Electronic Supplementary Material (ESI) for Chemical Science.

Asymmetric synthesis of (-)-naltrexone

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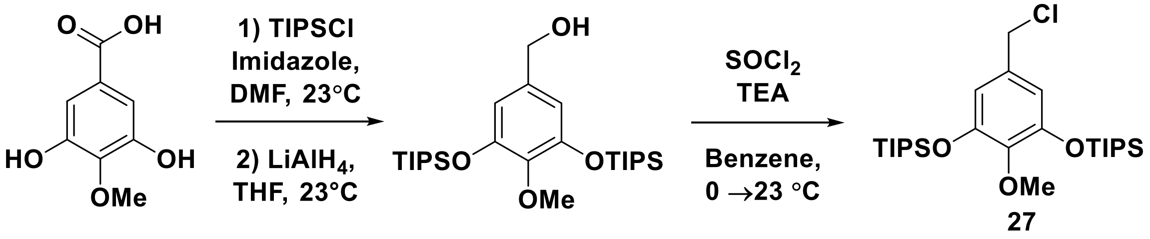
I. General procedures

General Experimental Procedures: Unless otherwise noted, all reactions were carried out under inert nitrogen atmosphere. Products and starting materials were visualized on TLC using UV light or by staining with $KMnO_4$ or *p*-anisaldehyde. Dichloromethane, tetrahydrofuran, toluene, dioxane, and dimethylformaldehyde were sparged with argon and purified by elution through a column of activated alumina under argon before use. Ethyl acetate, chloroform, and benzene were purified by elution through a column of activated alumina before use. Methanol, triethylamine, pyridine were distilled over CaH_2. Molecular sieves were dried at 200˚C overnight under vacuum. Unless otherwise noted, all reagents were purchased from commercial sources and used without further purification. Pent-4-ynal(**21**)[1] was prepared exactly according to published procedures. Flash column chromatography was performed with either silica gel (230-400 mesh), SiliaFlash® P60 (230-400 mesh) silica gel using a Biotage SP1 flash purification system (Biotage model SP1-B1A) or by reverse phase chromatography with a Teledyne Isco automated chromatography system using C18 gold columns. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on either a 400, 500, or 600 MHz instrument. Data are reported in the following format: chemical shift in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, m = multiplet, dd = doublet of doublets, etc.), coupling constant *J* in Hz, and integration. $CDCl_3$ was used as received. NMR chemical shifts are reported in ppm relative to $CDCl_3$ (7.26 ppm ^1H and 77.2 ppm ^{13}C). Partial IR spectra are reported. Melting points are reported uncorrected. High-resolution mass spectra (HRMS) were obtained using electrospray ionization (ESI) on a time of flight (TOF) mass spectrometer. Enantiomeric ratios were determined using an Agilent 1100 series HPLC equipped with Chiralcel AS-H column and a multiwavelength detector.

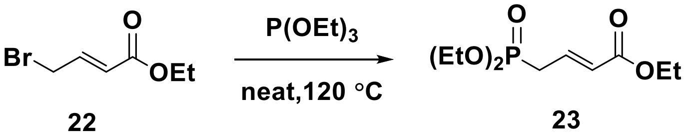
II. Experimental Procedures



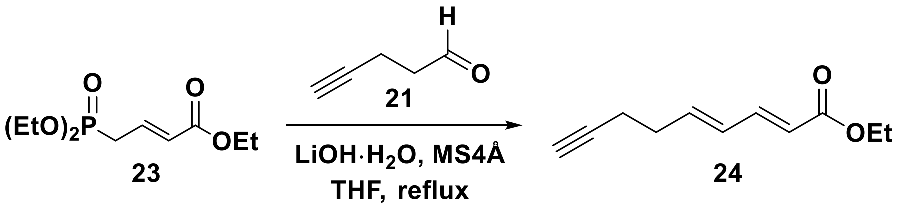
((5-(Chloromethyl)-2-methoxy-1,3-phenylene)bis(oxy))bis(*tert*-butyldimethylsilane) (27): To a 1000 mL round bottom flask equipped with a magnetic stir bar, rubber septum with a N_2 inlet and bubbler was added DMF (120 mL) to which was added 4-O-methyl-3,5-dihydroxybenzoic acid (13.5 g, 73.3 mmol, 1.00 equiv) and imidazole (17.5 g, 257 mmol, 3.50 equiv). The flask was cooled to 0 °C and TIPSCl (54.9 mL, 257 mmol, 3.50 equiv) was added in one portion. The reaction mixture was allowed to gradually warm up room temperature and was stirred for 17 h. The reaction was quenched with sat. aq. NH_4Cl (200 mL). The mixture was transferred to a separatory funnel and was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with sat. aq. NaCl (150 mL) and H_2O (150 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product gave the silylated ester (47.9 g, quantitative) as a yellow oil. The product was taken onto the next step without further purification. **IR** (neat) 2944, 2876, 1701, 1578, 1463, 1354, 1226, 1096 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 (s, 2H), 3.82 (s, 3H), 1.41 - 1.34 (m, 3H). 1.37 - 1.25 (m, 6H), 1.13-1.09 (m, 54H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 165.9, 150.1, 146.9, 126.1, 115.7, 60.4, 18.1, 18.0, 13.0, 12.3. **HRMS** (ESI): Mass calcd for $C_{35}H_{69}O_5Si_3^+$ $[M+H]^+$, 653.4447. Found $[M+H]^+$, 653.4450.

A solution of the ester (47.9 g, 73.3 mmol, 1.00 equiv) in tetrahydrofuran (500 mL) was added to a suspension of lithium aluminum hydride (8.35 g, 220 mmol, 3.00 equiv) in tetrahydrofuran (500 mL) in 2000 mL round bottom flask over 30 min via a pressure equalizing addition funnel under N_2. After completion of addition, the mixture was stirred for 18 h at room temperature. After 18 h, the flask was cooled to 0 °C and the excess amount of lithium aluminum hydride was slowly quenched with ice water added dropwise [this step is exothermic and therefore the ice water should be added slowly with caution]. Once the reaction was quenched, sat. aq. of Na_2SO_4 (50 mL) was added, and the mixture was stirred for 30 min. The mixture was filtered through a pad of celite layered with Na_2SO_4 eluting with ethyl acetate. The H_2O remaining in the filtrate was dried with Na_2SO_4 and the solution was concentrated. The crude residue was purified by silica gel chromatography (85:15 hexane:EtOAc) to provide the alcohol intermediate (30.5 g, 86%) as a yellow oil. **IR** (neat) 3342, 2843, 2892, 2866, 2376 1463, 1431, 1098 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.50 (s, 2H), 4.50 (d, *J* = 5.9 Hz, 2H), 3.76 (s, 3H), 1.32 - 1.22 (m, 6H), 1.13 - 1.09 (m, 36H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.5, 142.0, 135.9, 112.3, 65.4, 60.4, 18.1, 13.0. **HRMS**(ESI): Mass calcd for $C_{26}H_{51}O_4Si_2^+$ [M+H]$^+$, 483.3320. Found [M+H]$^+$, 483.3327.

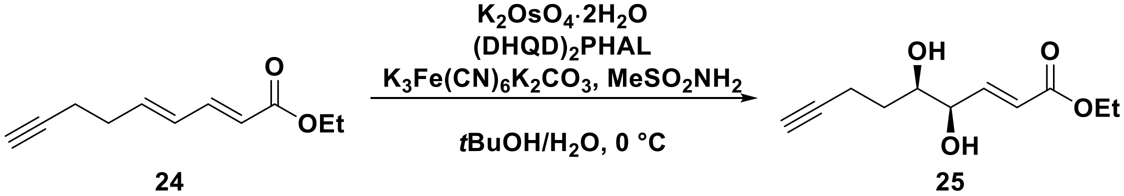
To a 500 mL round bottom flask was added benzene (160 mL) and $SOCl_2$ (4.16 mL, 57.0 mmol, 1.80 equiv), and the solution was cooled to 0 °C under N_2. To the solution was added Et_3N (6.59 mL, 47.5 mmol, 1.50 equiv) dropwise. The alcohol (15.3 g, 31.7 mmol, 1.00 equiv) dissolved in benzene (160 mL) was added dropwise over 60 min through a pressure equalizing addition funnel. After completion of addition, the reaction mixture was stirred at 0 °C for 1 h and was allowed to gradually warm to room temperature and was further stirred for 12 h. The reaction was quenched with sat. aq. $NaHCO_3$ (200 mL), and the resulting mixture was transferred to a separatory funnel and extracted with EtOAc (3 x 100 mL). The combined organic layers were then dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (98:2 hexane:EtOAc) to give benzyl chloride **27** (13.3 g, 84%) as a clear oil. **IR** (neat) 2944, 2867, 1579, 1495, 1430, 1354, 1225 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.52 (s, 2H), 4.42 (s, 2H), 3.76 (s, 3H), 1.31 - 1.20 (m, 6H), 1.13 - 1.05 (m, 36H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 150.5, 142.7, 132.2, 114.0, 60.4, 46.6, 18.1, 13.0. **HRMS** (ESI): Mass calcd for $C_{26}H_{50}ClO_3Si_2^+$ [M+H]$^+$, 501.2982. Found [M+H]$^+$, 501.2981.



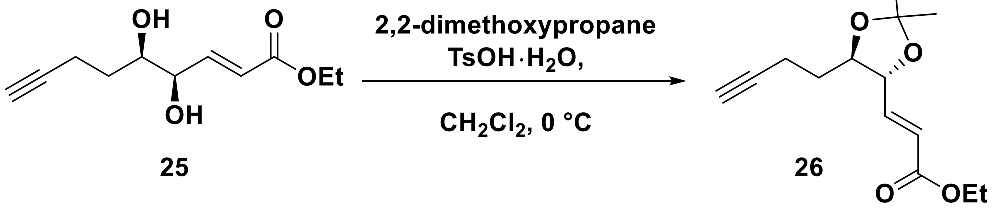
Ethyl (*E*)-4-(diethoxyphosphoryl)but-2-enoate (23): Compound **23** was prepared by modified procedure based on the literature procedure.[2] To a 100 mL round bottom flask was added triethylphosphite (33.7 g, 203 mmol, 1.00 equiv) and ethyl 4-bromocrotonate **22** (40.3 g, 209 mmol, 1.03 equiv) [ethyl 4-bromocrotonate was purified by flash chromatography (95:5 hexane:EtOAc) prior to use]. The flask was equipped with a reflux condenser under N_2 and was placed in a preheated oil bath at 120 °C, and the reaction mixture was stirred for 3.5 h. The reaction mixture was cooled down to room temperature, and the product was directly purified via flash chromatography to produce **23** (46.9 g, 92%) as a transparent oil. The characterization data matched those reported in the literature.[2] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.92 - 6.84 (m, 1H), 5.98 - 5.94 (m 1H), 4.20 (q, *J* = 7.3 Hz, 2H), 4.16 - 4.09 (m, 4H), 2.74 (dd, *J* = 22.9, 7.9, 2H), 1.34 (t, *J* = 7.3 Hz, 6H), 1.27 (t, *J* = 7.3 Hz, 3H).



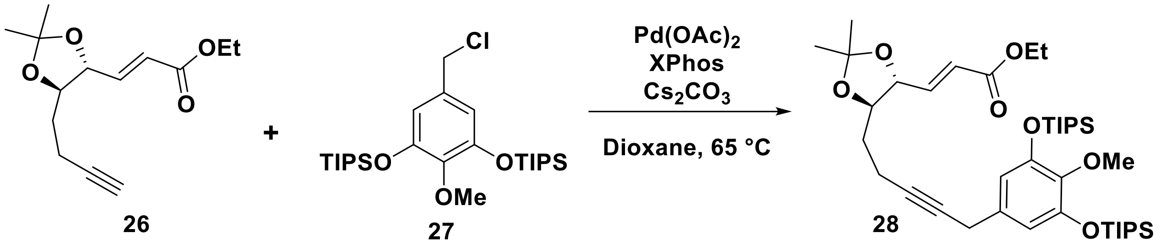
Ethyl (2*E*,4*E*)-nona-2,4-dien-8-ynoate (24): Compound **24** was prepared by modified procedure based on the literature procedure.[3] To a 2000 mL flask was added THF (700 mL), to which was added in the following order: aldehyde **21** (9.20 g, 112 mmol, 1.65 equiv), ethyl (E)-4-diethoxyphosphorylbut-2-enoate **23** (17.0 g, 67.9 mmol, 1.00 equiv), activated 4 Å molecular sieves (100 g), and LiOH·H_2O (3.13 g, 74.7mmol, 1.10 equiv). The reaction mixture was heated at reflux under an N_2 atmosphere for 14 h. The reaction mixture was cooled to room temperature, and the mixture was filtered through a pad of SiO_2, eluting with ethyl acetate. The filtrate was concentrated, and the crude product was purified by silica gel chromatography (9:1 hexane:EtOAc) to provide **24** (8.05 g, 67%) as a yellow oil. This material, which was approximately 95% pure, was taken on directly to the next step. The product matched the literature data.[1] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 15.4, 10.2 Hz, 1H), 6.27 – 6.12 (m, 2H), 5.82 (d, *J* = 15.4 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.42 – 2.31 (m, 4H), 1.98 (t, *J* = 2.6 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H).



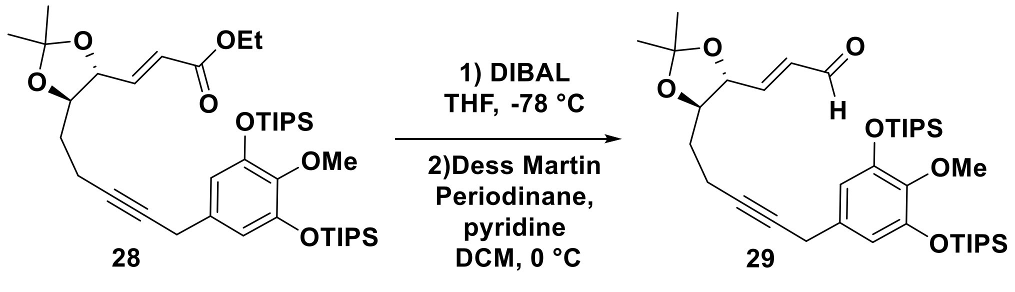
(4R,5R,E)-ethyl 4,5-dihydroxynon-2-en-8-ynoate (25): To a 3-neck 1000 mL round bottom flask was added a finely ground mixture of $K_3Fe(CN)_6$ (77.6 g, 236 mmol, 3.00 equiv), K_2CO_3 (32.6 g, 236 mmol, 3.00 equiv), and $MeSO_2NH_2$ (7.49 g, 78.6 mmol, 1.00 equiv) using a mortar and pestle. To the flask was added $K_2OsO_4 \cdot 2H_2O$ (289 mg, 0.785 mmol, 0.0100 equiv) and $(DHQD)_2PHAL$ (3.0 g, 3.86 mmol, 0.050 equiv), followed by H_2O (78 mL) and ^{t}BuOH (26 mL). A mechanical stirrer was inserted into the round bottom flask, and the mixture was stirred for 15 min. The reaction flask was then placed into a crycooler and cooled to 0 °C, at which time the dienoate **24** (14.0 g, 78.6 mmol 1.00 equiv) dissolved in ^{t}BuOH (36 mL) was added to the flask and the reaction mixture was stirred at 0 °C for 90 h. The reaction was then quenched with sat. aq. Na_2SO_3 (100 mL), and the mixture was stirred for 10 min. The solution was then poured into a separatory funnel and extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with sat. aq. NaCl and dried over Na_2SO_4. The solution was then concentrated under reduced pressure. The product was purified by silica gel chromatography (6:4 hexane:EtOAc) to give **25** (13.0 g, 78%) as a white solid. **Melting Point** 39–42 °C. **[α]$_D$** + 32.4°, ($CHCl_3$, *c* = 0.85). **IR** (neat) 3340, 3287, 2943, 2866, 1705, 1574, 1463, 1430, 1345, 1211, cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.95 (dd, *J* = 15.7, 5.1 Hz, 1H), 6.15 (d, *J* = 15.7 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.20 – 4.17 (m, 1H) 3.80 – 3.76 (m, 1H), 2.40 – 2.29 (m, 4H), 2.00 (dd, J = 2.7, 2.7 Hz, 1H), 1.78 - 1.74 (m, 2H), 1.30 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 166.2, 146.4, 123.0, 83.7, 74.1, 72.8, 69.5, 60.8, 31.7, 15.0, 14.4. Enantiomeric ratio (3:97) was measured by chiral HPLC analysis: Chiralcel AS-H, 10% IPA/Hexanes, 1.0 mL/min, t_R = 14.76 (4S,5S), t_R = 16.99 (4R,5R)]. **HRMS** (ESI): Mass calcd for $C_{11}H_{17}O_4^+$ [M+H]$^+$, 213.1121. Found [M+H]$^+$, 213.1122.



(4R,5R,E)-Ethyl 4,5-dihydroxynon-2-en-8-ynoate (26): To a 1000 mL round bottom flask under nitrogen was added the diol **25** (11.8 g, 55.5 mmol, 1.00 equiv) and CH_2Cl_2 (185 mL). The flask was cooled to 0 °C and 2, 2-dimethoxypropane (68.2 mL, 555 mmol, 10.0 equiv) was added, followed by TsOH•H_2O (1.05 g, 5.55 mmol, 0.100 equiv) in one portion. The reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (150 mL), and then the resulting mixture was transferred to a separatory funnel. The organic layer was separated and was extracted with CH_2Cl_2 (3 x 150 mL), and the combined organic layers were washed with sat. aq. NaCl (120 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated. The crude mixture was purified by silica gel chromatography (98:2 hexane:EtOAc) to give **26** (12.6 g, 90%) as a transparent oil. **[α]$_D$** +20.3°, ($CHCl_3$, *c* = 1.19). **IR** (neat) 2985, 2935, 1719, 1662, 1370, 1301, 1257, 1160 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.87 (dd, *J* = 15.6, 5.9 Hz, 1H), 6.12 (dd, *J* = 15.6, 1.1 Hz, 1H), 4.23 - 4.19 (m, 3H), 3.86 (ddd, *J* = 8.4, 8.4, 3.6 Hz, 1H), 2.43 - 2.29 (m, 2H), 1.97 (dd, *J* = 2.7, 2.7 Hz, 1H), 1.88 - 1.77 (m, 2H), 1.43 (s, 3H), 1.41 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.0, 143.7, 123.2, 109.8, 83.3, 79.9, 79.1, 69.2, 60.8, 31.0, 27.4, 26.8, 15.3, 14.4. **HRMS** (ESI): Mass calcd for $C_{14}H_{21}O_4^+$ [M+H]$^+$, 253.1434. Found [M+H]$^+$, 253.1417.

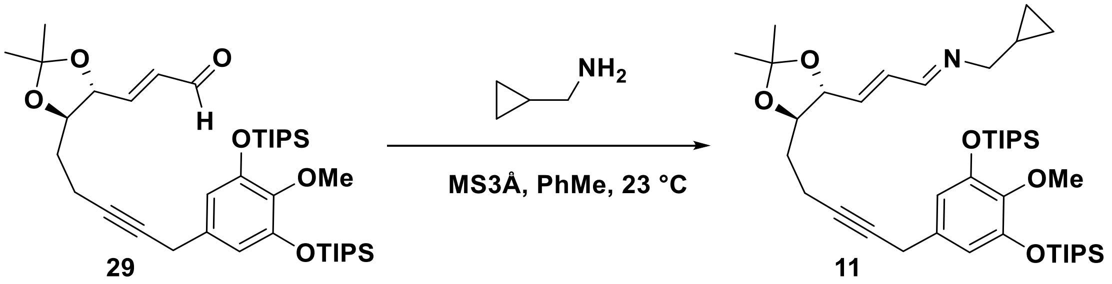


Ethyl (*E*)-3-((4*R*,5*R*)-5-(5-(4-methoxy-3,5-bis((triisopropylsilyl)oxy)phenyl)pent-3-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (19): In a glove box, to a 100 mL round bottom flask was added Pd(OAc)$_2$ (41.8 mg, 0.186 mmol, 0.05 equiv), XPhos (266 mg, 0.559 mmol, 0.150 equiv), Cs$_2$CO$_3$ (1.82 g, 5.59 mmol, 1.50 equiv)[dried at 120 °C under vacuum for 14 h prior to use] and dioxane (20 mL). To the mixture was added benzyl chloride **27** (2.43 g, 4.84 mmol, 1.30 equiv) as a solution in 10 mL of dioxane. The mixture was stirred at room temperature for 5 min. To the mixture was then added the alkyne **26** (940 mg, 3.73 mmol, 1.00 equiv) as a solution in 10 mL of dioxane. The flask was taken out of the glove box and was placed in an oil bath preheated to 65 °C, and the mixture was stirred vigorously. After 10 h, the flask was allowed to cool to room temperature, the mixture was filtered through a pad of celite, and the solvent was removed under reduced pressure. The crude mixture was purified by purified by silica gel chromatography (97:3 hexane : EtOAc) to provide **28** (2.03 g, 79%) as a yellow clear oil. **[α]$_D$** +9.2°, (CHCl$_3$, *c* = 0.39). **IR** (neat) 2944, 2867, 1724, 1432, 1224 cm^{-1}. **^{1}H NMR** (400 MHz, CDCl$_3$) δ 6.88 (dd, *J* = 15.6, 5.9 Hz, 1H), 6.49 (s, 2H), 6.13 (dd, *J* = 15.6, 1.4 Hz, 1H), 4.24 - 4.19 (m, 3H), 3.85 - 3.80 (m, 1H), 3.75 (s, 3H), 3.41 (d, *J* = 2.1, 2.1 Hz 2H), 2.48 - 2.26 (m, 2H), 1.89 - 1.78 (m, 2H), 1.44 (s, 3H), 1.42 (s, 3H), 1.32 - 1.23 (m, 9H), 1.12 - 1.10 (m, 36H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 166.0, 150.2, 143.8, 140.9, 131.9, 123.2, 113.2, 109.8, 81.4, 80.1, 79.6, 78.6, 60.8, 60.4, 31.9, 27.4, 26.9, 24.8, 18.1, 15.8, 14.4, 12.9. **HRMS** (ESI): Mass calcd for $C_{40}H_{69}O_7Si_2^+$ $[M+H]^+$, 717.4576. Found $[M+H]^+$, 717.4575.



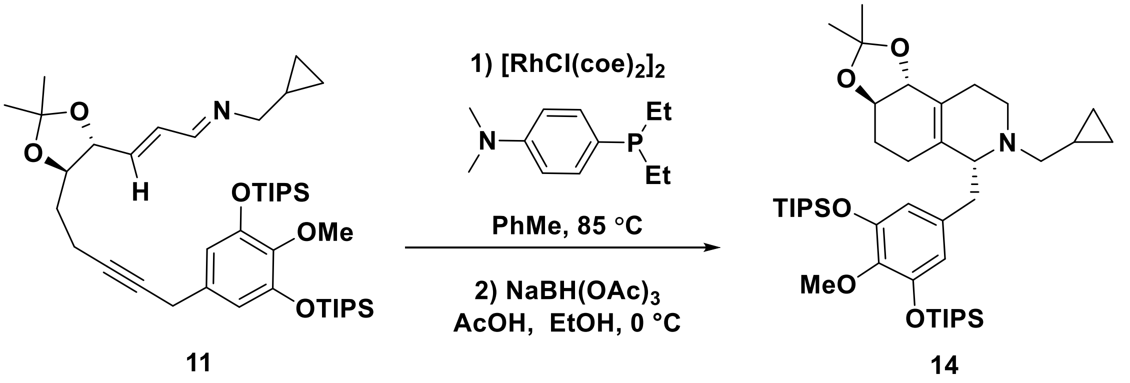
***E*)-3-((4*R*,5*R*)-5-(5-(4-Methoxy-3,5-bis((triisopropylsilyl)oxy)phenyl)pent-3-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylaldehyde (29):** To a 100 mL round bottom flask equipped with a stir bar was added ester **28** (1.83 g, 2.55 mmol, 1.00 equiv) in THF (25 mL). The flask was cooled to -78 °C over 30 min. To the reaction mixture was then added DIBAL (1M in hexane, 10.2 mL, 10.2 mmol, 4.00 equiv) via syringe pump over 4 h. The reaction was quenched with MeOH (5 mL) via syringe pump over 30 min [quenching is highly exothermic and a low temperature must be maintained by slow addition of MeOH in order to obtain a high yield]. Once the reaction had been quenched, sat. aq. Rochelle salt (20 mL) was added in one portion, and the reaction flask was gradually allowed to warm to room temperature with vigorous stirring over 14 h. The reaction mixture was transferred to a separatory funnel, the organic layer was separated, and the aqueous layer was then extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with sat. aq. NaCl and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography (8:2 hexane : EtOAc) to provide the allylic alcohol (1.53 g, 89%) as a light yellow oil. **$[\alpha]_D$** +6.1°, ($CHCl_3$, *c* = 0.92). **IR**(neat) 3418, 2943, 2867, 1578, 1494, 1437, 1369, 1223 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.48 (s, 2H), 6.00 – 5.95 (m, 1H), 5.73 -5.68 (m, 1H), 4.19 - 4.15 (m, 2H), 4.05 (t, *J* = 7.8 Hz, 1H), 3.77 - 3.73 (m, 1H), 3.74 (s, 3H), 3.40 - 3.39 (m, 2H), 2.45 - 2.25 (m, 2H), 1.81 - 1.74 (m, 2H), 1.41 (s, 6H), 1.30 - 1.23 (m, 6H), 1.11 - 1.09 (m, 36H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 150.2, 140.9, 134.6, 132.0, 127.8, 113.1, 108.9, 81.7, 81.5, 79.7, 78.3, 62.9, 60.4, 31.7, 27.4, 27.2, 24.8, 18.1, 15.9, 12.9. **HRMS** (ESI): Mass calcd for $C_{38}H_{67}O_6Si_2^+$ [M+H]$^+$, 697.4290. Found [M+H]$^+$, 675.4294.

To a 250 mL round bottom flask containing the allylic alcohol (3.91 g, 6.62 mmol, 1.00 equiv) in CH_2Cl_2 (45 mL), and the flask was cooled to 0 °C under N_2. To the reaction mixture was added pyridine (3.20 mL, 39.7 mmol, 6.00 equiv) and Dess-Martin periodinane (4.91 g, 11.6 mmol, 1.75 equiv) sequentially. The reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with a 1:1 solution of sat. aq. $NaHCO_3$ / sat. aq. $Na_2S_2O_3$ (20 mL), and the resulting mixture was stirred for 5 min. The mixture was transferred to a separatory funnel, the organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with sat. aq. NaCl (50 mL) and dried over Na_2SO_4 . The crude material was purified by silica gel chromatography (9:1 hexane:EtOAc) to provide **29** (3.00 g, 77%) as a yellow oil. **$[\alpha]_D$** +13.4°, ($CHCl_3$, *c* = 0.50). **IR** (neat) 2943, 2866, 1697, 1494, 1432, 1350, 1224 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.59 (d, *J* = 7.7 Hz, 1H), 6.75 (dd, *J* = 15.7, 5.5 Hz, 1H), 6.48 (s, 2H), 6.38 (dd, *J* = 15.7, 7.7 Hz, 1H), 4.35 - 4.32 (m, 1H), 3.90 - 3.85 (m, 1H), 3.74 (s, 3H), 3.41 - 3.37 (m, 2H), 2.47 - 2.30 (m, 2H), 1.87 - 1.83 (m, 2H), 1.45 (s, 3H), 1.42 (s, 3H), 1.30 - 1.22 (m, 6H), 1.14 - 1.03 (m, 36H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 193.0, 152.1, 150.2, 141.0, 133.0, 131.9, 113.1, 110.1, 81.1, 79.9, 79.5, 78.9, 60.4, 31.9, 27.4, 26.8, 24.8, 18.1, 15.7, 12.9. **HRMS** (ESI): Mass calcd for $C_{38}H_{65}O_6Si_2^+$ [M+H]$^+$, 697.4290. Found [M+H]$^+$, 675.4294.



