

SUPPORTING INFORMATION

Preparation of enantioenriched iodinated pyrrolinones by iodocyclization of α -amino-ynones.

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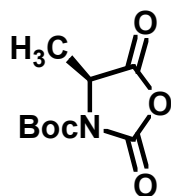
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I. General remarks

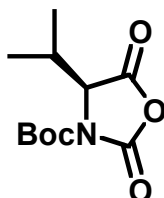
All commercially available compounds were used as received from commercial suppliers (Aldrich, Fluka, Chem, ISO-CHEM). Boc-Ala-NCA and Boc-Phe-NCA were diluted in AcOEt and washed with a saturated solution of NaHCO₃ to remove traces of corresponding acid derivative. The solvents were purified by distillation over a drying agent. NMR spectra were recorded at room temperature with the appropriate deuterated solvent (CDCl₃, CD₃OD or d₆-DMSO). Chemical shifts (δ) of ¹H NMR and ¹³C NMR spectra are reported in ppm relative to residual solvent signals (CHCl₃ in CDCl₃: δ = 7.27 ppm for ¹H and CDCl₃: δ = 77.04 ppm for ¹³C NMR. *J* values are given in Hz. ¹H and ¹³C NMR spectra were registered on Bruker Avance-300 MHz and Bruker Avance 400 MHz. Microwave-assisted reactions were performed in sealed vessel with a Biotage Initiator 60 EXP[®] instrument. The temperature was measured with an IR sensor on the outer surface of the reaction vial. Analytical high performance liquid chromatography (HPLC) was performed on a

Waters Millenium 717 equipped with Autosampler, with a variable wavelength diode detector using a CHROMOLITH RP18 column (50 x 4,6 mm), flow 5 mL/min, linear gradient CH₃CN in water 0-100% (+ 0.1% TFA) in 4.5 min. LC-MS analysis were performed with HPLC Waters Alliance 2695 (UV Waters 2489), column Onyx C₁₈, (25 x 4.6 mm), flow 3 mL/min linear gradient CH₃CN in water 0-100% (+ 0.1% HCO₂H) in 2.5 min. HRMS analysis were performed on a Q-ToF (Waters, 2001) with ESI ionization mode. Chiral HPLC analysis were performed with Beckman Coulter System Gold 126 Solvent Module and Beckman Coulter System Gold 168 Detector. Columns: Chiralpak AD-H (0.46 x 25 cm), Chiralcel OD-H (0.46 x 25 cm); Chiral HPLC reverse phase: Chiralcel OD-RH (0.46 x 25 cm). $[\alpha]_D^{20}$ measurement were performed on a Perkin Elmer Instrument Polarimeter, model 341 Polarimeter, OROT 589 nm, 20°C, [10 mg/mL]; solvent: dichloromethane.

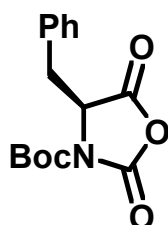
II. Spectral data for UNCAs.



Boc-Ala-NCA, CAS Registry Number: [125814-30-4]; ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 4.67 (q, J = 6.9 Hz, 1H), 1.69 (d, J = 6.9 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 166.7, 147.4, 146.2, 86.0, 55.8, 27.9, 16.9.



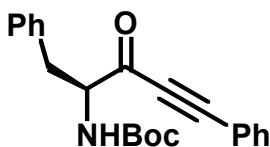
Boc-Val-NCA, CAS Registry Number: [141468-55-5]; ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 4.56 (d, J = 3.5 Hz, 1H), 2.63-2.47 (m, 1H), 1.58 (s, 9H), 1.20 (d, J = 7.1 Hz, 3H), 0.99 (d, J = 6.9 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 164.8, 147.6, 146.6, 86.0, 64.6, 30.0, 27.9, 17.8, 15.7; ESI-MS m/z : 266.1 (M+Na)⁺, 188.2 (M+H-*t*-Bu)⁺, 509.2 (2M+Na)⁺.



Boc-Phe-NCA, CAS Registry Number: [142955-51-9]; ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 7.37-7.34 (m, 3H), 7.13-7.10 (m, 2H), 4.95 (dd, J = 2.6, 5.8 Hz, 1H), 3.57 (dd, J = 5.8, 14.2 Hz, 1H), 3.36 (dd, J = 2.6, 14.2 Hz, 1H), 1.66 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 165.8, 147.7, 145.8, 132.3, 129.5, 129.2, 128.3, 86.1, 60.8, 35.3, 28.0; ESI-MS m/z : 292.0 (M+H)⁺, 314.1 (M+Na)⁺, 236.0 (M+H-*t*-Bu)⁺, 605.3 (2M+Na)⁺.

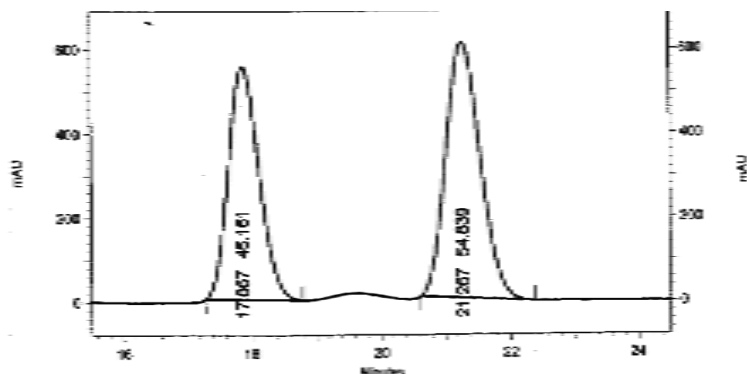
III. Synthesis of α -amino-ynones 2a-2i.

(1-Benzyl-2-oxo-4-phenyl-but-3-ynyl)-carbamic acid *tert*-butyl ester (2a). A solution of phenylacetylene (264 mg, 2.58 mmol) in anhydrous THF (6 mL) was added dropwise to a stirred solution of BuLi (1.6 mL of a 1.6 M solution in hexane, 2.58 mmol) in anhydrous THF at -78°C. To the resulting mixture, maintained at -78°C under stirring, a solution of LiBr (159 g, 1.82 mmol) in THF (3 mL) was added. After 0.5 h, Boc-Phe-NCA (500 mg, 1.72 mg), diluted in anhydrous THF, was slowly added under nitrogen at the same temperature. The resulting mixture was stirred for additional 4h and then allowed to warm up to room temperature. After quenching with a saturated solution of NH₄Cl, the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over MgSO₄. After filtration, the solvent was evaporated to obtain crude **2a** that was purified by column chromatography on silica gel (9:1 v/v cyclohexane-AcOEt) to afford 351 mg (60 %) of the title compound as a yellow solid.



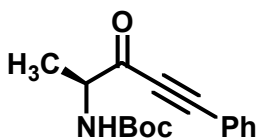
M.p. 90-94°C, *e.e.* 10 %; ¹H NMR (CDCl₃, 400 MHz), δ (ppm): 7.60 (d, J = 7.5 Hz, 2H), 7.52-7.50 (m, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.33- 7.23 (m, 6H), 5.15 (d, J = 7.4 Hz, 1H), 4.82 (dd, J = 6.1, 13 Hz, 1H), 3.34 Hz (dd, J = 5.8, 14.0 Hz, 1H), 3.29 (dd, J = 5.8, 14.0 Hz, 1H), 1.45 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 186.1, 155.2, 135.8, 133.4, 131.3, 129.7, 128.8, 128.7, 127.2, 119.7, 95.0, 86.6, 80.2, 62.2, 37.6, 28.5; ESI-MS m/z : 350.2 (M+H)⁺, 372.3 (M+Na)⁺, 294.2 (M+H-*t*-Bu)⁺, 250.2 (M+H-Boc)⁺, 699.4 (2M+H)⁺; HMRS (ESI) calcd. For C₂₂H₂₄NO₃ (M+H)⁺: 350.1756, found: 350.1748; HPLC chiralpak AD-H, *i*-propanol / hexane = 2/98, flow rate 1.0 mL/ min, λ = 214 nm, t_{major} = 21.267 min, t_{minor} = 17.867 min.

Chiral HPLC Chromatogram of **2a**



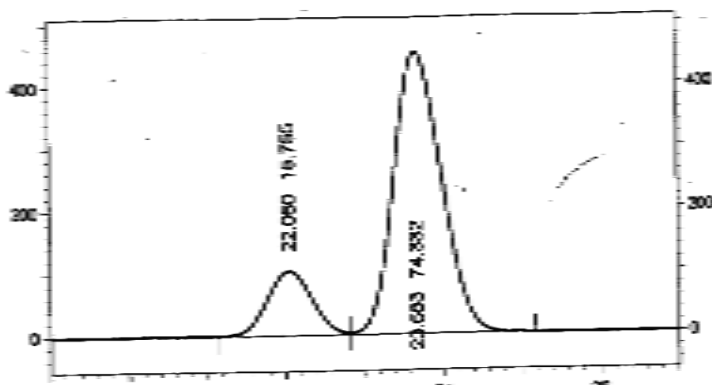
(1-Methyl-2-oxo-4-phenyl-but-3-ynyl)-carbamic acid *tert*-butyl ester (2b). A solution of

phenylacetylene (705 mg, 6.9 mmol) in anhydrous THF (3 mL) was added dropwise to a stirred solution of BuLi (4.3 mL of a 1.6 M solution in hexane, 6.9 mmol) in anhydrous THF (5 mL) at -40°C. To the resulting mixture, maintained at -40°C under stirring, a solution of LiBr (426 g, 4.9 mmol) in THF (3 mL) was added. After 0.5 h, Boc-Ala-NCA (1.00 g, 4.65 mmol), diluted in anhydrous THF (3 mL), was slowly added under nitrogen at the same temperature. The resulting mixture was stirred for additional 4h and then allowed to warm up to room temperature. After quenching with a saturated solution of NH₄Cl, the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over MgSO₄. After filtration, the solvent was evaporated to obtain crude **2b** that was purified by column chromatography on silica gel (9:1 v/v cyclohexane-AcOEt) to afford 385 mg, (35%) of the title compound as a pale yellow solid.



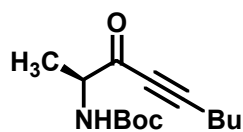
CAS Registry Number:[1169845-20-8]; m.p. 65-67°C; lit^[1] 64-66°C. *e.e.* 65 %; $[\alpha]_D^{25} = +0.005^\circ$ (10 mg/mL CH₂Cl₂); ¹H NMR (CDCl₃, 300 MHz) δ (ppm): 7.61-7.59 (m, 2H), 7.49-7.38 (m, 3H), 5.24 (d, *J* = 5.7 Hz, 1H), 4.57-4.52 (m, 1H), 1.51 (d, 3H), 1.46 (s, 9H); ¹³C NMR (CDCl₃, 75 MHz) δ (ppm): 187.1, 155.1, 133.1, 131.0, 128.6, 119.5, 94.3, 85.8, 79.9, 56.9, 28.3, 17.8; ESI-MS *m/z* 274.2 (M+H)⁺, 296.2 (M+Na)⁺, 218.2 (M+H-*t*-Bu)⁺, 174.0 (M+H-Boc)⁺, 569.2 (2M⁺ Na)⁺; HMRS (ESI) calcd. For C₁₆H₂₀NO₃ (M+H)⁺: 274.1443, found: 274.1442; HPLC chiralpak AD-H, *i*-propanol / hexane = 2/98, flow rate 1.0 mL/ min, λ = 214 nm, *t*_{major} = 23.683 min, *t*_{minor} = 22.050 min.

Chiral HPLC Chromatogram of **2b**



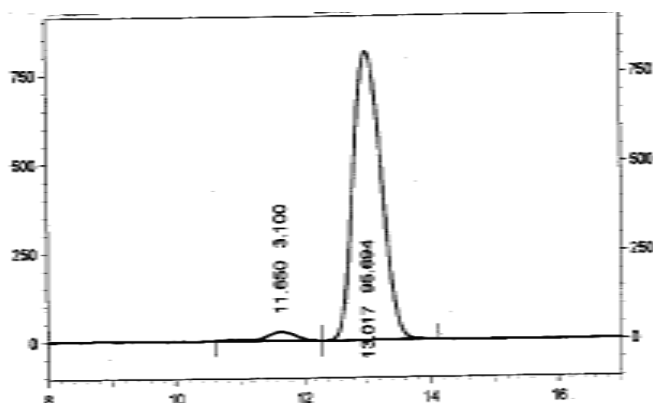
(1-Methyl-2-oxo-oct-3-ynyl)-carbamic acid *tert*-butyl ester (**2c**). A solution of hexyne (254 mg, 3.09 mmol) in anhydrous THF was added dropwise to a stirred solution of BuLi (1.9 mL of a 1.6 M solution in hexane, 3.09 mmol) in anhydrous THF at -78°C. To the resulting mixture, maintained at

-78°C, under stirring, a solution of LiBr (190 g, 2.18 mmol) in THF (3 mL) was added. After 0.5 h, Boc-Ala-NCA (500 mg, 2.32 mmol), diluted in anhydrous THF, was slowly added under nitrogen at the same temperature. The resulting mixture was stirred for additional 4h and then allowed to warm up to room temperature. After quenching with a saturated solution of NH₄Cl, the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over MgSO₄. After filtration, the solvent was evaporated to afford the pure product **2c** (560 mg, 95 %) of the title compound.



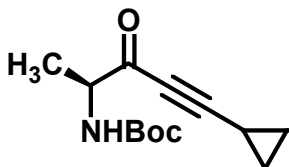
Pale oil, *e.e.* 94%; $[\alpha]_D^{25} = +0.026^\circ$ (10 mg/mL CH₂Cl₂); ¹H NMR (CDCl₃, 400 MHz), δ (ppm): 5.20 (d, *J* = 7.5 Hz, 1H), 4.42-4.35 (m, 1H), 2.40 (t, *J* = 6.8 Hz, 2H), 1.62-1.40 (m, 4H), 1.45 (s, 9H), 0.93 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz), δ (ppm): 187.1, 155.0, 98.3, 79.8, 78.8, 57.0, 29.6, 28.3, 28.0, 22.0, 17.9, 13.5; ESI-MS *m/z* 254.1 (M+H)⁺, 276.2 (M+Na)⁺, 198.1 (M+H-*t*-Bu)⁺, 154.1 (M+H-Boc)⁺, 529.3 (2M+Na)⁺; HMRS (ESI) calcd. For C₁₄H₂₄NO₃ (M+H)⁺: 254.1756, found: 254.1756; HPLC chiralpak AD-H, *i*-propanol / hexane = 2/98, flow rate 1.0 mL/min, λ = 214 nm, *t*_{major} = 13.017 min, *t*_{minor} = 11.65 min.

Chiral HPLC Chromatogram of **2c**



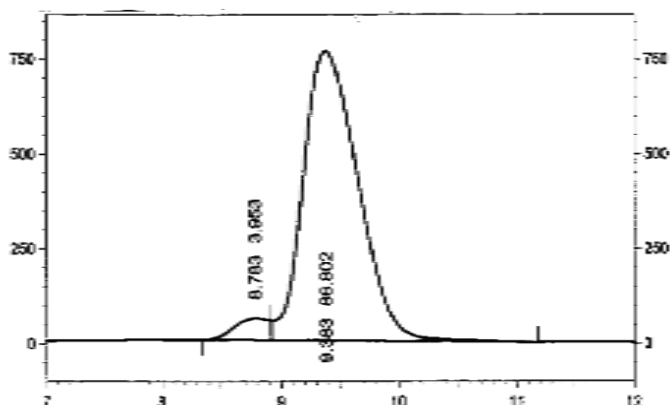
(4-Cyclopropyl-1-methyl-2-oxo-but-3-ynyl)-carbamic acid *tert*-butyl ester (2d). A solution of cyclopropylacetylene (160 mg, 2.42 mmol) in anhydrous THF (1.5 mL) was added dropwise to a stirred solution of BuLi (1.5 mL of a 1.6 M solution in hexane, 2.42 mmol) in anhydrous THF at -78°C. To the resulting mixture, maintained at -78°C under stirring, a solution of LiBr (171 mg, 1.97 mmol) in THF (1.5 mL) was added. After 0.5h, Boc-Ala-NCA (400 mg, 1.86 mmol), diluted in anhydrous THF (2.5 mL), was slowly added under nitrogen at the same temperature. The resulting mixture was stirred for additional 4h and then allowed to warm up to room temperature. After quenching with a saturated solution of NH₄Cl, the mixture was extracted with ethyl acetate. The

combined organic layers were washed with brine and then dried over MgSO₄. After filtration, the solvent was evaporated affording 401 mg of the pure product **2d** (80 %).



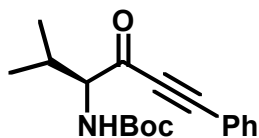
Pale yellow solid, m.p. 62-65°C, *e.e.* 90 %; $[\alpha]_D^{25} = +16^\circ$ (10 mg/mL CH₂Cl₂); ¹H NMR (CDCl₃, 400 MHz), δ (ppm): 5.18 (d, *J* = 5.5 Hz, 1H), 4.35 (t, *J* = 7.2 Hz, 1H), 1.44 (s, 9H), 1.44 (m, 1H), 1.39 (d, *J* = 6.0 Hz, 3H), 1.05-0.98 (m, 2H), 0.97-0.91 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 186.8, 155.0, 102.6, 79.8, 74.6, 56.8, 28.3, 17.9, 10.0, -0.15; ESI-MS *m/z*: 238.1 (M+H)⁺, 260.1 (M+Na)⁺, 182.1 (M+H-*t*-Bu)⁺, 138.1 (M+H-Boc)⁺, 475.2 (2M+H)⁺, 497.1 (2M+Na)⁺; HMRS (ESI) calcd. For C₁₃H₂₀NO₃ (M+H)⁺ 238.1445, found: 238.1443; HPLC chiralpak AD-H, *i*-propanol / hexane = 2/98, flow rate 1.0 mL/min, $\lambda = 214$ nm, *t*_{major} = 8.783 min, *t*_{minor} = 9.383 min.

Chiral HPLC Chromatogram of **2d**



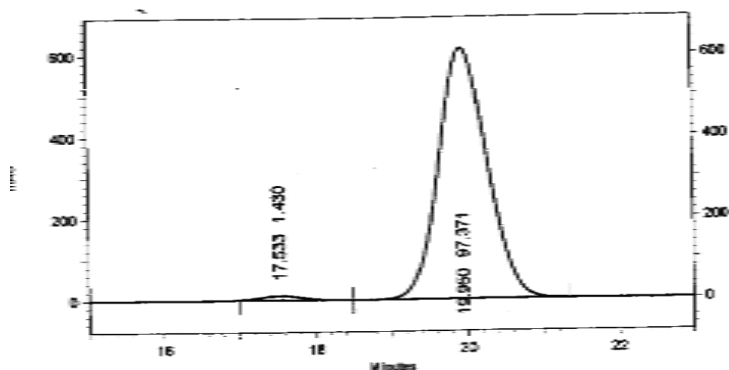
(1-Isopropyl-2-oxo-4-phenylbut-3-ynyl)-carbamic acid *tert*-butyl ester (2e). A solution of phenylacetylene (315 mg, 3.09 mmol) in anhydrous THF (5 mL) was added dropwise to a stirred solution of BuLi (1.9 mL of a 1.6 M solution in hexane, 3.09 mmol) in anhydrous THF at -60° C. To the resulting mixture, maintained at -60° C under stirring, a solution of LiBr (190 g, 2.18 mmol) in THF was added. After 0.5 h, Boc-Val-NCA (500 mg, 2.06 mmol), diluted in anhydrous THF, was slowly added under nitrogen at the same temperature. The resulting mixture was stirred for additional 4h and then allowed to warm up to room temperature. After quenching with a saturated solution of NH₄Cl, the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over MgSO₄. After filtration, the solvent was evaporated to obtain crude **2e** that was purified by column chromatography on silica gel (9:1 v/v cyclohexane-AcOEt) to

afford 384 mg (62 %), *e.e.* 97%, $[\alpha]_D^{25} = +0.035^\circ$.



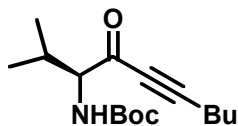
CAS Registry Number: [1169845-48-0], pale yellow solid, m.p. 102-105°C, *lit.*^[1] 100-102°C, ¹H NMR (CDCl₃, 300 MHz), δ (ppm): 7.59-7.59 (m, 2H), 7.49-7.45 (m, 1H), 7.41-7.37 (m, 2H), 5.17 (d, $J = 8.9$ Hz, 1H), 4.51 (dd, $J = 3.5, 8.9$ Hz, 1H), 2.53-2.46 (m, 1H), 1.45 (s, 9H), 1.08 (d, $J = 6.8$ Hz, 3H), 0.89 (d, $J = 6.8$ Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz), δ (ppm): 187.0, 155.8, 133.1, 130.1, 128.6, 119.6, 94.1, 86.7, 79.8, 65.9, 30.5, 28.3, 19.7, 16.7; ESI-MS m/z 302.2 (M+H)⁺, 324.0 (M+Na)⁺, 246.1(M+H-*t*-Bu)⁺, 202.1 (M+H-Boc)⁺; HMRS (ESI) calcd. For C₁₈H₂₄NO₃ (M+H)⁺: 302.1756, found: 302.1751; HPLC chiralpak AD-H, *i*-propanol/ hexane = 2/98, flow rate 1.0 ml/ min, λ 214 nm, $t_{major} = 19.95$ min, $t_{minor} = 17.533$ min.

Chiral HPLC Chromatogram of 2e



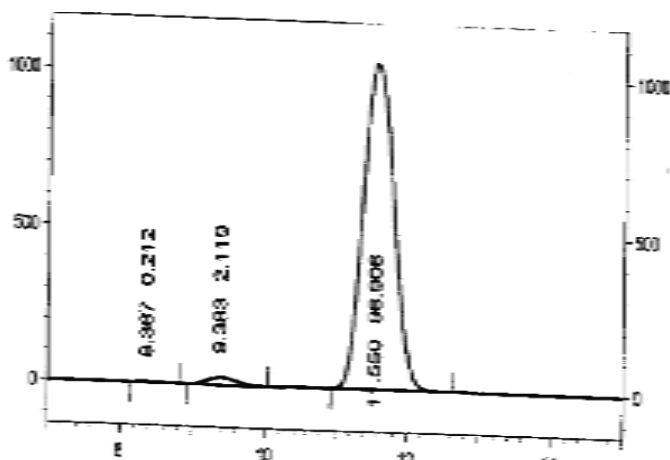
(1-Isopropyl-2-oxo-oct-3-ynyl)-carbamic acid *tert*-butyl ester (2f). A solution of hexyne (254 mg, 3.09 mmol) in anhydrous THF was added dropwise to a stirred solution of BuLi (1.9 mL of a 1.6 M solution in hexane, 3.09 mmol) in anhydrous THF at -78°C. To the resulting mixture, maintained at -78°C under stirring, a solution of LiBr (190 g, 2.18 mmol) in THF (3 mL) was added. After 0.5 h, Boc-Val-NCA (500 mg, 2.06 mmol), diluted in anhydrous THF (3 mL), was slowly added under nitrogen at the same temperature. The resulting mixture was stirred for additional 4h and then allowed to warm up to room temperature. After quenching with a saturated solution of NH₄Cl, the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over MgSO₄. After filtration, the solvent was evaporated to obtain

crude **2f** that was purified by column chromatography on silica gel (9:1 v/v cyclohexane-AcOEt) to afford 472 mg (81 %) of the title compound **2f**.



