

A Selective Deprotection Strategy for the Construction of *trans*-2-Aminocyclopropanecarboxylic Acid Derived Peptides

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Supporting Information

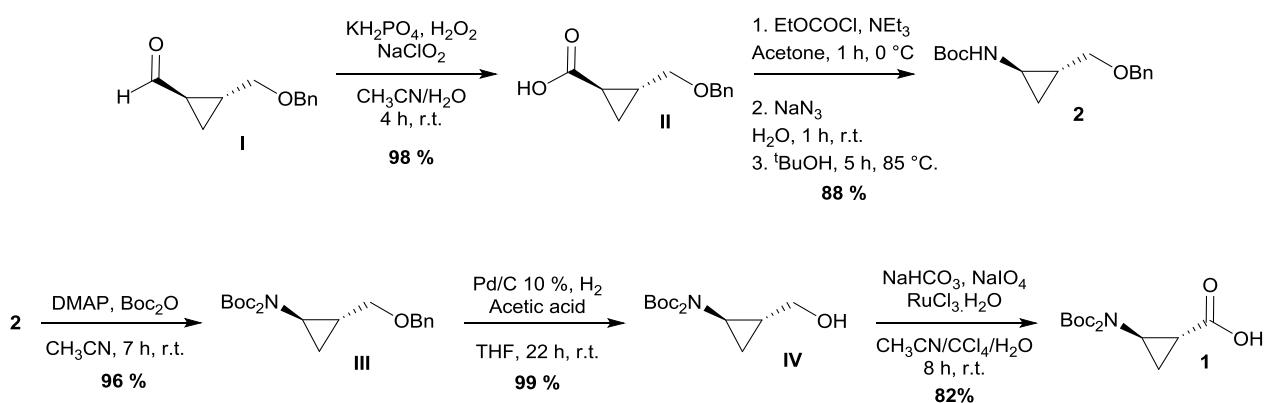
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1. General Experimental

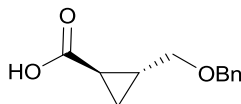
All reagents and solvents were of commercial grade and were used without further purification. Dichloromethane was dried over activated alumina, THF was distilled from sodium/benzophenone and acetone was distilled from potassium carbonate. Other solvents were purchased from VWR Chemicals or Carlo Erba and used as received. Flash chromatography was performed on 35–70 μm columns of silica gel (Merk-Chimie SAS). Analytical thin-layer chromatography was performed with 0.25 mm commercial silica gel plates (EMD, Silica Gel 60F254). TLC plates were visualized by UV fluorescence at 254 nm, then revealed using a phosphomolybdic acid solution (10% in EtOH) or a ninhydrin solution (0.3% in n-BuOH). Retention factors (R_f) are given for such analyses. Routine nuclear magnetic resonance (NMR) data were acquired on a spectrometer operating at 250 MHz, 300 MHz or 360 MHz for ^1H and at 63 MHz, 75 MHz, 90 MHz or 100 MHz for ^{13}C . Chemical shifts (δ) are reported in parts per million (ppm) with respect to the residual proton signal in deuterated solvent ($\delta = 7.26$ ppm for CDCl_3 , $\delta = 3.31$ ppm for CD_3OD for ^1H and $\delta = 77.16$ ppm for CDCl_3 , $\delta = 49.00$ ppm for CD_3OD for ^{13}C). Splitting patterns for ^1H NMR signals are designated as: s (singlet), d (doublet), t (triplet), q (quadruplet), quint (quintuplet), m (multiplet), br. (broad signal), or app. (apparent). Coupling constants (J) are reported in hertz. High-resolution mass spectrometry (HRMS) data were recorded using the electrospray ionization technique in positive mode (ESI+) or negative mode (ESI-) on a Bruker Daltonics MicroTOF-Q. Melting points were measured in open capillary tubes on a Büchi B-540 apparatus and are uncorrected. Optical rotations were measured on a Specord 205 instrument (Analytik-Jena) using a 10 cm quartz cell; values for $[\alpha]_D^T$ were obtained with the D-line of sodium at the indicated temperature T , using solutions of concentration (c) in units of $\text{g}\cdot 100\text{ mL}^{-1}$. Details on X-ray diffraction analysis data are given below in the corresponding part.

2. Synthetic procedures

2.1 Preparation of compounds 1 and 2



(1*R*,2*R*)-2-((Benzyloxy)methyl)cyclopropanecarboxylic acid **II**



To a solution of (1*R*,2*R*)-2-((Benzyloxy)methyl)cyclopropanecarbaldehyde **I**^{S1} (1.16 g, 6.07 mmol) in acetonitrile (17.5 mL) were added at 0 °C a solution of KH₂PO₄ (0.83 g, 6.07 mmol) in H₂O (8.7 mL), H₂O₂ (30% w/v, 1.86 mL, 18.21 mmol), and a solution of NaClO₂ (2.06 g, 18.21 mmol) in H₂O (18.2 mL). After 5 min, the reaction mixture was allowed to warm slowly to room temperature and stirred for 4 h. Then the reaction mixture was quenched with Na₂SO₃ (1.50 g) and stirred for 1 h. The reaction was then diluted with an aqueous solution of KHSO₄ (1M, 30 mL) and extracted with EtOAc. The combined organic phases were dried over Na₂SO₄ and concentrated under reduced pressure, to give the cleaned (1*R*,2*R*)-2-((benzyloxy)methyl)cyclopropanecarboxylic acid **II** (1.23 g, 98%) as a colourless oil which was engaged to the following step without any purification.

Rf (20% EtOAc/Petroleum Ether): 0.12; [α]_D²⁴ -85 (c 0.52, CHCl₃) [lit.^{S1} [α]_D²² -152 (c 0.51, CHCl₃); ¹H NMR (360 MHz, CDCl₃) δ 7.39-7.25 (m, 5H), 4.53 (s, 2H), 3.48 (d of A of AB quartet, *J* = 10.4, 5.8 Hz, 1H), 3.36 (d of B of AB quartet, *J* = 10.4, 6.5 Hz, 1H), 1.86-1.74 (m, 1H), 1.58 (dt, *J* = 8.6, 4.4 Hz, 1H), 1.28 (dt, *J* = 9.0, 4.4 Hz, 1H), 0.95 (ddd, *J* = 8.2, 6.5, 4.4 Hz, 1H), COOH is not observed; ¹³C NMR (63 MHz, CDCl₃) δ 180.3 (C), 138.1 (C), 128.6 (2CH), 127.8 (3CH), 72.8 (CH₂), 71.3 (CH₂), 22.7 (CH), 18.5 (CH), 13.8 (CH₂); **HRMS (ESI-)** *m/z* : theor. 205.0870 (calc. for C₁₂H₁₃O₃), meas. 205.0861. *Spectral data were identical to those described in the literature.*^{S1}

tert-Butyl ((1*R*,2*R*)-2-((benzyloxy)methyl)cyclopropyl)carbamate **2**



Based on literature procedures.^{S2,S3}

To a solution of acid **II** (618 mg, 3.0 mmol) in acetone (30 mL) was added the triethylamine (0.63 mL, 4.5 mmol). The reaction mixture was cooled to 0 °C before ethyl chloroformate (0.43 mL, 4.5 mmol) was added dropwise and the reaction was stirred at 0 °C for 1 h. The solution was warmed to room temperature and a solution of NaN₃ (293 mg, 4.5 mmol) in H₂O (9 mL) was added. The reaction was stirred for additional 1.5 h before being extracted with dichloromethane, dried over MgSO₄ and concentrated under reduced pressure. The intermediate acyl azide was dissolved in ^tBuOH (13.5 mL) and heated at 85 °C for 5 h. After cooling to room temperature, the solution was diluted with EtOAc and washed with H₂O. The combined organic phases were dried over Na₂SO₄ and concentrated under reduced pressure to give the cleaned *tert*-butyl ((1*R*,2*R*)-2-((benzyloxy)methyl)-cyclopropyl)carbamate **2** (730 mg, 88%) as a thick colourless oil which was engaged to the following step without any purification.

Rf (15% EtOAc/Petroleum Ether): 0.20; [α]_D²⁵ -40 (c 0.39, CHCl₃) [lit.^{S1} [α]_D²² -30 (c 0.40, CHCl₃); ¹H NMR (250 MHz, CDCl₃) δ 7.37-7.27 (m, 5H), 4.70 (br. s, 1H), 4.52 (s, 2H), 3.47 (d of A of AB quartet, *J* = 10.2, 6.6 Hz, 1H), 3.29 (d of B of AB quartet, *J* = 10.2, 7.0 Hz, 1H), 2.42 (br. m, 1H), 1.43 (s, 9H), 1.29-1.16 (m, 1H), 0.81-0.66 (m, 2H); ¹³C NMR (90 MHz, CDCl₃) δ 156.5 (C), 138.4 (C), 128.4 (2CH), 127.7 (2CH), 127.6 (CH), 79.4 (C), 72.7 (CH₂), 71.8 (CH₂), 28.4 (3CH₃), 28.2 (CH), 20.0 (CH), 12.1 (CH₂); **HRMS (ESI+)** *m/z* : theor. 278.1751 (calc. for C₁₆H₂₄NO₃), meas. 278.1746. *Spectral data were identical to those described in the literature.*^{S1}

^{S1} Armstrong, A.; Scutt, J. N. *Org. Lett.* **2003**, 5, 2331-2334.

^{S2} Martín-Vilà, M.; Muray, E.; Aguado, G. P.; Alvarez-Larena, A.; Branchadell, V.; Minguillón, C.; Giralt, E.; Ortuño, R. M. *Tetrahedron: Asymmetry* **2000**, 11, 3569-3584.

^{S3} Miller, J. A.; Hennessy, E. J.; Marshall, W. J.; Scialdone, M. A.; Nguyen, S. T. *J. Org. Chem.* **2003**, 68, 7884-7886.

(1*R*,2*R*)-*O*-Benzyl-*N,N*-di-Boc 2-aminocyclopropane alcohol III

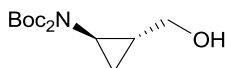


Based on a literature procedure.^{S1}

To a solution of compound **2** (174 mg, 0.63 mmol) in acetonitrile (4 mL) were added Boc₂O (413 mg, 1.89 mmol) and DMAP (23 mg, 0.19 mmol). The reaction mixture was stirred at room temperature for 7 h, over which time it turned dark orange, then the reaction mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (10% EtOAc/Petroleum Ether) to give the (1*R*,2*R*)-*O*-benzyl-*N,N*-di-Boc amino alcohol **III** (228 mg, 96%) as a thick colourless oil.

Rf (15% EtOAc/Petroleum Ether): 0.57; $[\alpha]_D^{25}$ -42 (c 0.52, CHCl₃) [lit.^{S1} $[\alpha]_D^{22}$ -44 (c 0.37, CHCl₃); **¹H NMR (360 MHz, CDCl₃)** δ 7.40-7.26 (m, 5H), 4.56 (s, 2H), 3.85 (dd, *J* = 10.0, 4.5 Hz, 1H), 3.22 (app. t, *J* = 8.3 Hz, 1H), 2.57-2.49 (m, 1H), 1.54 (s, 18H), 1.43-1.37 (m, 1H), 1.04 (app. q, *J* = 6.5 Hz, 1H), 0.96-0.88 (m, 1H); **¹³C NMR (90 MHz, CDCl₃)** δ 152.8 (2C), 138.2 (C), 128.2 (2CH), 127.5 (2CH), 127.4 (CH), 82.0 (2C), 72.5 (CH₂), 70.7 (CH₂), 32.1 (CH), 27.9 (6CH₃), 22.4 (CH), 14.6 (CH₂); **HRMS (ESI+)** *m/z* : theor. 400.2094 (calc. for C₂₁H₃₁NO₅Na), meas. 400.2073. *Spectral data were identical to those described in the literature.*^{S1}

(1*R*,2*R*)-*N,N*-Di-Boc 2-aminocyclopropane alcohol IV

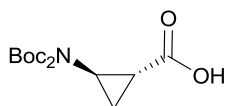


Based on a literature procedure.^{S1}

To a solution of compound **III** (600 mg, 1.59 mmol) in THF (20 mL) were added acetic acid (0.46 mL, 7.96 mmol) and Pd/C (10% by wt, 250 mg). The reaction mixture was then stirred under an atmosphere of hydrogen at room temperature for 4 h. The black suspension was then diluted with EtOAc and filtered through a pad of Celite®. The filtrate was washed with saturated solution of NaHCO₃ and brine, and the combined organic phases were dried over Na₂SO₄ and concentrated under reduced pressure to give the cleaned (*R,R*)-*N,N*-di-Boc amino alcohol **IV** (452 mg, 99%) as a thick colourless oil which was engaged to the following step without any purification.

Rf (15% EtOAc/Petroleum Ether): 0.15; $[\alpha]_D^{26}$ -5 (c 1.25, CHCl₃) [lit.^{S1} $[\alpha]_D^{22}$ -3 (c 1.99, CHCl₃); **¹H NMR (300 MHz, CDCl₃)** δ 3.82 (d of A of AB quartet, *J* = 10.9, 5.1 Hz, 1H), 3.10 (d of B of AB quartet, *J* = 10.9, 9.6 Hz, 1H), 2.97 (br. s, 1H), 2.45-2.38 (m, 1H), 1.47 (s, 18H), 1.29-1.20 (m, 1H), 0.89 (dd, *J* = 8.5, 5.4 Hz, 2H); **¹³C NMR (90 MHz, CDCl₃)** δ 153.5 (2C), 82.9 (2C), 64.9 (CH₂), 33.7 (CH), 28.1 (6CH₃), 24.9 (CH), 13.7 (CH₂); **HRMS (ESI+)** *m/z* : theor. 310.1625 (calc. for C₁₄H₂₅NO₅Na), meas. 310.1619. *Spectral data were identical to those described in the literature.*^{S1}

(1*R*,2*R*)-*N,N*-Di-Boc 2-aminocyclopropane carboxylic acid 1



Based on a literature procedure.^{S4}

To a solution of the alcohol **IV** (287 mg, 1.0 mmol) in a solvent mixture (CCl₄ (3 mL), acetonitrile (3 mL), and H₂O (4 mL)) under an argon atmosphere were added NaHCO₃ (0.42 g, 5.0 mmol), NaIO₄ (1.07 g, 5.0 mmol), and RuCl₃ (41 mg, 0.2 mmol). The biphasic solution was stirred at room temperature for 8 h and quenched with a saturated solution of NH₄Cl. The solution was then diluted with dichloromethane and the layers were separated. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography (30%

^{S4} Jain, R. P.; Vederas, J. C. *Org. Lett.* **2003**, 5, 4669-4672.

EtOAc/Petroleum Ether + 1% AcOH) to give the (*R,R*)-*N,N*-di-Boc β -aminocyclopropane carboxylic acid **1** (248 mg, 82%) as a colourless oil.

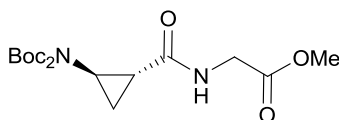
Rf (30% EtOAc/Petroleum Ether + 1% AcOH): 0.39; $[\alpha]_D^{18}$ -30 (c 0.64, CHCl₃) [*ent*-**1** lit.^{S4} $[\alpha]_D^{26}$ +36 (c 1.8, CHCl₃); ¹H NMR (360 MHz, CDCl₃) δ 10.12 (br. s, 1H), 3.09 (ddd, *J* = 7.8, 5.2, 2.9 Hz, 1H), 1.80 (ddd, *J* = 9.1, 6.2, 2.9 Hz, 1H), 1.62 (dd, *J* = 13.4, 6.2 Hz, 1H), 1.49 (s, 18H), 1.31-1.23 (m, 1H); ¹³C NMR (90 MHz, CDCl₃) δ 178.4 (C), 152.2 (2C), 83.2 (2C), 36.8 (CH), 28.1 (6CH₃), 24.9 (CH), 19.2 (CH₂); **HRMS (ESI-)** *m/z* : theor. 300.1453 (calc. for C₁₄H₂₂NO₆), meas. 300.1453. Spectral data were identical to those described in the literature.^{S4}

2.2 Coupling at the C-terminal

General procedure A for the coupling reaction between the acid **1** and aminoester **3a-d** using EDC in the presence of HOBt:

To a solution of acid **1** (1.0 equiv.) in dichloromethane (20 mL/mmol) were added, under argon atmosphere, aminoester **3a-d** (1.2 equiv.), 1-hydroxybenzotriazole hydrate (HOBt·H₂O) (1.2 equiv.) and triethylamine (2.5 equiv.). The mixture was stirred until all reagents were dissolved or at least 5 min and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDCI·HCl) (1.5 equiv.) was added. The solution was then stirred at room temperature for 24 h. The solution was concentrated before being diluted with EtOAc and washed with a solution of KHSO₄ (1M, 2 times), with a saturated solution of NaHCO₃ (2 times) and brine (1 time). The organic layer was then dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was then purified by column chromatography using the appropriate mixture of eluents to give the corresponding product **4a-d**.

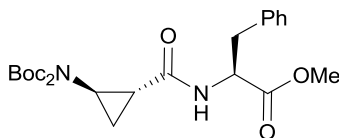
Boc₂N-*t*ACPrC-Gly-OMe **4a**



From a solution of acid **1** (41 mg, 0.14 mmol), HOBt·H₂O (22 mg, 0.16 mmol), triethylamine (47 μ L, 34 mg, 0.34 mmol), EDCI·HCl (39 mg, 0.20 mmol) and HCl·NH₂-Gly-OMe **3a** (21 mg, 0.16 mmol) in dichloromethane (3 mL) following the general procedure A and after purification by column chromatography (45% EtOAc/Petroleum Ether), Boc₂N-*t*ACPrC-Gly-OMe **4a** was obtained as a colourless oil (50 mg, 99%).

Rf (50% EtOAc/Petroleum Ether): 0.33; $[\alpha]_D^{26}$ -20 (c 0.53, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 6.55-6.47 (br. m, 1H), 4.16 (d of A of AB quartet, *J* = 18.4, 5.6 Hz, 1H), 3.97 (d of B of AB quartet, *J* = 18.4, 4.8 Hz, 1H), 3.75 (s, 3H), 2.97 (ddd, *J* = 7.6, 4.8, 3.0 Hz, 1H), 1.74 (ddd, *J* = 9.2, 6.3, 3.0 Hz, 1H), 1.61-1.50 (m, 1H), 1.48 (s, 18H), 1.11-1.02 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 170.9 (C), 170.5 (C), 152.7 (2C), 82.9 (2C), 52.5 (CH₃), 41.5 (CH₂), 35.4 (CH), 28.1 (6CH₃), 26.4 (CH), 16.8 (CH₂); **HRMS (ESI+)** *m/z* : theor. 395.1789 (calc. for C₁₇H₂₈N₂O₇Na), meas. 395.1797.

Boc₂N-*t*ACPrC-Phe-OMe **4b**

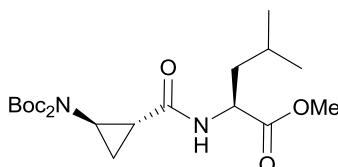


From a solution of acid **1** (75 mg, 0.25 mmol), HOBt·H₂O (41 mg, 0.3 mmol), triethylamine (87 μ L, 63 mg, 0.63 mmol), EDCI·HCl (72 mg, 0.38 mmol) and HCl·NH₂-Phe-OMe **3b** (65 mg, 0.3 mmol) in dichloromethane (4 mL) following the general procedure A and after purification by column chromatography

(25% to 30% EtOAc/Petroleum Ether), Boc₂N-*t*ACPrC-Phe-OMe **4b** was obtained as a colourless oil (104 mg, 90%).

Rf (20% EtOAc/Petroleum Ether): 0.19; [α]_D²¹ +41 (c 0.685, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.34-7.20 (m, 5H), 6.50 (d, *J* = 7.9 Hz, 1H), 4.94-4.86 (m, 1H), 3.71 (s, 3H), 3.19-3.05 (m, 2H), 2.96 (ddd, *J* = 7.6, 4.8, 3.0 Hz, 1H), 1.72 (ddd, *J* = 9.1, 6.4, 3.0 Hz, 1H), 1.60-1.54 (m, 1H), 1.50 (s, 18H), 1.06 (app. dt, *J* = 9.1, 5.4 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 172.1 (C), 170.4 (C), 152.7 (2C), 135.9 (C), 129.5 (2CH), 128.6 (2CH), 127.1 (CH), 82.6 (2C), 53.4 (CH₃), 52.3 (CH), 38.1 (CH₂), 35.3 (CH), 28.0 (6CH₃), 26.2 (CH), 16.5 (CH₂); **HRMS (ESI+)** *m/z* : theor. 485.2258 (calc. for C₂₄H₃₄N₂O₇Na), meas. 485.2268.

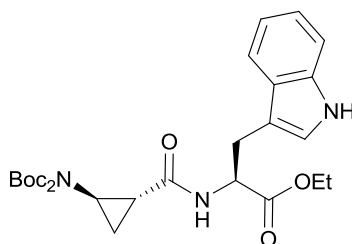
Boc₂N-*t*ACPrC-Leu-OMe **4c**



From a solution of acid **1** (75 mg, 0.25 mmol), HOBt·H₂O (41 mg, 0.3 mmol), triethylamine (87 μ L, 63 mg, 0.63 mmol), EDCI·HCl (72 mg, 0.38 mmol) and HCl·NH₂-Leu-OMe **3c** (55 mg, 0.3 mmol) in dichloromethane (4 mL) following the general procedure **A** and after purification by column chromatography (20% to 30% EtOAc/Petroleum Ether), Boc₂N-*t*ACPrC-Leu-OMe **4c** was obtained as a colourless oil (88 mg, 73%).

Rf (30% EtOAc/Petroleum Ether): 0.32; [α]_D²³ -23 (c 0.5, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 6.34 (br. d, *J* = 8.0 Hz, 1H), 4.60 (app. td, *J* = 8.4, 5.6 Hz, 1H), 3.71 (s, 3H), 2.94 (ddd, *J* = 7.6, 4.8, 3.1 Hz, 1H), 1.74-1.50 (m, 5H), 1.47 (s, 18H), 1.07-0.99 (m, 1H), 0.91 (d, *J* = 6.3 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 173.8 (C), 170.7 (C), 152.7 (2C), 82.7 (2C), 52.4 (CH₃), 51.0 (CH), 42.0 (CH₂), 35.3 (CH), 28.1 (6CH₃), 26.4 (CH), 24.9 (CH), 22.8 (CH₃), 22.1 (CH₃), 16.7 (CH₂); **HRMS (ESI+)** *m/z* : theor. 451.2415 (calc. for C₂₁H₃₆N₂O₇Na), meas. 451.2421.

Boc₂N-*t*ACPrC-Trp-OEt **4d**



From a solution of acid **1** (60 mg, 0.2 mmol), HOBt·H₂O (33 mg, 0.24 mmol), triethylamine (70 μ L, 51 mg, 0.5 mmol), EDCI·HCl (58 mg, 0.3 mmol) and HCl·NH₂-Trp-OEt **3d** (64 mg, 0.24 mmol) in dichloromethane (3 mL) following the general procedure **A** and after purification by column chromatography (30% to 40% EtOAc/Petroleum Ether), Boc₂N-*t*ACPrC-Trp-OEt **4d** was obtained as a white solid (93 mg, 90%).

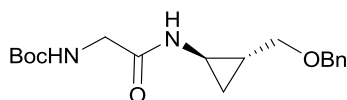
Rf (40% EtOAc/Petroleum Ether): 0.49; [α]_D²¹ +32 (c 0.5, CHCl₃); **Mp:** 169-170 °C; ¹H NMR (250 MHz, CDCl₃) δ 8.18 (br. s, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.23-7.05 (m, 3H), 6.39 (br. d, *J* = 7.6 Hz, 1H), 4.87 (app. td, *J* = 7.4, 5.7 Hz, 1H), 4.17-3.98 (m, 2H), 3.31 (dd, *J* = 5.6, 3.4 Hz, 2H), 2.98 (ddd, *J* = 7.6, 4.8, 3.1 Hz, 1H), 1.65-1.43 (m, 2H), 1.45 (s, 18H), 1.18 (t, *J* = 7.1 Hz, 3H), 1.04 (app. dt, *J* = 9.1, 5.4 Hz, 1H); ¹³C NMR (90 MHz, CDCl₃) δ 172.2 (C), 170.6 (C), 152.7 (2C), 136.4 (C), 127.6 (C), 123.4 (CH), 122.2 (CH), 119.6 (CH), 118.6 (CH), 111.4 (CH), 109.7 (C), 82.7 (2C), 61.5 (CH₂), 53.3 (CH), 35.3 (CH), 28.1 (6CH₃), 27.8 (CH₂), 26.4 (CH), 17.0 (CH₂), 14.1 (CH₃); **HRMS (ESI+)** *m/z* : theor. 538.2524 (calc. for C₂₇H₃₇N₃O₇Na), meas. 538.2517; **X-ray:** CCDC 1841687.

2.3 Coupling at the N-terminal

General procedure B for the deprotection step of the protected aminocyclopropane **2** followed by the coupling reaction with the protected α -amino acid **6a-b** using EDC in the presence of HOBt:

To a solution of compound **2** (1.0 equiv.) in dichloromethane (35 mL/mmol) was added at 0°C TFA (30 equiv.). After 2 h at room temperature, the solvent and excess of TFA was evaporated under reduced pressure to give the corresponding TFA salt. It was directly introduced in a solution of *N*-protected amino acid **6a-b** (1 equiv.) in dichloromethane (20 mL/mmol) under argon atmosphere. Then, 1-hydroxybenzotriazole hydrate (HOBt·H₂O) (1.2 equiv.) and triethylamine (3.5 equiv.) were added. The mixture was stirred until all reagents were dissolved or at least 5 min and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDCI·HCl) (1.5 equiv.) was added. The solution was then stirred at room temperature for 24 h. The solution was concentrated before being diluted with EtOAc and washed with a solution of KHSO₄ (1M, 2 times), with a saturated solution of NaHCO₃ (2 times) and brine (1 time). The organic layer was then dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was then purified by column chromatography using the appropriate mixture of eluents to give the corresponding product **7a-b**.

