Supporting Information

Enantioselective Total Synthesis of (+)-Cylindricine B

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Table of Contents

1. General Methods

All reactions were performed using flame-dried round-bottomed flasks or reaction vessels unless otherwise stated. Reactions were carried out under an inert atmosphere of nitrogen with dry solvents, unless otherwise stated. Dry toluene ($PhCH_3$), dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), dimethylformamide (DMF), benzene (PhH), and tetrahydrofuran (THF) were obtained by passing the previously degassed solvents through activated alumina columns. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography carried out on Sorbtech silica gel plates (glass-backed, 60G, F-254). TLC plates were visualized using ultraviolet light and an appropriate developing agent. NMR spectra were recorded on a Bruker Avance III 400, 600, or 700 MHz NMR spectrometers and were calibrated using residual solvent as an internal reference ($CDCl_3$: ^1H NMR δ = 7.26, ^{13}C NMR δ = 77.16; C_6D_6: ^1H δ = 7.16, ^{13}C NMR δ = 128.06). The following abbreviations or combinations thereof were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Flash column chromatography was performed using Sorbtech silica gel (premium Rf grade, 60A, 40-75μM). High-resolution mass spectra (HRMS) were recorded on an Agilent 6230 TOF-MS spectrometer (ESI). Optical rotations were recorded on a Rudolph Research Analytical Autopolv V polarimeter. Determination of enantiopurity was carried out on a Jasco SFC (supercritical fluid chromatography) using a Daicel ChiralPak IA column. Data for SFC spectra is reported in enantiomeric excess (*ee*).

2. Experimental Procedures and Characterization of Substrates

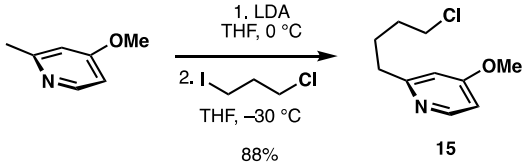
a. General Procedure for the Preparation of Grignard reagents

General Procedure A for the preparation of Grignard reagents

LiCl (0.210 g, 5 mmol, 1 equiv.) was added to a flask and flame dried under reduced pressure. Once cooled, Mg turnings (0.194 g, 8 mmol, 1.6 equiv.), I_2 (single crystal, catalytic amount), and THF (1 mL) were added. 1 mL of a solution of halide in THF (4 mL) was added and the contents stirred until the disappearance of color (gentle heating may be required). The remaining halide solution was added, and the reaction allowed to stir for 2 h. The resulting Grignard was titrated with I_2.

b. Initial approach to cylindricine scaffold

Pyridine 15



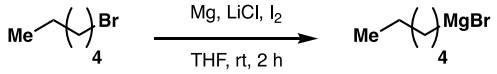
Pyridine **15** is commercially available or can be prepared by the following procedure: To a stirred solution of lithium diisopropylamide, prepared from diisopropylamine (0.7 mL, 4.9 mmol, 1.2 equiv) and n-BuLi (2.3 M in hexanes, 1.9 mL, 4.5 mmol, 1.1 equiv), in THF (13.5 mL, 0.3 M) at 0 °C was added 4-methoxy-2-methylpyridine (0.500 g, 4.1 mmol, 1 equiv) and the solution was allowed to stir for 1 h at 0 °C. The solution was then cooled to –30 °C with an acetonitrile/dry ice bath, and 1-chloro-3-iodopropane (0.53 mL, 4.9 mmol, 1.2 equiv) was added dropwise. The reaction was allowed to stir for 6 h or until the consumption of starting material was observed, as determined by TLC. The reaction was quenched with the addition of water and warmed to room temperature. The product was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (25 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (70% EtOAc/Hexanes) to afford 1.44 g (88% yield) of pyridine **15**.

Physical State: Light yellow oil, light yellow solid below room temperature

R_f: 0.33 (80% EtOAc/Hexanes)

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.33 (d, J = 5.7 Hz, 1H), 6.68 – 6.62 (m, 2H), 3.83 (s, 3H), 3.55 (t, J = 6.4 Hz, 2H), 2.76 (t, J = 7.4 Hz, 2H), 1.93 – 1.74 (m, 4H).

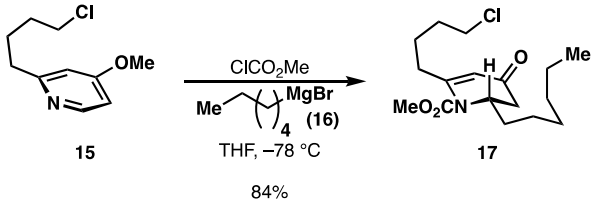
n-hexylmagnesium bromide 16



Prepared by General Procedure A

LiCl (0.210 g, 5 mmol, 1 equiv.) was added to a flask and flame dried under reduced pressure. Once cooled, Mg turnings (0.194 g, 8 mmol, 1.6 equiv.), I_2 (single crystal, catalytic amount), and THF (1 mL) were added. 1 mL of a solution of 1-bromohexane in THF (4 mL) was added and the contents stirred until the disappearance of color. The remaining solution was added, and the reaction allowed to stir for 2 h. The grignard was titrated with I_2 (0.6 M to 0.7 M) and used for the dearomatization of substituted pyridines.

Piperidenone 17



A modified procedure from Harutyunan was employed.[1]

To a flame dried 25 mL round bottom flask was added pyridine **15** (1.17 g, 5.86 mmol, 1 equiv) and THF (20 mL, 0.3 M). Methyl chloroformate (1.4 mL, 17.6 mmol, 3 equiv.) was added dropwise and the solution was stirred for 0.5 h at room temperature. The reaction mixture was then cooled to –78 °C and *n*-hexylmagnesium bromide **16** (25 mL, 0.717 M,

3 equiv.) was added dropwise. The solution was allowed to warm to room temperature overnight. After 16 h, the reaction was quenched with 1M HCl (5 mL) and stirred for 0.25 h. The mixture was then neutralized with the addition of sat. aqueous $NaHCO_3$, and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (25 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (20% EtOAc/Hexanes) to afford 1.62 g (84% yield) of piperidenone **17**.

Physical State: Light orange oil

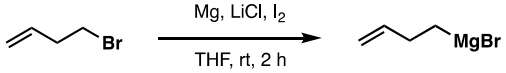
R_f: 0.33 (20% EtOAc/Hexanes)

^{1}H NMR (700 MHz, $CDCl_3$) δ 5.42 (s, 1H), 4.75 – 4.66 (m, 1H), 3.83 (s, 3H), 3.54 (td, J = 6.6, 1.3 Hz, 2H), 3.07 (ddd, J = 14.8, 9.2, 5.8 Hz, 1H), 2.78 (dd, J = 17.0, 6.0 Hz, 1H), 2.43 – 2.26 (m, 2H), 1.81 (tt, J = 8.1, 4.1 Hz, 2H), 1.72 (ddq, J = 13.5, 10.0, 5.0 Hz, 1H), 1.66 – 1.59 (m, 2H), 1.55 – 1.48 (m, 1H), 1.38 – 1.18 (m, 8H), 0.87 (t, J = 7.1 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 193.8, 157.8, 154.1, 112.9, 56.5, 53.8, 44.5, 41.3, 35.2, 32.2, 31.8, 30.4, 29.1, 26.3, 25.5, 22.7, 14.2.

HRMS (ESI) m/z: $[M+H]^+$ calc'd for $C_{17}H_{29}ClNO_3^+$ 330.1830; found 330.1835

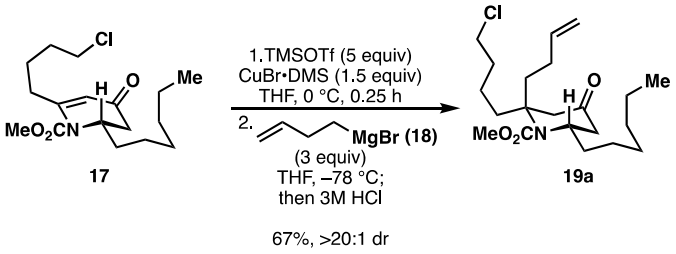
Butenylmagnesium bromide 18



Prepared by General Procedure A

LiCl (0.210 g, 5 mmol, 1 equiv.) was added to a flask and flame dried under reduced pressure. Once cooled, Mg turnings (0.194 g, 8 mmol, 1.6 equiv.), I_2 (single crystal, catalytic amount), and THF (1 mL) were added. 1 mL of a solution of 4-bromo-1-butene in THF (4 mL) was added and the contents stirred until the disappearance of color. The remaining solution was added, and the reaction allowed to stir for 2 h. The grignard was titrated with I_2 (0.6 M to 0.8 M).

Chloropiperdinone 19a



To a flame dried 25 mL round bottom flask was added CuBr·DMS (0.93 g, 4.5 mmol, 1.5 equiv.) followed by piperdenone **17** (1.0 g, 3.0 mmol, 1 equiv.) and THF (15 mL, 0.2 M). The reaction mixture was cooled to 0 °C and TMSOTf (2.7 mL, 15 mmol, 5 equiv.) was added dropwise. The resultant solution was stirred for 0.25 h at 0 °C then cooled to –78 °C. Butenylmagnesium bromide **18** (12 mL, 0.75 M, 3 equiv.), prepared by General Procedure A, was added to the reaction flask via a syringe pump over one hour. Once the syringe pump addition is complete, the reaction was allowed to stir at –78 °C until the consumption of starting material was observed, as determined by TLC. The reaction was quenched with a 1:1 solution of sat. aqueous NH_4Cl and aqueous NH_4OH (15 mL) and warmed to room temperature. The product was extracted with EtOAc (3 x 50 mL) and the combined organic layer stirred with 1 M HCl for 0.25 h. After 0.25 h, the solution was neutralized with the addition of K_2CO_3. The layers were separated and the organic layer washed with water (50 mL), brine (50 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (10% EtOAc/Hexanes) to afford 0.78 g (67% yield) of chloropiperidinone **19a**.

Physical State: Light yellow oil

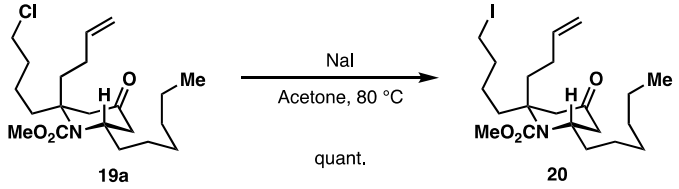
R_f: 0.5 (20% EtOAc/Hexanes)

^{1}H NMR (700 MHz, $CDCl_3$) δ 5.73 – 5.64 (m, 1H), 4.96 (d, J = 17.1 Hz, 1H), 4.91 (d, J = 10.1 Hz, 1H), 4.43 (s, 1H), 3.69 (s, 3H), 3.56 – 3.49 (m, 2H), 2.85 (d, J = 17.3 Hz, 1H), 2.63 (dd, 1H), 2.47 (d, 1H), 2.44 – 2.34 (m, 2H), 2.11 (s, 1H), 1.97 – 1.88 (m, 2H), 1.79 – 1.68 (m, 4H), 1.46 – 1.35 (m, 2H), 1.34 – 1.17 (m, 10H), 0.86 (t, J = 7.0 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 208.7, 137.7, 115.2, 61.2, 52.5, 52.2, 46.9, 44.9, 41.6, 39.4, 37.6, 37.5, 32.5, 31.8, 29.1, 29.0, 27.1, 22.7, 21.5, 14.2.

HRMS (ESI) m/z: $[M+Na]^+$ calc'd for $C_{21}H_{36}ClNO_3Na^+$ 408.2276; found 408.2300.

Iodopiperdinone 20



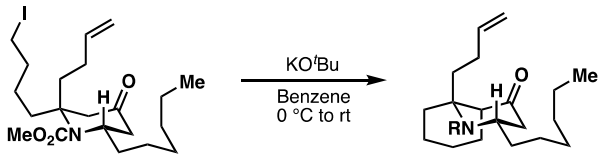
To a sealed tube was added chloropiperidinone **19a** (0.320 g, 0.83 mmol, 1 equiv.), sodium iodide (1.2 g, 8.3 mmol, 10 equiv.), and acetone (3 mL, 0.3 M). The reaction flask was heated to 80 °C and stirred for 16 h or until consumption of starting material was observed, as determined by ^{1}H NMR. The reaction was cooled to room temperature then poured into water. The product was extracted with EtOAc (3 x 10 mL) and the combined organic layer washed with brine (15 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was used without any further purification.

Physical State: Light orange oil

R_f: 0.5 (20% EtOAc/Hexanes)

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.70 (ddt, J = 16.7, 10.1, 6.5 Hz, 1H), 4.98 (dd, J = 17.1, 1.5 Hz, 1H), 4.93 (d, J = 10.1 Hz, 1H), 4.44 (s, 1H), 3.71 (s, 3H), 3.21 (tq, J = 6.3, 2.9 Hz, 2H), 2.87 (d, J = 17.2 Hz, 1H), 2.69 – 2.61 (m, 1H), 2.53 – 2.44 (m, 1H), 2.39 (d, J = 17.3 Hz, 2H), 2.12 (s, 1H), 1.94 (dt, J = 10.6, 5.2 Hz, 2H), 1.86 – 1.70 (m, 4H), 1.44 (dt, J = 13.6, 8.1 Hz, 1H), 1.33 – 1.22 (m, 11H), 0.88 (t, J = 6.9 Hz, 3H).

Azadecalinone 21a



20 65% **21a** (R = CO_2Me)

A modified procedure from Padwa was employed.[2]

To a 50 mL round bottom flask was added iodopiperdinone **20** (0.200 g, 0.42 mmol, 1 equiv.) and benzene (21 mL, 0.02 M). The solution was cooled to 0 °C and a 0.5 M solution of *t*BuOK (0.188 g, 1.68 mmol, 4 equiv.) in THF (3 mL) was added via syringe pump over one hour. After the addition was completed, the reaction solution was allowed to warm to room temperature and stirred until consumption of starting material was observed, as determined by TLC. The reaction was quenched with 0.1 M HCl (10 mL) and the product extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with water (25 mL), brine (25 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (5% EtOAc/Hexanes) to afford 0.081 g (60% yield) of azadecalinone **21a**.

Physical State: Light yellow oil

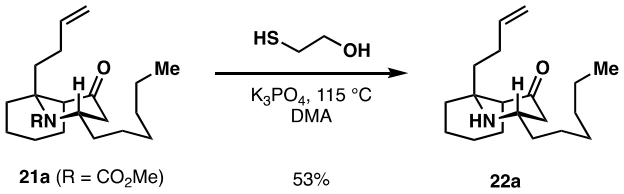
R_f: 0.57 (20% EtOAc/Hexanes)

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.70 (dt, J = 16.7, 8.6 Hz, 1H), 4.95 (d, J = 17.1 Hz, 1H), 4.90 (d, J = 10.0 Hz, 1H), 4.44 (s, 1H), 3.70 (s, 3H), 3.04 (d, J = 10.9 Hz, 1H), 2.78 (d, J = 9.9 Hz, 1H), 2.70 (dd, 1H), 2.46 (d, 1H), 2.26 – 2.17 (m, 1H), 2.06 (d, J = 14.0 Hz, 1H), 1.94 – 1.87 (m, 1H), 1.86 – 1.78 (m, 2H), 1.73 (t, J = 11.5 Hz, 2H), 1.68 – 1.57 (m, 2H), 1.52 – 1.38 (m, 2H), 1.41 – 1.33 (m, 2H), 1.35 – 1.18 (m, 8H), 0.88 (t, J = 6.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 209.3, 138.4, 114.8, 63.1, 54.7, 52.3, 52.2, 41.4, 39.5, 39.1, 31.9, 31.5, 29.2, 29.1, 27.7, 25.0, 22.7, 22.5, 20.8, 14.2.

HRMS (ESI) m/z: $[M+Na]^+$ calc'd for $C_{21}H_{35}NO_3Na^+$ 372.2509; found 327.2540

Aminoketone 22a



21a (R = CO_2Me) 53% **22a**

A modified procedure from Chen was employed.[3]

To a sealed tube was added azadecalinone **21a** (0.075 g, 0.22 mmol, 1 equiv.), potassium phosphate tribasic (0.182 g, 0.86 mmol, 4 equiv.), 2-mercaptoethanol (0.03 mL, 0.43 mmol, 2 equiv.), and DMA (0.86 mL, 0.25 M). The reaction mixture was heated to 115 °C for 16 h or until consumption of starting material was observed, as determined by TLC. The reaction was cooled to room temperature then poured into water (5 mL). The product was extracted with EtOAc (3 x 5 mL) and washed with water (2 x 10 mL), then brine (2 x 10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (10% EtOAc/Hexanes) to afford 0.033 g (53% yield) of aminoketone **22a**.

Physical State: Light yellow oil

R_f: 0.47 (10% EtOAc/Hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (ddt, J = 16.8, 10.1, 6.6 Hz, 1H), 4.98 (dd, J = 17.1, 1.6 Hz, 1H), 4.94 – 4.88 (m, 1H), 2.94 (dq, J = 10.6, 6.1 Hz, 1H), 2.20 (dd, J = 14.5, 11.1 Hz, 1H), 2.12 (dd, J = 14.5, 3.5 Hz, 1H), 2.06 (dd, J = 12.3, 4.2 Hz, 1H), 2.04 – 1.99 (m, 1H), 1.91 (qd, J = 12.1, 5.4 Hz, 1H), 1.85 – 1.71 (m, 3H), 1.63 – 1.50 (m, 4H), 1.49 – 1.41 (m, 2H), 1.37 (dq, J = 15.0, 6.7 Hz, 1H), 1.33 – 1.25 (m, 8H), 1.22 – 1.12 (m, 3H), 0.88 (t, J = 7.0 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 214.7, 138.7, 114.6, 58.3, 55.0, 50.6, 44.2, 38.1, 37.7, 35.8, 31.9, 29.5, 27.1, 26.5, 25.8, 25.5, 22.8, 21.0, 14.2.

HRMS (ESI) m/z: $[M+H]^+$ calc'd for $C_{19}H_{34}NO^+$ 292.2635; found 292.2646

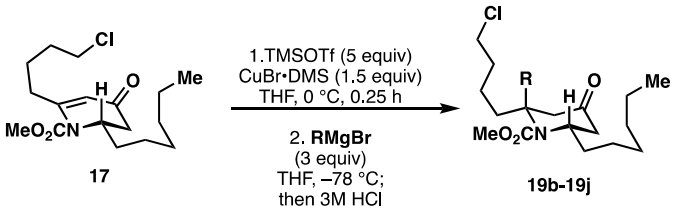
Table S1: Aminoketone ^{1}H NMR Chemical Shift Comparison

Snider (300 mHz, $CDCl_3$)	Aminoketone 22a (400 mHz, $CDCl_3$)

5.87 (ddt, J=16.9, 10.2, 6.6 Hz, 1H)	5.77 (ddt, 16.8, 10.1, 6.6 Hz, 1H)
5.07 (br d, J=16.9 Hz, 1H)	4.98, (dd, J=17.1, 1.6, 1H)
4.99 (bd d, J=10.2 Hz, 1H)	4.94–4.88 (m, 1H)
3.12 (dddd, J= 11.5, 2.7, 6.0, 6.0 Hz, 1H)	2.94 (dq, J=10.6, 6.1 Hz, 1H)
2.37 (dd, J=13.5, 2.7, 1H)	2.20 (dd, J=14.5, 11.1 Hz, 1H)
2.25 (dd, J=4.0, 4.0 Hz, 1H)	2.12 (dd, J=14.5, 3.5 Hz, 1H)
2.21–2.05 (m, 2H)	2.06 (dd, J=12.3, 4.2 Hz, 1H), 2.04–1.99 (m, 1H)
1.96 (dd, J=13.5, 11.5 Hz, 1H)	1.91 (qd, J=12.1, 5.4 Hz, 1H)
1.87–1.20 (m, 20H)	1.85–1.71 (m, 1H), 1.63–1.50 (m, 4H), 1.49–1.41 (m, 2H), 1.37 (dq, J=15.0, 6.7 Hz, 1H), 1.33–1.25 (m, 8H), 1.22–1.12 (m, 3H)
0.88 (t, J=6.5 Hz, 3H)	0.88 (t, J=7.0, 3H)

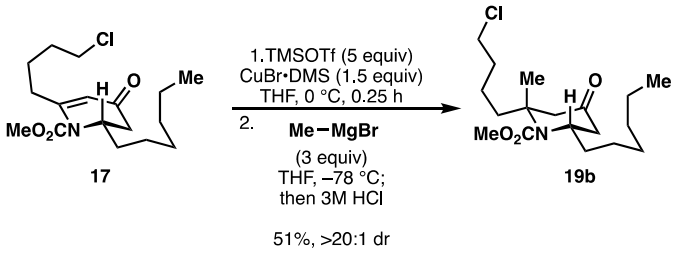
c. Synthesis of multiply-substituted piperidinones

General procedure B for the Grignard addition to piperdenones



To a flame dried 25 mL round bottom flask was added CuBr·DMS (1.5 equiv.) followed by piperidenone **17** (1 equiv.) and THF (0.2 M). The reaction mixture was cooled to 0 °C and TMSOTf (5 equiv.) was added dropwise. The resultant solution was stirred for 0.25 h at 0 °C then cooled to –78 °C. The Grignard solution (3 equiv.) was added to the reaction flask via a syringe pump over one hour. Once the syringe pump addition is complete, the reaction was allowed to stir at –78 °C until the consumption of starting material was observed, as determined by TLC. The reaction was quenched with a 1:1 solution of sat. aqueous NH_4Cl and aqueous NH_4OH (15 mL) and warmed to room temperature. The product was extracted with EtOAc (3 x 50 mL) and the combined organic layer stirred with 1 M HCl for 0.25 h. After 0.25 h, the solution was neutralized with the addition of K_2CO_3. The layers were separated and the organic layer washed with water (25 mL), brine (25 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography.

Piperidone 19b



Piperidone **19b** was synthesized according to general procedure B using CuBr·DMS (0.047 g, 0.228 mmol, 1.5 equiv.), piperdenone **17** (0.05 g, 0.152 mmol, 1.0 equiv.), TMSOTf (0.14 mL, 0.758 mmol, 5.0 equiv.), THF (0.8 mL, 0.2 M), and methylmagnesium bromide (0.28 mL, 1.66 M, 3 equiv.). Following addition of the Grignard reagent, the reaction was complete in 1 h. Purification via flash chromatography (10% EtOAc/Hexanes) afforded the pure product **19b** (0.026 g, 51% yield).

Physical State: Light yellow oil

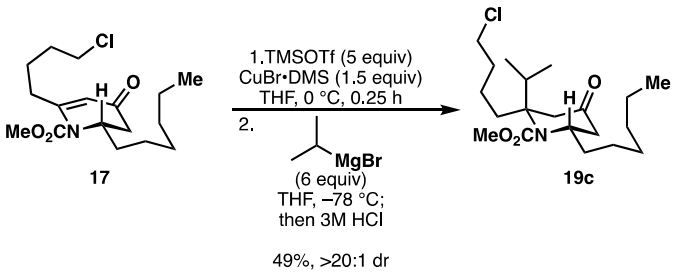
R_f: 0.37 (15% EtOAc/Hexanes)

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.42 (s, 1H), 3.70 (s, 3H), 3.54 (tq, *J* = 8.1, 4.2 Hz, 2H), 2.96 (d, *J* = 17.1 Hz, 1H), 2.67 – 2.59 (m, 1H), 2.52 – 2.45 (m, 2H), 2.15 (d, *J* = 17.1 Hz, 1H), 1.82 – 1.72 (m, 2H), 1.71 – 1.65 (m, 1H), 1.46 – 1.32 (m, 5H), 1.30 – 1.23 (m, 10H), 0.87 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 208.7, 58.3, 52.4, 52.3, 50.1, 44.9, 41.6, 39.5, 37.5, 32.4, 31.8, 29.8, 29.1, 27.5, 27.0, 22.7, 21.6, 14.2.