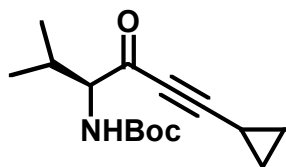
Pale oil, *e.e.* 96 %, $[\alpha]_D^{20} = +60^\circ$ (10 mg/mL CH₂Cl₂); ¹H NMR (CDCl₃, 400 MHz), δ (ppm): 5.08 (d, *J* = 8.6 Hz, 1H), 4.35 (dd, *J* = 3.6, 8.6 Hz, 1H), 2.39 (t, *J* = 7.0 Hz, 2H), 1.60-1.53 (m, 2H), 1.47-1.38 (m, 2H), 1.43 (s, 9H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz), δ (ppm): 187.0, 155.7, 97.7, 79.7, 79.6, 65.8, 30.4, 29.6, 28.2, 21.9, 19.7, 18.7, 16.5, 13.4; ESI-MS *m/z* 282.2 (M+H)⁺, 304.2 (M+Na)⁺, 226.2 (M+H-*t*-Bu)⁺, 182.2 (M+H-Boc)⁺, 563.3 (2M+H)⁺, 585.2 (2M+ Na)⁺; HMRS (ESI) calcd. for C₁₆H₂₈NO₃ (M+H)⁺: 282.2069, found: 282.2060; HPLC chiralpak AD-H, *i*-propanol/hexane = 2/98, flow rate 1.0 mL/ min, $\lambda = 214$ nm, $t_{major} = 11.55$ min, $t_{minor} = 9.383$ min.

Chiral HPLC Chromatogram of **2f**



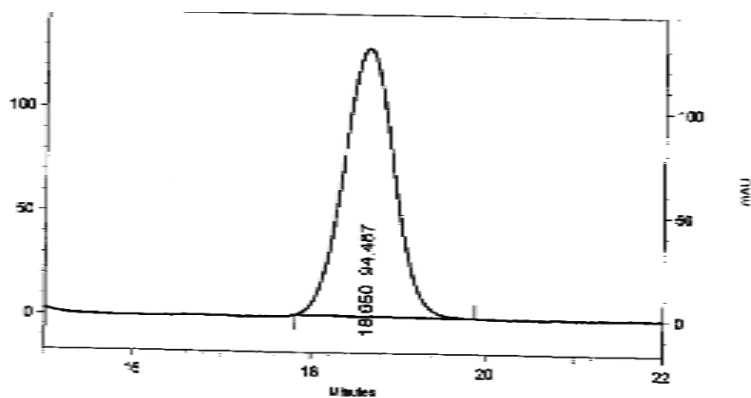
(4-Cyclopropyl-1-isopropyl-2-oxo-but-3-ynyl)-carbamic acid *tert*-butyl ester (2g). A solution of cyclopropylacetylene (284 mg, 4.3 mmol) in anhydrous THF was added dropwise to a stirred solution of BuLi (2.7 mL of a 1.6 M solution in hexane, 4.3 mmol) in anhydrous THF at -60°C. To the resulting mixture, maintained at -60°C under stirring, a solution of LiBr (304 mg, 3.49 mmol) in THF (3 mL) was added. After 0.5 h, Boc-Val-NCA (800 mg, 3.29 mmol), diluted in anhydrous THF, was slowly added under nitrogen at the same temperature. The resulting mixture was stirred for additional 4h and then allowed to warm up to room temperature. After quenching with a saturated solution of NH₄Cl, the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over MgSO₄. After filtration, the solvent was

evaporated to obtain crude **2g** that was purified by column chromatography on silica gel (9:1 v/v cyclohexane-AcOEt) to afford 816 mg (94 %) of **2g** as a pure compound.



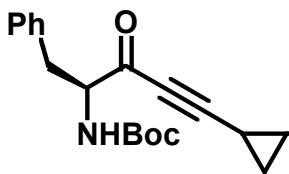
White solid, m.p. 40-45°C, *e.e.* 100%, $[\alpha]_D^{25} = + 50^\circ$ (10 mg/mL CH₂Cl₂); ¹H NMR (CDCl₃, 400 MHz), δ (ppm): 5.06 (d, *J* = 8.5 Hz, 1H), 4.31 (dd, *J* = 3.7, 8.9 Hz, 1H), 2.38-2.32 (m, 1H), 1.48-1.35 (m, 1H), 1.49 (s, 9H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.98-0.90 (m, 4H), 0.80 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz), δ (ppm): 186.7, 155.7, 102.3, 79.6, 75.4, 65.6, 30.4, 28.2, 26.8, 19.6, 16.5, 9.9, 0.18; ESI-MS *m/z* 266.2 (M+H)⁺, 288.2 (M+Na)⁺, 210.1 (M+H-*t*-Bu)⁺, 166.1 (M+H-Boc)⁺, 531.3 (2M+H)⁺, 553.3 (2M+Na)⁺; HMRS (ESI) calcd. For C₁₅H₂₄NO₃ (M+H)⁺: 266.1756, found: 266.1750; HPLC chiralpak AD-H, *i*-propanol / hexane = 2/98, flow rate 1.0 mL/ min, λ = 214 nm, *t* = 18.65 min.

Chiral HPLC Chromatogram of **2g**



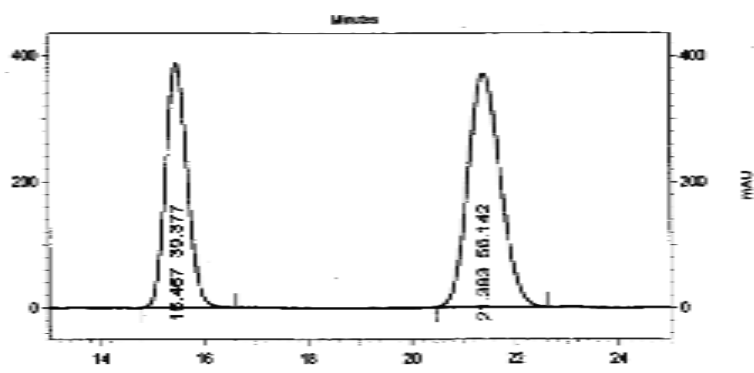
(1-Benzyl-4-cyclopropyl-2-oxo-but-3-ynyl)-carbamic acid *tert*-butyl ester (2h). A solution of cyclopropylacetylene (147 mg, 2.24 mmol) in anhydrous THF (1.5 mL) was added dropwise to a stirred solution of BuLi (1.4 mL of a 1.6 M solution in hexane, 2.24 mmol) in anhydrous THF at -78°C. To the resulting mixture, maintained at -78°C under stirring, a solution of LiBr (158 mg, 1.82 mmol) in THF (1.5 mL) was added. After 0.5 h, Boc-Phe-NCA (500 mg, 1.72 mmol), diluted in anhydrous THF (2.5 mL), was slowly added under nitrogen at the same temperature. The resulting mixture was stirred for additional 4h and then allowed to warm up to room temperature. After quenching with a saturated solution of NH₄Cl, the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over MgSO₄. After filtration,

the solvent was evaporated to obtain crude **2h** that was purified by column chromatography on silica gel (9:1 v/v cyclohexane-AcOEt) to afford 343 mg (64 %) of title compound **2h**.



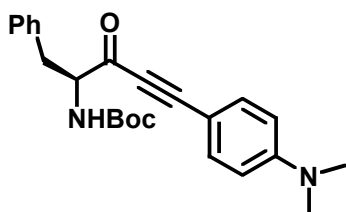
White solid; m.p. 88-90°C; *e.e.* 18 %; ^1H NMR (CDCl_3 , 400 MHz), δ (ppm): 7.32-7.24 (m, 3H), 7.19-7.16 (m, 2H), 5.05 (d, $J = 7.6$ Hz, 1H), 4.63 (dd, $J = 6.0, 13.7$ Hz, 1H), 3.21 (dd, $J = 5.9, 14.0$ Hz, 1H), 3.16 (dd, $J = 5.9, 14.0$ Hz, 1H), 1.46-1.39 (m, 1H), 1.42 (s, 9H), 1.05-0.98 (m, 2H), 0.97-0.90 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz), δ (ppm): 185.6, 155.1, 135.8, 129.5, 128.5, 127.0, 103.1, 79.9, 75.2, 61.8, 37.5, 28.3, 10.1, 10.0, -0.10; ESI-MS m/z : 314.1 ($\text{M}+\text{H}$) $^+$, 336.1 ($\text{M}+\text{Na}$) $^+$, 258.1 ($\text{M}+\text{H}-t\text{-Bu}$) $^+$, 214.1 ($\text{M}+\text{H}-\text{Boc}$) $^+$, 627.2 ($2\text{M}+\text{H}$) $^+$, 649.1 ($2\text{M}+\text{Na}$) $^+$; HMRS (ESI) calcd. For $\text{C}_{19}\text{H}_{24}\text{NO}_3$ ($\text{M}+\text{H}$) $^+$: 314.1756, found: 314.1761; HPLC chiralpak AD-H, *i*-propanol / hexane = 2/98, flow rate 1.0 mL/min, $\lambda = 214$ nm, $t_{\text{major}} = 21.383$ min, $t_{\text{minor}} = 15.467$ min.

Chiral HPLC Chromatogram of **2h**



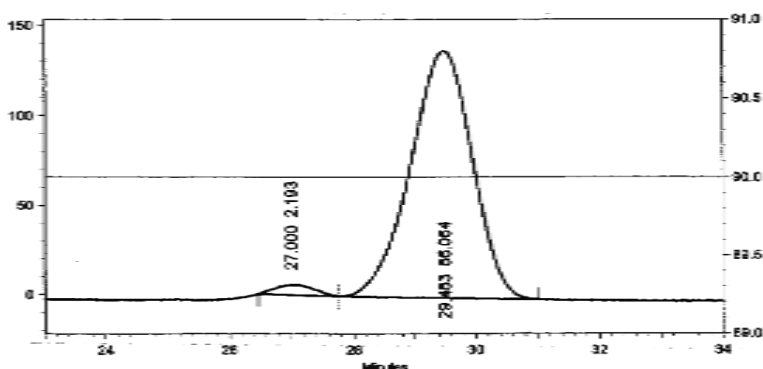
Tert-butyl 5-(4-(dimethylamino)phenyl)-3-oxo-1-phenylpent-4-yn-2-ylcarbamate (2i). A solution of 4-ethynyl-*N,N*-dimethylaniline (313 mg, 2.16 mmol) in anhydrous THF (1.5 mL) was added dropwise to a stirred solution of BuLi (1.4 mL of a 1.6 M solution in hexane, 2.16 mmol) in anhydrous THF at -78°C. To the resulting mixture, maintained at -78°C under stirring, a solution of LiBr (153 mg, 1.76 mmol) in THF (1.5 mL) was added. After 0.5 h, Boc-Phe-NCA (485 mg, 1.66 mmol), diluted in anhydrous THF (2.5 mL), was slowly added under nitrogen at the same temperature. The resulting mixture was stirred for additional 4h and then allowed to warm up to room temperature. After quenching with a saturated solution of NH_4Cl , the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over MgSO_4 . After filtration, the solvent was evaporated to obtain crude **2i** that was purified by column chromatography on silica gel (8:2 cyclohexane-AcOEt) to afford 299 mg (46 %) of the title

compound.



Yellow solid; m.p. 132-134°C; *e.e.* 95 %; $[\alpha]_D^{20} = -102^\circ$ (10 mg/mL CH₂Cl₂); ¹H NMR (CDCl₃, 400 MHz), δ (ppm): 7.48 (d, *J* = 8.9 Hz, 2H), 7.31-7.24 (m, 5H), 6.67 (d, *J* = 9.0 Hz, 2H), 5.22 (d, *J* = 7.8 Hz, 1H), 4.82 (dd, *J* = 5.9, 13.5 Hz, 1H), 3.34 (dd, *J* = 5.9, 14.0 Hz, 1H), 3.28 (dd, 5.7, 14.0 Hz, 1H), 3.1 (s, 6H), 1.46 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz), δ (ppm): 185.5, 155.2, 152.1, 136.2, 135.5, 129.8, 128.6, 127.0, 111.6, 105.0, 99.9, 87.6, 79.9, 61.9, 40.1, 37.9, 28.5; ESIMS *m/z*: 393.1 (M+H)⁺, 337.1 (M+H-*t*-Bu)⁺, 293.1 (M+H-Boc)⁺; HMRS (ESI) calcd. For C₂₄H₂₉N₂O₃ (M+H)⁺: 393.2178, found: 393.2183; HPLC chiralpak AD-H, *i*-propanol / hexane = 10/90, flow rate 1.0 mL/ min, λ = 214 nm, *t*_{major} = 29.483 min, *t*_{minor} = 27.000 min.

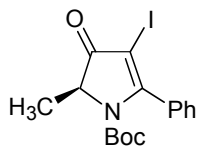
Chiral HPLC Chromatogram of 2i



IV. Typical experimental procedure for iodocyclization reaction in CH₃CN.

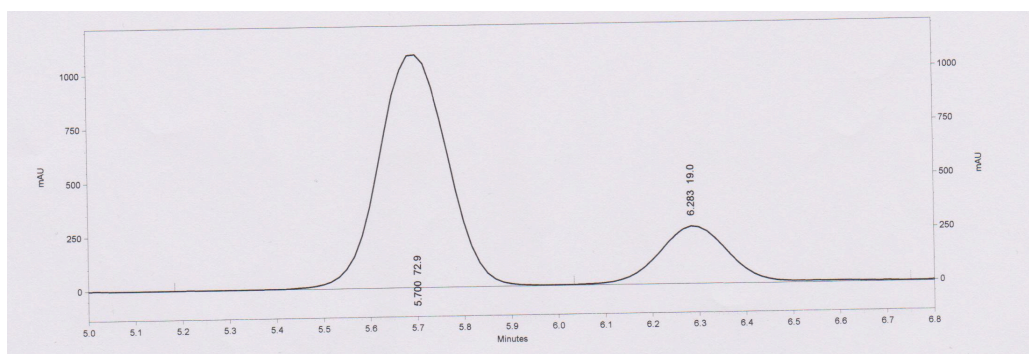
A typical experimental procedure for the iodocyclisation of **2e** is described. To a stirred solution of substrate **2** (0.1 mmol), NaHCO₃ (25.2 mg, 0.3 mmol) in 0.5 mL of CH₃CN, a solution of I₂ (76.2 mg) in 0.5 mL of CH₃CN was added. After 2h at r.t, the organic phase was evaporated under vacuum. The crude was dissolved in AcOEt and washed with a saturated solution of thiosulphate (Na₂S₂O₃) to neutralize the excess of iodine, affording the product **3**.

β -Iodopyrrolin-4-one (3b). Based on the typical procedure, and starting from 18.1 mg of **2b**, 28.7 mg (98% isolated yield) were obtained.

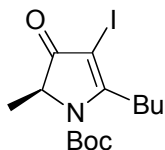


Yellow oil, *e.e.* 60% ; ^1H NMR (CDCl_3 , 400 MHz), δ (ppm): 7.49-7.47 (m, 3H), 7.39-7.36 (m, 2H), 4.41 (q, $J = 7.04$ Hz, 1H), 1.64 (d, $J = 7.04$ Hz, 3H), 1.20 (s, 9H). ^{13}C NMR (CDCl_3 , 100 MHz), δ (ppm): 197.3, 170.8, 148.7, 133.3, 130.0, 128.1, 127.8, 83.3, 78.0, 61.8, 27.6, 17.8. ESI-MS m/z 400.0 ($\text{M}+\text{H}$) $^+$, 422.1 ($\text{M}+\text{Na}$) $^+$, 344.1 ($\text{M}+\text{H}-t\text{-Bu}$) $^+$, 300.0 ($\text{M}+\text{H}-\text{Boc}$) $^+$, 821.1 ($2\text{M}+\text{Na}$) $^+$. HMRS (ESI) calcd. For $\text{C}_{16}\text{H}_{19}\text{NO}_3\text{I}$ ($\text{M}+\text{H}$) $^+$: 400.0410, found: 400.0407. HPLC Chiralcel OD-RH, ACN / H_2O (+0.01% TFA) = 60/40, flow rate 1.0 mL / min, $\lambda = 214$ nm, $t_{\text{major}} = 6.283$ min, $t_{\text{minor}} = 5.700$ min.

Chiral HPLC Chromatogram of **3b**

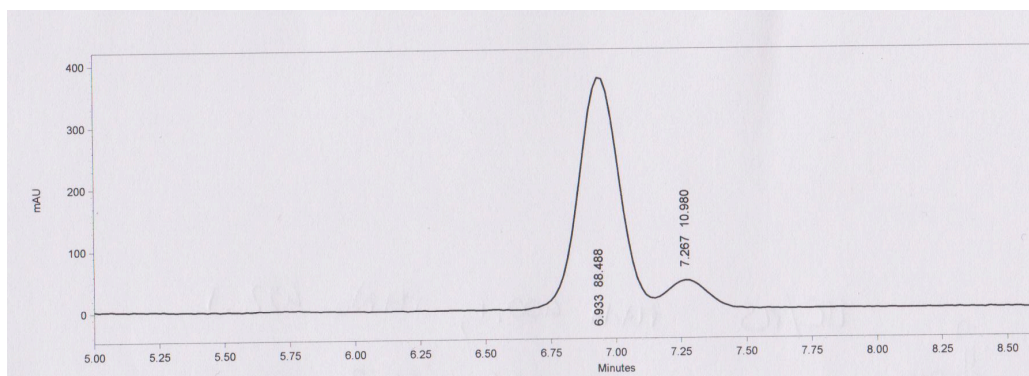


β -Iodopyrrolin-4-one (3c). Based on the typical procedure, and starting from 25.7 mg of **2c**, 27.9 mg (76% isolated yield) of **3c** were obtained.

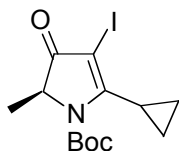


Yellow oil, *e.e.* 78%. ^1H NMR (CDCl_3 , 400 MHz), δ (ppm): 4.20 (q, $J = 7.0$ Hz, 1H), 3.16-3.03 (m, 2H), 1.68-1.44 (m, 4H), 1.49 (s, 9H), 1.44 (d, $J = 7.0$ Hz, 3H), 0.98 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz), δ (ppm): 196.7, 175.3, 148.3, 83.5, 76.8, 76.0, 61.8, 32.0, 29.8, 28.1, 22.8, 17.8, 13.9. ESI-MS m/z 380.1 ($\text{M}+\text{H}$) $^+$, 402.0 ($\text{M}+\text{Na}$) $^+$, 324.0 ($\text{M}+\text{H}-t\text{-Bu}$) $^+$. Confirmed by chiral LC/MS. HMRS (ESI) calcd. For $\text{C}_{14}\text{H}_{23}\text{NO}_3\text{I}$ ($\text{M}+\text{H}$) $^+$: 380.0723, found: 380.0731. HPLC Chiralcel OD-RH, ACN / H_2O (+0.01% TFA) = 60/40, flow rate 1.0 mL / min, $\lambda = 214$ nm, $t_{\text{major}} = 7.267$ min, $t_{\text{minor}} = 6.933$ min.

Chiral HPLC Chromatogram of **3c**

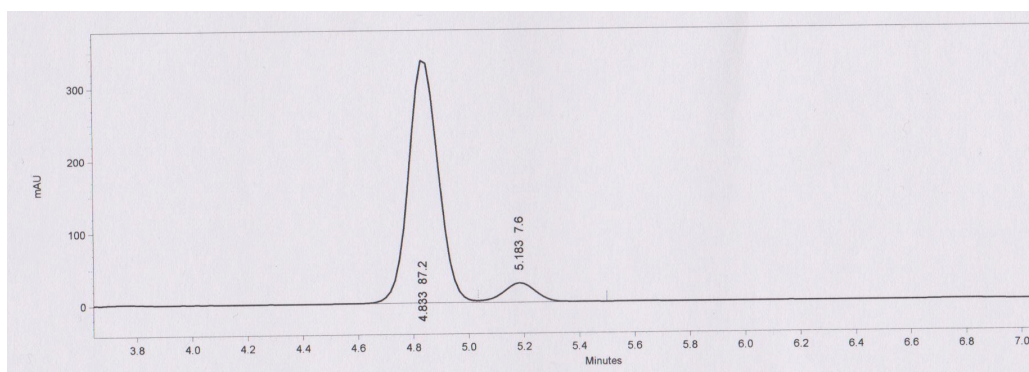


β -Iodopyrrolin-4-one (3d). Based on the typical procedure, and starting from 24.3 mg of **2d**, 36.4 mg (98% isolated yield) of **3d** were obtained.



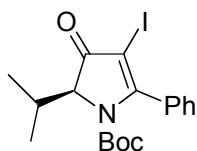
Yellow oil, *e.e.* 84%; ^1H NMR (CDCl_3 , 400 MHz), δ (ppm): 4.12 (q, $J = 7.0$ Hz, 1H), 2.32-2.24 (m, 1H), 1.47 (s, 9 Hz), 1.45 (d, $J = 7.0$ Hz, 3H), 1.18-1.10 (m, 4H); ^{13}C NMR (CDCl_3 , 100 MHz), δ (ppm): 197.6, 172.9, 148.9, 83.2, 73.9, 61.6, 28.2, 17.8, 13.4, 10.3, 9.9. ESIMS m/z 364.0 ($\text{M}+\text{H}$) $^+$, 386.0 ($\text{M}+\text{Na}$) $^+$, 308.0 ($\text{M}+\text{H}-t\text{-Bu}$) $^+$. Confirmed by chiral LC/MS. HMRS (ESI) calcd. for $\text{C}_{13}\text{H}_{19}\text{NO}_3\text{I}$ ($\text{M}+\text{H}$) $^+$: 364.0410, found: 364.0407. HPLC Chiralcel OD-RH, ACN / H_2O (+0.01% TFA) = 60/40, flow rate 1.0 mL / min, $\lambda = 214$ nm, $t_{\text{major}} = 5.183$ min, $t_{\text{minor}} = 4.833$ min.

Chiral HPLC Chromatogram of **3d**



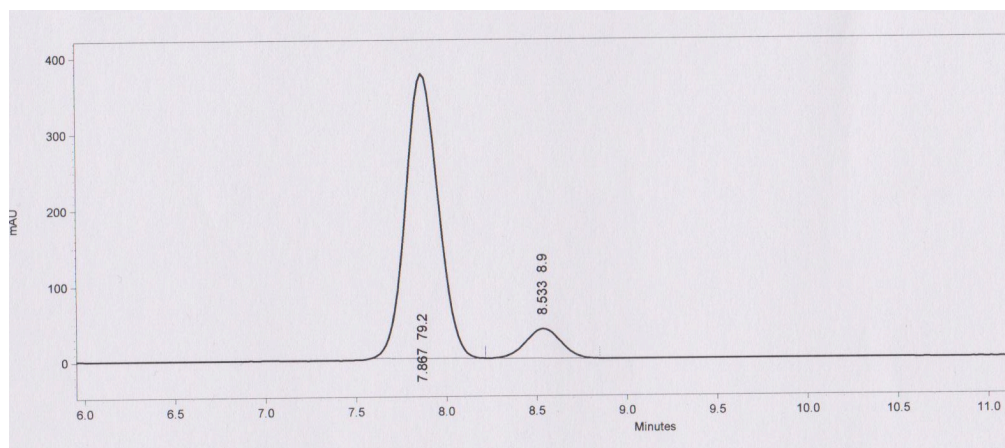
β -Iodopyrrolin-4-one (3e). Based on the typical procedure, and starting from 34.1 mg of **2e**, 47.3 mg (98% isolated yield) of **3e** were obtained.

