, NCH_3*), 3.31 (3H, s, OCH_3), 3.97 (1H, t, *J* = 5.6 Hz, Thrβ-H*), 4.05 (1H, qd, *J* = 6.2, 5.8 Hz, Thrβ-H), 4.62 (1H, d, *J* = 4.8 Hz, Thrα-Hs*), 4.87 (1H, d, *J* = 4.8 Hz, Thrα-H); **^{1}H NMR (400 MHz, $CDCl_3$)** (Boc-*N*-MeDhb-COOH **S9**, 2:1 isomer ratio, * denotes minor isomer signals)**:** δ 1.39 (9H, s, $C(CH_3)_3$), 1.81 (3H, d, *J* = 7.2 Hz, Dhbγ-H_3), 2.97 (3H, s, NCH_3), 6.85 (1H, q, *J* = 7.1 Hz, Dhbβ-H), 6.99 (1H, q, *J* = 7.1 Hz, Dhbβ-H*).

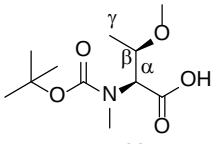
Benzyl 2-((*tert*-butoxycarbonyl)(methyl)amino-3-methoxybutanoate S10



S10

To a stirring solution of Boc-*N*-MeThr(OMe)-COOH:Boc-*N*-MeDhb-COOH **S8:S9** (1.50 g, 2:1) in anhydrous DMF (10 mL) was added Cs_2CO_3 (2.44 g, 7.5 mmol), and the resulting suspension stirred at room temperature for 15 min. To this was added benzyl bromide (0.9 mL, 7.5 mmol) at 0 °C and the reaction mixture stirred for 30 min at 0 °C and a further 16 h at room temperature. The suspension was diluted with EtOAc (50 mL) and washed successively with saturated aqueous $NaHCO_3$ (50 mL), water (2 x 50 mL) and brine (50 mL). The organic extract was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (hexanes:EtOAc, 6:1) to afford the *title compound* **S10** as a colourless oil (1.10 g, 48% over two steps); $\mathbf{[\alpha]_D^{20}}$ = +18.7 (*c* 1.00, $CHCl_3$); **HRMS (EI):** *m/z* $[M + Na]^+$ calculated for $C_{18}H_{27}NNaO_5$: 360.1787, observed: 360.1785; **IR (film)** $\boldsymbol{\nu_{max}}$: 2976, 2933, 1748, 1688, 1480, 1455, 1391, 1366, 1314, 1139, 1079, 872, 697; **^{1}H NMR (400 MHz, $CDCl_3$)** (2:1 rotamer ratio, * denotes minor rotamer signals)**:** δ 1.14 (3H, d, *J* = 6.4 Hz, Thrγ-H_3), 1.16 (3H, d, *J* = 6.4 Hz, Thrγ-H_3*), 1.41 (9H, s, $C(CH_3)_3$*), 1.46 (9H, s, $C(CH_3)_3$), 2.96 (3H, s, NCH_3), 2.97 (3H, s, NCH_3*), 3.21 (3H, s, OCH_3), 3.24 (3H, s, OCH_3*), 3.96 (1H, qd, *J* = 6.1, 6.0 Hz, Thrβ-H *), 4.03 (1H, qd, *J* = 6.4, 4.8 Hz, Thrβ-H), 4.62 (1H, d, *J* = 5.3 Hz, Thrα-H*), 4.97 (1H, d, *J* = 4.6 Hz, Thrα-H), 5.13 (1H, d, *J* = 12.4, CH_2), 5.15 (1H, d, *J* = 12.4, CH_2*), 5.24 (1H, d, *J* = 12.4, CH_2), 7.32–7.35 (5H, m, Ar-H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 15.3 (CH_3, Thrγ-C), 15.8 (CH_3, Thrγ-C*), 28.5 (CH_3, OC(CH_3)$_3$), 32.8 (CH_3, NCH_3*), 33.2 (CH_3, NCH_3), 57.2 (CH_3, OCH_3), 62.3 (CH, Thrα-C), 63.8 (CH, Thrα-C*), 66.7 (CH_2, CH_2*), 66.8 (CH_2, CH_2), 76.5 (CH, Thrβ-C*), 77.1 (CH, Thrβ-C), 80.6 (C, $C(CH_3)_3$), 80.4 (C, $C(CH_3)_3$*), 128.3 (CH, 2 x Ar-CH), 128.4 (CH, Ar-CH*), 128.6 (CH, 2 x Ar-CH), 128.7 (CH, Ar-CH), 135.8 (C, Ar-C*), 135.9 (C, Ar-C), 155.9 (C, CON*), 157.1 (C, CON), 170.2 (C, COO*), 170.4 (C, COO).

(2*S*,3*R*)-2-((*tert*-butoxycarbonyl)(methyl)amino)-3-methoxybutanoic acid 22

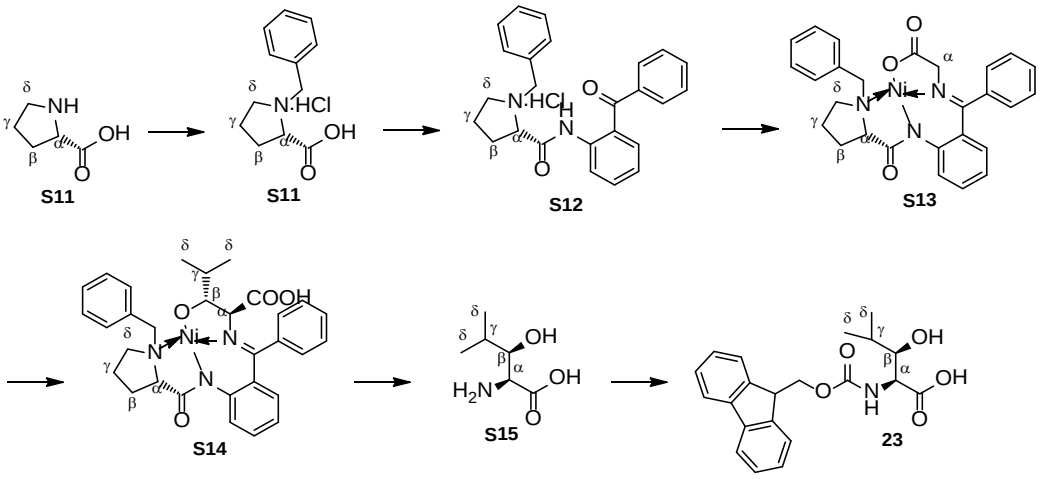


22

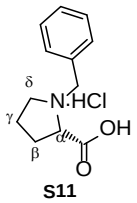
To a stirring solution of Boc-*N*-MeThr(OMe)-CO_2Bn **S10** (1.0 g, 3.0 mmol) in MeOH (10 mL) was added palladium on activated carbon (10%, 70 mg, 0.6 mmol). The resulting mixture was stirred under an atmosphere of H_2 (balloon) at room temperature for 6 h. The reaction mixture was filtered through a pad of Celite®, the filtrate concentrated under reduced pressure and the crude residue

was purified by flash column chromatography (hexanes:EtOAc, 2:1) to afford the *title compound* **22** as a white solid (610 mg, 82%); $[\alpha]_D^{20}$ = +9.6 (*c* 1.25, MeOH); **HRMS (EI):** *m/z* $[M + Na]^+$ calculated for $C_{11}H_{21}NNaO_5$: 270.1317, observed: 270.1317; **IR (film)** ν_{max}: 3105, 2976, 2936, 1740, 1640, 1483, 1457, 1366, 1321, 1253, 1150, 1081, 872, 745, 670; **mp** 72-75 °C; **^{1}H NMR (400 MHz, CD_3OD)** (3:2 rotamer ratio, * denotes minor rotamer signals)**:** δ 1.16 (3H, d, *J* = 6.3 Hz, Thrγ-H_3), 1.20 (3H, d, *J* = 6.2 Hz, Thrγ-H_3*), 1.46 (9H, s, $C(CH_3)_3$*), 1.48 (9H, s, $C(CH_3)_3$), 2.93 (3H, s, NCH_3*), 2.95 (3H, s, NCH_3), 3.33 (3H, s, OCH_3), 4.00 (1H, qd, *J* = 6.2, 6.0 Hz, Thrβ-H*), 4.05 (1H, qd, *J* = 6.3, 4.9 Hz, Thrβ-H), 4.55 (1H, d, *J* = 5.4 Hz, Thrα-H*), 4.77 (1H, d, *J* = 4.7 Hz, Thrα-H); **^{13}C NMR (100 MHz, CD_3OD)**: δ 15.8 (CH_3, Thrγ-C), 16.3 (CH_3, Thrγ-C*), 28.6 (CH_3, $OC(CH_3)_3$), 33.5 (CH_3, NCH_3*), 33.6 (CH_3, NCH_3), 57.5 (CH_3, OCH_3), 63.4 (CH, Thrα-C), 65.0 (CH, Thrα-C*), 77.6 (CH, Thrβ-C*), 78.0 (CH, Thrβ-C), 81.4 (C, $C(CH_3)_3$), 81.8 (C, $C(CH_3)_3$*), 157.8 (C, CON*), 158.7 (C, CON), 173.1 (C, COO*), 173.3 (C, COO).

2.4 Synthesis of (2*S*,3*R*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino-3-hydroxy-4-methylpentanoic acid 23



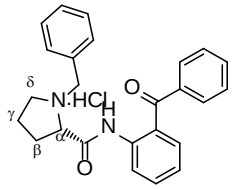
(*S*)-1-Benzylpyrrolidine-2-carboxylic acid hydrochloride S11



A suspension of L-proline (10.1 g, 87.7 mmol) and potassium hydroxide (18.7 g, 333 mmol) in isopropanol (85 mL) was heated at 40 °C until mostly dissolved. To this was added benzyl chloride (15.2 mL, 132 mmol) dropwise at 0 °C, and the reaction mixture was stirred at 40 °C for 6 h. The resultant suspension was cooled to room temperature and acidified with concentrated HCl to pH 4. CH_2Cl_2 (150 mL) was added and the mixture stored at 4 °C overnight. The solid was removed by

filtration and the filtrate was concentrated under reduced pressure to give a solid residue that was suspended in acetone with stirring. The precipitate was isolated by filtration and air dried to afford the *title compound* **S11** as a white solid (12.5 g, 59%); **$[\alpha]_D^{20}$** = -24.6 (*c* 1.00, EtOH) (lit.[4] -25.8 *c* 1.00, EtOH); **^{1}H NMR (400 MHz, D_2O):** δ 1.96–2.06 (1H, m, Proγ-H_AH_B), 2.08–2.24 (2H, m, Proβ-H_AH_B, Proγ-H_AH_B), 2.51–2.59 (1H, m, Proβ-H_AH_B), 3.31–3.38 (1H, m, Proδ-H_AH_B), 3.63–3.69 (1H, m, Proδ-H_AH_B), 4.20 (1H, dd, *J* = 9.4, 7.3, Proα-H), 4.43 (1H, d, *J* = 12.9, NCH_2C), 4.47 (1H, d, *J* = 12.9, NCH_2C), 7.52 (5H, br s, Ar-H); **^{13}C NMR (100 MHz, D_2O)**: δ 22.5 (CH_2, Proγ-C), 28.5 (CH_2, Proβ-C), 54.8 (CH_2, Proδ-C), 58.5 (CH_2, N*C*H_2C), 67.1 (CH, Proα-C), 129.2 (CH, 2 x Ar-CH), 129.8 (C, Ar-C), 130.1 (CH, Ar-CH), 130.6 (CH, 2 x Ar-CH), 172.3 (C, COOH). The spectroscopic data[5] and optical rotation[4] were in agreement with that reported in the literature.

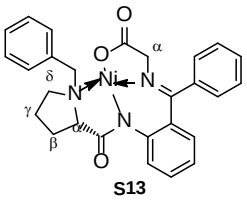
(*S*)-2-[*N*-(*N*'-Benzylpropyl)amino]benzophenone hydrochloride S12



S12

To a stirring solution of *N*-methylimidazole (5.88 mL, 73.8 mmol) in anhydrous CH_2Cl_2 (90 mL) at 0 °C under an atmosphere of N_2, was added methanesulfonyl chloride (1.44 mL, 18.5 mmol) followed by BP·HCl **S11** (4.475 g, 18.5 mmol). The reaction mixture was stirred for 5 min, after which 2-aminobenzophenone (3.29 g, 16.7 mmol) was added at room temperature. The resultant mixture was stirred at 48 °C for 19 h, and then quenched with saturated ammonium chloride solution (40 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was diluted with minimal acetone, acidified with concentrated HCl to pH 2 and stirred at room temperature for 3 h. The resulting solid was filtered, washed with ice cold acetone and air dried to afford the *title compound* **S12** as a pale cream solid (6.47 g, 83%); **$[\alpha]_D^{20}$** = -114 (*c* 1.00, MeOH) (lit.[4] -134 *c* 1.00, MeOH); **^{1}H NMR (400 MHz, CD_3OD):** δ 1.59–1.68 (1H, m, Proβ-H_AH_B), 1.83–1.94 (1H, m, Proγ-H_AH_B), 2.11–2.21 (1H, m, Proγ-H_AH_B), 2.37–2.47 (1H, m, Proβ-H_AH_B), 3.32–3.39 (2H, m, Proδ-H_AH_B), 3.56–3.61 (1H, m, Proδ-H_AH_B), 4.32–4.40 (3H, m, Proα-H, N*C*H_2C), 7.40–7.80 (14H, m, Ar-H, NH); **^{13}C NMR (100 MHz, CD_3OD)**: δ 23.8 (CH_2, Proγ-C), 29.5 (CH_2, Proβ-C), 55.8 (CH_2, Proδ-C), 59.3 (CH_2, N*C*H_2C), 68.0 (CH, Proα-C), 125.6 (CH, Ar-CH), 126.9 (CH, Ar-CH), 129.5 (CH, 2 x Ar-CH), 130.2 (CH, 2 x Ar-CH), 131.1 (C, Ar-C), 131.2 (CH, 3 x Ar-CH), 131.5 (CH, Ar-CH), 132.0 (CH, 2 x Ar-CH), 133.1 (CH, Ar-CH), 134.3 (CH, Ar-CH), 136.0 (C, Ar-C), 138.5 (C, Ar-C), 167.2 (C, *C*ONH), 197.6 (C, C_2*C*O). The spectroscopic data[5] and optical rotation[4] are in agreement with that reported in the literature.

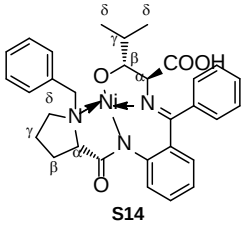
(*S*)-Glycine-nickel-(*S*)-2-[*N*-(*N*'-benzylpropyl)amino]benzophenone S13



S13

To a stirring solution of BPB·HCl **S12** (6.0 g, 14.3 mmol) in methanol (60 mL) at 50 °C under an atmosphere of N_2, was added glycine (5.5 g, 73.3 mmol), $Ni(NO_3)_2{\cdot}6H_2O$ (8.3 g, 28.6 mmol) and KOH (6.8 g, 121.4 mmol). The suspension was stirred under reflux for 1 h, cooled to room temperature, neutralised with acetic acid and stirred at room temperature for 15 min. Water (240 mL) was added and the mixture allowed to stand at room temperature for 15 h. The aqueous layer was extracted with CH_2Cl_2 (3 x 200 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the resulting residue by flash column chromatography (CH_2Cl_2: acetone, 7:1 to 2:1) afforded the *title compound* **S13** as a bright red solid (4.42 g, 62%); $\mathbf{[\alpha]_D^{20}}$ = +2392 (*c* 0.15, MeOH) (lit.[4] +2006 *c* 0.10, MeOH); **mp** 206-210 °C (lit.[6] 208-212 °C); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 2.07–2.15 (2H, m, Proγ-H_AH_B, Proδ-H_AH_B), 2.36–2.47 (1H, m, Proβ-H_AH_B), 2.52–2.60 (1H, m, Proβ-H_AH_B), 3.26–3.36 (1H, m, Proγ-H_AH_B), 3.45–3.48 (1H, m, Proα-H), 3.65–3.80 (4H, m, Proδ-H_AH_B, NCH_2C, Glyα-H_2), 4.48 (1H, d, *J* = 12.6 Hz, NCH_2C), 6.69 (1H, t, *J* = 7.1 Hz, Ar-H), 6.78–6.80 (1H, m, Ar-H), 6.95–6.99 (1H, m, Ar-H), 7.09 (1H, d, *J* = 6.0 Hz, Ar-H), 7.20 (1H, t, *J* = 7.1 Hz, Ar-H), 7.28–7.32 (1H, m, Ar-H), 7.40–7.44 (2H, m, Ar-H), 7.47–7.52 (3H, m, Ar-H), 8.07 (2H, d, *J* = 6.9 Hz, Ar-H), 8.29 (1H, d, *J* = 8.5 Hz, Ar-H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 23.8 (CH_2, Proγ-C), 30.8 (CH_2, Proβ-C), 57.6 (CH_2, Proδ-C), 61.5 (CH_2, Glyα-C), 63.3 (CH_2, N*C*H_2C), 70.0 (CH, Proα-C), 120.9 (CH, Ar-CH), 124.4 (CH, Ar-CH), 125.3 (C, Ar-C), 125.8 (CH, Ar-CH), 126.4 (CH, Ar-CH), 129.0 (CH, 2 x Ar-CH), 129.2 (CH, Ar-CH), 129.5 (CH, Ar-CH), 129.7 (CH, Ar-CH), 129.8 (CH, Ar-CH), 131.8 (CH, 2 x Ar-CH), 132.3 (CH, Ar-CH), 133.3 (CH, Ar-CH), 133.4 (C, Ar-C), 134.8 (C, Ar-C), 142.7 (C, Ar-C), 171.8 (C, C_2*C*N), 177.4 (C, *C*OO), 181.5 (C, *C*ON). The spectroscopic data[5] and optical rotation[4] are in agreement with that reported in the literature.