HRMS (ESI) m/z: $[M+H]^+$ calc'd for $C_{18}H_{33}ClNO_3^+$ 346.2143; found 346.2146

Piperidone 19c



Piperidone **19c** was synthesized according to general procedure B using CuBr·DMS (0.047 g, 0.228 mmol, 1.5 equiv.), piperdenone **17** (0.05 g, 0.152 mmol, 1.0 equiv.), TMSOTf (0.14 mL, 0.758 mmol, 5.0 equiv.), THF (0.8 mL, 0.2 M), and Isopropylmagnesium chloride lithium chloride complex (0.75 mL, 1.21 M, 6 equiv.). Following addition of the Grignard reagent, the reaction was complete in 1 h. Purification via flash chromatography (10% EtOAc/Hexanes) afforded the pure product **19c** (0.028 g, 49% yield).

Physical State: Light yellow oil

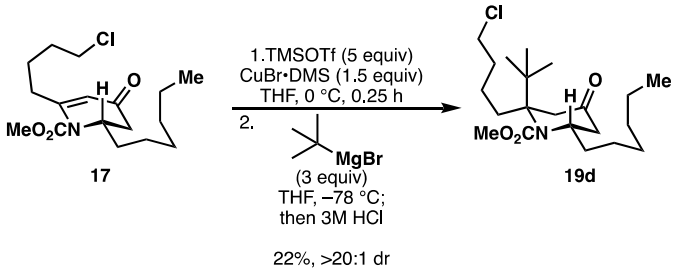
R_f: 0.30 (10% EtOAc/Hexanes)

^{1}H NMR (700 MHz, $CDCl_3$) δ 4.47 (s, 1H), 3.70 (s, 2H), 3.55 (tq, J = 17.2, 9.1 Hz, 3H), 2.77 – 2.70 (m, 2H), 2.62 (d, J = 17.2 Hz, 1H), 2.46 – 2.40 (m, 3H), 1.82 – 1.72 (m, 2H), 1.47 – 1.36 (m, 2H), 1.36 – 1.20 (m, 11H), 0.90 (d, J = 7.0 Hz, 3H), 0.88 (t, J = 6.7 Hz, 3H), 0.81 (d, J = 7.1 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 209.7, 65.3, 52.5, 52.2, 45.0, 43.0, 40.9, 38.1, 32.5, 31.9, 29.0, 27.4, 22.7, 22.2, 19.8, 17.8, 14.2.

HRMS (ESI) m/z: $[M+H]^+$ calc'd for $C_{20}H_{37}ClNO_3^+$ 374.2456; found 374.2454

Piperidone 19d



Piperidone **19d** was synthesized according to general procedure B using CuBr·DMS (0.047 g, 0.228 mmol, 1.5 equiv.), piperdenone **17** (0.05 g, 0.152 mmol, 1.0 equiv.), TMSOTf (0.14 mL, 0.758 mmol, 5.0 equiv.), THF (0.8 mL, 0.2 M), and tert-butylmagnesium chloride (0.5 mL, 0.917 M, 3 equiv.). Following addition of the Grignard reagent, the reaction was complete in 1 h. Purification via flash chromatography (5% EtOAc/Hexanes) afforded the pure product **19d** (0.013 g, 22% yield).

Physical State: Light yellow oil

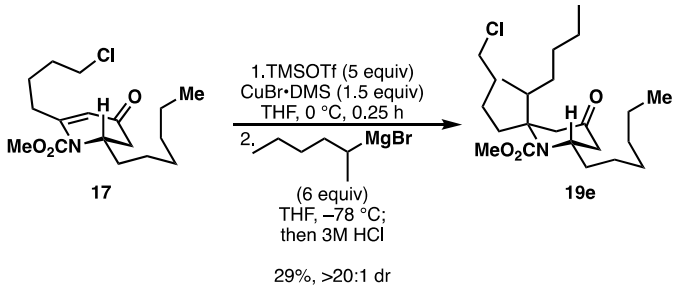
R_f: 0.30 (10% EtOAc/Hexanes)

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.34 (td, J = 6.8, 3.2 Hz, 1H), 3.67 (s, 3H), 3.55 (t, J = 6.5 Hz, 2H), 2.84 – 2.76 (m, 2H), 2.62 (q, J = 17.2 Hz, 2H), 2.49 – 2.43 (m, 1H), 1.84 – 1.71 (m, 3H), 1.52 – 1.33 (m, 2H), 1.31 – 1.18 (m, 11H), 1.00 (s, 9H), 0.88 (t, J = 6.9 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 210.8, 157.1, 68.4, 53.8, 52.4, 46.4, 45.1, 42.1, 41.1, 38.1, 34.3, 32.7, 31.9, 29.1, 28.6, 27.6, 22.7, 22.3, 14.2.

HRMS (ESI) m/z: $[M+H]^+$ calc'd for $C_{21}H_{39}ClNO_3^+$ 388.2613; found 388.2597

Piperidone 19e



Piperidone **19e** was synthesized according to general procedure B using CuBr·DMS (0.047 g, 0.228 mmol, 1.5 equiv.), piperdenone **17** (0.05 g, 0.152 mmol, 1.0 equiv.), TMSOTf (0.14 mL, 0.758 mmol, 5.0 equiv.), THF (0.8 mL, 0.2 M), and 2-hexanylmagnesium bromide (0.5 mL, 0.430 M, 6 equiv.), prepared following general procedure A. Following addition of the Grignard reagent, the reaction was complete in 1 h. Purification via flash chromatography (5% EtOAc/Hexanes) afforded the pure product **19e** (0.018 g, 29% yield).

Physical State: Light yellow oil

R_f: 0.40 (10% EtOAc/Hexanes)

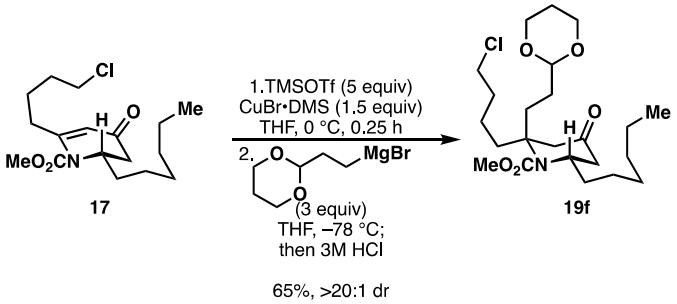
^{1}H NMR (600 MHz, $CDCl_3$) δ 4.48 (s, 1H), 3.70 (s, 3H), 3.60 – 3.50 (m, 2H), 2.78 – 2.68 (m, 1H), 2.67 – 2.59 (m, 1H), 2.55 – 2.33 (m, 3H), 1.82 – 1.74 (m, 3H), 1.51 – 1.19 (m, 17H), 1.16 (d, J = 10.0 Hz, 1H), 1.09 – 0.99 (m, 1H), 0.87 (dt, J = 11.9, 5.9 Hz, 6H), 0.79 (d, J = 7.0 Hz, 3H).

Overlay of spectrum displays an approximate diastereomeric ratio of 2.3:1 about the methyl center.

^{13}C NMR (176 MHz, $CDCl_3$) δ 209.8, 65.7, 52.6, 45.0, 43.8, 41.0, 38.3, 32.7, 32.6, 31.9, 31.7, 31.1, 30.5, 29.9, 29.1, 27.4, 23.1, 22.7, 22.2, 22.1, 16.6, 14.2, 14.2.

HRMS (ESI) m/z: $[M+H]^+$ calc'd for $C_{23}H_{43}ClNO_3^+$ 416.2926; found 416.2904

Piperidone 19f



Piperidone **19f** was synthesized according to general procedure B using CuBr·DMS (0.047 g, 0.228 mmol, 1.5 equiv.), piperdenone **17** (0.05 g, 0.152 mmol, 1.0 equiv.), TMSOTf (0.14 mL, 0.758 mmol, 5.0 equiv.), THF (0.8 mL, 0.2 M), and (2-(1,3-dioxan-2-yl)ethyl)magnesium bromide (0.46 mL, 1.0 M, 3 equiv.), prepared following general procedure A. Following addition of the Grignard reagent, the reaction was complete in 1 h. Purification via flash chromatography (40% EtOAc/Hexanes) afforded the pure product **19f** (0.044 g, 65% yield).

Physical State: Light yellow oil

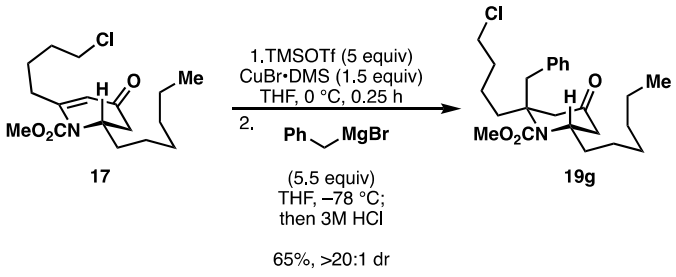
R_f: 0.40 (40% EtOAc/Hexanes)

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.41 (t, J = 5.0 Hz, 2H), 4.07 – 4.00 (m, 2H), 3.76 – 3.59 (m, 5H), 3.53 (tq, J = 8.5, 4.3 Hz, 2H), 2.82 (d, J = 17.4 Hz, 1H), 2.69 – 2.62 (m, 1H), 2.50 – 2.43 (m, 1H), 2.39 (s, 1H), 2.33 (d, J = 17.4 Hz, 1H), 1.83 – 1.63 (m, 5H), 1.54 – 1.44 (m, 2H), 1.46 – 1.30 (m, 2H), 1.34 – 1.20 (m, 10H), 0.87 (t, J = 7.0 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 208.5, 102.1, 67.0, 66.9, 60.9, 52.5, 52.2, 46.7, 44.9, 41.5, 37.5, 34.2, 32.5, 31.9, 30.4, 29.8, 29.1, 27.1, 25.8, 22.7, 21.4, 14.2.

HRMS (ESI) m/z: $[M+H]^+$ calc'd for $C_{23}H_{41}ClNO_5^+$ 446.2668; found 446.2666

Piperidone 19g



Piperidone **19g** was synthesized according to general procedure B using CuBr·DMS (0.047 g, 0.228 mmol, 1.5 equiv.), piperdenone **17** (0.05 g, 0.152 mmol, 1.0 equiv.), TMSOTf (0.14 mL, 0.758 mmol, 5.0 equiv.), THF (0.8 mL, 0.2 M), and benzylmagnesium bromide (4.7 mL, 0.177 M, 5.5 equiv.), prepared following general procedure A. Following

addition of the Grignard reagent, the reaction was complete in 1 h. Purification via flash chromatography (10% EtOAc/Hexanes) afforded the pure product **19g** (0.083 g, 65% yield).

Physical State: Light yellow oil

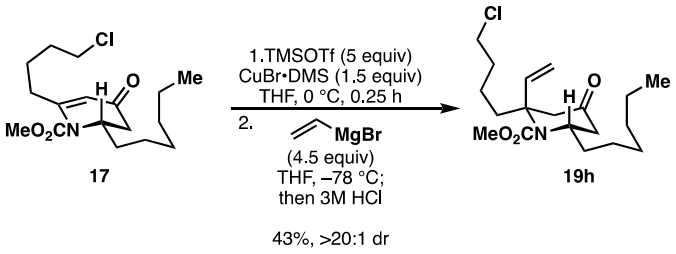
R_f: 0.30 (10% EtOAc/Hexanes)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 – 7.16 (m, 3H), 7.08 – 7.01 (m, 2H), 4.24 (s, 1H), 3.80 (s, 3H), 3.61 – 3.46 (m, 2H), 3.45 (d, J = 10.8 Hz, 1H), 2.90 (d, J = 13.3 Hz, 1H), 2.76 (d, J = 17.9 Hz, 1H), 2.57 (s, 1H), 2.44 (d, J = 17.9 Hz, 1H), 2.12 – 2.06 (m, 1H), 1.77 (tp, J = 14.0, 7.1 Hz, 3H), 1.65 (dt, J = 13.2, 6.4 Hz, 1H), 1.43 – 1.14 (m, 12H), 0.86 (t, J = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 208.6, 137.0, 131.1, 128.5, 127.2, 62.0, 52.7, 52.1, 47.3, 44.9, 41.0, 37.5, 32.4, 31.8, 29.0, 27.0, 22.7, 21.3, 14.2.

HRMS (ESI) m/z: $[M+H]^+$ calc'd for $C_{24}H_{36}ClNO_3Na^+$ 444.2276; found 444.2303

Piperidone 19h



Piperidone **19h** was synthesized according to general procedure B using CuBr·DMS (0.047 g, 0.228 mmol, 1.5 equiv.), piperdenone **17** (0.05 g, 0.152 mmol, 1.0 equiv.), TMSOTf (0.14 mL, 0.758 mmol, 5.0 equiv.), THF (0.8 mL, 0.2 M), and vinylmagnesium bromide (1.06 mL, 0.66 M, 4.5 equiv.). Following addition of the Grignard reagent, the reaction was complete in 1 h. Purification via flash chromatography (15% EtOAc/Hexanes) afforded the pure product **19h** (0.024 g, 43% yield).

Physical State: Light yellow oil

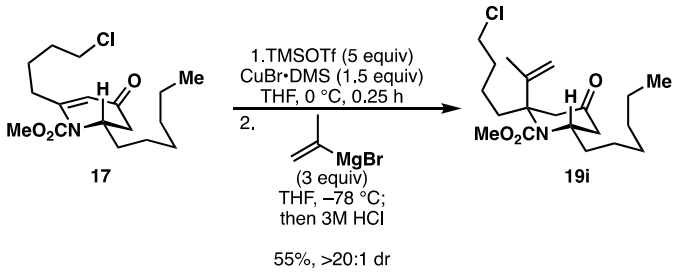
R_f: 0.33 (15% EtOAc/Hexanes)

^{1}H NMR (700 MHz, $CDCl_3$) δ 6.04 (dd, J = 17.4, 10.9 Hz, 1H), 5.06 (d, J = 10.8 Hz, 1H), 4.95 (d, J = 17.5 Hz, 1H), 4.47 (s, 1H), 3.71 (s, 3H), 3.55 (tq, J = 8.3, 4.3 Hz, 2H), 2.97 (d, J = 17.5 Hz, 1H), 2.64 (dd, 1H), 2.57 (t, J = 11.1 Hz, 1H), 2.48 – 2.41 (m, 2H), 1.83 – 1.76 (m, 2H), 1.77 – 1.67 (m, 1H), 1.44 – 1.36 (m, 4H), 1.31 – 1.21 (m, 8H), 0.88 (t, J = 7.0 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 208.0, 142.1, 113.1, 62.0, 52.8, 52.6, 47.4, 44.8, 41.7, 38.4, 37.6, 32.4, 31.9, 29.9, 29.1, 27.0, 22.7, 21.2, 14.2.

HRMS (ESI) m/z: $[M+H]^+$ calc'd for $C_{19}H_{33}ClNO_3^+$ 358.2143; found 358.2136

Piperidone 19i



Piperidone **19i** was synthesized according to general procedure B using CuBr·DMS (0.047 g, 0.228 mmol, 1.5 equiv.), piperdenone 17 (0.05 g, 0.152 mmol, 1.0 equiv.), TMSOTf (0.14 mL, 0.758 mmol, 5.0 equiv.), THF (0.8 mL, 0.2 M), and isopropenylmagnesium bromide (1.3 mL, 0.35 M, 3 equiv.). Following addition of the Grignard reagent, the reaction was complete in 1 h. Purification via flash chromatography (25% EtOAc/Hexanes) afforded the pure product **19i** (0.031 g, 55% yield).

Physical State: Light yellow oil

R_f: 0.60 (30% EtOAc/Hexanes)

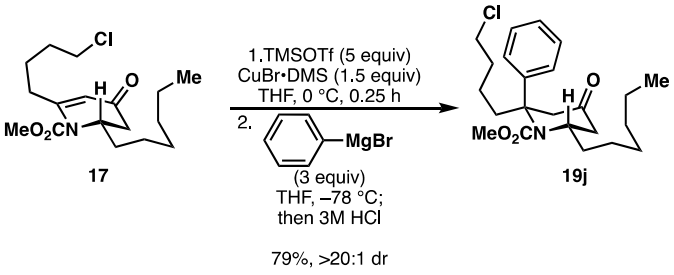
^{1}H NMR (600 MHz, $CDCl_3$) δ 4.90 (s, 1H), 4.73 (s, 1H), 4.49 (s, 1H), 3.69 (s, 3H), 3.61 – 3.51 (m, 2H), 2.96 (d, *J* = 17.1 Hz, 1H), 2.78 – 2.70 (m, 1H), 2.61 (s, 1H), 2.50 (d, *J* =

17.1 Hz, 1H), 2.43 – 2.37 (m, 1H), 1.79 (tq, *J* = 14.3, 6.9 Hz, 3H), 1.73 (s, 3H), 1.48 – 1.36 (m, 3H), 1.36 – 1.12 (m, 9H), 0.88 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 208.1, 146.7, 112.1, 65.2, 52.7, 52.7, 47.1, 44.9, 40.3, 37.9, 37.0, 32.4, 31.9, 29.8, 29.1, 27.1, 22.7, 21.5, 19.3, 14.2.

HRMS (ESI) m/z: $[M+H]^+$ calc'd for $C_{20}H_{35}ClNO_3^+$ 372.2300; found 372.2301

Piperidone 19j



Piperidone **19j** was synthesized according to general procedure B using CuBr·DMS (0.047 g, 0.228 mmol, 1.5 equiv.), piperdenone **17** (0.05 g, 0.152 mmol, 1.0 equiv.), TMSOTf (0.14 mL, 0.758 mmol, 5.0 equiv.), THF (0.8 mL, 0.2 M), and phenylmagnesium bromide (0.17 mL, 2.76 M, 3 equiv.). Following addition of the Grignard reagent, the reaction was complete in 1 h. Purification via flash chromatography (15 % EtOAc/Hexanes) afforded the pure product **19j** (0.049 g, 79% yield).

Physical State: Light yellow oil

R_f: 0.33 (15% EtOAc/Hexanes)

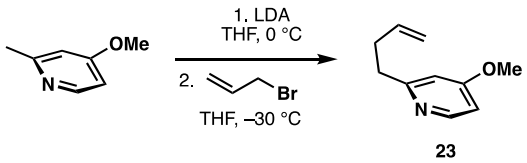
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.7 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 1H), 7.14 (d, *J* = 7.5 Hz, 2H), 4.63 (s, 1H), 3.69 (s, 3H), 3.63 – 3.52 (m, 2H), 3.24 (d, *J* = 17.3 Hz, 1H), 2.76 (s, 1H), 2.68 (d, *J* = 17.3 Hz, 1H), 2.59 – 2.51 (m, 1H), 2.46 – 2.39 (m, 1H), 1.89 (dd, *J* = 12.8, 4.5 Hz, 1H), 1.85 – 1.75 (m, 3H), 1.58 (tq, *J* = 12.2, 7.3 Hz, 1H), 1.51 – 1.40 (m, 2H), 1.40 – 1.23 (m, 8H), 0.89 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 207.5, 145.4, 128.7, 127.1, 125.3, 64.2, 53.2, 52.8, 51.5, 44.8, 41.4, 40.8, 37.7, 32.4, 31.9, 29.1, 27.0, 22.7, 21.8, 14.2.

HRMS (ESI) m/z: $[M+H]^+$ calc'd for $C_{23}H_{35}ClNO_3^+$ 408.2300; found 408.2296

d. Synthesis of cylindricine B

Pyridine 23



23

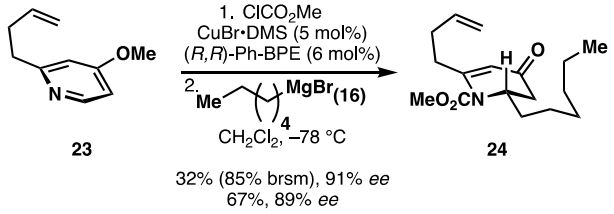
Pryidine **23** is commercially available or can be prepared by the following procedure: To a stirred solution of lithium diisopropylamide, prepared from diisopropylamine (4 mL, 29 mmol, 1.2 equiv) and n-BuLi (2.3 M in hexanes, 11 mL, 27 mmol, 1.1 equiv), in THF (81 mL, 0.3 M) at 0 °C was added 4-methoxy-2-methylpyridine (3.0 g, 24 mmol, 1 equiv) and the solution was allowed to stir for 1 h at 0 °C. The solution was then cooled to –30 °C with an acetonitrile/dry ice bath, and allyl bromide (2.5 mL, 29 mmol, 1.2 equiv) was added dropwise. The reaction was allowed to stir for 6 h or until the consumption of starting material was observed, as determined by TLC. The reaction was quenched with the addition of water and warmed to room temperature. The product was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (25 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was used without further purification.

Physical State: Light brown oil

R_f: 0.53 (70% EtOAc/Hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 5.6 Hz, 1H), 6.65 (dt, J = 8.1, 2.4 Hz, 2H), 5.87 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.05 (dt, J = 17.1, 1.6 Hz, 1H), 4.97 (dd, J = 10.2, 1.6 Hz, 1H), 3.83 (s, 3H), 2.87 – 2.79 (m, 2H), 2.53 – 2.43 (m, 2H).

Piperdenone 24



A modified procedure from Harutyunan was employed.[1]

To a flame-dried Schlenk flask was added CuBr·DMS (3 mg, 15 µmol, 5 mol%), ligand (R,R)-Ph-BPE (9 mg, 18 µmol, 6 mol%) and DCM (3 mL, 0.1 M) and stirred for 20 min. Pyridine **23** (50 mg, 0.31 mmol, 1.0 equiv.) was added at once and stirred for 5 min. Methyl chloroformate (0.07 mL, 0.9 mmol, 3.0 equiv.) was added dropwise and stirred for 10 min. The reaction was cooled to –78 °C and n-hexylmagnesium bromide was added dropwise over 10 min. The reaction was allowed to stir at –78 °C for 12 h or until the consumption of starting material was observed, as determined by TLC. The reaction was quenched with 1.0 M HCl. The product was extracted with DCM (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (20% EtOAc/Hexanes) to afford 0.06 g (67% yield, 89% *ee*) of piperdenone **24**.

Physical State: Light orange oil

R_f: 0.40 (20% EtOAc/Hexanes)

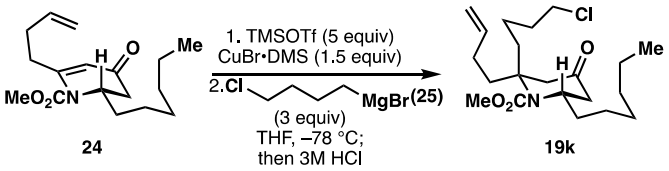
^{1}H NMR (600 MHz, $CDCl_3$) δ 5.76 (ddt, J = 16.8, 10.2, 6.5 Hz, 1H), 5.42 (s, 1H), 5.07 – 4.93 (m, 2H), 4.70 (q, J = 6.4 Hz, 1H), 3.81 (s, 3H), 3.11 (ddd, J = 14.7, 8.5, 6.3 Hz, 1H), 2.77 (dd, J = 17.0, 6.0 Hz, 1H), 2.50 – 2.42 (m, 1H), 2.34 (d, J = 17.0 Hz, 1H), 2.22 (dh, J = 15.6, 6.9 Hz, 2H), 1.70 (dtd, J = 13.6, 9.6, 4.9 Hz, 1H), 1.54 – 1.45 (m, 1H), 1.25 (dt, J = 16.7, 5.5 Hz, 8H), 0.86 (t, J = 7.0 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 193.8, 157.7, 154.2, 136.8, 115.9, 113.0, 56.5, 53.7, 41.2, 35.3, 32.1, 31.7, 30.4, 29.1, 26.2, 22.7, 14.1.

