Supporting Information

A Concise Synthesis of the Erythrina Alkaloid 3−Demethoxyerythratidinone via Combined Rhodium Catalysis

Jung Min Joo,[†] Ramoncito A. David,[†] Yu Yuan,[†] and Chulbom Lee*[,‡]

[†]Department of Chemistry, Princeton University, Princeton, New Jersey 08544, U.S.A. and [‡]Department of Chemistry, Seoul National University, Seoul 151-747, South Korea

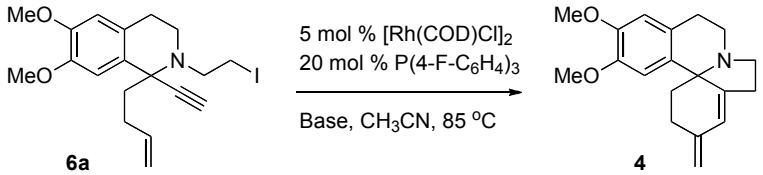
I. Rhodium-Catalyzed Tandem Cyclization

Table S1. Control experiments of iodide 6a[a]

entry	solvent	control	temp.	recovered **6a**[b]
1	CH_3CN	—	85 °C	96%
2	CH_3CN	0.2 equiv $P(4–F–C_6H_4)_3$	85 °C	96%
3	CH_3CN	2.0 equiv Et_3N	85 °C	12%
4	DMF	2.0 equiv Et_3N	85 °C	10%
5	DMF	2.0 equiv Et_3N	40 °C	25%
6	DMF	2.0 equiv Et_3N	25 °C	51%

[a] All reactions were performed with 0.20 mmol of iodide **6a** and a control reagent in solvent (0.1 M) for 1 h. [b] Isolated yield.

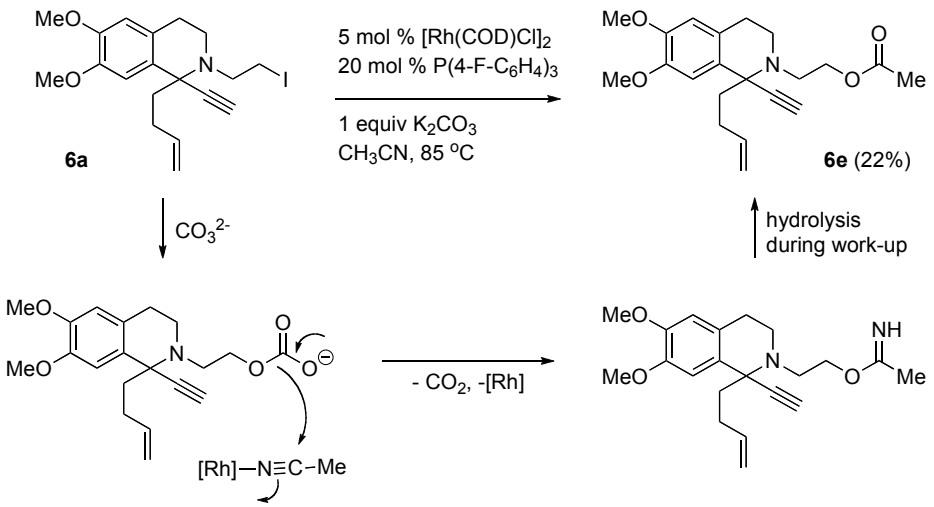
Table S2. Base effects[a]



entry	base	amount (equiv)	time	yield[b]
1	—	—	18 h	25%
2	Et_3N	0.1	1 h	29%
3	Et_3N	1.0	1 h	24%
4	Et_3N	2.0	1 h	29%
5	iPr_2NEt	2.0	2 h	14%
6	nBu_3N	1.0	1 h	21%
7	PMP[c]	1.0	1 h	14%
8	pyrrolidine	1.0	1 h	<5%
9	DTBMP[d]	1.0	1 h	(s.m. 96%)
10	DBU[e]	1.0	1 h	16%
11	Proton–sponge®	1.0	2 h	21%
12	BEMP[f]	1.0	1 h	20%
13	K_2CO_3	1.0	1 h	side product[g]
14	MgO	1.0	20 h	<5%

[a] All reactions were performed with 0.20 mmol of iodide **6a**, base, 5 mol % of $[Rh(COD)Cl]_2$, and 20 mol % of $P(4–F–C_6H_4)_3$ at 85 °C in CH_3CN (0.1 M). [b] Isolated yield. [c] PMP = 1,2,2,6,6–pentamethyl piperidine. [d] 2,6–di–*tert*–butyl–4–methylpyridine. [e] DBU = 1,8–diazabicyclo[5.4.0]undec–7–ene. [f] BEMP = 2–*tert*–butylimino–2–diethylamino–1,3–dimethyl–perhydro–1,3,2–diazaphosphorine. [g] See page S3.

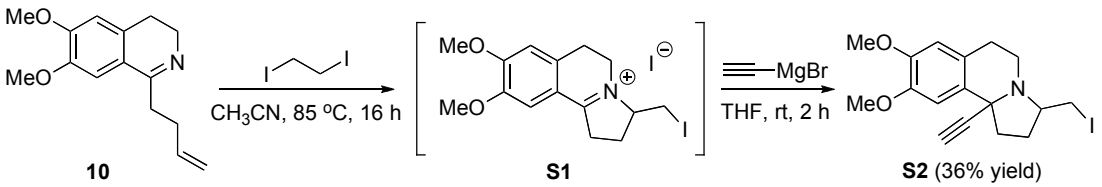
Interestingly, a carbonate base, K_2CO_3, provided acetate **6e** as the only isolable product,[1] indicating that alkylation by a carbonate followed by CO_2 extrusion and addition to acetonitrile might occur under the influence of the rhodium catalyst (Scheme S-1).[2]



Scheme S1. A proposed mechanism for the formation of acetate **6e**

II. *N*–Alkylation of Cyclic Imine 10 with 1,2–Diiodoethane

As illustrated in the text, 1,2-diiodoethane did not permit a similar *N*-alkylation, but instead led to cyclic iodide **S2** as the only isolable product (Scheme S2). Subjection of imine **10** to iodine resulted in the same product, thereby indicating that 1,2-diiodoethane facilitated the iodinium-induced cyclization to give ammonium salt **S1**, which then underwent a Grignard reaction to provide cyclic iodide **S2**.



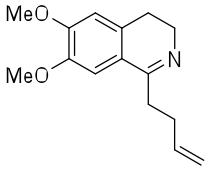
Scheme S2. Reaction with 1,2-diiodoethane

[1] The structure of **6e** was confirmed by characterization and comparison of the putative acetate obtained from the reaction of iodide **6a** with sodium acetate.

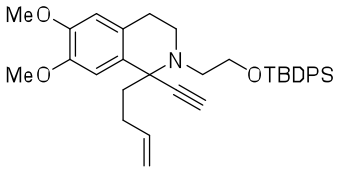
[2] For a similar transformation of alcohols in the presence of nitriles by ruthenium catalysis, see: Naota, T.; Shichijo, Y.; Murahashi, S.-i. *J. Chem. Soc., Chem. Commun.* **1994**, 1359.

III. Experimental Procedure and Characterization Data

All reactions were performed in round bottom flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. All solvents were dried by passing through activated alumina columns. Commercially available reagents were used without further purification. Thin layer chromatography (TLC) was performed using Silicycle 60 F254 plates. TLC plates were visualized by exposure to UV light (254 nm) and/or stained by anisaldehyde or potassium permanganate solutions. Flash column chromatography was performed on Silicycle silica gel 60 (40-63 μm) using the indicated solvent system. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Varian Inova 500 MHz or Bruker Avance 500 MHz spectrometers. Chemical shifts in ^{1}H NMR spectra were reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.26 ppm). Data for ^{1}H NMR are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet), coupling constant in Hertz (Hz) and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift in ppm from the central peak of $CDCl_3$ (77.2 ppm). FT-IR spectra were obtained on a Perkin-Elmer Paragon 500 and reported in frequency of the absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained from the Princeton University Mass Spectrometry Facility.

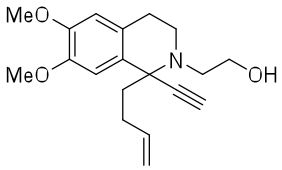


1-But-3-enyl-6,7-dimethoxy-3,4-dihydro-isoquinoline (10). 4-Pentenoyl chloride (**8**, 1.66 mL, 15.0 mmol) was slowly added to a solution of 2-(3,4-dimethoxyphenyl)ethylamine **7** (2.72 g, 15.0 mmol) and triethylamine (3.14 mL, 22.5 mmol) in CH_2Cl_2 (30 mL) at 0 °C. After stirring at room temperature for 12 h, the mixture was concentrated by rotary evaporation. The residue was diluted with EtOAc (50 mL) and 1 N HCl solution (50 mL). The layers were separated. The aqueous layer was extracted with EtOAc (3×50 mL). The combined organic extracts were washed with brine (100 mL) and dried over Na_2SO_4. The solvent was evaporated to give the corresponding amide, which was used in the next step without further purification. To a solution of the amide in anhydrous CH_3CN (80 mL) was added $POCl_3$ (10 mL, 105 mmol) at room temperature. The mixture was stirred at 95 °C for 1.5 h. After being cooled to room temperature, it was carefully poured into aqueous K_2CO_3 (100 mL) at 0 °C while keeping pH in the range of 9-10. The layers were separated. The aqueous layer was extracted with EtOAc (3×80 mL). The combined organic extracts were washed with brine (50 mL), dried over K_2CO_3, filtered, and concentrated to give imine **10** (3.66 g, 99%) as a yellow oil. The crude imine was either directly used for Grignard reactions or purified by flash column chromatography (EtOAc, 1% Et_3N) for transition metal catalyzed reactions. R_f 0.28 (hexanes:EtOAc:Et_3N = 4:4:1); IR (film) 3392, 3076, 2938, 2836, 1626, 1573, 1146 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.00 (s, 1H), 6.70 (s, 1H), 5.93 (ddt, *J* = 16.8, 10.1, 6.7 Hz, 1H), 5.06 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.00 (d, *J* = 10.0 Hz, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.65 (t, *J* = 7.5 Hz, 2H), 2.79 (t, *J* = 7.8 Hz, 2H), 2.62 (t, *J* = 7.5 Hz, 2H), 2.46-2.41 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 151.0, 147.6, 138.1, 131.8, 121.8, 115.2, 110.4, 108.7, 56.4, 56.1, 46.8, 35.2, 31.4, 26.0; HRMS (ESI-TOF) calcd for $C_{15}H_{20}NO_2$ $[M+H]^+$ 246.1494, found 246.1492.



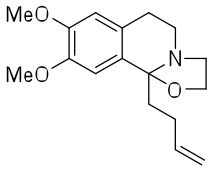
1-(But-3-enyl)-2-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-1-ethynyl-6,7-dimethoxy-1,2,3,4-

tetrahydroisoquinoline (12a). To a solution of imine **10** (0.328 g, 1.34 mmol) in CH_3CN (10 mL) at room temperature was added *tert*-butyl(2-iodoethoxy)diphenylsilane (0.565 g, 1.47 mmol). The mixture was stirred at 85 °C for 24 h. After being cooled to room temperature, the solution was concentrated to give the corresponding *N*-alkyliminium iodide, which was directly used for Grignard reaction without further purification. To a solution of the crude *N*-alkyliminium iodide dissolved in THF (5 mL) was added ethynyl magnesium bromide (0.5 M in THF, 16.0 mL, 8.00 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The mixture was diluted with EtOAc (20 mL) and aqueous 1.0 N HCl (20 mL). After the organic layer was separated, the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (hexanes:EtOAc = 3:1) to give alkyne **12a** (0.659 g, 89%) as a colorless oil. R_f 0.35 (hexanes:EtOAc:Et_3N = 4:4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75-7.67 (m, 4H), 7.45-7.35 (m, 6H), 6.83 (s, 1H), 6.50 (s, 1H), 5.57 (ddt, *J* = 15.7, 12.7, 6.4 Hz, 1H), 4.77 (d, *J* = 11.3 Hz, 1H), 4.77 (d, *J* = 16.0 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.76 (t, *J* = 6.6 Hz, 2H), 3.11 (dt, *J* = 13.7, 6.8 Hz, 1H), 3.00-2.89 (m, 1H), 2.89-2.79 (m, 1H), 2.74 (td, *J* = 11.2, 2.6 Hz, 1H), 2.60-2.49 (m, 1H), 2.47 (d, *J* = 15.2 Hz, 1H), 2.39 (s, 1H), 2.15-1.95 (m, 3H), 1.47-1.36 (m, 1H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 147.7, 138.7, 135.7, 135.7, 133.9, 133.8, 130.0, 129.7, 128.2, 127.9, 127.8, 114.1, 110.9, 110.0, 86.2, 72.4, 63.5, 60.7, 56.2, 55.8, 53.6, 46.8, 40.0, 29.8, 29.6, 27.4, 27.0, 26.9, 19.3; HRMS (EI) calcd for $C_{35}H_{43}NO_3Si$ $[M]^+$ 553.3012, found 553.3006.



2-(1-But-3-enyl-1-ethynyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethanol (12b). To a solution of alkyne **12a** (1.14 g, 2.06 mmol) in THF (15 mL) was added TBAF (1.0 M in THF, 4.12 mL, 4.12 mmol) at room temperature. The mixture was stirred at room temperature for 2 h and poured into saturated aqueous NH_4Cl (20 mL). After the organic layer was separated, the aqueous layer was extracted with EtOAc (3×15 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The residue was purified by flash column chromatography (hexanes:EtOAc = 2:1) to give alcohol **12b** (622 mg, 95%) as a

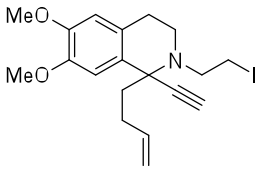
colorless oil. R_f 0.32 (hexanes:EtOAc = 1:1); IR (film) 3301, 3073, 2922, 2255, 1614, 1520, 1252, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.87 (s, 1H), 6.54 (s, 1H), 5.69 (ddt, *J* = 16.8, 10.1, 6.4 Hz, 1H), 4.94-4.84 (m, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.78 (td, *J* = 10.4, 3.4 Hz, 1H), 3.66-3.59 (m, 1H), 3.18 (ddd, *J* = 13.4, 9.8, 5.2 Hz, 1H), 3.0 (ddd, *J* = 11.6, 4.6, 3.4 Hz, 1H), 2.85 (ddd, *J* = 15.3, 10.7, 4.9 Hz, 1H), 2.74 (td, *J* = 11.3, 3.1 Hz, 1H), 2.60 (dt, *J* = 15.6, 3.1 Hz, 1H), 2.55 (dt, *J* = 13.4, 3.4 Hz, 1H), 2.47 (br s, 1H), 2.45 (s, 1H), 2.27-2.20 (m, 1H), 2.12-1.99 (m, 2H), 1.62-1.54 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.7, 147.5, 137.9, 129.4, 127.4, 114.3, 110.6, 109.9, 85.4, 72.8, 60.5, 59.1, 55.9, 55.6, 52.6, 44.5, 39.2, 29.0, 27.5; HRMS (ESI-TOF) calcd for $C_{19}H_{26}NO_3$ $[M+H]^+$ 316.1913, found 316.1916.



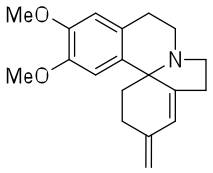
10b-But-3-enyl-8,9-dimethoxy-2,3,6,10b-tetrahydro-5*H*-oxazolo[2,3-*a*] isoquinoline (14). To a 25-mL round bottom flask equipped with an air-condenser were added imine **10** (980 mg, 3.99 mmol), 2-iodoethanol (0.343 mL, 4.39 mmol), and CH_3CN (5.00 mL). This mixture was stirred at 85 °C for 24 h. After being cooled to room temperature, the solvent was evaporated to give the intermediate **13**, which was either directly used for Grignard reaction (vide infra) or purified by flash column chromatography (hexanes:EtOAc = 3:1, 1% Et_3N) to give *N*,*O*-acetal **14**. R_f 0.35 (hexanes:EtOAc:Et_3N = 4:4:1); IR (film) 3073, 2941, 2833, 1611, 1516, 1266, 1161 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.56 (s, 1H), 5.73 (ddt, *J* = 16.8, 10.1, 6.7 Hz, 1H), 4.92 (dd, *J* = 17.1, 1.5 Hz, 1H), 4.86 (d, *J* = 10.1 Hz, 1H), 3.92-3.83 (m, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.49 (dt, *J* = 11.3, 7.6 Hz, 1H), 3.09 (dt, *J* = 11.3, 5.8 Hz, 1H), 3.04 (dt, *J* = 10.7, 4.6 Hz, 1H), 2.86 (td, *J* = 10.4, 3.4 Hz, 1H), 2.82-2.74 (m, 1H), 2.64 (dt, *J* = 15.6, 4.0 Hz, 1H), 2.09-2.00 (m, 1H), 2.00-1.85 (m, 2H), 1.79-1.61 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 148.0, 138.8, 129.1, 127.7, 114.1, 110.0, 109.3, 97.8, 62.6, 56.1, 56.0, 52.8, 47.4, 39.2, 29.5, 28.2; HRMS (ESI-TOF) calcd for $C_{17}H_{24}NO_3$ $[M+H]^+$ 290.1756, found 290.1751.

