

Supporting Information

4*R*- and 4*S*-Iodophenyl Hydroxyproline, 4*R*-Pentynoyl Hydroxyproline, and *S*-Propargyl-4-Thiolphenylalanine: Conformationally Biased and Tunable Amino Acids for Bioorthogonal Reactions

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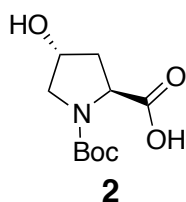
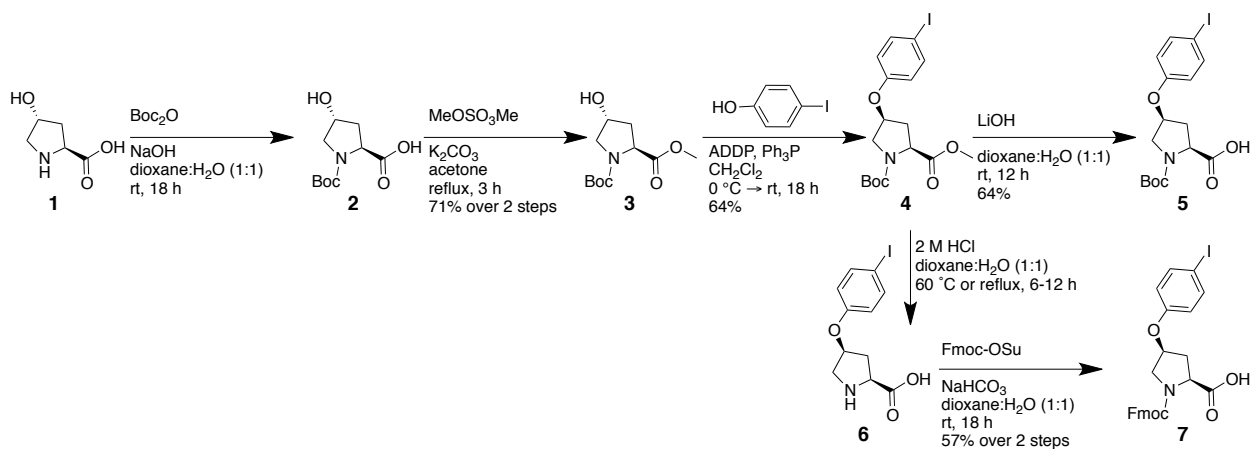
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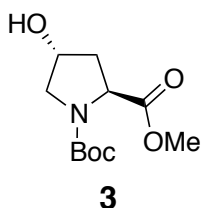
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Materials

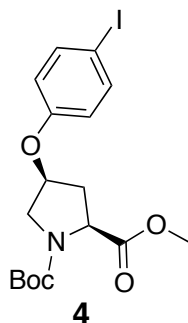
(2*S*,4*R*)-4-Hydroxyproline (Hyp), Boc-4-iodo-L-phenylalanine, *N,N*-diisopropylethylamine (DIPEA), Fmoc-protected amino acids, HBTU, HATU, Rink Amide resin, di-*tert*-butyl dicarbonate (Boc₂O), and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI) were purchased from Chem-Impex (Wood Dale, IL). 1,1'-(Azodicarbonyl)dipiperidine (ADDP) was purchased from Accela ChemBio (San Diego, CA). Palladium(II) acetate (Pd(OAc)₂), 4-azidoaniline, and 1,10-phenanthroline were purchased from Aldrich. All solvents, copper(II) sulfate (CuSO₄), potassium carbonate (K₂CO₃), sodium bicarbonate (NaHCO₃), sodium hydroxide (NaOH), lithium hydroxide (LiOH), and hydrochloric acid (HCl) were purchased from Fisher Scientific. 2-Amino-4,6-dihydropyrimidine was purchased from Alfa Aesar. 4-Methoxyphenylboronic acid was purchased from Combi Blocks (San Diego, CA). *N,N'*-Diisopropylcarbodiimide (DIC), 4-dimethylaminopyridine (DMAP), 4-pentynoic acid, sodium L-ascorbate, and all other reagents were purchased from Acros. Methylene chloride (CH₂Cl₂) was dried using a solvent purification system from Innovative Technologies (Port Washington, NY). Thin layer chromatography was conducted using Silicycle glass-backed plates (silica gel, 250 μm, 60 Å, F254). Flash chromatography was performed using 230-400 mesh (32-63 μm, 60 Å) silica gel from Silicycle. NMR spectra were recorded on a Brüker 400 MHz NMR spectrometer equipped with a cryogenic QNP probe or a Brüker 600 MHz NMR spectrometer equipped with a 5-mm Brüker SMART probe. High resolution mass spectrometry was performed on a Brüker 7 Tesla FT-MS. CD spectra were collected using a quartz cell with path length of 0.1 cm at 20 °C Jasco model J-810 Spectropolarimeter. Individual spectra were collected every nm with an averaging time of 4 s and three accumulations. CD spectra were background corrected but were not smoothed; error bars indicate standard error based on at least three independent trials. Chiral analysis was performed either via normal phase HPLC on a Daicel ChiralPak 1A column (250 x 4.6 mm, 5 μm particle, 1.0 mL/min) using an isocratic mixture of isopropanol in hexanes or via reverse phase HPLC on a Daicel ChiralPak AD-RH column (150 x 4.6 mm, 5 μm particle, 1.0 mL/min) using an isocratic mixture of Buffer B (80% CH₃CN, 20% H₂O, 0.05% TFA) in Buffer A (98% H₂O, 2% CH₃CN, 0.06% TFA).



Boc-(2*S*,4*R*)-4-hydroxyproline (2). **1** (15.2 g, 116 mmol) and Boc_2O (36 g, 165 mmol) were dissolved in 1,4-dioxane (300 mL). A solution of NaOH (1 M in H_2O , 300 mL) was added to the solution. The solution was stirred at room temperature for 18 hours. Dioxane was removed under reduced pressure and the crude product was acidified with 4 M HCl (200 mL). The crude product was extracted with ethyl acetate (3×200 mL). **2** was used as a crude reagent in the next step without purification. The NMR data corresponded to literature values.¹



Boc-(2*S*,4*R*)-4-hydroxyproline methyl ester (3). **2** (24.9 g, 108 mmol), dimethyl sulfate (15.3 mL, 161 mmol), and K_2CO_3 (45.5 g, 329 mmol) were dissolved in acetone (1 L). The solution was heated at reflux for 3 hours. The solution was allowed to cool to room temperature and solvent was removed under reduced pressure. The crude product was dissolved in ethyl acetate (200 mL) and washed with distilled water (3×200 mL). The organic layer was dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to produce a colorless oil in 71% yield over two steps. **3** (20 g, 82 mmol) was used as a crude reagent in the next step without purification. The NMR data corresponded to the literature values.¹



Boc-(2*S*,4*S*)-*p*-iodophenyl-4-hydroxyproline methyl ester (4). **3** (500 mg, 2.04 mmol) was dissolved in anhydrous CH₂Cl₂ (20.4 mL). The solution was cooled to 0 °C and placed under nitrogen. Triphenylphosphine (Ph₃P) (963 mg, 3.67 mmol), ADDP (540 mg, 2.14 mmol), and 4-iodophenol (449 mg, 2.04 mmol) were added to the solution. The solution was stirred at 0 °C for 2 h. The solution was then removed from the ice bath, allowed to warm to room temperature, and stirred for an additional 16 hours. The reaction mixture was washed with brine (3 × 75 mL). The organic layer was dried over Na₂SO₄ and filtered. The solvent was removed under reduced pressure and the crude product was redissolved in hexanes (15 mL). The crude product was purified via column chromatography (0 to 25% ethyl acetate in hexanes v/v) to yield **4** (583 mg, 1.30 mmol) as a colorless oil in 64% yield. NMR spectra reflected a mixture of *cis* and *trans* proline rotamers (1:1.3 ratio, respectively). ¹H NMR (400 MHz, CDCl₃) δ 7.55 (d, *J* = 8.8 Hz), 7.53 (d, *J* = 8.7 Hz) (sum of 7.55 ppm and 7.53 ppm resonances = 2H), 6.59 (d, *J* = 8.8 Hz), 6.57 (d, *J* = 8.8 Hz) (sum of 6.59 ppm and 6.57 ppm resonances = 2H), 4.89-4.85 (m, 1H), 4.54 (dd, *J* = 8.7 Hz, 2.4 Hz), 4.43 (dd, *J* = 7.6 Hz, 4.0 Hz) (sum of 4.54 ppm and 4.43 ppm resonances = 1H), 3.80-3.62 (m, 2H), 3.73 (s), 3.71 (s) (sum of 3.73 ppm and 3.71 ppm resonances = 2H), 2.51-2.37 (m, 2H), 1.48 (s), 1.43 (s) (sum of 1.48 ppm and 1.43 ppm resonances = 9H). ¹³C NMR (100.6 MHz, CDCl₃) δ 172.45, 172.06, 156.39, 154.15, 153.77, 138.40, 138.39, 117.86, 83.66, 80.38, 80.28, 75.55, 74.50, 57.76, 57.39, 52.36, 52.22, 51.86, 51.46, 36.14, 35.25, 28.40, 28.29. HRMS (LIFDI-TOF) *m/z*: [M+H]⁺ calcd for C₁₇H₂₂INO₅ 447.0543, found 447.0515.

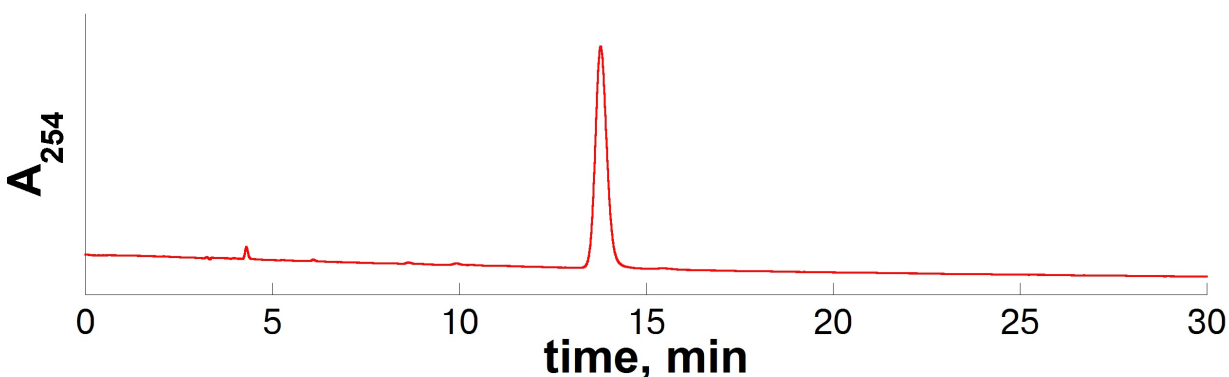


Figure S1. HPLC chromatogram of **4**, Boc-(2*S*,4*S*)-*p*-iodophenyl-4-hydroxyproline methyl ester (ChiralPak 1A, 250 x 4.6 mm, 5 μm particle, 1.0 mL/min, isocratic 5% isopropanol/hexanes).

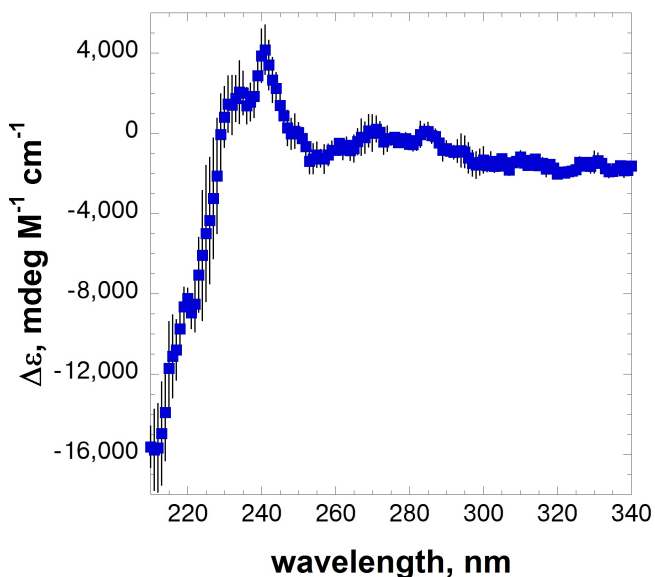
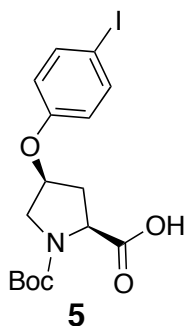


Figure S2. CD spectrum of **4**, Boc-(2*S*,4*S*)-*p*-iodophenyl-4-hydroxyproline methyl ester. Sample concentrations were between 0.54 mM and 0.99 mM **4** in methanol at 20 °C. Error bars indicate standard error. Data below 210 nm are not reported due to high dynode voltage.



Boc-(2*S*,4*S*)-*p*-iodophenyl-4-hydroxyproline (5**).** **4** (100 mg, 0.22 mmol) was dissolved in 1,4-dioxane (1.1 mL). LiOH (5.6 mg, 0.23 mmol) was dissolved in a solution of water (1.1 mL). The LiOH solution (210 mM) was added to the solution of **4**, and the solution was stirred for 12 hours at room temperature. The mixture was acidified to pH 2 with 1 M HCl and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na₂SO₄ and filtered. The solvent was removed under reduced pressure and the resultant solid was redissolved in CH₂Cl₂. The crude product was purified via column chromatography (0 to 1.5% methanol in CH₂Cl₂ v/v) to obtain compound **5** (60 mg, 0.14 mmol) as an off-white solid in 64% yield. NMR spectra reflected a mixture of *cis* and *trans* proline rotamers (1:1.5 ratio, respectively). ¹H (400 MHz, CD₃OD) δ 7.45 (d, *J* = 8.7 Hz, 2H), 6.59 (d, *J* = 8.9 Hz), 6.58 (d, *J* = 8.9 Hz) (sum of 6.59 ppm and 6.58 ppm resonances = 2H), 4.88 (m, 1H), 4.34-4.28 (m, 1H), 3.67-3.61 (m, 1H), 3.52-3.47 (m, 1H), 2.49-2.36 (m, 1H), 2.29 (m, 1H), 1.37 (s), 1.34 (s) (sum of 1.37 ppm and 1.34 ppm resonances = 9H). ¹³C NMR (100.6 MHz, CD₃OD) δ 175.45, 175.28, 158.03, 157.99, 156.05, 155.94, 139.49, 119.18, 119.14, 84.06, 81.57, 81.56, 76.95, 75.99, 59.12, 58.77, 53.31, 52.79, 36.78, 36.02, 28.67, 28.52. HRMS (LIFDI-TOF) *m/z*: [M+H]⁺ calcd for C₁₆H₂₀INO₅ 433.0386, found 433.0384.

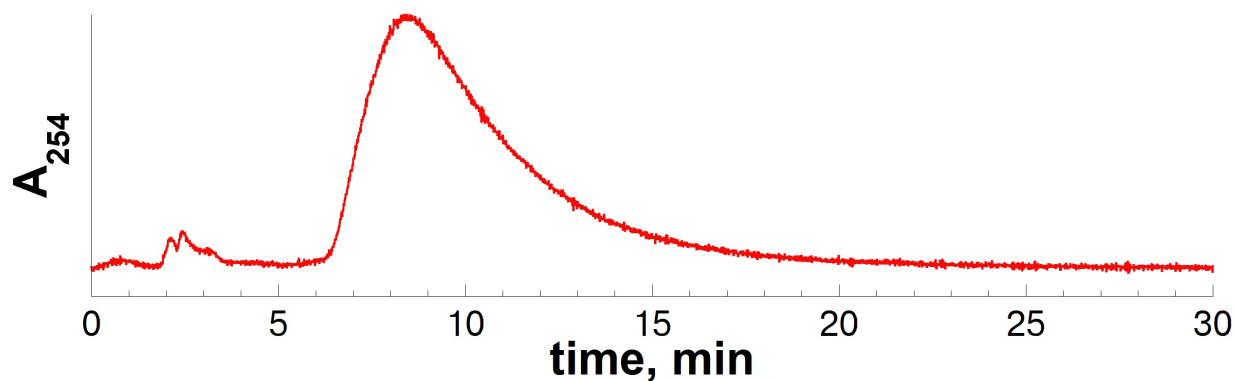


Figure S3. HPLC chromatogram of **5**, Boc-(2*S*,4*S*)-*p*-iodophenyl-4-hydroxyproline (ChiralPak AD-RH, 150 x 4.6 mm, 5 μ m particle, 1.0 mL/min, isocratic 60% buffer B in buffer A).

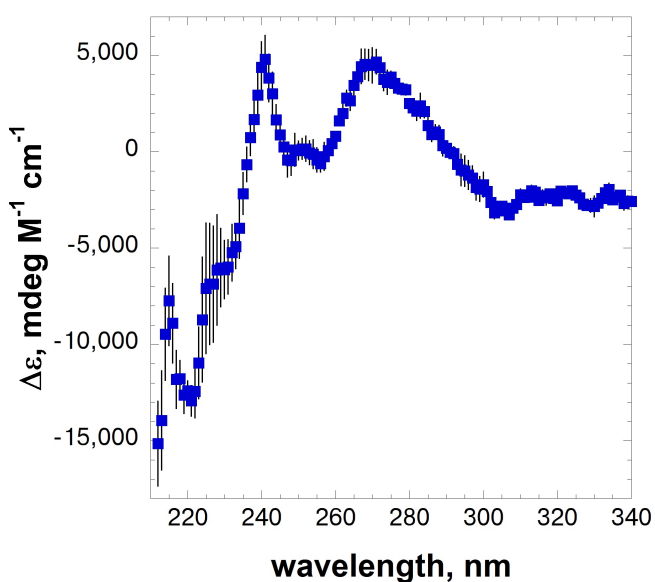
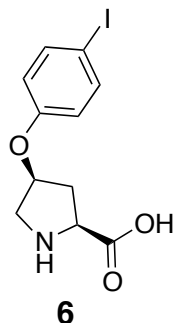
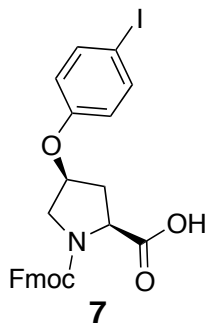


Figure S4. CD spectrum of **5**, Boc-(2*S*,4*S*)-*p*-iodophenyl-4-hydroxyproline. Sample concentrations were between 0.33 mM and 1.0 mM **5** in methanol at 20 °C. Error bars indicate standard error. Data below 210 nm are not reported due to high dynode voltage.



(2*S*,4*S*)-*p*-iodophenyl-4-hydroxyproline (6). **4** (0.10 g, 0.22 mmol) was dissolved in 1,4-dioxane (1.1 mL). A solution of 4 M HCl (1.1 mL) was added, and the mixture was stirred at 60 °C for 6 h, or until the disappearance of **4** was confirmed via TLC. The solvent was removed under reduced pressure. The crude product **6** was used without further purification. ¹H (600 MHz, CD₃OD) δ 7.61 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 2H), 5.19 (s, 1H), 4.59 (d, *J* = 7.2 Hz, 1H), 3.68 (d, *J* = 12.4 Hz, 1H), 3.59 (dd, *J* = 12.8, 3.4 Hz, 1H), 2.72-2.57 (m, 2H). ¹³C NMR (150.9 MHz, CD₃OD) δ 157.31, 139.85, 119.36, 85.13, 76.46, 52.53, 35.59. ESI-MS *m/z*: [M+H]⁺ calcd for C₁₁H₁₂INO₃ 333.0, found 334.1.



Fmoc-(2*S*,4*S*)-*p*-iodophenyl-4-hydroxyproline (7). Compound **4** (1.33 g, 2.98 mmol) was dissolved in 1,4-dioxane (15 mL). A solution of HCl (4 M, 15 mL) was added to the reaction, and the solution was heated to reflux and stirred for 12 hours. After verifying disappearance of **4** via TLC, the mixture was neutralized with NaHCO₃ (approx. 7 g). Fmoc-OSu (1.20 g, 3.56 mmol) was added directly to the crude mixture, and the reaction was stirred at room temperature for 18 h. The mixture was acidified to pH 2 with 1 M HCl and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over Na₂SO₄ and filtered. The solvent was removed under reduced pressure and the resultant solid was redissolved in CH₂Cl₂. The crude product was purified via column chromatography (0 to 1.5% methanol in CH₂Cl₂ v/v) to obtain compound **7** (940 mg, 1.69 mmol) as an off-white solid in 57% yield. NMR spectra reflected a mixture of *cis* and *trans* proline rotamers (1:1 ratio). ¹H (600 Hz, CD₃OD) δ 7.79 (d, *J* = 7.6 Hz), 7.77 (d, *J* = 7.8 Hz) (sum of 7.79 ppm and 7.77 ppm resonances = 2H), 7.62 (d, *J* = 7.8 Hz), 7.59 (d, *J* = 8.9 Hz), 7.60 (d, *J* = 8.4 Hz), 7.56 (d, *J* = 8.8 Hz) (sum of 7.62 ppm, 7.59 ppm, 7.60 ppm, and 7.56 ppm resonances = 4H), 7.38 (t, *J* = 7.6 Hz), 7.36 (t, *J* = 8.3 Hz) (sum of 7.30 ppm and 7.24 ppm resonances = 2H), 7.29 (m), 7.24 (t, *J* = 7.4 Hz) (sum of 7.29 ppm and 7.24 ppm resonances = 2H), 6.70 (d, *J* = 8.6 Hz), 5.01 (br s, 1H), 4.50-4.43 (m), 4.41-4.35 (m), 4.35-4.30 (m) (sum of 4.47 ppm, 4.38 ppm, and 4.33 resonances = 3H), 4.27 (t, *J* = 6.6 Hz), 4.21 (t, *J* = 6.8 Hz) (sum of 4.27 ppm and 4.21 resonances = 1H), 3.78 (dd, *J* = 12.2 Hz, 4.8 Hz), 3.70 (dd, *J* =

12.2 Hz, 4.7 Hz) (sum of 3.78 ppm and 3.70 resonances = 1H), 3.66 (d, $J = 12.2$ Hz), 3.63 (d, $J = 12.2$ Hz) (sum of 3.66 ppm and 3.63 resonances = 1H), 2.58-2.40 (m, 2H). ^{13}C NMR (150.9 MHz, CD_3OD) δ 175.18, 174.89, 158.07, 156.62, 145.37, 145.17, 145.11, 142.7, 142.64, 142.58, 142.54, 139.62, 139.58, 128.84, 128.83, 128.24, 128.20, 126.24, 126.19, 126.15, 126.11, 120.94, 120.91, 119.51, 119.37, 84.25, 84.16, 77.07, 76.22, 69.08, 68.83, 59.26, 59.15, 53.50, 53.01, 48.49, 48.37, 37.04, 36.18. HRMS (LIFDI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{26}\text{H}_{22}\text{INO}_5$ 555.0543, found 555.0546.

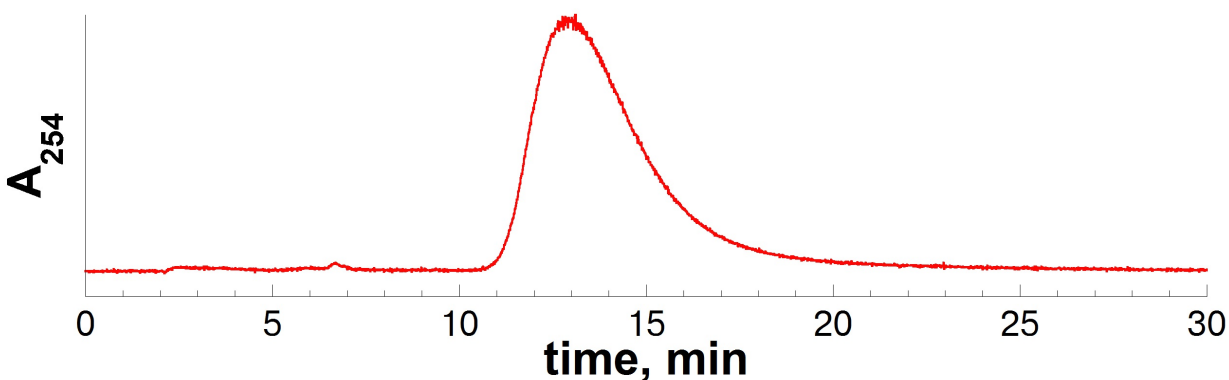


Figure S5. HPLC chromatogram of **7**, Fmoc-(2*S*,4*S*)-*p*-iodophenyl-4-hydroxyproline (ChiralPak AD-RH, 150 x 4.6 mm, 5 μm particle, 1.0 mL/min, isocratic 75% buffer B in buffer A).

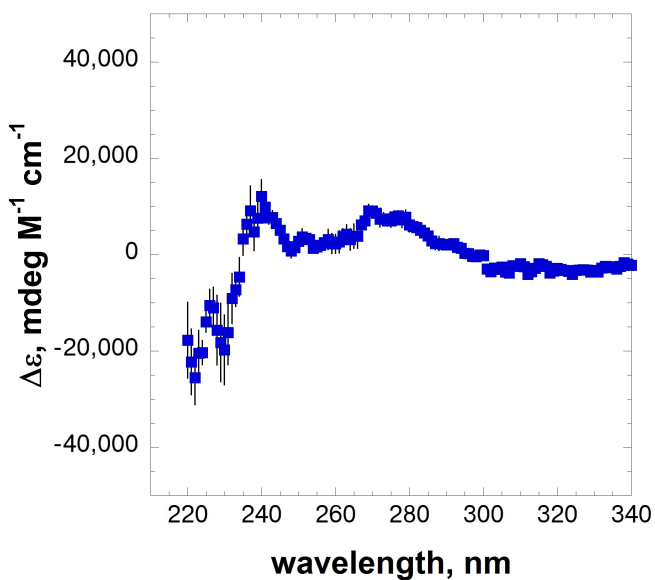
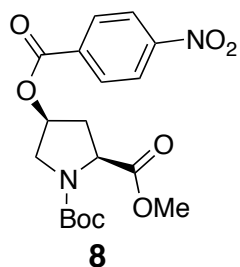
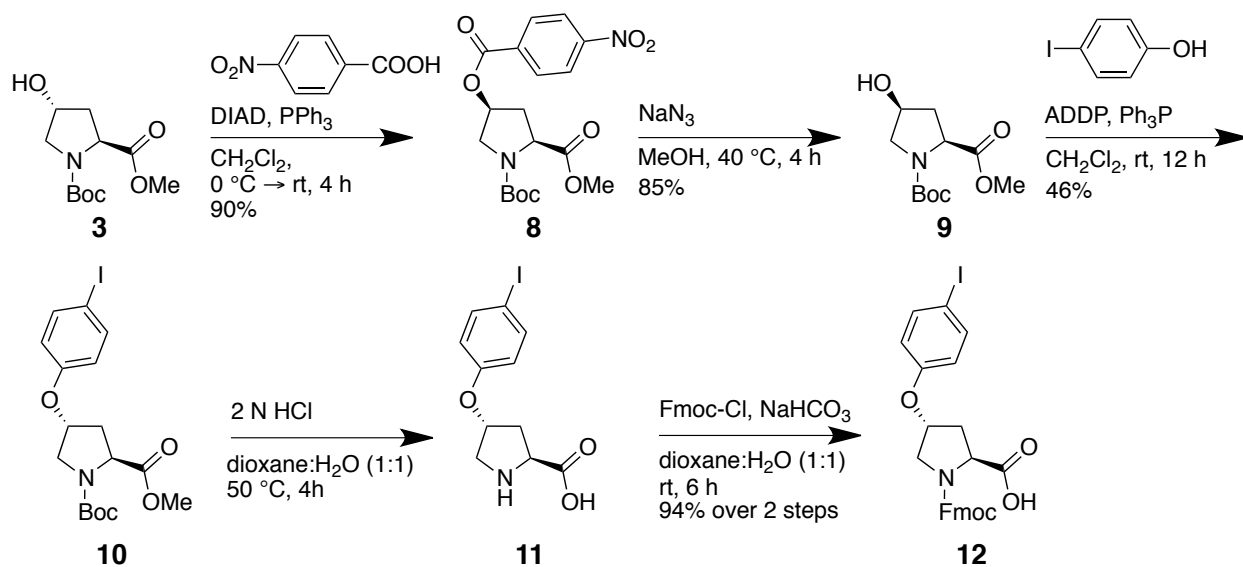
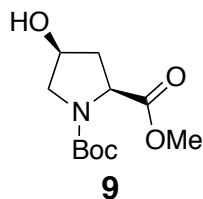


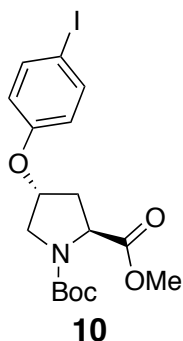
Figure S6. CD spectrum of compound **7**, Fmoc-(2*S*,4*S*)-*p*-iodophenyl-4-hydroxyproline. Sample concentrations were between 0.50 mM and 1.3 mM **7** in methanol at 20 °C. Error bars indicate standard error. Data below 220 nm are not reported due to high dynode voltage.



Boc-(2S,4S)-4-nitrobenzoyl-hydroxyproline methyl ester (8). **3** (1.10 g, 4.48 mmol), triphenylphosphine (PPh₃, 1.41 g, 5.38 mmol), and *p*-nitrobenzoic acid (0.82 g, 4.93 mmol) were dissolved in anhydrous CH₂Cl₂ (100 mL), and the resultant solution was cooled to 0 °C under a nitrogen atmosphere. DIAD (1.09 g, 5.38 mmol) was added dropwise to the solution over 2 min under nitrogen. The solution was stirred at 0 °C for 1 hour, then allowed to warm to room temperature and stirred for an additional 3 hours. The solvent was removed under reduced pressure. To the crude product was added 100 mL of water, and the product was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (1 × 15 mL), dried over anhydrous Na₂SO₄, and the solvent removed under reduced pressure. The crude product was purified by column chromatography using 15% ethyl acetate in hexanes (v/v) to yield **8** (1.58 g, 4.00 mmol) in 90% yield as thick oil that solidified to a white solid upon standing at room temperature. NMR data corresponded to the literature values.²



Boc-(2*S*,4*S*)-4-hydroxyproline methyl ester (9). **8** (1.58 g, 4.01 mmol) was dissolved in methanol (50 mL). Sodium azide (520 mg, 8.02 mmol) was added to the reaction mixture, and the mixture stirred at 40 °C for 4 hours. The solution was allowed to cool to room temperature and methanol was removed under reduced pressure. Water (30 mL) was added to the crude dried mixture to dissolve unreacted sodium azide. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined, then washed with brine and dried over anhydrous Na₂SO₄ and solvent removed under reduced pressure to yield the crude product. The compound was purified by column chromatography (0 to 3% methanol in CH₂Cl₂ (v/v)) to obtain **9** as colorless oil (840 mg, 3.42 mmol) in 85% yield. NMR data corresponded to literature values.²



Boc-(2*S*,4*R*)-*p*-iodophenyl-4-hydroxyproline methyl ester (10). **9** (840 mg, 3.42 mmol), triphenylphosphine (PPh₃, 1.08 g, 4.12 mmol), 4-iodophenol (910 mg, 4.12 mmol), and ADDP (1.04 g, 4.12 mmol) were dissolved in anhydrous CH₂Cl₂ (50 mL). The solution was stirred at room temperature for 12 hours. The solvent was removed under reduced pressure. To the crude product was added 50 mL of water containing 1.5% NaOH, and the aqueous layer extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (1 × 15 mL), dried over anhydrous Na₂SO₄, and the solvent removed under reduced pressure. The product was purified by column chromatography using 15% ethyl acetate in hexanes (v/v) to yield **10** (696 mg, 1.56 mmol) as a colorless oil in 46% yield. NMR spectra reflected a mixture of *cis* and *trans* proline rotamers (1:1.5 ratio, respectively). ¹H NMR (600 MHz, CDCl₃) δ 7.57 (d, *J* = 8.7 Hz), 7.56 (d, *J* = 8.6 Hz) (sum of 7.57 ppm and 7.56 ppm = 2H), 6.64 (d, *J* = 8.9 Hz), 6.63 (d, *J* = 8.9 Hz) (sum of 6.64 ppm and 6.63 ppm = 2H), 4.92-4.80 (m, 1H), 4.48 (t, *J* = 7.7 Hz), 4.41 (t, *J* = 8.0 Hz) (sum of 4.48 ppm and 4.41 ppm = 1H), 3.80-3.77 (m, 2H), 3.75 (s), 3.76 (s) (sum of singlets at 3.75 ppm and 3.76 ppm = 3H), 2.59-2.45 (m, 1H), 2.24-2.20 (m, 1H), 1.45 (s), 1.42 (s) (sum of singlets 1.42 ppm and 1.45 ppm = 9H). ¹³C NMR (150.9 MHz, CDCl₃) δ 175.33, 173.13, 156.75, 156.73, 154.29, 153.62, 138.48, 138.44, 117.85, 83.71, 80.55, 75.47, 74.77, 57.92, 57.53, 52.41, 52.20, 51.99, 51.76, 36.43, 35.49, 28.35, 28.24. HRMS (LIFDI-TOF) *m/z*: [M+H]⁺ calcd for C₁₇H₂₂INO₅ 447.0543, found 447.0550.

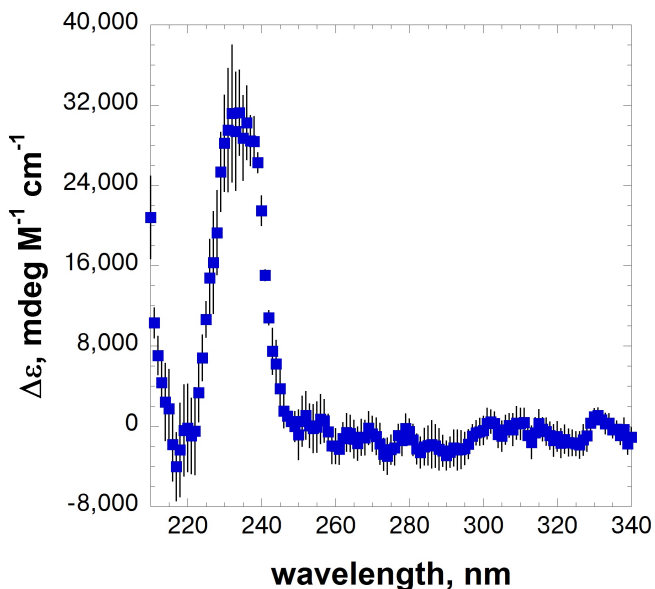
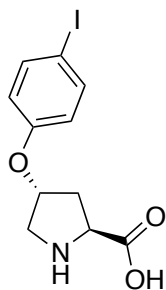
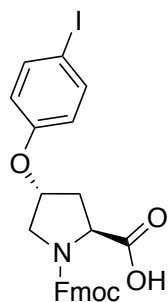


Figure S7. CD spectrum of **10**, Boc-(2*S*,4*R*)-*p*-iodophenyl-4-hydroxyproline methyl ester. Sample concentrations were between 0.85 mM and 1.00 mM **10** in methanol at 20 °C. Error bars indicate standard error. Data below 210 nm are not reported due to high dynode voltage.



11

(2*S*,4*R*)-*p*-iodophenyl-4-hydroxyproline (11**).** **10** (490 mg, 1.10 mmol) was dissolved in a 20 mL solution of water and 1,4-dioxane (1:1, v/v) containing 2 M HCl. The mixture was stirred at 50 °C for 4 hours. Dioxane and water were removed under reduced pressure. The crude product (470 mg) was used in the subsequent reaction directly without further purification. ¹H NMR (600 MHz, CD₃OH) 7.88 (s, 1H), 7.63 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 5.21 (t, *J* = 4.0 Hz, 1H), 4.55 (dd, *J* = 11.0, 8.0 Hz, 1H), 3.67 (dd, *J* = 13.0 Hz, 4.1 Hz, 1H), 3.58 (d, *J* = 13.0 Hz, 1H), 2.69 (dd, *J* = 14.4 Hz, 7.1 Hz, 1H), 2.42 (ddd, *J* = 14.3 Hz, 10.4 Hz, 4.6 Hz, 1H). ¹³C NMR (150.9 MHz, CD₃OH) 156.1, 138.50, 117.79, 83.71, 75.80, 58.49, 50.89, 34.53. HRMS (LIFDI-TOF) *m/z*: [M+H]⁺ calcd for C₁₁H₁₂INO₃ 332.9862, found 332.9843.



12

Fmoc-(2*S*,4*R*)-*p*-iodophenyl-4-hydroxyproline (12). **11** (470 mg) was dissolved in a 20 mL solution of water and 1,4-dioxane (1:1, v/v), and NaHCO₃ was added to neutralize the residual HCl from the previous reaction. Fmoc-Cl (341 mg, 1.32 mmol) and NaHCO₃ (185 mg, 2.20 mmol) were added, and the reaction mixture was stirred at room temperature for 6 hours. The solution was acidified to pH 3 using 2 M HCl. The crude product was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (1 × 10 mL), dried over Na₂SO₄, and the solvent removed under reduced pressure. The product was purified by column chromatography with 0-4% methanol in CH₂Cl₂ containing 0.5% acetic acid to yield **12** (572 mg, 1.03 mmol) as a white solid in 94% yield over two steps. NMR spectra reflected a mixture of *cis* and *trans* proline rotamers (1:2.5 ratio). ¹H (600 Hz, CDCl₃) δ 7.72 (d, *J* = 7.7 Hz), 7.69 (d, *J* = 8.0 Hz), (sum of 7.72 ppm and 7.69 ppm resonances = 2H), 7.58 (d, *J* = 8.8 Hz), 7.54 (d, *J* = 8.5 Hz), 7.47 (d, *J* = 7.5 Hz), 7.43 (d, *J* = 7.5 Hz), 7.39-7.27 (m), 7.32-7.23 (m) (sum of 7.58 ppm, 7.54 ppm, 7.47 ppm, 7.43 ppm, 7.36 ppm, and 7.29 ppm resonances = 6H), 7.22 (t, *J* = 7.5 Hz), 7.17 (t, *J* = 7.4 Hz) (sum of 7.22 ppm and 7.17 ppm resonances = 2H), 6.60 (d, *J* = 8.7 Hz), 6.60 (d, *J* = 8.1 Hz) (sum of 6.60 ppm and 6.60 ppm resonances = 2H), 4.86-4.82 (m), 4.82-4.79 (m) (sum of 4.84 ppm and 4.81 ppm resonances = 1H), 4.56-4.29 (m, 3H), 4.20 (t, *J* = 7.3 Hz), 4.17 (t, *J* = 6.4 Hz) (sum of 4.20 ppm and 4.17 ppm resonances = 1H), 3.86 (d, *J* = 12.2 Hz), 3.80 (d, *J* = 12.1 Hz) (sum of 3.86 ppm and 3.80 ppm resonances = 1H), 3.76 (dd, *J* = 12.0 Hz, 4.4 Hz), 3.69 (dd, *J* = 12.0 Hz, 4.3 Hz) (sum of 3.76 ppm and 3.69 ppm resonances = 1H), 2.62-2.54 (m), 2.53-2.44 (m) (sum of 2.58 ppm and 2.49 ppm resonances = 1H), 2.44-2.34 (m), 2.31-2.23 (m) (sum of 2.39 ppm and 2.27 ppm resonances = 1H). ¹³C NMR (150.9 MHz, CDCl₃) δ 175.18, 174.89, 156.53, 156.14, 143.53, 143.50, 141.27, 138.60, 138.51, 127.81, 127.72, 127.67, 127.11, 127.09, 125.07, 124.92, 120.02, 119.96, 117.88, 117.81, 83.95, 75.10, 74.65, 68.17, 67.71, 67.10, 58.51, 57.44, 52.37, 51.88, 47.19, 46.99, 36.60, 34.85. HRMS (LIFDI-TOF) *m/z*: [M+H]⁺ calcd for C₂₆H₂₂INO₅, 555.0543, found 555.0532.

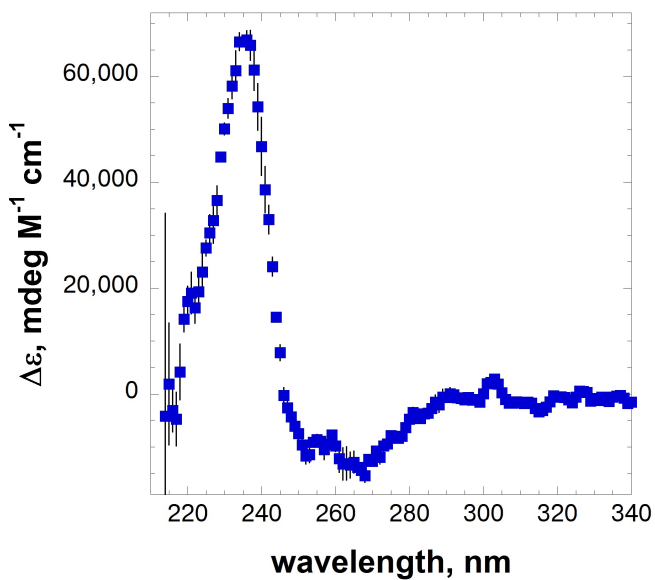
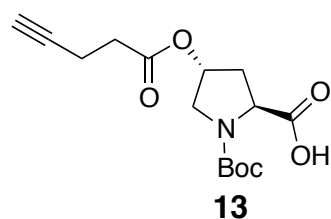
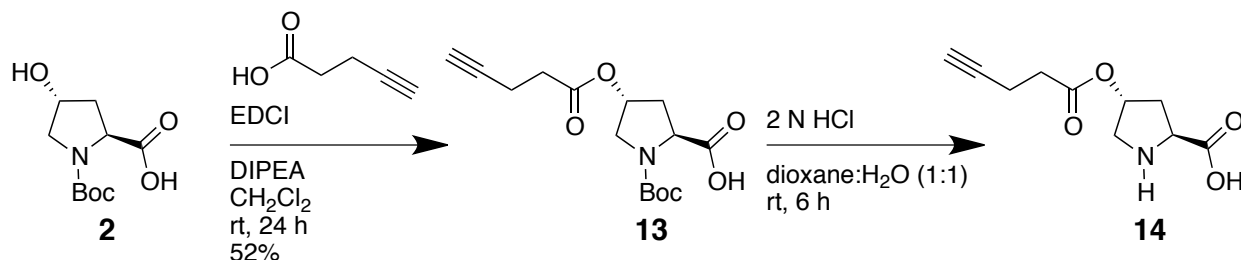
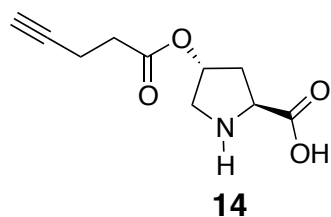


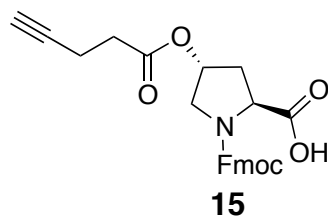
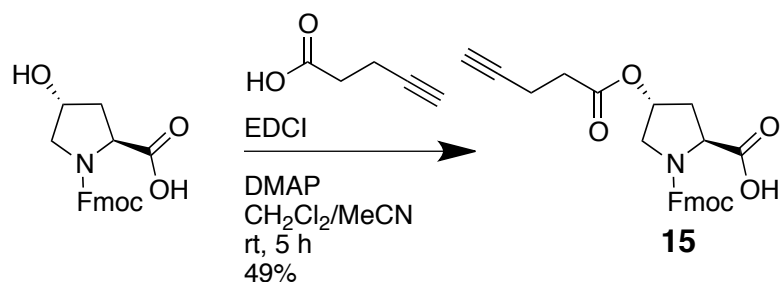
Figure S8. CD spectrum of **12**, Fmoc-(2*S*,4*R*)-*p*-iodophenyl-4-hydroxyproline. Sample concentrations were between 0.8 mM and 1.0 mM **12** in methanol at 20 °C. Error bars indicate standard error. Data below 210 nm are not reported due to high dynode voltage.



