Dearomative Spirocyclization of Ynamides

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Supporting Information

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1. Materials and Methods

All reactions were carried out in a flame-dried glassware under positive pressure of nitrogen in dry solvents using standard Schlenk techniques unless otherwise indicated. Thin layer chromatography was performed on TLC Silica gel 60 F254 plates. Visualization was accomplished with short wave UV light, and/or iodine, *p*-anisaldehyde, $KMnO_4$, phosphomolybdic acid (PMA), and Hanessian's (cerium ammonium molybdate) stains. Flash chromatography was performed on Apollo Scientific silica gel (40–63 mesh) by standard technique eluting with solvents as indicated.

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker Avance II 400 or Avance II 500 in the indicated solvents. Chemical shifts (δ) are given in ppm relative to TMS. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm). ^{19}F NMR spectra is referenced according to the proton resonance of TMS as the primary reference for the unified chemical shift scale (IUPAC recommendation 2001). High resolution mass spectrometry (HRMS) spectra were obtained on a Bruker miorOTOF-QII instrument, Bruker maXis impact II, and Thermo Fisher Scientific Dionex UltiMate 3000 UPLC-Q Exactive Plus.

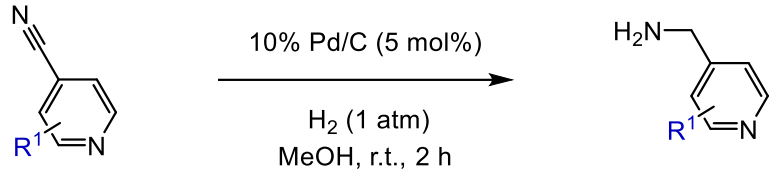
Tetrahydrofuran, diethyl ether, toluene and dichloromethane (HPLC grade, non-stabilized, BioLab) were dried using Innovative Technology PureSolv PS-MD-2 solvent purifier (aluminum oxide columns) and kept under positive pressure of nitrogen (99.9999% purity grade). Methylmagnesium bromide solution in diethyl ether (3.0 M) was purchased from Aldrich and used as received. Other Grignard reagents were prepared according to standard procedure and titrated before use.[1-2] All organometallic compounds, dry solvents and reagents were transferred using plastic single use graduated syringes and oven dried stainless-steel needles. Copper (I) bromide – dimethylsulfide complex, copper(I) iodide, amines, alkynes, and other commercially available chemicals were obtained from BLD pharm, Across Organics, Aldrich Chemical Co., and Alfa Assar.

2. Preparation of Starting Materials

All ynamides were prepared on a multi-gram scale according to a literature procedure for copper-catalyzed C–N bond formation between bromoalkynes and protected 4-(aminoalkyl)pyridines.[3-5] All bromoalkynes were prepared according to a previously published procedure.[3]

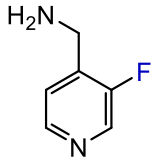
Preparation of 4-(aminomethyl)pyridines

General procedure:



An oven-dried reaction Schlenk flask was charged with 10% Pd/C (5.0 mol%) and cyanide (1.0 equiv.), followed by the addition of MeOH (0.1 M) under air. The flask was purged with H_2 gas three times and then set to a pressure of 1 atm. Upon completion of the reaction (monitored by TLC on silica gel with 5% MeOH in DCM), the reaction mixture was filtered through Celite. The filter cake was washed with ethyl acetate, and the resulting solution was concentrated under reduced pressure. The residue was purified by column chromatography.

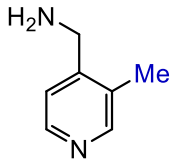
(3-Fluoropyridin-4-yl)methanamine



Following general procedure on 5 mmol scale. Purification via column chromatography with 5% MeOH in DCM. The product was isolated as a brown oil (0.3 g, 2.4 mmol, 48%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 – 8.34 (m, 2H), 7.34 (t, *J* = 5.8, 1H), 3.93 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.8 (d, *J* = 254.7 Hz), 146.0 (d, *J* = 5.1 Hz), 138.5 (d, *J* = 12.6 Hz), 137.5 (d, *J* = 24.0 Hz), 122.9 (d, *J* = 2.2 Hz), 39.2 (d, *J* = 3.6 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -134.0 (d, *J* = 6.4 Hz).

(3-Methylpyridin-4-yl)methanamine



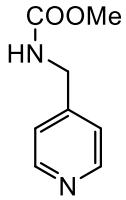
Following general procedure on 3 mmol scale. Purification via column chromatography with 5% MeOH in DCM. The product was isolated as a brown oil (0.16 g, 1.3 mmol, 43%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 5.0 Hz, 1H), 8.33 (q, *J* = 0.7 Hz, 1H), 7.29 (d, *J* = 5.1, 0.9 Hz, 1H), 3.86 (d, *J* = 0.7 Hz, 2H), 2.26 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.4, 149.5, 148.0, 130.6, 120.7, 42.8, 15.6.

Preparation of protected 4-(aminoalkyl)pyridines

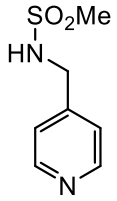
The preparation of methyl (pyridin-4-ylmethyl)carbamate, *N*-(pyridin-4-ylmethyl)methanesulfonamide, methyl ((3-fluoropyridin-4-yl)methyl)carbamate and methyl (2-(pyridin-4-yl)ethyl)carbamate was carried our according to the literature.[4-5]

Methyl (pyridin-4-ylmethyl)carbamate



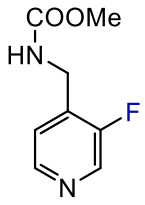
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 – 8.33 (m, 2H), 7.24 – 7.10 (m, 2H), 5.30 (s, 1H), 4.36 (s, 2H), 3.71 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.3, 149.8, 149.7, 148.1, 122.4, 122.0, 52.4, 43.8.

***N*-(Pyridin-4-ylmethyl)methanesulfonamide**



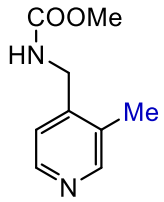
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 – 8.48 (m, 2H), 7.35 – 7.28 (m, 2H), 5.20 (s, 1H), 4.35 (s, 2H), 2.95 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.7, 147.8, 122.3, 46.8, 43.9.

Methyl ((3-fluoropyridin-4-yl)methyl)carbamate



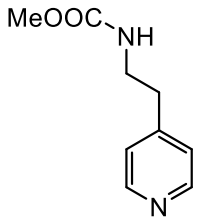
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 1.7 Hz, 1H), 8.40 – 8.36 (m, 1H), 7.34 (t, *J* = 5.7 Hz, 1H), 4.46 (d, *J* = 6.3 Hz, 2H), 3.70 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.7 (d, *J* = 256.6 Hz), 157.0, 145.59 (d, *J* = 5.3 Hz), 135.0 (d, *J* = 12.2 Hz), 123.5, 52.5, 38.1; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -132.7 (d, *J* = 6.4 Hz).

Methyl ((3-methylpyridin-4-yl)methyl)carbamate



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 5.0 Hz, 1H), 8.39 – 8.35 (m, 1H), 7.21 (t, *J* = 5.8 Hz, 1H), 4.37 (d, *J* = 6.0 Hz, 2H), 3.73 (d, *J* = 0.6 Hz, 3H), 2.30 (d, *J* = 2.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.0, 152.0, 150.0, 148.7, 147.2, 121.2, 52.5, 41.9, 15.7.

Methyl (2-(pyridin-4-yl)ethyl)carbamate

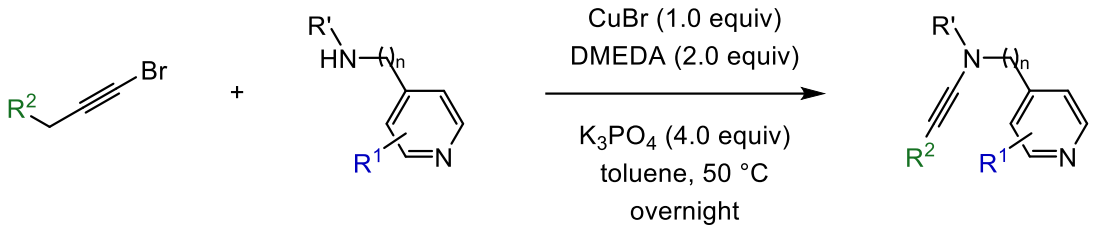


^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (q, *J* = 1.4 Hz, 2H), 7.12 – 7.09 (m, 2H), 4.94 (s, 1H), 3.64 (s, 3H), 3.47 – 3.40 (m, 2H), 2.83 – 2.77 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.9, 149.9, 149.9, 149.8, 124.1, 124.0, 53.8, 35.5, 27.7.

Preparation of Ynamides

The preparation of the following ynamides was carried out according to the literature[6] as follows:

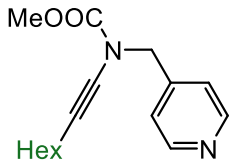
General procedure:



A flame-dried three-necked round-bottomed flask equipped with an inert gas inlet, water condenser and a magnetic stirring bar was connected to a nitrogen line. The protected 4-(aminoalkyl)pyridine (1.5 equiv.), CuBr (1.0 equiv.), DMEDA (2.0 equiv.) and K_3PO_4 (4.0 equiv.) were placed into the flask followed by the addition of the corresponding 1-bromoalkyne (1.2 equiv.) and freshly distilled toluene (0.2 M) as the resulting mixture was heated at 50 °C and was stirred for 16 h. Progress of the reaction was monitored by TLC analysis. Upon the completion, the mixture was cooled to room temperature and filtrated. Filter cake was washed with ethyl acetate, and the solvent were removed on a rotary evaporator. The resulting crude was purified by flash chromatography on silica gel (30-40% ethyl acetate in hexane) to afford the final product.

The following ynamides were prepared:

Methyl oct-1-yn-1-yl(pyridin-4-ylmethyl)carbamate (1a)

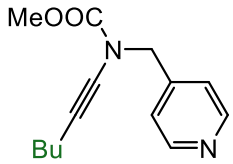


Following general procedure on 10 mmol scale. Purification via column chromatography with 30% ethyl acetate in hexane. The product was isolated as a yellow oil (2.2 g, 8 mmol, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 6.0 Hz, 2H), 7.24 (d, *J* = 6.1 Hz, 2H), 4.61 (s, 2H), 3.83 (s, 3H), 2.24 (t, *J* = 7.0 Hz, 2H), 1.50 – 1.40 (m, 2H), 1.36 – 1.17 (m, 6H), 0.87 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.1, 150.6, 149.9, 145.1, 122.8, 122.6, 73.3, 70.8, 54.2, 52.8, 31.2, 28.7, 28.4, 22.5, 18.3, 14.0.

HRMS (ESI): calculated $[C_{16}H_{22}N_2O_2+H]^+$: 275.1754, found: 275.1741.

Methyl hex-1-yn-1-yl(pyridin-4-ylmethyl)carbamate (1h)

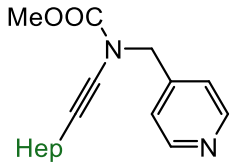


Following general procedure on 5 mmol scale. Purification via column chromatography with 30% ethyl acetate in hexane. The product was isolated as a yellow oil (0.92 g, 3.75 mmol, 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (bs, 2H), 7.28 (d, *J* = 5.0 Hz, 2H), 4.62 (s, 2H), 3.82 (s, 3H), 2.24 (t, *J* = 7.0 Hz, 2H), 1.48 – 1.40 (m, 2H), 1.38 – 1.26 (m, 2H), 0.87 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.1, 151.2, 149.9, 145.1, 122.6, 122.1, 73.3, 70.7, 54.2, 52.8, 30.8, 21.7, 18.0, 13.5.

HRMS (ESI): calculated $[C_{14}H_{18}N_2O_2+H]^+$: 274.1441, found: 274.1441.

Methyl non-1-yn-1-yl(pyridin-4-ylmethyl)carbamate (1j)

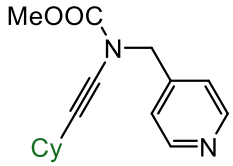


Following general procedure on 5 mmol scale. Purification via column chromatography with 30% ethyl acetate in hexane. The product was isolated as a yellow oil (1.1 g, 3.75 mmol, 78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (bs, 2H), 7.27 (bs, 2H), 4.61 (s, 2H), 3.82 (s, 3H), 2.23 (t, *J* = 7.0 Hz, 2H), 1.51 – 1.39 (m, 2H), 1.30 – 1.19 (m, 8H), 0.91 – 0.83 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.1, 149.9, 145.1, 122.6, 73.3, 70.8, 54.2, 52.8, 31.7, 28.8, 28.7, 28.6, 22.5, 18.3, 14.0.

HRMS (ESI): calculated $[C_{17}H_{24}N_2O_2+H]^+$: 288.1910, found: 288.1895.

Methyl (cyclohexylethynyl)(pyridin-4-ylmethyl)carbamate (1k)

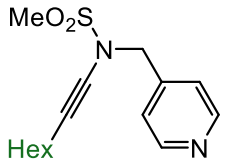


Following general procedure on 5 mmol. Purification via column chromatography with 30% ethyl acetate in hexane. The product was isolated as a yellow oil (0.88 g, 3.25 mmol, 65%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 – 8.55 (m, 2H), 7.30 (d, *J* = 5.1 Hz, 2H), 4.63 (s, 2H), 3.82 (s, 3H), 2.44 (ddt, *J* = 12.7, 8.9, 3.8 Hz, 1H), 1.72 (q, *J* = 8.9, 7.4 Hz, 2H), 1.61 (dq, *J* = 6.2, 3.2 Hz, 2H), 1.51 – 1.41 (m, 1H), 1.38 – 0.95 (m, 5H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.0, 149.9, 145.1, 122.7, 74.8, 73.6, 54.1, 52.8, 32.7, 28.6, 25.8, 24.6.

HRMS (ESI): calculated $[C_{16}H_{20}N_2O_2+H]^+$: 273.1597, found: 273.1600.

***N*-(Oct-1-yn-1-yl)-*N*-(pyridin-4-ylmethyl)methanesulfonamide (1o)**

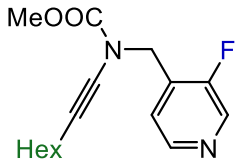


Following general procedure on 5 mmol scale. Purification via column chromatography with 30% ethyl acetate in hexane. The product was isolated as a yellow oil (1.1 g, 3.75 mmol, 76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 5.4 Hz, 2H), 7.32 (d, *J* = 5.5 Hz, 2H), 4.58 (s, 2H), 3.03 (s, 3H), 2.23 (t, *J* = 7.1 Hz, 2H), 1.48 – 1.42 (m, 2H), 1.35 – 1.17 (m, 6H), 0.91 – 0.84 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.2, 143.9, 122.9, 72.4, 71.9, 54.1, 38.3, 31.2, 28.6, 28.4, 22.5, 18.3, 14.0.

HRMS (ESI): calculated $[C_{15}H_{22}N_2O_2S+H]^+$: 295.1474, found: 295.1466.

Methyl ((3-fluoropyridin-4-yl)methyl)(oct-1-yn-1-yl)carbamate (1p)

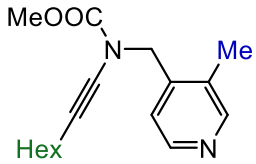


Following general procedure on 1 mmol scale. Purification via column chromatography with 30% ethyl acetate in hexane. The product was isolated as a yellow oil (0.18 g, 0.6 mmol, 60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.39 (d, *J* = 5.0 Hz, 1H), 7.30 (t, *J* = 5.4 Hz, 1H), 4.72 (s, 2H), 3.82 (s, 3H), 2.21 (t, *J* = 7.0 Hz, 2H), 1.47 – 1.31 (m, 2H), 1.35 – 1.11 (m, 6H), 0.93 – 0.66 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.9 (d, *J* = 253.5 Hz), 156.0, 145.8 (d, *J* = 5.3 Hz), 138.0 (d, *J* = 23.6 Hz), 131.9 (d, *J* = 13.2 Hz), 123.4, 72.8, 70.8, 54.3, 46.8, 31.2, 28.7, 28.3, 22.5, 18.3, 14.0; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -132.39.

HRMS (ESI): calculated $[C_{16}H_{21}FN_2O_2+H]^+$: 293.1659, found: 293.1653.

Methyl ((3-methylpyridin-4-yl)methyl)(oct-1-yn-1-yl)carbamate (1q)



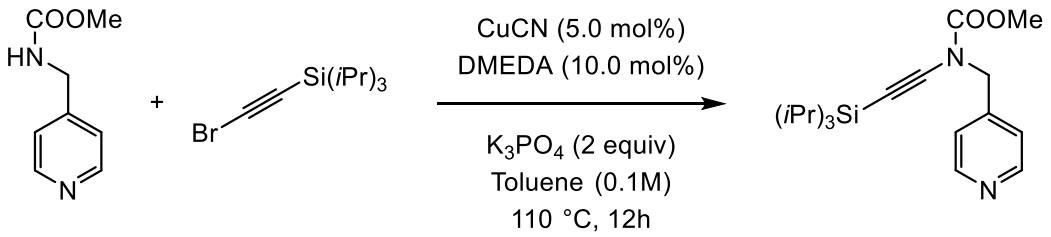
Following general procedure on 1 mmol scale. Purification via column chromatography with 30% ethyl acetate in hexane. The product was isolated as a yellow oil (0.155 g, 0.54 mmol, 54%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 5.1 Hz, 1H), 8.40 (s, 1H), 7.20 (d, *J* = 5.0 Hz, 1H), 4.62 (s, 2H), 3.82 (s, 3H), 2.31 (s, 3H), 2.20 (t, *J* = 7.1, 2H), 1.46 – 1.38 (m, 2H), 1.33 – 1.16 (m, 6H), 0.88 – 0.83 (t, *J* = 7.14 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.1, 150.5, 147.5, 143.3, 131.3, 122.0, 102.1, 73.3, 70.8, 54.2, 50.6, 31.2, 28.7, 28.4, 22.5, 18.3, 15.91, 14.0.

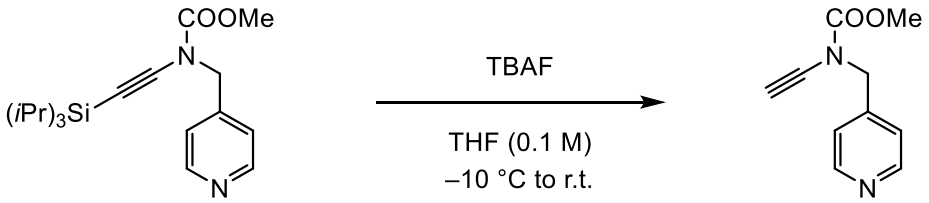
HRMS (ESI): calculated $[C_{17}H_{24}N_2O_2+H]^+$: 289.1910, found: 289.1905.

Preparation of other ynamides

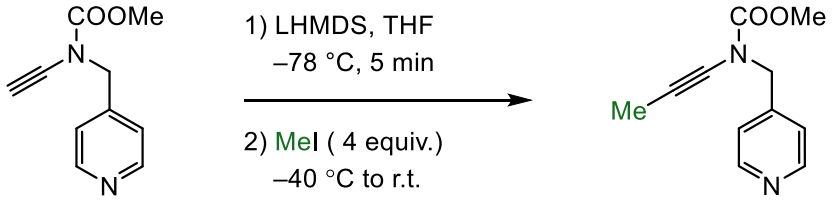
Methyl prop-1-yn-1-yl(pyridin-4-ylmethyl)carbamate (1g)



Following a modified literature procedure,[7] to a flame-dried three-necked round-bottomed flask equipped with an inert gas inlet, water condenser and a magnetic stirring bar was connected to a nitrogen line, methyl (pyridin-4-ylmethyl)carbamate (2.1 g, 8.0 mmol), K_3PO_4 (3.41 g, 10.0 mmol), and CuCN (35.0 mg, 0.4 mmol, 5.0 mol%) were added. TIPS-protected bromo acetylene (1.34 g, 8 mmol) was then added in a solution of anhydrous toluene (80 ml, 0.1 M) followed by the addition of *N,N*-dimethylethylenediamine (70 mg, 0.08 mmol). The reaction mixture was heated using oil bath at 100 °C for 12 h. Upon the completion of the reaction (monitored by TLC with 3% MeOH in DCM), the crude was filtered through a small bed of silica gel and concentrated under vacuum. Purification of the residue by silica gel chromatography (20% of ethyl acetate in hexane) afforded methyl (pyridin-4-ylmethyl)((triisopropylsilyl)ethynyl)carbamate (1.66 g, 4.8 mmol, 60%).



A solution of methyl (pyridin-4-ylmethyl)((triisopropylsilyl)ethynyl)carbamate (1.55 g, 4.5 mmol) in anhydrous THF (45 ml) was cooled to –10 °C under nitrogen. Then, TBAF (9 ml, 9.0 mmol, 1.0 M in THF) was added, and the reaction mixture was stirred at the indicated temperature for 5 min. After warming to room temperature, the reaction was quenched with saturated solution of NH_4Cl (8 ml). The crude mixture was extracted with diethyl ether (3 x 20ml), dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography (70% ethyl acetate in hexane) afforded methyl ethynyl(pyridin-4-ylmethyl)carbamate (0.427 g 2.25 mmol, 50%).

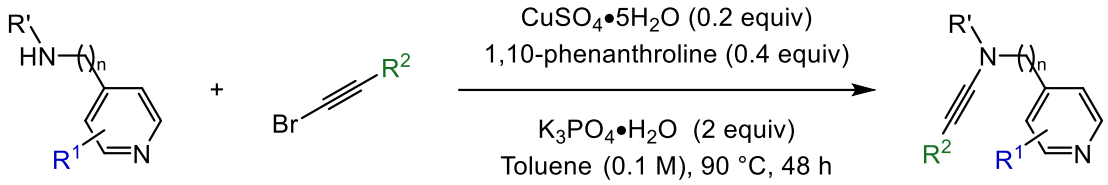


A solution of methyl ethynyl(pyridin-4-ylmethyl)carbamate (0.38 g, 2 mmol) in anhydrous THF (20 ml) was cooled to –78 °C using a dry ice/acetone bath. Then, a solution of LiHMDS (3 ml, 3 mmol, 1 M in THF) was added dropwise over 5 min at the indicated temperature. The reaction mixture was then allowed to warm slowly to -40 °C and stirred for 1 h. Then, a THF solution (2 ml) of MeI (0.5 ml, 1.12 g, 8 mmol) was added dropwise over 15 min, and the mixture was slowly warmed to room temperature. The reaction was then quenched with a saturated solution of NH_4Cl, extracted with diethyl ether (3 x 20 ml), dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography (60% ethyl acetate in hexane) afforded the title compound as a yellow oil (0.155 g, 0.76 mmol, 38%). The product was present as a 1.6:1 mixture of amide bond rotamers. The signals of both rotamers are listed.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (bs, 5H), 7.40 – 7.30 (m, 5H), 4.72 (s, 1.2H), 4.65 (s, 2H), 3.90 (s, 2H), 3.88 (s, 3H), 2.00 (s, 2.4H), 1.96 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.6, 149.6, 149.4, 149.4, 122.9, 121.2, 71.7, 71.0, 54.0, 53.8, 53.6, 2.8, 2.7.

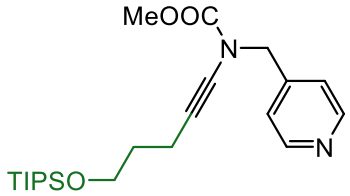
HRMS (ESI): calculated $[C_{11}H_{12}N_2O_2+H]^+$: 205.0971, found: 205.0971.

Methyl alkynyl (pyridin-4-ylethyl)carbamate derivatives



Following a modified literature procedure,[8] a slurry of carbamate (5.0 mmol 1.0 equiv.), 1-bromooct-1-yne (1.12 g, 6 mmol), $CuSO_4 \cdot 5H_2O$ (250 mg, 1 mmol), 1,10-phenanthroline monohydrate (0.36 g, 2 mmol), and $K_3PO_4 \cdot H_2O$ (2.3 g, 10 mmol) in toluene (60 mL) was stirred at 90 °C for 48 h. The mixture was cooled to room temperature, diluted with DCM and filtered through silica, washed with DCM, concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel with 30% ethyl acetate in hexane.

Methyl (pyridin-4-ylmethyl)(5-((triisopropylsilyl)oxy)pent-1-yn-1-yl)carbamate (1m)

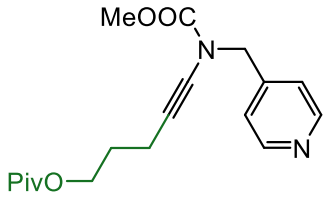


Following general procedure on 2 mmol scale. Purification via column chromatography with 30% ethyl acetate in hexane. The product was isolated as a yellow oil (0.444 g, 1.1 mmol, 55%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, *J* = 6.1 Hz, 1H), 8.57 (d, *J* = 6.14 Hz, 1H), 7.53 (d, *J* = 6.05 Hz, 1H), 7.23 (d, *J* = 5.31 Hz, 2H), 4.60 (s, 2H), 3.81 (s, 3H), 3.69 (t, *J* = 6.1 Hz, 2H), 2.36 (t, *J* = 7.0 Hz, 2H), 1.71 – 1.61 (m, 2H), 1.09 – 0.9 (m, 3H), 1.03 (s, 18H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.8, 150.0, 145.1, 125.2, 122.5, 120.4, 70.4, 61.7, 54.2, 52.8, 32.1, 18.0, 14.8, 11.9.

HRMS (ESI): calculated $[C_{22}H_{36}N_2O_3Si+H]^+$: 405.2568, found: 405.2556.

5-((Methoxycarbonyl)(pyridin-4-ylmethyl)amino)pent-4-yn-1-yl pivalate (1n)

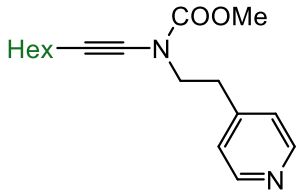


Following general procedure on 2 mmol scale. Purification via column chromatography with 30% ethyl acetate in hexane. The product was isolated as a yellow oil (0.378 g, 1.14 mmol, 57%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 6.1 Hz, 2H), 7.22 (d, *J* = 6.1 Hz, 2H), 4.59 (t, *J* = 0.8 Hz, 2H), 4.09 (q, *J* = 7.3 Hz, 2H), 3.81 (s, 3H), 2.33 (t, *J* = 7.1 Hz, 2H), 1.77 (m, 2H), 1.16 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.4, 156.0, 150.0, 144.9, 142.9, 122.5, 74.0, 69.1, 62.8, 60.3, 54.2, 38.7, 27.9, 27.1, 15.1.

HRMS (ESI): calculated $[C_{18}H_{24}N_2O_4+H]^+$: 333.1808, found: 333.1814.

Methyl oct-1-yn-1-yl(2-(pyridin-4-yl)ethyl)carbamate (1w)

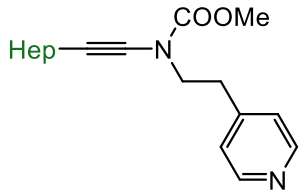


Following general procedure on 5 mmol scale. Purification via column chromatography with 30% ethyl acetate in hexane. The product was isolated as a yellow oil (0.576 g, 2.0 mmol, 40%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 5.2 Hz, 2H), 7.17 (d, *J* = 4.4 Hz, 2H), 3.76 – 3.70 (m, 5H), 2.89 (t, *J* = 7.35 Hz, 2H), 2.28 (t, *J* = 7.1 Hz, 2H), 1.48 – 1.41 (m, 2H), 1.37 – 1.28 (m, 2H), 1.27 – 1.21 (m, 4H), 0.83 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.1, 149.9, 147.4, 124.4, 54.0, 50.0, 33.4, 31.4, 29.1, 28.6, 22.7, 18.5, 14.1.

HRMS (ESI): calculated $[C_{17}H_{24}N_2O_2+H]^+$: 289.1910, found: 289.1898.

Methyl non-1-yn-1-yl(2-(pyridin-4-yl)ethyl)carbamate (1z)

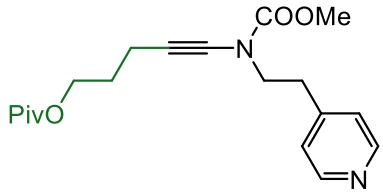


Following general procedure on 2 mmol scale. Purification via column chromatography with 30% ethyl acetate in hexane. The product was isolated as a yellow oil (0.217 g, 0.72 mmol, 36%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.4 Hz, 2H), 7.15 (bs, 2H), 3.80 – 3.65 (m, 5H), 2.95 (t, *J* = 6.9, 2.0 Hz, 2H), 2.28 (t, *J* = 7.1 Hz, 1H), 1.50 (p, *J* = 7.1 Hz, 2H), 1.43 – 1.34 (m, 2H), 1.29 (m, 8H), 0.92 – 0.82 (m, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.9, 149.7, 147.2, 124.4, 73.0, 70.9, 54.0, 49.8, 33.3, 31.7, 28.9, 28.8, 28.7, 22.6, 18.4, 14.0.

HRMS (ESI): calculated $[C_{17}H_{26}N_2O_2+H]^+$: 303.2067, found: 303.2055.

5-((Methoxycarbonyl)(2-(pyridin-4-yl)ethyl)amino)pent-4-yn-1-yl pivalate (1aa)



Following general procedure on 2 mmol scale. Purification via column chromatography with 30% ethyl acetate in hexane. The product was isolated as a yellow oil (0.228 g, 0.66 mmol, 33%).

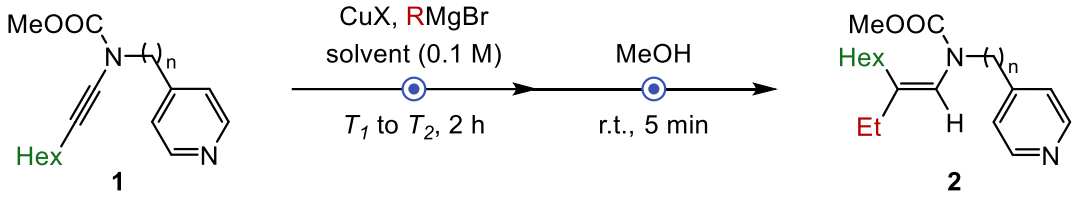
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 – 8.43 (m, 2H), 7.17 – 7.10 (m, 2H), 4.13 (t, *J* = 6.3 Hz, 2H), 3.75 – 3.64 (m, 5H), 2.93 (t, *J* = 7.4 Hz, 2H), 2.37 (t, *J* = 7.1 Hz, 2H), 1.86 – 1.78 (m, 2H), 1.19 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.4, 155.8, 149.7, 147.1, 124.2, 73.8, 69.1, 62.9, 60.3, 53.96, 38.7, 33.3, 28.0, 27.1, 15.2.

HRMS (ESI): calculated $[C_{19}H_{26}N_2O_4+H]^+$: 347.1965, found: 347.1952.

3. Reaction Optimization

Carbometalation reaction

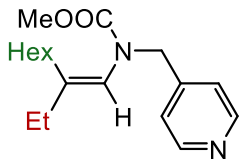
General procedure:



An oven-dried reaction vessel (10 mL screw-cap vial) equipped with a stirring bar was allowed to cool to room temperature under vacuum. Then, copper source and methyl ynamide **1** (0.2 mmol) were added under air. The vessel was then depressurized and pressurized with nitrogen gas three times, followed by addition of dry solvent (2 ml, 0.1 M). After cooling the solution to the indicated temperature, a solution of EtMgBr (2M in diethyl ether) was added dropwise keeping the indicated temperature. The resulting solution was stirred for 5 min then allowed to warm to room temperature. Stirring was continued for 2 h at the indicated temperature (monitored by TLC on silica gel). After quenching the reaction by the addition of MeOH, the solution was concentrated under reduced pressure. NMR yield was calculated using dibromomethane as internal standard. Further purification of the crude via column chromatography (0-40% ethyl acetate in hexane) afforded the desired product.

The following products were isolated using the optimized reaction conditions:

Methyl (*Z*)-(2-ethyloct-1-en-1-yl)(pyridin-4-ylmethyl)carbamate (2a)



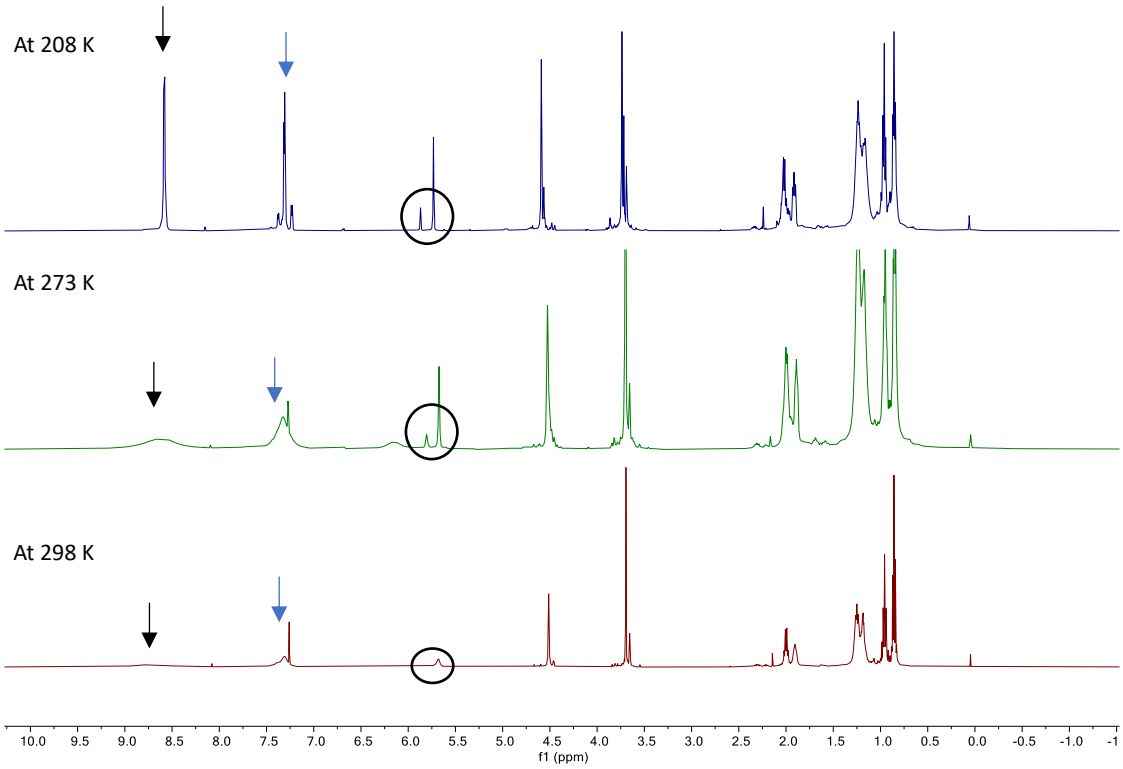
Following the general procedure on 0.2 mmol scale. The product was isolated as a brown oil (47 mg, 0.156 mmol, 79%, *single isomer*).

Due to broadening in the NMR spectra at room temperature caused by fast amide bond rotation, we could not locate both the aromatic and alkynyl peaks in ^{1}H and ^{13}C NMR. Therefore, we conducted NMR experiments at different low temperatures. Clear spectra were obtained at 208 K (Supplementary Fig. 1). However, a ~3.5:1 mixture of amide bond rotamers was observed. In this case, only the peaks of the major rotamer are listed.