To a solution of the crude mixture in THF (10 mL) at 0 °C was added ethynyl magnesium bromide (0.5 M in THF, 24.0 mL, 12.0 mmol). After stirring at room temperature for 2 h, the mixture was poured into saturated aqueous NH_4Cl (40 mL). The layers were separated. The

aqueous layer was extracted with EtOAc (2×30 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (hexanes:EtOAc = 2:1) provided alcohol **12b** (1.11 g, 88%) as a colorless oil.

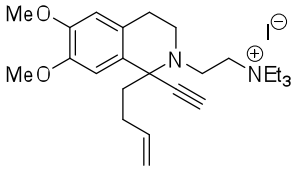


1-But-3-enyl-1-ethynyl-2-(2-iodo-ethyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline (6a). To a solution of alcohol **12b** (0.159 g, 0.504 mmol) in THF (5 mL) at 0 °C were added Ph_3P (0.198 g, 0.756 mmol), imidazole (0.103 g, 1.51 mmol), and I_2 (0.192 g, 0.756 mmol). After being stirred at 0 °C for 15 min, the mixture was diluted with EtOAc (10 mL) and washed with saturated aqueous $Na_2S_2O_3$ (15 mL). The aqueous layer was then extracted with EtOAc (2×15 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (hexanes:EtOAc = 5:1) to provide iodide **6a** (0.200 g, 93%) as a colorless oil. R_f 0.63 (hexanes:EtOAc = 1:1); IR (film) 3289, 2933, 2255, 1613, 1520, 1253, 1153 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.52 (s, 1H), 5.72 (ddt, *J* = 16.8, 10.4, 6.7 Hz, 1H), 4.94-4.84 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.34-3.24 (m, 2H), 3.22-3.16 (m, 1H), 2.96-2.86 (m, 2H), 2.82-2.72 (m, 2H), 2.60-2.54 (m, 1H), 2.43 (s, 1H), 2.29-2.20 (m, 1H), 2.18-2.02 (m, 2H), 1.57-1.46 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 147.7, 138.4, 129.5, 127.7, 114.4, 110.7, 109.7, 85.8, 72.6, 60.4, 56.1, 55.8, 54.4, 45.6, 39.9, 29.4, 27.6, 5.5; HRMS (EI) calcd for $C_{19}H_{24}INO_2$ $[M]^+$ 425.0852, found 425.0839.



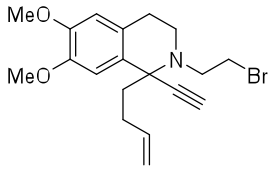
11,12-Dimethoxy-3-methylene-2,3,5,6,8,9-hexahydro-1*H*-indolo[1-*a*]isoquinoline (4). To a flame dried one-dram glass vial equipped with a screw-cap and a Teflon septum were added $[Rh(COD)Cl]_2$ (4.9 mg, 0.0099 mmol), $P(4\text{-}F\text{-}C_6H_4)_3$ (12 mg, 0.039 mmol), and THF (0.50 mL).

The mixture was stirred for 5 min before iodoenyne **6a** (82 mg, 0.19 mmol) in THF (0.50 mL) was added via syringe at 25 °C. The syringe was washed with THF (2×0.50 mL). After addition of Et_3N (56 μL, 0.40 mmol), the reaction vial was moved to a pre-heated sand bath (85 °C). After stirring for 12 h, the reaction mixture was cooled to room temperature and loaded directly onto a silica gel column. Purification by flash column chromatography (hexanes:EtOAc = 1:1, 1% Et_3N) yielded diene **4** (40 mg, 70%) as a colorless oil. R_f 0.19 (hexanes:EtOAc:Et_3N = 4:4:1); IR (film) 2932, 2844, 1607, 1510, 1464, 1253, 1110 1049 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.62 (s, 1H), 6.59 (s, 1H), 6.19 (s, 1H), 4.93 (s, 1H), 4.87 (s, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.54-3.46 (m, 1H), 3.22 (dd, *J* = 14.3, 7.3 Hz, 1H), 3.04 (ddd, *J* = 17.2, 11.8, 7.6 Hz, 1H), 2.96 (td, *J* = 8.9, 1.9 Hz, 1H), 2.79 (dd, *J* = 17.3, 8.9 Hz, 1H), 2.60-2.50 (m, 3H), 2.45 (dd, *J* = 16.6, 3.2 Hz, 1H), 2.38 (dd, *J* = 17.2, 9.3 Hz, 1H), 2.09-2.03 (m, 1H), 1.71-1.64 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.9, 146.6, 146.2, 142.5, 129.2, 125.6, 123.6, 112.0, 111.6, 110.4, 62.8, 56.1, 56.0, 46.1, 40.9, 36.5, 27.9, 26.0, 21.8; HRMS (ESI-TOF) calcd for $C_{19}H_{24}NO_2$ $[M+H]^+$ 298.1807, found 298.1803.

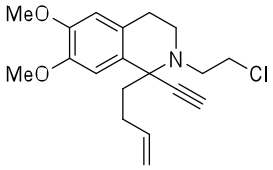


[2-(1-But-3-enyl-1-ethynyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-triethyl-ammonium iodide (16). To a one-dram glass vial were added iodide **6a** (85 mg, 0.20 mmol), Et_3N (0.084 mL, 0.60 mmol), and CH_3CN (2.0 mL). The vial was sealed with a screw-cap and a Teflon septum and moved to a pre-heated sand bath (85 °C). The reaction mixture was stirred for 2 h at 85 °C. After cooling to room temperature, evaporation of solvent provided the quaternary ammonium salt **16** (105 mg, 100%) as a white solid. IR (film) 3427, 3299, 3076, 2936, 2254, 2190, 1612, 1520, 1253, 1010 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.87 (s, 1H), 6.54 (s, 1H), 5.73 (ddt, *J* = 15.9, 10.4, 5.5 Hz, 1H), 4.98-4.90 (m, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.69 (dt, *J* = 15.6, 5.8 Hz, 1H), 3.64-3.52 (m, 7H), 3.24 (dt, *J* = 14.3, 7.0 Hz, 1H), 3.14 (dt, *J* = 13.4, 6.4 Hz, 1H), 3.06 (dt, *J* = 13.1, 5.8 Hz, 1H), 2.95 (dt, *J* = 15.0, 5.8 Hz, 1H), 2.86 (dt, *J* = 16.8, 6.4 Hz, 1H), 2.73 (dt, *J* = 16.8, 5.8 Hz, 1H), 2.65 (s, 1H), 2.11-2.06 (m, 2H), 1.94-1.89 (m, 2H), 1.43 (t, *J* = 7.2 Hz, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 147.1, 137.4, 128.3, 125.7, 114.6, 110.8, 109.7, 85.0, 74.7, 61.2, 55.8, 55.6, 55.5, 53.8, 43.9, 43.7, 39.6, 28.1, 26.0, 8.2; HRMS (ESI-TOF)

calcd for $C_{25}H_{39}N_2O_2$ $[M]^+$ 399.3012, found 399.3010.

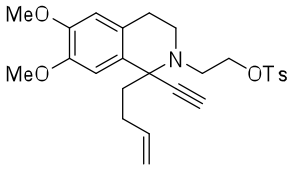


2-(2-Bromo-ethyl)-1-but-3-enyl-1-ethynyl-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline (6b). To a solution of alcohol **12b** (510 mg, 1.62 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added PPh_3 (594 mg, 1.79 mmol) and CBr_4 (804 mg, 2.42 mmol). After stirring at 0 °C for 10 min, the reaction mixture was concentrated by rotary evaporation. The residue was purified by flash column chromatography (hexanes:EtOAc = 5:1) to afford bromide **6b** (485 mg, 79%) as a colorless oil. R_f 0.38 (hexanes:EtOAc = 3:1); IR (film) 3287, 2952, 2833, 2254, 1613, 1518, 1464, 1254, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.85 (s, 1H), 6.52 (s, 1H), 5.71 (ddt, *J* = 16.9, 10.2, 6.5 Hz, 1H), 4.89 (dd, *J* = 17.2, 1.6 Hz, 1H), 4.85 (d, *J* = 10.3 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.52-3.40 (m, 2H), 3.37-3.30 (m, 1H), 2.97-2.91 (m, 1H), 2.91-2.76 (m, 3H), 2.56 (d, *J* = 14.3 Hz, 1H), 2.43 (d, *J* = 0.9 Hz, 1H), 2.26-2.10 (m, 2H), 2.06 (ddd, *J* = 14.2, 11.8, 4.7 Hz, 1H) 1.55-1.46 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 147.7, 138.4, 129.5, 127.7, 114.4, 110.7, 109.7, 85.8, 72.6, 60.5, 56.1, 55.8, 53.9, 46.1, 40.0, 31.4, 29.4, 27.5; HRMS (ESI-TOF) calcd for $C_{19}H_{25}BrNO_2$ $[M+H]^+$ 378.1069, found 378.1066.

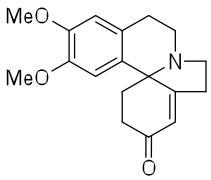


1-But-3-enyl-2-(2-chloro-ethyl)-1-ethynyl-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline (6c). To a solution of alcohol **12b** (269 mg, 0.853 mmol) and pyridine (2 mL) at 0 °C was added *p*-toluenesulfonyl chloride (179 mg, 0.938 mmol). After stirring at room temperature for 15 h, the mixture was diluted with ether (10 mL) and poured into saturated aqueous $NaHCO_3$ (10 mL) at 0 °C. After the organic phase was separated, the aqueous phase was further extracted with ether (2×15 mL). The combined organic extracts were washed with 2 N HCl (3×20 mL) and water (20 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (hexanes:EtOAc = 3:1) provided chloride **6c** (166 mg, 58%) as a colorless oil.

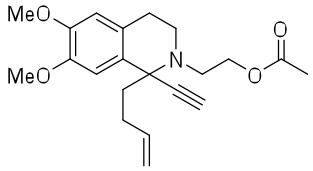
R_f 0.68 (hexanes:EtOAc = 1:1); IR (film) 3287, 2952, 2832, 1518, 1217, 641 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.85 (s, 1H), 6.52 (s, 1H), 5.71 (ddt, *J* = 16.8, 10.4, 6.4 Hz, 1H), 4.92 (d, *J* = 17.3 Hz, 1H), 4.88 (d, *J* = 10.4 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.66-3.56 (m, 2H), 3.29 (dt *J* = 14.6, 7.6 Hz, 1H), 2.97-2.80 (m, 3H), 2.72 (ddd, *J* = 14.2, 7.4, 5.1 Hz, 1H), 2.55 (d, *J* = 15.0 Hz, 1H), 2.43 (s, 1H), 2.25-2.02 (m, 3H), 1.56-1.45 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 147.7, 138.5, 129.5, 127.7, 114.4, 110.7, 109.7, 85.8, 72.6, 60.5, 56.2, 55.8, 53.8, 46.3, 43.0, 40.1, 29.5, 27.4; HRMS (EI) calcd for $C_{19}H_{24}ClNO_2$ $[M]^+$ 333.1496, found 333.1492.



Toluene-4-sulfonic acid 2-(1-but-3-enyl-1-ethynyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl ester (6d). *p*-Toluenesulfonic anhydride (517 mg, 1.59 mmol) was added to a solution of alcohol **12b** (250 mg, 0.793 mmol), Et_3N (0.220 mL, 1.59 mmol), and DMAP (4.45 mg, 39.6 μmol) in CH_2Cl_2 (5 mL) at room temperature. After stirring at room temperature for 30 min, the mixture was diluted with EtOAc (10 mL) and poured into saturated aqueous $NaHCO_3$ (10 mL). After the organic phase was separated, the aqueous phase was further extracted with EtOAc (2×15 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (hexanes:EtOAc = 2:1) provided tosylate **6d** (83 mg, 22%) as a colorless oil. R_f 0.46 (hexanes:EtOAc = 1:1); IR (film) 3281, 2952, 2834, 2255, 1518, 1359, 1253, 1189 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 6.80 (s, 1H), 6.49 (s, 1H), 5.61 (ddt, *J* = 16.8, 10.1, 6.4 Hz, 1H), 4.83 (d, *J* = 18.6 Hz, 1H), 4.82 (d, *J* = 9.5 Hz, 1H), 4.16-4.05 (m, 2H), 3.84 (s, 3H), 3.84 (s, 3H), 3.22 (dt, *J* = 14.6, 6.7 Hz, 1H), 2.84-2.72 (m, 3H), 2.60 (dt, *J* = 15.0, 5.2 Hz, 1H), 2.50-2.45 (m, 1H), 2.44 (s, 3H), 2.38 (s, 1H), 2.07-1.96 (m, 3H), 1.44-1.35 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.9, 147.8, 144.9, 138.4, 133.1, 130.0, 129.4, 128.1, 127.7, 114.4, 110.7, 109.7, 85.6, 72.7, 72.7, 69.0, 60.5, 56.2, 55.9, 55.9, 50.4, 46.5, 40.1, 29.4, 27.3, 21.8; MS (EI) calcd for $C_{26}H_{32}NO_5S$ $[M]^+$ 470.2, found 470.2.

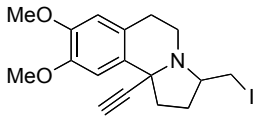


3-Demethoxyerythratidinone (3). To a solution of diene **4** (100 mg, 0.336 mmol) in acetone (1.50 mL) and water (0.50 mL) were added *N*-methylmorpholine *N*-oxide (118 mg, 1.00 mmol) and $K_2OsO_2(OH)_4$ (2.00 mg, 0.00534 mmol) at room temperature. The resulting solution was stirred at room temperature for 9 h before addition of $NaIO_4$ (216 mg, 1.00 mmol). After stirring at room temperature for 1 h, the reaction mixture was treated with saturated aqueous $NaHSO_3$ (1.0 mL). The resulting solution was diluted with EtOAc (10 mL) and 1 N NaOH (10 mL). After the organic layer was separated, the aqueous layer was extracted with EtOAc (4×10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The residue was purified by flash column chromatography (EtOAc:CH_3CN = 1:1, 1% Et_3N) to provide ketone **4** (72 mg, 72%) as a colorless oil. R_f 0.32 (EtOAc:Et_3N = 8:1); IR (film) 2934, 2847, 1668, 1511, 1464, 1330, 1254, 1107 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.65 (s, 1H), 6.55 (s, 1H), 6.11 (s, 1H), 3.86 (s, 3H), 3.74 (s, 3H), 3.54-3.41 (m, 1H), 3.32-3.19 (m, 1H), 3.06 (dt, *J* = 17.0, 10.2 Hz, 2H), 2.86 (dd, *J* = 17.0, 8.6 Hz, 1H), 2.79-2.64 (m, 1H), 2.62-2.50 (m, 3H), 2.46 (dd, *J* = 18.0, 5.2 Hz, 1H), 2.31 (dd, *J* = 12.2, 5.3 Hz, 1H), 2.22-2.13 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.8, 169.4, 148.5, 146.9, 125.8, 124.7, 123.9, 112.9, 110.3, 63.7, 56.1, 56.0, 45.9, 40.2, 36.3, 33.0, 28.8, 21.6; HRMS (ESI-TOF) calcd for $C_{18}H_{22}NO_3$ $[M+H]^+$ 300.1600, found 300.1595.



