

Supporting Information

A Novel Dipeptidomimetic Containing a Cyclic Threonine

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Experimental Section

Materials and equipment: All commercial reagents and solvents were used as received if not stated otherwise. Solution reactions were performed in round-bottomed flasks. Solid-phase synthesis was performed in polypropylene syringes. Reactions were monitored by thin layer chromatography on Merck F254 plates, compounds were detected at 254 nm and staining was performed with either Ninhydrin in ethanol or KMnO_4 in 1M Na_2CO_3 . Silica gel from SDS (France) was used for flash chromatography. Microwave reactions were performed in a CEM Discovery in silicon sealed 10 mL pressure tubes. RP-HPLC was performed on a Waters instrument. The columns and conditions used were as follow: Nucleosil C18 column (4 mm, 25 cm), flow rate 1mL/min, and Symmetry C18 (7.8 mm, 10cm), flow rate 3 mL/min, both from Waters, eluents: B = MeCN with 0.036% TFA and A = water with 0.045% TFA. 1D- (^1H and ^{13}C) and 2D-NMR experiments (HSQC, COSY, ROESY) were performed on a Mercury (400 MHz) and a Gemini (200 MHz) spectrometer from Varian. Chemical shifts (δ) are expressed in parts per million downfield from tetramethylsilane. Coupling constants are expressed in Hertz. ROESY spectra were measured with a mixing time of 300 ms. ESI-MS was measured on a LC-MS system from Waters with a mass detector (Micromass ZQ), HR-MS spectra were obtained on a Bruker Daltonics Microtof (ESI-TOF). IR were measured on a ThermoNicolet 510 FT-IR spectrophotometer (Nexus), values are given in wave numbers [cm^{-1}].

General procedure for lactam formation. A solution of amino acid methyl or *t*-Bu ester free base, which was obtained by washing the corresponding hydrochloride in DCM with saturated NaHCO_3 , in anhydrous dioxane (~ 0.2 M) containing epoxide **3**, or **9** (1.2 eq) respectively, was transferred to a 10-mL pressure MW reaction vessel. After addition of $\text{Ca}(\text{OTf})_2$ (1.2 eq) the vessel was sealed, shaken and put in a CEM discovery microwave reactor without delay to avoid clumping of $\text{Ca}(\text{OTf})_2$ at the bottom of the vessel. The reaction was then carried out at 150 W and 120°C for 20 min. After filtration, the solvent was evaporated. Subsequent purification by column chromatography in EtOAc/hexane 2/1 to 3/1 gave the amine as a mixture of both diastereoisomers. Lactamization was carried out in toluene by heating at reflux for 12 to 24 h. After evaporation, the lactam was isolated as a pale yellow oil by column chromatography in EtOAc/hexane 1/1 to 3/1. Usually two product fractions were obtained, one containing the threo-isomer and the other an enriched mixture of erythro-isomer.

General procedure for Z-deprotection. A mixture of the Z-protected peptide and palladium (10% on charcoal, 100 mg/mmol) in MeOH was stirred under a hydrogen atmosphere at room temperature for 30 min. After filtration over celite the solvent was removed and the amine obtained was used for the next step without further purification.

General procedure for peptide coupling in solution. 1/1 (~ 50 mM) HATU (1.2 eq), HOAt (1.2 eq) and DIPEA (3 eq) were added to a solution of peptide and amino acid (1.2 eq) in DCM/DMF and the mixture was stirred at room temperature. After complete consumption of the amine, as followed by TLC, DCM

was added and the organic layer was washed with 0.1 M HCl, saturated NaHCO₃ and water. After drying the organic solution over Na₂SO₄, the solvent was removed under reduced pressure. Coevaporation with toluene followed (three to five times) to remove residual amounts of DMF. The pure peptide was obtained after column chromatography in EtOAc/hexane 1/1 to 3/1.

General procedure for peptide coupling on solid phase. Fmoc cleavage was carried out in a syringe containing a filter by treatment of the resin with 20% piperidine in DMF for 4 min and then a further 8 minutes. After washing the resin 10 times with DMF, the resin was incubated with a solution of Fmoc amino acid (5 eq), HATU (4.8 eq), HOAt (4.8 eq) and DIPEA (10 eq) in DMF (1 mL/100 mg resin) for 20 min. The solution was sucked off and the resin was washed with DMF (10 times) and DCM (two times), and subsequently dried. Completion of the coupling reaction was ensured by checking a small amount of resin on free amino groups by the Kaisertest.

Z-cThr-Val-OMe 5a. The epoxide opening reaction was carried out with H-Val-OMe free base (100 mg, 0.76 mmol) and **3** following the general procedure, to give **4a** (246 mg, 81%). Major isomer: ¹H-NMR [400 MHz, CDCl₃]: 7.30-7.37 (m, 5 H, arenes), 5.61 (d, *J* = 9.0 Hz, 1 H, NH^Z), 5.15 (d, *J* = 5.7 Hz, 1 H), 5.13 (s, 2 H, CH₂^{Bn}), 4.34 (dd, *J* = 9.4, 1.4 Hz, 1 H, H α), 4.07-4.11 (m, 1 H), 3.71-3.80 (m, 7 H), 2.97 (d, *J* = 5.7 Hz, 1 H), 2.92 (dd, *J* = 12.0, 3.6 Hz, 1 H, H γ), 2.35 (dd, *J* = 11.9, 10.2 Hz, 1 H, H γ'), 1.91-1.99 (m, 1 H, H β ^{Val}), 0.94 (d, *J* = 6.8 Hz, 3 H, H γ ^{Val}), 0.91 (d, *J* = 6.8 Hz, 3 H, H γ' ^{Val}).

Lactamization of **4a** gave **5a** (206 mg, 96%; 165 mg of *threo*-**5a** and 41 mg of *erythro*-**5a**, enriched). *threo*-**5a**: *R_f* (EtOAc) = 0.61, ¹H-NMR [400 MHz, CDCl₃]: 7.31-7.36 (m, 5 H, arenes), 5.80 (br. s, 1 H, NH^Z), 5.12 (s, 2 H, CH₂^{Bn}), 4.98 (br. s., 1 H, OH), 4.49 (d, *J* = 9.4 Hz, 1 H, H α ^{Val}), 4.35 (dt, *J* = 8.0 Hz, 1 H, H β ^{cThr}), 4.11 (dd, *J* = 8.1, 2.1 Hz, 1 H, H α ^{cThr}), 3.99 (dd, *J* = 9.4, 8.1 Hz, 1 H, H γ ^{cThr}), 3.70 (s, 3 H, CH₃), 3.22 (dd, *J* = 9.3, 8.2 Hz, 1 H, H γ ^{cThr'}), 2.15-2.24 (m, 1 H, H β ^{Val}), 0.96 (d, *J* = 6.7, 3 H, H γ ^{Val}), 0.93 (d, *J* = 6.8 Hz, 3 H, H γ' ^{Val}), ¹³C-NMR [100 MHz, CDCl₃]: 170.4, 169.5, 157.9, 135.7, 128.5, 128.3, 128.0, 73.3 (C β ^{cThr}), 67.5 (CH₂^{Bn}), 60.2 (C α ^{cThr}), 59.6 (C α ^{Val}), 52.0 (CH₃), 47.8 (C γ ^{cThr}), 28.7 (C β ^{Val}), 19.2 (C γ ^{Val}), 19.1 (C γ' ^{Val}), IR (KBr): 3434.7, 3285.0, 1702.6, 1676.5, 1451.4, 1257.3, HR-MS (ESI-TOF) calc. for C₁₈H₂₅N₂O₆ [M+H]⁺: 365.1707, found: 365.1703.

erythro-**5a**: ¹H-NMR [400 MHz, CDCl₃]: 7.30-7.35 (m, 5 H, arenes), 5.57-5.58 (m, 1 H, NH^Z), 5.10-5.17 (m, 3 H, CH₂^{Bn} a. OH), 4.40-4.54 (m, 3 H, H α ^{Val}, H α ^{cThr} a. H β ^{cThr}), 3.69-3.72 (m, 4 H, CH₃ a. H γ ^{cThr}), 3.53 (dd, *J* = 11.1, 3.1 Hz, 1 H, H γ ^{cThr'}), 2.15-2.24 (m, 1 H, H β ^{Val}), 0.96 (d, *J* = 6.7, 3 H, H γ ^{Val}), 0.89 (d, *J* = 6.8, 3 H, H γ' ^{Val}), ¹³C-NMR [100 MHz, CDCl₃]: 171.2, 171.2, 156.7, 136.0, 128.5, 128.2, 128.1, 67.3 (CH₂^{Bn}), 67.0 (C β ^{cThr}), 60.0 (C α ^{Val}), 56.9 (C α ^{cThr}), 52.2 (CH₃), 50.3 (C γ ^{cThr}), 28.6 (C β ^{Val}), 19.2 (C γ ^{Val}).

Z-cThr-Phe-OMe 5b. The epoxide opening reaction was carried out with H-Phe-OMe free base (180 mg, 1 mmol) and **3** following the general procedure, to give **4b** (360 mg, 81%). Major isomer: ¹H-NMR [400 MHz, CDCl₃]: 7.13-7.35 (m, 10 H, arenes), 5.64 (m, 1 H, NH^Z), 5.10 (s, 2 H, CH₂^{Bn}), 4.27 (m, 1 H, H α),

4.07 (m, 1 H, H β), 3.74 (s, 3 H, CH₃), 3.69 (s, 3 H, CH₃), 3.51 (m, 1 H, H α^{Phe}), 3.02 (m, 1 H, H β^{Phe}), 2.91 (m, 1 H, H γ), 2.88 (m, 1 H, H $\beta^{\text{Phe}'}$), 2.40 (m, 1 H, H γ'), ¹³C-NMR [100 MHz, CDCl₃]: 171.0, 170.1, 156.6, 136.6, 129.1, 128.6, 128.5, 128.0, 127.0, 69.6 (C β), 67.2 (CH₂^{Bn}), 63.1 (C α^{Phe}), 56.0 (C α), 52.7 (CH₃), 52.1 (CH₃), 50.6 (C γ), 39.3 (C β^{Phe}), HR-MS (ESI-TOF) calc. for C₂₃H₂₉N₂O₇ [M+H]⁺: 445.1969, found: 445.1960.

Lactamization gave **5b** (314 mg, 94%; 250 mg of *threo*-**5b**, 34 mg of *erythro*-**5b** and 30 mg of mixed fraction). *threo*-**5b**: *R_f* (EtOAc/Hex 1/1) = 0,34, ¹H-NMR [400 MHz, CDCl₃]: 7.14-7.37 (m, 10 H, arenes), 5.63 (s, 1 H, NH), 5.11 (s, 2 H, CH₂^{Bn}), 5.05 (dd, *J* = 11.5, 5.0 Hz, 1 H, H α^{Phe}), 4.92 (s, 1 H, OH), 4.32 (dt, *J* = 8.1 Hz, 1 H, H β^{cThr}), 3.81 (dd, *J* = 8.2, 1.7 Hz, 1 H, H α^{cThr}), 3.75 (s, 3 H, CH₃), 3.69 (dd, *J* = 8.5 Hz, 1 H, H γ^{cThr}), 3.39 (dd, *J* = 14.7, 5.0 Hz, 1 H, H β^{Phe}), 3.15 (dd, *J* = 8.6 Hz, 1 H, H $\gamma^{\text{cThr}'}$), 2.96 (dd, *J* = 14.7, 11.5 Hz, 1 H, H $\beta^{\text{Phe}'}$), ¹³C-NMR [100 MHz, CDCl₃]: 170.1, 169.3, 157.9, 135.8, 128.8, 128.6, 128.4, 128.0, 127.2, 73.3 (C β^{cThr}), 67.5 (CH₂^{Bn}), 60.1 (C α^{cThr}), 54.9 (C α^{Phe}), 52.6 (CH₃), 47.8 (C γ^{cThr}), 35.2 (C β^{Phe}), IR (KBr): 3506.5, 1722.2, 1689.9, 1440.4, 1260.3, HR-MS (ESI-TOF) calc. for C₂₂H₂₅N₂O₆ [M+H]⁺: 413.1707, found: 413.1699.

erythro-**5b**: *R_f* (EtOAc/Hex 1/1) = 0,25, ¹H-NMR [400 MHz, CDCl₃]: 7.15-7.36 (m, 10 H, arenes), 5.47 (d, *J* = 5.2 Hz, 1 H, NH), 5.09-5.16 (m, 4 H, CH₂^{Bn}, H α^{Phe} a. OH), 4.39 (br. s, 1 H, H β^{cThr}), 4.10-4.17 (m, 1 H, H α^{cThr}), 3.75 (s, 3 H, CH₃), 3.43-3.47 (m, 2 H, H γ^{cThr}), 3.39 (dd, *J* = 14.8, 5.2 Hz, 1 H, H β^{Phe}), 2.93 (dd, *J* = 14.8, 11.4 Hz, 1 H, H $\beta^{\text{Phe}'}$), ¹³C-NMR [100 MHz, CDCl₃]: 171.1, 156.5, 136.0, 135.8, 128.8, 128.5, 128.2, 128.1, 128.0, 127.2, 67.2 (CH₂^{Bn}), 67.0 (C β^{cThr}), 56.9 (C α^{cThr}), 54.6 (C α^{Phe}), 52.8 (CH₃), 50.0 (C γ), 35.1 (C β^{Phe}).

Z-cThr-Glu(tBu)-OMe 5c. The epoxide opening reaction was carried out with H-Glu(tBu)-OMe free base (72 mg, 0.33 mmol) and **3** following the general procedure, to give **4c** (121 mg, 76 %). Major isomer: *R_f* (EtOAc/Hex 2/1) = 0.5, ¹H-NMR [400 MHz, CDCl₃]: 7.30-7.36 (m, 5 H, arenes), 5.62 (d, *J* = 9.3 Hz, 1 H, NH^Z), 5.12 (s, 2 H, CH₂^{Bn}), 4.33 (d, *J* = 9.6 Hz, 1 H, H α), 4.05-4.09 (m, 1 H, H β), 3.76 (s, 3 H, CH₃), 3.73 (s, 3 H, CH₃), 3.23 (dd, *J* = 8.7, 5.4 Hz, 1 H, H α^{Glu}), 2.94 (dd, *J* = 12.2, 3.4 Hz, 1 H, H γ), 2.26-2.39 (m, 3 H, H γ' a. H γ^{Glu}), 1.94-2.02 (m, 1 H, H β^{Glu}), 1.77-1.86 (m, 1 H, H $\beta^{\text{Glu}'}$), 1.43 (s, 3 H, tBu), ¹³C-NMR [100 MHz, CDCl₃]: 174.9, 172.4, 171.1, 156.6, 136.2, 128.5, 128.1, 128.0, 80.7 (CMe₃), 70.1 (C β), 67.1 (CH₂^{Bn}), 61.3 (C α^{Glu}), 56.0 (C α), 52.6 (CH₃), 52.1 (CH₃), 51.0 (C γ), 32.1 (C γ^{Glu}), 28.5 (C β^{Glu}), 28.0 (tBu), HR-MS (ESI-TOF) calc. for C₂₃H₃₅N₂O₉ [M+H]⁺: 483.2337, found: 483.2331.

Lactamization gave **5c** (82 mg, 76%; 61 mg of *threo*-**5c** and 21 mg as a 3/2 mixture with *erythro*-**5c**). *threo*-**5c**: ¹H-NMR [400 MHz, CDCl₃]: 7.32-7.39 (m, 5 H, arenes), 5.73 (br. s, 1 H, NH^Z), 5.14 (s, 2 H, CH₂^{Bn}), 4.95-4.99 (m, 1 H, OH), 4.73 (dd, *J* = 10.6, 4.4 Hz, 1 H, H α^{Glu}), 4.44 (dt, *J* = 8.0 Hz, 1 H, H β^{cThr}), 4.14 (dd, *J* = 8.0, 1.9 Hz, 1 H, H α^{cThr}), 3.72-3.79 (m, 4 H, CH₃ a. H γ^{cThr}), 3.22 (t, *J* = 8.6, 1H, H $\gamma^{\text{cThr}'}$), 2.23-2.33 (m, 3 H, H β^{Glu} a. H γ^{Glu}), 1.90-1.97 (m, 1 H, H $\beta^{\text{Glu}'}$), 1.44 (s, 9 H, tBu), ¹³C-NMR [100 MHz, CDCl₃]: 171.1, 170.1, 169.6, 157.9, 135.7, 128.6, 128.4, 128.0, 81.1 (CMe₃), 73.3 (C β^{cThr}), 67.5 (CH₂^{Bn}),

60.3 (C α ^{cThr}), 53.4 (C α ^{Glu}), 52.6 (CH₃), 47.6 (C γ ^{cThr}), 31.9 (C γ ^{Glu}), 28.0(tBu), 24.4 (C β ^{Glu}), HR-MS (ESI-TOF) calc. for C₂₂H₃₀N₂NaO₈ [M+Na]⁺: 473.1894, found: 473.1898.

erythro-5c: ¹H-NMR [400 MHz, CDCl₃]: 7.29-7.39 (m, 5 H, arenes), 5.51 (m, 1 H, NH^Z), 5.14 (s, 2 H, CH₂^{Bn}), 4.96 (br. s., 1 H, OH), 4.45 (m, 1 H, H α ^{cThr}), 4.35 (m, 1H, H β ^{cThr}), 3.72 (m, 3 H, CH₃), 3.60 (m, 1 H, H γ ^{cThr}), 3.42 (m, 1 H, H γ ^{cThr'}), 4.70 (m, 1 H, H α ^{Glu}), 2.17-2.35 (m, 3 H, H β ^{Glu} a. H γ ^{Glu}), 1.90-1.97 (m, 1 H, H β ^{Glu'}), 1.43 (s, 9 H, tBu), ¹³C-NMR [100 MHz, CDCl₃]: 171.5, 171.2, 169.7, 156.6, 136.0, 128.5, 128.2, 128.1, 81.1 (CMe₃), 73.4 (C β ^{cThr}), 67.6 (C α ^{cThr}), 67.5 (CH₂^{Bn}), 53.8 (C α ^{Glu}), 52.8 (CH₃), 50.1 (C γ ^{cThr}), 32.0 (C γ ^{Glu}), 28.0(tBu), 24.3 (C β ^{Glu}).

Z-cThr-Tyr-OMe 5d. The epoxide opening reaction was carried out with H-Tyr-OMe free base (62 mg, 0.32 mmol) and **3** following the general procedure, to give **4d** (112 mg, 76 %). Major isomer: *R_f* (EtOAc/Hex 3/1) = 0.39, ¹H-NMR [400 MHz, CDCl₃]: 7.29-7.36 (m, 5 H, arenes), 6.95 (d, *J* = 8.3 Hz, 2 H, arenes), 6.70 (d, *J* = 8.4 Hz, 2 H, arenes), 5.71 (d, *J* = 9.2, 1 H, NH^Z), 5.10 (s, 2 H, CH₂^{Bn}), 4.29 (d, *J* = 9.4, 1 H, H α), 4.05 (m, 1 H, H β), 3.70 (s, 3 H, CH₃), 3.69 (s, 3 H, CH₃), 3.41 (dd, *J* = 7.6, 5.7 Hz, 1 H, H α ^{Tyr}), 3.29 (m, 1 H, NH), 2.93 (dd, *J* = 13.8, 5.5 Hz, 1 H, H β ^{Tyr}), 2.86 (dd, *J* = 12.4, 3.5 Hz, 1 H, H γ), 2.77 (dd, *J* = 13.8, 7.6 Hz, 1 H, H β ^{Tyr'}), 2.37 (dd, *J* = 12.2, 9.7 Hz, 1 H, H γ'), ¹³C-NMR [100 MHz, CDCl₃]: 174.7, 171.2, 155.0, 136.0, 130.2, 128.5, 128.2, 128.0, 115.5, 69.8 (C β), 67.2 (CH₂^{Bn}), 63.2 (C α ^{Tyr}), 56.0 (C α), 52.7 (CH₃), 52.1 (CH₃), 50.5 (C γ), 38.5 (C β ^{Tyr}), IR (KBr): 3328.3, 2924.3, 1684.3, 1517.6, 1258.4, HR-MS (ESI-TOF) calc. for C₂₃H₂₈N₂NaO₈ [M+Na]⁺: 461.1918, found: 461.1931.