HRMS (ESI) m/z: $[M+H]^+$ calc'd for $C_{17}H_{28}NO_3^+$ 294.2064; found 294.2073

$[\alpha]^{25}_D$: +252.857 (c: 0.014 g/mL $CHCl_3$)

Piperidone 19k



56%, >20:1 dr

To a flame dried 100 mL round bottom flask was added CuBr·DMS (1.4 g, 6.7 mmol, 1.5 equiv.) followed by piperdenone **24** (1.3 g, 4.4 mmol, 1 equiv.) and THF (22 mL, 0.2 M). The reaction mixture was cooled to 0 °C and TMSOTf (1.2 mL, 6.7 mmol, 5 equiv.) was added dropwise. The resultant solution was stirred for 0.5 h at 0 °C then cooled to –78 °C. Chlorobutylmagnesium bromide **25** (14.6 mL, 0.91 M, 3 equiv.), prepared by General Procedure A, was added to the reaction flask via a syringe pump over one hour. Once the syringe pump addition is complete, the reaction was allowed to stir at –78 °C until the consumption of starting material was observed, as determined by TLC. The reaction was quenched with a 1:1 solution of sat. aqueous NH_4Cl and aqueous NH_4OH (15 mL) and warmed to room temperature. The product was extracted with EtOAc (3 x 50 mL) and the combined organic layer stirred with 1 M HCl for 0.25 h. After 0.25 h, the solution was neutralized with the addition of K_2CO_3. The layers were separated and the organic layer washed with water (30 mL), brine (30 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (10% EtOAc/Hexanes) to afford 0.94 g (55% yield) of chloropiperdinone **19k**.

Physical State: Light yellow oil

R_f: 0.43 (10% EtOAc/Hexanes)

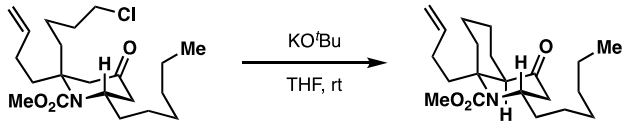
^{1}H NMR (600 MHz, $CDCl_3$) δ 5.80 (ddt, J = 16.8, 10.2, 6.6 Hz, 1H), 5.04 (dd, J = 17.1, 1.5 Hz, 1H), 4.97 (d, J = 9.0 Hz, 1H), 4.44 (s, 1H), 3.71 (s, 3H), 3.52 – 3.46 (m, 2H), 2.88 (d, J = 17.2 Hz, 1H), 2.67 – 2.60 (m, 1H), 2.53 – 2.47 (m, 2H), 2.39 (d, J = 17.2 Hz, 1H), 2.06 (s, 1H), 1.95 (q, J = 7.4 Hz, 2H), 1.70 (ddd, J = 16.9, 13.8, 7.1 Hz, 4H), 1.48 – 1.38 (m, 2H), 1.37 – 1.19 (m, 10H), 0.88 (t, J = 7.0 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 208.6, 137.9, 115.0, 61.1, 52.4, 52.2, 46.8, 44.6, 41.3, 39.4, 37.7, 37.5, 32.7, 31.7, 29.7, 29.0, 28.7, 27.1, 22.6, 21.9, 14.0.

HRMS (ESI) m/z: $[M+H]^+$ calc'd for $C_{21}H_{37}ClNO_3^+$ 386.2456; found 386.2442

$[\alpha]^{25}_D$: –65.400 (c: 0.005 g/mL $CHCl_3$)

Azadecalinone 21b



19k **21b**

72%

To a 50 mL round bottom flask was added chloropiperdinone **19k** (0.120 g, 0.31 mmol, 1 equiv.) and THF (15.5 mL, 0.02 M). A 0.5 M solution of ^{t}BuOK (0.28 g, 2.5 mmol, 8 equiv.) in THF (5 mL) was added via syringe pump over one hour. After addition was completed, the reaction solution was allowed to stir until consumption of starting material was observed, as determined by TLC. The reaction was quenched with 0.1 M HCl (5 mL) and the product extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (5% EtOAc/Hexanes) to afford 0.078 g (72% yield) of azadecalinone **21b**.

Physical State: Light yellow oil

R_f: 0.53 (15% EtOAc/Hexanes)

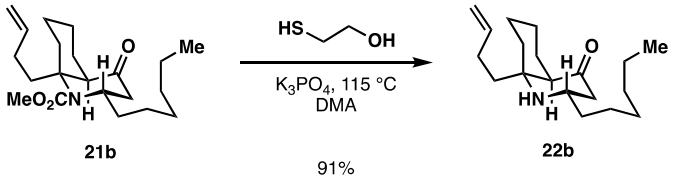
^{1}H NMR (700 MHz, $CDCl_3$) δ 5.83 (dddd, J = 16.0, 12.6, 8.5, 4.3 Hz, 1H), 5.04 (d, J = 17.2 Hz, 1H), 4.96 (d, J = 10.1 Hz, 1H), 4.42 (s, 1H), 3.69 (s, 3H), 2.79 – 2.52 (m, 5H), 2.41 (d, J = 13.8 Hz, 1H), 1.99 – 1.86 (m, 3H), 1.75 – 1.68 (m, 1H), 1.56 (tt, J = 13.9, 4.3 Hz, 1H), 1.52 – 1.42 (m, 3H), 1.39 – 1.34 (m, 1H), 1.33 – 1.20 (m, 9H), 1.15 (dt, J = 13.5, 4.4 Hz, 1H), 0.87 (t, J = 7.1 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 209.6, 138.5, 114.9, 61.8, 52.4, 51.6, 48.8, 41.6, 37.6, 31.9, 29.1, 28.7, 27.2, 22.7, 22.2, 22.1, 21.4, 14.2.

HRMS (ESI) m/z: $[M+H]^+$ calc'd for $C_{21}H_{36}NO_3^+$ 350.2690; found 350.2709

$[\alpha]^{25}_{D}$: –109.000 (c: 0.006 g/mL $CHCl_3$)

Amine 22b



A modified procedure from Chen was employed.[3]

To a sealed tube was added azadecalinone **21b** (0.127 g, 0.36 mmol, 1 equiv.), potassium phosphate tribasic (0.308 g, 1.4 mmol, 4 equiv.), 2-mercaptoethanol (0.05 mL, 0.73 mmol, 2 equiv.), and DMA (1.5 mL, 0.25 M). The reaction mixture was heated to 115 °C for 16 h or until consumption of starting material was observed, as determined by TLC. The reaction was cooled to room temperature then poured into water (5 mL). The product was extracted with EtOAc (3 x 5 mL) and washed with water (2 x 10 mL), then brine (2 x 10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (10% EtOAc/Hexanes) to afford 0.096 g (91% yield) of amine **22b**. The characterization data of amine 22b has been previously reported.[4]

Physical State: Light yellow oil

R_f: 0.47 (10% EtOAc/Hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (ddt, J = 16.8, 10.1, 6.6 Hz, 1H), 5.07 (dd, J = 17.1, 1.7 Hz, 1H), 4.98 (d, J = 10.1 Hz, 1H), 3.12 (dtd, J = 11.7, 6.1, 2.9 Hz, 1H), 2.36 (dd, J = 13.5, 2.9 Hz, 1H), 2.24 (s, 1H), 2.21 – 2.04 (m, 3H), 1.95 (t, J = 12.2 Hz, 1H), 1.80 (ddd, J = 16.3, 11.1, 5.3 Hz, 1H), 1.68 (ddd, J = 14.2, 11.5, 5.5 Hz, 1H), 1.62 – 1.52 (m, 2H), 1.49 – 1.35 (m, 6H), 1.30 (d, J = 16.2 Hz, 10H), 0.88 (t, J = 6.7 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 211.1, 138.9, 114.7, 58.2, 53.8, 50.0, 48.8, 37.8, 37.6, 31.8, 31.6, 29.3, 27.3, 25.6, 22.6, 22.6, 21.4, 21.1, 14.1.

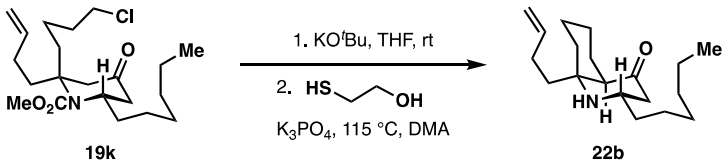
HRMS (ESI) m/z: $[M+H]^+$ calc'd for $C_{19}H_{34}NO^+$ 292.2635; found 292.2647

$[\alpha]^{25}_D$: –20.200 (c: 0.005 g/mL $CHCl_3$)

Table S2: Aminoketone ^1H NMR Chemical Shift Comparison

Snider[4] (300 mHz, $CDCl_3$)	Aminoketone22b (400 mHz, $CDCl_3$)
5.87 (ddt, J=16.9, 10.2, 6.6 Hz, 1H)	5.87 (ddt, J=16.8, 10.1, 6.6 Hz, 1H)
5.07 (br d, J=16.9 Hz, 1H)	5.07 (dd, J=17.1, 1.7 Hz, 1H)
4.99 (bd d, J=10.2 Hz, 1H)	4.98 (d, J=10.1 Hz, 1H)
3.12 (dddd, J= 11.5, 2.7, 6.0, 6.0 Hz, 1H)	3.12 (dtd, J=11.7, 6.1, 2.9 Hz, 1H)
2.37 (dd, J=13.5, 2.7, 1H)	2.36 (dd, J=13.5, 2.9 Hz, 1H)
2.25 (dd, J=4.0, 4.0 Hz, 1H)	2.24 (s, 1H)
2.21–2.05 (m, 2H)	2.21–2.04 (m, 3H)
1.96 (dd, J=13.5, 11.5 Hz, 1H)	1.95 (t, J=12.2 Hz, 1H)
1.87–1.20 (m, 20H)	1.80 (ddd, J=16.3, 11.1, 5.3 Hz, 1H), 1.68 (ddd, J=14.2, 11.5, 5.5 Hz, 1H), 1.62–1.52 (m. 2H), 1.49–1.35 (m, 6H), 1.30 (d, J=16.2 Hz, 10H)
0.88 (t, J=6.5 Hz, 3H)	0.88 (t, J=6.7 Hz, 3H)

Amine 22b – One Pot Strategy

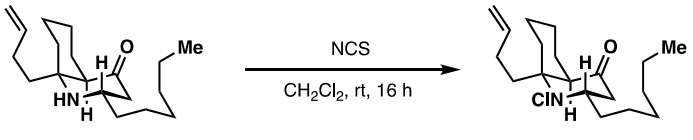


28%

To a 50 mL round bottom flask was added chloropiperdinone **19k** (0.020 g, 0.052 mmol, 1 equiv.) and THF (0.5 mL, 0.1 M). A 0.5 M solution of ^{t}BuOk (0.058 g, 0.518 mmol, 10 equiv.) in THF (1 mL) was added via syringe pump over one hour. After addition was completed, the reaction solution was allowed to stir until consumption of starting material was observed, as determined by TLC. DMA (0.5 mL, 0.1 M) was added to the reaction flask followed by potassium phosphate tribasic (0.022 g, 0.104 mmol, 4 equiv.) and 2-mercaptoethanol (0.02 mL, 0.207 mmol, 2 equiv.). The reaction mixture was heated to 115 °C for 16 h or until consumption of starting material was observed, as determined by TLC. The reaction was cooled to room temperature then poured into water (5 mL). The

product was extracted with EtOAc (3 x 5 mL) and washed with water (2 x 10 mL), then brine (2 x 10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (10% EtOAc/Hexanes) to afford 0.05 g (28% yield) of amine **22b**.

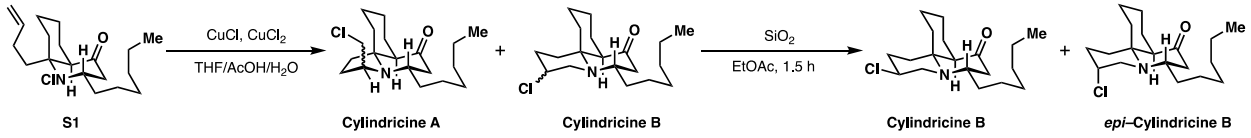
Chloroamine S1



To a flame dried flask was added amine **22b** (0.025 g, 0.086 mmol, 1 equiv.), N-chlorosuccinimide (0.023 g, 0.17 mmol, 2.5 equiv.), and DCM (3 mL, 0.03M). The solution was allowed to stir at room temperature for 16 h or until consumption of starting material was observed, as determined by TLC. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (10% EtOAc/Hexanes) to afford 0.028 g (>99% yield) of chloroamine **S1**. The characterization data of chloroamine **S1** has been previously reported.[4]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 – 5.80 (m, 1H), 5.12 – 4.91 (m, 2H), 3.55 (s, 1H), 2.69 – 2.49 (m, 2H), 2.25 (d, J = 14.8 Hz, 3H), 2.09 – 1.89 (m, 3H), 1.87 – 1.59 (m, 3H), 1.55 – 1.14 (m, 14H), 0.88 (t, J = 6.5 Hz, 3H).

Cylindricines A and B



To a flame dried flask was added chloroamine **S1** (0.024 g, 0.074 mmol, 1 equiv.) and THF (1.8 mL, 0.04 M). The reaction flask was then cooled to 0 °C and treated with a solution of CuCl (0.007 g, 0.066 mmol, 0.9 equiv.) and $CuCl_2$ (0.034 g, 0.25 mmol, 3.4

equiv.) in 1.2 mL of THF/H_2O/AcOH (2:1:1, 0.06 M) over 10 min. The solution was stirred at 0 °C for 1 h or until consumption of starting material was observed, as determined by TLC. The reaction was neutralized with sat. aqueous $NaHCO_3$ to ~pH 7. The product was extracted with DCM (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure to yield 1:1 dr of cylindricine A and *epi*–cylindricine A. The crude mixture was purified by flash column chromatography (3% EtOAc/Hexanes) to afford 0.016 g (67% yield, 1:2) of cylindricine A and cylindricine B. The mixture was stirred with 0.100 g SiO_2 in 2 mL of EtOAc for 1.5 h, then filtered to afford cylindricine B and a 9:1 mixture of *epi*–cylindricine B and *epi*-cylindricine A. The characterization data of cylindricine B has been previously reported.[5]

Physical State: Light yellow oil

R_f: 0.37 (5% EtOAc/Hexanes)

(+)-cylindricine B

^{1}H NMR (600 MHz, C_6D_6) δ 3.83 (tt, *J* = 9.7, 4.5 Hz, 1H), 3.01 (d, *J* = 8.1 Hz, 1H), 2.68 (s, 1H), 2.38 (dd, *J* = 11.7, 9.9 Hz, 1H), 2.28 (dd, *J* = 13.7, 2.1 Hz, 1H), 2.16 (dd, *J* = 14.1, 3.4 Hz, 1H), 2.04 – 1.97 (m, 1H), 1.87 (dd, *J* = 13.7, 4.1 Hz, 2H), 1.70 – 1.56 (m, 2H), 1.53 – 1.40 (m, 2H), 1.40 – 1.24 (m, 5H), 1.24 – 1.07 (m, 8H), 1.04 – 0.86 (m, 6H).

^{13}C NMR (151 MHz, C_6D_6) δ 207.6, 59.1, 57.2, 54.2, 50.0, 45.7, 34.1, 33.0, 32.2, 30.6, 29.9, 23.9, 23.0, 22.2, 21.9, 21.5, 14.3.

HRMS (ESI) m/z: $[M+H]^+$ calc'd for $C_{19}H_{33}ClNO^+$ 326.2245; found 326.2260

$[\alpha]^{25}_D$: +29.000 (c: 0.0016 g/mL CH_2Cl_2)

Reported literature value for (–)-cylindricine B: **$[\alpha]^{25}_D$:** –20.100 (c: 0.00075 g/mL CH_2Cl_2)[5]

Table S3: Cylindricine B ^{1}H NMR Chemical Shift Comparison

Fuwa[5] (500 MHz, C_6D_6) C_6HD_5: δ_H = 7.15 ppm	Observed (600 MHz, C_6D_6) C_6HD_5: δ_H = 7.16 ppm
3.82 (dddd, J=10.0, 10.0, 5.0, 5.0 Hz, 1H)	3.83 (tt, J=9.7, 4.5 Hz, 1H)
3.02–2.98 (m, 1H)	3.01 (d, J=8.1, 1H)
2.70–2.63 (m, 1H)	2.68 (s, 1H)

2.36 (dd, J=12.0, 10.0 Hz, 1H)	2.38 (ddm J=11.7, 9.9 Hz, 1H)
2.27 (dddd, J=14.0, 2.0, 2.0, 2.0 Hz, 1H)	2.28 (dd, J= 13.7, 2.1 Hz, 1H)
2.15 (dd, J=12.5, 3.5 Hz, 1H)	2.16 (dd, J=14.1, 3.4, 1H)
2.00 (dd, J=12.5, 12.5 Hz, 1H)	2.04–1.97 (m, 1H)
1.87–1.82 (m, 2H)	1.87 (dd, J=13.7, 4.1 Hz, 2H)
1.67–1.57 (m, 2H)	1.70–1.56 (m, 2H)
1.51–1.23 (m, 6H)	1.56–1.40 (m, 2H)
1.21–0.89 (m, 15H)	1.40–1.24 (m 5H), 1.24–1.07 (m, 8H), 1.04–0.86 (m, 6H)

Table S4: Cylindricine B ^{13}C NMR Chemical Shift Comparison

Fuwa[5] (125 MHz, C_6D_6) C_6HD_5: δ_H = 128.0 ppm	Observed (151 MHz, C_6D_6) C_6HD_5: δ_H = 128.06 ppm
207.6	207.6
59.1	59.1
57.2	57.2
54.1	54.2
53.9	Not observed
49.9	50.0
45.6	45.7
34.0	34.1
32.9	33.0
32.1	32.2
30.5	30.6
29.8	29.9
23.8	23.9
23.0	23.0
22.1	22.2
21.8	21.9
21.4	21.5
21.2	Not observed
14.3	14.3

epi–cylindricine B

Physical State: Light yellow oil

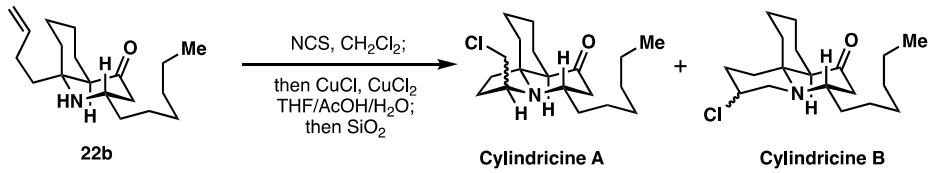
R_f: 0.33 (5% EtOAc/Hexanes)

^{1}H NMR (600 MHz, C_6D_6) δ 3.81 (tt, *J* = 9.0, 4.1 Hz, 1H), 3.07 – 2.95 (m, 1H), 2.79 (d, *J* = 9.6 Hz, 1H), 2.57 – 2.51 (m, 1H), 2.29 (d, *J* = 11.9 Hz, 1H), 2.11 (d, *J* = 9.7 Hz, 1H), 2.03 (dd, *J* = 14.5, 2.9 Hz, 1H), 1.96 – 1.89 (m, 1H), 1.83 (dt, *J* = 14.1, 4.7 Hz, 1H), 1.67 (s, 1H), 1.62 – 1.56 (m, 1H), 1.43 – 1.25 (m, 7H), 1.20 – 1.12 (m, 7H), 1.06 – 0.79 (m, 7H).

^{13}C NMR (151 MHz, C_6D_6) δ 207.7, 59.0, 57.4, 53.3, 47.7, 43.0, 33.7, 32.2, 32.0, 30.8, 29.6, 25.5, 23.0, 22.3, 21.7, 21.4, 14.3.

HRMS (ESI) m/z: $[M+H]^+$ calc'd for $C_{19}H_{33}ClNO^+$ 326.2245; found 326.2280

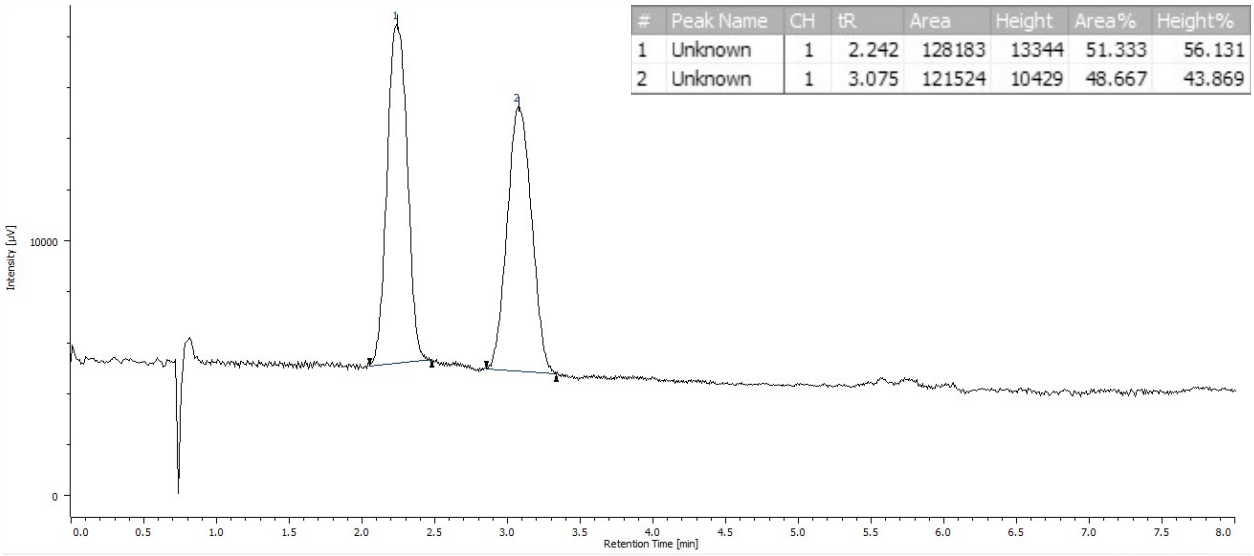
Cylindricine A – One Pot Strategy



To a flame dried flask was added amine **22b** (0.020 g, 0.068 mmol, 1 equiv.), N-chlorosuccinimide (0.023 g, 0.17 mmol, 2.5 equiv.), and DCM (2 mL, 0.03M). The solution was allowed to stir at room temperature for 16 h or until consumption of starting material was observed, as determined by TLC. The reaction mixture was then cooled to 0 °C and treated with a solution of CuCl (0.006 g, 0.061 mmol, 0.9 equiv.) and $CuCl_2$ (0.031 g, 0.23 mmol, 3.4 equiv.) in 1.7 mL of THF/H_2O/AcOH (2:1:1, 0.04 M) over 10 min. The solution was stirred at 0 °C for 1 h or until consumption of starting material was observed, as determined by TLC. The reaction was neutralized with sat. aqueous $NaHCO_3$ to ~pH 7. The product was extracted with DCM (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (3% EtOAc/Hexanes) to afford 0.006 g (30% yield) of cylindricine A and cylindricine B.

