
The Synthesis of Mycobactin Analogs and Heterocyclic Scaffolds From Acylnitroso Hetero-Diels-Alder Cycloadducts

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Publication Date

15-07-2008

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Citation for this work (American Psychological Association 7th edition)

Bodnar, B. S. (2008). *The Synthesis of Mycobactin Analogs and Heterocyclic Scaffolds From Acylnitroso Hetero-Diels-Alder Cycloadducts* (Version 1). University of Notre Dame. <https://doi.org/10.7274/2n49t15093d>

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THE SYNTHESIS OF MYCOBACTIN ANALOGS AND HETEROCYCLIC
SCAFFOLDS FROM ACYLNITROSO HETERO-DIELS-ALDER CYCLOADDUCTS

VOLUME II

A Dissertation

Submitted to the Graduate School
of the University of Notre Dame
in Partial Fulfillment of the Requirements
for the Degree of

Doctor of Philosophy

by

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Notre Dame, Indiana

July 2008

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CHAPTER 8:

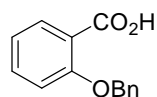
EXPERIMENTAL DATA

8.1 General comments

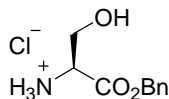
All chemicals purchased were reagent grade and used without purification unless noted otherwise. Dry CH_2Cl_2 , CH_3CN , and Et_3N were prepared by distillation from calcium hydride under Ar. Dry THF was prepared by distillation from sodium/benzophenone ketyl radical under Ar. Reactions were carried out under an inert atmosphere of argon only when specified in the experimental details, and were monitored by TLC as described in the experimental procedure using aluminum-backed 0.2 mm silica gel 60 F-254 plates. Visualization of TLC plates was performed under a UV lamp irradiating at 254 nm or by staining with CAM stain (Ceric Ammonium Molybdate stain, Hanessian's stain), ferric chloride stain, or ninhydrin stain. Column chromatography was conducted using silica gel 60 (230-400 mesh). All melting points were measured on a Thomas-Hoover Melting Apparatus and are uncorrected. All NMR spectra were recorded on a Varian 300 MHz or 500 MHz instrument under ambient temperatures unless otherwise noted. Chemical shift values for NMR spectra are reported as δ in ppm relative to the solvent residual peak or to an internal tetramethylsilane standard. Infrared spectra were recorded using an FT-IR spectrometer and are reported in cm^{-1} . Mass spectra were obtained as specified. Optical rotations were measured on a Rudolph Research Autopol III. Analytical LC/MS analyses were carried out on a Waters ZQ

instrument consisting of chromatography module Alliance HT, photodiode array detector 2996, and mass spectrometer Micromass ZQ, using a 3 x 50 mm Pro C18 YMC reverse phase column (Waters). Compounds were eluted using a gradient of 5-80% CH₃CN in 10 mM ammonium acetate over 10 min at a flow rate of 0.7 mL/min. The MS electrospray source was operated at capillary voltage 3.5 kV and a desolvation temperature of 300 °C.

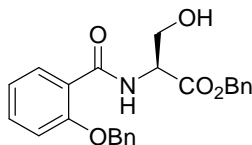
8.2 Experimental procedures for chapter 3



2-Benzyloxy-benzoic acid (3.2). Methyl salicylate (5.87 g, 5.0 mL, 38.6 mmol) was added to K₂CO₃ (15.38 g, 111.3 mmol) and CH₃CN (150 mL) at 20°C. The reaction was stirred at 60°C overnight. The reaction was filtered and concentrated to yield a clear oil. 10% aqueous KOH was added to the oil (65 mL) and the reaction was heated to 100°C for 2.5 h. The mixture was washed with CH₂Cl₂ (2 x 100 mL), and acidified to an apparent pH of 2 using 1M HCl. The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined EtOAc layers were washed with H₂O (2 x 100 mL) and brine (2 x 100 mL). The EtOAc was dried over Na₂SO₄, filtered, and concentrated to yield a white solid that was recrystallized from MeOH (8.54 g, 97%). mp 74-75°C; ¹H NMR (300 MHz, CDCl₃) δ 5.31 (s, 2H), 7.12-7.20 (m, 2H), 7.40-7.48 (m, 5H), 7.57 (ddd, *J* = 1.8, 7.5, 8.1 Hz, 1H), 8.22 (dd, *J* = 1.8, 7.8 Hz, 1H) ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd, 229.0865; obsd, 229.0841.



***L*-Serine benzyl ester hydrochloride (3.4).** A 1-L round-bottomed flask was charged with Boc-*L*-serine (10.08 g, 49.11 mmol) and K₂CO₃ (8.86 g, 64.1 mmol). DMF (400 mL) was added and the mixture was stirred under a stream of Ar for a few min. Benzyl bromide (6.20 mL, 52.2 mmol) was added to the reaction and the mixture was stirred vigorously at RT under Ar. After stirring overnight, the white solid was removed by vacuum filtration and washed with 200 mL of DMF. The filtrate was concentrated under vacuum and the residue was partitioned between H₂O (100 mL) and EtOAc (200 mL). The layers were separated and the organic layer was washed with saturated NaHCO₃ (3 x 100 mL) and brine (2 x 100 mL), dried over Na₂SO₄, filtered, and concentrated under vacuum to yield a yellow oil (14.159 g, 98% crude). The crude material was dissolved in 500 mL of anhydrous ether in a 1-L round-bottomed flask. The solution was cooled in an ice/H₂O bath to 4°C. Freshly prepared dry HCl gas was bubbled through the solution for 2h. (HCl gas was prepared by adding conc. HCl dropwise to anhydrous CaCl₂, and the gas was then dried by bubbling through conc. H₂SO₄). The solution had turned opaque and the HCl gas flow was ceased. The opaque solution was stirred (with the attached septum) at RT overnight. The white solid was collected by vacuum filtration to yield only ~4 g (~35% yield). The filtrate was left to stand overnight to precipitate out more solid. A second crop of solid was collected to yield additional white solid. Compound **3.4** was isolated as a white solid (9.8439 g, 86.5% yield from Boc-serine).

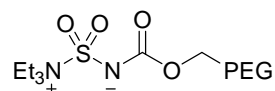


(S)-Benzyl 2-(2-(benzyloxy)benzamido)-3-hydroxypropanoate (3.5) using EDC-mediated amide coupling. Dichloromethane (160 mL) was added to **3.4** (6.83 g, 29.5 mmol) and **3.2** (8.11 g, 35.5 mmol) under Ar. Et₃N (4.80 mL, 34.5 mmol) was added followed by EDC•HCl (6.57 g, 34.3 mmol), and the mixture was stirred at rt overnight under Ar. The mixture was washed with H₂O (3 x 100 mL), saturated NaHCO₃ (3 x 100 mL), 5% aqueous citric acid (3 x 100 mL), and brine (3 x 100 mL), dried over MgSO₄, filtered, and concentrated to yield a white solid (11.2 g, 93.3% yield).

Compound 3.5 from the acid chloride. Compound **3.2** (13.21 g, 56.72 mmol) was dissolved in 150 mL of anhydrous CH₂Cl₂ in a 500-mL round-bottomed flask. Oxalyl chloride (9.95 mL, 114 mmol) was added to the colorless solution slowly, followed by a catalytic amount of anhydrous DMF (0.10 mL, 1.3 mmol). The light yellow solution bubbled profusely and was stirred at RT under Ar. Bubbling ceased after ~2h, and the reaction became yellow in color. After 4h, the reaction was concentrated under vacuum, then dissolved in toluene and concentrated under vacuum (2x), then dissolved in CHCl₃ and concentrated under vacuum (2x) to yield the crude acid chloride.

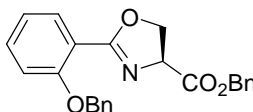
The crude acid chloride (8.59 g, 34.1 mmol) was dissolved in 170 mL of anhydrous CH₂Cl₂ in a 500-mL round-bottomed flask under Ar. **3.4** (8.39 g, 36.2 mmol) was added to the flask and the mixture cooled in an ice/H₂O bath under Ar. Diisopropylethylamine (14.9 mL, 85.6 mmol) was added to the reaction slowly. Most of the solid material dissolved, and the light orange solution was warmed to RT and stirred

under Ar overnight. After 19h, TLC of the reaction (90% CH₂Cl₂/acetone) indicated the reaction was complete. The orange solution was concentrated under vacuum to yield an orange oil. The oil was partitioned between EtOAc (~300 mL) and H₂O (~150 mL). The layers were separated and the organic layer was washed with H₂O (1 x 100 mL), 5% citric acid (3 x 100 mL), H₂O (1 x 100 mL), saturated NaHCO₃ (3 x 100 mL), H₂O (1 x 100 mL), and brine (2 x 100 mL), dried over Na₂SO₄, filtered and concentrated to yield **3.5** as a fluffy white solid (13.5 g, 97.8% yield). mp 119-120°C; ¹H NMR (300 MHz, CDCl₃) δ 1.76 (br, 1H, -OH), 3.92 (m, *J* = 3.9 Hz, 1H, -NH), 4.89 (dt, *J* = 3.9, 6.9 Hz, 1H, α-CH), 5.12-5.30 (m, 4H, OCH₂-Ph), 7.05 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.11 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.30-7.48 (m, 10H, Ar-H), 8.20 (dd, *J* = 1.5, 7.8 Hz, 1H, Ar-H), 8.80 (d, *J* = 6.6 Hz, 1H, Ar-H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 55.62, 63.79, 67.39, 71.47, 113.0, 121.3, 121.7, 128.2, 128.3, 128.6, 128.8, 129.0, 132.5, 133.4, 135.5, 135.7, 157.2, 165.8, 170.4 ppm; HRMS-FAB (*m/z*) [M + H]⁺ found 406.



PEG-supported Burgess's Reagent (3.7). Polyethylene glycol (PEG) (6.96 g, 9.29 mmol) was dried in vacuo for 4 h and added dropwise as a solution in 20 mL of benzene to a solution of chlorosulfonyl isocyanate (1.20 g, 0.74 mL, 8.47 mmol) in 20 mL of benzene at RT. The reaction was allowed to stir for an additional 1h before concentrating to yield a yellow-tan oil. The oil was stored under vacuum overnight. The oil was dissolved in 20 mL of benzene and added dropwise to a solution of Et₃N (1.97 g,

2.74 mL, 19.5 mmol) in 15 mL of benzene at RT. The reaction was stirred for an additional 15 min, filtered, and concentrated to afford a tan solid (8.14 g). mp ~ 20-25 °C.

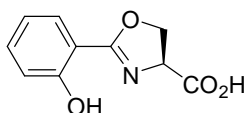


(S)-Benzyl 2-(2-(benzyloxy)phenyl)-4,5-dihydrooxazole-4-carboxylate (3.8)

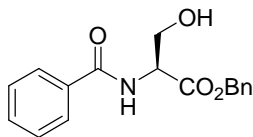
using PEG-Burgess reagent. Compound **3.5** (0.59 g, 1.46 mmol) and compound **3.7** (2.8 g, 2.8 mmol) were dissolved in 10 mL 1:1 THF/dioxane at RT. The reaction was heated to 95 °C for 3 h. The solvent was removed to yield a yellow oil. Chromatography through silica gel using a solvent system of 95% CH₂Cl₂/EtOAc provided **3.8** as a white solid (0.428 g, 76%).

General procedure for the preparation of oxazolines using DAST. Oxazoline 3.8 using DAST. Amide **3.5** (3.27 g, 8.07 mmol) was dissolved in 100 mL of CH₂Cl₂ under Ar. The solution was cooled to -78 °C (dry ice/acetone bath) and DAST (1.20 mL, 9.16 mmol) was added dropwise over 4 min. The reaction was stirred at -78 °C for 3.5 h. The reaction was monitored by TLC (1:1 hexanes/EtOAc – UV lamp) for the disappearance of amide **3.5**. K₂CO₃ (3.03 g, 21.9 mmol) was added to the reaction in one portion and the mixture was allowed to reach RT over 45 min. The mixture was poured into 100 mL of saturated NaHCO₃ and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were washed with H₂O (2 x 100 mL) and brine (2 x 100 mL), dried over MgSO₄, filtered, and concentrated to yield a yellow oil that solidified in the freezer overnight. Recrystallized from MeOH to

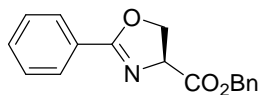
yield oxazoline **3.8** as a white solid (2.87 g, 91.7%). mp = 69-70 °C. ^1H NMR (CDCl_3 , 300 MHz) δ 4.55-5.70 (m, 2H), 5.03 (dd, J = 7.9, 10.6 Hz, 1H), 5.20-5.32 (m, 4H), 7.00 (m, 2H), 7.27-7.44 (m, 10H), 7.50 (dd, J = 0.9, 8.1 Hz, 2H), 7.82 (ddd, J = 0.6, 1.8, 8.1 Hz, 1H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 171.0, 165.7, 157.6, 136.8, 135.5, 132.6, 131.6, 128.5, 128.4, 128.3, 128.2, 127.5, 126.7, 120.7, 117.2, 113.8, 70.6, 69.2, 68.8, 67.1 ppm. $[\alpha]_{\text{D}}^{23}$ = +105 ° (c = 1, MeOH). HRMS (FAB) m/z $[\text{M}+\text{H}]^+$ calcd, 388.1549; obsd, 388.1549.



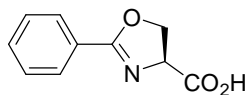
(S)-2-(2-Hydroxy-phenyl)-4,5-dihydro-oxazole-4-carboxylic acid (2.62). To an Ar-purged solution of **3.8** (2.00 g, 5.16 mmol) in MeOH (100 mL) was added 10 wt% Pd/C catalyst (3.75 mg, 18 wt %). The solution was stirred under H_2 (balloon) for 3.5h. The reaction was filtered through celite and the filtrate was concentrated and triturated from EtOAc/hexanes to yield **2.62** as a white solid (1.06 g, 99%). mp 149-150 °C (turns pink). ^1H NMR (500 MHz, d^6 -DMSO, 30 °C) δ 7.63 (dd, J = 8.0, 2.0 Hz, 1H), 7.46 (ddd, J = 9.0, 7.0, 1.5 Hz, 1H), 7.00 (dd, J = 8.5, 1.0 Hz, 1H), 6.94 (ddd, J = 8.0, 7.5, 1.0 Hz, 1H), 5.02 (dd, J = 10.0, 7.5 Hz, 1H), 4.63 (m, 2H) ppm. ^{13}C NMR (125 MHz, d^6 -DMSO, 30 °C) δ 171.6, 166.1, 159.1, 134.0, 127.9, 119.0, 116.5, 109.6, 69.2, 66.7 ppm. HRMS (FAB) m/z calcd for $\text{C}_{10}\text{H}_9\text{NO}_4$, 208.0610; obsd, 208.0609.



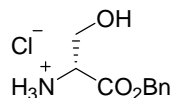
(S)-Benzyl 2-benzamido-3-hydroxypropanoate (3.9). Compound **3.4** (8.018 g, 34.609 mmol) and benzoic acid (4.692 g, 38.42 mmol) were added to a flame-dried 500-mL round-bottomed flask along with 150 mL of dry CH_2Cl_2 under Ar. Et_3N (5.20 mL, 37.0 mmol) was added to the suspension, followed by EDC•HCl (7.79 g, 40.6 mmol). After stirring for 2h under Ar at RT, the suspended material had fully dissolved and the resultant colorless solution was stirred at RT under Ar overnight. After ~26 h, the reaction was concentrated and the resultant orange oil was partitioned between EtOAc (300 mL) and H_2O (200 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 150 mL). The combined organic layers were washed with H_2O (200 mL), 5% citric acid (3 x 200 mL), H_2O (1 x 200 mL), saturated NaHCO_3 (3 x 200 mL), H_2O (1 x 200 mL), and brine (2 x 200 mL), dried over Na_2SO_4 , filtered, and concentrated to yield **3.9** as a white solid (9.94 g, 95.9% yield). mp = 91-92 °C. ^1H NMR (300 MHz, CDCl_3) δ 3.36 (t, J = 5.4 Hz, 1H), 3.90 – 4.05 (m, 2H), 4.82 (dt, J = 7.5, 3.3 Hz, 1H), 5.15 (s, 2H), 7.29 – 7.34 (m, 7H), 7.42 (t, J = 7.5 Hz, 1H), 7.74 (d, J = 7.5 Hz, 2H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 55.48, 63.41, 127.19, 128.08, 128.44, 128.62, 131.76, 133.93, 135.39, 167.74, 170.44 ppm. HRMS (FAB) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{17}\text{NO}_4$, 300.1236; obsd, 300.1231.



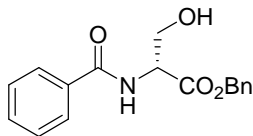
(S)-Benzyl 2-phenyl-4,5-dihydrooxazole-4-carboxylate (3.10). Compound **3.9** (5.123 g, 17.12 mmol) was dissolved in 100 mL of CH_2Cl_2 in a flame-dried 250-mL round-bottomed flask and cooled to -78°C in a dry ice/acetone bath under Ar. Diethylaminosulfur trifluoride (2.50 mL, 18.9 mmol) was added dropwise to the reaction over ~5 min. The reaction was stirred under Ar at -78°C . After 4 h, the reaction was complete by TLC (1:1 hexanes/EtOAc - UV lamp), and K_2CO_3 (6.31 g, 45.7 mmol) was added to the reaction in one portion. The reaction was removed from the dry ice/acetone bath and allowed to warm to RT under Ar over ~30 min while stirring. The solution was poured into ~100 mL of saturated NaHCO_3 and H_2O was added until all of the solid material had dissolved. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 60 mL). The combined CH_2Cl_2 layers were washed with saturated NaHCO_3 (1 x 80 mL), H_2O (2 x 80 mL), and brine (1 x 80 mL), dried over Na_2SO_4 , filtered, and concentrated to yield a yellow oil that solidified upon storage at -10°C overnight to a white solid (4.96 g). Recrystallization from EtOAc/hexanes afforded oxazoline **3.10** as a white solid (4.103 g, 85.2% yield). mp = $49-50^\circ\text{C}$. ^1H NMR (500 MHz, CDCl_3) δ 7.99 (m, 2H), 7.50 (m, 1H), 7.42-7.32 (m, 7H), 5.28 (d, $J = 12$ Hz, 1H), 5.22 (d, $J = 12$ Hz, 1H), 4.98 (dd, $J = 10.5, 8.0$ Hz, 1H), 4.67 (t, $J = 8.5$ Hz, 1H), 4.60 (dd, $J = 10.5, 8.5$ Hz, 1H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 170.9, 166.3, 135.3, 131.8, 128.49, 128.47, 128.31, 128.26, 128.2, 126.8, 69.5, 68.6, 67.2 ppm.



(S)-2-Phenyl-4,5-dihydrooxazole-4-carboxylic acid (3.11). To an Ar-purged solution of **3.10** (1.71 g, 6.07 mmol) in MeOH (50 mL) was added 10 wt% Pd/C catalyst (0.283 g, 17 wt %). The solution was stirred under H₂ (balloon) for 2.5h. The reaction was filtered through celite and the filtrate was concentrated and triturated from EtOAc/hexanes to yield **3.11** as an off-white solid (1.16 g, 99%). mp 128-131 °C (turns red at 125 °C). ¹H NMR (300 MHz, d⁶-DMSO) δ 7.89 (d, *J* = 7.2 Hz, 2H), 7.58 (m, 1H), 7.49 (m, 2H), 4.86 (m, 1H), 4.62-5.51 (m, 2H) ppm.

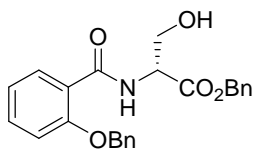


D-Serine benzyl ester hydrochloride (3.12). Compound **3.12** was prepared following the same procedure used for compound **3.4**. Boc-*D*-serine (2.00 g, 9.77 mmol) afforded **3.12** as a white solid (2.10 g, 93%).



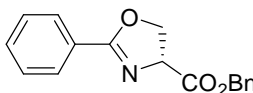
(R)-Benzyl 2-benzamido-3-hydroxypropanoate (3.13). Compound **3.13** was prepared following the same procedure used for compound **3.9**. Benzoic acid (0.250 g, 2.05 mmol) and **3.12** (0.401 g, 1.73 mmol) provided **3.13**. Recrystallization from EtOAc/hexanes provided **3.13** as a white solid (0.386 g, 75%). mp = 103-104 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.80 (d, *J* = 7.5 Hz, 1H), 7.49 (m, 1H), 7.34 - 7.41 (m, 5H),

7.24 (d, $J = 7.5$ Hz, 1H), 5.22 (s, 2H), 4.88 (m, 1H), 4.07 (dd, $J = 11.1, 3.6$ Hz, 1H), 4.00 (dd, $J = 11.4, 3.3$ Hz, 1H), 3.05 (br-s, 1H) ppm. ^{13}C NMR (75 MHz, CDCl_3) δ 170.4, 167.7, 135.1, 133.4, 131.9, 128.60, 128.56, 128.47, 128.1, 127.1, 67.5, 63.3, 55.2 ppm.



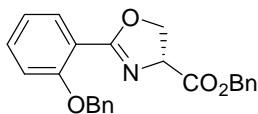
(*R*)-Benzyl 2-(2-(benzyloxy)benzamido)-3-hydroxypropanoate (3.14).

Compound **3.14** was prepared following the same procedure used for compound **3.5** using EDC-mediated amide coupling. **3.2** (0.476 g, 2.09 mmol) and **3.12** (0.401 g, 1.73 mmol) provided **3.14**. Recrystallization from EtOAc/hexanes yielded amide **3.14** as a white solid (0.559 g, 80%). mp = 118-120 °C. ^1H NMR (300 MHz, CDCl_3) δ 8.86 (d, $J = 6.9$ Hz, 1H), 8.19 (dd, $J = 8.1, 1.8$ Hz, 1H), 7.32 – 7.46 (m, 10H), 7.02 – 7.10 (m, 2H), 5.17 (s, 2H), 5.13 (m, 2H), 4.88 (m, 1H), 3.91 (m, 2H), 2.25 (br-s, 1H) ppm. ^{13}C NMR (75 MHz, CDCl_3) δ 170.1, 165.6, 156.9, 135.5, 135.3, 133.2, 132.3, 128.7, 128.3, 128.1, 128.0, 121.5, 112.8, 71.3, 67.2, 63.6, 55.4 ppm.



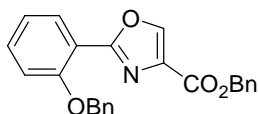
(*R*)-Benzyl 2-phenyl-4,5-dihydrooxazole-4-carboxylate (3.15). Compound

3.15 was prepared following the same procedure used for oxazoline **3.10**. **3.13** (0.204 g, 0.682 mmol) and DAST (0.110 mL, 0.839 mmol) provided oxazoline **3.15** as a colorless oil (0.166 g, 86%).



(R)-Benzyl 2-(2-(benzyloxy)phenyl)-4,5-dihydrooxazole-4-carboxylate (3.16).

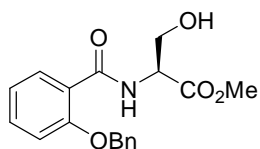
Compound **3.16** was prepared following the same procedure used for oxazoline **3.10**. **3.14** (0.301 g, 0.743 mmol) and DAST (0.110 mL, 0.839 mmol) provided oxazoline **3.16**. Recrystallization from MeOH yielded **3.16** as a white solid (0.201 g, 70%). mp = 60.5-62.5 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.82 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.50 (m, 2H), 7.27 – 7.43 (m, 9H), 6.99 (m, 2H), 5.25 (m, 2H), 5.19 (s, 2H), 5.01 (dd, *J* = 10.5, 7.8 Hz, 1H), 4.53 – 4.69 (m, 2H) ppm.



Benzyl 2-(2-(benzyloxy)phenyl)oxazole-4-carboxylate (3.17). Compound **3.8**

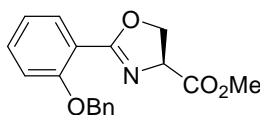
(0.101 g, 0.261 mmol) was dissolved in 2.6 mL of CH₂Cl₂ in a flame-dried 10-mL flask under Ar. The solution was cooled in a dry ice/acetone bath maintained at -25 to -20 °C. Bromotrichloromethane (0.186 g, 0.937 mmol) was added dropwise to the reaction followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (0.140 mL, 0.936 mmol). The reaction was stirred for 5 min in the dry ice/acetone bath, then warmed to 4 °C in an ice/H₂O bath and stirred for 2.5 h under Ar. The reaction was complete by TLC (3:2 hexanes/EtOAc – UV lamp) and the reaction was warmed to RT. The mixture was quenched with saturated NaHCO₃, then poured into 10 mL of saturated NaHCO₃ and diluted with 12 mL of EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), 1M HCl (2 x 10

mL), brine (10 mL), 0.5% NaOCl (2 x 10 mL), and brine (2 x 10 mL), dried over MgSO₄, filtered, and concentrated to yield an oil residue. Chromatography through 13 g of silica using 100% CH₂Cl₂ provided oxazole **3.17** as a colorless oil (70.6 mg, 70%). ¹H NMR (300 MHz, CDCl₃) δ 8.32 (s, 1H), 8.07 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.53 (m, 2H), 7.29 – 7.49 (m, 9H), 7.06 (m, 2H), 5.41 (s, 2H), 5.22 (s, 2H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ 161.4, 161.3, 156.7, 143.9, 135.6, 133.9, 132.4, 131.1, 128.54, 128.46, 128.3, 127.7, 126.8, 121.0, 116.2, 113.5, 70.5, 66.6 ppm.



(S)-Methyl 2-(2-(benzyloxy)benzamido)-3-hydroxypropanoate (3.19).

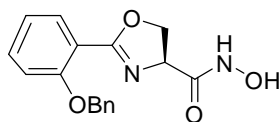
Compound **3.19** was prepared following the same procedure used for compound **3.5** using EDC-mediated amide formation. **3.18** (3.15 g, 20.3 mmol), **3.2** (5.55 g, 24.3 mmol), Et₃N (3.33 mL, 24.0 mmol), and EDC•HCl (4.50 g, 23.5 mmol) provided amide **3.19** as a white solid (6.19 g, 93%). mp = 127-128 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.78 (d, *J* = 7.0 Hz, 1H), 8.18 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.48 – 7.35 (m, 5H), 7.06 – 7.03 (m, 2H), 5.22 (m, 2H), 4.82 (m, 1H), 3.88 (m, 2H), 3.68 (s, 3H) ppm.



(S)-Methyl 2-(2-(benzyloxy)phenyl)-4,5-dihydrooxazole-4-carboxylate (3.20).

Prepared following the same procedure used for oxazoline **3.10**. **3.19** (6.78 g, 20.6 mmol) and DAST (3.00 mL, 22.7 mmol) provided oxazoline **3.20**. Recrystallization

from MeOH provided shiny, off-white crystals (5.57 g, 87%). mp = 121-123 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.81 (dd, *J* = 13, 2.5 Hz, 1H), 7.50 (m, 2H), 7.42 – 7.28 (m, 4H), 7.01 – 6.95 (m, 2H), 5.18 (s, 2H), 4.97 (dd, *J* = 17.5, 13.5 Hz, 1H), 4.67 (t, *J* = 13.5 Hz, 1H), 4.57 (dd, *J* = 17.5, 14.5 Hz, 1H), 3.80 (s, 3H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 171.7, 165.6, 157.6, 136.8, 132.6, 131.6, 128.3, 127.5, 126.7, 120.7, 117.2, 113.7, 70.6, 69.1, 68.6, 52.5 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₈H₁₈NO₄⁺, 312.1236; obsd, 312.1247.

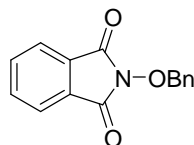


(S)-2-(2-(Benzyloxy)phenyl)-N-hydroxy-4,5-dihydrooxazole-4-carboxamide

(3.21). A methanolic solution of KOH (400 mg, 7.14 mmol) in 5 mL of MeOH (~1.4M) was slowly added to a solution of hydroxylamine hydrochloride (242 mg, 3.48 mmol) in 2.5 mL of MeOH at 0 °C. A solution of **3.20** (509 mg, 1.63 mmol) in 10 mL of MeOH was added to the reaction and the reaction was stirred for 3h at 0 °C and then stored at -10 °C overnight. The reaction was acidified to an apparent pH of 4 through the dropwise addition of 1M HCl. EtOAc and H₂O were added to the reaction and the biphasic solution was extracted with EtOAc (3 x 30 mL). The combined EtOAc layers were washed with H₂O (2 x 40 mL) and brine (3 x 40 mL), dried over MgSO₄, filtered, and concentrated to yield hydroxamate **3.21** as a white solid (108 mg, 22%). mp = 115-120 °C (dec.). ¹H NMR (300 MHz, d⁶-DMSO) δ 4.45 (t, *J* = 8.1 Hz, 1H), 4.52 (t, *J* = 8.1 Hz, 1H), 4.67 (dd, *J* = 9.5, 8.4 Hz, 1H), 5.22 (s, 2H), 7.02 (t, *J* = 7.3 Hz, 1H), 7.19 (d, *J* = 8.1

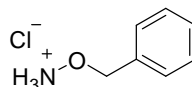
Hz, 1H), 7.27-7.52 (m, 6H), 7.72 (dd, $J = 7.5, 1.3$ Hz, 1H), 9.02 (s, 1H), 10.77 (s, 1H) ppm. HRMS (FAB) m/z $[M+H]^+$ calcd for $C_{17}H_{17}N_2O_4^+$, 313.1188; obsd, 313.1198.

General procedure for hydroxamate formation from esters using Me_3Al and hydroxylamines. Attempted formation of hydroxamate **3.22** from ester **3.20** (Table **3.7**, entry **6**). *O*-allylhydroxylamine hydrochloride (0.160 g, 1.46 mmol) was suspended in 5 mL of CH_2Cl_2 and cooled under Ar in an ice/ H_2O bath. Trimethylaluminum (2.0M in heptane, 0.740 mL, 1.48 mmol) was added dropwise and the resultant mixture was warmed to RT and stirred for 1 h, at which time the solid material was fully in solution. The solution was cooled in the ice/ H_2O bath again as a solution of ester **3.20** (0.250 g, 0.800 mmol) in 5 mL of CH_2Cl_2 was added dropwise to the reaction. The reaction was allowed to reach RT and stirred overnight under Ar. 10% Citric acid (5 mL) was added dropwise to the reaction and the mixture was stirred at RT for 1 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with 10% citric acid (2 x 25 mL), H_2O (20 mL), saturated $NaHCO_3$ (2 x 30 mL), and brine (2 x 40 mL), dried over $MgSO_4$, filtered, and concentrated.



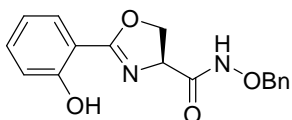
***N*-Benzyloxy-phthalimide (3.25).** Compound **3.25** was prepared following the procedure outlined by Welch and Seper.¹ *N*-hydroxyphthalimide (70.0 g, 429 mmol) and benzyl bromide (55.0 mL, 463 mmol) were dissolved in 550 mL of CH_3CN . The solution

was warmed and Et₃N (47.3 g, 65.0 mL, 467 mmol) was added slowly to the solution. The mixture was heated at reflux for 6 h until all of the solid material dissolved. The reaction was cooled to RT and poured into 300 mL of H₂O and extracted with EtOAc (3 x 500 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated to yield a yellow solid. Recrystallization from MeOH provided **3.25** as pale yellow crystals (87.4 g, 80%). mp 142-143°C (lit.¹ 141-142°C). ¹H NMR (300 MHz, CDCl₃) δ 7.82 - 7.70 (m, 4H), 7.53 (m, 2H), 7.37 (m, 3H), 5.21 (s, 2H) ppm.



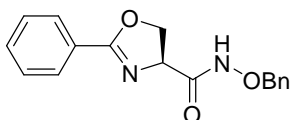
***O*-Benzylhydroxylamine hydrochloride, OBHA•HCl (3.27).** EtOH (400 mL) was added to compound **3.25** (20.0 g, 79.0 mmol) in a 1-L round-bottomed flask. The mixture was heated to 40 °C in an oil bath and anhydrous hydrazine (2.90 mL, 92.4 mmol) was added. After 1 min, most of the solid material was in solution. The flask was equipped with a jacketed condenser and the yellow solution was heated at reflux overnight (oil bath temp at 100 °C). After a few min, a white solid started to precipitate out of the solution. After heating to reflux for 18 h, the reaction was allowed to cool to RT and stirred for an additional 7 h. The mixture was filtered under vacuum to afford the by-product **3.26**, as a white solid (12.7 g, 99%) and a yellow filtrate. The filtrate was concentrated under vacuum to afford a yellow solid that was partitioned between CH₂Cl₂ (400 mL) and 3M NaOH (300 mL). The layers were separated and the CH₂Cl₂ layer was washed with 3M NaOH (2 x 250 mL), H₂O (250 mL), and brine (250 mL), dried over Na₂SO₄, filtered, and concentrated to yield free *O*-benzylhydroxylamine as a thin yellow oil (9.3 g, ~96%).

The free amine was dissolved in 500 mL of anhydrous Et₂O. HCl gas (prepared by adding conc. HCl to a round-bottomed flask containing anhydrous CaCl₂, then bubbling through conc. H₂SO₄ to dry) was bubbled through the solution for 10 min. White solid began to precipitate out of solution immediately. After standing for a few days, HCl was bubbled through the solution for an additional 45 min (more solid precipitated out during this time) in order to saturate the solution with an excess of HCl. The white solid was collected via vacuum filtration. The remaining amount of solid in the filtrate was collected via vacuum filtration through a coarse glass frit and provided **3.27** as a white solid (10.3 g, 82%). mp = 238 °C (sublimes). ¹H NMR (300 MHz, d⁶-DMSO) δ 11.25 (s, 2H), 7.41 (s, 5H), 5.06 (s, 2H) ppm. ¹³C NMR (75 MHz, d⁶-DMSO) δ 133.6, 129.2, 129.0, 128.6, 75.6 ppm.



General procedure for hydroxamate formation under aqueous conditions using EDC•HCl. *(S)-N-(Benzyloxy)-2-(2-hydroxyphenyl)-4,5-dihydrooxazole-4-carboxamide (3.28).* Carboxylic acid **2.62** (0.105 g, 0.508 mmol) and **3.27** (0.245 g, 1.54 mmol) were dissolved in 5 mL of 3:2 THF/H₂O. The apparent pH of the mixture was adjusted to 4.5 using a dilute aqueous solution of NaOH. EDC•HCl (0.162 g, 0.845 mmol) was added to the reaction in portions and the mixture was stirred at RT, maintaining an apparent pH of 4.5 by adding aqueous HCl to the reaction mixture. The reaction was complete when adding portions of EDC•HCl no longer had a significant effect on the apparent pH of the reaction mixture. The mixture was diluted with H₂O (20

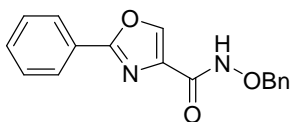
mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with 5% citric acid (3 x 15 mL) and brine (3 x 15 mL), dried over MgSO₄, filtered, and concentrated to yield a white solid (94% crude yield). Chromatography through 15 g of silica using 95:5 CH₂Cl₂/EtOAc provided hydroxamate **3.28** as a white solid (130.7 mg, 83%). mp = 178-180 °C (turns red, then melts). R_f = 0.302 (1:1 hexanes/EtOAc – UV lamp). ¹H NMR (500 MHz, CDCl₃) δ 11.15 (br-s, 1H), 8.93 (s, 1H), 7.66 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.42 – 7.31 (m, 6H), 6.99 (dd, *J* = 8.5, 0.5 Hz, 1H), 6.90 (m, 1H), 4.93 (s, 2H), 4.88 (dd, *J* = 11, 8.0 Hz, 1H), 4.68 (m, 1H), 4.61 (dd, *J* = 11, 9.0 Hz, 1H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 168.0, 167.7, 159.5, 134.4, 129.3, 128.9, 128.6, 128.5, 119.2, 116.8, 109.8, 78.5, 69.3, 66.8 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₇H₁₇N₂O₄⁺, 313.1188; obsd, 313.1215.



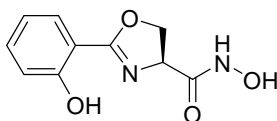
(S)-N-(Benzyloxy)-2-phenyl-4,5-dihydrooxazole-4-carboxamide (3.29).

Compound **3.29** was prepared following the same procedure used for the preparation of hydroxamate **3.28**. Carboxylic acid **3.11** (0.169 g, 0.882 mmol), **3.27** (0.422 g, 2.64 mmol) and EDC•HCl (0.262 g, 1.37 mmol) provided hydroxamate **3.29**. Chromatography through 15 g of silica using 4:1 CH₂Cl₂/EtOAc yielded **3.29** as a white solid (0.103 g, 39%). mp = 104-106 °C. ¹H NMR (500 MHz, CDCl₃) δ 9.38 (s, 1H), 7.85 (d, *J* = 7.0 Hz, 2H), 7.50 (td, *J* = 7.5, 1.0 Hz, 1H), 7.40 – 7.30 (m, 7H), 4.92 (s, 2H), 4.77 (dd, *J* = 11.0, 8.0 Hz, 1H), 4.68 (t, *J* = 8.0 Hz, 1H), 4.62 (dd, *J* = 11.0, 9.0 Hz, 1H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 168.7, 166.5, 134.8, 132.1, 129.25, 129.21, 128.8,

128.5, 128.4, 128.0, 126.5, 78.4, 70.1, 67.8 ppm. HRMS (FAB) m/z $[M+H]^+$ calcd for $C_{17}H_{17}N_2O_3^+$, 297.1239; obsd, 297.1219.

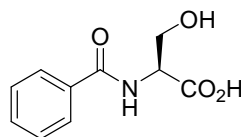


***N*-(Benzyloxy)-2-phenyloxazole-4-carboxamide (3.31).** Compound **3.31** was prepared following the same procedure used for the preparation of hydroxamate **3.28**. Carboxylic acid **3.30** (0.492 g, 2.60 mmol), **3.27** (0.540 g, 3.38 mmol), and EDC•HCl (0.615 g, 3.21 mmol) provided hydroxamate **3.31**. Chromatography through 50 g of silica using a solvent gradient from 100% CH_2Cl_2 to 90% CH_2Cl_2 /EtOAc yielded **3.31** as a white solid (0.506 g, 66%). mp = 140-142 °C. R_f = 0.21 (95:5 CH_2Cl_2 /EtOAc – UV lamp). 1H NMR (500 MHz, $CDCl_3$) δ 9.46 (br-s, 1H), 8.30 (s, 1H), 7.97 (m, 2H), 7.46-7.38 (m, 8H), 5.06 (s, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6, 158.6, 141.4, 135.1, 135.0, 131.2, 129.2, 128.84, 128.77, 128.6, 126.6, 126.2, 78.8 ppm. HRMS (FAB) m/z $[M+H]^+$ calcd for $C_{17}H_{15}N_2O_3^+$, 295.1083; obsd, 295.1073.

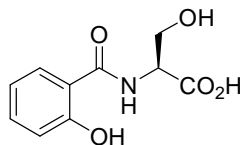


(*S*)-N-Hydroxy-2-(2-hydroxyphenyl)-4,5-dihydrooxazole-4-carboxamide (3.32). All glassware was washed with 6M HCl, then rinsed with H_2O and acetone before using in order to remove residual metals. MeOH (25 mL) was added to **3.28** (0.487 g, 1.56 mmol) in a 100-mL round-bottomed flask under Ar. The solid did not dissolve completely. EtOAc was added to the mixture until the solid completely

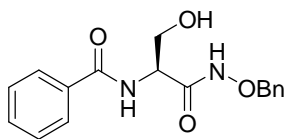
dissolved (~8 mL). The solution was purged with Ar for 10 min and 10 wt% Pd/C (52 mg, ~11 wt%) was added to the solution. The reaction was purged with Ar for 5 min, then H₂ for 5 min, then stirred under H₂ (balloon) for 2 h, after which time a more polar, FeCl₃-positive spot was observed by TLC analysis. The reaction was purged with Ar for 10 min, then filtered through a small amount of celite. The filtrate was concentrated to yield a white solid (336 mg, 98%). mp = 154-155 °C. R_f = 0.42 (9:1 CH₂Cl₂/MeOH-UV lamp, FeCl₃ stain). ¹H NMR (300 MHz, d⁶-DMSO) δ 11.69 (s, 1H), 11.04 (s, 1H), 9.11 (s, 1H), 7.63 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.46 (ddd, *J* = 9.0, 7.5, 1.8 Hz, 1H), 7.01 – 6.92 (m, 2H), 4.81 (dd, *J* = 9.9, 7.5 Hz, 1H), 4.64 – 4.51 (m, 2H) ppm. ¹³C NMR (125 MHz, d⁶-DMSO) δ 166.2, 165.8, 158.9, 133.9, 127.9, 118.9, 116.4, 109.7, 68.9, 65.3 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₀H₁₁N₂O₄⁺, 223.0719; obsd, 223.0711.



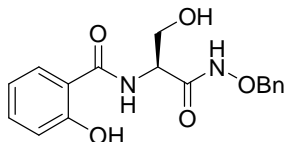
(S)-2-Benzamido-3-hydroxypropanoic acid (3.33). Compound **3.33** was prepared following the same procedure used for the preparation of **2.62**. Compound **3.9** (0.725 g, 2.42 mmol) provided **3.33** as a white foam (0.516 g, 99% yield). ¹H NMR (300 MHz, CD₃OD) δ 7.87 (m, 2H), 7.45 – 7.58 (m, 3H), 4.72 (t, *J* = 4.2 Hz, 1H), 3.94 – 4.06 (m, 2H) ppm. ¹³C NMR (75 MHz, CD₃OD) δ 173.5, 170.2, 135.3, 133.0, 129.6, 128.5, 63.0, 56.8 ppm.



(S)-3-Hydroxy-2-(2-hydroxybenzamido)propanoic acid (3.34). Compound **3.34** was prepared following the same procedure used for the preparation of **2.62**. Compound **3.5** (1.41 g, 3.47 mmol) provided **3.34** as a light purple foam (0.784 g, 99%). ^1H NMR (500 MHz, d^6 -DMSO, 30 °C) δ 11.85 (br, 1H), 8.93 (d, $J = 7.5$ Hz, 1H), 7.95 (dd, $J = 7.5, 1.0$ Hz, 1H), 7.39 (m, 1H), 6.93 (m, 2H), 4.53 (dt, $J = 6.5, 4.5$ Hz, 1H), 3.86 (dd, $J = 16.0, 5.0$ Hz, 1H), 3.80 (dd, $J = 11.0, 4.0$ Hz, 1H) ppm. ^{13}C NMR (125 MHz, d^6 -DMSO, 30 °C) δ 171.7, 167.1, 158.3, 133.4, 129.2, 118.9, 117.1, 116.5, 61.1, 55.0 ppm. HRMS (FAB) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{12}\text{NO}_5^+$, 226.0715; obsd, 226.0717.

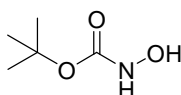


(S)-N-(1-(Benzyloxyamino)-3-hydroxy-1-oxopropan-2-yl)benzamide (3.35). Compound **3.35** was prepared following the same procedure used for the preparation of hydroxamate **3.28**. Carboxylic acid **3.33** (58 mg, 0.28 mmol), **3.27** (51 mg, 0.32 mmol), and EDC•HCl (65 mg, 0.34 mmol) provided **3.35** as a white solid (62 mg, 71%).

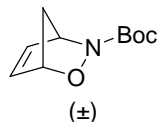


(S)-N-(1-(Benzyloxyamino)-3-hydroxy-1-oxopropan-2-yl)-2-hydroxybenzamide (3.36). Compound **3.36** was prepared following the same procedure

used for the preparation of hydroxamate **3.28**. Carboxylic acid **3.34** (74 mg, 0.33 mmol), **3.27** (57 mg, 0.36 mmol), and EDC•HCl (73 mg, 0.38 mmol) provided **3.36** as a fluffy white solid (77 mg, 71%).

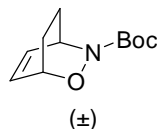


tert-Butyl N-hydroxycarbamate (3.37). Hydroxylamine hydrochloride (10.00 g, 144.0 mmol) was suspended in 240 mL of THF and 60 mL of H₂O in a 1-L flask. NaHCO₃ (24.25 g, 288.7 mmol) was added (some bubbling was observed). The biphasic mixture (aq. layer was cloudy) was stirred vigorously at RT for 5-10 min. Di-*tert*-butyldicarbonate (33.0 g, 151 mmol) was added in one portion (bubbling observed), and the mixture was stirred vigorously at RT for 3.75 h. The mixture was diluted with 200 mL of H₂O and 150 mL of EtOAc (most of the solid dissolved), and the aqueous layer was acidified to an apparent pH of 4 (pH paper) by adding a 10 wt% solution of citric acid (bubbled profusely). The layers were separated and the aqueous layer was extracted with EtOAc (3x 150 mL). The combined organic layers were washed with brine (1x 200 mL), dried (Na₂SO₄), filtered, and concentrated to yield a colorless oil. The oil was dried under vacuum overnight and provided **3.37** as a white solid (18.8 g, 98% yield). mp = 47-50 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.28 (br-s, 1H), 1.44 (s, 9H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ 158.9, 82.0, 28.1 ppm.



(±)-tert-Butyl 3-oxa-2-aza-bicyclo[2.2.1]hept-5-ene-2-carboxylate (3.38).

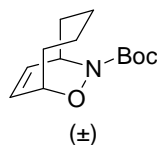
Freshly cracked cyclopentadiene (8.20 mL, 99.0 mmol) was added to a solution of **3.37** (3.24 g, 24.3 mmol) in 4:1 MeOH/H₂O (200 mL) at 4 °C (internal temperature). A solution of sodium periodate (5.71 g, 26.7 mmol) in H₂O (60 mL) was added dropwise to the reaction mixture over 35 min. The reaction mixture turned slightly yellow after 2 min, and a considerable amount of white solid was observed. The reaction was stirred for an additional 1.5 h at 4 °C, then filtered to remove the solid material and the volume was reduced with a minimal amount of heating to about 50 mL. The mixture was diluted with H₂O (30 mL), and brine (50 mL), and extracted with EtOAc (5 x 85 mL). The combined organic layers were washed with brine (3 x 85 mL), dried over MgSO₄, filtered, and concentrated to a brown oil. The oil was chromatographed through 150 g of silica using 4:1 hexanes/EtOAc to yield a yellow oil. Recrystallization from hexanes yielded **3.38** as a white solid (2.76 g, 58%). mp = 43-45 °C. ¹H NMR (500 MHz, CDCl₃) δ 6.36 (m, 2H), 5.16 (m, 1H), 4.93 (m, 1H), 1.93 (dt, *J* = 8.5, 2.0 Hz, 1H), 1.68 (d, *J* = 8.5 Hz, 1H), 1.41 (s, 9H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 158.5, 134.0, 132.9, 83.5, 82.0, 64.9, 48.0, 28.1 ppm.



(±)-tert-Butyl 3-oxa-2-aza-bicyclo[2.2.2]oct-5-ene-2-carboxylate (3.39).

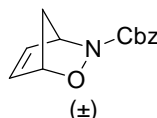
Compound **3.39** was prepared following the same procedure used for cycloadduct **3.38**.

3.37 (3.23 g, 24.3 mmol), 1,3-cyclohexadiene (4.0 mL, 41.9 mmol), and sodium periodate (5.63 g, 26.3 mmol) provided a crude orange oil. Chromatography through 200 g of silica using 4:1 hexanes/EtOAc yielded **3.39** as an orange oil that solidified to an orange waxy solid upon storage (3.53 g, 69%). $R_f = 0.40$ (1:1 hexanes/EtOAc – UV lamp, CAM stain). ^1H NMR (500 MHz, CDCl_3) δ 6.56 – 6.50 (m, 2H), 4.72 (m, 2H), 2.20 – 2.14 (m, 1H), 2.11 – 2.07 (m, 1H), 1.50 – 1.44 (m, 1H), 1.45 (s, 9H), 1.36 – 1.31 (m, 1H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 157.7, 131.7, 131.5, 81.6, 70.7, 50.1, 28.2, 23.6, 20.5 ppm.



(±)-*tert*-Butyl 8-oxa-7-aza-bicyclo[4.2.2]dec-9-ene-7-carboxylate (**1c**). *tert*-Butyl hydroxycarbamate (12.1 g, 90.6 mmol) was dissolved in 470 mL of MeOH in a 1-L 3-necked round-bottomed flask equipped with a mechanical stirrer and an addition funnel. The solution was cooled in a crushed ice/ H_2O bath to 3 °C (internal temperature). *cis,cis*-1,3-cyclooctadiene (15.0 mL, 120 mmol) was suspended in the reaction while stirring vigorously and a solution of sodium periodate (20.6 g, 95.3 mmol) in 230 mL of H_2O was added to the reaction dropwise through the addition funnel. After a few minutes, the reaction turned yellow and a lot of white solid formed. After 1.5 h, the addition of the NaIO_4 solution was complete and the reaction was stirred at 25 °C for an additional 5.5 h. The solid material was removed by filtration and washed with EtOAc (150 mL) until all of the yellow color was removed from the solid. The volume of the orange filtrate was reduced by rotary evaporation to about 300 mL (35-40 °C, 21 mm

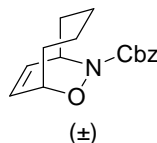
Hg). 250 mL of brine and 200 mL of Et₂O were added and the layers were separated. The aqueous layer was extracted with Et₂O (3 x 200 mL) and the combined Et₂O layers were washed with brine (2 x 200 mL), dried over MgSO₄, filtered, and concentrated (35-40 °C, 21 mm Hg) to yield an orange solid. The crude material was loaded onto silica and purified in two portions through a Biotage 40M column using a solvent gradient from 90% CH₂Cl₂/hexanes to 100% CH₂Cl₂ to afford **1c** as a light yellow solid (10.2 g, 47% yield). mp = 88-89 °C. ¹H NMR (500 MHz, CDCl₃) δ 6.37 (dd, *J* = 9.7, 6.9 Hz, 1H), 5.76 (dd, *J* = 10.1, 4.4 Hz, 1H), 4.90 (br-m, 1H), 4.56 (br-m, 1H), 2.15-1.96 (m, 2H), 1.80-1.53 (m, 6H), 1.46 (s, 9H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 157.9, 131.9, 126.2, 81.1, 75.2, 54.0, 34.1, 31.4, 28.0, 25.7, 22.1 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₃H₂₂NO₂⁺, 240.1600; obsd, 240.1606.



(±)-Benzyl 3-oxa-2-aza-bicyclo[2.2.1]hept-5-ene-2-carboxylate (3.42).

Compound **3.41** (7.34 g, 43.9 mmol) was dissolved in 460 mL of MeOH in a 3-necked 2-L flask and cooled to 2 °C (internal temperature) in an ice/H₂O bath. Freshly cracked cyclopentadiene (18.0 mL, 217 mmol) was added to the reaction and sodium periodate (9.92 g, 46.4 mmol) was added dropwise over 75 min. White solid formed in the reaction and the mixture turned yellow in color after a few min. The reaction was stirred for an additional 2 h at 2 °C, and workup of the reaction was completed following the workup procedure for cycloadducts **3.38-3.40**. Chromatography of the crude amber oil through silica using a solvent gradient from 85% hexanes/EtOAc to 70% hexanes/EtOAc yielded

3.42 as a yellow oil (6.31 g, 62%). ^1H NMR (500 MHz, CDCl_3) δ 7.33 – 7.29 (m, 5H), 6.35 (m, 2H), 5.21 (m, 1H), 5.17 (d, $J = 12.5$ Hz, 1H), 5.10 (d, $J = 12.5$ Hz, 1H), 5.02 (m, 1H), 1.97 (dt, $J = 8.5, 2.0$ Hz, 1H), 1.72 (d, $J = 8.5$ Hz, 1H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 159.1, 135.4, 134.2, 132.8, 128.3, 128.1, 127.9, 67.6, 64.9, 48.0 ppm.



(±)-Benzyl 8-oxa-7-aza-bicyclo[4.2.2]dec-9-ene-7-carboxylate (3.43). 3.41

(5.00 g, 29.9 mmol) was dissolved in 200 mL of MeOH in a 1-L flask and cooled to 4 °C in an ice/ H_2O bath. *cis,cis*-1,3-cyclooctadiene (9.5 mL, 76 mmol) was added, followed by a solution of sodium periodate (6.47 g, 30.3 mmol) in H_2O (0.43 M solution) dropwise over 20 min. A lot of white solid was observed in the reaction. The mixture was stirred vigorously at 4 °C for 1.5 h, then allowed to reach RT slowly. After 6 h, workup of the reaction was completed following the workup procedure for cycloadducts **3.38-3.40**. The crude amber oil was purified through silica using a solvent gradient from 95% CH_2Cl_2 to 100% CH_2Cl_2 and yielded **3.43** as an amber oil (3.35 g, 41%). ^1H NMR (300 MHz, CDCl_3) δ 7.35 (m, 5H), 6.36 (dd, $J = 10.2, 6.9$ Hz, 1H), 5.79 (dd, $J = 10.2, 4.5$ Hz, 1H), 5.18 (m, 2H), 4.93 (br-m, 1H), 4.68 (br-m, 1H), 2.20 – 1.60 (m, 8H) ppm. ^{13}C NMR (75 MHz, CDCl_3) δ 157.9, 136.1, 131.7, 128.4, 128.0, 127.8, 126.4, 76.0, 67.6, 34.2, 31.4, 25.4, 22.2 ppm. HRMS (FAB) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{20}\text{NO}_3^+$, 274.1443; obsd, 274.1440.

General procedure for acylnitroso HDA reaction using Bu₄NIO₄ as oxidant.

Preparation of cycloadduct 3.40 (Table 3.4, entry 4). Tetrabutylammonium periodate (4.31 g, 9.92 mmol) was dissolved in 30 mL of CH₂Cl₂ in a flame-dried 200-mL flask under Ar. The solution was cooled in an ice/H₂O bath and *cis,cis*-1,3-cyclooctadiene (1.50 mL, 12.0 mmol) was added. A solution of **3.37** (1.32 g, 9.89 mmol) in 20 mL of CH₂Cl₂ was added dropwise to the reaction using an addition funnel over a period of ~20 min. The reaction turned yellow, and a white solid was observed after the addition was complete. The reaction was stirred under Ar, allowing the ice/H₂O bath to melt and the reaction to reach RT gradually. During this time, the reaction became orange. The mixture was stirred overnight under Ar (24 h). Most of the solid had dissolved, and the reaction was reddish-orange in color. The reaction was washed with H₂O (2 x 50 mL) and brine (50 mL), dried over MgSO₄, filtered, and concentrated. The crude material was filtered through a plug of silica gel (~30 g), eluting with Et₂O (300 mL). The yellow filtrate was concentrated by rotary evaporation to yield a light yellow solid (1.54 g, 65.1% yield). ¹H-NMR shows residual diene. The solid was dissolved in ~50 mL of toluene and concentrated by rotary evaporation with heating to get remove the excess diene, providing **3.40** as a light yellow solid (1.29 g, 54% yield).

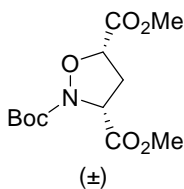
General procedure for acylnitroso HDA reaction using CuCl/*t*BuOOH as oxidant. Preparation of cycloadduct 3.40 (Table 3.4, entry 6). Compound **3.37** (1.00 g, 7.52 mmol) was dissolved in 15 mL of CH₂Cl₂ in a 50-mL round-bottomed flask under Ar and cooled in a -20 °C dry ice/acetone bath. CuCl (111.3 mg, 1.124 mmol) was added, followed by 5.0 M *tert*-butylhydroperoxide in decane (1.6 mL, 8.0 mmol). After 5

min, the reaction was removed from the dry ice/acetone bath and stirred in an ice/H₂O bath. The reaction was stirred in the ice/H₂O bath as it slowly melted. The reaction color changed from colorless to yellow, then green, then dark green, then finally blue over the course of the reaction. The reaction was quenched by adding 10 wt% sodium thiosulfate (20 mL). The layers were separated and the CH₂Cl₂ layer was washed with 10 wt% sodium thiosulfate (20 mL), H₂O (2 x 20 mL), brine (2 x 20 mL), dried over MgSO₄, filtered, and concentrated by rotary evaporation (35°C, 21 torr) to yield a blue liquid. The liquid was stored at 4 °C overnight to afford a light blue solid. Chromatography through 150 g of silica using 100% CH₂Cl₂ provided **3.40** as a light blue solid, contaminated with Cu-salts (0.587 g, 32.6% yield).

General procedure for performing acylnitroso HDA reaction using FeCl₃/H₂O₂ as oxidant. Preparation of cycloadduct 3.43 (Table 3.4, entry 7). Compound **3.41** (5.07 g, 30.3 mmol) was dissolved in 50 mL of CH₂Cl₂ in a 250-mL round-bottomed flask. *Cis,cis*-1,3-cyclooctadiene (4.0 mL, 32.1 mmol) was added, followed by FeCl₃•6H₂O (249.8 mg, 0.924 mmol, 3.0 mol%) and 1,2-ethylenediamine (0.31 mL, 4.63 mmol, 15.2 mol%). The yellow solution turned deep red in color upon the addition of FeCl₃ and 1,2-ethylenediamine. To this blood-red solution was added 30 wt% aqueous H₂O₂ (22.0 mL, 215 mmol) dropwise over 50 min. Bubbling was observed as the internal temperature of the reaction climbed to 35-40 °C. The reaction was stirred for an additional 1 h at RT. Analysis of the bottom (CH₂Cl₂) layer by TLC (1:1 hexanes/EtOAc - CAM stain, UV lamp) indicated a complex mixture. The reaction was allowed to stir for an additional 4 h. CH₂Cl₂ (50 mL) and H₂O (100 mL) were added and

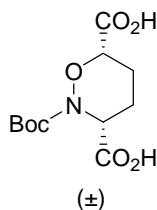
the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic layers were washed with H_2O (50 mL), and brine (50 mL). No product was isolated – complex mixture. NOTE: all layers were quenched by adding 10 wt% sodium thiosulfate until negative to KI-starch test paper.

General procedure for preparing an ethereal solution of diazomethane (CH_2N_2) safely from Diazald. [IMPORTANT NOTE: Only the proper glassware should be used for the preparation of diazomethane! All glassware should not have ground-glass joints and should be free of all cracks and scratched surfaces! A blast shield should always be in place when preparing or using diazomethane until all sources of diazomethane have been quenched!] A solution of Diazald (0.867 g, 4.05 mmol) in 10 mL of Et_2O (0.4 M) was added dropwise to a solution of KOH (1.46 g, 26.0 mmol) in 9 mL of 5:4 $\text{EtOH}/\text{H}_2\text{O}$ (2.9 M) that was heated in an oil bath (bath temp 68-70 °C) using the diazomethane glassware kit. It was important that the oil bath temperature was maintained within this range before, during, and after the addition of the Diazald solution. The resultant ethereal diazomethane solution was immediately condensed with a dry ice/acetone-filled condenser into a flask containing the compound to be reacted with diazomethane, or is condensed into a flask for distribution to alternative reaction vessel(s). The yellow diazomethane solution is quenched by the addition of 10 vol% HOAc in Et_2O until bubbling ceases and the yellow color has completely disappeared.



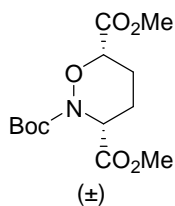
(±)-Isoxazolidine-2,3,5-tricarboxylic acid 2-tert-butyl ester 3,5-dimethyl ester

(3.44). NaIO₄ (6.79 g, 31.7 mmol) was added to a biphasic mixture of **3.38** (1.52 g, 7.70 mmol) in 45 mL of CCl₄/CH₃CN/H₂O (1:1:1). The mixture was cooled to 0 °C and RuCl₃•H₂O (35.7 mg, 0.172 mmol) was added. The solution was stirred at 0 °C for 3.5 h. The solid was removed by filtration. The solid was washed with several portions of Et₂O into the filtrate. The filtrate was separated and the aqueous was extracted with Et₂O (3 x 50 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated to yield a light brown oil. The oil was dissolved in 25 mL Et₂O and treated with excess CH₂N₂ (see next procedure below!) at 0 °C. The reaction was quenched with 5% HOAc in H₂O. The aqueous layer was made basic (pH ~8) by adding solid NaHCO₃ and saturated NaHCO₃. The aqueous was extracted with Et₂O (3 x 100 mL) and the combined Et₂O layers were dried over MgSO₄, filtered, and concentrated to yield **3.44** as a white solid (1.40 g, 63% from **3.38**). ¹H NMR (300 MHz, CDCl₃) δ 1.49 (s, 9H), 2.77 - 2.83 (m, 2H), 3.77 (s, 3H), 3.78 (s, 3H), 4.59 (t, *J* = 7.2 Hz, 1H), 4.81 (dd, *J* = 8.1, 5.2 Hz, 1H) ppm.



(±)-(3*R*,6*S*)-2-(*tert*-Butoxycarbonyl)morpholine-3,6-dicarboxylic acid (3.46).

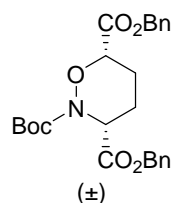
Na₂CO₃ (0.761 g, 7.18 mmol) was added to a solution of **3.39** (1.51 g, 7.13 mmol) in 44:1 acetone/*tert*-BuOH (60 mL). The solution was cooled to -10 °C (ice/NaCl/H₂O bath) and KMnO₄ (3.16 g, 20.0 mmol) was added slowly to maintain an internal reaction temperature less than 4 °C. The reaction was stirred at -10 °C for 1 h, and an additional 19 h at 23 °C. The reaction was diluted with 75 mL of EtOAc and quenched with 75 mL of 10% Na₂S₂O₅. The reaction was acidified to an apparent pH of 2 (1M HCl), and the aqueous layer was saturated with NaCl and extracted with EtOAc (2 x 75 mL). The combined EtOAc layers were dried over MgSO₄, filtered, and concentrated. Crude diacid **3.46** was obtained as an off-white solid (1.65 g, 84.5%) and used directly without further purification.



(±)-(3*R*,6*S*)-2-*tert*-Butyl 3,6-dimethyl morpholine-2,3,6-tricarboxylate (3.45).

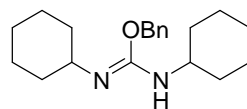
Crude diacid **3.46** (0.503 g, 1.83 mmol) was stirred as a suspension in 20 mL of Et₂O and treated with excess CH₂N₂ at 0 °C. The reaction was quenched with 5% HOAc in Et₂O. The aqueous layer was made basic (pH = 8) with NaHCO₃ and extracted with Et₂O (3 x 15 mL). The combined Et₂O layers were dried over MgSO₄, filtered, and concentrated to

yield a light yellow oil. The crude material was chromatographed through 50 g of silica using a solvent gradient from 80% hexanes/EtOAc to 65% hexanes/EtOAc and provided **3.45** as a colorless oil (0.349 g, 63% yield, 53% from cycloadduct **3.39**). ^1H NMR (300 MHz, CDCl_3) δ 4.78 (d, $J = 2.7$ Hz, 1H), 4.39 (dd, $J = 11.7, 2.1$ Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 2.41 (m, 1H), 2.02 – 1.70 (m, 4H), 1.49 (s, 9H) ppm. ^{13}C NMR (75 MHz, CDCl_3) δ 169.87, 168.93, 82.54, 78.86, 52.66, 52.32, 28.09, 24.29, 23.52, 17.43 ppm. HRMS (FAB) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{22}\text{NO}_7^+$, 304.1396; obsd, 304.1405.

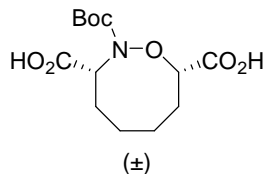


(±)-(3R,6S)-3,6-Dibenzyl 2-tert-butyl morpholine-2,3,6-tricarboxylate (3.48).

Crude diacid **3.46** (0.520 g, 1.89 mmol) and **3.47** (2.95 g, 9.38 mmol) were dissolved in 20 mL of toluene and stirred for 4.5 h at 90–95 °C. The reaction was filtered, diluted with CH_2Cl_2 (20 mL) and concentrated to yield a yellow oil (2.98 g). The oil was chromatographed through silica using 4:1 hexanes/EtOAc and provided **3.48** as a light yellow oil (0.704 g, 82% yield, 69% from cycloadduct **3.39**). ^1H NMR (300 MHz, CDCl_3) δ 7.35 – 7.29 (m, 10H), 5.28 – 5.15 (m, 4H), 4.85 (m, 1H), 4.45 (dd, $J = 12.0, 2.4$ Hz, 1H), 2.47 – 2.42 (m, 1H), 2.00 – 1.70 (m, 3H), 1.43 (s, 9H) ppm. HRMS (FAB) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{30}\text{NO}_7^+$, 456.2022; obsd, 456.2042.



***O*-Benzyl-*N, N'*-dicyclohexylisourea (3.47).** *N, N'*-dicyclohexylcarbodiimide (10.42 g, 50.50 mmol) was added to a flame-dried 100-mL round-bottomed flask under Ar and placed in a 55 °C oil bath. When the carbodiimide completely melted, benzyl alcohol (5.40 mL, 52.2 mmol) was added, followed by CuCl (151 mg, 1.52 mmol). The mixture was stirred under Ar overnight in the 55 °C oil bath. A small amount of white solid was observed in the reaction. After 16 h of stirring, the brown mixture was cooled to RT under Ar. The mixture was diluted with 80 mL of hexanes and filtered through a plug of neutral alumina (Al₂O₃), eluting with 20 mL of hexanes. Green solid remained on top of the alumina. The colorless filtrate was concentrated and dried under vacuum for 1 h and provided **3.47** as a colorless/light yellow oil (14.9 g, 94%). The oil was stored at -10 to 4 °C until ready to use. ¹H NMR (500 MHz, CDCl₃) δ 7.40 – 7.28 (m, 5H), 5.13 (s, 2H), 3.57 (br-m, 1H), 3.49 (br-m, 1H), 2.84 (br-m, 1H), 1.94 (m, 2H), 1.77 – 1.69 (m, 6H), 1.60 (m, 2H), 1.32 – 1.07 (m, 10H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 151.1, 138.1, 128.1, 127.4, 127.2, 66.44, 66.41, 54.8, 50.3, 34.4, 25.9, 25.6, 25.2, 24.9 ppm.

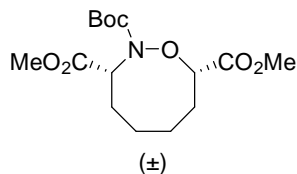


(±)-(3*R*,8*S*)-2-(*tert*-Butoxycarbonyl)-1,2-oxazocane-3,8-dicarboxylic acid (3.50). Prepared using RuO₄. Cycloadduct **3.40** (2.06 g, 8.60 mmol) was dissolved in 3:2:2 H₂O/CH₃CN/CCl₄ (84 mL) in a 250-mL flask and cooled to 4 °C in an ice/H₂O

bath. Sodium periodate (7.36 g, 34.4 mmol) was added, followed by ruthenium(III) chloride hydrate (45.7 mg, 0.220 mmol). The mixture immediately turned brown and was stirred vigorously at 4 °C for 30 min, then warmed to RT and stirred for an additional 1.5 h. The white solid was removed by filtration through a pad of celite. The celite was washed with EtOAc (80 mL) and the filtrate was diluted with brine (50 mL). The aqueous layer was acidified to a pH of 2-3 (pH paper) using 1M HCl and saturated with NaCl. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 75 mL) and the combined organic layers were washed with brine (2 x 100 mL), dried over MgSO₄, filtered, and concentrated to yield crude **3.50** as a brown/purple oil (2.58 g, 99% crude yield). The crude material was used directly without purification.

Preparation of diacid 3.50 using KMnO₄. Cycloadduct **3.40** (3.07 g, 12.8 mmol) was dissolved in 123 mL of 40:1 acetone/*t*BuOH in a 250-mL flask and cooled to -8 °C (internal temp.) in an ice/NaCl/H₂O bath. Na₂CO₃ (1.43 g, 13.5 mmol) was added and the suspension was stirred for 2 min. The suspension turned from light yellow to orange, and KMnO₄ (5.67 g, 35.9 mmol) was added to the reaction slowly over a period of 2 min while stirring vigorously. The resultant purple mixture was stirred in the ice/NaCl/H₂O bath for 30 min, during which time the internal temperature climbed to -2 °C. The purple/brown slurry was then warmed to RT and stirred vigorously overnight (20 h). The reaction was quenched by adding 150 mL of 10 wt% aqueous Na₂S₂O₅ (exothermic) and was stirred for 15 min at RT. EtOAc (100 mL) was added to the reaction and the aqueous layer was acidified by adding 6 M HCl slowly until the brown aqueous mixture became colorless (pH of about 2-3 - pH paper). The layers were

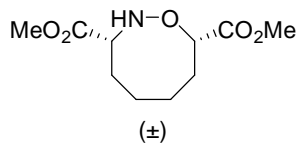
separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (2 x 75 mL), dried over Na₂SO₄, filtered, and concentrated to yield crude diacid **3.50** as a yellow foam (3.51 g, 90% crude yield). The material was used directly without purification.



(±)-(3*R*,8*S*)-2-*tert*-Butyl 3,8-dimethyl 1,2-oxazocane-2,3,8-tricarboxylate (3.52). Crude diacid **3.50** (2.58 g, 8.49 mmol), prepared using RuO₄ oxidation, was dissolved in 85 mL of ether and cooled in an ice/H₂O bath. The solution was treated with excess diazomethane (prepared as an ethereal solution from Diazald). The reaction was stirred for 15 min, then quenched by adding 10 vol% HOAc in ether until the yellow tint disappeared and bubbling ceased. The mixture was poured into saturated NaHCO₃ (150 mL) and the layers were separated. The aqueous layer (pH 7-8) was extracted with ether (2 x 75 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over MgSO₄, filtered, and concentrated to yield a brown oil. The oil was chromatographed through 200 g of silica using a solvent gradient from 98% CH₂Cl₂/EtOAc to 95% CH₂Cl₂/EtOAc to yield **3.52** as a thick yellow oil (2.02 g, 71% yield from cycloadduct **3.40**).

Preparation of compound 3.52 from cycloadduct 3.40 using ozonolysis: O₃, KOH, CH₂Cl₂/MeOH.³ Cycloadduct **3.40** (1.20 g, 5.03 mmol) was dissolved in 40 mL of CH₂Cl₂ and cooled to -78 °C in a dry ice/acetone bath. 10 mL of 2.5M methanolic

KOH (25 mmol) was added, and the colorless solution immediately turned light yellow. The reaction was stirred at -78 °C as ozone was bubbled through the reaction. The reaction immediately turned bright orange and a precipitate formed. After 85 min, the flow of ozone was stopped, the reaction was removed from the dry ice/acetone bath, and the reaction was diluted with Et₂O (50 mL), then H₂O (50 mL) until the orange reaction became completely colorless and the solid dissolved. The reaction was stirred for a few min to reach RT, then the layers were separated and the aqueous layer was extracted with Et₂O (3 x 75 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over MgSO₄, filtered, and concentrated to yield a light yellow oil (1.36 g, 82% crude yield). The crude material was loaded onto silica and chromatographed through a Biotage 40S column (40 g of silica) using 97% CH₂Cl₂/EtOAc and provided **3.52** as a light yellow oil (466 mg, 28% yield). ¹H NMR (500 MHz, CDCl₃) δ 4.85 – 4.68 (br-m, 1H), 4.44 – 4.28 (br-m, 1H), 3.70 (s, 3H), 3.69 (s, 3H), 2.14 – 2.02 (m, 2H), 1.95 – 1.85 (m, 2H), 1.72 – 1.67 (m, 1H), 1.47 – 1.32 (m, 10H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 170.2, 82.3, 81.1, 80.4, 63.5, 61.9, 52.2, 51.9, 29.0, 28.1, 26.8, 25.8, 24.1, 24.03, 23.99, 23.96 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₅H₂₆NO₇⁺, 332.1709; obsd, 332.1685.

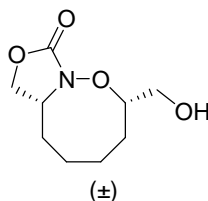


(±)-(3R,8S)-Dimethyl 1,2-oxazocane-3,8-dicarboxylate (3.53). MeOH (100 mL) was added to a 250-mL round-bottomed flask under Ar, then cooled in an ice/H₂O bath. Thionyl chloride (4.00 mL, 55.0 mmol) was added slowly and the solution was stirred for 5 min. A solution of crude **3.50** (4.14 g, 13.6 mmol) in 40 mL of MeOH was

transferred to the flask via cannula, and the reaction was stirred in the ice/H₂O bath under Ar. After 25 min, the reaction was removed from the ice/H₂O bath and allowed to stir at RT. After 22 h, the reaction was concentrated to yield a brown oil. The oil was partitioned between 75 mL of CH₂Cl₂ and 200 mL of saturated aqueous NaHCO₃ (bubbled profusely). The layers were separated and the aqueous layer (pH 8 - pH paper) was extracted with CH₂Cl₂ (3 x 75 mL). The combined CH₂Cl₂ layers were washed with brine (1 x 80 mL), dried (Na₂SO₄), filtered, and concentrated to yield a brown oil (2.27 g, 72% crude yield). The oil was loaded onto silica and chromatographed through a Biotage 40S column (40 g of silica) using a solvent gradient of 100% CH₂Cl₂ to 95% CH₂Cl₂/EtOAc and provided **3.53** as a yellow oil (1.93 g, 61% from cycloadduct **3.40**). R_f = 0.26 (1:1 hexanes/EtOAc – CAM stain). ¹H NMR (500 MHz, CDCl₃) δ 6.27 (br-s, 1H), 4.22 (dd, *J* = 10.0, 3.5 Hz, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 2.42 – 2.22 (m, 1H), 2.08 – 1.92 (m, 3H), 1.73 – 1.68 (m, 3H), 1.57 – 1.52 (m, 1H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ 172.4, 171.4, 80.7, 62.0, 51.8, 51.6, 28.0, 26.9, 26.0, 24.1 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₀H₁₈NO₅⁺, 232.1185; obsd, 232.1198.

Attempted formation of compounds 3.56 and 3.57 by ozonolysis of cycloadduct 3.40. Cycloadduct **3.40** (501 mg, 1.83 mmol) was dissolved in 18 mL of 5:1 CH₂Cl₂/MeOH in a single-necked 50-mL round-bottomed flask. The light yellow solution was cooled to -78 °C in a dry ice/acetone bath and NaHCO₃ (602 mg, 7.17 mmol) was added. Ozone was bubbled into the solution until the color changed to deep blue (5 min). The solution was purged with Ar until the blue color disappeared. The mixture was allowed to warm to RT and the solid material was removed by filtration.

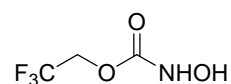
The solid was rinsed with portions of CH₂Cl₂ (10 mL), and the filtrate was concentrated to yield a white foam. The foam was dissolved in anhydrous 1:1 CH₂Cl₂/pyridine (20 mL) in a single-necked 100-mL round-bottomed flask under Ar. Distilled acetic anhydride (0.70 mL, 7.5 mmol) was added to the reaction and the colorless solution was stirred under Ar at RT. The solution gradually turned from colorless to yellow, then yellow/orange. After 2 days, the reaction was concentrated by passing a stream of air over the solution for ~2 h. The orange residue was partitioned between 1M HCl (50 mL) and EtOAc (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with 1M HCl (2 x 20 mL), H₂O (20 mL), saturated NaHCO₃ (2 x 20 mL), and brine (2 x 20 mL), dried over MgSO₄, filtered, and concentrated to yield a reddish-orange, sweet-smelling oil (~0.432 g crude yield). Analysis of the crude material indicated a complex mixture of products.



(±)-(2*S*,6*aR*)-2-(Hydroxymethyl)-hexahydrooxazolo[3,4-*b*][1,2]oxazocin-

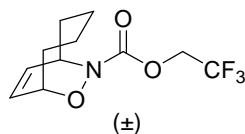
9(2H)-one (3.59). Cycloadduct **3.43** (1.18 g, 4.32 mmol) was dissolved in 42 mL of 5:1 CH₂Cl₂/MeOH in a single-necked 100-mL round-bottomed flask and cooled to -78 °C in a dry ice/acetone. Ozone was bubbled through the light yellow solution until the blue color of ozone was observed in the solution (~5 min). The solution was purged with Ar until the blue color disappeared then the reaction was removed from the dry ice/acetone bath and transferred to a crushed ice/NaCl/H₂O bath. NaBH₄ (1.02 g, 27.0 mmol) was

added to the reaction in portions over 60 min. Bubbling was observed during this time. After the addition was complete, the cloudy mixture was allowed to slowly reach RT over 45 min. The volume of the mixture was reduced by rotary evaporation (40-45 °C, 21 mm Hg) to 5 mL, at which time a white precipitate was observed. The mixture was partitioned between H₂O (50 mL) and EtOAc (50 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 30 mL) and the combined organic layers were washed with brine (2 x 30 mL), dried over MgSO₄, filtered, and concentrated to yield a colorless oil. The oil was chromatographed through 150 g of silica gel and yielded **3.59** as a tan-colored solid (423.3 mg, 48% yield). mp = 64-65 °C. ¹H NMR (300 MHz, CDCl₃) δ 4.38 (dd, *J* = 8.4, 7.5 Hz, 1H), 4.27 (dd, *J* = 11.1, 3.9 Hz, 1H), 3.98 – 3.88 (m, 1H), 3.88 (dd, *J* = 11.4, 8.4 Hz, 1H), 3.76 – 3.65 (m, 1H), 3.51 – 3.32 (m, 1H), 1.92 – 1.31 (m, 8H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ 162.1, 85.7, 67.1, 63.4, 60.9, 27.1, 24.8, 22.7, 22.0 ppm. MS (FAB) *m/z* [M+H]⁺ at 202.



2,2,2-Trifluoroethyl *N*-hydroxycarbamate (3.63). *N,N'*-Carbonyldiimidazole (2.468 g, 15.22 mmol) was dissolved in 50 mL of anhydrous THF in a flame-dried single-necked 250-mL round-bottomed flask under Ar. To this solution was added 2,2,2-trifluoroethanol (1.00 mL, 13.9 mmol). The resultant solution was stirred under Ar at RT for 2 h. In a separate flame-dried single-necked 100-mL round-bottomed flask, hydroxylamine hydrochloride (1.111 g, 15.99 mmol) was dissolved in about 40 mL of anhydrous pyridine and transferred via cannula to the flask containing the acylimidazole. The light yellow solution immediately became cloudy and warmed slightly. After

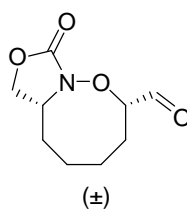
stirring for about 2 h, the reaction was analyzed by TLC and a FeCl₃-positive spot was observed. The reaction mixture was concentrated and the yellow oil/solid mixture was partitioned between EtOAc (50 mL) and H₂O (50 mL). 6M HCl (10 mL) was added and the layers were separated. The organic layer was washed with portions of 3M HCl (2 x 25 mL) and brine (20 mL), dried over Na₂SO₄, filtered, concentrated and provided **3.63** as a yellow oil (1.29 g, 58% yield). R_f = 0.30 (1:1 hexanes/EtOAc – FeCl₃ stain). ¹H NMR (500 MHz, CDCl₃) δ 7.72 (s, 1H), 4.52 (qd, *J* = 8.0, 0.5 Hz, 2H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 157.1, 122.6 (q, *J* = 276 Hz), 61.5 (q, *J* = 37 Hz) ppm. MS (FAB) *m/z* [M+H]⁺ at 160.



(±)-2,2,2-Trifluoroethyl 8-oxa-7-aza-bicyclo[4.2.2]dec-9-ene-7-carboxylate

(3.64). Compound **3.63** (1.289 g, 8.104 mmol) was dissolved in 40 mL of methanol in a 250-mL round-bottomed flask. *cis,cis*-1,3-cyclooctadiene (1.30 mL, 10.4 mmol) was added. The reaction was stirred vigorously as a solution of sodium periodate (1.925 g, 8.910 mmol) in 20 mL of H₂O was added dropwise over about 30 min. A yellow color was observed immediately, and a white solid was observed after a few minutes into the addition. After the addition was complete, the mixture was stirred vigorously at RT. After 2 h, no **3.63** remained by TLC. The white solid was removed by filtration and washed with EtOAc (10 mL). The volume of the orange filtrate was reduced to half by rotary evaporation and partitioned between EtOAc (50 mL) and brine (50 mL). The layers were separated and the aqueous was extracted with EtOAc (4 x 25 mL). The

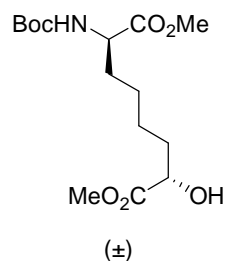
combined organic layers were washed with brine (25 mL), dried over Na₂SO₄, filtered, and concentrated to yield a brown oil (1.93 g). The oil was chromatographed through 200 g of silica using a solvent gradient from 90% CH₂Cl₂/hexanes to 100% CH₂Cl₂ to yield **3.64** as a yellow oil (1.103 g, 51.3% yield). The NMR spectra for compound **3.64** indicated a significant amount of impurities; however, the MS spectrum confirmed the presence of a 1:1 adduct. MS (FAB) m/z [M+H]⁺ at 266.



(±)-(2*S*,6*aR*)-9-Oxo-octahydrooxazolo[3,4-*b*][1,2]oxazocine-2-carbaldehyde

(3.66). Oxalyl chloride (0.12 mL, 1.4 mmol) was added to 5 mL of anhydrous CH₂Cl₂ in a flame-dried, single-necked 50-mL round-bottomed flask cooled to -78 °C (dry ice/acetone) under Ar. In a separate flame-dried single-necked 10-mL round-bottomed flask was added anhydrous dimethyl sulfoxide (0.17 mL, 2.4 mmol) to 5 mL of anhydrous CH₂Cl₂. The DMSO solution was added to the oxalyl chloride solution dropwise over about 1 min and the resultant solution was stirred at -78 °C for 10 min under Ar. In a separate flame-dried single-necked 25-mL round-bottomed flask under Ar was dissolved **3.59** (0.151 g, 0.750 mmol) in 5 mL of anhydrous CH₂Cl₂. This solution was transferred slowly to the flask that contained the oxidant via cannula. The resultant solution was stirred at -78 °C for 45 min, then triethylamine (0.60 mL, 4.3 mmol) was added. The reaction was stirred at -78 °C for 20 min, then removed from the dry ice/acetone bath and allowed to reach RT while stirring under Ar. After 2 h, the reaction

was diluted with CH₂Cl₂ (20 mL) and H₂O (50 mL) and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (2 x 20 mL) and the combined organic layers were washed with brine (20 mL), dried over MgSO₄, filtered, and concentrated to yield a yellow oil (149 mg). The crude material was analyzed by TLC and was composed of mostly one spot with the same R_f as the starting material but that stained darker to CAM stain. The crude material was chromatographed through 20 g of silica using a solvent gradient from 100% CH₂Cl₂ to 90% CH₂Cl₂/EtOAc and provided **3.66** as a yellow oil (80.5 mg, 54% yield). ¹H NMR (300 MHz, CDCl₃) δ 10.14 (s, 1H), 4.40 (dd, *J* = 8.4, 7.2 Hz, 1H), 4.21 (ddd, *J* = 11.4, 2.7, 0.6 Hz, 1H), 3.89 (dd, *J* = 11.4, 8.4 Hz, 1H), 3.82 – 3.71 (m, 1H), 2.19 – 2.05 (m, 1H), 2.00 – 1.86 (m, 3H), 1.81 – 1.69 (m, 3H), 1.58 – 1.43 (m, 1H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ 204.0, 166.8, 89.0, 66.5, 60.9, 27.4, 24.7, 22.5, 22.0 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₉H₁₄NO₄⁺, 200.1923; obsd, 200.0935.



(±)-(2*R*,7*S*)-Dimethyl 2-(*tert*-butoxycarbonylamino)-7-hydroxyoctanedioate (3.69). General procedure for N-O bond reduction using samarium diiodide (Table 3.5, entry 4). To a flame-dried 50-mL round-bottomed flask under Ar was added samarium metal (160 mg, 1.06 mmol, 40 mesh) and 9 mL of anhydrous THF. The mixture was stirred vigorously and cooled in an ice/H₂O bath to 4°C under Ar.

Diiodomethane (0.072 mL, 0.89 mmol) was added slowly and the mixture was stirred in the ice/H₂O bath under Ar. After 15 min, the solution had turned from colorless to light yellow to a deep blue-green color (indicating formation of SmI₂). After 1.5 h of stirring, **3.52** (144 mg, 0.435 mmol) was dissolved in 1 mL of anhydrous THF in a flame-dried 5-mL flask under Ar and transferred to the SmI₂ solution via cannula. After a few min, the blue-green color turned to a dark green color. No further color change was observed. Reaction progress was monitored by TLC (1:1 hexanes/EtOAc - CAM stain). After 5 h, no starting material was observed and a new, more polar spot (R_f ~0.21) was observed by TLC. The reaction was diluted with CH₂Cl₂ (30 mL) and 10 wt% aqueous Na₂S₂O₃ (20 mL) was added to quench the reaction. An emulsion formed and H₂O (~50-60 mL) was added. 1M HCl (~20 mL) was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (2 x 20 mL). The combined organic layers were washed with 1M HCl (1 x 30 mL), dried over MgSO₄, filtered through a pad of celite, and concentrated by rotary evaporation (30°C, 21 mm Hg) to afford a pungent-smelling yellow/white solid/oil. The crude material was chromatographed through 50 g of silica using a solvent gradient from 100% CH₂Cl₂ to 80% CH₂Cl₂/EtOAc and yielded **3.69** as a colorless oil (57.0 mg, 39% yield). R_f = 0.21 (1:1 hexanes/EtOAc - CAM stain). ¹H NMR (500 MHz, CDCl₃) δ 5.04 (br-d, *J* = 7.5 Hz, 1H), 4.26 (m, 1H), 4.15 (dd, *J* = 7.5, 4.0 Hz, 1H), 3.76 (s, 3H), 3.71 (s, (3H), 2.52 (br, 1H), 1.79 – 1.73 (m, 2H), 1.64 – 1.57 (m, 2H), 1.41 (s, 9H), 1.45 – 1.33 (m, 4H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 175.6, 173.3, 155.3, 79.8, 70.1, 53.3, 52.5, 52.2, 34.0, 32.5, 28.2, 24.9, 24.3 ppm. MS (FAB) *m/z* [M+H]⁺ at 334, 278, 234 (base peak), 174.

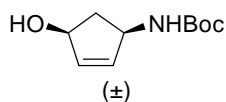
General procedure for N-O bond reduction using Mo(CO)₆. Attempted reduction of 3.52 (Table 3.5, entry 2). Compound **3.52** (0.101 g, 0.303 mmol) was dissolved in 15:1 CH₃CN/H₂O (4.4 mL) in a 25-mL flask. Molybdenum hexacarbonyl (59 mg, 0.22 mmol) was added and the solution was heated at reflux (oil bath temperature 85-100 °C) overnight. The color of the solution changed to yellow, then deep brown. The mixture was cooled to RT, then cooled at 0 °C for 1 h and filtered through a pad of celite, rinsing the solid residue with portions of EtOAc. The filtrate was concentrated to yield a pale yellow residue. Analysis of the crude material did not indicate the presence of the desired product, compound **3.69**.

General procedure for N-O bond reduction using Zn/HOAc. Attempted reduction of 3.52 (Table 3.5, entry 3). Zinc dust (0.329 g, 5.03 mmol), previously activated by rinsing with conc. HCl and drying in the oven, was added to **3.52** (0.100 g, 0.303 mmol) in 2.5 mL of glacial acetic acid in a 10-mL flask. The mixture was stirred at RT overnight. Analysis of the mixture only indicated the presence of **3.52** and the mixture was heated in an oil bath maintained at 75-80 °C overnight. No change was observed during this time.

General procedure for N-O bond reduction using Na-Hg. Attempted reduction of 3.52 (Table 3.5, entry 5). Compound **3.52** (0.122 g, 0.367 mmol) was added to a flame-dried 25-mL flask and dissolved in 2:1 MeOH/THF (6 mL) under Ar. The solution was cooled to 4 °C in an ice/H₂O bath and Na₂HPO₄ (0.264 g, 1.86 mmol) was added. 5% sodium-mercury amalgam (0.868 g, 1.90 mmol sodium) was added and

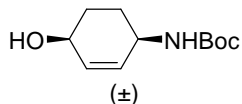
the resultant cloudy mixture was stirred for 2 h. Liquid mercury was observed in the bottom of the flask and the mixture was warmed to RT. The mixture was stirred at RT for 2 h and the solution was decanted from the liquid mercury and filtered through celite. Multiple portions of EtOAc and MeOH were added to the reaction flask, decanted from the residual mercury, and filtered through celite. The filtrate was concentrated to yield a white solid. Analysis of the solid material did not indicate the presence of the desired compound.

General procedure for N-O bond reduction using hydrogenolysis. Attempted reduction of 3.53 (Table 3.5, entry 7). Acetyl chloride (0.075 mL, 1.1 mmol) was added to 5 mL of anhydrous methanol under Ar in a 250-mL Parr bomb. After 30 min, **3.53** (0.204 g, 0.882 mmol) in 5 mL of methanol was added and the Parr bomb was evacuated and purged with Ar (2x). 10% Pd/C (33 mg, 16 wt%) was added and the reaction flask was evacuated and purged with Ar (2x), then evacuated and purged with H₂ (2x). The mixture was shaken under H₂ (2.8 bar, 30 psi) using a Parr hydrogenation apparatus for 6 h. The mixture was evacuated and purged with Ar (3x), then filtered through celite. The filtrate was concentrated to yield a pale yellow residue. Analysis of the residue indicated mostly **3.53** remained in the mixture in addition to a small amount of baseline ninhydrin-positive material (presumably amine **3.70**) and a less polar product. Transesterification may have occurred in the reaction, but this was not confirmed.



(±)-tert-Butyl (1R,4S)-4-hydroxycyclopent-2-enylcarbamate (3.71).

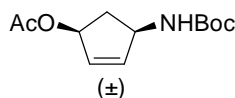
Cycloadduct **3.38** (1.11 g, 5.63 mmol) was dissolved in 20 mL of 4:1 CH₃CN/H₂O. Mo(CO)₆ (598 mg, 2.27 mmol) was added, followed by NaBH₄ (660 mg, 17.4 mmol). The reaction bubbled and turned bright yellow. The reaction was heated to 70 °C with a condenser and stirred under mild reflux. The reaction turned brown after 30 min. The reaction was monitored by TLC (1:1 hexanes/EtOAc). After 12 h, the reaction was cooled to room temperature and then cooled to 0 °C for 30 min. The reaction was filtered through a pad of celite to remove the solid. The celite was washed with EtOAc and CH₃CN and the yellow filtrate was concentrated to yield a dark yellow oil (1.29 g). The oil was chromatographed through 100 g of silica using 1:1 hexanes/EtOAc to yield **3.71** as a yellow oil (898 mg, 80%). R_f = 0.20 (1:1 hexanes/EtOAc – UV lamp, CAM stain). ¹H NMR (500 MHz, CDCl₃) δ 5.94 (m, 1H), 5.80 (m, 1H), 5.01 (m, 1H), 4.65 (m, 1H), 4.42 (m, 1H), 3.37 (br, 1H), 2.69 (m, 1H), 1.49 (d, *J* = 14.5 Hz, 1H), 1.41 (s, 10H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 155.3, 136.0, 134.1, 79.5, 75.0, 54.7, 41.3, 28.4 ppm.



(±)-tert-Butyl (1R,4S)-4-hydroxycyclohex-2-enylcarbamate (3.72).

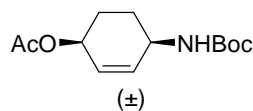
Prepared following the same procedure used for **3.71**. Cycloadduct **3.39** (1.05 g, 4.97 mmol), Mo(CO)₆ (525 mg, 1.99 mmol), and NaBH₄ (600 mg, 15.9 mmol) provided a dark yellow oil (1.12 g). The oil was chromatographed through 75 g of silica using 1:1

hexanes/EtOAc to yield **3.72** as a yellow oil (903 mg, 85%). ^1H NMR (300 MHz, CDCl_3) δ 5.861 (dq, $J = 9.9$ Hz, 1H), 5.741 (dd, $J = 10.2, 2.7$ Hz, 1H), 4.596 (br-m, 1H), 4.151 (br-m, 1H), 1.855 (m, 2H), 1.675 (m, 2H), 1.443 (s, 9H) ppm.



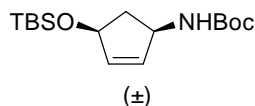
(±)-Acetic acid 4-tert-butoxycarbonylamino-cyclopent-2-enyl ester (3.73).

Alcohol **3.71** (852 mg, 4.28 mmol) was dissolved in 30 mL of CH_2Cl_2 . Imidazole (501 mg, 7.36 mmol) was added to the reaction and the reaction was cooled to 0 °C. Acetyl chloride (0.460 mL, 6.45 mmol) was added slowly to the reaction. A white precipitate formed. The reaction was stirred overnight and monitored by TLC (1:1 hexanes/EtOAc). After 18 h, 1 equiv more acetyl chloride was added to the reaction. No change was observed after 4 h. The reaction was diluted and partitioned between CH_2Cl_2 and H_2O . The aqueous layer (pH 2) was extracted with CH_2Cl_2 . The combined organic layers were washed with 1M HCl, dried over Na_2SO_4 , filtered, and concentrated to yield an orange oil (867 mg). The oil was chromatographed through 87 g of silica using 4:1 to 3:1 hexanes/EtOAc to yield a colorless oil. Recrystallization from hexanes yielded **3.73** as white needlelike crystals (673 mg, 65%). mp = 48-51 °C. ^1H NMR (500 MHz, CDCl_3) δ 5.95 (d, $J = 5.5$ Hz, 1H), 5.89 (d, $J = 5.5$ Hz, 1H), 5.49 (m, 1H), 4.65 (m, 1H), 2.79 (m, 1H), 2.00 (s, 3H), 1.49 (dt, $J = 14.5, 4.0$ Hz, 1H), 1.41 (m, 10H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 170.5, 154.9, 136.9, 132.0, 79.5, 77.4, 54.2, 38.5, 28.3, 21.1 ppm.



(±)-Acetic acid 4-tert-butoxycarbonylamino-cyclohex-2-enyl ester (3.74).

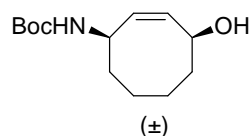
Compound **3.74** was prepared following the same procedure for compound **3.73**. Alcohol **3.72** (903 mg, 4.23 mmol), imidazole (489 mg, 7.18 mmol), and acetyl chloride (0.450 mL, 6.31 mmol) provided a yellow oil (900 mg). The oil was chromatographed through 90 g of silica using 4:1 to 3:1 hexanes/EtOAc to yield **3.74** as a white solid (630 mg, 59%). mp = 82-83 °C. ¹H NMR (500 MHz, CDCl₃) δ 5.81 (dd, *J* = 10, 2.5 Hz, 1H), 5.76 (d, *J* = 10 Hz, 1H), 5.14 (m, 1H), 4.60 (d, *J* = 7.0 Hz, 1H), 4.11 (m, 1H), 2.00 (s, 3H), 1.87 – 1.69 (m, 3H), 1.63 – 1.54 (m, 1H), 1.40 (s, 9H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 170.4, 155.1, 133.5, 127.9, 79.4, 68.1, 66.8, 45.8, 28.3, 25.7, 21.2 ppm.



(±)-tert-Butyl (1R,4S)-4-(tert-butyldimethylsilyloxy)cyclopent-2-

enylcarbamate (3.75). Compound **3.71** (201 mg, 1.01 mmol) was dissolved in 20 mL of anhydrous DMF in a flame-dried 50-mL round-bottomed flask under Ar. Imidazole (277 mg, 4.07 mmol) was added, followed by TBSCl (303 mg, 2.01 mmol) and the solution was stirred at RT under Ar. After 4 h, TLC of the reaction (1:1 hexanes/EtOAc - CAM stain) did not show any starting material and the reaction was complete. The reaction was concentrated to 10 mL by rotary evaporation. H₂O (75 mL) and EtOAc (50 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 50 mL), and the combined organic layers were washed with brine (2 x 35 mL), dried

over MgSO_4 , filtered, and concentrated to yield a yellow oil. The oil was chromatographed through 30 g of silica using 100% CH_2Cl_2 and provided **3.75** as a colorless oil (0.288 g, 91%). ^1H NMR (500 MHz, CDCl_3) δ 5.85 – 5.78 (m, 2H), 4.69 (t, J = 6.0 Hz, 1H), 4.61 (br-m, 1H), 4.57 (br-m, 1H), 2.71 (m, 1H), 1.40 (s, 9H), 1.36 (m, 1H), 0.89 (s, 9H), 0.07 (s, 6H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 155.1, 136.6, 133.6, 75.4, 54.4, 42.8, 28.4, 25.9, 18.2, -4.7 ppm.

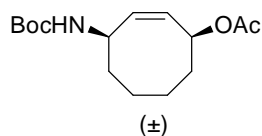


(±)-tert-Butyl (1R,4S,Z)-4-hydroxycyclooct-2-enylcarbamate (3.76).

Cycloadduct **3.40** (1.50 g, 6.27 mmol) was dissolved in 64 mL of 15:1 $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ in a 250-mL round-bottomed flask and heated in a 55 °C oil bath. Molybdenum hexacarbonyl (1.19 g, 4.52 mmol) was added to the reaction in one portion. A jacketed condenser was attached to the flask and the reaction was heated to reflux (oil temp = 95 °C). The reaction turned yellow after 15 min of heating, then turned brown and finally black overnight. After 19 h, the TLC analysis (1:1 hexanes/EtOAc - CAM stain), the of the reaction showed clean, but incomplete conversion to the product. Additional $\text{Mo}(\text{CO})_6$ (0.462 g, 1.75 mmol) was added (total $\text{Mo}(\text{CO})_6$ = 1 equivalent) and the reaction was heated to reflux for an additional 2 h. The reaction was cooled to RT, then filtered through a pad of celite. The brown filtrate was concentrated to yield a brown oil and a glassy solid. The mixture was partitioned between EtOAc (75 mL) and H_2O (75 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 60 mL) and the combined organic layers were washed with brine (2 x 75 mL), dried over

MgSO₄, filtered, and concentrated to yield a tan solid. The crude material was loaded onto silica and chromatographed through a Biotage 40M column (90 g of silica) using a solvent gradient from 75% CH₂Cl₂/EtOAc to 60% CH₂Cl₂/EtOAc to yield **3.76** as a white solid (1.44 g, 95%). mp = 137-139 °C. R_f = 0.25 (1:1 hexanes/EtOAc – CAM stain). ¹H NMR (500 MHz, CDCl₃) δ 5.57 (dd, *J* = 11, 7.5 Hz, 1H), 5.23 (ddd, *J* = 11.5, 10.5, 1.5 Hz, 1H), 4.63 (br, 1H), 4.34 (br, 1H), 2.44 (br, 1H), 1.91 – 1.81 (m, 2H), 1.61 – 1.53 (m, 2H), 1.48 – 1.41 (m, 3H), 1.41 (s, 9H), 1.33 – 1.25 (m, 1H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 155.2, 134.7, 130.0, 79.4, 69.3, 48.8, 38.2, 36.5, 28.4, 24.0, 23.4 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₃H₂₄NO₃⁺, 242.1756; obsd, 242.1754.

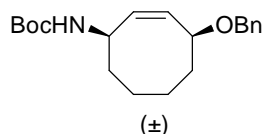
Preparation of 3.76 using SmI₂. Compound **3.76** was prepared following the general procedure for N-O bond reduction using samarium diiodide. Cycloadduct **3.40** (102 mg, 0.426 mmol) was treated with 2.5 eq of samarium diiodide prepared from samarium metal (0.161 g, 1.07 mmol) and diiodomethane (0.070 mL, 0.87 mmol) and provided **3.76** as a white foam after chromatography through 10 g of silica (81 mg, 79%).



(±)-(1S,4R,Z)-4-(tert-Butoxycarbonylamino)cyclooct-2-enyl acetate (3.77).

Alcohol **3.76** (2.59 g, 10.7 mmol) was dissolved in 50 mL of anhydrous pyridine in a flame-dried single-necked 250-mL round-bottomed flask under Ar. Acetic anhydride (2.50 mL, 26.5 mmol) was added and the light yellow solution was stirred at RT under Ar. After 25 h, the reaction was concentrated by rotary evaporation to yield a light

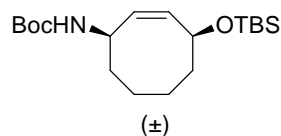
yellow solid. The solid was partitioned between 1M HCl (100 mL) and EtOAc (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 40 mL). The combined organic layers were washed with 1M HCl (2 x 35 mL), H₂O (35 mL), saturated NaHCO₃ (2 x 35 mL), and brine (35 mL), dried over MgSO₄, filtered, and concentrated to yield a white solid (2.99 g, 98% yield). Further purification was not necessary, but could be carried out by chromatography through silica using a solvent gradient from 100% CH₂Cl₂ to 80% CH₂Cl₂. mp = 117-119 °C. ¹H NMR (500 MHz, CDCl₃) δ 5.60 (m, 1H), 5.54 (dd, *J* = 10.2, 7.6 Hz, 1H), 5.33 (t, *J* = 9.3 Hz, 1H), 4.57 (br-m, 1H), 4.37 (br-m, 1H), 2.00 (s, 3H), 1.92 (m, 2H), 1.62-1.44 (m, 4H), 1.41 (s, 9H), 1.36-1.29 (m, 2H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 170.0, 154.9, 131.2, 129.7, 79.2, 72.1, 49.0, 36.2, 35.1, 28.3, 23.8, 23.0, 21.2 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₅H₂₆NO₄⁺, 284.1862; obsd, 284.1847.



(±)-*tert*-Butyl (1*R*,4*S*,*Z*)-4-(benzyloxy)cyclooct-2-enylcarbamate (3.78).

Alcohol **3.76** (0.504 g, 2.09 mmol) was dissolved in 20 mL of anhydrous THF under Ar in a flame-dried 100-mL round-bottomed flask. Benzyl bromide (0.50 mL, 4.5 mmol) was added and the light yellow solution was cooled in an ice/H₂O bath under Ar. Sodium hydride (0.214 g, 50% dispersion in mineral oil, 4.46 mmol) was added to the reaction in one portion. The reaction immediately turned cloudy. The cloudy suspension was stirred in the ice/H₂O bath, slowly reaching RT under Ar overnight. Monitored reaction by TLC (4:1 hexanes/EtOAc - CAM stain). Alcohol **3.76** remained after stirring overnight and

over the weekend (3 days). An additional 20 mL of anhydrous THF was added to the white suspension and the reaction was stirred under Ar at RT. After 2 days (5 days total) no **3.76** was observed by TLC of the reaction mixture. The reaction was cooled in an ice/H₂O bath and quenched by adding H₂O dropwise until all of the white solid dissolved completely (~15 mL - some bubbling observed). Et₂O (50 mL) was added and the layers were separated. The aqueous layer was extracted with Et₂O (2 x 50 mL), and the combined organic layers were washed with brine (2 x 50 mL), dried over MgSO₄, filtered, and concentrated to yield a light yellow oil. The crude material was loaded onto silica and chromatographed through a 40S Biotage column (40 g of silica) using a solvent gradient from 100% hexanes to 80% hexanes/EtOAc and provided **3.78** as a light yellow oil (553 mg, 80% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.41 – 7.28 (m, 5H), 5.67 (ddd, *J* = 11, 7.0, 1.0 Hz, 1H), 5.46 (ddd, *J* = 11, 8.0, 1.5 Hz, 1H), 4.73 (d, *J* = 7.0 Hz, 1H), 4.65 (d, *J* = 11.5 Hz, 1H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.39 (br, 2H), 2.07 – 2.01 (m, 1H), 1.91 (m, 1H), 1.63 – 1.51 (m, 13H), 1.51 (s, 9H), 1.38 – 1.29 (m, 1H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 155.0, 138.4, 133.1, 132.0, 128.2, 127.7, 127.3, 79.1, 76.2, 70.8, 49.0, 36.7, 35.8, 28.3, 24.2, 23.3 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₂₀H₃₀NO₃⁺, 332.2226; obsd, 332.2200.

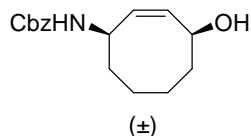


(±)-*tert*-Butyl

(1*R*,4*S*,*Z*)-4-(*tert*-butyldimethylsilyloxy)cyclooct-2-

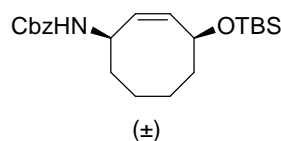
enylcarbamate (**3.79**). Alcohol **3.76** (1.44 g, 5.96 mmol) was dissolved in 60 mL of DMF in a single-necked 250-mL round-bottomed flask under Ar. Imidazole (1.76 g, 25.9

mmol) was added, followed by TBSCl (1.81 g, 12.0 mmol). The solution was stirred at RT under Ar. After 2.5 days, the reaction was complete by TLC analysis of the reaction mixture (4:1 hexanes/EtOAc - CAM stain). The yellow solution was concentrated by rotary evaporation (55 °C, 20 mm Hg) to about 10 mL, then partitioned between H₂O (50 mL) and EtOAc (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 75 mL). Some brine was added to the biphasic mixture during separation to break the emulsion that formed. The combined EtOAc layers were washed with H₂O (50 mL), and brine (2 x 50 mL), dried over MgSO₄, filtered, and concentrated by rotary evaporation (45 °C, 20 mm Hg) to yield 2.8 g of a yellow oil. The oil was chromatographed through 200 g of silica using a solvent gradient from 90% CH₂Cl₂/hexanes to 100% CH₂Cl₂ and yielded **3.79** as a white solid (2.02 g, 95% yield). mp = 84-85 °C. ¹H NMR (500 MHz, CDCl₃) δ 5.54 (dd, *J* = 11.0, 7.0 Hz, 1H), 5.17 (ddd, *J* = 11.0, 8.5, 1.5 Hz, 1H), 4.53 (br, 2H), 4.34 (br, 1H), 1.89 – 1.79 (m, 2H), 1.55 – 1.44 (m, 5H), 1.43 (s, 9H), 1.31 – 1.24 (m, 1H), 0.88 (s, 9H), 0.063 (s, 3H), 0.057 (s, 3H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 155.0, 135.7, 128.5, 79.2, 70.2, 49.0, 39.3, 36.9, 28.4, 25.8, 24.2, 23.4, 18.2, -4.6, -4.8 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₉H₃₈NO₃Si⁺, 356.2621; obsd, 356.2633.



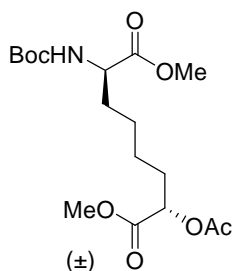
(±)-Benzyl (1R,4S,Z)-4-hydroxycyclooct-2-enylcarbamate (3.80). Compound **3.80** was prepared following the same procedure for **3.76**. Cycloadduct **3.43** (5.73 g, 21.0 mmol) and molybdenum hexacarbonyl (5.55 g, 21.0 mmol) provided a brown solid.

Chromatography through 180 g of silica using a solvent gradient from 100% CH₂Cl₂ to 60% CH₂Cl₂/EtOAc provided **3.80** as a white solid (5.01 g, 87%). mp = 125-126 °C. Rf = 0.18 (1:1 hexanes/EtOAc – CAM stain). ¹H NMR (500 MHz, CDCl₃) δ 7.35 (m, 5H), 5.61 (dd, *J* = 11.0, 7.5 Hz, 1H), 5.27 (ddd, *J* = 11.0, 8.5, 1.5 Hz, 1H), 5.08 (s, 2H), 4.85 (br, 1H), 4.65 (br, 1H), 4.42 (br, 1H), 2.12 (br, 1H), 1.90 (m, 2H), 1.61 (m, 2H), 1.49 (m, 2H), 1.38 – 1.25 (m, 1H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 155.6, 136.4, 134.9, 129.7, 128.5, 128.1, 69.4, 66.7, 49.3, 38.3, 36.5, 24.0, 23.3 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₆H₂₂NO₃⁺, 276.1600; obsd, 276.1592.



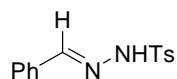
(±)-Benzyl (1R,4S,Z)-4-(tert-butyldimethylsilyloxy)cyclooct-2-enylcarbamate (3.81). Compound **3.81** was prepared following the same procedure for **3.79**. Alcohol **3.80** (3.00 g, 10.9 mmol), TBDMSCl (3.32 g, 22.0 mmol), and imidazole (2.98 g, 43.8 mmol) provided 4.5 g of crude material. Chromatography through 200 g of silica using a solvent gradient from 90% CH₂Cl₂/hexanes to 100% CH₂Cl₂ yielded **3.81** as a colorless oil that solidified upon standing (3.96 g, 93%). mp = 80-82 °C. Rf = 0.50 (2:1 hexanes/EtOAc – CAM stain). ¹H NMR (500 MHz, CDCl₃) δ 7.35 (m, 5H), 5.58 (m, 1H), 5.21 (ddd, *J* = 10.5, 8.0, 1.5 Hz, 1H), 5.11 (m, 2H), 4.81 (br, 1H), 4.57 (br, 1H), 4.43 (br, 1H), 1.90 – 1.82 (m, 2H), 1.60 – 1.48 (m, 5H), 1.32 (m, 1H), 0.90 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 155.4, 136.1, 128.5, 128.3, 128.0, 70.2, 66.6, 49.4, 39.2, 36.7, 25.8, 24.1, 23.4, 18.2, -4.6, -4.9 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₂₂H₃₆NO₃Si⁺, 390.2464; obsd, 390.2458.

Attempted Kornblum-DeLaMare rearrangement of 3.40. Cycloadduct **3.40** (0.108 g, 0.451 mmol) was dissolved in 5 mL of anhydrous CH₂Cl₂ in a flame-dried single-necked 25-mL round-bottomed flask under Ar. Dry triethylamine (0.020 mL, 0.14 mmol) was added and the solution was stirred at RT under Ar. After 2 days at RT, only **3.40** was observed by TLC. No change was observed after stirring at RT for a few additional days or after the addition of excess triethylamine.



(±)-(2*S*,7*R*)-Dimethyl 2-acetoxy-7-(*tert*-butoxycarbonylamino)octanedioate (3.86). Compound **3.77** (507.8 mg, 1.792 mmol) was dissolved in 17.5 mL of CCl₄/CH₃CN/H₂O (2:2:3) in a 50-mL round-bottomed flask, and cooled to 4°C in an ice/H₂O bath. NaIO₄ (1.542 g, 7.21 mmol) was added to the reaction, followed by RuCl₃ hydrate (15 mg, 0.072 mmol). The reaction immediately turned light brown. After 1 h the reaction mixture was still brown and was stirred at RT. After 3.5 h, the reaction had become jet black in color. 20 mL of 10% Na₂S₂O₅ was added to the reaction and the mixture was stirred for 10 min before filtering through a pad of celite and rinsing the reaction flask with 50 mL of EtOAc. The layers in the filtrate were separated and the aqueous layer (dark green in color, pH 2-3 by pH paper) was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated

to yield a brown oil (720 mg). The crude material was dissolved in Et₂O (15 mL) in a 50-mL flask and treated with excess diazomethane, prepared from Diazald as described in the general procedure, at 4 °C (ice/H₂O bath). Bubbling was observed in the reaction flask during the addition of fresh diazomethane solution. The reaction was stirred for an 15 min at 4 °C, then was quenched by adding 10 vol% HOAc in Et₂O slowly until no bubbles were observed in the reaction. The light brown solution was poured into 50 mL of saturated NaHCO₃ and the layers were separated. The aqueous layer (pH 8 - pH paper) was extracted with Et₂O (2 x 20 mL), and the combined Et₂O layers were washed with brine (20 mL), dried over MgSO₄, filtered, and concentrated to yield a brown oil (~640 mg). The crude material was chromatographed through 75 g of silica using a solvent gradient from 100% CH₂Cl₂ to 80% CH₂Cl₂/EtOAc to yield **3.86** as a yellow oil (503.5 mg, 74.8% yield) as well as minor amounts of two additional products (24.5 mg and 18 mg, respectively). The byproducts were not fully characterized. ¹H NMR (500 MHz, CDCl₃) δ 5.04 (m, 1H), 4.92 (m, 1H), 4.23 (m, 1H), 3.67 (s, 6H), 2.07 (s, 3H), 1.80 – 1.72 (m, 3H), 1.63 – 1.53 (m, 2H), 1.42 – 1.28 (m, 12H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 173.1, 170.5, 170.3, 155.2, 82.2, 79.7, 77.9, 71.9, 53.1, 52.1, 32.3, 30.7, 28.2, 24.7, 24.6, 20.4 ppm. MS (FAB) *m/z* [M+H]⁺ at 376; 320, 276 (base), 260, 216.



***N'*-Benzylidene-4-methylbenzenesulfonohydrazide (3.87).** *p*-

Toluenesulfonylhydrazide (14.24 g, 76.5 mmol) was suspended in 25 mL of MeOH in a 125-mL Erlenmeyer flask. Benzaldehyde (7.0 mL, 68.9 mmol), purified from the benzaldehyde-bisulfite adduct, was added rapidly to the slurry while stirring. The solid

material dissolved after 1 min and a mildly exothermic reaction was observed. The yellow solution was left to stand and reach RT. After a few minutes, the product began to crystallize out of the solution. After 40 min, the mixture was filtered under vacuum and the white crystals were washed with a small amount of cold methanol. The crystals were dried under the aspirator vacuum to yield **3.87** as white needle-like crystals (15.675 g, 83% yield). mp = 126-128 °C (lit. 124-125 °C).

General procedure for preparation of phenyldiazomethane from 3.87. A freshly prepared solution of 1.05 M sodium methoxide in MeOH (5.30 mL, 5.57 mmol) was added to **3.87** (1.48 g, 5.39 mmol) in a single-necked 25-mL round-bottomed flask. The mixture was swirled until the solid dissolved and the resultant yellow solution was concentrated by rotary evaporation (45 °C, 21 mm Hg) to yield a white solid. The solid was dried under vacuum (<1 mm Hg) for 30 min. The flask was fitted with a short-path distillation apparatus and a receiver flask, then evacuated (<1 mm Hg). The receiver flask was cooled to -50 to -60 °C in a dry ice/acetone bath and a safety shield was set in front of the apparatus. The flask containing the hydrazone salt was heated in an oil bath. The oil temperature was raised slowly to ~200 °C over 45-60 min. At an oil temperature of ~110 °C, red phenyldiazomethane (**3.88**) was observed collecting in the receiver flask. At an oil temperature of ~200 °C, phenyldiazomethane was not observed collecting in the receiver flask anymore and the oil bath was allowed to cool to < 100 °C before the apparatus was disassembled. **3.88** was used immediately without warming to RT (it has been reported to be explosive at room temperature). Workup procedures for reactions utilizing phenyldiazomethane follow the same procedure used for diazomethane

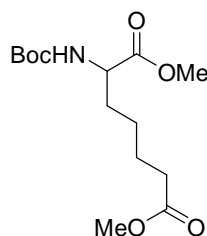
reactions. All remaining and excess diphenyldiazomethane was quenched by adding a dilute solution of acetic acid in ether.

General procedure for oxidative alkene cleavage reactions using OsO₄/Oxone. Attempted oxidative cleavage of 3.77 (Table 3.6, entry 10). Compound **3.77** (148.1 mg, 0.523 mmol) was dissolved in 3 mL of anhydrous DMF in a flame-dried 10-mL round-bottomed flask under Ar. OsO₄ (0.07 mL, 2.5 wt% in *t*BuOH, 0.006 mmol) was added to the solution (the reaction turned slightly yellow). After 5 min, Oxone (1.285 g, 2.09 mmol) was added to the reaction in one portion and the mixture was stirred vigorously at RT under Ar. The reaction was monitored by TLC (1:1 hexanes/EtOAc - CAM stain). After 4 h, some products were observed, but not the desired dicarboxylic acid products (*R_f* was too high, just below **3.77**), as well as remaining **3.77**. After stirring overnight at RT, no change was observed. The reaction was quenched by adding 6 equiv of Na₂SO₃ and stirring at RT. Reactions using added sodium bicarbonate followed the same procedure except for the addition of 7 equivalents of NaHCO₃ to the reaction mixture.

General procedure for attempted dihydroxylation of an olefin using OsO₄/NMO. Attempted dihydroxylation of 3.77. Compound **3.77** (117.3 mg, 0.414 mmol) was dissolved in 4 mL of THF in a single-necked 25-mL round-bottomed flask. NMO (50 wt% in H₂O, 0.18 mL, 0.87 mmol) was added to the reaction followed by 2 drops of OsO₄ (2.5 wt% in *t*BuOH). The solution was stirred at RT. TLC analysis (1:1

hexanes/EtOAc - CAM stain) of the solution after 4 h showed only starting material. After stirring at RT for 2 days, no change was observed.

General procedure for attempted dihydroxylation of an olefin using $\text{RuCl}_3/\text{NaIO}_4/\text{CeCl}_3$. Attempted dihydroxylation of **3.79.** H_2O (0.10 mL) was added to NaIO_4 (65.2 mg, 0.305 mmol) and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (10.5 mg, 0.028 mmol) in a 1-dram vial. The mixture was heated until the color changed to bright yellow, then was cooled in a crushed ice/ H_2O bath. CH_3CN (0.30 mL) was added, followed by a 0.1 M aqueous solution of RuCl_3 (0.01 mL, 0.001 mmol). After stirring for 2 min, **3.79** (71 mg, 0.20 mmol) was added to the brown suspension as a solution in EtOAc (0.30 mL). The mixture was stirred in the ice/ H_2O bath and analyzed by TLC (1:1 hexanes/EtOAc - CAM stain) for the disappearance of **3.79**. After 15 min, TLC analysis indicated the reaction was progressing and two new, more polar spots were observed by TLC, but **3.79** still remained. After 45 min, the initial two new spots had not increased in intensity, but about 4 new spots started to emerge and a complex mixture was obtained.

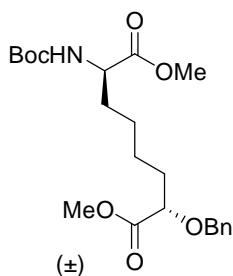


(±)-Dimethyl 2-(tert-butoxycarbonylamino)heptanedioate (3.90). Compound **3.77** (734.5 mg, 2.592 mmol) was dissolved in 21 mL of CH_2Cl_2 . 5.2 mL of 2.5M methanolic KOH (13 mmol) was added and the colorless solution immediately became light yellow. The solution was cooled in a dry ice/acetone bath and O_3/O_2 was bubbled

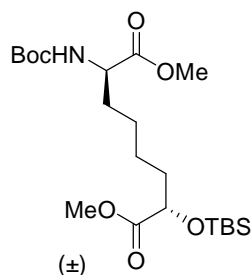
through the solution. The reaction immediately turned a deep tangerine-orange color and a yellow/orange precipitate formed in the reaction. After 1 h, the ozone bubbling was stopped and the reaction was diluted with Et₂O (15 mL) then H₂O until the reaction became colorless and the solid material dissolved completely. The tangerine/orange suspension became a colorless solution as the reaction was warmed to RT. The layers were separated and the aqueous layer was extracted with Et₂O (3 x 40 mL), and the combined organic layers were washed with brine (2 x 30 mL), dried over MgSO₄, filtered, and concentrated to yield a light yellow oil (708 mg). TLC analysis (1:1 hexanes/EtOAc - CAM stain) shows clean conversion to a mixture of 2 compounds. The crude material was chromatographed through a 40S Biotage column (40g of silica) using a solvent gradient from 70% hexanes/EtOAc to 50% hexanes/EtOAc to yield **3.69** as a residue (74 mg, 8%) and **3.90** as a light yellow oil (309 mg, 39%). ¹H NMR (500 MHz, CDCl₃) δ 5.00 (d, *J* = 8.0 Hz, 1H), 4.29 (dd, *J* = 13.5, 8.0 Hz, 1H), 3.73 (s, 3H), 3.66 (s, 3H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.86 – 1.76 (m, 1H), 1.66 – 1.59 (m, 4H), 1.44 (s, 9H), 1.40 – 1.34 (m, 1H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 173.8, 173.2, 155.3, 79.8, 53.2, 52.2, 51.5, 33.7, 32.4, 28.2, 24.8, 24.4 ppm. MS (FAB) *m/z* [M+H]⁺ at 304, 248, 204 (base), 144.

General procedure for removal of an acetate using K₂CO₃. Compound 3.69 from saponification of 3.86. Compound **3.86** (0.398 g, 1.06 mmol) was dissolved in 11 mL of anhydrous methanol in a 100-mL round-bottomed flask under Ar. Potassium carbonate (0.208 g, 1.51 mmol) was added and the yellow mixture was stirred at RT under Ar. The reaction was monitored by TLC (1:1 hexanes/EtOAc - CAM stain). After

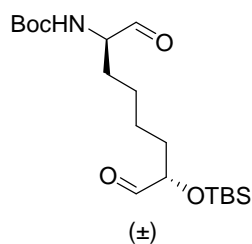
30 min, only a small amount of **3.86** was observed and a more polar spot was observed. After 1.5 h, the reaction was partitioned between H₂O (25 mL), brine (25 mL), and EtOAc (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine (25 mL), dried over MgSO₄, filtered, and concentrated to yield **3.69** as a yellow oil (0.277 g, 78% yield). See above for characterization data.



(±)-(2S,7R)-Dimethyl 2-(benzyloxy)-7-(tert-butoxycarbonylamino) octanedioate (3.91). Compound **3.91** was prepared following the same procedure used for compound **3.90**. The use of **3.78** (469 mg, 1.41 mmol) provided a colorless oil (471 mg). The oil was loaded onto silica and chromatographed through a Biotage 40S column (40 g of silica) using a solvent gradient from 100% CH₂Cl₂ to 90% CH₂Cl₂/EtOAc to yield **3.91** as a yellow oil (118.5 mg, 20%). The product was not pure by NMR; however, spectral information for the appropriate NMR signals are presented here from the impure sample: ¹H NMR (300 MHz, CDCl₃) δ 7.34 (m, 5H), 5.05 (d, *J* = 8.1 Hz, 1H), 4.69 (d, *J* = 11.7 Hz, 1H), 4.38 (d, *J* = 11.7 Hz, 1H), 4.28 (m, 1H), 3.93 (t, *J* = 6.3 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 2.36 – 2.29 (m, 1H), 1.79 – 1.60 (m, 6H), 1.44 (s, 9H), 1.43 – 1.31 (m, 2H) ppm.

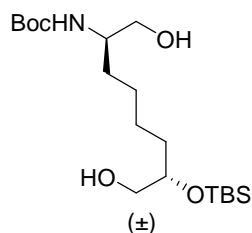


(±)-(2*R*,7*S*)-Dimethyl 2-(*tert*-butoxycarbonylamino)-7-(*tert*-butyldimethylsilyloxy)octanedioate (**3.92**). Compound **3.92** was prepared following the same procedure used for **3.90**. The use of **3.79** (514.7 mg, 1.45 mmol) provided a yellow oil. The oil was chromatographed through 65 g of silica using a solvent gradient from 100% CH₂Cl₂ to 90% CH₂Cl₂/EtOAc to afford **3.92** as a pale yellow oil (351.9 mg, 54%). The product contained TBS-containing impurities by NMR. ¹H NMR (500 MHz, CDCl₃) δ 4.99 (br, 1H), 4.26 (br, 1H), 4.16 (t, *J* = 6.0 Hz, 1H), 3.70 (s, 3H), 3.68 (s, 3H), 2.29 (t, *J* = 7.0 Hz, 1H), 1.77 (m, 1H), 1.69 – 1.64 (m, 2H), 1.63 – 1.55 (m, 1H), 1.41 (s, 9H), 1.38 – 1.29 (m, 2H), 0.90 (s, impurity), 0.87 (s, 9H), 0.23 (s, impurity), 0.04 (s, 3H), 0.02 (s, 3H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 174.1, 173.3, 155.3, 79.8, 72.0, 53.4, 52.1, 51.7, 35.6, 34.8, 32.6, 32.4, 28.3, 25.7, 25.5, 25.0, 24.8, 24.7, 24.6, 18.2, 17.5, -4.9, -5.0, -5.4 ppm.



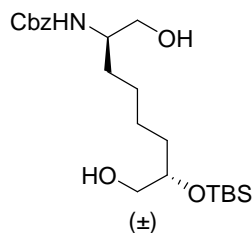
(±)-*tert*-Butyl (2*R*,7*S*)-7-(*tert*-butyldimethylsilyloxy)-1,8-dioxooctan-2-ylcarbamate (**3.93**). Compound **3.79** (149.6 mg, 0.421 mmol) was dissolved in 5 mL of

4:1 CH₂Cl₂/MeOH in a single-necked 25-mL round-bottomed flask. The solution was cooled in a dry ice/actone bath to -78 °C and a stream of ozone was bubbled through the solution. The blue color of ozone was observed in the solution after ~5 min, and the ozone flow was stopped after 10 min. The solution was purged of ozone by bubbling Ar through the solution until the blue color disappeared (5 min), and polymer-supported triphenylphosphine (0.8 mmol/g, 1.2 g, 0.96 mmol) was added to the reaction. The mixture was removed from the dry ice/acetone bath and stirred at RT for 1.5 h. The PS-PPh₃ was removed by filtration and washed with CH₂Cl₂ (5-10 mL). The filtrate was concentrated to yield a light yellow oil (146 mg crude). The crude material was analyzed by TLC (2:1 hexanes/EtOAc - CAM stain) and was composed of one major spot plus some baseline material. The oil was chromatographed through 20 g of silica gel using a solvent gradient from 100% CH₂Cl₂ to 85% CH₂Cl₂/EtOAc to afford **3.93** as a colorless oil (113.0 mg, 69.3%). ¹H NMR (500 MHz, CDCl₃) δ 9.56 (d, *J* = 1.0 Hz, 1H), 9.55 (s, 1H), 5.07 (d, *J* = 6.5 Hz, 1H), 4.19 (dd, *J* = 7.0, 6.0 Hz, 1H), 3.99 (m, 1H), 1.88 (m, 1H), 1.61 (m, 2H), 1.43 (s, 9H), 1.37 (m, 4H), 0.90 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 204.1, 199.7, 155.5, 80.0, 77.3, 59.7, 32.3, 29.0, 28.2, 25.7, 25.0, 24.4, 18.1, -4.7, -5.0 ppm. HRMS (FAB) *m/z* [M]⁺ calcd for C₁₉H₃₇NO₅Si⁺, 387.2441; obsd, 387.2446.

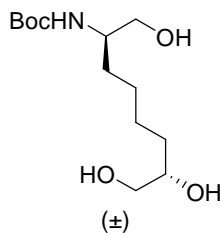


(±)-*tert*-Butyl (2*R*,7*S*)-7-(*tert*-butyldimethylsilyloxy)-1,8-dihydroxyoctan-2-ylcarbamate (**3.94**). Compound **3.79** (3.035 g, 8.535 mmol) was dissolved in 100 mL of 4:1 CH₂Cl₂/MeOH in a single-necked 250-mL round-bottomed flask. The solution was cooled in a dry ice/actone bath to -78 °C and a stream of ozone was bubbled through the solution. The blue color of ozone was observed in the solution after ~10 min, and the ozone flow was stopped. The solution was purged of ozone by bubbling Ar through the solution until the blue color disappeared (20 min). The reaction was removed from the dry ice/acetone bath and placed in a crushed ice/NaCl/H₂O bath, at which time NaBH₄ (2.03, 53.7 mmol) was added to the reaction in portions over 60 min. Bubbling was observed and the reaction was allowed to stir in the ice/NaCl/H₂O bath for 1 h, then warmed to RT and stirred for an additional 1 h. The reaction was diluted with H₂O (100 mL) and EtOAc (200 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over MgSO₄, filtered, and concentrated to yield a colorless oil. The oil was chromatographed through 250 g of silica gel using a solvent gradient from 50% hexanes/EtOAc to 30% hexanes/EtOAc to yield **3.94** as a colorless oil (3.30 g, 99%). R_f = 0.13 (1:1 hexanes/EtOAc – CAM stain). ¹H NMR (500 MHz, CDCl₃) δ 4.77 (d, *J* = 8.0 Hz, 1H), 3.68 (m, 1H), 3.58 (m, 2H), 3.50 (m, 2H), 3.41 (m, 1H), 3.08 (br-s, 1H), 2.24 (br-s, 1H), 1.46 (m, 3H), 1.40 (s, 9H), 1.33-1.22 (m, 5H), 0.86 (s, 9H), 0.04 (s, 6H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 156.4, 79.4, 72.6, 66.0, 65.5, 52.5, 33.7, 31.4, 28.3,

26.1, 25.8, 25.0, 18.0, -4.6, -4.7 ppm. HRMS (FAB) m/z $[M+H]^+$ calcd for $C_{19}H_{42}NO_5Si^+$, 392.2832; obsd, 392.2838.

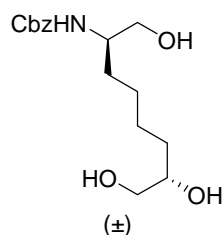


(±)-Benzyl (2R,7S)-7-(tert-butyldimethylsilyloxy)-1,8-dihydroxyoctan-2-ylcarbamate (3.95). Compound **3.95** was prepared following the procedure for **3.94**. **3.81** (1.949 g, 5.003 mmol) was treated with ozone at -78 °C, then $NaBH_4$ (1.23 g, 32.5 mmol) at -10 °C. The crude material was purified through 100 g of silica gel using a solvent gradient from 50% EtOAc/hexanes to 60% EtOAc/hexanes to afford **3.95** as a colorless oil (2.02 g, 95%). R_f = 0.11 (1:1 hexanes/EtOAc – CAM stain). 1H NMR (500 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.09 (s, 2H), 4.91 (d, J = 7.5 Hz, 1H), 3.0 (m, 3H), 3.56 (m, 2H), 3.43 (m, 1H), 2.33 (br-s, 1H), 1.96 (t, J = 6.5 Hz, 1H), 1.49-1.25 (m, 8H), 0.89 (s, 9H), 0.07 (s, 6H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 136.3, 128.5, 128.2, 128.1, 72.6, 66.8, 66.1, 65.5, 53.1, 33.7, 31.3, 26.1, 25.9, 25.1, 18.1, -4.5, -4.6 ppm.



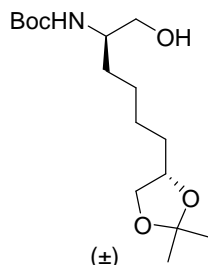
(±)-tert-Butyl (2R,7S)-1,7,8-trihydroxyoctan-2-ylcarbamate (3.96). Compound **3.94** (0.418 g, 1.07 mmol) was dissolved in 5 mL of anhydrous THF in a flame-dried

single-necked 25-mL round-bottomed flask under Ar. TBAF (1.0 M, 1.60 mL, 1.60 mmol) was added dropwise and the resultant light-yellow solution was stirred at RT under Ar. After 4.5 h, the reaction was complete by TLC analysis (9:1 EtOAc/MeOH - CAM stain). The reaction was concentrated by rotary evaporation (40-45 °C, 21 mm Hg), and the resultant yellow oil was chromatographed through 10 g of silica gel using a solvent gradient from 100% EtOAc to 90% EtOAc/MeOH to afford **80** as a colorless oil (285.5 mg, 87%). The oil solidified upon standing for ~1 week. ¹H NMR (500 MHz, d⁶-DMSO) δ 6.32 (d, *J* = 8.0 Hz, 1H), 4.45 (t, *J* = 5.5 Hz, 1H), 4.32 (t, *J* = 5.5 Hz, 1H), 4.22 (d, *J* = 5.0 Hz, 1H), 3.33 – 3.28 (m, 2H), 3.26 – 3.19 (m, 3H), 1.51 – 1.45 (m, 1H), 1.40 – 1.37 (m, 11H), 1.31 – 1.27 (m, 1H), 1.25 – 1.17 (m, 4H) ppm. ¹³C NMR (125 MHz, d⁶-DMSO) δ 155.3, 77.1, 70.9, 65.8, 63.5, 52.1, 33.3, 30.9, 28.1, 25.6, 25.1 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₃H₂₈NO₅⁺, 278.1967; obsd, 278.1952.



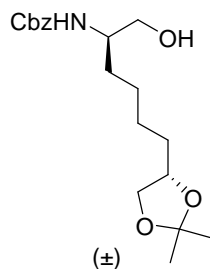
(±)-Benzyl (2R,7S)-1,7,8-trihydroxyoctan-2-ylcarbamate (3.97). Compound **3.97** was prepared following the procedure for **3.96**. Compound **3.95** (1.00 g, 2.35 mmol) was treated with 3.0 mL of 1.0 M TBAF (3.0 mmol). The crude material was purified through 75 g of silica gel using a solvent gradient from 100% EtOAc to 90% EtOAc/MeOH to yield **3.97** as a colorless oil that solidified upon standing (0.641 g, 88%). mp = 81-83 °C. R_f = 0.26 (9:1 EtOAc/MeOH – CAM stain). ¹H NMR (500 MHz, CD₃OD) δ 7.35 – 7.28 (m, 5H), 5.07 (s, 2H), 3.58 (br-m, 2H), 3.49 – 3.39 (m, 4H),

1.62 – 1.30 (m, 8H) ppm. ^{13}C NMR (125 MHz, CD_3OD) δ 158.9, 138.5, 129.5, 129.0, 128.8, 73.2, 67.40, 67.36, 65.4, 54.4, 34.4, 32.3, 27.2, 26.6 ppm.

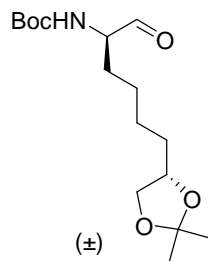


(±)-tert-Butyl (R)-6-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-hydroxyhexan-2-ylcarbamate (3.98). Compound **3.96** (1.499 g, 5.405 mmol) was dissolved in 55 mL of anhydrous THF in a flame-dried single-necked 250-mL round-bottomed flask under Ar. 2,2-Dimethoxypropane (0.70 mL, 5.7 mmol) was added to the reaction, followed by anhydrous *p*-toluenesulfonic acid (48.1 mg, 0.279 mmol). The reaction was stirred at RT under Ar for 6 h, at which time TLC analysis of the reaction mixture (1:1 hexanes/EtOAc and 9:1 EtOAc/MeOH - CAM stain) only shows a small amount of starting material and mostly one product. About 300 mg of solid sodium carbonate was added to the reaction and the mixture was concentrated by rotary evaporation (30-35 °C, 21 mm Hg) to a yellow oil. Saturated NaHCO_3 (50 mL), H_2O (20 mL), and EtOAc (75 mL) were added to the oil and the layers were separated. The combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4 , filtered, and concentrated to yield a yellow oil. The oil was purified through 150 g of silica gel using a solvent gradient from 75% hexanes/EtOAc to 33% hexanes/EtOAc to yield a light yellow oil. The oil was dried under vacuum (1.5 mm Hg) overnight to afford **3.98** as a waxy white solid (1.64 g, 96%). R_f = 0.14 (1:1 hexanes/EtOAc – CAM stain). ^1H NMR (500 MHz, CDCl_3) δ 4.73 (d, J =

7.0 Hz, 1H), 4.10 – 3.98 (m, 2H), 3.62 – 3.54 (br-m, 2H), 3.51 – 3.47 (m, 1H), 3.46 (t, J = 7.0 Hz, 1H), 2.83 (br, 1H), 1.61 – 1.57 (m, 1H), 1.52 – 1.35 (m, 7H), 1.41 (s, 9H), 1.37 (s, 3H), 1.32 (s, 3H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 156.4, 108.6, 79.5, 75.9, 69.4, 65.7, 52.6, 33.3, 31.3, 28.3, 26.9, 25.9, 25.7, 25.6 ppm. HRMS (FAB) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{32}\text{NO}_5^+$, 318.2280; obsd, 318.2259.



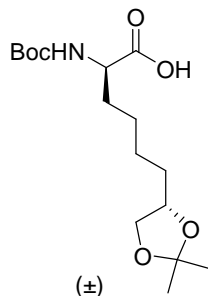
(±)-Benzyl (R)-6-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-hydroxyhexan-2-ylcarbamate (**3.99**). Compound **3.99** was prepared following the same procedure for **3.98**. The use of **3.97** (0.641 g, 2.06 mmol), 2,2-dimethoxypropane (0.35 mL, 2.85 mmol), and *p*-toluenesulfonic acid hydrate (27.8 mg, 0.146 mmol) provided a yellow oil. The oil was chromatographed through 75 g of silica using a solvent gradient from 75% hexanes/EtOAc to 33% hexanes/EtOAc and yielded **3.99** as an oil that solidified to a waxy solid upon standing (0.614 g, 85%). ^1H NMR (500 MHz, CDCl_3) δ 7.35 – 7.30 (m, 5H), 5.09 (s, 2H), 4.95 (d, J = 7.5 Hz, 1H), 4.06 – 3.99 (m, 2H), 3.67 (br-m, 2H), 3.55 (br-m, 1H), 3.47 (t, J = 7.5 Hz, 1H), 2.41 (br, 1H), 1.64 – 1.24 (m, 8H), 1.39 (s, 3H), 1.34 (s, 3H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 156.7, 136.3, 128.5, 128.14, 128.08, 108.7, 75.9, 69.4, 66.8, 65.4, 53.1, 33.3, 31.2, 26.9, 25.9, 25.7, 25.6 ppm.