Boc-(2*S*,4*R*)-4'-pentynoyl-4-hydroxyproline (13). **2** (0.50 g, 2.16 mmol) was dissolved in anhydrous CH_2Cl_2 (20.0 mL) under a nitrogen atmosphere. 4-Pentynoic acid (212 mg, 2.16 mmol) was added to the solution, followed by EDCI (456 mg, 2.38 mmol). DIPEA (578 μL , 3.24 mmol) was added, and the reaction mixture was stirred vigorously for 24 h. The reaction was quenched by addition of 20 mL water, then acidified to pH 1-2 using dilute HCl (1 M solution), and the aqueous phase extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed once with brine (10 mL) and then dried over anhydrous Na_2SO_4 . The organic solution was concentrated *in vacuo* and purified via column chromatography (0-2% methanol in CH_2Cl_2) to yield **13** (350 mg, 1.12 mmol) as viscous oil in 52% yield. NMR spectra reflected a mixture of *cis* and *trans* proline rotamers (1:1.9 ratio). ^1H NMR (CDCl_3 , 400 MHz) δ 5.35 (br s, 1H), 4.51 (dd, $J = 8.1, 7.7$ Hz), 4.39 (dd, $J = 8.1, 7.8$ Hz) (sum of 4.51 ppm and 4.39 ppm resonances = 1H), 3.71 (d, $J = 2.2$ Hz), 3.64 (d, $J = 3.1$ Hz) (sum of 3.71 ppm and 3.64 ppm resonances = 2H), 2.64-2.54 (m), 2.54-2.42 (m), 2.42-2.20 (m) (sum of 2.58 ppm, 2.49 ppm, and 2.31 ppm resonances = 5H), 1.49 (s), 1.44 (s) (sum of 1.49 ppm and 1.44 ppm resonances = 9H). ^{13}C NMR (CDCl_3 , 100.6 MHz) 171.16, 82.66, 72.28, 69.36, 52.54, 34.12, 33.28, 28.33, 28.23, 14.38. HRMS (ESI) $[\text{M}]^-$ m/z calcd for $\text{C}_{15}\text{H}_{20}\text{O}_6\text{N}$ 310.1296, found 310.1298



(2*S*,4*R*)-4'-pentynoyl-4-hydroxyproline (14). **13** (250 mg, 0.80 mmol) was dissolved in 1,4-dioxane (4.0 mL), and dilute HCl (4 N, 4.0 mL) was added to the solution. The reaction mixture was stirred at room temperature for 6 h. The solvent was removed *in vacuo*, and the residue was washed with hexanes (3×5 mL) to yield **14** (140 mg, 0.66 mmol) in 83% yield as a viscous oil. ^1H NMR (DMSO-d_6 , 400 MHz) δ 5.27 (m, 1H), 4.42 (br s, 1H), 4.40-4.35 (m, 1H), 3.39-3.25 (m, 2H), 3.08 (s, 1H), 2.53-2.51 (m, 4H), and 2.28-2.02 (m, 2H); ^{13}C NMR (DMSO-d_6 , 100 MHz) 171.1, 168.2, 79.8, 72.2, 69.1, 58.2, 53.7, 37.7, 34.6, 14.1. MS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{13}\text{NO}_4$ 211, found 212.



Fmoc-(2*S*,4*R*)-4'-pentynoyl-4-hydroxyproline (15). 4-Pentynoic acid (65 mg, 0.67 mmol) was dissolved in CH_2Cl_2 (10 mL) under a nitrogen atmosphere. EDCI (128 mg, 0.67 mmol) was added to the solution, followed by DMAP (24 mg, 0.20 mmol). 4-Pentynoic acid was activated in this reaction mixture for 30 min. Fmoc-(2*S*,4*R*)-4-hydroxyproline (200 mg, 0.57 mmol) was dissolved in acetonitrile (10 mL) and added dropwise to the activated pentynoic acid solution. This solution was allowed to stir at room temperature for 5 hours under nitrogen. The solvent was removed under reduced pressure. Water (50 mL) was added to the crude oil, and the product was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine (1×10 mL) and dried over Na_2SO_4 . The crude product was purified by column chromatography using 0-4% methanol in CH_2Cl_2 containing 0.5% acetic acid to yield **15** (121 mg, 0.27 mmol) as a white solid in 49% yield. NMR spectra reflected a mixture of *cis* and *trans* proline rotamers (1:1.7 ratio). ^1H (600 Hz, CDCl_3) δ 7.77 (d, $J = 7.7$ Hz), 7.74 (d, $J = 7.6$ Hz) (sum of 7.77 ppm and 7.74 ppm resonances = 2H), 7.57 (t, $J = 7.5$ Hz), 7.55 (t, $J = 6.8$ Hz) (sum of 7.57 ppm and 7.55 ppm resonances = 2H), 7.42-7.35 (m, 2H), 7.34-7.28 (m, 2H), 5.39-5.34 (m), 5.34-5.31 (m) (sum of 5.36 ppm and 5.32 ppm resonances = 1H), 4.56-4.46 (m), 4.45-4.38 (m), 4.36 (t, $J = 8.1$ Hz) (sum of 4.51 ppm, 4.41 ppm, and 4.36 ppm resonances = 3H), 4.26 (t, $J = 7.0$ Hz), 4.18 (t, $J = 6.3$ Hz) (sum of 4.26 ppm and 4.18 ppm resonances = 1H), 3.81-3.69 (m, 2H), 2.60-2.37 (m), 2.31-2.23 (m) (sum of 2.50 ppm and 2.27 ppm resonances = 6H), 2.00-1.94 (m, 1H). ^{13}C NMR (150.9 MHz, CDCl_3) δ 171.10, 143.63, 141.36, 127.87, 127.72, 127.66, 127.14, 127.08, 124.98, 124.92, 124.77, 120.09, 119.99, 81.93, 72.61, 71.99, 69.42, 69.38, 68.19, 68.02, 52.53, 52.26, 47.19, 47.08, 36.69, 34.96, 33.30, 14.01. HRMS (LIFDI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{23}\text{NO}_6$, 433.1525, found 433.1528.

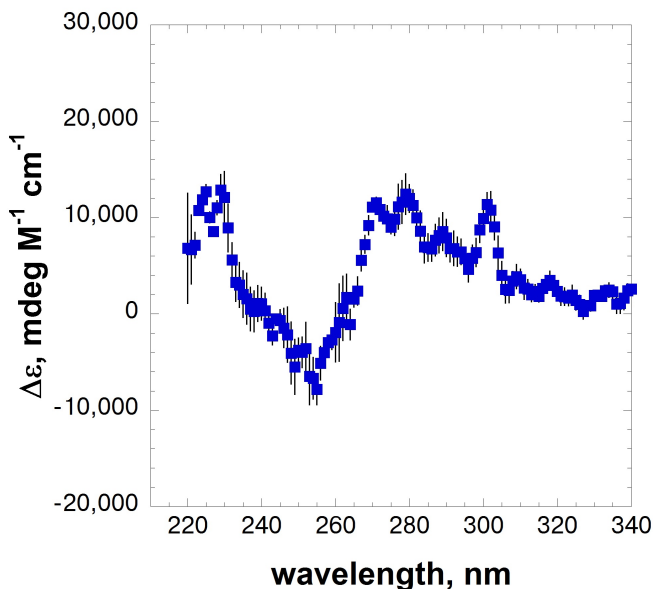
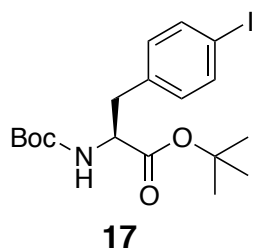
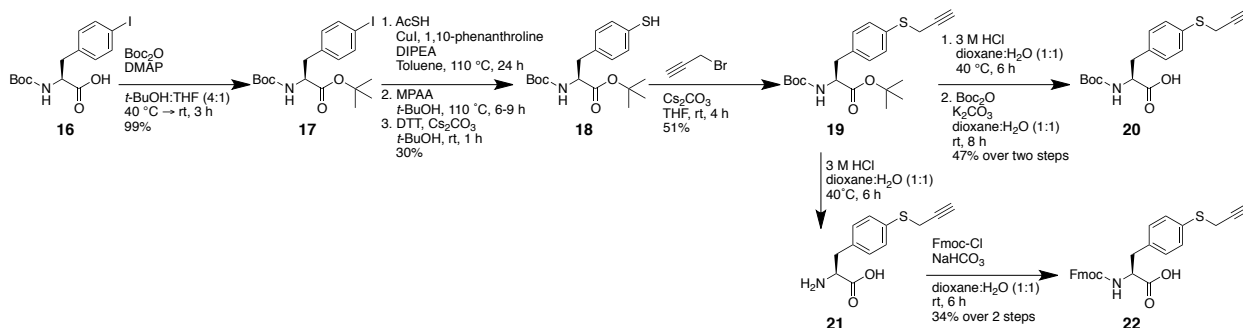


Figure S9. CD spectrum of **15**, Fmoc-(2*S*,4*R*)-4-pentynoyl-4-hydroxyproline. Sample concentrations were between 0.8 mM and 1.0 mM **15** in methanol at 20 °C. Error bars indicate standard error. Data below 220 nm are not reported due to high dynode voltage.



Boc-4-iodo-L-phenylalanine-O-tert-butyl ester (17). Boc-4-iodo-L-phenylalanine (**16**, 300 mg, 0.77 mmol) was dissolved in tetrahydrofuran (307 μ L). Boc_2O (434 mg, 1.99 mmol) and *tert*-butanol (1.23 mL) were added, and the mixture was warmed to 40 °C to allow **16** to completely dissolve. DMAP (28 mg, 0.23 mmol) was added, and the mixture was stirred at room temperature for 3 hours, or until the disappearance of **16** was observed via TLC. Dilute HCl (1 M, 20 mL) was added, and the product was extracted with CH_2Cl_2 (3 \times 20 mL). The combined organic layers were dried over sodium sulfate and filtered. The solvent was removed under reduced pressure. The crude product was purified via column chromatography (0-1% methanol

in CH_2Cl_2 (v/v)) to yield **17** (340 mg, 0.76 mmol) as a colorless oil in 99% yield. Enantiopurity was verified via chiral HPLC. The ^1H NMR and ^{13}C NMR spectra of the resultant product corresponded with literature values.³

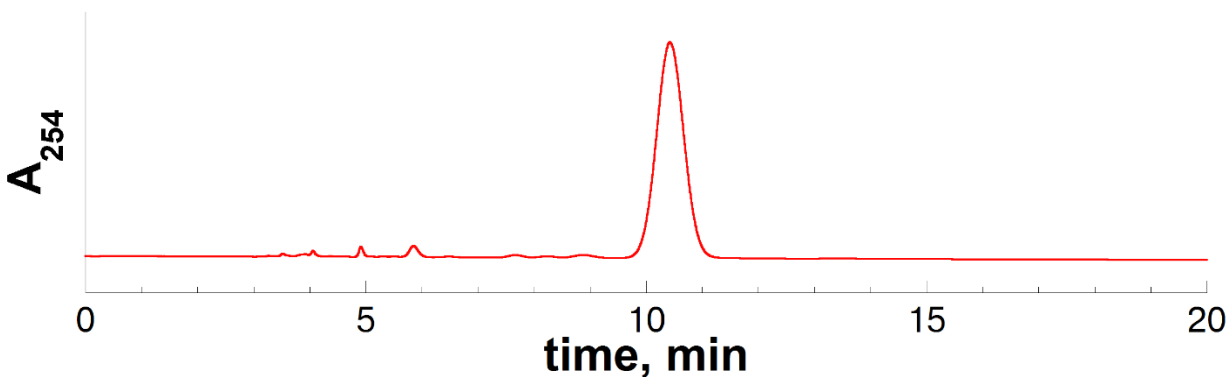


Figure S10. HPLC chromatogram of **17**, Boc-4-iodo-L-phenylalanine-O-*tert*-butyl ester (ChiralPak 1A, 250 x 4.6 mm, 5 μm particle, 1.0 mL/min, isocratic 20% isopropanol/hexanes). The peak at 10.3 minutes is the desired compound.

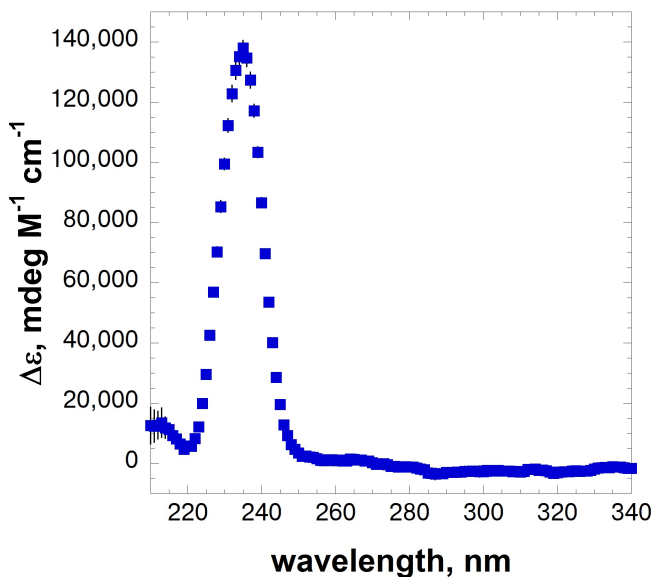
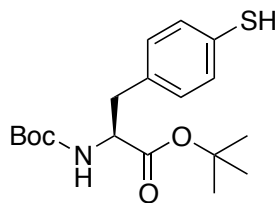


Figure S11. CD spectrum of **17**, Boc-4-iodo-L-phenylalanine-O-*tert*-butyl ester. Sample concentrations were between 0.20 mM and 1.3 mM **7** in methanol at 20 °C. Error bars indicate standard error. Data below 210 nm are not reported due to high dynode voltage.



18

Boc-4-thiol-L-phenylalanine-O-tert-butyl ester (18). **17** (400 mg, 0.89 mmol), copper(I) iodide (17 mg, 89 μ mol), and 1,10-phenanthroline (32 mg, 180 μ mol) were placed in an oven-dried glass vial with a stir bar. Toluene (1.8 mL) and DIPEA (470 μ L, 2.7 mmol) were added, and the mixture was stirred at room temperature under nitrogen for 5 minutes. Thioacetic acid (128 μ L, 1.8 mmol) was added to the solution at room temperature, the vial was sealed, and the mixture was heated to 110 °C in an oil bath and stirred for 24 hours. During this time, the reaction darkened to a red-brown color as iodine was formed. The solution was cooled to room temperature, and the solvent was removed under reduced pressure. The crude residue was redissolved in *t*-butanol (1.8 mL), and 4-mercaptophenylacetic acid (MPAA, 150 mg, 0.89 mmol) was added. The reaction mixture was stirred at 110 °C for 6-9 hours. The solution was then cooled to room temperature, and DTT (150 mg, 0.97 mmol) and cesium carbonate (320 mg, 0.98 mmol) were added. This mixture was stirred at room temperature for 1 hour. The crude mixture was diluted with ethyl acetate (10 mL) and added to dilute HCl (1 M, 20 mL). The crude product was extracted with ethyl acetate (3 \times 25 mL) and the combined organic layers were dried over Na₂SO₄. The solvent was removed under reduced pressure, and the crude product was redissolved in CH₂Cl₂. The product was purified via column chromatography (0-10% ethyl acetate in hexanes (v/v)) to yield **18** as a separable mixture of free thiol and disulfides. The disulfide products of **18** were recovered, and the solvent removed under reduced pressure. The resultant yellow oil was redissolved in THF (1.8 mL), and DTT (150 mg, 0.97 mmol) and Cs₂CO₃ (320 mg, 0.98 mmol) were added. The solution was stirred for 1 hour at room temperature. The crude mixture was diluted with ethyl acetate (10 mL) and added to dilute HCl (1 M, 20 mL). The crude product was extracted with ethyl acetate (3 \times 25 mL) and the combined organic layers were dried over Na₂SO₄. The solvent was removed under reduced pressure, and the crude product was redissolved in CH₂Cl₂. This additional **18** generated from recovered disulfide products was purified via column chromatography (0-10% ethyl acetate in hexanes (v/v)), and combined with **18** from the initial purification.

The free thiol product is prone to form a charge transfer complex with residual iodine from the reaction, resulting in a yellow oil that can rapidly form disulfides. In order to disrupt the charge transfer complex and remove the iodine, the combined product **18** was precipitated from hexanes, or recrystallized from 25% ethyl acetate in hexanes (v/v), and the white, crystalline solids were filtered. The product after reduction of recovered disulfides and removal of iodine was obtained in 30% yield (95 mg, 0.27 mmol). NMR spectra reflected a mixture of *cis* and *trans* rotamers (1:5.7 ratio) about the carbamate bond. ¹H NMR (400 MHz, CDCl₃) δ 7.20 (d, *J* = 8.1 Hz, 2H), 7.04 (d, *J* = 8.1 Hz, 2H), 4.98 (d, *J* = 8.0 Hz), 4.70 (br s) (sum of 4.98 ppm and 4.70 ppm resonances = 1H), 4.41 (ddd, *J* = 7.7 Hz, 6.1 Hz, 6.1 Hz), 4.22 (br s) (sum of 4.41 ppm and 4.22 ppm resonances = 1H), 3.41 (s, 1H), 3.00 (ddd, *J* = 13.8 Hz, 6.2 Hz, 6.0 Hz), 2.90 (br s) (sum of 3.00 ppm and 2.90 ppm resonances = 2H), 1.42 (s), 1.41 (s) (sum of 1.42 ppm and 1.41 ppm resonances = 18H). ¹³C NMR (100.6 MHz, CDCl₃) δ 170.78, 155.02, 133.99, 130.28, 129.48, 128.85, 82.18, 79.71, 54.68, 37.89, 28.30, 27.95. HRMS (LIFDI-TOF) *m/z*: [M+H]⁺

calcd for $C_{36}H_{52}N_2O_8S_2$ 353.1661, found 353.1673.

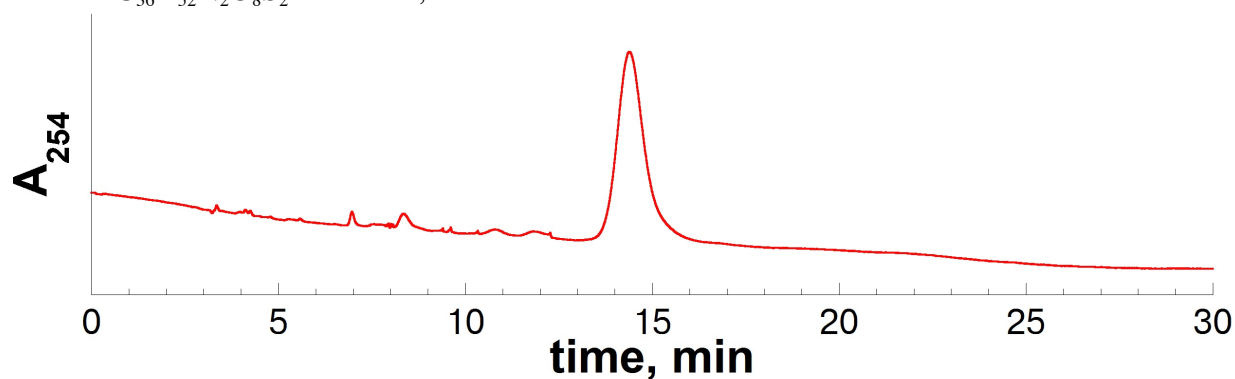


Figure S12. Chiral HPLC chromatogram of **18**, Boc-4-thiol-L-phenylalanine-O-*tert*-butyl ester (ChiralPak 1A column, 250×4.6 mm, $5 \mu\text{m}$ particle, 1.0 mL/min flow rate, isocratic 10% isopropanol/hexanes). The peaks at 8.4 min and 14.4 min are D- and L-isomers of **18**, respectively (95% ee).

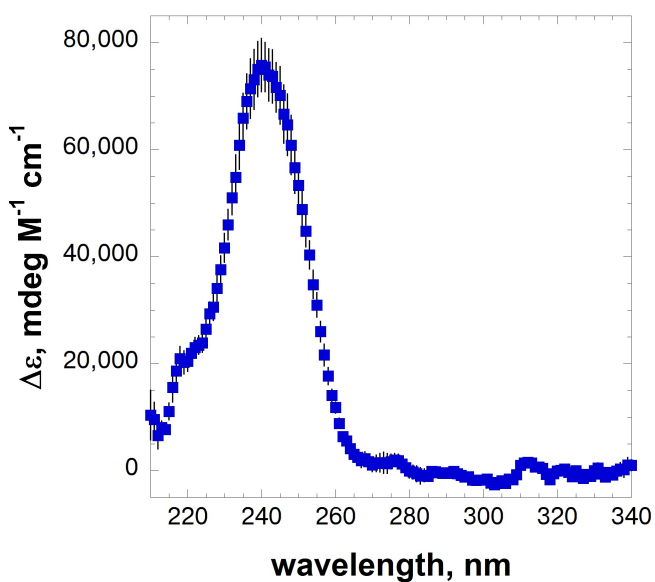
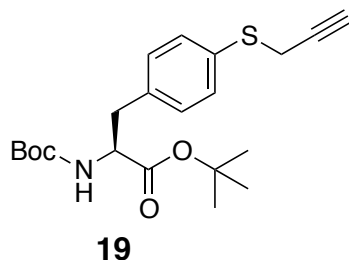


Figure S13. CD spectrum of **18**, Boc-4-thiol-L-phenylalanine-O-*tert*-butyl ester. Sample concentrations were between 0.40 mM and 0.80 mM **18** in methanol at 20 °C. Error bars indicate standard error. Data below 210 nm are not reported due to high dynode voltage.



Boc-4-(S-propargyl)-thiol-L-phenylalanine-O-tert-butyl ester (19). **18** (180 mg, 0.51 mmol) was dissolved in THF (5.1 mL). Propargyl bromide (150 μ L, 1.4 mmol, 80% wt in toluene) and cesium carbonate (331 mg, 1.02 mmol) were added, and the mixture was stirred at room temperature for 4 h, or until the disappearance of **18** was confirmed via TLC. The reaction mixture was quenched with dilute HCl (1 M, 40 mL), and the crude product was extracted with ethyl acetate (3 \times 40 mL). The combined organic layers were dried over Na₂SO₄, filtered, and the solvent was removed under reduced pressure to produce a pale yellow oil. The crude product was dissolved in hexanes (10 mL) and purified via column chromatography (5-12% ethyl acetate in hexanes v/v) to obtain **19** (101 mg, 0.258 mmol) as a yellow oil in 51% yield. NMR spectra reflected a mixture of cis and trans rotamers (1:5.9 ratio) about the carbamate bond. ¹H (600 MHz, CDCl₃) δ 7.38 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 8.2 Hz, 2H), 5.01 (d, J = 7.7 Hz), 4.73 (br s) (sum of 5.01 ppm and 4.73 ppm resonances = 1H), 4.44 (dd, J = 13.5 Hz, 6.3 Hz), 4.25 (br s) (sum of 4.44 ppm and 4.25 ppm resonances = 1H), 3.58 (d, J = 2.6 Hz, 2H), 3.03 (ddd, J = 13.9, 6.5, 6.3 Hz), 2.93 (br s) (sum of 3.03 ppm and 2.93 ppm resonances = 2H), 2.22 (t, J = 2.6 Hz, 1H), 1.42 (s), 1.40 (s) (sum of 1.42 ppm and 1.40 ppm resonances = 18H). ¹³C NMR (150.9 MHz, CDCl₃) δ 170.80, 155.04, 135.60, 133.20, 130.34, 130.20, 82.17, 79.85, 79.73, 71.56, 54.73, 38.15, 28.33, 27.97, 22.77. HRMS (LIFDI-TOF) m/z : [M+H]⁺ calcd for C₂₅H₃₁SNO₄ 391.1817, found 391.1809.

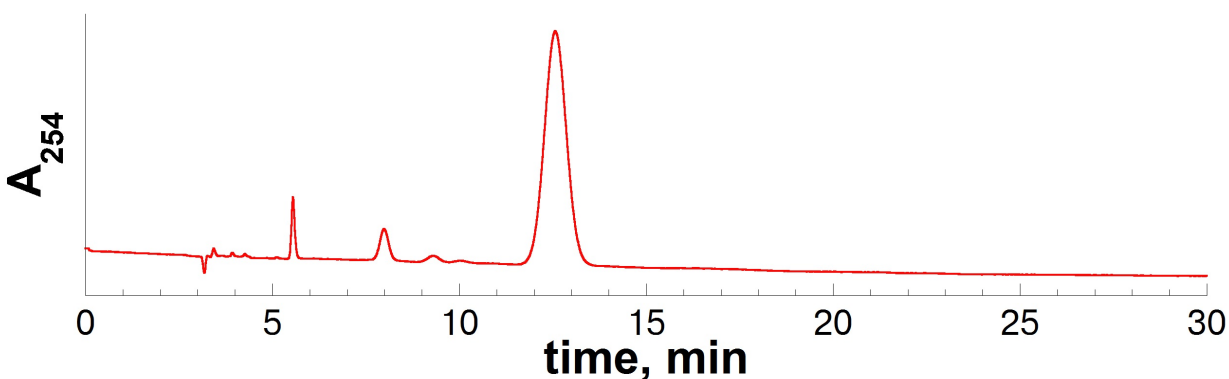


Figure S14. HPLC chromatogram of **19**, Boc-4-(S-propargyl)-thiol-L-phenylalanine-O-tert-butyl ester (ChiralPak 1A, 250 \times 4.6 mm, 5 μ m particle, 1.0 mL/min, isocratic 20% isopropanol/hexanes). The peaks at 8.0 min and 12.6 min are D- and L-isomers of **19**, respectively (90% ee).

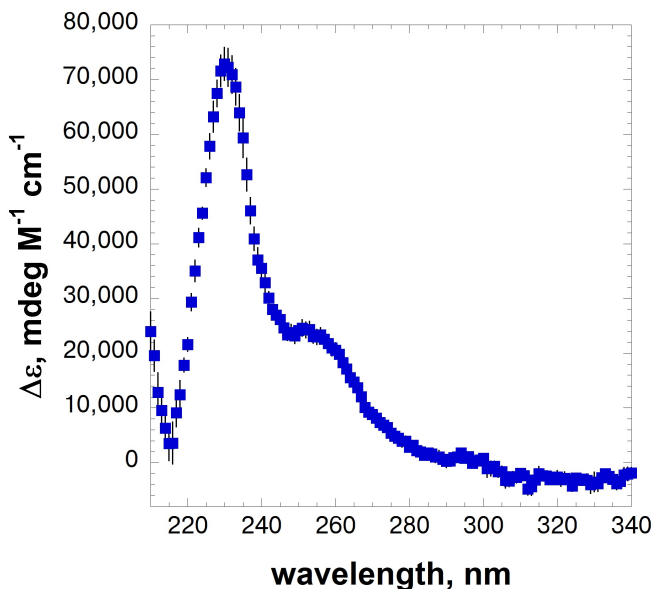
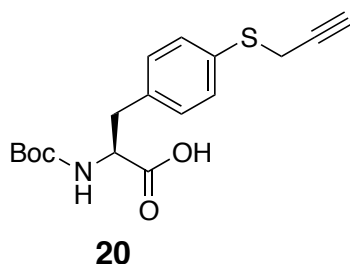


Figure S15. CD spectrum of **19**, Boc-4-(S-propargyl)-thiol-L-phenylalanine-O-*tert*-butyl ester. Sample concentrations were between 0.50 mM and 1.1 mM **19** in methanol at 20 °C. Error bars indicate standard error. Data below 210 nm are not reported due to high dynode voltage.



Boc-4-(S-propargyl)-thiol-L-phenylalanine (20). **19** (32 mg, 0.082 mmol) was dissolved in 1,4-dioxane (1.6 mL). A solution of HCl (6 M, 1.6 mL) was added, and the resultant solution was stirred at 40 °C for 6 hours to produce **21**. The crude mixture was dried *in vacuo*, and the residue was redissolved in water (330 μ L) and 1,4-dioxane (330 μ L). Potassium carbonate was added until the pH was 9 (approximately 460 mg). Boc₂O (35 mg, 0.16 mmol) was added, and the resultant mixture was stirred at room temperature for 8 h. 1 M HCl (20 mL) was added to the mixture, and the product was extracted with ethyl acetate (3 \times 20 mL). The combined organic layers were dried over Na₂SO₄ and filtered. The solvent was removed under reduced pressure and the resultant solid was redissolved in CH₂Cl₂. The crude product was purified via column chromatography (0-6% methanol in CH₂Cl₂ v/v) to obtain **20** (13 mg, 0.039 mmol) as an off-white solid in 47% yield over two steps. ¹H (400 MHz, CD₃OD) δ 7.37 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 4.32 (dd, *J* = 4.9 Hz, 9.1 Hz), 4.25 (br m) (sum of 4.32 ppm and 4.25 ppm resonances = 1H), 3.62 (d, *J* = 2.6 Hz, 2H), 3.14 (dd, *J* = 4.9 Hz, 13.8 Hz, 1 H), 2.88 (dd, *J* = 9.2 Hz, 13.9 Hz, 1H), 2.54 (t, *J* = 2.5 Hz, 1H), 1.38 (s), 1.33 (s) (sum of 1.38 ppm and 1.33 ppm resonances = 9H). ¹³C NMR (100.6 MHz, CD₃OD) δ 175.41, 157.83, 138.02, 137.65, 134.83, 132.20, 131.13, 131.02, 119.86, 80.99, 80.54, 72.56, 57.68, 56.25, 38.85, 38.30, 28.69, 28.47, 22.97. HRMS (LIFDI-TOF) *m/z*: [M+H]⁺ calcd for C₁₇H₂₁SNO₄ 335.1191, found 335.1183.

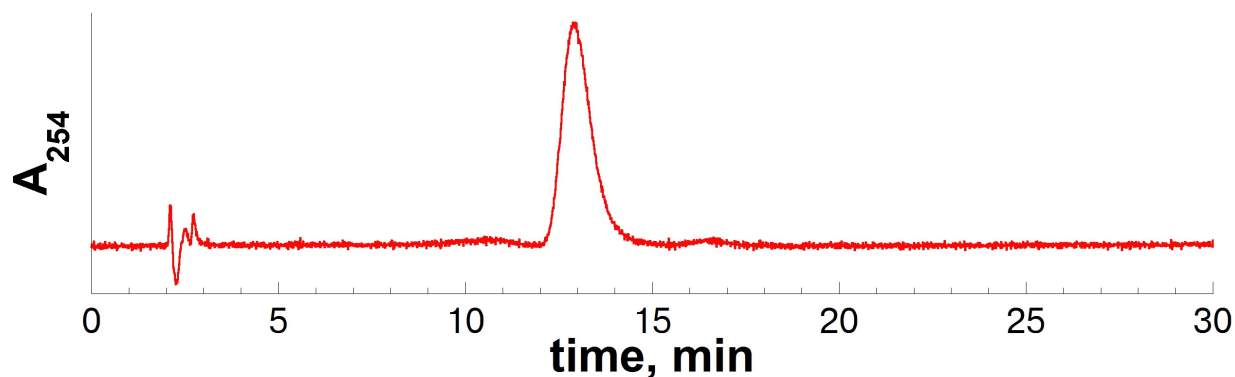


Figure S16. HPLC chromatogram of **20**, Boc-4-(S-propargyl)-thiol-L-phenylalanine (ChiralPak AD-RH, 150 x 4.6 mm, 5 μ m particle, 1.0 mL/min, isocratic 40% buffer B in buffer A).

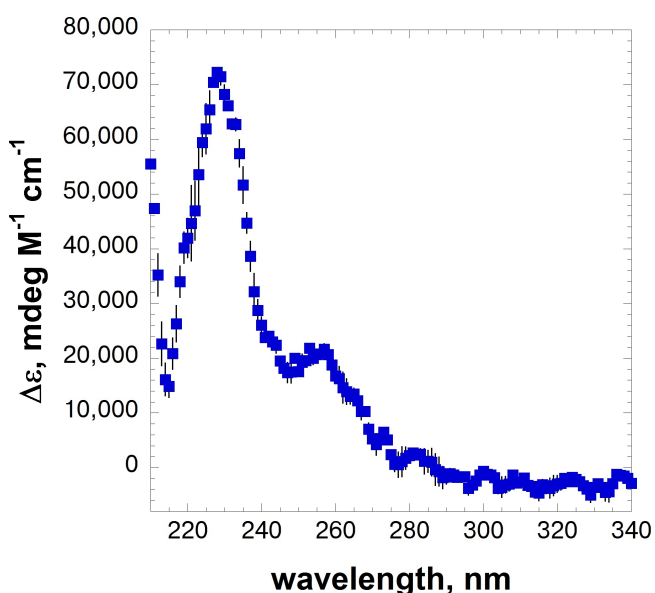
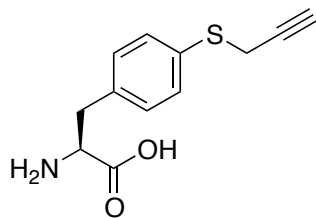


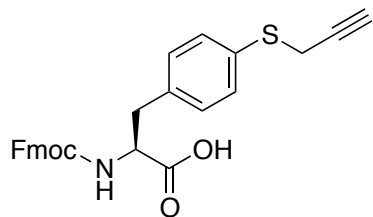
Figure S17. CD spectrum of **20**, Boc-4-(S-propargyl)-thiol-L-phenylalanine. Sample concentrations were between 0.50 mM and 1.0 mM **20** in methanol at 20 °C. Error bars indicate standard error. Data below 210 nm are not reported due to high dynode voltage.



21

4-(S-propargyl)-thiol-L-phenylalanine (21). **19** (32 mg, 0.082 mmol) was dissolved in 1,4-dioxane (1.6 mL). A solution of 6 M HCl (1.6 mL) was added, and the mixture was stirred at 40 °C for 6 h, or until the disappearance of **19** was confirmed via TLC. The solvent was removed under reduced pressure. The crude product **21** was used without purification. ^1H (600 MHz, CD_3OD) δ 7.44 (d, $J = 8.2$ Hz, 2H), 7.27 (d, $J = 8.1$ Hz, 2H), 4.25 (dd, $J = 7.6, 5.5$ Hz, 1H), 3.68

(d, $J = 2.6$ Hz, 2H), 3.25 (dd, $J = 8.3$ Hz, 15.2 Hz), 3.13 (dd, $J = 7.8$ Hz, 14.6 Hz) (sum of 3.25 ppm and 3.13 resonances = 2H), 2.57 (t, $J = 2.5$ Hz, 1H). ^{13}C NMR (150.9 MHz, CD_3OD) δ 171.17, 136.69, 134.10, 131.51, 131.20, 131.14, 72.65, 55.03, 55.84, 47.82, 37.16, 36.92, 22.52. HRMS (LIFDI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{13}\text{SNO}_2$ 235.0667, found 235.0677.



22

Fmoc-4-(S-propargyl)-thiol-L-phenylalanine (22). **19** (0.10 g, 0.26 mmol) was dissolved in 1,4-dioxane (5.1 mL). A solution of HCl (6 M, 5.1 mL) was added to the reaction, and the solution was stirred at 40 °C for 6 hours to produce **21**. The crude mixture was concentrated *in vacuo*, the mixture was neutralized with NaHCO_3 (approximately 1.8 g), and then Fmoc-Cl (132 mg, 0.51 mmol) was added to the mixture, and the resultant solution was stirred at room temperature for 6 hours. As needed, additional NaHCO_3 was added to maintain basic conditions (pH approximately 8). After confirming disappearance of **21** via TLC, 1 M HCl (20 mL) was added to the mixture, and the product was extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the resultant solid was redissolved in CH_2Cl_2 . The crude product was purified via column chromatography (0-5% methanol in CH_2Cl_2 v/v) to obtain **22** (40 mg, 0.088 mmol) as an off-white solid in 34% yield over two steps. ^1H (400 MHz, CD_3OD) δ 7.78 (d, $J = 7.6$ Hz, 2H), 7.60 (d, $J = 7.4$ Hz), 7.59 (d, $J = 7.4$ Hz) (sum of 7.60 ppm and 7.59 ppm resonances = 2H), 7.52 (d, $J = 7.1$ Hz, 0.3H), 7.38 (t, $J = 7.5$ Hz), 7.34 (d, $J = 8.2$ Hz), 7.29 (m) (sum of 7.38 ppm, 7.34 ppm, and 7.29 ppm resonances = 7H), 7.20 (d, $J = 8.1$ Hz, 2H), 7.04 (d, $J = 7.3$ Hz, 0.3H), 4.41 (dd, $J = 4.7$ Hz, 9.8 Hz, 1H), 4.31 (dd, $J = 10.4$ Hz, 7.0 Hz, 1H), 4.20 (dd, $J = 10.3$ Hz, 7.1 Hz, 1H), 4.14 (t, $J = 6.8$ Hz, 1H), 3.56 (d, $J = 2.6$ Hz, 2H), 3.20 (dd, $J = 14.0$ Hz, 4.7 Hz, 1H), 2.91 (dd, $J = 13.8$ Hz, 9.9 Hz, 1H), 2.49 (t, $J = 2.6$ Hz, 1H). ^{13}C NMR (100.6 MHz, CD_3OD) δ 175.02, 158.42, 145.25, 142.58, 137.62, 134.95, 131.13, 131.03, 128.80, 128.21, 126.39, 126.28, 120.93, 72.56, 67.98, 56.65, 38.11, 22.91. HRMS (LIFDI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{30}\text{H}_{25}\text{SNO}_6$ 457.1348, found 457.1372.

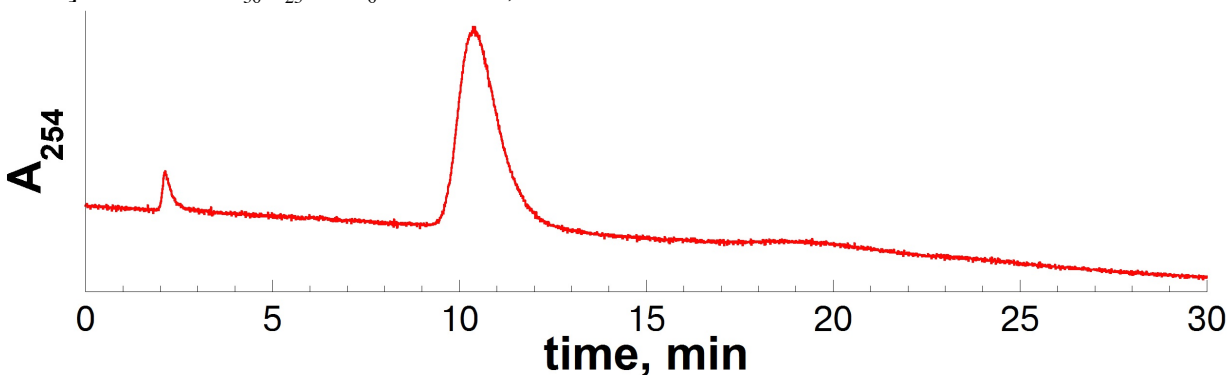


Figure S18. HPLC chromatogram of **22**, Fmoc-4-(S-propargyl)-thiol-L-phenylalanine (ChiralPak AD-RH, 150 x 4.6 mm, 5 μm particle, 1.0 mL/min, isocratic 60% buffer B in buffer A).

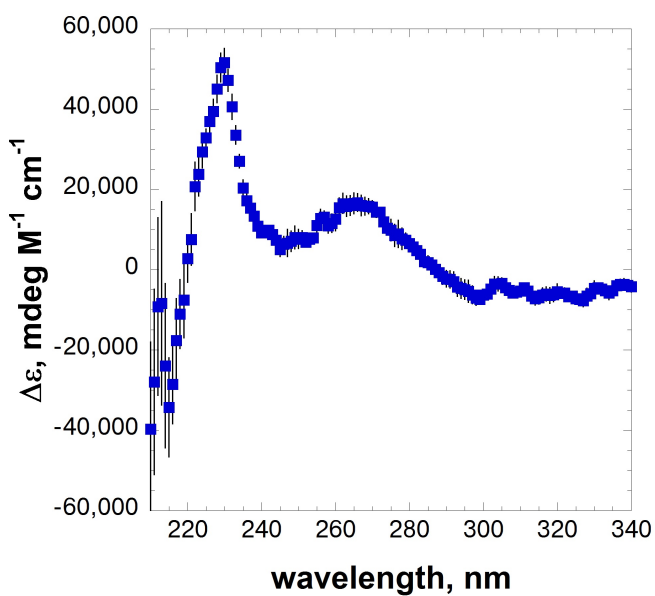


Figure S19. CD spectrum of **22**, Fmoc-4-(S-propargyl)-thiol-L-phenylalanine. Sample concentrations were between 0.50 mM and 1.0 mM **22** in methanol at 20 °C. Error bars indicate standard error. Data below 210 nm are not reported due to high dynode voltage.

Peptide synthesis and characterization

Peptides (0.1 or 0.25 mmol) were synthesized manually on Rink amide resin via standard Fmoc solid phase peptide synthesis using HBTU as a coupling reagent. 60 minute coupling reactions were performed with 4 equivalents of Fmoc amino acids and HBTU. 2 hour coupling reactions using 1.5 equivalents and HATU were used for the non-canonical amino acids. Peptides were acetylated on the N-terminus and contained C-terminal amides.

Peptides were cleaved from the resin and deprotected for 2 hours under standard conditions (either 90% TFA/5% TIS/5% H₂O or 90% TFA/2.5% thioanisole/1.5% TIS/5% H₂O/1% phenol). TFA was removed by evaporation under nitrogen. Peptides were precipitated with cold ether and the precipitate was dried. The peptides were dissolved in water or phosphate buffer, then filtered using a 0.45 μ m syringe filter. The peptides were purified and the purity was determined using reverse phase HPLC on a Vydac C18 semi-preparative column (250 \times 10 mm, 5-10 μ m particle, 300 Å pore) or on a Varian Microsorb MV C18 analytical column (250 \times 4.6 mm, 3-5 μ m particle, 100 Å pore) using a linear gradient of buffer B (20% water, 80% MeCN, 0.05% TFA) in buffer A (98% water, 2% MeCN, 0.06% TFA). Peptide purity was verified via reinjection on an analytical HPLC column. Peptides were characterized by ESI-MS (positive ion mode) on an LCQ Advantage (Finnigan) mass spectrometer, or on an LCMS 2020 (Shimadzu) mass spectrometer (positive or negative ion mode).

NMR spectra were collected at 298 K (unless indicated otherwise) on a Brüker AVN 600 MHz NMR spectrometer equipped with a triple resonance cryoprobe or a TXI probe. Spectra were internally referenced with 0.1 mM TSP. 1-D spectra were collected with a Brüker w5 watergate pulse sequence and a relaxation delay of 1.7-2 s. 2-D spectra were collected with a watergate TOCSY pulse sequence. Well-resolved peaks in the NMR spectra were integrated after phasing and baseline correction. $K_{\text{trans/cis}}$ was calculated based on the average integrated ratios of 2-3 pairs of peaks.