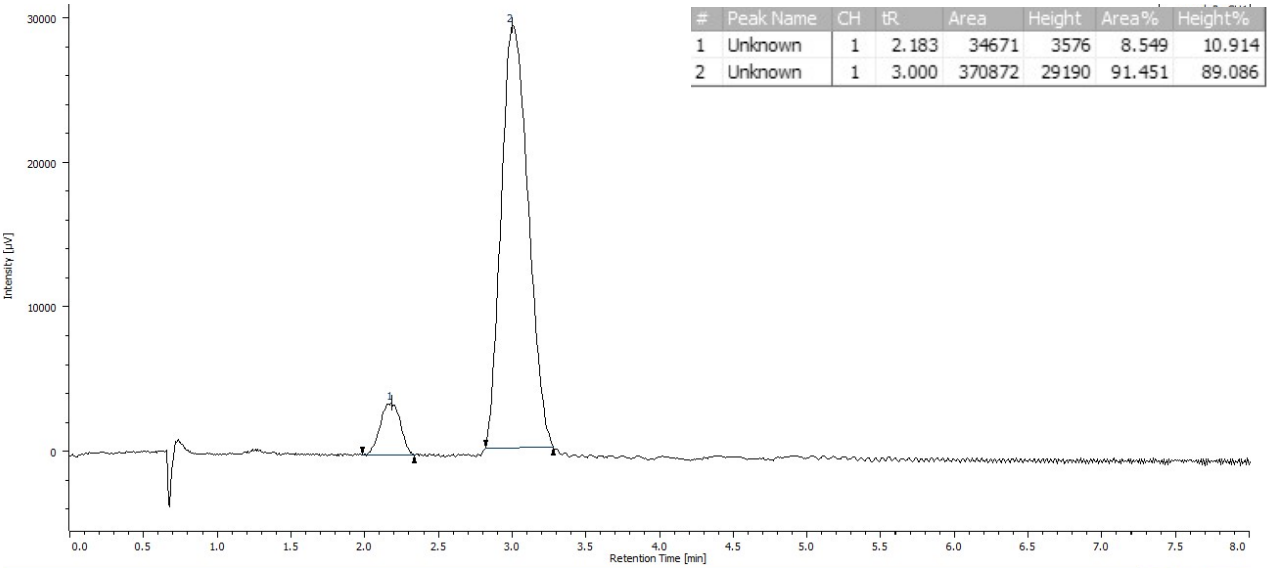
e. Determination of Enantiomeric Excess of 24

Conditions: ChiralPak IA; 25 °C; 3% IPA/CO2 over 12 min; 3.0 mL/min; 254 nm



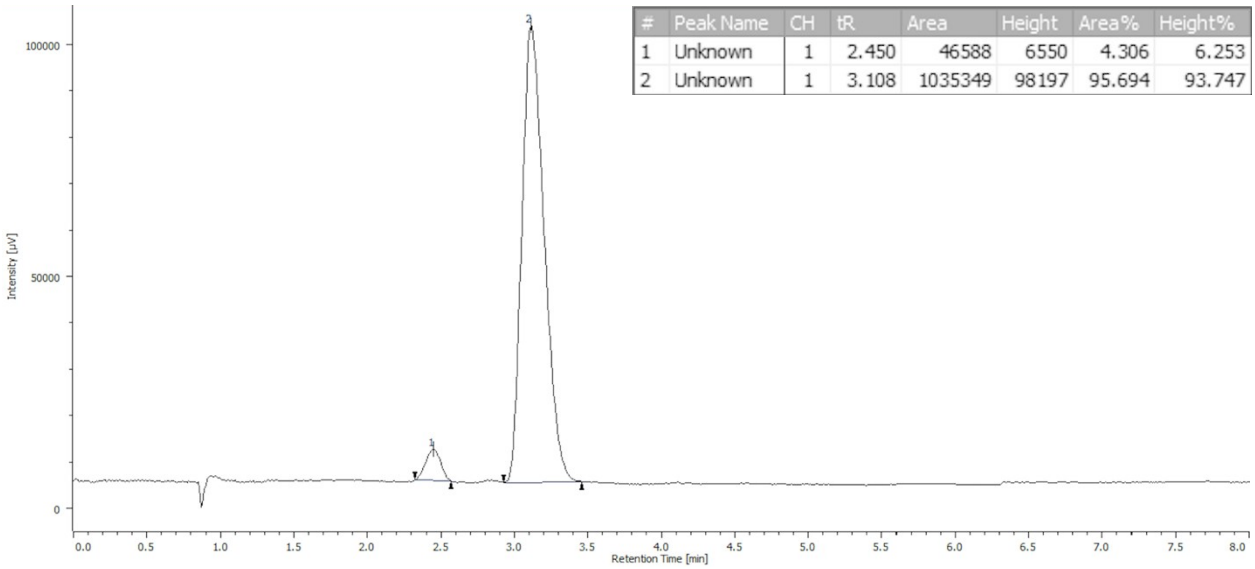
#	Peak Name	CH	tR	Area	Height	Area%	Height%
1	Unknown	1	2.242	128183	13344	51.333	56.131
2	Unknown	1	3.075	121524	10429	48.667	43.869

Figure S1: Chromatogram of (±)-24; 2.6% *ee*



#	Peak Name	CH	tR	Area	Height	Area%	Height%
1	Unknown	1	2.183	34671	3576	8.549	10.914
2	Unknown	1	3.000	370872	29190	91.451	89.086

Figure S2: Chromatogram of (–)-24; 83.0% *ee* *81.5% *ee* average of 3 runs.



#	Peak Name	CH	tR	Area	Height	Area%	Height%
1	Unknown	1	2.450	46588	6550	4.306	6.253
2	Unknown	1	3.108	1035349	98197	95.694	93.747

Figure S3: Chromatogram of (–)-24; 91.4% *ee*

3. References

(1) Guo, Y.; Reis, M. C.; Kootstra, J.; Harutyunyan, S. *ACS Catalysis* **2021**, *11*(14), 8476–8483

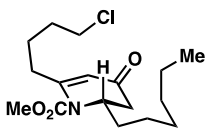
(2) Flick, A. C.; Caballero, M. J. A.; Padwa, A. *Organic Letters* **2008**, *10*(9), 1871–1874

(3) Scarrolin, T.; Gharbaoui T.; Chen C. *Organic Letters* **2022**, *24*(20), 3736–3740

(4) Snider, B.; Liu, T. *The Journal of Organic Chemistry* **1997**, *62*(16), 5630–5633

(5) Hanzawa, R.; Fuwa, H. *Org. Lett.* **2023**, *25*(11), 1984–1988

4. ^{1}H NMR and ^{13}C NMR Spectra



17

	Parameter	Value
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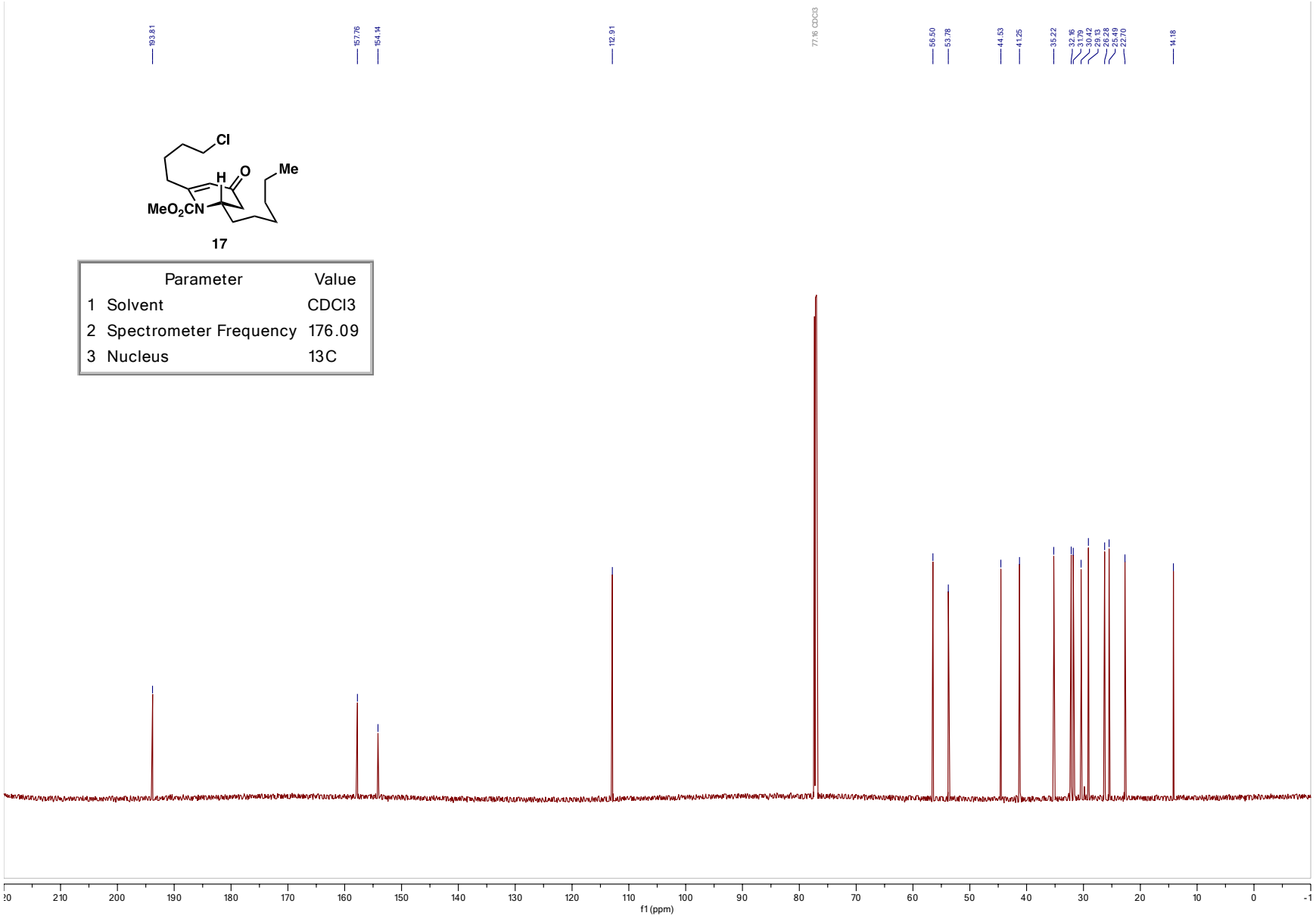
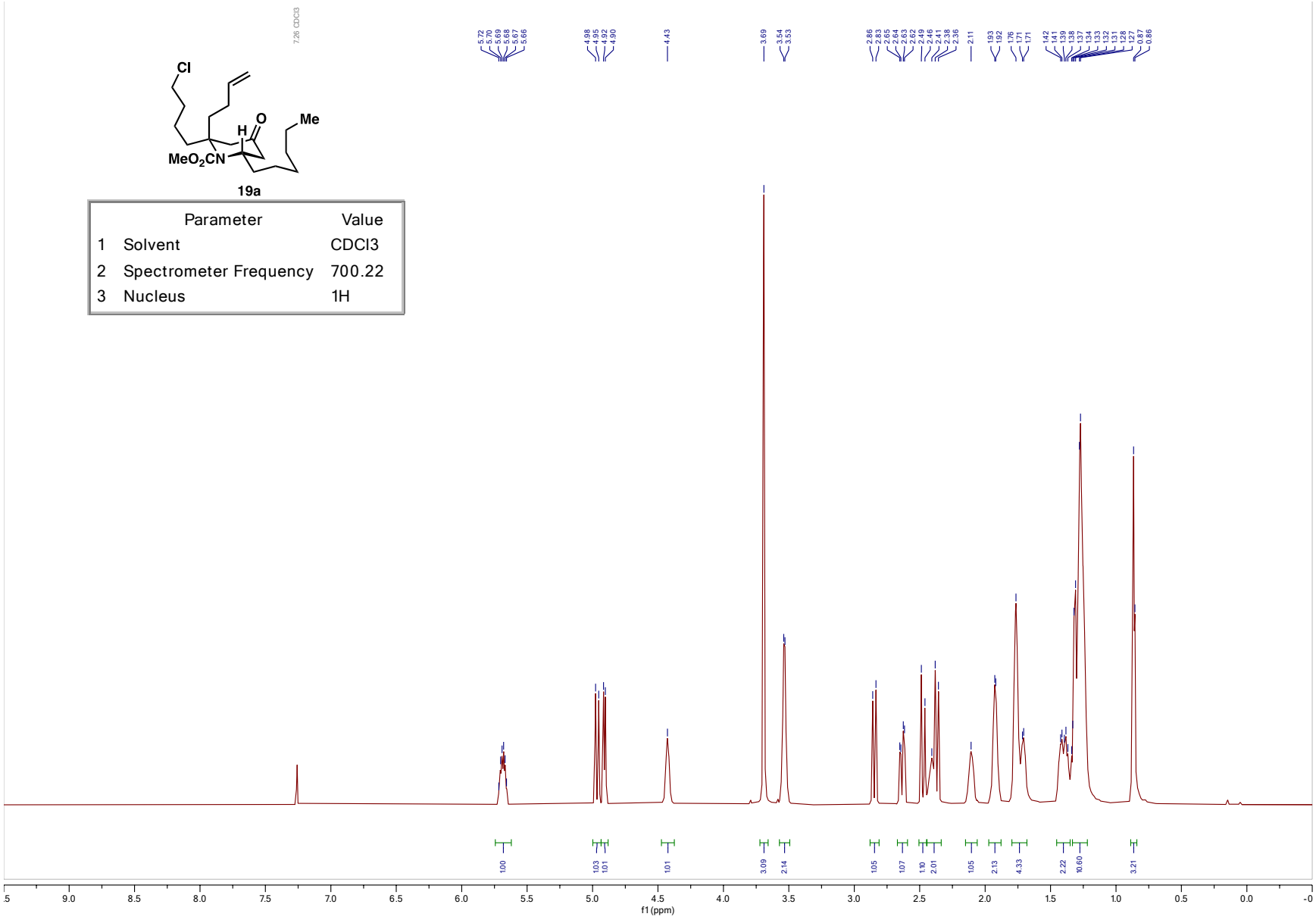
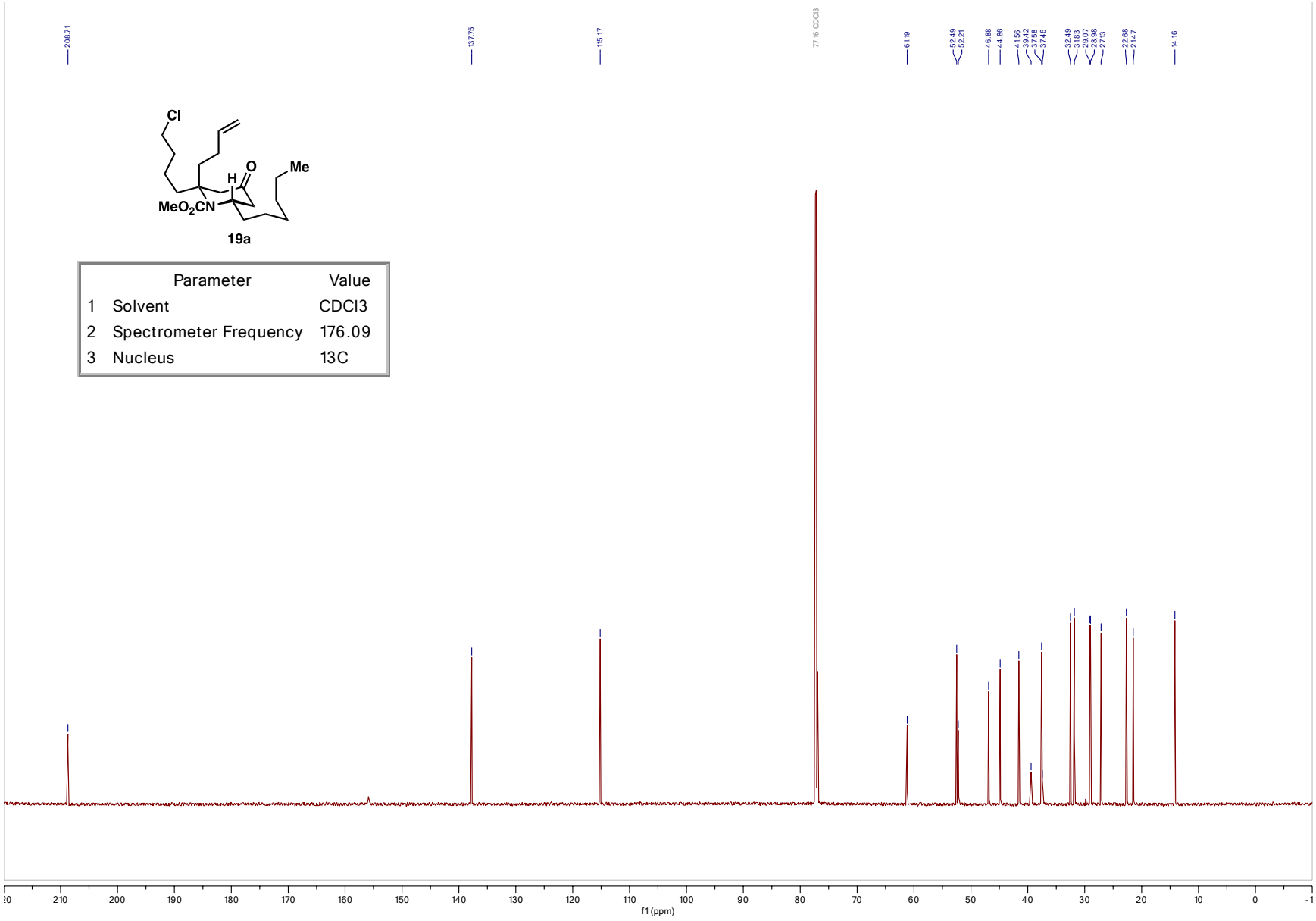
3	Nucleus	1H

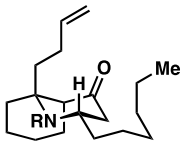

193.81
157.76
154.14
112.91
77.16 CDCl3
56.50
53.78
44.53
41.25
35.22
32.16
31.79
30.42
29.53
26.28
25.49
22.70
14.18
Cl
H
O
Me
MeO2CN
17
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 176.09
3 Nucleus 13C
f1 (ppm)



	Parameter	Value
1	Solvent	CDCl3
2	Spectrometer Frequency	700.22
3	Nucleus	1H



	Parameter	Value
1	Solvent	CDCl3
2	Spectrometer Frequency	176.09
3	Nucleus	13C



21a (R = CO_2Me)

	Parameter	Value
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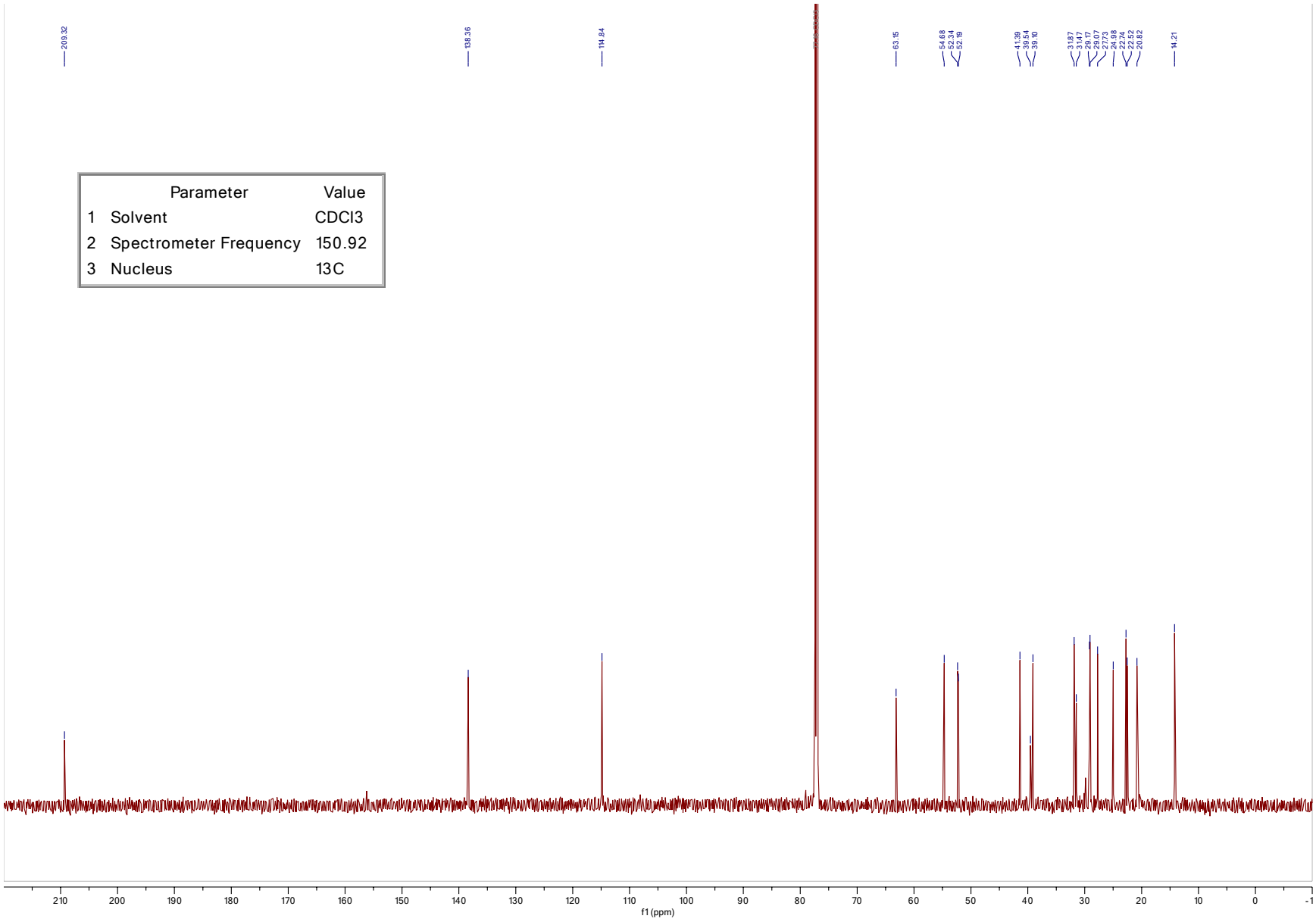
2	Spectrometer Frequency	600.13
3	Nucleus	1H


209.32
138.36
114.84
63.15
54.68
52.34
52.19
41.39
39.54
39.10
31.87
31.47
30.77
29.07
27.73
24.98
22.74
22.52
20.82
14.21
Parameter Value
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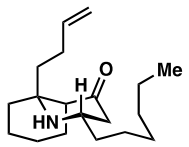
2 Spectrometer Frequency 150.92
3 Nucleus 13C
f1 (ppm)



22a

	Parameter	Value
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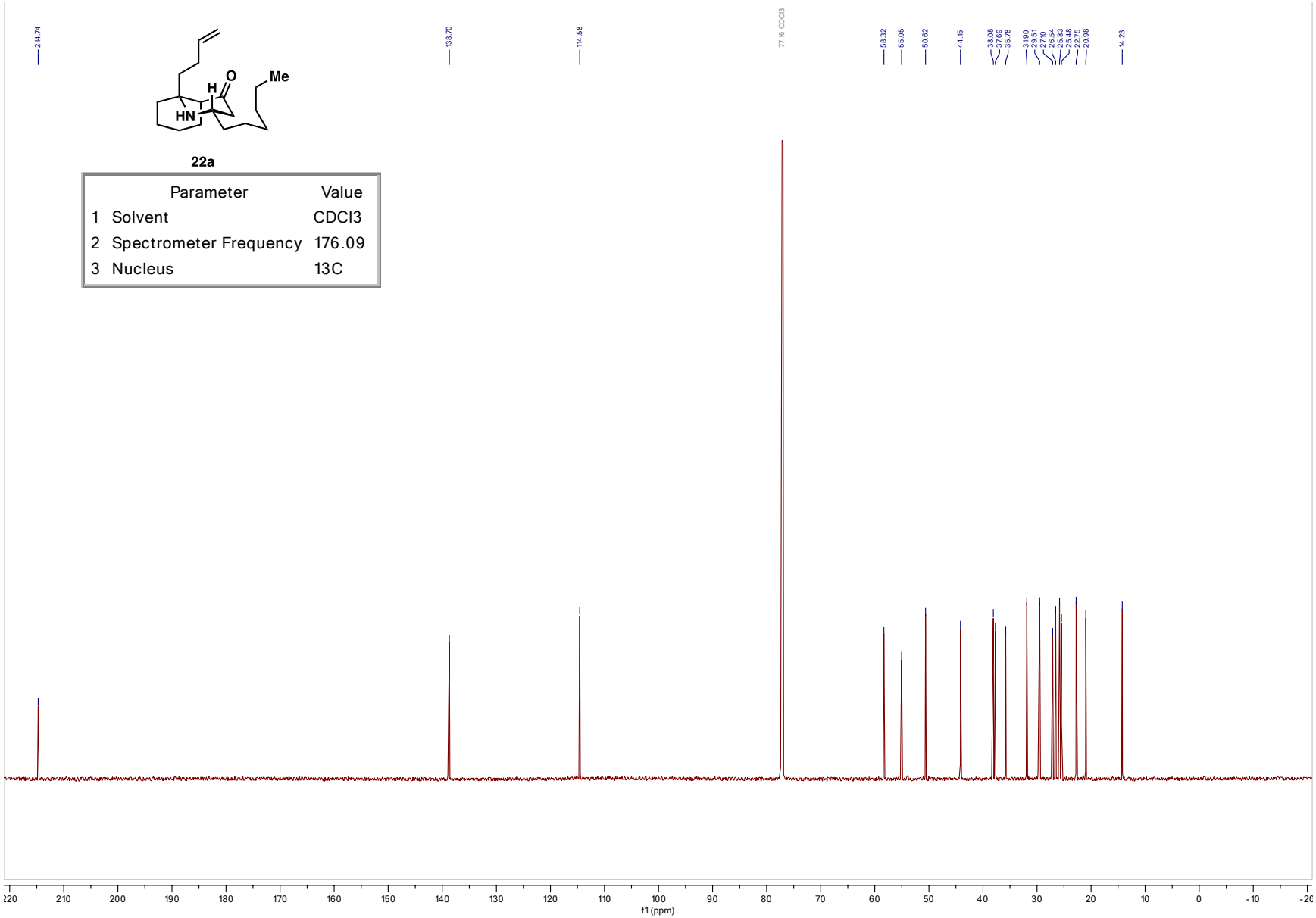
2	Spectrometer Frequency	700.22
3	Nucleus	1H



