Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

Selective ring-rearrangement or ring-closing metathesis of bicyclo[3.2.1]octenes

Evgeniya Semenova, Sarah K. Scott, Ouidad Lahtigui, Matthew Albritton, Ion Ghiviriga, Khalil A. Abboud, Adrian E. Roitberg and Alexander J. Grenning*

Table of Contents

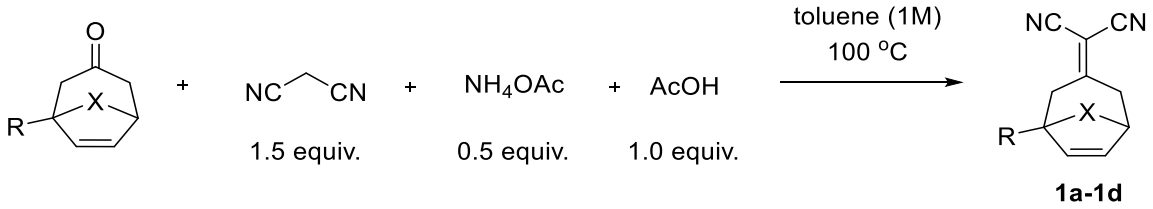
General Experimental Information

All commercial materials were used without further purification. Commercially available TFE and DMPU were used for cycloadditions and α-alkylation of Knoevenagel adducts respectively. All other reactions (with the exception of Knoevenagel condensation reactions) were carried out using anhydrous solvents dried by passing through activated alumina columns. Bicyclo[3.2.1]oct-6-en-3-ones were prepared according to literature procedure.[1] Allylic electrophiles were also prepared according to literature procedure.[2,3] All other protocols are outlined below.

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ (with $CHCl_3$ residual peak as an internal standard), DMSO-d_6 (with DMSO-d_5 residual peak as an internal standard), toluene-d_8 (with toluene-d_7 residual peak as an internal standard) or D_2O (with H_2O residual peak as an internal standard) using a 400 MHz or 600 MHz spectrometer. Variable temperature NMR (80 °C) was used to record all samples run in DMSO-d_6 or toluene-d_8. All ^{13}C NMR spectra were recorded with complete proton decoupling. HRMS data were recorded on Agilent Time of Flight 6200 spectrometer. Reaction progress was monitored by thin-layer chromatography (TLC) and visualized by UV light and KMnO4 stain.

Experimental Protocols

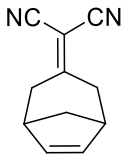
General Procedure A: Knoevenagel condensation



1a-1d

The ketone, malononitrile (1.5 eq), ammonium acetate (0.5 eq) and acetic acid (1.0 eq) were dissolved in toluene(1M) in a round-bottom flask equipped with a Dean-Stark apparatus and a condenser. The reaction mixture was heated at 110 °C until the ketone was completely consumed as shown on TLC (4-12 hrs). After cooling, the reaction mixture was concentrated under reduced pressure. Then, the mixture was extracted with EtOAc and washed with sodium bicarbonate and brine. The organic layer was dried over anhydrous sodium sulfate. The crude mixture was concentrated under reduced pressure and purified by flash column chromatography.

2-(bicyclo[3.2.1]oct-6-en-3-ylidene)malononitrile (1a)



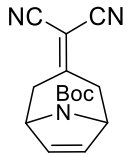
Brown solid, 68% yield, 1.21 g

Purified using 7% EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.99 (dt, J = 1.7, 0.9 Hz, 2H), 2.99 (dtd, J = 18.3, 2.4, 1.1 Hz, 2H), 2.95 – 2.88 (m, 2H), 2.58 (dtd, J = 15.5, 2.6, 1.0 Hz, 2H), 2.10 (dtt, J = 10.4, 5.2, 2.5 Hz, 1H), 1.68 (s, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 183.40, 134.84, 111.48, 87.96, 42.35, 38.80, 37.10.

tert-butyl 3-(dicyanomethylene)-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (1b)



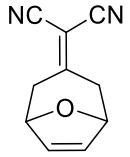
Yellow solid, 61% yield, 840 mg

Purified using 5-10% gradient EtOAc in hexanes

^{1}H NMR (400 MHz, DMSO-d_6) δ 6.25 (dd, J = 1.5, 0.9 Hz, 2H), 4.67 (dp, J = 3.3, 1.2 Hz, 2H), 2.94 – 2.85 (m, 2H), 2.85 – 2.74 (m, 2H), 1.46 (s, 9H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 180.72, 151.93, 133.95, 111.90, 88.18, 80.41, 56.79, 35.97, 28.55.

2-(8-oxabicyclo[3.2.1]oct-6-en-3-ylidene)malononitrile (1c)



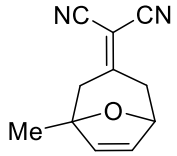
Yellow solid, 40% yield, 3.70 g

Purified using 20% EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.24 (d, J = 0.9 Hz, 2H), 5.01 (d, J = 4.5 Hz, 2H), 2.98 – 2.74 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 177.82, 132.79, 111.00, 88.95, 77.29, 36.83.

2-(1-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-ylidene)malononitrile (1d)



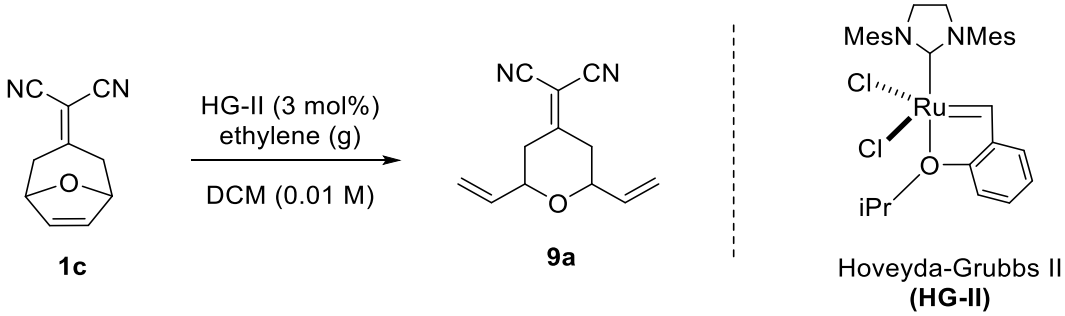
Yellow oil, 55% yield, 1.8 g

Purified using 15% EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.15 (dd, J = 5.9, 1.8 Hz, 1H), 6.01 (d, J = 5.9 Hz, 1H), 5.02 (dt, J = 4.5, 1.6 Hz, 1H), 2.95 (dd, J = 16.1, 1.3 Hz, 1H), 2.87 (dt, J = 16.1, 1.3 Hz, 1H), 2.77 (dddd, J = 16.1, 4.7, 1.9, 1.1 Hz, 1H), 2.59 (dt, J = 15.9, 1.4 Hz, 1H), 1.52 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 178.48, 136.06, 132.68, 111.12, 111.04, 88.20, 83.78, 77.96, 42.60, 36.17, 22.81.

Synthesis of 9a: Ring-opening cross-metathesis w/ethylene



1c **9a**

Hoveyda-Grubbs II
(HG-II)

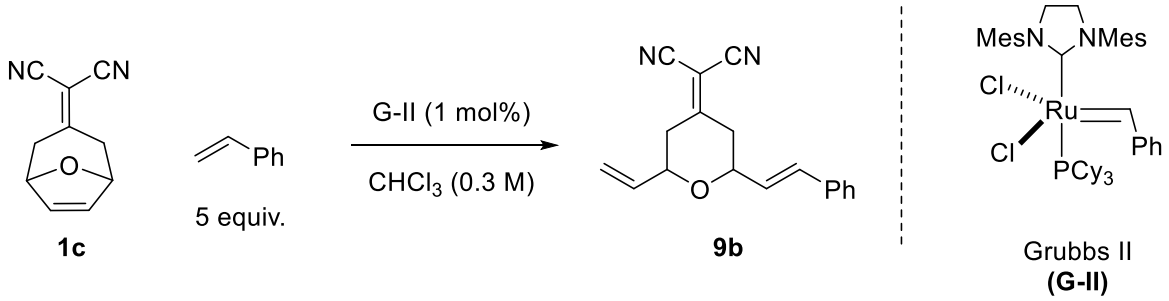
The procedure is based on published literature.[4] **1c** (200 mg, 1.16 mmol) was dissolved in DCM (120 mL, 0.01 M). The HG-II catalyst (22 mg, 0.04 mmol, 3 mol%) was added, and the solution was sparged with ethylene gas. The reaction proceeded at room temperature overnight under an ethylene atmosphere. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (5-10% gradient EtOAc in hexanes) to yield 155 mg (69% yield) of **9a** as a clear oil.

2-(2,6-divinyltetrahydro-4H-pyran-4-ylidene)malononitrile (9a)

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.90 (ddd, J = 17.2, 10.6, 5.6 Hz, 2H), 5.39 (dt, J = 17.3, 1.2 Hz, 2H), 5.28 (dt, J = 10.6, 1.2 Hz, 2H), 3.97 (dddd, J = 10.7, 5.2, 2.3, 1.3 Hz, 2H), 3.04 (dt, J = 13.3, 1.8 Hz, 2H), 2.38 – 2.28 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 177.36, 135.92, 117.61, 111.15, 84.28, 77.47, 39.76.

Synthesis of 9b: Ring-opening cross-metathesis w/styrene



1c **9b**

Grubbs II
(G-II)

The procedure is based on published literature.[4] In a Schlenk flask under nitrogen atmosphere, **1c** (100 mg, 0.58 mmol) and styrene (334 µL, 2.9 mmol, 5 equiv.) were dissolved in $CHCl_3$ (2 mL, 0.3 M). The G-II catalyst (24 mg, 0.03 mmol, 1 mol%) was added. The reaction proceeded at room temperature overnight under nitrogen. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (0-5% gradient EtOAc in hexanes) to yield 105 mg (66% yield) of **9b** as a yellow solid.

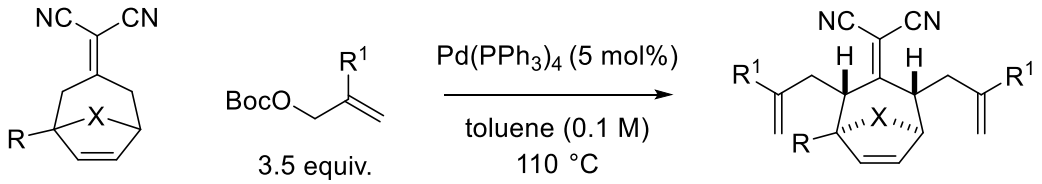
2-(2-styryl-6-vinyltetrahydro-4H-pyran-4-ylidene)malononitrile (9b)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 – 7.38 (m, 2H), 7.37 – 7.32 (m, 2H), 7.31 – 7.27 (m, 1H), 6.71 (d, 1H), 6.24 (dd, J = 16.0, 6.1 Hz, 1H), 5.99 – 5.91 (m, 1H), 5.44 (dt, J = 17.2, 1.2 Hz, 1H), 5.32 (dt, J = 10.6, 1.1 Hz,

1H), 4.15 (dddd, J = 10.9, 6.2, 2.4, 1.2 Hz, 1H), 4.03 (dddt, J = 9.4, 5.0, 2.4, 1.2 Hz, 1H), 3.11 (ddt, J = 31.5, 14.3, 2.3 Hz, 2H), 2.43 (ddd, J = 39.5, 14.2, 10.9 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 177.21, 135.88, 135.79, 132.81, 128.70, 128.36, 126.75, 126.70, 117.86, 117.68, 111.17, 84.36, 77.73, 77.63, 77.52, 53.48, 40.27, 39.77.

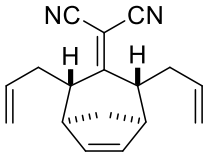
General Procedure B: One-pot iterative allylation/Cope rearrangement



1a-1d **2a** (R^1 = H) **2c** (R^1 = Me) **6a-6d**

The $Pd(PPh_3)_4$ catalyst (5 mol%) was added to a Schlenk flask in the glove box. The solvent was added under inert atmosphere, then the Knoevenagel adduct **1a-1d** and allyl electrophile **2a-2c** were added into the reaction mixture. The mixture was heated at 110 °C for 2-4 hours until completion was observed on TLC. The reaction mixture was concentrated under reduced pressure, then purified by flash column chromatography.

2-((1R*,2R*,4S*,5S*)-2,4-diallylbicyclo[3.2.1]oct-6-en-3-ylidene)malononitrile (6a)



White solid, 88% yield, 258 mg, >20:1 dr

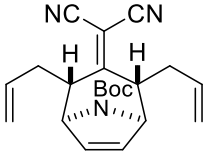
Purified using 1-5% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.04 – 5.97 (m, 2H), 5.83 (ddt, *J* = 17.2, 10.2, 7.2 Hz, 2H), 5.18 – 5.11 (m, 4H), 2.98 (tdd, *J* = 8.2, 2.5, 1.2 Hz, 2H), 2.73 (dq, *J* = 6.9, 2.5, 2.1 Hz, 2H), 2.41 (tt, *J* = 8.3, 1.2 Hz, 4H), 2.12 (d, *J* = 11.9 Hz, 1H), 1.72 – 1.63 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 189.25, 136.30, 134.53, 118.47, 111.67, 89.91, 45.39, 41.56, 39.60, 30.05.

Note: NMR shows 2.5% inseparable impurity.

tert-butyl (1R*,2S*,4R*,5S*,Z)-3-(2-(l2-azaneylidene)-1-cyano-2l3-ethylidene)-2,4-diallyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (6b)



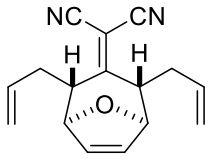
Yellow solid, 59% yield, 132 mg, >20:1 dr

Purified using 2-5% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, DMSO-d_6) δ 6.31 (t, J = 1.1 Hz, 2H), 5.93 (ddt, J = 17.1, 10.1, 7.0 Hz, 2H), 5.25 – 5.16 (m, 4H), 4.75 (s, 2H), 3.06 (s, 2H), 3.04 – 2.98 (m, 2H), 2.32 – 2.24 (m, 2H), 1.45 (s, 9H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 185.98, 153.49, 135.18, 134.93, 118.73, 111.88, 90.37, 80.37, 79.58, 59.54, 46.78, 38.02, 28.47.

2-((1R*,2S*,4R*,5S*)-2,4-diallyl-8-oxabicyclo[3.2.1]oct-6-en-3-ylidene)malononitrile (6c)



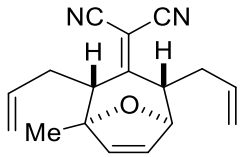
White solid, 75% yield, 254 mg, >20:1 dr

Purified using 5-10% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.21 (d, *J* = 0.9 Hz, 1H), 6.00 – 5.72 (m, 1H), 5.28 – 5.10 (m, 2H), 4.77 (s, 1H), 2.83 (dd, *J* = 9.3, 5.7 Hz, 1H), 2.68 (dddt, *J* = 13.8, 8.9, 7.7, 1.0 Hz, 1H), 2.42 (dddt, *J* = 13.7, 6.9, 5.7, 1.3 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 184.36, 133.93, 133.40, 119.39, 111.19, 90.55, 79.37, 45.76, 38.20.

2-((1S*,2R*,4S*,5R*)-2,4-diallyl-1-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-ylidene)malononitrile (6d)



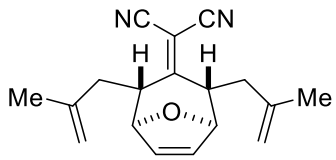
White solid, 57% yield, 162 mg, >20:1 dr

Purified using 7% EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.11 (dd, J = 5.9, 1.8 Hz, 1H), 5.99 (d, J = 5.9 Hz, 1H), 5.89 – 5.68 (m, 2H), 5.26 – 5.04 (m, 4H), 4.80 – 4.75 (m, 1H), 2.92 (dd, J = 9.4, 5.8 Hz, 1H), 2.82 – 2.71 (m, 2H), 2.67 – 2.54 (m, 1H), 2.43 – 2.28 (m, 2H), 1.44 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 184.46, 137.27, 134.53, 134.11, 132.92, 119.23, 118.90, 111.72, 111.39, 89.99, 85.53, 80.32, 49.35, 45.73, 37.25, 35.79, 20.40.

2-((1R*,2S*,4R*,5S*)-2,4-bis(2-methylallyl)-8-oxabicyclo[3.2.1]oct-6-en-3-ylidene)malononitrile (6p)



White solid, 60% yield, 145 mg, >20:1 dr

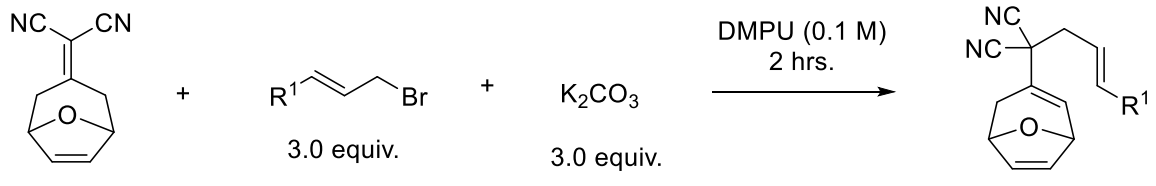
Purified using 5-15% gradient EtOAc in hexanes

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (s, *J* = 0.9 Hz, 1H), 4.96 (q, *J* = 1.5 Hz, 1H), 4.91 – 4.86 (m, 1H), 4.75 (s, 1H), 2.87 (dd, *J* = 10.9, 3.9 Hz, 1H), 2.74 – 2.61 (m, 1H), 2.24 – 2.13 (dd, 1H), 1.83 (s, *J* = 1.6, 0.7 Hz, 3H).

^{13}C NMR (101 MHz, CDCl3) δ 186.52, 140.83, 133.55, 115.37, 111.09, 89.98, 78.52, 43.66, 42.04, 21.84.

See the appendix for the NMR conformational analysis of **6p**.

General Procedure C: Deconjugative α-alkylation

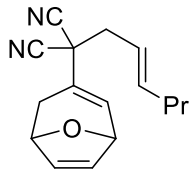


1a

2b (R^1 = Pr)
SI1 (R^1 = H)

4a was dissolved in DMPU (0.1 M) with allyl bromide electrophile (**2b** or **SI1**) (3.0 equiv.) and pulverized K_2CO_3 (3.0 equiv.). The reaction proceeded at room temperature for 2 hours. Then, the mixture was extracted with EtOAc and washed with 2.0 M HCl, brine, and then dried over anhydrous sodium sulfate. The mixture was then concentrated under reduced pressure and purified by flash column chromatography.

(E)-2-(8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl)-2-(hex-2-en-1-yl)malononitrile (3e)



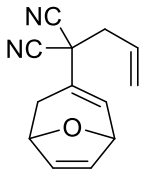
Yellow oil, 48% yield, 143 mg

Purified using 5-15% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.67 – 6.60 (t, 1H), 6.55 (t, J = 6.0 Hz, 1H), 6.06 (t, J = 5.9 Hz, 1H), 5.79 (dq, J = 12.5, 6.1, 5.5 Hz, 1H), 5.40 (dq, J = 12.7, 6.5, 5.6 Hz, 1H), 5.08 (t, J = 5.8 Hz, 1H), 4.92 – 4.85 (m, 1H), 2.76 (dt, J = 12.2, 5.8 Hz, 1H), 2.68 (q, J = 6.2, 5.8 Hz, 2H), 2.08 (p, J = 6.4, 5.8 Hz, 2H), 1.91 – 1.81 (m, 1H), 1.48 – 1.39 (m, 2H), 0.97 – 0.85 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 140.04, 137.43, 132.82, 127.79, 124.52, 119.58, 113.63, 113.59, 99.99, 75.15, 40.77, 34.52, 26.22, 22.07, 13.53.

2-allyl-2-(8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl)malononitrile (SI2)



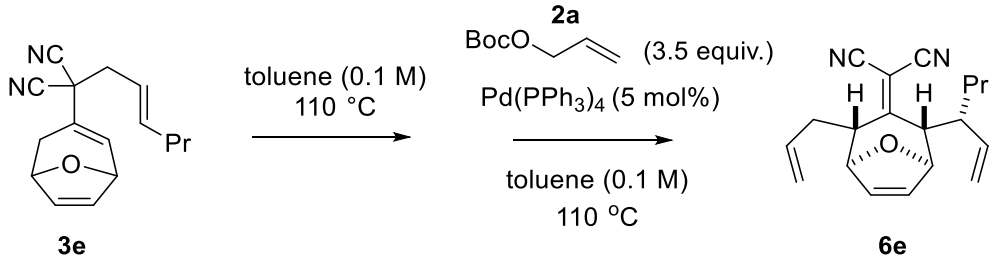
Yellow oil, 74% yield, 132 mg,

Purified using 5-10% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.64 (dt, J = 4.4, 1.7 Hz, 1H), 6.53 (dd, J = 5.9, 1.7 Hz, 1H), 6.04 (dd, J = 6.0, 1.9 Hz, 1H), 5.76 (ddt, J = 17.3, 10.2, 7.2 Hz, 1H), 5.45 – 5.33 (m, 2H), 5.07 (dd, J = 6.1, 1.9 Hz, 1H), 4.88 (dt, J = 4.6, 1.4 Hz, 1H), 3.36 (s, 1H), 2.81 – 2.65 (m, 3H), 1.84 (dd, J = 17.6, 1.4 Hz, 1H).

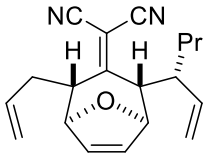
13C NMR (151 MHz, $CDCl_3$) δ 137.46, 133.13, 128.04, 127.83, 124.25, 123.38, 113.41, 113.37, 75.14, 42.91, 41.44, 29.44, 26.16.

Synthesis of 6e: One-Pot Cope Rearrangement/allylation of 3e



3e (143 mg, 0.58 mmol) was dissolved in toluene (6 mL, 0.1 M) in a Schlenk flask and heated at 110 °C until full conversion of the starting material was observed by TLC. The reaction was cooled, then allyl electrophile **2a** (305 mg, 1.93 mmol, 3.5 equiv.) and $Pd(PPh_3)_4$ (30 mg, 0.027 mmol, 5 mol%) (in 1 mL toluene) were added to the reaction mixture under inert atmosphere. The reaction was heated to 110 °C for 2-4 hours until completion is observed by TLC. The reaction mixture was cooled then concentrated under reduced pressure and purified by flash column chromatography (10% EtOAc in hexanes) to give 72 mg (44%, >20:1 dr) **6e** as a yellow solid.

2-((1S*,2R*,4S*,5R*)-2-allyl-4-((R*)-hex-1-en-3-yl)-8-oxabicyclo[3.2.1]oct-6-en-3-ylidene)malononitrile (6e)

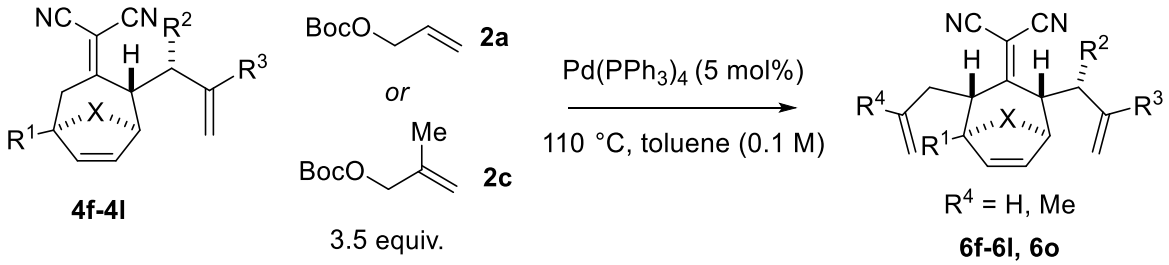


^{1}H NMR (600 MHz, $CDCl_3$) δ 6.19 (s, 2H), 5.87 – 5.74 (m, 1H), 5.74 – 5.58 (m, 1H), 5.28 – 5.11 (m, 4H), 4.99 – 4.94 (m, 2H), 4.78 (s, 1H), 2.75 (dd, J = 10.5, 4.1 Hz, 1H), 2.71 – 2.52 (m, 3H), 2.38 – 2.27 (m, 1H), 1.75 (dddd, J = 12.8, 9.5, 5.9, 2.8 Hz, 1H), 1.52 – 1.17 (m, 4H), 0.90 (dt, J = 19.9, 7.3 Hz, 4H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 183.25, 138.43, 134.28, 133.59, 132.80, 119.17, 118.20, 112.01, 111.26, 91.24, 79.35, 78.80, 50.89, 47.91, 46.35, 36.63, 34.98, 20.06, 13.95.

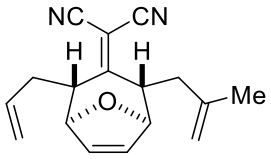
Note: NMR shows 17% inseparable impurity.

General Procedure D: One-pot deconjugative allylation/Cope rearrangement



The starting material (**4f-4l**) was dissolved in toluene (0.1 M) in a Schlenk flask. Then, **2a** (3.5 equiv.) and $Pd(PPh_3)_4$ (5 mol%) catalyst in toluene were added to the flask. The reaction proceeded at 110 °C for 2-4 hours until completion as indicated by TLC. Then, the mixture was concentrated under reduced pressure and purified by flash column chromatography.

2-((1S*,2R*,4S*,5R*)-2-allyl-4-(2-methylallyl)-8-oxabicyclo[3.2.1]oct-6-en-3-ylidene)malononitrile (6f)



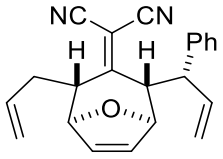
Yellow solid, 73% yield, 60 mg, >20:1 dr

Purified using 5-10% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.22 (d, J = 0.9 Hz, 2H), 5.85 (dddd, J = 16.1, 10.8, 7.7, 6.8 Hz, 1H), 5.25 – 5.18 (m, 2H), 4.98 (t, J = 1.7 Hz, 1H), 4.89 (dt, J = 2.7, 1.0 Hz, 1H), 4.76 (d, J = 2.9 Hz, 2H), 2.86 (ddd, J = 24.6, 10.1, 4.8 Hz, 2H), 2.74 – 2.64 (m, 2H), 2.42 (dddt, J = 13.8, 6.9, 5.8, 1.3 Hz, 1H), 2.20 (dt, J = 13.4, 2.4 Hz, 1H), 1.88 – 1.81 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 185.42, 140.82, 133.93, 133.51, 133.44, 119.39, 115.37, 111.22, 111.05, 90.26, 79.29, 78.60, 45.72, 43.71, 41.78, 38.46, 21.83.

2-((1S*,2R*,4S*,5R*)-2-allyl-4-((R*)-1-phenylallyl)-8-oxabicyclo[3.2.1]oct-6-en-3-ylidene)malononitrile (6g)



White solid, 71% yield, 176 mg, >20:1 dr

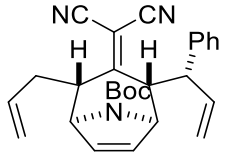
Purified using 5-10% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (t, J = 7.6 Hz, 2H), 7.37 – 7.34 (m, 2H), 7.32 – 7.28 (m, 1H), 6.23 – 6.13 (m, 2H), 6.05 (dd, J = 6.0, 1.8 Hz, 1H), 5.89 (dddd, J = 17.0, 10.1, 8.3, 5.6 Hz, 1H), 5.32 (dq, J = 17.2, 1.4

Hz, 1H), 5.27 (dt, J = 10.1, 1.3 Hz, 1H), 5.15 (dd, J = 10.1, 1.4 Hz, 1H), 5.07 – 5.01 (m, 1H), 4.87 – 4.74 (m, 1H), 4.47 – 4.34 (m, 1H), 3.88 (t, J = 10.5 Hz, 1H), 3.16 (d, J = 11.1 Hz, 1H), 2.84 (dd, J = 10.4, 4.1 Hz, 1H), 2.77 (ddd, J = 13.6, 10.3, 8.3 Hz, 1H), 2.47 (dtd, J = 13.4, 5.1, 1.6 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 150.51, 140.91, 138.06, 134.22, 133.64, 132.82, 129.37, 127.97, 127.55, 119.41, 117.91, 112.12, 111.19, 92.08, 79.51, 78.97, 55.01, 51.95, 46.20, 37.06.

tert-butyl (1S*,2R*,4S*,5R*)-2-allyl-3-(dicyanomethylene)-4-((R*)-1-phenylallyl)-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (6h)



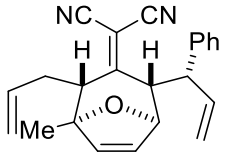
White solid, 49% yield, 70 mg, >20:1 dr

Purified using 5-10% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, DMSO-d_6) δ 7.45 – 7.38 (m, 4H), 7.31 (td, J = 7.1, 1.6 Hz, 1H), 6.30 (dd, J = 5.9, 2.3 Hz, 1H), 6.25 (dd, J = 5.9, 2.3 Hz, 1H), 6.04 – 5.89 (m, 2H), 5.29 (dt, J = 17.1, 1.4 Hz, 1H), 5.23 (d, J = 10.2 Hz, 1H), 5.09 (dd, J = 10.1, 1.5 Hz, 1H), 5.04 – 4.96 (m, 1H), 4.83 (t, J = 2.0 Hz, 1H), 4.44 (t, J = 2.0 Hz, 1H), 3.70 (t, J = 10.2 Hz, 1H), 3.47 – 3.28 (m, 1H), 3.06 – 3.01 (m, 1H), 2.64 – 2.56 (m, 1H), 2.37 – 2.27 (m, 1H), 1.40 (s, 9H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 183.93, 141.49, 139.05, 135.45, 134.96, 134.77, 129.30, 128.48, 127.51, 118.84, 117.77, 112.65, 111.72, 91.99, 80.68, 60.54, 55.02, 51.99, 47.02, 40.83, 40.81, 40.69, 40.55, 40.53, 36.99, 28.38.

2-((1S*,2R*,4S*,5R*)-2-allyl-1-methyl-4-((R*)-1-phenylallyl)-8-oxabicyclo[3.2.1]oct-6-en-3-ylidene)malononitrile (6i)



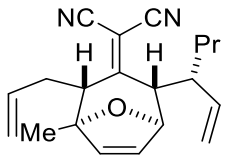
White solid, 48% yield, 92 mg, >20:1 dr

Purified using 5-10% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 2H), 7.34 – 7.31 (m, 2H), 7.29 (ddt, J = 8.6, 6.8, 1.3 Hz, 1H), 6.19 (dt, J = 16.9, 9.8 Hz, 1H), 5.97 (d, J = 0.7 Hz, 2H), 5.91 (dddd, J = 16.9, 10.1, 7.9, 6.0 Hz, 1H), 5.25 (dq, J = 17.0, 1.5 Hz, 1H), 5.21 – 5.14 (m, 2H), 5.05 (dt, J = 16.9, 1.1 Hz, 1H), 4.40 (s, 1H), 3.90 – 3.74 (m, 1H), 3.14 (dt, J = 11.2, 0.9 Hz, 1H), 2.95 (t, J = 6.6 Hz, 1H), 2.88 – 2.76 (m, 1H), 2.48 (dddt, J = 14.7, 6.8, 6.0, 1.7 Hz, 1H), 1.48 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 183.09, 141.03, 138.02, 137.57, 135.64, 132.38, 129.33, 129.29, 127.93, 127.49, 127.43, 118.42, 118.18, 112.32, 111.65, 91.22, 86.30, 80.03, 54.17, 51.85, 50.07, 34.82, 20.84.

2-((1S*,2R*,4S*,5R*)-2-allyl-4-((R*)-hex-1-en-3-yl)-1-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-ylidene)malononitrile (6j)



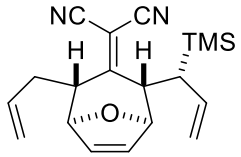
White solid, 42% yield, 79 mg, >20:1 dr

Purified using 3-5% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.10 (dd, J = 5.9, 1.9 Hz, 1H), 5.99 (d, J = 5.9 Hz, 1H), 5.83 (dddd, J = 16.9, 10.1, 8.2, 5.7 Hz, 1H), 5.65 (dt, J = 17.0, 10.1 Hz, 1H), 5.21 – 5.14 (m, 2H), 5.11 (dq, J = 10.1, 1.3 Hz, 1H), 5.05 – 4.99 (m, 1H), 4.97 (dd, J = 17.0, 1.7 Hz, 1H), 2.86 (t, J = 6.6 Hz, 1H), 2.72 – 2.61 (m, 2H), 2.56 (qd, J = 10.1, 3.1 Hz, 1H), 2.38 – 2.28 (m, 1H), 1.75 (dddd, J = 12.9, 9.5, 5.8, 3.1 Hz, 1H), 1.44 (s, 3H), 1.43 – 1.40 (m, 1H), 1.31 (dtd, J = 12.6, 10.0, 4.3 Hz, 1H), 1.27 – 1.18 (m, 1H), 0.91 (t, J = 7.3 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 184.01, 138.51, 137.61, 135.84, 132.38, 118.29, 118.03, 112.27, 111.75, 90.45, 86.24, 79.62, 50.73, 50.23, 47.23, 34.76, 34.41, 20.77, 19.91, 13.96.

2-((1S*,2R*,4S*,5R*)-2-allyl-4-((R*)-1-(trimethylsilyl)allyl)-8-oxabicyclo[3.2.1]oct-6-en-3-ylidene)malononitrile (6k)



Reaction note: Heated up to 145 °C.

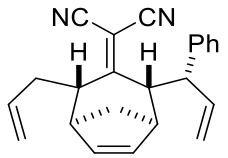
White solid, 54% yield, 46 mg, >20:1 dr

Purified using 10% EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.20 (d, *J* = 0.9 Hz, 2H), 5.84 – 5.74 (m, 1H), 5.63 (ddd, *J* = 16.9, 11.5, 10.1 Hz, 1H), 5.21 (d, *J* = 16.5 Hz, 2H), 5.03 (dd, *J* = 10.1, 1.8 Hz, 1H), 4.85 (s, 1H), 4.83 (ddd, *J* = 16.9, 1.8, 0.9 Hz, 1H), 4.77 (s, 1H), 2.99 (d, *J* = 11.5 Hz, 1H), 2.73 (dd, *J* = 10.5, 4.0 Hz, 1H), 2.64 – 2.56 (m, 1H), 2.39 – 2.30 (m, 2H), 0.15 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 184.3, 136.3, 134.7, 133.8, 132.8, 119.2, 116.2, 112.1, 111.4, 90.3, 80.5, 79.4, 47.1, 46.5, 40.0, 36.9, -1.4.

2-((1S*,2S*,4S*,5R*)-2-allyl-4-((R*)-1-phenylallyl)bicyclo[3.2.1]oct-6-en-3-ylidene)malononitrile (6l)



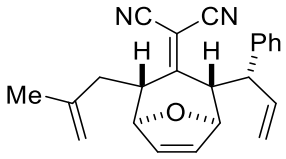
White solid, 49% yield, 73 mg, >20:1 dr

Purified using 1% EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 2H), 7.32 – 7.27 (m, 3H), 6.17 (dt, J = 16.8, 9.8 Hz, 1H), 5.99 (dd, J = 5.7, 2.9 Hz, 1H), 5.88 (dt, J = 4.8, 2.5 Hz, 1H), 5.88 – 5.81 (m, 1H), 5.27 – 5.18 (m, 2H), 5.11 (dd, J = 9.9, 1.3 Hz, 1H), 5.05 – 4.96 (m, 1H), 3.55 (dd, J = 11.3, 9.7 Hz, 1H), 3.30 (ddt, J = 11.5, 2.5, 1.2 Hz, 1H), 3.02 (tdd, J = 6.5, 2.6, 1.3 Hz, 1H), 2.79 (dt, J = 5.1, 2.8 Hz, 1H), 2.59 – 2.43 (m, 2H), 2.31 (dt, J = 5.2, 2.8 Hz, 1H), 2.26 (d, J = 11.8 Hz, 1H), 1.57 (tdd, J = 6.8, 3.3, 1.7 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 186.60, 141.09, 138.93, 136.53, 135.80, 134.60, 129.29, 127.47, 127.36, 118.51, 117.23, 112.61, 111.67, 91.59, 56.93, 51.25, 45.88, 42.15, 41.48, 38.44, 30.21.

2-((1S*,2R*,4S*,5R*)-2-(2-methylallyl)-4-((R*)-1-phenylallyl)-8-oxabicyclo[3.2.1]oct-6-en-3-ylidene)malononitrile (6o)



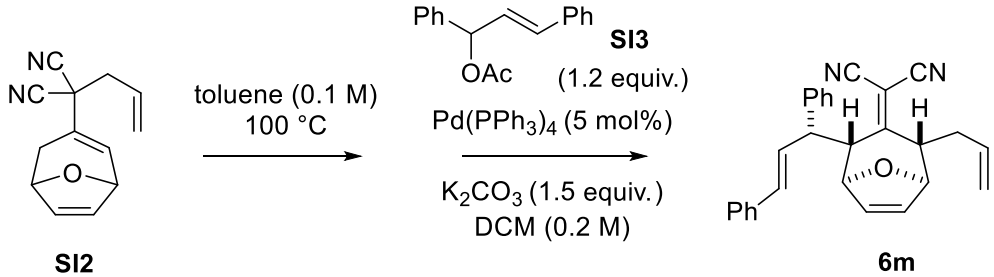
White solid, 63% yield, 126 mg, >20:1 dr

Purified using 5-10% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) 7.49 – 7.36 (m, 4H), 7.35 – 7.27 (m, 1H), 6.29 – 6.05 (m, 3H), 5.17 (dd, J = 10.0, 1.4 Hz, 1H), 5.11 – 4.99 (m, 3H), 4.86 (d, J = 1.8 Hz, 1H), 4.44 (s, 1H), 3.89 (t, J = 10.6 Hz, 1H), 3.18 (d, J = 11.0 Hz, 1H), 2.99 – 2.76 (m, 2H), 2.26 (d, J = 12.6 Hz, 1H), 1.90 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 182.99, 140.93, 140.88, 138.04, 133.70, 132.86, 129.36, 127.95, 127.54, 117.88, 115.36, 112.11, 111.12, 91.84, 78.88, 78.84, 76.76, 55.14, 51.95, 44.00, 40.87, 21.82.

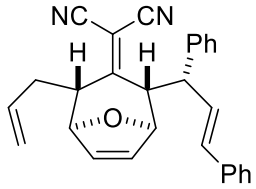
Synthesis of 6m: Cope rearrangement/deconjugative α-alkylation/transient Cope rearrangement



SI2 (50 mg, 0.236 mmol) was dissolved in toluene (2.5 mL, 0.1 M) in a Schlenk flask. The solution was heated at 100 °C for 12 hours. Then, the reaction mixture was cooled and concentrated under reduced pressure. The mixture was then transferred back to a Schlenk flask to which DCM (2 mL, 0.2 M), **SI3** (71 mg, 0.283 mmol, 1.2 equiv.), K_2CO_3 (48 mg, 0.353 mmol, 1.5 equiv.) and $Pd(PPh_3)_4$ (14 mg, 0.012 mmol, 5 mol%) in DCM were added under inert atmosphere. The reaction continued at room temperature for 4 hours. Then, the mixture was extracted with DCM and washed with 2 M HCl and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The mixture was

purified using flash column chromatography (5% EtOAc in hexanes) to give 25 mg (26% yield, 5:1 dr) **6m** as a yellow solid.

2-(2-(1,3-diphenylallyl)-4-(2-methylallyl)-8-oxabicyclo[3.2.1]oct-6-en-3-ylidene)malononitrile (6m)

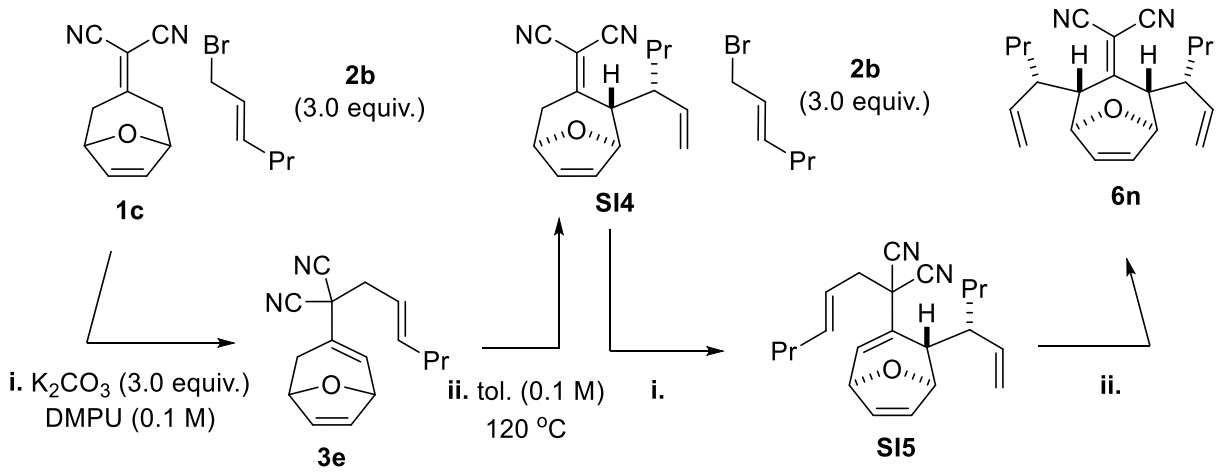


Major diastereomer:

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.36 (m, 2H), 7.34 – 7.29 (m, 3H), 7.27 – 7.24 (m, 1H), 6.52 (ddd, J = 15.6, 9.9, 5.1 Hz, 1H), 6.36 (d, J = 15.6 Hz, 1H), 6.26 – 6.18 (m, 1H), 6.10 (dd, J = 6.0, 1.9 Hz, 1H), 5.93 – 5.82 (m, 1H), 5.33 (dt, J = 16.3, 1.5 Hz, 1H), 5.25 (pt, J = 10.0, 1.3 Hz, 1H), 4.86 (d, J = 1.9 Hz, 1H), 4.51 – 4.43 (m, 1H), 4.04 (t, J = 10.6 Hz, 1H), 3.30 – 3.22 (m, 1H), 2.90 – 2.79 (m, 2H), 2.51 (ddt, J = 10.7, 5.6, 1.7 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 182.31, 140.98, 136.21, 134.11, 133.69, 132.84, 132.64, 129.45, 129.33, 128.71, 127.92, 127.91, 127.60, 126.45, 119.51, 119.34, 112.12, 111.06, 92.11, 79.61, 79.00, 54.32, 52.18, 46.24, 37.38.

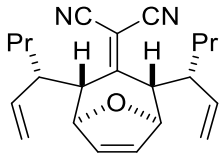
Synthesis of 6n: Iterative α-alkylation and Cope rearrangement sequence



To a round-bottomed flask **1c** was added (500 mg, 2.9 mmol) to DMPU (30 mL, 0.1 M) followed by K_2CO_3 (1.2 g, 8.71 mmol, 3.0 equiv.) and 2b (1.42 g, 8.71 mmol, 3.0 equiv.). The reaction proceeded at room temperature for 2 hours, then extracted with EtOAc and washed with 2.0 M HCl and brine. The organic layer was dried by anhydrous sodium sulfate, concentrated under reduced pressure and purified by flash column chromatography (5-15% EtOAc in hexanes) to produce 449 mg (61% yield) of **3e** as a clear oil. Then, **3e** was dissolved in toluene (18 mL, 0.1 M) and heated at 110 °C until full conversion was observed by TLC. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (10% EtOAc in hexanes) to give 298 mg (68% yield, >20:1 dr) of **SI4** as a white solid. Step **i.** was then repeated using **SI4**. After purification by flash column chromatography (5% EtOAc

in hexanes) 288 mg (73% yield) of **SI5** was produced as a clear oil. Step **ii.** was repeated with **SI5**, which after purification by flash column chromatography (3% EtOAc in hexanes) gave the final product **6n** (112 mg, 60% yield, > 20:1 dr) as a white solid.