Table S1. HPLC purification of peptides

Peptide	HPLC Conditions	Retention time (min)	Expected Mass	Observed Mass
Ac-TYHyp(4-iodophenyl)N-NH ₂	40 minutes 0-45% buffer B in buffer A	31.6	752.2	775.2 (M+Na) ⁺
Ac-TPhe(4-S-propargyl)PN-NH ₂	60 minutes 0-55% buffer B in buffer A	27.3	588.2	611.2 (M+Na) ⁺

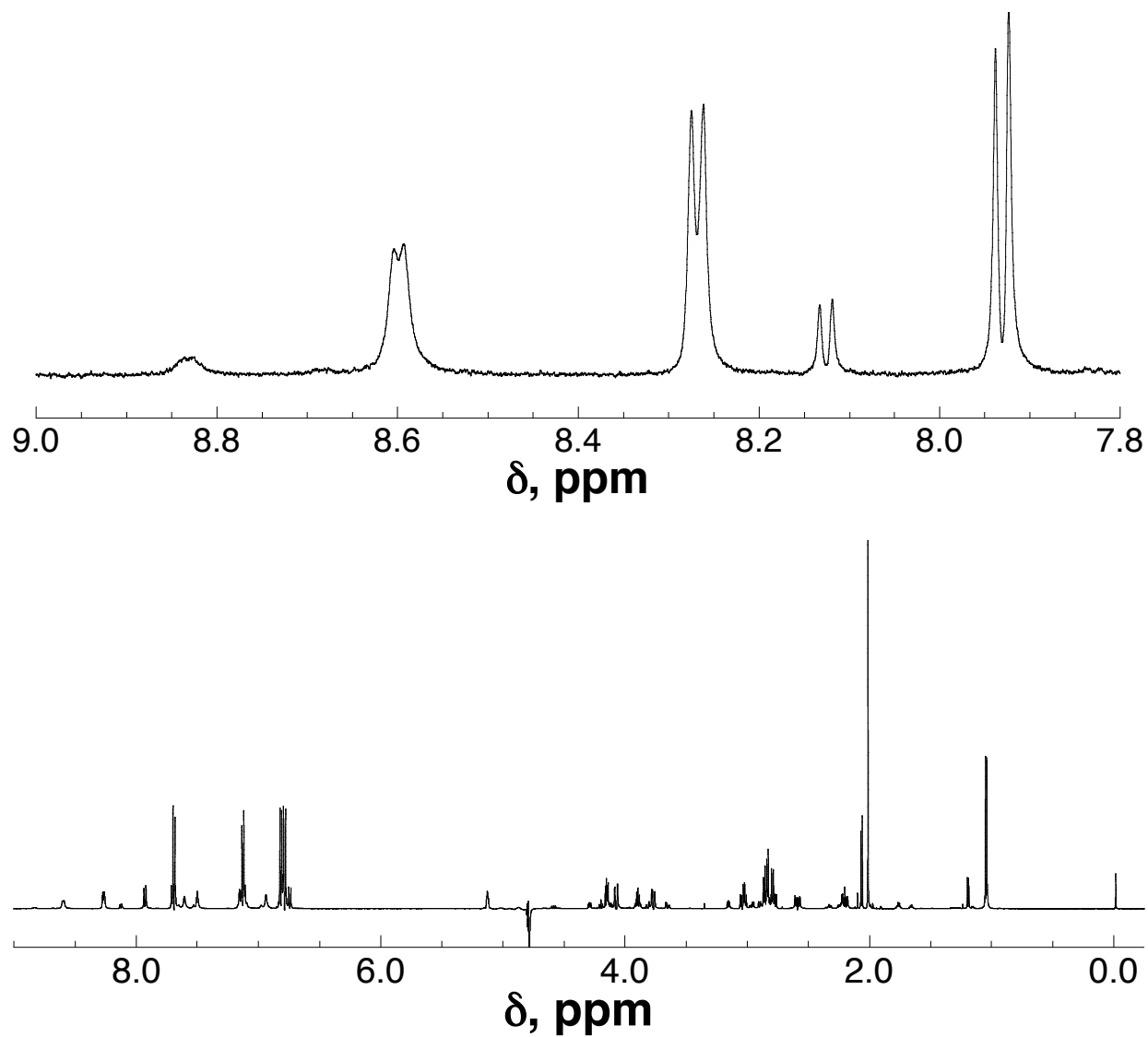


Figure S20. ¹H NMR spectrum of the peptide Ac-TYHyp(4-iodophenyl)N-NH₂ at pH 4.0 in 90% H₂O/10% D₂O at 298 K. Samples contained 5 mM phosphate, 25 mM NaCl, and 0.1 mM TSP. Top: amide region; bottom: full spectrum.

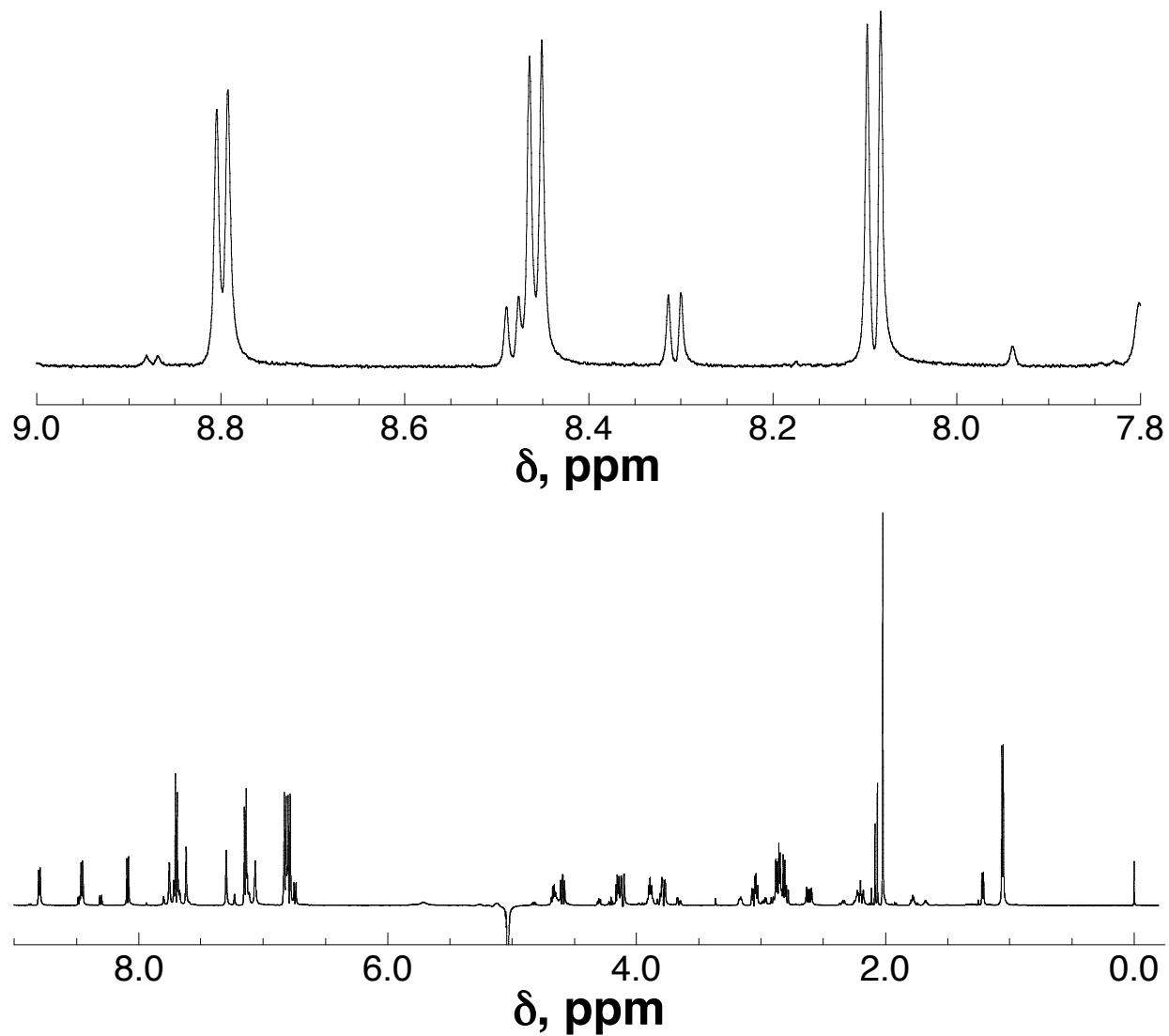


Figure S21. ^1H NMR spectrum of the peptide Ac-TYHyp(4-iodophenyl)N-NH₂ at pH 4.0 in 90% H₂O/10% D₂O at 277 K. Samples contained 5 mM phosphate, 25 mM NaCl, and 0.1 mM TSP. Top: amide region; bottom: full spectrum.

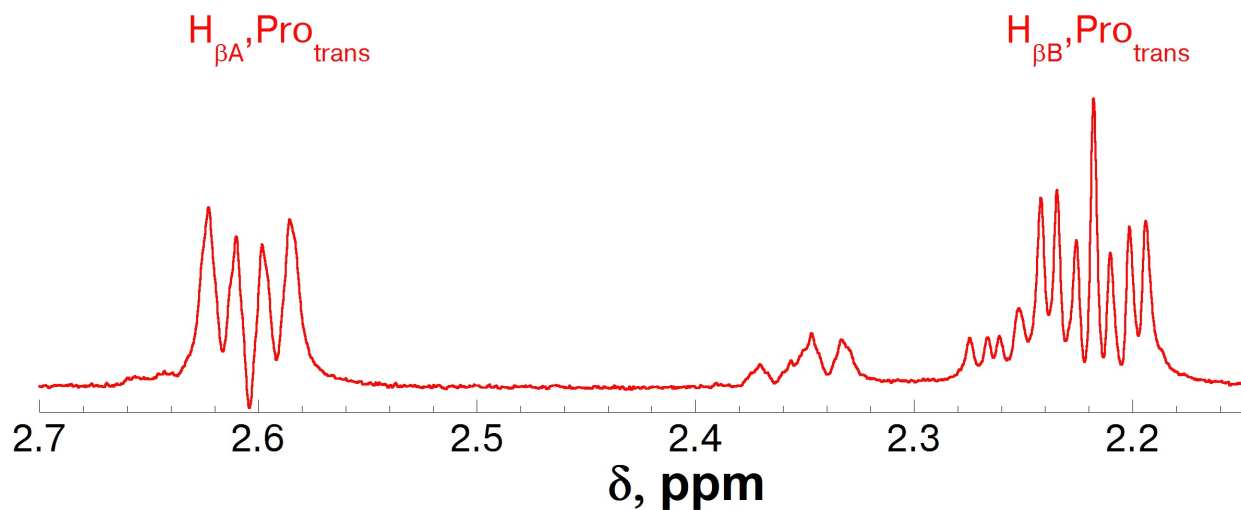


Figure S22. ^1H NMR spectrum of the peptide Ac-TYHyp(4-iodophenyl)N-NH₂ at pH 4.0 in 90% H₂O/10% D₂O at 298 K showing the dispersion of H β . H β_A and H β_B are separated by 0.39 ppm indicating *exo* ring pucker of modified proline residue in the peptide. Samples contained 5 mM phosphate, 25 mM NaCl, and 0.1 mM TSP.

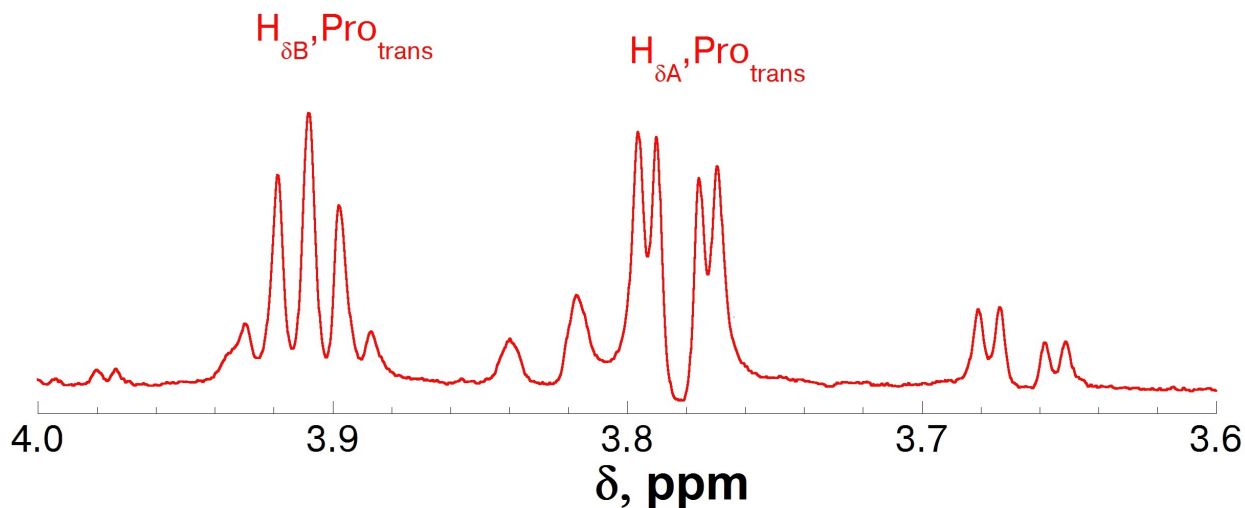


Figure S23. ^1H NMR spectrum of the peptide Ac-TYHyp(4-iodophenyl)N-NH₂ at pH 4.0 in 90% H₂O/10% D₂O at 298 K showing the dispersion of H δ . H δ_A and H δ_B are separated by 0.13 ppm indicating *exo* ring pucker of modified proline residue in the peptide. Samples contained 5 mM phosphate, 25 mM NaCl, and 0.1 mM TSP.

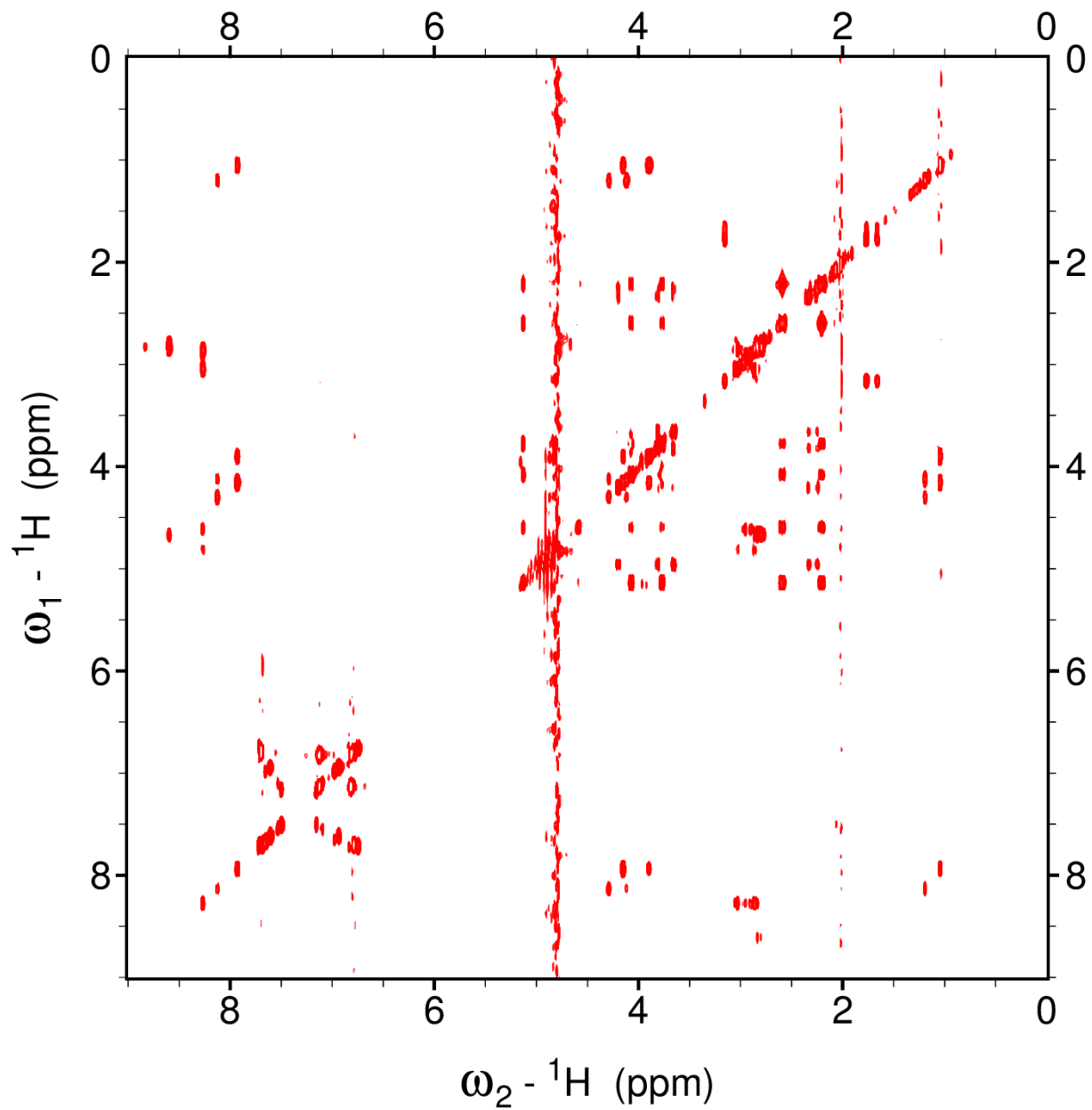


Figure S24. TOCSY NMR spectrum of the peptide Ac-TYHyp(4-iodophenyl)N-NH₂ at pH 4.0 in 90% H₂O/10% D₂O at 298 K. Samples contained 5 mM phosphate, 25 mM NaCl, and 0.1 mM TSP.

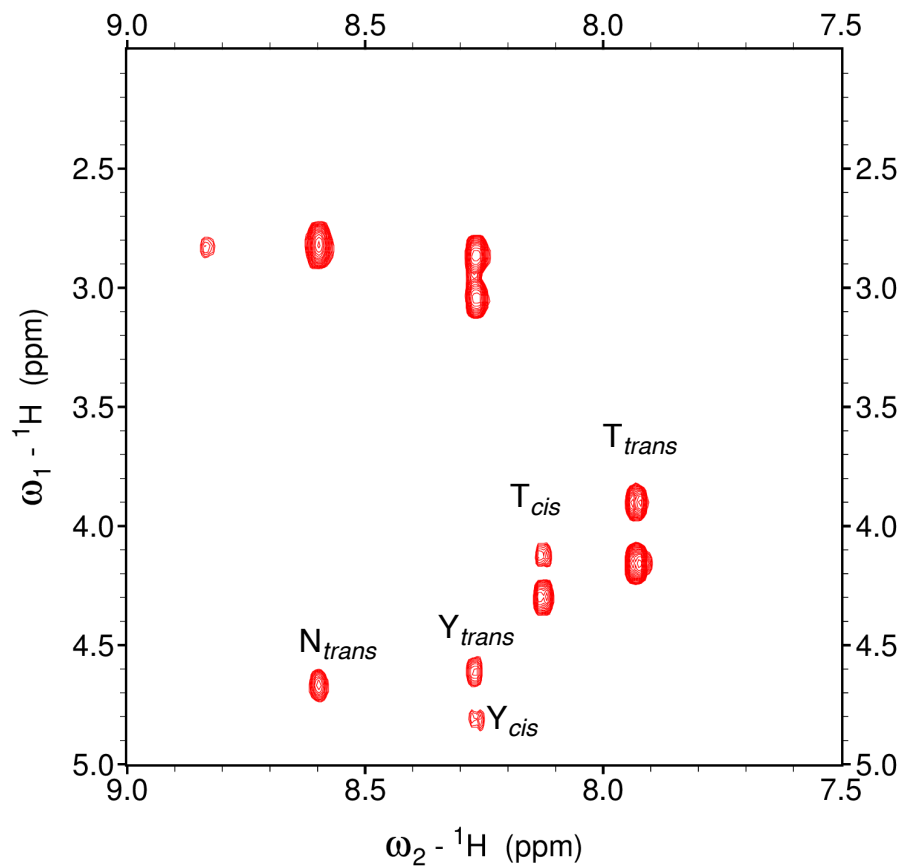


Figure S25. TOCSY NMR spectrum for amide fingerprint region of the peptide Ac-TYHyp(4-iodophenyl)N-NH₂ at pH 4.0 in 90% H₂O/10% D₂O at 298 K. Amide signals from the Tyr residue in *trans* and *cis* conformations exhibit spectral overlap. Samples contained 5 mM phosphate, 25 mM NaCl, and 0.1 mM TSP.

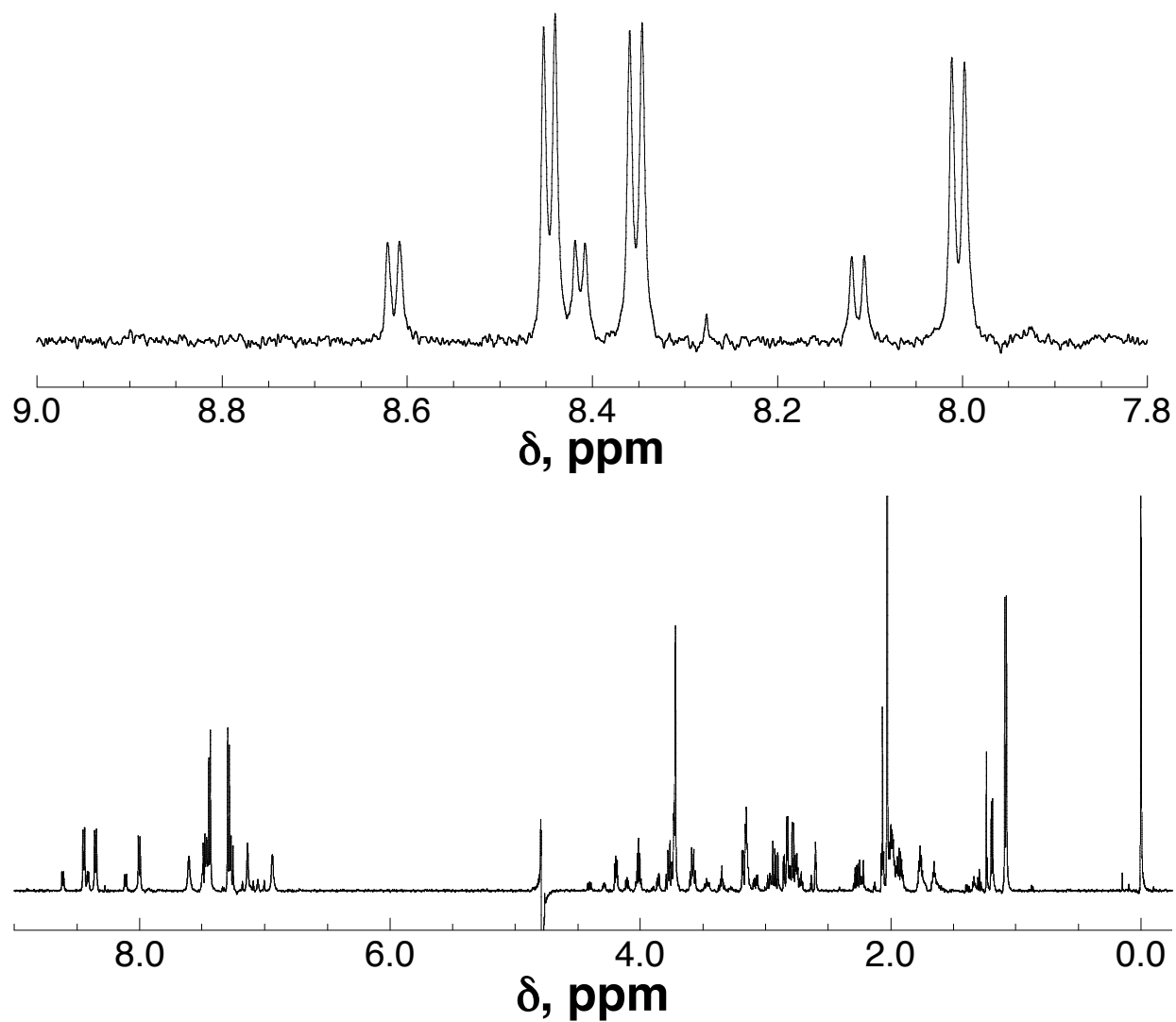
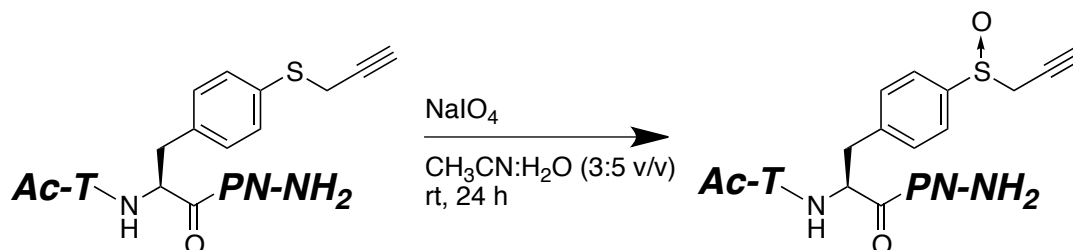


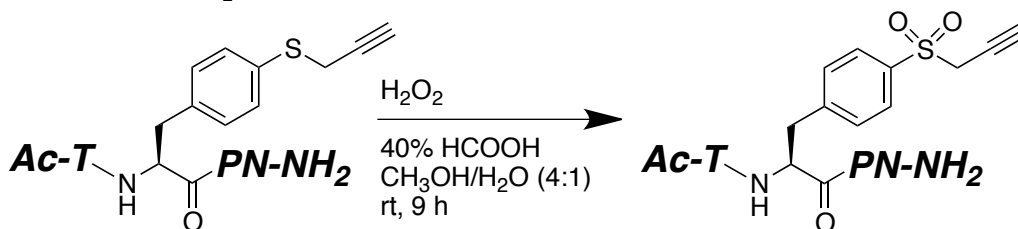
Figure S26. ^1H NMR spectrum of the peptide Ac-TPhe(4-S-propargyl)PN-NH₂ at pH 3.6 in 90% H₂O/10% D₂O at 298 K. Samples contained 5 mM phosphate, 25 mM NaCl, and 0.1 mM TSP. Top: amide region; bottom: full spectrum.

Oxidation of Ac-TPhe(S-propargyl)PN-NH₂ to the sulfoxide Ac-TPhe(S(O)-propargyl)PN-NH₂.

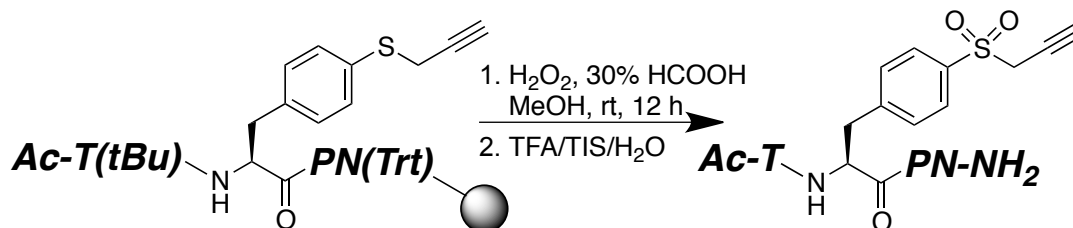


The peptide Ac-TPhe(4-S-propargyl)PN-NH₂ (approximately 5 nmol) was dissolved in a mixture of H₂O:MeCN (5:3 v/v, 80 μ L). NaIO₄ was then added (2.4 μ L of a 12.3 mg/mL solution in water). The mixture was stirred at room temperature for 24 h to produce the peptide Ac-TPhe(4-S(O)-propargyl)PN-NH₂ as an inseparable mixture of sulfoxide diastereomers. The peptide was purified via HPLC using a gradient of 0–40% buffer B in buffer A over 60 minutes: t_R 18.9 min, exp. 604.2, obs. 627.1 (M + Na)⁺.

Oxidation of Ac-TPhe(S-propargyl)PN-NH₂ to the sulfone Ac-TPhe(SO₂-propargyl)PN-NH₂ in solution and on solid-phase.



The peptide Ac-TPhe(4-S-propargyl)PN-NH₂ (approximately 5 nmol) was dissolved in methanol (100 μ L). 95% Formic acid (150 μ L, final concentration 40%) was added to this solution, followed by a solution of 30% H₂O₂ in water (100 μ L). The solution was allowed to incubate at room temperature for 9 hours to produce the peptide Ac-TPhe(4-SO₂-propargyl)PN-NH₂. The reaction mixture was diluted with 1.5 mL of H₂O and the solvents were removed under reduced pressure. The peptide was purified via HPLC using a linear gradient of 0-10% buffer B in buffer A over 30 minutes: t_R 26.1 min, exp. 620.2, obs. 643.1 (M + Na)⁺.



The peptide Ac-TPhe(4-SO₂-propargyl)PN-NH₂ was alternatively synthesized via oxidization on solid-phase. MeOH was added to the protected peptide Ac-T(*t*-Bu)Phe(4-S-propargyl)PN(Trt)-NH-resin in a disposable, fritted column. Formic acid (1 mL 90% formic acid, final concentration 30% formic acid) and H₂O₂ (200 μ L, 30% solution in water, final concentration 2%) were added, and the resultant solution was subjected to rotary mixing for 12 h at room temperature. The solution was removed and the resin washed with DMF (3 \times) and

CH_2Cl_2 (3 \times), and dried. The peptide was cleaved from the resin with simultaneous deprotection of side chains using 96% TFA, 2% H_2O , and 2% triisopropylsilane for 60 min. The peptide was purified via HPLC, to generate the peptide Ac-TPhe(4-SO₂-propargyl)PN-NH₂, which was identical by NMR to the peptide synthesized by solution-phase oxidation.

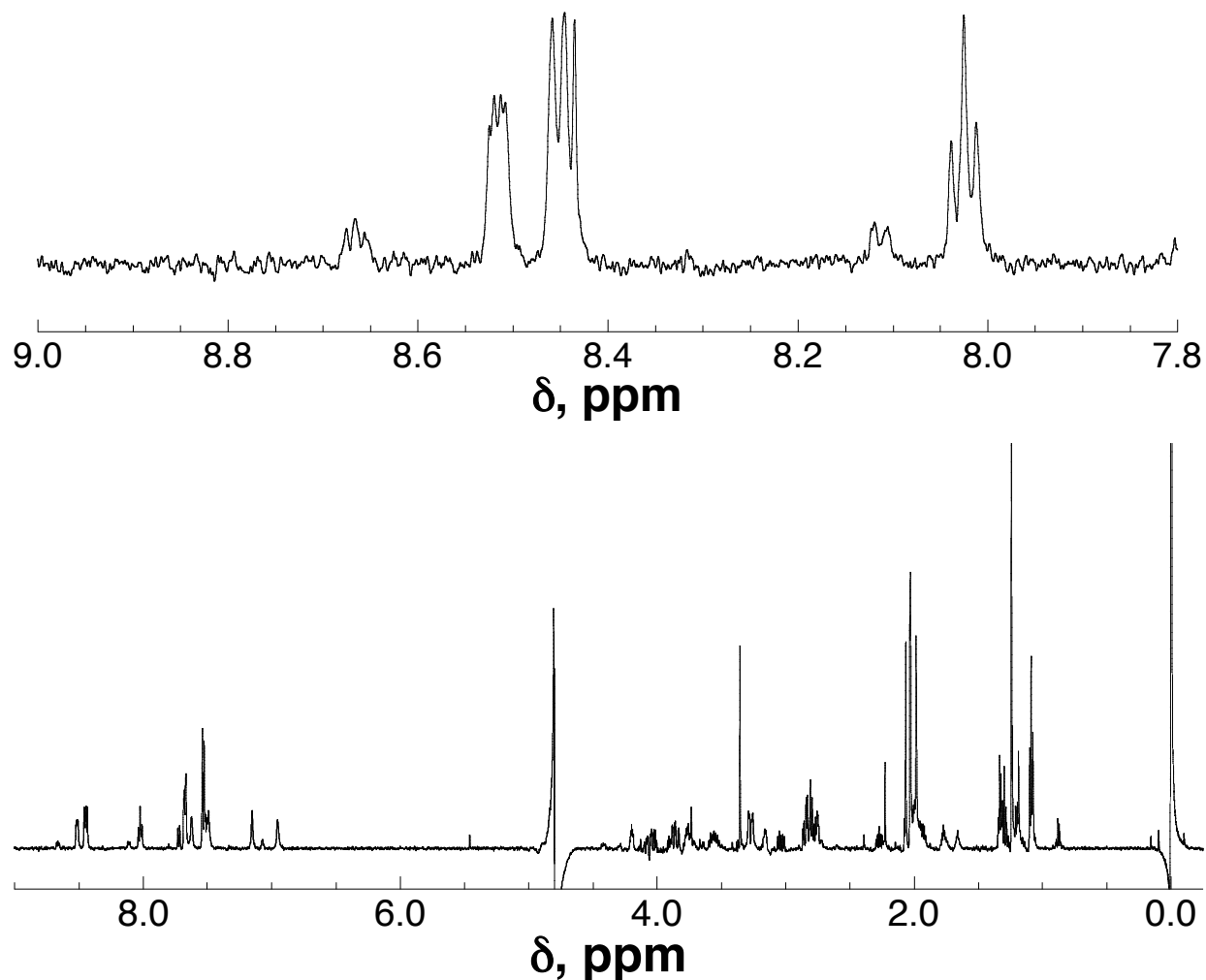


Figure S27. ¹H NMR spectrum of the peptide Ac-TPhe(4-S(O)-propargyl)PN-NH₂ at pH 4 in 90% H₂O/10% D₂O at 298 K. The sample contains a mixture of sulfoxide diastereomers. Samples contained 5 mM phosphate, 25 mM NaCl, and 0.1 mM TSP. Top: amide region; bottom: full spectrum.

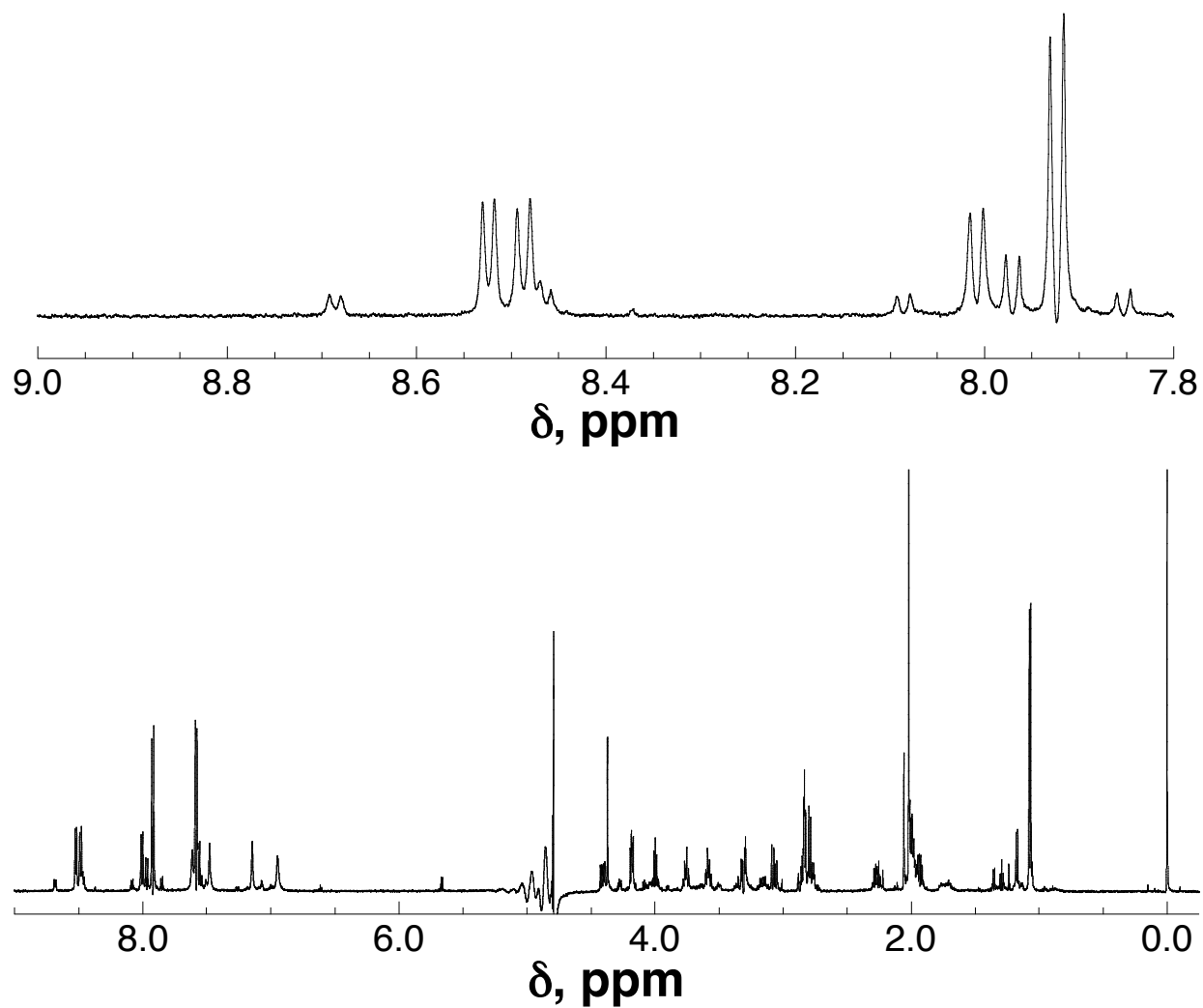
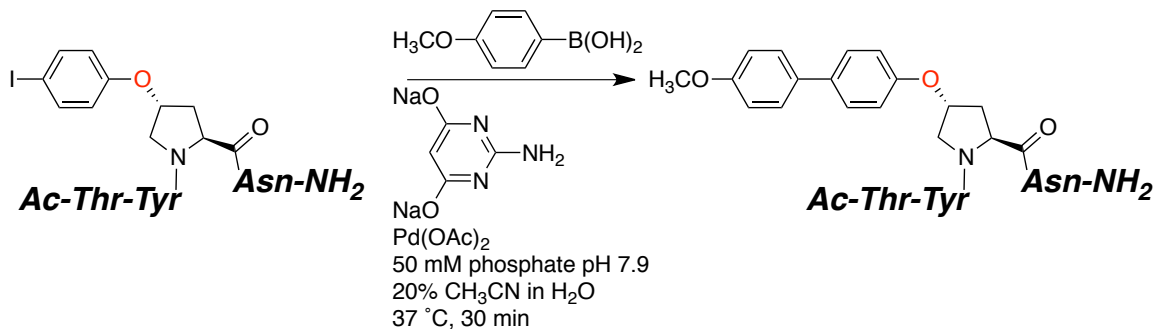


Figure S28. ¹H NMR spectrum of the peptide Ac-TPhe(4-SO₂-propargyl)PN-NH₂ at pH 4.0 in 90% H₂O/10% D₂O at 298 K. Samples contained 5 mM phosphate, 25 mM NaCl, and 0.1 mM TSP. Top: amide region; bottom: full spectrum.

Suzuki-Miyaura reaction on Ac-TYHyp(4-I-Ph)N-NH₂ with 4-methoxyphenylboronic acid.



The Suzuki-Miyaura reaction on the peptide Ac-TYHyp(4-I-Ph)N-NH₂ was conducted using identical conditions as previously described for the diastereomeric peptide Ac-TYhyp(4-I-Ph)N-NH₂.⁴ The peptide Ac-TYHyp(4-I-Ph)N-NH₂ (50 nmol) was dissolved in phosphate buffer (500 μ L, pH 7.9, 50 mM phosphate) containing 20% acetonitrile. To this solution, Pd(OAc)₂•ligand (20 μ L of 10 mM stock in 100 mM NaOH solution, 400 μ M final concentration) and 4-methoxyphenylboronic acid (7.6 mg, 50 μ mol, 100 mM final concentration) were added, and the resultant solution was incubated at 37 °C for 30 minutes to produce the conjugated peptide. The peptide was purified via HPLC using a linear gradient of 0-50% buffer B in buffer A over 60 minutes: t_R 43.0 min, exp. 732.3, obs. 755.4 (M + Na)⁺.

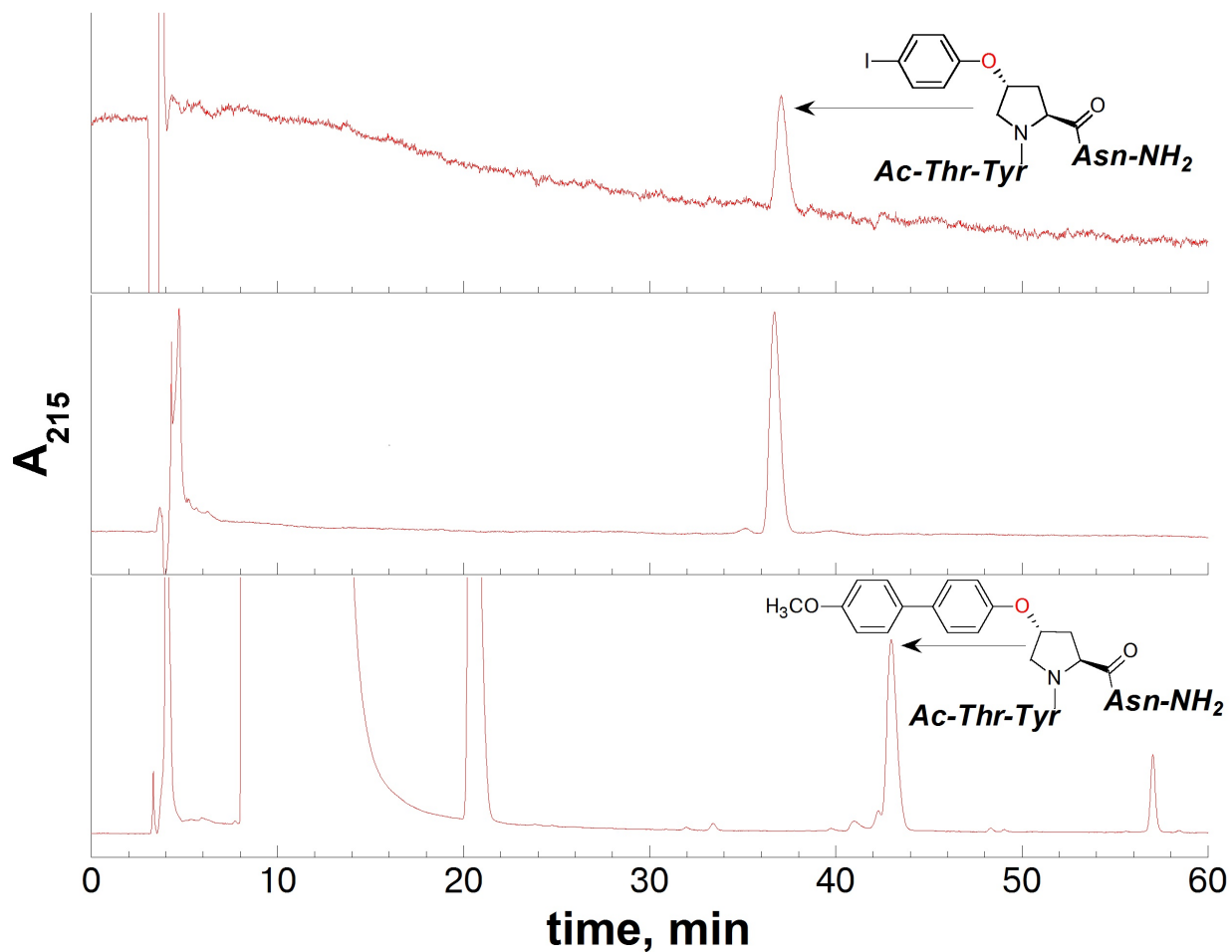


Figure S29. Crude HPLC chromatograms of the Suzuki-Miyaura reaction on the peptide Ac-TYHyp(4-I-Ph)N-NH₂. Top: Ac-TYHyp(4-I-Ph)N-NH₂; middle: Ac-TYHyp(4-I-Ph)N-NH₂ and the reaction mixture prior to the addition of 4-methoxyphenylboronic acid; bottom: reaction mixture after 30 minutes. The indicated products were confirmed via ESI-MS.