Lactamization gave **5d** (92 mg, 88%; 64 mg of *threo-5d* and 28 mg *erythro-5d*, enriched). *threo-5d*: *R_f* (EtOAc/Hex 2/1) = 0.27, ¹H-NMR [400 MHz, CDCl₃]: 7.30-7.38 (m, 5 H, arenes), 6.98 (d, *J* = 8.4 Hz, 2 H, arenes), 6.69 (d, *J* = 8.4 Hz, 2 H, arenes), 5.60 (d, *J* = 2.8 Hz, 1 H, NH^Z), 5.03-5.10 (m, 3 H, H α ^{Tyr} a. CH₂^{Bn}), 4.30 (dt, *J* = 8.1 Hz, 1 H, H β ^{cThr}), 3.90 (dd, *J* = 8.4, 3.2 Hz, 1 H, H α ^{cThr}), 3.76 (s, 3 H, CH₃), 3.71 (dd, *J* = 8.6 Hz, 1 H, H γ ^{cThr}), 3.31 (dd, *J* = 14.9, 4.8 Hz, 1 H, H β ^{Tyr}), 3.11 (dd, *J* = 8.7 Hz, 1 H, H γ ^{cThr'}), 2.85 (dd, *J* = 14.8, 11.8 Hz, 1 H, H β ^{Tyr'}), ¹³C-NMR [100 MHz, CDCl₃]: 170.2, 170.0, 158.0, 155.2, 135.7, 129.6, 128.6, 128.4, 128.0, 115.8, 73.2 (C β ^{cThr}), 67.7 (CH₂^{Bn}), 59.9 (C α ^{cThr}), 54.9 (C α ^{Tyr}), 52.7 (CH₃), 47.7 (C γ ^{cThr}), 34.4 (C β ^{Tyr}), HR-MS (ESI-TOF) calc. for C₂₂H₂₅N₂O₇ [M+H]⁺: 429.1656, found: 429.1669.

erythro-5d: *R_f* (EtOAc/Hex 2/1) = 0.21, ¹H-NMR [400 MHz, CDCl₃]: 7.29-7.35 (m, 5 H, arenes), 6.96 (d, *J* = 8.2 Hz, 2 H, arenes), 6.70 (d, *J* = 8.4 Hz, 2 H, arenes), 5.55 (d, *J* = 5.4 Hz, 1 H, NH^Z), 5.02-5.10 (m, 3 H, H α ^{Tyr} a. CH₂^{Bn}), 4.30-4.34 (m, 1 H, H β ^{cThr}), 4.15-4.18 (m, 1 H, H α ^{cThr}), 3.68-3.78 (m, 4 H, CH₃ a. H γ ^{cThr}), 3.37-3.44 (m, 1 H, H γ ^{cThr'}), 3.30 (dd, *J* = 14.9, 4.5 Hz, 1 H, H β ^{Tyr}), 2.82 (dd, *J* = 14.6, 12.0 Hz, 1 H, H β ^{Tyr'}), ¹³C-NMR [100 MHz, CDCl₃]: 171.7, 171.1, 156.7, 155.4, 135.9, 129.3, 128.5, 128.2, 128.1, 127.0, 115.8, 67.4 (CH₂^{Bn}), 67.0(C β ^{cThr}), 56.8 (C α ^{cThr}), 54.9 (C α ^{Tyr}), 52.8 (CH₃), 50.1 (C γ ^{cThr}), 34.2 (C β ^{Tyr}).

Fmoc-Lys(Boc)-cThr-Val-OMe (7a). The peptide coupling was carried out with *threo-5a* (77 mg, 0.21 mmol) following the general procedure to give **7a** (115 mg, 80 %, after column chromatography). R_f (EtOAc/Hex 2/1) = 0.26, $^1\text{H-NMR}$ [400 MHz, CDCl_3]: 7.75 (d, $J = 7.5$ Hz, 2 H, arenes), 7.58 (d, $J = 6.5$ Hz, 2 H, arenes), 7.39 (dd, $J = 7.5$ Hz, 1 H, arenes), 7.30 (dd, $J = 7.3$ Hz, 2 H, arenes), 7.11 (br. s, 1 H, NH^{amide}), 5.68 (br. s, 1 H, NH^{Fmoc}), 4.69 (br. s, 1 H, NH^{Boc}), 4.50 (d, $J = 9.4$ Hz, 1 H, $\text{H}\alpha^{\text{Val}}$), 4.39 (m, 2 H, $\text{CH}_2^{\text{Fmoc}}$), 4.29 (m, 1 H, $\text{H}\beta^{\text{cThr}}$), 4.28 (m, 1 H, $\text{H}\alpha^{\text{Lys}}$), 4.23 (m, 1 H, $\text{H}\alpha^{\text{cThr}}$), 4.20 (t, $J = 6.8$ Hz, 1 H, H-9^{Fmoc}), 4.00 (dd, $J = 9.4, 7.9$ Hz, 1 H, $\text{H}\gamma^{\text{cThr}}$), 3.70 (s, 3 H, CH_3), 3.24 (dd, $J = 8.6$ Hz, 1 H, $\text{H}\gamma^{\text{cThr}}$), 3.04-3.12 (m, 2 H, $\text{H}\epsilon^{\text{Lys}}$), 2.15-2.25 (m, 1 H, $\text{H}\beta^{\text{Val}}$), 1.79-1.86 (m, 1 H, CH_2^{Lys}), 1.64-1.72 (m, 1 H, CH_2^{Lys}), 1.33-1.48 (m, 13 H, tBu a. CH_2^{Lys}), 0.97 (d, $J = 6.7$ Hz, 3 H, $\text{H}\gamma^{\text{Val}}$), 0.93 (d, $J = 6.7$ Hz, 3 H, $\text{H}\gamma^{\text{Val}}$), $^{13}\text{C-NMR}$ [100 MHz, CDCl_3]: 174.7, 170.4, 169.6, 156.2, 143.8, 143.6, 141.2, 127.7, 127.1, 125.0, 119.8, 79.2 (CMe_3), 72.6 ($\text{C}\beta^{\text{cThr}}$), 67.1 ($\text{CH}_2^{\text{Fmoc}}$), 60.5 ($\text{C}\alpha^{\text{cThr}}$), 59.8 ($\text{C}\alpha^{\text{Val}}$), 54.7 ($\text{C}\alpha^{\text{Lys}}$), 52.1 (CH_3), 48.0 ($\text{C}\gamma^{\text{cThr}}$), 47.1 (CH^{Fmoc}), 39.7 ($\text{C}\epsilon^{\text{Lys}}$), 32.1 (CH_2^{Lys}), 29.6 (CH_2^{Lys}), 28.7 ($\text{C}\beta^{\text{Val}}$), 28.4 (tBu), 22.4 (CH_2^{Lys}), 19.2 ($\text{C}\gamma^{\text{Val}}$), 19.1 ($\text{C}\gamma^{\text{Val}}$), HR-MS (ESI-TOF) calc. for $\text{C}_{36}\text{H}_{49}\text{N}_4\text{O}_9$ $[\text{M}+\text{H}]^+$: 681.3494, found: 681.3494.

Fmoc-Ala-cThr-Val-OMe (7b). The peptide coupling was carried out with *threo-5a* (77 mg, 0.21 mmol) following the general procedure to give **7b** (90 mg, 81 %, after column chromatography). R_f (EtOAc/Hex 2/1) = 0.24, $^1\text{H-NMR}$ [400 MHz, CDCl_3]: 7.75 (d, $J = 7.5$ Hz, 2 H, arenes), 7.57-7.59 (m, 2 H, arenes), 7.39 (dd, $J = 7.4$ Hz, 1 H, arenes), 7.31 (dd, $J = 7.4$ Hz, 2 H, arenes), 7.05 (br. s, 1 H, NH^{amide}), 5.44 (br. s, 1 H, NH^{Fmoc}), 4.52 (d, $J = 9.4$ Hz, 1 H, $\text{H}\alpha^{\text{Val}}$), 4.41 (m, 2 H, $\text{CH}_2^{\text{Fmoc}}$), 4.37 (m, 1 H, $\text{H}\alpha^{\text{Ala}}$), 4.29 (m, 1 H, $\text{H}\beta^{\text{cThr}}$), 4.23 (m, 1 H, $\text{H}\alpha^{\text{cThr}}$), 4.21 (t, $J = 6.6$ Hz, 1 H, H-9^{Fmoc}), 4.01 (dd, $J = 8.6$ Hz, 1 H, $\text{H}\gamma^{\text{cThr}}$), 3.71 (s, 3 H, CH_3), 3.25 (dd, $J = 8.7$ Hz, 1 H, $\text{H}\gamma^{\text{cThr}}$), 2.17-2.26 (m, 1 H, $\text{H}\beta^{\text{Val}}$), 1.41 (d, $J = 5.9$ Hz, 3 H, $\text{H}\beta^{\text{Ala}}$), 0.98 (d, $J = 6.7$ Hz, 3 H, $\text{H}\gamma^{\text{Val}}$), 0.94 (d, $J = 6.7$ Hz, 3 H, $\text{H}\gamma^{\text{Val}}$), $^{13}\text{C-NMR}$ [100 MHz, CDCl_3]: 175.2, 170.4, 169.6, 155.8, 143.7, 141.3, 127.7, 127.1, 125.0, 120.0, 72.8 ($\text{C}\beta^{\text{cThr}}$), 67.1 ($\text{CH}_2^{\text{Fmoc}}$), 60.7 ($\text{C}\alpha^{\text{cThr}}$), 59.8 ($\text{C}\alpha^{\text{Val}}$), 52.1 (CH_3), 50.3 ($\text{C}\alpha^{\text{Ala}}$), 48.0 ($\text{C}\gamma^{\text{cThr}}$), 47.1 (CH^{Fmoc}), 28.7 ($\text{C}\beta^{\text{Val}}$), 19.2 ($\text{C}\gamma^{\text{Val}}$), 19.1 ($\text{C}\gamma^{\text{Val}}$), HR-MS (ESI-TOF) calc. for $\text{C}_{28}\text{H}_{34}\text{N}_3\text{O}_7$ $[\text{M}+\text{H}]^+$: 524.2391, found: 524.2390.

Fmoc-Asn(Trt)-cThr-Phe-OMe (7c). The peptide coupling was carried out with *threo-5b* (115 mg, 0.28 mmol) following the general procedure to give **7c** (181 mg, 76 %, after column chromatography). R_f (EtOAc/Hex 2/1) = 0.26, $^1\text{H-NMR}$ [400 MHz, CDCl_3]: 7.74-7.77 (m, 2 H, arenes), 7.55 (d, $J = 7.2$ Hz, 2 H, arenes), 7.40 (dd, $J = 7.3$ Hz, 2 H, arenes), 7.13-7.33 (m, 23 H, arenes a. NH^{amide}), 6.86 (br. s, 1 H, NH^{amide}), 6.42 (d, $J = 9.1$ Hz, 1 H, NH^{Fmoc}), 5.09 (dd, $J = 5.2, 11.1$ Hz, 1 H, $\text{H}\alpha^{\text{Phe}}$), 4.57-4.62 (m, 1 H, $\text{H}\alpha^{\text{Asn}}$), 4.30-4.41 (m, 2 H, $\text{CH}_2^{\text{Fmoc}}$), 4.19 (m, 1 H, H-9^{Fmoc}), 4.14 (m, 1 H, $\text{H}\beta^{\text{cThr}}$), 3.85 (d, $J = 7.9$ Hz, 1 H, $\text{H}\alpha^{\text{cThr}}$), 3.72-3.76 (m, 4 H, $\text{CH}_3^{\text{ester}}$ a. $\text{H}\gamma^{\text{cThr}}$), 3.38 (dd, $J = 14.7, 5.2$ Hz, 1 H, $\text{H}\beta^{\text{Phe}}$), 3.15-3.20 (m, 2 H, $\text{H}\beta^{\text{Asn}}$ a. $\text{H}\gamma^{\text{cThr}}$), 2.96 (dd, $J = 14.6, 11.1$ Hz, 1 H, $\text{H}\beta^{\text{Phe}}$), 2.58-2.63 (m, 1 H, $\text{H}\beta^{\text{Asn}}$), $^{13}\text{C-NMR}$ [100 MHz, CDCl_3]: 173.8, 170.1, 170.0, 169.1, 144.1, 141.2, 135.7, 128.7, 128.5, 128.0, 127.7, 127.2, 127.0, 125.1, 119.9, 72.2 ($\text{C}\beta^{\text{cThr}}$), 70.9, 67.5 ($\text{CH}_2^{\text{Fmoc}}$), 60.4 ($\text{C}\alpha^{\text{cThr}}$), 54.6 ($\text{C}\alpha^{\text{Phe}}$), 52.6 (CH_3), 51.5 ($\text{C}\alpha^{\text{Asn}}$),

47.6 (CH^{Fmoc}), 46.9 ($\text{C}\gamma^{\text{Thr}}$), 37.8 ($\text{C}\beta^{\text{Asn}}$), 35.3 ($\text{C}\beta^{\text{Phe}}$), HR-MS (ESI-TOF) calc. for $\text{C}_{52}\text{H}_{49}\text{N}_4\text{O}_8$ $[\text{M}+\text{H}]^+$: 857.3545, found: 857.3552.

(9-Fluorenylmethoxycarbonyl)-D-methioninesulfoxide methylester 10. A mixture of H-L-Met-OMe hydrochloride (10 g, 0.05 mol), FmocOSu (17 g, 0.05 mol) and DIPEA (16.5 mL, 0.1 mol) in THF (250 mL) was stirred over night. After evaporation the residue was dissolved in EtOAc. The organic layer was washed with 0.1 M HCl, saturated NaHCO_3 and water. After drying the organic layer over Na_2SO_4 , the solvent was removed. $^1\text{H-NMR}$ [400 MHz, CDCl_3]: 7.77 (d, $J = 7.6$ Hz, 2 H, arenes), 7.60 (dd, $J = 7.0$, 3.0 Hz, 2 H, arenes), 7.40 (dd, $J = 7.4$ Hz, 2 H, arenes), 7.32 (dd, $J = 7.4$ Hz, 2 H, arenes), 5.45 (d, $J = 7.9$ Hz, 1 H, NH), 4.48-4.53 (m, 1 H), 4.42 (d, $J = 6.9$ Hz, 2 H), 4.23 (dd, $J = 6.9$ Hz, 1 H), 3.76 (s, 3 H, $\text{CH}_3^{\text{ester}}$), 2.51-2.54 (m, 2 H), 2.13-2.21 (m, 1 H), 2.09 (s, 3 H, SMe), 1.92-2.02 (m, 1 H).

[9-Fluorenylmethoxycarbonyl]-vinylglycine methylester 11. The crude product was dissolved in MeOH (200 mL) and a solution of NaIO_4 (10.7 g, 0.05 mmol) in H_2O (150 mL) was added dropwise at 4°C . After stirring the solution for 24 h, the white precipitate was filtered off and the MeOH was evaporated. The water layer was extracted twice with DCM. The combined organic layers were washed with 1 M HCl, saturated NaHCO_3 and water, dried over Na_2SO_4 and evaporated. $^1\text{H-NMR}$ [400 MHz, CDCl_3]: 7.77 (d, $J = 7.6$ Hz, 2 H, arenes), 7.57-7.63 (m, 2 H, arenes), 7.40 (dd, $J = 7.4$ Hz, 2 H, arenes), 7.29-7.34 (m, 2 H, arenes), 5.79 and 5.70 (d, $J = 7.7$ Hz, 1 H, NH, two conformers), 4.41-4.51 (m, 3 H), 4.22 (dd, $J = 6.7$ Hz, 1 H), 3.78 (s, 3 H, $\text{CH}_3^{\text{ester}}$), 2.68-2.82 (m, 2 H), 2.57 (s, 3 H, SMe), 2.36-2.44 (m, 1 H), 2.12-2.24 (m, 1 H), $^{13}\text{C-NMR}$ [100 MHz, CDCl_3]: 171.7, 156.0, 143.7, 143.5, 141.2, 127.7, 127.0, 125.0, 119.9, 67.0, 52.7, 47.1, 38.5, HR-MS (ESI-TOF) calc. for $\text{C}_{21}\text{H}_{24}\text{NO}_5$ $[\text{M}+\text{H}]^+$: 402.1355, found: 402.1370.

The product was then dissolved in xylene (250 mL) and heated at reflux until complete consumption of the starting material was detected by TLC. After evaporation, pure vinyl glycine (14.0 g, 83 %) was isolated by column chromatography in Hex/EtOAc 4/1 to 2/1. R_f (EtOAc/Hex 1/2) = 0.31, $^1\text{H-NMR}$ [250 MHz, CDCl_3]: 7.77 (d, $J = 7.3$ Hz, 2 H, arenes), 7.61 (d, $J = 7.3$ Hz, 2 H, arenes), 7.41 (dd, $J = 7.3$ Hz, 2 H, arenes), 7.32 (dd, $J = 7.4$ Hz, 2 H, arenes), 5.92 (ddd, $J = 16.5$, 10.0 Hz, 1 H, H β), 5.50 (d, $J = 6.9$ Hz, 1 H, NH), 5.35 (d, $J = 16.5$ Hz, 1 H, H γ), 5.27 (d, $J = 9.6$ Hz, 1 H, H γ'), 4.95 (dd, $J = 6.8$ Hz, 1 H, H α), 4.43 (d, $J = 6.8$ Hz, 2 H, $\text{CH}_2^{\text{Fmoc}}$), 4.23 (dd, $J = 6.8$ Hz, 1 H, H-9 $^{\text{Fmoc}}$), 3.79 (s, 3 H, CH_3), $^{13}\text{C-NMR}$ [100 MHz, CDCl_3]: 170.9, 155.5, 143.7, 141.3, 132.3, 127.7, 127.0, 125.0, 120.0, 117.8, 67.1, 56.1, 52.8, 47.1, HR-MS (ESI-TOF) calc. for $\text{C}_{20}\text{H}_{20}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 338.1389, found: 338.1387.