^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ 8.69 (bs, 2H), 7.33 (bs, 2H), 5.67 (s, 1H), 4.29 (s, 2H), 3.71 (s, 3H), 2.01 (q, J = 7.3 Hz, 2H), 1.90 (bs, 2H), 1.35 – 1.09 (m, 8H), 0.97 (t, J = 7.4 Hz, 3H), 0.87 (t, J = 7.0 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.0, 143.4, 121.1, 53.9, 53.1, 31.8, 29.8, 29.6, 26.9, 26.2, 22.7, 14.1, 12.7.

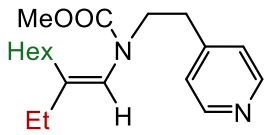
^{1}H NMR (500 MHz, $CDCl_3$, 208 K) δ 8.58 (d, J = 5.7 Hz, 2H), 7.31 (d, J = 6.0 Hz, 2H), 5.73 (s, 1H), 4.59 (s, 2H), 3.74 (s, 3H), 2.02 – 1.93 (m, 2H), 1.91 (t, J = 7.9 Hz, 2H), 1.29 – 1.10 (m, 8H, overlaps with another rotamer), 0.96 (t, J = 7.4 Hz, 3H), 0.86 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.8, 148.2, 143.5, 123.01, 122.2, 120.0, 53.5, 52.2, 31.7, 29.5, 28.7, 26.6, 25.6, 22.7, 14.4, 12.3.

HRMS (ESI): calculated $[C_{18}H_{28}N_2O_2+H]^+$: 305.2223, found: 305.2218.



Supplementary Figure 1. ^{1}H NMR experiments for **2a** at different temperatures. Slow amide bond rotation is observed at lower temperatures.

Methyl (*Z*)-(2-ethyloct-1-en-1-yl)(2-(pyridin-4-yl)ethyl)carbamate (2w)



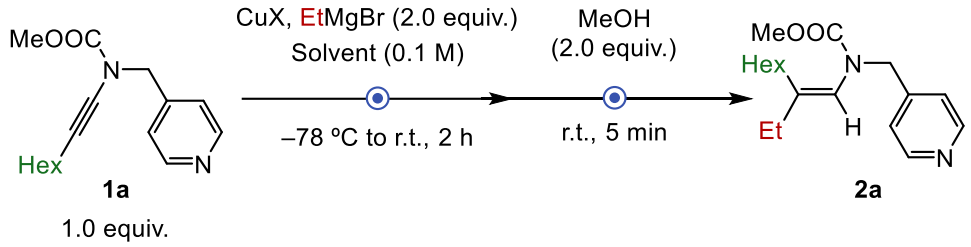
Following the general procedure on 0.2 mmol scale. The product was isolated as a yellow oil (42 mg, 0.134 mmol, 67%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (bs, 2H), 7.06 (bs, 2H), 5.60 (s, 1H), 3.65 (s, 3H), 3.60 (t, *J* = 7.6, 2H), 2.83 (t, *J* = 7.7 Hz, 2H), 2.02 (q, *J* = 7.9 Hz, 2H), 1.94 (t, *J* = 7.9 Hz, 2H), 1.40 – 1.19 (m, 8H), 0.99 (t, *J* = 7.6 Hz, 3H), 0.86 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.4, 149.7, 148.2, 142.7, 124.2, 121.1, 52.6, 50.0, 33.5, 31.6, 29.5, 29.1, 26.8, 26.1, 22.5, 14.0, 12.6.

HRMS (ESI): calculated $[C_{19}H_{30}N_2O_2+H]^+$: 319.2380, found: 319.2366.

Screening various reaction conditions

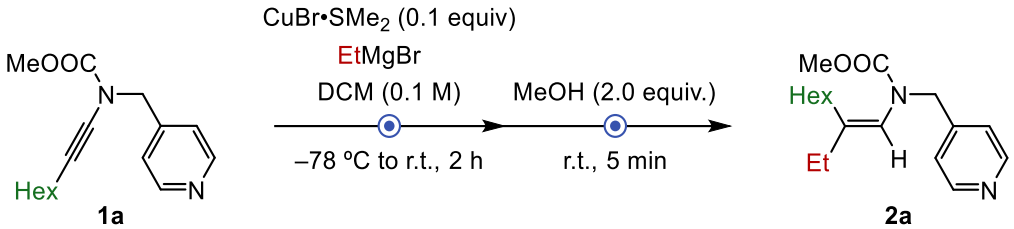
Table S1. Evaluation of copper salts and solvents.



Entry	CuX (equiv.)	Solvent	Yield of **2a** (%)[a]
1	CuI (0.1)	Et_2O	40
2	CuI (0.2)	Et_2O	35
3	CuBr•SMe_2 (0.1)	Et_2O	51
4	CuI (0.1.)	THF	38
5	CuI (0.1)	Toluene	33
6	CuBr•SMe_2 (0.1)	THF	48
7	CuBr•SMe_2 (0.1)	Toluene	43
8[b]	CuBr•SMe_2 (0.1)	DCM	64[c]
9	**CuBr•SMe_2 (0.1)**	**DCM**	**79 (75)[c]**
10	CuI (0.1)	DCM	30
11	CuBr (0.1)	DCM	33
12	CuBr•SMe_2 (2.0)	DCM	60

Reactions were performed under N_2 with 0.2 mmol of **2a**. [a]NMR yields were determined by using CH_2Br_2 as internal standard. [b]PhMgBr was used instead of EtMgBr. [c]Isolated yield.

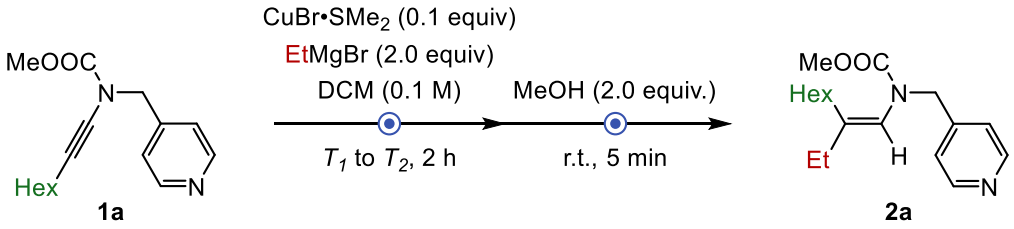
Table S2. Evaluation of the amount of Grignard reagent.



Entry	EtMgBr (equiv.)	Yield of **2a** (%)[a]
1	1.0	14
2	1.5	45
3	**2.0**	**79**
4	3.0	60

Reactions were performed under N_2 with 0.2 mmol of **2a**. [a]NMR yields were determined by using CH_2Br_2 as internal standard.

Table S3. Evaluation of reaction temperature.

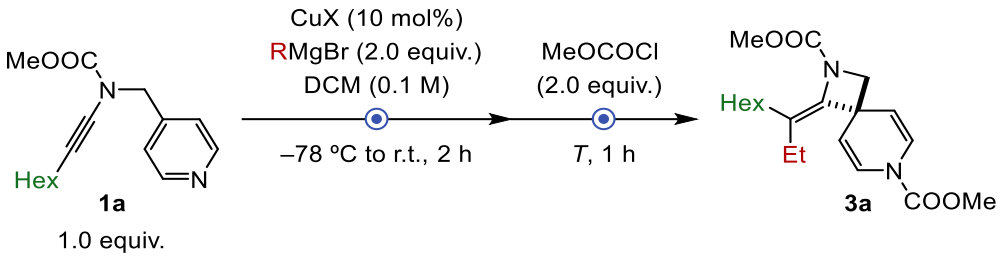


Entry	T_1 (°C)	T_2 (°C)	Yield of **2a** (%)[a]
1	0	0	56
2	**–78**	**r.t.**	**79**
2	–50	–50	n.d.
3	–78	–78	n.d.

Reactions were performed under N_2 with 0.2 mmol of **2a**. [a]NMR yields were determined by using CH_2Br_2 as internal standard.

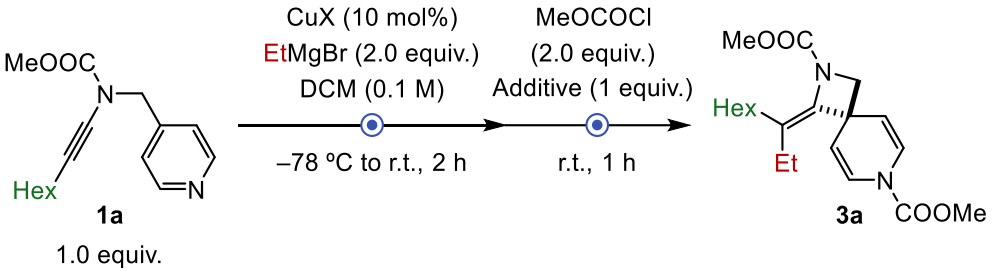
Carbometalation-dearomatization reaction

General procedure:



An oven dried Schlenk flask equipped with a stirring bar was allowed to cool to room temperature under vacuum. CuX (10% mmol), and methyl oct-1-yn-1-yl(pyridin-4-ylmethyl)carbamate **1a** (55.0 mg , 0.2 mmol, 1.0 equiv.) were added under air. The vessel was then depressurized and pressurized with nitrogen three times, followed by addition of dry solvent (0.1 M, 2.0 ml). The solution was cooled to –78 °C using dry ice/acetone bath. Then, a solution of RMgBr (2.0 equiv., in diethyl ether) was added dropwise at –78 °C. The resulting solution was stirred for 5 min then allowed to warm to room temperature. Stirring was continued for 2 h at the indicated temperature. Upon the completion of the reaction, methyl chloroformate (0.4 mmol, 2.0 equiv.) was added dropwise at the indicated temperature. After stirring for 1 h, the solution concentrated under reduced pressure. NMR yield was calculated using dibromomethane as internal standard. Further purification of the crude via column chromatography (0-10% ethyl acetate in hexane) afforded the desired product.

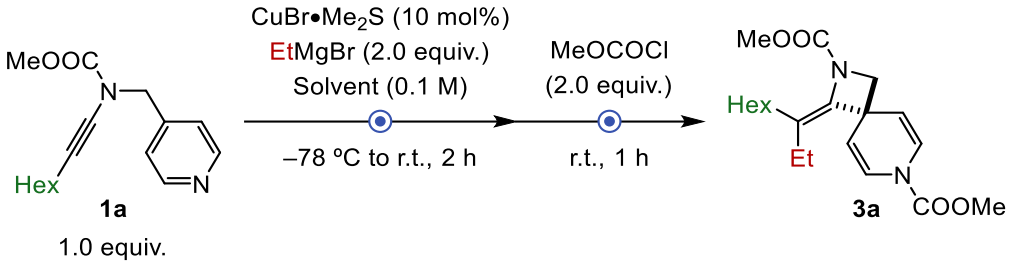
Table S4. Evaluation of copper salts and additive.



Entry	CuX (equiv.)	Additive (1equiv.)	Yield of **3a** (%)[a]
1	**CuBr•SMe$_2$ (0.1)**	**-**	**72 (68)[b]**
2	CuI (0.1)	-	30
3	CuBr	-	33
4	CuBr•SMe$_2$ (2.0)	-	60
5	CuBr•SMe$_2$ (0.1)	DMPU	48
6	CuBr•SMe$_2$ (0.1)	TMEDA	60

Reactions were performed under N_2 with 0.2 mmol of **3a**. [a]NMR yields were determined by using CH_2Br_2 as internal standard. [b]Isolated yield.

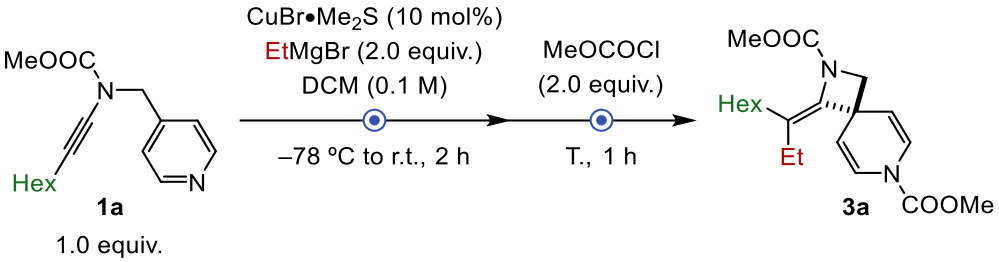
Table S5. Evaluation of solvents.



Entry	Solvent	Yield of **3a** (%)[a]
1	**DCM**	**72**
2	Toluene	43
3	THF	48

Reactions were performed under N_2 with 0.2 mmol of **3**. [a]NMR yields were determined by using CH_2Br_2 as internal standard.

Table S6. Evaluation of different reaction temperature.

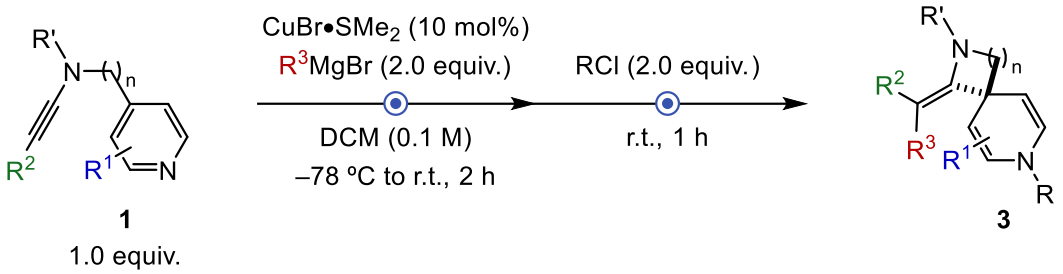


Entry	T (°C)	Yield of **3a** (%)[a]
1	**rt**	**72**
2	–78 °C	26
3	0 °C	65

Reactions were performed under N_2 with 0.2 mmol of **3a**. [a]NMR yields were determined by using CH_2Br_2 as internal standard.

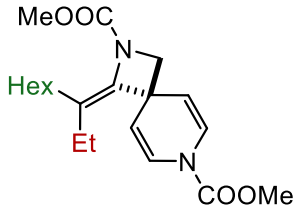
4. The Dearomative Spirocyclization Products

General procedure:



An oven dried Schlenk flask equipped with a stirring bar was allowed to cool to room temperature under vacuum. CuBr•Me_2S complex (10.0 mol%), and ynamide (1.0 equiv.) were added under air. The vessel was then depressurized and pressurized with nitrogen three times, followed by addition of dry DCM (0.1 M). The solution was cooled to –78 °C using dry ice/acetone bath. A solution of RMgBr (2.0 equiv., in diethyl ether) was added dropwise keeping the indicated temperature. The resulting solution was stirred for 5 min then allowed to warm to room temperature. Stirring was continued for 2 h at the indicated temperature (monitored by TLC on silica gel using 30% ethyl acetate in hexane as eluent). Upon completion of the first step, the acylating agents (2.0 equiv.) was added dropwise to reaction mixture. Stirring was continued for 1 h at the indicated temperature (monitored by TLC on silica gel using 30% ethyl acetate in hexane as eluent). Upon the completion of second step, the resulting solution was concentrated under reduced pressure, and the residue was purified by column chromatography (5-10% ethyl acetate in hexane unless otherwise indicated) to afford the final product.

Dimethyl (*Z*)-1-(decan-3-ylidene)-2,7-diazaspiro[3.5]nona-5,8-diene-2,7-dicarboxylate (3a)



Following the general procedure on 0.5 mmol scale. Purification via column chromatography with 5% ethyl acetate in hexane. The product was isolated as a yellow oil (121 mg, 0.33 mmol, 68%). The product was present as a 1:1 mixture of amide bond rotamers. The signals of both rotamers are listed in ^{13}C NMR.

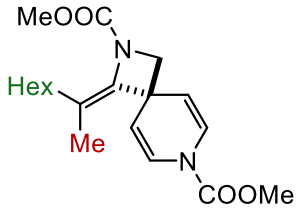
For gram scale reaction (1.00 g, 3.6 mmol), the product was isolated as a as a yellow oil (939.3 mg, 2.6 mmol, 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (bs, 1H), 6.79 (bs, 1H), 5.09 (bs, 1H), 5.02 (bs, 1H), 3.82 (s, 3H), 3.68 (s, 3H), 3.66 (s, 2H), 2.34 (d, J = 15.0 Hz, 2H), 2.00 – 1.84 (m, 2H), 1.36 – 1.15 (m, 8H), 0.92 – 0.81 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.1, 153.0, 151.6, 151.6, 141.9, 141.8, 122.6, 122.3, 109.8, 109.4, 64.7, 53.6, 53.6, 52.3, 52.3, 42.2, 42.2, 31.9, 31.6, 29.5, 29.3, 28.9, 28.5, 28.4, 27.4, 22.6, 22.6, 22.6, 22.5, 20.9, 14.1, 14.0, 14.0, 13.2, 13.2.

IR ν = 2960 (w), 2931 (w), 2858 (w), 1717 (s), 1685 (s), 1440 (s), 1370 (m) 1318 (s), 1366 (w), 1212 (m) 1192 (m), 1125 (w), 1015 (w), 961 (m), 760 (s).

HRMS (ESI): calculated $[C_{20}H_{30}N_2O_4+H]^+$: 363.2278, found: 363.2272.

Dimethyl (*Z*)-1-(3-oxooctan-2-ylidene)-2,7-diazaspiro[3.5]nona-5,8-diene-2,7-dicarboxylate (3b)



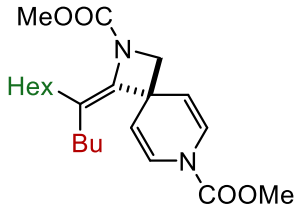
Following the general procedure on 0.5 mmol scale. Purification via column chromatography with 5% ethyl acetate in hexane. The product was isolated as a yellow oil (85.2 mg, 0.24 mmol, 49%). The product was present as a 1:1 mixture of amide bond rotamers. The signals of both rotamers are listed in ^{13}C NMR.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (bs, 1H), 6.81 (bs, 1H), 5.08 (bs, 1H), 5.01 (bs, 1H), 3.83 (s, 3H), 3.69 (s, 2H), 3.69 (s, 3H), 2.33 (t, *J* = 7.7 Hz, 2H), 1.50 (s, 3H), 1.37 (q, *J* = 7.0 Hz, 2H), 1.32 – 1.20 (m, 6H), 0.90 – 0.83 (m, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) 153.1, 151.6, 141.3, 122.8, 122.5, 116.3, 109.2, 108.8, 64.6, 53.6, 52.3, 42.1, 32.7, 31.9, 31.5, 29.2, 28.1, 22.6, 22.6, 14.5, 14.1, 14.0.

IR ν = 2955 (w), 2923 (w), 2853 (w), 1734 (s), 1717 (s), 1700 (s), 1684 (s), 1653 (w), 1441 (s), 1362 (m), 1338 (s), 1314 (s), 1209 (s), 1193 (m), 1097 (m), 967 (s), 758 (s), 700 (w).

HRMS (ESI): calculated $[C_{19}H_{28}N_2O_4+H]^+$: 349.2121, found: 349.2110.

Dimethyl (*Z*)-1-(dodecan-5-ylidene)-2,7-diazaspiro[3.5]nona-5,8-diene-2,7-dicarboxylate (3c)



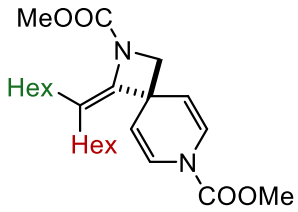
Following the general procedure on 0.5 mmol scale. Purification via column chromatography with 5% ethyl acetate in hexane. The product was isolated as a yellow oil (111 mg, 0.28 mmol, 57%). The product was present as a 1:1 mixture of amide bond rotamers. The signals of both rotamers are listed in ^{13}C NMR.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (bs, 1H), 6.78 (bs, 1H), 5.09 (bs, 1H), 5.02 (bs, 1H), 3.82 (s, 3H), 3.68 (s, 3H), 3.66 (s, 2H), 2.33 (t, *J* = 7.6 Hz, 2H), 1.95 – 1.83 (m, 2H), 1.40 – 1.14 (m, 12H), 0.92 – 0.75 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.0, 151.6, 151.6, 142.1, 122.6, 122.3, 121.2, 121.2, 109.9, 109.5, 53.6, 53.6, 52.3, 42.3, 42.2, 31.9, 31.6, 30.7, 30.6, 29.5, 29.3, 29.3, 29.2, 29.0, 28.5, 28.3, 27.8, 27.5, 22.8, 22.7, 22.7, 22.6, 22.6, 14.1, 14.1, 14.0, 13.8.

IR ν = 2957 (w), 2922 (w), 2855 (w), 1723 (s), 1700 (s), 1684 (s), 1442 (s), 1367 (m), 1340 (w), 1316 (s), 1212 (m), 1193 (w), 1128 (w), 966 (w), 757 (m).

HRMS (ESI): calculated $[C_{22}H_{34}N_2O_4+H]^+$: 391.2591, found: 391.2577.

Dimethyl (*Z*)-1-(tetradecan-7-ylidene)-2,7-diazaspiro[3.5]nona-5,8-diene-2,7-dicarboxylate (3d)



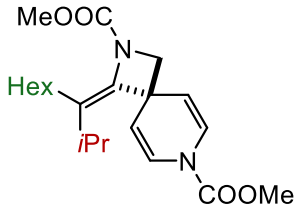
Following the general procedure on 0.5 mmol scale. Purification via column chromatography with 5% ethyl acetate in hexane. The product was isolated as a yellow oil (100 mg, 0.24 mmol, 48%). The product was present as a 1:1 mixture of amide bond rotamers. The signals of both rotamers are listed in ^{13}C NMR.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (bs, 1H), 6.73 (bs, 1H), 5.03 (bs, 1H), 4.96 (bs, 1H), 3.76 (s, 3H), 3.62 (s, 3H), 3.61 (s, 2H), 2.28 (s, 2H), 1.83 (t, *J* = 7.9 Hz, 2H), 1.30 – 1.10 (m, 16H), 0.80 (dt, *J* = 9.4, 6.9 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.0, 151.6, 142.1, 122.6, 122.3, 121.3, 109.9, 109.5, 64.7, 53.6, 52.3, 42.3, 31.9, 31.8, 31.6, 30.0, 30.0, 29.5, 29.3, 29.3, 29.3, 28.5, 28.4, 27.9, 27.5, 22.7, 22.6, 22.6, 22.5, 14.1, 14.0.

IR ν = 2955 (w), 2925 (w), 2852 (w), 1726 (m), 1700 (m), 1441 (m), 1367 (w), 1336 (m), 1314 (s), 1213 (m), 1193 (w), 1128 (w), 966 (m), 757 (m).

HRMS (ESI): calculated $[C_{24}H_{38}N_2O_4+H]^+$: 419.2904, found: 419.2882.

Dimethyl (*Z*)-1-(2-methyl-4-oxononan-3-ylidene)-2,7-diazaspiro[3.5]nona-5,8-diene-2,7-dicarboxylate (3e)



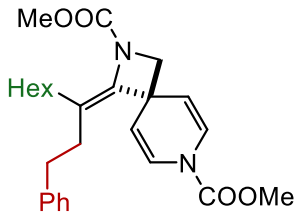
Following the general procedure on 0.5 mmol scale. Purification via column chromatography with 5% ethyl acetate in hexane. The product was isolated as a yellow oil (47 mg, 0.33 mmol, 25%). The product was present as a 1:1 mixture of amide bond rotamers. The signals of both rotamers are listed in ^{13}C NMR.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (bs, 1H), 6.79 (bs, 1H), 5.11 (bs, 1H), 5.03 (bs, 1H), 3.83 (d, *J* = 4.9 Hz, 3H), 3.69 (d, *J* = 1.2 Hz, 3H), 3.67 (d, *J* = 6.7 Hz, 2H), 2.20 (q, *J* = 5.9, 4.7 Hz, 1H), 1.94 – 1.86 (m, 2H), 1.41 – 1.18 (m, 8H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.87 – 0.81 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.2, 151.7, 151.6, 142.0, 141.6, 127.2, 125.9, 122.4, 109.9, 109.4, 64.9, 64.8, 53.6, 53.6, 52.4, 52.3, 42.7, 42.2, 31.9, 31.8, 31.5, 30.3, 30.2, 29.7, 29.0, 27.5, 25.8, 25.0, 22.6, 21.7, 21.3, 14.1, 14.0, 14.0.

IR ν = 2953 (w), 2929 (w), 2852 (w), 1720 (s), 1684 (s), 1441 (m), 1370 (m), 1340 (s), 1310 (m), 1210 (m), 1009 (w), 966 (m), 757 (m), 700 (m).

HRMS (ESI): calculated $[C_{21}H_{32}N_2O_4+H]^+$: 477.2414, found: 477.2439.

Dimethyl (*Z*)-1-(4-oxo-1-phenylnonan-3-ylidene)-2,7-diazaspiro[3.5]nona-5,8-diene-2,7-dicarboxylate (3f)



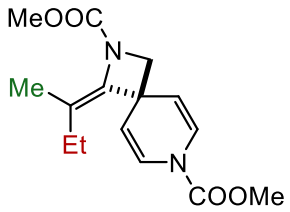
Following the general procedure on 0.5 mmol scale. Purification via column chromatography with 5% ethyl acetate in hexane. The product was isolated as a yellow oil (59 mg, 0.135 mmol, 27%). The product was present as a 1:1 mixture of amide bond rotamers. The signals of both rotamers are listed in ^{13}C NMR.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.12 (m, 2H), 7.10 – 7.06 (m, 1H), 7.03 – 6.99 (m, 2H), 6.87 (bs, 1H), 6.71 (bs, 1H), 4.98 (bs, 1H), 4.91 (bs, 1H), 3.75 (s, 3H), 3.64 (s, 3H), 3.62 (s, 2H), 2.57 – 2.51 (m, 2H), 2.43 – 2.37 (m, 2H), 2.15 – 2.08 (m, 2H), 1.38 – 1.20 (m, 8H), 0.84 – 0.79 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.0, 151.6, 151.5, 143.1, 142.9, 142.5, 142.4, 128.6, 128.3, 128.2, 128.0, 125.6, 125.5, 122.6, 120.1, 119.9, 109.3, 64.7, 53.6, 53.6, 52.4, 42.3, 42.3, 35.3, 34.7, 31.9, 31.6, 31.2, 30.9, 29.5, 29.5, 29.3, 28.6, 28.5, 28.2, 22.7, 22.6, 14.1, 14.0, 14.0.

IR ν = 2953 (w), 2929 (w), 2856 (w), 1727 (s), 1700 (s), 1514 (w), 1439 (m), 1370 (m), 1334 (s), 1316 (s), 1240 (m), 1214 (m), 1128 (w), 967 (w), 757 (m), 700 (w).

HRMS (ESI): calculated $[C_{26}H_{34}N_2O_4+H]^+$: 439.2591, found: 439.2597.

Dimethyl (*E*)-1-(butan-2-ylidene)-2,7-diazaspiro[3.5]nona-5,8-diene-2,7-dicarboxylate (3g)



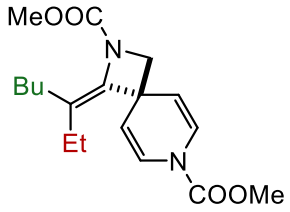
Following the general procedure on 0.5 mmol scale. Purification via column chromatography with 5% ethyl acetate in hexane. The product was isolated as a yellow oil (91 mg, 0.315 mmol, 63%). The product was present as a 1:1 mixture of amide bond rotamers. The signals of both rotamers are listed in ^{13}C NMR.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (bs, 1H), 6.96 (bs, 1H), 4.85 (bs, 1H), 4.73 (bs, 1H), 3.86 (s, 3H), 3.86 (s, 2H), 3.64 (s, 3H), 1.66 – 1.56 (m, 1H), 1.00 (d, J = 6.8 Hz, 3H), 0.80 (t, J = 7.5 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.3, 155.5, 150.5, 124.6, 124.3, 105.7, 104.8, 102.9, 53.4, 52.8, 51.2, 46.4, 42.2, 33.4, 28.6, 25.6, 16.5, 10.9, 10.7.

IR ν = 2952 (w), 2917 (w), 2867 (w), 1726 (s), 1704 (s), 1441 (s), 1335 (m), 1318 (m), 1214 (w), 1193 (w), 1135 (m), 913 (s), 740 (s).

HRMS (ESI): calculated $[C_{15}H_{20}N_2O_4+H]^+$: 293.1659, found: 293.1660.

Dimethyl (*Z*)-1-(heptan-3-ylidene)-2,7-diazaspiro[3.5]nona-5,8-diene-2,7-dicarboxylate (3h)



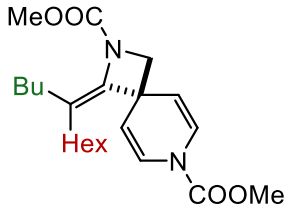
Following the general procedure on 0.5 mmol scale. Purification via column chromatography with 5% ethyl acetate in hexane. The product was isolated as a yellow oil (85 mg, 0.255 mmol, 51%). The product was present as a 1:1 mixture of amide bond rotamers. The signals of both rotamers are listed in ^{13}C NMR.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (bs, 1H), 6.80 (bs, 1H), 5.11 (bs, 1H), 5.04 (bs, 1H), 3.84 (s, 3H), 3.69 (s, 3H), 3.68 (s, 2H), 2.36 (t, *J* = 7.3 Hz, 2H), 1.96 (q, *J* = 7.4 Hz, 2H), 1.40 – 1.24 (m, 4H), 0.90 (t, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.0, 150.6, 140.9, 121.5, 121.3, 121.2, 108.7, 108.4, 63.7, 52.6, 51.3, 41.2, 29.6, 27.6, 21.7, 19.9, 13.1, 12.2.

IR ν = 2958 (w), 2922 (w), 2870 (w), 1720 (s), 1684 (m), 1440 (m), 1367 (m), 1340 (m), 1315 (s), 1212 (m), 1193 (w), 1125 (w), 1016 (w), 966 (w), 757 (w).

HRMS (ESI): calculated $[C_{18}H_{26}N_2O_4+H]^+$: 335.1965, found: 335.1960.

Dimethyl (*E*)-1-(undecan-5-ylidene)-2,7-diazaspiro[3.5]nona-5,8-diene-2,7-dicarboxylate (3i)



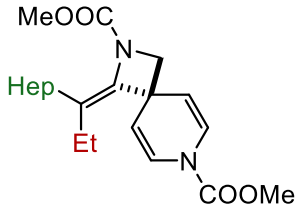
Following general procedure on 0.5 mmol scale. Purification via column chromatography with 5% ethyl acetate in hexane. The product was isolated as a yellow oil (89.7 mg, 0.23 mmol, 46%). The product was present as a 1:1 mixture of amide bond rotamers. The signals of both rotamers are listed in ^{13}C NMR.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (bs, 1H), 6.79 (bs, 1H), 5.09 (bs, 1H), 5.03 (bs, 1H), 3.83 (s, 3H), 3.68 (s, 3H), 3.67 (s, 2H), 2.35 (s, 2H), 1.92 – 1.85 (m, 2H), 1.36 – 1.11 (m, 12H), 0.87 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.0, 151.6, 142.1, 122.6, 122.3, 121.3, 109.9, 109.5, 64.7, 53.6, 5.5, 52.3, 42.3, 31.6, 30.6, 29.5, 29.0, 28.5, 27.9, 22.7, 22.6, 14.1, 14.0, 14.0.

IR ν = 2954 (w), 2927 (w), 2853 (w), 1726(s), 1687 (m), 1440 (m), 1340 (m), 1338 (m), 1315 (s), 1221(m), 1193 (w), 1125 (w), 1016 (w), 966 (w), 757 (w).

HRMS (ESI): calculated $[C_{22}H_{34}N_2O_4+H]^+$: 391.2591, found: 391.2583.

Dimethyl (*Z*)-1-(decan-3-ylidene)-2,7-diazaspiro[3.5]nona-5,8-diene-2,7-dicarboxylate (3j)



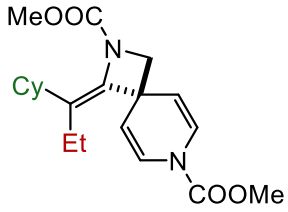
Following general procedure on 0.5 mmol scale. Purification via column chromatography with 5% ethyl acetate in hexane. The product was isolated as a yellow oil (97.7 mg, 0.26 mmol, 52%). The product was present as mixture of amide bond rotamers. The signals of both rotamers are listed.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (bs, 1H), 6.80 (bs, 1H), 5.11 (bs, 1H), 5.03 (bs, 1H), 3.83 (s, 3H), 3.69 (s, 3H), 3.67 (s, 2H), 2.34 (t, *J* = 7.6 Hz, 2H), 1.95 (q, *J* = 7.4 Hz, 2H) 1.34 – 1.12 (m, 10H), 0.93 – 0.85 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.1, 151.7, 141.9, 122.6, 122.3, 122.2, 109.8, 109.4, 64.7, 53.6, 52.3, 42.2, 31.9, 29.6, 28.9, 28.4, 22.7, 22.6, 20.9, 14.1, 13.2.

IR ν = 2960 (w), 2923 (w), 2853 (w), 1725 (s), 1688 (m), 1440 (m), 1369 (m), 1341 (m), 1315 (s) 1212 (m), 1195 (w), 1125 (w), 1014 (w), 967 (w), 758 (w).

HRMS (ESI): calculated $[C_{21}H_{32}N_2O_4+H]^+$: 377.2434, found: 377.2422.

Dimethyl (*Z*)-1-(1-cyclohexylpropylidene)-2,7-diazaspiro[3.5]nona-5,8-diene-2,7-dicarboxylate (3k)



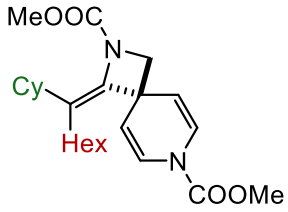
Following general procedure on 0.5 mmol scale. Purification via column chromatography with 5% ethyl acetate in hexane. The product was isolated as a yellow oil (97 mg, 0.27 mmol, 55%). The product was present as a 1:1 mixture of amide bond rotamers. The signals of both rotamers are listed in ^{13}C NMR.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (bs, 1H), 6.80 (bs, 1H), 5.10 (bs, 1H), 5.04 (bs, 1H), 3.83 (s, 3H), 3.69 (s, 3H), 3.67 (s, 2H), 3.11 – 3.02 (m, 1H), 1.98 (q, *J* = 7.6 Hz, 2H), 1.75 – 1.55 (m, 5H), 1.36 – 1.23 (m, 5H), 0.95 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.2, 152.8, 151.6, 151.6, 142.2, 142.0, 127.9, 127.2, 122.5, 122.2, 110.0, 109.6, 65.0, 64.4, 53.7, 53.6, 52.4, 52.3, 42.6, 42.0, 39.7, 38.6, 32.1, 31.7, 26.9, 26.7, 26.3, 26.0, 22.6, 19.7, 18.3, 16.4, 15.4, 14.1.

IR ν = 2955 (w), 2928 (w), 2853 (w), 1718 (s), 1682 (m), 1440 (m), 1354 (m), 1340 (m), 1315 (s), 1210 (m), 1195 (w), 1162 (w), 1125 (w), 1018 (w), 966 (w), 757 (w).

HRMS (ESI): calculated $[C_{22}H_{28}N_2O_4+H]^+$: 361.2121, found: 361.2111.