Determination of an approximate rate constant for the Suzuki-Miyaura reaction of Ac-TYHyp(4-I-Ph)N-NH₂ with 4-methoxyphenylboronic acid

The Suzuki-Miyaura reaction proceeded to completion within 30 min for 100 μM Ac-TYHyp(4-I-Ph)N-NH₂ with 100 mM 4-methoxyphenylboronic acid. These conditions were employed to directly compare to prior results on the diastereomeric peptide containing 4*S*-iodophenyl hydroxyproline.⁴ In addition, experiments were conducted using lower concentrations of boronic acid (5 mM, 10 mM, and 20 mM). These reactions were analyzed as a function of time. 100 μM peptide was allowed to react with the specified concentration of 4-methoxyphenylboronic acid in a solution of Pd(OAc)₂•ligand (400 μM final concentration) in 45 mM phosphate buffer with 20% acetonitrile incubated at 37 °C. 100 or 200 μL aliquots of the reaction were injected on the HPLC (0–50% of buffer B in A over 60 minutes) at various time points and the amount of peptide reacted was quantified by integrating the area under the HPLC peaks for the product and the reactant (relative absorbance at 215 nm). At 5 mM 4-methoxyphenylboronic acid, the reaction was 21%, 76%, 94%, and 97% complete in 30 min, 120 min, 210 min, and 300 min respectively (Figure S30 and S31). The reaction with 10 mM 4-methoxyphenylboronic acid was 51% and 94% complete after 30 min and 120 min respectively (Figure S32). For 20 mM boronic acid, the reaction was 75% complete in 1 hour (Figure S33). In each case, the second order rate constant k was estimated to be $\sim 3 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$ (based on $k_{\text{obs}} = 0.693/t_{1/2}$, where k_{obs} is the pseudo-first order rate constant, and $k_{\text{obs}} = k [4\text{-methoxyphenylboronic acid}]$).

where

$$\% \text{conversion} = 100 \times (1 - e^{-k_{\text{obs}}t})$$
$$\% \text{ conversion} = \frac{[\text{Product}]}{[\text{Product}] + [\text{Peptide}]} \times 100 \quad \text{[Equation 1]}$$

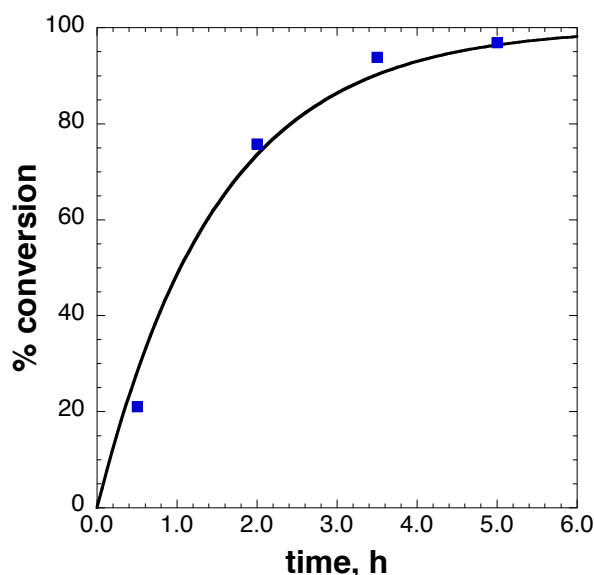


Figure S30. Time course of reaction of Ac-TYHyp(4-I-Ph)N-NH₂ with 5 mM 4-methoxyphenyl boronic acid and 400 μM Pd(OAc)₂•ligand. The solid line represents the linear least squares fit of the data according to equation 1. The half-life ($t_{1/2}$) is calculated to be 1.05 h (3780 s). The pseudo-first order rate constant (k_{obs}) is thus estimated to be $1.7 \times 10^{-4} \text{ s}^{-1}$. The second order rate constant is thus estimated to be $\sim 3 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$.

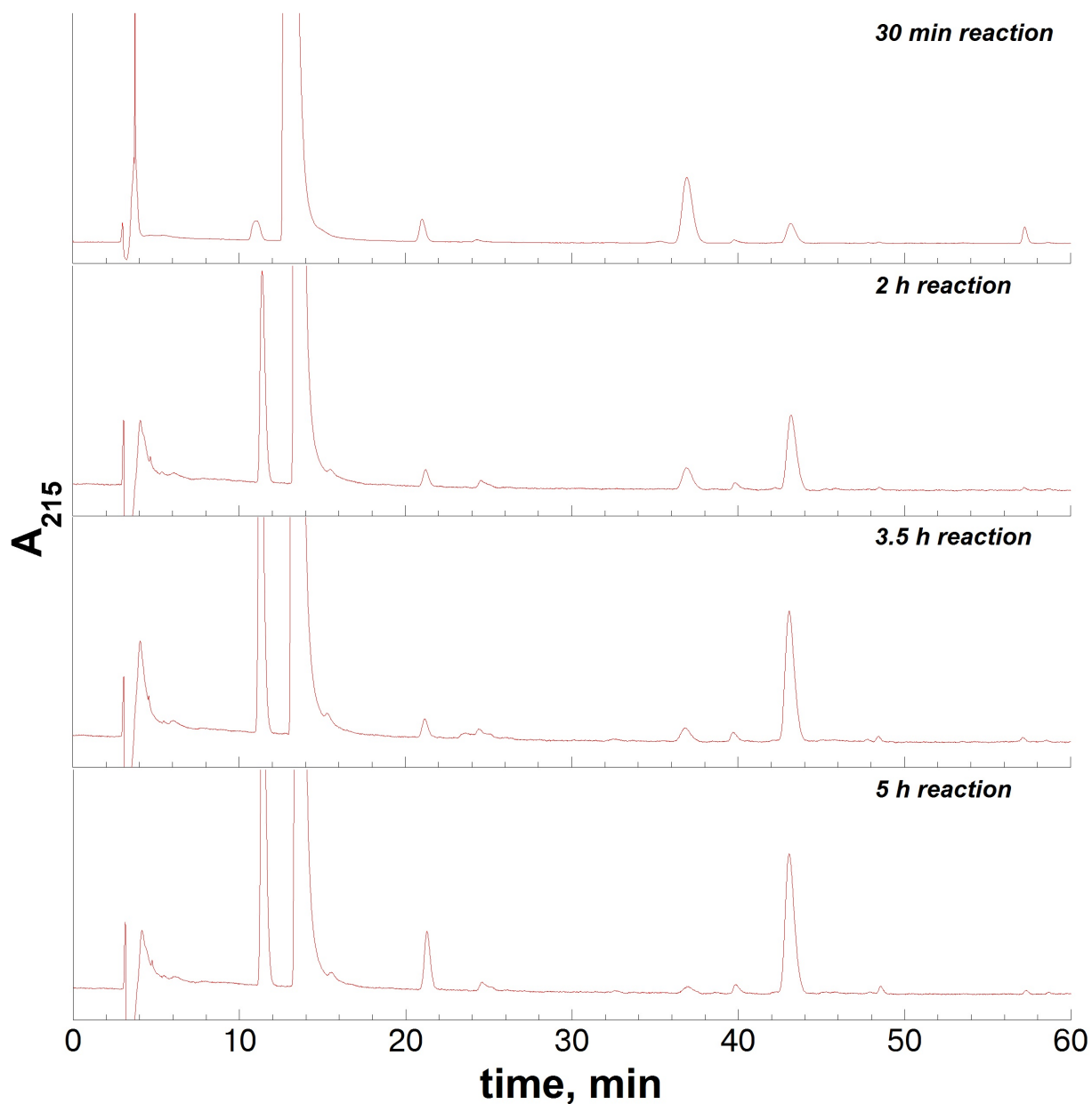


Figure S31. Crude HPLC chromatograms of the Suzuki-Miyaura reaction of 100 μM Ac-TYHyp(4-I-Ph)N-NH₂ with 5 mM 4-methoxyphenylboronic acid and 400 μM Pd(OAc)₂•ligand at the indicated reaction times. Ac-TYHyp(4-I-Ph)N-NH₂ has a t_{R} of 37 minutes; the Suzuki-Miyaura product has a t_{R} of 43 minutes.

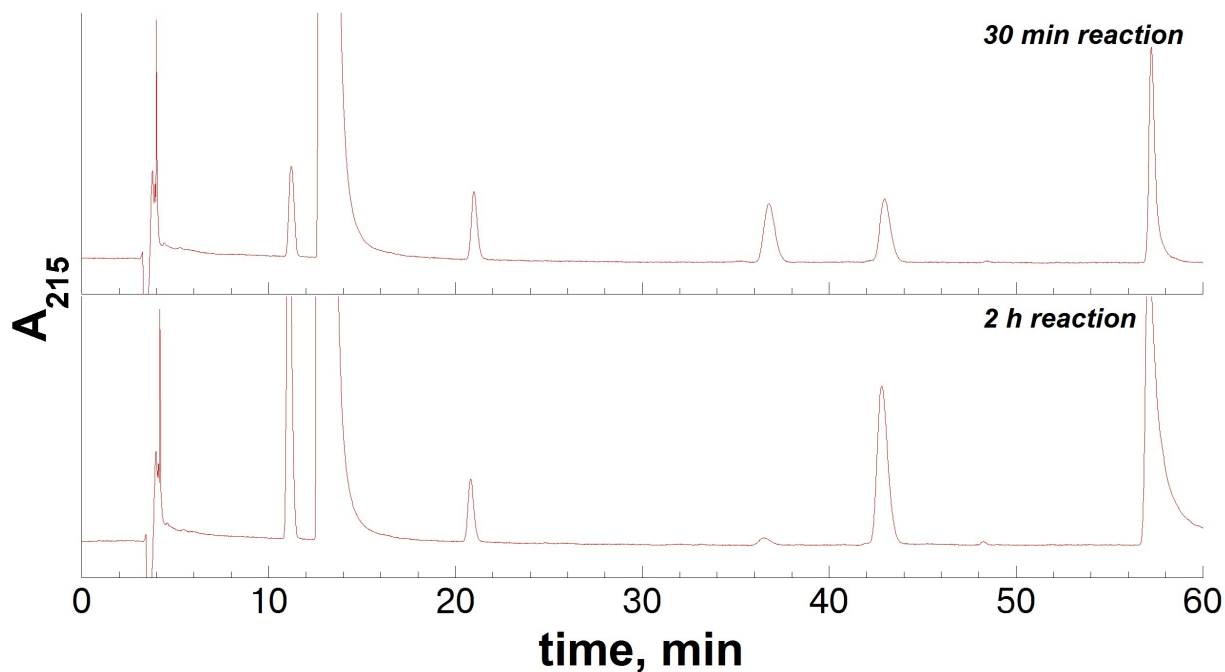


Figure S32. Crude HPLC chromatograms of the Suzuki-Miyaura reaction of 100 μM Ac-TYHyp(4-I-Ph)N-NH₂ with 10 mM 4-methoxyphenylboronic acid and 400 μM Pd(OAc)₂•ligand at the indicated reaction times. Ac-TYHyp(4-I-Ph)N-NH₂ has a t_{R} of 37 minutes; the Suzuki-Miyaura product has a t_{R} of 43 minutes.

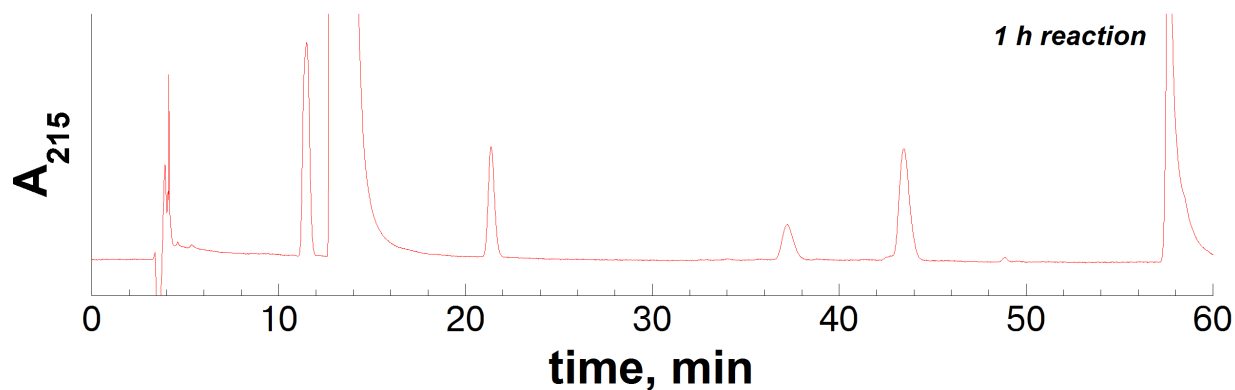
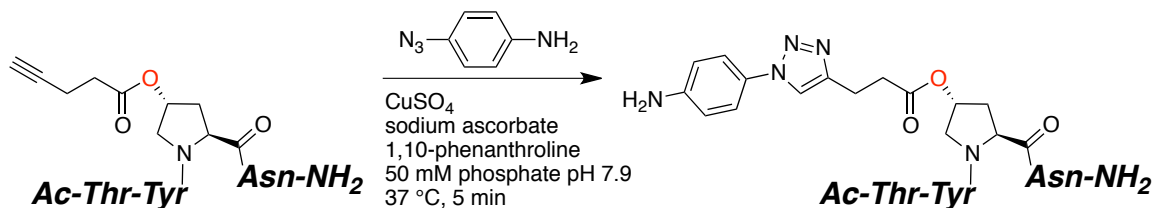


Figure S33. Crude HPLC chromatogram of the Suzuki-Miyaura reaction of 100 μM Ac-TYHyp(4-I-Ph)N-NH₂ with 20 mM 4-methoxyphenylboronic acid and 400 μM Pd(OAc)₂•ligand at 1 h. The Ac-TYHyp(4-I-Ph)N-NH₂ has a t_{R} of 37 minutes; the Suzuki-Miyaura product has a t_{R} of 43 minutes.

Huisgen azide-alkyne 1,3-cycloaddition reaction of Ac-TYHyp(C(O)CH₂CH₂CCH)N-NH₂ with 4-azidoaniline.



The peptide Ac-TYHyp(C(O)CH₂CH₂CCH)N-NH₂ (approximately 50 nmol; 100 μM final concentration) was dissolved in phosphate buffer (500 μL of 50 mM phosphate buffer pH 7.9). To this solution, copper(II) sulfate (50 μL of a 10 mM solution in water), sodium ascorbate (5.0 mg, 50 mM final concentration), and 1,10-phenanthroline (10 μL of a 10 mM solution in DMSO) were added. To this solution 4-azidoaniline·HCl (4.5 mg, 50 mM final concentration) was added. The reaction mixture was allowed to incubate at 37 °C for 5 minutes to generate the conjugated peptide. The crude solution was diluted with deionized water (300 μL), and diethyl ether (1 mL) was added. After thorough mixing, the ether layer was removed via pipet, and CH₂Cl₂ (1 mL) was added. After thorough mixing, the aqueous layer was removed and filtered through a nylon filter (0.45 μm). The peptide was purified via HPLC using a linear gradient of 0-15% buffer B in buffer A over 30 minutes: *t_R* 29.6 min, exp. 764.3, obs. 787.3 (M + Na)⁺.

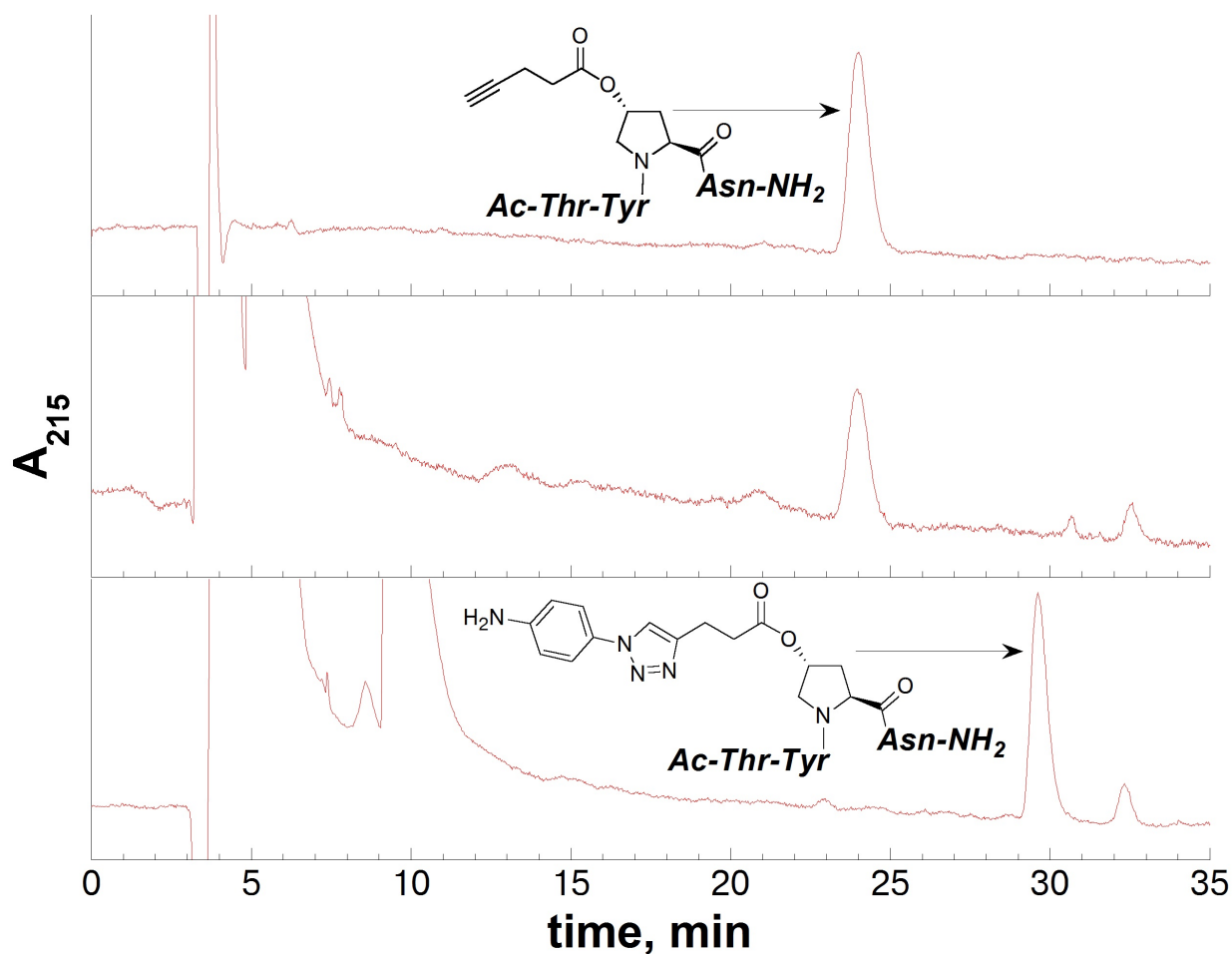
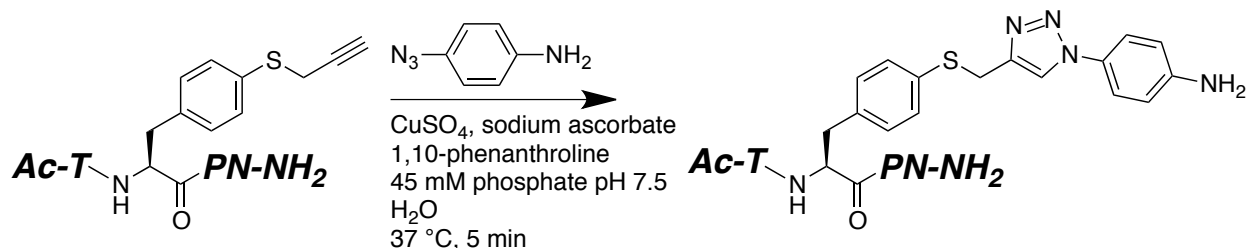


Figure S34. Crude HPLC chromatograms of the Huisgen azide-alkyne 1,3-cycloaddition reaction on the peptide $\text{Ac-TYHyp}(\text{C}(\text{O})\text{CH}_2\text{CH}_2\text{CCH})\text{N-NH}_2$. Top: purified $\text{Ac-TYHyp}(\text{C}(\text{O})\text{CH}_2\text{CH}_2\text{CCH})\text{N-NH}_2$; middle: the reaction mixture of peptide and reagents prior to addition of 4-azidoaniline; bottom: reaction products after 5 minutes. The middle and bottom panels are chromatograms of the aqueous layer after the solutions were subjected to organic extraction (ether (1×1 mL) and CH_2Cl_2 (1×1 mL)) using identical procedures prior to their injection on the HPLC. The indicated products were confirmed via ESI-MS.

Huisgen azide-alkyne 1,3-cycloaddition reaction of Ac-TPhe(4-S-propargyl)PN-NH₂ with 4-azidoaniline



The peptide Ac-TPhe(4-S-propargyl)PN-NH₂ (approximately 17 nmol; 70 μ M final concentration) was dissolved in phosphate buffer (250 μ L of 50 mM phosphate, pH 7.5). To the peptide-containing solution, copper(II) sulfate (25 μ L of a 10 mM solution in water), sodium ascorbate (2.5 mg, 50 mM final concentration), and 1,10-phenanthroline (5 μ L of a 10 mM solution in DMSO) were added. To this solution was subsequently added 4-azidoaniline·HCl (2.7 mg; 60 mM final concentration), and the resultant solution was allowed to incubate at 37 °C for 5 minutes to produce the conjugated peptide. The crude solution was diluted with deionized water (300 μ L), and diethyl ether (1 mL) was added. After thorough mixing, the ether layer was removed via pipet, and CH₂Cl₂ (1 mL) was added. After thorough mixing, the aqueous layer was removed and filtered through a nylon filter (0.45 μ m). The peptide was purified via HPLC using a linear gradient of 0-20% buffer B in buffer A over 60 minutes: t_R 48.5 min, exp. 722.3, obs. 745.4 (M + Na)⁺.

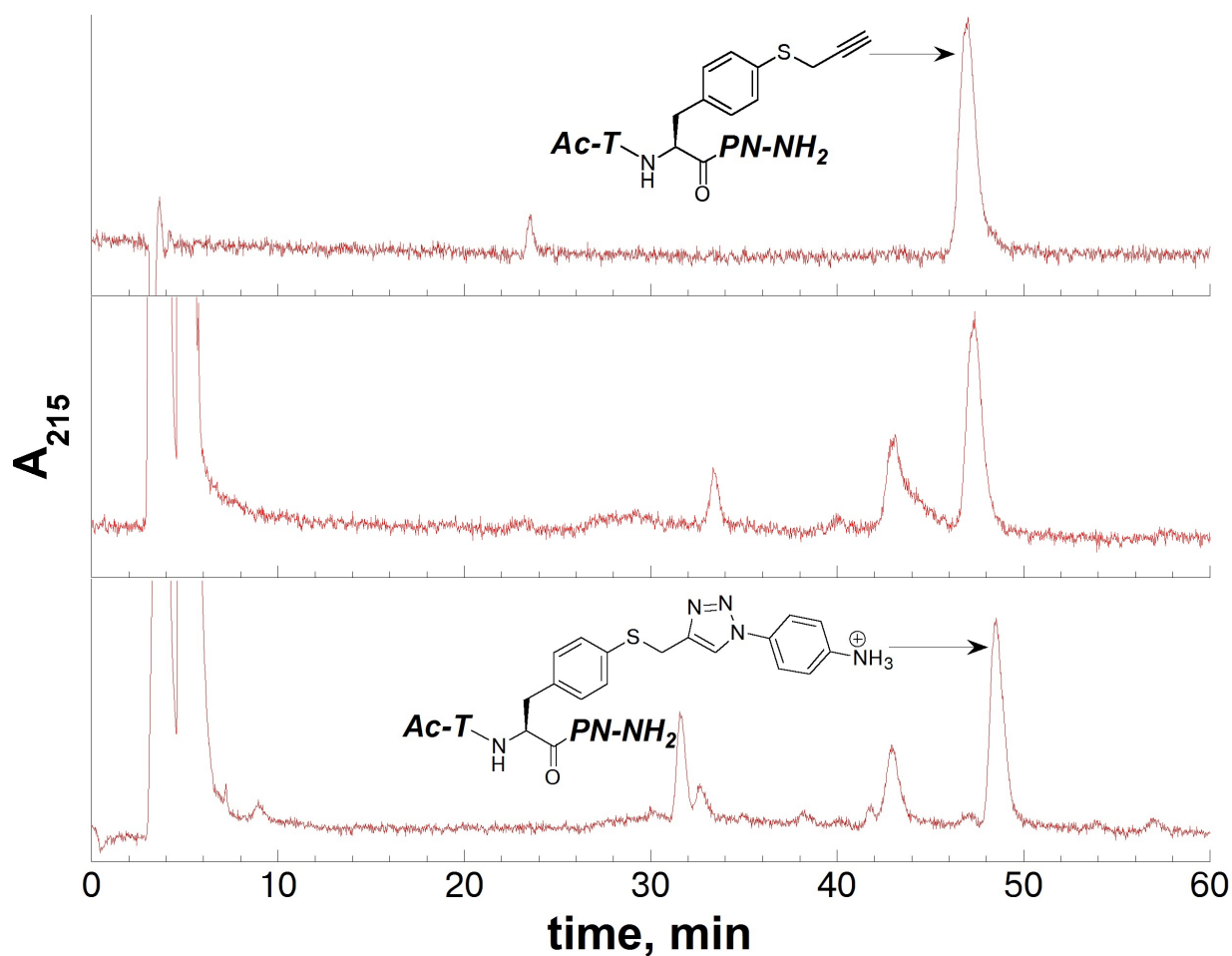
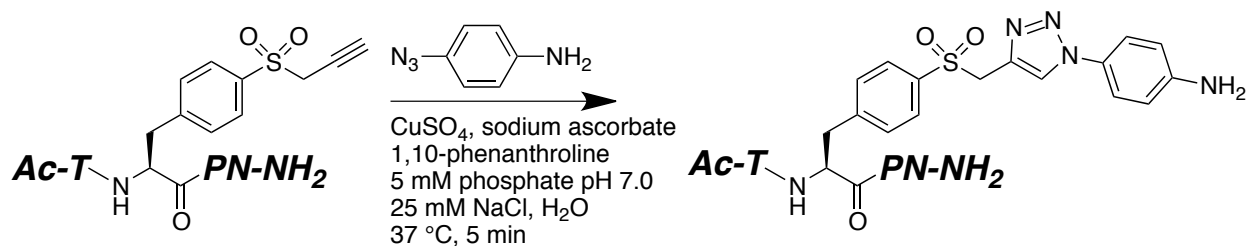


Figure S35. Crude HPLC chromatograms of the Huisgen azide-alkyne 1,3-cycloaddition reaction on the peptide Ac-T-Phe(4-S-propargyl)PN-NH₂. Top: purified Ac-T-Phe(4-S-propargyl)PN-NH₂; middle: the aqueous work-up of the peptide and reaction reagents prior to the addition of 4-azidoaniline; bottom: reaction products after 5 minutes. The middle and bottom panels are chromatograms of the aqueous layer after the solutions were subjected to organic extraction (ether (1 × 1 mL) and CH₂Cl₂ (1 × 1 mL)) using identical procedures prior to their injection on the HPLC. The indicated products were confirmed via ESI-MS.

Huisgen azide-alkyne 1,3-cycloaddition reaction of Ac-TPhe(4-SO₂-propargyl)PN-NH₂ with 4-azidoaniline



The peptide Ac-TPhe(4-SO₂-propargyl)PN-NH₂ (approximately 17 nmol; 70 μM final concentration) was dissolved in phosphate buffer (250 μL of 50 mM phosphate pH 7.5). To the peptide-containing solution, copper(II) sulfate (25 μL of a 10 mM solution in water), sodium ascorbate (2.5 mg, 50 mM final concentration), and 1,10-phenanthroline (5 μL of a 10 mM solution in DMSO) were added. To this solution was subsequently added 4-azidoaniline·HCl (2.5 mg; 50 mM final concentration), and the resultant solution was allowed to incubate at 37 °C for 5 minutes to produce the conjugated peptide. The crude solution was diluted with deionized water (300 μL), and diethyl ether (1 mL) was added. After thorough mixing, the ether layer was removed via pipet, and CH₂Cl₂ (1 mL) was added. After thorough mixing, the aqueous layer was removed and filtered through a nylon filter (0.45 μm). The peptide was purified via HPLC using a linear gradient of 0-15% buffer B in buffer A over 60 minutes: t_R 38.2 min, exp. 754.3, obs. 777.2 (M + Na)⁺.

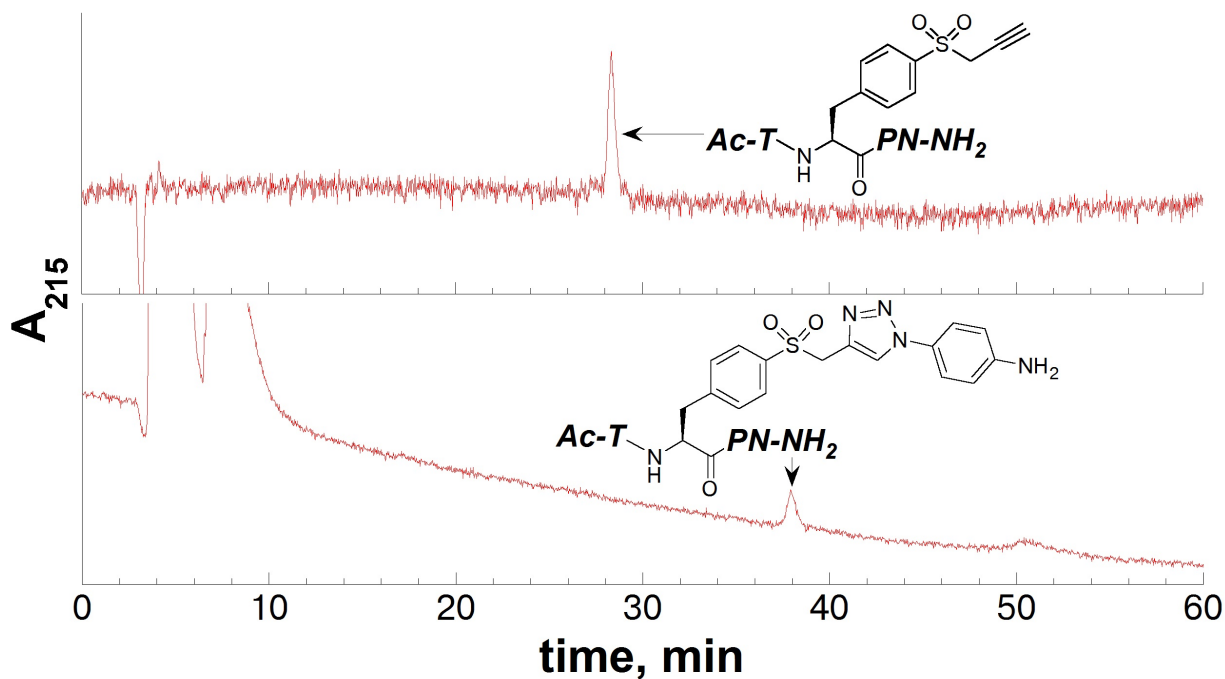


Figure S36. Crude HPLC chromatograms of the Huisgen azide-alkyne 1,3-cycloaddition reaction on the peptide *Ac-T*Phe(4-SO₂-propargyl)*PN-NH₂*. Top: purified *Ac-T*Phe(4-SO₂-propargyl)*PN-NH₂*; bottom: reaction products after 5 minutes. The bottom panel is the chromatogram of the aqueous layer after the solution was subjected to organic extraction (ether (1 × 1 mL) and CH₂Cl₂ (1 × 1 mL)) prior to its injection on the HPLC. The indicated product was confirmed via ESI-MS.

Cambridge Structural Database analysis: methodology and parameters

The Cambridge Structural Database (version 5.36 + 3 updates, released in May 2015) was searched for entries containing aryl ethers, aryl thioethers, aryl sulfoxides, or aryl sulfones ($\text{Ph-O-C}^{\text{sp}^3}$, $\text{Ph-S-C}^{\text{sp}^3}$, $\text{Ph-S(O)-C}^{\text{sp}^3}$, or $\text{Ph-SO}_2\text{-C}^{\text{sp}^2}$, respectively). The release of the database used in the current study contained over 710,000 molecules. Searches were set up and carried out using ConQuest (version 1.17 Cambridge Crystallographic Data Centre, 2014).

The search parameters for aryl ethers and each oxidation state of aryl thioethers were defined as shown in Figure S37. The coordination number of sulfur was defined as indicated, and the coordination number of C (C1) was defined as 4 in all queries. Thioether sulfoxides were defined using the two different structures indicated, and the results were combined. Only error-free, non-disordered structures where $R < 0.10$ were included, and powder pattern structures were excluded.

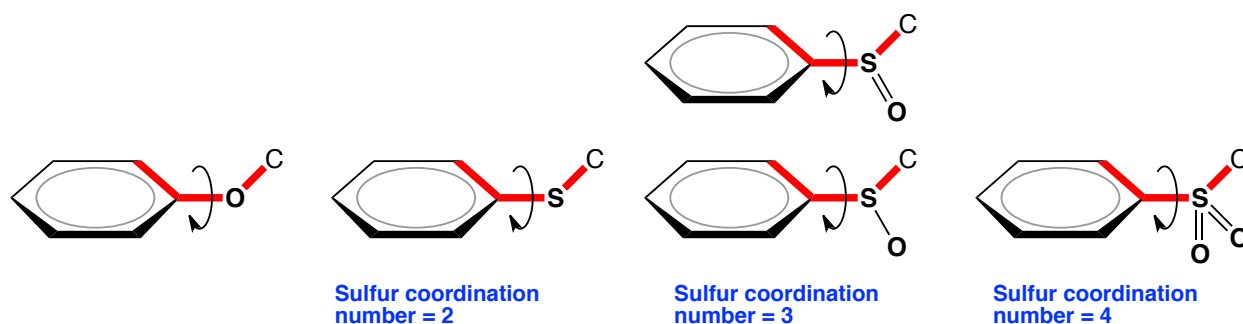


Figure S37. Defined structural parameters for the search query in the Cambridge Structural Database using Conquest. The torsion angle indicated in red was measured for all structures.

Torsion angles were measured for each structure obtained in the defined query (C3-C2-S-C1 , as indicated in red in Figure S37, where C3 and C2 are aromatic carbons and C1 is the aliphatic carbon). The absolute value of the torsion angle was measured, and then a logical function was applied, where if the resultant torsion angle was greater than 90° , then 180° was subtracted from the torsion angle and the absolute value taken. Use of this logic function converts all torsion angles to a range of 0° to 90° , where the S-C1 or O-C1 bond is measured as between being planar or perpendicular to the aromatic ring (Figure S38). In addition, bond lengths (S-C1 or O-C1) and bond angles (C2-S-C1 or C2-O-C1) were accumulated for each of these queries.

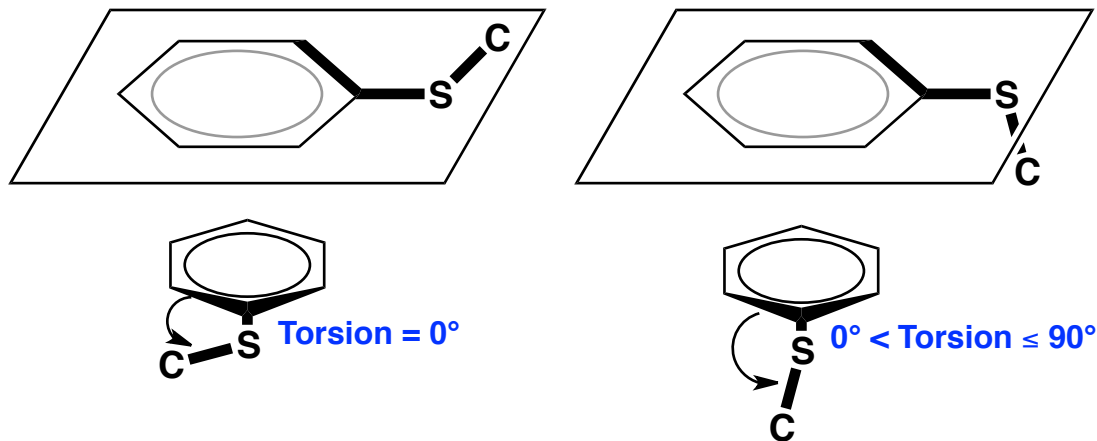


Figure S38. The absolute values of torsion angles obtained through ConQuest resulted in angles ranging from 180° to 0° . These torsion angles were converted using a logic function to range from 0° – 90° to represent O–C or S–C bonds that were between the limiting cases of co-planar with the aromatic ring (left, torsion angle near 0°) or orthogonal to the aromatic ring (right, torsion angle near 90°).

X-ray structural analysis for **5**, **7**, and **10**

Crystals were mounted using viscous oil onto a plastic mesh and cooled to the data collection temperature. Data were collected on a Bruker-AXS APEX II DUO CCD diffractometer with Mo-K α radiation ($\lambda = 0.71073 \text{ \AA}$) monochromated with graphite. Unit cell parameters were obtained from 36 data frames, $0.5^\circ \omega$, from three different sections of the Ewald sphere. The systematic absences in the diffraction data are consistent with P21 and P21/m for **7** and **10**; and, uniquely, for P212121 for **5**. The absence of a molecular mirror, known chirality, and occupancy of two for **7** and **10** is consistent with the non-centrosymmetric option, P21. The data-sets were treated with multi-scan absorption corrections (Apex3 software suite, Madison, WI, 2015). The structures were solved using direct methods and refined with full-matrix, least-squares procedures on F2.⁵ Refinement of the absolute structure parameter for each structure yielded nil, indicating the true hand of the data has been determined. A molecule of methanol solvent was found in H-bonding association with the compound molecule in **7**. All non-hydrogen atoms were refined with anisotropic displacement parameters. H-atoms were placed in calculated positions with Uiso equal to 1.2 (1.5 for methyl H) Ueq of the attached atom. Atomic scattering factors are contained in the SHELXTL program library.⁵ The CIFs have been deposited with the Cambridge Crystallographic Database under CCDC 1438138-1438140 (**5**, **7**, and **10**, respectively).

Crystal Structure of Boc-(2*S*,4*S*)-*p*-iodophenyl-4-hydroxyproline (**5**)

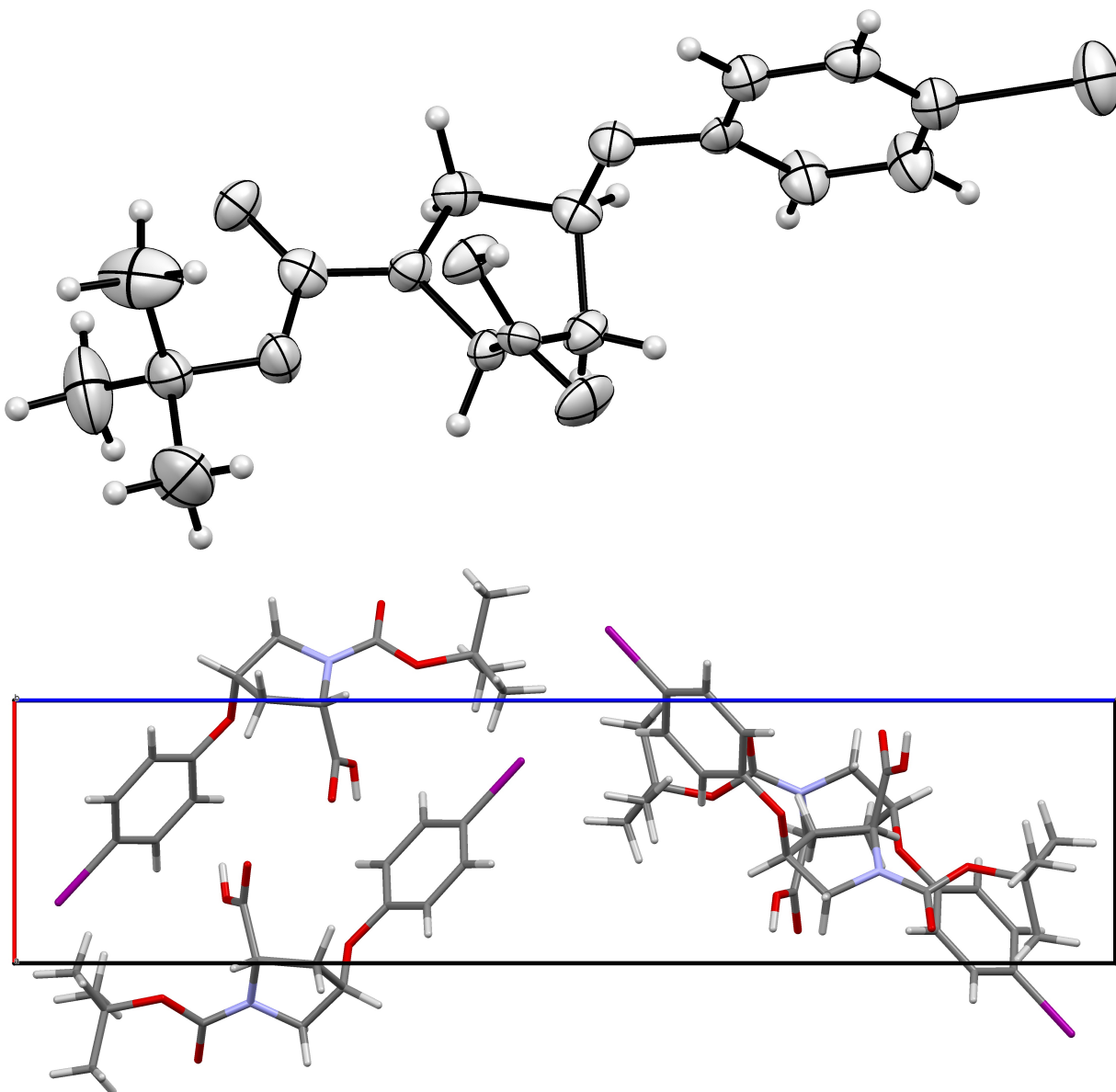


Figure S39. Crystal structure of Boc-(2*S*,4*S*)-*p*-iodophenyl-4-hydroxyproline (**5**). Top: ORTEP diagram of **5** with ellipsoids shown at 50% probability; bottom: overall crystal packing. Diffractable crystals were obtained by slow evaporation at room temperature from a solution of **5** in ethyl acetate in hexanes.