[9-Fluorenylmethoxycarbonyl]-oxiranylglycine methylester 9. A solution of Fmoc-VGly-OMe (1.1 g, 3.3 mmol) in DCM (50 mL) containing mCPBA (2.8 g) was stirred for three days at room temperature. The reaction mixture was then filtered, and the solution was cooled in an ice bath and 20 mL of saturated Na_2SO_3 were added. It was filtered again and the phases were separated. The organic layer was washed with Na_2SO_3 , then with saturated NaHCO_3 and water which was then repeated two times. After drying over Na_2SO_4 the solvent was evaporated. Pure **9** (1.1 g, 95 %) could be obtained after column

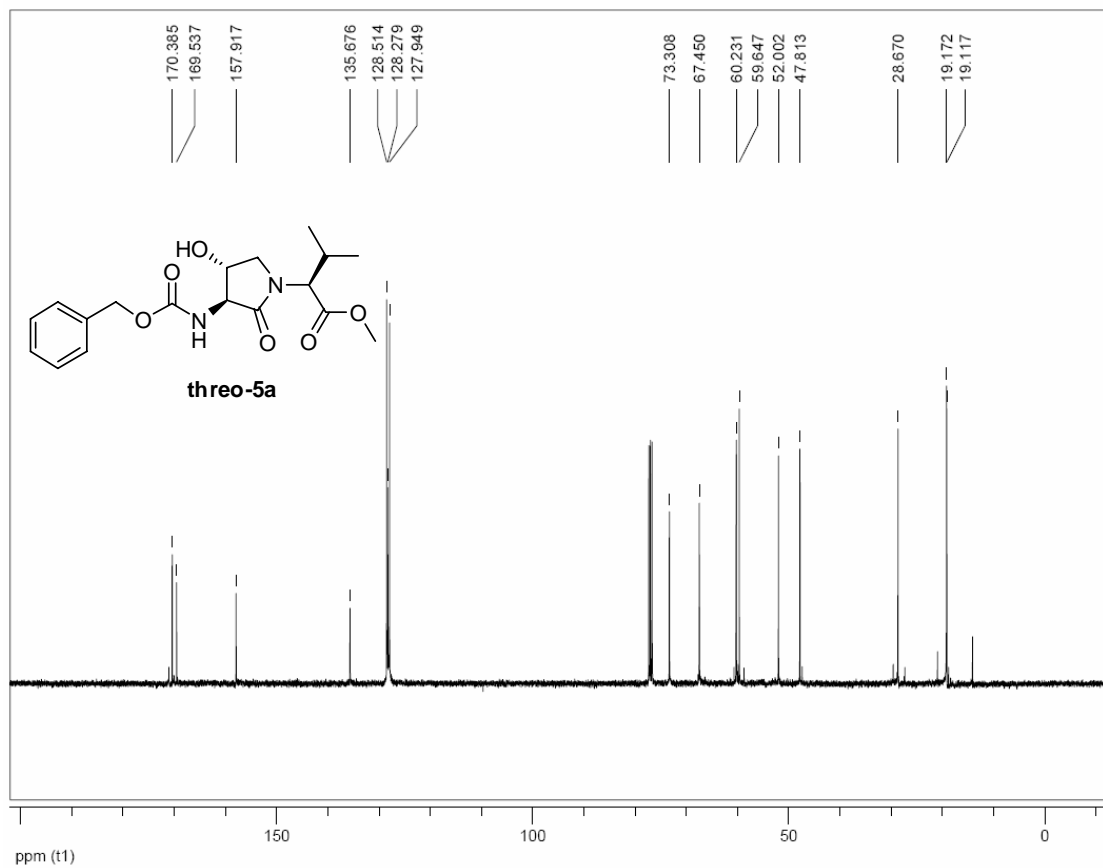
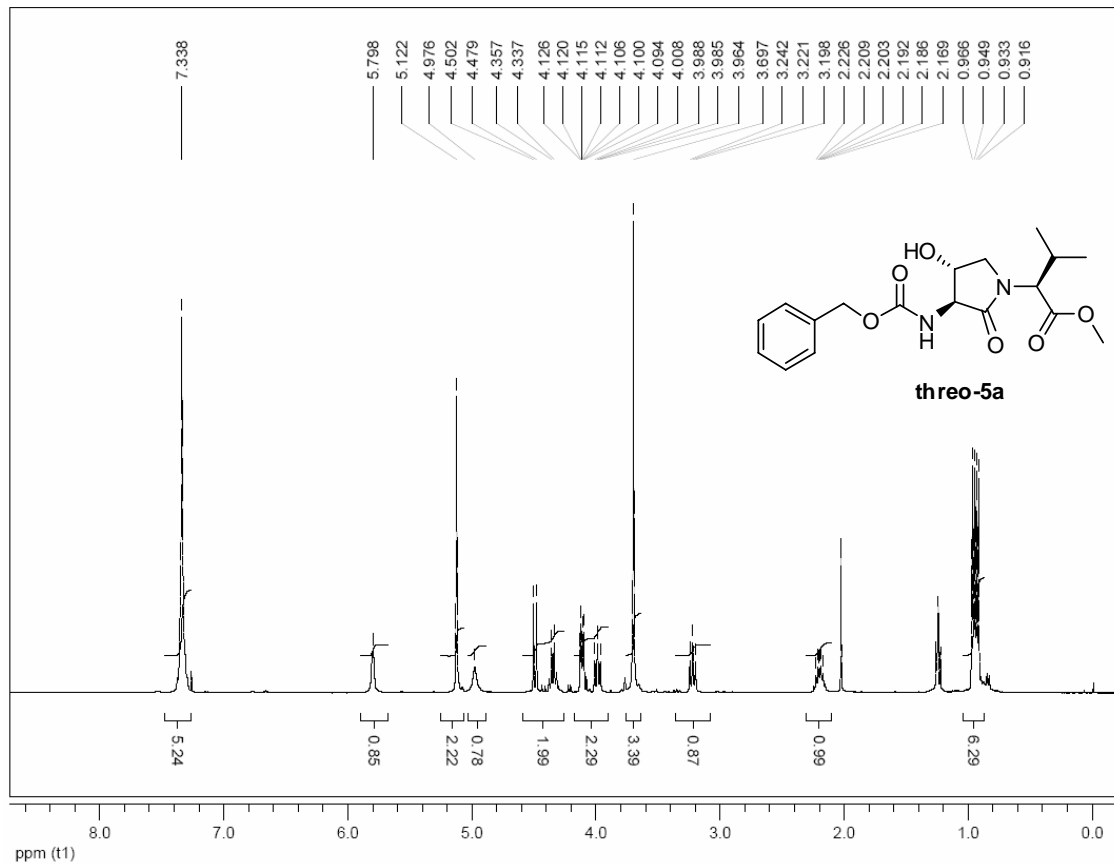
chromatography in Hex/EtOAc 3/1 to 1/1 as a mixture of both diastereoisomers in a 6/1 ratio of *threo/erythro*. Major isomer: $^1\text{H-NMR}$ [400 MHz, CDCl_3]: 7.77 (d, $J = 7.5$ Hz, 2 H, arenes), 7.57-7.61 (m, 2 H, arenes), 7.41 (dd, $J = 7.4$ Hz, 2 H, arenes), 7.30-7.35 (m, 2 H, arenes), 5.30 (d, $J = 8.6$ Hz, 1 H, NH), 4.72 (dd, $J = 8.9, 1.5$ Hz, 1 H, $\text{H}\alpha$), 4.43 (d, $J = 6.8$ Hz, 2 H, $\text{CH}_2^{\text{Fmoc}}$), 4.22 (dd, $J = 6.8$ Hz, 1 H, H-9^{Fmoc}), 3.83 (s, 3 H, CH_3), 3.48 (br. s., 1 H), 2.79 (dd, $J = 4.2$ Hz, 1 H), 2.62 (dd, $J = 4.0, 2.5$ Hz, 1 H), $^{13}\text{C-NMR}$ [100 MHz, CDCl_3]: 170.4, 156.3, 144.0, 143.7, 141.6, 141.5, 128.0, 127.3, 125.3, 120.2, 67.5, 53.3, 53.2, 51.4, 47.3, 44.1, IR (KBr): 3288.5, 1750.9, 1693.0, 1545.1, 1339.8, 1259.7, 1216.1, 1094.8, 735.0, HR-MS (ESI-TOF) calc. for $\text{C}_{20}\text{H}_{20}\text{NO}_5$ $[\text{M}+\text{H}]^+$: 354.1340, found: 354.1336.

Fmoc-cThr-Phe-OtBu 12. The epoxide opening reaction was carried out with H-Phe-OtBu free base (88 mg, 0.40 mmol) and **9** following the general procedure. After filtration the crude product was directly used for lactam formation to give **12** (132 mg, 78%). *threo-12* (major isomer): $^1\text{H-NMR}$ [400 MHz, CDCl_3]: 7.76 (d, $J = 7.5$ Hz, 2 H, arenes), 7.57 (d, $J = 7.5$ Hz, 2 H, arenes), 7.41 (dd, $J = 7.4$ Hz, 2 H, arenes), 7.28-7.34 (m, 4 H, arenes), 7.19-7.25 (m, 3 H, arenes), 5.67 (br. s., 1 H, NH), 4.96 (dd, $J = 11.4, 5.1$ Hz, 1 H, $\text{H}\alpha^{\text{Phe}}$), 4.93 (br. s., 1 H, OH), 4.40 (d, $J = 6.9$ Hz, 2 H, $\text{CH}_2^{\text{Fmoc}}$), 4.30 (ddd, $J = 8.1$ Hz, 1 H, $\text{H}\beta^{\text{cThr}}$), 4.21 (dd, $J = 6.9$ Hz, 1 H, H-9^{Fmoc}), 3.82 (dd, $J = 8.1, 1.7$ Hz, 1 H, $\text{H}\alpha^{\text{cThr}}$), 3.72 (dd, $J = 8.5$ Hz, 1 H, $\text{H}\gamma^{\text{cThr}}$), 3.36 (dd, $J = 14.7, 5.1$ Hz, 1 H, $\text{H}\beta^{\text{Phe}}$), 3.14 (dd, $J = 8.7$ Hz, 1 H, $\text{H}\gamma^{\text{cThr}}$), 2.95 (dd, $J = 14.7, 11.4$ Hz, 1 H, $\text{H}\beta^{\text{Phe}}$), 1.47 (s, 9 H, tBu), $^{13}\text{C-NMR}$ [100 MHz, CDCl_3]: 169.2, 168.7, 158.0, 143.4, 143.5, 141.3, 136.1, 128.7, 128.5, 127.8, 125.0, 124.9, 120.0, 82.7 (CMe_3), 73.5 ($\text{C}\beta^{\text{cThr}}$), 67.6 ($\text{CH}_2^{\text{Fmoc}}$), 60.1 ($\text{C}\alpha^{\text{cThr}}$), 55.5 ($\text{C}\alpha^{\text{Phe}}$), 47.8 ($\text{C}\gamma^{\text{cThr}}$), 46.9 (CH^{Fmoc}), 35.3 ($\text{C}\beta^{\text{Phe}}$), 28.0 (CCH_3), HR-MS (ESI-TOF) calc. for $\text{C}_{32}\text{H}_{35}\text{N}_2\text{O}_6$ $[\text{M}+\text{H}]^+$: 543.2504, found: 543.2490.

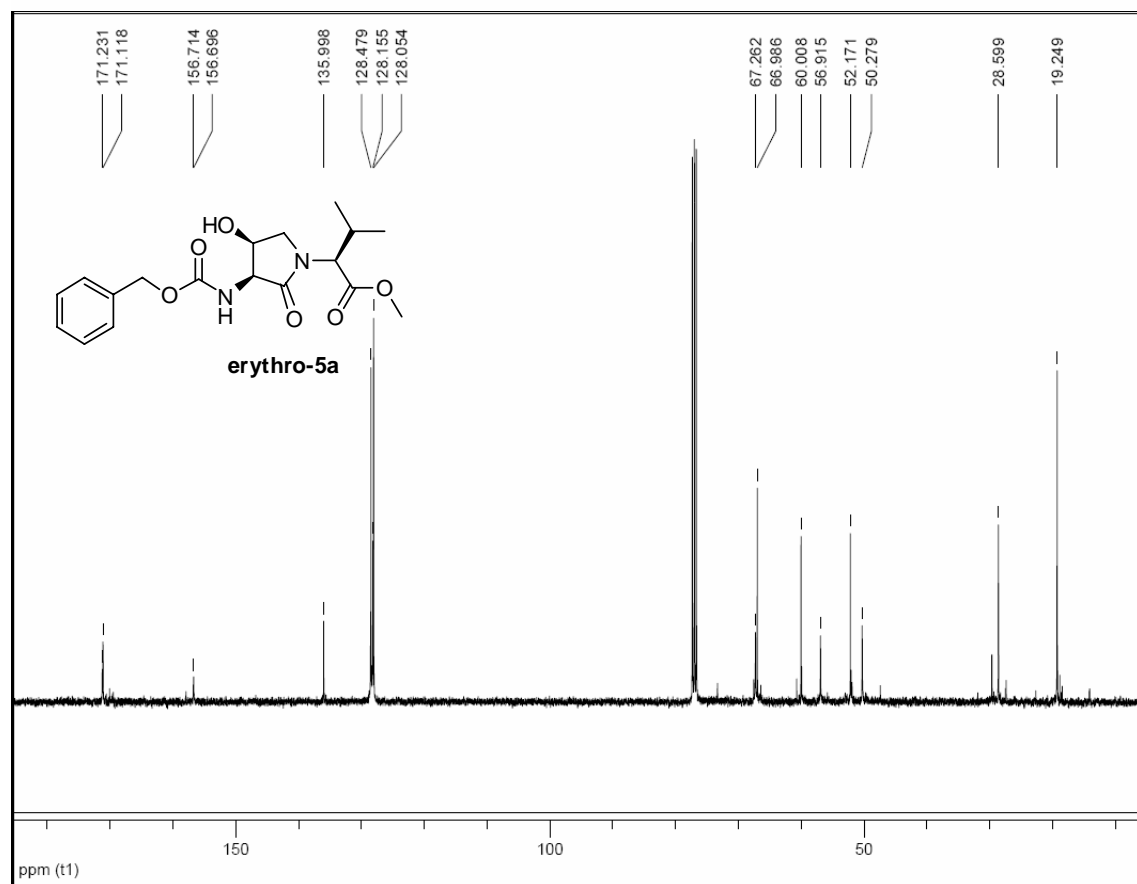
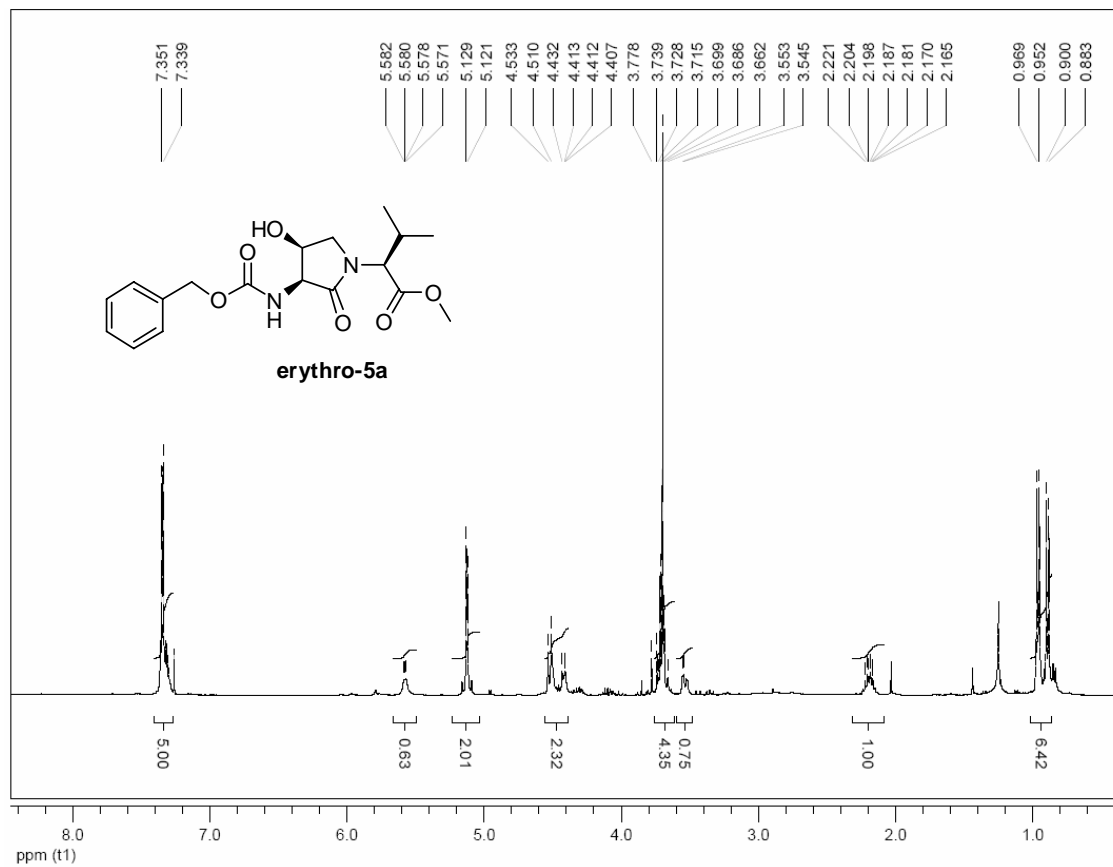
Fmoc-Ala-Gly-cThr-Phe-Phe-NH₂ 15. Pentapeptide mimetic **15** was synthesized on solid phase by using a Rinkamide-AM-PS resin (0.63 mmol/g, 65 mg, 40.9 μmol) following the general method with amino acids Fmoc-Phe-OH, **13**, Fmoc-Gly-OH and Fmoc-Ala-OH. Before coupling, dipeptide mimetic **13** was prior to coupling obtained from the corresponding *t*-Bu ester **12** (100 mg, 0.18 mmol) by acidic hydrolysis in TFA/DCM 1/1 (5 mL) for 30 minutes at room temperature and was activated directly after evaporation. The crude peptide was cleaved from the resin by treatment with TFA/water/TIS 95/2.5/2.5 for 30 min. To ensure complete cleavage the resin was incubated additionally with pure TFA for 1 h. The combined solution was evaporated and the crude product was further purified by RP-HPLC (3 mL/min, 35-65% B in 30 min, $t_{\text{R}} = 15.5$ min) to give peptide **15** (12 mg, 37%). R_f (DCM/MeOH 9/1) = 0.58, $^1\text{H-NMR}$ [400 MHz, DMSO-d_6]: 8.43 (d, $J = 7.4$ Hz, 1 H, NH^{cThr}), 8.13 (t, $J = 5.6$ Hz, 1 H, NH^{Gly}), 8.04 (d, $J = 8.4$ Hz, 1 H, NH^{Phe}), 7.88 (d, $J = 7.5$ Hz, 2 H, arenes), 7.71 (dd, $J = 8.5$ Hz, 2 H, arenes), 7.52 (d, $J = 7.4$ Hz, 1 H, NH^{Ala}), 7.41 (dd, $J = 7.4$ Hz, 2 H, arenes), 7.35 (br. s., 1 H, $\text{NH}_2^{\text{amide}}$), 7.32 (dd, $J = 7.4$ Hz, 2 H, arenes), 7.16-7.27 (m, 10 H, arenes), 7.07 (br. s., 1 H, $\text{NH}_2^{\text{amide}}$), 4.98 (ddd, $J = 6.3$ Hz, 1 H, $\text{H}\beta^{\text{cThr}}$), 4.91 (dd, $J = 11.2, 4.4$ Hz, 1 H, $\text{H}\alpha^{\text{Phe}}$ (A)), 4.47 (ddd, $J = 8.5, 5.1, 4.6$ Hz, 1 H, $\text{H}\alpha^{\text{Phe}}$ (B)), 4.17-4.28 (m, 3 H, H-9^{Fmoc} a. $\text{CH}_2^{\text{Fmoc}}$), 4.06 (dq, $J = 7.1$ Hz, 1 H, $\text{H}\alpha^{\text{Ala}}$), 3.98 (dd, $J = 7.5, 6.7$ Hz, $\text{H}\alpha^{\text{cThr}}$), 3.74 (d, $J =$

5.3 Hz, 2 H, H α ^{Gly}), 3.52 (m, 1 H, H γ ^{cThr}), 3.18 (dd, $J = 14.5, 4.5$ Hz, 1 H, H β ^{Phe(A)}), 3.05 (dd, $J = 13.9, 4.6$ Hz, 1 H, H β ^{Phe(B)}), 3.00 (dd, $J = 10.4, 5.3$ Hz, 1 H, H γ ^{cThr}), 2.86 (dd, $J = 13.4, 10.5$ Hz, 1 H, H β ^{Phe(B)}), 2.78 (dd, $J = 14.8, 10.8$ Hz, 1 H, H β ^{Phe(A)}), 1.98 (s, 3 H, CH₃^{Ac}), 1.21 (d, $J = 7.1$ Hz, 3 H, CH₃^{Ala}), ¹³C-NMR [100 MHz, DMSO-d₆]: 181.9, 172.6, 169.9, 169.4, 168.7, 168.5, 155.6, 143.8, 143.7, 140.6, 138.0, 137.2, 129.0, 128.6, 128.1, 128.0, 127.5, 127.0, 126.3, 126.2, 125.2, 120.0, 71.6 (C β ^{cThr}), 65.5 (CH₂^{Fmoc}), 54.9 (C α ^{cThr}), 54.7 (C α ^{Phe(A)}), 54.3 (C α ^{Phe(B)}), 49.9 (C α ^{Ala}), 46.5 (CH^{Fmoc}), 46.3 (C γ ^{cThr}), 41.6 (C α ^{Gly}), 37.1 (C β ^{Phe(B)}), 33.8 (C β ^{Phe(A)}), 20.5 (CH₃^{Ac}), 18.0 (C β ^{Ala}), HR-MS (ESI-TOF) calc. for C₄₄H₄₇N₆O₉ [M+H]⁺: 803.3414, found: 803.3399.