Ni(II)-(*S*)-BPB/(2*S*,3*R*)-2-amino-3-hydroxy-4-methyl-pentanoic acid Schiff base complex S14

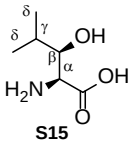


S14

To a stirring solution of glycine-Ni(II)-BPB **S13** (1.00 g, 2.0 mmol) in anyhydrous THF (12 mL) under an atmosphere of Ar was added sodium hydride (80 mg, 2.0 mmol, 60% dispersion in mineral oil). The

stirred mixture was cooled with liquid nitrogen and degassed *via* the freeze/thaw technique. To the degassed mixture was added isobutyraldehyde (0.36 mL, 4.0 mmol) at 16 °C under an atmosphere of Ar. The reaction mixture was stirred at this temperature for 10 min, after which it was quenched by pouring into 10% aqueous acetic acid (75 mL). The aqueous layer was extracted with EtOAc (3 x 150 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the resulting residue by flash column chromatography (EtOAc: acetone, 4:1) afforded the *title compound* **S14** as a red solid (875 mg, 77%); **$[\alpha]_D^{20}$** = +2836 (*c* 0.16, $CHCl_3$) (lit.[7] +3100 *c* 0.04, $CHCl_3$); **mp** 154-155 °C (lit.[7] 157 °C); **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 0.83 (3H, d, *J* = 5.9 Hz, β-Hyleuδ-H_3), 1.16 (3H, d, *J* = 6.0 Hz, β-Hyleuδ-H_3), 2.15 (2H, m, Proγ-H_AH_B, Proδ-H_AH_B), 2.54 (2H, m, Proβ-H_AH_B, β-Hyleuγ-H), 2.84 (1H, Proβ-H_AH_B), 3.53 (3H, Proγ-H_AH_B, Proδ-H_AH_B, Proα-H), 3.59 (1H, d, *J* = 12.5 Hz, NCH_2C), 3.94 (1H, m, β-Hyleuβ-H), 4.13 (1H, d, *J* = 5.1 Hz, β-Hyleuα-H), 4.43 (1H, d, *J* = 12.5 Hz, NCH_2C), 6.69 (2H, m, Ar-H), 7.00 (1H, d, *J* = 6.6 Hz, Ar-H), 7.16–7.22 (2H, m, Ar-H), 7.32–7.39 (3H, m, Ar-H), 7.48–7.54 (3H, m, Ar-H), 8.11 (2H, d, *J* = 6.6 Hz, Ar-H), 8.25 (1H, d, *J* = 8.4 Hz, Ar-H); **^{13}C NMR (100 MHz, $CDCl_3$)**: *δ* 15.8 (CH_3, β-Hyleuδ-C), 21.9 (CH_3, β-Hyleuδ-C), 23.7 (CH_2, Proγ-C), 30.1 (CH, β-Hyleuγ-C), 30.8 (CH_2, Proβ-C), 57.2 (CH_2, Proδ-C), 63.4 (CH_2, N*C*H_2C), 70.6 (CH, Proα-C), 73.2 (CH, β-Hyleuα-C), 77.7 (CH, β-Hyleuβ-C), 120.8 (CH, Ar-CH), 123.4 (CH, Ar-CH), 126.6 (C, Ar-C), 127.2 (CH, Ar-CH), 128.9 (CH, 2 x Ar-CH), 129.0 (CH, 3 x Ar-CH), 129.2 (CH, Ar-CH), 129.9 (CH, Ar-CH), 131.6 (CH , 2 x Ar-CH), 132.5 (CH, Ar-CH), 133.4 (C, Ar-C), 133.9 (CH, Ar-CH), 134.3 (C, Ar-C), 142.6 (C, Ar-C), 172.2 (C, C_2*C*N), 178.7 (C, *C*OO), 180.4 (C, *C*ON). The spectroscopic data[7] and optical rotation[7] are in agreement with that reported in the literature.

(2*S*,3*R*)-2-amino-3-hydroxy-4-methylpentanoic acid S15

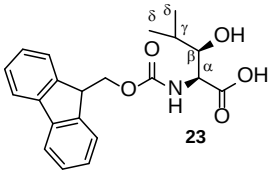


S15

To a stirring solution of (2*S*,3*R*)-hydroxyleucine-Ni(II)-BPB **S14** (80 mg, 0.14 mmol) in methanol (2 mL) was added 2M aqueous HCl (1.4 mL) and the mixture stirred under reflux for 1 h. The reaction mixture was cooled to room temperature and basified with 25% aqueous NH_3 to pH 9. The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL), concentrated under reduced pressure and the crude residue purified by ion exchange chromatography (DOWEX-50Wx4-50, water then 5% aqueous NH_3) and lyophilised to afford the *title compound* **S15** as a white fluffy solid (19 mg, 93%); **$[\alpha]_D^{20}$** = +23.0 (*c* 1.00, 5N HCl) (lit.[7] +19.0 *c* 1.00, 5N HCl); **^{1}H NMR (400 MHz, D_2O):** *δ* 0.83 (3H, d, *J* = 6.8 Hz, β-Hyleuδ-H_3), 0.88 (3H, d, *J* = 6.6 Hz, β-Hyleuδ-H_3), 1.63 (1H, m, β-Hyleuγ-H), 3.64 (1H, dd, *J* = 7.9, 3.8 Hz, β-Hyleuβ-H), 3.70 (1H, d, *J* = 3.8 Hz, β-Hyleuα-H); **^{13}C NMR (100 MHz, D_2O)**: *δ* 17.4 (CH_3, β-Hyleuδ-C),

18.4 (CH_3, β-Hyleuδ-C), 30.2 (CH, β-Hyleuγ-C), 56.9 (CH, β-Hyleuα-C), 75.1 (CH, β-Hyleuβ-C), 173.4 (C, *C*OO). The spectroscopic data[8] and optical rotation[7] are in agreement with that reported in the literature.

(2*S*,3*R*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino-3-hydroxy-4-methylpentanoic acid 23



23

To a stirring solution of (2*S*,3*R*)-hydroxyleucine **S15** (40 mg, 0.27 mmol) in a mixture of 10% aqueous Na_2CO_3 (4 mL) and 1,4-dioxane (3 mL) was added a solution of *N*-fluorenylmethoxycarbonyl succinimide (108 mg, 0.32 mmol) in 1,4-dioxane (3 mL) dropwise. The resultant suspension was stirred at room temperature for 24 h. The reaction mixture was acidified with 1 M HCl to pH 3 and the aqueous phase was extracted with EtOAc (4 x 10 mL). The combined organic extracts were washed with saturated NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (hexane:EtOAc, 3:1 to 1:1) afforded the *title compound* **23** as a colourless foam (70 mg, 70%); $\mathbf{[\alpha]_D^{20}}$ = -2.8 (*c* 1.00, $CHCl_3$); **HRMS (EI):** *m/z* [M + Na]$^+$ calculated for $C_{21}H_{23}NNaO_5$: 392.1474; observed: 392.1468; **IR (film)** $\boldsymbol{\nu_{max}}$: 3350, 3066, 2962, 2926, 1713, 1522, 1450, 1415, 1328, 1249, 1218, 1117, 1055, 758, 740; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 0.93 (3H, d, *J* = 6.6 Hz, β-Hyleuδ-H_3), 1.03 (3H, d, *J* = 6.6 Hz, β-Hyleuδ-H_3), 1.75 (1H, m, β-Hyleuγ-H), 3.82 (1H, d, *J* = 9.2 Hz, β-Hyleuβ-H), 4.21 (1H, t, *J* = 7.1, C*H*CH_2), 4.40 (2H, m, CHC*H*$_2$), 4.57 (1H, d, *J* = 8.7, β-Hyleuα-H), 5.79 (1H, d, *J* = 9.3, NH), 7.29 (2H, t, *J* = 7.3 Hz, Ar-H), 7.38 (2H, t, *J* = 7.4 Hz, Ar-H), 7.58 (2H, t, *J* = 6.8 Hz, Ar-H), 7.74 (2H, t, *J* = 7.4 Hz, Ar-H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 19.0 (CH_3, β-Hyleuδ-C), 19.3 (CH_3, β-Hyleuδ-C), 30.9 (CH, β-Hyleuγ-C), 47.2 (CH, *C*HCH_2), 56.4 (CH, β-Hyleuα-C), 67.5 (CH_2, CH*C*H_2), 77.4 (CH, β-Hyleuβ-C), 120.1 (CH, 2 x Ar-CH), 125.2 (CH, Ar-CH), 125.3 (CH, Ar-CH), 127.2 (CH, 2 x Ar-CH), 127.8 (CH, 2 x Ar-CH), 141.4 (C, 2 x Ar-C), 143.7 (C, Ar-C), 144.0 (C, Ar-C), 157.2 (C, *C*ON), 175.9 (C, *C*OOH).

3. General procedure for peptide synthesis

The peptides were assembled manually by Fmoc-solid phase peptide synthesis (Fmoc-SPPS) using a fritted glass reaction vessel.

Method 1. **Attachment of *C*-terminal residue:** To 2-chlorotrityl chloride resin (100 mg, 0.1 mmol) pre-swollen in anhydrous CH_2Cl_2 (10 mL, 5 min), was added a solution of Fmoc-Hyleu-COOH **23** (74 mg, 0.2 mmol) and $^{i}Pr_2EtN$ (85 µL, 0.50 mmol) in anhydrous CH_2Cl_2 (2 mL). The reaction mixture was gently agitated at room temperature for 1 h. The resin was filtered and washed with CH_2Cl_2 (2 x 5 mL). A mixture of CH_2Cl_2:MeOH:$^{i}Pr_2EtN$ (8:1.5:0.5, v/v, 2 mL) was added and the reaction agitated for 10 min, filtered and repeated once for a further 10 min. The resin was filtered and washed with CH_2Cl_2 (1 x 5 mL) and DMF (2 x 5 mL).

Method 2. General procedure for removal of N^{α}-Fmoc-protecting group: The peptidyl resin was treated with a solution of 20% piperidine in DMF (2 mL) and the mixture agitated at room temperature for 5 min, filtered and repeated once for a further 15 min. The resin was filtered and washed with DMF (3 x 5 mL).

Method 3. Coupling method 1: To the peptidyl resin was added a mixture of Fmoc-*N*-MeAla-COOH **6** (98 mg, 0.30 mmol), HBTU (111 mg, 0.29 mmol) and $^{i}Pr_2EtN$ (104 µL, 0.60 mmol) in DMF (2 mL). The reaction mixture was agitated at room temperature for 1 h, after which the resin was filtered and washed with DMF (3 x 5 mL).

Method 4. Coupling method 2: To the peptidyl resin was added a mixture of Fmoc-*N*-MeCys(S^{t}Bu)-Ala-COOH **8** (78 mg, 0.15 mmol), HATU (56 mg, 0.15 mmol), HOAt (20 mg, 0.15 mmol) and $^{i}Pr_2EtN$ (52 µL, 0.30 mmol) in DMF (2 mL). The reaction mixture was agitated at room temperature for 2 h, after which the resin was filtered and washed with DMF (3 x 5 mL).

Method 5. Coupling method 3: To the peptidyl resin was added a mixture of Ac-Thr-D-Pla-COOH **15** (46 mg, 0.15 mmol), HATU (56 mg, 0.15 mmol), HOAt (20 mg, 0.15 mmol) and $^{i}Pr_2EtN$ (52 µL, 0.30 mmol) in DMF (2 mL). The reaction mixture was agitated at room temperature for 24 h, filtered and repeated once for a further 24 h. The resin was filtered and washed with DMF (2 x 5 mL) and CH_2Cl_2 (2 x 5 mL).

Method 6. Coupling method 4: To the peptidyl resin was added a mixture of Boc-*N*-MeThr(OMe)-COOH **22** (37 mg, 0.15 mmol), DIC (23 µL, 0.15 mmol) and DMAP (1.8 mg, 0.015 mmol) in CH_2Cl_2:DMF (19:1, 2 mL). The reaction mixture was agitated at room temperature for 2 h, after which the resin was filtered and washed with DMF (3 x 5 mL).

Method 7. Deprotection of *N*-MeCys(S^{t}Bu) and bis-alkylation-elimination to *N*-MeDha: To the peptidyl resin was added a mixture of dithiothreitol (80 mg, 0.52 mmol) and ^{i}Pr$_2$EtN (174 µL, 1.00 mmol) in DMF (2 mL). The reaction mixture was agitated at room temperature for 12 h, after which the resin was filtered and washed with DMF (3 x 5 mL). The peptidyl resin was suspended in DMF (2 mL) and solid K_2CO_3 (138 mg, 1.00 mmol) and 1,4-dibromobutane (44 µL, 0.36 mmol) was added. The reaction mixture was agitated at room temperature for 5 h, after which the resin was filtered, washed with DMF (5 mL) and H_2O (5 mL) alternately (3 x), CH_2Cl_2 (2 x 5 mL) and air-dried.

Method 8. Cleavage of peptide from linker with concomitant removal of protecting groups: To the peptidyl resin was added a solution of trifluoroacetic acid:H_2O (9:1, 2 mL) and the reaction agitated for 10 min, filtered and repeated once for a further 10 min. The combined filtrates were partially concentrated under a gentle stream of N_2, diluted with H_2O:CH_3CN + 0.1% TFA (1:1, 10 mL) and lyophilised.

4. Synthesis of peptides 5 and YM-280193 (1)

Linear YM-280193 5.

The *C*-terminal residue, Fmoc-Hyleu-COOH **23**, was attached to 2-chlorotrityl chloride resin according to **Method 1.** The N^{α}-Fmoc-protecting group was removed using **Method 2** and Fmoc-*N*-MeAla-COOH **6** was coupled using **Method 3.** The substitution level of an air-dried sample was 0.68 mmol/g as determined according to the method of Meienhofer *et al*.[9] The N^{α}-Fmoc-protecting group was removed using **Method 2** and Fmoc-*N*-MeCys(S^{t}Bu)-Ala-COOH **8** was coupled according to **Method 4.** The N^{α}-Fmoc-protecting group was removed using **Method 2** followed by coupling of Ac-Thr-D-Pla-COOH **15** via **Method 5,** and subsequently the coupling of Boc-*N*-MeThr(OMe)-COOH **22** via **Method 6.** Deprotection of *N*-MeCys(S^{t}Bu) and bis-alkylation-elimination to *N*-MeDha was performed according to **Method 7.** The resin-bound peptide was cleaved from the linker using **Method 8**, and the crude residue was purified by semi-preparative RP-HPLC to afford the *title compound* **5** as white fluffy flakes (9 mg, 16%); $\boldsymbol{R_t}$ 20.7 min; *m/z* (ESI-MS) 807.4 ([M + H]$^{+}$ requires 807.41).