Table S2. Crystallographic data and refinement details for Boc-(2*S*,4*S*)-*p*-iodophenyl-4-hydroxyproline (**5**).

empirical formula	C ₁₆ H ₂₀ INO ₅	
formula weight	433.23	
<i>T</i> (K)	200(2)	
wavelength (Å)	0.71073	
crystal system, space group	Orthorhombic, P2 ₁ 2 ₁ 2 ₁	
Unit cell dimensions (Å, °)	a = 6.4983(17)	α = 90
	b = 10.457(3)	β = 90
	c = 27.274(7)	γ = 90
Volume (Å ³)	1853.4(8)	
Z, Z', calcd density (g/cm ³)	4, 0, 1.553	
absorption coefficient (mm ⁻¹)	1.750	
F(000)	864	
crystal size (mm)	0.248 x 0.210 x 0.078	
θ range for data collection	1.493 to 27.637°	
Index ranges	-7 ≤ h ≤ 8, -13 ≤ k ≤ 13, -31 ≤ l ≤ 35	
Reflections collected/ unique	14104/4306 [R(int) = 0.0694]	
Coverage of independent reflections	99.9%	
Absorption correction	multi-scan	
Max. and min. transmission	0.7456 and 0.5887	
Structure solution technique	direct methods	
Refinement method	Full-matrix least-squares on F ²	
Function minimized	Σ w(F _o ² - F _c ²) ²	
Data / restraints / parameters	4306/ 0 / 244	
Goodness-of-fit on F ²	1.017	
Final <i>R</i> indices	5212 data; I > 2σ(I)	R1 = 0.0454, wR2 = 0.0756
	all data	R1 = 0.0905, wR2 = 0.0924
Weighting scheme	w = 1/[σ ² (F _o ²) + (0.0974P) ² + 0.0719P] where P = (F _o ² + 2F _c ²)/3	
Largest diff. peak and hole	0.408 and -0.738 eÅ ⁻³	
R.M.S. deviation from mean	0.090 eÅ ⁻³	

Table S3. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{Å}^2 \times 10^3$) for Boc-(2*S*,4*S*)-*p*-iodophenyl-4-hydroxyproline (**5**). U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U(eq)
I1	0.76825(8)	0.72164(5)	0.04001(2)	0.0588(2)
N1	0.8510(8)	0.6642(5)	0.2856(2)	0.0293(13)
O1	0.8668(7)	0.6410(5)	0.36591(17)	0.0393(12)
O2	0.6335(6)	0.7812(5)	0.33309(17)	0.0370(11)
O3	0.2428(7)	0.7360(4)	0.30754(16)	0.0405(11)
O4	0.3739(7)	0.5449(5)	0.2883(2)	0.0474(14)
O5	0.0688(6)	0.7486(4)	0.19643(16)	0.0340(12)
C1	0.0128(10)	0.5698(6)	0.2800(3)	0.0282(17)
C2	0.9949(11)	0.5323(6)	0.2259(2)	0.0325(17)
C3	0.9099(10)	0.6532(6)	0.2015(3)	0.0327(17)
C4	0.7600(10)	0.7043(6)	0.2386(2)	0.0333(15)
C5	0.7717(10)	0.7014(6)	0.3288(2)	0.0341(15)
C6	0.2280(11)	0.6161(6)	0.2922(2)	0.0290(15)
C7	0.2193(9)	0.7337(6)	0.1611(2)	0.0283(14)
C8	0.2195(12)	0.6406(6)	0.1254(2)	0.0414(18)
C9	0.3768(11)	0.6366(7)	0.0914(3)	0.044(2)
C10	0.5309(9)	0.7259(7)	0.0924(2)	0.0361(16)
C11	0.5317(10)	0.8190(7)	0.1281(2)	0.0363(18)
C12	0.3760(10)	0.8222(7)	0.1624(2)	0.0340(17)
C13	0.8239(12)	0.6723(7)	0.4175(3)	0.043(2)
C14	0.9644(16)	0.5820(9)	0.4443(3)	0.076(3)
C15	0.8849(16)	0.8111(8)	0.4265(3)	0.081(3)
C16	0.6008(14)	0.6461(11)	0.4294(3)	0.082(4)

Table S4. Bond lengths [Å] and angles [°] for Boc-(2*S*,4*S*)-*p*-iodophenyl-4-hydroxyproline (**5**).Bond lengths

I1-C10	2.102(6)	N1-C5	1.345(8)
N1-C1	1.450(8)	N1-C4	1.472(8)
O1-C5	1.343(7)	O1-C13	1.472(8)
O2-C5	1.232(7)	O3-C6	1.326(7)
O3-H3	0.84	O4-C6	1.210(7)
O5-C7	1.383(7)	O5-C3	1.442(7)
C1-C6	1.516(9)	C1-C2	1.531(9)
C1-H1A	1.0	C2-C3	1.531(9)
C2-H2A	0.99	C2-H2B	0.99
C3-C4	1.502(8)	C3-H3A	1.0
C4-H4A	0.99	C4-H4B	0.99
C7-C8	1.376(8)	C7-C12	1.377(8)
C8-C9	1.381(9)	C8-H8A	0.95
C9-C10	1.370(9)	C9-H9A	0.95
C10-C11	1.378(9)	C11-C12	1.377(9)
C11-H11A	0.95	C12-H12A	0.95
C13-C14	1.503(11)	C13-C16	1.510(11)
C13-C15	1.525(11)	C14-H14A	0.98
C14-H14B	0.98	C14-H14C	0.98
C15-H15A	0.98	C15-H15B	0.98
C15-H15C	0.98	C16-H16A	0.98
C16-H16B	0.98	C16-H16C	0.98

Bond angles

C5-N1-C1	124.5(6)	C5-N1-C4	121.8(5)
C1-N1-C4	113.2(5)	C5-O1-C13	121.9(5)
C6-O3-H3	109.5	C7-O5-C3	119.7(5)
N1-C1-C6	115.4(5)	N1-C1-C2	102.7(5)
C6-C1-C2	111.2(5)	N1-C1-H1A	109.1
C6-C1-H1A	109.1	C2-C1-H1A	109.1
C3-C2-C1	103.6(5)	C3-C2-H2A	111.0
C1-C2-H2A	111.0	C3-C2-H2B	111.0
C1-C2-H2B	111.0	H2A-C2-H2B	109.0
O5-C3-C4	106.4(5)	O5-C3-C2	110.8(5)
C4-C3-C2	103.6(5)	O5-C3-H3A	111.9
C4-C3-H3A	111.9	C2-C3-H3A	111.9
N1-C4-C3	102.9(5)	N1-C4-H4A	111.2
C3-C4-H4A	111.2	N1-C4-H4B	111.2
C3-C4-H4B	111.2	H4A-C4-H4B	109.1
O2-C5-O1	125.6(6)	O2-C5-N1	124.0(6)
O1-C5-N1	110.4(6)	O4-C6-O3	123.5(7)
O4-C6-C1	120.5(5)	O3-C6-C1	116.0(6)
C8-C7-C12	119.6(6)	C8-C7-O5	125.0(6)
C12-C7-O5	115.4(5)	C7-C8-C9	119.8(7)
C7-C8-H8A	120.1	C9-C8-H8A	120.1
C10-C9-C8	120.5(7)	C10-C9-H9A	119.7
C8-C9-H9A	119.7	C9-C10-C11	119.8(6)
C9-C10-I1	120.6(5)	C11-C10-I1	119.6(5)
C12-C11-C10	119.7(7)	C12-C11-H11A	120.2
C10-C11-H11A	120.2	C11-C12-C7	120.6(6)
C11-C12-H12A	119.7	C7-C12-H12A	119.7
O1-C13-C14	102.1(6)	O1-C13-C16	110.3(7)
C14-C13-C16	111.4(8)	O1-C13-C15	108.4(6)
C13-C14-H14A	109.5	C13-C14-H14B	109.5
H14A-C14-H14B	109.5	C13-C14-H14C	109.5
H14A-C14-H14C	109.5	H14B-C14-H14C	109.5
C13-C15-H15A	109.5	C13-C15-H15B	109.5
H15A-C15-H15B	109.5	C13-C15-H15C	109.5
H15A-C15-H15C	109.5	H15B-C15-H15C	109.5
C13-C16-H16A	109.5	C13-C16-H16B	109.5
H16A-C16-H16B	109.5	C13-C16-H16C	109.5

H16A-C16-H16C	109.5	H16B-C16-H16C	109.5
C13-C14-H14A	109.5	C13-C14-H14B	109.5
H14A-C14-H14B	109.5	C13-C14-H14C	109.5
C13-C15-H15A	109.5	C13-C15-H15B	109.5
H15A-C15-H15B	109.5	C13-C15-H15C	109.5
H15A-C15-H15C	109.5	H15B-C15-H15C	109.5
C13-C16-H16A	109.5	C13-C16-H16B	109.5
H16A-C16-H16B	109.5	C13-C16-H16C	109.5
H16A-C16-H16C	109.5	H16B-C16-H16C	109.5

Table S5. Anisotropic atomic displacement parameters (\AA^2) for Boc-(2*S*,4*S*)-*p*-iodophenyl-4-hydroxyproline (**5**). The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2[h^2 a^2 U_{11} + \dots + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
I1	0.0432(3)	0.0847(4)	0.0484(3)	-0.0074(3)	0.0104(3)	-0.0099(3)
N1	0.024(3)	0.031(3)	0.033(3)	0.002(3)	-0.002(2)	0.004(2)
O1	0.038(3)	0.049(3)	0.031(3)	0.004(2)	0.003(2)	0.006(2)
O2	0.025(2)	0.040(3)	0.046(3)	-0.006(3)	-0.003(2)	0.006(2)
O3	0.025(2)	0.033(2)	0.063(3)	-0.005(2)	-0.007(2)	0.002(3)
O4	0.027(3)	0.041(3)	0.075(4)	-0.002(3)	0.000(3)	0.013(2)
O5	0.035(2)	0.029(3)	0.038(3)	-0.002(2)	0.004(2)	-0.005(2)
C1	0.024(4)	0.026(4)	0.035(4)	0.001(3)	0.006(3)	0.001(3)
C2	0.034(4)	0.025(4)	0.038(4)	-0.006(3)	0.000(4)	-0.001(3)
C3	0.031(4)	0.031(4)	0.037(4)	0.000(3)	-0.003(3)	-0.009(3)
C4	0.025(3)	0.032(4)	0.042(4)	0.004(3)	-0.002(3)	-0.002(4)
C5	0.024(3)	0.038(4)	0.040(4)	0.002(3)	-0.002(3)	-0.008(4)
C6	0.033(4)	0.024(3)	0.030(3)	0.009(3)	0.001(4)	0.003(4)
C7	0.027(3)	0.027(3)	0.031(3)	0.003(3)	-0.001(3)	0.010(4)
C8	0.043(4)	0.041(4)	0.040(4)	-0.006(3)	0.003(4)	-0.015(4)
C9	0.051(5)	0.048(5)	0.034(4)	-0.011(4)	0.004(4)	-0.017(4)
C10	0.031(3)	0.044(4)	0.034(4)	-0.001(4)	-0.002(3)	0.000(4)
C11	0.031(4)	0.031(4)	0.047(5)	0.007(4)	-0.005(3)	-0.004(3)
C12	0.031(4)	0.035(4)	0.036(4)	0.000(3)	-0.002(3)	0.000(3)
C13	0.056(5)	0.040(4)	0.032(4)	0.000(4)	0.002(4)	0.002(4)
C14	0.105(8)	0.081(7)	0.043(6)	0.011(5)	-0.006(6)	0.020(6)
C15	0.130(9)	0.052(6)	0.060(6)	-0.008(5)	-0.039(6)	-0.016(6)
C16	0.073(7)	0.115(10)	0.057(7)	-0.016(6)	0.029(6)	-0.016(7)

Table S6. Hydrogen atomic coordinates and isotropic atomic displacement parameters (\AA^2) for Boc-(2*S*,4*S*)-*p*-iodophenyl-4-hydroxyproline (**5**).

	x/a	y/b	z/c	U(eq)
H3	0.3675	0.7553	0.3110	0.049
H1A	-0.0201	0.4937	0.3008	0.034
H2A	0.1309	0.5092	0.2122	0.039
H2B	-0.1005	0.4594	0.2216	0.039
H3A	-0.1582	0.6339	0.1695	0.039
H4A	-0.2506	0.7985	0.2365	0.04
H4B	-0.3783	0.6664	0.2340	0.04
H8A	0.1117	0.5793	0.1242	0.05
H9A	0.3781	0.5714	0.0672	0.053
H11A	0.6390	0.8806	0.1292	0.044
H12A	0.3767	0.8862	0.1871	0.041
H14A	-0.0783	0.4937	0.4379	0.115
H14B	-0.0429	0.5992	0.4796	0.115
H14C	0.1060	0.5944	0.4329	0.115
H15A	-0.1984	0.8673	0.4057	0.121
H15B	0.0308	0.8226	0.4187	0.121
H15C	-0.1387	0.8327	0.4611	0.121
H16A	-0.4330	0.5578	0.4205	0.123
H16B	-0.4868	0.7050	0.4108	0.123
H16C	-0.4224	0.6586	0.4646	0.123

Table S7. Torsion angles ($^\circ$) for Boc-(2*S*,4*S*)-*p*-iodophenyl-4-hydroxyproline (**5**).

C5-N1-C1-C6	-76.6(8)	C4-N1-C1-C6	111.2(6)
C5-N1-C1-C2	162.3(5)	C4-N1-C1-C2	-9.9(7)
N1-C1-C2-C3	29.0(6)	C6-C1-C2-C3	-95.0(6)
C7-O5-C3-C4	-173.8(5)	C7-O5-C3-C2	74.2(7)
C1-C2-C3-O5	75.9(6)	C1-C2-C3-C4	-37.9(6)
C5-N1-C4-C3	174.0(5)	C1-N1-C4-C3	-13.5(7)
O5-C3-C4-N1	-85.7(6)	C2-C3-C4-N1	31.2(6)
C13-O1-C5-O2	-4.6(9)	C13-O1-C5-N1	174.3(5)
C1-N1-C5-O2	-179.6(6)	C4-N1-C5-O2	-8.0(9)
C1-N1-C5-O1	1.4(8)	C4-N1-C5-O1	173.0(5)
N1-C1-C6-O4	-179.5(6)	C2-C1-C6-O4	-63.0(8)
N1-C1-C6-O3	1.6(8)	C2-C1-C6-O3	118.0(6)

C3-O5-C7-C8	7.9(9)	C3-O5-C7-C12	-173.4(5)
C12-C7-C8-C9	0.2(10)	O5-C7-C8-C9	178.8(6)
C7-C8-C9-C10	-1.1(11)	C8-C9-C10-C11	1.4(11)
C8-C9-C10-I1	-179.1(5)	C9-C10-C11-C12	-0.7(10)
I1-C10-C11-C12	179.8(5)	C10-C11-C12-C7	-0.2(10)
C8-C7-C12-C11	0.5(9)	O5-C7-C12-C11	-178.3(6)
C5-O1-C13-C14	-179.9(6)	C5-O1-C13-C16	61.6(9)
C5-O1-C13-C15	-62.4(8)		

Crystal Structure of Fmoc-(2*S*,4*S*)-*p*-iodophenyl-4-hydroxyproline (**7**)

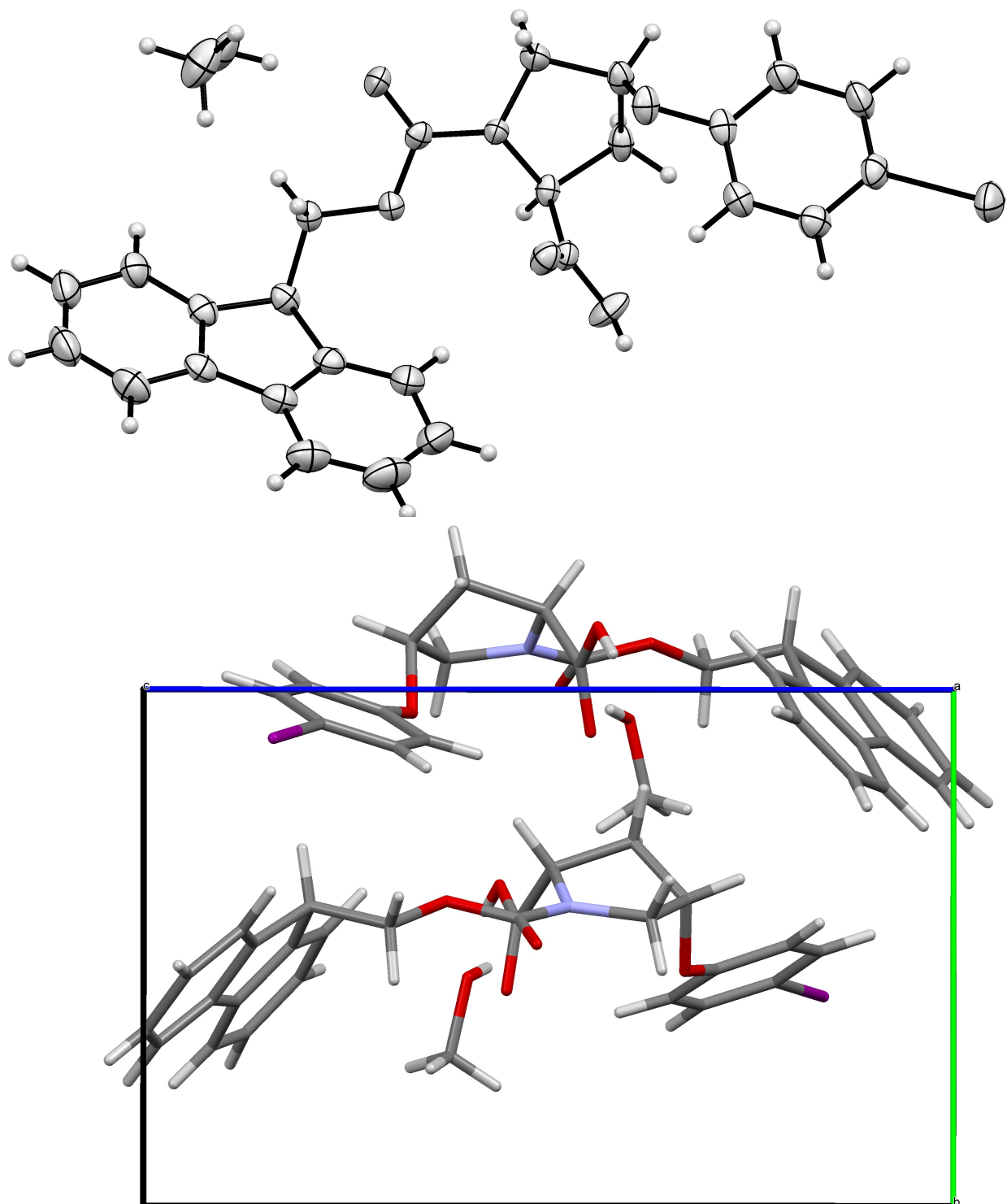


Figure S40. Crystal structure of Fmoc-(2*S*,4*S*)-*p*-iodophenyl-4-hydroxyproline (**7**). Top: ORTEP diagram of **7** with ellipsoids shown at 50% probability; bottom: overall crystal packing. Diffractable crystals were obtained by slow evaporation at room temperature from a solution of **7** in methanol.

Table S8. Crystallographic data and refinement details for Fmoc-(2*S*,4*S*)-*p*-iodophenyl-4-hydroxyproline (**7**).

empirical formula	C ₂₇ H ₂₆ INO ₆	
formula weight	587.39	
<i>T</i> (K)	200(2)	
wavelength (Å)	0.71073	
crystal system, space group	Monoclinic, P2 ₁	
Unit cell dimensions (Å, °)	a = 9.8340(9)	α = 90
	b = 8.9990(8)	β = 106.4220
	c = 14.7646(14)	γ = 90
Volume (Å ³)	1253.3(2)	
Z, Z', calcd density (g/cm ³)	2, 0, 1.556	
absorption coefficient (mm ⁻¹)	1.320	
F(000)	592	
crystal size (mm)	0.324 x 0.281 x 0.180	
θ range for data collection	2.159 to 27.780°	
Index ranges	-12 ≤ h ≤ 12, -11 ≤ k ≤ 11, -19 ≤ l ≤ 19	
Reflections collected/ unique	19303/5883 [R(int) = 0.0306]	
Coverage of independent reflections	99.5%	
Absorption correction	multi-scan	
Max. and min. transmission	0.7970 and 0.6740	
Structure solution technique	direct methods	
Refinement method	Full-matrix least-squares on F ²	
Function minimized	Σ w(F _o ² - F _c ²) ²	
Data / restraints / parameters	5883 / 2 / 323	
Goodness-of-fit on F ²	1.017	
Final <i>R</i> indices	5212 data; I > 2σ(I)	R1 = 0.0281, wR2 = 0.0590
	all data	R1 = 0.0352, wR2 = 0.0626
Weighting scheme	w = 1/[σ ² (F _o ²) + (0.0974P) ² + 0.0719P] where P = (F _o ² + 2F _c ²)/3	
Largest diff. peak and hole	0.502 and -0.394 eÅ ⁻³	
R.M.S. deviation from mean	0.052 eÅ ⁻³	

Table S9. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{Å}^2 \times 10^3$) for Fmoc-(2*S*,4*S*)-*p*-iodophenyl-4-hydroxyproline (**7**). U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U(eq)
I1	0.05011(3)	0.59476(4)	0.16072(2)	0.05246(10)
N1	0.4139(3)	0.4205(3)	0.4748(2)	0.0226(6)
O1	0.4131(3)	0.4099(3)	0.62584(18)	0.0253(6)
O2	0.2182(3)	0.4935(3)	0.51450(18)	0.0323(6)
O3	0.7959(3)	0.3787(3)	0.5606(2)	0.0416(7)
O4	0.6641(2)	0.5827(3)	0.55182(16)	0.0316(5)
O5	0.5401(3)	0.5457(2)	0.33157(18)	0.0307(6)
O6	0.0135(3)	0.5578(4)	0.5994(3)	0.0490(9)
C1	0.5513(4)	0.3465(4)	0.4952(2)	0.0242(7)
C2	0.5545(4)	0.2946(4)	0.3961(3)	0.0288(8)
C3	0.4644(4)	0.4071(4)	0.3300(3)	0.0290(8)
C4	0.3456(4)	0.4406(4)	0.3741(2)	0.0295(8)
C5	0.3391(3)	0.4441(4)	0.5367(2)	0.0229(7)
C6	0.6734(4)	0.4513(4)	0.5389(2)	0.0260(7)
C7	0.6541(4)	0.5422(4)	0.2940(3)	0.0285(8)
C8	0.6403(5)	0.4942(5)	0.2028(3)	0.0370(9)
C9	0.7558(5)	0.5071(5)	0.1656(3)	0.0418(10)
C10	0.8819(4)	0.5661(4)	0.2200(3)	0.0334(9)
C11	0.8963(4)	0.6114(5)	0.3117(2)	0.0336(8)
C12	0.7816(3)	0.5973(6)	0.3486(2)	0.0327(7)
C13	0.3440(4)	0.4551(4)	0.6960(2)	0.0261(7)
C14	0.4395(4)	0.4191(4)	0.7940(2)	0.0276(7)
C15	0.5841(4)	0.4946(4)	0.8164(3)	0.0321(8)
C16	0.6938(4)	0.4699(5)	0.7772(3)	0.0433(10)
C17	0.8148(4)	0.5576(6)	0.8077(3)	0.0532(15)
C18	0.8244(5)	0.6662(6)	0.8746(4)	0.0586(13)
C19	0.7156(5)	0.6902(5)	0.9154(3)	0.0473(11)
C20	0.5941(3)	0.6049(6)	0.8861(2)	0.0338(7)
C21	0.4647(3)	0.6010(6)	0.9161(2)	0.0316(7)
C22	0.4236(5)	0.6853(5)	0.9830(3)	0.0445(10)
C23	0.2924(5)	0.6605(5)	0.9968(3)	0.0490(11)
C24	0.2025(5)	0.5516(5)	0.9457(3)	0.0442(11)
C25	0.2420(4)	0.4660(5)	0.8785(3)	0.0375(9)
C26	0.3742(4)	0.4911(4)	0.8647(3)	0.0302(8)

C27 0.0175(6) 0.7098(6) 0.6215(5) 0.0599(15)

Table S10. Bond lengths [Å] and angles [°] for Fmoc-(2*S*,4*S*)-*p*-iodophenyl-4-hydroxyproline (7).

Bond lengths

I1-C10	2.095(3)	N1-C5	1.341(4)
N1-C1	1.459(5)	N1-C4	1.460(4)
O1-C5	1.347(4)	O1-C13	1.448(4)
O2-C5	1.224(4)	O3-C6	1.328(4)
O3-H3	0.80(4)	O4-C6	1.205(5)
O5-C7	1.384(4)	O5-C3	1.449(4)
O6-C27	1.404(6)	O6-H6	0.82(4)
C1-C6	1.520(5)	C1-C2	1.545(5)
C1-H1A	1.0	C2-C3	1.508(6)
C2-H2A	0.99	C2-H2B	0.99
C3-C4	1.519(5)	C3-H3A	1.0
C4-H4A	0.99	C4-H4B	0.99
C7-C12	1.377(5)	C7-C8	1.385(5)
C8-C9	1.399(6)	C8-H8A	0.95
C9-C10	1.379(6)	C9-H9A	0.95
C10-C11	1.383(5)	C11-C12	1.390(4)
C11-H11A	0.95	C12-H12A	0.95
C13-C14	1.520(5)	C13-H13A	0.99
C13-H13B	0.99	C14-C26	1.517(5)
C14-C15	1.526(5)	C14-H14A	1.0
C15-C16	1.379(6)	C15-C20	1.412(6)
C16-C17	1.393(7)	C16-H16A	0.95
C17-C18	1.373(7)	C17-H17A	0.95
C18-C19	1.385(7)	C18-H18A	0.95
C19-C20	1.382(6)	C19-H19A	0.95
C20-C21	1.462(5)	C21-C22	1.392(6)
C21-C26	1.402(6)	C22-C23	1.381(7)
C22-H22A	0.95	C23-C24	1.391(6)
C23-H23A	0.95	C24-C25	1.395(6)
C24-H24A	0.95	C25-C26	1.390(5)
C25-H25A	0.95	C27-H27A	0.98
C27-H27B	0.98	C27-H27C	0.98

Bond angles

C5-N1-C1	125.9(3)	C5-N1-C4	119.4(3)
C1-N1-C4	113.5(3)	C5-O1-C13	113.7(3)
C6-O3-H3	115.(4)	C7-O5-C3	116.4(3)
C27-O6-H6	109.(3)	N1-C1-C6	112.3(3)
N1-C1-C2	102.1(3)	C6-C1-C2	111.4(3)
N1-C1-H1A	110.3	C6-C1-H1A	110.3
C2-C1-H1A	110.3	C3-C2-C1	104.1(3)
C3-C2-H2A	110.9	C1-C2-H2A	110.9
C3-C2-H2B	110.9	C1-C2-H2B	110.9
H2A-C2-H2B	109.0	O5-C3-C2	111.2(3)
O5-C3-C4	106.0(3)	C2-C3-C4	103.8(3)
O5-C3-H3A	111.8	C2-C3-H3A	111.8
C4-C3-H3A	111.8	N1-C4-C3	102.9(3)
N1-C4-H4A	111.2	C3-C4-H4A	111.2
N1-C4-H4B	111.2	C3-C4-H4B	111.2
H4A-C4-H4B	109.1	O2-C5-N1	123.6(3)
O2-C5-O1	124.0(3)	N1-C5-O1	112.4(3)
O4-C6-O3	123.3(3)	O4-C6-C1	126.1(3)
O3-C6-C1	110.5(3)	C12-C7-C8	120.3(3)
C12-C7-O5	117.6(3)	C8-C7-O5	122.0(3)
C7-C8-C9	119.3(4)	C7-C8-H8A	120.4
C9-C8-H8A	120.4	C10-C9-C8	119.9(4)
C10-C9-H9A	120.0	C8-C9-H9A	120.0
C9-C10-C11	120.7(3)	C9-C10-I1	119.3(3)
C11-C10-I1	119.9(3)	C10-C11-C12	119.2(3)
C10-C11-H11A	120.4	C12-C11-H11A	120.4
C7-C12-C11	120.6(3)	C7-C12-H12A	119.7
C11-C12-H12A	119.7	O1-C13-C14	109.4(3)
O1-C13-H13A	109.8	C14-C13-H13A	109.8
O1-C13-H13B	109.8	C14-C13-H13B	109.8
H13A-C13-H13B	108.2	C26-C14-C13	107.2(3)
C26-C14-C15	102.1(3)	C13-C14-C15	113.5(3)
C26-C14-H14A	111.2	C13-C14-H14A	111.2
C15-C14-H14A	111.2	C16-C15-C20	121.2(4)
C16-C15-C14	128.9(4)	C20-C15-C14	109.9(3)
C15-C16-C17	118.1(4)	C15-C16-H16A	121.0
C17-C16-H16A	121.0	C18-C17-C16	121.0(4)

C18-C17-H17A	119.5	C16-C17-H17A	119.5
C17-C18-C19	121.3(4)	C17-C18-H18A	119.4
C19-C18-H18A	119.4	C20-C19-C18	118.9(4)
C20-C19-H19A	120.6	C18-C19-H19A	120.6
C19-C20-C15	119.6(4)	C19-C20-C21	131.9(4)
C15-C20-C21	108.4(4)	C22-C21-C26	120.1(3)
C22-C21-C20	130.8(4)	C26-C21-C20	109.1(3)
C23-C22-C21	119.2(4)	C23-C22-H22A	120.4
C21-C22-H22A	120.4	C22-C23-C24	120.7(4)
C22-C23-H23A	119.7	C24-C23-H23A	119.7
C23-C24-C25	120.9(4)	C23-C24-H24A	119.6
C25-C24-H24A	119.6	C26-C25-C24	118.3(4)
C26-C25-H25A	120.8	C24-C25-H25A	120.8
C25-C26-C21	120.8(3)	C25-C26-C14	128.8(4)
C21-C26-C14	110.3(3)	O6-C27-H27A	109.5
O6-C27-H27B	109.5	H27A-C27-H27B	109.5
O6-C27-H27C	109.5	H27A-C27-H27C	109.5
H27B-C27-H27C	109.5		

Table S11. Anisotropic atomic displacement parameters (\AA^2) for Fmoc-(2*S*,4*S*)-*p*-iodophenyl-4-hydroxyproline (**7**). The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^2 U_{11} + \dots + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
I1	0.04115(14)	0.0792(2)	0.04425(15)	0.01176(19)	0.02384(11)	0.00458(19)
N1	0.0191(14)	0.0276(15)	0.0221(14)	-0.0027(12)	0.0075(11)	-0.0011(12)
O1	0.0255(13)	0.0291(13)	0.0231(13)	0.0004(10)	0.0098(10)	0.0007(10)
O2	0.0215(12)	0.0454(15)	0.0317(14)	-0.0043(12)	0.0104(11)	0.0027(11)
O3	0.0218(14)	0.0335(15)	0.067(2)	-0.0039(14)	0.0087(14)	0.0061(11)
O4	0.0269(10)	0.0288(13)	0.0404(12)	-0.0078(15)	0.0115(9)	0.0004(14)
O5	0.0388(14)	0.0225(13)	0.0371(14)	-0.0012(9)	0.0210(11)	-0.0036(10)
O6	0.0250(13)	0.055(2)	0.074(2)	-0.0156(17)	0.0243(14)	-0.0049(13)
C1	0.0255(17)	0.0218(16)	0.0284(18)	-0.0005(14)	0.0128(14)	0.0027(14)
C2	0.036(2)	0.0217(18)	0.035(2)	-0.0071(15)	0.0206(17)	-0.0042(15)
C3	0.0334(19)	0.0291(19)	0.0283(18)	-0.0074(15)	0.0150(15)	-0.0084(15)
C4	0.0266(18)	0.036(2)	0.0259(18)	-0.0040(15)	0.0063(14)	-0.0025(15)
C5	0.0213(16)	0.0200(15)	0.0281(18)	-0.0027(13)	0.0081(14)	-0.0040(13)
C6	0.0246(17)	0.0289(18)	0.0270(18)	-0.0004(14)	0.0112(14)	0.0034(14)
C7	0.039(2)	0.0205(16)	0.0307(18)	0.0053(13)	0.0178(16)	0.0014(14)
C8	0.039(2)	0.043(2)	0.030(2)	-0.0024(17)	0.0115(17)	-0.0097(18)
C9	0.053(3)	0.051(2)	0.027(2)	-0.0045(18)	0.0205(19)	-0.005(2)
C10	0.0353(18)	0.037(3)	0.0326(17)	0.0083(16)	0.0172(14)	0.0001(16)
C11	0.0351(16)	0.033(2)	0.0327(16)	0.002(2)	0.0100(13)	-0.003(2)
C12	0.0419(17)	0.0324(16)	0.0266(15)	-0.001(2)	0.0140(13)	0.000(3)
C13	0.0272(17)	0.0283(18)	0.0257(17)	-0.0006(14)	0.0122(14)	-0.0007(14)
C14	0.0319(19)	0.0253(17)	0.0254(18)	0.0003(14)	0.0082(14)	-0.0026(14)
C15	0.0305(19)	0.037(2)	0.0252(18)	0.0059(16)	0.0027(15)	0.0025(16)
C16	0.034(2)	0.064(3)	0.030(2)	0.004(2)	0.0060(17)	0.007(2)
C17	0.0279(19)	0.082(4)	0.048(2)	0.008(2)	0.0068(18)	0.004(2)
C18	0.035(2)	0.066(3)	0.066(3)	0.008(3)	0.000(2)	-0.014(2)
C19	0.041(2)	0.049(3)	0.045(3)	-0.002(2)	0.000(2)	-0.007(2)
C20	0.0360(16)	0.0338(18)	0.0282(15)	0.002(2)	0.0037(13)	-0.002(2)
C21	0.0380(16)	0.0322(17)	0.0230(14)	0.005(2)	0.0060(12)	0.000(2)
C22	0.055(3)	0.042(2)	0.035(2)	-0.0104(18)	0.010(2)	-0.002(2)
C23	0.061(3)	0.059(3)	0.031(2)	-0.004(2)	0.020(2)	0.012(2)
C24	0.047(2)	0.060(3)	0.033(2)	0.0074(18)	0.0216(18)	0.006(2)
C25	0.040(2)	0.046(2)	0.030(2)	0.0052(17)	0.0145(17)	-0.0043(18)
C26	0.038(2)	0.0291(19)	0.0244(18)	0.0055(14)	0.0097(16)	0.0018(16)
C27	0.045(3)	0.047(3)	0.095(4)	-0.006(3)	0.033(3)	0.004(2)

Table S12. Hydrogen atomic coordinates and isotropic atomic displacement parameters (\AA^2) for Fmoc-(2*S*,4*S*)-*p*-iodophenyl-4-hydroxyproline (**7**).

	x/a	y/b	z/c	U(eq)
H3	0.865(5)	0.430(5)	0.579(3)	0.05
H6	0.078(5)	0.539(5)	0.576(4)	0.059
H1A	0.5539	0.2589	0.5373	0.029
H2A	0.6526	0.2944	0.3907	0.035
H2B	0.5143	0.1935	0.3824	0.035
H3A	0.4272	0.3671	0.2644	0.035
H4A	0.3105	0.5436	0.3601	0.035
H4B	0.2655	0.3707	0.3512	0.035
H8A	0.5534	0.4530	0.1658	0.044
H9A	0.7474	0.4753	0.1029	0.05
H11A	0.9834	0.6517	0.3491	0.04
H12A	0.7912	0.6258	0.4121	0.039
H13A	0.2526	0.4022	0.6852	0.031
H13B	0.3245	0.5632	0.6907	0.031
H14A	0.4494	0.3093	0.8041	0.033
H16A	0.6870	0.3952	0.7307	0.052
H17A	0.8918	0.5421	0.7819	0.064
H18A	0.9072	0.7259	0.8932	0.07
H19A	0.7243	0.7640	0.9627	0.057
H22A	0.4852	0.7589	1.0187	0.053
H23A	0.2632	0.7185	1.0418	0.059
H24A	0.1130	0.5353	0.9566	0.053
H25A	0.1802	0.3923	0.8431	0.045
H27A	-0.0635	0.7347	0.6450	0.09
H27B	0.0129	0.7683	0.5648	0.09
H27C	0.1058	0.7324	0.6703	0.09

Table S13. Torsion angles (°) for Fmoc-(2*S*,4*S*)-*p*-iodophenyl-4-hydroxyproline (**7**).

C5-N1-C1-C6	-83.1(4)	C4-N1-C1-C6	109.7(3)
C5-N1-C1-C2	157.5(3)	C4-N1-C1-C2	-9.7(4)
N1-C1-C2-C3	28.8(3)	C6-C1-C2-C3	-91.2(3)
C7-O5-C3-C2	68.1(4)	C7-O5-C3-C4	-179.7(3)
C1-C2-C3-O5	76.2(3)	C1-C2-C3-C4	-37.4(3)
C5-N1-C4-C3	178.8(3)	C1-N1-C4-C3	-13.0(4)
O5-C3-C4-N1	-86.5(3)	C2-C3-C4-N1	30.8(3)
C1-N1-C5-O2	-172.6(3)	C4-N1-C5-O2	-6.0(5)
C1-N1-C5-O1	8.6(5)	C4-N1-C5-O1	175.2(3)
C13-O1-C5-O2	-7.7(5)	C13-O1-C5-N1	171.1(3)
N1-C1-C6-O4	-4.0(5)	C2-C1-C6-O4	109.8(4)
N1-C1-C6-O3	177.0(3)	C2-C1-C6-O3	-69.3(4)
C3-O5-C7-C12	-128.3(4)	C3-O5-C7-C8	55.7(4)
C12-C7-C8-C9	-2.2(6)	O5-C7-C8-C9	173.7(3)
C7-C8-C9-C10	0.5(6)	C8-C9-C10-C11	0.7(6)
C8-C9-C10-I1	-176.8(3)	C9-C10-C11-C12	-0.2(7)
I1-C10-C11-C12	177.3(3)	C8-C7-C12-C11	2.8(7)
O5-C7-C12-C11	-173.3(4)	C10-C11-C12-C7	-1.5(7)
C5-O1-C13-C14	-177.0(3)	O1-C13-C14-C26	170.7(3)
O1-C13-C14-C15	58.7(4)	C26-C14-C15-C16	177.2(4)
C13-C14-C15-C16	-67.7(5)	C26-C14-C15-C20	-4.4(4)
C13-C14-C15-C20	110.7(4)	C20-C15-C16-C17	-0.4(6)
C14-C15-C16-C17	177.8(4)	C15-C16-C17-C18	-0.3(7)
C16-C17-C18-C19	1.4(7)	C17-C18-C19-C20	-1.5(7)
C18-C19-C20-C15	0.7(7)	C18-C19-C20-C21	178.5(5)
C16-C15-C20-C19	0.2(6)	C14-C15-C20-C19	-178.3(4)
C16-C15-C20-C21	-178.0(4)	C14-C15-C20-C21	3.5(4)
C19-C20-C21-C22	1.4(8)	C15-C20-C21-C22	179.3(4)
C19-C20-C21-C26	-178.8(5)	C15-C20-C21-C26	-0.9(5)
C26-C21-C22-C23	-0.9(6)	C20-C21-C22-C23	178.9(4)
C21-C22-C23-C24	0.8(7)	C22-C23-C24-C25	-0.7(7)
C23-C24-C25-C26	0.7(6)	C24-C25-C26-C21	-0.8(6)
C24-C25-C26-C14	-177.1(4)	C22-C21-C26-C25	0.9(6)
C20-C21-C26-C25	-178.9(4)	C22-C21-C26-C14	177.8(4)
C20-C21-C26-C14	-2.0(4)	C13-C14-C26-C25	60.9(5)
C15-C14-C26-C25	-179.6(4)	C13-C14-C26-C21	-115.8(3)
C15-C14-C26-C21	3.8(4)		

Crystal Structure of Boc-(2*S*,4*R*)-*p*-iodophenyl-4-hydroxyproline methyl ester (**10**)

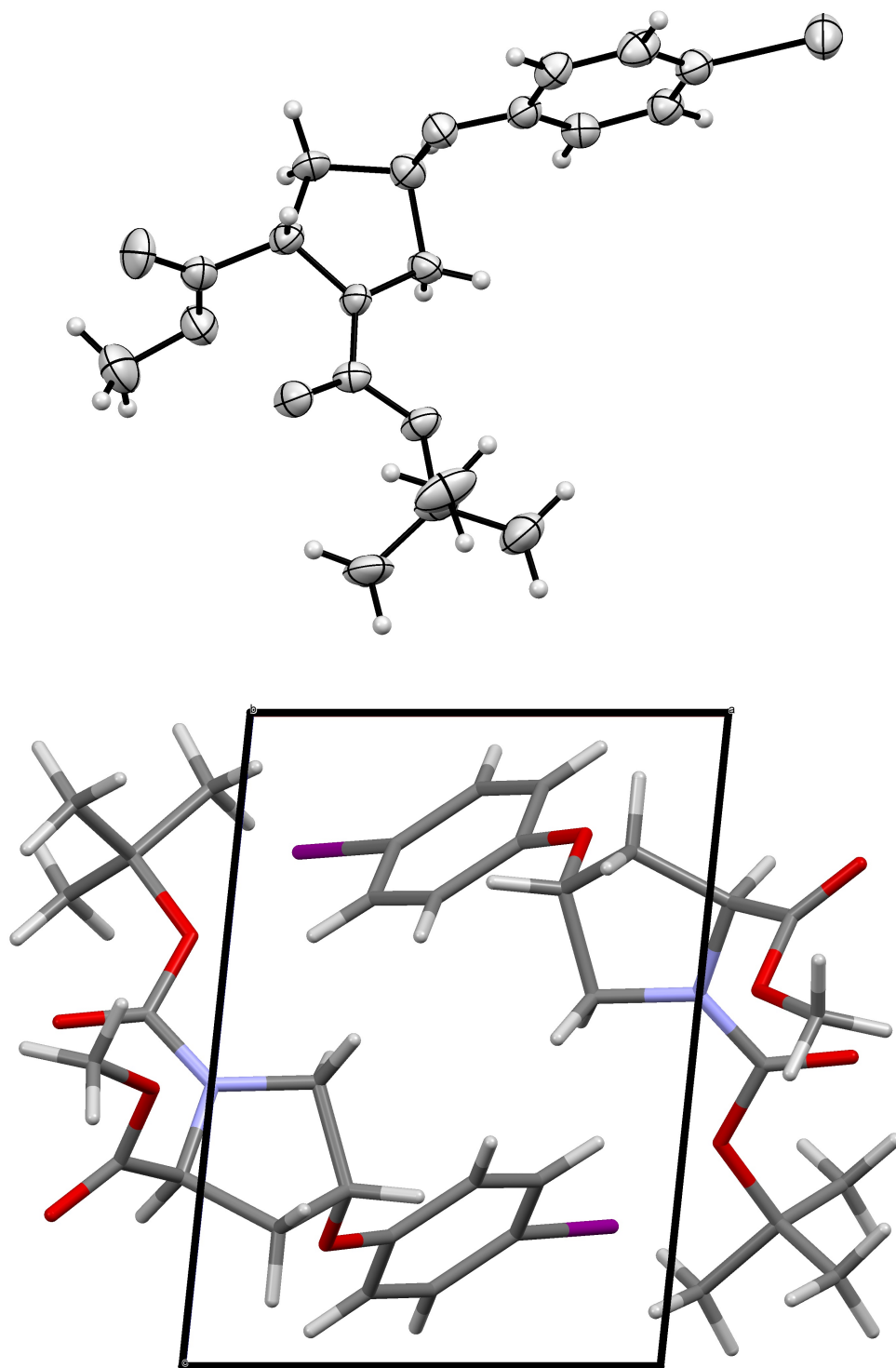


Figure S41. Crystal structure of Boc-(2*S*,4*R*)-*p*-iodophenyl-4-hydroxyproline methyl ester (**10**). Top: ORTEP diagram of **10** with ellipsoids shown at 50% probability; bottom: overall crystal packing. Diffractable crystals were obtained by slow evaporation at room temperature from a solution of **10** in CDCl₃.