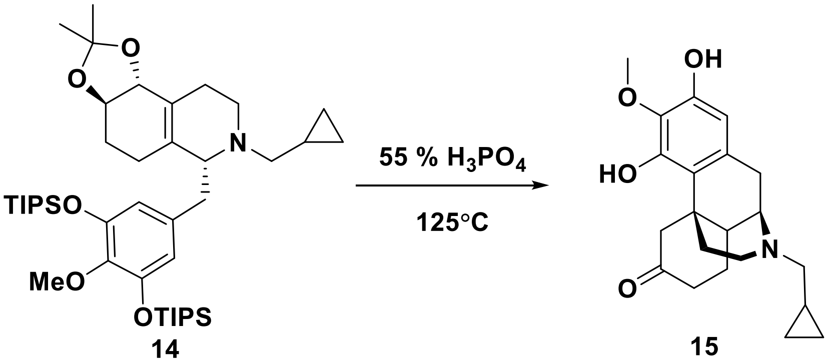
29 → 11

(1*E*,2*E*)-*N*-(Cyclopropylmethyl)-3-((4*R*,5*R*)-5-(5-(4-methoxy-3,5-bis((triisopropylsilyl)oxy)phenyl)pent-3-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-imine (11): In a glove box, to a 250 mL round bottom flask containing the aldehyde **29** (3.47 g, 5.16 mmol, 1.00 equiv) was added toluene (51 mL) and MS3**Å** (12 g) and cyclopropylmethylamine (0.537 mL, 6.19 mmol, 1.20 equiv). The reaction mixture was stirred at room temperature for 1 h in the glovebox. The mixture was then filtered through a pad of celite with toluene and concentrated while stirring in the glovebox. The removal of the solvent and excess of cyclopropylmethylamine provided the crude imine **11** as a yellow oil. The compound was used without further purification (5.16 mmol, assuming 100% theoretical yield). Analytical data for **11**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 9.1 Hz, 1H), 6.50 (dd, *J* =15.3, 9.1 Hz, 1H), 6.48 (s, 2H), 6.10 (dd, *J* =15.3, 6.9 Hz, 1H), 4.20 - 4.17 (m, 1H), 3.83 - 3.80 (m, 1H), 3.74 (s, 3H), 3.41 - 3.38 (m, 2H), 3.33 – 3.32 (m, 2H), 2.46 - 2.27 (m, 2H), 1.84 - 1.76 (m, 2H), 1.425 (s, 3H), 1.416 (s, 3H), 1.30 - 1.23 (m, 6H), 1.10 - 1.09 (m, 36H), 1.05 - 1.03 (m, 1H), 0.54 - 0.52 (m, 2H), 0.21 - 0.20 (m, 2H).

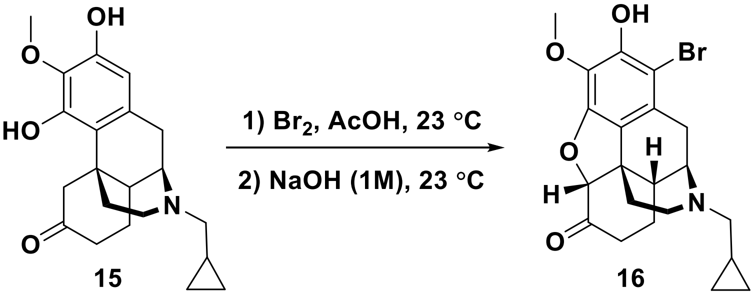


11 → 14

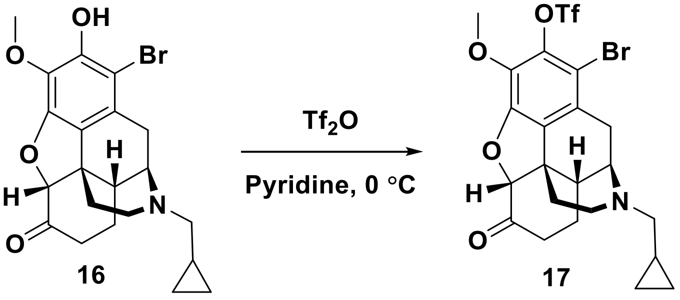
(3a*R*,6*R*,9b*R*)-7-(Cyclopropylmethyl)-6-(4-methoxy-3,5-bis((triisopropylsilyl)oxy)benzyl)-2,2-dimethyl-3a,4,5,6,7,8,9,9b-octahydro-[1,3]dioxolo[4,5-*f*]isoquinoline (14): In a glove box, to a 250 mL round bottom flask containing the imine **11** (5.16 mmol assuming 100% theoretical yield, 1.00 equiv) was added toluene (50 mL), $[RhCl(coe)_2]_2$ (185 mg, 0.258 mmol, 0.0500 equiv) and 4-(diethylphosphino)-*N*,*N*-dimethylaniline (108 mg, 0.516 mmol, 0.100 equiv) in sequential order. After ensuring the reaction contents were fully dissolved, 500 µL of the reaction mixture was transferred to a JYoung NMR tube [The JYoung tube was equipped with an internal standard tetrafluorobenzaldehyde dissolved in *d*-toluene in a capillary tube to monitor the progress of the reaction]. The flask was sealed with a rubber septum and parafilmed and both the flask and the JYoung tube were taken out of the glove box, and the reaction mixture was heated at 85 °C for 90 min after which the reaction was determined to be complete by NMR analysis. The flask and the JYoung tube were cooled to room temperature and the contents were transferred with toluene (50 mL) to a stirred solution of $NaHB(OAc)_3$ (5.46 g, 25.8 mmol, 5.00 equiv) in EtOH (50 mL) precooled to 0 °C. After transferring the mixture, to the solution was added AcOH (13.5 mL). The reaction mixture was stirred for 2 h maintained at 0 °C. The reaction was slowly quenched with sat. aq. $NaHCO_3$ (200 mL) to ensure that the aqueous layer was pH 8. The aq. layer was then extracted with EtOAc (3 x 60 mL). The combined organic layers were then washed with sat. aq. NaCl (100 mL) and dried over Na_2SO_4. The material was then filtered and concentrated under reduced pressure. The mixture was purified by silica gel chromatography (95:5:0.5 CH_2Cl_2:MeOH:NH_4OH) to provide **14** (2.50 g, 67%) as an orange oil. **[α]D** +25.4°, ($CHCl_3$, *c* = 0.80). **IR** (neat) 2943, 2867, 1590, 1429, 1225 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.37 (s, 2H), 3.99 (d, *J* = 8.1 Hz, 1H), 3.74 (s, 3H), 3.58 - 3.54 (m, 1H), 3.19-3.16 (m, 1H), 3.04 - 2.92 (m, 2H), 2.76 (dd, *J* = 13.9, 6.0 Hz, 1H), 2.53 - 2.48 (m, 2H), 2.30 - 2.20 (m, 2H), 2.07 - 1.99 (m, 3H), 1.94 -1.86 (m, 1H), 1.74 - 1.67 (m, 1H), 1.45 (s, 6H), 1.30 - 1.22 (m, 6H), 1.11 - 1.09 (m, 36H), 0.80 - 0.72 (m, 1H), 0.51 - 0.41 (m, 2H), 0.08 - -0.01 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.0, 140.6, 135.9, 132.0, 126.7, 114.4, 110.9, 80.0, 78.3, 63.0, 60.4, 59.0, 42.3, 37.8, 29.8, 27.2, 24.6, 21.8, 18.1, 13.0, 9.8, 4.7, 3.3. **HRMS** (ESI): Mass calcd for $C_{42}H_{74}NO_5Si_2^+$ $[M+H]^+$,728.5106. Found $[M+H]^+$, 728.5106.



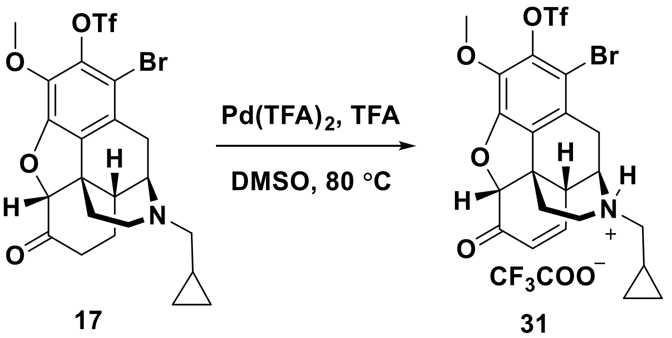
(4b*S*,9*R*)-11-(Cyclopropylmethyl)-2,4-dihydroxy-3-methoxy-8,8a,9,10-tetrahydro-5*H*-9,4b-(epiminoethano)phenanthren-6(7*H*)-one (15): In a glovebox, to a 75 mL pressure tube vial containing the tetrahydropyridine **14** (1.59 g, 2.18 mmol, 1.00 equiv) equipped with a stir bar was added a mixture of H_3PO_4 (85 % in H_2O, 14.4 mL) and HPLC grade H_2O (7.6 mL) [both sparged with N_2 for 30 min prior to use]. The tube was taken out of the glovebox and the reaction mixture was heated at 125 °C with vigorous stirring over 5 h. The reaction mixture was cooled to room temperature, transferred to a separatory funnel with H_2O (20 mL), and the aqueous layer was washed with $CHCl_3$ (3 x 50 mL) to discard the silyl byproducts dissolved in the organic layer. To the remaining aqueous layer was added ice and NH_4OH was slowly added dropwise until the pH was confirmed to be pH 8 [because the reaction is exothermic, the NH_4OH should be added slowly with caution]. A solvent mixture of 5% MeOH in $CHCl_3$ was used to extract out the phenol (6 x 50 mL). The combined organic layer was concentrated under reduced pressure. The crude product was purified by silica gel chromatography (90:10:1 CH_2Cl_2:MeOH:NH_4OH) to provide **15** (517 mg, 66%) as a tan colored solid. **Melting Point** 145 - 148 °C. **[α]$_D$** +84.6°, ($CHCl_3$, *c* = 0.73). **IR** (neat) 3520, 3296, 2923, 2870, 1707, 1603, 1504, 1429, 1364, 1216 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.24 (s, 1H), 4.12 (dd, *J* = 13.5, 1.8 Hz, 1H), 3.80 (s, 3H), 3.40 - 3.36 (m, 1H), 2.87 - 2.77 (m, 2H), 2.74 - 2.63 (m, 1H), 2.61 - 2.53 (m, 1H), 2.48 - 2.30 (m, 3H), 2.29 - 2.22 (m, 2H), 2.14 - 2.07 (m, 1H), 1.94 - 1.80 (m, 3H), 1.71 - 1.62 (m, 1H), 1.03 - 0.92 (m, 1H), 0.61 - 0.56 (m, 2H), 0.22 – 0.15 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 211.4, 148.6, 147.1, 133.7, 115.6, 107.1, 61.4, 59.7, 55.1, 50.6, 45.2, 44.2, 41.4, 41.2, 38.1, 27.3, 24.9, 8.8, 4.4, 4.1 (two aromatic Cs overlapped). **HRMS** (ESI): Mass calcd for $C_{21}H_{28}NO_4^+$ [M+H]$^+$, 358.2013. Found [M+H]$^+$, 358.2016.



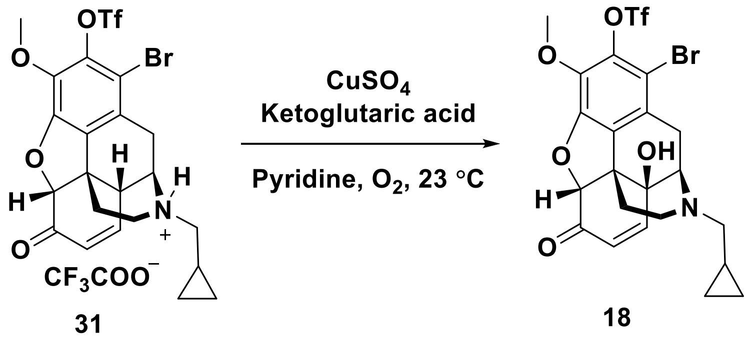
(4*R*,4a*R*,7a*R*,12b*S*)-11-Bromo-3-(cyclopropylmethyl)-10-hydroxy-9-methoxy-2,3,4,4a,5,6-hexahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7(7a*H*)-one (16): To a 50 mL round bottom flask was added the phenol **15** (197 mg, 0.551 mmol, 1.00 equiv) and acetic acid (5.5 mL). The flask was equipped with a pressure equalizing addition funnel under N_2. To the funnel was added a stock solution of Br_2 (0.057 mL, 1.10 mmol, 2.00 equiv) dissolved in acetic acid (3.7 mL) and the solution was added dropwise over 50 min. The reaction mixture was further stirred for 30 min, and then the reaction mixture was transferred dropwise to a stirred solution containing aq. NaOH (100 mL, 1M) at 0 °C and the solution was confirmed to be basified to pH 12. The reaction mixture was stirred for 10 min before adding HCl (1M) until acidified to pH 7. The solution was transferred to a separatory funnel and extracted with 5% MeOH in $CHCl_3$ (6 x 50 mL). The combined organic layers were concentrated under reduced pressure. The crude product was purified by silica gel chromatography (93:7:0.5 CH_2Cl_2:MeOH:NH_4OH) to give **16** (153 mg, 63%) as a white solid. **Melting Point** 144 - 146 °C. **[α]$_D$** -123.0, ($CHCl_3$, c = 0.33). **IR** (neat) 2925, 2830, 1725, 1608, 1463, 1426, 1218 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.65 (s, 1H), 4.12 (s, 3H), 3.53 - 3.50 (m, 1H), 2.82 (d, *J* = 7.6 Hz, 1H), 2.78 (d, *J* = 18.9 Hz, 1H), 2.60 - 2.58 (m, 1H), 2.51 - 2.48 (m, 1H), 2.42 - 2.33 (m, 3H), 2.17 - 2.13 (m, 1H), 2.08 - 2.06 (m, 2H), 1.85 - 1.82 (m, 1H), 1.75 - 1.74 (m, 1H), 1.24 - 1.18 (m, 1H), 0.90 - 0.84 (m, 1H), 0.54 - 0.53 (m, 2H), 0.17 - 0.14 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 207.5, 145.4, 145.3, 131.2, 127.1, 119.8, 100.1, 92.1, 60.5, 59.7, 56.7, 47.2, 44.9, 42.3, 40.2, 35.4, 25.6, 22.2, 9.3, 4.0, 3.7. **HRMS** (ESI): Mass calcd for $C_{21}H_{25}BrNO_4^+$ $[M+H]^+$, 434.0961. Found $[M+H]^+$, 434.0986.



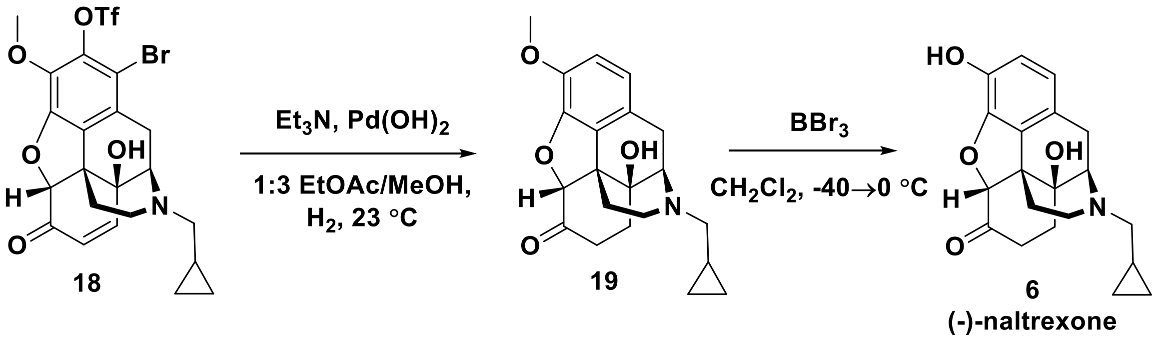
(4*R*,4a*R*,7a*R*,12b*S*)-11-Bromo-3-(cyclopropylmethyl)-9-methoxy-7-oxo-2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-10-yl trifluoromethanesulfonate (17): To a 100 mL round bottom flask was added the phenol **16** (140 mg, 0.322 mmol, 1.00 equiv) and freshly distilled pyridine (4 mL) under N_2, and the flask was then cooled to 0 °C. Triflic anhydride (0.179 mL, 1.06 mmol, 3.30 equiv) was added via syringe dropwise, and the resulting mixture was stirred for 2 h at 0 °C. Upon completion, the reaction was quenched with H_2O, which was added dropwise (10 mL). The resulting mixture was stirred for 10 min before being transferred to a separatory funnel. The product was extracted from the aqueous layer with $CHCl_3$ (4 x 15 mL). The combined organic layers were washed with sat. aq. NaCl and dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude mixture was purified by silica gel chromatography (95:5:0.5 CH_2Cl_2:MeOH:NH_4OH) to afford **17** (144 mg, 92%) as a yellow foamy solid. **Melting Point** 50 - 52 °C. **[α]$_D$** -102.8°, ($CHCl_3$, *c* = 0.36). **IR** (neat) 2921, 1729, 1601, 1471, 1420, 1344, 1202, 1131 cm^{-1} . **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.71 (s, 1H), 4.15 (s, 3H), 3.53 (dd, *J* = 5.7, 2.4 Hz, 1H), 2.85 - 2.82 (m, 2H), 2.63 - 2.59 (m, 1H), 2.49 - 2.43 (m, 2H), 2.40 - 2.32 (m, 2H), 2.15 (dd, *J* = 18.8, 5.7 Hz, 1H), 2.12 - 2.01 (m, 2H), 1.90 - 1.86 (m, 1H), 1.81 - 1.78 (m, 1H), 1.22 - 1.15 (qd, *J* = 13.5, 3.2 Hz, 1H), 0.87 - 0.82 (m, 1H), 0.55 - 0.53 (m, 2H), 0.17 - 0.13 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 206.6, 146.4, 139.0, 137.2, 128.8, 127.6, 118.6 (q, *J* = 329 Hz), 107.9, 92.3, 60.6, 59.9, 56.7, 47.8, 44.8, 42.3, 40.2, 35.5, 25.7, 22.7, 9.6, 4.2, 3.9. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -72.7. **HRMS** (ESI): Mass calcd for $C_{22}H_{24}BrF_3NO_6S^+$ $[M+H]^+$, 566.0454. Found $[M+H]^+$, 566.0470.



(4*R*,4a*R*,7a*R*,12b*S*)-11-Bromo-3-(cyclopropylmethyl)-9-methoxy-7-oxo-2,3,4,4a,7,7a-hexahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-10-yl trifluoromethanesulfonate, 2,2,2-trifluoroacetate salt (**31**)**:** To a 10 mL conical shaped vial was added **17** (57.1 mg, 0.101 mmol, 1.00 equiv), and to the flask was added acetonitrile (1 mL) and trifluoroacetic acid (0.150 mL, 2.02 mmol, 20.0 equiv) dropwise. The solution was evaporated to dryness. Once dried, a stock solution containing DMSO (0.5 mL) with Pd(TFA)$_2$ (46.9 mg, 0.141 mmol, 1.40 equiv) fully dissolved was added to the flask. The reaction flask was capped with a rubber septum under an air atmosphere. The flask was heated to 80 °C for 5.5 h. The reaction flask was cooled to room temperature and the crude material was directly transferred to a precolumn of the C-18 reverse phase. The mixture was purified using a C18-reverse phase column, with a gradient of 0 to 50% acetonitrile buffered with 0.1% of TFA in H_2O buffered with 0.1% of TFA. The fractions containing the desired product were collected and concentrated under reduced pressure to give **31** (54.8 mg, 82%) as a foamy yellow solid. **Melting Point** 64 - 66 °C. **[α]$_D$** -141.5°, ($CHCl_3$, *c* = 0.20). **IR** (neat) 2962, 1671, 1419, 1198 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.63 (d, *J* = 10.1 Hz, 1H), 6.22 (dd, *J* = 10.1, 2.0 Hz, 1H), 4.92 (s, 1H), 4.65 - 4.60 (m, 1H), 4.11 (s, 3H), 4.00 - 3.96 (bs, 1H), 3.75 - 3.69 (m, 1H), 3.18 - 3.15 (m, 1H), 3.05 – 3.02 (m, 2H), 2.76 - 2.63 (m, 3H), 2.10 - 2.08 (m, 1H), 1.20 - 1.13 (m, 1H), 0.86 - 0.84 (m, 2H), 0.49 - 0.47 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 191.3, 145.8, 144.4, 139.6, 138.3, 134.1, 128.7, 122.5, 118.6 (q, *J* = 322.3 Hz), 108.9, 87.7, 60.8, 59.4, 56.7, 46.1, 42.6, 37.8, 31.3, 23.7, 5.8, 5.0, 4.9. **^{19}F NMR** (471 MHz, $CDCl_3$) δ -72.7, -75.7. **HRMS** (ESI): Mass calcd for $C_{22}H_{22}BrF_3NO_6S^+$ [M+H]$^+$, 564.0298. Found [M+H]$^+$, 564.0296.



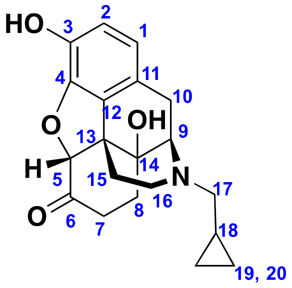
(4*R*,4a*S*,7a*R*,12b*S*)-11-Bromo-3-(cyclopropylmethyl)-4a-hydroxy-9-methoxy-7-oxo-2,3,4,4a,7,7a-hexahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-10-yl trifluoromethanesulfonate (18): To a 50 mL round bottom flask equipped with a stir bar was added the enone **31** (31.0 mg, 0.0458 mmol, 1.00 equiv), pyridine (6.9 mL), and a potassium phosphate buffer solution (6.9 mL, 50.0 mM, pH 7.0) [both solvents were sparged with O_2 for 20 min prior to addition]. Next, a freshly made solution of ketoglutaric acid (1.37 mL of a 0.150 M solution in H_2O, 0.206 mmol, 4.50 equiv) and a freshly made solution of $CuSO_4$ (0.18 mL of a 5.0 mM solution in H_2O, 0.0092 mmol, 0.020 equiv) were added to the reaction mixture. The flask was purged with O_2 before being sealed under a balloon of O_2. The reaction mixture was vigorously stirred at room temperature over 48 h before being transferred to a separatory funnel, diluted with H_2O (15 mL), and extracted with chloroform (5 x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (99:1:0.1 CH_2Cl_2:MeOH:NH_4OH) to provide **18** (14.9 mg, 56%) as a tan foamy solid. **Melting Point** 68 - 70 °C. **[α]$_D$** -207.0° ($CHCl_3$, *c* = 0.10). **IR** (neat) 3420, 1686, 1472, 1423, 1344, 1204, 1132 cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.66 (d, *J* = 10.1 Hz, 1H), 6.23 (d, *J* = 10.1 Hz, 1H), 4.78 (s, 1H), 4.05 (s, 3H), 3.44 (d, *J* = 5.8 Hz, 1H), 3.04 (d, *J* = 18.8 Hz, 1H), 2.81 (dd, *J* = 12.4, 5.8 Hz, 1H), 2.50 - 2.41 (m, 2H), 2.47 (d, *J* = 7.1 Hz, 2H) 2.21 (dd, *J* = 12.4, 3.7 Hz, 1H), 1.74 - 1.71 (m, 1H), 0.92 - 0.86 (m, 1H), 0.62 - 0.60 (m, 2H), 0.20 - 0.19 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 192.8, 147.5, 145.2, 138.9, 136.9, 134.9, 131.4, 125.9, 118.5 (q, *J* = 320.3 Hz), 107.7, 87.8, 67.1, 61.1, 60.4, 59.0, 47.2, 43.1, 29.5, 25.1, 9.2, 4.1, 3.9. **^{19}F NMR** (471 MHz, $CDCl_3$) δ -72.7. **HRMS** (ESI) Mass calcd for $C_{22}H_{22}BrF_3NO_7S^+$ [M+H]$^+$, 580.0247. Found [M+H]$^+$, 580.0248.



(-)-Naltrexone (6):[4,5] To a 10 mL pear shaped flask equipped with a stir bar was added **18** (21.0 mg, 0.0362 mmol, 1.00 equiv) and 20 wt.% $Pd(OH)_2/C$ (4.2 mg). The flask was capped with a rubber septum and EtOAc (0.4 mL) and MeOH (1.2 mL) were added under N_2. Freshly distilled Et_3N (0.0504 mL, 0.362 mmol, 10.0 equiv) was added to the flask and the headspace was purged with N_2. The N_2 needle was subsequently replaced with a H_2 balloon, and the headspace was purged with H_2. The reaction mixture was stirred vigorously at room temperature for 2 h. After 2 h, the H_2 balloon was disconnected and the headspace was purged with N_2. The reaction mixture was filtered through a pad of celite, and the filtrate was transferred to a separatory funnel. To a separatory funnel was added H_2O (15 mL) and the solution was made basic to pH 8 with NH_4OH. The aqueous layer was extracted with 5% MeOH in $CHCl_3$ (4 x 15 mL). The organic layers were collected and dried with Na_2SO_4. The compound was concentrated *in vacuo* overnight and used for the next step without further purification. Analytical data for **19**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.70 (d, *J* = 8.2 Hz, 1H), 6.62 (d, *J* = 8.2 Hz, 1H), 4.68 (s, 1H), 3.89 (s, 3H), 3.26 - 3.19 (m, 1H), 3.09 - 2.99 (m, 2H), 2.73 (dd, *J* = 12.1, 4.6 Hz, 1H), 2.59 (dd, *J* = 19.0, 5.9 Hz 1H), 2.48 - 2.42 (m, 3H), 2.30 (dd, *J* = 14.0, 2.9, 2.9 Hz, 1H), 2.15 (dd, *J* = 12.0, 4.1, 4.1 Hz, 1H), 1.90 (ddd, *J* = 12.0, 4.8, 2.9 Hz, 1H), 1.67 - 1.56 (m, 2H), 0.91 - 0.83 (m, 1H), 0.59 - 0.54 (m, 2H), 0.17 - 0.14 (m, 2H).