Yellow oil, *e.e.* 80%; ^1H NMR (CDCl_3 , 400 MHz), δ (ppm): 7.49-7.40 (m, 5H), 4.35 (d, $J = 3.5$ Hz, 1H), 2.60 (m, 1H), 1.18 (d, $J = 7.0$ Hz, 3H),

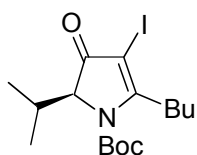


1.16 (s, 9H), 0.95 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz), δ (ppm): 197.0, 171.2, 149.3, 133.6, 130.0, 128.1, 127.8, 83.1, 80.72, 69.8, 32.2, 27.5, 17.1, 16.8. HMRS (ESI) calcd. for $\text{C}_{18}\text{H}_{23}\text{NO}_3\text{I}$ ($\text{M}+\text{H}$) $^+$: 428.0723, found: 428.0714. ESI-MS m/z 427.9 ($\text{M}+\text{H}$) $^+$, 449.9 ($\text{M}+\text{Na}$) $^+$, 371.9 ($\text{M}+\text{H}-t\text{-Bu}$) $^+$, 327.9 ($\text{M}+\text{H}-\text{Boc}$). Confirmed by chiral LC/MS. HPLC Chiralcel OD-RH, ACN / H_2O (+0.01% TFA) = 60/40, flow rate 1.0 mL / min, $\lambda = 214$ nm, $t_{\text{major}} = 8.533$ min, $t_{\text{minor}} = 7.867$ min.

Chiral HPLC Chromatogram of **3e**

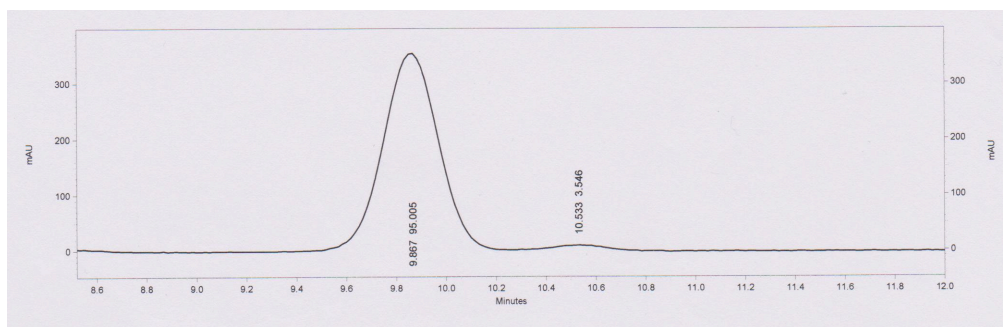


β -Iodopyrrolin-4-one (3f**)**. Based on the typical procedure, and starting from 27.6 mg of **2f**, 37.4 mg (96% isolated yield) of **3f** were obtained.

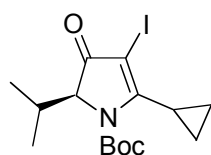


Yellow oil, *e.e.* 93%; ^1H NMR (CDCl_3 , 400 MHz), δ (ppm): 4.16 (d, $J = 3.4$ Hz, 1H), 3.24-3.17 (m, 1H), 3.00-2.96 (m, 1H), 2.45-2.39 (m, 1H), 1.67-1.44 (m, 4H), 1.47 (s, 9H), 1.15 (d, $J = 7.1$ Hz, 3H), 0.96 (t, $J = 7.0$ Hz, 3H), 0.76 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz), δ (ppm): 196.0, 175.7, 148.5, 83.4, 77.2; 69.6, 32.3, 31.2, 30.1, 28.1, 22.9, 17.4, 15.9, 13.9; HMRS (ESI) calcd. for $\text{C}_{16}\text{H}_{27}\text{NO}_3\text{I}$ ($\text{M}+\text{H}$) $^+$: 408.1036, found: 408.1030; ESI-MS m/z 408.0($\text{M}+\text{H}$) $^+$, 429.2 ($\text{M}+\text{Na}$) $^+$, 352.0 ($\text{M}+\text{H}-t\text{-Bu}$) $^+$, 837.1 ($2\text{M}+\text{Na}$) $^+$. Confirmed by chiral LC/MS. HPLC Chiralcel OD-RH, ACN / H_2O (+0.01% TFA) = 60/40, flow rate 1.0 mL / min, $\lambda = 214$ nm, $t_{\text{major}} = 10.533$ min, $t_{\text{minor}} = 9.867$ min.

Chiral HPLC Chromatogram of **3f**

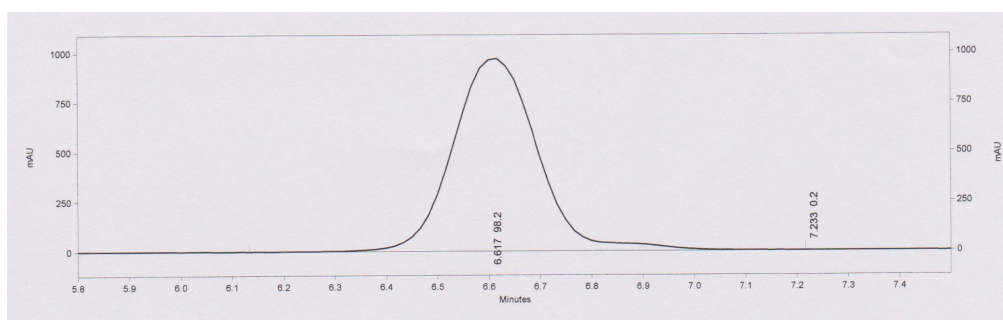


β -Iodopyrrolin-4-one (3g). Based on the typical procedure, and starting from 26.5 mg of **2g**, 37.0 mg (95% isolated yield) of **3g** were obtained.



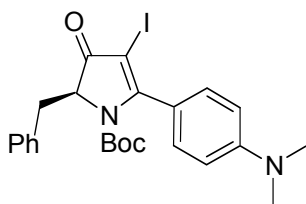
Yellow oil, *e.e.* 99%; ^1H NMR (CDCl_3 , 400 MHz), δ (ppm): 4.13 (d, $J = 3.1$ Hz, 1H), 2.45-2.39 (m, 1H), 2.28-2.21 (m, 1H), 1.51 (s, 9H), 1.33-1.1 (m, 4H), 1.03 (d, $J = 7.0$ Hz, 3H), 0.74 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz), δ (ppm): 197.2, 173.8, 149.3, 83.1, 77.4, 69.6, 31.5, 28.1, 17.2, 16.2, 13.9, 10.6, 9.5. HMRS (ESI) calcd. for $\text{C}_{15}\text{H}_{23}\text{NO}_3\text{I}$ ($\text{M}+\text{H}$) $^+$: 392.0723, found: 392.0721. ESI-MS m/z 392.0 ($\text{M}+\text{H}$) $^+$, 414.0 ($\text{M}+\text{Na}$) $^+$, 336.0 ($\text{M}+\text{H}-t\text{-Bu}$) $^+$. Confirmed by chiral LC/MS. HPLC Chiralcel OD-RH, ACN / H_2O (+0.01% TFA) = 60/40, flow rate 1.0 mL / min, $\lambda = 214$ nm, $t_{\text{major}} = 6.9$ min, $t_{\text{minor}} = 6.617$ min.

Chiral HPLC Chromatogram of **3g**



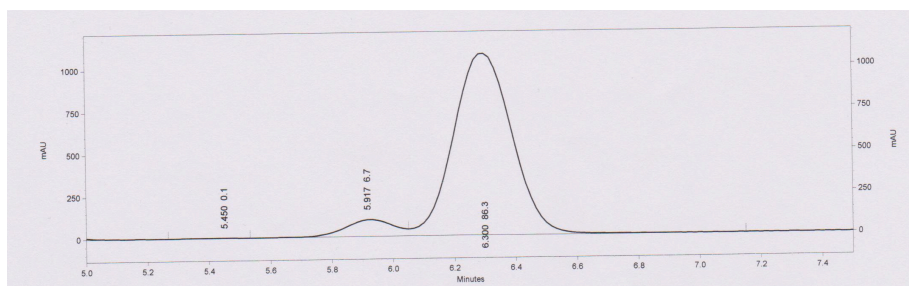
β -Iodopyrrolin-4-one (3i). Based on the typical procedure, and starting from 20.4 mg of **2i**, 27.4 mg (94% isolated yield) of **3i** were obtained.

Orange oil, *e.e.* 86%; ^1H NMR (CDCl_3 , 400 MHz), δ (ppm): 7.32-7.27 (m, 4H), 7.14 (m, 2H), 6.92 (d, $J = 8.0$ Hz, 2H), 6.67 (d, $J = 8.3$ Hz, 2H), 4.63 (dd, $J = 6.3$ and 2.4 Hz, 1H), 3.59 (dd, $J = 13.3$ and 6.3 Hz, 1H), 3.46 (dd, $J = 13.3$ and 2.4 Hz, 1H), 3.05 (s, 6H), 1.38 (s, 9H); ^{13}C



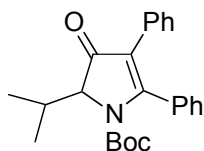
NMR (CDCl₃, 100 MHz), δ (ppm): 196.3, 172.2, 151.5, 149.4, 134.5, 129.7, 128.0, 127.2, 119.0, 110.3, 82.8, 77.5, 66.0, 40.1, 38.0, 27.9; ESI-MS m/z 519.0 (M+H)⁺; HMRS (ESI) calcd. for C₂₄H₂₈NO₃I (M+H)⁺: 519.1145, found: 519.1158; HPLC Chiralcel OD-RH, ACN / H₂O (+0.01% TFA) = 60/40, flow rate 1.0 mL / min, λ = 214 nm, t_{major} = 6.300 min, t_{minor} = 5.917 min.

Chiral HPLC Chromatogram of **3i**



VI. Cross-coupling reactions.

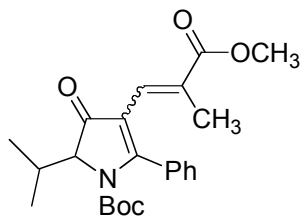
Pyrrolin-4-one (4e). A mixture of β -iodopyrrolin-4-one **3e** (1 equiv., 41.7 mg), Pd(OAc)₂ (0.05 eq., 1.1 mg), Ph-B(OH)₂ (1.5 eq., 18.3 mg), K₂CO₃ (3 eq., 41.4 mg) and PEG₃₄₀₀ (400 mg) was heated under microwave irradiation at 100°C. After 1h a full conversion of substrate was observed. The mixture was cooled down, dissolved in a small amount of CH₂Cl₂ and cooled for 4h at -18°C for a complete precipitation of PEG. After filtration the crude product was purified by column chromatography (cyclohexane/AcOEt = 8/2 v/v) to afford 26.9 mg (71%) of pure product **4e**.



¹H NMR (CDCl₃, 400 MHz), δ (ppm): 7.30-7.19 (m, 5H), 7.10-7.08 (m, 3H), 6.95-6.92 (m, 2H), 4.23 (d, J = 3.5 Hz, 1H), 2.59 (m, 1H), 1.15 (d, J = 6.9 Hz, 3H), 1.12 (s, 9H), 0.98 (d, J = 6.9 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz), δ (ppm): 199.7, 166.6, 150.5, 132.9, 129.6, 129.4, 129.3, 128.1, 128.0, 127.0, 124.1, 82.5, 70.2, 32.3, 27.7, 26.9, 17.1. ESI-MS m/z 378.2 (M+H)⁺, 400.2 (M+Na)⁺, 322.2 (M+H-*t*-Bu)⁺, 278.1 (M+H-Boc), 777.5 (2M+Na)⁺. HMRS (ESI) calcd. for C₂₄H₂₈NO₃ (M+H)⁺: 378.2069, found: 378.2068.

Pyrrolin-4-one (5e). A mixture of β -iodopyrrolin-4-one **3e** (1 eq., 24 mg), PdCl₂(PPh₃)₃ (0.02 eq., 0.8 mg), methyl methacrylate (5 eq., 30 mg), TEA (3 eq., 18.2 mg) and PEG₃₄₀₀ (400 mg) was

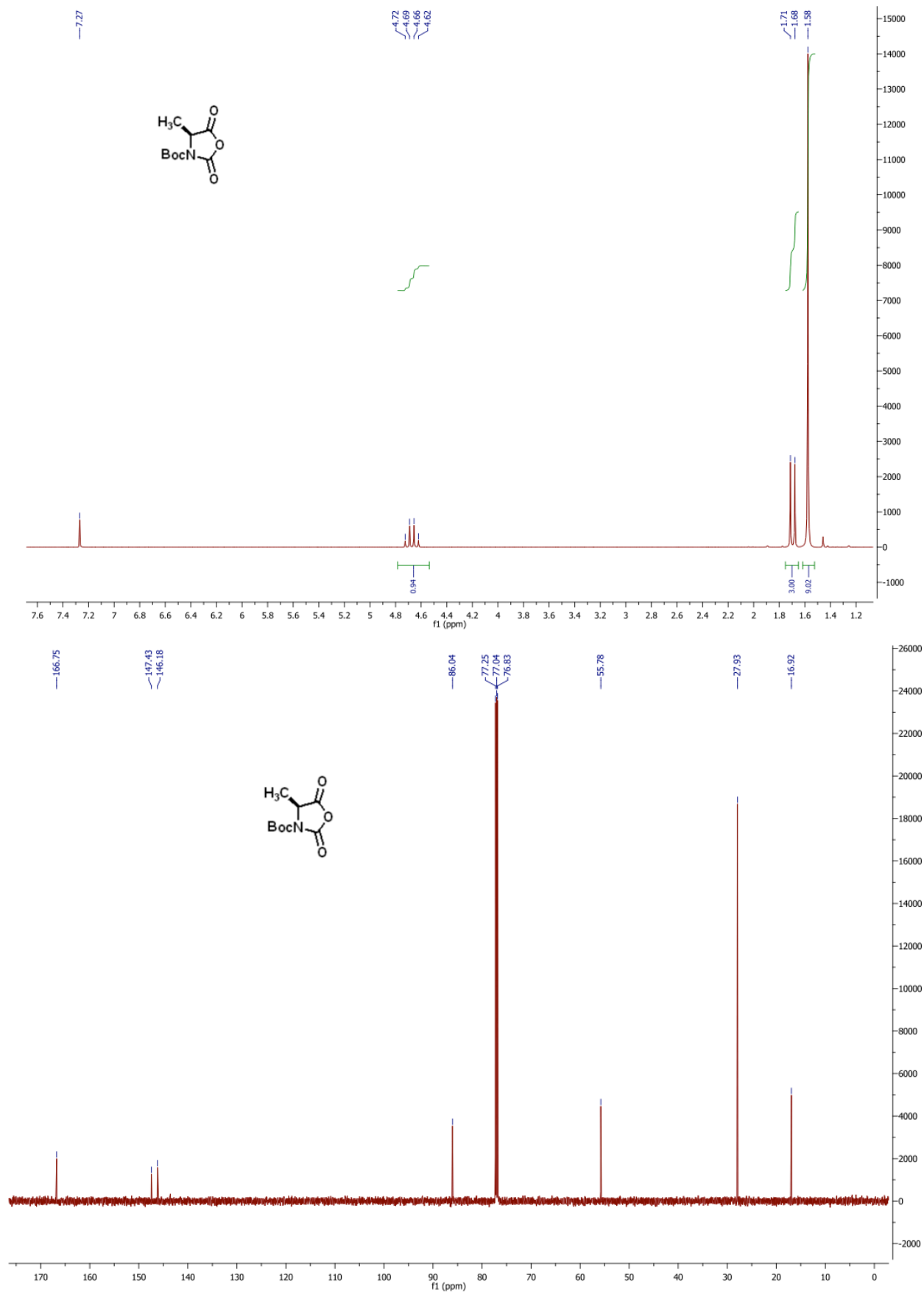
heated under microwave irradiation at 100°C. After 30 min. a full conversion of substrate was observed. The mixture was cooled down, dissolved in a small amount of CH₂Cl₂ and cooled for 4h at -18°C for a complete precipitation of PEG. After filtration the crude product was purified by column chromatography (cyclohexane/AcOEt = 8/2 v/v) to afford 13.6 mg (61%) of pure product **5e**.



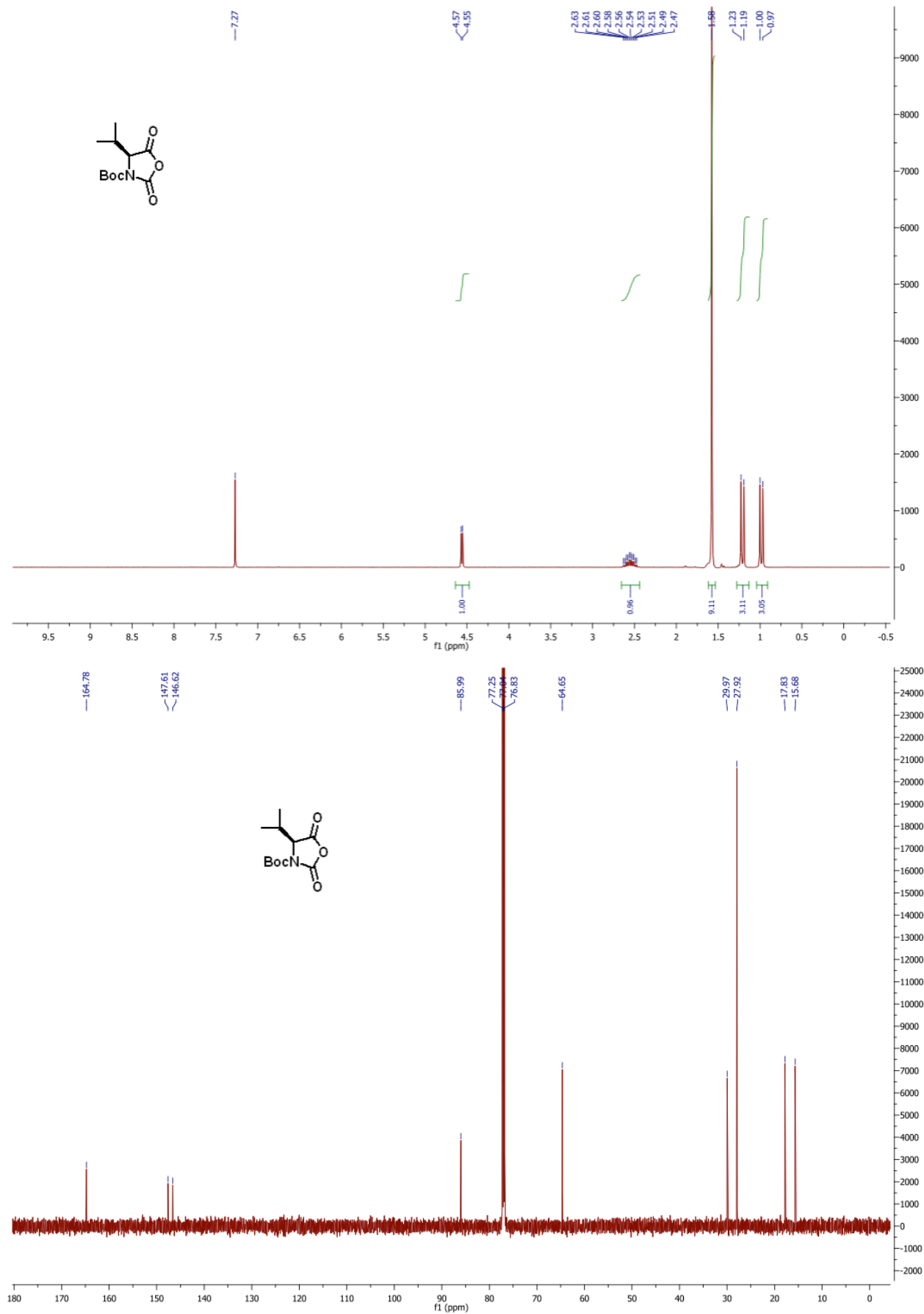
¹H NMR (CDCl₃, 400 MHz), δ (ppm): 7.46-7.43 (m, 3H), 7.36-7.27 (m, 2H), 6.77 (q, J = 1.3 Hz, 1H), 4.24 (d, J = 3.5 Hz, 1H), 3.69 (s, 3H), 2.66 (m, 1H), 1.87 (d, J = 1.3 Hz, 3H), 1.22 (s, 9H), 1.20 (d, J = 7.0 Hz, 3H), 1.00 (d, J = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz), δ (ppm): 197.3, 169.7, 168.4, 150.2, 132.5, 131.4, 130.3, 128.1, 127.7, 120.7, 83.1, 70.5, 51.9, 32.3, 27.6, 17.2, 17.0, 15.9; ESI-MS m/z 400.1 (M+H)⁺, 422.1 (M+Na)⁺, 344.1 (M+H-*t*-Bu)⁺, 300.2 (M+H-Boc)⁺; HMRS (ESI) calcd. for C₂₃H₃₀NO₅ (M+H)⁺: 400.2124, found: 400.2113.