Dimethyl (*Z*)-1-(1-cyclohexylheptylidene)-2,7-diazaspiro[3.5]nona-5,8-diene-2,7-dicarboxylate (3l)



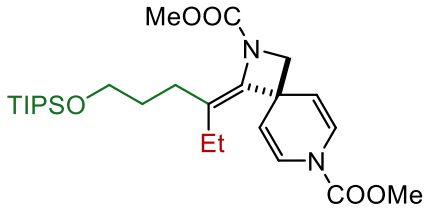
Following general procedure on 0.5 mmol scale. Purification via column chromatography with 5% ethyl acetate in hexane. The product was isolated as a yellow oil (98 mg, 0.23 mmol, 47%). The product was present as a 1:1 mixture of amide bond rotamers. The signals of both rotamers are listed in ^{13}C NMR.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (bs, 1H), 6.80 (s, 1H), 5.11 (bs, 1H), 5.05 (bs, 1H), 3.84 (d, *J* = 9.3 Hz, 3H), 3.70 (d, *J* = 4.8 Hz, 3H), 3.68 (s, 2H), 2.31 – 2.15 (m, 1H), 1.69 (d, *J* = 11.9 Hz, 2H), 1.45 – 0.98 (m, 18H), 0.86 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.7, 151.6, 151.5, 142.3, 142.0, 125.9, 122.5, 122.2, 110.0, 109.8, 64.9, 64.3, 53.7, 52.3, 42.1, 38.6, 32.2, 32.0, 31.9, 31.7, 31.6, 31.5, 30.6, 30.2, 29.7, 29.6, 28.8, 27.4, 26.9, 26.8, 26.5, 26.3, 26.0, 25.8, 22.7, 22.6, 14.1, 14.0, 14.0.

IR ν = 2962 (w), 2928 (w), 2848 (w), 1725 (s), 1684 (m), 1440 (m), 1372 (m), 1340 (m), 1316 (s), 1211 (m), 1162 (w), 1125 (w), 1092 (w), 966 (w), 757 (w).

HRMS (ESI): calculated $[C_{24}H_{36}N_2O_4+H]^+$: 417.2747, found: 417.2741.

Dimethyl (*Z*)-1-(6-((triisopropylsilyl)oxy)hexan-3-ylidene)-2,7-diazaspiro[3.5]nona-5,8-diene-2,7-dicarboxylate (3m)



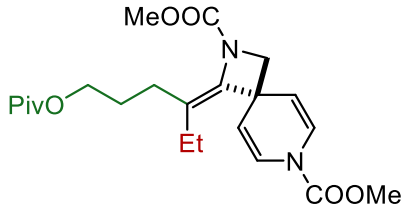
Following general procedure on 0.5 mmol scale. Purification via column chromatography with 10% ethyl acetate in hexane. The product was isolated as a yellow oil (105.7 mg, 0.215 mmol, 43%). The product was present as a 1:1 mixture of amide bond rotamers. The signals of both rotamers are listed in ^{13}C NMR.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (bs, 1H), 6.81 (bs, 1H), 5.09 (bs, 1H), 5.03 (bs, 1H), 3.83 (s, 3H), 3.67 (d, *J* = 1.3 Hz, 7H), 2.43 – 2.34 (m, 2H), 1.96 (q, *J* = 7.4 Hz, 2H), 1.69 – 1.57 (m, 2H), 1.15 – 0.94 (m, 21H), 0.91 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.0, 150.6, 141.2, 121.6, 121.2, 120.8, 108.7, 108.2, 63.7, 62.4, 52.6, 51.3, 41.3, 30.9, 24.2, 20.1, 17.0, 16.9, 12.1, 11.0, 10.9.

IR ν = 2954 (w), 2952 (w), 2865 (w), 3361 (w), 1734 (m), 1723 (m), 1653 (m), 1560 (m), 1441 (m),1373 (m), 1339 (m), 1317 (m), 1212 (w), 1099 (w), 964 (w), 913 (s), 742 (s).

HRMS (ESI): calculated $[C_{26}H_{44}N2O_5Si+H]^+$: 493.3092, found: 493.3074.

Dimethyl (*Z*)-1-(6-(pivaloyloxy)hexan-3-ylidene)-2,7-diazaspiro[3.5]nona-5,8-diene-2,7-dicarboxylate (3n)



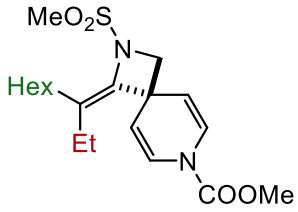
Following general procedure on 0.5 mmol scale. Purification via column chromatography with 5% ethyl acetate in hexane. The product was isolated as a yellow oil (105 mg, 0.25 mmol, 50%). The product was present as a 1:1 mixture of amide bond rotamers. The signals of both rotamers are listed in ^{13}C NMR.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (bs, 1H), 6.80 (bs, 1H), 5.09 (bs, 1H), 5.02 (bs, 1H), 4.04 (t, *J* = 6.8 Hz, 2H), 3.83 (s, 3H), 3.67 (s, 2H), 3.67 (s, 2H), 2.42 (td, *J* = 7.2, 3.1 Hz, 2H), 1.95 (q, *J* = 7.3 Hz, 2H), 1.75 – 1.64 (m, 2H), 1.18 (s, 9H), 0.90 (t, *J* = 7.4 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 177.6, 177.5, 166.7, 152.0, 150.6, 141.9, 139.1, 131.4, 129.8, 127.7, 121.7, 121.3, 119.6, 108.5, 108.1, 63.8, 63.7, 63.3, 52.7, 52.6, 52.6, 52.5, 51.6, 51.5, 51.4, 41.3, 37.7, 26.4, 26.1, 24.2, 19.8, 12.1.

IR ν = 2874 (w), 2859 (w), 2361 (w), 1726(m), 1685 (m), 1442 (m),1366 (m), 1340 (m), 1316 (m), 1211 (w), 1160 (w), 964 (w), 913 (s), 744 (s).

HRMS (ESI): $[C_{22}H_{32}N_2O_6+H]^+$: 421.2333, found: 421.2325.

Methyl (*Z*)-2-(methylsulfonyl)-1-(nonan-3-ylidene)-2,7-diazaspiro[3.5]nona-5,8-diene-7-carboxylate (3o)



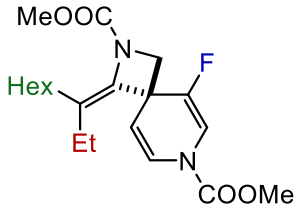
Following general procedure on 0.5 mmol scale. Purification via column chromatography with 10% ethyl acetate in hexane. The product was isolated as a yellow oil (118 mg, 0.31 mmol, 62%). The product was present as a 1:1 mixture of amide bond rotamers. The signals of both rotamers are listed in ^{13}C NMR.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (bs, 1H), 6.84 (bs, 1H), 5.07 (bs, 1H), 5.03 (bs, 1H), 3.85 (s, 3H), 3.75 (s, 2H), 2.95 (s, Hz, 3H), 2.26 – 2.19 (m, 2H), 1.97 (q, J = 7.4 Hz, 2H), 1.37 – 1.21 (m, 8H), 0.91 (t, J = 7.3 Hz, 3H), 0.87 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.5, 151.4, 150.2, 142.4, 12.1, 127.1, 122.9, 122.7, 115.6, 109.0, 108.6, 77.3, 77.0, 76.7, 66.0, 66.0, 64.6, 61.2, 53.8, 42.1, 36.4, 36.3, 31.7, 29.3, 27.9, 27.6, 22.6, 22.6, 20.6, 14.0, 13.0.

IR ν = 2960 (w), 2927 (w), 2853 (w), 1729 (s), 1700 (s) 1684 (m), 1653 (s), 1440 (m), 1340 (m), 1315 (s), 1211 (w), 1164 (m), 966 (w), 761 (w).

HRMS (ESI): calculated $[C_{19}H_{30}N_2O_4S + H]^+$: 383.1999, found: 383.1978.

Dimethyl (*Z*)-5-fluoro-1-(octan-3-ylidene)-2,7-diazaspiro[3.5]nona-5,8-diene-2,7-dicarboxylate (3p)



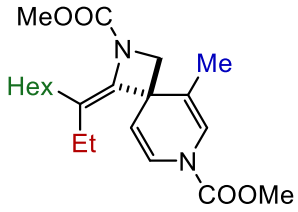
Following general procedure on 0.2 mmol scale. Purification via column chromatography with 10% ethyl acetate in hexane. The product was isolated as a yellow oil (40.2 mg, 0.106 mmol, 53%). The product was present as a mixture of the two-amide bond rotamers. The signals of all rotamers are listed in ^{13}C and ^{19}F NMR.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 – 6.69 (m, 2H), 5.24 – 5.02 (m, 1H), 4.16 (d, *J* = 8.1 Hz, 1H), 3.85 (s, 2H), 3.70 (s, 3H), 4.16 (d, *J* = 8.1 Hz, 1H), 2.41 – 2.35 (t, *J* = 7.2 Hz, 2H), 2.03 – 1.89 (m, 2H), 1.40 – 1.22 (m, 12H), 0.91 (t, *J* = 7.5 Hz, 3H), 0.89 – 0.85 (t, *J* = 6.9 Hz, 4H); **^{13}C NMR** (126 MHz, CDCl3) δ 156.1, 152.0, 151.0, 150.1 (d, *J* = 21.5 Hz), 149.9 (d, *J* = 21.1 Hz), 136.3, 123.9 (d, *J* = 48.5 Hz), 122.5, 120.9 (d, *J* = 48.7 Hz), 110.2 (d, *J* = 34.0 Hz), 108.3 (d, *J* = 24.8 Hz), 107.5 (d, *J* = 20.2 Hz), 107.3 (d, *J* = 21) Hz 105.3, 58.9, 53.0, 52.9, 51.4, 51.6, 48.1, 43.9, 43.7, 42.71, 30.8, 30.8, 30.6, 30.5, 30.5, 28.6, 28.6, 28.4, 28.3, 28.2, 28.0, 27.3, 27.2, 27.2, 26.4, 23.7, 23.5, 22.6, 21.7, 21.6, 21.6, 21.6, 21.5, 21.5, 21.4, 20.0, 13.10, 13.0, 13.0, 12.0, 11.9, 10.9, 10.5; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -141.81, -142.03, δ -148.17 (t, *J* = 8.3 Hz), -148.65 (t, *J* = 8.3 Hz).

IR ν = 2962 (w), 2929 (w), 2858 (w), 1727 (s), 1442 (s), 1368 (s), 1331 (s), 1309 (s), 1220 (m), 119 (w), 907 (w), 772 (s).

HRMS (ESI): calculated $[C_{20}H_{29}FN_2O_4+H]^+$: 381.2184, found: 381.2175.

Dimethyl (*Z*)-5-methyl-1-(nonan-3-ylidene)-2,7-diazaspiro[3.5]nona-5,8-diene-2,7-dicarboxylate (3q)



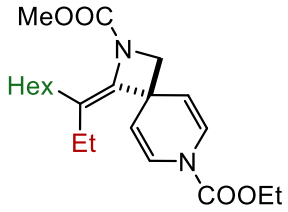
Following general procedure on 0.2 mmol scale. Purification via column chromatography with 10% ethyl acetate in hexane. The product was isolated as a yellow oil (31.5 mg, 0.084 mmol, 42%). The product was present as a 1:1 mixture of amide bond rotamers. The signals of both rotamers are listed in ^{13}C NMR.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 – 6.58 (m, 2H), 5.02 (dd, *J* = 44.3, 7.4 Hz, 1H), 4.00 (d, *J* = 8.1 Hz, 1H), 3.82 (s, 3H), 3.70 (s, 3H), 3.52 (d, *J* = 8.3 Hz, 1H), 2.47 (m, 1H), 2.36 – 2.22 (m, 1H), 2.00 – 1.87 (m, 2H), 1.77 (s, 3H), 1.38 – 1.24 (m, 8H), 0.89 (p, *J* = 7.2 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.0, 150.5, 138.3, 121.2, 120.7, 118.3, 118.0, 114.2, 113.7, 108.8, 108.4, 59.7, 52.5, 52.3, 51.4, 44.8, 30.9, 30.5, 28.6, 28.3, 27.7, 27.3, 21.6, 21.6, 19.8, 13.1, 11.8.

IR ν = 2984 (w), 2952 (w), 2929 (w), 1733 (s), 1373 (m), 1239 (s), 1210 (s), 1045 (s), 910 (s), 728 (s).

HRMS (ESI): calculated $[C_{21}H_{32}N_2O_4+H]^+$: 377.2434, found: 299.2426.

7-Ethyl 2-methyl (*Z*)-1-(decan-3-ylidene)-2,7-diazaspiro[3.5]nona-5,8-diene-2,7-dicarboxylate (3r)



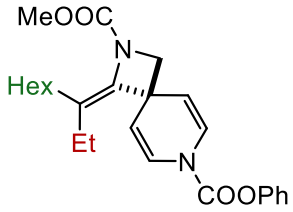
Following general procedure on 0.5 mmol scale. Purification via column chromatography with 5% ethyl acetate in hexane. The product was isolated as a yellow oil (118 mg, 0.3 mmol, 62%). The product was present as a 1:1 mixture of amide bond rotamers. The signals of both rotamers are listed in ^{13}C NMR.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (bs, 1H), 6.82 (bs, 1H), 5.09 (bs, 1H), 5.02 (bs, 1H), 4.31 – 4.21 (m, 2H), 3.69 (s, 3H), 3.67 (s, 2H), 2.35 (m, 2H), 1.96 (q, J = 7.4 Hz, 2H), 1.35 – 1.28 (m, 11H), 0.92 – 0.86 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.2, 153.0, 151.1, 151.1, 142.0, 141.9, 122.6, 122.4, 122.3, 109.6, 109.2, 77.0, 64.8, 64.8, 63.1, 62.9, 62.8, 62.7, 52.37, 52.3, 42.3, 42.3, 31.9, 31.6, 31.6, 31.4, 29.5, 29.3, 28.9, 28.5, 28.4, 27.5, 27.4, 14.3, 14.1, 14.0, 13.3, 13.2, 12.0.

IR ν = 2933 (w), 2860 (w), 1729 (s), 1700 (s) 1626 (w), 1518 (w), 1446 (w), 1375 (m), 1336 (m), 1210 (s), 1234 (m), 1212 (w), 1126 (w), 1015 (w), 961 (w), 758 (w).

HRMS (ESI): calculated $[C_{21}H_{32}N_2O_4+H]^+$: 377.2560, found: 377.2564.

2-Methyl 7-phenyl (*Z*)-1-(decan-3-ylidene)-2,7-diazaspiro[3.5]nona-5,8-diene-2,7-dicarboxylate (3s)



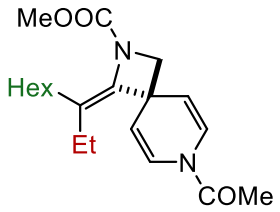
Following general procedure on 0.5 mmol scale. Purification via column chromatography with 5% ethyl acetate in hexane. The product was isolated as a yellow oil (122 mg, 0.27mmol, 55%). The product was present as a mixture of amide bond rotamers. The peaks of all rotamers are listed. *Decomposition was observed on the NMR timescale.*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.34 (m, 4H), 7.30 – 7.21 (m, 2H), 7.19 – 7.11 (m, 4H), 7.04 (d, *J* = 8.3 Hz, 1H), 6.99 (d, *J* = 8.6 Hz, 1H), 5.23 (d, *J* = 8.3 Hz, 1H), 5.17 (d, *J* = 8.0 Hz, 1H), 3.74 (d, *J* = 3.0 Hz, 2H), 3.71 (s, 3H), 2.42 – 2.34 (m, 2H), 2.06 – 1.93 (m, 2H), 1.43 – 1.18 (m, 16H), 0.93 (t, *J* = 7.5 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.91 – 0.80 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.1, 153.2, 153.1, 150.5, 150.4, 149.7, 149.7, 149.6, 141.5, 141.4, 129.5, 129.5, 129.5, 126.1, 122.9, 122.6, 122.6, 122.3, 122.2, 121.4, 121.3, 120.2, 115.3, 111.0, 110.9, 110.4, 110.3, 73.5, 64.4, 52.4, 42.3, 31.9, 31.6, 29.6, 29.5, 29.4, 28.9, 28.5, 28.4, 27.6, 21.1, 14.1, 14.1, 13.3, 13.2.

IR ν = 2954 (w), 2931 (w), 2831 (w), 1734 (m), 1690 (m), 1371 (m), 1340 (m), 1315 (s), 1197 (s), 1136 (w), 966 (w), 750 (w).

HRMS (ESI): calculated $[C_{25}H_{32}N_2O_4+H]^+$: 425.2434, found: 425.2442.

Methyl (*Z*)-7-acetyl-1-(decan-3-ylidene)-2,7-diazaspiro[3.5]nona-5,8-diene-2-carboxylate (3t)



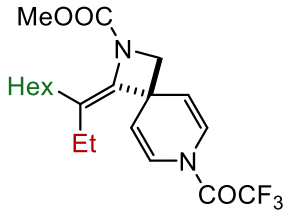
Following general procedure on 0.5 mmol scale. Purification via column chromatography with 5% ethyl acetate in hexane. The product was isolated as a yellow oil (91.5 mg, 0.25 mmol, 56%). The product was present as a ~1:0.3 mixture of amide bond rotamers. The peaks of both rotamers are listed.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.4 Hz, 0.3H), 7.25 (d, *J* = 8.9 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 0.3H), 6.61 (d, *J* = 8.5 Hz, 1H), 5.19 (dd, *J* = 8.2, 2.3 Hz, 1H), 5.10 (dd, *J* = 8.2, 2.6 Hz, 1H), 4.84 (d, *J* = 8.4 Hz, 0.3H), 4.79 (d, *J* = 8.0 Hz, 0.3H), 3.7 – 3.67 (m, 5H), 2.37 – 2.31 (m, 2H), 2.24 (d, *J* = 2.0 Hz, 3H), 1.96 – 1.87 (m, 2H), 1.39 – 1.14 (m, 13H), 0.97 (t, *J* = 7.4 Hz, 1.5H), 0.92 – 0.82 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.1, 166.1, 166.0, 153.0, 141.4, 141.2, 125.8, 124.1, 123.1, 122.7, 122.5, 121.1, 121.1, 111.1, 110.5, 107.5, 107.0, 64.2, 64.2, 52.41, 52.4, 52.2, 42.6, 42.5, 31.9, 31.6, 31.4, 29.6, 29.3, 28.9, 28.5, 28.4, 27.5, 27.5, 24.7, 22.6, 22.6, 22.6, 22.6, 21.4, 21.3, 21.3, 21.0, 14.1, 14.0, 14.0, 13.3, 13.2.

IR ν = 2964 (w), 2931 (w), 2857 (w), 1700 (s), 1672 (m), 1622 (w), 1539 (w), 1357 (m), 1327 (m), 1309 (s), 1247 (w), 1215 (w), 958 (w), 762 (w).

HRMS (ESI): calculated $[C_{20}H_{30}N_2O_3+H]^+$: 347.2329, found: 347.2330.

Methyl (*Z*)-1-(nonan-3-ylidene)-7-(2,2,2-trifluoroacetyl)-2,7-diazaspiro[3.5]nona-5,8-diene-2-carboxylate (3u)



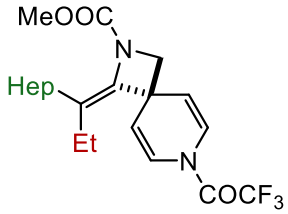
Following general procedure on 0.5 mmol scale. Purification via column chromatography with 5% ethyl acetate in hexane. The product was isolated as a yellow oil (84 mg, 0.21 mmol, 42%). The product was present as a 1:1 mixture of amide bond rotamers. The signals of both rotamers are listed in ^{13}C NMR.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (dd, *J* = 8.4, 1.9 Hz, 1H), 6.75 (dd, *J* = 8.3, 2.2 Hz, 1H), 5.52 (dd, *J* = 8.4, 2.5 Hz, 1H), 5.34 (dd, *J* = 8.4, 2.5 Hz, 1H), 3.76 (s, 2H), 3.71 (s, 3H), 2.36 (td, *J* = 7.1, 2.4 Hz, 2H), 1.87 (d, *J* = 7.4 Hz, 2H), 1.35 – 1.25 (m, 8H), 0.93 – 0.83 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.0, 151.9, 151.7 (d, *J* = 5.1 Hz), 151.3 (d, *J* = 5.1 Hz), 138.5, 138.4, 122.5, 122.3, 119.8, 116.3, 114.7 (q, *J* = 287.3 Hz), 114.7, 113.4, 112.7, 110.5, 61.8, 61.7, 51.5, 51.4, 41.2, 41.2, 30.8, 30.5, 28.6, 28.3, 27.9, 27.6, 27.3, 26.7, 21.7, 21.6, 21.6, 20.1, 13.1, 13.0, 12.9, 12.9, 12.2, 12.1; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -68.81.

IR ν = 2957 (w), 2930 (w), 2872 (w), 1700 (s), 1652 (m), 1456 (w), 1364 (w), 1196 (m), 1162 (w), 1153 (m).

HRMS (ESI): calculated $[C_{20}H_{27}F_3N_2O_4+H]^+$: 401.2046, found: 401.2049.

Methyl (*Z*)-1-(decan-3-ylidene)-7-(2,2,2-trifluoroacetyl)-2,7-diazaspiro[3.5]nona-5,8-diene-2-carboxylate (3v)



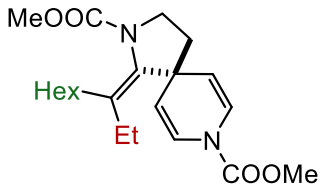
Following general procedure on 0.5 mmol scale. Purification via column chromatography with 5% ethyl acetate in hexane. The product was isolated as a yellow oil (99.3 mg, 0.24 mmol, 48%). The product was present as a 1:1 mixture of amide bond rotamers. The signals of both rotamers are listed in ^{13}C NMR.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.75 (dd, *J* = 8.4, 2.0 Hz, 1H), 5.52 (dd, *J* = 8.4, 2.5 Hz, 1H), 5.33 (dd, *J* = 8.4, 2.5 Hz, 1H), 3.75 (s, 2H), 3.70 (s, 3H), 2.36 (td, *J* = 7.1, 2.6 Hz, 2H), 1.88 (t, *J* = 7.6 Hz, 2H), 1.42 – 1.12 (m, 10H), 0.95 – 0.82 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.0, 151.9, 151.7 (d, *J* = 5.1 Hz), 151.3 (d, *J* = 5.1 Hz),138.5, 138.4, 122.5, 122.3, 119.8, 119.8, 114.7, 114.7 (q, *J* = 286.2 Hz), 112.7, 64.2, 61.8, 61.7, 51.5, 51.4, 41.2, 41.2, 30.8, 30.6, 28.9, 28.6, 28.3, 28.0, 28.0, 27.9, 27.8, 27.7, 27.6, 27.4, 27.3, 26.7, 21.6, 21.5, 21.5, 20.1, 18.1, 13.0, 13.0, 13.0, 12.2, 12.1; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.15.

IR ν = 2960 (w), 2930 (w), 2857 (w), 1709 (s), 1688 (s), 1630 (w), 1430 (m), 1373 (m), 1340 (w), 1239 (m), 1212 (s), 1195 (s), 1148 (s), 1013 (w), 958 (w), 934 (w), 750 (w).

HRMS (ESI): calculated $[C_{21}H_{29}F_3N_2O_4+H]^+$: 415.2203 found: 415.2189.

Dimethyl (*Z*)-1-(nonan-3-ylidene)-2,8-diazaspiro[4.5]deca-6,9-diene-2,8-dicarboxylate (3w)



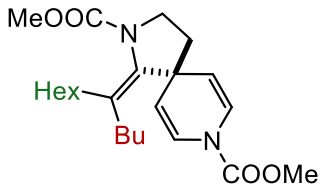
Following general procedure on 0.5 mmol scale. Purification via column chromatography with 10% ethyl acetate in hexane. The product was isolated as a yellow oil (84 mg, 0.31 mmol, 63%). The product was present as a 1:1 mixture of amide bond rotamers. The signals of both rotamers are listed in ^{13}C NMR.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (d, *J* = 8.3 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 4.89 (d, *J* = 8.3 Hz, 1H), 4.79 (d, *J* = 8.4 Hz, 1H), 3.82 (s, 3H), 3.69 (s, 3H), 2.18 (q, *J* = 7.5 Hz, 2H), 2.06 – 1.94 (m, 2H), 1.75 (t, *J* = 6.9 Hz, 2H), 1.35 – 1.29 (m, 2H), 1.28 – 1.19 (m, 8H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.88 – 0.84 (m, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.8, 151.8, 151.8, 151.5, 137.4, 137.2, 133.6, 133.4, 120.2, 119.8, 112.8, 112.3, 53.7, 53.4, 53.4, 52.7, 52.6, 52.6, 52.6, 51.7, 45.1, 45.0, 44.8, 42.7, 42.7, 31.7, 31.7, 31.7, 31.6, 31.6, 31.5, 31.4, 29.5, 29.3, 29.3, 29.2, 29.1, 28.0, 28.0, 27.4, 26.8, 26.7, 25.2, 24.7, 22.6, 22.6, 22.6, 22.6, 22.5, 21.7, 14.0, 14.0, 14.0, 12.8, 12.5, 11.9, 11.6.

IR ν = 2955 (w), 2930 (w), 2857 (w), 1708 (s), 1523(w), 1442 (s), 1366 (m), 1337 (m), 1315 (s), 1250 (w), 1213 (w), 1194 (w), 1125 (w), 966 (w), 757 (w).

HRMS (ESI): calculated $[C_{21}H_{32}N_2O_4+H]^+$: 377.2434, found: 377.2430.

Dimethyl (*Z*)-1-(undecan-5-ylidene)-2,8-diazaspiro[4.5]deca-6,9-diene-2,8-dicarboxylate (3x)



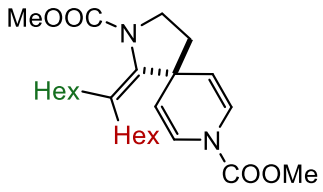
Following general procedure on 0.5 mmol scale. Purification via column chromatography with 10% ethyl acetate in hexane. The product was isolated as a yellow oil (117 mg, 0.29 mmol, 58%). The product was present as a 1:1 mixture of amide bond rotamers. The signals of both rotamers are listed in ^{13}C NMR

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, *J* = 8.4 Hz, 1H), 6.68 (d, *J* = 8.3 Hz, 1H), 4.88 (d, *J* = 8.4 Hz, 1H), 4.79 (d, *J* = 6.8 Hz, 1H), 3.82 (s, 3H), 3.70 (s, 3H), 2.15 (t, *J* = 7.6 Hz, 2H), 2.03 – 1.93 (m, 2H), 1.76 (t, *J* = 6.9 Hz, 2H), 1.36 – 1.16 (m, 14H), 0.86 (t, *J* = 7.0 Hz, 3H), 0.83 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.8, 150.5, 136.7, 131.3, 125.3, 123.6, 122.1, 119.2, 111.9, 106.7, 52.7, 52.4, 51.7, 51.0, 50.7, 45.9, 44.1, 43.7, 41.7, 36.9, 36.5, 30.9, 30.7, 30.6, 30.6, 30.6, 28.7, 28.4, 26.5, 21.8, 21.6, 21.6, 13.1, 13.0, 12.9, 12.8.

IR ν = 2960 (w), 2942 (w), 2873 (w), 1734 (s), 1700 (s), 1442 (w), 1354 (m), 1386 (w), 1336 (m), 1318 (s), 1212 (w), 1133 (w), 961 (w),

HRMS (ESI): calculated $[C_{23}H_{36}N_2O_4+H]^+$: 404.2675, found: 404.2658.

Dimethyl 1-(tridecan-7-ylidene)-2,8-diazaspiro[4.5]deca-6,9-diene-2,8-dicarboxylate (3y)



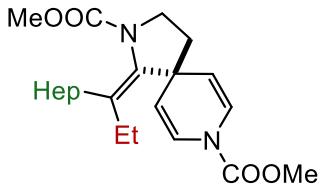
Following general procedure on 0.5 mmol scale. Purification via column chromatography with 10% ethyl acetate in hexane. The product was isolated as a yellow oil (112 mg, 0.26 mmol, 52%). The product was present as a 1:1 mixture of amide bond rotamers. The signals of both rotamers are listed in ^{13}C NMR

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, *J* = 8.4 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 4.88 (d, *J* = 8.4 Hz, 1H), 4.79 (d, *J* = 8.4 Hz, 1H), 3.82 (s, 3H), 3.70 (s, 3H), 2.14 (d, *J* = 8.1 Hz, 2H), 1.98 (dd, *J* = 8.3, 6.9 Hz, 2H), 1.76 (t, *J* = 7.0 Hz, 2H), 1.37 – 1.16 (m, 16H), 0.89 – 0.82 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.8, 151.5, 151.4, 151.4, 137.7, 132.4, 124.4, 120.8, 108.0, 107.7, 53.7, 53.4, 52.7, 52.0, 51.8, 46.9, 45.1, 44.8, 37.9, 37.5, 31.9, 31.6, 29.2, 27.5, 22.6, 14.0.

IR ν = 2956 (w), 2930 (w), 2858 (w),1732 (s), 1704 (s), 1444 (m), 1370 (m), 1336 (m) 1318 (s), 1213 (w), 1193 (w), 964 (w), 908 (w), 732 (s).

HRMS (ESI): calculated $[C_{25}H_{40}N_2O_4+H]^+$: 433.3060, found: 433.3044.

Dimethyl (*Z*)-1-(decan-3-ylidene)-2,8-diazaspiro[4.5]deca-6,9-diene-2,8-dicarboxylate (3z)



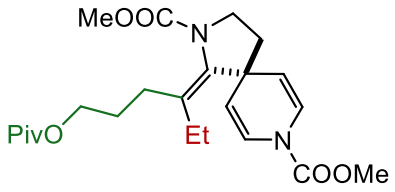
Following general procedure on 0.5 mmol scale. Purification via column chromatography with 10% ethyl acetate in hexane. The product was isolated as a yellow oil (101 mg, 0.26 mmol, 51%). The product was present as a 1:1 mixture of amide bond rotamers. The signals of both rotamers are listed in ^{13}C NMR.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, *J* = 7.0 Hz, 1H), 6.68 (d, *J* = 7.0 Hz, 1H), 4.89 (d, *J* = 6.9 Hz, 1H), 4.80 (d, *J* = 7.0 Hz, 1H), 3.82 (s, 3H), 3.70 (s, 3H), 2.18 (q, *J* = 7.4 Hz, 2H), 2.02 – 1.97 (m, 2H), 1.75 (t, *J* = 6.9 Hz, 3H), 1.40 – 1.19 (m, 19H), 0.91 (t, *J* = 7.4 Hz, 4H), 0.89 – 0.84 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.8, 151.8, 151.8, 151.5, 137.4, 137.2, 133.6, 133.4, 124.4, 120.3, 119.9, 119.3, 112.9, 112.4, 110.8, 108.0, 53.7, 53.7, 53.4, 53.4, 52.7, 52.7, 51.7, 48.4, 45.2, 45.0, 44.8, 42.7, 42.7, 31.9, 31.8, 31.8, 31.7, 31.5, 29.6, 29.6, 29.2, 29.1, 29.1, 28.9, 28.1, 28.0, 27.5, 26.8, 22.6, 22.6, 22.6, 22.5, 21.7, 14.1, 14.0, 14.0, 12.8, 11.9, 11.7.

IR ν = 2958 (w), 2930 (w), 2858 (w),1732 (s), 1700 (s), 1442 (m), 1367 (m), 1336 (m) 1318 (s), 1250 (w), 1212 (w), 1193 (w), 1129 (w), 960 (w), 760 (s).

HRMS (ESI): calculated $[C_{22}H_{34}N_2O_4+H]^+$: 391.2591, found: 391.2592.

Dimethyl (*Z*)-1-(6-(pivaloyloxy)hexan-3-ylidene)-2,8-diazaspiro[4.5]deca-6,9-diene-2,8-dicarboxylate (3aa)



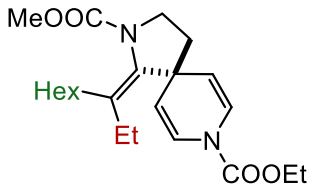
Following general procedure on 0.5 mmol scale. Purification via column chromatography with 10% ethyl acetate in hexane. The product was isolated as a yellow oil (101 mg, 0.23 mmol, 47%). The product was present as a 1:1 mixture of amide bond rotamers. The signals of both rotamers are listed.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (d, *J* = 7.3 Hz, 1H), 6.70 (d, *J* = 7.1 Hz, 1H), 4.89 (s, 1H), 4.82 (s, 1H), 3.99 (t, *J* = 6.5 Hz, 2H), 3.83 (s, 3H), 3.70 (s, 3H), 3.51 (d, *J* = 5.8 Hz, 2H), 2.21 (q, *J* = 7.6 Hz, 2H), 2.13 – 2.05 (m, 2H), 1.76 (t, *J* = 6.9 Hz, 2H), 1.18 (s, 10H), 0.93 (t, *J* = 7.4 Hz, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.6, 151.8, 151.5, 138.5, 131.9, 120.4, 119.7, 112.6, 112.1, 64.1, 64.0, 53.5, 52.8, 45.1, 44.9, 42.9, 38.7, 29.7, 28.1, 27.1, 25.8, 21.7, 12.7.

IR ν = 2940 (w), 2360 (w), 2330 (w), 1728 (m), 1442 (m),1365 (m), 1319 (m), 1211 (w), 1157 (w), 964 (w), 902 (s), 725 (s).

HRMS (ESI): calculated $[C_{23}H_{34}N_2O_6+H]^+$: 435.2489, found: 435.2482.

8-Ethyl 2-methyl (*Z*)-1-(nonan-3-ylidene)-2,8-diazaspiro[4.5]deca-6,9-diene-2,8-dicarboxylate (3ab)



Following general procedure on 0.5 mmol scale. Purification via column chromatography with 10% ethyl acetate in hexane. The product was isolated as a yellow oil (109 mg, 0.28 mmol, 56%). The product was present as a 1:1 mixture of amide bond rotamers. The signals of both rotamers are listed.

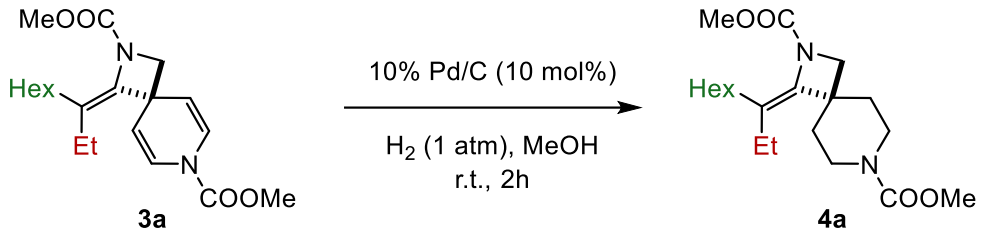
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 0.5H), 6.94 (s, 0.5H), 6.83 (d, *J* = 8.1 Hz, 1H), 6.70 (d, *J* = 8.2 Hz, 1H), 4.95 – 4.63 (m, 3.2H), 3.70 (s, 3H), 2.23 – 2.16 (m, 2H), 2.05 – 1.96 (m, 2H), 1.76 (t, *J* = 6.8 Hz, 3H), 1.33 (m, 7H), 1.29 – 1.17 (m, 12H), 0.92 (t, *J* = 7.4 Hz, 3H), 0.86 (td, *J* = 7.1, 3.6 Hz, 5H), 0.79 (t, *J* = 7.4 Hz, 1.5H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.8, 151.0, 124.7, 124.5, 107.8, 106.7, 63.0, 62.5, 52.0, 51.8, 48.3, 47.9, 37.9, 37.5, 32.0, 31.9, 31.6, 31.5, 31.4, 29.6, 29.5, 29.4, 29.4, 27.4, 24.8, 22.6, 14.3, 14.0, 12.1, 12.0.