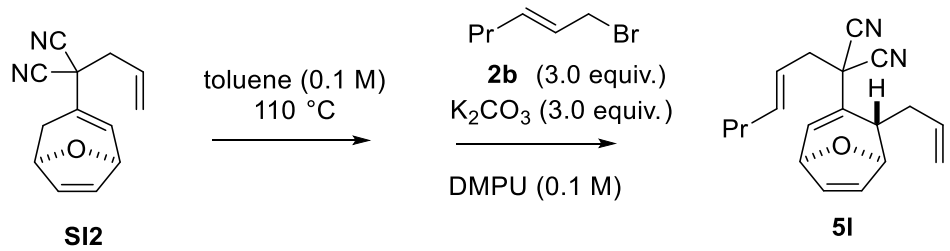
2-((1R*,2S*,4R*,5S*)-2-((R*)-hex-1-en-3-yl)-4-((S*)-hex-1-en-3-yl)-8-oxabicyclo[3.2.1]oct-6-en-3-ylidene)malononitrile (6n)



^{1}H NMR (600 MHz, $CDCl_3$) δ 6.20 (d, J = 2.5 Hz, 1H), 5.64 (dtd, J = 16.9, 9.8, 2.5 Hz, 1H), 5.24 – 5.12 (m, 1H), 5.10 – 4.98 (m, 2H), 2.68 (dd, J = 10.2, 2.5 Hz, 1H), 2.56 (qd, J = 9.8, 3.2 Hz, 1H), 1.78 (ddd, J = 13.1, 5.9, 2.8 Hz, 1H), 1.47 – 1.33 (m, 2H), 1.23 (ddt, J = 12.8, 9.5, 6.5 Hz, 1H), 0.92 (td, J = 7.4, 2.5 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 181.35, 138.79, 133.32, 118.24, 112.34, 92.38, 79.08, 51.16, 45.60, 34.28, 19.74, 13.93.

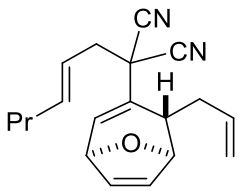
Synthesis of 5l: Telescoped Cope rearrangement/α-alkylation



SI2 **5l**

SI2 (50 mg, 0.236 mmol) was dissolved in toluene (2.5 mL, 0.1 M) in a Schlenk flask. The solution was heated at 100 °C overnight. Then, the reaction mixture was cooled and concentrated under reduced pressure. The mixture was then transferred back to round-bottom flask to which **2b** (115 mg, 0.707 mmol, 3.0 equiv.), K_2CO_3 (98 mg, 0.707 mmol, 3.0 equiv.) and DMPU (2.5 mL, 0.1 M) were added. The reaction proceeded at room temperature for 2 hours. Then, the mixture was extracted with EtOAc and washed with 1 M HCl and brine. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by flash column chromatography (10% EtOAc in hexanes) to give 17 mg (25% yield) **5l** as a clear oil.

2-((1S*,4S*,5R*)-4-allyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl)-2-((E)-hex-2-en-1-yl)malononitrile (5l)



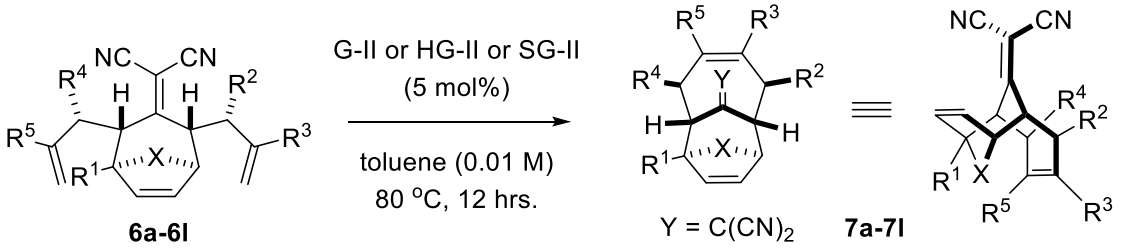
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.60 (td, J = 5.6, 1.4 Hz, 2H), 6.05 – 5.96 (m, 1H), 5.87 (dddd, J = 16.9, 10.0, 8.6, 5.3 Hz, 1H), 5.83 – 5.76 (m, 1H), 5.46 – 5.36 (m, 1H), 5.28 – 5.18 (m, 2H), 4.91 (d, J = 2.0 Hz, 1H), 4.81 (dd, J = 4.2, 1.7 Hz, 1H), 2.82 (dddd, J = 14.4, 6.9, 2.9, 1.7 Hz, 1H), 2.79 – 2.72 (m, 1H), 2.73 – 2.63 (m,

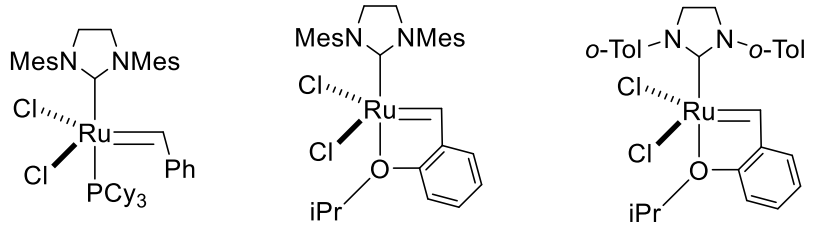
1H), 2.55 – 2.45 (m, 1H), 2.12 – 2.02 (m, 2H), 1.99 (dd, J = 10.4, 2.8 Hz, 1H), 1.43 (h, J = 7.3 Hz, 3H), 0.92 (td, J = 7.4, 2.2 Hz, 4H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 140.24, 139.17, 135.13, 134.51, 127.84, 119.86, 118.65, 114.62, 114.20, 99.99, 79.68, 76.82, 75.51, 42.81, 38.50, 36.27, 34.56, 22.05, 13.58.

Note: NMR shows 16% inseparable impurity.

General Procedure E: Ring-closing Metathesis

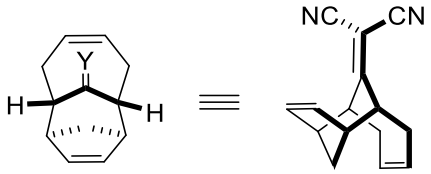




Grubbs II **(G-II)** | Hoveyda-Grubbs II **(HG-II)** | Stewart-Grubbs **(SG-II)**

The starting material was dissolved in toluene (0.01 M) in a Schlenk flask under inert atmosphere. The catalyst was added to the reaction mixture. The reaction was heated at 80 °C for 12 hours or until completion is observed on TLC. Then, the reaction mixture was cooled, concentrated under reduced pressure and purified by flash column chromatography.

2-(tricyclo[4.4.1.12,5]dodeca-3,8-dien-11-ylidene)malononitrile (7a)



Y = $C(CN)_2$

Reaction note: HG-II

White solid, 75% yield, 12 mg

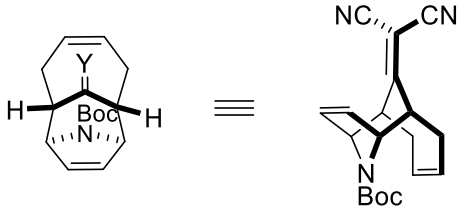
Purified using 0-5% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.10 (d, J = 1.6 Hz, 2H), 5.53 (d, J = 2.1 Hz, 2H), 3.38 – 3.31 (m, 2H), 2.74 (d, J = 7.5 Hz, 1H), 2.71 (dd, J = 6.1, 3.2 Hz, 3H), 2.62 (s, 1H), 2.50 – 2.42 (m, 2H), 1.58 (dtd, J = 11.4, 4.5, 2.2 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 187.49, 135.79, 125.74, 110.40, 85.65, 45.66, 41.79, 32.90, 32.64.

HRMS (DART) m/z: $[M + NH_4]^+$ $C_{15}H_{14}N_2$ Calculated for 240.1495; Found 240.1485

tert-butyl 11-(dicyanomethylene)-12-azatricyclo[4.4.1.12,5]dodeca-3,8-diene-12-carboxylate (7b)



Y = $C(CN)_2$

Reaction note: HG-II

Yellow solid, 59% yield, 35 mg

Purified using 5-10% gradient EtOAc in hexanes

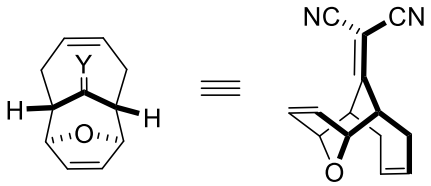
^{1}H NMR (600 MHz, DMSO-d_6) δ 6.39 (s, 2H), 5.42 (s, 2H), 4.71 (s, 2H), 3.31 (d, J = 7.1 Hz, 2H), 2.67 (ddt, J = 18.5, 4.1, 2.0 Hz, 2H), 2.51 – 2.49 (m, 2H), 1.41 (s, 9H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 185.52, 151.88, 136.15, 125.19, 111.72, 86.08, 79.23, 47.88, 43.92, 32.63, 28.68.

Note: In ^{1}H NMR, two protons are overlapping with the DMSO CH_3 peak.

HRMS (ESI – TOF) m/z: $[M + Na]^+$ $C_{19}H_{21}N_3O_2$ Calculated for 346.1526; Found 346.1588

(12-oxatricyclo[4.4.1.12,5]dodeca-3,8-dien-11-ylidene)malononitrile (7c)



Y = $C(CN)_2$

1. Reaction note: HG-II

White solid, 77% yield, 27 mg

2. Reaction note: G-II

White solid, 52% yield, 23 mg

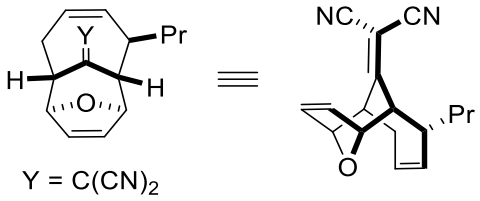
Purified using 5-10% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.33 (s, 2H), 5.68 – 5.49 (m, 2H), 4.74 (s, 2H), 3.15 (d, J = 6.3 Hz, 2H), 2.78 – 2.48 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 184.15, 134.38, 125.65, 110.87, 87.54, 83.91, 43.47, 33.51.

HRMS (DART) m/z: $[M + H]^+$ $C_{14}H_{12}N_2O$ Calculated for 225.1022; Found 225.1026

2-(7-propyl-12-oxatricyclo[4.4.1.12,5]dodeca-3,8-dien-11-ylidene)malononitrile (7e)



Reaction note: G-II

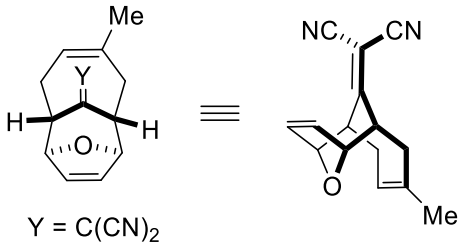
White solid, 63% yield, 10 mg

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.32 – 6.17 (m, 2H), 5.59 – 5.37 (m, 2H), 4.68 (dt, J = 4.4, 1.5 Hz, 2H), 3.07 – 3.00 (m, 1H), 2.99 – 2.92 (m, 1H), 2.71 (dddd, J = 8.7, 7.1, 3.2, 1.5 Hz, 1H), 2.64 (dddt, J = 18.1, 5.3, 2.4, 1.5 Hz, 1H), 2.53 (ddq, J = 18.0, 9.7, 2.6 Hz, 1H), 1.52 – 1.42 (m, 1H), 1.41 – 1.28 (m, 3H), 0.89 (t, J = 7.0 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 183.32, 134.18, 133.82, 132.02, 123.99, 111.71, 111.17, 88.77, 84.45, 84.41, 48.54, 45.60, 43.53, 38.43, 32.61, 20.76, 13.96.

HRMS (DART) m/z: $[M + H]^+$ $C_{17}H_{18}N_2O$ Calculated for 267.1491; Found 267.1505

2-(8-methyl-12-oxatricyclo[4.4.1.12,5]dodeca-3,8-dien-11-ylidene)malononitrile (7f)



Reaction note: HG-II

White solid, 56% yield, 13 mg

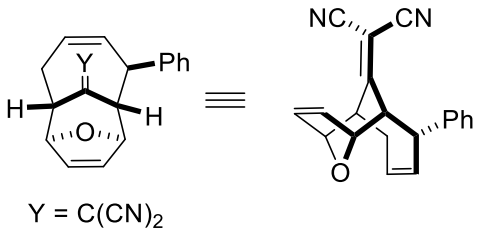
Purified using 5-10% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.32 (d, J = 1.0 Hz, 2H), 5.38 (dtt, J = 3.9, 2.7, 1.4 Hz, 1H), 4.83 – 4.61 (m, 2H), 3.28 – 3.02 (m, 2H), 2.74 – 2.61 (m, 2H), 2.61 – 2.50 (m, 2H), 1.81 – 1.71 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 183.42, 133.43, 133.28, 131.37, 120.09, 109.95, 109.89, 82.85, 82.71, 42.92, 42.28, 36.98, 32.72, 26.84.

HRMS (ESI – TOF) m/z: $[M - H]^-$ $C_{15}H_{14}N_2O$ Calculated for 237.1033; Found 237.1030

2-(7-phenyl-12-oxatricyclo[4.4.1.12,5]dodeca-3,8-dien-11-ylidene)malononitrile (7g)



1. Reaction note: G-II

White solid, 33% yield, 11 mg

2. Reaction note: HG-II

White solid, 58% yield, 22 mg

Purified using 5-10% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H), 7.27 – 7.23 (m, 1H), 7.11 – 7.02 (m, 2H), 6.25 (qd, J = 6.0, 1.6 Hz, 2H), 5.79 (dddd, J = 12.8, 5.6, 3.0, 1.5 Hz, 1H), 5.65 (dddt, J = 12.8, 5.3, 2.5, 1.1 Hz, 1H), 4.91 (t, J = 1.5 Hz, 1H), 4.75 (t, J = 1.5 Hz, 1H), 4.23 – 4.07 (m, 1H), 3.23 – 2.92 (m, 2H), 2.86 – 2.59 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 179.58, 140.80, 134.31, 134.12, 129.51, 129.29, 128.29, 127.82, 126.79, 111.07, 109.75, 89.40, 84.54, 83.95, 83.95, 52.34, 51.53, 43.22, 33.06, 29.72.

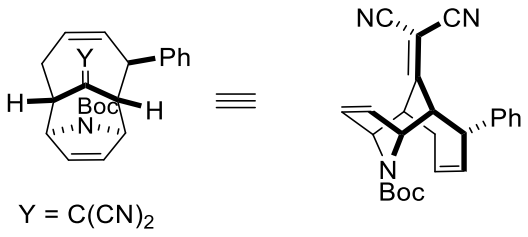
HRMS (ESI – TOF) m/z: $[M + Na]^+$ $C_{20}H_{16}N_2O$ Calculated for 323.1155; Found 323.1164

When prepared from **6m**:

Reaction note: HG-II

66% yield, 39 mg

tert-butyl 11-(dicyanomethylene)-7-phenyl-12-azatricyclo[4.4.1.12,5]dodeca-3,8-diene-12-carboxylate (7h)



Yellow solid, 92% yield, 105 mg

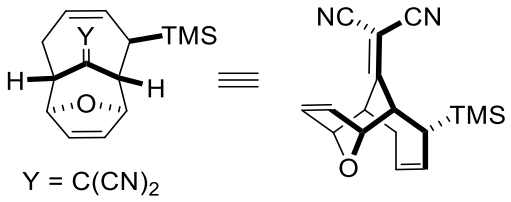
Purified using 5-10% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, DMSO-d_6) δ 7.32 (dd, J = 8.4, 6.8 Hz, 2H), 7.28 – 7.23 (m, 1H), 7.22 – 7.17 (m, 2H), 6.48 – 6.29 (m, 2H), 5.69 (d, J = 7.8 Hz, 1H), 5.50 (s, 1H), 5.04 (s, 1H), 4.79 (s, 1H), 4.19 (dd, J = 4.8, 2.4 Hz, 1H), 3.32 – 3.18 (m, 2H), 2.86 – 2.74 (m, 1H), 2.68 (s, 1H), 1.45 (s, 9H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 181.80, 151.11, 141.84, 136.12, 136.11, 135.99, 129.15, 129.15, 128.80, 128.66, 127.60, 126.54, 111.73, 110.39, 88.66, 79.73, 79.59, 62.37, 52.54, 50.49, 43.55, 40.69, 32.60, 28.70.

HRMS (ESI – TOF) m/z: $[M + H]^+$ $C_{25}H_{25}N_3O_2$ Calculated for 400.2020; Found 400.2022

2-(7-(trimethylsilyl)-12-oxatricyclo[4.4.1.12,5]dodeca-3,8-dien-11-ylidene)malononitrile (7k)



Reaction note: DCM (0.001 M), room temperature, HG-II

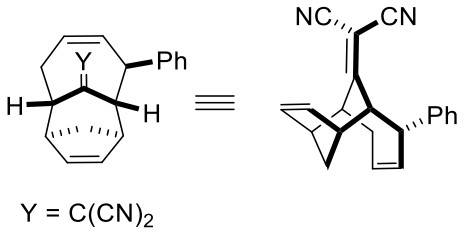
White solid, 66% yield, 12 mg

Purified using 10-20% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.26 – 6.08 (m, 2H), 5.62 – 5.48 (m, 1H), 5.44 – 5.29 (m, 1H), 4.63 (t, *J* = 1.5 Hz, 1H), 4.56 (t, *J* = 1.5 Hz, 1H), 3.05 (d, *J* = 5.7, 1.5 Hz, 1H), 2.98 – 2.92 (m, 1H), 2.60 (dddt, *J* = 18.0, 6.3, 2.5, 1.3 Hz, 1H), 2.43 (dddd, *J* = 18.0, 6.7, 3.0, 1.1 Hz, 1H), 2.25 – 2.08 (m, 1H), 0.00 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 185.7, 134.7, 133.8, 129.2, 122.4, 112.2, 111.4, 88.4, 88.3, 84.9, 45.8, 45.0, 39.7, 32.6, -2.1.

2-(7-phenyltricyclo[4.4.1.12,5]dodeca-3,8-dien-11-ylidene)malononitrile (7l)



White solid, 49% yield, 22 mg

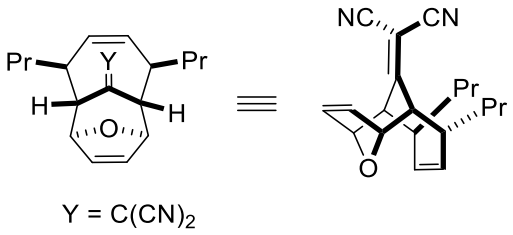
Purified using 0-5% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (dd, J = 8.1, 6.5 Hz, 2H), 7.34 – 7.29 (m, 1H), 7.16 – 7.10 (m, 2H), 6.14 – 6.06 (m, 2H), 5.84 (ddt, J = 13.1, 5.1, 2.5 Hz, 1H), 5.67 (dddd, J = 13.2, 5.9, 2.8, 1.2 Hz, 1H), 3.95 (ddd, J = 4.8, 3.2, 1.6 Hz, 1H), 3.30 (ddd, J = 8.0, 3.5, 1.7 Hz, 1H), 3.26 (dt, J = 2.9, 1.6 Hz, 1H), 3.00 (q, J = 3.5 Hz, 1H), 2.93 (d, J = 11.5 Hz, 1H), 2.85 (ddq, J = 19.1, 8.0, 3.0 Hz, 1H), 2.78 (q, J = 3.4 Hz, 1H), 2.61 (ddq, J = 19.1, 5.1, 1.6 Hz, 1H), 1.62 (dtd, J = 11.3, 4.4, 1.9 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 184.13, 142.28, 136.89, 136.55, 130.07, 129.24, 128.31, 128.07, 127.63, 111.63, 110.25, 88.43, 52.17, 51.91, 47.80, 47.66, 42.51, 41.90, 33.95, 33.81, 29.72.

HRMS (ESI – TOF) m/z: $[M + NH_4]^+$ $C_{21}H_{18}N_2$ Calculated for 316.1808; Found 316.1808

2-(7,10-dipropyl-12-oxatricyclo[4.4.1.12,5]dodeca-3,8-dien-11-ylidene)malononitrile (7n)



Reaction note: SG-II (5 mol%), toluene (0.002 M), ethylene gas atmosphere

White solid, 12% yield, 7 mg

Purified using 5-10% gradient EtOAc in hexanes

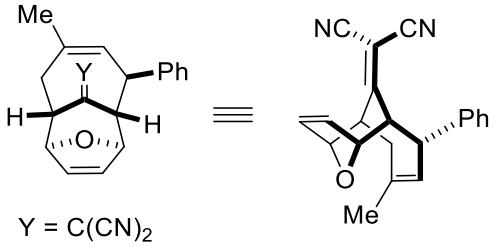
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.27 (s, 2H), 5.51 (d, J = 2.8 Hz, 2H), 4.75 (d, J = 1.5 Hz, 2H), 2.97 (h, J = 3.3 Hz, 2H), 2.91 – 2.86 (m, 2H), 1.49 – 1.39 (m, 8H), 0.98 – 0.93 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 183.73, 133.76, 131.90, 111.76, 89.02, 83.90, 49.48, 43.05, 38.80, 20.69, 14.02.

Note: Extra peak in ^{13}C NMR at 30 ppm is from grease.

HRMS (ESI – TOF) m/z: $[M + NH_4]^+$ $C_{20}H_{24}N_2O$ Calculated for 326.2227; Found 326.2227

2-(9-methyl-7-phenyl-12-oxatricyclo[4.4.1.12,5]dodeca-3,8-dien-11-ylidene)malononitrile (7o)



Reaction note: SG-II (5 mol%), DCM (0.02 M), 40 °C, ethylene gas atmosphere

White solid, 28% yield, 5 mg

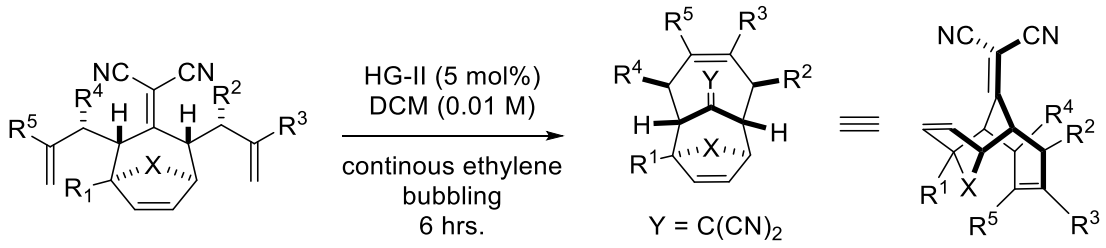
Purified using 5-10% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 2H), 7.34 – 7.28 (m, 1H), 7.18 – 7.11 (m, 2H), 6.30 (d, J = 0.9 Hz, 2H), 5.53 (dq, J = 3.2, 1.6 Hz, 1H), 4.98 – 4.88 (m, 1H), 4.82 – 4.76 (m, 1H), 4.32 – 4.10 (m, 1H), 3.13 (ddt, J = 7.3, 3.1, 1.4 Hz, 1H), 3.08 (dt, J = 2.9, 1.6 Hz, 1H), 2.81 (dd, J = 17.3, 3.1 Hz, 1H), 2.70 (dd, J = 17.3, 7.4 Hz, 1H), 1.88 (t, J = 1.5 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 180.87, 141.92, 141.92, 134.36, 134.21, 134.17, 129.21, 128.28, 127.61, 125.67, 111.16, 110.13, 88.60, 84.09, 83.49, 52.73, 51.09, 42.90, 37.07, 27.60.

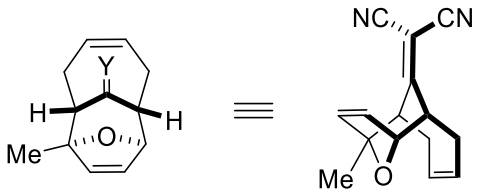
HRMS (ESI – TOF) m/z: $[M + NH_4]^+$ $C_{21}H_{18}N_2O$ Calculated for 332.1757; Found 332.1757

General Procedure F: Room-temperature ring-closing metathesis with ethylene



The procedure is based on published literature.[5] The starting material was dissolved in DCM (0.01 M) in a Schlenk flask under inert atmosphere. The Hoveyda-Grubbs II (5 mol%) catalyst was added into the flask. The solution was sparged with ethylene gas, and the reaction proceeded at room temperature with continuous bubbling of ethylene gas through the solution. After 6 hours, the reacton mixture was concentrated under reduced pressure and purified by column chromatography.

2-(2-methyl-12-oxatricyclo[4.4.1.12,5]dodeca-3,8-dien-11-ylidene)malononitrile (7d)



White solid, 25% yield, 6 mg

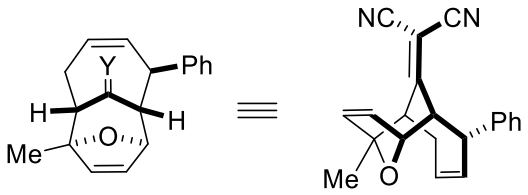
Purified using 5-10% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.26 (dd, J = 5.8, 1.8 Hz, 1H), 6.10 (d, J = 5.8 Hz, 1H), 5.63 (ddt, J = 11.9, 5.4, 2.8 Hz, 1H), 5.60 – 5.54 (m, 1H), 4.84 – 4.66 (m, 1H), 3.14 (dd, J = 6.3, 2.0 Hz, 1H), 3.11 – 3.03 (m, 1H), 2.84 – 2.75 (m, 1H), 2.73 – 2.58 (m, 2H), 2.43 – 2.32 (m, 1H), 1.47 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 186.30, 138.59, 134.34, 126.72, 125.31, 111.07, 110.99, 86.60, 86.02, 84.66, 47.00, 43.06, 33.36, 29.24, 19.88.

HRMS (ESI – TOF) m/z: $[M + NH_4]^+$ $C_{15}H_{14}N_2O$ Calculated for 256.1444; Found 256.1444

2-(2-methyl-7-phenyl-12-oxatricyclo[4.4.1.12,5]dodeca-3,8-dien-11-ylidene)malononitrile (7i)



White solid, 46% yield, 17 mg

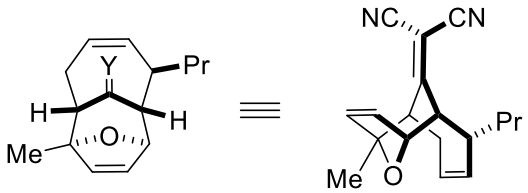
Purified using 5-10% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (dd, J = 8.2, 6.5 Hz, 2H), 7.34 – 7.29 (m, 1H), 7.18 – 7.11 (m, 2H), 6.24 (dd, J = 5.8, 1.8 Hz, 1H), 6.09 (d, J = 5.8 Hz, 1H), 5.90 – 5.81 (m, 1H), 5.78 (ddd, J = 12.5, 5.7, 2.2 Hz, 1H), 4.97 (t, J = 1.6 Hz, 1H), 4.19 (dq, J = 4.3, 2.1 Hz, 1H), 3.15 – 3.06 (m, 1H), 3.03 (ddd, J = 6.6, 3.1, 1.1 Hz, 1H), 2.95 (ddd, J = 17.9, 6.4, 3.1 Hz, 1H), 2.53 (dtd, J = 17.9, 5.4, 2.5 Hz, 1H), 1.50 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 181.11, 139.90, 137.42, 133.01, 130.24, 128.25, 128.25, 127.19, 127.19, 126.71, 125.38, 110.15, 109.11, 87.36, 85.90, 83.27, 50.83, 50.10, 45.42, 27.60, 18.80.

HRMS (ESI – TOF) m/z: $[M + NH_4]^+$ $C_{21}H_{18}N_2O$ Calculated for 332.1757; Found 332.1757

2-(2-methyl-7-propyl-12-oxatricyclo[4.4.1.12,5]dodeca-3,8-dien-11-ylidene)malononitrile (7j)



Y = $C(CN)_2$

White solid, 53% yield, 26 mg

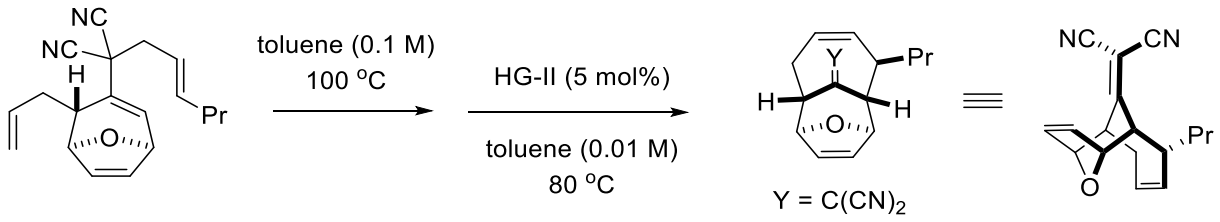
Purified using 5-10% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.23 (dd, J = 5.8, 1.7 Hz, 1H), 6.07 (d, J = 5.8 Hz, 1H), 5.63 (dd, J = 12.5, 5.2 Hz, 1H), 5.54 (dddd, J = 11.8, 5.8, 3.4, 1.4 Hz, 1H), 4.75 (t, J = 1.7 Hz, 1H), 2.99 (dd, J = 6.9, 3.2 Hz, 1H), 2.97 (d, J = 2.5 Hz, 1H), 2.80 (ddd, J = 17.4, 6.4, 3.5 Hz, 2H), 2.40 – 2.29 (m, 1H), 1.52 – 1.33 (m, 7H), 0.95 (t, J = 6.7 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 185.60, 138.35, 133.79, 133.44, 124.12, 111.88, 111.30, 87.72, 86.84, 84.74, 48.31, 46.78, 44.74, 38.22, 28.17, 20.74, 19.77, 13.98.

HRMS (ESI – TOF) m/z: $[M + Na]^+$ $C_{18}H_{20}N_2O$ Calculated for 303.1468; Found 303.1468

Synthesis of 7e: One-Pot Cope rearrangement/ring-closing metathesis



5l Y = $C(CN)_2$ **7e**

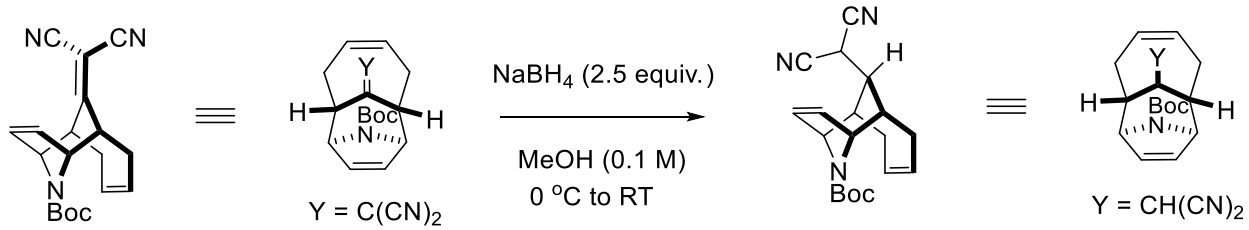
5l (25 mg, 0.085 mmol) was dissolved in toluene (1 mL, 0.1 M) in a Schlenk flask and heated at 100 °C overnight. The reaction mixture was cooled, then the mixture was diluted with toluene (7 mL, 0.01 M) and HG-II (2.5 mg, 0.004 mmol, 5 mol%) was added under inert atmosphere. The reaction was heated at 80 °C until completion was indicated by TLC. The mixture was then cooled, concentrated

under reduced pressure and purified by flash column chromatography (10% EtOAc in hexanes) to give 10 mg (42% yield) **7e** as a white solid.

Spectroscopic data matches **7e** synthesized by General Procedure E, as reported above.

Protocols for Diversification of 7b

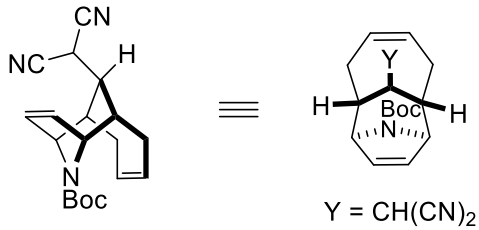
Synthesis of 10: Alkylidene reduction



7b **10**

7b (50 mg, 0.154 mmol) was dissolved in methanol (1.5 mL, 0.1 M) and cooled to 0 °C. Then, $NaBH_4$ (15 mg, 0.386 mmol, 2.5 equiv.) was slowly added while stirring. After addition, the mixture was warmed to room temperature, and the reaction proceeded until completion was observed by TLC (1 hr.). The reaction was quenched with NH_4Cl, then extracted with EtOAc and washed with 1 M HCl and brine. The organic layer was dried with anhydrous sodium sulfate, concentrated under reduced pressure and purified by flash column chromatography (10-20% gradient EtOAc in hexanes) to yield 33 mg (66% yield, >20:1 dr) **10** as a white solid.

tert-butyl 11-(dicyanomethyl)-12-azatricyclo[4.4.1.12,5]dodeca-3,8-diene-12-carboxylate (10)



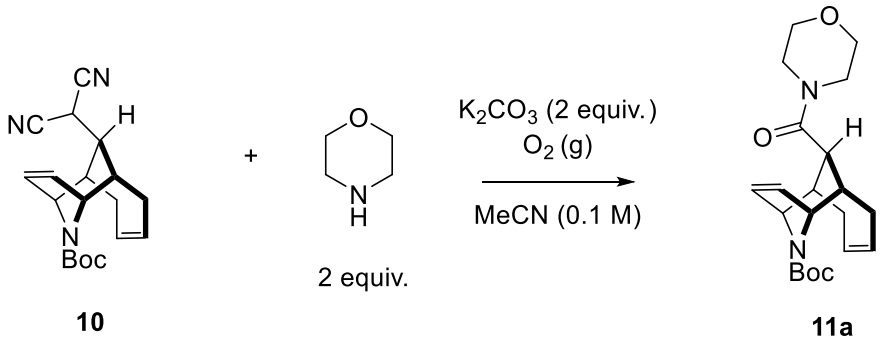
^{1}H NMR (600 MHz, DMSO-d_6) δ 6.39 (s, 2H), 5.36 (s, 2H), 4.86 (d, J = 11.8 Hz, 1H), 4.52 (s, 2H), 2.44 (td, J = 21.0, 14.7 Hz, 6H), 2.08 (d, J = 6.3 Hz, 2H), 1.39 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 151.09, 136.25, 125.65, 114.26, 78.77, 63.09, 61.91, 36.67, 34.51, 31.07, 28.72.

Note: DMSO signal at 2.5 ppm overlapping with product signal. There is a water peak at 3.07 ppm.

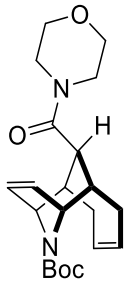
HRMS (ESI – TOF) m/z: $[M + Na]^+$ $C_{19}H_{23}N_3O_2$ Calculated for 348.1682; Found 348.1691

Synthesis of 11a: Oxidative amidation



The procedure is based on published literature.[6] **10** (50 mg, 0.154 mmol) was dissolved in acetonitrile (1.5 mL, 0.1 M), then K_2CO_3 (42 mg, 0.307 mmol, 2.0 equiv.) and morpholine (27 µL, 0.307 mmol, 2.0 equiv.) were added. The reaction mixture was sparged with oxygen and proceeded for 12 hours in an oxygen atmosphere at room temperature. Then, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (20-50% gradient EtOAc in hexanes) to yield 40 mg (69% yield) **11a** as a white solid.

tert-butyl 11-(morpholine-4-carbonyl)-12-azatricyclo[4.4.1.12,5]dodeca-3,8-diene-12-carboxylate (11a)



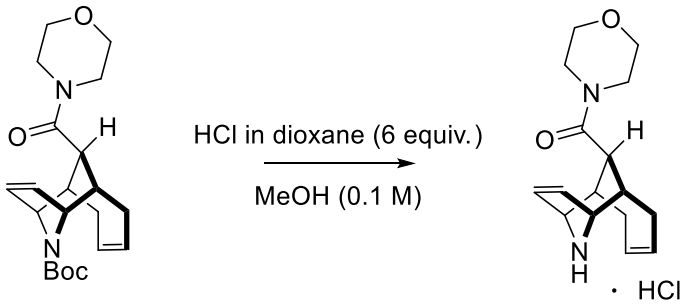
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.09 (qd, J = 5.9, 2.2 Hz, 2H), 5.57 – 5.28 (m, 2H), 4.54 (t, J = 2.4 Hz, 1H), 4.48 (t, J = 2.4 Hz, 1H), 3.69 – 3.57 (m, 4H), 3.38 (d, J = 155.8 Hz, 4H), 2.65 (s, 1H), 2.61 – 2.54 (m, 1H), 2.53 – 2.45 (m, 3H), 2.42 – 2.36 (m, 1H), 2.29 (dd, J = 7.1, 2.6 Hz, 1H), 1.41 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 174.87, 151.38, 134.61, 133.89, 125.85, 125.78, 78.87, 66.77, 62.85, 62.85, 61.65, 41.67, 36.13, 36.13, 35.86, 34.79, 34.41, 28.61.

Note: Extra protons are from DMSO signal at 2.5 ppm overlapping with product signal. There is a water peak at 3.07 ppm.

HRMS (ESI – TOF) m/z: $[M + H]^+$ $C_{21}H_{30}N_2O_4$ Calculated for 375.2278; Found 375.2296

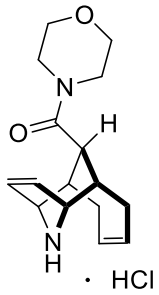
Synthesis of 11b: NBoc deprotection



11a **11b**

11a (38 mg, 0.101 mmol) was dissolved in methanol (1 mL, 0.1 M), then HCl in dioxane (11 µL, 0.304 mmol, 3.0 equiv.) was added dropwise. The reaction continued for 3 hours, after which another 3 equivalents of HCl in dioxane were added. The reaction was stopped after 3 hours when full conversion of starting material was observed on TLC. The reaction mixture was concentrated under reduced pressure to yield 26 mg (81% yield) **11b** as a brown salt without further purification.

morpholino(12-azatricyclo[4.4.1.12,5]dodeca-3,8-dien-11-yl)methanone hydrochloride (11b)

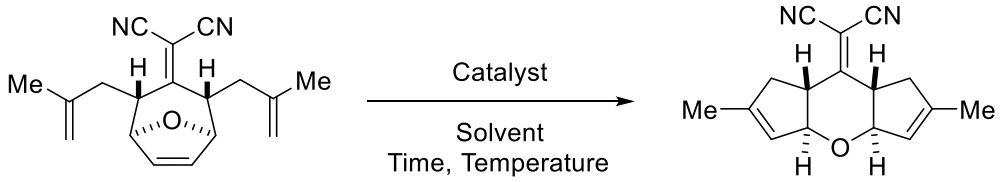


^{1}H NMR (600 MHz, D_2O) δ 6.29 (s, 2H), 5.98 – 5.94 (m, 2H), 4.51 (d, J = 2.6 Hz, 2H), 3.89 – 3.76 (m, 5H), 3.71 – 3.51 (m, 4H), 3.22 (s, 1H), 2.94 (dd, J = 16.9, 6.1 Hz, 2H), 2.83 – 2.76 (m, 2H), 2.76 – 2.68 (m, 2H).

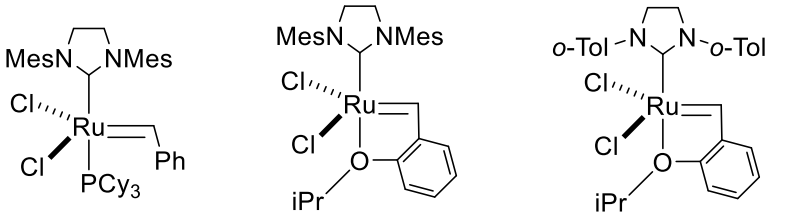
^{13}C NMR (151 MHz, D_2O) δ 174.98, 131.19, 128.87, 71.67, 70.80, 66.45, 66.14, 64.63, 63.67, 60.41, 46.70, 43.25, 40.12, 34.66, 33.13, 31.70.

HRMS (ESI – TOF) m/z: $[M + Na]^+$ $C_{16}H_{22}N_2O_2$ Calculated for 275.1754; Found 275.1756

Studies on ring-opening/cross-metathesis and ring-rearrangement selectivity



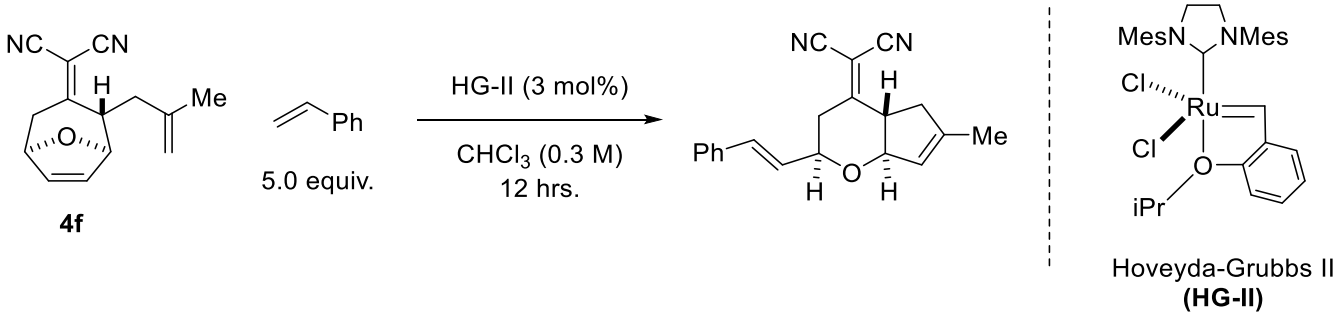
6p



Grubbs II **(G-II)** | Hoveyda-Grubbs II **(HG-II)** | Stewart-Grubbs **(SG-II)**

Entry	Catalyst	Temp. (°C)	Solvent	Ethylene (g)	Time (hrs)	Yield (Conversion)
1	G II (5 mol%)	65	toluene (0.02 M)	No	12	No rxn
2	G II (3 mol%)	80	DCM (0.02 M)	No	12	No rxn
3	G II (5 mol%)	80	toluene (0.02 M)	Yes	12	No rxn
4	HG II (5 mol%)	80	toluene (0.02 M)	Yes	12	No rxn
5	HG II (5 mol%)	50	DCM (0.02 M)	Yes	12	No rxn
6	HG II (5 mol%)	80	toluene (0.005 M)	Yes	12	No rxn
7	SG II (5 mol%)	40	DCM (0.02 M)	Yes	12	No rxn
8	SG II (10 mol%)	RT	DCM (0.01 M)	Yes	6	No rxn

Table 1: Attempts at ring-rearrangement metathesis of **6p**

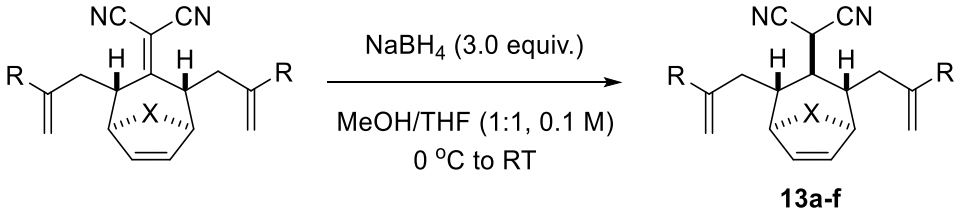


4f

Hoveyda-Grubbs II **(HG-II)**

Reaction note: No ring-opening cross-metathesis product observed and starting material was recovered.

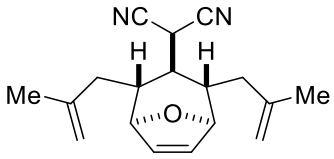
General Procedure G: Alkylidene reduction



13a-f

The starting material was dissolved in a mixture of methanol and THF (1:1, 0.1 M) and cooled to 0 °C. Then, $NaBH_4$ (2.5 equiv.) was slowly added while stirring. After addition, the mixture was warmed to room temperature, and the reaction proceeded until completion was observed by TLC (1 hr.). The reaction was quenched with NH_4Cl, then extracted with EtOAc and washed with 1 M HCl and brine. The organic layer was dried with anhydrous sodium sulfate, concentrated under reduced pressure and purified by flash column chromatography.

2-((1R*,2S*,3S*,4R*,5S*)-2,4-bis(2-methylallyl)-8-oxabicyclo[3.2.1]oct-6-en-3-yl)malononitrile (13a)



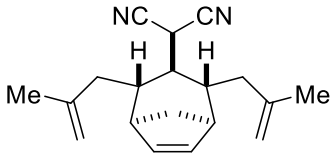
Clear oil, 37% yield, 11 mg, > 20:1 dr

Purified using 5-10% gradient EtOAc in hexanes

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.31 (s, 2H), 4.93 (p, J = 1.5 Hz, 2H), 4.84 (dd, J = 2.1, 1.2 Hz, 2H), 4.64 (s, 2H), 4.03 (d, J = 11.6 Hz, 1H), 2.53 (ddd, J = 13.6, 8.4, 1.0 Hz, 2H), 2.33 (ddd, 2H), 2.03 (d, J = 11.6 Hz, 1H), 1.77 (s, 6H), 1.66 (t, J = 8.4, 7.0 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.09, 134.36, 114.65, 112.56, 80.00, 44.58, 40.94, 33.91, 31.46, 22.05.

2-((1R*,2R*,3R*,4S*,5S*)-2,4-bis(2-methylallyl)bicyclo[3.2.1]oct-6-en-3-yl)malononitrile (13b)



Reaction note: DMPU used as solvent.