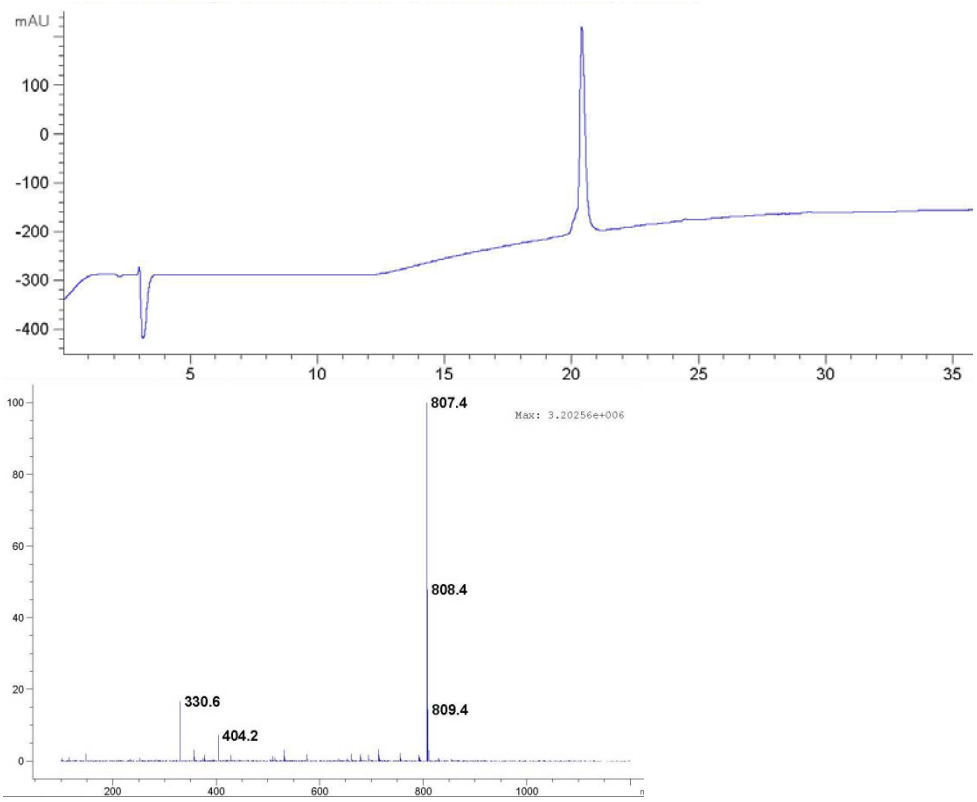


Figure 1. LC-MS profile of linear YM-280193 **5** (5% B to 95% B over 30 min, 0.3 mL min^{-1}$^{+}$).

Synthesis of YM-280193 (1)

To a stirring solution of $^{i}Pr_2EtN$ (2 µL, 11.5 µmol) in CH_2Cl_2 (2 mL) was added a mixture peptide **5** (1.5 mg, 2.2 µmol), HATU (2.5 mg, 6.6 µmol) and HOAt (0.9 mg, 6.6 µmol) in CH_2Cl_2:DMF (9:1, 2 mL) dropwise at a rate of 0.5 mL/h. After complete addition of reagents, the reaction mixture was concentrated under reduced pressure, diluted with H_2O:CH_3CN + 0.1% TFA (5:1, 2.4 mL) and purified by analytical RP-HPLC to afford the *title compound* (**1**) as white fluffy flakes (0.4 mg, 27%); $[\alpha]_D^{20}$ = -52.0 (*c* 0.08, MeOH) (lit.[10] -61.3 *c* 0.30, MeOH); R_t 23.2 min; **HRMS (EI):** *m/z* $[M + Na]^+$ calculated for $C_{38}H_{56}N_6NaO_{12}$: 811.3854, observed: 811.3857; *m/z* $[M + H]^+$ calculated for $C_{38}H_{57}N_6O_{12}$: 789.4034, observed: 789.4052; **IR (film)** ν_{max}: 3329, 2970, 2937, 1749, 1654, 1638, 1529, 1449, 1413, 1381, 1312, 1280, 1176, 1137, 1069, 965, 799, 700.

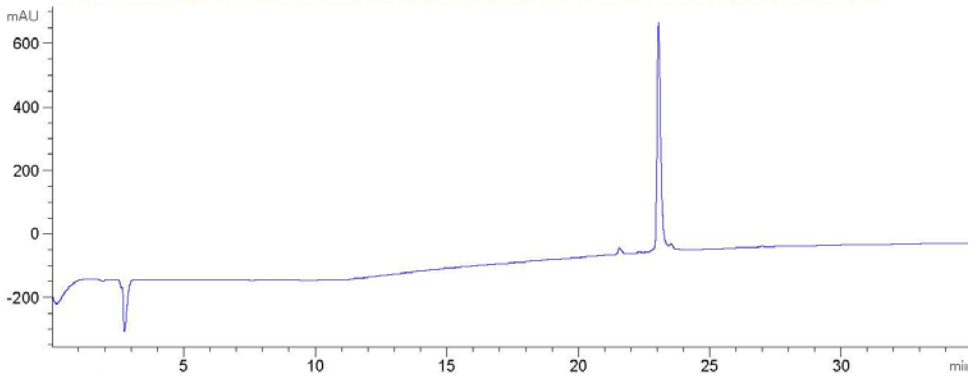


Figure 2. LC-MS profile of YM-280193 (**1**) (5% B to 95% B over 30 min, 0.3 mL min^{-1}).

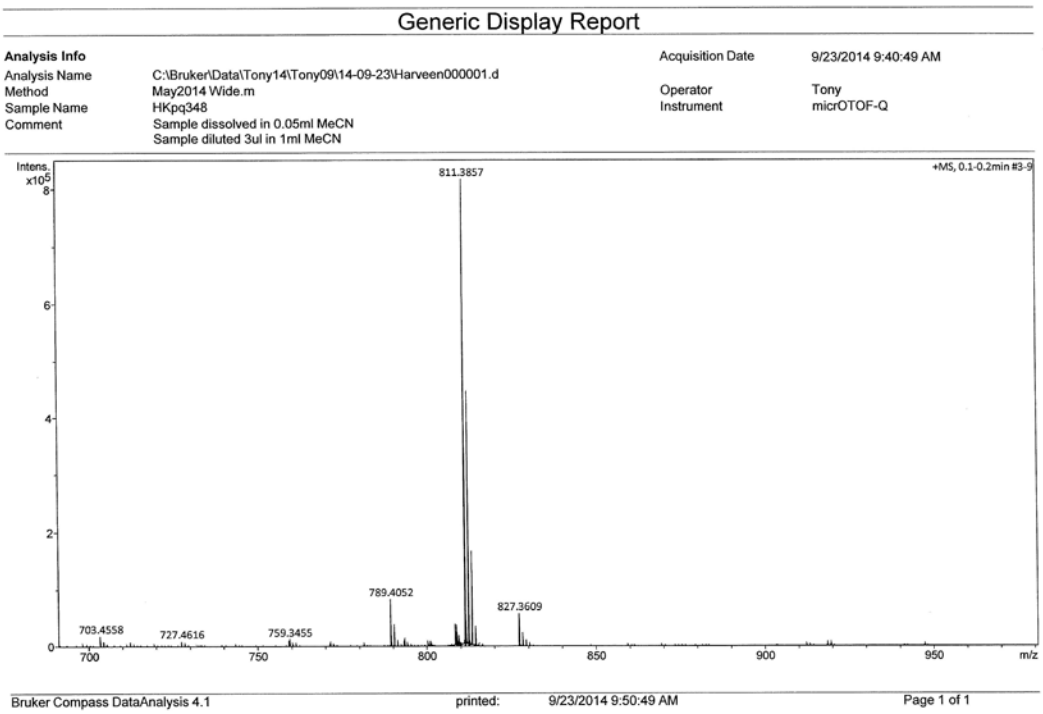


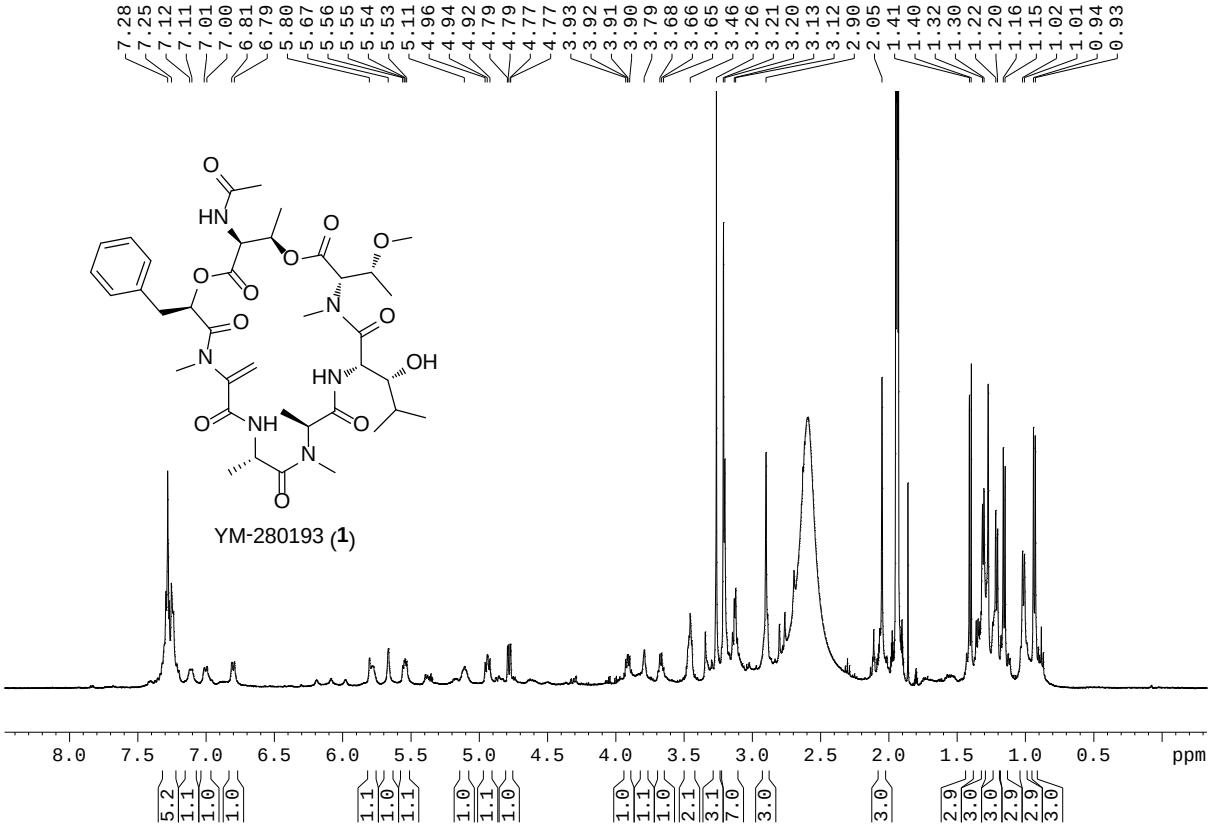
Figure 3. HRMS profile of YM-280193 (**1**).

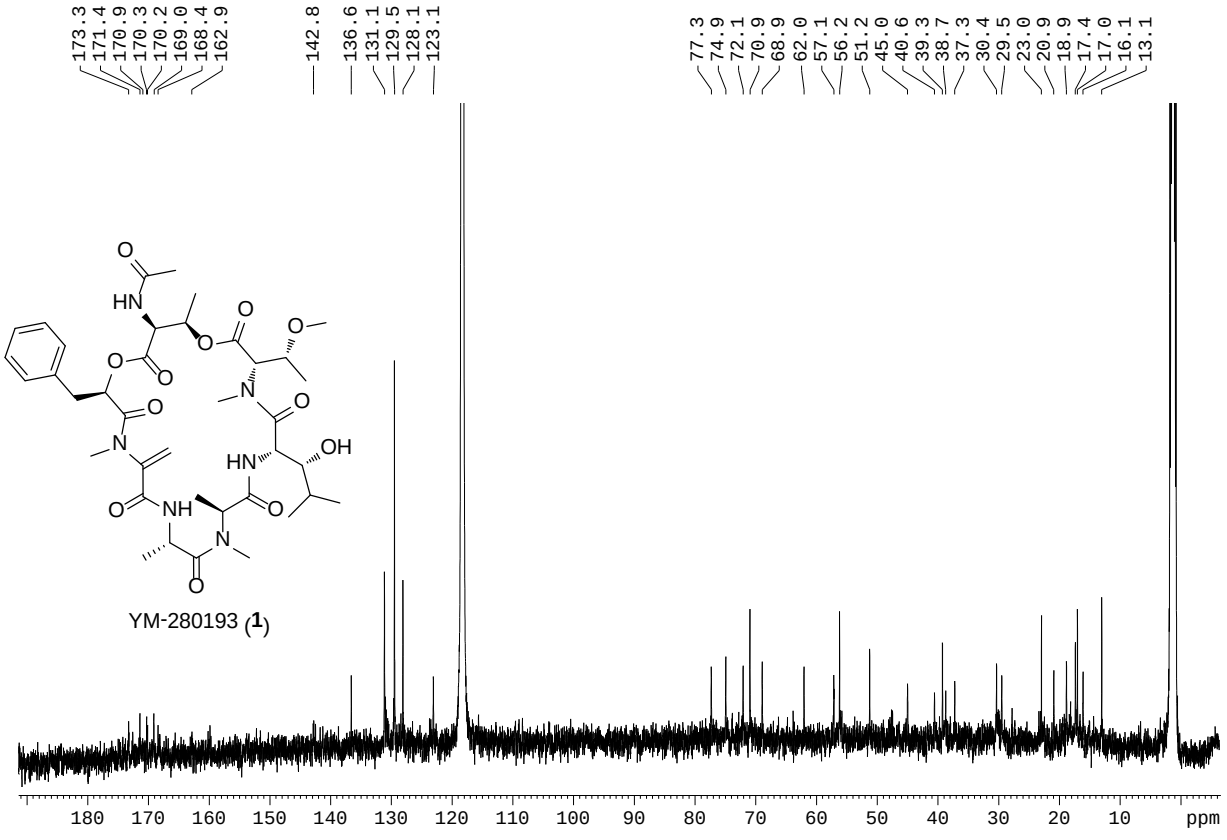
Table 1. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) assignment in CD_3CN for the major conformer of naturally occurring and synthetic YM-280193 (1):

Residue	^{13}C (natural)	^{13}C (synthetic)	^{1}H (natural)	^{1}H (synthetic)
β-Hyleu				
α	51.3	51.2	4.93 (dd, 10.1, 7.0)	4.94 (dd, 9.8, 7.3)
β	77.3	77.3	3.45 (m)	3.45 (m)
γ	29.5	29.5	1.94 (m)	1.94 (m)
δ	21.0	20.9	1.01 (d, 7.0)	1.01 (d, 6.9)
δ	16.1	16.1	0.93 (d, 6.7)	0.93 (d, 6.7)
CO	171	170.9	-	-
NH	-	-	7.00 (d, 10.1)	7.00 (d, 9.9)
***N,O*-Me$_2$Thr**				
α	69.0	68.9	3.45 (d, 8.9)	3.45 (m)
β	75.0	74.9	3.90 (dq, 8.9, 5.8)	3.91 (dq, 8.7, 6.0)
γ	18.9	18.9	1.31 (d, 5.8)	1.31 (d, 5.7)
CO	168.5	168.4	-	-
NMe	40.7	40.6	3.21 (s)	3.21 (s)
OMe	57.2	57.1	3.26 (s)	3.26 (s)
Acetyl				
1	171.4	171.4	-	-
2	23.0	23.0	2.05 (s)	2.05 (s)
Thr				
α	56.2	56.2	4.78 (dd, 9.5, 2.4)	4.78 (dd, 9.5, 2.5)
β	71.0	70.9	5.79 (m)	5.80 (m)
γ	17.1	17.0	1.15 (d, 6.4)	1.15 (d, 6.5)
CO	170.2	170.2	-	-
NH	-	-	6.80 (d, 9.5)	6.80 (d, 9.5)
D-Pla				
1	169.1	169.0	-	-
2	72.1	72.1	5.55 (dd, 10.2, 5.4)	5.55 (dd, 9.5, 5.4)
3	39.3	39.3	3.12 (m)	3.13 (m)
4	136.6	136.6	-	-
5,9	131.2	131.1	7.24 (m)	7.25 (m)
6,8	129.5	129.5	7.28 (m)	7.28 (m)
7	128.1	128.1	7.28 (m)	7.28 (m)
***N*-MeDha**				
α	142.9	142.8	-	-
β	123.4	123.1	5.65 (br s)	5.67 (br s)
β	-	-	3.77 (br s)	3.79 (br s)
CO	162.8	162.9	-	-
NMe	37.3	37.3	2.90 (s)	2.90 (s)
Ala				
α	45.0	45.0	5.12 (dq, 7.8, 6.7)	5.11 (m)
β	17.5	17.4	1.21 (d, 6.7)	1.21 (d, 6.8)
CO	173.3	17.3.3	-	-
NH	-	-	7.10 (d, 7.8)	7.11 (d, 7.9)
***N*-MeAla**				
α	62.1	62.0	3.66 (q, 7.0)	3.67 (q, 6.7)
β	13.1	13.1	1.40 (d, 7.0)	1.40 (d, 6.9)
CO	170.3	170.3	-	-
NMe	38.8	38.7	3.20 (s)	3.20 (s)