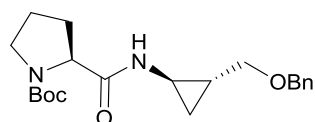
tert-butyl 2-(((1*R*,2*R*)-2-(benzyloxymethyl)cyclopropylamino)-2-oxoethylcarbamate **7a**



From a solution of protected aminocyclopropane **2** (344 mg, 1.24 mmol), TFA (2.85 mL, 4.25 g, 37.3 mmol) in dichloromethane (30 mL), then (HOBt·H₂O) (201 mg, 1.49 mmol), triethylamine (604 μ L, 440 mg, 4.35 mmol), EDCI·HCl (357 mg, 1.86 mmol) and *N*-protected glycine **6a** (218 mg, 1.24 mmol) in dichloromethane (25 mL) following the general procedure **B** and after purification by column chromatography (50% to 70% EtOAc/Petroleum Ether), *tert*-butyl 2-(((1*R*,2*R*)-2-(benzyloxymethyl)cyclopropylamino)-2-oxoethylcarbamate **7a** was obtained as a colourless oil (357 mg, 86%).

Rf (50% EtOAc/Petroleum Ether): 0.22; $[\alpha]_D^{22}$ -38 (c 0.5, CHCl₃); ¹H NMR (250 MHz, CDCl₃) δ 7.36-7.27 (m, 5H), 6.33 (br. s, 1H), 5.16 (br. s, 1H), 4.53 (s, 2H), 3.72 (d, *J* = 5.8 Hz, 2H), 3.38 (dd, *J* = 6.7, 4.5 Hz, 2H), 2.64-2.56 (m, 1H), 1.44 (s, 9H), 1.29-1.20 (m, 1H), 0.82-0.73 (m, 2H); ¹³C NMR (63 MHz, CDCl₃) δ 170.7 (C), 156.1 (C), 138.4 (C), 128.6 (2CH), 127.9 (2CH), 127.8 (CH), 80.5 (C), 72.9 (CH₂), 71.8 (CH₂), 44.6 (CH₂), 28.4 (3CH₃), 27.8 (CH), 19.9 (CH), 11.9 (CH₂); **HRMS** (ESI+) *m/z* : theor. 357.1785 (calc. for C₁₈H₂₆N₂O₄Na), meas. 357.1799.

(*S*)-*tert*-butyl 2-(((1*R*,2*R*)-2-(benzyloxymethyl)cyclopropylcarbamoyl)pyrrolidine-1-carboxylate **7b**



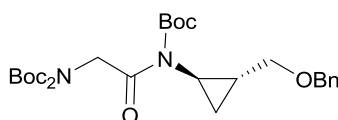
From a solution of protected aminocyclopropane **2** (723 mg, 2.61 mmol), TFA (6 mL, 8.93 g, 78.3 mmol) in dichloromethane (60 mL), then (HOBt·H₂O) (423 mg, 3.13 mmol), triethylamine (1.27 mL, 925 mg, 9.14 mmol), EDCI·HCl (752 mg, 3.92 mmol) and *N*-protected (*S*)-proline **6b** (562 mg, 2.61 mmol) in dichloromethane (50 mL) following the general procedure **B** and after purification by column chromatography (70% EtOAc/Petroleum Ether to EtOAc), (*S*)-*tert*-butyl 2-(((1*R*,2*R*)-2-(benzyloxymethyl)cyclopropylcarbamoyl)pyrrolidine-1-carboxylate **7b** was obtained as a colourless oil (854 mg, 87%).

Rf (60% EtOAc/Petroleum Ether): 0.26; $[\alpha]_D^{26}$ -100 (c 0.5, CHCl₃); **¹H NMR (250 MHz, CDCl₃)** δ 7.36-7.24 (m, 5H), 4.53 (s, 2H), 4.17 (br. s, 1H), 3.40 (br. s, 4H), 2.65-2.54 (m, 1H), 2.45-1.64 (m, 5H), 1.43 (s, 9H), 1.28-1.13 (m, 1H), 0.87-0.69 (m, 2H); **¹³C NMR (90 MHz, CDCl₃)** δ 173.6 (0.5C), 172.9 (0.5C), 155.0 (0.5C), 153.8 (0.5C), 137.9 (C), 127.29 (2CH), 127.2 (2CH), 127.1 (CH), 79.6 (C), 72.1 (br. CH₂), 71.2 (CH₂), 60.3 (0.5CH), 59.3 (0.5CH), 46.6 (CH₂), 30.7 (CH₂), 27.9 (3CH₃), 27.1 (CH), 24.1 (0.5CH₂), 23.3 (0.5CH₂), 19.1 (CH), 11.3 (CH₂); **HRMS (ESI+)** m/z : theor. 397.2098 (calc. for C₂₁H₃₀N₂O₄Na), meas. 397.2136.

General procedure C for the protection step of the products 7a-b:

To a solution of product **7a-b** (1.0 equiv.) in acetonitrile (25 mL/mmol) were added Boc₂O (6.0 equiv.) and DMAP (0.6 equiv. or 1 equiv.) in two portions. The reaction mixture was stirred at room temperature for 48 h, over which time it turned dark orange/red, then the reaction mixture was concentrated under reduced pressure before being diluted with EtOAc and washed with a solution of KHSO₄ (1M, 1 time), with a saturated solution of NaHCO₃ (1 time) and brine (1 time). The organic layer was then dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was then purified by column chromatography using the appropriate mixture of eluents to give the corresponding product **8a-b**.

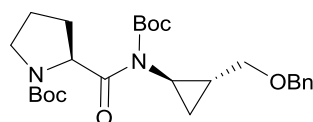
tert-butyl 2-di(*tert*-butoxycarbonyl)aminoacetyl((1*R*,2*R*)-2-(benzyloxymethyl)cyclopropyl)carbamate **8a**



From a solution of product **7a** (350 mg, 1.046 mmol), Boc₂O (1.37 g, 6.28 mmol) and DMAP (128 mg, 1.046 mmol, 0.6 equiv.) in acetonitrile (35 mL) following the general procedure **C** and after purification by column chromatography (10% to 20% EtOAc/Petroleum Ether), *tert*-butyl 2-di(*tert*-butoxycarbonyl)aminoacetyl((1*R*,2*R*)-2-(benzyloxymethyl)cyclopropyl)carbamate **8a** was obtained as a white solid (409 mg, 73%).

Rf (10% EtOAc/Petroleum Ether): 0.34; $[\alpha]_D^{24}$ -36 (c 0.435, CHCl₃); **Mp:** 85-86 °C; **¹H NMR (300 MHz, CDCl₃)** δ 7.34-7.23 (m, 5H), 4.75 (A of AB quartet, J = 18.0 Hz, 1H), 4.68 (B of AB quartet, J = 18.0 Hz, 1H), 4.51 (s, 2H), 3.86 (dd, J = 10.1, 4.4 Hz, 1H), 3.14 (dd, J = 10.1, 7.8 Hz, 1H), 2.41 (app. dt, J = 7.3, 3.8 Hz, 1H), 1.49 (s, 9H), 1.48 (s, 18H), 1.33-1.23 (m, 1H), 1.06 (dd, J = 13.6, 6.7 Hz, 1H), 0.88-0.79 (m, 1H); **¹³C NMR (75 MHz, CDCl₃)** δ 172.1 (C), 153.6 (C), 152.5 (2C), 138.4 (C), 128.5 (2CH), 127.8 (2CH), 127.7 (CH), 83.5 (C), 82.7 (2C), 72.8 (CH₂), 71.1 (CH₂), 52.0 (CH₂), 31.4 (CH), 28.2 (9CH₃), 22.6 (CH), 15.0 (CH₂); **HRMS (ESI+)** m/z : theor. 557.2833 (calc. for C₂₈H₄₂N₂O₈Na), meas. 557.2861.

(*S*)-*tert*-butyl 2-(((1*R*,2*R*)-2-(benzyloxymethyl)cyclopropyl)(*tert*-butoxycarbonyl)carbamoyl)pyrrolidine-1-carboxylate **8b**



From a solution of product **7b** (360 mg, 0.961 mmol), Boc₂O (1.26 g, 5.77 mmol) and DMAP (117 mg, 0.96 mmol, 1 equiv.) in acetonitrile (50 mL) following the general procedure **C** and after purification by column chromatography (15% EtOAc/Petroleum Ether to 100% EtOAc), (*S*)-*tert*-butyl 2-(((1*R*,2*R*)-2-(benzyloxymethyl)cyclopropyl)(*tert*-butoxycarbonyl)carbamoyl)pyrrolidine-1-carboxylate **8b** was obtained as a pale yellow oil (381 mg, 84%, 93% BRSM).

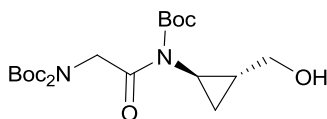
Rf (20% EtOAc/Petroleum Ether): 0.35; $[\alpha]_D^{24}$ -89 (c 0.35, CHCl₃); **¹H NMR (360 MHz, CDCl₃)** δ 7.29-7.15 (m, 5H), 4.97 (dd, J = 8.6, 2.6 Hz, 1H), 4.44 (s, 1H), 4.43 (s, 1H), 3.74 (app. td, J = 9.7, 4.7 Hz, 1H),

3.56-3.44 (m, 1H), 3.42-3.26 (m, 1H), 3.12 (ddd, $J = 13.6, 10.1, 7.7$ Hz, 1H), 2.41-2.34 (m, 1H), 2.26-2.11 (m, 1H), 1.90-1.68 (m, 3H), 1.42 (s, 4.5H), 1.40 (s, 4.5H), 1.37 (s, 4.5H), 1.31 (s, 4.5H), 1.25-1.11 (m, 1H), 1.07-0.95 (m, 1H), 0.85-0.72 (m, 1H); ^{13}C NMR (90 MHz, CDCl_3) δ 177.3 (0.5C), 176.3 (0.5C), 154.5 (0.5C), 153.73 (0.5C), 153.66 (0.5C), 153.4 (0.5C), 138.4 (0.5C), 138.2 (0.5C), 128.4 (CH), 128.3 (CH), 127.66 (CH), 127.65 (CH), 127.6 (0.5CH), 127.5 (0.5CH), 83.2 (0.5C), 82.9 (0.5C), 79.33 (0.5C), 79.30 (0.5C), 72.7 (0.5CH₂), 72.5 (0.5CH₂), 71.0 (0.5CH₂), 70.8 (0.5CH₂), 61.3 (0.5CH), 60.4 (0.5CH), 46.9 (0.5CH₂), 46.6 (0.5CH₂), 31.6 (0.5CH), 31.5 (0.5CH), 31.0 (0.5CH₂), 30.4 (0.5CH₂), 28.5 (1.5CH₃), 28.4 (1.5CH₃), 28.0 (1.5CH₃), 27.9 (1.5CH₃), 23.7 (0.5CH₂), 23.1 (0.5CH₂), 22.0 (0.5CH), 21.6 (0.5CH), 15.6 (0.5CH₂), 15.3 (0.5CH₂); HRMS (ESI+) m/z : theor. 497.2622 (calc. for $\text{C}_{26}\text{H}_{38}\text{N}_2\text{O}_6\text{Na}$), meas. 497.2642.

General procedure D for the hydrogenolysis of the products 8a-b:

To a solution of protected alcohol **8a-b** (1.0 equiv.) in THF (30 mL/mmol) was added acetic acid (5.0 equiv.) and Pd/C (10% by wt) and the solution was stirred under an atmosphere of hydrogen at room temperature for 2 h. The black suspension was then diluted with EtOAc and filtered through a pad of Celite®. The filtrate was washed with saturated solution of NaHCO_3 and brine, and the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to give the cleaned alcohol **9a-b** which was engaged to the following step without any purification.

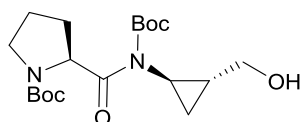
tert-butyl 2-di(*tert*-butoxycarbonyl)aminoacetyl((1*R*,2*R*)-2-(hydroxymethyl)cyclopropyl)carbamate **9a**



From a solution of protected alcohol **8a** (350 mg, 0.66 mmol), acetic acid (190 μL , 196 mg, 3.27 mmol) and Pd/C (100 mg) in THF (35 mL) under an atmosphere of hydrogen following the general procedure **D**, *tert*-butyl 2-di(*tert*-butoxycarbonyl)aminoacetyl((1*R*,2*R*)-2-(hydroxymethyl)-cyclopropyl)carbamate **9a** was obtained as a white solid (289 mg, 99%).

Rf (20% EtOAc/Petroleum Ether): 0.20; $[\alpha]_D^{20}$ -5 (c 0.5, CHCl_3); **Mp**: 118-119 °C; ^1H NMR (360 MHz, CDCl_3) δ 4.76 (A of AB quartet, $J = 18.1$ Hz, 1H), 4.69 (B of AB quartet, $J = 18.1$ Hz, 1H), 3.89 (dd, $J = 10.8, 4.6$ Hz, 1H), 3.17 (br. s, 1H), 3.06 (app. t, $J = 10.3$ Hz, 1H), 2.41-2.35 (m, 1H), 1.51 (s, 9H), 1.48 (s, 18H), 1.27-1.18 (m, 1H), 0.95 (dd, $J = 13.8, 6.8$ Hz, 1H), 0.89 (ddd, $J = 10.1, 6.6, 4.5$ Hz, 1H); ^{13}C NMR (90 MHz, CDCl_3) δ 173.0 (C), 153.2 (C), 152.6 (2C), 84.0 (C), 82.9 (2C), 65.1 (CH₂), 51.9 (CH₂), 32.8 (CH), 28.2 (9CH₃), 25.0 (CH), 13.9 (CH₂); HRMS (ESI+) m/z : theor. 467.2364 (calc. for $\text{C}_{21}\text{H}_{36}\text{N}_2\text{O}_8\text{Na}$), meas. 467.2356.

(*S*)-*tert*-butyl 2-(*tert*-butoxycarbonyl((1*R*,2*R*)-2-(hydroxymethyl)cyclopropyl)carbamoyl)pyrrolidine-1-carboxylate **9b**



From a solution of protected alcohol **8b** (381 mg, 0.80 mmol), acetic acid (229 μL , 240 mg, 4.0 mmol) and Pd/C (100 mg) in THF (35 mL) under an atmosphere of hydrogen following the general procedure **D**, (*S*)-*tert*-butyl 2-(*tert*-butoxycarbonyl((1*R*,2*R*)-2-(hydroxymethyl)cyclopropyl)-carbamoyl)pyrrolidine-1-carboxylate **9b** was obtained as a colourless oil (308 mg, 99%).

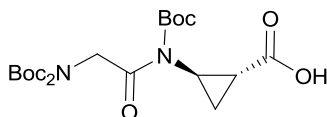
Rf (50% EtOAc/Petroleum Ether): 0.33; $[\alpha]_D^{26}$ -67 (c 0.52, CHCl_3); ^1H NMR (250 MHz, CDCl_3) δ 5.06 (ddd, $J = 18.2, 8.6, 3.0$ Hz, 1H), 3.91 (dd, $J = 10.7, 4.7$ Hz, 1H), 3.62-3.28 (m, 2H), 3.11 (dd, $J = 10.7, 9.7$ Hz, 1H), 2.99 (app. t, $J = 10.4$ Hz, 1H), 2.42-2.21 (m, 2H), 1.98-1.77 (m, 3H), 1.53 (s, 4H), 1.50 (s, 5H), 1.43

(s, 5H), 1.38 (s, 4H), 1.25-1.11 (m, 1H), 1.08-0.84 (m, 2H); ^{13}C NMR (63 MHz, CDCl_3) δ 179.5 (0.6C), 177.4 (0.4C), 154.7 (0.6C), 153.8 (0.4C), 153.5 (0.4C), 153.1 (0.6C), 83.9 (0.4C), 83.5 (0.6C), 79.8 (0.6C), 79.6 (0.4C), 65.4 (0.6CH₂), 65.1 (0.4CH₂), 61.5 (0.6CH), 60.7 (0.4CH), 47.2 (0.6CH₂), 46.8 (0.4CH₂), 33.3 (0.6CH), 33.0 (0.4CH), 31.0 (0.4CH₂), 30.4 (0.6CH₂), 28.6 (3CH₃), 28.2 (3CH₃), 24.8 (0.4CH), 24.1 (0.6CH₂), 24.0 (0.6CH), 23.1 (0.4CH₂), 14.9 (0.6CH₂), 14.4 (0.4CH₂); HRMS (ESI+) m/z : theor. 407.2153 (calc. for $\text{C}_{19}\text{H}_{32}\text{N}_2\text{O}_6\text{Na}$), meas. 407.2193.

General procedure E for the oxidation step of the products 9a-b:

To a solution of alcohol **9a-b** (1.0 equiv.) in a solvent mixture (CCl_4 (10 mL/mmol), acetonitrile (10 mL/mmol) and H_2O (15 mL/mmol)) under an argon atmosphere were added NaHCO_3 (5.0 equiv.), NaIO_4 (5.0 equiv.), and RuCl_3 (0.2 equiv.). The biphasic solution was stirred at room temperature for 8 h and quenched with a saturated solution of NH_4Cl . The solution was then diluted with dichloromethane and the layers were separated. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was then purified by column chromatography using the appropriate mixture of eluents to give the corresponding carboxylic acid **10a-c**.

Boc₂N-Gly-*t*ACPrC(NBoc)-OH **10a**

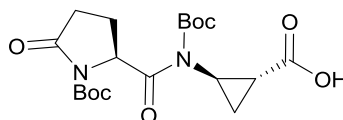


From a solution of alcohol **9a** (289 mg, 0.65 mmol), NaHCO_3 (273 mg, 3.25 mmol), NaIO_4 (696 mg, 3.25 mmol), and RuCl_3 (27 mg, 0.13) in a solvent mixture (CCl_4 (4 mL), acetonitrile (4 mL) and H_2O (6 mL)) following the general procedure **E** and after purification by column chromatography (30% EtOAc/Petroleum Ether + 1% AcOH), Boc₂N-Gly-*t*ACPrC(NBoc)-OH **10a** was obtained as colourless oil (278 mg, 93%).

Rf (40% EtOAc/Petroleum Ether + 1% AcOH): 0.5; $[\alpha]_D^{19}$ -45 (c 0.22, CHCl_3); ^1H NMR (360 MHz, CDCl_3) δ 9.16 (br. s, 1H), 4.77 (A of AB quartet, J = 18.1 Hz, 1H), 4.68 (B of AB quartet, J = 18.1 Hz, 1H), 3.07-3.00 (m, 1H), 1.78-1.64 (m, 2H), 1.51 (s, 9H), 1.48 (s, 18H), 1.32-1.26 (m, 1H); ^{13}C NMR (90 MHz, CDCl_3) δ 178.3 (C), 172.0 (C), 152.9 (C), 152.6 (2C), 84.3 (C), 83.0 (2C), 52.0 (CH₂), 35.7 (CH), 28.2 (6CH₃), 28.0 (3CH₃), 24.5 (CH), 19.0 (CH₂); HRMS (ESI-) m/z : theor. 457.2192 (calc. for $\text{C}_{21}\text{H}_{33}\text{N}_2\text{O}_9$), meas. 457.2184.

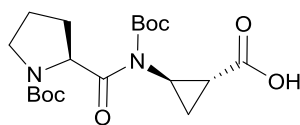
BocN-Pyr-*t*ACPrC(NBoc)-OH **10b** and BocN-Pro-*t*ACPrC(NBoc)-OH **10c**

From a solution of alcohol **9b** (285 mg, 0.74 mmol), NaHCO_3 (311 mg, 3.71 mmol), NaIO_4 (793 mg, 3.71 mmol), and RuCl_3 (31 mg, 0.15) in a solvent mixture (CCl_4 (4 mL), acetonitrile (4 mL) and H_2O (6 mL)) following the general procedure **E** and after purification by column chromatography (40% to 70% EtOAc/Petroleum Ether + 1% AcOH), BocN-Pyr-*t*ACPrC(NBoc)-OH **10b** (200 mg, 65%) as a white solid and BocN-Pro-*t*ACPrC(NBoc)-OH **10c** (50 mg, 17%) as a white solid were obtained.



10b:

Rf (40% EtOAc/Petroleum Ether + 1% AcOH): 0.1; $[\alpha]_D^{26}$ -93 (c 0.51, CHCl_3); **Mp**: 161-162 °C; ^1H NMR (360 MHz, CDCl_3) δ 9.49 (br. s, 1H), 5.36 (dd, J = 9.2, 1.9 Hz, 1H), 3.12-2.89 (m, 1H), 2.60-2.27 (m, 3H), 1.95-1.86 (m, 1H), 1.76-1.67 (m, 2H), 1.50 (s, 9H), 1.44 (s, 9H), 1.33-1.27 (m, 1H); ^{13}C NMR (90 MHz, CDCl_3) δ 177.6 (C), 174.6 (C), 174.0 (C), 152.8 (C), 149.8 (C), 84.7 (C), 83.5 (C), 60.6 (CH), 35.6 (CH), 31.0 (CH₂), 27.9 (3CH₃), 27.9 (3CH₃), 23.6 (CH), 21.7 (CH₂), 19.4 (CH₂); HRMS (ESI-) m/z : theor. 411.1773 (calc. for $\text{C}_{19}\text{H}_{27}\text{N}_2\text{O}_8$), meas. 411.1782.



10c:

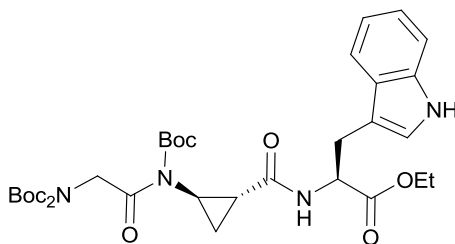
Rf (40% EtOAc/Petroleum Ether + 1% AcOH): 0.27; $[\alpha]_D^{26}$ -105 (c 0.54, CHCl₃); **Mp:** 158-159 °C; **¹H NMR (360 MHz, CDCl₃)** δ 9.65 (br. s, 1H), 5.05 (dd, J = 8.7, 2.8 Hz, 0.5H), 4.99 (dd, J = 8.7, 2.7 Hz, 0.5H), 3.61-3.49 (m, 1H), 3.49-3.31 (m, 1H), 3.09-2.98 (m, 1H), 2.36-2.17 (m, 1H), 1.95-1.77 (m, 3.5H), 1.76-1.61 (m, 1.5H), 1.51 (s, 4.5H), 1.49 (s, 4.5H), 1.43 (s, 4.5H), 1.38 (s, 4.5H), 135-1.28 (m, 1H); **¹³C NMR (90 MHz, CDCl₃)** δ 178.4 (0.5C), 177.7 (0.5C), 177.6 (0.5C), 176.0 (0.5C), 154.8 (0.5C), 153.8 (0.5C), 153.2 (0.5C), 152.8 (0.5C), 84.2 (0.5C), 83.7 (0.5C), 79.9 (0.5C), 79.8 (0.5C), 61.5 (0.5CH), 60.5 (0.5CH), 47.1 (0.5CH₂), 46.7 (0.5CH₂), 35.9 (0.5CH), 35.8 (0.5CH), 31.1 (0.5CH₂), 30.4 (0.5CH₂), 28.6 (1.5CH₃), 28.5 (1.5CH₃), 28.1 (1.5CH₃), 27.9 (1.5CH₃), 23.9 (0.5CH₂), 23.9 (0.5CH), 23.5 (0.5CH), 23.2 (0.5CH₂), 19.6 (0.5CH₂), 19.4 (0.5CH₂); **HRMS (ESI-) m/z** : theor. 397.1980 (calc. for C₁₉H₂₉N₂O₇), meas. 397.1973.

2.4 Synthesis of the tripeptides

General procedure F for the coupling reaction between the acid 10a-b and HCl·NH₂-Trp-OEt 3d using EDC in the presence of HOBt:

To a solution of acid **10a-b** (1.0 equiv.) in dichloromethane (20 mL/mmol) were added, under argon atmosphere, HCl·NH₂-Trp-OEt **3d** (1.2 equiv.), 1-hydroxybenzotriazole hydrate (HOBt·H₂O) (1.2 equiv.) and triethylamine (2.5 equiv.). The mixture was stirred until all reagents were dissolved or at least 5 min and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDCI·HCl) (1.5 equiv.) was added. The solution was then stirred at room temperature for 24 h. The solution was concentrated before being diluted with EtOAc and washed with a solution of KHSO₄ (1M, 2 times), with a saturated solution of NaHCO₃ (2 times) and brine (1 time). The organic layer was then dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was then purified by column chromatography using the appropriate mixture of eluents to give the corresponding product **11a-b**.

Boc₂N-Gly-*t*ACPrC(NBoc)-Trp-OEt 11a

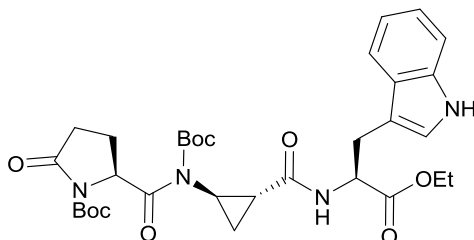


From a solution of acid **10a** (230 mg, 0.5 mmol), HOBt·H₂O (81 mg, 0.6 mmol), triethylamine (174 μ L, 1.25 mmol), EDCI·HCl (144 mg, 0.75 mmol) and HCl·NH₂-Trp-OEt **3d** (161 mg, 0.6 mmol) in dichloromethane (15 mL) following the general procedure **F** and after purification by column chromatography (30% to 40% EtOAc/Petroleum Ether), Boc₂N-Gly-*t*ACPrC(NBoc)-Trp-OEt **11a** was obtained as a white solid (289 mg, 86%).