Table S14. Crystallographic data and refinement details for Boc-(2*S*,4*R*)-*p*-iodophenyl-4-hydroxyproline methyl ester (**10**).

empirical formula	C ₁₇ H ₂₁ INO ₅	
formula weight	447.25	
<i>T</i> (K)	200(2)	
wavelength (Å)	0.71073	
crystal system, space group	Monoclinic, P2 ₁	
Unit cell dimensions (Å, °)	a = 6.5131(13)	α = 90
	b = 16.581(3)	β = 95.961(3)
	c = 8.9446(18)	γ = 90
Volume (Å ³)	960.7(3)	
Z, Z', calcd density (g/cm ³)	2, 0, 1.546	
absorption coefficient (mm ⁻¹)	1.691	
F(000)	448	
crystal size (mm)	0.266 x 0.123 x 0.114	
θ range for data collection	2.289 to 28.677°	
Index ranges	-8 ≤ h ≤ 8, -22 ≤ k ≤ 22, -12 ≤ l ≤ 12	
Reflections collected/ unique	15874/4955 [R(int) = 0.0432]	
Coverage of independent reflections	99.9%	
Absorption correction	multi-scan	
Max. and min. transmission	0.7458 and 0.6471	
Structure solution technique	direct methods	
Refinement method	Full-matrix least-squares on F ²	
Function minimized	Σ w(F _o ² - F _c ²) ²	
Data / restraints / parameters	4955 / 1 / 221	
Goodness-of-fit on F ²	0.964	
Final <i>R</i> indices	5212 data; I > 2σ(I)	R1 = 0.0374, wR2 = 0.0725
	all data	R1 = 0.0480, wR2 = 0.0765
Weighting scheme	w = 1/[σ ² (F _o ²) + (0.0974P) ² + 0.0719P] where P = (F _o ² + 2F _c ²)/3	
Largest diff. peak and hole	0.856 and -0.385 eÅ ⁻³	
R.M.S. deviation from mean	0.064 eÅ ⁻³	

Table S15. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{Å}^2 \times 10^3$) for Boc-(2*S*,4*R*)-*p*-iodophenyl-4-hydroxyproline methyl ester (**10**). U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U(eq)
C1	0.1765(7)	0.6926(4)	0.3126(5)	0.0364(13)
C2	0.0454(7)	0.6172(3)	0.2903(6)	0.0327(11)
C3	0.8280(8)	0.6352(3)	0.2110(6)	0.0381(12)
C4	0.6938(8)	0.5697(3)	0.2698(6)	0.0359(11)
C5	0.7788(7)	0.5612(3)	0.4345(5)	0.0341(11)
C6	0.1507(7)	0.5619(3)	0.5390(5)	0.0300(10)
C7	0.2175(8)	0.4929(4)	0.7814(6)	0.0408(13)
C8	0.0670(10)	0.4578(5)	0.8849(7)	0.0596(18)
C9	0.3492(12)	0.5579(5)	0.8615(8)	0.055(2)
C10	0.3440(12)	0.4261(5)	0.7201(8)	0.066(2)
C11	0.2525(11)	0.8074(4)	0.4641(9)	0.067(2)
C12	0.4279(8)	0.4371(3)	0.2833(6)	0.0356(11)
C13	0.2960(8)	0.3714(3)	0.2840(6)	0.0369(12)
C14	0.3310(8)	0.3034(3)	0.2025(6)	0.0369(12)
C15	0.4964(8)	0.3005(3)	0.1161(6)	0.0412(12)
C16	0.6271(10)	0.3664(4)	0.1132(7)	0.0381(15)
C17	0.5941(7)	0.4352(3)	0.1980(5)	0.0324(11)
I1	0.13246(5)	0.20461(3)	0.21343(4)	0.05095(13)
N1	0.9979(6)	0.5792(3)	0.4308(4)	0.0307(9)
O1	0.3068(5)	0.7091(4)	0.2317(4)	0.0561(10)
O2	0.1230(6)	0.7374(2)	0.4248(4)	0.0460(9)
O3	0.3318(5)	0.5758(2)	0.5268(4)	0.0395(9)
O4	0.0757(5)	0.5275(2)	0.6582(4)	0.0358(8)
O5	0.7265(6)	0.4977(2)	0.1864(4)	0.0378(8)

Table S16. Bond lengths [Å] and angles [°] for Boc-(2*S*,4*R*)-*p*-iodophenyl-4-hydroxyproline methyl ester (**10**).

Bond lengths

C1-O1	1.202(6)	C1-O2	1.325(6)
C1-C2	1.516(8)	C2-N1	1.468(6)
C2-C3	1.546(7)	C2-H2	1.0
C3-C4	1.522(7)	C3-H3A	0.99
C3-H3B	0.99	C4-O5	1.435(7)
C4-C5	1.526(7)	C4-H4	1.0
C5-N1	1.461(6)	C5-H5A	0.99
C5-H5B	0.99	C6-O3	1.218(6)
C6-O4	1.345(6)	C6-N1	1.345(6)
C7-O4	1.478(6)	C7-C9	1.512(10)
C7-C10	1.517(9)	C7-C8	1.532(8)
C8-H8A	0.98	C8-H8B	0.98
C8-H8C	0.98	C9-H9A	0.98
C9-H9B	0.98	C9-H9C	0.98
C10-H10A	0.98	C10-H10B	0.98
C10-H10C	0.98	C11-O2	1.456(7)
C11-H11A	0.98	C11-H11B	0.98
C11-H11C	0.98	C12-C17	1.388(7)
C12-C13	1.388(8)	C12-H12	0.95
C13-C14	1.374(7)	C13-H13	0.95
C14-C15	1.390(7)	C14-I1	2.096(5)
C15-C16	1.387(8)	C15-H15	0.95
C16-C17	1.399(9)	C16-H16	0.95
C17-O5	1.359(6)		

Bond angles

O1-C1-O2	125.9(6)	O1-C1-C2	122.2(6)
O2-C1-C2	111.9(4)	N1-C2-C1	114.1(4)
N1-C2-C3	102.2(4)	C1-C2-C3	112.2(4)
N1-C2-H2	109.4	C1-C2-H2	109.4
C3-C2-H2	109.4	C4-C3-C2	103.6(4)
C4-C3-H3A	111.0	C2-C3-H3A	111.0
C4-C3-H3B	111.0	C2-C3-H3B	111.0
H3A-C3-H3B	109.0	O5-C4-C3	107.0(4)
O5-C4-C5	111.5(4)	C3-C4-C5	103.6(4)
O5-C4-H4	111.4	C3-C4-H4	111.4
C5-C4-H4	111.4	N1-C5-C4	102.5(4)
N1-C5-H5A	111.3	C4-C5-H5A	111.3
N1-C5-H5B	111.3	C4-C5-H5B	111.3
H5A-C5-H5B	109.2	O3-C6-O4	125.9(4)
O3-C6-N1	123.1(5)	O4-C6-N1	111.0(4)
O4-C7-C9	110.9(5)	O4-C7-C10	109.6(5)
C9-C7-C10	112.9(6)	O4-C7-C8	102.0(4)
C9-C7-C8	110.6(5)	C10-C7-C8	110.3(6)
C7-C8-H8A	109.5	C7-C8-H8B	109.5
H8A-C8-H8B	109.5	C7-C8-H8C	109.5
H8A-C8-H8C	109.5	H8B-C8-H8C	109.5
C7-C9-H9A	109.5	C7-C9-H9B	109.5
H9A-C9-H9B	109.5	C7-C9-H9C	109.5
H9A-C9-H9C	109.5	H9B-C9-H9C	109.5
C7-C10-H10A	109.5	C7-C10-H10B	109.5
H10A-C10-H10B	109.5	C7-C10-H10C	109.5
H10A-C10-H10C	109.5	H10B-C10-H10C	109.5
O2-C11-H11A	109.5	O2-C11-H11B	109.5
H11A-C11-H11B	109.5	O2-C11-H11C	109.5
H11A-C11-H11C	109.5	H11B-C11-H11C	109.5
C17-C12-C13	120.2(5)	C17-C12-H12	119.9
C13-C12-H12	119.9	C14-C13-C12	120.3(5)
C14-C13-H13	119.8	C12-C13-H13	119.8
C13-C14-C15	120.3(5)	C13-C14-I1	118.6(4)
C15-C14-I1	121.1(4)	C16-C15-C14	119.7(5)
C16-C15-H15	120.2	C14-C15-H15	120.2
C15-C16-C17	120.2(6)	C15-C16-H16	119.9

C17-C16-H16	119.9	O5-C17-C12	124.1(5)
O5-C17-C16	116.5(5)	C12-C17-C16	119.3(5)
C6-N1-C5	126.3(4)	C6-N1-C2	120.1(4)
C5-N1-C2	113.6(4)	C1-O2-C11	116.0(5)
C6-O4-C7	120.4(4)	C17-O5-C4	117.8(4)
C17-C16-H16	119.9	O5-C17-C12	124.1(5)
O5-C17-C16	116.5(5)	C12-C17-C16	119.3(5)
C6-N1-C5	126.3(4)	C6-N1-C2	120.1(4)
C5-N1-C2	113.6(4)	C1-O2-C11	116.0(5)
C6-O4-C7	120.4(4)	C17-O5-C4	117.8(4)

Table S17. Anisotropic atomic displacement parameters (\AA^2) for Boc-(2*S*,4*R*)-*p*-iodophenyl-4-hydroxyproline methyl ester (**10**). The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2[h^2 a^2 U_{11} + \dots + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	0.032(2)	0.041(4)	0.035(2)	0.007(3)	-0.0012(19)	-0.002(2)
C2	0.030(2)	0.043(3)	0.026(2)	0.005(2)	0.005(2)	0.000(2)
C3	0.039(3)	0.042(3)	0.030(3)	0.010(2)	-0.008(2)	-0.003(2)
C4	0.028(2)	0.042(3)	0.037(3)	0.003(2)	0.001(2)	0.000(2)
C5	0.025(2)	0.049(3)	0.028(2)	0.000(2)	0.0002(19)	-0.006(2)
C6	0.029(2)	0.035(3)	0.026(2)	-0.001(2)	0.0009(19)	0.005(2)
C7	0.041(3)	0.054(4)	0.025(3)	0.005(2)	-0.006(2)	0.005(3)
C8	0.061(4)	0.078(5)	0.040(3)	0.020(3)	0.007(3)	-0.004(4)
C9	0.051(4)	0.082(6)	0.030(3)	0.010(4)	-0.012(3)	-0.001(4)
C10	0.089(5)	0.065(5)	0.042(4)	0.016(4)	0.007(4)	0.039(4)
C11	0.073(5)	0.051(4)	0.073(5)	-0.003(4)	-0.007(4)	-0.024(4)
C12	0.036(3)	0.038(3)	0.032(3)	0.000(2)	0.001(2)	0.001(2)
C13	0.034(2)	0.045(3)	0.032(3)	0.002(2)	0.005(2)	-0.001(2)
C14	0.043(3)	0.037(3)	0.031(3)	0.001(2)	0.003(2)	0.000(2)
C15	0.052(3)	0.040(3)	0.033(3)	-0.002(2)	0.008(2)	0.006(3)
C16	0.039(3)	0.042(3)	0.034(4)	0.005(3)	0.009(3)	0.002(3)
C17	0.032(3)	0.038(3)	0.028(3)	0.005(2)	0.002(2)	0.000(2)
I1	0.0611(2)	0.04622(19)	0.0475(2)	-0.0040(2)	0.01471(15)	-0.0145(2)
N1	0.0239(19)	0.043(2)	0.025(2)	0.0061(18)	0.0033(16)	-0.0053(17)
O1	0.0467(18)	0.068(3)	0.057(2)	0.009(4)	0.0203(16)	-0.016(3)
O2	0.048(2)	0.046(2)	0.044(2)	-0.0052(17)	0.0051(18)	-0.0139(17)
O3	0.0249(18)	0.060(3)	0.034(2)	0.0059(19)	0.0046(15)	0.0007(17)
O4	0.0273(16)	0.052(2)	0.0282(18)	0.0097(17)	0.0028(14)	0.0062(16)
O5	0.0381(19)	0.040(2)	0.035(2)	-0.0021(16)	0.0045(16)	-0.0065(16)

Table S18. Hydrogen atomic coordinates and isotropic atomic displacement parameters (\AA^2) for Boc-(2*S*,4*R*)-*p*-iodophenyl-4-hydroxyproline methyl ester (**10**).

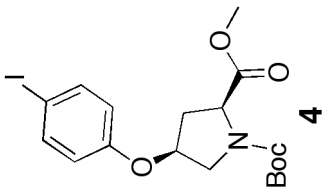
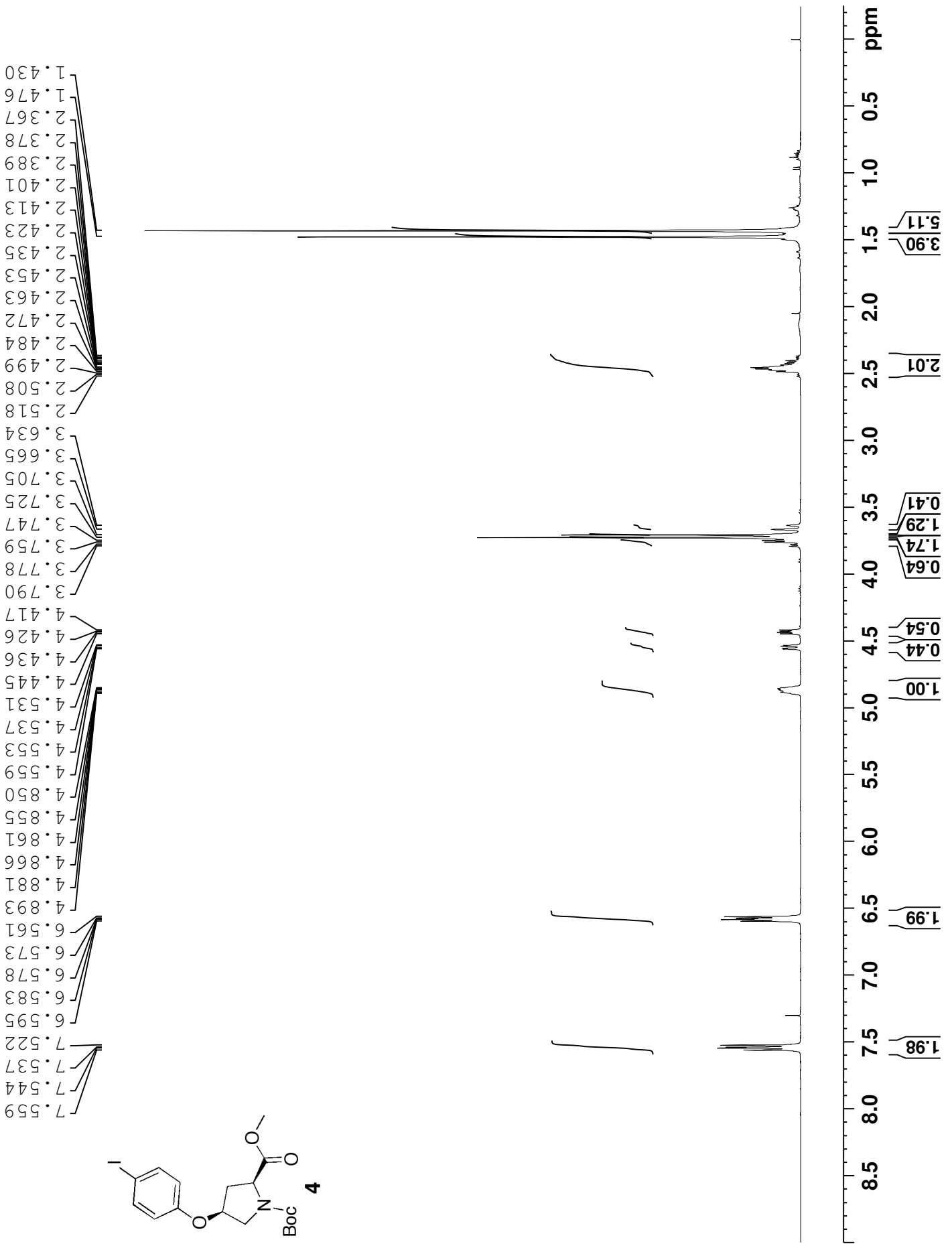
	x/a	y/b	z/c	U(eq)
H2	1.1164	0.5772	0.2296	0.039
H3A	0.7804	0.6895	0.2380	0.046
H3B	0.8269	0.6318	0.1004	0.046
H4	0.5449	0.5856	0.2593	0.043
H5A	0.7129	0.6001	0.4986	0.041
H5B	0.7584	0.5058	0.4718	0.041
H8A	0.9780	0.5009	0.9166	0.089
H8B	1.1448	0.4338	0.9736	0.089
H8C	0.9818	0.4163	0.8308	0.089
H9A	1.4376	0.5823	0.7916	0.083
H9B	1.4355	0.5342	0.9466	0.083
H9C	1.2599	0.5995	0.8984	0.083
H10A	1.2517	0.3880	0.6627	0.098
H10B	1.4224	0.3978	0.8037	0.098
H10C	1.4398	0.4493	0.6543	0.098
H11A	1.3963	0.7901	0.4863	0.1
H11B	1.2064	0.8338	0.5528	0.1
H11C	1.2419	0.8454	0.3798	0.1
H12	0.4044	0.4835	0.3415	0.043
H13	0.1809	0.3734	0.3410	0.044
H15	0.5198	0.2535	0.0593	0.049
H16	0.7393	0.3648	0.0534	0.046

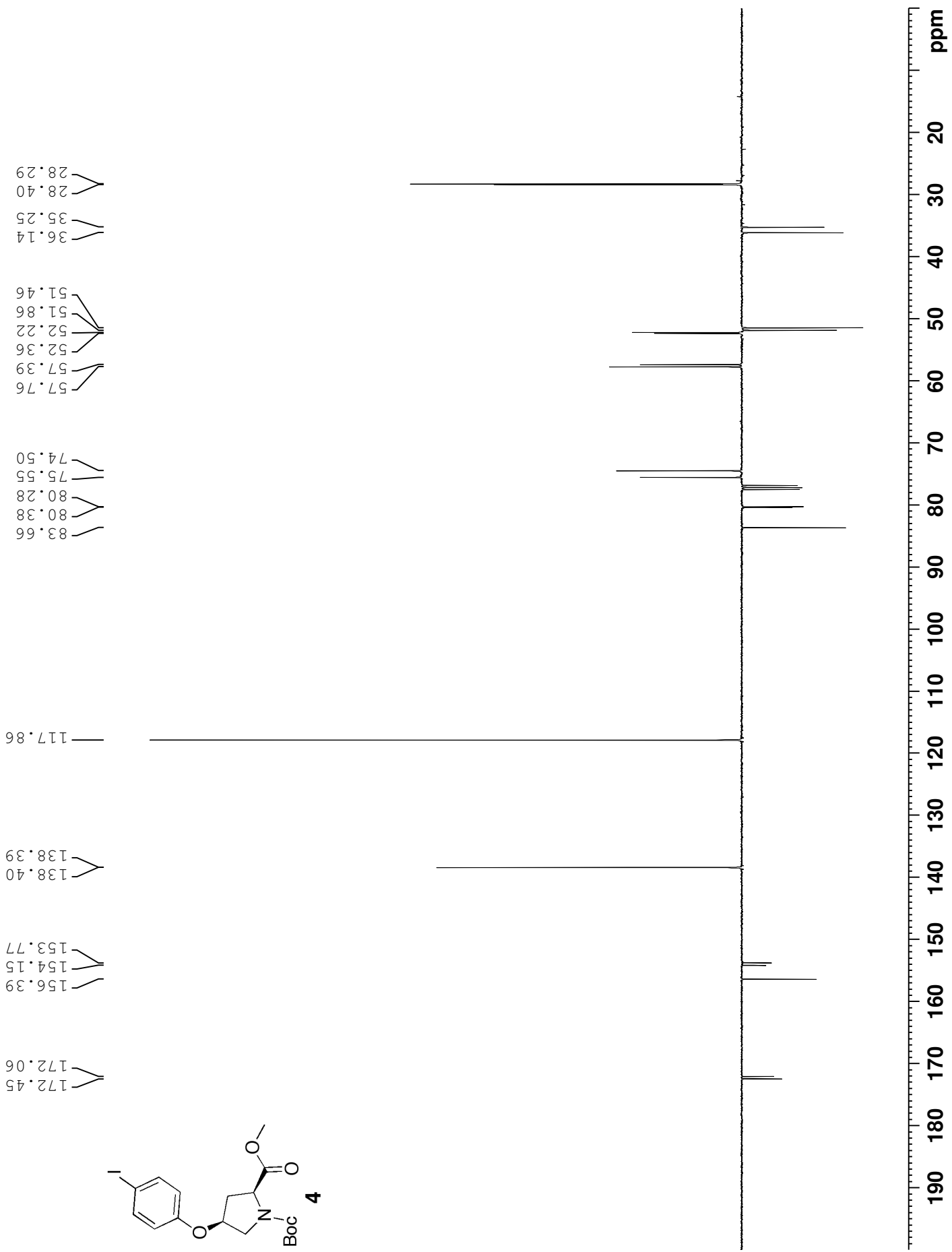
Table S19. Torsion angles (°) for Boc-(2*S*,4*R*)-*p*-iodophenyl-4-hydroxyproline methyl ester (**10**).

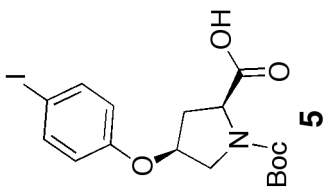
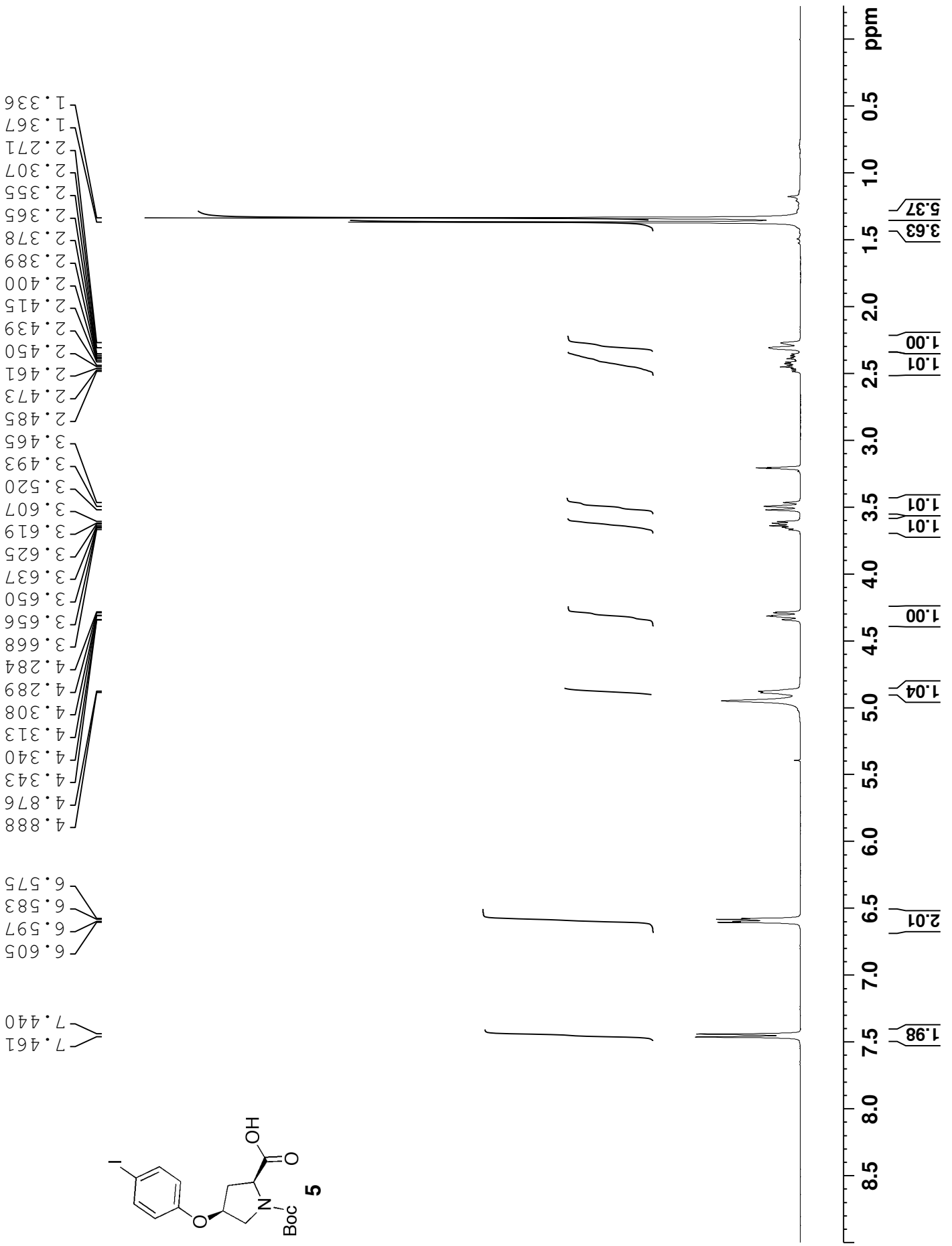
O1-C1-C2-N1	143.4(5)	O2-C1-C2-N1	-39.2(6)
O1-C1-C2-C3	-100.9(6)	O2-C1-C2-C3	76.4(5)
N1-C2-C3-C4	-28.9(5)	C1-C2-C3-C4	-151.5(4)
C2-C3-C4-O5	-79.5(5)	C2-C3-C4-C5	38.5(5)
O5-C4-C5-N1	82.5(5)	C3-C4-C5-N1	-32.3(5)
C17-C12-C13-C14	1.2(8)	C12-C13-C14-C15	-1.4(8)
C12-C13-C14-I1	178.0(4)	C13-C14-C15-C16	0.4(8)
I1-C14-C15-C16	-178.9(4)	C14-C15-C16-C17	0.7(9)
C13-C12-C17-O5	177.5(5)	C13-C12-C17-C16	-0.2(8)
C15-C16-C17-O5	-178.6(5)	C15-C16-C17-C12	-0.8(9)
O3-C6-N1-C5	177.2(5)	O4-C6-N1-C5	-2.4(7)
O3-C6-N1-C2	-0.4(8)	O4-C6-N1-C2	180.0(4)
C4-C5-N1-C6	-163.2(5)	C4-C5-N1-C2	14.5(6)
C1-C2-N1-C6	-51.9(6)	C3-C2-N1-C6	-173.2(5)
C1-C2-N1-C5	130.3(5)	C3-C2-N1-C5	9.0(6)
O1-C1-O2-C11	-8.3(8)	C2-C1-O2-C11	174.5(5)
O3-C6-O4-C7	-8.3(8)	N1-C6-O4-C7	171.3(4)
C9-C7-O4-C6	65.0(7)	C10-C7-O4-C6	-60.4(7)
C8-C7-O4-C6	-177.3(5)	C12-C17-O5-C4	1.1(7)
C16-C17-O5-C4	178.8(5)	C3-C4-O5-C17	-167.5(4)
C5-C4-O5-C17	79.8(5)		

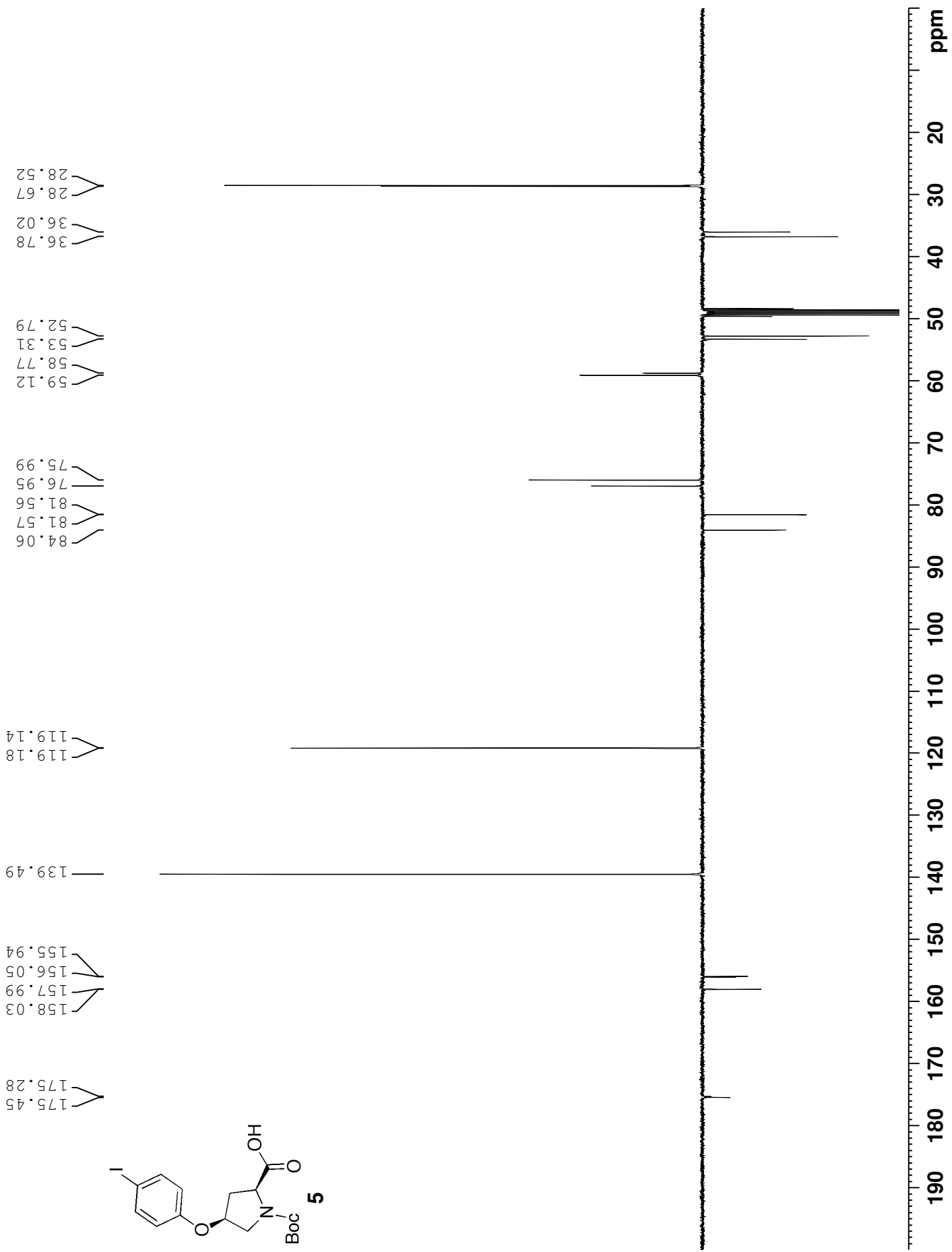
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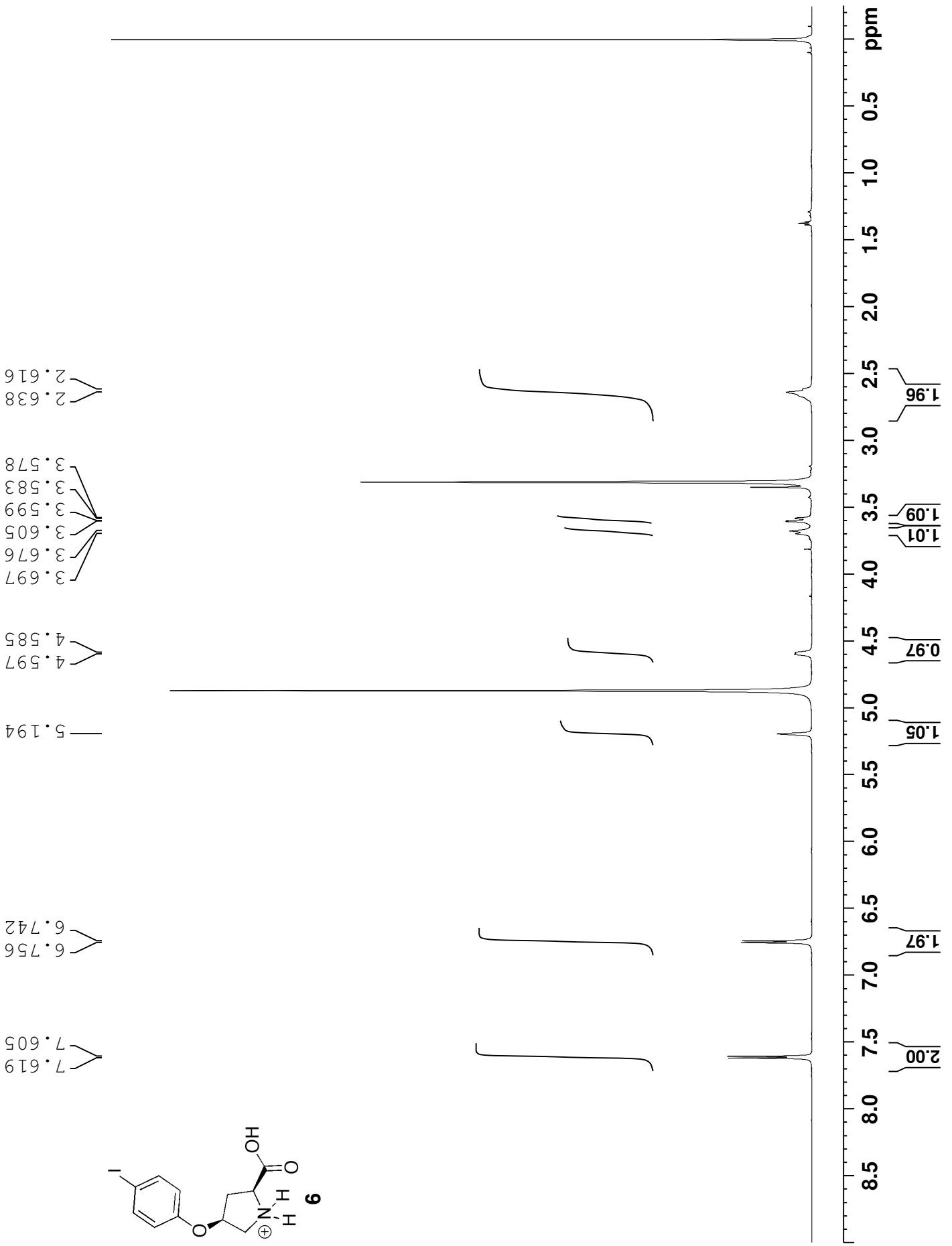
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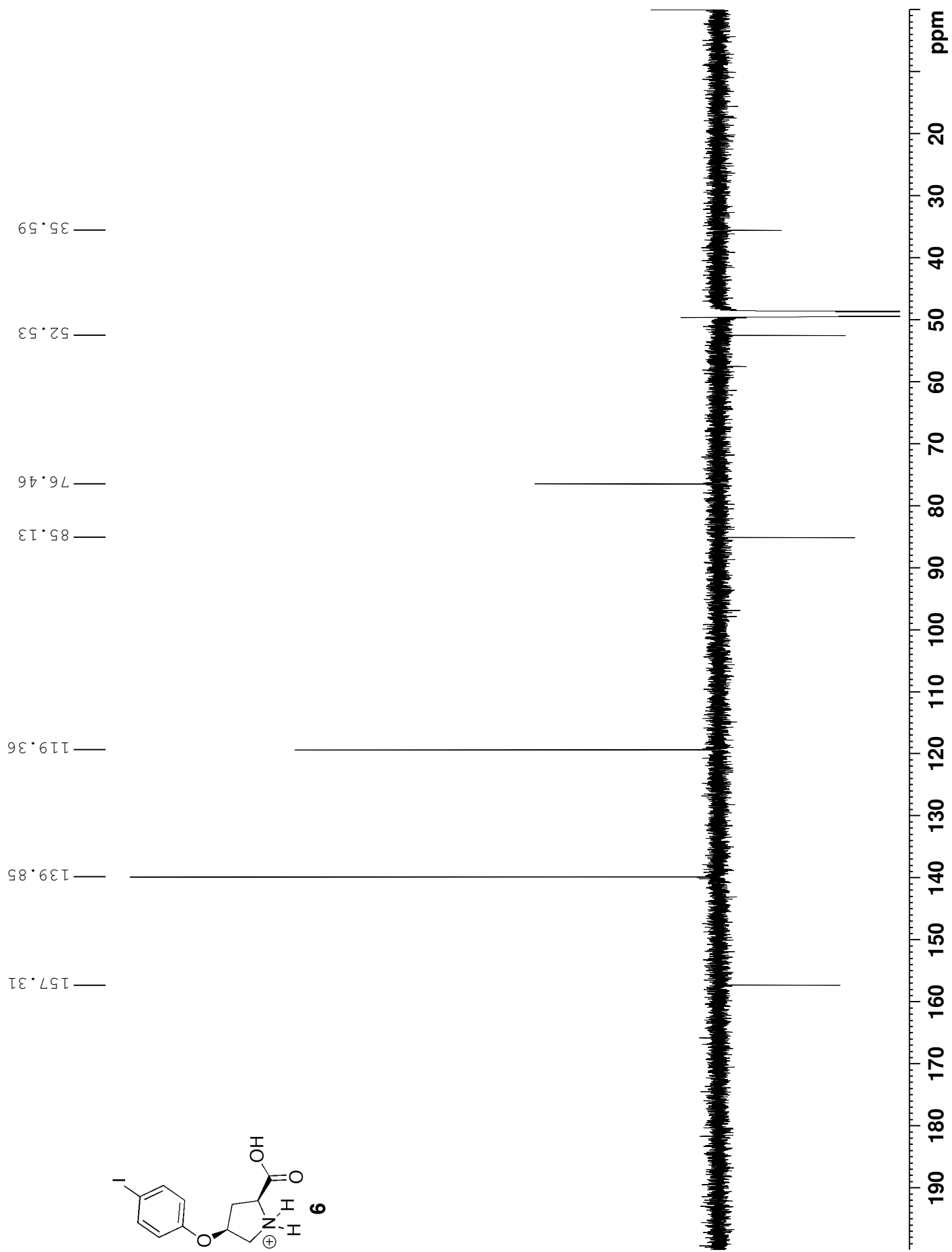


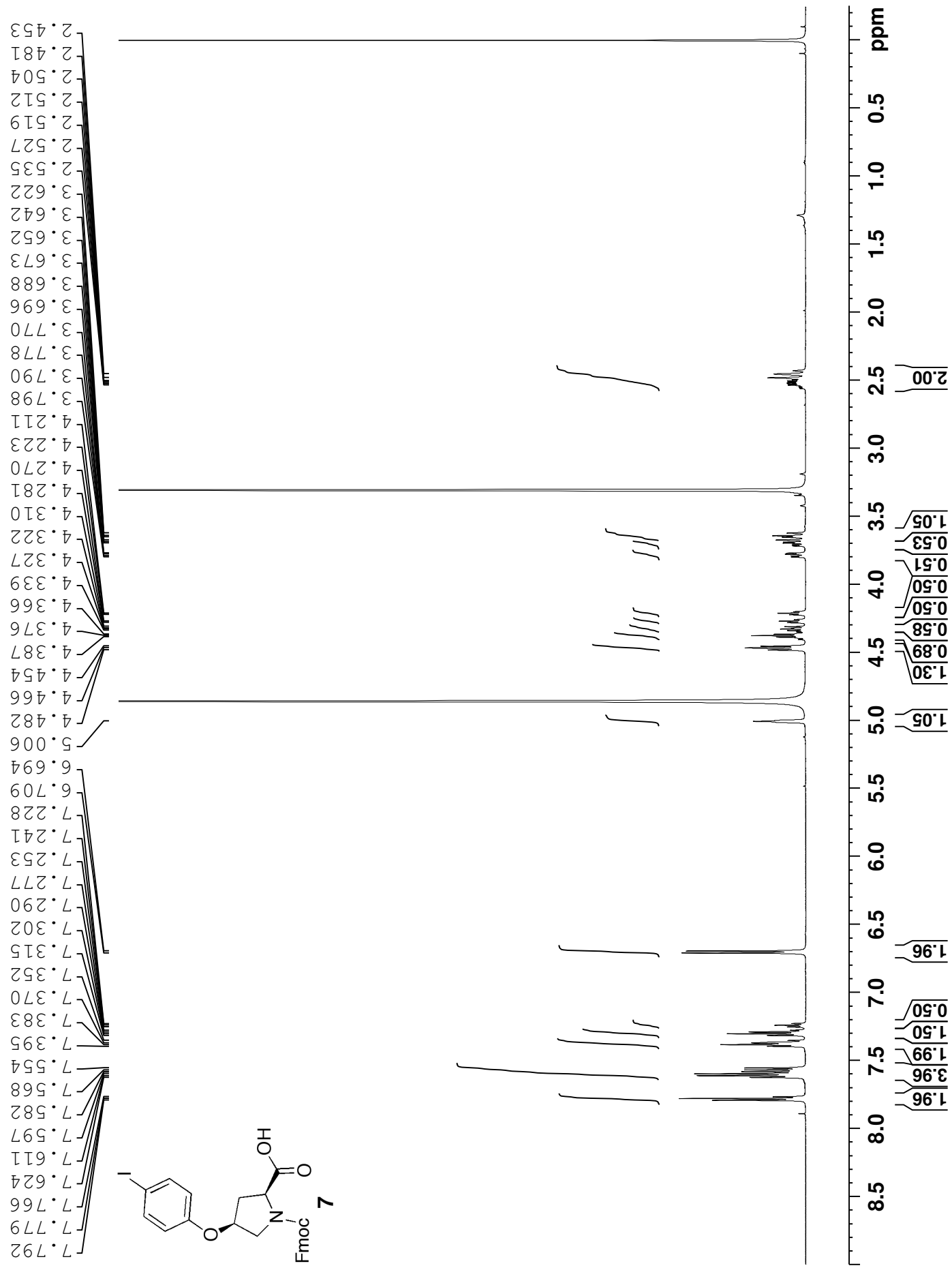


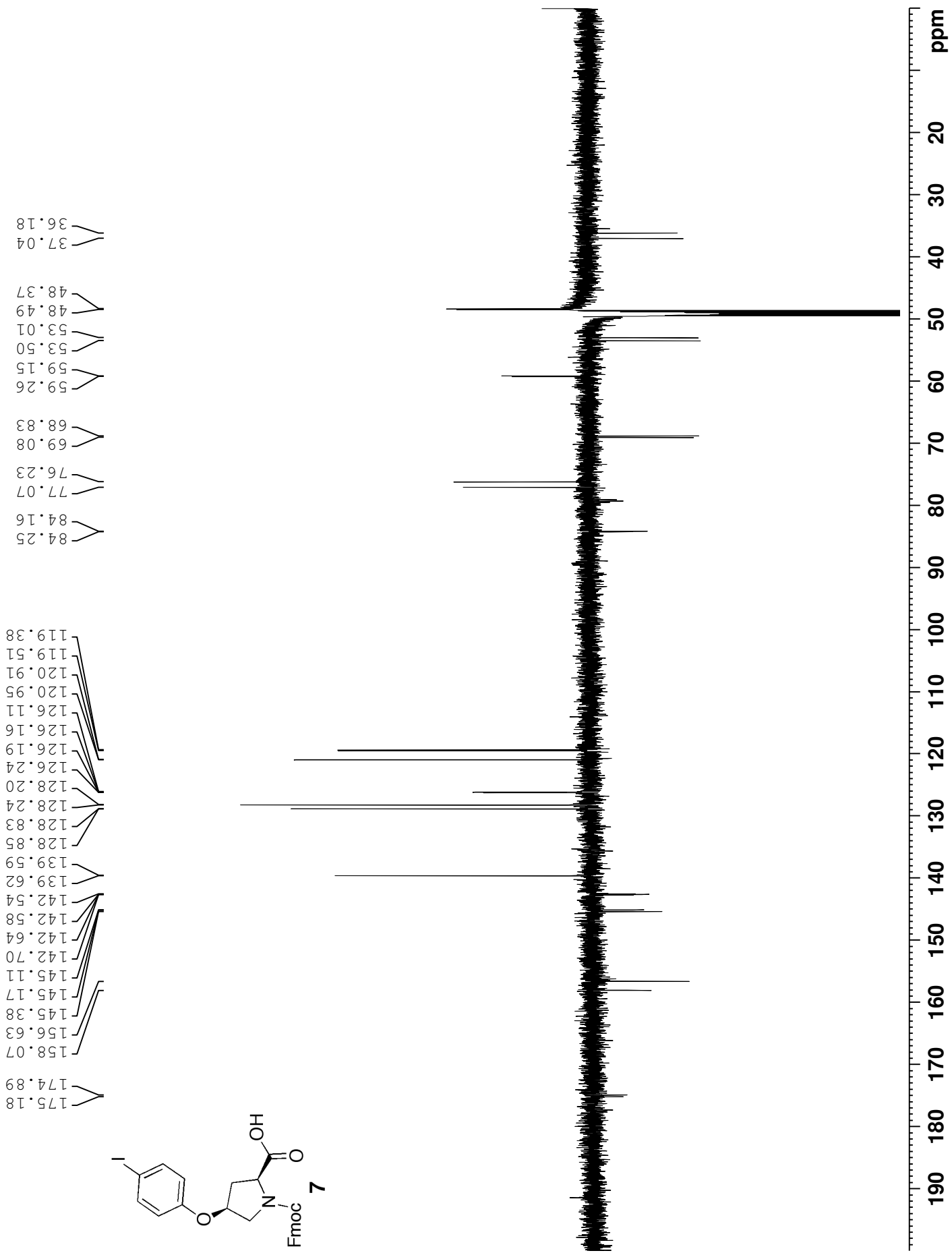


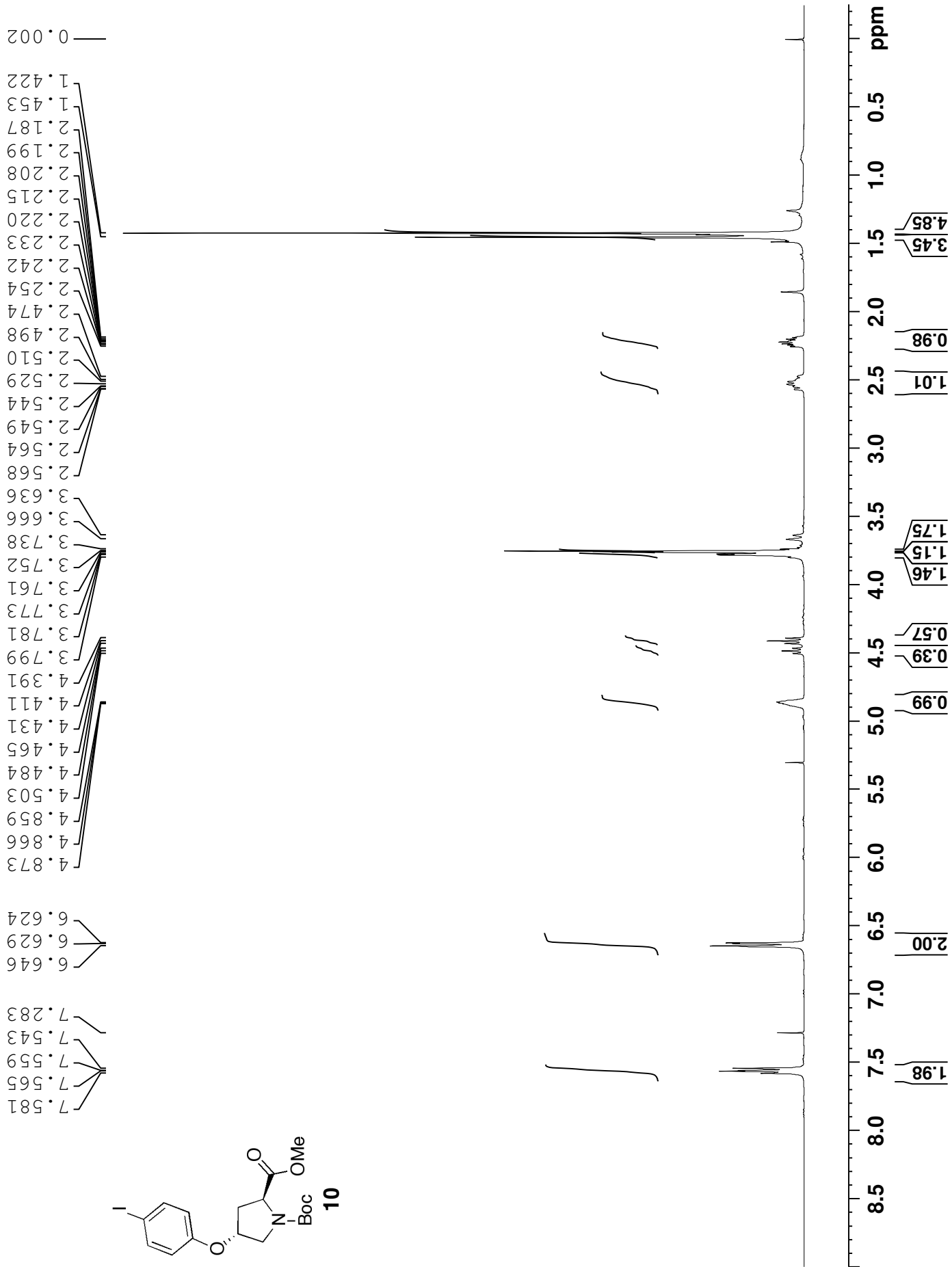
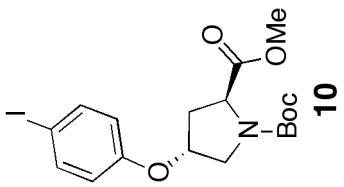