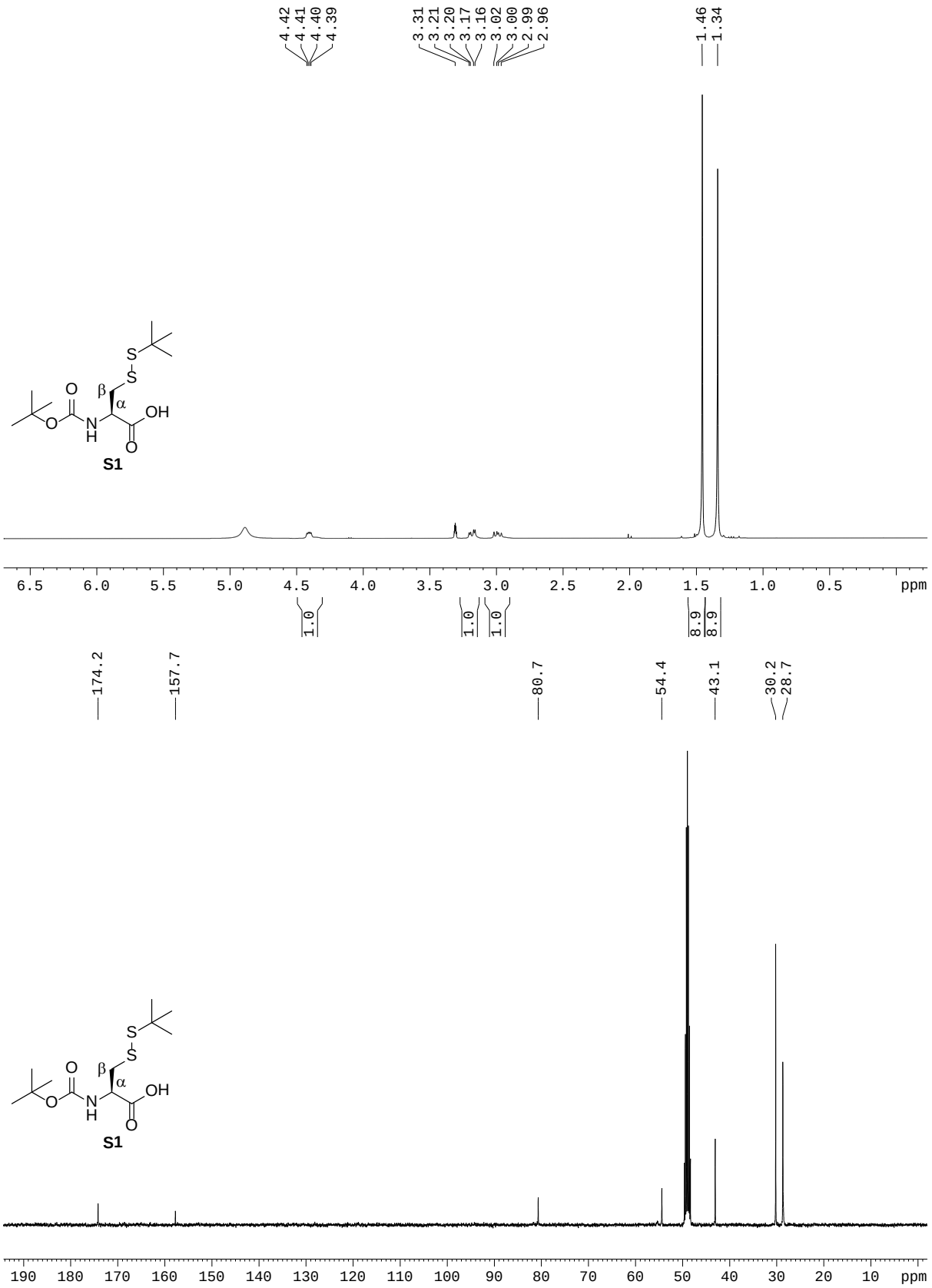
5. ^{1}H and ^{13}C Spectra

^{1}H (500 MHz, CD_3CN) and ^{13}C (125 MHz, CD_3CN) spectra of YM-280193 (**1**).

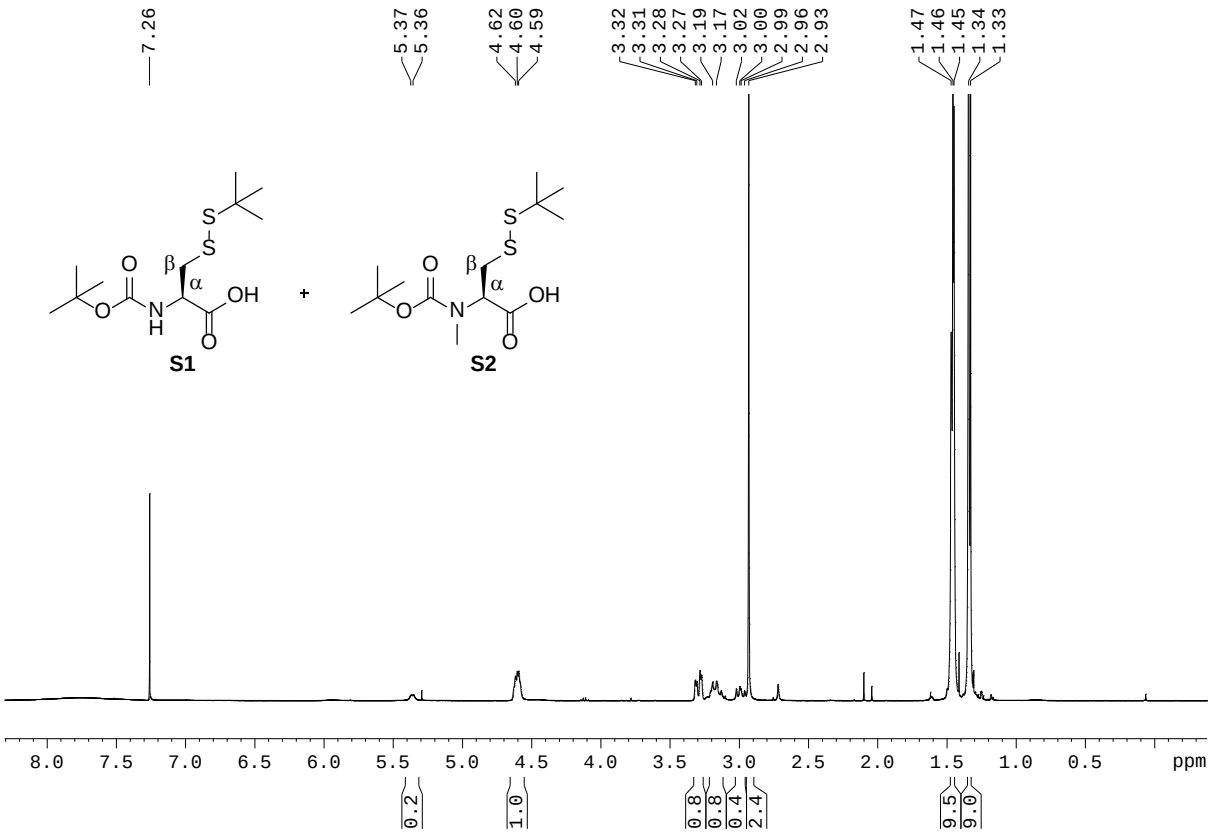




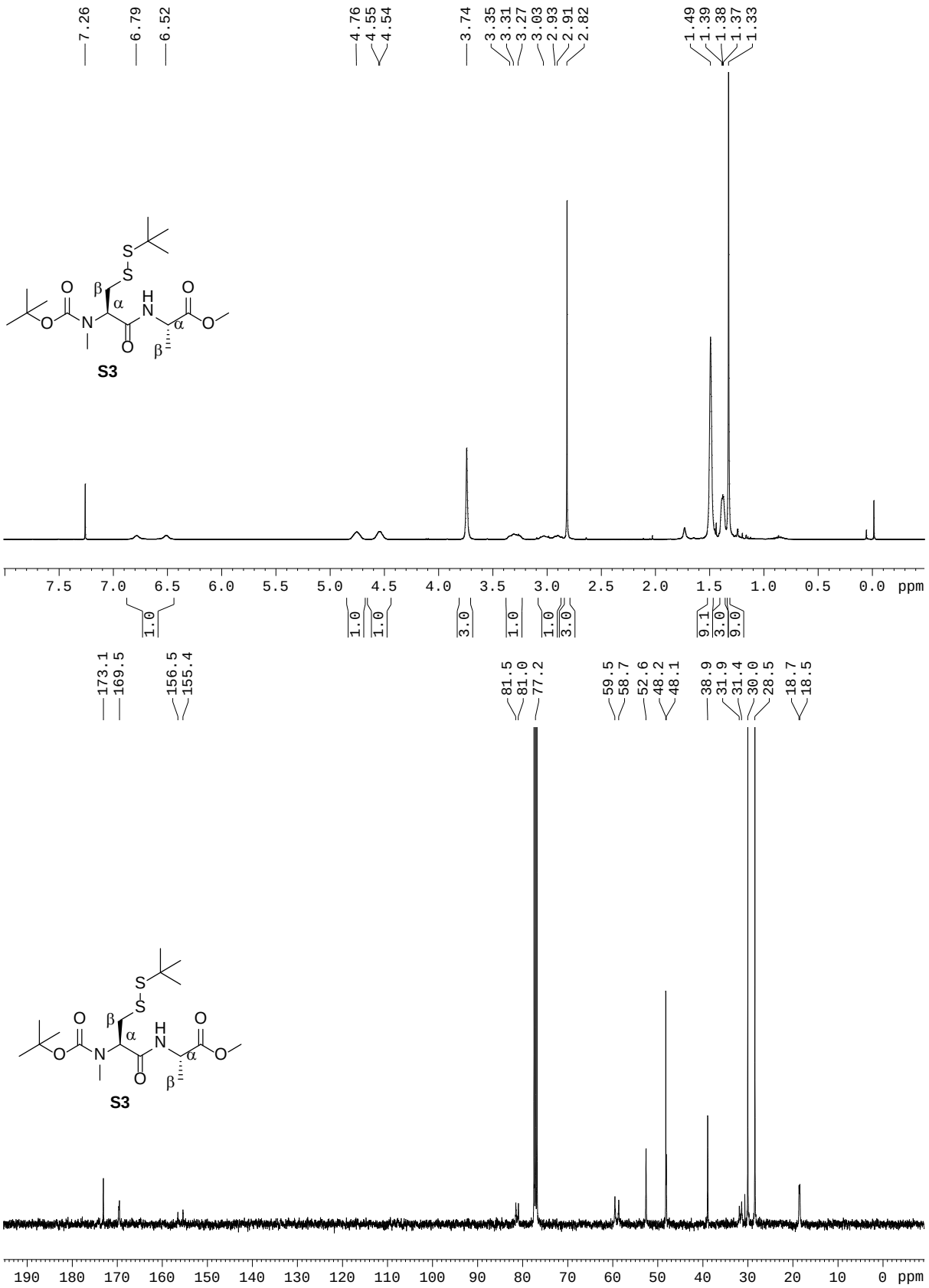
^{1}H (400 MHz, CD_3OD) and ^{13}C (100 MHz, CD_3OD) spectra of (*R*)-2-((*tert*-butoxycarbonyl)amino)-3-(*tert*-butyldisulfanyl)propanoic acid **S1**.



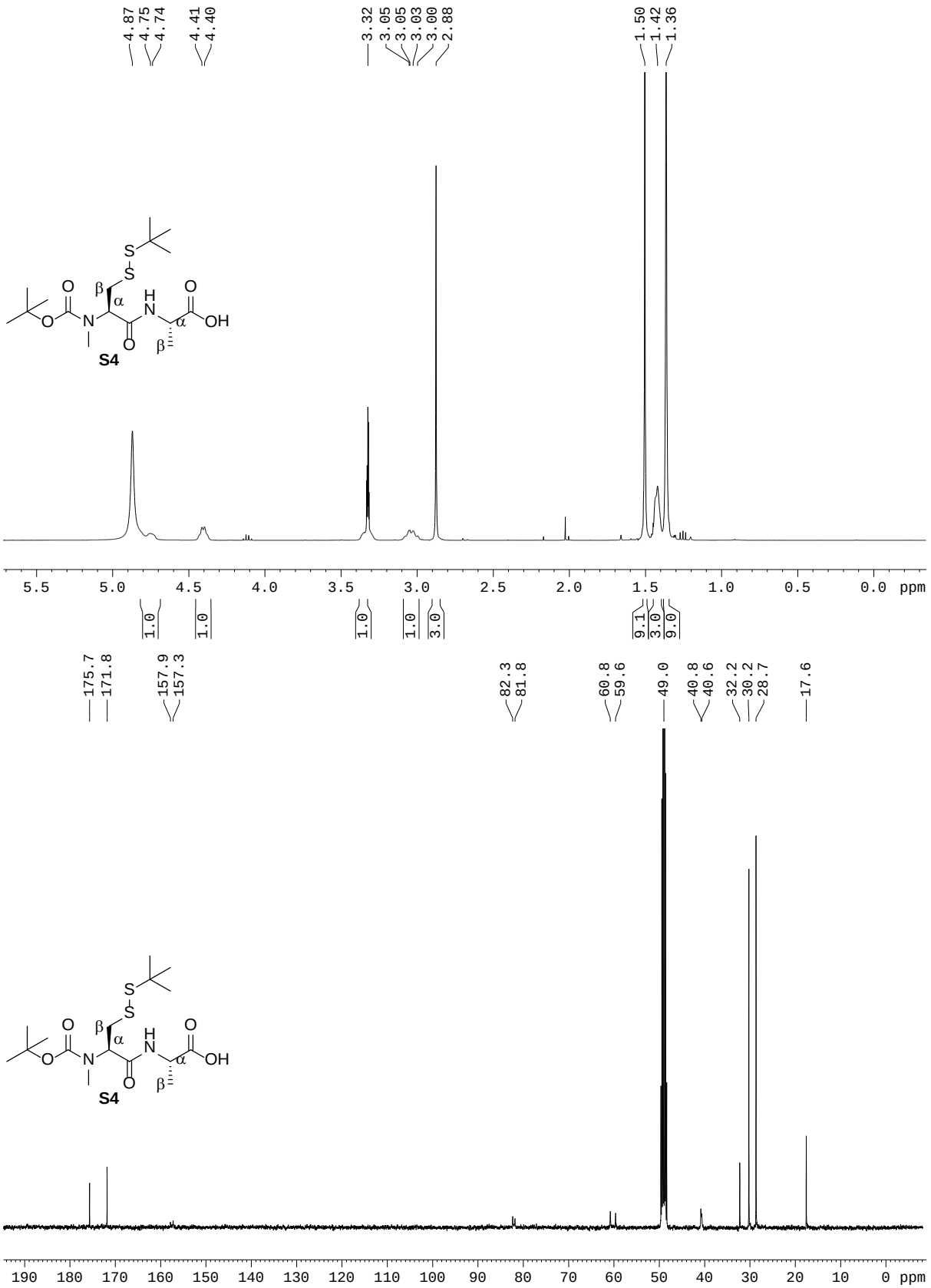
^{1}H (400 MHz, $CDCl_3$) spectra of mixture of (*R*)-2-((*tert*-butoxycarbonyl)amino)-3-(*tert*-butyldisulfanyl)propanoic acid **S1** and 2-((*tert*-butoxycarbonyl)(methyl)amino)-3-(*tert*-butyldisulfanyl)propanoic acid **S2**.