Rf (40% EtOAc/Petroleum Ether): 0.42; $[\alpha]_D^{23}$ +64 (c 0.51, CHCl₃); **Mp:** 74-75 °C; **¹H NMR (360 MHz, CDCl₃)** δ 8.99 (s, 1H), 7.72 (d, J = 2.3 Hz, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.13 (app. t, J = 7.4 Hz, 1H), 7.05 (app. t, J = 7.4 Hz, 1H), 6.35 (d, J = 8.4 Hz, 1H), 4.97-4.88 (m, 1H), 4.82 (A of AB quartet, J = 17.9 Hz, 1H), 4.68 (B of AB quartet, J = 17.9 Hz, 1H), 4.14-3.90 (m, 2H), 3.46 (d of A of AB

quartet, $J = 14.7, 5.0$ Hz, 1H), 3.25 (d of B of AB quartet, $J = 14.7, 5.0$ Hz, 1H), 2.97-2.86 (m, 1H), 1.71 (dd, $J = 13.5, 6.7$ Hz, 2H), 1.53 (s, 9H), 1.53-1.49 (m, 1H), 1.43 (s, 18H), 1.16 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (90 MHz, CDCl_3) δ 174.0 (C), 171.7 (C), 169.7 (C), 152.9 (2C), 152.8 (C), 136.1 (C), 127.7 (C), 125.7 (CH), 121.6 (CH), 119.1 (CH), 118.5 (CH), 111.4 (CH), 108.2 (C), 84.1 (C), 83.5 (2C), 61.6 (CH_2), 52.6 (CH_2), 52.1 (CH), 34.9 (CH), 28.2 (3CH_3), 28.1 (6CH_3), 27.9 (CH_2), 26.5 (CH), 16.4 (CH_2), 14.1 (CH_3); HRMS (ESI+) m/z : theor. 695.3263 (calc. for $\text{C}_{34}\text{H}_{48}\text{N}_4\text{O}_{10}\text{Na}$), meas. 695.3272.

BocN-Pyr-*t*ACPrC(NBoc)-Trp-OEt 11b



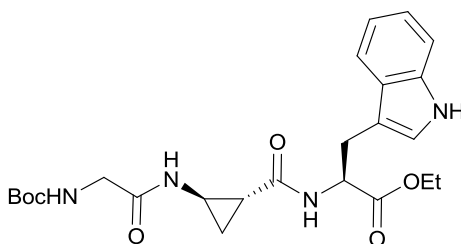
From a solution of acid **10b** (145 mg, 0.35 mmol), HOBT·H₂O (57 mg, 0.42 mmol), triethylamine (123 μL , 89 mg, 0.88 mmol), EDCI·HCl (101 mg, 0.53 mmol) and HCl·NH₂-Trp-OEt **3d** (113 mg, 0.42 mmol) in dichloromethane (10 mL) following the general procedure **F** and BocN-Pyr-*t*ACPrC(NBoc)- Trp-OEt **11b** was obtained as a white solid (186 mg, 84%).

Rf (5% MeOH/dichloromethane): 0.51; $[\alpha]_{\text{D}}^{25} +45$ (c 0.53, CHCl_3); **Mp**: 103-104 °C; ^1H NMR (360 MHz, CDCl_3) δ 9.03 (s, 1H), 7.69 (d, $J = 2.3$ Hz, 1H), 7.45 (d, $J = 8.1$ Hz, 1H), 7.38 (d, $J = 8.1$ Hz, 1H), 7.13 (app. t, $J = 7.4$ Hz, 1H), 7.03 (app. t, $J = 7.4$ Hz, 1H), 6.19 (d, $J = 8.4$ Hz, 1H), 5.32 (d, $J = 8.2$ Hz, 1H), 4.96-4.89 (m, 1H), 4.11-3.90 (m, 2H), 3.46 (d of A of AB quartet, $J = 14.6, 3.7$ Hz, 1H), 3.21 (d of B of AB quartet, $J = 14.6, 4.9$ Hz, 1H), 3.01-2.94 (m, 1H), 2.83-2.69 (m, 1H), 2.62-2.52 (m, 1H), 2.41-2.26 (m, 1H), 2.18-2.09 (m, 1H), 1.73 (dd, $J = 13.6, 6.8$ Hz, 2H), 1.53 (s, 9H), 1.35-1.27 (m, 1H), 1.24 (s, 9H), 1.16 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (90 MHz, CDCl_3) δ 178.0 (C), 175.5 (C), 171.4 (C), 169.6 (C), 152.4 (C), 151.0 (C), 136.0 (C), 127.6 (C), 125.3 (CH), 121.5 (CH), 118.9 (CH), 118.3 (CH), 111.5 (CH), 108.0 (C), 84.4 (C), 84.3 (C), 61.6 (CH), 61.5 (CH_2), 51.6 (CH), 35.2 (CH), 31.3 (CH_2), 28.0 (3CH_3), 27.9 (CH_2), 27.5 (3CH_3), 25.7 (CH), 21.1 (CH_2), 17.0 (CH_2), 14.0 (CH_3); HRMS (ESI+) m/z : theor. 649.2844 (calc. for $\text{C}_{32}\text{H}_{42}\text{N}_4\text{O}_9\text{Na}$), meas. 649.2849.

General procedure G for the tert-butoxycarbonyl cleavage of the protected tripeptide 11 using $\text{Mg}(\text{ClO}_4)_2$:

To a solution of protected tripeptide **11a-b** (1.0 equiv.) in dichloromethane (80 mL/mmol) under argon atmosphere was added $\text{Mg}(\text{ClO}_4)_2$ (4.0 equiv.) by portion over 8 h and the reaction mixture was concentrated under reduced pressure. The crude product was then purified by column chromatography using the appropriate mixture of eluents to give the corresponding product **12a-b**.

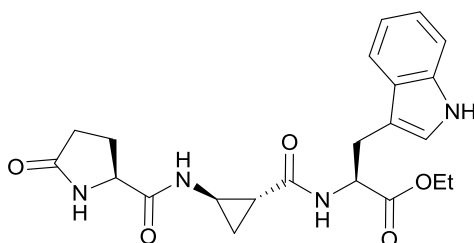
BocNH-Gly-*t*ACPrC-Trp-OEt 12a



From a solution of acid **11a** (34 mg, 0.05 mmol) and $\text{Mg}(\text{ClO}_4)_2$ (44 mg, 0.2 mmol) in dichloromethane (5 mL) following the general procedure **G** and after purification by column chromatography (2% to 10% MeOH/dichloromethane), BocNH-Gly-*t*ACPrC-Trp-OEt **12a** was obtained as a white solid (17 mg, 71%).

Rf (10% MeOH/dichloromethane): 0.5; $[\alpha]_{\text{D}}^{20}$ -22 (c 0.15, MeOH); **Mp**: 98-100 °C; **^1H NMR (400 MHz, CD_3OD)** δ 7.53 (d, J = 7.9 Hz, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.15 (s, 1H), 7.08 (app. t, J = 7.5 Hz, 1H), 7.01 (app. t, J = 7.5 Hz, 1H), 4.70 (app. t, J = 6.7 Hz, 1H), 4.57 (br. s, 1H), 4.07 (d of A of AB quartet, J = 7.0, 3.1 Hz, 1H), 4.04 (d of B of AB quartet, J = 7.0, 2.9 Hz, 1H), 3.66 (br. s, 2H), 3.28 (d of A of AB quartet, J = 14.5, 6.2 Hz, 1H), 3.20 (d of B of AB quartet, J = 14.5, 7.1 Hz, 1H), 3.07- 2.99 (m, 1H), 1.78 (ddd, J = 8.8, 5.7, 2.9 Hz, 1H), 1.45 (s, 9H), 1.33-1.23 (m, 2H), 1.11 (t, J = 7.1 Hz, 3H), 3NH are not observed; **^{13}C NMR (100 MHz, CD_3OD)** δ 173.70 (C), 173.67 (C), 173.6 (C), 158.5 (C), 138.0 (C), 128.8 (C), 124.7 (CH), 122.4 (CH), 119.8 (CH), 119.2 (CH), 112.3 (CH), 110.5 (C), 80.8 (C), 62.3 (CH_2), 55.2 (CH), 44.5 (CH_2), 31.3 (CH), 28.7 (3CH_3), 28.6 (CH_2), 23.7 (CH), 14.3 (CH_3), 13.8 (CH_2); **HRMS (ESI+)** m/z : theor. 473.2395 (calc. for $\text{C}_{24}\text{H}_{33}\text{N}_4\text{O}_6$), meas. 473.2390.

NH-Pyr-*t*ACPrC-Trp-OEt **12b**

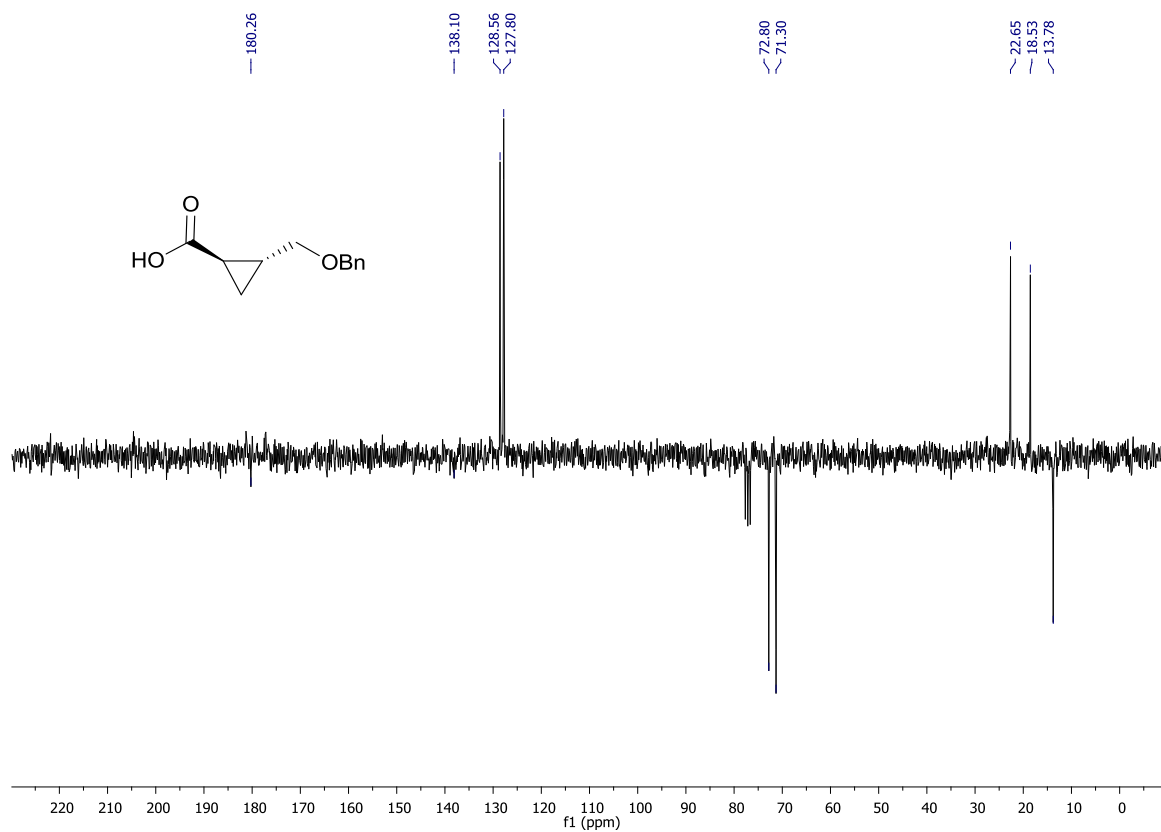
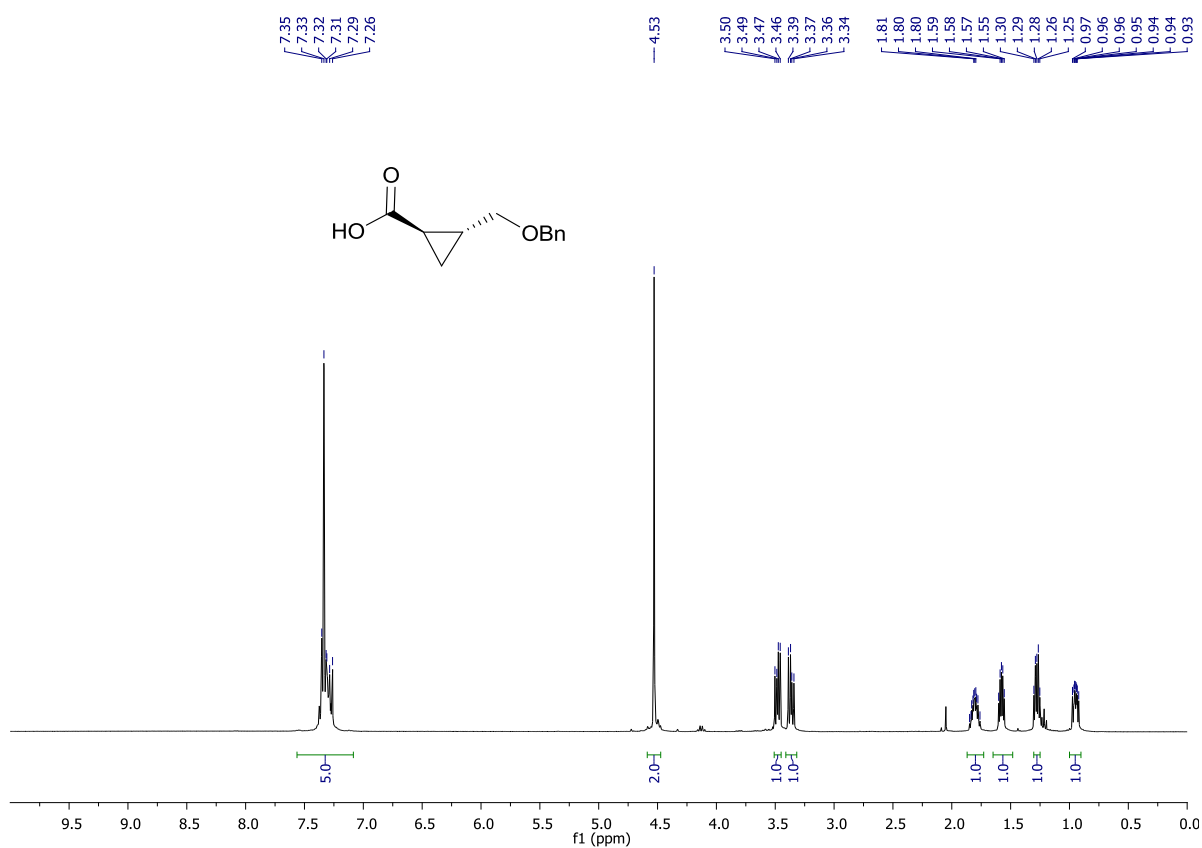


From a solution of acid **11b** (45 mg, 0.07 mmol) and $\text{Mg}(\text{ClO}_4)_2$ (64 mg, 0.29 mmol) in dichloromethane (5 mL) following the general procedure **G** and after purification by column chromatography (5% to 10% MeOH/dichloromethane), BocNH-Pyr-*t*ACPrC-Trp-OEt **12b** was obtained as a white solid (22 mg, 72%).

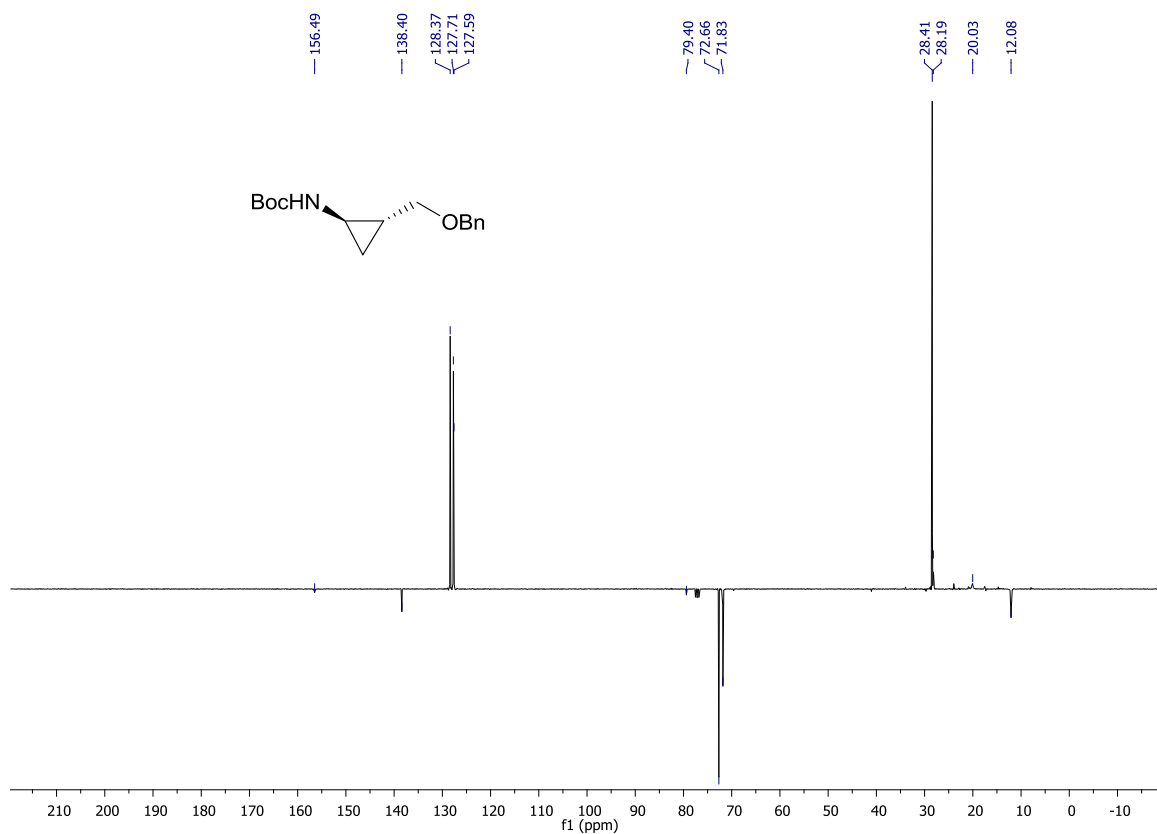
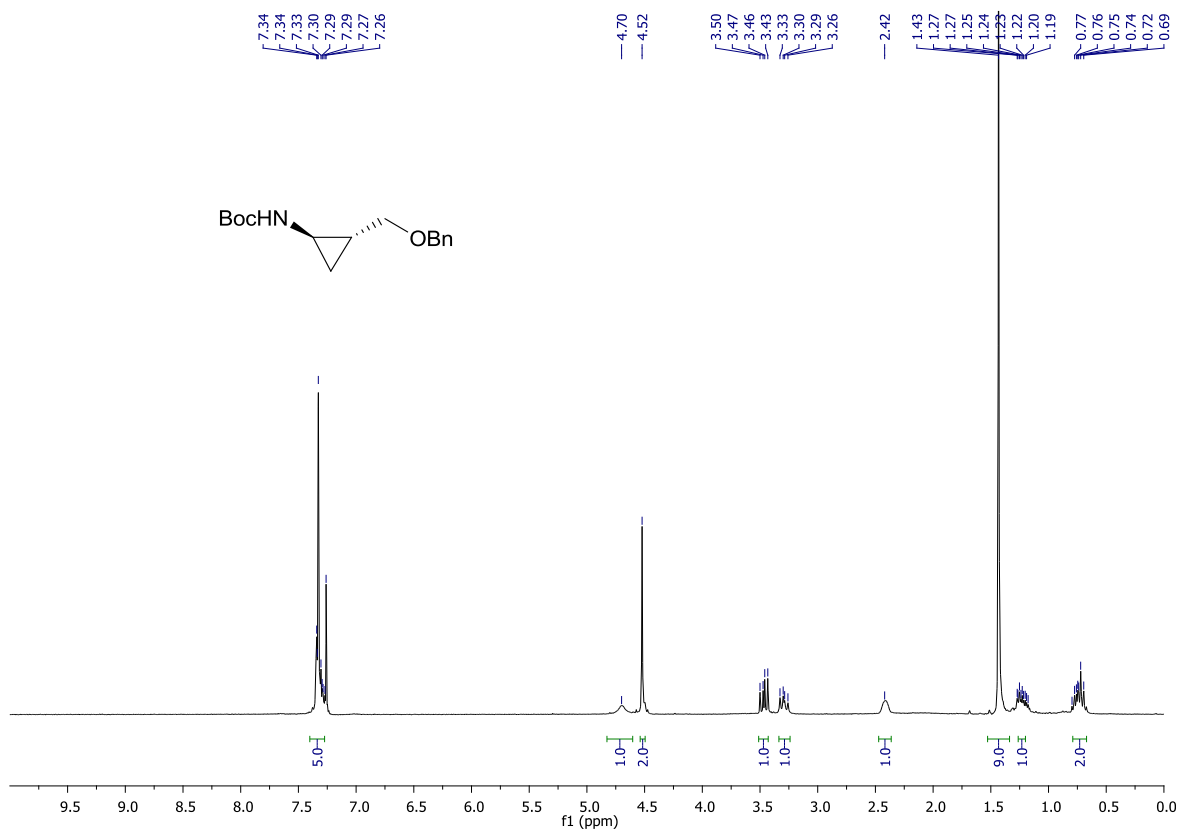
Rf (10% MeOH/dichloromethane): 0.33; $[\alpha]_{\text{D}}^{20}$ -5 (c 0.15, MeOH); **Mp**: 120-122 °C; **^1H NMR (360 MHz, CD_3OD)** δ 7.53 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.15 (s, 1H), 7.08 (app. t, J = 7.5 Hz, 1H), 7.01 (app. t, J = 7.5 Hz, 1H), 4.70 (app. t, J = 6.7 Hz, 1H), 4.61 (br. s, 1H), 4.11 (dd, J = 8.3, 4.7 Hz, 1H), 4.08 (d of A of AB quartet, J = 7.1, 2.6 Hz, 1H), 4.04 (d of B of AB quartet, J = 7.1, 2.6 Hz, 1H), 3.28 (d of A of AB quartet, J = 14.4, 6.3 Hz, 1H), 3.20 (d of B of AB quartet, J = 14.4, 7.2 Hz, 1H), 3.07 (ddd, J = 8.0, 5.1, 3.0 Hz, 1H), 2.51-2.25 (m, 3H), 2.11-1.99 (m, 1H), 1.80 (ddd, J = 8.8, 5.7, 3.0 Hz, 1H), 1.32-1.24 (m, 2H), 1.12 (t, J = 7.1 Hz, 3H), 3NH are not observed; **^{13}C NMR (90 MHz, CD_3OD)** δ 181.6 (C), 176.0 (C), 173.7 (C), 173.6 (C), 137.9 (C), 128.7 (C), 124.7 (CH), 122.4 (CH), 119.8 (CH), 119.1 (CH), 112.3 (CH), 110.4 (C), 62.3 (CH_2), 58.0 (CH), 55.2 (CH), 31.4 (CH), 30.5 (CH_2), 28.6 (CH_2), 26.6 (CH_2), 23.5 (CH), 14.2 (CH_3), 13.9 (CH_2); **HRMS (ESI+)** m/z : theor. 449.1795 (calc. for $\text{C}_{22}\text{H}_{26}\text{N}_4\text{O}_5\text{Na}$), meas. 449.1778.