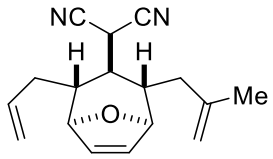
Clear oil, 48% yield, 24 mg, > 20:1 dr

Purified using 0-2.5% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.10 – 6.04 (m, 2H), 4.87 (p, J = 1.6 Hz, 2H), 4.79 – 4.74 (m, 2H), 3.92 (d, J = 10.1 Hz, 1H), 2.51 (dt, J = 4.6, 1.9 Hz, 2H), 2.24 (qdd, J = 13.3, 7.7, 1.0 Hz, 4H), 1.86 (d, J = 11.4 Hz, 1H), 1.82 (dt, J = 10.1, 2.2 Hz, 1H), 1.78 – 1.75 (m, 8H), 1.68 – 1.60 (m, 1H), 1.28 – 1.23 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 142.69, 137.18, 113.83, 112.94, 46.50, 42.41, 41.36, 34.55, 31.78, 29.77, 21.85.

2-((1S*,2R*,3R*,4S*,5R*)-2-allyl-4-(2-methylallyl)-8-oxabicyclo[3.2.1]oct-6-en-3-yl)malononitrile (13c)



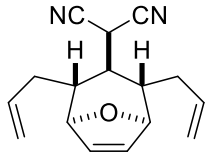
Clear oil, 25% yield, 10 mg, > 20:1 dr

Purified using 0-10% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.40 – 6.23 (m, 2H), 5.80 (dddd, J = 16.9, 10.3, 7.7, 6.6 Hz, 1H), 5.25 – 5.13 (m, 2H), 4.94 (p, J = 1.7 Hz, 1H), 4.88 – 4.74 (m, 1H), 4.65 (dd, J = 15.9, 1.6 Hz, 2H), 3.98 (d, J = 11.6 Hz, 1H), 2.60 – 2.51 (m, 1H), 2.49 (ddd, J = 13.5, 7.8, 1.0 Hz, 1H), 2.44 – 2.36 (m, 1H), 2.36 – 2.31 (m, 1H), 2.06 (d, J = 11.6 Hz, 1H), 1.87 – 1.72 (m, 3H), 1.66 (t, J = 7.7 Hz, 1H), 1.58 (t, J = 7.7 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 142.03, 135.20, 134.30, 118.91, 114.71, 112.54, 112.50, 80.28, 80.21, 47.87, 44.48, 40.29, 39.87, 36.07, 33.80, 31.44, 22.03.

2-((1R*,2S*,3S*,4R*,5S*)-2,4-diallyl-8-oxabicyclo[3.2.1]oct-6-en-3-yl)malononitrile (13d)



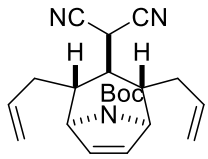
Clear oil, 25% yield, 12 mg, > 20:1 dr

Purified using 0-10% gradient EtOAc in hexanes

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (s, 2H), 5.79 (dddd, J = 16.8, 10.2, 7.9, 6.5 Hz, 2H), 5.26 – 5.09 (m, 4H), 4.65 (s, 2H), 3.94 (d, J = 11.6 Hz, 1H), 2.52 (dtt, J = 13.7, 6.8, 1.4 Hz, 2H), 2.46 – 2.34 (m, 2H), 2.09 (d, 1H), 1.65 – 1.44 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 135.19, 134.26, 118.96, 112.50, 80.40, 40.21, 38.86, 35.88, 31.42.

tert-butyl (1R*,2S*,3S*,4R*,5S*)-2,4-diallyl-3-(dicyanomethyl)-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (13e)



Clear oil, 35% yield, 56 mg, > 20:1 dr

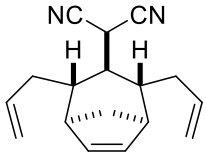
Purified using 0-15% gradient EtOAc in hexanes

^{1}H NMR (400 MHz, DMSO-d_6) δ 6.33 – 6.18 (m, 2H), 5.87 (ddt, J = 17.2, 10.3, 7.1 Hz, 2H), 5.24 – 5.08 (m, 4H), 4.65 (d, J = 9.2 Hz, 1H), 4.58 (q, J = 1.2 Hz, 2H), 2.34 (dddt, J = 14.1, 8.1, 6.9, 1.3 Hz, 2H), 2.27 – 2.16 (m, 2H), 1.93 – 1.82 (m, 1H), 1.65 (ddt, J = 8.2, 6.5, 1.8 Hz, 2H), 1.44 (s, 9H).

Note: Water peak at 3.1 ppm.

^{13}C NMR (101 MHz, DMSO-d_6) δ 153.79, 136.09, 135.23, 118.18, 114.28, 79.63, 60.04, 41.26, 38.11, 31.27, 28.55.

2-((1R*,2R*,3R*,4S*,5S*)-2,4-diallylbicyclo[3.2.1]oct-6-en-3-yl)malononitrile (13f)



Reaction note: DMPU used as solvent.

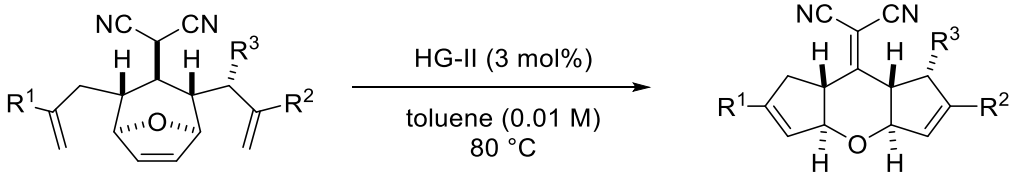
Clear oil, 28% yield, 35 mg, > 20:1 dr

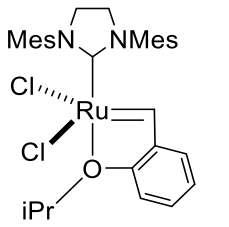
Purified using 0-5% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.13 – 6.00 (m, 2H), 5.79 (dddd, J = 16.9, 10.1, 7.7, 6.7 Hz, 2H), 5.20 – 5.03 (m, 4H), 3.89 (d, J = 10.3 Hz, 1H), 2.64 – 2.44 (m, 2H), 2.35 – 2.18 (m, 4H), 1.92 (dt, J = 10.4, 2.1 Hz, 1H), 1.84 (d, J = 11.4 Hz, 1H), 1.71 – 1.63 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 137.08, 135.83, 118.08, 112.96, 42.03, 42.02, 39.93, 36.49, 31.77, 30.20.

General Procedure H: Ring-rearrangement metathesis

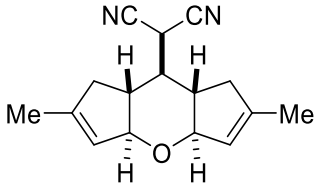




Hoveyda-Grubbs II
(HG-II)

The starting material **13a-f** was dissolved in toluene (0.01 M) in a round-bottom Schlenk flask under nitrogen atmosphere. Then, the HG-II catalyst (5 mol%) was added and the reaction proceeded at 80 °C until full conversion of the starting material was observed by TLC (4-12 hrs). The reaction mixture was cooled down, concentrated under reduced pressure and then purified by flash column chromatography.

2-((3aR*,4aS*,7aS*,8s*,8aR*)-2,6-dimethyl-3a,4a,7,7a,8,8a-hexahydro-1H-dicyclopenta[b,e]pyran-8-yl)malononitrile (14a)



White solid, 69% yield, 20 mg

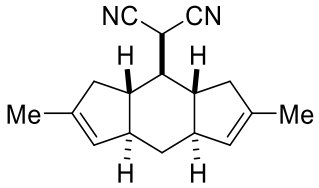
Purified using 0-10% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.65 (s, 2H), 4.45 – 4.21 (m, 2H), 3.77 (d, J = 3.6 Hz, 1H), 2.63 – 2.43 (m, 1H), 2.41 – 2.24 (m, 2H), 2.17 – 1.95 (m, 4H), 1.78 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 141.90, 126.16, 111.47, 89.20, 51.53, 43.23, 35.12, 25.28, 17.52.

HRMS (ESI – TOF) m/z: $[M + NH_4]^+$ $C_{16}H_{18}N_2O$ Calculated for 272.1757; Found 272.1750

2-((3aR*,4r*,4aS*,7aR*,8aS*)-2,6-dimethyl-3,3a,4,4a,5,7a,8,8a-octahydro-s-indacen-4-yl)malononitrile (14b)



White solid, 67% yield, 6 mg

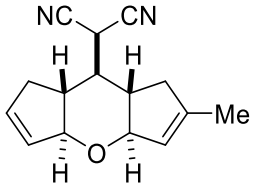
Purified using 0-5% gradient EtOAc in hexanes

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (q, J = 1.9 Hz, 2H), 3.80 (d, J = 2.8 Hz, 1H), 2.38 (t, J = 11.2 Hz, 2H), 2.34 – 2.21 (m, 3H), 2.16 (dt, J = 12.1, 3.4 Hz, 1H), 2.13 – 2.04 (m, 2H), 1.88 – 1.77 (m, 2H), 1.75 (s, 6H), 1.12 (q, J = 11.9 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 140.73, 128.40, 111.90, 52.54, 52.15, 44.90, 38.34, 33.29, 25.55, 17.25.

HRMS (ESI – TOF) m/z: $[M + NH_4]^+$ $C_{17}H_{20}N_2$ Calculated for 270.1965; Found 270.1968

2-((3aS*,4aS*,7aR*,8R*,8aS*)-2-methyl-3a,4a,7,7a,8,8a-hexahydro-1H-dicyclopenta[b,e]pyran-8-yl)malononitrile (14c)



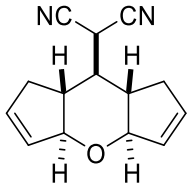
White solid, 56% yield, 5 mg

Purified using 0-10% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.07 (dq, J = 6.0, 1.4 Hz, 1H), 5.92 (dtd, J = 6.0, 2.8, 1.4 Hz, 1H), 5.67 (p, J = 1.5 Hz, 1H), 4.33 (dddd, J = 8.5, 7.4, 3.7, 2.2 Hz, 2H), 3.78 (d, J = 3.5 Hz, 1H), 2.61 – 2.47 (m, 2H), 2.43 – 2.34 (m, 1H), 2.11 – 1.99 (m, 3H), 1.79 (dt, J = 2.2, 1.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 142.12, 132.94, 131.40, 126.01, 89.55, 89.10, 51.49, 51.29, 43.23, 35.08, 30.87, 25.28, 17.53.

2-((3aR*,4aS*,7aR*,8s*,8aS*)-3a,4a,7,7a,8,8a-hexahydro-1H-dicyclopenta[b,e]pyran-8-yl)malononitrile (14d)



White solid, 71% yield, 12 mg

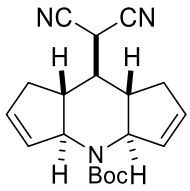
Purified using 0-15% gradient EtOAc in hexanes

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 – 6.01 (m, 2H), 5.99 – 5.83 (m, 2H), 4.41 – 4.24 (m, 2H), 3.81 (d, 1H), 2.65 – 2.45 (m, 3H), 2.20 – 1.96 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 132.76, 131.63, 111.33, 89.45, 51.27, 43.18, 30.84, 25.29.

HRMS (ESI – TOF) m/z: $[M + NH_4]^+$ $C_{14}H_{14}N_2O_2$ Calculated for 244.1444; Found 244.1440

tert-butyl (3aR*,4aS*,7aR*,8s*,8aS*)-8-(dicyanomethyl)-3a,4a,7,7a,8,8a-hexahydrodicyclopenta[b,e]pyridine-4(1H)-carboxylate (14e)



White solid, 43% yield, 10 mg

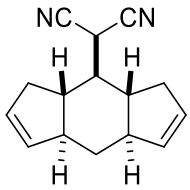
Purified using 0-20% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.39 (dd, J = 5.9, 2.4 Hz, 1H), 6.34 (dd, J = 5.9, 2.3 Hz, 1H), 5.53 – 5.32 (m, 2H), 4.69 (t, J = 2.4 Hz, 1H), 4.59 (t, J = 2.3 Hz, 1H), 4.36 (d, J = 12.2 Hz, 1H), 2.67 – 2.48 (m, 4H), 2.44 (d, J = 12.2 Hz, 1H), 2.22 – 2.11 (m, 2H), 1.43 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 151.19, 136.46, 135.71, 125.48, 124.91, 112.43, 112.37, 79.71, 62.72, 61.54, 41.03, 36.66, 36.36, 34.42, 34.24, 30.66, 28.52.

HRMS (ESI – TOF) m/z: $[M + H]^+$ $C_{19}H_{23}N_3O_2$ Calculated for 326.1863; Found 326.1850

2-((3aR*,4r*,4aS*,7aS*,8aR*)-3,3a,4,4a,5,7a,8,8a-octahydro-s-indacen-4-yl)malononitrile (14f)



White solid, 61% yield, 19 mg

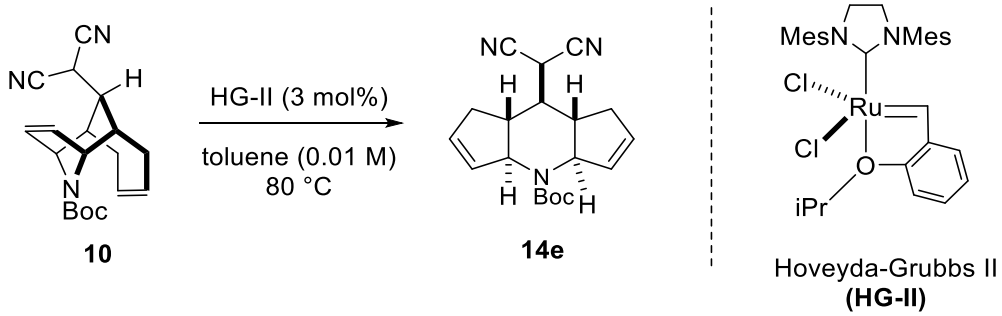
Purified using 0-10% gradient EtOAc in hexanes

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.92 – 5.75 (m, 4H), 3.85 (d, J = 2.8 Hz, 1H), 2.49 – 2.46 (m, 1H), 2.45 (dt, J = 6.7, 1.6 Hz, 1H), 2.40 (ddt, J = 14.3, 6.0, 2.9 Hz, 2H), 2.36 (td, J = 10.9, 2.8 Hz, 1H), 2.28 (dt, J = 11.9, 3.3 Hz, 1H), 2.15 – 2.06 (m, 2H), 1.79 (qd, J = 11.1, 6.6 Hz, 2H), 1.20 (q, J = 11.9 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 135.04, 130.75, 111.79, 76.82, 51.97, 44.83, 33.90, 32.61, 25.59.

HRMS (ESI – TOF) m/z: $[M + NH_4]^+$ $C_{15}H_{16}N_2$ Calculated for 242.1652; Found 242.1648

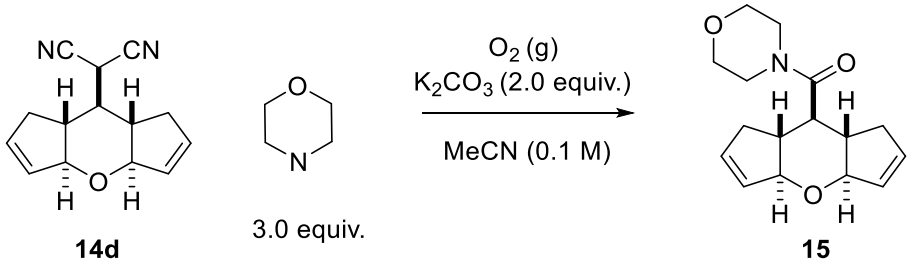
Synthesis of 14e: Ring-rearrangement metathesis of 10



The starting material **10** (40 mg, 0.12 mmol) was dissolved in toluene (12 mL, 0.01 M) under nitrogen atmosphere. The catalyst HG-II (2.3 mg, 0.004 mmol, 3 mol%) was added, and the reaction proceeded at 80 oC overnight. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (0-15% gradient EtOAc in hexanes) to give 16 mg (40% yield) **14e** as a white solid.

Spectroscopic data matches **14e** synthesized by General Procedure H, as reported above.

Synthesis of 15: Oxidative amidation



The procedure is based on published literature.[6] **14d** (30 mg, 0.13 mmol) was dissolved in MeCN (2 mL, 0.1 M), then K_2CO_3 (37 mg, 0.26 mmol, 2.0 equiv) and morpholine (23 µL, 0.26 mmol, 2.0 equiv.) were added. The reaction mixture was sparged with oxygen and proceeded for 12 hours in an oxygen atmosphere at room temperature. Then, the reaction mixture was concentrated under reduced pressure and purified by column chromatography (20-70% gradient EtOAc in hexanes) to yield 17 mg (47% yield) **10b** as a white solid.

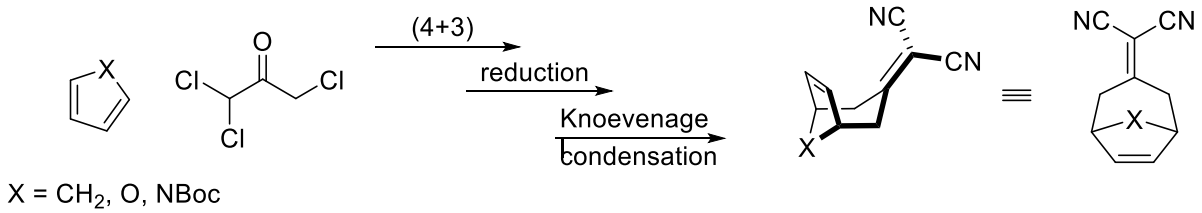
((3aR*,4aS*,7aR*,8s*,8aS*)-3a,4a,7,7a,8,8a-hexahydro-1H-dicyclopenta[b,e]pyran-8-yl)(morpholino)methanone (15)

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.04 (ddd, J = 6.9, 2.5, 1.1 Hz, 2H), 5.89 (dtd, J = 5.8, 2.9, 1.6 Hz, 2H), 4.28 (dddt, J = 10.1, 3.7, 2.6, 1.4 Hz, 2H), 3.67 (d, J = 4.3 Hz, 6H), 3.61 (dd, J = 5.6, 3.8 Hz, 2H), 3.01 (t, J = 10.5 Hz, 1H), 2.43 – 2.32 (m, 2H), 2.26 (qd, J = 10.5, 6.5 Hz, 2H), 1.81 (ddtd, J = 14.2, 11.0, 2.9, 1.6 Hz, 2H).

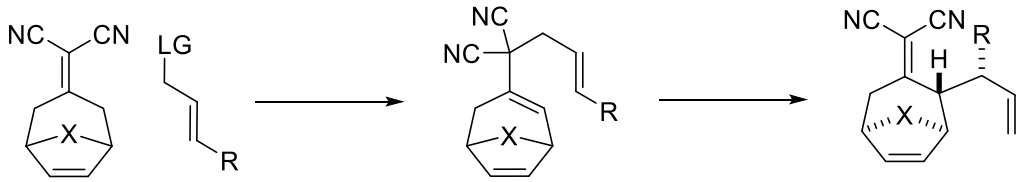
^{13}C NMR (151 MHz, $CDCl_3$) δ 171.21, 132.95, 132.04, 89.05, 67.19, 66.91, 51.81, 51.71, 46.23, 43.17, 42.24, 31.58.

HRMS (ESI – TOF) m/z: $[M + H]^+$ $C_{19}H_{21}NO_3$ Calculated for 276.1594; Found 276.1583

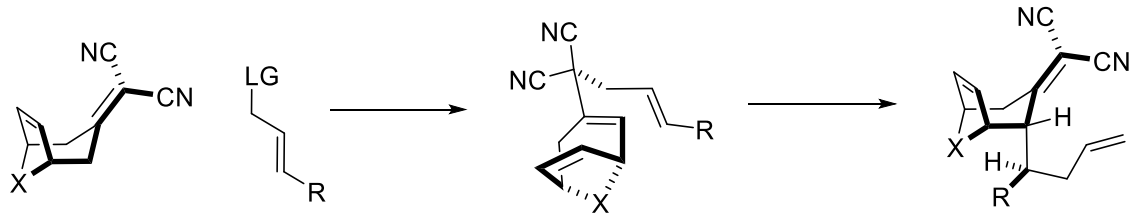
Appendix A: Stereochemical Scheme



X = CH_2, O, NBoc

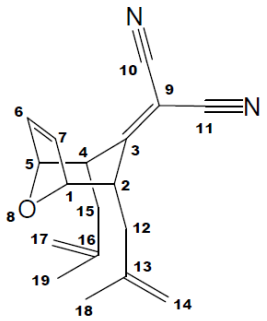


LG = Br, OBoc
R = H, Ph, Pr



Appendix B: Report on the Stereochemistry of 6p

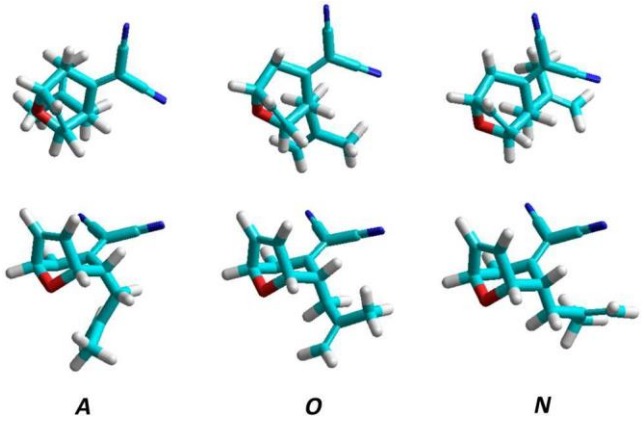
by Ion Ghiviriga, *Director of the Center for NMR, Department of Chemistry, University of Florida*



The atom numbering is given in figure. The assignment of the ^{1}H and ^{13}C chemical shifts, with plots of the relevant spectra, is given in the mnova file.

The configuration at C2 was determined by *J-analysis* and supported by nOes. $^{2}J_{H2\text{-}C1}$ = 0 Hz indicates an *anti* orientation of H2 and O (C12 and O *cis* on the cycloheptene ring). The ratio of the nOes at H1 vs. H6 when H2 is inverted was 2.22 (3.20 expected for *cis* and 18.25 for *trans*, based on distances from the MM model).

The conformational space of this molecule is defined by rotations about C2-C12 and C12-C13 bonds. For C2-C12 there are three staggered conformations which we call ***A***, ***O*** and ***N*** based on the relative position of H2 and C13, ***A*** – anti, ***O*** – *gauche* towards the oxygen bridge and ***N*** – *gauche* towards the cyano groups.



Comparison of the coupling constants in Table 2 with the literature data in Table 1 indicate that in the preferred conformation H2 and H12" are *anti* ($^{3}J_{H2\text{-}H12''}$ = 10.9 Hz) like in conformations ***O*** and ***N***. The proton in position 12 *gauche* to H2, H12' has a large-medium coupling constant with C1 and a small -medium constant with C3, therefore the prevalent conformation is ***O***, and H12" is *pro-S*. A large $^{2}J_{H2\text{-}C13}$ is expected for ***A***, and in fact the value is 0.

The ratios of the nOes at H12' and H12" to the nOe at H2 when H1 is inverted give a more precise picture. First, the ratio is credible, since a value of 0.76 was expected for H6, and a value of 0.80 was observed. The distances measured on the MM+ model are given in columns 2-4 of Table 3, and the calculated ratios for the H12' and H12" in the three conformations in columns 5-6. Comparison with the experimental

values indicate that conformer ***A*** is not part of the mix - it would increase the ratio nOe12'/noe2. From the ratio nOe12"/nOe2 one can estimate that the molar fraction of conformer ***O*** is 0.80.

Rotations about C12-C13 give two conformations in which C2-C12 bisects the plane C13-C14-C18. In conformers ***O*** and ***N***, we call these conformations ***a*** when C18 is *anti* to H12" and ***s*** when it is *syn*. In ***A***, there is no proton H12" *anti* to H2, therefore the conformations are ***o*** when C18 points towards the oxygen and ***n*** when it points towards the cyano groups. The conformations in the figure above are ***Ao***, ***Oa*** and ***Ns***.

Comparison of the coupling constants of H12' and H12" with C14 and C18 to the values in Table 1 is not appropriate since the system is unsaturated, however, the larger value of $^3J_{H12''\text{-}C18}$ than $^3J_{H12'\text{-}C18}$ suggests that the ***a*** conformation is preferred. NOes do not allow for a more precise picture, given the precision with which the distances involved can be calculated.

The table/graph on the last page displays all the possible 36 conformations, 6 symmetrical ones and 15 pairs of enantiomers, their energies and the distance C14-C17 in those conformers where these atoms are close.

According to the 1.36 rule, the first 11 conformers account for 99% of the population. Their molar fraction calculated from the Boltzmann distribution is given in Table 4. From these the molar fraction of O conformers is 0.68 (*vs*. 0.80 from nOes) and of ***a*** conformers 0.79. Although energies calculated by MM are generally not accurate enough to calculate populations, the fit with the nOe population is within 10%, which might be expected in this case where the energy differences are dictated by steric interactions. Thus, we expect that the occurrence of the lowest energy conformation in which the double bonds are close, ***NaNa***, is 1 in 10^3 and that of the more favorable ***AA*** conformations 1 in 10^9.

In conclusion conformations in which the two double bonds are close represent less than 0.1 % of the conformer populations. These conformations exist however, *ca*. 12 kcal/mol higher than the lowest energy conformer, and they can be accessed in the conditions of a reaction. A better approach would be to calculate the activation energy of the reaction.

Table 1. $^3J_{H,H}$ and $^{2,3}J_{C,H}$ Values (Hz) for Anti and Gauche Orientations in Acyclic Systems

	$^3J_{H,H}$		$^2J_{C,H}$		$^3J_{C,H}$	
oxygenation	anti large	gauche small	gauche[a] large	anti[b] small	anti large	gauche small
none	9−12	2−4	−[c]	−	6−8	1−3
mono	8−11	1−4	−5 to −7[d]	0 to −2[d]	6−8	1−3
di	7−10	0[e]−3	−4 to −6[f]	2−0[f]	5−7[g]	1−3[g]

[from *J. Org. Chem.* **1999**, *64*, 866-876]

Table 2. Relevant coupling constants. The proton carbon coupling constants were measured in the IPAP HSMBC experiment. [*Magn. Reason. Chem*. **2013** *51(9)*, 509-516]

J (Hz)	H12'	H12"	C1
H2	4.0	10.9	0.0
C1	5.8	3.7	
C3	3.1	2.0	
C14	5.4	5.8	
C18	2.7	5.1	

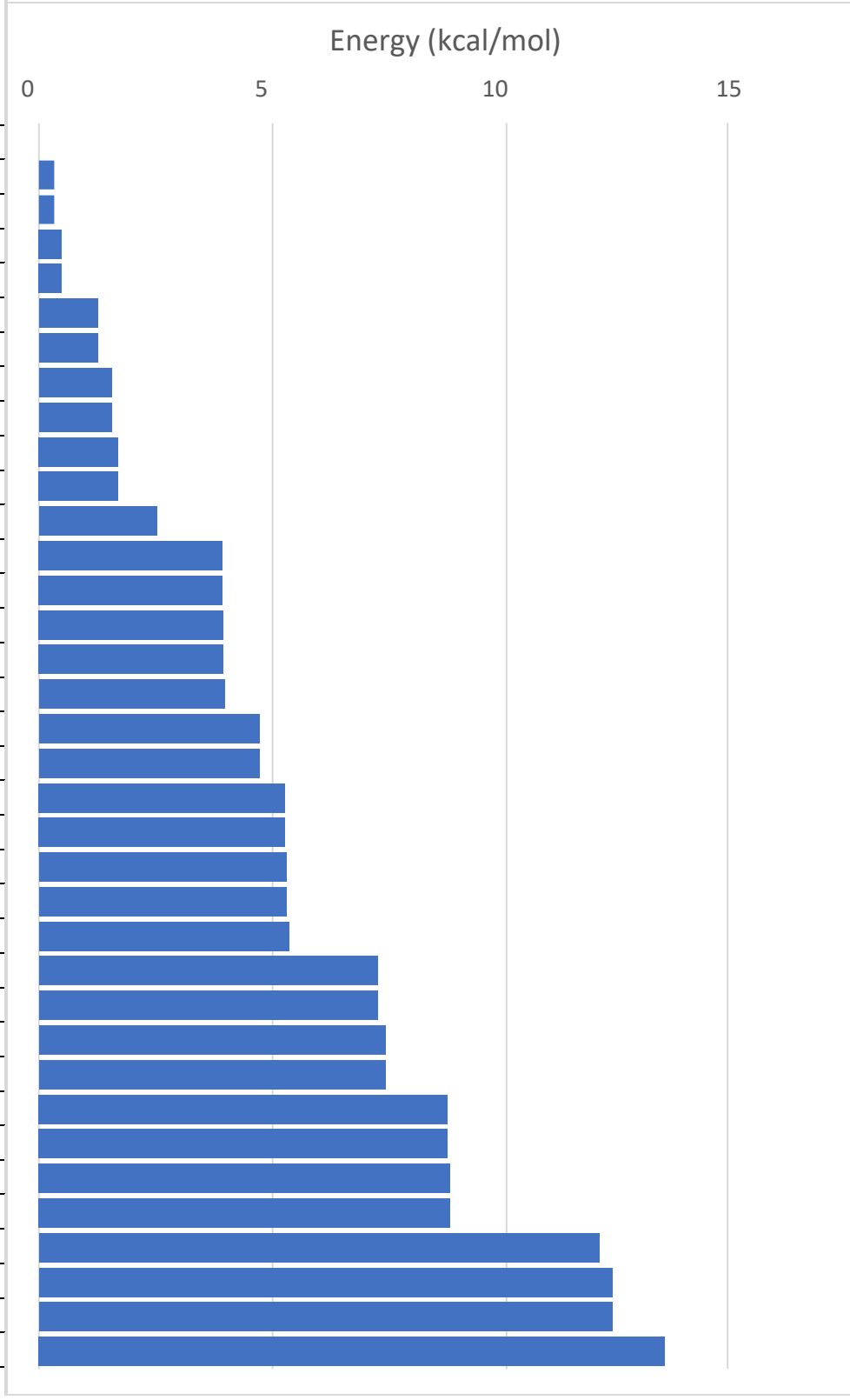
Table 3. Distances and nOe ratios in conformers.

conformer	H1-H12 ProR	H1-H12 Pro-S"	H1-H2	Calc. nOe12'/nOe2	Calc. nOe12"/nOe2	Exp. nOe12'/nOe2	Exp. nOe12"/nOe2
O	3.75	3.04	2.54	0.10	0.34	0.09	0.63
N	2.96	2.3		0.40	1.81		
A	2.39	3.68		1.44	0.11		

Table 4. Molar fractions for the conformers which represent 99% of the population.

conformation	Energy	x mol	O	a
OaOa	0.00	0.28	0.57	0.57
OaNa	0.33	0.16	0.16	0.33
OaNa	0.33	0.16	0.16	0.33
OaNs	0.49	0.12	0.12	0.12
OaNs	0.49	0.12	0.12	0.12
OaOs	1.26	0.03	0.07	0.03
OaOs	1.26	0.03	0.07	0.03
OsNa	1.56	0.02	0.02	0.02
OsNa	1.56	0.02	0.02	0.02
OsNs	1.70	0.02	0.02	
OsNs	1.70	0.02	0.02	
Total			1.35	1.58
x			0.68	0.79

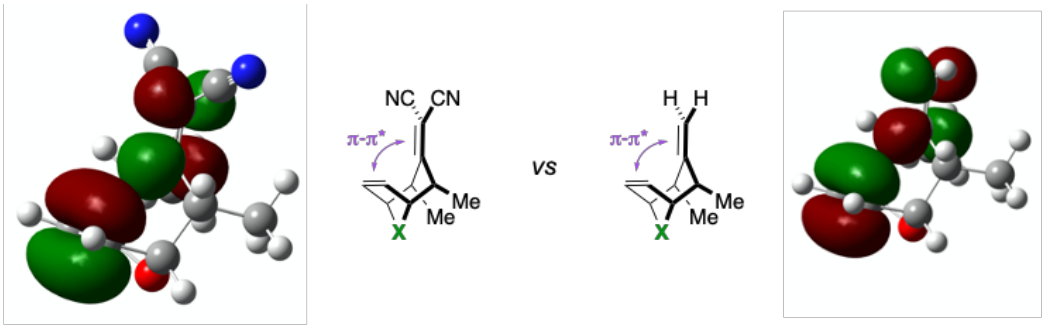
Energy	conformation	C14-C17
0.00	**OaOa**	6.56
0.33	**OaNa**	
0.33	**OaNa**	
0.49	**OaNs**	
0.49	**OaNs**	
1.26	**OaOs**	
1.26	**OaOs**	
1.56	**OsNa**	
1.56	**OsNa**	
1.70	**OsNs**	
1.70	**OsNs**	
2.51	**OsOs**	8.35
3.93	**AoOa**	
3.93	**AoOa**	
3.94	**AnOa**	
3.94	**AnOa**	
3.98	**NaNa**	3.84
4.72	**NaNs**	
4.72	**NaNs**	
5.26	**AoOs**	
5.27	**AoOs**	
5.29	**AnOs**	
5.29	**AnOs**	
5.34	**NsNs**	
7.25	**AoNs**	
7.25	**AoNs**	
7.41	**AoNa**	
7.41	**AoNa**	
8.75	**AnNa**	
8.75	**AnNa**	
8.79	**AnNs**	
8.79	**AnNs**	
11.99	**AoAo**	3.06
12.26	**AoAn**	3.70
12.26	**AoAn**	
13.39	**AnAn**	3.30



Appendix C: Computational analysis of a π-π* anchimeric effect

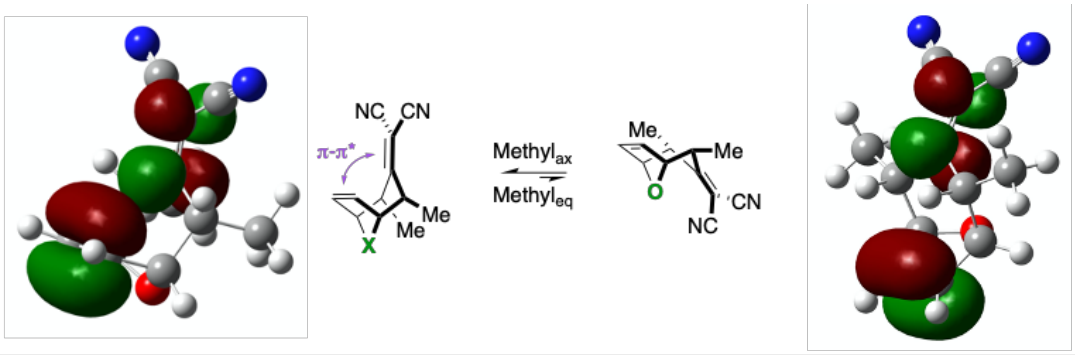
Interaction energies between the cycloalkene π bond and the π∗ bond of the alkylidenemalononitrile were quantified in Gaussian 09[7] by Natural bond orbital calculations[8]
We built the initial structures and locally optimize them using the DFT level of theory M062x/cc-pvdz.
We checked that the qualitative trends do not change when using a different functional of basis set combination. We found the localized bond orbitals for the π and π* orbitals of interest and used the second order energy between them as computed in NBO 3.1 using the same level of theory shown above to quantify the extent of the interaction.
For the cycloalkene–alkylidenemalononitrile substrate, we find that the interaction energy was 1.9 kcal/mol. When the CN groups are removed, the interaction energy drops to 1 kcal/mol. This shows the effect of the substituents on the π- π* interaction, in accordance with our hypothesis that the two double bonds interact *via* an anchimeric effect (Figure 1).

Figure 1: Comparison of cycloalkene–alkylidenemalononitrile- and cycloalkene–exomethylene-containing substrates.



1.9 kcal/mol π-π* interaction energy between the cycloalkene and the alkylidenemalononitrile. 1.0 kcal/mol π-π* interaction energy between the cycloalkene and the exomethylene.

We also want to point out that the interaction energy is conformation dependent. In the boat conformation, the computed interaction energy is lower than 0.01 kcal/mol, which is to be expected given the longer distance between the orbitals studied (Figure 2).



1.9 kcal/mol π-π* interaction energy in the methyl$_{ax}$ conformation. No π-π* interaction in the methyl$_{eq}$ conformation.

Appendix D: X-Ray Crystallography Data and Experimental

X-Ray of **7b**

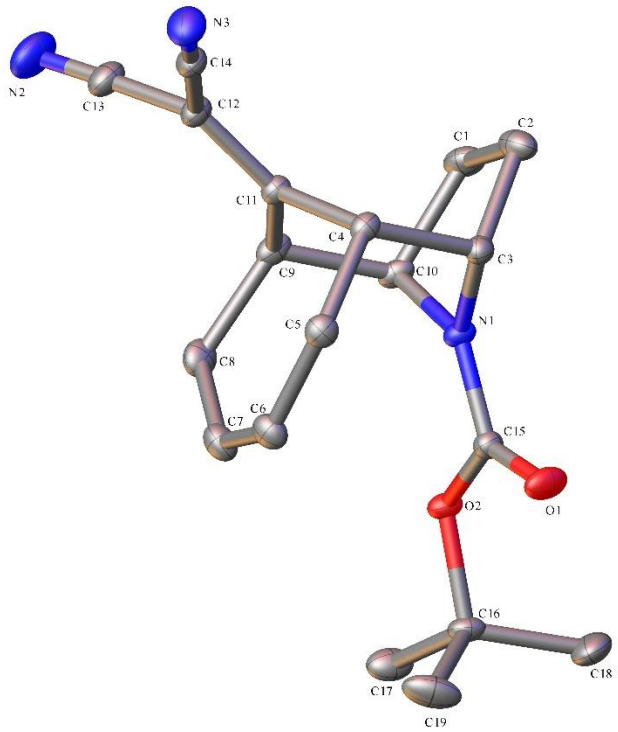


Table 1. Crystal data and structure refinement for 7b.

Identification code	7b	
Empirical formula	C19 H21 N3 O2	
Formula weight	323.39	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 8.5708(2) Å	α = 90°.
	b = 17.0112(4) Å	β = 106.2848(6)°.
	c = 12.3358(3) Å	γ = 90°.
Volume	1726.40(7) $Å^3$	
Z	4	
Density (calculated)	1.244 Mg/m^3	
Absorption coefficient	0.082 mm^{-1}	
F(000)	688	
Crystal size	0.268 x 0.229 x 0.104 mm^3	
Theta range for data collection	2.096 to 36.362°.	
Index ranges	-14≤h≤13, -28≤k≤28, -20≤l≤20	
Reflections collected	55483	

Independent reflections	8378 [R(int) = 0.0340]
Completeness to theta = 25.000°	100.0 %
Absorption correction	Integration
Max. and min. transmission	0.9938 and 0.9799
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8378 / 0 / 220
Goodness-of-fit on F^2	0.999
Final R indices [I>2sigma(I)]	R1 = 0.0402, wR2 = 0.1078 [6168]
R indices (all data)	R1 = 0.0603, wR2 = 0.1148
Extinction coefficient	n/a
Largest diff. peak and hole	0.526 and -0.203 e.$Å^{-3}$

$R1 = \sum(||F_o| - |F_c||) / \sum|F_o|$

$wR2 = [\sum[w(F_o^2 - F_c^2)^2] / \sum w(F_o^2)^2]]^{1/2}$

$S = [\sum w(F_o^2 - F_c^2)^2] / (n-p)]^{1/2}$

$w= 1/[\sigma^2(F_o^2)+(m*p)^2+n*p]$, $p = [\max(F_o^2,0)+ 2* F_c^2]/3$, m & n are constants.

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 7b. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O1	3056(1)	1741(1)	8715(1)	22(1)
O2	1874(1)	1690(1)	6808(1)	14(1)
N1	3877(1)	2538(1)	7512(1)	13(1)
N2	2948(1)	5634(1)	5080(1)	34(1)
N3	4692(1)	5927(1)	8768(1)	23(1)
C1	5787(1)	2958(1)	6624(1)	20(1)
C2	6466(1)	3086(1)	7903(1)	20(1)
C3	4973(1)	3027(1)	8361(1)	13(1)
C4	4165(1)	3840(1)	8366(1)	13(1)
C5	2635(1)	3806(1)	8788(1)	15(1)
C6	1066(1)	3478(1)	8042(1)	17(1)
C7	488(1)	3399(1)	6923(1)	19(1)
C8	1207(1)	3591(1)	5974(1)	19(1)
C9	3070(1)	3658(1)	6214(1)	15(1)
C10	3942(1)	2855(1)	6424(1)	14(1)
C11	3740(1)	4197(1)	7202(1)	13(1)
C12	3851(1)	4983(1)	7056(1)	15(1)
C13	3371(1)	5344(1)	5957(1)	20(1)
C14	4348(1)	5511(1)	8002(1)	17(1)
C15	2937(1)	1967(1)	7756(1)	13(1)
C16	738(1)	1055(1)	6877(1)	16(1)
C17	-361(1)	1020(1)	5672(1)	23(1)
C18	1675(1)	292(1)	7199(1)	28(1)
C19	-262(1)	1260(1)	7680(1)	29(1)

Table 3. Bond lengths [Å] and angles [°] for 7b.