IR ν = 2957 (w), 2929 (w), 2867 (w), 1722 (s), 1704 (s), 1532 (w), 1456 (w), 1413 (w), 1335 (m), 1375 (m), 1333 (m), 1310 (s), 1214 (w), 1133 (w), 1135 (m), 958 (w), 914 (s), 743 (s).

HRMS (ESI): calculated $[C_{22}H_{34}N_2O_4+H]^+$: 391.2591, found: 391.2590.

5. Diversification

Partial reduction



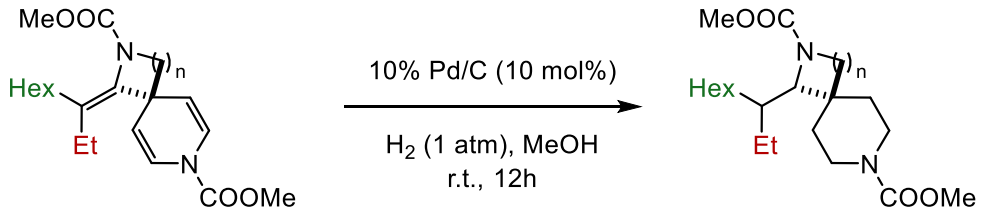
To a solution of dimethyl (*Z*)-1-(decan-3-ylidene)-2,7-diazaspiro[3.5]nona-5,8-diene-2,7-dicarboxylate **3a** (90.5 mg, 0.25 mmol, 1.0 equiv.) in MeOH (2.0 mL) was added 10% Pd/C (21.2 mg, 10.0 mol%). The reaction mixture was vigorously stirred for 2 h under H_2 (1 atm). Upon the completion of the reaction, the solution was filtrated through celite. Filter cake was washed with EtOAc, and the solvent was removed on a rotary evaporator. The crude was purified by flash column chromatography (silica gel, 30% ethyl acetate in hexane) to afford dimethyl (*Z*)-1-(4-oxononan-3-ylidene)-2,7-diazaspiro[3.5]nonane-2,7-dicarboxylate (**4a**) as colorless oil (85.5 mg, 0.22 mmol, 90%). The product was present as a 1:1 mixture of amide bond rotamers. The signals of both rotamers are listed.

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 4.11 (bs, 2H), 3.69 (s, 3H), 3.69 (s, 3H), 3.64 (s, 2H), 2.65 (t, *J* = 12.9 Hz, 2H), 2.36 – 2.26 (m, 1H), 1.96 – 1.86 (m, 4H), 1.77 (s, 1H), 1.74 (s, 1H), 1.60 – 1.21 (m, 8H), 0.96 (t, *J* = 7.4, 3H), 0.87 (t, *J* =6.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.4, 155.9, 155.8, 155.8, 153.5, 139.2, 139.1, 121.1, 120.9, 56.9, 52.6, 52.4, 44.3, 44.3, 40.9, 33.5, 33.4, 31.9, 31.8, 31.6, 29.5, 29.3, 29.2, 29.2, 28.9, 28.6, 28.3, 28.0, 28.0, 27.8, 27.6, 22.7, 22.6, 22.6, 22.5, 22.5, 14.1, 14.0, 14.0, 14.0, 13.6, 13.4, 12.0.

IR ν = 2931 (w), 2861 (w), 2360 (s), 2337 (w), 1689 (s), 1519 (m), 1458 (m),1396 (m), 1249 (m), 1211 (w), 1157 (w), 964 (w), 915 (s), 721 (s).

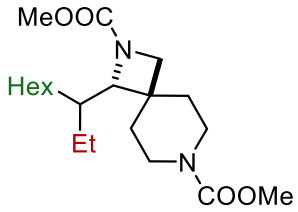
HRMS (ESI): calculated $[C_{20}H_{34}N_2O_4+H]^+$: 381.2792, found: 381.2786.

Complete reduction



To a solution of aza-spiro dihydropyridine (0.25 mmol, 1.0 equiv.) in MeOH (2.0 mL) was added 10% Pd/C (21.2 mg, 10.0 mol%). The reaction mixture was vigorously stirred for 12 h under H_2 (1 atm). Upon the completion of the reaction, the solution was filtrated through celite. Filter cake was washed with EtOAc, and the solvent was removed on a rotary evaporator. The crude was purified by flash column chromatography (silica gel, ethyl acetate in hexane) to afford the final product.

Dimethyl 1-(nonan-3-yl)-2,7-diazaspiro[3.5]nonane-2,7-dicarboxylate (5a)



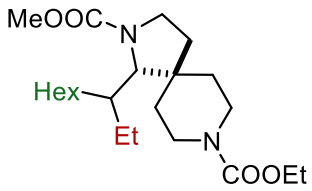
Following general procedure on 0.25 mmol scale. Purification via column chromatography with 30% ethyl acetate in hexane. The product was isolated as a yellow oil (81.1 mg, 0.21 mmol, 85%). The product was present as a 1:1 mixture of amide bond rotamers. The signals of both rotamers are listed.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (bs, 2H), 3.65 (d, J = 7.8 Hz, 1H), 3.62 (s, 3H), 3.62 (d, J = 1.9 Hz, 1H), 3.59 (s, 3H), 3.58 – 3.55 (d, J = 7.8 Hz, 2H), 2.72 (t, J = 12.8 Hz, 1H), 2.58 (t, J = 12.8 Hz, 1H), 1.78 – 1.73 (d, J = 13.3 Hz, 1H), 1.65 (d, J = 13.3 Hz, 1H), 1.57 (m, 4H), 1.45 (m, 1H), 1.24 – 1.14 (m, 10H), 0.88 – 0.73 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.7, 155.8, 73.7, 57.3, 52.6, 52.2, 40.8, 40.5, 40.0, 37.9, 37.1, 32.3, 31.8, 30.6, 29.7, 27.0, 23.0, 22.6, 14.1, 11.50.

IR ν = 2928 (w), 2870 (w), 1695 (s), 1454 (m), 1388 (m), 1270 (m), 905 (s), 718 (s).

HRMS (ESI): calculated $[C_{20}H_{36}N_2O_4+H]^+$: 383.2788, found: 383.2780.

8-Ethyl 2-methyl 1-(nonan-3-yl)-2,8-diazaspiro[4.5]decane-2,8-dicarboxylate (5b)



Following general procedure on 0.25 mmol scale. Purification via column chromatography with 30% ethyl acetate in hexane. The product was isolated as a yellow oil (81.3 mg, 0.205 mmol, 82%). The product was present as a 1:1 mixture of amide bond rotamers. The signals of both rotamers are listed.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71 (s, 3H), 3.69 (s, 3H), 3.63 (d, *J* = 3.8 Hz, 2H), 3.33 (t, *J* = 10.1 Hz, 2H), 3.08 – 3.01 (m, 2H), 2.78 (q, *J* = 6.4 Hz, 1H), 1.96 – 1.84 (m, 4H), 1.77 (d, *J* = 6.8 Hz, 1H), 1.63 – 1.48 (m, 4H), 1.27 – 1.16 (m, 10H), 0.87 – 0.80 (m, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.9, 154.8, 51.6, 48.0, 46.3, 45.6, 39.0, 30.6, 30.5, 30.4, 29.8, 29.8, 28.2, 26.3, 24.2, 23.6, 2.59, 21.5, 21.5, 13.0, 10.7.

IR ν = 2954 (w), 2931 (w), 2870 (w),1689 (s), 1458 (m), 1381 (m), 1265 (m), 910 (s), 732 (s).

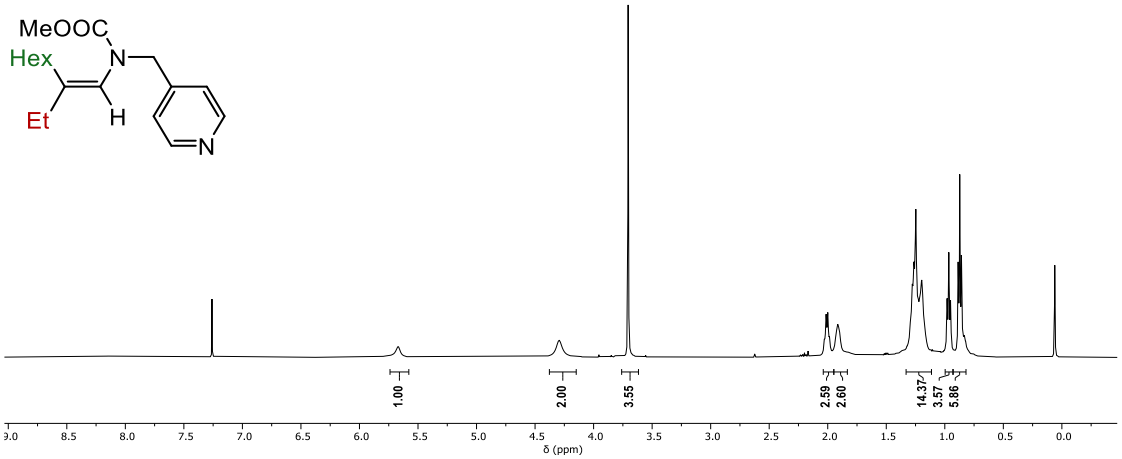
HRMS (ESI): calculated $[C_{20}H_{36}N_2O_4+H]^+$: 397.2723, found: 397.2730.

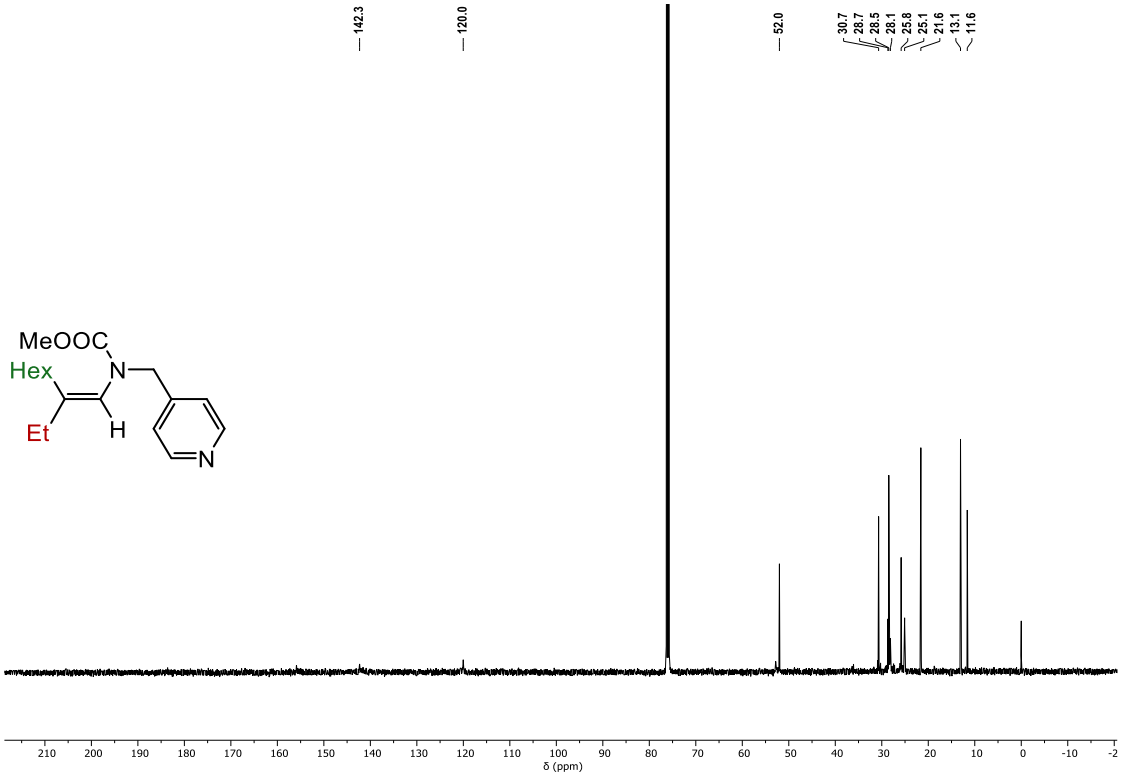
6. References

1. M. Orchin*, J. Chem. Educ*. 1989, **66**, 586.
2. J. Tammiku, P. Burk and A. Tuulmets, *J. Phys. Chem. A.* 2001*,* **105**, 8554.
3. I. Yenice, S. Basceken and M. Balci, *Beilstein J. Org. Chem*. 2017, **13**, 825.
4. P. Tundo, S. Bressanello, A. Loris and G. Sathicq, *Pure Appl. Chem*. 2005, **77**, 1719.
5. L. Andna and L. Miesch, *Org. Biomol. Chem.* 2019*,* **17**, 5688.
6. Y.-Q. Zhang, Y.-B. Chen, J.-R. Liu, S.-Q. Wu, X.-Y. Fan, Z.-X. Zhang, X. Hong and L.-W. Ye, *Nat. Chem*. 2021, **13**, 1093.
7. M. O. Frederick, J. A. Mulder, M. R. Tracey, R. P. Hsung, J. Huang, K. C. M. Kurtz, L. Shen and C. J. Douglas, *J. Am. Chem. Soc*. 2003, **125**, 2368.
8. P. Starkov, J. T. Moore, D. C. Duquette, B. M. Stoltz and I. Marek, *J. Am. Chem. Soc.* 2017, **139**, 9615.

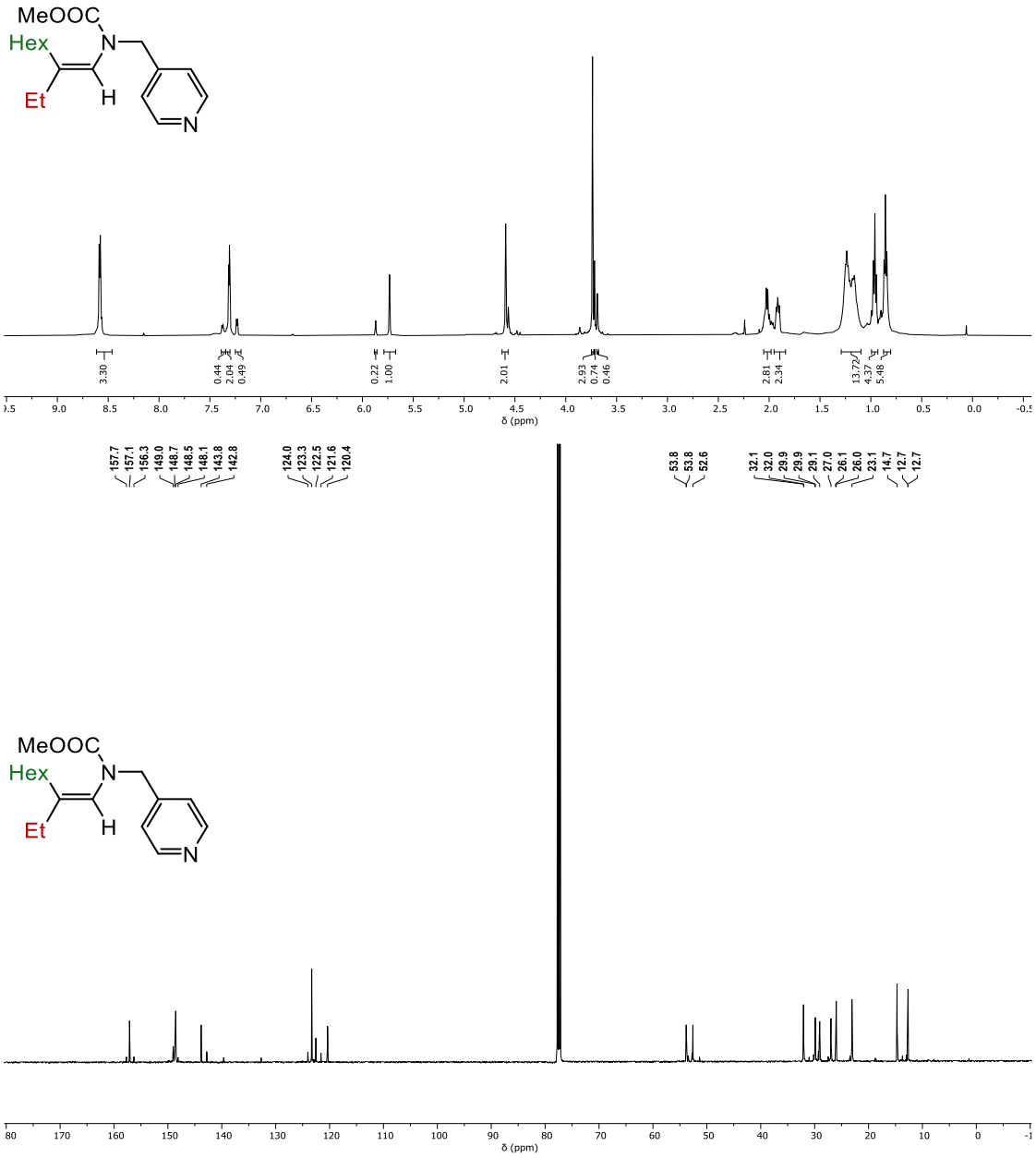
6. NMR Spectra

^{1}H and ^{13}C NMR spectra for compound **2a at -273K**

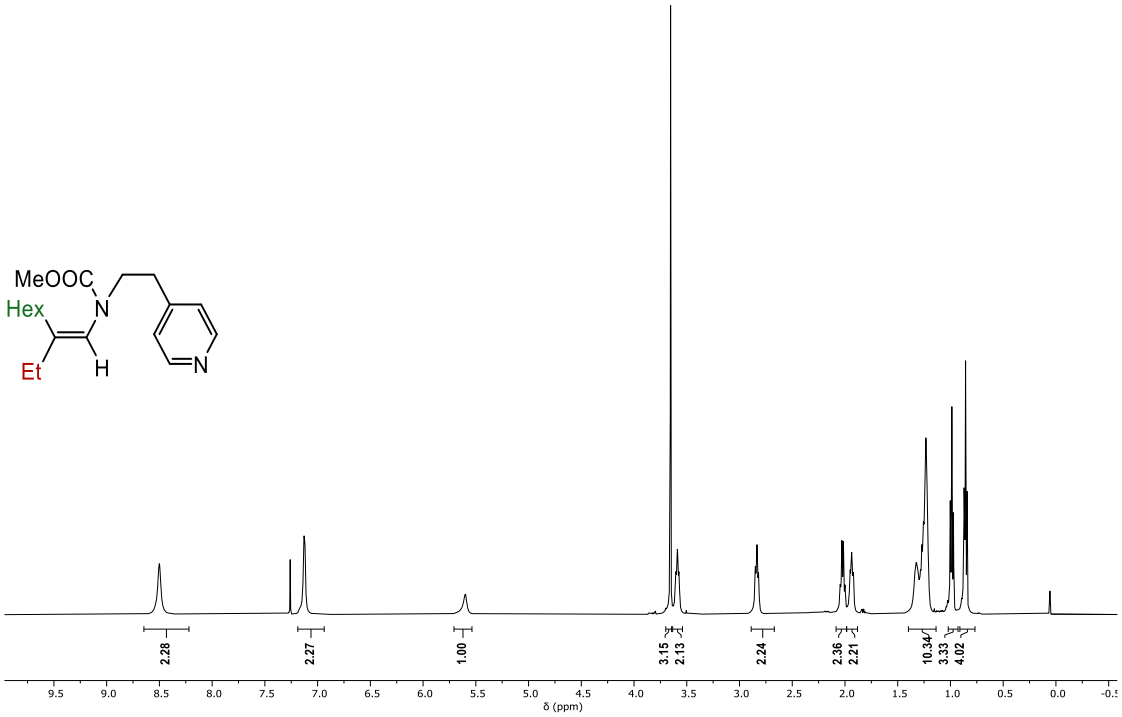


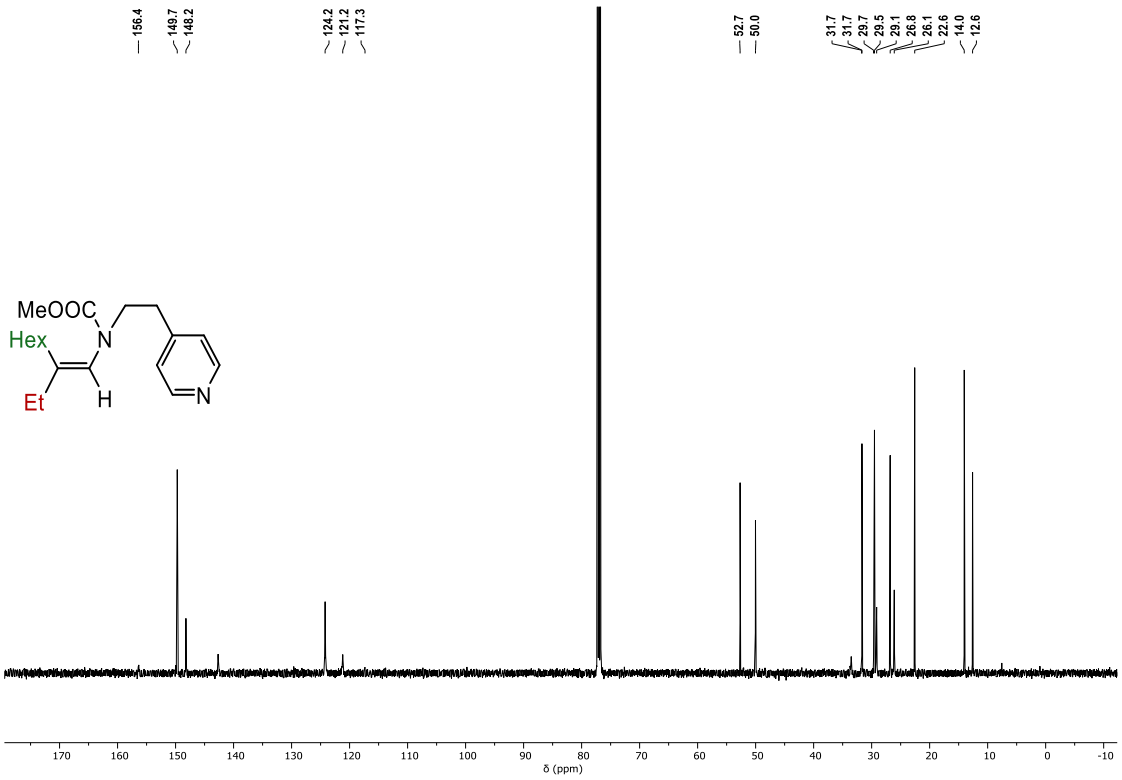


^{1}H and ^{13}C NMR spectra for compound **2a at -208K**

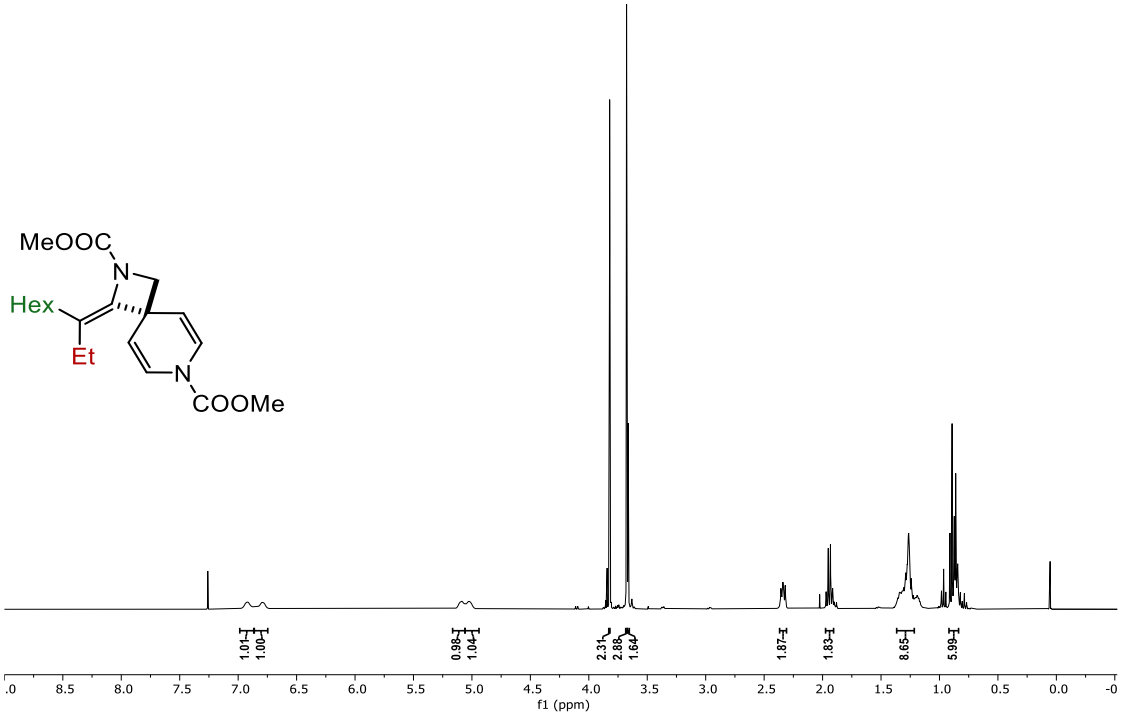


^{1}H and ^{13}C NMR spectra for compound **2u**

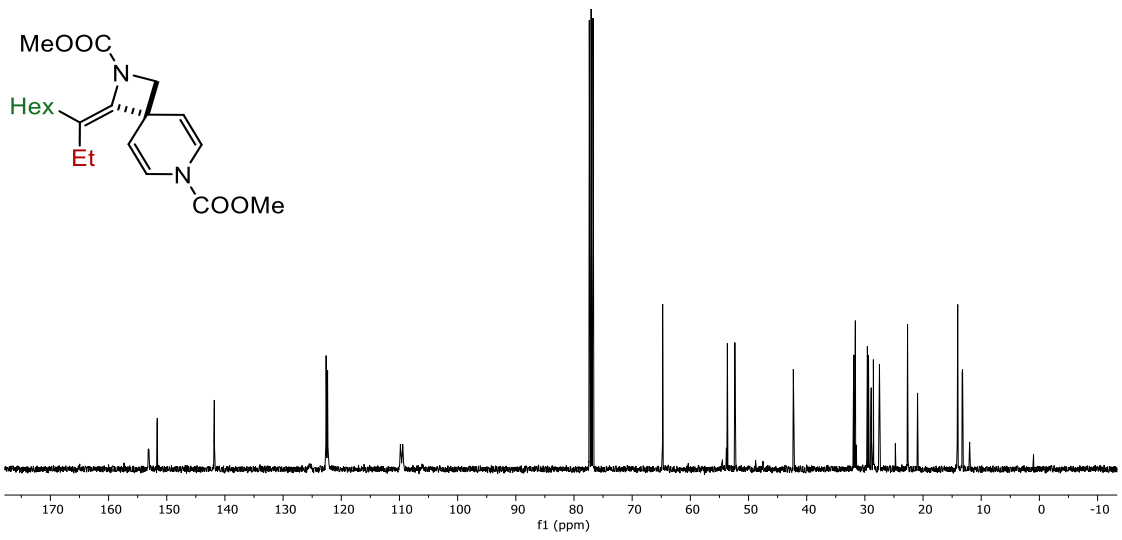




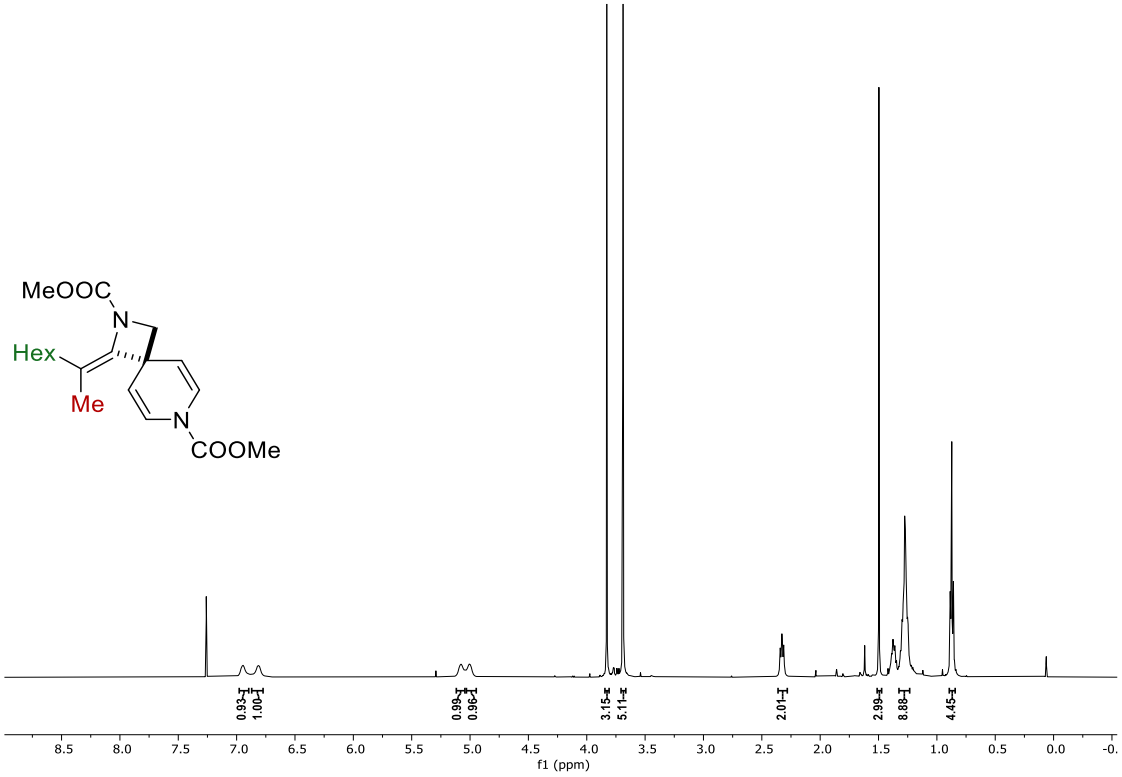
^{1}H and ^{13}C NMR spectra for compound **3a**

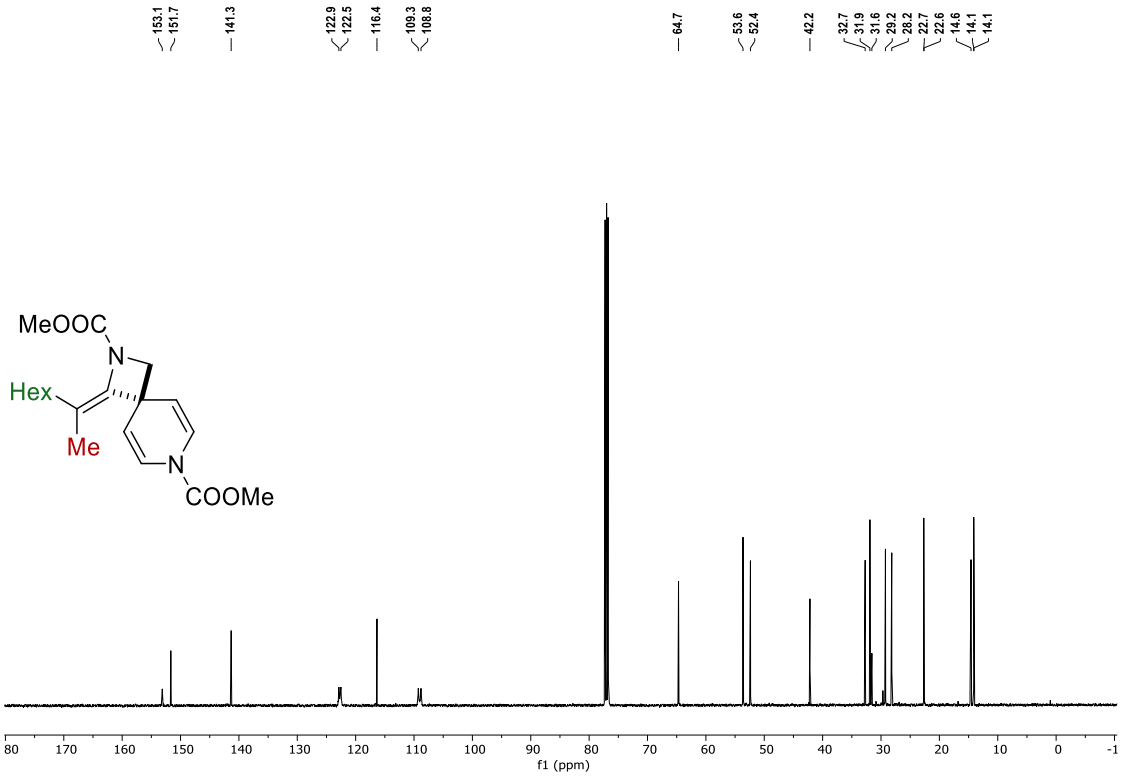


153.2 153.1 151.7 151.6 142.0 141.8 122.6 122.4 109.8 109.4 64.8 53.7 53.6 52.4 52.3 42.3 42.3 31.9 31.6 29.6 29.4 28.9 28.5 28.4 27.5 22.7 22.7 22.6 22.6 20.9 14.1 14.1 14.0 13.3 13.2