VI. Spectral data.

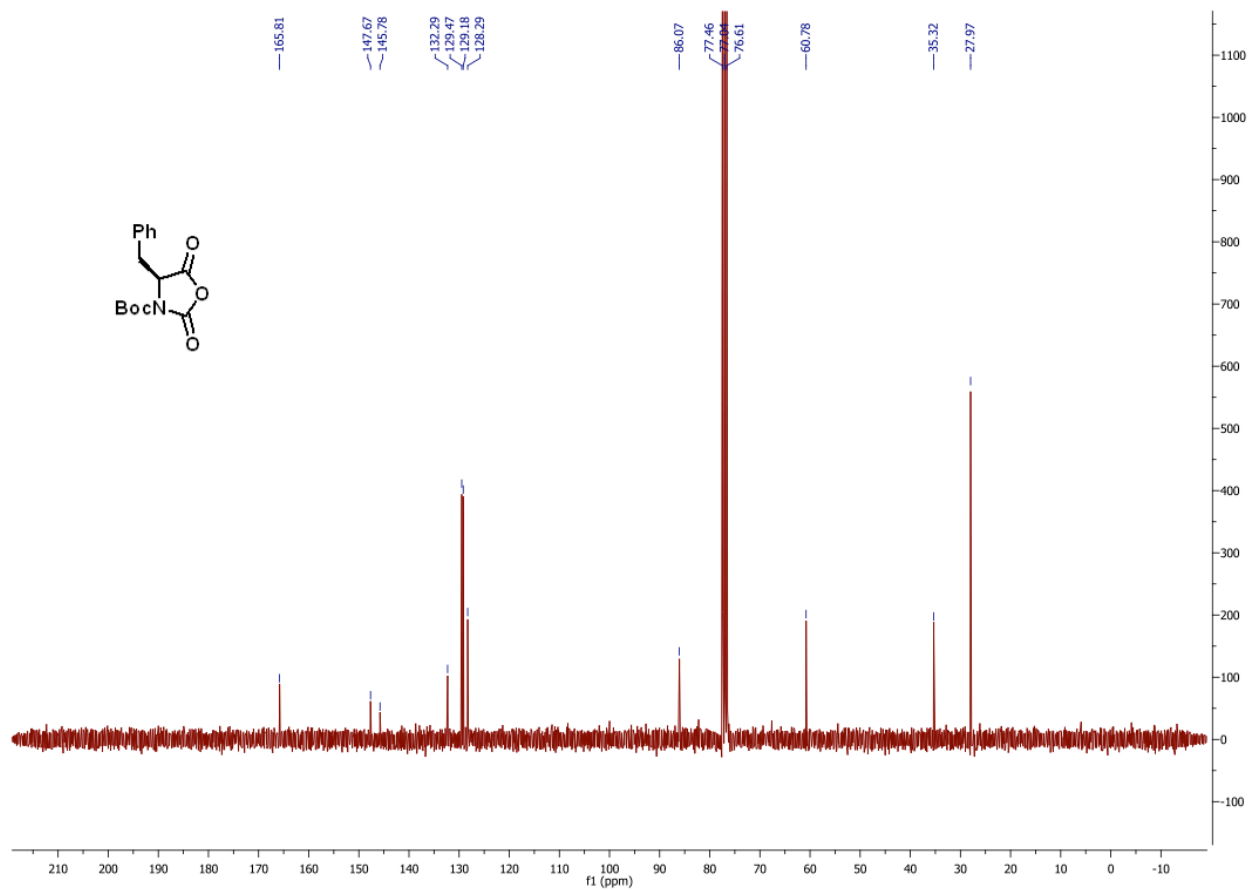
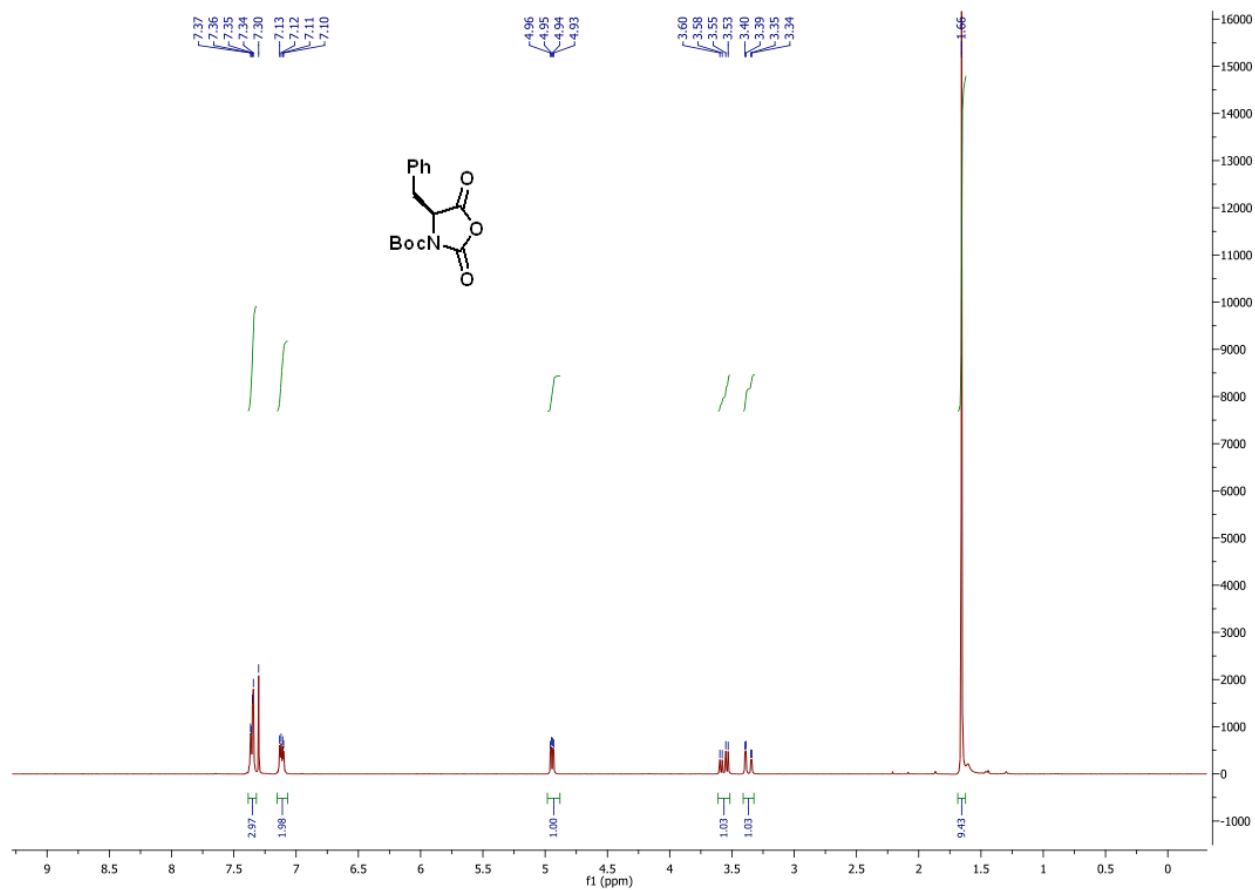
^1H and ^{13}C NMR of compound **Boc-Ala-NCA**



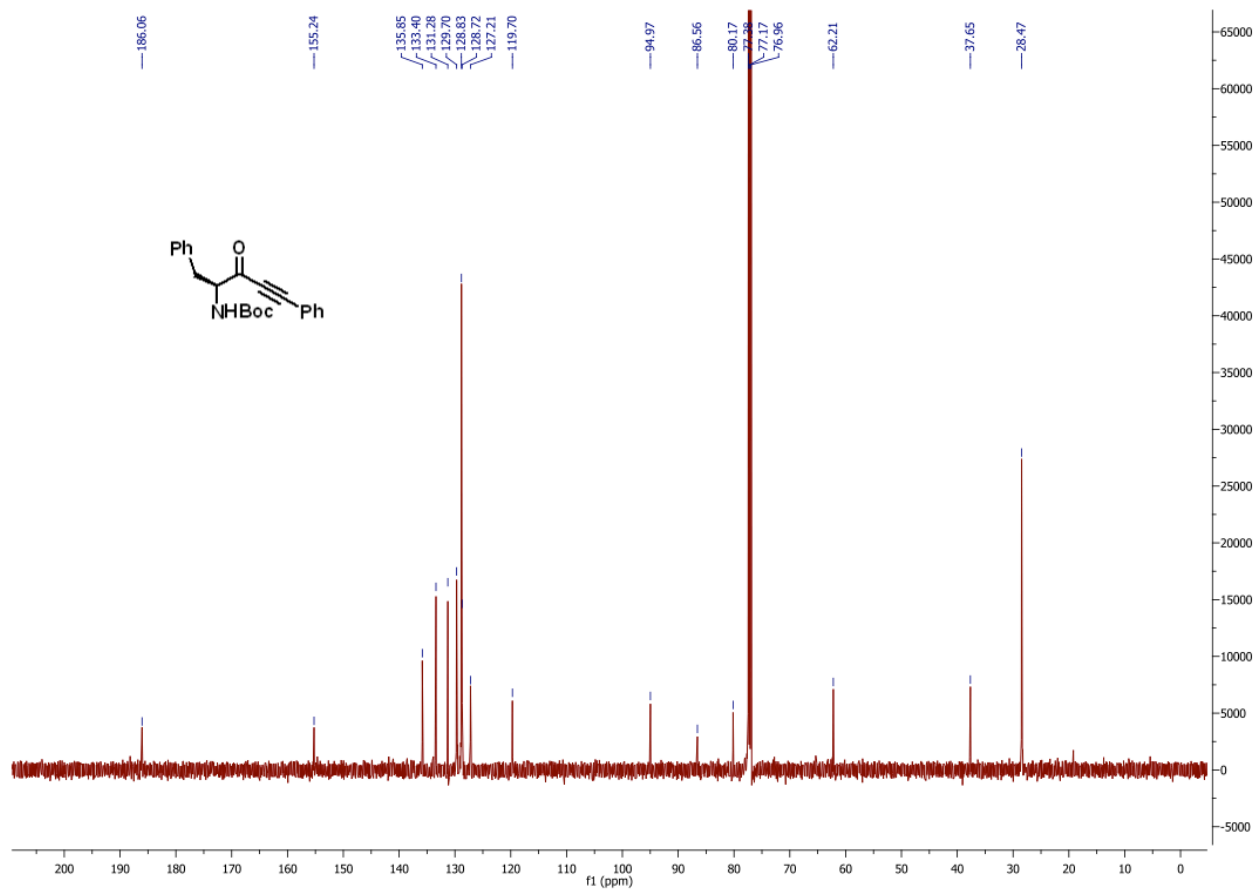
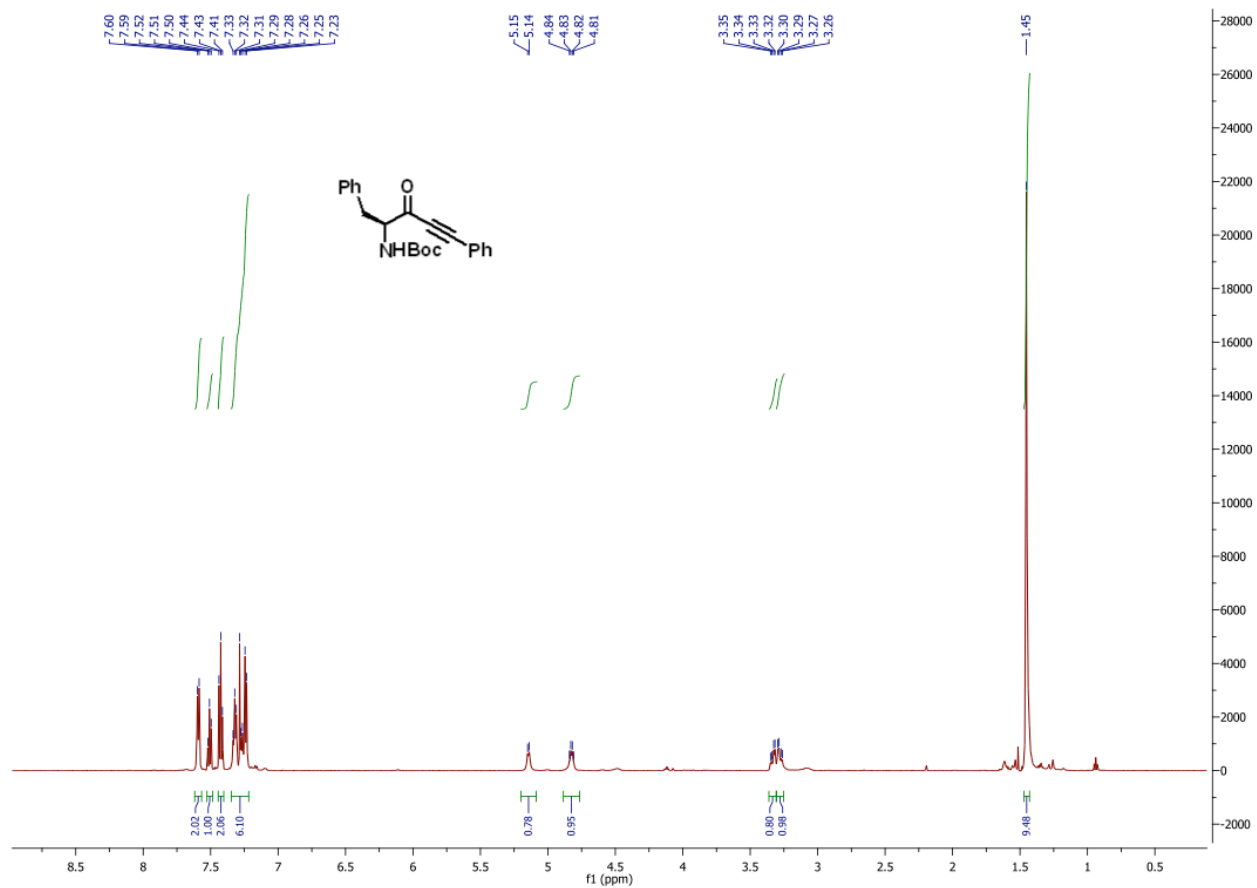
^1H and ^{13}C NMR of compound **Boc-Val-NCA**



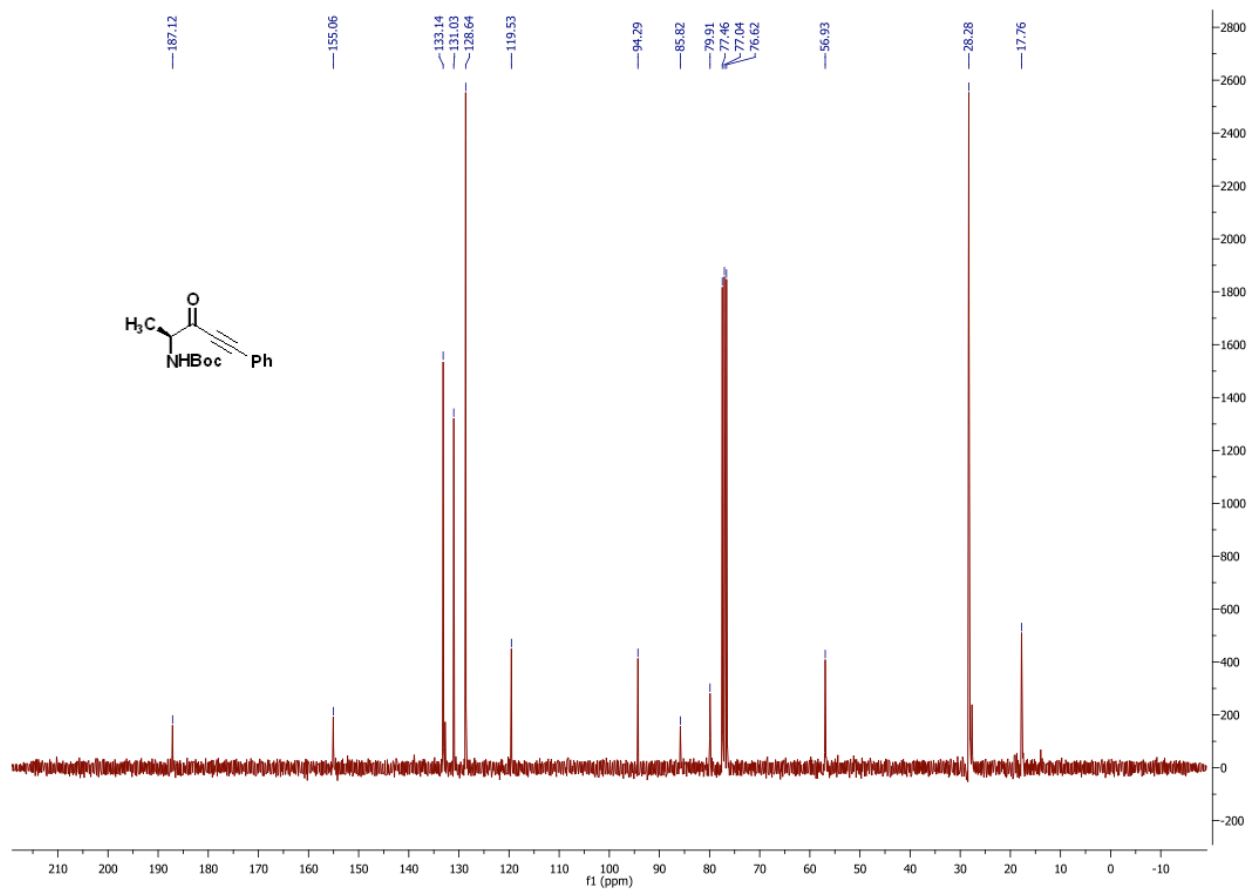
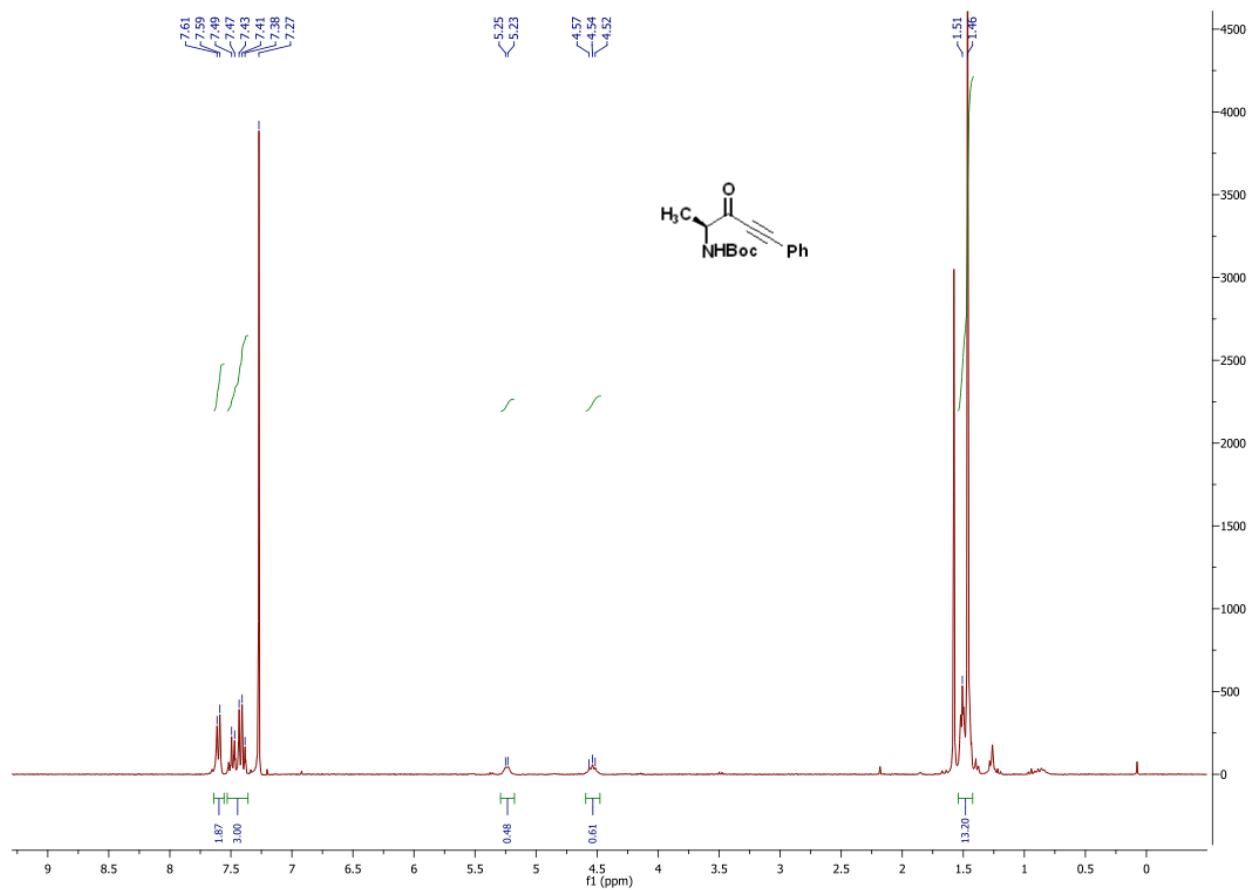
^1H and ^{13}C NMR of compound **Boc-Phe-NCA**