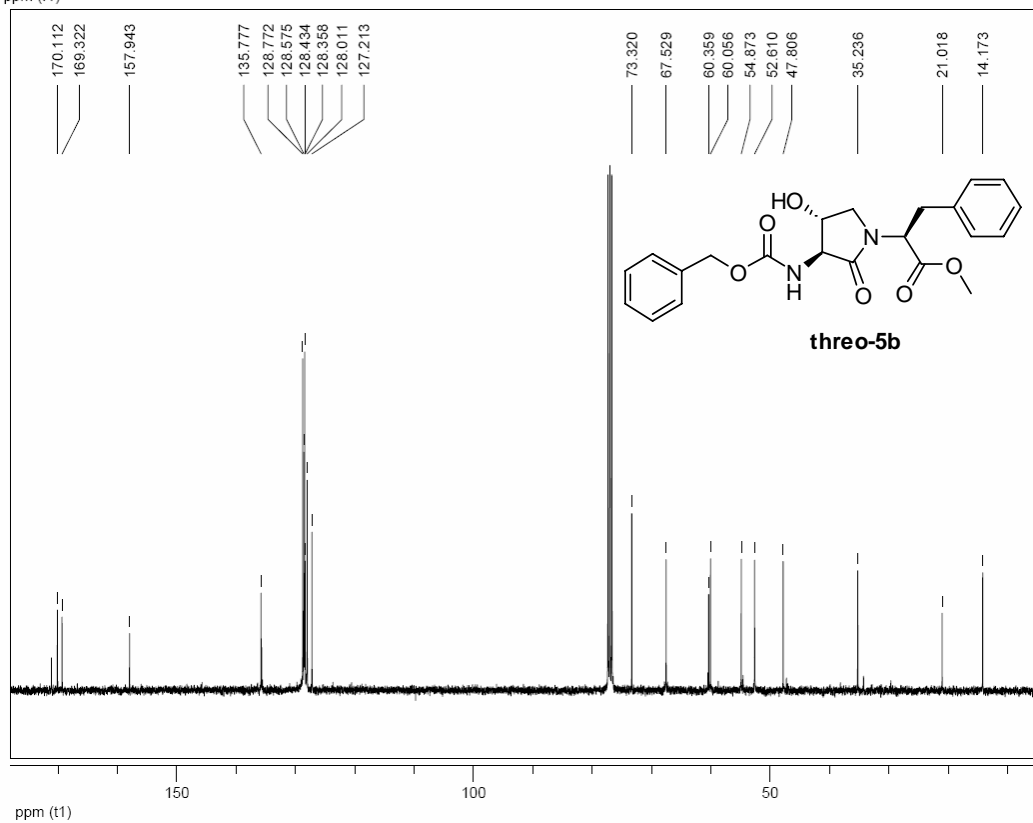
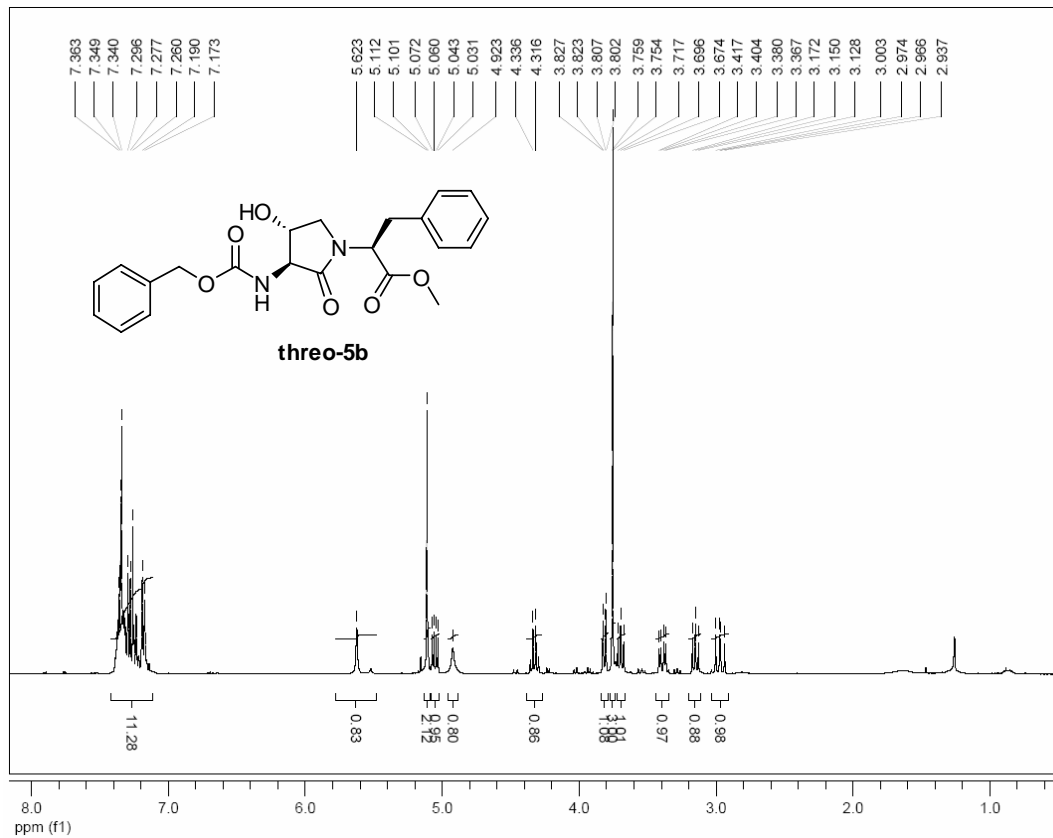
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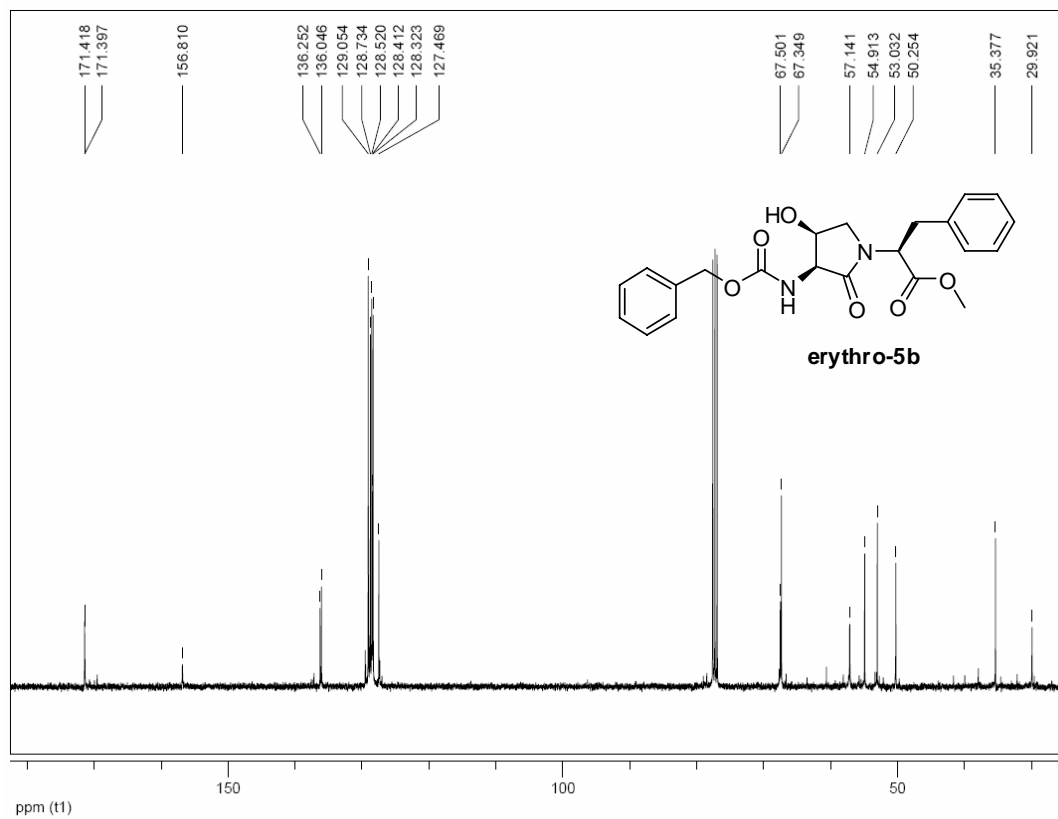
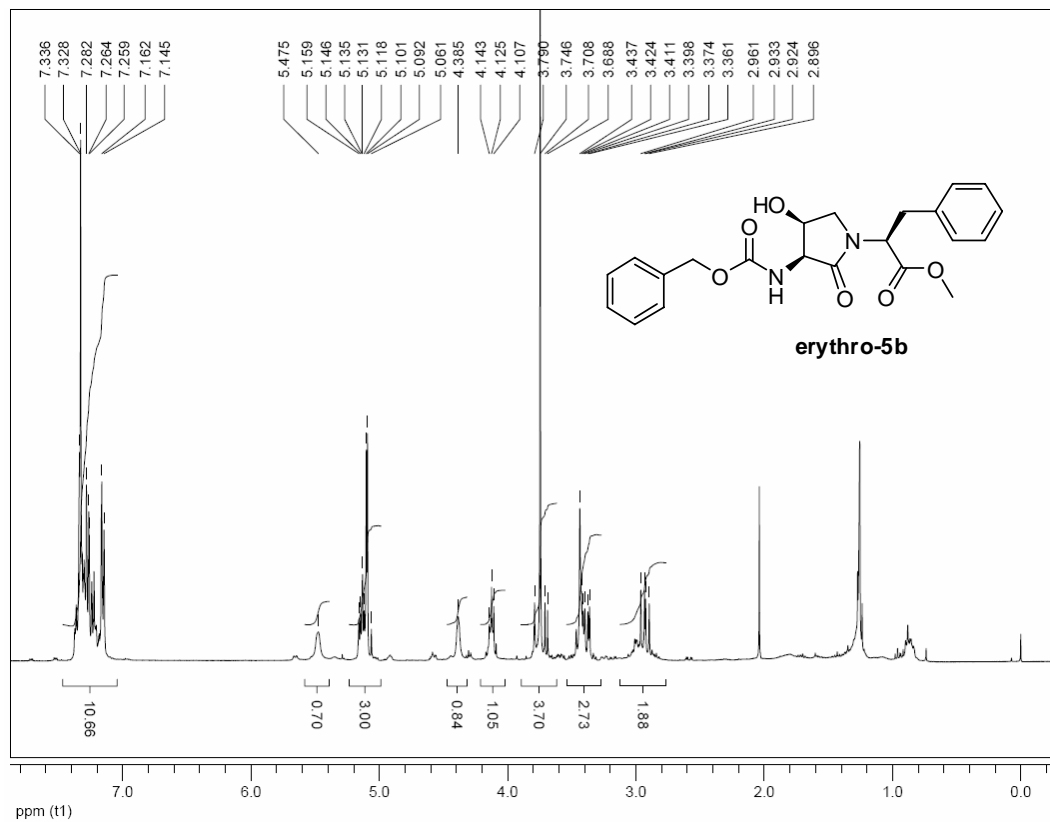
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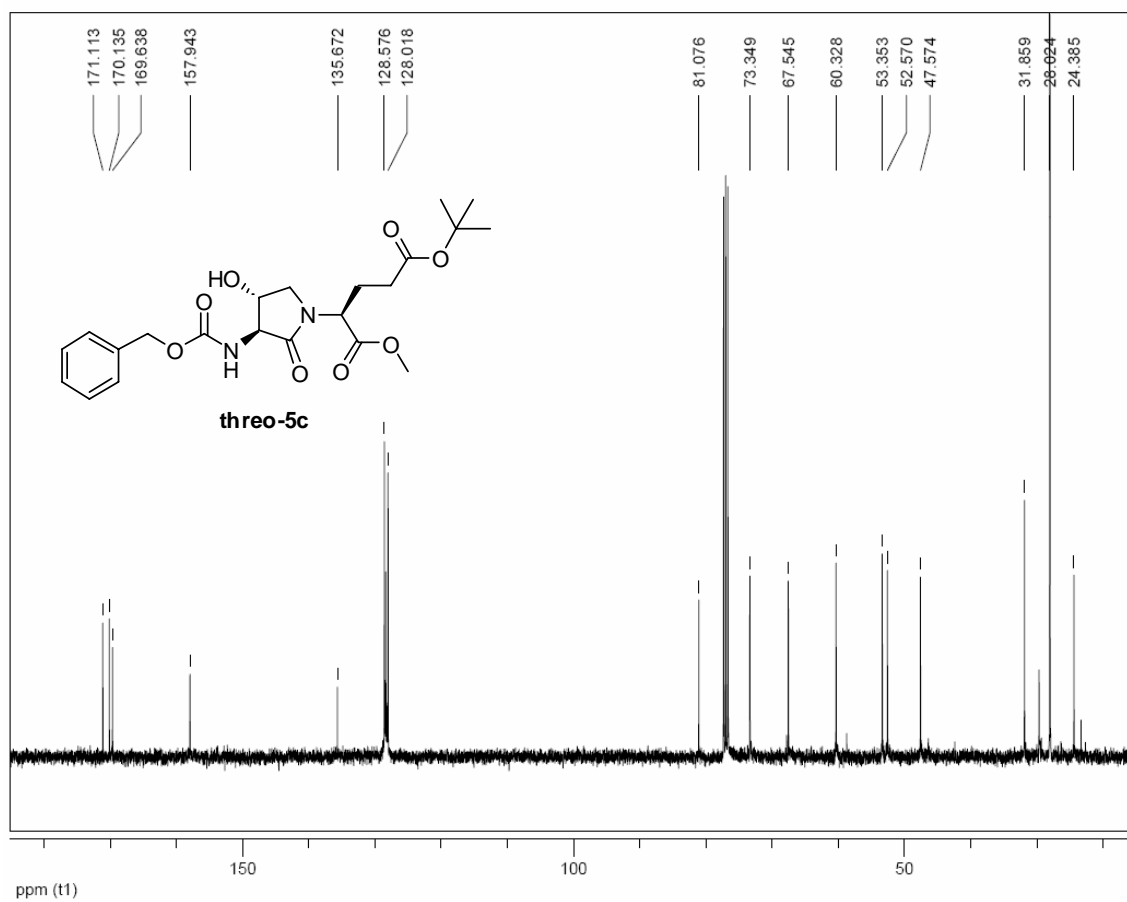
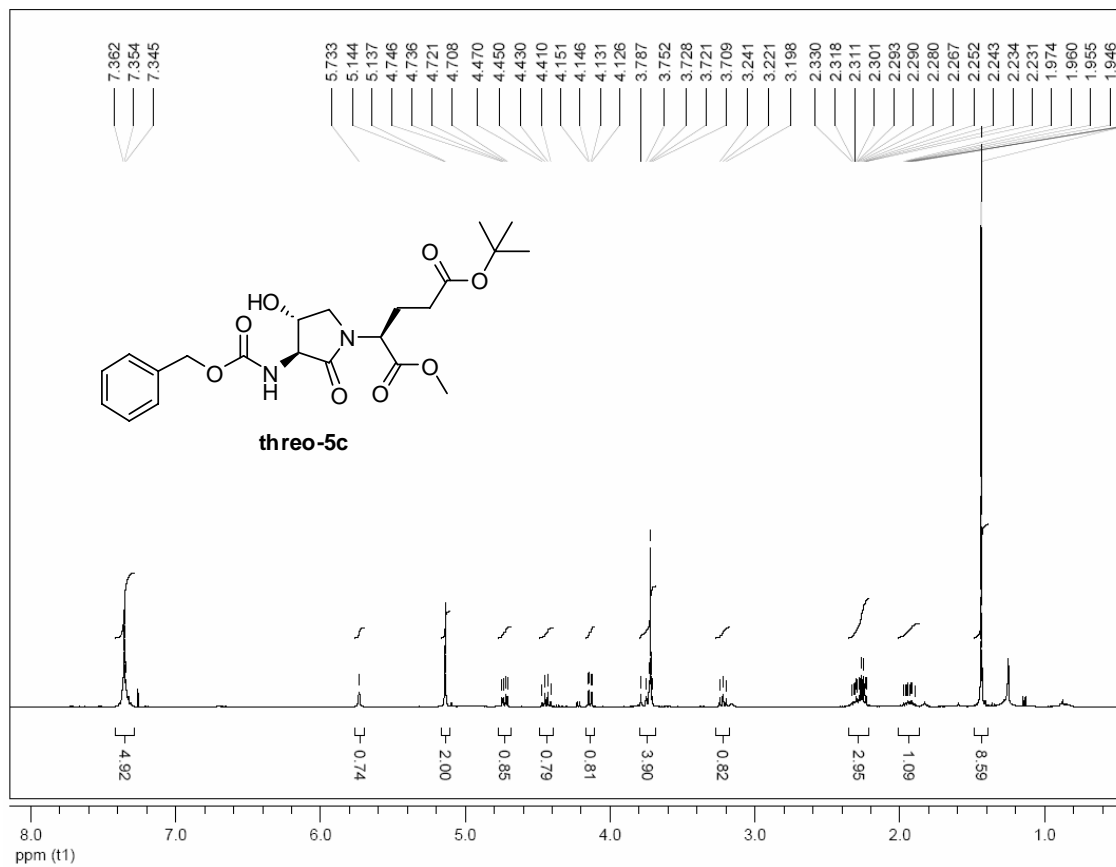
S3) *threo-5b*