2-(1-(But-3-enyl)-1-ethynyl-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl acetate (6e). To a flame dried one-dram glass vial equipped with a screw-cap and a Teflon septum were added $[Rh(COD)Cl]_2$ (3.7 mg, 0.0075 mmol), $P(4\text{-}F\text{-}C_6H_4)_3$ (10 mg, 0.030 mmol), and CH_3CN (0.50 mL). This mixture was stirred for 5 min before iodoenyne **6a** (64 mg, 0.15 mmol) in CH_3CN (0.50 mL) was added via syringe at 25 °C. The syringe was washed with CH_3CN (0.50 mL). After addition of anhydrous K_2CO_3 (21 mg, 0.15 mmol), the reaction vial was moved to a

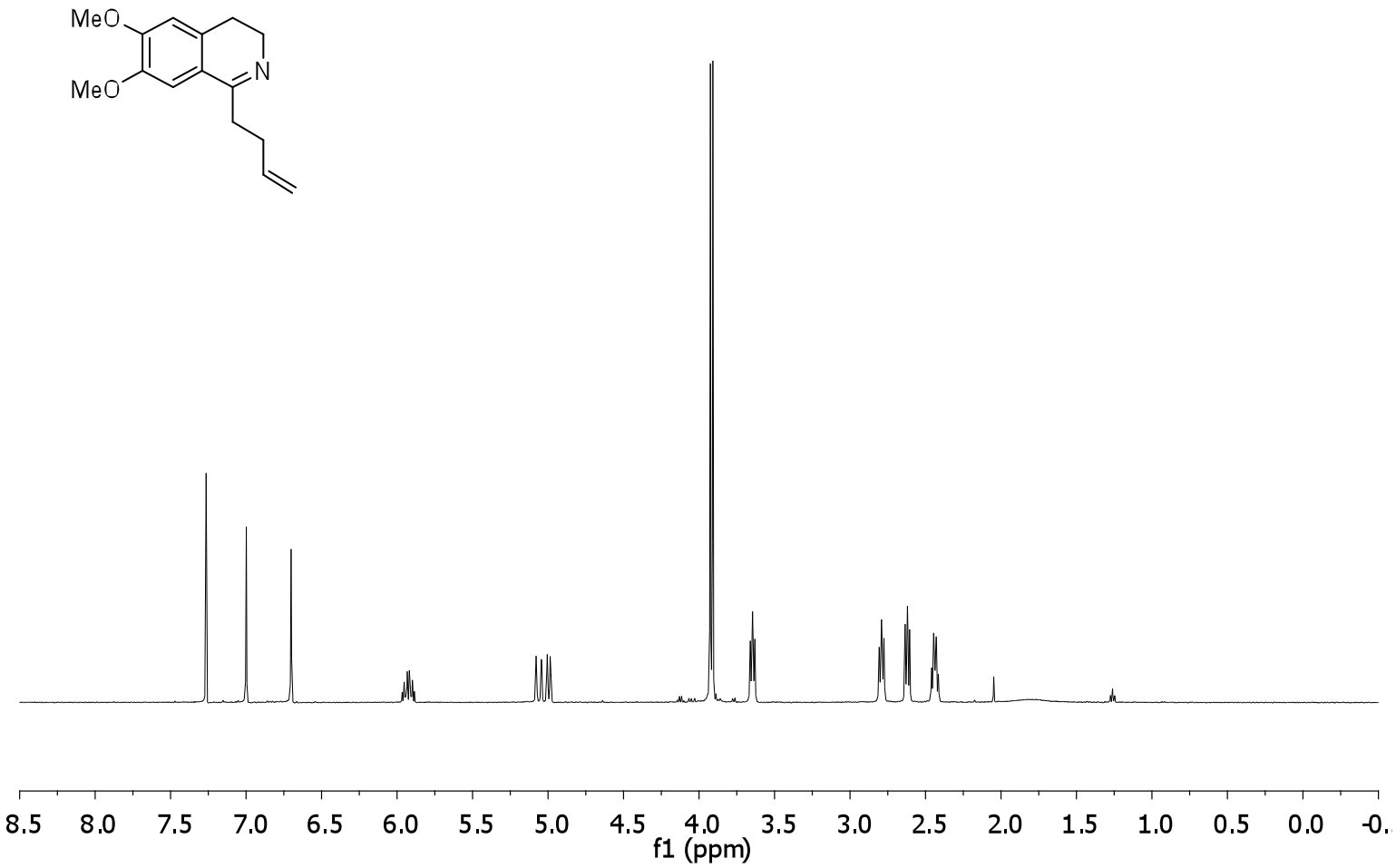
pre-heated sand bath (85 °C). After stirring at 85 °C for 1 h, the reaction mixture was cooled to room temperature and loaded directly onto a silica gel column. Purification by flash column chromatography (hexanes:EtOAc = 1:1, 1% Et_3N) yielded acetate **6e** (12 mg, 22%) as a colorless oil. R_f 0.60 (hexanes:EtOAc = 1:1); IR (film) 3281, 2934, 1739, 1613, 1519, 1252 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.52 (s, 1H), 5.70 (ddt, *J* = 16.8, 10.3, 6.4 Hz, 1H), 4.89 (dd, *J* = 17.4, 1.7 Hz, 1H), 4.86 (dd, *J* = 11.4, 1.2 Hz, 1H), 4.29 (ddd, *J* = 11.3, 8.7, 5.2 Hz, 1H), 4.13 (ddd, *J* = 4.2, 5.9, 10.8 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.21 (ddd, *J* = 14.4, 8.6, 6.1 Hz, 1H), 2.96 (ddd, *J* = 11.3, 4.9, 2.3 Hz, 1H), 2.91-2.81 (m, 1H), 2.74 (td, *J* = 11.3, 2.7 Hz, 1H), 2.53 (t, *J* = 4.4 Hz, 1H), 2.51 (t, *J* = 4.5 Hz, 1H), 2.41 (s, 1H), 2.24-2.00 (m, 3H), 2.05 (s, 3H), 1.57-1.46 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 148.0, 147.9, 138.7, 129.8, 128.2, 114.3, 110.9, 110.0, 85.9, 72.6, 62.9, 60.6, 56.3, 56.0, 50.3, 46.0, 40.0, 29.7, 27.2, 21.3; HRMS (ESI-TOF) calcd for $C_{21}H_{28}NO_4$ $[M+H]^+$ 358.2018, found 358.2009.



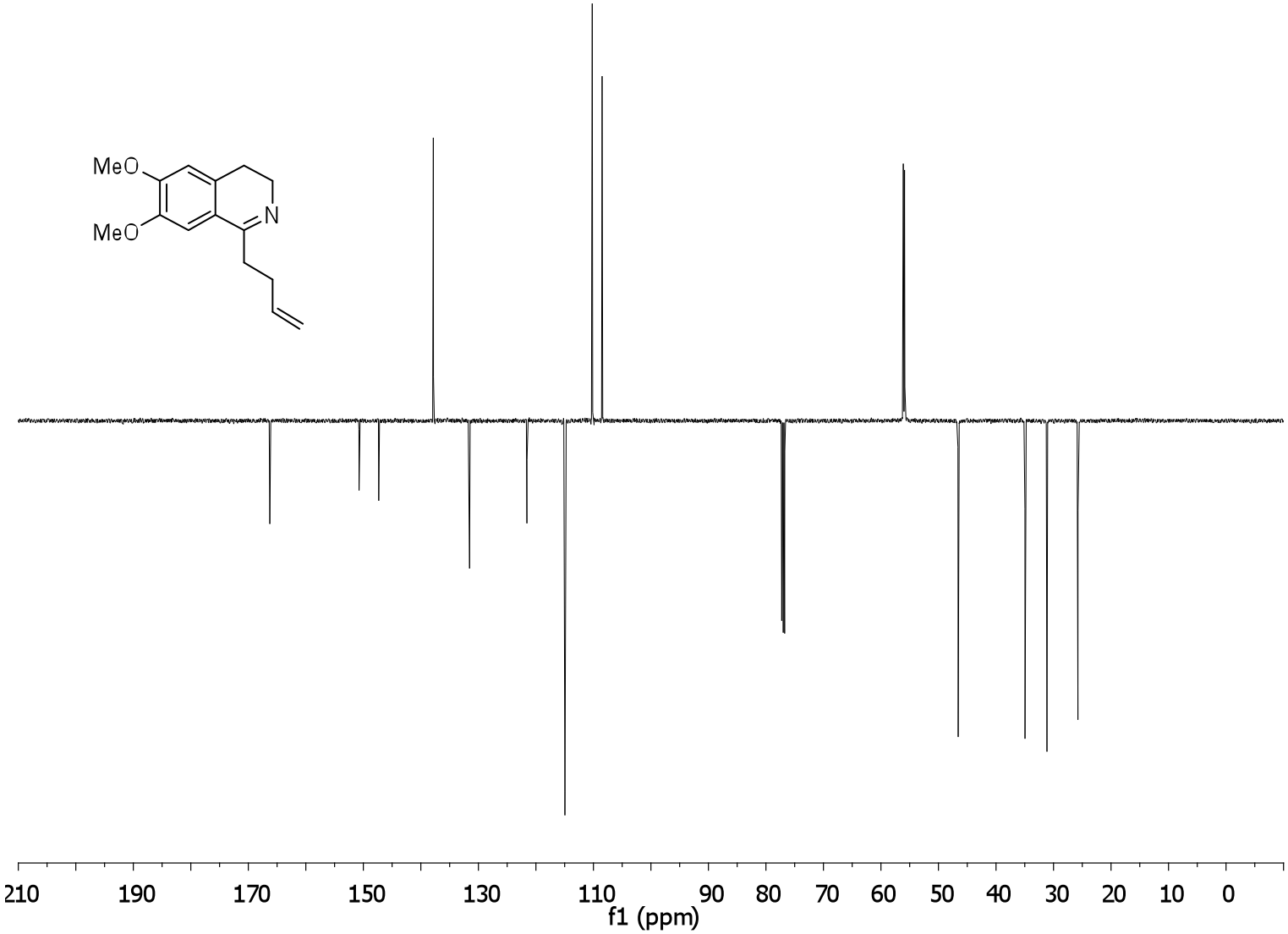
10b-Ethynyl-3-(iodomethyl)-8,9-dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*] isoquinoline (S2). To a one-dram glass vial were added imine **10** (190 mg, 0.774 mmol), 1,2-diiodoethane (0.218 mg, 0.774 mmol), and CH_3CN (1.00 mL). The vial was sealed with a screw-cap and a Teflon septum and moved to a pre-heated sand bath (85 °C). This mixture was stirred at 85 °C for 16 h. After being cooled to room temperature, the mixture was concentrated by rotary evaporation. The residue was directly used for Grignard reaction. To a solution of the crude material in THF (5 mL) was added ethynyl magnesium bromide (0.5 M in THF, 4.65 mL, 2.32 mmol) at 0 °C. After stirring at room temperature for 2 h, the mixture was poured into saturated aqueous NH_4Cl (10 mL). The layers were separated. The aqueous layer was extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (EtOAc, 1% Et_3N) provided iodide **S2** (110 mg, 36%) as a yellow oil. R_f 0.38 (EtOAc only); ^1H NMR (500 MHz, $CDCl_3$) δ 6.70 (s, 1H), 6.62 (s, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.42 (dd, *J* = 10.0, 2.3 Hz, 1H), 3.19 (dd, *J* = 9.9, 7.6 Hz, 1H), 3.08-3.00 (m, 2H), 2.98-2.90 (m, 1H), 2.80-2.72 (m, 2H), 2.50-2.40 (m, 1H), 2.48 (s, 1H), 2.35-2.25 (m, 1H), 1.94 (q, *J* = 10.3 Hz, 1H), 1.75-1.67 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 147.5, 131.6, 125.9, 111.6, 108.1, 84.5, 74.9, 59.9, 56.2,

56.0, 48.4, 41.7, 35.7, 29.9, 29.0, 12.6.