22a

	Parameter	Value
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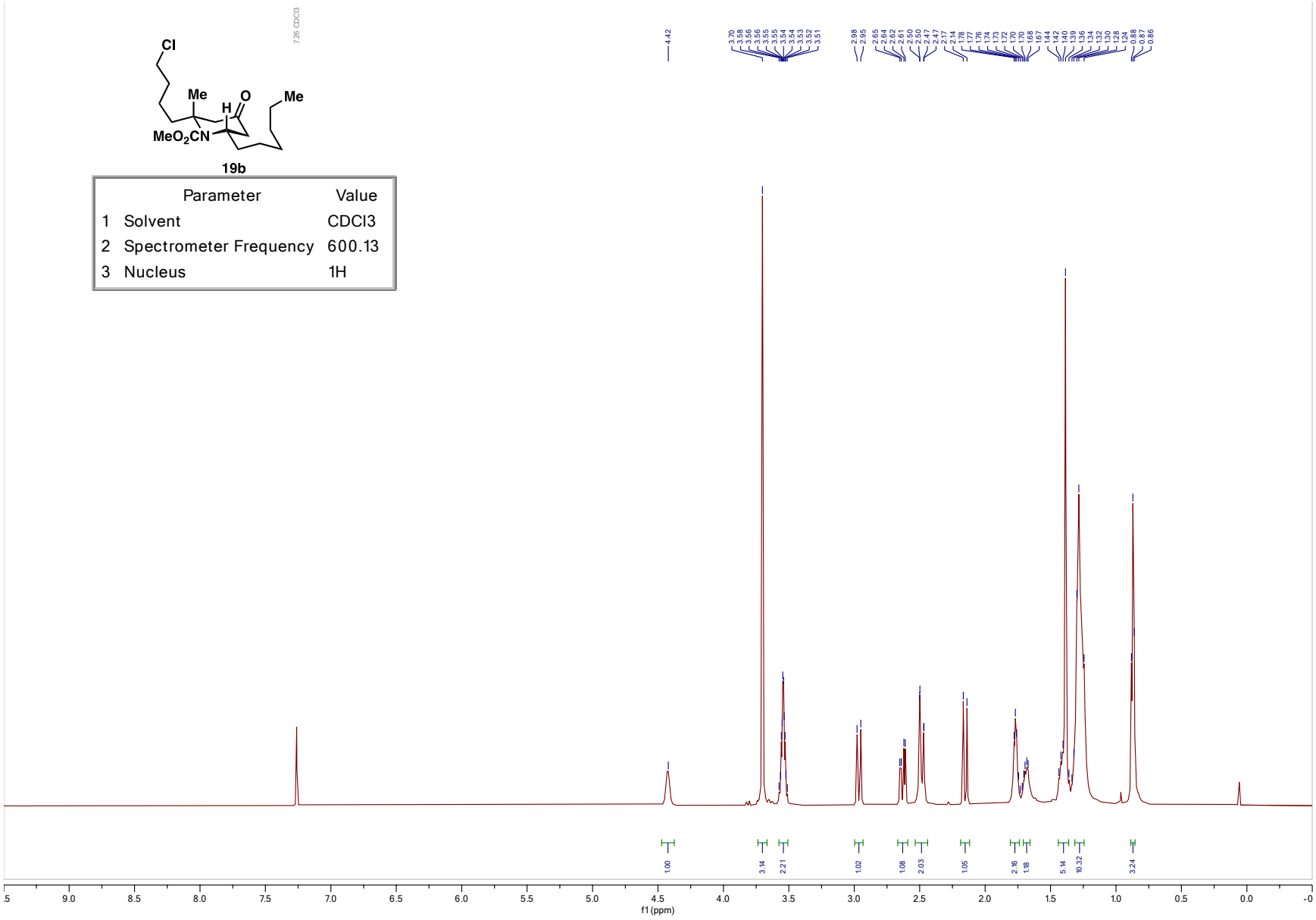
2	Spectrometer Frequency	176.09
3	Nucleus	13C



	Parameter	Value
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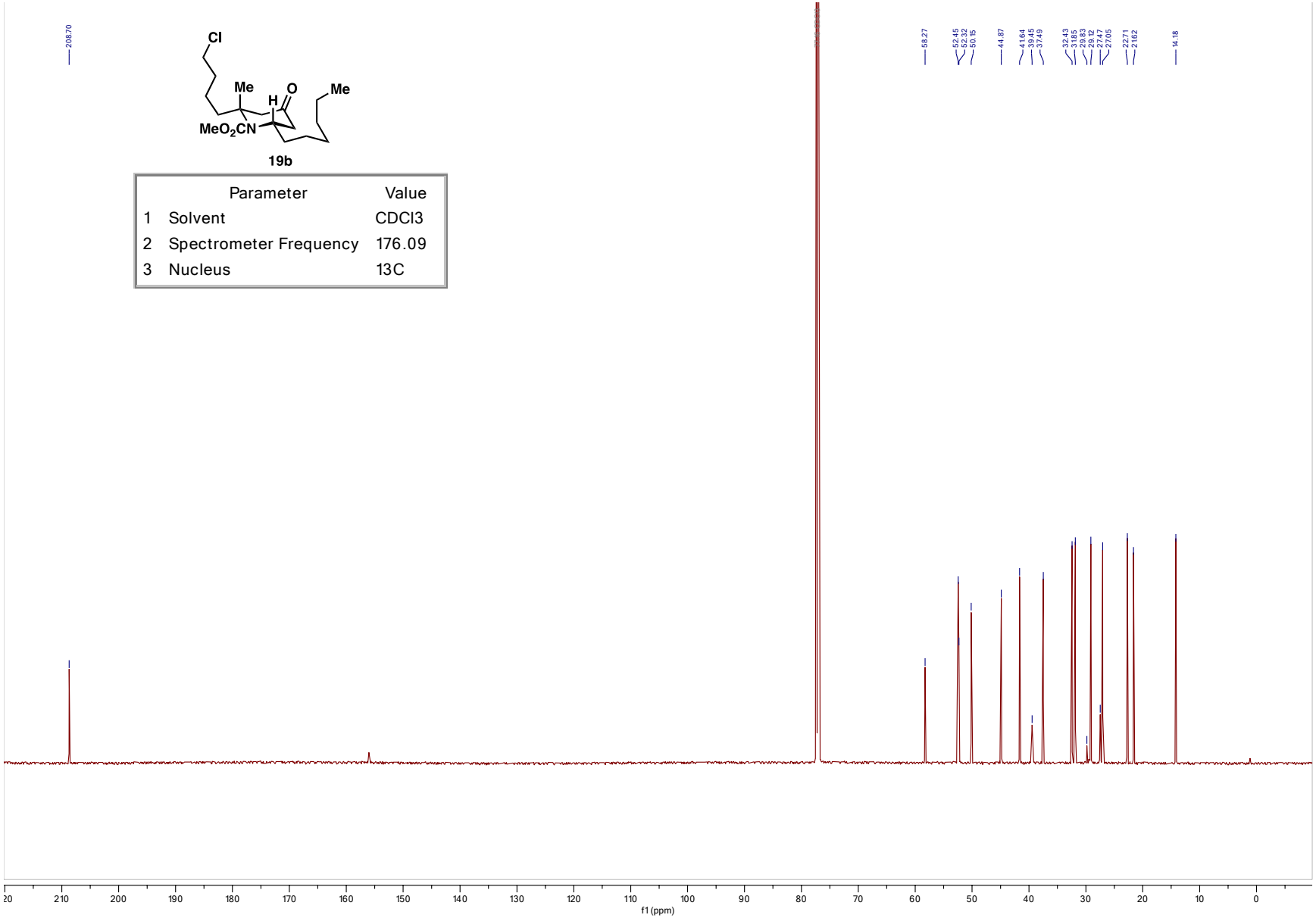
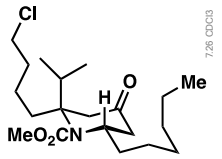
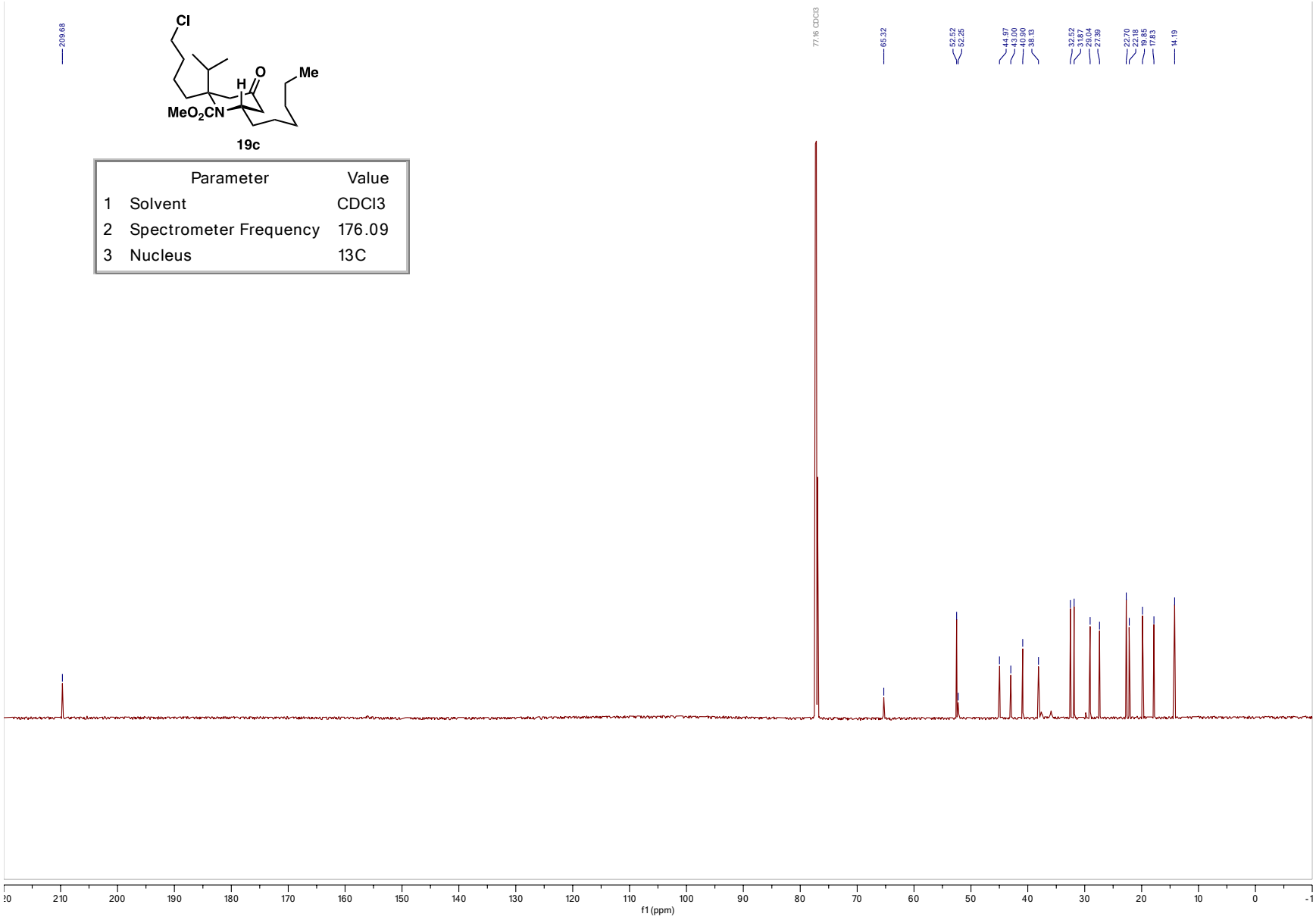
2	Spectrometer Frequency	600.13
3	Nucleus	1H


Cl
Me
O
H
Me
MeO2CN
19b
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 176.09
3 Nucleus 13C
208.70
58.27
52.45
52.32
50.15
44.87
41.64
39.45
37.49
32.43
31.85
29.83
29.12
27.17
27.05
22.71
21.62
14.18
f1 (ppm)

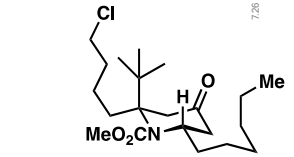


19c

	Parameter	Value
1	Solvent	CDCl3
2	Spectrometer Frequency	700.22
3	Nucleus	1H

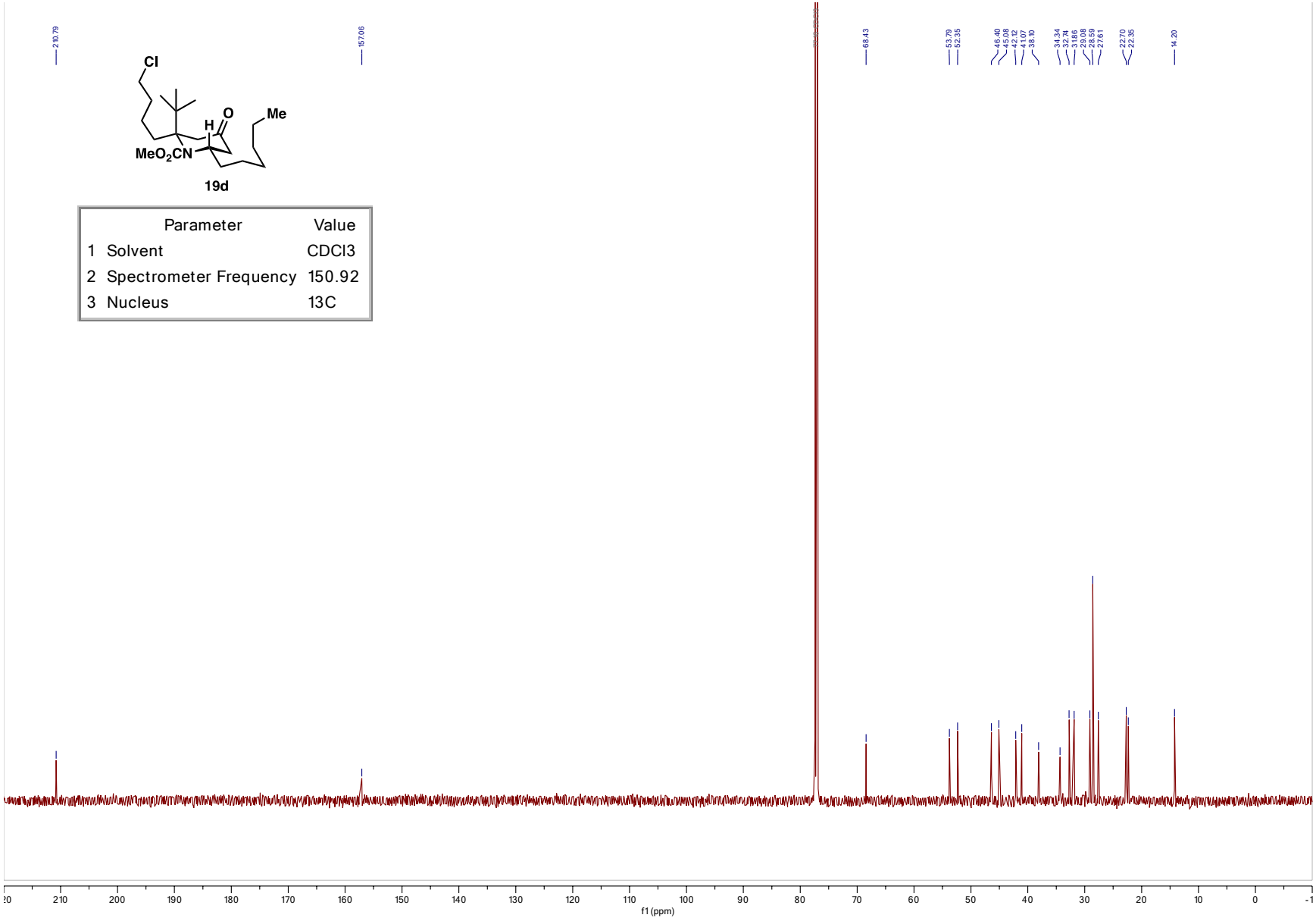


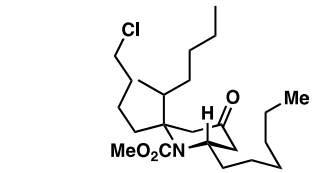
	Parameter	Value
1	Solvent	CDCl3
2	Spectrometer Frequency	176.09
3	Nucleus	13C



19d

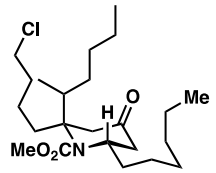
	Parameter	Value
1	Solvent	CDCl3
2	Spectrometer Frequency	600.13
3	Nucleus	1H


Cl
O
H
Me
MeO2CN
19d
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 150.92
3 Nucleus 13C
210.79
157.06
77.32
68.43
53.79
52.35
46.40
45.08
43.23
41.07
38.10
34.34
32.74
31.86
29.08
28.59
27.61
22.70
22.35
14.20
f1 (ppm)



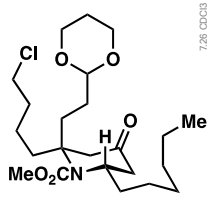
19e

	Parameter	Value
1	Solvent	CDCl3
2	Spectrometer Frequency	600.13
3	Nucleus	1H



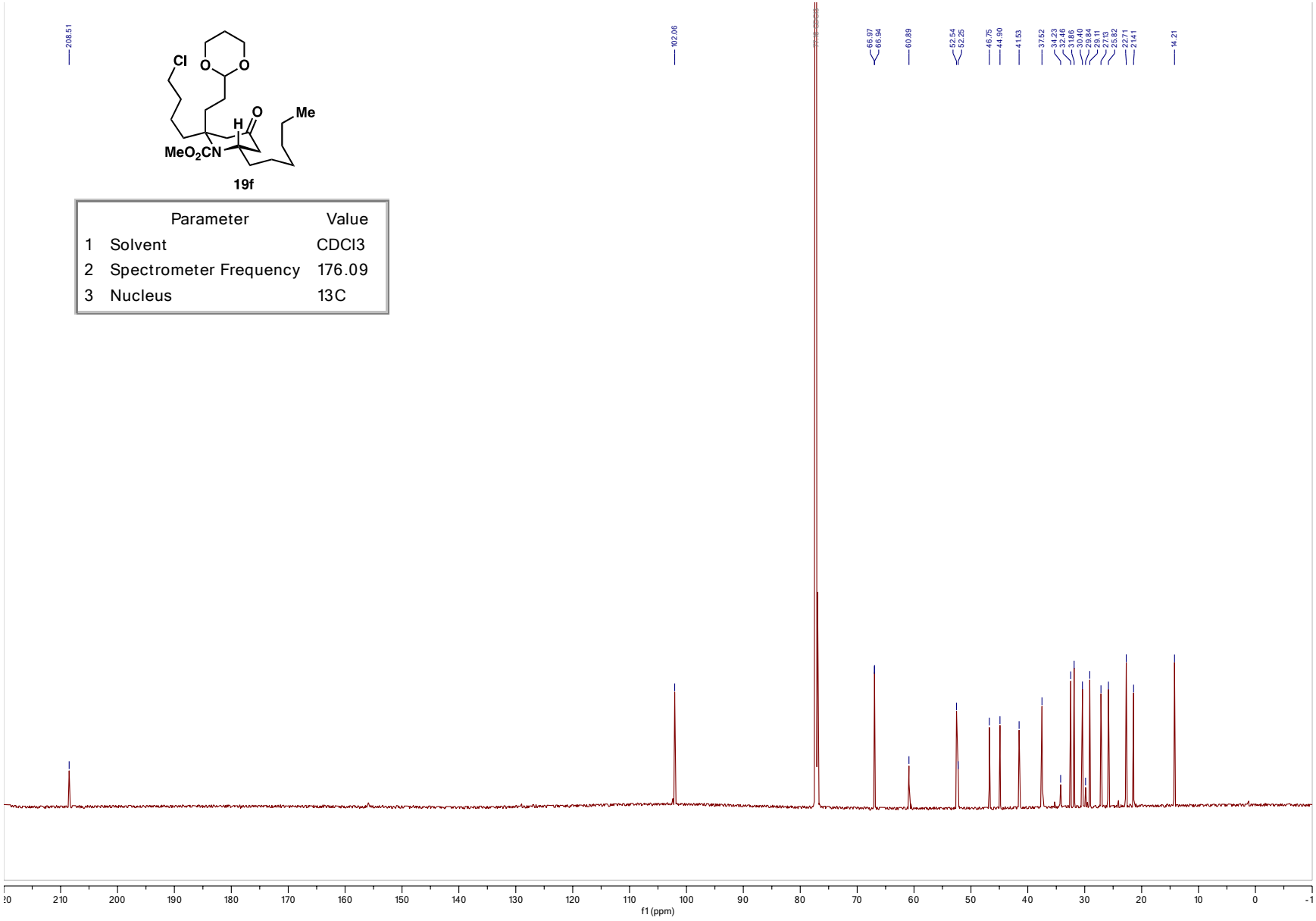
19e

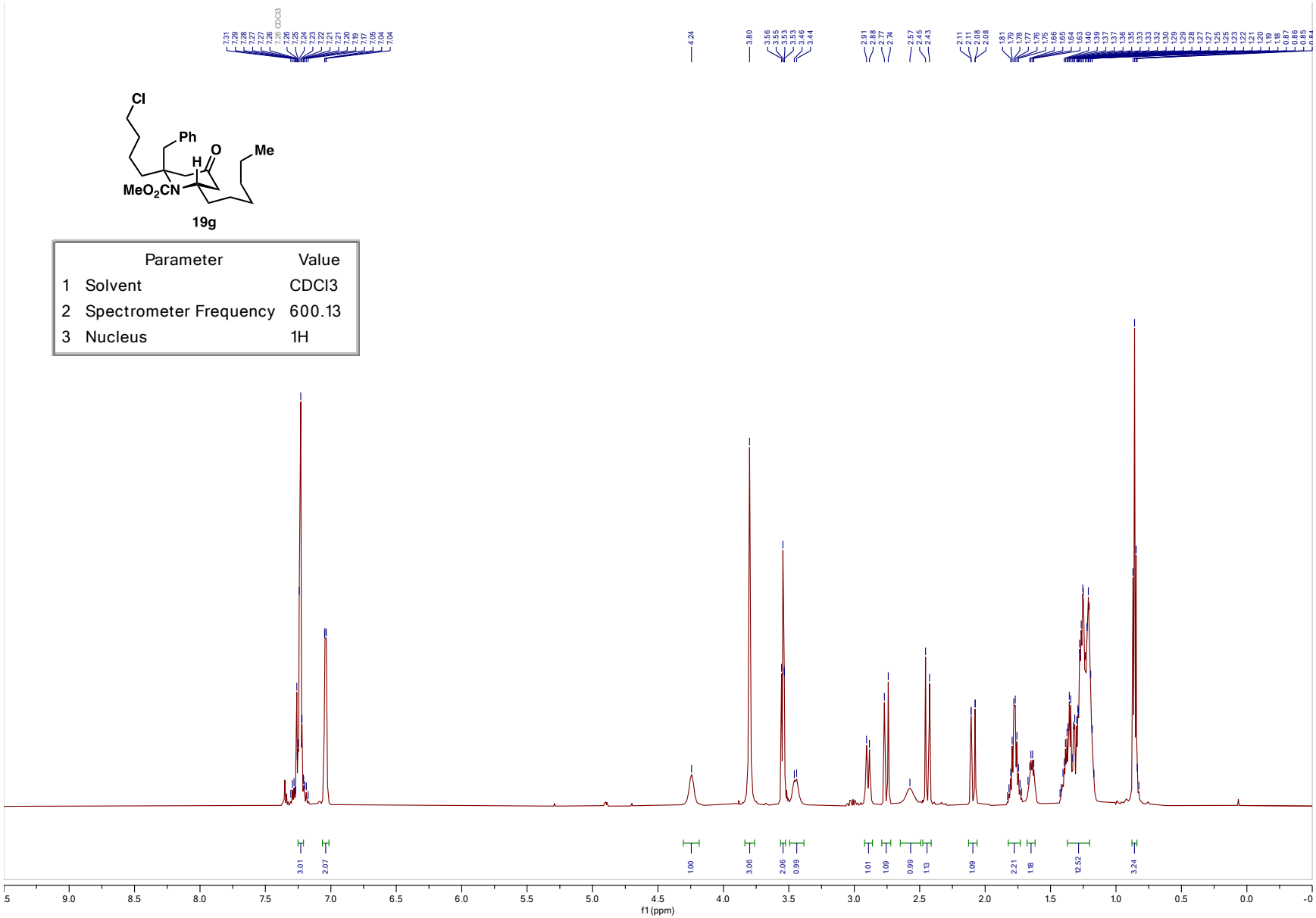
	Parameter	Value
1	Solvent	CDCl3
2	Spectrometer Frequency	176.09
3	Nucleus	13C