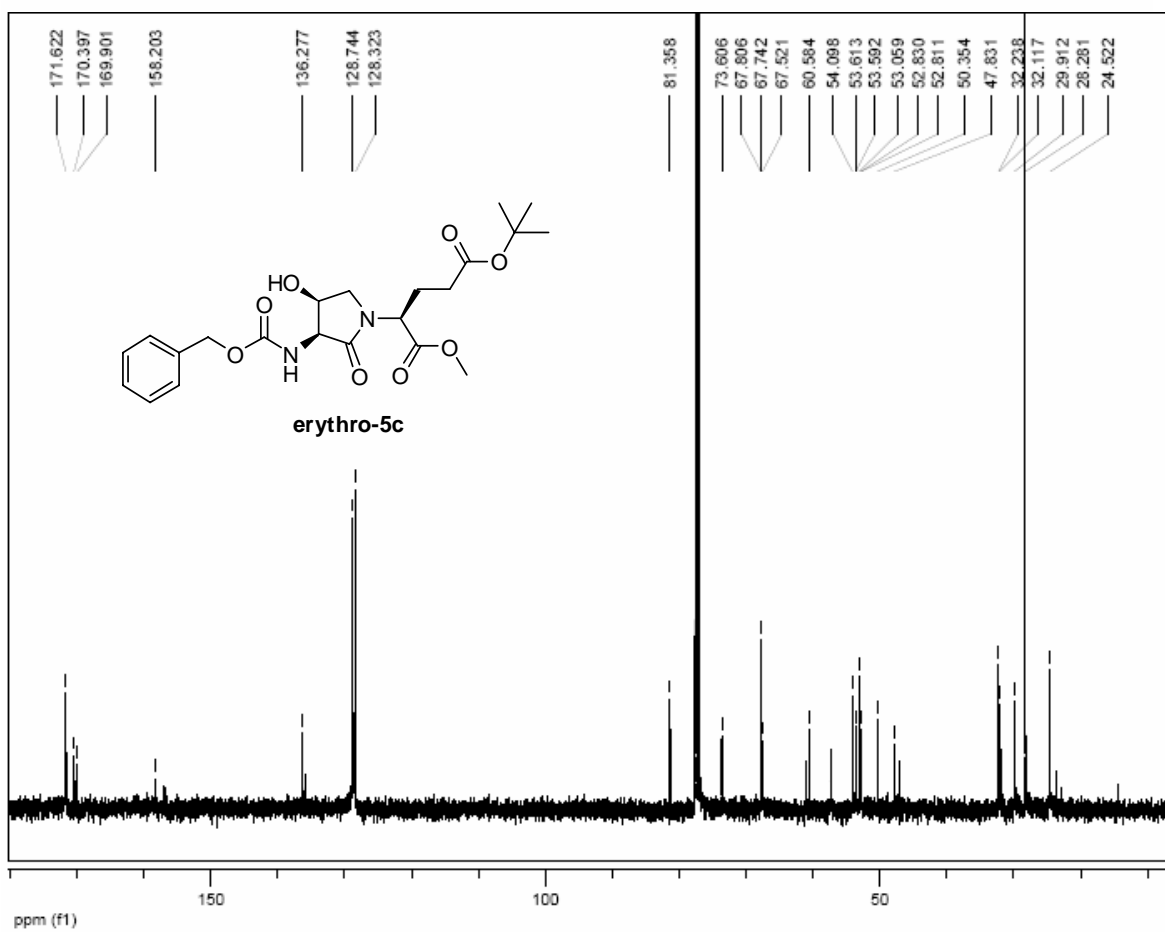
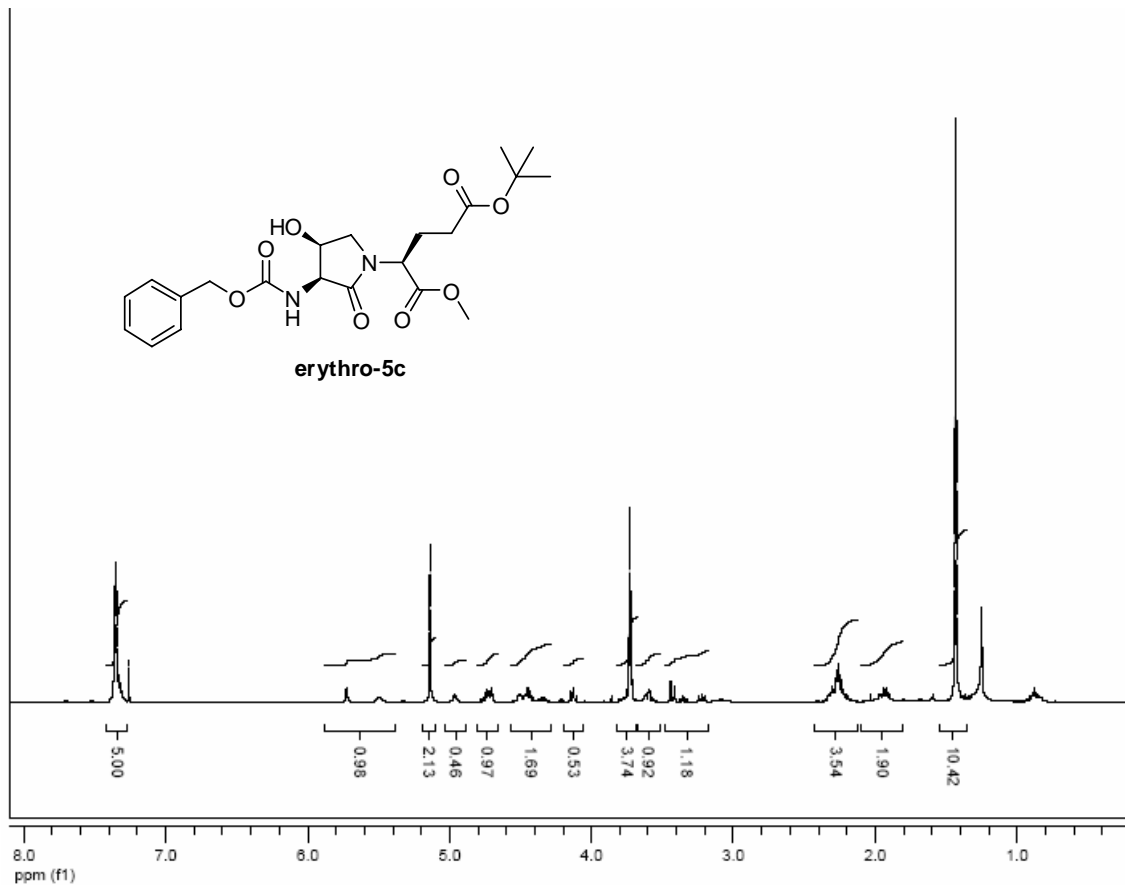
S4) erythro-5b



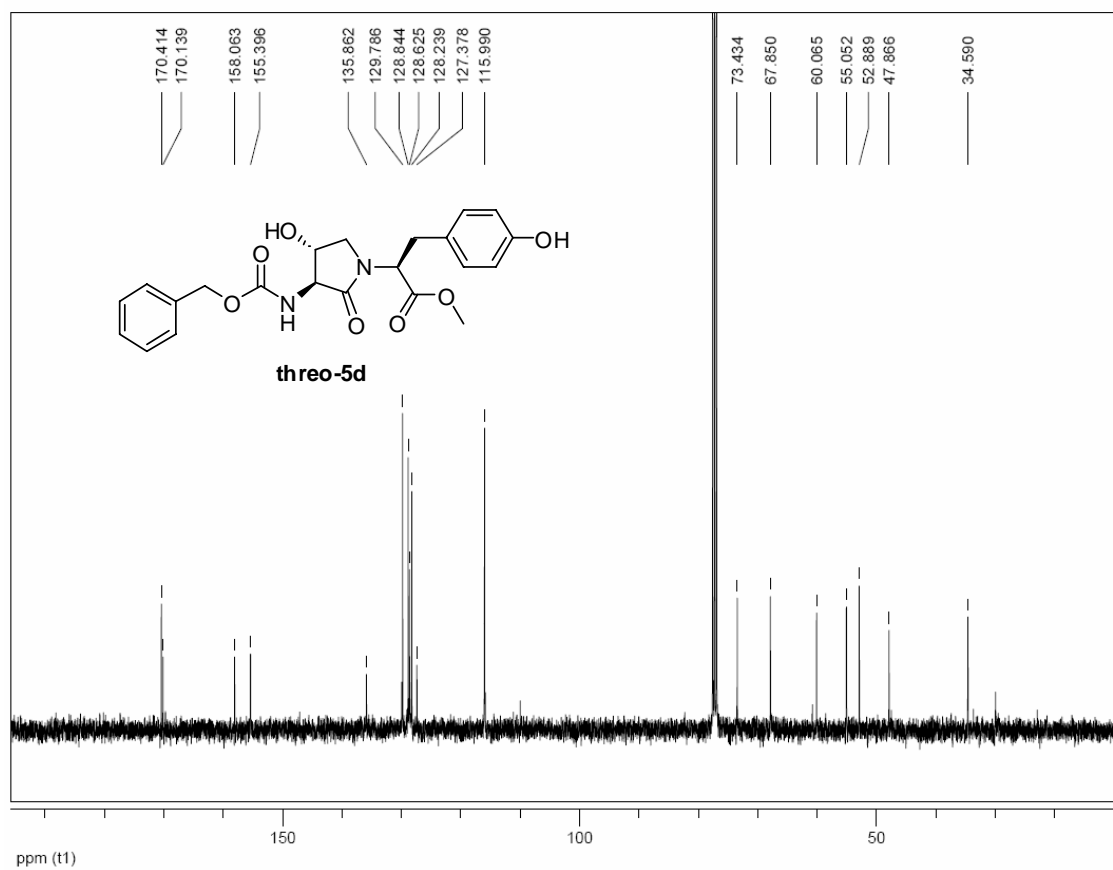
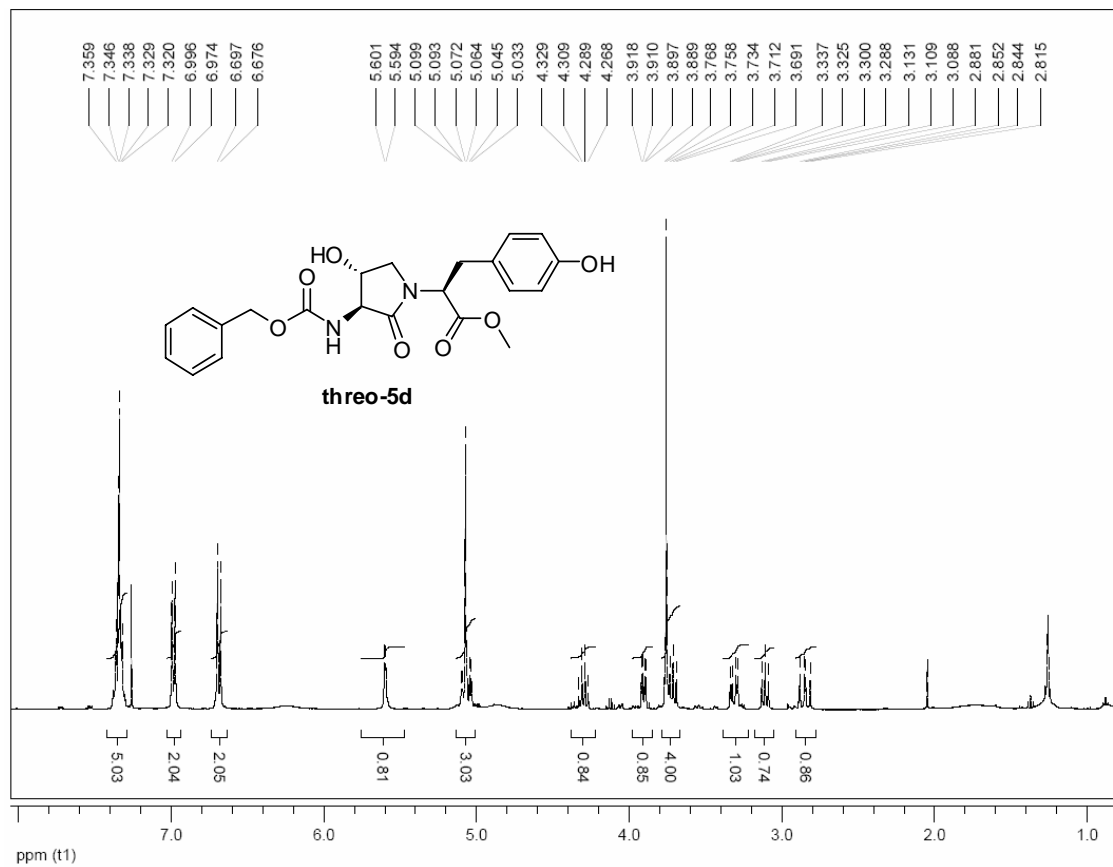
S5) *threo*-5c



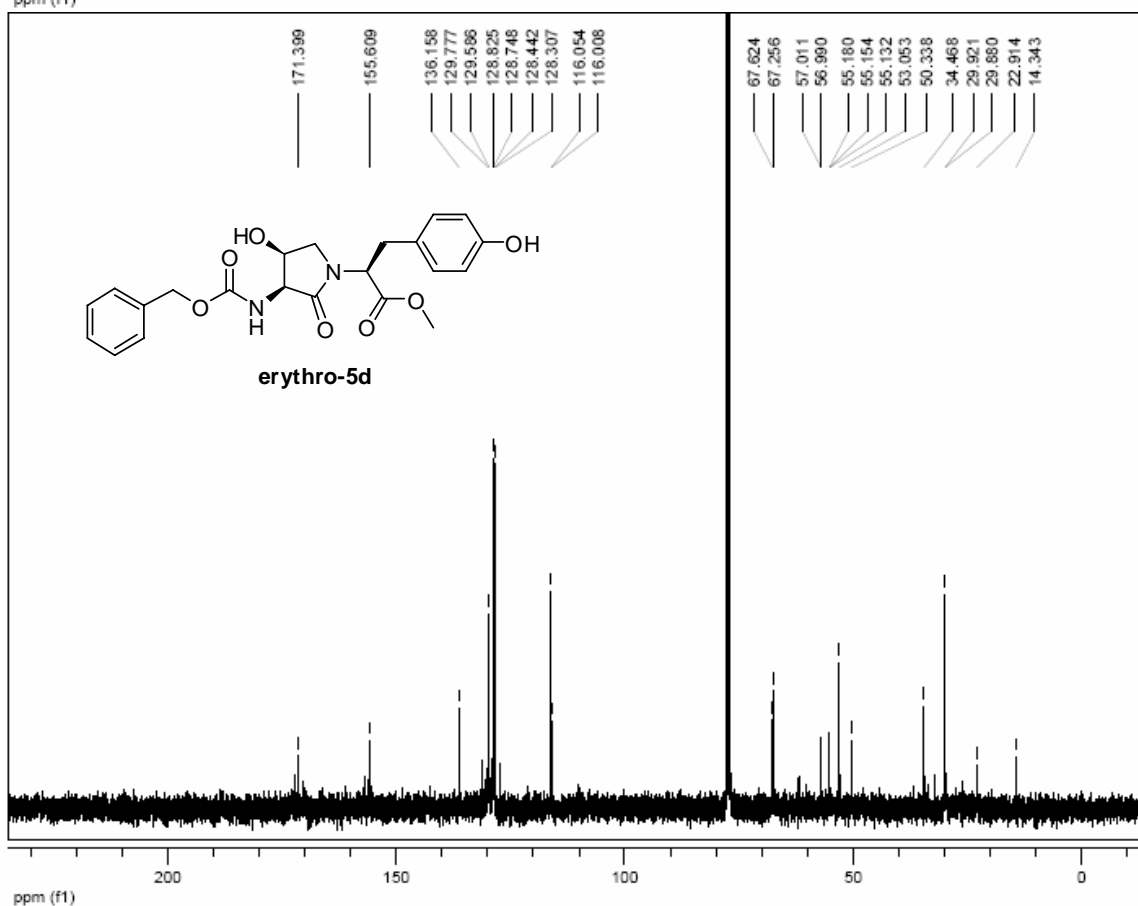
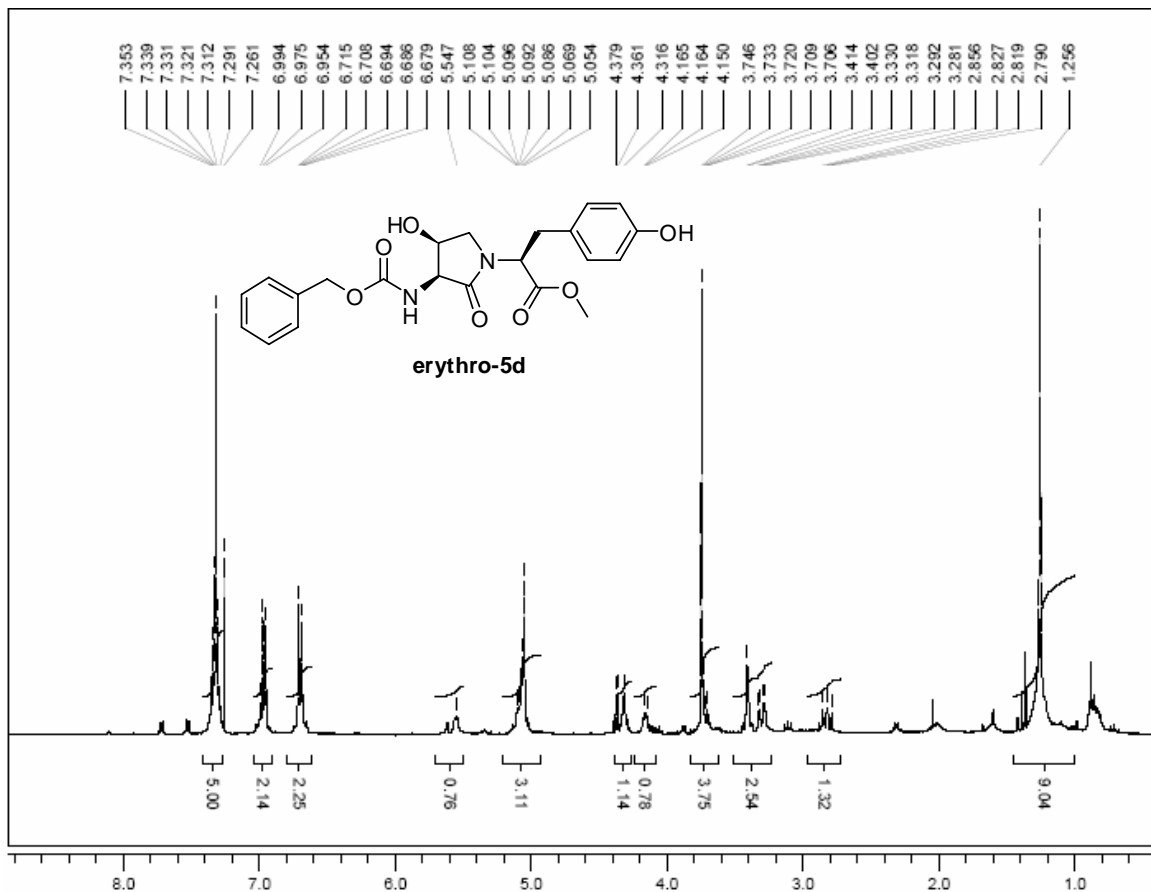
S6) *erythro*-5c (contains *threo*-5c)