3. Supplementary figures: ^1H and ^{13}C NMR spectra

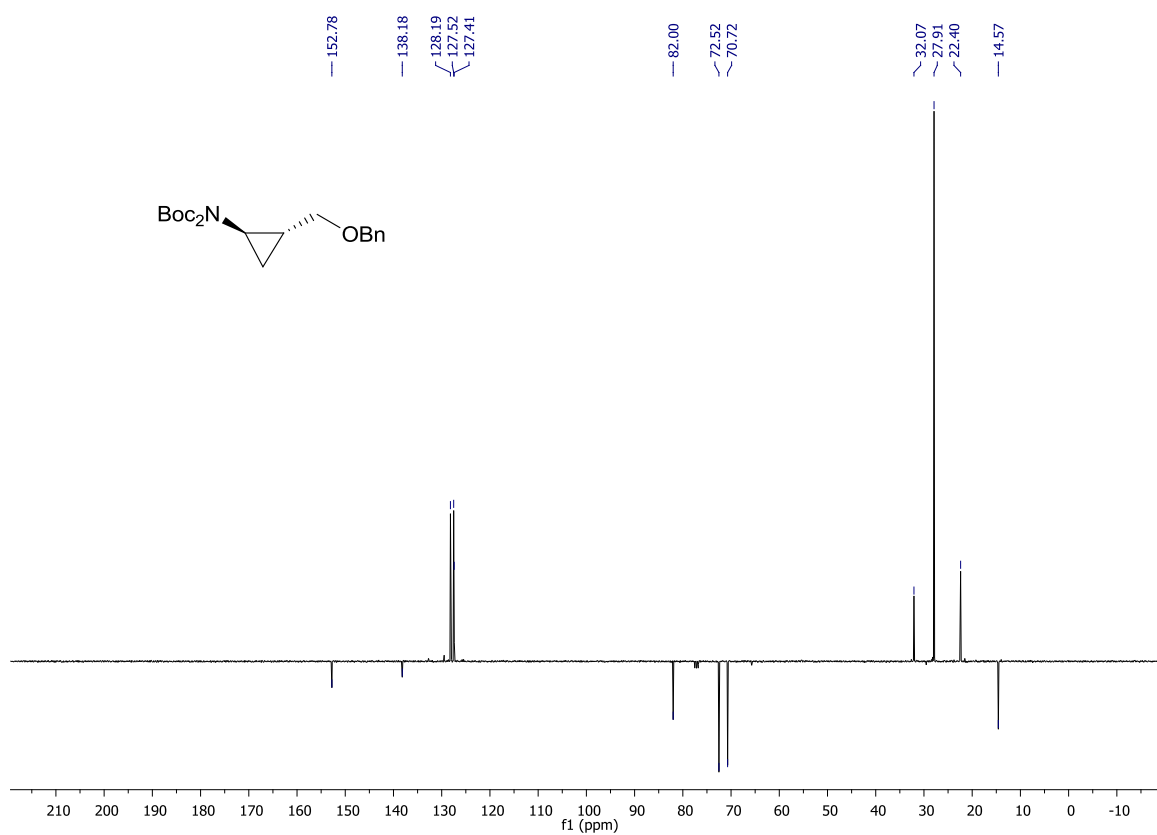
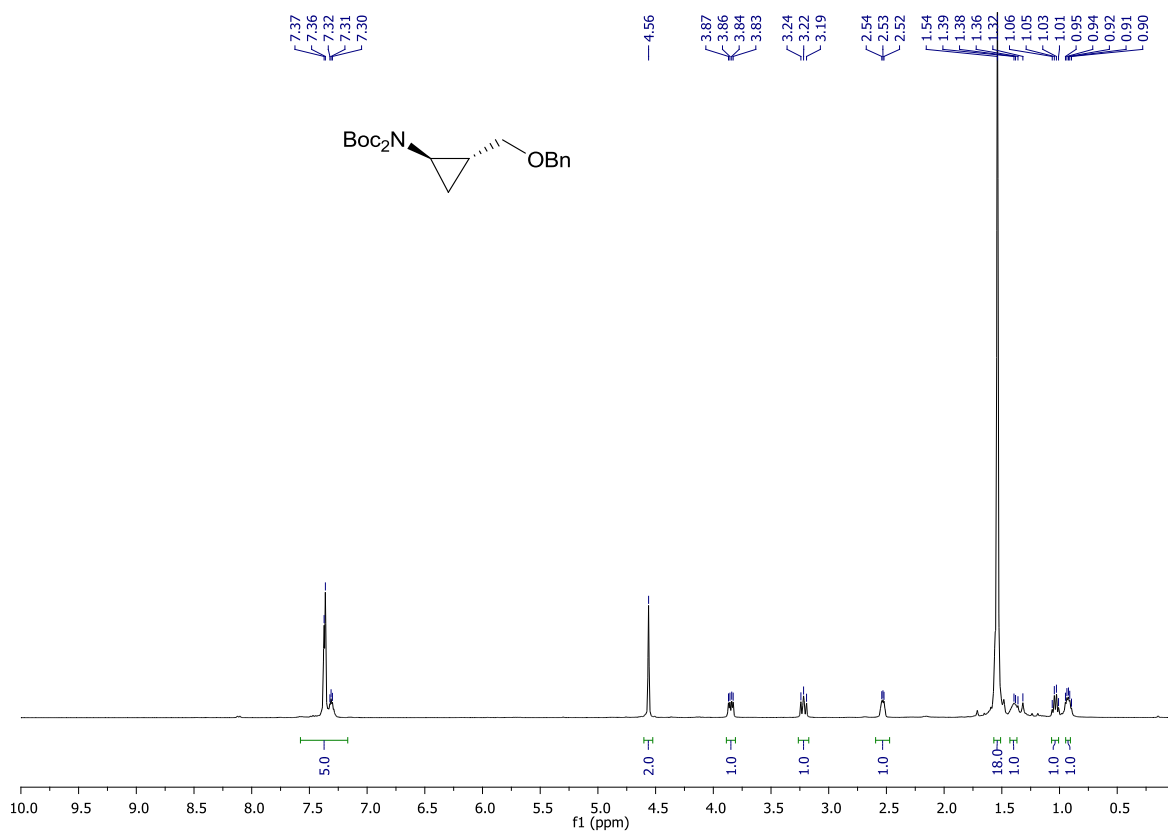
(1*R*,2*R*)-2-((Benzyloxy)methyl)cyclopropanecarboxylic acid II



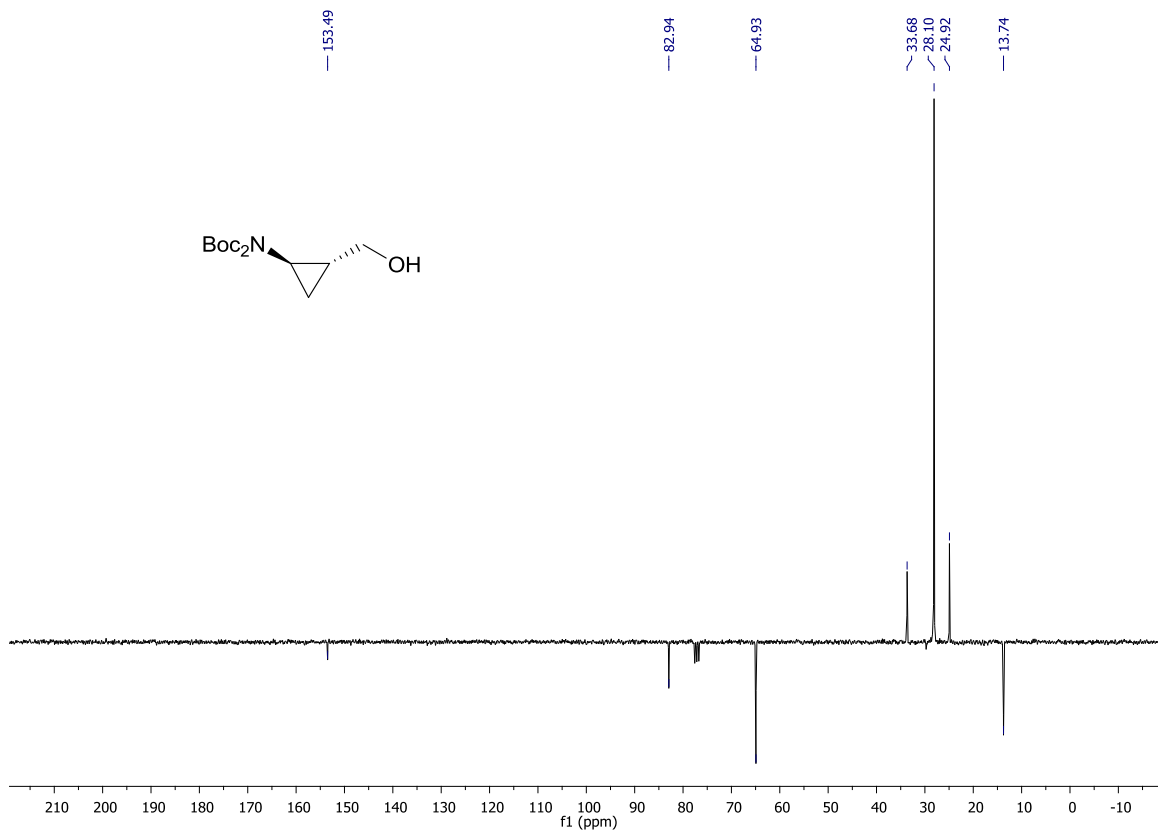
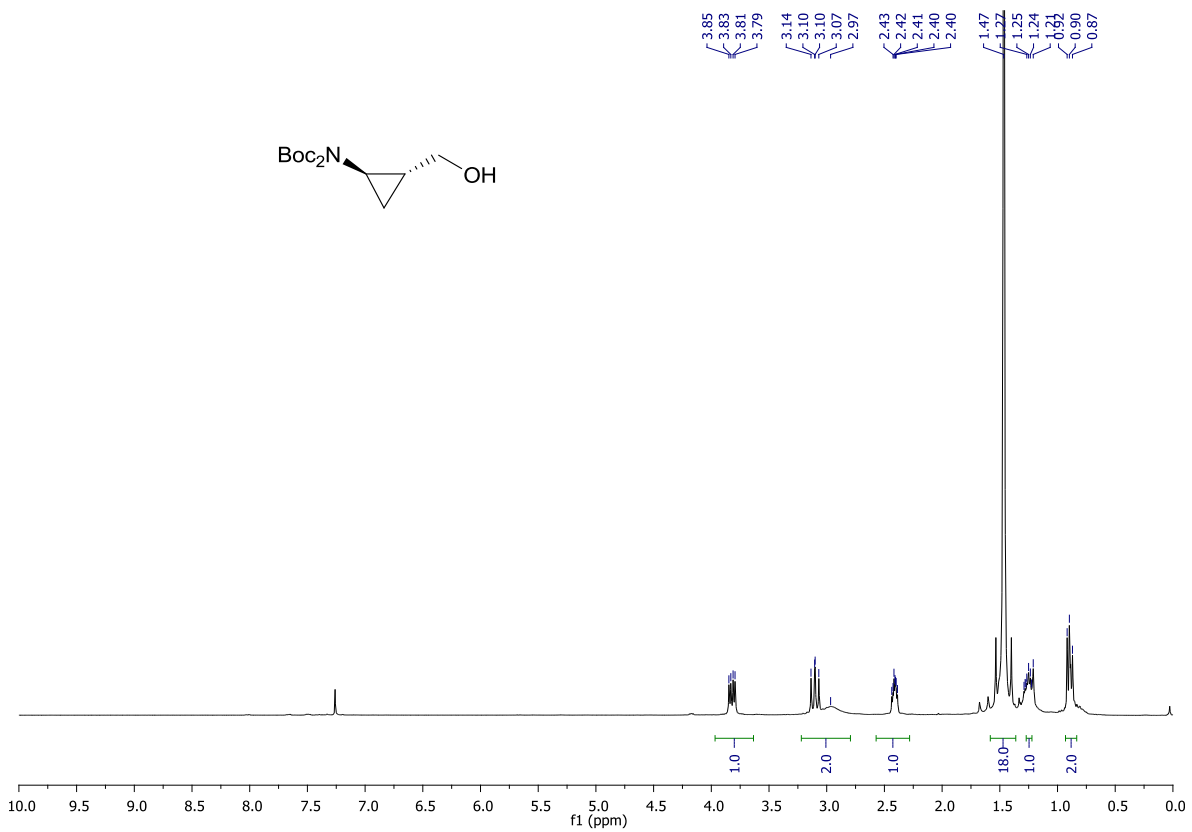
tert*-Butyl ((1*R*,2*R*)-2-((benzyloxy)methyl)cyclopropyl)carbamate **2*



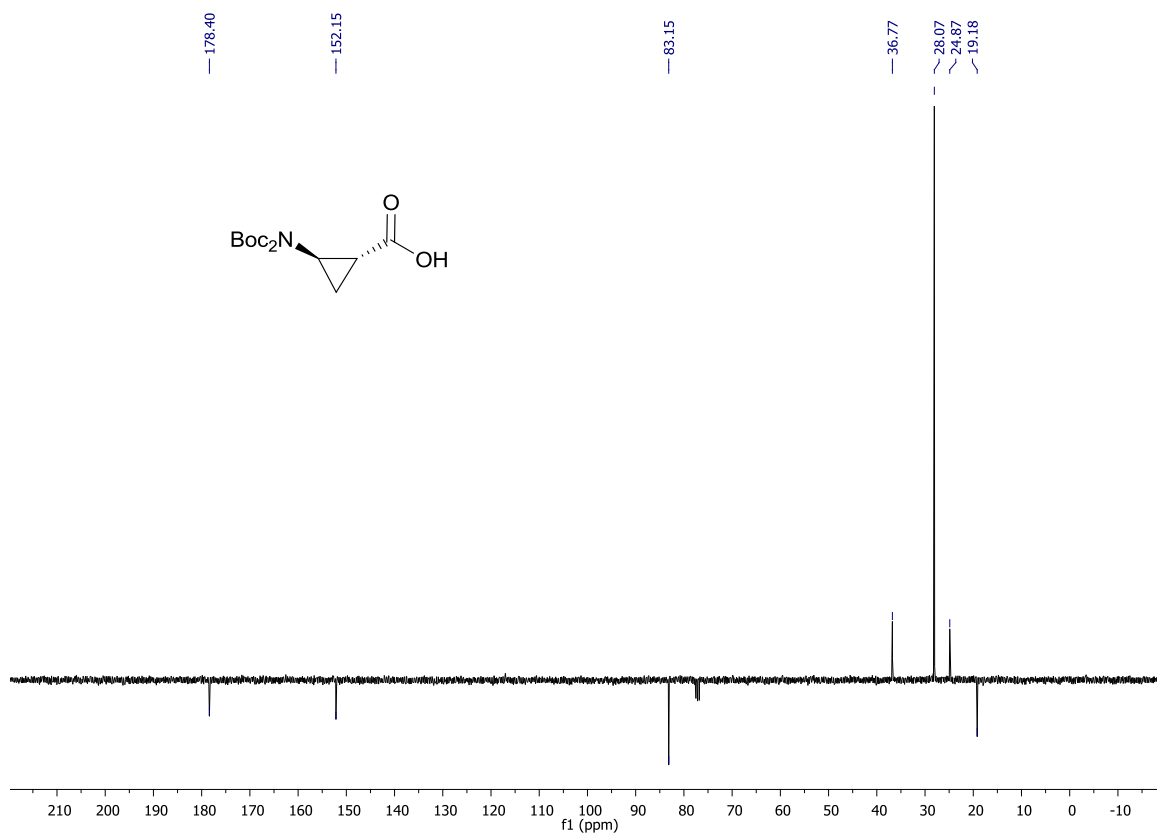
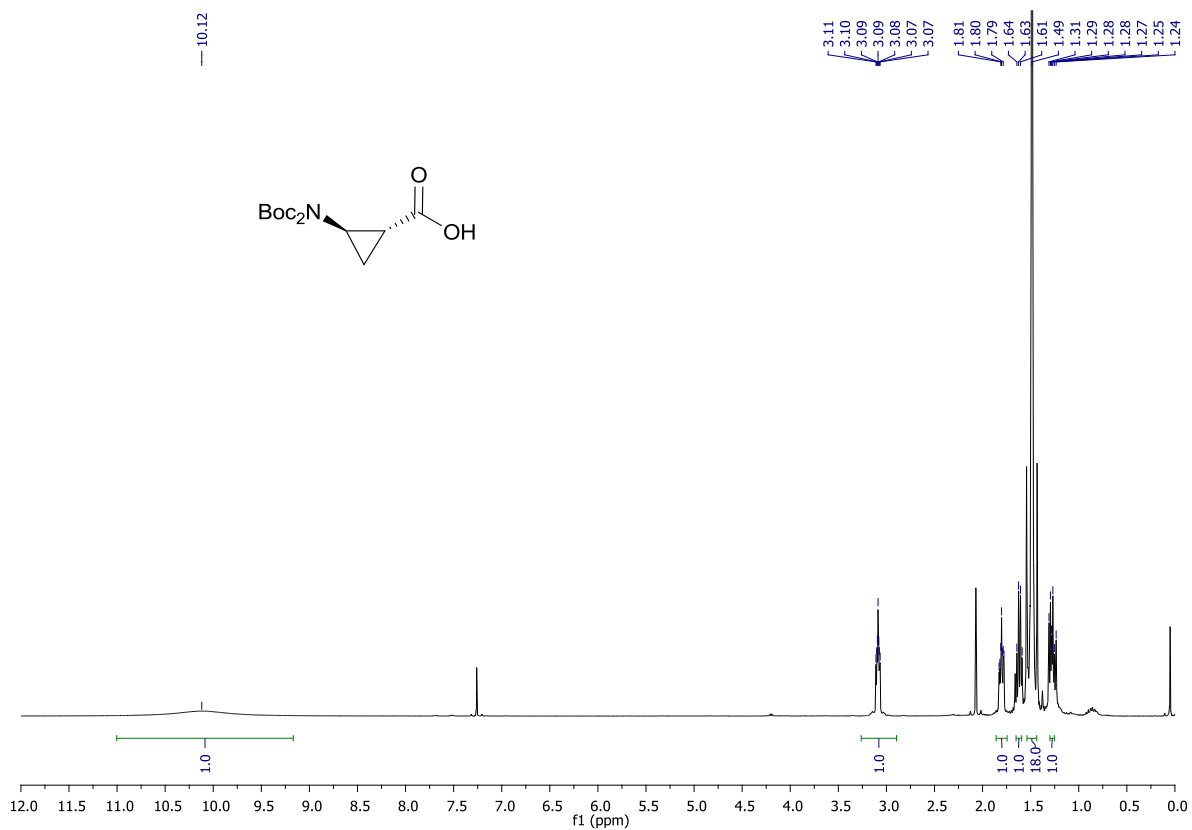
(1*R*,2*R*)-*O*-Benzyl-*N,N*-di-Boc 2-aminocyclopropane alcohol III



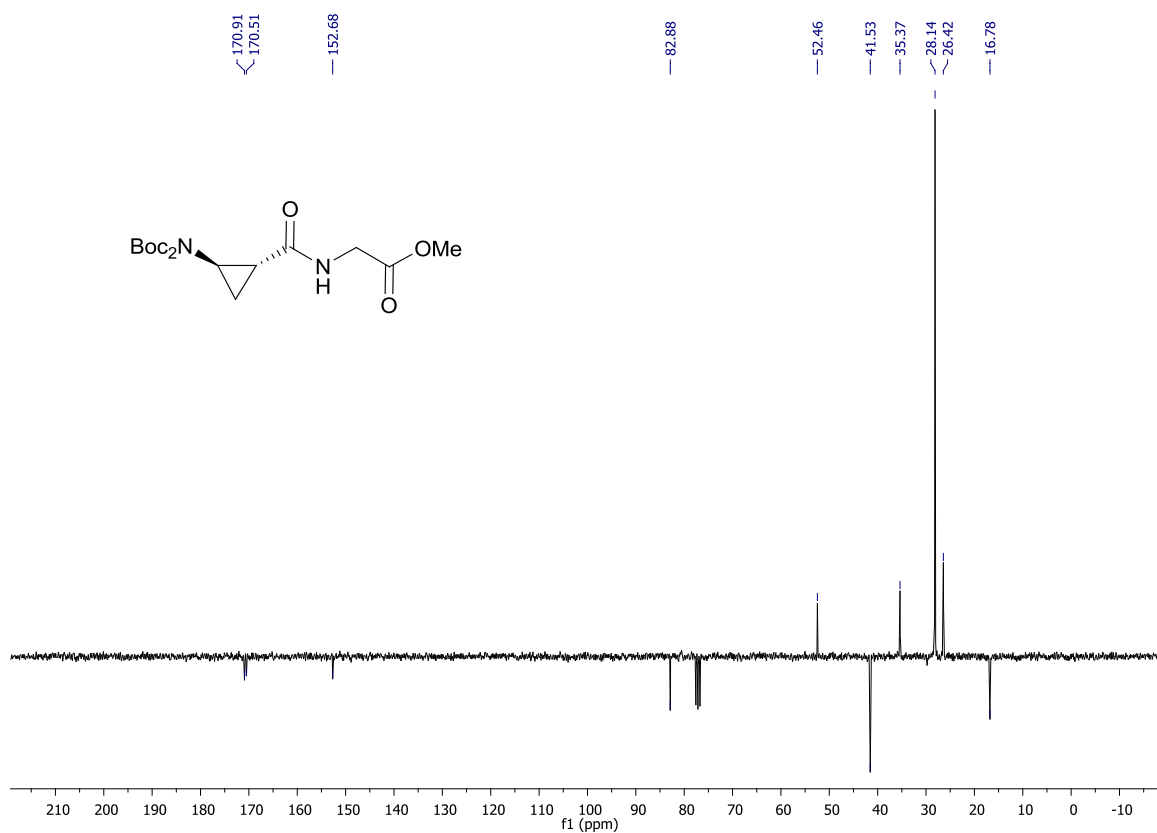
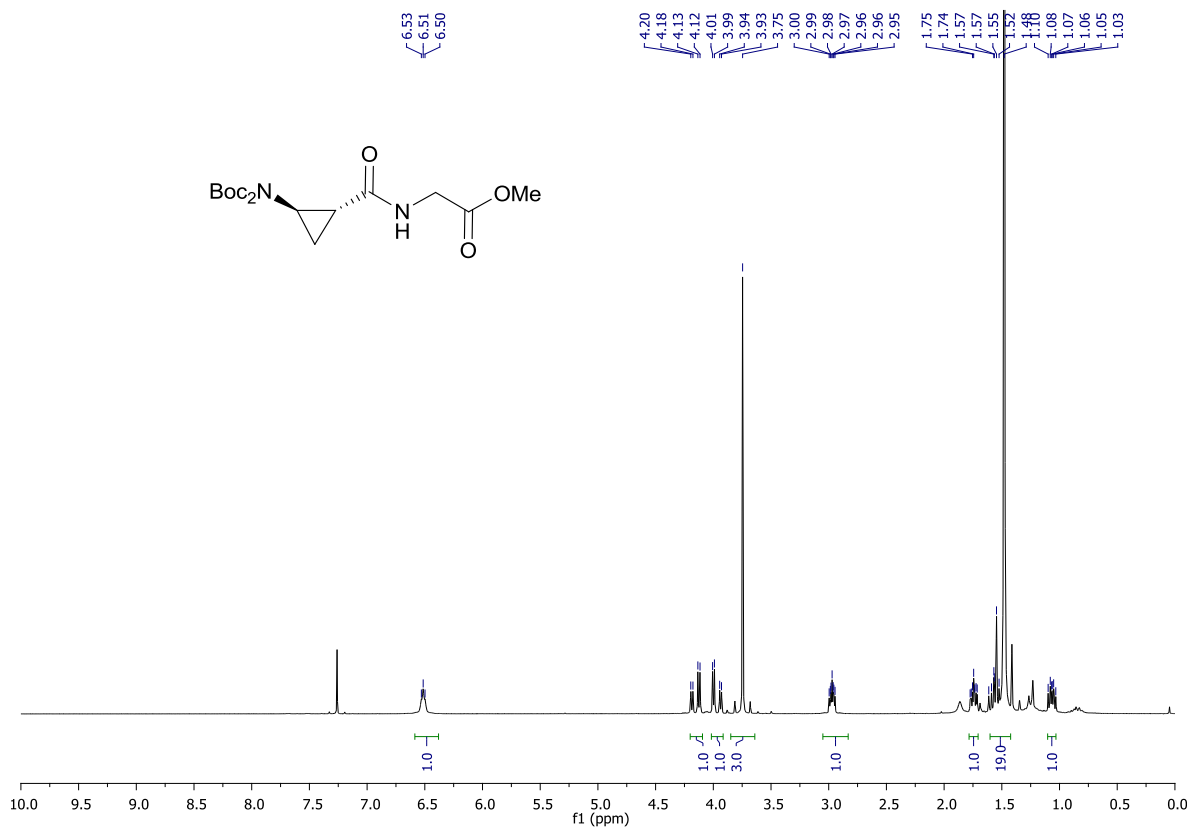
(1*R*,2*R*)-*N,N*-Di-Boc 2-aminocyclopropane alcohol IV