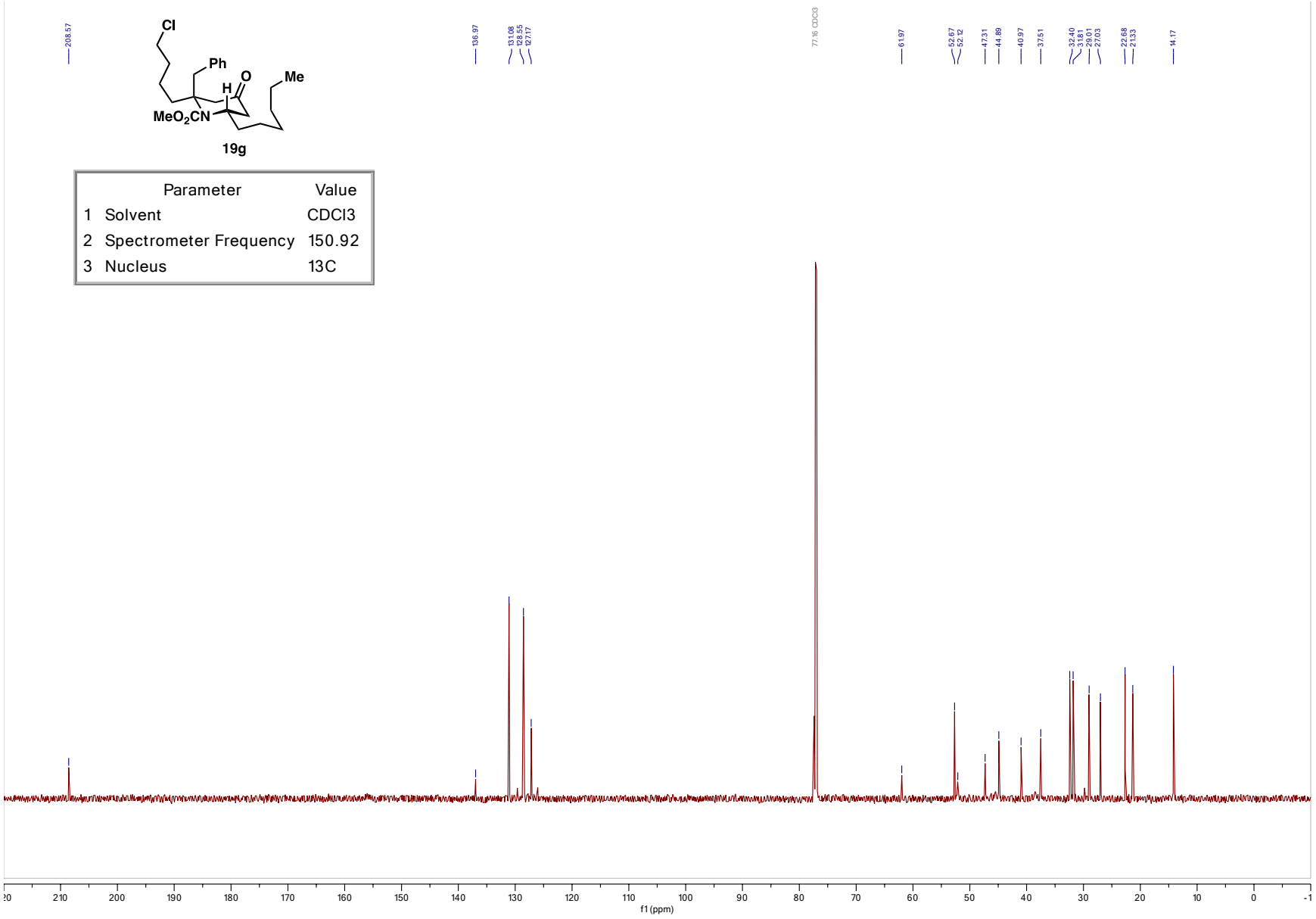


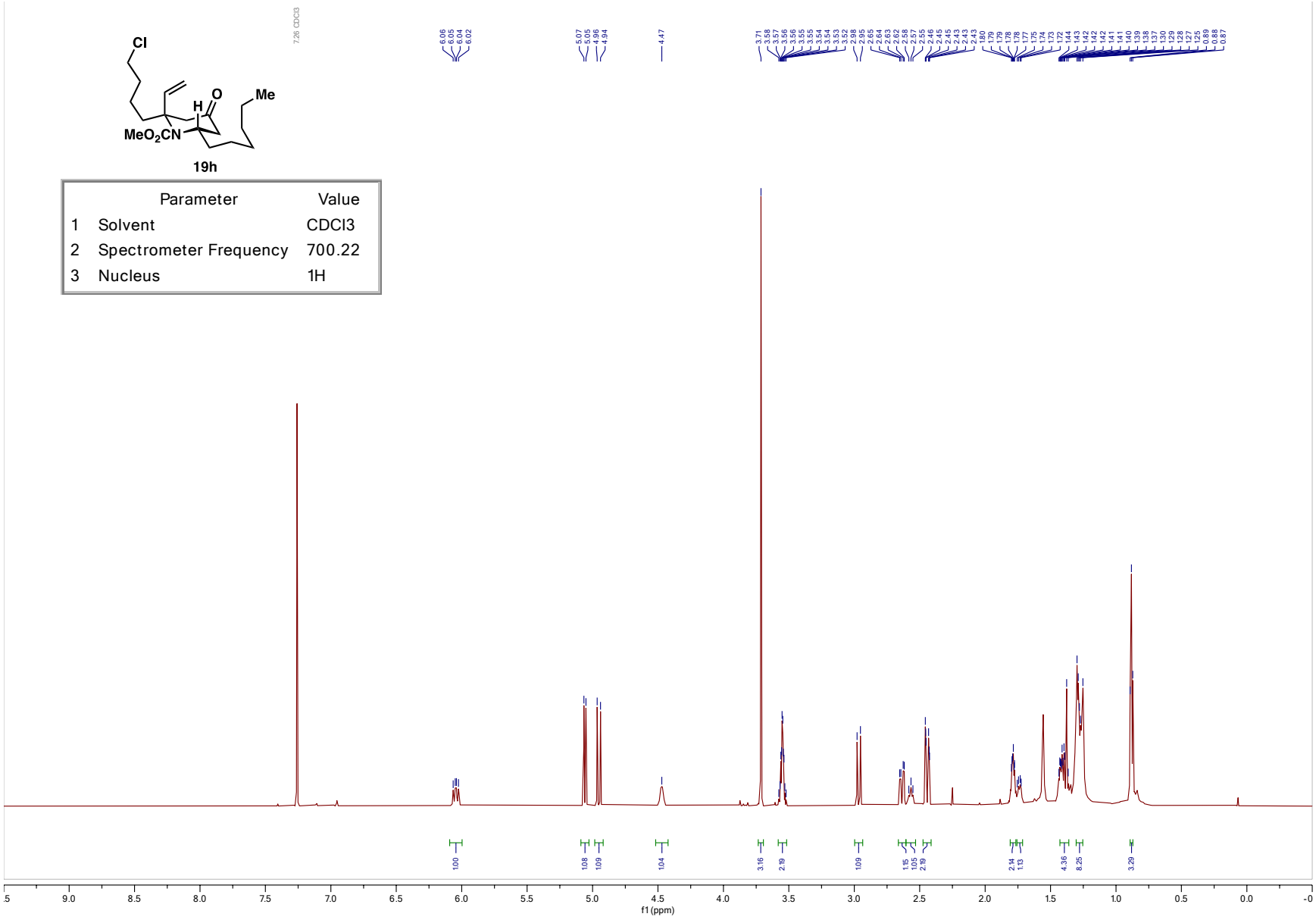
19f

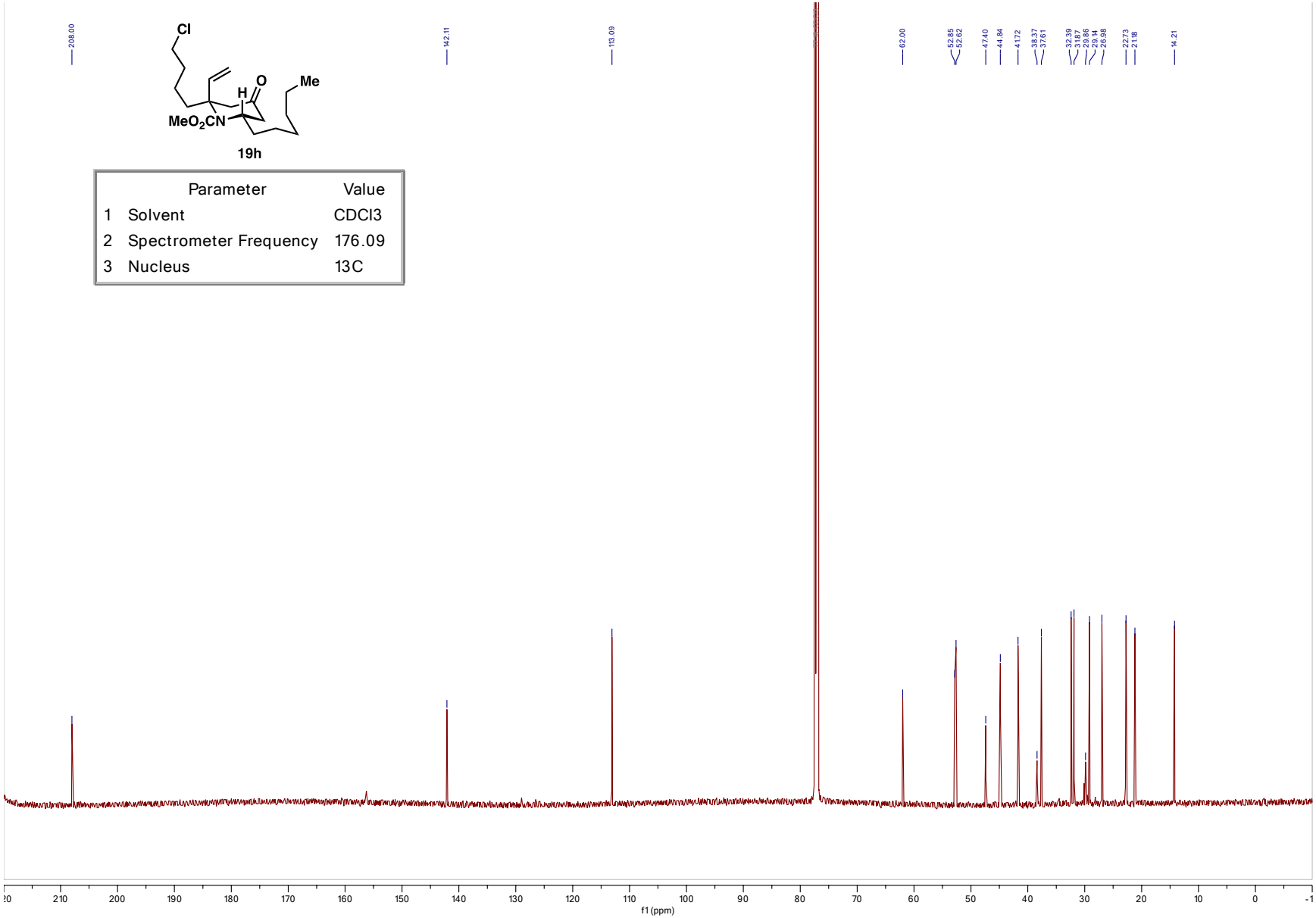
	Parameter	Value
1	Solvent	CDCl3
2	Spectrometer Frequency	600.13
3	Nucleus	1H


208.51
102.06
77.16
66.97
66.94
60.89
52.54
52.25
46.75
44.90
41.53
37.52
34.23
32.46
31.86
30.40
29.84
29.11
27.13
25.82
22.71
21.41
14.21
Cl
O
O
H
O
Me
MeO2CN
19f
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 176.09
3 Nucleus 13C
f1 (ppm)

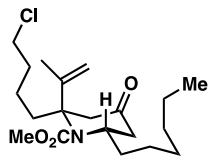

Cl
Ph
O
H
Me
MeO2CN
19g
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 600.13
3 Nucleus 1H
f1 (ppm)


208.57
136.97
131.08
128.55
127.17
77.16 CDCl3
61.97
52.67
52.12
47.31
44.89
40.97
37.51
32.40
31.81
29.01
27.03
22.68
21.33
14.17
Cl
Ph
O
H
Me
MeO2CN
19g
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 150.92
3 Nucleus 13C
f1 (ppm)


Cl
O
H
Me
MeO2CN
19h
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 700.22
3 Nucleus 1H
f1 (ppm)

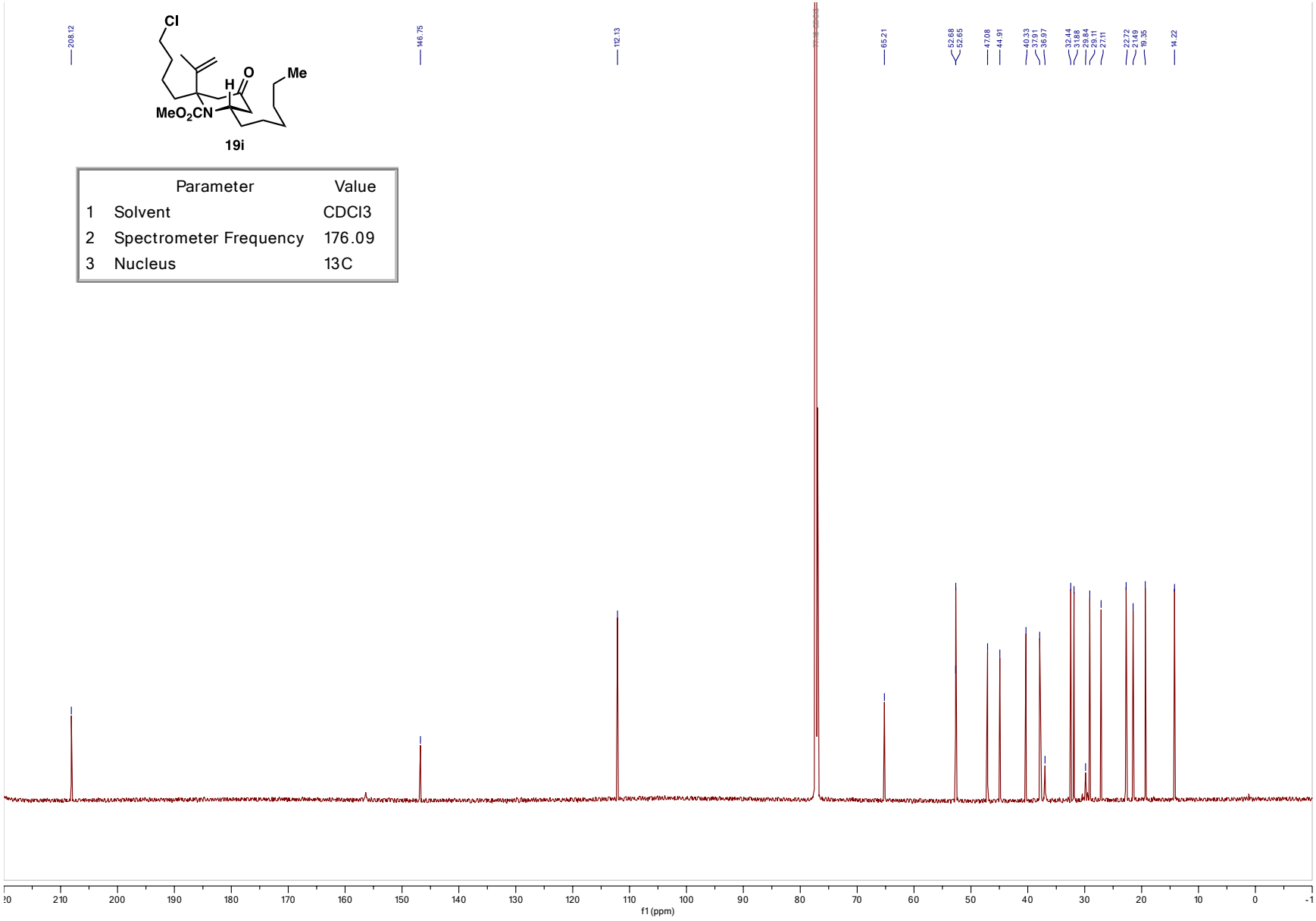


	Parameter	Value
1	Solvent	CDCl3
2	Spectrometer Frequency	176.09
3	Nucleus	13C

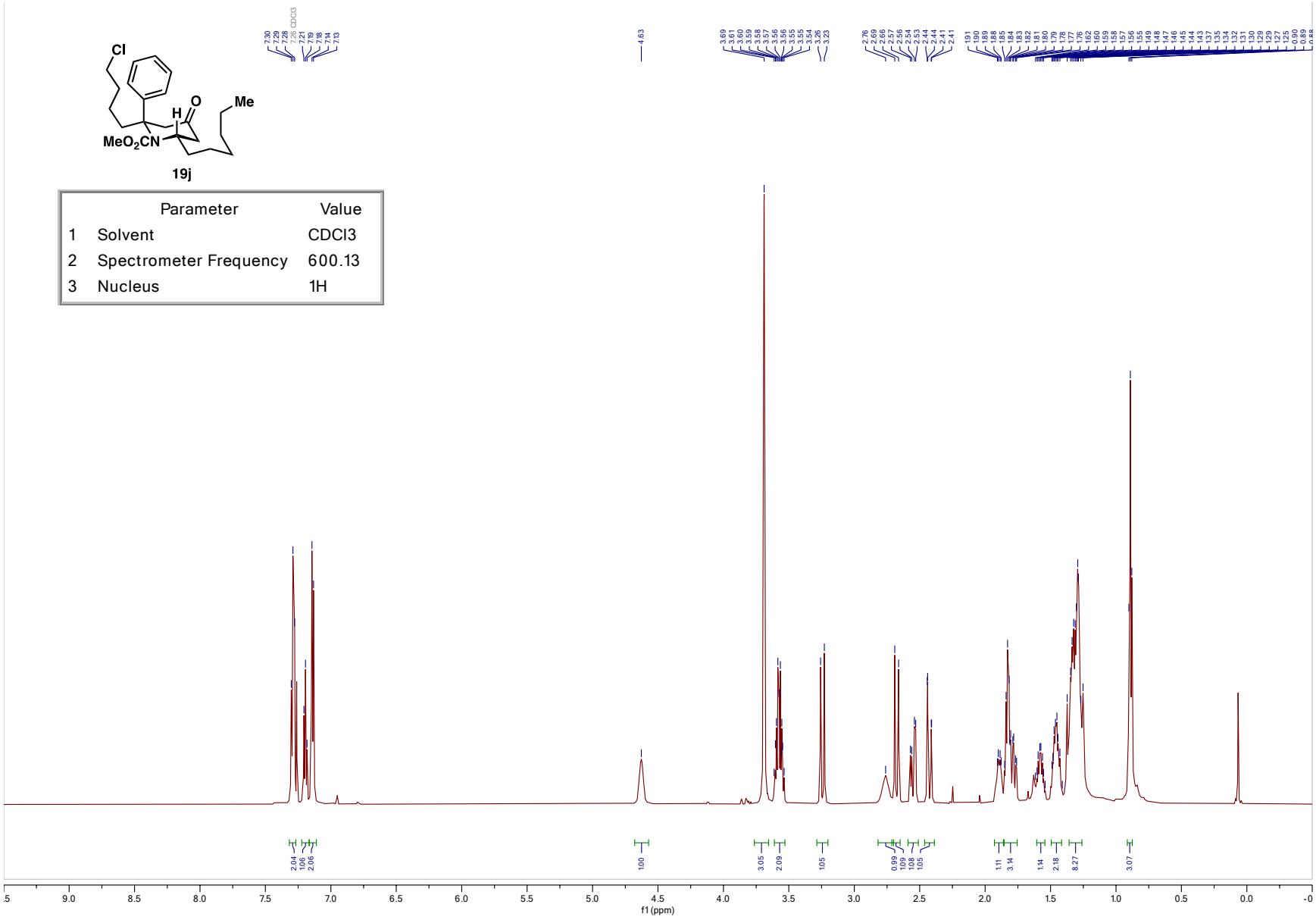


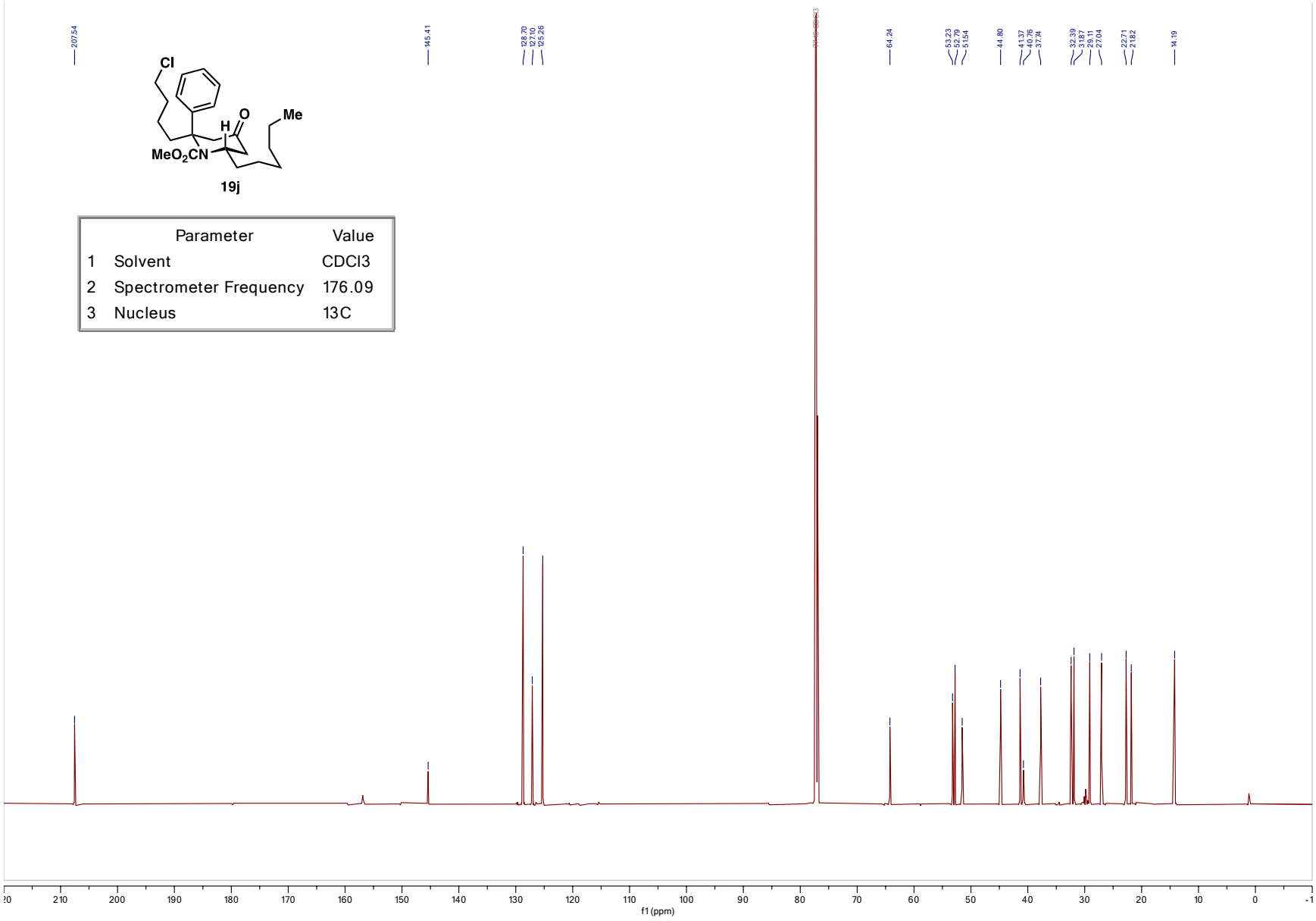
19i

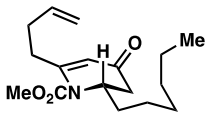
	Parameter	Value
1	Solvent	CDCl3
2	Spectrometer Frequency	600.13
3	Nucleus	1H