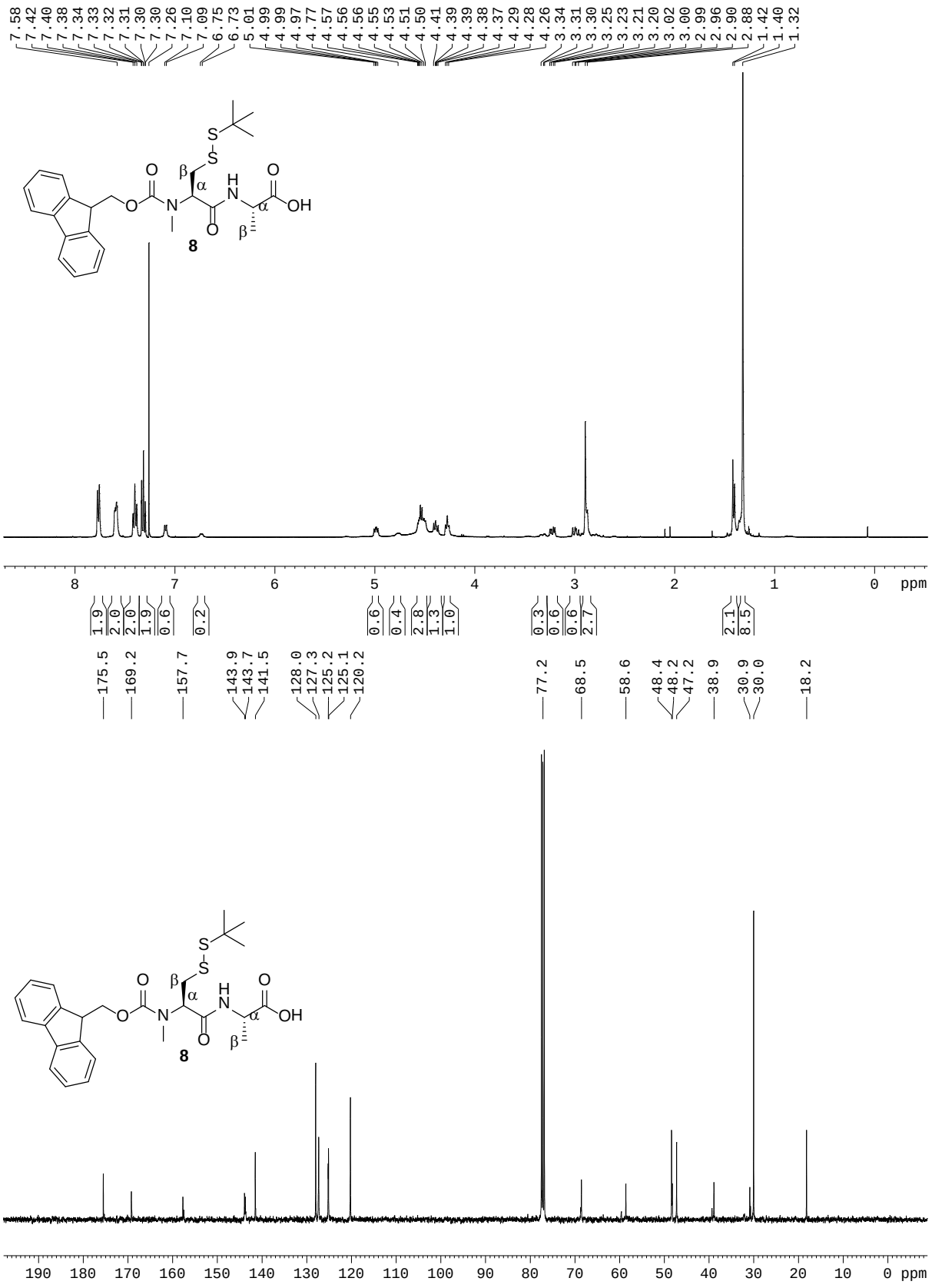
^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz, $CDCl_3$) spectra of (*S*)-methyl 2-((*R*)-2-((*tert*-butoxycarbonyl)(methyl)amino)-3-(*tert*-butyldisulfanyl)propanamido)propanoate **S3**.



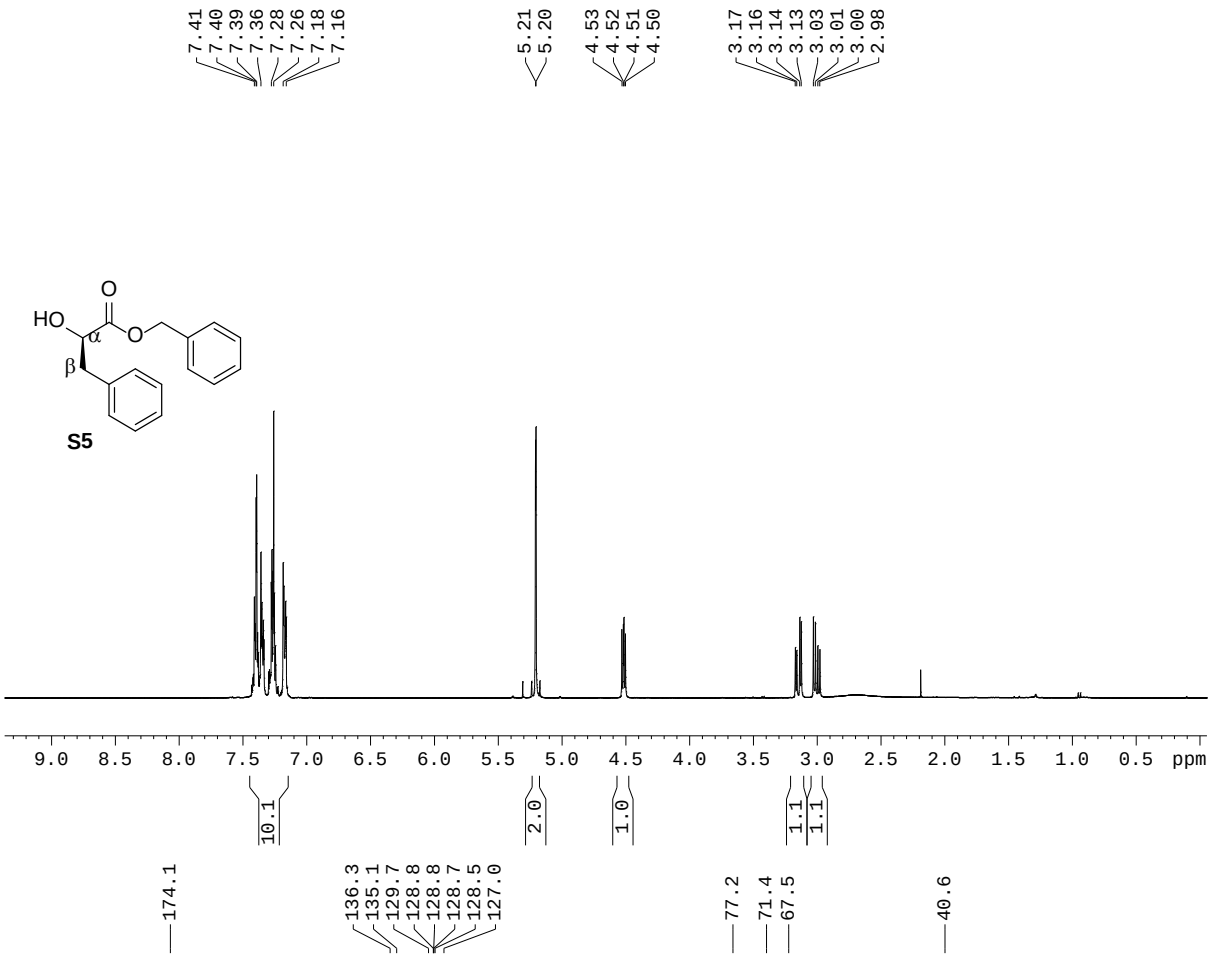
^{1}H (400 MHz, CD_3OD) and ^{13}C (100 MHz, CD_3OD) spectra of (*S*)-2-((*R*)-2-((*tert*-butoxycarbonyl)(methyl)amino)-3-(*tert*-butyldisulfanyl)propanamido)propanoic acid **S4**.

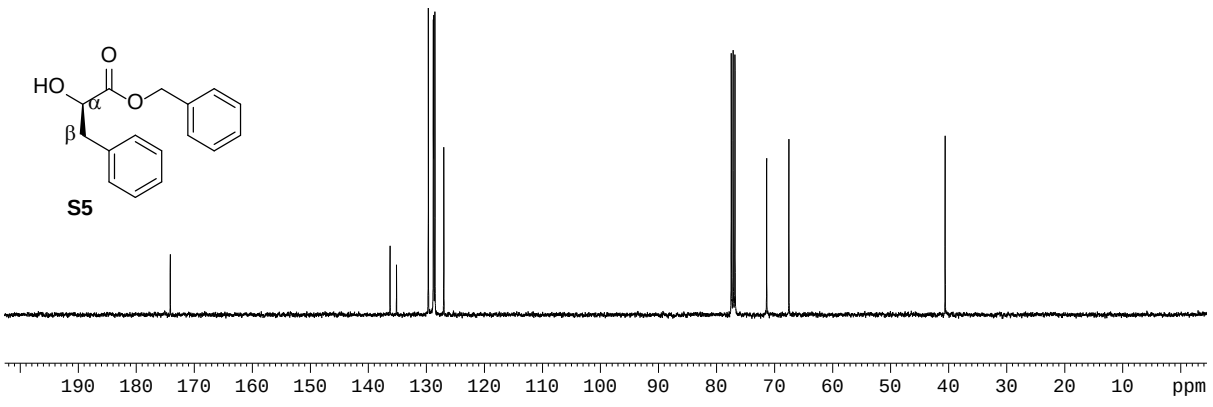


^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz, $CDCl_3$) spectra of (*S*)-2-((*R*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-3-(*tert*-butyldisulfanyl)propanamido)propanoic **8**.

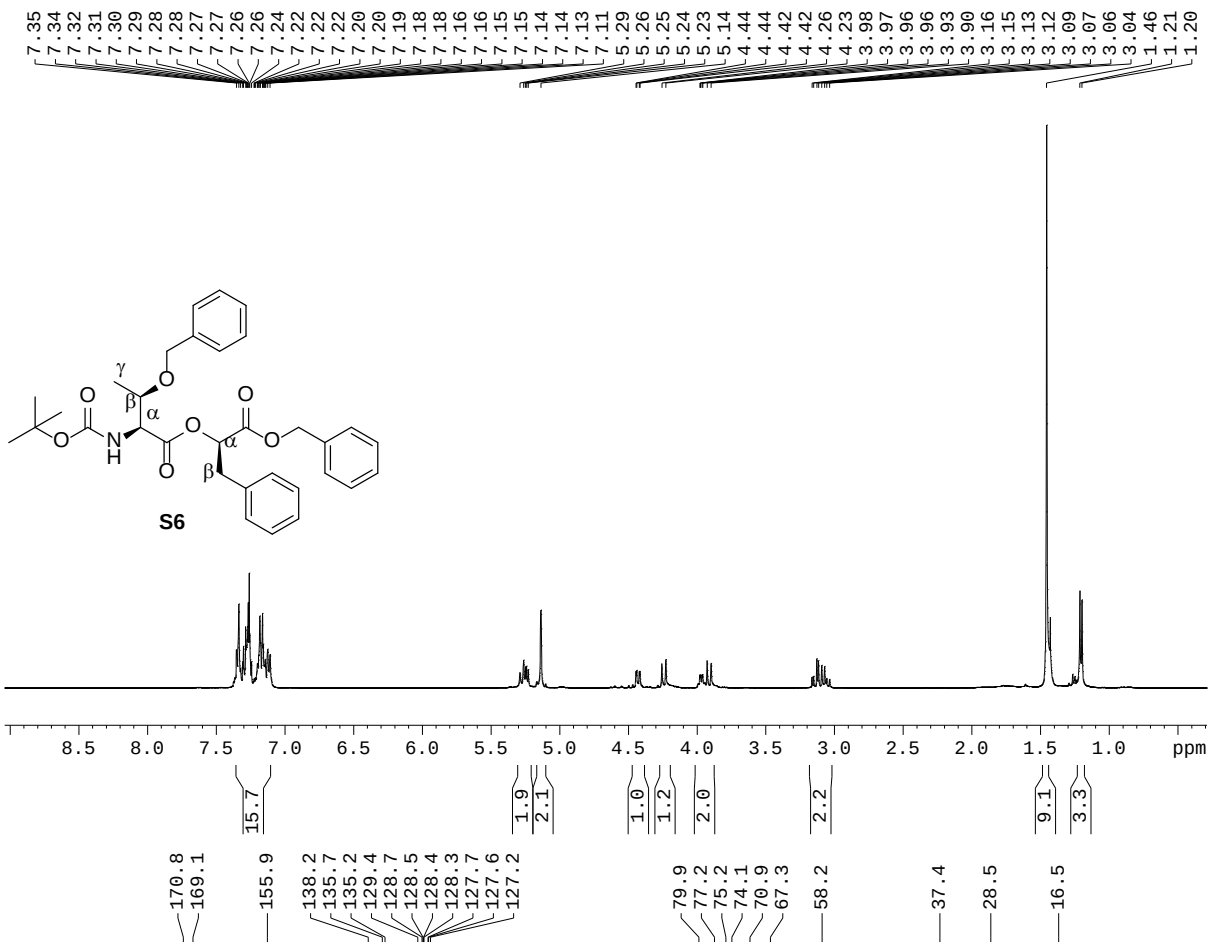


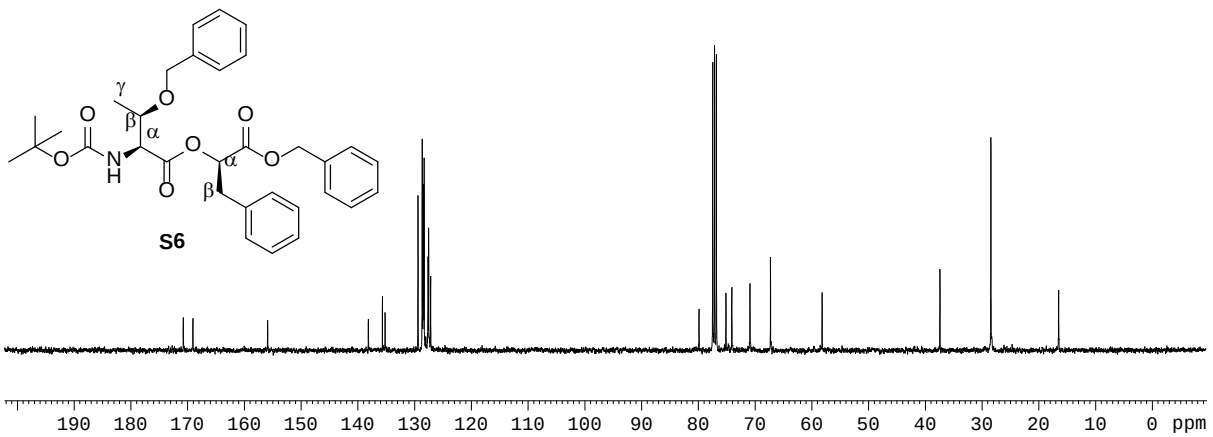
^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz, $CDCl_3$) spectra of (*R*)-benzyl 2-hydroxy-3-phenylpropanoate **S5**.