O1-C15	1.2217(8)
O2-C15	1.3496(8)
O2-C16	1.4720(8)
N1-C15	1.3492(9)
N1-C3	1.4557(8)
N1-C10	1.4620(8)
N2-C13	1.1508(10)
N3-C14	1.1519(9)
C1-C2	1.5361(11)
C1-C10	1.5404(10)
C1-H1A	0.9900
C1-H1B	0.9900
C2-C3	1.5401(10)
C2-H2A	0.9900
C2-H2B	0.9900
C3-C4	1.5472(9)
C3-H3A	1.0000
C4-C11	1.5069(9)
C4-C5	1.5420(9)
C4-H4A	1.0000
C5-C6	1.5083(10)
C5-H5A	0.9900
C5-H5B	0.9900
C6-C7	1.3357(10)
C6-H6A	0.9500
C7-C8	1.5035(11)
C7-H7A	0.9500
C8-C9	1.5447(10)
C8-H8A	0.9900
C8-H8B	0.9900
C9-C11	1.5035(9)
C9-C10	1.5447(10)
C9-H9A	1.0000
C10-H10A	1.0000
C11-C12	1.3555(9)
C12-C14	1.4386(10)
C12-C13	1.4395(9)
C16-C18	1.5201(11)
C16-C19	1.5211(10)
C16-C17	1.5215(10)

C17-H17A	0.9800
C17-H17B	0.9800
C17-H17C	0.9800
C18-H18A	0.9800
C18-H18B	0.9800
C18-H18C	0.9800
C19-H19A	0.9800
C19-H19B	0.9800
C19-H19C	0.9800

C15-O2-C16	120.20(5)
C15-N1-C3	123.82(5)
C15-N1-C10	130.43(5)
C3-N1-C10	105.52(5)
C2-C1-C10	104.90(5)
C2-C1-H1A	110.8
C10-C1-H1A	110.8
C2-C1-H1B	110.8
C10-C1-H1B	110.8
H1A-C1-H1B	108.8
C1-C2-C3	104.68(6)
C1-C2-H2A	110.8
C3-C2-H2A	110.8
C1-C2-H2B	110.8
C3-C2-H2B	110.8
H2A-C2-H2B	108.9
N1-C3-C2	101.97(5)
N1-C3-C4	108.33(5)
C2-C3-C4	111.25(5)
N1-C3-H3A	111.6
C2-C3-H3A	111.6
C4-C3-H3A	111.6
C11-C4-C5	109.63(5)
C11-C4-C3	110.19(5)
C5-C4-C3	113.08(5)
C11-C4-H4A	107.9
C5-C4-H4A	107.9
C3-C4-H4A	107.9
C6-C5-C4	120.31(5)
C6-C5-H5A	107.2
C4-C5-H5A	107.2
C6-C5-H5B	107.2

C4-C5-H5B	107.2
H5A-C5-H5B	106.9
C7-C6-C5	132.59(7)
C7-C6-H6A	113.7
C5-C6-H6A	113.7
C6-C7-C8	131.94(7)
C6-C7-H7A	114.0
C8-C7-H7A	114.0
C7-C8-C9	119.61(5)
C7-C8-H8A	107.4
C9-C8-H8A	107.4
C7-C8-H8B	107.4
C9-C8-H8B	107.4
H8A-C8-H8B	107.0
C11-C9-C8	109.88(5)
C11-C9-C10	110.32(5)
C8-C9-C10	113.09(6)
C11-C9-H9A	107.8
C8-C9-H9A	107.8
C10-C9-H9A	107.8
N1-C10-C1	101.32(5)
N1-C10-C9	109.75(5)
C1-C10-C9	110.62(6)
N1-C10-H10A	111.6
C1-C10-H10A	111.6
C9-C10-H10A	111.6
C12-C11-C9	121.24(6)
C12-C11-C4	121.10(6)
C9-C11-C4	117.50(5)
C11-C12-C14	121.58(6)
C11-C12-C13	122.27(6)
C14-C12-C13	116.01(6)
N2-C13-C12	178.30(9)
N3-C14-C12	177.41(8)
O1-C15-N1	123.35(6)
O1-C15-O2	125.59(6)
N1-C15-O2	111.06(5)
O2-C16-C18	109.39(6)
O2-C16-C19	111.85(6)
C18-C16-C19	112.24(7)
O2-C16-C17	102.18(5)
C18-C16-C17	110.98(7)

C19-C16-C17	109.77(6)
C16-C17-H17A	109.5
C16-C17-H17B	109.5
H17A-C17-H17B	109.5
C16-C17-H17C	109.5
H17A-C17-H17C	109.5
H17B-C17-H17C	109.5
C16-C18-H18A	109.5
C16-C18-H18B	109.5
H18A-C18-H18B	109.5
C16-C18-H18C	109.5
H18A-C18-H18C	109.5
H18B-C18-H18C	109.5
C16-C19-H19A	109.5
C16-C19-H19B	109.5
H19A-C19-H19B	109.5
C16-C19-H19C	109.5
H19A-C19-H19C	109.5
H19B-C19-H19C	109.5

Symmetry transformations used to generate equivalent atoms:

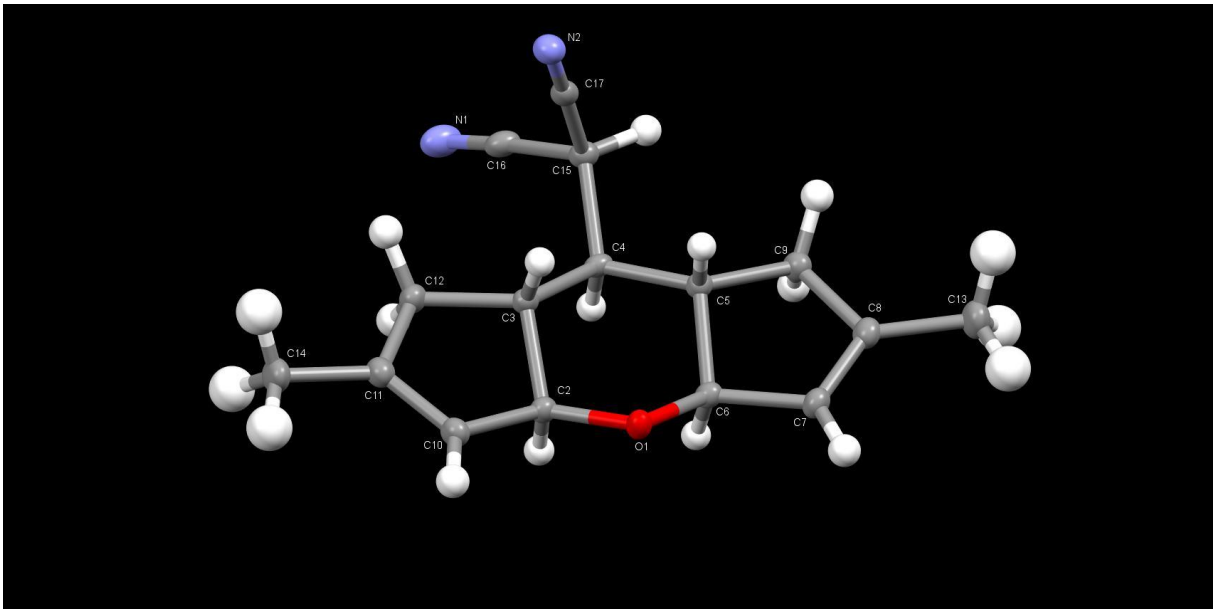
Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 7b. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	26(1)	25(1)	14(1)	5(1)	2(1)	-9(1)
O2	16(1)	14(1)	13(1)	-1(1)	5(1)	-5(1)
N1	16(1)	12(1)	12(1)	-1(1)	5(1)	-3(1)
N2	45(1)	28(1)	25(1)	11(1)	4(1)	-6(1)
N3	26(1)	17(1)	24(1)	-4(1)	2(1)	-2(1)
C1	22(1)	18(1)	25(1)	-1(1)	14(1)	-4(1)
C2	15(1)	18(1)	29(1)	-4(1)	9(1)	-2(1)
C3	13(1)	12(1)	14(1)	0(1)	2(1)	-1(1)
C4	16(1)	11(1)	10(1)	-1(1)	3(1)	-1(1)
C5	18(1)	16(1)	12(1)	-2(1)	5(1)	0(1)
C6	15(1)	20(1)	18(1)	-3(1)	6(1)	2(1)
C7	14(1)	22(1)	19(1)	-3(1)	2(1)	2(1)
C8	21(1)	20(1)	13(1)	0(1)	-1(1)	-1(1)
C9	22(1)	13(1)	10(1)	-1(1)	4(1)	-3(1)
C10	20(1)	12(1)	13(1)	-2(1)	9(1)	-3(1)
C11	15(1)	12(1)	12(1)	0(1)	4(1)	-1(1)
C12	17(1)	12(1)	14(1)	0(1)	3(1)	-1(1)
C13	26(1)	15(1)	19(1)	3(1)	4(1)	-3(1)
C14	16(1)	12(1)	20(1)	1(1)	3(1)	-1(1)
C15	14(1)	13(1)	14(1)	1(1)	4(1)	-1(1)
C16	16(1)	18(1)	16(1)	0(1)	6(1)	-6(1)
C17	24(1)	27(1)	16(1)	-2(1)	4(1)	-10(1)
C18	27(1)	17(1)	39(1)	5(1)	5(1)	-6(1)
C19	24(1)	46(1)	22(1)	-9(1)	14(1)	-15(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 7b.

	x	y	z	U(eq)
H1A	6269	2484	6382	24
H1B	6019	3418	6202	24
H2A	6984	3609	8066	24
H2B	7277	2677	8243	24
H3A	5253	2776	9124	16
H4A	4973	4192	8885	15
H5A	2918	3496	9496	18
H5B	2409	4349	8992	18
H6A	348	3290	8447	21
H7A	-574	3181	6682	23
H8A	730	4096	5642	23
H8B	830	3184	5385	23
H9A	3299	3901	5537	18
H10A	3475	2478	5794	17
H17A	-1183	610	5616	34
H17B	292	897	5156	34
H17C	-898	1529	5468	34
H18A	909	-142	7163	43
H18B	2397	335	7969	43
H18C	2322	190	6673	43
H19A	-1113	864	7617	44
H19B	-763	1778	7484	44
H19C	446	1271	8457	44

X-Ray of **14a**



X-Ray Intensity data were collected at 100 K on a Bruker **D8 Venture** diffractometer using MoKα radiation (λ = 0.71073 Å) and a Photon III area detector.

Raw data frames were read by program SAINT[9] and integrated using 3D profiling algorithms. The resulting data were reduced to produce hkl reflections and their intensities and estimated standard deviations. The data were corrected for Lorentz and polarization effects and numerical absorption corrections were applied based on indexed and measured faces.

The structure was solved and refined in *SHELXTL2014*, using full-matrix least-squares refinement. The non-H atoms were refined with anisotropic thermal parameters and all of the H atoms were calculated in idealized positions and refined riding on their parent atoms. The asymmetric unit consists of the molecule and an ethyl acetate solvent molecule. There is an intra molecular hydrogen bond between N1 and O2, and an intermolecular hydrogen bond between N2 and a symmetrically equivalent of O1 from another molecule. In the final cycle of refinement, 4510 reflections (of which 4143 are observed with $I > 2\sigma(I)$) were used to refine 174 parameters and the resulting R_1, wR_2 and S (goodness of fit) were 3.97%, 9.76% and 1.033, respectively. The refinement was carried out by minimizing the wR_2 function using F^2 rather than F values. R_1 is calculated to provide a reference to the conventional R value but its function is not minimized.

Table 1. Crystal data and structure refinement for 14a.

Identification code	14a
Empirical formula	C16 H18 N2 O
Formula weight	254.32
Temperature	100(2) K
Wavelength	0.71073 Å

Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 7.7143(2) Å	α = 90°.
	b = 8.7813(3) Å	β = 90°.
	c = 20.0769(7) Å	γ = 90°.
Volume	1360.04(8) $Å^3$	
Z	4	
Density (calculated)	1.242 Mg/m^3	
Absorption coefficient	0.079 mm^{-1}	
F(000)	544	
Crystal size	0.269 x 0.217 x 0.065 mm^3	
Theta range for data collection	2.532 to 32.414°.	
Index ranges	-11≤h≤11, -12≤k≤12, -30≤l≤19	
Reflections collected	22337	
Independent reflections	4510 [R(int) = 0.0430]	
Completeness to theta = 25.242°	99.1 %	
Absorption correction	None	
Max. and min. transmission	0.9954 and 0.9838	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4510 / 0 / 174	
Goodness-of-fit on F^2	1.033	
Final R indices [I>2sigma(I)]	R1 = 0.0397, wR2 = 0.0976 [4143]	
R indices (all data)	R1 = 0.0440, wR2 = 0.1013	
Absolute structure parameter	0.0(5)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.351 and -0.197 $e.Å^{-3}$	

$R1 = \sum(||F_o| - |F_c||) / \sum|F_o|$ $wR2 = [\sum[w(F_o^2 - F_c^2)^2] / \sum[w(F_o^2)^2]]^{1/2}$

$S = [\sum[w(F_o^2 - F_c^2)^2] / (n-p)]^{1/2}$ $w = 1/[\sigma^2(F_o^2)+(m*p)^2+n*p]$, $p = [max(F_o^2,0)+ 2* F_c^2]/3$, m & n are constants.

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 14a. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O1	3247(1)	5918(1)	7212(1)	16(1)
N1	10338(2)	3088(2)	6349(1)	26(1)
N2	9541(2)	7889(2)	6776(1)	21(1)
C14	4573(2)	5931(2)	4786(1)	28(1)
C11	4659(2)	5661(2)	5519(1)	20(1)
C12	6316(2)	5110(2)	5852(1)	19(1)
C3	5950(2)	5501(2)	6582(1)	14(1)
C4	6916(2)	4792(1)	7170(1)	14(1)
C5	6062(2)	5512(1)	7780(1)	14(1)
C9	6536(2)	5088(2)	8498(1)	18(1)
C8	4916(2)	5604(2)	8869(1)	18(1)
C13	4934(2)	5846(2)	9604(1)	27(1)
C6	4095(2)	5218(2)	7770(1)	15(1)
C7	3566(2)	5724(2)	8453(1)	18(1)
C2	3990(2)	5218(2)	6632(1)	15(1)
C10	3373(2)	5774(2)	5965(1)	18(1)
C15	8909(2)	5086(2)	7146(1)	16(1)
C16	9755(2)	3998(2)	6691(1)	19(1)
C17	9308(2)	6664(2)	6941(1)	16(1)

Table 3. Bond lengths [Å] and angles [°] for 14a.

O1-C6	1.4354(16)
O1-C2	1.4367(15)
N1-C16	1.145(2)
N2-C17	1.1398(19)
C14-C11	1.493(2)
C14-H14C	0.9800
C14-H14B	0.9800
C14-H14A	0.9800
C11-C10	1.340(2)
C11-C12	1.5212(19)
C12-C3	1.5322(18)
C12-H12B	0.9900
C12-H12A	0.9900
C3-C4	1.5292(18)
C3-C2	1.5355(17)
C3-H3A	1.0000
C4-C5	1.5271(17)
C4-C15	1.5600(17)
C4-H4A	1.0000
C5-C9	1.5338(18)
C5-C6	1.5391(17)
C5-H5A	1.0000
C9-C8	1.5236(19)
C9-H9B	0.9900
C9-H9A	0.9900
C8-C7	1.3387(19)
C8-C13	1.491(2)
C13-H13C	0.9800
C13-H13B	0.9800
C13-H13A	0.9800

C6-C7	1.4993(18)
C6-H6A	1.0000
C7-H7A	0.9500
C2-C10	1.5012(18)
C2-H2A	1.0000
C10-H10A	0.9500
C15-C16	1.4747(19)
C15-C17	1.4784(19)
C15-H15A	1.0000

C6-O1-C2	105.52(9)
C11-C14-H14C	109.5
C11-C14-H14B	109.5
H14C-C14-H14B	109.5
C11-C14-H14A	109.5
H14C-C14-H14A	109.5
H14B-C14-H14A	109.5
C10-C11-C14	127.91(14)
C10-C11-C12	110.64(12)
C14-C11-C12	121.37(13)
C11-C12-C3	101.16(10)
C11-C12-H12B	111.5
C3-C12-H12B	111.5
C11-C12-H12A	111.5
C3-C12-H12A	111.5
H12B-C12-H12A	109.4
C4-C3-C12	123.92(11)
C4-C3-C2	111.34(10)
C12-C3-C2	101.97(10)
C4-C3-H3A	106.1
C12-C3-H3A	106.1
C2-C3-H3A	106.1

C5-C4-C3	103.91(10)
C5-C4-C15	112.43(11)
C3-C4-C15	112.92(10)
C5-C4-H4A	109.1
C3-C4-H4A	109.1
C15-C4-H4A	109.1
C4-C5-C9	123.38(11)
C4-C5-C6	110.16(11)
C9-C5-C6	101.96(10)
C4-C5-H5A	106.8
C9-C5-H5A	106.8
C6-C5-H5A	106.8
C8-C9-C5	101.03(10)
C8-C9-H9B	111.6
C5-C9-H9B	111.6
C8-C9-H9A	111.6
C5-C9-H9A	111.6
H9B-C9-H9A	109.4
C7-C8-C13	127.83(14)
C7-C8-C9	110.90(12)
C13-C8-C9	121.21(13)
C8-C13-H13C	109.5
C8-C13-H13B	109.5
H13C-C13-H13B	109.5
C8-C13-H13A	109.5
H13C-C13-H13A	109.5
H13B-C13-H13A	109.5
O1-C6-C7	117.59(11)
O1-C6-C5	112.81(10)
C7-C6-C5	101.88(11)
O1-C6-H6A	108.0
C7-C6-H6A	108.0

C5-C6-H6A	108.0
C8-C7-C6	109.63(12)
C8-C7-H7A	125.2
C6-C7-H7A	125.2
O1-C2-C10	117.20(11)
O1-C2-C3	112.05(10)
C10-C2-C3	101.63(10)
O1-C2-H2A	108.5
C10-C2-H2A	108.5
C3-C2-H2A	108.5
C11-C10-C2	109.69(12)
C11-C10-H10A	125.2
C2-C10-H10A	125.2
C16-C15-C17	110.04(11)
C16-C15-C4	110.37(11)
C17-C15-C4	111.64(11)
C16-C15-H15A	108.2
C17-C15-H15A	108.2
C4-C15-H15A	108.2
N1-C16-C15	175.82(15)
N2-C17-C15	176.97(15)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 14a. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	14(1)	20(1)	13(1)	1(1)	0(1)	3(1)
N1	19(1)	24(1)	36(1)	-3(1)	5(1)	1(1)
N2	19(1)	22(1)	21(1)	0(1)	-1(1)	-2(1)
C14	27(1)	42(1)	14(1)	3(1)	-1(1)	-5(1)
C11	20(1)	24(1)	16(1)	0(1)	-1(1)	-3(1)
C12	16(1)	24(1)	16(1)	-1(1)	2(1)	-1(1)
C3	12(1)	16(1)	15(1)	0(1)	0(1)	0(1)
C4	11(1)	14(1)	17(1)	1(1)	2(1)	0(1)
C5	13(1)	14(1)	14(1)	2(1)	0(1)	1(1)
C9	16(1)	21(1)	15(1)	3(1)	-1(1)	0(1)
C8	20(1)	19(1)	15(1)	2(1)	2(1)	-1(1)
C13	28(1)	38(1)	16(1)	1(1)	-1(1)	0(1)
C6	13(1)	16(1)	15(1)	2(1)	0(1)	1(1)
C7	17(1)	20(1)	16(1)	1(1)	3(1)	1(1)
C2	13(1)	18(1)	15(1)	0(1)	1(1)	0(1)
C10	17(1)	22(1)	16(1)	2(1)	-3(1)	-1(1)
C15	13(1)	16(1)	18(1)	2(1)	0(1)	1(1)
C16	13(1)	20(1)	26(1)	3(1)	2(1)	-1(1)
C17	12(1)	21(1)	16(1)	-2(1)	0(1)	0(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 14a.

	x	y	z	U(eq)
H14C	3404	6269	4665	41
H14B	4844	4984	4549	41
H14A	5415	6717	4662	41
H12B	7345	5663	5682	22
H12A	6486	4002	5789	22
H3A	6111	6627	6623	17
H4A	6699	3670	7176	17
H5A	6224	6638	7739	17
H9B	6729	3979	8547	21
H9A	7579	5643	8652	21
H13C	3785	6181	9752	41
H13B	5794	6627	9716	41
H13A	5236	4891	9828	41
H6A	3907	4093	7739	17
H7A	2445	6076	8573	21
H2A	3786	4095	6657	18
H10A	2243	6149	5874	22
H15A	9389	4923	7604	19

References

1 B. Föhlisch, E. Gehrlach and R. Herter, *Angew. Chemie Int. Ed. English*, 1982, **21**, 137–137.

2 O. Lahtigui, F. Emmetiere, W. Zhang, L. Jirmo, S. Toledo-Roy, J. C. Hershberger, J. M. Macho and A. J. Grenning, *Angew. Chem. Int. Ed.*, 2016, **55**, 15792–15796.

3 L. Bayeh, P. Q. Le and U. K. Tambar, *Nature*, 2017, **547**, 196–200.

4 D. L. Wright, L. C. Usher and M. Estrella-Jimenez, *Org. Lett.*, 2001, **3**, 4275–4277.

5 P. Ghosh, W. R. Judd, T. Ribelin and J. Aubé, *Org. Lett.*, 2009, **11**, 4140–4142.

6 J. Li, M. J. Lear and Y. Hayashi, *Angew. Chem. Int. Ed.*, 2016, **55**, 9060–9064.

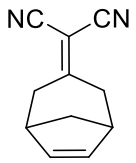
7. Gaussian 09, Revision A.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.

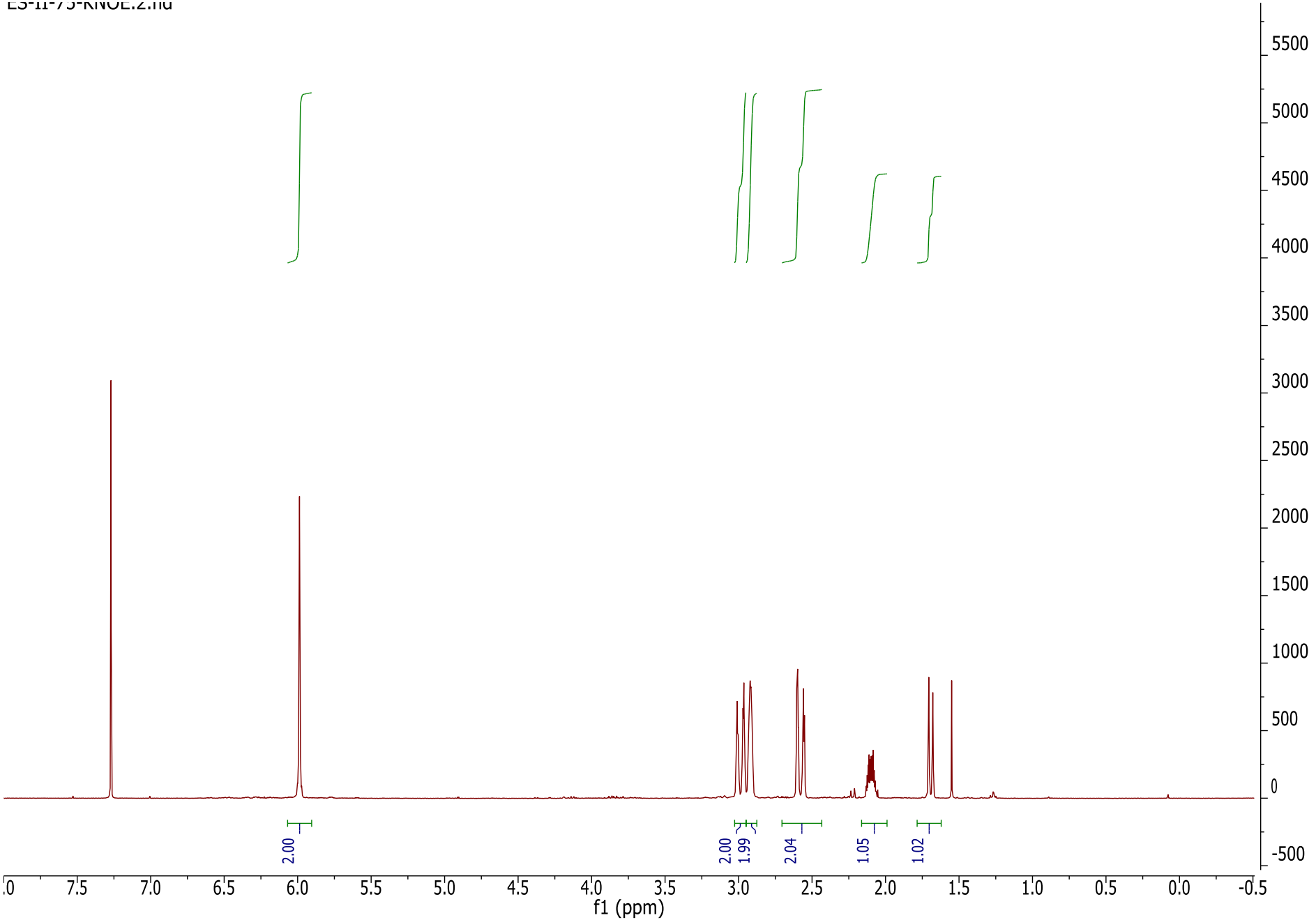
8. nbo: "NBO Version 3.1, E. D. Glendening, A. E. Reed, J. E. Carpenter, and F. Weinhold."

9. Sheldrick, G. M. (2015). *Acta Cryst.* C71, 3–8.

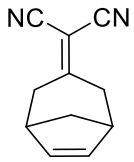
NMR Reprints

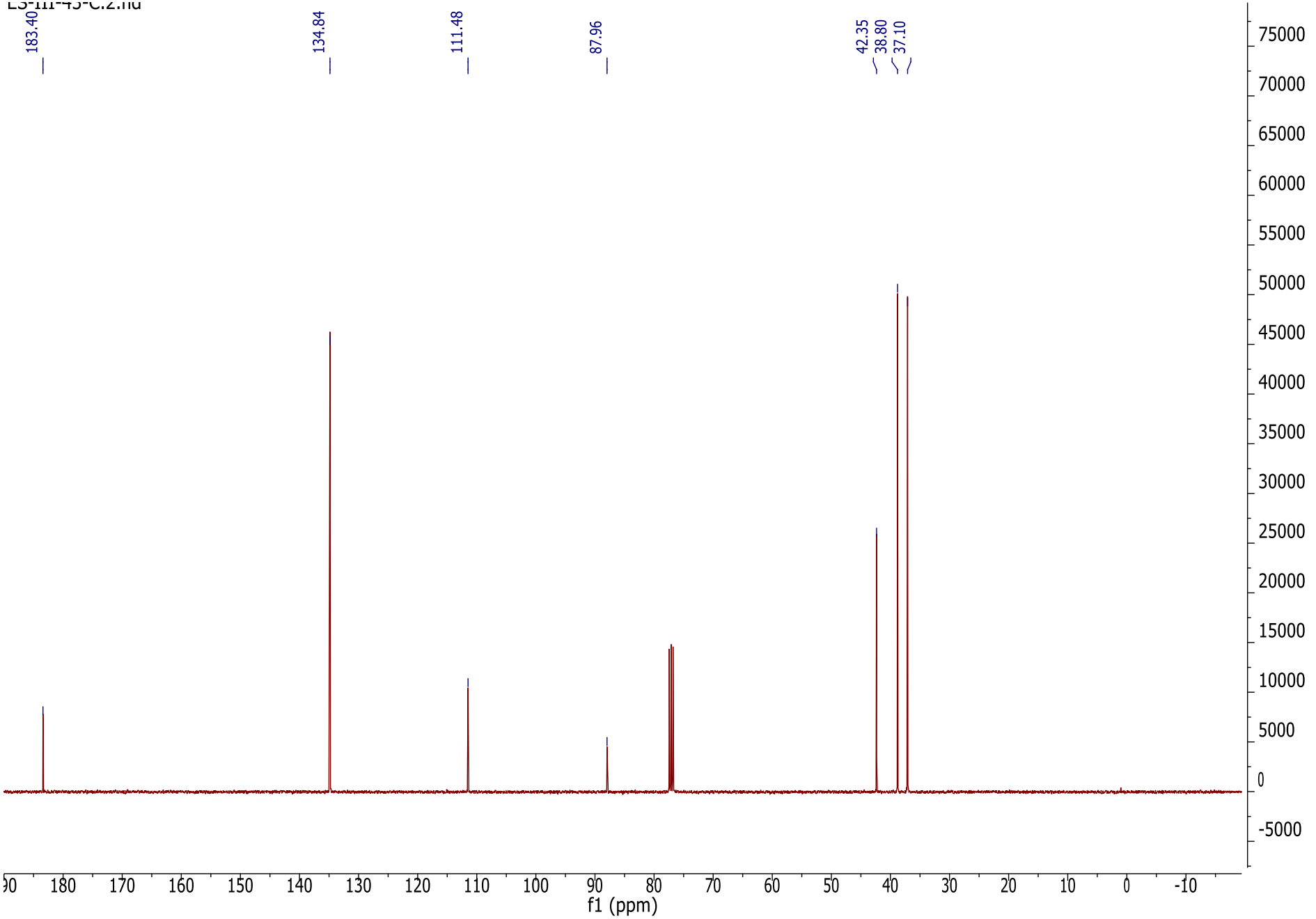
^{1}H NMR of **1a**


NC
CN

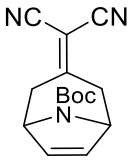

5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
2.00
2.00
1.99
2.04
1.05
1.02
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

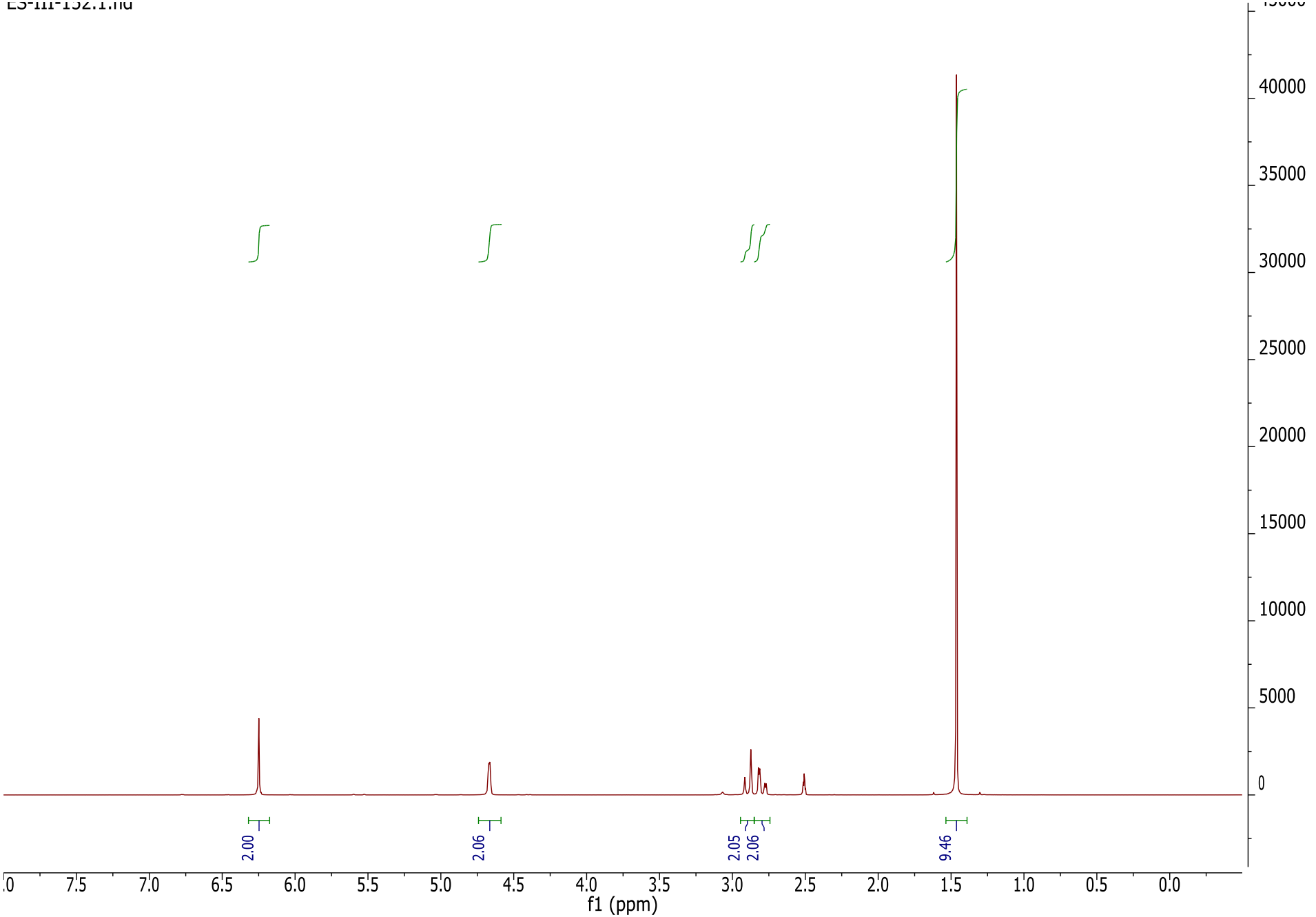
^{13}C NMR of **1a**


NC
CN

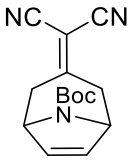

183.40
134.84
111.48
87.96
42.35
38.80
37.10
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

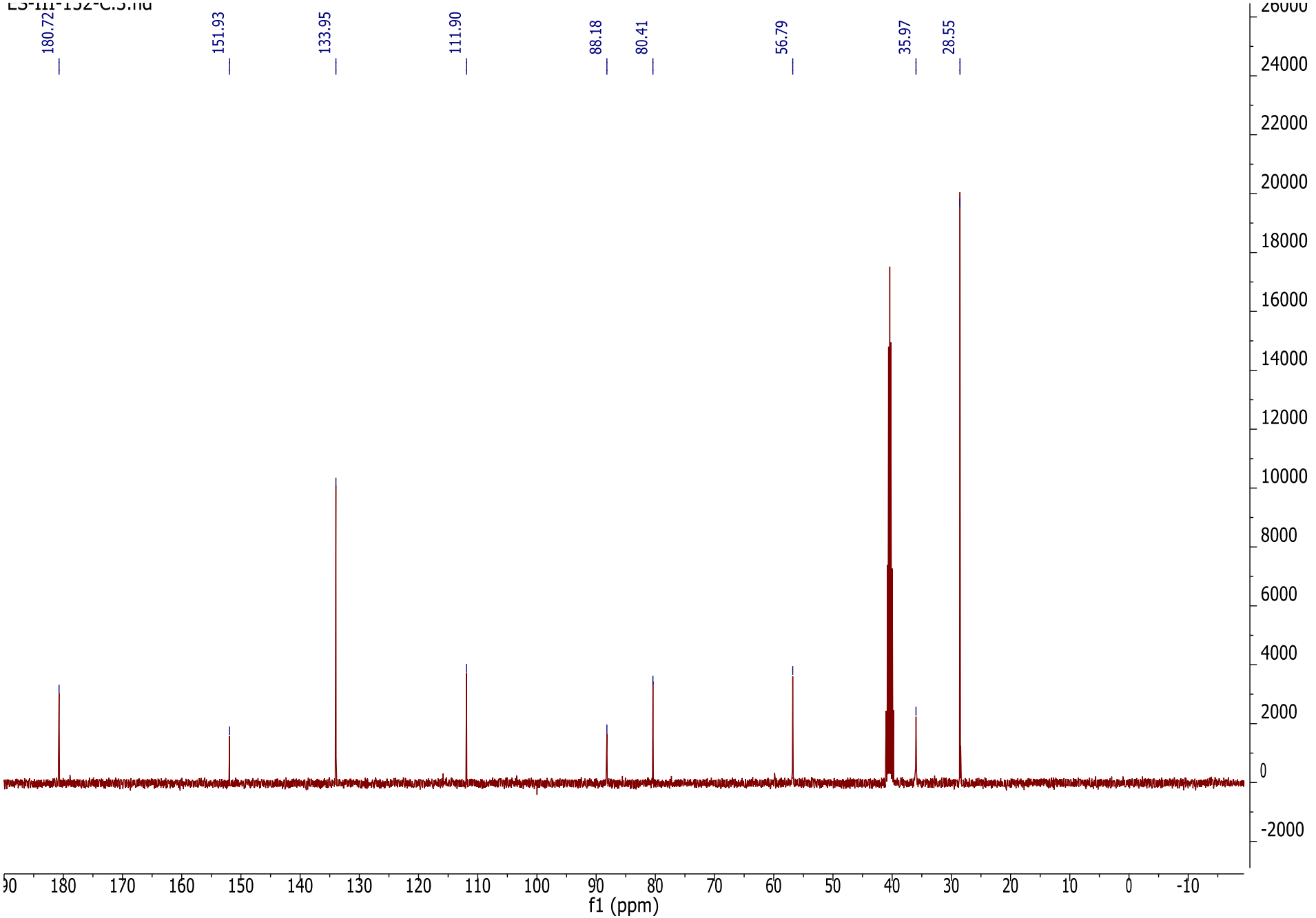
^{1}H NMR of **1b**


NC
CN
Boc
N

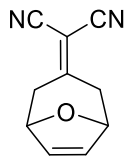

40000
35000
30000
25000
20000
15000
10000
5000
0
2.00
2.06
2.05
2.06
9.46
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

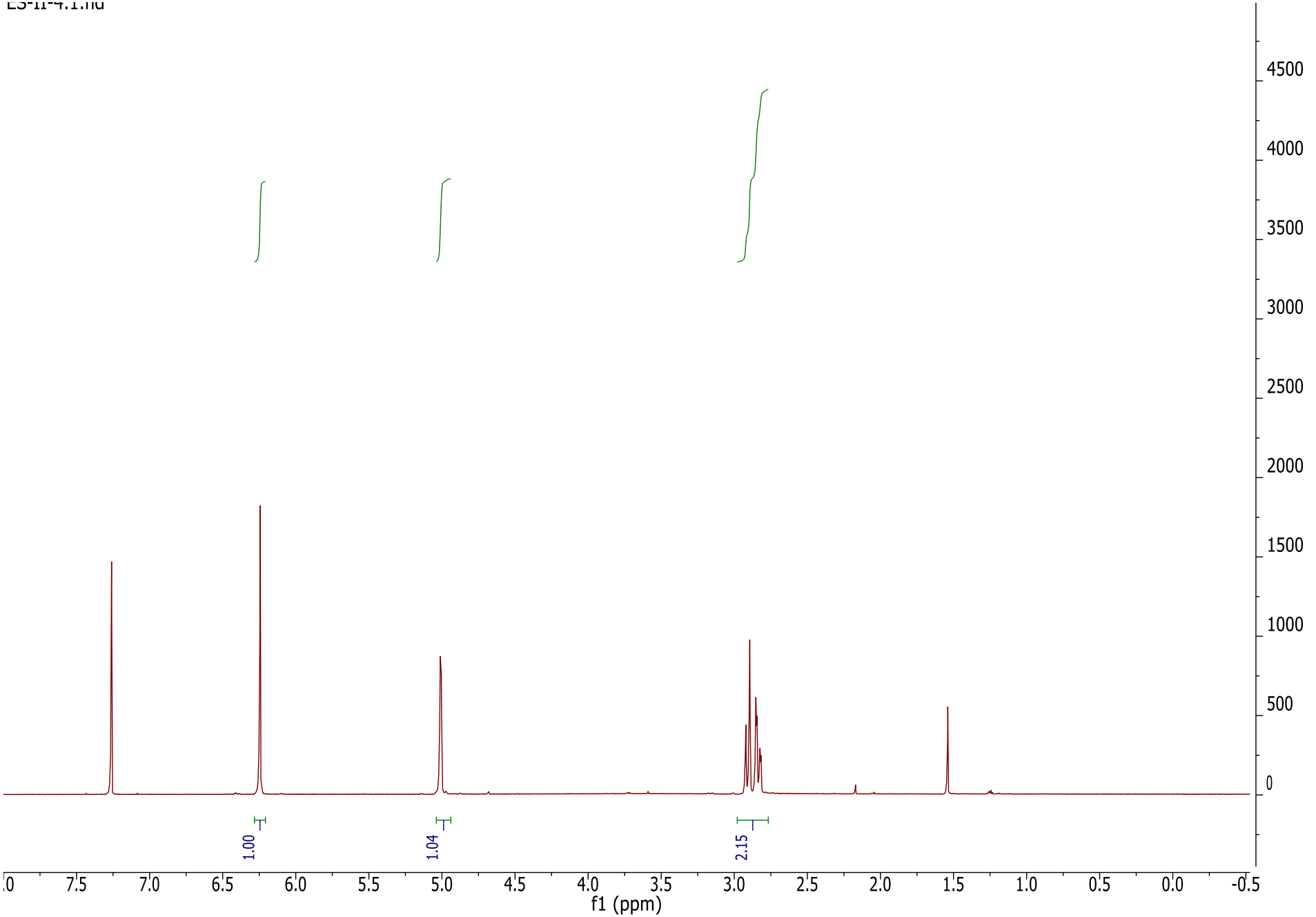
^{13}C NMR of **1b**


NC
CN
Boc
N

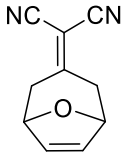

180.72
151.93
133.95
111.90
88.18
80.41
56.79
35.97
28.55
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
f1 (ppm)

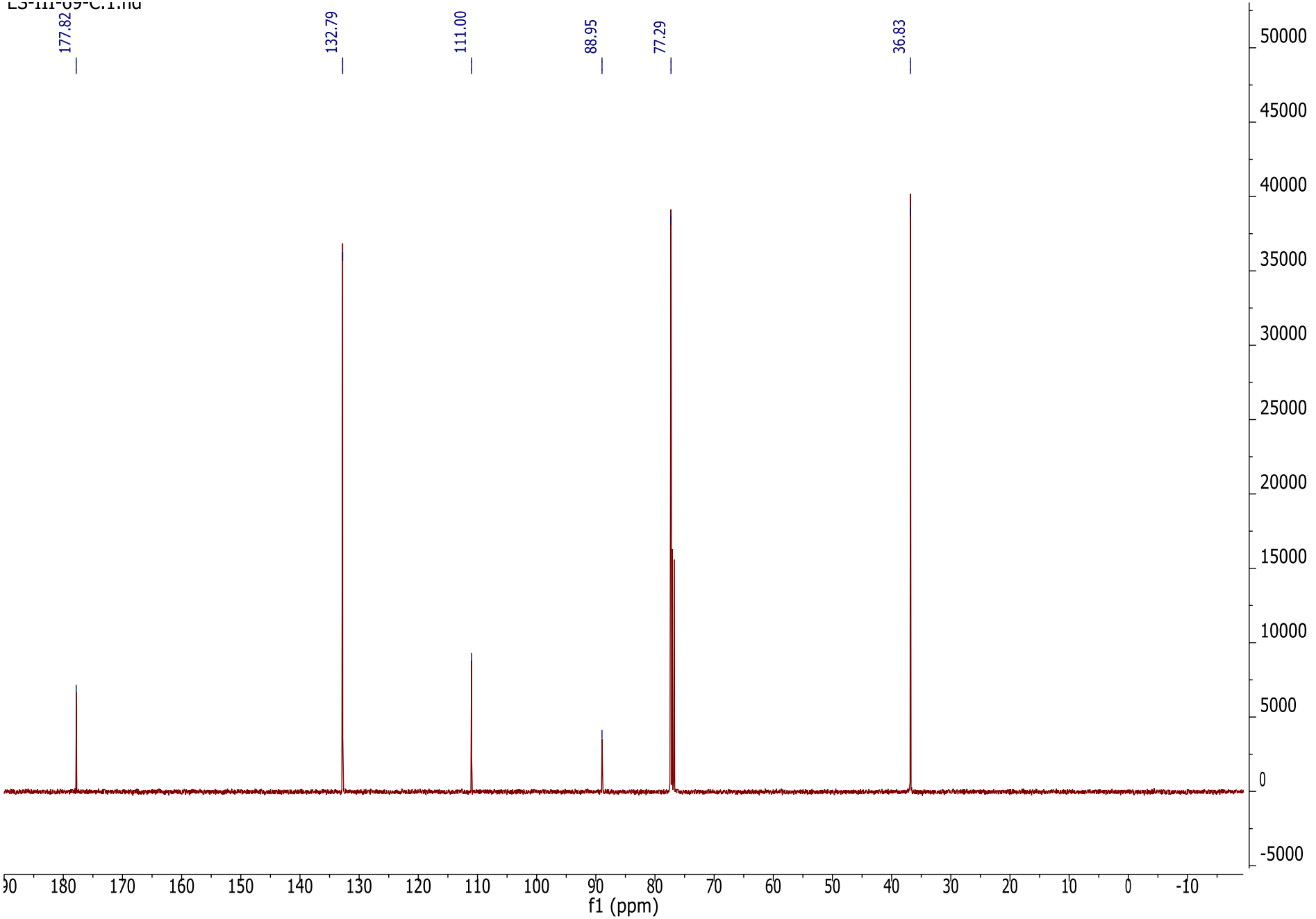
^{1}H NMR of **1c**


NC
CN
O

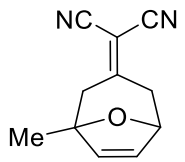

4500
4000
3500
3000
2500
2000
1500
1000
500
0
1.00
1.04
2.15
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

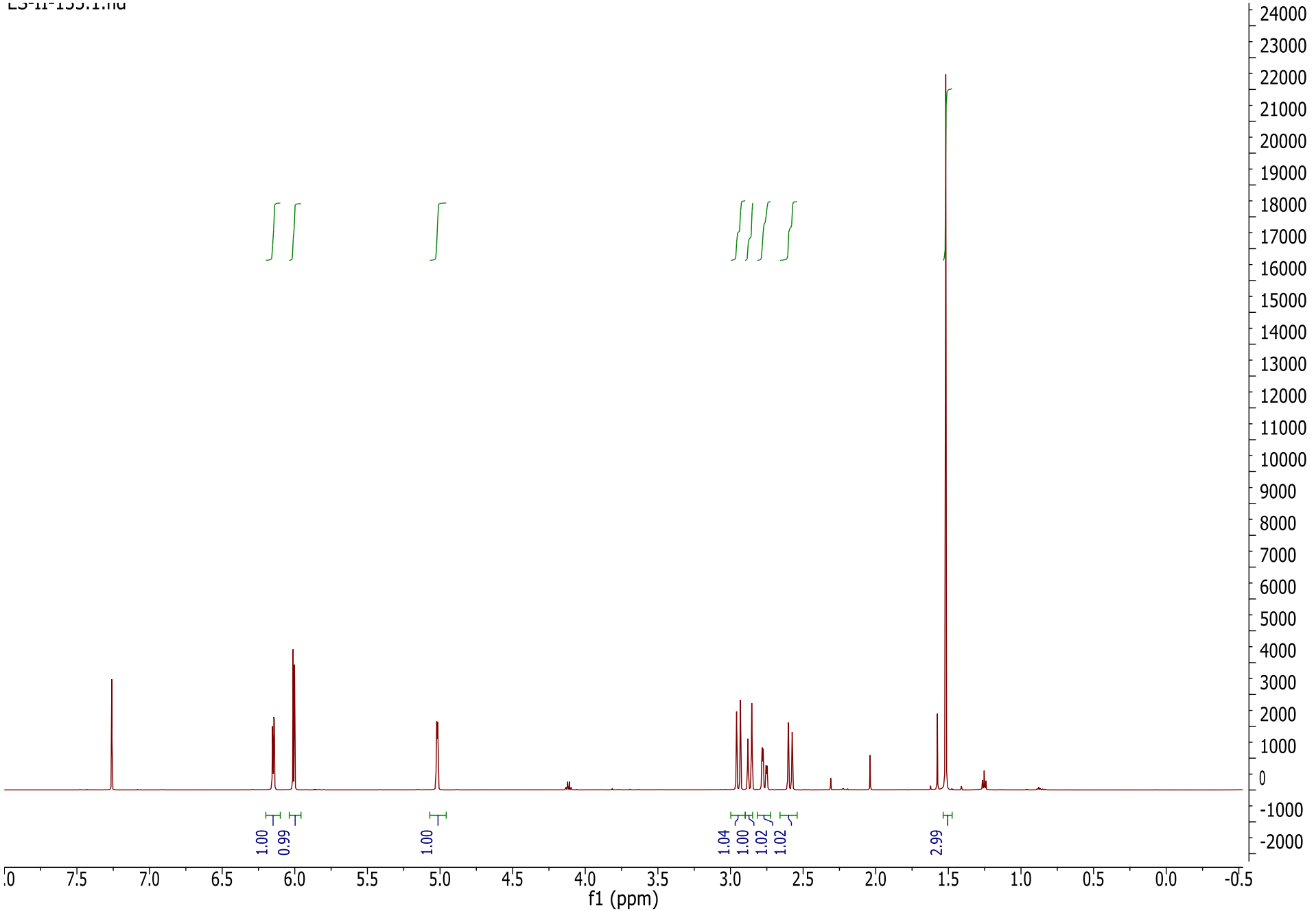
^{13}C NMR of **1c**


NC
CN
O

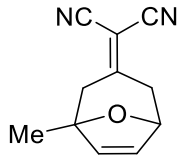

177.82
132.79
111.00
88.95
77.29
36.83
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