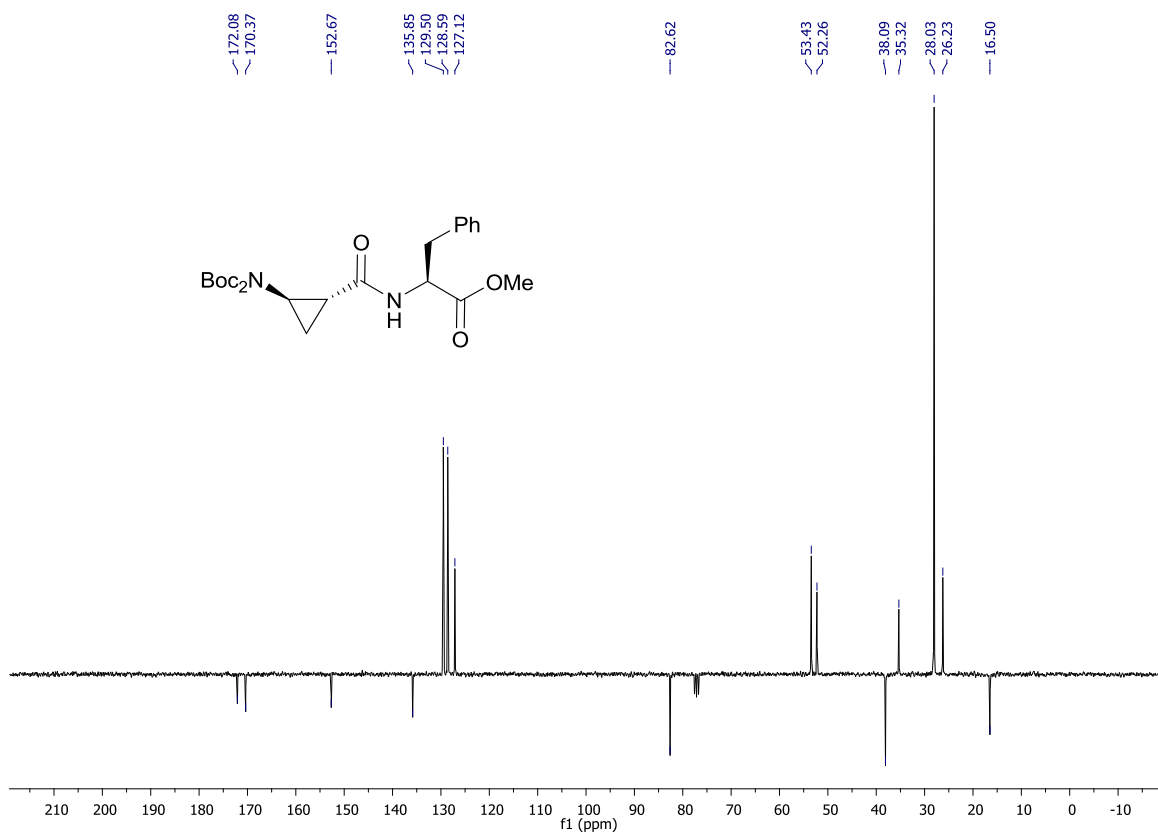
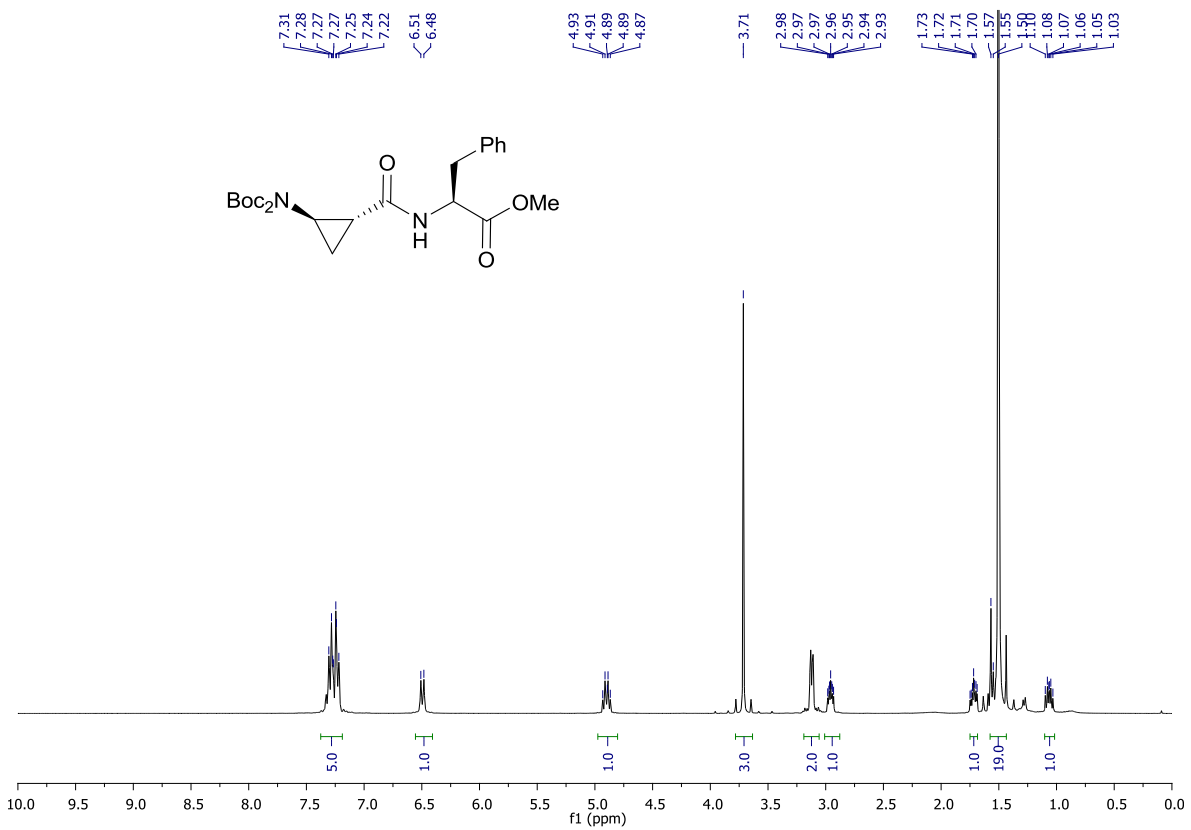
(1*R*,2*R*)-*N,N*-Di-Boc 2-aminocyclopropane carboxylic acid 1



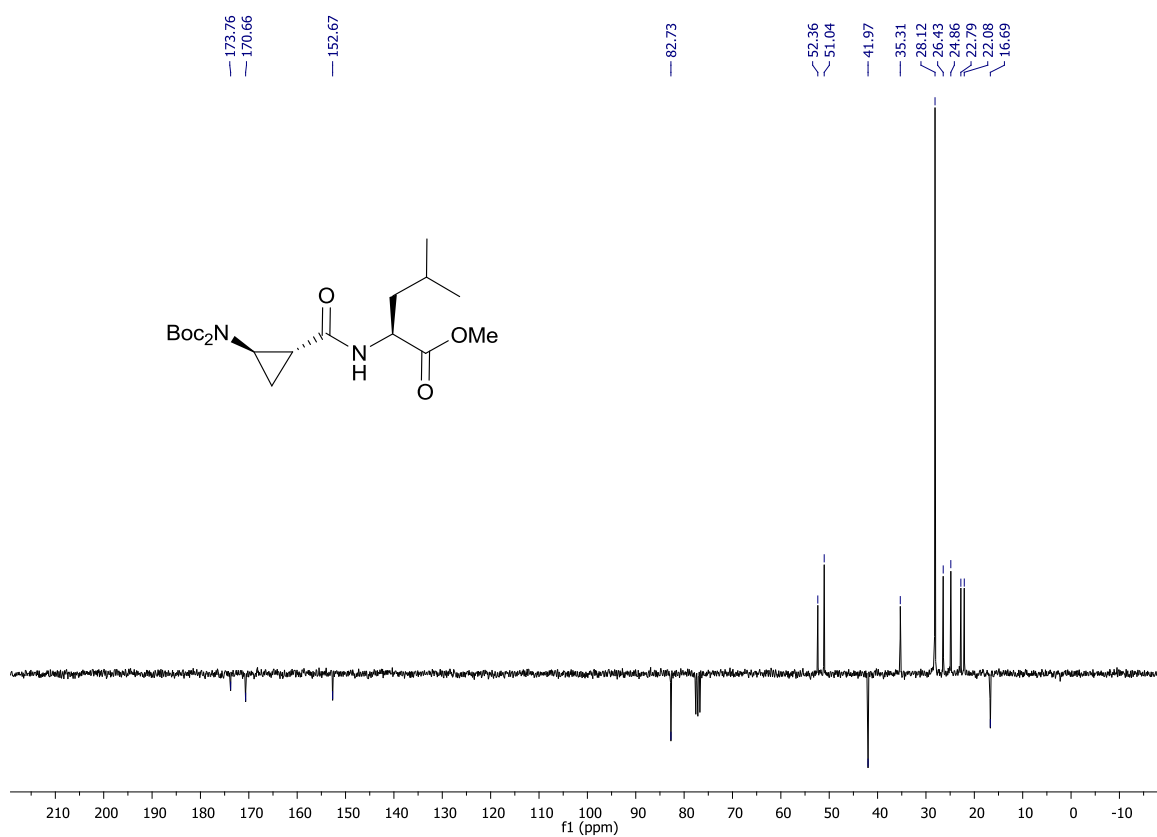
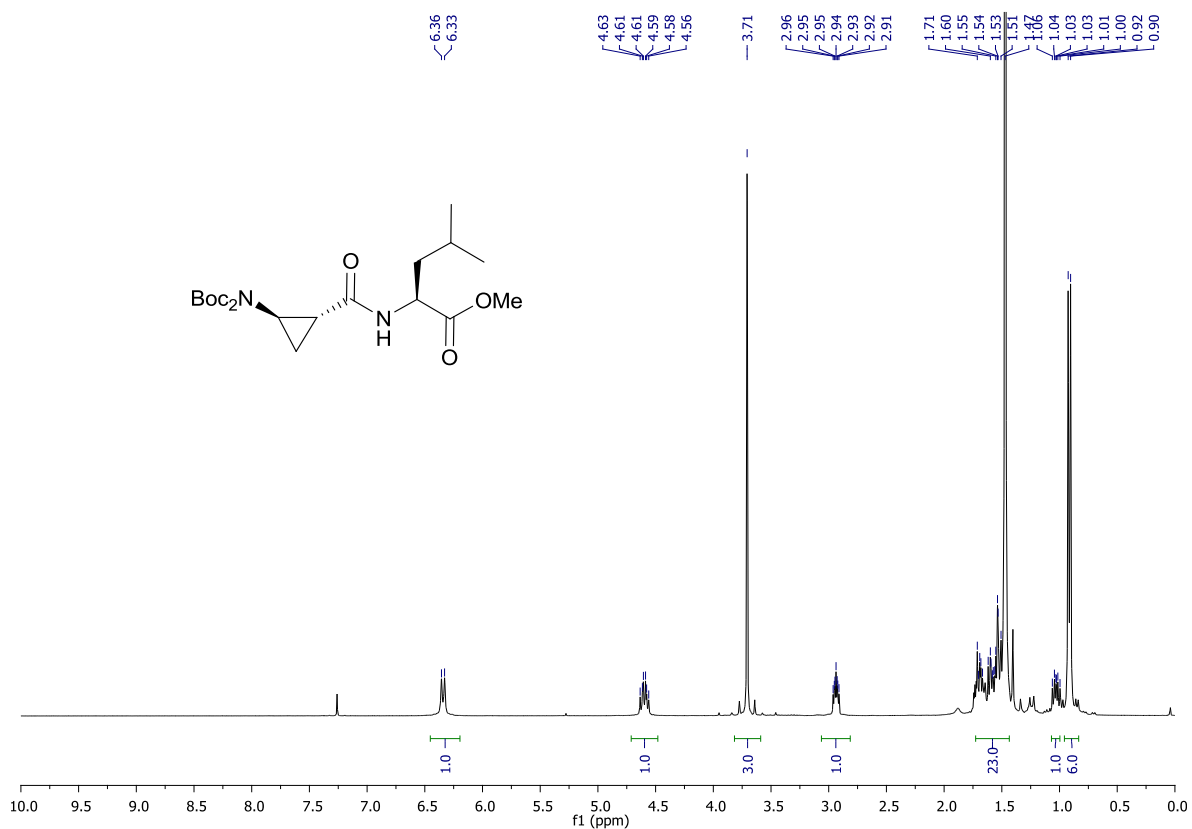
Boc₂N-*t*ACPrC-Gly-OMe 4a



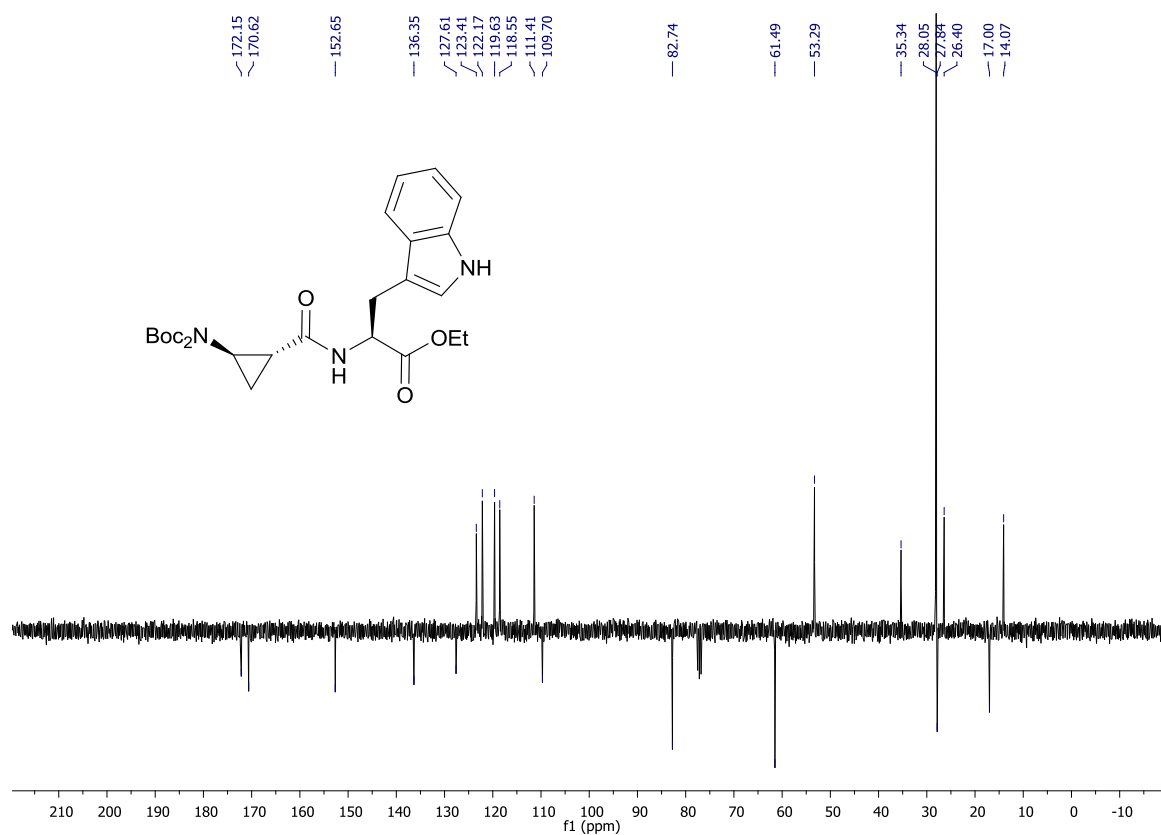
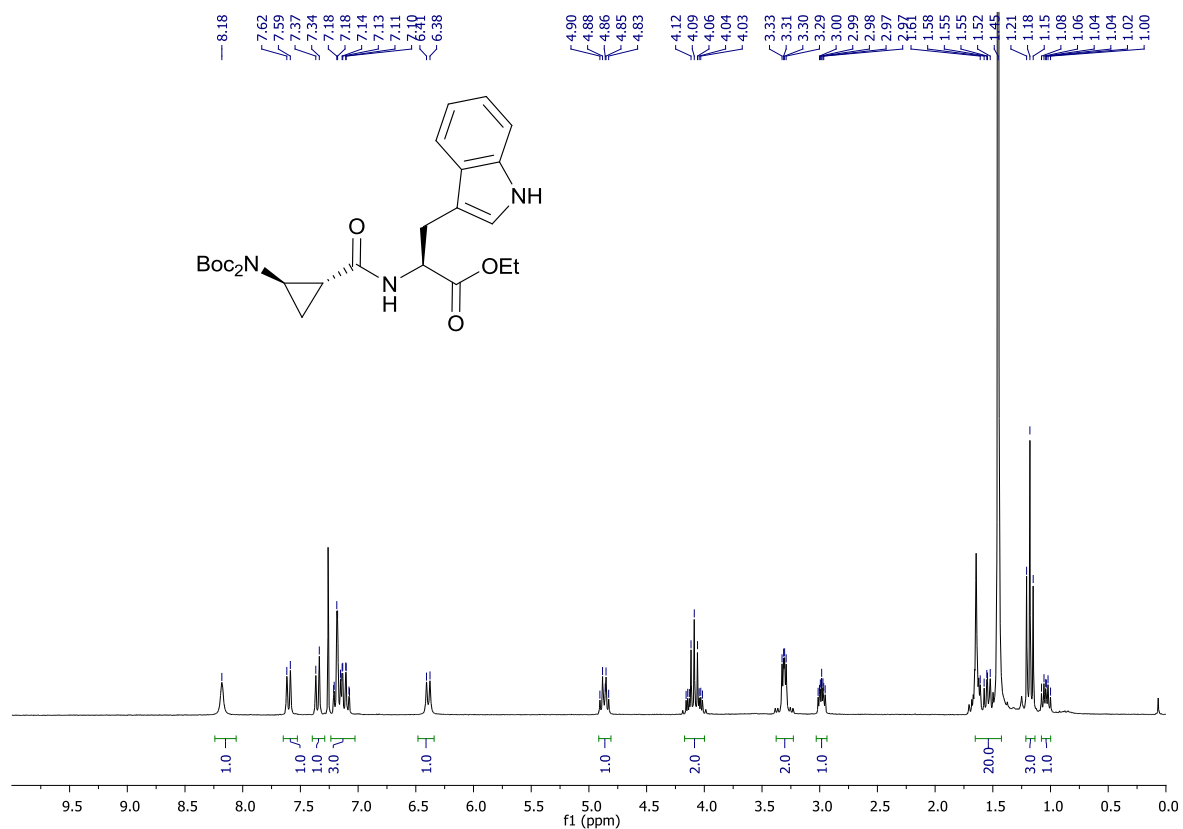
Boc₂N-*t*ACPrC-Phe-OMe 4b



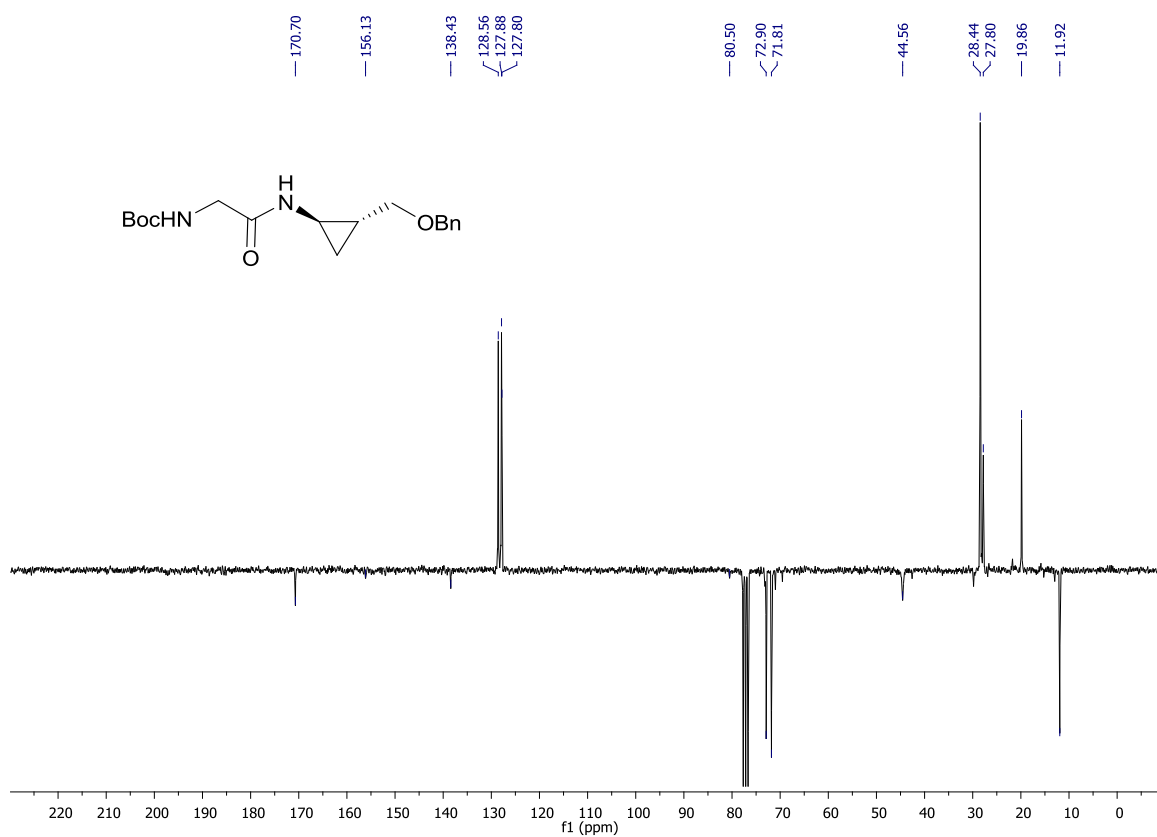
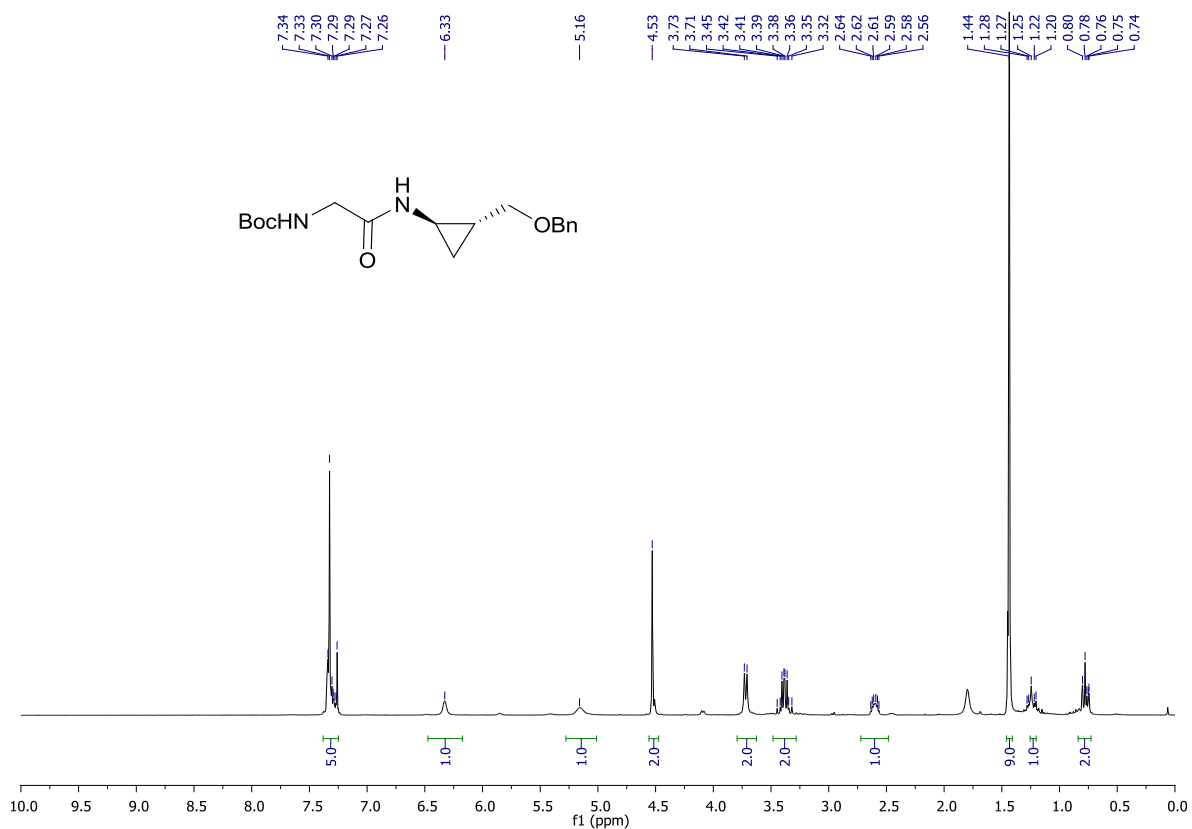
Boc₂N-*t*ACPrC-Leu-OMe 4c



Boc₂N-*t*ACPrC-Trp-OEt 4d

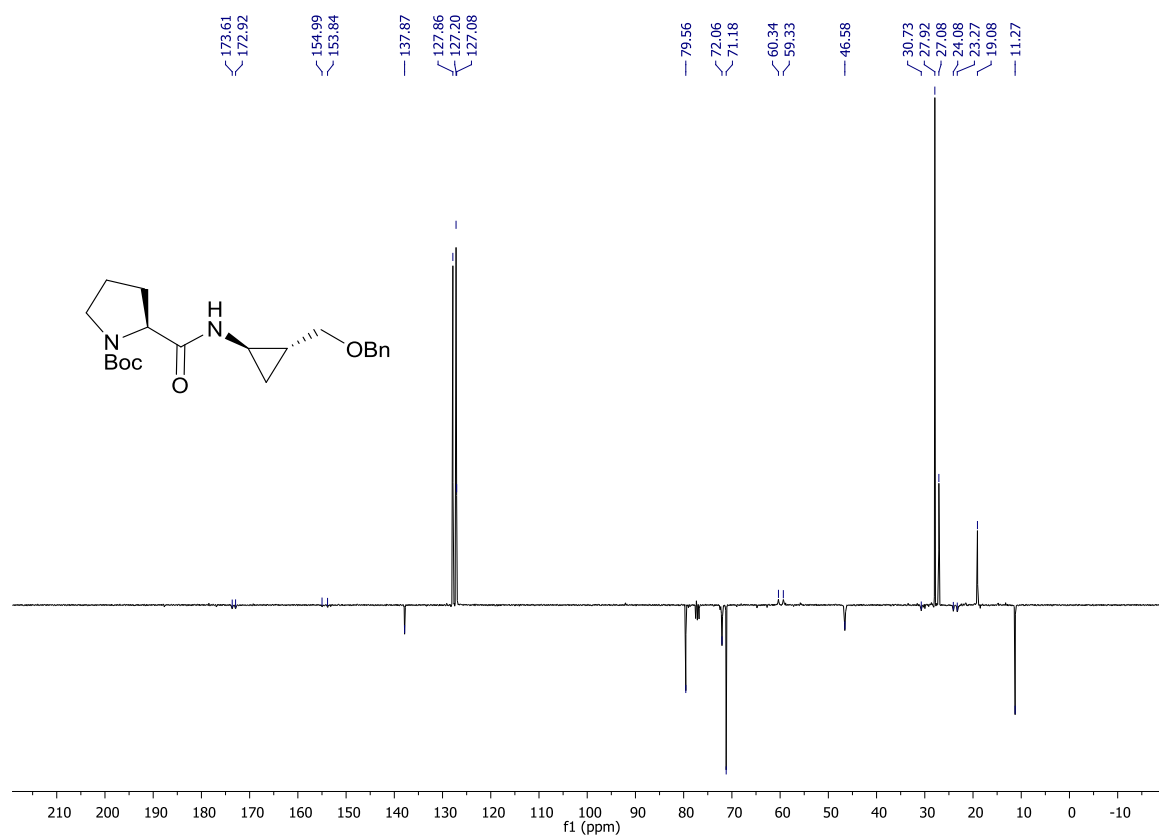
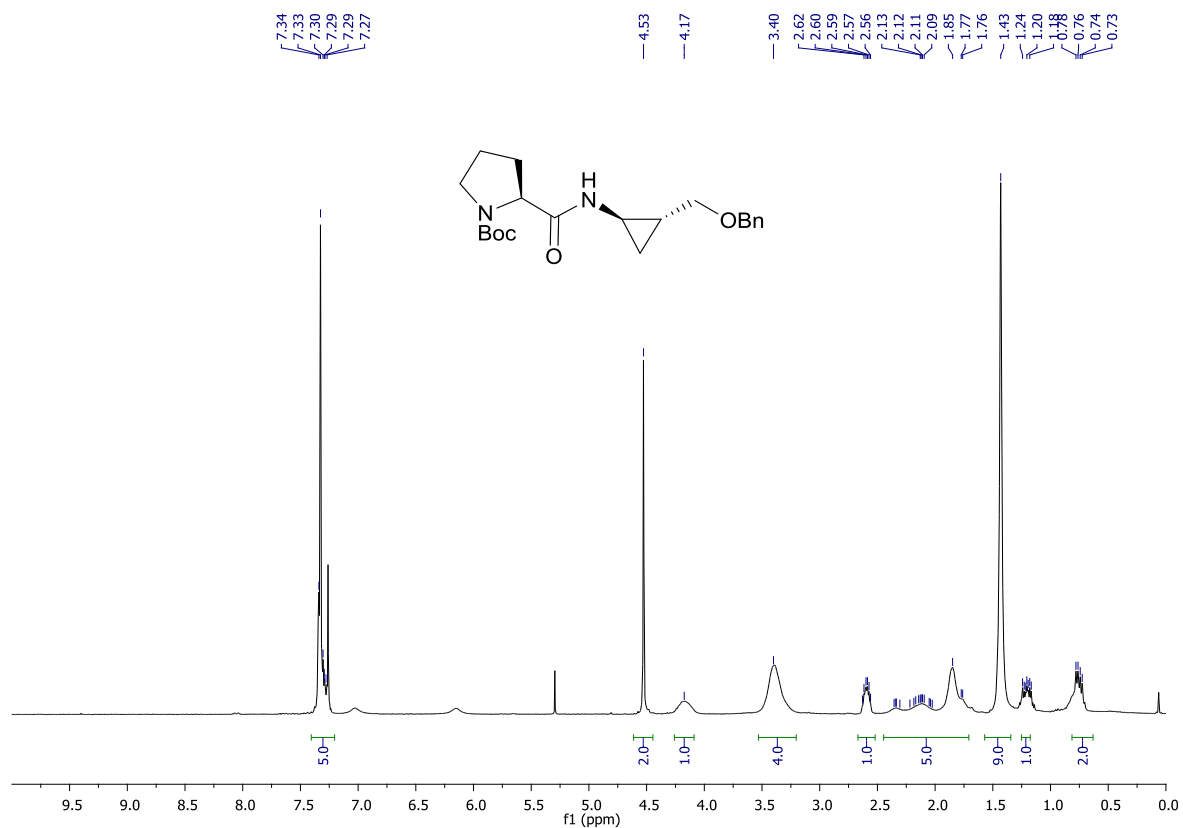


tert*-butyl 2-(((1*R*,2*R*)-2-(benzyloxymethyl)cyclopropylamino)-2-oxoethylcarbamate **7a*