The crude product **19** was dissolved in CH_2Cl_2 (0.8 mL) in a 10 mL round bottom flask and was cooled to -40 °C. A solution of BBr_3 (0.0172 mL, 0.181 mmol, 5.00 equiv) in $CHCl_3$ (0.2 mL) was added dropwise to the reaction mixture. The mixture was stirred at -40 °C for 15 min, and the reaction flask was transferred to a 0 °C bath, and the reaction mixture was stirred for 30 min. H_2O (2 mL) was added slowly to quench the reaction. The mixture was transferred to a separatory funnel. The solution was made basic with NH_4OH to pH 8 and extracted with 5% MeOH in $CHCl_3$ (6 x 15 mL). The combined organic layers were washed with sat. aq. NaCl and dried with Na_2SO_4. The mixture was purified by C18 - reverse phase column chromatography with a gradient of 0 to 80% MeOH in H_2O buffered with 0.1% Et_3N to give 8.3 mg (67%) of (-)-naltrexone (**6)** over two steps as a white solid. **Melting Point** 158 - 160 °C [lit. 159-161 °C (MeOH)[6,7], 174–175 °C[8] , 167-169 °C ($CHCl_3$)[9]]. **$[\alpha]_D$** -145.4 ($CHCl_3$, *c* = 0.46) [lit. -207.00, ($CHCl_3$, c=1.0)[6], -84.8, ($CHCl_3$, c= 1.0)[9]]. **IR** (neat) 3220, 2927, 1728, 1461, 1242, 1111 cm^{-1}. For **^{1}H** and **^{13}C** NMR spectra, see Section III (Spectral Data Comparison of (-)-Naltrexone). **HRMS** (ESI): Mass calcd for $C_{20}H_{24}NO_4^+$ $[M+H]^+$, 342.1705. Found $[M+H]^+$, 342.1702.

III. Spectral Data Comparison of (-)-Naltrexone



(Protons and carbons assigned by ^{1}H, ^{13}C, HSQC, and HMBC)

	^{13}C NMR		^{1}H NMR	
	Hudlicky Synthesis[7]	This Synthesis	Hudlicky Synthesis[7]	This Synthesis
	150 MHz, CDCl$_3$	126 MHz, CDCl$_3$	600 MHz, CDCl$_3$	500 MHz, CDCl$_3$
1	119.90	120.1	6.60 (d, *J* = 8.1 Hz, 1H)	6.59 (d, *J* = 8.1 Hz, 1H)
2	117.91	118.2	6.74 (d, *J* = 8.1 Hz, 1H)	6.72 (d, *J* = 8.1 Hz, 1H)
3	138.80	139.1	-	-
4	142.51	143.7	-	-
5	90.60	90.7	4.74 (s, 1H)	4.68 (s, 1H),
6	210.02	210.3	-	-
7	36.21	36.3	3.11 - 3.03 (m, 2H) 2.34 (ddd, *J* =14.5, 3.0, 3.0 Hz, 1H),	3.07 - 3.02 (m, 2H) 2.32 (ddd, *J* = 14.5, 3.0, 3.0 Hz, 1H)
8	31.36	31.5	1.91 (m, 1H), 1.66 (ddd, *J* =14.2, 14.2, 3.3 Hz, 1H),	1.91 - 1.87 (m, 1H) 1.64 (ddd, 14.4, 14.4, 3.1, 1H)
9	62.01	62.2	3.21 (d, *J* = 5.9 Hz, 1H)	3.19 (d, *J* = 5.9 Hz, 1H)
10	22.62	22.8	3.11 - 3.03 (m, 2H)	3.11 - 3.02 (m, 2H)
			2.58 (dd, *J* =18.4, 6.0 Hz, 1H),	2.56 (dd, *J* = 18.6, 5.9 Hz, 1H)
11	124.25	124.3	-	-
12	129.05	129.1	-	-
13	51.07	51.2	-	-
14	70.32	70.4	-	-
15	30.65	30.8	2.49 - 2.39 (m, 3H) 1.59 (ddd, *J* =12.8, 2.7 Hz, 1H),	2.48 - 2.40 (m, 3H) 1.59 - 1.55 (m, 1H)
16	43.60	43.8	2.72 (dd, *J* = 12.0, 4.8 Hz, 1H) 2.18 (ddd, *J* = 12.2, 3.8, 3.8 Hz, 1H)	2.71 (dd, *J* =12.1, 4.4 Hz, 1H) 2.17 (ddd, *J* = 12.1, 4.0, 4.0 Hz, 1H)
17	59.21	59.4	2.49 - 2.39 (m, 3H)	2.48 - 2.40 (m, 3H),
18	9.42	9.5	0.88 (m, 1H),	0.91 - 0.85 (m, 1H)
19 20	4.02, 3.81	4.2, 4.0	0.57 (m, 2H) 0.16 (m, 2H)	0.58 - 0.55 (m, 2H) 0.16 - 0.14 (m 2H)
OH	-	-	5.82 (bs, 1H, OH)	-

IV. References

1) E. M. Phillips, T. Mesganaw, A. Patel, S. Duttwyler, B. Q. Mercado, K. N. Houk and J. A. Ellman, *Angew. Chem. Int. Ed.,* 2015, **54***,* 12044.

2) B. Bennacer, D. Trubuil, C. Rivalle and D. S. Grierson, *Eur. J. Org. Chem.*, 2003, **23**, 4561.

3) J. M. Takacs, M. R. Jaber, F. Clement and C. Walters, *J. Org. Chem.*, 1998, **63**, 6757.

4) A. P. Kozikowski, W. Tuckmantel and C. George, *J. Org. Chem.*, 2000, **65**, 5371.

5) I. Iijima, J. Minamikawa, A. E. Jacobson, A. Brossi, K. C. Rice, and W. A. Klee, *J.Med. Chem.,* 1978, **21**, 398.

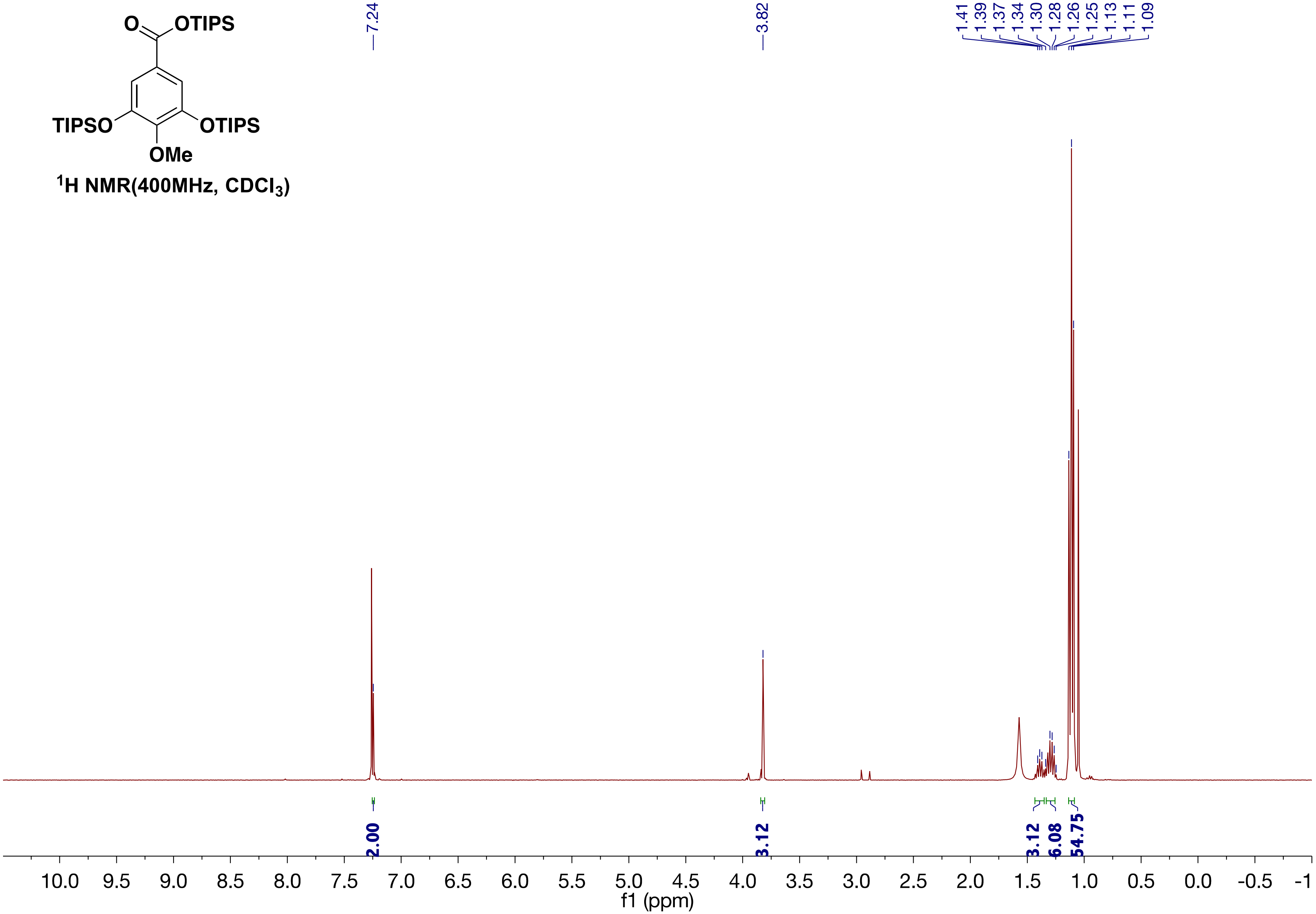
6) L. Werner, M. Wernerova, A. Machara, M. A. Endoma-Arias, J. Duchek, D. R. Adams, D. P. Cox, and T. Hudlicky, *Adv. Synth. Cat.*, 2012, **354**, 2706.

7) A. Machara, D. P. Cox and T. Hudlicky, *Adv. Synth. Catal.*, 2012, **354**, 2713.

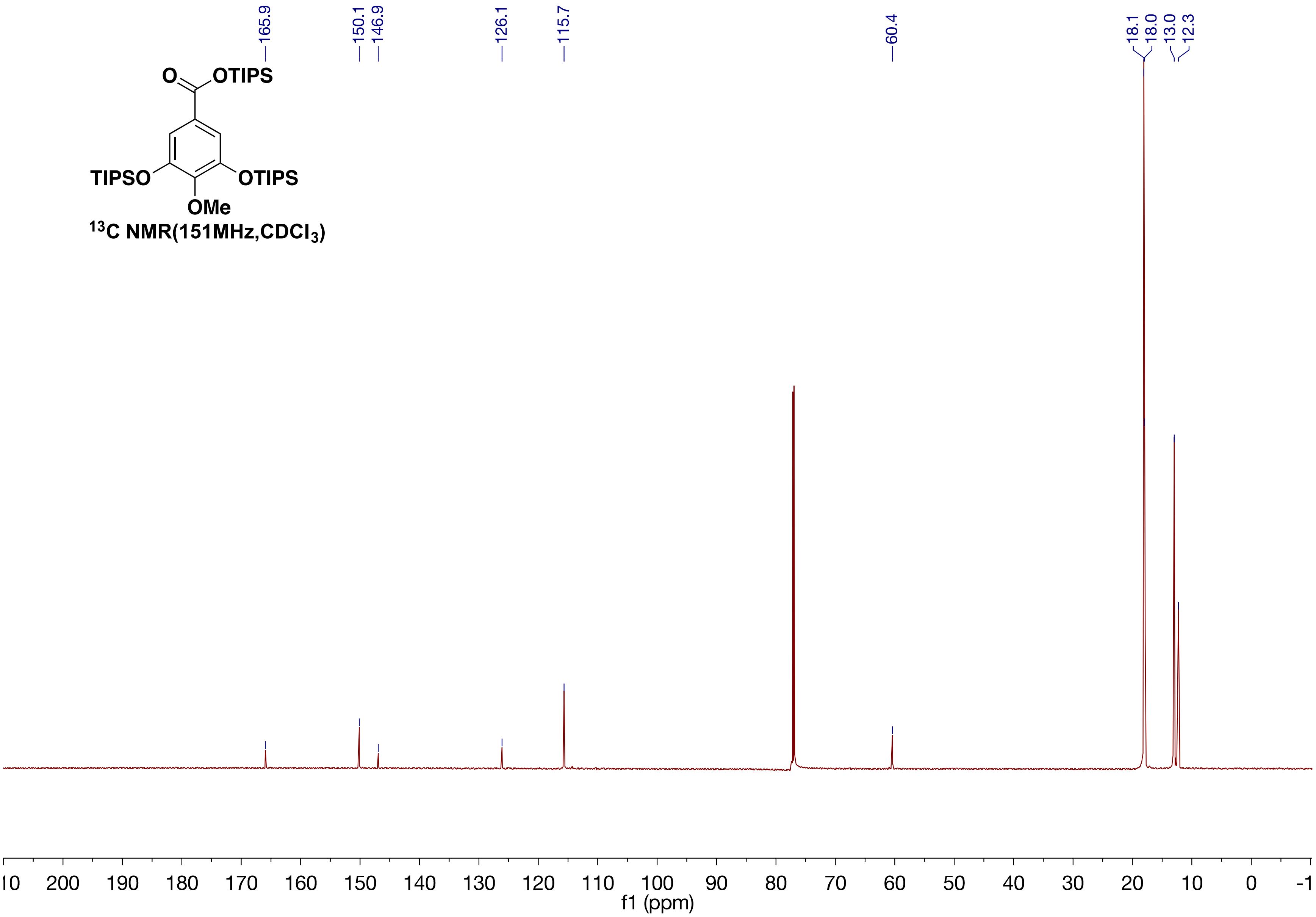
8) G. B. Kok and P. J. Scammells, *RSC Adv.*, 2012, **2**, 11318.

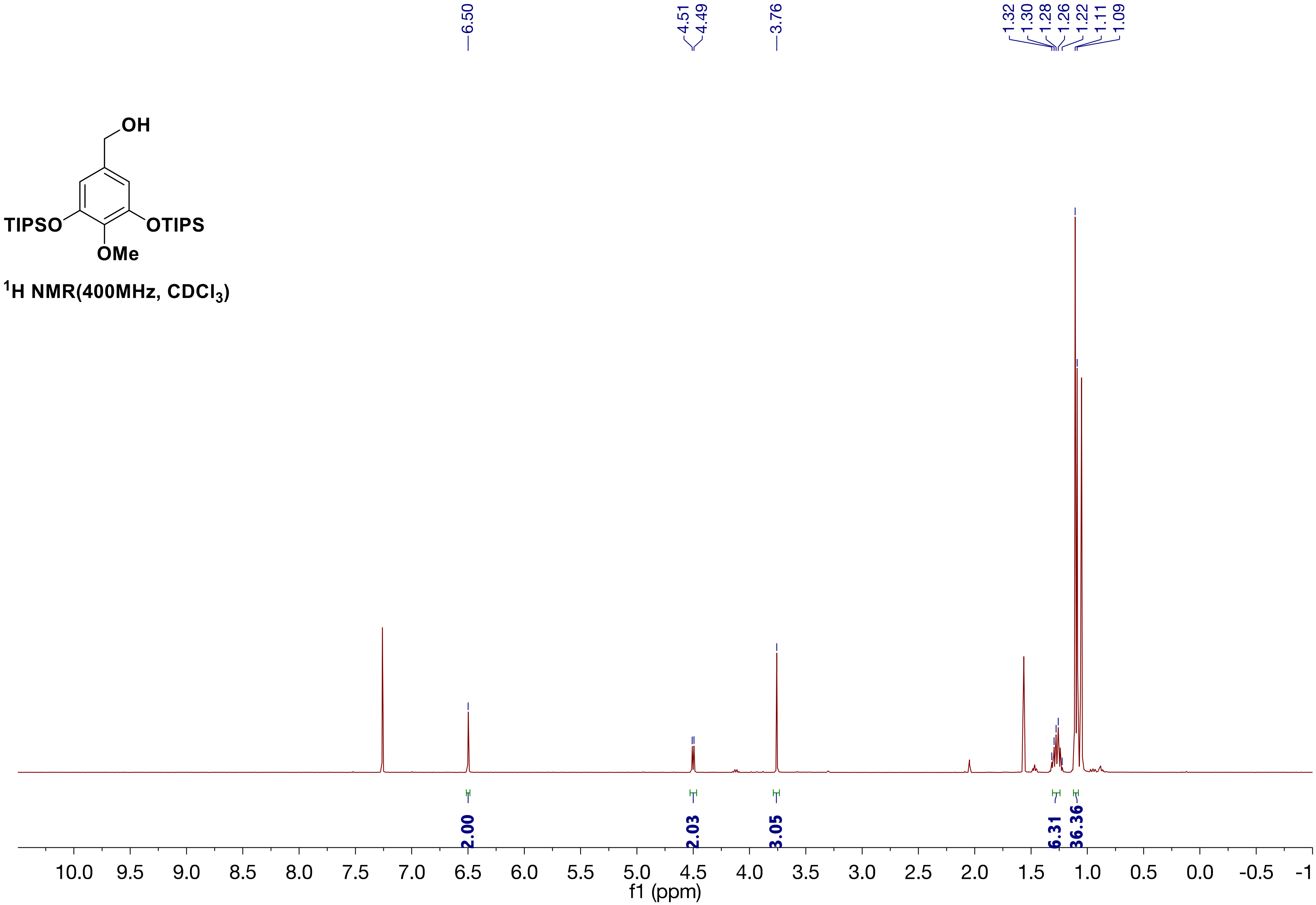
9) A. Machara, L. Werner, H. Leisch, R. J. Carroll, D. R. Adams, D. M. Haque, D. P. Cox, T. Hudlicky, *Synlett*, 2015, 2101.

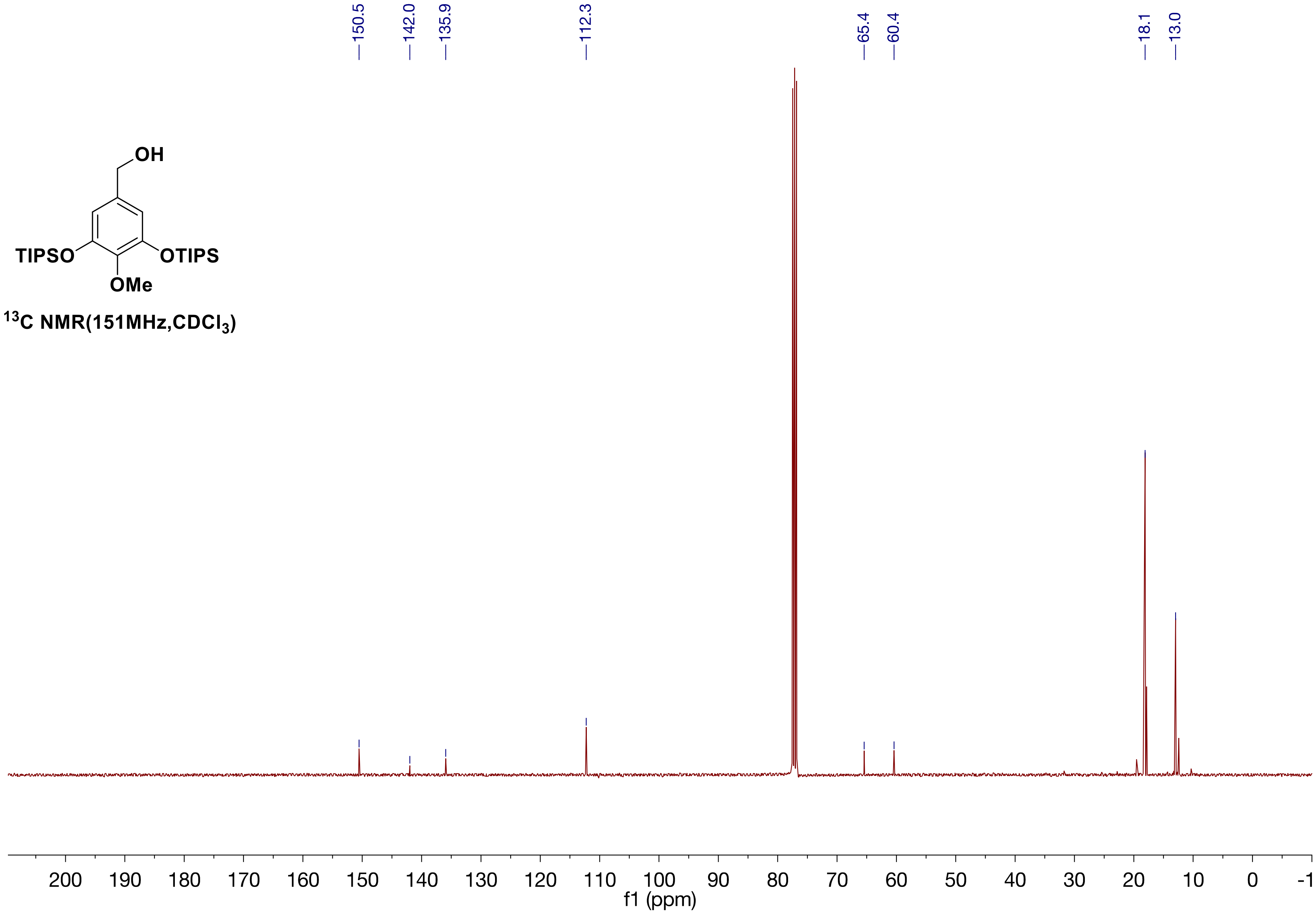
V. NMR Spectra

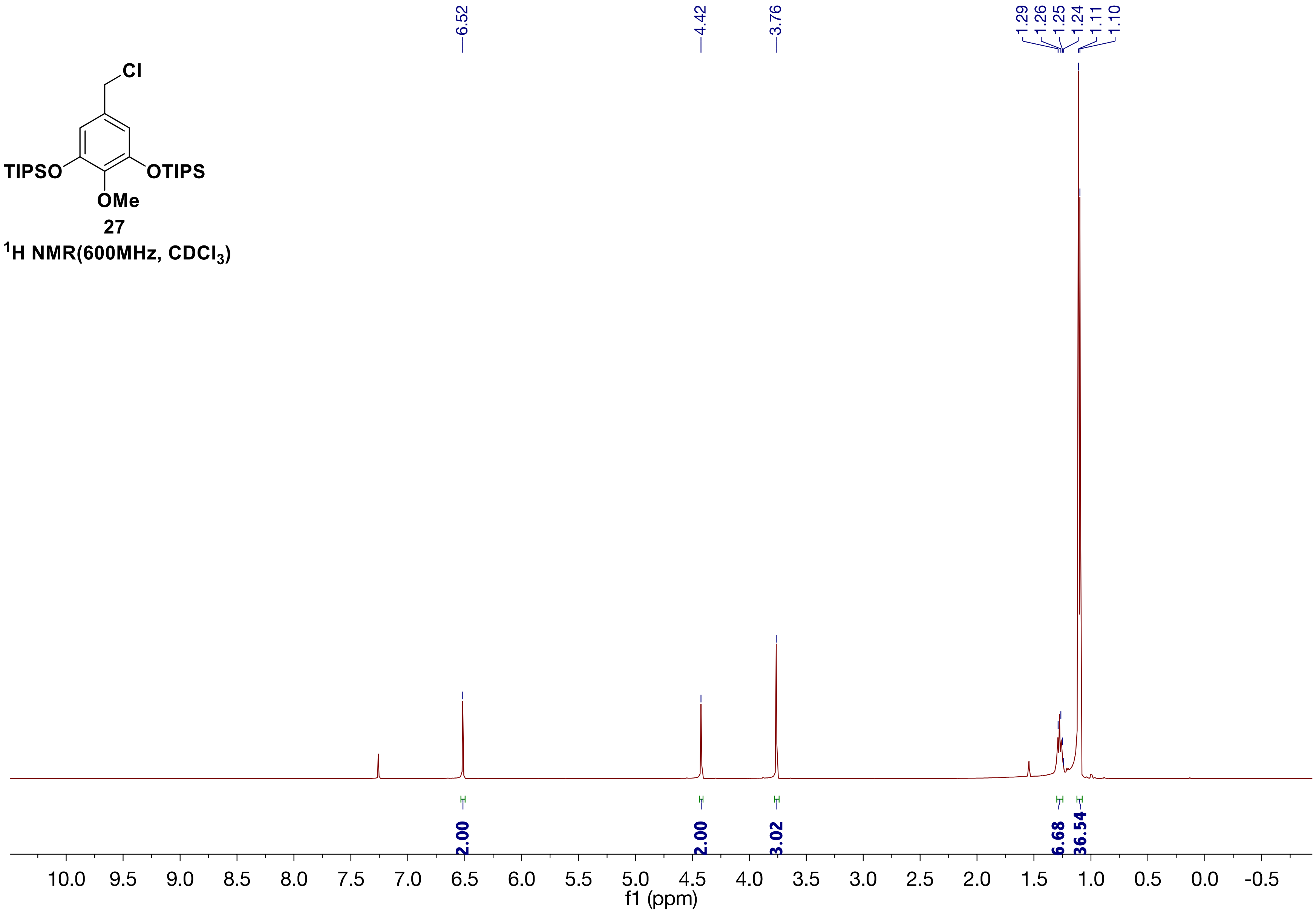


^{1}H NMR(400MHz, $CDCl_3$)


165.9
150.1
146.9
126.1
115.7
60.4
18.1
18.0
13.0
12.3
O
OTIPS
TIPSO
OTIPS
OMe
^{13}C NMR(151MHz,CDCl$_3$)
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

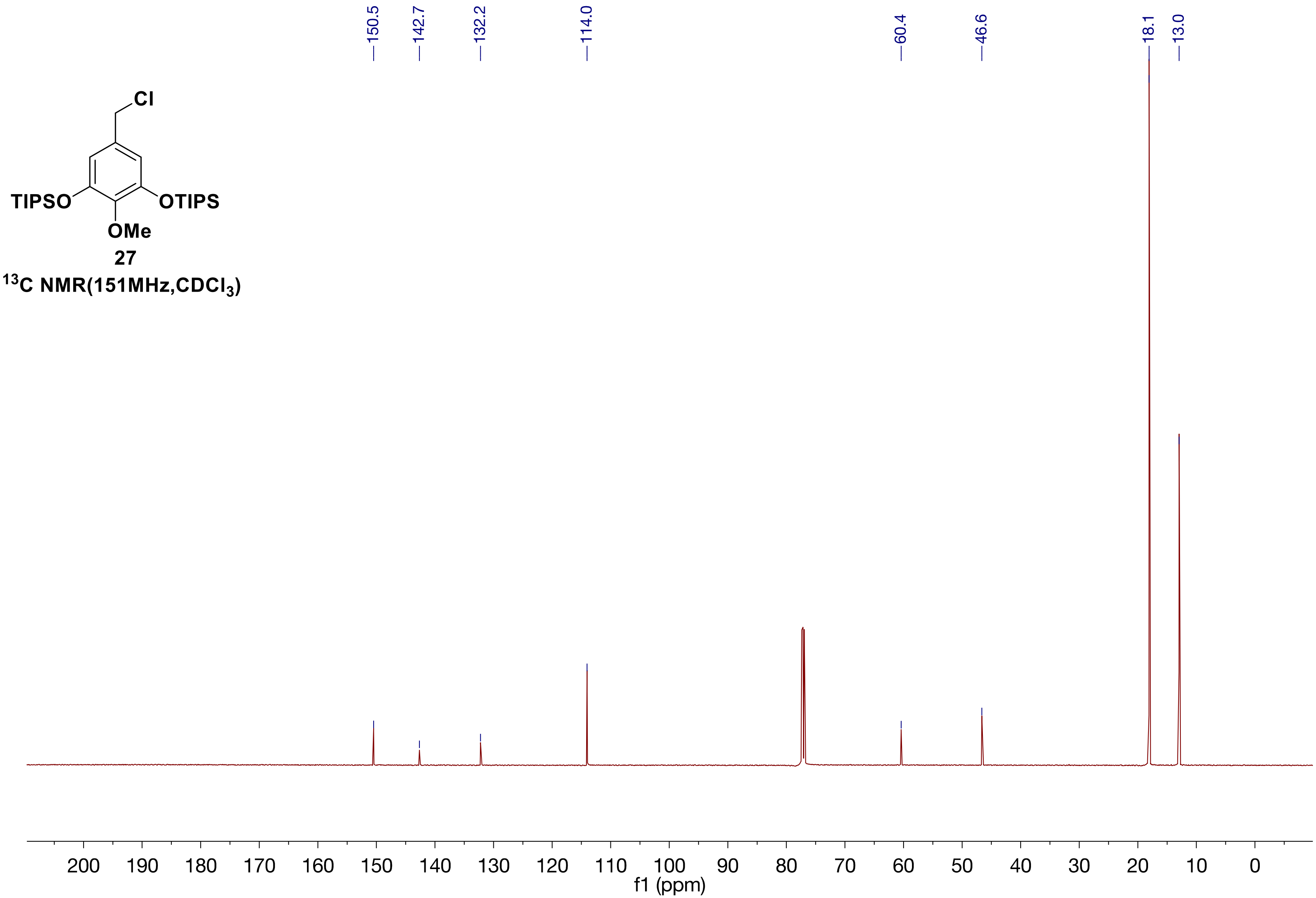

OH
TIPSO
OTIPS
OMe
^{1}H NMR(400MHz, CDCl$_3$)
6.50
4.51
4.49
3.76
1.32
1.30
1.28
1.26
1.22
1.11
1.09
2.00
2.03
3.05
6.31
36.36
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)