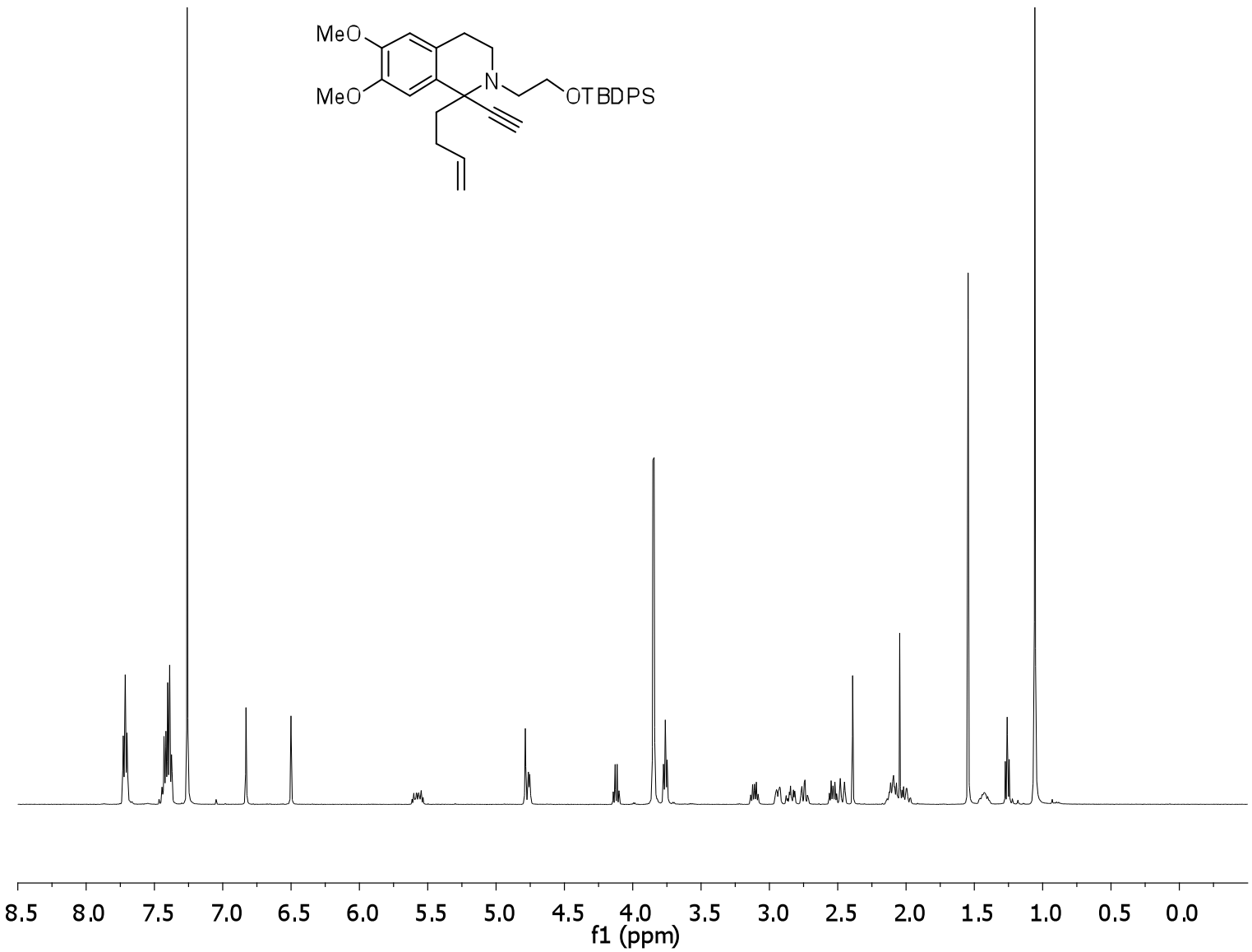
^{1}H NMR spectrum of 10



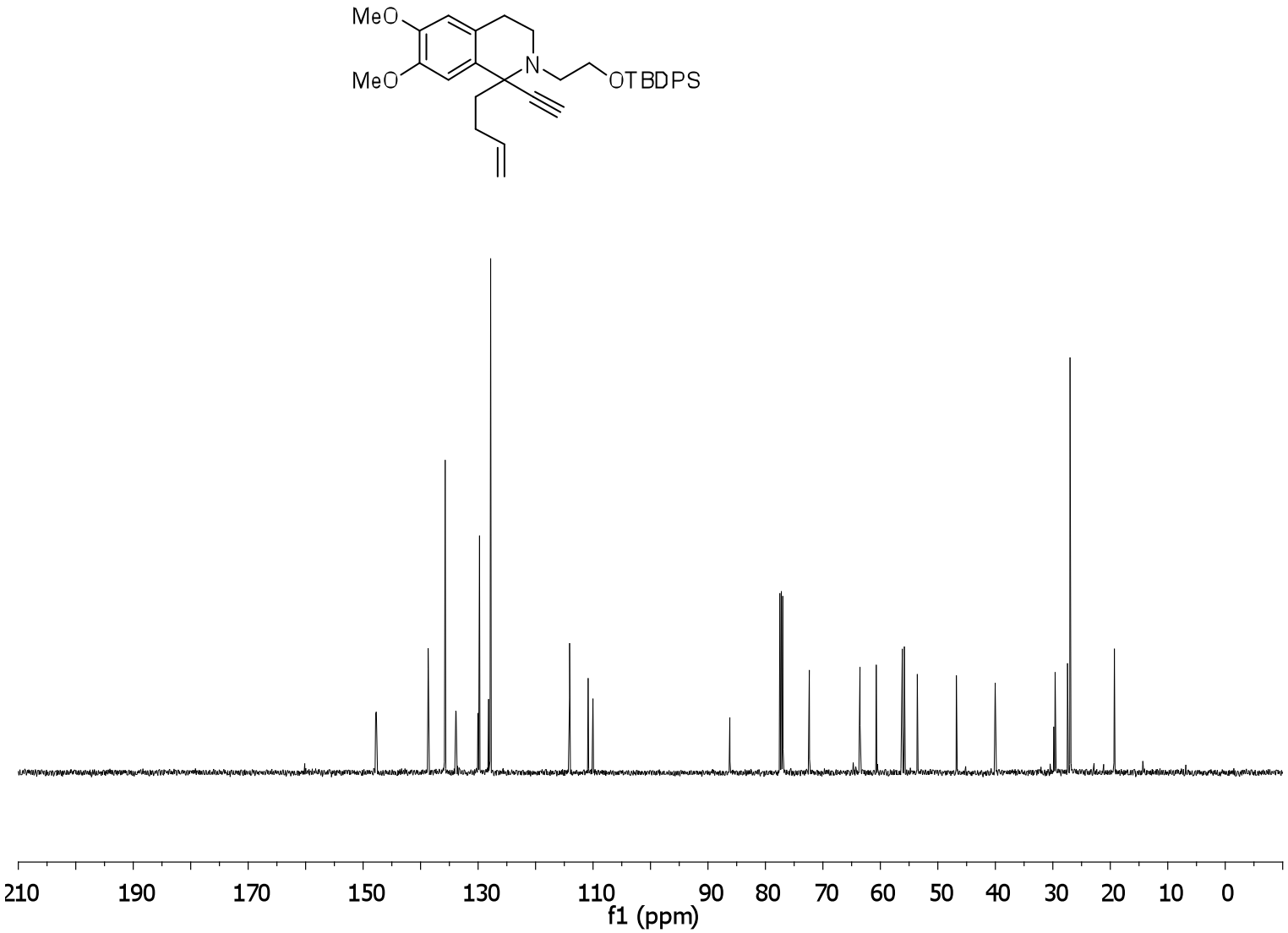
^{13}C NMR spectrum of 10



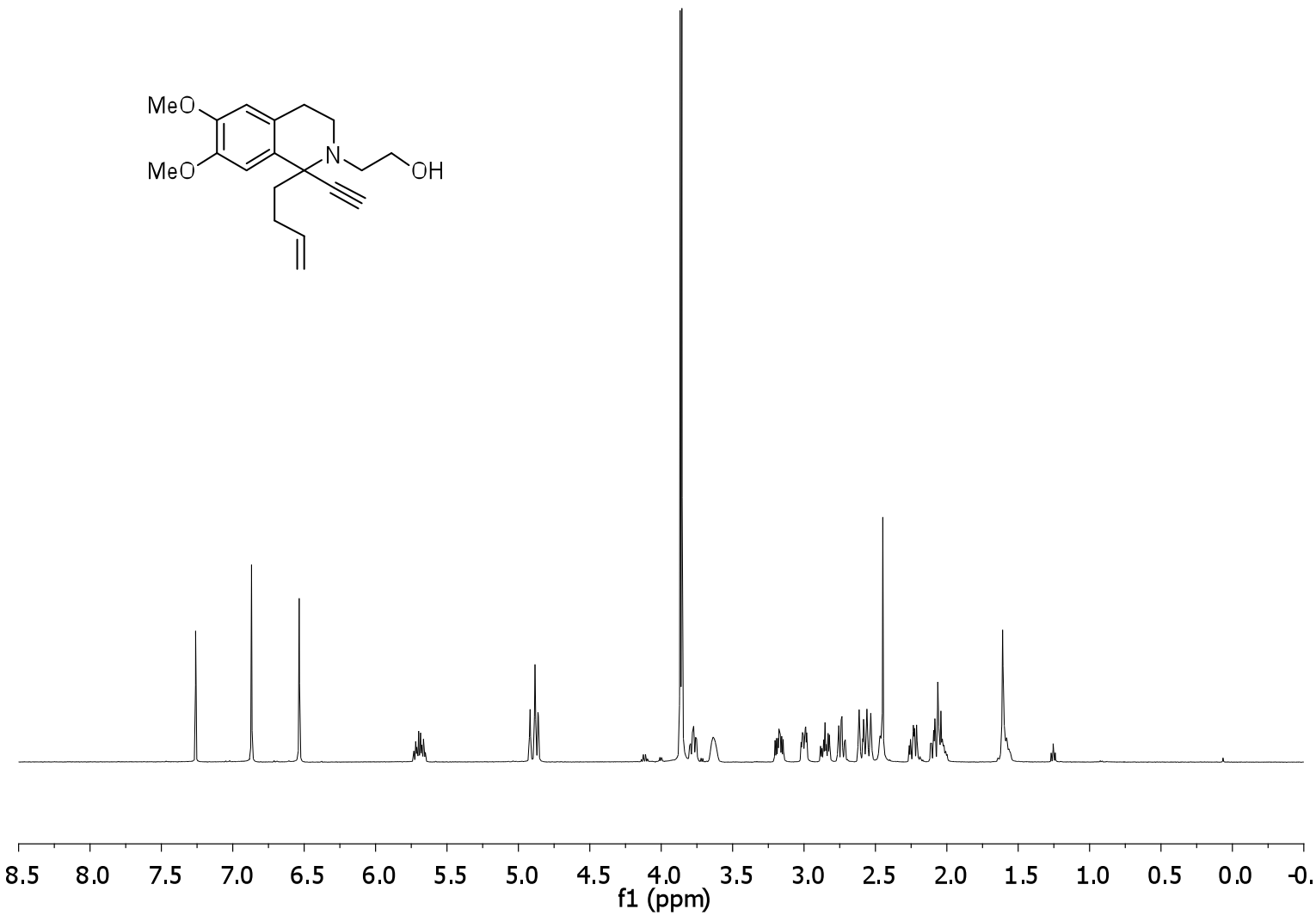
^{1}H NMR spectrum of 12a



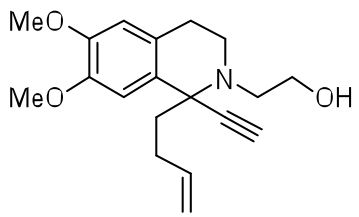
^{13}C NMR spectrum of 12a

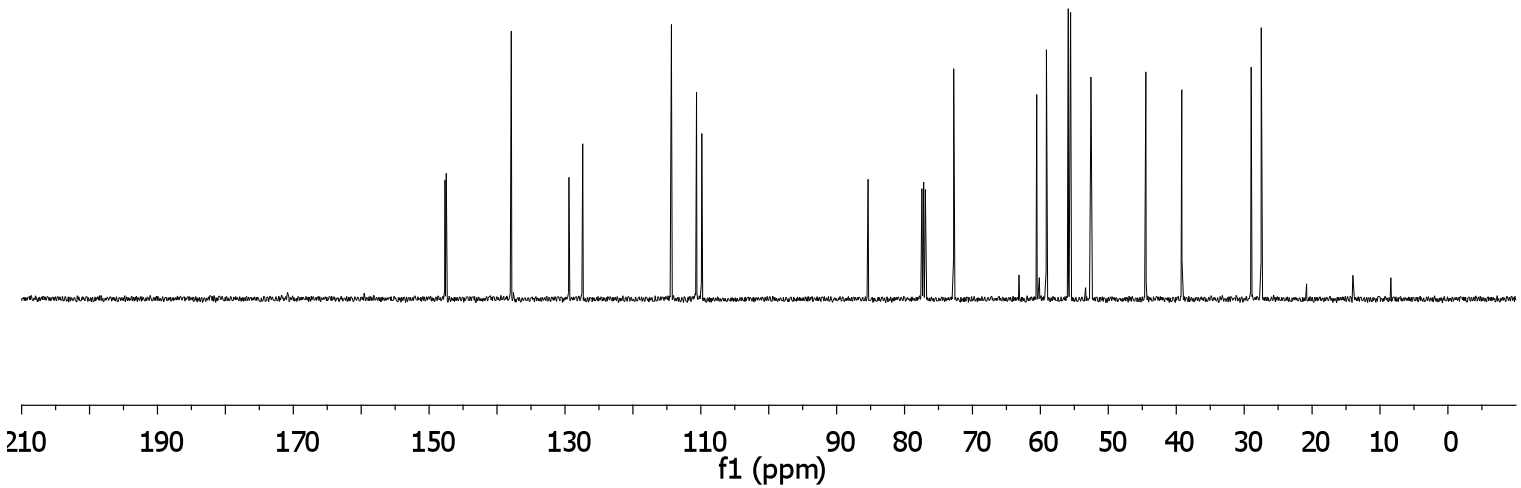


^{1}H NMR spectrum of 12b