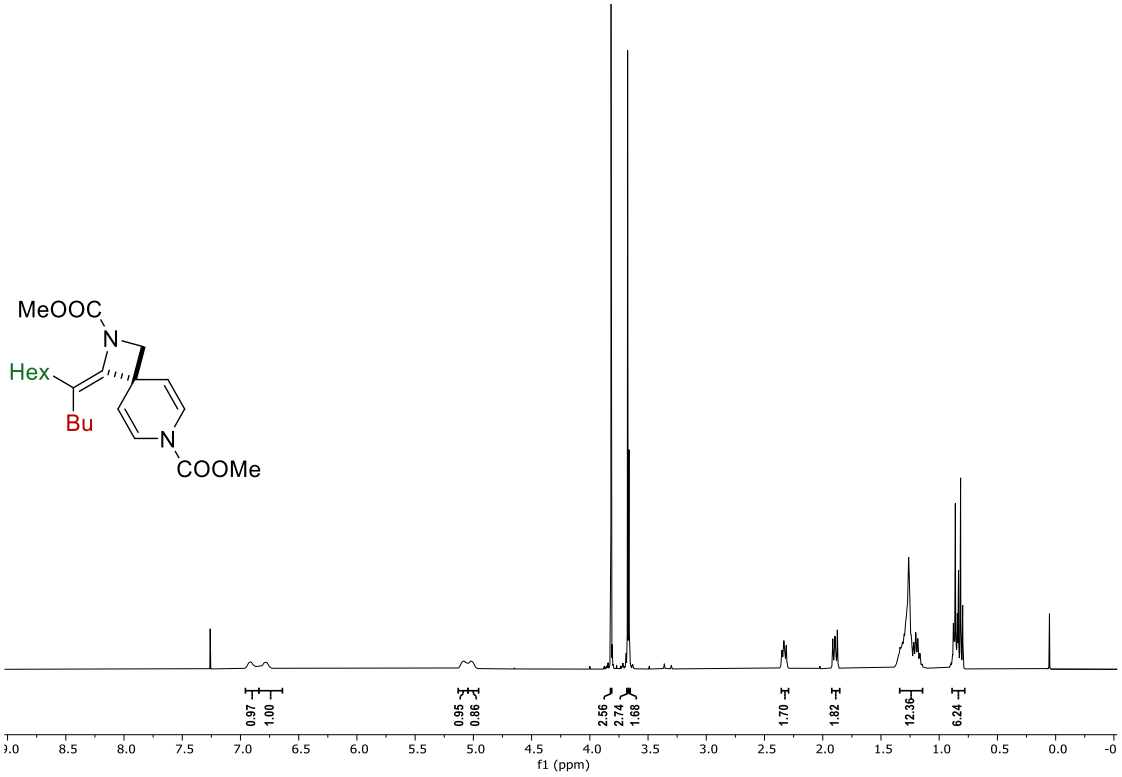


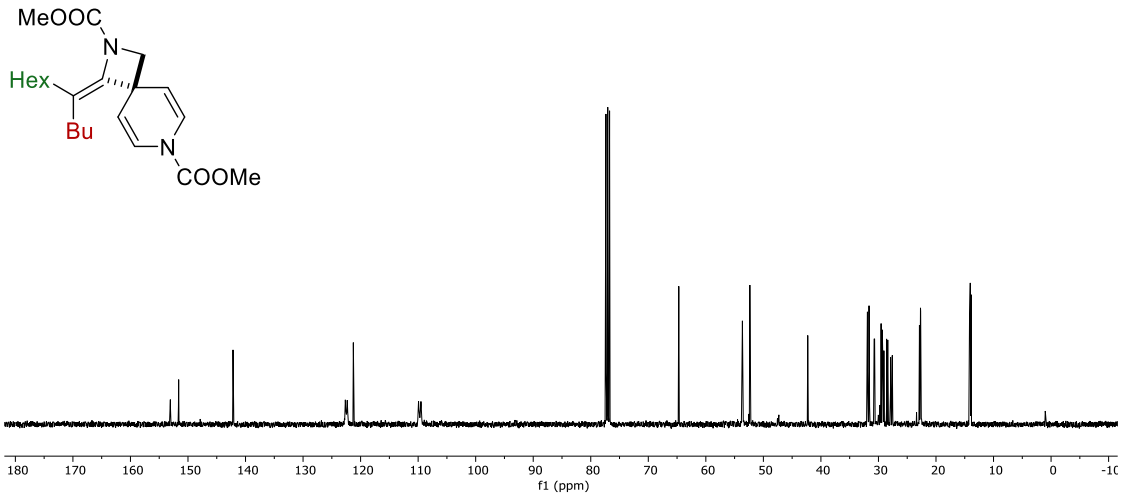
^{1}H and ^{13}C NMR spectra for compound **3b**



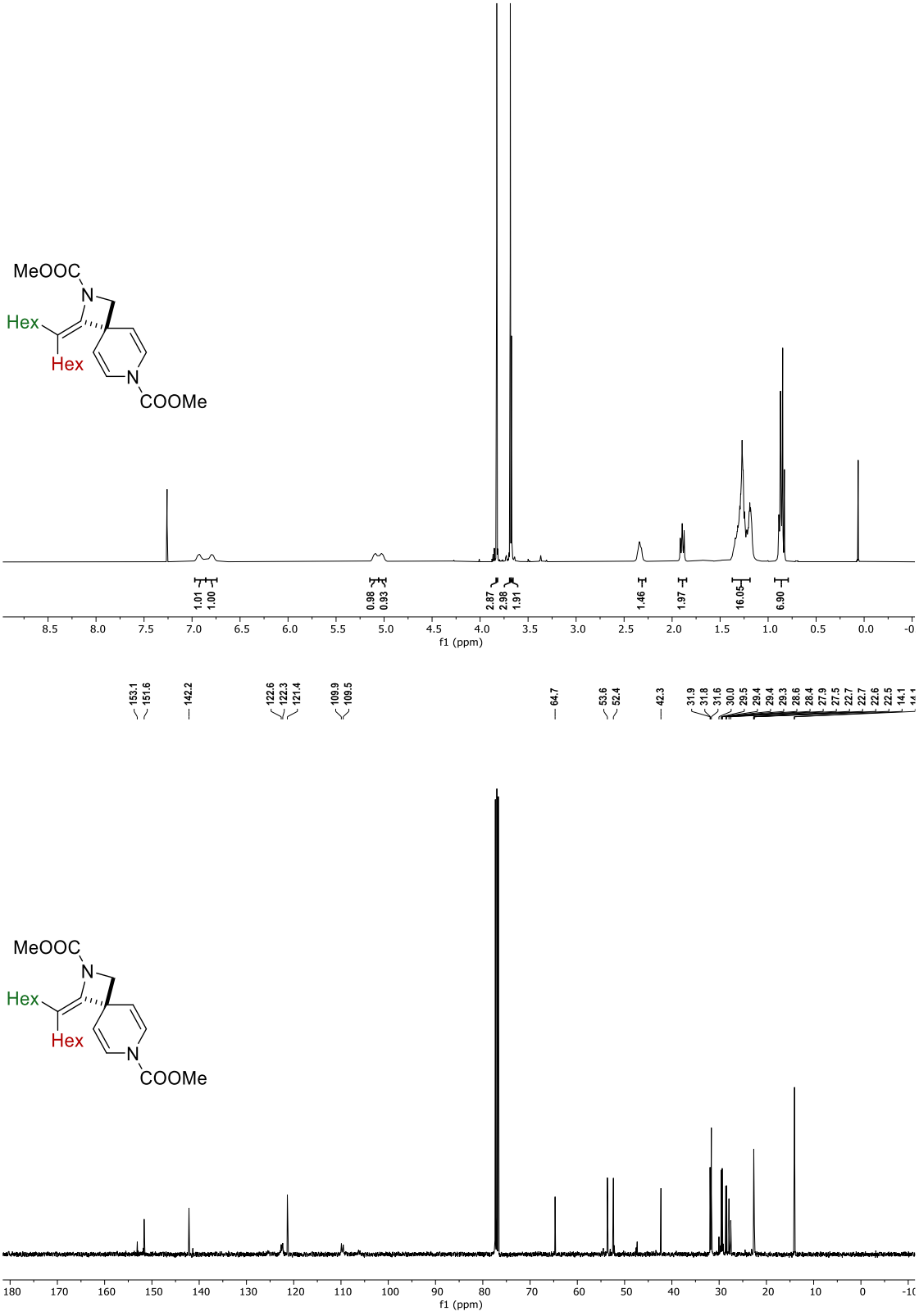


^{1}H and ^{13}C NMR spectra for compound **3c**

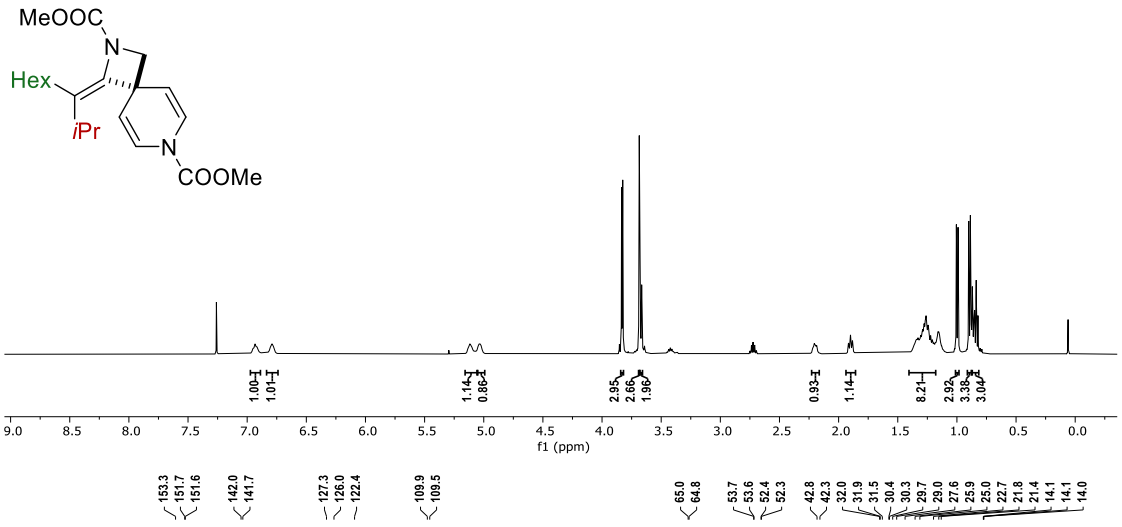


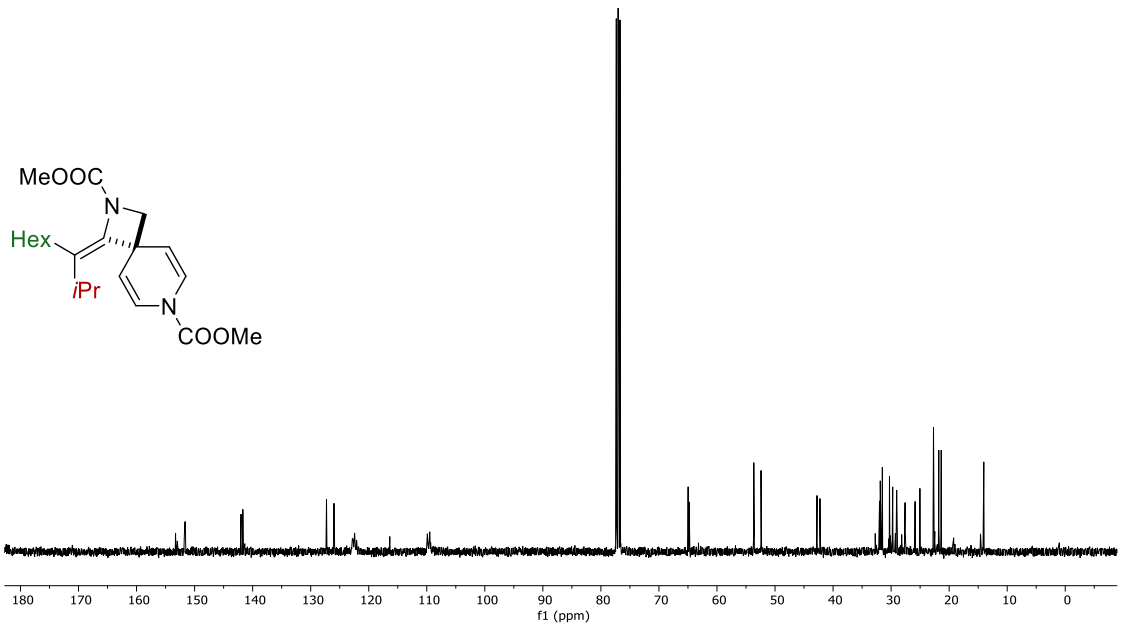


^{1}H and ^{13}C NMR spectra for compound **3d**

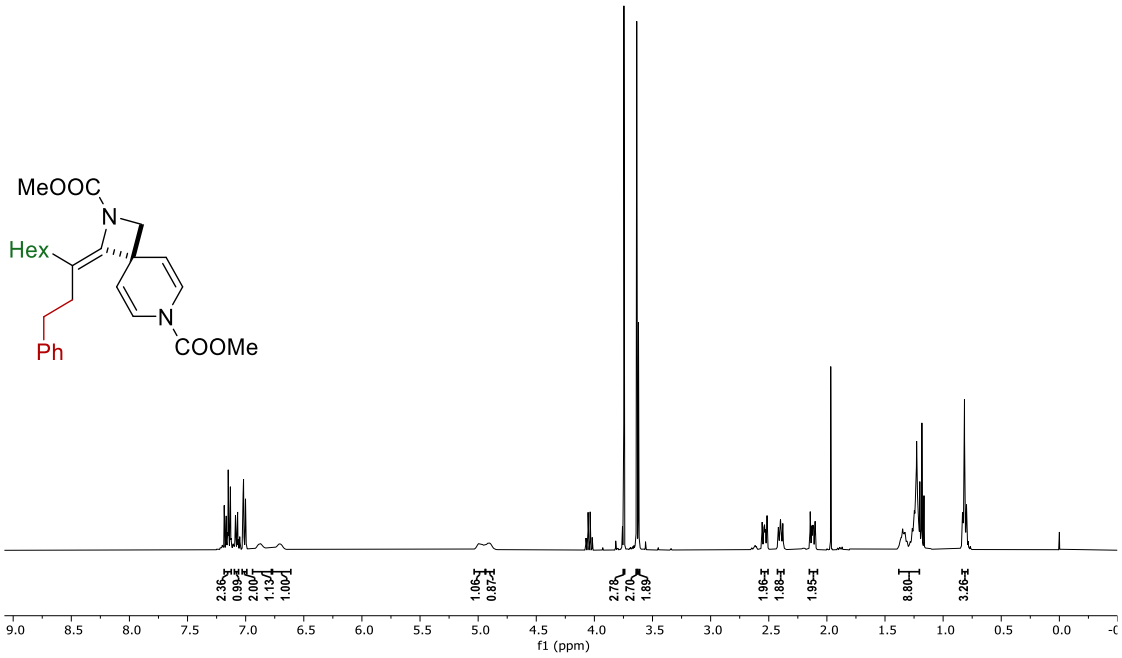


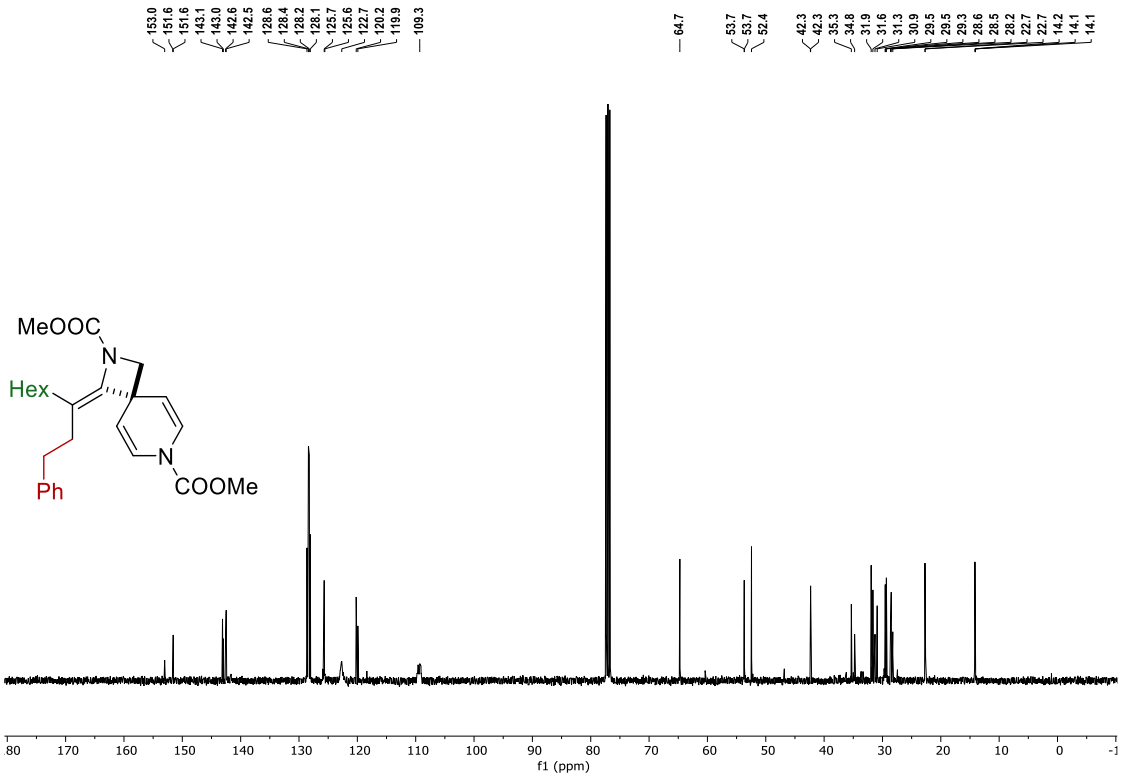
^{1}H and ^{13}C NMR spectra for compound **3e**



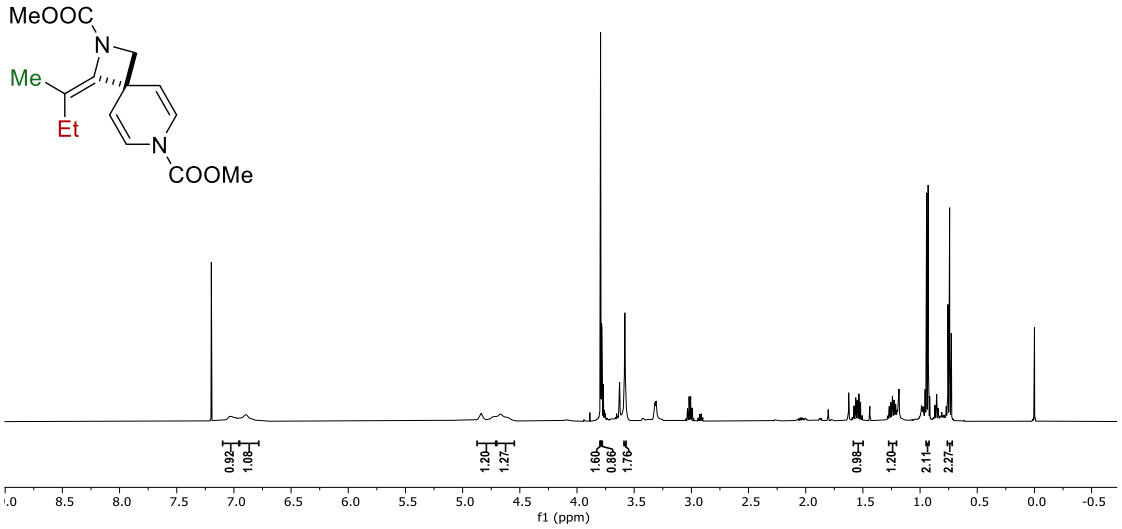


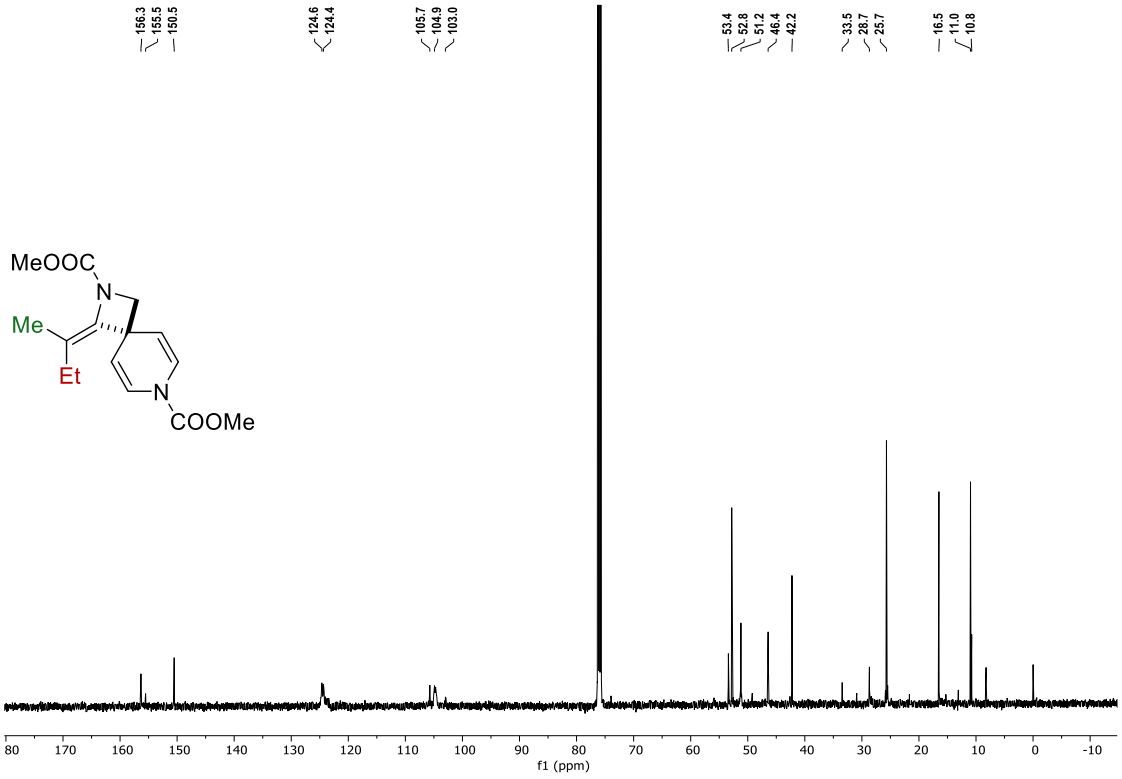
^{1}H and ^{13}C NMR spectra for compound **3f**



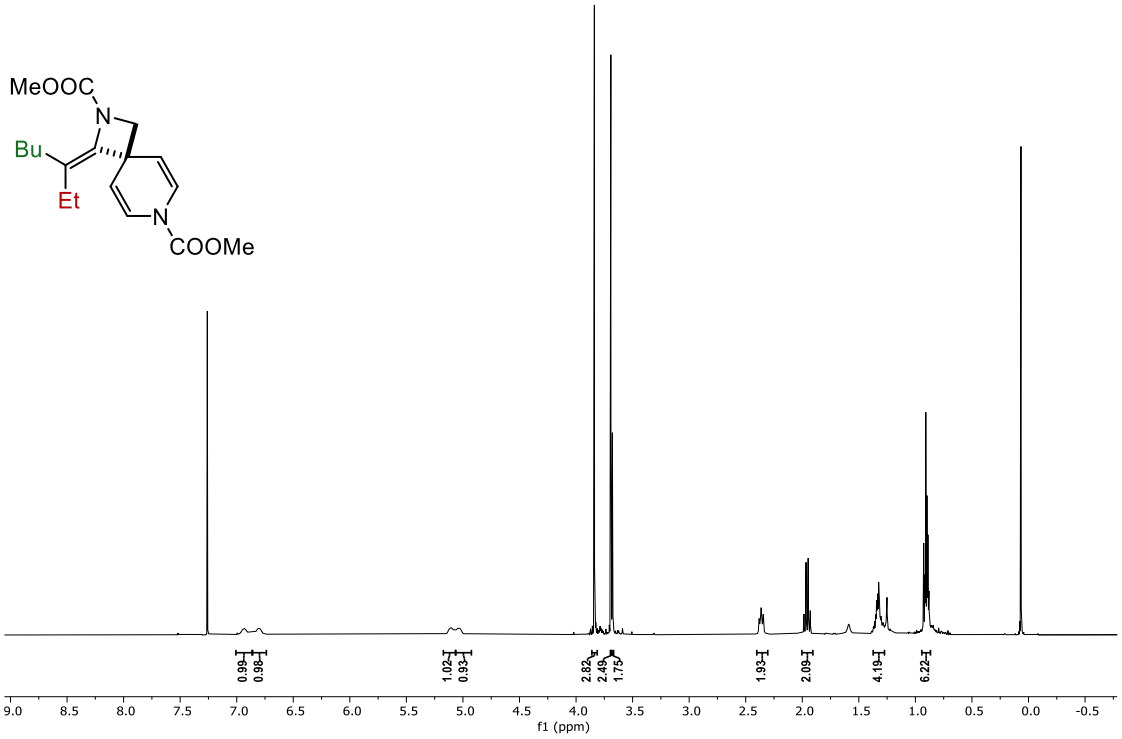


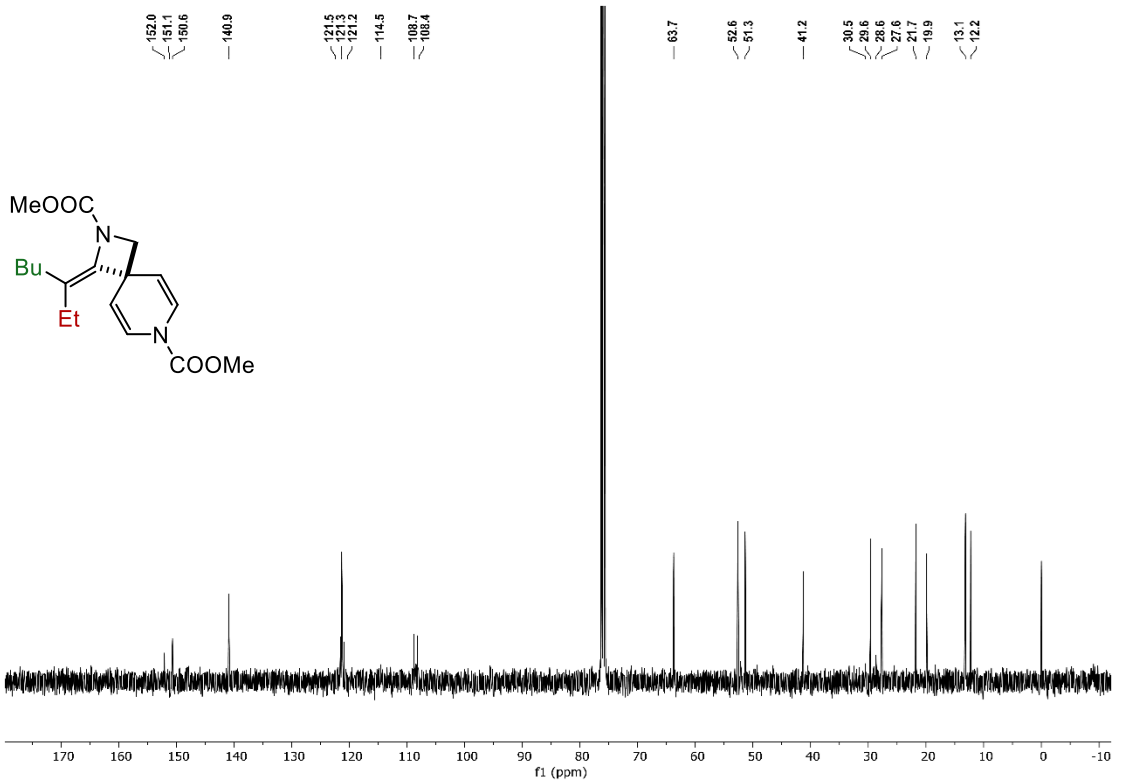
^{1}H and ^{13}C NMR spectra for compound **3g**



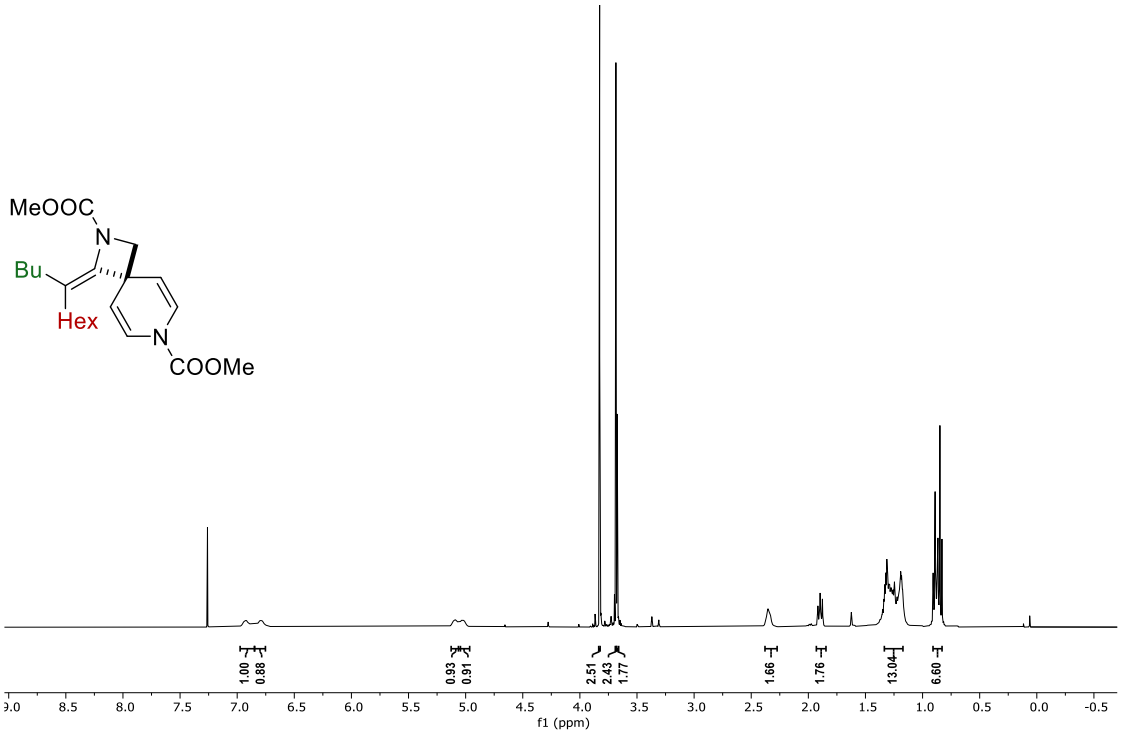


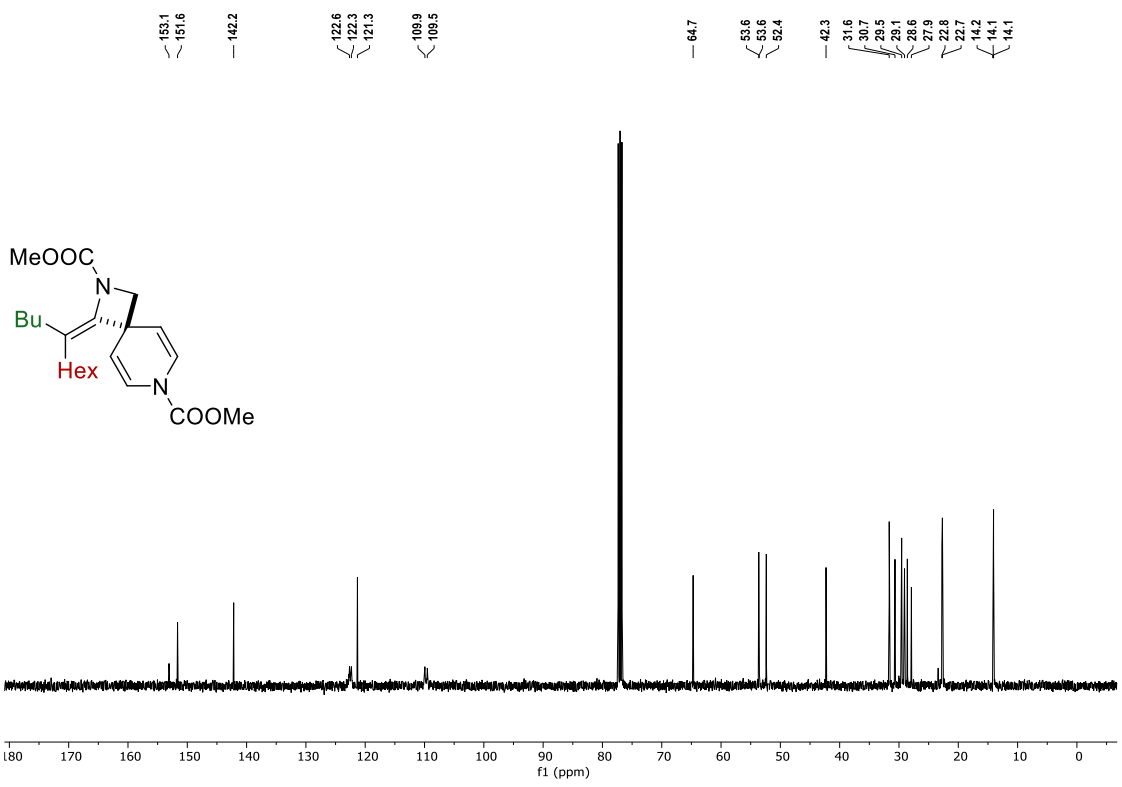
^{1}H and ^{13}C NMR spectra for compound **3h**



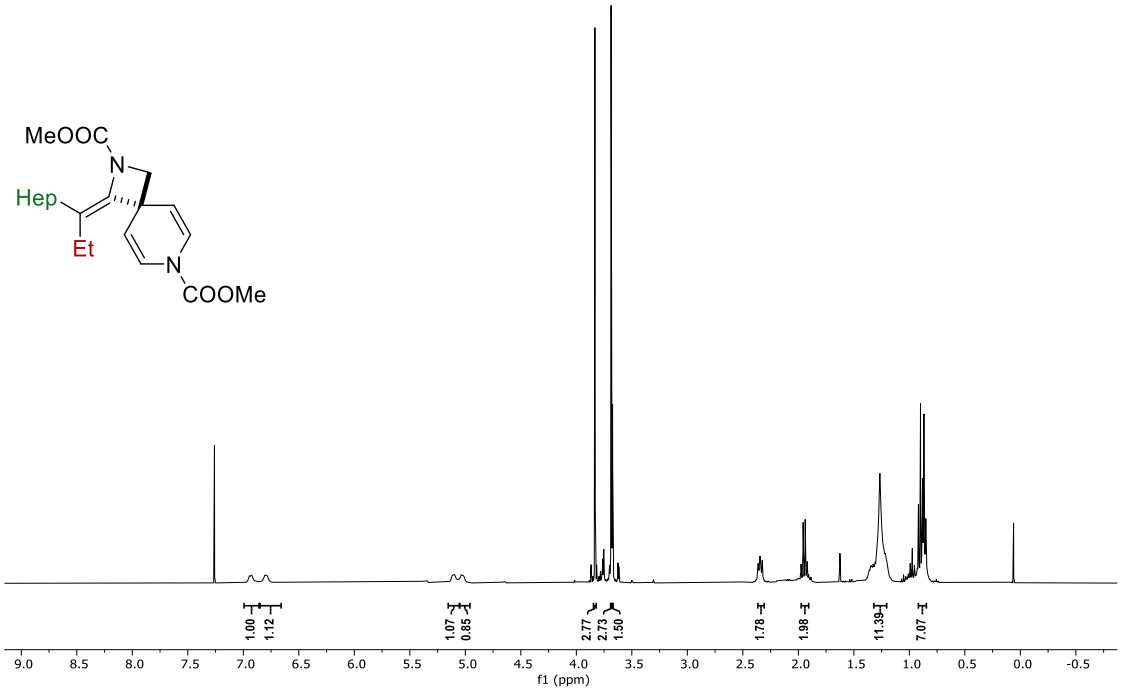


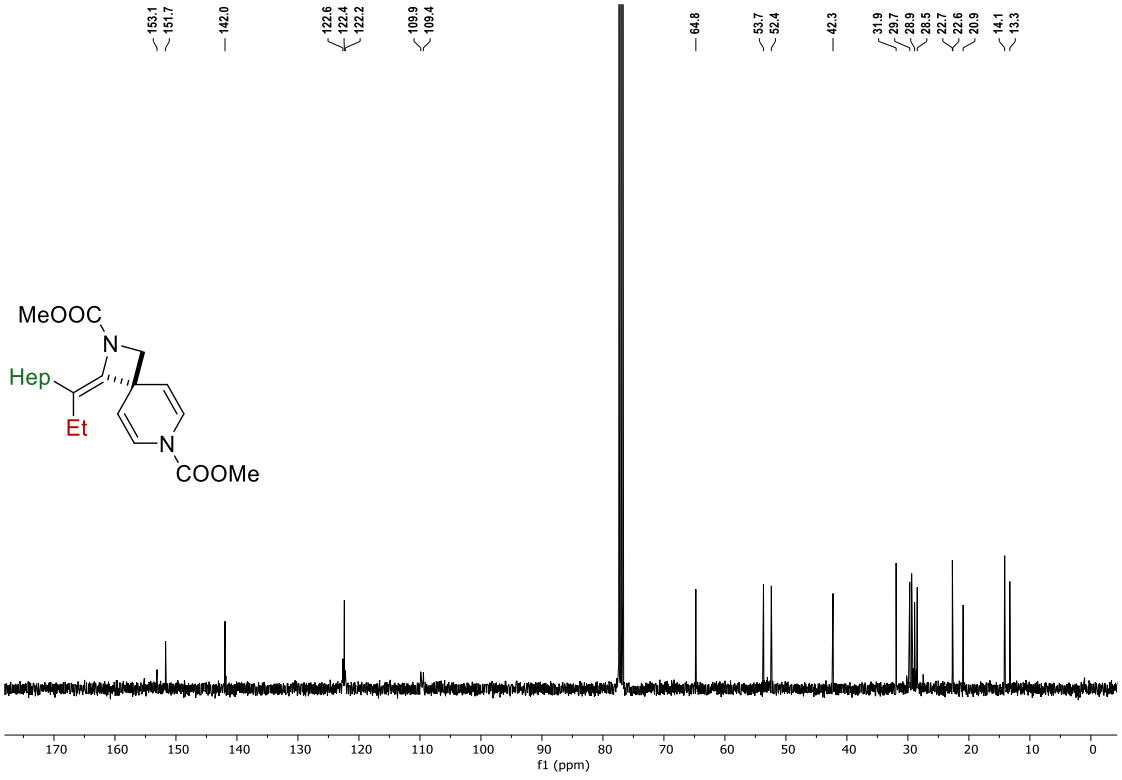
^{1}H and ^{13}C NMR spectra for compound **3i**