150.5
142.0
135.9
112.3
65.4
60.4
18.1
13.0
OH
TIPSO
OTIPS
OMe
^{13}C NMR(151MHz,CDCl$_3$)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)



27

^{1}H NMR(600MHz, $CDCl_3$)

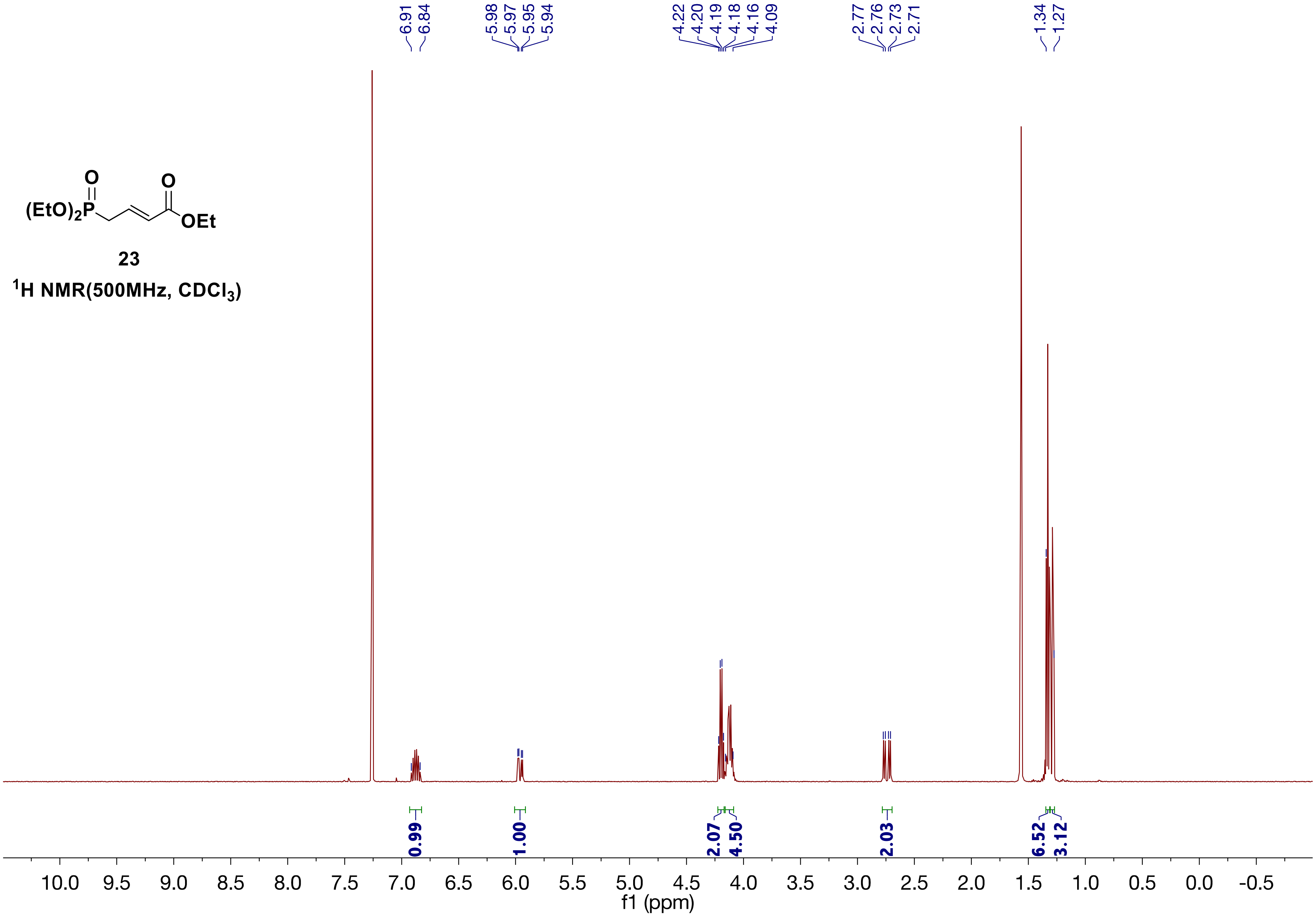


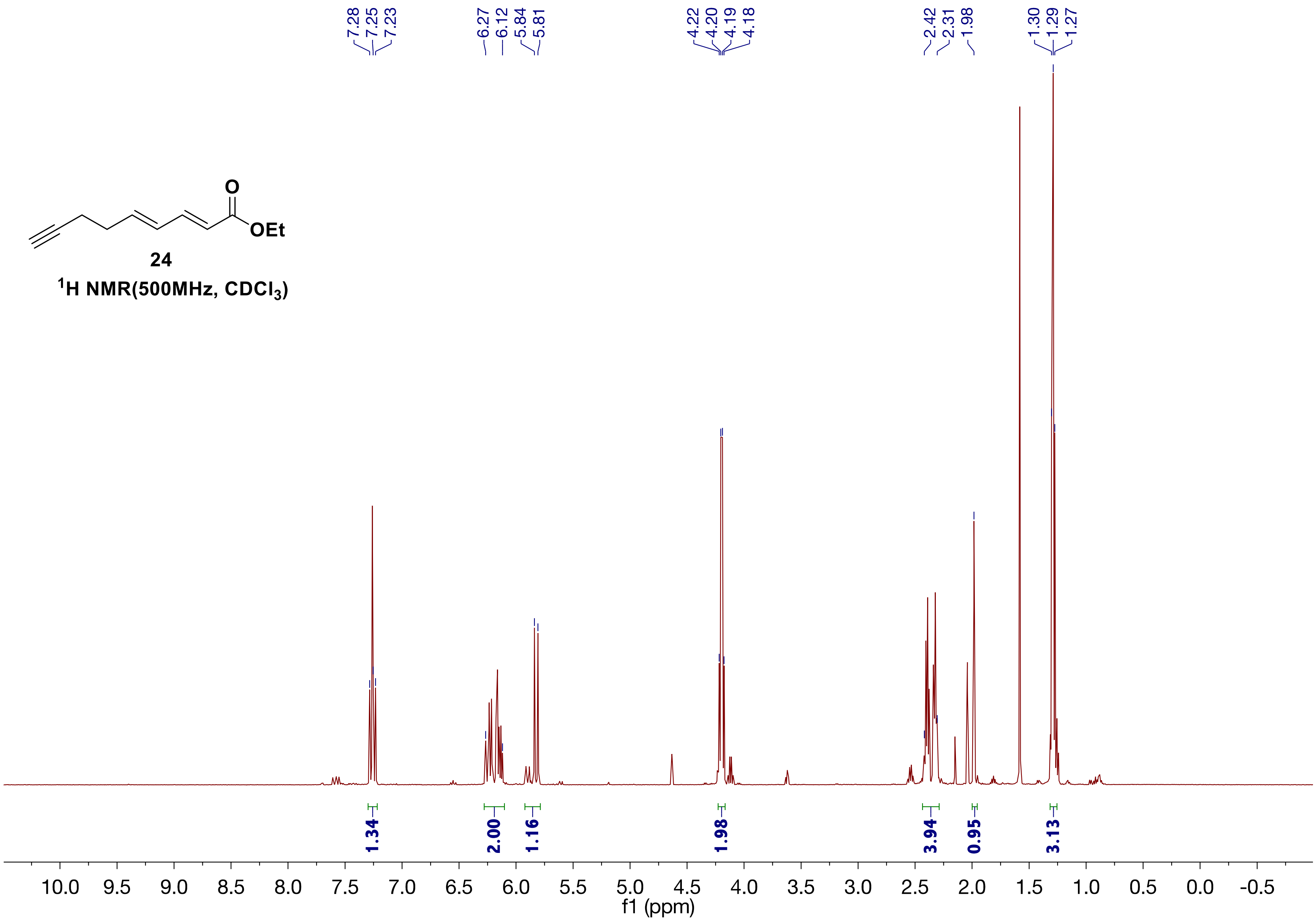
27

^{13}C NMR(151MHz,CDCl$_3$)

23

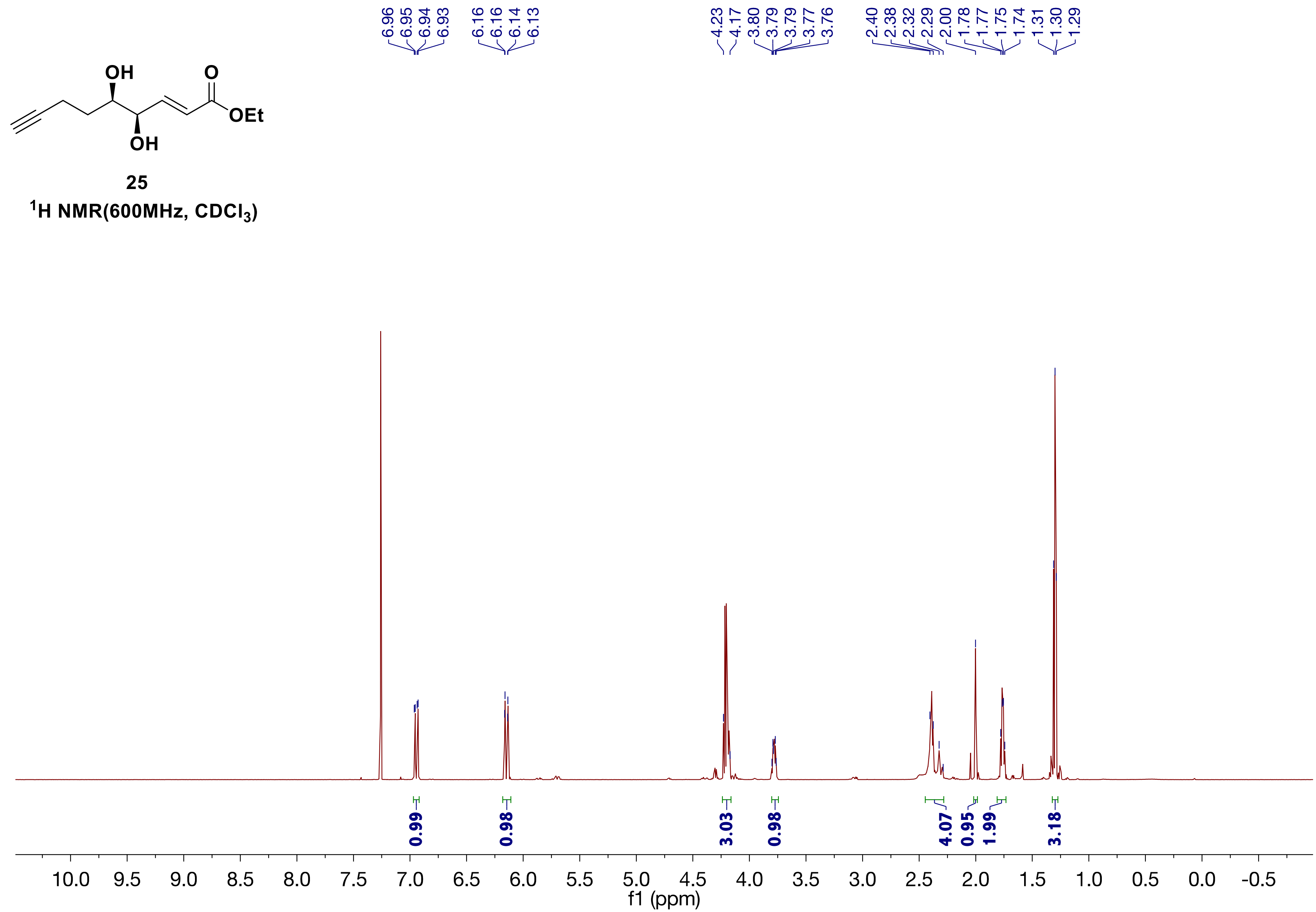
^{1}H NMR(500MHz, CDCl$_3$)





24

^{1}H NMR(500MHz, $CDCl_3$)

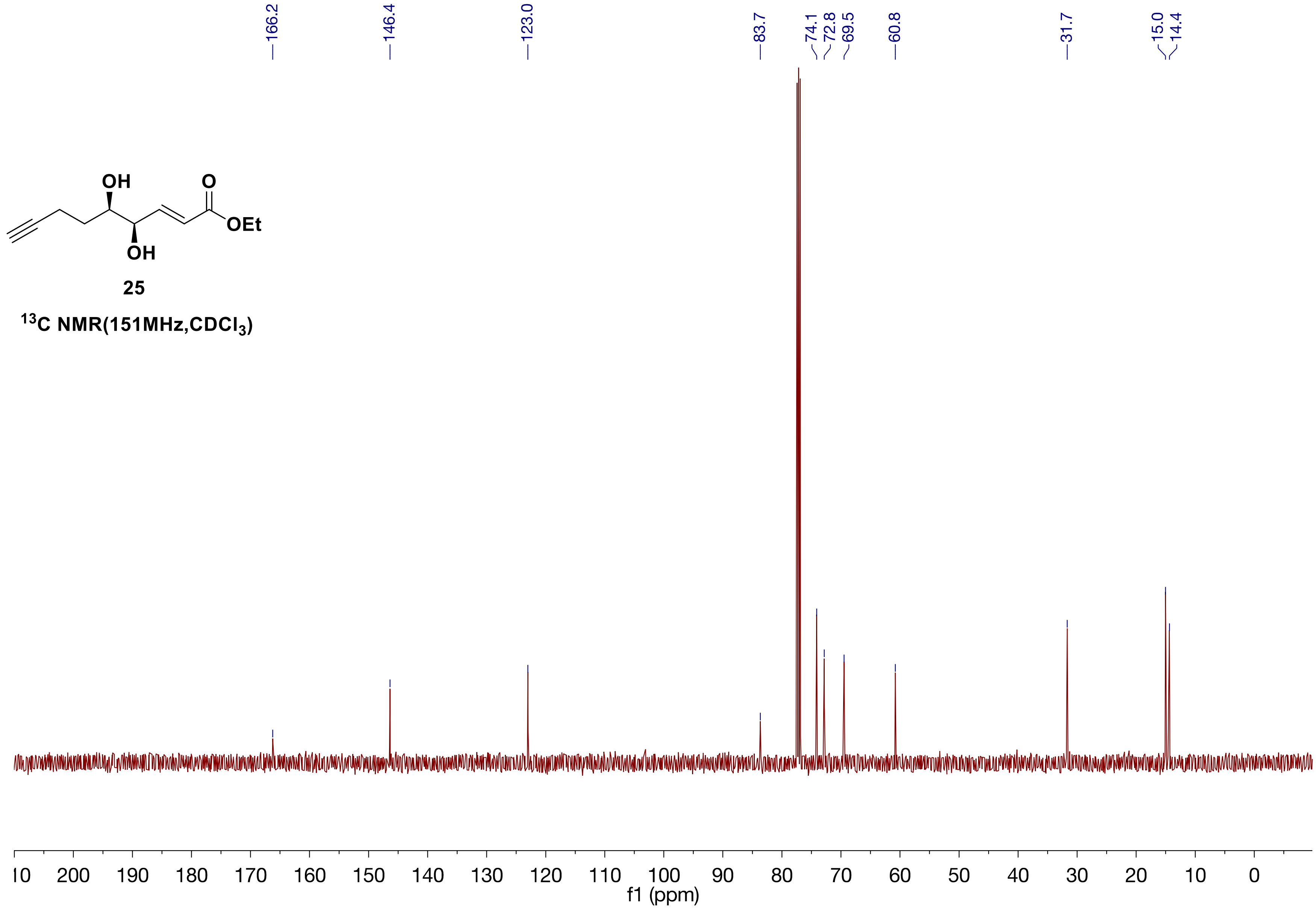


25

^{1}H NMR(600MHz, CDCl$_3$)

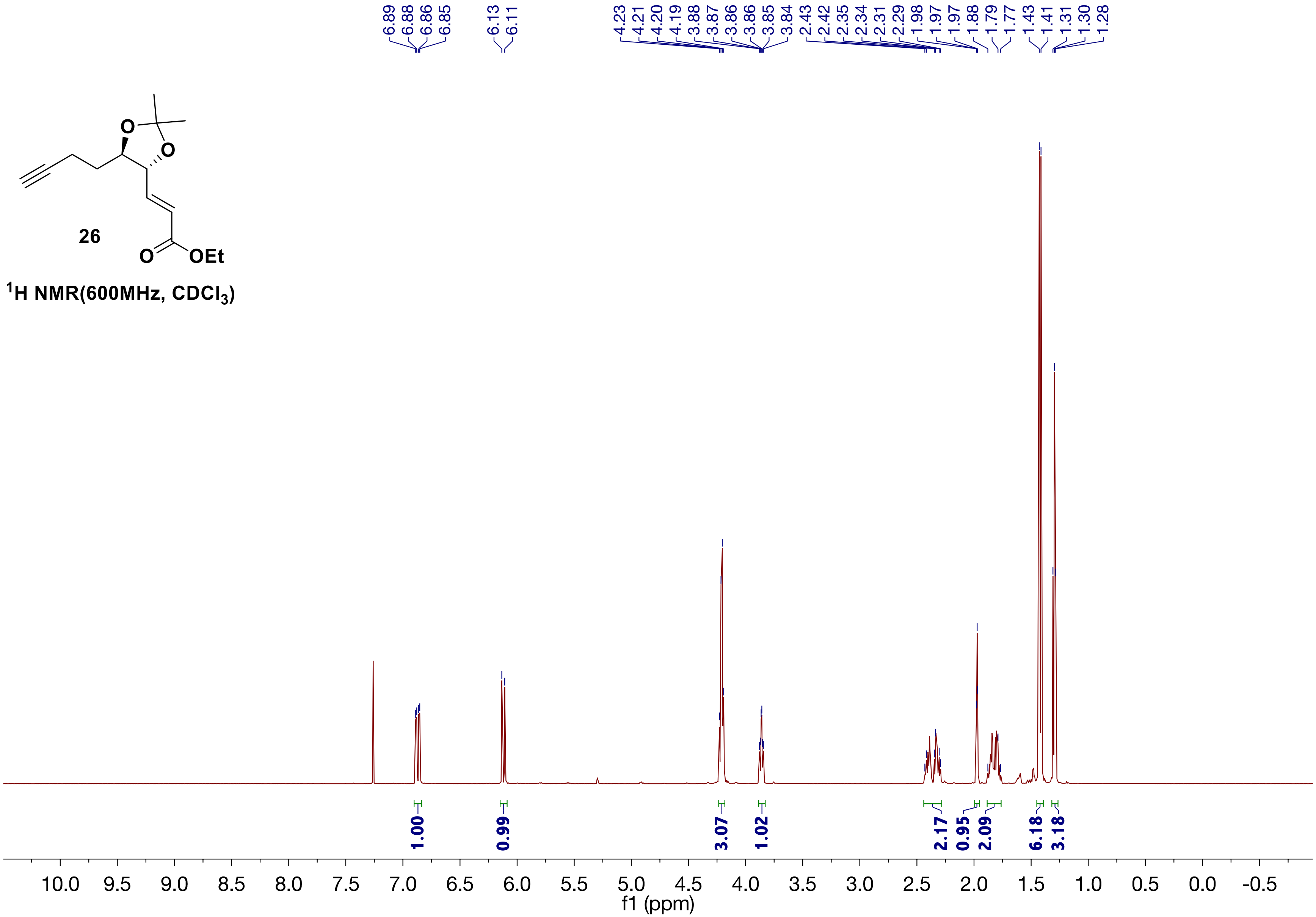
25

^{13}C NMR(151MHz,CDCl$_3$)



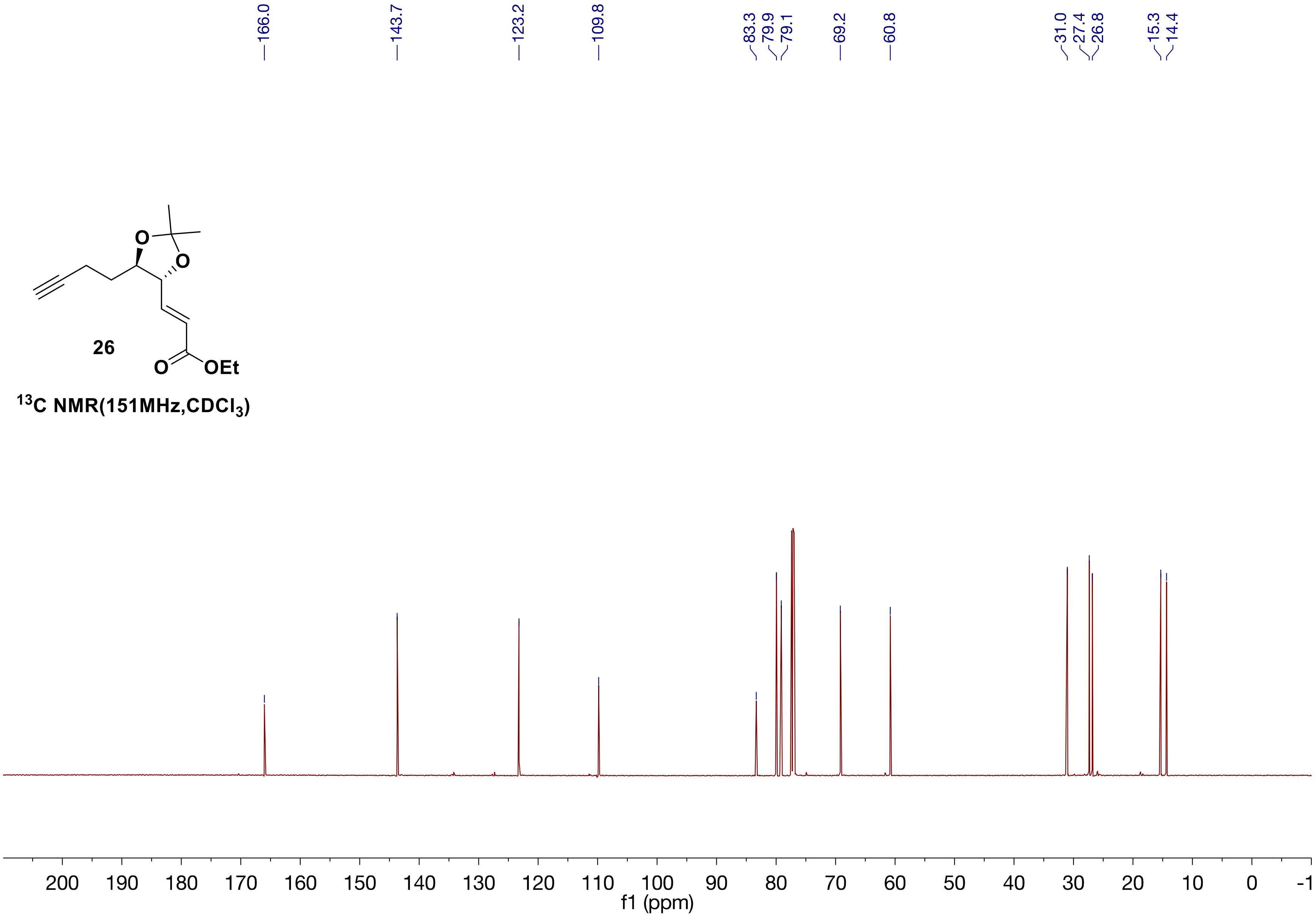
26

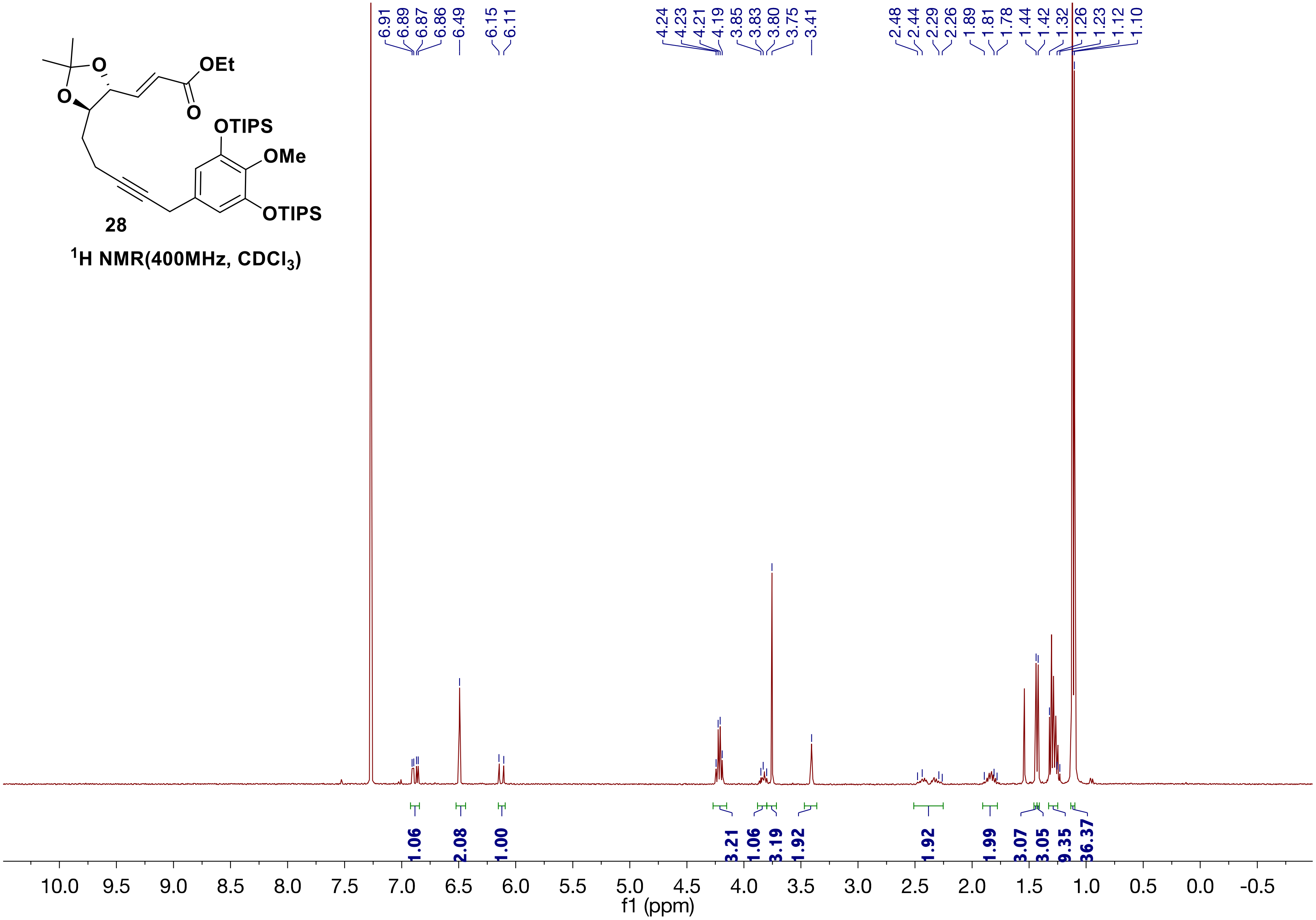
^{1}H NMR(600MHz, $CDCl_3$)