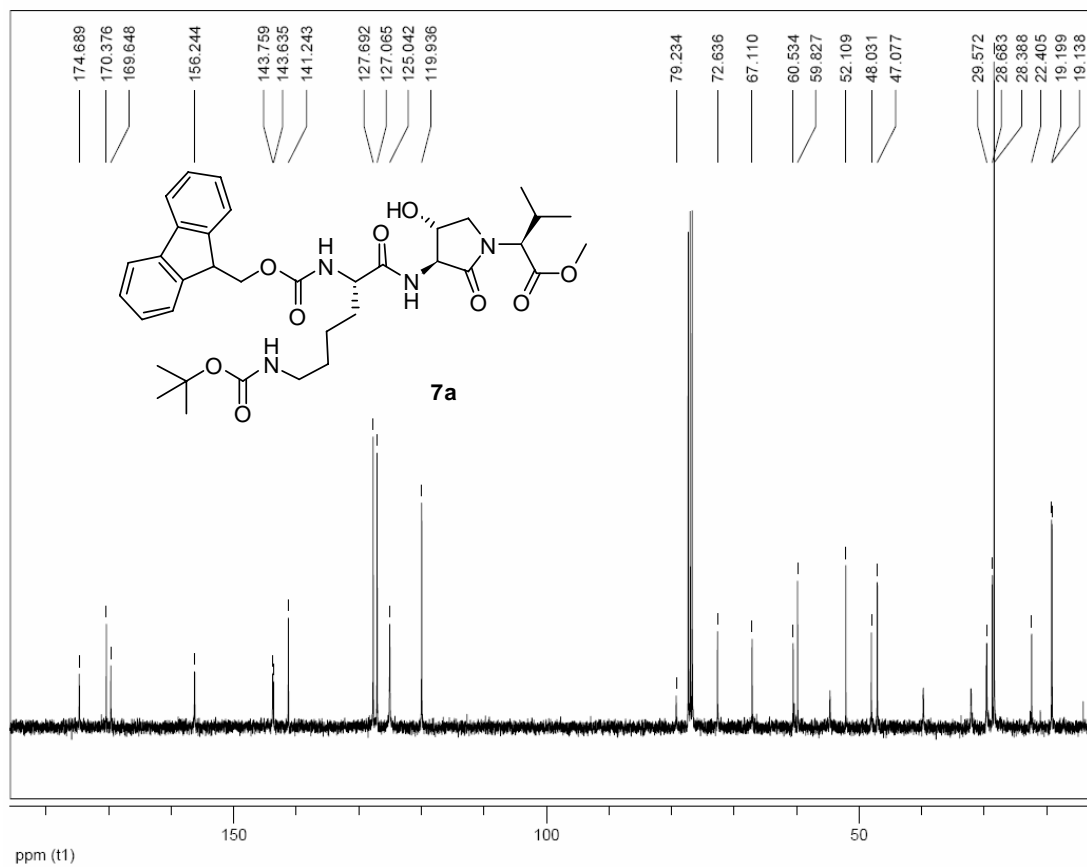
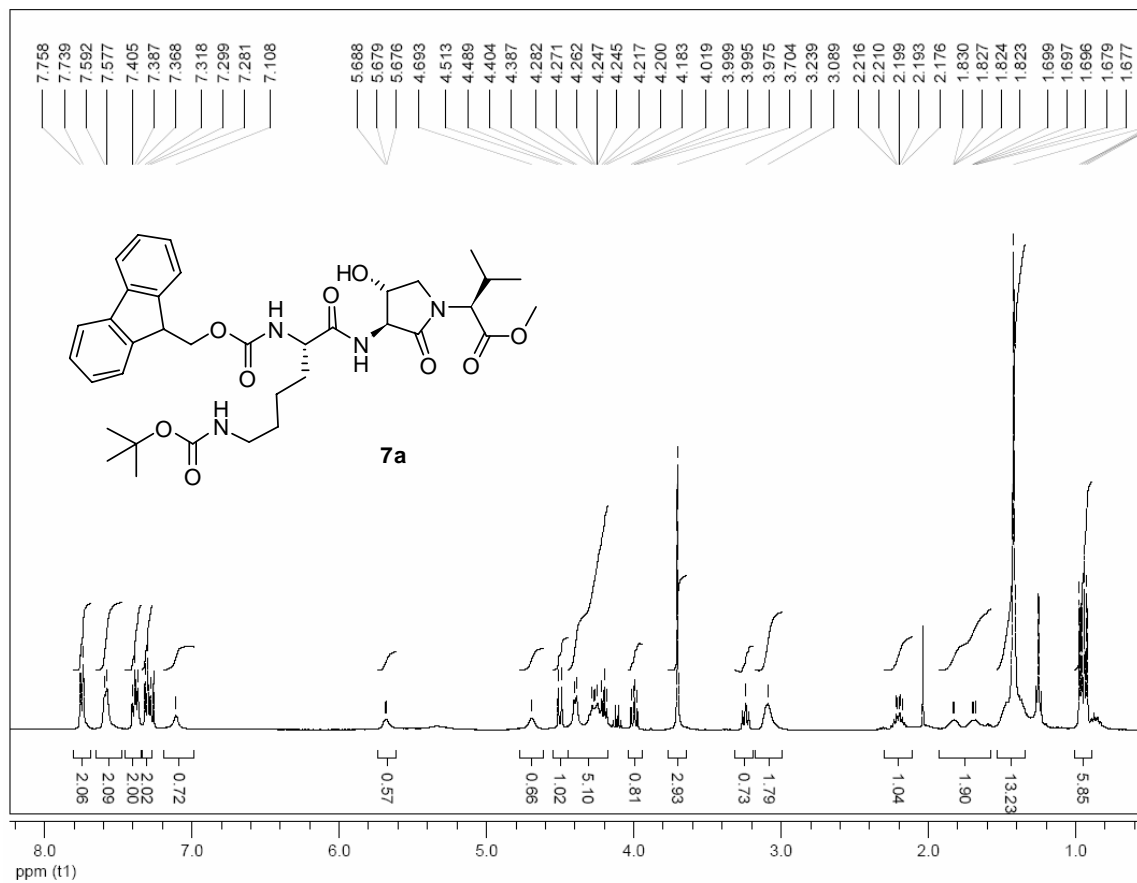
S7) *threo*-5d



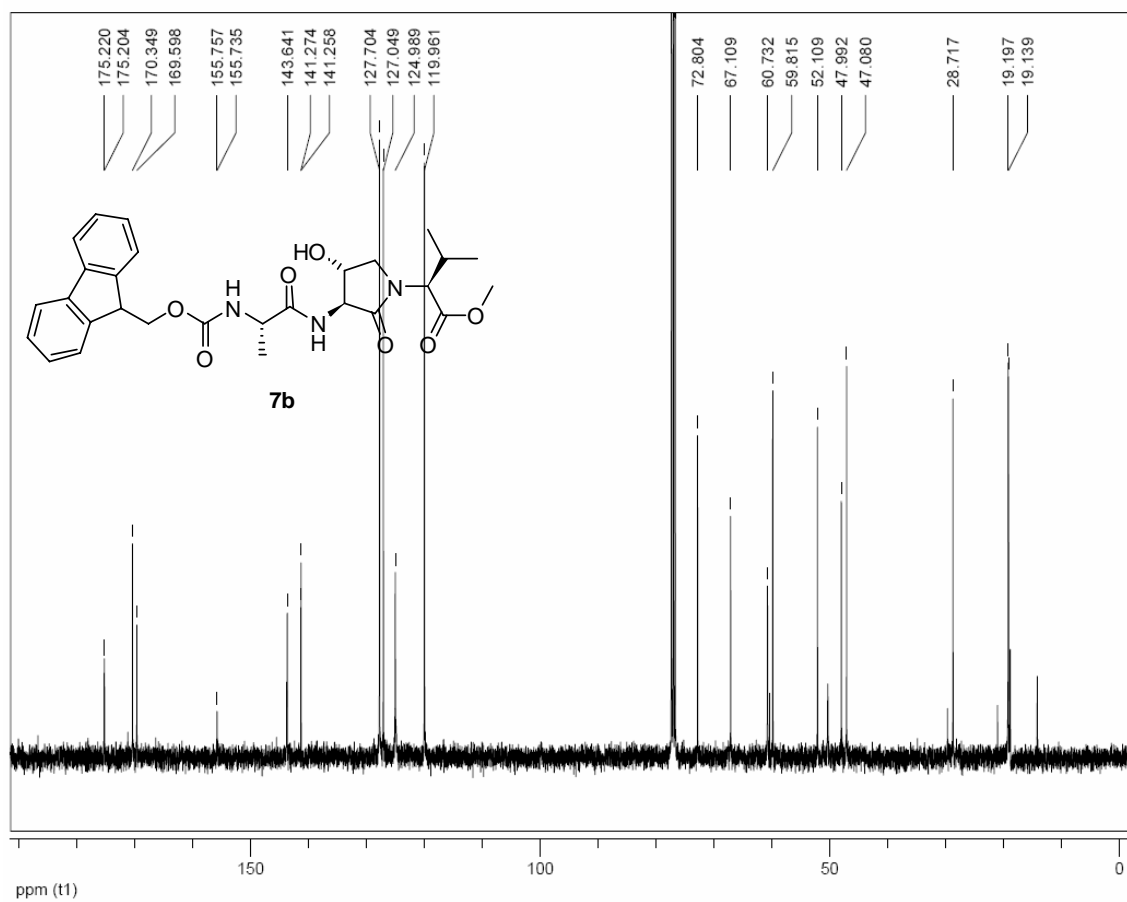
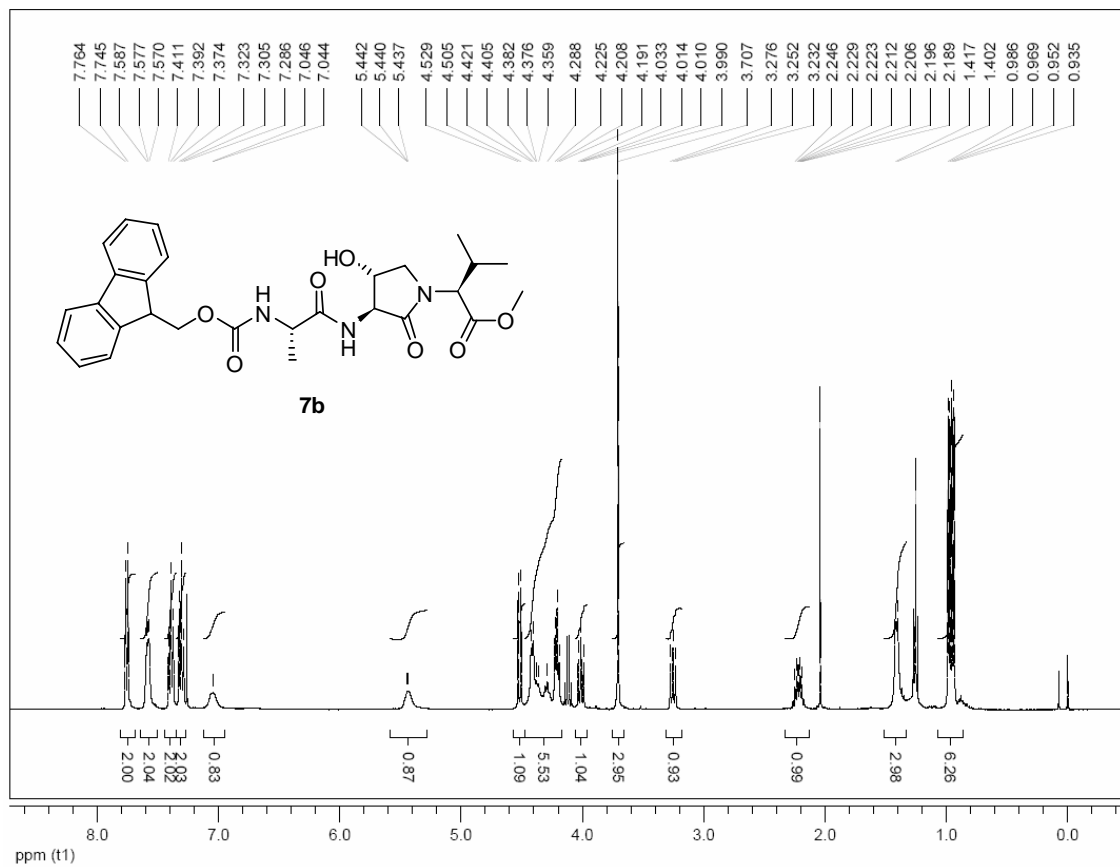
S8) *erythro*-5d (contains *threo*-5d)



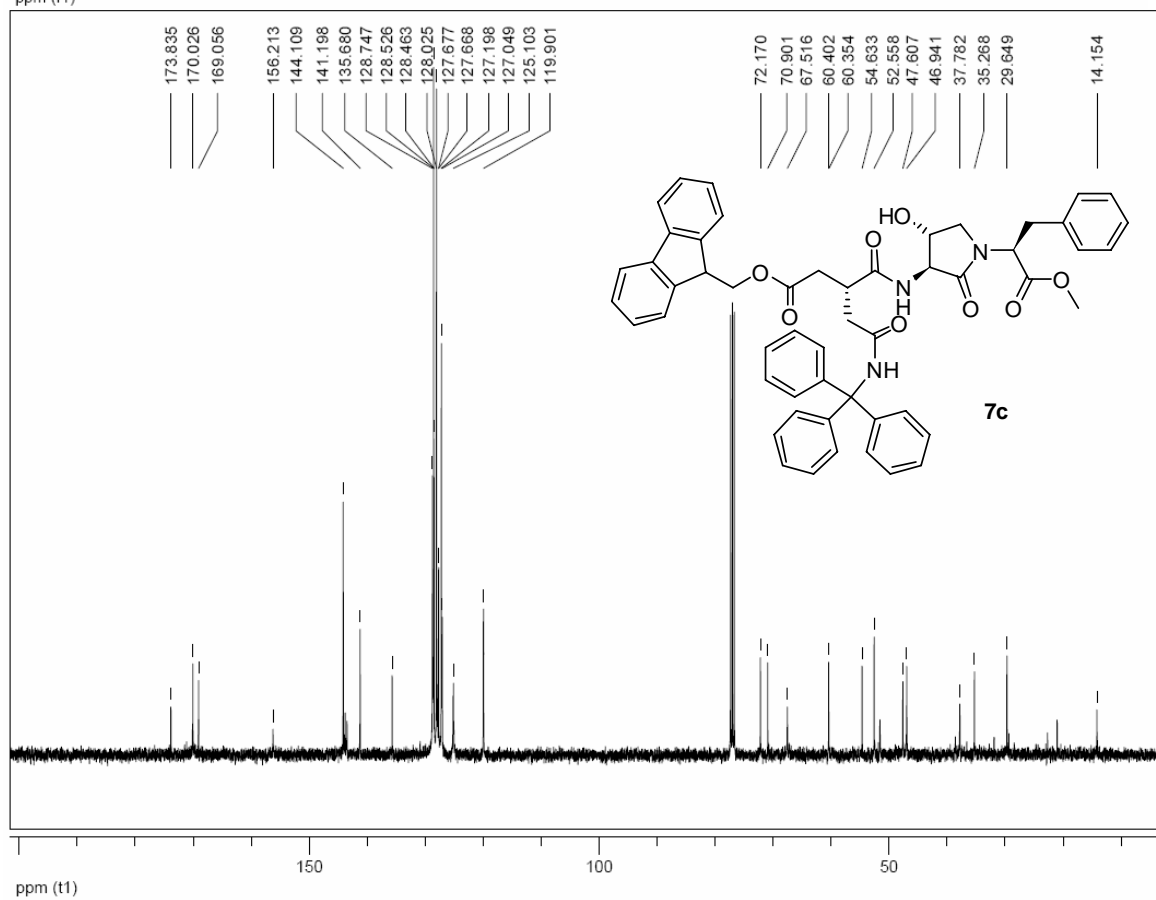
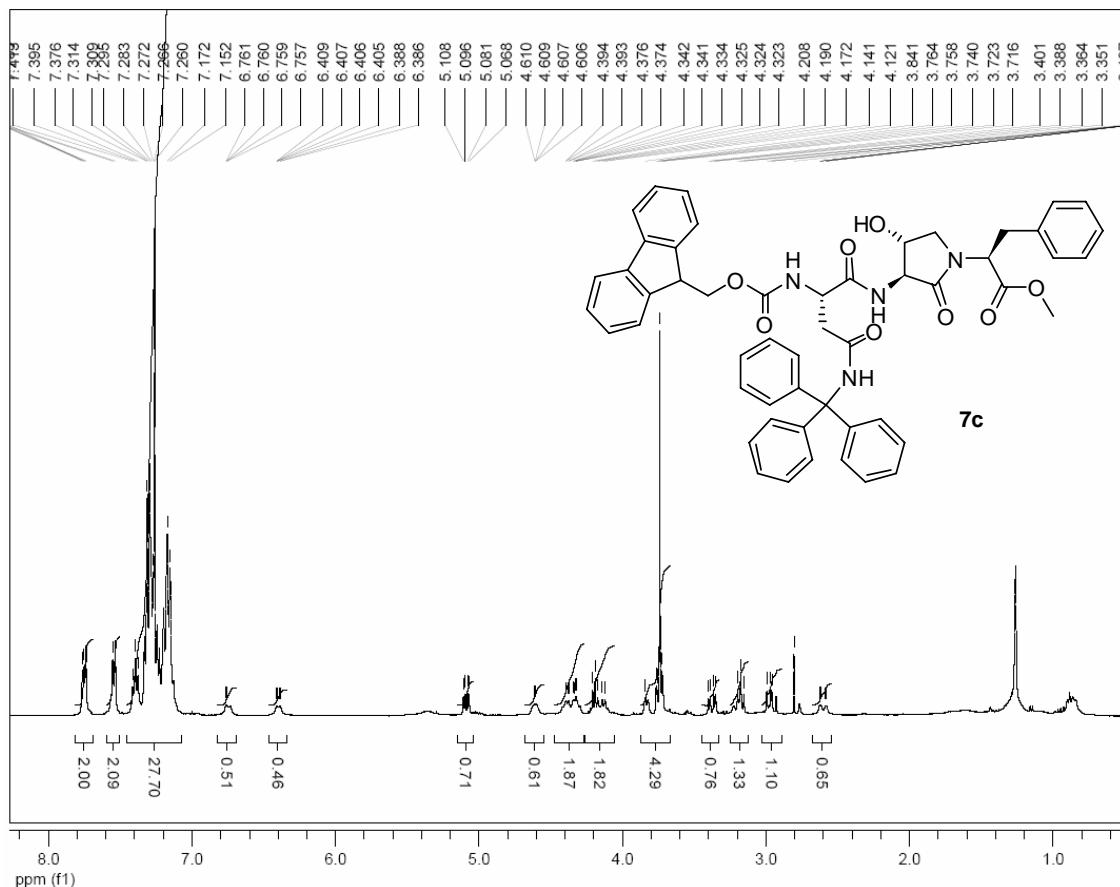
S9) 7a