(±)-tert-Butyl (R)-6-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-oxohexan-2-ylcarbamate (3.100). Alcohol **3.98** (0.5158 g, 1.625 mmol) was dissolved in 10 mL of anhydrous CH₂Cl₂ in a flame-dried single-necked 50-mL round-bottomed flask under Ar. Dess-Martin periodinane (15 wt% in CH₂Cl₂, 5.10 mL, 2.40 mmol) was added and the resultant cloudy yellow mixture was stirred at RT. The reaction was monitored by TLC (1:1 hexanes/EtOAc - CAM stain). After 4 h, starting material remained and additional DMP was added (1 mL, ~0.3 eq). After stirring for 45 min, 40 mL of 1:1 saturated NaHCO₃/10 wt% Na₂S₂O₃ was added to the reaction along with 10 mL of EtOAc. The mixture was stirred at RT for 30 min until the solid material had completely dissolved. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with saturated NaHCO₃ (3 x 50 mL), H₂O (50 mL) and brine (50 mL), dried over Na₂SO₄, filtered, and concentrated to yield a yellow oil. The oil was purified through 50 g of silica using a solvent gradient from 100% CH₂Cl₂ to 80% CH₂Cl₂/EtOAc to afford **3.100** as a light yellow oil that solidified upon standing to a waxy solid (0.489 g, 95%). R_f = 0.40 (1:1 hexanes/EtOAc – CAM stain). ¹H NMR (500 MHz, CDCl₃) δ 9.57 (br-s, 1H), 5.08 (d, *J* = 6.0 Hz, 1H), 4.21 (dd, *J* = 6.5, 6.0 Hz, 1H), 4.06-4.00 (m, 2H), 3.48 (t, *J* = 7.0 Hz, 1H), 1.88 (br-m, 1H), 1.60-1.46 (m, 5H), 1.44 (s, 9H), 1.39 (s, 3H), 1.34 (s, 3H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 199.8,

155.5, 108.7, 80.1, 75.8, 69.4, 59.7, 33.2, 29.0, 28.3, 26.9, 25.7, 25.6, 25.1 ppm. HRMS (FAB) m/z $[M+H]^+$ calcd for $C_{16}H_{30}O_5N^+$, 316.2124; obsd, 316.2119.

Aldehyde 3.100 from alcohol 3.98 by Swern oxidation. Oxalyl chloride (0.20 mL, 2.3 mmol) was added to 5 mL of anhydrous CH_2Cl_2 in a flame-dried, single-necked 50-mL round-bottomed flask cooled to $-78\text{ }^{\circ}C$ (dry ice/acetone) under Ar. In a separate flame-dried single-necked 10-mL round-bottomed flask was dissolved anhydrous dimethyl sulfoxide (0.35 mL, 4.9 mmol) in 5 mL of anhydrous CH_2Cl_2 . The DMSO solution was added to the oxalyl chloride solution slowly via cannula and the resultant solution was stirred at $-78\text{ }^{\circ}C$ for 20 min under Ar. In a separate flame-dried single-necked 25-mL round-bottomed flask under Ar was dissolved **3.98** (0.507 g, 1.60 mmol) in 10 mL of anhydrous CH_2Cl_2 . This solution was transferred dropwise to the reaction flask via cannula. The resultant mixture was stirred at $-78\text{ }^{\circ}C$ for 1 h, then Et_3N (1.25 mL, 8.89 mmol) was added. The mixture was stirred for 1 h at $-78\text{ }^{\circ}C$, then the dry ice/acetone bath was removed and the mixture was allowed to slowly reach RT under Ar. After 1 h, the reaction mixture was diluted with H_2O (25 mL) and CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL) and the combined CH_2Cl_2 layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated to yield an orange oil. The crude material was chromatographed through 50 g of silica using a solvent gradient from 100% CH_2Cl_2 to 75% $CH_2Cl_2/EtOAc$ and yielded **3.100** as a yellow oil (0.460 g, 91.3% yield).



(±)-(R)-2-(*tert*-Butoxycarbonylamino)-6-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)hexanoic acid (**3.101**). **Oxidation using KMnO₄.** Compound **3.100** (0.1592 g, 0.5048 mmol) was dissolved in 10 mL of MeOH in a single-necked 50-mL round-bottomed flask. A solution of KMnO₄ (0.185 g, 1.17 mmol) and benzyltriethylammonium chloride (5 mg, 0.02 mmol) in 15 mL of H₂O was added and the mixture was stirred vigorously at RT. The temperature of the mixture increased slightly and the color of the mixture changed from deep purple to a brownish/purple color. After 5 h, the reaction was filtered. EtOAc (20 mL) and H₂O (10 mL) were added to the murky brown filtrate. The aqueous layer was acidified to pH 3 using 6M HCl (3 drops). 10 wt% sodium meta bisulfite (about 5 mL) was added and the brown mixture turned colorless. The layers were separated and the aqueous was quickly extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated to afford a colorless oil. The oil was dried under vacuum (1.5 mm Hg) to afford a colorless oil (152.5 mg, 91.2% yield). ¹H NMR (300 MHz, CDCl₃) δ 9.93 (br-s, 1H), 6.31 (m, 1H), 5.11 (d, *J* = 8.1 Hz, 1H), 4.27 (m, 1H), 4.07-3.99 (m, 3H), 3.47 (t, *J* = 6.9 Hz, 1H), 1.82 (m, 1H), 1.66-1.57 (m, 3H), 1.41-1.32 (m, 2H), 1.42 (s, 9H), 1.38 (s, 3H), 1.32 (s, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ 176.8, 155.5, 108.7, 80.0, 75.8, 69.3, 53.1, 33.2, 33.1, 32.2, 28.2, 26.8, 25.6, 25.3, 25.2 ppm.

Oxidation conditions for aldehyde 3.100 using NaClO₂ (Table 3.7, entry 2).

Aldehyde **3.100** (55.0 mg, 0.174 mmol) was dissolved in 5 mL of 1:1 *t*BuOH/H₂O in a 20-mL scintillation vial. 2-Methyl-2-butene (0.40 mL, 3.8 mmol) was added followed by sodium chlorite (51.9, 0.574 mmol) and monobasic sodium phosphate (63.9 mg, 0.463 mmol). The mixture was stirred at RT for about 6 h, then partitioned between H₂O (5 mL) and EtOAc (5 mL). The aqueous layer was carefully acidified to a pH of 2-3 (pH paper) using 1M HCl and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL) and the combined organic layers were dried over Na₂SO₄, filtered, and concentrated.

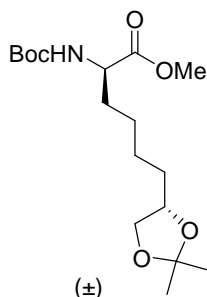
Oxidation conditions for aldehyde 3.100 using Oxone (Table 3.7, entry 3).

Aldehyde **3.100** (72.8 mg, 0.231 mmol) was dissolved in 4 mL of DMF in a 20-mL scintillation vial. Oxone (160 mg, 0.26 mmol) was added in one portion and the mixture was stirred at RT for 5 h. The reaction was partitioned between H₂O (10 mL) and EtOAc (10 mL). The aqueous layer was a pH of 2-3 (pH paper). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated to afford a residue.

Oxidation conditions for aldehyde 3.100 using Ag₂O (Table 3.7, entry 5).

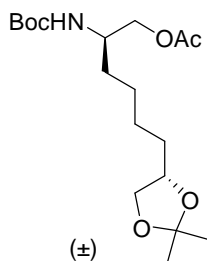
Aldehyde **3.100** (59.7 mg, 0.189 mmol) was dissolved in 3 mL of EtOH in a 20 mL scintillation vial. A solution of silver nitrate (82 mg, 0.48 mmol) in 0.5 mL of H₂O was added, followed by the dropwise addition of a solution of KOH (62 mg, 1.1 mmol) in 1.5 mL of H₂O. A brown solid precipitated out of solution immediately. The mixture was

stirred at RT for about 4 h. The brown solid was removed by filtration and the filtrate was diluted with EtOAc (5 mL) and H₂O (5 mL). The aqueous layer was carefully acidified to a pH of about 2-3 (pH paper) using 1M HCl. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated to afford a residue.

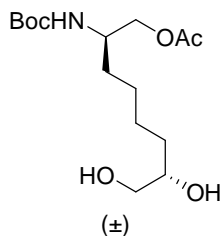


(±)-(R)-Methyl 2-(*tert*-butoxycarbonylamino)-6-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)hexanoate (**3.102**). Crude **3.101**, prepared as described above from oxidation of **3.100** (79.8 mg, 0.253 mmol) using KMnO₄, was dissolved in about 10 mL of Et₂O and 2 mL of THF and treated with an excess of diazomethane in Et₂O. The resultant yellow solution was quenched with a 10 vol% acetic acid/Et₂O solution until the yellow color disappeared. Saturated NaHCO₃ (20 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL) and the combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered, and concentrated. The crude material was chromatographed through 5 g of silica using a solvent gradient from 100% CH₂Cl₂ to 90% CH₂Cl₂/EtOAc to afford **3.102** as a yellow oil (63.2 mg, 72.3% yield). R_f = 0.46 (1:1 hexanes/EtOAc – CAM stain). ¹H NMR (500 MHz, CDCl₃) δ 5.03 (d, *J* = 8.5 Hz, 1H), 4.26 (dd, *J* = 13.0, 7.5 Hz, 1H), 4.06-3.99 (m, 2H), 3.71 (s, 3H), 3.47 (t, *J* = 7.0 Hz, 1H), 1.90-1.75 (m, 1H), 1.70-1.55 (m, 2H), 1.50-

1.30 (m, 3H), 1.42 (s, 9H), 1.38 (s, 3H), 1.32 (s, 3H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 173.3, 155.3, 108.6, 79.8, 75.8, 69.4, 53.3, 52.2, 33.2, 32.5, 28.3, 26.9, 25.7, 25.3, 25.2 ppm. HRMS (FAB) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{32}\text{NO}_6^+$, 346.2230; obsd, 346.2219.



(±)-(R)-2-(tert-butoxycarbonylamino)-6-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)hexyl acetate (3.105). Compound **3.105** was prepared following the same procedure used for **3.77**. The use of **3.98** (0.503 g, 1.58 mmol) and acetic anhydride (0.40 mL, 4.2 mmol) provided a yellow oil. The oil was chromatographed through a Biotage 40S column using a solvent gradient from 100% CH_2Cl_2 to 85% $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ and yielded **3.105** as a colorless oil. The oil was dried under vacuum overnight to provide **3.105** (0.529 g, 92.9% yield). R_f = 0.44 (1:1 hexanes/EtOAc – CAM stain). ^1H NMR (300 MHz, CDCl_3) δ 4.53 (d, J = 9.0 Hz, 1H), 4.04 (m, 4H), 3.83 (br, 1H), 3.49 (t, J = 6.9 Hz, 1H), 2.07 (s, 3H), 1.70 – 1.35 (m, 8H), 1.45 (s, 9H), 1.41 (s, 3H), 1.35 (s, 3H) ppm. ^{13}C NMR (75 MHz, CDCl_3) δ 170.9, 155.4, 108.6, 75.9, 69.4, 66.3, 49.4, 33.3, 31.7, 28.3, 26.9, 25.8, 25.7, 25.6, 20.8 ppm. HRMS (FAB) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{34}\text{NO}_6^+$, 360.2386; obsd, 360.2388.



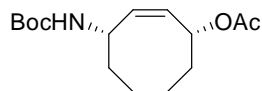
(±)-(2*R*,7*S*)-2-(*tert*-Butoxycarbonylamino)-7,8-dihydroxyoctyl acetate (3.106).

Compound **3.105** (0.253 g, 0.703 mmol) was dissolved in 6 mL of MeOH in a 20-mL scintillation vial. Pyridinium *para*-toluenesulfonate (21.4 mg, 0.0852 mmol) was added and the mixture was stirred at RT. After 1.5 h, the distinct aroma of 2,2-dimethoxypropane was detected in the reaction mixture. TLC of the reaction indicated a new more polar spot (just above baseline, 1:1 hexanes/EtOAc - CAM stain), but **3.105** remained ($R_f = 0.44$). After 24 h, no change was observed. The reaction was concentrated (to remove the 2,2-dimethoxypropane), and the resultant colorless oil was dissolved in 5 mL of MeOH and stirred at RT. Only a small amount of **3.105** remained after stirring for 1 day. The reaction was concentrated and the colorless oil was partitioned between EtOAc (20 mL), and H₂O (10 mL). The layers were separated and the organic layer was washed with 1M HCl (3 x 5 mL), H₂O (5 mL), saturated NaHCO₃ (2 x 5 mL), and brine (5 mL), dried over Na₂SO₄, filtered, and concentrated to yield a colorless oil. The oil was chromatographed through 15 g of silica using 100% EtOAc to yield **3.106** as a light yellow oil (171.1 mg, 76.2% yield). $R_f = 0.2$ (100% EtOAc - CAM stain). ¹H NMR (300 MHz, CDCl₃) δ 4.74 (d, $J = 7.8$ Hz, 1H), 4.04 (m, 2H), 3.83 (br, 1H), 3.69 – 3.60 (m, 2H), 3.42 (dd, $J = 11.1, 7.5$ Hz, 1H), 3.32 (br, 2H), 2.07 (s, 3H), 1.52 – 1.32 (m, 8H), 1.44 (s, 9H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ 171.0, 155.6, 79.4, 72.0, 66.6, 49.3, 32.7, 28.3, 25.6, 25.2, 20.8 ppm.

Attempted oxidation of 3.106 using trichloroisocyanuric acid/TEMPO.

Compound **3.106** (59.7 mg, 0.187 mmol) was dissolved in 2 mL of CH₂Cl₂ in a 20-mL scintillation vial and cooled in an ice/H₂O bath. Trichloroisocyanuric acid (47.0 mg, 0.202 mmol) was added, followed by TEMPO (1 mg, 0.006 mmol). The yellow reaction was stirred in the ice/H₂O bath. A complex mixture was observed after 1 h.

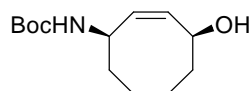
Enzymatic resolution of (±)-3.76 using Novozyme 435. CH₂Cl₂ (40 mL) and wet *n*-heptane (50 mL) were added to (±)-**3.76** (2.268 g, 9.40 mmol) in a 250-mL erlenmeyer flask. To the slurry was added vinyl acetate (2.90 mL, 31.5 mmol), followed by immobilized *C. antarctica* B lipase enzyme (Novozyme 435, 255 mg). The mixture was not completely in solution. The mixture was shaken at 37 °C overnight. After 15 h, an aliquot was removed, concentrated, and the resultant solid was analyzed by ¹H NMR. The reaction was determined to have proceeded to 50% conversion. The immobilized enzyme was removed from the mixture by filtration and washed with portions of EtOAc (10 mL) and CH₂Cl₂ (10 mL). The filtrate was concentrated to yield a white solid. The solid was chromatographed through 250 g of silica using a solvent gradient from 100% CH₂Cl₂ to 80% CH₂Cl₂/EtOAc to elute (+)-**3.77** and 50% CH₂Cl₂/EtOAc to elute (-)-**3.76**. Total recovery was 97%.



(+)-(1R,4S,Z)-4-(tert-Butoxycarbonylamino)cyclooct-2-enyl acetate (+)-3.77.

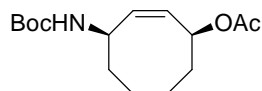
Compound (+)-**3.77** was isolated as above as an off-white crystalline solid (1.24 g, 46%

yield). NMR spectra matches racemic **3.77**. mp = 125-126 °C. $[\alpha]^{23} = +69.6$ (c = 0.53 in MeOH). HRMS (FAB) m/z $[M+H]^+$ calcd for $C_{15}H_{26}NO_4^+$, 284.1862; obsd, 284.1885.



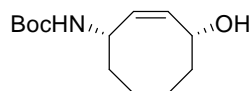
(-)-tert-Butyl (1R,4S,Z)-4-hydroxycyclooct-2-enylcarbamate (-)-3.76.

Compound **(-)-3.76** was isolated as above as a white amorphous solid (1.14 g, 50% yield). NMR spectra matches racemic **3.76**. mp = 151-152 °C. $[\alpha]^{23} = -84.1$ (c = 0.52 in MeOH). HRMS (FAB) m/z $[M+H]^+$ calcd for $C_{13}H_{24}NO_3^+$, 242.1756; obsd, 242.1739.



(-)-(1S,4R,Z)-4-(tert-Butoxycarbonylamino)cyclooct-2-enyl acetate (-)-3.77.

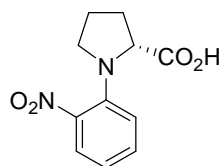
Compound **(-)-3.77** was prepared following the same procedure for **(±)-3.77**. Compound **(-)-3.76** (0.153 g, 0.632 mmol) and acetic anhydride (0.15 mL, 1.59 mmol) provided **(-)-3.77** as an off-white solid (0.167 g, 93% yield). NMR spectra matches racemic **3.77**.



(+)-tert-Butyl (1S,4R,Z)-4-hydroxycyclooct-2-enylcarbamate (+)-3.76.

General procedure for acetate removal using K_2CO_3 . A 100-mL round-bottomed flask was charged with potassium carbonate (0.731 g, 5.29 mmol) and flame-dried under Ar. **(+)-3.77** (1.05 g, 3.70 mmol) was added and dissolved in 20 mL of anhydrous methanol. The mixture was stirred at RT under Ar. After 2.5 h, the reaction was

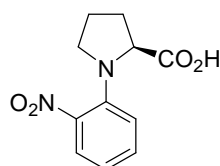
complete by TLC (1:1 hexanes/EtOAc - CAM stain) analysis. The yellow mixture was partitioned between EtOAc (50 mL), H₂O (25 mL), and brine (25 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 25 mL) and the combined organic layers were washed with H₂O (25 mL) and brine (2 x 25 mL), dried over MgSO₄, filtered, and concentrated to yield a white solid. The solid was dried under vacuum overnight (1.5 mm Hg) to yield (+)-**3.76** as a white solid (0.884 g, 99% yield). NMR spectra matches racemic **3.76**. mp = 150.5-151.5 °C. $[\alpha]^{23} = +109$ (c = 0.50 in MeOH).



(R)-1-(2-Nitrophenyl)pyrrolidine-2-carboxylic acid, R-2-NPP (3.108). *D*-

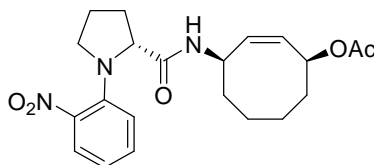
Proline (1.06 g, 9.18 mmol) was dissolved in 100 mL of EtOH/H₂O (1:1) in a 250-mL round-bottomed flask fitted with a stir bar and condenser. Sodium bicarbonate (2.08 g, 24.8 mmol) was added, followed by 1-fluoro-2-nitrobenzene (0.96 mL, 9.1 mmol). The reaction was heated to reflux in an oil bath (oil temperature = 95-100 °C). After about 10 min, the color of the solution changed from yellow to red. After 5 h, the mixture was cooled and stirred at RT overnight. The volume of the red solution was reduced to about 30-40 mL by rotary evaporation and the red mixture was acidified to pH 2-3 (pH paper) by adding 1M HCl (25-30 mL). Yellow solid precipitated out of the solution. The mixture was diluted with EtOAc (75 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organic layers were dried over MgSO₄, filtered, and concentrated to yield a sticky orange oil. The oil was dried

under vacuum (~2 torr). After the sticky oil was scratched with a spatula and left to stand overnight at 4 °C, the oil solidified to yield **3.108** as a yellow solid (2.2 g, ~100% yield). $[\alpha]^{23} = +933$ (c = 1.0 in MeOH); lit.⁶ = +1020 (c = 1.0 in MeOH). ¹H NMR (500 MHz, CDCl₃) δ 10.28 (br, 1H), 7.73 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.39 (tdd, *J* = 7.5, 1.5, 0.5 Hz, 1H), 6.86 (m, 2H), 4.43 (t, *J* = 7.5 Hz, 1H), 3.55 (td, *J* = 9.5, 7.5 Hz, 1H), 3.07 (ddd, *J* = 9.5, 7.5, 4.0 Hz, 1H), 2.49 (dtd, *J* = 12, 7.0, 5.0 Hz, 1H), 2.20 – 2.07 (m, 2H), 1.98 – 1.89 (m, 1H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 177.9, 141.2, 138.9, 133.2, 126.6, 118.2, 116.8, 61.7, 51.9, 30.9, 24.8 ppm.



(S)-1-(2-Nitrophenyl)pyrrolidine-2-carboxylic acid, S-2-NPP (3.109).

Compound **3.109** was prepared following the same procedure used for **3.108**. *L*-proline (1.05 g, 9.12 mmol), 1-fluoro-2-nitrobenzene (0.96 mL, 9.08 mmol), and sodium bicarbonate (2.0 g, 24 mmol) provided **3.109** as a sticky orange oil (2.10 g, 98% yield). NMR spectra is identical to **3.108**. $[\alpha]^{23} = -941$ (c = 1.0 in MeOH); lit. = -1080 (c = 1.0 in MeOH).



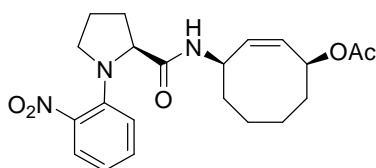
(1S,4R,Z)-4-((R)-1-(2-Nitrophenyl)pyrrolidine-2-carboxamido)cyclooct-2-enyl

acetate (3.110). Compound **(-)-3.77** (126 mg, 0.445 mmol) was dissolved in 5 mL of

CH₂Cl₂ in a 25-mL round-bottomed flask. Triethylsilane (0.080 mL, 0.50 mmol) was added, followed by trifluoroacetic acid (0.50 mL, 6.7 mmol). The light yellow solution was stirred at RT under Ar. The reaction was monitored by TLC (1:1 hexanes/EtOAc - CAM stain, ninhydrin stain) for the disappearance of (-)-**3.77**. After 1.5 h, the reaction was still incomplete and an additional 0.5 mL (6.7 mmol) TFA was added. After 2 h, the reaction was complete and the reaction was diluted with CH₂Cl₂ (10 mL) and poured into 50 mL of saturated NaHCO₃. The pH of the aqueous layer was adjusted to 8 (pH paper) by adding portions of solid Na₂CO₃. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated to yield a yellow oil (59.3 mg, 73% yield of free amine).

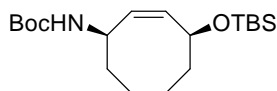
The free amine intermediate (28.2 mg, 0.154 mmol) and HOBt (26.2 mg, 0.194 mmol) were dissolved in 2 mL of CH₃CN in a 25-mL round-bottomed flask under Ar. **3.108** (44.4 mg, 0.188 mmol) was added as a solution in 3 mL of dry CH₃CN. EDC•HCl (44 mg, 0.23 mmol) was added to the yellow solution and the mixture was stirred at RT under Ar. After 2 days, the reaction was analyzed by TLC (1:1 hexanes/EtOAc - UV lamp). The mixture was concentrated and the yellow residue was partitioned between H₂O (10 mL), and EtOAc (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with H₂O (20 mL), saturated NaHCO₃ (2 x 20 mL), H₂O (20 mL), 10 wt% citric acid (2 x 20 mL), H₂O (20 mL), and brine (20 mL), dried over Na₂SO₄, filtered, and concentrated. The crude material was chromatographed through 15 g of silica using a solvent gradient from 100% CH₂Cl₂ to 60% CH₂Cl₂/EtOAc to yield **3.110** as a bright yellow oil (49.8 mg,

80.6% yield). $R_f = 0.31$ (3:2 $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ – UV lamp). ^1H NMR (300 MHz, CDCl_3) δ 7.76 (dd, $J = 8.4, 1.8$ Hz, 1H), 7.41 (ddd, $J = 8.7, 7.2, 1.5$ Hz, 1H), 7.03 (d, $J = 8.4$ Hz, 1H), 6.96 – 6.87 (m, 2H), 5.59 (m, 1H), 5.44 (ddd, $J = 10.8, 7.2, 1.2$ Hz, 1H), 5.05 (ddd, $J = 11.1, 8.4, 1.5$ Hz, 1H), 4.63 (m, 1H), 4.41 (t, $J = 7.5$ Hz, 1H), 3.64 (m, 1H), 2.82 (m, 1H), 2.58 (m, 1H), 2.03 – 1.85 (m, 6H), 1.62 – 1.25 (m, 6H) ppm. ^{13}C NMR (75 MHz, CDCl_3) δ 171.4, 169.9, 142.0, 140.1, 133.6, 130.2, 130.1, 126.2, 119.4, 117.5, 72.0, 63.2, 53.1, 47.6, 35.8, 34.9, 31.6, 25.5, 23.8, 23.0, 21.2 ppm. HRMS (FAB) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{28}\text{N}_3\text{O}_5^+$, 402.2029; obsd, 402.2003.

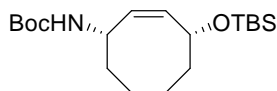


(1*S*,4*R*,*Z*)-4-((*S*)-1-(2-Nitrophenyl)pyrrolidine-2-carboxamido)cyclooct-2-enyl acetate (3.111). Compound **3.111** was prepared following the same procedure used for **3.110**. Used the free amine intermediate (28.9 mg, 0.158 mmol), HOBT (25.0 mg, 0.185 mmol), **3.109** (46.0 mg, 0.195 mmol), and EDC•HCl (43 mg, 0.22 mmol) to provide **3.111** as a bright yellow oil (62.6 mg, 98.9% yield). $R_f = 0.31$ (3:2 $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ – UV lamp). ^1H NMR (300 MHz, CDCl_3) δ 7.76 (dd, $J = 8.4, 2.1$ Hz, 1H), 7.41 (ddd, $J = 8.7, 7.2, 1.5$ Hz, 1H), 7.03 (d, $J = 8.4$ Hz, 1H), 6.93 (td, $J = 8.4, 1.2$ Hz, 1H), 6.85 (d, $J = 7.2$ Hz, 1H), 5.66 – 5.27 (m, 2H), 5.33 (m, 1H), 4.62 (m, 1H), 4.41 (t, $J = 7.5$ Hz, 1H), 3.64 (m, 1H), 2.81 (m, 1H), 2.56 (m, 1H), 2.10 – 1.80 (m, 6H), 1.70 – 1.30 (m, 6H) ppm. ^{13}C NMR (75 MHz, CDCl_3) δ 171.4, 170.0, 141.9, 140.0, 133.4, 130.4, 130.0, 126.1, 119.3,

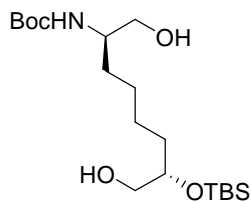
117.3, 72.0, 63.4, 53.0, 47.6, 35.5, 34.9, 31.5, 25.6, 23.7, 22.9, 21.2 ppm. HRMS (FAB) m/z $[M+H]^+$ calcd for $C_{21}H_{28}N_3O_5^+$, 402.2029; obsd, 402.2009.



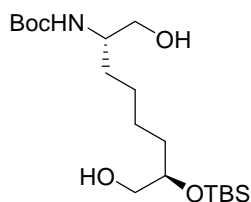
(-)-*tert*-Butyl (1*R*,4*S*,*Z*)-4-(*tert*-butyldimethylsilyloxy)cyclooct-2-enylcarbamate (1*R*,4*S*)-3.79. The title compound was prepared following the same procedure used for racemic **3.79**. The use of (-)-**3.76** (0.916 g, 3.80 mmol), imidazole (1.05 g, 15.5 mmol), and *tert*-butyldimethylsilyl chloride (1.03 g, 6.84 mmol) provided (-)-**3.79** as a white solid (1.148 g, 85.1% yield). mp = 85.5-86.5 °C. NMR spectra matches racemic **3.79**. $[\alpha]^{23} = -12.5$ (c = 0.52 in MeOH).



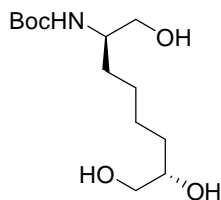
(+)-*tert*-Butyl (1*S*,4*R*,*Z*)-4-(*tert*-butyldimethylsilyloxy)cyclooct-2-enylcarbamate (1*S*,4*R*)-3.79. The title compound was prepared following the same procedure used for racemic **3.79**. The use of (+)-**3.76** (1.36 g, 5.65 mmol), imidazole (1.54 g, 22.6 mmol), and *tert*-butyldimethylsilyl chloride (1.54 g, 10.2 mmol) provided (+)-**3.79** as a white solid (1.91 g, 95.1% yield). mp = 85.5-86.5 °C. NMR spectra matches racemic **3.79**. $[\alpha]^{23} = +17.1$ (c = 0.53 in MeOH).



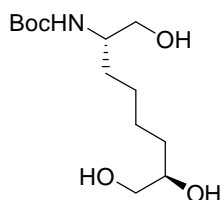
tert*-Butyl (2*R*,7*S*)-7-(*tert*-butyldimethylsilyloxy)-1,8-dihydroxyoctan-2-ylcarbamate (2*R*,7*S*)-3.94.** The title compound was prepared following the same procedure used for racemic **3.94**. The use of (-)-**3.79** (2.45 g, 6.89 mmol) and sodium borohydride (1.41 g, 37.3 mmol) provided (**2*R*,7*S)-**3.94** as a light yellow sticky oil (2.71 g, 99% yield). NMR spectra matches racemic **3.94**. $[\alpha]^{23} \sim 0$ ($c = 0.5$ in MeOH). HRMS (FAB) m/z $[M+H]^+$ calcd for $C_{19}H_{42}NO_5Si^+$, 392.2832; obsd, 392.2812.



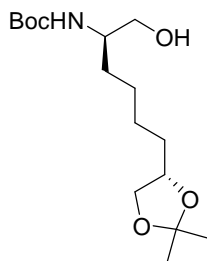
tert*-Butyl (2*S*,7*R*)-7-(*tert*-butyldimethylsilyloxy)-1,8-dihydroxyoctan-2-ylcarbamate (2*S*,7*R*)-3.94.** The title compound was prepared following the same procedure used for racemic **3.94**. The use of (+)-**3.79** (1.84 g, 5.19 mmol) and sodium borohydride (1.01 g, 26.7 mmol) provided (**2*S*,7*R)-**3.94** as a light yellow sticky oil (1.63 g, 80.2% yield). NMR spectra matches racemic **3.94**. $[\alpha]^{23} \sim 0$ ($c = 0.5$ in MeOH). HRMS (FAB) m/z $[M+H]^+$ calcd for $C_{19}H_{42}NO_5Si^+$, 392.2832; obsd, 392.2841.



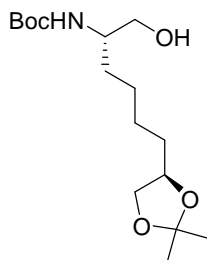
tert*-Butyl (2*R*,7*S*)-1,7,8-trihydroxyoctan-2-ylcarbamate (2*R*,7*S*)-3.96.** The title compound was prepared following the same procedure used for racemic **3.96**. The use of (**2*R*,7*S)-**3.94** (2.56 g, 6.54 mmol) and 1.0M TBAF in THF (8.0 mL, 8.0 mmol) provided (**2*R*,7*S***)-**3.96** as a white solid (1.64 g, 90.3% yield). mp = 75-77 °C. NMR spectra matches racemic **3.96**. $[\alpha]^{23} = -1.1$ ($c = 0.47$ in MeOH).



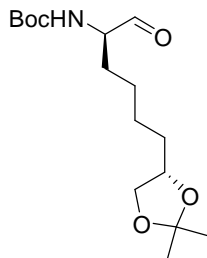
tert*-Butyl (2*S*,7*R*)-1,7,8-trihydroxyoctan-2-ylcarbamate (2*S*,7*R*)-3.96.** The title compound was prepared following the same procedure used for racemic **3.96**. The use of (**2*S*,7*R)-**3.94** (1.55 g, 3.96 mmol) and 1.0M TBAF in THF (4.8 mL, 4.8 mmol) provided (**2*S*,7*R***)-**3.96** as a white solid (0.982 g, 89.3% yield). mp = 74-76 °C. NMR spectra matches racemic **3.96**. $[\alpha]^{23} = -5.2$ ($c = 0.33$ in MeOH).



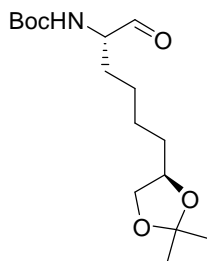
tert-Butyl (R)-6-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-hydroxyhexan-2-ylcarbamate (2R,7S)-3.98. The title compound was prepared following the same procedure used for racemic **3.98**. The use of **(2R,7S)-3.96** (1.52 g, 5.49 mmol), 2,2-dimethoxypropane (0.70 mL, 5.7 mmol), and *p*-toluenesulfonic acid (45 mg, 0.26 mmol) provided **(2R,7S)-3.98** as a yellow oil that solidified upon standing (1.64 g, 95.5% yield). NMR spectra matches racemic **3.98**. $[\alpha]^{23} \sim 0$ ($c = 0.5$ in MeOH). HRMS (FAB) m/z $[M+H]^+$ calcd for $C_{16}H_{32}NO_5^+$, 318.2280; obsd, 318.2259.



tert-Butyl (S)-6-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-hydroxyhexan-2-ylcarbamate (2S,7R)-3.98. The title compound was prepared following the same procedure used for racemic **3.98**. The use of **(2S,7R)-3.96** (0.837 g, 3.02 mmol), 2,2-dimethoxypropane (0.38 mL, 3.1 mmol), and *p*-toluenesulfonic acid (25 mg, 0.15 mmol) provided **(2S,7R)-3.98** as a yellow oil that solidified upon standing (0.683 g, 71.4% yield). NMR spectra matches racemic **3.98**. $[\alpha]^{23} \sim 0$ ($c = 0.5$ in MeOH). HRMS (FAB) m/z $[M+H]^+$ calcd for $C_{16}H_{32}NO_5^+$, 318.2280; obsd, 318.2268.

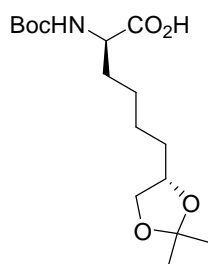


(-)-*tert*-Butyl (R)-6-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-oxohexan-2-ylcarbamate (2R,7S)-3.100. The title compound was prepared following the same procedure used for racemic **3.100** by Swern oxidation. **(2R,7S)-3.98** (0.560 g, 1.76 mmol), oxalyl chloride (0.23 mL, 2.7 mmol), DMSO (0.33 mL, 4.6 mmol), and triethylamine (1.20 mL, 8.54 mmol) provided **(2R,7S)-3.100** as a yellow oil that solidified (0.447 g, 80.3% yield). mp = 42-45 °C. NMR spectra matches racemic **3.100**. $[\alpha]^{23} = -7.7$ (c = 0.59 in CHCl₃). HRMS (FAB) m/z [M+H]⁺ calcd for C₁₆H₃₀NO₅⁺, 316.2124; obsd, 316.2131.

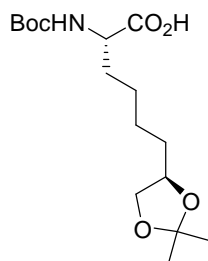


(+)-*tert*-Butyl (S)-6-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-oxohexan-2-ylcarbamate (2S,7R)-3.100. The title compound was prepared following the same procedure used for racemic **3.100** by Swern oxidation. **(2S,7R)-3.98** (0.411 g, 1.30 mmol), oxalyl chloride (0.18 mL, 2.1 mmol), DMSO (0.33 mL, 4.6 mmol), and triethylamine (0.90 mL, 6.4 mmol) provided **(2S,7R)-3.100** as a yellow oil that solidified

(0.353 g, 86.3% yield). mp = 45-47 °C. NMR spectra matches racemic **3.100**. $[\alpha]^{23} = +36.2$ (c = 0.54 in CHCl₃). HRMS (FAB) m/z $[M+H]^+$ calcd for C₁₆H₃₀NO₅⁺, 316.2124; obsd, 316.2131.

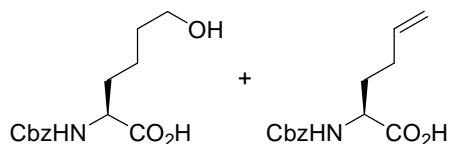


(R)-2-(tert-Butoxycarbonylamino)-6-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)hexanoic acid (2R,7S)-3.101. The title compound was prepared following the same procedure used for racemic **3.101** by KMnO₄ oxidation. **(2R,7S)-3.100** (0.458 g, 1.45 mmol), KMnO₄ (0.506 g, 3.20 mmol), and benzyltriethylammonium chloride (17.4 mg, 0.0764 mmol) provided **(2R,7S)-3.101** as a yellow oil (0.435 g, 90.5% yield). NMR spectra matches racemic **3.101**. $[\alpha]^{23} = -5.2$ (c = 0.35 in CHCl₃). HRMS (FAB) m/z $[M+H]^+$ calcd for C₁₆H₃₀NO₆⁺, 332.2073; obsd, 332.2054.



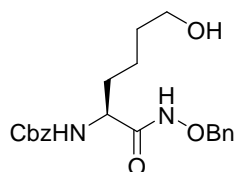
(S)-2-(tert-Butoxycarbonylamino)-6-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)hexanoic acid (2S,7R)-3.101. The title compound was prepared following the same procedure used for racemic **3.101** by KMnO₄ oxidation. **(2S,7R)-3.100** (0.372 g, 1.18

mmol), KMnO_4 (0.412 g, 2.61 mmol), and benzyltriethylammonium chloride (15.7 mg, 0.0689 mmol) provided **(2*S*,7*R*)-3.101** as a yellow oil (0.307 g, 78.6% yield). NMR spectra matches racemic **3.101**. $[\alpha]^{23} = -2.1$ ($c = 0.39$ in CHCl_3). HRMS (FAB) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{30}\text{NO}_6^+$, 332.2073; obsd, 332.2048.



Procedure for diazotization of *L*-lysine. Preparation of intermediate carboxylic acids 3.113 and 3.114. A 3-necked 500-mL round-bottomed flask was charged with Cbz-*L*-Lys-OH (**3.112**, 10.34 g, 36.88 mmol) and 150 mL of H_2O . The flask was fitted with a temperature probe and a pH probe and the solution was heated to 60 °C (internal temperature) in an oil bath. The pH of the solution was adjusted to 9.5 through the addition of 3M NaOH (or 6M HCl if too basic). Sodium nitroferricyanide dihydrate (13.20 g, 44.30 mmol) was added to the solution in portions while the solution was stirred vigorously at 60 °C. As the reaction became more acidic, the pH was maintained at 9.5 by the addition of 3M NaOH. Bubbles were observed and the color of the solution changed from colorless to yellow to a brick red suspension. After the addition was complete, the reaction was stirred vigorously while the internal temperature was maintained at 60 °C and the pH was maintained at 9.5 for 4 h. The mixture was cooled to RT, then filtered through a pad of celite. The filter cake was washed with H_2O (200 mL) and the reddish-orange filtrate was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over MgSO_4 , filtered, and concentrated to yield a yellow oil (11.7 g crude material). The crude

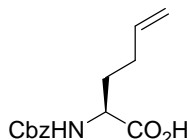
material was used directly for the preparation of compounds **3.115-3.118** without purification.



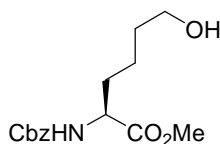
(S)-Benzyl 1-(benzyloxyamino)-6-hydroxy-1-oxohexan-2-ylcarbamate (3.115).

The crude mixture of **3.113** and **3.114** (36.9 mmol) was dissolved in 300 mL of THF and 225 mL of H₂O in a 1-L beaker equipped with a stir bar and pH probe. *O*-Benzyloxyamine hydrochloride (8.90 g, 55.8 mmol) was added and the pH of the yellow solution was adjusted to 4.5 by adding 3M NaOH (~10-15 mL). To the yellow solution was added EDC•HCl (30.1 g, 157 mmol) in portions over 80 min. The pH of the reaction was re-adjusted to 4.5 by adding 6M HCl as the pH of the solution increased. The mixture became cloudy after ~1-2 equivalents of EDC was added. After the addition of EDC•HCl was complete, the mixture was stirred for an additional 50 min (~2 h total reaction time) as the pH was maintained at 4.5 by adding 6M HCl. EtOAc (150 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 150 mL), and the combined organic layers were washed with brine (2 x 100 mL), dried over Na₂SO₄, filtered, and concentrated to yield a light yellow solid. The crude material was purified through 500 g of silica using 80% CH₂Cl₂/EtOAc to afford the alkene product, **3.116** (see below), then 100% EtOAc to afford the alcohol product, **3.115** as a fluffy white solid (6.14 g, 43.1% yield from **3.112**). mp = 115-117 °C. ¹H NMR (500 MHz, CDCl₃) δ 9.89 (s, 1H), 7.31 (m, 10H), 5.76 (d, *J* = 8.5 Hz, 1H), 5.02 (d, *J* = 12.5 Hz, 1H), 4.95 (d, *J* = 12.5 Hz, 1H), 4.87 (d, *J* = 11 Hz, 1H), 4.84 (d, *J* = 11 Hz, 1H), 4.04

(q, $J = 7.5$ Hz, 1H), 3.50 (m, 2H), 2.58 (br, 1H), 1.76 – 1.68 (m, 1H), 1.63 – 1.55 (m, 1H), 1.50 – 1.48 (m, 2H), 1.35 – 1.30 (m, 2H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 169.3, 156.3, 135.9, 135.0, 129.2, 128.7, 128.5, 128.4, 128.2, 127.9, 78.1, 67.1, 62.0, 52.3, 32.1, 31.7, 21.7 ppm. HRMS (FAB) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{27}\text{N}_2\text{O}_5^+$, 387.1920; obsd, 387.1927.

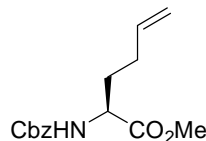


(S)-2-(Benzyloxycarbonylamino)hex-5-enoic acid (3.116). Compound **3.116** was isolated as described above as a yellow oil that solidified upon standing (3.96 g, 29.2% yield from **3.112**). Still contains impurities by NMR. ^1H NMR (500 MHz, CDCl_3) δ 9.43 (s, 1H), 7.36 – 7.30 (m, 10H), 5.73 (td, $J = 16.8, 6.5$ Hz, 1H), 5.56 (d, $J = 8.5$ Hz, 1H), 5.05 – 4.95 (m, 5H), 4.88 (s, 2H), 4.05 (q, $J = 7.5$ Hz, 1H), 2.10 – 1.95 (m, 2H), 1.89 – 1.81 (m, 1H), 1.73 – 1.65 (m, 1H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 169.1, 156.2, 136.8, 135.8, 135.0, 129.2, 128.7, 128.5, 128.2, 128.0, 127.9, 115.8, 78.2, 67.1, 51.8, 31.2, 29.4, 17.9 ppm. MS (FAB) m/z $[\text{M}+\text{H}]^+$ at 369 (base peak), 325, 246, 214.



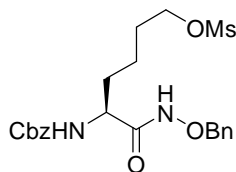
(S)-Methyl 2-(benzyloxycarbonylamino)-6-hydroxyhexanoate (3.118). The crude mixture of **3.13** and **3.14** (12 mmol) was dissolved in about 100 mL of anhydrous

Et₂O. The blue-green solution was cooled in a crushed ice/H₂O bath and a solution of excess CH₂N₂ in ether was added dropwise to the mixture. The reaction was stirred in the ice/H₂O bath for an additional 20 min then quenched by adding 10% acetic acid in Et₂O (some bubbling was observed). The mixture was poured into 100 mL of saturated NaHCO₃ and the layers were separated. The aqueous layer was extracted with Et₂O (2 x 75 mL) and the combined organic layers were washed with brine (75 mL), dried over Na₂SO₄, filtered, and concentrated to yield a light orange oil. TLC analysis of the crude mixture was performed with 1:1 hexanes/EtOAc and 2:1 CH₂Cl₂/EtOAc (UV lamp, CAM stain). The crude material was loaded onto silica and purified through a Biotage 40M column using a solvent gradient from 100% CH₂Cl₂ to 50% CH₂Cl₂/EtOAc and provided **3.117** (see below) and **3.118** as a cloudy oil (1.346 g, 38% yield from **3.112**). ¹H NMR (500 MHz, CDCl₃) δ 7.35 – 7.30 (m, 5H), 5.47 (d, *J* = 8.0 Hz, 1H), 5.09 (s, 2H), 4.37 (td, *J* = 8.0, 5.5 Hz, 1H), 3.72 (s, 3H), 3.60 (t, *J* = 6.5 Hz, 2H), 2.00 (br, 1H), 1.84 (m, 1H), 1.67 (m, 1H), 1.54 (m, 2H), 1.41 (m, 2H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 173.0, 155.9, 136.1, 128.4, 128.1, 128.0, 66.9, 62.2, 53.7, 52.3, 32.3, 31.9, 21.5 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₅H₂₂NO₅⁺, 296.1498; obsd, 296.1518.



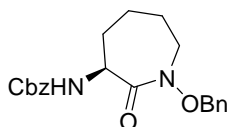
(S)-Methyl 2-(benzyloxycarbonylamino)hex-5-enoate (3.117). Compound **3.117** was isolated as described above as a cloudy oil (0.665 g, 20% yield from **3.112**). Contains impurities by NMR. ¹H NMR (500 MHz, CDCl₃) δ 7.36 – 7.32 (m, 5H), 5.78 (tdd, *J* = 13.0, 10.5, 6.5 Hz, 1H), 5.33 (d, *J* = 8.5 Hz, 1H), 5.01 (m, 2H), 4.40 (td, *J* = 8.5,

5.5 Hz, 1H), 3.75 (s, 3H), 3.68 (m, 1H), 2.17 – 2.05 (m, 2H), 1.98 – 1.91 (m, 1H), 1.80 – 1.69 (m, 1H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 172.9, 155.8, 136.7, 128.5, 128.2, 128.15, 128.07, 115.8, 67.0, 53.3, 52.3, 31.8, 29.3 ppm. HRMS (FAB) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{20}\text{NO}_4^+$, 278.1392; obsd, 278.1411.



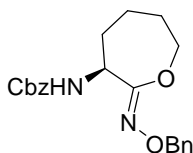
(S)-6-(Benzyloxyamino)-5-(benzyloxycarbonylamino)-6-oxohexyl

methanesulfonate (3.119). Compound **3.115** (2.376 g, 6.15 mmol) was dissolved in 45 mL of anhydrous pyridine in a flame-dried single-necked 200-mL round-bottomed flask under Ar. The solution was cooled in an ice/ H_2O bath and methanesulfonyl chloride (0.58 mL, 7.5 mmol) was added dropwise over 10 min. The solution was stirred for 1 h at 0 °C under Ar. The reaction was partitioned between EtOAc (200 mL) and 1M HCl (200 mL). The layers were separated and the organic layer was washed with 1M HCl (3 x 100 mL), H_2O (100 mL), and brine (100 mL), dried over Na_2SO_4 , filtered, and concentrated to yield a white solid (2.714 g, 95.0% yield). ^1H NMR (300 MHz, CDCl_3) δ 9.19 (s, 1H), 7.35 – 7.32 (m, 10H), 5.45 (d, J = 8.4 Hz, 1H), 5.04 (d, J = 12 Hz, 1H), 4.99 (d, J = 12 Hz, 1H), 4.88 (s, 2H), 4.15 (m, 2H), 4.01 (q, J = 7.2 Hz, 1H), 2.96 (s, 3H), 1.80 – 1.55 (m, 4H), 1.45 – 1.35 (m, 2H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 169.0, 156.2, 135.8, 134.9, 129.2, 128.7, 128.49, 128.47, 128.2, 127.9, 78.2, 69.5, 67.1, 52.1, 37.2, 31.5, 28.4, 21.3 ppm.

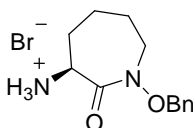


(S)-Benzyl 1-(benzyloxy)-2-oxoazepan-3-ylcarbamate (3.120). Mesylate **3.119**

(6.32 g, 13.6 mmol) was dissolved in 350 mL of reagent grade acetone in a single-necked 1-L round-bottomed flask. Potassium carbonate (5.80 g, 42.0 mmol) was added, the flask was fitted with a water condenser and heated to reflux (oil bath temperature = 85-95 °C) overnight. After 23 h, the reaction was cooled slowly to RT and allowed to stir for an additional 2 days before diluting with EtOAc (150 mL) and H₂O (150 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine (2 x 75 mL), dried over Na₂SO₄, filtered, and concentrated to yield a yellow oil. The oil was chromatographed through a Biotage 40M column using a solvent gradient from 100% CH₂Cl₂ to 80% CH₂Cl₂/EtOAc to afford **3.121** (see below), **3.120** as a colorless oil, and a mixture of **3.121** and **3.120** (4.64 g total, 92.6% total yield). Compound **3.120** was recovered as a colorless oil that solidified upon standing (3.33 g, 67% yield total). mp = 62-64 °C. R_f = 0.36 (9:1 CH₂Cl₂/EtOAc – CAM stain). ¹H NMR (500 MHz, CDCl₃) δ 7.43-7.30 (m, 10H), 6.15 (d, *J* = 6.0 Hz, 1H), 5.11 (m, 2H), 4.98 (d, *J* = 10.5 Hz, 1H), 4.88 (d, *J* = 10.5 Hz, 1H), 4.27 (ddd, *J* = 11.0, 6.5, 1.5 Hz, 1H), 3.58 (dd, *J* = 16.0, 11.5 Hz, 1H), 3.46 (dd, *J* = 16.0, 5.0 Hz, 1H), 2.03 (d, *J* = 12.0 Hz, 1H), 1.92-1.85 (m, 1H), 1.69-1.63 (m, 2H), 1.56-1.48 (m, 1H), 1.43-1.35 (m, 1H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 170.0, 155.4, 136.4, 135.0, 129.6, 128.8, 128.5, 128.4, 128.0, 127.9, 76.8, 66.6, 53.2, 52.6, 31.8, 27.5, 26.1 ppm.

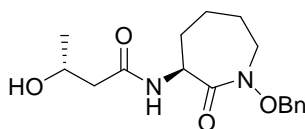


(S)-Benzyl 2-(benzyloxyimino)oxepan-3-ylcarbamate (3.121). Compound **3.121** was isolated as a glassy solid (1.31 g, 26% yield) as described above. $R_f = 0.54$ (9:1 $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ - CAM stain). ^1H NMR (500 MHz, CDCl_3) δ 7.38-7.28 (m, 10H), 5.93 (d, $J = 6$ Hz, 1H), 5.10 (s, 2H), 5.00 (s, 2H), 4.45 (dd, $J = 9.5, 7.0$ Hz, 1H), 4.37 (dd, $J = 12.5, 4.5$ Hz, 1H), 4.10 (m, 1H), 2.21 (d, $J = 11.5$ Hz, 1H), 1.90 (m, 2H), 1.72-1.58 (m, 4H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 155.6, 155.2, 137.5, 136.3, 128.5, 128.4, 128.2, 128.12, 128.07, 127.8, 76.4, 70.2, 66.8, 50.7, 35.0, 29.6, 26.2 ppm.



(S)-1-(Benzyloxy)-2-oxoazepan-3-amonium bromide (3.122). Hydroxamate **3.120** (2.128 g, 5.776 mmol) was dissolved in 60 mL of anhydrous CH_2Cl_2 in a flame-dried 250-mL round-bottomed flask under Ar. 33% HBr in acetic acid (6.0 mL, 35 mmol) was added to the solution slowly and the Ar inlet needle was removed. The reaction was stirred at RT under Ar. White solid was observed after 2 min. After 3 h, no starting material was observed by TLC (4:1 $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ - CAM stain, ninhydrin stain) and a ninhydrin-positive baseline spot was observed. The mixture was diluted with CH_2Cl_2 (20 mL), and concentrated by rotary evaporation (40 °C, 21 mm Hg) to yield a light orange slurry. The slurry was concentrated from toluene (3 x 50 mL) to remove traces of acetic acid and water to afford a tan/orange solid. The solid was dried under

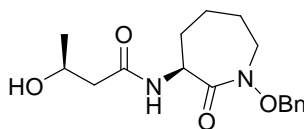
vacuum (1.5 mm Hg) overnight to afford HBr salt **3.122** as an off-white solid (1.80 g, 99% yield). ^1H NMR (500 MHz, $\text{d}^6\text{-DMSO}$) δ 8.25 (br, 3H), 7.47 – 7.38 (m, 5H), 4.93 (d, J = 10.0 Hz, 1H), 4.90 (d, J = 10.0 Hz, 1H), 4.24 (d, J = 5.0 Hz, 1H), 3.88 (dd, J = 16.0, 11.5 Hz, 1H), 3.60 (dd, J = 16.0, 5.0 Hz, 1H), 1.86 (m, 2H), 1.73 – 1.50 (m, 3H), 1.33 – 1.25 (m, 1H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 167.1, 135.0, 129.3, 128.7, 128.4, 75.7, 51.3, 51.2, 28.2, 26.1, 25.8 ppm.



(*R*)-*N*-((*S*)-1-(Benzyloxy)-2-oxoazepan-3-yl)-3-hydroxybutanamide (3.124).

Anhydrous CH_3CN (30 mL) was added to a 100-mL round-bottomed flask containing **3.122** (1.00 g, 3.17 mmol), (*R*)-3-hydroxybutyric acid (0.3906 g, 3.752 mmol), and HOBt (0.501 g, 3.71 mmol). To the mixture was added triethylamine (0.50 mL, 3.6 mmol), followed by EDC•HCl (0.761 g, 3.97 mmol). The mixture was stirred at RT under Ar. After 1 h, the solid material had fully dissolved. The reaction was stirred overnight at RT under Ar. The cloudy peach-colored solution was concentrated and the residue was partitioned between H_2O (25 mL) and EtOAc (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 25 mL). The combined organic layers were washed with H_2O (30 mL), saturated NaHCO_3 (2 x 30 mL), H_2O (30 mL), and brine (30 mL), dried over Na_2SO_4 , filtered, and concentrated to yield a white solid. The solid was chromatographed through a 40S Biotage column using 100% EtOAc to yield **3.124** as a white solid (0.891 g, 87.7% yield). mp = 120-123 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.42-7.34 (m, 5H), 7.09 (d, J = 6.5 Hz, 1H), 4.97 (d, J = 10.5 Hz, 1H), 4.88 (d, J = 10.5

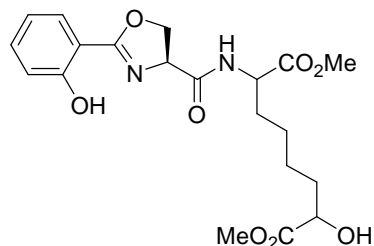
Hz, 1H), 4.48 (ddd, $J = 11.0, 6.5, 1.5$ Hz, 1H), 4.17 (m, 1H), 3.94 (m, 1H), 3.60 (dd, $J = 16.0, 11.5$ Hz, 1H), 3.47 (dd, $J = 16.0, 5.0$ Hz, 1H), 2.43 (dd, $J = 15.5, 3.0$ Hz, 1H), 2.32 (dd, $J = 15.5, 9.0$ Hz, 1H), 1.98 (d, $J = 12.5$ Hz, 1H), 1.91 (m, 1H), 1.71-1.65 (m, 2H), 1.49-1.30 (m, 2H), 1.21 (d, $J = 6.0$ Hz, 3H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 171.5, 170.0, 134.9, 129.6, 128.9, 128.6, 76.8, 64.7, 52.7, 51.6, 43.6, 31.3, 27.5, 26.1, 22.6 ppm. HRMS (FAB) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{25}\text{N}_2\text{O}_4^+$, 321.1814; obsd, 321.1810.



(S)-N-((S)-1-(Benzyloxy)-2-oxoazepan-3-yl)-3-hydroxybutanamide (3.125).

Compound **3.125** was prepared following the same procedure used for **3.124**. The use of **3.122** (1.20 g, 3.81 mmol), (*S*)-3-hydroxybutyric acid (0.479 g, 4.60 mmol), HOBT (0.617 g, 4.57 mmol), EDC•HCl (0.938 g, 4.89 mmol), and triethylamine (0.60 mL, 4.27 mmol) provided **3.125** as a white solid (0.863 g, 70.7% yield). $R_f = 0.14$ (100% EtOAc – CAM stain). mp = 135-137 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.41-7.40 (m, 2H), 7.37-7.35 (m, 3H), 6.99 (d, $J = 6.5$ Hz, 1H), 4.98 (d, $J = 10.5$ Hz, 1H), 4.89 (d, $J = 10.5$ Hz, 1H), 4.47 (ddd, $J = 11.5, 7.0, 2.0$ Hz, 1H), 4.18 (m, 1H), 3.61 (dd, $J = 16.0, 11.5$ Hz, 1H), 3.48 (dd, $J = 16.0, 5.0$ Hz, 1H), 2.40 (dd, $J = 15.0, 3.0$ Hz, 1H), 2.32 (dd, $J = 15.0, 9.0$ Hz, 1H), 1.98 (m, 1H), 1.92 (m, 1H), 1.71-1.65 (m, 2H), 1.54-1.35 (m, 2H), 1.23 (d, $J = 6.5$ Hz, 3H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 171.8, 170.1, 134.9, 129.6, 128.9, 128.6, 76.8, 64.9, 52.7, 51.8, 44.1, 31.2, 27.5, 26.1, 22.7 ppm. HRMS (FAB) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{25}\text{N}_2\text{O}_4^+$, 321.1814; obsd, 321.1802.

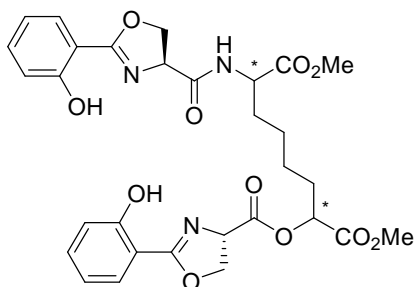
8.3 Experimental procedures for chapter 4



Dimethyl 2-hydroxy-7-((S)-2-(2-hydroxyphenyl)-4,5-dihydrooxazole-4-carboxamido)octanedioate (4.5a and 4.5b). Compound **3.69** (130.8 mg, 0.392 mmol) was dissolved in 5 mL of anhydrous Et₂O in a 25-mL round-bottomed flask. The solution was cooled in an ice/H₂O bath and HCl gas (generated by adding conc. H₂SO₄ dropwise to conc. HCl/NaCl then drying by bubbling through conc. H₂SO₄) was bubbled through the solution for 30 min. The solution was brownish in color, and no significant precipitate was observed. Bubbling was ceased and the reaction was warmed to RT and stirred for an additional 4 h. The reaction was concentrated by rotary evaporation to yield the amine•HCl salt as a brown semi-solid residue. The crude material was used immediately without purification.

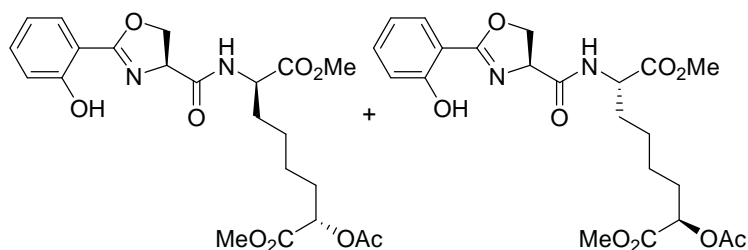
Anhydrous CH₃CN (5 mL) was added to the crude amine (105.8 mg, 0.452 mmol) and **2.62** (102.4 mg, 0.494 mmol) in a 25-mL round-bottomed flask under Ar. Distilled triethylamine (0.10 mL, 0.71 mmol) was added and most of the solid material dissolved. To the resultant yellow solution was added HOBt (67.4 mg, 0.499 mmol) and EDC•HCl (108.1 mg, 0.564 mmol). The reaction was stirred at RT under Ar. After 4 days, the reaction was concentrated by rotary evaporation (35°C, 21 mm Hg). The orange residue was partitioned between EtOAc (20 mL) and H₂O (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with saturated aqueous NaHCO₃ (2 x 20 mL), H₂O (1 x 20 mL), 5

wt% aqueous citric acid (2 x 20 mL), H₂O (1 x 20 mL), and brine (2 x 20 mL), dried over Na₂SO₄, filtered, and concentrated by rotary evaporation (35°C, 21 mm Hg) to yield an orange oil (200 mg). The oil was purified through 20 g of silica using a solvent gradient from 100% CH₂Cl₂ to 50% CH₂Cl₂/EtOAc to yield a mixture of **4.5a** and **4.5b** as a cloudy pink residue (59.7 mg, 31.3% yield) and **4.6** (see below). Recovered as a mixture of diastereomers by NMR: ¹H NMR (500MHz, CDCl₃) δ 7.67 (m, 2H), 7.41 (m, 2H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.91 - 6.87 (m, 2H), 4.98 - 4.93 (m, 2H), 4.70 - 4.55 (m, 6H), 4.17 (dd, *J* = 7.6, 4.0 Hz, 1H), 4.11 (dd, *J* = 7.7, 4.0 Hz, 1H), 3.77 (s, 3H, CH₃), 3.75 (s, 3H), 3.72 (s, 3H), 3.69 (s, 3H), 1.93 - 1.24 (m, 16H) ppm. MS (FAB) *m/z* [M+H]⁺ at 423; 363, 162.



Diacylated byproduct (4.6). Compound **4.6** was isolated as described above as a cloudy yellow oil (63.6 mg, 23.0% yield). Recovered as a mixture of diastereomers by NMR: ¹H NMR (500 MHz, CDCl₃) δ 7.69 – 7.62 (m, 2H), 7.46 – 7.53 (m, 2H), 7.07 – 7.00 (m, 2H), 6.91 – 6.82 (m, 2H), 5.12 – 5.04 (m, 3H), 4.78 – 4.55 (m, 4H), 3.75 (s, 3H), 3.73 (s, 3H), 3.72 (s, 3H), 3.70 (s, 3H), 1.95 – 1.70 (m, 4H), 1.47 – 1.30 (m, 4H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 172.2, 172.0, 169.99, 169.92, 169.87, 169.8, 169.7, 168.2, 168.1, 168.0, 159.9, 159.8, 134.7, 134.2, 128.7, 128.4, 119.2, 118.8, 116.93, 116.90, 72.9,

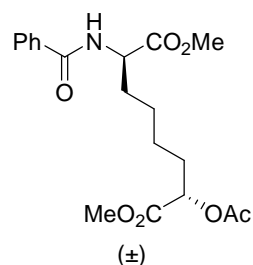
69.9, 69.0, 67.0, 66.3, 52.5, 52.1, 31.9, 31.8, 31.54, 30.47, 29.6, 24.8, 24.6 ppm. MS (FAB) m/z $[M+H]^+$ at 612 (base peak), 307, 208.



Dimethyl 2-acetoxy-7-((S)-2-(2-hydroxyphenyl)-4,5-dihydrooxazole-4-carboxamido)octanedioate (mixture of diastereomers 4.7a and 4.7b). Compound **3.86** (194 mg, 0.517 mmol) was dissolved in 10 mL of anhydrous Et₂O in a 50-mL round-bottomed flask. Anhydrous HCl gas (generated by adding conc. H₂SO₄ dropwise to NaCl/HCl, then passed through conc. H₂SO₄) was bubbled through the solution. After 30 min, the solution appeared slightly cloudy. After 1.5 h, TLC of the solution (1:1 hexanes/EtOAc - CAM stain, ninhydrin stain) indicated no starting material remained and a new, ninhydrin positive spot appeared on the baseline. The solution was concentrated to afford a yellow oil (mass recovery was >100%). The oil was used immediately without purification.

Anhydrous CH₃CN (5 mL) was added to the yellow oil in a 50-mL round-bottomed flask under Ar. Anhydrous triethylamine (0.10 mL, 0.712 mmol) was added and the solid dissolved. To the light orange/yellow solution was added **2.62** (114 mg, 0.550 mmol) and the color of the solution changed to deep orange/red. EDC•HCl (122 mg, 0.636 mmol) was added and the solution was stirred under Ar at RT overnight. The reaction was concentrated by rotary evaporation (35°C, 21 mm Hg). The orange residue was partitioned between EtOAc (20 mL) and H₂O (30 mL). The layers were separated

and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with saturated aqueous NaHCO₃ (2 x 20 mL), H₂O (1 x 20 mL), 5 wt% aqueous citric acid (2 x 20 mL), H₂O (1 x 20 mL), and brine (2 x 20 mL), dried over Na₂SO₄, filtered, and concentrated by rotary evaporation (35°C, 21 mm Hg) to yield a yellow oil. The oil was purified through 20 g of silica using CH₂Cl₂/EtOAc to afford the mixture of diastereomers **4.7a** and **4.7b** as a yellow oil (75.8 mg, 31.6% yield). ¹H NMR (500 MHz, CDCl₃) δ 11.33 (br-s, 2H), 7.68 - 7.65 (m, 2H), 7.42 - 7.37 (m, 2H), 7.02 - 7.00 (m, 2H), 6.90 - 6.81 (m, 4H), 4.99 - 4.90 (m, 4H), 4.68 - 4.53 (m, 6H), 3.75 (s, 3H), 3.72 (s, 3H), 3.69 (s, 3H), 3.68 (s, 3H), 2.11 (s, 3H), 2.07 (s, 3H), 1.90 - 1.64 (m, 10H), 1.42 - 1.23 (m, 12H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 172.06, 171.97, 170.50, 170.46, 170.38, 170.33, 170.26, 167.99, 167.75, 159.70 (2), 134.23, 128.49, 128.46, 119.02, 116.89, 116.86, 109.90, 109.88, 71.88, 71.84, 69.44, 69.42, 67.94, 67.88, 52.43, 52.40, 52.17, 52.11, 51.91, 31.98, 31.92, 30.72, 30.64, 29.58, 24.82, 24.77, 24.57, 25.50, 20.53, 20.48 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd. for C₂₂H₂₉N₂O₈⁺, 465.1873; obsd, 465.1855.



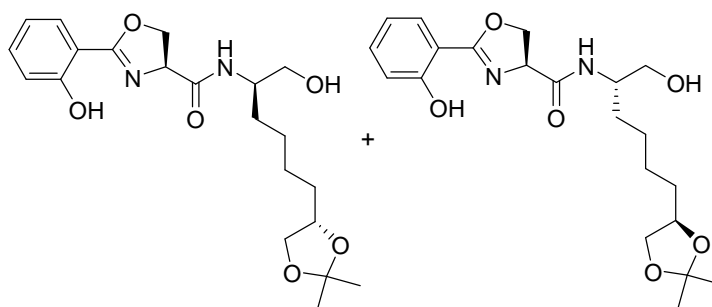
(±)-(2*S*,7*R*)-Dimethyl 2-acetoxy-7-benzamidooctanedioate (**4.8**). Compound **3.86** (138 mg, 0.366 mmol) was dissolved in 1 mL of CH₂Cl₂ in a 10-mL round-bottomed flask and cooled in a crushed ice/H₂O bath under Ar. TFA (0.20 mL, 2.7 mmol) was

added to the reaction and the resultant light pink solution was stirred in the crushed ice/H₂O bath for 60 min. TLC of the reaction (1:1 hexanes/EtOAc - CAM stain) indicates a complex mixture, but some amine present on the baseline. The reaction was warmed to RT and allowed to stir for an additional 60 min, then concentrated and used immediately without purification.

The crude material was dissolved in CH₂Cl₂ (1.5 mL). Benzoyl chloride (0.090 mL, 0.77 mmol) and Et₃N (0.75 mL, 5.3 mmol) were added and the reaction was stirred at RT overnight. The reaction was diluted with H₂O (10 mL) and CH₂Cl₂ (10 mL) and the layers were separated. The aqueous layer was washed with CH₂Cl₂ (5 mL) and the combined CH₂Cl₂ layers were washed with saturated NaHCO₃ (2 x 15 mL), H₂O (15 mL), 10 wt% citric acid (2 x 15 mL), H₂O (15 mL), and brine (15 mL), dried over MgSO₄, filtered, and concentrated to yield a yellow oil. The oil was chromatographed through 20 g of silica using a solvent gradient from 100% CH₂Cl₂ to 85% CH₂Cl₂/EtOAc and provided **4.8** as a yellow oil (117 mg, 84% yield). Evidence of epimerization is observed from the ¹³C NMR spectrum. ¹H NMR (500 MHz, CDCl₃) δ 7.77 (d, *J* = 7.0 Hz, 2H), 7.46 (m, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 6.83 (d, *J* = 7.5 Hz, 1H), 4.93 (t, *J* = 6.0 Hz, 1H), 4.76 (td, *J* = 8.0, 6.0 Hz, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 2.06 (s, 3H), 1.80 – 1.74 (m, 4H), 1.43 – 1.34 (m, 4H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 172.9, 171.0, 170.5, 170.4, 166.9, 133.7, 131.6, 128.4, 126.9, 71.9, 60.2, 52.33, 52.27, 52.1, 32.1, 30.7, 24.8, 24.6, 20.9, 20.5 ppm. MS (FAB) *m/z* [M+H]⁺ found at 380.

Attempted saponification of compound 4.8. Compound **4.8** (22 mg, 0.058 mmol) was dissolved in 0.6 mL of 2:1 THF/H₂O in a 1-dram screw-cap vial. LiOH (6

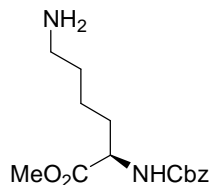
mg, 0.25 mmol) was added and the mixture was stirred at RT. Monitored by TLC (1:1 hexanes/EtOAc and 100% EtOAc - UV lamp, CAM stain). After 45 min the reaction was nearly complete, and after 1 h, no **4.8** was observed by TLC. 1 mL of 1M HCl was added to the vial and the acidic mixture (pH ~2-3 - pH paper) was extracted with EtOAc (10 x 1 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated to yield a light yellow residue (18.9 mg, ~100% yield). Residue did not dissolve in CDCl₃, but dissolved in EtOAc. MS data did not show evidence of the desired product. No identifiable peaks were found in the LC-MS traces of the aqueous layer.



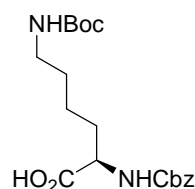
(4S)-N-(6-(2,2-Dimethyl-1,3-dioxolan-4-yl)-1-hydroxyhexan-2-yl)-2-(2-hydroxyphenyl)-4,5-dihydrooxazole-4-carboxamide (mixture of diastereomers **4.10a and **4.10b**).** Compound (\pm)-**3.99** (74.1 mg, 0.211 mmol) was dissolved in 10 mL of methanol in a flame-dried single-necked 25-mL round-bottomed flask. The solution was purged with Ar and 10 wt% Pd/C (17.7 mg) was added. The solution was purged with Ar, then H₂, and stirred under 1 atm of H₂ (balloon). After 4 h, TLC analysis of the reaction mixture (1:1 hexanes/EtOAc - CAM stain, ninhydrin stain) indicated the starting material was consumed and a new, ninhydrin/CAM stain positive spot was observed on the baseline. The reaction was purged with Ar, then filtered through a pad of celite. The

celite was rinsed with MeOH (5 mL) and the filtrate was concentrated to yield a colorless residue. The material was used immediately without purification.

The residue (41 mg, 0.20 mmol) and HOBt (25 mg, 0.19 mmol) were dissolved in 5 mL of dry acetonitrile in a single-necked 25-mL round-bottomed flask under Ar. EDC•HCl (43 mg, 0.22 mmol) was added and the peach-colored solution was stirred at RT under Ar overnight. H₂O (30 mL) and EtOAc (20 mL) were added to the solution and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 15 mL) and the combined organic layers were washed successively with saturated NaHCO₃ (2 x 20 mL), H₂O (20 mL), 10 wt% citric acid (2 x 20 mL), and brine (2 x 20 mL), dried over MgSO₄, filtered, and concentrated to yield a light yellow residue. The residue was chromatographed through 15 g of silica gel using a solvent gradient from 2:1 CH₂Cl₂/EtOAc to 100% EtOAc to afford one of the diastereomers of **4.10** pure (14.0 mg, 19.7% yield), and mixtures of diastereomers **4.10a** and **4.10b** (46.6 mg, 65.8% yield). Total yield of **4.10** was 60.6 mg (85.5% yield). Analysis of the pure diastereomer isolated: mp = 112-115 °C. R_f = 0.15 (1:2 CH₂Cl₂/EtOAc – UV lamp; other isomer R_f = 0.09). ¹H NMR (500 MHz, CDCl₃) δ 11.37 (s, 1H), 7.69 (m, 1H), 7.43 (m, 1H), 7.02 (d, *J* = 8.5 Hz, 1H), 6.91 (td, *J* = 8.0, 0.5 Hz, 1H), 6.48 (d, *J* = 8.0 Hz, 1H), 4.95 (dd, *J* = 11.0, 8.0 Hz, 1H), 4.70 (dd, *J* = 11.0, 9.0 Hz, 1H), 4.62 (t, *J* = 8.5 Hz, 1H), 4.06 (m, 1H), 4.02 (dd, *J* = 7.5, 6.0 Hz, 1H), 3.95 (m, 1H), 3.65 (d, *J* = 10.5 Hz, 1H), 3.56 (dd, *J* = 11.0, 5.5 Hz, 1H), 3.50 (t, *J* = 7.5 Hz, 1H), 2.46 (br-s, 1H), 1.66-1.40 (m, 8H), 1.40 (s, 3H), 1.35 (s, 3H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 171.4, 168.0, 159.6, 134.4, 128.6, 119.2, 110.0, 108.7, 75.9, 69.8, 69.4, 68.0, 65.2, 51.9, 33.4, 30.9, 29.7, 26.9, 26.1, 25.7, 25.6 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₂₁H₃₁N₂O₆⁺, 407.2182; obsd, 407.2176.

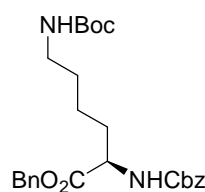


(R)-Methyl 6-amino-2-(benzyloxycarbonylamino)hexanoate (4.15). Methanol (10 mL) was cooled under Ar to 4 °C in an ice/H₂O bath. Thionyl chloride (0.35 mL, 4.8 mmol) was added and the resultant solution was transferred via cannula to a stirred suspension of **4.14** (1.03 g, 3.67 mmol) in 30 mL of MeOH under Ar at 4 °C. The mixture was stirred for 1 h, then warmed to RT and stirred for an additional 7.5 h. The reaction was concentrated to yield a yellow oil. The oil was dissolved in saturated NaHCO₃ (100 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated to yield **4.15** as a reddish-brown oil (1.05 g, 97% yield). The oil was stored at -10 °C and used immediately, otherwise decomposition was observed.

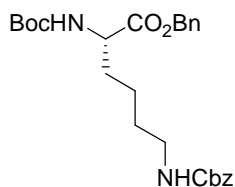


(R)-13,13-Dimethyl-3,11-dioxo-1-phenyl-2,12-dioxo-4,10-diazatetradecane-5-carboxylic acid (4.16). Sodium bicarbonate (0.343 g, 4.08 mmol) was added to **4.14** (0.454 g, 1.62 mmol) in 12 mL of 2:1 THF/H₂O, followed by di-*tert*-butyldicarbonate (0.411 g, 1.88 mmol). The mixture was stirred at RT overnight. The THF was removed *in vacuo* and the reaction was diluted with H₂O (50 mL) and CH₂Cl₂ (20 mL). The

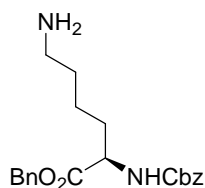
aqueous layer was acidified to a pH of 2-3 (pH paper) using 1M HCl. The layers were separated and the aqueous was extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over MgSO₄, filtered, and concentrated to a pale yellow oil. The oil was dried under vacuum to yield **4.16** as a white foam (0.577 g, 94% yield). The crude material was used directly without further purification.



2S-Benzyloxycarbonylamino-6-tert-butoxycarbonylamino-hexanoic acid benzyl ester (4.17). Crude **4.16** (651 mg, 1.71 mmol) was dissolved in 10 mL of CH₃CN. K₂CO₃ (548 mg, 3.96 mmol) was added, followed by benzyl bromide (0.30 mL, 2.53 mmol). The reaction was stirred for 24 h and monitored by TLC (3:1 hexanes/EtOAc – ninhydrin stain). The solid was removed by filtration and the filtrate was concentrated to yield a cloudy oil (1.20 g). Chromatographed through 40 g of silica using 3:1 hexanes/EtOAc to yield **4.17** as a colorless oil (747 mg, 93%). ¹H NMR (300 MHz, CDCl₃) δ 7.347 (s, 10H), 5.386 (d, *J* = 7.2 Hz, 1H), 5.167 (d, *J* = 6.0 Hz, 2H), 5.101 (s, 2H), 4.507 (br-s, 1H), 4.399 (m, 1H), 3.047 (m, 1H), 1.826 – 1.626 (m, 2H), 1.422 (s, 9H) ppm.

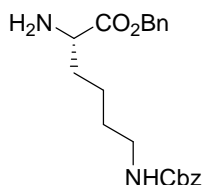


6-Benzyloxycarbonylamino-2*S*-tert-butoxycarbonylamino-hexanoic acid benzyl ester (4.20). Compound **4.20** was prepared following the procedure used for **4.17**. The use of **4.19** (801 mg, 2.10 mmol), K₂CO₃ (735 mg, 5.32 mmol), and BrBr (0.38 mL, 3.20 mmol) afforded a colorless oil (1.20 g). Chromatographed through 50 g of silica using 3:1 hexanes/EtOAc provided **4.20** as a light yellow oil (986 mg, 100%). ¹H NMR (500 MHz, CDCl₃) δ 7.36 – 7.34 (m, 10H), 5.20 (d, *J* = 12 Hz, 1H), 5.11 (d, *J* = 12 Hz, 1H), 5.09 (br-s, 4H), 4.77 (m, 1H), 4.33 (m, 1H), 3.14 (m, 2H), 1.80 (m, 1H), 1.65 (m, 1H), 1.42 (s, 9H), 1.45 – 1.29 (m, 4H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 172.6, 156.4, 155.4, 136.5, 135.3, 128.5, 128.44, 128.39, 128.3, 128.1, 128.0, 79.8, 66.9, 66.5, 53.2, 40.5, 32.2, 29.3, 28.2, 22.3 ppm.

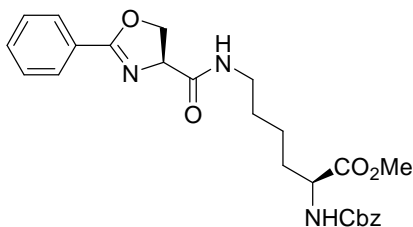


(*R*)-Benzyl 6-amino-2-(benzyloxycarbonylamino)hexanoate (4.18). HCl gas, prepared by adding conc. H₂SO₄ dropwise to NaCl/conc. HCl and dried by bubbling through conc. H₂SO₄, was bubbled through a solution of **4.17** (0.634 g, 1.35 mmol) in Et₂O at 0 °C for 2.5 h. The reaction was monitored by TLC for the disappearance of **4.17**. The solvent was removed to yield a pale yellow oil. The oil was dissolved in saturated NaHCO₃ (50 mL) and CH₂Cl₂ (20 mL) was added. The layers were separated

and the aqueous layer was extracted with CH₂Cl₂ (2 x 20 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated to yield **4.18** as a pale yellow oil (0.461 g, 92% yield). The material was used immediately without purification.

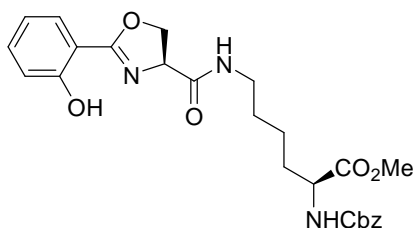


(S)-Benzyl 2-amino-6-(benzyloxycarbonylamino)hexanoate (4.21). Compound **4.21** was prepared following the same procedure used for **4.18**. **4.20** (0.980 g, 2.08 mmol) provided **4.21** as a pale yellow oil (0.697 g, 90% yield). The material was used immediately without purification.



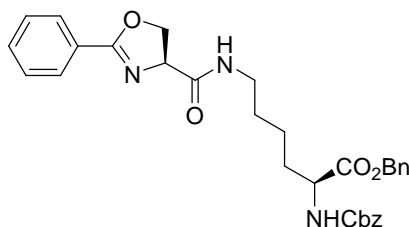
(S)-Methyl 2-(benzyloxycarbonylamino)-6-((S)-2-phenyl-4,5-dihydrooxazole-4-carboxamido)hexanoate (4.22). Compound **3.11** (135 mg, 0.708 mmol) and **4.15** (250 mg, 0.848 mmol) were dissolved in CH₃CN (20 mL). EDC•HCl (166 mg, 0.865 mmol) was added and the reaction was stirred at 23°C for 15 h. The reaction was monitored by TLC (2:3 hexanes/EtOAc). The reaction was diluted with H₂O (50 mL) and extracted with EtOAc (4 x 30 mL). The combined EtOAc layers were washed with saturated NaHCO₃ (3 x 20 mL), 5% citric acid (3 x 20 mL), and brine (2 x 30 mL), dried (MgSO₄), filtered, and concentrated to yield a pale orange oil (170 mg).

Chromatographed through 17 g of silica using 3:2 CH₂Cl₂/EtOAc to yield **4.22** as an orange oil (135 mg, 41%). R_f = 0.111 (2:3 hexanes/EtOAc). ¹H NMR (300 MHz, CDCl₃) δ 7.96 (dd, *J* = 8.1, 0.9 Hz, 2H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.34 (m, 5H), 6.72 (br-t, 1H), 5.44 (d, *J* = 8.1 Hz, 1H, NHCbz), 5.09 (s, 2H), 4.821 (dd, *J* = 10.8, 8.7 Hz, 1H), 4.68 – 4.54 (m, 2H), 4.34 (m, 1H), 3.71 (s, 3H), 3.34 – 3.15 (m, 2H), 1.88 – 1.60 (m, 2H), 1.53 – 1.33 (m, 4H) ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₂₅H₃₀N₃O₆⁺, 468.2135; obsd, 468.2144.

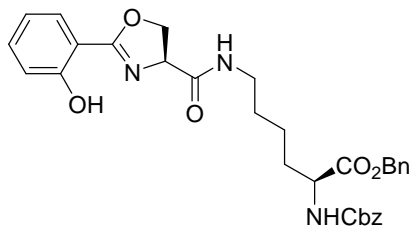


(S)-Methyl 2-(benzyloxycarbonylamino)-6-(((S)-2-(2-hydroxyphenyl)-4,5-dihydrooxazole-4-carboxamido)hexanoate (4.23). Compound **4.23** was prepared following the same procedure used for **4.22**. The use of oxazoline **2.62** (0.104 g, 0.502 mmol), amine **4.15** (0.174 g, 0.591 mmol), and EDC•HCl (0.125 g, 0.653 mmol) provided a pale orange oil (0.149 g, 61%). Chromatography through 20 g of silica using 4:1 CH₂Cl₂/EtOAc afforded **4.23** as a white solid (0.127 g, 52%). mp = 142-143 °C. R_f = 0.189 (2:3 hexanes/EtOAc). ¹H NMR (300 MHz, CDCl₃) δ 7.68 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.42 (td, *J* = 8.7, 1.5 Hz, 1H), 7.35 (m, 5H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.91 (t, *J* = 7.8 Hz, 1H), 6.42 (br-t, 1H, NHBoc), 5.41 (d, *J* = 8.1 Hz, 1H, NHCbz), 5.10 (s, 2H), 4.90 (t, *J* = 9.5 Hz, 1H), 4.67 – 4.58 (m, 2H), 4.34 (m, 1H), 3.72 (s, 3H), 3.27 (m, 2H), 1.84 – 1.60 (m, 2H), 1.56 – 1.25 (m, 4H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ 170.7, 167.9, 159.6, 155.9, 136.2, 134.3, 128.50, 128.46, 128.1, 119.2, 116.8, 110.0, 69.9, 67.9, 67.0,

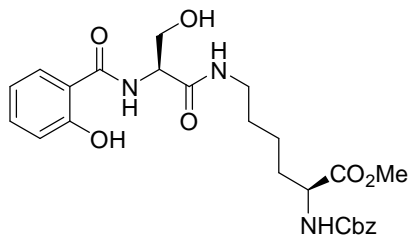
53.6, 52.3, 38.8, 31.9, 28.9, 22.3 ppm. HRMS (FAB) m/z $[M+H]^+$ calcd for $C_{25}H_{30}N_3O_7^+$, 484.2084; obsd, 484.2107.



(S)-Benzyl 2-(benzyloxycarbonylamino)-6-((S)-2-phenyl-4,5-dihydrooxazole-4-carboxamido)hexanoate (4.24). Compound **4.24** was prepared following the same procedure used for **4.22**. The use of acid **3.11** (89 mg, 0.47 mmol), amine **4.18** (204 mg, 0.550 mmol), and EDC•HCl (112 mg, 0.583 mmol) provided a light orange oil (156 mg). Chromatography through 16 g of silica using a solvent gradient from 3:1 to 3:2 CH_2Cl_2 /EtOAc yielded **4.24** as a white solid (89 mg, 35%). mp = 125-128 °C. Rf = 0.167 (2:3 hexanes/EtOAc). 1H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, J = 7.2 Hz, 2H), 7.52 (t, J = 7.3 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.34 (br-s, 10H), 6.72 (br-t, J = 5.1 Hz, 1H), 5.48 (d, J = 6.9 Hz, 1H, NHCbz), 5.15 (d, J = 2.7 Hz, 2H), 5.09 (s, 2H), 4.814 (dd, J = 10.8, 9.0 Hz, 1H), 4.68 – 4.55 (m, 2H), 4.42 – 4.35 (m, 1H), 3.28 – 3.15 (m, 2H), 1.83 (m, 1H), 1.71 (m, 1H), 1.49 (m, 2H), 1.33 (m, 2H) ppm. HRMS (FAB) m/z $[M+H]^+$ calcd for $C_{31}H_{34}N_3O_6^+$, 544.2448; obsd, 544.2452.

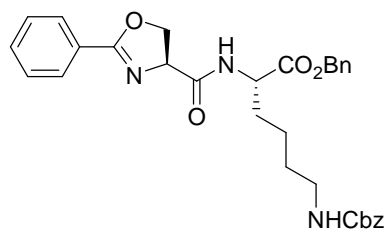


(S)-Benzyl 2-(benzyloxycarbonylamino)-6-((S)-2-(2-hydroxyphenyl)-4,5-dihydrooxazole-4-carboxamido)hexanoate (4.25). Compound **4.25** was prepared following the same procedure used for **4.22**. The use of acid **2.62** (109 mg, 0.524 mmol), amine **4.18** (234 mg, 0.631 mmol), and EDC•HCl (127 mg, (0.663 mmol) provided a light orange oil (148 mg). Chromatography through 15 g of silica using 1:1 hexanes/EtOAc yielded **4.25** as a white solid (106 mg, 36%). mp = 149-151 °C. Rf = 0.270 (2:3 hexanes/EtOAc). ¹H NMR (300 MHz, CDCl₃) δ 7.68 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.42 (m, 1H), 7.34 (m, 10H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.91 (t, *J* = 7.8 Hz, 1H), 6.37 (br-t, 1H), 5.41 (d, *J* = 8.1 Hz, 1H, NHCbz), 5.16 (d, *J* = 3.3 Hz, 2H), 5.10 (s, 2H), 4.89 (t, *J* = 9.6 Hz, 1H), 4.67 – 4.60 (m, 2H), 4.42 – 4.35 (m, 1H), 3.26 – 3.18 (m, 2H), 1.83 (m, 1H), 1.70 (m, 1H), 1.51 (m, 2H), 1.31 (m, 2H) ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₃₁H₃₄N₃O₇⁺, 560.2397; obsd, 560.2406.



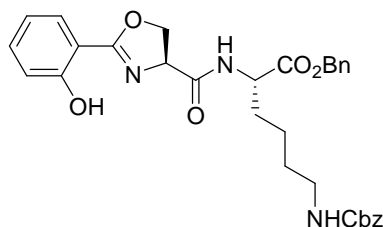
(S)-Methyl 2-(benzyloxycarbonylamino)-6-((S)-3-hydroxy-2-(2-hydroxybenzamido)propanamido)hexanoate (4.26). Compound **4.26** was prepared following the same procedure used for **4.22**. The use of acid **2.62** (90 mg, 0.399 mmol),

amine **4.15** (123 mg, 0.418 mmol), and EDC•HCl (95 mg, 0.498 mmol) provided a pale yellow oil (217 mg). Chromatography through 25 g of silica using 1:4 hexanes/EtOAc yielded **4.26** as a white glassy solid (158 mg, 79%). ¹H NMR (300 MHz, CDCl₃) δ 7.99 (m, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.32 – 7.26 (m, 5H), 7.09 (t, *J* = 5.1 Hz, 1H), 6.89 (d, *J* = 8.1 Hz, 1H), 6.76 (t, *J* = 7.5 Hz, 1H), 5.77 (d, *J* = 7.8 Hz, 1H), 5.02 (s, 2H), 4.61 (m, 1H), 4.27 (m, 1H), 4.03 (m, 1H), 3.74 (q, *J* = 5.4 Hz, 1H), 3.65 (s, 3H), 3.19 (m, 2H), 1.76 – 1.30 (m, 6H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ 172.7, 170.6, 170.2, 161.1, 156.1, 136.3, 134.4, 128.4, 128.1, 127.9, 126.6, 119.0, 118.3, 114.3, 67.1, 62.6, 54.4, 52.1, 39.1, 32.0, 28.7, 22.4 ppm.

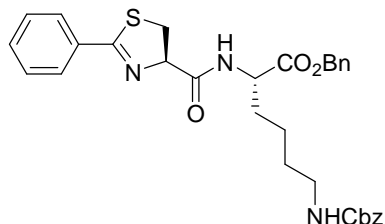


(S)-Benzyl 6-(benzyloxycarbonylamino)-2-((S)-2-phenyl-4,5-dihydrooxazole-4-carboxamido)hexanoate (4.27). Compound **4.27** was prepared following the same procedure used for **4.22**. The use of acid **3.11** (106 mg, 0.529 mmol), amine **4.21** (263 mg, 0.710 mmol), and EDC•HCl (143 mg, 0.748 mmol) provided a light orange oil (228 mg). Chromatography through 25 g of silica using a solvent gradient from 85:15 to 4:1 CH₂Cl₂/EtOAc yielded **4.27** as a white solid (195 mg, 65%). mp = 102-104 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.99 (dd, *J* = 8.4, 1.5 Hz, 2H), 7.51 (tt, *J* = 7.3, 1.5 Hz, 1H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.35 (m, 10H), 7.23 (d, *J* = 7.8 Hz, 1H), 5.21 (d, *J* = 12 Hz, 1H), 5.18 (d, *J* = 12 Hz, 1H), 5.06 (s, 2H), 4.86 (m, 2H), 4.61 (m, 3H), 3.06 (m, 2H), 1.83 (m,

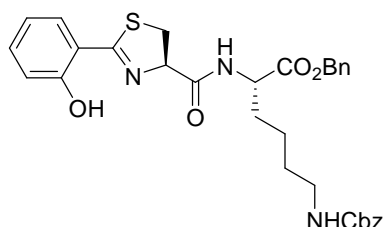
1H), 1.70 (m, 1H), 1.43 (m, 2H), 1.27 (m, 2H) ppm. HRMS (FAB) m/z $[M+H]^+$ calcd for $C_{31}H_{34}N_3O_6^+$, 544.2448; obsd, 544.2445.



(S)-Benzyl 6-(benzyloxycarbonylamino)-2-((S)-2-(2-hydroxyphenyl)-4,5-dihydrooxazole-4-carboxamido)hexanoate (4.28). Compound **4.28** was prepared following the same procedure used for **4.22**. The use of acid **2.62** (56.9 mg, 0.275 mmol), amine **4.21** (95.8 mg, 0.259 mmol), and EDC•HCl (62 mg, 0.32 mmol) provided a cloudy oil (150 mg). Chromatography through 15 g of silica using 90% CH_2Cl_2 /EtOAc yielded **4.28** as an oil (111.5 mg, 77.1%). 1H NMR (500 MHz, $CDCl_3$) δ 11.44 (br, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.41 – 7.29 (m, 10H), 7.02 (d, J = 8.5 Hz, 1H), 6.97 (d, J = 7.5 Hz, 1H), 6.90 (t, J = 8 Hz, 1H), 5.22 (d, J = 12.5 Hz, 1H), 5.16 (d, J = 12.5 Hz, 1H), 5.06 (s, 2H), 4.92 (m, 2H), 4.62 (m, 3H), 3.08 (q, J = 6.5 Hz, 2H), 1.86 – 1.83 (m, 1H), 1.75 – 1.67 (m, 1H), 1.48 – 1.39 (m, 2H), 1.27 – 1.21 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 170.3, 167.7, 159.6, 156.3, 136.5, 135.1, 134.2, 128.6, 128.5, 128.43, 128.36, 128.26, 128.0, 127.9, 119.0, 116.9, 109.9, 69.3, 67.9, 67.2, 66.4, 51.9, 40.4, 31.7, 29.6, 29.1, 22.2 ppm. HRMS (FAB) m/z $[M+H]^+$ calcd for $C_{31}H_{34}N_3O_7^+$, 560.2397; obsd, 560.2375.

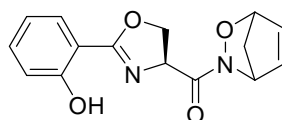


(S)-Benzyl 6-(benzyloxycarbonylamino)-2-((R)-2-phenyl-4,5-dihydrothiazole-4-carboxamido)hexanoate (4.31). Compound **4.31** was prepared following the same procedure used for **4.22**. The use of thiazoline **4.29** (53.3 mg, 0.257 mmol), amine **4.21** (96.5 mg, 0.261 mmol), and EDC•HCl (60.6 mg, 0.316 mmol) provided a yellow oil (159 mg). Chromatography through 15 g of silica using 90% CH₂Cl₂/EtOAc yielded **4.31** as a yellow oil (109 mg, 75%). R_f = 0.24 (1:1 hexanes/EtOAc – UV lamp). ¹H NMR (500 MHz, CDCl₃) δ 7.88 (d, *J* = 7.5 Hz, 2H), 7.50 (t, *J* = 7.0 Hz, 1H), 7.44 – 7.33 (m, 12H), 5.21 – 5.16 (m, 4H), 5.10 – 5.05 (m, 2H), 4.84 (m, 1H), 4.69 (td, *J* = 7.5, 5.5 Hz, 1H), 3.66 (m, 2H), 3.06 (m, 2H), 1.91 – 1.83 (m, 1H), 1.71 – 1.66 (m, 1H), 1.50 – 1.41 (m, 2H), 1.30 – 1.25 (m, 2H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 171.6, 171.3, 171.0, 156.2, 136.5, 135.1, 132.3, 131.9, 128.6, 128.5, 128.44, 128.41, 128.39, 128.2, 128.1, 128.03, 127.97, 78.8, 67.1, 66.4, 51.8, 40.5, 35.5, 32.1, 28.9, 22.2 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₃₁H₃₄N₃O₅S⁺, 560.2219; obsd, 560.2228.



(S)-Benzyl 6-(benzyloxycarbonylamino)-2-((R)-2-(2-hydroxyphenyl)-4,5-dihydrothiazole-4-carboxamido)hexanoate (4.32). Compound **4.32** was prepared

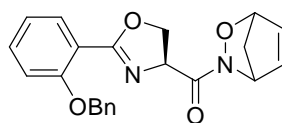
following the same procedure used for **4.22**. The use of thiazoline **4.30** (57.5 mg, 0.258 mmol), amine **4.21** (86.7 mg, 0.234 mmol), and EDC•HCl (56.5 mg, 0.295 mmol) provided a yellow oil. Chromatography through 10 g of silica using 90% CH₂Cl₂/EtOAc yielded **4.32** as an off-white solid (86.2 mg, 64%). Minor epimerization was observed from analysis of ¹H and ¹³C spectra. ¹H NMR (500 MHz, CDCl₃) δ 11.95 (br, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.35 – 7.29 (m, 10H), 7.03 (d, *J* = 8.5 Hz, 1H), 6.89 (t, *J* = 7.5 Hz, 2H), 5.28 – 5.06 (m, 6H), 4.88 (br-m, 1H), 4.66 (td, *J* = 8.0, 5.5 Hz, 1H), 3.69 (dd, *J* = 11, 8.0 Hz, 1H), 3.60 (m, 1H), 3.07 (m, 2H), 1.87 (m, 1H), 1.70 (m, 1H), 1.44 (m, 2H), 1.27 (m, 2H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 175.8, 171.4, 169.8, 158.8, 156.3, 136.6, 135.1, 133.8, 130.8, 128.6, 128.51, 128.49, 128.4, 128.3, 128.2, 128.03, 127.98, 119.3, 117.3, 115.8, 77.9, 67.3, 66.5, 52.1, 40.5, 33.9, 31.8, 29.0, 22.2 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₃₁H₃₄N₃O₆S⁺, 576.2168; obsd, 576.2143.



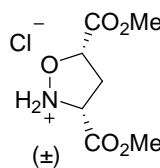
3-Oxa-2-aza-bicyclo[2.2.1]hept-5-en-2-yl((S)-2-(2-hydroxyphenyl)-4,5-dihydrooxazol-4-yl)methanone (mixture of diastereomers **4.36 and **4.36'**).** Hydroxamic acid **3.32** (0.304 g, 1.37 mmol) was dissolved in 14 mL of MeOH in a 100-mL round-bottomed flask with a stir bar. The flask and stir bar were previously washed with 6M HCl, H₂O, and acetone to remove any trace metals in the glassware. The methanolic solution was cooled in an ice/H₂O bath to 4 °C (internal temp.). Freshly cracked cyclopentadiene (0.60 mL, 7.2 mmol) was added to the reaction followed immediately by the dropwise addition of a solution of NaIO₄ (0.315 g, 1.47 mmol) in 4

mL of H₂O (0.36M). After 1 min, a white solid was observed in the reaction. The addition of the NaIO₄ solution was complete after 8 min. The reaction was stirred in the ice/H₂O bath for an additional 40 min, after which time the reaction was complete as observed by TLC (1:1 hexanes/EtOAc and 9:1 CH₂Cl₂/MeOH - UV lamp). The white solid was removed by vacuum filtration and washed with EtOAc (50 mL). Brine (50 mL) was added to the filtrate, and solid immediately crashed out of solution. H₂O was added until all of the solid dissolved (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined EtOAc layers were washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated by rotary evaporation (bath temp <40°C) to yield a yellow oil (497 mg). The oil was chromatographed through a Biotage 40S column using a solvent gradient from 2:1 hexanes/EtOAc to 3:2 hexanes/EtOAc to yield the two isomers **4.36** (164.5 mg, 42%) and **4.36'** (114.8 mg, 29.3%), as well as mixed **4.36** and **4.36'** (71.4 mg, 18.2%), all as colorless oils. Total combined yield of **4.36** and **4.36'** was 350.7 mg (90%). Absolute configuration of the stereochemistry was not assigned. **4.36**: R_f = 0.21 (1:1 hexanes/EtOAc – UV lamp, CAM stain). ¹H NMR (500 MHz, CDCl₃) δ 11.76 (br, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 8.5 Hz, 1H), 6.81 (m, 1H), 6.56 (m, 1H), 6.41 (ddd, *J* = 5.5, 2.5, 1.5 Hz, 1H), 5.32 (br-m, 2H), 5.00 (m, 1H), 4.68 (t, *J* = 8.0 Hz, 1H), 4.46 (dd, *J* = 10.0, 9.0 Hz, 1H), 1.97 (d, *J* = 8.0 Hz, 1H), 1.84 (d, *J* = 8.5 Hz, 1H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 171.5, 166.9, 159.7, 136.5, 133.5, 132.5, 118.4, 116.5, 110.1, 84.8, 68.2, 66.5, 62.3, 48.1 ppm. **4.36'**: Isolated with impurity (imp) as described herein. R_f = 0.14 (1:1 hexanes/EtOAc – UV lamp, CAM stain). ¹H NMR (500 MHz, CDCl₃) δ 11.78 (br, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 6.96 (dd, *J* = 8.0, 0.5 Hz, 1H),

6.82 (m, 1H), 6.59 (td, $J = 5.5, 2.0$ Hz, 1H), 6.36 (m, 1H), 5.34 (m, 2H), 5.07 (dd, $J = 9.5, 8.5$ Hz, 1H), 4.42 (m, 2H), 2.02 (d, $J = 8.5$ Hz, 1H), 1.85 (d, $J = 9.0$ Hz, 1H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 171.1, 167.1, 164.8 (imp), 159.7, 159.4 (imp), 136.8, 134.0 (imp), 133.9 (imp), 133.5, 133.1, 132.7 (imp), 128.4 (imp), 128.0, 118.9 (imp), 118.4, 116.6, 110.1, 84.7, 83.8 (imp), 68.1 (imp), 67.4, 66.5, 66.4 (imp), 64.6 (imp), 62.0, 48.4, 48.2 (imp).



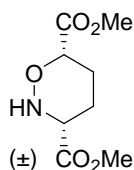
3-Oxa-2-aza-bicyclo[2.2.1]hept-5-en-2-yl((S)-2-(2-(benzyloxy)phenyl)-4,5-dihydrooxazol-4-yl)methanone (mixture of diastereomers 4.37 and 4.37'). The mixture of diastereomers was prepared following the same procedure for **4.36** and **4.36'**. The use of hydroxamate **3.21** (52 mg, 0.166 mmol), cyclopentadiene (0.100 mL, 1.25 mmol), and NaIO_4 (60 mg, 0.282 mmol) provided a yellow oil. Chromatography through silica gel using 4:1 EtOAc/hexanes yielded a colorless oil composed of both diastereomers **4.36** and **4.36'** as well as a mixture of other impurities (37 mg).



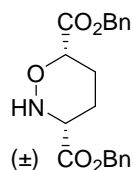
(±)-(3R,5S)-3,5-Bis(methoxycarbonyl)isoxazolidin-2-ium chloride (4.38).

Compound **3.44** (0.153 mg, 0.529 mmol) was dissolved in Et_2O (25 mL) and HCl gas, produced from the addition of concentrated H_2SO_4 to a mixture of concentrated HCl and

NaCl, was bubbled through the solution for 1.5 h. White solid was observed and the reaction was monitored by TLC. The solvent was evaporated and the residue was used immediately without purification.

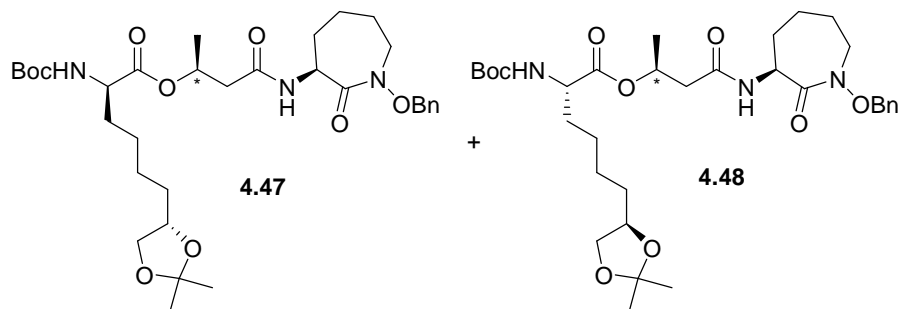


(±)-(3R,6S)-Dimethyl morpholine-3,6-dicarboxylate (4.41). TFA (0.50 mL, 6.5 mmol) was added slowly to a solution containing **3.45** (0.246 g, 0.811 mmol) in CH₂Cl₂ (10 mL) at 4 °C (ice/H₂O bath). The mixture was stirred for 10 min, then warmed to RT and stirred for an additional 3 g. **3.45** was still present by TLC, so an additional 4 eq. of TFA was added to the reaction. After stirring for 1.5 h at RT, 25 mL of 10 wt% aqueous Na₂CO₃ was added to the solution slowly and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL) and the combined organic layers were dried over MgSO₄, filtered, and concentrated to yield **4.41** as a yellow oil (0.141 g, 86%). The oil was used immediately without purification. R_f = 0.16 (1:1 hexanes/EtOAc – CAM stain). ¹H NMR (300 MHz, CDCl₃) δ 4.41 (dd, *J* = 7.8, 4.2 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.71 (dd, *J* = 9.0, 4.2 Hz, 1H), 2.21 – 1.82 (m, 4H) ppm.



(±)-(3R,6S)-Dimethyl morpholine-3,6-dicarboxylate (4.42). Compound **4.42** was prepared following the same procedure for **4.41**. Compound **3.48** (0.623 g, 1.37

mmol) provided **4.42** as a yellow oil (0.443 g, 91%). The oil was used directly without purification. $R_f = 0.38$ (1:1 hexanes/EtOAc – CAM stain). ^1H NMR (300 MHz, CDCl_3) δ 7.35 (m, 10H), 6.50 (d, $J = 2.7$ Hz, 1H), 5.30 – 5.14 (m, 4H), 4.45 (dd, $J = 6.9, 4.8$ Hz, 1H), 3.75 (dt, $J = 5.4, 4.2$ Hz, 1H), 2.26 – 1.90 (m, 4H) ppm.



(S)-4-((S)-1-(Benzyloxy)-2-oxoazepan-3-ylamino)-4-oxobutan-2-yl 2-(tert-butoxycarbonylamino)-6-(2,2-dimethyl-1,3-dioxolan-4-yl)hexanoate (mixture of diastereomers **4.47 and **4.48**).** Preparation using Yamaguchi esterification conditions. Acid (\pm)-**3.101** (52.9 mg, 0.160 mmol) and **3.125** (52.4 mg, 0.164 mmol) were dissolved in 3 mL of anhydrous CH_2Cl_2 in a 25-mL round-bottomed flask under Ar. DMAP (5.8 mg, 0.047 mmol) was added, followed by triethylamine (0.045 mL, 0.32 mmol) and 2,4,6-trichlorobenzoyl chloride (0.050 mL, 0.32 mmol). The solution was stirred at RT under Ar. After about 1 day, the reaction was progressing by TLC (100% EtOAc - UV lamp, CAM stain), but also incomplete. The reaction was allowed to stir at RT under Ar. After 3 days, an additional 3 mL of CH_2Cl_2 was added to replace the amount that had evaporated. After 5 days, not much had changed by TLC and the reaction was diluted with EtOAc (15 mL) and H_2O (10 mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with saturated NaHCO_3 (20 mL) and brine (20 mL), dried

over Na₂SO₄, filtered, and concentrated to yield a colorless residue. The residue was chromatographed through 12 g of silica using a solvent gradient from 100% CH₂Cl₂ to 100% EtOAc to afford the mixture of diastereomers **4.47** and **4.48** as a colorless residue (54.7 mg, 54.1% yield) and unreacted cobactin **3.125** as a white solid (4.1 mg, 7.8% recovery). ¹H NMR (500 MHz, CDCl₃) δ 7.44 – 7.41 (m, 2H), 7.40 – 7.37 (m, 3H), 7.08 (m, 1H), 5.36 – 5.19 (m, 2H), 5.00 (dd, *J* = 10.5, 3.0 Hz, 1H), 4.90 (dd, *J* = 10.5, 3.0 Hz, 1H), 4.48 (m, 1H), 4.25 (m, 1H), 4.07 – 3.89 (m, 2H), 3.68 – 3.61 (m, 1H), 3.53 – 3.46 (m, 2H), 2.60 – 2.55 (m, 1H), 2.50 – 2.44 (m, 1H), 2.03 – 1.96 (m, 1H), 1.94 – 1.88 (m, 1H), 1.86 – 1.78 (m, 1H), 1.76 – 1.58 (m, 4H), 1.50 – 1.30 (m, 19H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 171.9, 171.8, 170.0, 169.9, 168.2, 168.1, 155.4, 155.3, 134.90, 134.87, 129.5, 128.9, 128.8, 128.52, 128.50, 108.5, 79.6, 79.5, 76.8, 75.79, 75.77, 69.3, 68.9, 53.5, 52.64, 52.58, 51.73, 51.65, 42.6, 42.5, 33.29, 33.27, 33.2, 32.3, 32.2, 31.4, 28.3, 28.2, 27.5, 26.8, 26.1, 25.6, 25.42, 25.37, 25.3, 25.24, 25.22, 19.7, 19.6 ppm. HRMS (FAB) *m/z* [M]⁺ calcd for C₃₃H₅₁N₃O₉⁺, 633.3625; obsd, 633.3602.

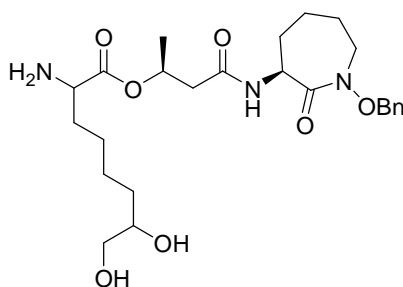
Preparation of the mixture of diastereomers 4.47 and 4.48 using EDC and DMAP (Table 4.2, entry 5). Acid **3.101** (0.472 g, 1.43 mmol) and **3.125** (0.457 g, 1.43 mmol) were dissolved in 10 mL of anhydrous CH₂Cl₂ in a 100-mL round-bottomed flask under Ar. DMAP (180 mg, 1.48 mmol) was added, followed by EDC•HCl (1.28 g, 6.68 mmol). The mixture was stirred at RT under Ar and monitored by TLC (100% EtOAc - UV lamp, CAM stain). The volume of the reaction was reduced to ~5 mL and the orange mixture was partitioned between EtOAc (50 mL) and H₂O (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined

organic layers were washed with H₂O (25 mL), 10 wt% citric acid (2 x 25 mL), H₂O (25 mL), saturated NaHCO₃ (2 x 25 mL), and brine (25 mL), dried over MgSO₄, filtered, and concentrated to yield a yellow oil. The oil was chromatographed through 100 g of silica using a solvent gradient from 100% CH₂Cl₂ to 1:3 CH₂Cl₂/EtOAc to yield a mixture of **4.47** and **4.48** as a light yellow oil. The oil was dried under vacuum (2 mm Hg) for 1 h to yield a white foam (0.626 g, 69.3% yield).

Preparation of the mixture of diastereomers 4.47 and 4.48 using EDC, DMAP, and 4-pyrrolidinopyridine (Table 4.2, entry 6). Acid **3.101** (0.805 mmol) and **3.125** (0.265 g, 0.826 mmol) were dissolved in 5 mL of anhydrous CH₂Cl₂ in a 25-mL round-bottomed flask under Ar. DMAP (25 mg, 0.205 mmol) and 4-pyrrolidinopyridine (25 mg, 0.17 mmol) were added, followed by EDC•HCl (0.660 g, 3.44 mmol). The mixture was stirred at RT under Ar and monitored by TLC (100% EtOAc - UV lamp, CAM stain). The reaction was diluted with EtOAc (20 mL) and H₂O (20 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 20 mL), and the combined organic layers were washed with H₂O (20 mL) and brine (20 mL), dried over MgSO₄, filtered, and concentrated to a yellow oil. The oil was chromatographed through 50 g of silica using a solvent gradient from 100% CH₂Cl₂ to 25% CH₂Cl₂/EtOAc and yielded a mixture of **4.47** and **4.48** as a yellow oil (0.354 g, 69% yield).

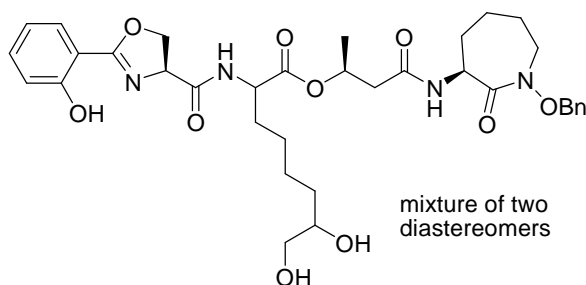
Attempted deprotection of 4.47 and 4.48 using TMSOTf and 2,6-lutidine. A mixture of **4.47** and **4.48** (75.6 mg, 0.119 mmol) was dissolved in 2 mL of anhydrous CH₂Cl₂ in a flame-dried 10-mL round-bottomed flask under Ar. 2,6-Lutidine (0.030 mL,

0.26 mmol) was added, followed by trimethylsilyl trifluoromethanesulfonate (0.035 mL, 0.18 mmol) dropwise. The solution was stirred at RT under Ar and monitored by TLC (100% EtOAc - CAM stain, ninhydrin stain). After 15 min, the reaction was not clean by TLC, and starting material remained. After stirring for 3 days, with no change observed by TLC, additional 2,6-lutidine (0.030 mL, 0.26 mmol) and TMSOTf (0.035 mL, 0.18 mmol) was added. The reaction was stirred at RT under Ar for 20 min, then diluted with CH₂Cl₂ (5 mL) and saturated NaHCO₃ (10 mL) was added. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 7 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated to yield a yellow oil (103.6 mg). The mixture was analyzed by LC-MS and was found to contain large amounts of 2,6-lutidine (rt = 3.80 min), and starting material **4.47** and **4.48** (rt = 9.02 min). Approximately equal amounts of **4.51** (rt = 6.10 min, MW = 535) **4.52** (rt = 6.60 min, MW = 595) were observed in the LC trace as well as **4.53**.



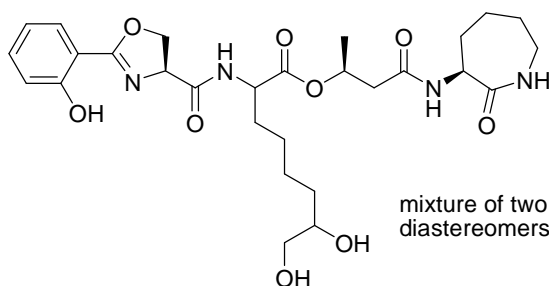
(S)-4-((S)-1-(Benzyloxy)-2-oxoazepan-3-ylamino)-4-oxobutan-2-yl 2-amino-7,8-dihydroxyoctanoate (4.53). A mixture of **4.47** and **4.48** (0.185 g, 0.291 mmol) was dissolved in 4 mL of 90% TFA/H₂O in a 25-mL round-bottomed flask. The brown solution was stirred at RT for 20 min, then added dropwise to a beaker containing saturated NaHCO₃ (50 mL). Solid sodium carbonate was added to the mixture until the

aqueous layer was a pH of 8-9 (pH paper). CH₂Cl₂ (15 mL) was added and the layers were separated. The cloudy aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over MgSO₄, filtered, concentrated to yield crude **4.53** as a yellow oil (92.8 mg, 64.6% yield). The material was used without purification. ¹H NMR (300 MHz, CDCl₃) δ 7.40 – 7.36 (m, 5H), 4.98 – 4.85 (m, 2H), 4.46 (m, 1H), 3.66 – 3.35 (m, 5H), 2.98 (br, 3H), 2.61 – 2.42 (m, 2H), 2.00 – 1.30 (m, 17H) ppm.



(S)-4-(((S)-1-(Benzyloxy)-2-oxoazepan-3-ylamino)-4-oxobutan-2-yl)-7,8-dihydroxy-2-((S)-2-(2-hydroxyphenyl)-4,5-dihydrooxazole-4-carboxamido)octanoate (4.54). Amine **4.53** (92.8 mg, 0.188 mmol), **2.62** (40.7 mg, 0.196 mmol), and HOBt (29.6 mg, 0.219 mmol) were dissolved in 5 mL of anhydrous CH₂Cl₂ in a 25-mL round-bottomed flask under Ar. EDC•HCl (51.7 mg, 0.270 mmol) was added in one portion and the mixture was stirred at RT under Ar. After 17 h, product formation was observed by TLC (9:1 EtOAc/MeOH - UV lamp, CAM stain). The reaction was diluted with EtOAc (25 mL) and H₂O (25 mL) and the layers were separated. The cloudy aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with saturated NaHCO₃ (2 x 20 mL), H₂O (2 x 20 mL), and brine (20 mL), dried over MgSO₄, filtered, and concentrated to yield a yellow oil. The oil was chromatographed through 10 g of silica using a solvent gradient from 100% EtOAc to

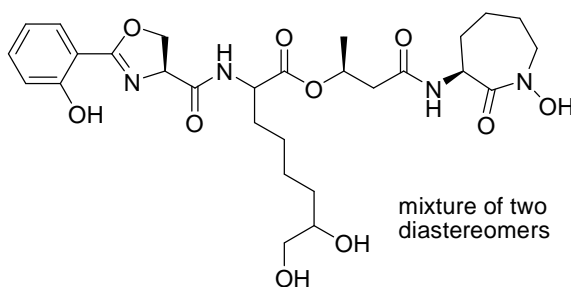
90% EtOAc/MeOH and yielded **4.54** as a colorless residue (83.1 mg, 64.7% yield). R_f = 0.28 (9:1 EtOAc/MeOH – UV lamp, CAM stain). ¹H NMR (500 MHz, CDCl₃) δ 7.77 – 7.67 (m, 1H), 7.42 – 7.35 (m, 5H), 7.21 – 7.16 (m, 0.5H), 7.09 – 7.01 (m, 2H), 7.94 – 7.89 (m, 1H), 5.36 – 5.33 (m, 0.5H), 5.26 (m, 0.5H), 5.02 – 4.95 (m, 2H), 4.89 (t, *J* = 10.5 Hz, 1H), 4.82 – 4.78 (m, 0.5H), 4.68 – 4.59 (m, 2H), 4.54 – 4.43 (m, 2H), 3.71 – 3.57 (m, 2H), 3.55 – 3.47 (m, 2H), 3.39 – 3.33 (m, 1H), 2.58 (dd, *J* = 10.5, 8.0 Hz, 0.5H), 2.50 (dd, *J* = 14.5, 4.5 Hz, 0.5H), 2.41 (d, *J* = 7.0 Hz, 1H), 2.00 – 1.85 (m, 3H), 1.80 – 1.60 (m, 3H), 1.50 – 1.20 (m, 11H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 170.99, 170.97, 170.61, 170.57, 170.4, 170.23, 170.20, 170.17, 170.1, 170.0, 168.9, 168.8, 168.4, 168.3, 167.6, 167.22, 167.18, 159.7, 159.4, 135.02, 134.98, 134.82, 134.81, 134.2, 134.1, 129.5, 129.4, 128.94, 128.92, 128.58, 128.56, 128.5, 119.2, 119.1, 116.9, 116.7, 110.2, 110.0, 76.9, 71.9, 71.55, 71.45, 70.9, 69.74, 69.69, 69.5, 69.4, 69.21, 69.18, 67.9, 67.84, 67.81, 66.82, 66.76, 66.71, 66.69, 52.70, 52.67, 52.6, 52.3, 52.20, 52.15, 51.9, 51.7, 51.64, 51.60, 51.58 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₃₅H₄₇N₄O₁₀⁺, 683.2392; obsd, 683.3283.



(*S*)-4-Oxo-4-((*S*)-2-oxoazepan-3-ylamino)butan-2-yl 7,8-dihydroxy-2-((*S*)-2-(2-hydroxyphenyl)-4,5-dihydrooxazole-4-carboxamido)octanoate (4.55**).** All

glassware used was washed with 6M HCl (2x), then DI water to neutral pH (pH paper),

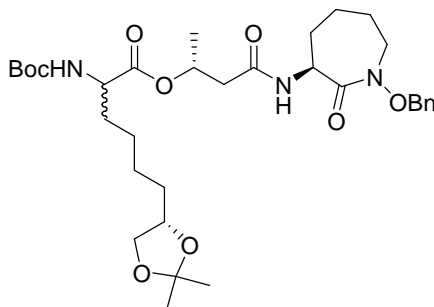
then acetone and was flame-dried before use to remove trace amounts of Fe and other metals. Anhydrous MeOH (2 mL) was added to **4.54** (11.6 mg, 0.0170 mmol) in a 10-mL round-bottomed flask. The mixture was purged with Ar and 10 wt% Pd/C (2 mg) was added. The black mixture was purged with Ar, then with H₂ for 30 seconds, then was stirred under H₂ (balloon). After 55 min, the mixture was analyzed by TLC (9:1 EtOAc/MeOH - UV lamp, CAM stain), but only starting material was observed. Glacial acetic acid (0.001 mL, 0.017 mmol, ~1 equiv) was added to the mixture. After 30 min, no change was observed. Additional 10 wt% Pd/C was added (about 3 mg) and the mixture was stirred under H₂. After 1 h, no starting material was observed by TLC, and a new, FeCl₃-positive spot was observed just above the baseline. The reaction was filtered through glass filter paper. The colorless filtrate was concentrated to yield a mixture of **4.55** and other impurities as a residue (6.8 mg, 67.5% crude yield). LC/MS (5 – 80% CH₃CN/10 mM NH₄OAc) R_t = 5.43 and 5.57 min; *m/z* [M+H]⁺ 577.5.



(S)-4-(((S)-1-Hydroxy-2-oxoazepan-3-ylamino)-4-oxobutan-2-yl) dihydroxy-2-((S)-2-(2-hydroxyphenyl)-4,5-dihydrooxazole-4-carboxamido)octanoate (4.56). All glassware used was washed with 6M HCl (2x), then H₂O to neutral pH (pH paper), then acetone and was oven-dried before use to remove trace amounts of metals. Anhydrous MeOH (10 mL) was added to **4.54** (70.6 mg, 0.103 mmol) in a 25-mL round-

bottomed flask. The mixture was purged with Ar (3 min) and 10 wt% Pd/C (31.5 mg, 45 wt% of **4.54**) was added. The black mixture was purged with Ar (2 min), then with H₂ (2 min), then was stirred under H₂ (balloon). After 1 h, no starting material remained by TLC analysis of the reaction mixture (9:1 EtOAc/MeOH - UV lamp, FeCl₃ stain), and a FeCl₃-positive spot was observed just above the baseline. The reaction was purged with Ar (3 min) and filtered through a pad of celite over glass filter paper. The filtrate was still contaminated with fine particles of Pd/C and was filtered through a 4mm acrodisc syringe filter and concentrated to yield a light orange oil. The oil was dried under vacuum (2 mm Hg) and solidified (51.2 mg, 83.6% crude yield). The crude material was dissolved in MeOH and analyzed by LC-MS. The desired product eluted at 5.32 min. Other peaks were observed at 6.62 min, 7.15 min, and a significant impurity at 7.72 min. The crude mixture was purified by trituration with acetonitrile and provided **4.56** as a white solid (26.2 mg, 42.8% yield). LC/MS (5%-80% CH₃CN/10mM NH₄OAc) R_t = 5.32 min. ¹H NMR (500 MHz, d⁶-DMSO, 30 °C) δ 8.64 (m, 1H), 8.04 (dd, *J* = 14, 7.0 Hz, 1H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.44 (m, 1H), 7.97 – 7.87 (m, 2H), 5.12 (m, 1H), 4.99 (m, 1H), 4.60 (q, *J* = 9.5 Hz, 1H), 4.50 (m, 1H), 4.44 (m, 1H), 4.21 (m, 0.5H), 4.15 (m, 0.5H), 3.86 (d, *J* = 11.5 Hz, 0.5H), 3.82 (d, *J* = 11.5 Hz, 0.5H), 3.51 – 3.45 (m, 1H), 3.38 – 3.21 (m, 5H), 2.54 – 2.39 (m, 1H), 1.84 – 1.58 (m, 6H), 1.47 – 1.21 (m, 8H), 1.19 (d, *J* = 6.5 Hz, 1.5H), 1.14 (d, *J* = 6.0 Hz, 1.5H) ppm. ¹³C NMR (125 MHz, d⁶-DMSO, 30 °C) δ 171.0, 170.8, 169.7, 169.6, 168.54, 168.45, 167.87, 167.78, 165.7, 133.77, 133.73, 128.0, 118.4, 116.8, 116.7, 109.98, 109.87, 70.9, 70.8, 69.0, 68.7, 68.5, 67.04, 67.00, 65.8, 52.4, 52.3, 52.2, 50.6, 41.2, 33.01, 32.98, 30.7, 30.59, 30.55, 30.4, 26.89, 26.86, 25.4, 25.33,

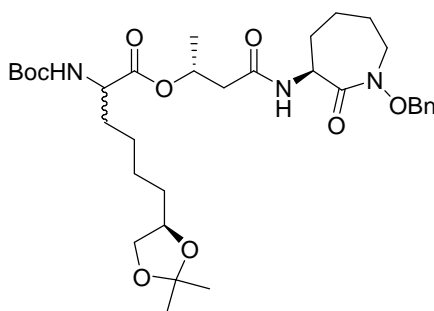
25.28, 24.7, 19.4, 19.2 ppm. HRMS (FAB) m/z $[M+H]^+$ calcd for $C_{29}H_{41}N_4O_{10}^+$, 593.2823; obsd, 593.2801.



(*R*)-4-((*S*)-1-(Benzyloxy)-2-oxoazepan-3-ylamino)-4-oxobutan-2-yl 2-(*tert*-butoxycarbonylamino)-6-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)hexanoate (4.57).

Compound **4.57** was prepared following the procedure used for **4.47** and **4.48** using EDC, DMAP, and 4-pyrrolidinopyridine. The use of acid (*2S,7R*)-**3.101** (0.246 g, 0.742 mmol), **3.124** (0.238 g, 0.742 mmol), EDC•HCl (0.650 g, 3.39 mmol), DMAP (33.0 mg, 0.270 mmol), and 4-pyrrolidinopyridine (40.0 mg, 0.270 mmol) provided a yellow oil. Chromatography through 50 g of silica using a solvent gradient from 100% CH_2Cl_2 to 33% CH_2Cl_2 /EtOAc yielded **4.58** as a light white foam (0.268 g, 57% yield). The product consisted of approximately a 2:1 mixture of epimers from 1H NMR data. R_f = 0.37 (100% EtOAc – CAM stain). LC/MS (5 – 80% CH_3CN /10 mM NH_4OAc) R_t = 8.95 min. 1H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.36 (m, 5H), 7.05 (d, J = 6.5 Hz, 1H), 7.02 (d, J = 6.5 Hz, 1H epimer), 5.35 – 5.19 (m, 2H), 4.98 (d, J = 10.5 Hz, 1H), 4.99 (d, J = 10.0 Hz, 1H epimer), 4.90 (d, J = 10.5 Hz, 1H), 4.46 (ddd, J = 11.0, 6.5, 1.0 Hz, 1H), 4.23 (m, 1H), 4.07 – 3.98 (m, 2H), 3.64 (d, J = 11.5 Hz, 1H epimer), 3.60 (d, J = 11.5 Hz, 1H), 3.53 – 3.45 (m, 2H), 2.59 – 2.45 (m, 2H), 1.98 – 1.88 (m, 2H), 1.81 – 1.61 (m, 5H), 1.51 – 1.33 (m, 19H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 170.00 (epimer),

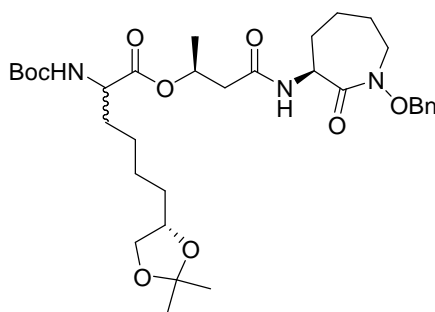
169.97, 168.2, 155.4, 134.93 (epimer), 134.90, 129.58 (epimer), 129.57, 128.89, 128.87 (epimer), 128.5, 108.58 (epimer), 108.56, 79.6, 76.8, 75.8, 69.3, 68.94, 68.88 (epimer), 53.6, 53.5 (epimer), 52.7, 51.7, 42.6 (epimer), 42.5, 33.3 (epimer), 33.2, 32.5, 32.4 (epimer), 31.5, 31.4, 28.3, 27.52 (epimer), 27.48, 26.9, 26.1, 25.7, 25.42, 25.40, 25.35, 25.42, 19.62 (epimer), 19.56 ppm. HRMS (FAB) m/z $[M+H]^+$ calcd for $C_{33}H_{52}N_3O_9^+$, 634.3704; obsd, 634.3709.



(*R*)-4-((*S*)-1-(Benzyloxy)-2-oxoazepan-3-ylamino)-4-oxobutan-2-yl 2-(*tert*-butoxycarbonylamino)-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)hexanoate (4.58).

Compound **4.58** was prepared following the procedure used for **4.47** and **4.48** using EDC, DMAP, and 4-pyrrolidinopyridine. The use of acid (*2S,7R*)-**3.101** (0.276 g, 0.832 mmol), **3.124** (0.268 g, 0.837 mmol), EDC•HCl (0.730 g, 3.81 mmol), DMAP (36.5 mg, 0.299 mmol), and 4-pyrrolidinopyridine (44 mg, 0.30 mmol) provided a yellow oil. Chromatography through 50 g of silica using a solvent gradient from 100% CH_2Cl_2 to 33% CH_2Cl_2 /EtOAc yielded **4.58** as a light yellow oil (0.292 g, 55% yield). The product consisted of approximately a 2:1 mixture of epimers from 1H NMR data. R_f = 0.37 (100% EtOAc – CAM stain). LC/MS (5 – 80% CH_3CN /10 mM NH_4OAc) R_t = 8.97 min. 1H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.36 (m, 5H), 7.03 (m, 1H epimer), 7.00 (d, J = 6.0 Hz, 1H), 5.35 – 5.18 (m, 2H), 4.99 (m, 1H), 4.90 (dd, J = 10.5, 2.0 Hz, 1H), 4.46 (dd, J =

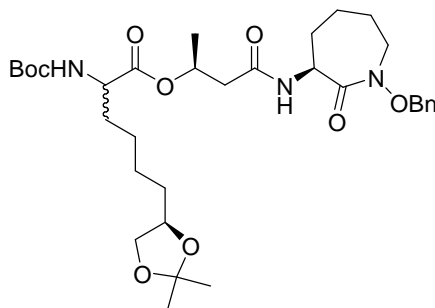
10.5, 6.5 Hz, 1H), 4.25 (dd, $J = 13.5, 8.0$ Hz, 1H), 4.08 – 3.99 (m, 2H), 3.62 (m, 1H), 3.53 – 3.45 (m, 2H), 2.59 – 2.45 (m, 2H), 1.99 – 1.96 (m, 1H), 1.92 – 1.88 (m, 1H), 1.82 (m, 1H), 1.75 – 1.60 (m, 4H), 1.48 – 1.31 (m, 19H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 171.91, 171.89, 170.0, 168.2, 155.4, 135.0, 129.6, 128.94, 128.91, 128.6, 108.6, 79.6, 76.9, 75.8, 69.4, 68.9, 53.5, 52.8, 51.7, 42.64, 42.59 (epimer), 33.32 (epimer), 33.27, 32.6 (epimer), 32.4, 31.6 (epimer), 31.5, 28.3, 27.6, 26.9, 26.2, 25.7, 25.5, 25.42, 25.38, 25.2, 19.7, 19.6 (epimer) ppm. HRMS (FAB) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{33}\text{H}_{52}\text{N}_3\text{O}_9^+$, 634.3704; obsd, 634.3706.



(*S*)-4-((*S*)-1-(Benzyloxy)-2-oxoazepan-3-ylamino)-4-oxobutan-2-yl 2-(*tert*-butoxycarbonylamino)-6-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)hexanoate (4.59).

Compound **4.59** was prepared following the procedure used for **4.47** and **4.48** using EDC, DMAP, and 4-pyrrolidinopyridine. The use of (*2R,7S*)-**3.101** (0.141 g, 0.425 mmol), 4-pyrrolidinopyridine (23.0 mg, 0.155 mmol), EDC•HCl (0.356 g, 1.86 mmol), DMAP (22.1 mg, 0.181 mmol), and **3.125** (0.136 g, 0.425 mmol) provided a colorless oil. Chromatography through 30 g of silica using a solvent gradient from 100% CH_2Cl_2 to 33% $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ yielded **4.59** as a yellow oil (0.177 g, 66% yield). Isolated as a mixture of epimers. $R_f = 0.36$ (100% EtOAc – CAM stain). ^1H NMR (500 MHz, CDCl_3) δ 7.44 – 7.32 (m, 5H), 7.12 (m, 1H), 5.40 (d, $J = 8.5$ Hz, 1H), 5.30 (m, 2H), 5.00

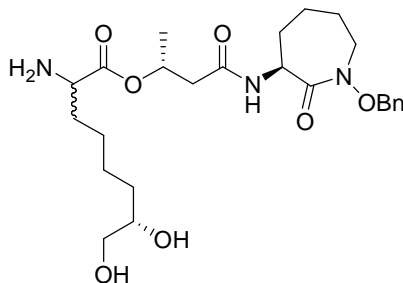
(dd, $J = 10.0, 2.5$ Hz, 1H), 4.89 (dd, $J = 10.5, 3.0$ Hz, 1H), 4.50 – 4.43 (m, 1H), 4.25 (m, 1H), 4.06 – 3.98 (m, 2H), 3.68 – 3.60 (m, 1H), 3.53 – 3.44 (m, 2H), 2.58 (dd, $J = 15.0, 7.0$ Hz, 1H), 2.51 – 2.45 (m, 1H), 2.04 – 1.97 (m, 1H), 1.94 – 1.88 (m, 1H), 1.86 – 1.80 (m, 1H), 1.76 – 1.58 (m, 4H), 1.50 – 1.25 (m, 19H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 171.75 (epimer), 171.70, 169.9, 169.8 (epimer), 168.1, 168.0 (epimer), 155.34, 155.25 (epimer), 134.80, 134.77 (epimer), 129.4, 128.73 (epimer), 128.69, 128.4, 108.4, 79.4 (epimer), 79.3, 76.6, 75.7 (epimer), 75.6, 69.22 (epimer), 69.20, 68.8, 53.4, 53.3 (epimer), 52.5, 52.4, 51.6 (epimer), 51.5, 42.5, 42.3 (epimer), 33.2 (epimer), 33.1, 32.2 (epimer), 32.0, 31.25, 31.22, 28.2, 28.1 (epimer), 27.3, 26.7, 26.0, 25.5, 25.3, 25.2, 25.1, 19.5 ppm.



(S)-4-((S)-1-(Benzyloxy)-2-oxoazepan-3-ylamino)-4-oxobutan-2-yl 2-(tert-butoxycarbonylamino)-6-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)hexanoate (4.60).

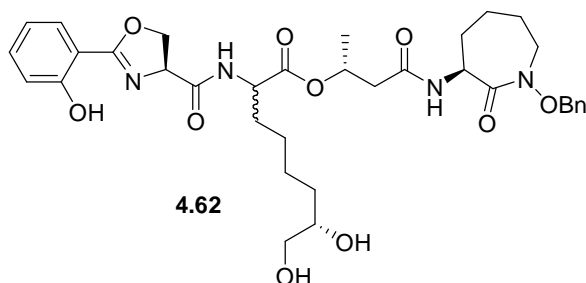
Compound **4.60** was prepared following the procedure used for **4.47** and **4.48** using EDC, DMAP, and 4-pyrrolidinopyridine. The use of (2*S*,7*R*)-**3.101** (33.8 mg, 0.102 mmol), 4-pyrrolidinopyridine (6.8 mg, 0.046 mmol), EDC•HCl (92.2 mg, 0.481 mmol), DMAP (8.0 mg, 0.65 mmol), and **3.125** (33.2 mg, 0.104 mmol) provided a yellow residue. Chromatography through 10 g of silica using a solvent gradient from 100% CH_2Cl_2 to 50% $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ yielded **4.60** as a yellow foam (40.0 mg, 62% yield). Isolated as a

mixture of epimers. $R_f = 0.36$ (100% EtOAc – CAM stain). ^1H NMR (500 MHz, CDCl_3) δ 7.44 – 7.37 (m, 5H), 7.07 (d, $J = 6.0$ Hz, 1H), 5.35 – 5.18 (m, 2H), 5.00 (m, 1H), 4.90 (m, 1H), 4.49 – 4.42 (m, 1H), 4.28 – 4.22 (m, 1H), 4.08 – 3.99 (m, 2H), 3.68 – 3.60 (m, 1H), 3.54 – 3.45 (m, 2H), 2.59 (dd, $J = 15.0, 6.0$ Hz, 1H), 2.46 (dd, $J = 15.0, 6.0$ Hz, 1H), 2.05 – 1.98 (m, 1H), 1.94 – 1.87 (m, 1H), 1.85 – 1.57 (m, 5H), 1.53 – 1.25 (m, 19H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 171.9, 170.02 (epimer), 169.97, 168.2 (epimer), 168.1, 155.4, 134.94 (epimer), 134.90, 129.6, 128.9, 128.6, 108.6, 79.64, 79.55 (epimer), 76.9, 75.8, 69.4, 68.9, 53.5, 52.7, 52.6 (epimer), 51.8, 51.7 (epimer), 42.7 (epimer), 42.5, 33.31 (epimer), 33.25, 32.4, 31.4, 28.31 (epimer), 28.27, 27.5, 26.9, 26.1, 25.7, 25.4, 25.3, 19.7 (epimer), 19.6 ppm.