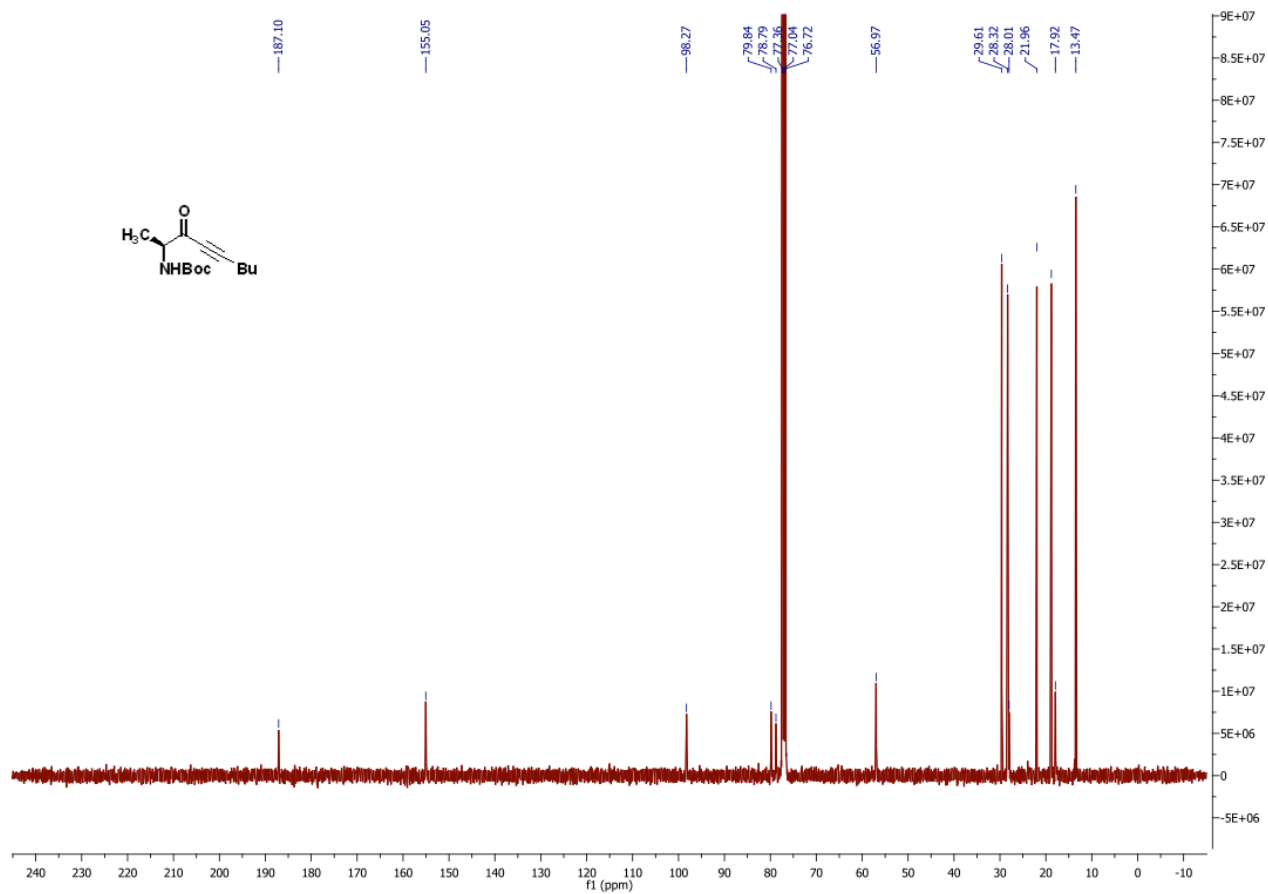
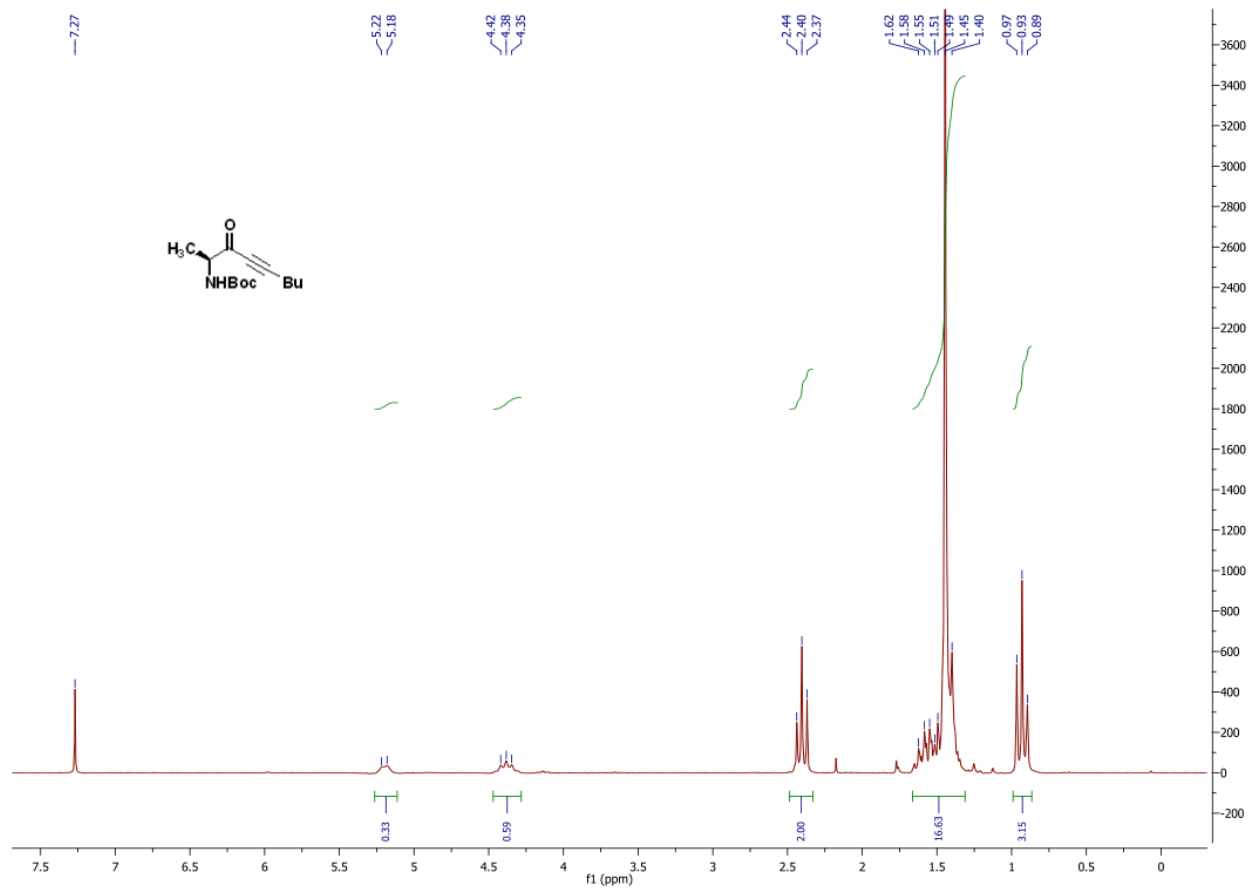
^1H and ^{13}C NMR of compound **2a**



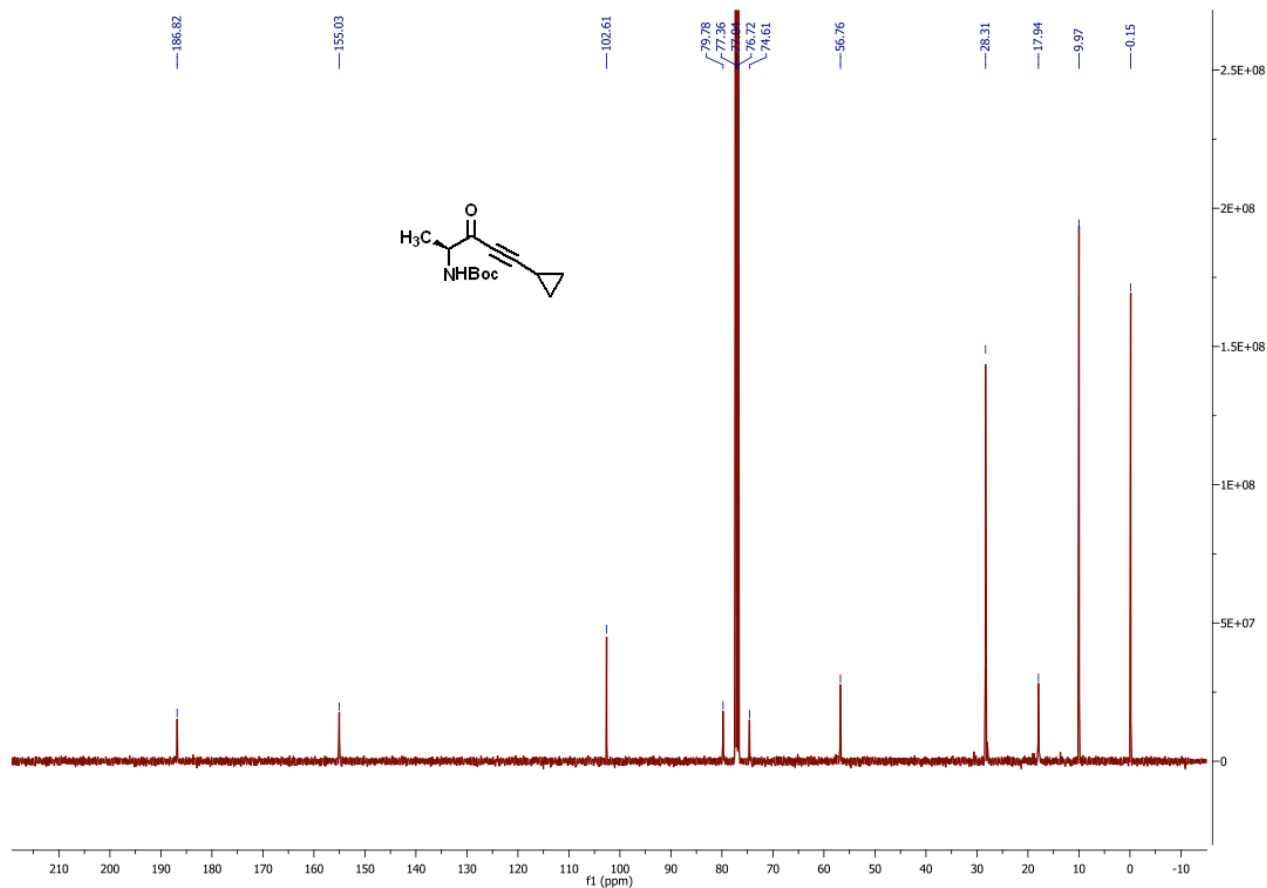
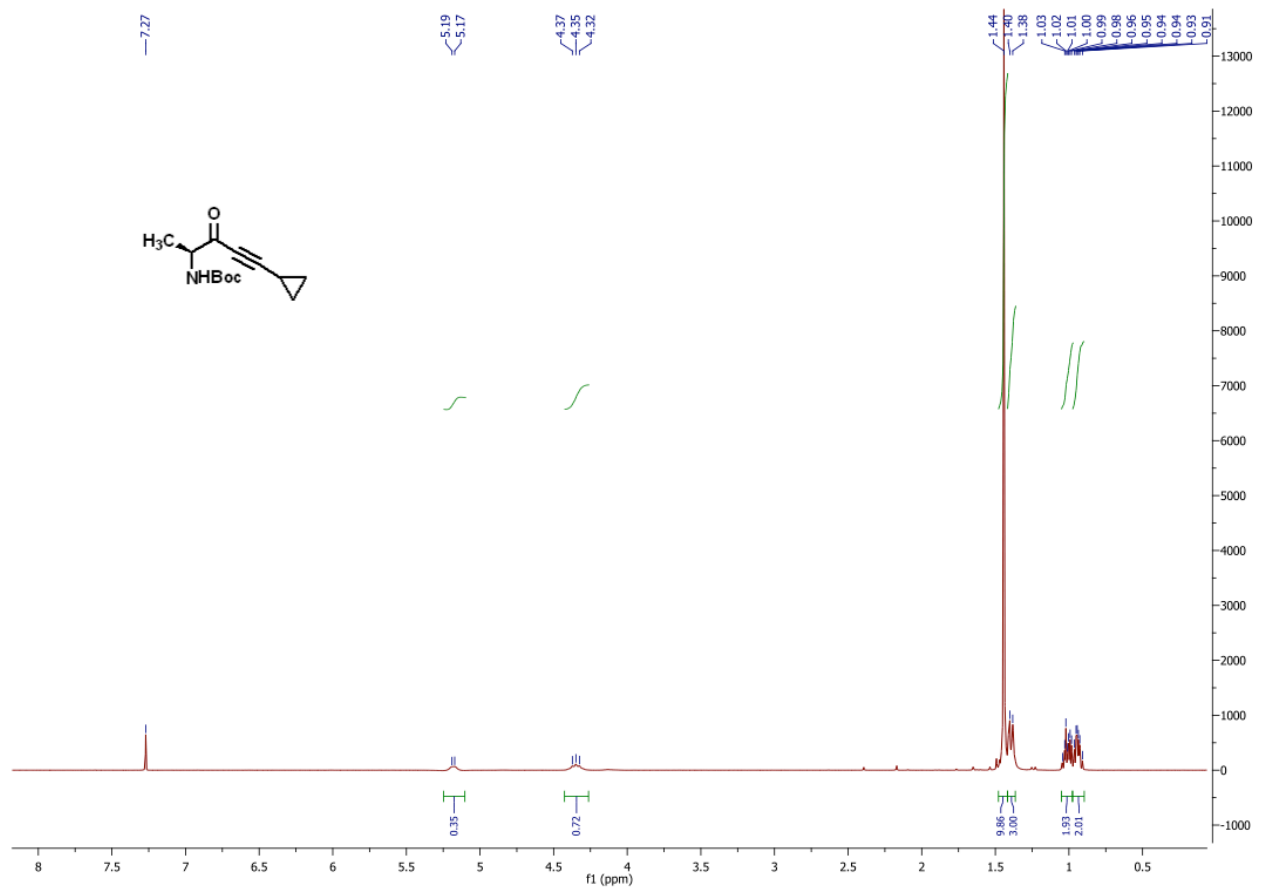
^1H and ^{13}C NMR of compound **2b**



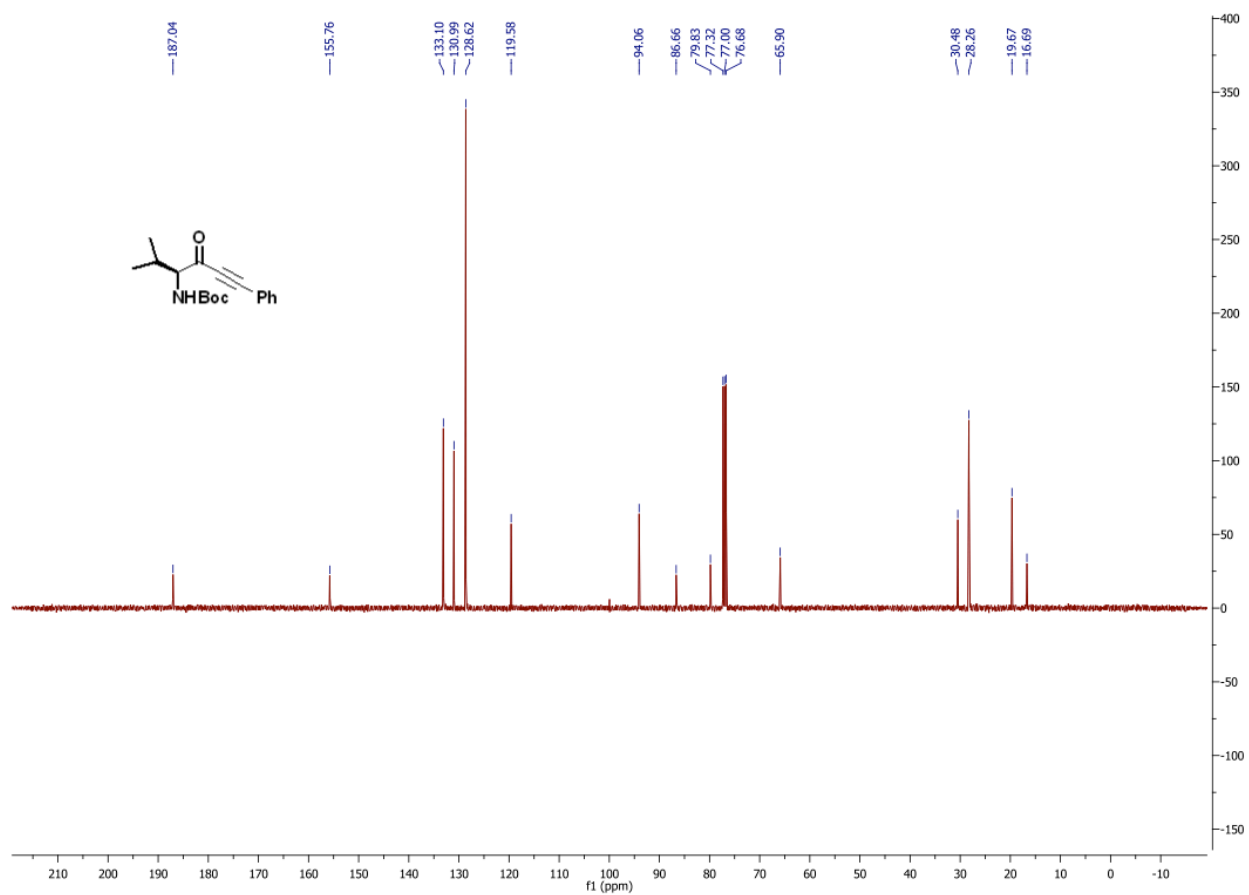
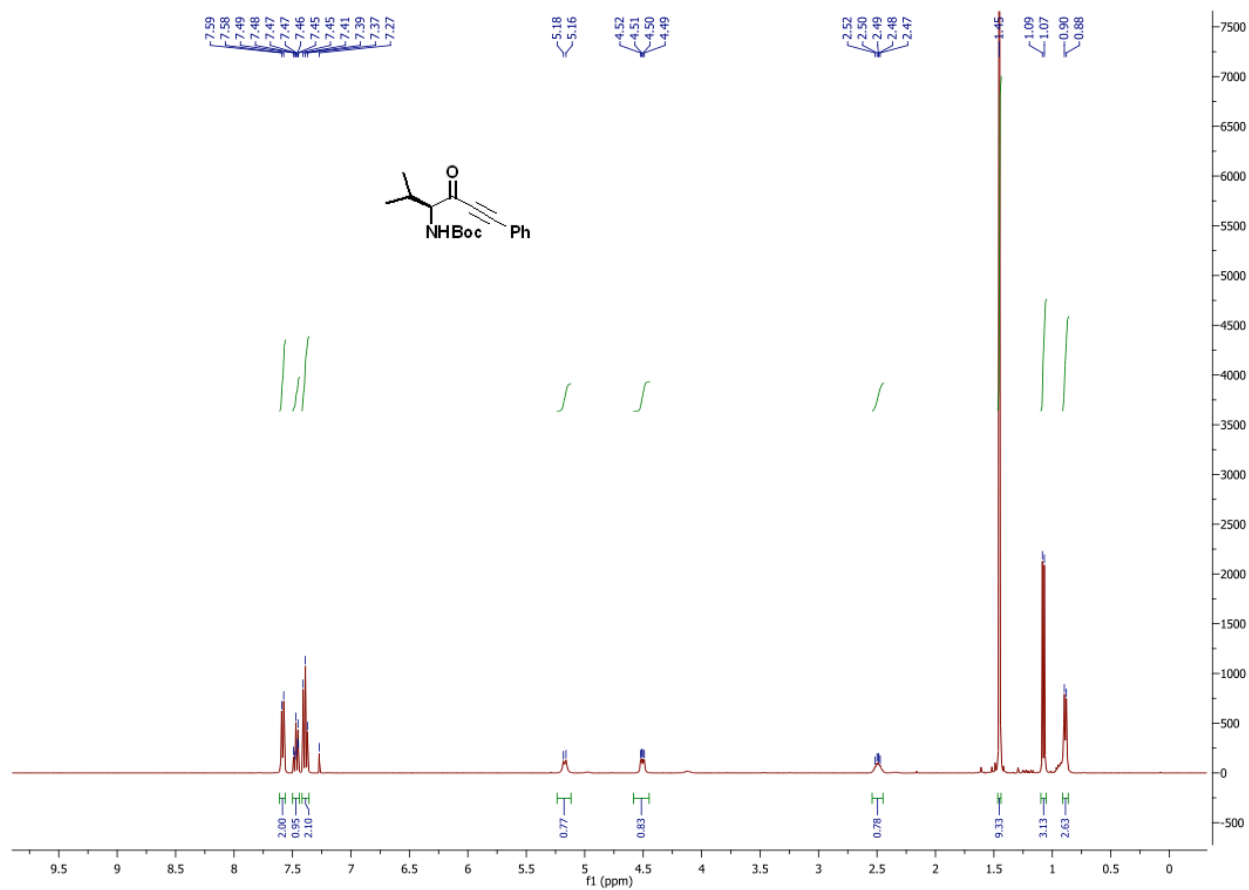
^1H and ^{13}C NMR of compound **2c**



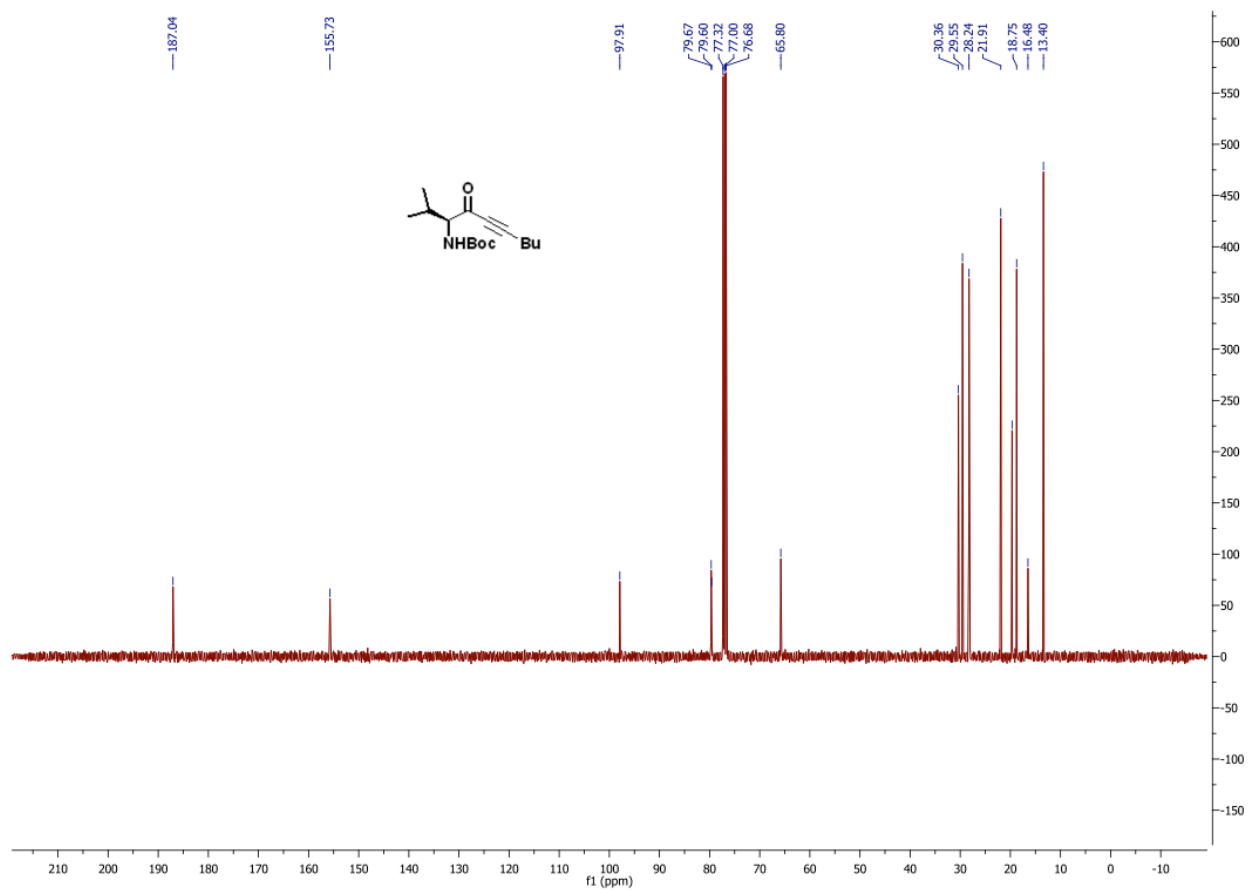
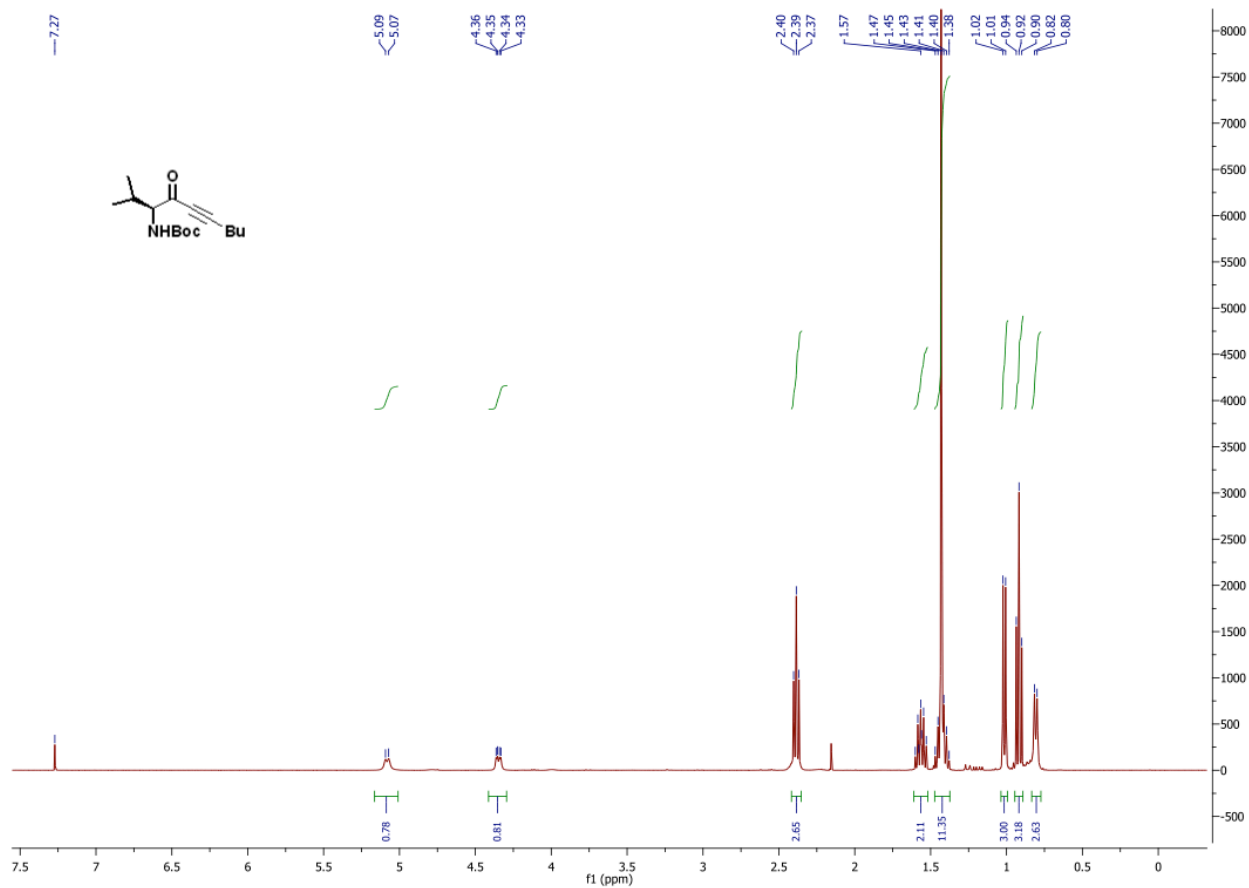
^1H and ^{13}C NMR of compound **2d**