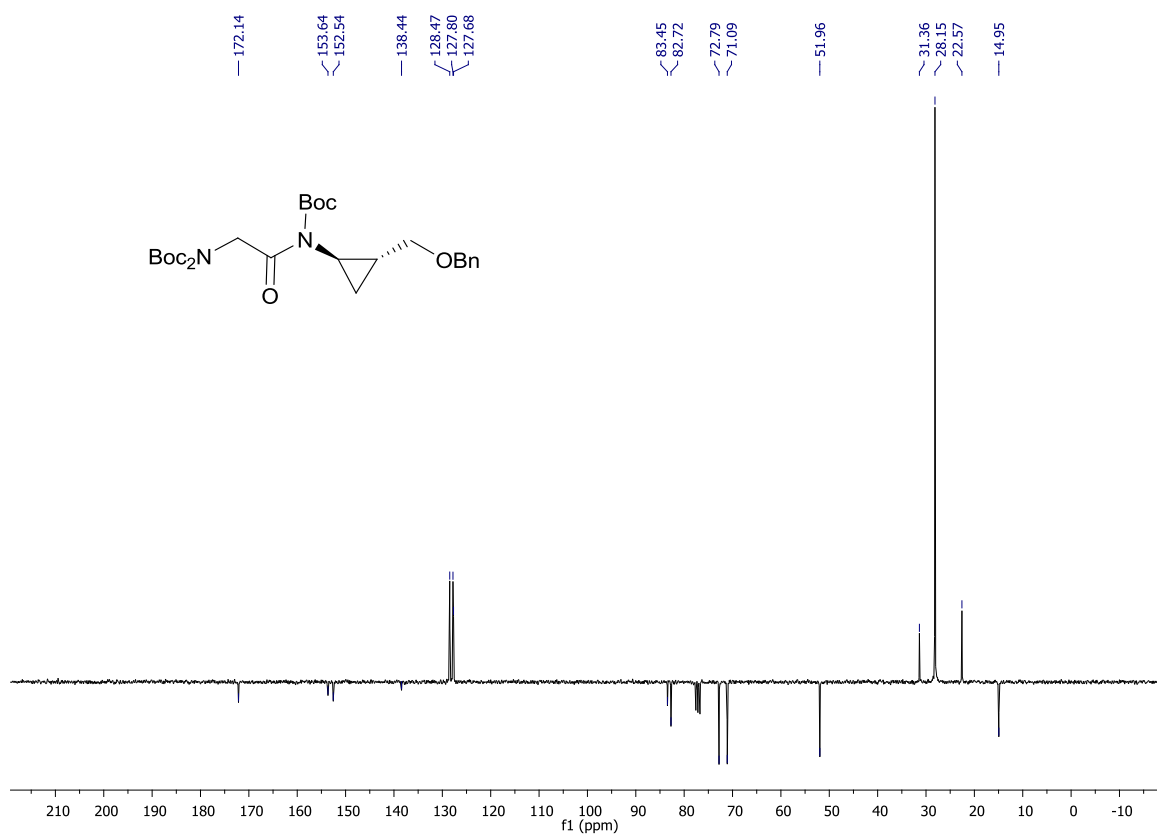
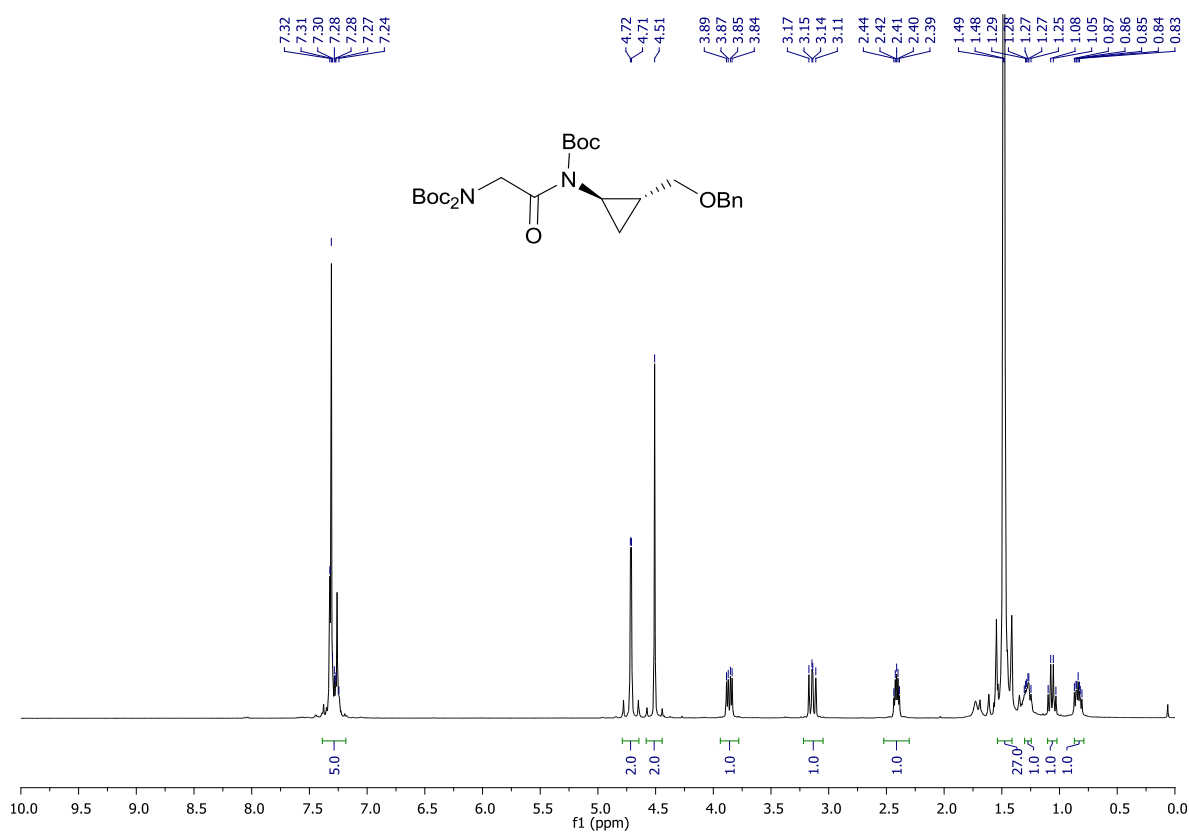


(*S*)-tert-butyl 2-((1*R*,2*R*)-2-(benzyloxymethyl)cyclopropylcarbamoyl)pyrrolidine-1-carboxylate
7b

(2 conformers; ratio 1:1)

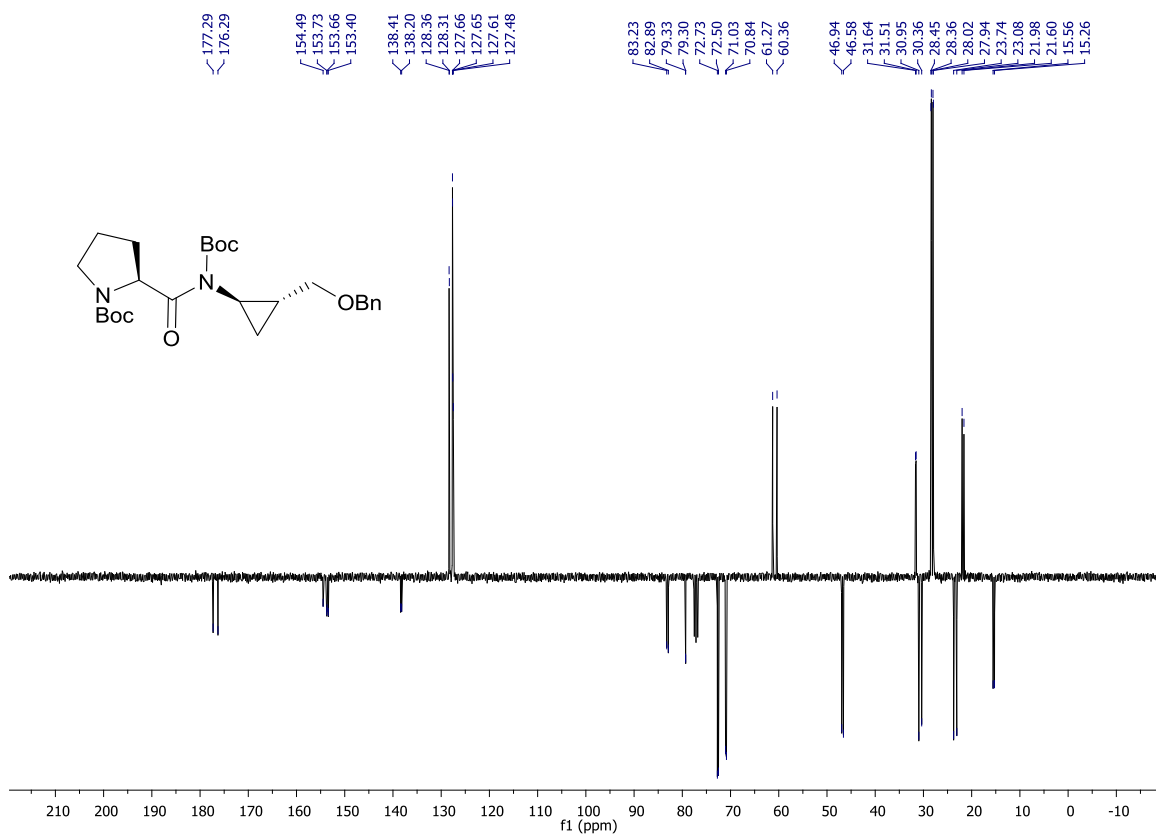
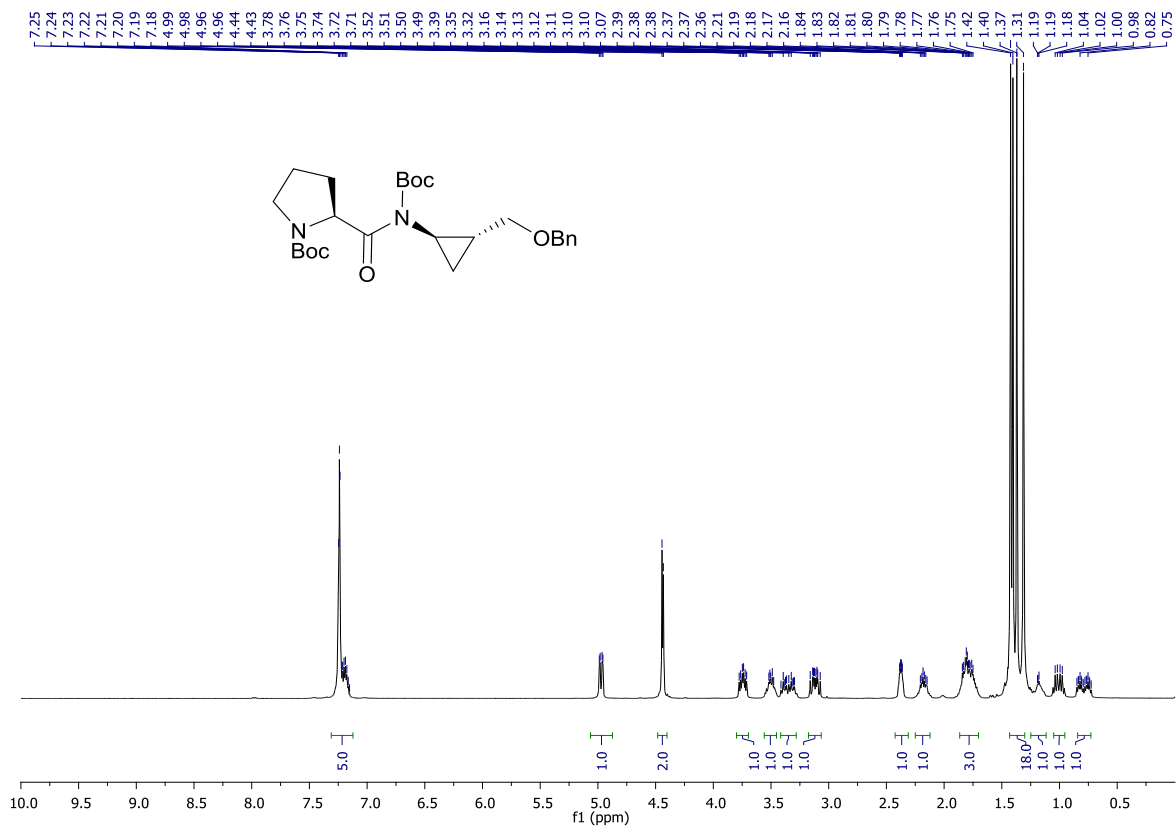


***tert*-butyl 2-di(*tert*-butoxycarbonyl)aminoacetyl((1*R*,2*R*)-2-(benzyloxymethyl)cyclopropyl)carbamate 8a**

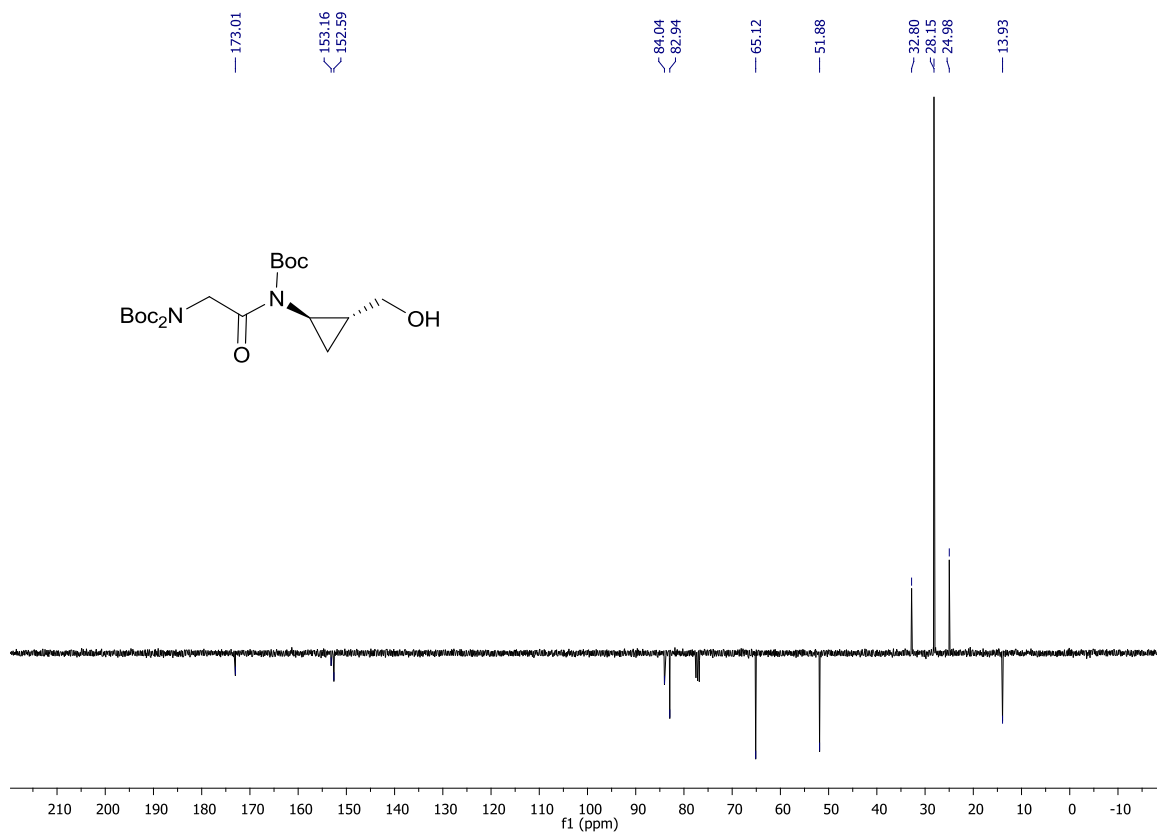
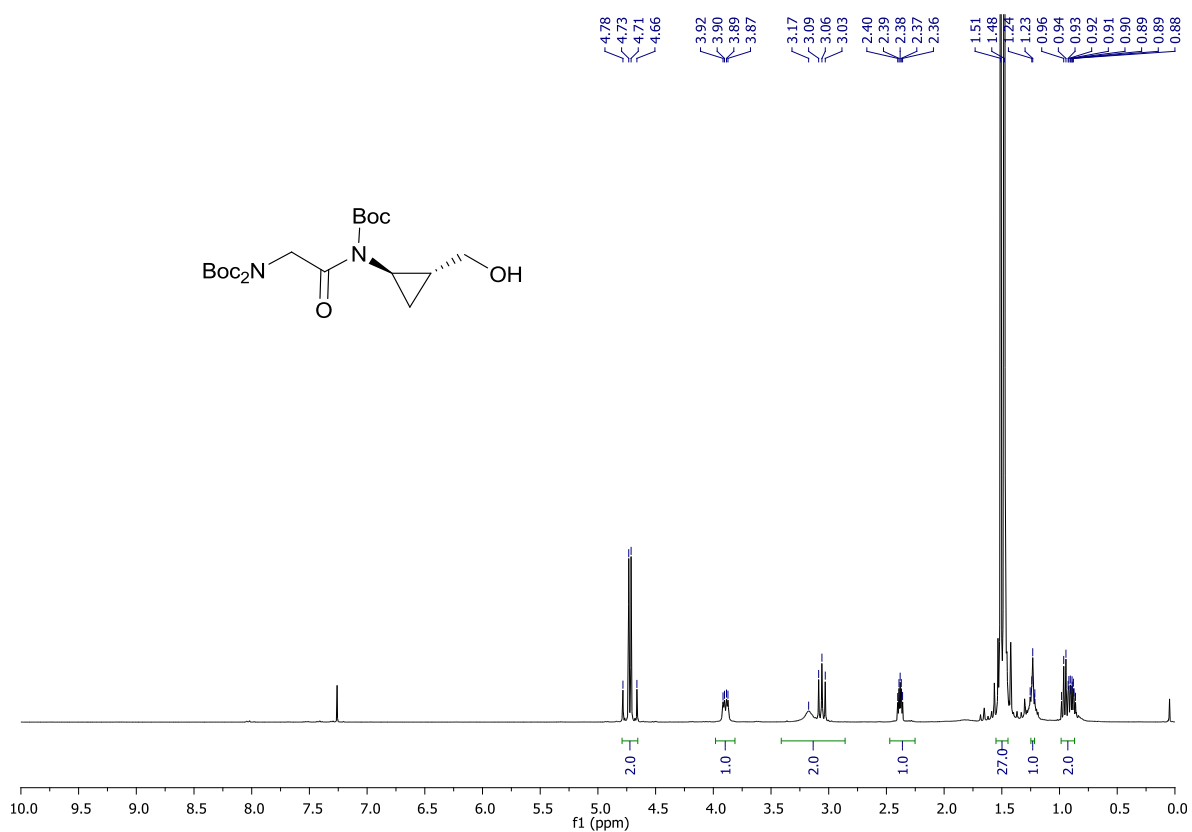


(S)-tert-butyl 2-(((1R,2R)-2-(benzyloxymethyl)cyclopropyl)(tert-butoxycarbonyl)carbamoyl)pyrrolidine-1-carboxylate 8b

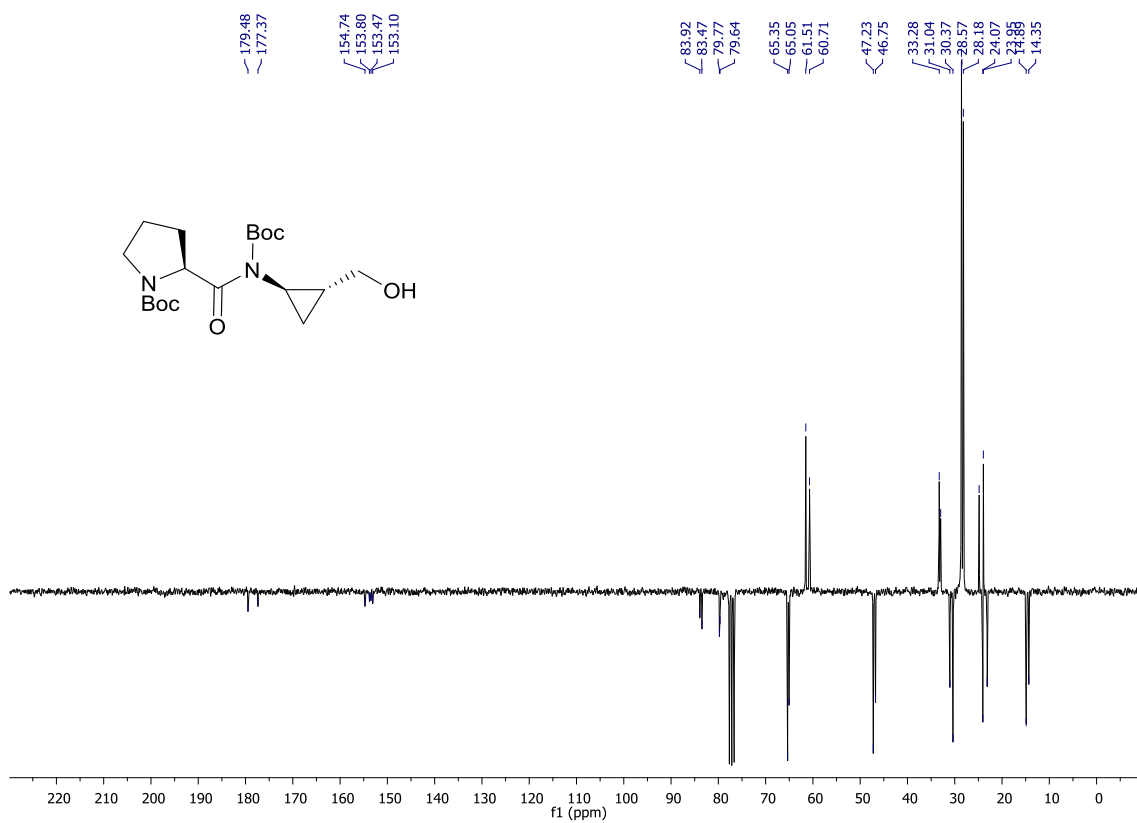
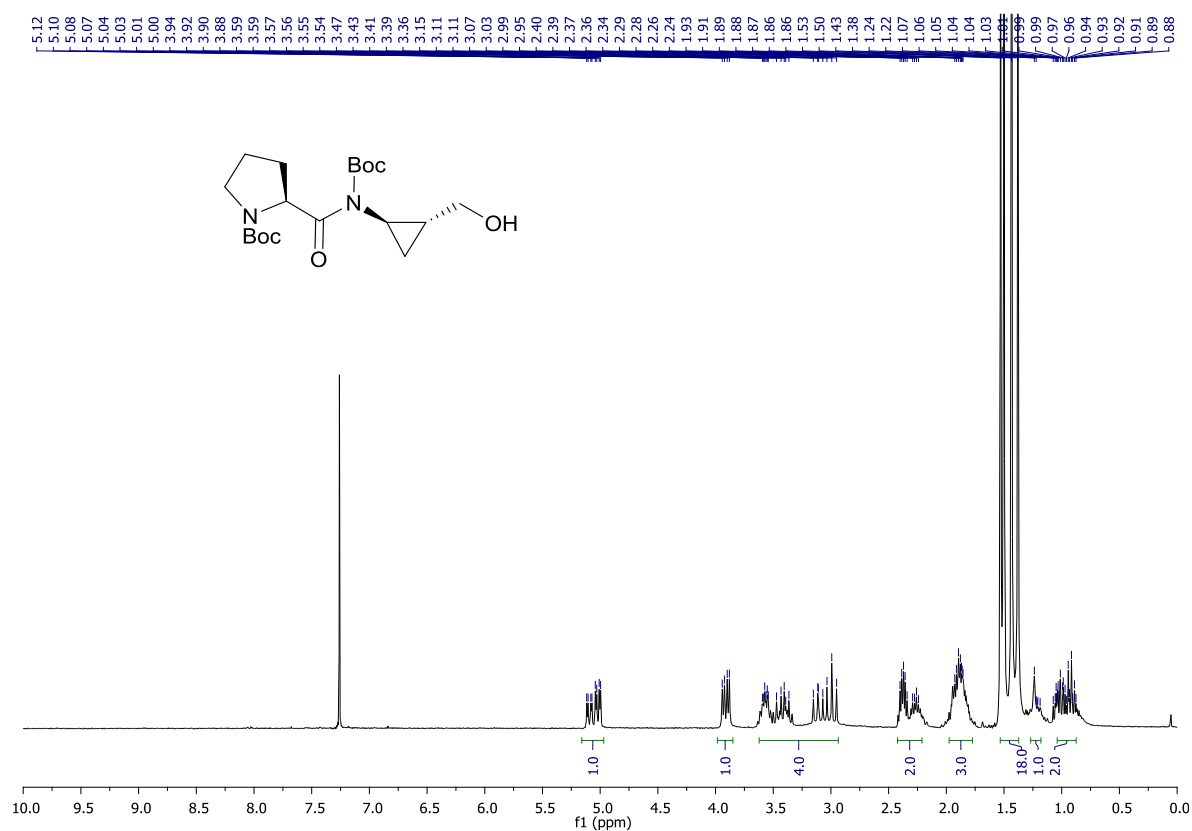
(2 conformers; ratio 1:1)