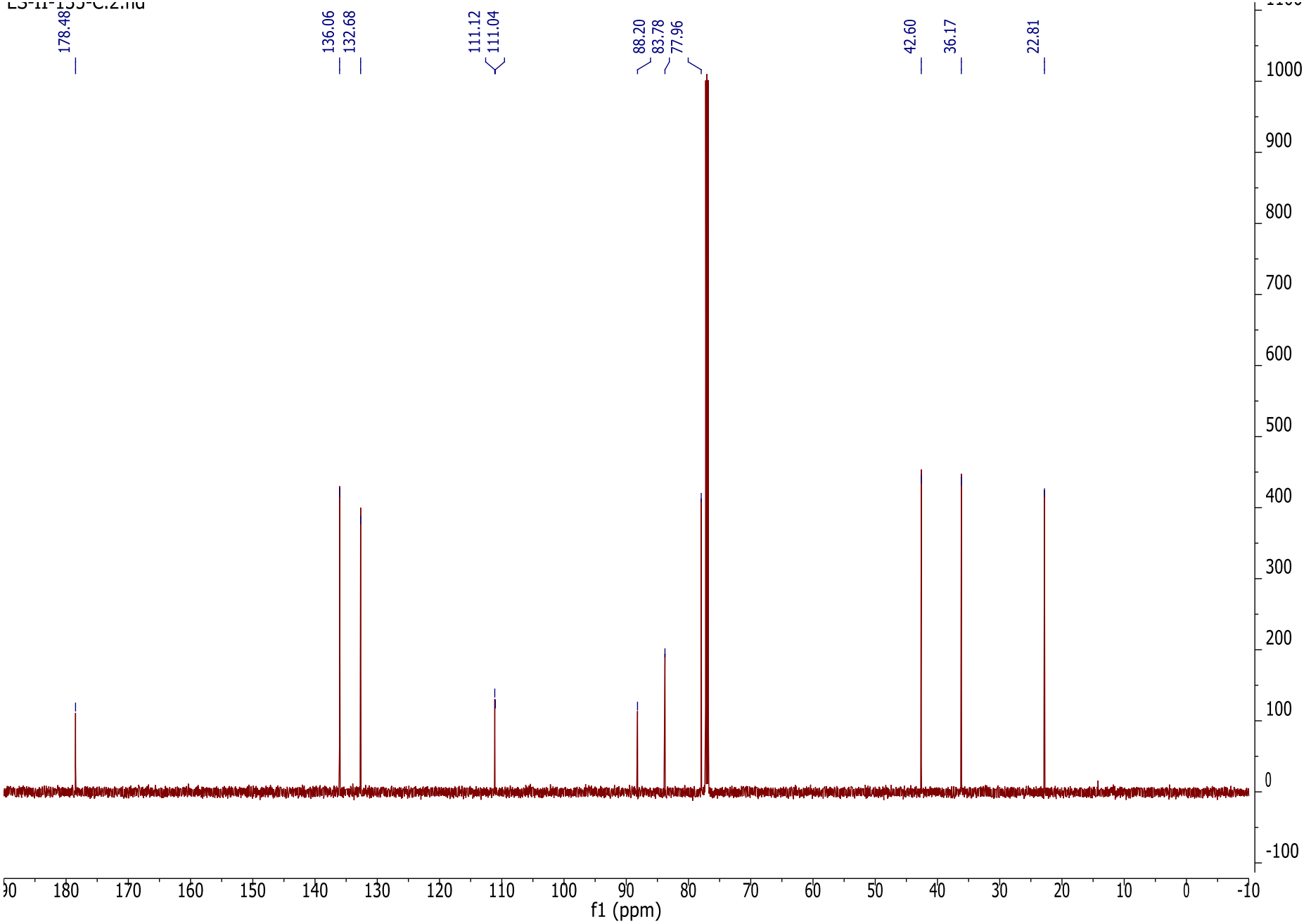
^{1}H NMR of **1d**


NC
CN
O
Me

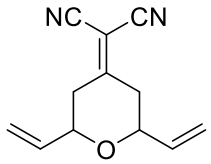

24000
23000
22000
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
1.00
0.99
1.00
1.04
1.00
1.02
1.02
2.99
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

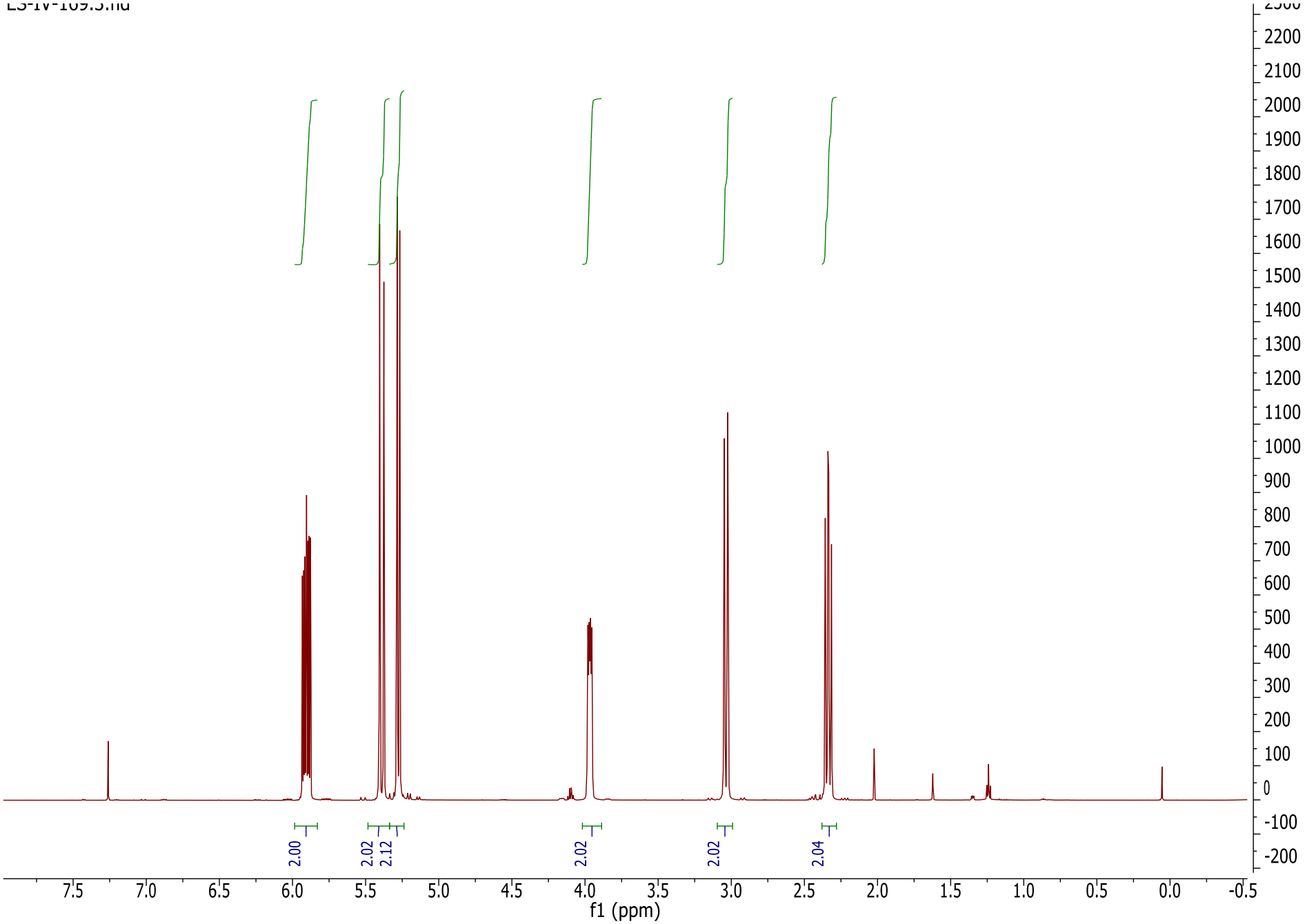
^{13}C NMR of **1d**


NC
CN
Me
O

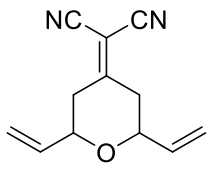

178.48
136.06
132.68
111.12
111.04
88.20
83.78
77.96
42.60
36.17
22.81
1000
900
800
700
600
500
400
300
200
100
0
-100
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

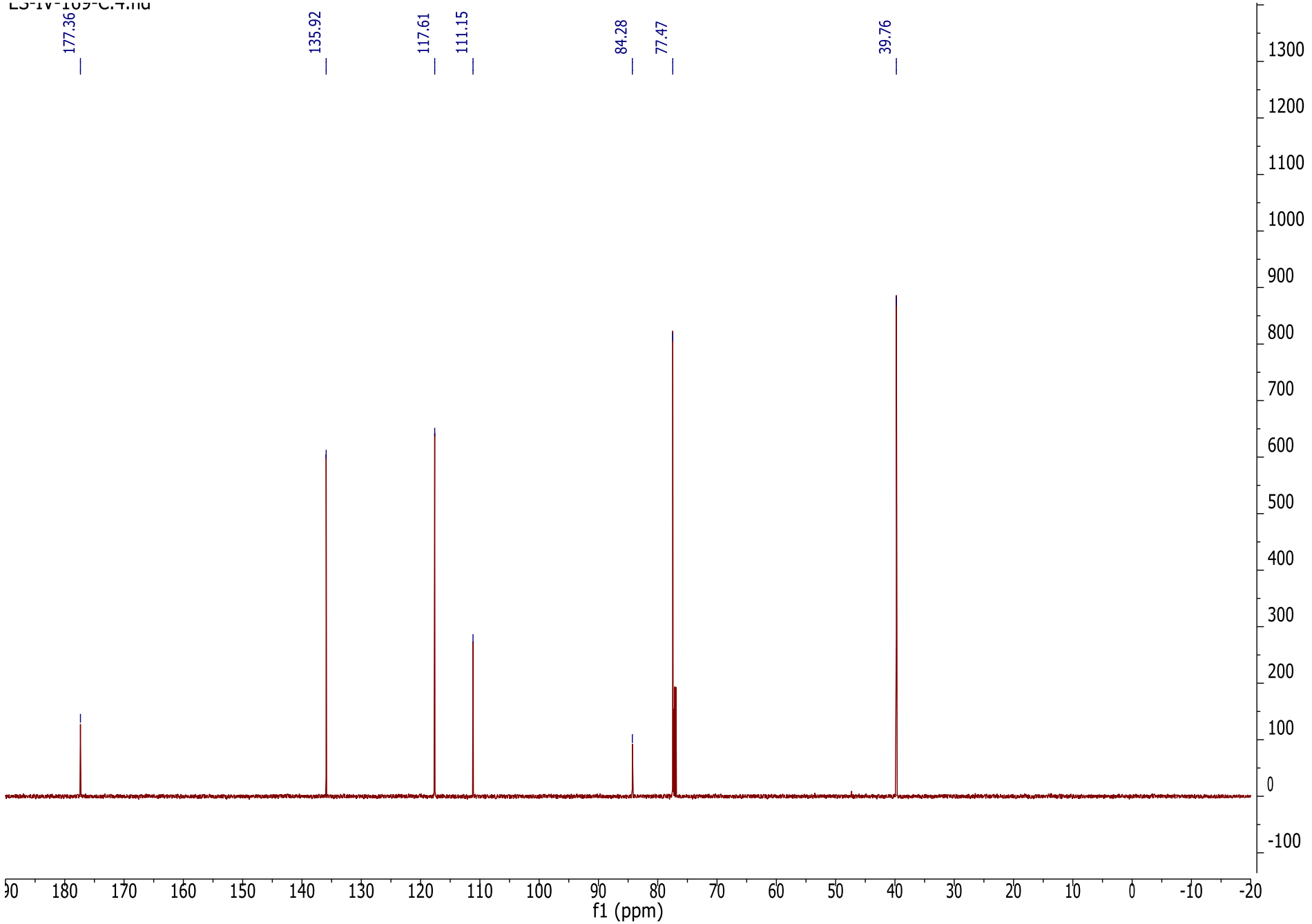
^{1}H NMR of **9a**



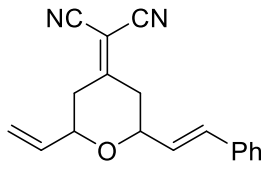


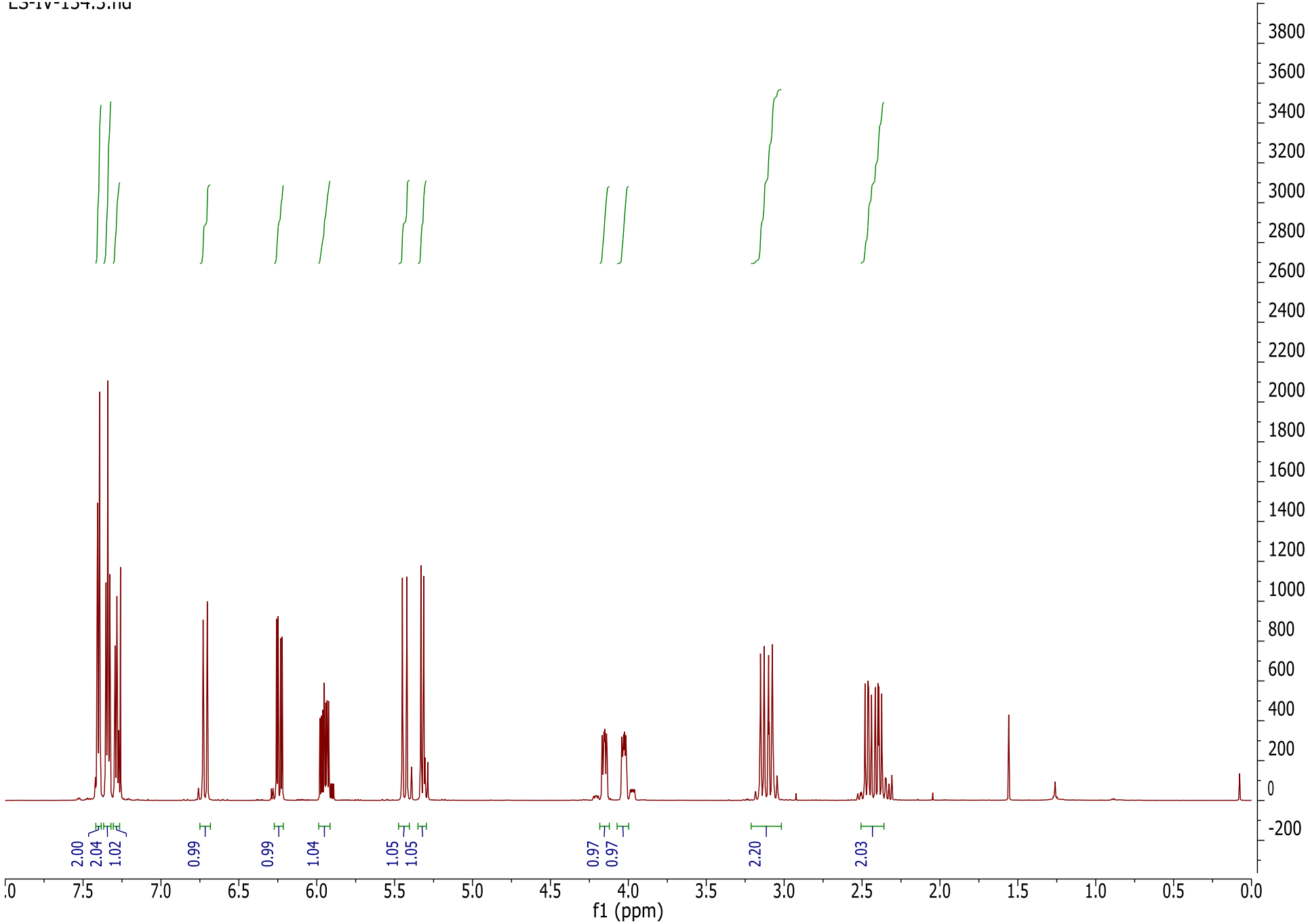
^{13}C NMR of **9a**


NC
CN
O

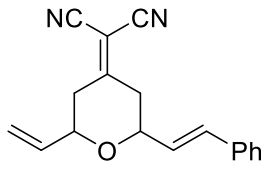

177.36
135.92
117.61
111.15
84.28
77.47
39.76
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
f1 (ppm)

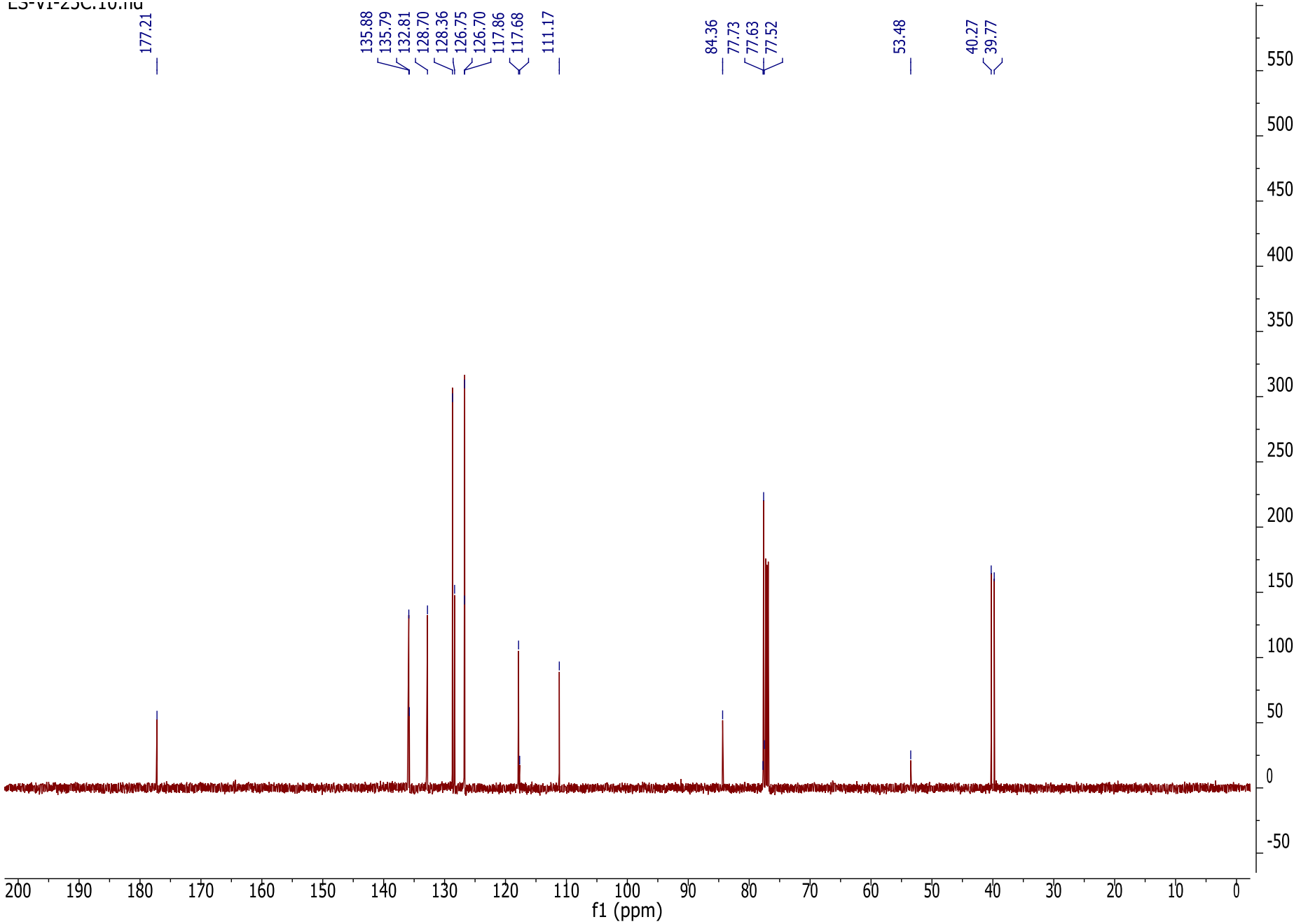
^{1}H NMR of **9b**


NC
CN
O
Ph

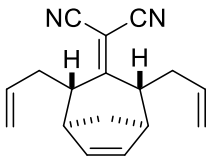

3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
2.00
2.04
1.02
0.99
0.99
1.04
1.05
1.05
0.97
0.97
2.20
2.03
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

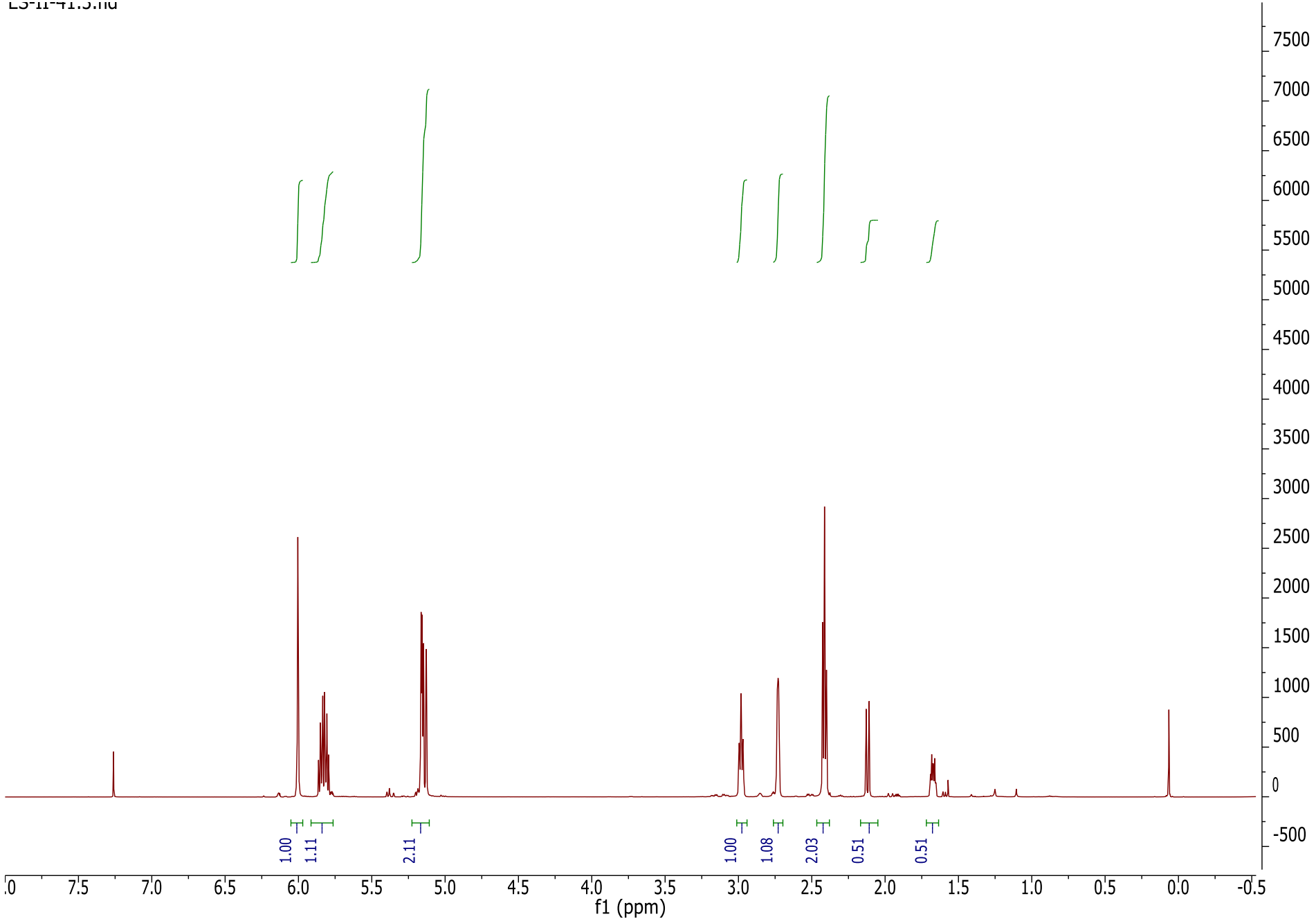
^{13}C NMR of **9b**


NC
CN
O
Ph

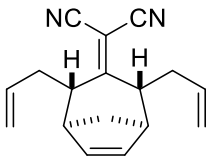

177.21
135.88
135.79
132.81
128.70
128.36
126.75
126.70
117.86
117.68
111.17
84.36
77.73
77.63
77.52
53.48
40.27
39.77
550
500
450
400
350
300
250
200
150
100
50
0
-50
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

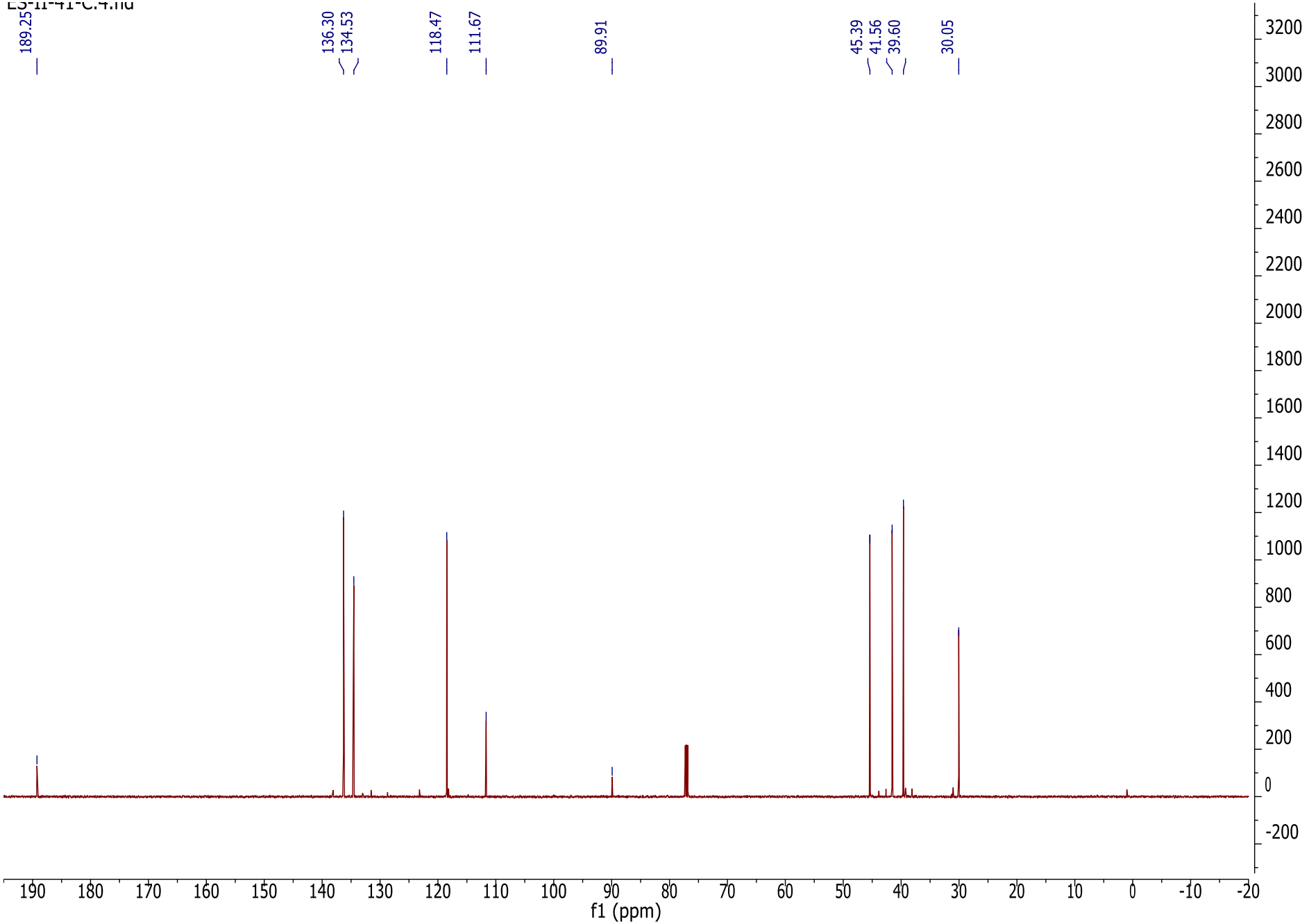
^{1}H NMR of **6a**


NC
CN
H
H

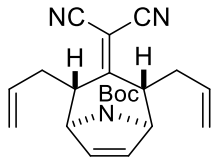

7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
1.00
1.11
2.11
1.00
1.08
2.03
0.51
0.51
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

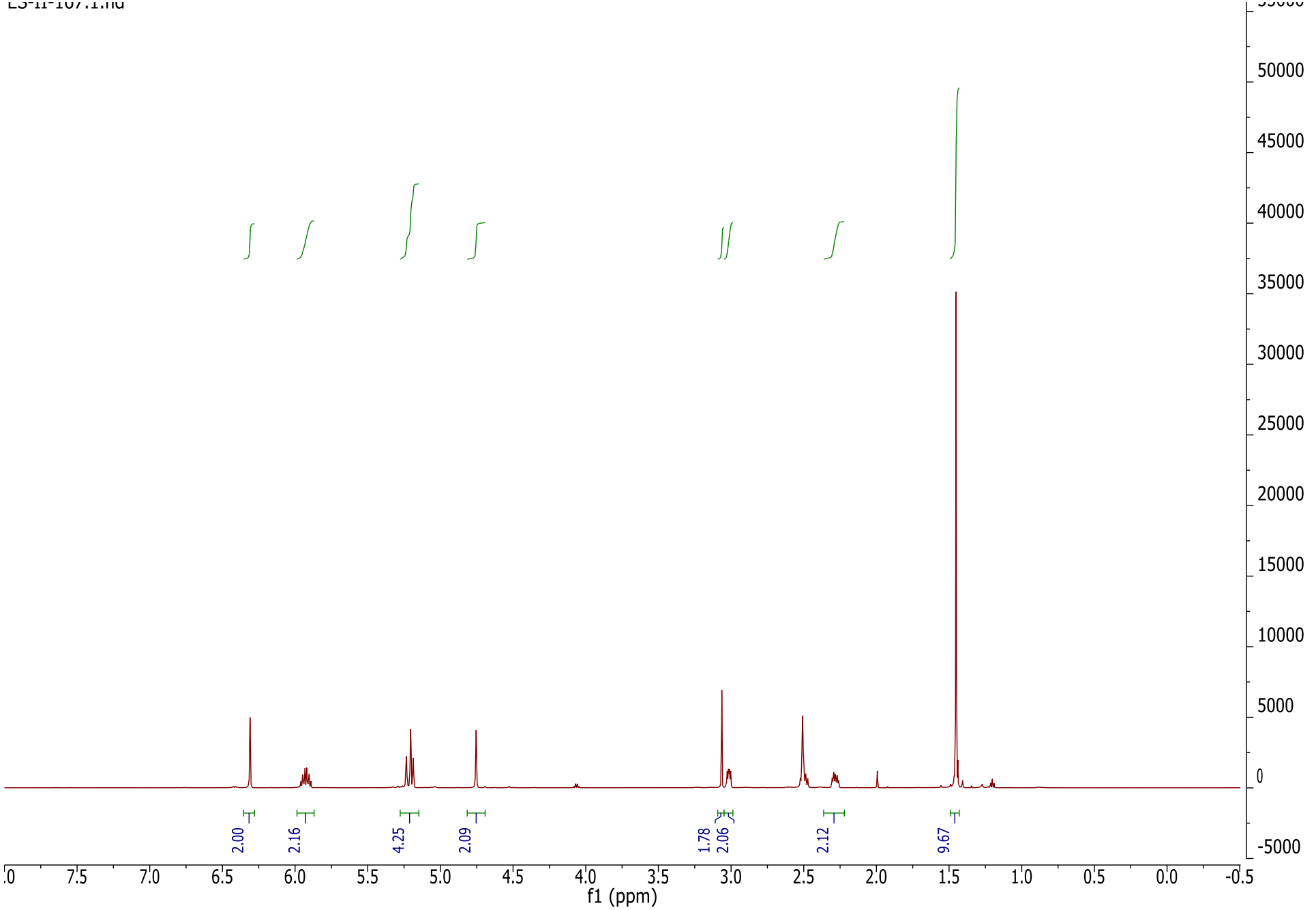
^{13}C NMR of **6a**


NC
CN
H
H

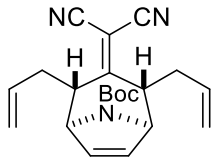

189.25
136.30
134.53
118.47
111.67
89.91
45.39
41.56
39.60
30.05
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

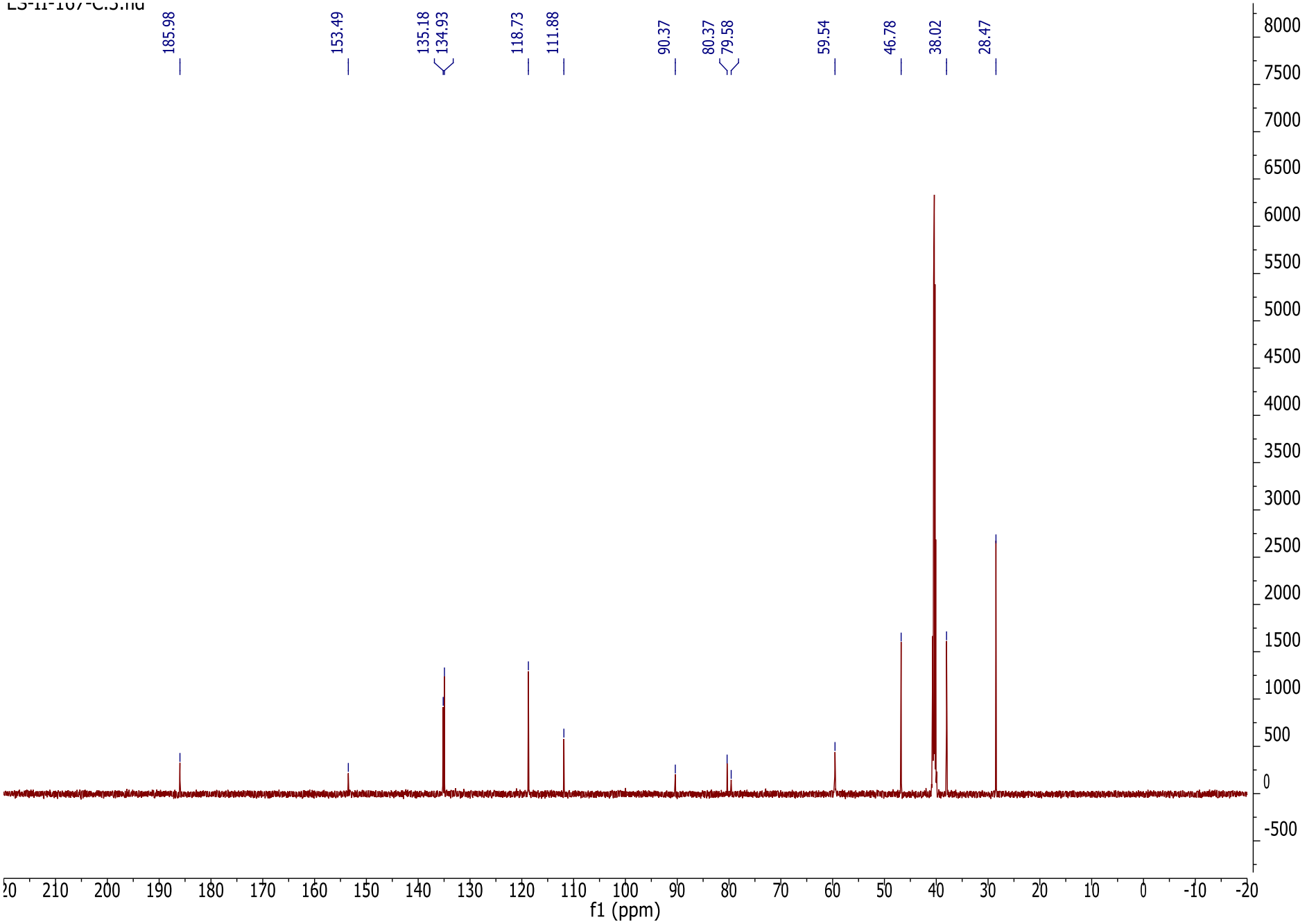
^{1}H NMR of **6b**


NC
CN
H
H
Boc
N

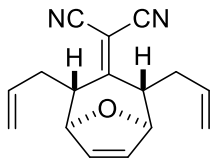

50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
2.00
2.16
4.25
2.09
1.78
2.06
2.12
9.67
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

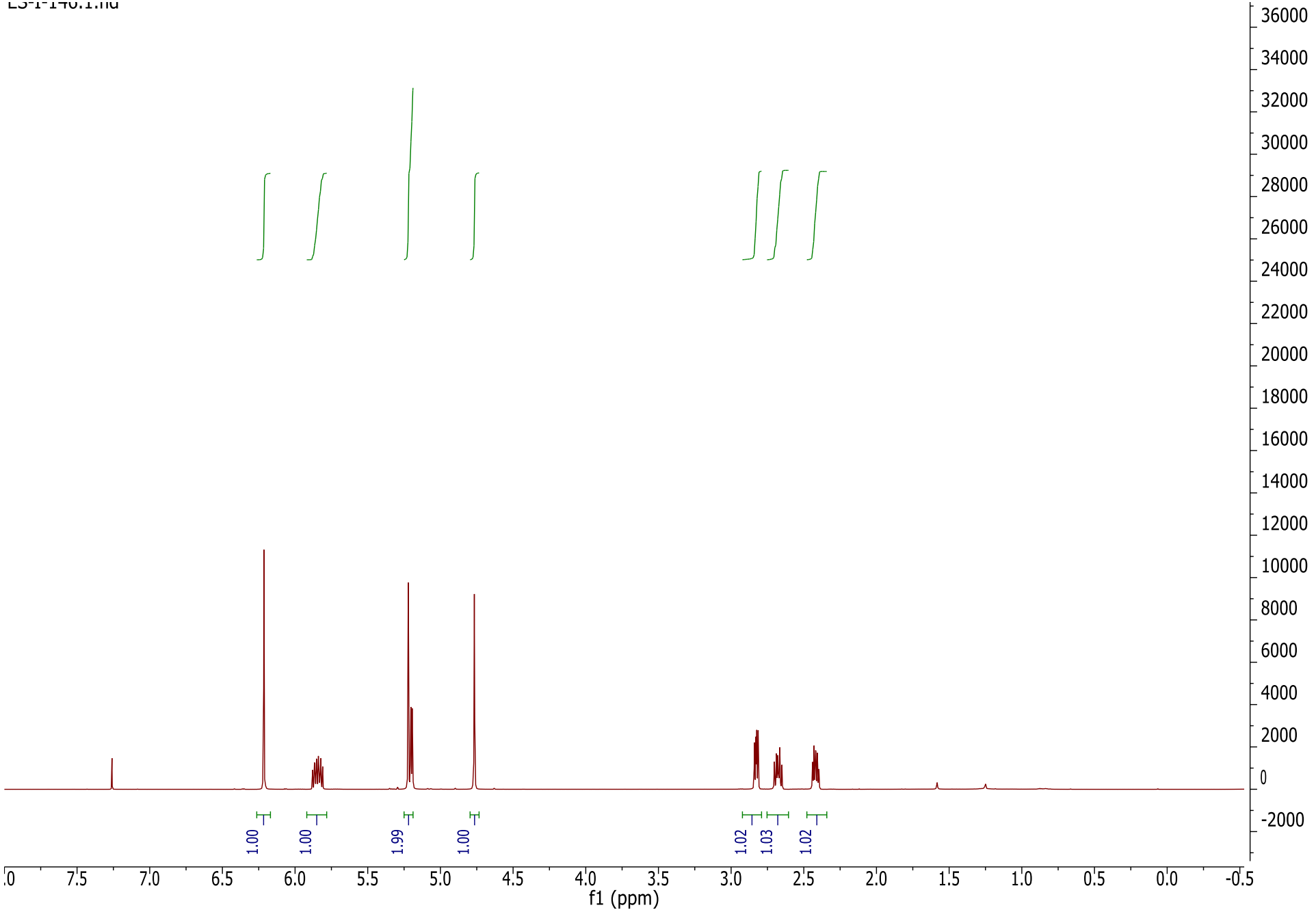
^{13}C NMR of **6b**


NC
CN
H
H
Boc
N

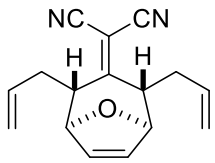

185.98
153.49
135.18
134.93
118.73
111.88
90.37
80.37
79.58
59.54
46.78
38.02
28.47
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

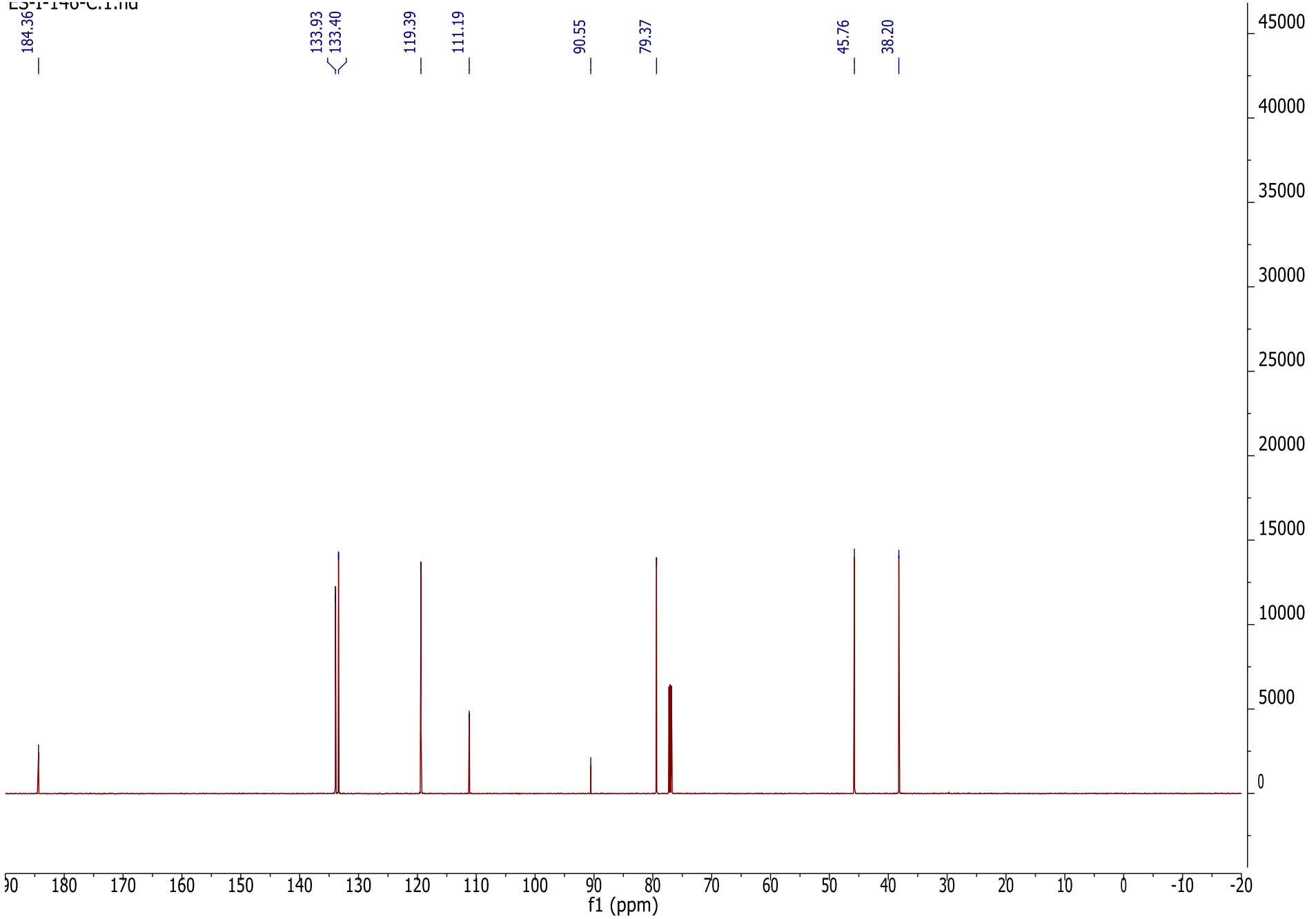
^{1}H NMR of **6c**


NC
CN
H
H
O

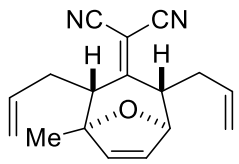

36000
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
1.00
1.00
1.99
1.00
1.02
1.03
1.02
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