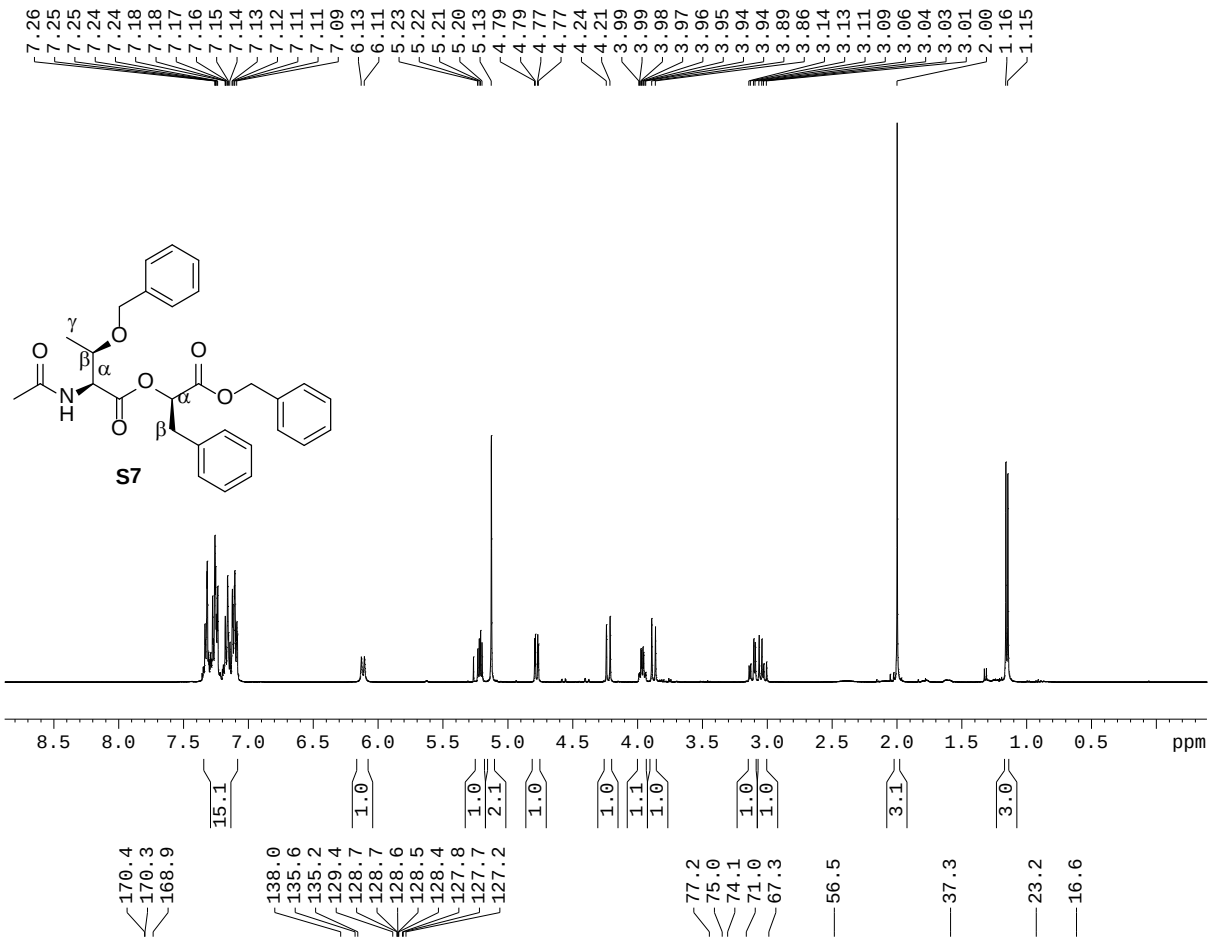


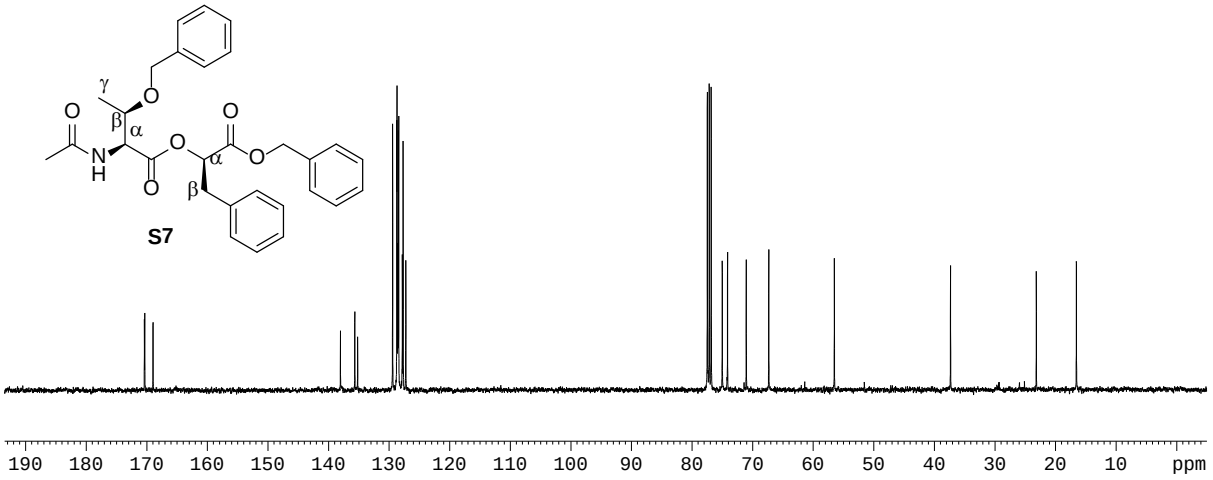
^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz, $CDCl_3$) spectra of (2*S*,3*R*)-(*R*)-1-(benzyloxy)-1-oxo-3-phenylpropan-2-yl 3-(benzyloxy)-2-((*tert*-butoxycarbonyl)aminobutanoate **S6**.



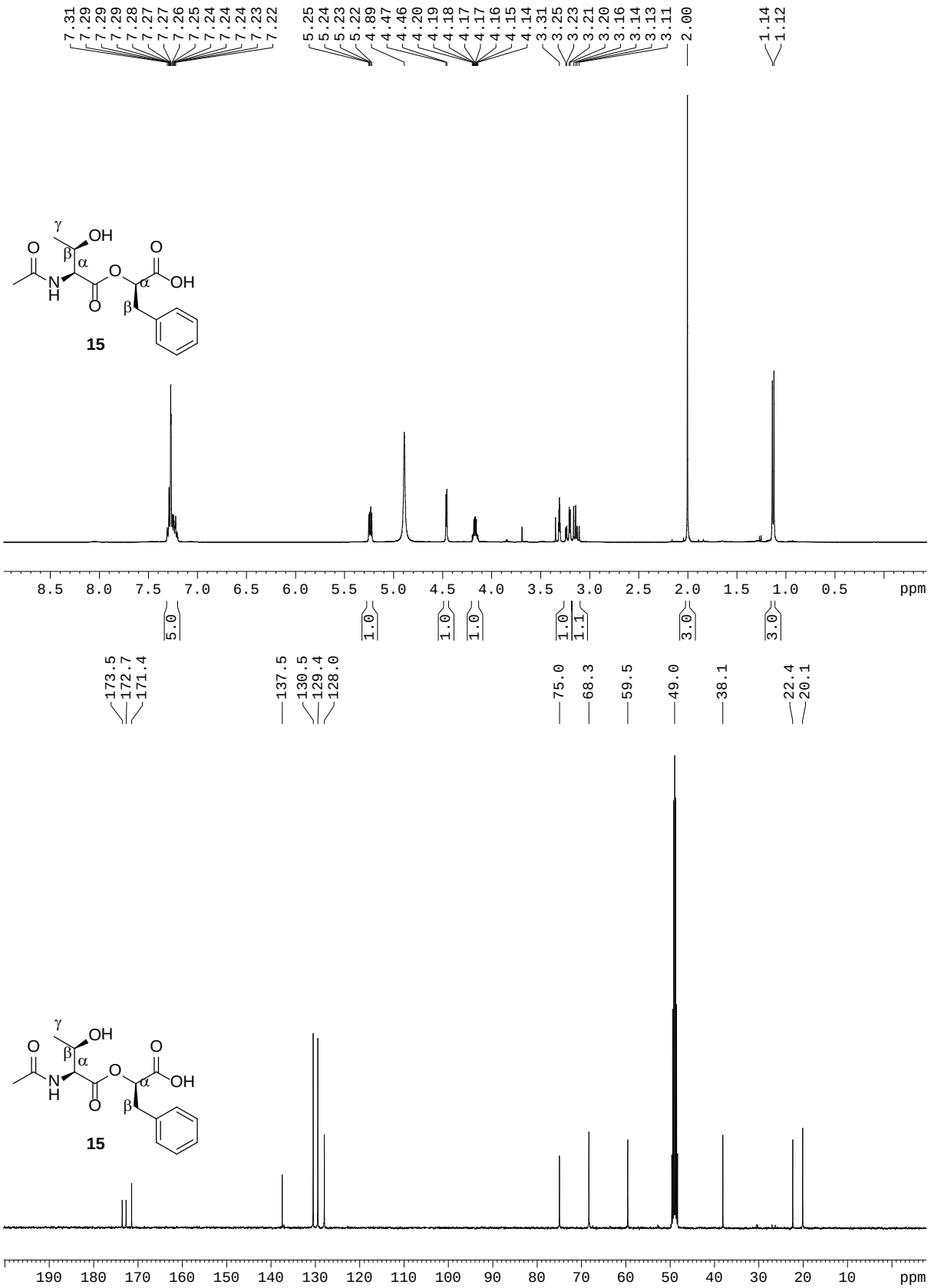


^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz, $CDCl_3$) spectra of (2*S*,3*R*)-(*R*)-1-(benzyloxy)-1-oxo-3-phenylpropan-2-yl 2-acetamido-3-(benzyloxy)butanoate **S7**.

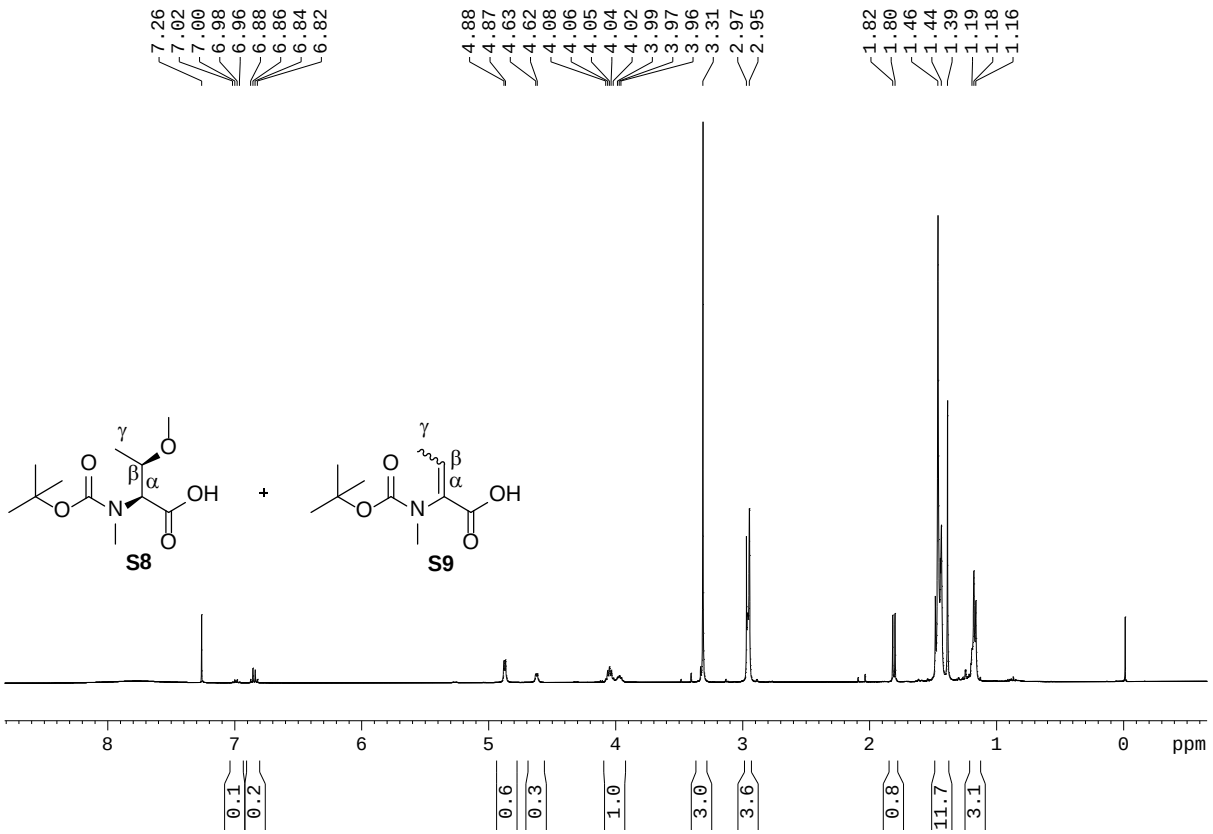




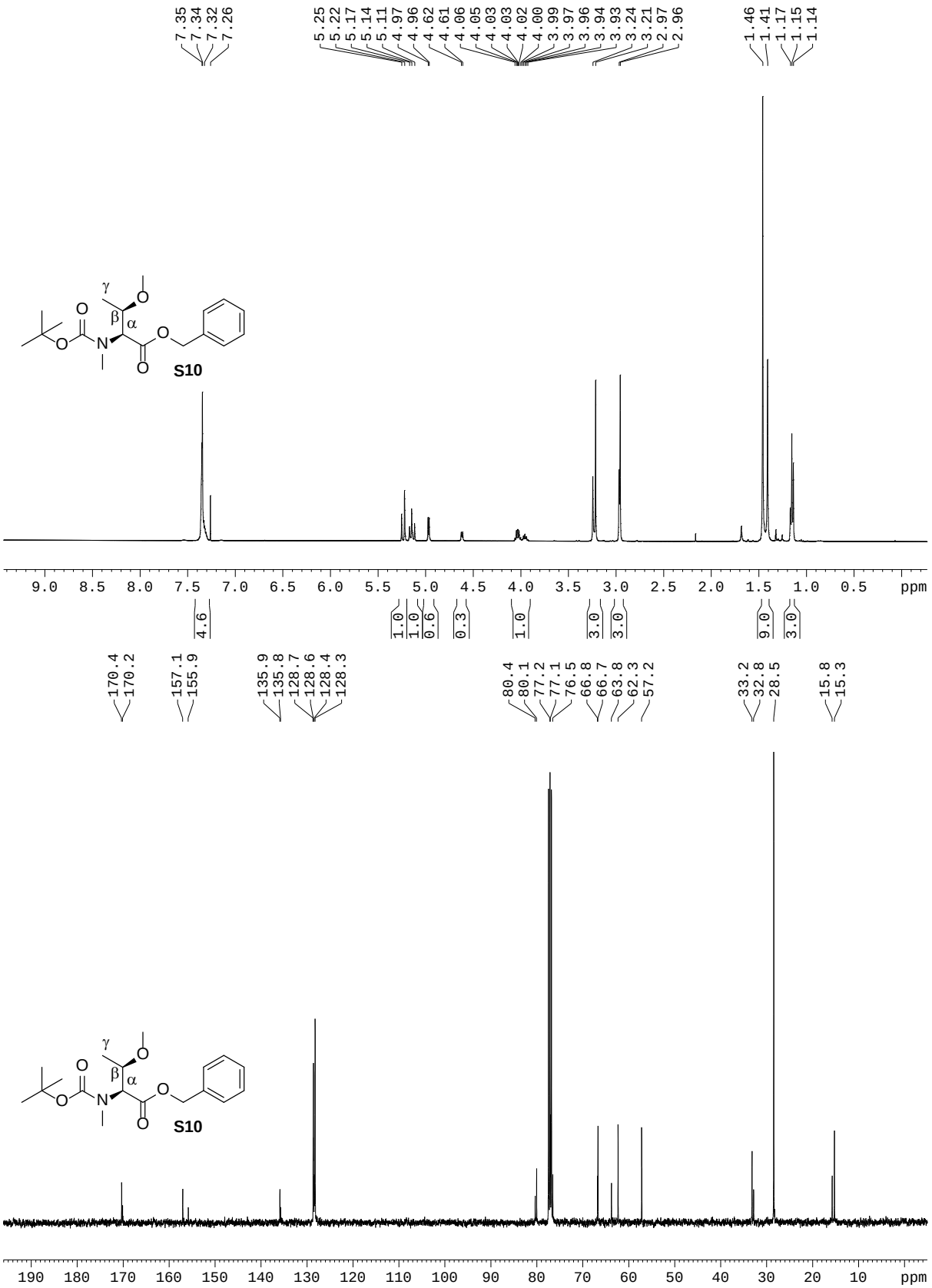
^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz, $CDCl_3$) spectra of (*R*)-2-(((2*S*,3*R*)-2-acetamido-3-hydroxybutanoyl)oxy)-3-phenylpropanoic acid **15**.