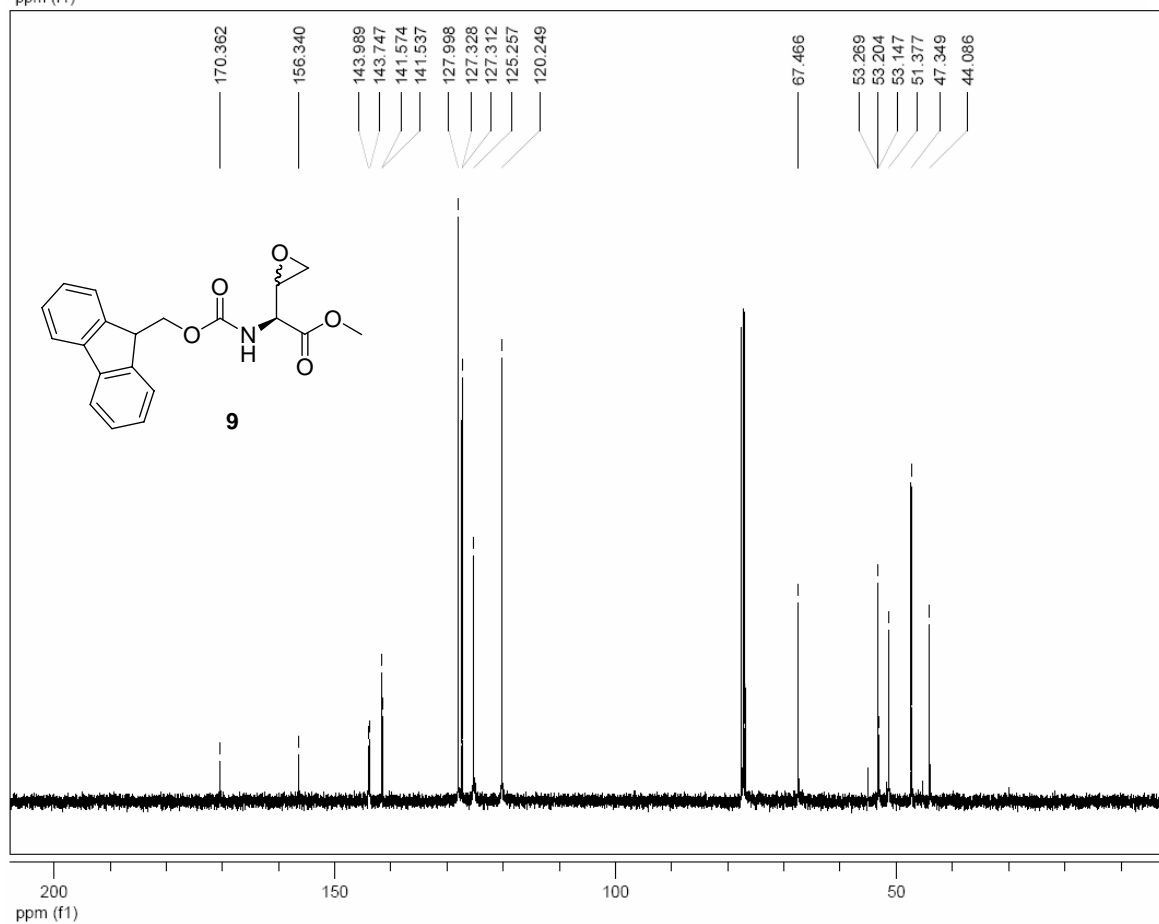
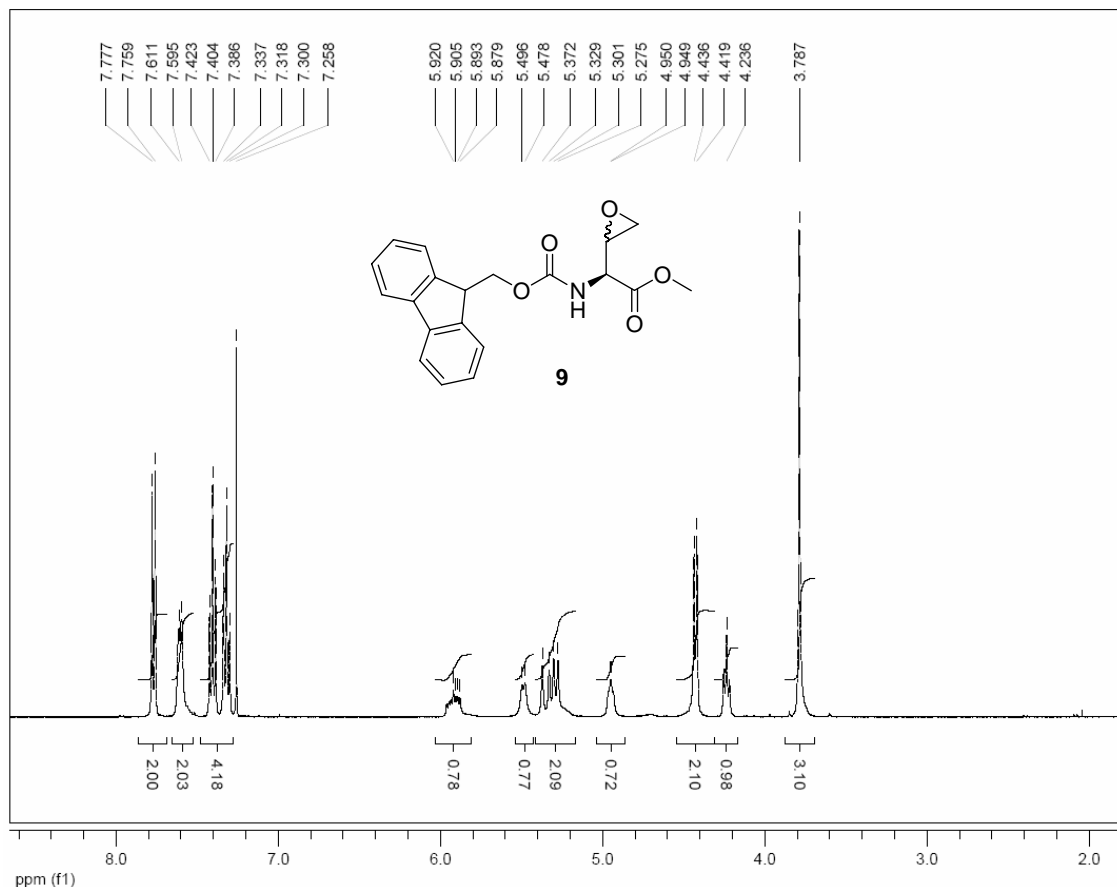
S10) 7b



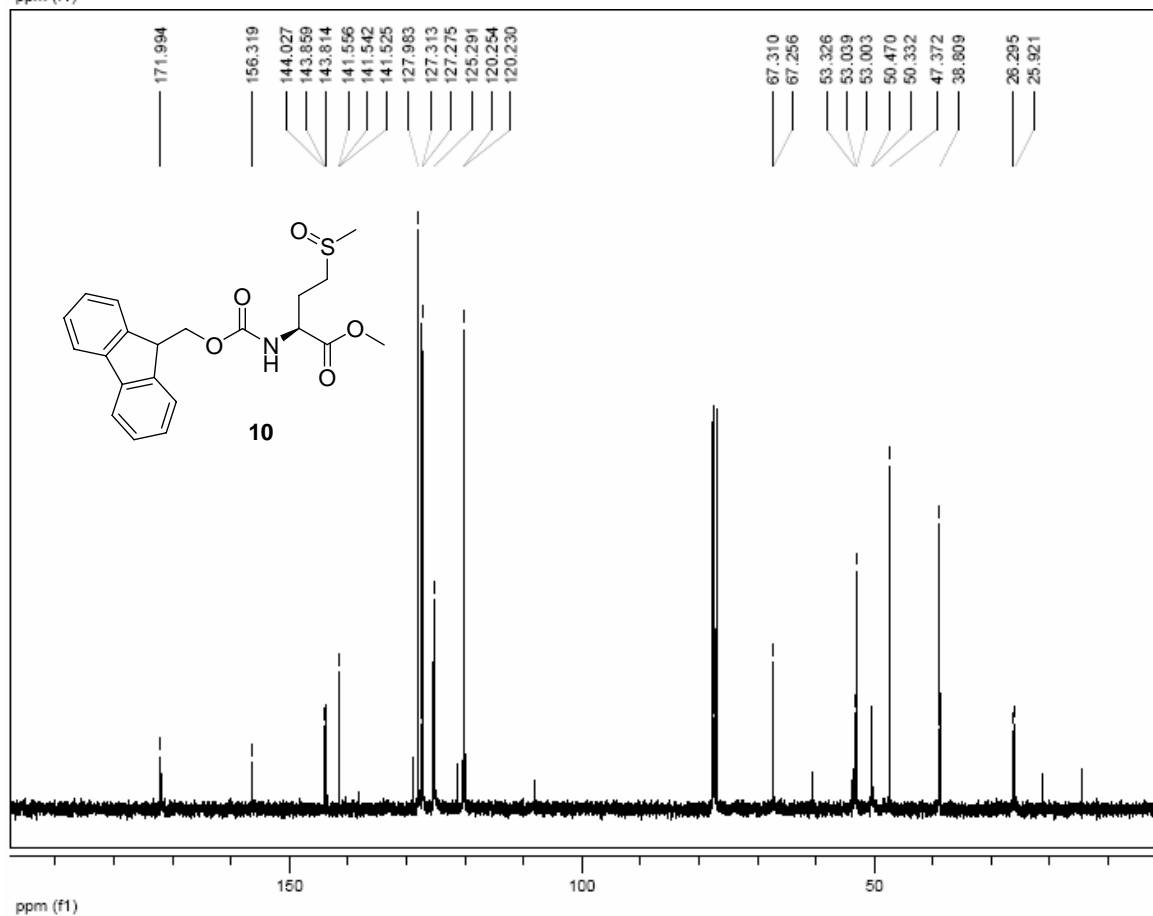
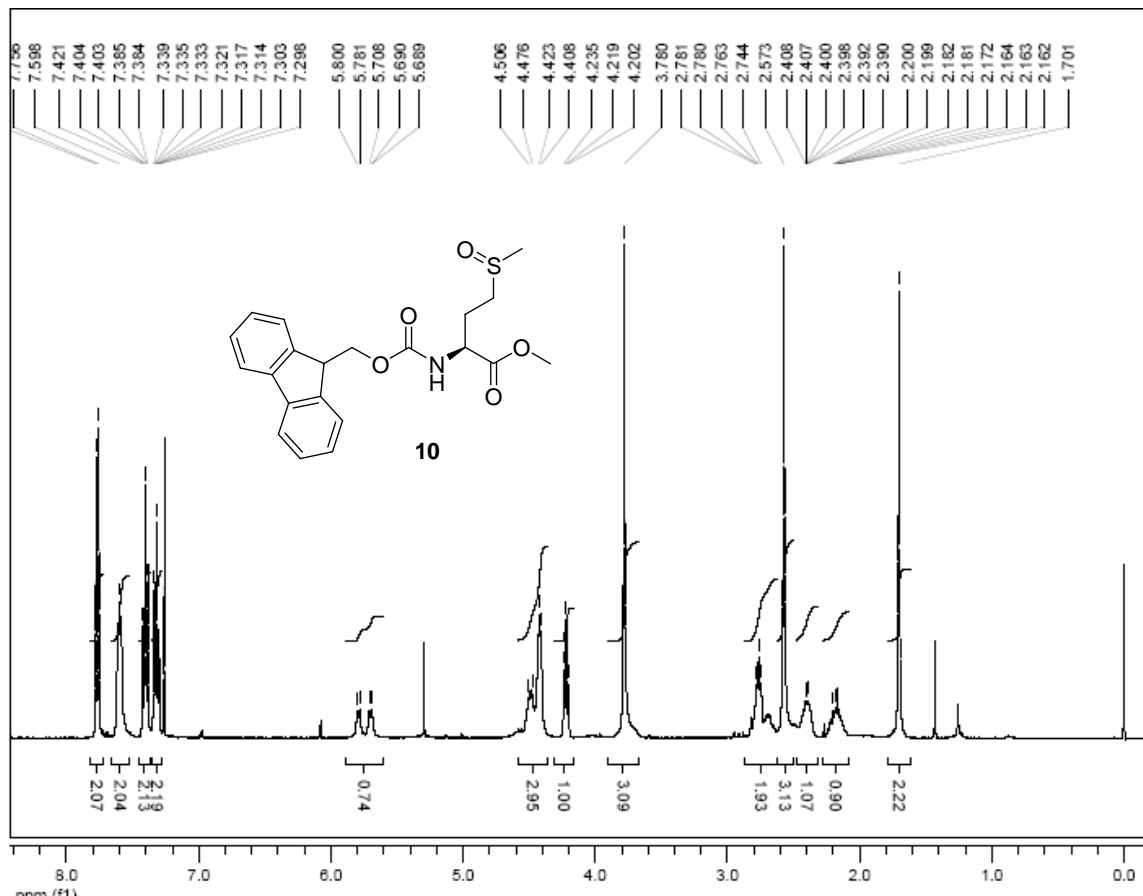
S11) 7c



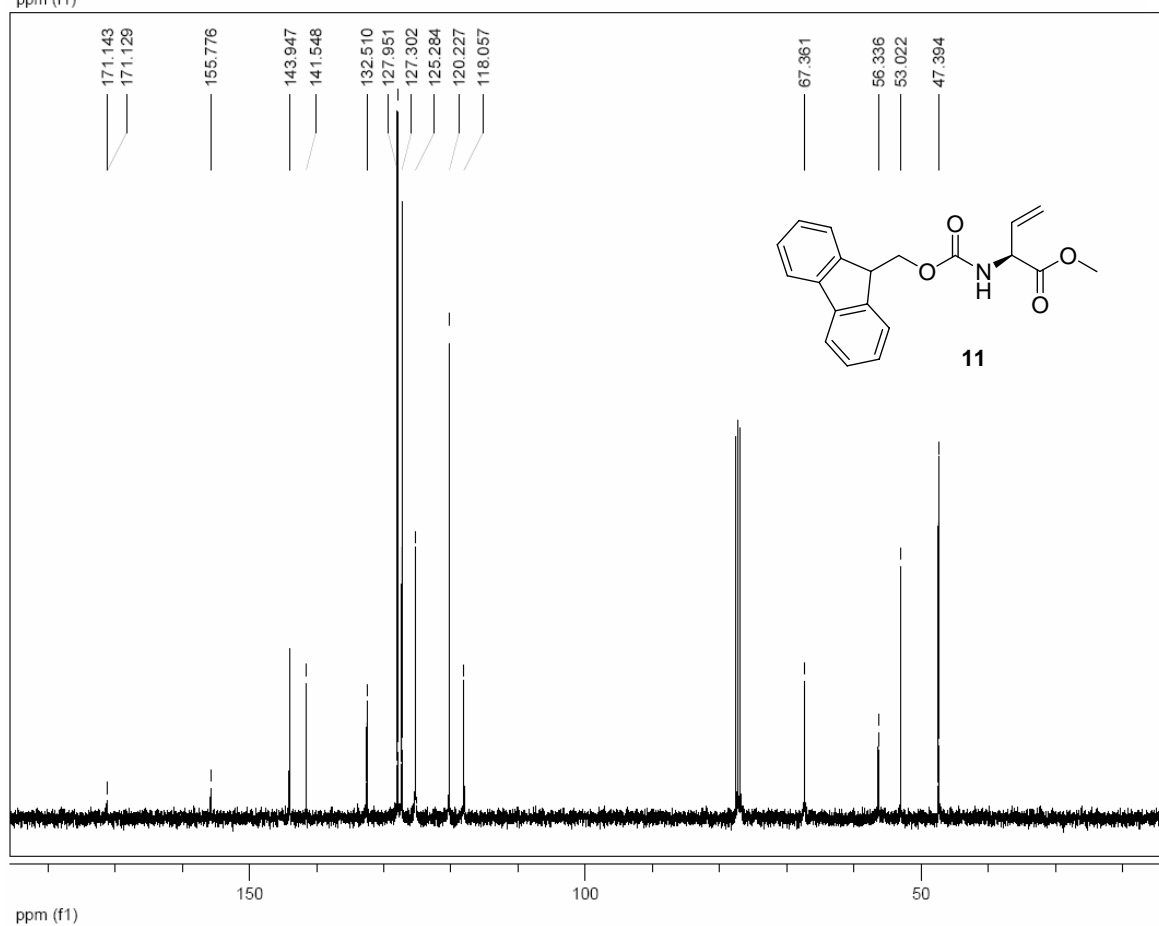
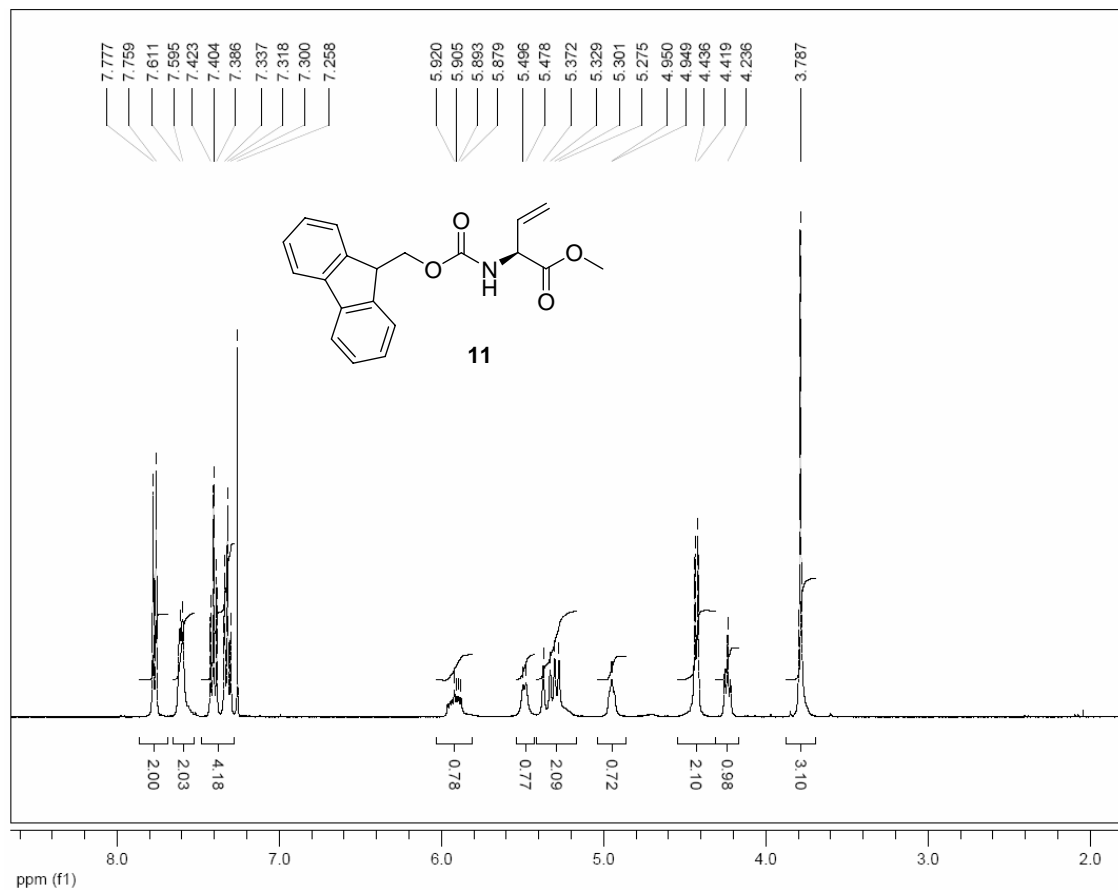
S12) 9