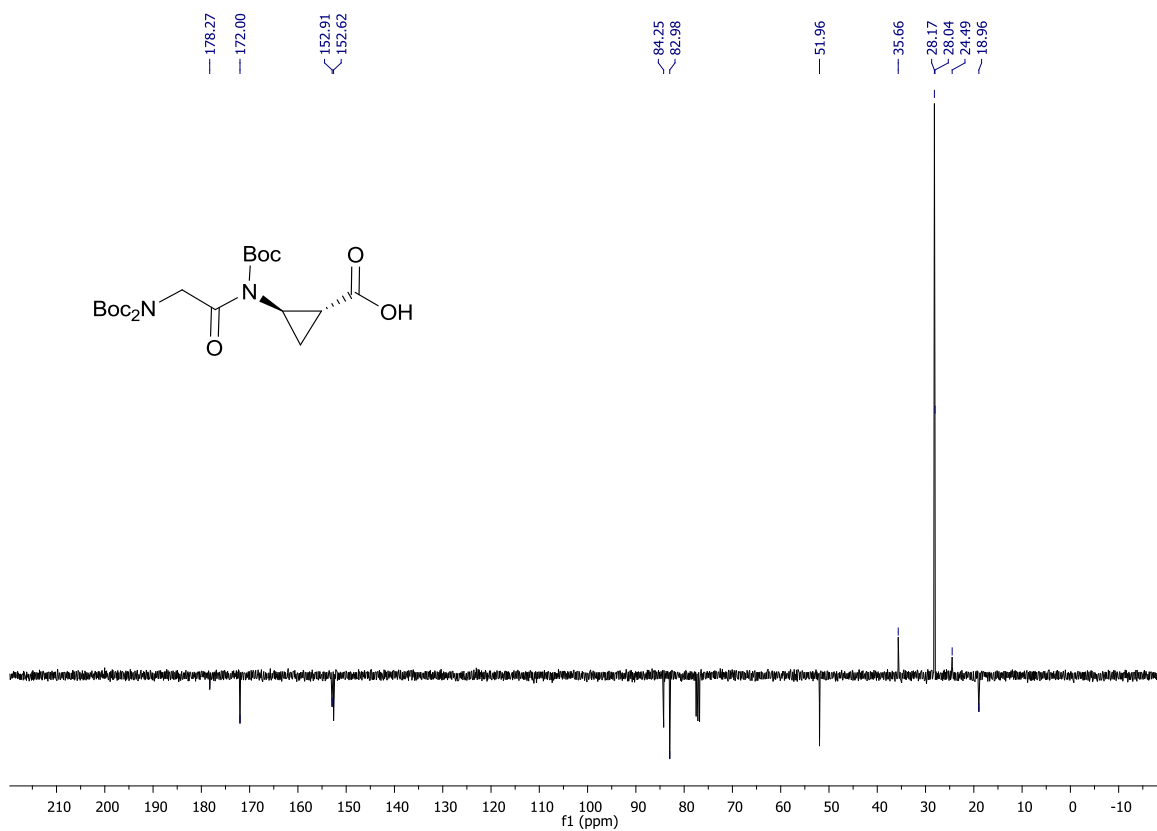
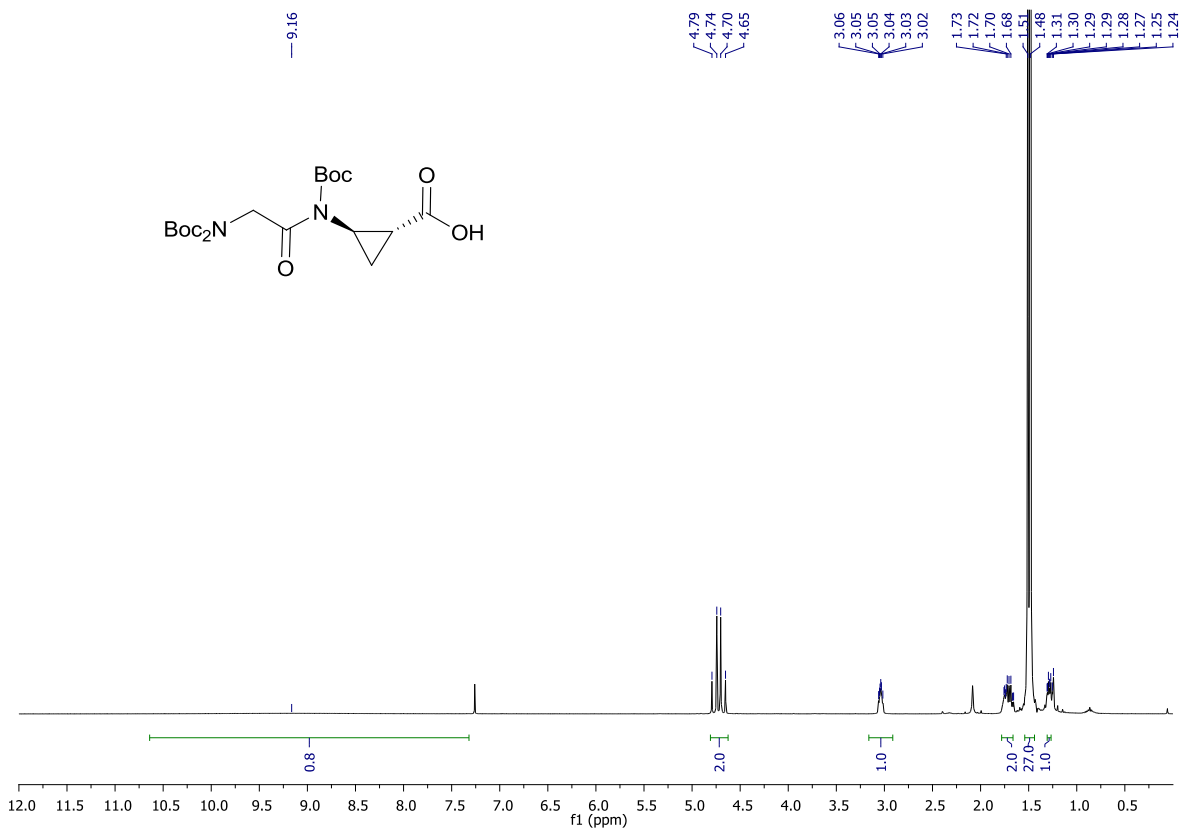
***tert*-butyl 2-di(*tert*-butoxycarbonyl)aminoacetyl((1*R*,2*R*)-2-(hydroxymethyl)cyclopropyl)carbamate 9a**



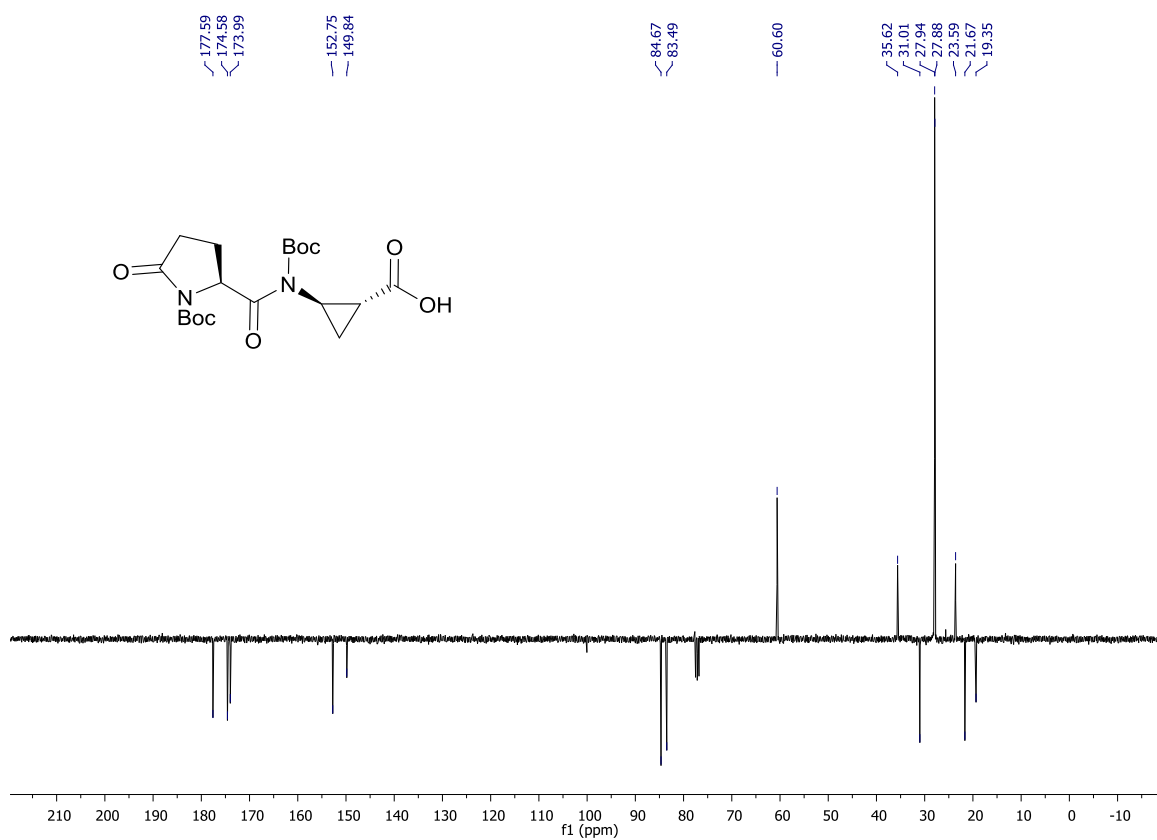
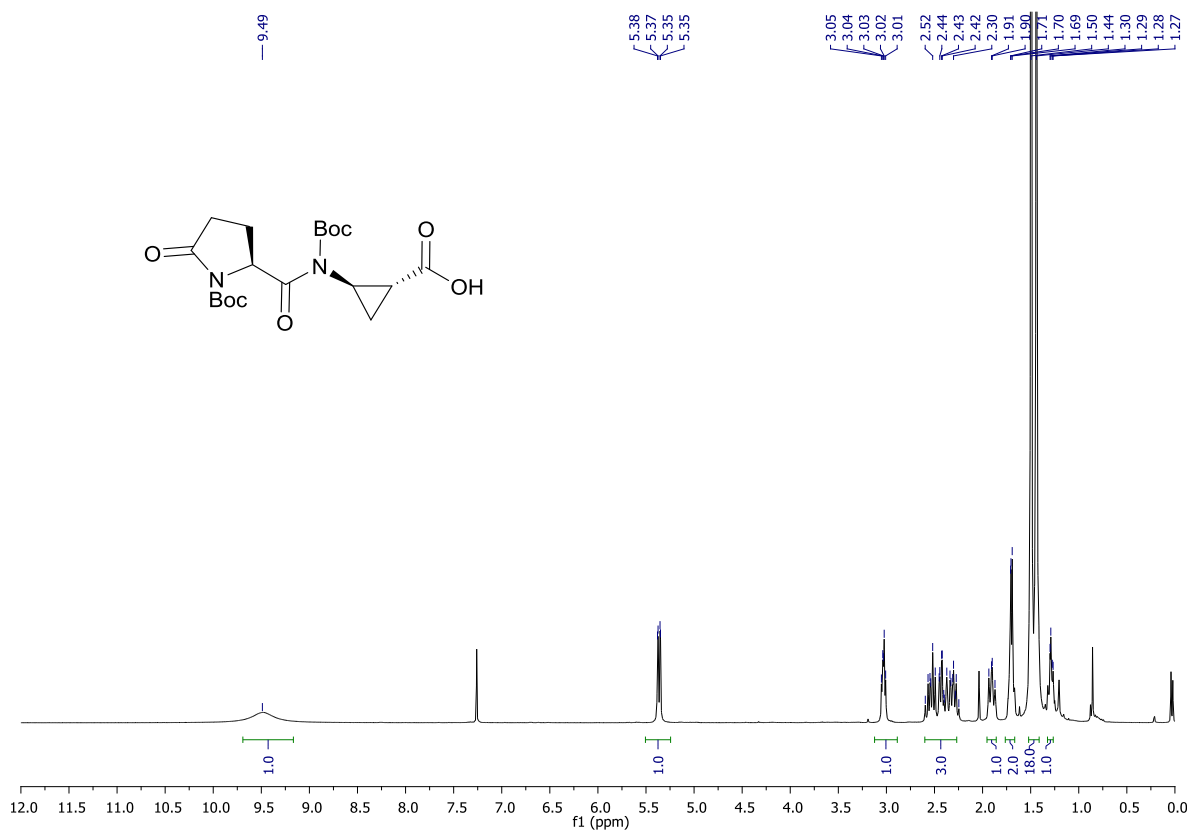
(S)-tert-butyl 2-(tert-butoxycarbonyl((1R,2R)-2-(hydroxymethyl)cyclopropyl)carbamoyl)pyrrolidine-1-carboxylate 9b
(2 conformers; ratio 1.5:1)



Boc₂N-Gly-*t*ACPrC(NBoc)-OH 10a

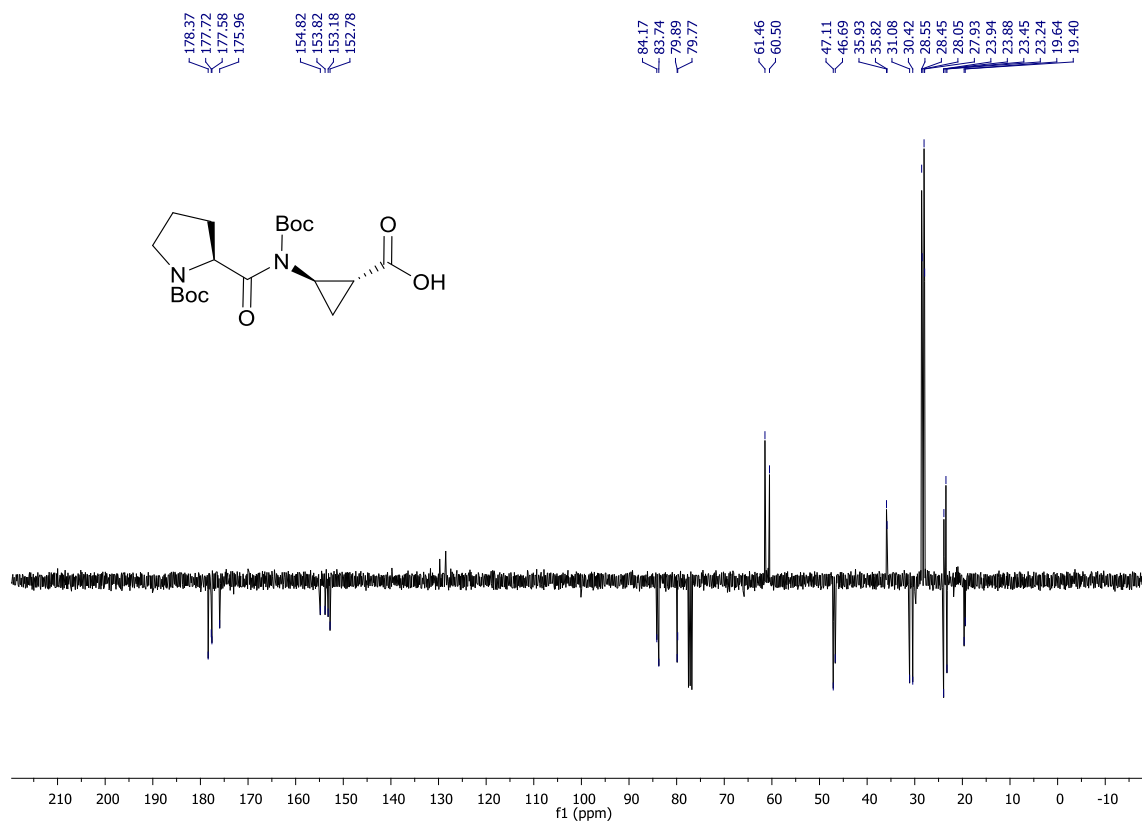
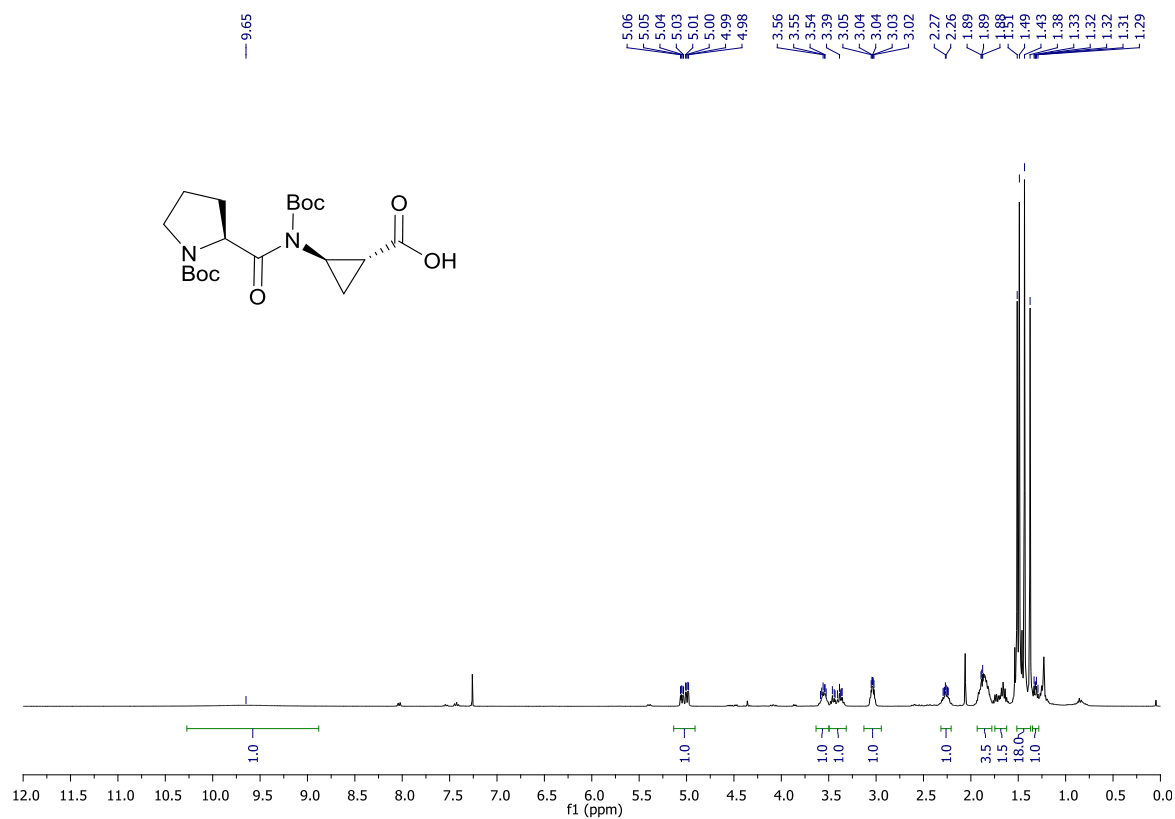


BocN-Pyr-*t*ACPrC(NBoc)-OH 10b

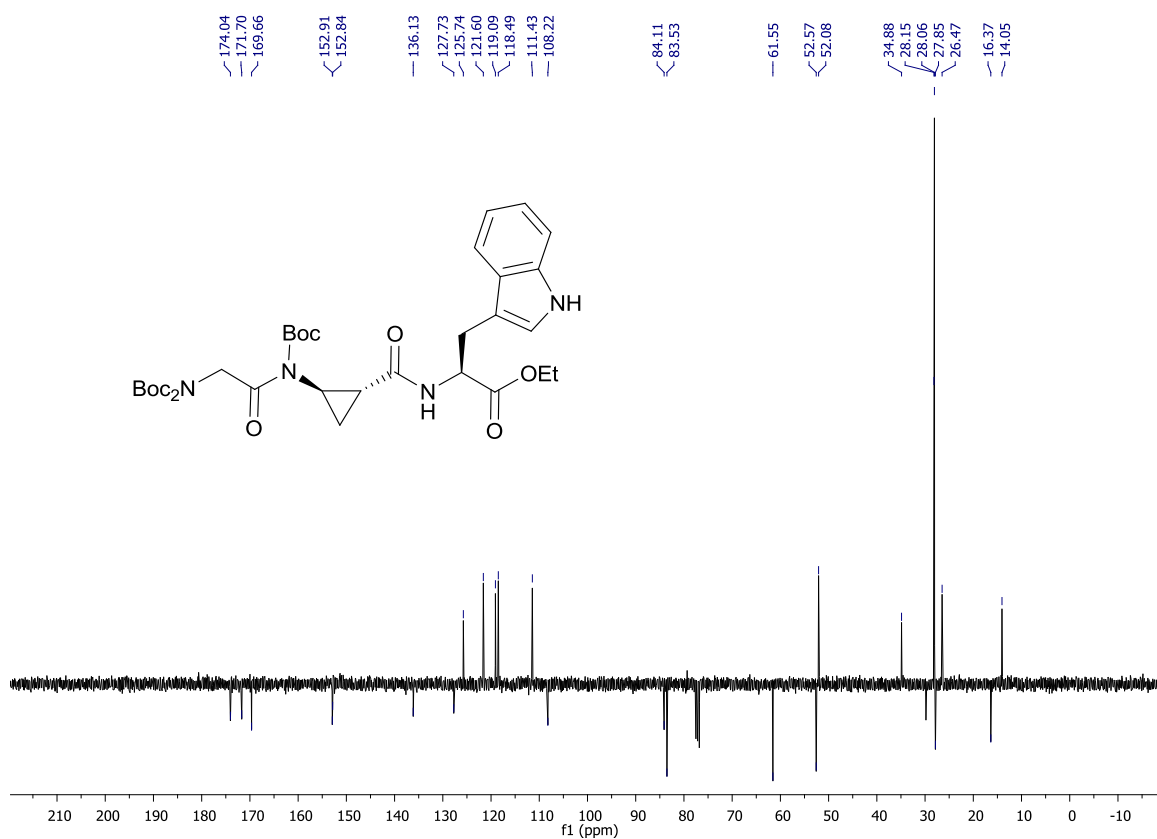
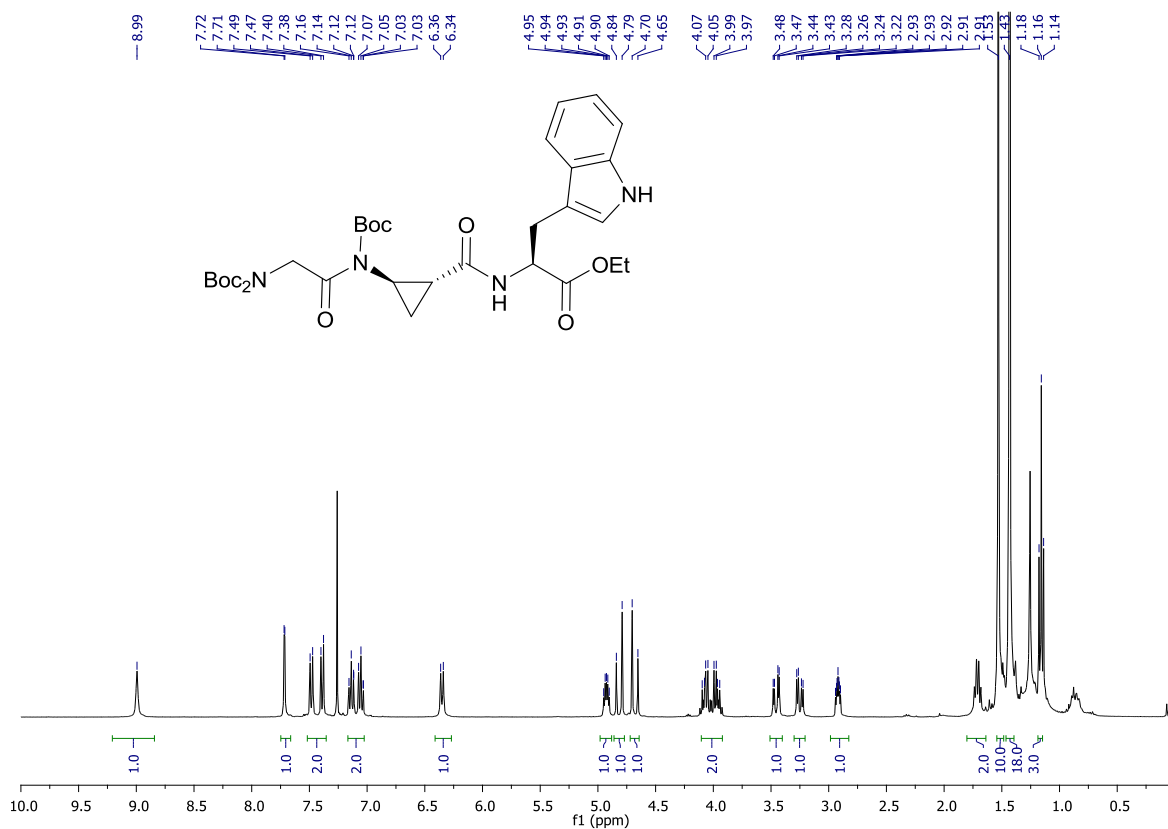