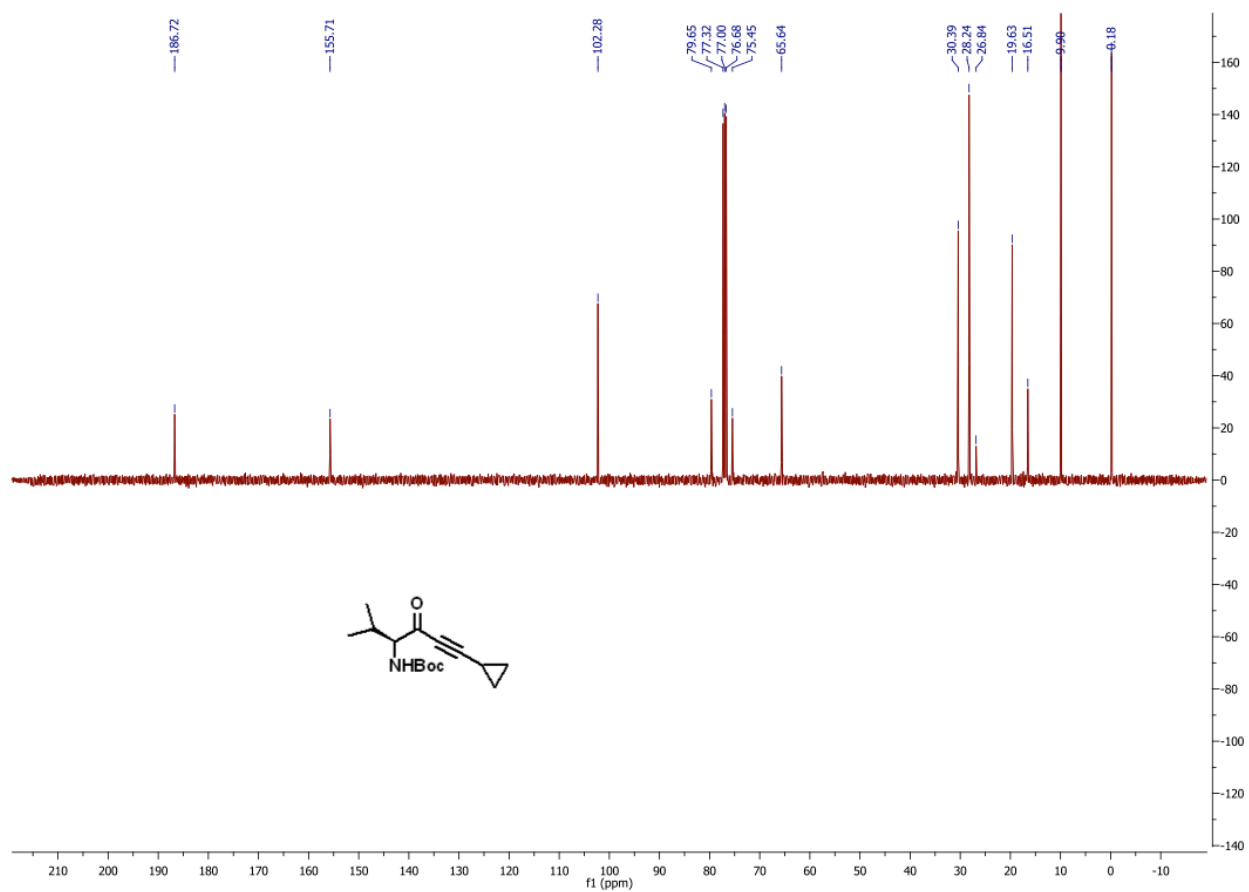
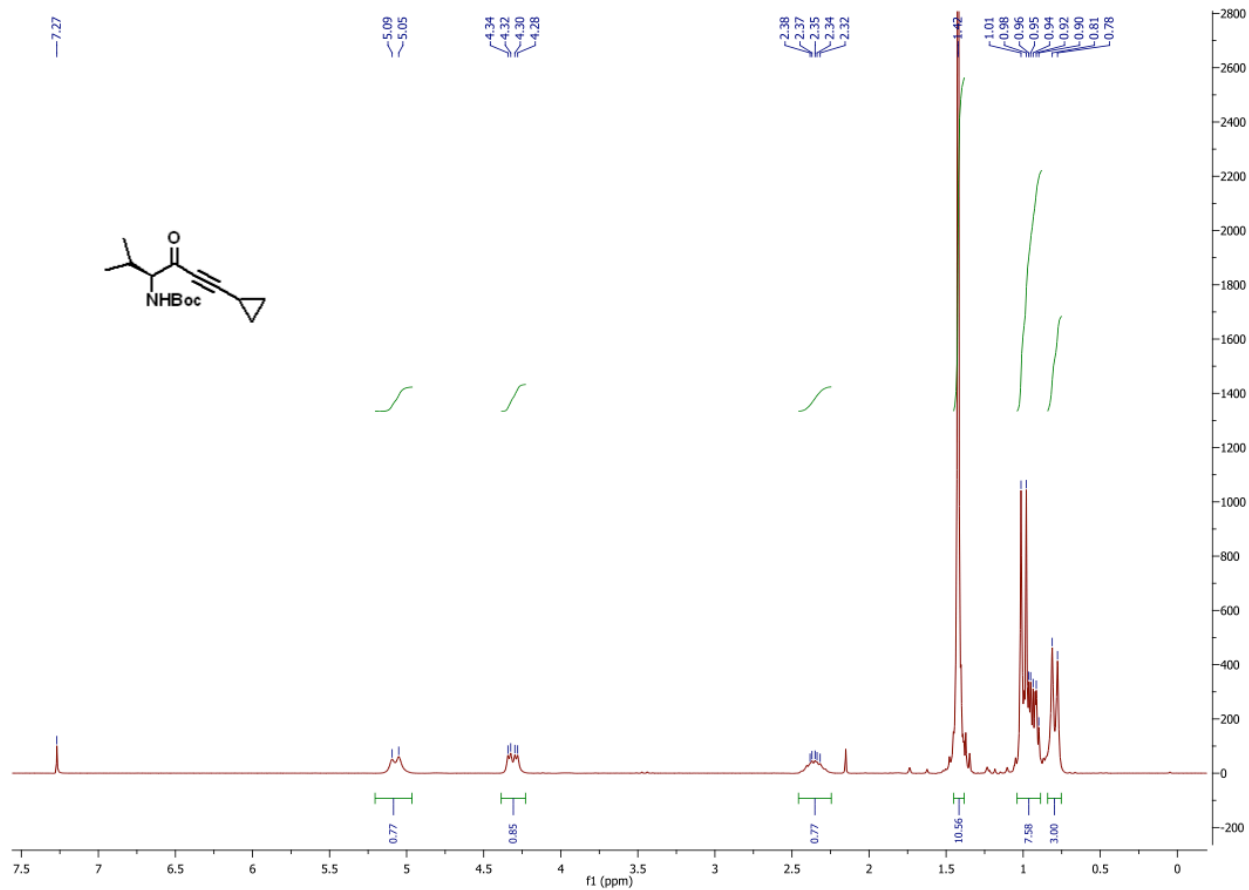
^1H and ^{13}C NMR of compound **2e**



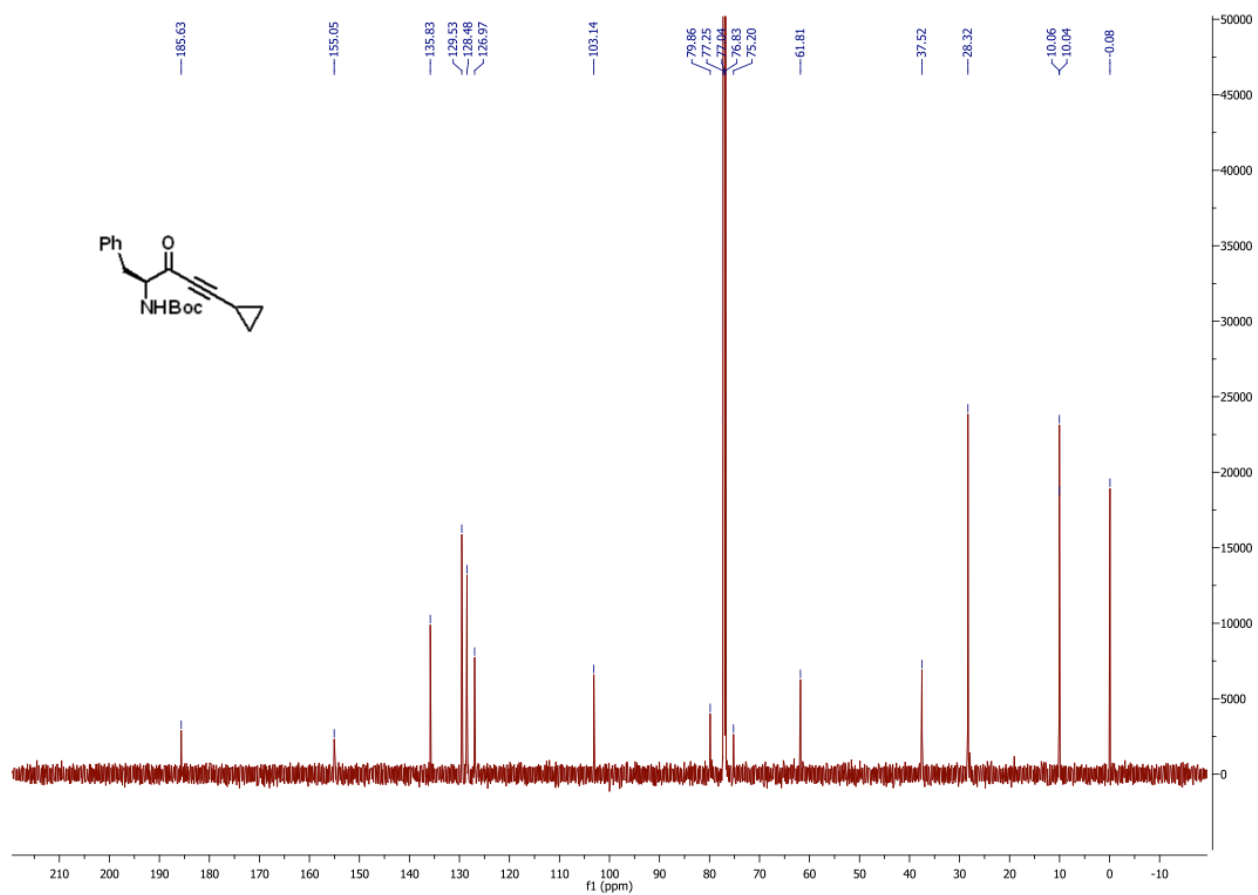
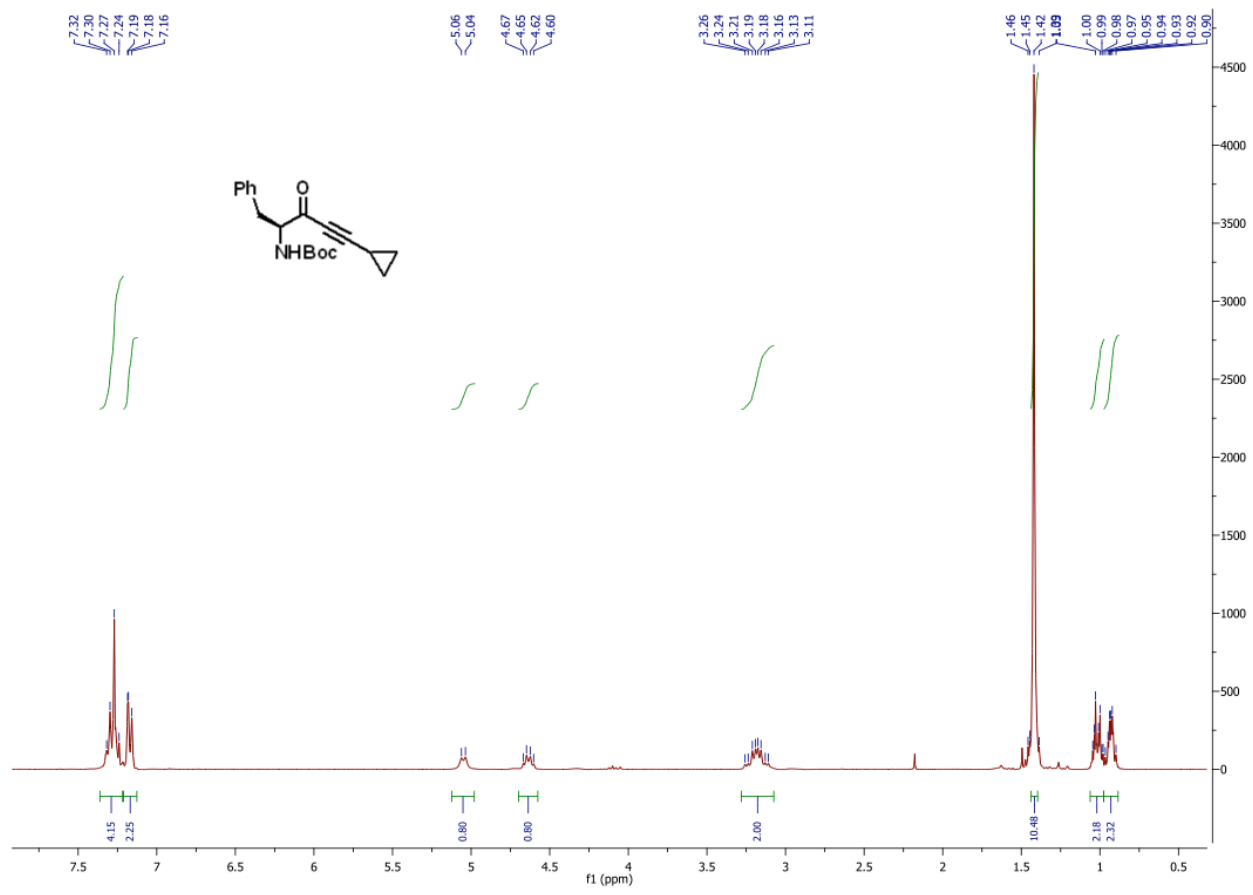
^1H and ^{13}C NMR of compound **2f**



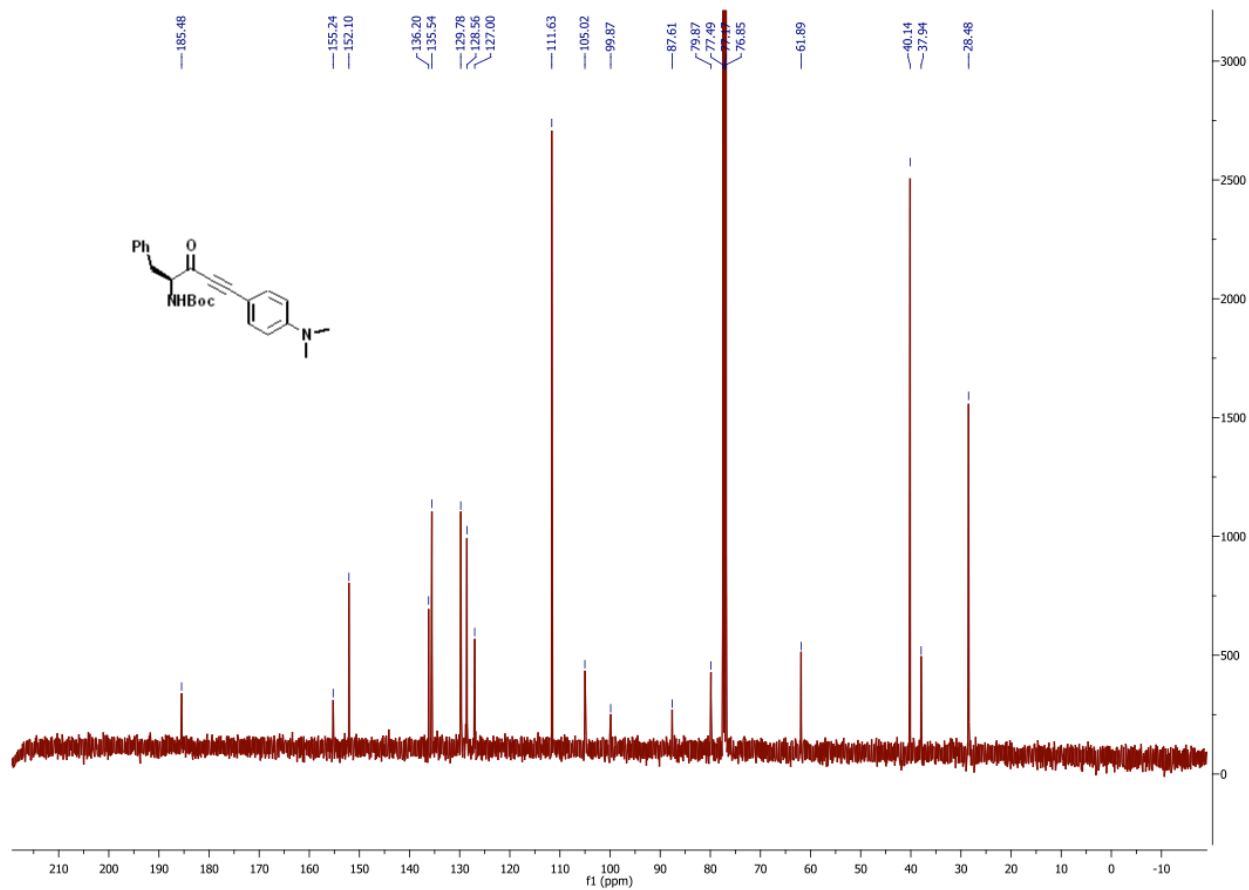
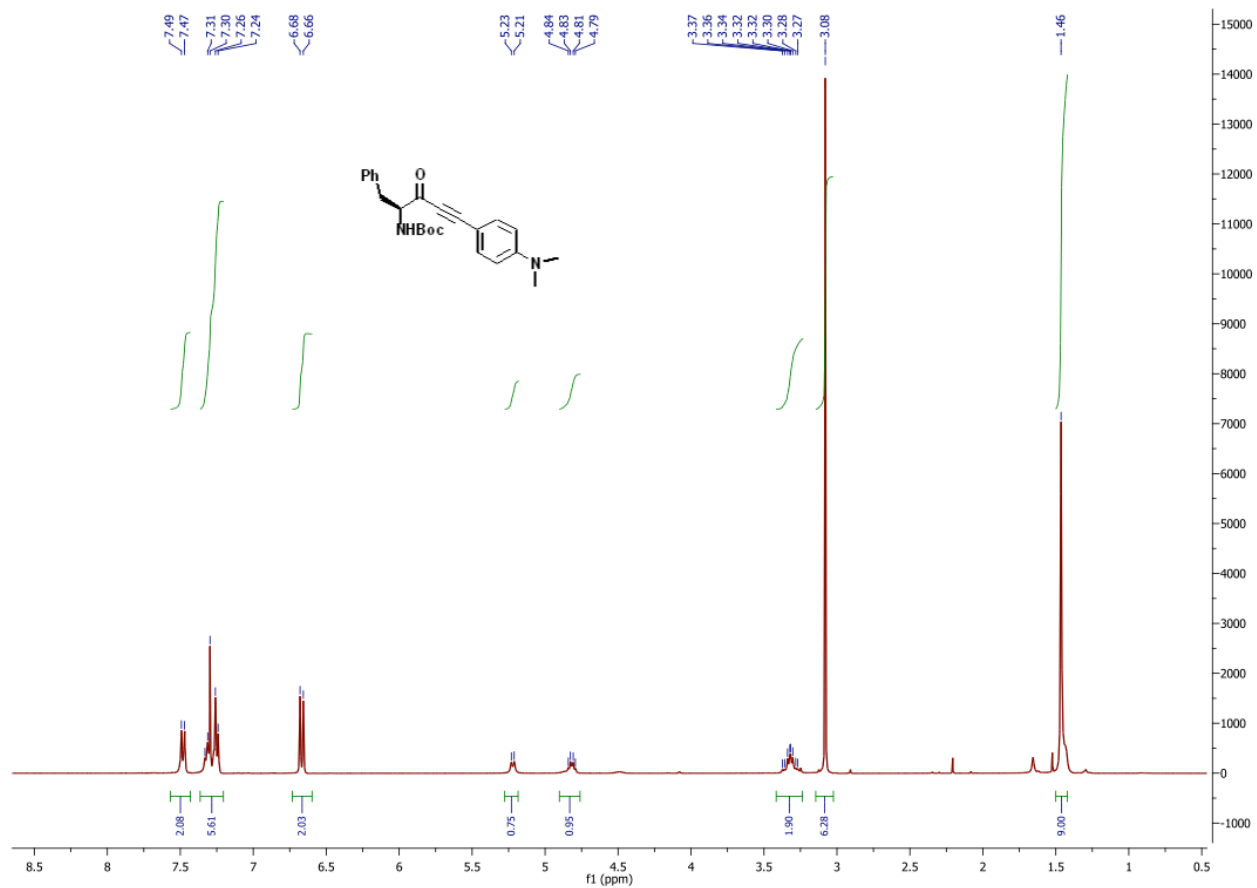
^1H and ^{13}C NMR of compound **2g**