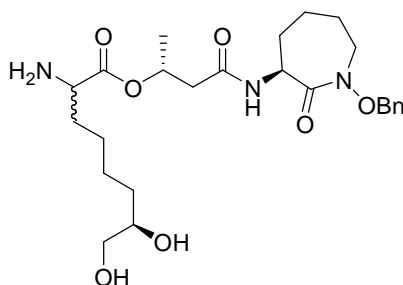
(S)-((R)-4-((S)-1-(Benzyloxy)-2-oxoazepan-3-ylamino)-4-oxobutan-2-yl) 2-amino-7,8-dihydroxyoctanoate (4.61). Compound **4.61** was prepared following the same procedure used for **4.53**. Compound **4.57** (0.175 g, 0.276 mmol) provided crude **4.61** as an off-white foam (98.9 mg, 73% yield). Isolated as a mixture of epimers. ^1H NMR (300 MHz, CDCl_3) δ 7.40 – 7.14 (m, 6H), 5.32 – 5.23 (m, 1H), 4.95 (d, $J = 10.2$ Hz, 1H), 4.85 (d, $J = 10.2$ Hz, 1H), 4.56 – 4.41 (m, 1H), 3.66 – 3.33 (m, 9H), 2.58 – 2.43 (m, 2H), 1.93 – 1.22 (m, 17H) ppm. ^{13}C NMR (75 MHz, CDCl_3) δ 174.0, 170.1, 169.9 (epimer), 168.6, 168.3 (epimer), 134.8, 129.5, 128.8, 128.5, 76.8, 71.6 (epimer), 71.4,

68.8, 66.5, 54.0, 52.6, 51.6, 42.3, 33.7, 32.5, 31.3, 27.4 (epimer), 27.3, 26.0, 24.9, 24.7, 19.7 ppm.

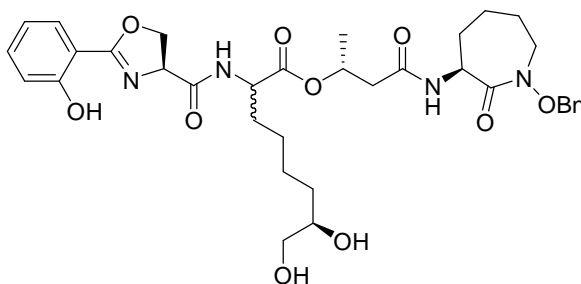


(S)-((R)-4-((S)-1-(Benzyloxy)-2-oxazepan-3-ylamino)-4-oxobutan-2-yl) 7,8-dihydroxy-2-((S)-2-(2-hydroxyphenyl)-4,5-dihydrooxazole-4-carboxamido)octanoate (4.62). Compound **4.62** was prepared following the same procedure used for **4.54**. Oxazoline **2.62** (44.4 mg, 0.214 mmol), EDC•HCl (53 mg, 0.276 mmol), HOBt (31.9 mg, 0.236 mmol), and **4.61** (98.9 mg, 0.200 mmol) provided an oil. Chromatography through 15 g of silica using a solvent gradient from 100% EtOAc to 95% EtOAc/MeOH yielded **4.62** as a white solid (73 mg, 53% yield). Isolated as a mixture of epimers. R_f = 0.27 (9:1 EtOAc/MeOH – CAM stain, UV lamp). ^1H NMR (500 MHz, CDCl_3) δ 11.45 (br, 1H), 6.68 (dt, J = 8.0, 1.5 Hz, 1H), 7.43 – 7.35 (m, 5H), 7.17 – 7.01 (m, 3H), 6.90 (t, J = 7.5 Hz, 1H), 5.37 – 5.23 (m, 1H), 4.99 – 4.93 (m, 2H), 4.89 – 4.86 (m, 1H), 4.68 – 4.62 (m, 2H), 4.58 – 4.54 (m, 1H), 4.47 – 4.42 (m, 1H), 3.72 – 3.34 (m, 5H), 2.62 – 2.43 (m, 2H), 1.96 – 1.84 (m, 3H), 1.78 – 1.64 (m, 3H), 1.50 – 1.26 (m, 11H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 170.9 (epimer), 170.8, 170.4 (epimer), 170.3, 170.1 (epimer), 170.0, 168.4, 168.3 (epimer), 167.9, 167.6 (epimer), 159.61, 159.59 (epimer), 134.9 (epimer), 134.8, 134.2, 129.53, 129.49 (epimer), 128.91, 128.85 (epimer), 128.6, 128.5 (epimer), 119.1, 116.89 (epimer), 116.87, 110.0, 76.8, 71.5 (epimer), 71.2, 69.45 (epimer), 69.41,

67.94 (epimer), 67.90, 66.8, 66.7 (epimer), 52.64 (epimer), 52.58, 52.2, 52.0 (epimer), 51.7 (epimer), 51.6, 42.4 (epimer), 42.2, 32.5, 31.9 (epimer), 31.8, 31.5, 31.3 (epimer), 27.4 (epimer), 27.3, 26.1 (epimer), 26.0, 24.72, 24.69, 24.5, 24.4, 19.69, 19.66 ppm.

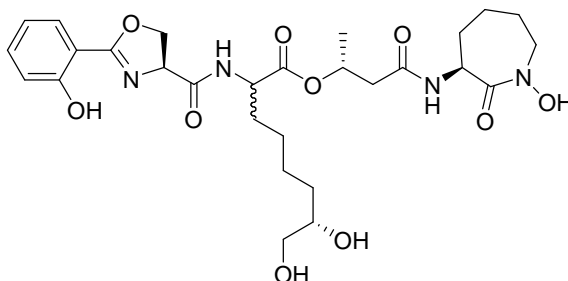


(*R*)-((*R*)-4-((*S*)-1-(Benzyloxy)-2-oxoazepan-3-ylamino)-4-oxobutan-2-yl) 2-amino-7,8-dihydroxyoctanoate (4.63). Compound **4.63** was prepared following the same procedure used for **4.53**. Compound **4.58** (0.254 g, 0.401 mmol) provided **4.63** as an off-white foam (125 mg, 63% yield). ^1H NMR (300 MHz, CDCl_3) δ 7.40 – 7.33 (m, 5H), 7.15 (d, J = 6.6 Hz, 1H), 5.27 (m, 1H), 4.95 (d, J = 10.2 Hz, 1H), 4.85 (d, J = 10.2 Hz, 1H), 4.43 (dd, J = 10.2, 6.3 Hz, 1H), 3.64 – 3.33 (m, 6H), 2.89 (br, 3H), 2.58 – 2.43 (m, 2H), 1.93 – 1.83 (m, 2H), 1.74 – 1.21 (m, 15H) ppm. ^{13}C NMR (75 MHz, CDCl_3) δ 174.9, 170.07, 170.00 (epimer), 168.5, 134.8, 129.5, 128.8, 128.5, 76.7, 71.8, 71.7 (epimer), 68.64 (epimer), 68.56, 66.5, 54.1 (epimer), 54.0, 52.6, 51.6, 42.5, 34.1, 32.7, 31.3, 27.4, 26.0, 25.3, 25.0, 19.8 ppm.

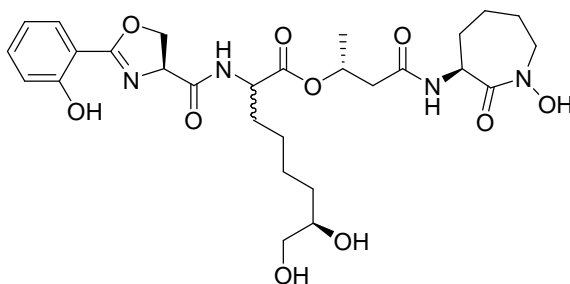


(*R*)-((*R*)-4-((*S*)-1-(Benzyloxy)-2-oxoazepan-3-ylamino)-4-oxobutan-2-yl) 7,8-dihydroxy-2-((*S*)-2-(2-hydroxyphenyl)-4,5-dihydrooxazole-4-carboxamido)octanoate (4.64). Compound **4.64** was prepared following the same procedure used for **4.54**. Oxazoline **2.62** (55.8 mg, 0.269 mmol), EDC•HCl (67.0 mg, 0.350 mmol), HOBT (41.2 mg, 0.305 mmol), and **4.63** (0.125 g, 0.253 mmol) provided an oil. Chromatography through 20 g of silica using a solvent gradient from 100% EtOAc to 95% EtOAc/MeOH yielded **4.64** as a white solid (94.4 mg, 55% yield). R_f = 0.25 (9:1 EtOAc/MeOH – UV lamp, CAM stain). ^1H NMR (500 MHz, CDCl_3) δ 7.65 (dd, J = 7.5, 1.0 Hz, 1H), 7.40 – 7.32 (m, 6H), 7.13 (m, 2H), 6.99 (d, J = 8.5 Hz, 1H), 6.87 (t, J = 7.5 Hz, 1H), 5.31 (m, 1H), 5.25 (m, 1H epimer), 4.96 – 4.90 (m, 2H), 4.86 – 4.83 (m, 1H), 4.63 – 4.58 (m, 2H), 4.55 – 4.51 (m, 1H), 4.47 – 4.40 (m, 1H), 3.63 – 3.57 (m, 2H), 3.52 (dd, J = 11.0, 3.0 Hz, 1H), 3.47 – 3.34 (m, 1H), 3.40 – 3.36 (m, 1H epimer), 3.33 (dd, J = 11, 7.5 Hz, 1H), 2.57 (dd, J = 15.0, 7.5 Hz, 1H), 2.49 (dd, J = 15.0, 5.0 Hz, 1H), 2.40 (dd, J = 15.0, 5.0 Hz, 1H epimer), 1.93 – 1.80 (m, 3H), 1.73 – 1.61 (m, 3H), 1.47 – 1.26 (m, 11H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 170.9, 170.7 (epimer), 170.5 (epimer), 170.2, 170.02, 170.0 (epimer), 168.4, 168.3 (epimer), 167.8 (epimer), 167.5, 159.54 (epimer), 159.50, 134.8, 134.7 (epimer), 134.2 (epimer), 134.1, 129.5 (epimer), 129.4, 128.9 (epimer), 128.8, 128.5, 128.4 (epimer), 119.0, 116.8, 109.9, 76.9, 71.7, 71.6 (epimer), 69.4, 69.3, 67.9,

67.8 (epimer), 66.65 (epimer), 66.61, 52.6, 52.1, 51.6, 42.3, 32.5 (epimer), 32.4, 31.7, 31.3, 27.4, 27.3 (epimer), 26.03, 26.00 (epimer), 25.0, 24.7, 19.6 ppm.

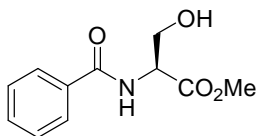


(S)-((R)-4-((S)-1-Hydroxy-2-oxoazepan-3-ylamino)-4-oxobutan-2-yl) 7,8-dihydroxy-2-((S)-2-(2-hydroxyphenyl)-4,5-dihydrooxazole-4-carboxamido)octanoate (4.65). Compound **4.65** was prepared following the same procedure for **4.56**. Compound **4.62** (12.0 mg, 0.018 mmol) was subjected to hydrogenolysis using 10 wt% Pd/C (6 mg) for 20 min. Trituration with acetonitrile yielded **4.65** as a white solid (3 mg, 30%). ^1H NMR (500 MHz, d^6 -DMSO, 30 °C) δ 8.62 (m, 1H), 8.02 (d, J = 7.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.38 (m, 1H), 6.91 – 6.78 (m, 2H), 5.10 (sextet, J = 6.5 Hz, 1H), 4.96 (m, 1H), 4.58 (m, 1H), 4.43 (dd, J = 9.5, 7.5 Hz, 2H), 4.19 (m, 1H), 3.84 (dd, J = 16.0, 11.5 Hz, 1H), 3.48 (m, 1H), 3.38 (m, 1H), 3.30 – 3.20 (m, 3H), 2.51 (m, 1H), 2.39 (dd, J = 14.5, 6.0 Hz, 1H), 1.82 (m, 1H), 1.72 – 1.58 (m, 3H), 1.46 – 1.34 (m, 3H), 1.46 – 1.18 (m, 10H) ppm. HRMS (FAB) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{28}\text{H}_{41}\text{N}_4\text{O}_{10}^+$, 593.2823; obsd, 593.2801.

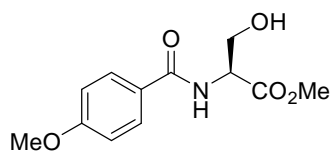


(R)-((R)-4-((S)-1-Hydroxy-2-oxazepan-3-ylamino)-4-oxobutan-2-yl) 7,8-dihydroxy-2-((S)-2-(2-hydroxyphenyl)-4,5-dihydrooxazole-4-carboxamido)octanoate (4.66). Compound **4.66** was prepared following the same procedure for **4.56**. Compound **4.64** (47.0 mg, 0.069 mmol) was subjected to hydrogenolysis using 10 wt% Pd/C (18 mg) for 20 min. Trituration with acetonitrile yielded **4.66** as a white solid (13 mg, 32% yield). ^1H NMR (500 MHz, $\text{d}^6\text{-DMSO}$, 30 °C) δ 8.67 (br, 1H), 8.02 (d, $J = 7.5$ Hz, 1H epimer), 7.98 (d, $J = 7.0$ Hz, 1H), 7.59 (d, $J = 8.0$ Hz, 1H), 7.40 (m, 1H), 6.92 (m, 1H), 6.83 (m, 1H), 5.11 (q, $J = 6.5$ Hz, 1H), 4.98 (dd, $J = 9.5, 7.5$ Hz, 1H), 4.60 (t, $J = 9$ Hz, 1H), 4.49 – 4.41 (m, 2H), 4.20 (m, 1H), 3.84 (dd, $J = 16.0, 11.5$ Hz, 1H), 3.46 (dd, $J = 15.5, 5.0$ Hz, 1H), 3.28 – 3.19 (m, 3H), 2.51 (m, 1H), 2.40 (dd, $J = 14.5, 6.5$ Hz, 1H), 1.83 – 1.58 (m, 6H), 1.46 – 1.16 (m, 11H) ppm. ^{13}C NMR (125 MHz, $\text{d}^6\text{-DMSO}$, 30 °C) δ 170.9, 170.8 (epimer), 169.8, 168.6, 168.5 (epimer), 167.9, 167.9 (epimer), 165.75, 165.69 (epimer), 133.7, 128.0, 118.2 (br), 116.8 (br), 109.9 (br), 70.9, 68.9, 68.7, 67.1, 65.9, 52.3, 52.2 (epimer), 50.7, 41.3, 41.2 (epimer), 33.0, 30.7, 30.3 (epimer), 30.1, 26.8, 25.4 (epimer), 25.3, 24.72 (epimer), 24.66, 19.3, 19.2 (epimer) ppm. HRMS (FAB) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{28}\text{H}_{41}\text{N}_4\text{O}_{10}^+$, 593.2823; obsd, 593.2825.

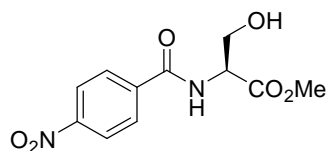
8.4 Experimental procedures for chapter 5



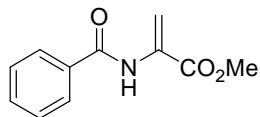
(S)-Methyl 2-benzamido-3-hydroxypropanoate (5.20). Compound **5.20** was prepared following the same procedure for compound **3.5** using EDC-mediated amide formation. Benzoic acid (3.55 g, 29.0 mmol), **3.18** (4.03 g, 25.9 mmol), EDC•HCl (5.57 g, 29.1 mmol), and triethylamine (3.85 mL, 27.4 mmol) provided **5.20** as an oil that solidified upon storage (3.64 g, 63% yield). mp = 84-86 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.78 (d, *J* = 6.9 Hz, 2H), 7.50 – 7.28 (m, 3H), 4.81 (dt, *J* = 7.5, 3.9 Hz, 1H), 4.06 – 3.94 (m, 2H), 3.75 (s, 3H), 3.53 (br, 1H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 171.0, 167.8, 133.3, 131.9, 128.5, 127.1, 63.0, 55.1, 52.7 ppm.



(S)-Methyl 3-hydroxy-2-(4-methoxybenzamido)propanoate (5.21). Compound **5.21** was prepared following the same procedure for compound **3.5** using EDC-mediated amide formation. 4-Anisic acid (0.558 g, 3.67 mmol), **3.18** (0.632 g, 4.06 mmol), EDC•HCl (0.780 g, 4.07 mmol), and triethylamine (0.60 mL, 4.3 mmol) provided **5.21** as a colorless oil (0.512 g, 55% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.79 (m, 2H), 7.08 (d, *J* = 6.9 Hz, 1H), 6.90 (m, 2H), 4.84 (td, *J* = 7.2, 3.6 Hz, 1H), 4.08 – 3.99 (m, 2H), 3.84 (s, 3H), 3.81 (s, 3H) ppm.

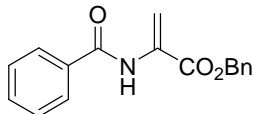


(S)-Methyl 3-hydroxy-2-(4-nitrobenzamido)propanoate (5.22). Compound **5.22** was prepared following the same procedure for compound **3.5** using EDC-mediated amide formation. 4-Nitrobenzoic acid (0.519 g, 3.11 mmol), **3.18** (0.413 g, 3.44 mmol), EDC•HCl (0.660 g, 3.44 mmol), and triethylamine (0.50 mL, 3.6 mmol) provided **5.22** as a light yellow solid (0.304 g, 36% yield). ^1H NMR (300 MHz, CDCl_3) δ 8.29 (m, 2H), 7.99 (m, 2H), 7.22 (d, $J = 7.2$ Hz, 1H), 4.88 (td, $J = 7.0, 3.4$ Hz, 1H), 4.14 (dd, $J = 11.4, 3.6$ Hz, 1H), 4.05 (dd, $J = 11.4, 3.6$ Hz, 1H), 3.84 (s, 3H), 2.40 (br, 1H) ppm.

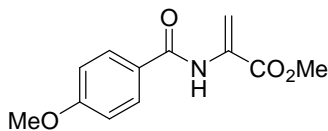


Methyl 2-benzamidoacrylate (5.23). Compound **5.20** (1.206 g, 5.403 mmol) was dissolved in 50 mL of dry CH_2Cl_2 in a flame-dried 100-mL round-bottomed flask under Ar. EDC•HCl (1.238 g, 6.458 mmol) was added to the solution in one portion followed by CuCl (160.7 mg, 1.623 mmol). The reaction was wrapped in foil and stirred under Ar at rt. After 2 h, TLC of the reaction (1:1 hexanes/EtOAc - UV lamp) indicated **5.20** had been completely consumed and a new, less polar compound was observed. After 3 h, H_2O (100 mL) was added to the reaction and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and the combined CH_2Cl_2 layers were washed with H_2O (100 mL), dried over MgSO_4 , filtered, and concentrated to yield a yellow oil. The oil was purified through a plug (30 g) of silica using 100% CH_2Cl_2 and yielded **5.23** as a colorless, cloudy liquid (1.06 g, 96% yield). ^1H NMR (500 MHz,

CDCl₃) δ 8.49 (br-s, 1H), 7.75 (dd, J = 5.1, 0.9 Hz, 2H), 7.43 (m, 1H), 7.37 (m, 2H), 6.71 (s, 1H), 5.90 (d, J = 0.6 Hz, 1H), 3.76 (s, 3H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 165.3, 164.3, 133.9, 131.7, 130.8, 128.4, 126.6, 108.5, 52.7 ppm. HRMS (FAB) m/z [M+H]⁺ calcd for C₁₁H₁₂NO₃⁺, 206.0817; obsd, 206.0818.

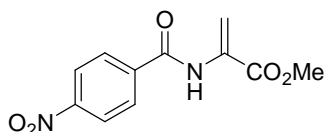


Benzyl 2-benzamidoacrylate (5.24). Compound **5.24** was prepared following the same procedure for **5.23**. Compound **3.9** (1.51 g, 5.03 mmol), EDC•HCl (1.17 g, 6.12 mmol), and CuCl (0.150 g, 1.51 mmol) provided an oil. Chromatography through silica using 100% CH₂Cl₂ yielded **5.24** as a white solid (1.45 g, 99% yield). mp = 51-52 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.56 (br-s, 1H), 7.84 (dd, J = 7.0, 1.5 Hz, 2H), 7.55 (m, 1H), 7.47 (m, 2H), 7.41 – 7.36 (m, 5H), 6.82 (s, 1H), 6.06 (m, 1H), 5.32 (s, 2H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 165.7, 164.2, 135.0, 134.2, 132.0, 131.0, 128.8, 128.7, 128.6, 128.2, 126.9, 109.1, 67.9 ppm. HRMS (FAB) m/z [M+H]⁺ calcd for C₁₇H₁₆NO₃⁺, 282.1130; obsd, 282.1140.

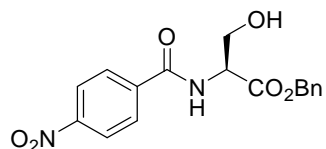


Methyl 2-(4-methoxybenzamido)acrylate (5.25). Compound **5.25** was prepared following the same procedure for **5.23**. Compound **5.21** (0.495 g, 1.95 mmol), EDC•HCl (0.448 g, 2.33 mmol), and CuCl (59.7 mg, 0.603 mmol) provided an oil. Chromatography through silica using 100% CH₂Cl₂ yielded **5.25** as a white solid (0.426

g, 93% yield). mp = 47.0-47.5 °C. Rf = 0.47 (1:1 hexanes/EtOAc – UV lamp). ¹H NMR (300 MHz, CDCl₃) δ 8.44 (br, 1H), 7.77 (m, 2H), 6.93 (m, 2H), 6.73 (s, 1H), 5.93 (d, *J* = 1.2 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ 165.2, 164.8, 162.6, 131.0, 128.8, 126.4, 113.9, 108.3, 55.4, 43.0 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₂H₁₄NO₄⁺, 236.0923; obsd, 236.0922.

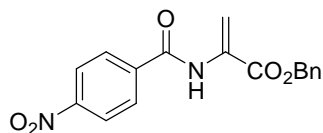


Methyl 2-(4-nitrobenzamido)acrylate (5.26). Compound **5.26** was prepared following the same procedure for **5.23**. Compound **5.22** (0.289 g, 1.08 mmol), EDC•HCl (0.249 g, 1.30 mmol), CuCl (36.0 mg, 0.363 mmol) provided an oil. Chromatography through silica using 100% CH₂Cl₂ yielded **5.26** as a white solid (0.244 g, 90% yield). mp = 158-159 °C. Rf = 0.45 (1:1 hexanes/EtOAc – UV lamp). ¹H NMR (500 MHz, CDCl₃) δ 8.57 (br, 1H), 8.33 (m, 2H), 8.00 (m, 2H), 6.81 (s, 1H), 6.06 (m, 1H), 3.91 (s, 3H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 164.5, 163.6, 149.8, 139.6, 130.6, 128.2, 124.0, 110.0, 53.3 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₁H₁₁N₂O₅⁺, 251.0668; obsd, 251.0670.



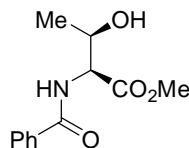
(S)-Benzyl 3-hydroxy-2-(4-nitrobenzamido)propanoate (5.27). Compound **5.27** was prepared following the same procedure for **3.5** using acid chloride-mediated amide formation. *p*-nitrobenzoic acid (1.01 g, 6.06 mmol), oxalyl chloride (1.10 mL,

12.6 mmol), and catalytic DMF provided the acid chloride intermediate as a yellow semi-solid. **3.4** (1.42 g, 6.12 mmol) and diisopropylethylamine (2.70 mL, 15.5 mmol) yielded a peach-colored solid. Chromatography through 150 g of silica using a solvent gradient from 90% CH₂Cl₂/EtOAc to 60% CH₂Cl₂/EtOAc yielded **5.27** as a light yellow solid (1.40 g, 67% yield). mp = 129.5-130.0 °C. R_f = 0.15 (1:1 hexanes/EtOAc - UV lamp). ¹H NMR (500 MHz, CDCl₃) δ 8.29 (d, *J* = 8.5 Hz, 2H), 7.99 (d, *J* = 9.0 Hz, 2H), 7.37 (m, 5H), 7.16 (d, *J* = 6.5 Hz, 1H), 5.29 (d, *J* = 12.0 Hz, 1H), 5.25 (d, *J* = 12.0 Hz, 1H), 4.92 (dt, *J* = 7.5, 3.5 Hz, 1H), 4.16 (dd, *J* = 11.5, 3.5 Hz, 1H), 2.18 (br, 1H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 170.1, 165.5, 139.1, 134.9, 128.7, 128.4, 128.3, 123.9, 67.9, 63.2, 55.3 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₇H₁₇N₂O₆⁺, 345.1087; obsd, 345.1111.



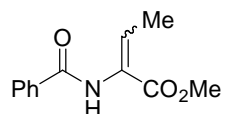
Benzyl 2-(4-nitrobenzamido)acrylate (5.28). Compound **5.28** was prepared following the same procedure for **5.23**. Compound **5.27** (0.945 g, 2.75 mmol), EDC•HCl (0.585 g, 3.05 mmol), and CuCl (83.9 mg, 0.847 mmol) provided an oil. Chromatography through silica using 100% CH₂Cl₂ yielded **5.28** as a white solid (0.869 g, 97% yield). mp = 144-145 °C. ¹H NMR (300 MHz, CDCl₃) δ 8.59 (br-s, 1H), 8.31 (dt, *J* = 9.0, 2.1 Hz, 2H), 7.98 (m, 2H), 7.40 (m, 5H), 6.83 (s, 1H), 6.12 (d, *J* = 1.2 Hz, 1H), 5.32 (s, 2H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ 163.9, 163.5, 149.8, 139.6, 134.8, 130.7, 128.7, 128.2, 128.1, 124.0, 110.2, 68.1 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₇H₁₅N₂O₅⁺, 327.0981; obsd, 327.0984.

General procedure for one-pot preparation of 2-amidoacrylates from benzoic acid and serine esters. Acrylate 5.24. Anhydrous CH₂Cl₂ (50 mL) was added to **3.4** (1.01 g, 4.37 mmol) and benzoic acid (0.542 g, 4.44 mmol) in a flame-dried single-necked 200-mL round-bottomed flask under Ar. Triethylamine (0.65 mL, 4.6 mmol) was added, followed by EDC•HCl (1.83 g, 9.55 mmol). The mixture was stirred at rt under Ar. After 1 h, the reaction was progressing by TLC (1:1 hexanes/EtOAc - UV lamp, ninhydrin stain). After 2.5 h, CuCl (0.137 g, 1.38 mmol) was added and the color of the solution turned light blue/green in color. After 4 h, there was no change in the reaction by TLC and more EDC•HCl (0.9 g, 4.7 mmol, ~1 equiv) was added. After about 10 h, the reaction color had changed to dark greenish/yellow, but was still incomplete by TLC. More CuCl (about 0.1 g, ~1 mmol, 22 mol%) was added and the solution was stirred at rt. The color of the reaction changed to orange and the reaction was complete. The reaction was diluted with CH₂Cl₂ (50 mL) and H₂O (100 mL) was added. The mixture was diluted with brine (100 mL) and EtOAc (~400 mL). The layers were separated and the organic layer was washed with brine (2 x 50 mL), dried over Na₂SO₄, filtered, and concentrated to yield a yellow oil. The oil was chromatographed through an Analogix SF 25-40g silica column using 100% CH₂Cl₂ and yielded **5.24** as a white solid (0.945 g, 77% yield).



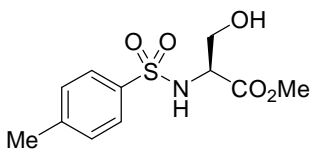
(2S,3R)-Methyl 2-benzamido-3-hydroxybutanoate (5.30). Compound **5.30** was prepared following the same procedure for compound **3.5** using EDC-mediated amide

formation. Benzoic acid (2.39 g, 19.6 mmol), **5.29** (2.97 g, 17.5 mmol), EDC•HCl (4.03 g, 21.0 mmol), and triethylamine (2.65 mL, 18.9 mmol) provided a yellow oil that solidified upon standing. Chromatography through an Analogix F40M column using a solvent gradient from 90% to 60% CH₂Cl₂/EtOAc yielded **5.30** as a white solid (2.61 g, 63% yield). mp = 95-96 °C. R_f = 0.5 (1:1 hexanes/EtOAc – UV lamp). ¹H NMR (500 MHz, CDCl₃) δ 7.82 (d, *J* = 7.5 Hz, 2H), 7.48 (m, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.13 (d, *J* = 9.0 Hz, 1H), 4.78 (dd, *J* = 9.0, 2.5 Hz, 1H), 4.42 (qd, *J* = 6.5, 2.5 Hz, 1H), 3.74 (s, 3H), 3.17 (br, 1H), 1.24 (d, *J* = 6.5 Hz, 3H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 171.5, 168.0, 133.5, 131.9, 128.5, 127.2, 68.0, 57.7, 52.6, 20.0 ppm.



Methyl 2-benzamidobut-2-enoate (5.31). Compound **5.31** was prepared following the same procedure for **5.23**. Compound **5.30** (1.21 g, 5.08 mmol), EDC•HCl (1.18 g, 6.13 mmol), and CuCl (0.150 g, 1.52 mmol) were stirred at rt for 2 h and concentrated. The mixture was chromatographed through 30 g of silica using a solvent gradient from 100% CH₂Cl₂ to 80% CH₂Cl₂/EtOAc and yielded **5.31** as a pale yellow oil that solidified upon storage (1.07 g, 97% yield). **5.31** was isolated as a 29:1 mixture of *Z*:*E* isomers based on NMR data. mp = 66-68 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.22 (br, 1H, *E* isomer), 7.86 (m, 2H, *Z* isomer), 7.79 (m, 2H, *E* isomer), 7.65 (br, 1H, *Z* isomer), 7.52 (t, *J* = 7.5 Hz, 1H), 7.44 (m, 2H), 7.37 (q, *J* = 8.0 Hz, 1H, *E* isomer), 6.88 (q, *J* = 7 Hz, 1H, *Z* isomer), 3.86 (s, 3H, *E* isomer), 3.76 (s, 3H, *Z* isomer), 2.12 (d, *J* = 7.5 Hz, 3H, *E* isomer), 1.83 (d, *J* = 7.0 Hz, 3H, *Z* isomer) ppm. ¹³C NMR (125 MHz,

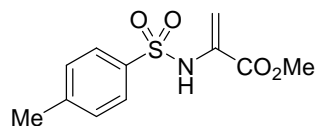
CDCl₃) δ 165.4 (*E*), 165.1 (*Z*), 133.85 (*E*), 133.77 (*Z*), 131.9 (*Z*), 131.7 (*E*), 128.6 (*Z*), 127.4 (*Z*), 126.8 (*E*), 126.0 (*E*), 52.4, 15.0 (*Z*), 14.1 (*E*) ppm. HRMS (FAB) m/z [M+H]⁺ calcd for C₁₂H₁₄NO₃⁺, 220.0974; obsd, 220.0975.



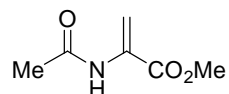
(*S*)-Methyl 3-hydroxy-2-(4-methylphenylsulfonamido)propanoate (5.32).

Compound **3.18** (2.107 g, 13.54 mmol), *p*-toluenesulfonyl chloride (2.87 g, 15.1 mmol), and anhydrous CH₂Cl₂ (100 mL) were added to a flame-dried single-necked 250-mL round-bottomed flask under Ar. *N,N*-Diisopropyl-*N*-ethylamine (5.50 mL, 31.6 mmol) was added and the solid material dissolved. The resultant solution was stirred at rt under Ar overnight. After 22 h, the reaction was analyzed by TLC (1:1 hexanes/EtOAc and 9:1 CH₂Cl₂/EtOAc - UV lamp) and one new polar spot was observed (along with unreacted TsCl). The light yellow solution was concentrated by rotary evaporation and the resultant residue was partitioned between EtOAc (100 mL) and H₂O (100 mL). The aqueous layer was extracted with EtOAc (2 x 50 mL) and the combined organic layers were washed with saturated NaHCO₃ (2 x 50 mL), H₂O (50 mL), 1M HCl (2 x 50 mL), H₂O (50 mL), and brine (2 x 50 mL), dried over Na₂SO₄, filtered, and concentrated to yield an orange oil. The oil solidified upon standing. The crude material was chromatographed through a Biotage 40S column using a solvent gradient from 100% CH₂Cl₂ to 50% CH₂Cl₂/EtOAc and yielded **5.32** as a white solid (3.04 g, 82% yield). mp = 89-90 °C. R_f = 0.11 (1:1 hexanes/EtOAc - UV lamp). ¹H NMR (500 MHz, CDCl₃) δ 7.75 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 5.85 (d, *J* = 8.0 Hz, 1H), 4.01 (dt, *J* = 8.0, 3.5 Hz, 1H), 3.89 (m,

2H), 3.61 (s, 3H), 2.61 (br, 1H), 2.42 (s, 3H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 170.1, 143.9, 136.4, 129.7, 127.2, 63.6, 57.6, 52.9, 21.5 ppm. HRMS (FAB) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{11}\text{H}_{16}\text{NO}_5\text{S}^+$, 274.0749; obsd, 274.0725.

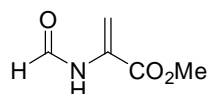


Methyl 2-(4-methylphenylsulfonamido)acrylate (5.33). Compound **5.33** was prepared following the same procedure for **5.23**. Compound **5.32** (1.01 g, 3.71 mmol), EDC•HCl (0.826 g, 4.31 mmol), and CuCl (0.120 g, 1.21 mmol) were stirred at rt for 1 h, concentrated, and chromatographed through a Biotage 40S column using 100% CH_2Cl_2 and yielded **5.33** as a free-flowing yellow solid (0.924 g, 98% yield). mp = 99-100 °C. R_f = 0.45 (1:1 hexanes/EtOAc – UV lamp). ^1H NMR (500 MHz, CDCl_3) δ 7.75 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 5.67 (m, 1H), 5.64 (m, 1H), 3.76 (s, 3H), 2.42 (s, 3H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 163.6, 144.3, 135.3, 130.8, 129.7, 127.5, 106.8, 53.2, 21.5 ppm. HRMS (FAB) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{11}\text{H}_{15}\text{NO}_4\text{S}^+$, 256.0644; obsd, 256.0668.



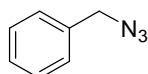
Methyl 2-acetamidoacrylate (5.34). To a flame-dried 50-mL round-bottomed flask containing **3.18** (2.021 g, 12.99 mmol) under Ar was added 15 mL of anhydrous triethylamine. The mixture was stirred at RT for 10 min, then cooled in a crushed ice/ H_2O bath. Acetic anhydride (3.00 mL, 32.0 mmol) was added slowly the reaction

under Ar. The mixture was stirred in the ice/H₂O bath for 15 min, then stirred at rt. After stirring 1 h, the reaction color changed from a white mixture to a yellow mixture. After 4 days, the brown mixture was partitioned between H₂O (100 mL) and EtOAc (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with 1M HCl (3 x 50 mL), H₂O (50 mL), and brine (50 mL), dried over MgSO₄, filtered, and concentrated to yield an orange oil (~0.8 g crude material). The oil solidified upon storage at 10 °C. The crude material was purified through 100 g of silica gel using a solvent gradient from 100% CH₂Cl₂ to 90% CH₂Cl₂/EtOAc and yielded **5.34** as a yellow oil that solidified upon standing (0.681 g, 37% yield). mp = 49-50 °C. R_f = 0.30 (1:1 hexanes/EtOAc – UV lamp). ¹H NMR (300 MHz, CDCl₃) δ 7.76 (br, 1H), 6.54 (s, 1H), 5.82 (d, *J* = 1.5 Hz, 1H), 3.80 (s, 3H), 2.09 (s, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ 168.8, 164.4, 130.8, 108.6, 52.8, 24.5 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₆H₁₀NO₃⁺, 144.0661; obsd, 144.0650.



Methyl 2-formamidoacrylate (5.35). Methyl formate (30 mL) was added to **3.18** (1.516 g, 9.744 mmol) and potassium carbonate (5.403 g, 39.10 mmol) in a single-necked 100-mL round-bottomed flask. One drop of triethylamine was added and the mixture was stirred at rt overnight. After 28 h, the solid material was removed by filtration and washed with small portions of methyl formate (20 mL). The colorless filtrate was concentrated to yield a light yellow oil. The oil was chromatographed through a short column of silica (~35 g) using 50% hexanes/EtOAc and yielded **5.35** as a

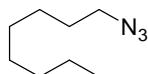
colorless oil that solidified upon standing to a white solid (0.88 g, 70% yield). Isolated as a mixture of rotamers (88:12 *trans:cis*). mp = 55-57 °C (lit. 56.9-57.2 °C). R_f = 0.29 (1:1 hexanes/EtOAc – UV lamp). ¹H NMR (500 MHz, CDCl₃) δ 8.53 (m, 1H, *cis*), 8.39 (s, 1H, *trans*), 8.06 (br, 1H, *trans*), 7.76 (br, 1H, *cis*), 6.60 (s, 1H, *trans*), 5.92 (s, 1H, *trans*), 5.67 (s, 1H, *cis*), 5.42 (s, 1H, *cis*), 3.81 (s, 3H, *trans/cis*) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 164.1, 161.1, 159.6, 131.8, 130.1, 110.3, 104.8, 95.8, 52.9 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₅H₈NO₃⁺, 130.0504; obsd, 130.0527.



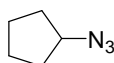
General procedure for the preparation of alkyl azides. Benzyl azide (5.36a).

CAUTION: Azides may be explosive and shock sensitive and should be handled with care. A blast shield was used for every reaction that involved the use or preparation of azides. 75 mL of DMSO was added to sodium azide (2.45 g, 37.7 mmol) in a 250-mL single-necked round-bottomed flask under Ar. The mixture was stirred at rt until the sodium azide dissolved. Benzyl bromide (4.00 mL, 34.6 mmol) was added and the solution was stirred at rt under Ar for 4 h. 100 mL of H₂O was added slowly to quench the reaction (exothermic), the resultant cloudy mixture was allowed to warm to rt (30 min), then poured into 100 mL of H₂O. The mixture was extracted with Et₂O (3 x 100 mL), and the combined Et₂O layers were washed with brine, dried over MgSO₄, filtered, and concentrated by rotary evaporation (30 °C, 21 mm Hg) and yielded **5.36a** as a colorless oil (4.604 g, 99.9% yield). Stored at 4 °C until ready to use. ¹H NMR (500 MHz, CDCl₃) δ 7.46 – 7.36 (m, 5H), 4.37 (s, 2H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ

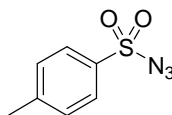
135.2, 128.7, 128.13, 128.06, 54.6 ppm. FT-IR (film) 3066, 3033, 2931, 2097 (N₃), 1496, 1456, 1256, 1203, 1078, 1029 cm⁻¹



1-Azidooctane (5.36b). Compound **5.36b** was prepared according to the general procedure for alkyl azides. 1-bromooctane (0.32 mL, 1.8 mmol) and sodium azide (0.112 g, 2.0 mmol) were stirred in DMSO at rt for 4 h and yielded **5.36b** as a pale yellow oil (0.251 g, 88% yield). ¹H NMR (300 MHz, CDCl₃) δ 3.25 (t, *J* = 6.9 Hz, 2H), 1.60 (m, 2H), 1.32 – 1.27 (m, 10H), 0.88 (t, *J* = 6.9 Hz, 3H) ppm. FT-IR (film) 2929 (CH), 2858 (CH), 2096 (N₃), 1467 (CH bend), 1378 (CH bend), 1349, 1260 (N₃) cm⁻¹.

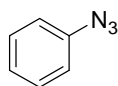


Azidocyclopentane (5.36c). Compound **5.36c** was prepared according to the general procedure for alkyl azides. Bromocyclopentane (1.00 mL, 9.14 mmol) and sodium azide (0.658 g, 10.1 mmol) were stirred in DMSO for 25 h and yielded **5.36c** as a pale yellow liquid (0.738 g, 73% yield). ¹H NMR (500 MHz, CDCl₃) δ 3.92 (m, 1H), 1.83 – 1.71 (m, 2H), 1.71 – 1.69 (m, 4H), 1.61 – 1.59 (m, 2H) ppm.



4-Methylbenzenesulfonyl azide (5.37). To a 500-mL round-bottomed flask cooled in an ice/H₂O bath was added *p*-toluenesulfonyl chloride (8.00 g, 42.0 mmol) and

240 mL of 1:1 acetone/H₂O. The resultant suspension was stirred vigorously as sodium azide (2.767 g, 42.6 mmol) was added in one portion to the reaction. The cloudy suspension was stirred vigorously for 6 h, allowing the reaction to slowly reach rt as the ice/H₂O bath melted. Most of the acetone was removed by rotary evaporation (~40°C, 21 mm Hg) to yield a light yellow oil beneath the aqueous layer. Et₂O (~100 mL) was added and the layers were separated. The aqueous layer was extracted with Et₂O (2 x 100 mL), and the combined ether layers were dried over MgSO₄, filtered, and concentrated by rotary evaporation (~30°C, 21 mm Hg) and yielded **5.37** as a colorless liquid that solidified upon storage at -10 °C (7.59 g, 92% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 2.48 (s, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ 146.2, 135.5, 130.3, 127.5, 21.8 ppm. FT-IR (film) 2360, 2128 (N₃), 1596, 1372, 1121, 1168, 1086, 814, 748, 665 cm⁻¹.

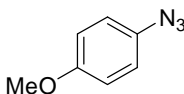


Phenyl azide (5.38a). Preparation using NaNO₂/HCl. 75 mL of H₂O and concentrated HCl (14.0 mL, 169 mmol) were added to a 500-mL 3-necked round-bottomed flask equipped with a thermometer and a 10-mL addition funnel. The flask was cooled in a ice/NaCl/H₂O bath to an internal temperature of about -5 °C. Phenylhydrazine (7.6 mL, 77.2 mmol) was added to the solution dropwise over 5 min. Phenylhydrazine-HCl precipitated out of the mixture as a fine white solid. 25 mL of Et₂O was added and the mixture was stirred vigorously as a solution of NaNO₂ (6.254 g, 90.64 mmol) in 7.5 mL of H₂O was added to the solution dropwise over about 25 min. During this time, the internal temperature of the reaction was maintained below 5 °C.

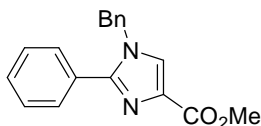
The white flakes of Phenylhydrazine-HCl had dissolved in the reaction and the mixture had turned a bright yellow color. After stirring for 10 min, the mixture was subjected to steam distillation until about 100 mL of distillate were collected. During the distillation, the mixture turned from yellow to brick red in color. An appreciable amount of tar was also formed. The orange ether layer of the distillate was removed and the aqueous layer was extracted with Et₂O (2 x 20 mL). The combined Et₂O layers were dried over MgSO₄ and filtered into a 100-mL round-bottomed flask. The Et₂O was removed by rotary evaporation (RT, 21 torr) to yield an orange oil. The oil was purified by vacuum distillation and yielded **5.38a** as a yellow oil (1.58 g, 17% yield). bp = 26-27 °C (1.5 mm Hg). Isolated with impurities.

Preparation of phenyl azide from aniline. Aniline (0.50 mL, 5.48 mmol) was suspended in 4 mL of H₂O and cooled in a crushed ice/H₂O bath. Conc. H₂SO₄ (1.20 mL, 21.7 mmol) was added dropwise and aniline hydrochloride precipitated out of the solution. To this mixture was added a solution of NaNO₂ (432 mg, 6.26 mmol) in 2.5 mL of H₂O dropwise. A yellow color was observed in the mixture. Hexanes (8 mL) was added, followed by a solution of NaN₃ (383 mg, 5.89 mmol) in 2.5 mL of H₂O dropwise to the biphasic mixture. A lot of bubbling was observed. The mixture was stirred vigorously in the ice/H₂O bath over 3 h, allowing the ice/H₂O bath to melt and reach rt. The layers were separated and the organic layer was dried over MgSO₄, filtered, and concentrated by rotary evaporation (30 °C, 21 mm Hg) and yielded **5.38a** as a yellow oil (465 mg, 71% yield). A blast shield was used when concentrating the azide as a precautionary measure. ¹H NMR (500 MHz, CDCl₃) δ 7.36 (m, 2H), 7.14 (m, 1H), 7.03

(m, 2H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 140.0, 129.7, 124.9, 119.0 ppm. FT-IR (film) 2130, 2096, 1594, 1493, 1296, 749 cm^{-1} .

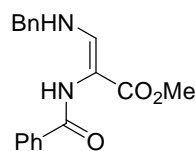


1-Azido-4-methoxybenzene (5.38b). Compound **5.38b** was prepared following the same procedure for **5.38a** from aniline. *p*-anisidine (0.662 g, 5.38 mmol), concentrated H_2SO_4 (1.20 mL, 21.7 mmol), NaNO_2 (0.434 g, 6.29 mmol), and sodium azide (0.375 g, 5.77 mmol) yielded **5.38b** as a brown oil (0.343 g, 44% yield). ^1H NMR (500 MHz, CDCl_3) δ 6.96 (m, 2H), 6.89 (m, 2H), 3.80 (s, 3H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 156.9, 132.3, 119.9, 115.1, 55.5 ppm. FT-IR (film) 2955, 2837, 2105, 1505, 1465, 1286, 1246, 1182, 1035, 825, 626 cm^{-1} .

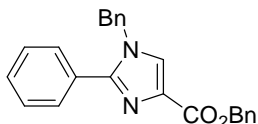


General procedure for the preparation of imidazoles from 2-amidoacrylates and azides. **Methyl 1-benzyl-2-phenyl-1H-imidazole-4-carboxylate (5.40a).** Compound **5.23** (116.2 mg, 0.5663 mmol) and benzyl azide (0.11 mL, 0.87 mmol) were dissolved in 5 mL of toluene in a sealed tube fitted with a stir bar. The tube was heated in an oil bath maintained at 190 $^{\circ}\text{C}$ overnight. After 1 h, the colorless solution turned yellow in color and gradually the color became brown. After 24 h, the reaction was cooled to rt and concentrated. The crude brown oil was purified through 25 g of silica gel using a solvent gradient from 100% CH_2Cl_2 to 80% $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ and yielded pure

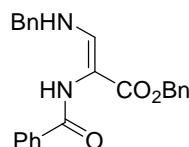
5.41a (see below) (26.5 mg, 15.1% yield), pure **5.40a** as an amber oil (84.1 mg, 50.8% yield), and a mixture of **5.41a** and **5.40a** (26.1 mg). Total yield of **5.40a** isolated as an amber oil was 90.1 mg (54% yield). **5.40a** was recrystallized from EtOAc/hexanes to produce light yellow crystals suitable for x-ray diffraction. $R_f = 0.14$ (1:1 hexanes/EtOAc – UV lamp). ^1H NMR (500 MHz, CDCl_3) δ 7.69 (s, 1H), 7.60 (m, 2H), 7.44 – 7.40 (m, 3H), 7.37 – 7.32 (m, 3H), 7.09 (m, 2H), 5.23 (s, 2H), 3.90 (s, 3H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 163.0, 148.8, 135.4, 132.5, 129.2, 129.0, 128.8, 128.7, 128.2, 127.9, 126.9, 126.5, 51.3, 50.5 ppm. HRMS (FAB) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{17}\text{N}_2\text{O}_2^+$, 293.1290; obsd, 293.1293.



(Z)-Methyl 2-benzamido-3-(benzylamino)acrylate (5.41a). Compound **5.41a** was isolated as an amber oil. Total yield isolated was 46.6 mg (27% yield). **5.41a** was recrystallized from 70% EtOH/ H_2O to yield colorless crystals suitable for x-ray diffraction. $R_f = 0.26$ (1:1 hexanes/EtOAc – UV lamp). ^1H NMR (500 MHz, CDCl_3) δ 8.00 (br, 1H), 7.84 (m, 2H), 7.51 (m, 1H), 7.44 (m, 2H), 7.37 – 7.26 (m, 6H), 6.50 (br, 1H), 4.42 (d, $J = 6.0$ Hz, 2H), 3.73 (s, 3H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 166.5, 164.8, 140.1, 138.5, 134.0, 131.6, 131.3, 128.73, 128.69, 128.6, 128.51, 128.46, 127.2, 127.1, 127.0, 126.9, 98.6, 52.5, 51.6 ppm. HRMS (FAB) m/z $[\text{M}]^+$ calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_3^+$, 310.1317; obsd, 310.1297.

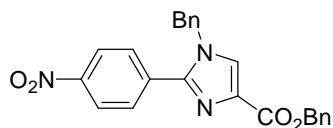


Benzyl 1-benzyl-2-phenyl-1H-imidazole-4-carboxylate (5.40b). Compound **5.40b** was prepared following the general procedure for the synthesis of imidazoles from acrylates and azides. Acrylate **5.24** (0.144 g, 0.513 mmol) and benzyl azide (0.10 mL, 0.79 mmol) were heated in toluene (5 mL) in a sealed tube for 24 h in a 190 °C oil bath. Chromatography through 25 g of silica using a solvent gradient from 100% CH₂Cl₂ to 90% CH₂Cl₂/EtOAc yielded pure **5.41b** (see below), **5.40b**, and a mixture of **5.40b** and **5.41b** as amber oils. Total yield of **5.40b** was 120 mg (63% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.65 (s, 1H), 7.56 (m, 2H), 7.44 (m, 2H), 7.42 – 7.29 (m, 9H), 7.05 (d, *J* = 7.0 Hz, 2H), 5.36 (s, 2H), 5.18 (s, 2H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 162.6, 149.2, 136.1, 135.6, 132.8, 129.4, 129.3, 129.1, 129.0, 128.44, 128.36, 128.3, 128.2, 128.0, 127.2, 126.7, 66.0, 50.7 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₂₄H₂₁N₂O₂⁺, 369.1603; obsd, 369.1602.



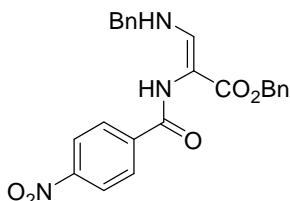
(Z)-Benzyl 2-benzamido-3-(benzylamino)acrylate (5.41b). Compound **5.41b** was isolated as an amber oil (35 mg, 18% yield). **5.41b** was isolated as an 8:1 mixture of isomers as evidenced by ¹H NMR data. ¹H NMR (500 MHz, CDCl₃) δ 9.04 (br, 1H), 7.84 (d, *J* = 7.5 Hz, 2H), 7.79 (d, *J* = 7.5 Hz, 2H, isomer), 7.51 (m, 1H), 7.45 – 7.26 (m, 13H), 6.59 (br, 1H), 5.21 (s, 2H), 4.44 (d, *J* = 6.0 Hz, 2H) ppm. ¹³C NMR (125 MHz,

CDCl₃) δ 164.9, 138.4, 136.5, 134.0, 131.6, 128.8, 128.7, 128.6, 128.53, 128.47, 128.02, 127.98, 127.5, 127.2, 127.1, 126.9, 66.1, 52.6 ppm. HRMS (FAB) m/z [M \cdot]⁺ calcd for C₂₄H₂₂N₂O₃⁺, 386.1630; obsd, 386.1628.



Benzyl 1-benzyl-2-(4-nitrophenyl)-1H-imidazole-4-carboxylate (5.69b).

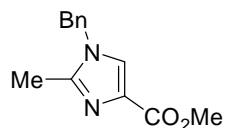
Compound **5.69b** was prepared following the general procedure for the synthesis of imidazoles from acrylates and azides. Acrylate **5.28** (0.166 g, 0.510 mmol) and benzyl azide (0.117 g, 0.879 mmol) were heated in toluene. Chromatography through 20 g of silica using a solvent gradient from 100% CH₂Cl₂ to 85% CH₂Cl₂/EtOAc provided **5.70b** (see below), **5.69b** (123 mg), and a mixture of **5.69b** and **5.70b** as amber oils. Total yield of **5.69b** was 135 mg (64% yield). ¹H NMR (500 MHz, CDCl₃) δ 8.20 (m, 2H), 7.75 (m, 2H), 7.72 (s, 1H), 7.43 (m, 2H), 7.37 – 7.26 (m, 6H), 7.04 (m, 2H), 5.35 (s, 2H), 5.25 (s, 2H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 162.1, 147.9, 146.5, 135.8, 135.2, 134.8, 133.4, 129.6, 129.1, 128.44, 128.40, 128.3, 128.0, 126.3, 123.6, 66.2, 51.0 ppm. HRMS (FAB) m/z [M+H]⁺ calcd for C₂₄H₂₀N₃O₄⁺, 414.1454; obsd, 414.1460.



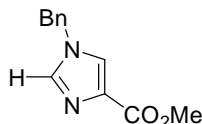
(Z)-Benzyl 3-(benzylamino)-2-(4-nitrobenzamido)acrylate (5.70b).

Compound **5.70b** was isolated as an amber oil with impurities (18.1 mg, 8% yield). ¹H

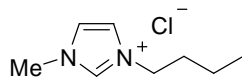
NMR (500 MHz, CDCl₃) δ 8.29 (m, 2H), 8.12 (br, 1H), 7.99 (m, 2H), 7.44 – 7.27 (m, 10H), 6.51 (br, 1H), 5.21 (s, 2H), 4.46 (d, J = 6.0 Hz, 2H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 162.5, 149.6, 139.5, 138.1, 136.3, 128.8, 128.6, 128.4, 128.2, 128.1, 127.7, 127.1, 123.9, 66.4, 52.8 ppm. HRMS (FAB) m/z [M•]⁺ calcd for C₂₄H₂₁N₃O₅⁺, 431.1481; obsd, 431.1465.



Methyl 1-benzyl-2-methyl-1H-imidazole-4-carboxylate (5.73). Compound **5.73** was prepared following the general procedure for the synthesis of imidazoles from acrylates and azides. Acrylate **5.34** (0.100 g, 0.701 mmol) and benzyl azide (0.122 g, 0.916 mmol) were heated in toluene (6 mL) in a sealed tube for 15 h in a 190 °C oil bath. Chromatography through 25 g of silica using a solvent gradient from 25% hexanes/EtOAc to 100% EtOAc provided **5.73** and **5.74**. Byproduct **5.74** was isolated with a large amount of impurities. Imidazole **5.73** was isolated as an amber oil (120 mg, 74% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.50 (s, 1H), 7.31 – 7.25 (m, 3H), 7.03 (d, J = 6.5 Hz, 2H), 5.02 (s, 2H), 3.80 (s, 3H), 2.31 (s, 3H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 163.2, 146.1, 134.9, 131.4, 129.0, 128.2, 126.7, 126.1, 51.4, 50.1, 13.0 ppm. HRMS (FAB) m/z [M+H]⁺ calcd for C₁₃H₁₅N₂O₂⁺, 231.1134; obsd, 231.1139.

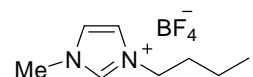


Methyl 1-benzyl-1H-imidazole-4-carboxylate (5.75). Compound **5.75** was prepared following the general procedure for the synthesis of imidazoles from acrylates and azides. Acrylate **5.35** (76.6 mg, 0.593 mmol) and benzyl azide (0.101 g, 0.756 mmol) were heated in toluene (6 mL) in a sealed tube in a 190 °C oil bath for 15 h. Chromatography through 25 g of silica using a solvent gradient from 50% hexanes/EtOAc to 33% hexanes/EtOAc provided **5.75** and **5.76**. Byproduct **5.76** was isolated with a large amount of impurities. Imidazole **5.75** was isolated as an amber oil (90.9 mg, 71% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.53 (d, J = 1.0 Hz, 1H), 7.50 (d, J = 1.0 Hz, 1H), 7.33 – 7.28 (m, 3H), 7.15 (m, 2H), 5.08 (s, 2H), 3.79 (s, 3H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 163.0, 137.9, 134.8, 133.7, 129.0, 128.5, 127.4, 125.2, 51.4, 51.1 ppm. HRMS (FAB) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{13}\text{N}_2\text{O}_2^+$, 277.0977; obsd, 277.0983.



3-Butyl-1-methyl-1H-imidazol-3-ium chloride, BMIM⁺Cl⁻ (5.67). Freshly distilled 1-methylimidazole (18.4 mL, 0.231 mol) was added to a 3-necked 250-mL round-bottomed flask fitted with a internal thermometer adapter, a condenser, under Ar. Dry acetonitrile (12.5 mL) was added, followed by 1-chlorobutane (31.5 mL, 0.299 mol). The colorless solution was heated in an oil bath (oil temp = 85-88 °C) to reflux (internal temperature = 75-80 °C). After 48 h, the yellow solution was cooled to rt, transferred to a single-necked 200-mL round-bottomed flask, and the volume was reduced by rotary

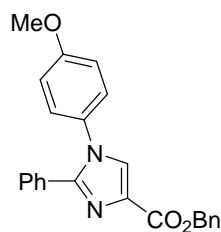
evaporation (55-60 °C, 21 mm Hg). The resultant thick yellow oil was stored under Ar at rt, then dried under vacuum (~1 mm Hg) for 5 h. The oil was dissolved in 32 mL of dry acetonitrile and added dropwise via cannula to a single-necked 500-mL round-bottomed flask containing EtOAc (125 mL) and one seed crystal of BMIM chloride (obtained from a previous preparation). The mixture is stirred vigorously during the addition and solid BMIM chloride crystallized immediately upon the addition of the acetonitrile solution. Once the addition was complete, the mixture was stirred vigorously under Ar and cooled in a -30 °C bath (dry ice/acetone) for 2 h. The mixture was quickly filtered while still cold and the white solid was washed with a minimal amount of EtOAc. (NOTE: The solid was very hygroscopic and started to turn into an oil very quickly). The solid was dried with P₂O₅ under vacuum (1 mm Hg) for 24 h. Yielded **5.67** as a white solid material (35.5 g, 88% yield). lit. 89% yield. ¹H NMR (500 MHz, CDCl₃) δ 10.31 (s, 1H), 7.54 (t, *J* = 2 Hz, 1H), 7.37 (t, *J* = 2 Hz, 1H), 4.07 (s, 2H), 3.85 (s, 3H), 1.63 (m, 2H), 1.09 (septet, *J* = 7.5 Hz, 2H), 0.67 (t, *J* = 7.5 Hz, 3H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 137.0, 123.3, 121.6, 49.1, 35.9, 31.6, 18.8, 12.8 ppm.



3-Butyl-1-methyl-1H-imidazol-3-ium tetrafluoroborate, BMIM⁺BF₄⁻ (5.68).

Compound **5.67** (30.46 g, 174.4 mmol) was dissolved in 35 mL of H₂O in a 125-mL erlenmeyer flask with a stir bar and thermometer. NaBF₄ (20.16 g, 183.6 mmol) was added to the solution in portions with stirring over 15 min. The NaBF₄ dissolved and the solution cooled to ~15 °C during the addition. The solution was stirred until reaching ambient temperature (~21 °C), then CH₂Cl₂ (30 mL) was added. The layers were

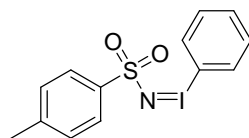
separated and the aqueous layer was extracted with CH₂Cl₂ (20 mL). The combined CH₂Cl₂ layers were washed with a solution of NaBF₄ (10 g in 20 mL of H₂O), dried over a mixture of Na₂SO₄ (1 g) and MgSO₄ (3 g), filtered, and concentrated by rotary evaporation (45 °C, 20 mm Hg). The resultant oil was dried under vacuum (~1 mm Hg) at ambient temperature for 24 h to yield **5.68** as a thick, colorless/light yellow oil (36.2 g, 92% yield). lit. 89% yield. ¹H NMR (300 MHz, CD₂Cl₂) δ 8.70 (s, 1H), 7.28 (dt, *J* = 6.0, 1.8 Hz, 2H), 4.13 (t, *J* = 7.2 Hz, 2H), 3.89 (s, 3H), 1.81 (m, 2H), 1.31 (sextet, *J* = 7.5 Hz, 2H), 0.91 (t, *J* = 7.5 Hz, 3H) ppm.



Benzyl 1-(4-methoxyphenyl)-2-phenyl-1H-imidazole-4-carboxylate (5.81).

Acrylate **5.24** (162.1 mg, 0.576 mmol) and azide **5.38b** (169.3 mg, 1.14 mmol) were dissolved in 5 mL of nitromethane in a single-necked 25-mL round-bottomed flask fitted with a stir bar and condenser. The solution was heated to reflux in an oil bath (oil temperature = 115 °C). The reaction was monitored by TLC (1:1 hexanes/EtOAc and 3:2 hexanes/EtOAc - UV lamp). The reaction color changed to deep brown overnight, but was incomplete. The reaction was still incomplete after 2 and 3 days at reflux. After heating for 4 days, no starting material was observed by TLC and the solution was cooled to rt and concentrated. The brown oil was chromatographed through 25 g of silica using a gradual solvent gradient from 100% CH₂Cl₂ to 85% CH₂Cl₂/EtOAc and yielded the major product **5.81** as an orange oil (46.3 mg, 21% yield). ¹H NMR (500 MHz, CDCl₃) δ

7.76 (s, 1H), 7.45 – 7.39 (m, 4H), 7.36 – 7.21 (m, 6H), 7.10 (m, 2H), 6.88 (m, 2H), 5.39 (s, 2H), 3.81 (s, 3H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 162.8, 159.6, 147.9, 136.2, 132.8, 130.4, 129.2, 128.9, 128.61, 128.57, 128.44, 128.38, 128.1, 126.9, 114.7, 66.2, 55.5 ppm. HRMS (FAB) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{21}\text{N}_2\text{O}_3^+$, 385.1552; obsd, 385.1532.



***N*-Tosyliminoisodosobenzene (5.82).** *p*-Toluenesulfonamide (3.405 g, 19.89 mmol) and KOH (3.30 g, 58.8 mmol) were dissolved in 30 mL of MeOH (exothermic). The solution was cooled in a crushed ice/ H_2O bath and became a white slurry that was hard to stir. About 10 mL of MeOH were added to the suspension. Iodobenzene diacetate (7.505 g, 23.30 mmol) was added to the vigorously stirred mixture in portions over about 5 min, maintaining an internal reaction temperature of less than 10 °C. The mixture turned yellow and most of the solid material dissolved. After about 5 minutes, white crystals were observed in the solution. The mixture was removed from the ice/ H_2O bath and stored in the refrigerator (about 5 °C) overnight. No solid was observed (except for the bit that did not dissolve) in the morning. The yellow solution was stirred at rt. After 30 min, yellow solid precipitated out of solution. The mixture was stirred for an additional 3 h at rt, then stored at 5 °C for 4 h. The solid was collected by filtration and **5.82** was obtained as an off-white solid (3.36 g, 45% yield). mp = 103-105 °C (dec.

violently). ^1H NMR (300 MHz, CDCl_3) δ 7.70 (m, 2H), 7.46 (m, 3H), 7.30 (m, 2H), 7.06 (m, 2H), 2.27 (s, 3H) ppm.

Attempted aziridination of acrylate **5.35 using iminoiodinane **5.82**.**

Anhydrous CH_3CN (10 mL) was added to a flame-dried single-necked 50-mL round-bottomed flask containing **5.35** (0.134 g, 1.04 mmol) and **5.82** (0.452 g, 1.21 mmol), under Ar. $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$ (21.9 mg, 0.0588 mmol) was added to the light yellow suspension. The color of the mixture changed immediately to a light lime-green color. After 2 min, most of the solid had dissolved and the mixture was a mint green color. The reaction flask was wrapped in foil and stirred at rt under Ar. After 2 h, the TLC of the reaction (1:1 hexanes/EtOAc - UV lamp) still showed mostly **5.35** and a two additional (faint) more nonpolar spots. The mixture was placed in an oil bath (oil temperature 55-60 $^\circ\text{C}$) and stirred under Ar. After stirring overnight, no change was observed and the oil bath temperature was raised to ~ 90 $^\circ\text{C}$. The reaction was heated to reflux overnight. No change by TLC. After heating for 4 days at reflux, no change was observed by TLC except for decomposition. Minor products were observed, but mostly starting material was left in the reaction.

Synthesis of imidazoles from oxazolines. Imidazole **5.40b from oxazoline**

3.10. Compound **3.10** (143.2 mg, 0.509 mmol) and benzyl azide (118.4 mg, 0.889 mmol) were dissolved in 5 mL of toluene in a 25-mL round-bottomed flask. *p*TsOH (24.0 mg, 0.139 mmol) was added and the solution was heated in an oil bath to reflux (oil temp ~ 123 $^\circ\text{C}$). The *p*TsOH did not seem to dissolve completely in the reaction. TLC analysis

of the reaction mixture (1:1 hexanes/EtOAc - UV lamp) indicated the reaction was complete after 4 days of reflux. The reaction was filtered, concentrated by rotary evaporation (40°C, 21 torr) and purified through 15 g of silica using a solvent gradient from 100% CH₂Cl₂ to 95% CH₂Cl₂/EtOAc and yielded **5.40b** as a brown/orange oil (92 mg, 49% yield).

8.5 Experimental procedures for chapter 6

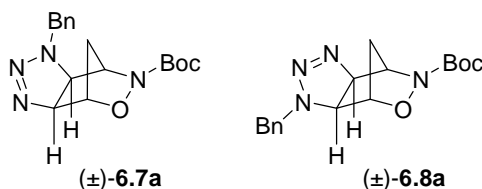
General Procedure for the Synthesis of Triazolines Using Method A. The alkene (1 mmol) and azide (1.5 mmol) were combined and stirred *neat* at 25 °C in a single-necked round-bottomed flask. The progress of the reaction was monitored by TLC or ¹H NMR for the disappearance of the alkene, and the crude material was purified through silica.

General Procedure for the Synthesis of Triazolines Using Method B. The alkene (1 mmol) and azide (1.5 mmol) were dissolved in 10 mL of CHCl₃ in a single-necked round-bottomed flask and stirred at 25 °C. The progress of the reaction was monitored by TLC or ¹H NMR for the disappearance of the alkene (typically 4 weeks), and the crude material was purified through silica.

General Procedure for the Synthesis of Triazolines Using Method C. The alkene (1 mmol) and azide (1.5 mmol) were dissolved in 10 mL of CHCl₃ in a single-

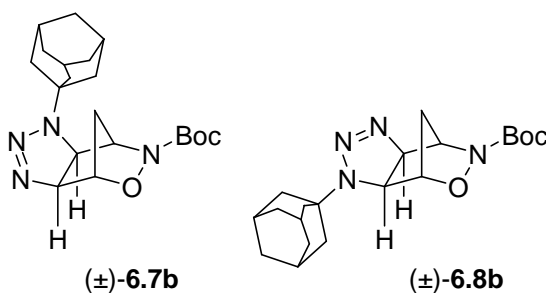
necked round-bottomed flask fitted with a condensor and heated to reflux in an oil bath (oil temp. = 80 °C). The progress of the reaction was monitored by TLC or ^1H NMR for the disappearance of the alkene (typically 3 days), and the crude material was purified through silica.

General Procedure for the Synthesis of Triazolines Using Method D. The alkene (1 mmol) and azide (1.5 mmol) were dissolved in 10 mL of PhCH_3 in a single-necked round-bottomed flask fitted with a condensor and heated to reflux in an oil bath (oil temp. = 125 °C). The progress of the reaction was monitored by TLC or ^1H NMR for the disappearance of the alkene (typically 3-4 h), and the crude material was purified through silica.



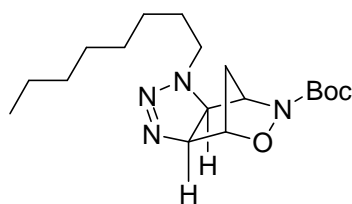
tert-Butyl (3 α ,4 β ,7 β ,7 α)-1-benzyl-3a,4,7,7a-tetrahydro-4,7-methano[1,2,3]triazole[4,5-d][1,2]oxazine-6(1*H*)-carboxylate (**6.7a**) and *tert*-butyl (3 α ,4 β ,7 β ,7 α)-3-benzyl-3a,4,7,7a-tetrahydro-4,7-methano[1,2,3]triazole[4,5-d][1,2]oxazine-6(3*H*)-carboxylate (**6.8a**). The title compounds were prepared following the general procedure for the synthesis of triazolines using Method A. Cycloadduct **3.38** (198 mg, 1.01 mmol) and benzyl azide (211 mg, 1.58 mmol) were reacted for 48 h. The brown crude material was purified through 15 g of silica using a solvent gradient of 100% CH_2Cl_2 to 98% $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ to afford triazoline **6.8a** (159 mg, 48% yield) as a

white solid, then 85% CH₂Cl₂/EtOAc to afford triazoline **6.7a** (170 mg, 51% yield) as a white solid (99% total combined yield). Analytical and x-ray crystallographic samples of **6.7a** and **6.8a** were prepared by recrystallization from EtOAc/hexanes. **6.7a**: mp = 104-105 °C. λ_{max} = 255 nm. ¹H NMR (500 MHz, CDCl₃) δ 7.37–7.27 (m, 5H), 4.92 (s, 1H), 4.90 (d, *J* = 14.5 Hz, 1H), 4.82 (d, *J* = 9.8 Hz, 1H), 4.72 (d, *J* = 14.5 Hz, 1H), 4.09 (s, 1H), 3.55 (d, *J* = 9.8 Hz, 1H), 1.70 (dt, *J* = 11.4, 1.5 Hz, 1H), 1.45 (d, *J* = 11.5 Hz, 1H), 1.39 (s, 9H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 156.4, 135.6, 128.8, 128.24, 128.17, 84.6, 82.6, 79.9, 61.2, 59.3, 53.4, 32.4, 27.9 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₇H₂₃N₄O₃⁺, 331.1770; obsd, 331.1745. **6.8a**: mp = 100-101 °C. λ_{max} = 255 nm. ¹H NMR (500 MHz, CDCl₃) δ 7.35-7.24 (m, 5H), 4.92 (d, *J* = 14.7 Hz, 1H), 4.85 (s, 1H), 4.84 (d, *J* = 9.9 Hz, 1H), 4.61 (d, *J* = 14.7 Hz, 1H), 4.09 (s, 1H), 3.50 (d, *J* = 9.9 Hz, 1H), 1.68 (d, *J* = 11.5 Hz, 1H), 1.45-1.43 (m, 10H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 156.4, 135.6, 128.8, 128.3, 128.2, 83.7, 82.7, 79.6, 61.5, 59.9, 53.6, 32.3, 27.9 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₇H₂₃N₄O₃⁺, 331.1770; obsd, 331.1753.

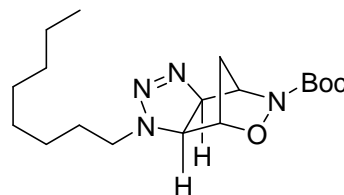


tert-Butyl (3α,4β,7β,7α)-1-(1-adamantyl)-3a,4,7,7a-tetrahydro-4,7-methano[1,2,3]triazole[4,5-d][1,2]oxazine-6(1*H*)-carboxylate (**6.7b**) and *tert*-butyl (3α,4β,7β,7α)-3-(1-adamantyl)-3a,4,7,7a-tetrahydro-4,7-methano[1,2,3]triazole[4,5-d][1,2]oxazine-6(3*H*)-carboxylate (**6.8b**). The title

compounds were prepared following the general procedure for the synthesis of triazolines using Method B. Cycloadduct **3.38** (104 mg, 0.527 mmol) and 1-azidoadamantane (140 mg, 0.79 mmol) were reacted for 4 weeks. The crude material was purified through 20 g of silica using a solvent gradient from 100% CH₂Cl₂ to 97% CH₂Cl₂/EtOAc to afford **6.8b** (86 mg, 43% yield) as a white solid, then 85% CH₂Cl₂/EtOAc to afford **6.7b** (102 mg, 52% yield) as a white solid (95% total combined yield). **6.7b**: mp > 144 °C (dec.). ¹H NMR (500 MHz, CDCl₃) δ 4.93 (s, 1H), 4.77 (dt, *J* = 9.5, 1.5 Hz, 1H), 4.42 (s, 1H), 3.85 (d, *J* = 9.5 Hz, 1H), 2.14-2.07 (m, 6H), 1.84-1.81 (m, 4H), 1.72-1.65 (m, 6H), 1.47 (m, 10H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 156.5, 83.2, 82.7, 80.4, 63.1, 57.2, 41.7, 36.0, 32.4, 29.2, 28.1 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₂₀H₃₁N₄O₃⁺, 375.2396; obsd, 375.2375. **6.8b**: mp > 166 °C (dec.). ¹H NMR (500 MHz, CDCl₃) δ 4.85 (m, 1H), 4.76 (dt, *J* = 10.0, 1.4 Hz, 1H), 4.49 (t, *J* = 1.4 Hz, 1H), 3.80 (dt, *J* = 10.0, 1.2 Hz, 1H), 2.12 (m, 2H), 2.03 (ddd, *J* = 11.6, 4.7, 3.0 Hz, 4H), 1.77 (m, 4H), 1.70-1.62 (m, 6H), 1.47 (m, 10H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 156.5, 82.782.3, 81.5, 61., 57.0, 56.7, 41.7, 36.0, 32.3, 29.2, 28.0 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₂₀H₃₁N₄O₃⁺, 375.2396; obsd, 375.2372.



(±)-**6.7c**



(±)-**6.8c**

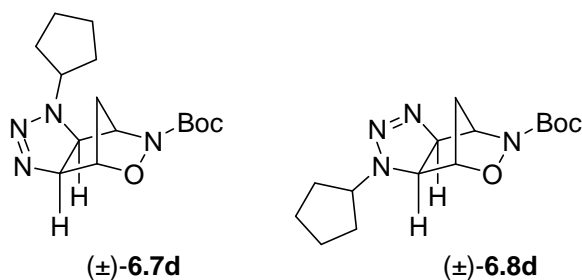
tert-Butyl

(3α,4β,7β,7α)-1-(*n*-octyl)-3a,4,7,7a-tetrahydro-4,7-

methano[1,2,3]triazole[4,5-d][1,2]oxazine-6(1*H*)-carboxylate (**6.7c**) and *tert*-butyl

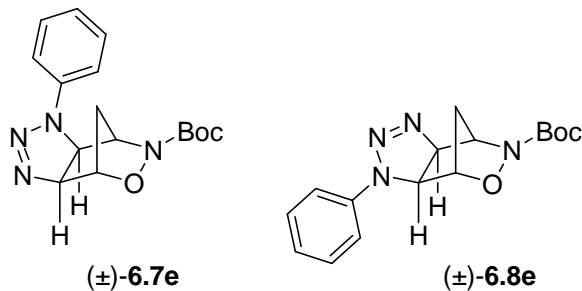
(3 α ,4 β ,7 β ,7 α)-3-(*n*-octyl)-3a,4,7,7a-tetrahydro-4,7-methano[1,2,3]triazole[4,5-d][1,2]oxazine-6(3*H*)-carboxylate (6.8c). The title compounds were prepared following the general procedure for the synthesis of triazolines using Method C. Cycloadduct **3.38** (199 mg, 1.01 mmol) and *n*-octyl azide (237 mg, 1.53 mmol) were reacted for 2 days. The crude material was purified through 40 g of silica using 80% hexanes/EtOAc to afford **6.8c** (124 mg, 35% yield), mixed **6.7c/6.8c** (192 mg, 54%), and **6.7c** (38 mg, 11% yield) as off-white semi-solids (99% total combined yield). **6.7c**: mp = 58-59 °C. ¹H NMR (500 MHz, CDCl₃) δ 4.97 (s, 1H), 4.87 (d, *J* = 9.5 Hz, 1H), 4.55 (s, 1H), 3.71-3.66 (m, 2H), 3.58-3.52 (m, 1H), 1.80 (dt, *J* = 11.5, 1.5 Hz, 1H), 1.70-1.64 (m, 2H), 1.50 (m, 10H), 1.33-1.24 (m, 12H), 0.88 (t, *J* = 7.0 Hz, 3H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 156.9, 84.0, 83.0, 80.2, 61.6, 60.1, 49.3, 32.4, 31.7, 29.7, 29.1, 28.8, 28.1, 26.7, 22.6, 14.1 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₈H₃₃N₄O₃⁺, 353.2553; obsd, 353.2525.

6.8c: mp = 49-50 °C. ¹H NMR (500 MHz, CDCl₃) δ 4.87 (m, 1H), 4.58 (s, 1H), 3.66-3.61 (m, 2H), 3.52-3.47 (m, 1H), 1.80 (dt, *J* = 11.5, 1.5 Hz, 1H), 1.61-1.58 (m, 2H), 1.48 (m, 10H), 1.30-1.24 (m, 12H), 0.86 (t, *J* = 7.0 Hz, 3H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 156.6, 83.0, 82.9, 80.0, 61.7, 60.1, 49.3, 32.4, 31.7, 29.0, 28.8, 28.1, 26.6, 22.6, 14.0 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₈H₃₃N₄O₃⁺, 353.2553; obsd, 353.2525.



tert-Butyl (3 α ,4 β ,7 β ,7 $\alpha\alpha$)-1-cyclopentyl-3a,4,7,7a-tetrahydro-4,7-methano[1,2,3]triazole[4,5-d][1,2]oxazine-6(1*H*)-carboxylate (**6.7d**) and *tert*-butyl (3 α ,4 β ,7 β ,7 $\alpha\alpha$)-3-cyclopentyl-3a,4,7,7a-tetrahydro-4,7-methano[1,2,3]triazole[4,5-d][1,2]oxazine-6(3*H*)-carboxylate (**6.8d**). The title compounds were prepared following the general procedure for the synthesis of triazolines using Method C. Cycloadduct **3.38** (201 mg, 1.02 mmol) and 1-azidocyclopentane (155 mg, 1.39 mmol) were reacted for 2 days. The crude material was purified through 30 g of silica using 80% hexanes/EtOAc to afford **6.8d** (88 mg, 28% yield) as a white solid, mixed **6.7d/6.8d** (194 mg, 62%) as an off-white solid, and **6.7d** (25 mg, 8% yield) as a colorless oil (97% total combined yield).

6.7d: mp >70 °C (dec.). ¹H NMR (500 MHz, CDCl₃) δ 4.96 (s, 1H), 4.85 (d, *J* = 9.5 Hz, 1H), 4.52 (s, 1H), 4.05 (p, *J* = 7.0 Hz, 1H), 3.70 (d, *J* = 9.5 Hz, 1H), 2.08-1.92 (m, 2H), 1.83-1.62 (m, 8H), 1.49 (m, 10H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 156.7, 83.7, 82.9, 80.3, 62.1, 60.9, 59.4, 32.5, 31.6, 31.1, 28.1, 23.6, 23.4 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₅H₂₅N₄O₃⁺, 309.1927; obsd, 309.1913. **6.8d**: mp > 120 °C (dec.). ¹H NMR (500 MHz, CDCl₃) δ 4.84 (s, 1H), 4.81 (d, *J* = 9.5 Hz, 1H), 4.55 (s, 1H), 3.97 (p, *J* = 7.0 Hz, 1H), 3.61 (d, *J* = 9.5 Hz, 1H), 2.02-1.95 (m, 1H), 1.87-1.83 (m, 1H), 1.78-1.57 (m, 7H), 1.45-1.42 (m, 10H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 156.5, 82.8, 82.7, 80.4, 61.6, 60.8, 59.8, 32.3, 31.5, 31.1, 28.0, 23.5, 23.3 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₅H₂₅N₄O₃⁺, 309.1927; obsd, 309.1913.



tert-Butyl (3 α ,4 β ,7 β ,7 α)-1-phenyl-3a,4,7,7a-tetrahydro-4,7-methano[1,2,3]triazole[4,5-d][1,2]oxazine-6(1*H*)-carboxylate (**6.7e**) and *tert*-butyl (3 α ,4 β ,7 β ,7 α)-3-phenyl-3a,4,7,7a-tetrahydro-4,7-methano[1,2,3]triazole[4,5-d][1,2]oxazine-6(3*H*)-carboxylate (**6.8e**). The title compounds were prepared following the general procedure for the synthesis of triazolines using Method D. Cycloadduct **3.38** (202 mg, 1.02 mmol) and phenyl azide (165 mg, 1.39 mmol) were reacted for 3 h. The crude material was purified through 35 g of silica using 100% CH₂Cl₂ to afford **6.8e** (175 mg, 54% yield) as a light yellow solid, then 80% CH₂Cl₂/EtOAc to afford **6.7e** (144 mg, 45% yield) as a light yellow oil that solidified upon standing (99% total combined yield).

6.7e: mp = 117-120 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.41-7.35 (m, 4H), 7.10 (t, *J* = 7.0 Hz, 1H), 5.09 (d, *J* = 10.0 Hz, 1H), 5.085 (s, 1H), 4.86 (s, 1H), 4.46 (d, *J* = 10.0 Hz, 1H), 1.91 (dt, *J* = 12.0, 2.0 Hz, 1H), 1.54 (m, 10H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 156.4, 139.3, 129.6, 123.0, 113.8, 83.9, 83.2, 79.7, 60.2, 57.1, 32.2, 28.0 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₆H₂₁N₄O₃⁺, 317.1614; obsd, 317.1622. **6.8e**: mp > 158 °C (dec.). ¹H NMR (500 MHz, CDCl₃) δ 7.37 (t, *J* = 8.0 Hz, 3H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.08 (t, *J* = 7.5 Hz, 1H), 5.10 (d, *J* = 9.5 Hz, 1H), 5.02 (s, 1H), 4.92 (s, 1H), 4.24 (d, *J* = 9.5 Hz, 1H), 1.86 (dt, *J* = 12.0, 2.0 Hz, 1H), 1.54 (m, 10H) ppm. ¹³C NMR (125

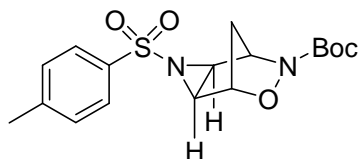
MHz, CDCl₃) δ 156.6, 139.4, 129.7, 123.1, 113.9, 83.2, 78.7, 61.4, 58.0, 32.3, 28.1 ppm.

HRMS (FAB) m/z [M+H]⁺ calcd for C₁₆H₂₁N₄O₃⁺, 317.1614; obsd, 317.1605.

Attempted formation of aziridine 6.9 directly from cycloadduct 3.38.

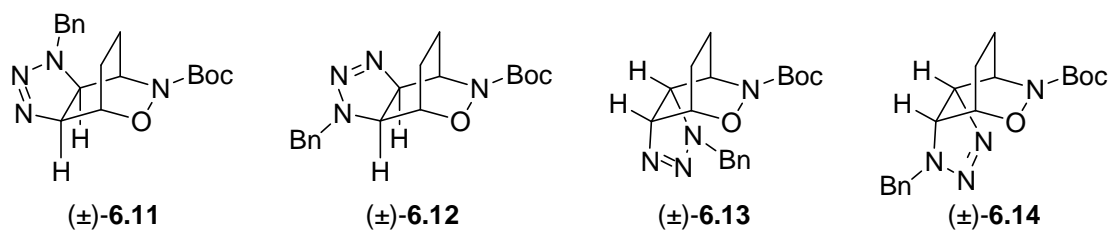
Compound **3.38** (197.0 mg, 0.9988 mmol) was dissolved in 10 mL of toluene in a 50-mL round-bottomed flask. Azidotrimethylsilane (0.20 mL, 1.5 mmol) was added and the reaction was heated to reflux (oil bath temp ~125°C) for 4 h. The reaction was concentrated by rotary evaporation (~20 torr, ~40°C) to yield an amber oil. No triazoline or aziridine products were observed by TLC or NMR.

Second reaction attempt without heating: A 1-dram screw-cap vial was charged with **3.38** (21 mg, 0.10 mmol) and dissolved in 1 mL of CDCl₃. Azidotrimethylsilane (21 μ L, 0.16 mmol) was added and the solution was stirred at rt. The reaction was monitored by ¹H NMR after 3, 7, 14, 22, and 28 days. No reaction was observed.



(±)-*tert*-Butyl (1 α ,2 β ,4 β ,5 α)-3-[(4-methylphenyl)sulfonyl]-6-oxa-3,7-diazatricyclo[3.2.1.0^{2,4}]octane-7-carboxylate (**6.10**). Cycloadduct **3.38** (205 mg, 1.04 mmol) and tosyl azide (268 mg, 1.36 mmol) were dissolved in 10 mL of PhCH₃ in a 25-mL single-necked round-bottomed flask fitted with a condenser and heated to reflux in an oil bath (oil temperature = 125 °C). The reaction was monitored by TLC (1:1 hexanes/EtOAc; UV lamp) for the disappearance of **3.38**. After 9 h, the reaction was complete and the solution was concentrated to yield a brown oil. The oil was purified

through 35 g of silica using a solvent gradient from 100% CH₂Cl₂ to 90% CH₂Cl₂/EtOAc to yield **6.10** as a tan solid (263 mg, 69% yield). mp = 111-115 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 4.78 (s, 1H), 4.62 (s, 1H), 3.26 (d, *J* = 6.0 Hz, 1H), 3.22 (d, *J* = 6.0 Hz, 1H), 2.40 (s, 3H), 2.01 (d, *J* = 11.0 Hz, 1H), 1.44 (s, 10H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 156.6, 145.0, 133.9, 129.7, 127.8, 82.9, 78.1, 59.4, 36.5, 36.2, 29.0, 27.9, 21.5 ppm. MS (FAB) *m/z* [M+H]⁺ at 367, 311, 267 (100%). HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₇H₂₃N₂O₅S⁺, 367.1328; obsd, 367.1314.

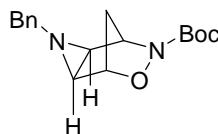


Reaction of 3.39 With Benzyl Azide: Formation of triazolines 6.11, 6.12, 6.13, and 6.14. Compound **3.39** (421 mg, 1.99 mmol) and benzyl azide (1.33 g, 9.97 mmol) were dissolved in 10 mL of toluene in a 25-mL single-necked round-bottomed flask fitted with a condenser and heated to reflux in an oil bath (oil temp. = 125 °C). The reaction was monitored by TLC (1:1 hexanes/EtOAc; UV lamp) for the disappearance of **3.39**. After 28 h, the deep brown solution was concentrated to yield a brown oil. The oil was chromatographed through silica using a solvent gradient from 100% hexanes to 50% hexanes/EtOAc to afford **6.12** (136 mg, 20% yield), **6.11** (128 mg, 19% yield), and an inseparable mixture of **6.13** and **6.14** (163 mg, 24% yield), all as brown solids (62% total combined yield). **6.11**: ¹H NMR (500 MHz, CDCl₃) δ 7.38-7.30 (m, 5H), 4.99 (ddd, *J* =

13.0, 4.5, 1.5 Hz, 1H), 4.85 (d, $J = 14.5$ Hz, 1H), 4.77 (d, $J = 14.5$ Hz, 1H), 4.54 (t, $J = 4.0$ Hz, 3.83 (br-s, 1H), 3.63 (dd, $J = 13.0, 4.0$ Hz, 1H), 1.98-1.90 (m, 1H), 1.76-1.70 (m, 1H), 1.63 (tdd, $J = 13.8, 4.2, 2.5$ Hz, 1H), 1.52-1.46 (m, 1H), 1.43 (m, 10H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 155.4, 132.9, 128.8, 128.5, 128.2, 81.9, 78.1, 69.5, 53.5, 47.2, 28.1, 19.6, 18.5 ppm. HRMS (FAB) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{25}\text{N}_4\text{O}_3^+$, 345.1927; obsd, 345.1931. **6.12:** ^1H NMR (500 MHz, CDCl_3) δ 7.32-7.21 (m, 5H), 4.90 (ddd, $J = 12.5, 4.0, 1.0$ Hz, 1H), 4.75 (d, $J = 14.5$ Hz, 1H), 4.66 (d, $J = 14.5$ Hz, 1H), 4.45 (m, 1H), 3.71 (m, 1H), 3.60 (dd, $J = 12.5, 4.5$ Hz, 1H), 1.86-1.80 (m, 1H), 1.77-1.70 (m, 1H), 1.55-1.49 (m, 1H), 1.47-1.43 (m, 1H), 1.42 (m, 10H) ppm. ^{13}C NMR (125 MHz, CDCl_3) δ 155.7, 134.9, 128.9, 128.7, 128.4, 82.1, 78.4, 70.3, 54.2, 54.1, 47.6, 47.6, 28.2, 20.2, 17.9 ppm; HRMS (FAB) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{25}\text{N}_4\text{O}_3^+$, 345.1927; obsd, 345.1931. **6.13** and **6.14** were obtained as ~1:1 mixture as evidenced by ^1H NMR. HRMS (FAB) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{25}\text{N}_4\text{O}_3^+$, 345.1927; obsd, 345.1931.

General procedure for the addition of benzyl azide to other alkenes (3.73, 3.74, 3.77, 3.40, and 6.15). Benzyl azide (1.5 equivalents or greater) was heated with the alkene (1 equivalent) in toluene or neat. Reactions were monitored by ^1H NMR and TLC for consumption of the alkene starting material. When alkene **3.73** was heated with 1.5 eq. of BnN_3 in toluene at reflux for 2 days, a complex mixture of triazoline products were observed by ^1H NMR; however, the reaction did not progress to completion. All other alkenes examined resulted in no reaction.

General procedure for investigation of the effect of Ru(II) catalyst **6.16 on azide [3+2] cycloaddition reactions.** Cycloadduct **3.38** or **3.40** (1 mmol) and benzyl azide (1.2 – 1.5 mmol) were dissolved in 10 mL of benzene in a 50-mL round-bottomed flask equipped with a stir bar and condenser. Catalyst **6.16** (0.05 mmol) was added to the reaction and the mixture was stirred at rt. Control reactions were performed as described above without the addition of catalyst **6.16**. The reaction was monitored by TLC for the disappearance of cycloadduct **3.38** or **3.40**. After 1 h, no reaction was observed and the reaction was stirred in a 55 °C oil bath for 3 days. The reaction was incomplete at this time. The mixture was heated to reflux (oil bath temperature = 85 °C) for 6 h and the mixture was concentrated. The residue was analyzed by TLC and ^1H NMR. % conversion was determined by ^1H NMR.



General Procedure for Photolysis of Triazolines. (\pm)-*tert*-Butyl (1 α ,2 β ,4 β ,5 α)-3-benzyl-6-oxa-3,7-diazatricyclo[3.2.1.0^{2,4}]octane-7-carboxylate (**6.17**). Compound **6.7a** (333 mg, 1.01 mmol) was dissolved in 300 mL of degassed CH_3CN and transferred to a 450-mL photochemical reaction vessel. The solution was irradiated in an immersion-well reactor under a stream of Ar with a Hanovia 450W mercury lamp equipped with a Vycor filter sleeve. Reaction progress was monitored by TLC and ^1H NMR for the disappearance of **6.7a**. After 3 h, the reaction was concentrated and the crude material was purified through 30 g of silica using a gradient consisting of 100% CH_2Cl_2 to 95% $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ to afford **6.17** as a colorless oil (205 mg, 67% yield). ^1H

NMR (500 MHz, CDCl₃) δ 7.35-7.27 (m, 5H), 4.79 (m, 1H), 4.62 (m, 1H), 3.40 (d, J = 13.5 Hz, 1H), 3.35 (d, J = 14.0 Hz, 1H), 2.29-2.22 (m, 3H), 1.50 (s, 9H), 1.39 (d, J = 10.5 Hz, 1H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 157.5, 138.6, 128.4, 127.7, 127.3, 82.3, 79.9, 60.7, 59.1, 37.1, 36.7, 29.4, 28.2 ppm. MS (FAB) m/z [M+H]⁺ at 303, 247, 203, 171 (100%). HRMS (FAB) m/z [M+H]⁺ calcd for C₁₇H₂₃N₂O₃⁺, 303.1709; obsd, 303.1712.

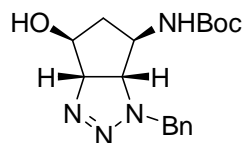
Attempted photolytic conversion of triazoline 6.7a to aziridine 6.17 using TPP as a sensitizer. Compound **6.7a** (100.6 mg, 0.305 mmol) and tetraphenylporphyrin (TPP, 1.9 mg, 0.0031 mmol) were dissolved in 10 mL of anhydrous CH₃CN and 2 mL of CH₂Cl₂ (to help solubilize the TPP). The solution was degassed with Ar for 5 min, then irradiated using a 250-W sunlamp while bubbling the solution with Ar. After 30 min, the heat of the sunlamp had melted the ice bath, part of the outlet needle, and the upper portion of the rubber septum (it made a big mess...). Only the triazoline **6.7a** and TPP were observed when the reaction mixture (now a darker purple color) was analyzed by TLC (1:1 hexanes/EtOAc - UV lamp, CAM stain). None of the desired product was observed, and no obvious decomposition of starting materials was observed either.

Attempted conversion of triazoline 6.7a to aziridine 6.17 with pyridine. Compound **6.7a** (101 mg, 0.306 mmol) was dissolved in 3 mL of toluene in a 25-mL round-bottomed flask. Pyridine (0.030 mL, 0.37 mmol) was added and the solution was heated to reflux (oil bath temp ~125 °C). After ~5 h, TLC of the reaction did not indicate the presence of aziridine **6.17**, and only showed starting material **6.7a** (1:1

hexanes/EtOAc - UV lamp). The reaction was heated at reflux overnight. Even when heated neat overnight, no reaction was observed.

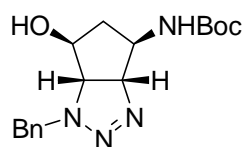
Attempted conversion of triazoline 6.7a to aziridine 6.17 using TMSOTf.

Compound **6.7a** (80.2 mg, 0.243 mmol) was dissolved in 2 mL of CHCl₃ in a 20-mL scintillation vial under Ar. TMSOTf (0.010 mL, 0.052 mmol) was added and the solution was stirred under Ar at RT. After 1 h, the initially yellow solution appeared slightly darker, however TLC of the reaction (1:1 hexanes/EtOAc - UV lamp) only showed triazoline **6.7a** plus a minor amount of decomposition.



General procedure for N-O bond reduction of triazolines using Mo(CO)₆/NaBH₄. (±)-*tert*-Butyl (3α,4α,6α,6α)-3-benzyl-6-hydroxy-3,3a,4,5,6,6a-hexahydrocyclopenta[d][1,2,3]triazol-4-ylcarbamate (**6.19**). Triazoline **6.7a** (207 mg, 0.628 mmol) was dissolved in 5 mL of 4:1 CH₃CN/H₂O in a 25-mL single-necked round-bottomed flask and heated in a 50 °C oil bath. Molybdenum hexacarbonyl (72 mg, 0.27 mmol) was added to the solution in one portion, followed by sodium borohydride (80 mg, 2.1 mmol) added in portions. Bubbling was observed and the color of the reaction changed from light yellow to a deep, murky brown. After the bubbling subsided, the reaction was heated to reflux (oil temperature = 70 °C) and monitored by TLC (1:1 hexanes/EtOAc; UV lamp) for the disappearance of **6.7a**. After 18 h, the reaction was cooled in a crushed ice/H₂O bath and the solid material was removed by filtration through

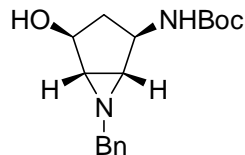
a pad of celite. The celite was washed with EtOAc (20 mL) and the filtrate was concentrated to yield an off-white solid, which was purified through 20 g of silica using 50% hexanes/EtOAc to afford **6.19** as a white solid (123 mg, 59% yield). mp = 153-155 °C (dec.). ¹H NMR (300 MHz, CDCl₃) δ 7.34-7.28 (m, 5H), 5.60 (d, *J* = 9.0 Hz, 1H), 5.15 (d, *J* = 15.0 Hz, 1H), 4.78 (d, *J* = 10.8 Hz, 1H), 4.63 (d, *J* = 15.0 Hz, 1H), 4.51 (d, *J* = 4.2 Hz, 1H), 4.11 (m, 1H), 3.66 (d, *J* = 10.8 Hz, 1H), 1.76 (d, *J* = 14.4 Hz, 1H), 1.55-1.49 (m, 1H), 1.43 (s, 9H) ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₇H₂₅N₄O₃⁺, 333.1927; obsd, 333.1906.



(±)-*tert*-Butyl

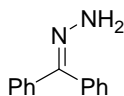
(3α,4α,6α,6α)-1-benzyl-6-hydroxy-1,3a,4,5,6,6a-

hexahydrocyclopenta[d][1,2,3]triazol-4-ylcarbamate (**6.20**). Compound **6.20** was prepared following the same procedure for **6.19**. **6.8a** (506 mg, 1.53 mmol), molybdenum hexacarbonyl (181 mg, 0.686 mmol) and NaBH₄ (220 mg, 5.8 mmol) provided an amber foam (540 mg). Chromatography through 10 g of silica using 83% CH₂Cl₂/EtOAc yielded **6.20** as a light yellow solid (295 mg, 58% yield). mp > 110 °C (dec.). ¹H NMR (500 MHz, CDCl₃) δ 7.30-7.20 (m, 5H), 5.63 (br-m, 1H), 4.91-4.85 (m, 2H), 4.63 (d, *J* = 15.0 Hz, 1H), 4.21 (t, *J* = 8.0 Hz, 1H), 4.07 (d, *J* = 4.0 Hz, 1H), 3.64 (d, *J* = 10.5 Hz, 1H), 1.69 (d, *J* = 14.0 Hz, 1H), 1.53 (br-s, 1H), 1.39 (s, 10H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 155.1, 136.0, 128.7, 128.2, 127.9, 89.4, 79.6, 76.0, 66.9, 56.7, 52.9, 37.8, 28.4 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₇H₂₅N₄O₃⁺, 333.1927; obsd, 333.1930.

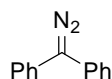


(±)-*tert*-Butyl (1 α ,2 α ,4 α ,5 α)-6-benzyl-4-hydroxy-6-aza-bicyclo[3.1.0]hexan-2-ylcarbamate (6.21). Triazoline **6.19** (108 mg, 0.323 mmol) was dissolved in 300 mL of degassed CH₃CN in a 450-mL photochemical reaction reaction vessel. The solution was irradiated in an immersion-well reactor under a stream of Ar with a Hanovia 450W mercury lamp fitted with a Vycor filter sleeve. The progress of the reaction was monitored by ¹H NMR. After 5 h, the solution was concentrated (40 °C, 21 torr) to yield an amber oil (110 mg). The oil was chromatographed through a pad of silica using a solvent gradient from 100% CH₂Cl₂ to 40% CH₂Cl₂/EtOAc and yielded **6.21** as a yellow oil (89.9 mg, 91% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.32-7.23 (m, 5H), 5.16 (m, 1H), 4.26 (d, *J* = 5.0 Hz, 1H), 4.08 (t, *J* = 7.5 Hz, 1H), 3.52 (d, *J* = 14 Hz, 1H), 3.32 (d, *J* = 14 Hz, 1H), 2.30 (m, 2H), 2.05 (m, 1H), 1.47 (d, *J* = 15 Hz, 1H), 1.43 (s, 9H), 1.25 (m, 1H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 155.4, 138.7, 128.3, 127.3, 126.9, 71.8, 60.7, 51.0, 48.4, 47.6, 39.8, 29.6, 28.3 ppm. HRMS (FAB) *m/z* [M]⁺ calcd for C₁₇H₂₄N₂O₃⁺, 304.1787; obsd, 304.1785.

8.6 Experimental procedures for chapter 7



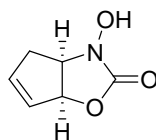
(Diphenylmethylene)hydrazine (7.12). Benzophenone (10.099 g, 55.323 mmol) was dissolved in 60 mL of absolute EtOH in a 250-mL round-bottomed flask. The solution was heated in a 50 °C oil bath and hydrazine monohydrate (4.10 mL, 82.8 mmol) was added. A condenser was attached to the flask and the colorless solution was heated to reflux (oil bath temp = 100 °C) overnight. After 16 h, the reaction was cooled to rt and the colorless solution was concentrated to yield a white solid. The solid was recrystallized from absolute EtOH to yield **7.12** as white needles (6.17 g, 57%). mp = 96-98 °C (lit.² 97-98 °C).



Diphenyldiazomethane (7.13). **7.12** (2.011 g, 10.25 mmol) was dissolved in 20 mL of anhydrous CH₂Cl₂ in a 100-mL round-bottomed flask and cooled in an ice/H₂O bath under Ar. Anhydrous MgSO₄ (3.21 g, 26.7 mmol) was added and the mixture was stirred vigorously. A blast shield was placed in front of the reaction as a precautionary measure as activated MnO₂ (88%, 1.187 g, 12.02 mmol) was added in one portion to the reaction. The reddish-purple suspension was stirred in the ice/H₂O bath for 2 h, then warmed to rt and stirred an additional 1 h. The solid material was removed by vacuum

filtration and washed with CH₂Cl₂. The filtrate was concentrated by rotary evaporation (~20 torr, ~30°C) to yield crude **7.13** as a deep purple-colored solid (2.02 g). The solid was stored in the freezer (-10°C) under Ar. The crude mixture of **7.13** was used without purification in further reactions.

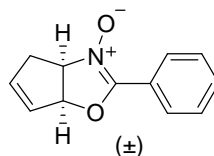
Treatment of cycloadduct 3.38 with diphenyldiazomethane. Compound **3.38** (207.8 mg, 1.054 mmol) and crude **7.13** (388 mg, 2.00 mmol) were dissolved in 5 mL of benzene in a 25-mL round-bottomed flask under Ar. The purple solution was purged with Ar and stirred at rt in the dark (covered in foil). The reaction was monitored by TLC (1:1 and 2:1 hexanes/EtOAc - UV lamp), and after 3 days the reaction appeared to be progressing; however, there was still a lot of starting material (**3.38**) in the reaction. After 10 days, the reaction was concentrated and a crude ¹H NMR of the residue indicated that the reaction was progressing. After stirring for another week, **3.38** was completely consumed.



(±)-(3aR,6aS)-3-Hydroxy-3a,4-dihydro-3H-cyclopenta[d]oxazol-2(6aH)-one (7.34). Initial preparation using un-purified dimethyl sulfate. Compound **3.38** (100.2 mg, 0.5080 mmol) was dissolved in 5 mL of anhydrous CH₂Cl₂ in a flame-dried single-necked 25-mL round-bottomed flask under Ar. Dimethyl sulfate (0.10 mL, 1.1 mmol, not distilled prior to use) was added and bubbling was observed. After 5 min, the bubbling had ceased and the reaction was analyzed by TLC (1:1 hexanes/EtOAc - UV

lamp, CAM stain). After 4 h, no cycloadduct was observed and anhydrous methanol (0.20 mL, 4.9 mmol) was added to the reaction. After 1 h, there was no change by TLC and the reaction was stirred overnight at rt under Ar. The reaction was concentrated and the residue was purified through 15 g of silica using a solvent gradient from 100% CH₂Cl₂ to 50% CH₂Cl₂/EtOAc and yielded **7.34** as a white solid (37.6 mg, 52% yield). Hydroxamate **7.34** was insoluble in CH₂Cl₂ and CHCl₃, sparingly soluble in MeOH, and soluble in DMSO and H₂O. See below for full characterization data.

Optimized synthesis of hydroxamate (±)-7.34 using catalytic triflic acid (TfOH). Cycloadduct **3.38** (1.07 g, 5.40 mmol) was dissolved in 50 mL of anhydrous THF in a 200-mL round-bottomed flask that was rinsed with concentrated HCl (2x), washed with H₂O, and acetone, then flame-dried under Ar. The solution was cooled in a crushed ice/H₂O bath under Ar and trifluoromethanesulfonic acid (0.010 mL, 0.11 mmol) was added. The solution was stirred in the ice/H₂O bath under Ar and monitored by TLC (1:1 hexanes/EtOAc - UV lamp, CAM stain). After 1 h, the reaction was complete and the solution was warmed to rt and concentrated by rotary evaporation to a yellow oil. The oil was triturated with Et₂O (50 mL) to yield pure **7.34** as a white powdery solid (0.562 g, 74% yield). ¹H NMR (500 MHz, d⁶-DMSO, 40 °C) δ 9.72 (s, 1H), 6.12 (d, *J* = 5.0 Hz, 1H), 5.85 (d, *J* = 5.0 Hz, 1H), 5.41 (d, *J* = 7.0 Hz, 1H), 4.34 (t, *J* = 6.0 Hz, 1H), 2.54 (m, 2H) ppm. ¹³C NMR (125 MHz, d⁶-DMSO, 40 °C) δ 156.1, 135.9, 128.2, 81.4, 59.3, 36.1 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₆H₈NO₃⁺, 142.0504; obsd, 142.0521.



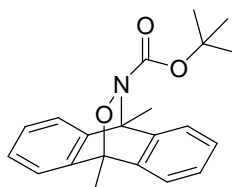
General procedure for the investigation of nitron formation under acid catalysis. (±)-(3a*R*,6a*S*)-2-Phenyl-4,6a-dihydro-3a*H*-cyclopenta[*d*]oxazole 3-oxide (**7.50**). Cycloadduct **7.49** (0.104 g, 0.517 mmol) was dissolved in 10 mL of anhydrous CH₂Cl₂ under Ar in a flame-dried single-necked 50-mL round-bottomed flask. Triflic acid (0.050 mL, 0.56 mmol) was added and the solution was stirred at rt and monitored by TLC. After 15 min, no starting material was observed by TLC (1:1 hexanes/EtOAc - UV lamp) and a new, more nonpolar spot was observed. Saturated NaHCO₃ (5 mL) was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (2 x 5 mL) and the combined organic layers were dried over Na₂SO₄, filtered, and concentrated to yield an off-white residue. The residue was chromatographed through 10 g of silica using 100% CH₂Cl₂ and yielded **7.50** as a yellow residue (19.5 mg, 20% yield). R_f = 0.48 (1:1 hexanes/EtOAc – UV lamp). ¹H NMR (300 MHz, CDCl₃) δ 7.85 (dd, *J* = 8.1, 1.3 Hz, 2H), 7.41 (m, 3H), 6.09 (dd, *J* = 5.7, 1.8 Hz, 1H), 5.97 (dd, *J* = 6.0, 1.8 Hz, 1H), 5.37 (m, 1H), 4.39 (q, *J* = 3.9 Hz, 1H), 2.71 (m, 2H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ 172.6, 133.9, 130.7, 129.6, 128.2, 125.9, 81.8, 72.0, 37.4 ppm. HRMS (FAB) *m/z* [M+H]⁺ calcd for C₁₂H₁₂NO₂⁺, 202.0868; obsd, 202.0869.

Attempted homo-Diels-Alder reaction with norbornadiene by direct oxidation of hydroxamate using NaIO₄. A solution of **3.37** (47.5 mg, 0.357 mmol) in 2.8 mL of MeOH/H₂O (4:1) was cooled to 0 °C (ice/H₂O bath). Norbornadiene (0.045 mL, 0.442 mmol) was added (did not dissolve), followed by the dropwise addition of a

solution of sodium periodate (84.5 mg, 0.395 mmol) in 1.5 mL of H₂O over 5 min using a syringe. White solid was observed in the reaction and the mixture was stirred in the ice/H₂O bath for 1.5 h. The mixture was diluted with H₂O (20 mL), saturated with NaCl, and extracted with EtOAc (5 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over MgSO₄, filtered, and concentrated to yield a light yellow oil (19 mg). NMR analysis did not indicate the formation of the desired adduct and was inconclusive.

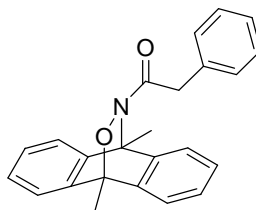
Attempted homo-Diels-Alder reaction with norbornadiene by direct oxidation of hydroxamate using Swern oxidation. Compound **3.37** (44.3 mg, 0.333 mmol) was dissolved in 5.1:1 CH₂Cl₂/DMSO under Ar and cooled to -78 °C in a dry ice/acetone bath. In a separate flask, 1.6 mL of CH₂Cl₂ was cooled to -78 °C and oxalyl chloride (0.12 mL, 1.40 mmol) was added followed by DMSO (0.15 mL, 2.11 mmol). This mixture was stirred for 5 min, then transferred to the flask containing **3.37** via cannula over 3-4 min. A yellow color was observed and the resultant solution was stirred at -78 °C for 20 min under Ar. Triethylamine (0.48 mL, 3.45 mmol) was added slowly over 5 min and the mixture was stirred at -78 °C for 5 min before slowly warming to rt. Et₂O (10 mL), EtOAc (7 mL), and 1M HCl (7 mL) were added to the mixture and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 10 mL) and the combined organic layers were washed with saturated NaHCO₃ (2 x 15 mL) and brine (2 x 15 mL), dried over MgSO₄, filtered, and concentrated to yield a yellow oil (25 mg). NMR analysis did not indicate the formation of the desired adduct and was inconclusive.

Attempted homo-Diels-Alder reaction with norbornadiene by direct oxidation of hydroxamate using Dess-Martin periodinane. Compound **7.65** (66.0 mg, 0.437 mmol) was dissolved in THF (4.5 mL) under Ar. Norbornadiene (0.050 mL, 0.492 mmol) was added and the solution was cooled to -78 °C in a dry ice/acetone bath. Dess-Martin periodinane (0.48M in CH₂Cl₂, 1.05 mL, 0.504 mmol) was added dropwise over 3 min and the mixture was stirred at -78 °C for 35 min under Ar, then warmed to rt and stirred for an additional 4 h. Saturated NaHCO₃ (5 mL) and saturated Na₂S₂O₃ (5 mL) were added and the mixture was stirred for 10 min until all of the solid material dissolved completely. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 15 mL). The combined organic layers were washed with saturated NaHCO₃ (2 x 40 mL) and brine (2 x 40 mL), dried over MgSO₄, filtered, and concentrated to yield a white solid (36 mg). NMR analysis did not indicate the formation of the desired adduct and was inconclusive.

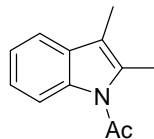


General procedure for cycloaddition reactions with 9,10-Dimethylantracene using Bu₄NIO₄. Cycloadduct 7.67. Tetrabutylammonium periodate (0.204 g, 0.471 mmol) and 9,10-dimethylantracene (80.8 mg, 0.392 mmol) were dissolved in 1 mL of CHCl₃ and cooled in an ice/H₂O bath. A solution of **3.37** (62.4 mg, 0.469 mmol) in 0.25 mL of DMF was added dropwise over 3 min. The resultant mixture was stirred in the ice/H₂O bath for 25 min, then at rt for an additional 1.5 h. The reaction was poured into

10 mL of EtOAc and washed with saturated $\text{Na}_2\text{S}_2\text{O}_3$ (2 x 10 mL), H_2O (10 mL), and brine (2 x 10 mL), dried over MgSO_4 , filtered, and concentrated to yield a yellow solid (204 mg). Chromatography through 20 g of silica using 3:2 CH_2Cl_2 /hexanes yielded **7.67** as a yellow solid (80.3 mg, 61% yield). Product obtained is 90% pure by NMR and contains 10% 9,10-dimethylantracene. ^1H NMR (300 MHz, CDCl_3) δ 7.45 (dd, $J = 5.9$, 2.9 Hz, 2H), 7.37 (dd, $J = 5.1$, 3.4 Hz, 2H), 7.25 (dd, $J = 5.6$, 3.4 Hz, 4H), 2.57 (s, 3H), 2.23 (s, 3H), 1.22 (s, 9H) ppm.



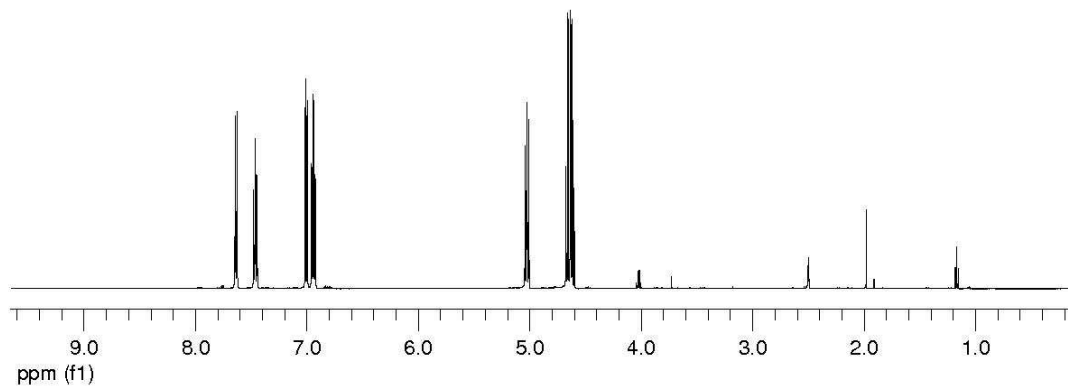
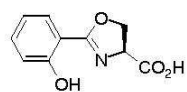
9,10-Dimethylantracene cycloadduct 7.68. Compound **7.68** was prepared following the same procedure for **7.67**. Hydroxamic acid **7.65** (71.1 mg, 0.470 mmol), 9,10-dimethylantracene (80.7 mg, 0.391 mmol), and tetrabutylammonium periodate (0.203 g, 0.469 mmol) provided a yellow oil. Chromatography through 30 g of silica using a solvent gradient from 2:1 to 3:1 CH_2Cl_2 /hexanes yielded **7.68** as a yellow oil (62.6 mg, 45% yield). ^1H NMR (300 MHz, CDCl_3) δ 7.49 (d, $J = 6.9$ Hz, 2H), 7.31 – 7.12 (m, 6H), 7.12 (d, $J = 6.3$ Hz, 3H), 6.82 (dd, $J = 7.5$, 1.8 Hz, 2H), 3.54 (s, 2H), 2.75 (s, 3H), 2.07 (s, 3H) ppm.



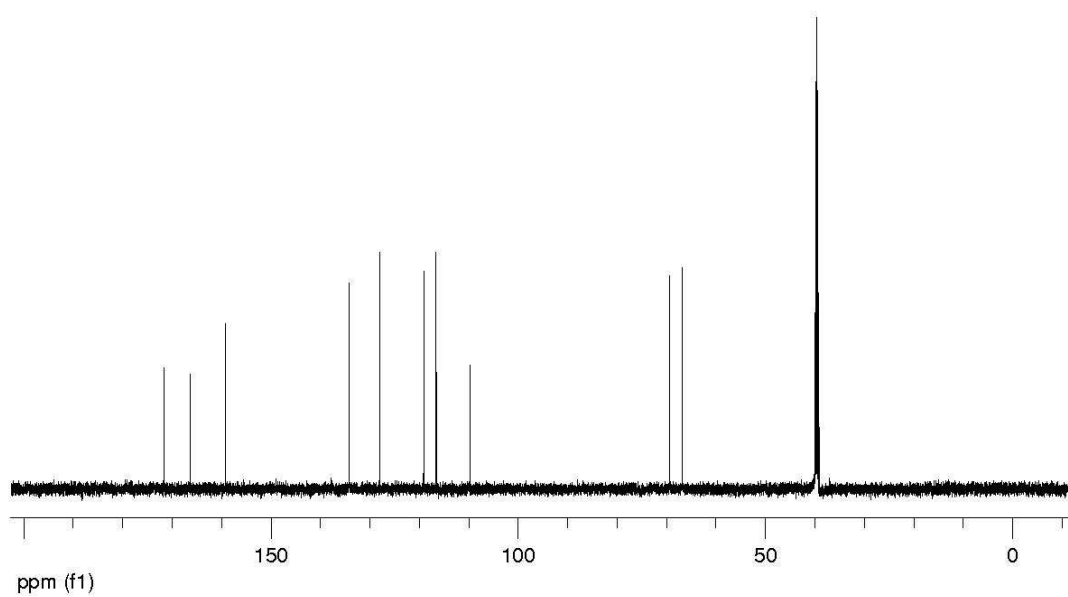
1-(2,3-Dimethyl-1H-indol-1-yl)ethanone (7.82). 2,3-Dimethylindole (5.00 g, 34.4 mmol) was dissolved in 75 mL of acetic anhydride in a single-necked 250-mL round-bottomed flask fitted with a stir bar and reflux condenser. *p*-Toluenesulfonic acid monohydrate (68 mg, 0.36 mmol) was added and the deep red solution was heated to reflux in an oil bath (oil temperature = 130 - 150 °C) overnight. After 15 h, the resultant black mixture was cooled to rt, then concentrated by rotary evaporation to afford a black solid. TLC of the crude mixture seems to indicate starting material remained, however the product also appears at the same R_f in the solvent systems used for visualization (3:7 ether/pet Eter and 85:15 hexanes/EtOAc). The solid was loaded onto silica and purified through a Biotage 40M column using 100% hexanes to 95% hexanes/EtOAc and yielded **7.82** as a white solid (4.61 g, 72% yield). The solid gradually became light orange after standing for 1 h to overnight, and was stored in a scintillation vial under Ar at -10 °C until use. mp = 66-68 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.99 (m, 1H), 7.45 (m, 1H), 7.27 (m, 2H), 2.72 (s, 3H), 2.57 (s, 3H), 2.21 (s, 3H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 170.1, 135.5, 132.5, 131.2, 123.6, 122.8, 118.1, 115.4, 114.9, 27.5, 14.4, 8.7 ppm. HRMS (FAB) *m/z* [M]⁺ calcd for C₁₂H₁₃NO⁺, 187.0997; obsd, 187.1003.

APPENDIX A:
NMR SPECTRA FOR SELECTED COMPOUNDS

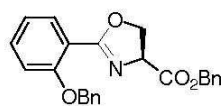
500 MHz, d6-DMSO, 30C



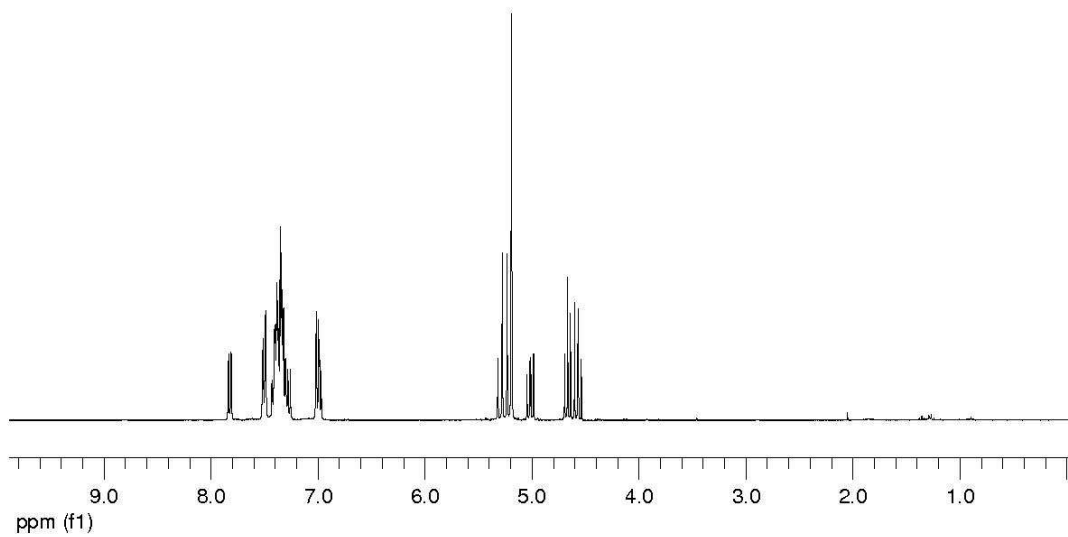
125 MHz, d6-DMSO, 30C



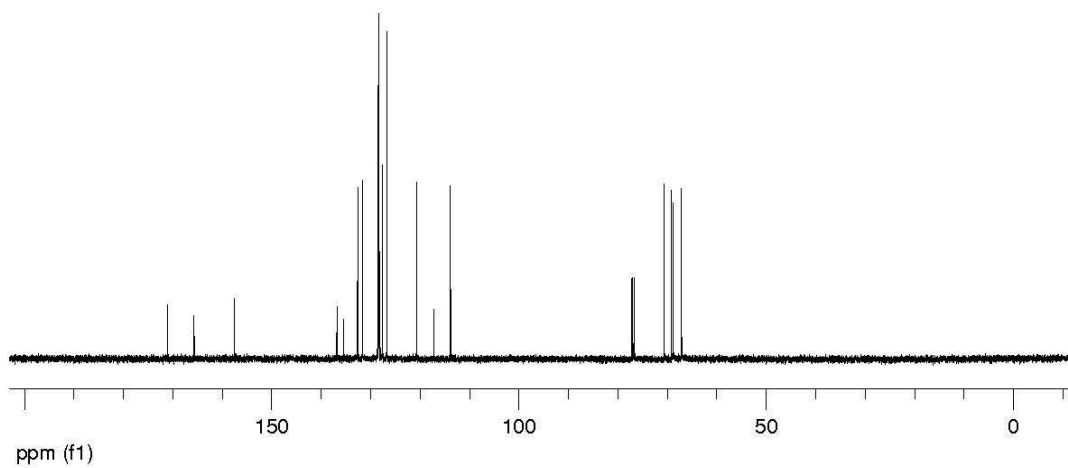
^1H and ^{13}C NMR spectra for compound **2.62**



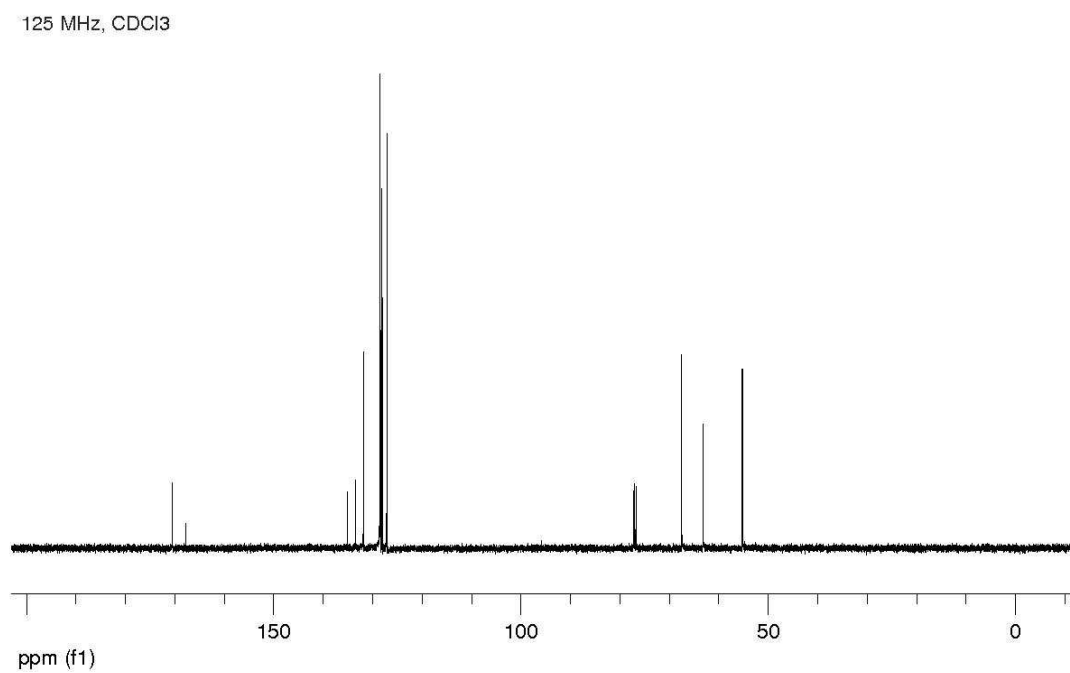
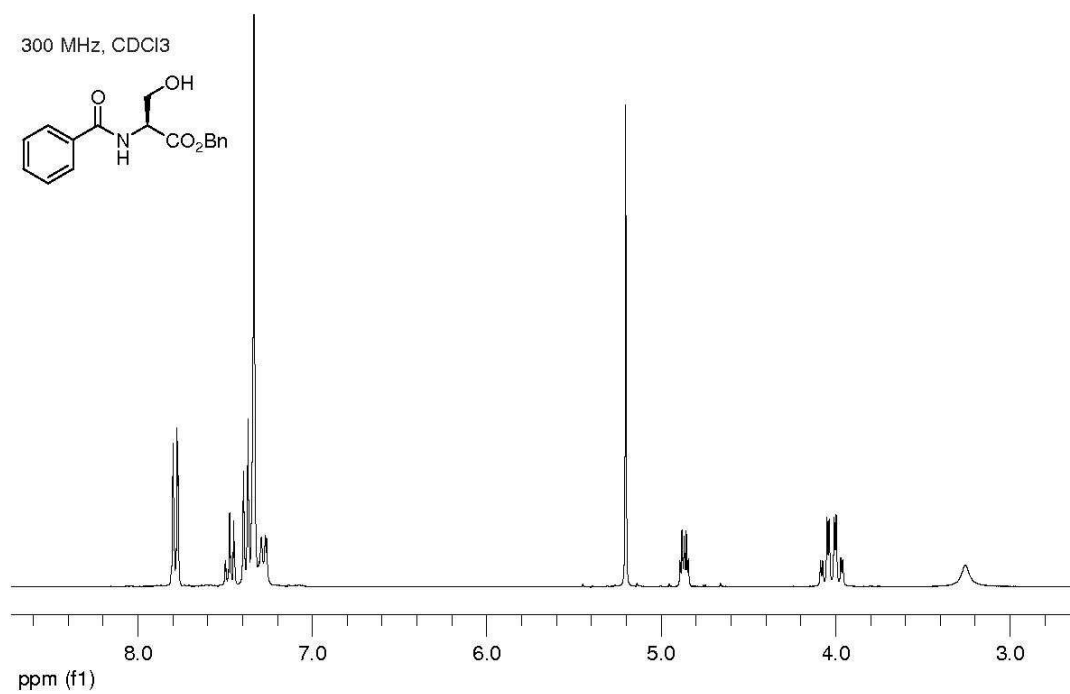
300 MHz, CDCl₃



125 MHz, CDCl₃

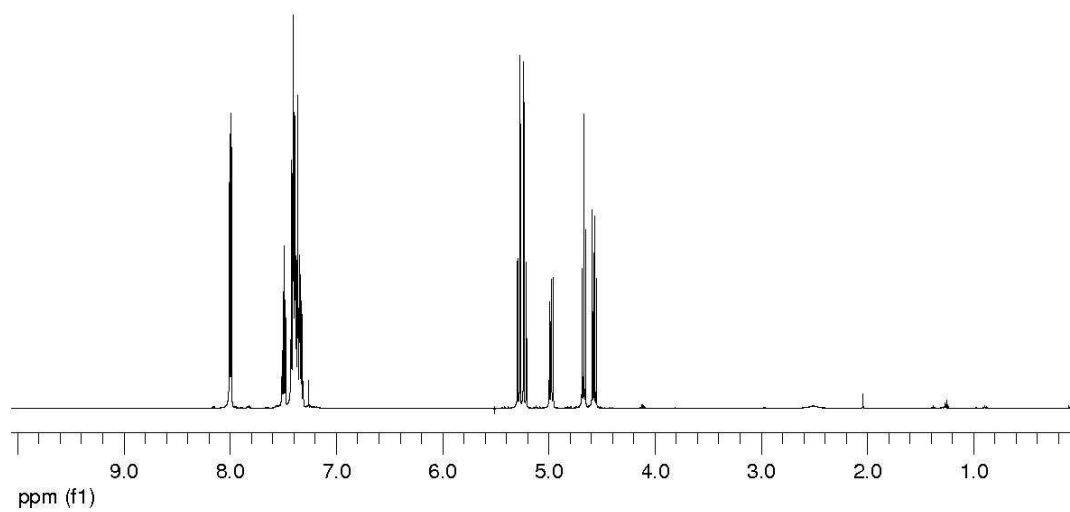
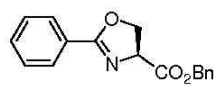


¹H and ¹³C NMR spectra for compound **3.8**

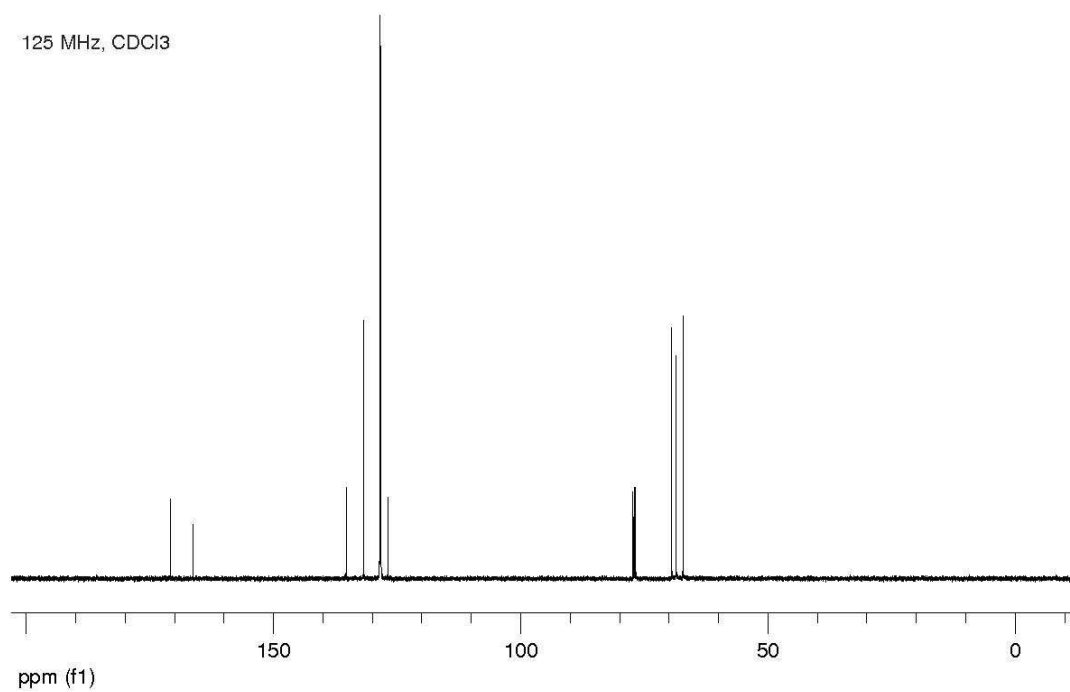


¹H and ¹³C NMR spectra for compound **3.9**

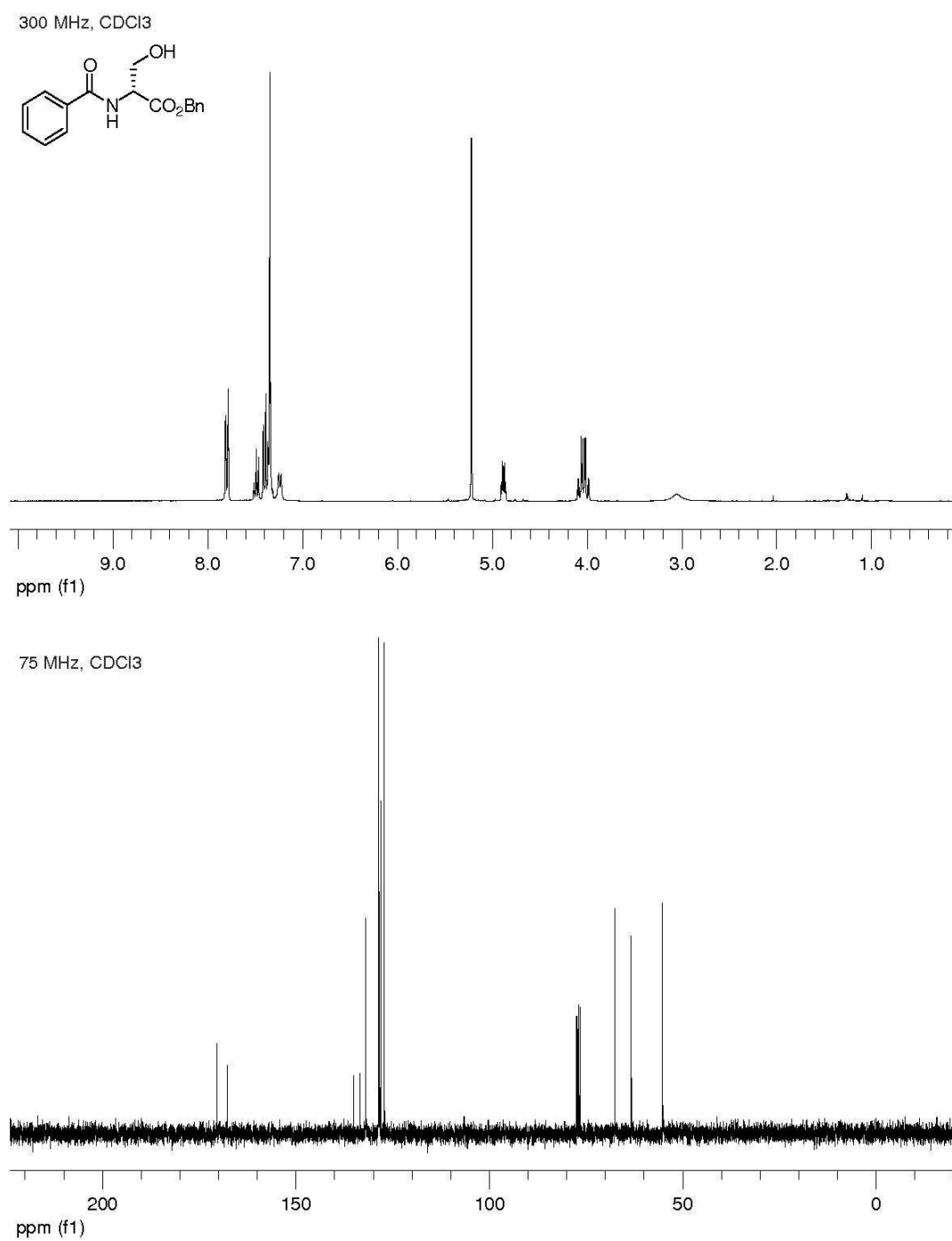
500 MHz, CDCl₃



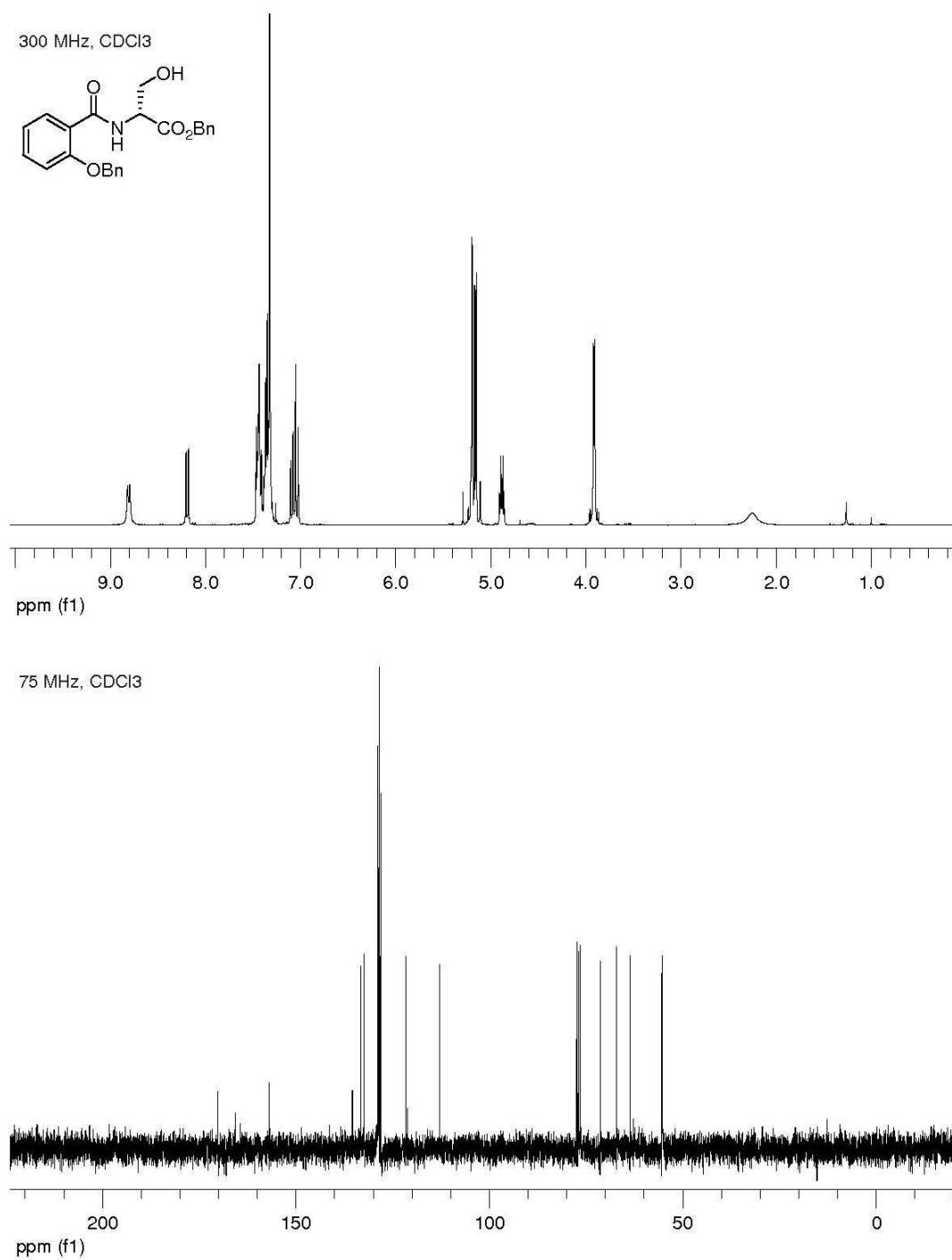
125 MHz, CDCl₃



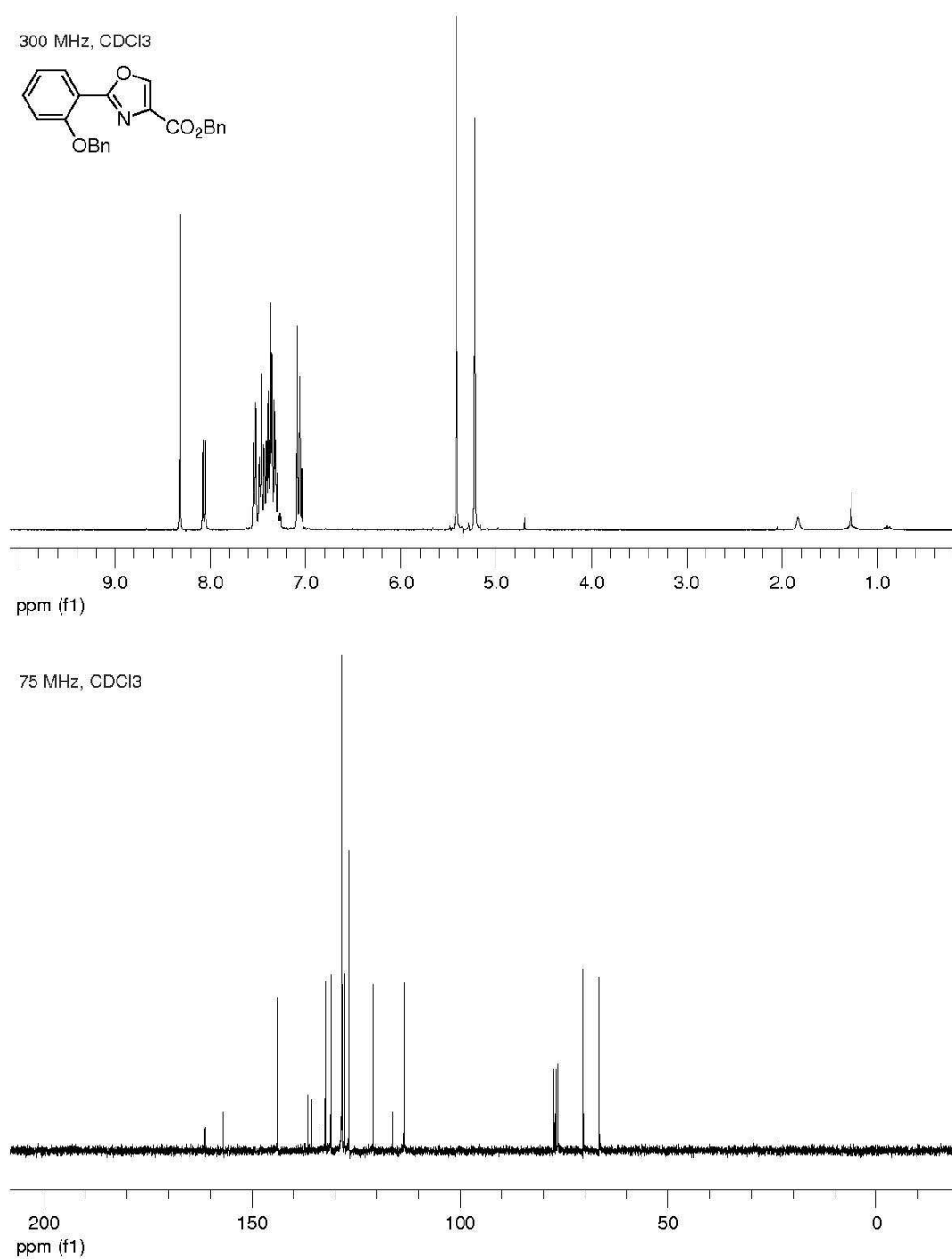
¹H and ¹³C NMR spectra for compound **3.10**