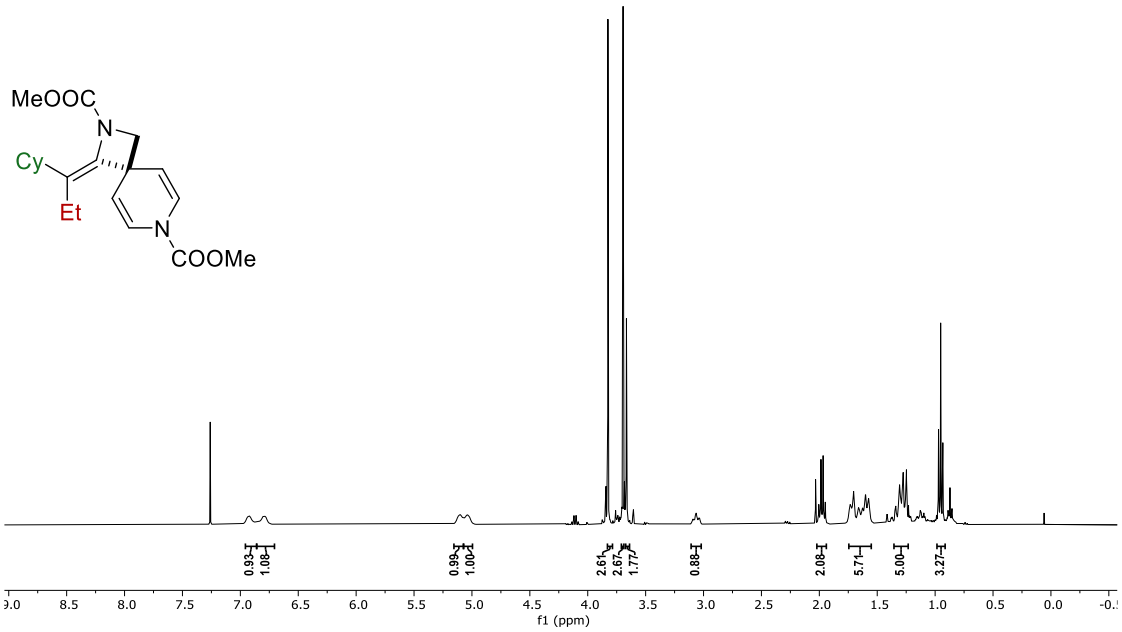


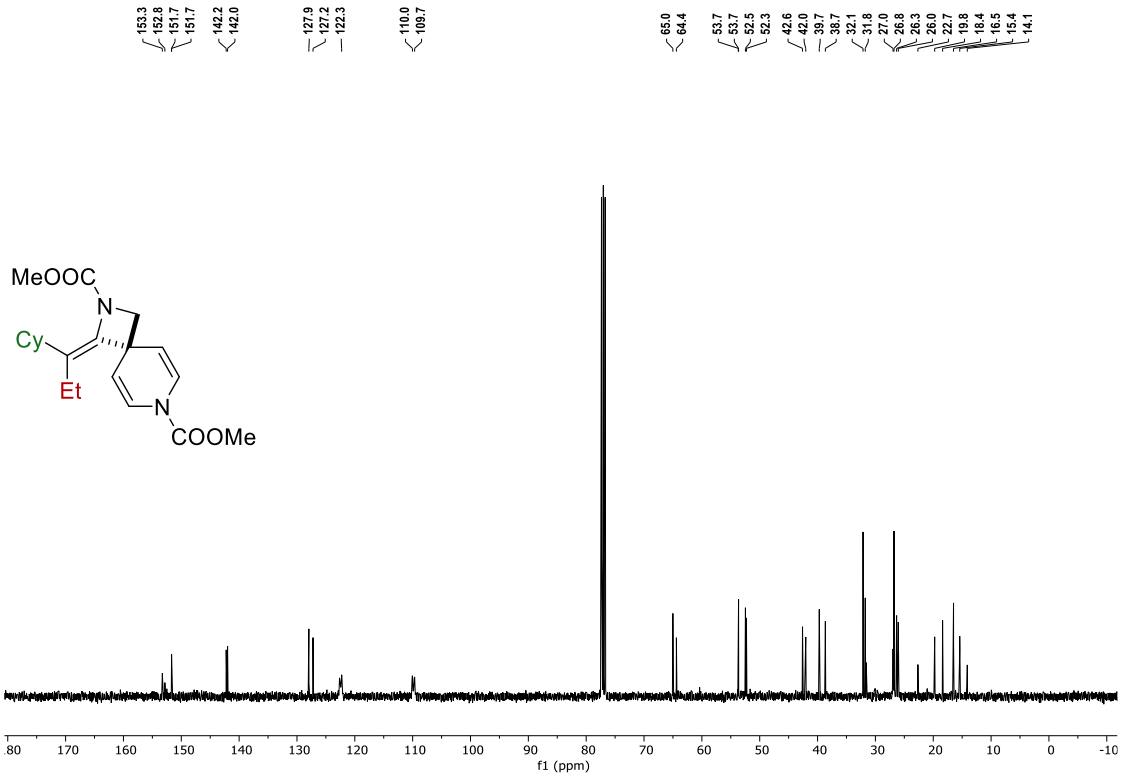
^{1}H and ^{13}C NMR spectra for compound **3j**



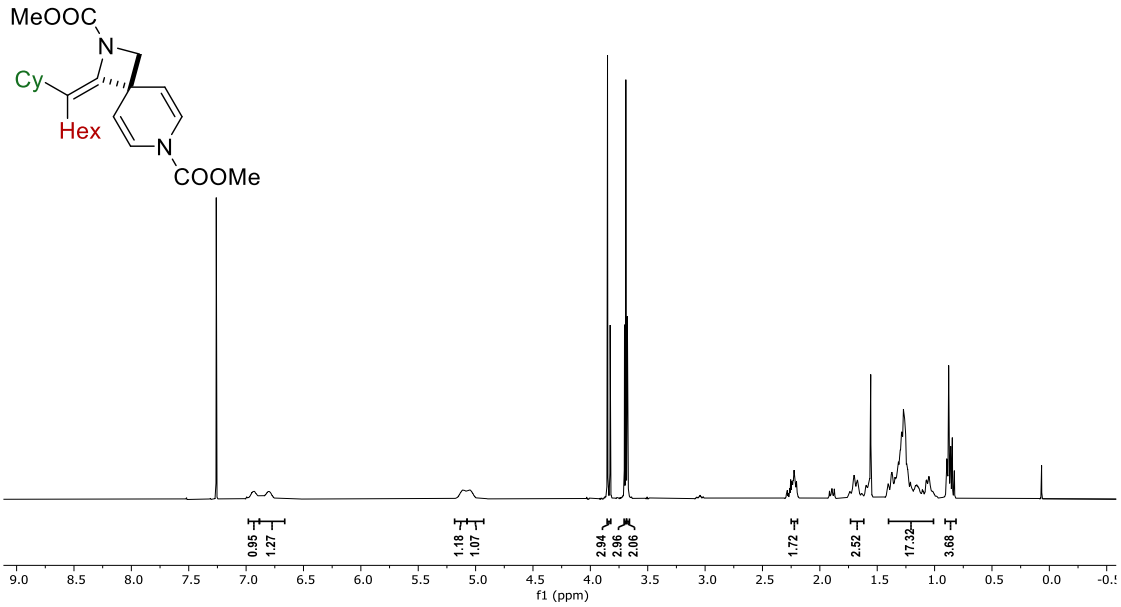


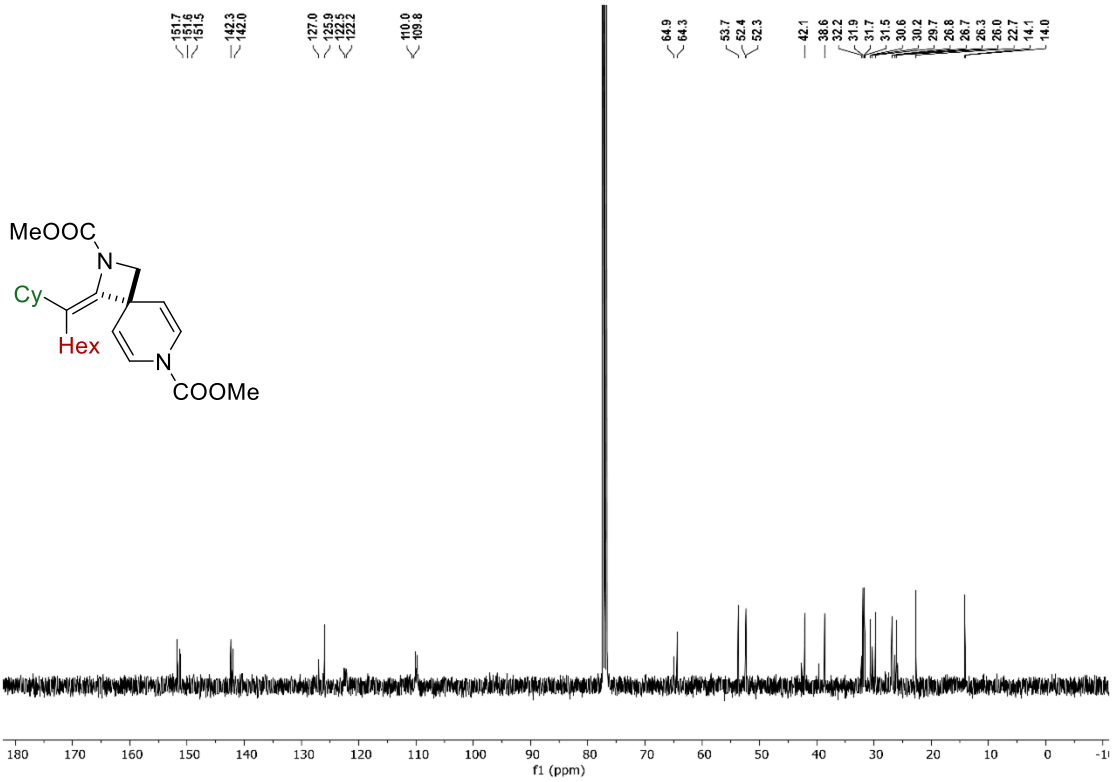
^{1}H and ^{13}C NMR spectra for compound **3k**



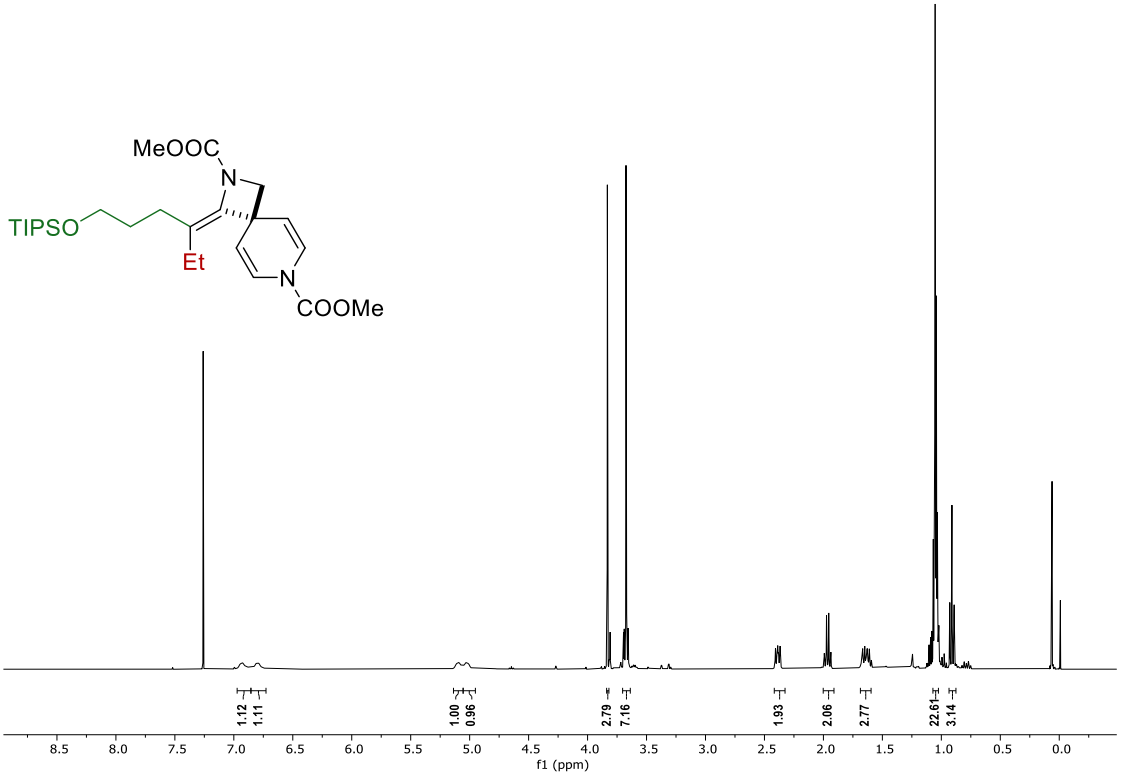


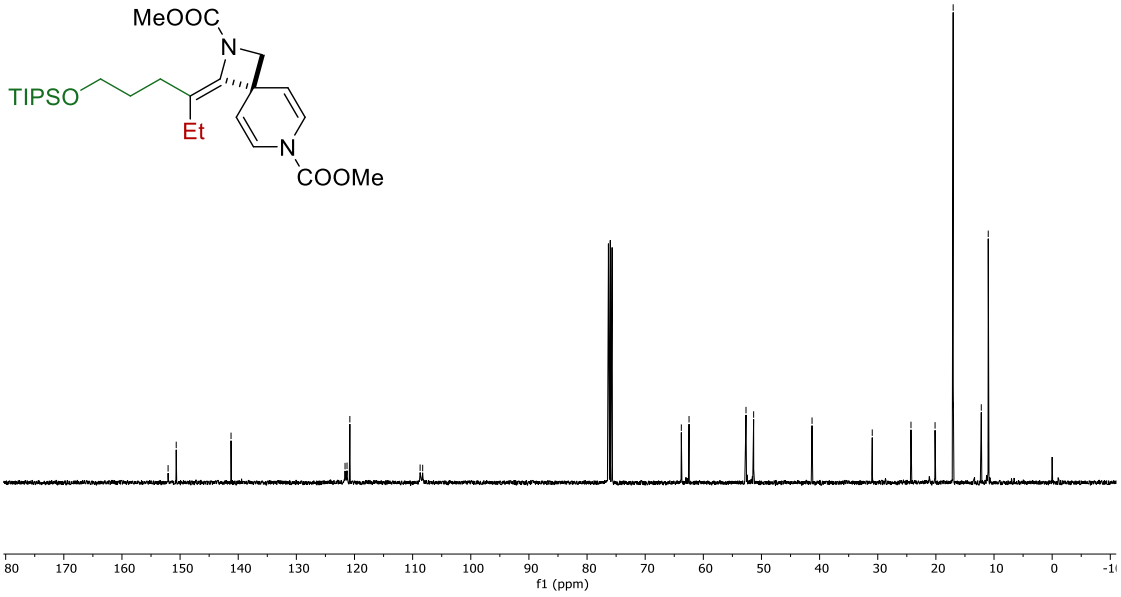
^{1}H and ^{13}C NMR spectra for compound **3l**



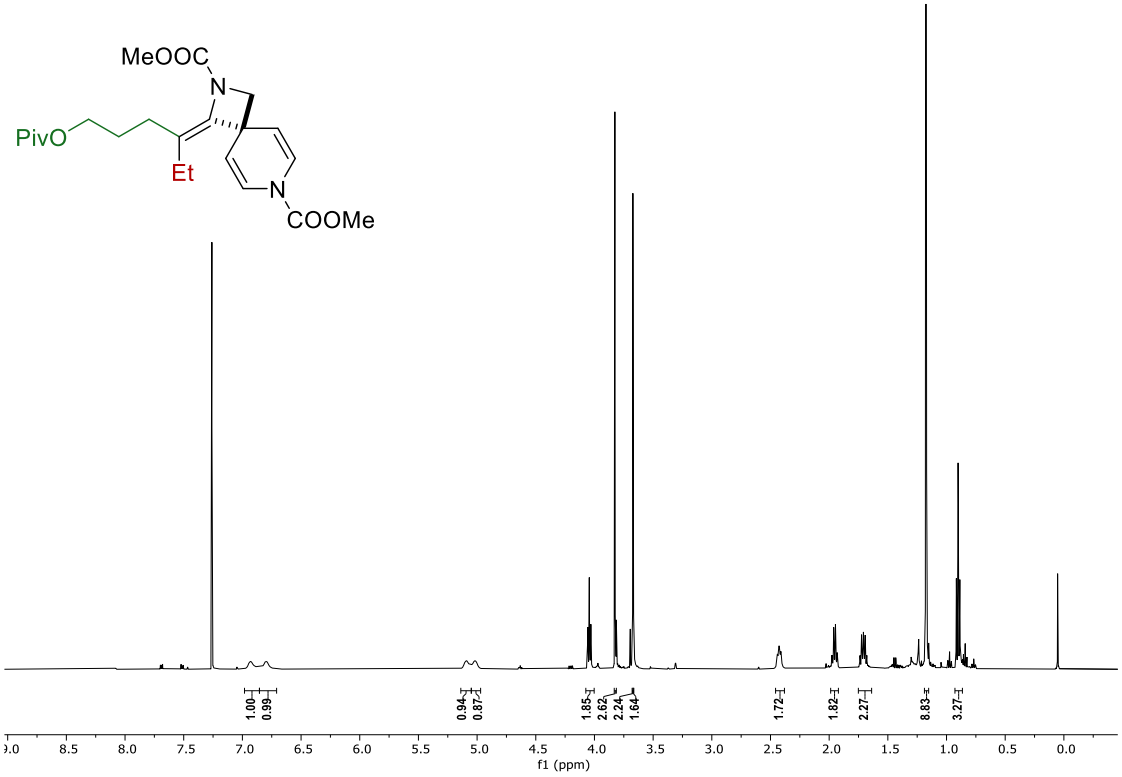


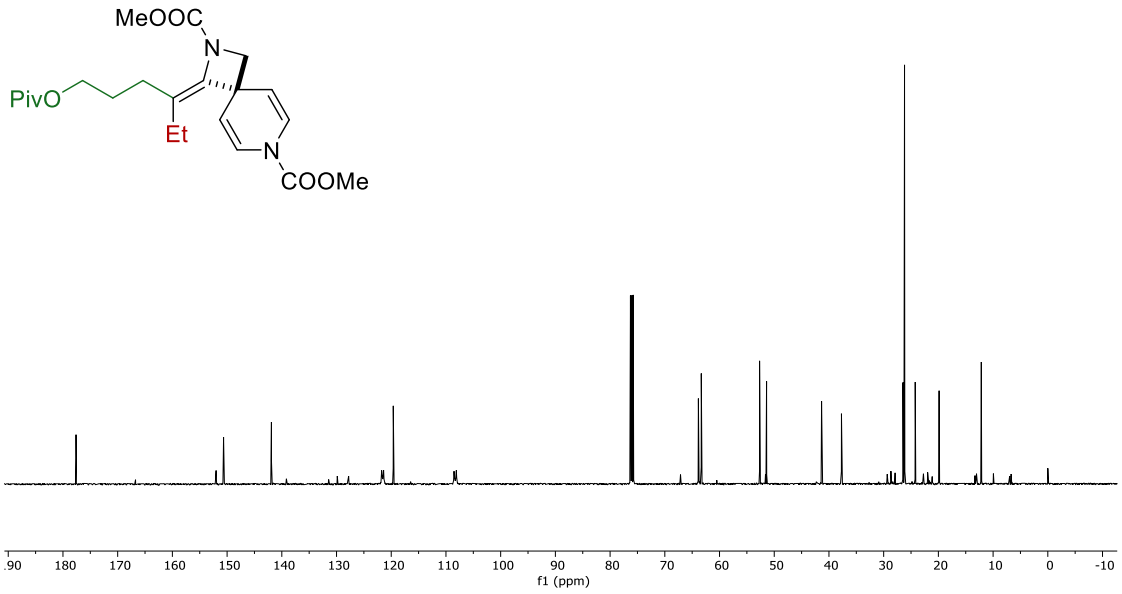
^{1}H and ^{13}C NMR spectra for compound **3m**



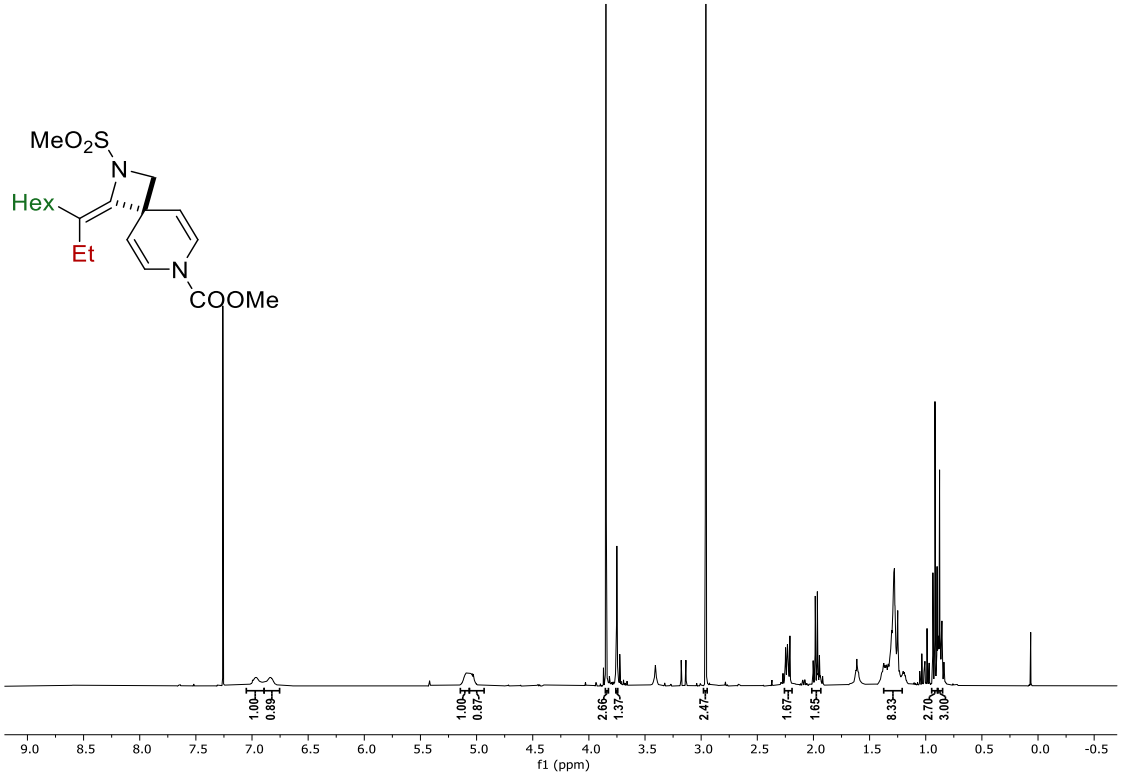


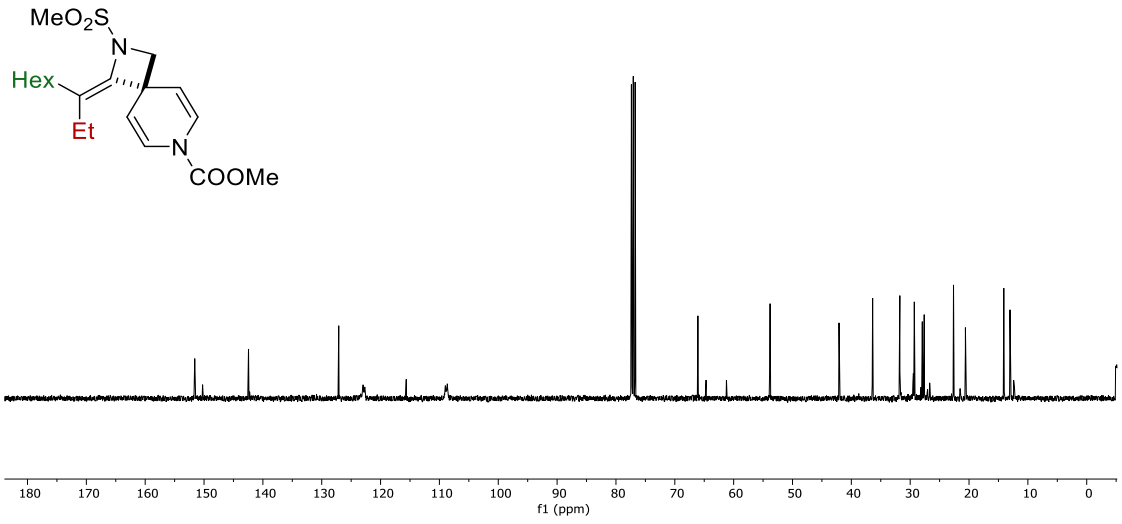
^{1}H and ^{13}C NMR spectra for compound **3n**



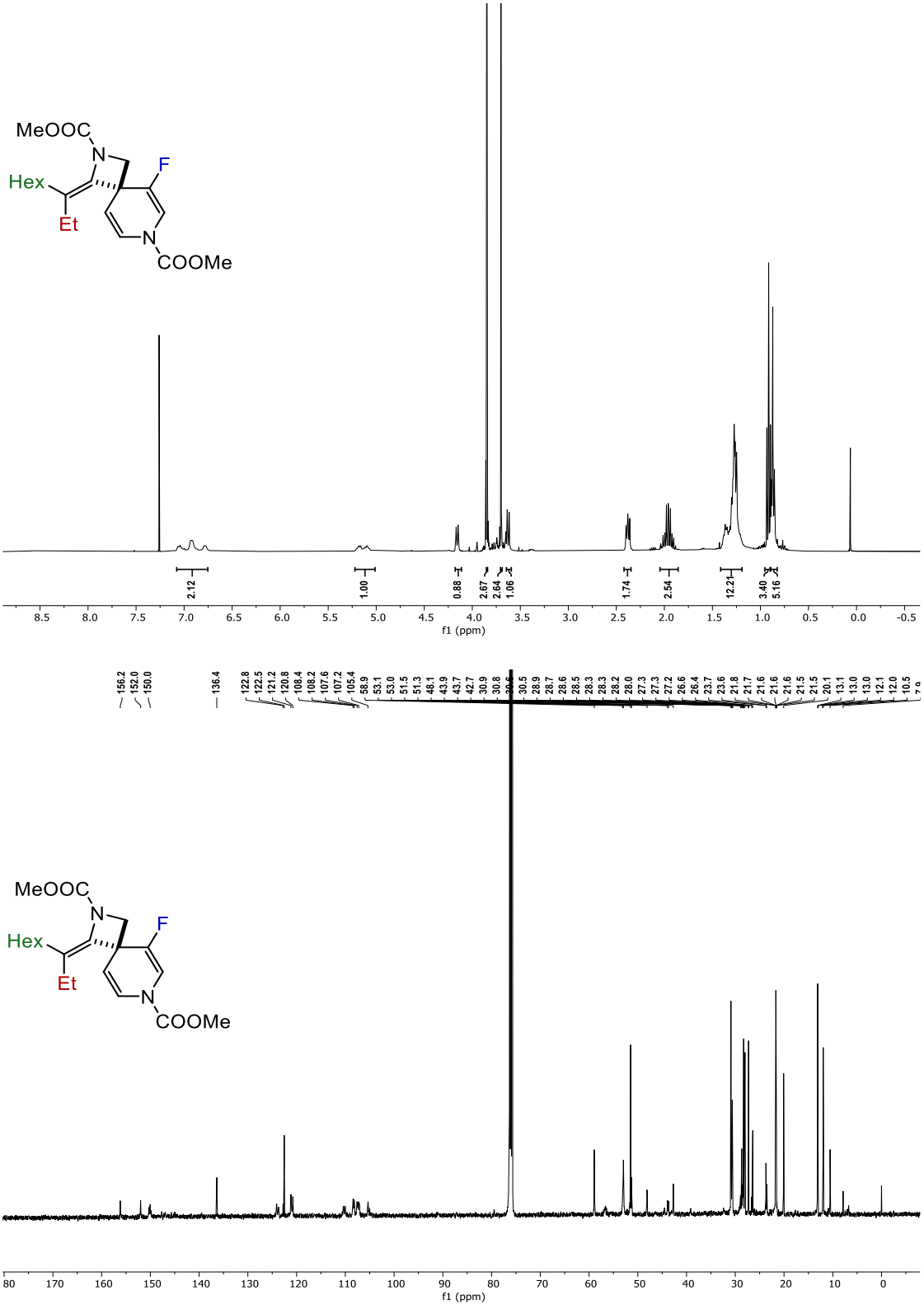


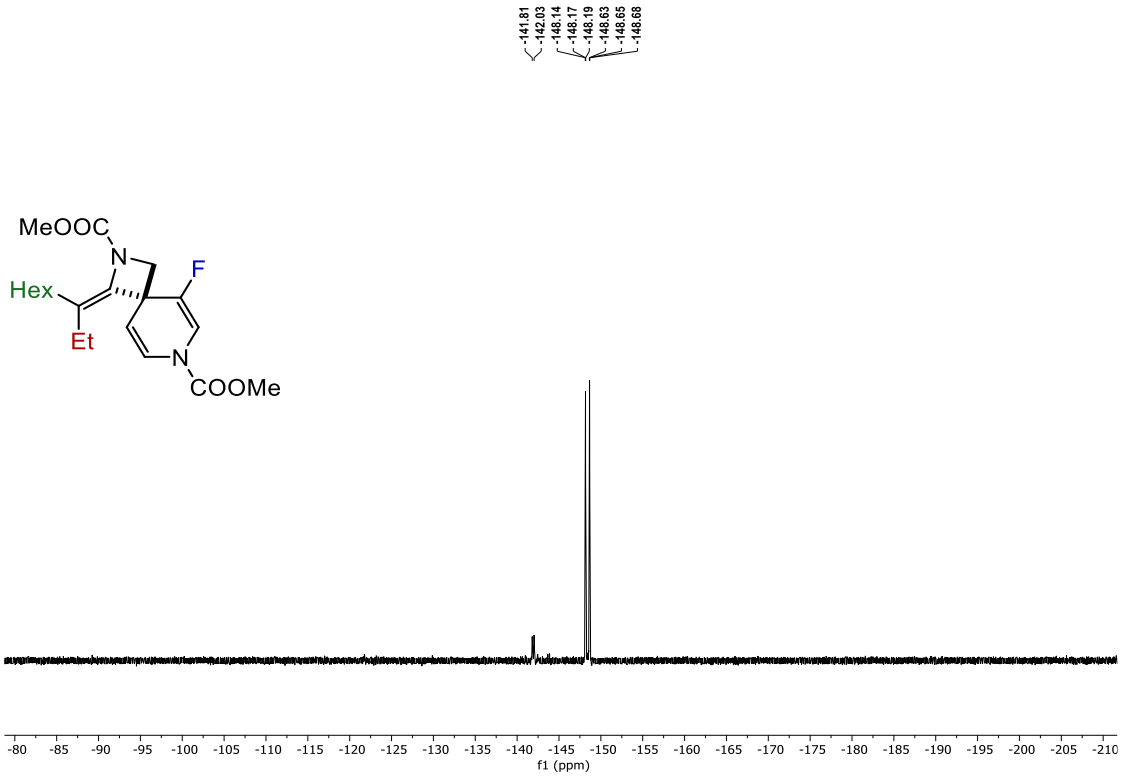
^{1}H and ^{13}C NMR spectra for compound **3o**