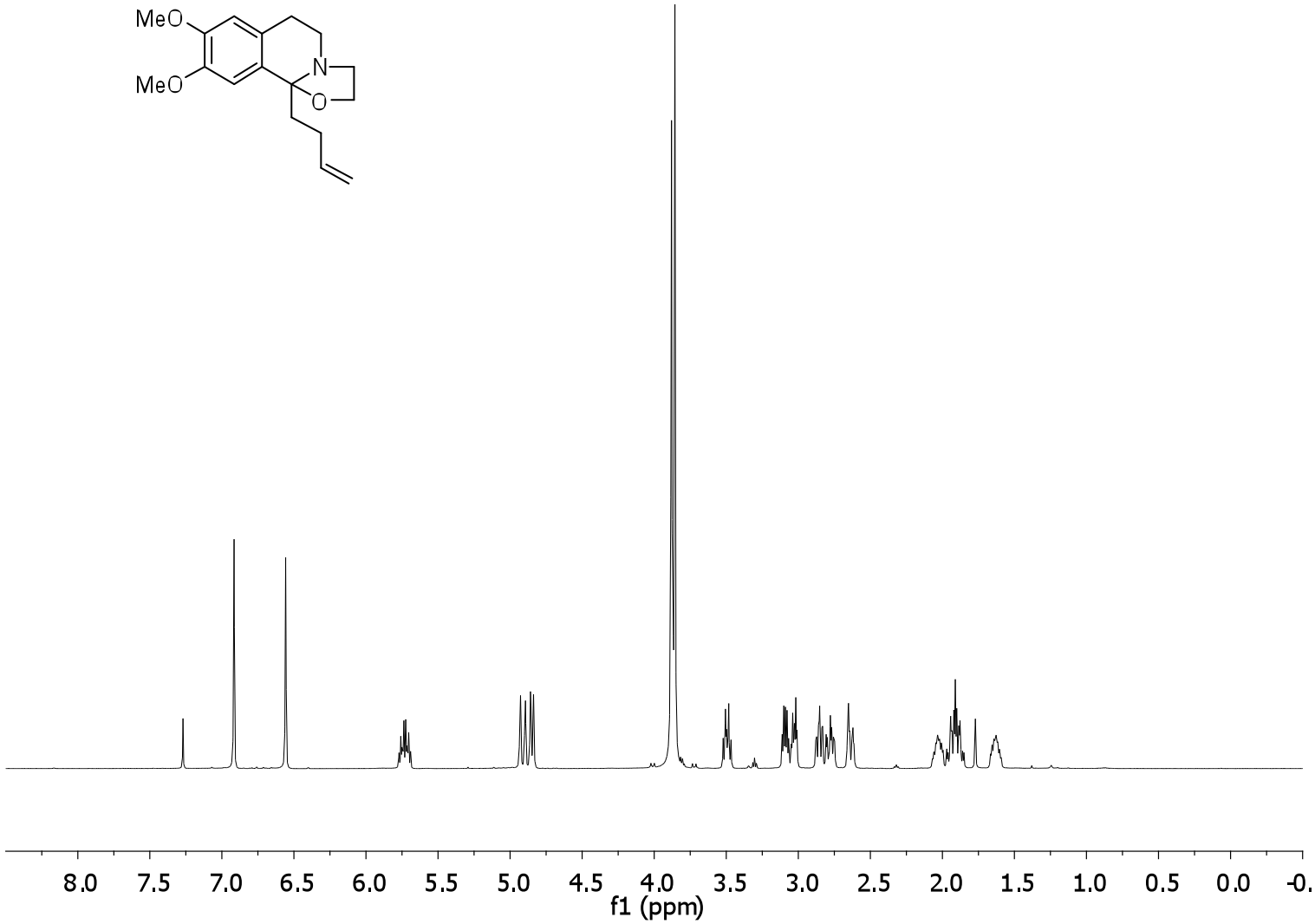


^{13}C NMR spectrum of 12b

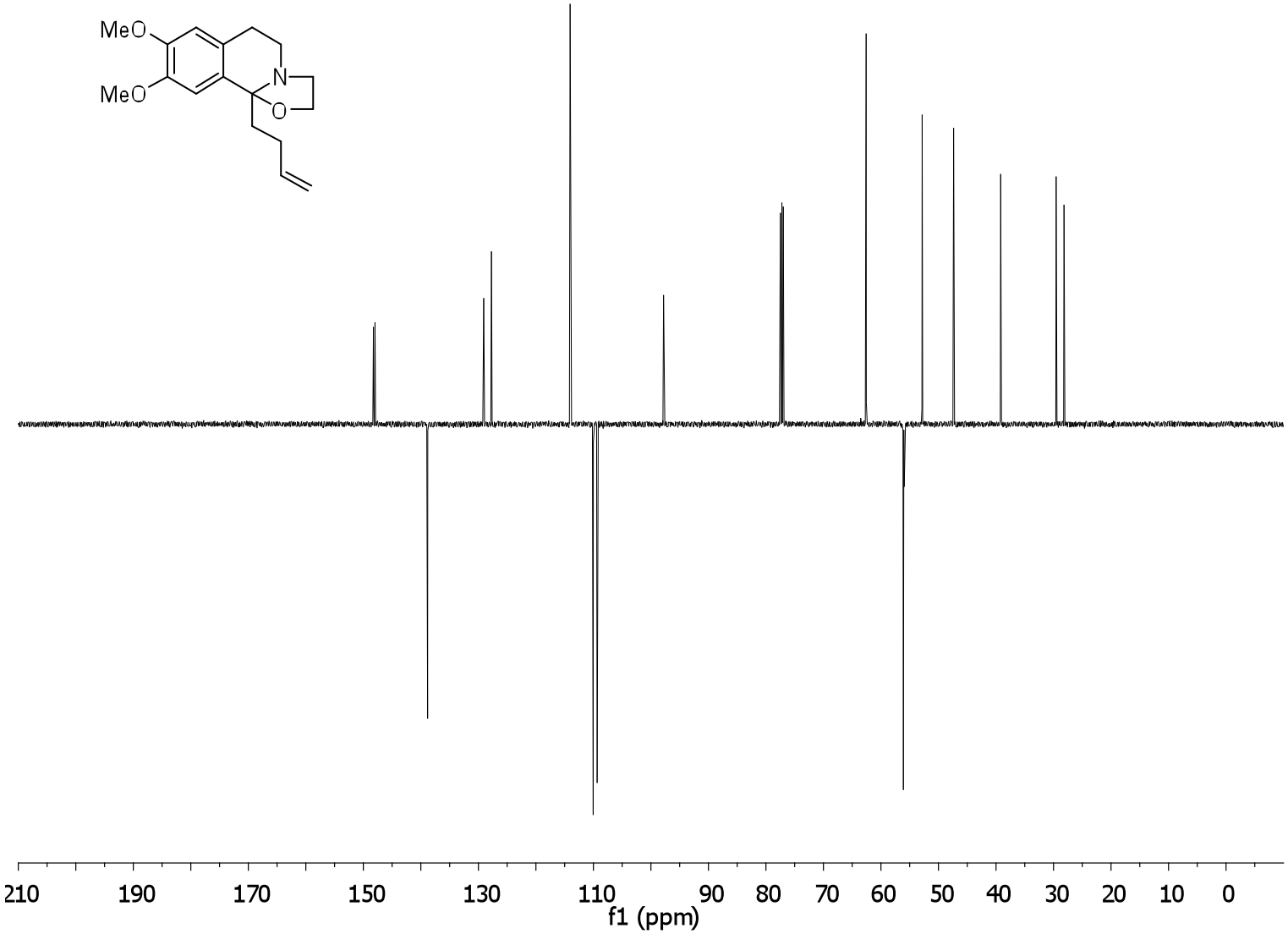




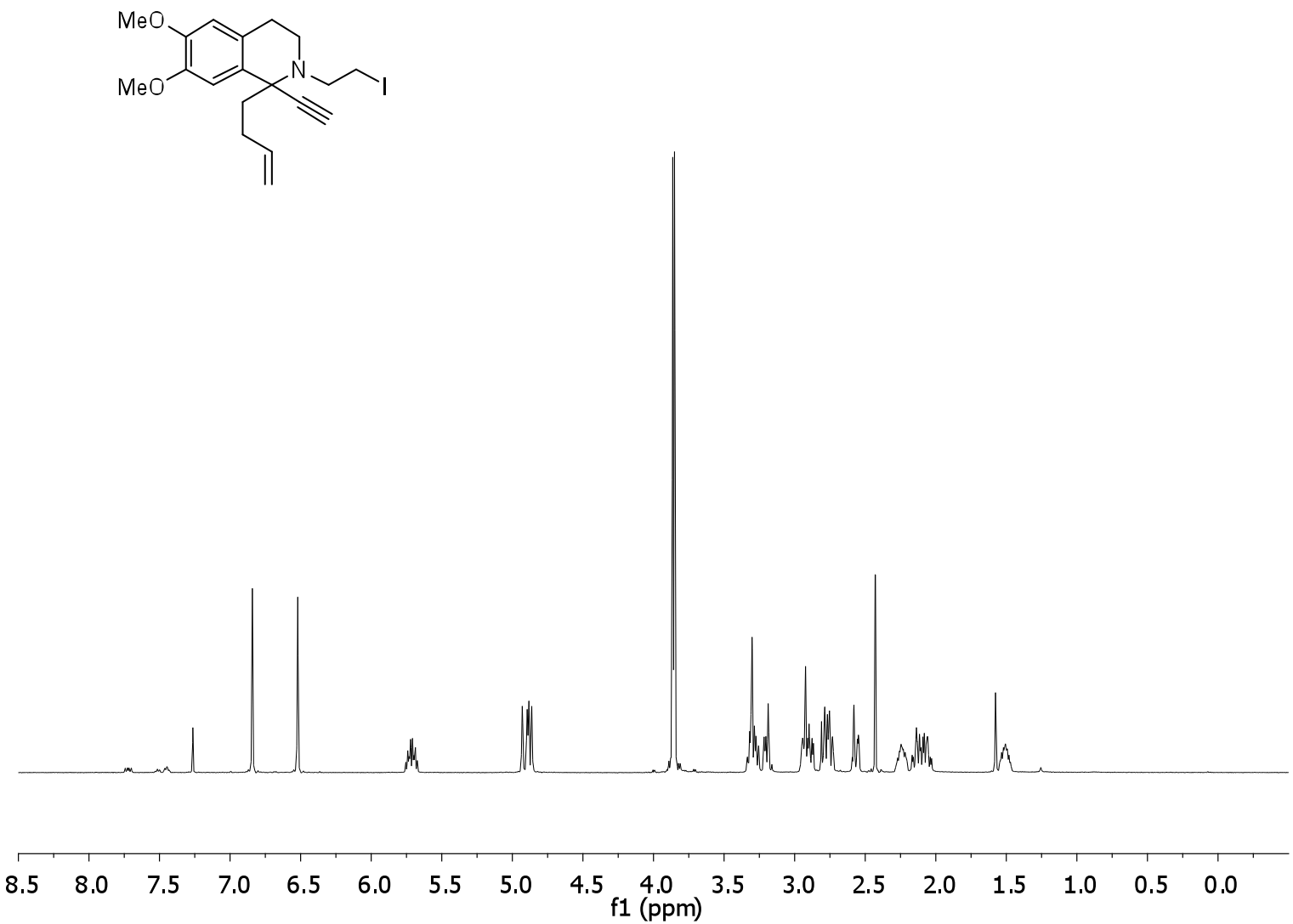
^{1}H NMR spectrum of 14



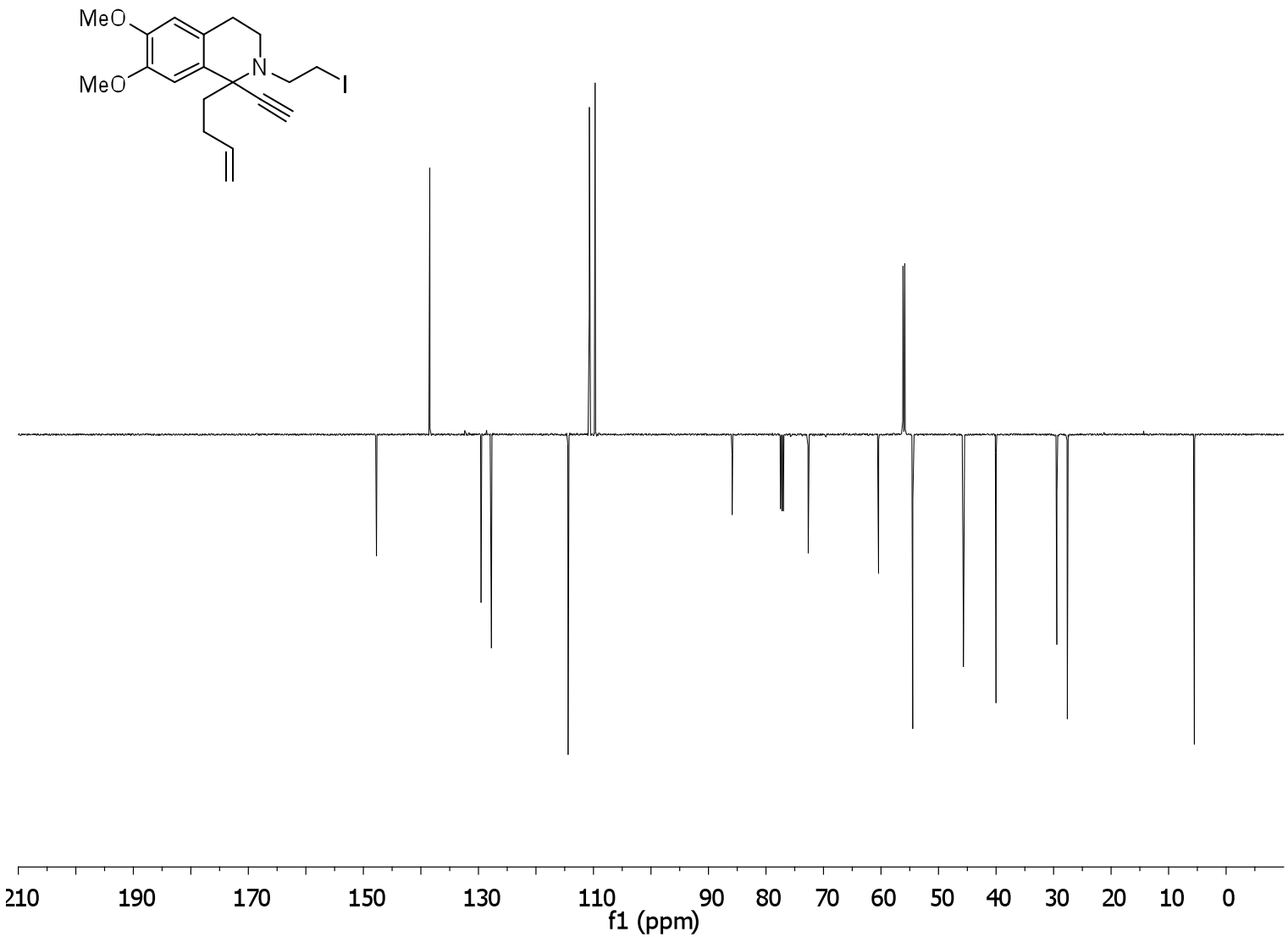
^{13}C NMR spectrum of 14



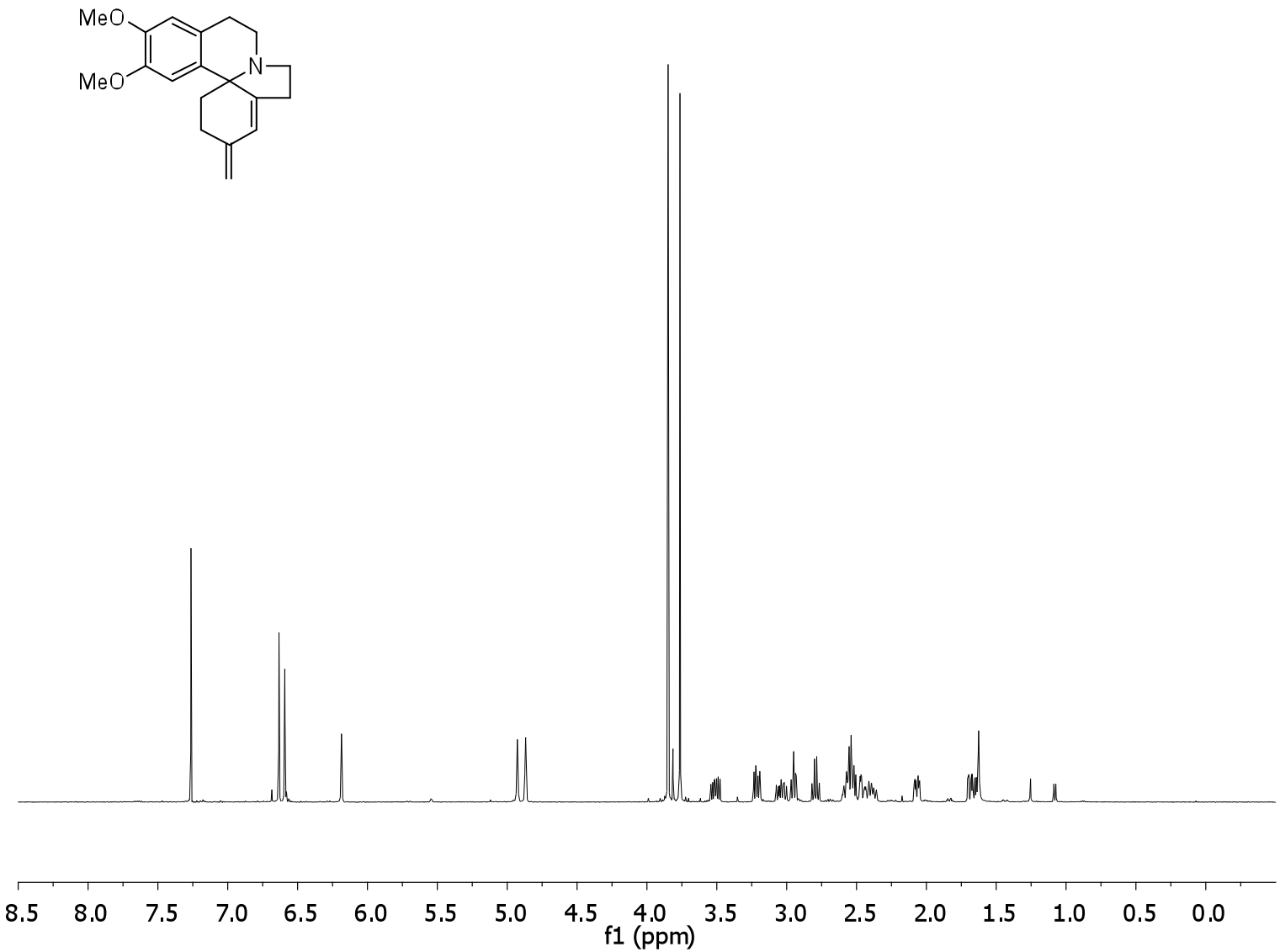
^{1}H NMR spectrum of 6a



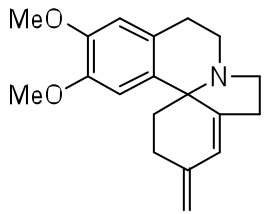