26

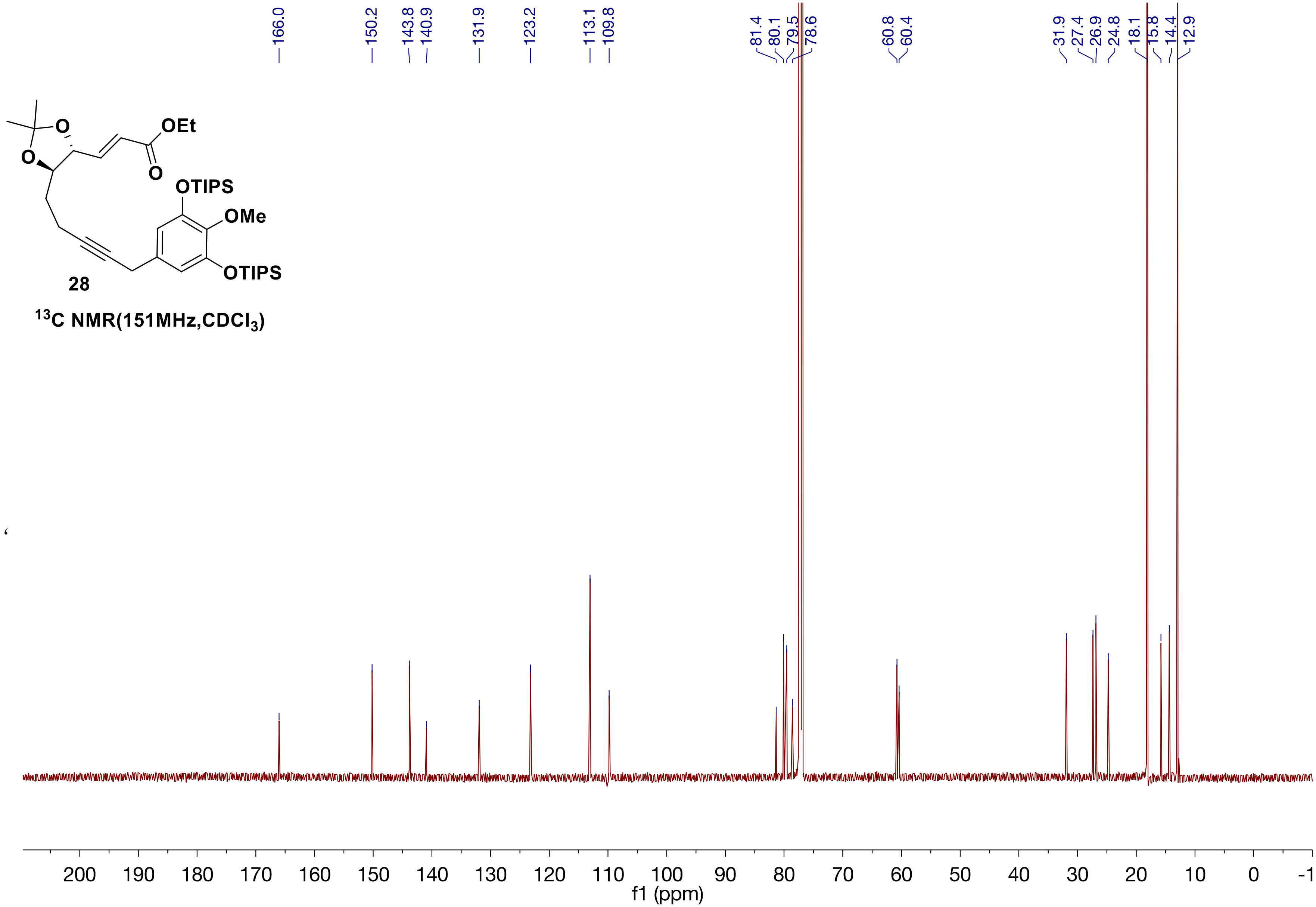
^{13}C NMR(151MHz,$CDCl_3$)





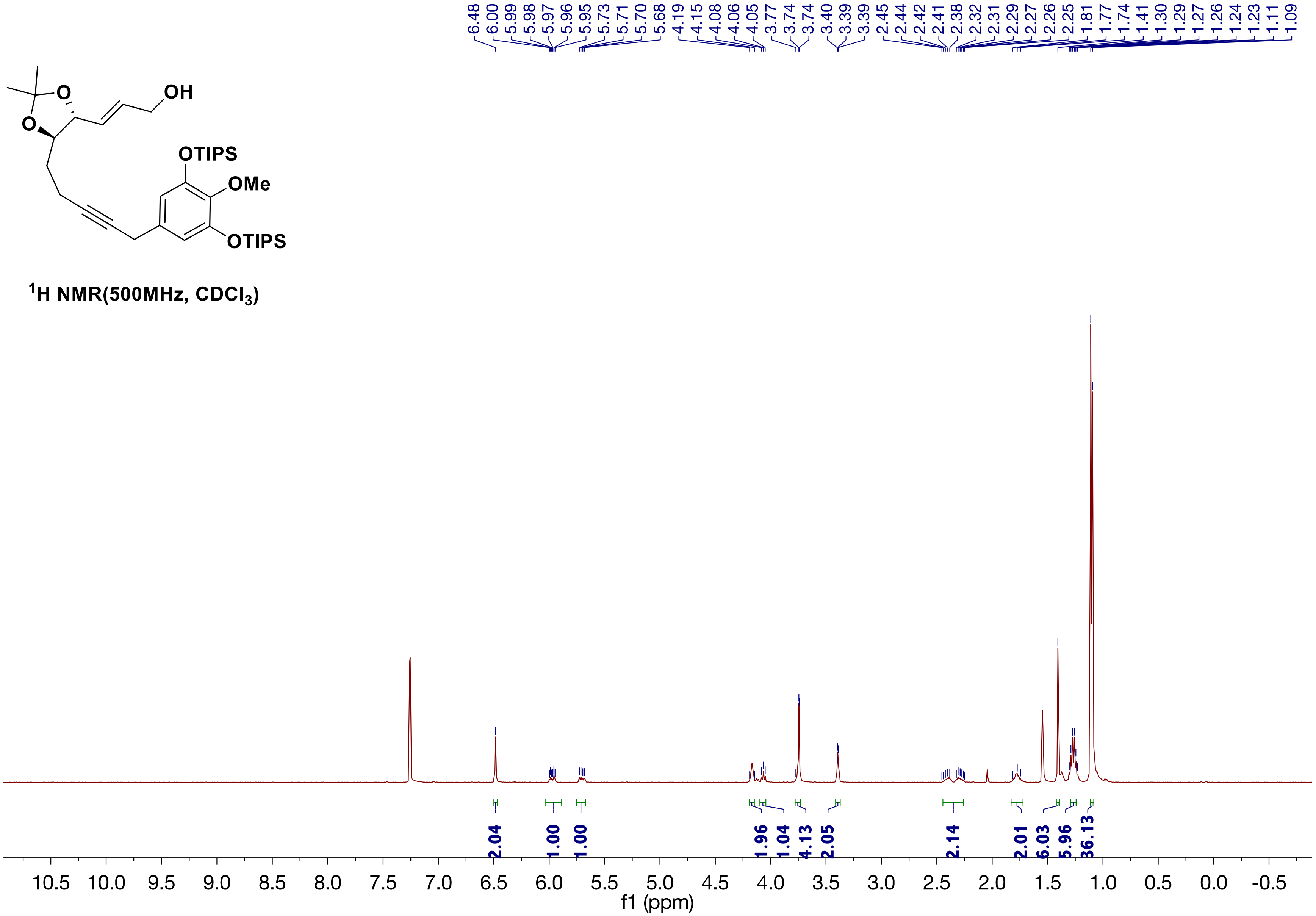
28

^{1}H NMR(400MHz, CDCl$_3$)

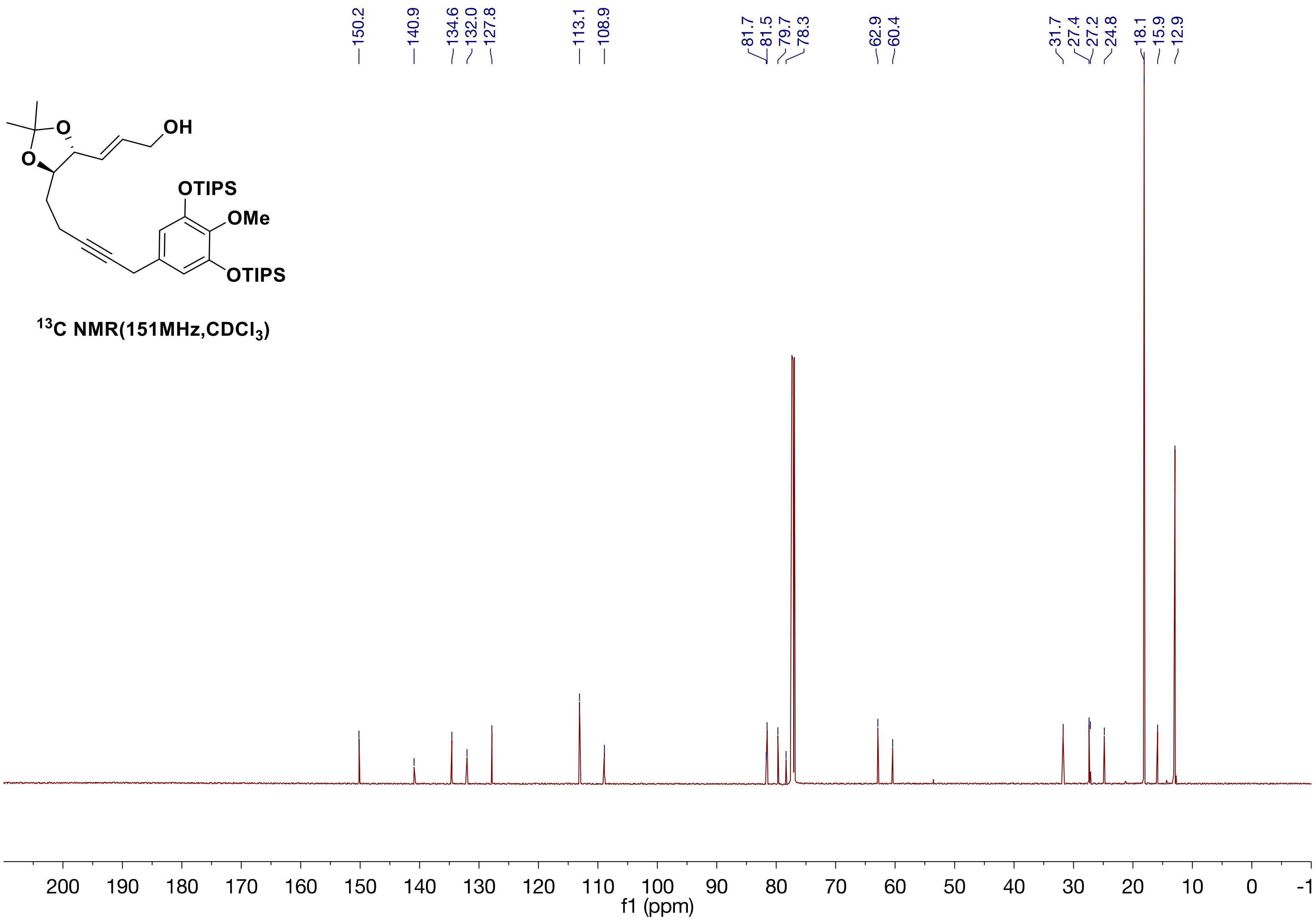


28

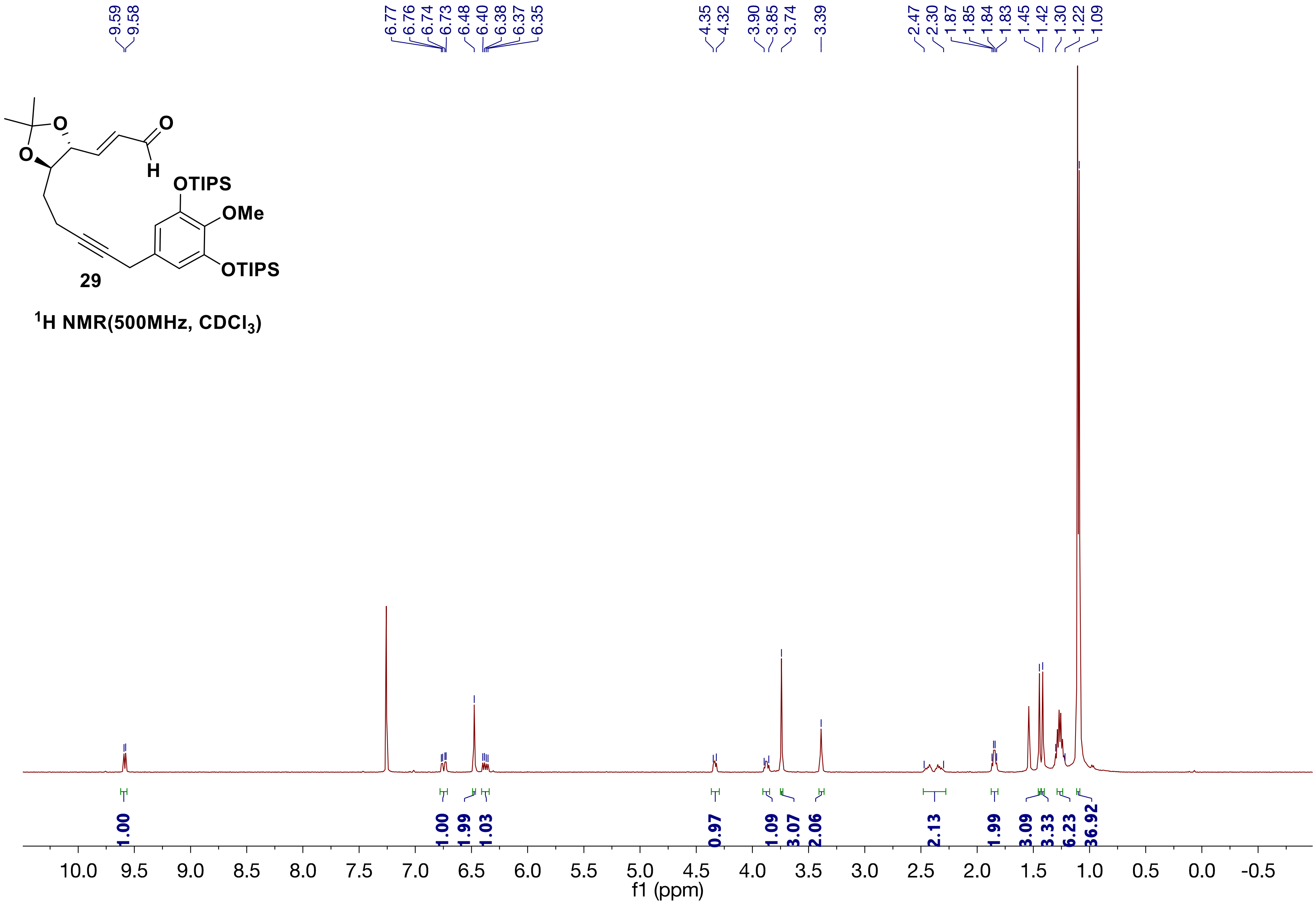
^{13}C NMR(151MHz,CDCl$_3$)



^{1}H NMR(500MHz, CDCl$_3$)

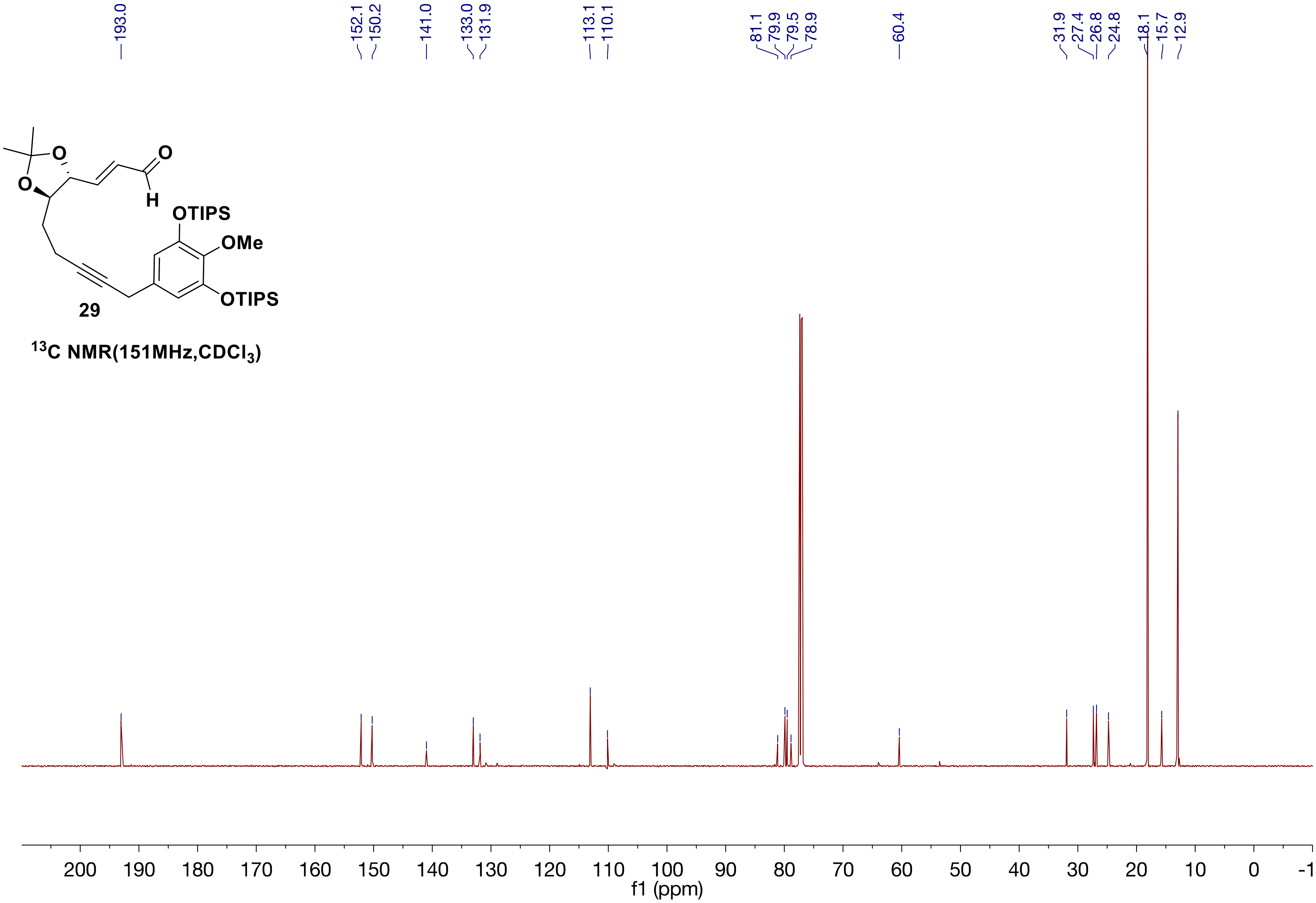


^{13}C NMR(151MHz,$CDCl_3$)

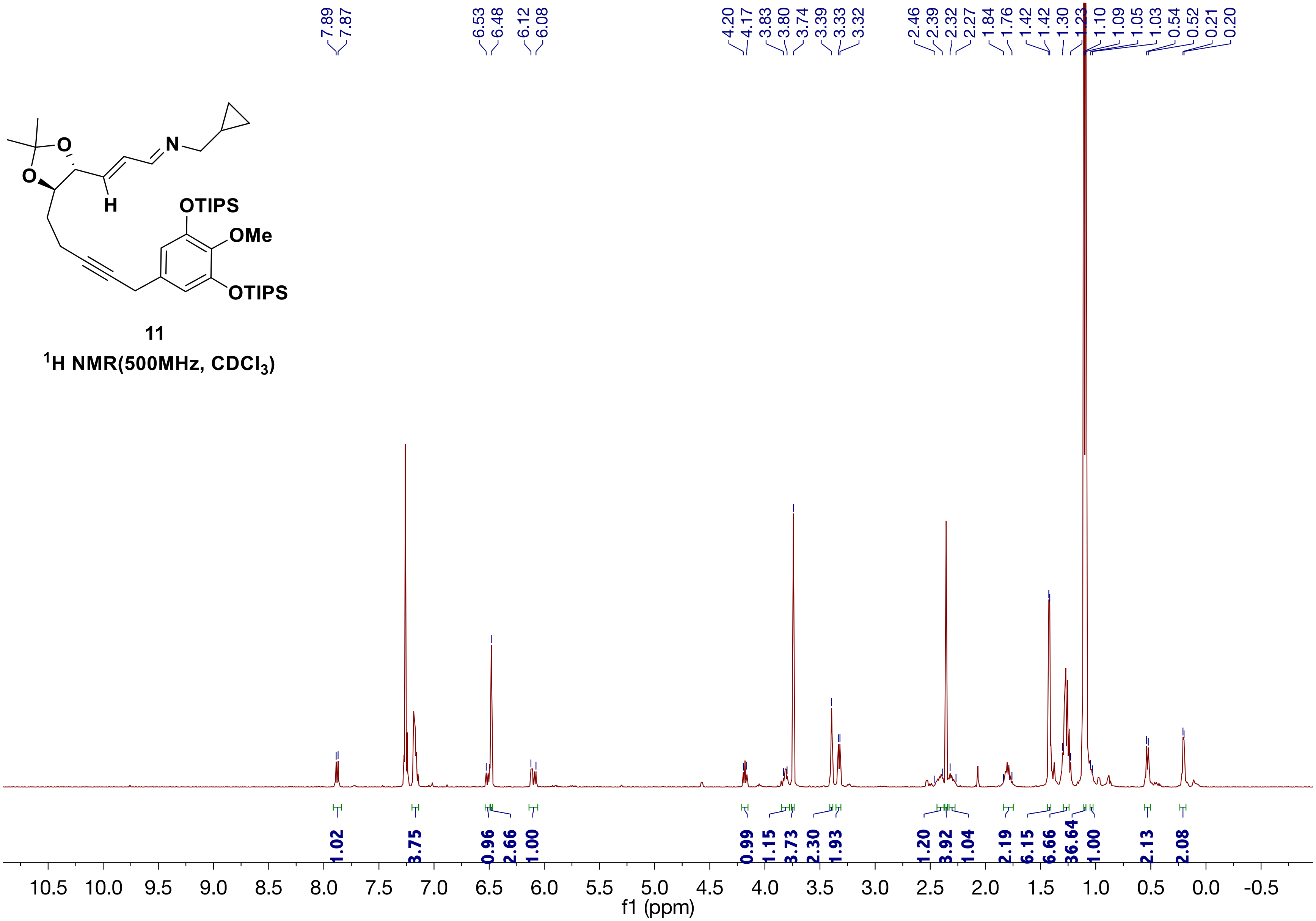


29

^{1}H NMR(500MHz, CDCl$_3$)

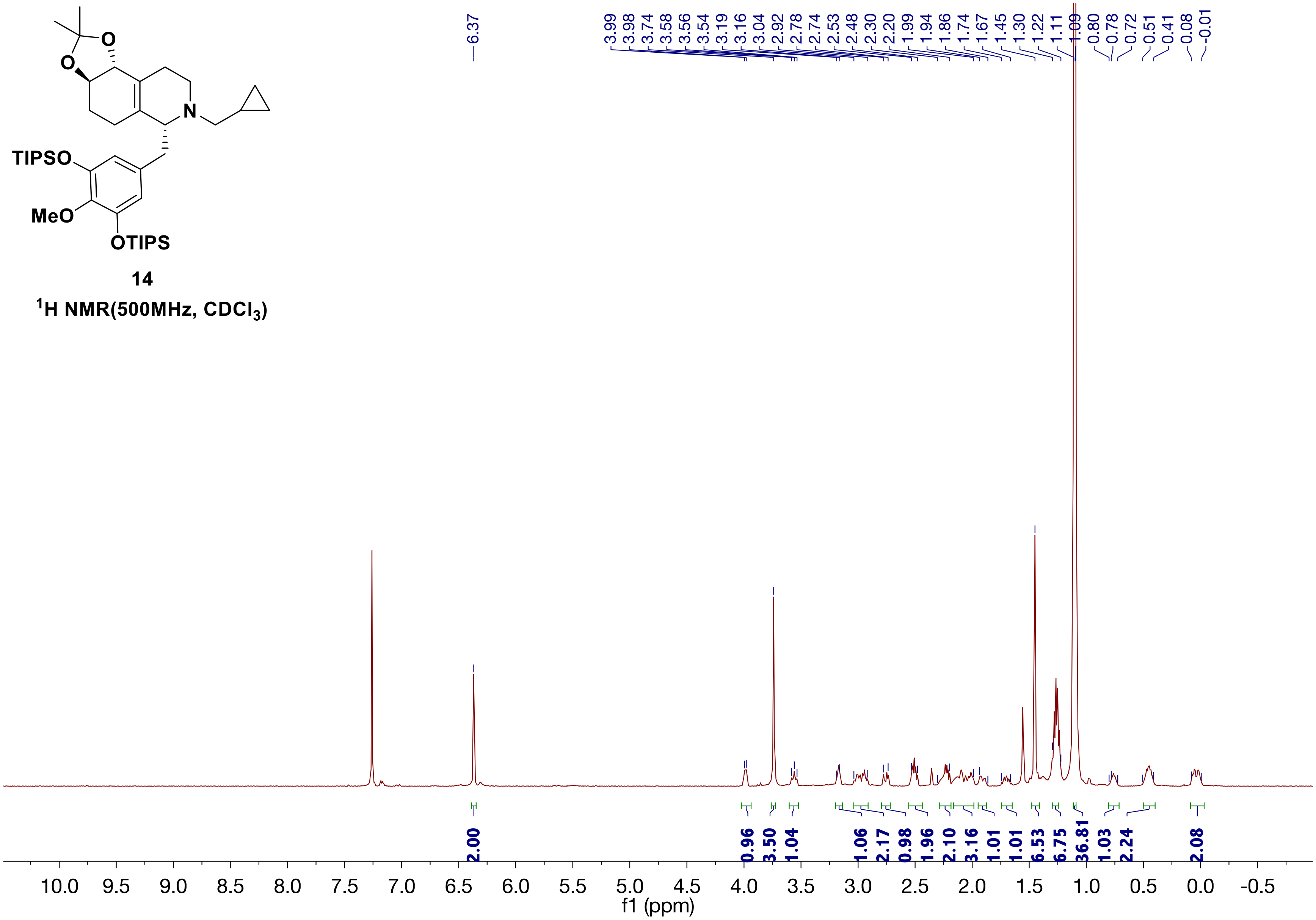

29

^{13}C NMR(151MHz,CDCl$_3$)