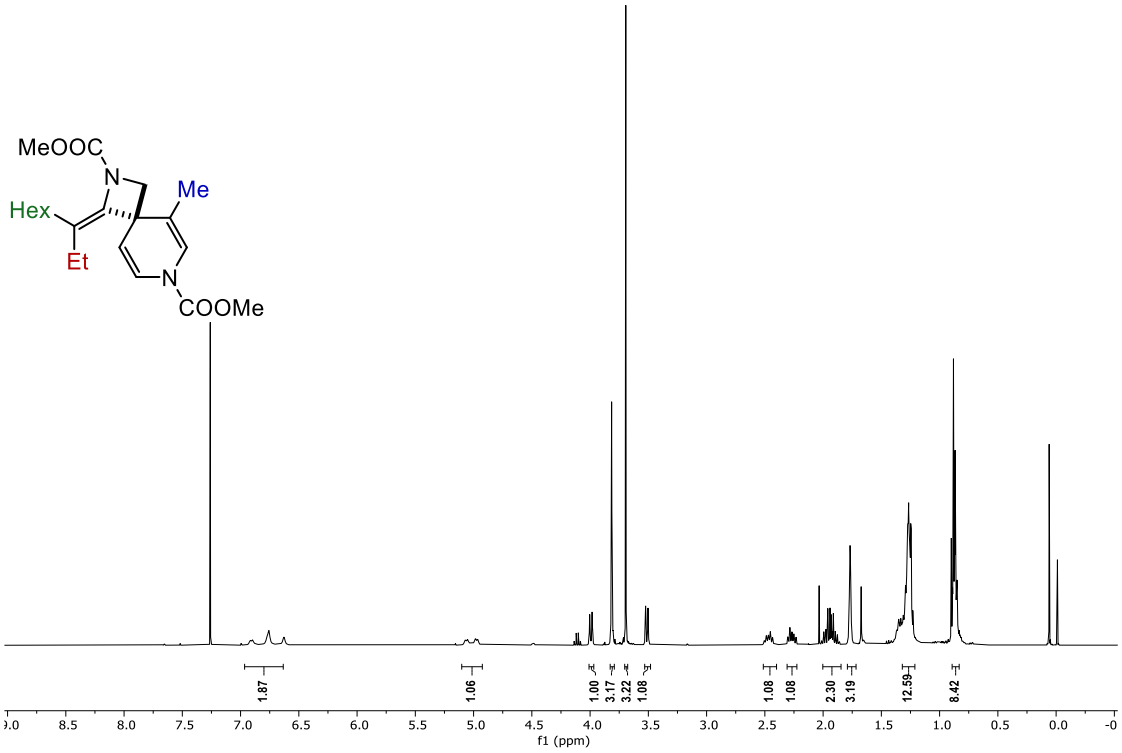


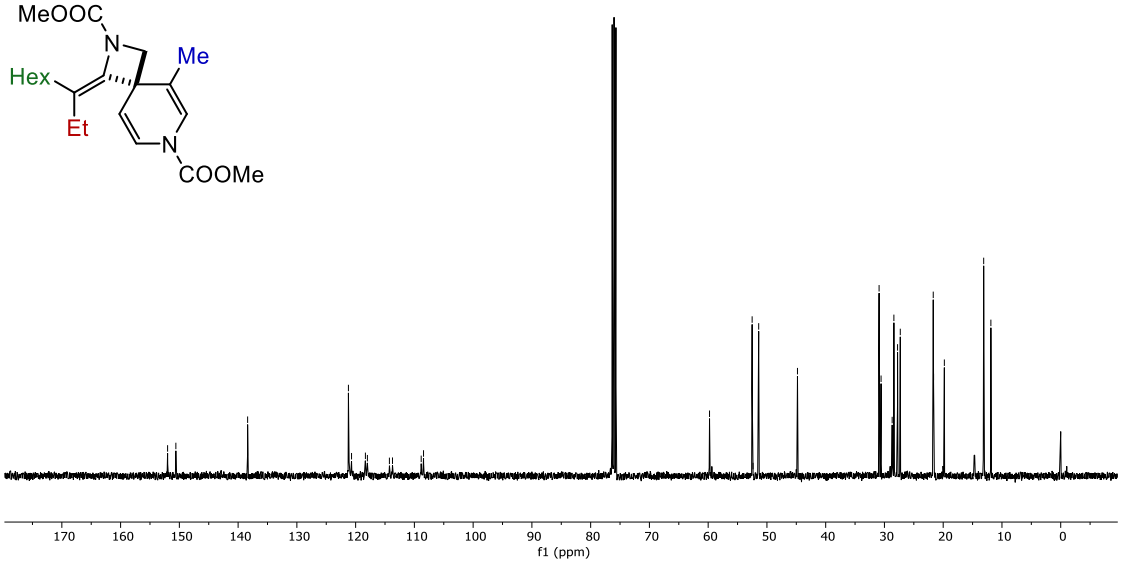
^{1}H, ^{13}C and ^{19}F NMR spectra for compound **3p**



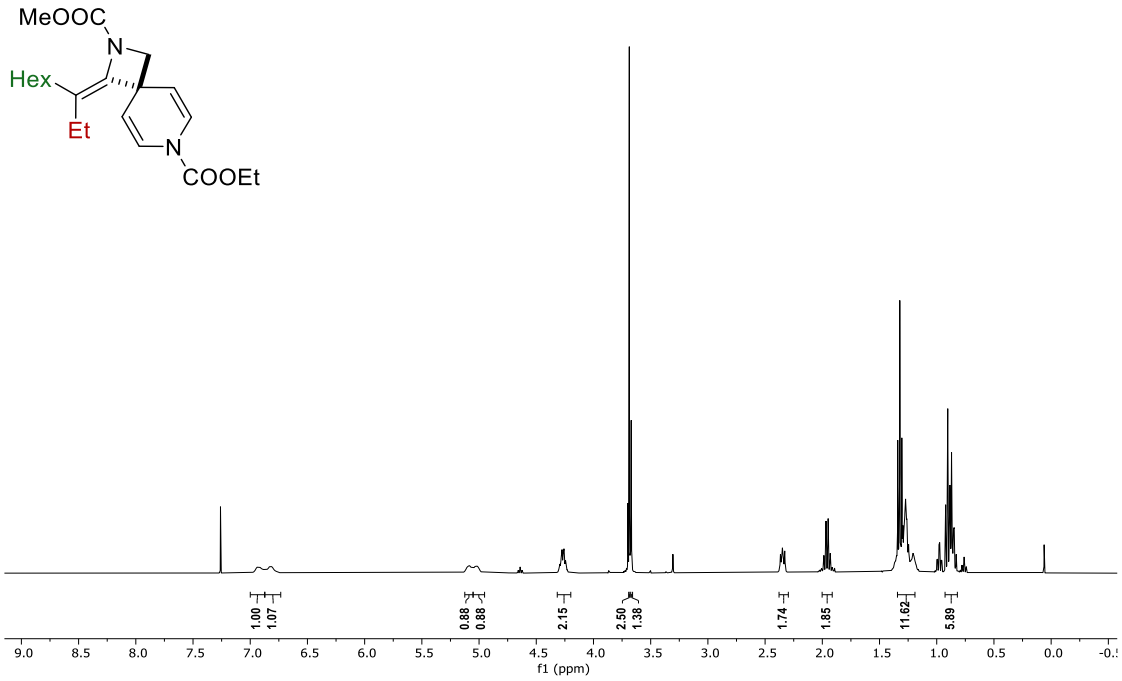

-141.81
-142.03
-148.14
-148.17
-148.19
-148.63
-148.65
-148.68
MeOOC
N
F
Hex
Et
N
COOMe
-80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180 -185 -190 -195 -200 -205 -210
f1 (ppm)

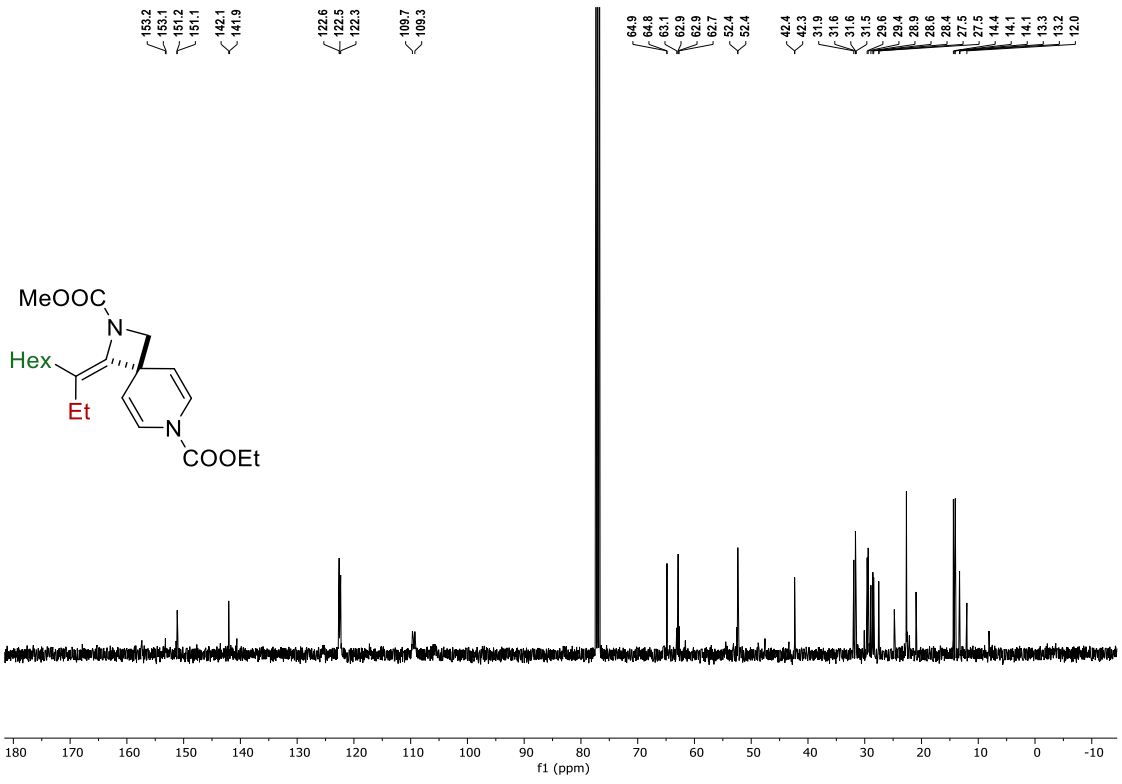
^{1}H and ^{13}C NMR spectra for compound **3q**



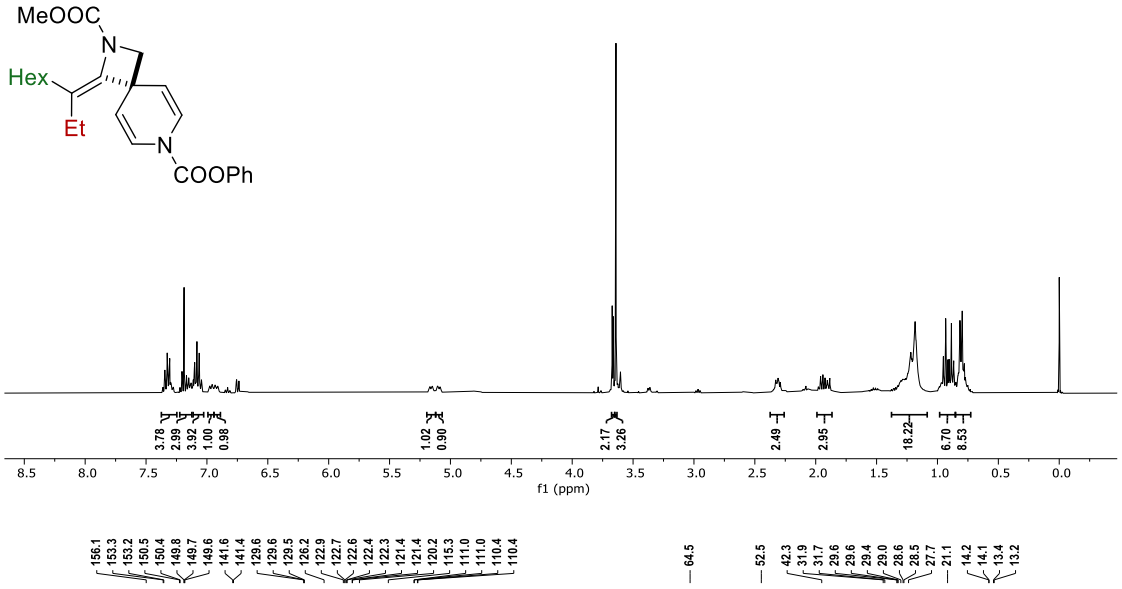


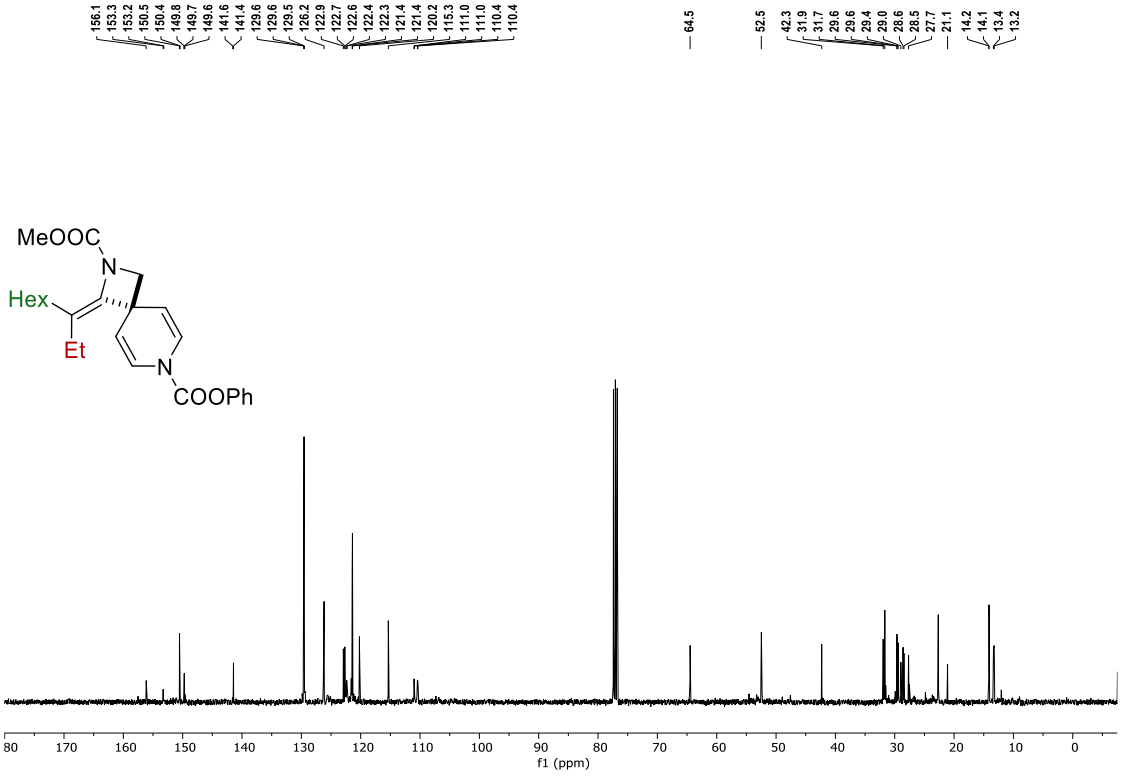
^{1}H and ^{13}C NMR spectra for compound **3r**



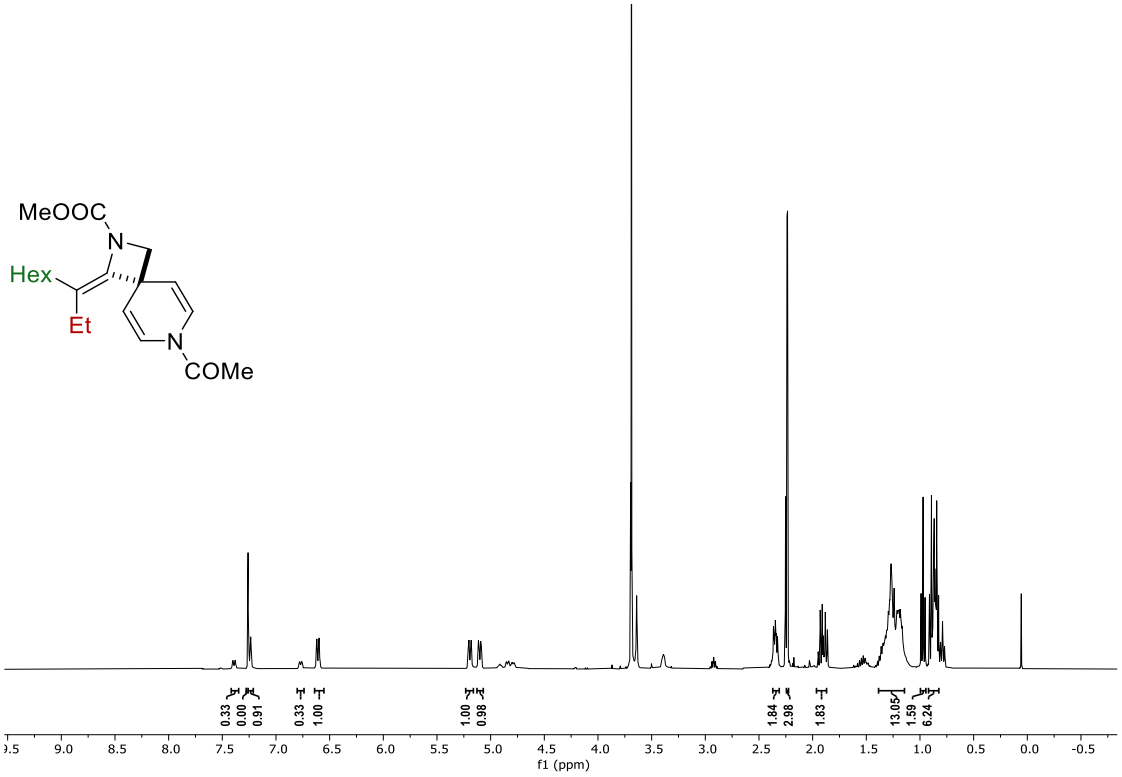


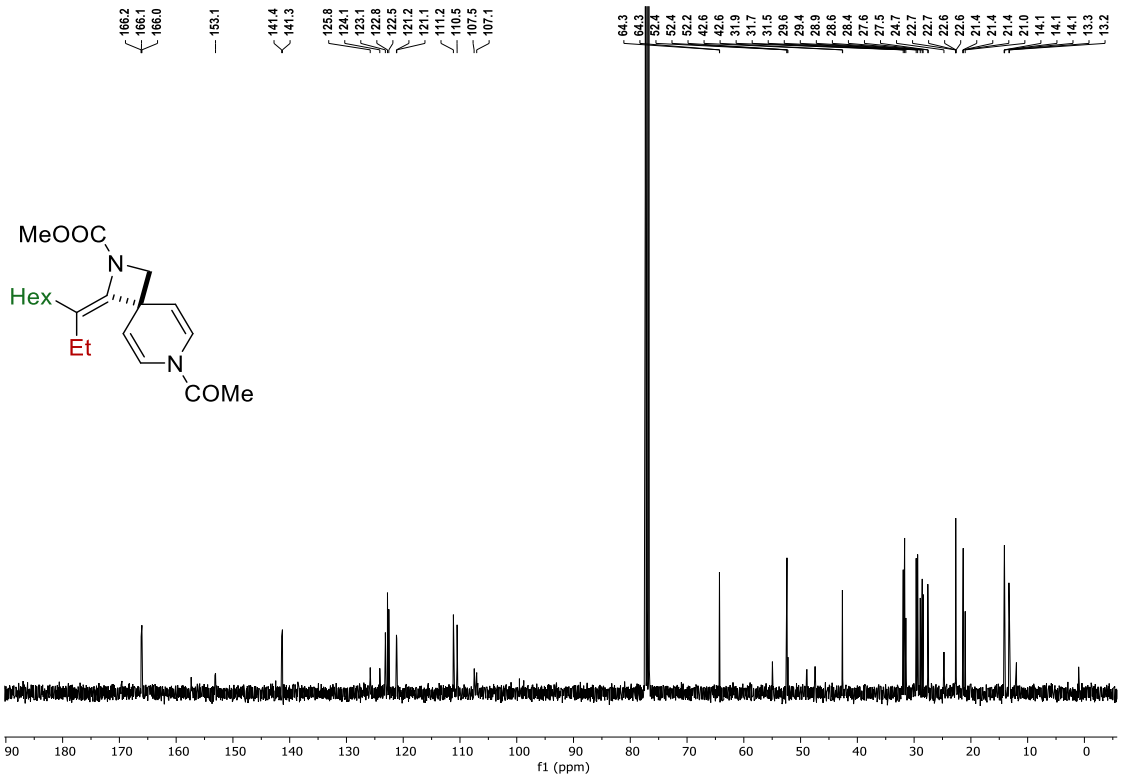
^{1}H and ^{13}C NMR spectra for compound **3s**



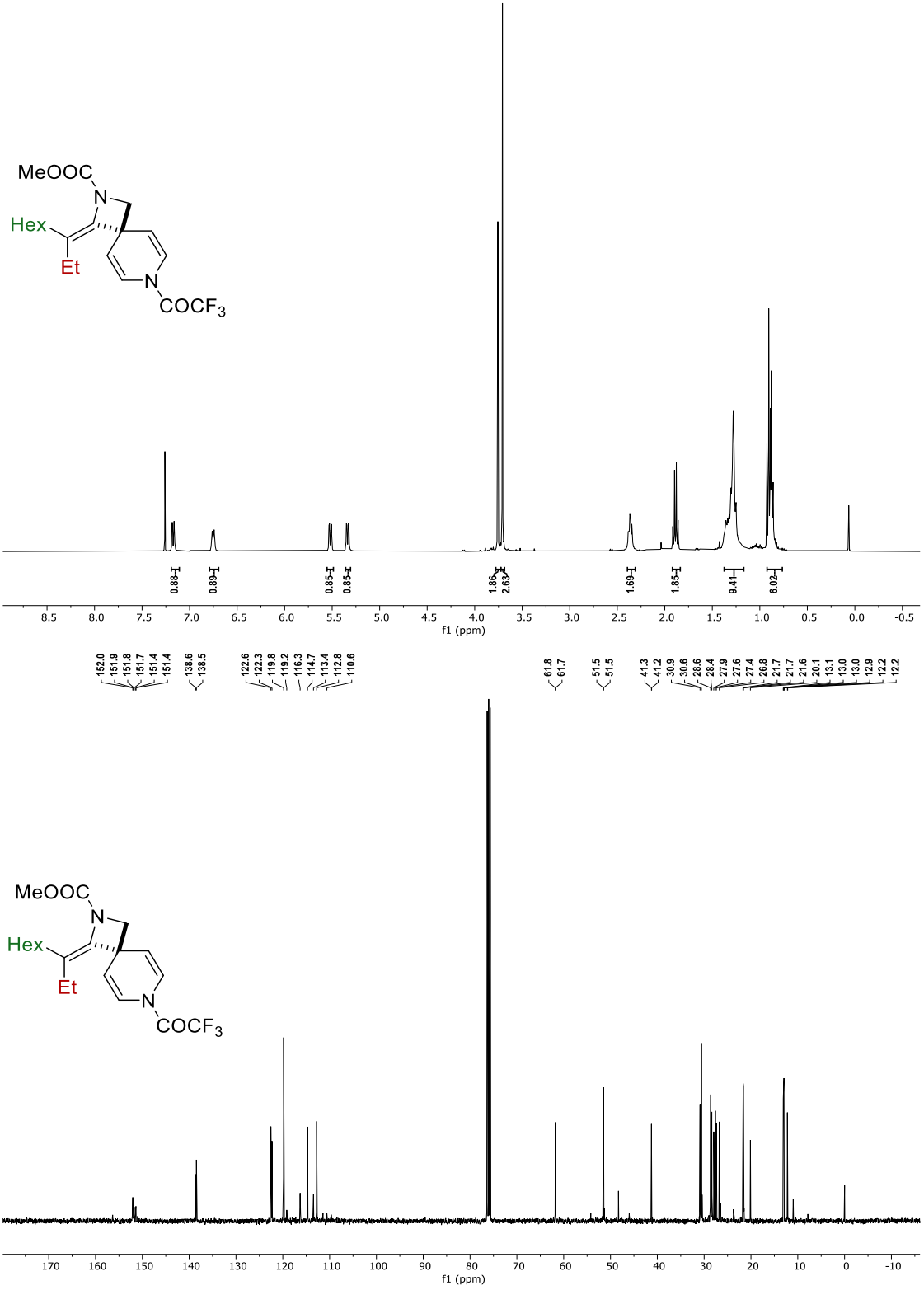


^{1}H and ^{13}C NMR spectra for compound **3t**



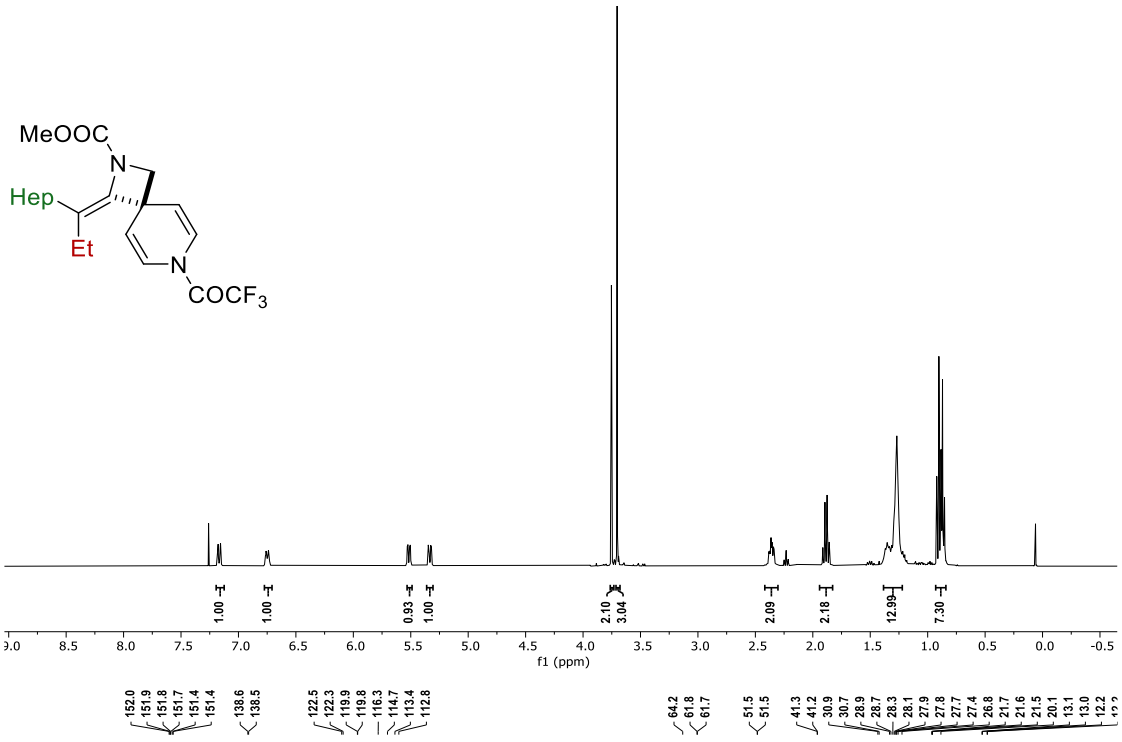


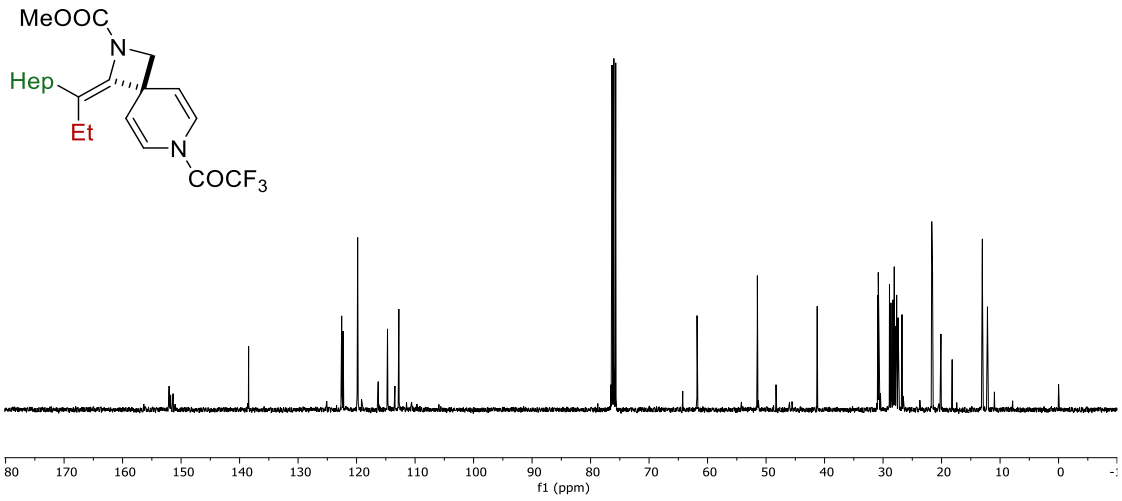
^{1}H, ^{13}C, and ^{19}F NMR spectra for compound **3u**

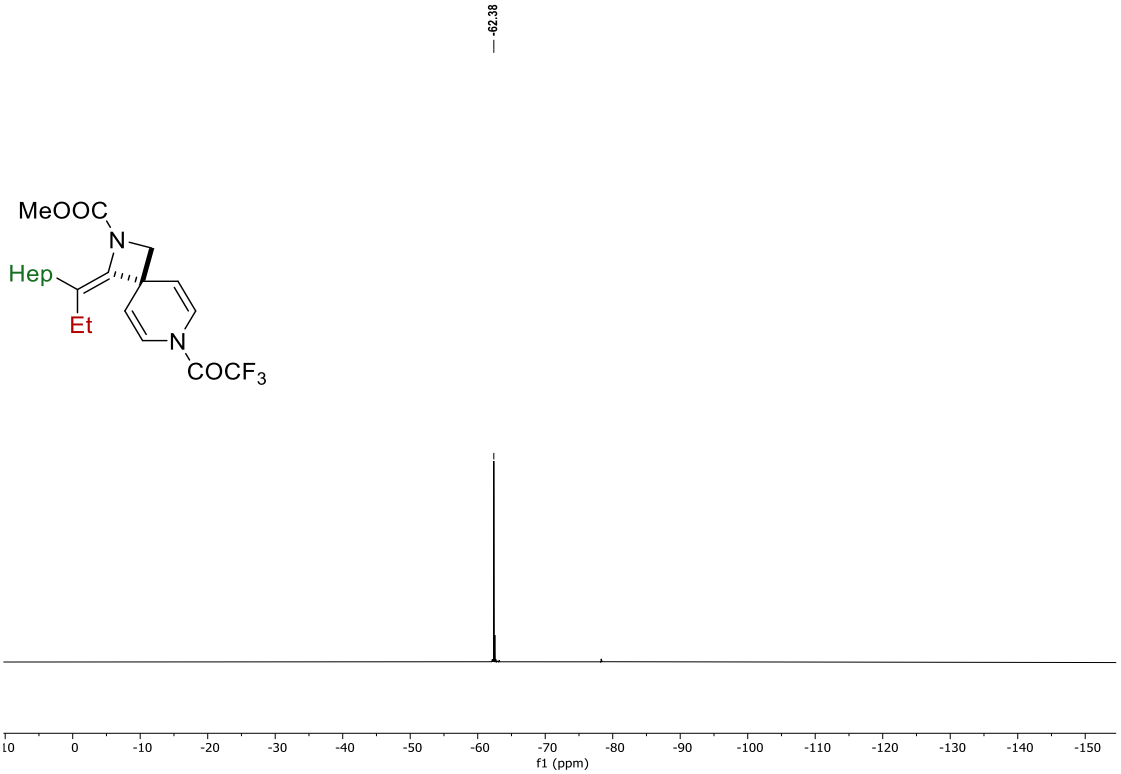



-68.81
MeOOC
N
Hex
Et
N
COCF3
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

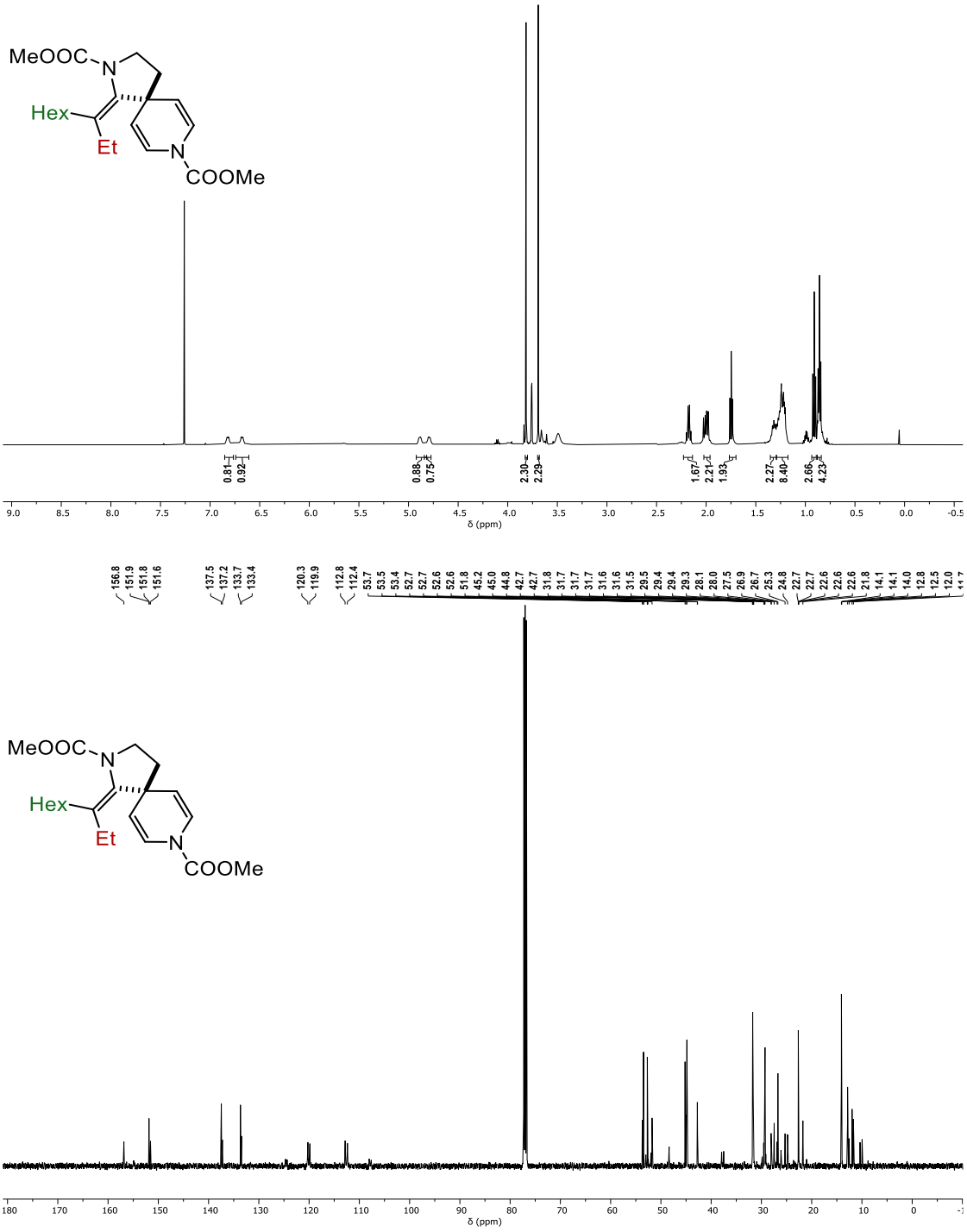
^{1}H, ^{13}C, and ^{19}F NMR spectra for compound **3v**