^{13}C NMR spectrum of 6a

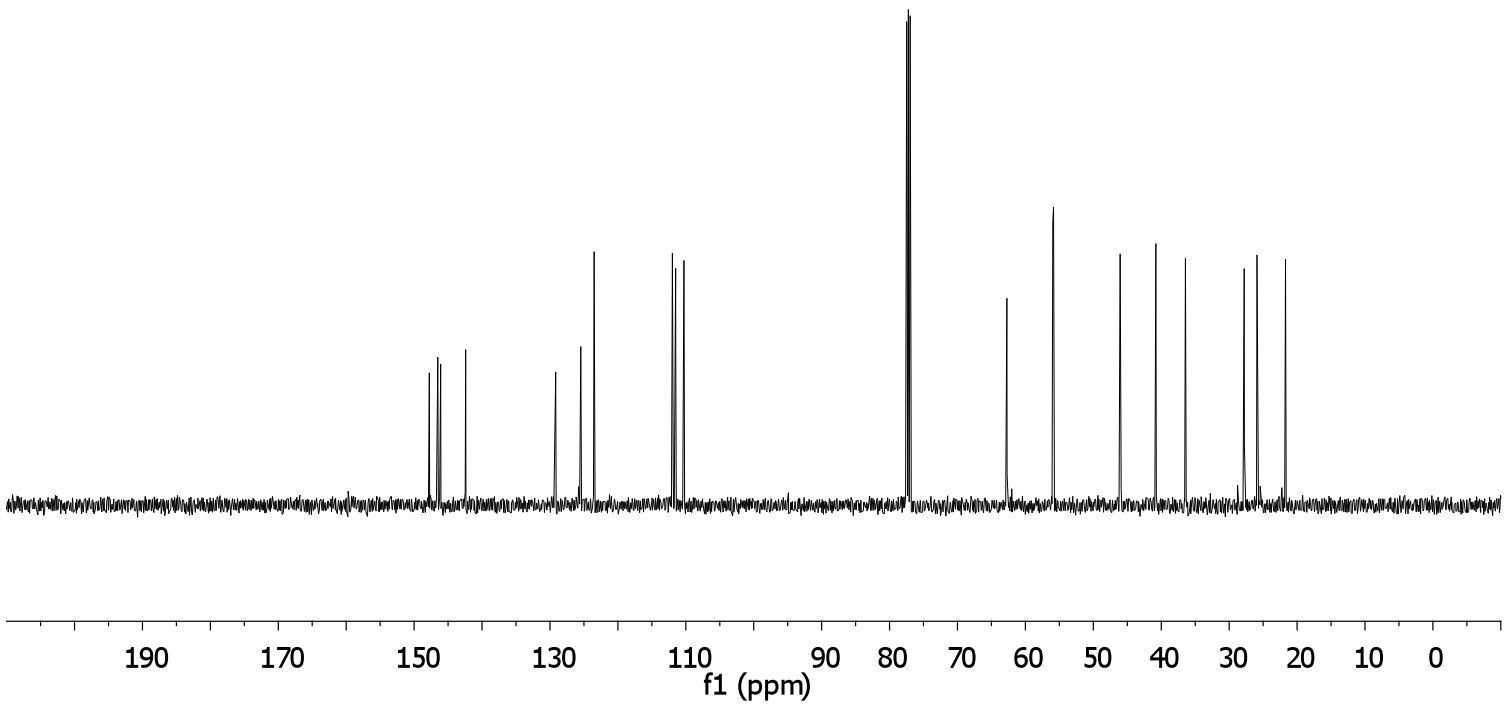


^{1}H NMR spectrum of 4

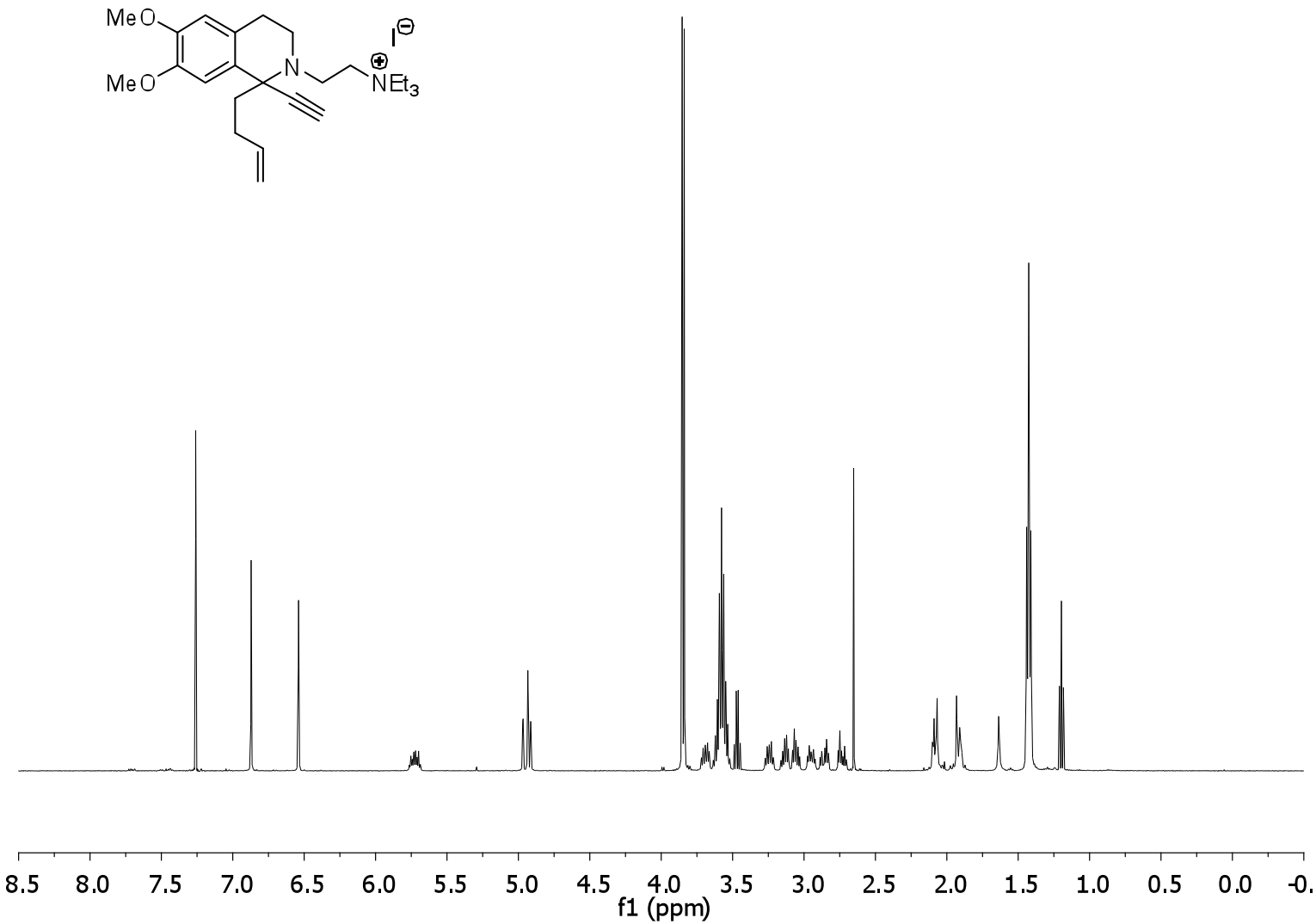


^{13}C NMR spectrum of 4

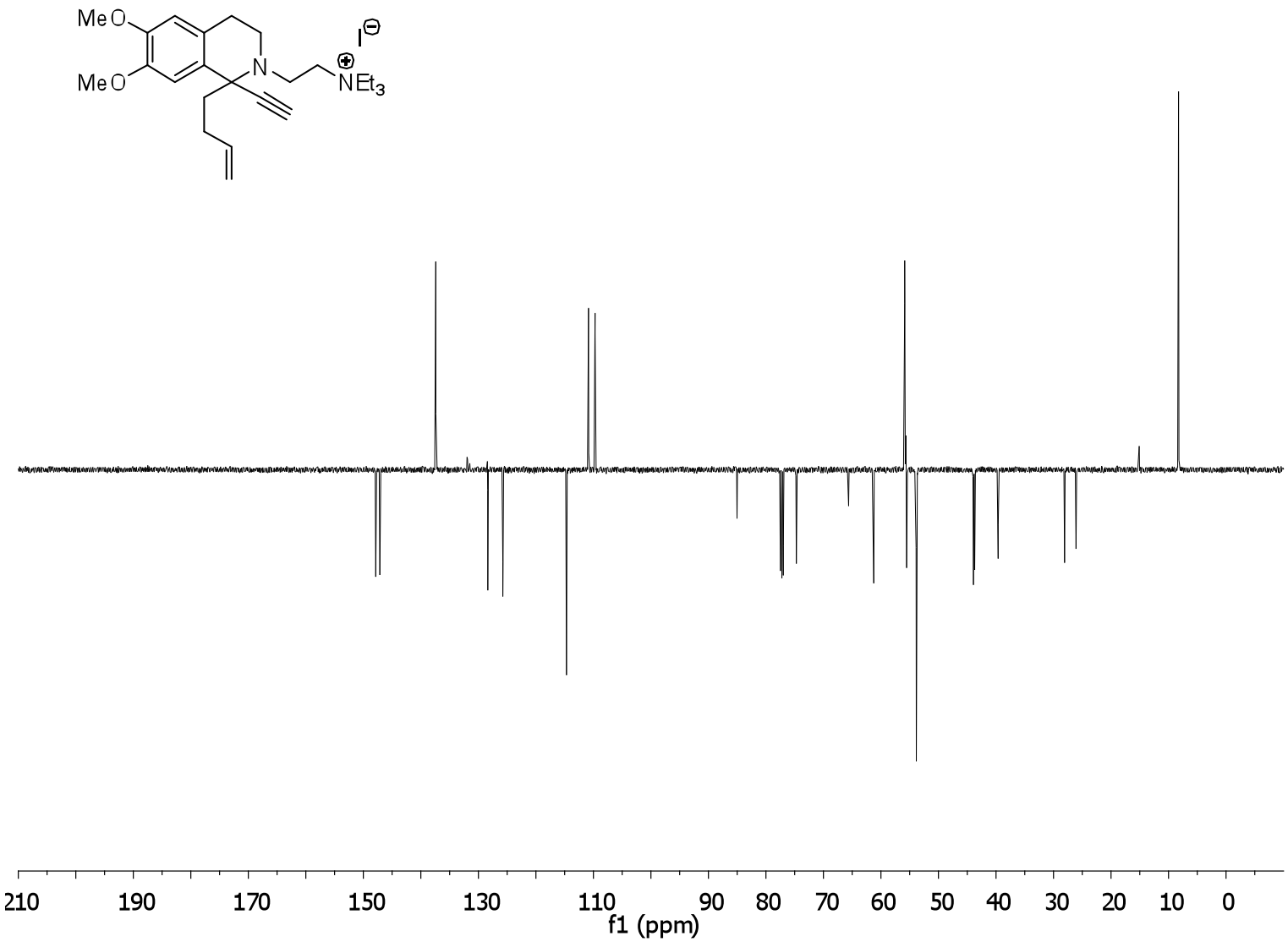




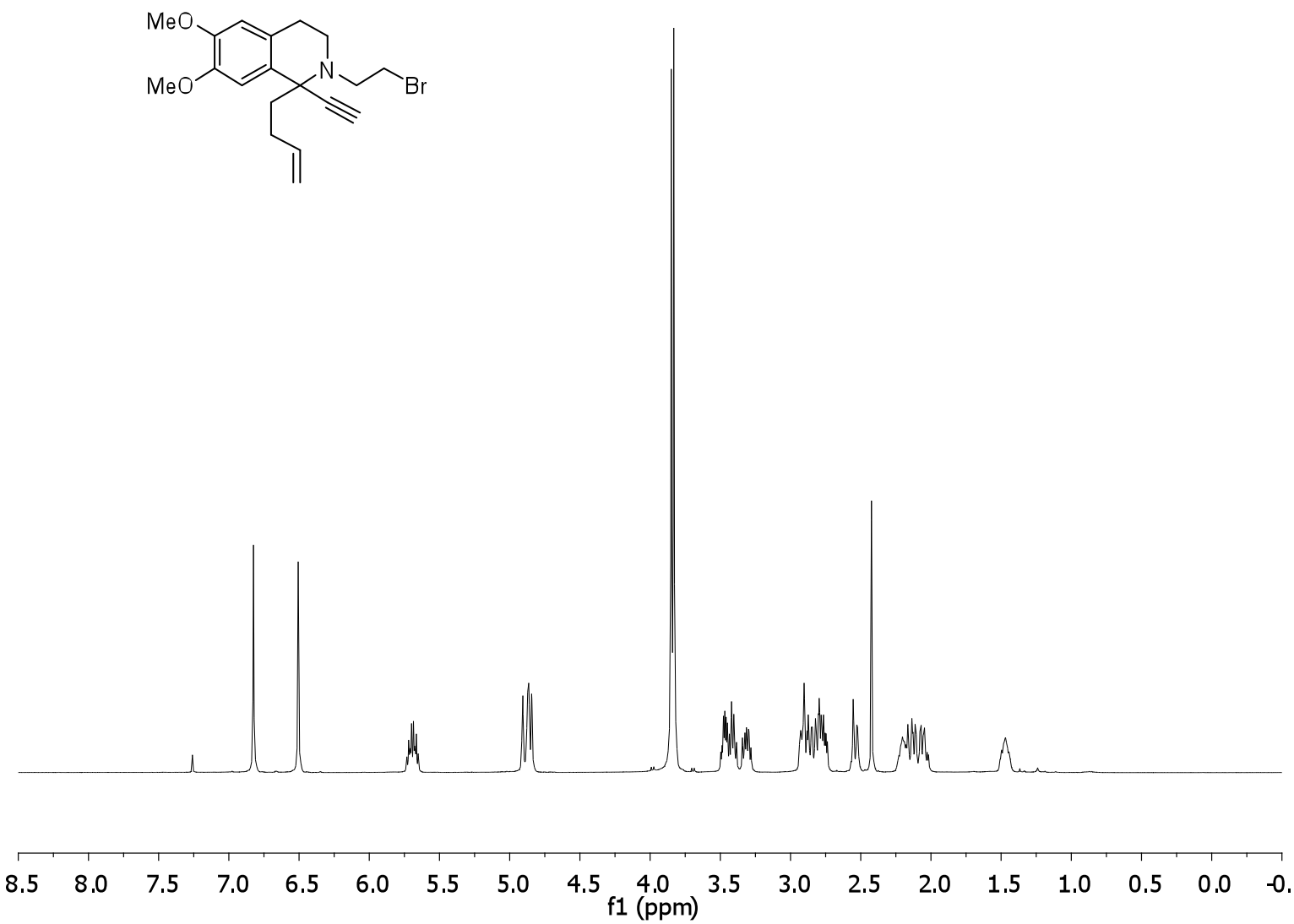
^{1}H NMR spectrum of 16



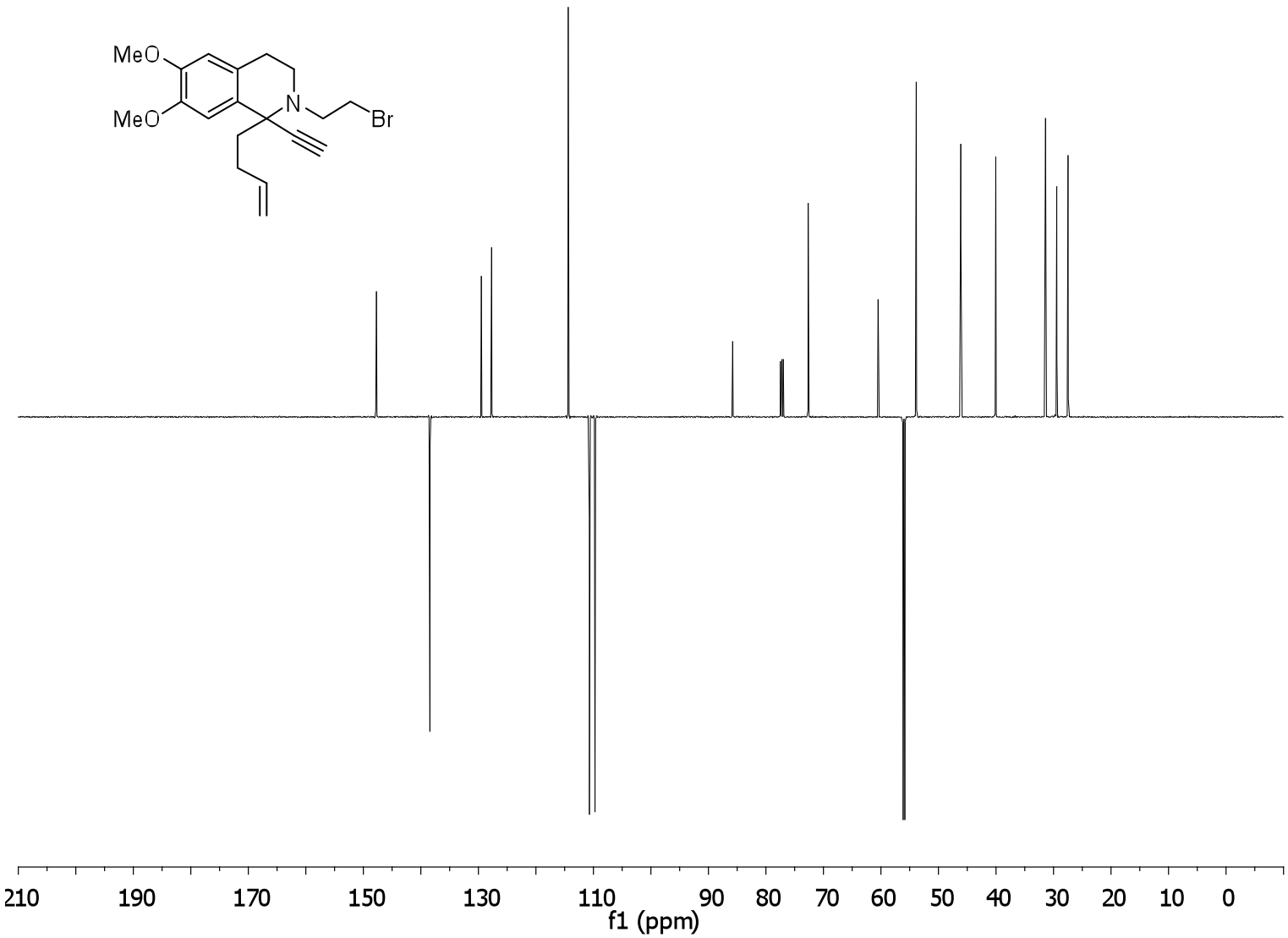
^{13}C NMR spectrum of 16