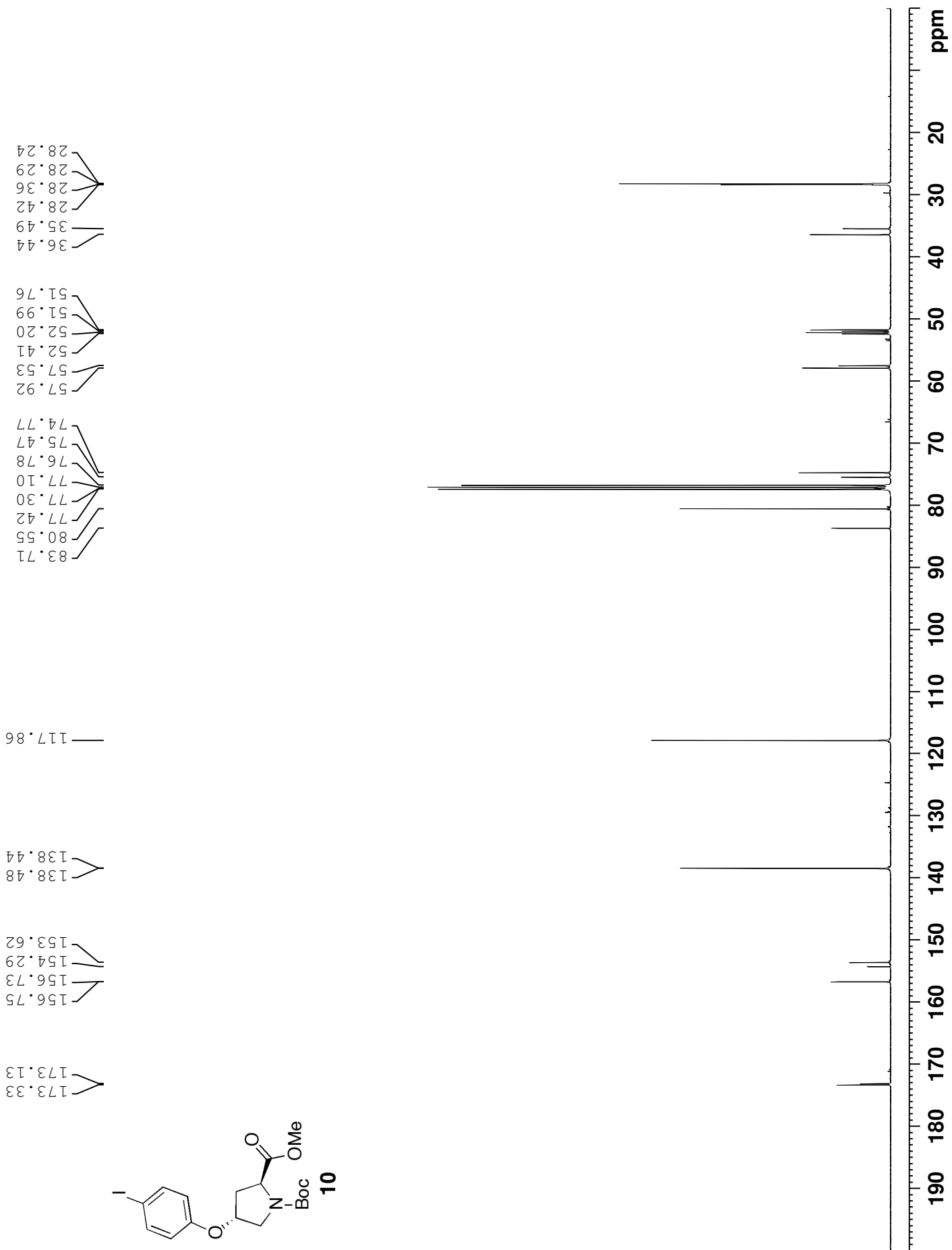


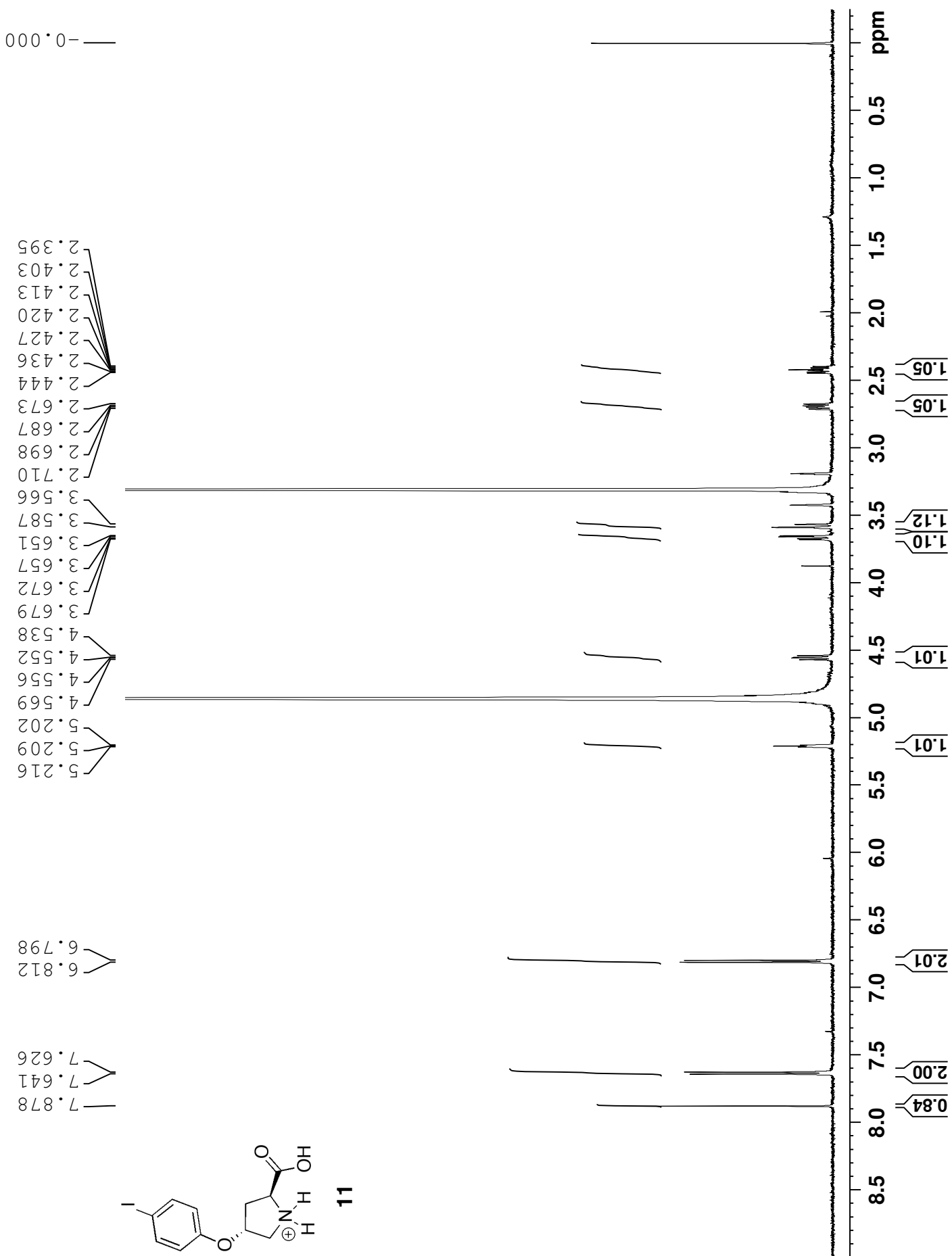


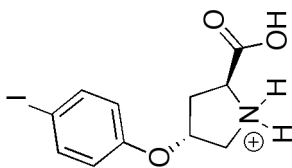
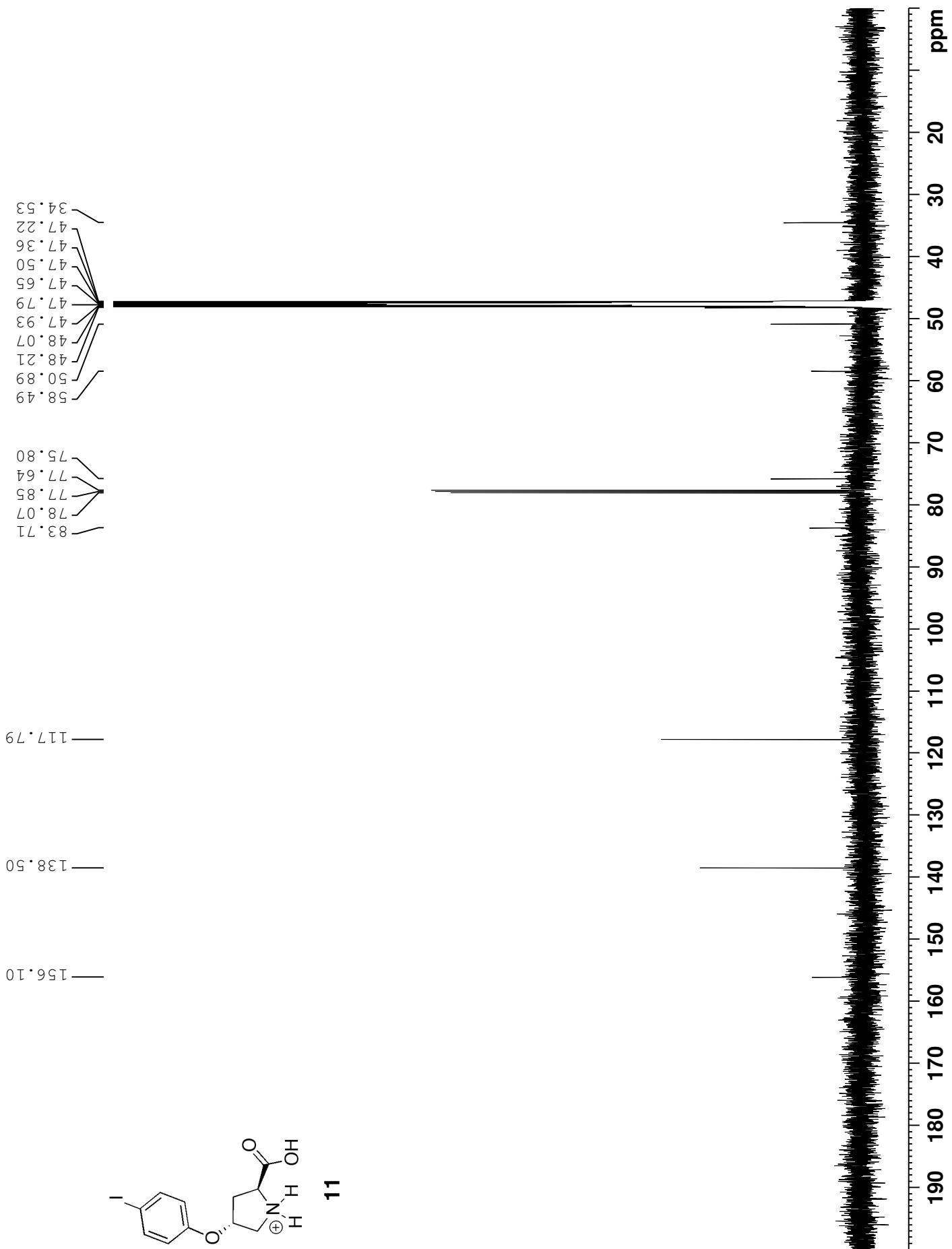




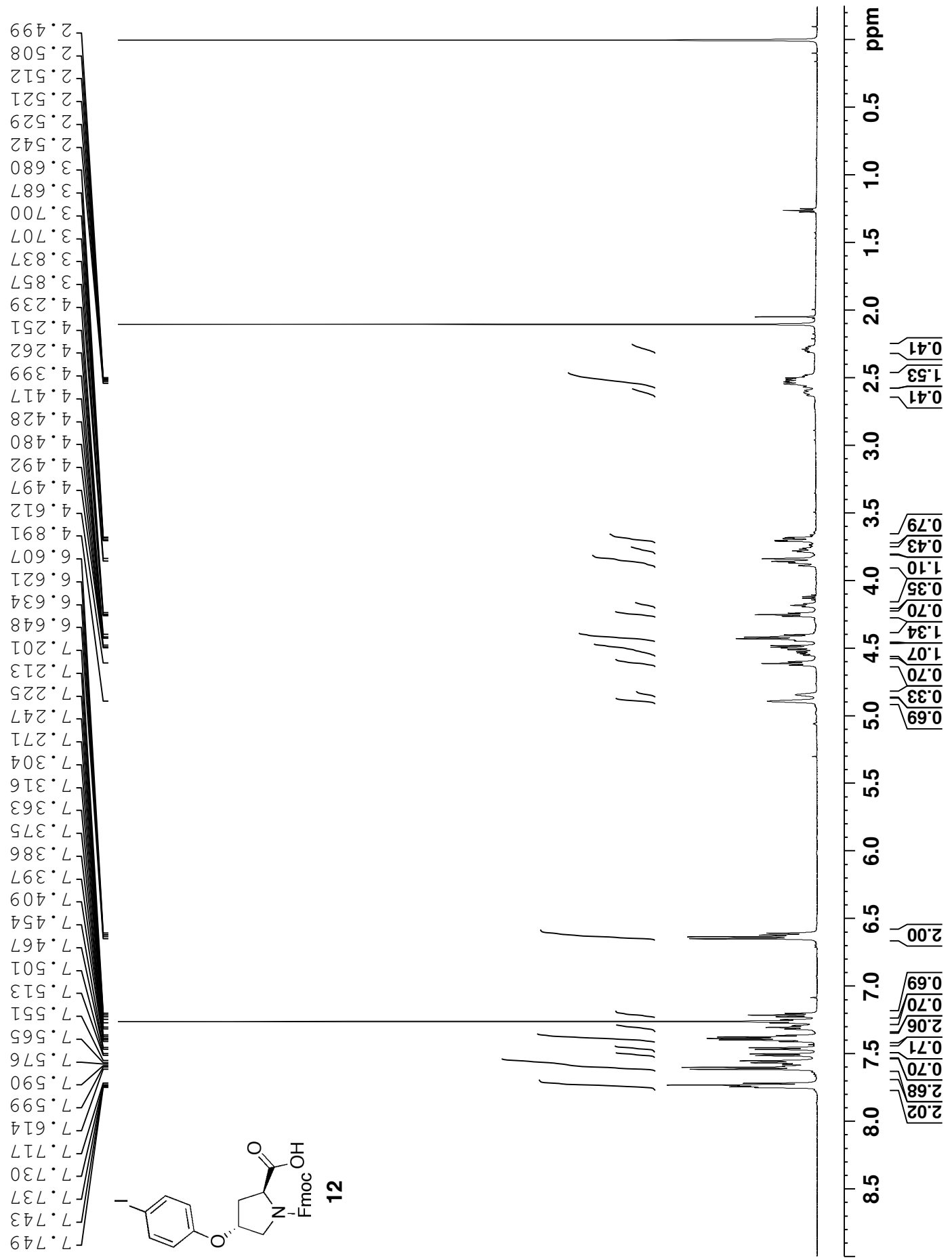


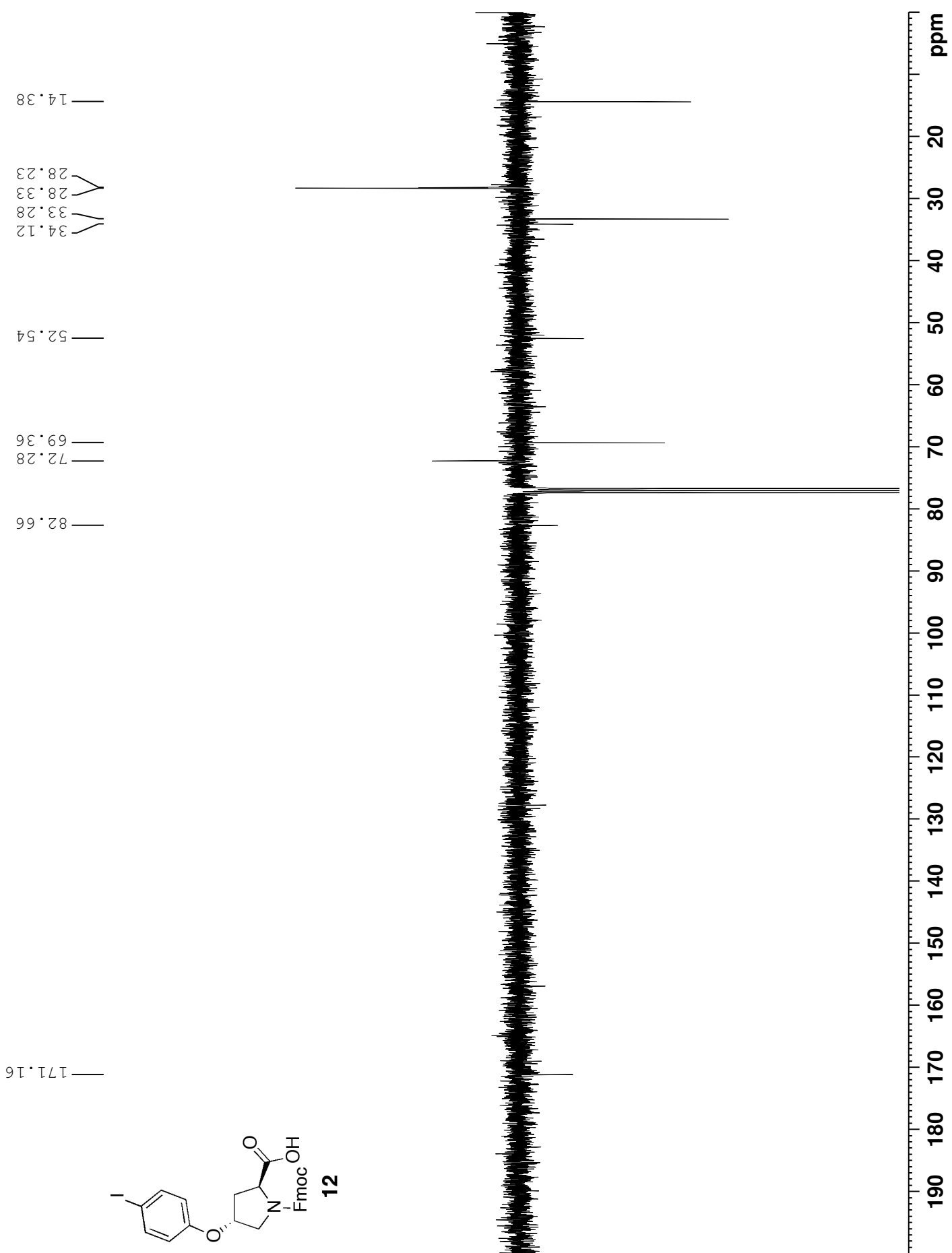
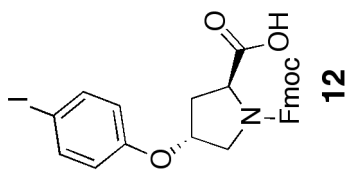


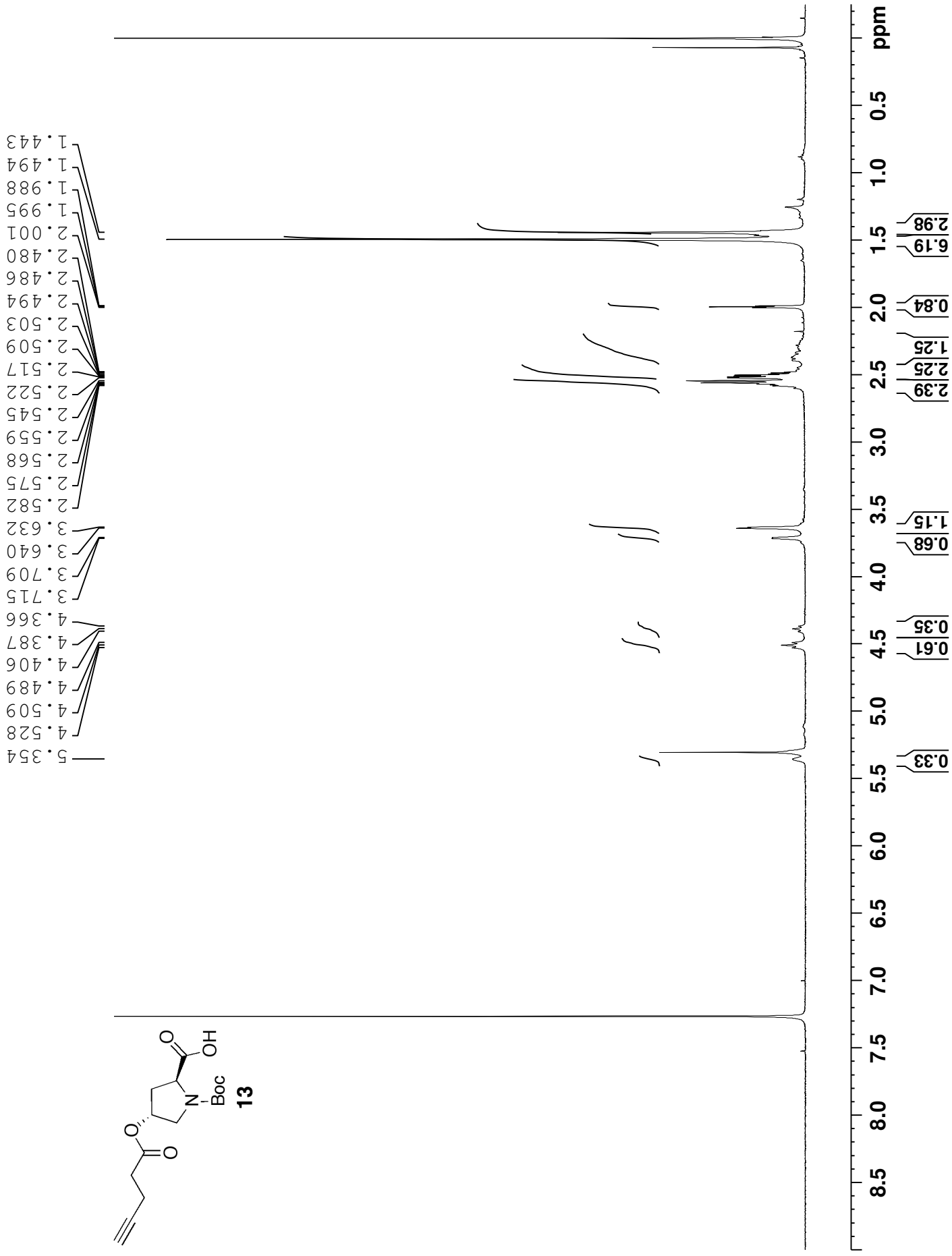
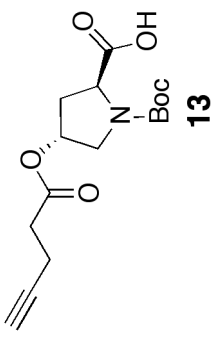


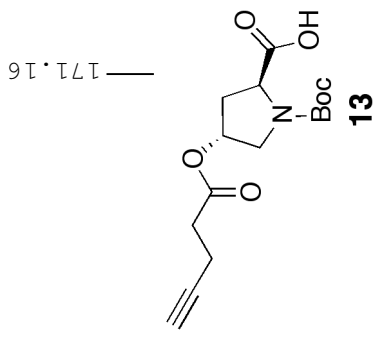


11









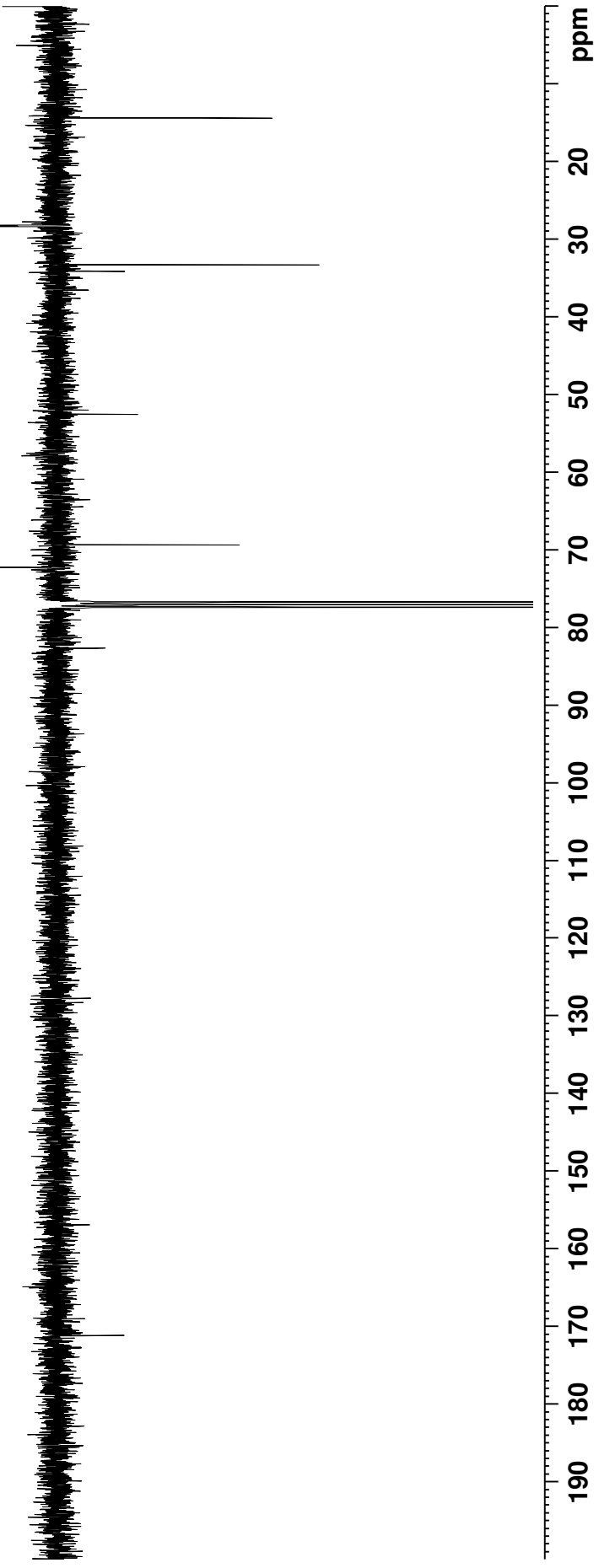
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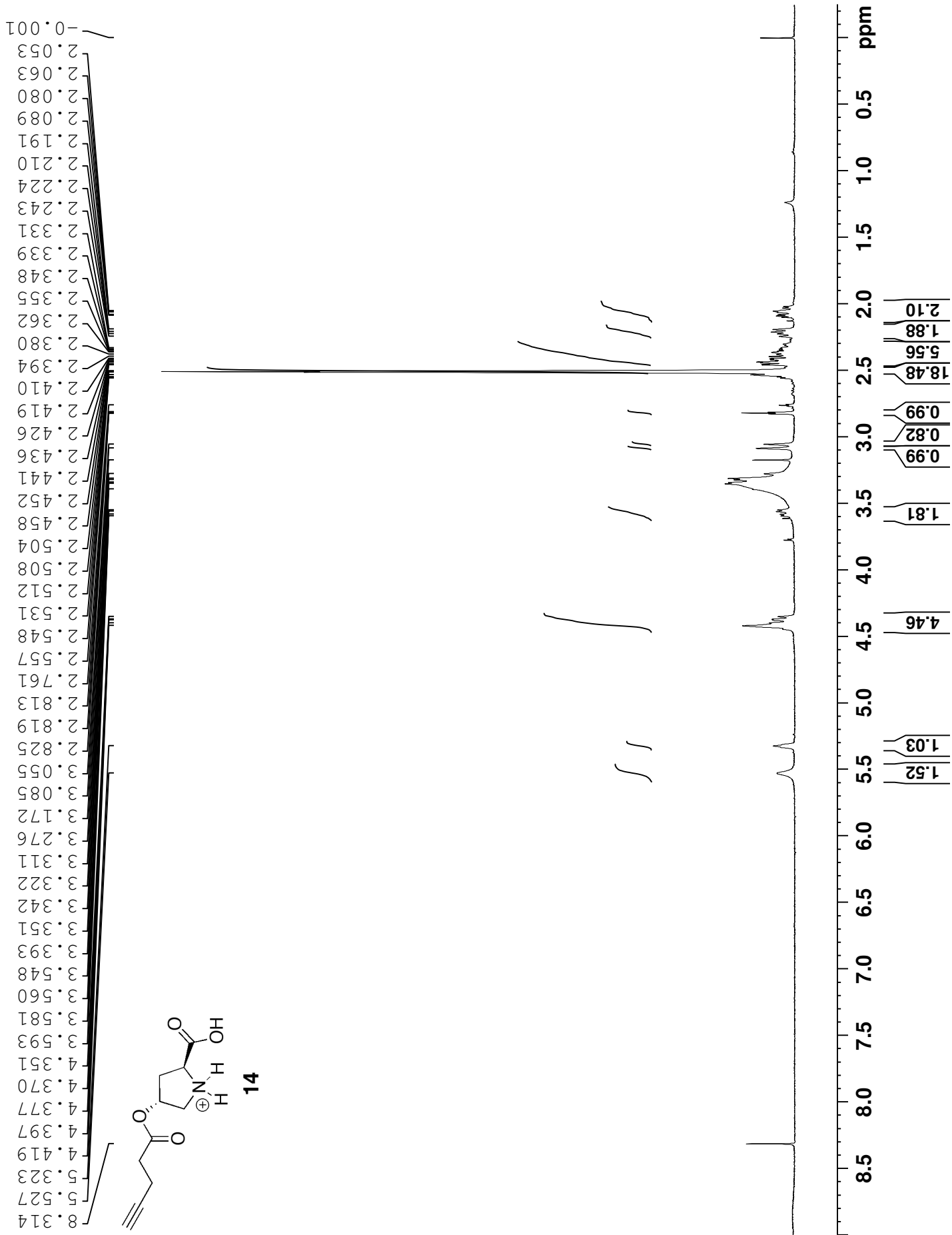
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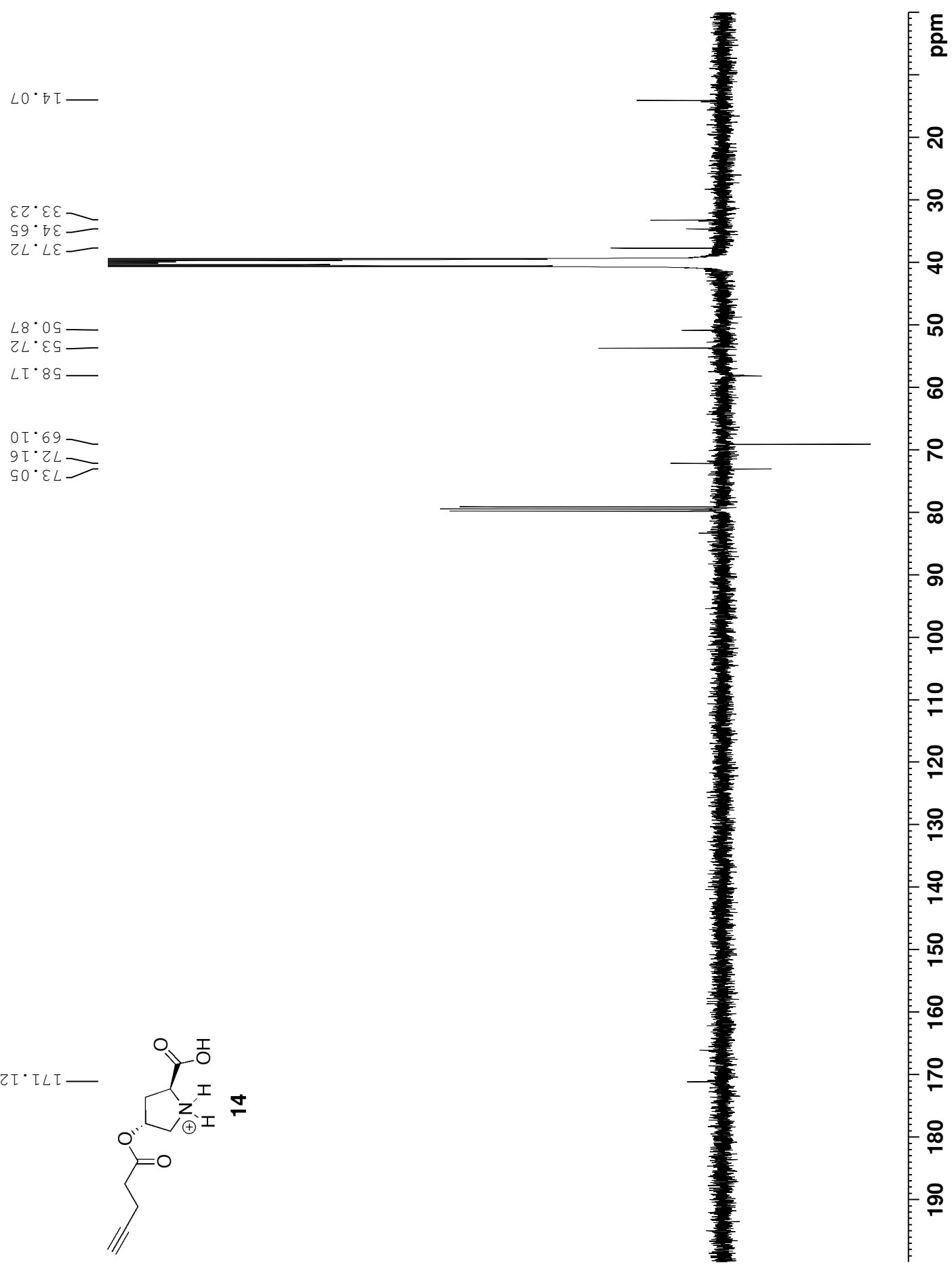
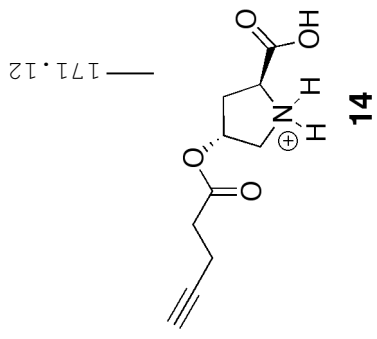
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— 69.36