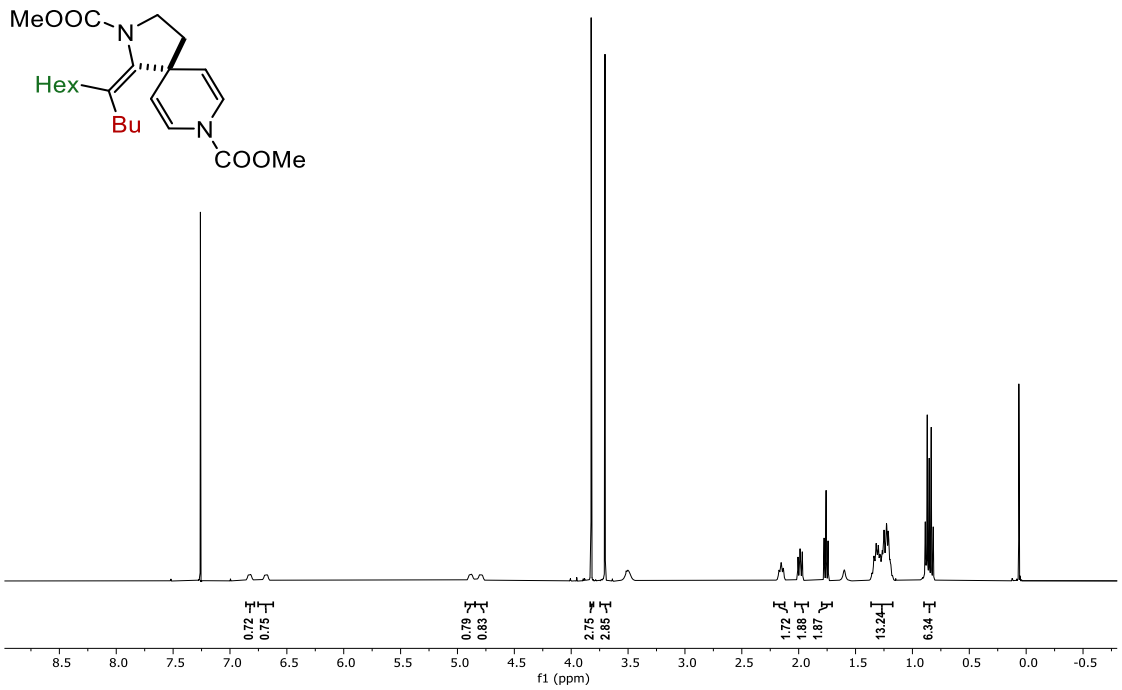


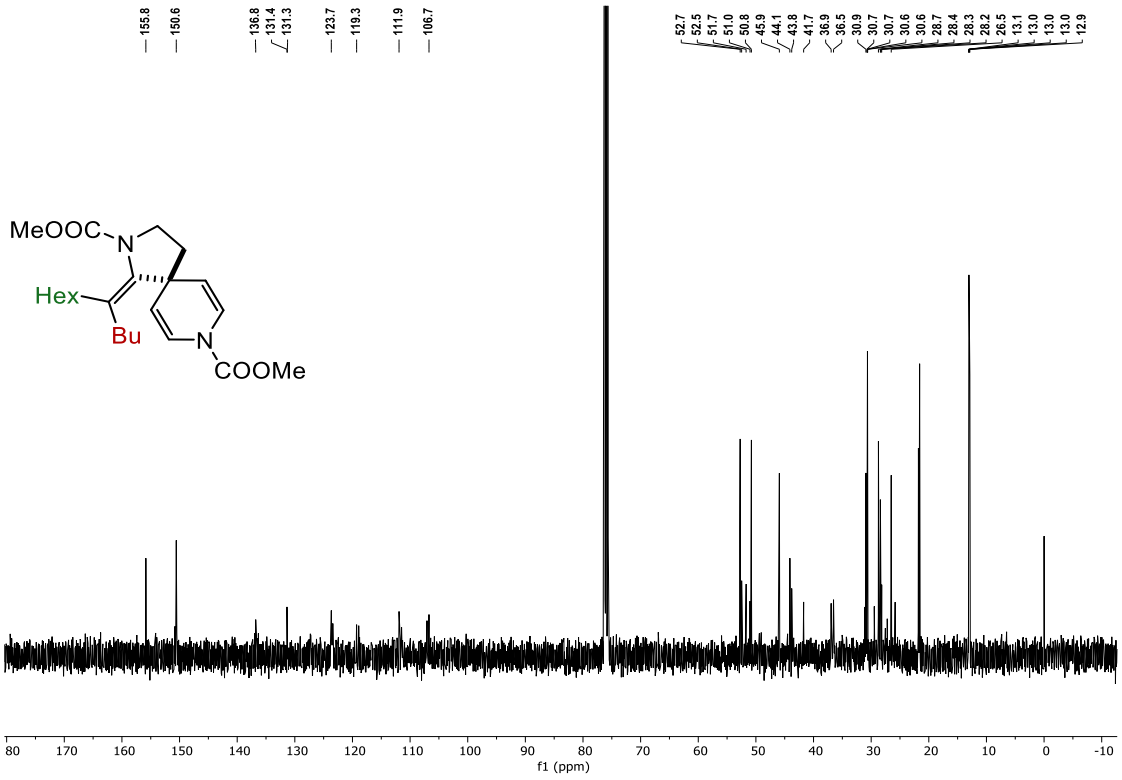

-62.38
MeOOC
N
Hep
Et
N
COCF3
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
f1 (ppm)

^{1}H and ^{13}C NMR spectra for compound **3w**

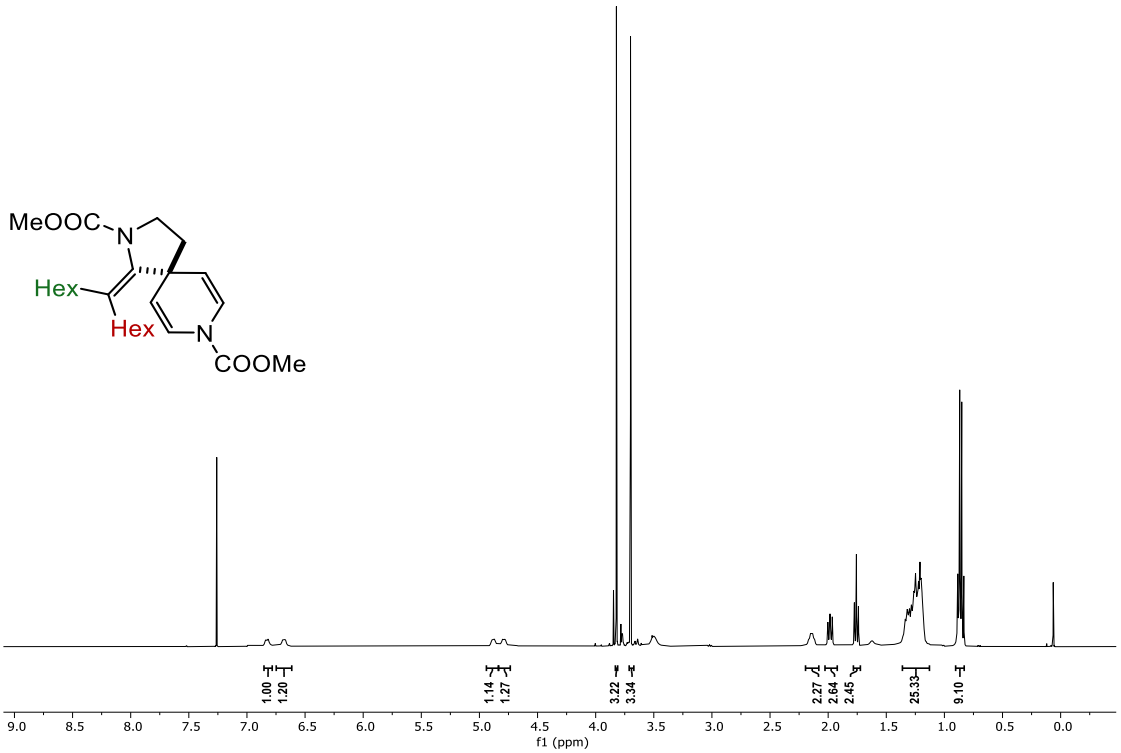


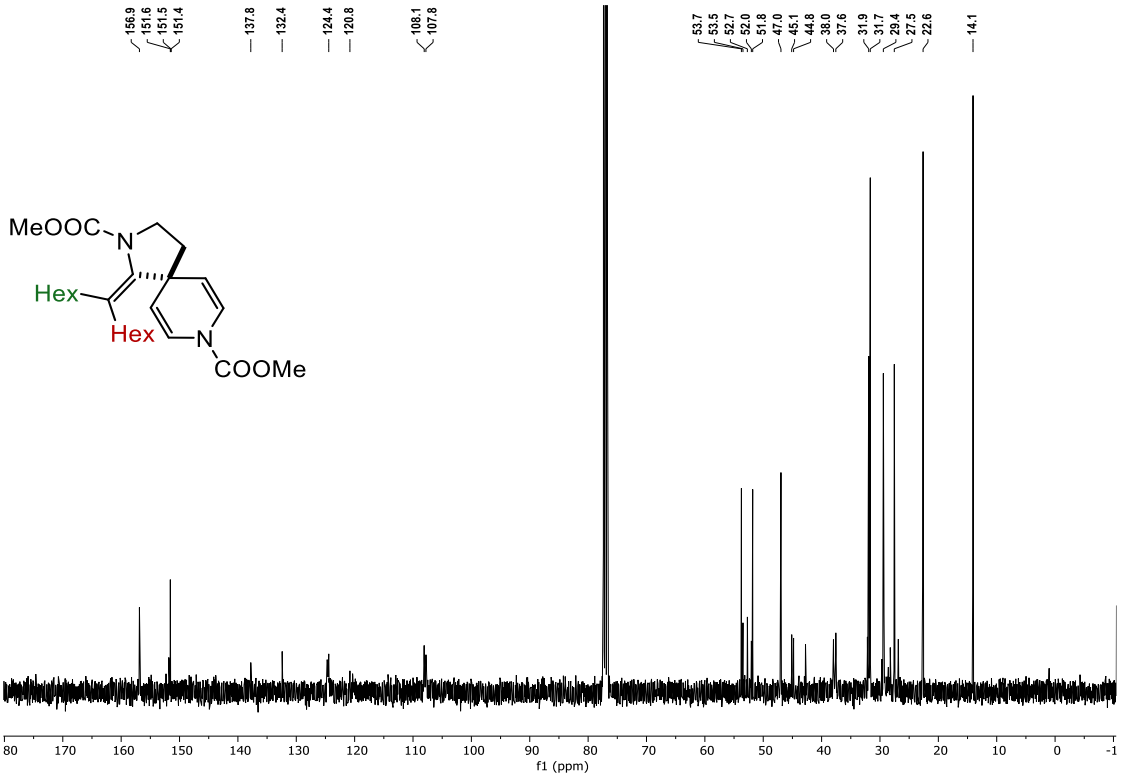
^{1}H and ^{13}C NMR spectra for compound **3x**



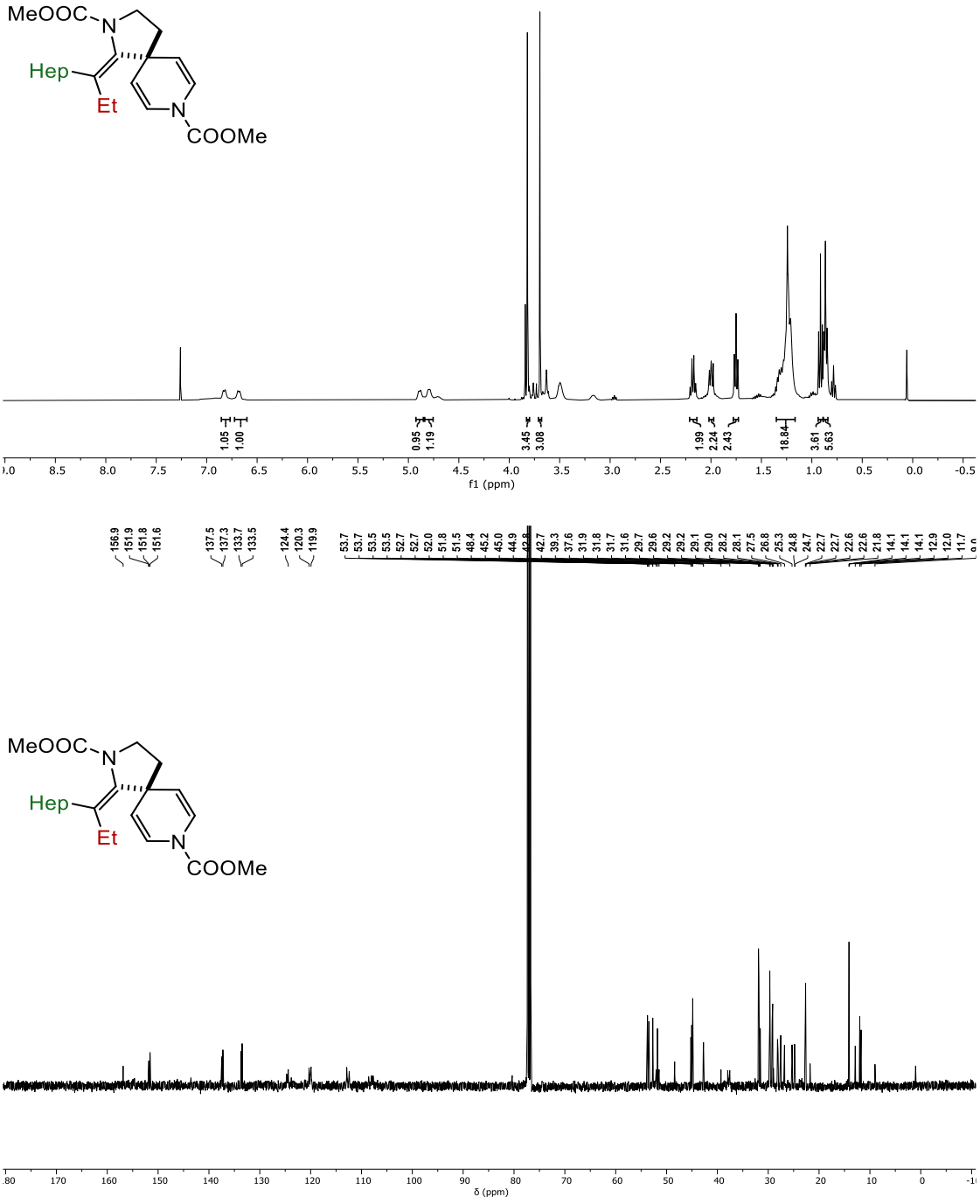


^{1}H and ^{13}C NMR spectra for compound **3y**

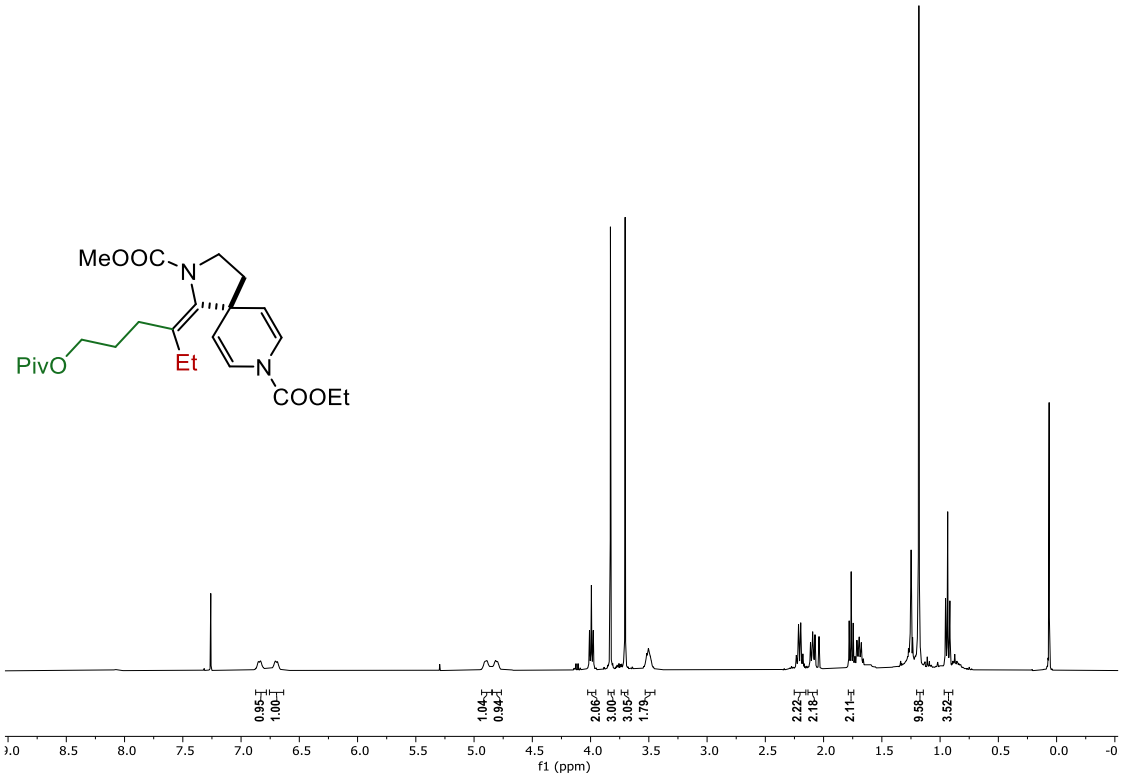


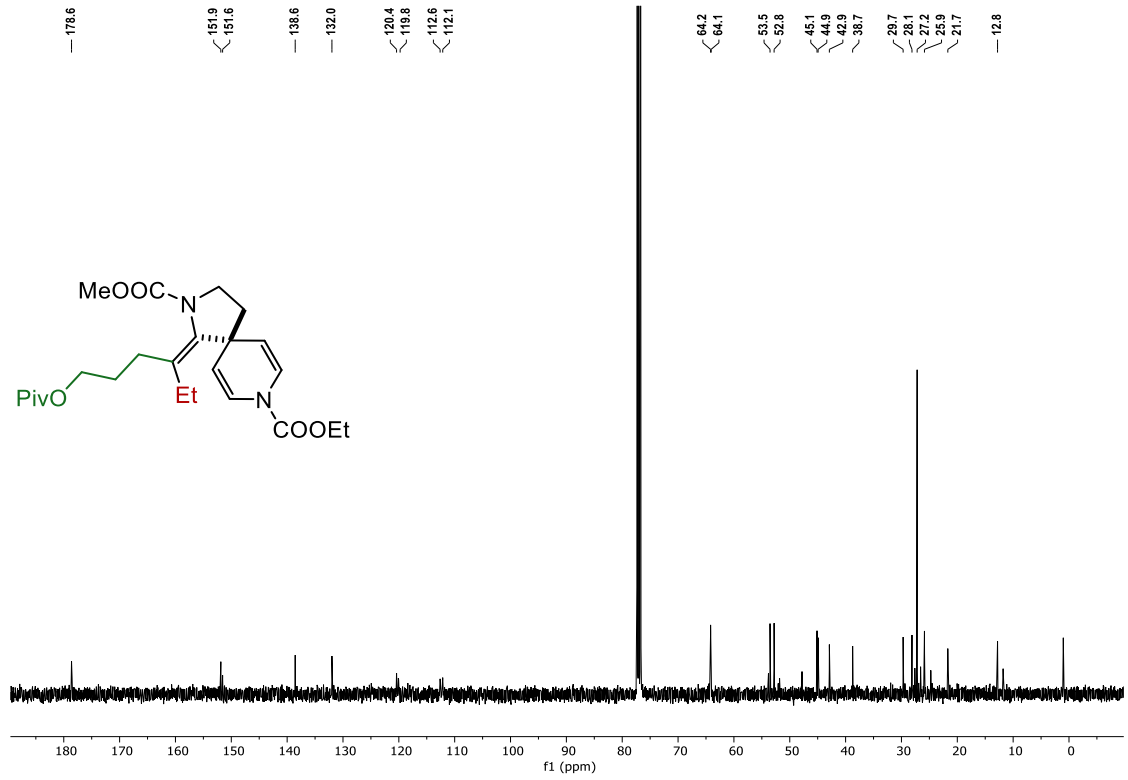


^{1}H and ^{13}C NMR spectra for compound **3z**

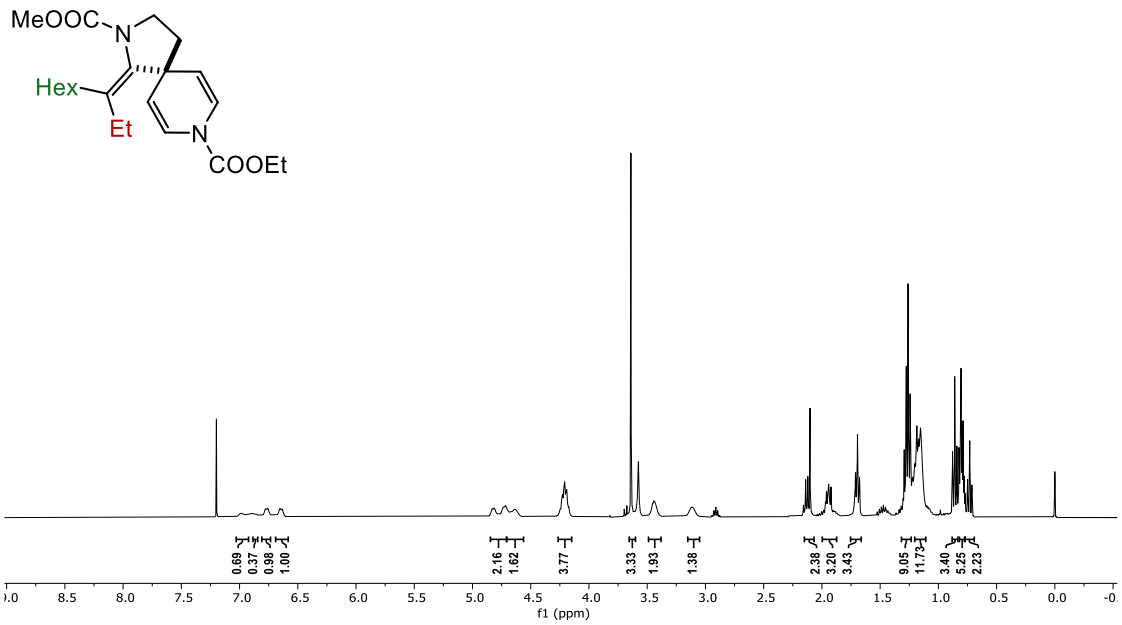


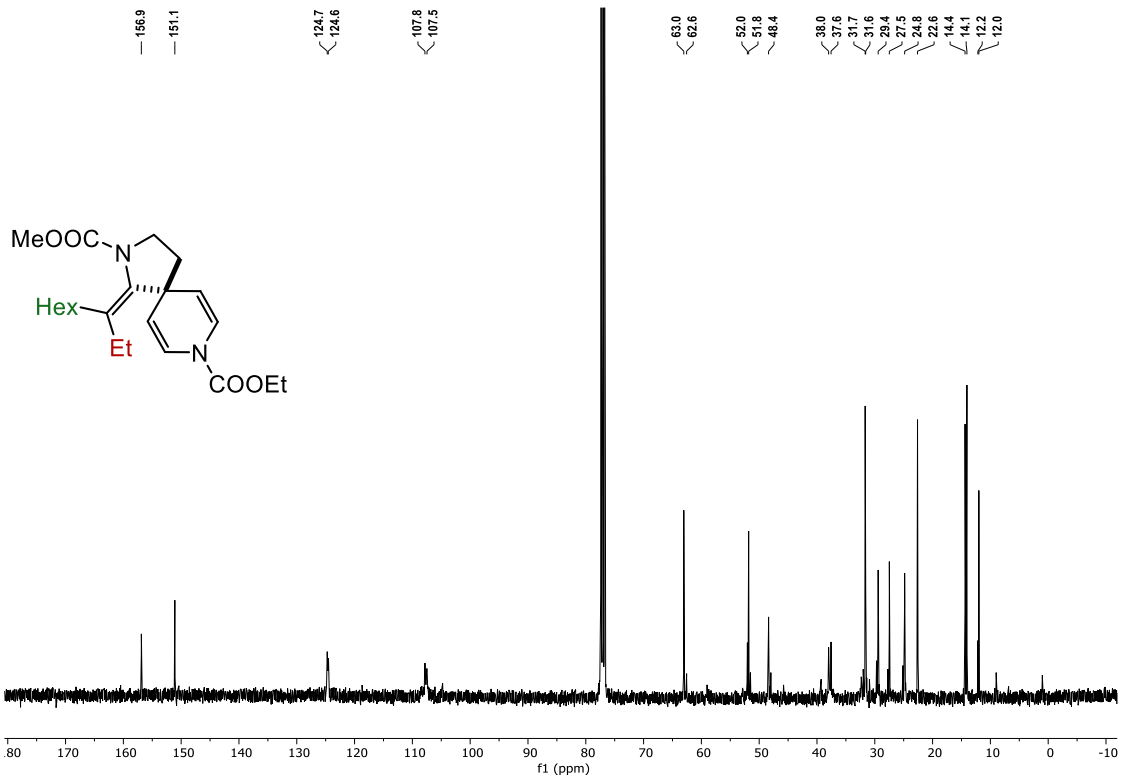
^{1}H and ^{13}C NMR spectra for compound **3aa**



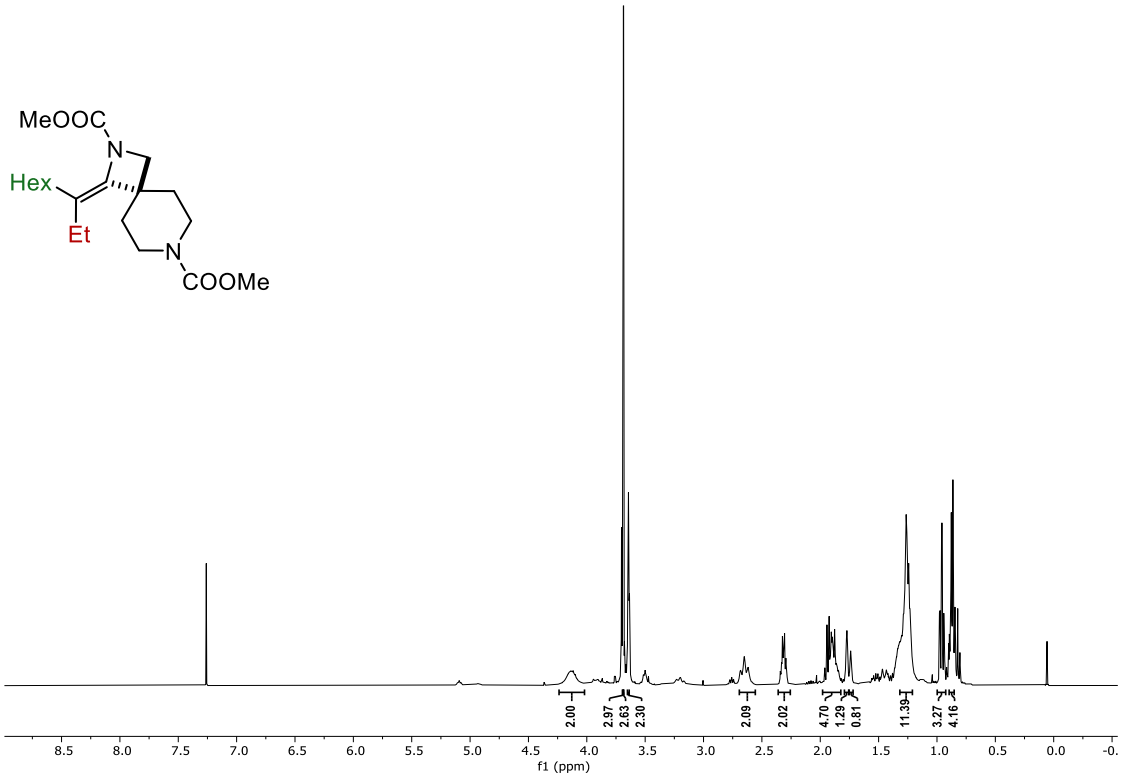


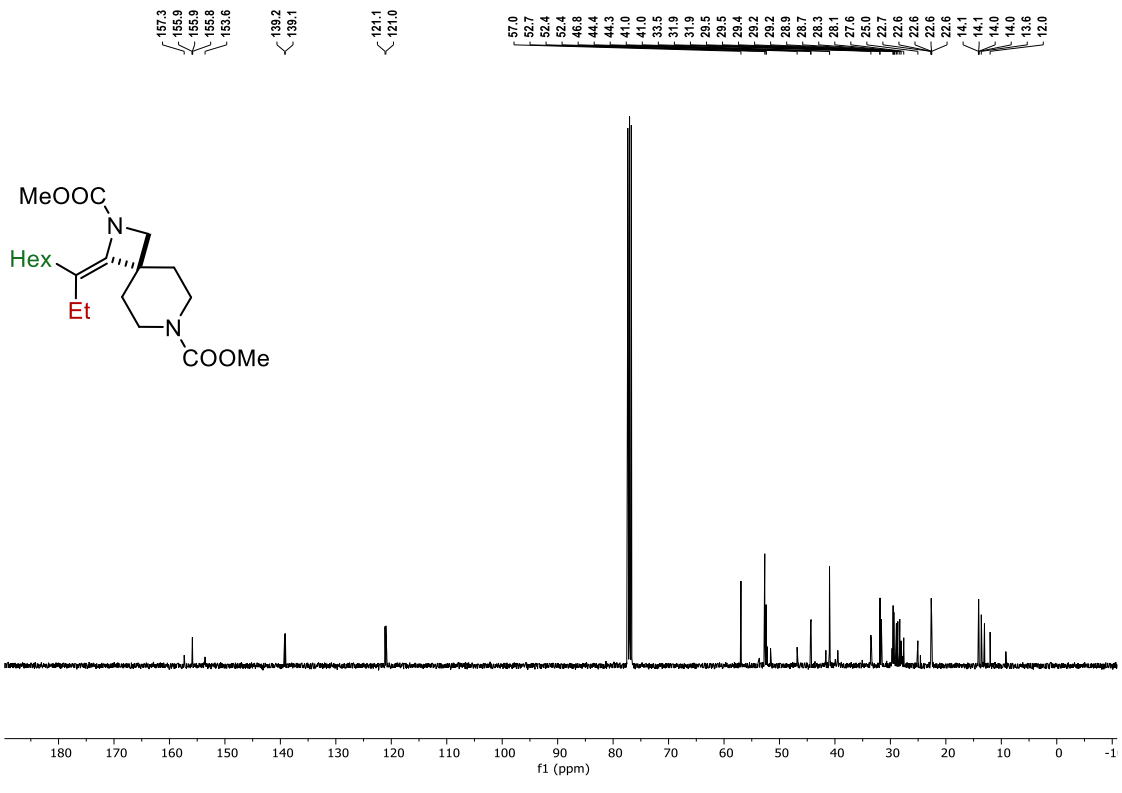
^{1}H and ^{13}C NMR spectra for compound **3ab**



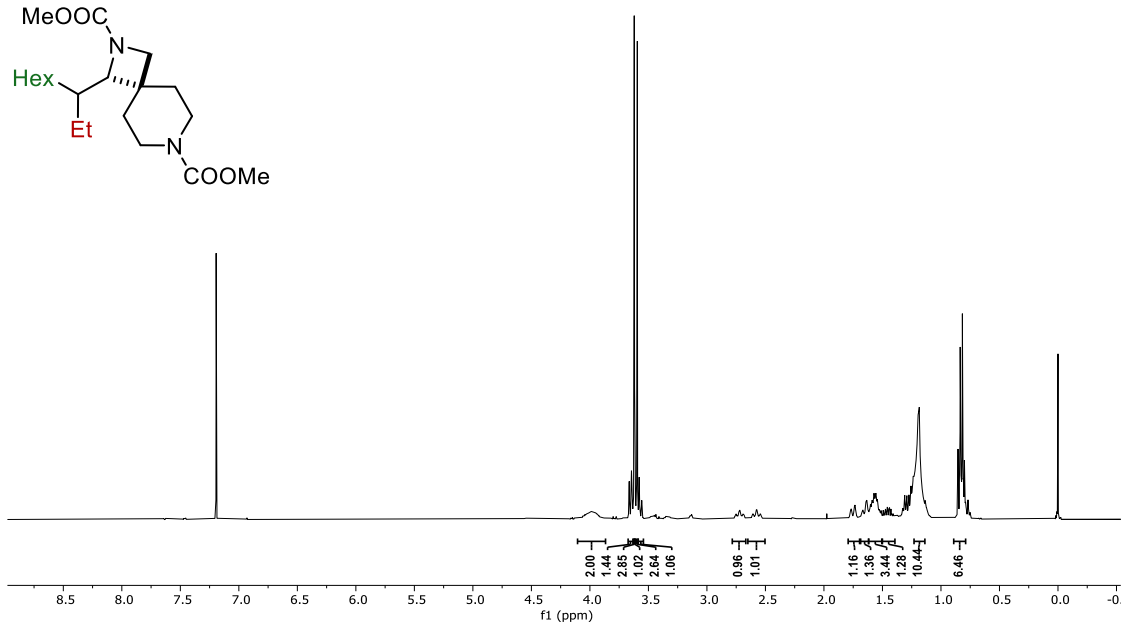


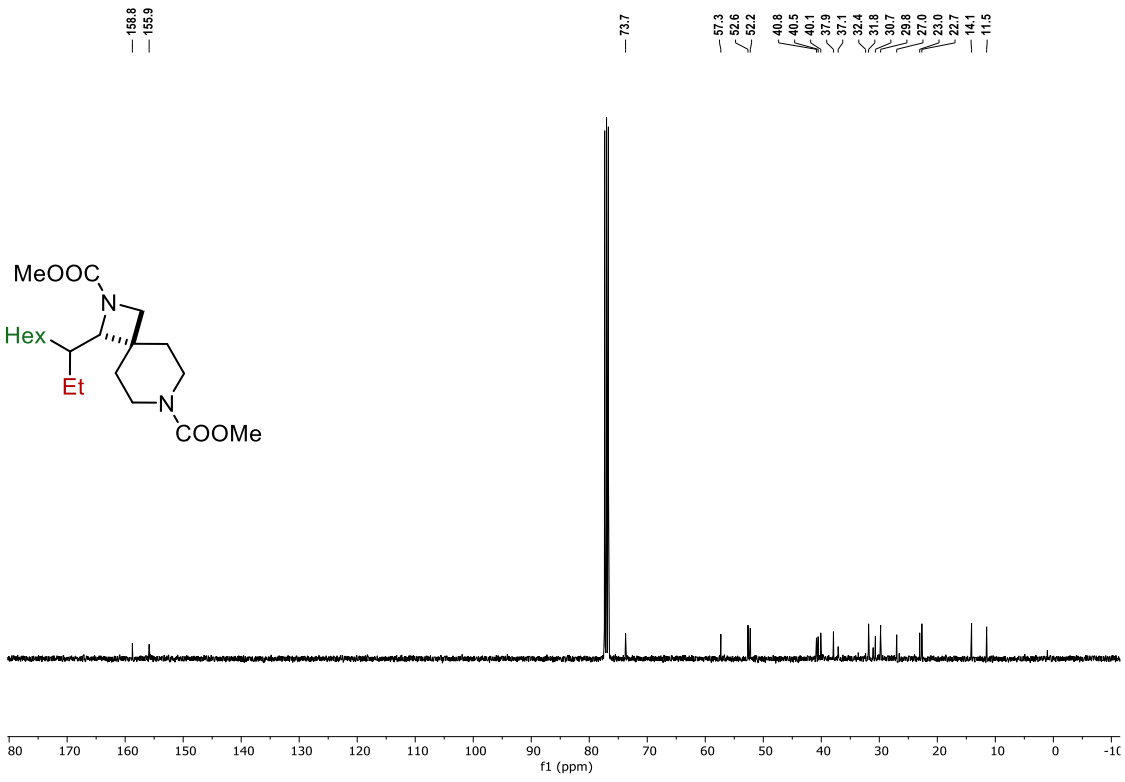
^{1}H and ^{13}C NMR spectra for compound **4a**





^{1}H and ^{13}C NMR spectra for compound **5a**





^{1}H and ^{13}C NMR spectra for compound **5b**