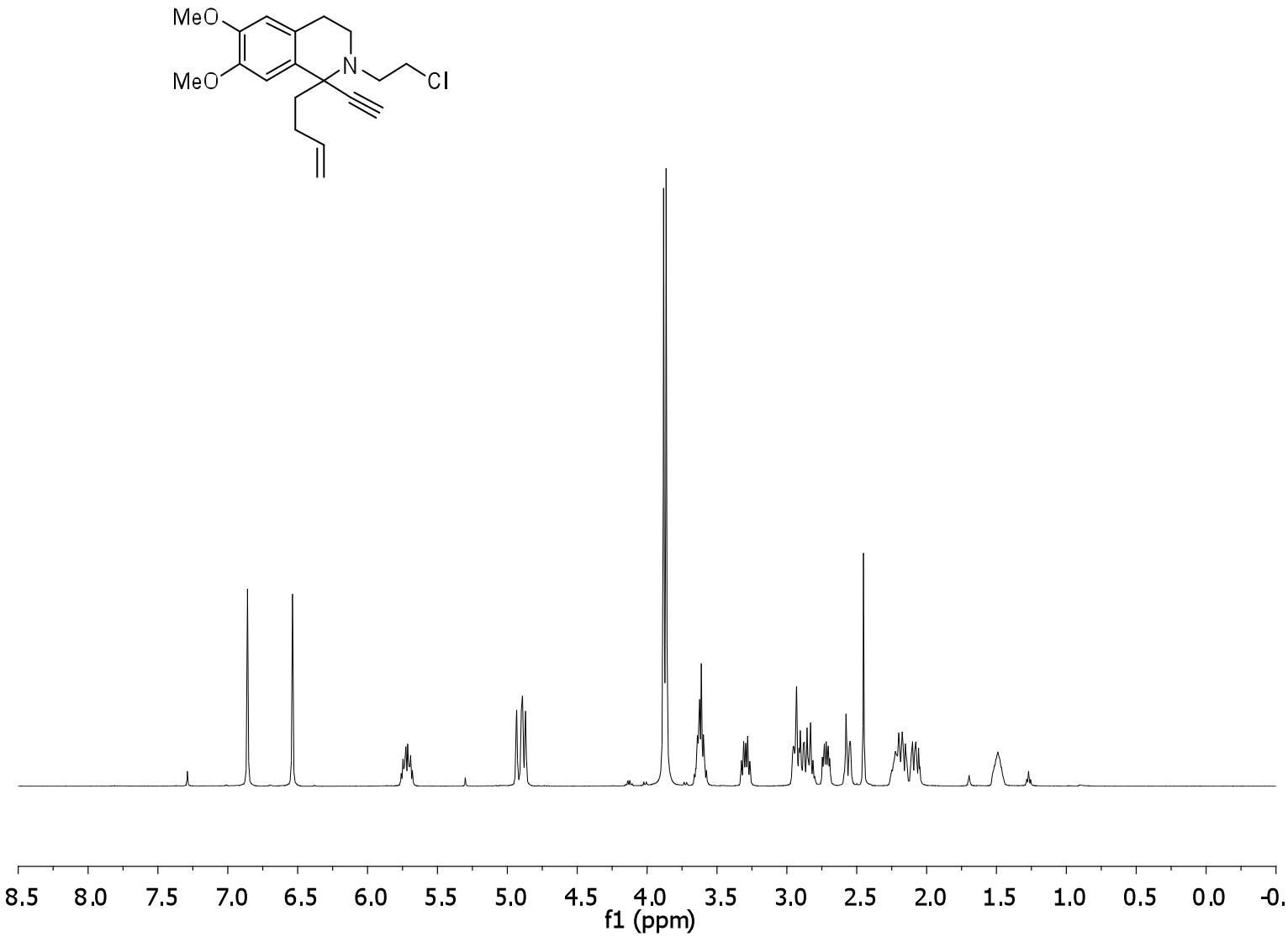
^{1}H NMR spectrum of 6b



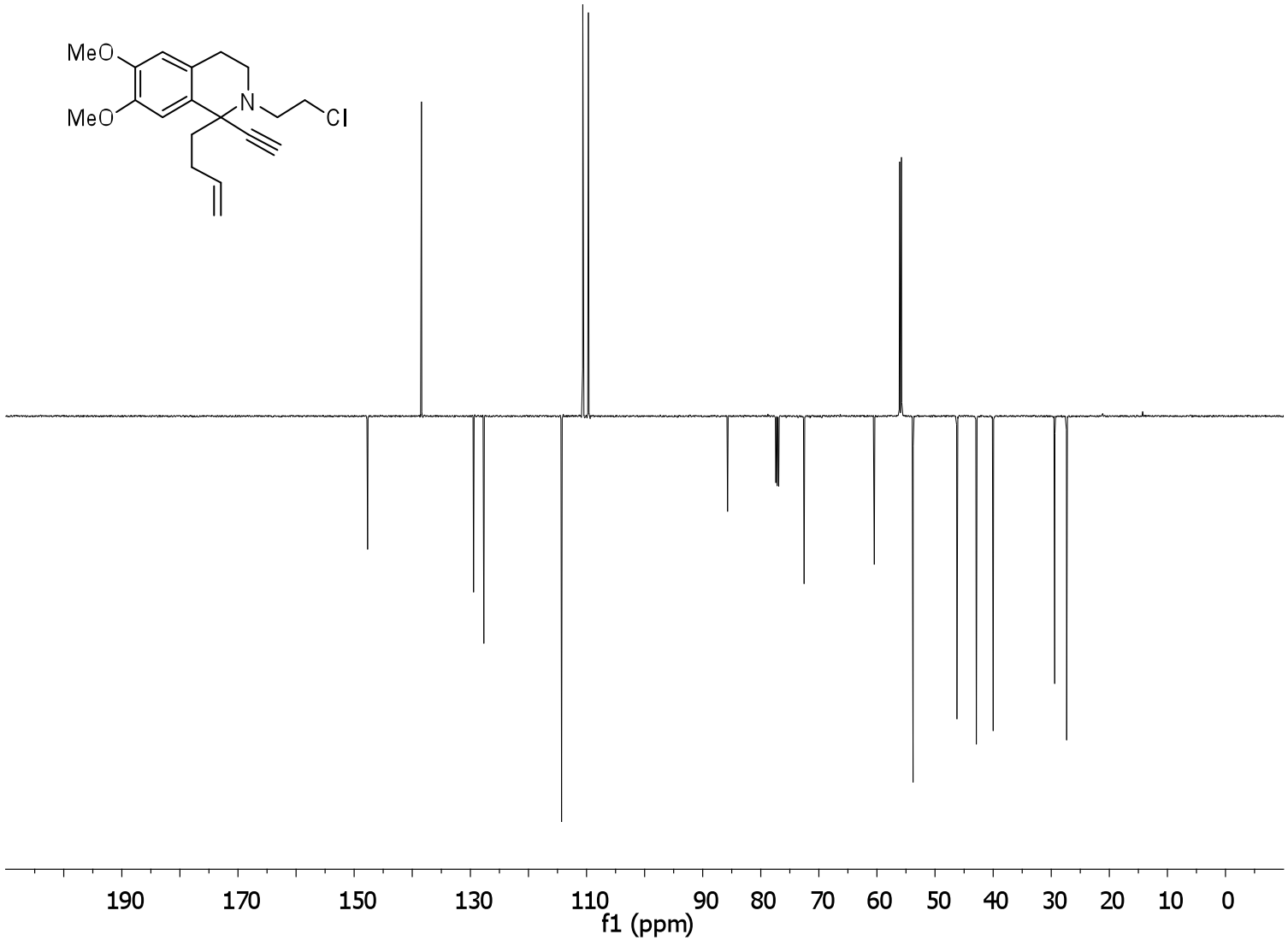
^{13}C NMR spectrum of 6b



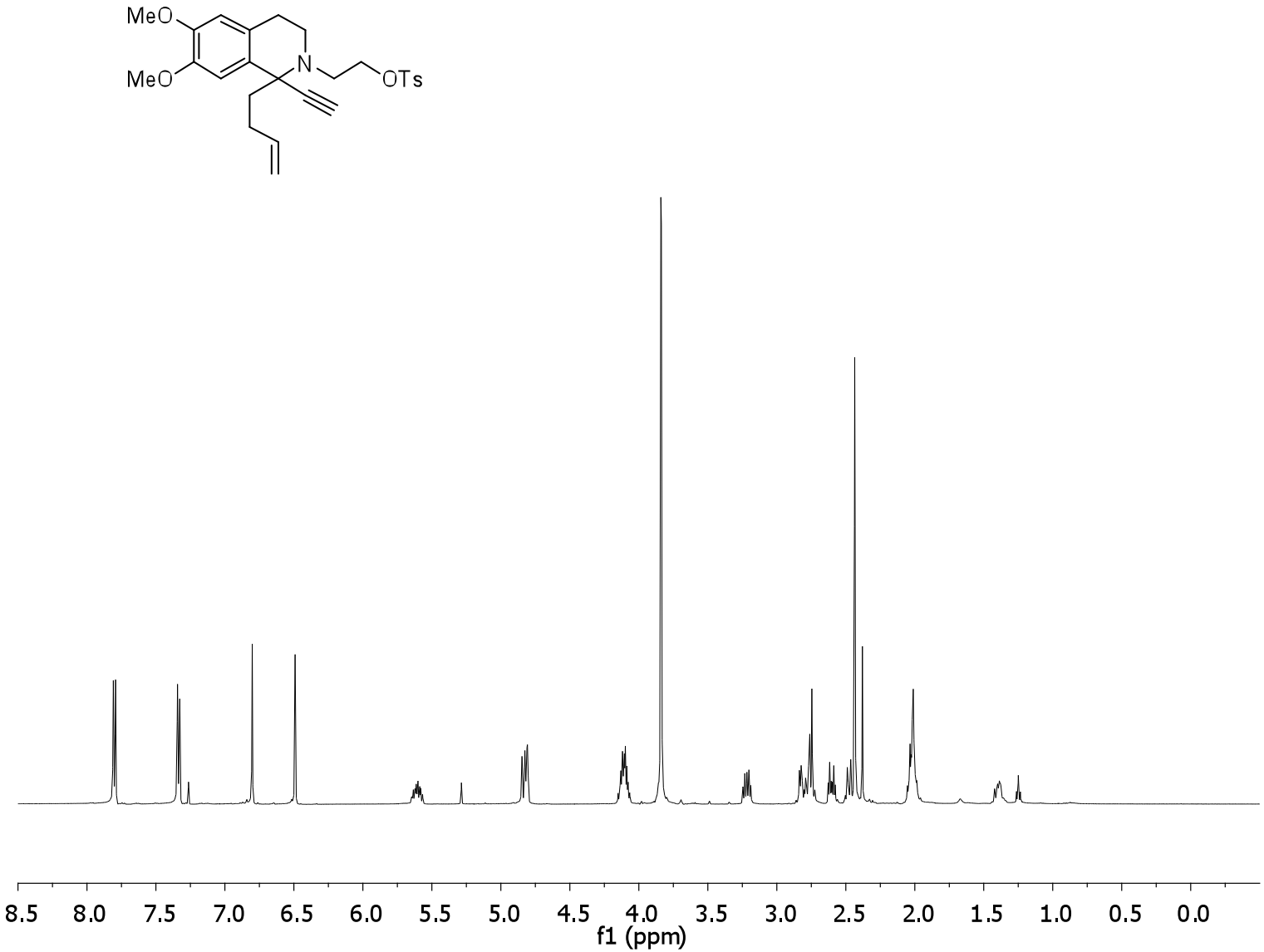
^{1}H NMR spectrum of 6c



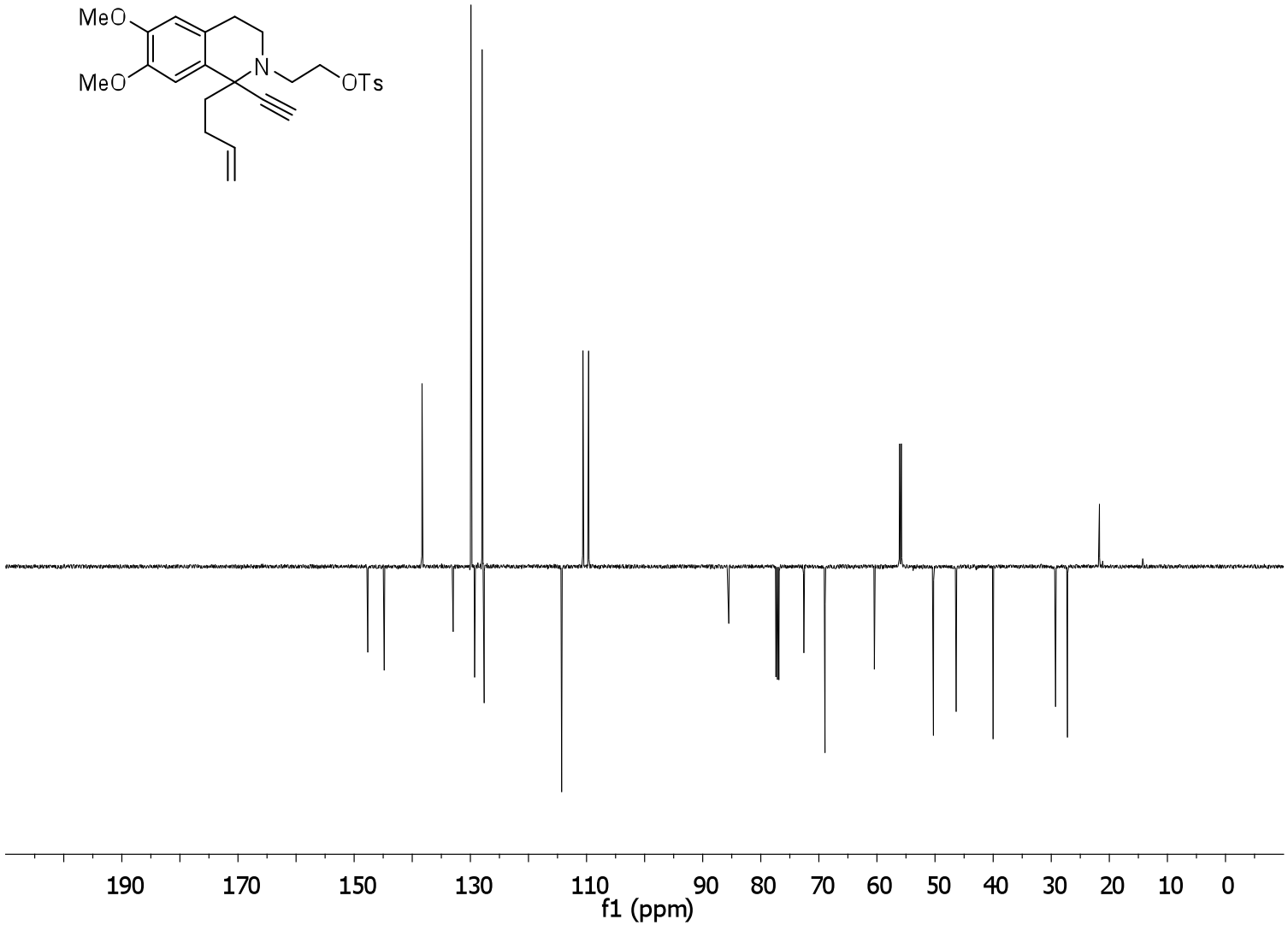
^{13}C NMR spectrum of 6c



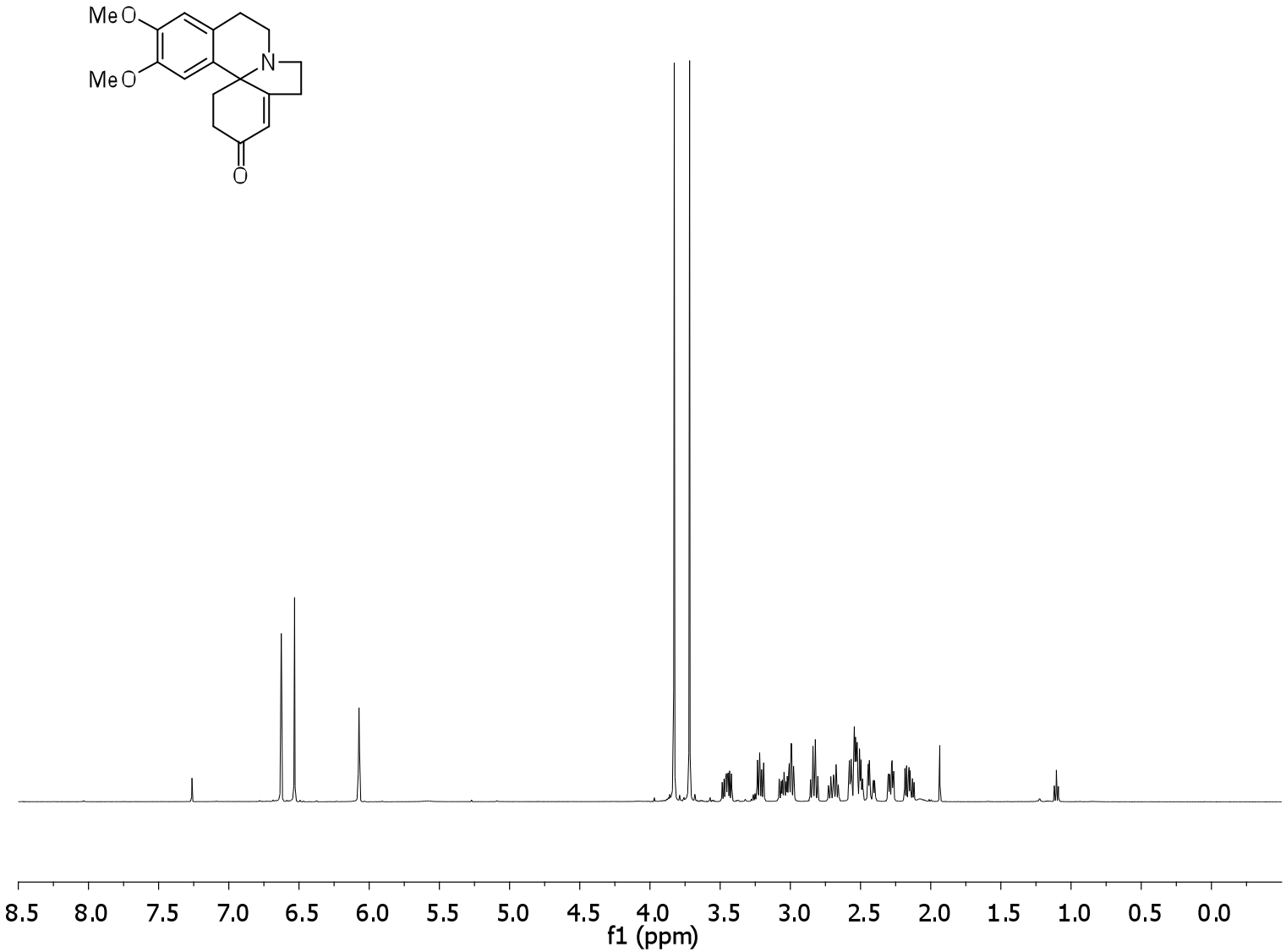
^{1}H NMR spectrum of 6d