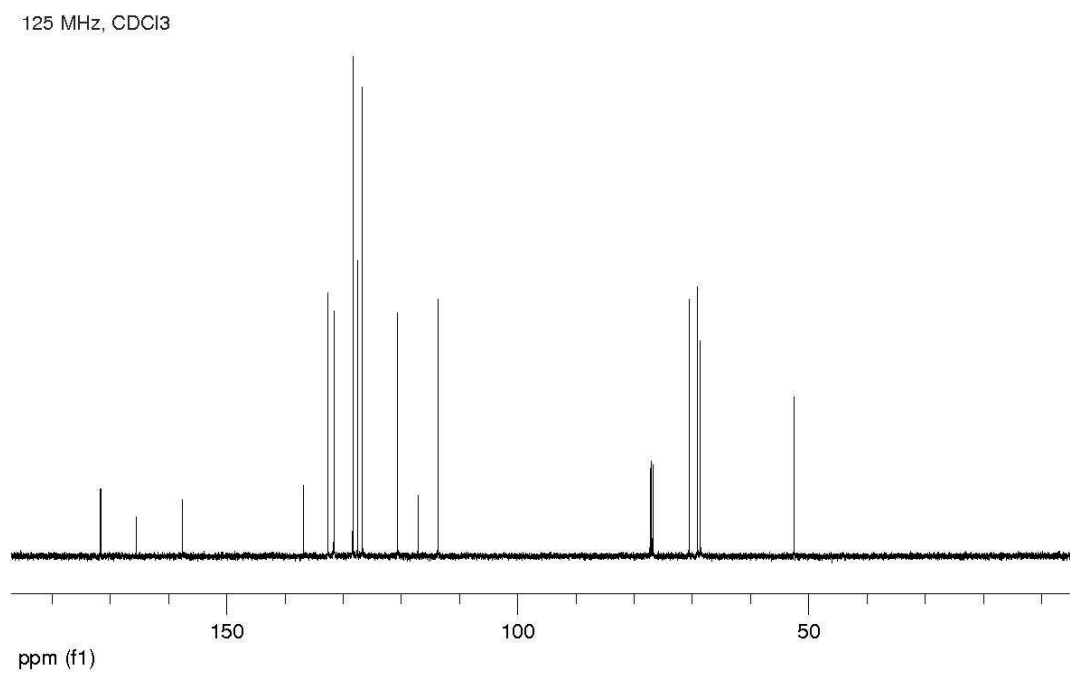
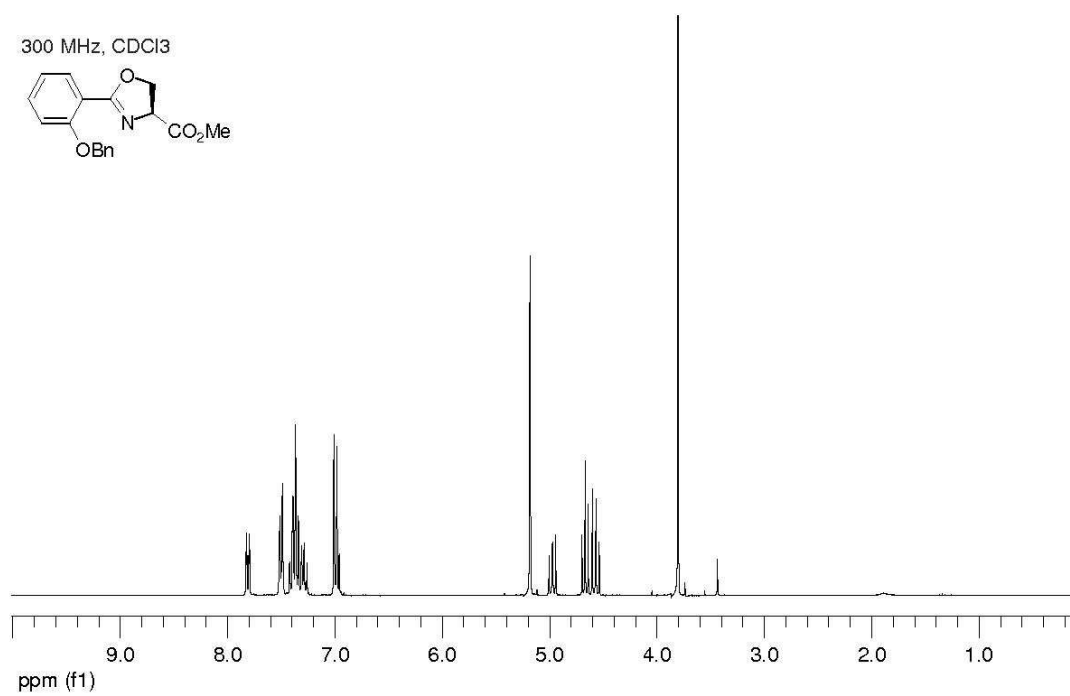
¹H and ¹³C NMR spectra for compound **3.14a**



¹H and ¹³C NMR spectra for compound **3.14b**

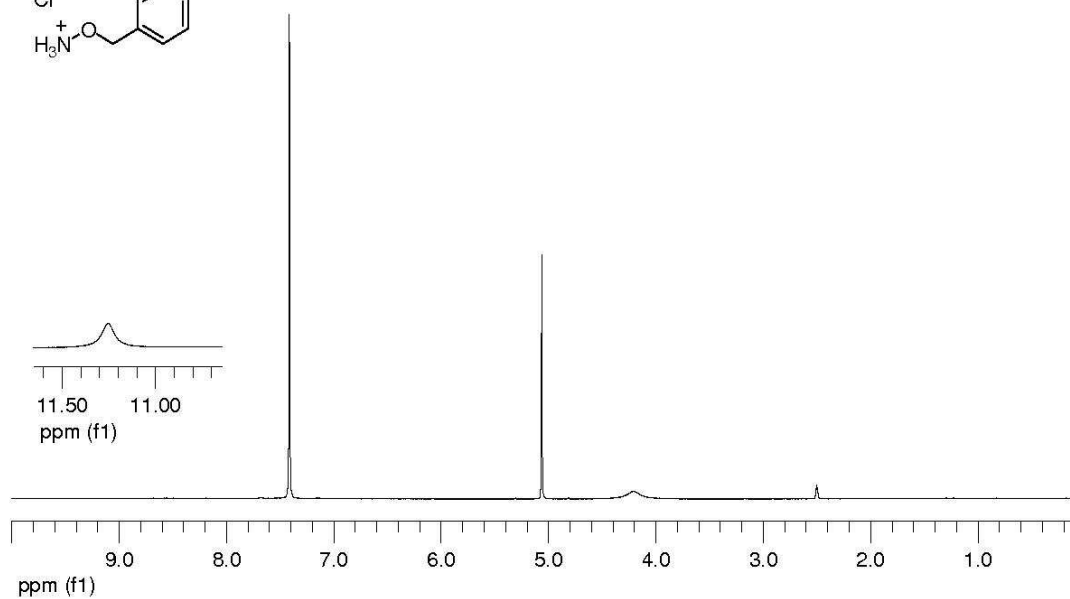
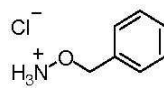


¹H and ¹³C NMR spectra for compound **3.17**

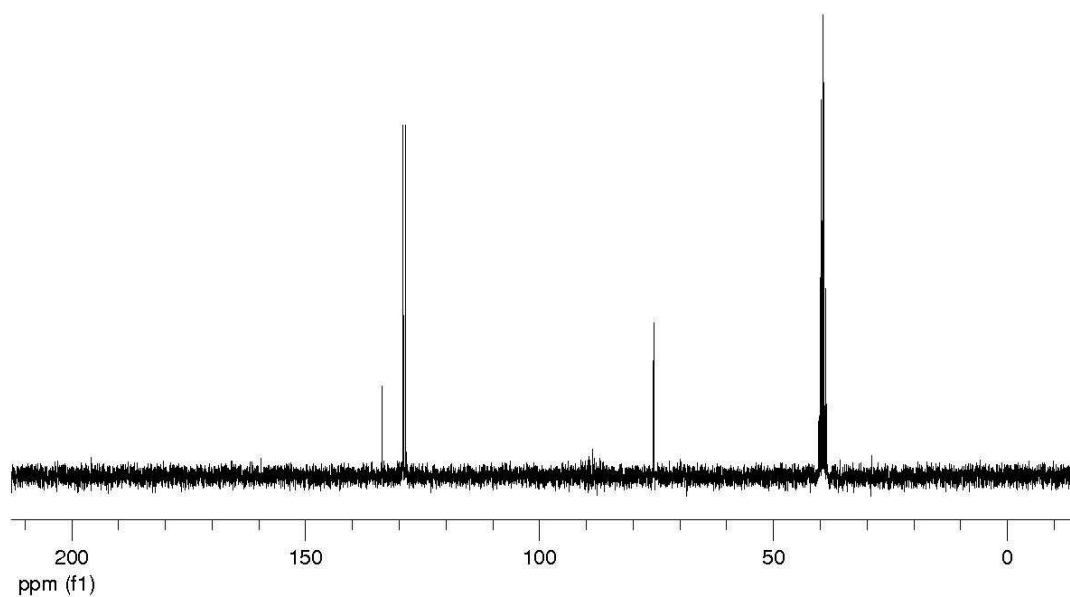


¹H and ¹³C NMR spectra for compound **3.20**

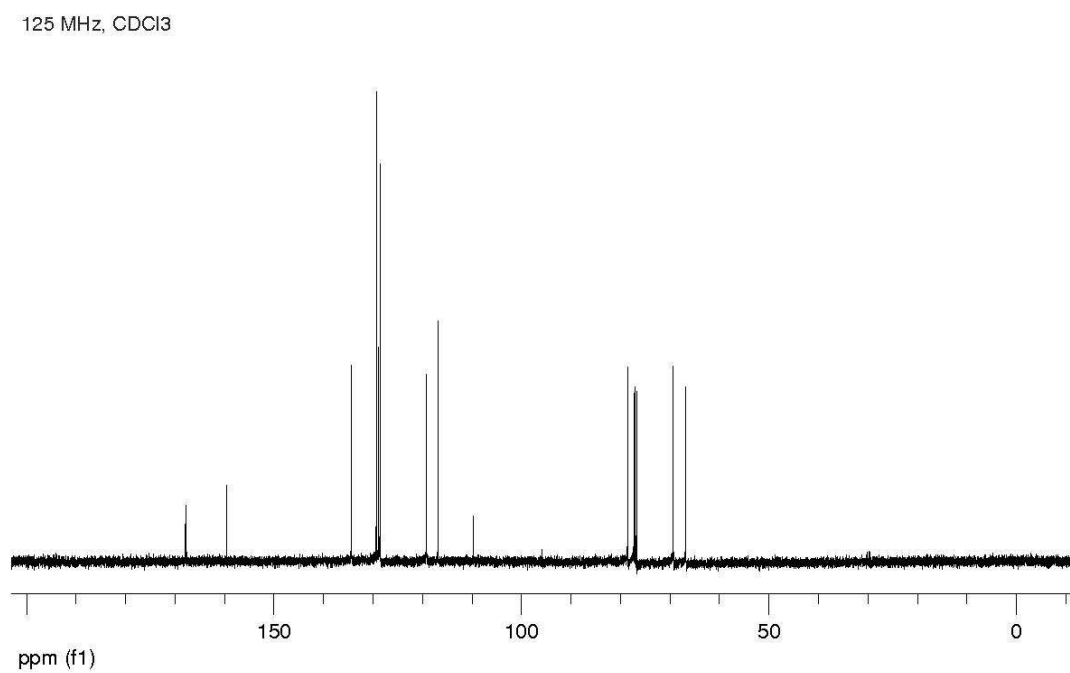
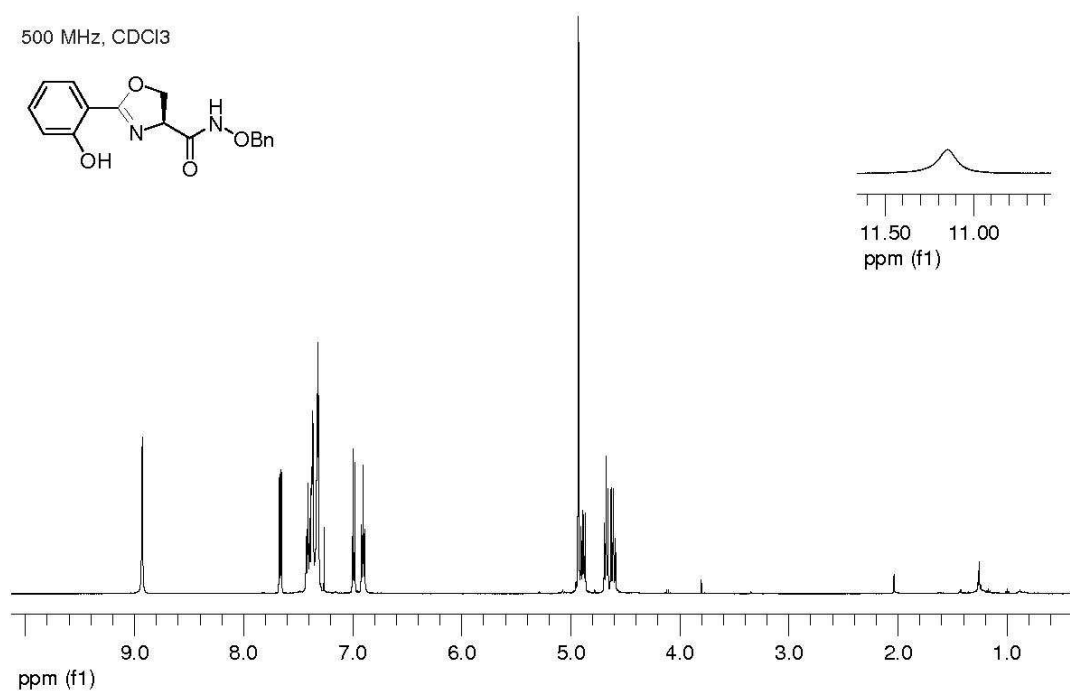
300 MHz, d6-DMSO



75 MHz, d6-DMSO

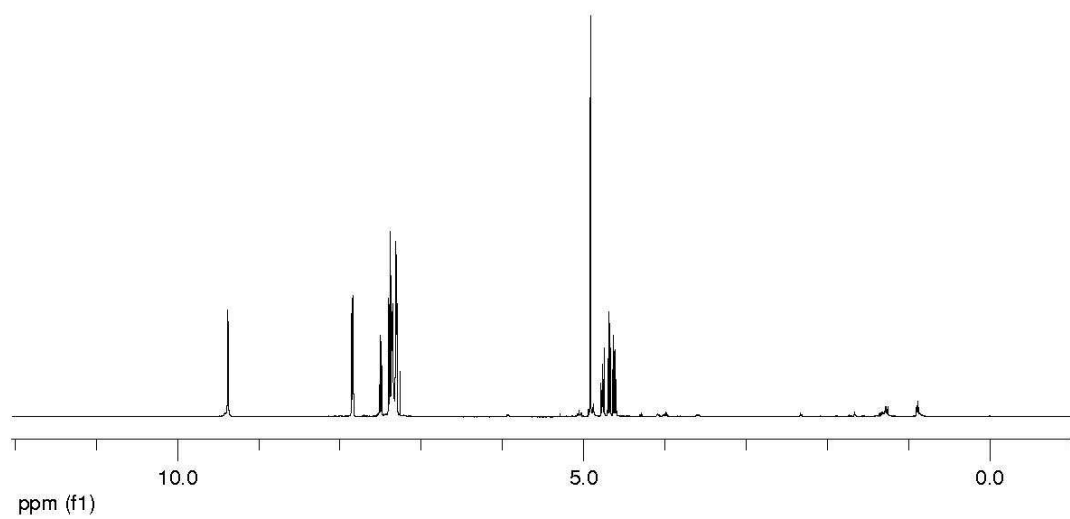
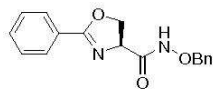


^1H and ^{13}C NMR spectra for compound **3.27**

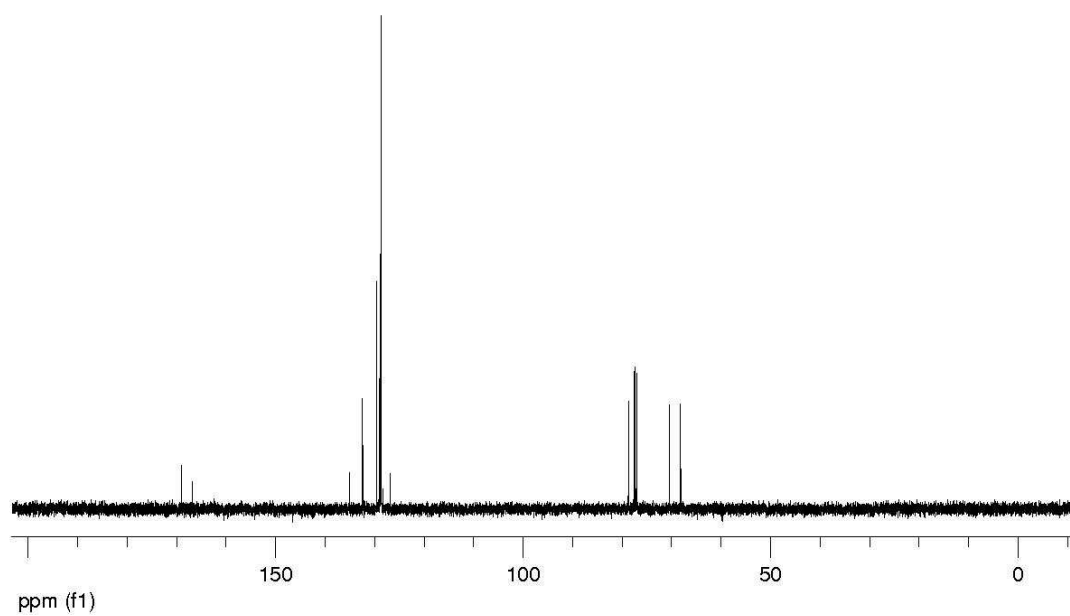


¹H and ¹³C NMR spectra for compound **3.28**

500 MHz, CDCl₃

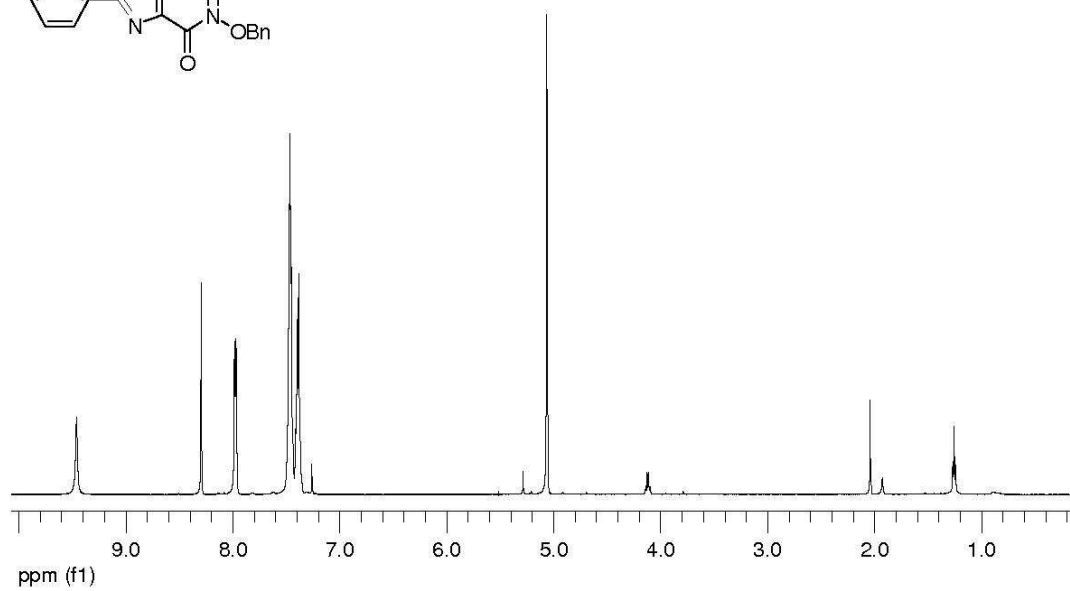
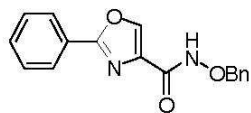


125 MHz, CDCl₃

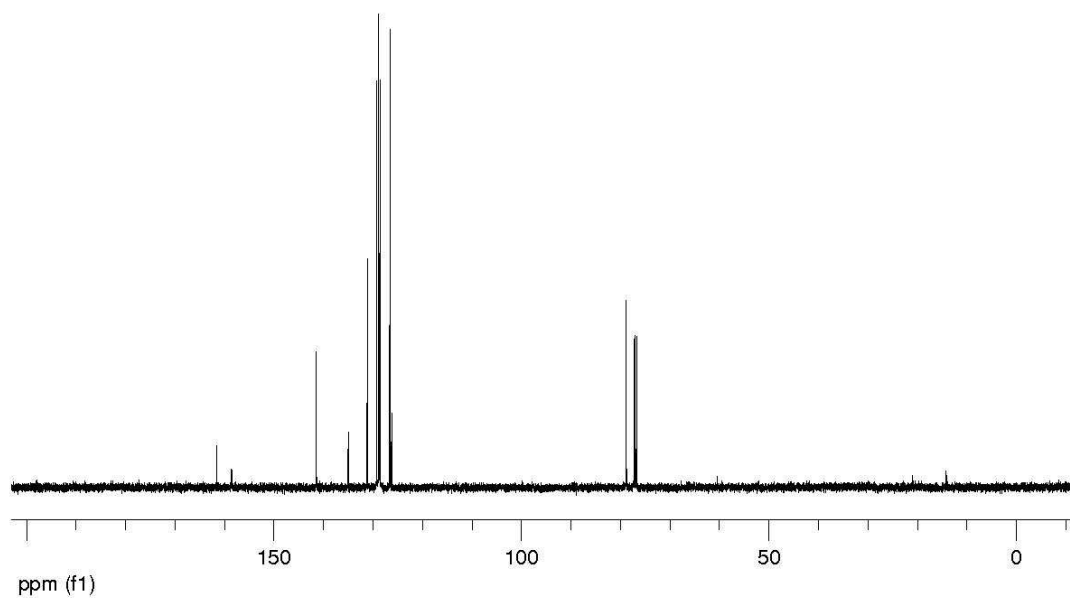


¹H and ¹³C NMR spectra for compound **3.29**

500 MHz, CDCl₃

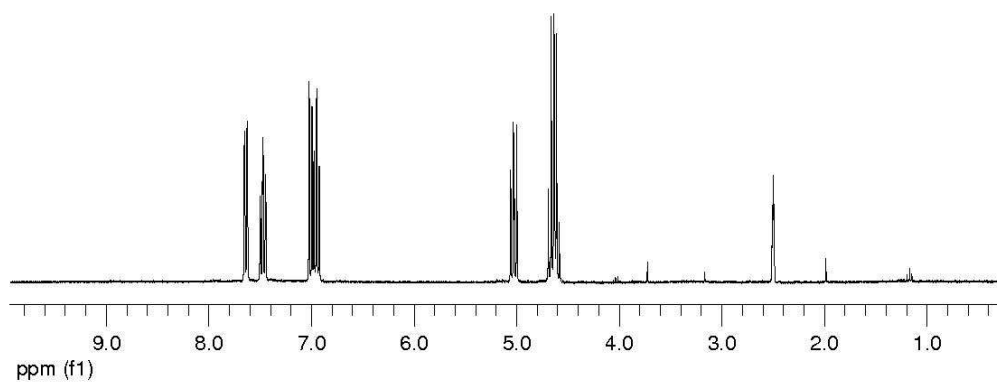
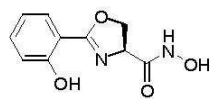


125 MHz, CDCl₃

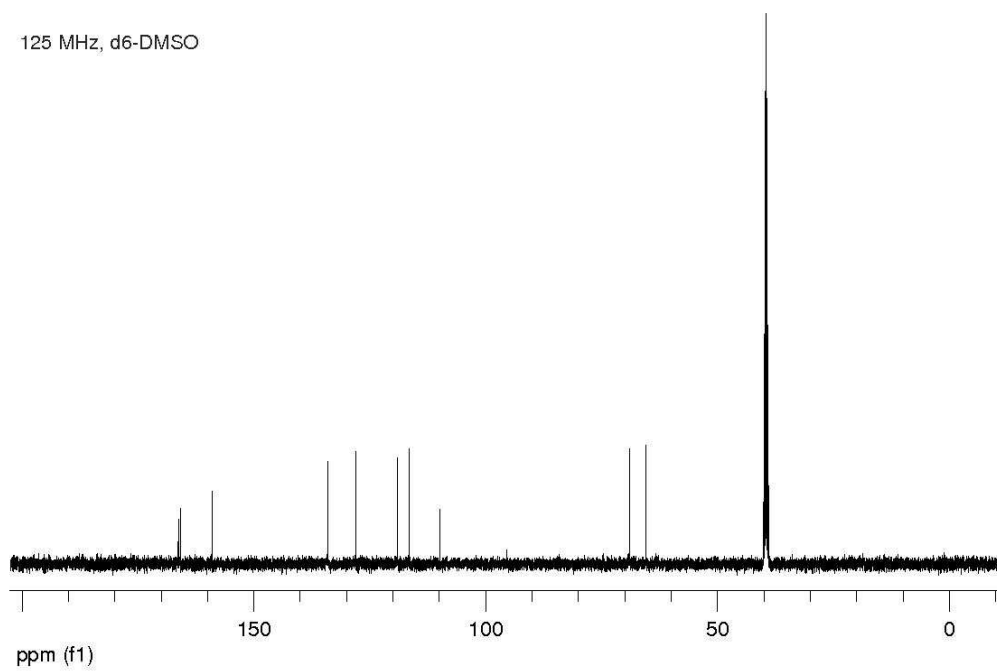


¹H and ¹³C NMR spectra for compound **3.31**

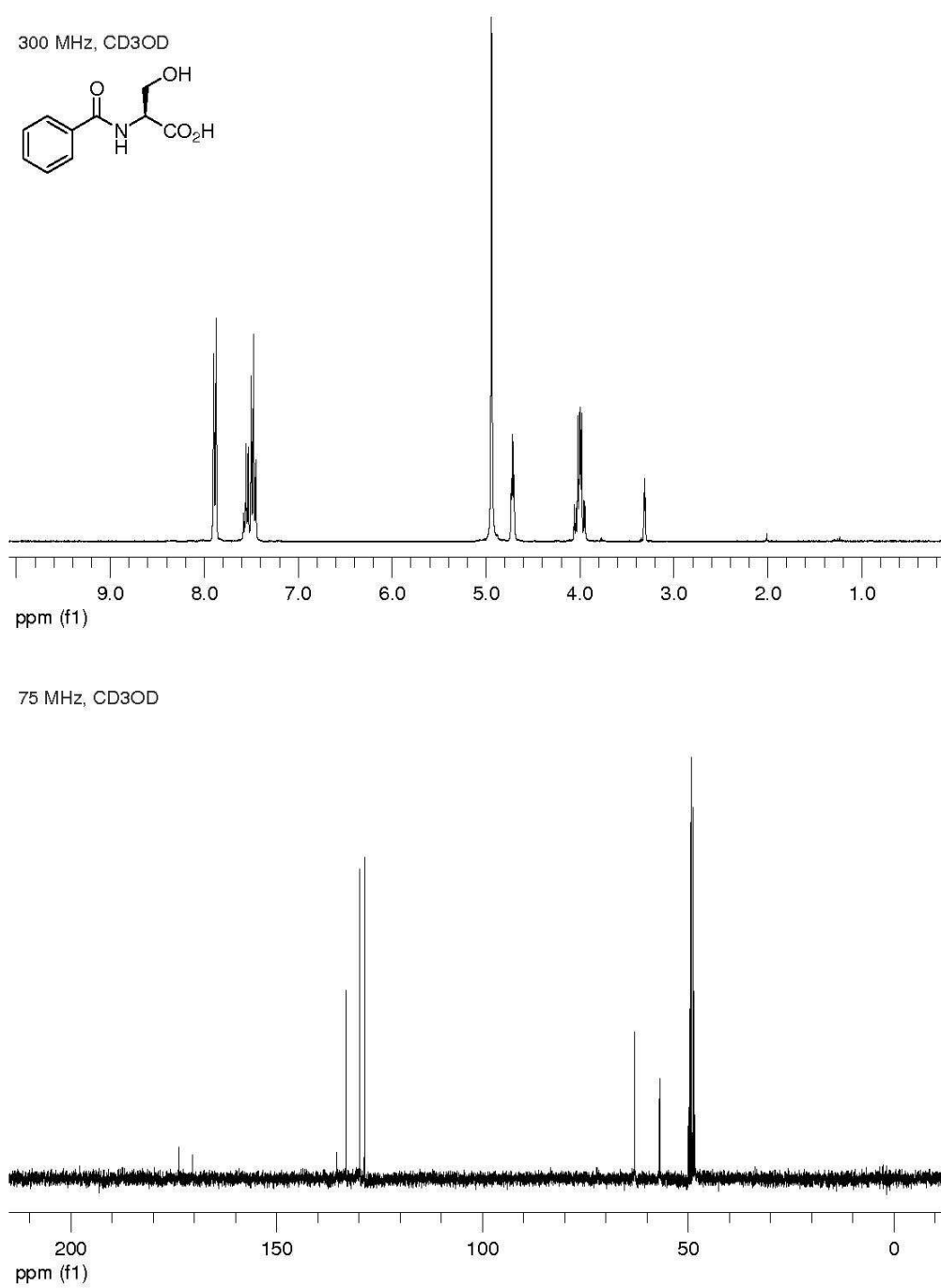
300 MHz, d6-DMSO



125 MHz, d6-DMSO

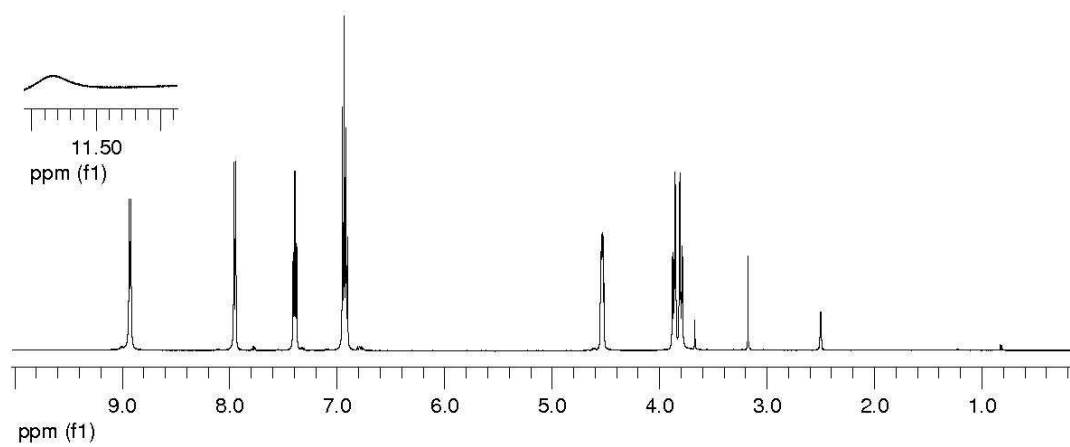
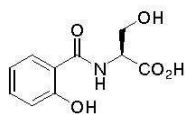


^1H and ^{13}C NMR spectra for compound **3.32**

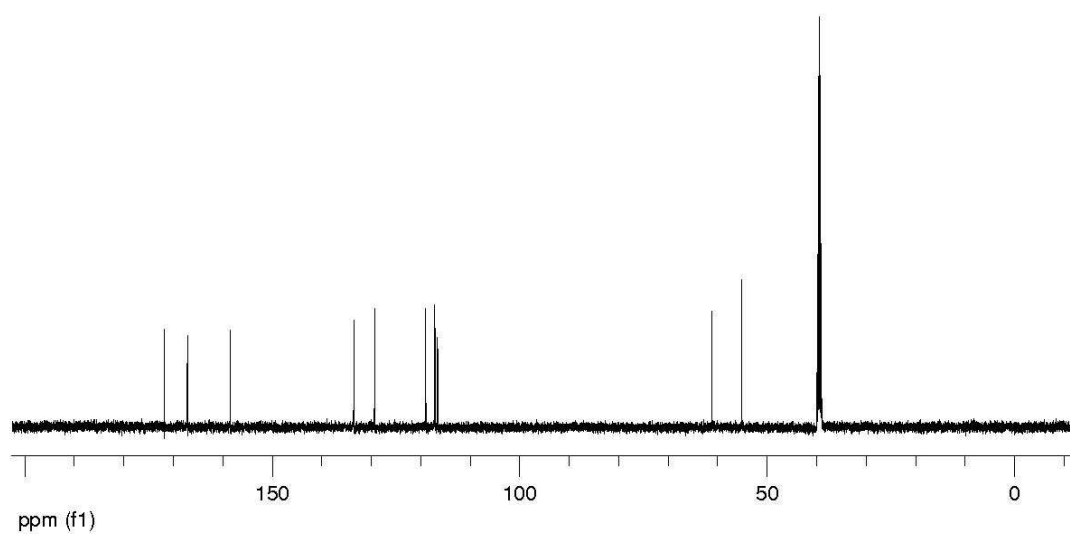


¹H and ¹³C NMR spectra for compound **3.33**

500 MHz, d6-DMSO

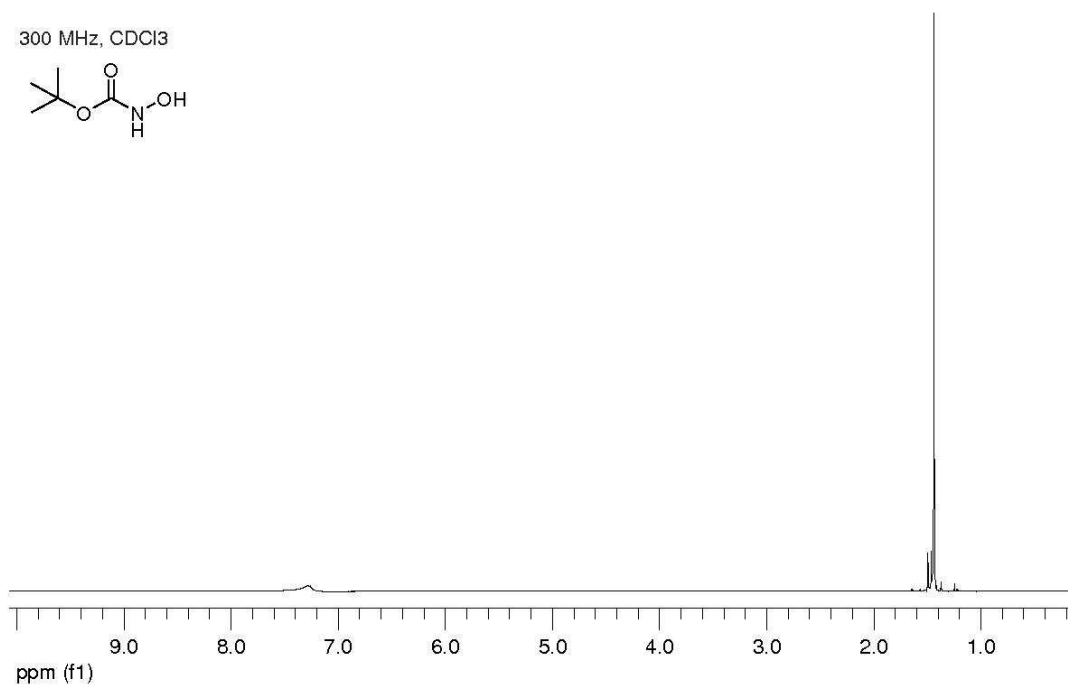
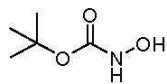


125 MHz, d6-DMSO

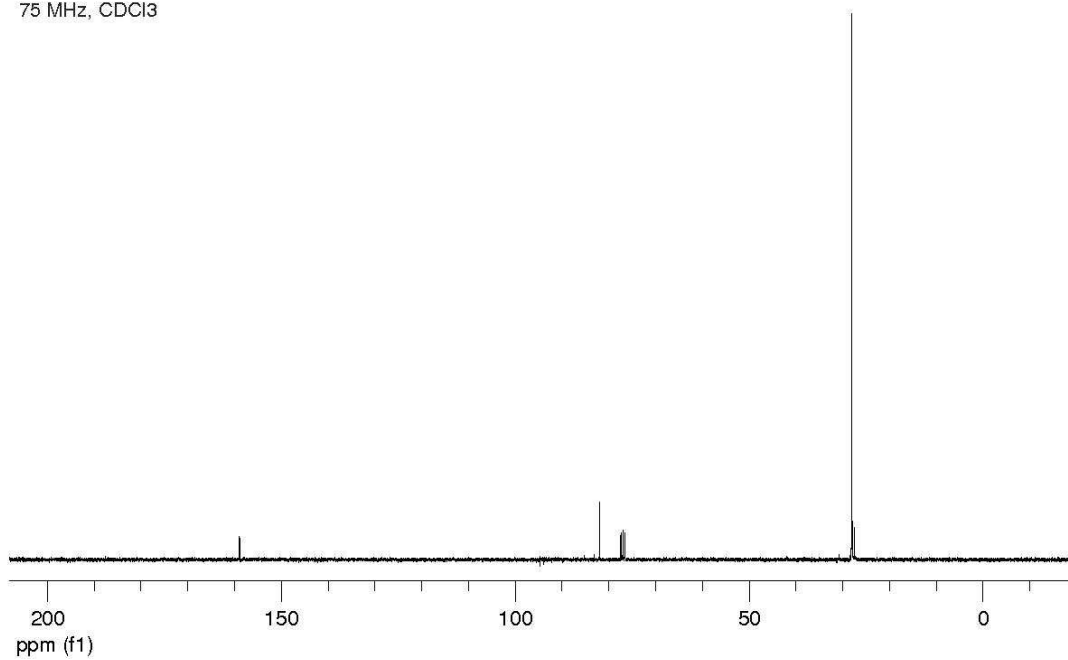


^1H and ^{13}C NMR spectra for compound **3.34**

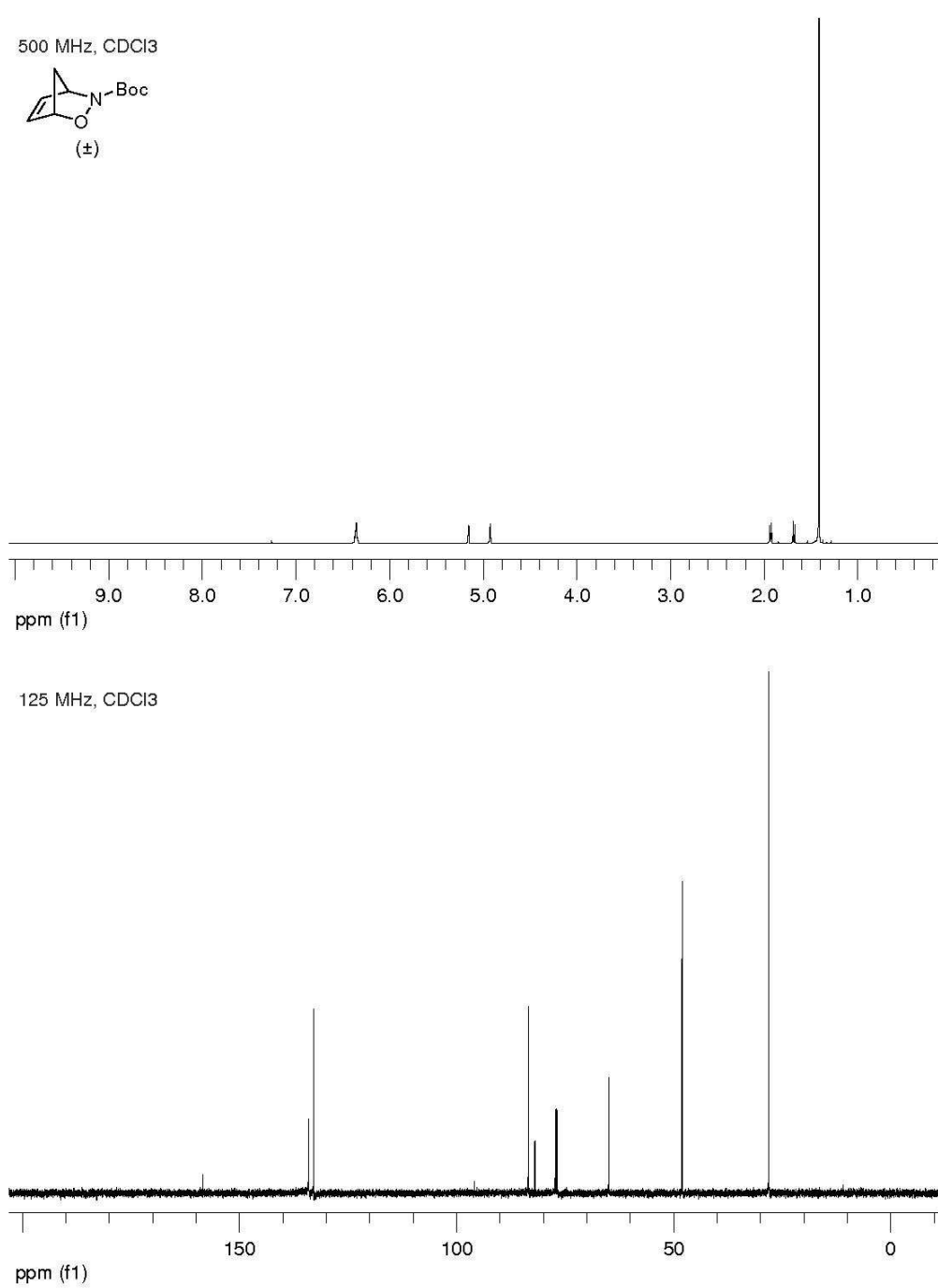
300 MHz, CDCl₃



75 MHz, CDCl₃

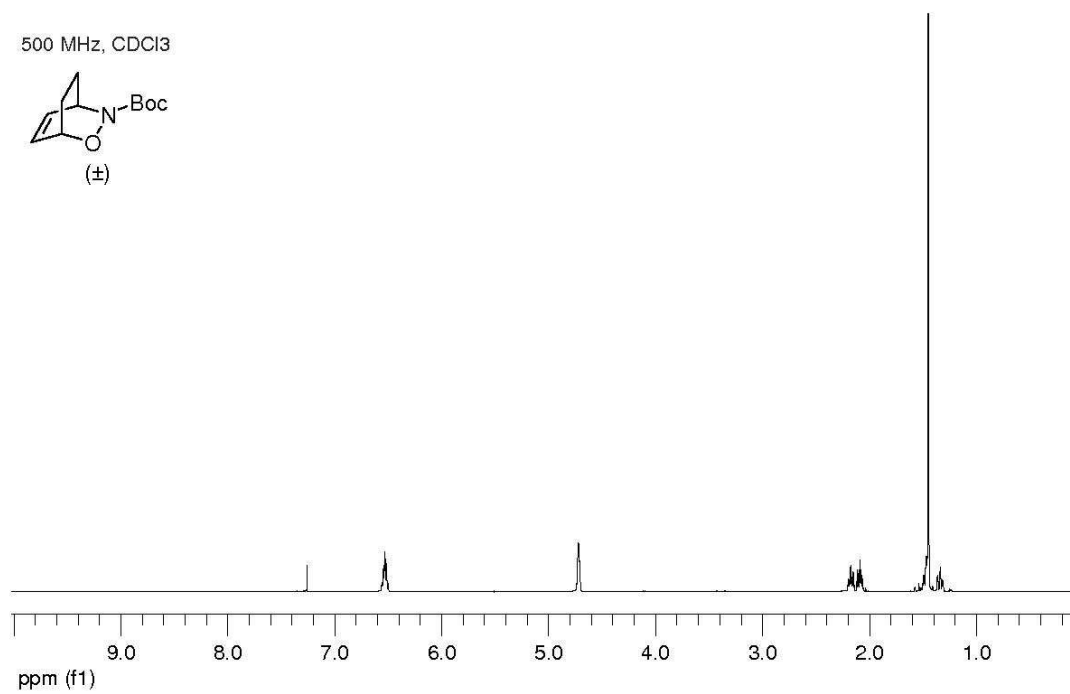
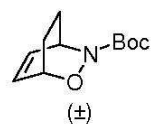


¹H and ¹³C NMR spectra for compound **3.37**

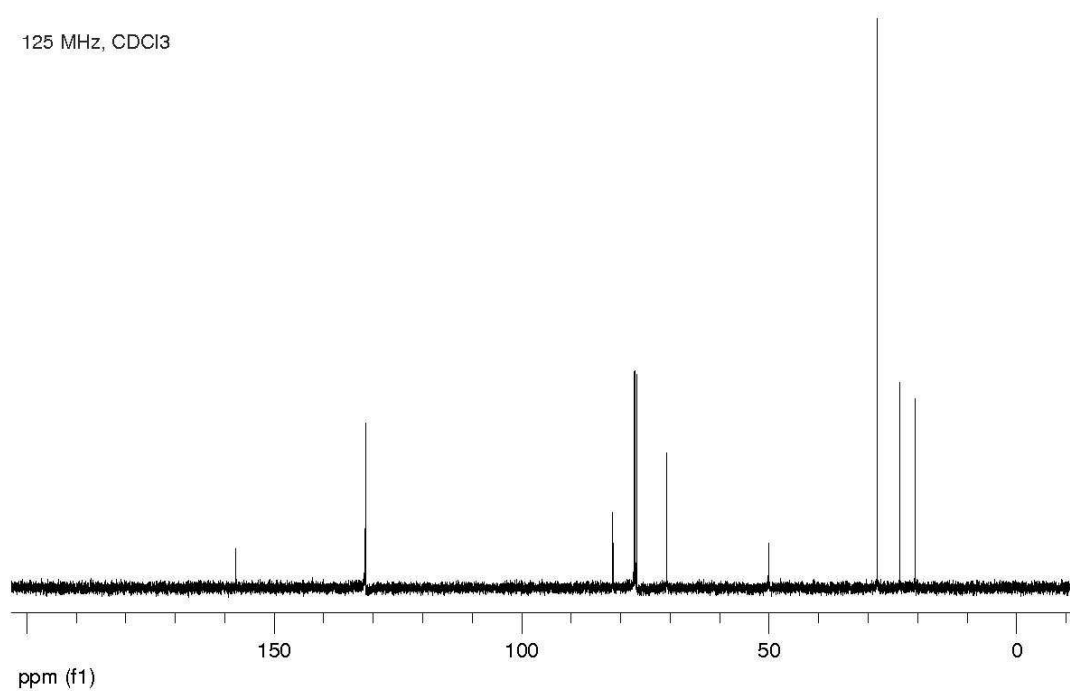


¹H and ¹³C NMR spectra for compound **3.38**

500 MHz, CDCl₃

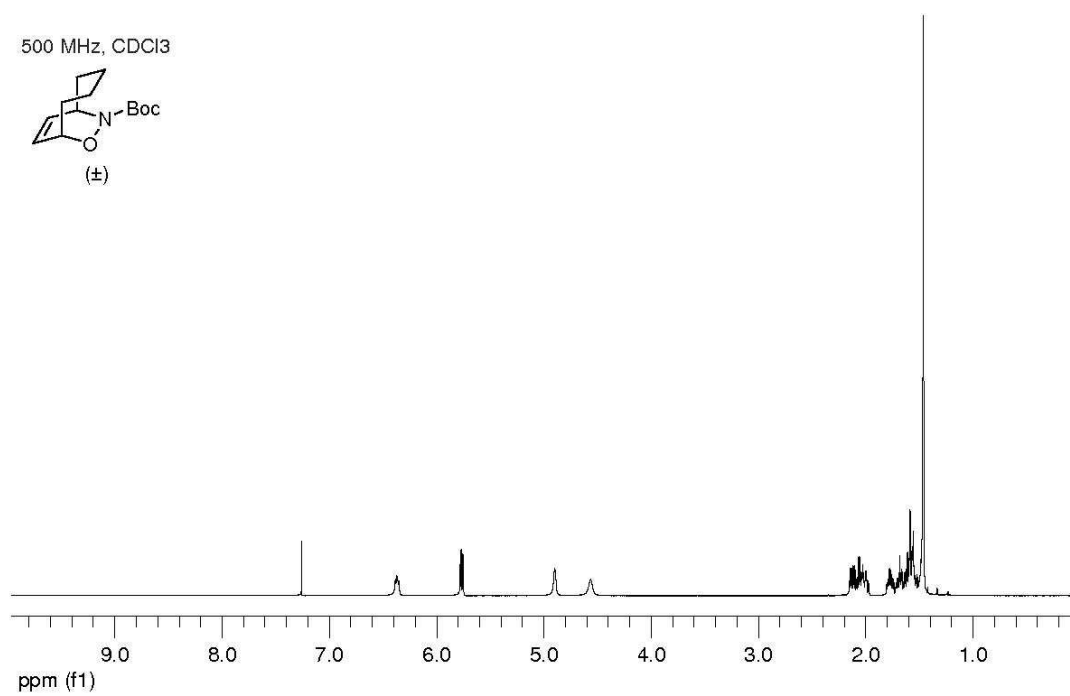
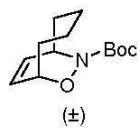


125 MHz, CDCl₃

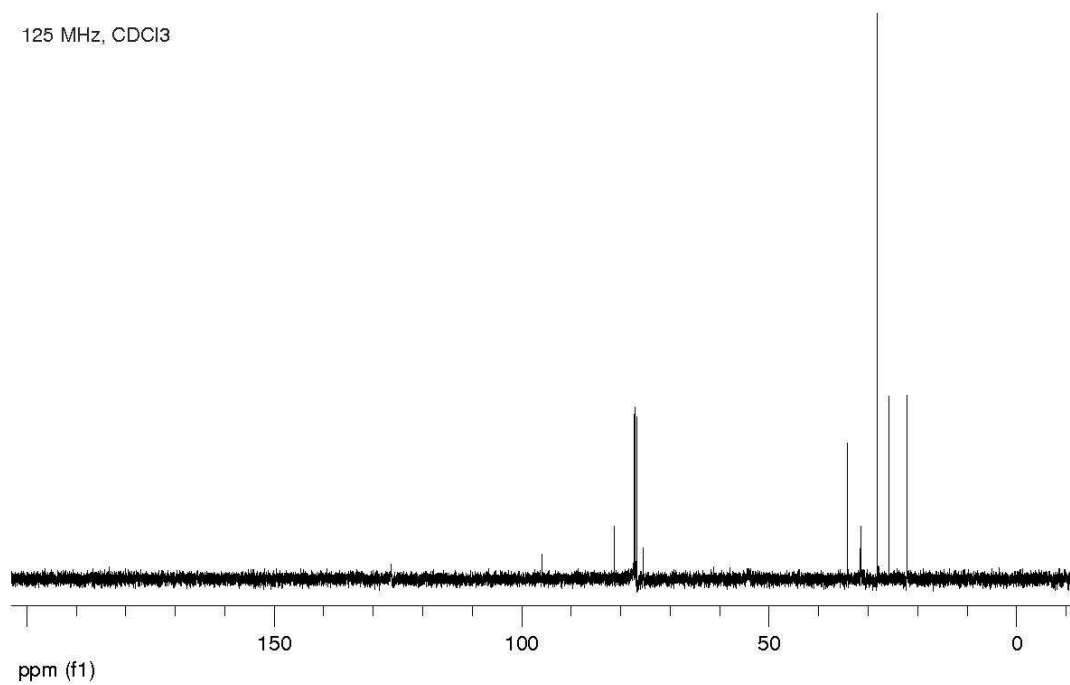


¹H and ¹³C NMR spectra for compound **3.39**

500 MHz, CDCl₃

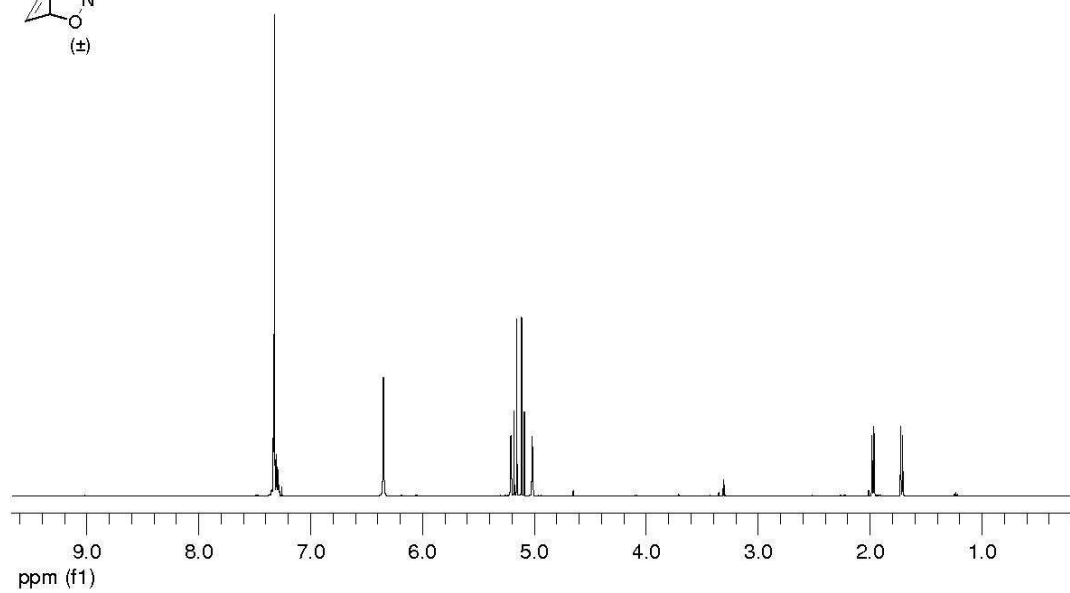
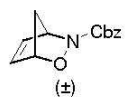


125 MHz, CDCl₃

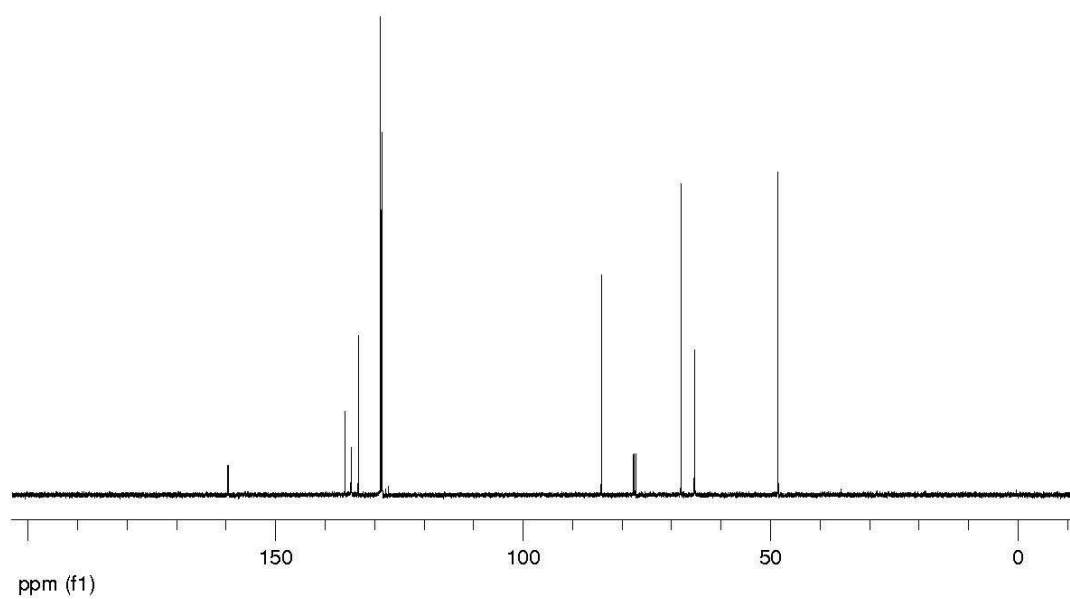


¹H and ¹³C NMR spectra for compound **3.40**

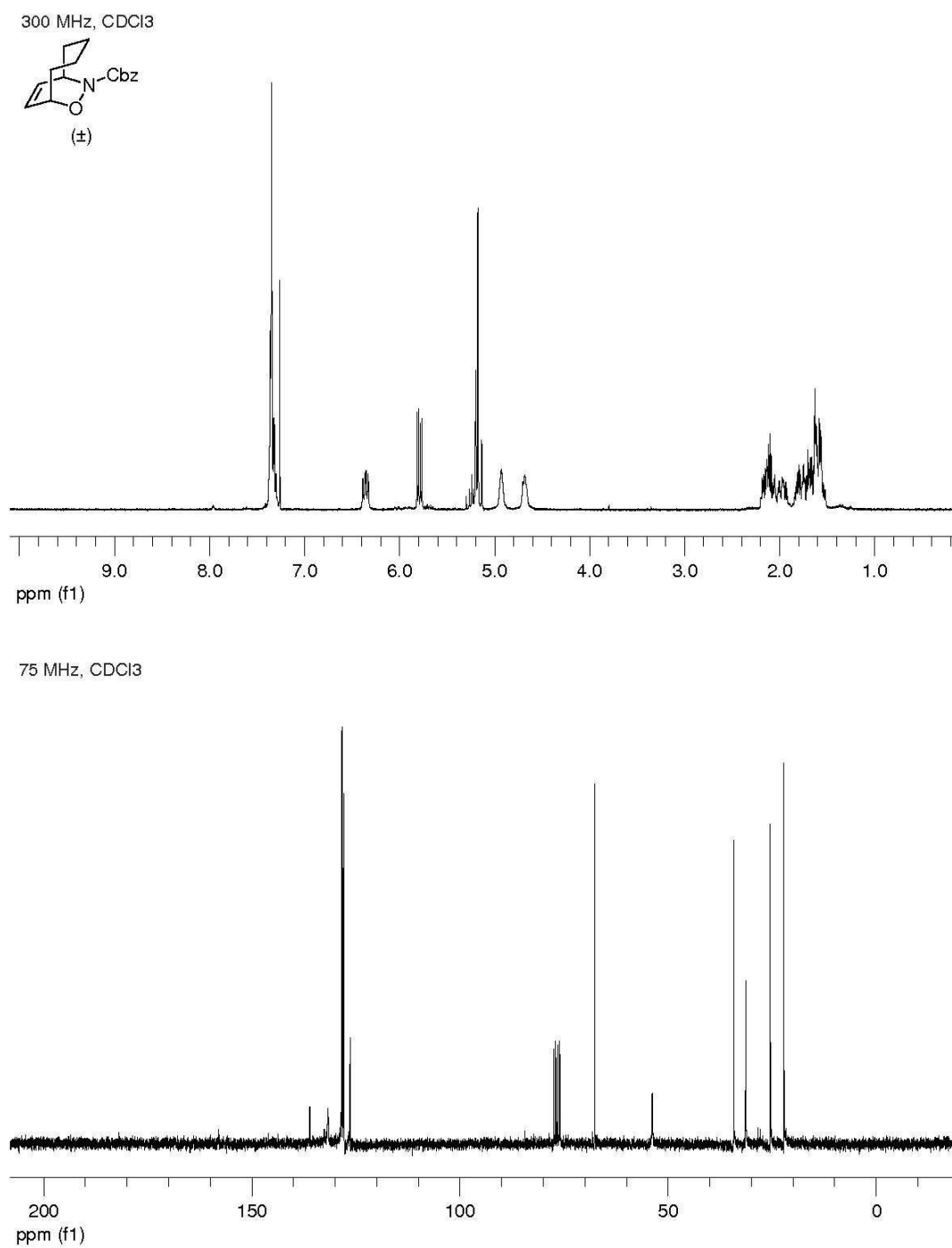
500 MHz, CDCl₃



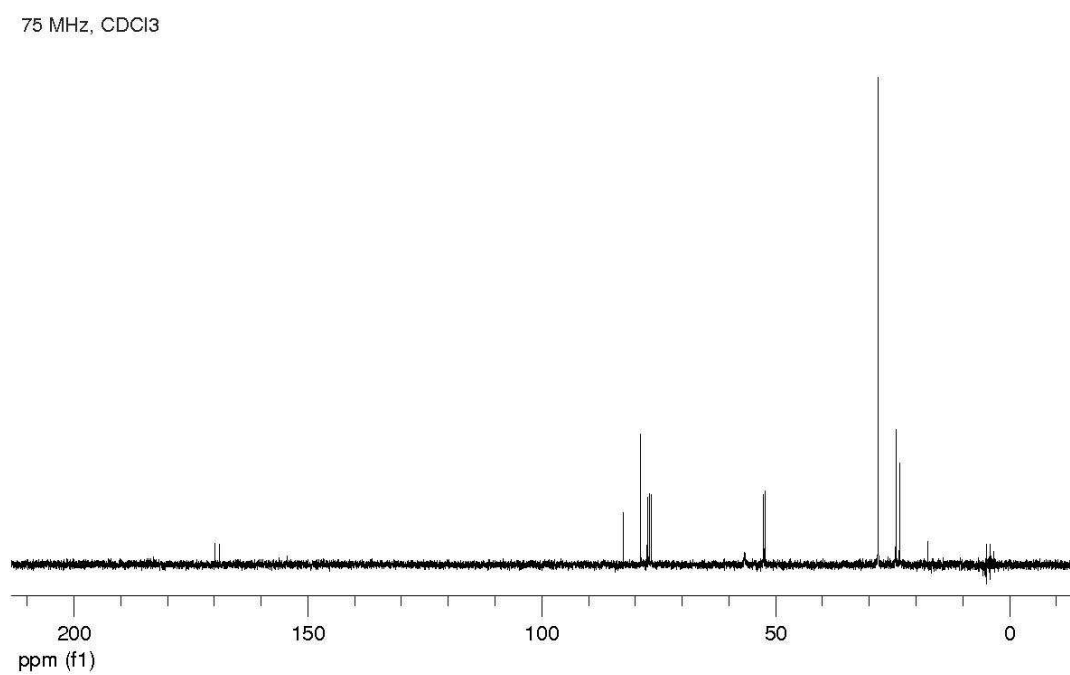
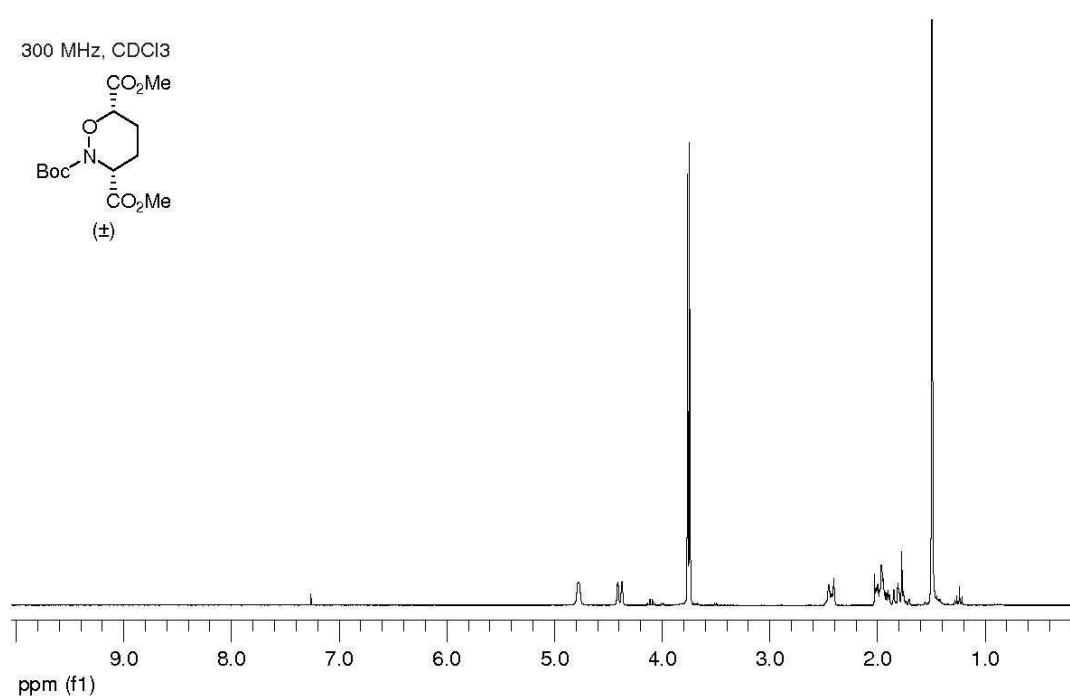
125 MHz, CDCl₃



¹H and ¹³C NMR spectra for compound **3.42**

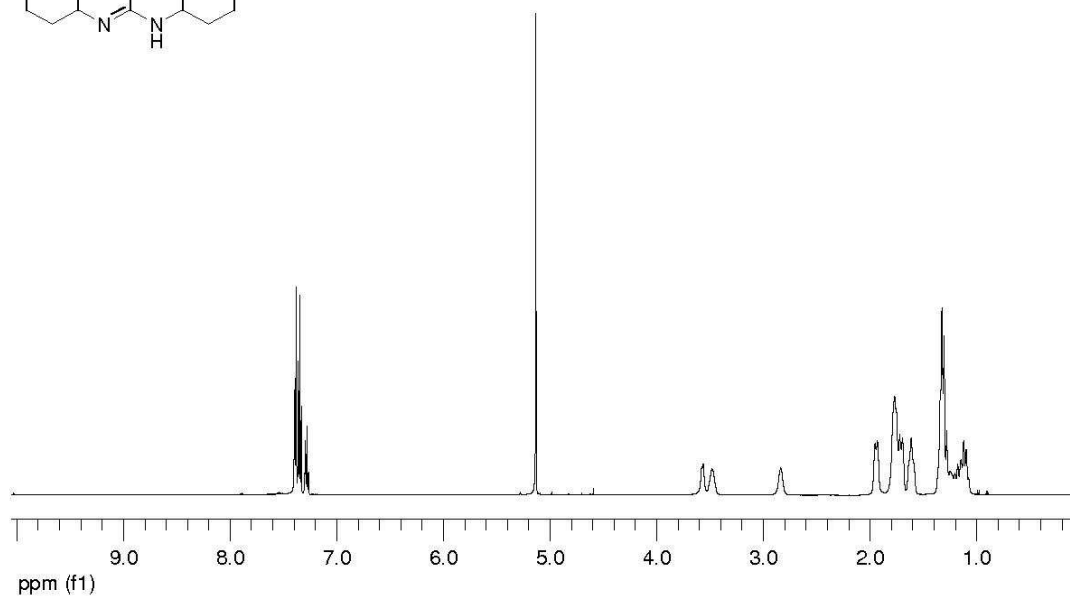
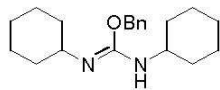


¹H and ¹³C NMR spectra for compound **3.43**

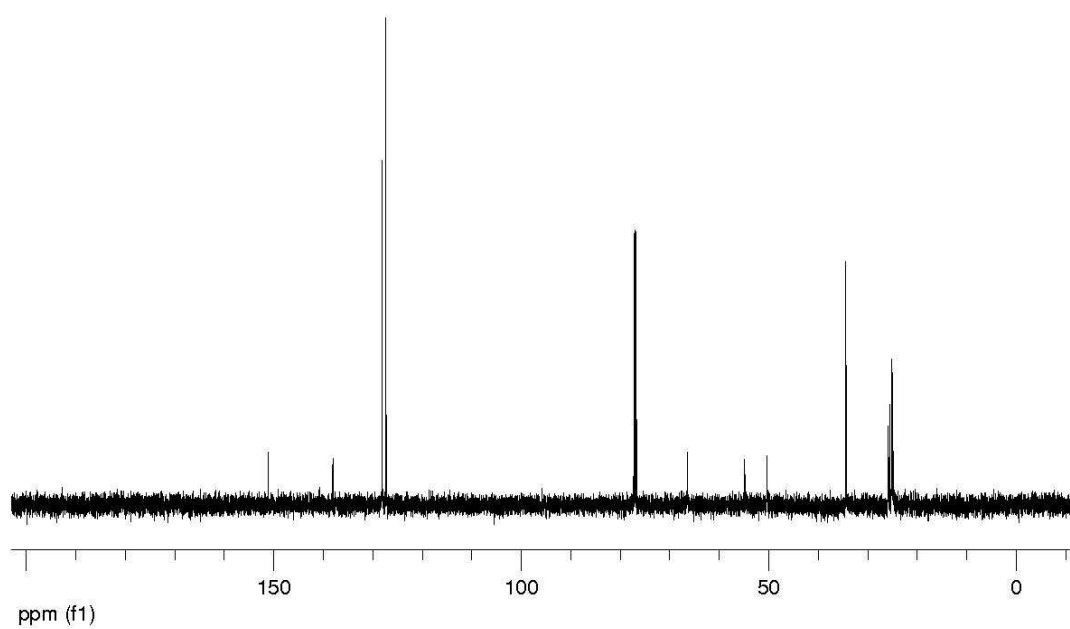


¹H and ¹³C NMR spectra for compound **3.45**

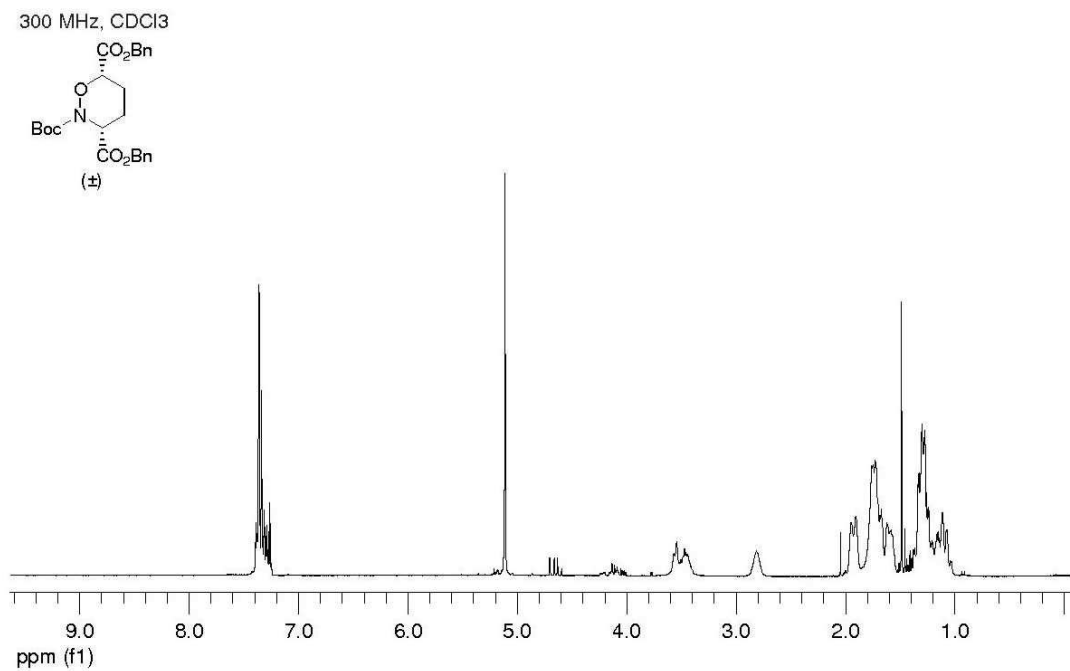
500 MHz, CDCl₃



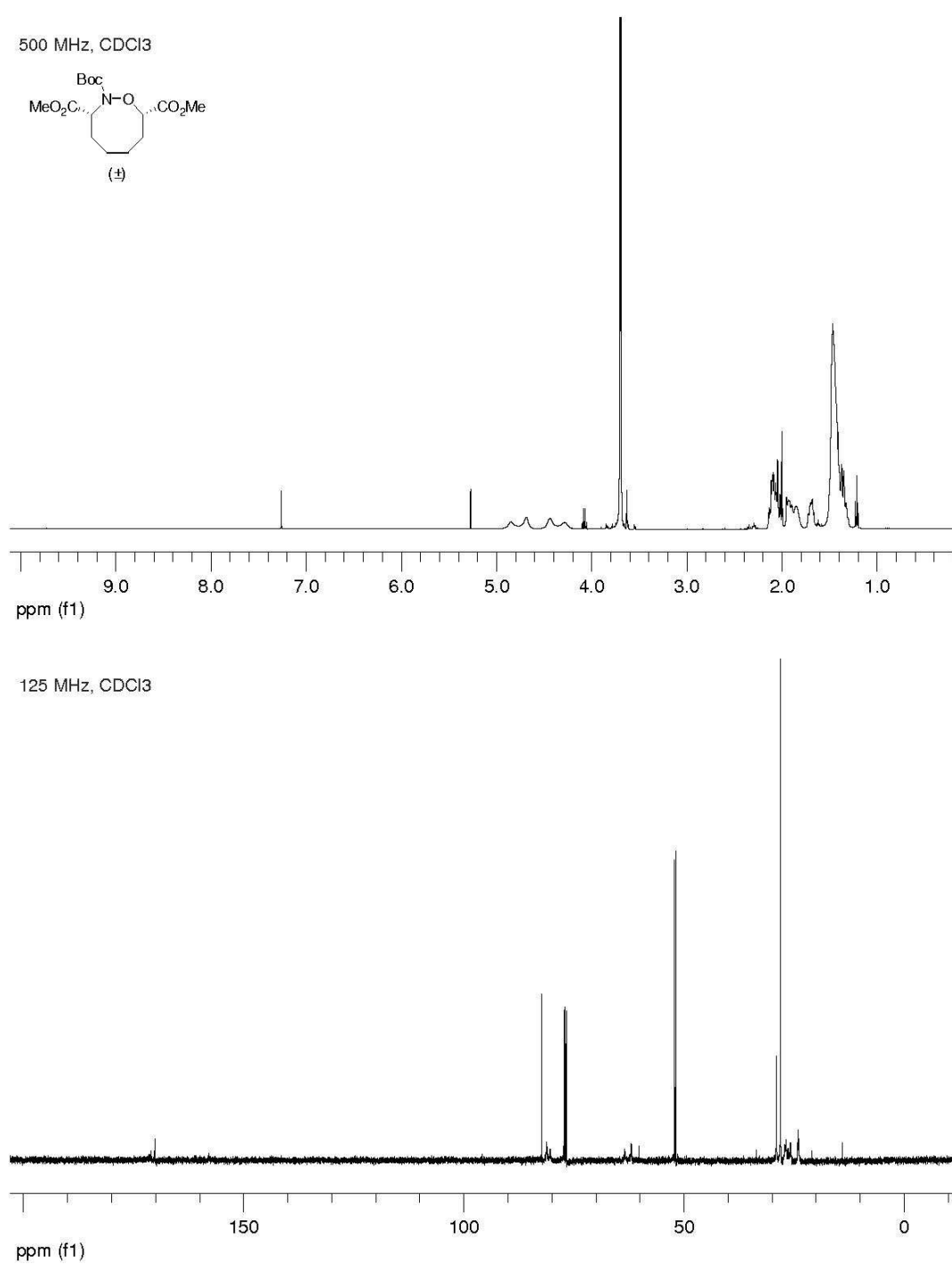
125 MHz, CDCl₃



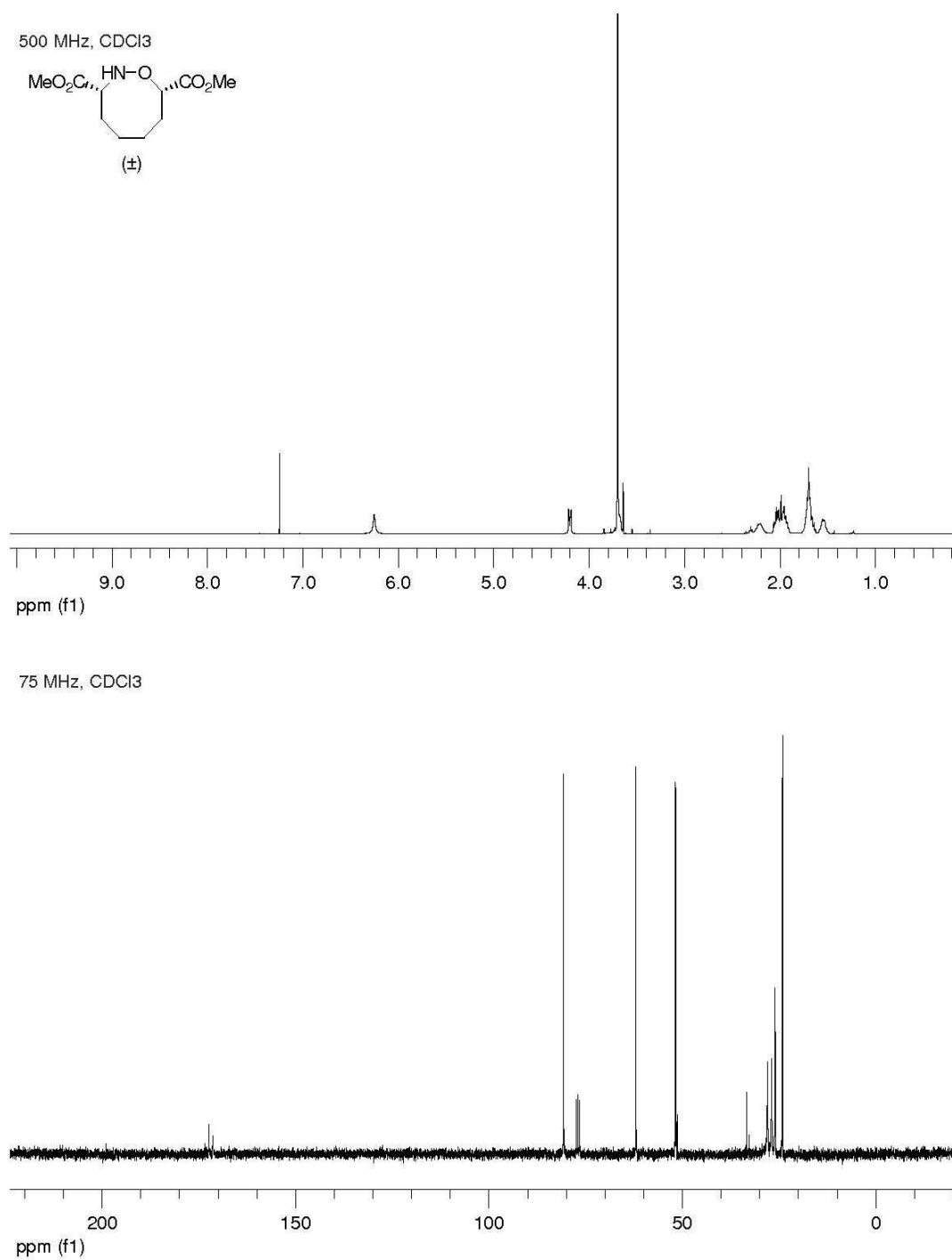
¹H and ¹³C NMR spectra for compound **3.47**



¹H NMR spectrum for compound **3.48**

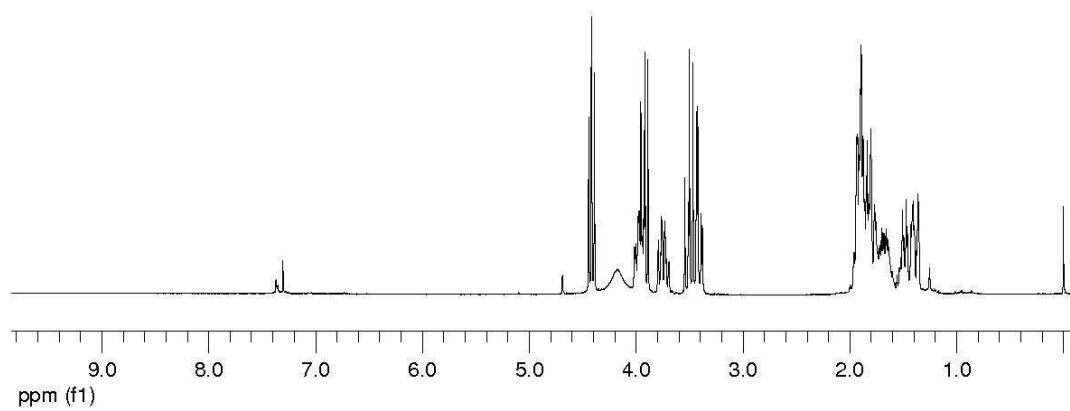
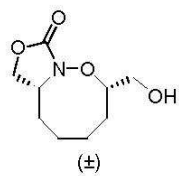


¹H and ¹³C NMR spectra for compound **3.52**

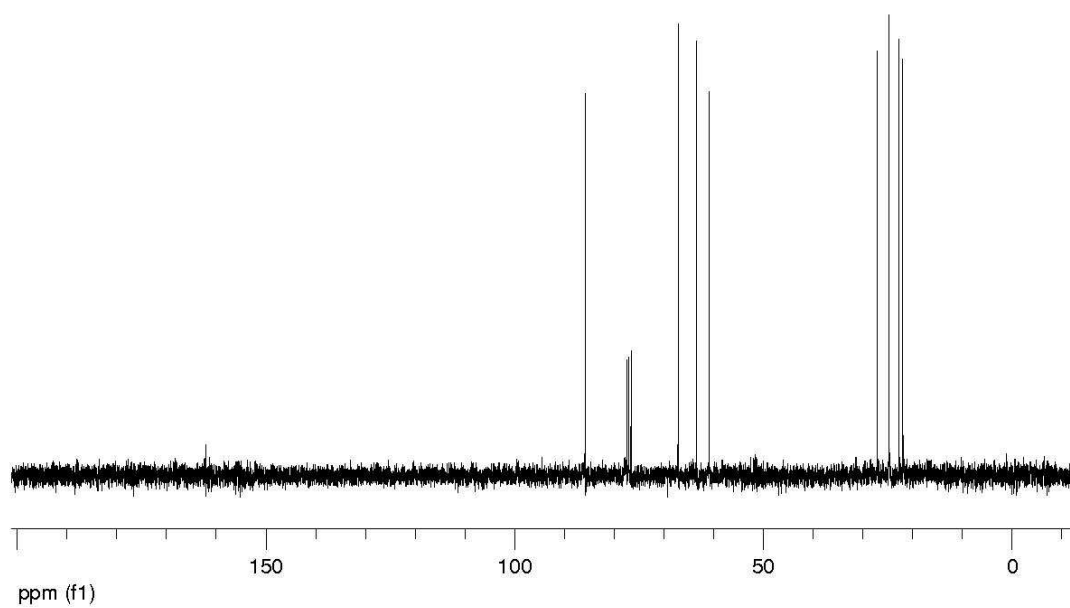


¹H and ¹³C NMR spectra for compound **3.53**

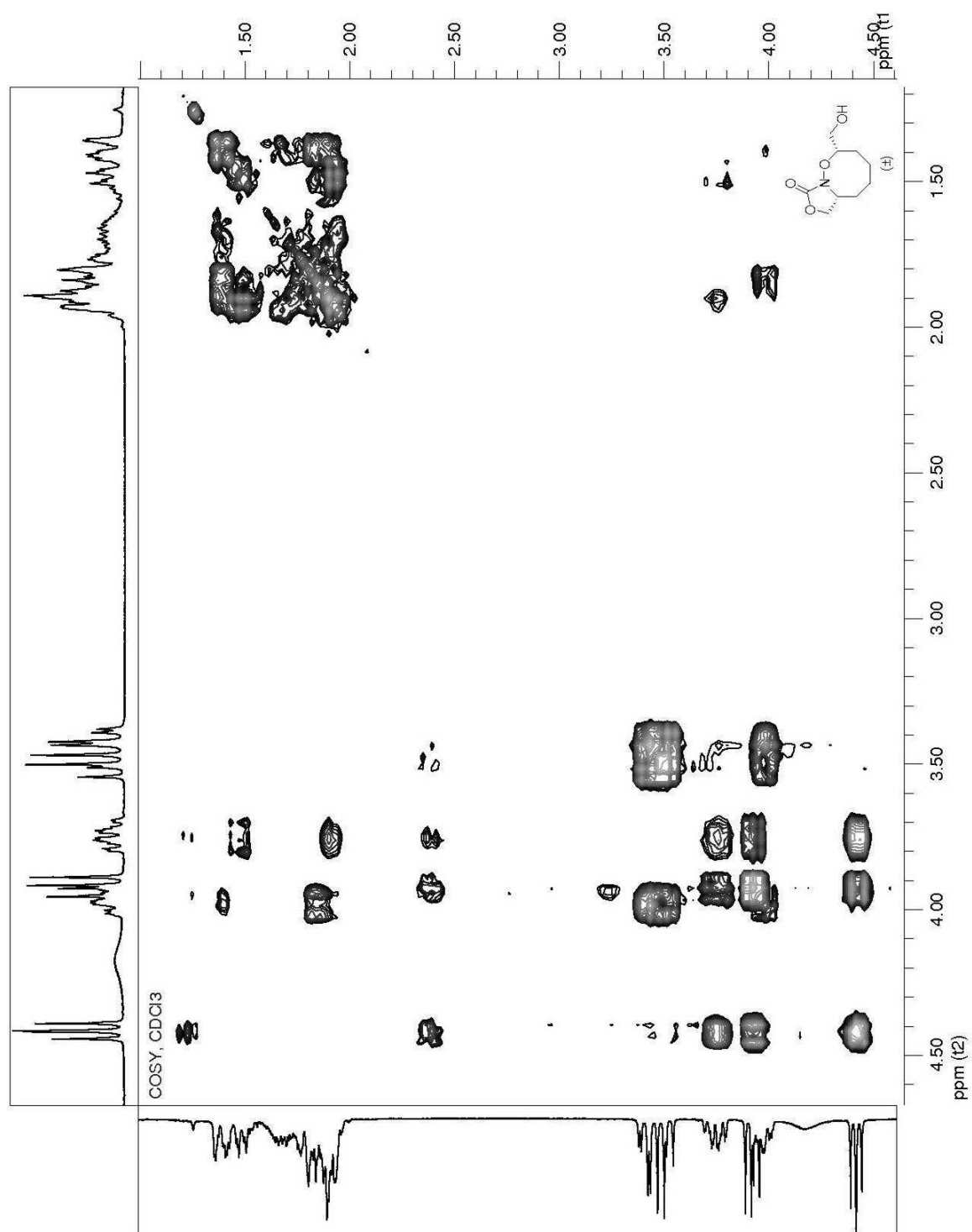
300 MHz, CDCl₃



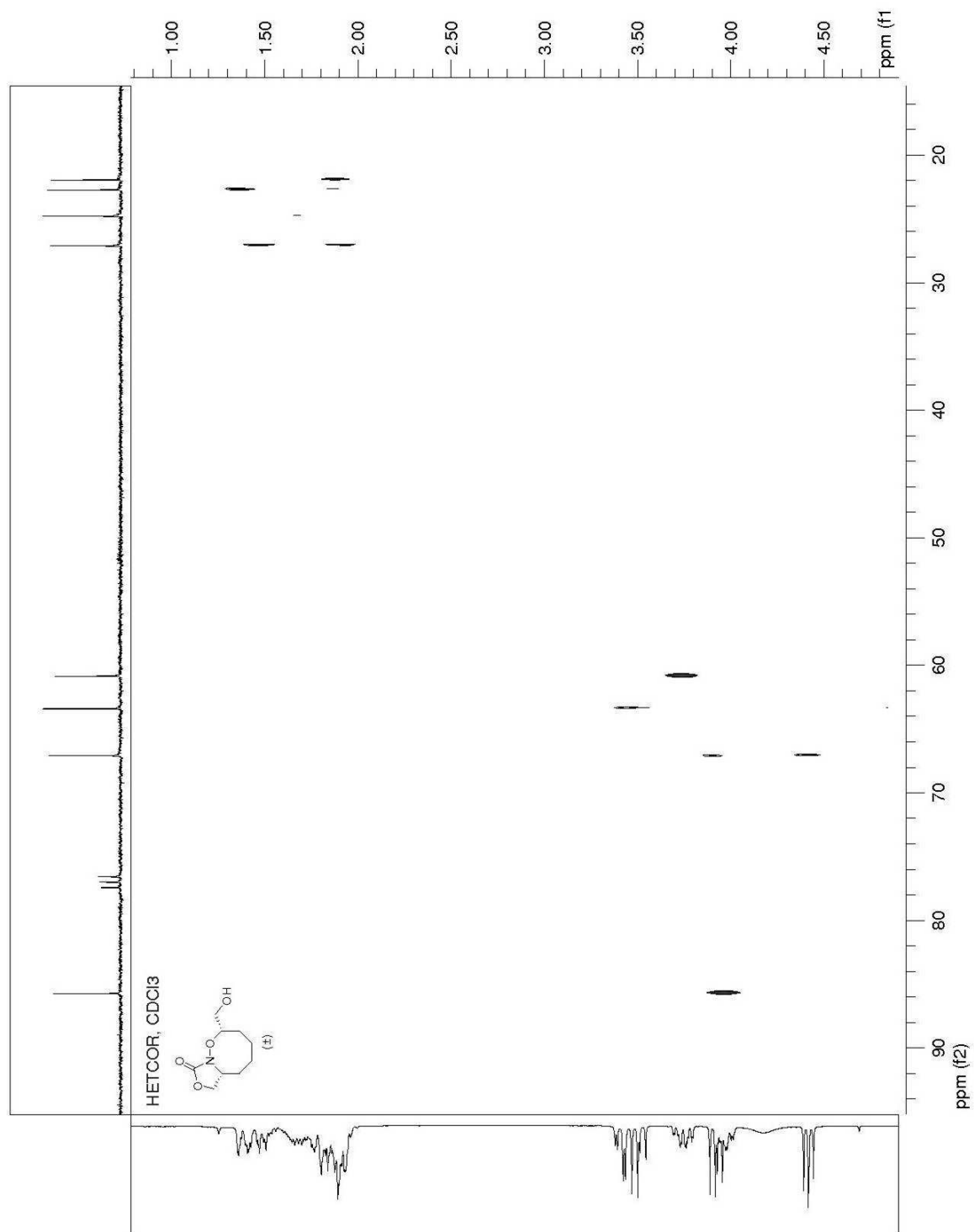
75 MHz, CDCl₃



¹H and ¹³C NMR spectra for compound **3.59**

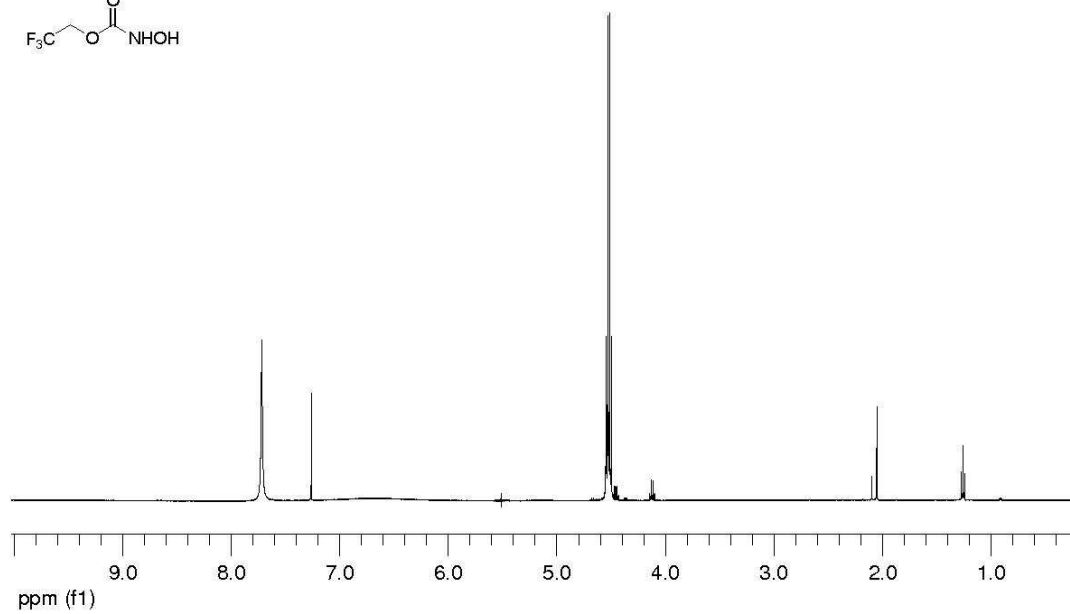
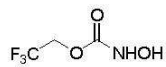


COSY NMR spectra for compound **3.59**

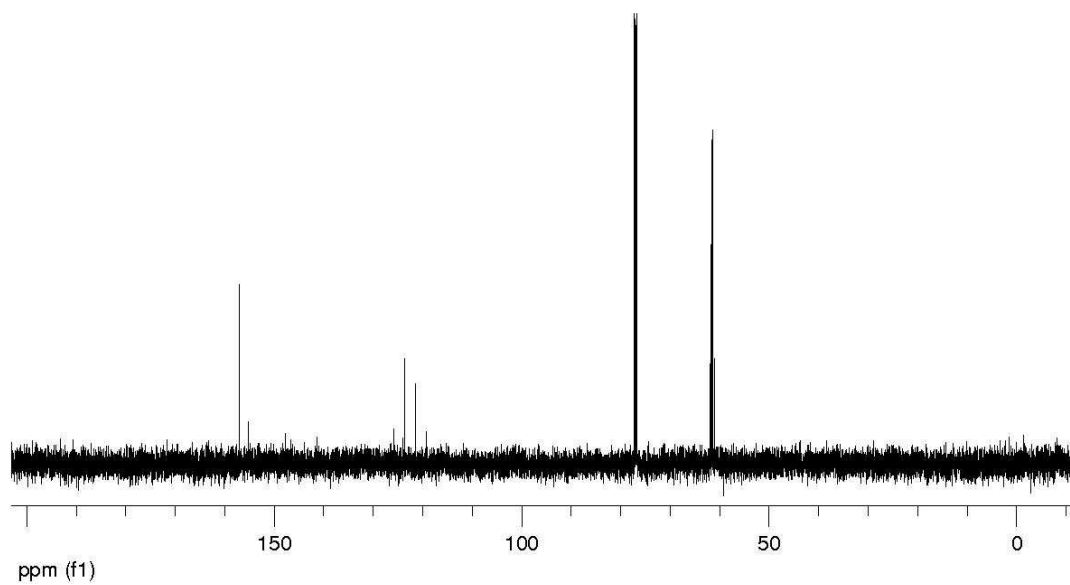


HETCOR NMR spectra for compound **3.59**

500 MHz, CDCl₃

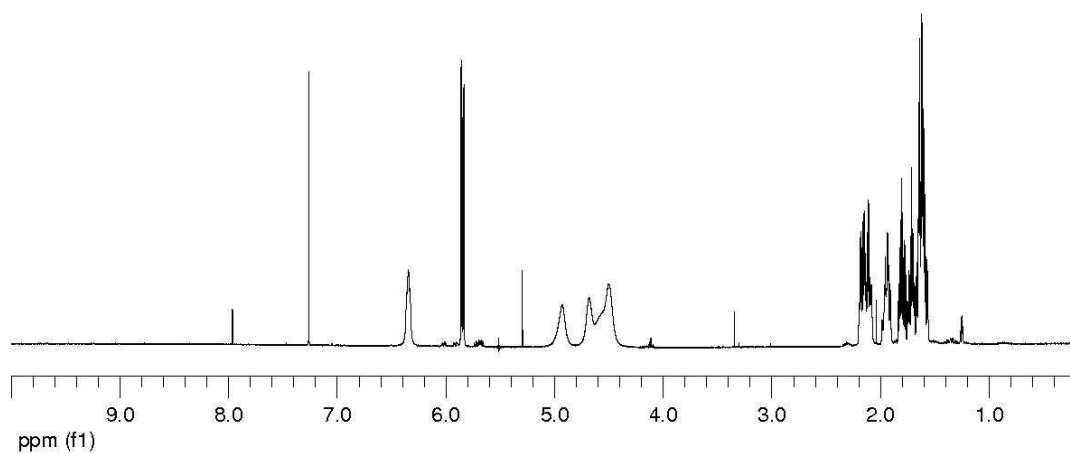
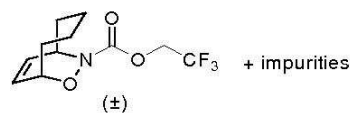


125 MHz, CDCl₃

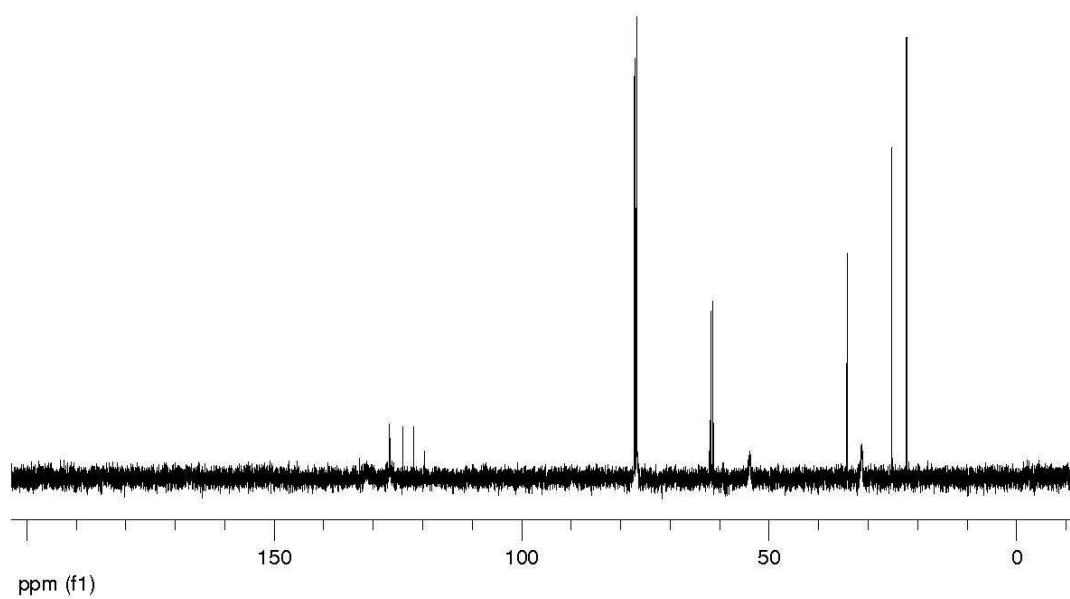


¹H and ¹³C NMR spectra for compound **3.63**

500 MHz, CDCl₃

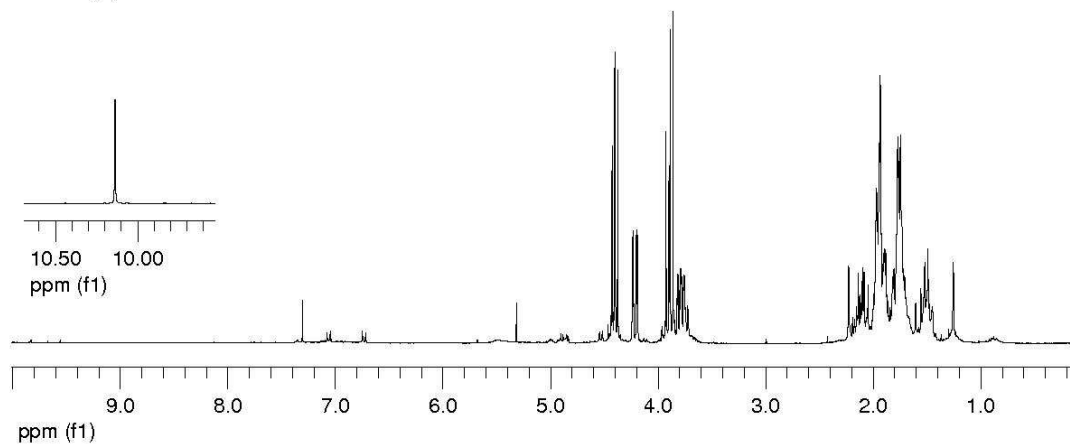
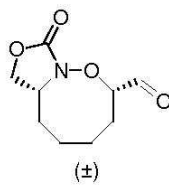


125 MHz, CDCl₃

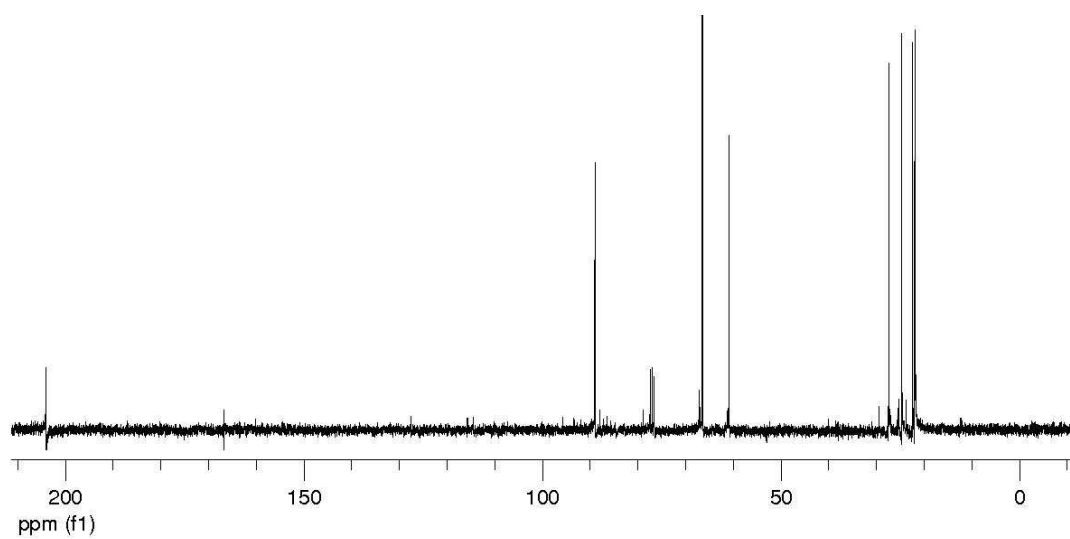


¹H and ¹³C NMR spectra for compound **3.64** (includes impurities)

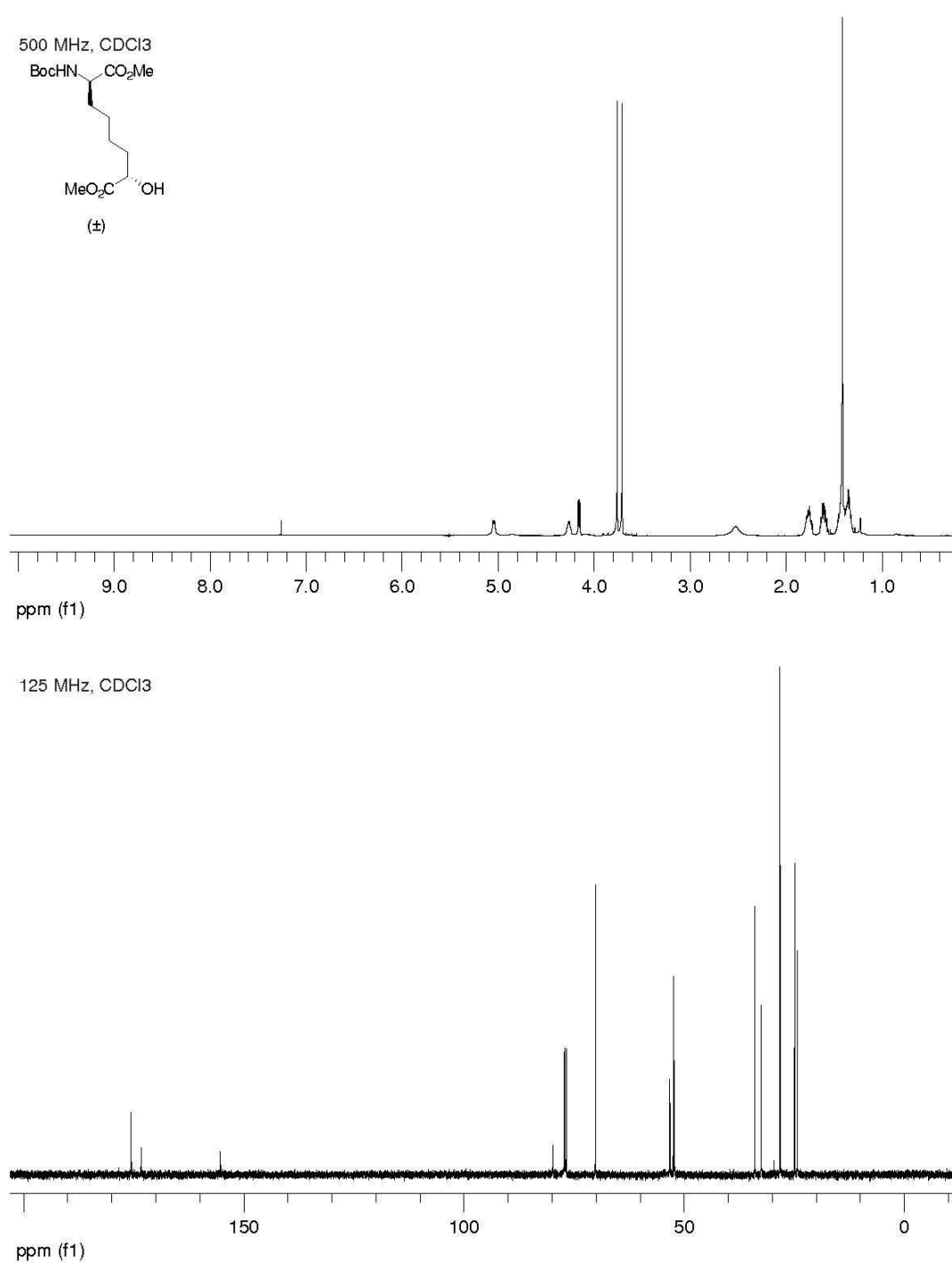
300 MHz, CDCl₃



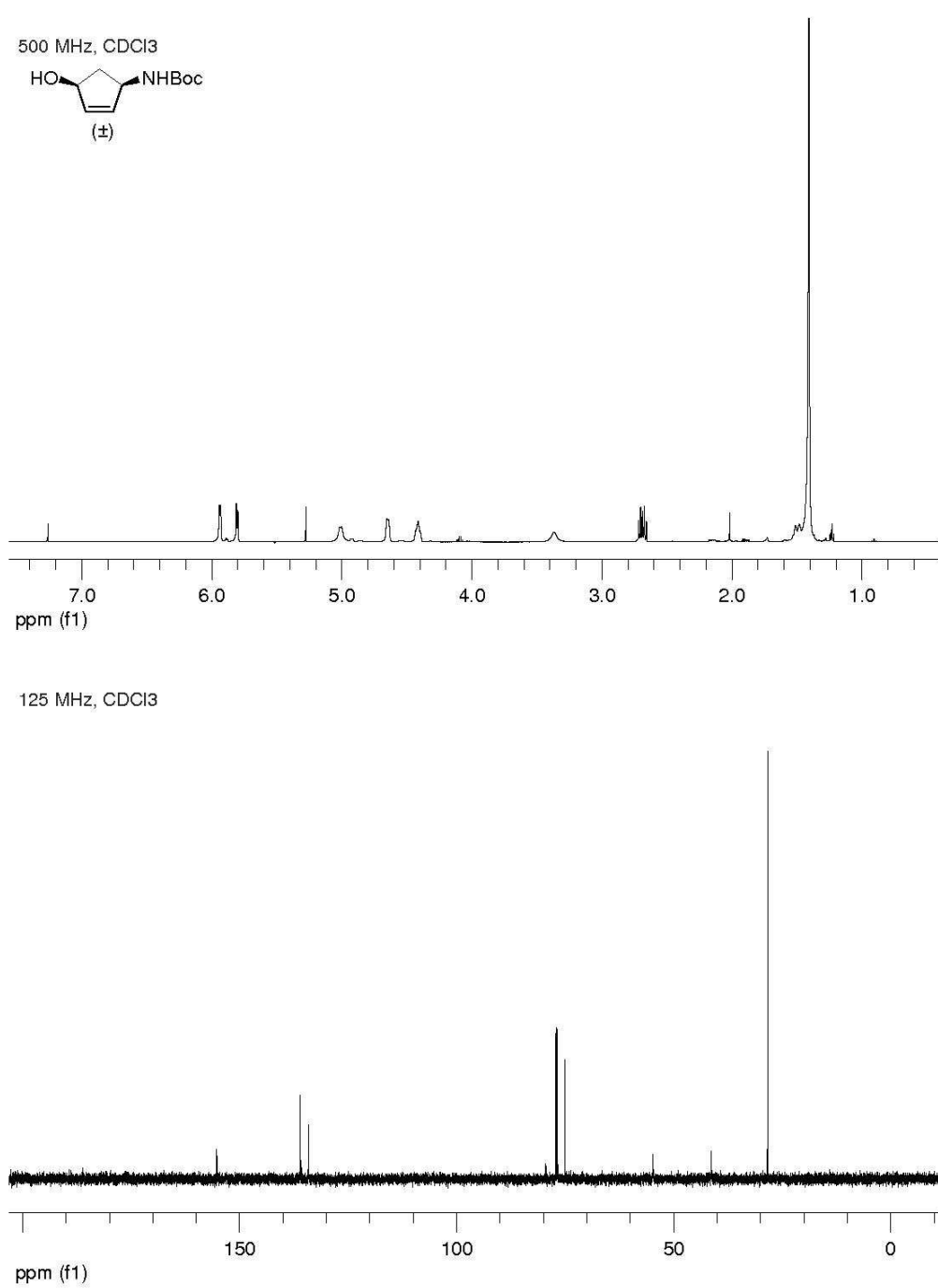
75 MHz, CDCl₃



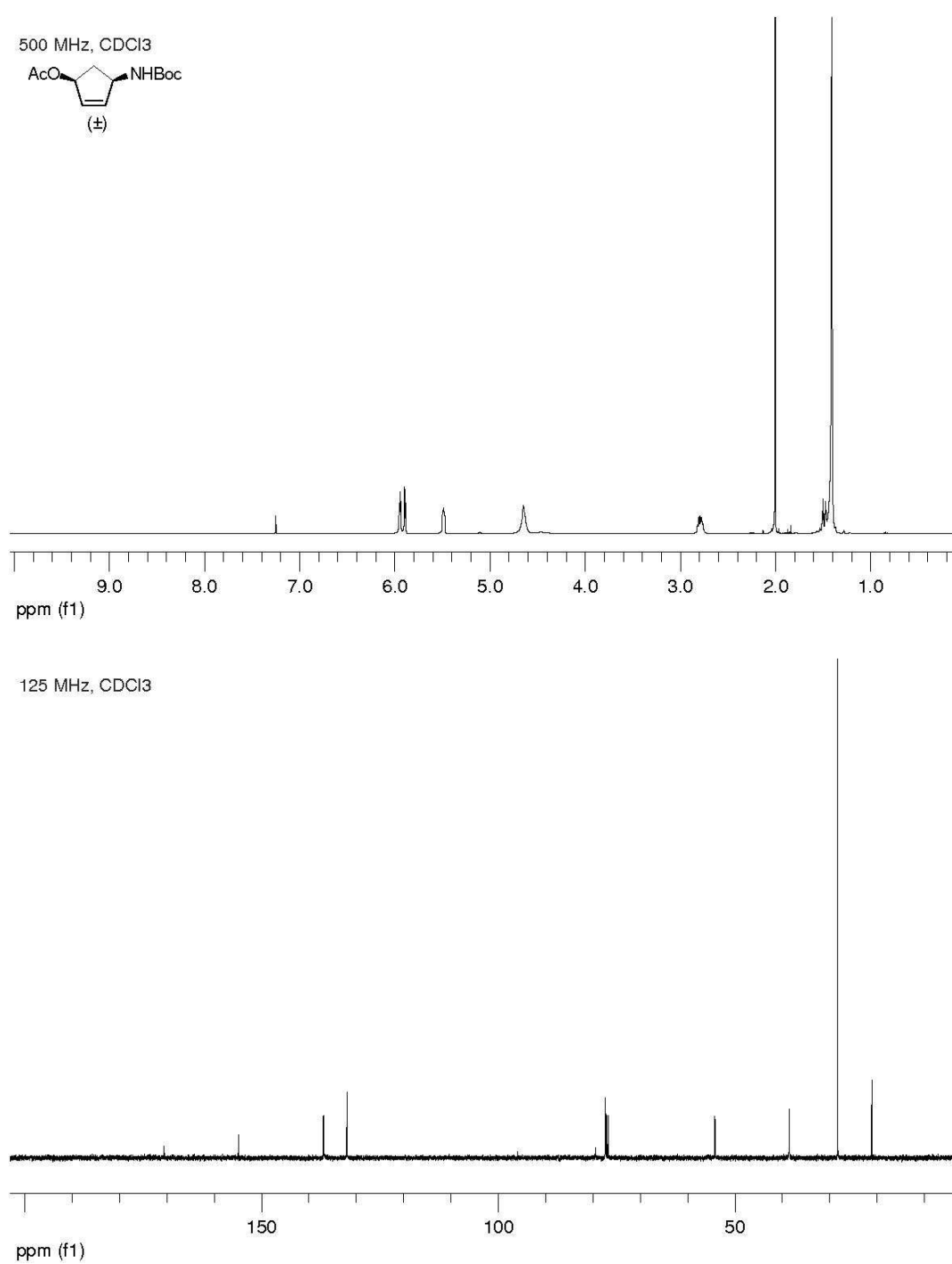
¹H and ¹³C NMR spectra for compound **3.66**



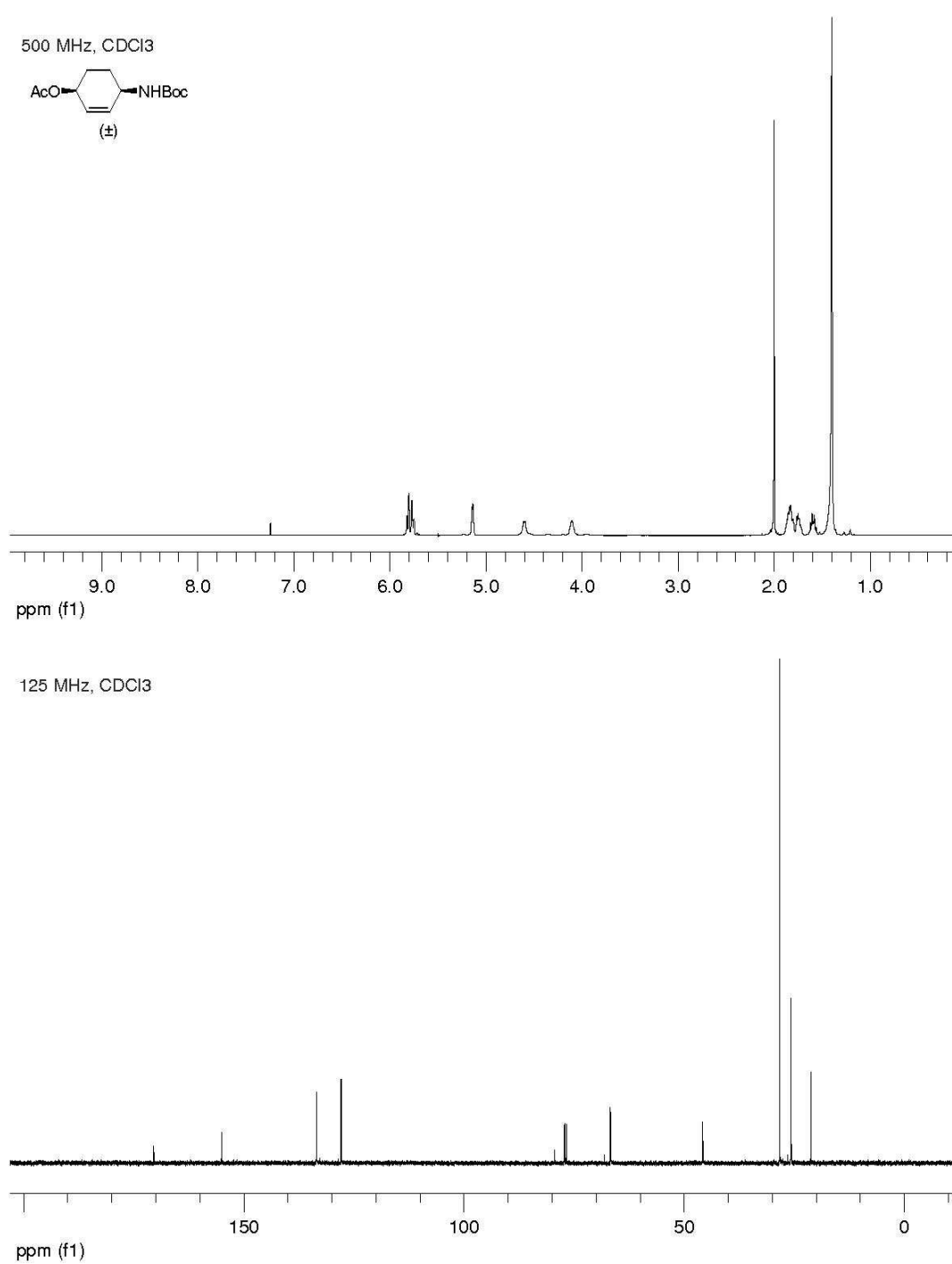
¹H and ¹³C NMR spectra for compound **3.69**



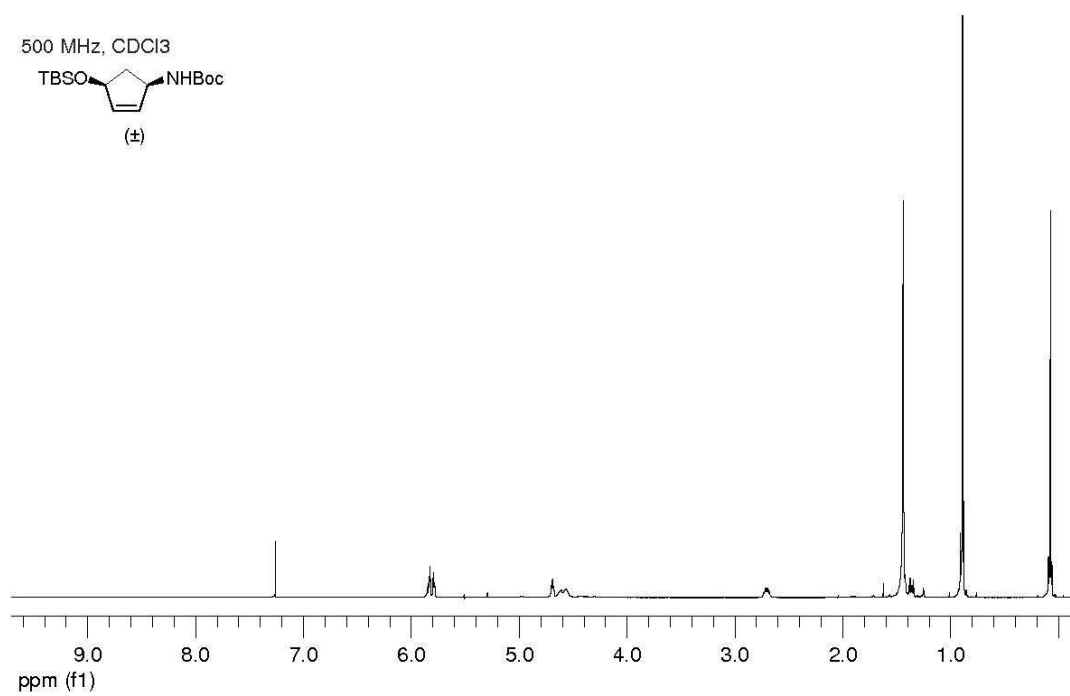
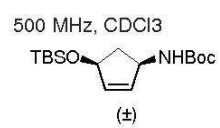
¹H and ¹³C NMR spectra for compound **3.71**



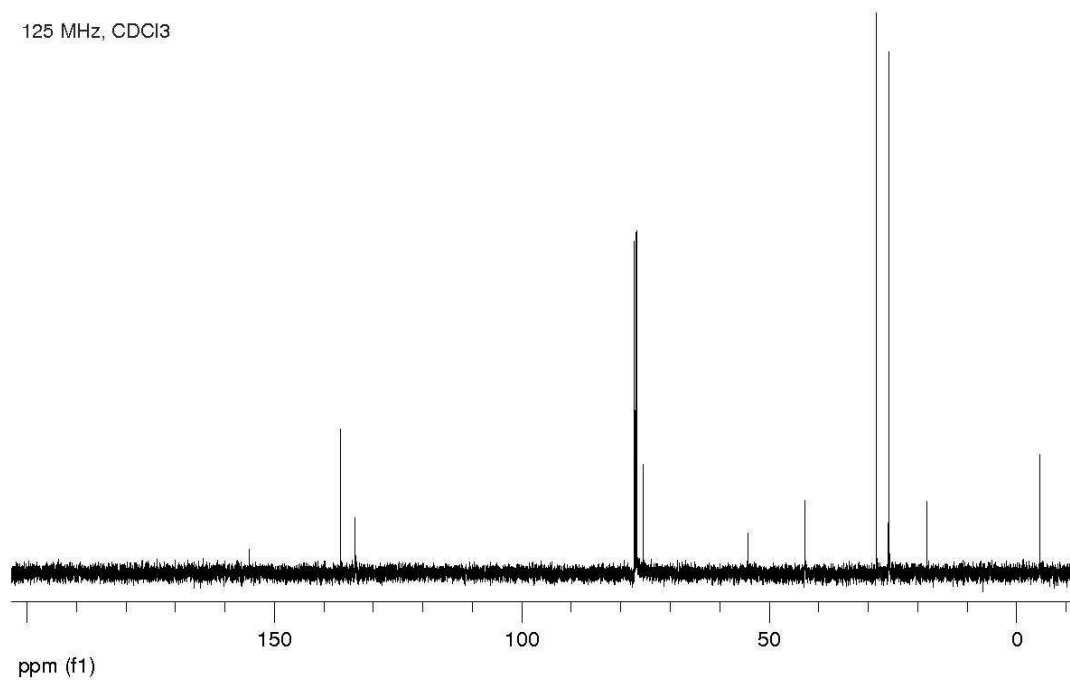
¹H and ¹³C NMR spectra for compound **3.73**



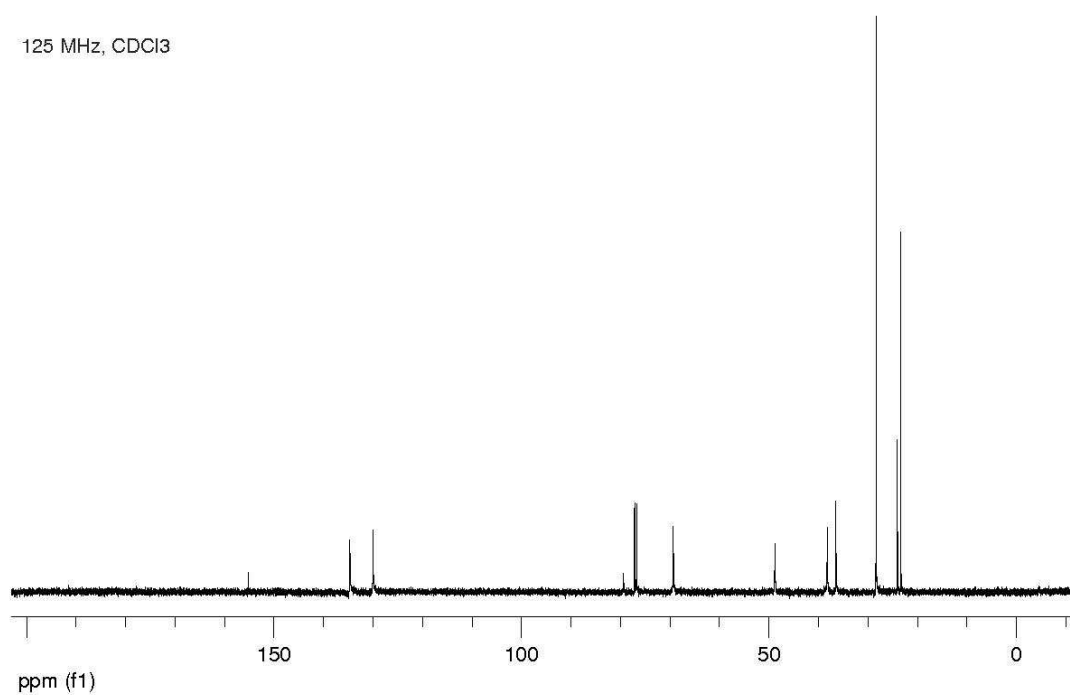
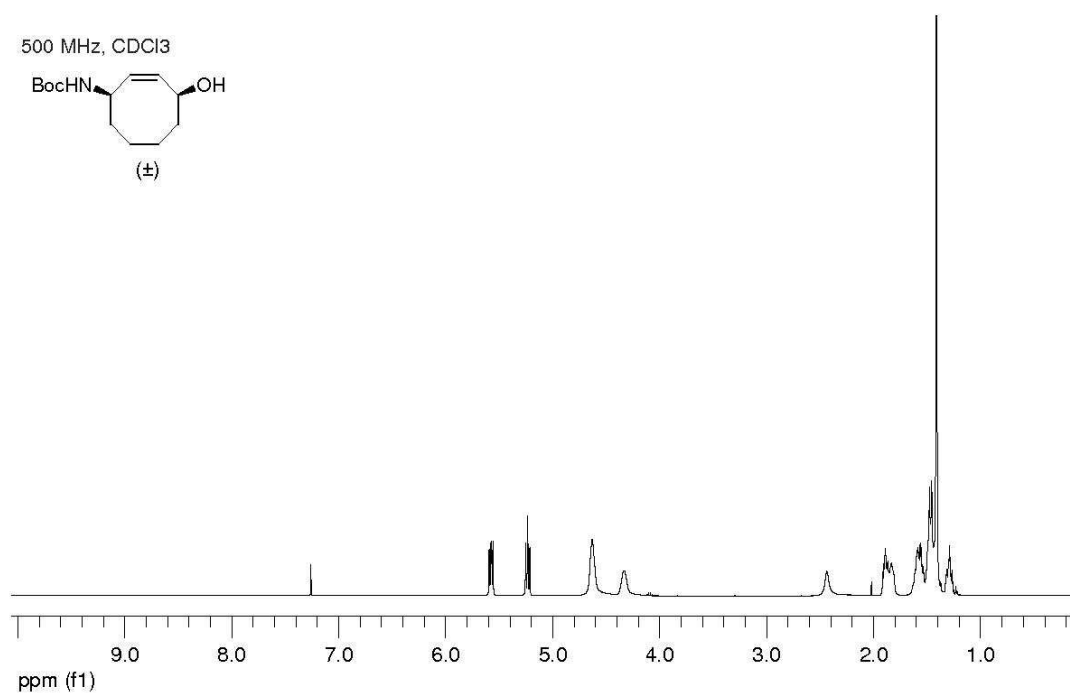
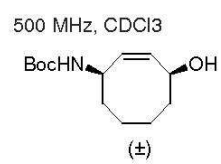
¹H and ¹³C NMR spectra for compound **3.74**



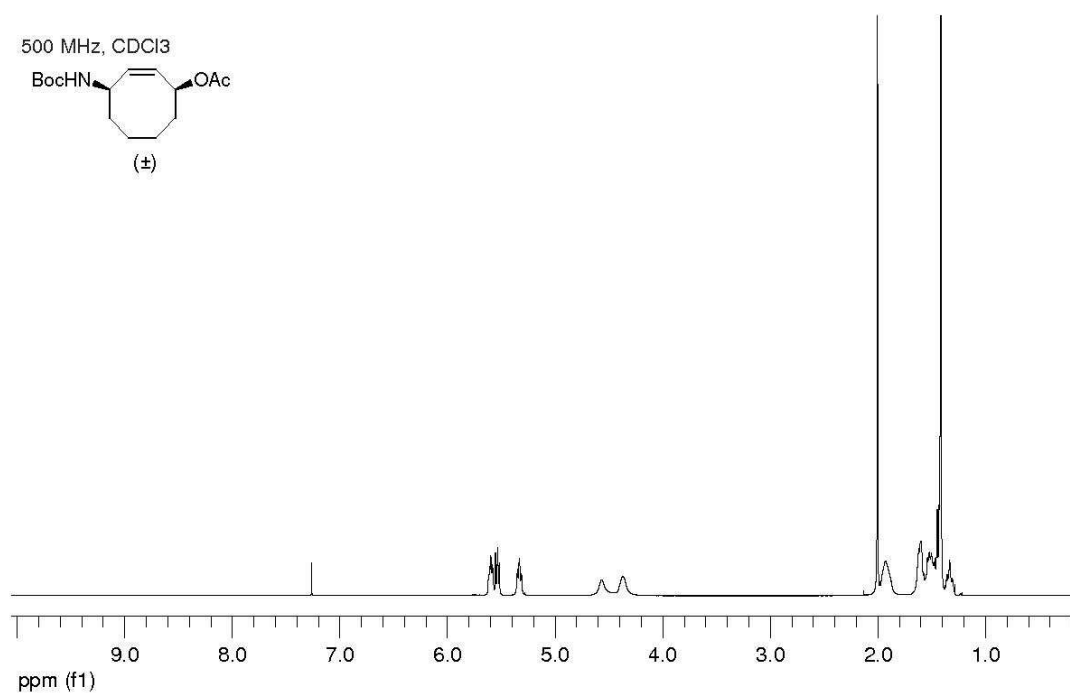
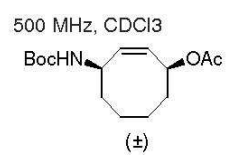
125 MHz, CDCl₃



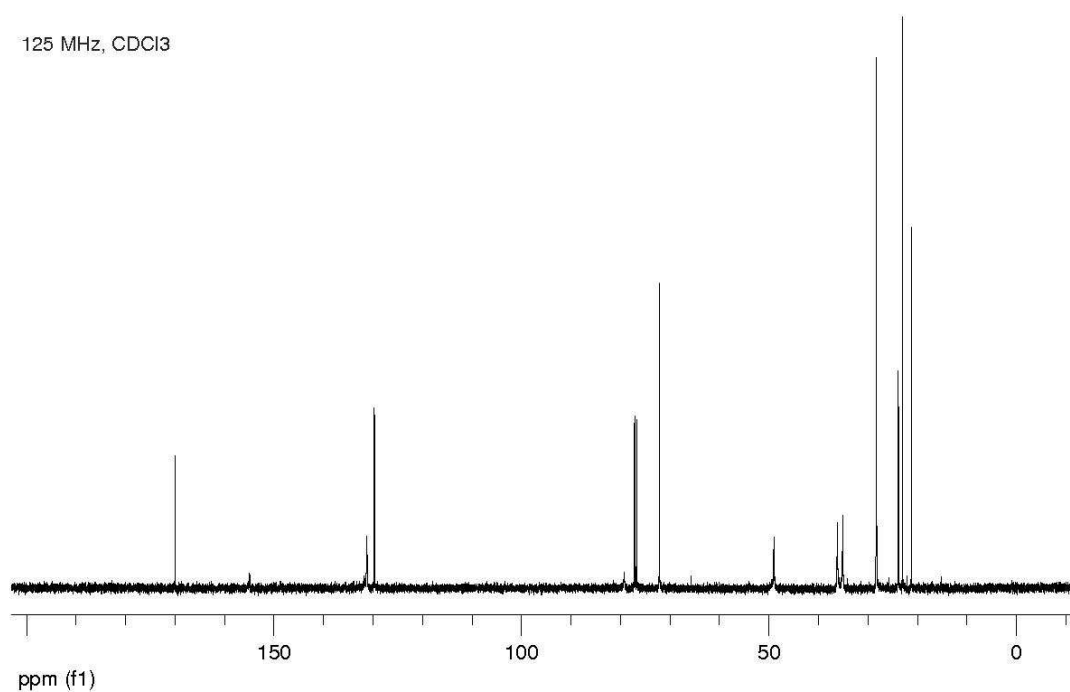
¹H and ¹³C NMR spectra for compound **3.75**



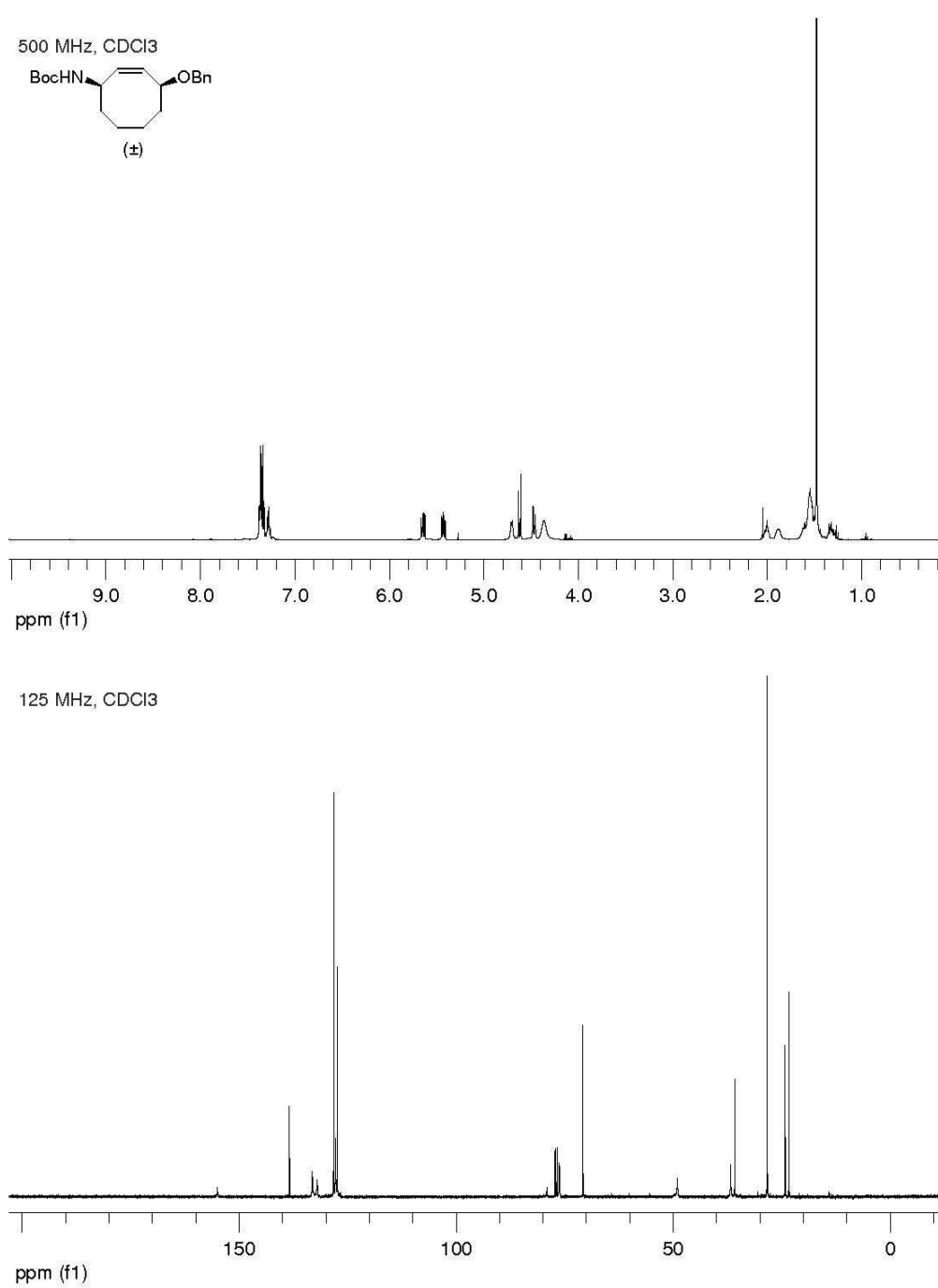
¹H and ¹³C NMR spectra for compound **3.76**