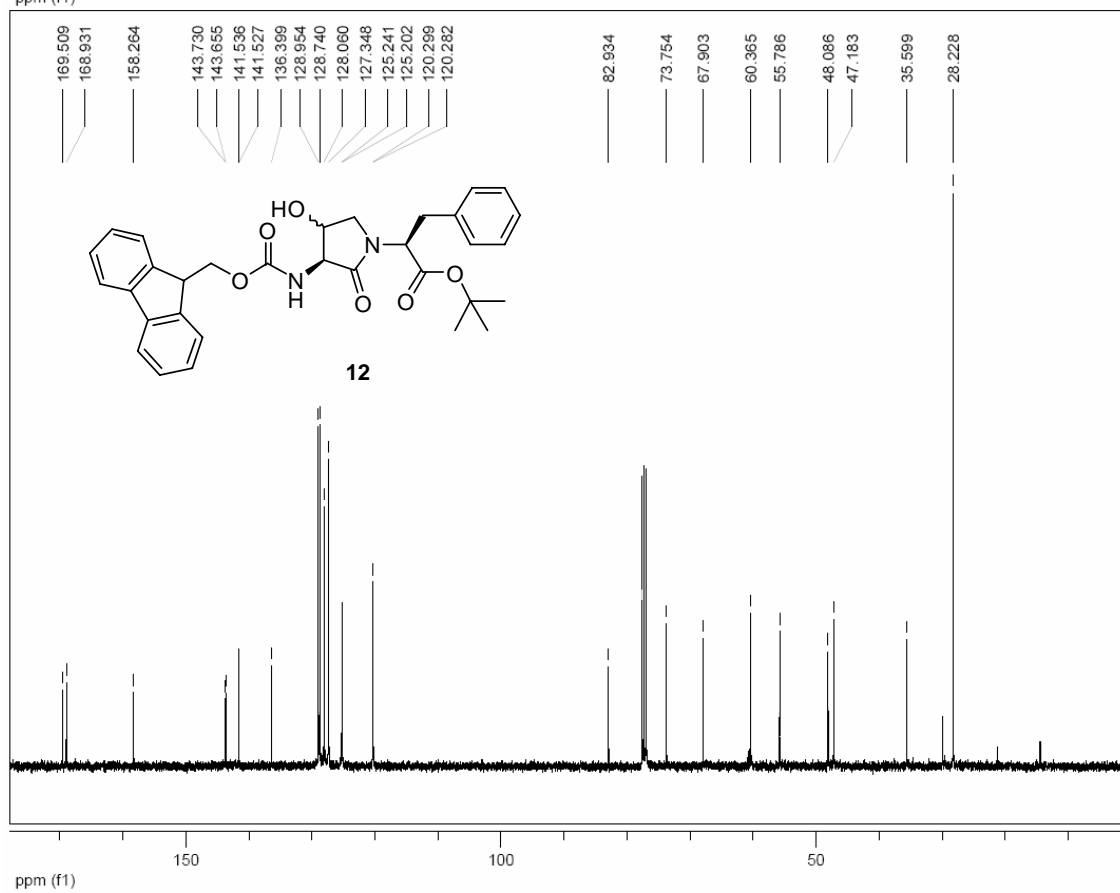
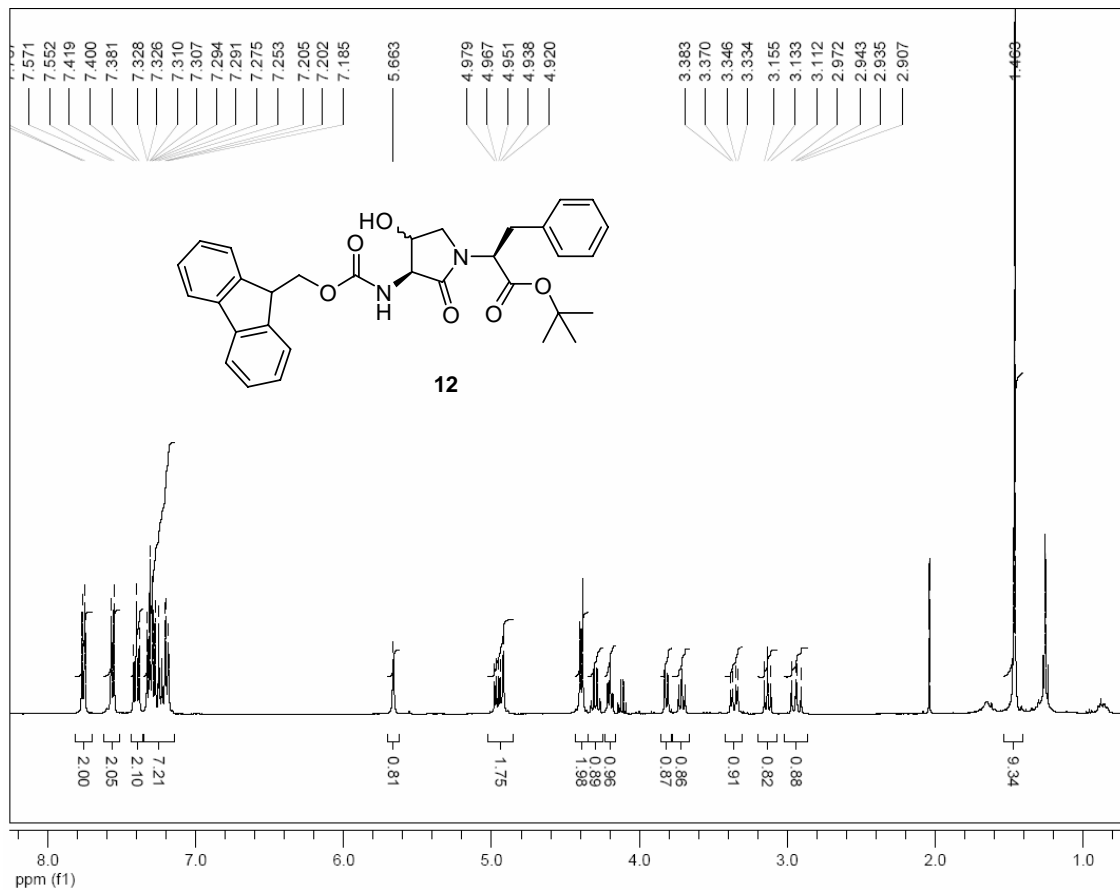
S13) 10



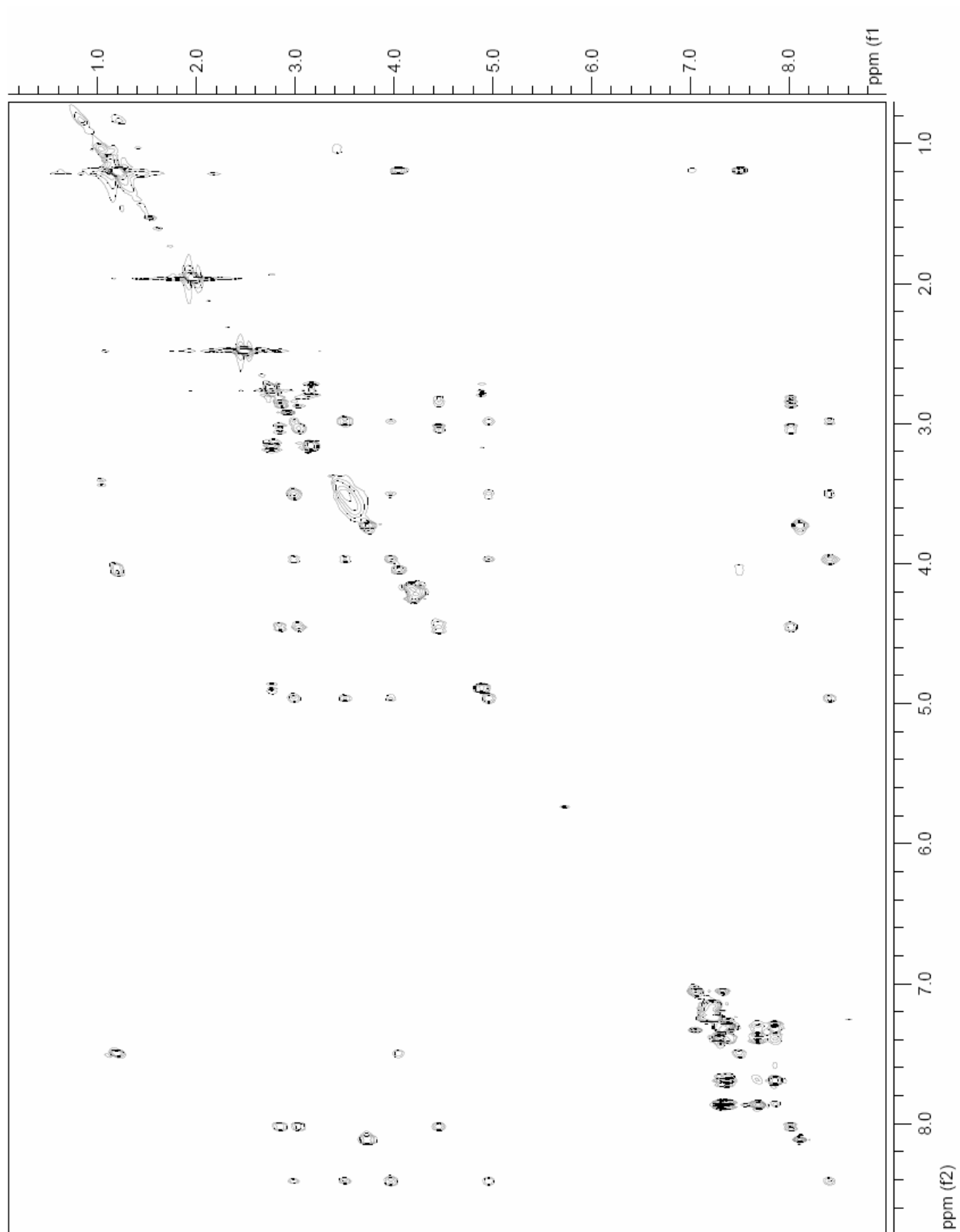
S14) 11



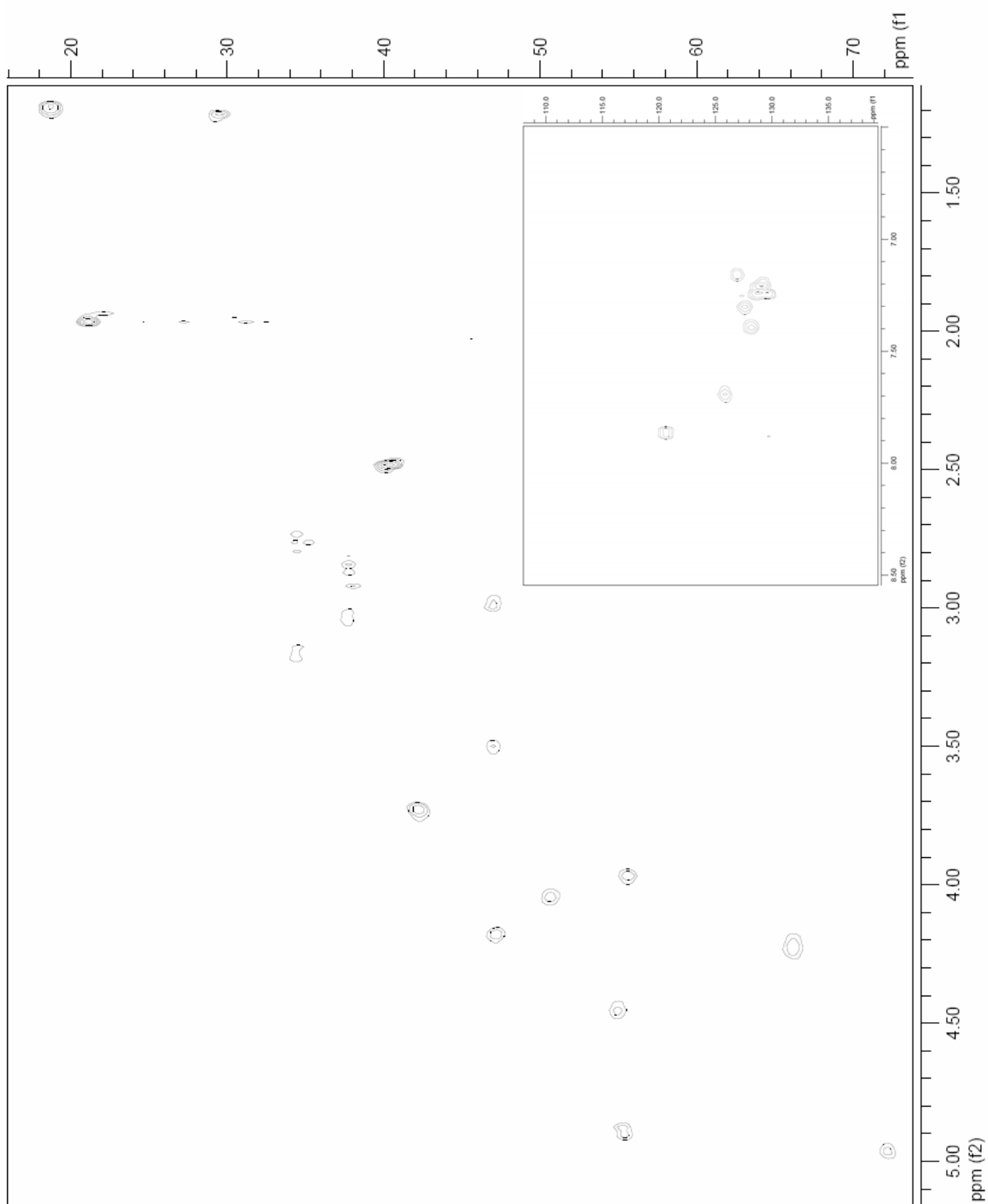
S15) 12



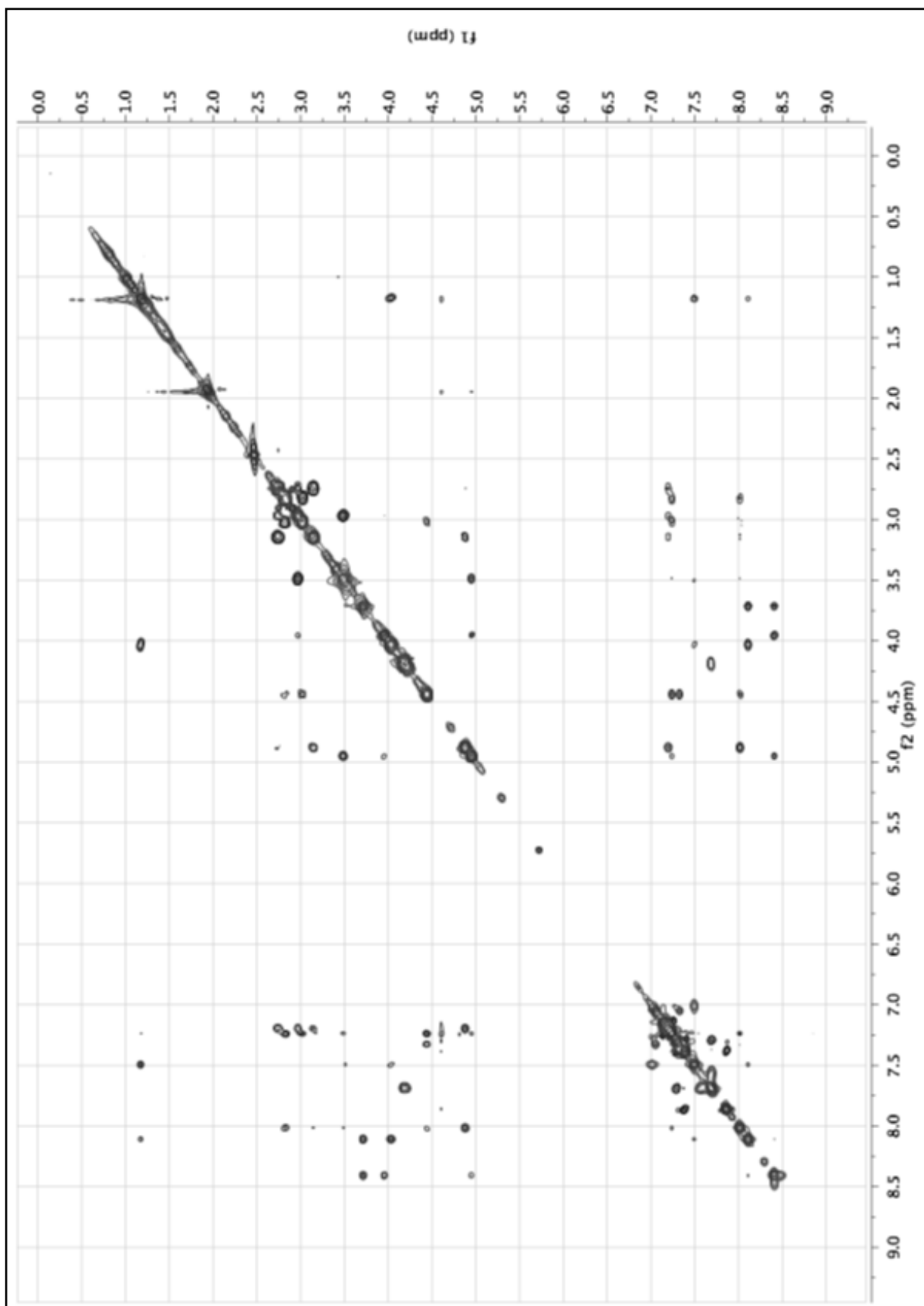
TOCSY-Spectrum of **15**



HSQC-Spectrum of **15**



ROESY-Spectrum of **15**



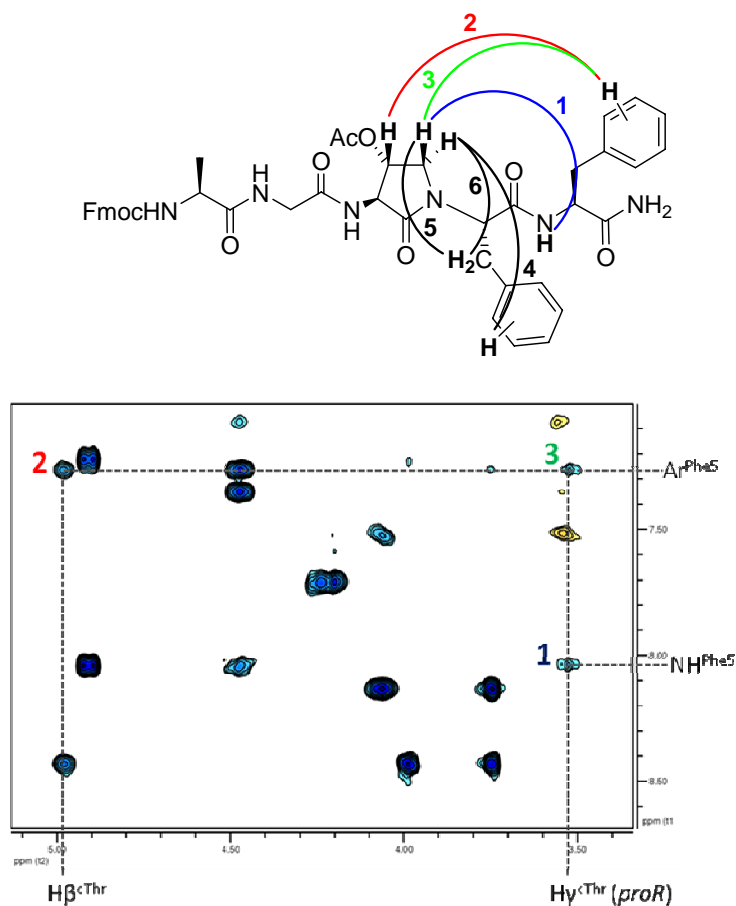


Figure S1. Interresidual contacts in **15** as determined by ROESY experiments.

Table S1. Significant interresidual contacts (cross-peak) in **15** as determined by ROESY [400 MHz, DMSO, $\tau_M = 300$ ms].^a

Crosspeak	δ^A [ppm]	H ^A	δ^B [ppm]	H ^B
1	8.04	NH ^{Phe5}	3.52	H γ^{cThr} (<i>proR</i>)
2	7.26	Ar ^{Phe5}	4.97	H β^{cThr}
3	7.26	Ar ^{Phe5}	3.52	H γ^{cThr} (<i>proR</i>)
4	7.22	Ar ^{Phe4}	3.00	H γ^{cThr} (<i>proS</i>)
5	3.52	H γ^{cThr} (<i>proR</i>)	2.77	H β^{Phe4}
6	3.00	H γ^{cThr} (<i>proS</i>)	2.77	H β^{Phe4}

^aProchirality of the γ^{cThr} protons were determined by measurement of the $H\gamma^{cThr1,2}$ -H β^{cThr} coupling constants