11

^{1}H NMR(500MHz, CDCl$_3$)

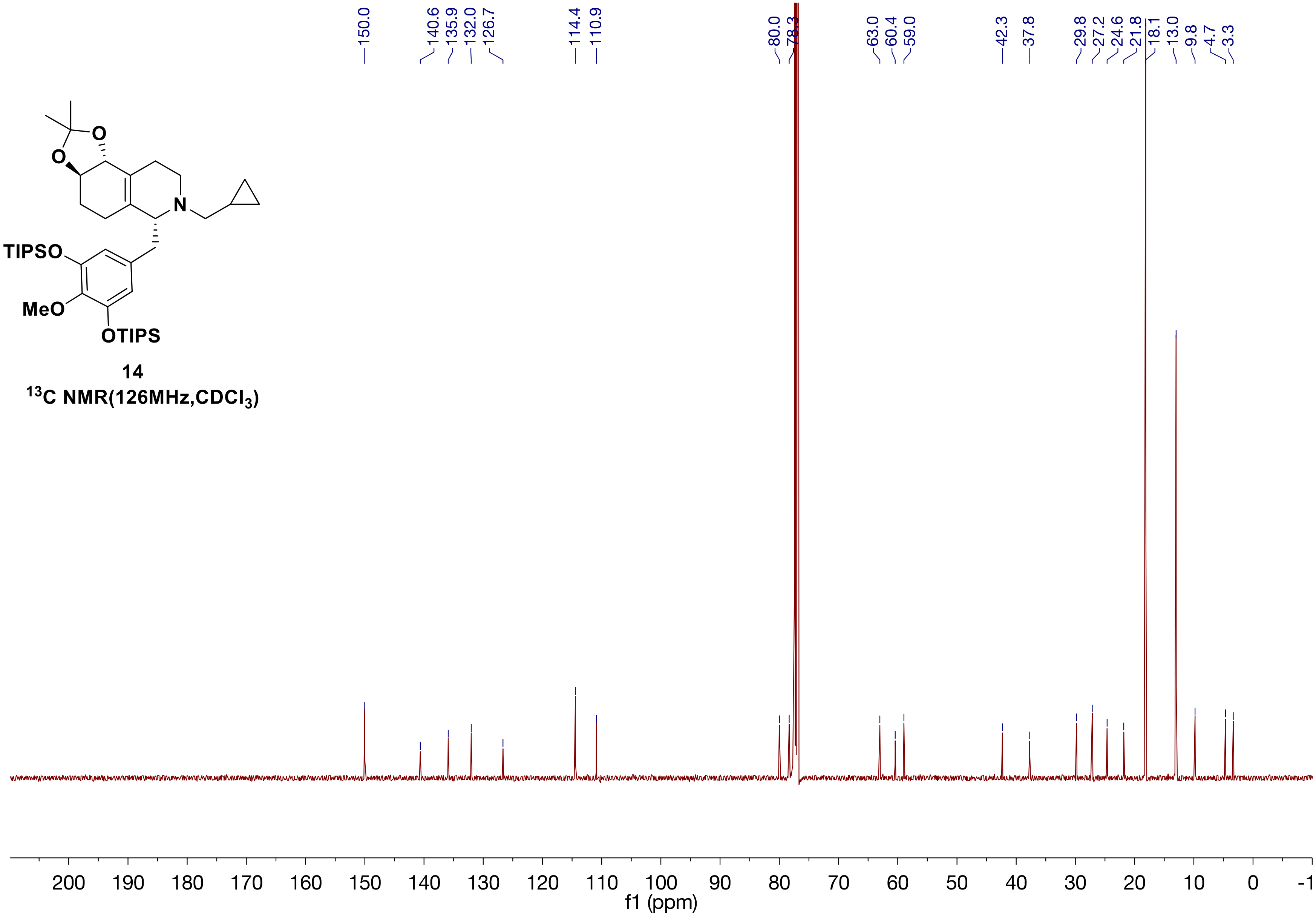


14

^{1}H NMR(500MHz, $CDCl_3$)

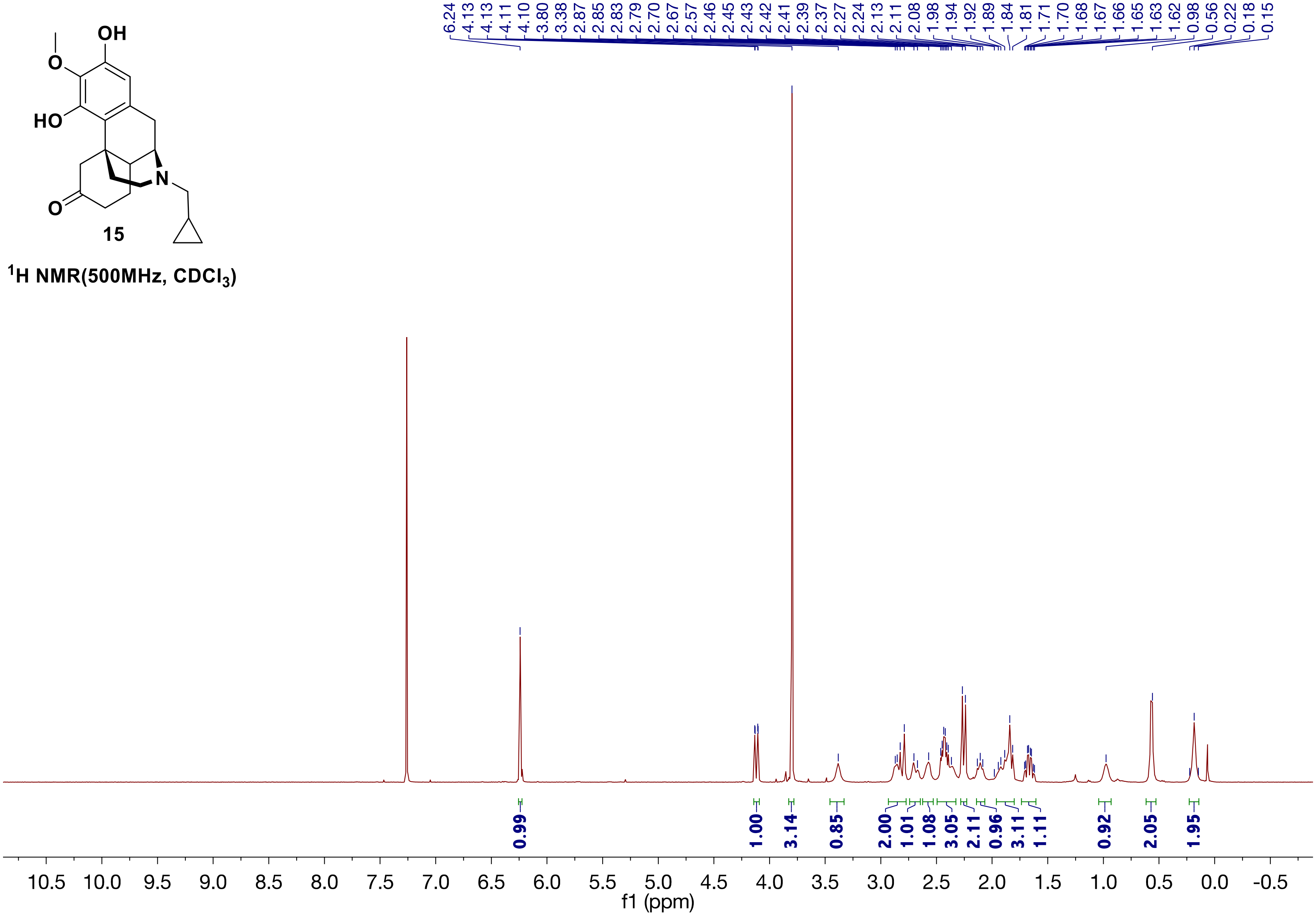
14

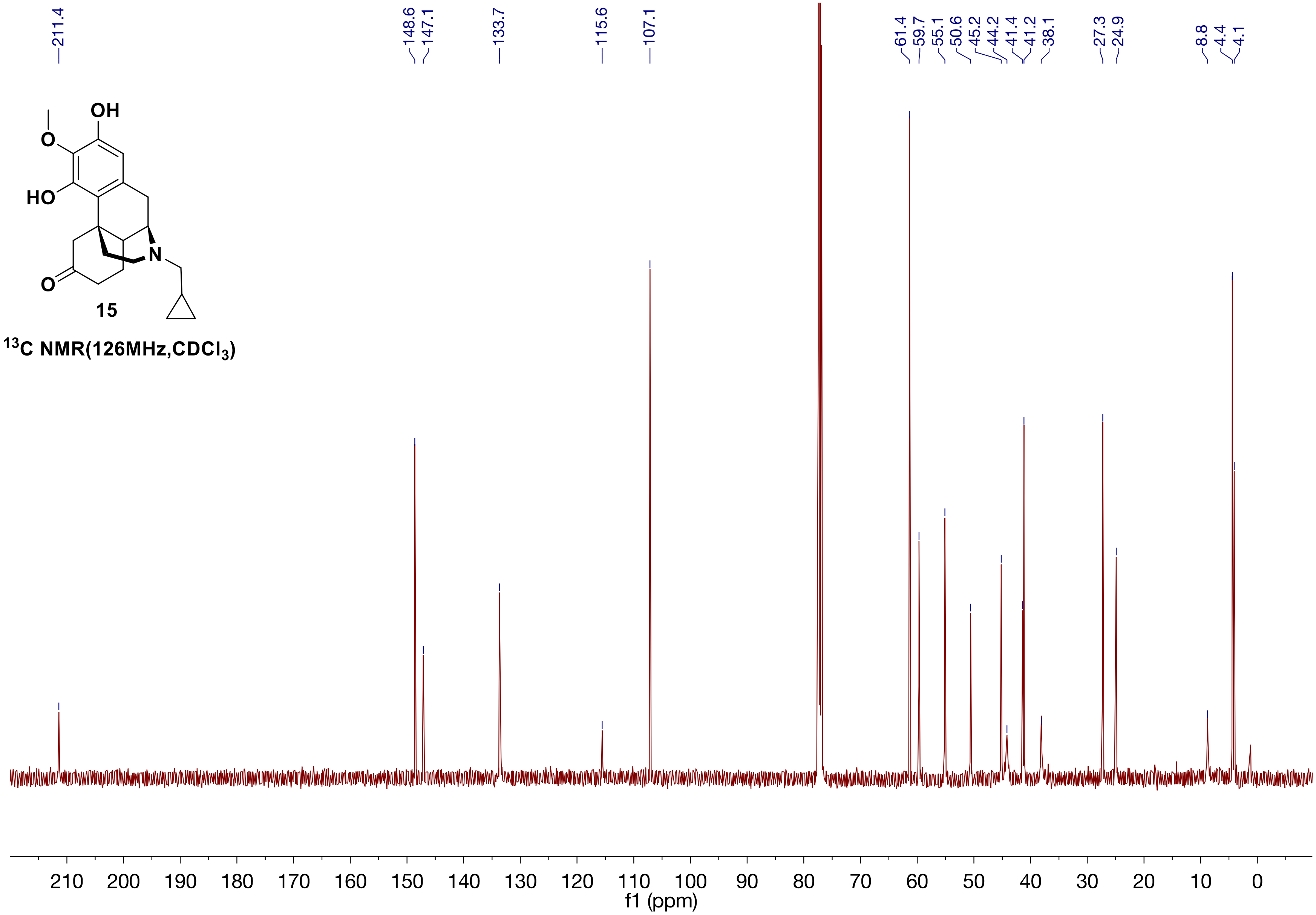
^{13}C NMR(126MHz,CDCl$_3$)

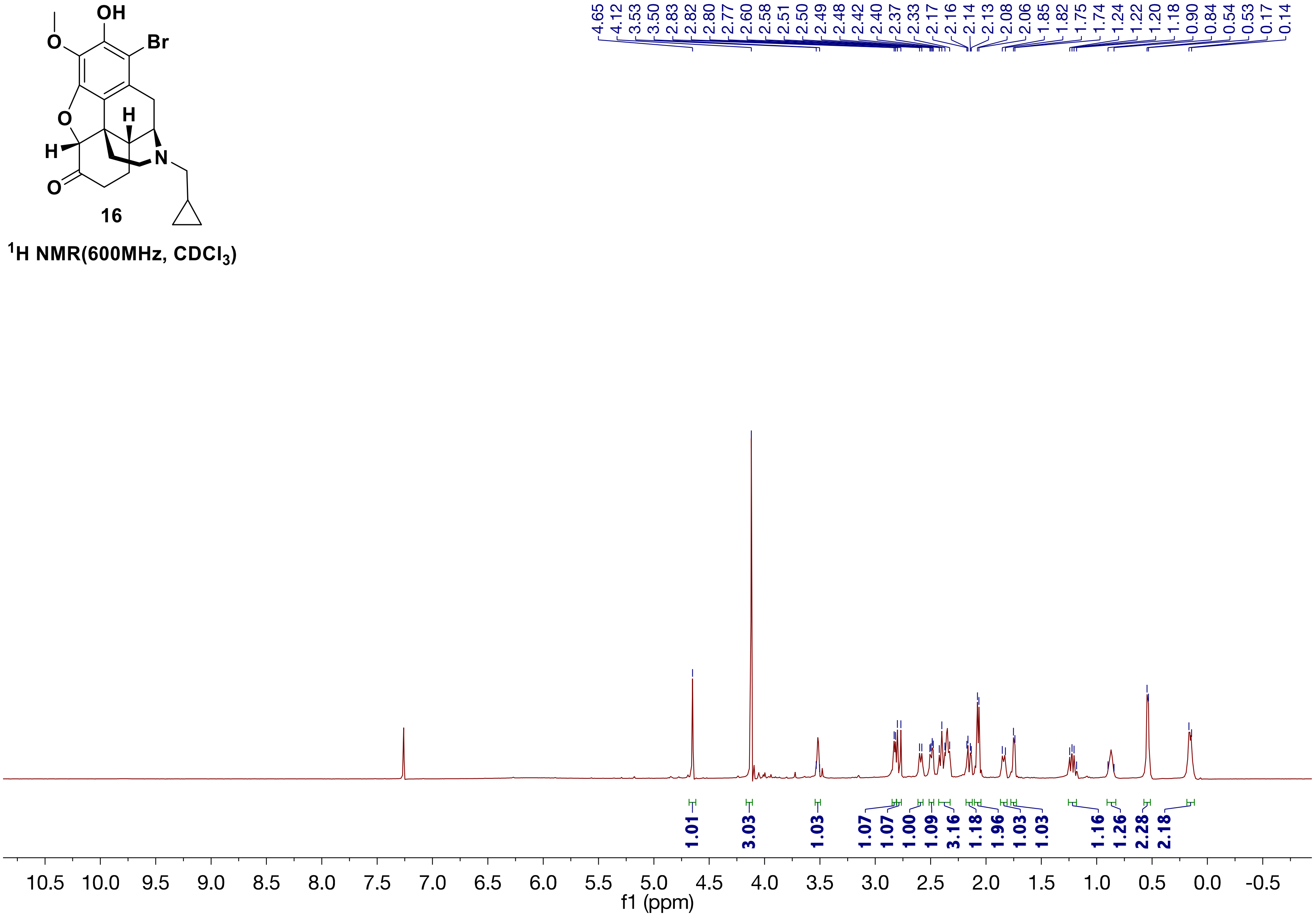


15

^{1}H NMR(500MHz, CDCl$_3$)

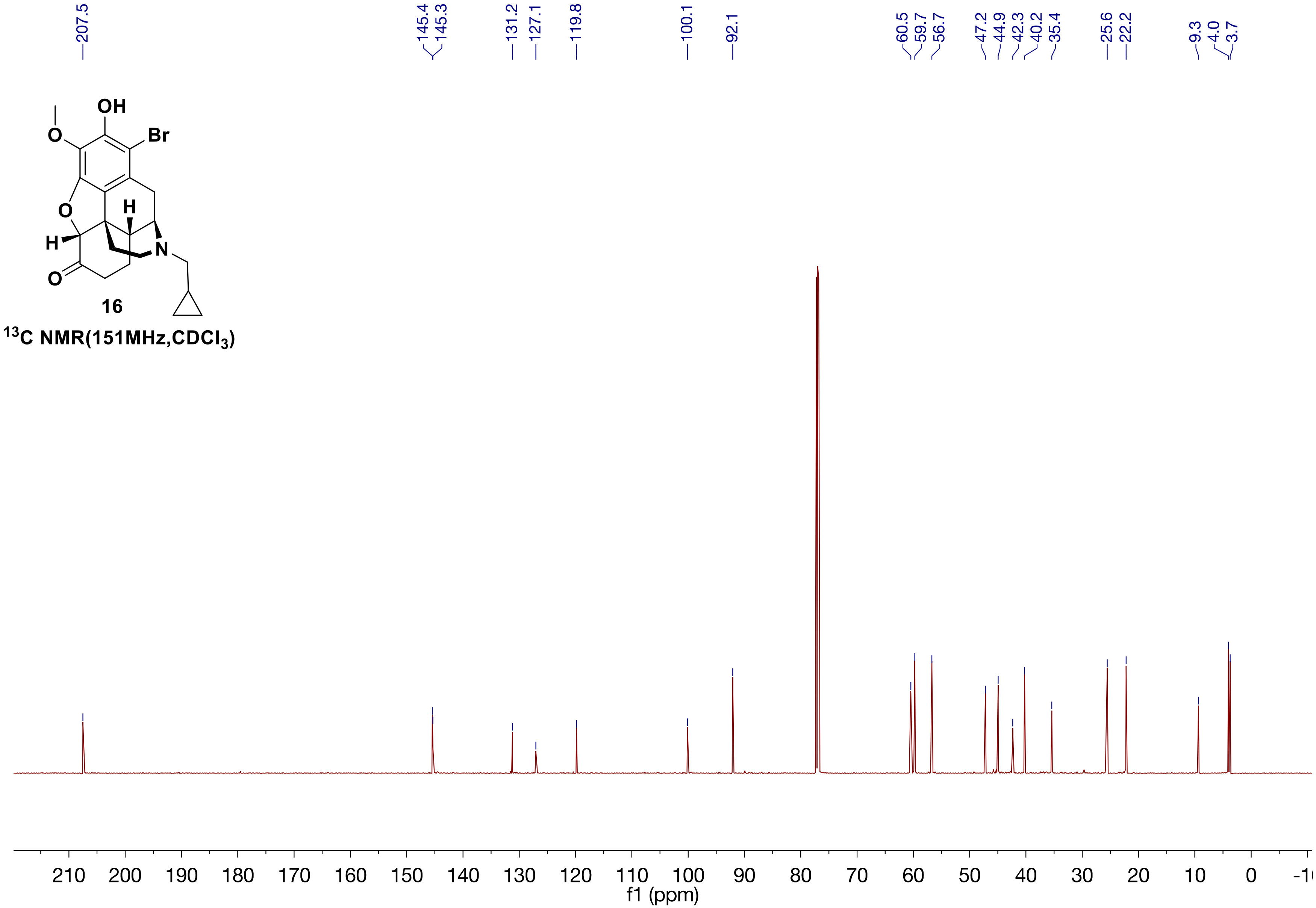



211.4
148.6
147.1
133.7
115.6
107.1
61.4
59.7
55.1
50.6
45.2
44.2
41.4
41.2
38.1
27.3
24.9
8.8
4.4
4.1
OH
O
HO
N
O
15
^{13}C NMR(126MHz,CDCl$_3$)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



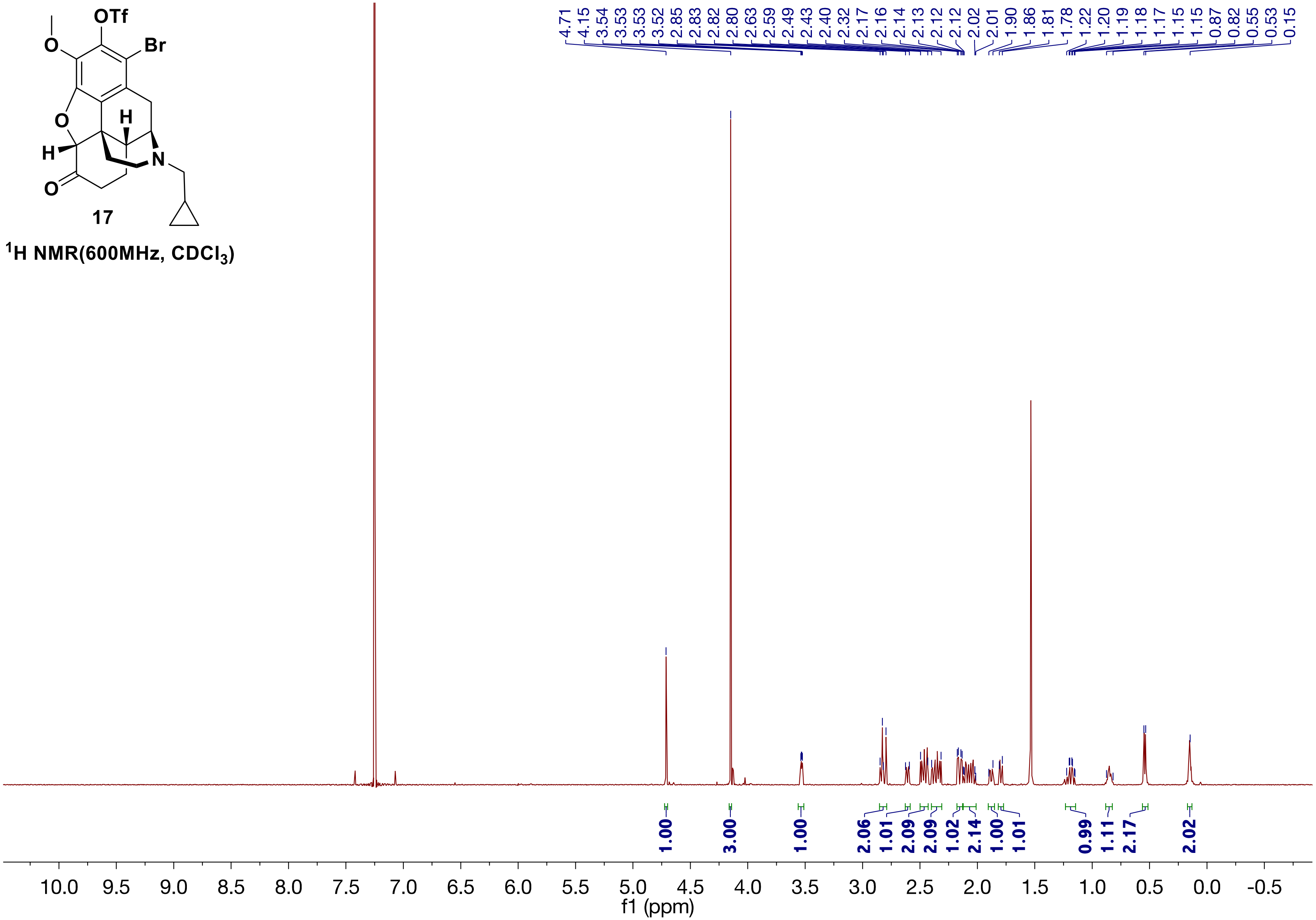
16

^{1}H NMR(600MHz, CDCl$_3$)



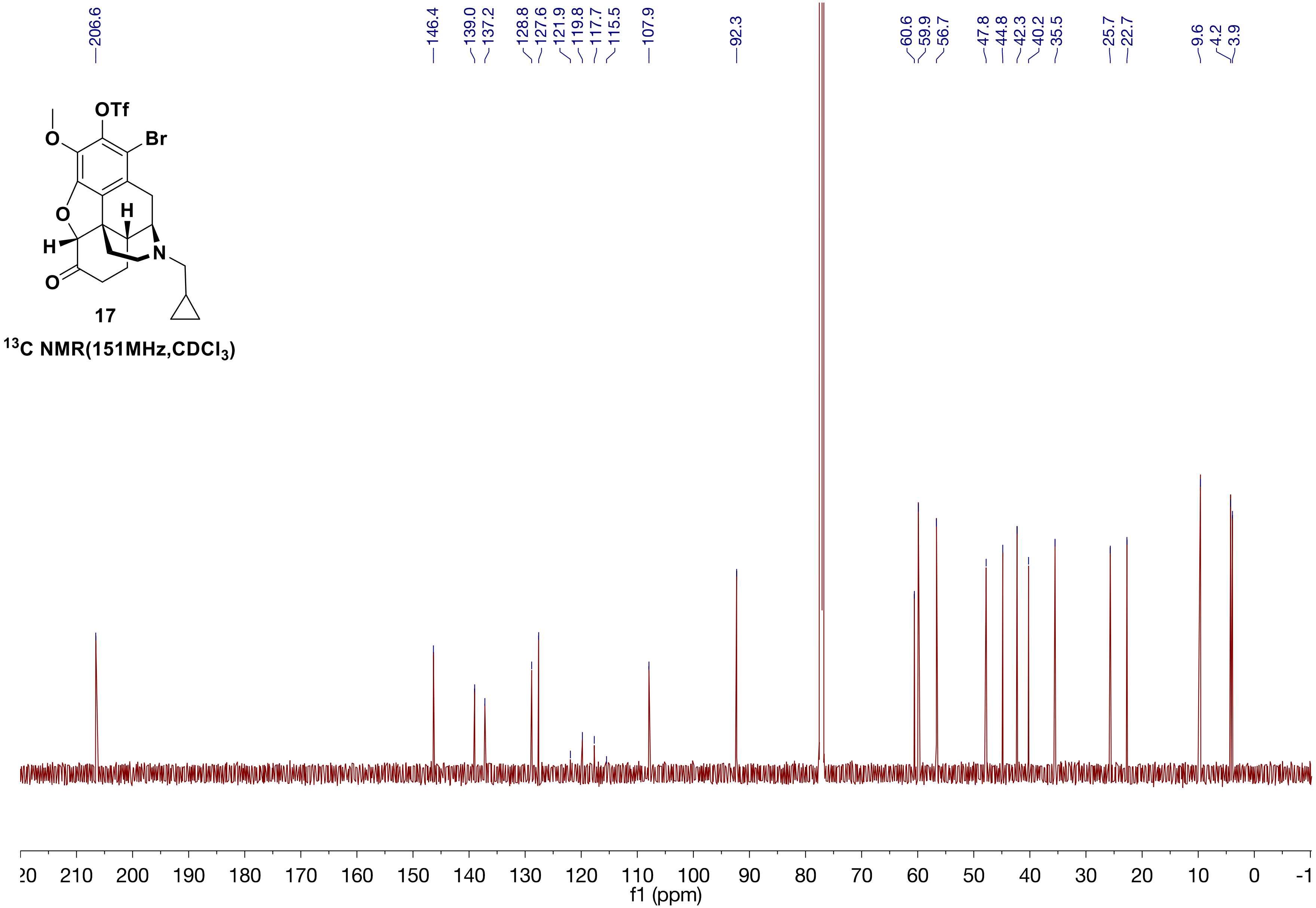
16

^{13}C NMR(151MHz,CDCl$_3$)