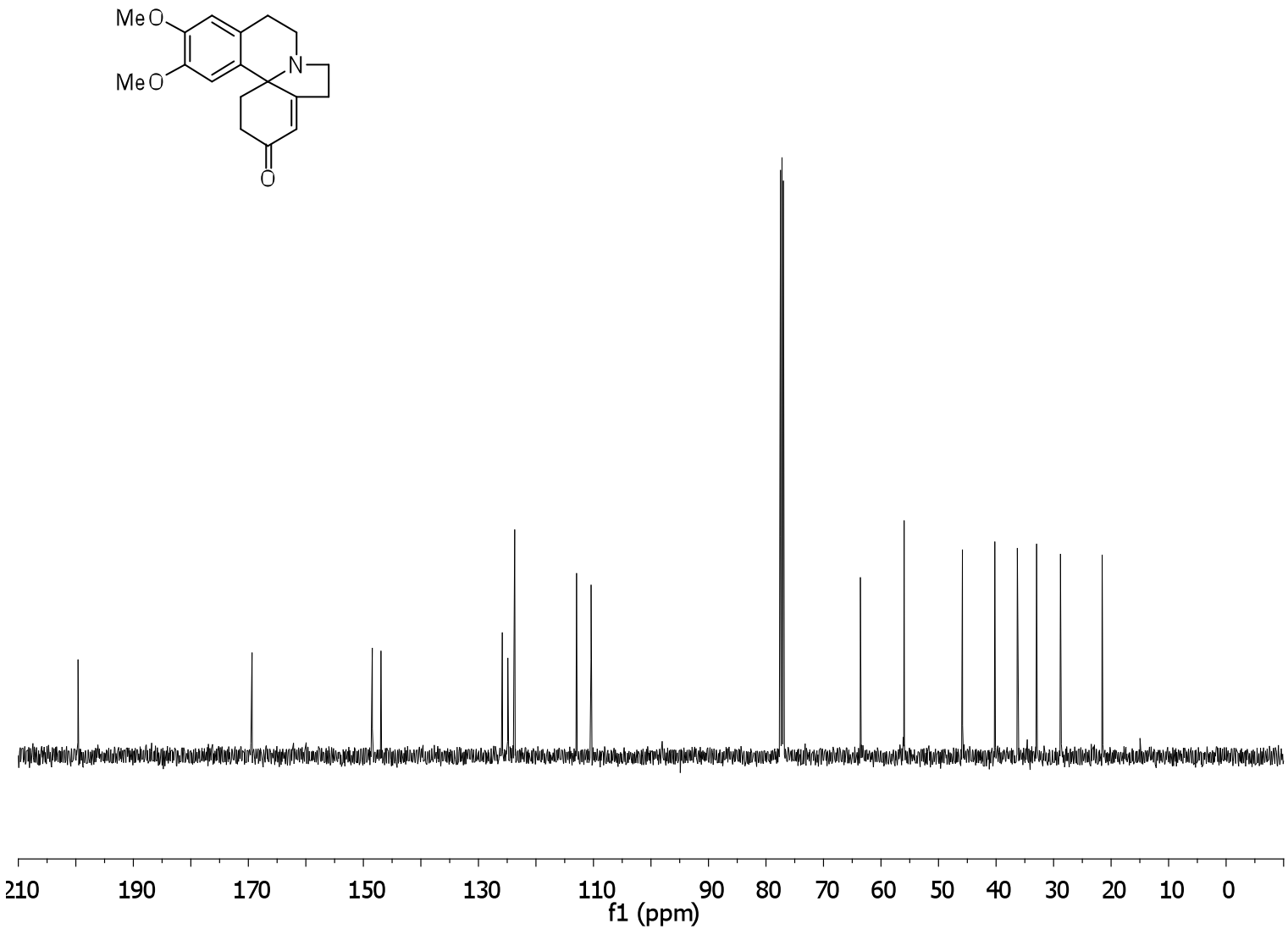
^{13}C NMR spectrum of 6d



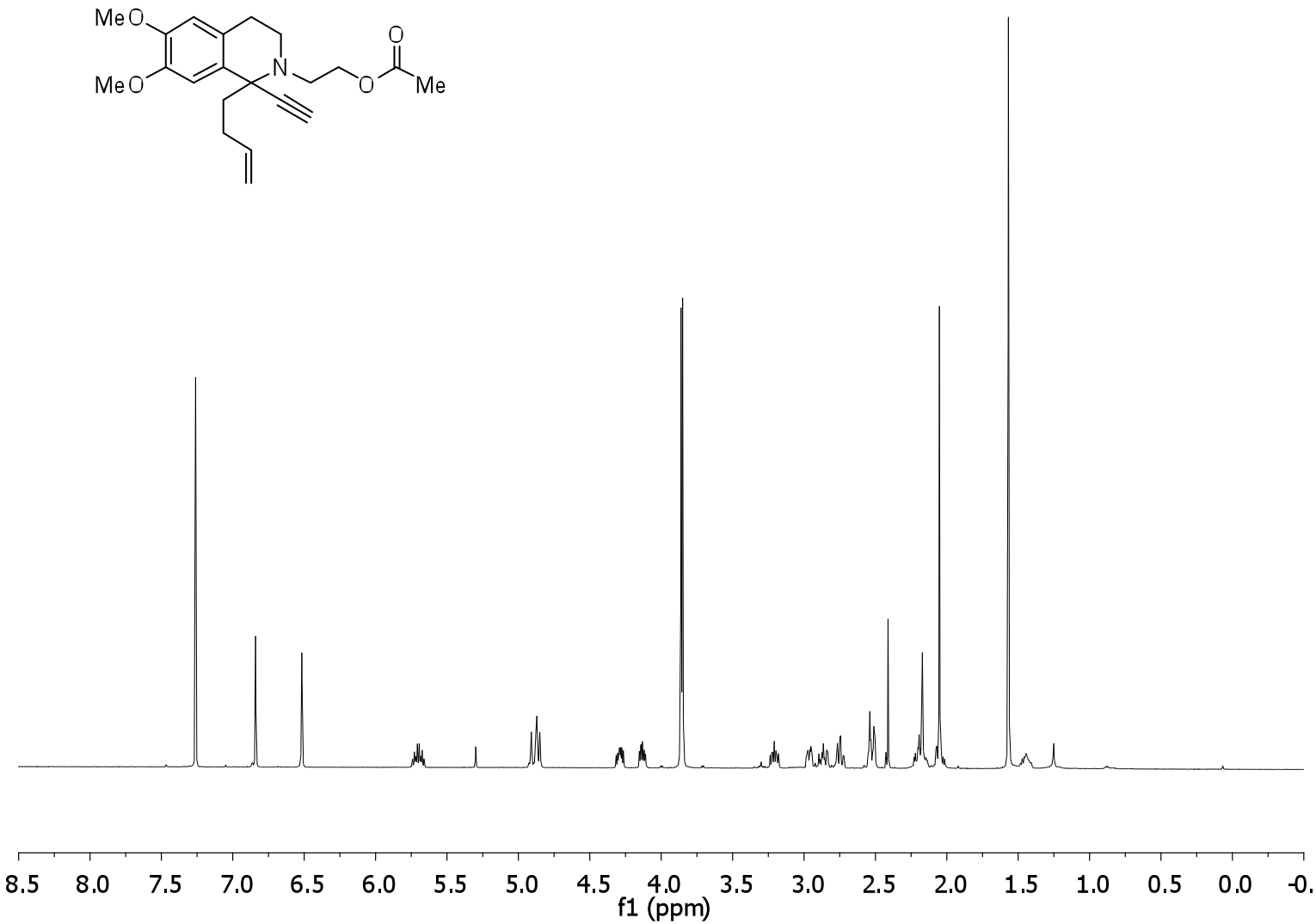
^{1}H NMR spectrum of 3



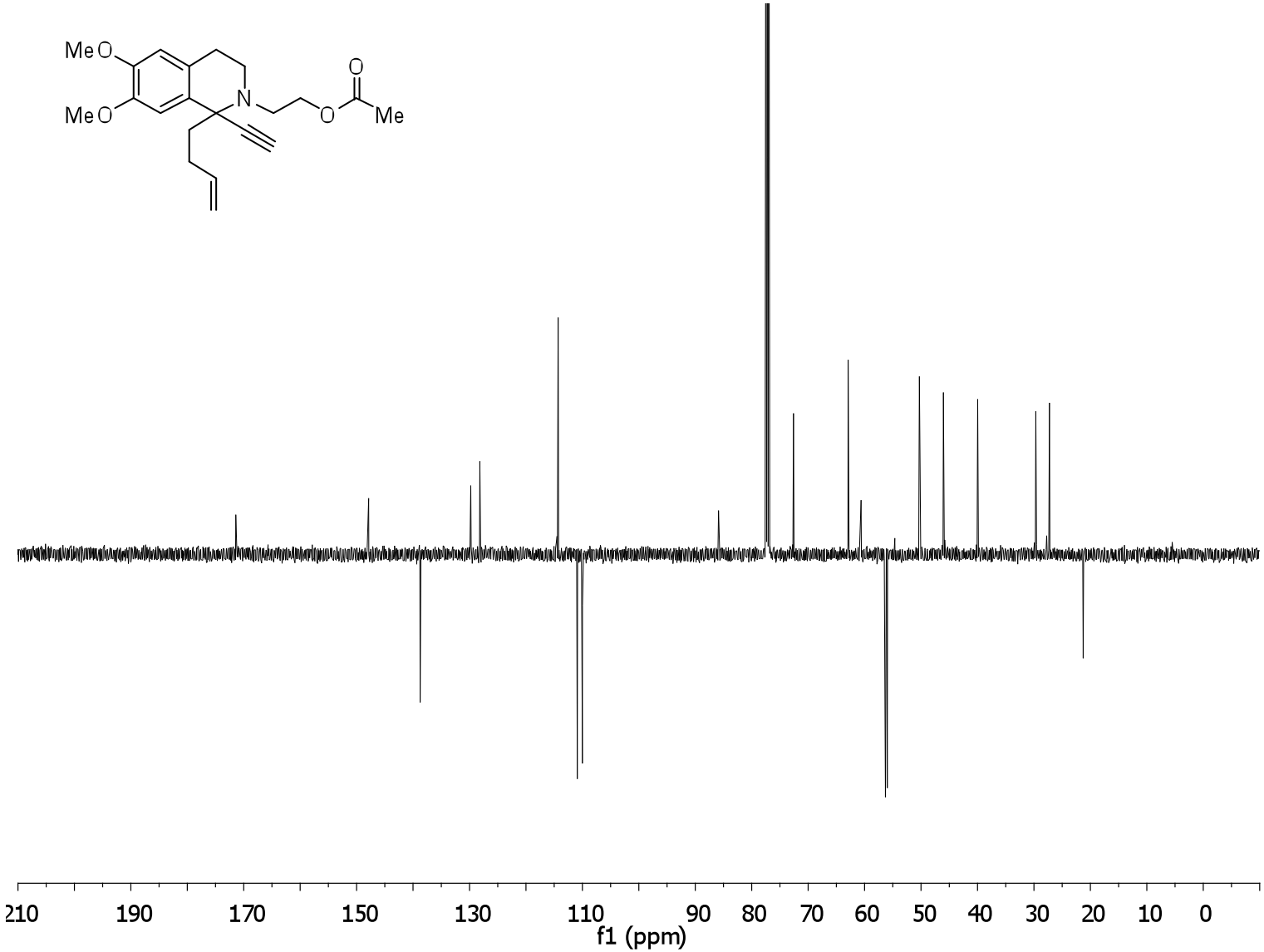
^{13}C NMR spectrum of 3



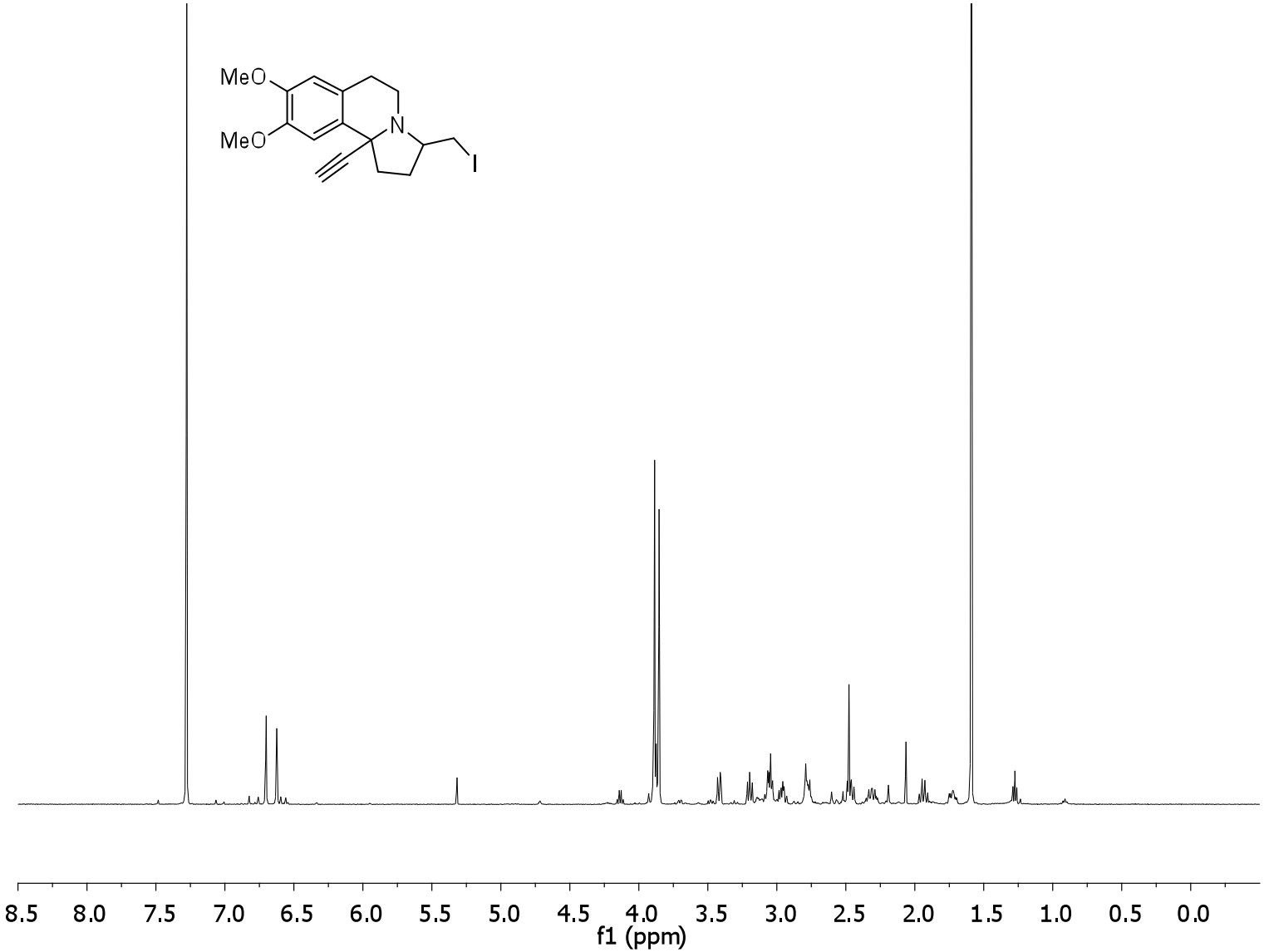
^{1}H NMR spectrum of 6e



^{13}C NMR spectrum of 6e



^{1}H NMR spectrum of S2



^{13}C NMR spectrum of S2