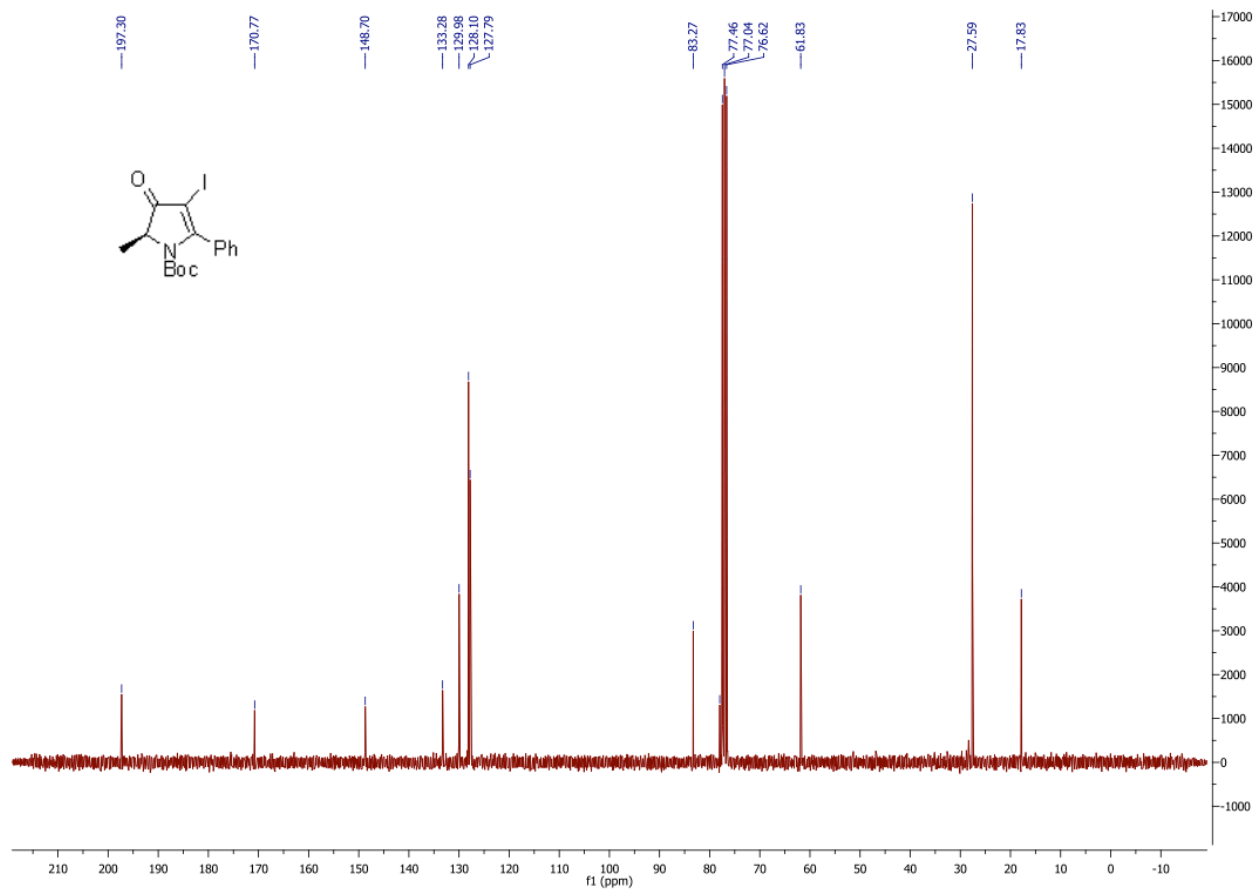
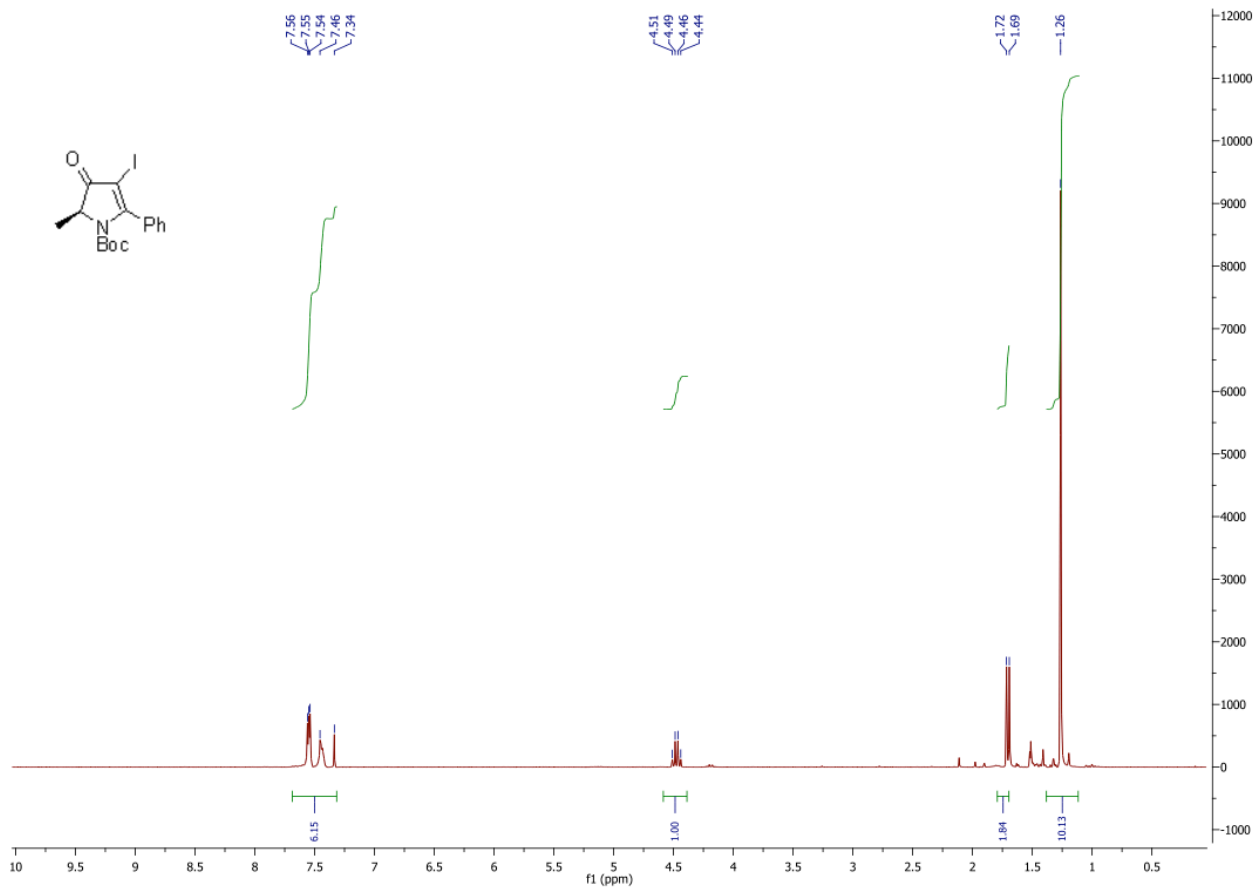
^1H and ^{13}C NMR of compound **2h**



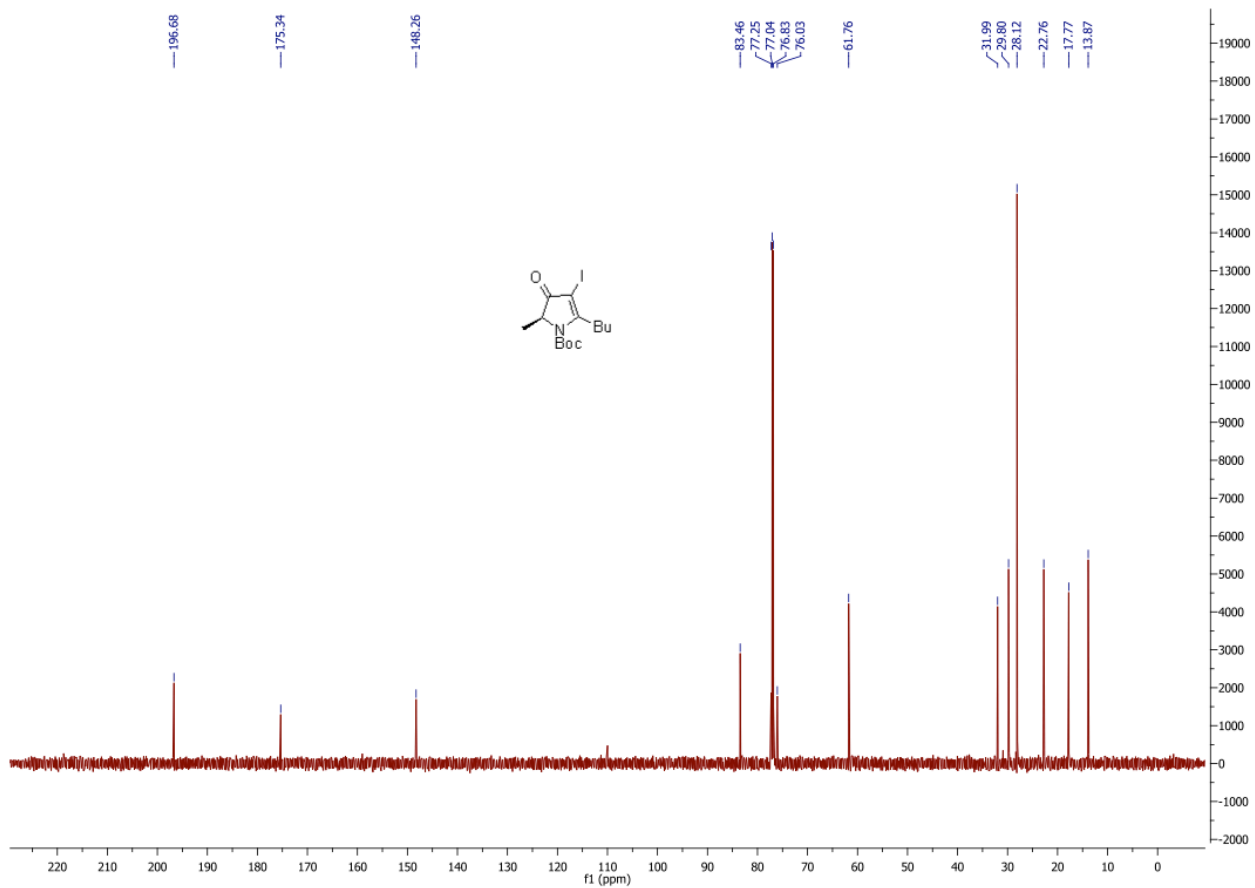
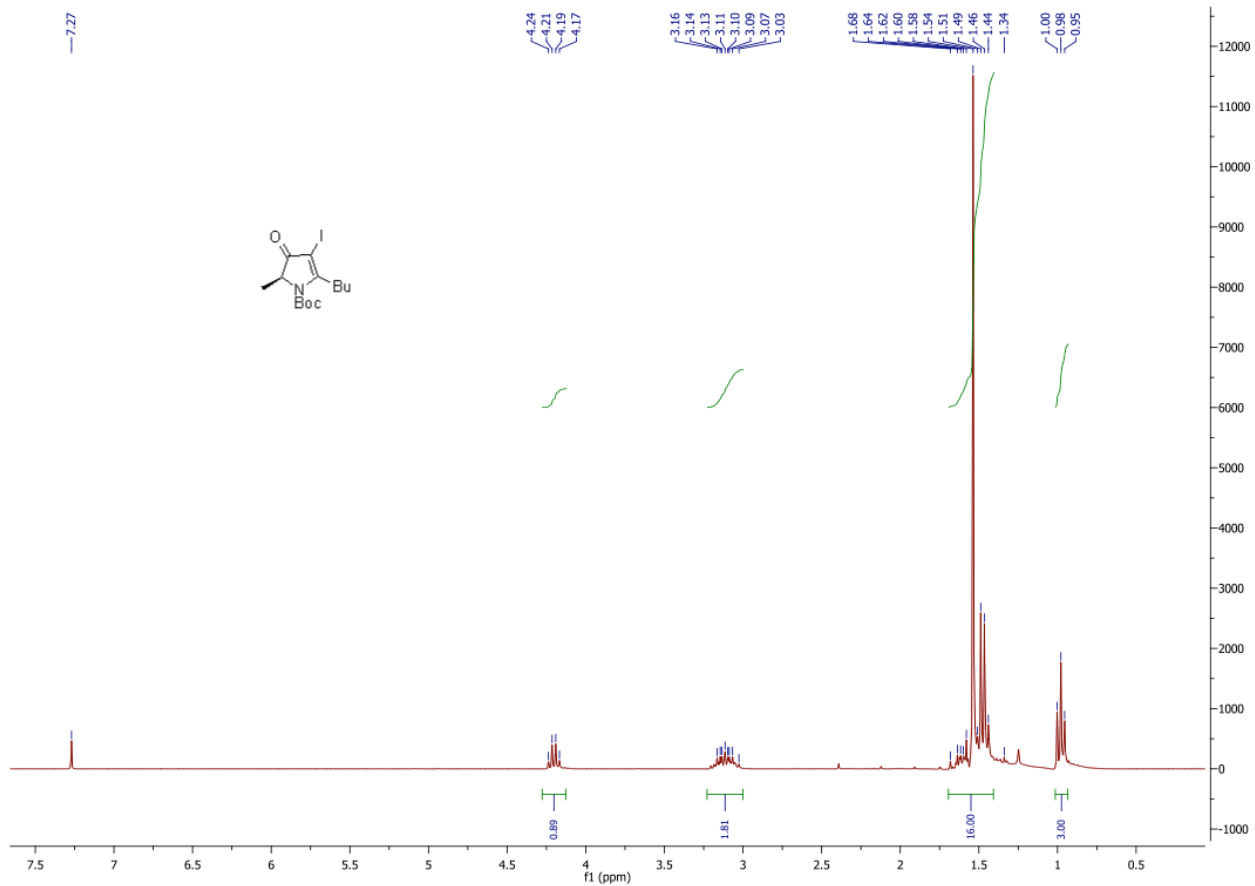
^1H and ^{13}C NMR of compound **2i**



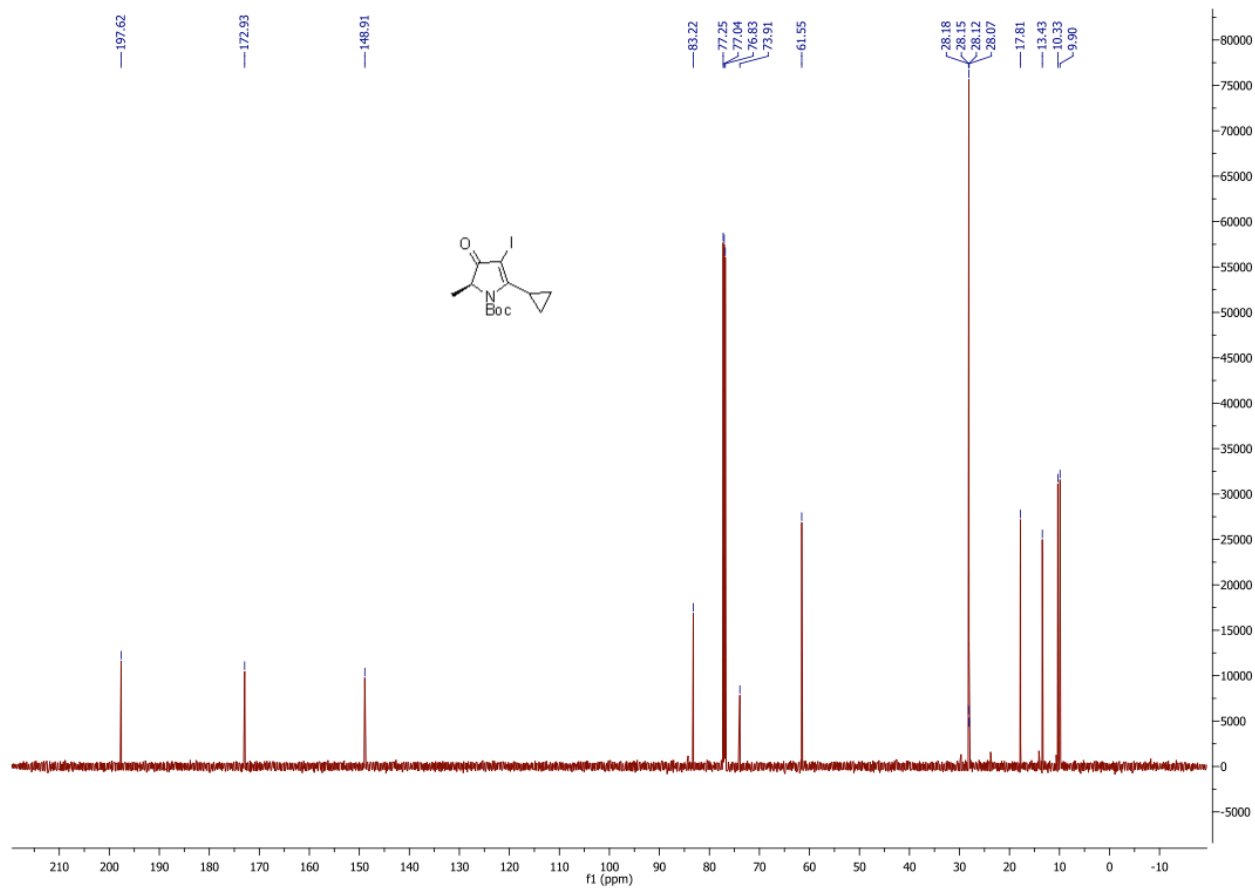
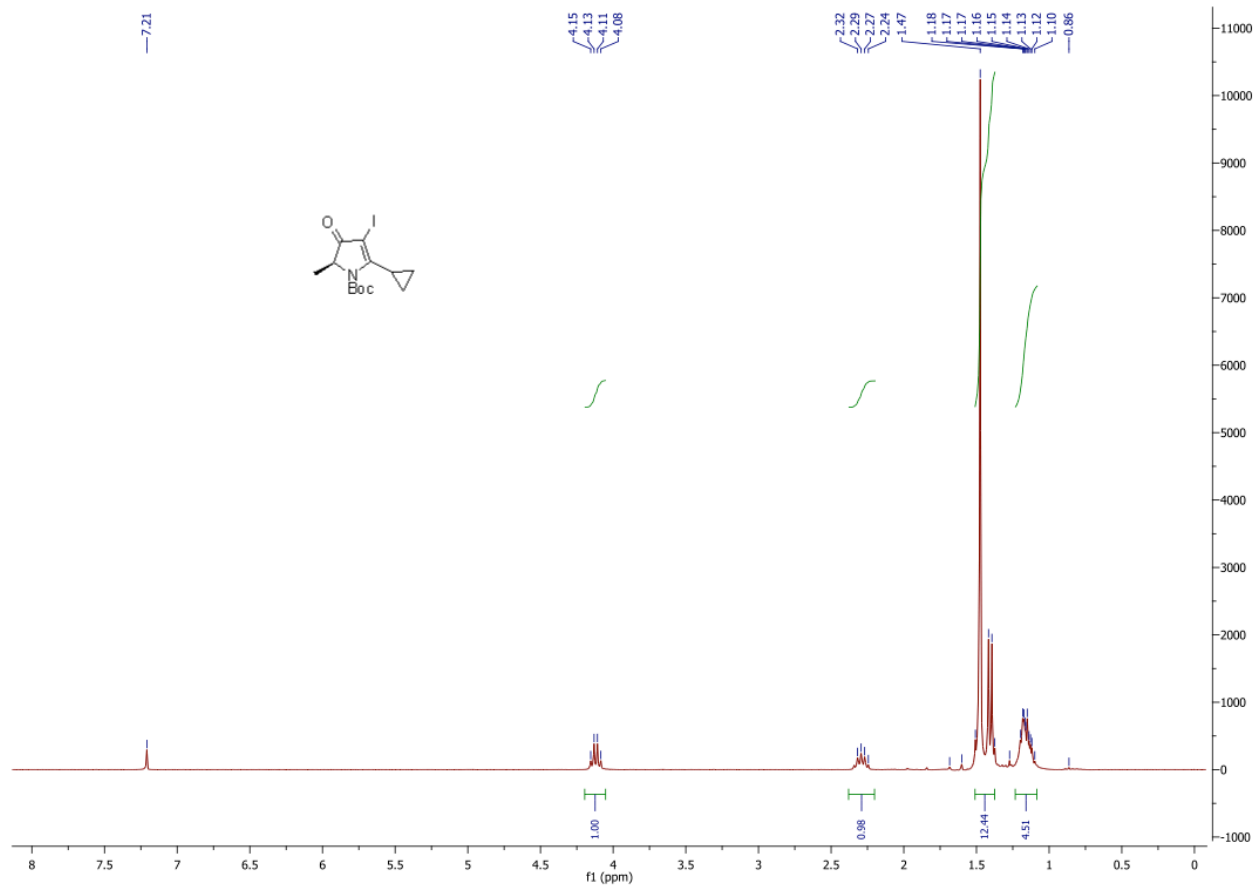
^1H and ^{13}C NMR of compound **3b**.