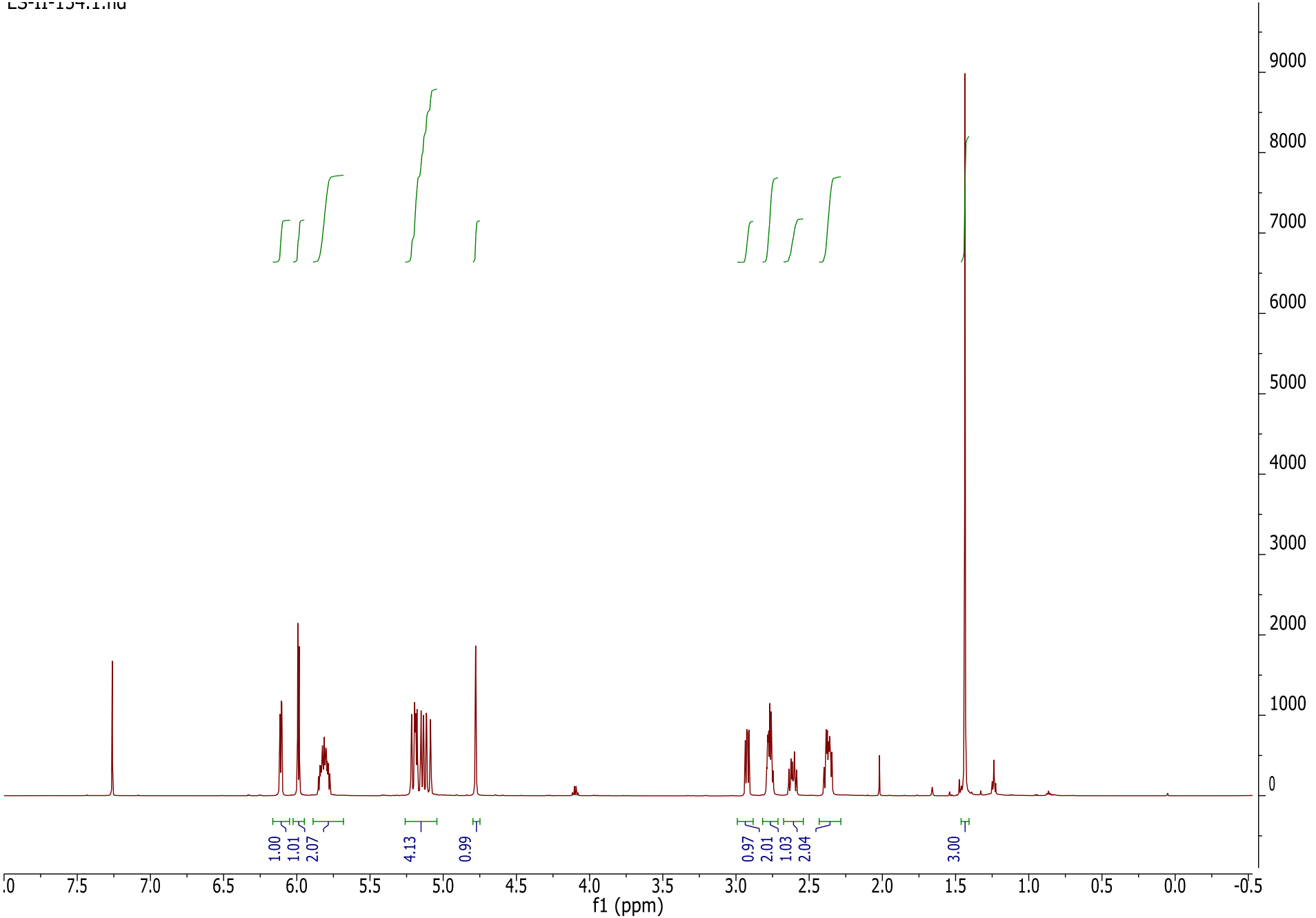
^{13}C NMR of **6c**


NC
CN
H
H
O

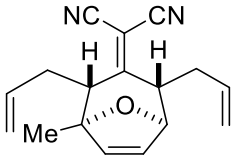

184.36
133.93
133.40
119.39
111.19
90.55
79.37
45.76
38.20
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

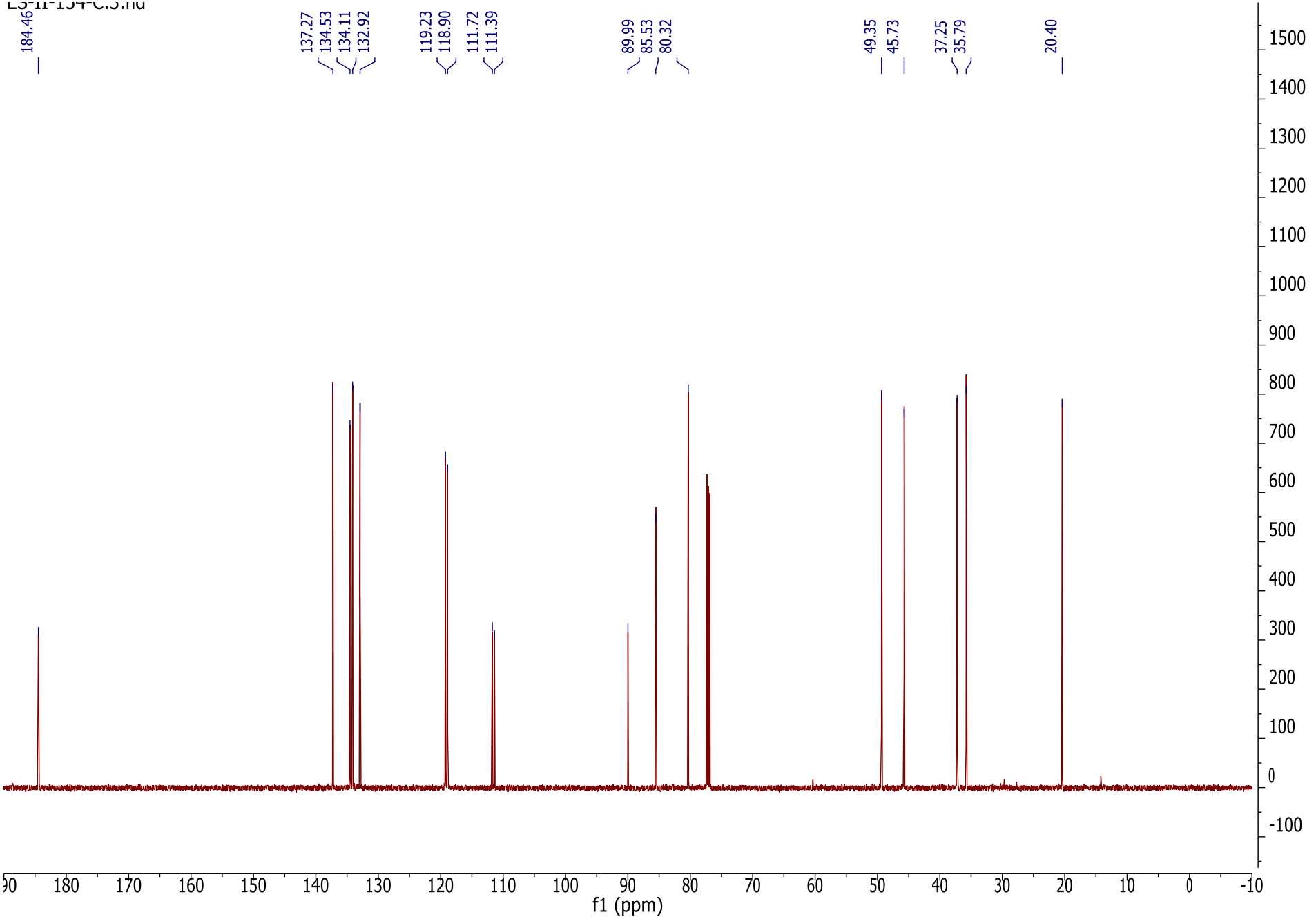
^{1}H NMR of **6d**


NC
CN
H
H
O
Me

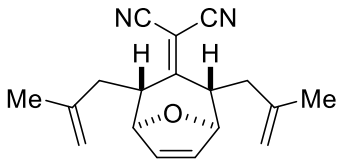

9000
8000
7000
6000
5000
4000
3000
2000
1000
0
1.00
1.01
2.07
4.13
0.99
0.97
2.01
1.03
2.04
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

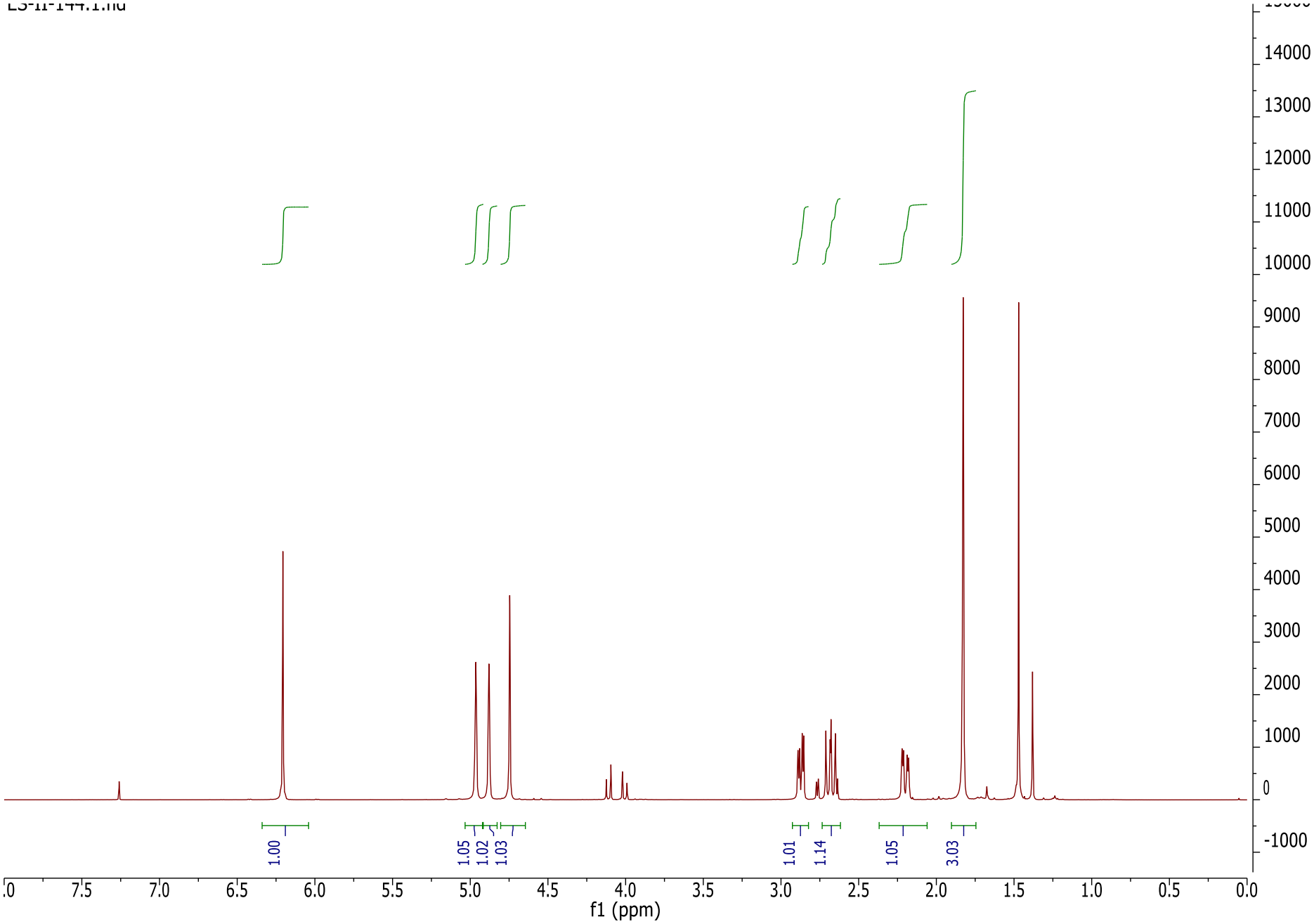
^{13}C NMR of **6d**


NC
CN
H
H
O
Me

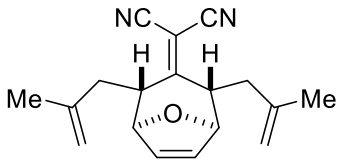

184.46
137.27
134.53
134.11
132.92
119.23
118.90
111.72
111.39
89.99
85.53
80.32
49.35
45.73
37.25
35.79
20.40
f1 (ppm)

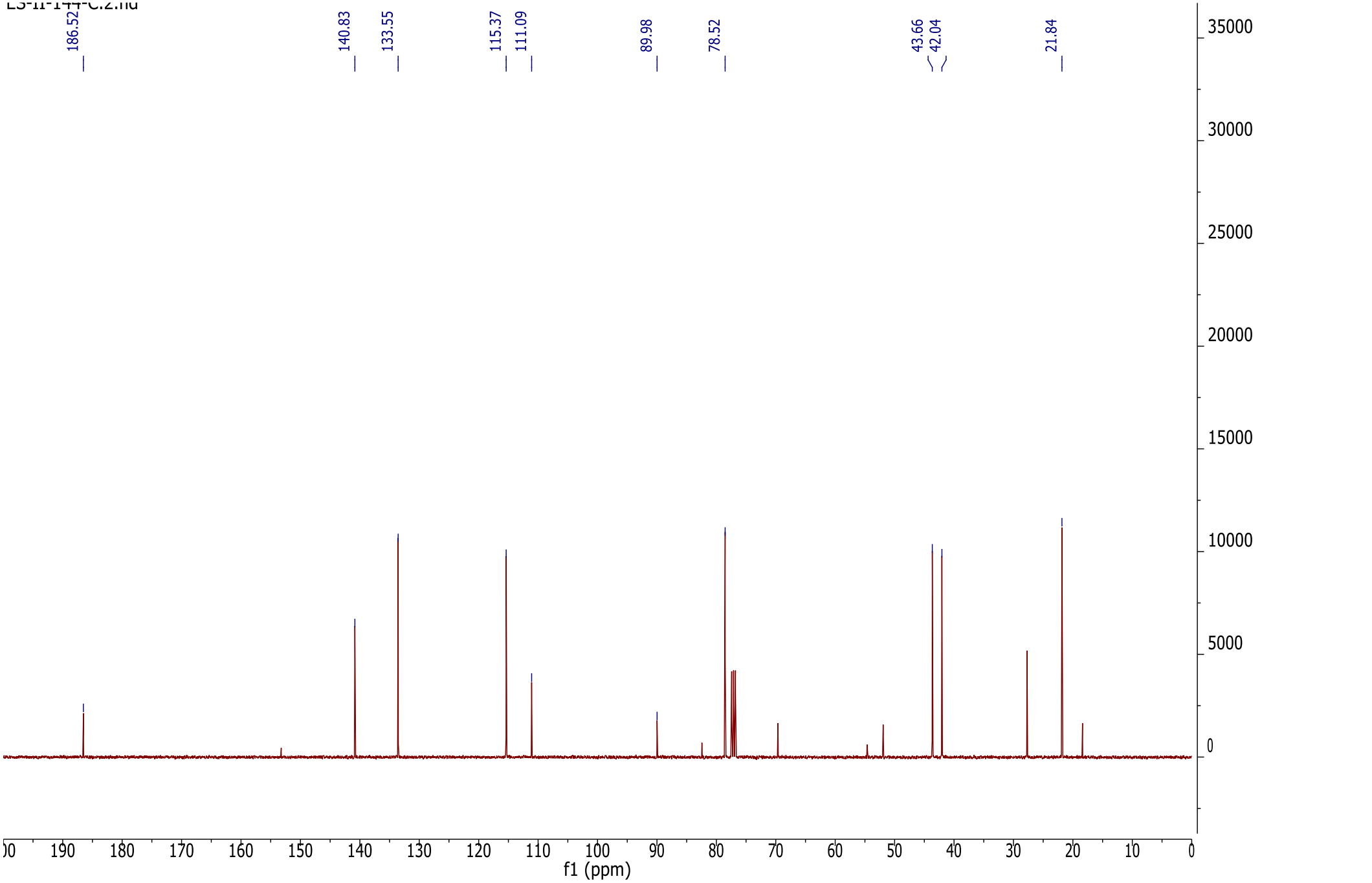
^{1}H NMR of **6p**


NC
CN
H
H
Me
Me
O

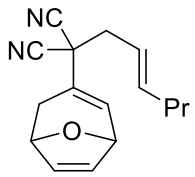

14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
1.00
1.05
1.02
1.03
1.01
1.14
1.05
3.03
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

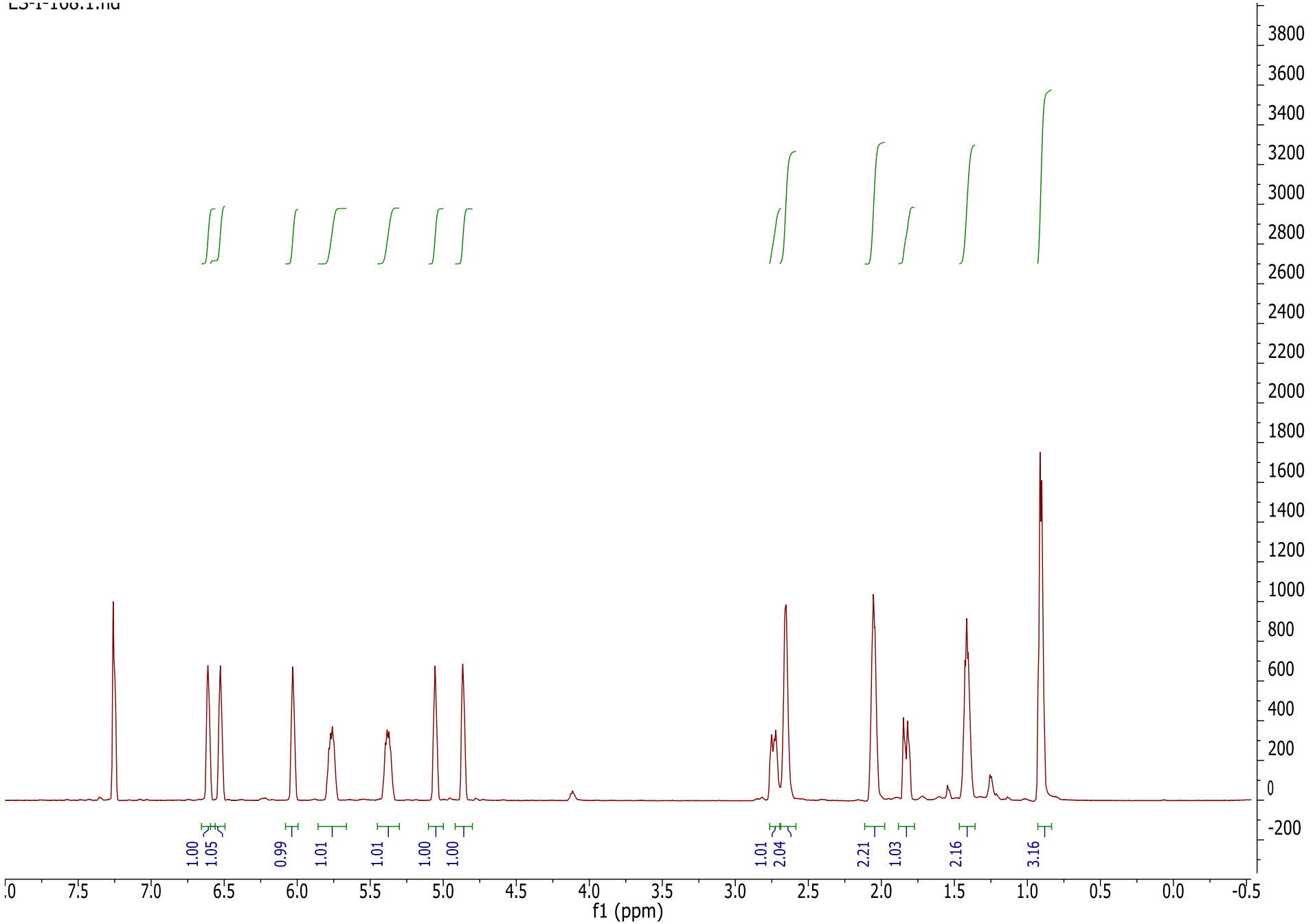
^{13}C NMR of **6p**


NC
CN
H
H
Me
Me
O

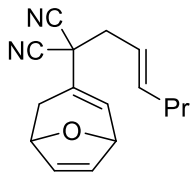

186.52
140.83
133.55
115.37
111.09
89.98
78.52
43.66
42.04
21.84
35000
30000
25000
20000
15000
10000
5000
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

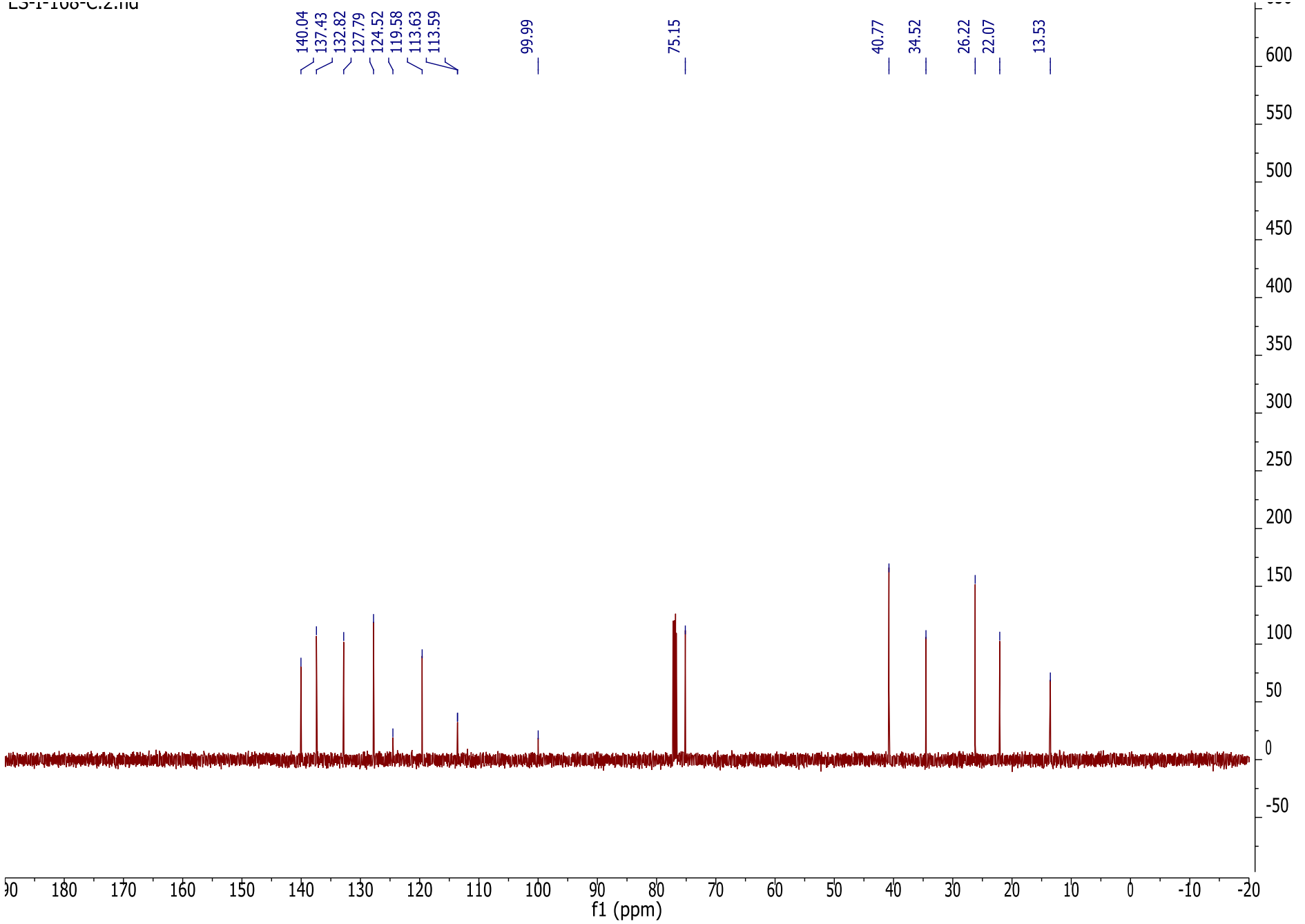
^{1}H NMR of **3e**


NC
NC
Pr
O

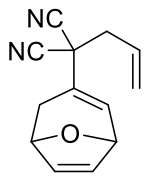

3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
1.00
1.05
0.99
1.01
1.01
1.00
1.00
1.01
2.04
2.21
1.03
2.16
3.16
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

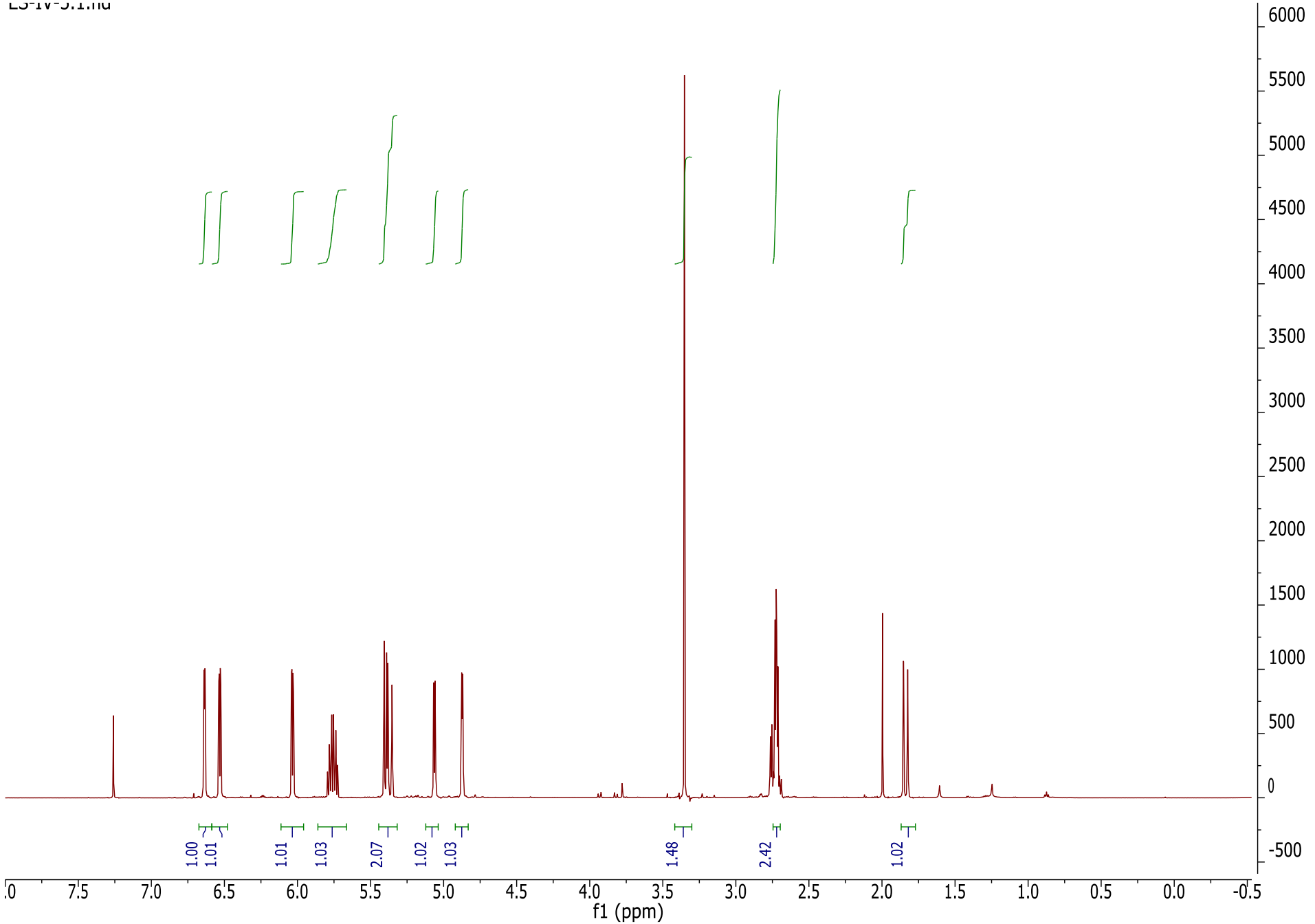
^{13}C NMR of **3e**


NC
NC
Pr
O

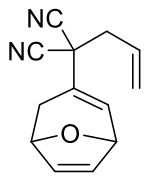

140.04
137.43
132.82
127.79
124.52
119.58
113.63
113.59
99.99
75.15
40.77
34.52
26.22
22.07
13.53
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

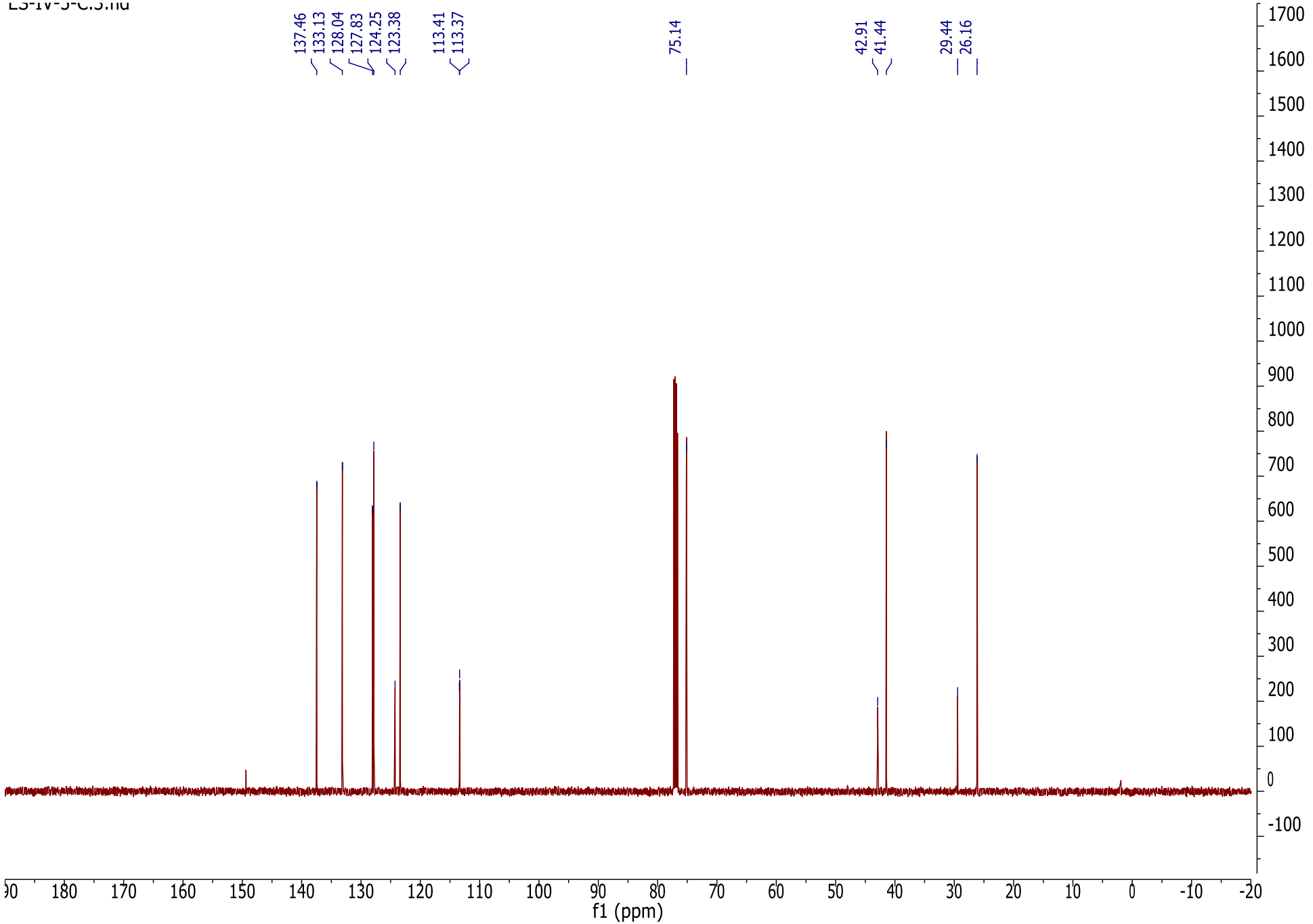
^{1}H NMR of **SI2**


NC
NC
O

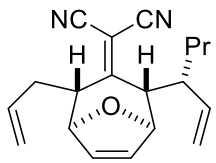

6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
1.00
1.01
1.01
1.03
2.07
1.02
1.03
1.48
2.42
1.02
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

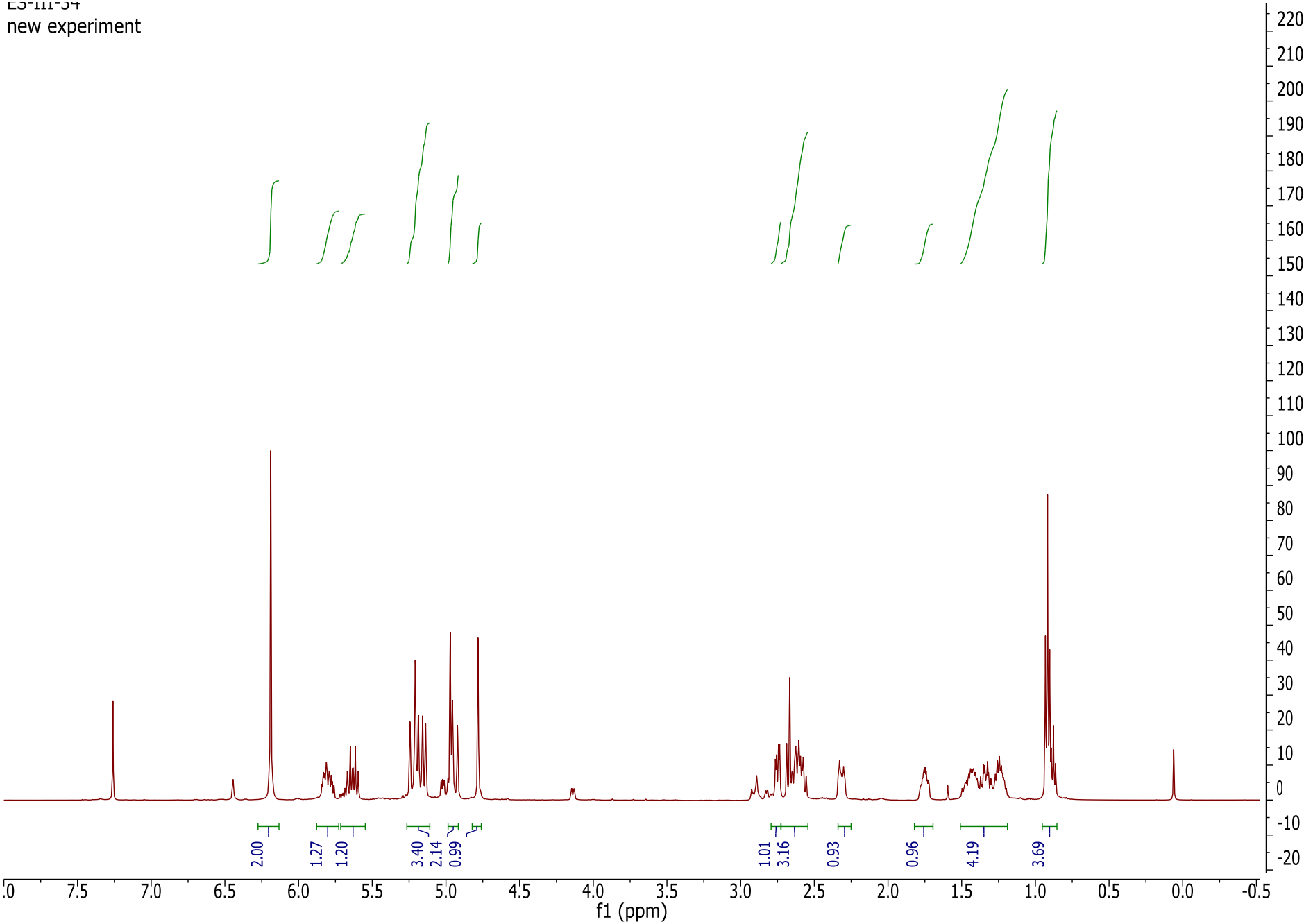
^{13}C NMR of **SI2**



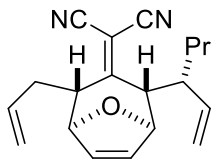


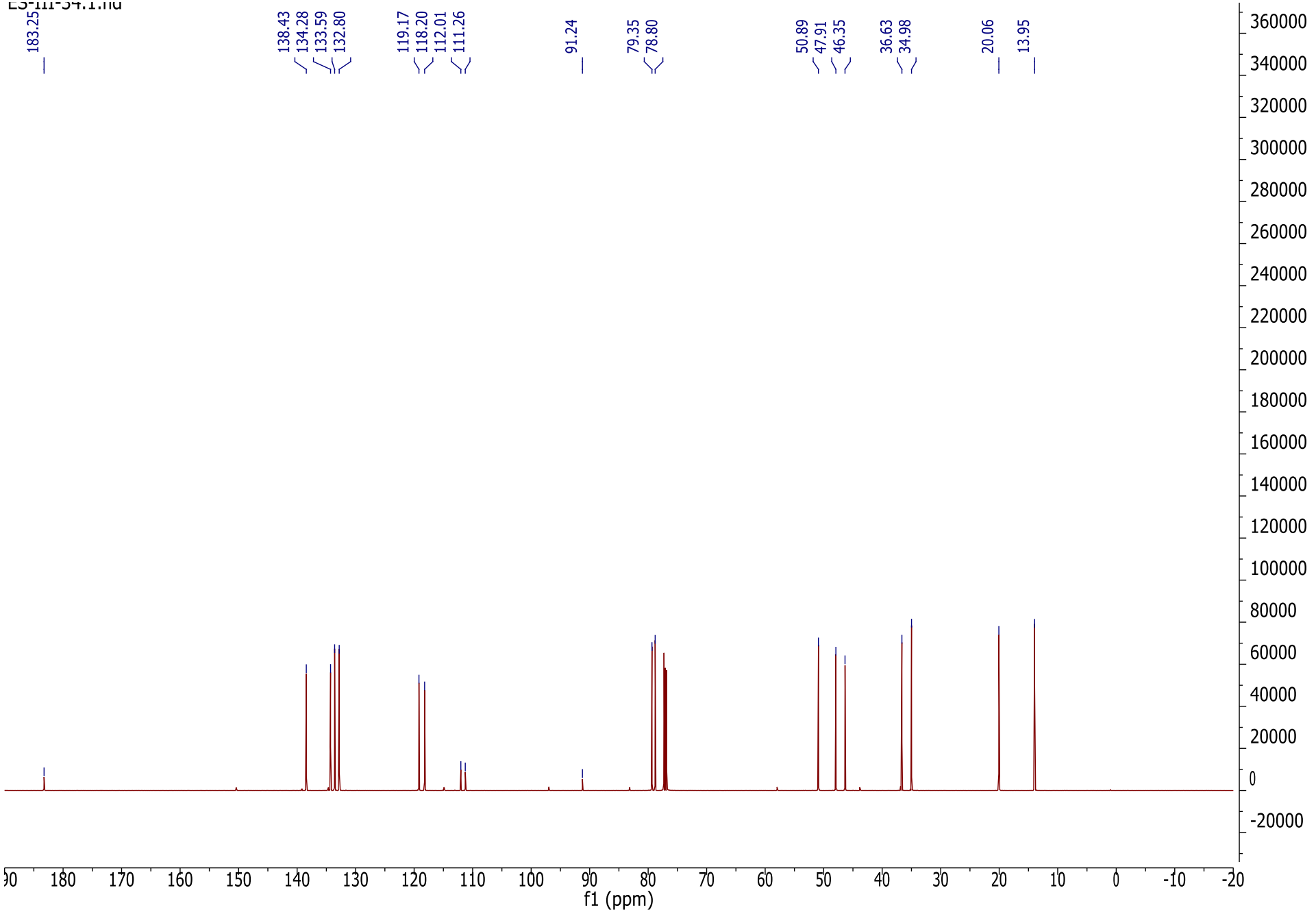
^{1}H NMR of **6e**


NC
CN
H
H
Pr
O

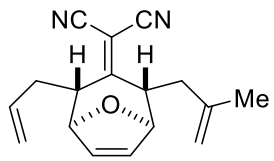

new experiment
2.00
1.27
1.20
3.40
2.14
0.99
1.01
3.16
0.93
0.96
4.19
3.69
f1 (ppm)

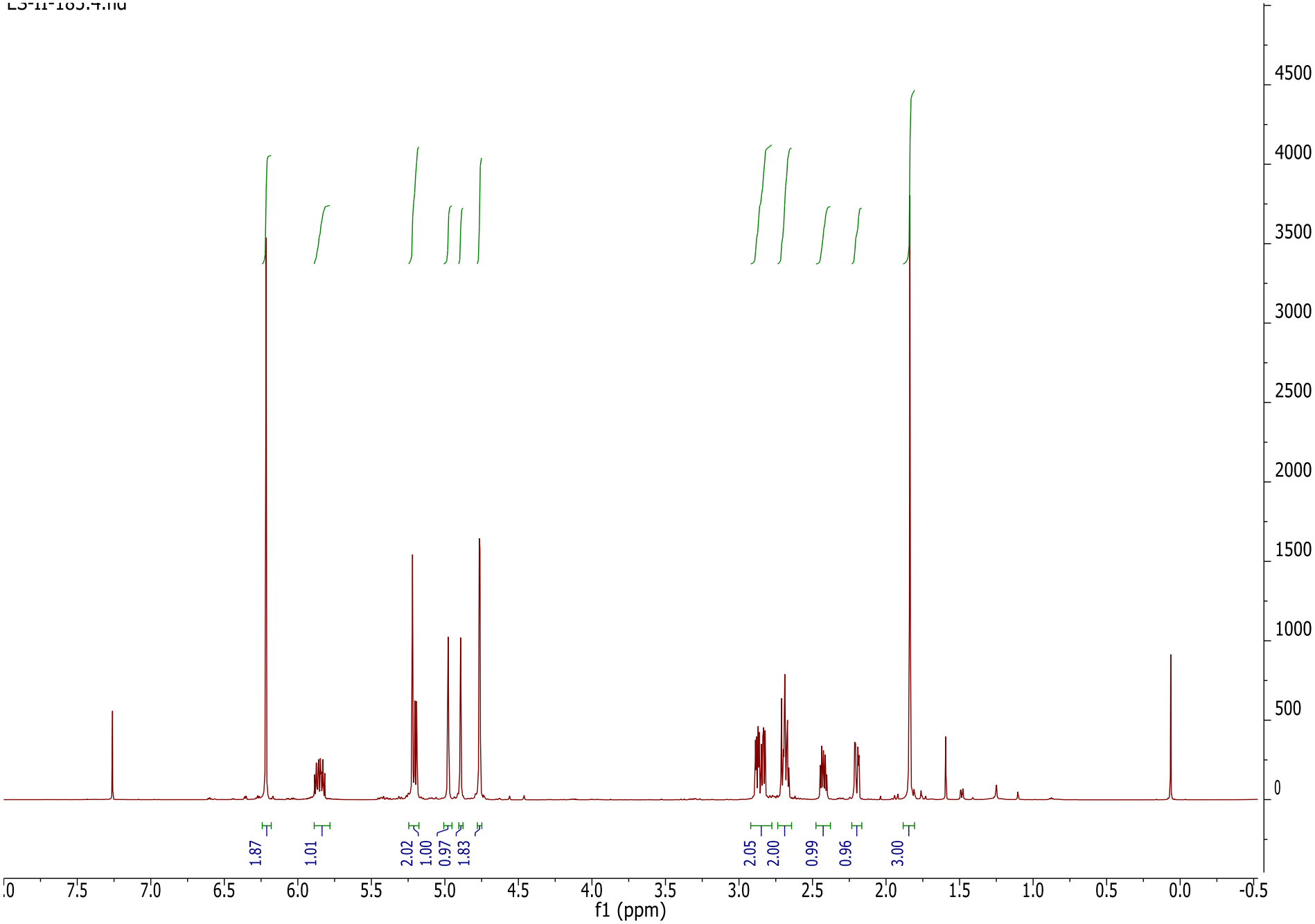
^{13}C NMR of **6e**


NC
CN
H
H
Pr
O

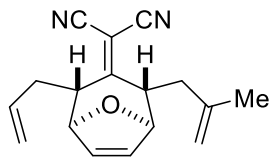

183.25
138.43
134.28
133.59
132.80
119.17
118.20
112.01
111.26
91.24
79.35
78.80
50.89
47.91
46.35
36.63
34.98
20.06
13.95
360000
340000
320000
300000
280000
260000
240000
220000
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
-20000
f1 (ppm)