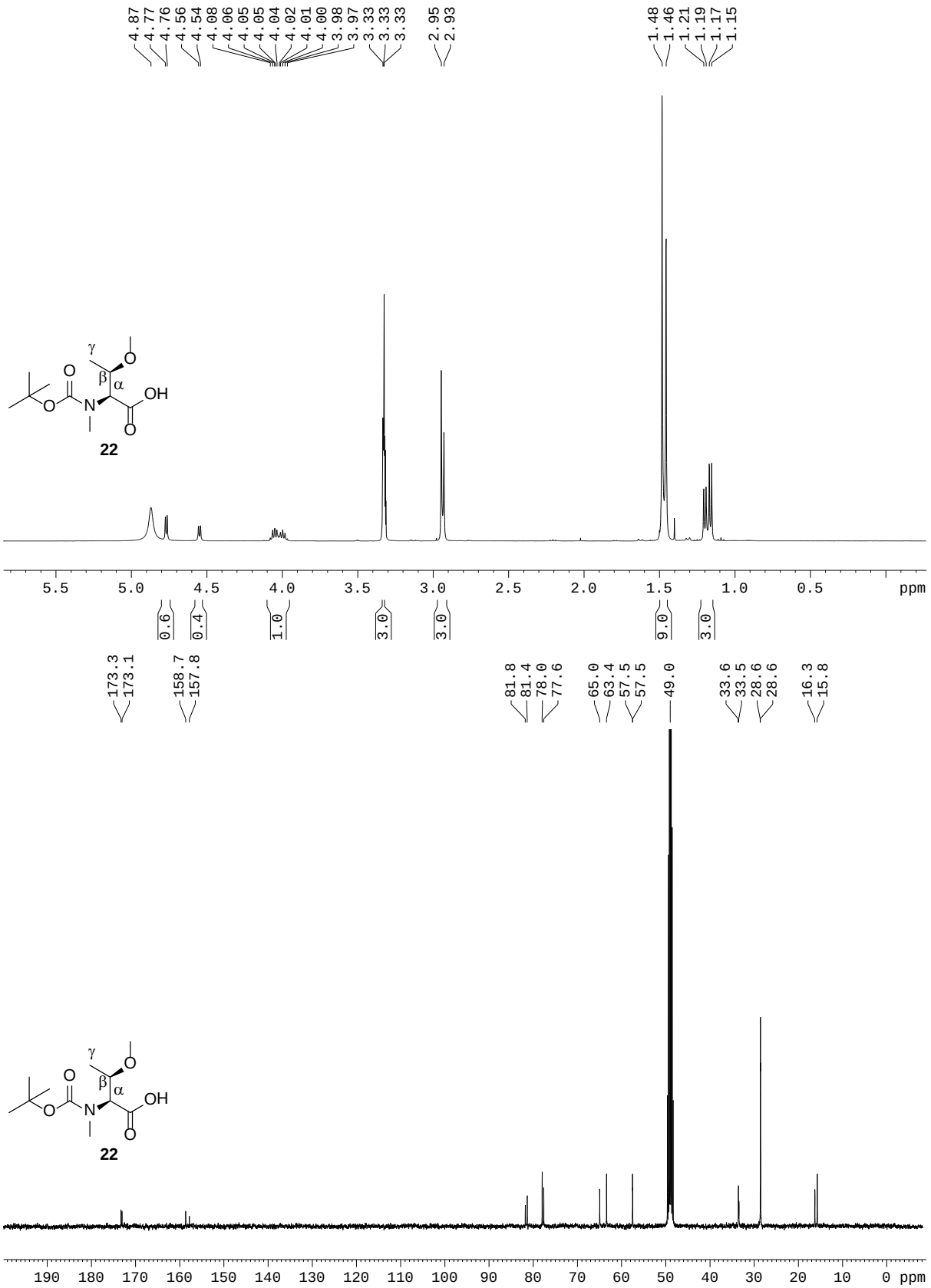
^{1}H (400 MHz, $CDCl_3$) spectra of mixture of (2*S*,3*R*)-2-((*tert*-butoxycarbonyl)(methyl)amino)-3-methoxybutanoic acid **S8** and 2-((*tert*-butoxycarbonyl)(methyl)amino)but-2-enoic acid **S9**.



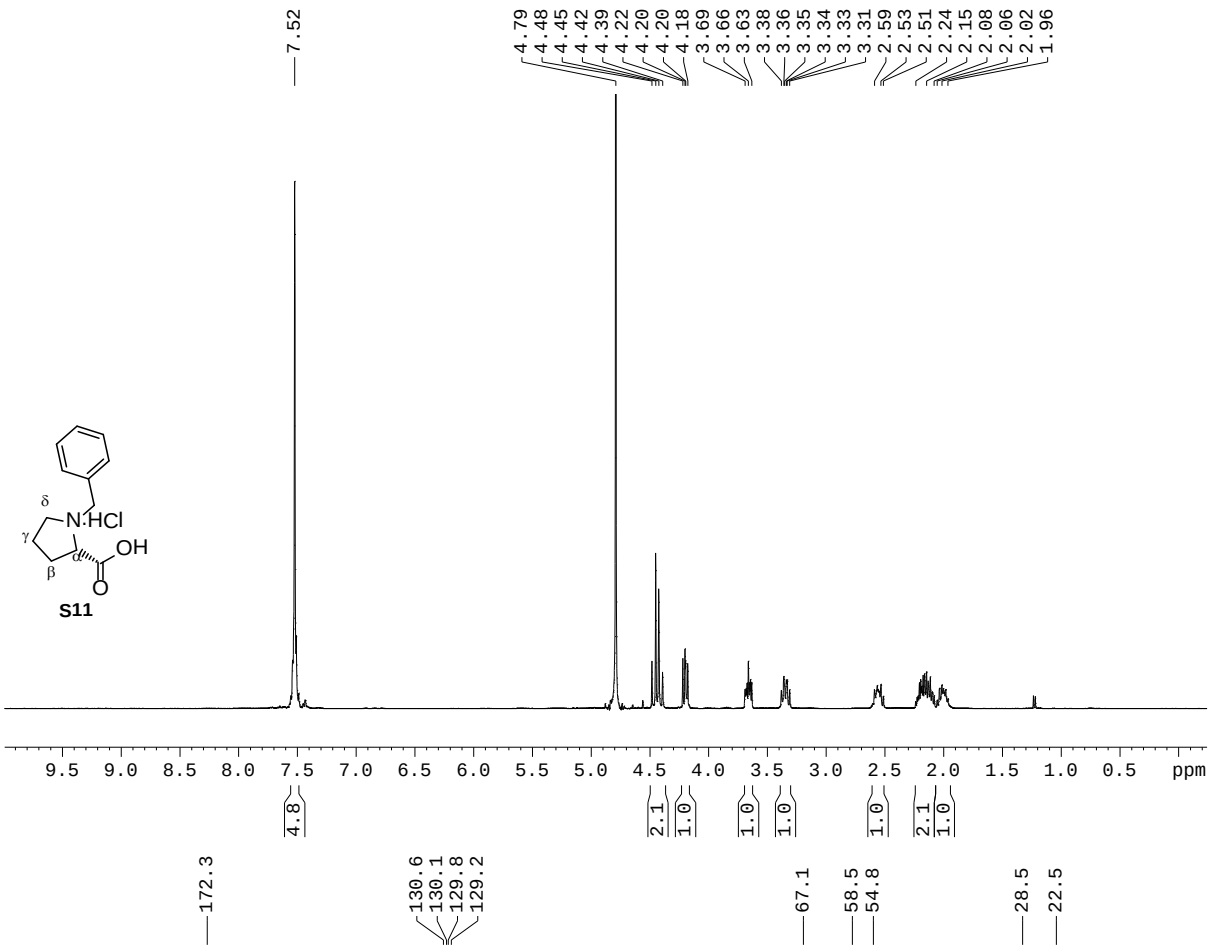
^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz, $CDCl_3$) spectra of benzyl 2-((*tert*-butoxycarbonyl)(methyl)amino-3-methoxybutanoate **S10**.

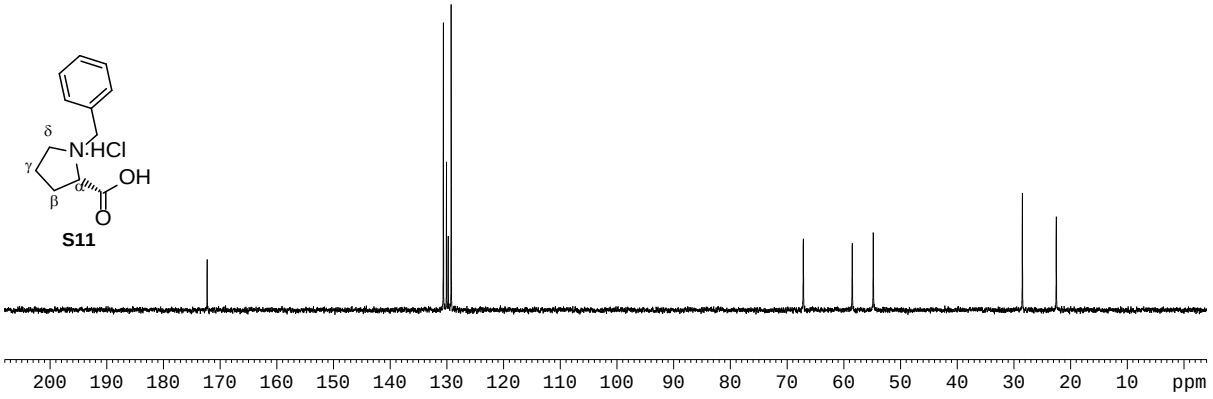


^{1}H (400 MHz, CD_3OD) and ^{13}C (100 MHz, CD_3OD) spectra of (2*S*,3*R*)-2-((*tert*-butoxycarbonyl)(methyl)amino)-3-methoxybutanoic acid **22**.

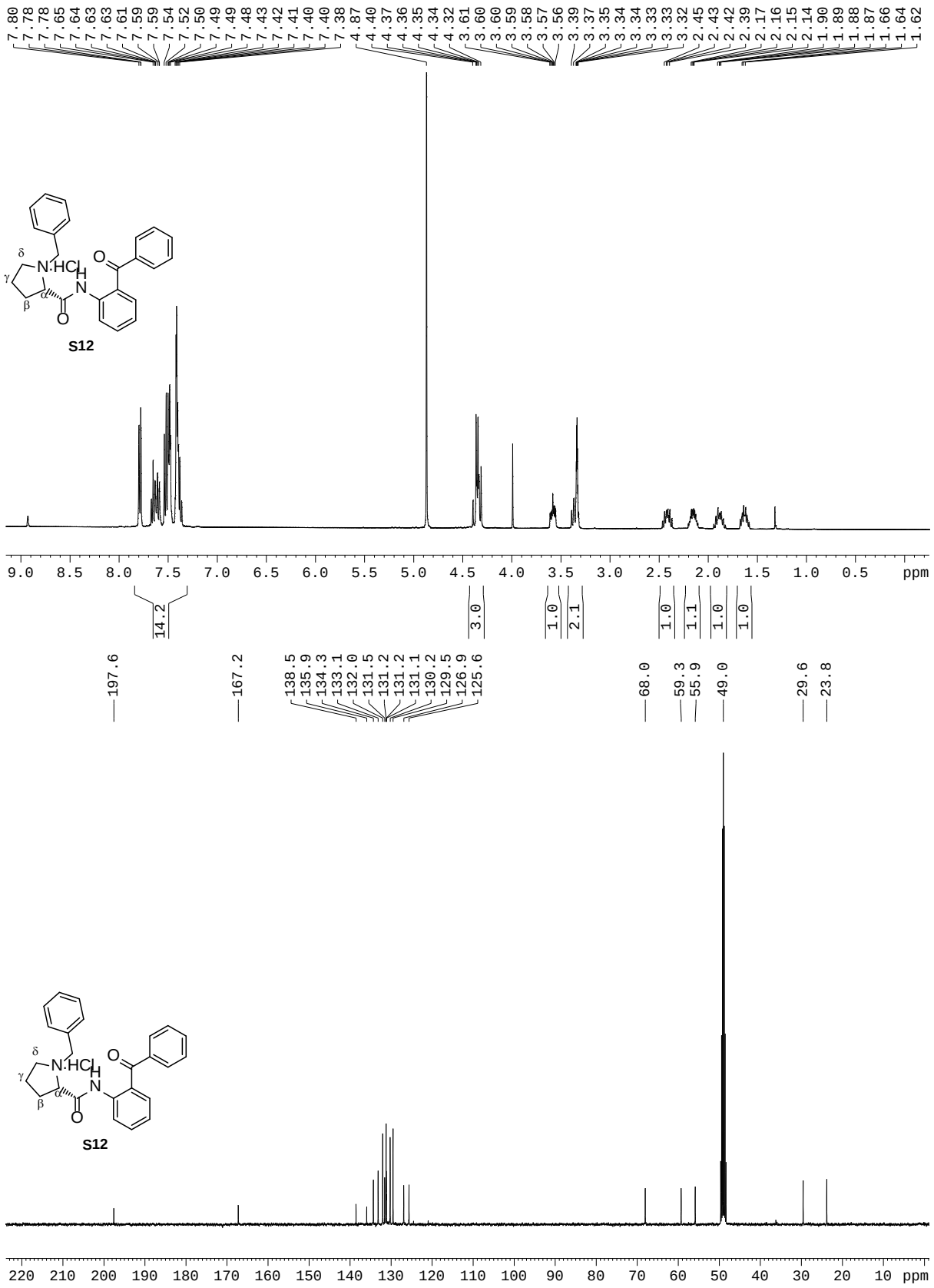


^{1}H (400 MHz, D_2O) and ^{13}C (100 MHz, D_2O) spectra of (*S*)-1-Benzylpyrrolidine-2-carboxylic acid hydrochloride **S11**.

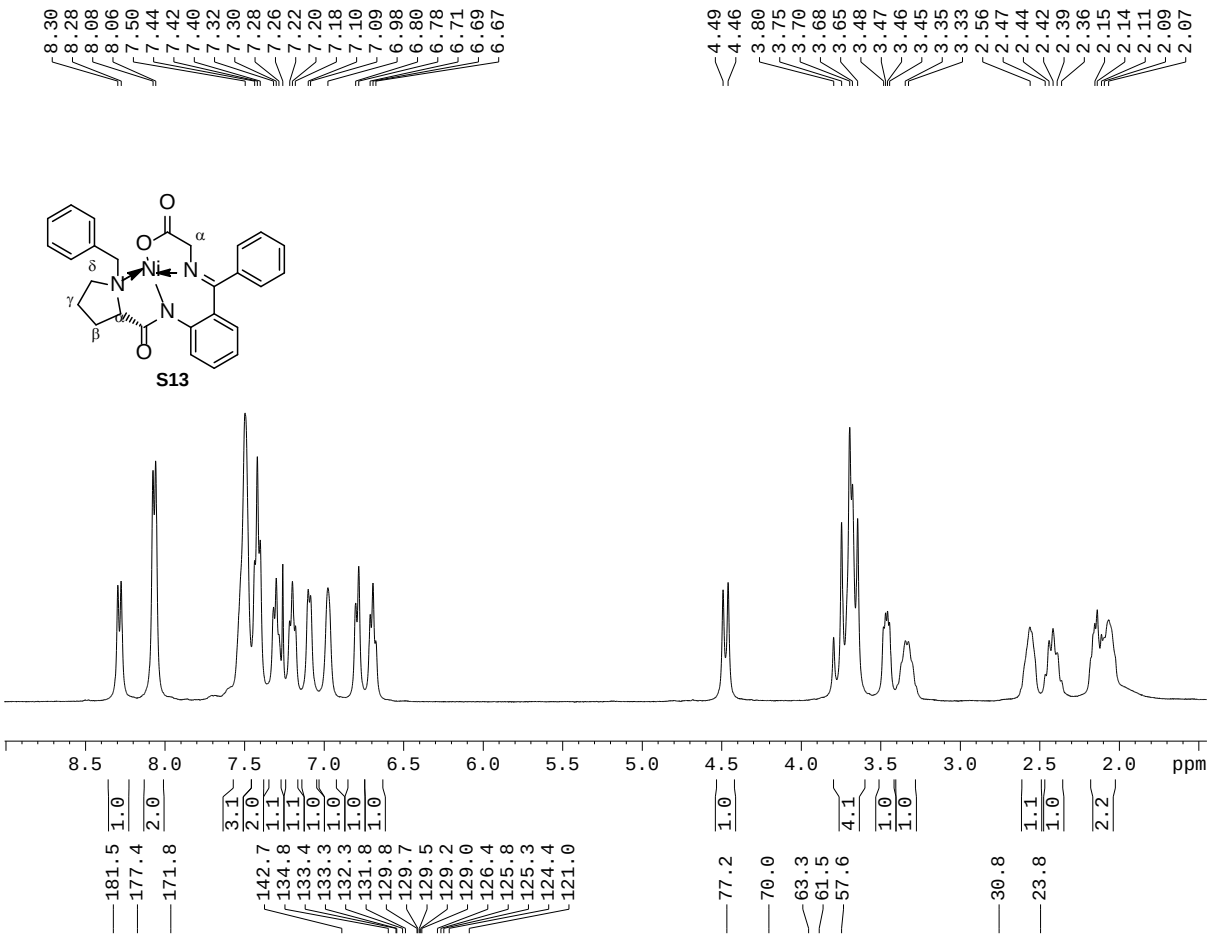


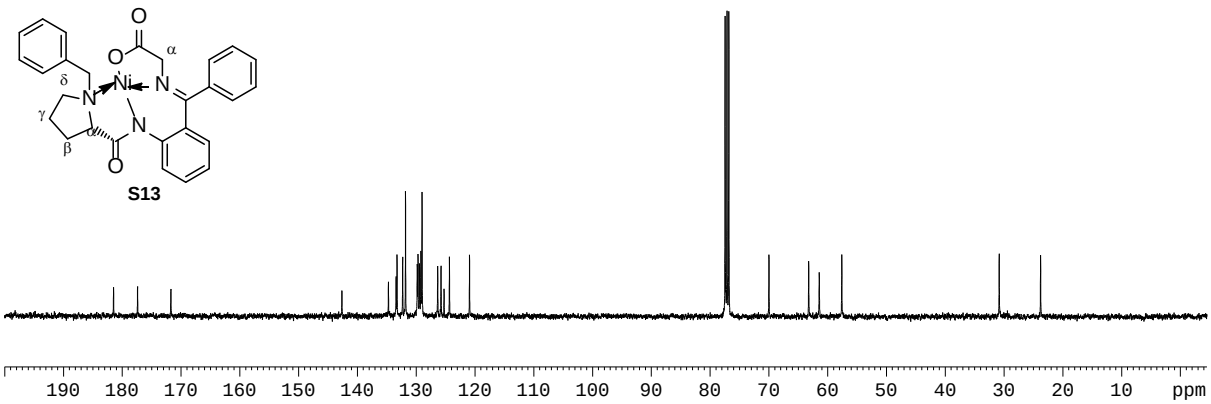


^{1}H (400 MHz, CD_3OD) and ^{13}C (100 MHz, CD_3OD) spectra of (*S*)-2-[*N*-(*N*'-benzylpropyl)amino]benzophenone hydrochloride **S12**.