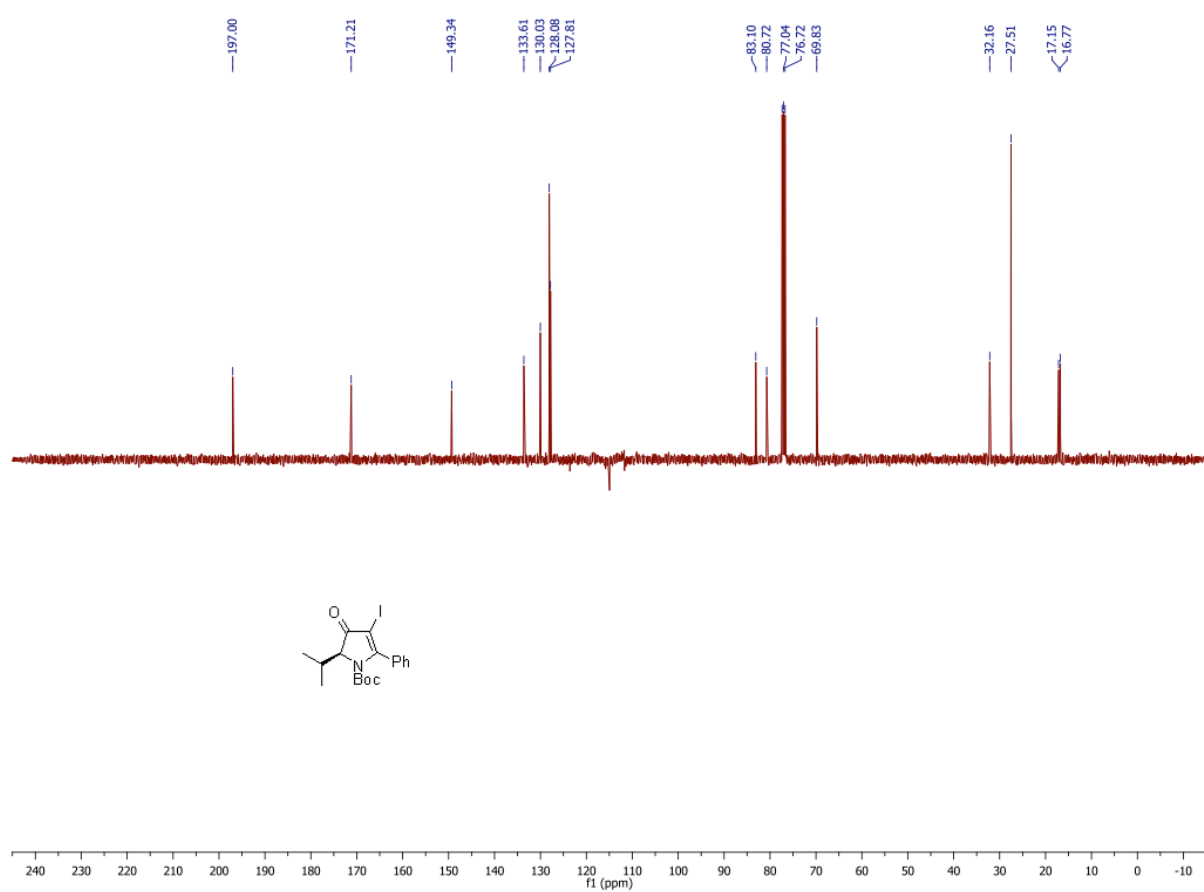
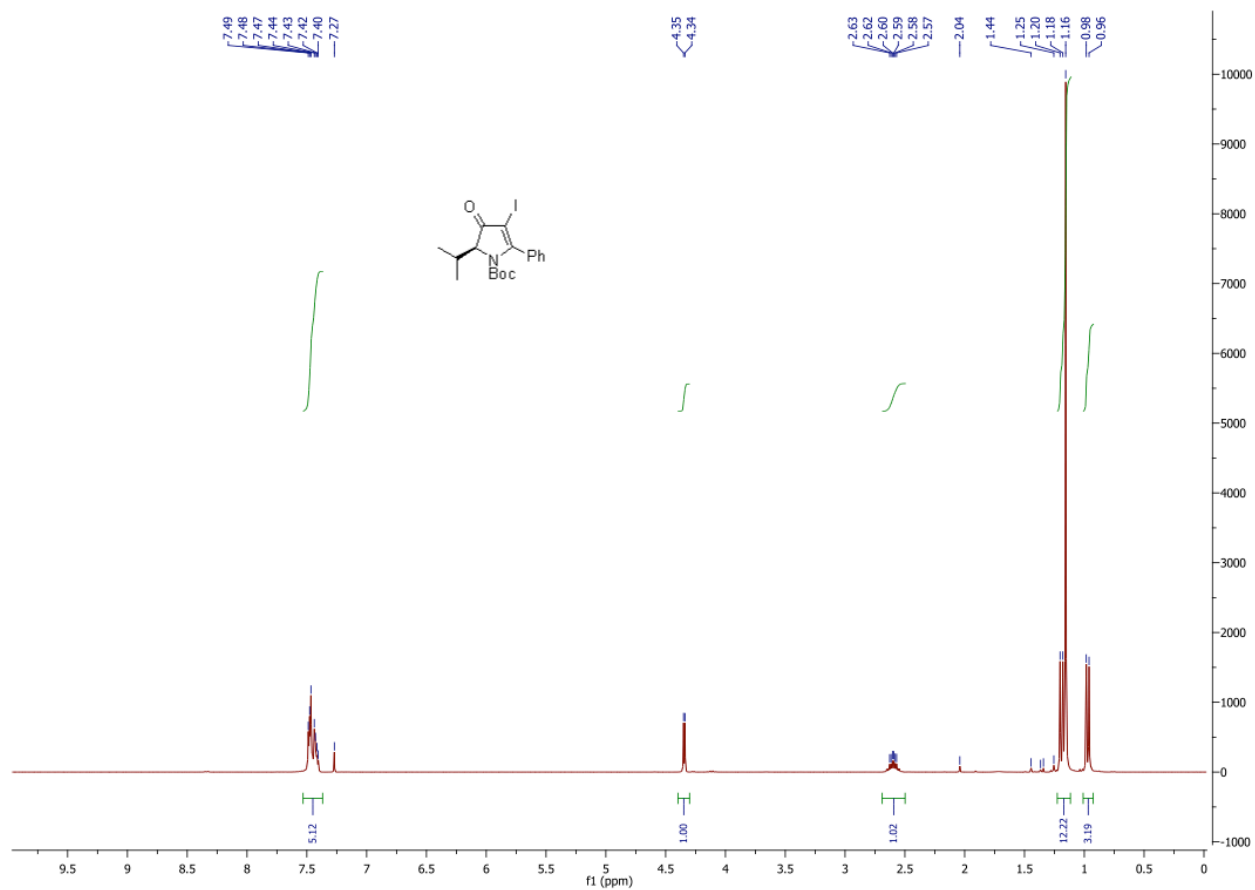
^1H and ^{13}C NMR of compound **3c**.



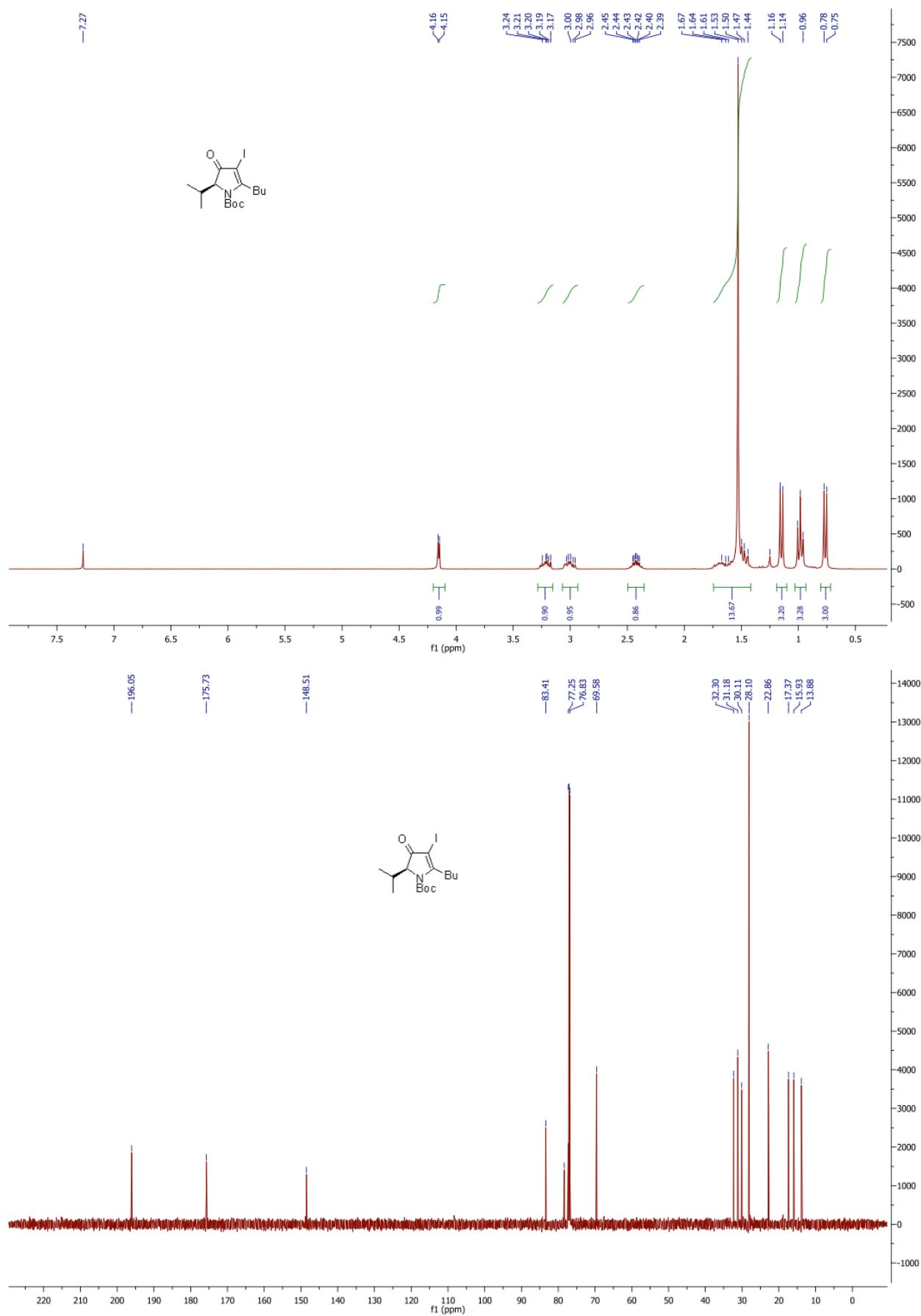
^1H and ^{13}C NMR of compound **3d**.



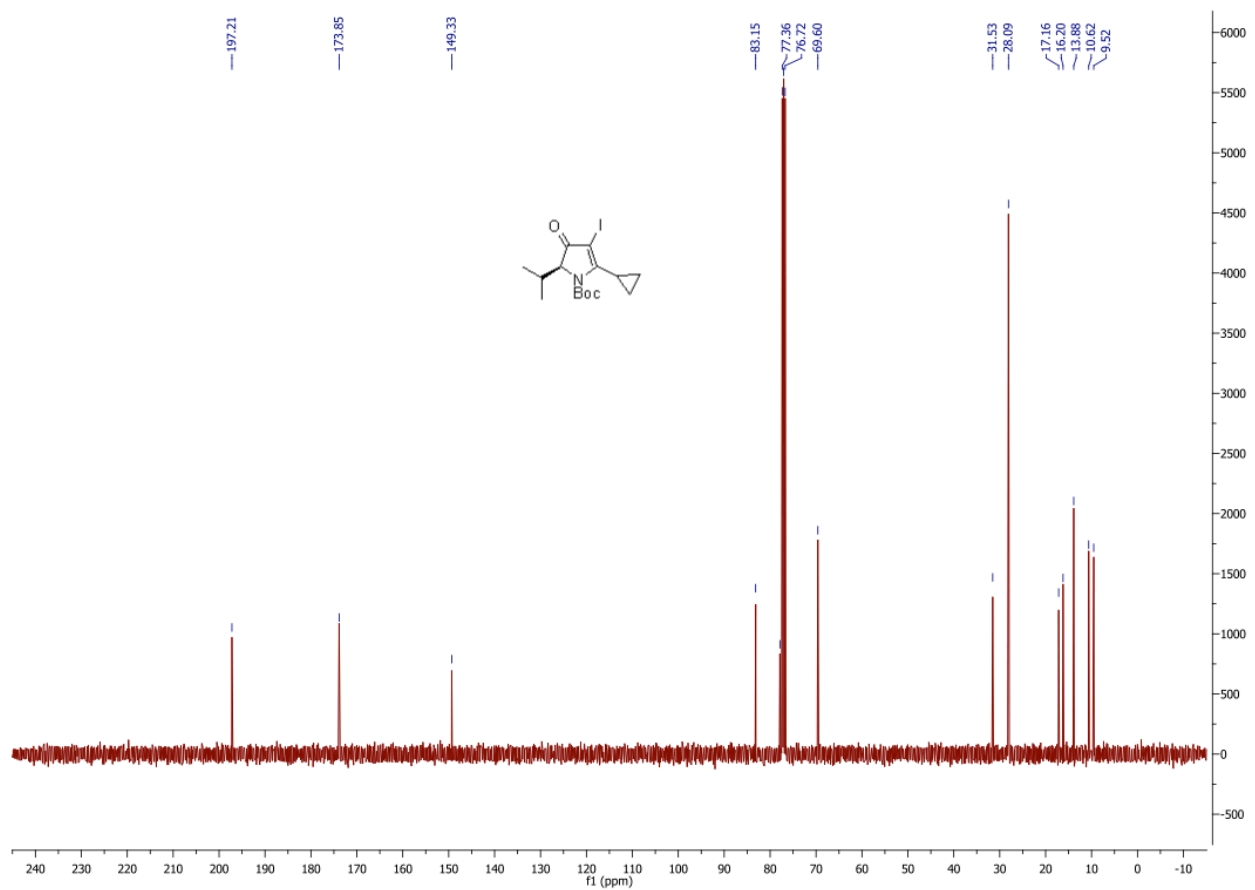
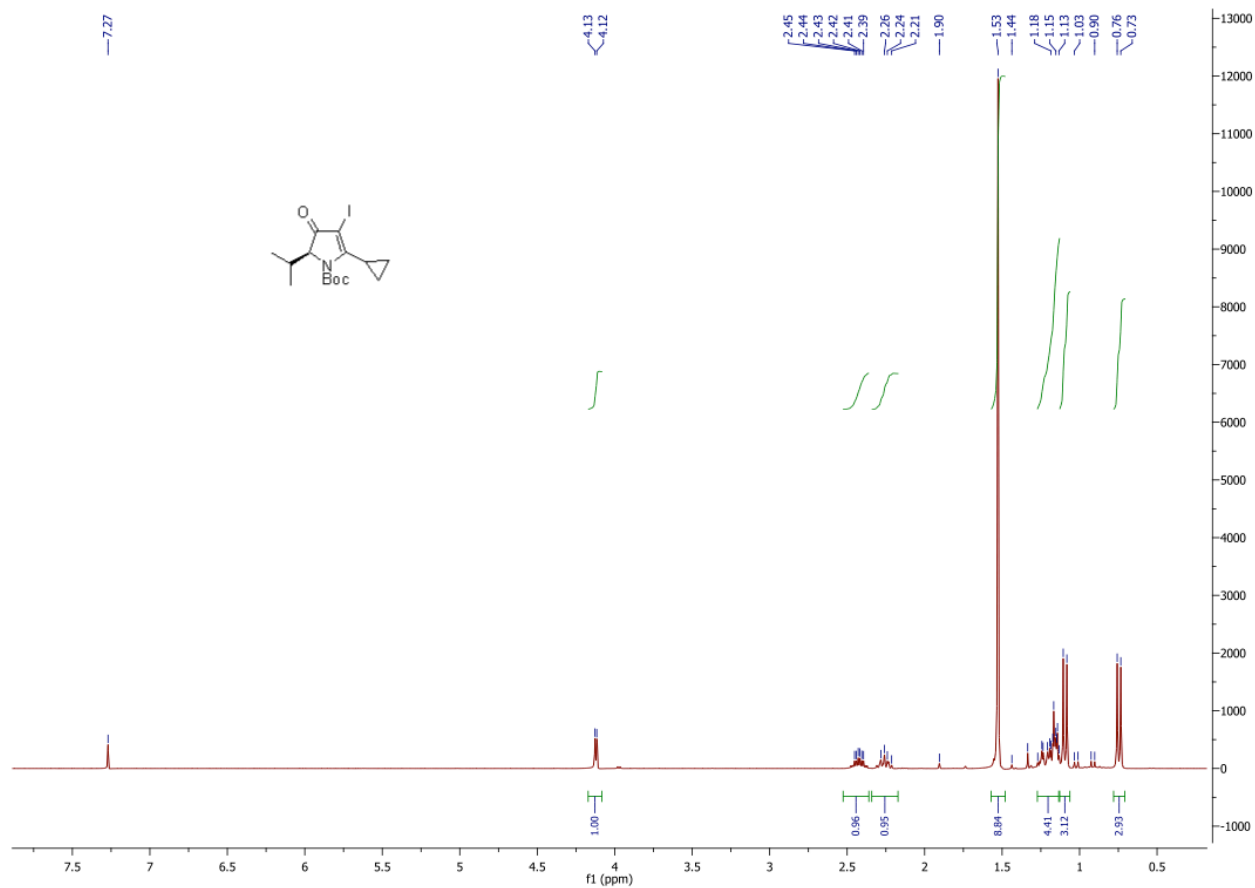
^1H and ^{13}C NMR of compound **3e**.



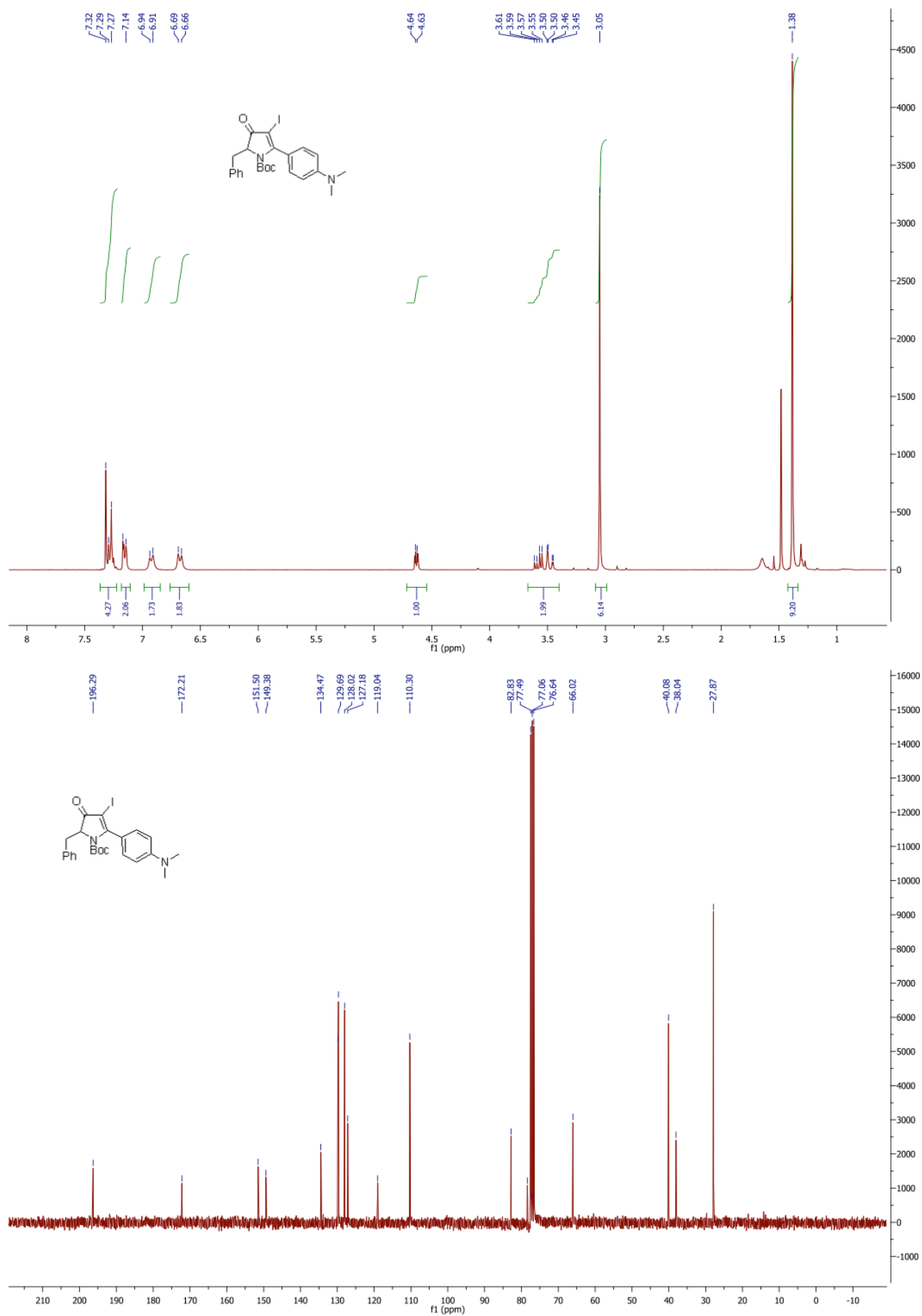
^1H and ^{13}C NMR of compound **3f**.



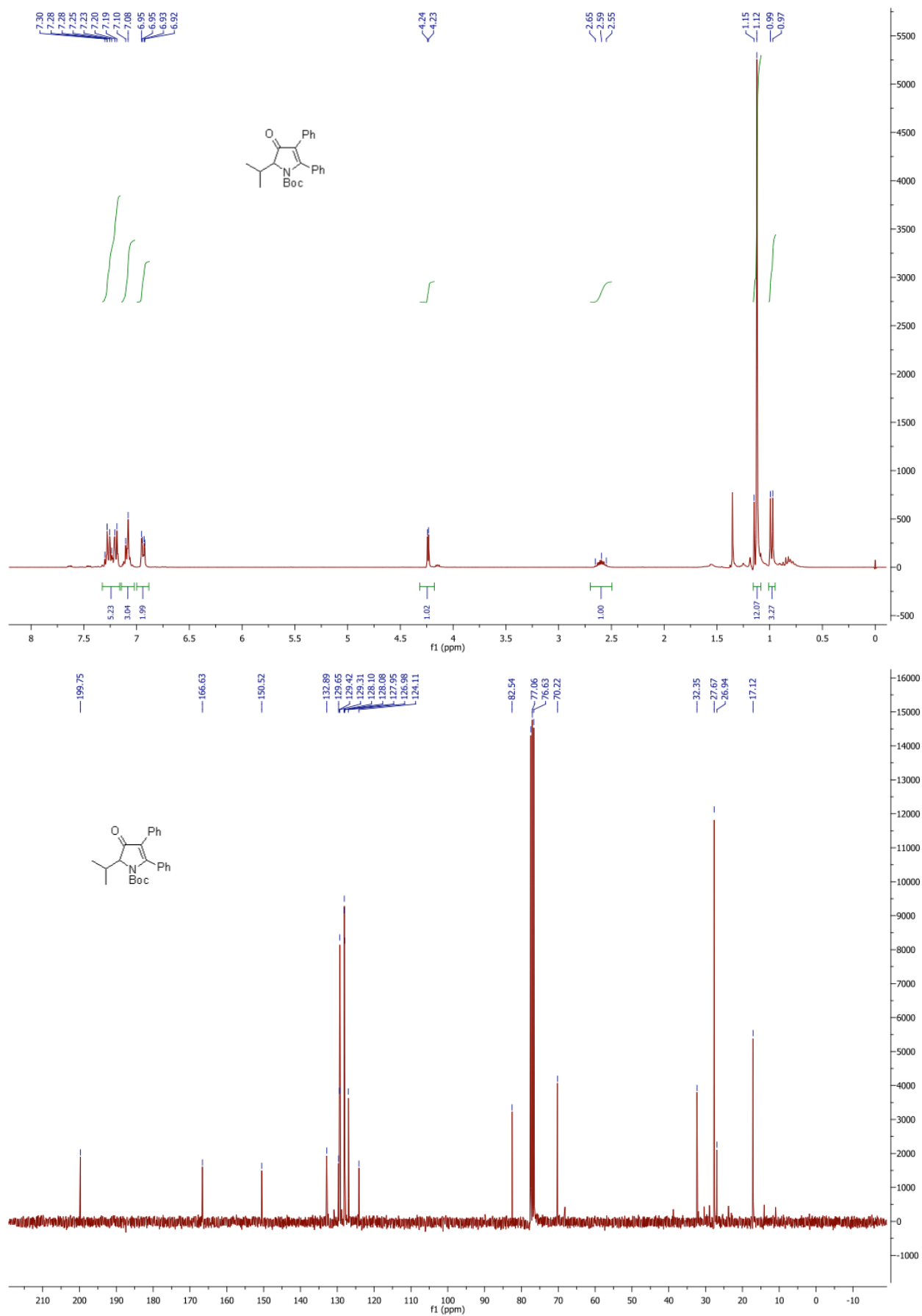
^1H and ^{13}C NMR of compound **3g**.



^1H and ^{13}C NMR of compound **3i**.



^1H and ^{13}C NMR of compound **4e**.



^1H and ^{13}C NMR of compound **5e**.