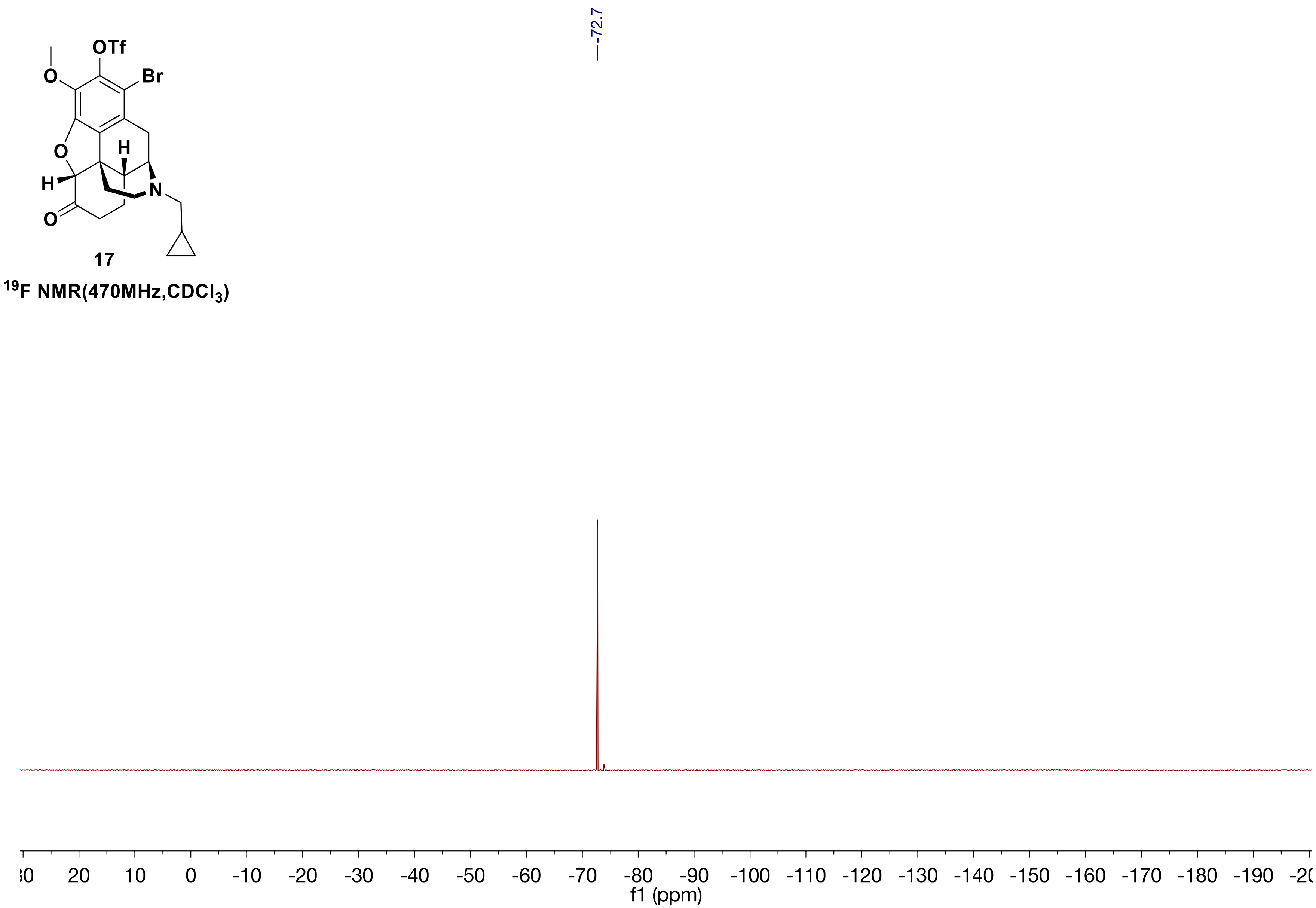
17

^{1}H NMR(600MHz, CDCl$_3$)



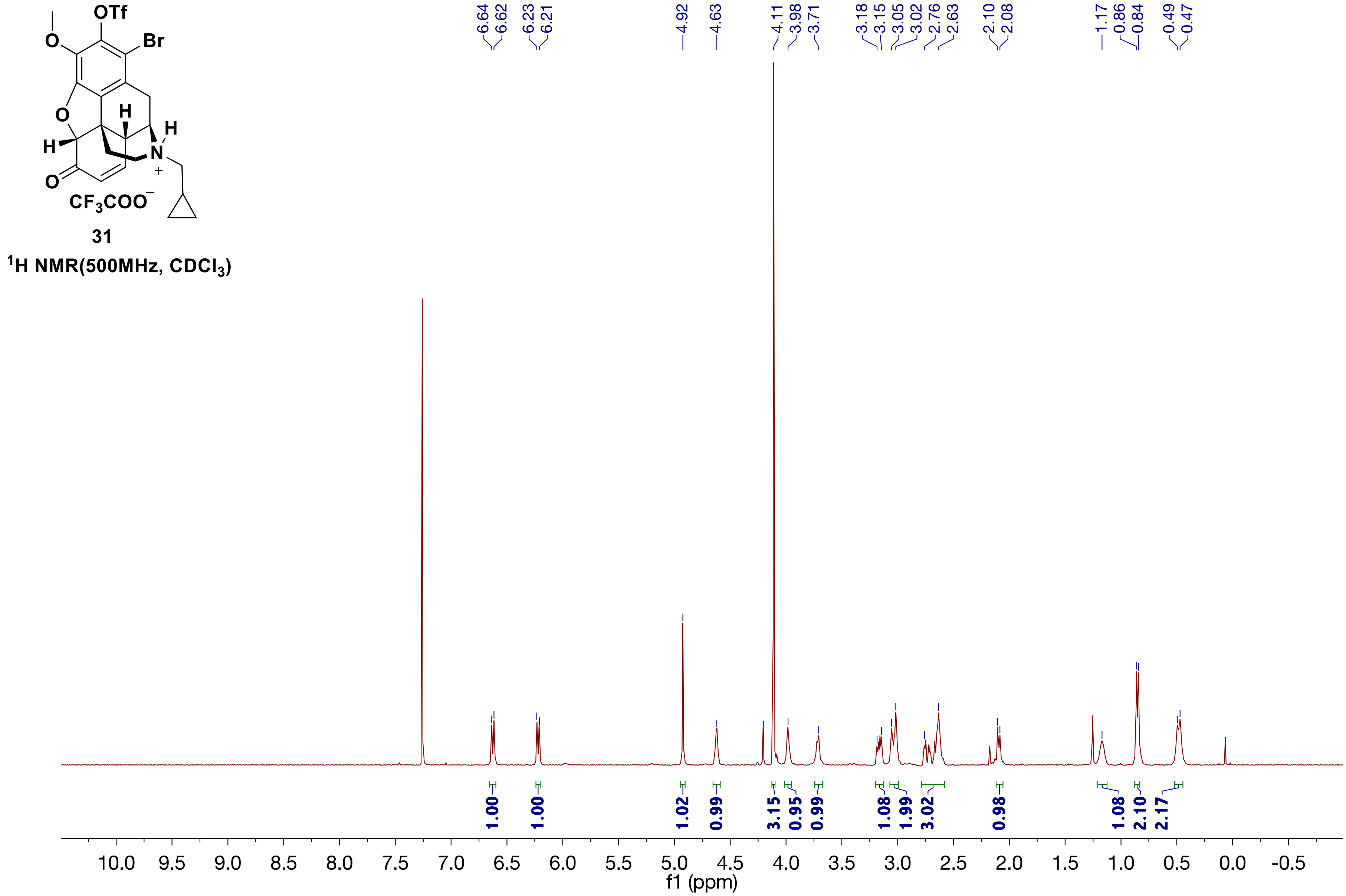
17

^{13}C NMR(151MHz,$CDCl_3$)



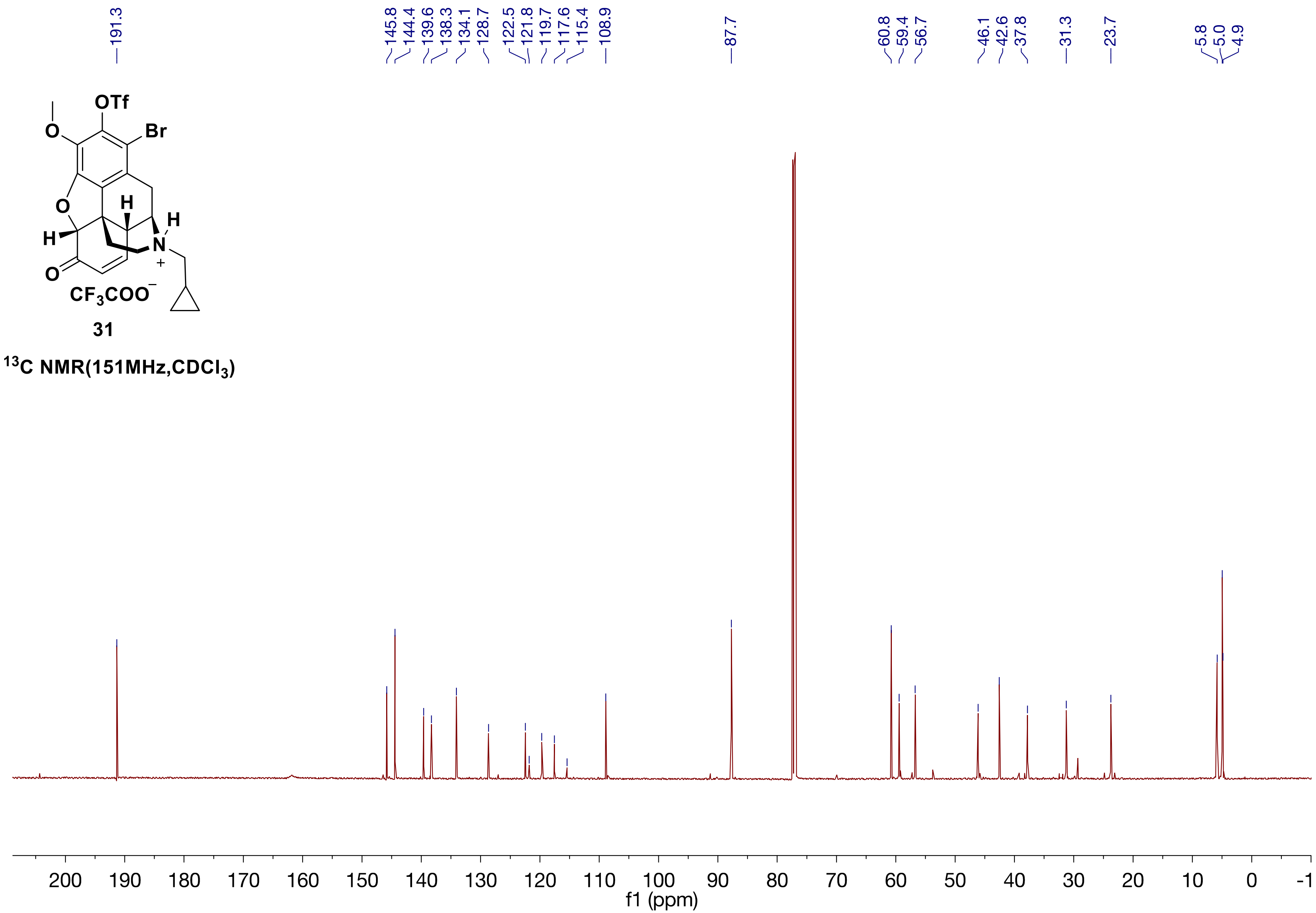
17

^{19}F NMR(470MHz,CDCl$_3$)



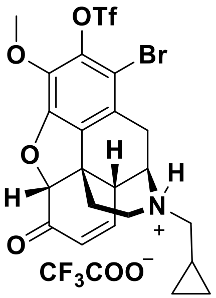
31

^{1}H NMR(500MHz, CDCl$_3$)



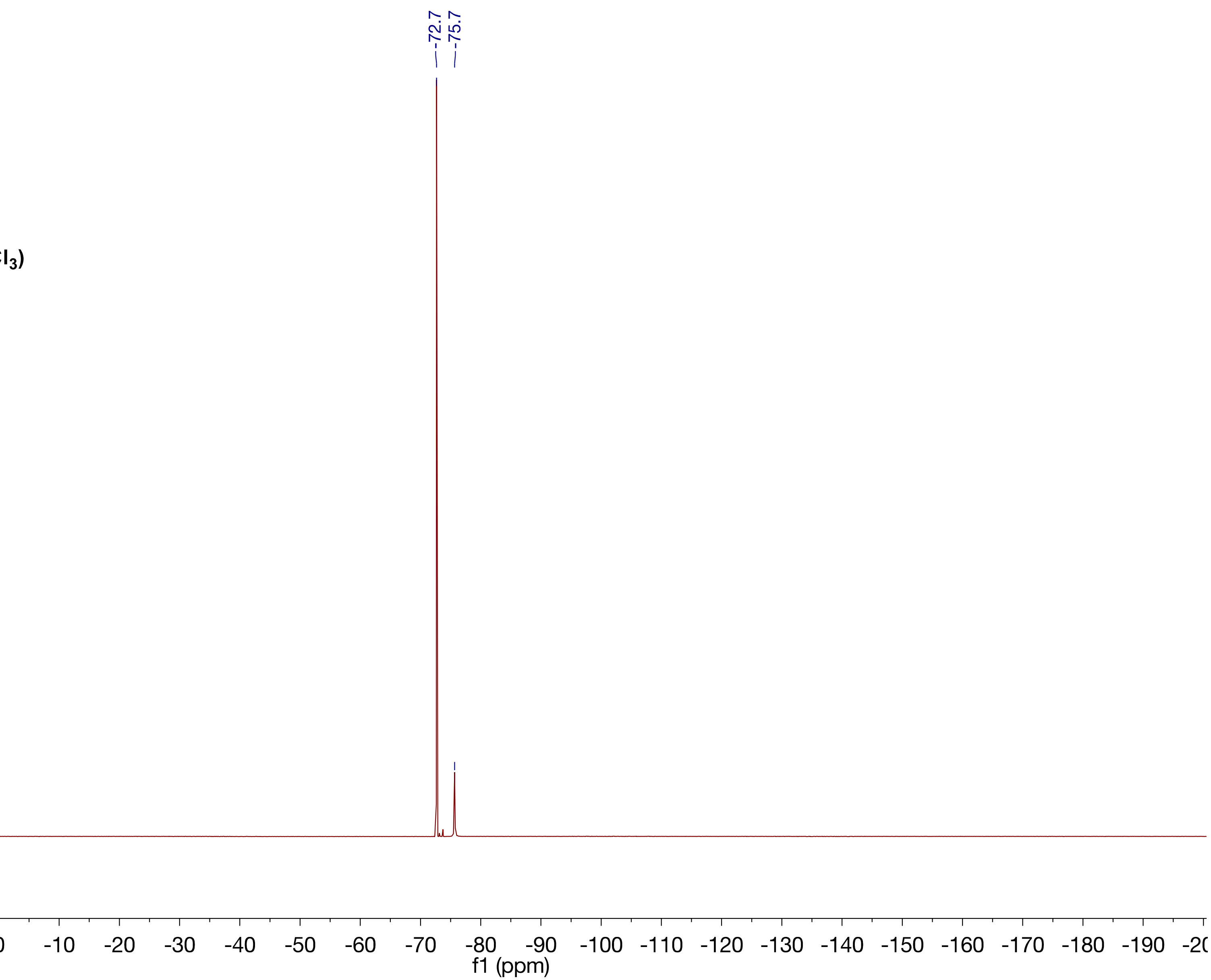
31

^{13}C NMR(151MHz,$CDCl_3$)



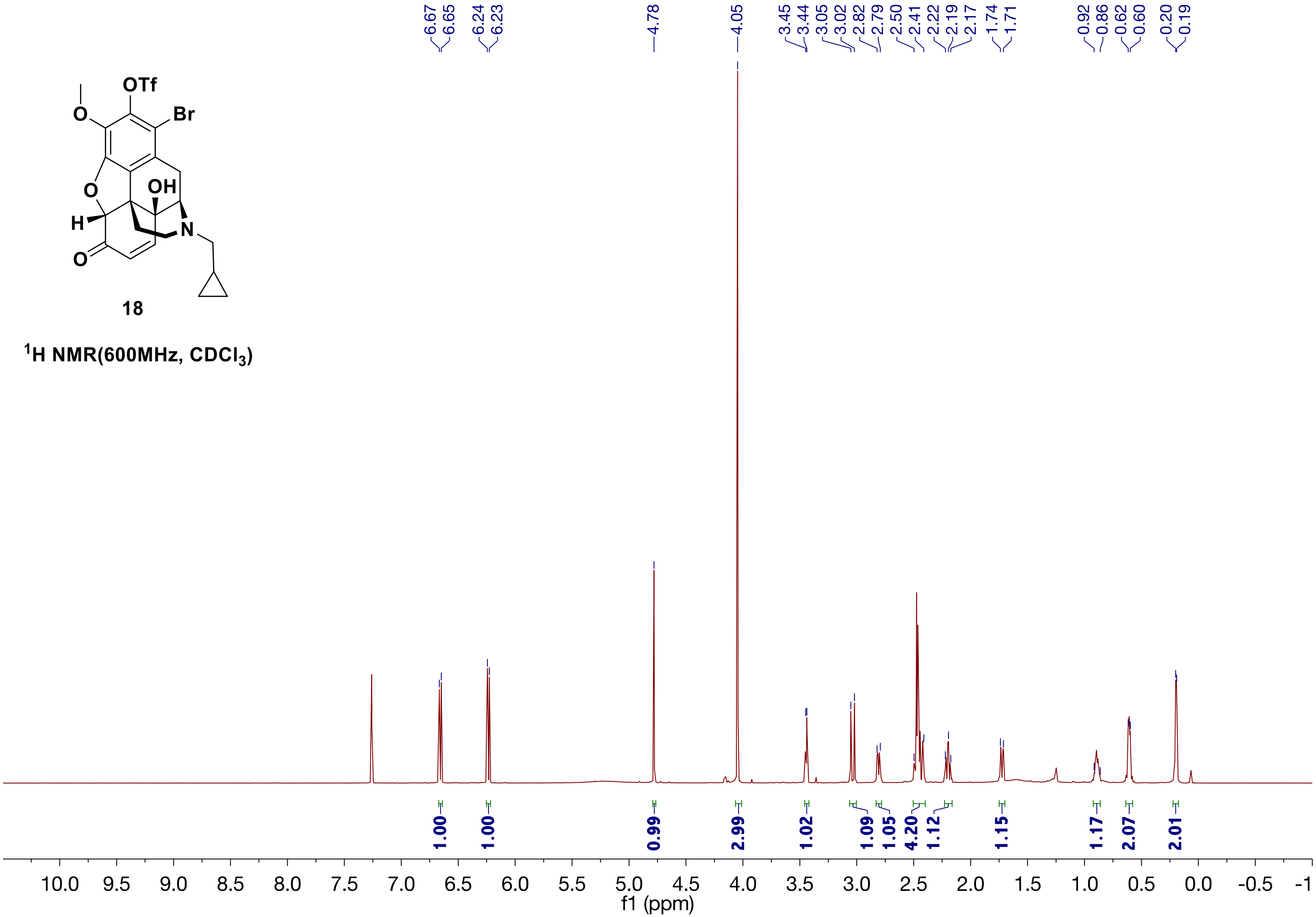
31

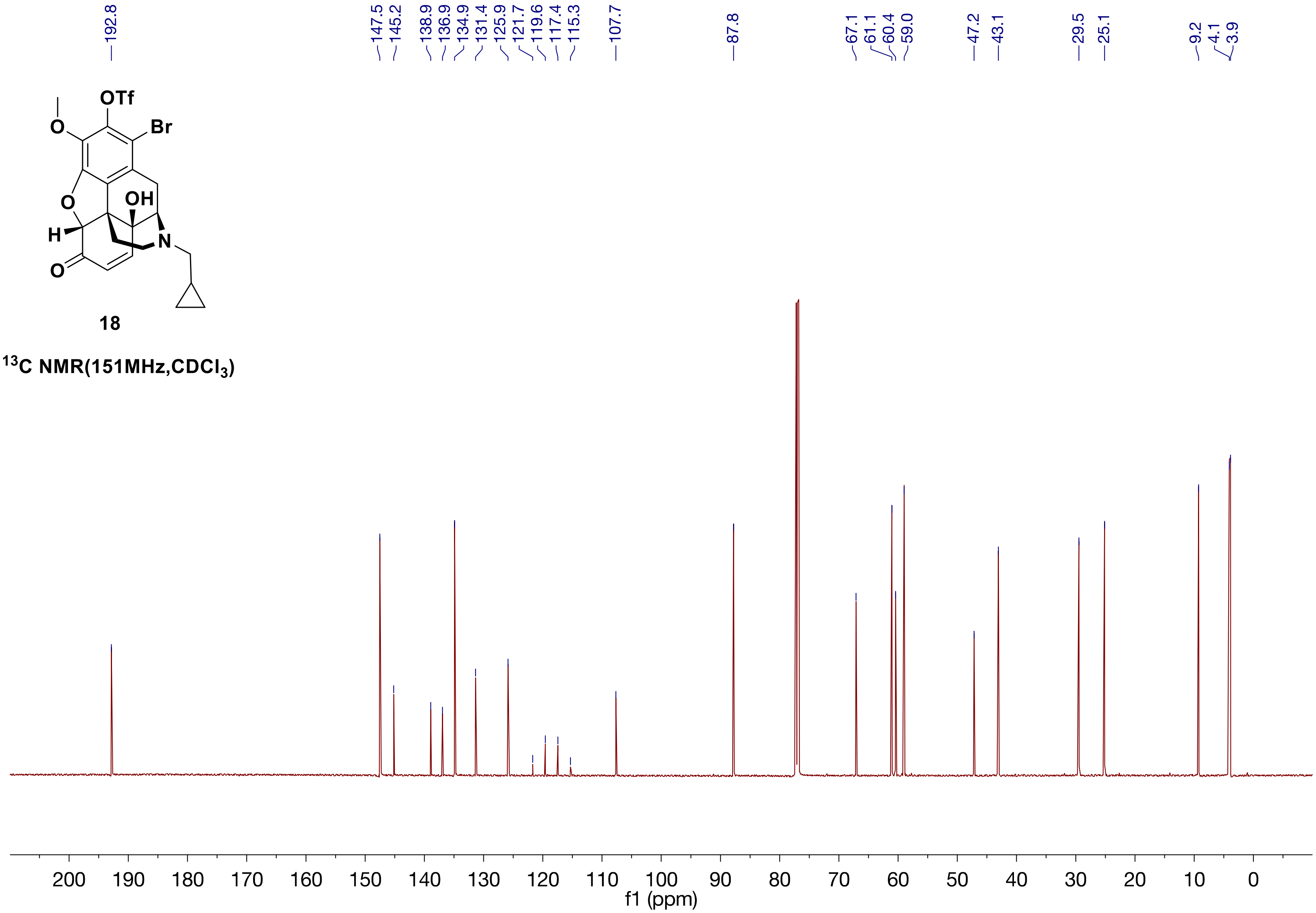
^{19}F NMR(470MHz,$CDCl_3$)



18

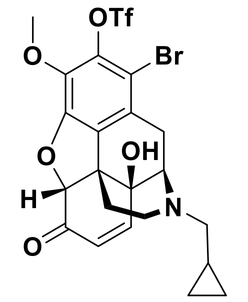
^{1}H NMR(600MHz, $CDCl_3$)





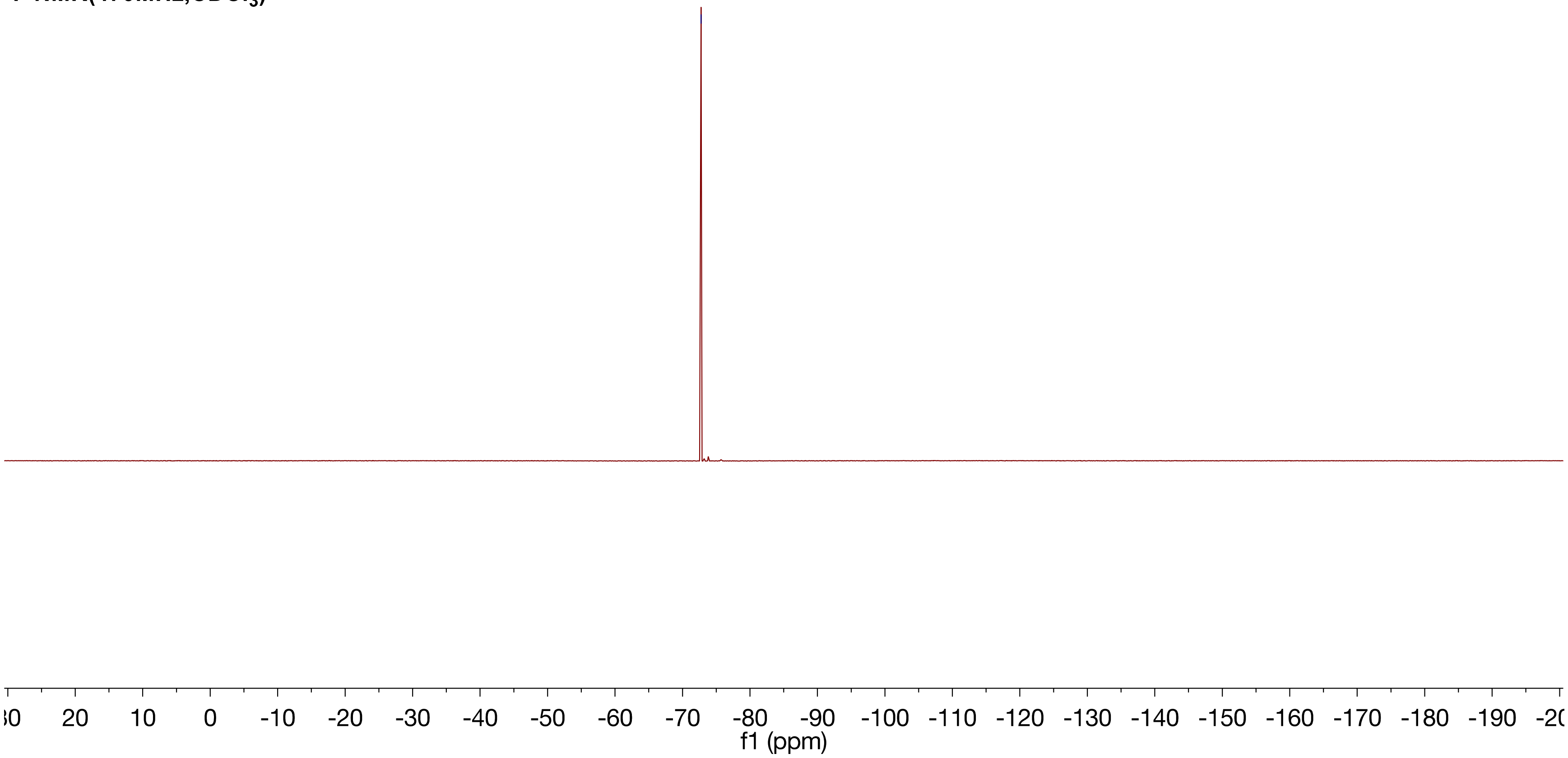
18

^{13}C NMR(151MHz,CDCl$_3$)