	Parameter	Value
1	Solvent	CDCl3
2	Spectrometer Frequency	176.09
3	Nucleus	13C

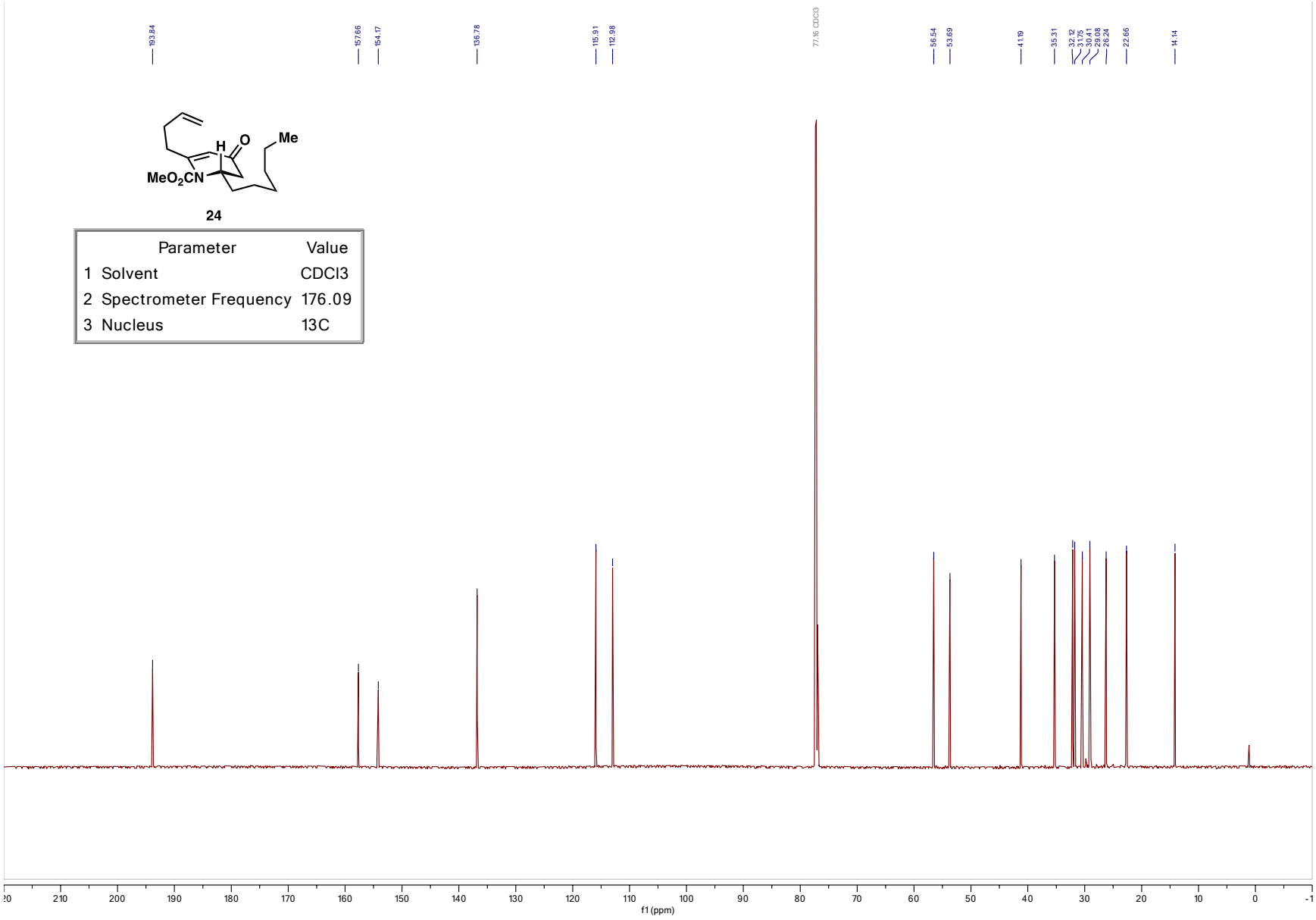

Cl
H
O
Me
MeO2CN
19j
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 600.13
3 Nucleus 1H
f1 (ppm)

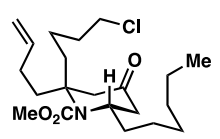

207.54
145.41
128.70
127.10
125.26
77.16
64.24
53.23
52.79
51.54
44.80
41.37
40.76
37.74
32.39
31.67
29.11
27.04
22.71
21.82
14.19
Cl
O
H
Me
MeO2CN
19j
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 176.09
3 Nucleus 13C
f1 (ppm)



24

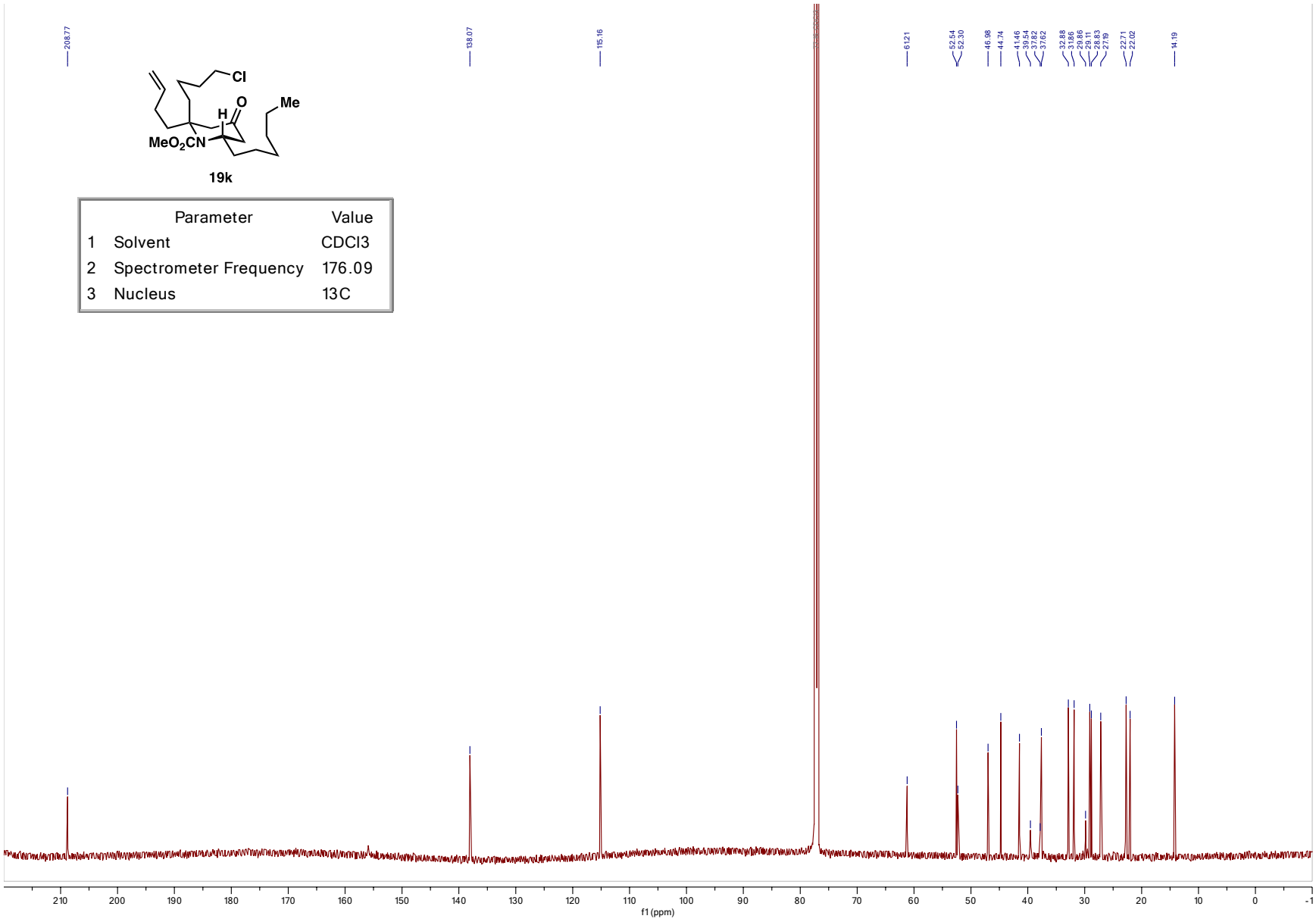
	Parameter	Value
1	Solvent	CDCl3
2	Spectrometer Frequency	600.13
3	Nucleus	1H


193.84
157.66
154.17
136.78
115.91
112.98
77.16 CDCl3
56.54
53.69
41.19
35.31
32.12
31.75
30.41
29.08
26.24
22.66
14.14
H
O
Me
MeO2CN
24
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 176.09
3 Nucleus 13C
f1 (ppm)

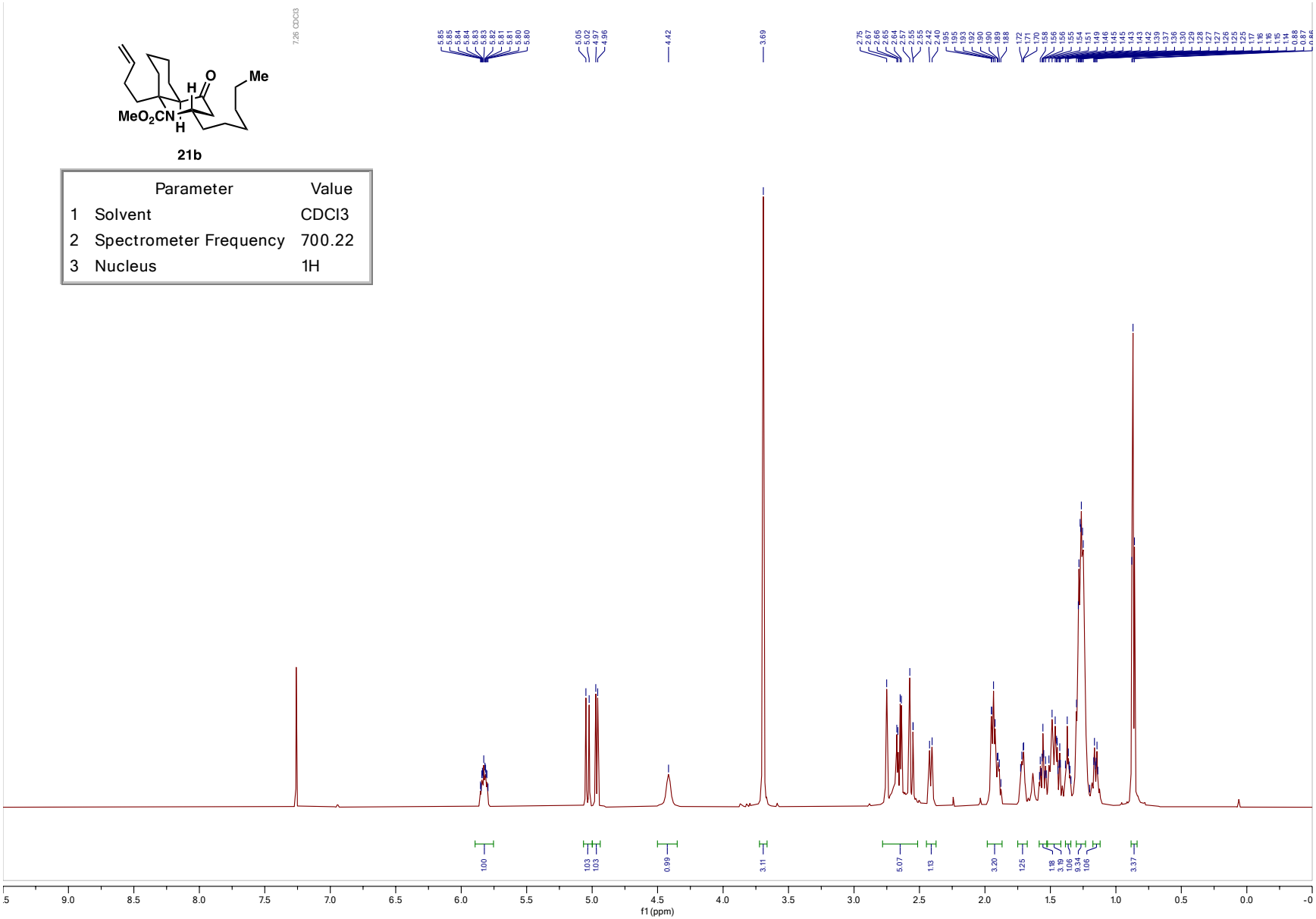


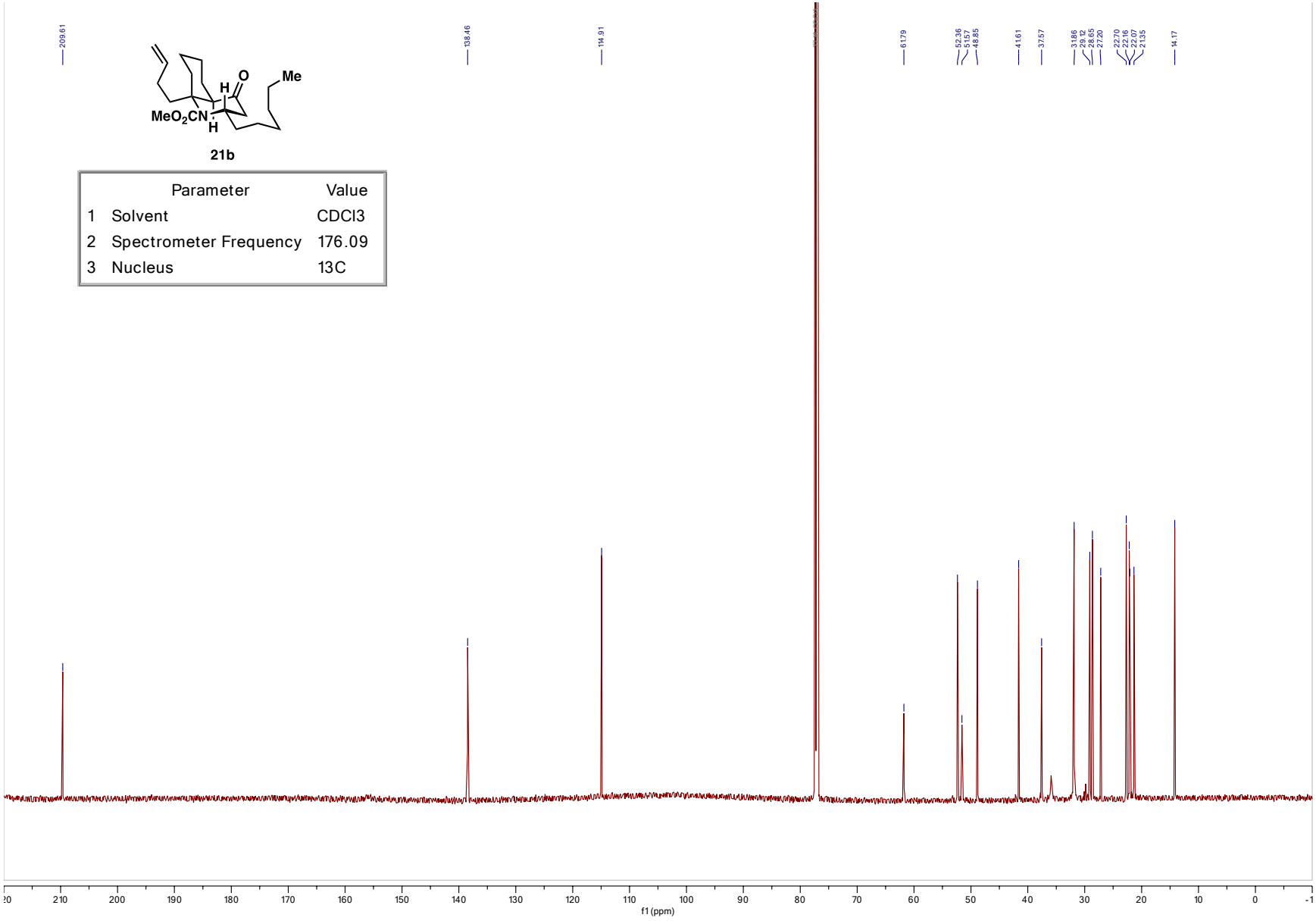
19k

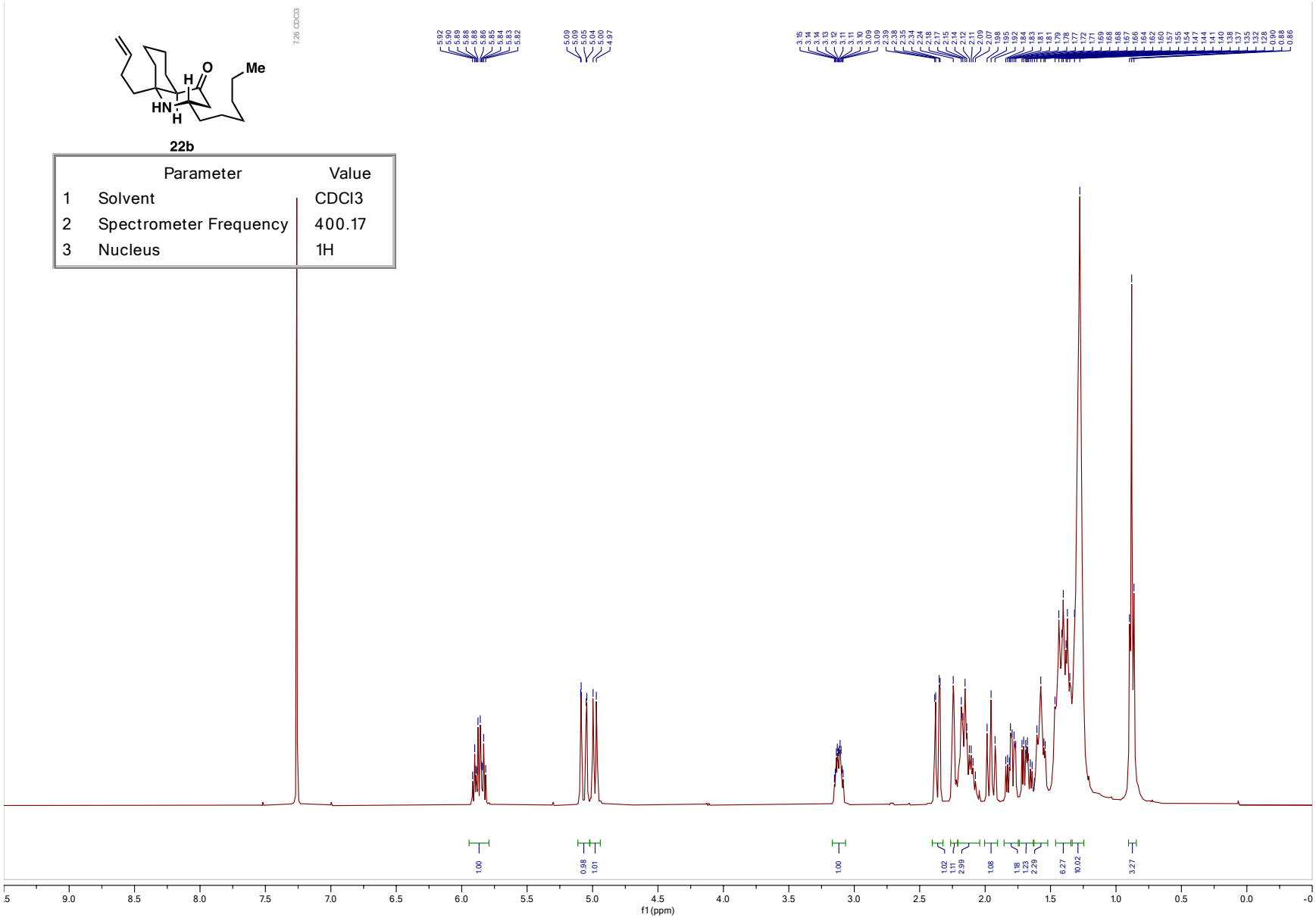
	Parameter	Value
1	Solvent	CDCl3
2	Spectrometer Frequency	600.13
3	Nucleus	1H