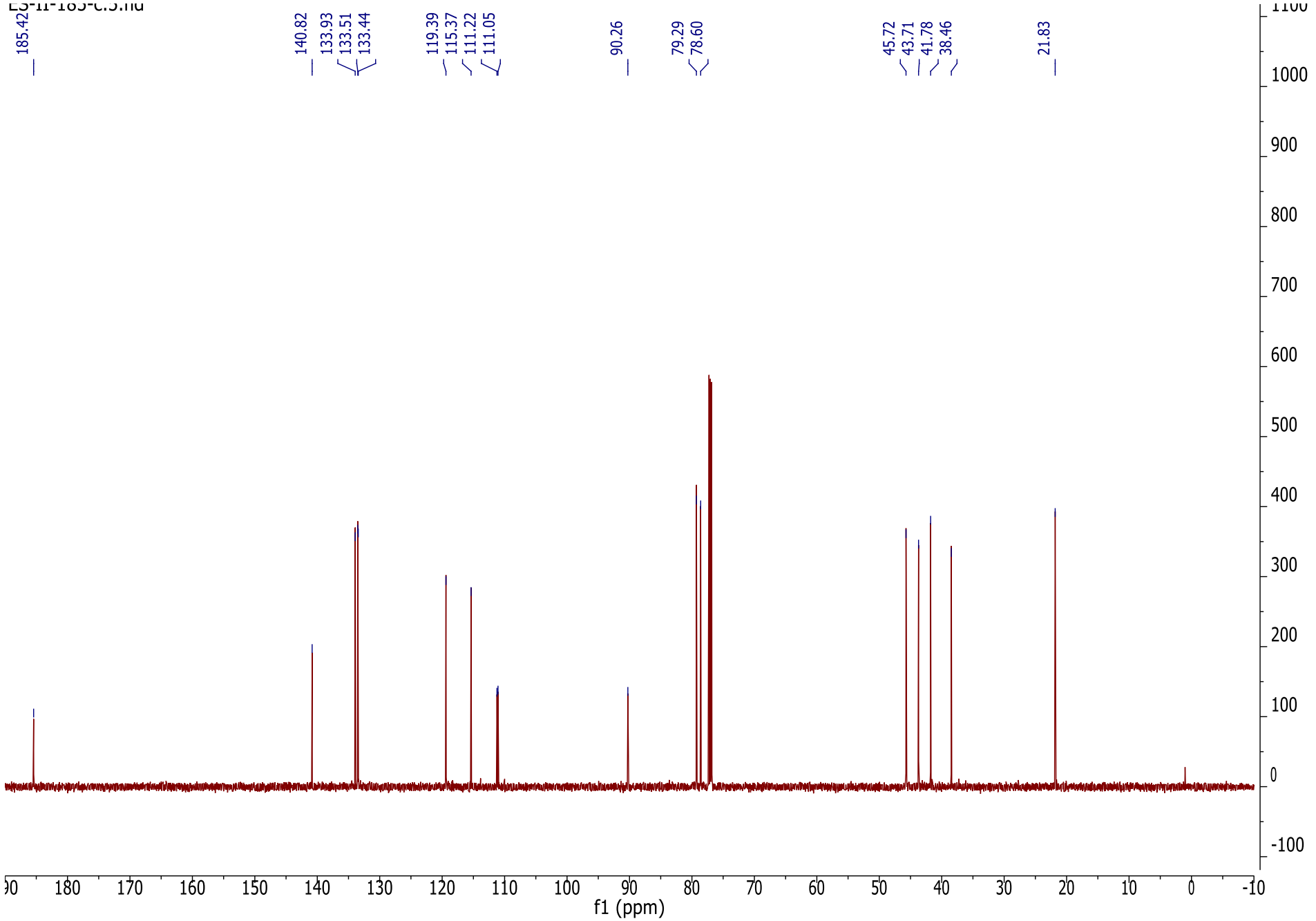
^{1}H NMR of **6f**


NC
CN
H
H
O
Me

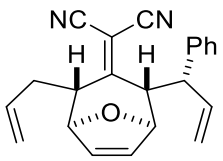

4500
4000
3500
3000
2500
2000
1500
1000
500
0
1.87
1.01
2.02
1.00
0.97
1.83
2.05
2.00
0.99
0.96
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

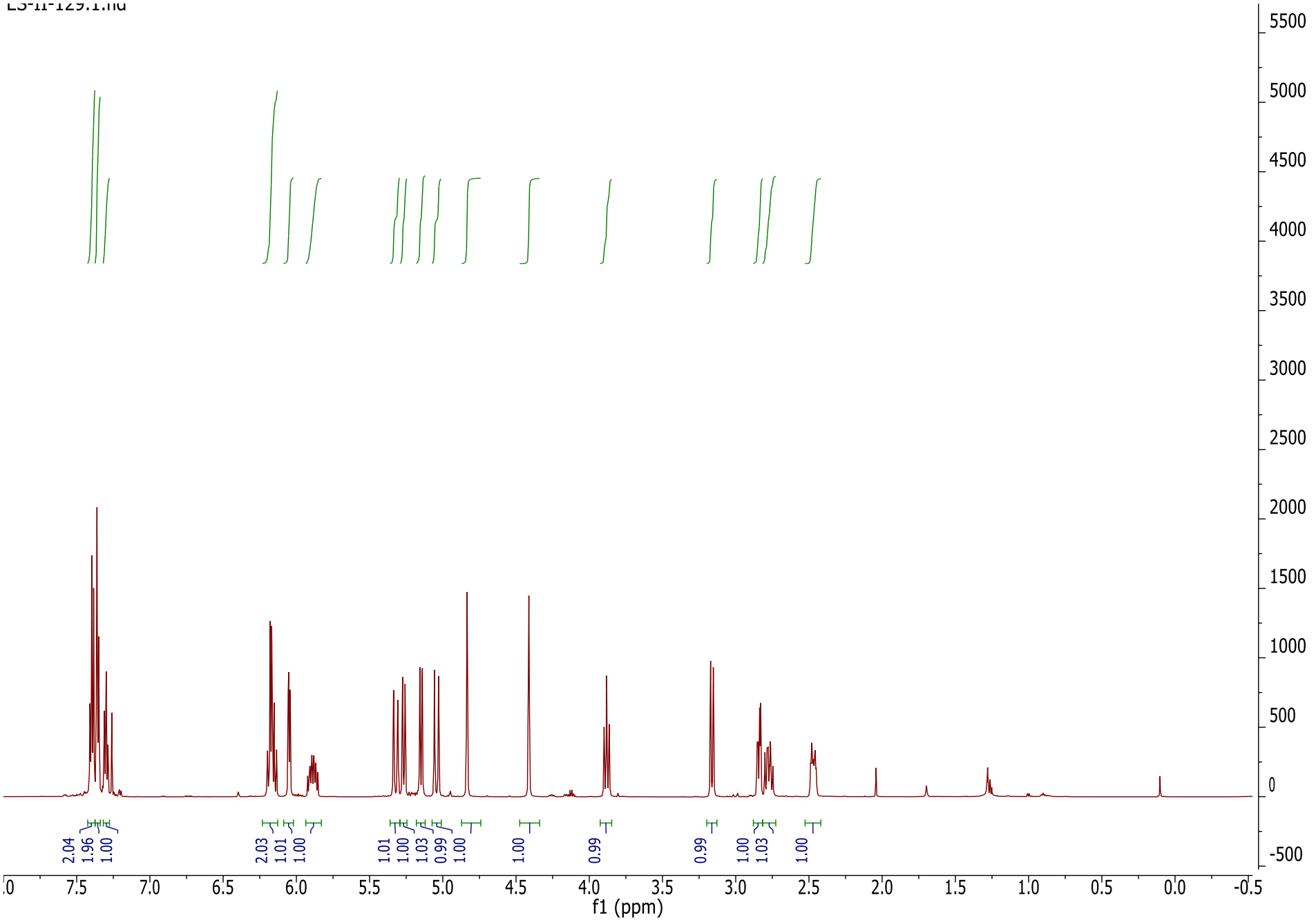
^{13}C NMR of **6f**


NC
CN
H
H
O
Me

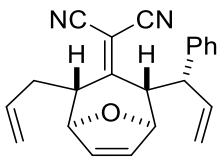

185.42
140.82
133.93
133.51
133.44
119.39
115.37
111.22
111.05
90.26
79.29
78.60
45.72
43.71
41.78
38.46
21.83
f1 (ppm)

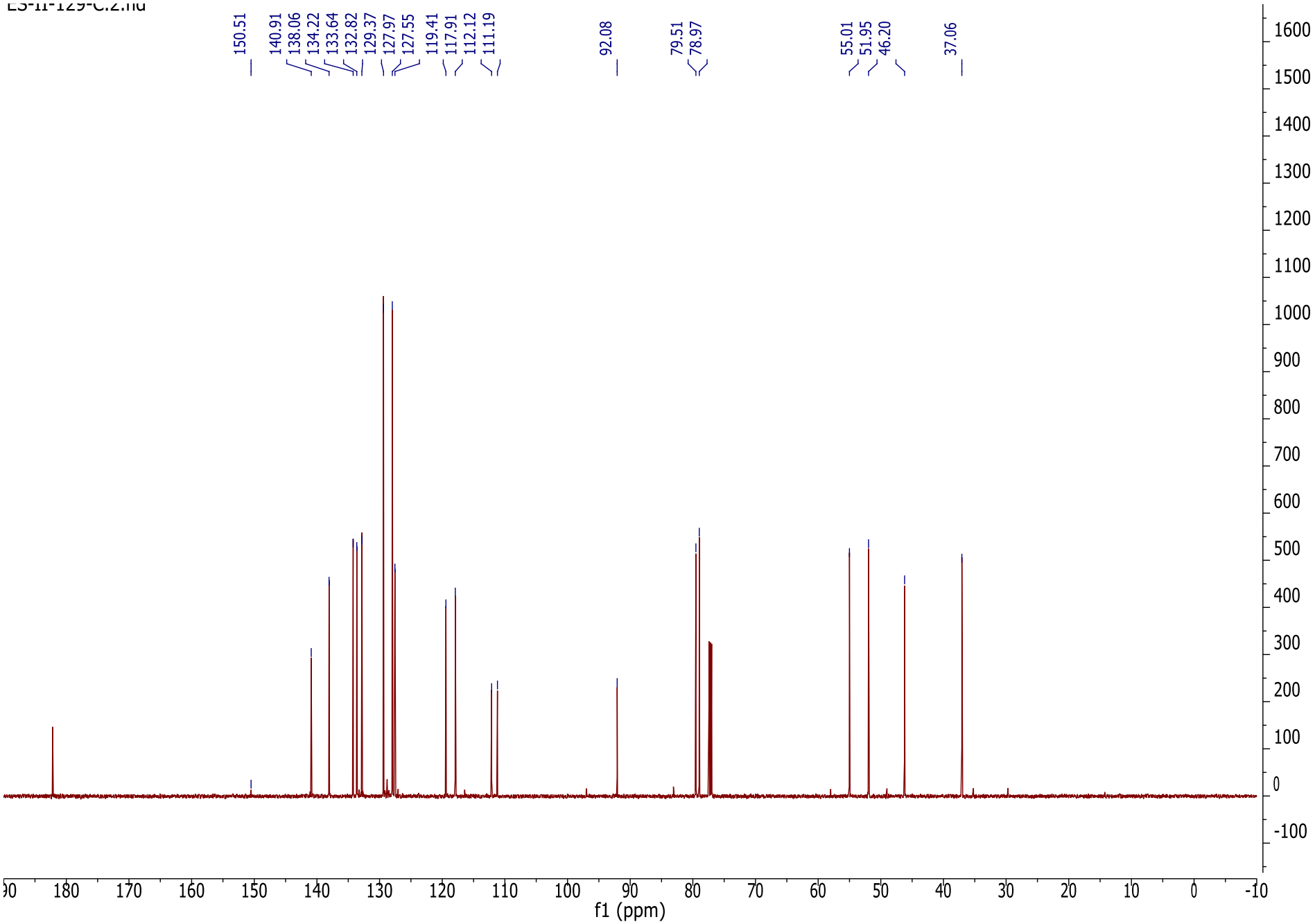
^{1}H NMR of **6g**


NC
CN
H
H
Ph
O

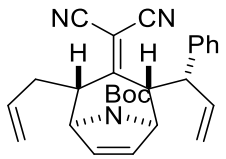

5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
2.04
1.96
1.00
2.03
1.01
1.00
1.01
1.00
1.03
0.99
1.00
1.00
0.99
0.99
1.00
1.03
1.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

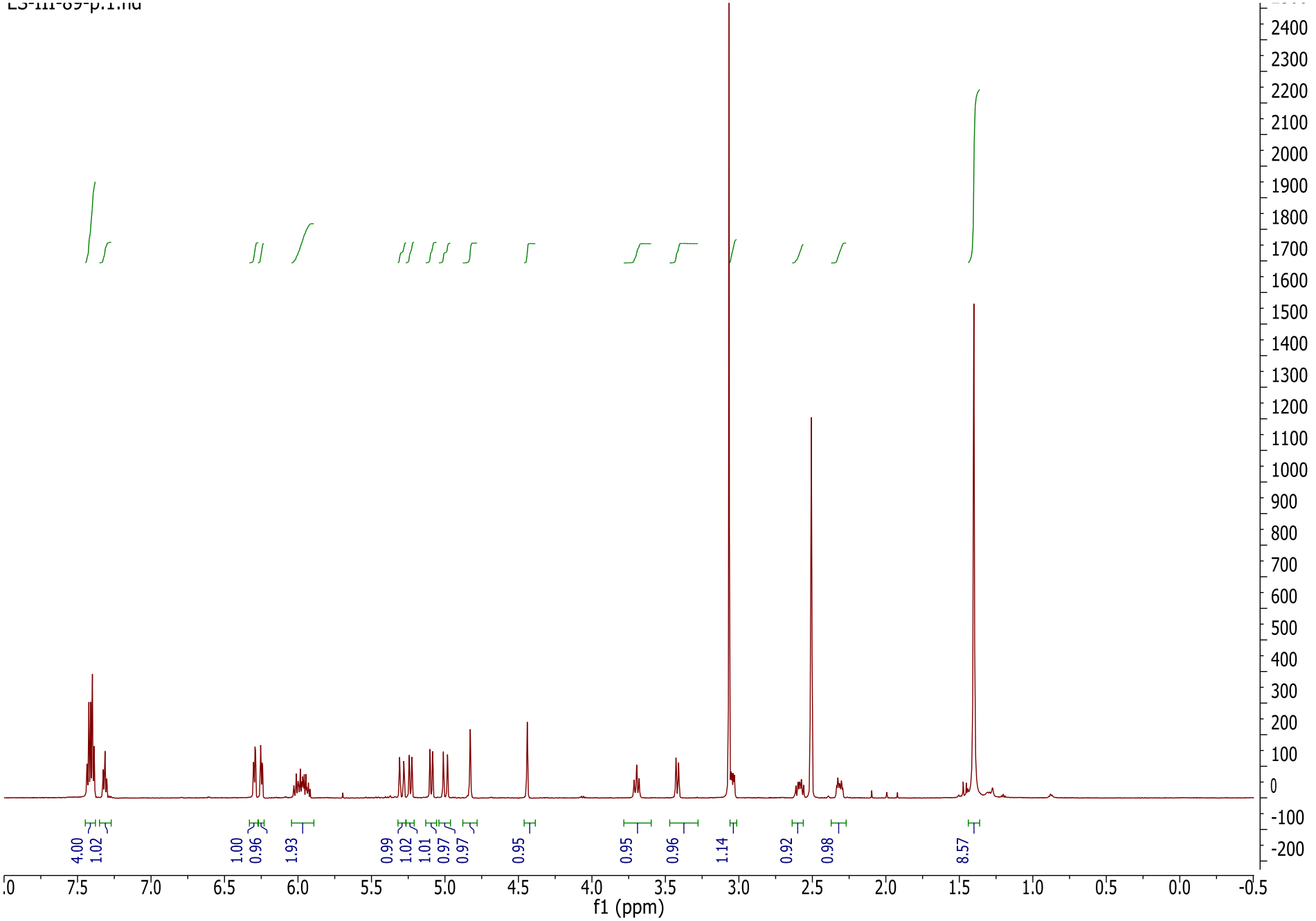
^{13}C NMR of **6g**


NC
CN
H
H
Ph
O

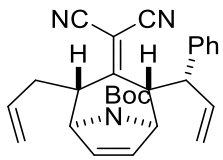

150.51
140.91
138.06
134.22
133.64
132.82
129.37
127.97
127.55
119.41
117.91
112.12
111.19
92.08
79.51
78.97
55.01
51.95
46.20
37.06
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

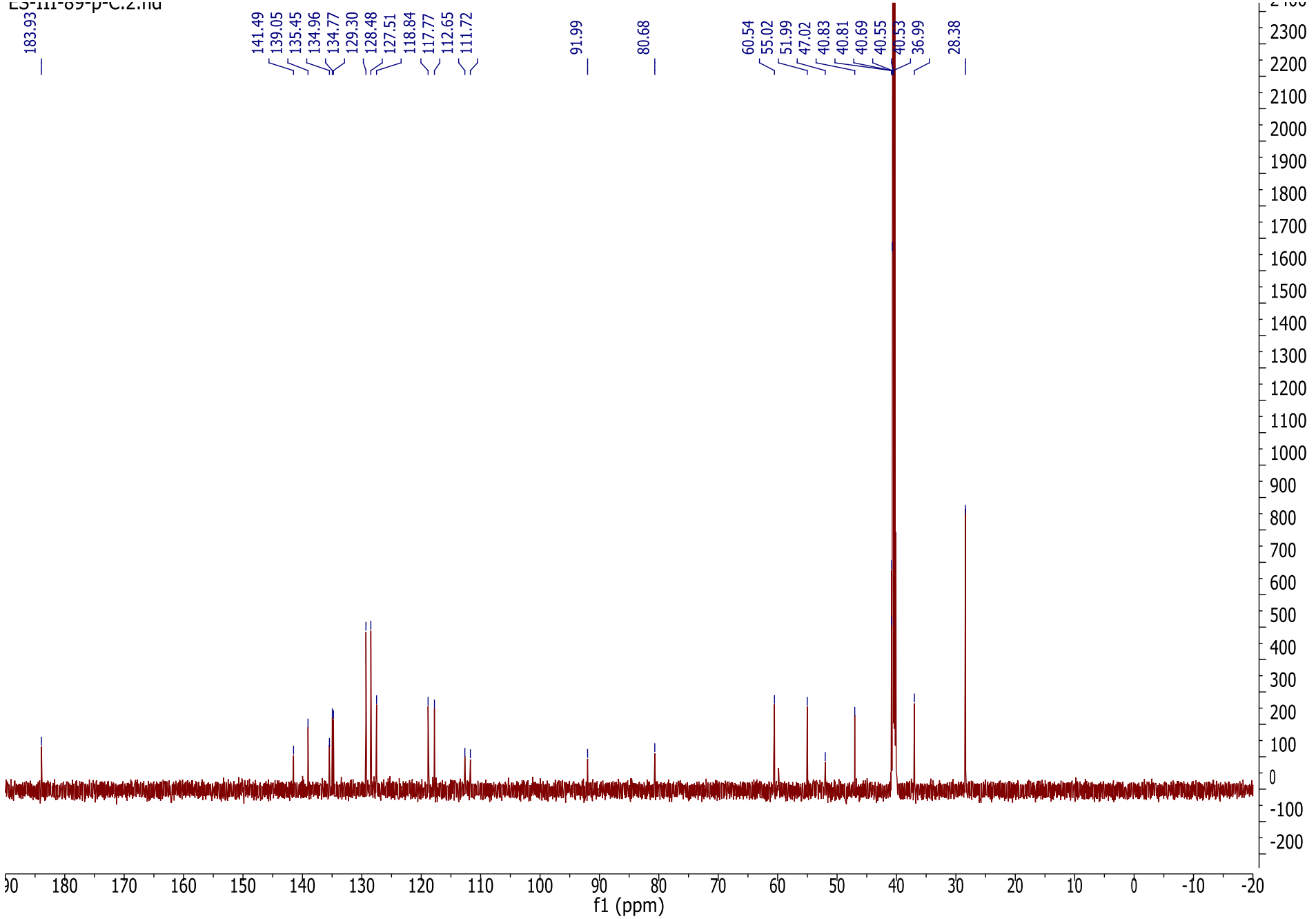
^{1}H NMR of **i**


NC
CN
H
H
Ph
Boc
N

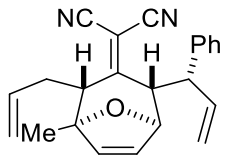

4.00
1.02
1.00
0.96
1.93
0.99
1.02
1.01
0.97
0.97
0.95
0.95
0.96
1.14
0.92
0.98
8.57
f1 (ppm)

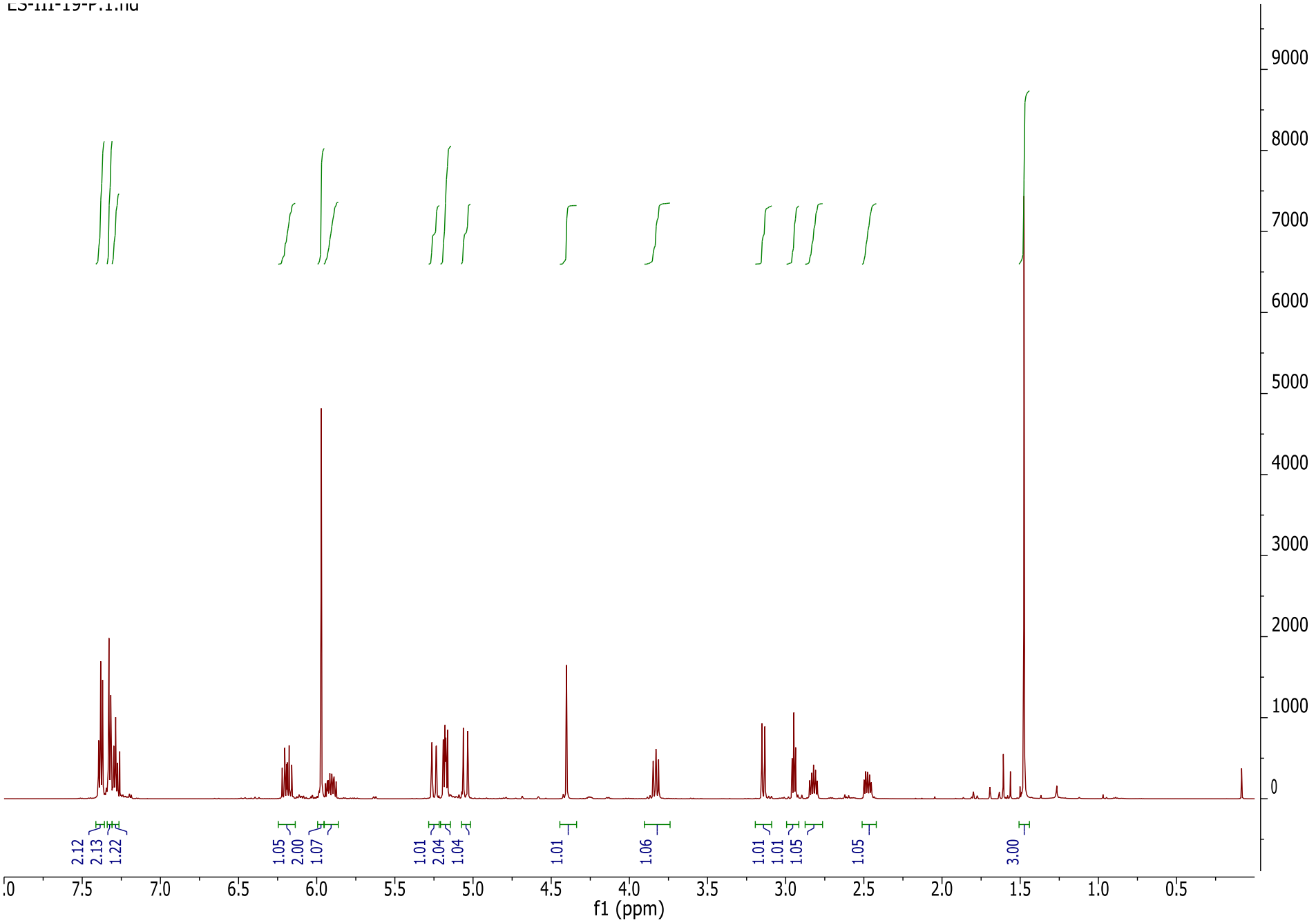
^{13}C NMR of **6h**


NC
CN
H
H
Ph
Boc
N

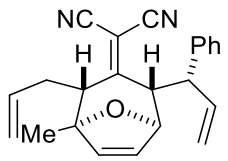

183.93
141.49
139.05
135.45
134.96
134.77
129.30
128.48
127.51
118.84
117.77
112.65
111.72
91.99
80.68
60.54
55.02
51.99
47.02
40.83
40.81
40.69
40.55
40.53
36.99
28.38
f1 (ppm)

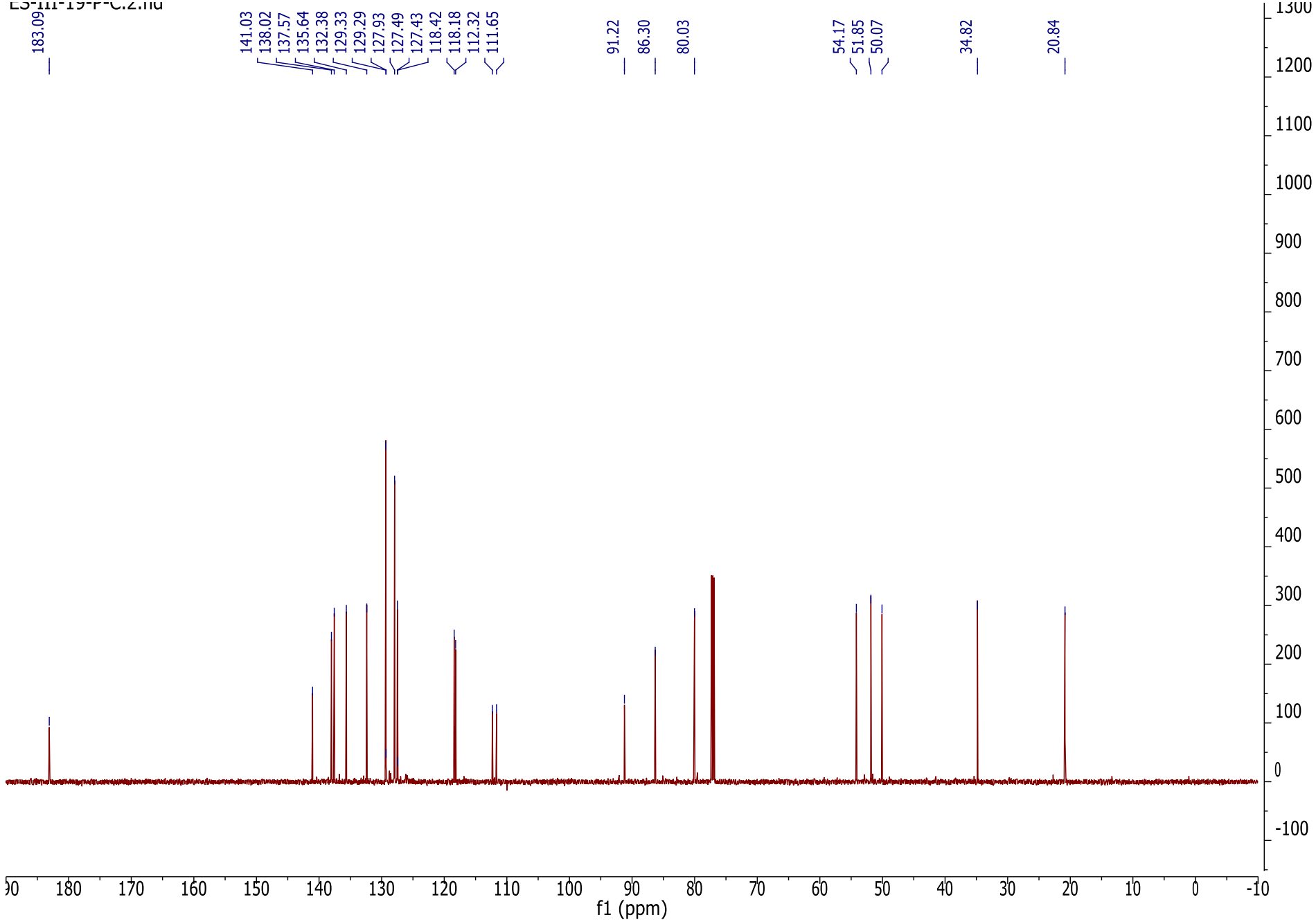
^{1}H NMR of **6i**


NC
CN
H
H
Ph
O
Me

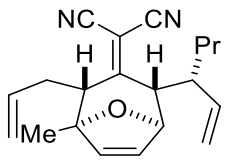

9000
8000
7000
6000
5000
4000
3000
2000
1000
0
2.12
2.13
1.22
1.05
2.00
1.07
1.01
2.04
1.04
1.01
1.06
1.01
1.01
1.05
1.05
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

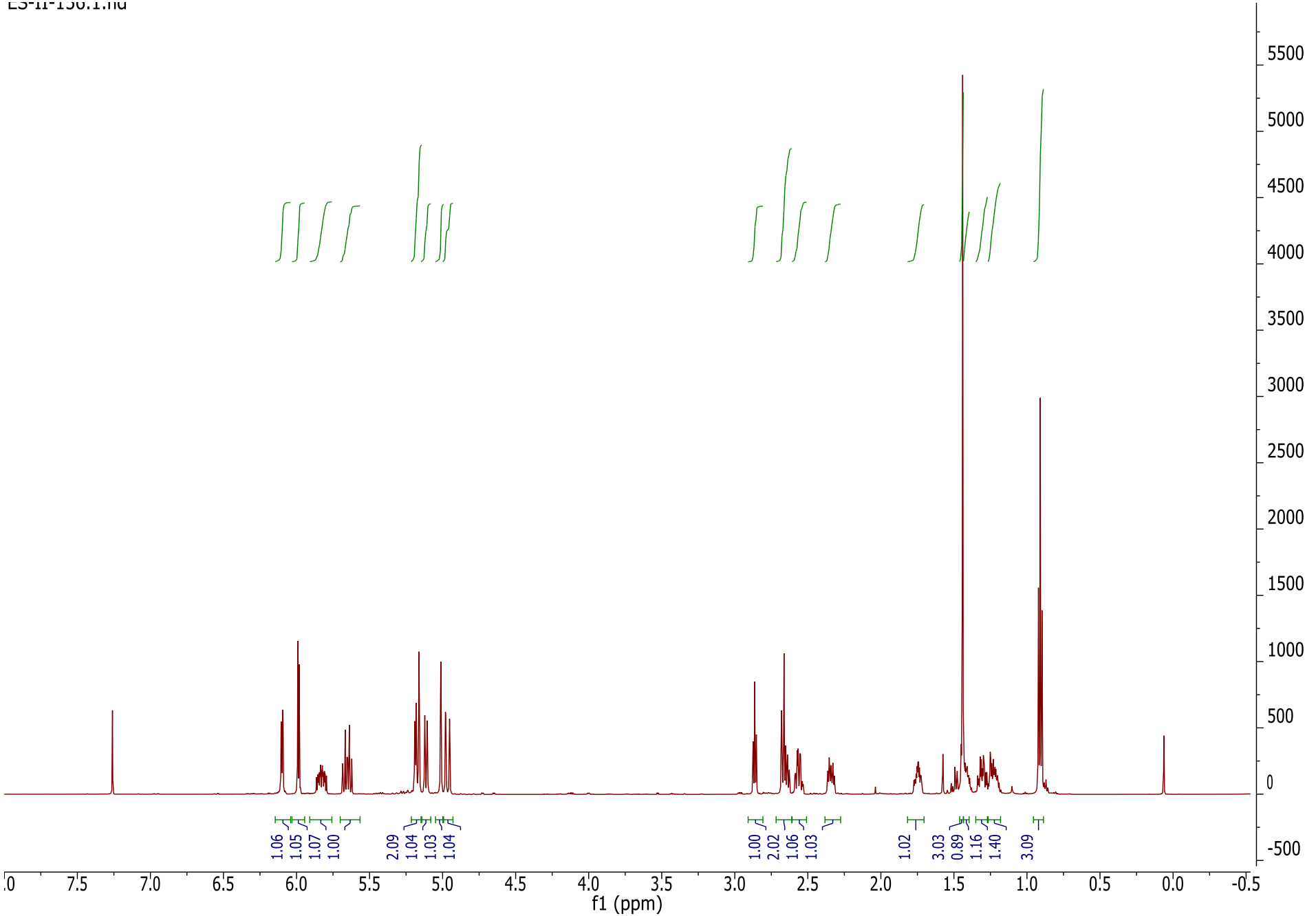
^{13}C NMR of **6i**


NC
CN
H
H
Ph
O
Me

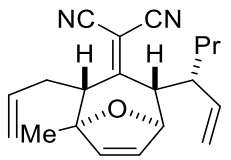

183.09
141.03
138.02
137.57
135.64
132.38
129.33
129.29
127.93
127.49
127.43
118.42
118.18
112.32
111.65
91.22
86.30
80.03
54.17
51.85
50.07
34.82
20.84
f1 (ppm)

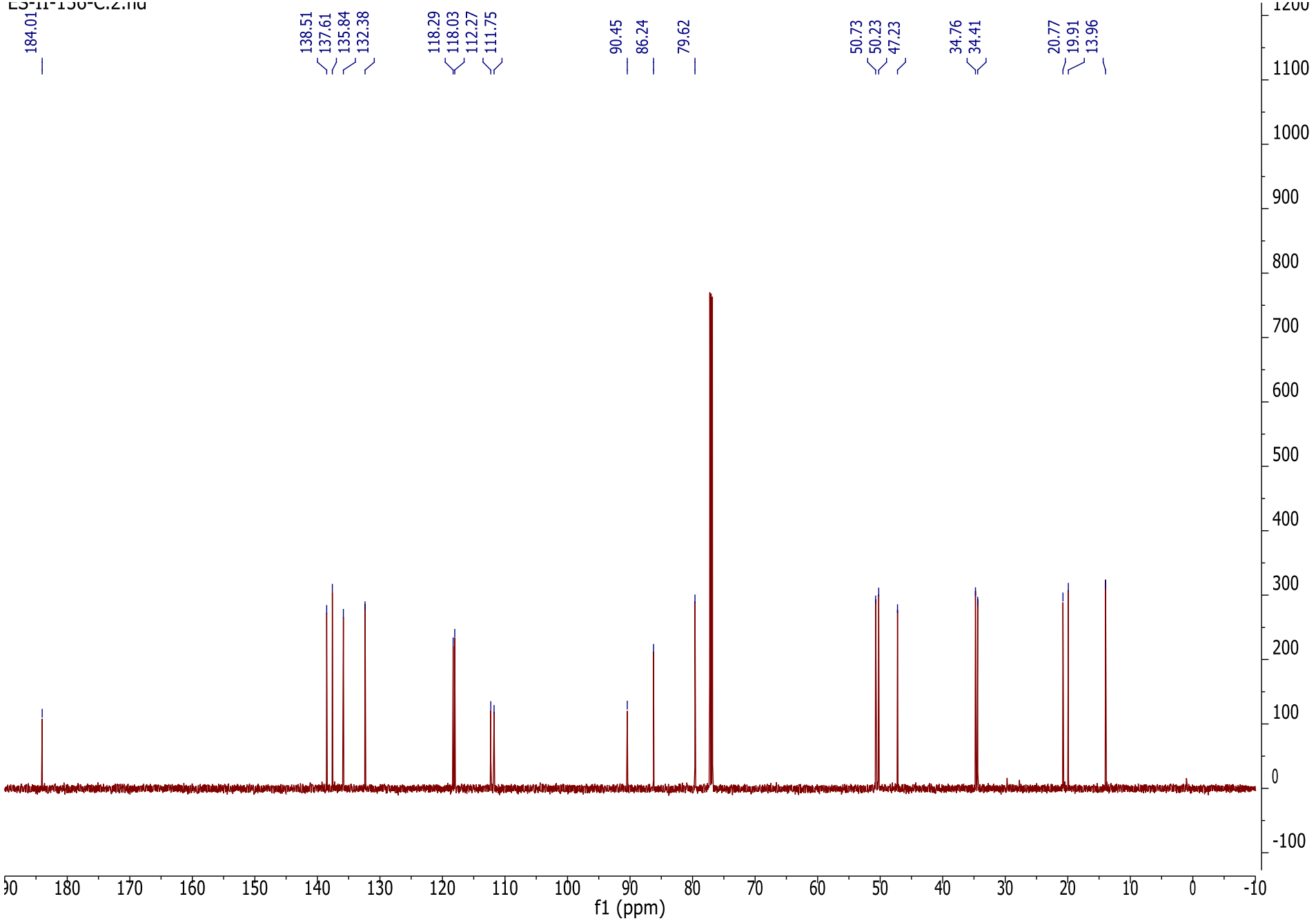
^{1}H NMR of **6j**


NC
CN
H
H
Pr
O
Me

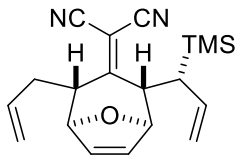

5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
1.06
1.05
1.07
1.00
2.09
1.04
1.03
1.04
1.00
2.02
1.06
1.03
1.02
3.03
0.89
1.16
1.40
3.09
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

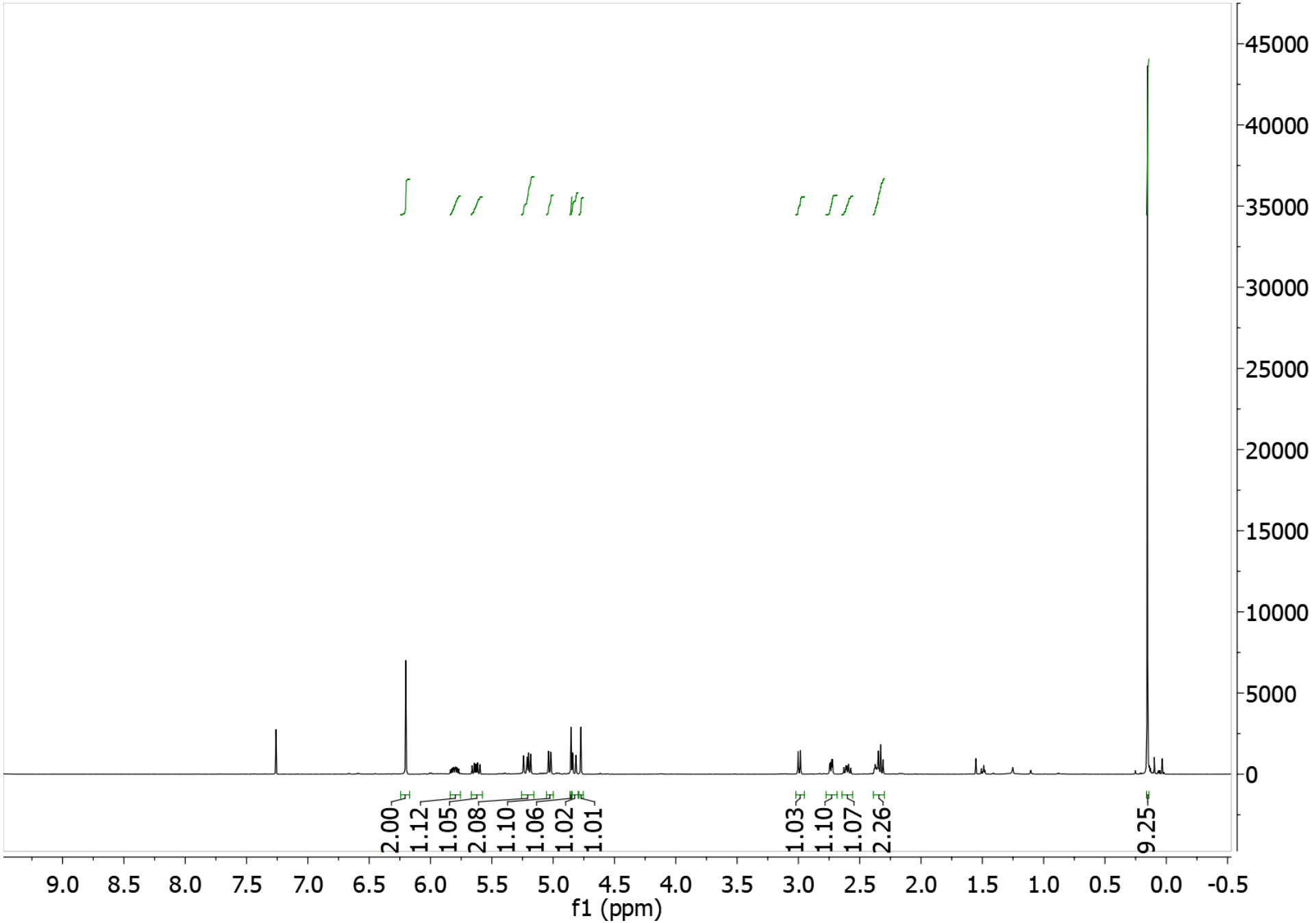
^{13}C NMR of **6j**


NC
CN
H
H
Pr
O
Me

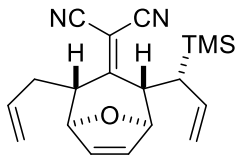

184.01
138.51
137.61
135.84
132.38
118.29
118.03
112.27
111.75
90.45
86.24
79.62
50.73
50.23
47.23
34.76
34.41
20.77
19.91
13.96
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