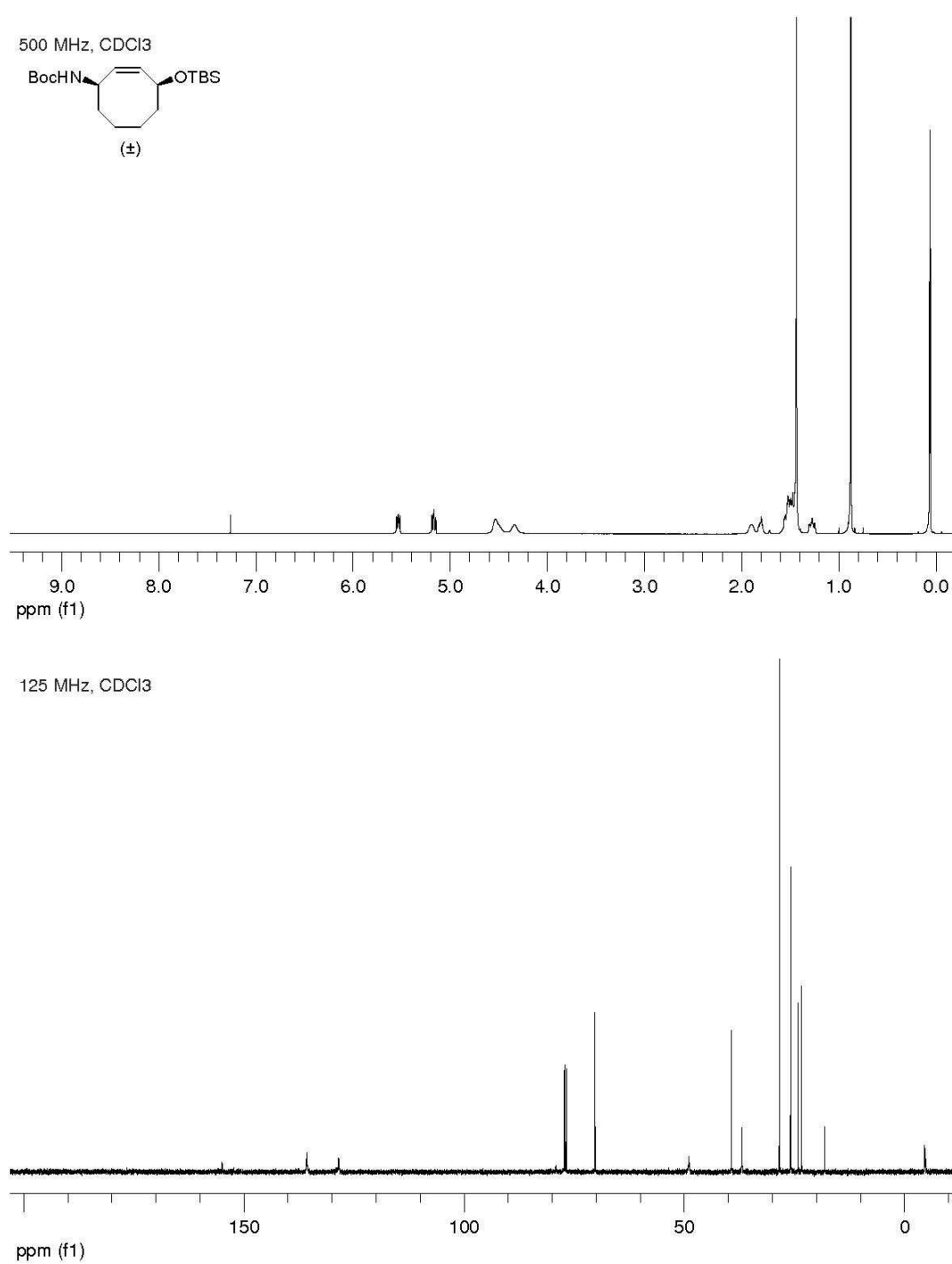
125 MHz, CDCl₃



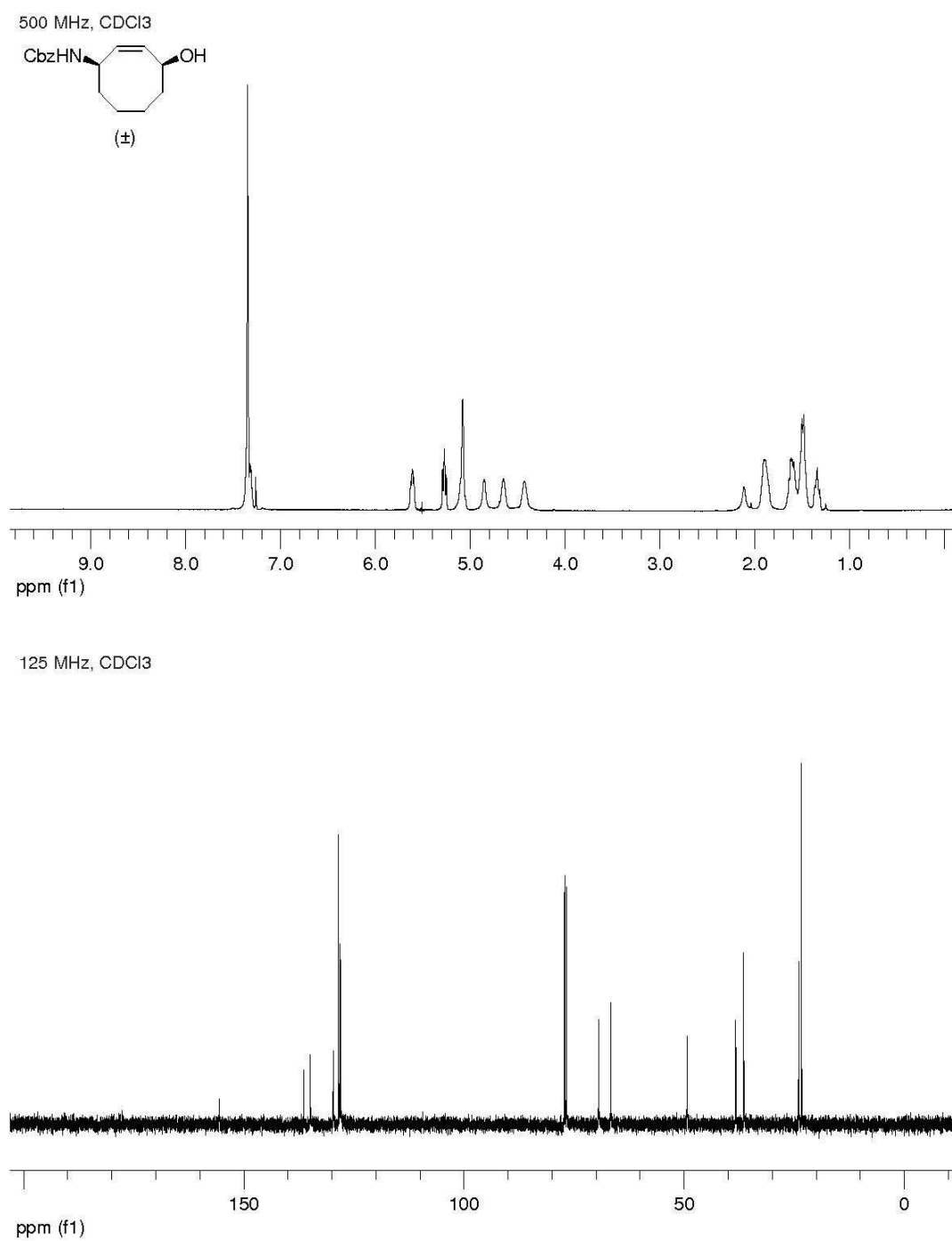
¹H and ¹³C NMR spectra for compound **3.77**



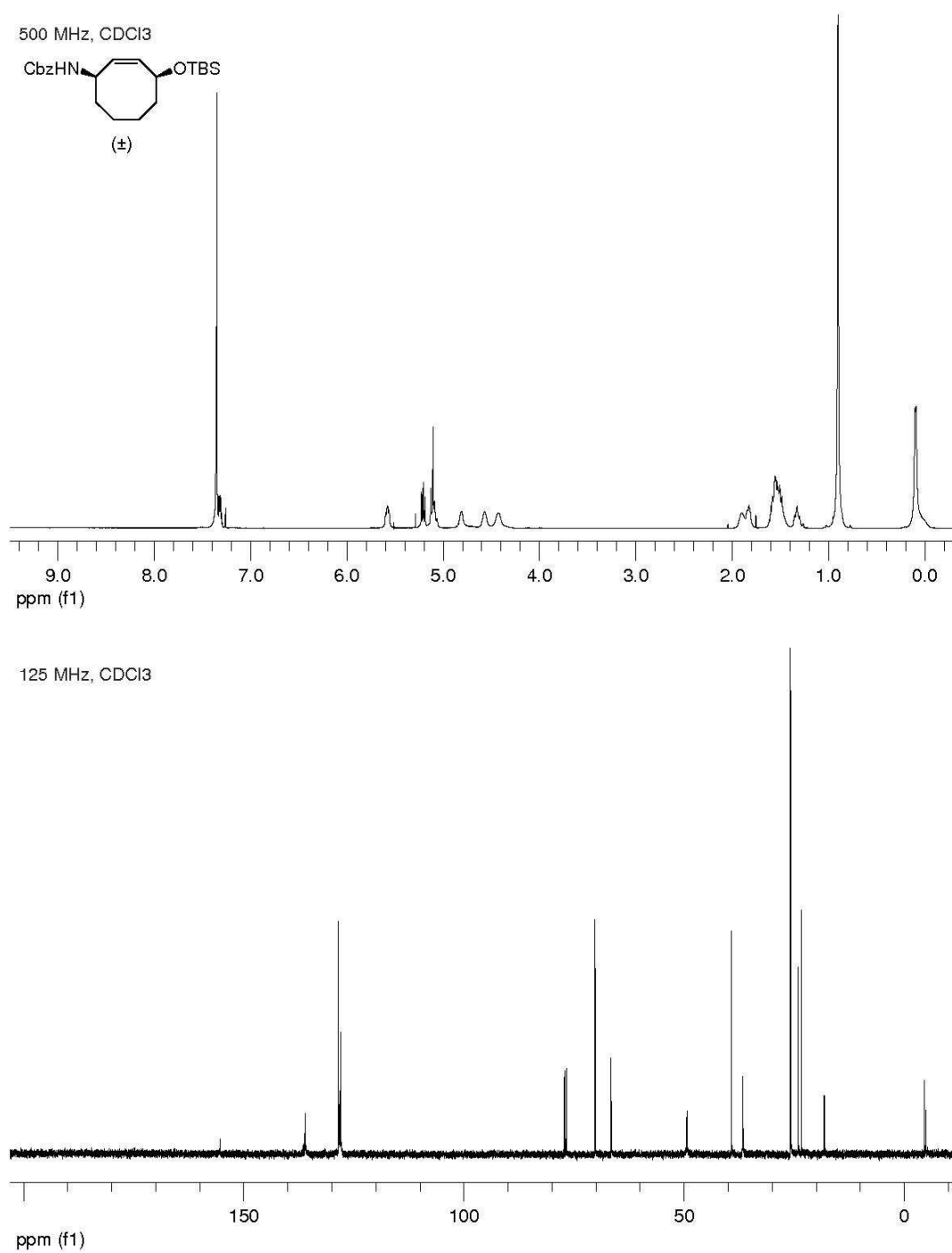
¹H and ¹³C NMR spectra for compound **3.78**



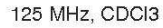
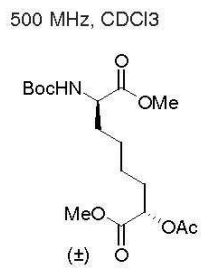
¹H and ¹³C NMR spectra for compound **3.79**

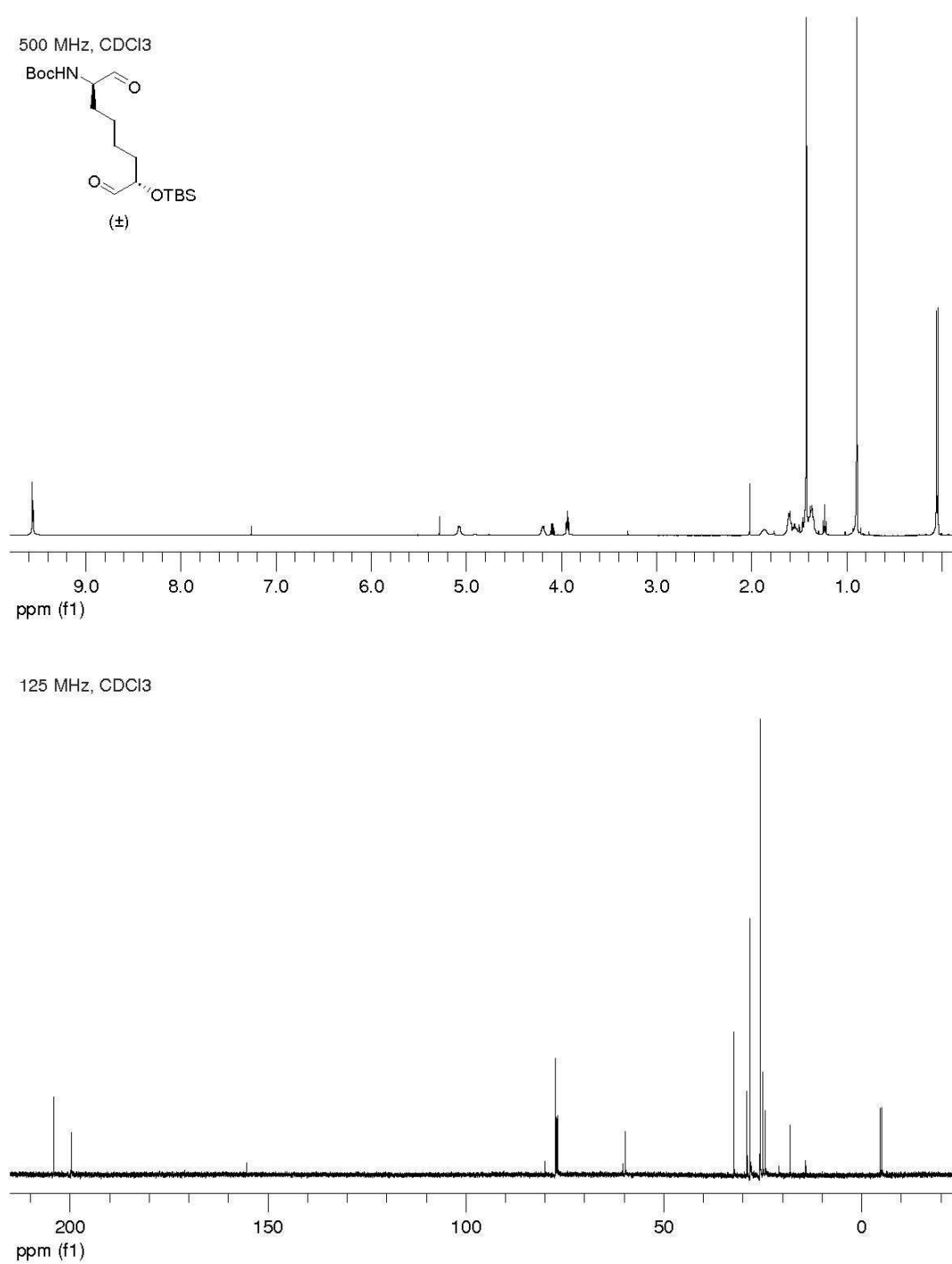


¹H and ¹³C NMR spectra for compound **3.80**

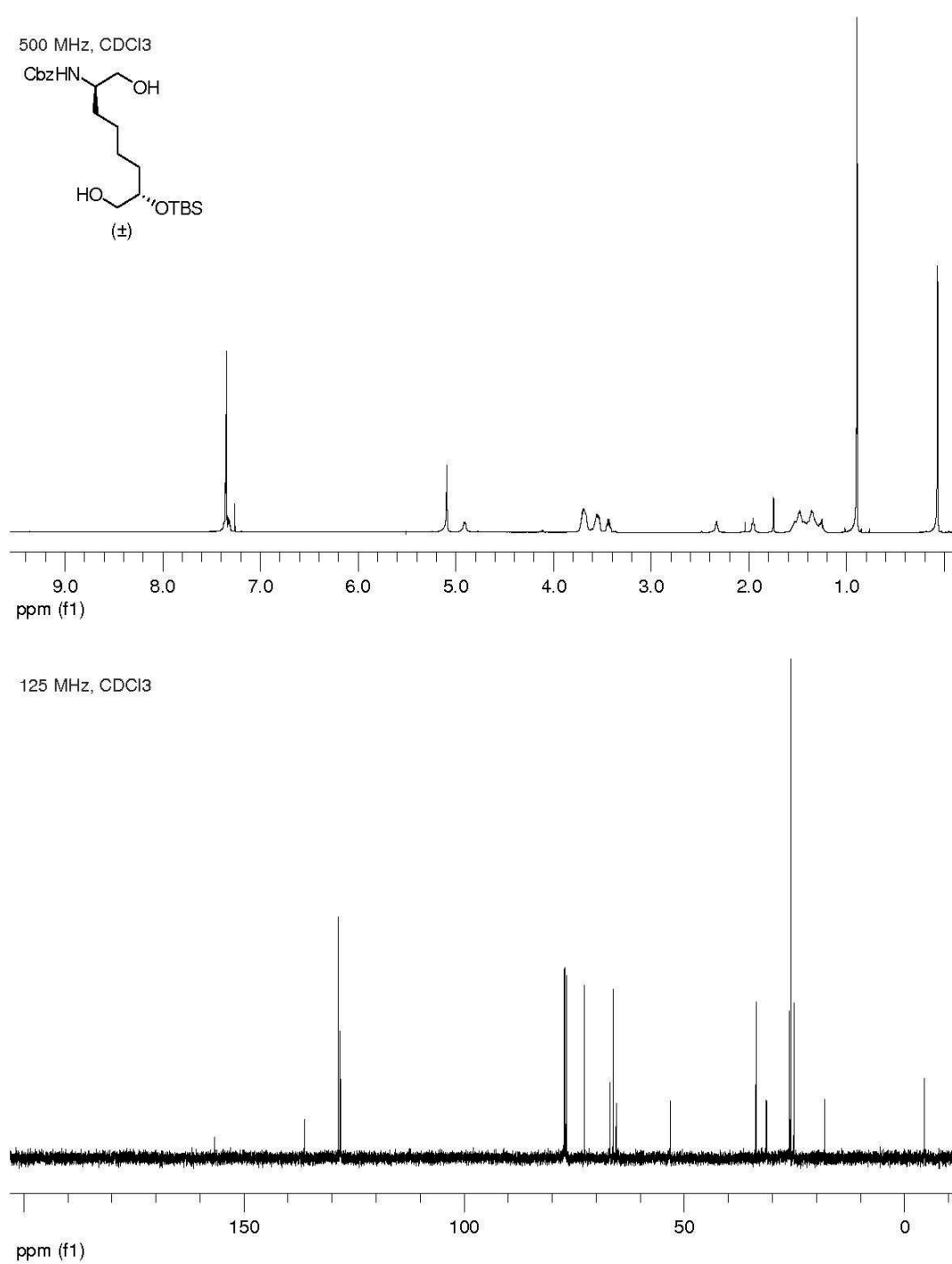


¹H and ¹³C NMR spectra for compound **3.81**

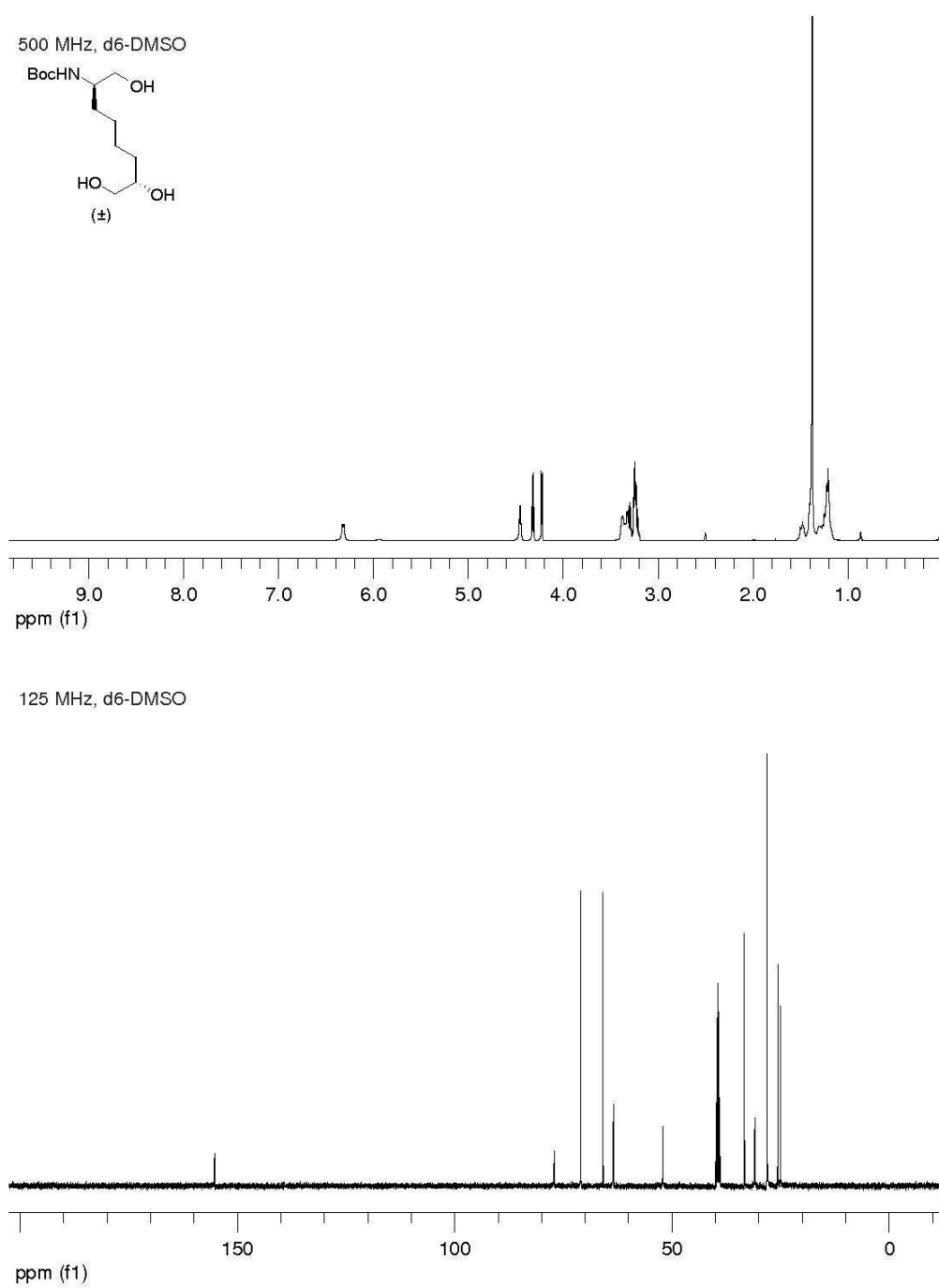




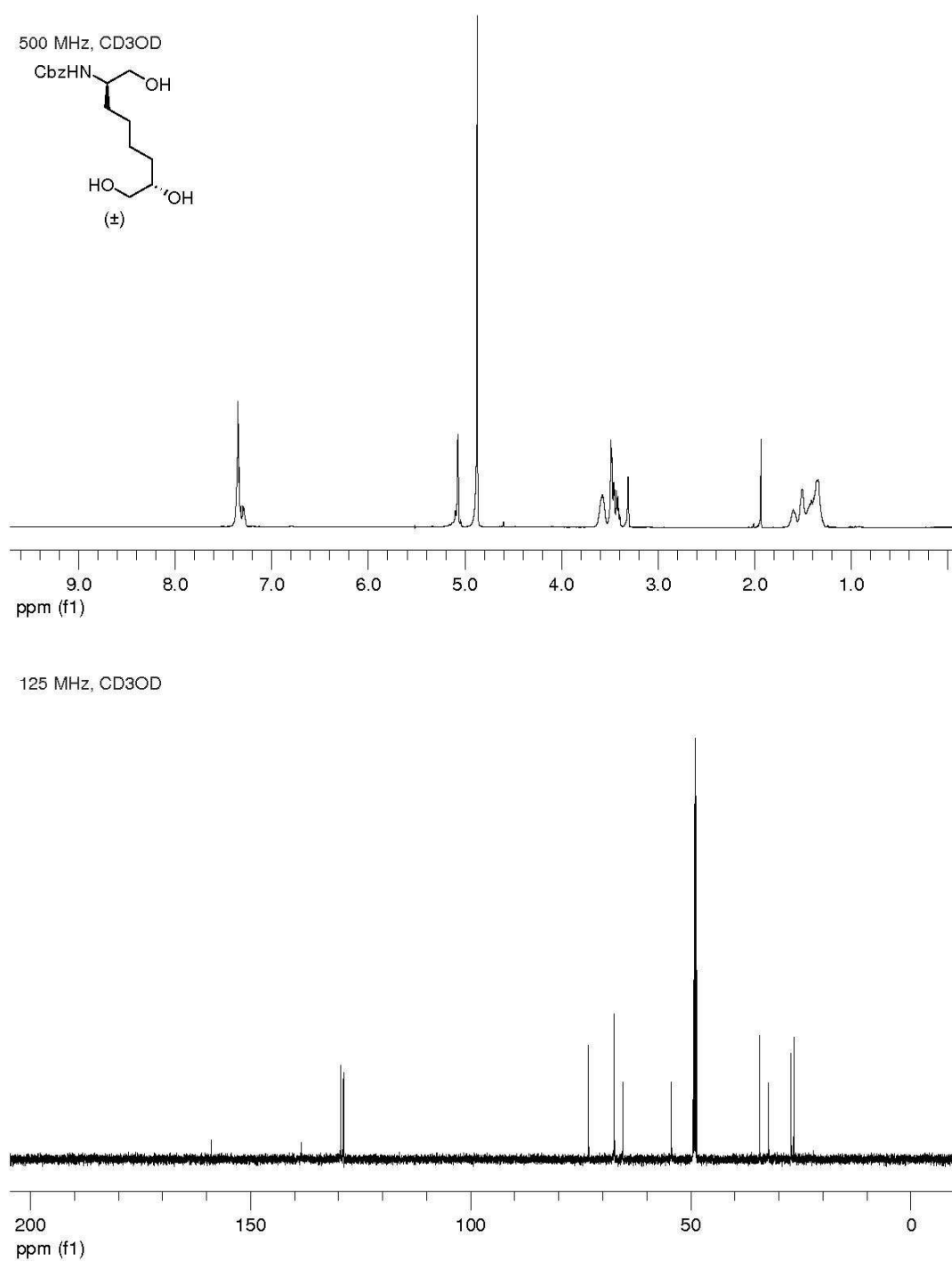
¹H and ¹³C NMR spectra for compound **3.93**



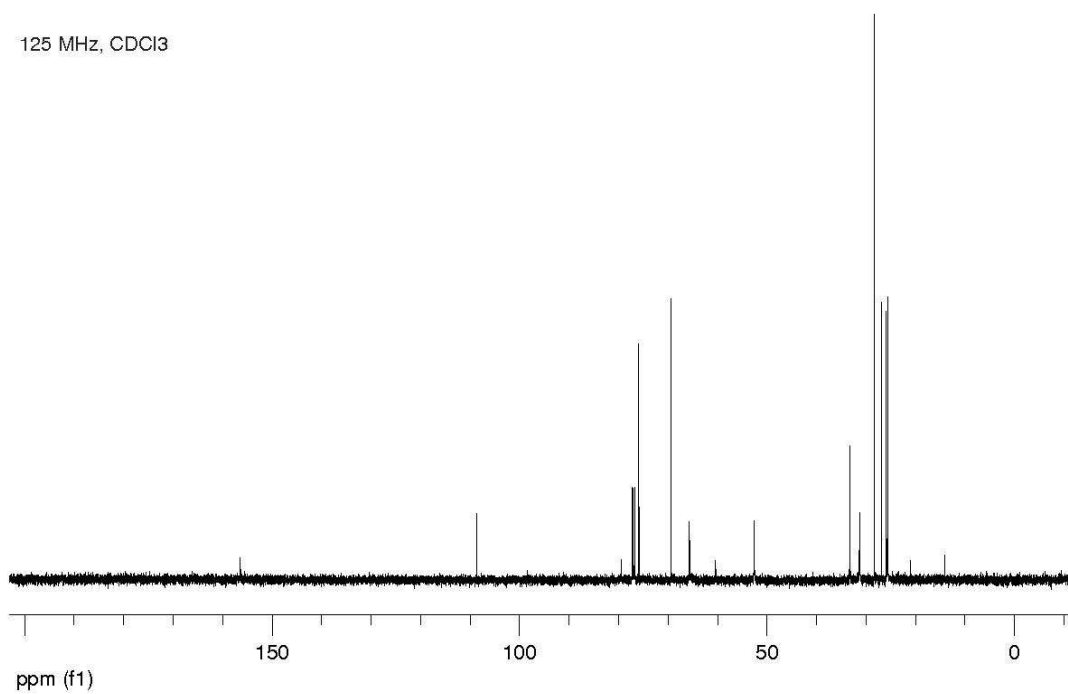
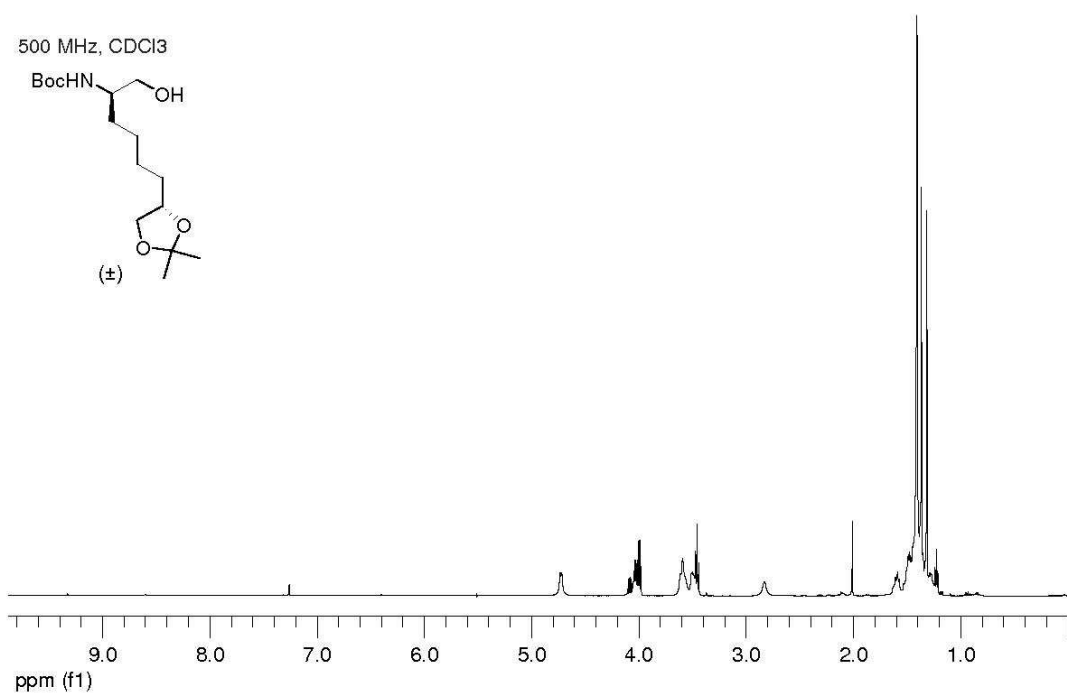
¹H and ¹³C NMR spectra for compound **3.95**



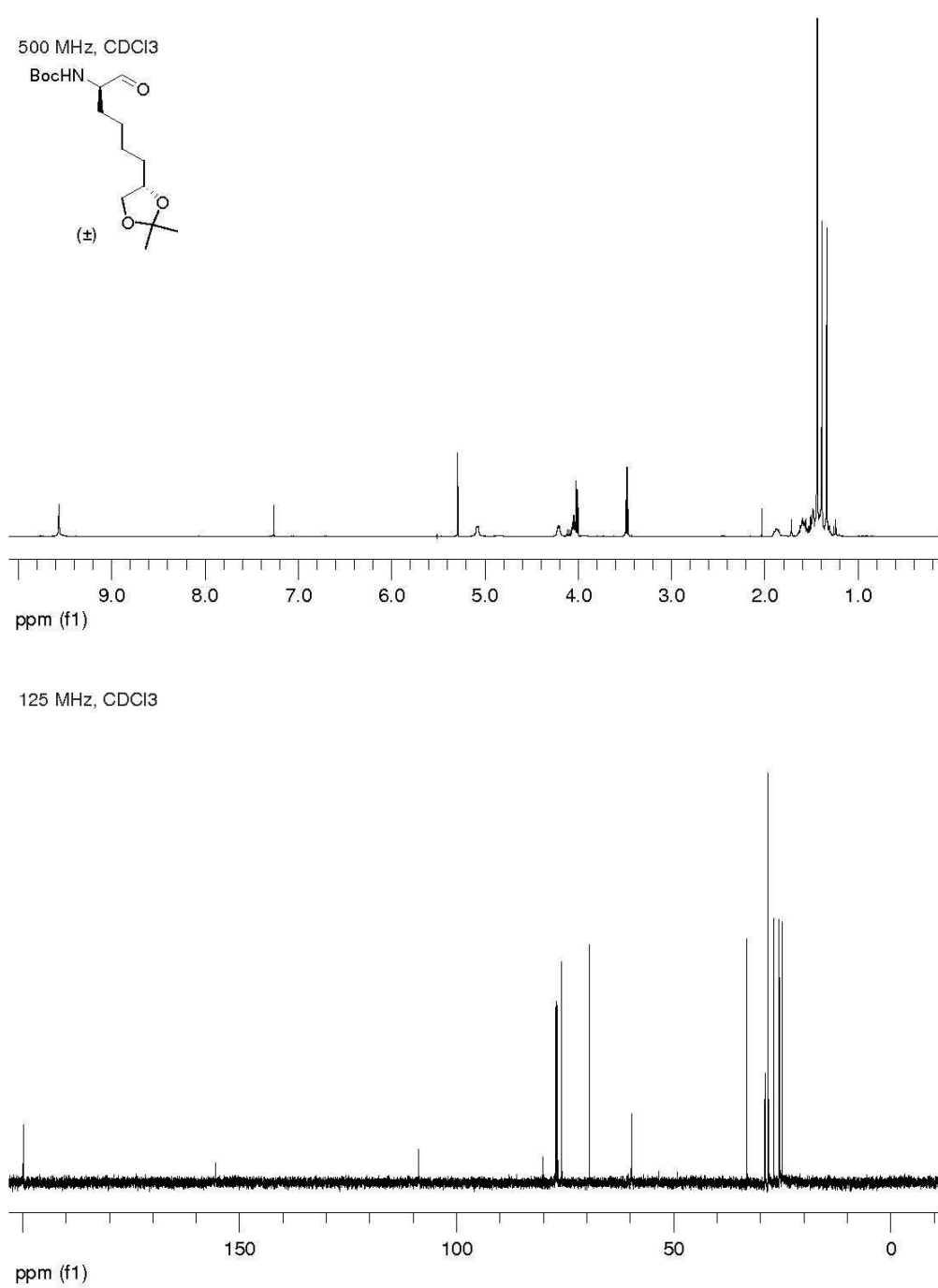
^1H and ^{13}C NMR spectra for compound **3.96**



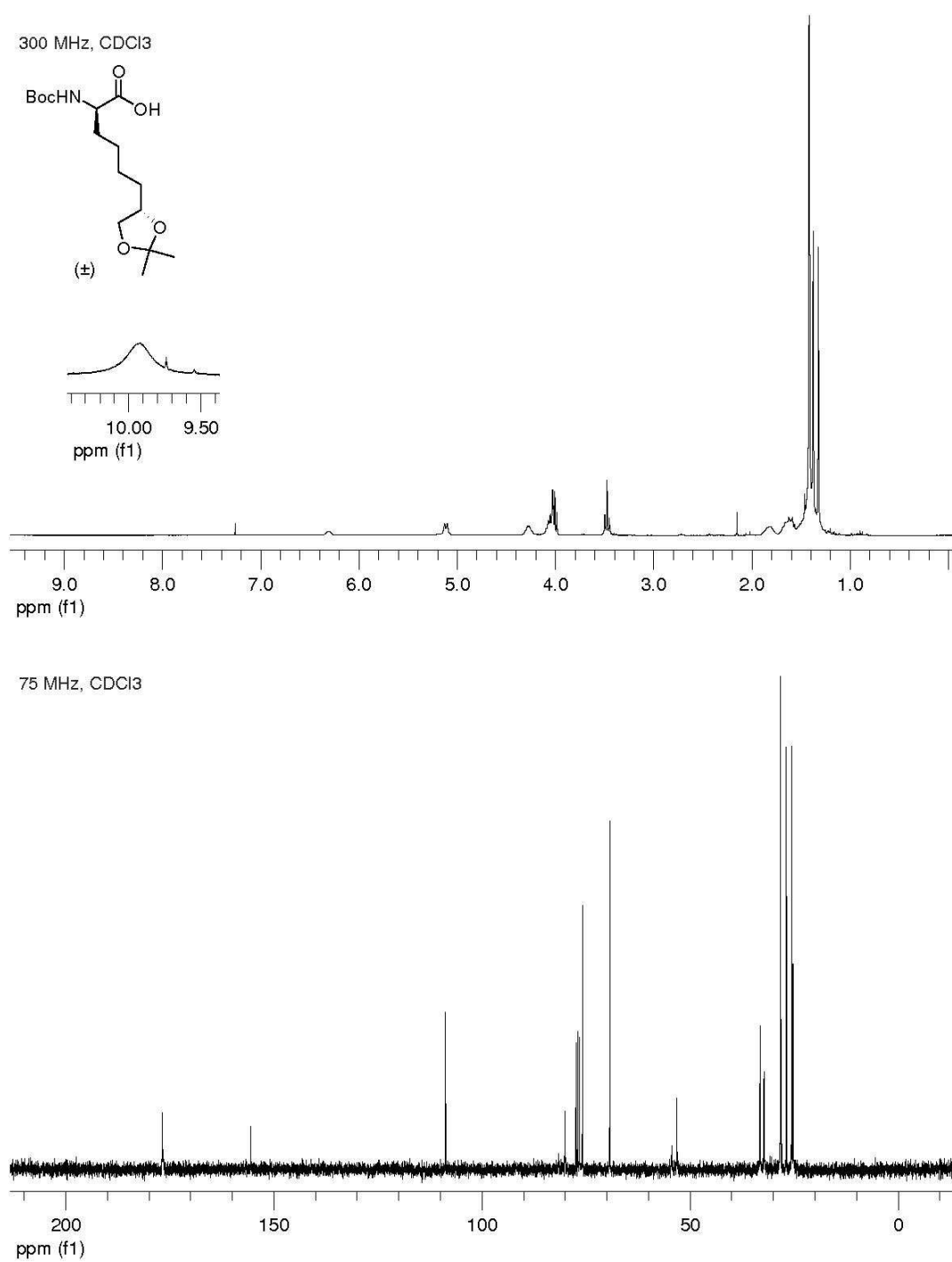
¹H and ¹³C NMR spectra for compound **3.97**



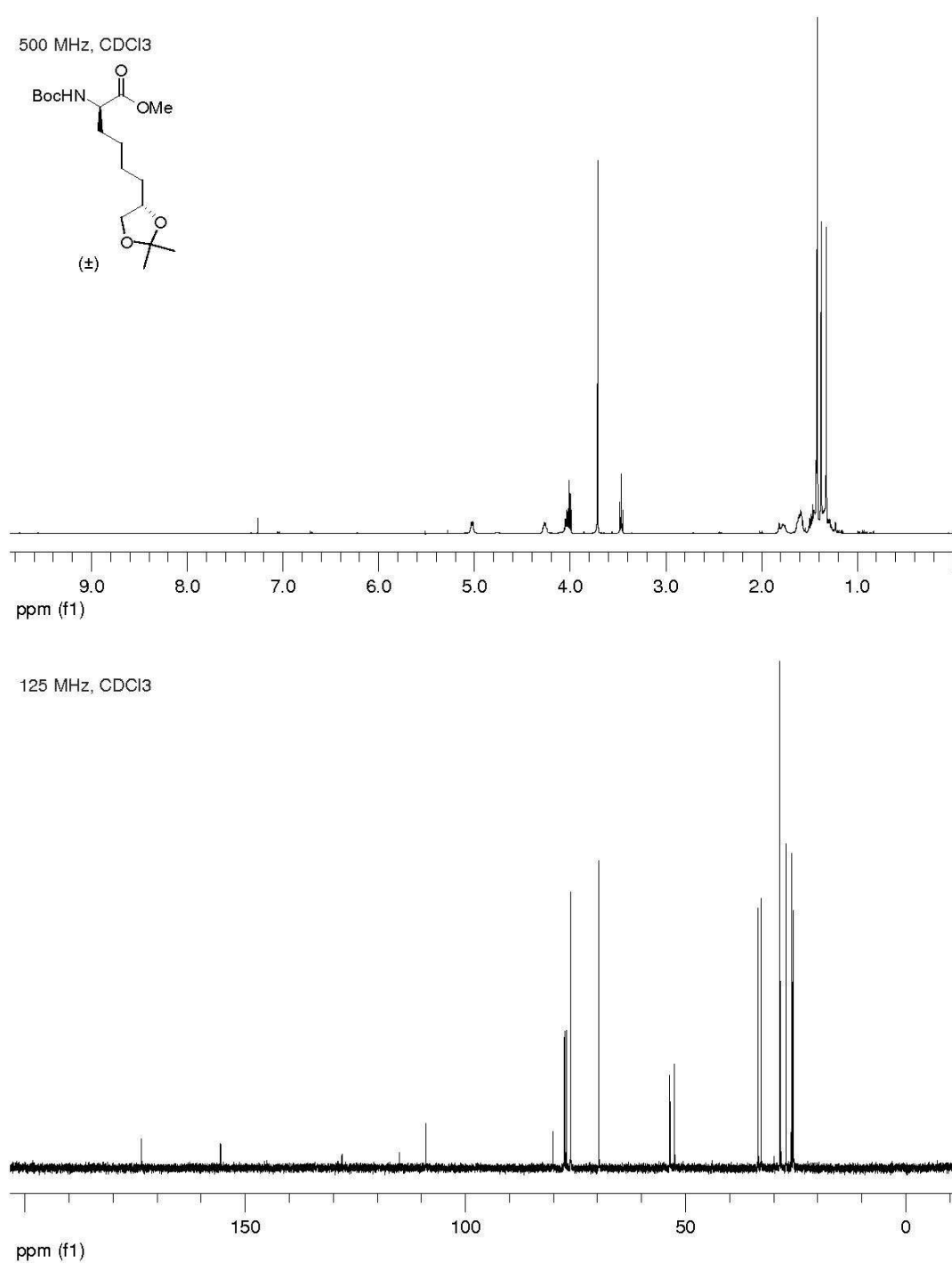
442



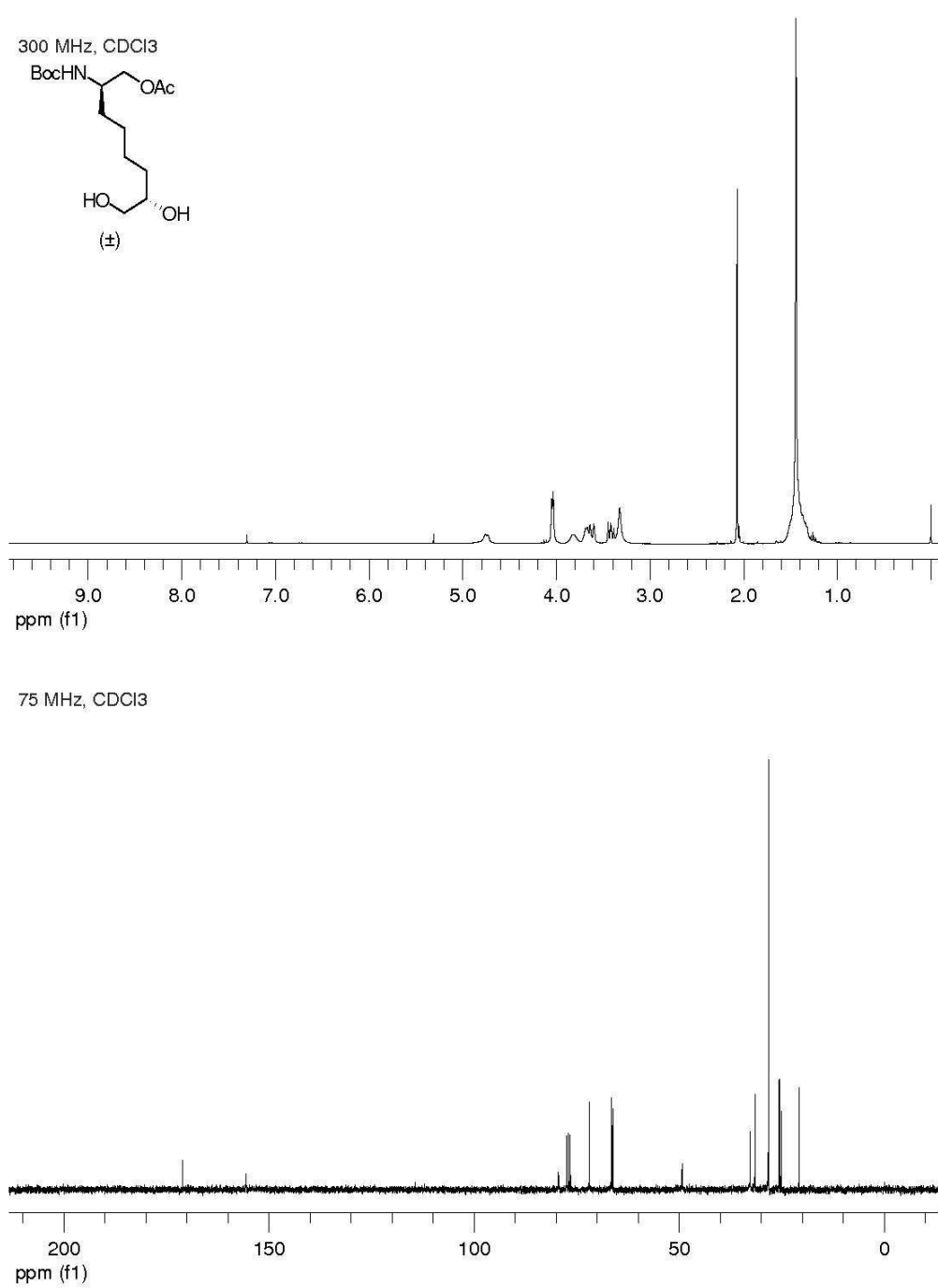
¹H and ¹³C NMR spectra for compound **3.100**



¹H and ¹³C NMR spectra for compound **3.101**

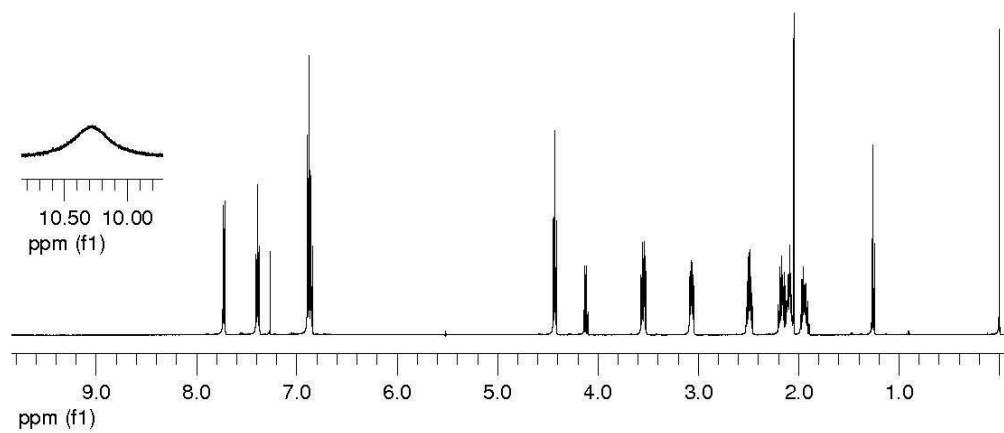
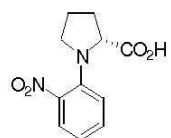


¹H and ¹³C NMR spectra for compound **3.102**

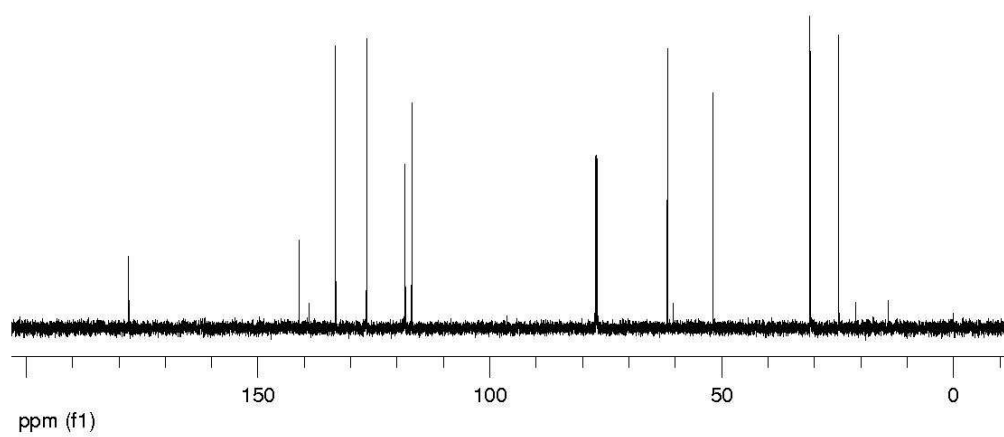


¹H and ¹³C NMR spectra for compound **3.106**

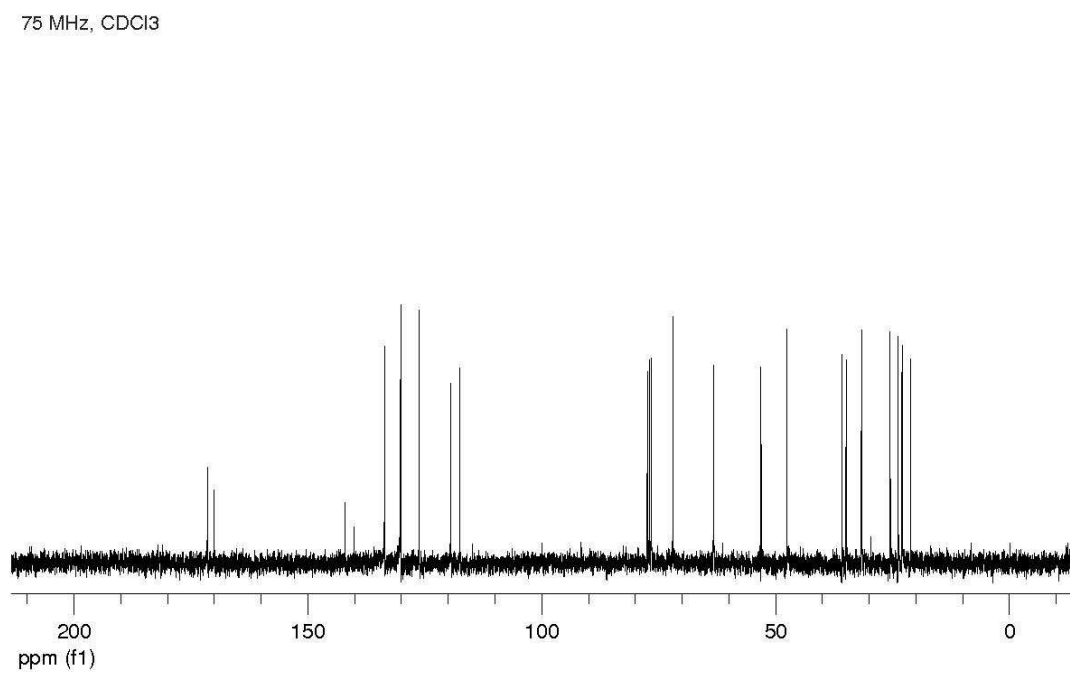
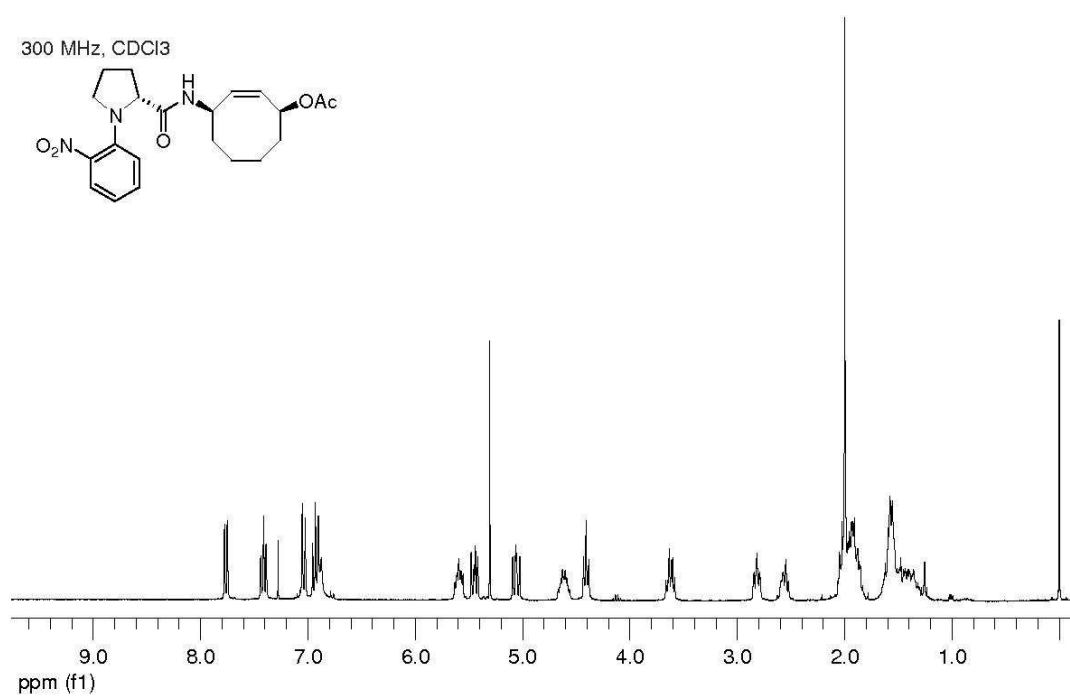
500 MHz, CDCl₃



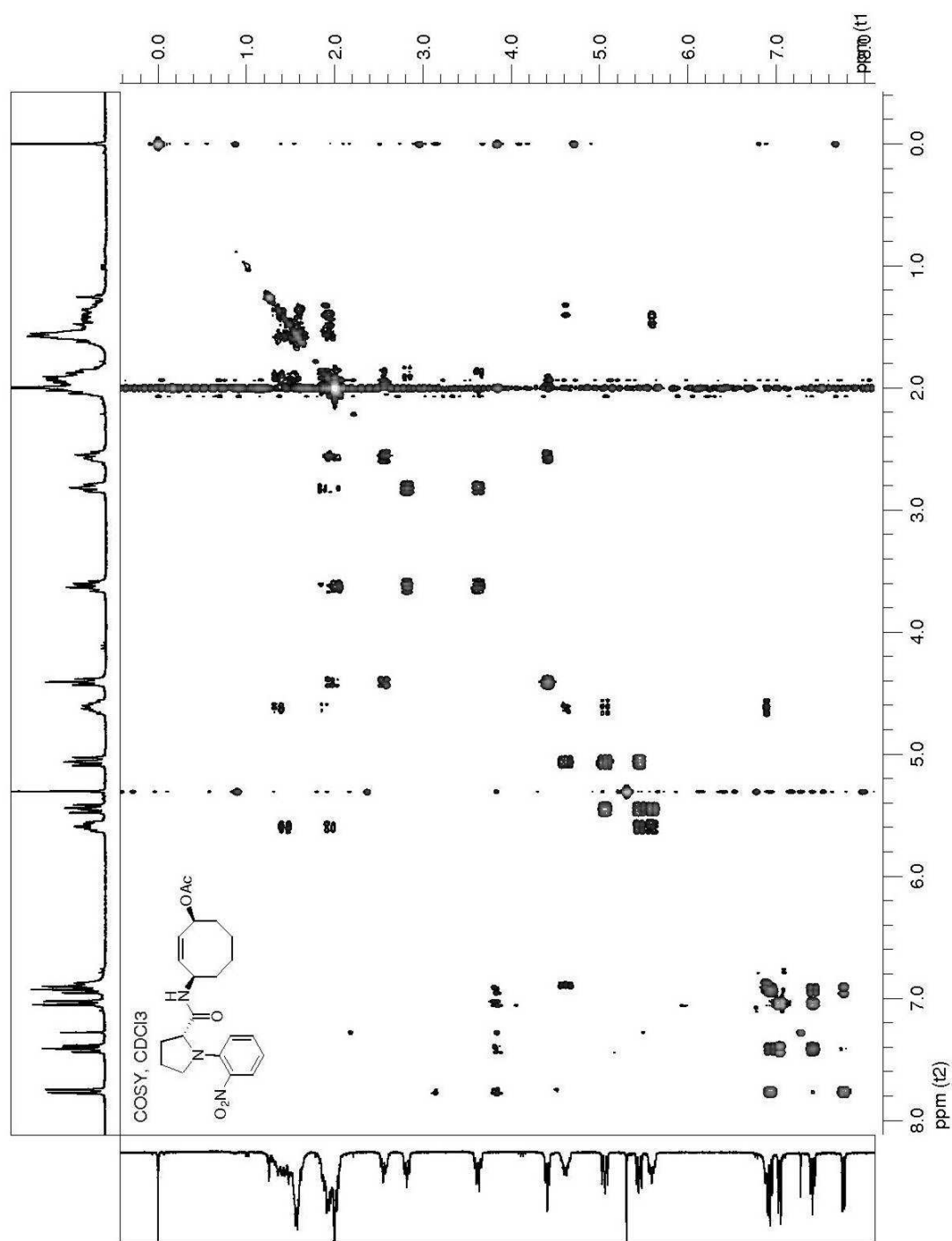
125 MHz, CDCl₃



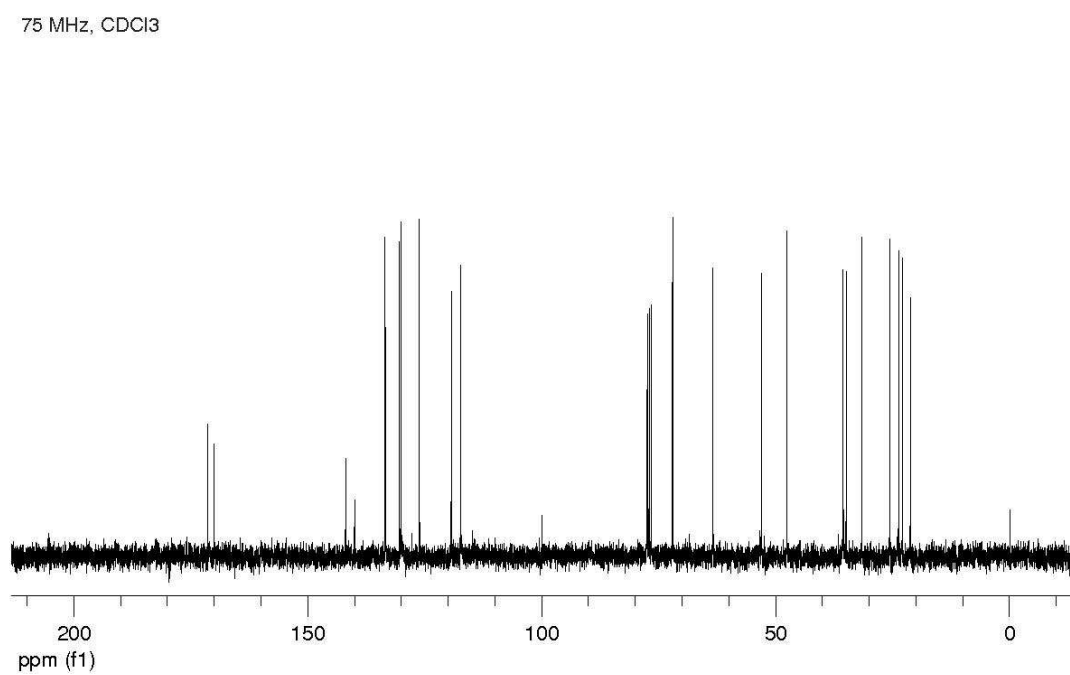
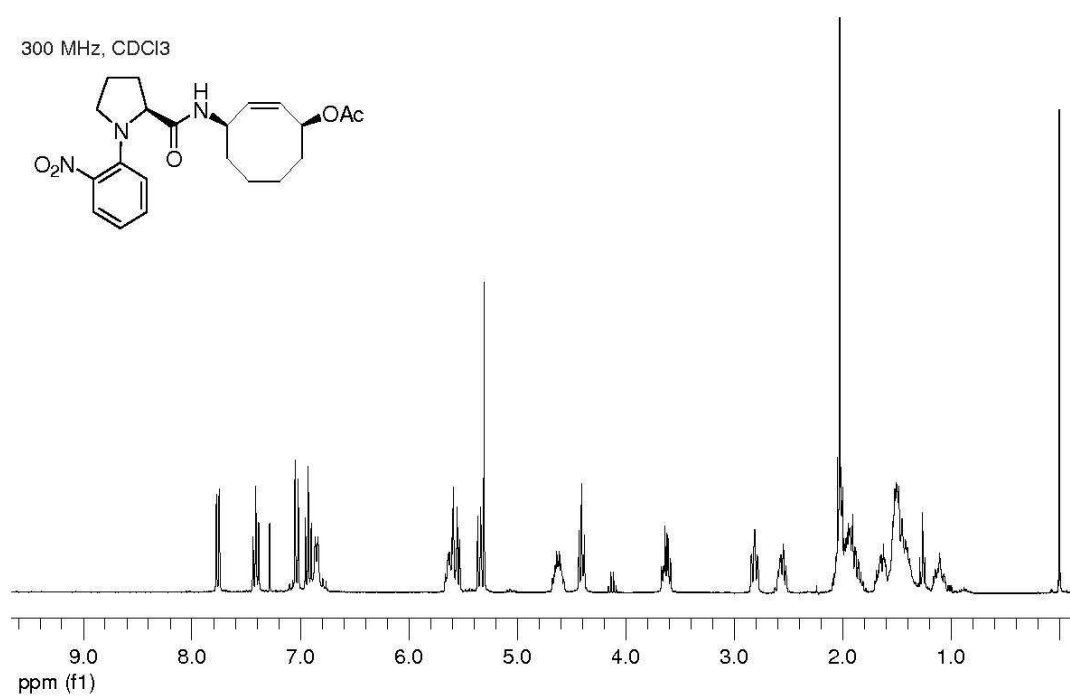
¹H and ¹³C NMR spectra for compound **3.108**



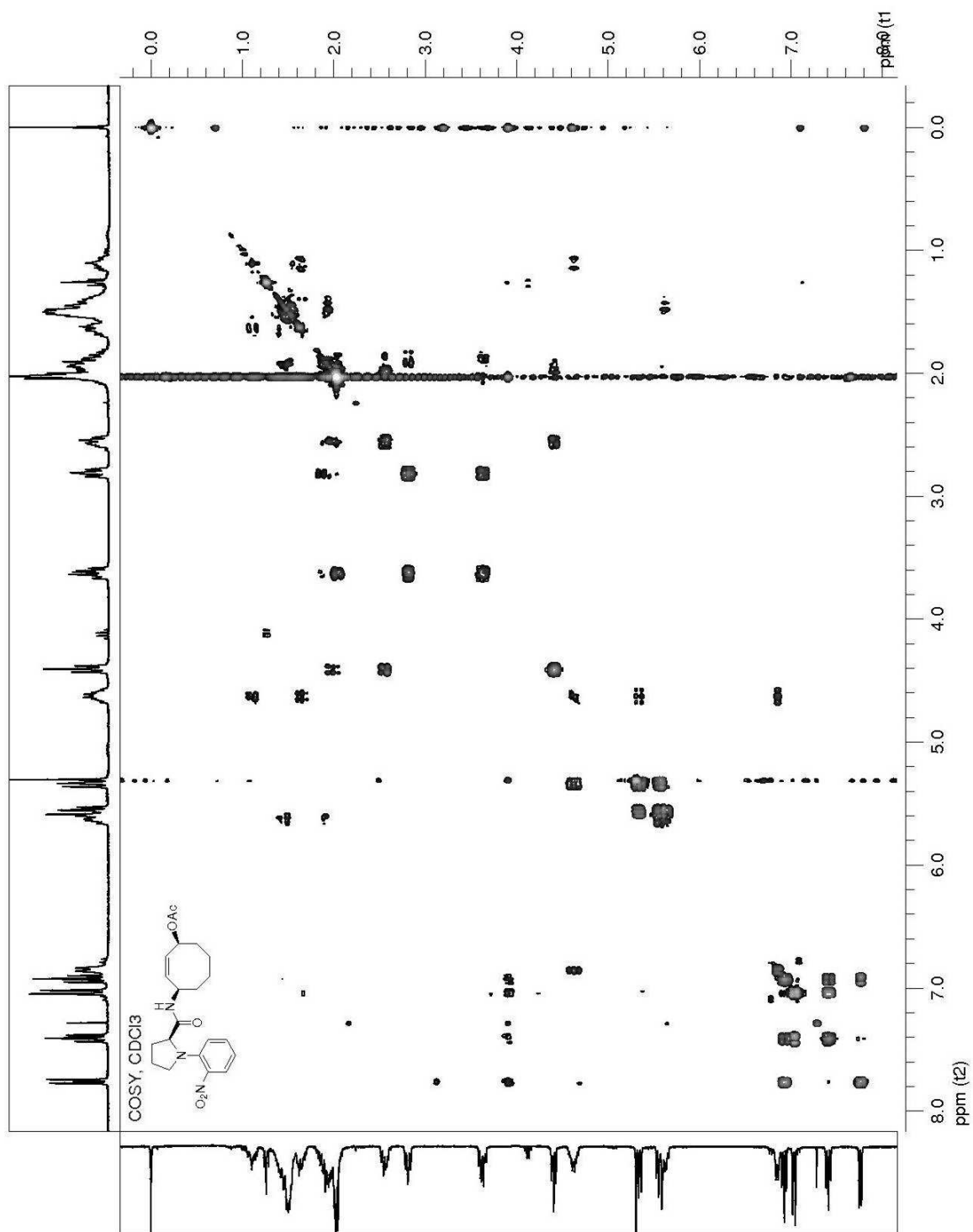
¹H and ¹³C NMR spectra for compound **3.110**



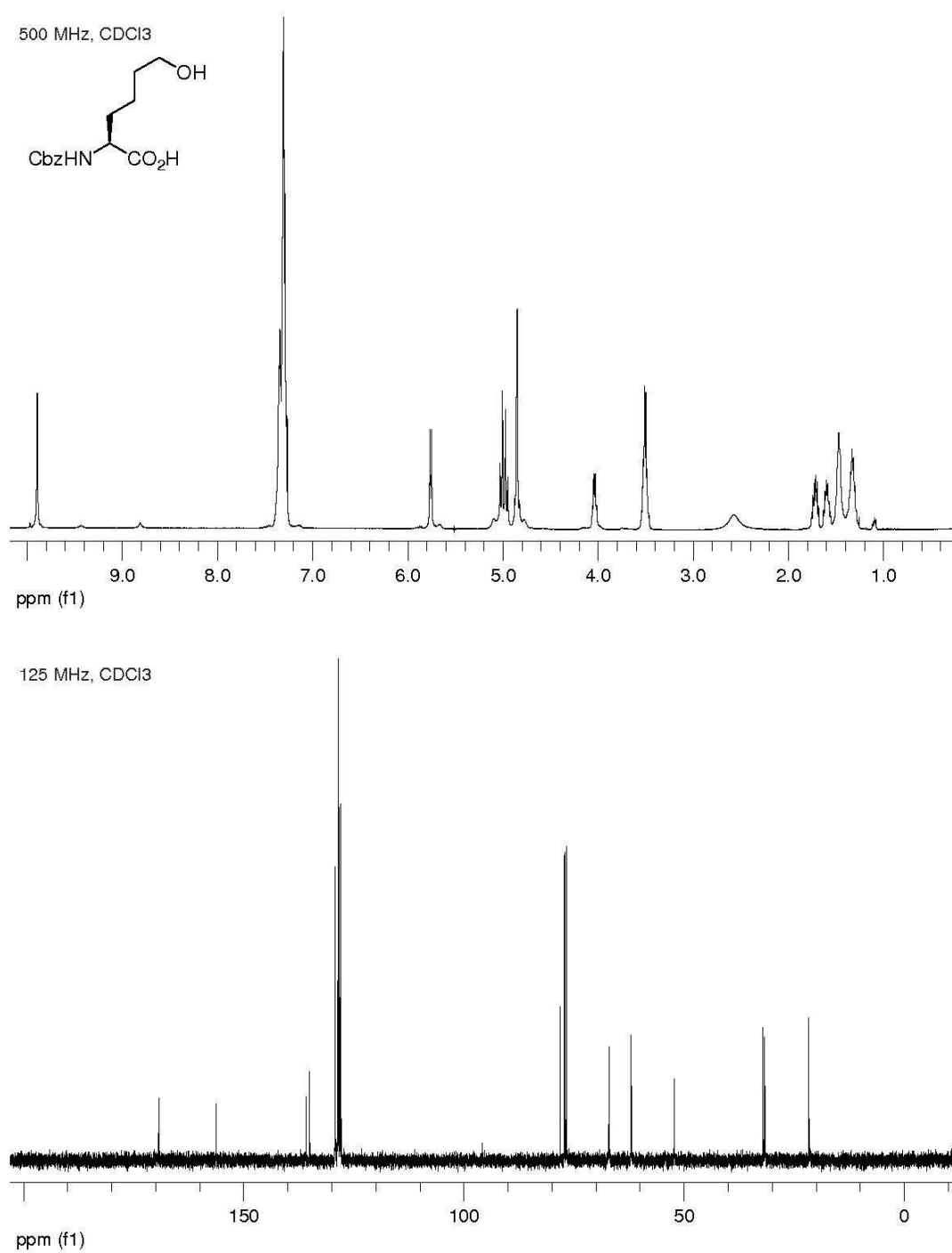
COSY NMR spectra for compound **3.110**



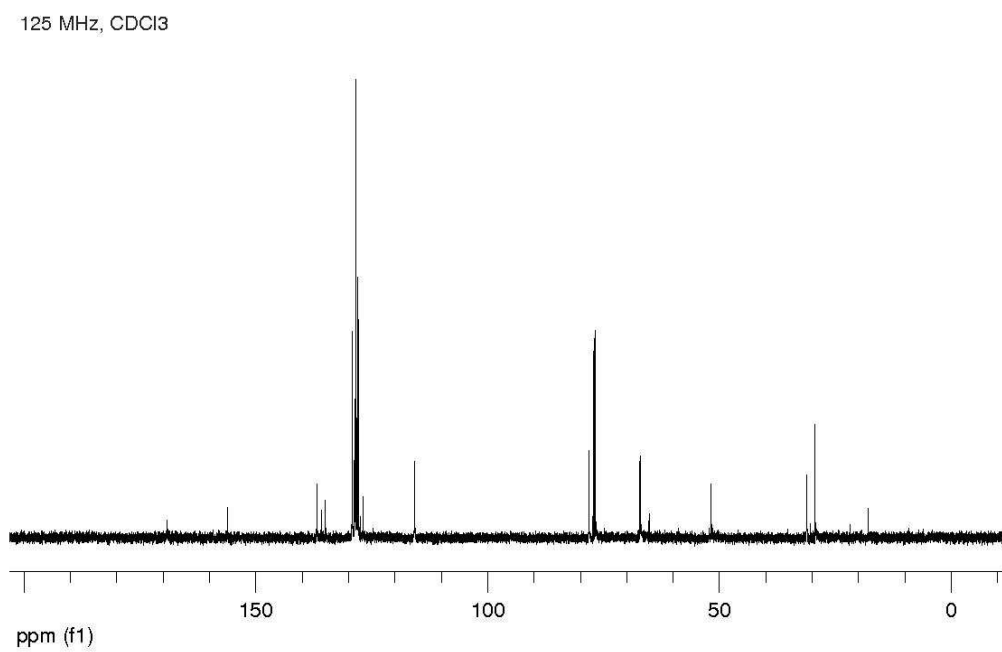
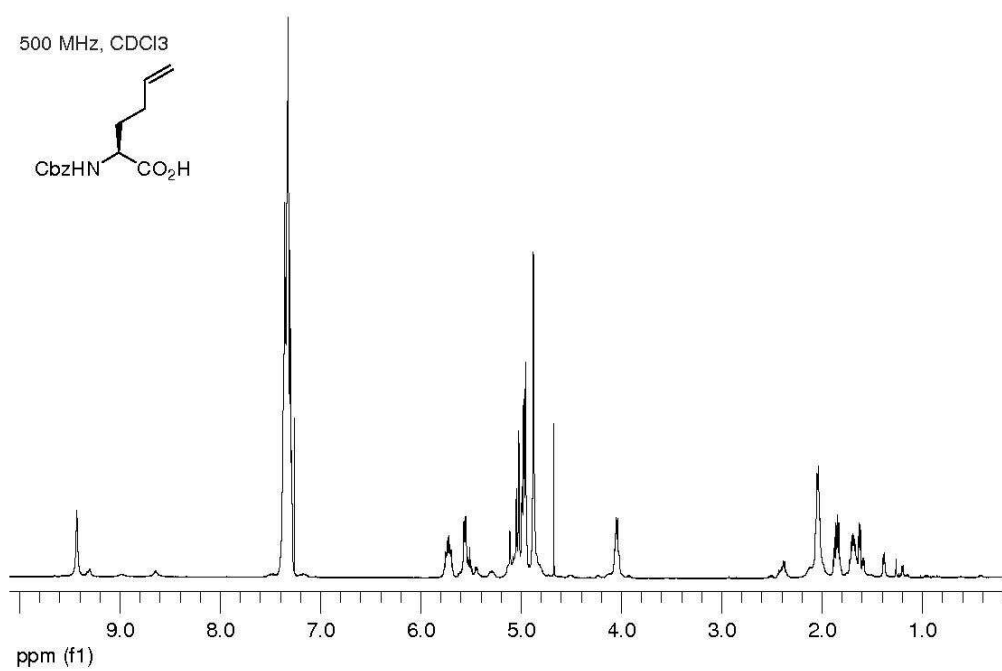
¹H and ¹³C NMR spectra for compound **3.111**



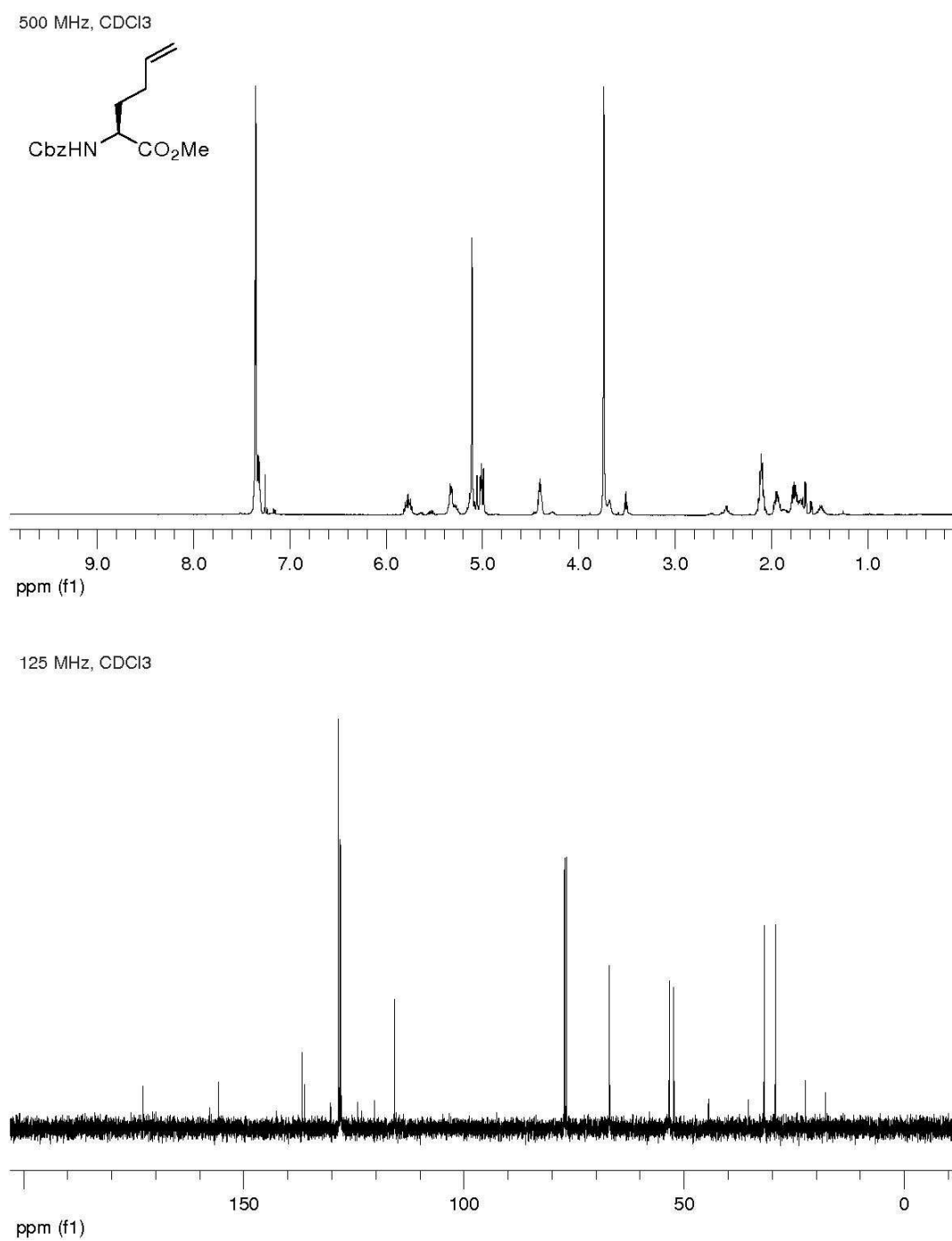
COSY NMR spectra for compound **3.111**



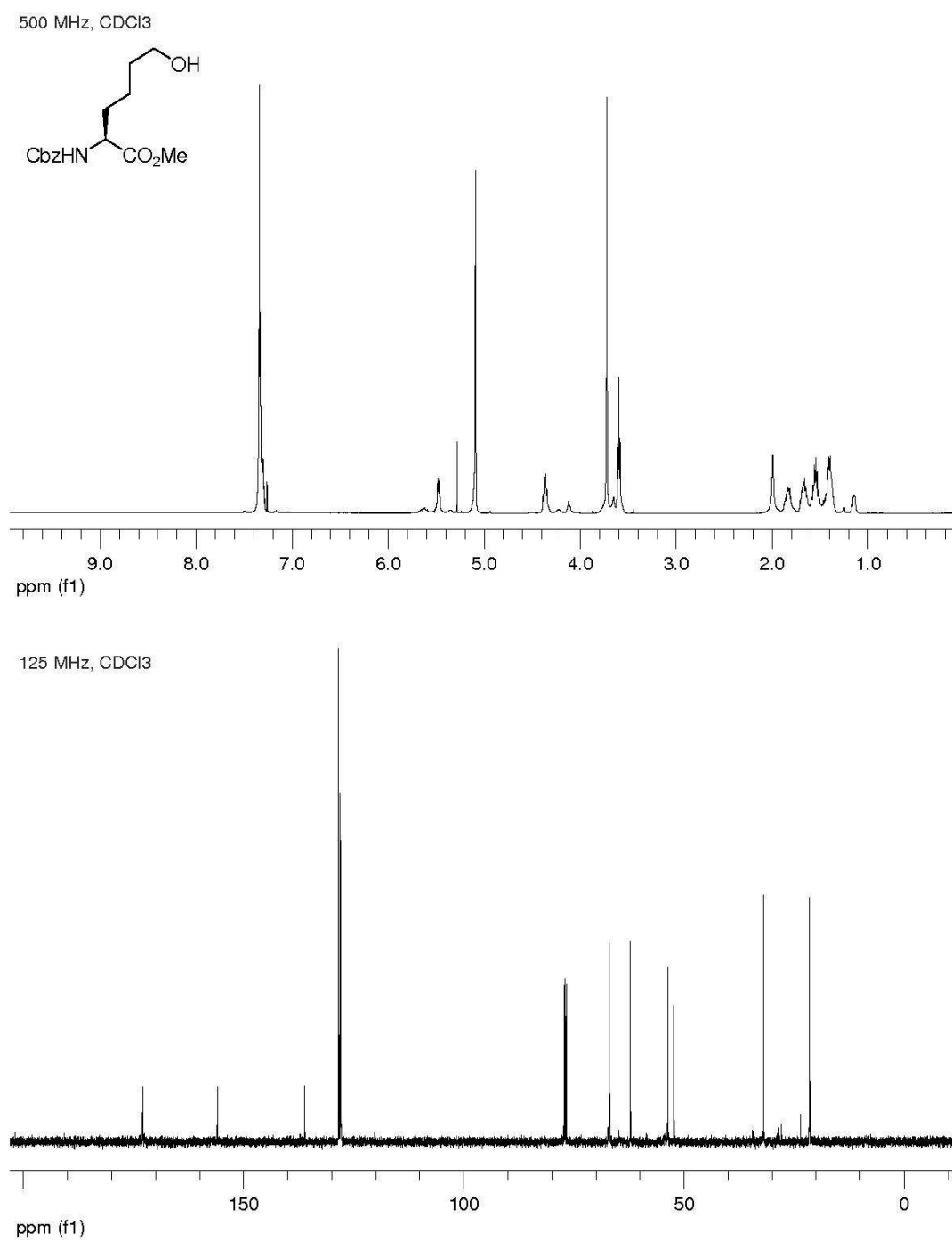
¹H and ¹³C NMR spectra for compound **3.115**



¹H and ¹³C NMR spectra for compound **3.116**

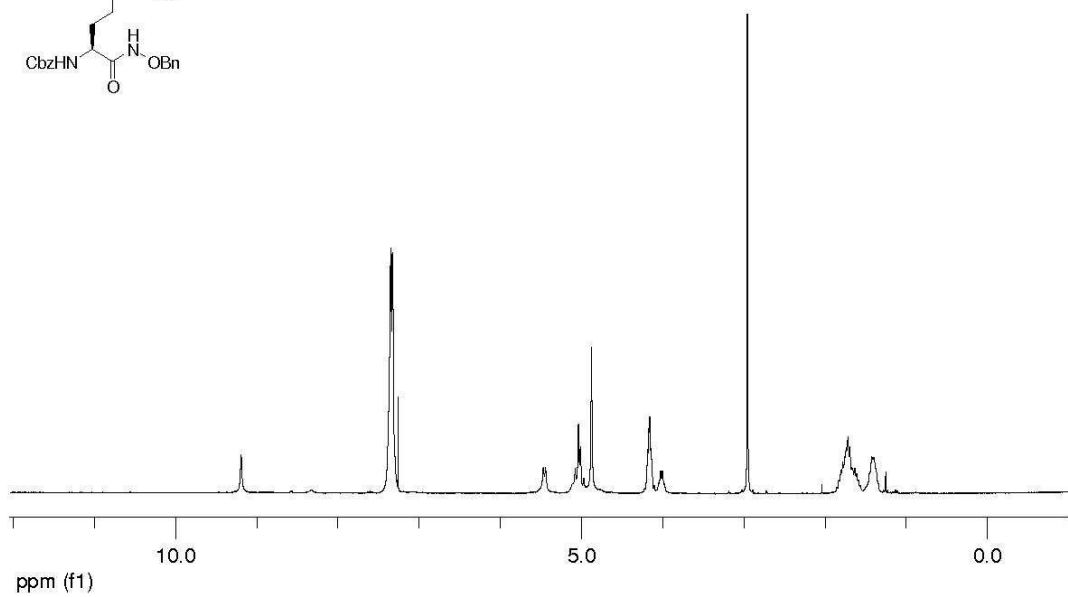
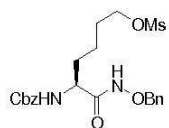


¹H and ¹³C NMR spectra for compound **3.117**

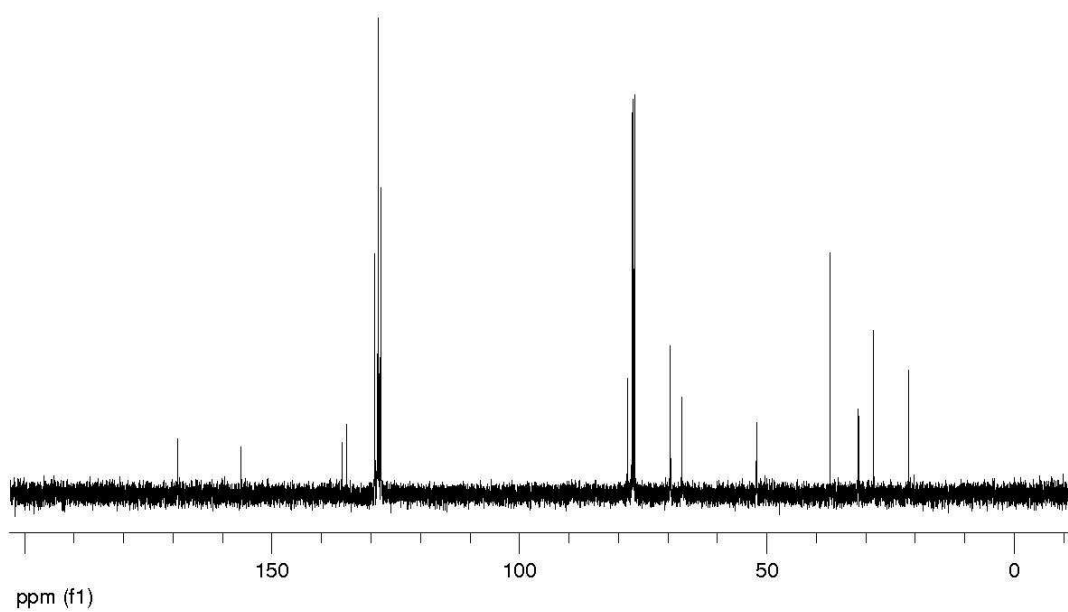


¹H and ¹³C NMR spectra for compound **3.118**

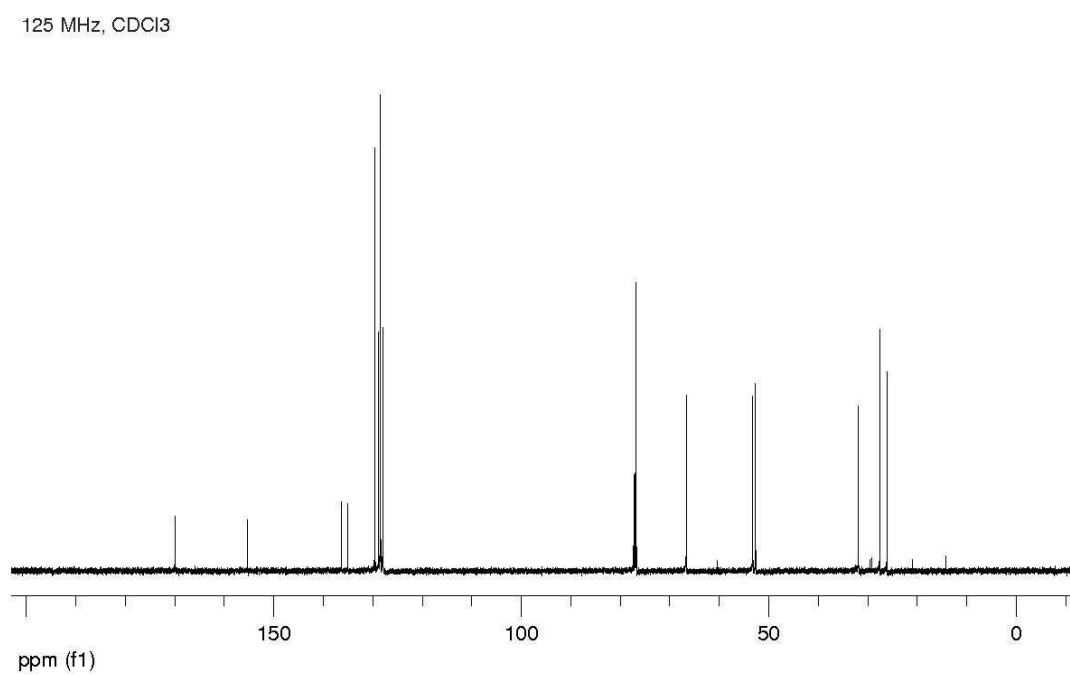
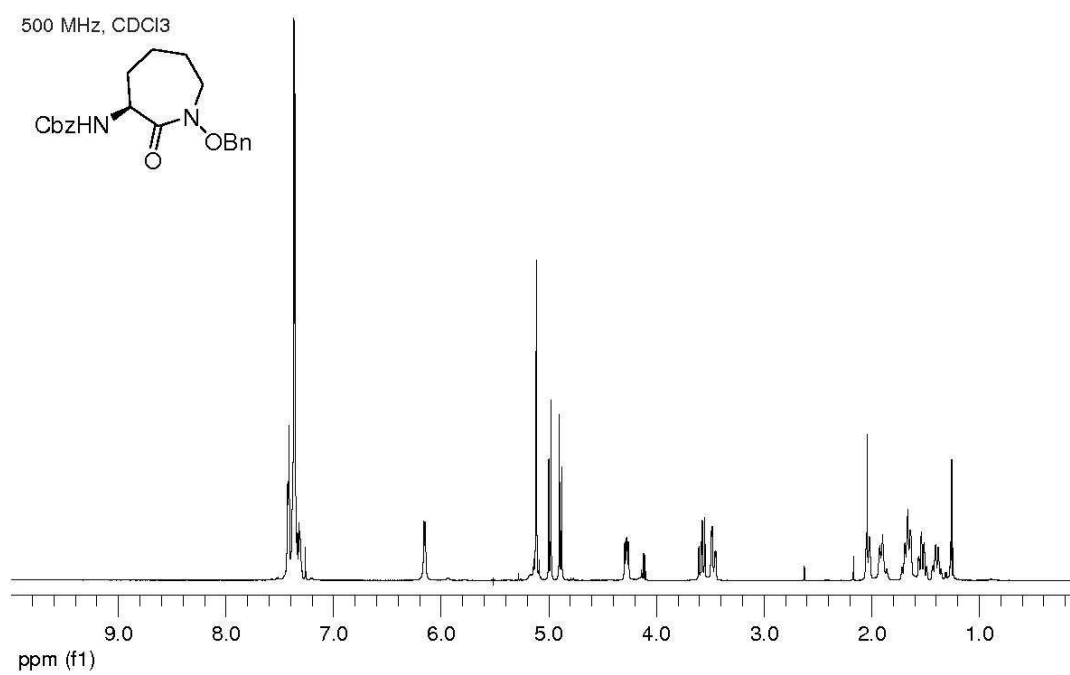
300 MHz, CDCl₃



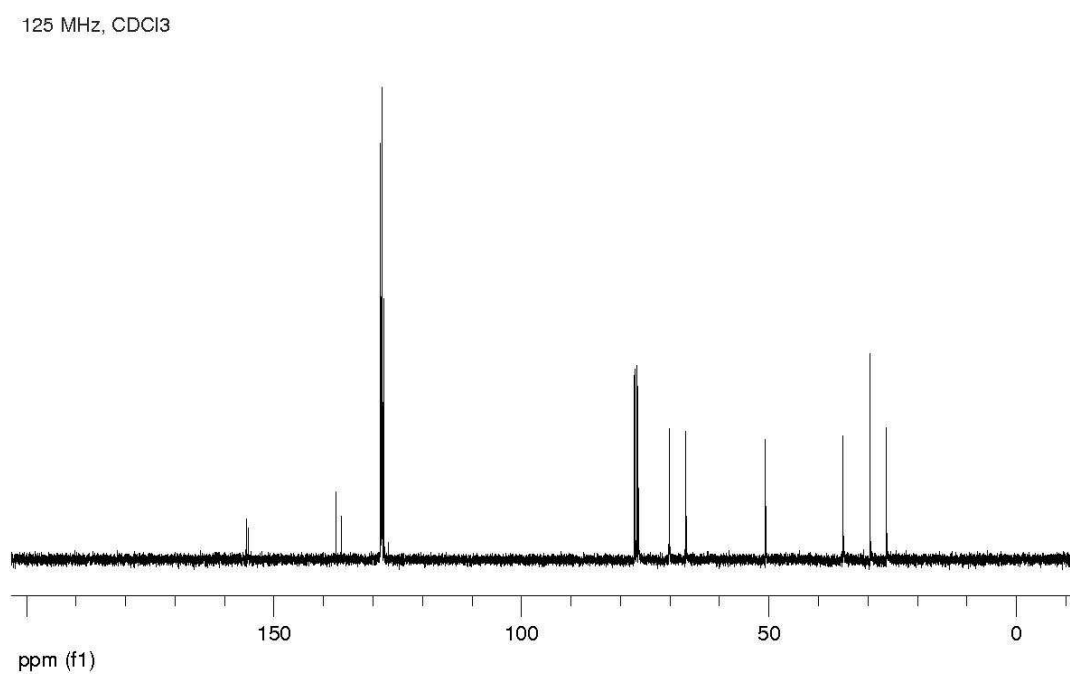
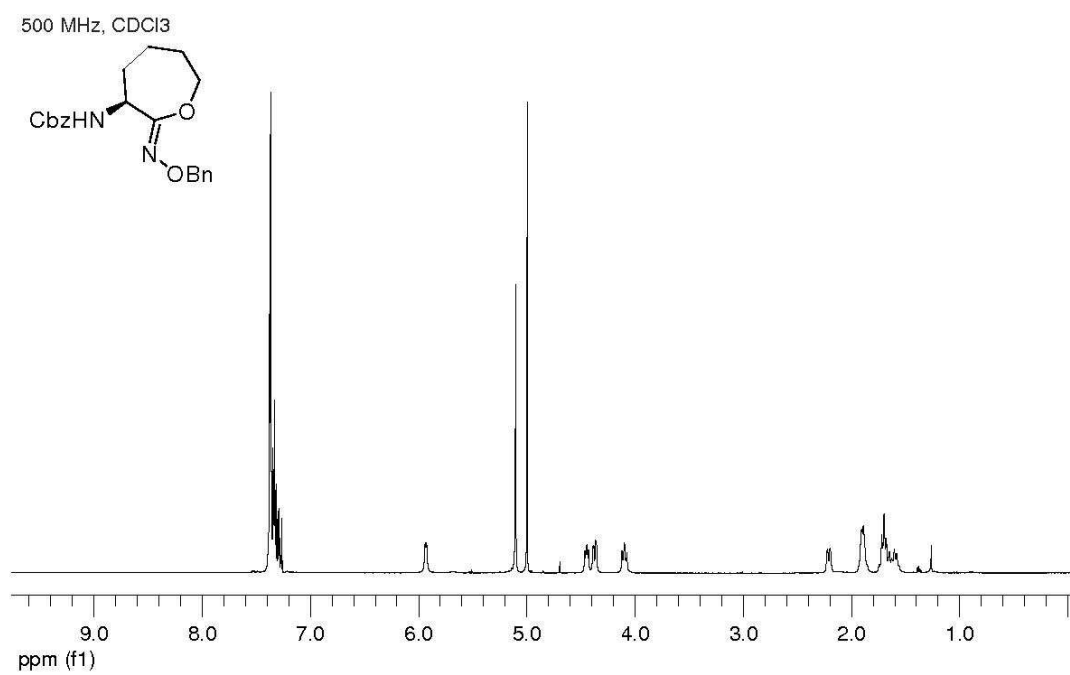
125 MHz, CDCl₃



¹H and ¹³C NMR spectra for compound **3.119**

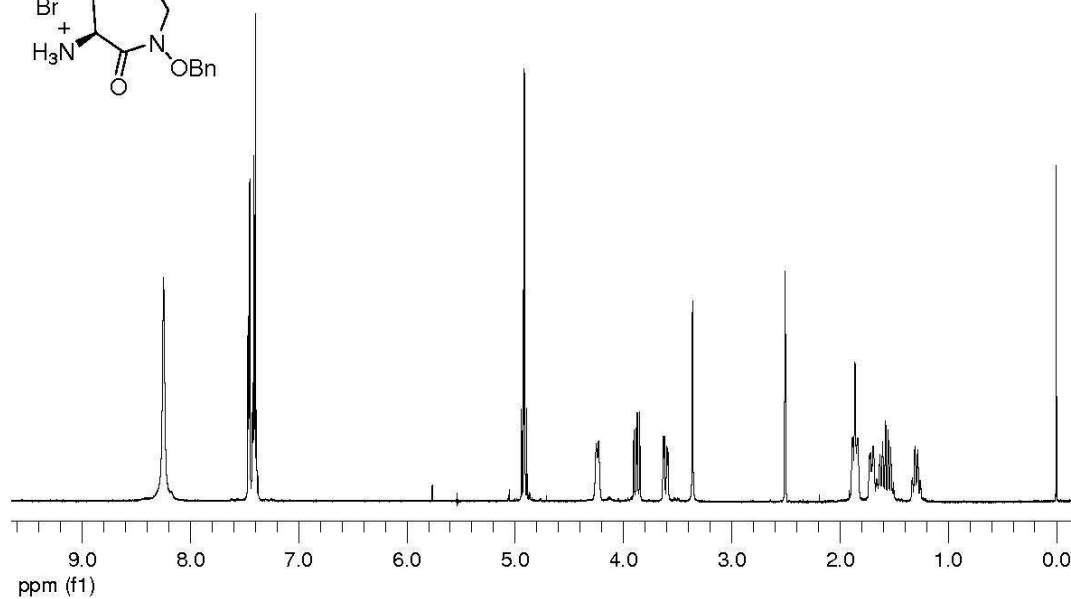
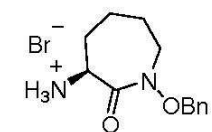


¹H and ¹³C NMR spectra for compound **3.120**

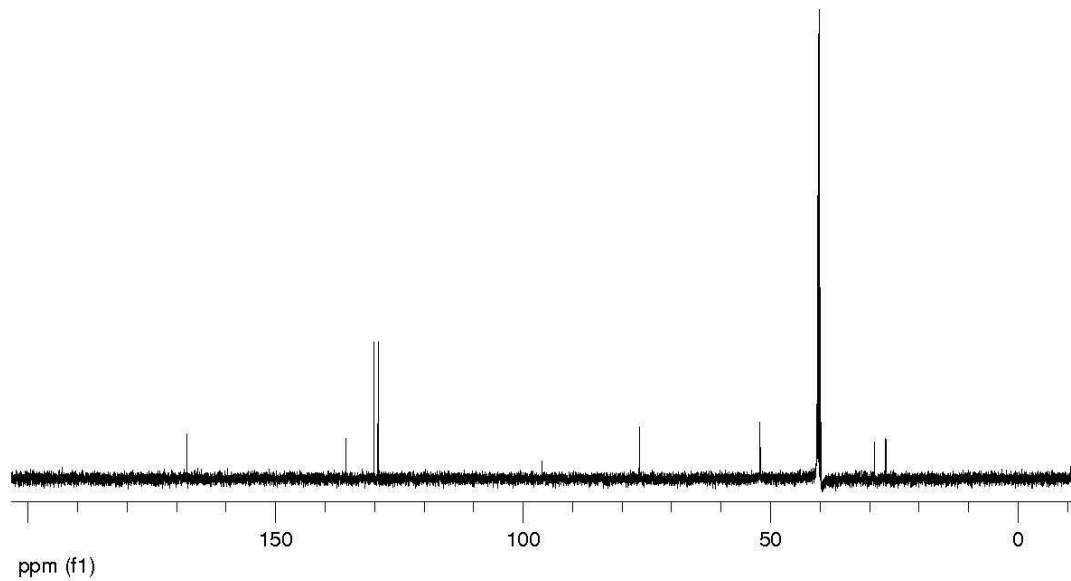


¹H and ¹³C NMR spectra for compound **3.121**

500 MHz, d6-DMSO

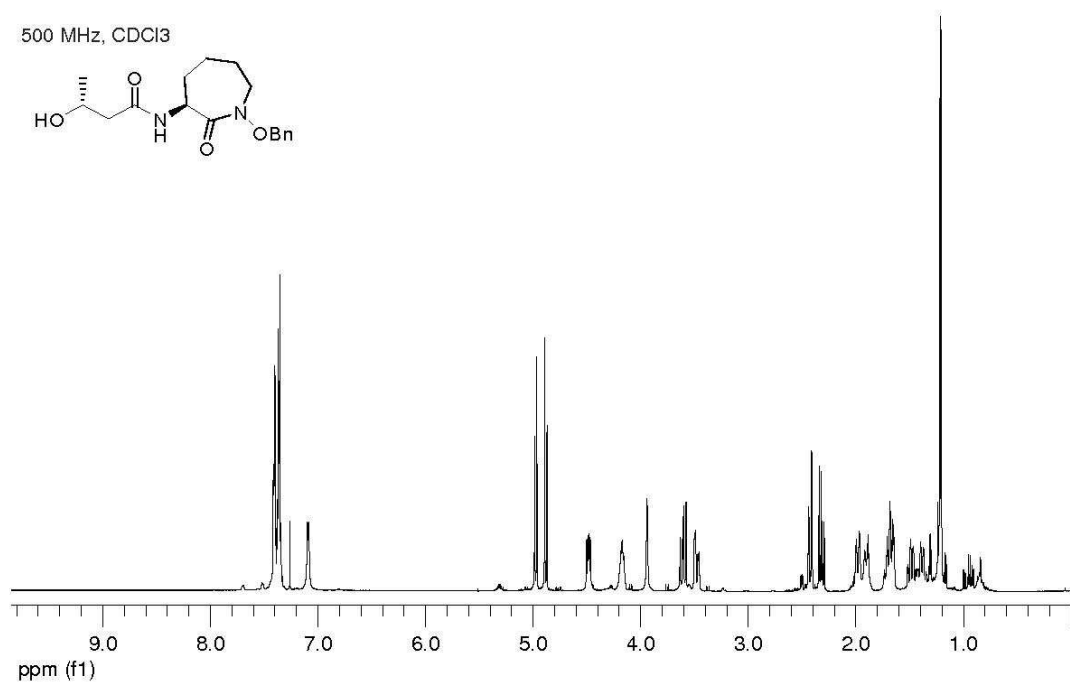
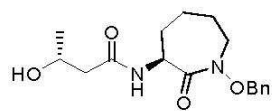


125 MHz, d6-DMSO

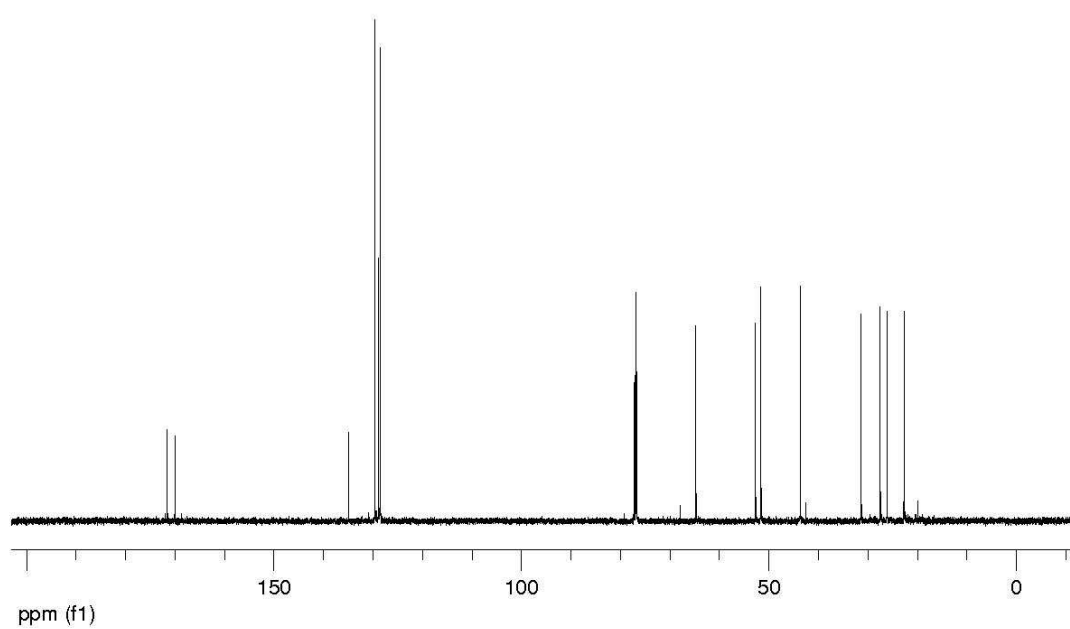


^1H and ^{13}C NMR spectra for compound **3.122**

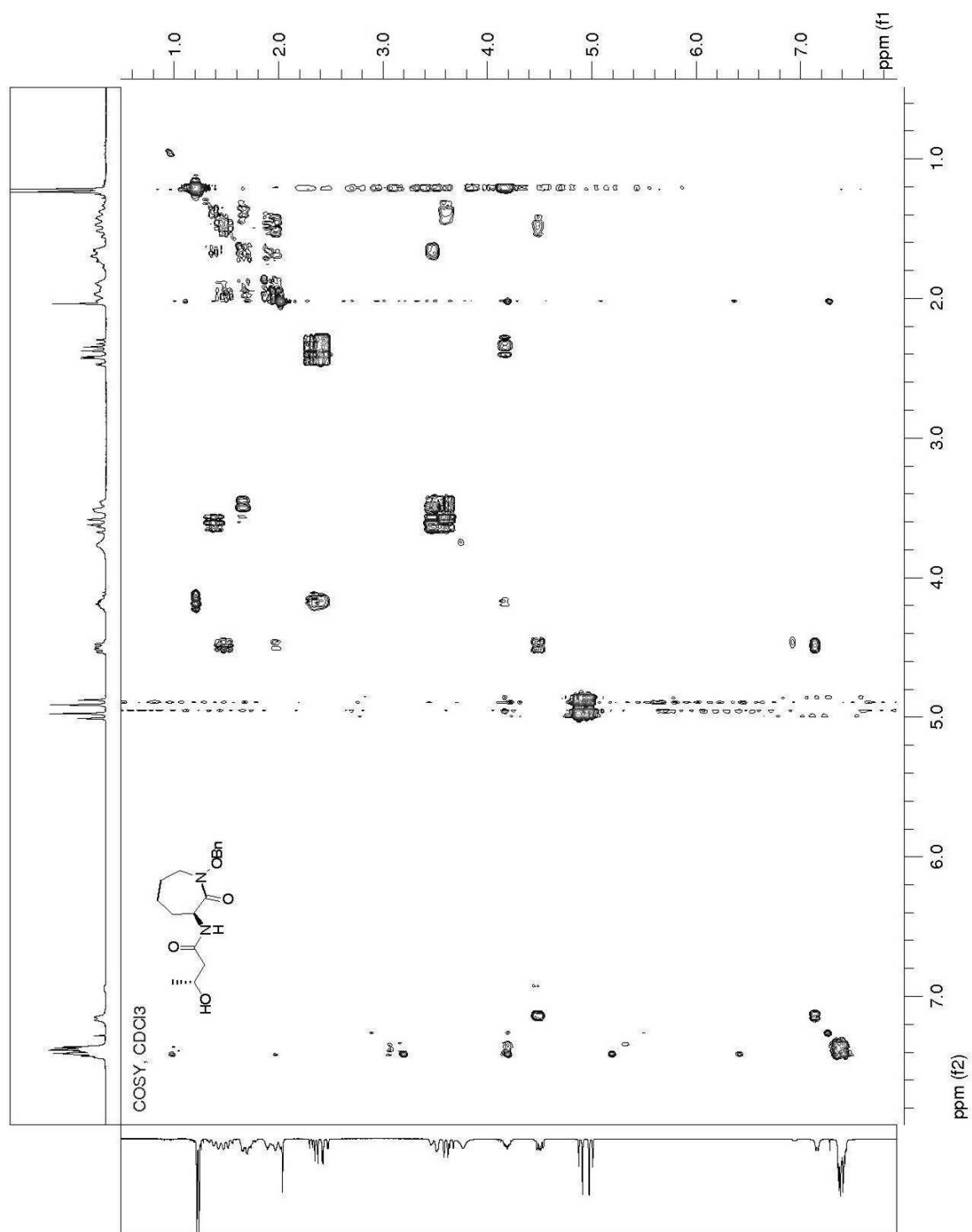
500 MHz, CDCl₃



125 MHz, CDCl₃

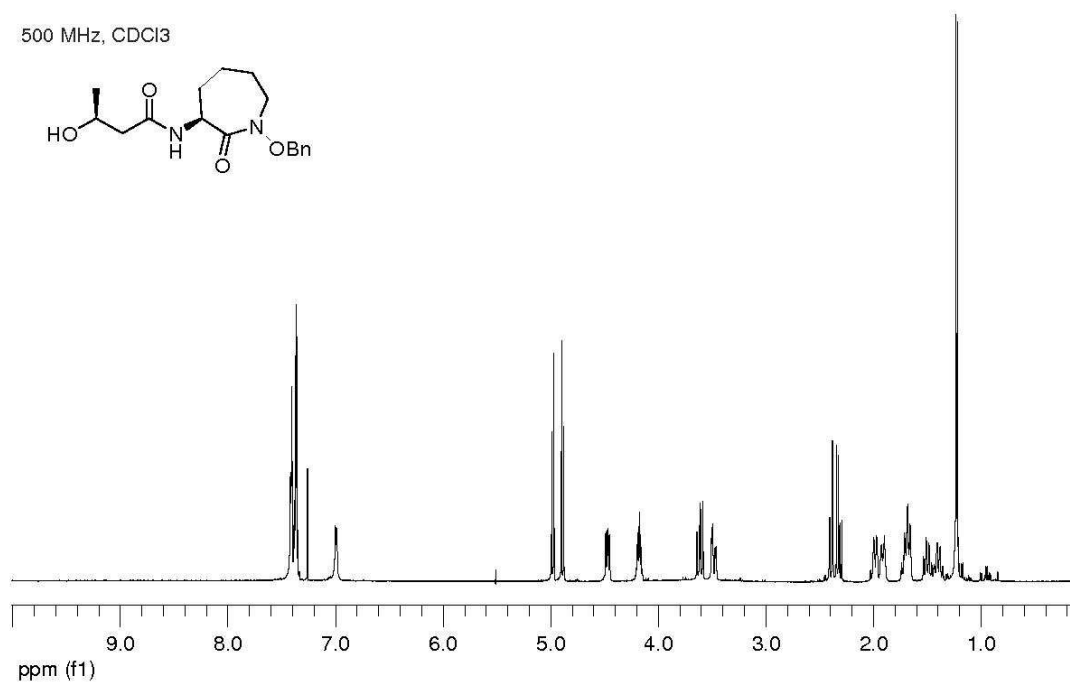
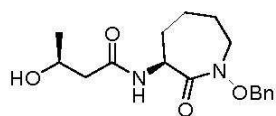


¹H and ¹³C NMR spectra for compound **3.124**

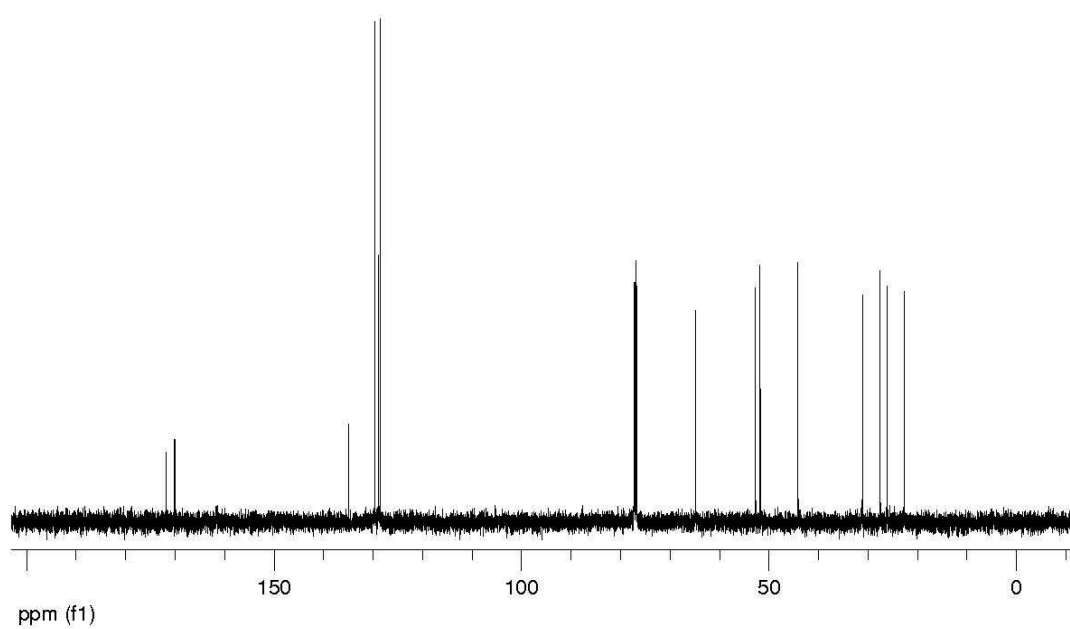


COSY NMR spectra for compound **3.124**

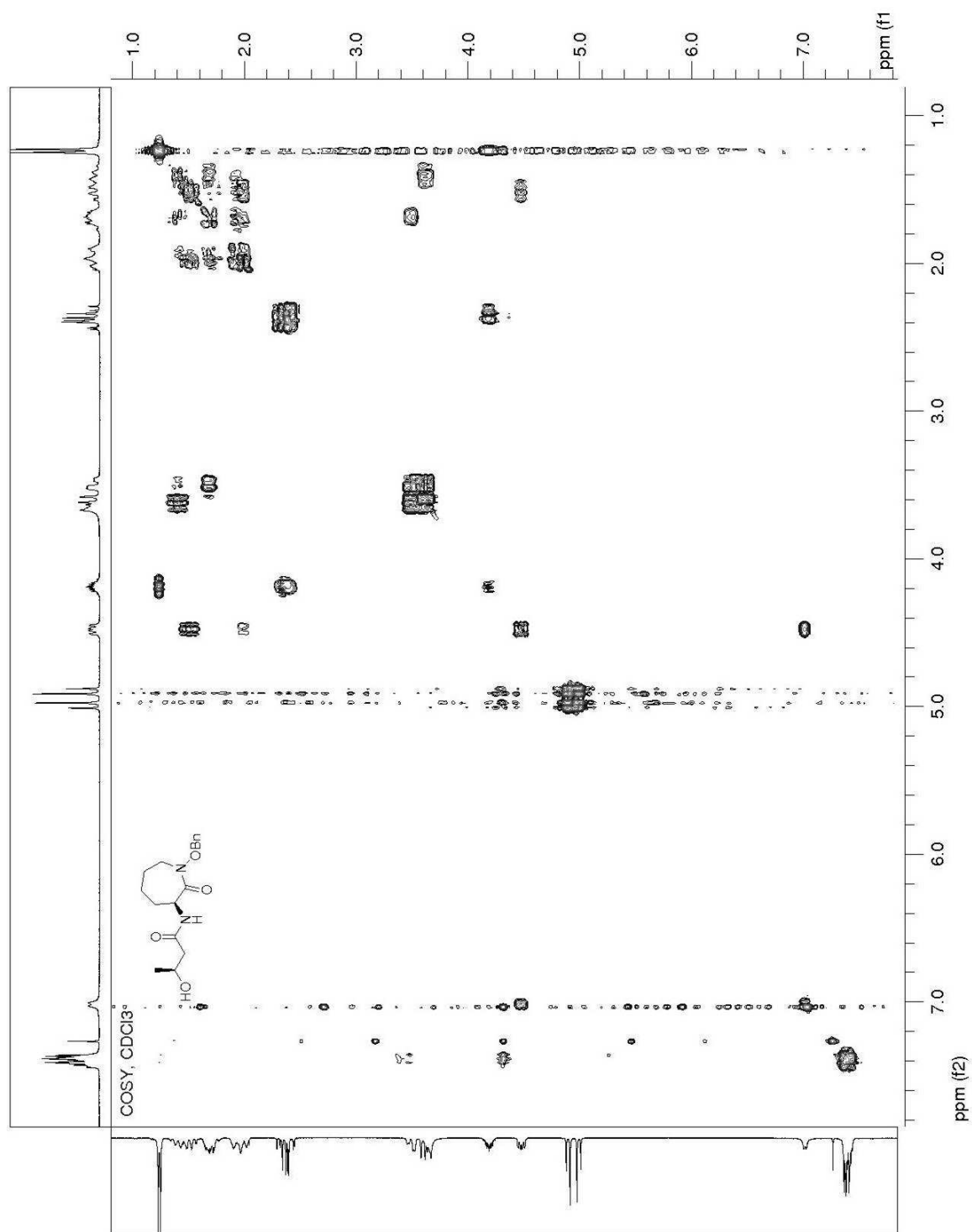
500 MHz, CDCl₃



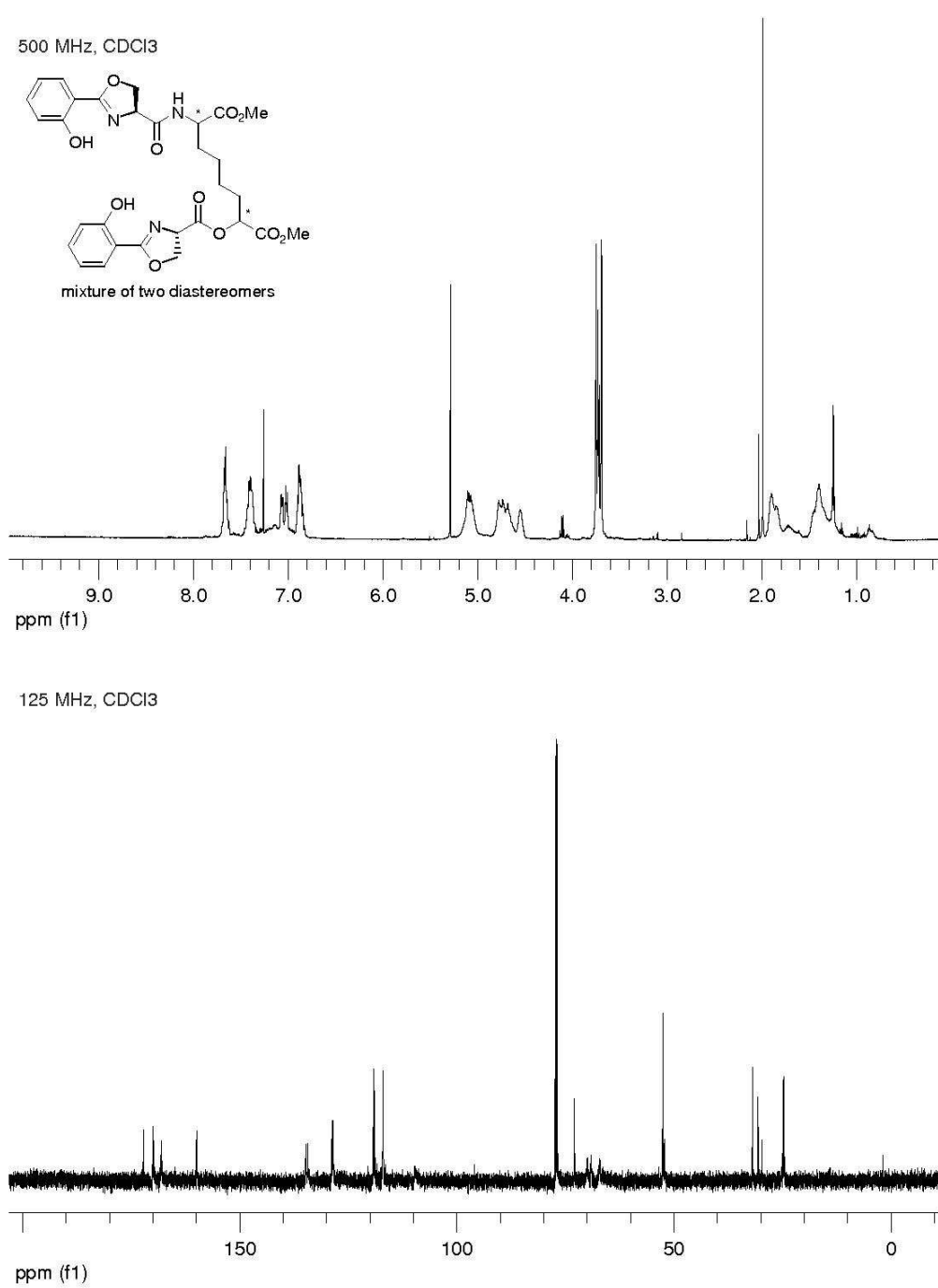
125 MHz, CDCl₃



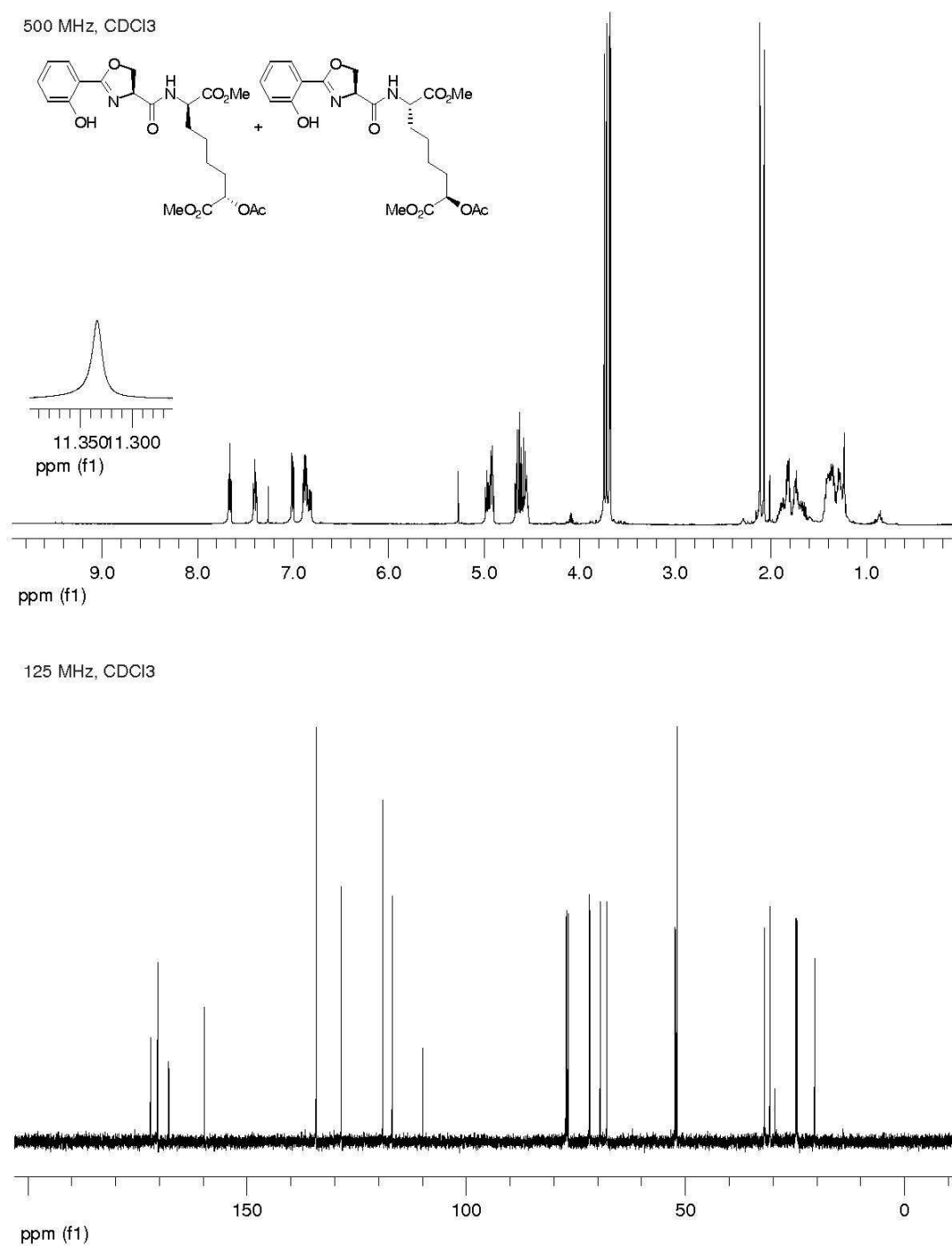
¹H and ¹³C NMR spectra for compound **3.125**



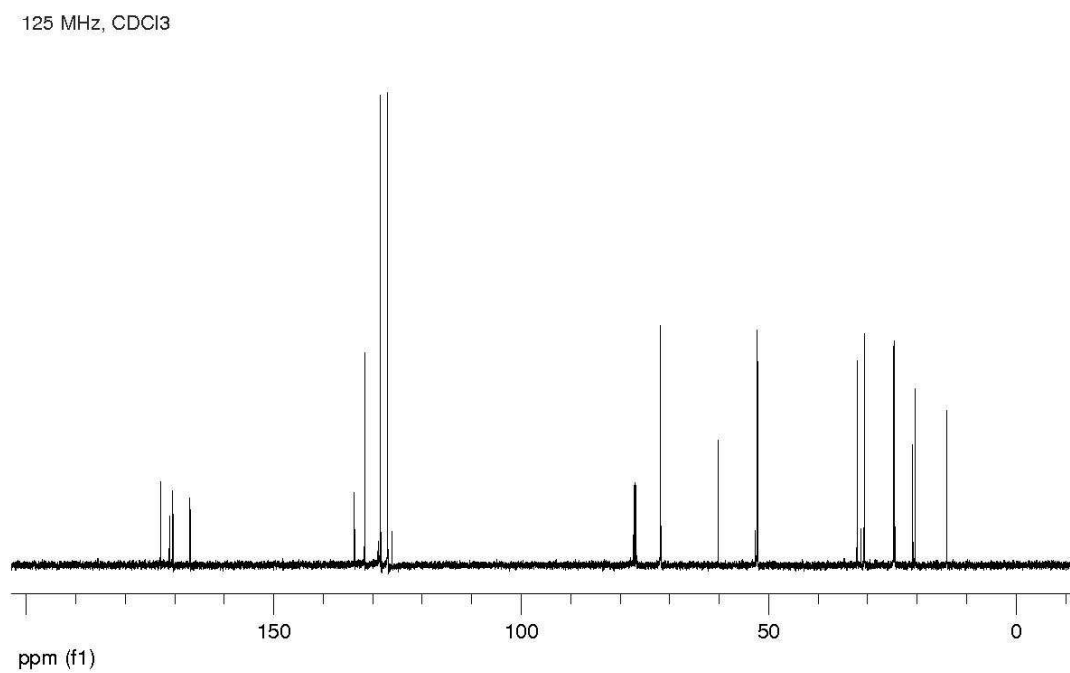
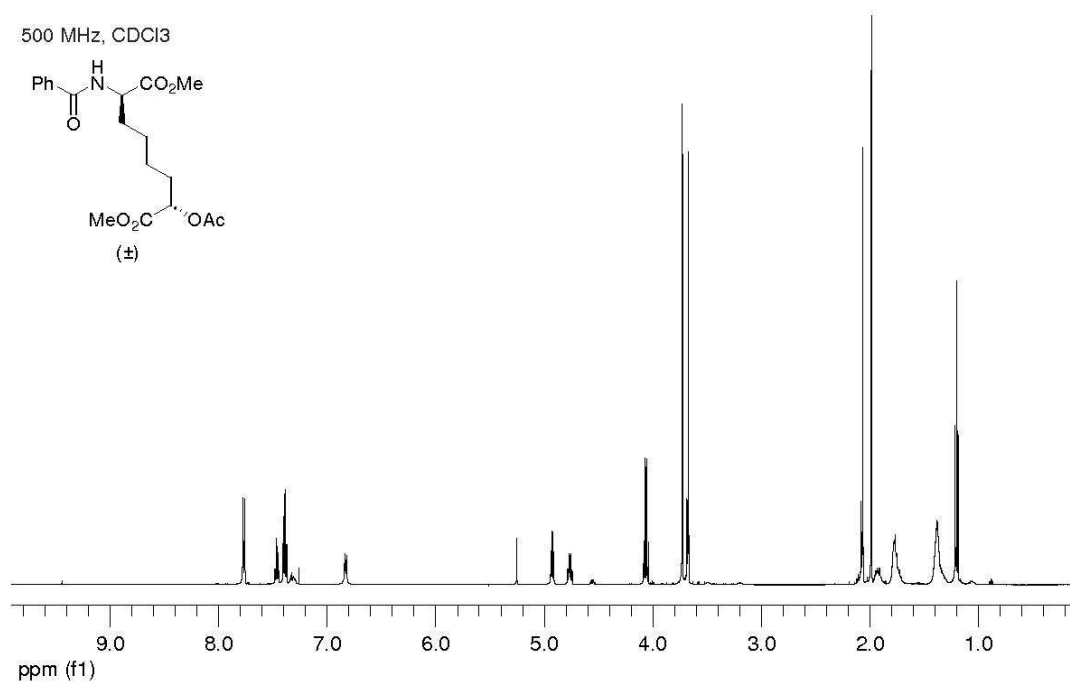
COSY NMR spectra for compound **3.125**



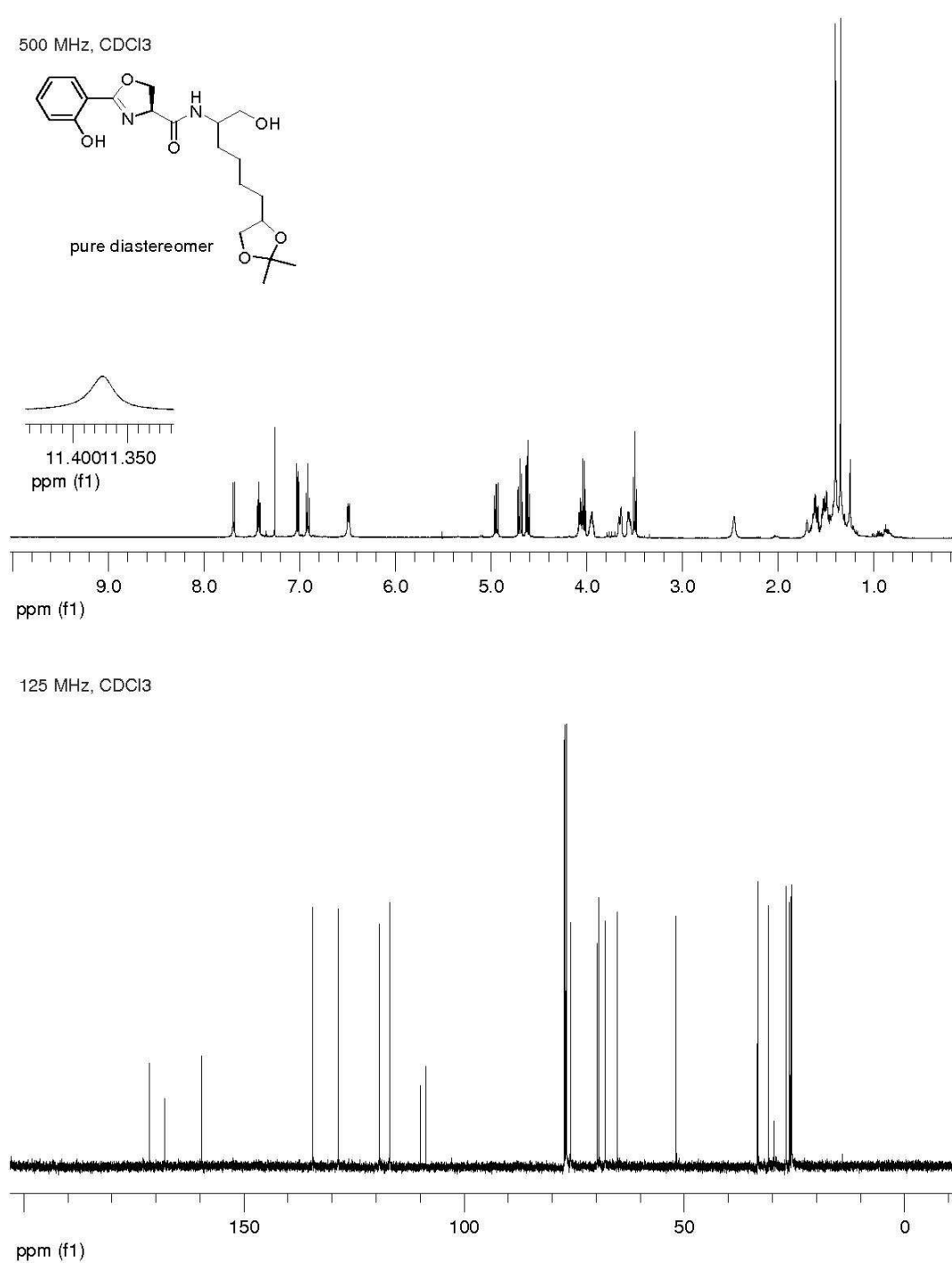
¹H and ¹³C NMR spectra for compound **4.6**



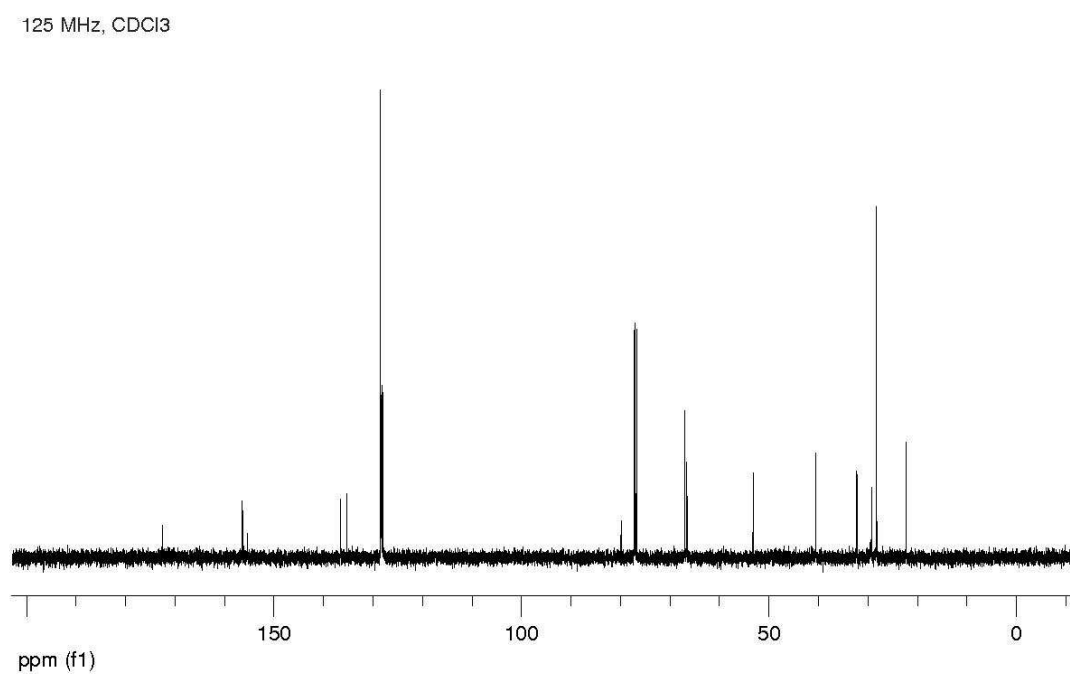
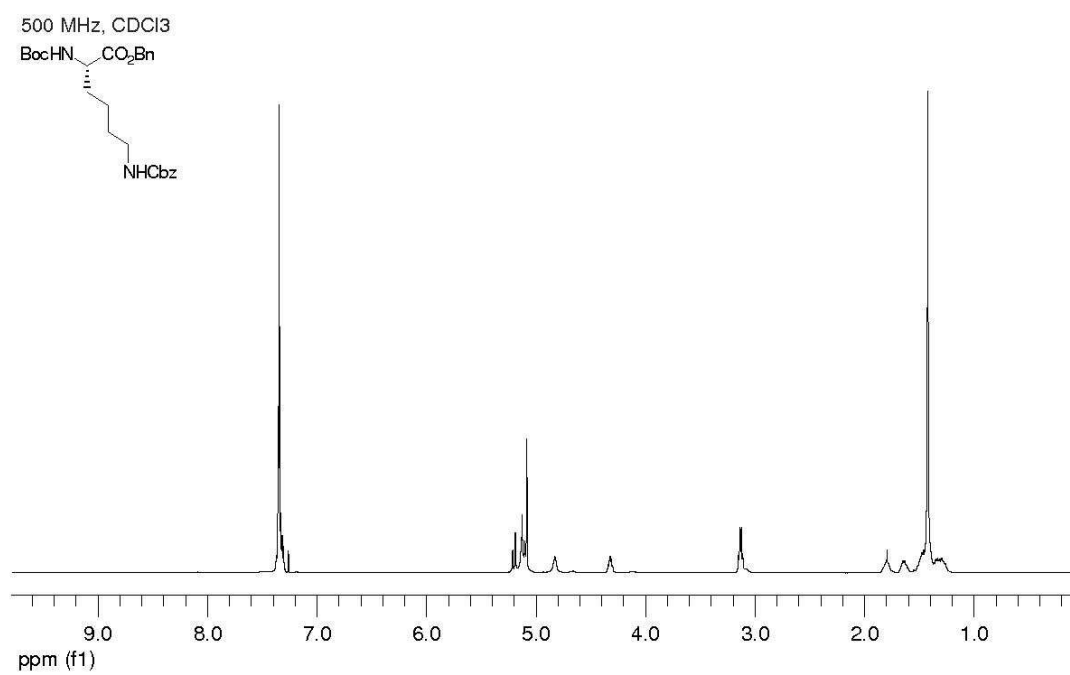
¹H and ¹³C NMR spectra for a mixture of compounds **4.7a** and **4.7b**