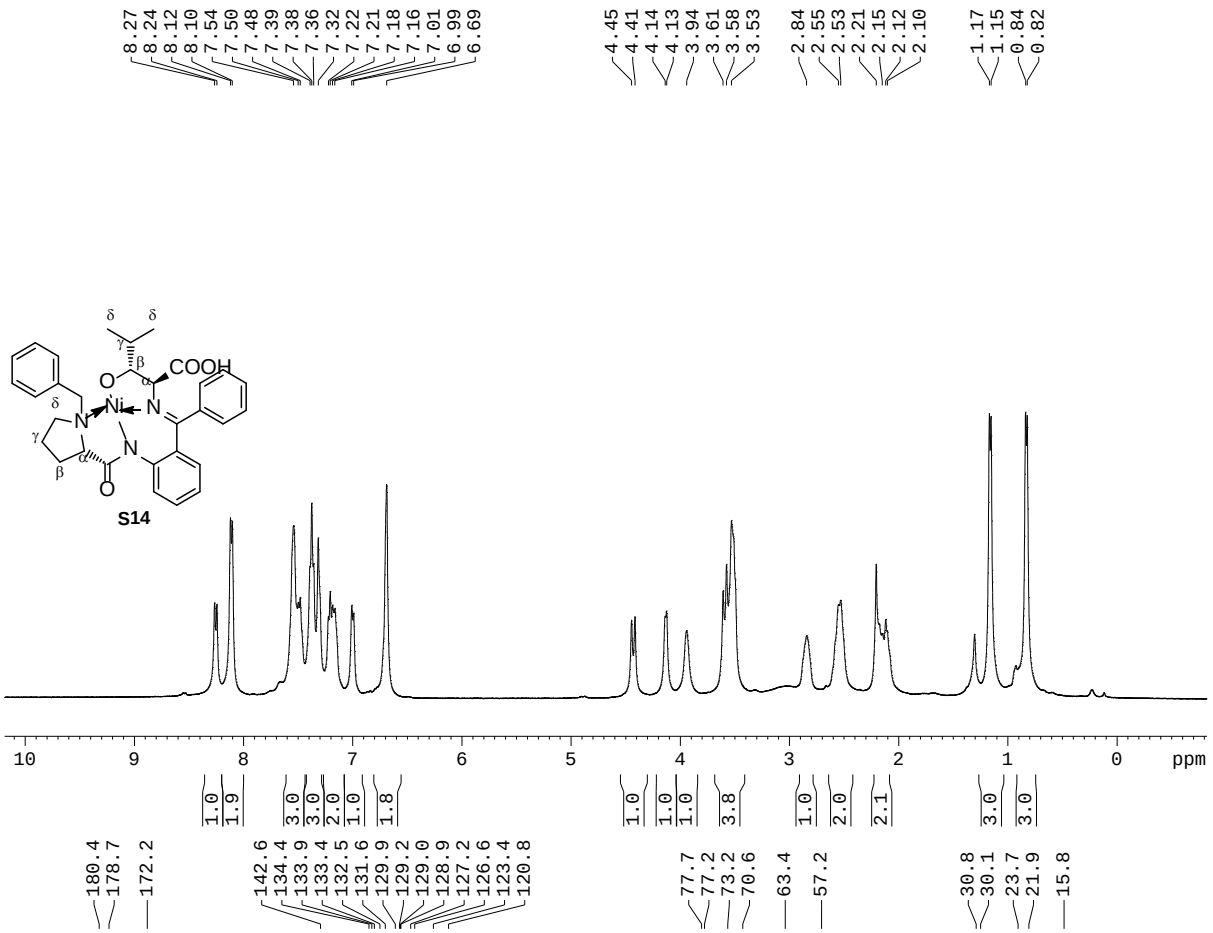


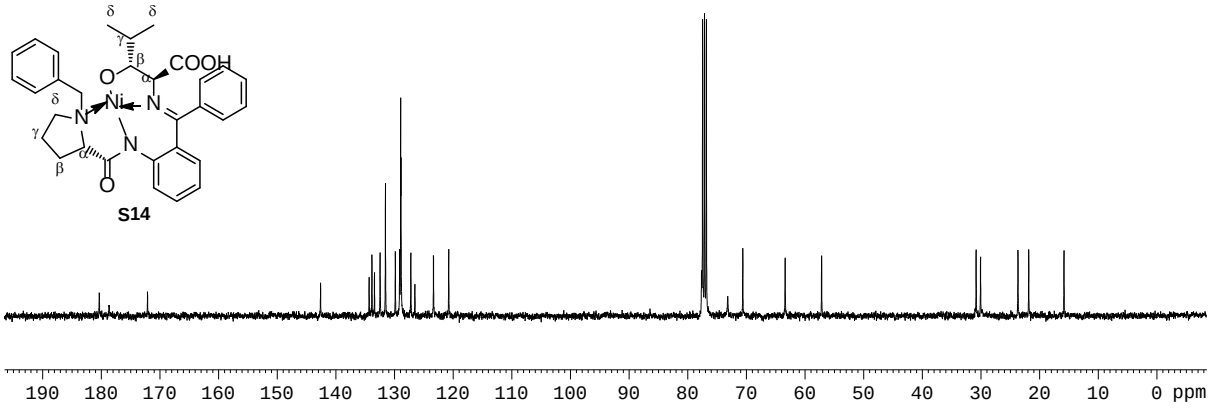
^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz, $CDCl_3$) spectra of (*S*)-Glycine-nickel-(*S*)-2-[*N*-(*N*'-benzylpropyl)amino]benzophenone **S13**.



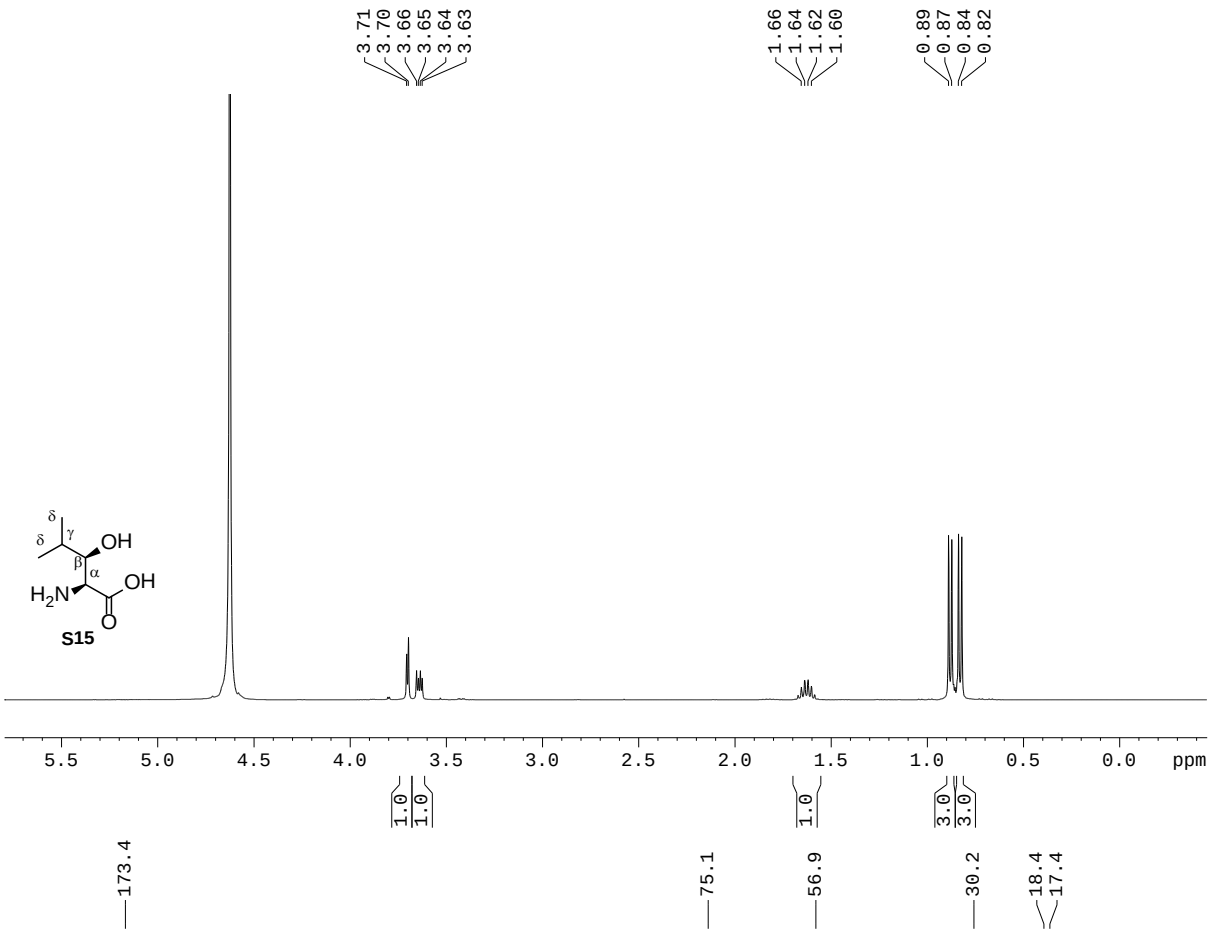


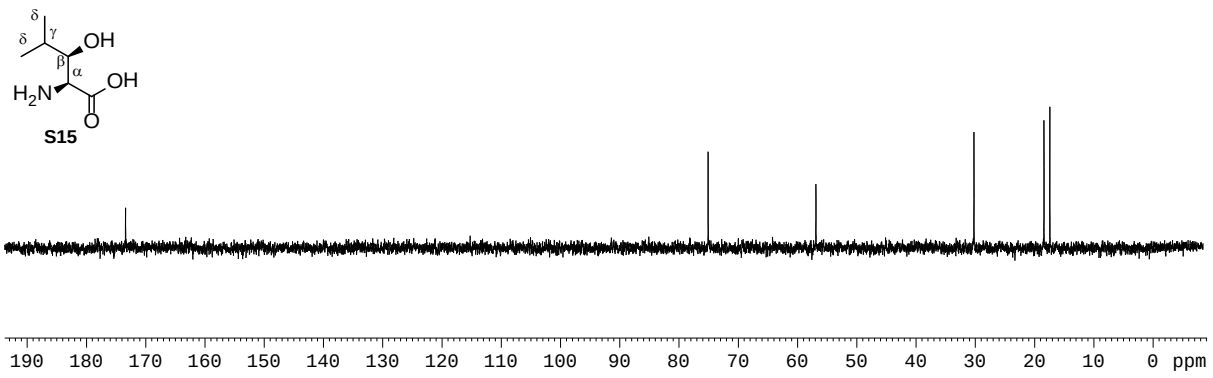
^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz, $CDCl_3$) spectra of Ni(II)-(*S*)-BPB/(2*S*,3*R*)-2-amino-3-hydroxy-4-methyl-pentanoic acid Schiff base complex **S14**.



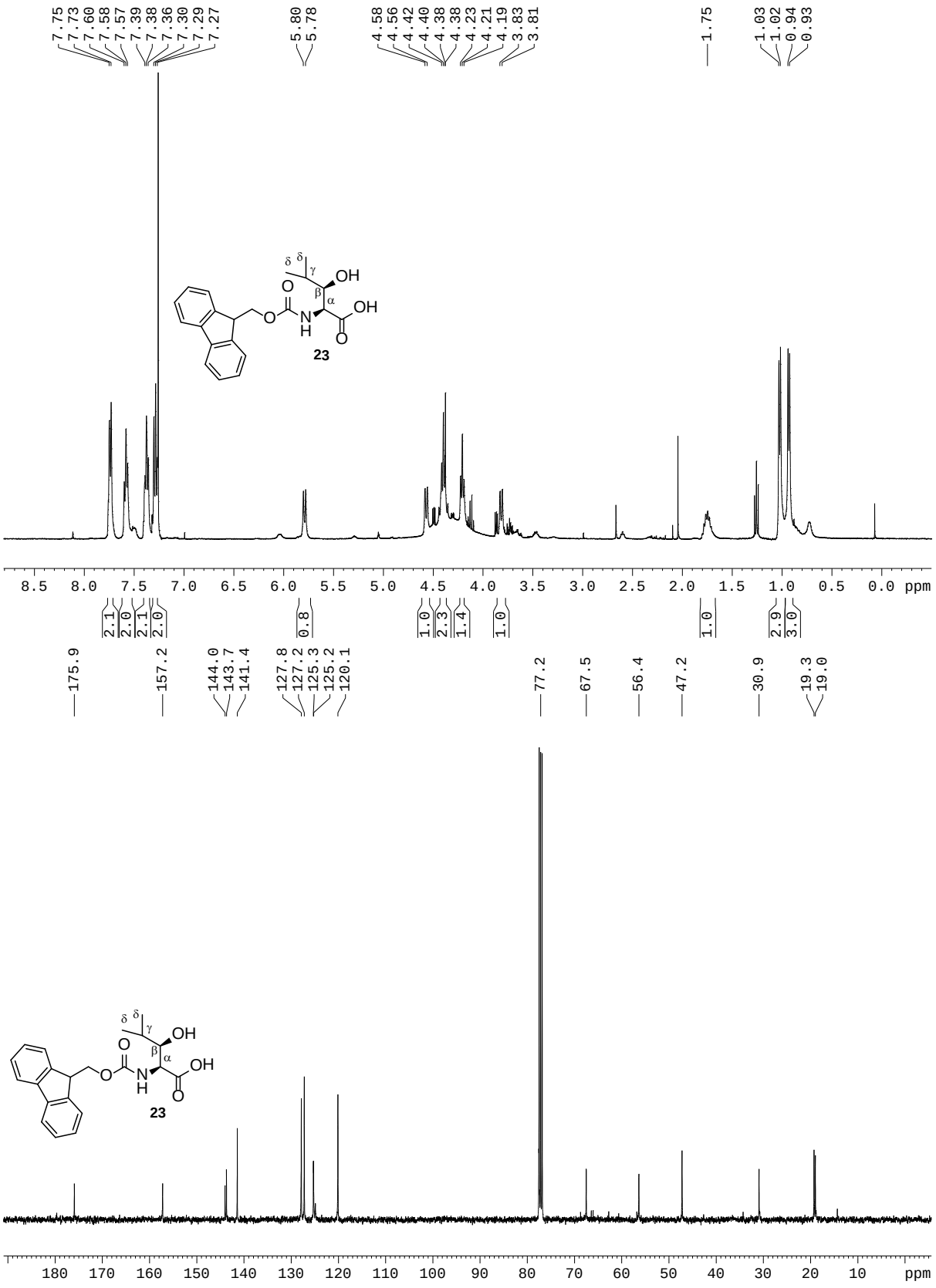


^{1}H (400 MHz, D_2O) and ^{13}C (100 MHz, D_2O) spectra of (2*S*,3*R*)-2-amino-3-hydroxy-4-methylpentanoic acid **S15**.





^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz, $CDCl_3$) spectra of (2*S*,3*R*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino-3-hydroxy-4-methylpentanoic acid **23**.



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