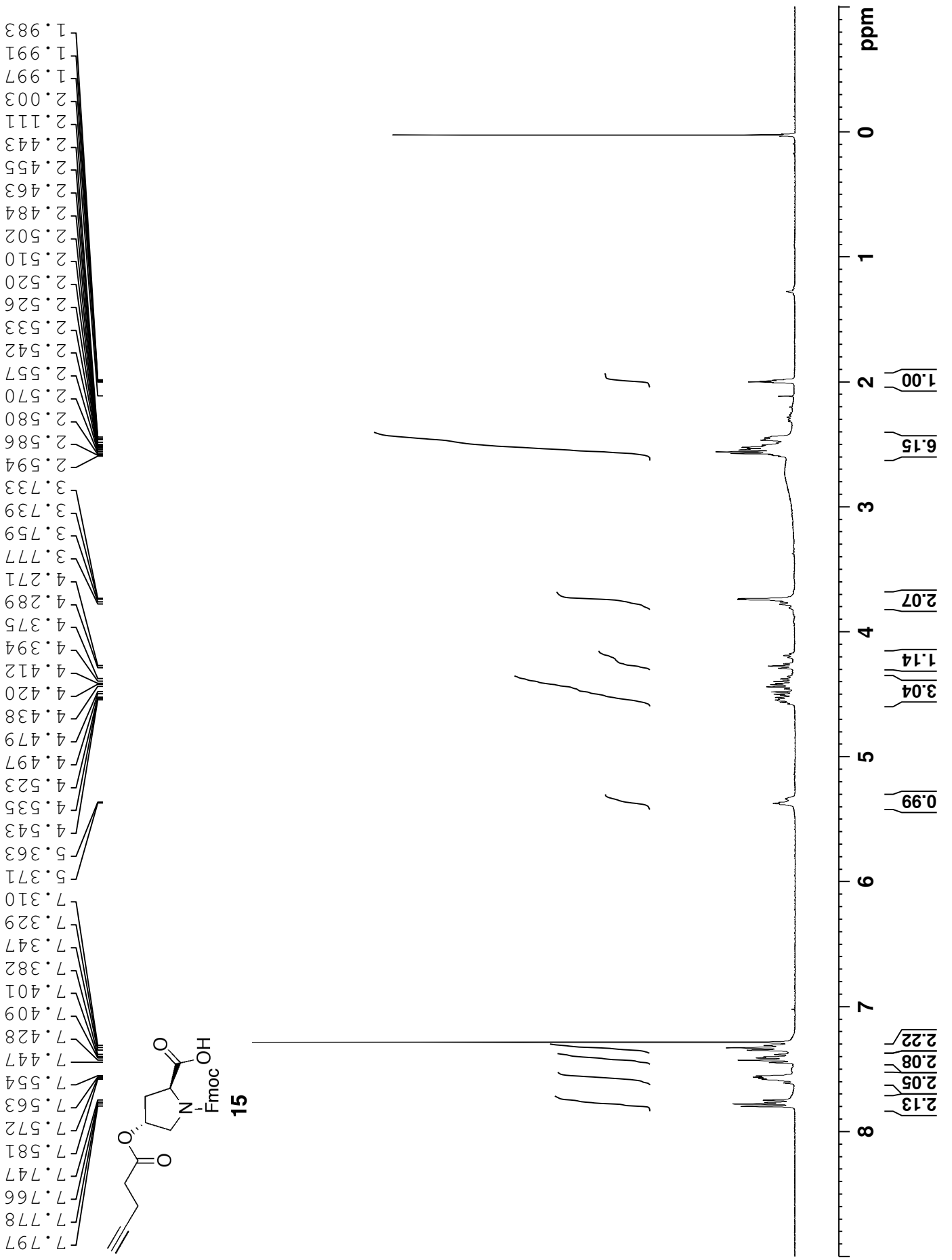
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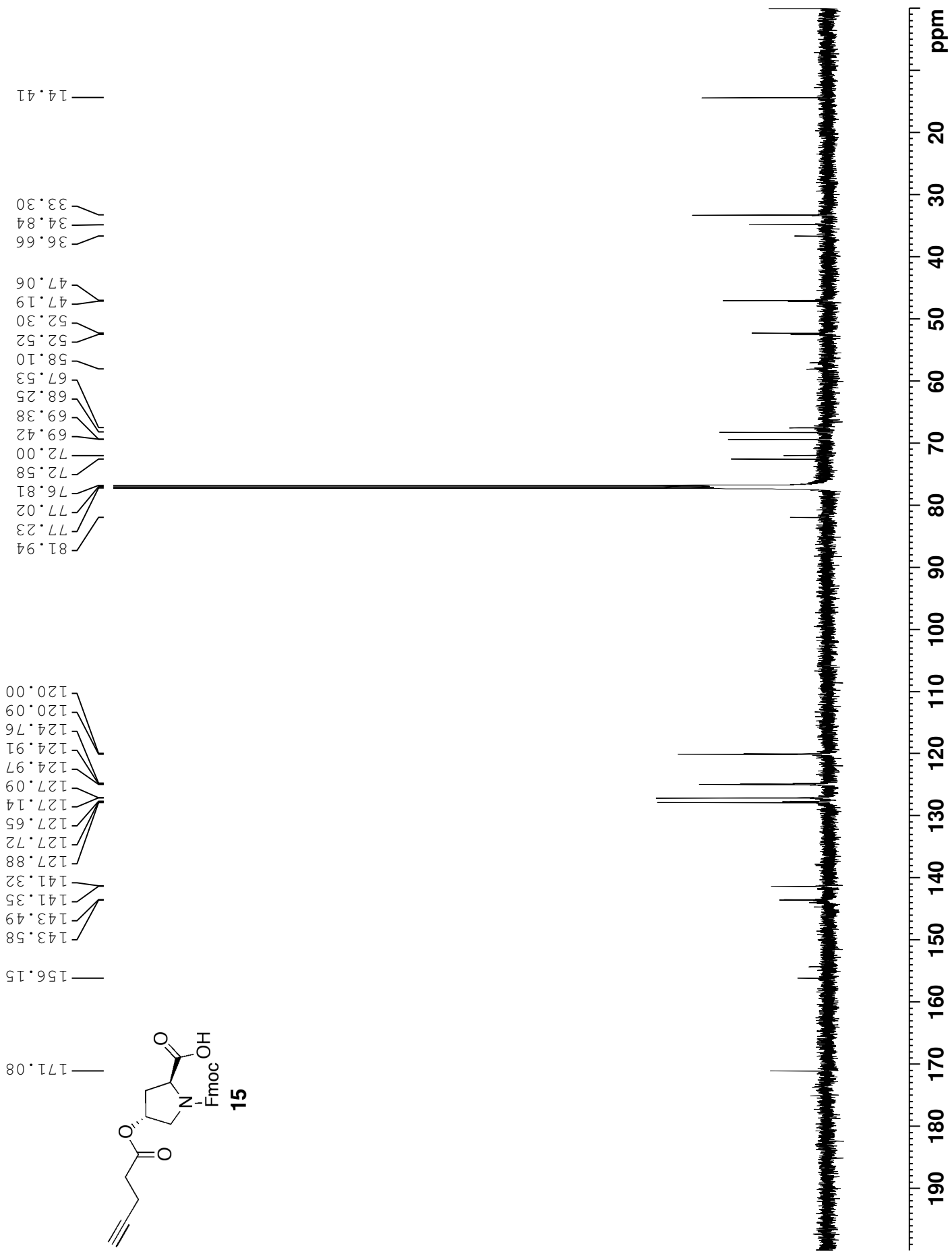
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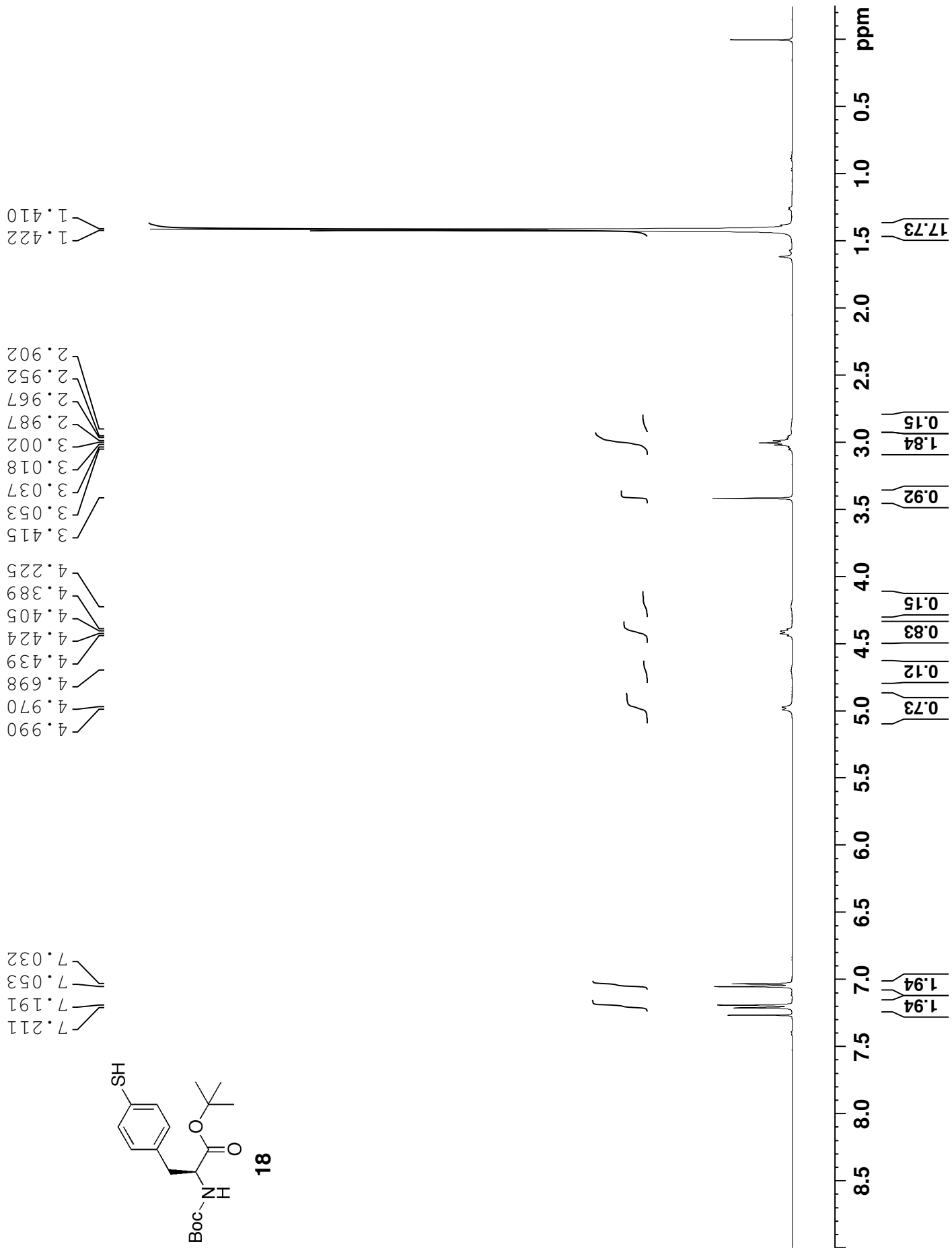


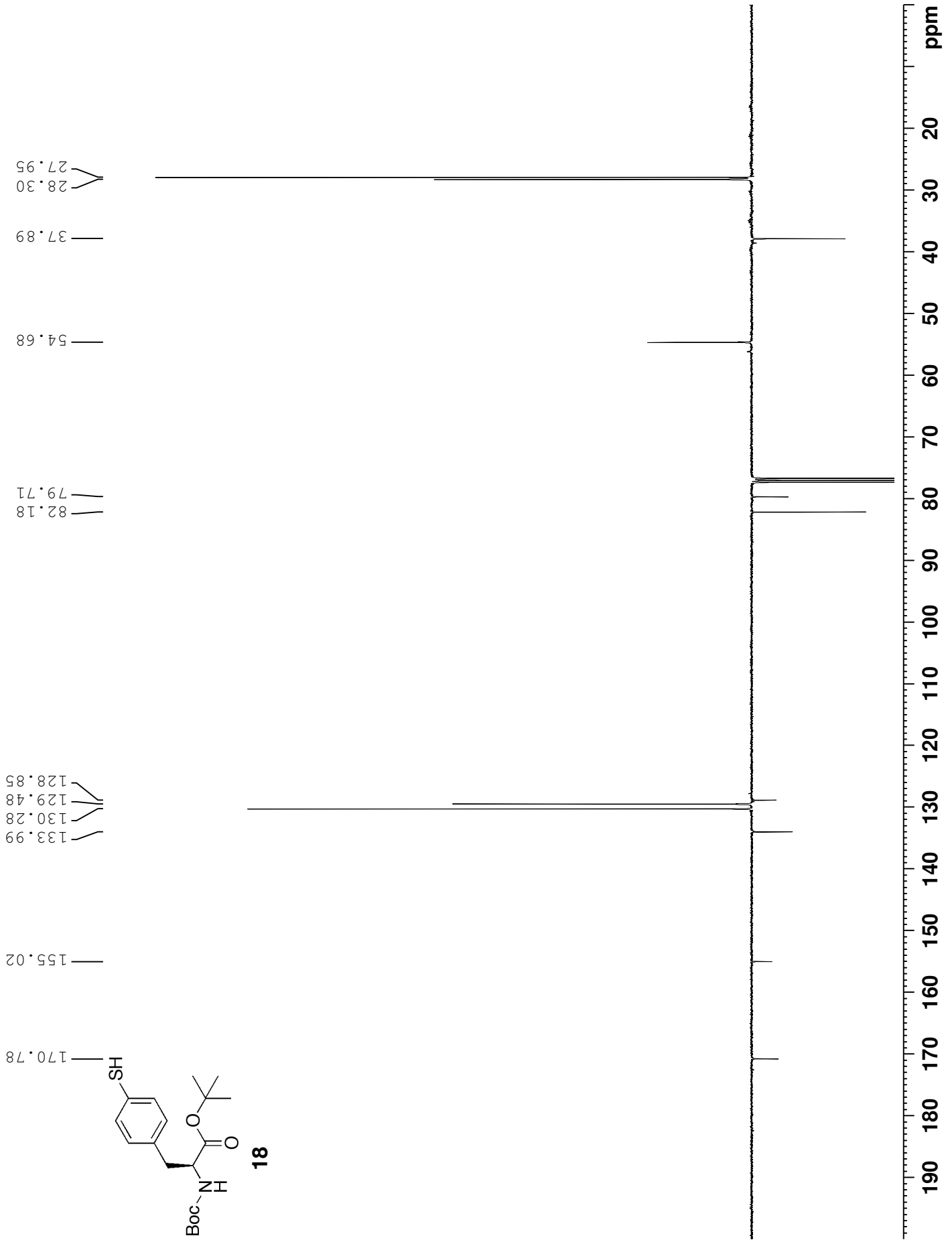


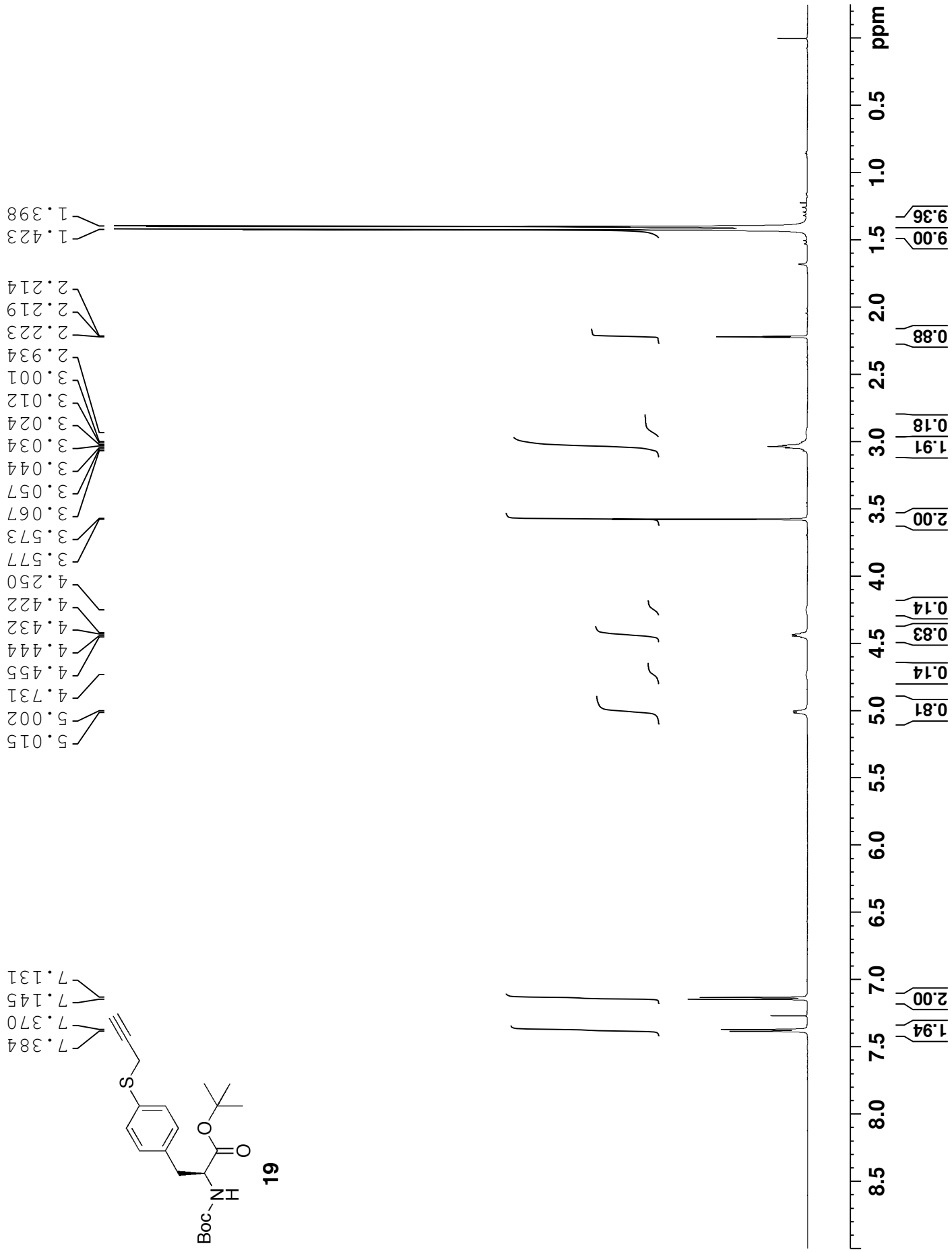


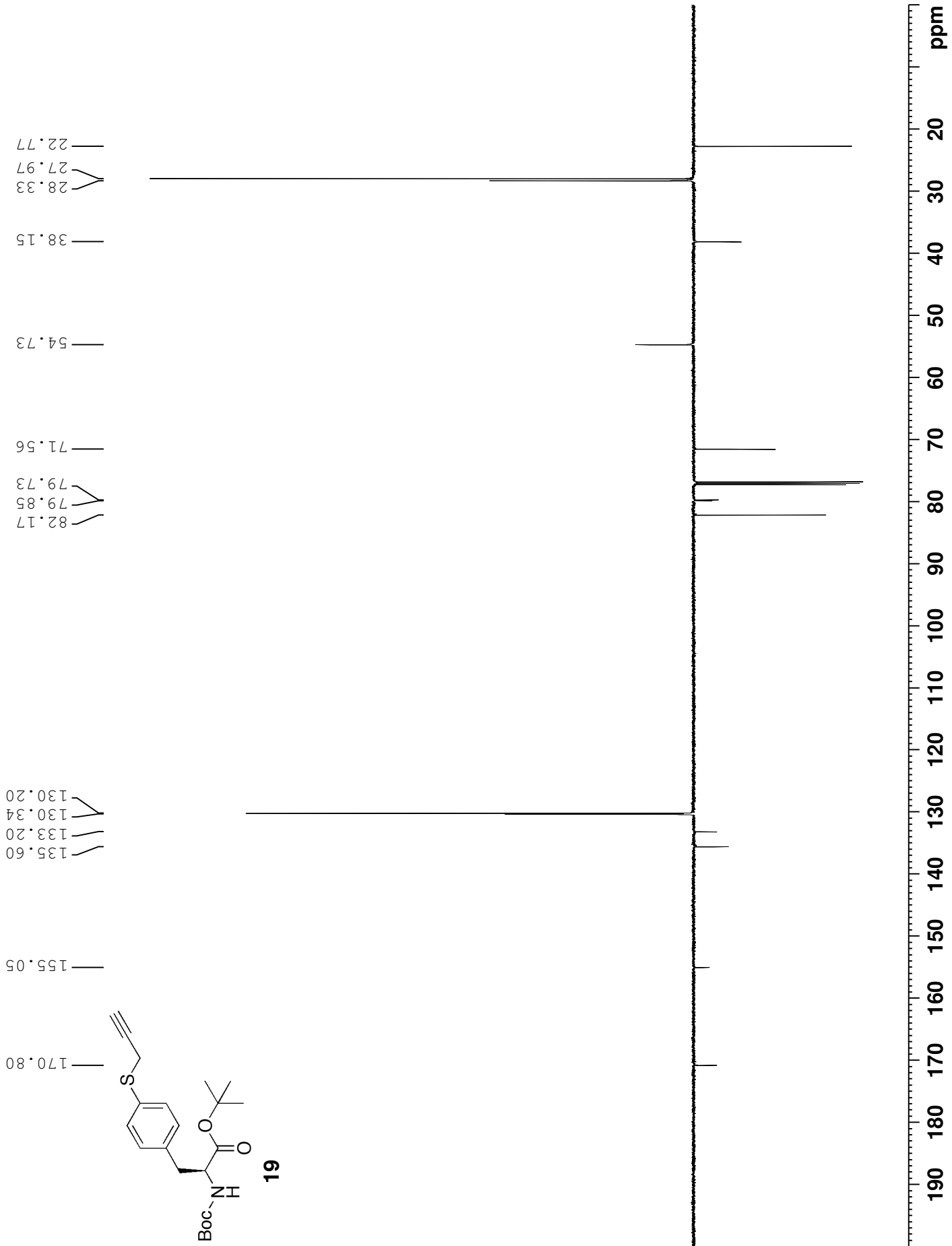


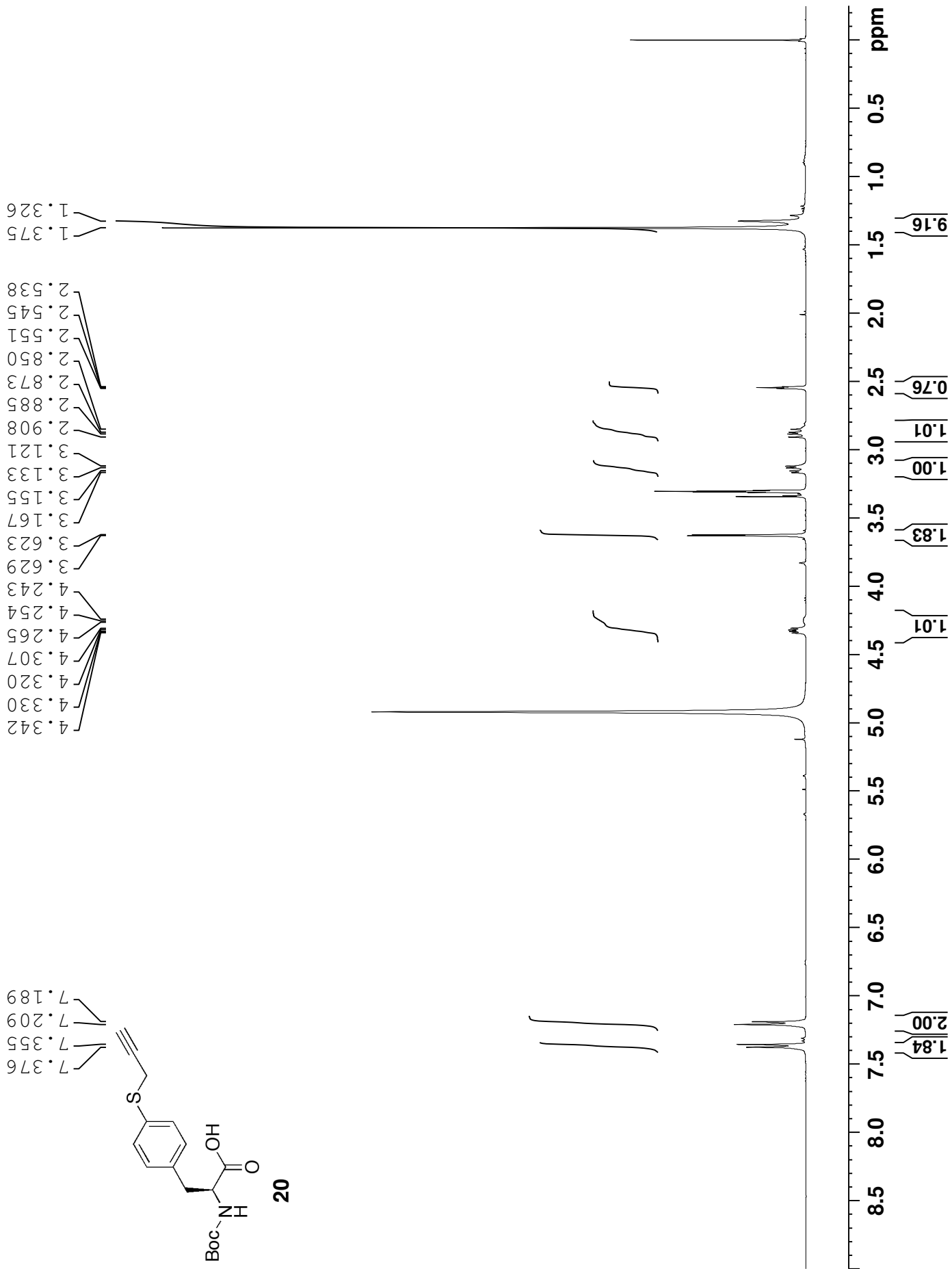


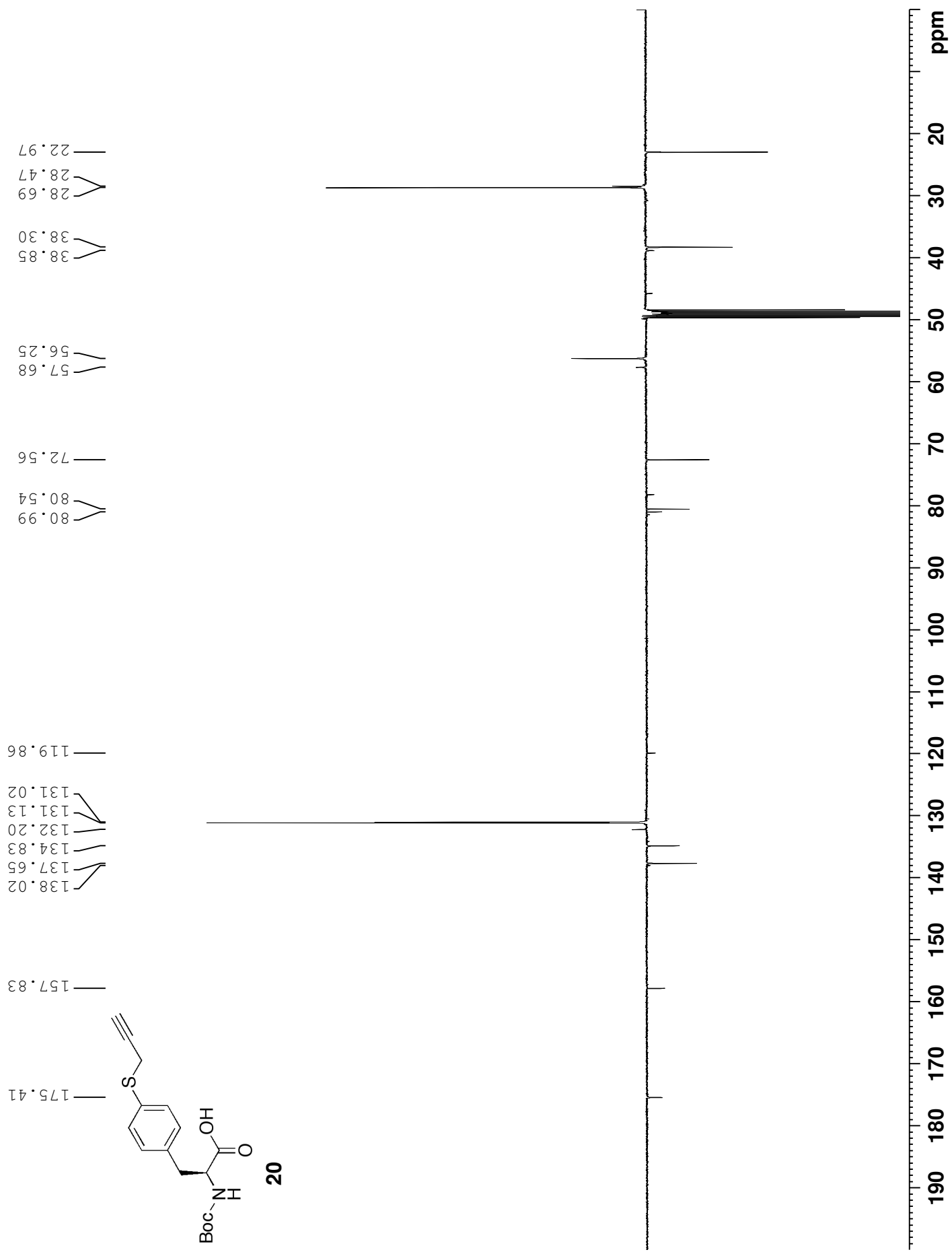


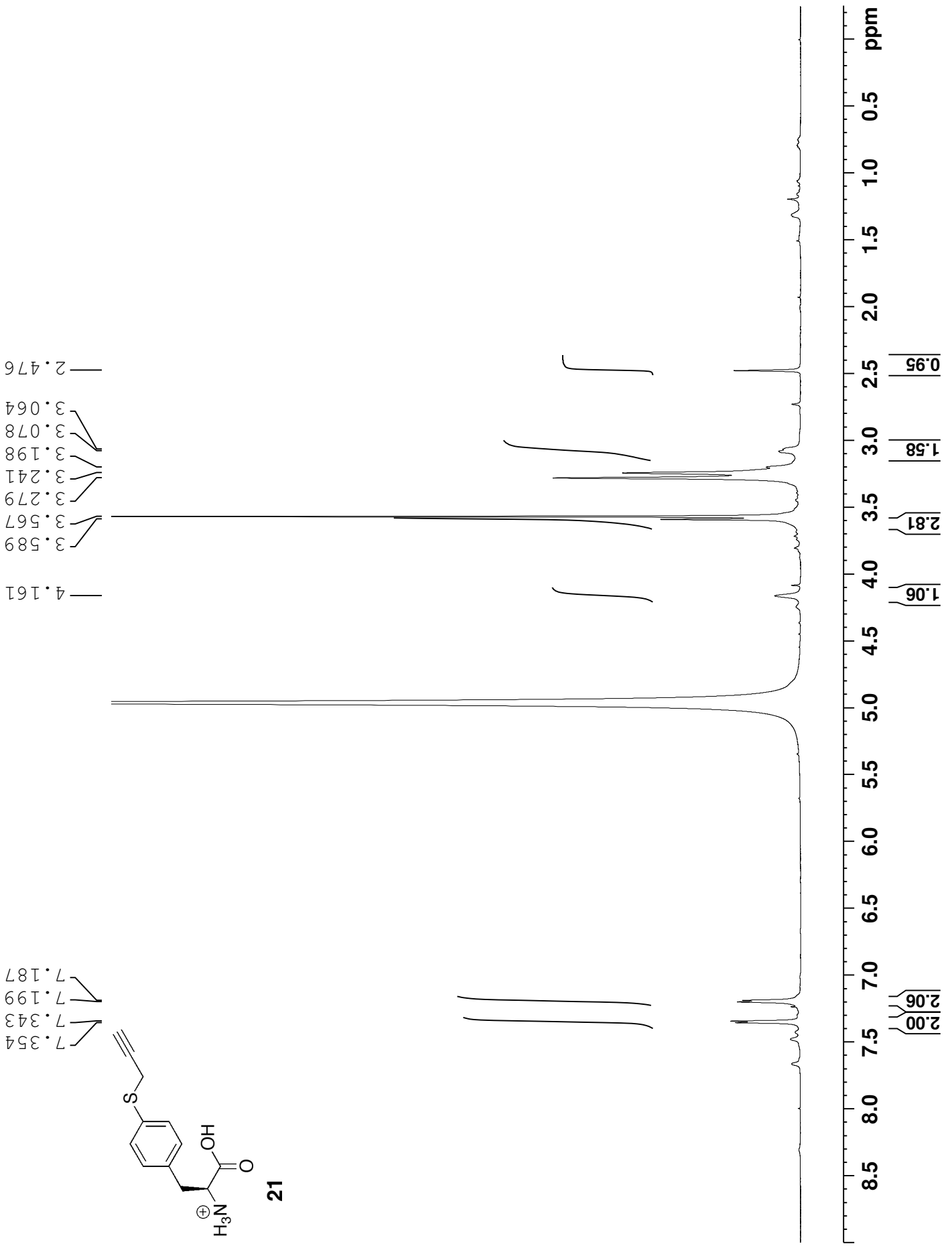


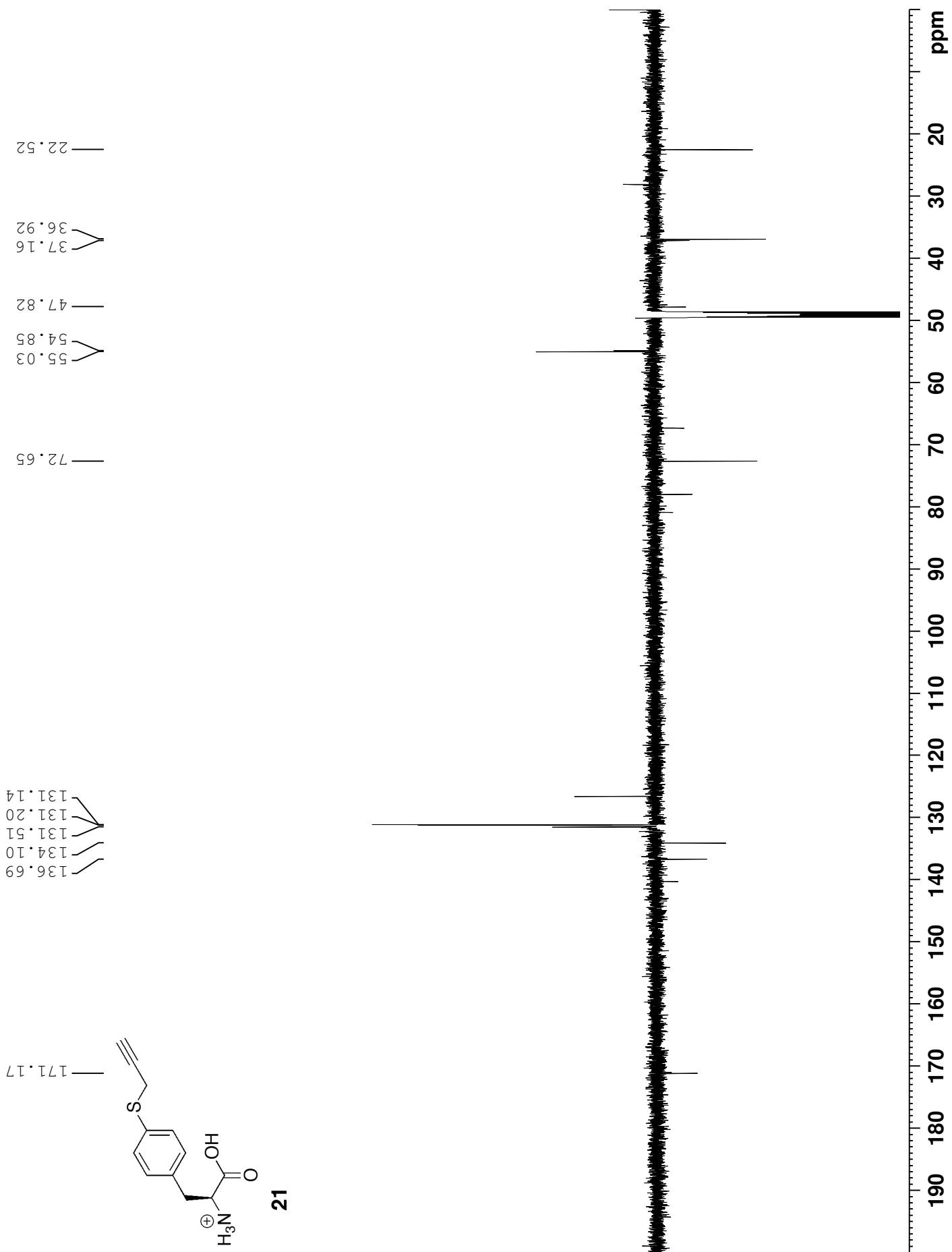


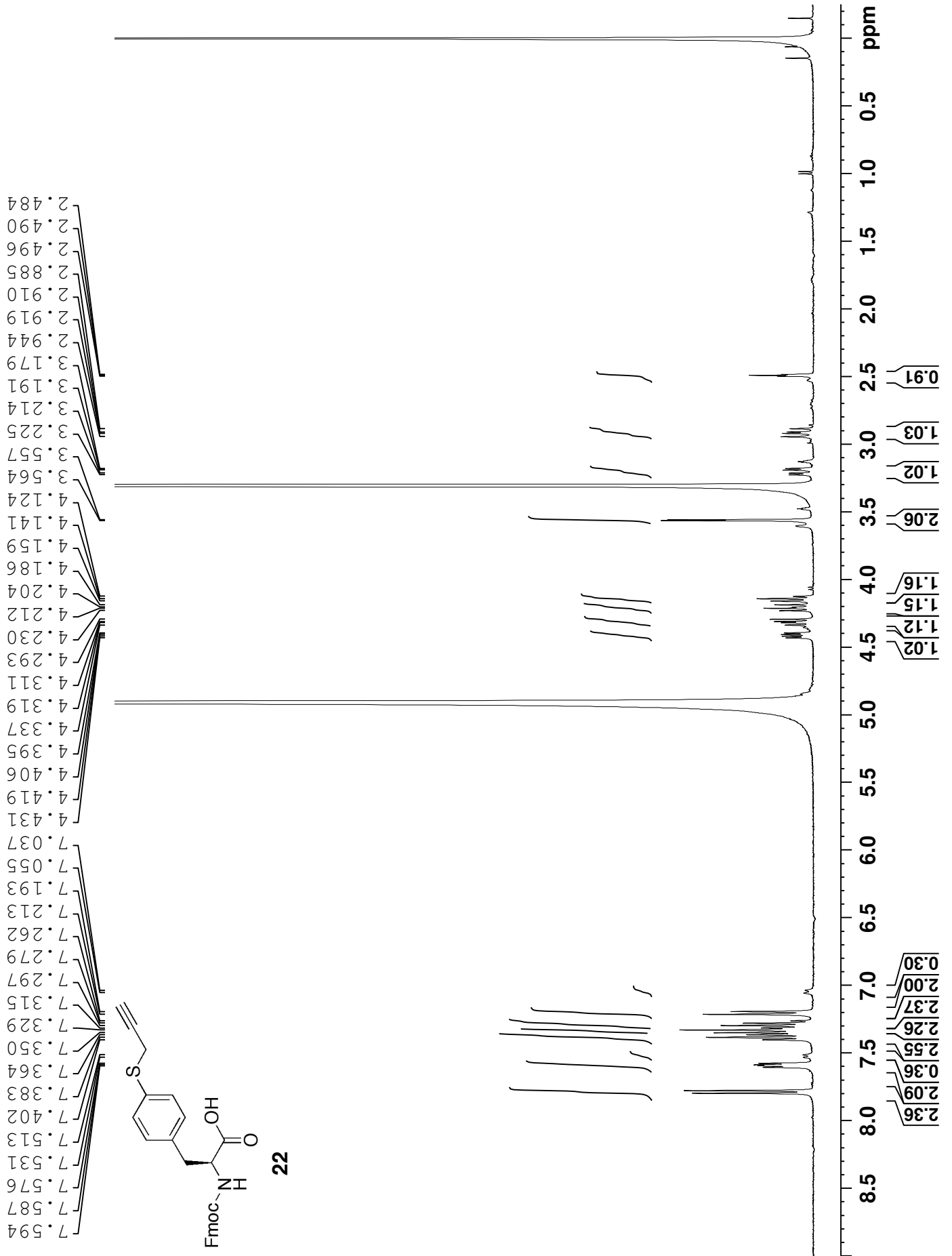


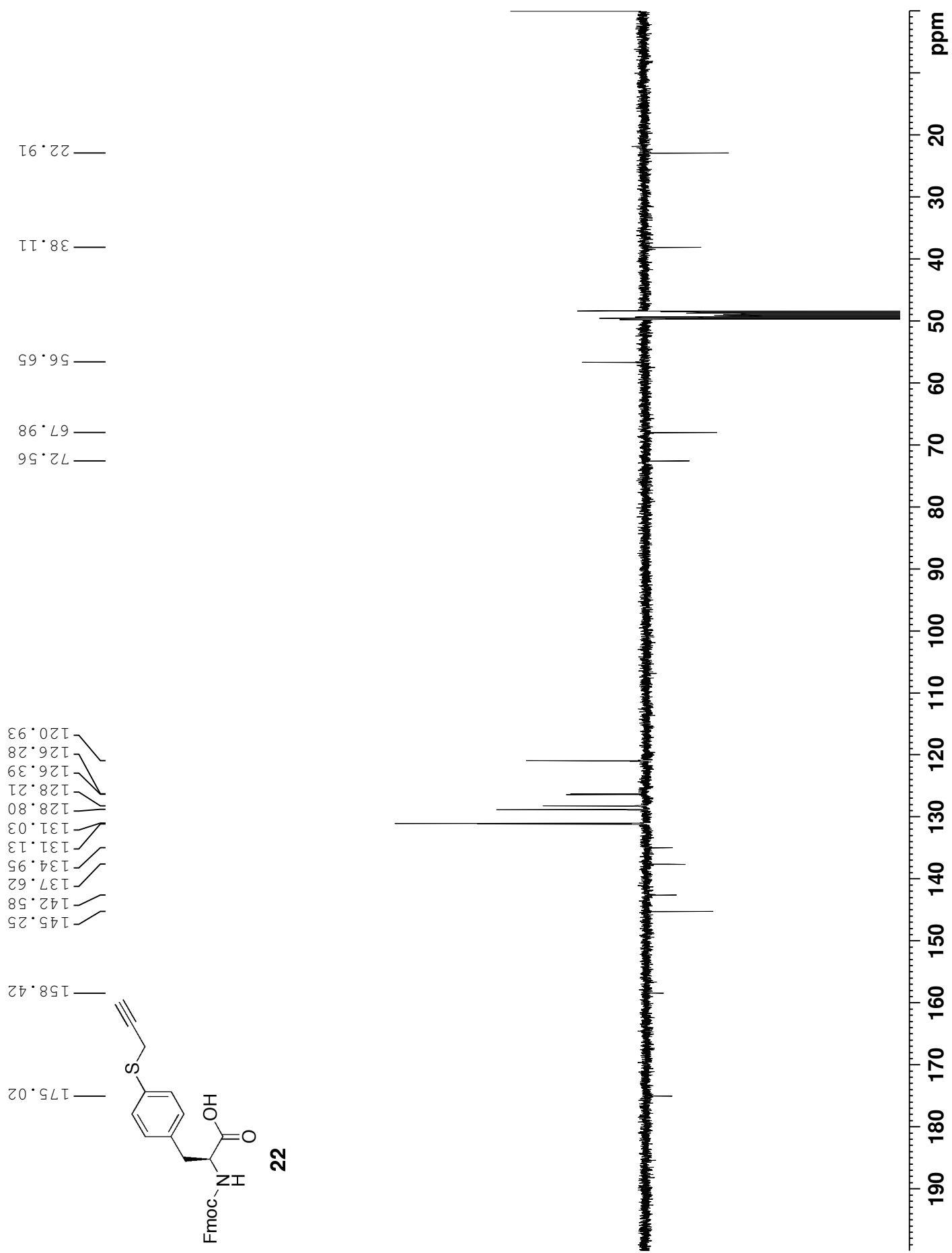


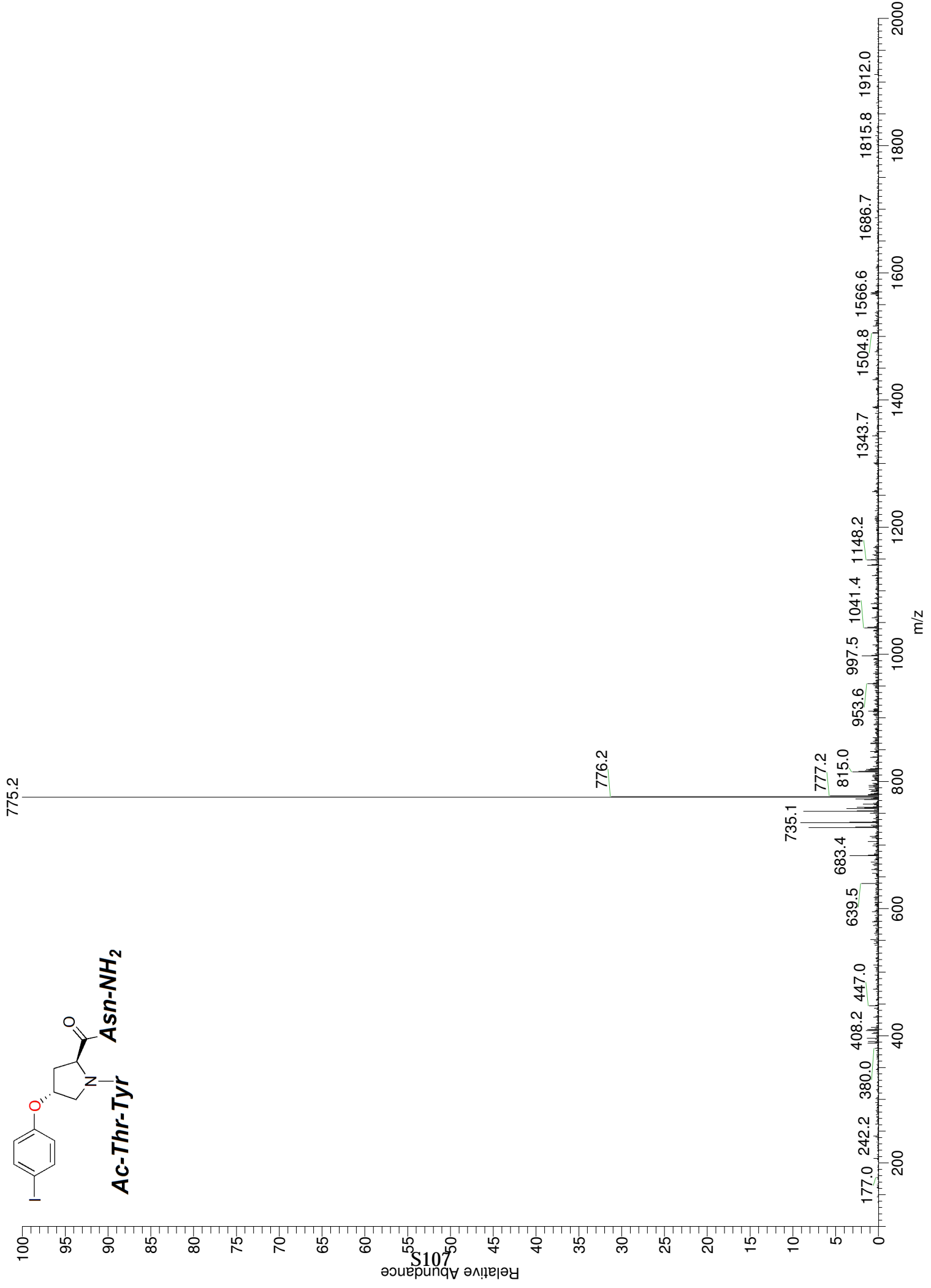
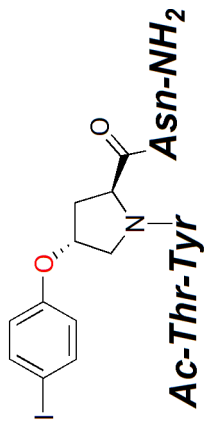




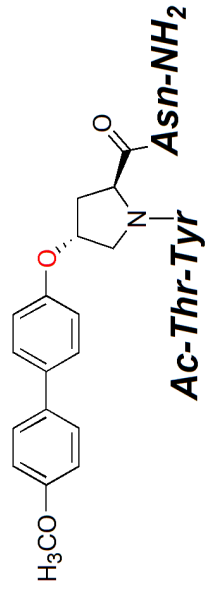








755.4



Relative Abundance

S108

756.4

733.1

757.3

430.9 491.4

599.5 715.9

838.6 891.0

1110.5

1246.1

1477.6

1616.6 1655.1

1806.4

1950.4

165.6 227.1 299.2 423.7

400

600

800

1000

1200

1400

1600

1800

2000

m/z