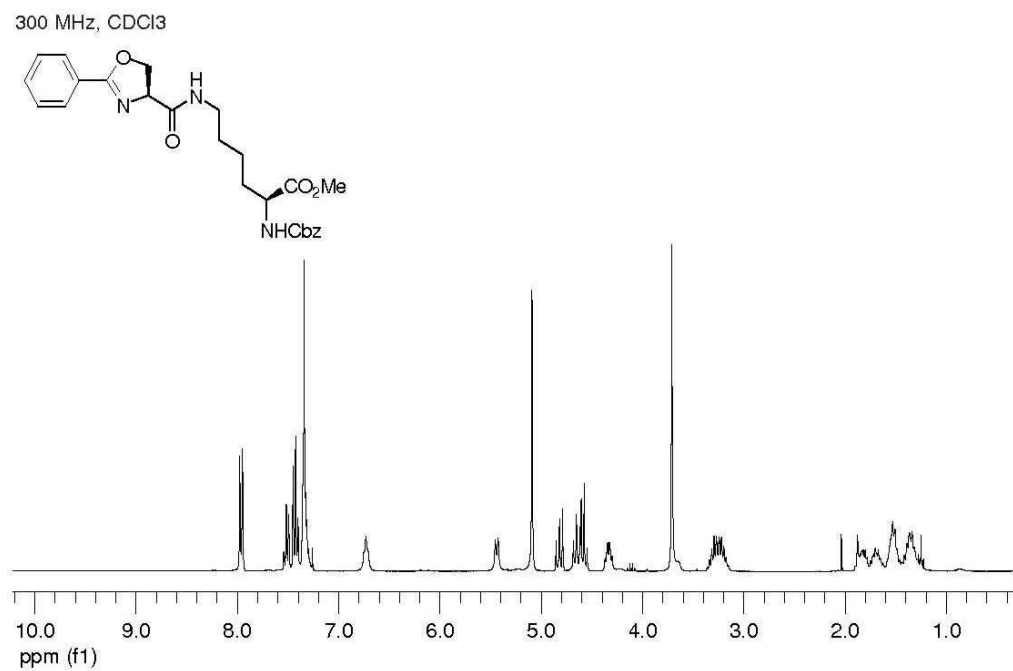
¹H and ¹³C NMR spectra for compound **4.8**



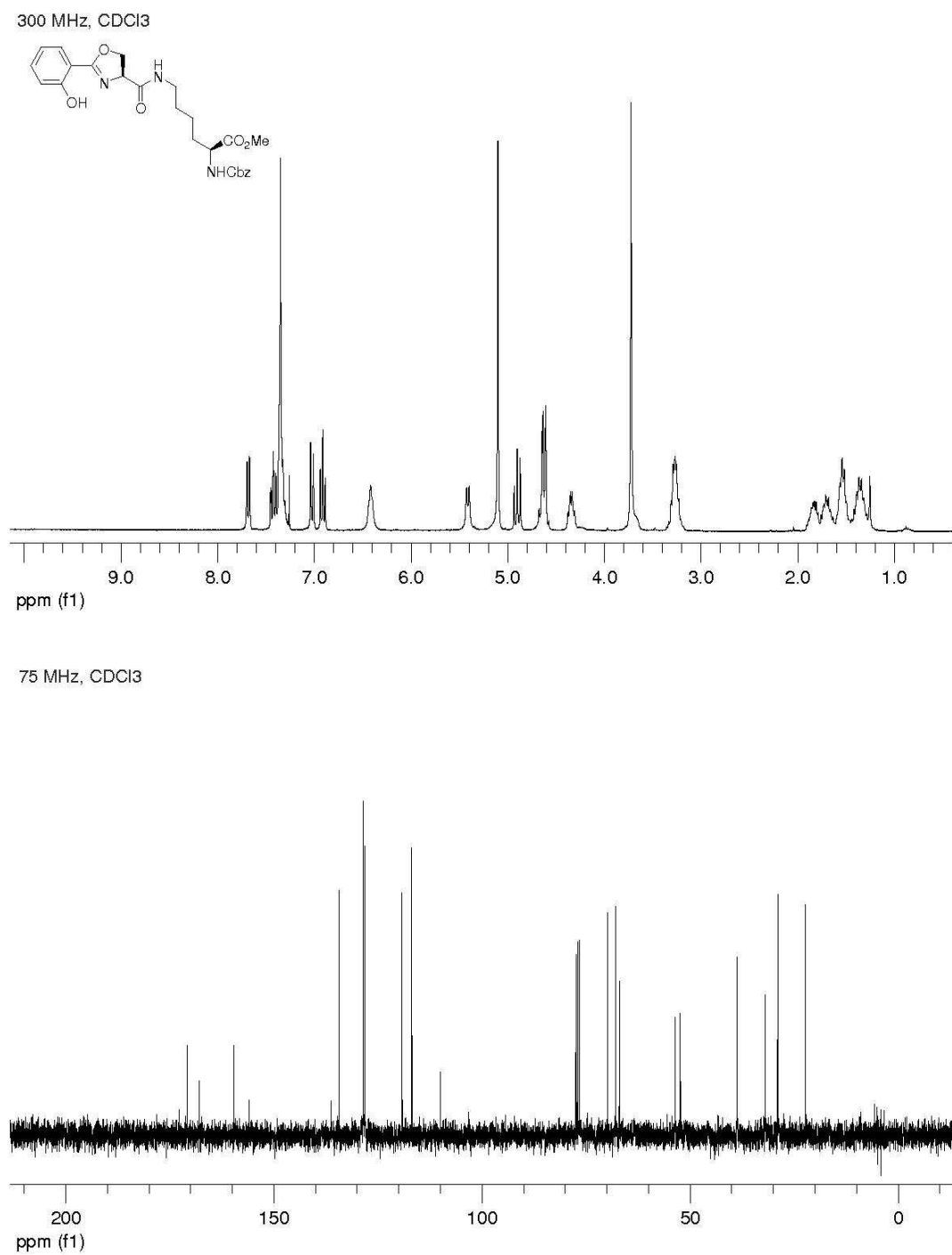
¹H and ¹³C NMR spectra for the purified diastereomer of compound **4.10**



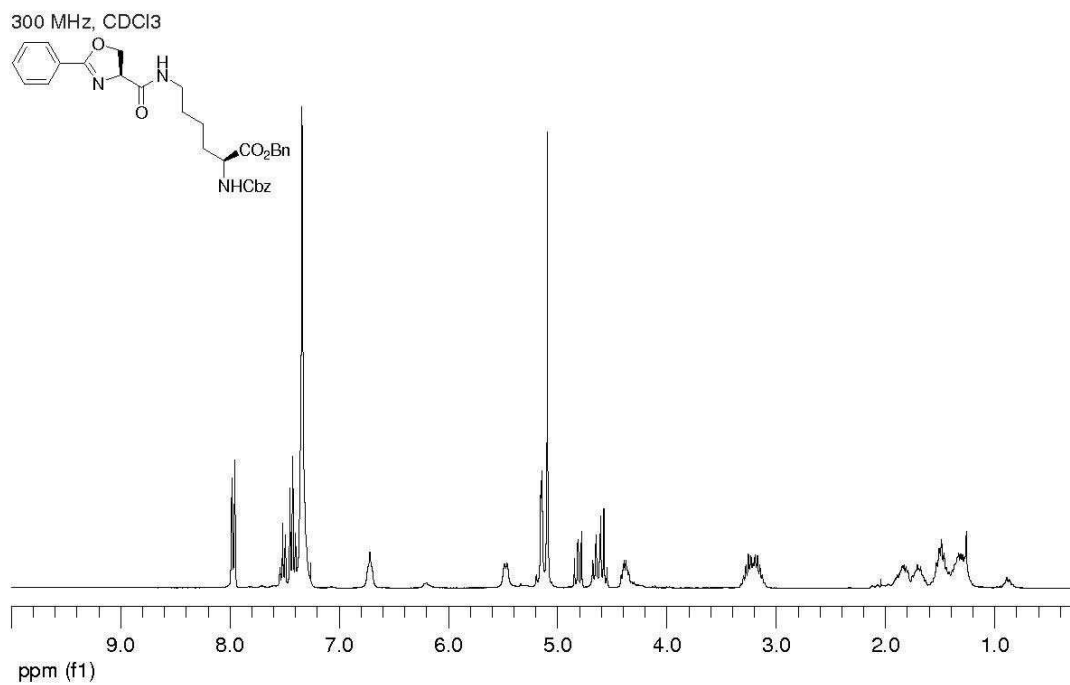
¹H and ¹³C NMR spectra for compound **4.20**



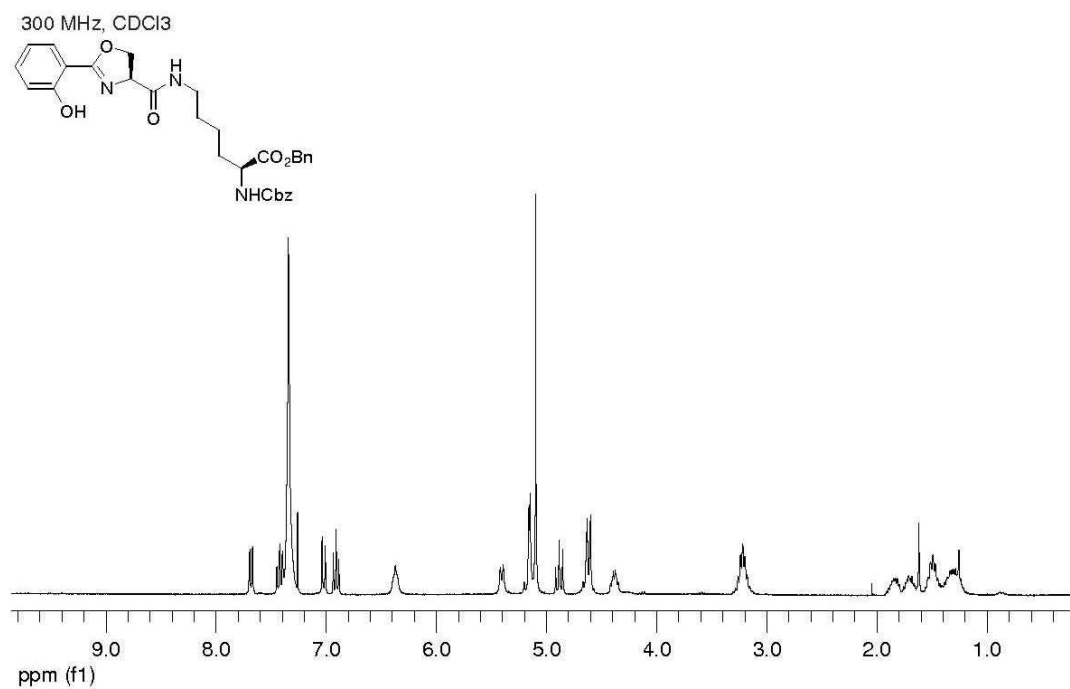
¹H NMR spectra for compound **4.22**



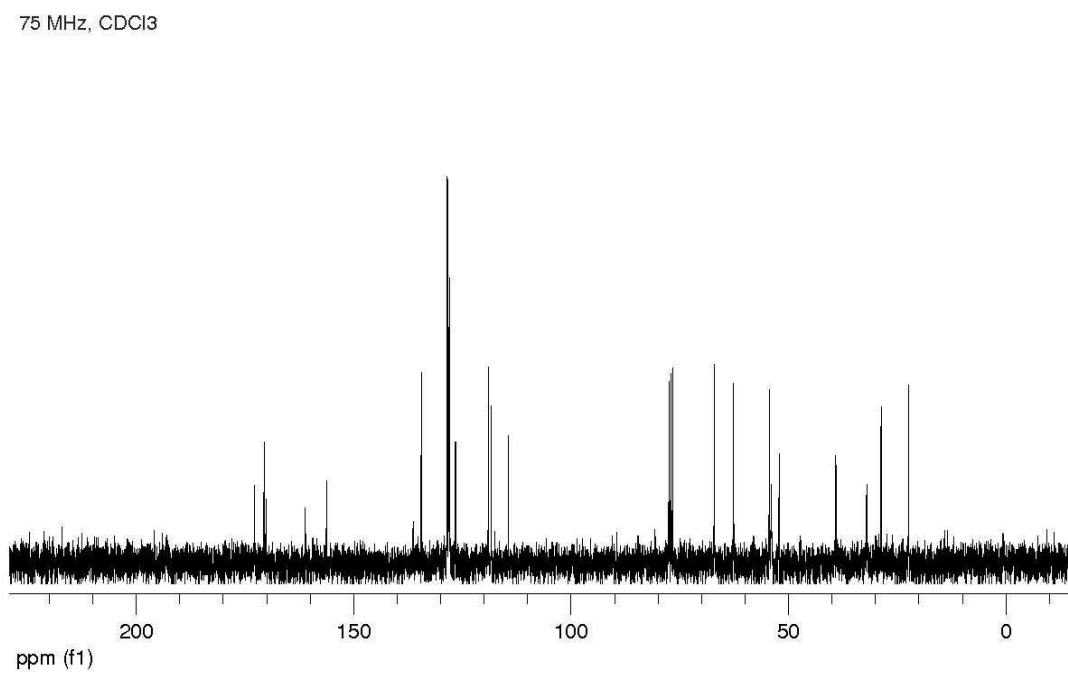
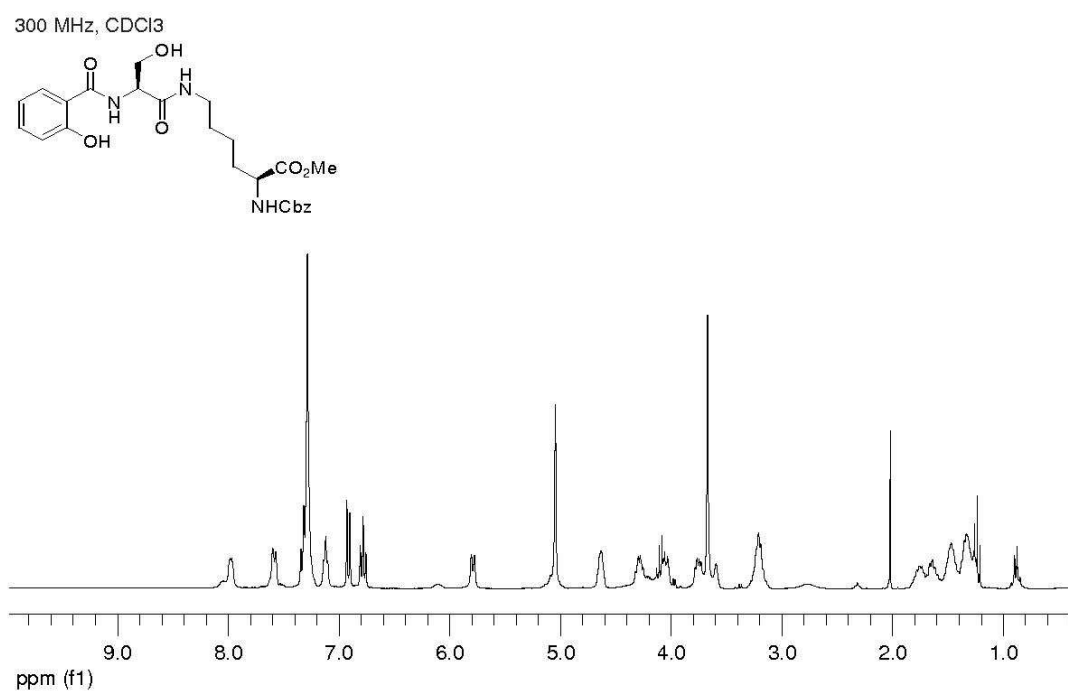
¹H and ¹³C NMR spectra for compound **4.23**



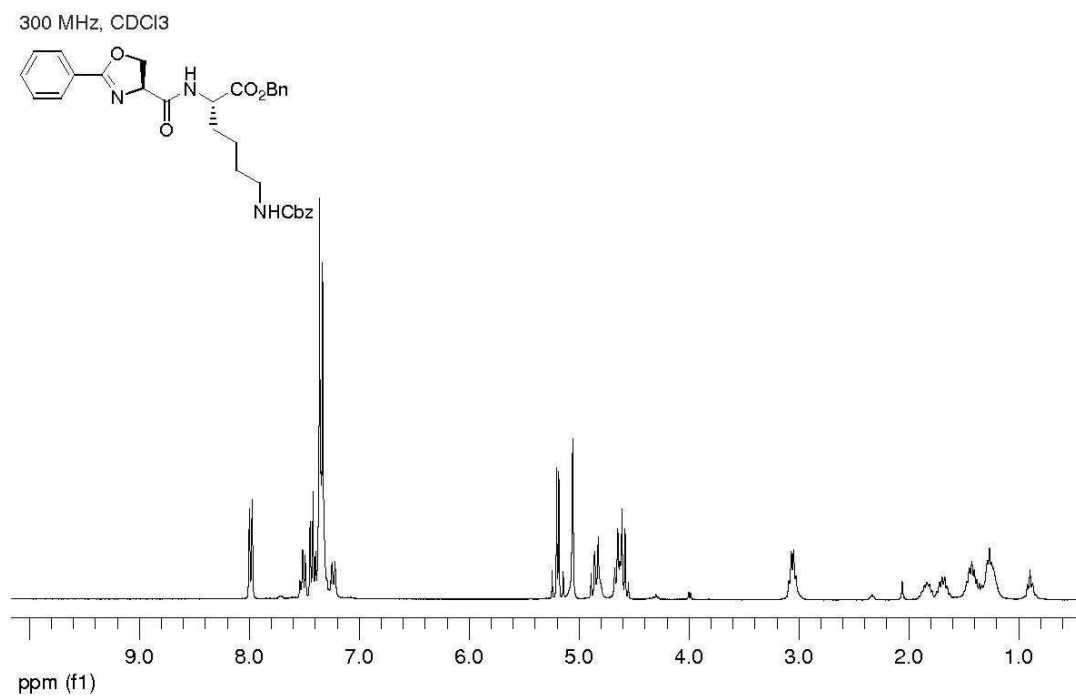
¹H NMR spectra for compound **4.24**



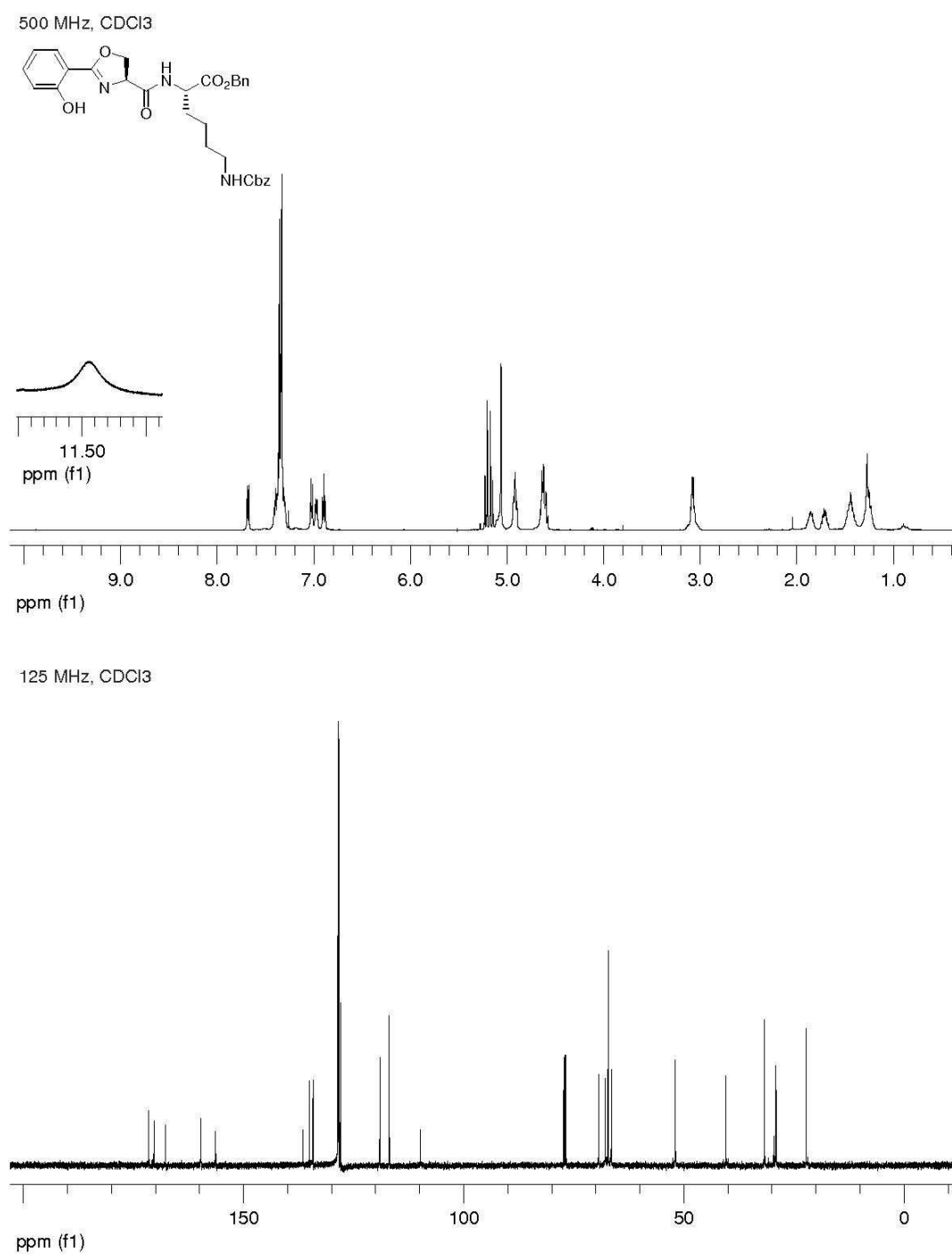
¹H NMR spectra for compound **4.25**



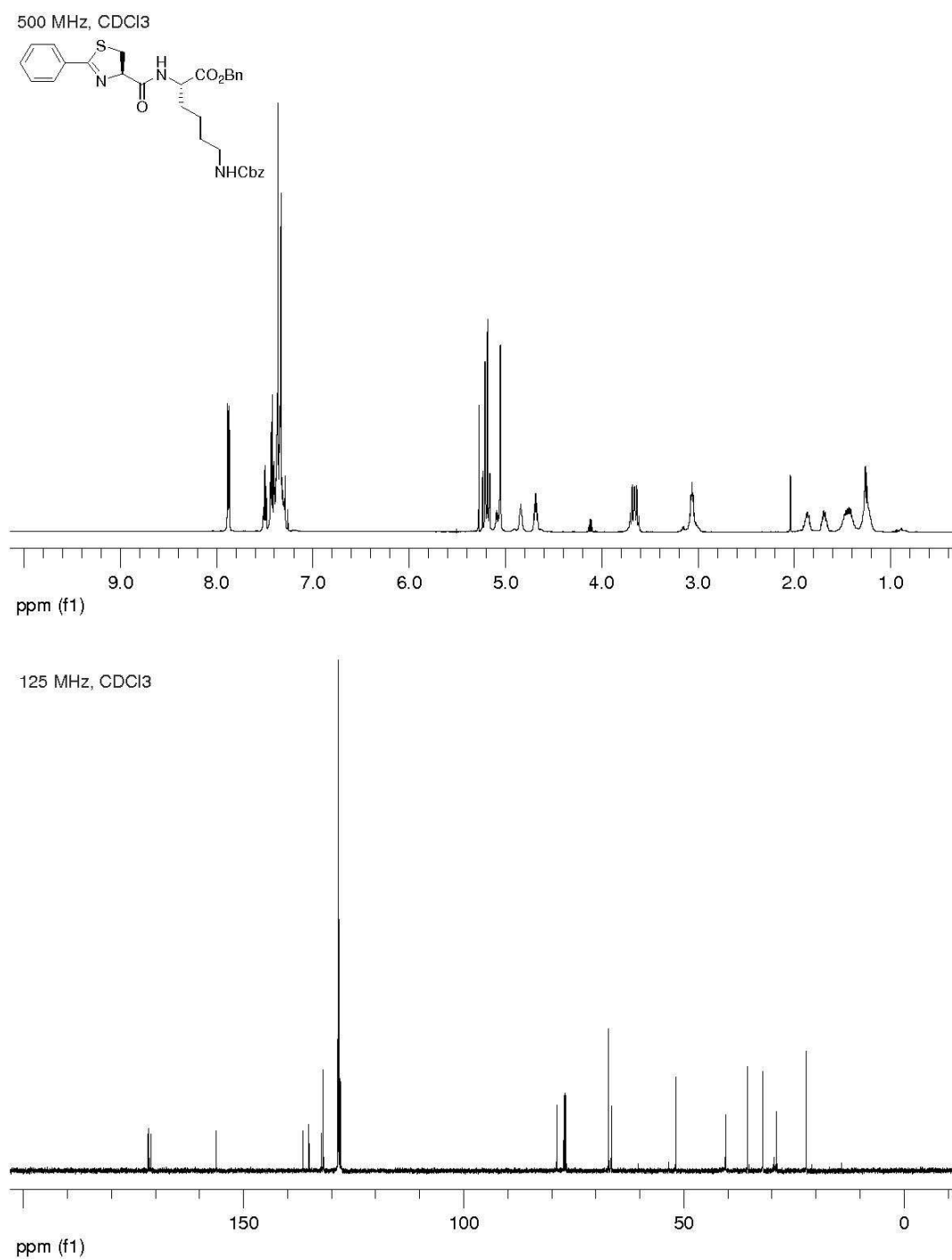
¹H and ¹³C NMR spectra for compound **4.26**



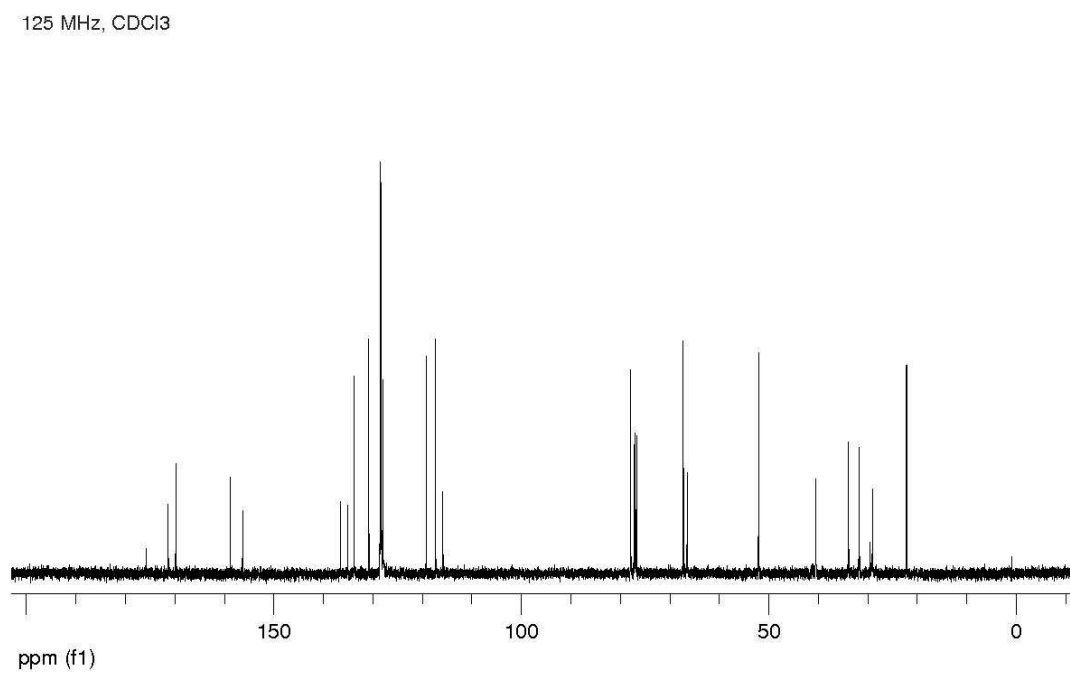
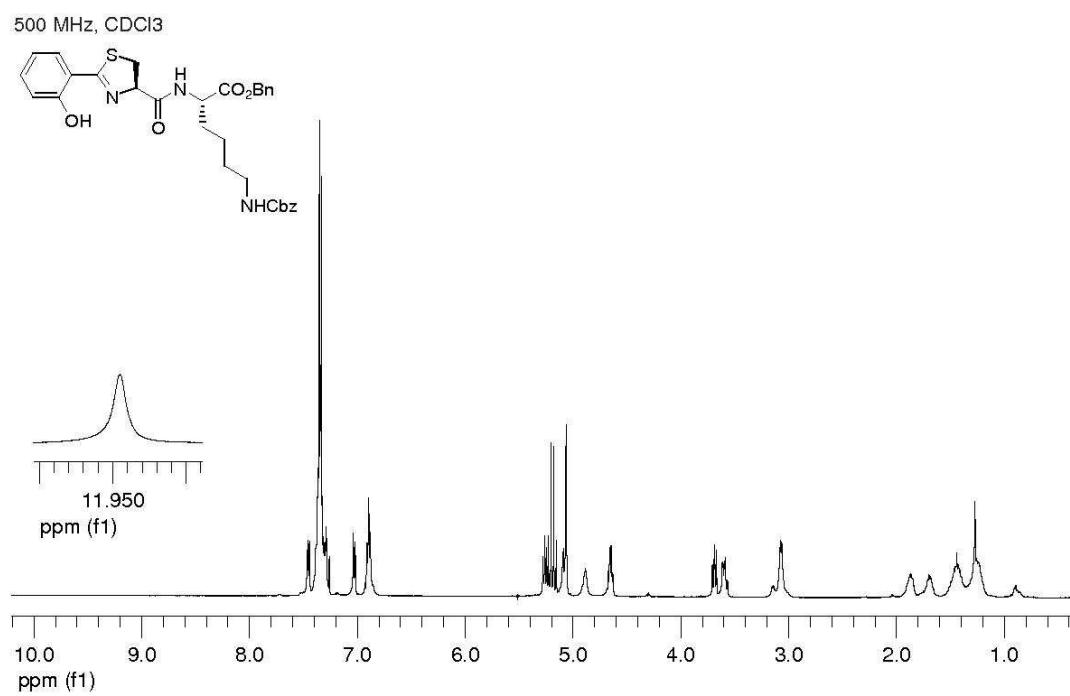
¹H NMR spectra for compound **4.27**



¹H and ¹³C NMR spectra for compound **4.28**

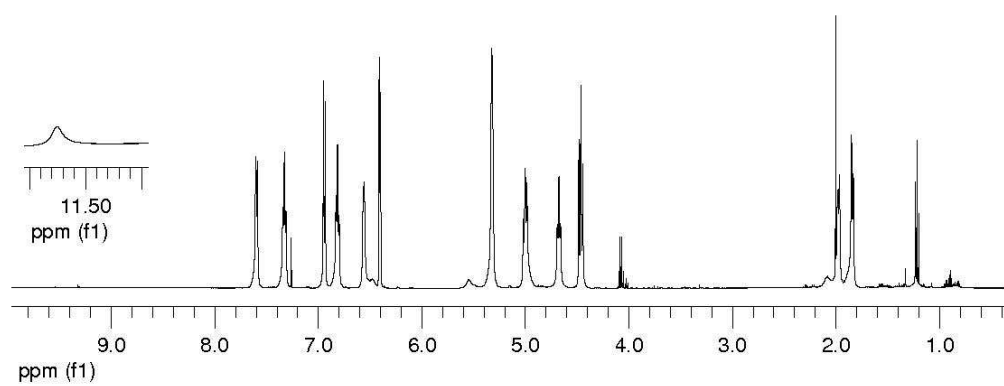
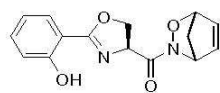


¹H and ¹³C NMR spectra for compound **4.31**

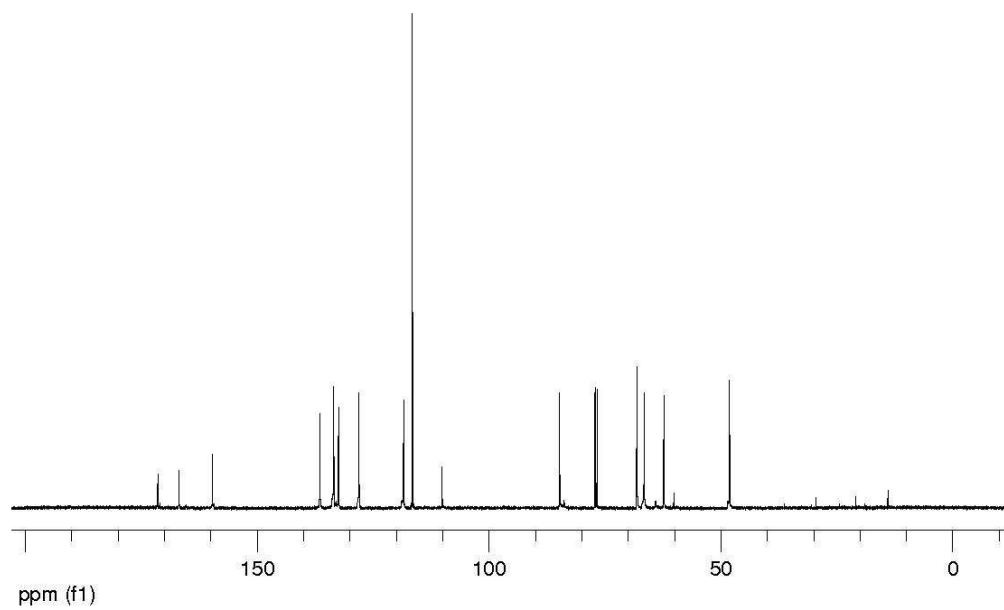


¹H and ¹³C NMR spectra for compound **4.32**

500 MHz, CDCl₃

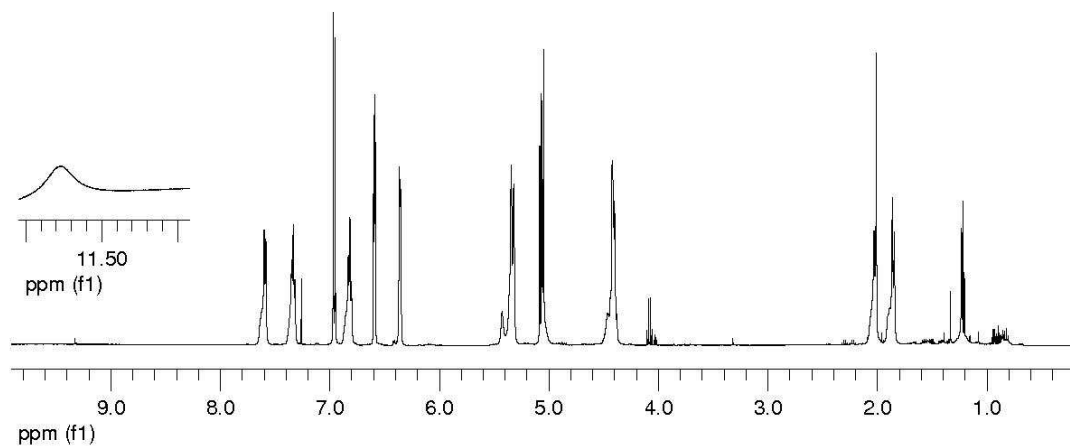
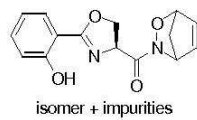


125 MHz, CDCl₃

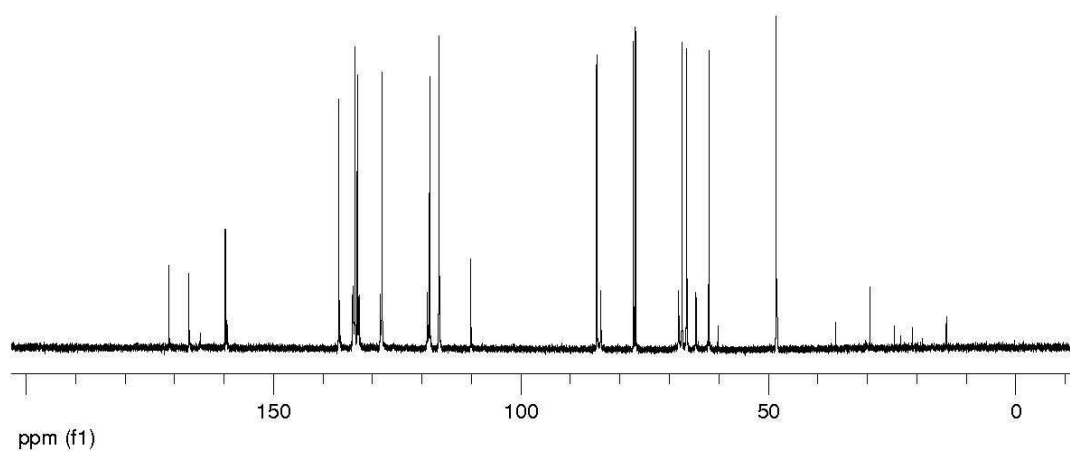


¹H and ¹³C NMR spectra for compound **4.36**

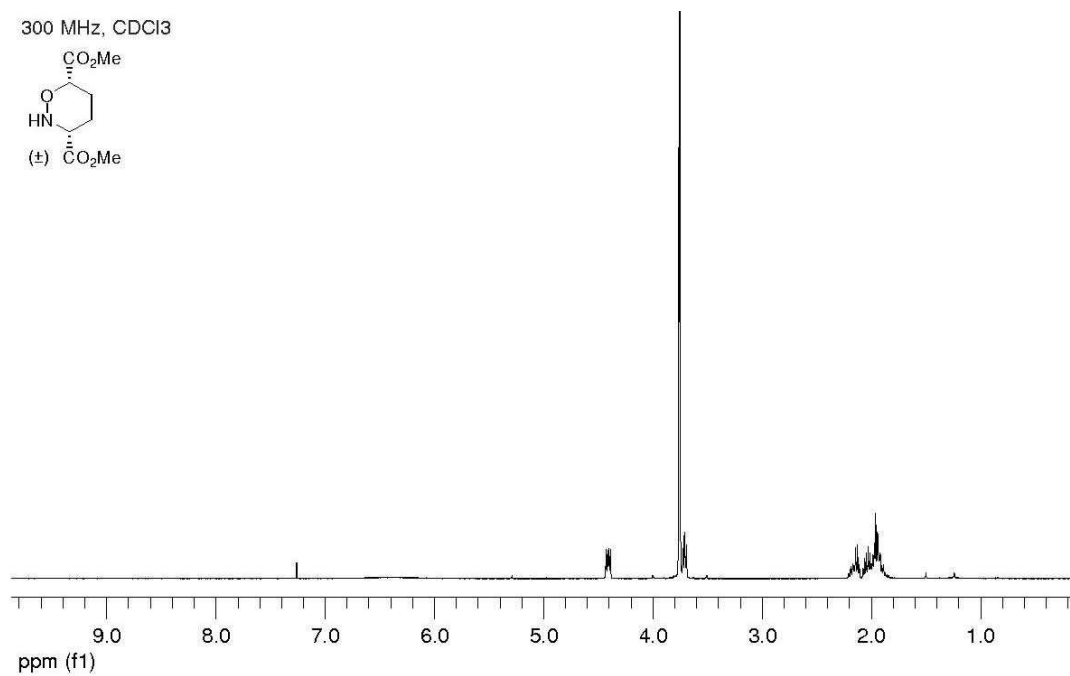
500 MHz, CDCl₃



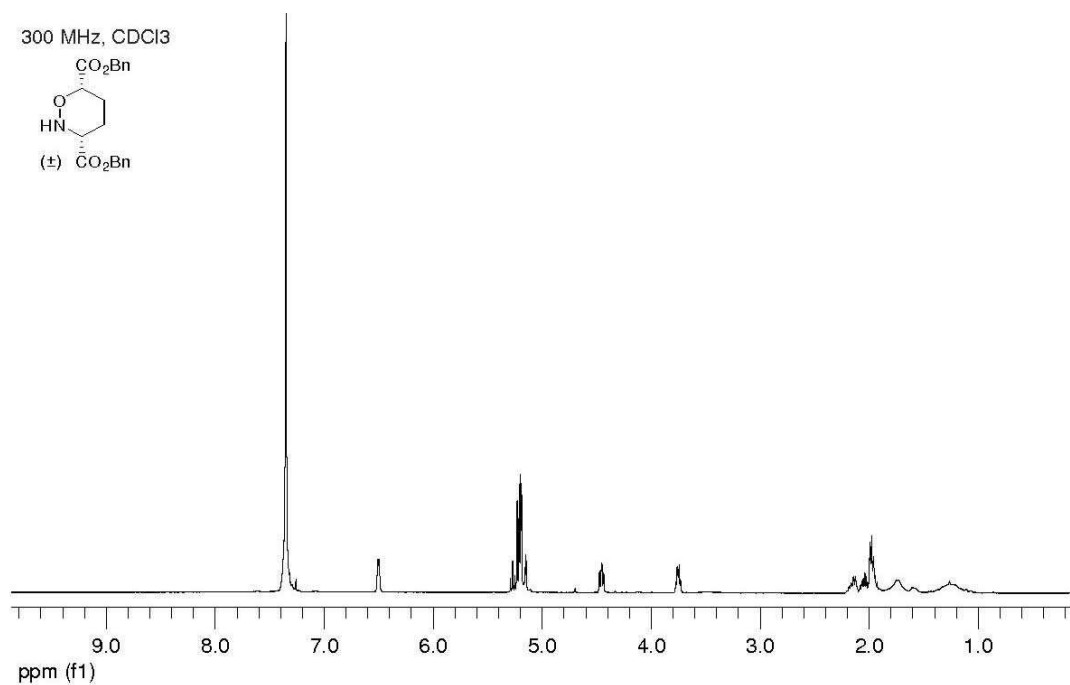
125 MHz, CDCl₃



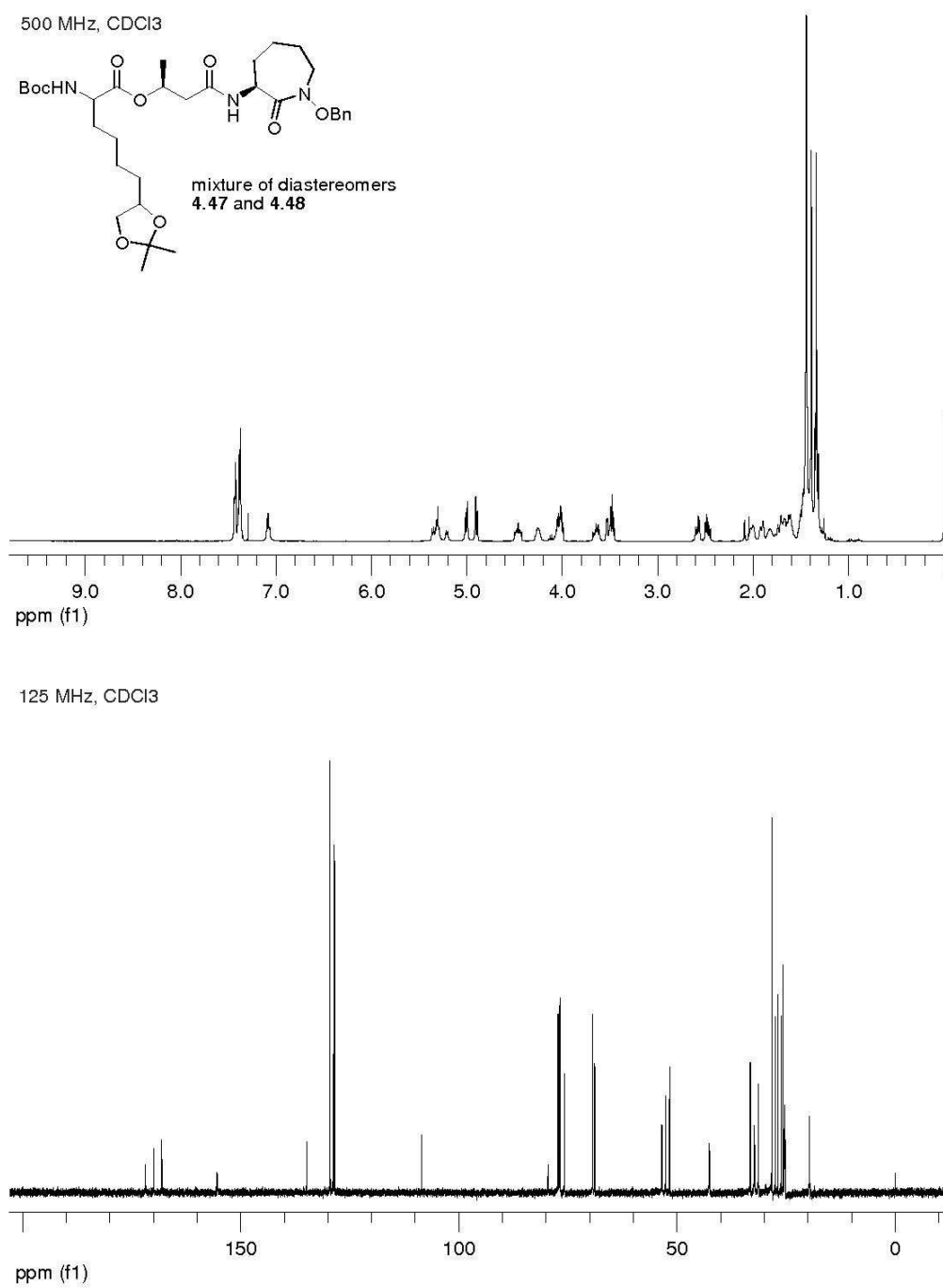
¹H and ¹³C NMR spectra for compound **4.36'**



¹H NMR spectra for compound **4.41**

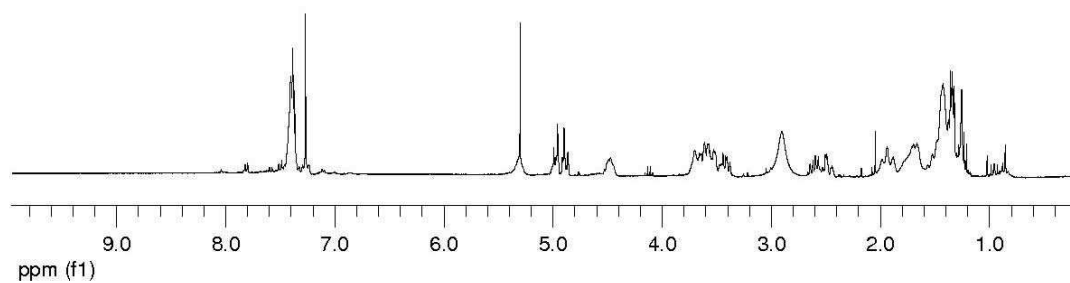
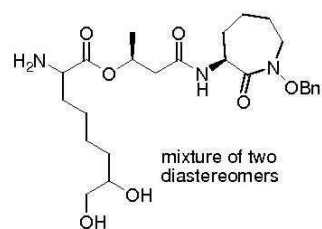


¹H and ¹³C NMR spectra for compound **4.42**

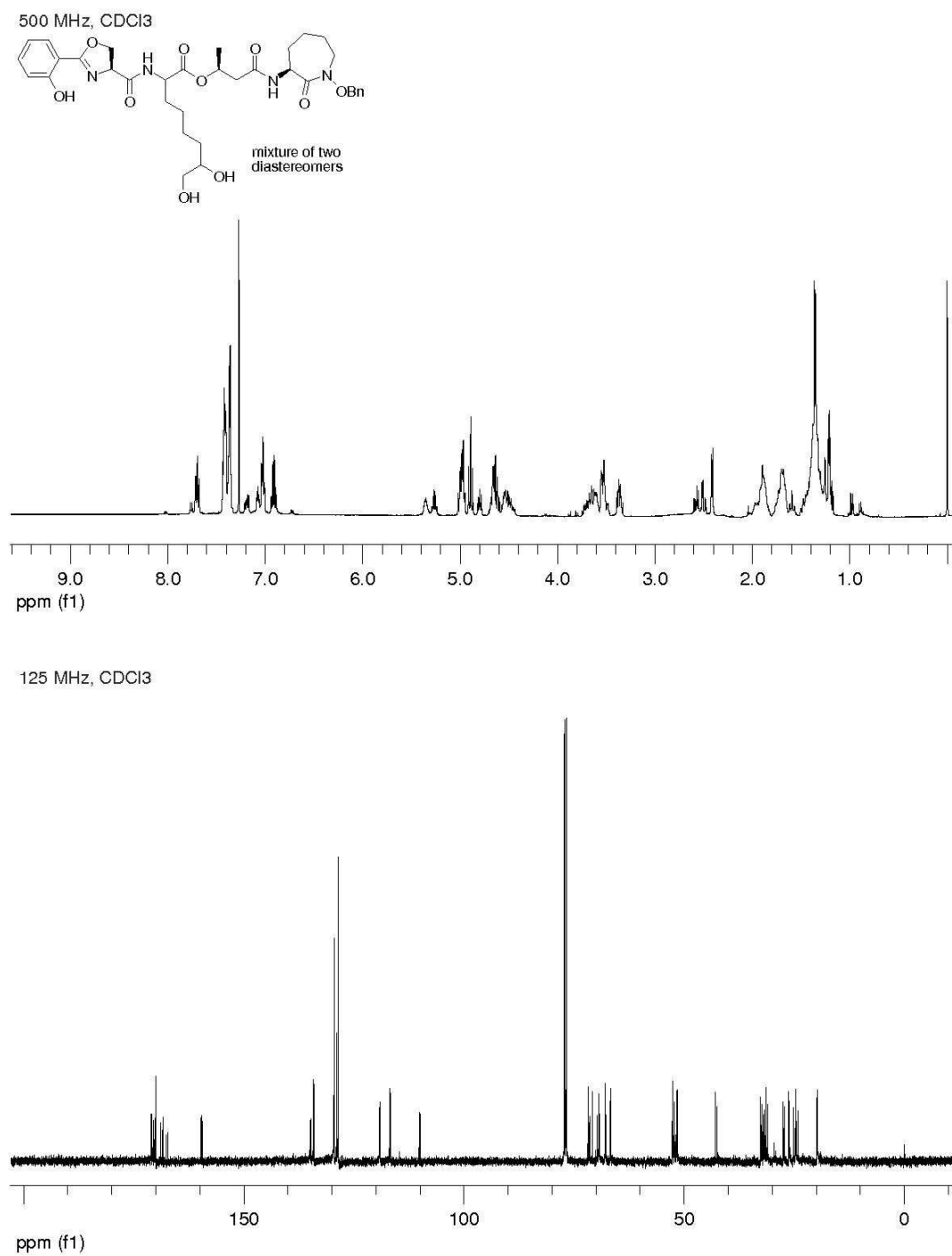


¹H and ¹³C NMR spectra for a mixture of diastereomers **4.47** and **4.48**

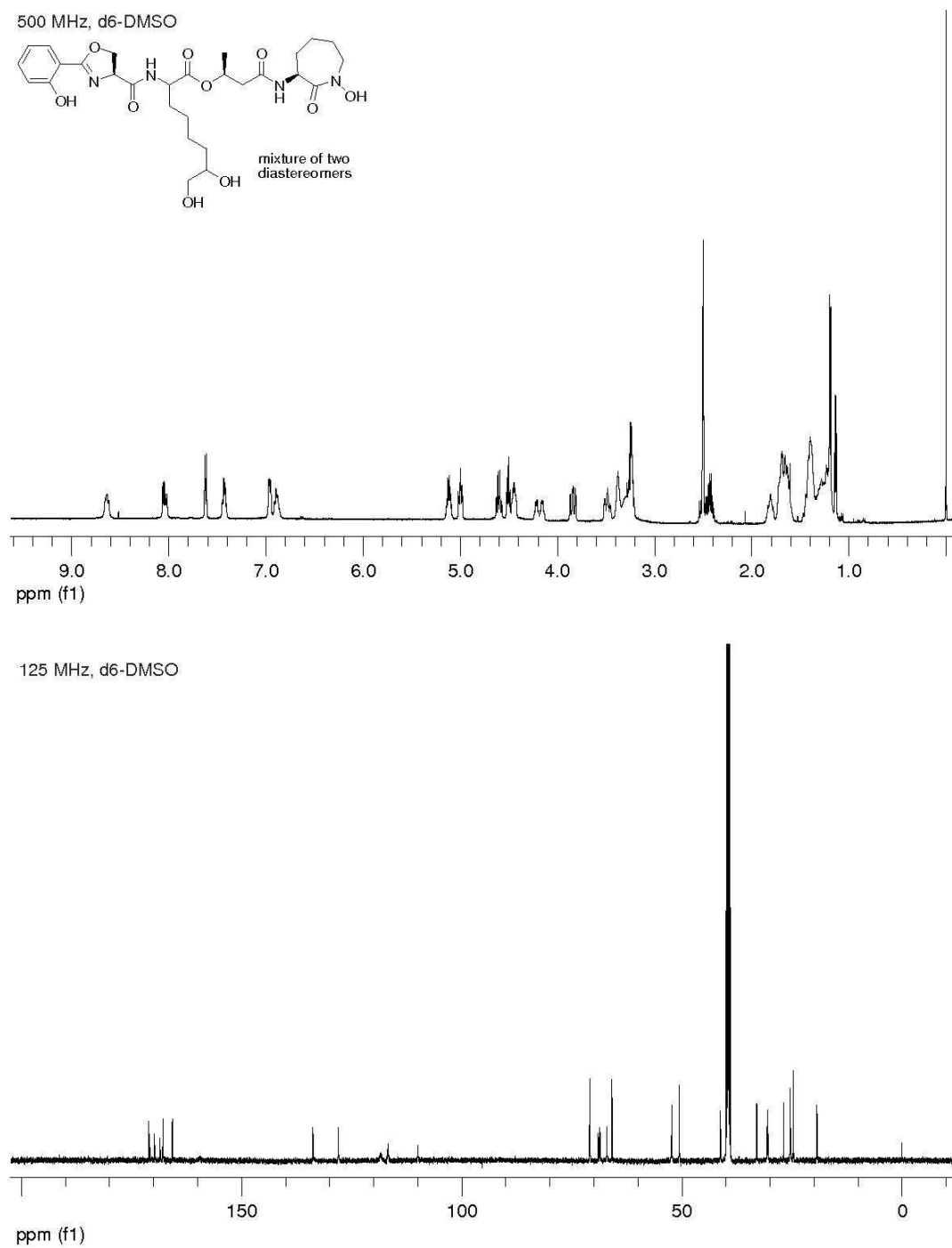
300 MHz, CDCl₃



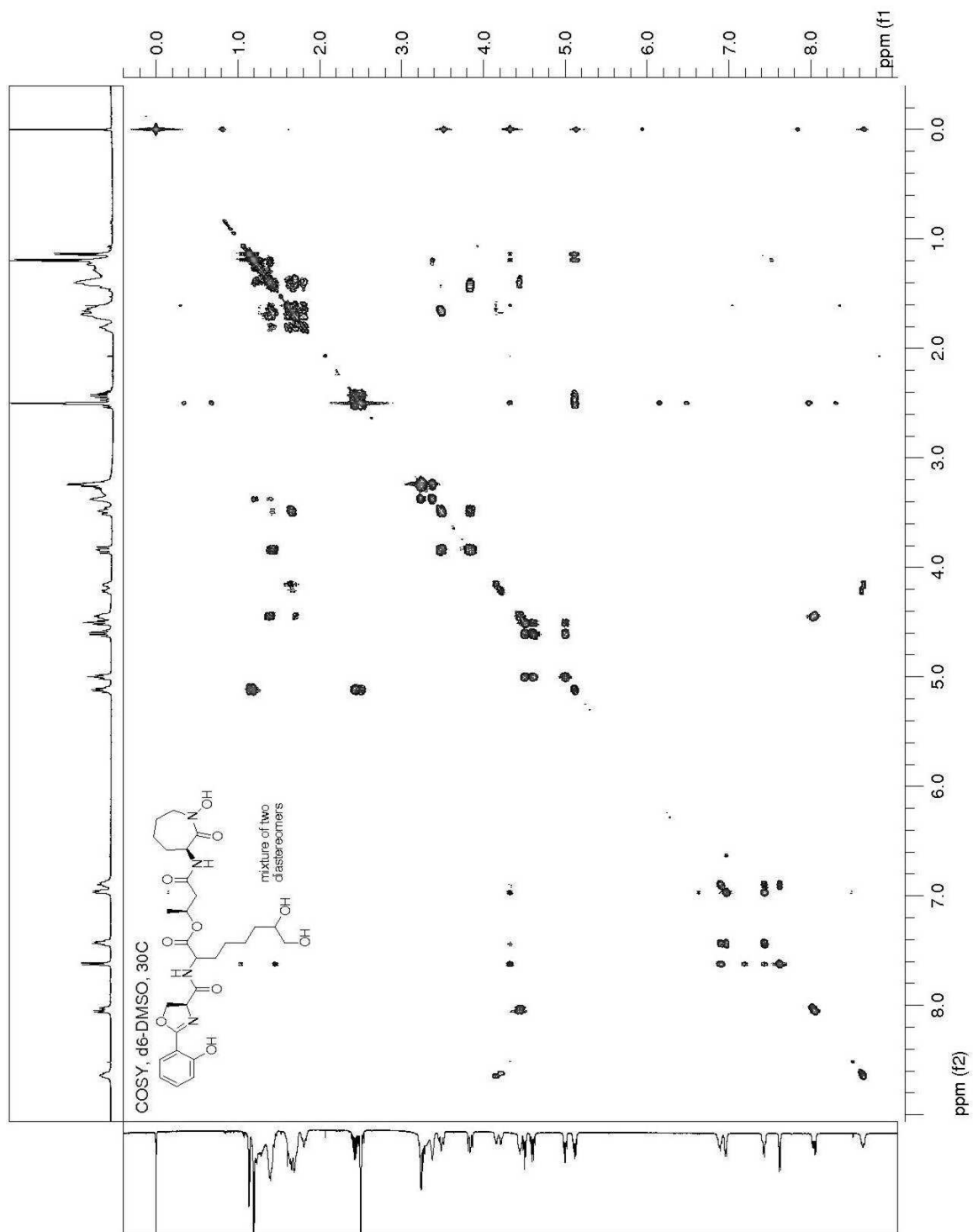
¹H NMR spectra for compound **4.53**



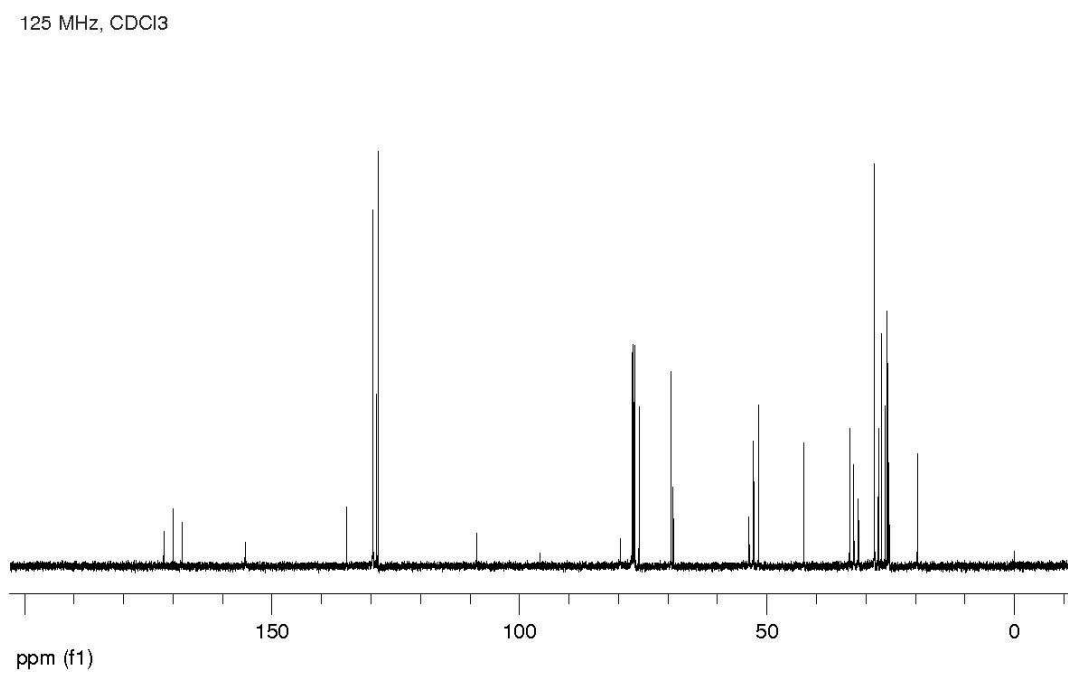
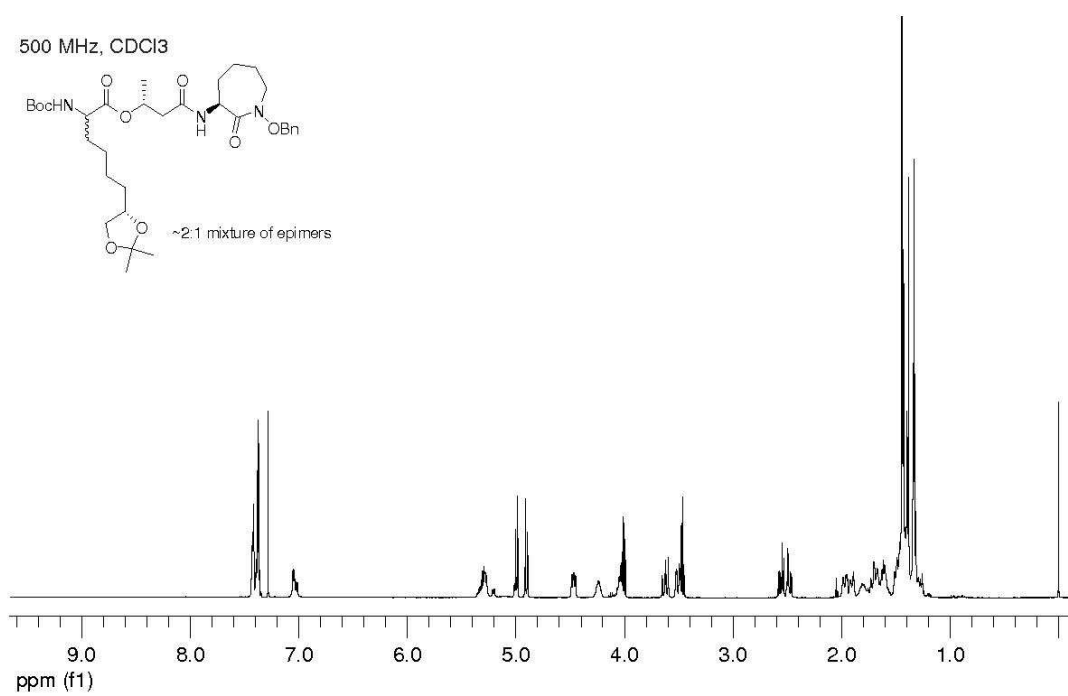
¹H and ¹³C NMR spectra for compound **4.54**



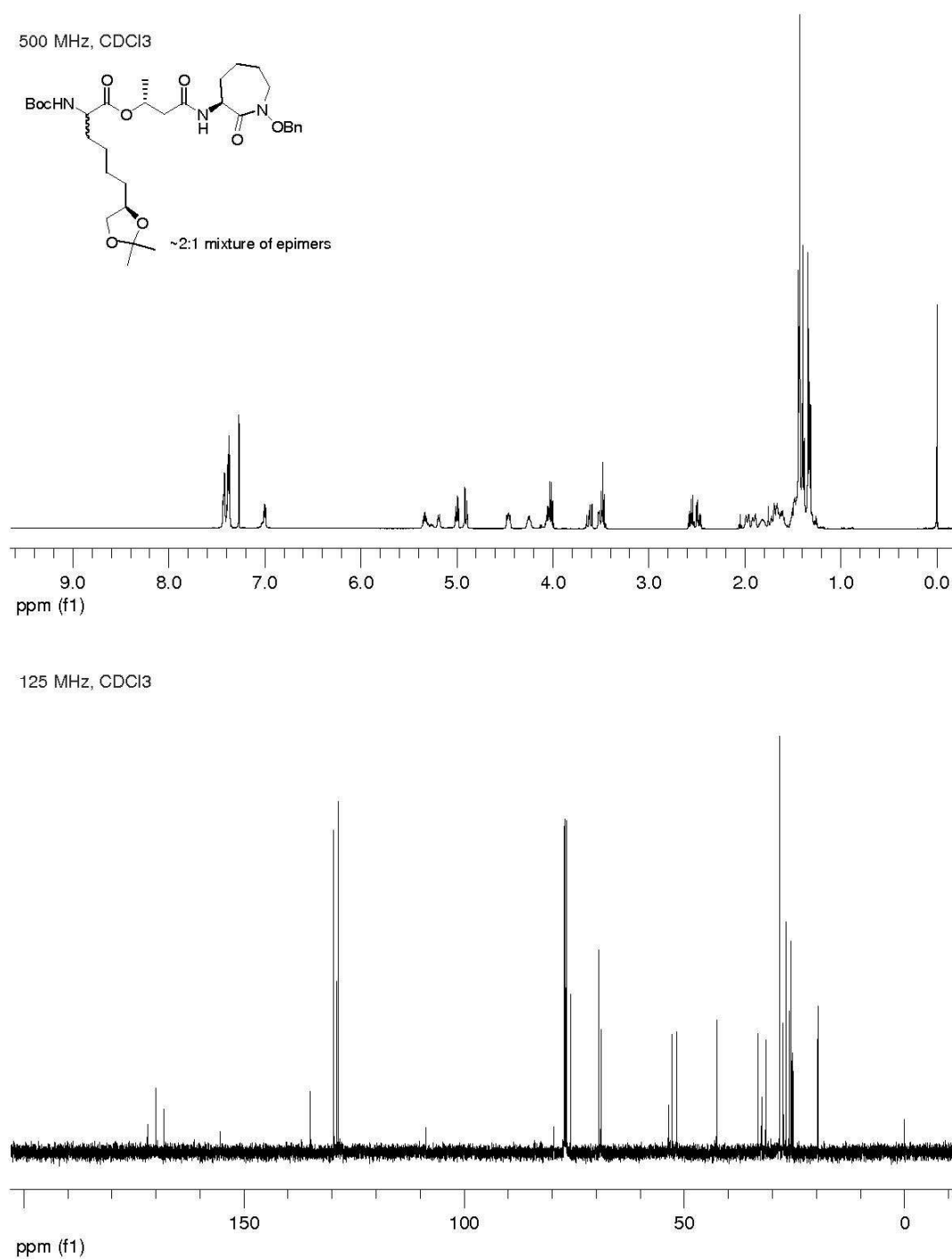
¹H and ¹³C NMR spectra for compound **4.56**



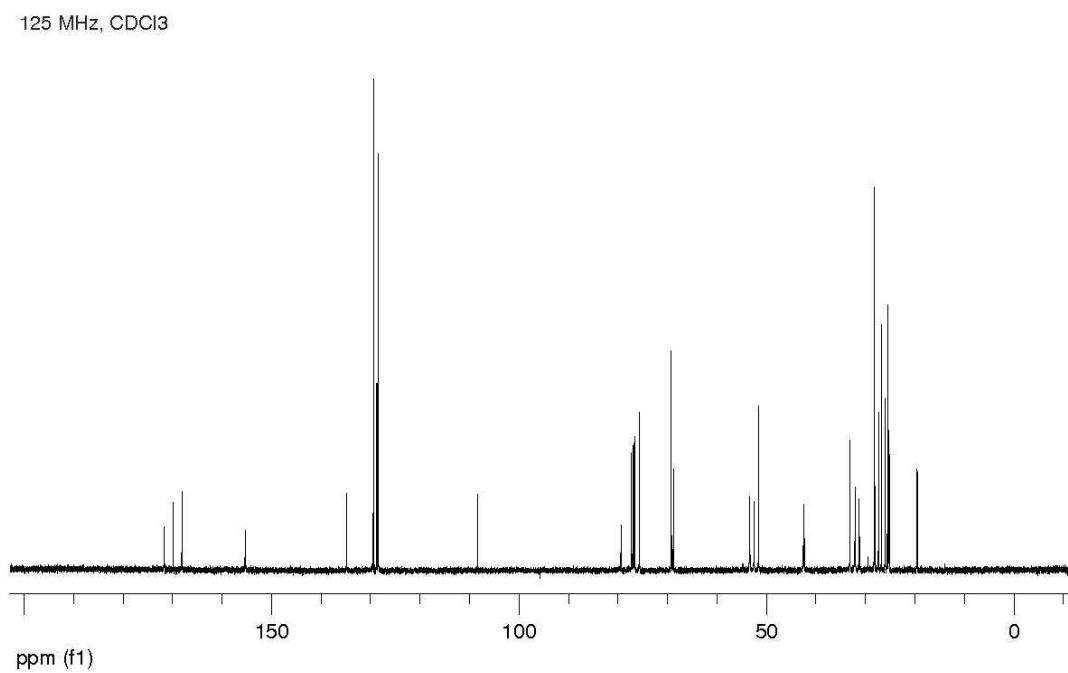
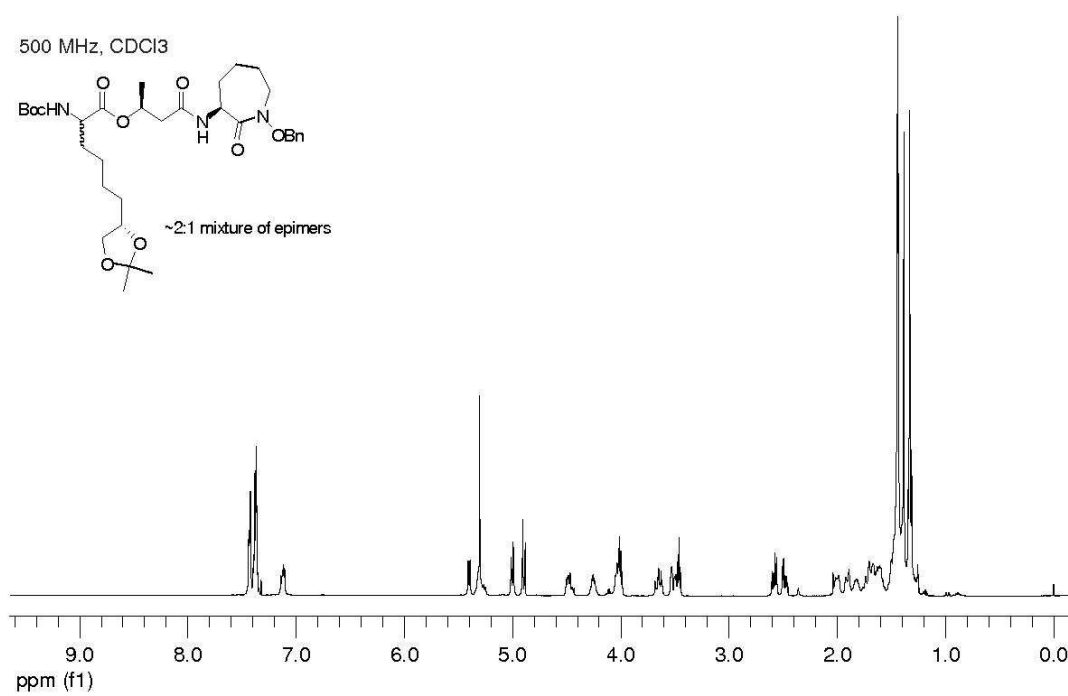
COSY NMR spectra for compound **4.56**



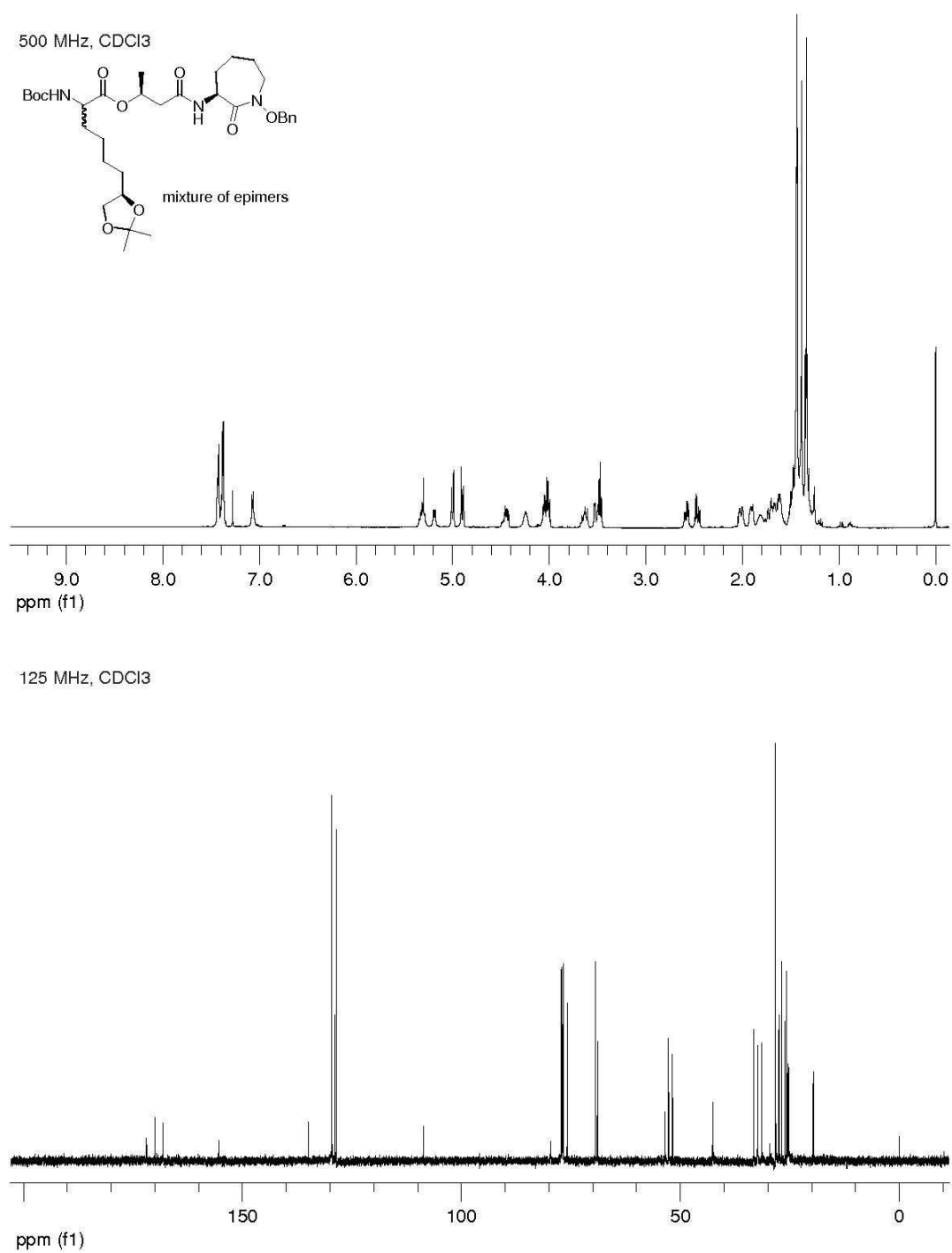
¹H and ¹³C NMR spectra for compound **4.57**



¹H and ¹³C NMR spectra for compound **4.58**

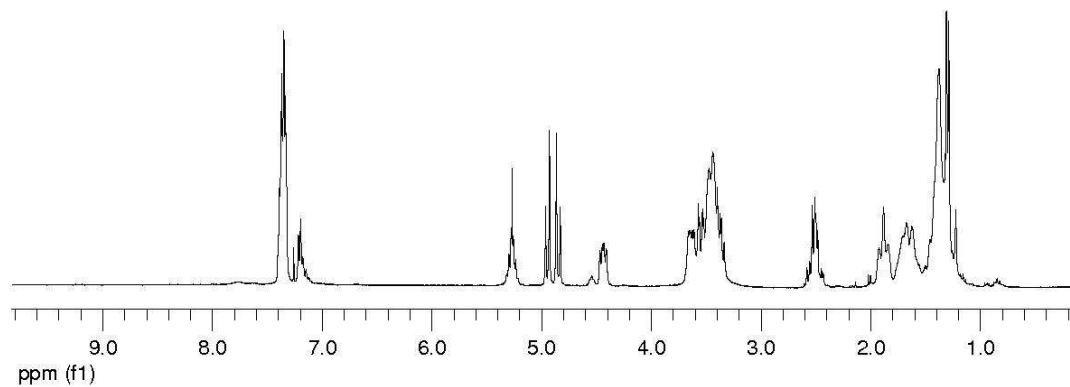
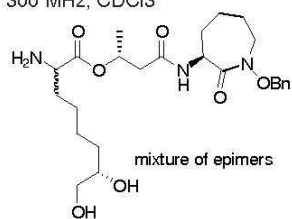


¹H and ¹³C NMR spectra for compound **4.59**

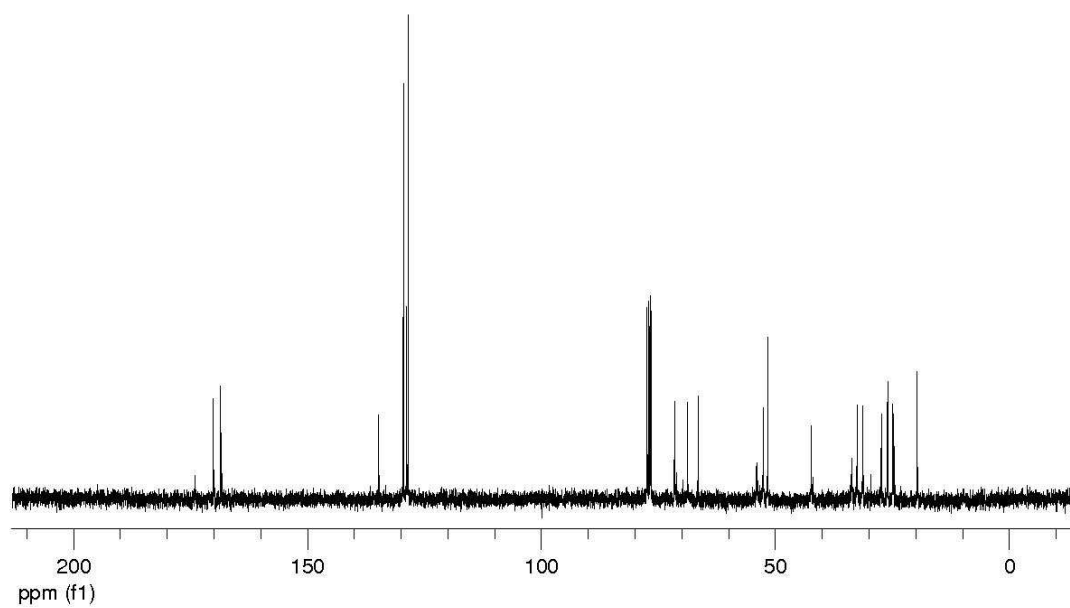


¹H and ¹³C NMR spectra for compound **4.60**

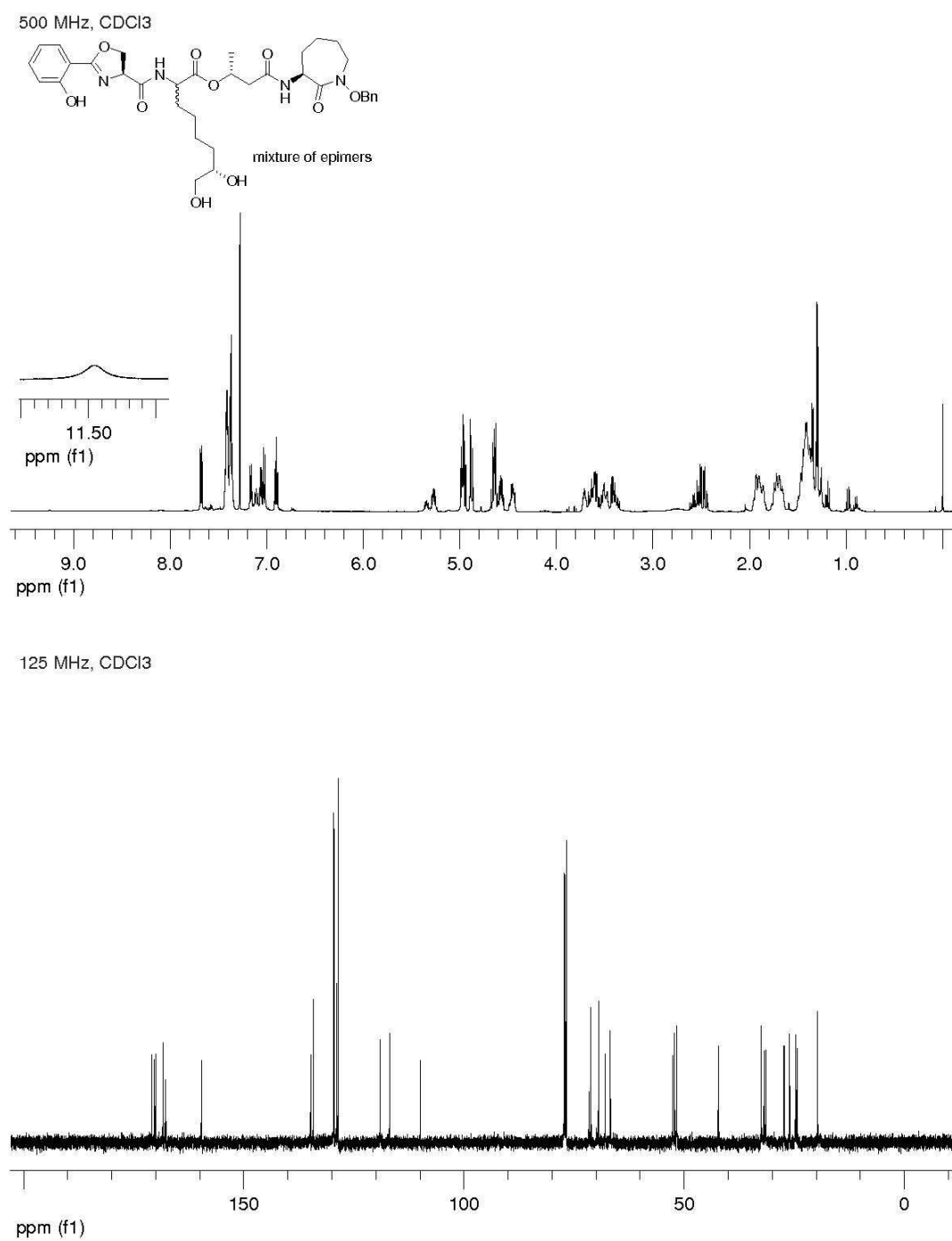
300 MHz, CDCl₃



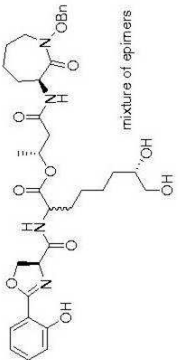
75 MHz, CDCl₃



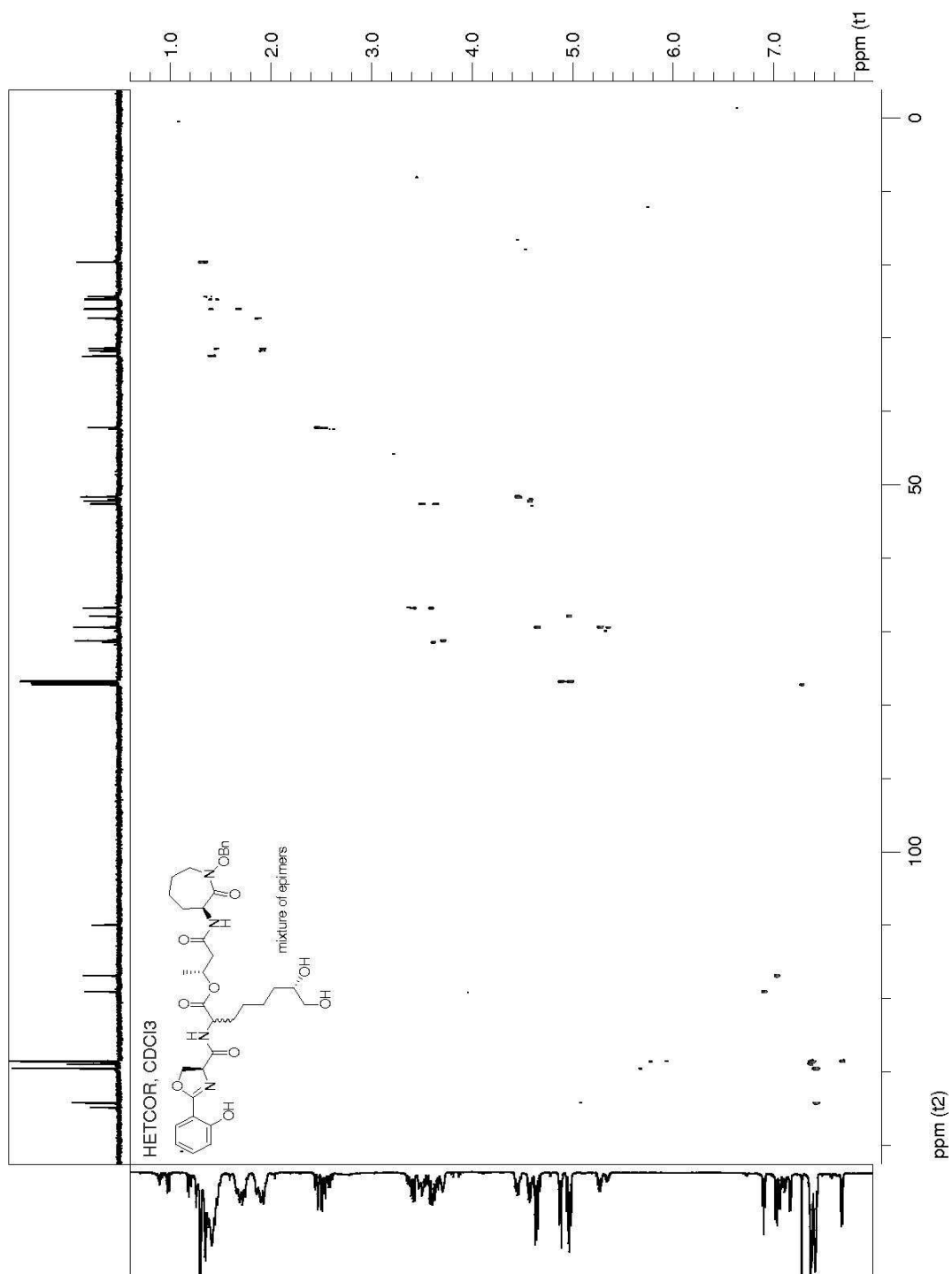
¹H and ¹³C NMR spectra for compound **4.61**



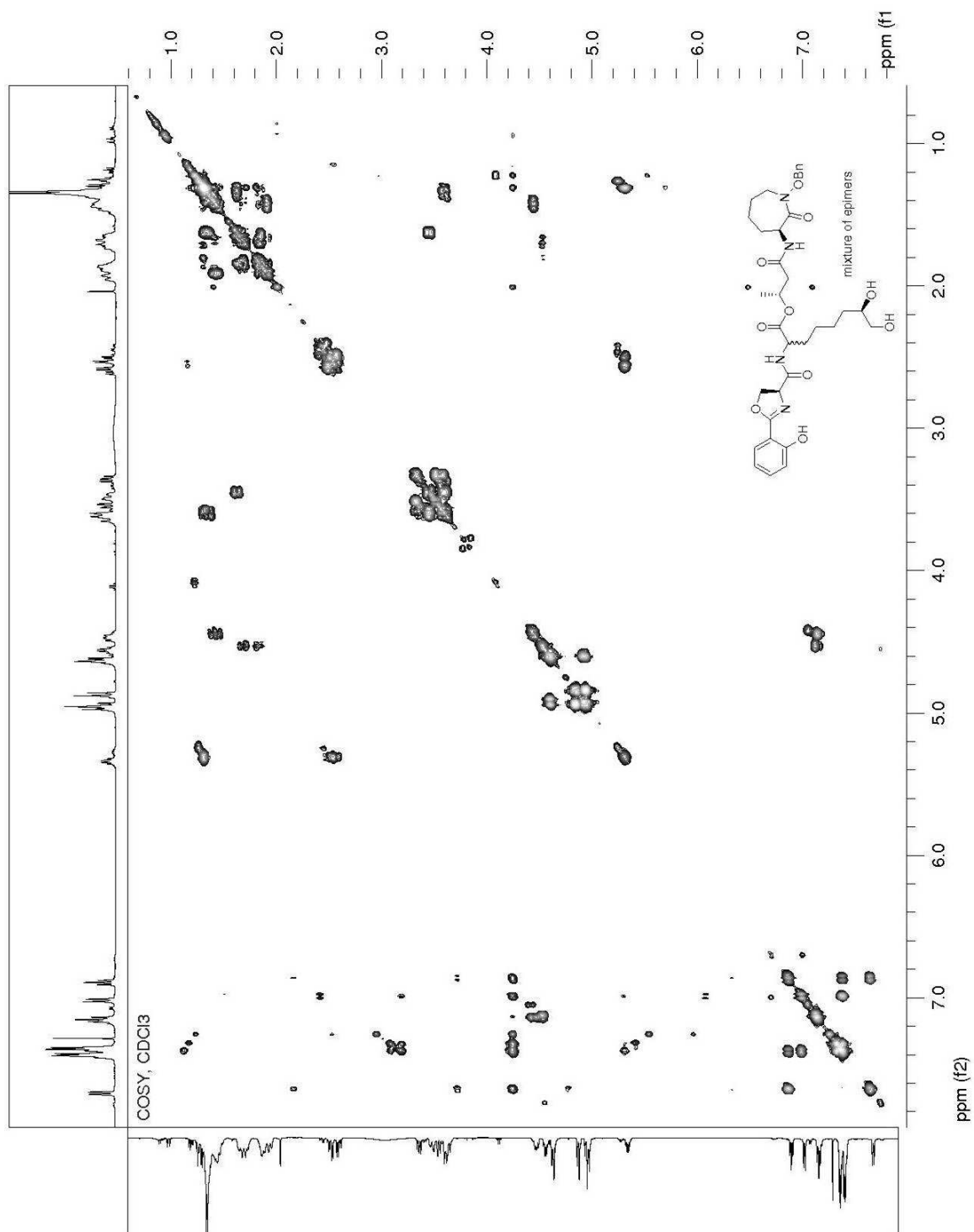
¹H and ¹³C NMR spectra for compound **4.62**



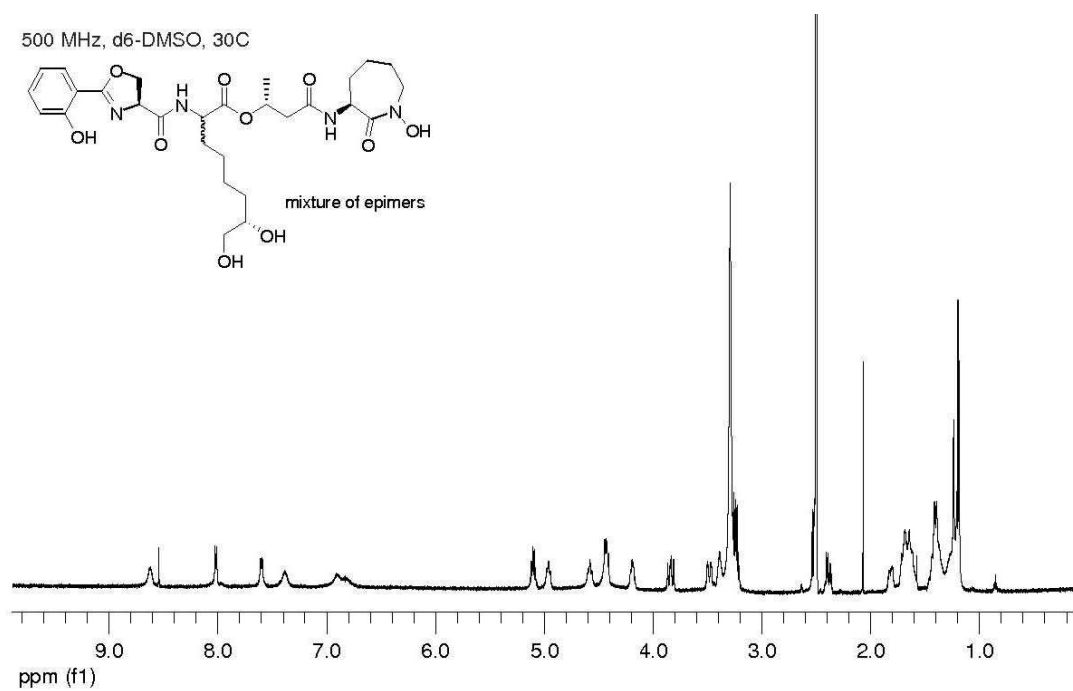
493



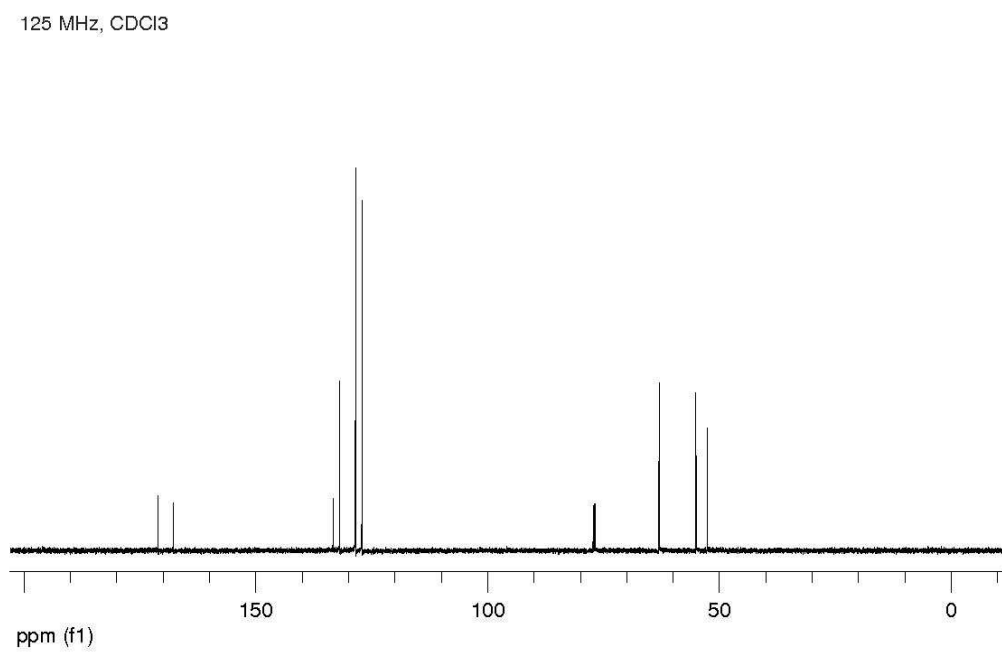
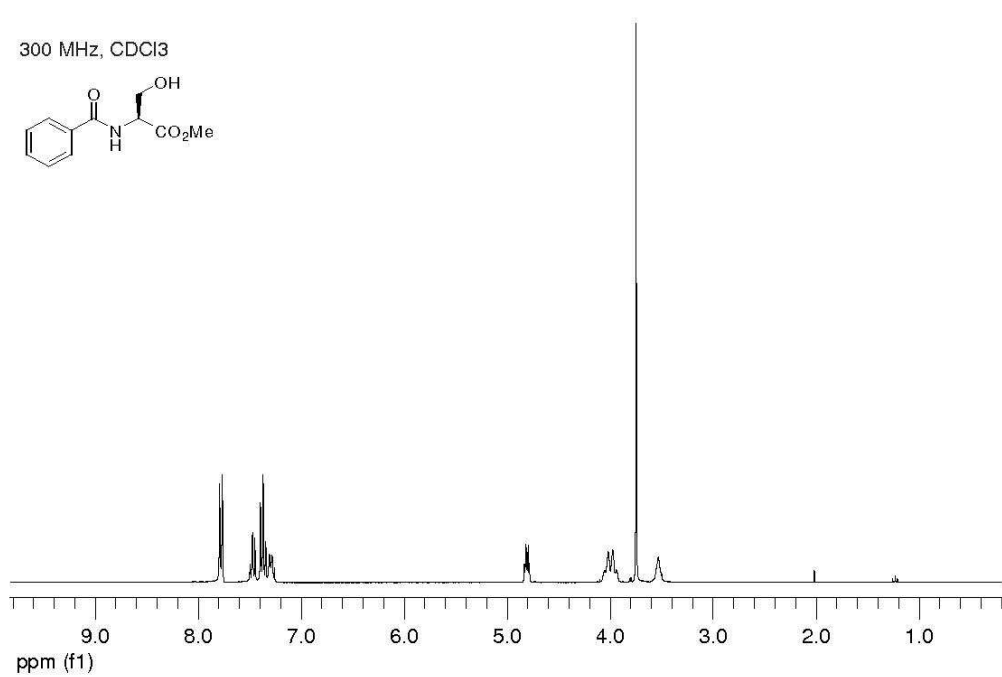
HETCOR NMR spectra for compound **4.62**



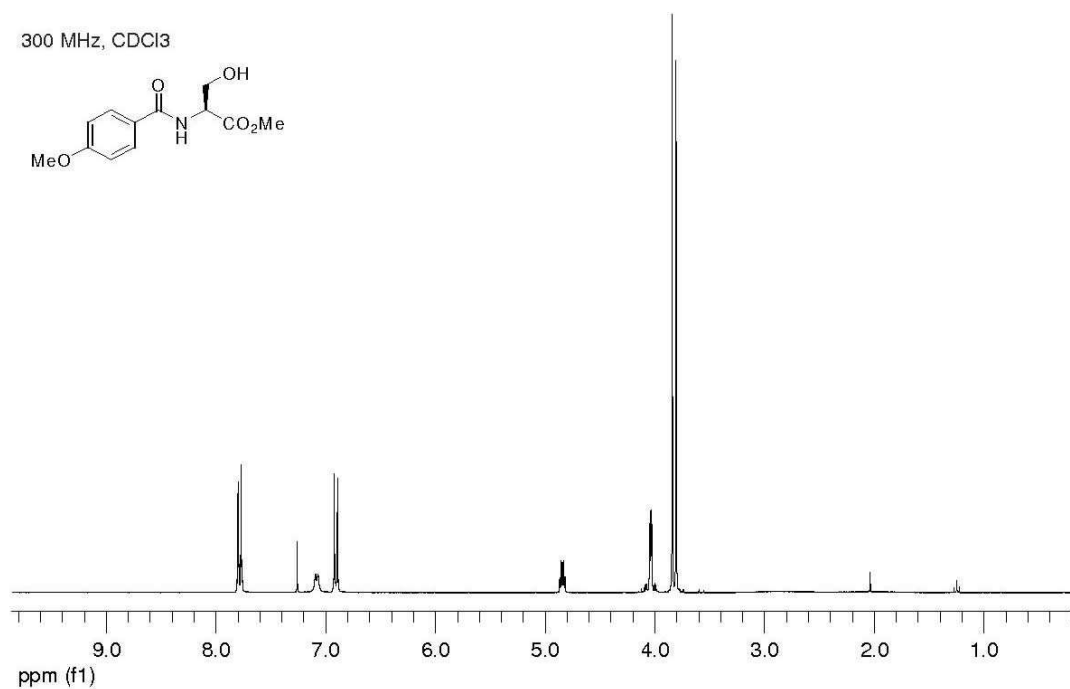
COSY NMR spectra for compound **4.64**



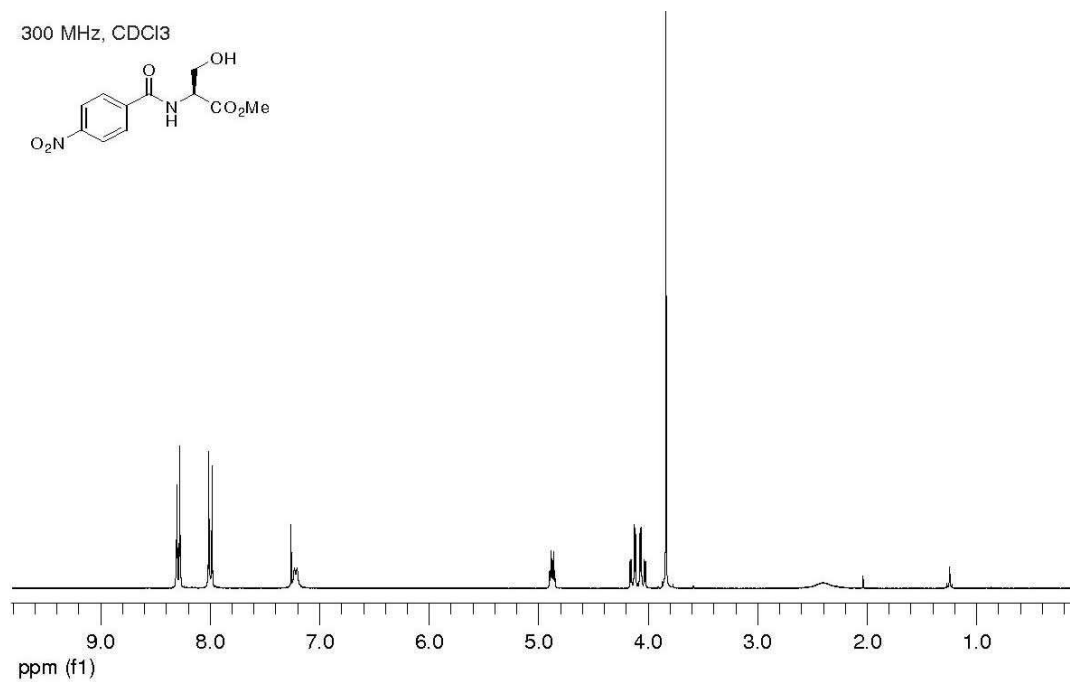
^1H NMR spectra for compound **4.65**



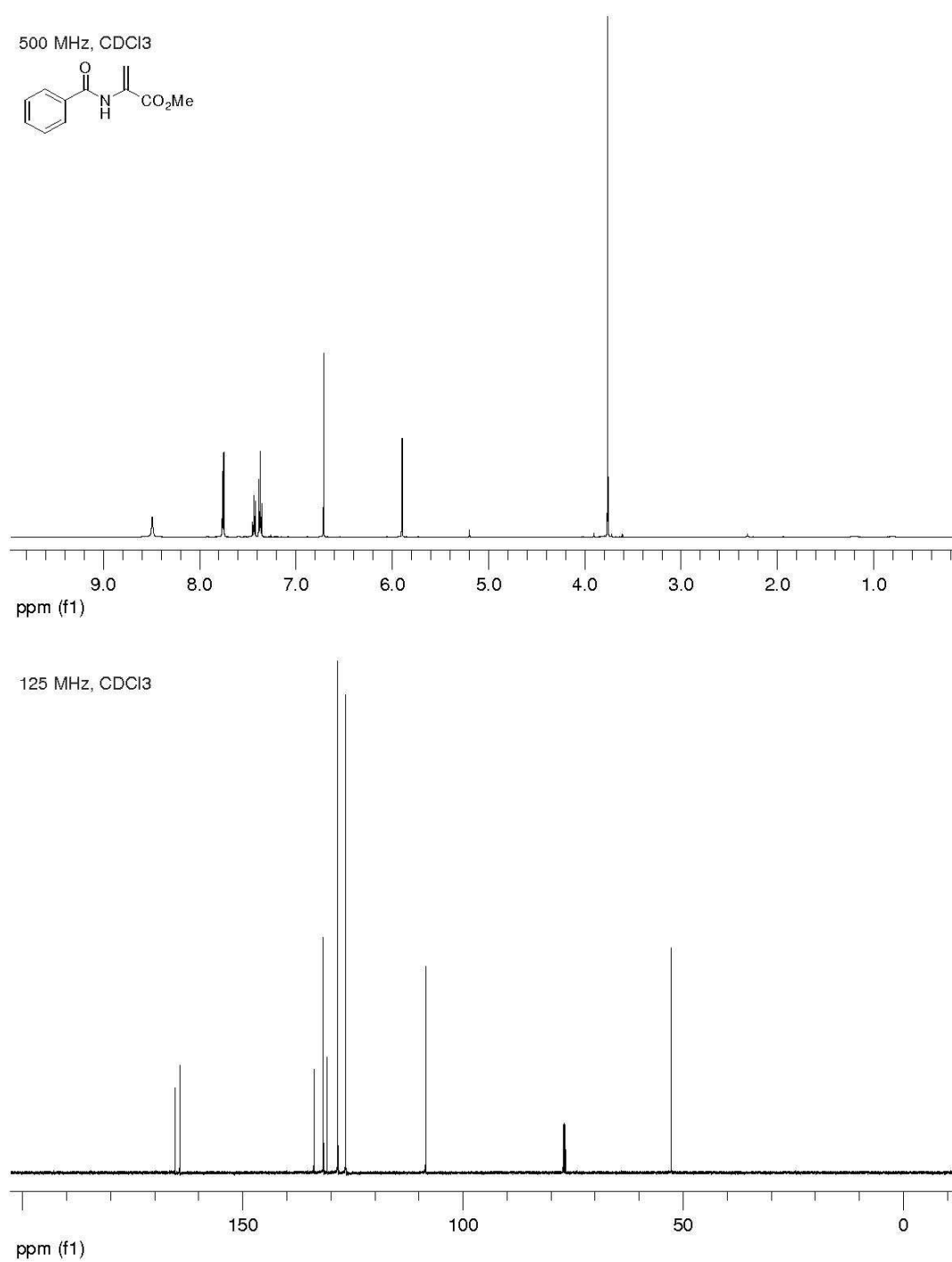
¹H and ¹³C NMR spectra for compound **5.20**



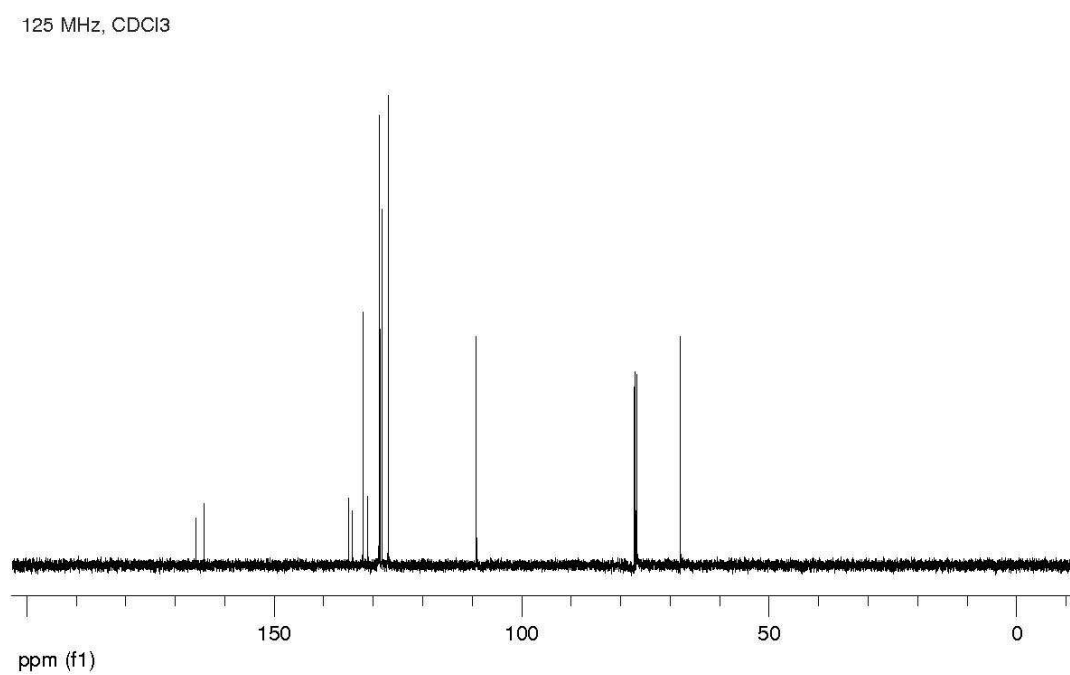
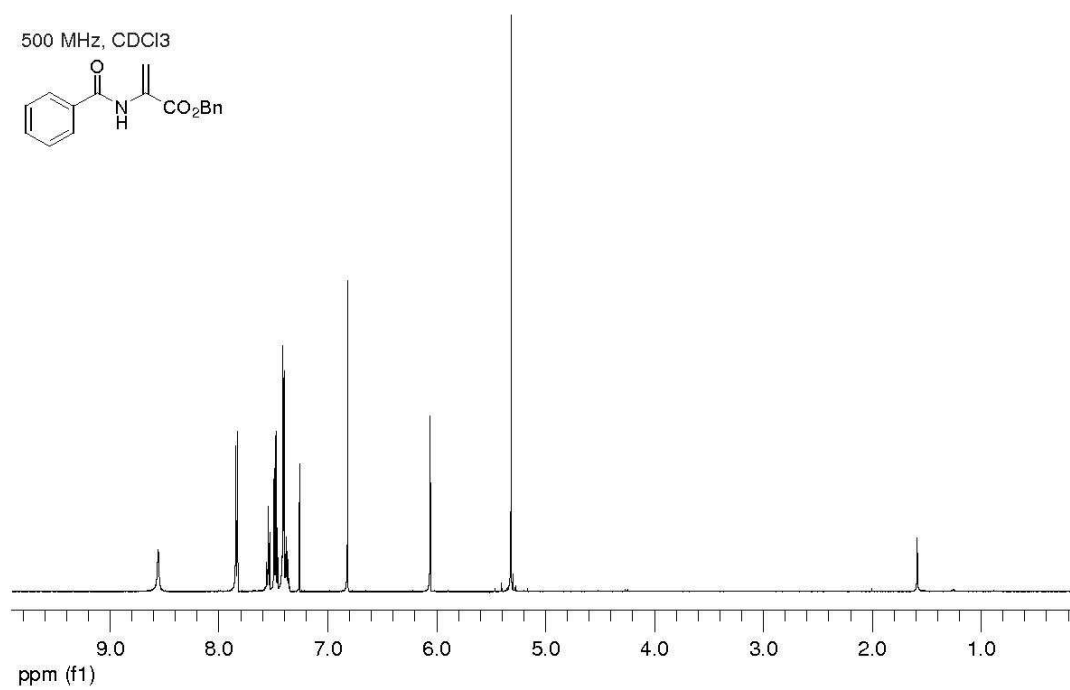
¹H NMR spectra for compound **5.21**



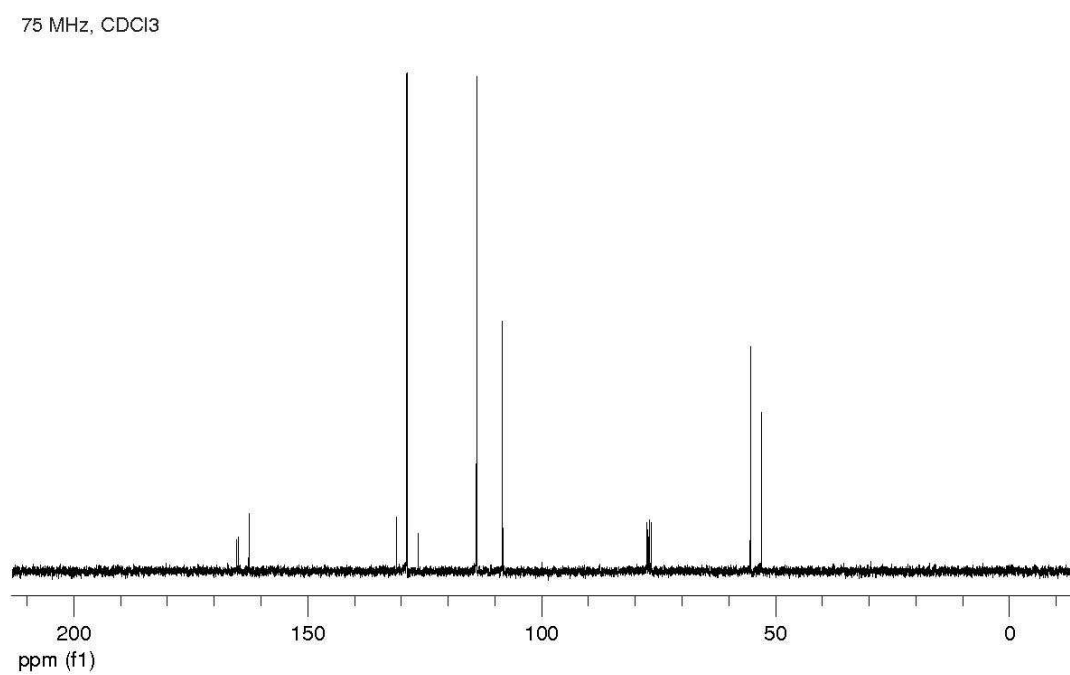
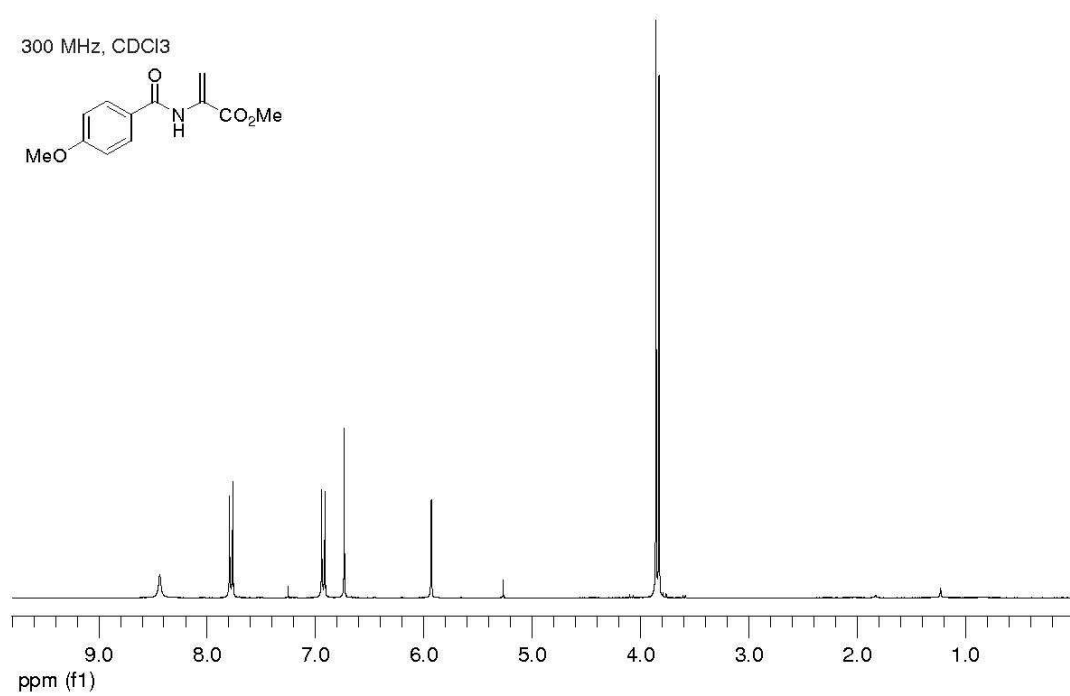
¹H NMR spectra for compound **5.22**



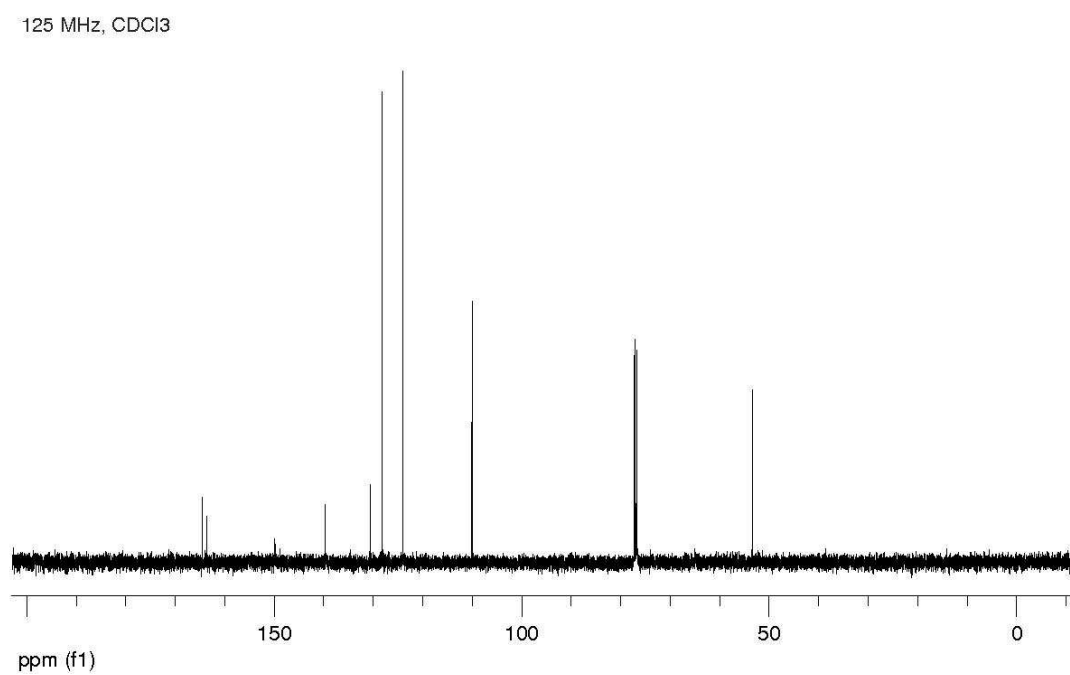
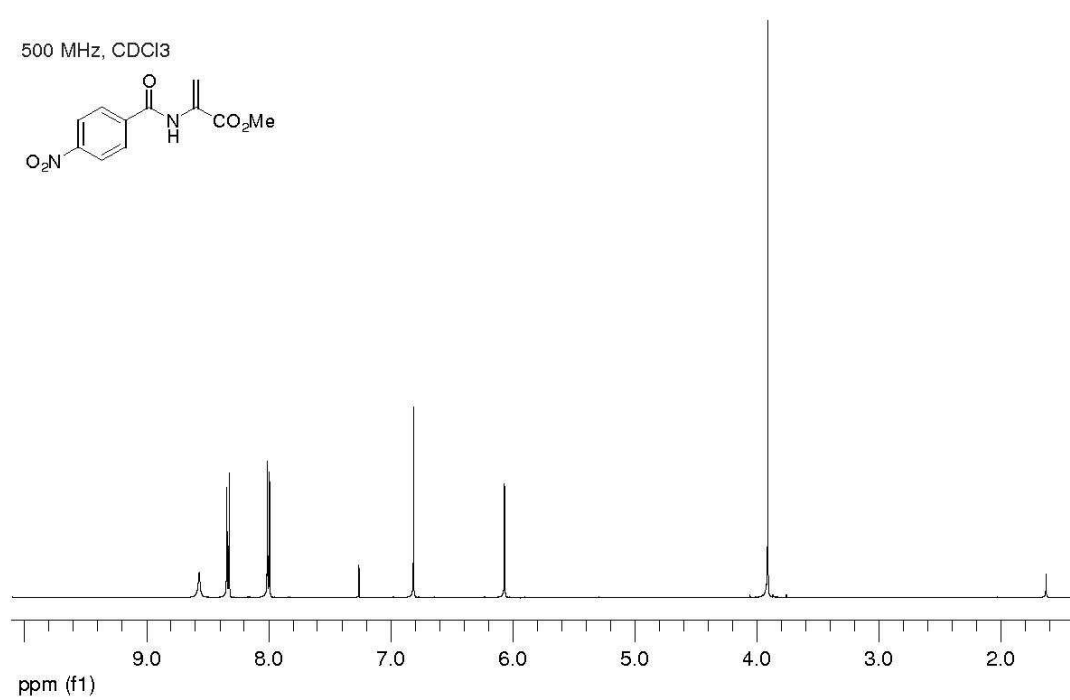
¹H and ¹³C NMR spectra for compound **5.23**



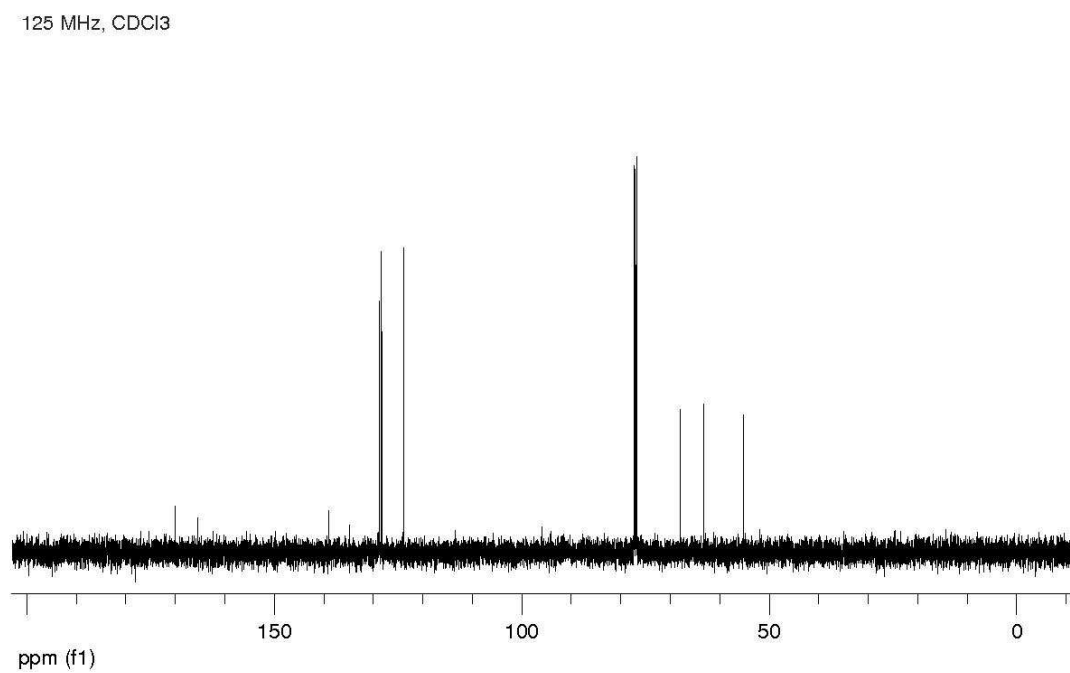
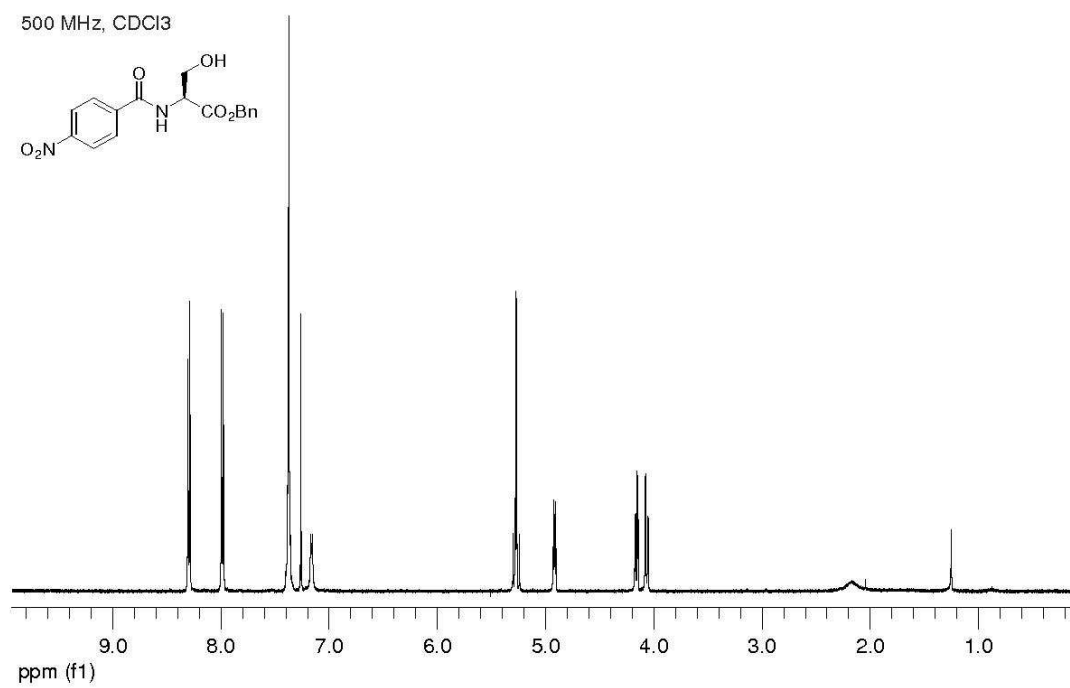
¹H and ¹³C NMR spectra for compound **5.24**



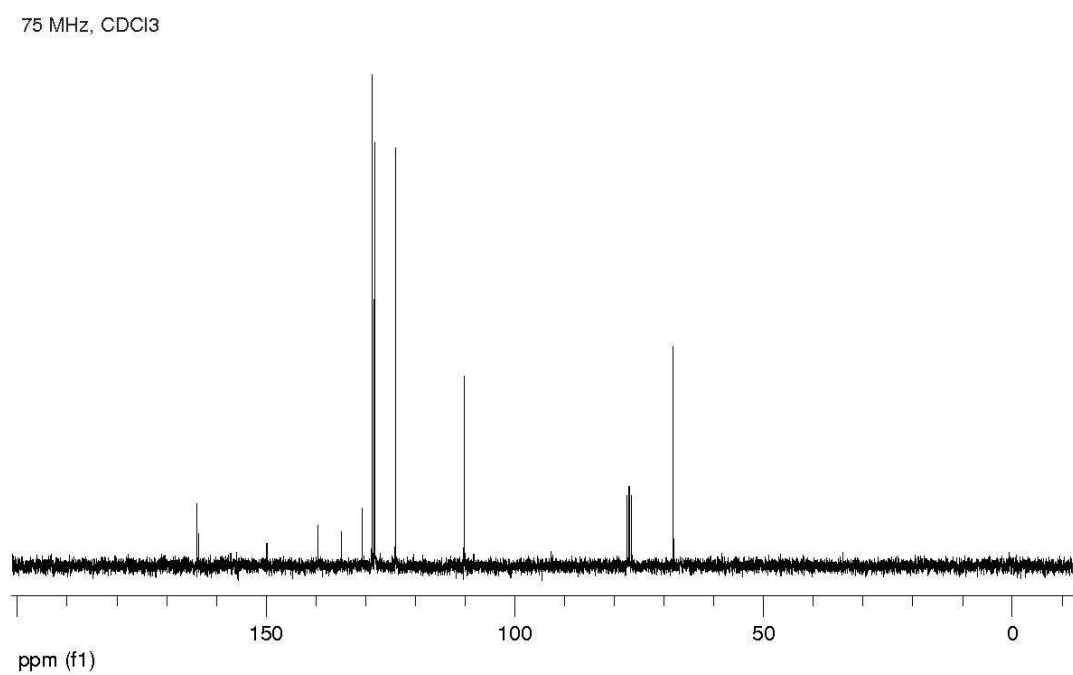
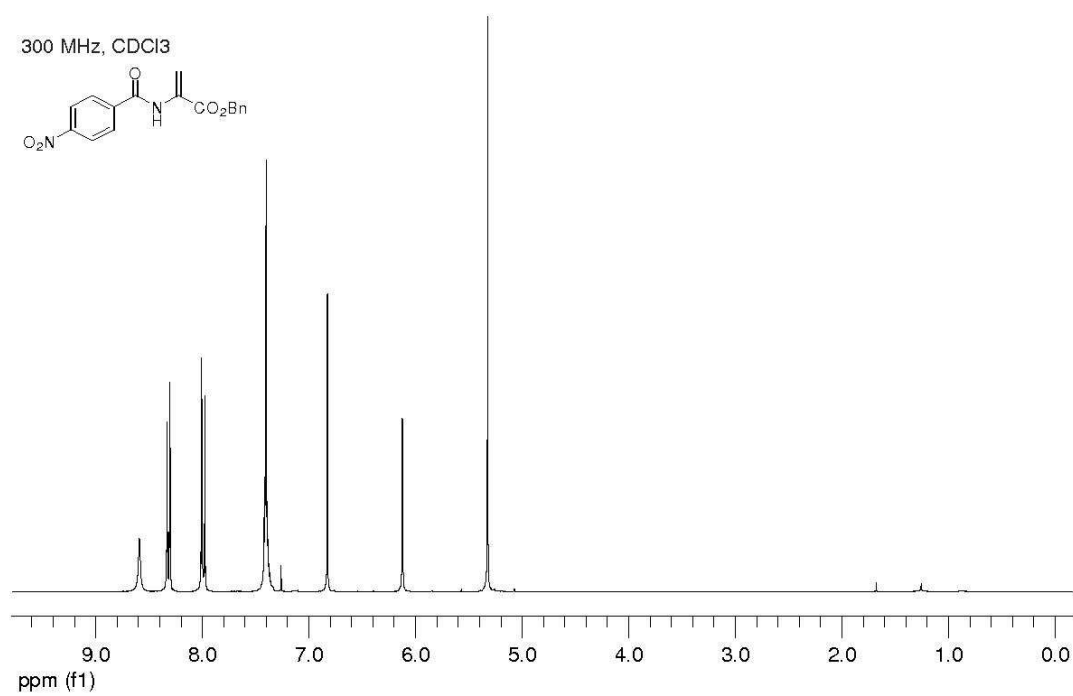
¹H and ¹³C NMR spectra for compound **5.25**



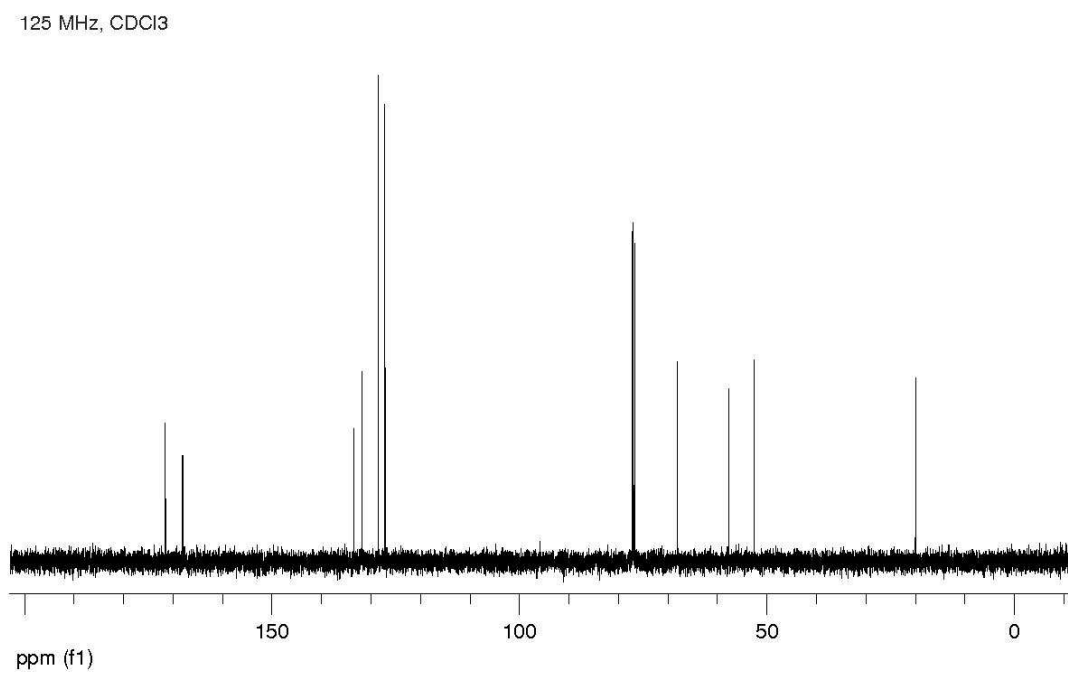
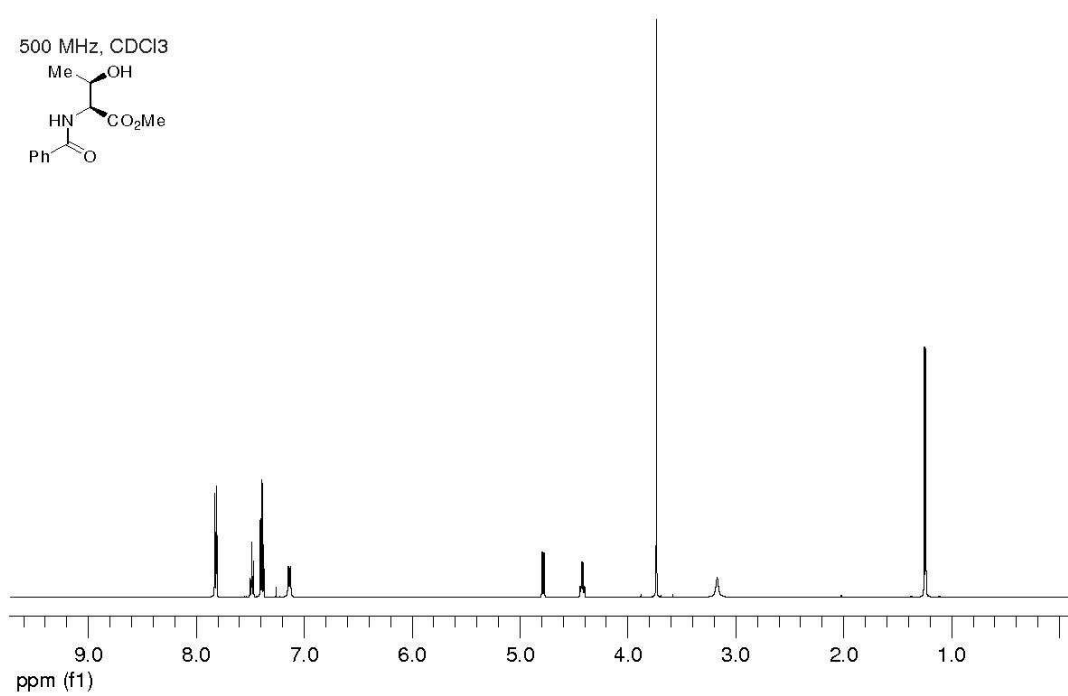
¹H and ¹³C NMR spectra for compound **5.26**



¹H and ¹³C NMR spectra for compound **5.27**

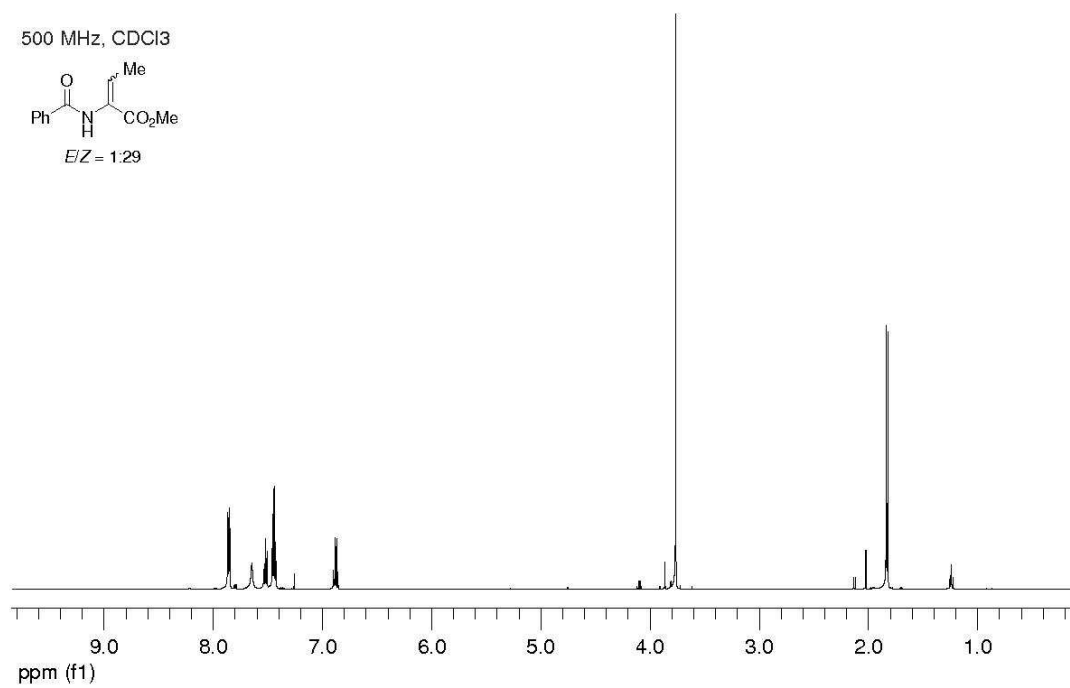
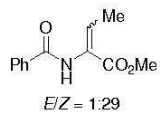