BocN-Pro-*t*ACPrC(NBoc)-OH 10c

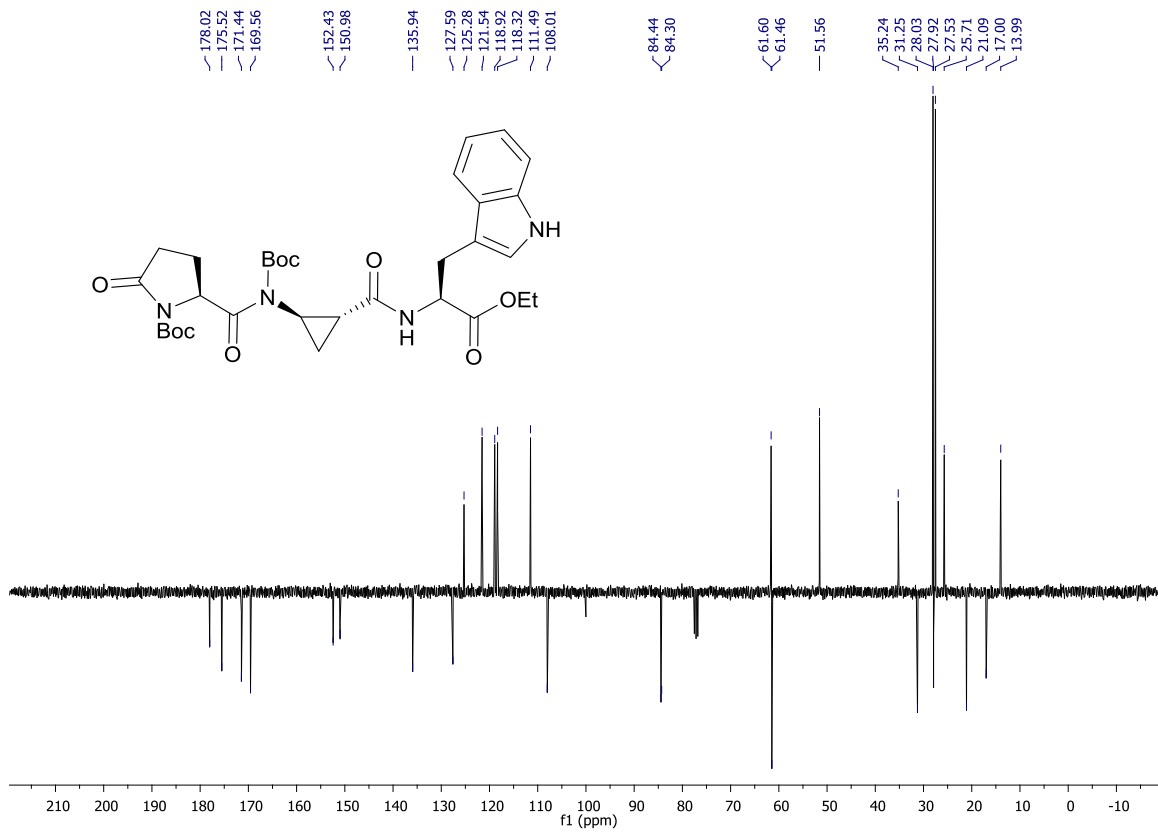
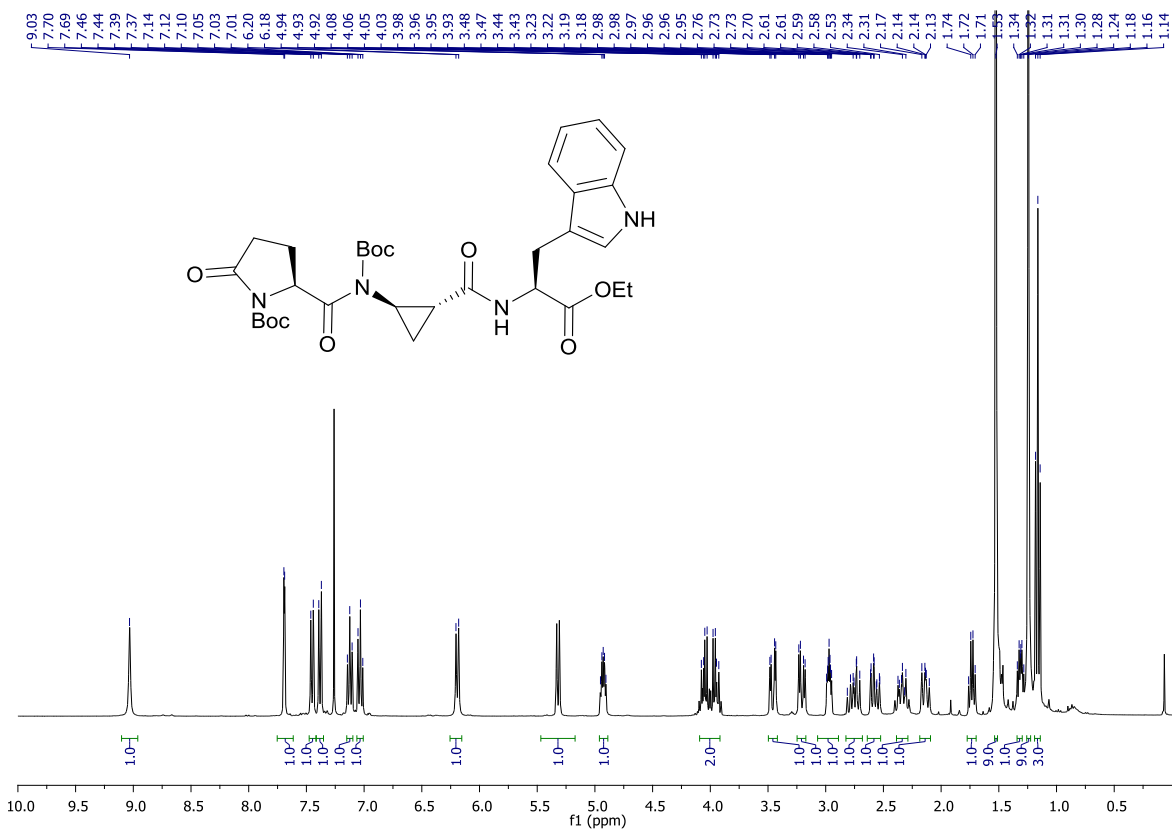
(2 conformers; ratio 1:1)



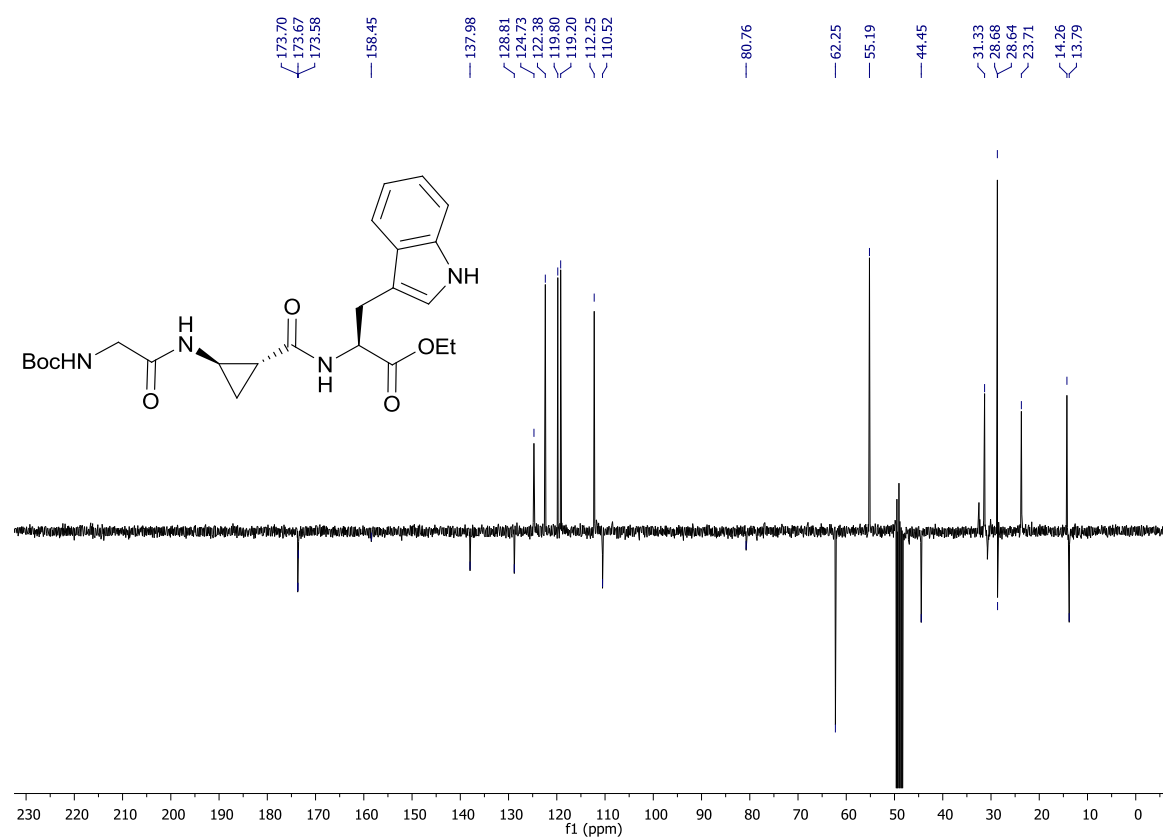
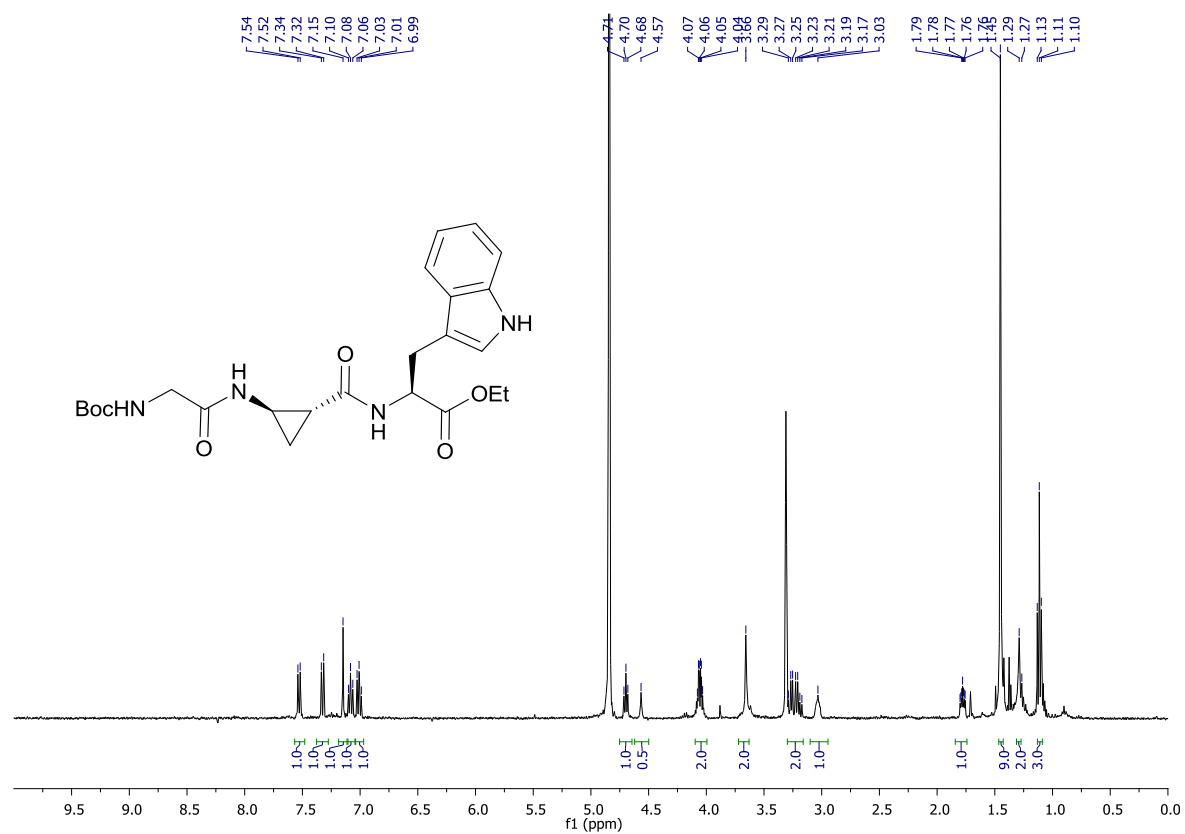
Boc₂N-Gly-*t*ACPrC(NBoc)-Trp-OEt 11a



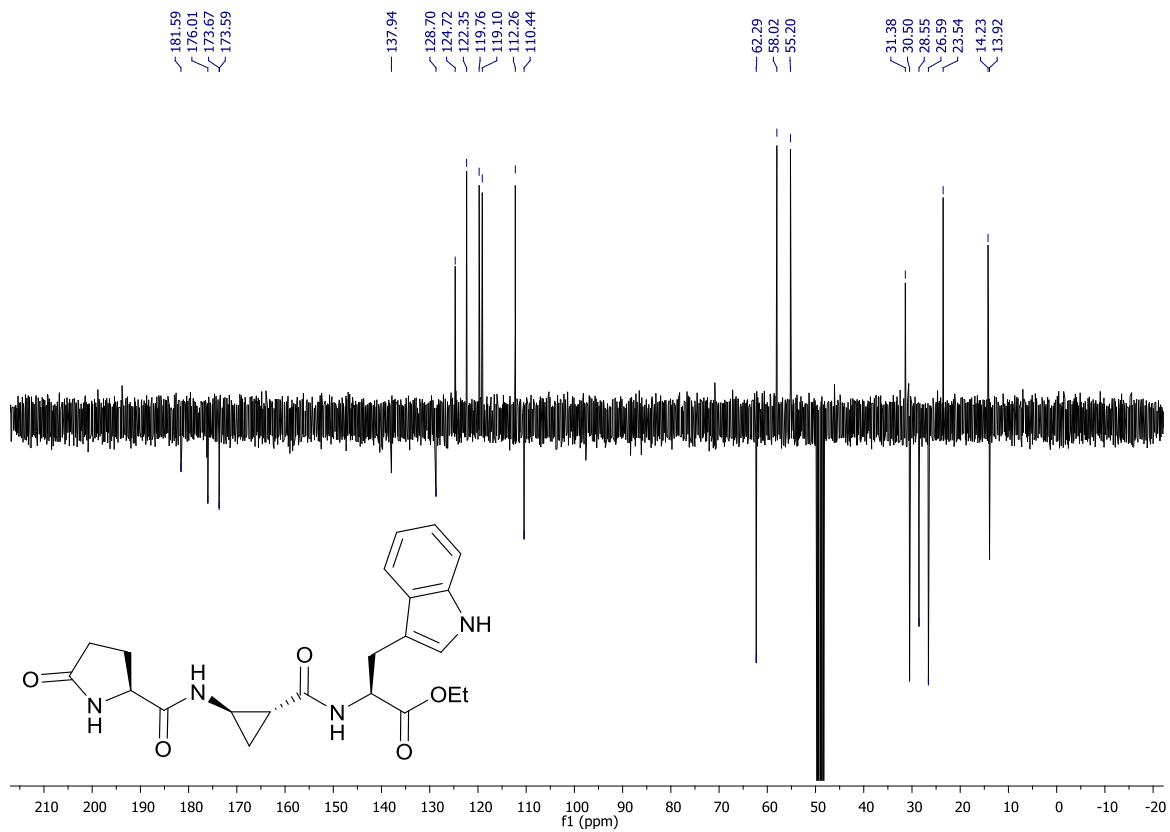
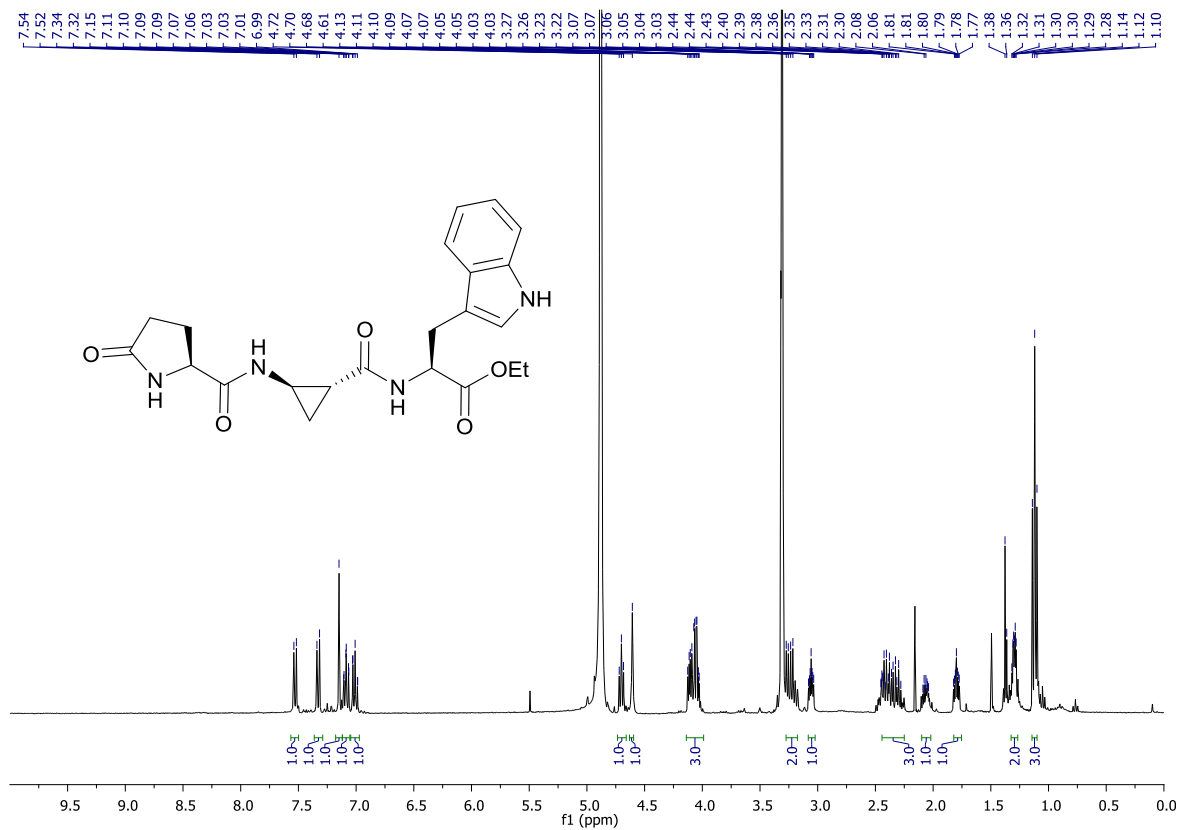
BocN-Pyr-*t*ACPrC(NBoc)-Trp-OEt 11b



BocNH-Gly-*t*ACPrC-Trp-OEt 12a



NH-Pyr-*t*ACPrC-Trp-OEt 12b



4. X-ray structure analysis of compounds 4d

X-ray diffraction data for compound **4d** (RX1) were collected by using X8 APEXII CCD Bruker diffractometer with graphite-monochromated MoK α radiation. Crystals were mounted on a CryoLoop (Hampton Research) with Paratone-N (Hampton Research) as cryoprotectant and then flashfrozen in a nitrogen-gas stream at 100 K. For compounds, the temperature of the crystal was maintained at the selected value by means of a 700 series Cryostream cooling device to within an accuracy of ± 1 K. The data were corrected for Lorentz polarization, and absorption effects. The structures were solved by direct methods using SHELXS-97^{S5} and refined against F² by full-matrix least-squares techniques using SHELXL-2018^{S6} with anisotropic displacement parameters for all non-hydrogen atoms. Hydrogen atoms were located on a difference Fourier map and introduced into the calculations as a riding model with isotropic thermal parameters. All calculations were performed by using the Crystal Structure crystallographic software package WINGX.^{S7}

The crystal data collection and refinement parameters are given in **Table S1**.

CCDC 1841687 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via <http://www.ccdc.cam.ac.uk/Community/Requestastructure>.

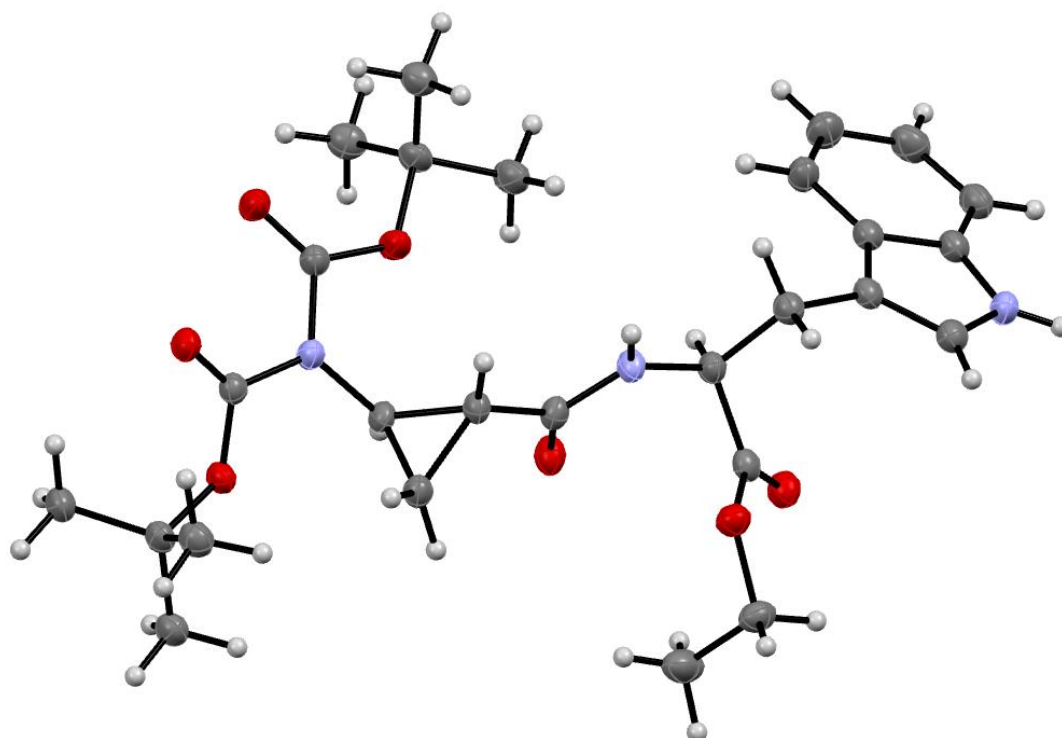


Figure S1: ORTEP diagram (50% probability thermal ellipsoids) of **4d** (RX1)

^{S5} Sheldrick, G. M. SHELXS-97, Program for Crystal Structure Solution, University of Göttingen, Göttingen, Germany, **1997**.

^{S6} Sheldrick, G. M. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **2008**, 64, 112-122.

^{S7} Farrugia, L. J. *J. Appl. Cryst.* **1999**, 32, 837-838.

Table S1. Crystallographic data and structure refinement details.

Compounds	4d (RX1)
CCDC Number	1841687
Empirical Formula	C ₂₇ H ₃₇ N ₃ O ₇
M_r	515.59
Crystal size, mm ³	0.28 x 0.17 x 0.04
Crystal system	monoclinic
Space group	$P 2_1$
a, Å	5.7051(9)
b, Å	21.044(4)
c, Å	11.619(2)
α , °	90
β , °	103.425(4)
γ , °	90
Cell volume, Å ³	1356.8(4)
Z ; Z'	2 ; 1
T, K	100(1)
Radiation type ; wavelength Å	MoK α ; 0.71073
F ₀₀₀	552
μ , mm ⁻¹	0.091
θ range, °	1.802 - 30.550
Reflection collected	17 488
Reflections unique	6 974
R _{int}	0.0503
GOF	1.021
Refl. obs. ($I > 2\sigma(I)$)	5 533
Parameters	341
wR ₂ (all data)	0.1249
Flack parameter ^{S8}	-0.3(5)
R value ($I > 2\sigma(I)$)	0.0494
Largest diff. peak and hole (e ⁻ ·Å ⁻³)	0.393 ; -0.293

^{S8} Bernardinelli, G.; Flack, H. D. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **1985**, *41*, 500-511.