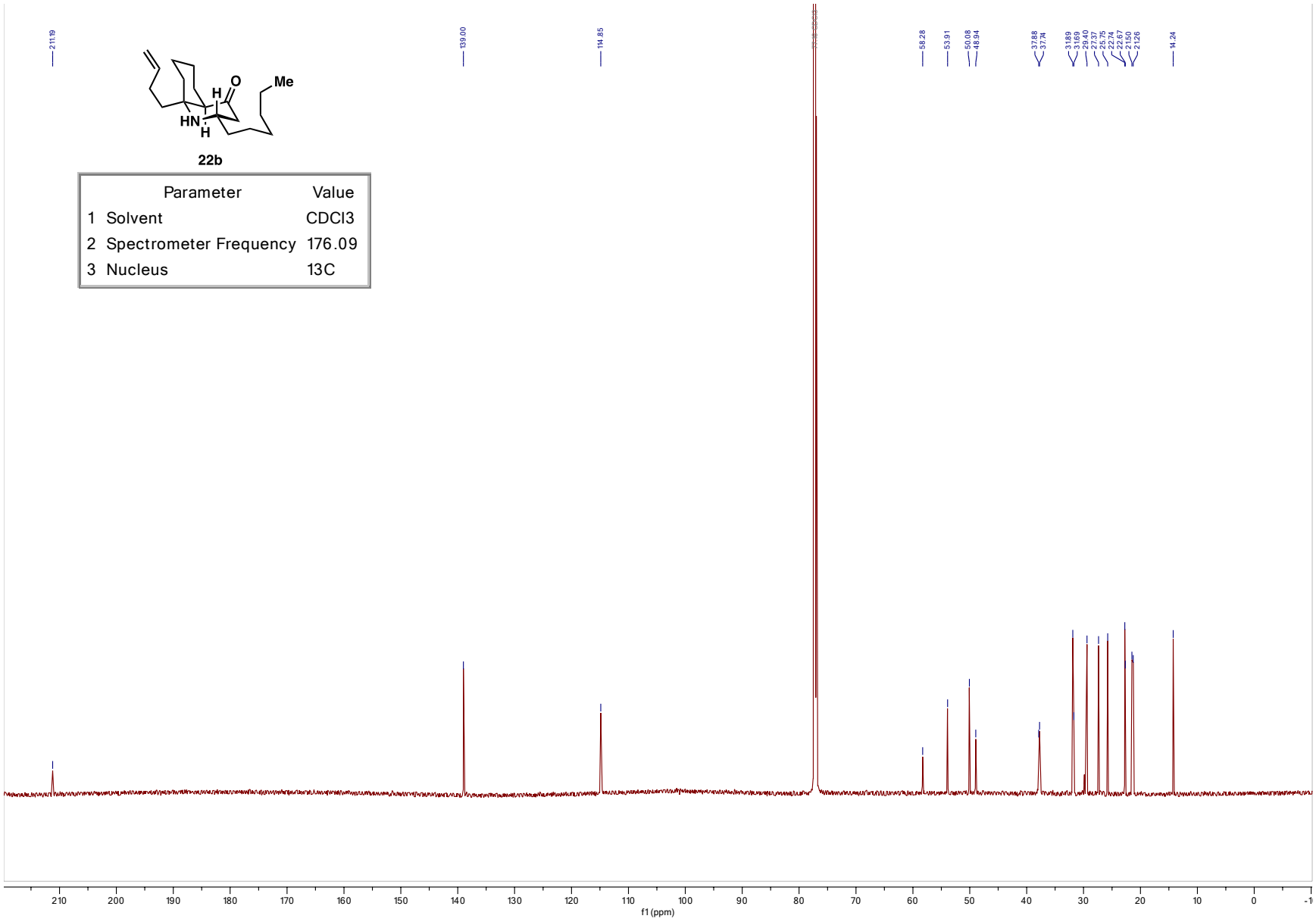


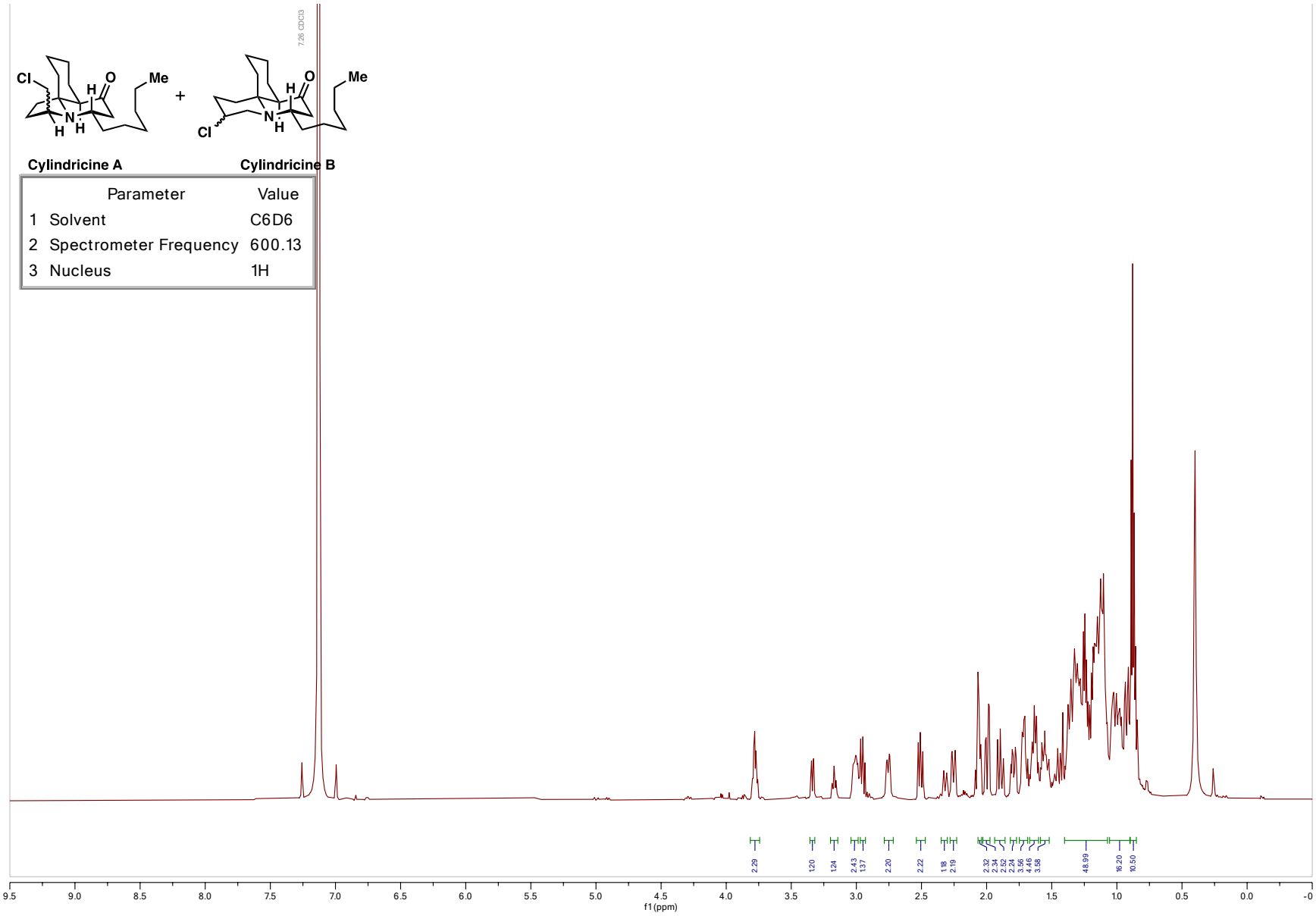
	Parameter	Value
1	Solvent	CDCl3
2	Spectrometer Frequency	176.09
3	Nucleus	13C

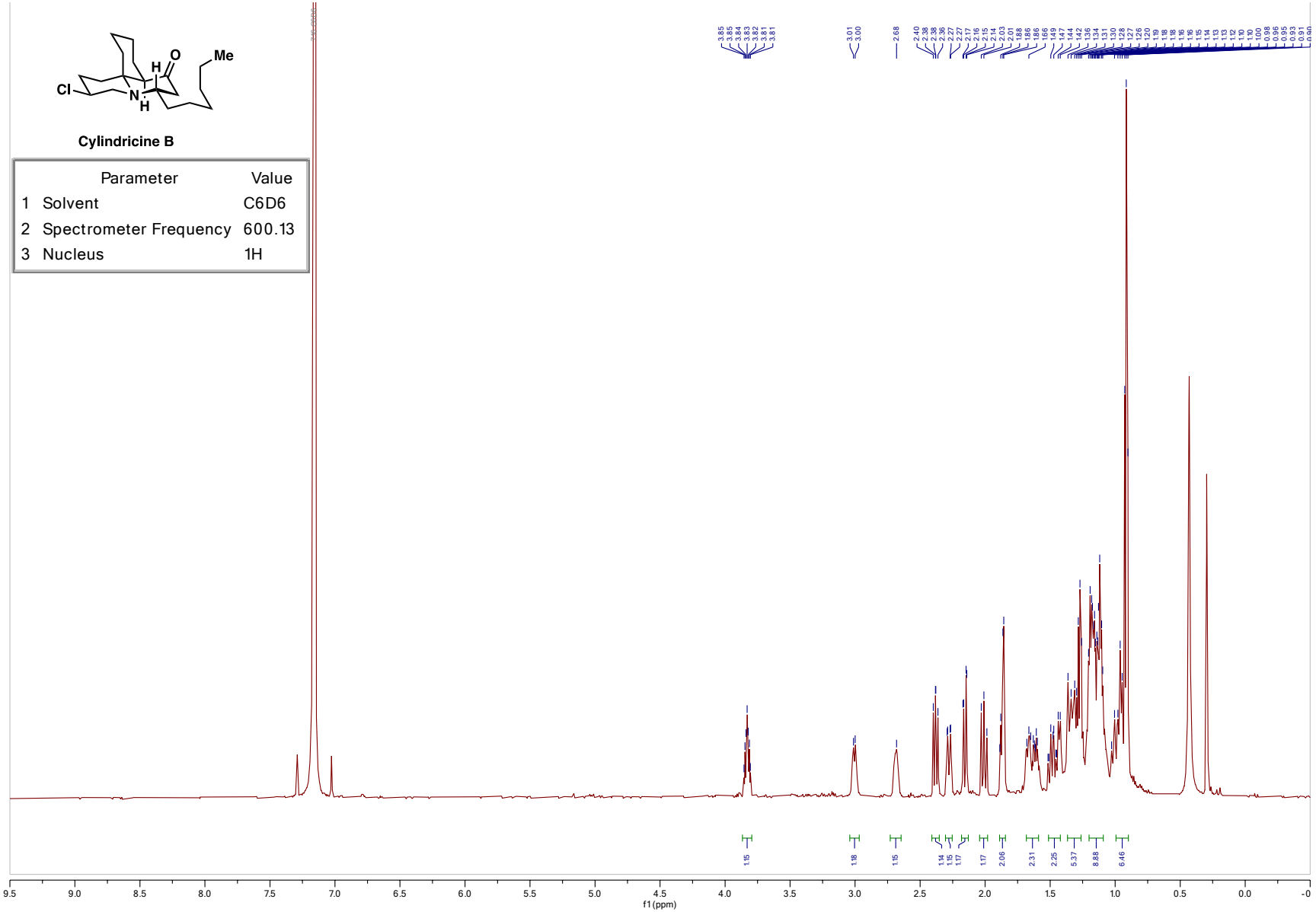

MeO2CN
H
O
Me
H
21b
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 700.22
3 Nucleus 1H
f1 (ppm)

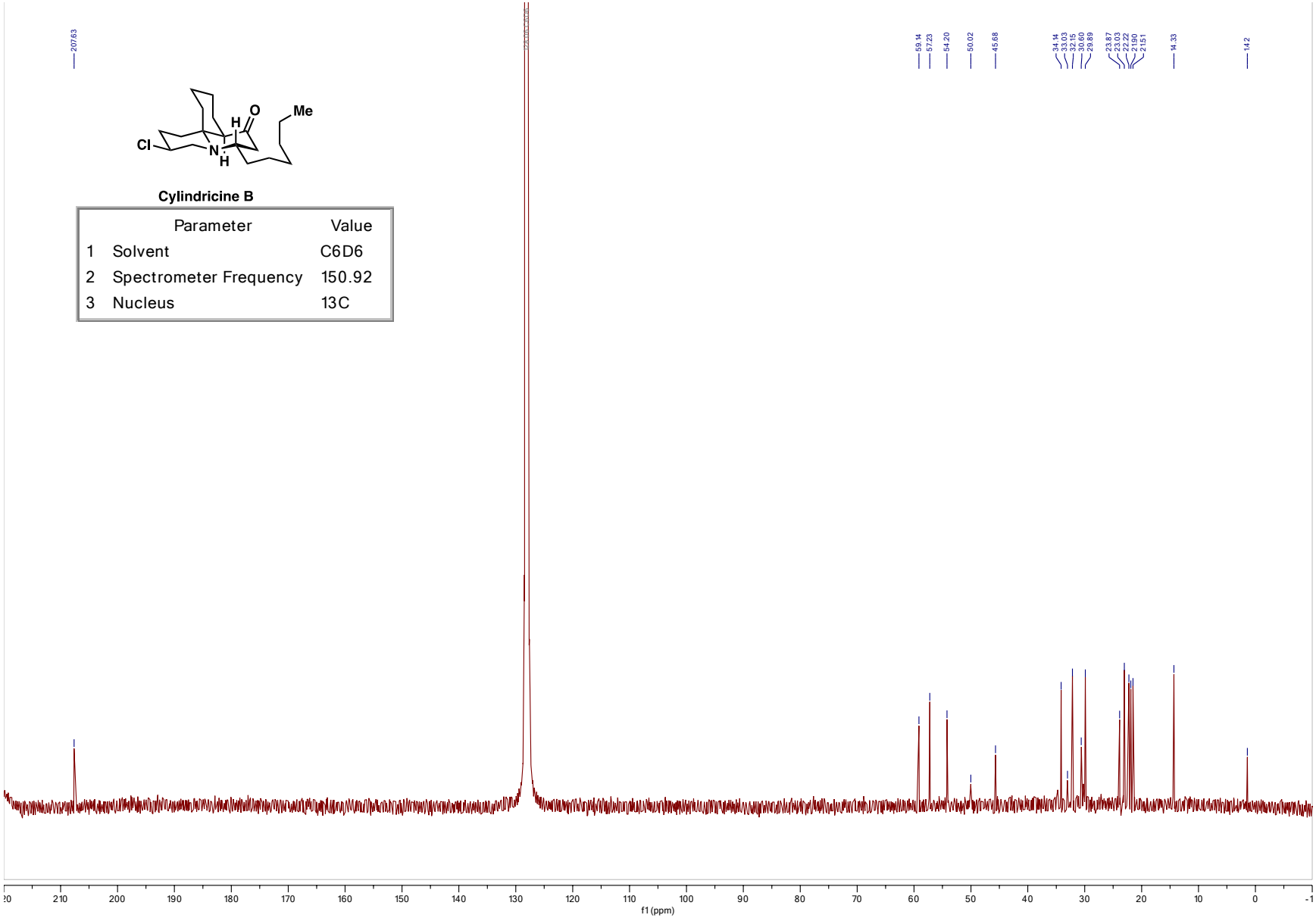

209.61
138.46
114.91
77.00
61.79
52.36
51.57
48.85
41.61
37.57
31.86
29.12
28.65
27.20
22.70
22.16
22.07
21.35
14.17
O
H
Me
MeO2CN
H
21b
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 176.09
3 Nucleus 13C
f1 (ppm)


O
H
Me
HN
H
22b
7.26 CDCl3
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 400.17
3 Nucleus 1H
f1 (ppm)


211.19
139.00
114.85
77.16 CDCl3
58.28
53.91
50.08
48.94
37.88
37.74
31.89
31.69
29.40
27.37
25.75
22.74
22.67
21.50
21.26
14.24
O
H
Me
HN
H
22b
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 176.09
3 Nucleus 13C
f1 (ppm)

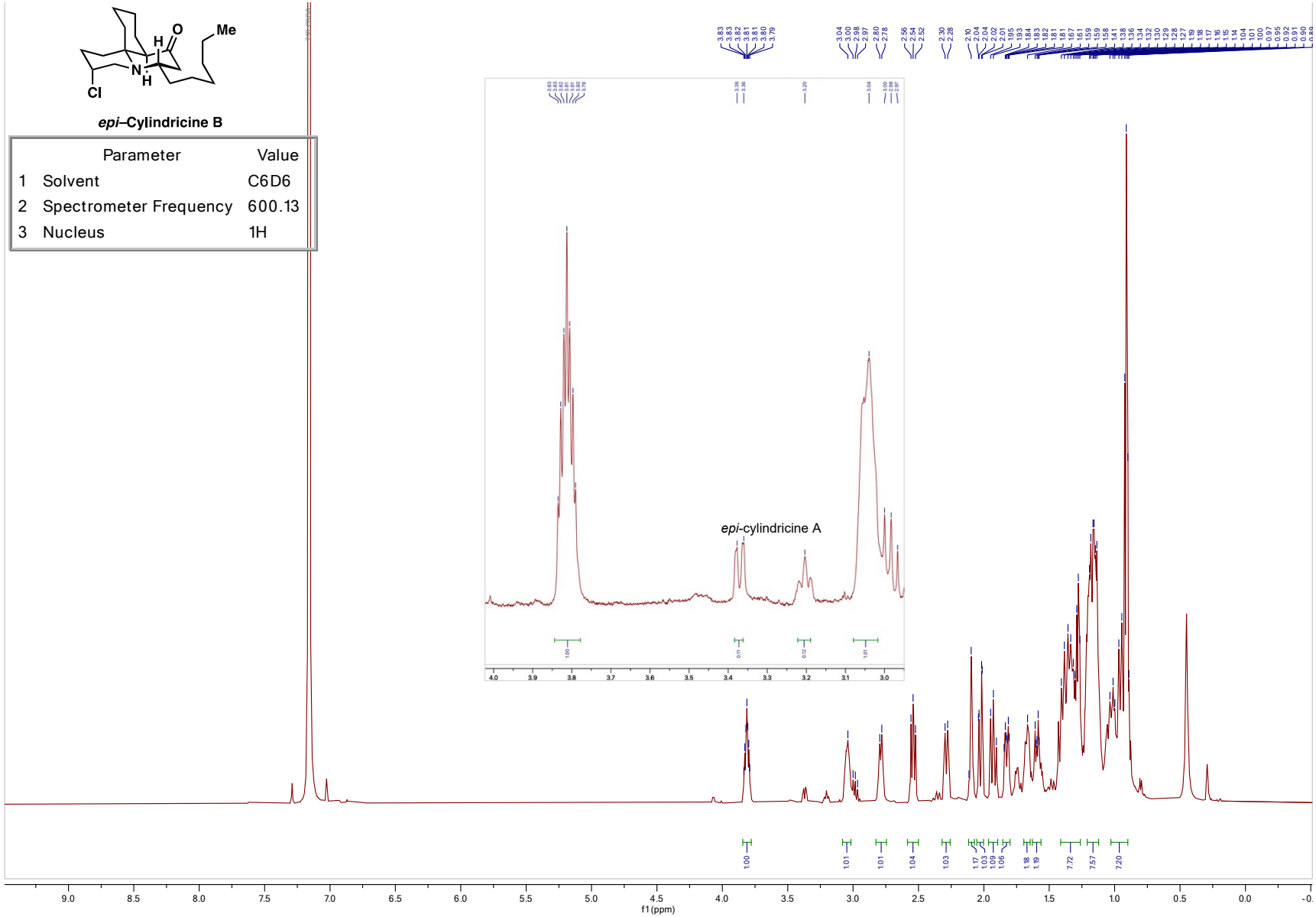

Cl
O
H
Me
N
H
H
+
Cl
O
H
Me
N
H
Cylindricine A
Cylindricine B
Parameter Value
1 Solvent C6D6
2 Spectrometer Frequency 600.13
3 Nucleus 1H
7.26 CDCl3
2.29
1.20
1.24
2.43
1.37
2.20
2.22
1.18
2.19
2.32
2.34
2.53
2.24
3.56
4.46
3.58
48.99
16.20
10.50
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

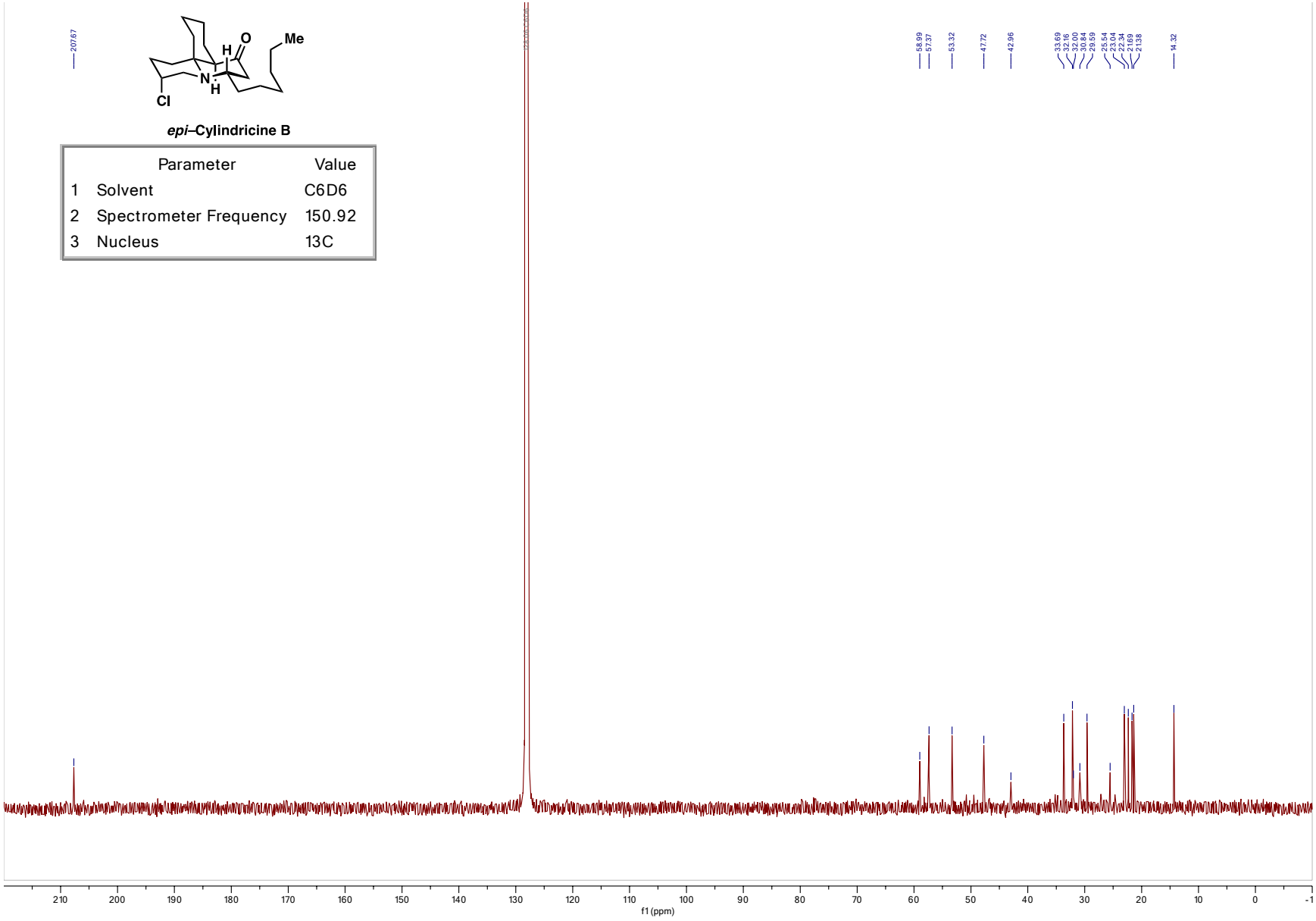

Cl
N
H
H
O
Me
Cylindricine B
Parameter Value
1 Solvent C6D6
2 Spectrometer Frequency 600.13
3 Nucleus 1H
f1 (ppm)



Cylindricine B

	Parameter	Value
1	Solvent	C6D6
2	Spectrometer Frequency	150.92
3	Nucleus	13C


Me
O
H
N
H
Cl
epi–Cylindricine B
Parameter Value
1 Solvent C6D6
2 Spectrometer Frequency 600.13
3 Nucleus 1H
epi-cylindricine A
f1 (ppm)



***epi*–Cylindricine B**

	Parameter	Value
1	Solvent	C6D6
2	Spectrometer Frequency	150.92
3	Nucleus	13C