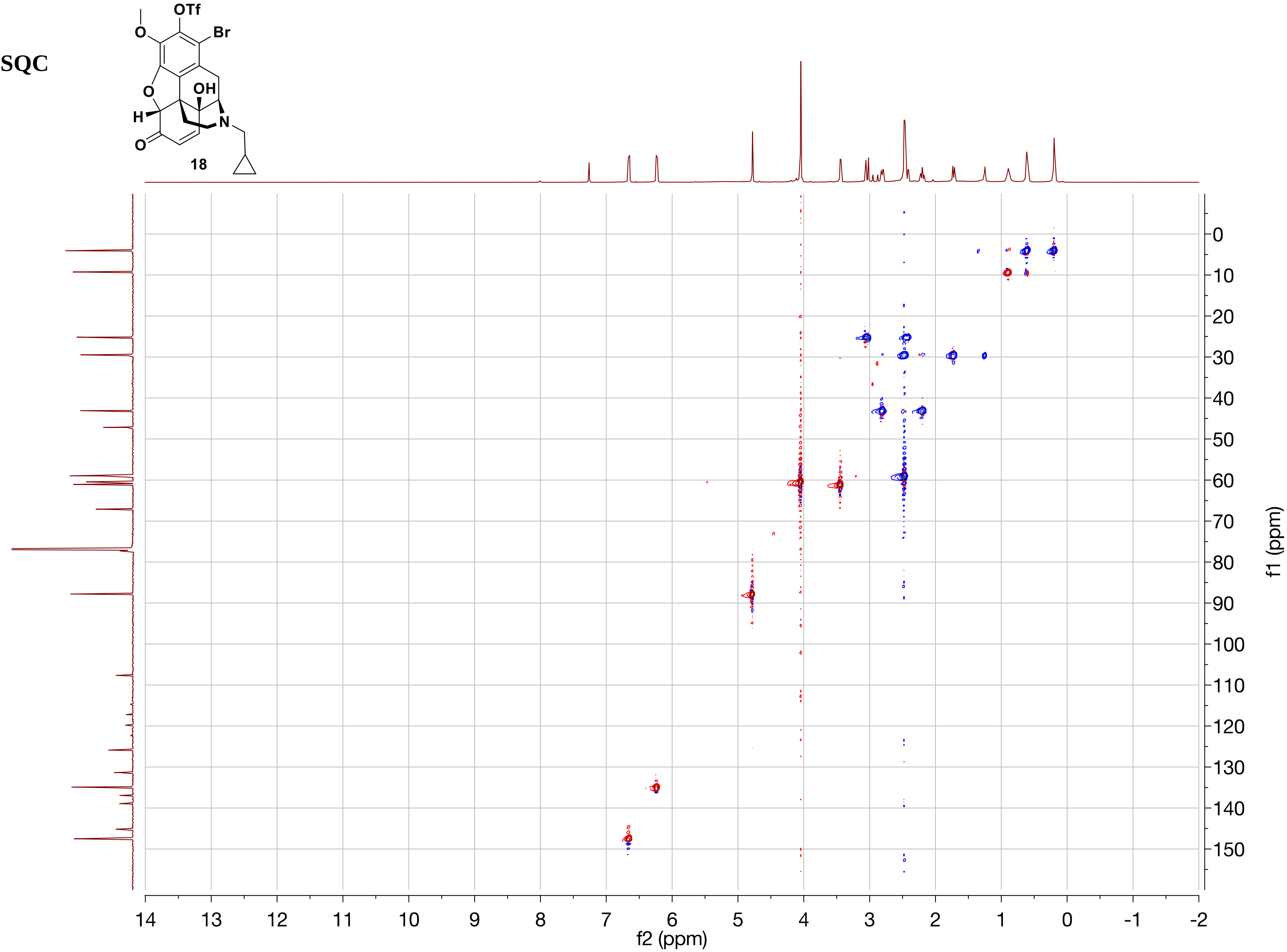


18

^{19}F NMR(470MHz,CDCl$_3$)

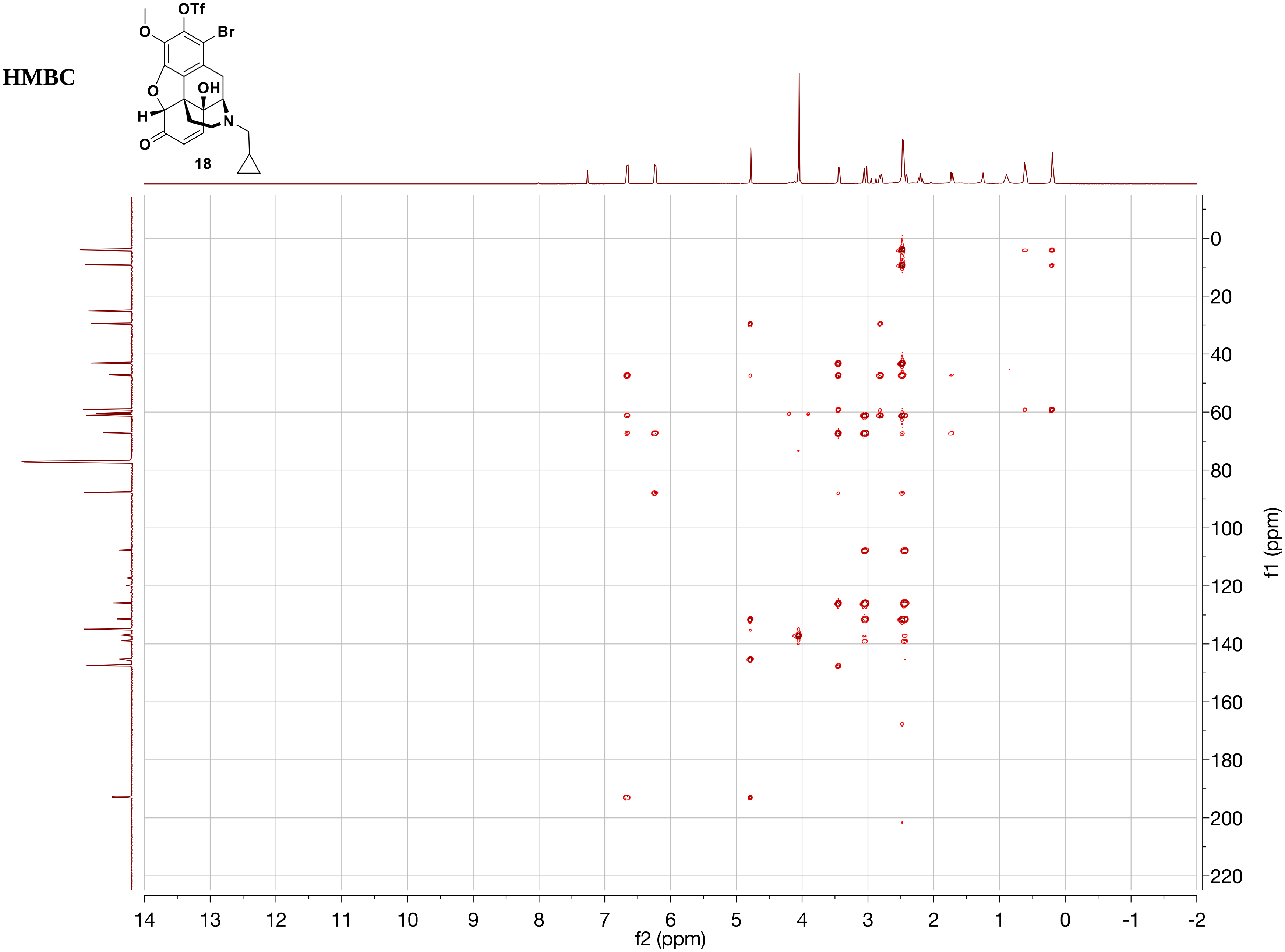


HSQC


OTf
O
Br
O
OH
H
N
O
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f2 (ppm)

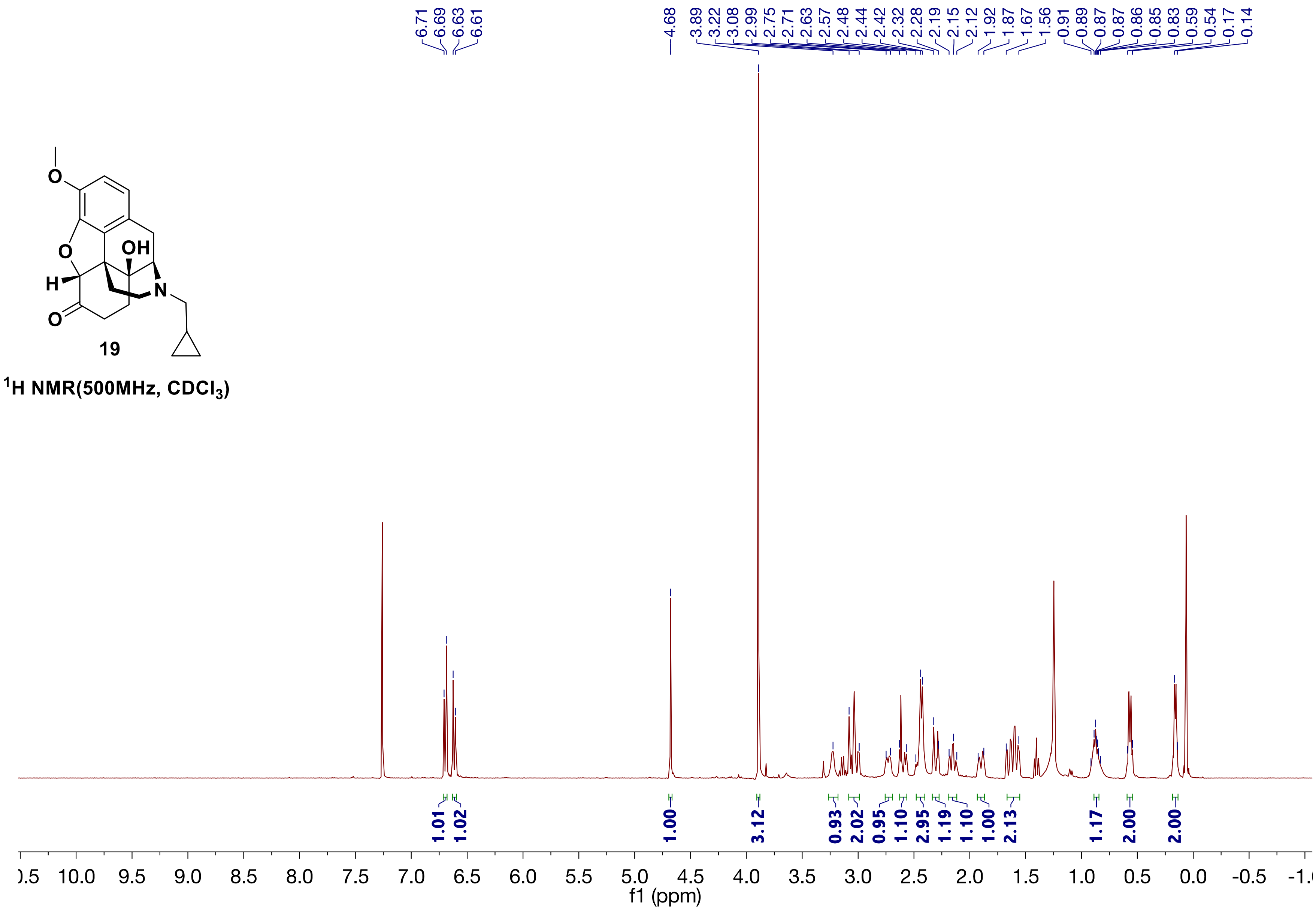
18

HMBC


OTf
O
Br
O
OH
H
N
O

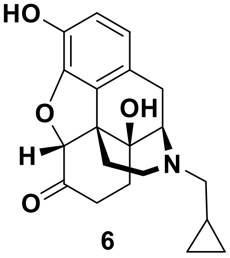
18

14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f2 (ppm)
0
20
40
60
80
100
120
140
160
180
200
220
f1 (ppm)



19

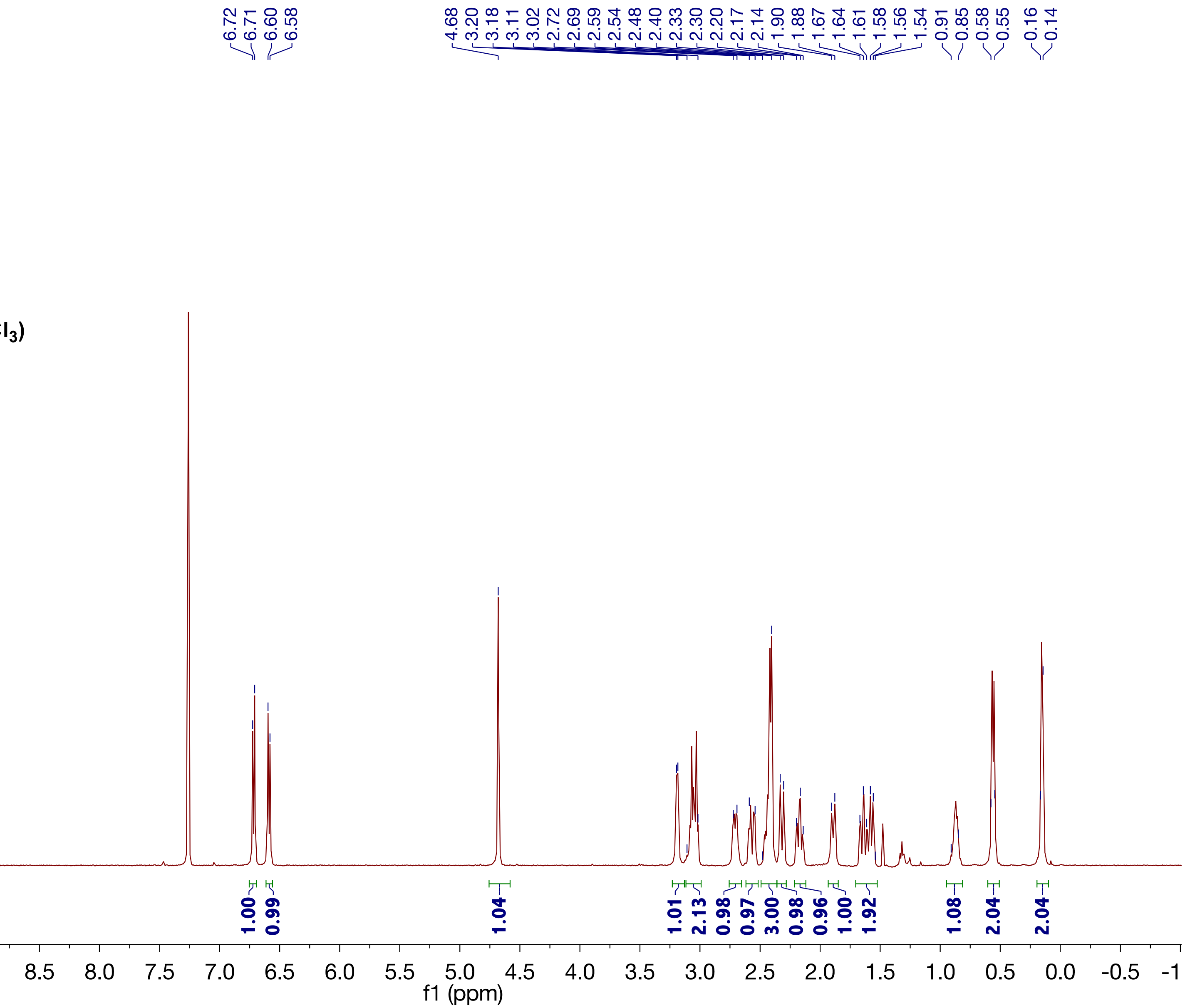
^{1}H NMR(500MHz, $CDCl_3$)

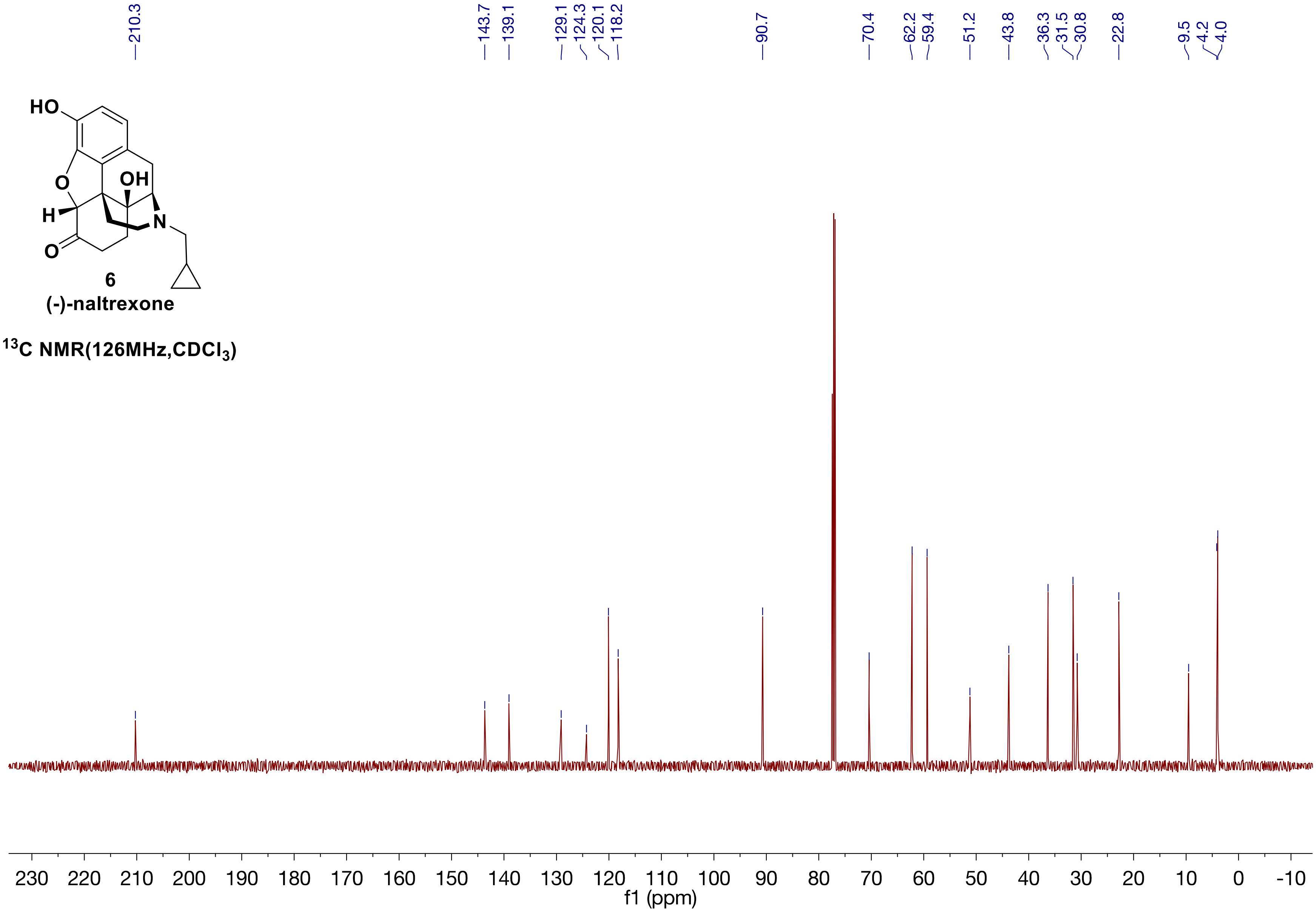


6

(-)-naltrexone

^{1}H NMR(500MHz, CDCl$_3$)



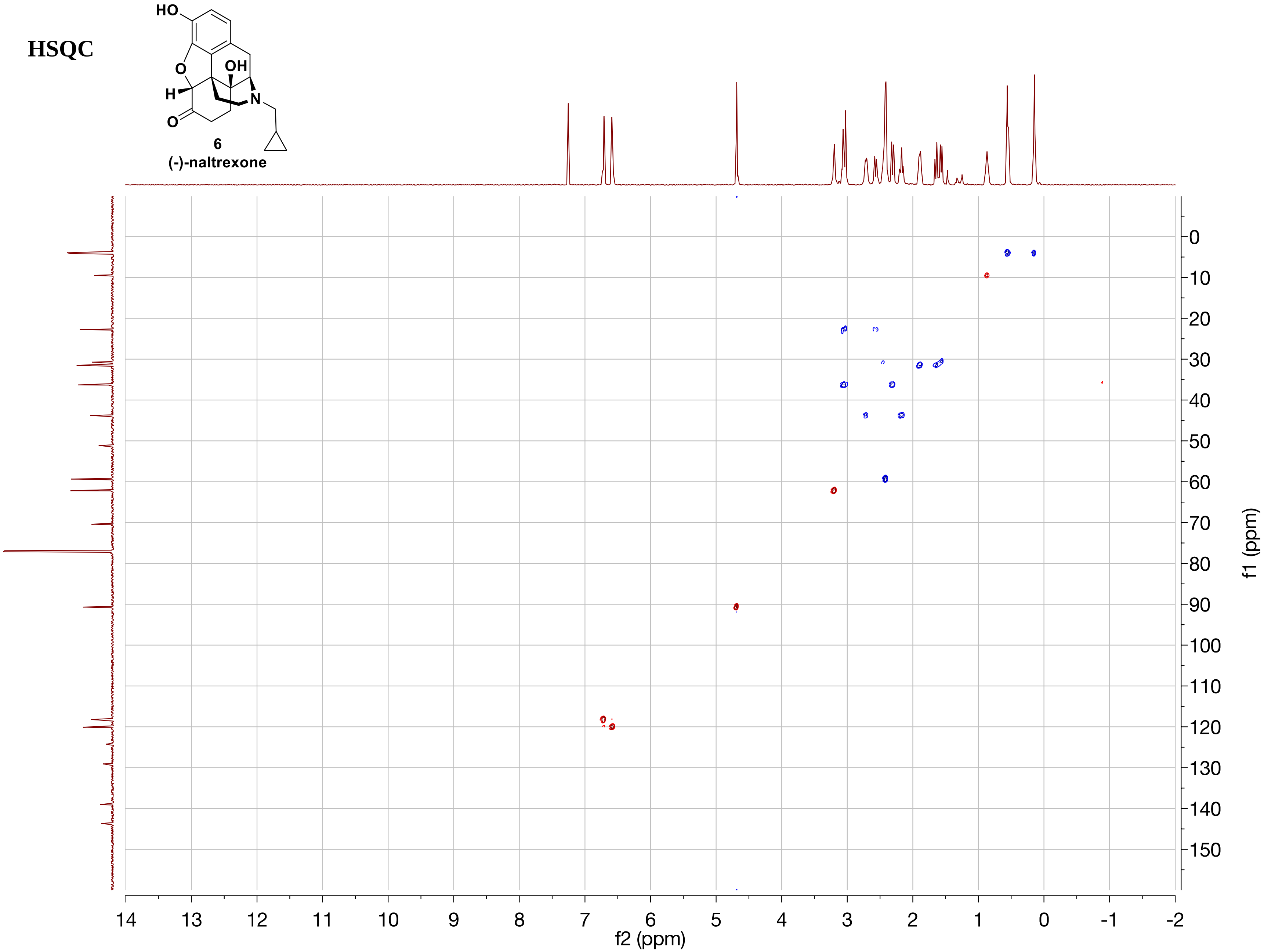


6

(-)-naltrexone

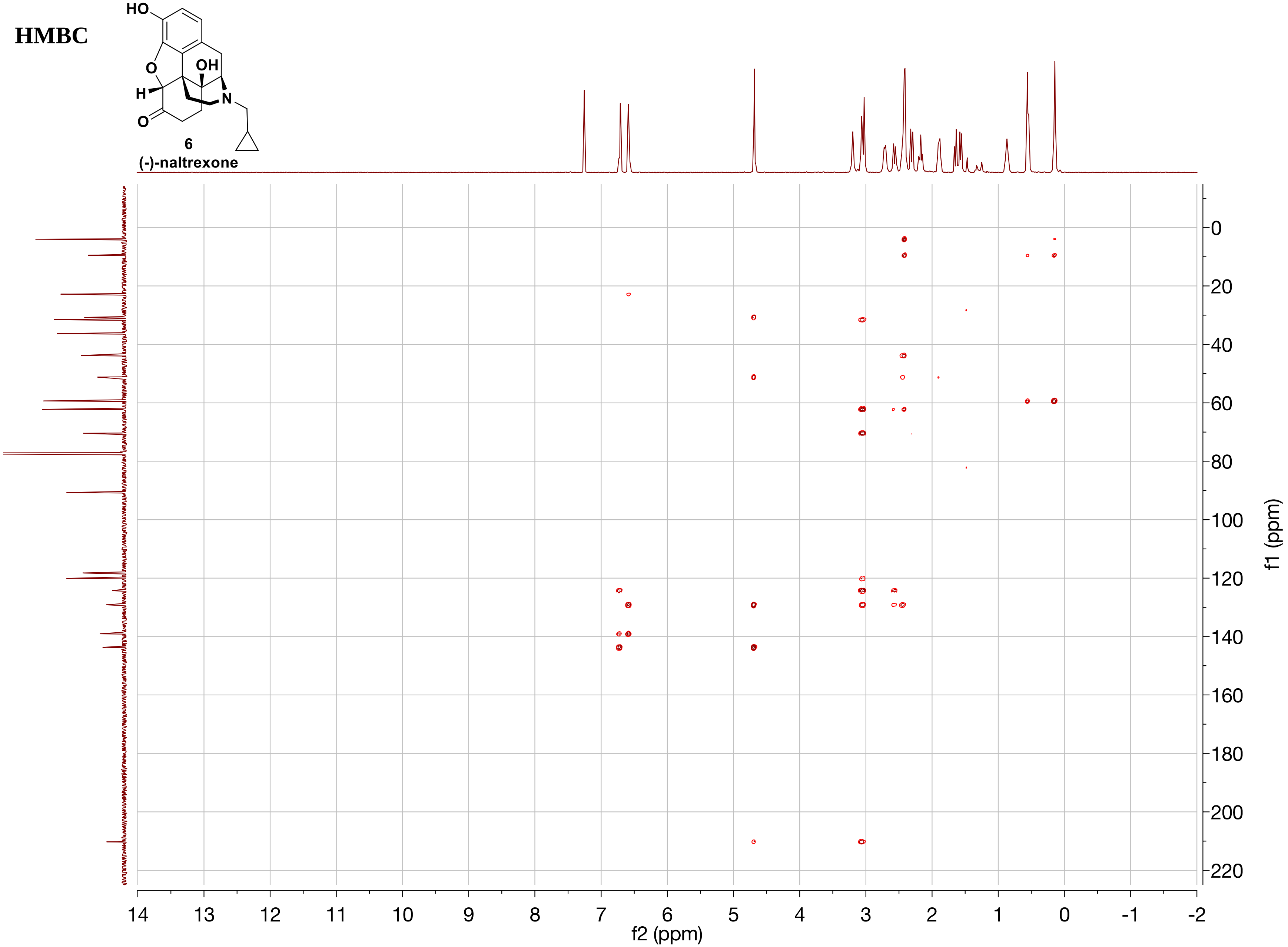
^{13}C NMR(126MHz,CDCl$_3$)

HSQC



6
(-)-naltrexone

HMBC


6
(-)-naltrexone