¹H and ¹³C NMR spectra for compound **5.28**

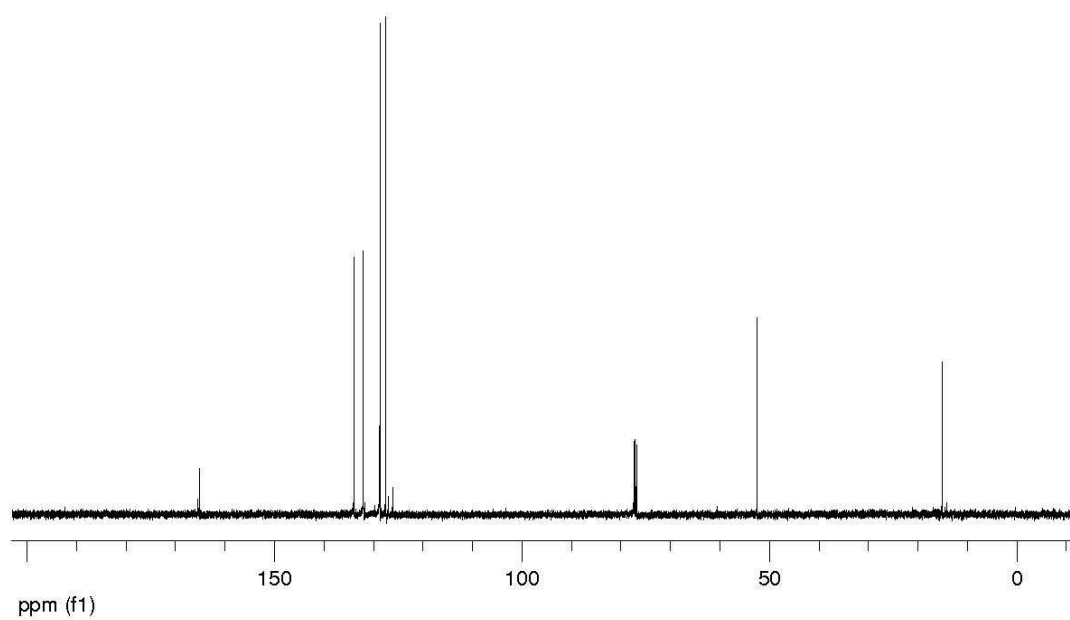


¹H and ¹³C NMR spectra for compound **5.30**

500 MHz, CDCl₃

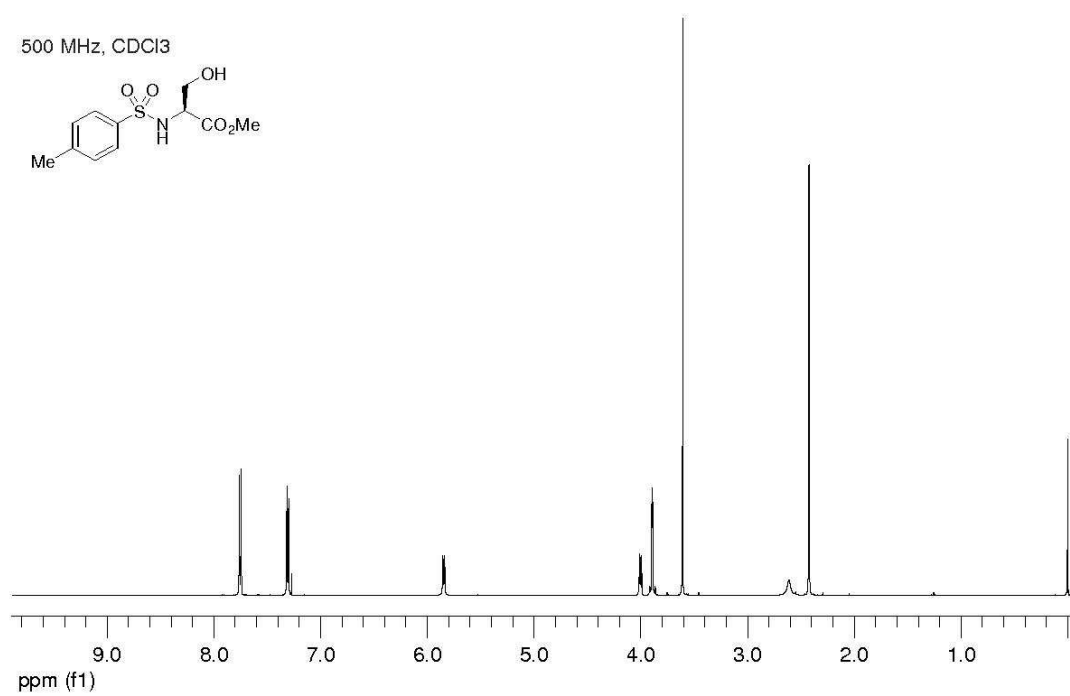
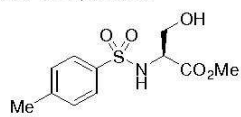


125 MHz, CDCl₃

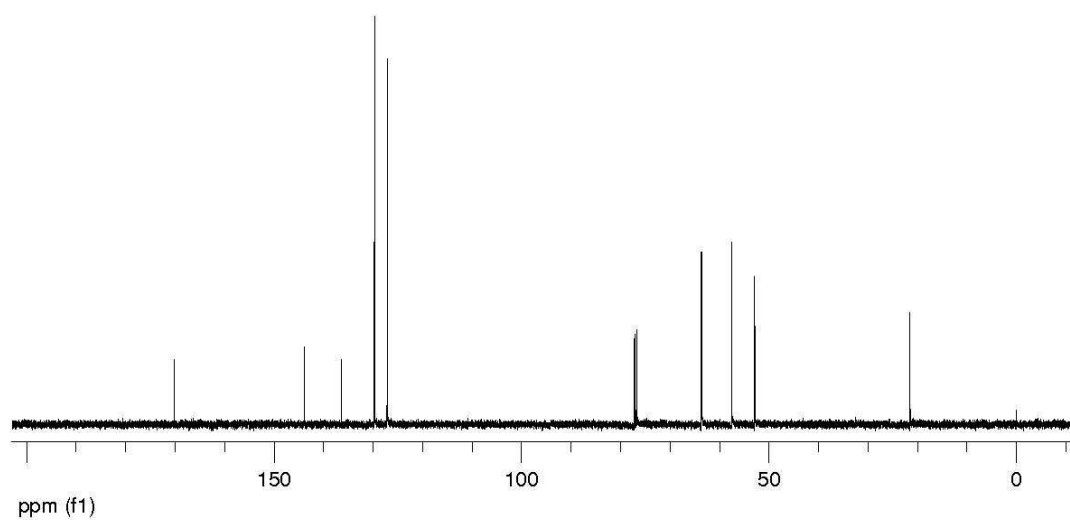


¹H and ¹³C NMR spectra for compound **5.31**

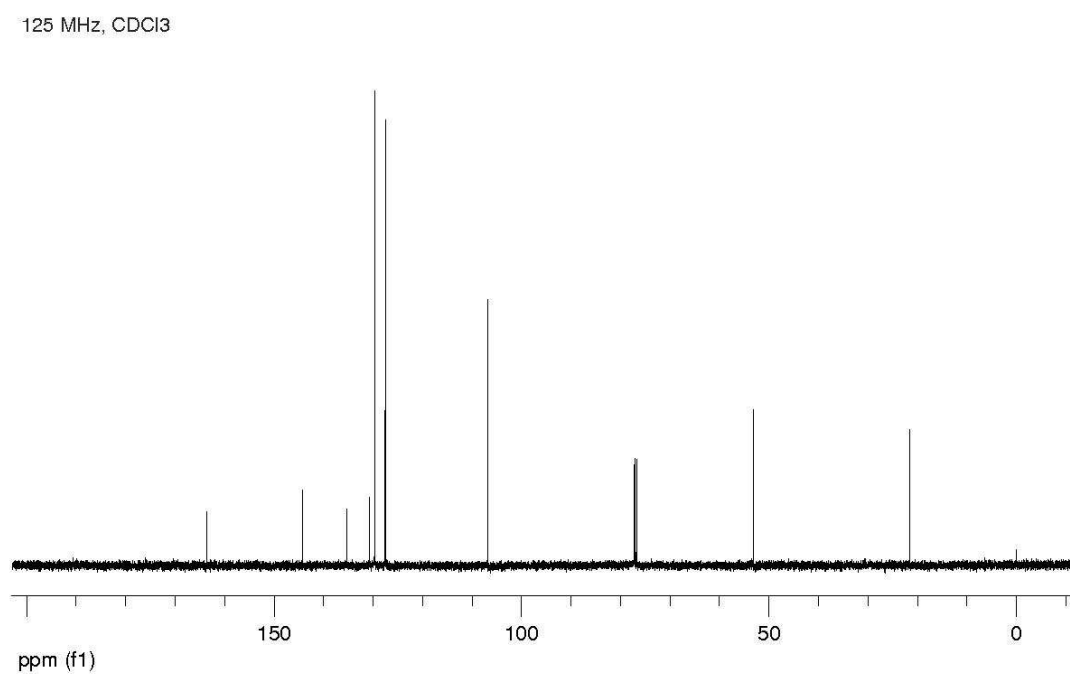
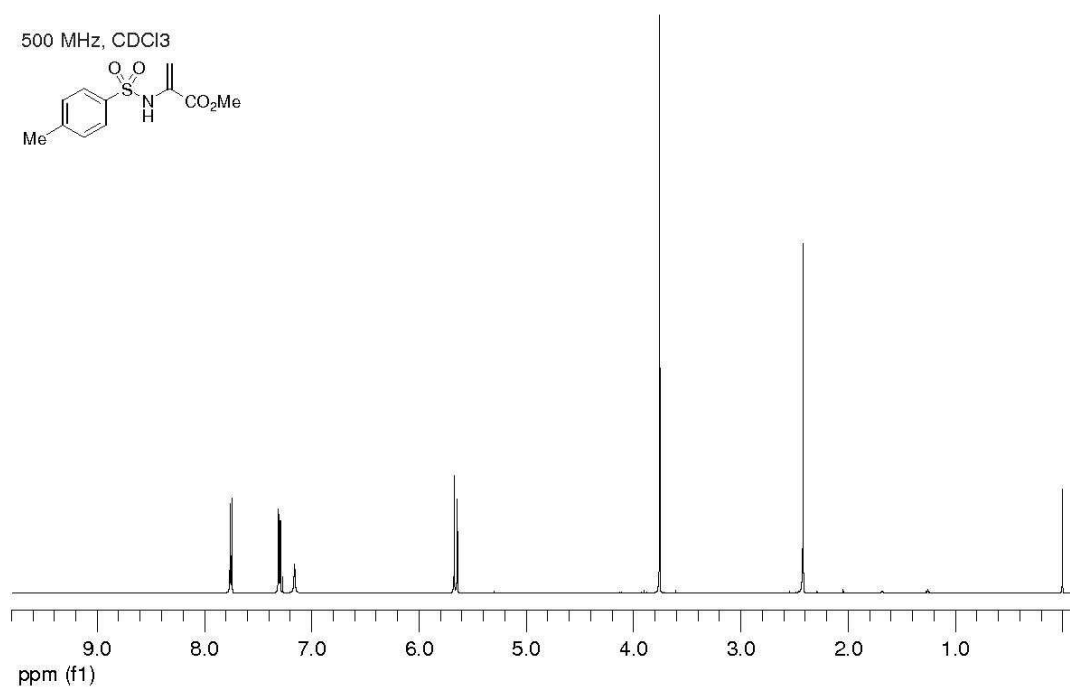
500 MHz, CDCl₃



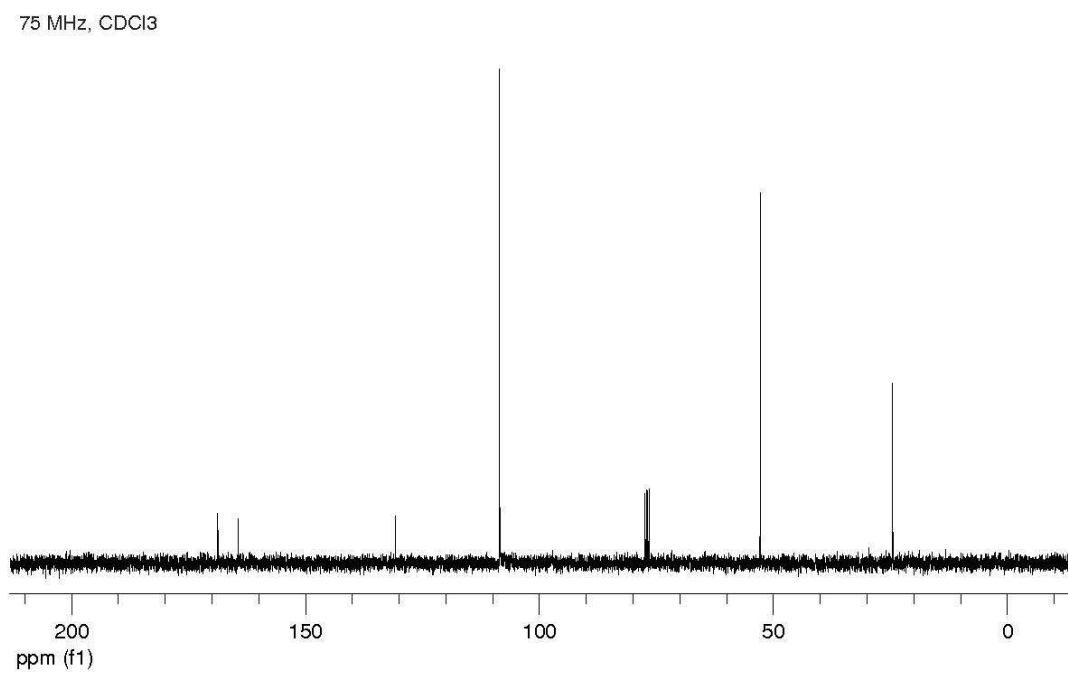
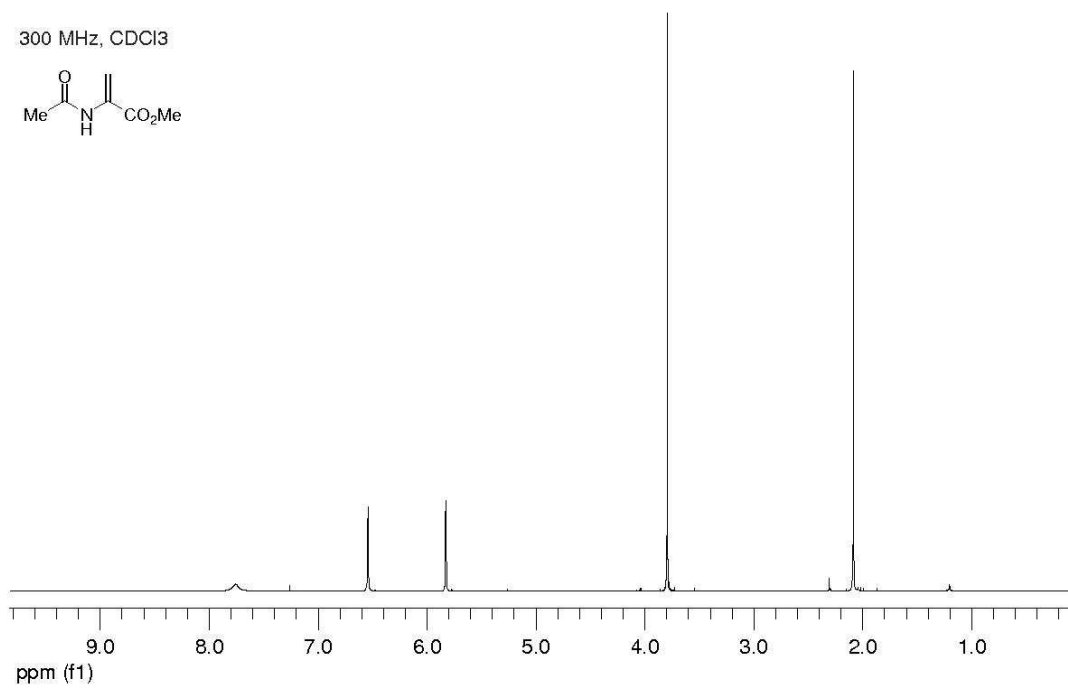
125 MHz, CDCl₃



¹H and ¹³C NMR spectra for compound **5.32**

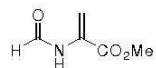


¹H and ¹³C NMR spectra for compound **5.33**

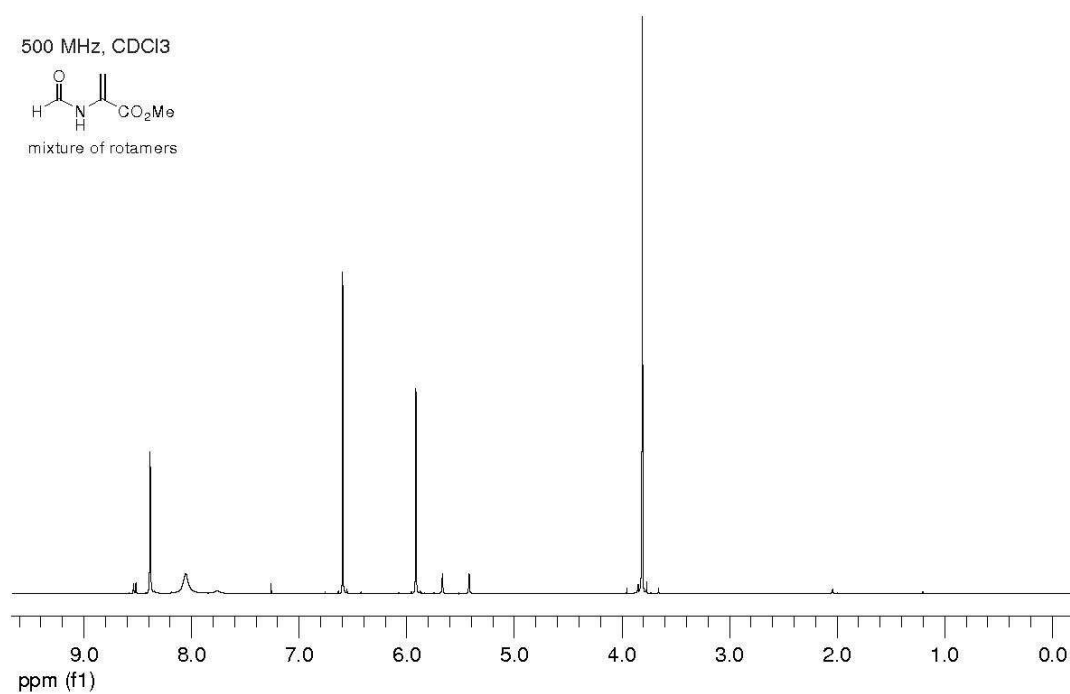


¹H and ¹³C NMR spectra for compound **5.34**

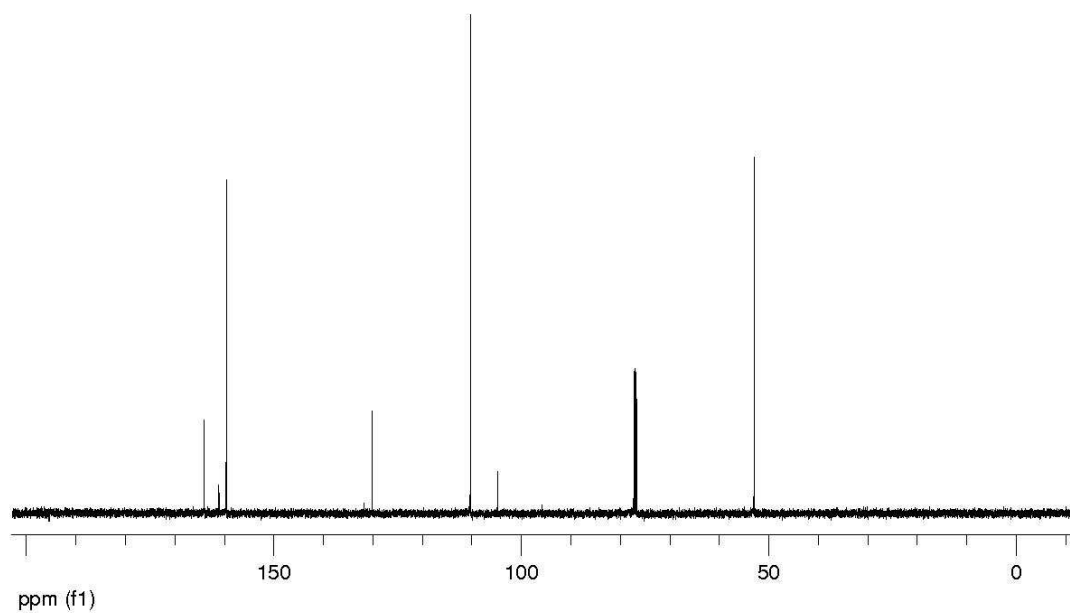
500 MHz, CDCl₃



mixture of rotamers

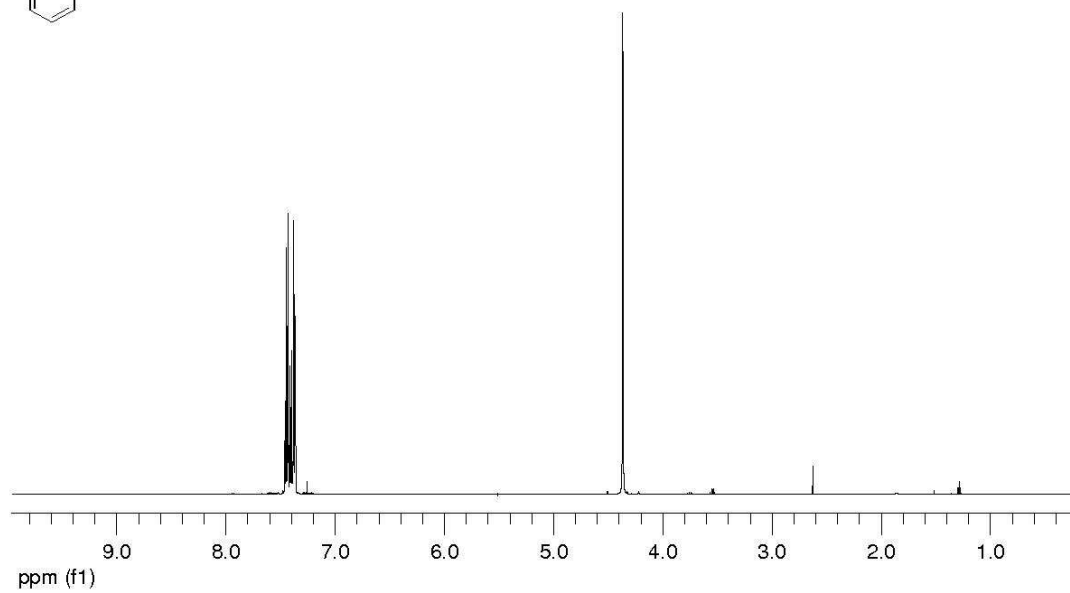
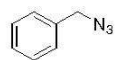


125 MHz, CDCl₃

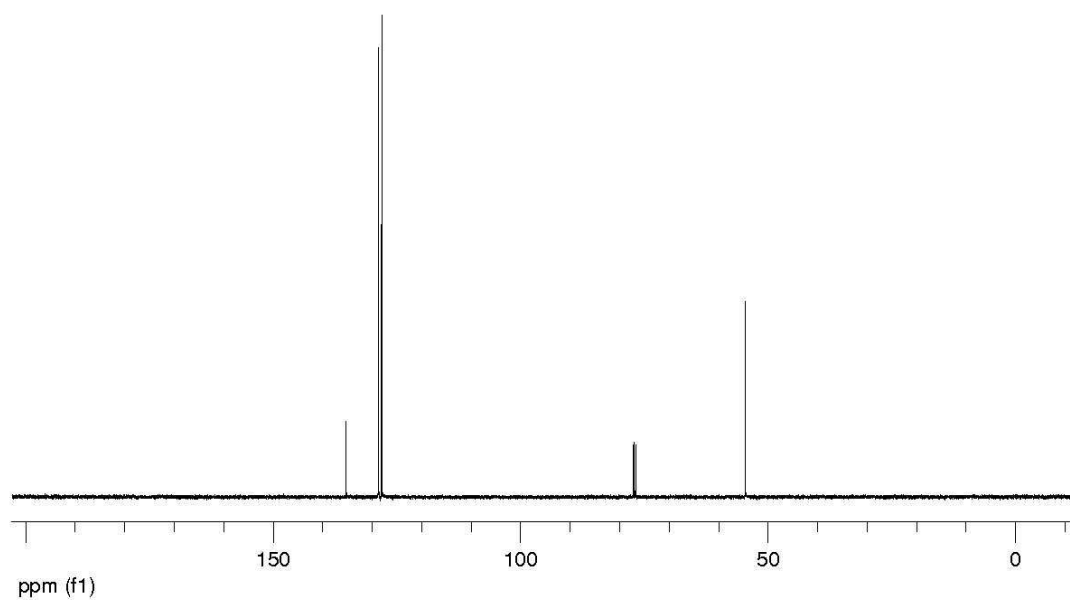


¹H and ¹³C NMR spectra for compound **5.35**

500 MHz, CDCl₃

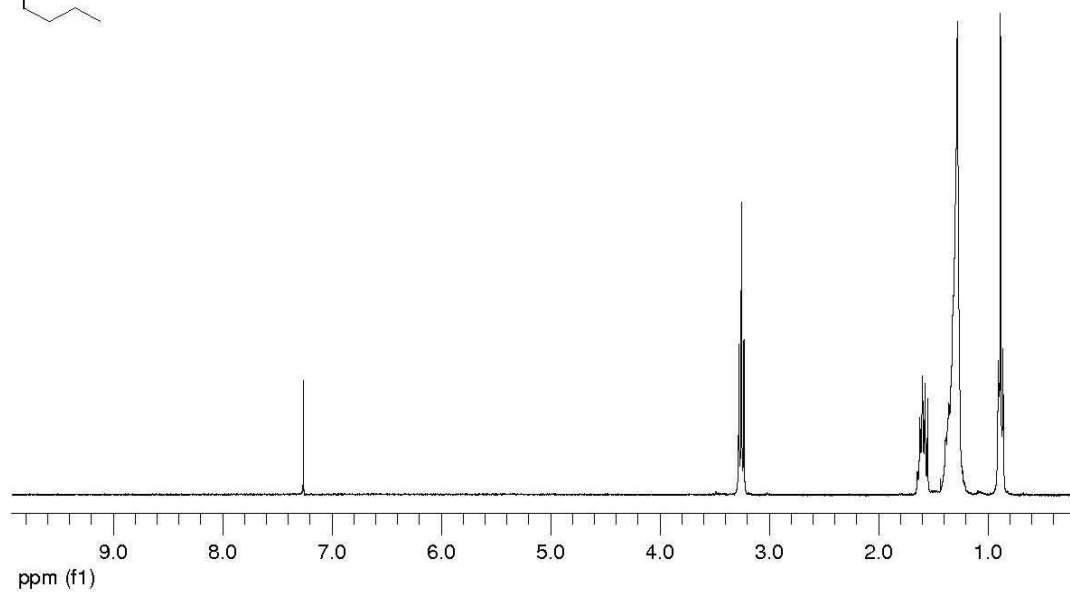
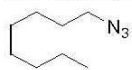


125 MHz, CDCl₃



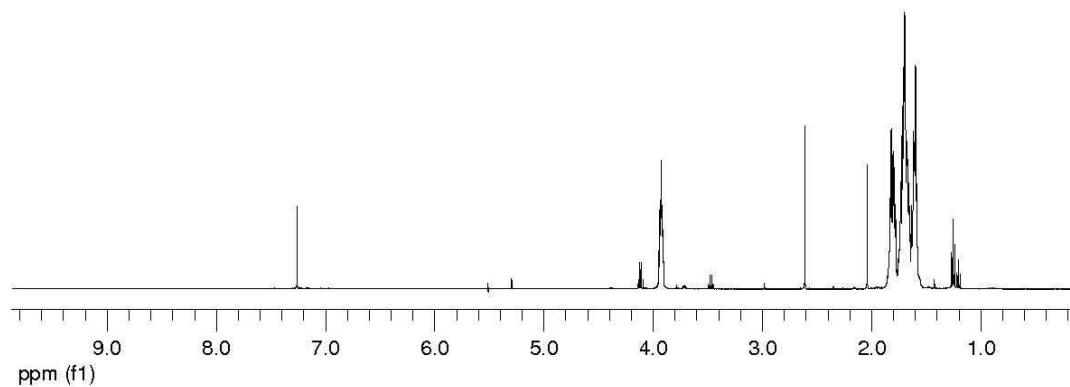
¹H and ¹³C NMR spectra for compound **5.36a**

300 MHz, CDCl₃



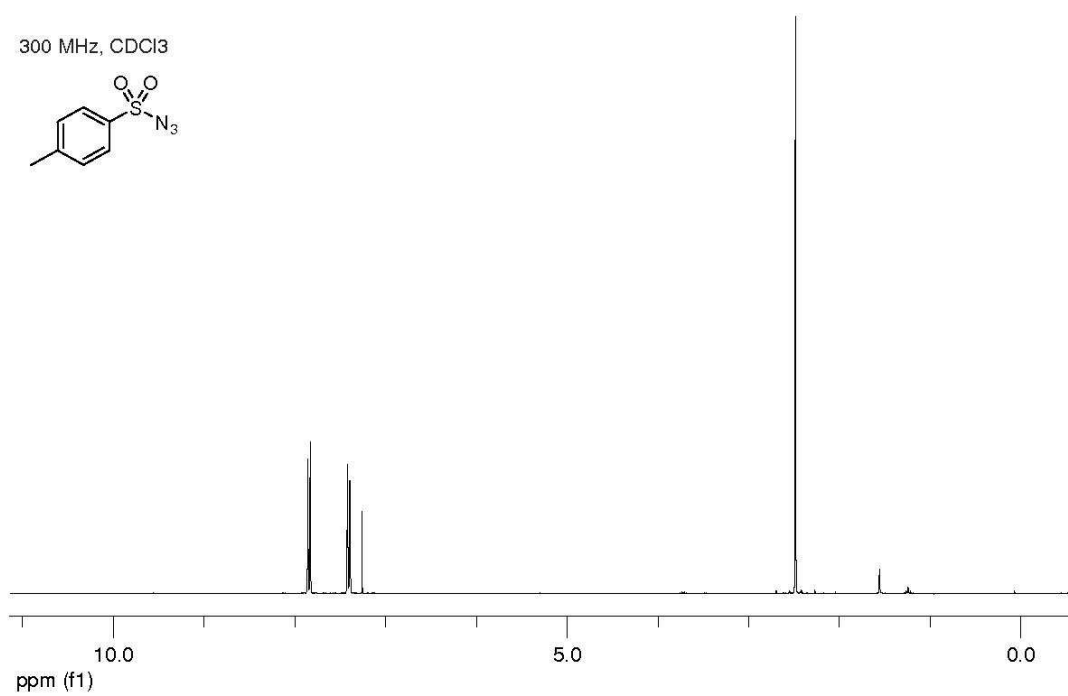
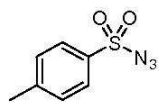
¹H NMR spectra for compound **5.36b**

500 MHz, CDCl₃

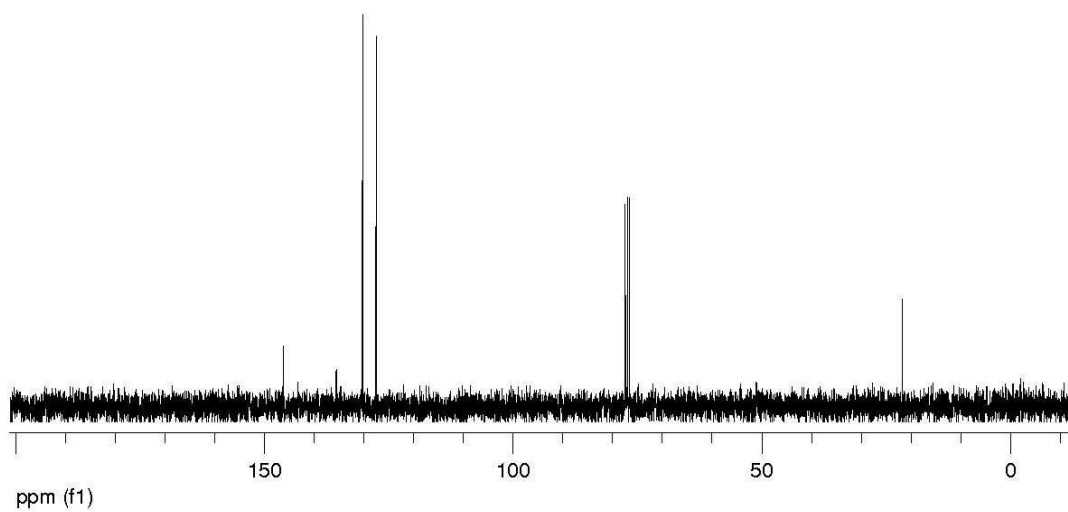


¹H NMR spectra for compound **5.36c**

300 MHz, CDCl₃

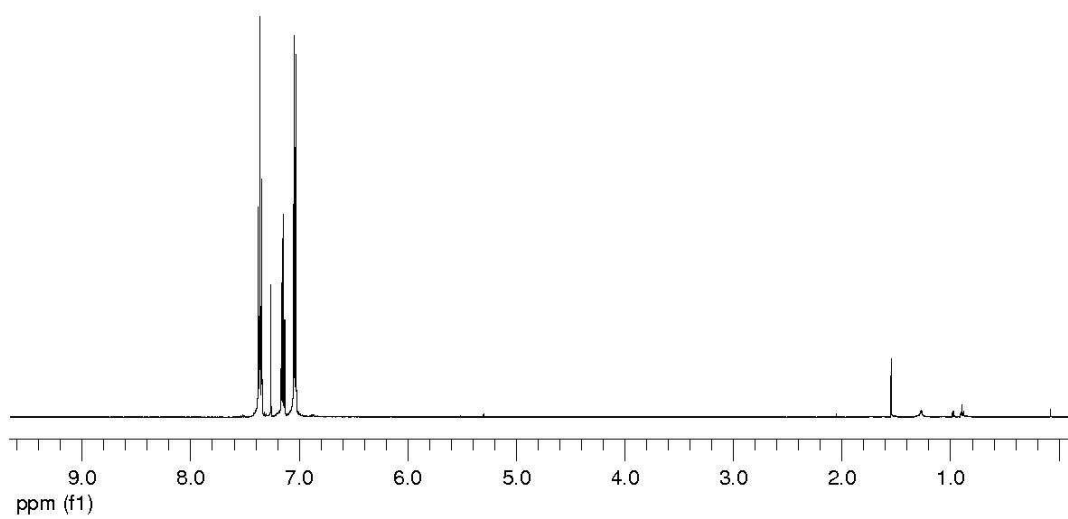
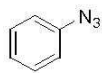


75 MHz, CDCl₃

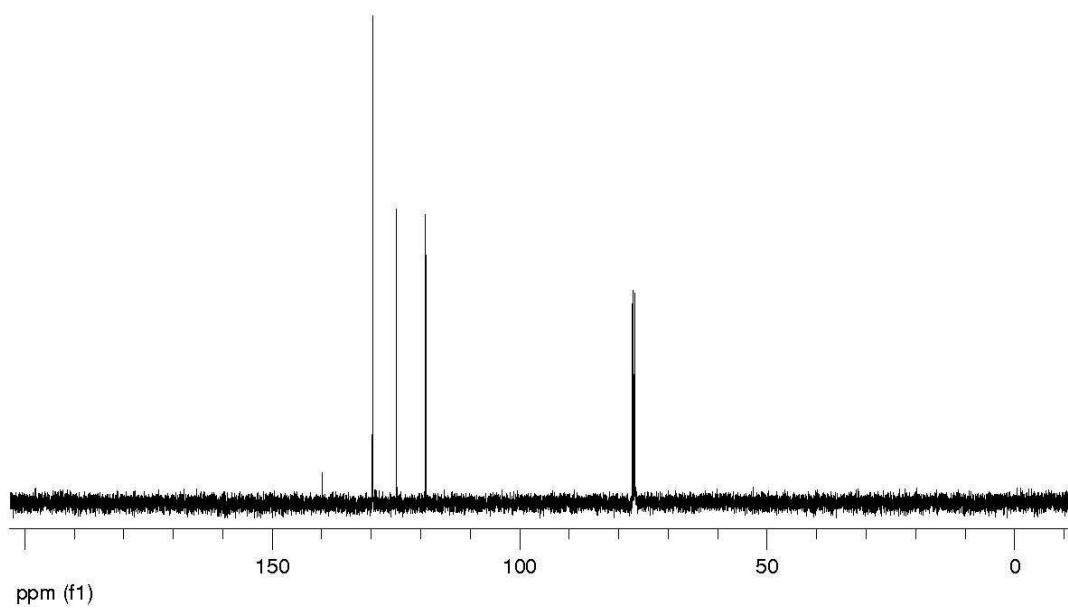


¹H and ¹³C NMR spectra for compound **5.37**

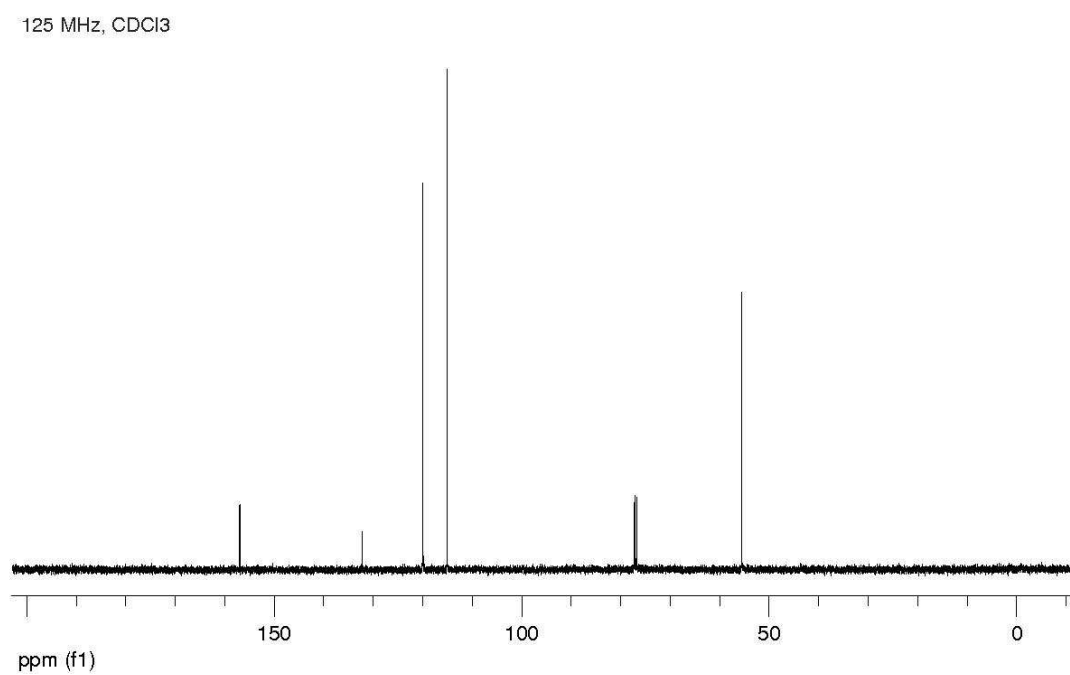
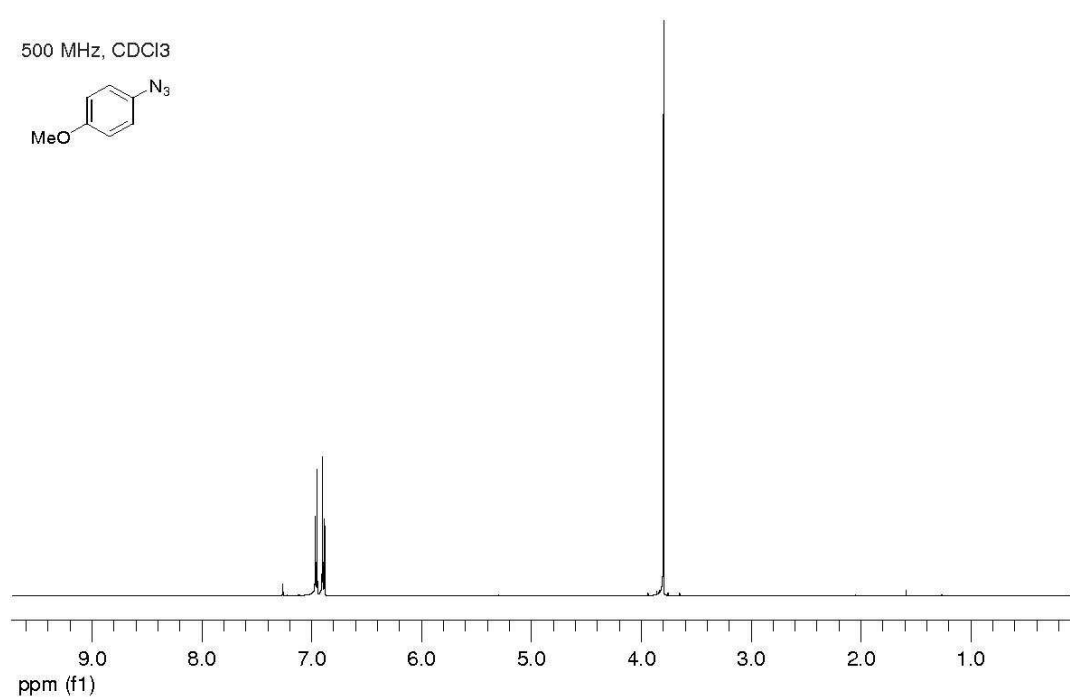
500 MHz, CDCl₃



125 MHz, CDCl₃

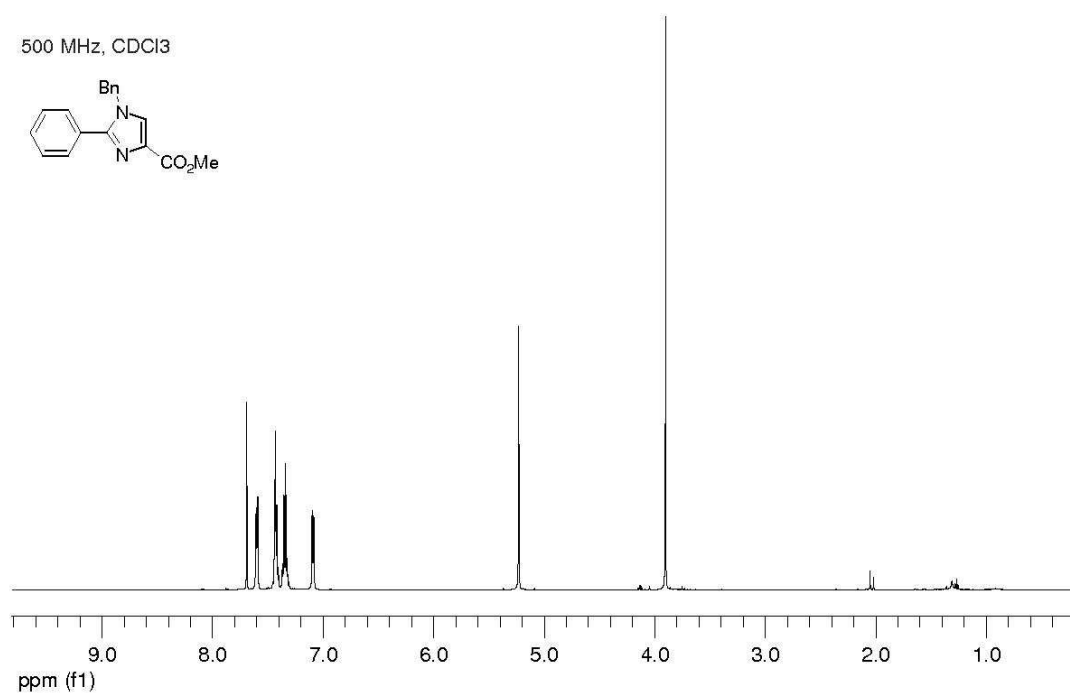
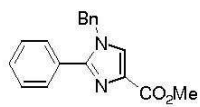


¹H and ¹³C NMR spectra for compound **5.38a**

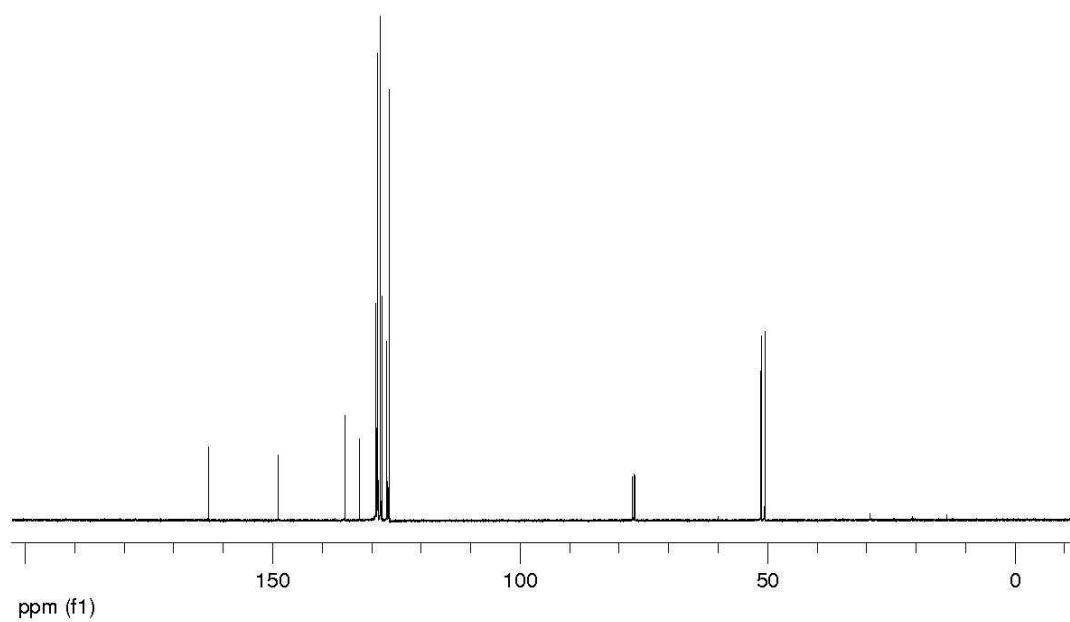


¹H and ¹³C NMR spectra for compound **5.38b**

500 MHz, CDCl₃

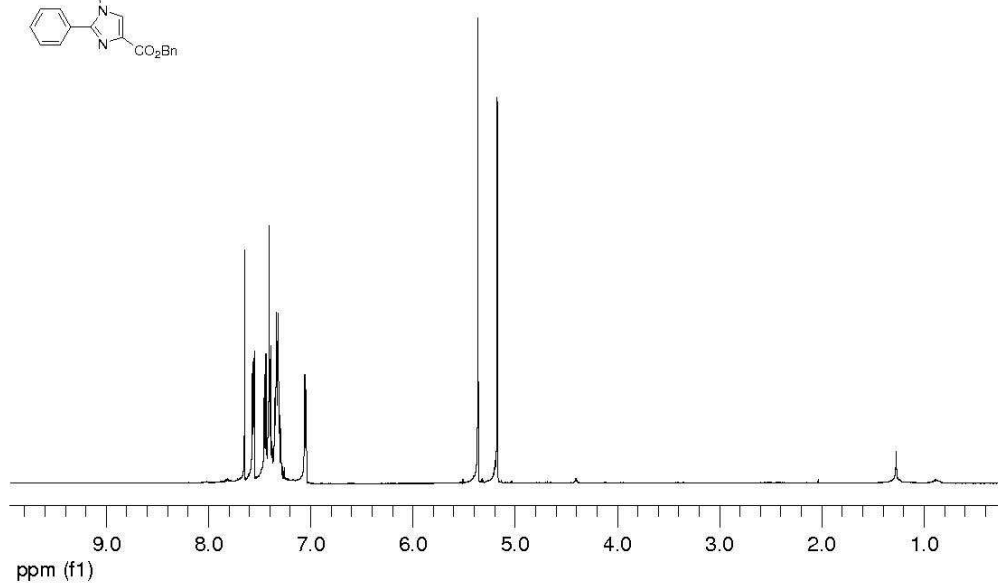
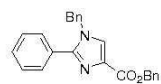


125 MHz, CDCl₃

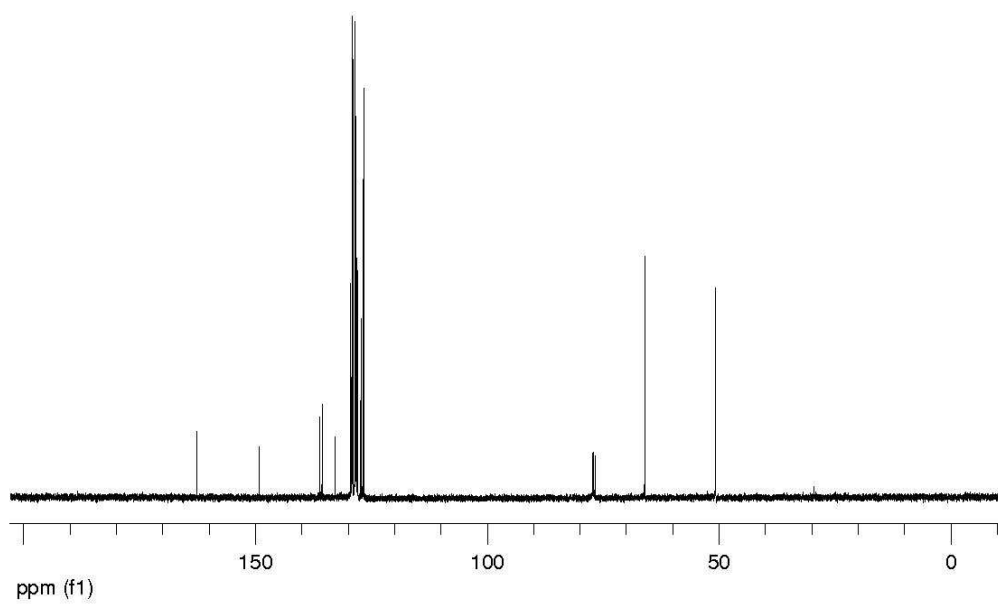


¹H and ¹³C NMR spectra for compound **5.40a**

500 MHz, CDCl₃

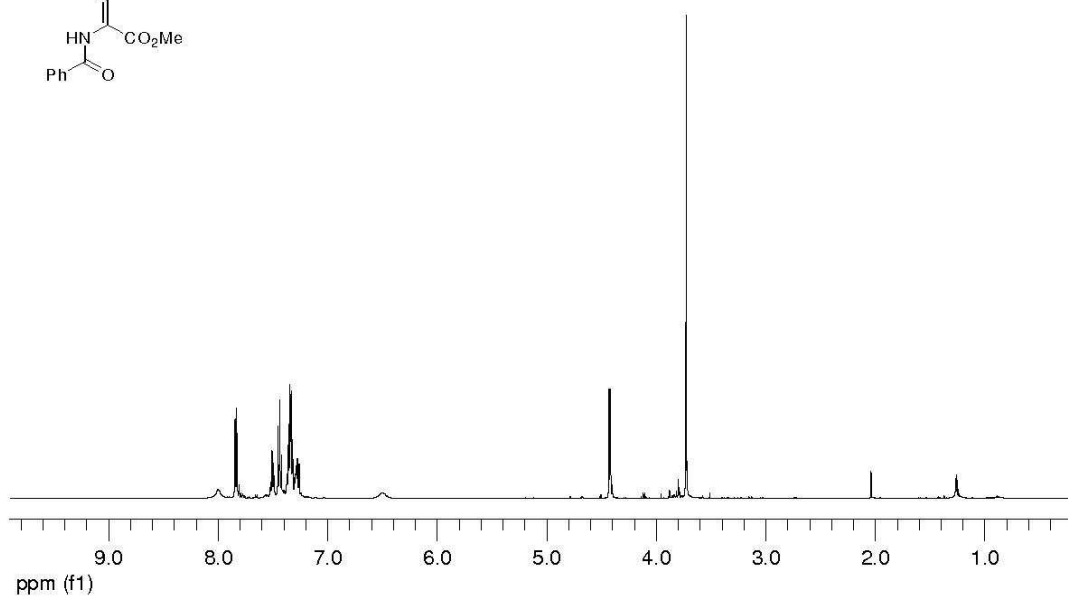
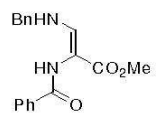


125 MHz, CDCl₃

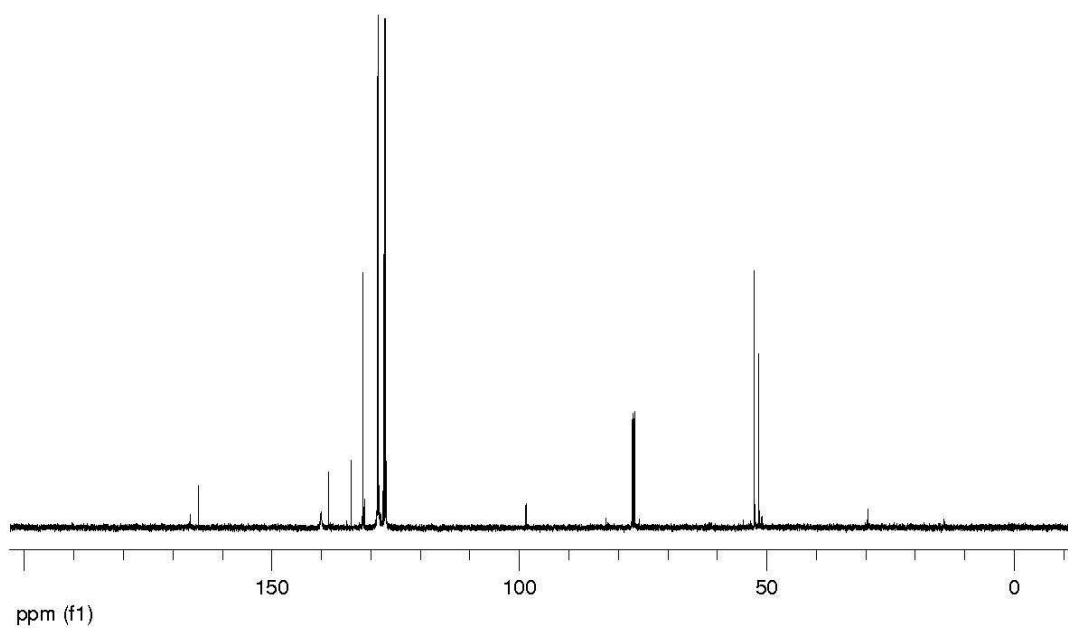


¹H and ¹³C NMR spectra for compound **5.40b**

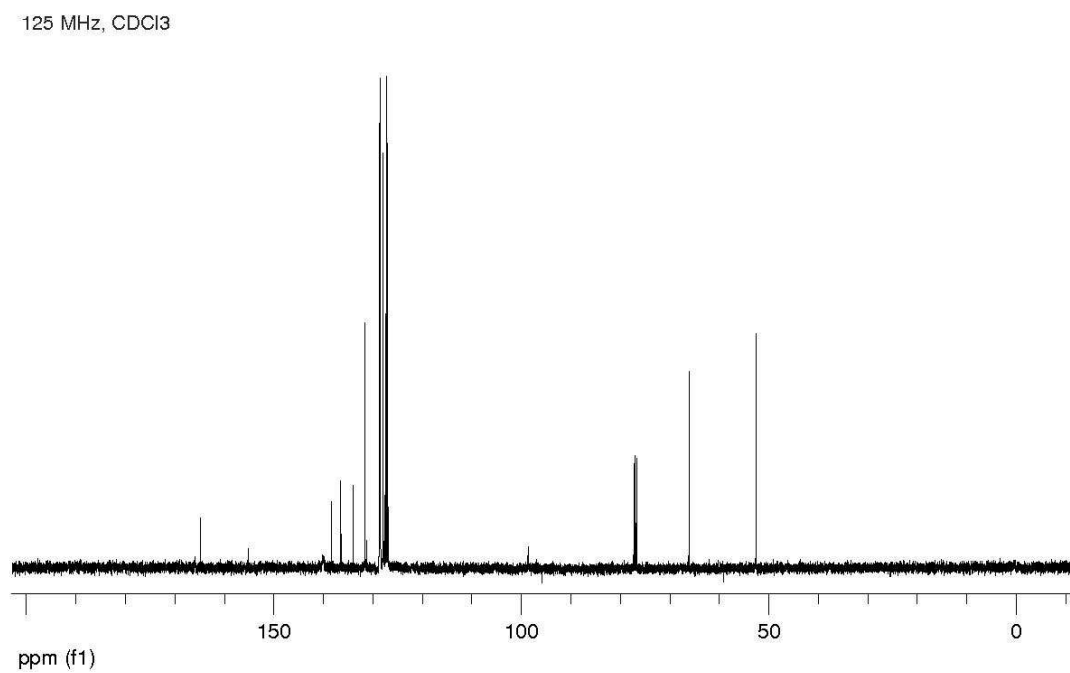
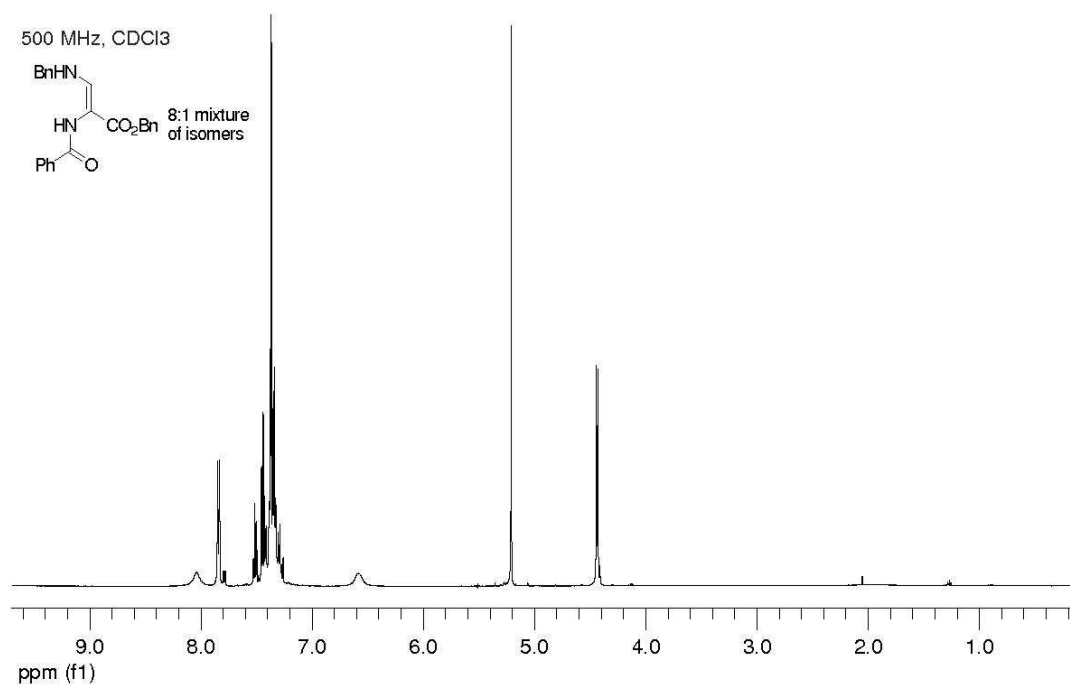
500 MHz, CDCl₃



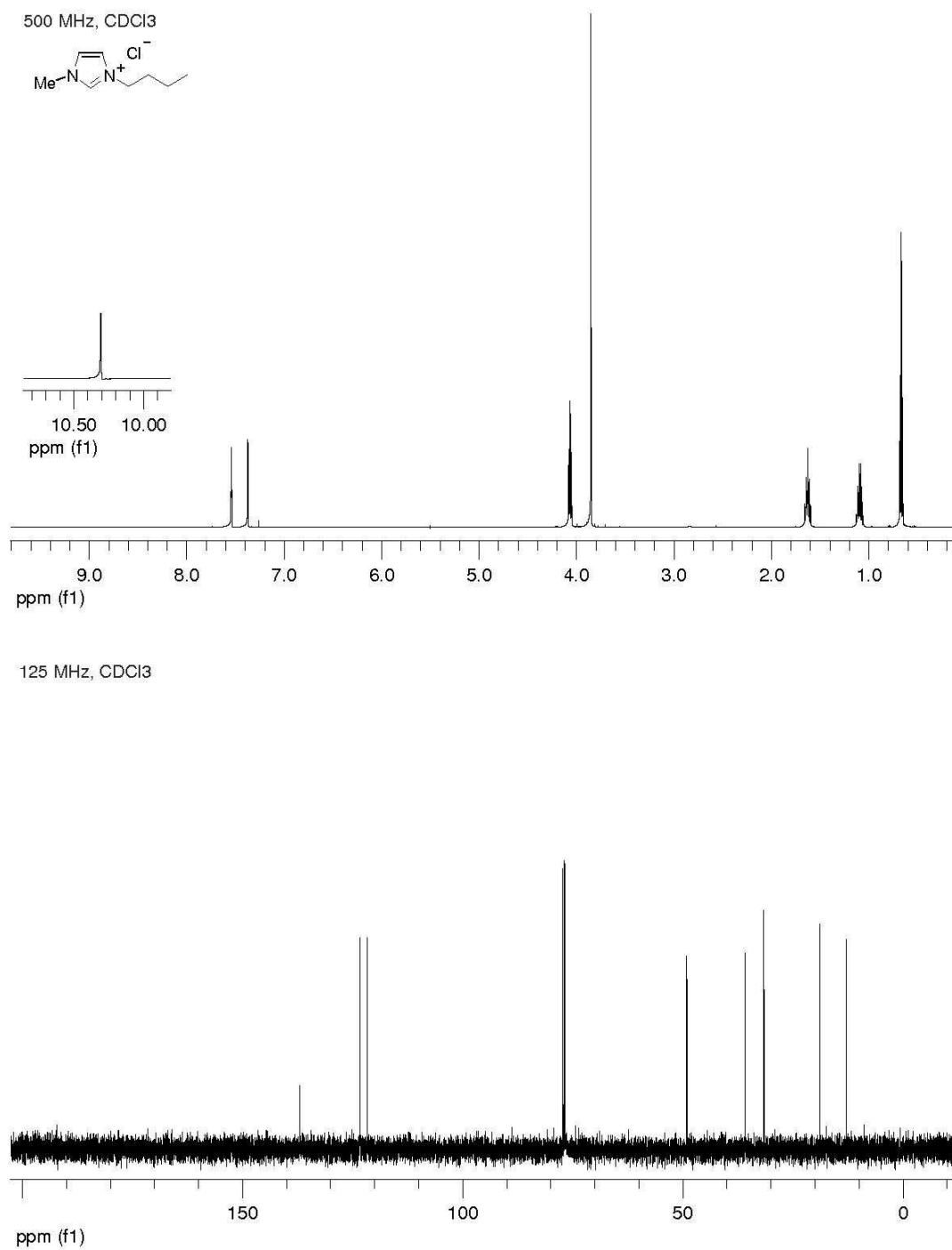
125 MHz, CDCl₃



¹H and ¹³C NMR spectra for compound **5.41a**

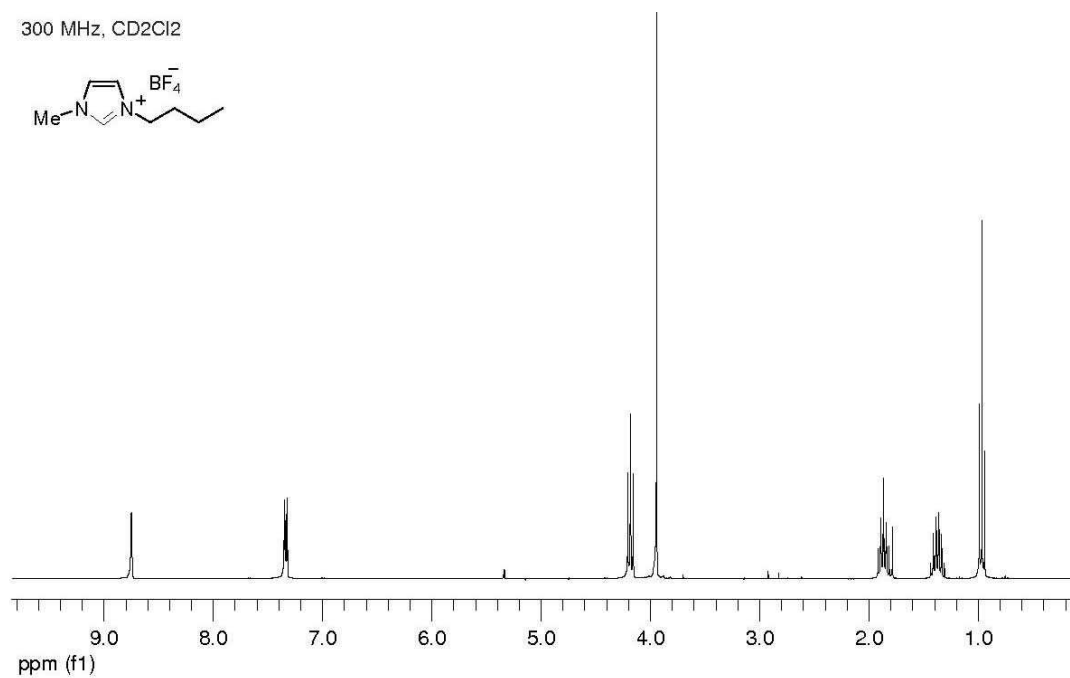
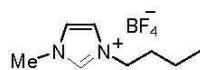


¹H and ¹³C NMR spectra for compound **5.41b**

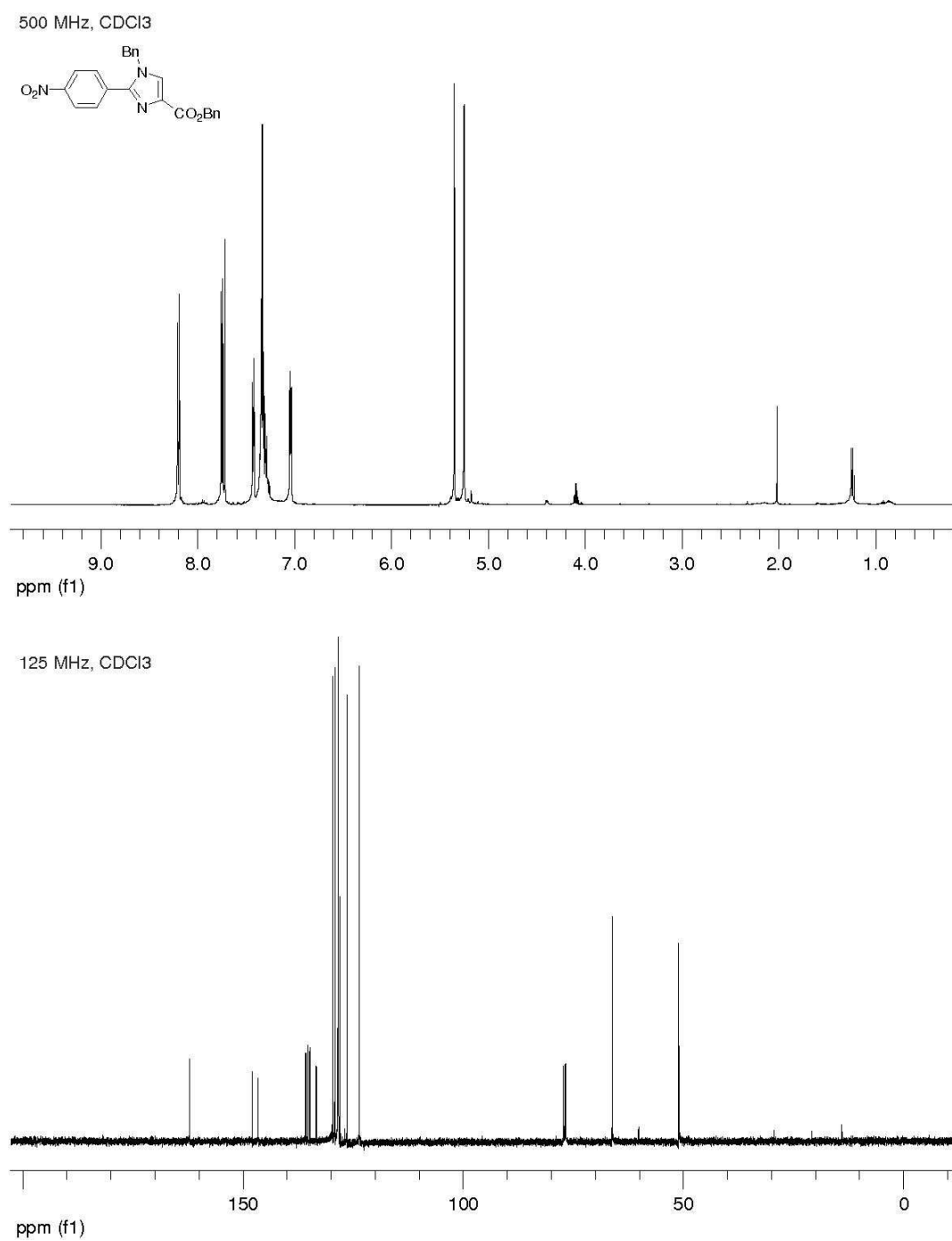


¹H and ¹³C NMR spectra for compound **5.67**

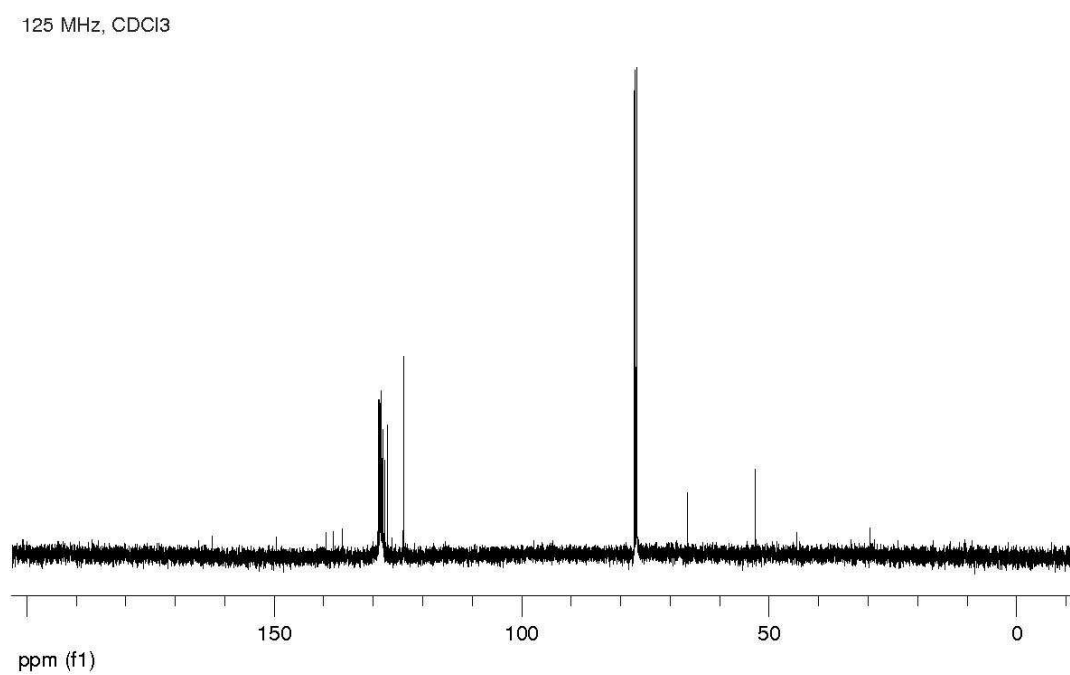
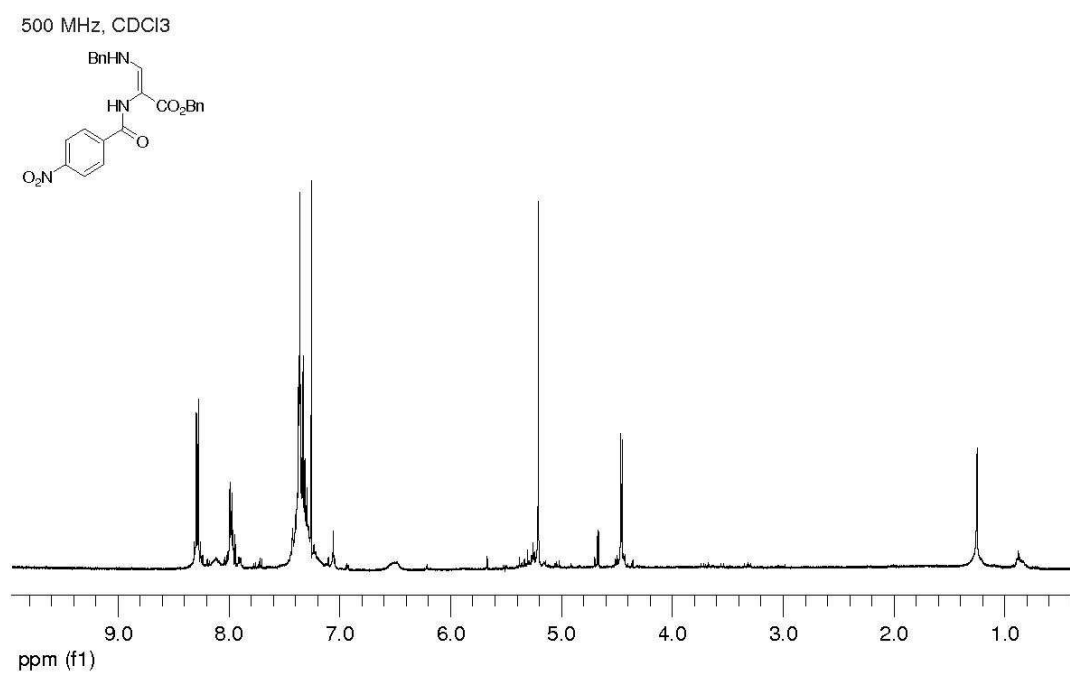
300 MHz, CD₂Cl₂



¹H NMR spectra for compound **5.68**

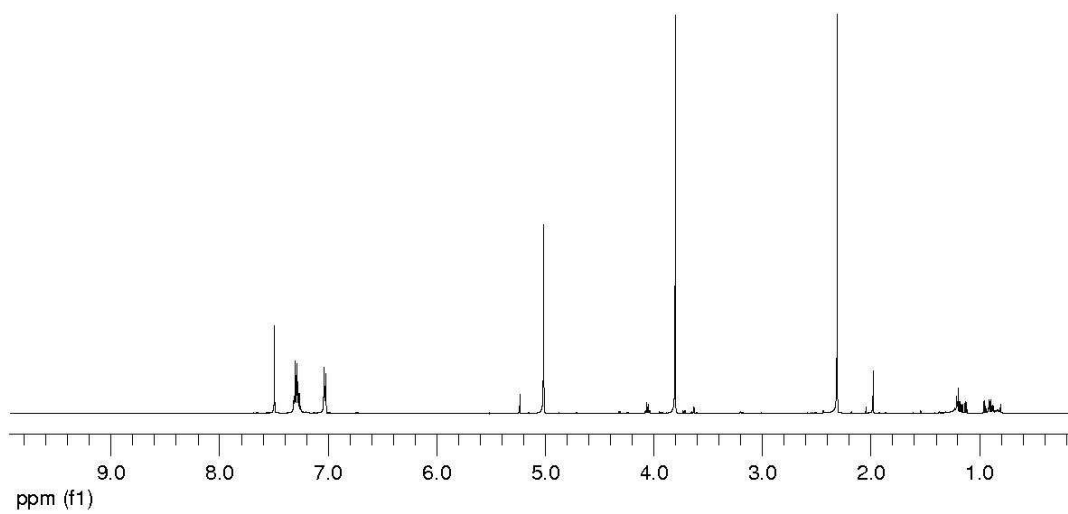
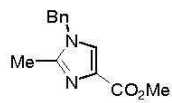


¹H and ¹³C NMR spectra for compound **5.69b**

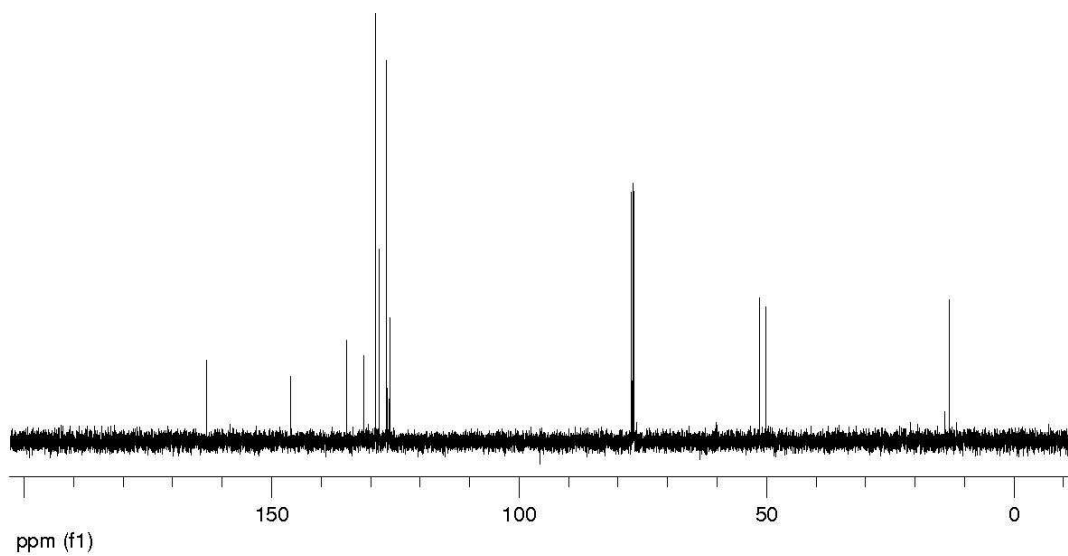


¹H and ¹³C NMR spectra for compound **5.70b**

500 MHz, CDCl₃

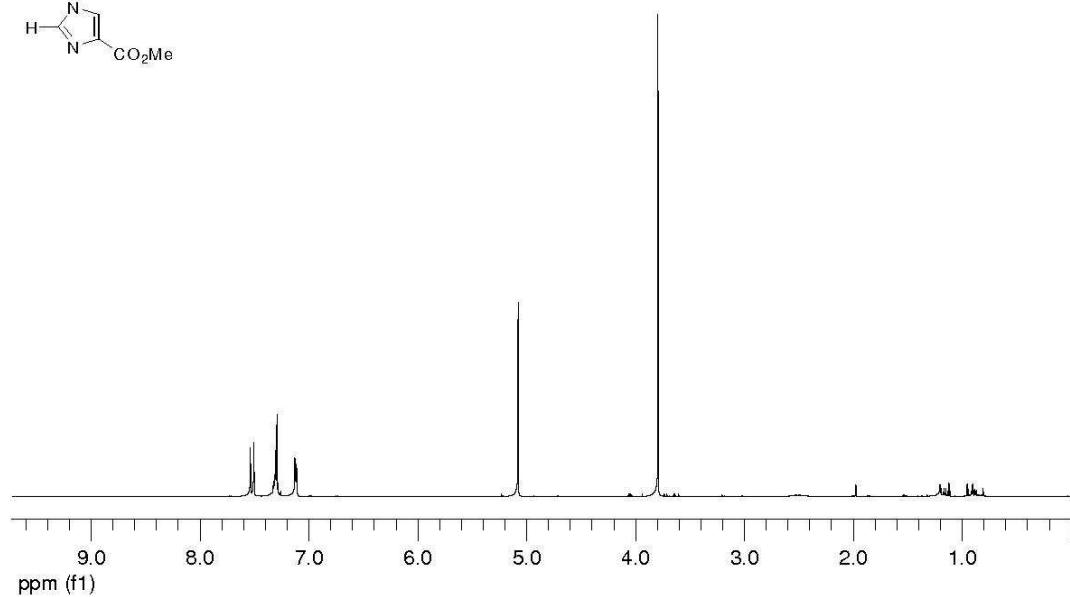
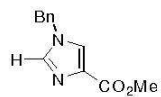


125 MHz, CDCl₃

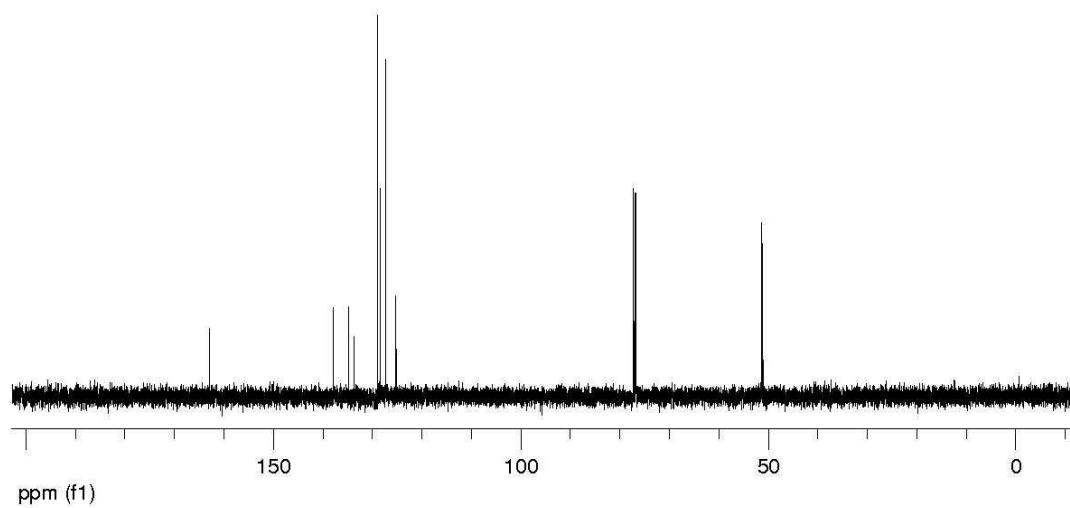


¹H and ¹³C NMR spectra for compound **5.73**

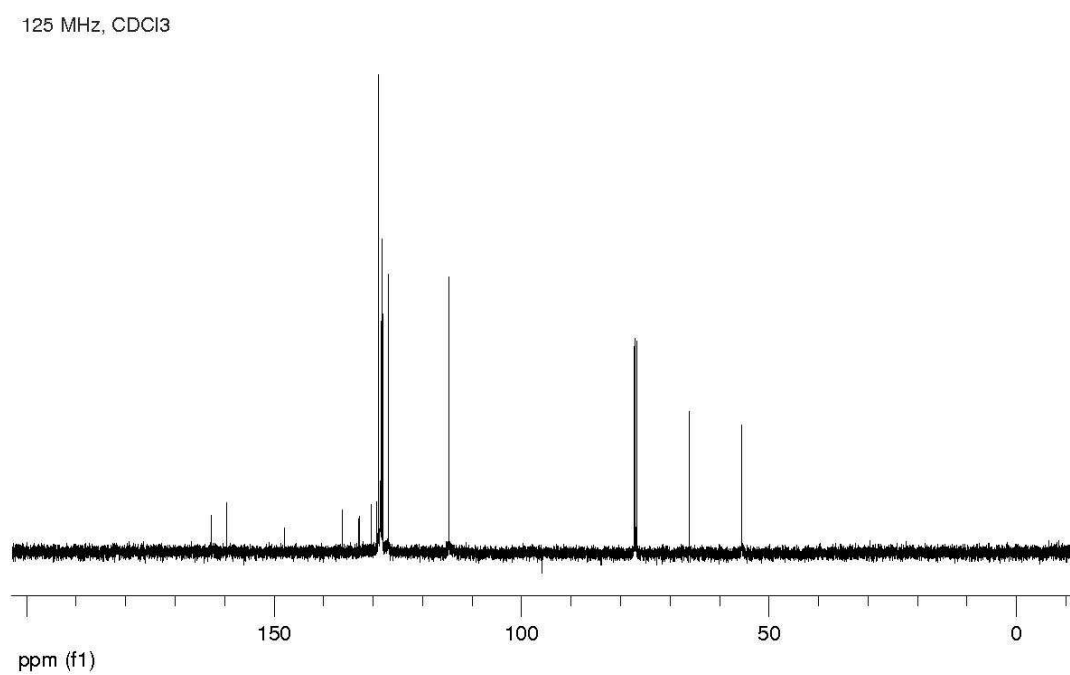
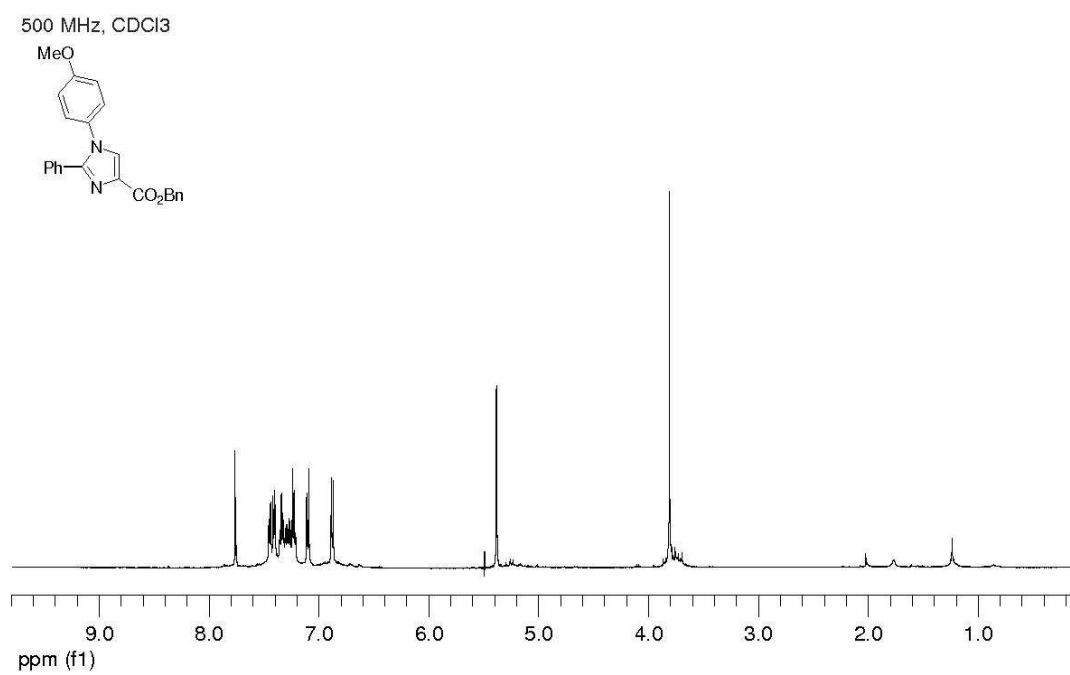
500 MHz, CDCl₃



125 MHz, CDCl₃

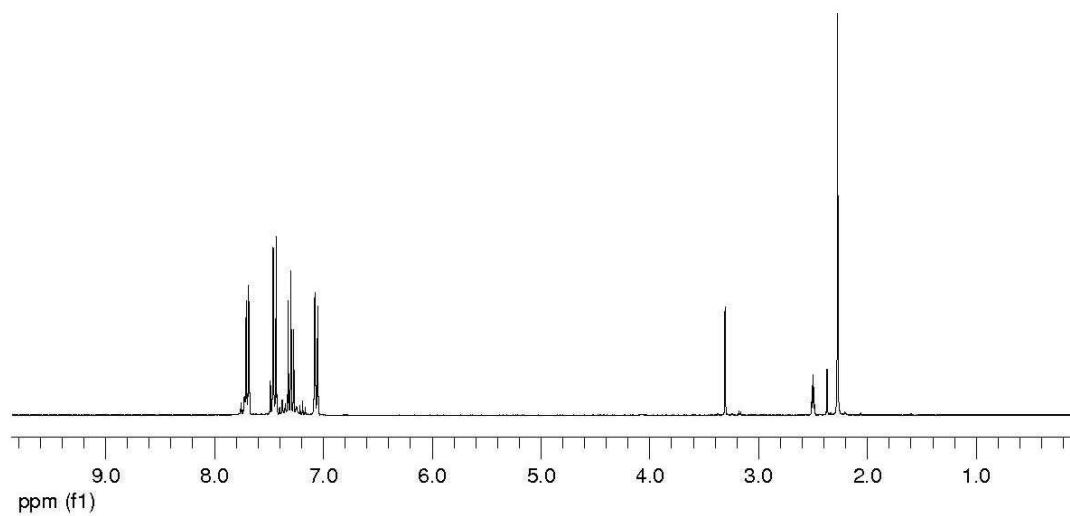
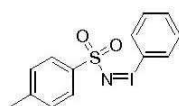


¹H and ¹³C NMR spectra for compound **5.75**



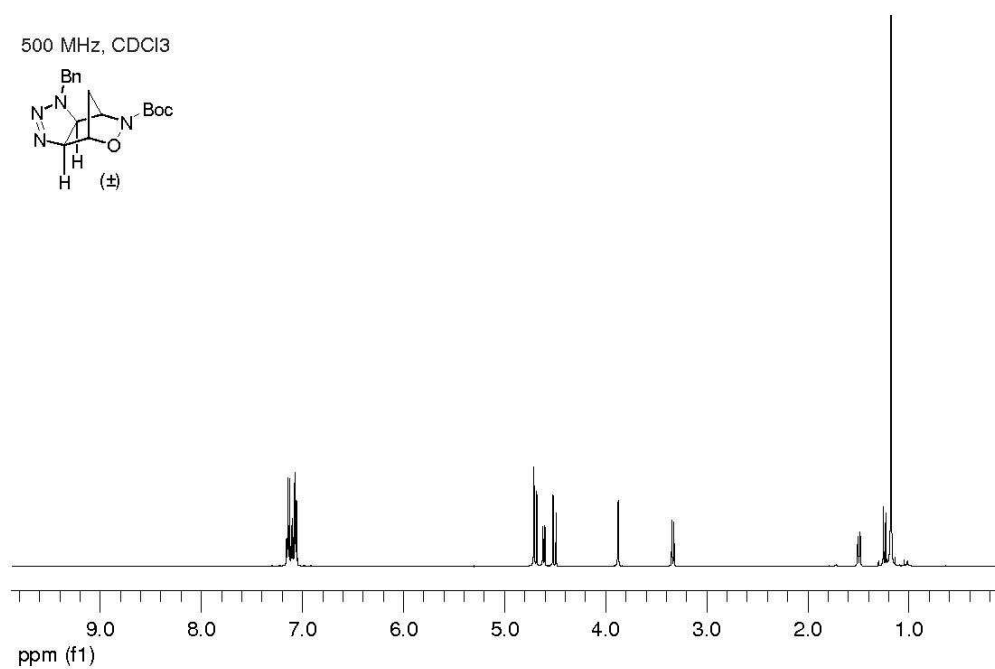
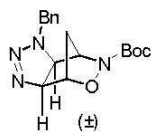
¹H and ¹³C NMR spectra for compound **5.81**

300 MHz, d6-DMSO

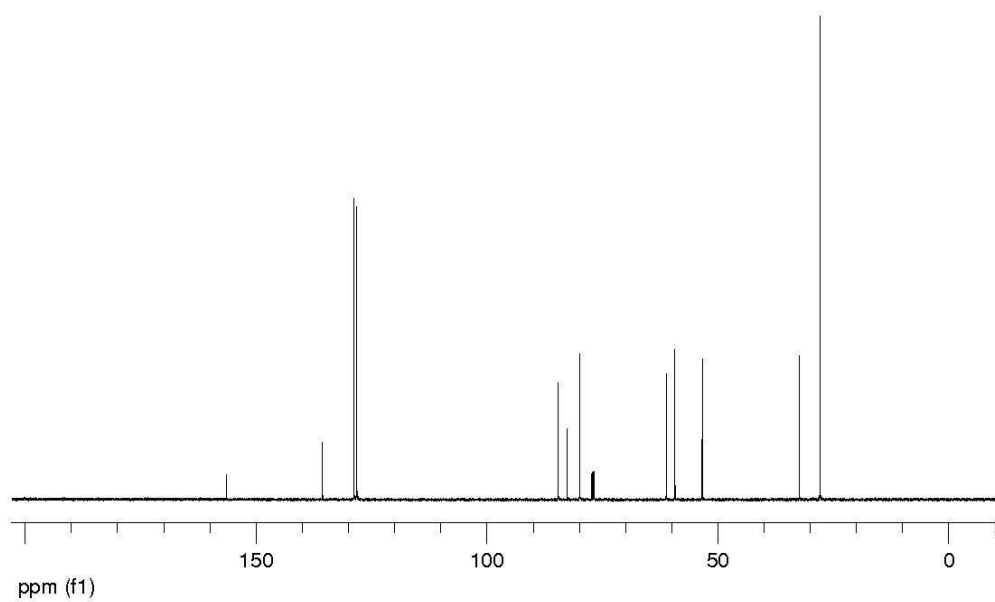


¹H NMR spectra for compound **5.82**

500 MHz, CDCl₃

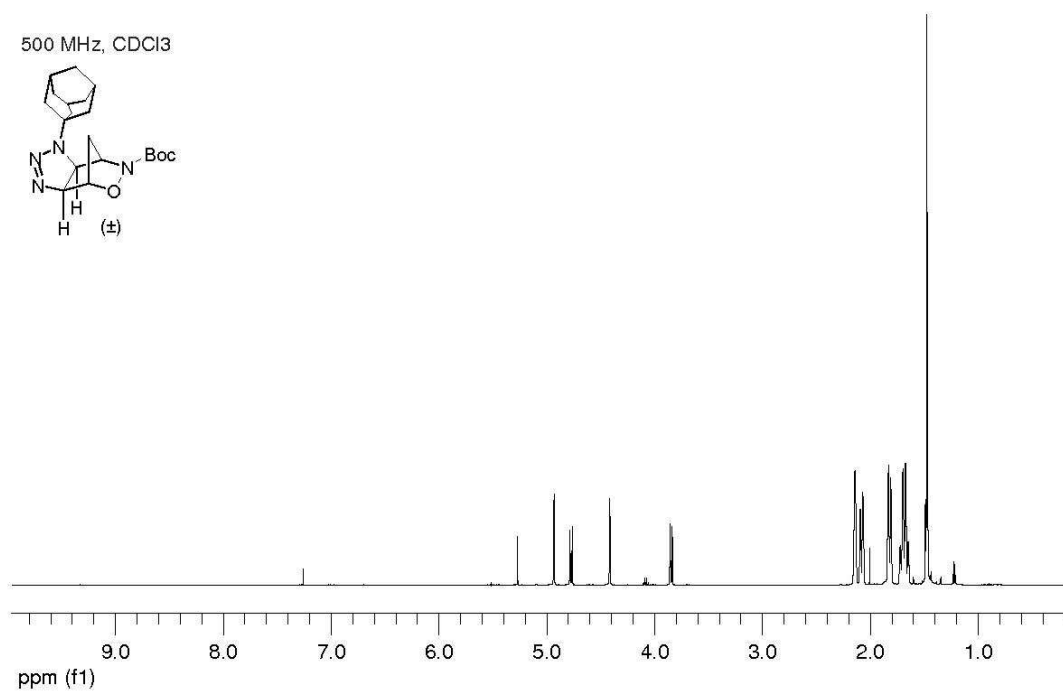


125 MHz, CDCl₃

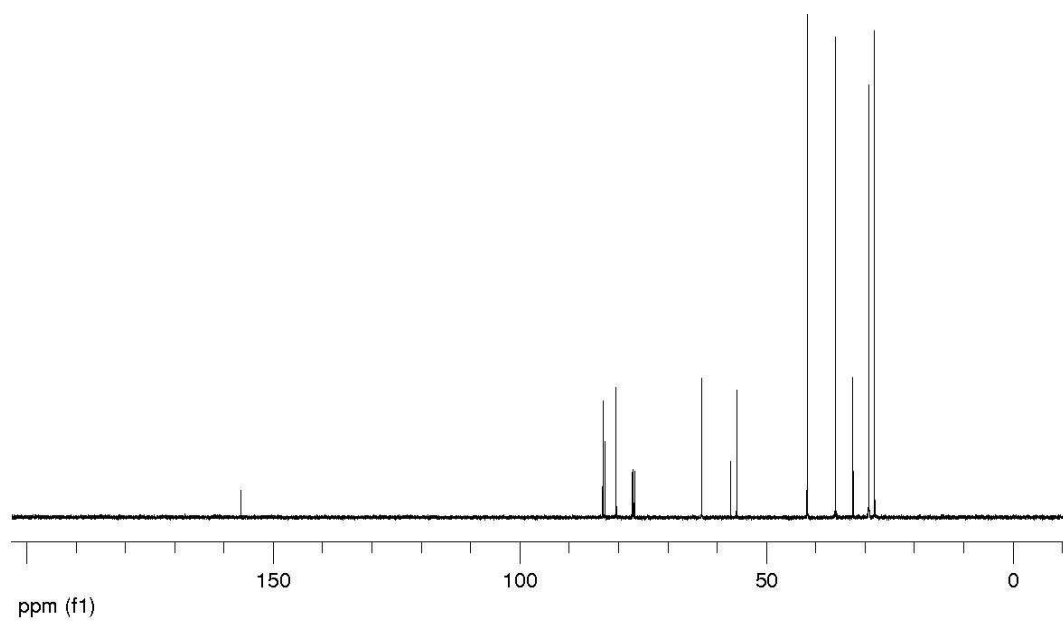


¹H and ¹³C NMR spectra for compound **6.7a**

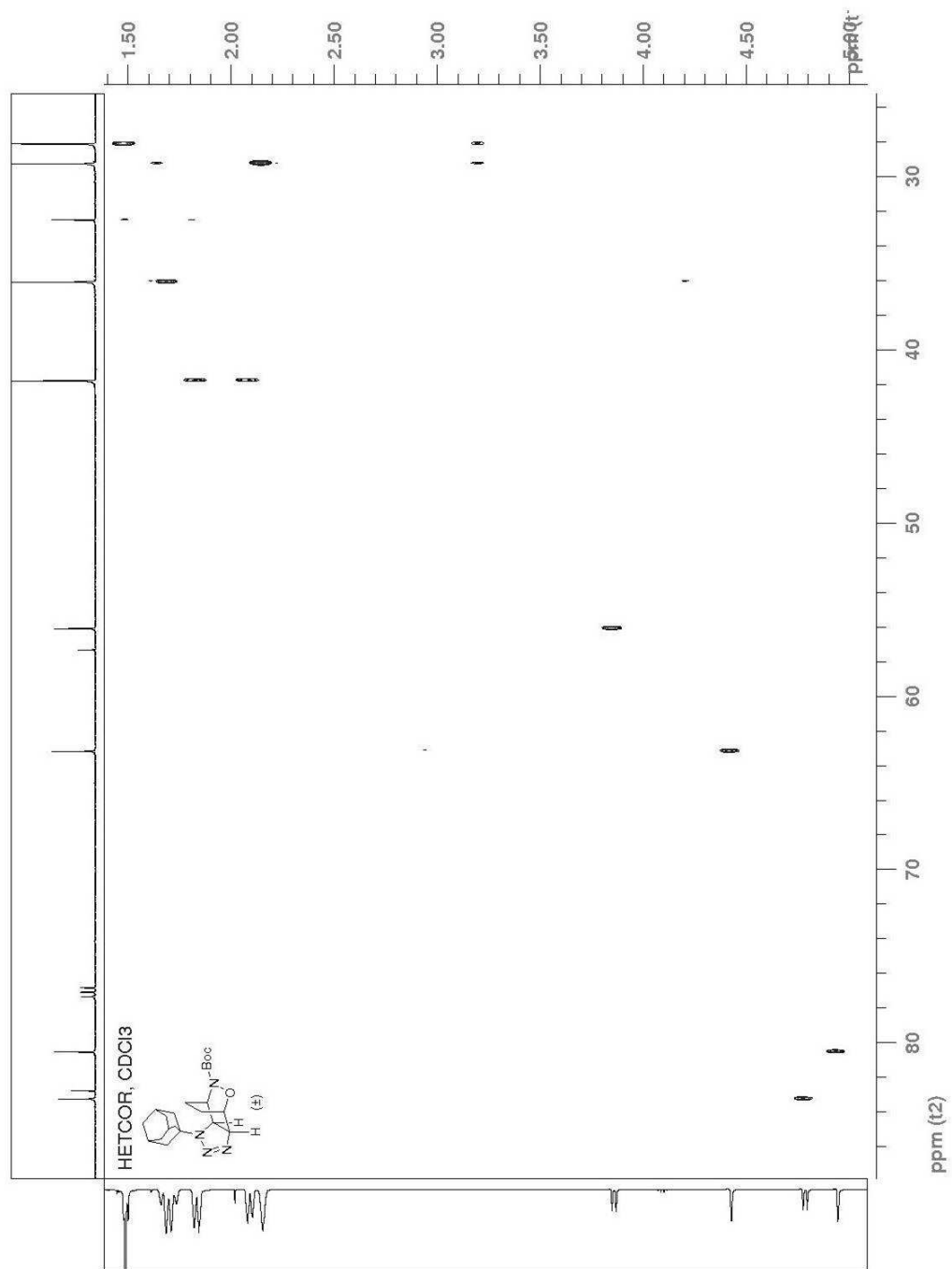
500 MHz, CDCl₃



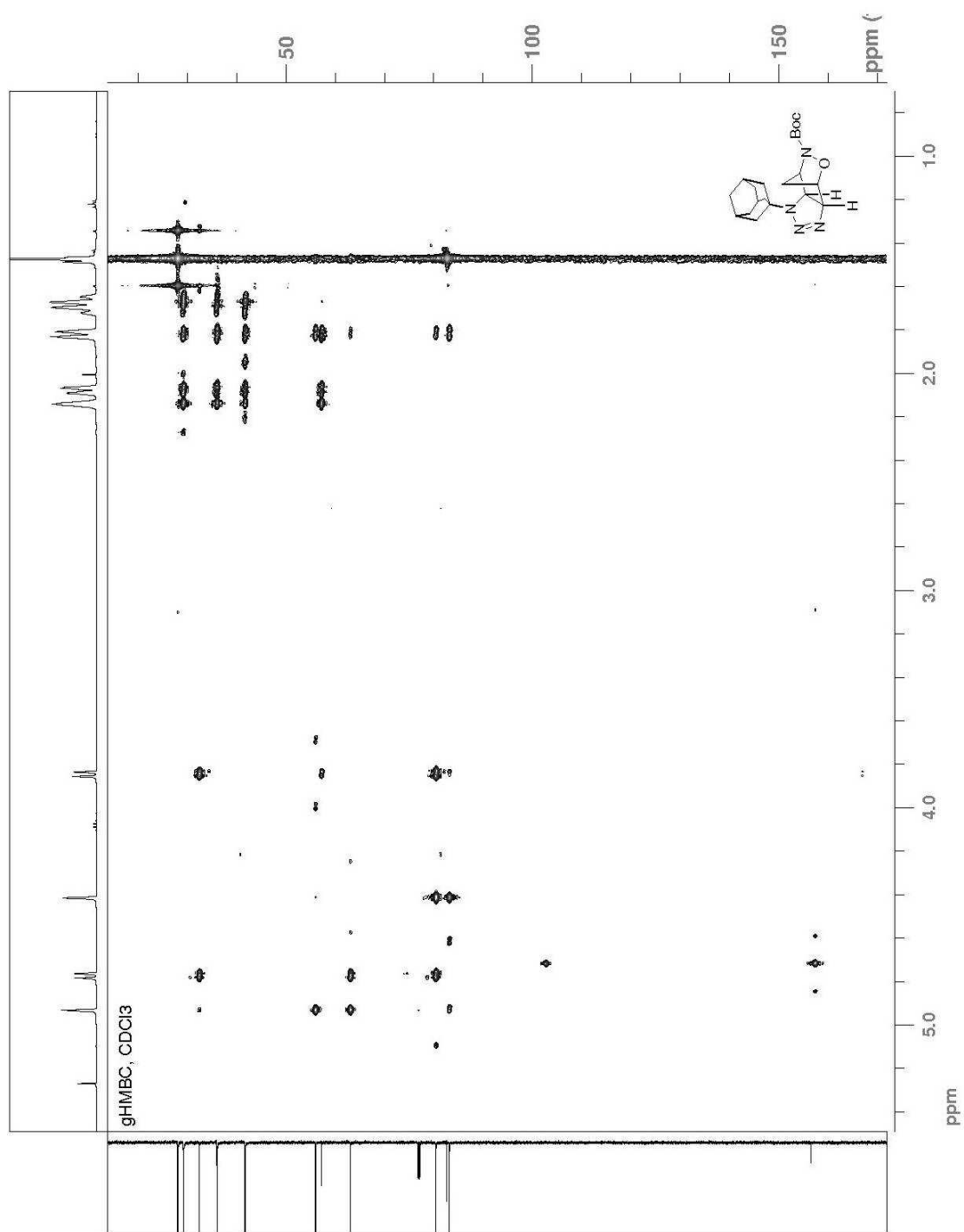
125 MHz, CDCl₃



¹H and ¹³C NMR spectra for compound **6.7b**

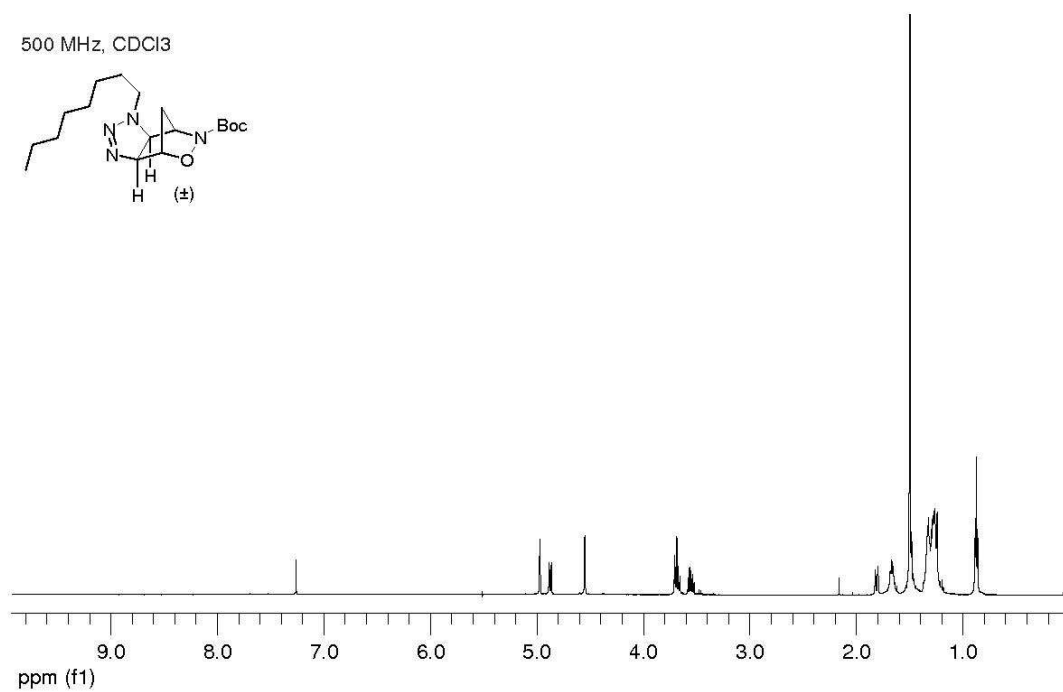
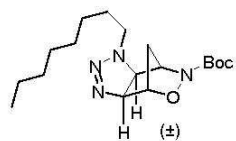


HETCOR NMR spectra for compound **6.7b**

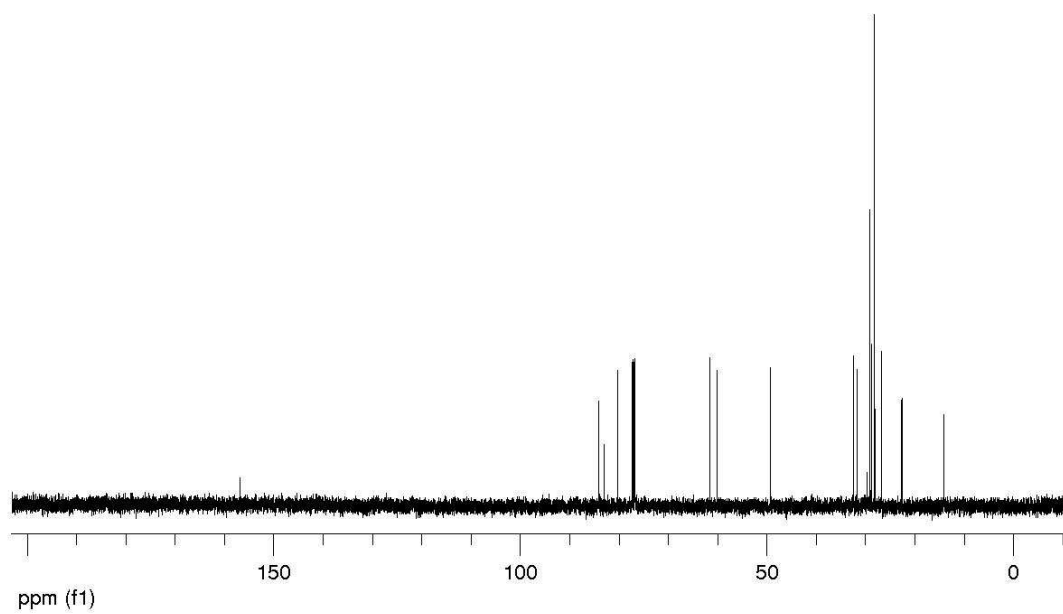


gHMBC NMR spectra for compound **6.7b**

500 MHz, CDCl₃

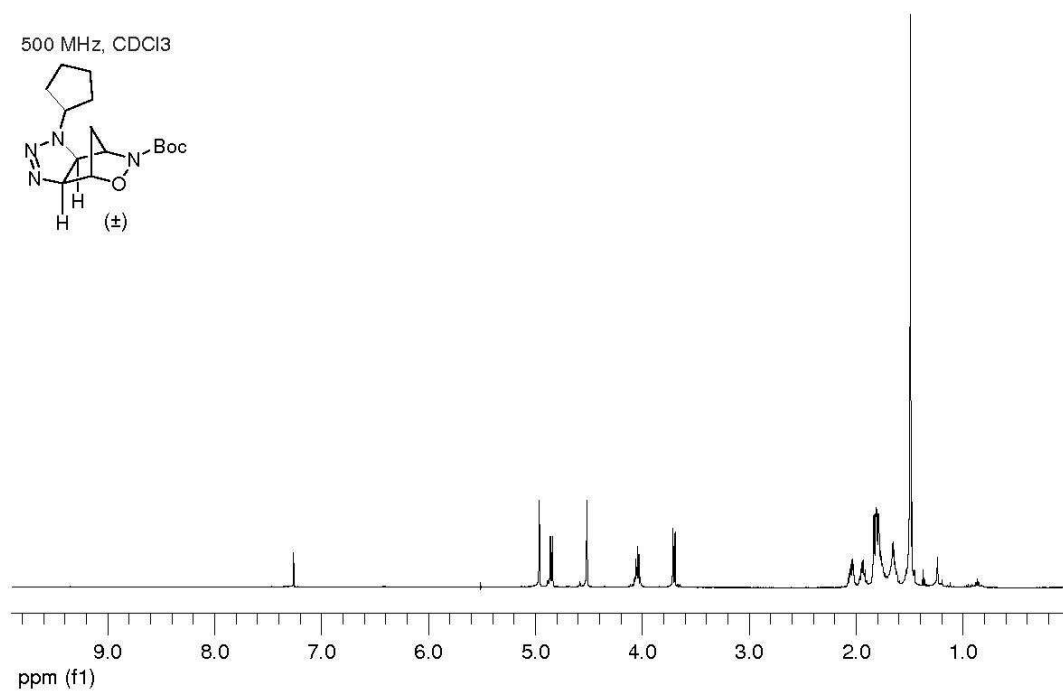
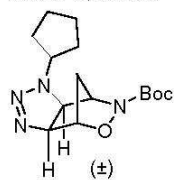


125 MHz, CDCl₃

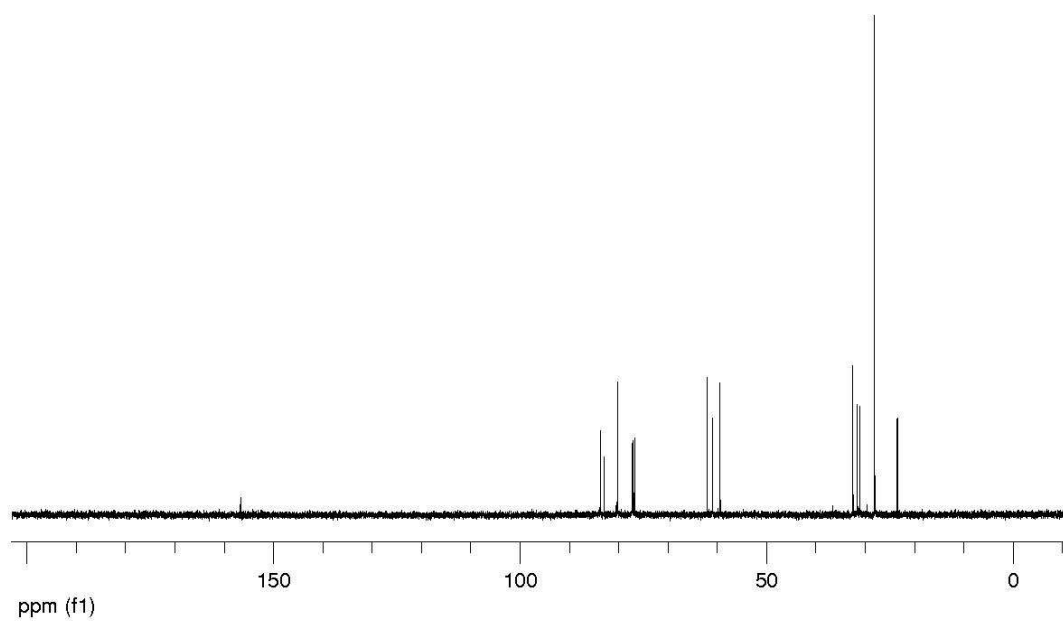


¹H and ¹³C NMR spectra for compound **6.7c**

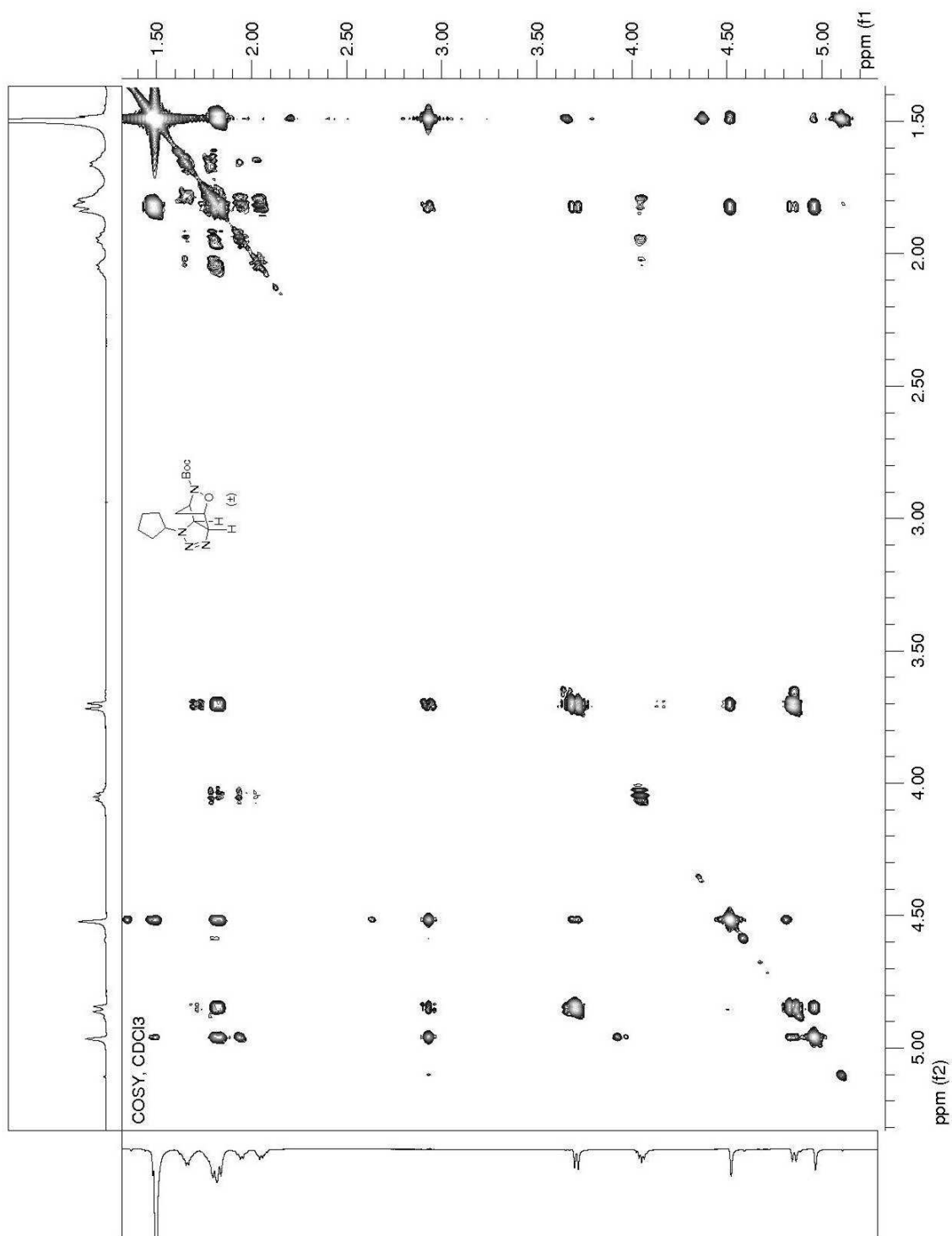
500 MHz, CDCl₃



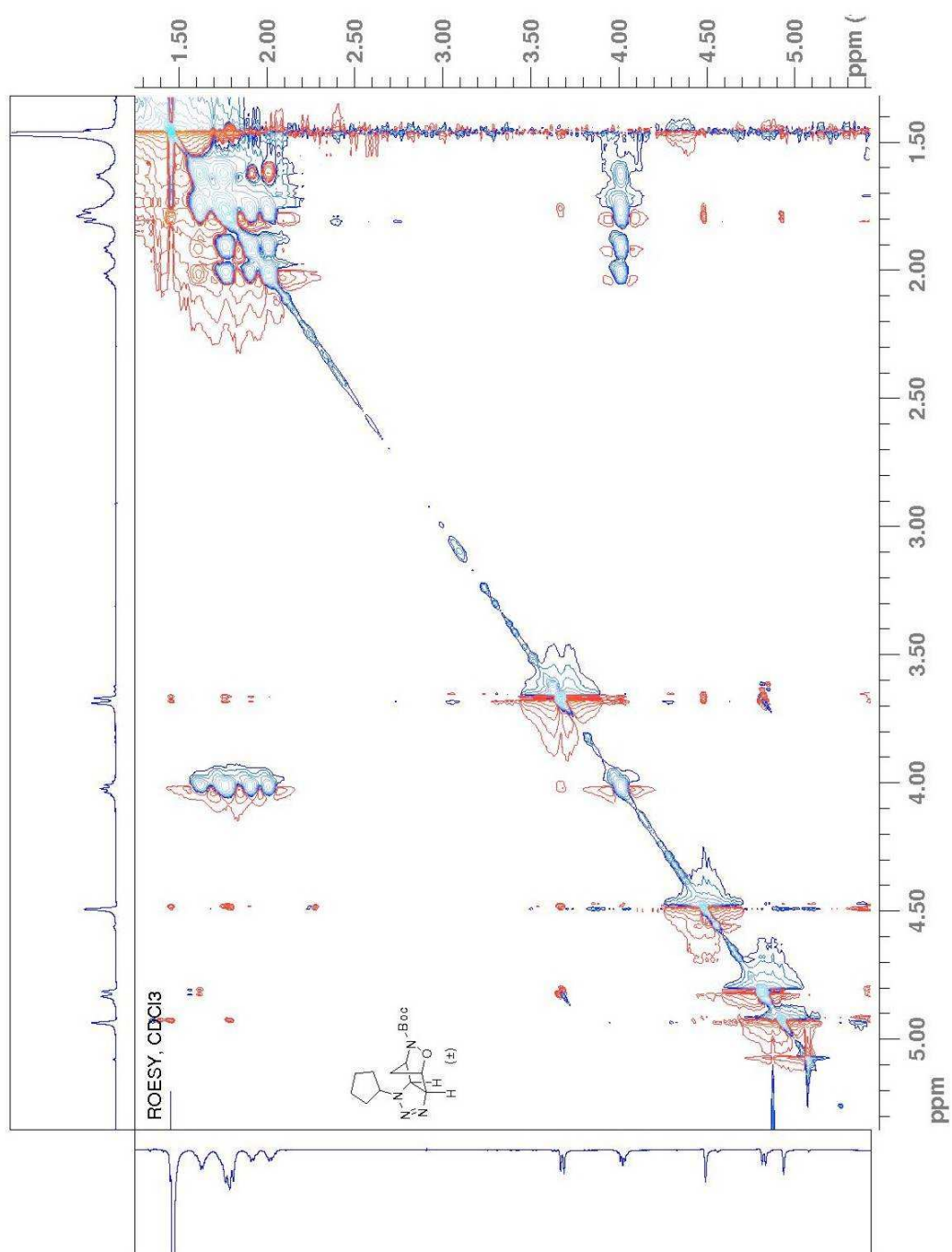
125 MHz, CDCl₃



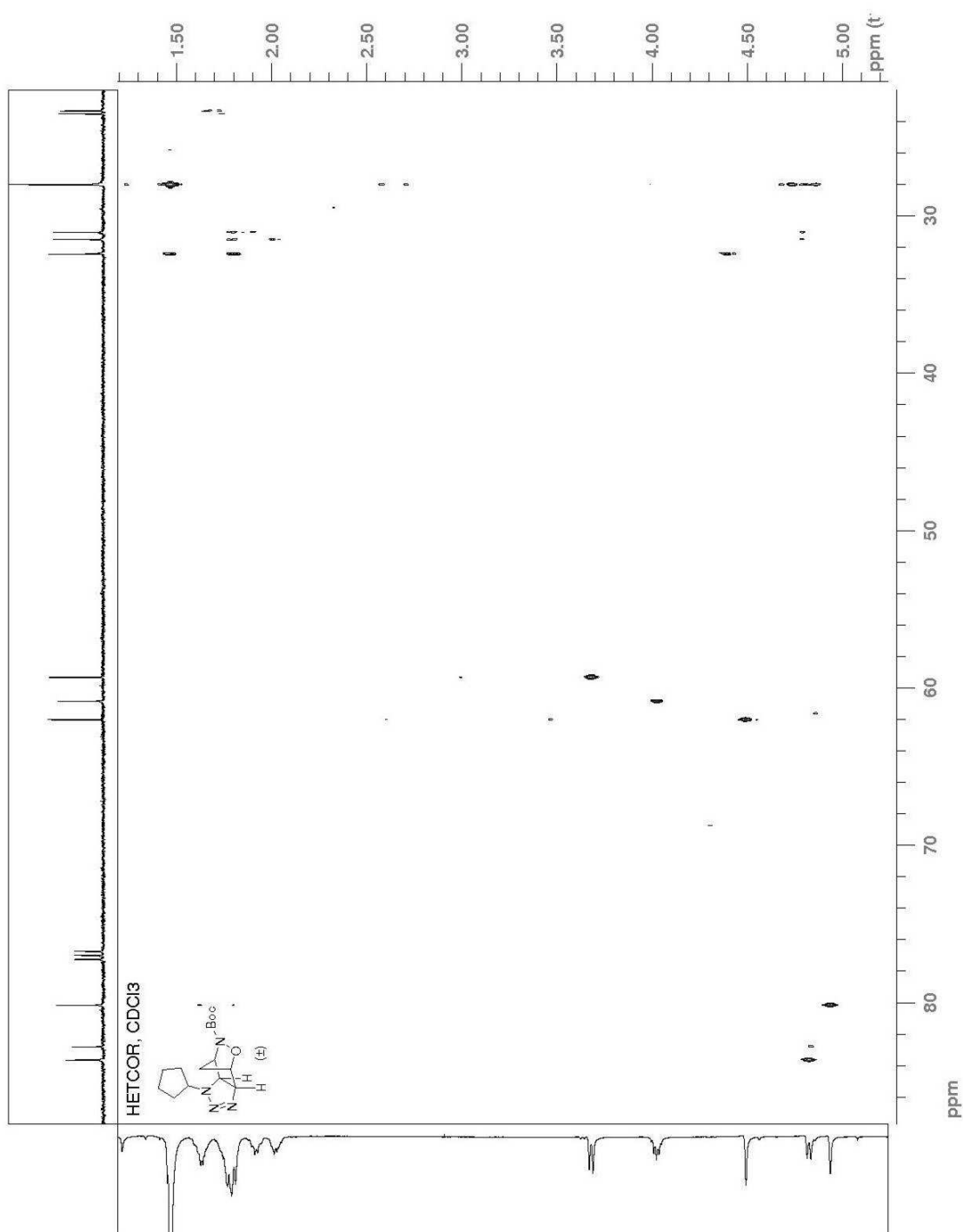
¹H and ¹³C NMR spectra for compound **6.7d**



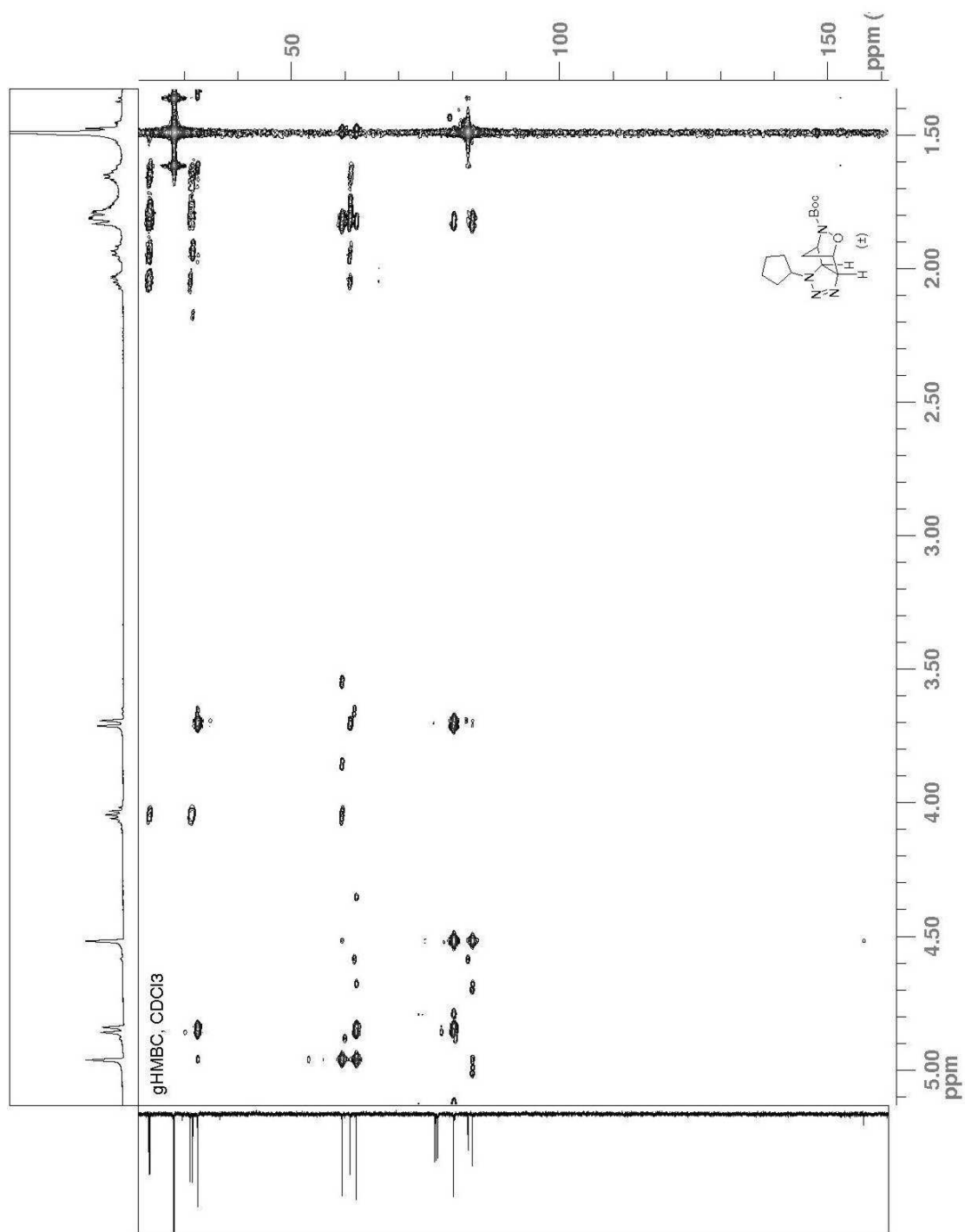
COSY NMR spectra for compound **6.7d**



ROESY NMR spectra for compound **6.7d**

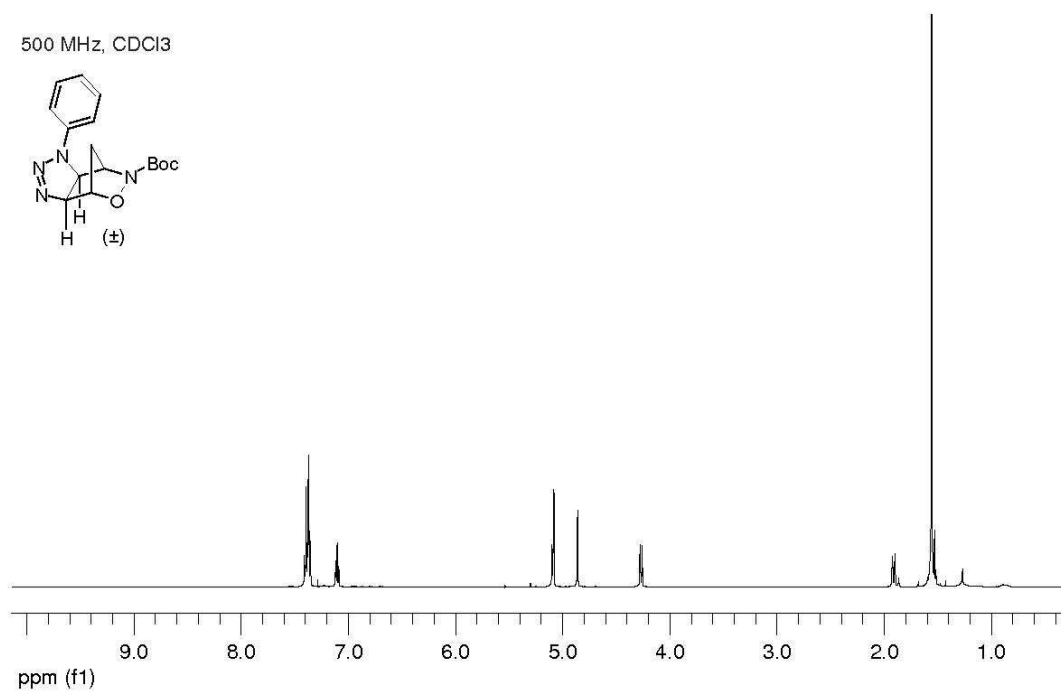
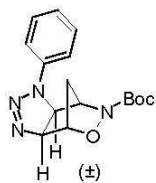


HETCOR NMR spectra for compound **6.7d**

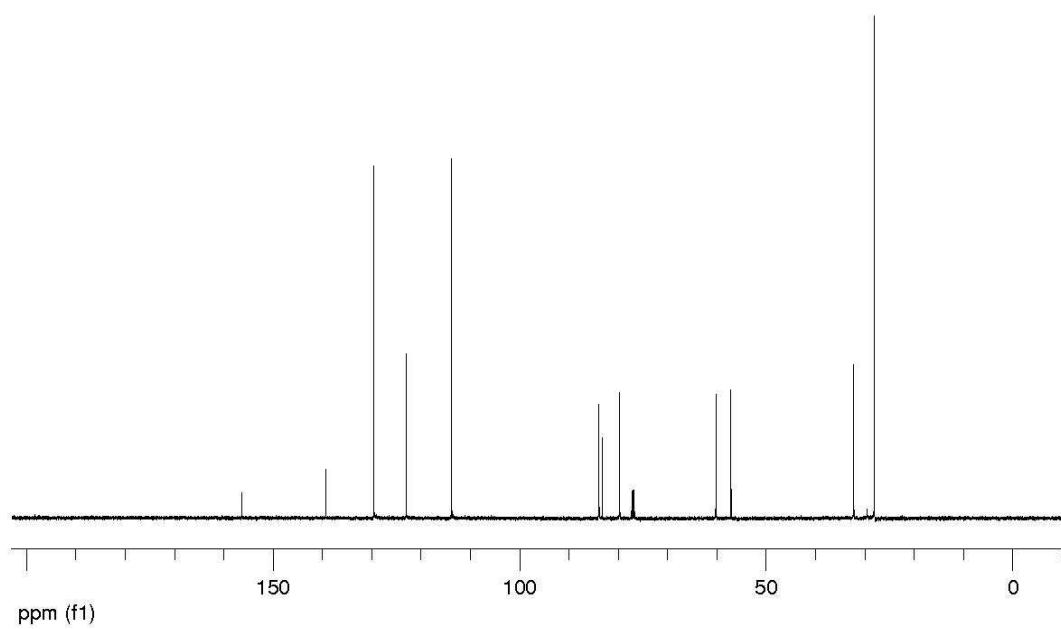


gHMBC NMR spectra for compound **6.7d**

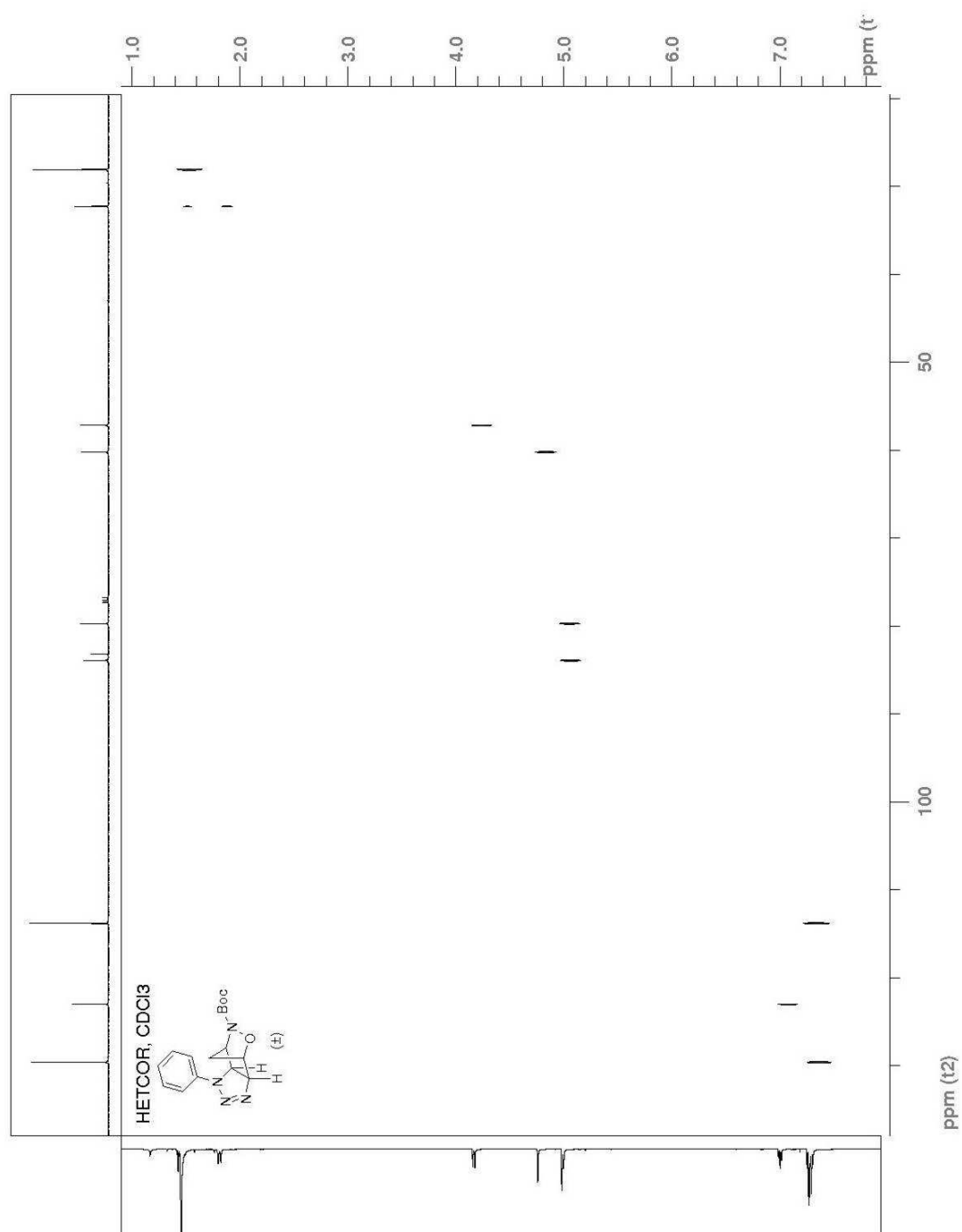
500 MHz, CDCl₃



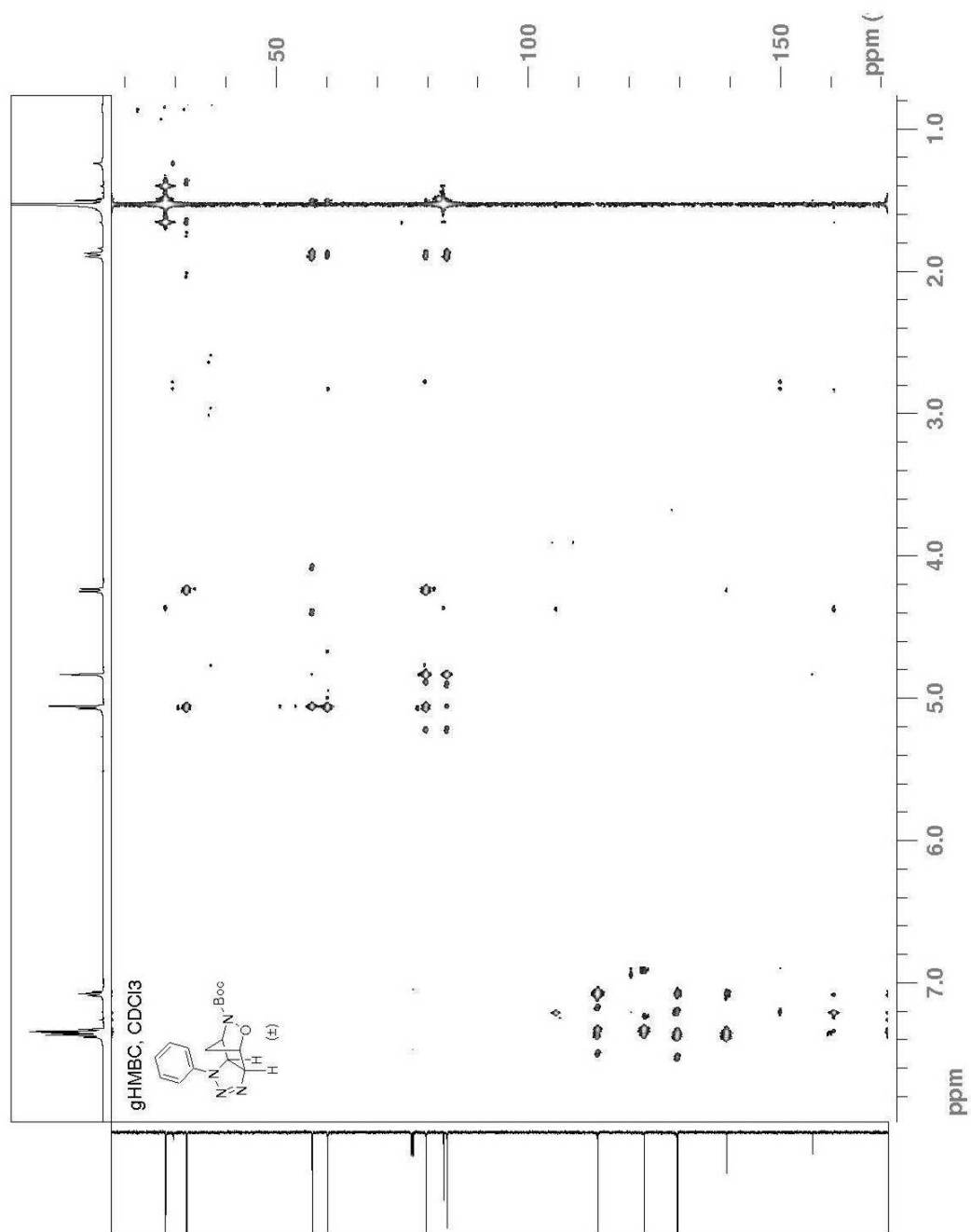
125 MHz, CDCl₃



¹H and ¹³C NMR spectra for compound **6.7e**

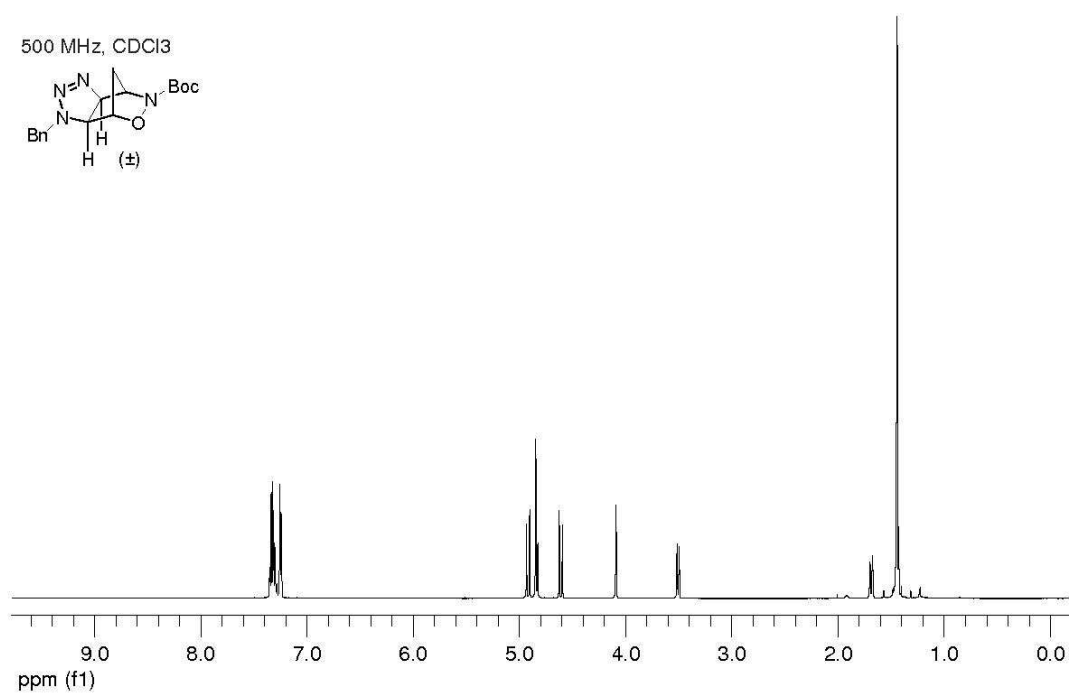
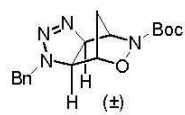


HETCOR NMR spectra for compound **6.7e**

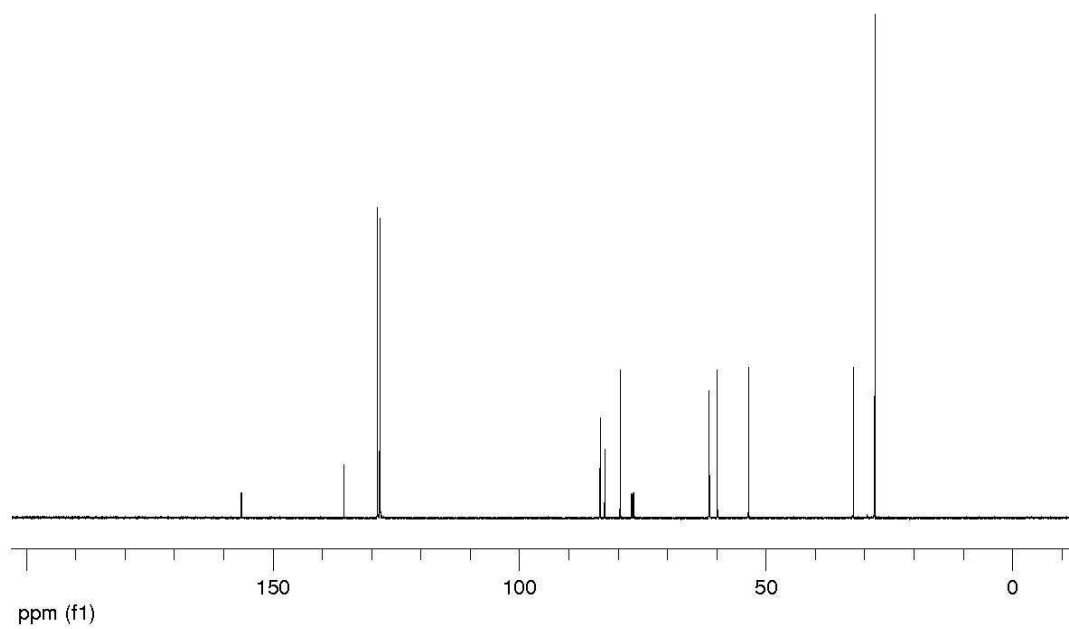


gHMBC NMR spectra for compound **6.7e**

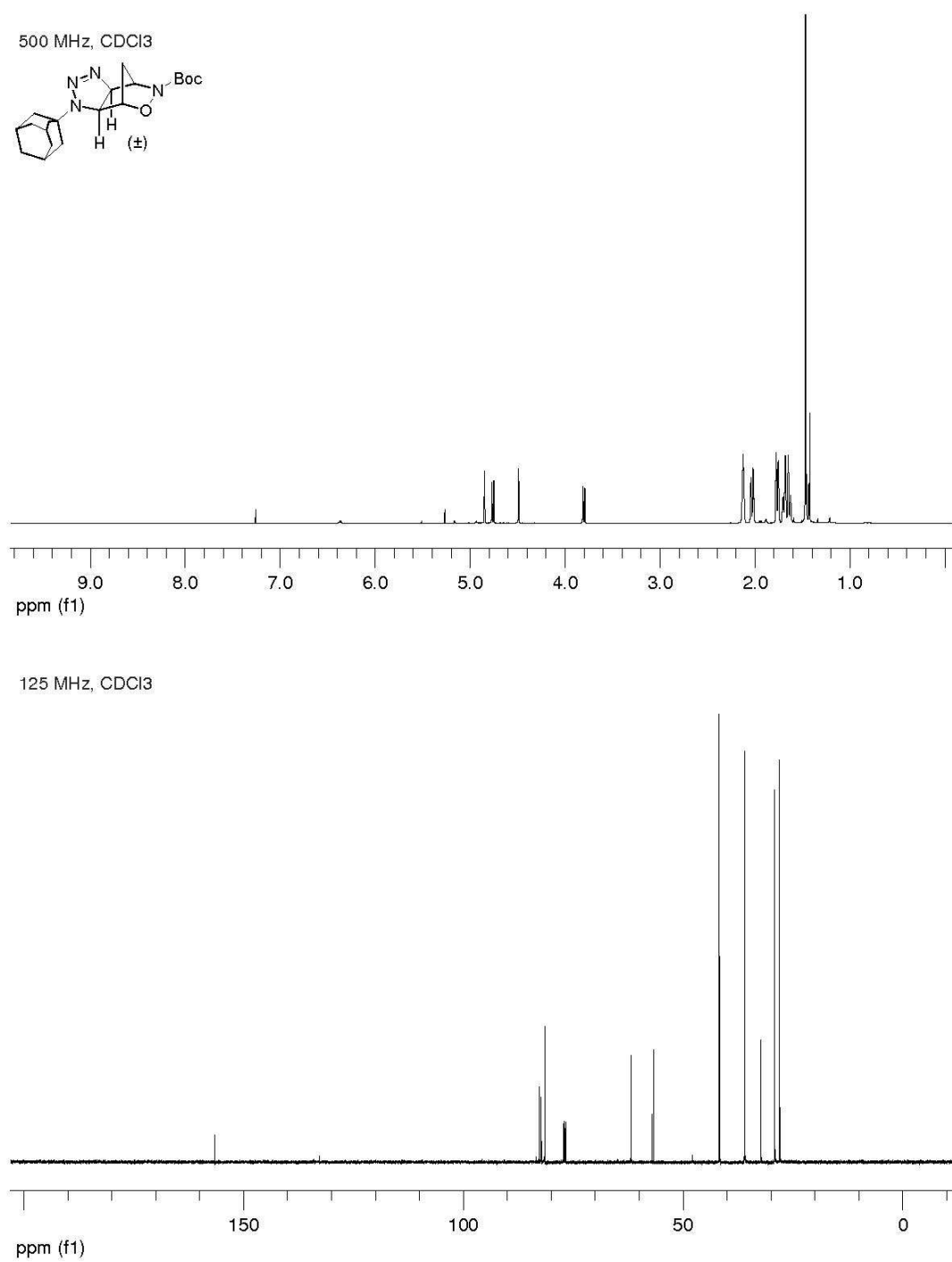
500 MHz, CDCl₃



125 MHz, CDCl₃

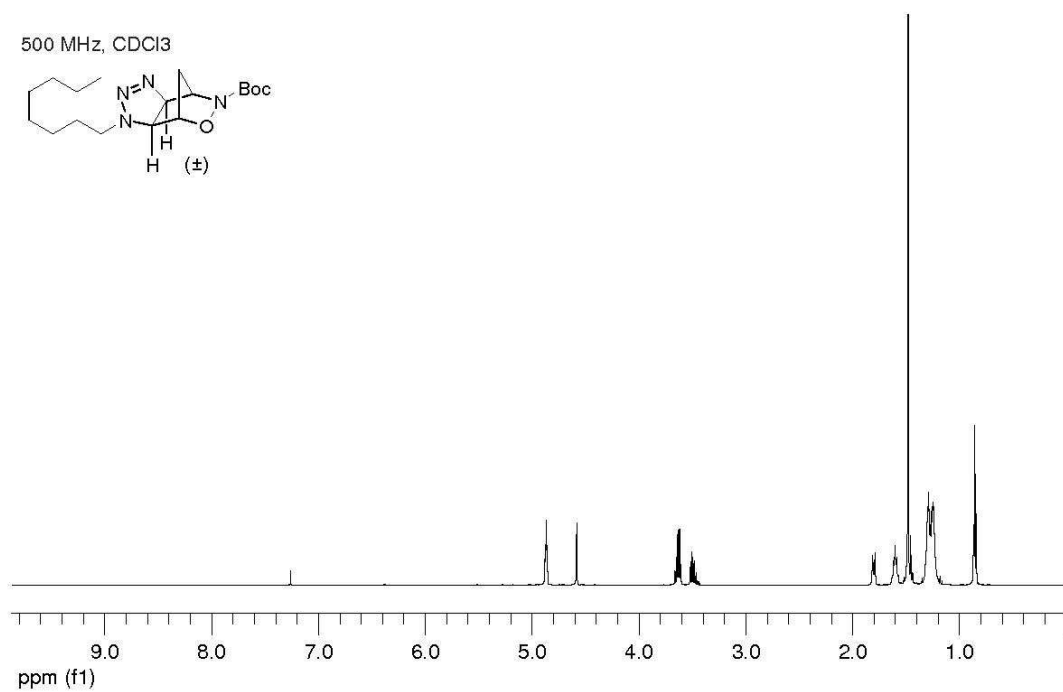
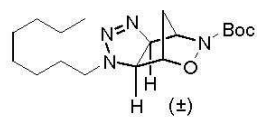


¹H and ¹³C NMR spectra for compound **6.8a**

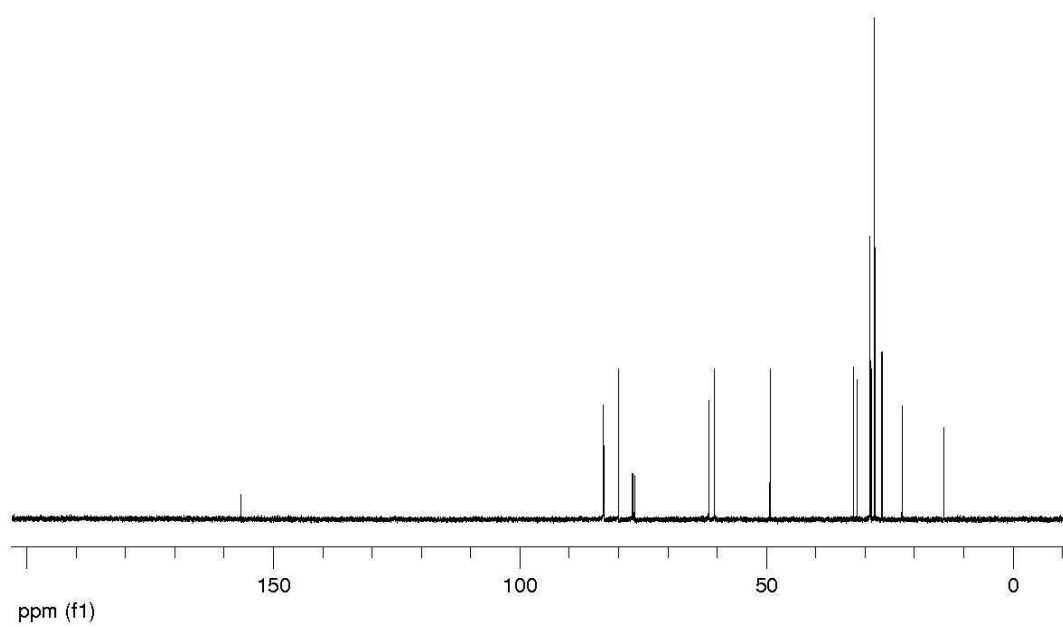


¹H and ¹³C NMR spectra for compound **6.8b**

500 MHz, CDCl₃

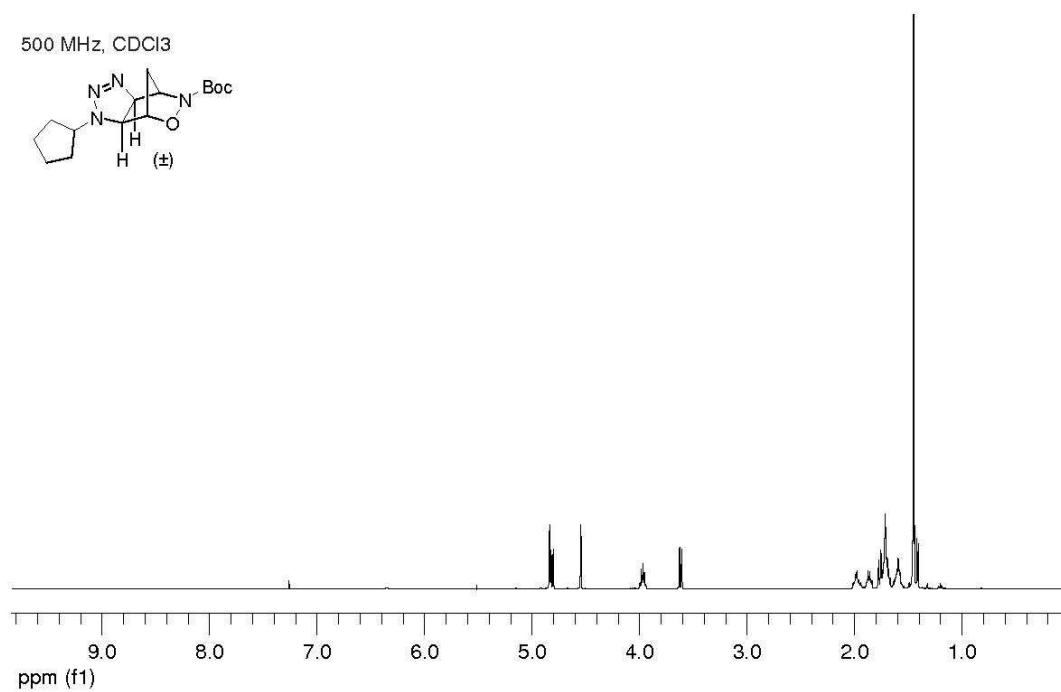
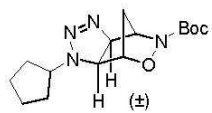


125 MHz, CDCl₃

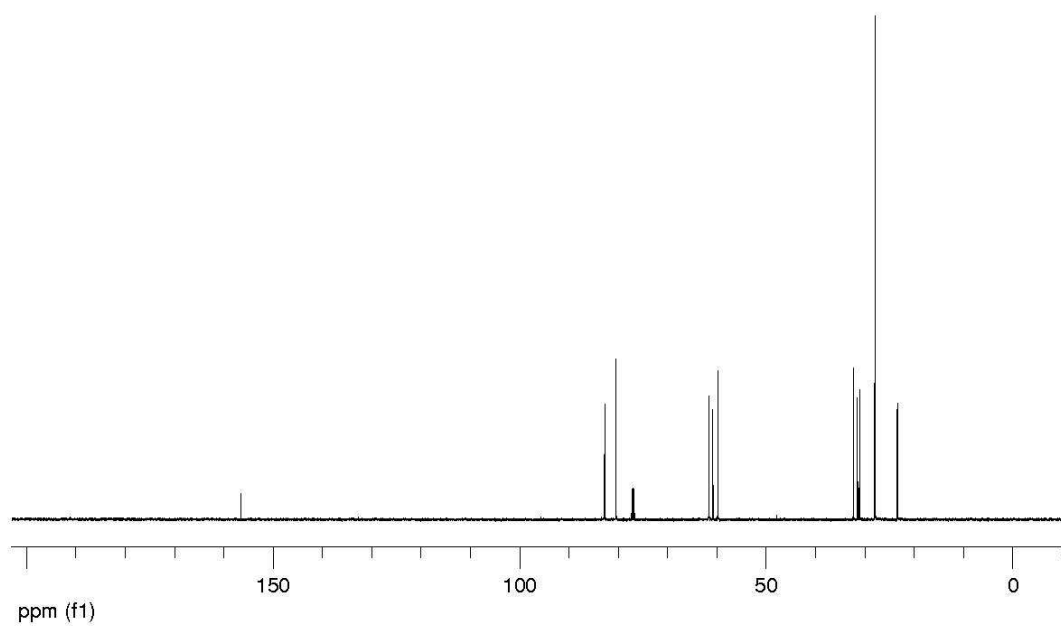


¹H and ¹³C NMR spectra for compound **6.8c**

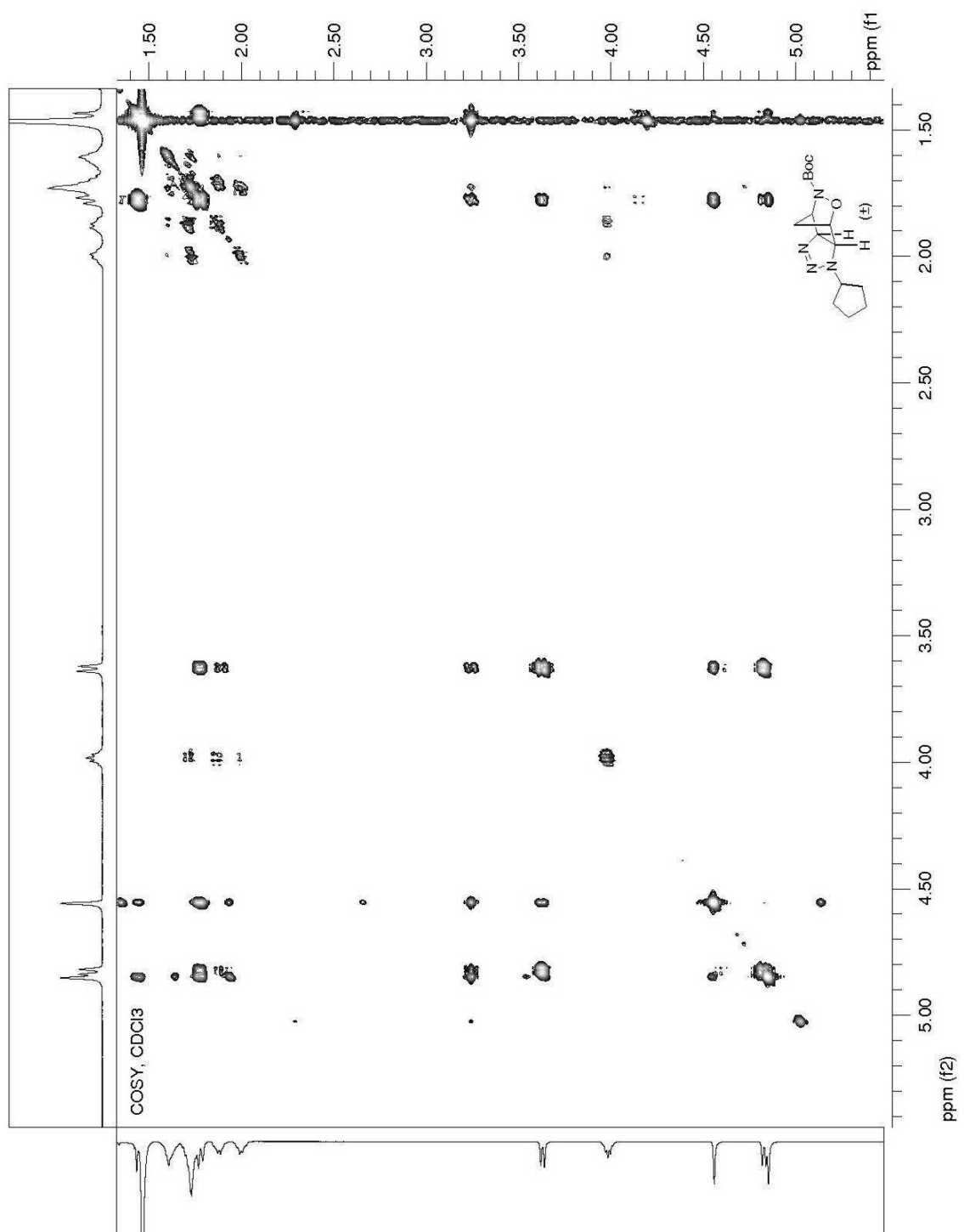
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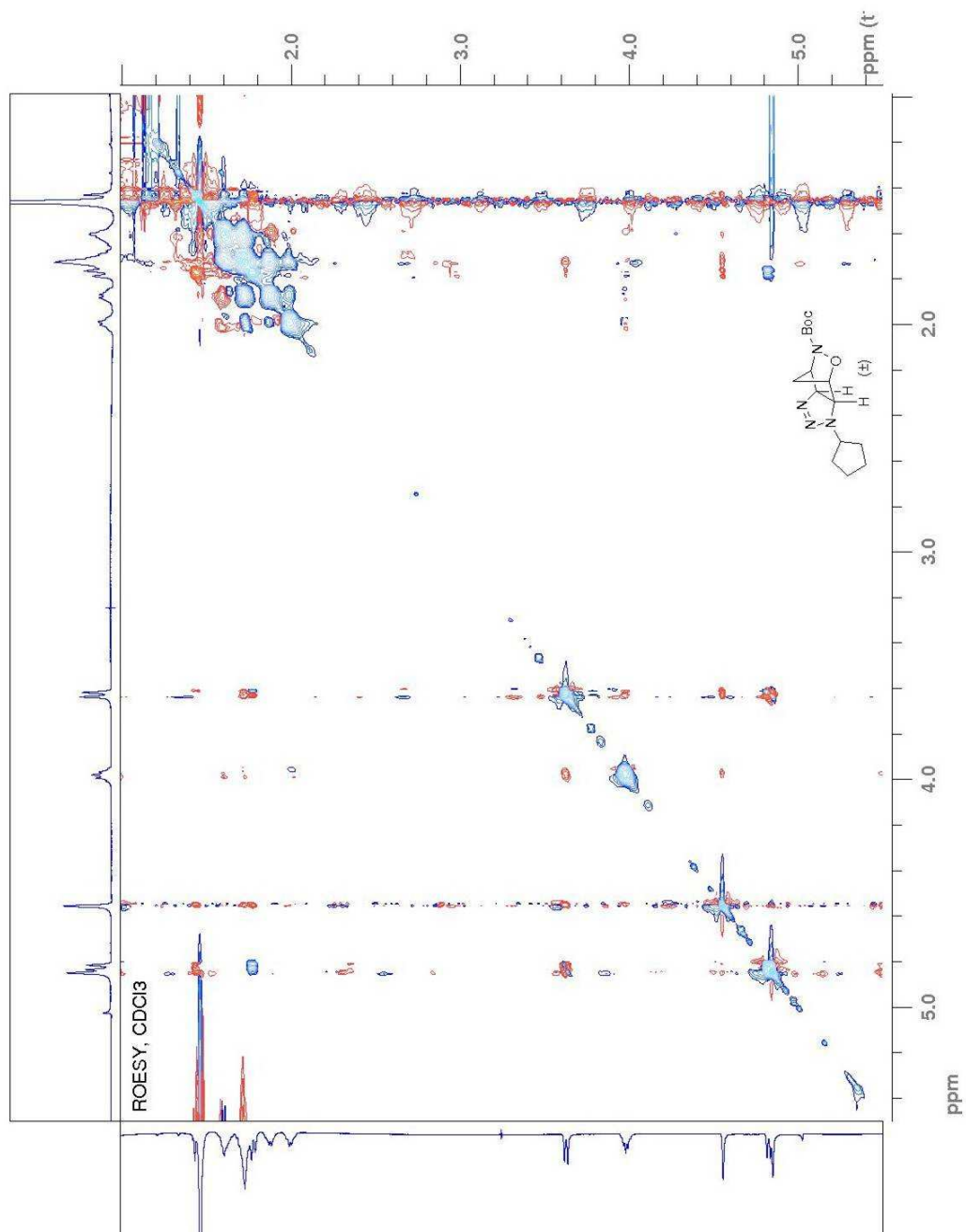
125 MHz, CDCl₃



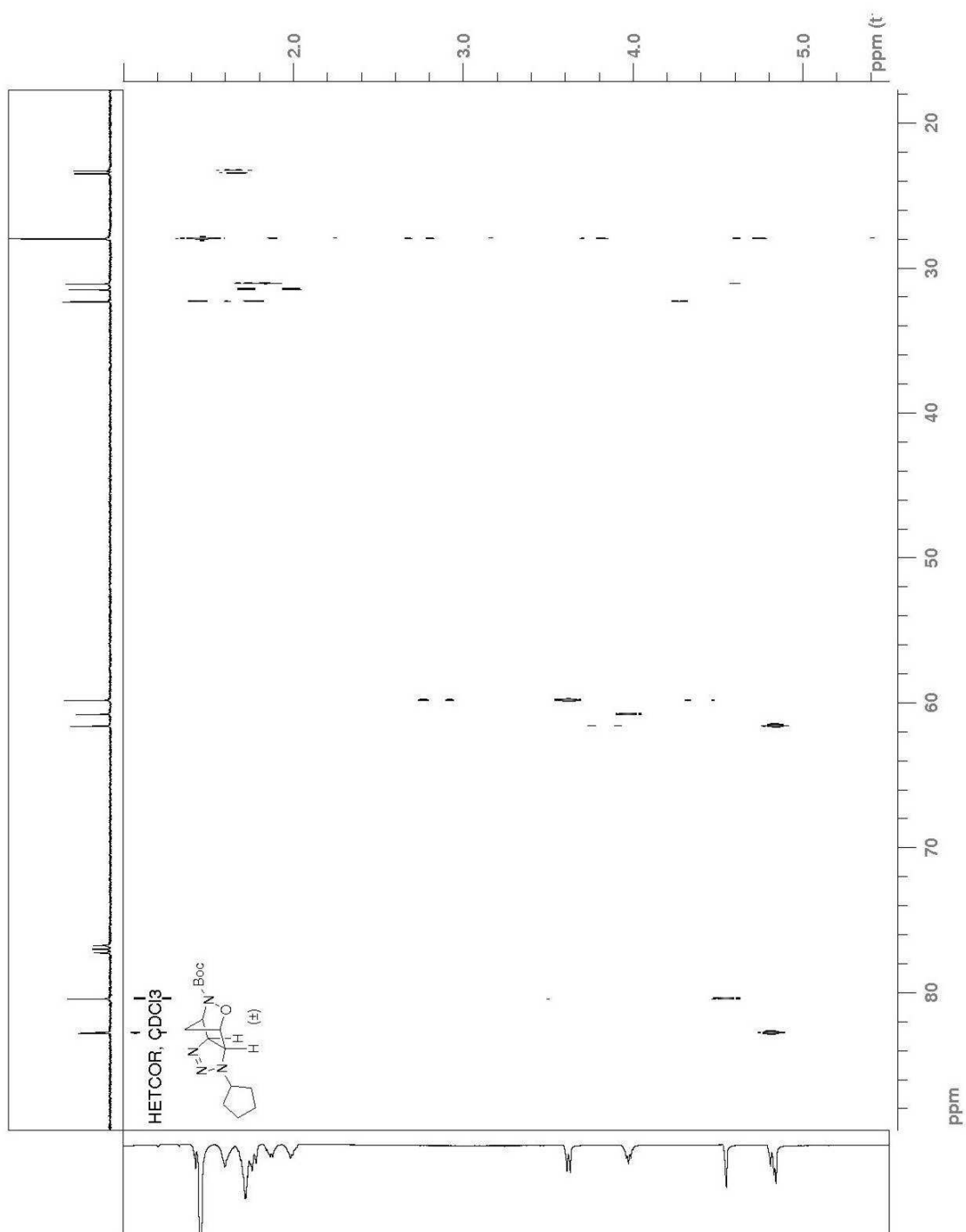
¹H and ¹³C NMR spectra for compound **6.8d**

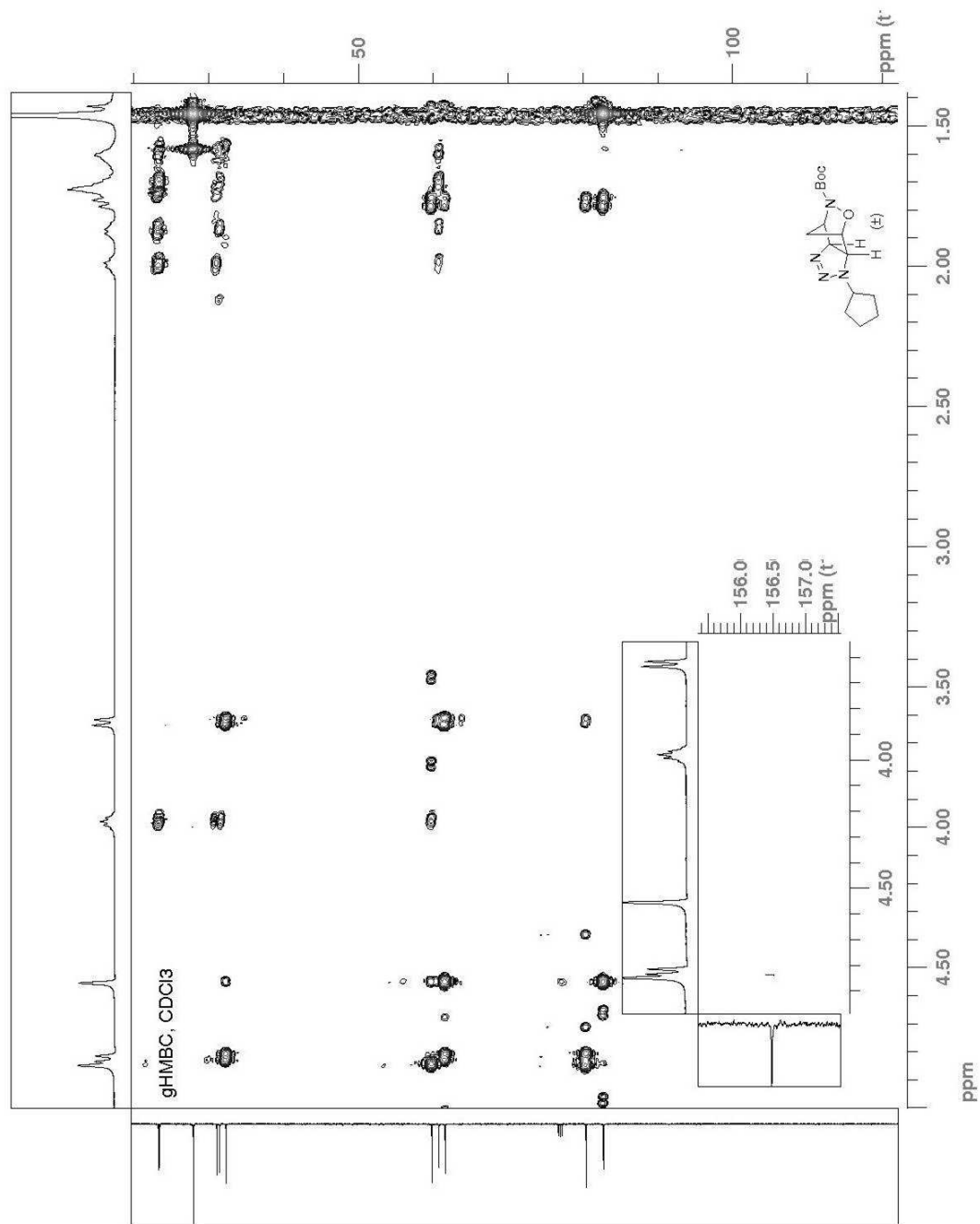


COSY NMR spectra for compound **6.8d**



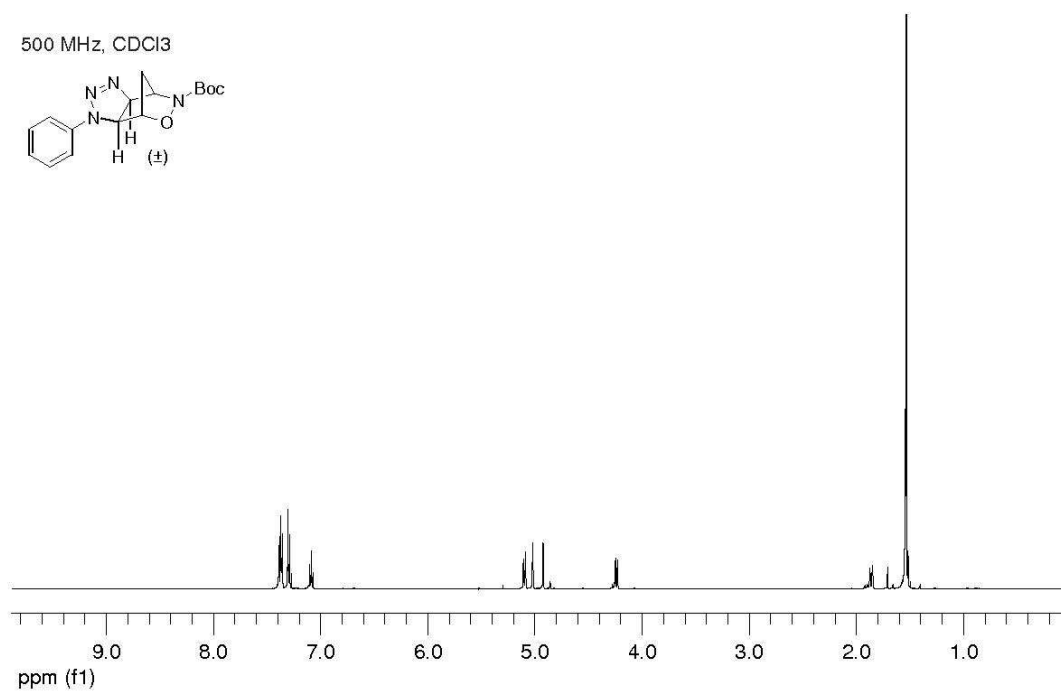
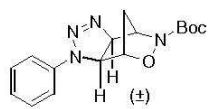
ROESY NMR spectra for compound **6.8d**



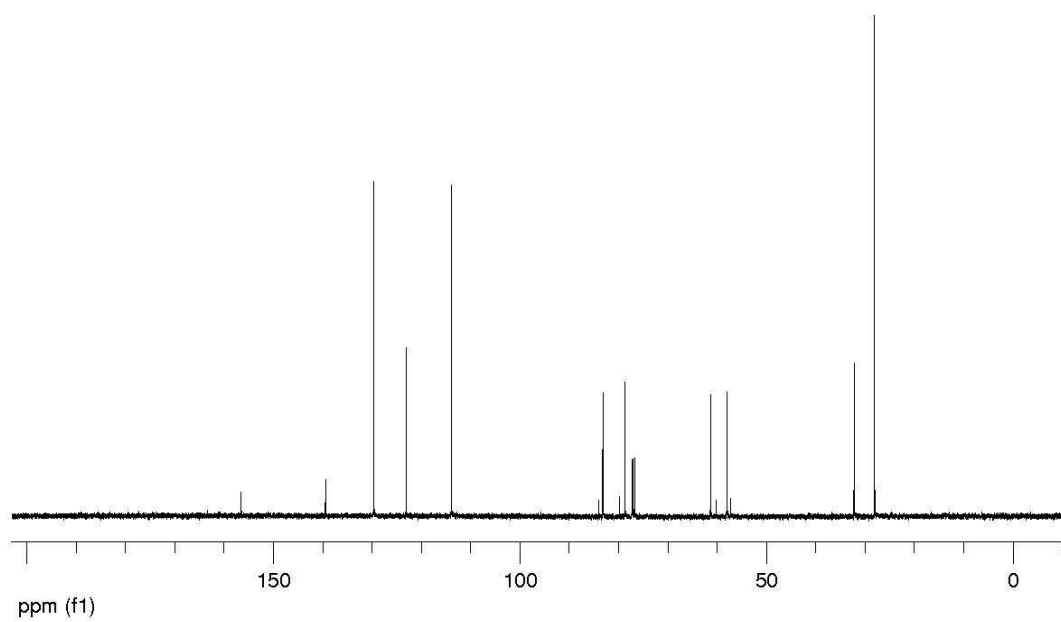


gHMBC NMR spectra for compound **6.8d**

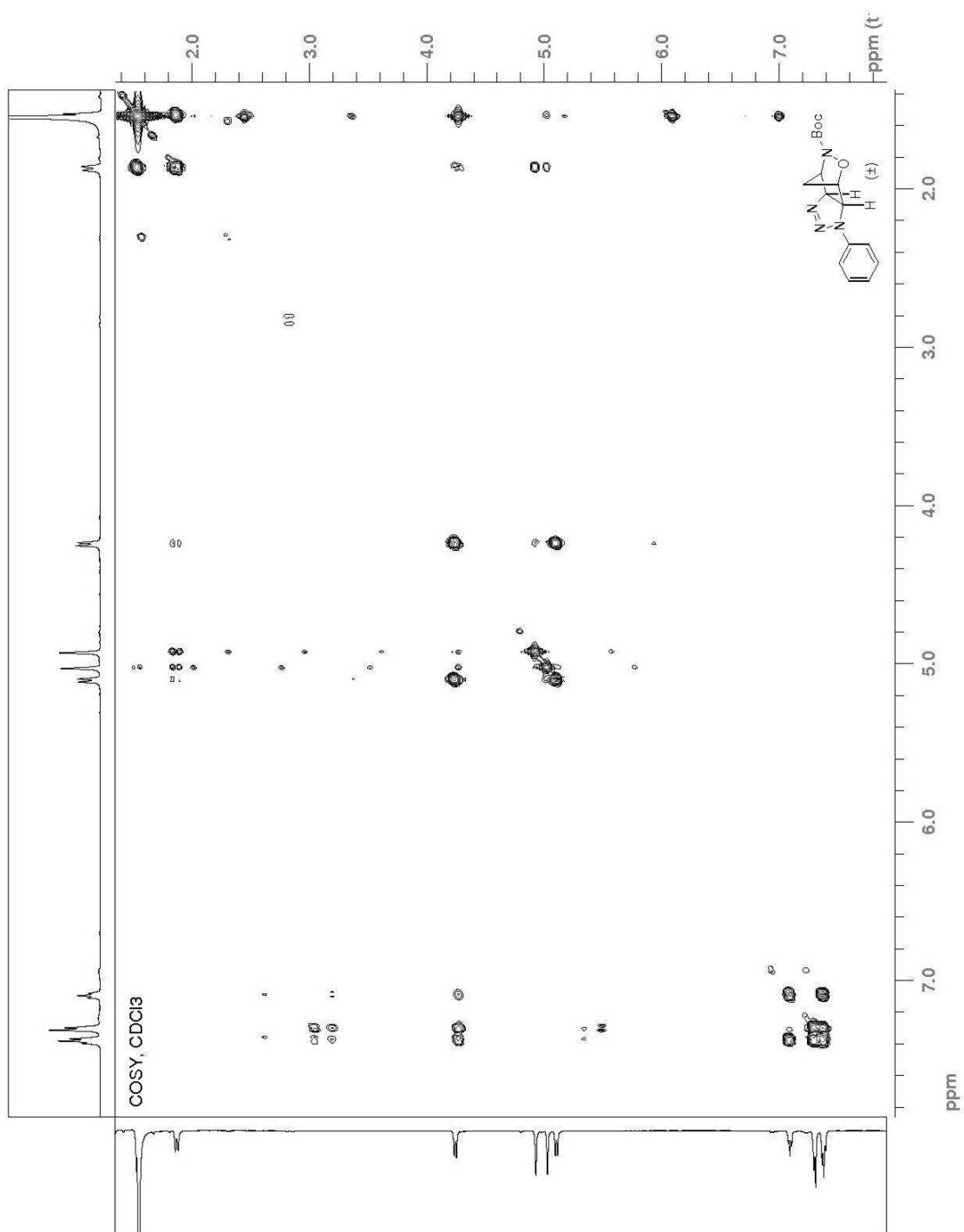
500 MHz, CDCl₃



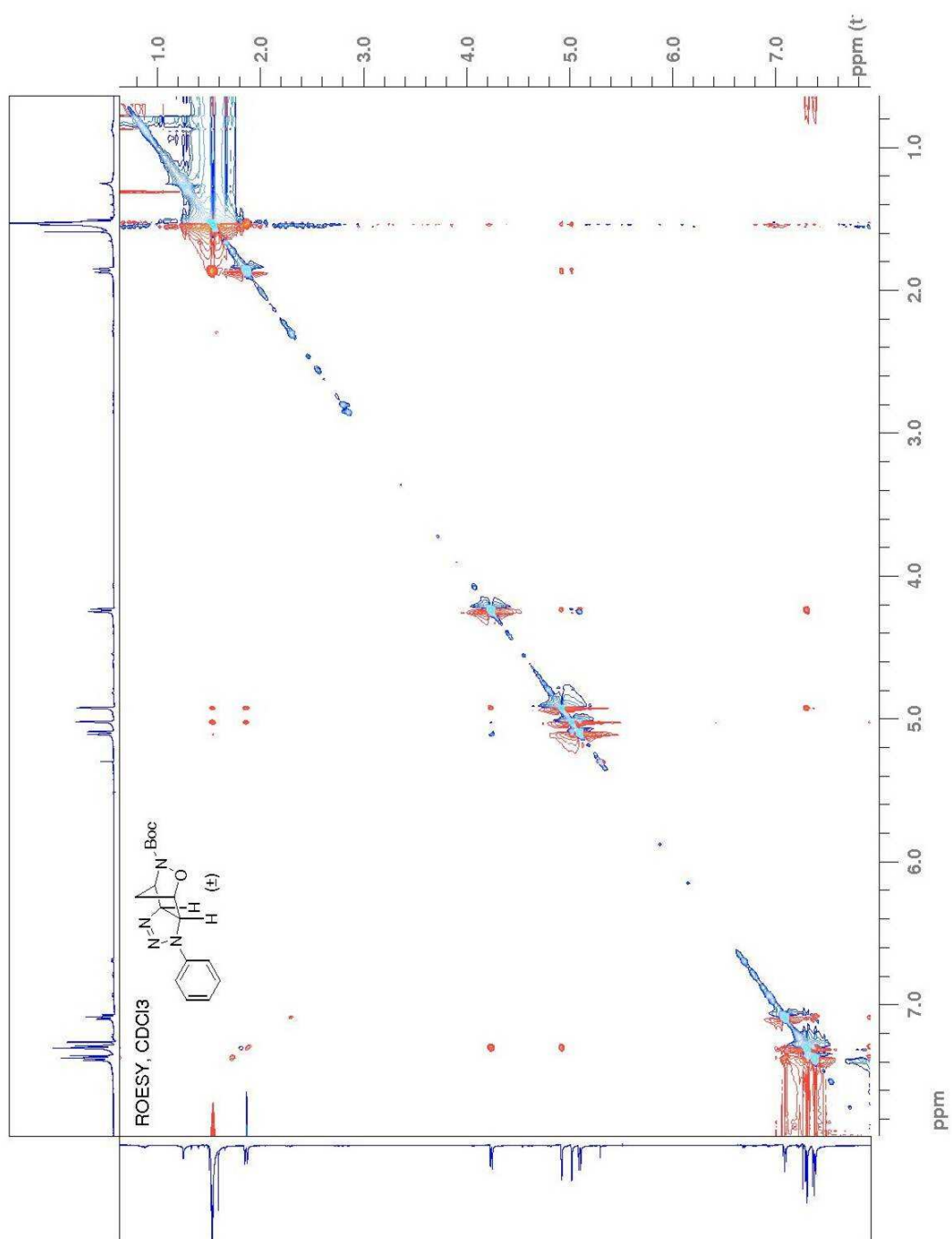
125 MHz, CDCl₃



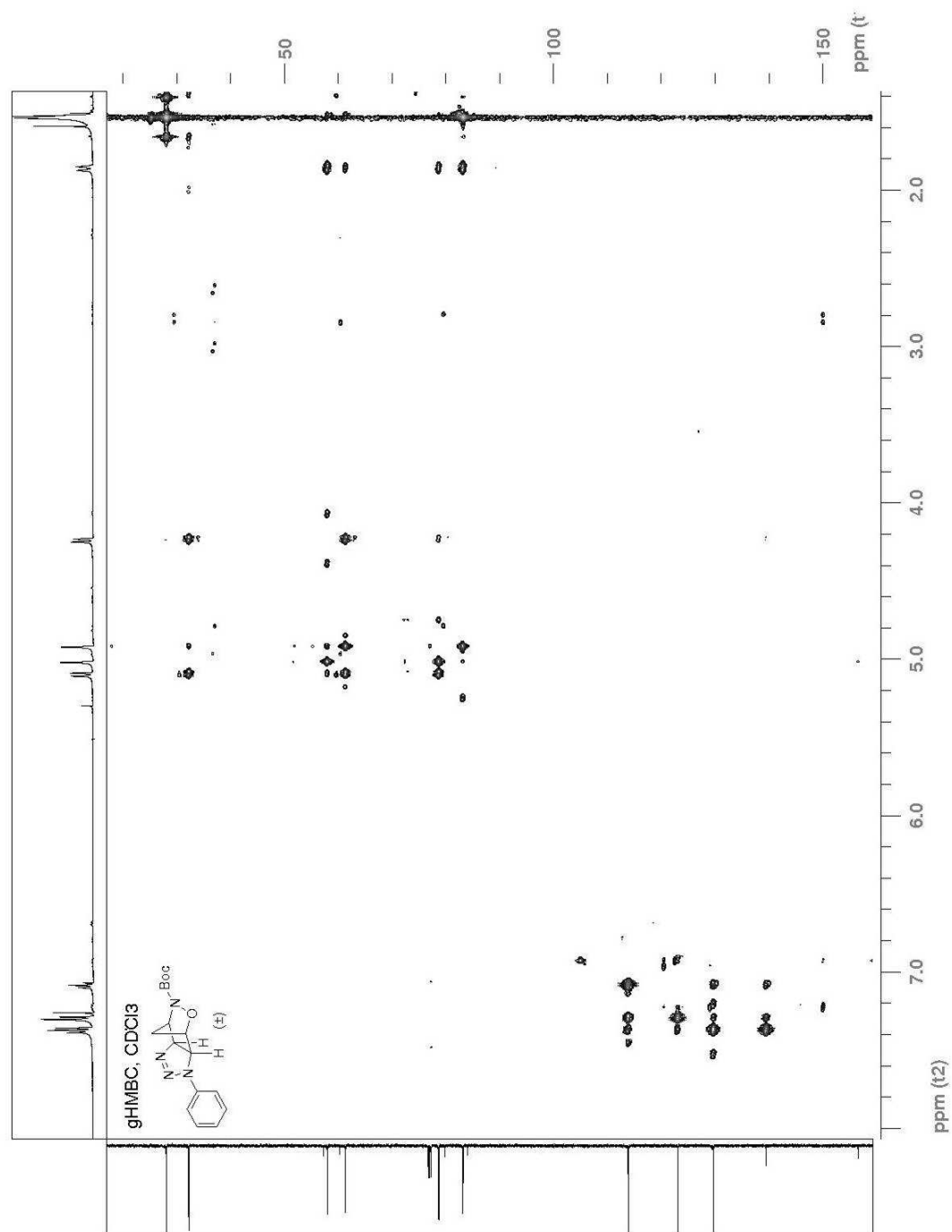
¹H and ¹³C NMR spectra for compound **6.8e**



COSY NMR spectra for compound **6.8e**

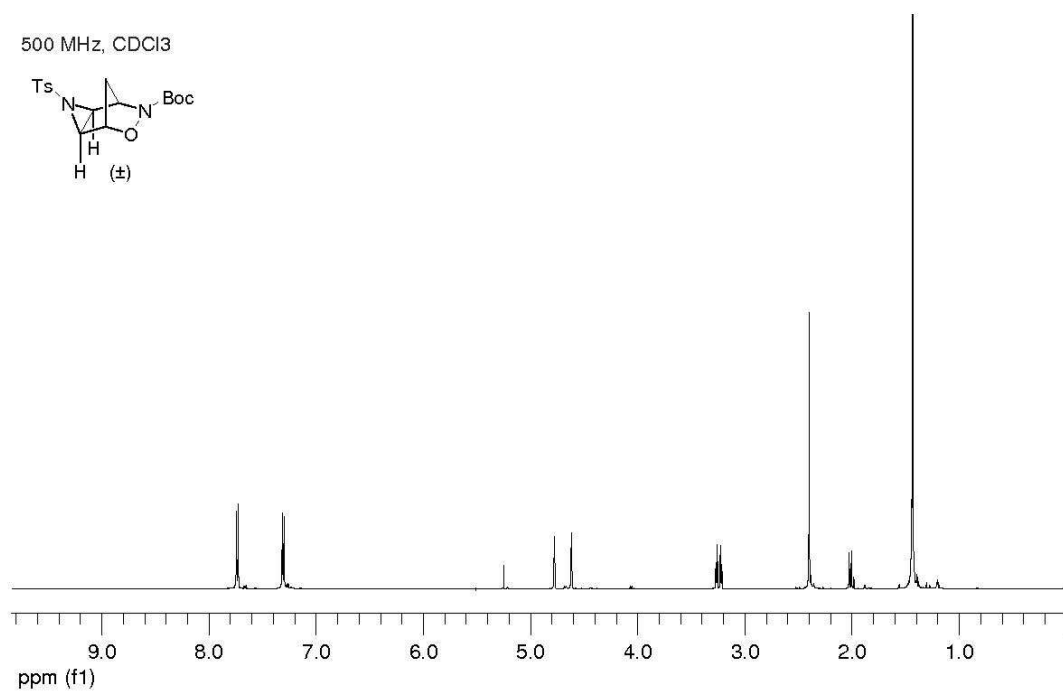
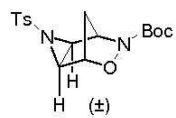


ROESY NMR spectra for compound **6.8e**

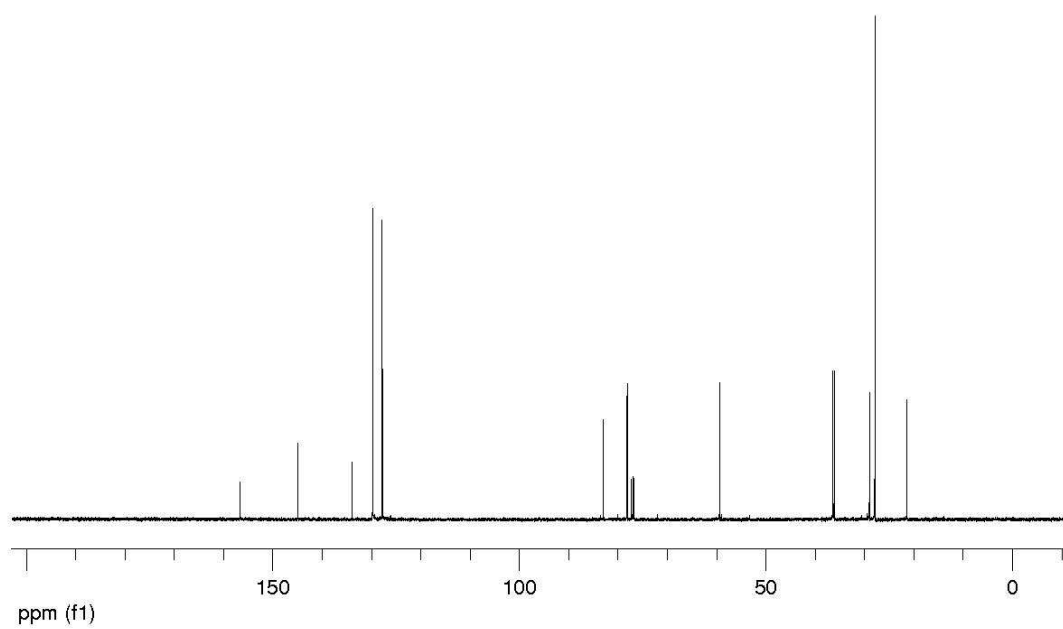


gHMBC NMR spectra for compound **6.8e**

500 MHz, CDCl₃

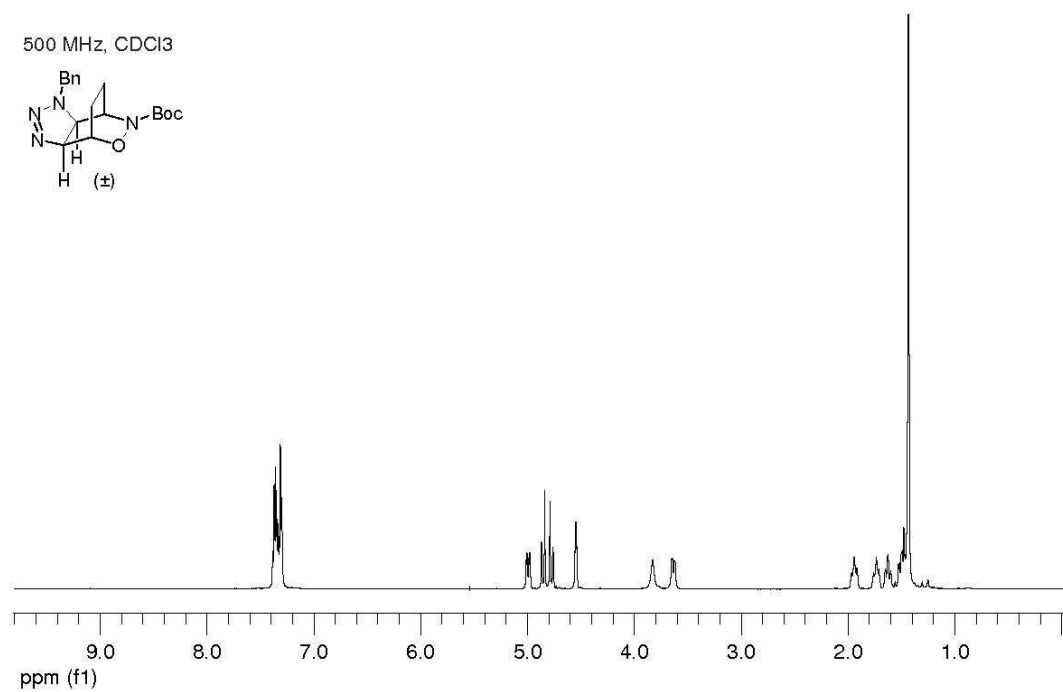
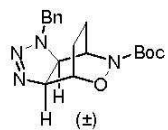


125 MHz, CDCl₃

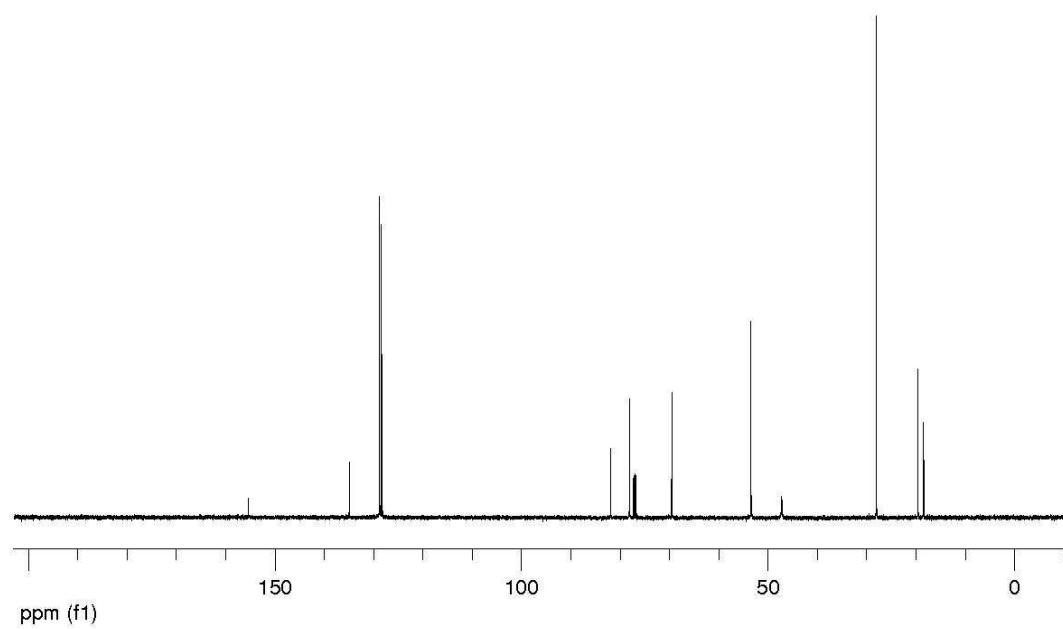


¹H and ¹³C NMR spectra for compound **6.10**

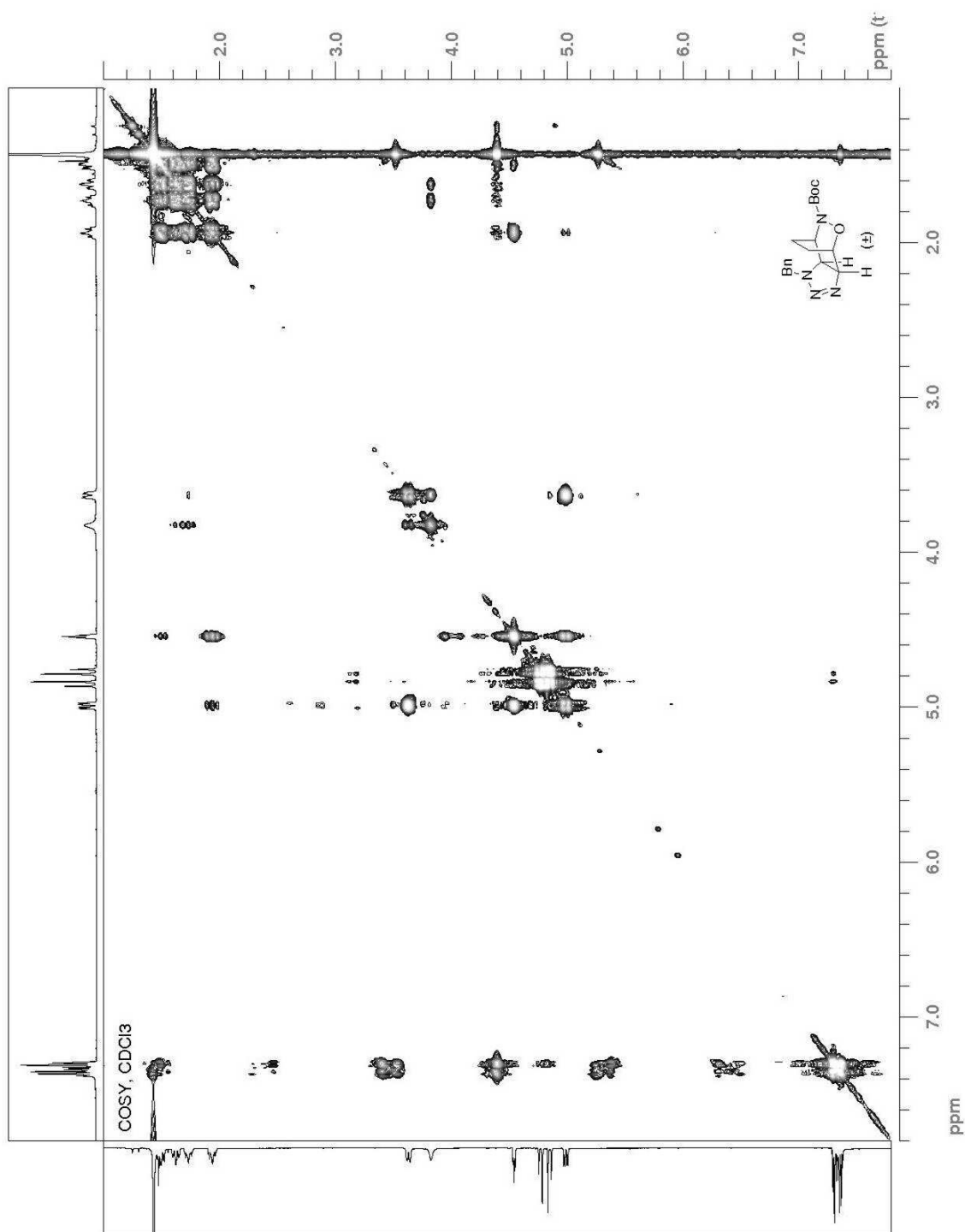
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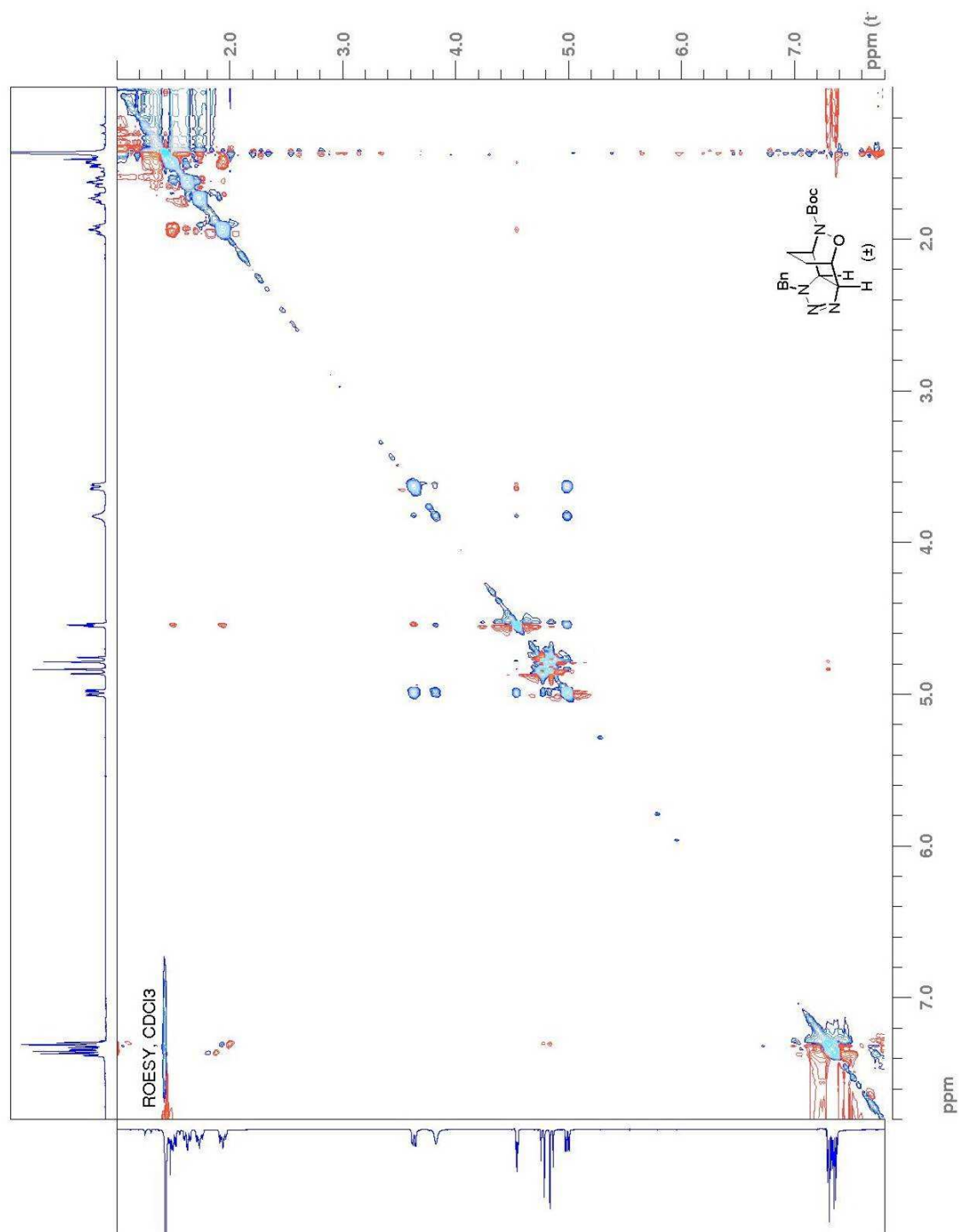
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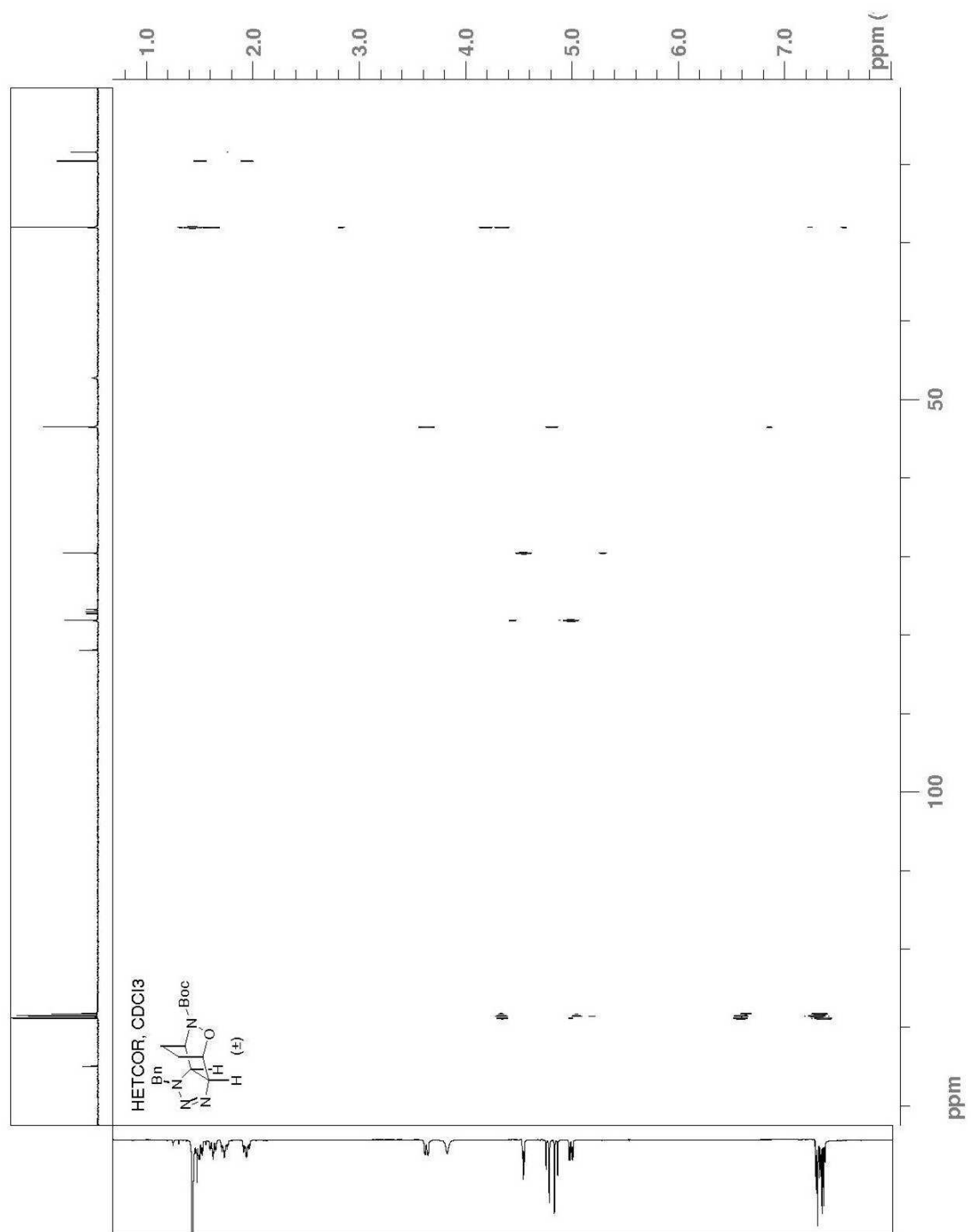
¹H and ¹³C NMR spectra for compound **6.11**



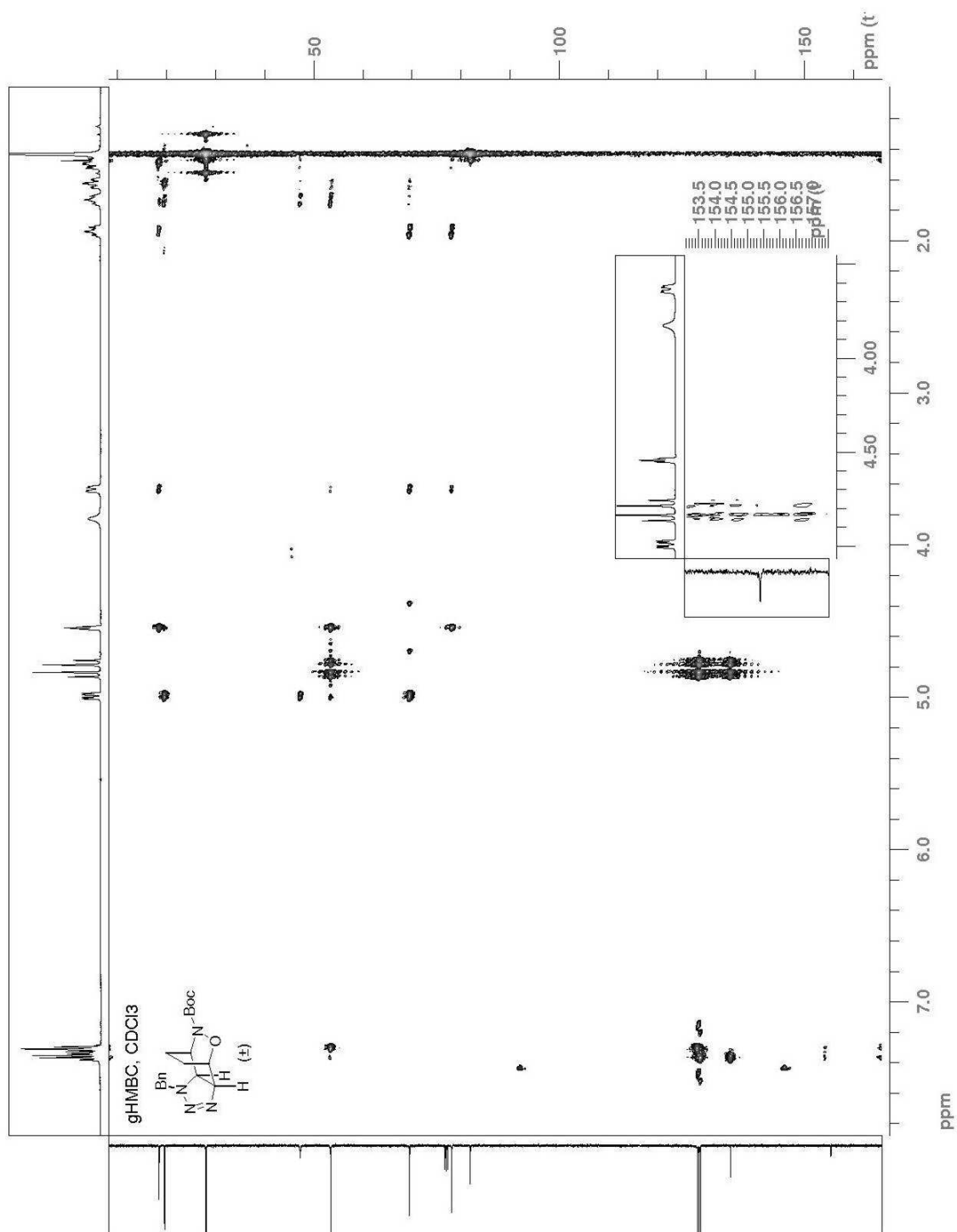
COSY NMR spectra for compound **6.11**



ROESY NMR spectra for compound **6.11**

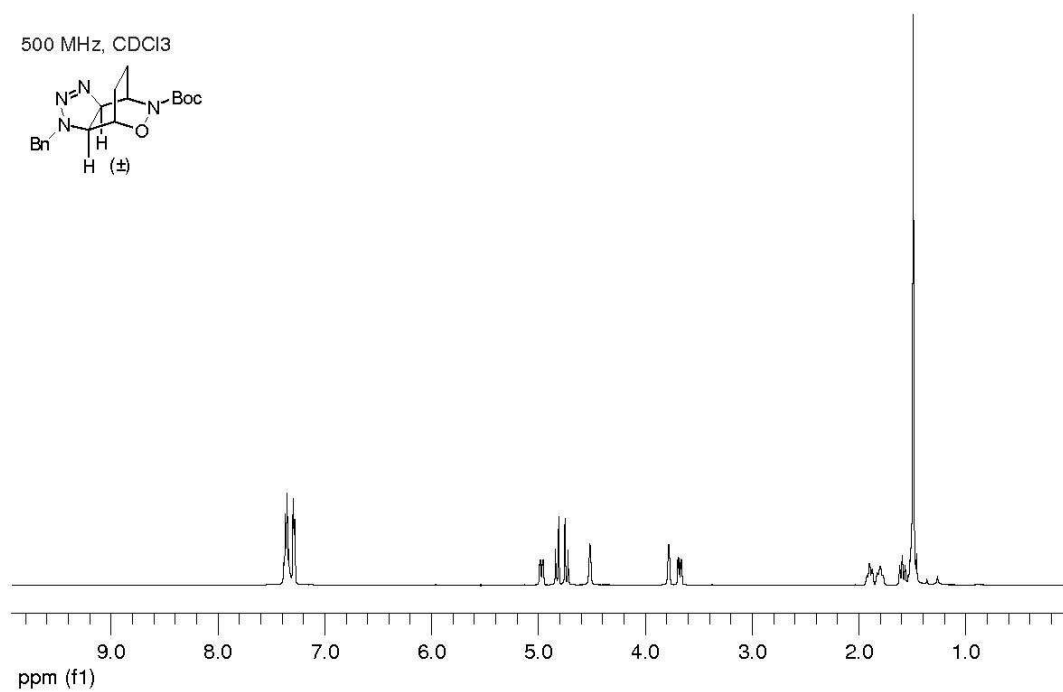
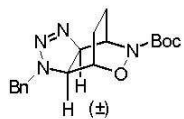


HETCOR NMR spectra for compound **6.11**

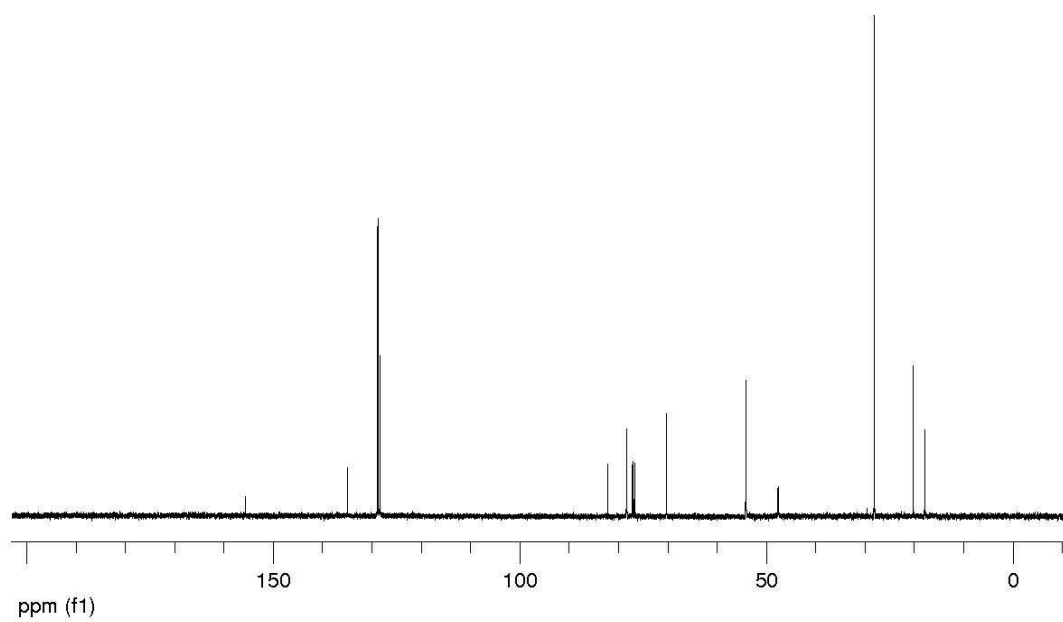


gHMBC NMR spectra for compound **6.11**

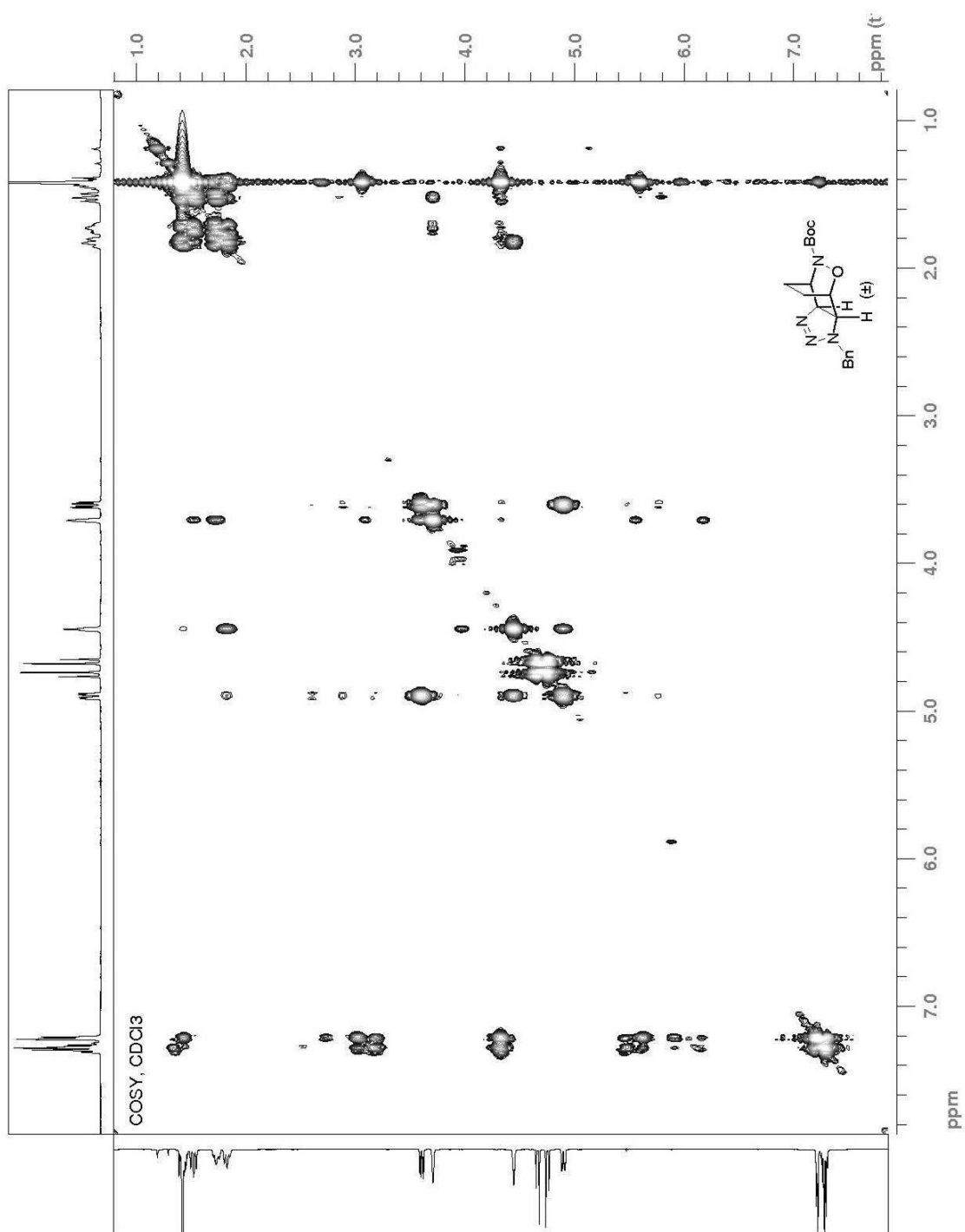
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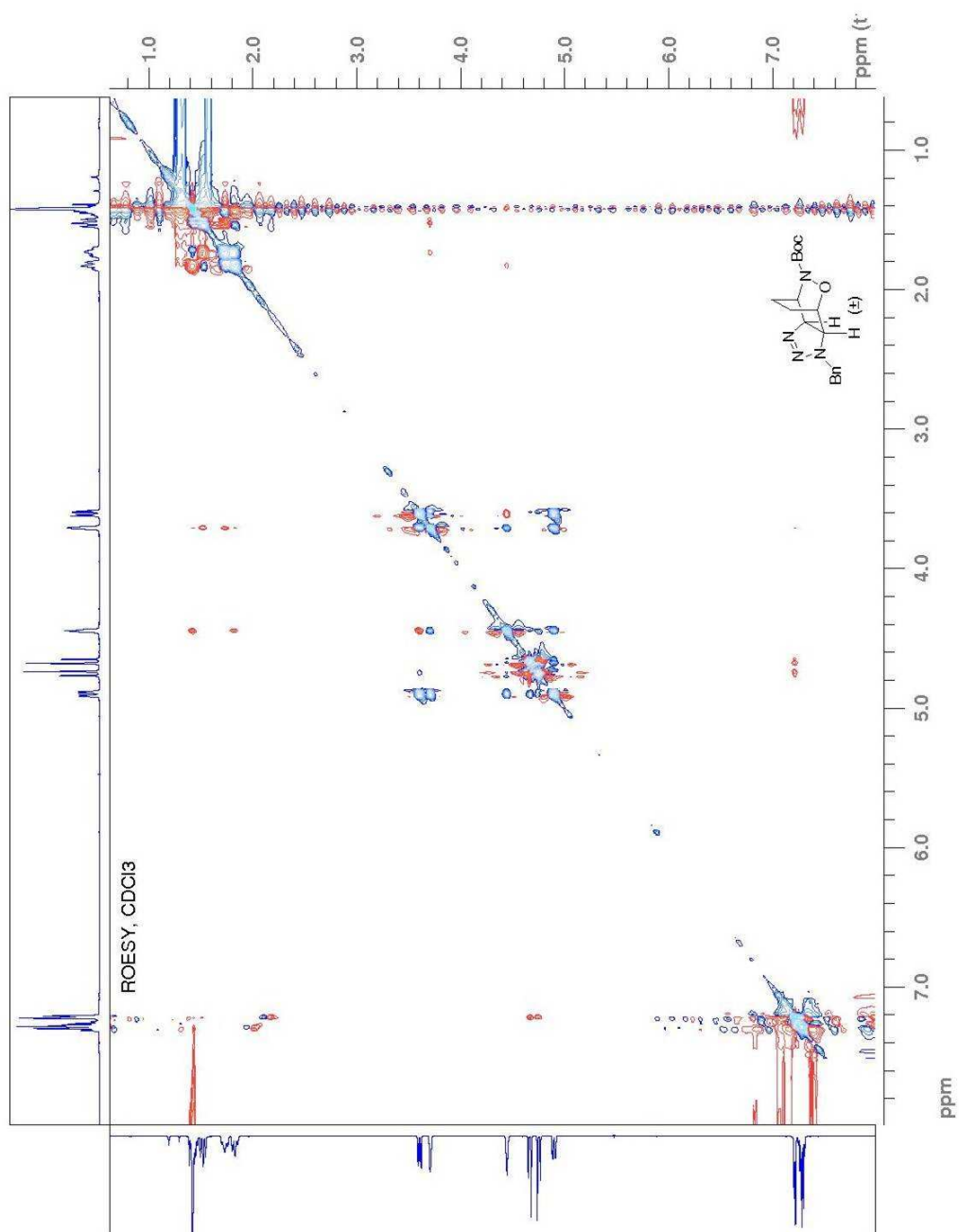
125 MHz, CDCl₃



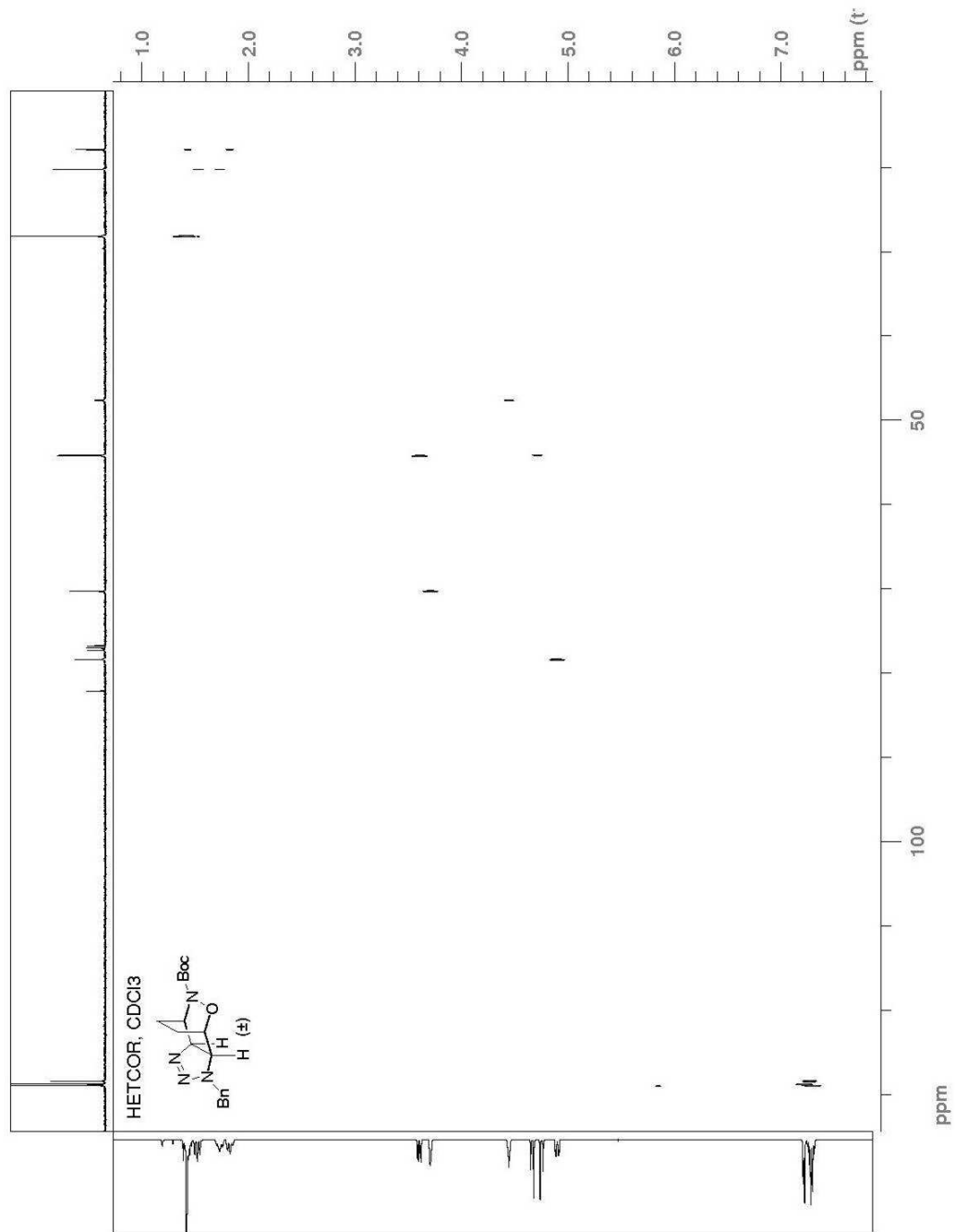
¹H and ¹³C NMR spectra for compound **6.12**



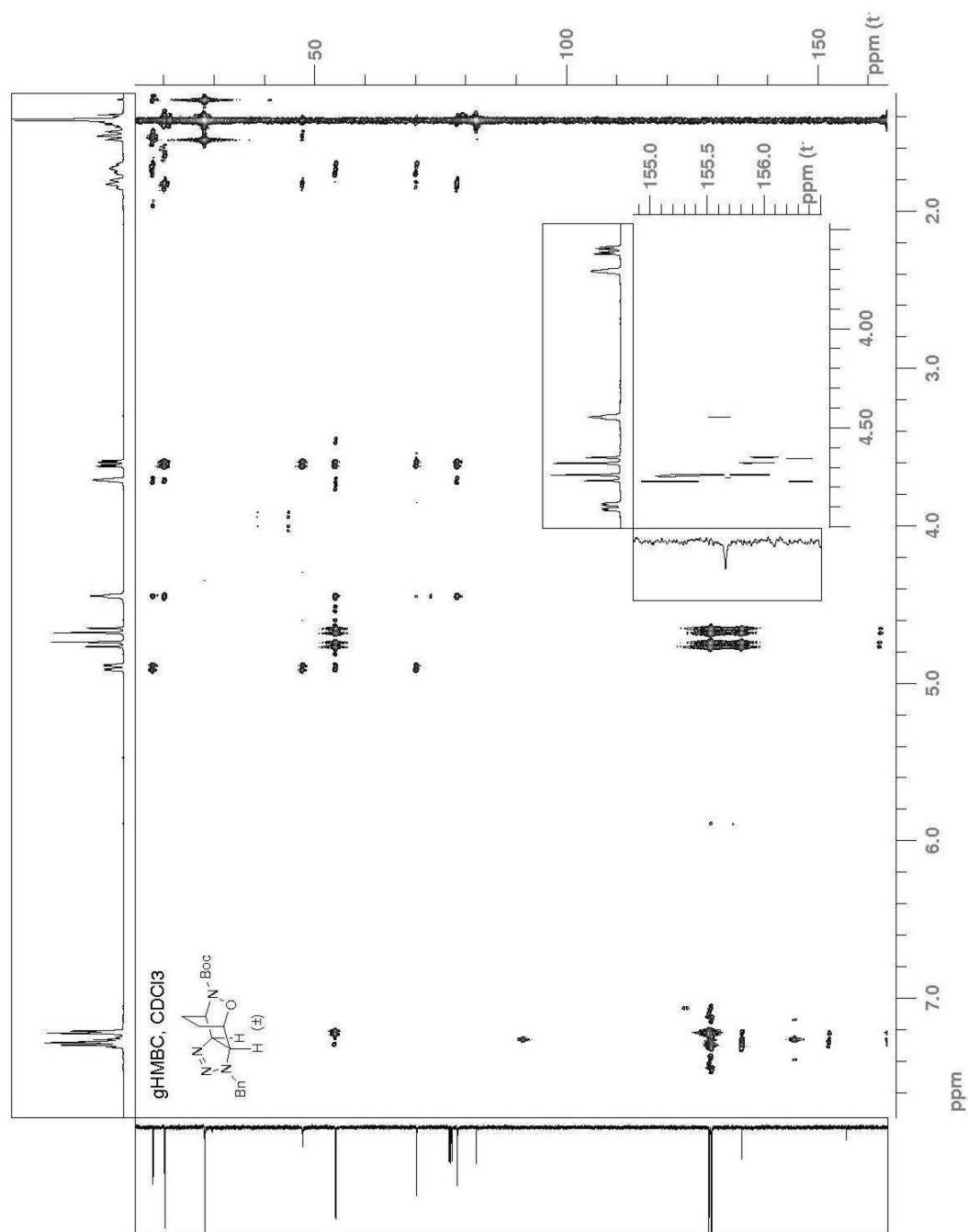
COSY NMR spectra for compound **6.12**



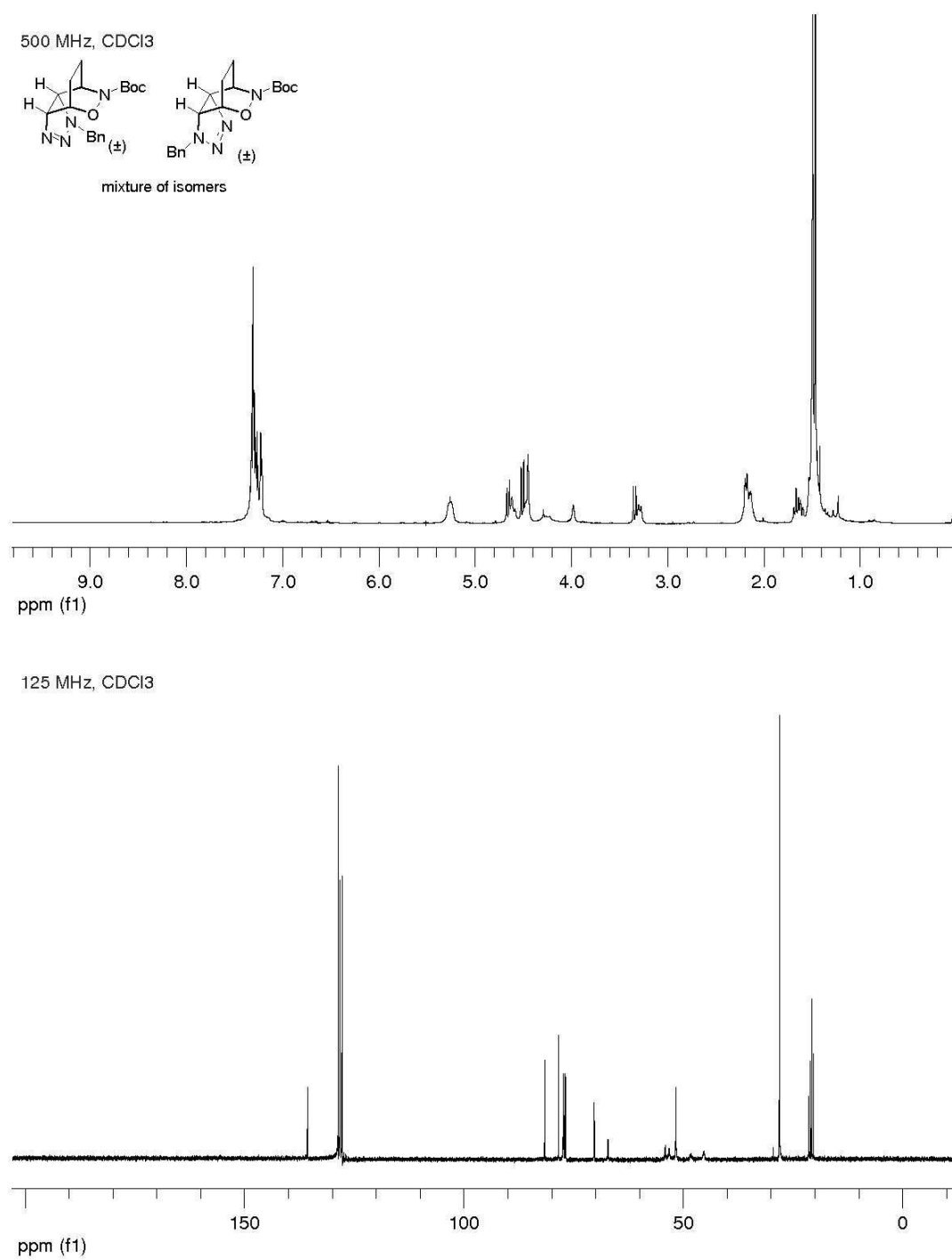
ROESY NMR spectra for compound **6.12**



HETCOR NMR spectra for compound **6.12**

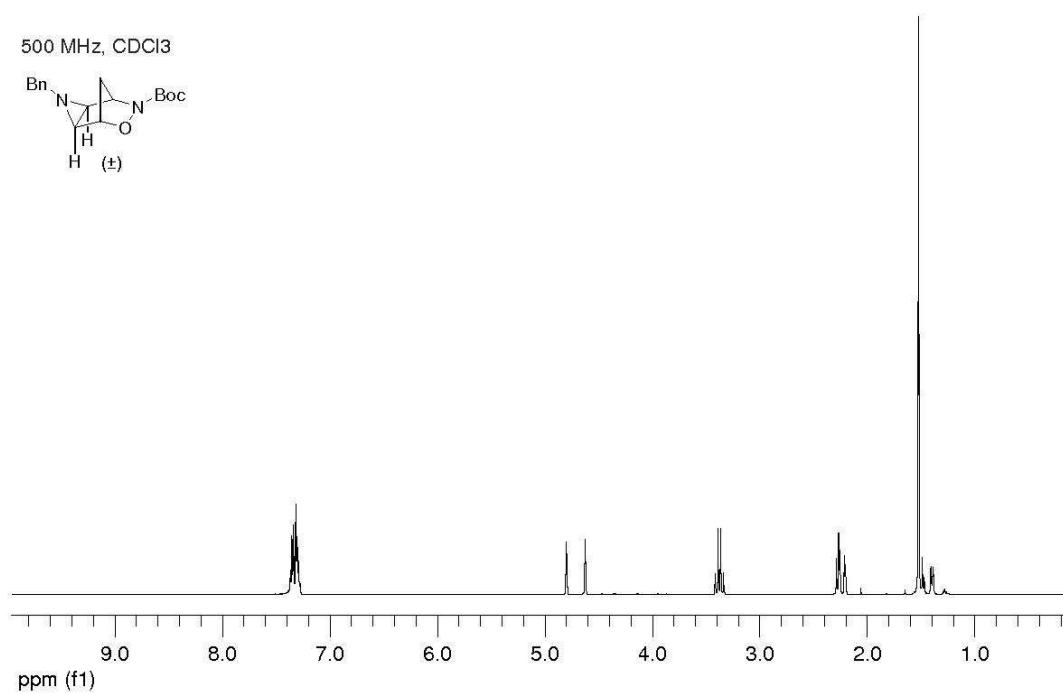
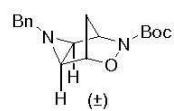


gHMBC NMR spectra for compound **6.12**

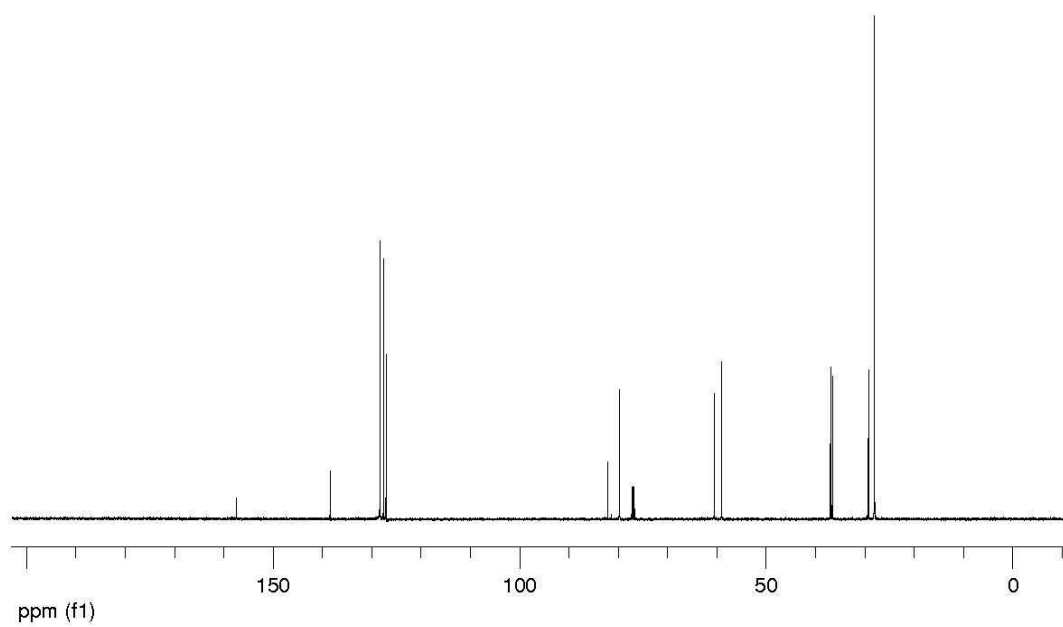


¹H and ¹³C NMR spectra for a mixture of compounds **6.13** and **6.14**

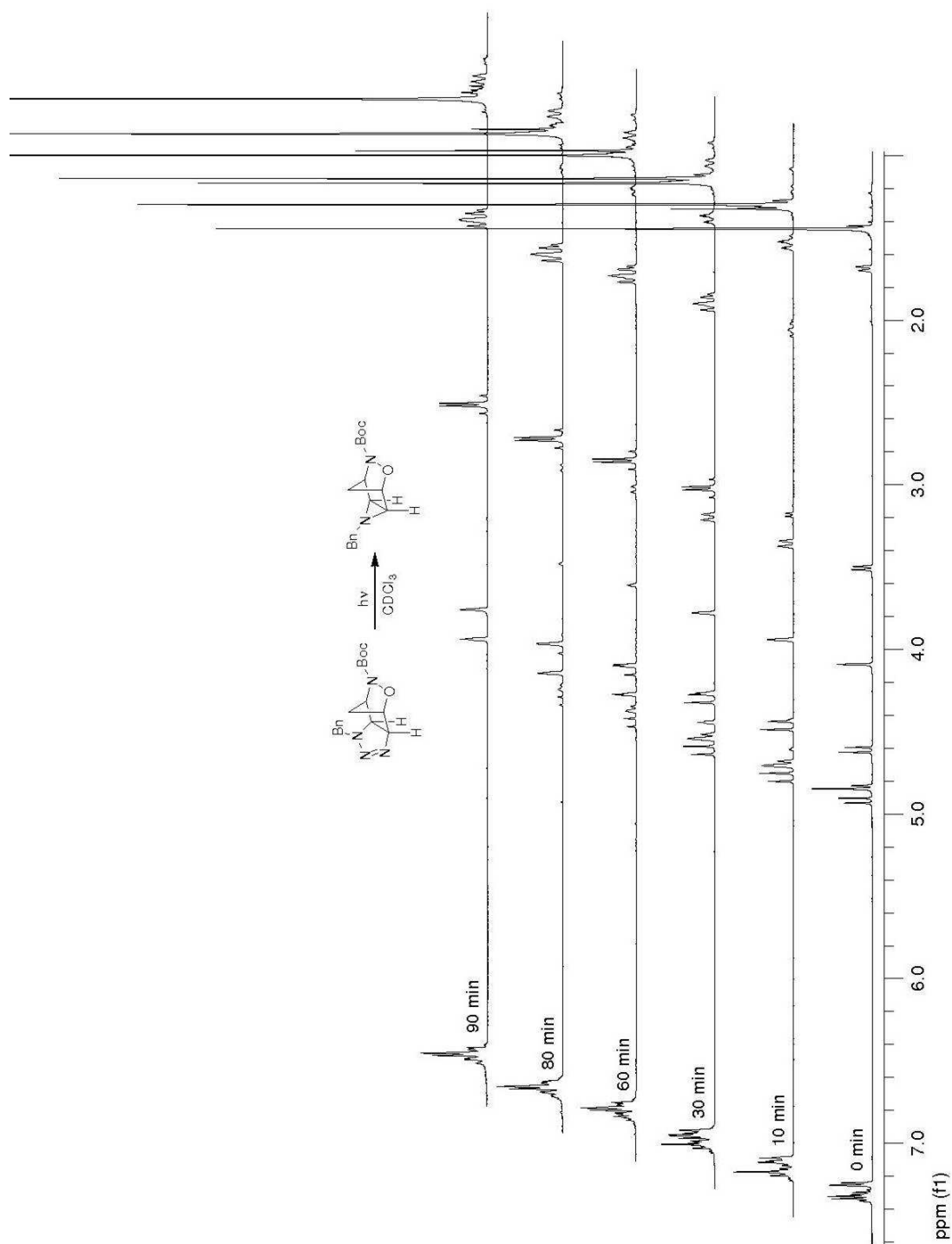
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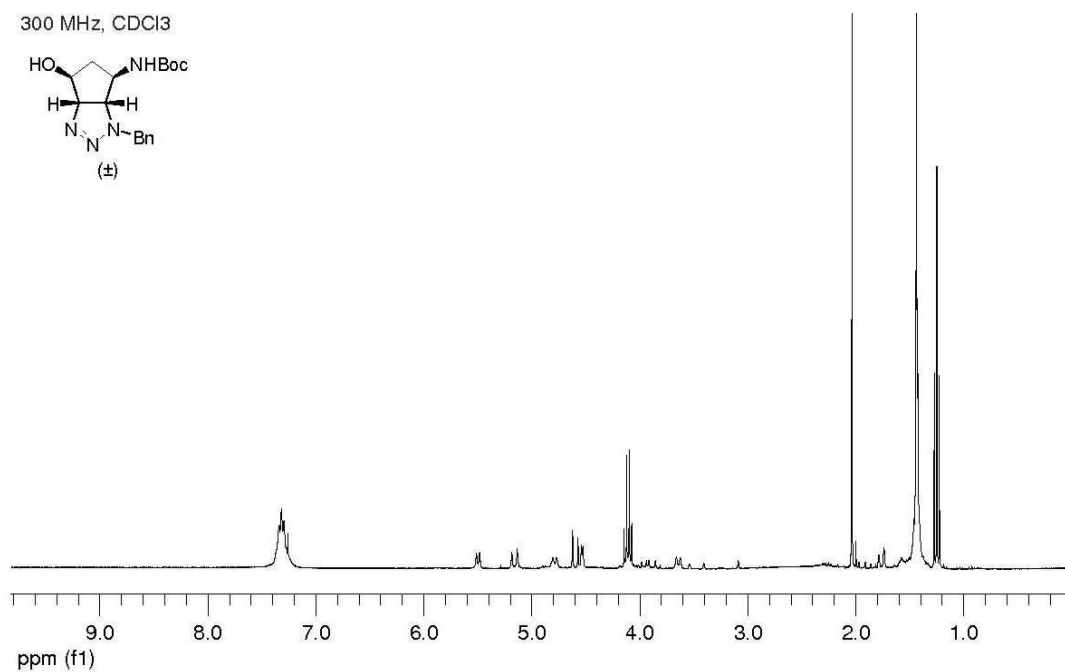
125 MHz, CDCl₃



¹H and ¹³C NMR spectra for compound **6.17**

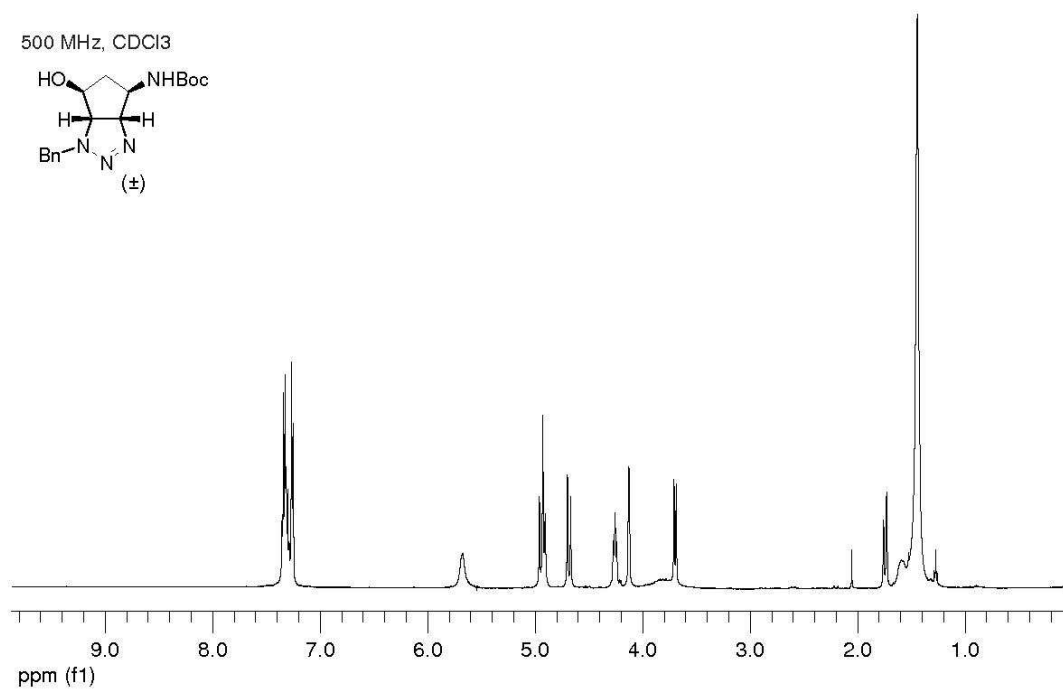
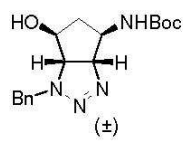


Formation of compound **6.17** monitored by ^1H NMR (CDCl_3 , 300 MHz)

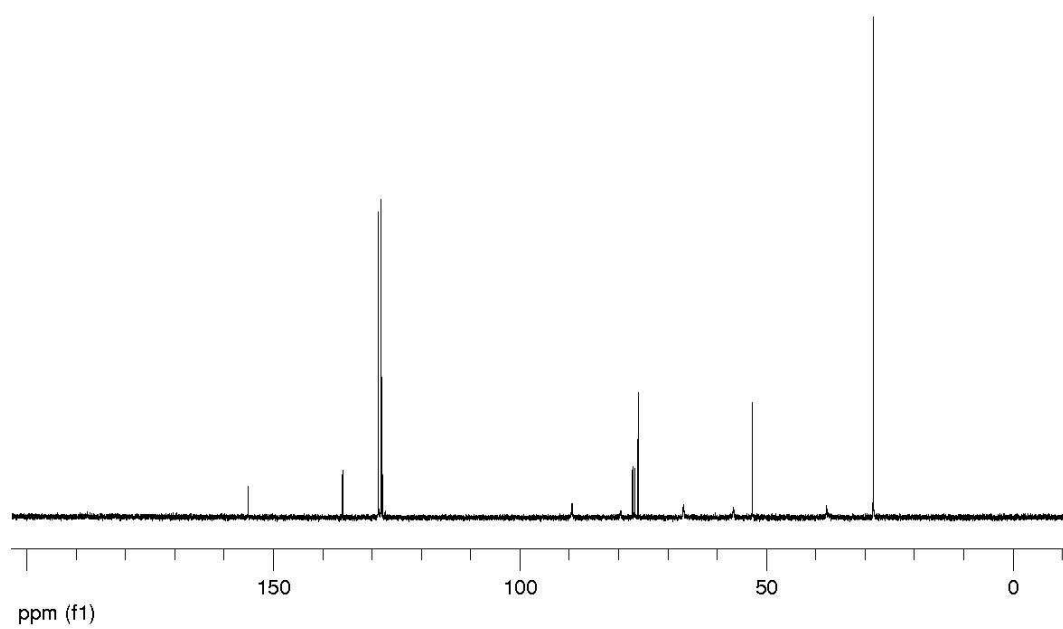


¹H NMR spectra for compound **6.19**

500 MHz, CDCl₃

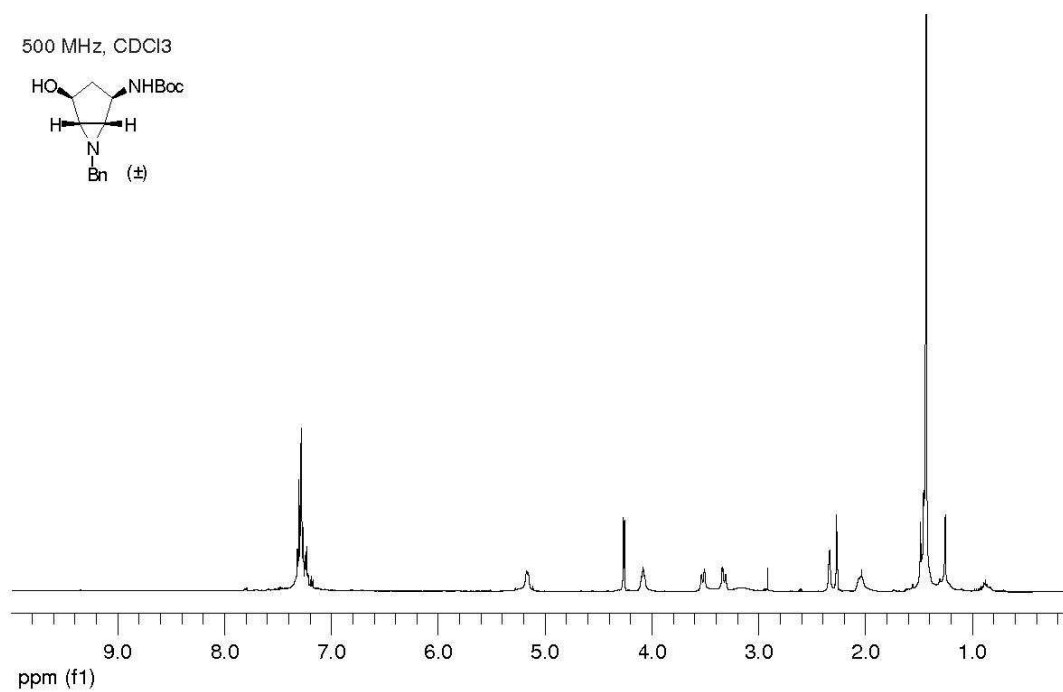
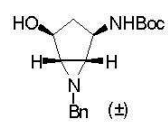


125 MHz, CDCl₃

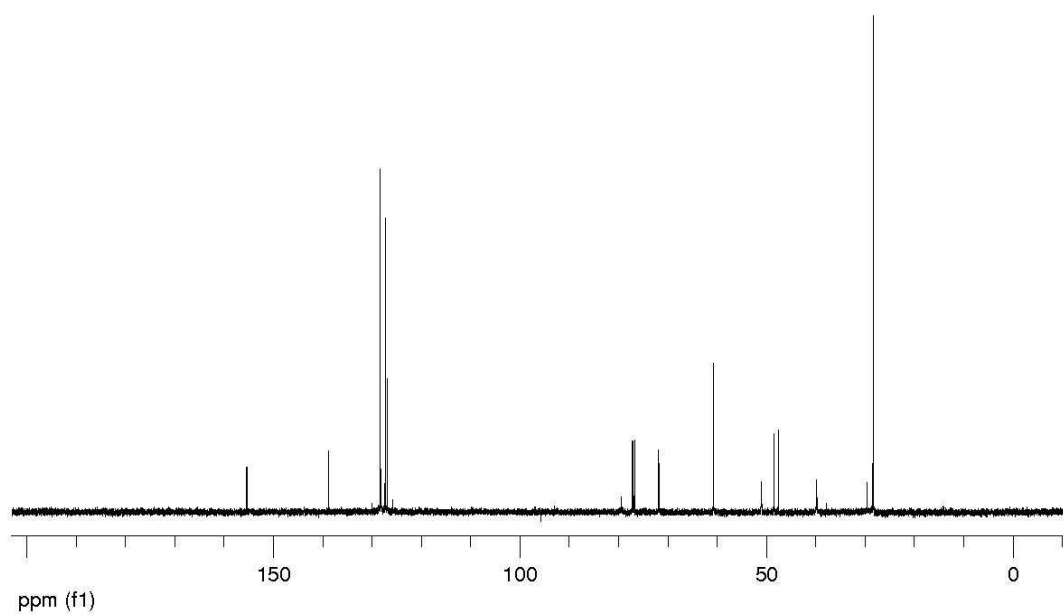


¹H and ¹³C NMR spectra for compound **6.20**

500 MHz, CDCl₃

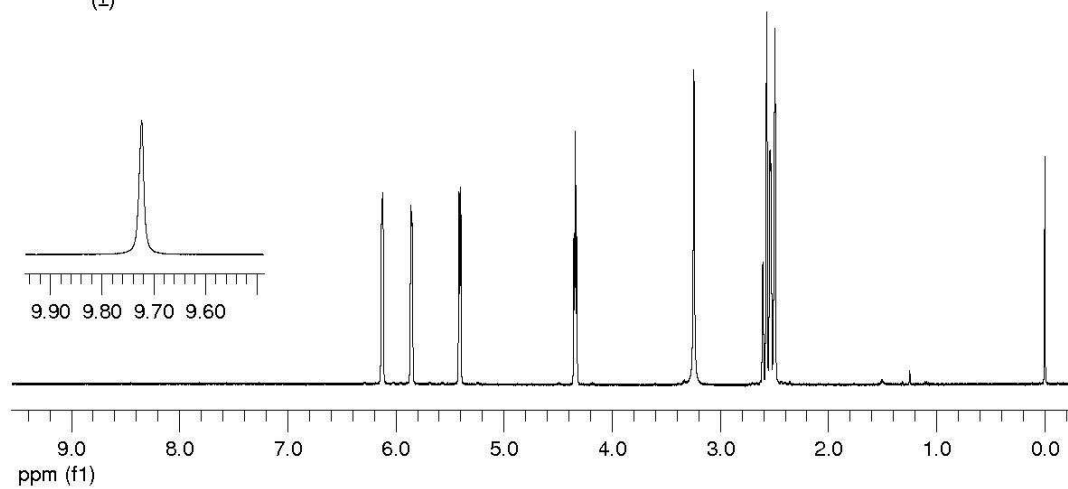
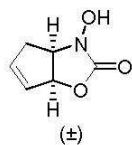


125 MHz, CDCl₃

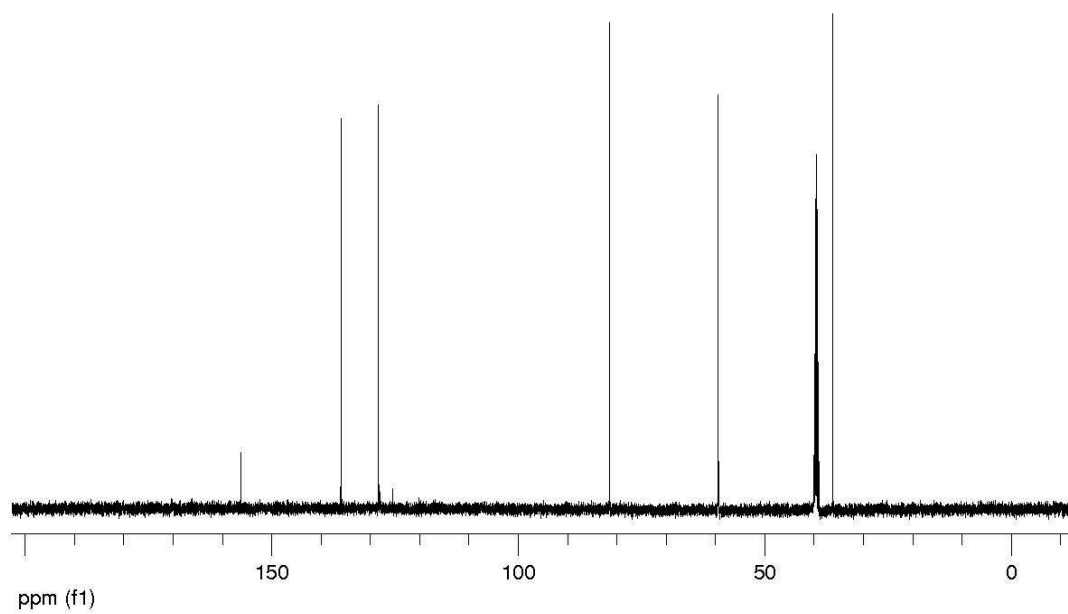


¹H and ¹³C NMR spectra for compound **6.21**

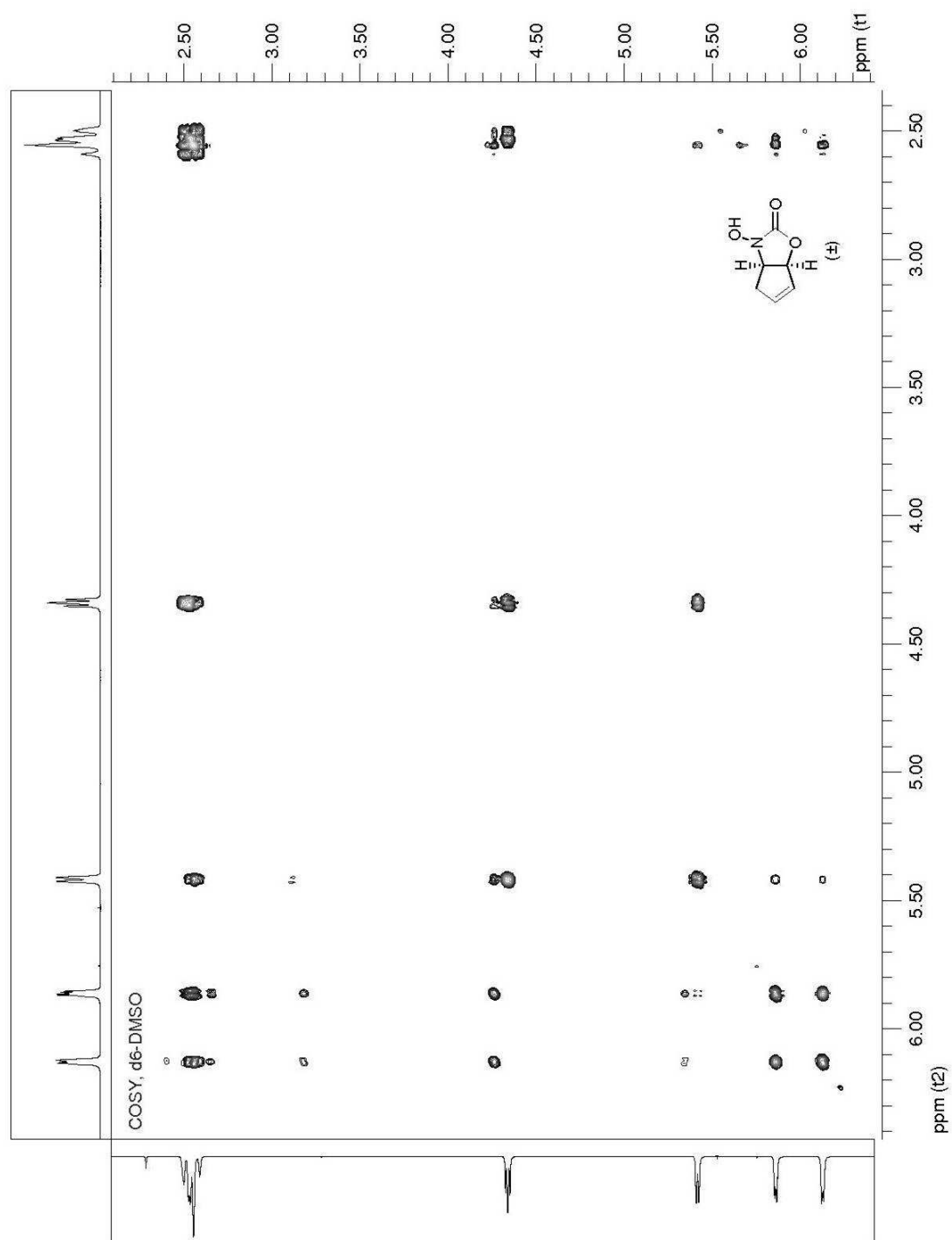
500 MHz, d6-DMSO



125 MHz, d6-DMSO

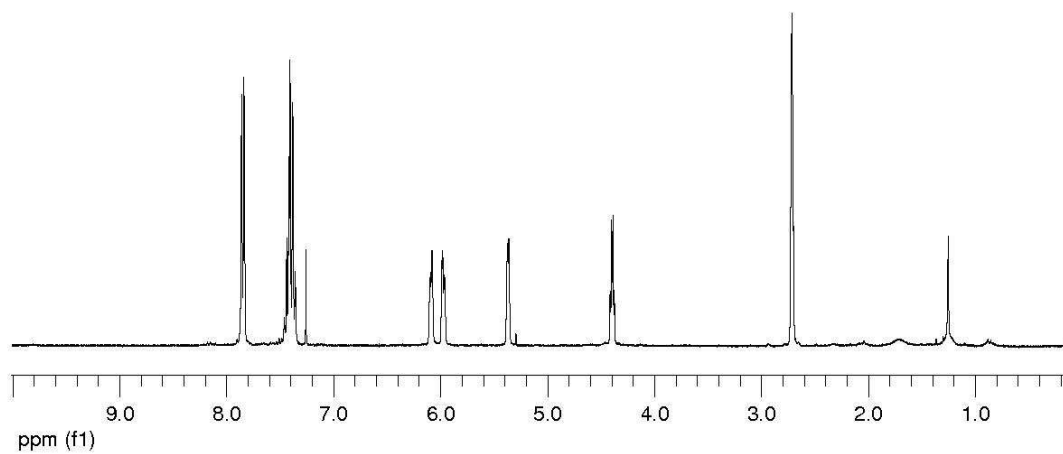
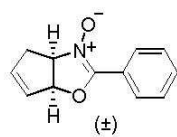


¹H and ¹³C NMR spectra for compound **7.34**

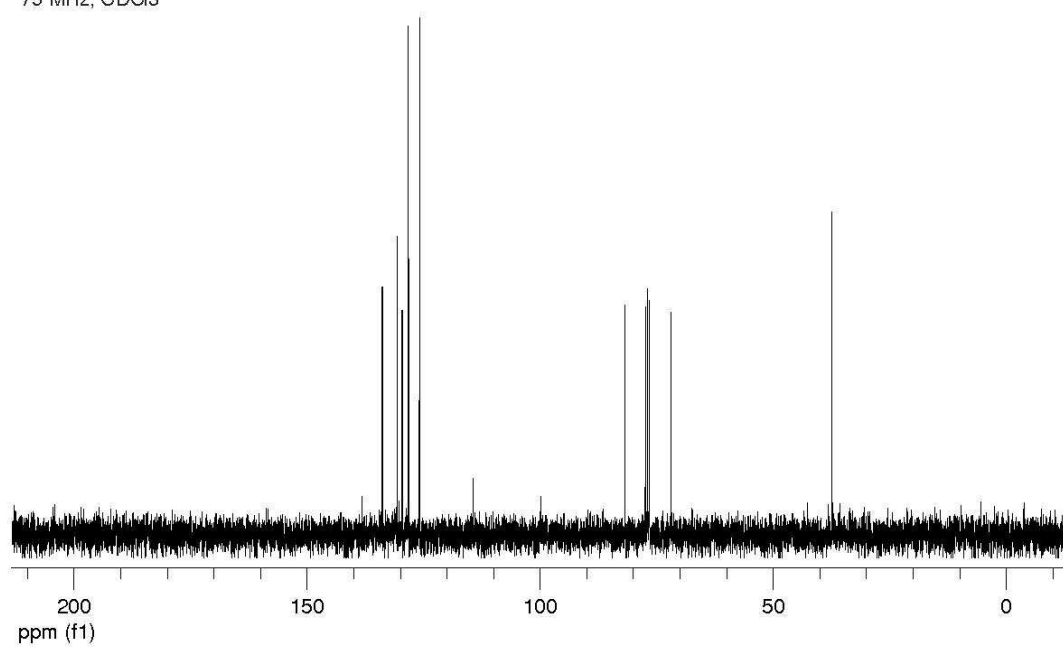


COSY NMR spectra for compound **7.34**

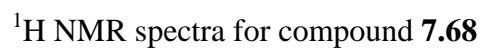
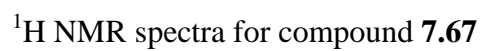
300 MHz, CDCl₃



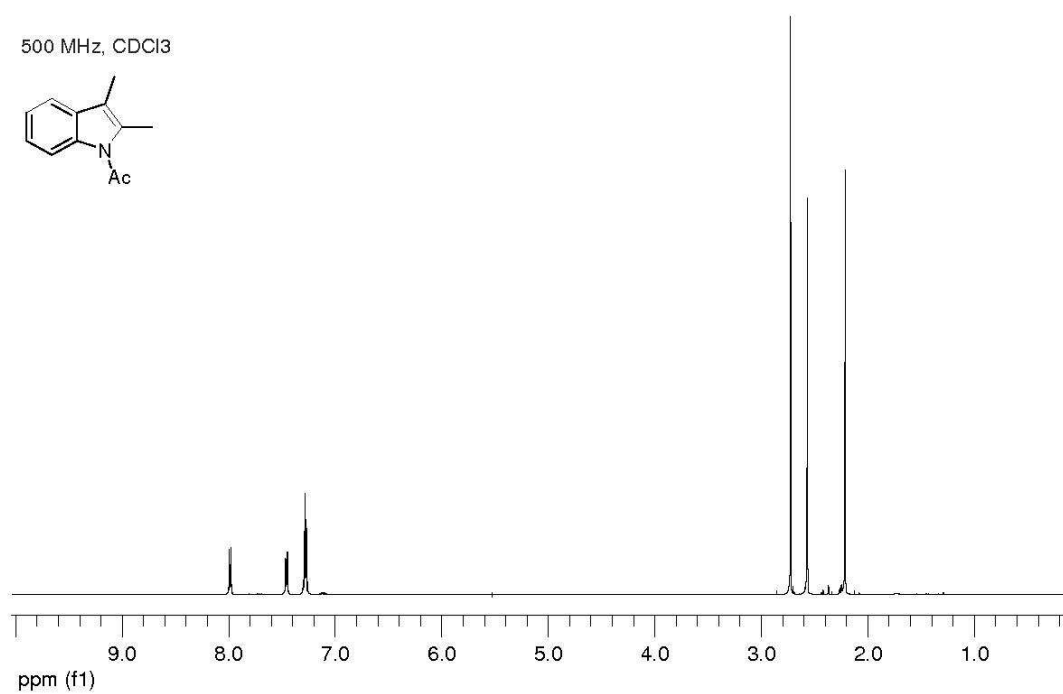
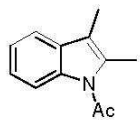
75 MHz, CDCl₃



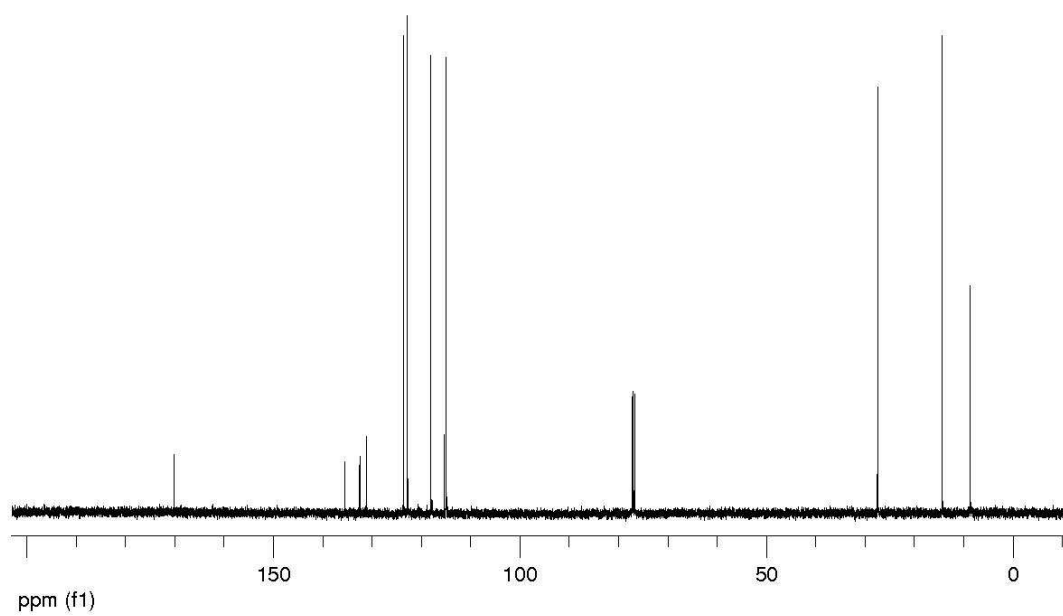
¹H and ¹³C NMR spectra for compound **7.50**



500 MHz, CDCl₃



125 MHz, CDCl₃



¹H and ¹³C NMR spectra for compound **7.82**

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