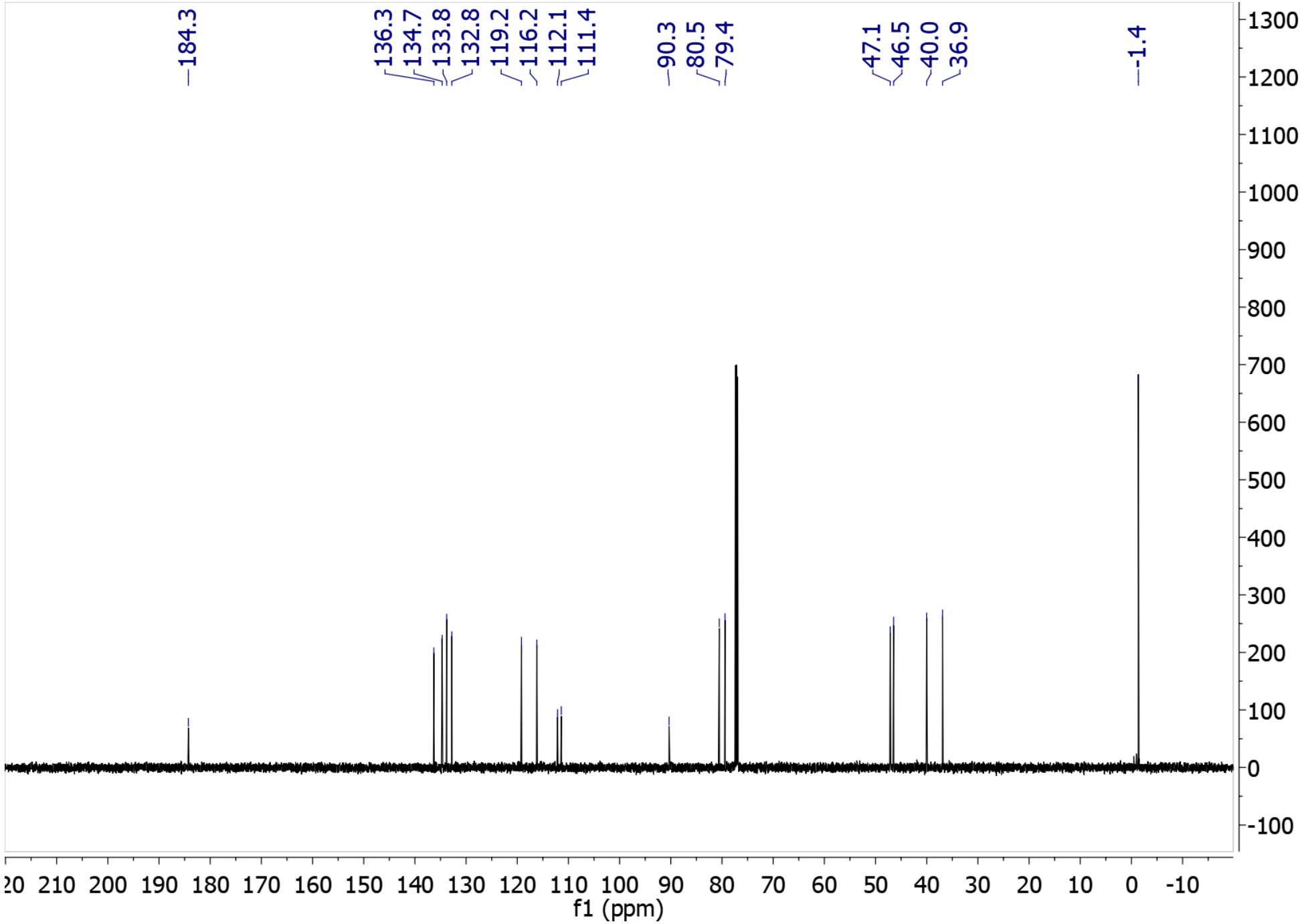
^{1}H NMR of **6k**


NC
CN
H
H
TMS
O

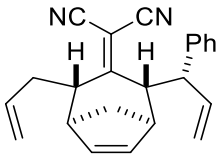

45000
40000
35000
30000
25000
20000
15000
10000
5000
0
2.00
1.12
1.05
2.08
1.10
1.06
1.02
1.01
1.03
1.10
1.07
2.26
9.25
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

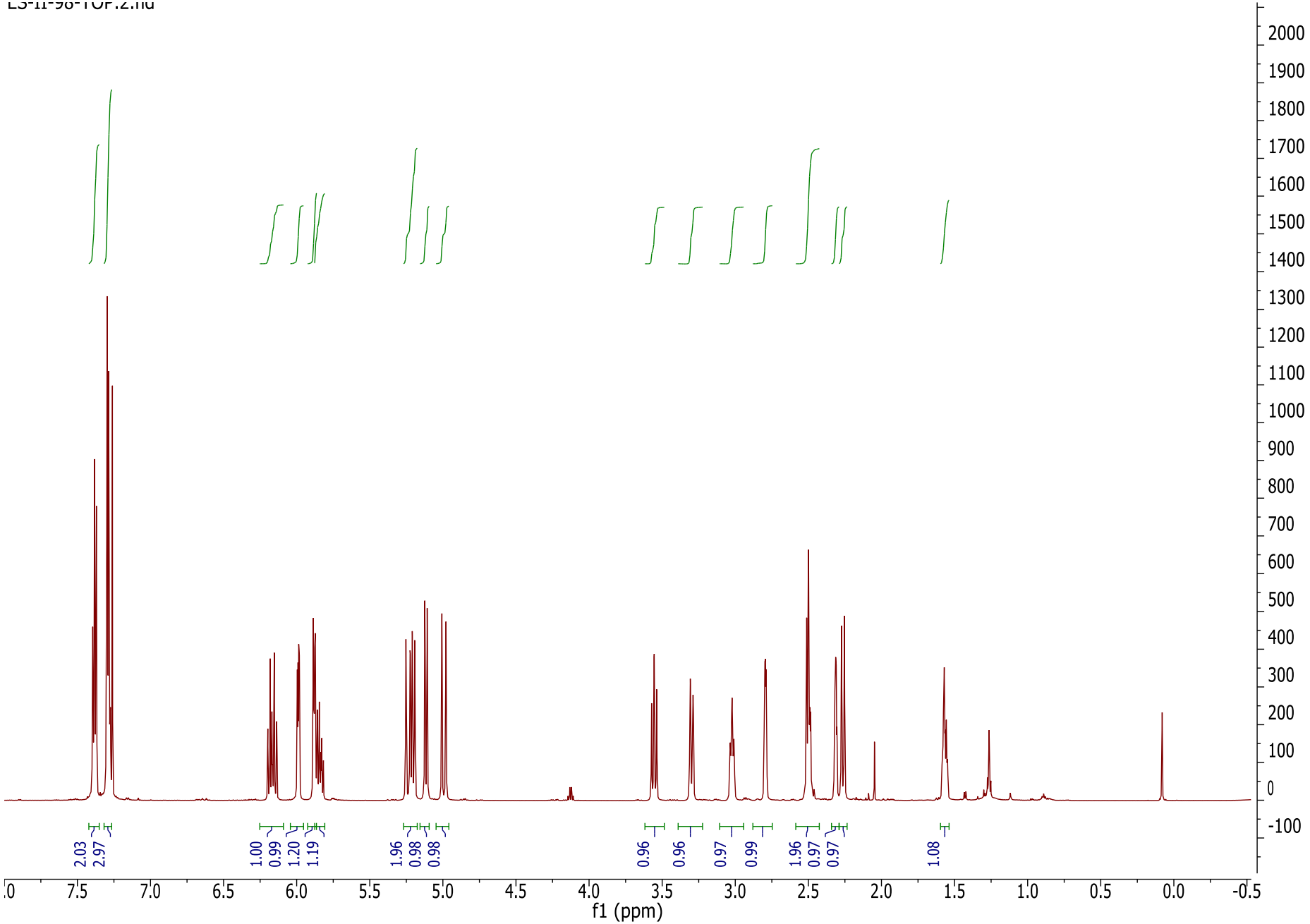
^{13}C NMR of **6k**


NC
CN
H
H
TMS
O

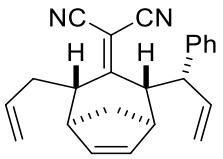

184.3
136.3
134.7
133.8
132.8
119.2
116.2
112.1
111.4
90.3
80.5
79.4
47.1
46.5
40.0
36.9
1.4
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

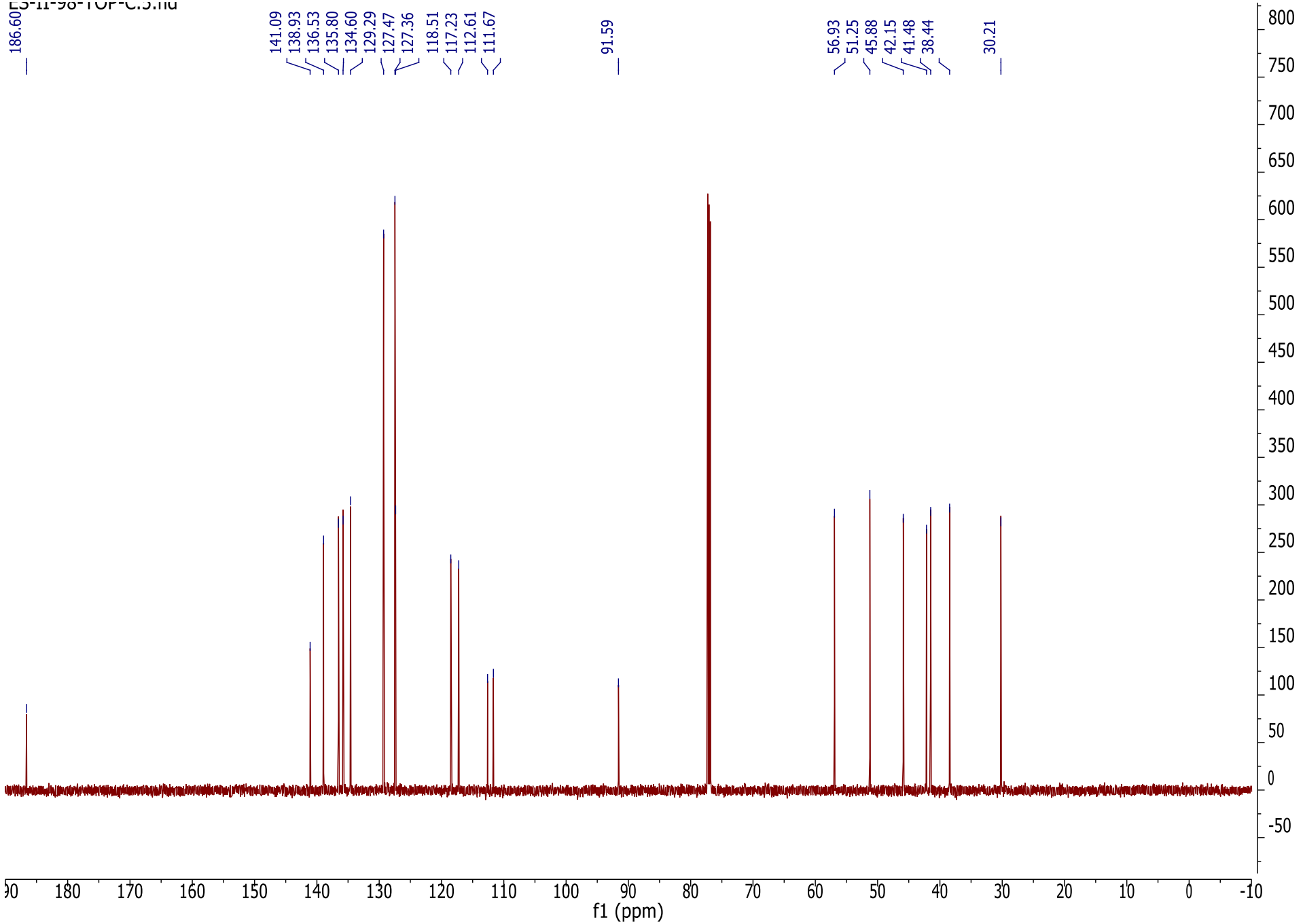
^{1}H NMR of **6l**


NC
CN
H
H
Ph

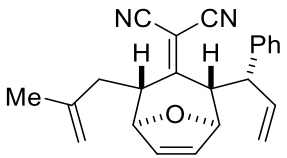

2.03
2.97
1.00
0.99
1.20
1.19
1.96
0.98
0.98
0.96
0.96
0.97
0.99
1.96
0.97
0.97
1.08
f1 (ppm)

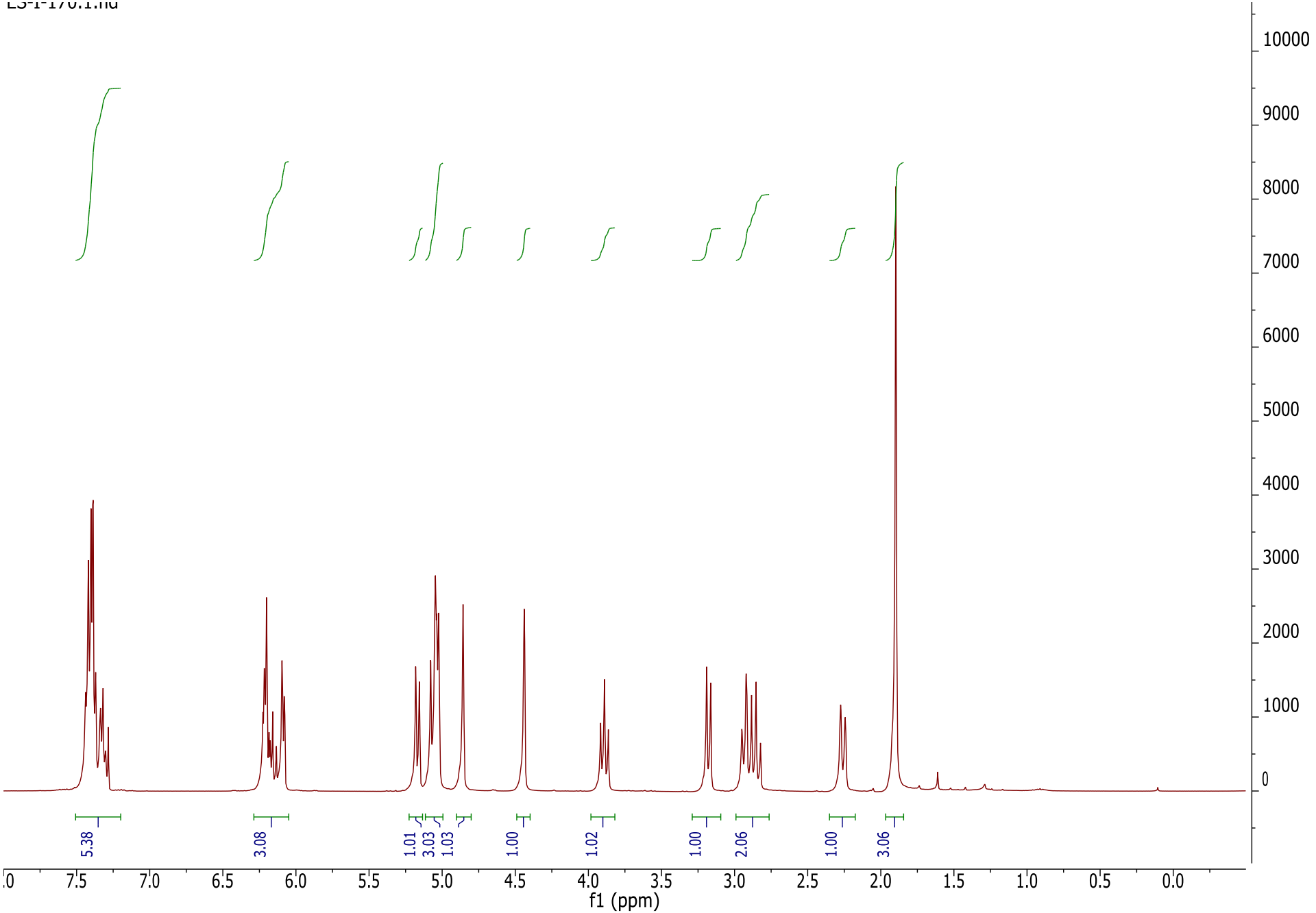
^{13}C NMR of **6l**


NC
CN
H
H
Ph

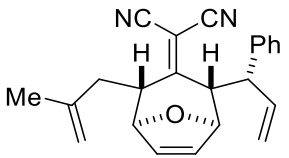

186.60
141.09
138.93
136.53
135.80
134.60
129.29
127.47
127.36
118.51
117.23
112.61
111.67
91.59
56.93
51.25
45.88
42.15
41.48
38.44
30.21
f1 (ppm)

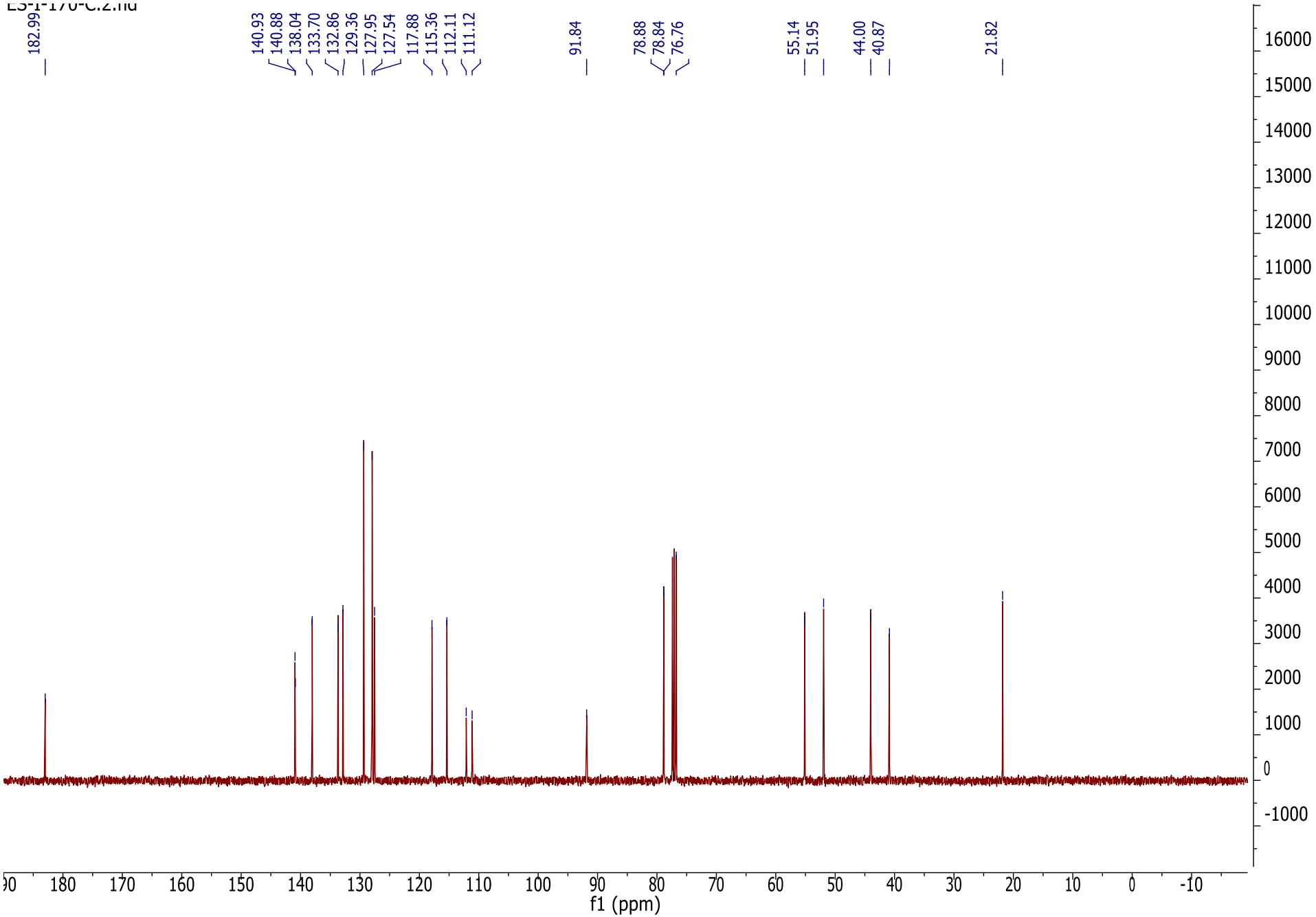
^{1}H NMR of **6o**


NC
CN
H
H
Ph
Me
O

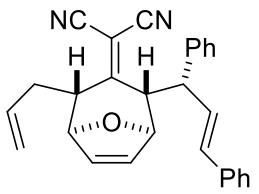

10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
5.38
3.08
1.01
3.03
1.03
1.00
1.02
1.00
2.06
1.00
3.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

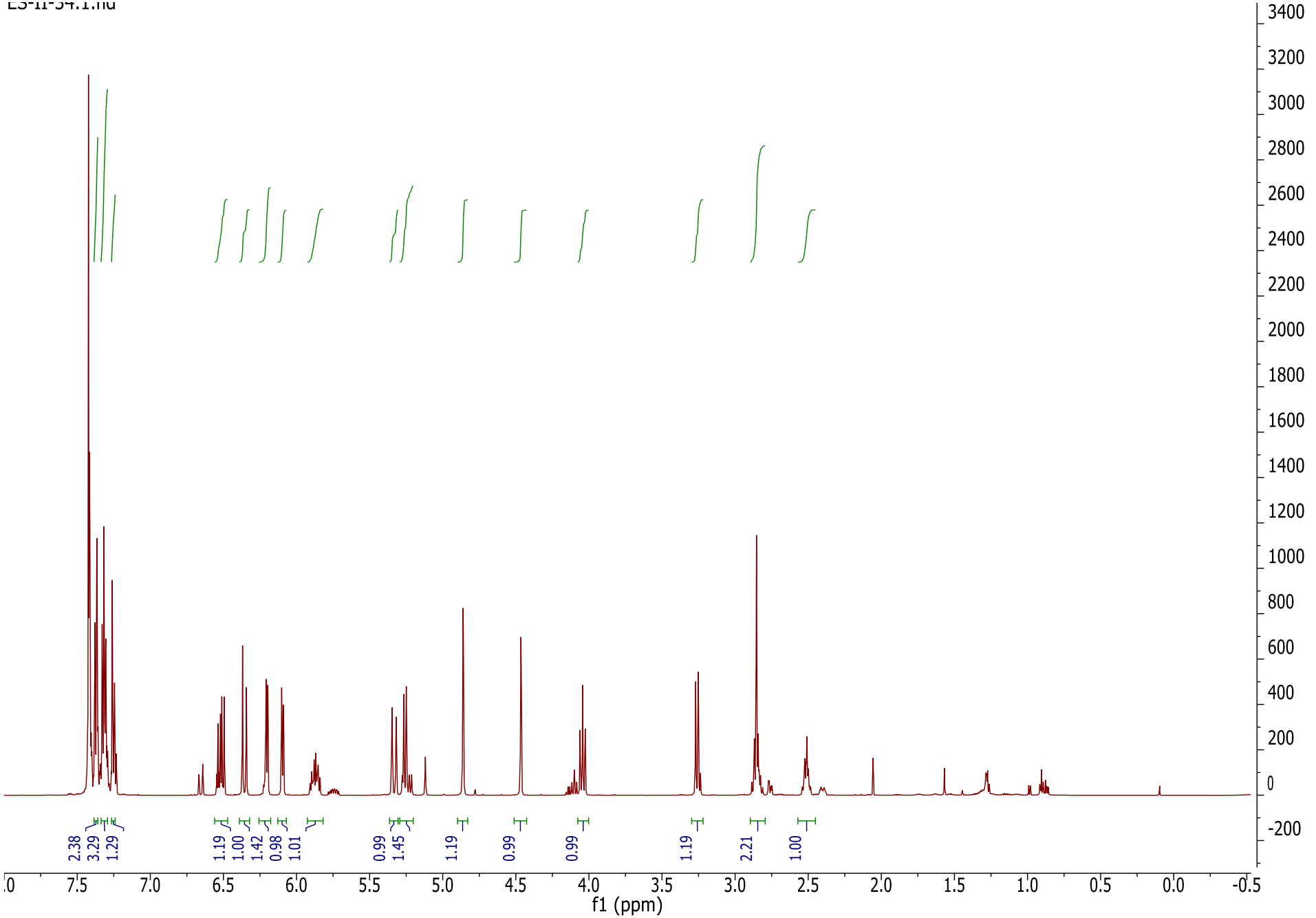
^{13}C NMR of **6o**


NC
CN
H
H
Ph
Me
O

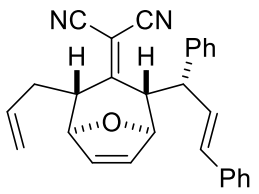

182.99
140.93
140.88
138.04
133.70
132.86
129.36
127.95
127.54
117.88
115.36
112.11
111.12
91.84
78.88
78.84
76.76
55.14
51.95
44.00
40.87
21.82
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

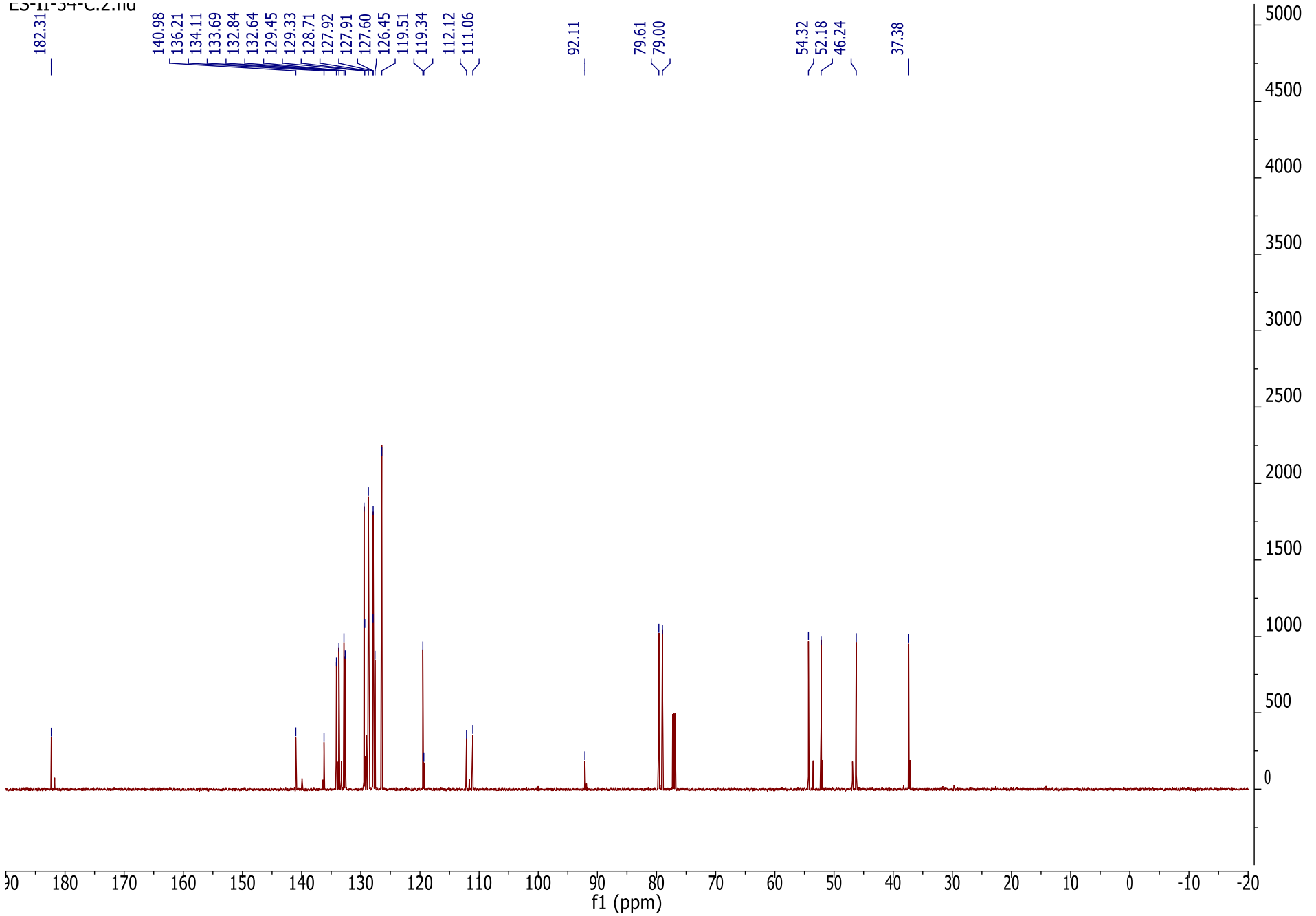
^{1}H NMR of **6m**


NC
CN
H
H
Ph
O
Ph

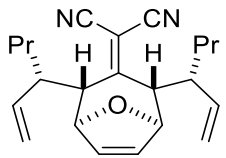

3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
2.38
3.29
1.29
1.19
1.00
1.42
0.98
1.01
0.99
1.45
1.19
0.99
0.99
1.19
2.21
1.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

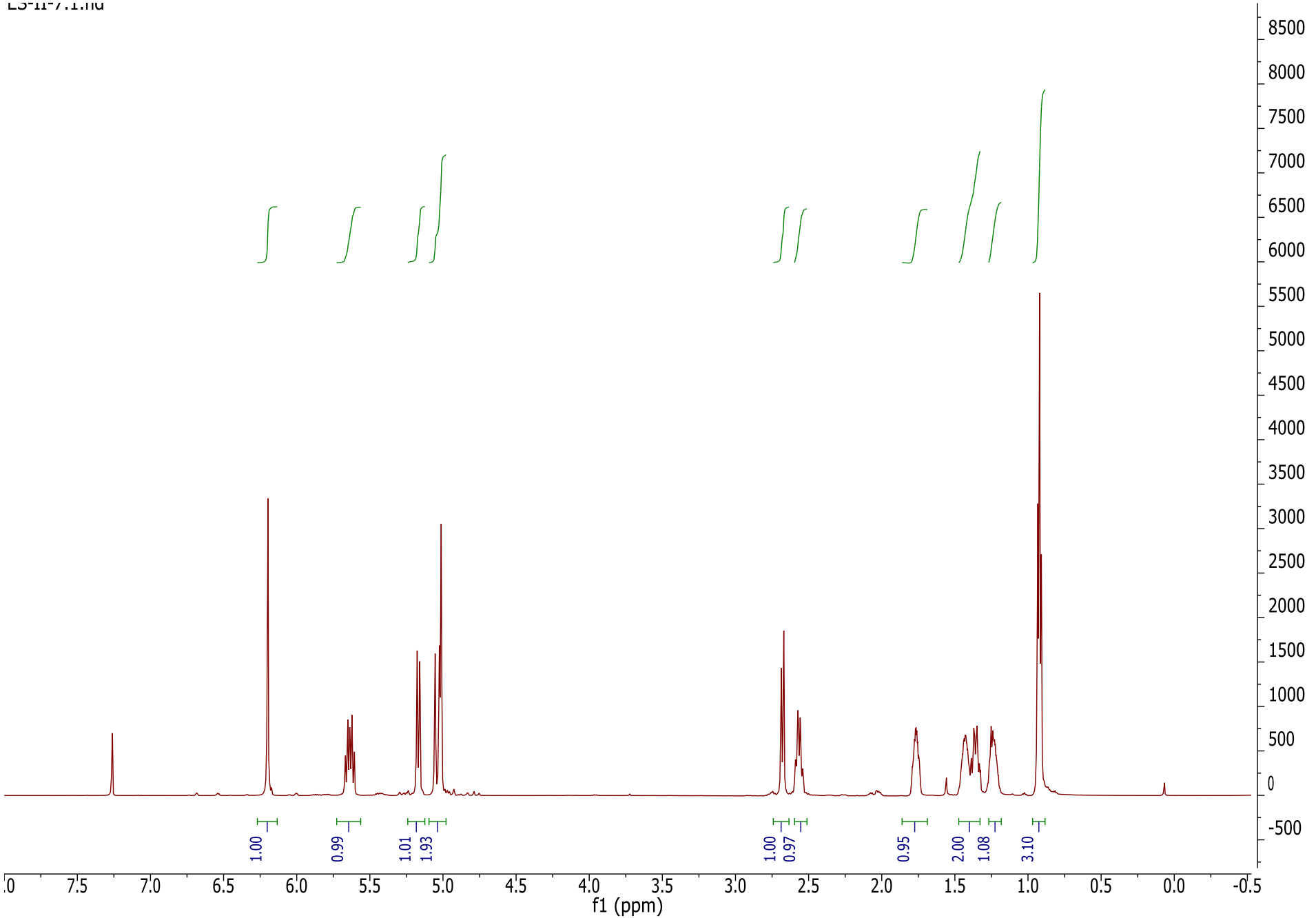
^{13}C NMR of **6m**


NC
CN
H
H
Ph
O
Ph

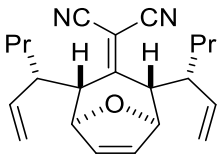

182.31
140.98
136.21
134.11
133.69
132.84
132.64
129.45
129.33
128.71
127.92
127.91
127.60
126.45
119.51
119.34
112.12
111.06
92.11
79.61
79.00
54.32
52.18
46.24
37.38
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
f1 (ppm)

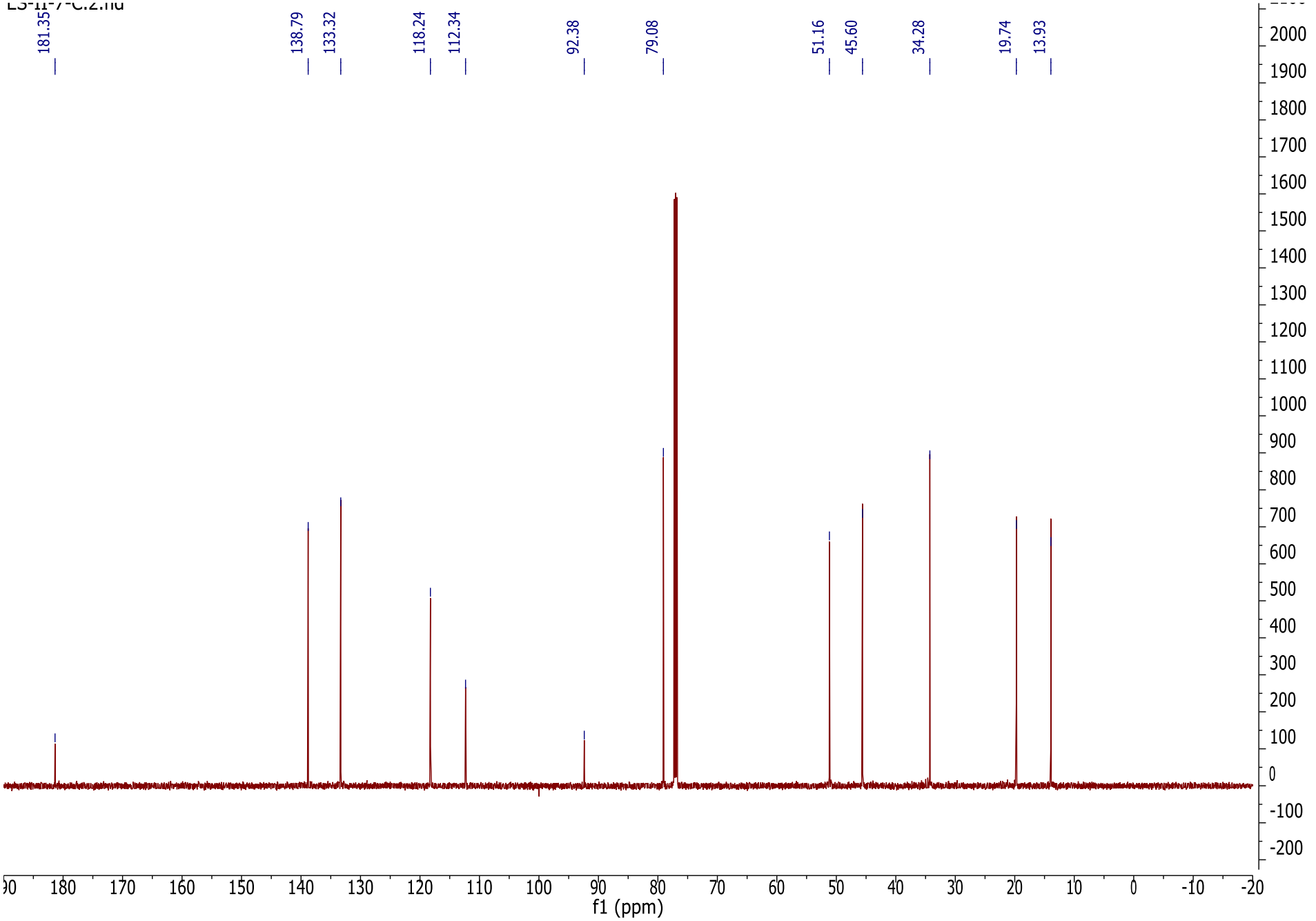
^{1}H NMR of **6n**


NC
CN
Pr
H
H
Pr
O

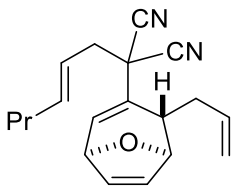

8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
1.00
0.99
1.01
1.93
1.00
0.97
0.95
2.00
1.08
3.10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

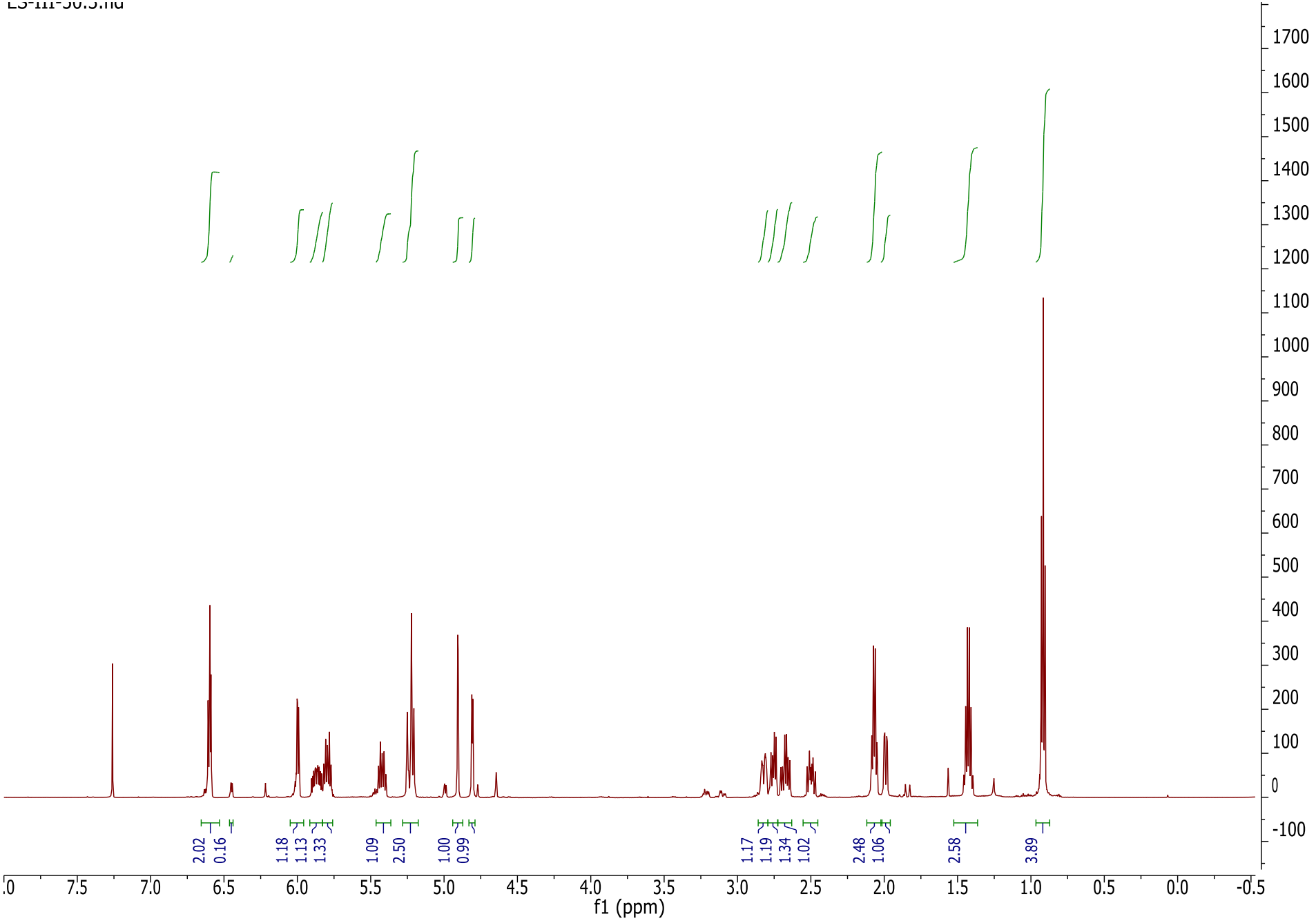
^{13}C NMR of **6n**


NC
CN
Pr
H
H
Pr
O

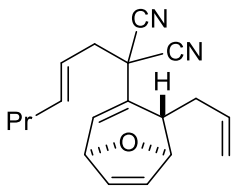

181.35
138.79
133.32
118.24
112.34
92.38
79.08
51.16
45.60
34.28
19.74
13.93
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

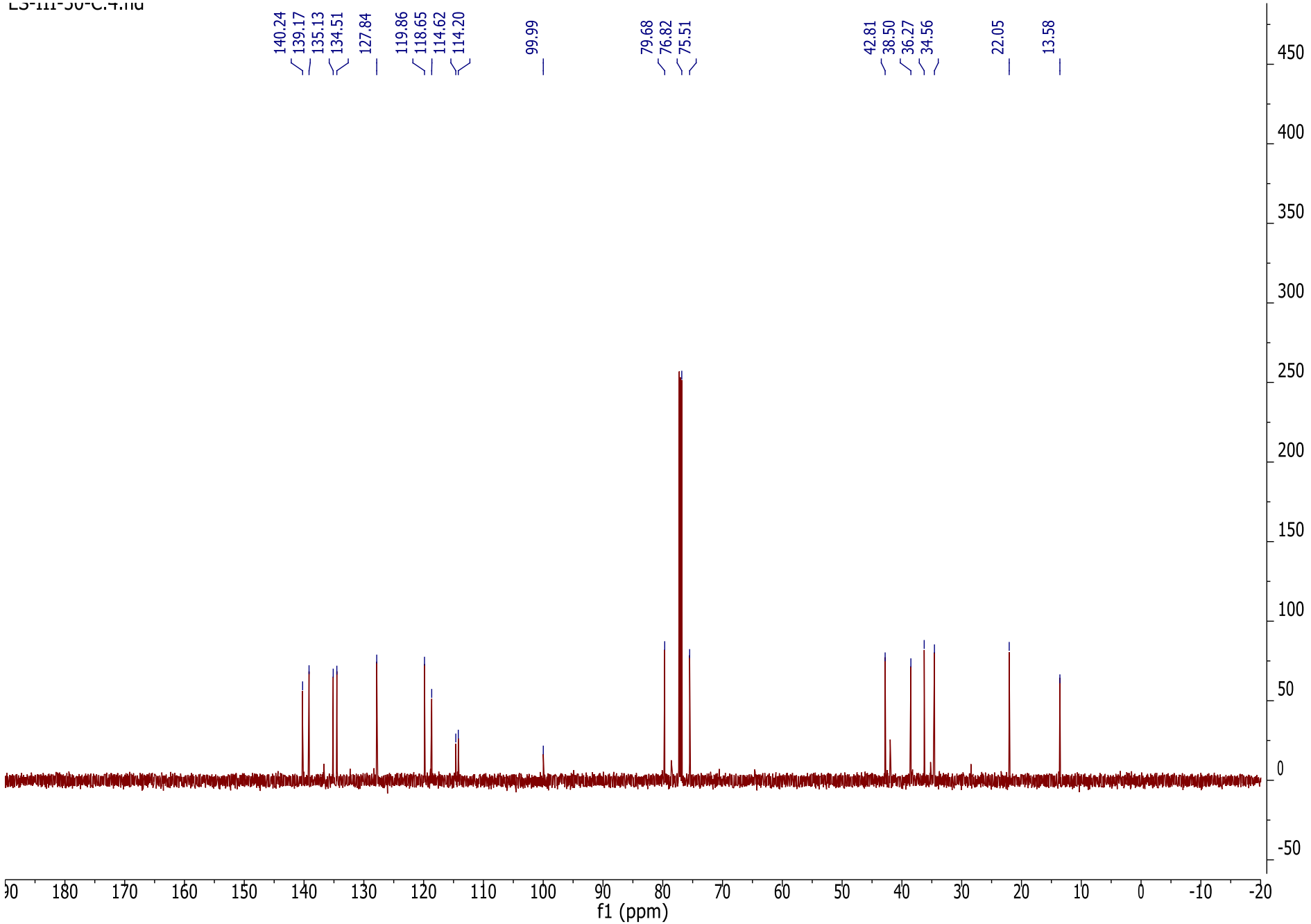
^{1}H NMR of **5l**


CN
CN
H
Pr
O

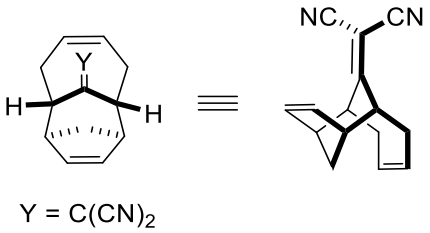

1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
2.02
0.16
1.18
1.13
1.33
1.09
2.50
1.00
0.99
1.17
1.19
1.34
1.02
2.48
1.06
2.58
3.89
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

^{13}C NMR of **5l**

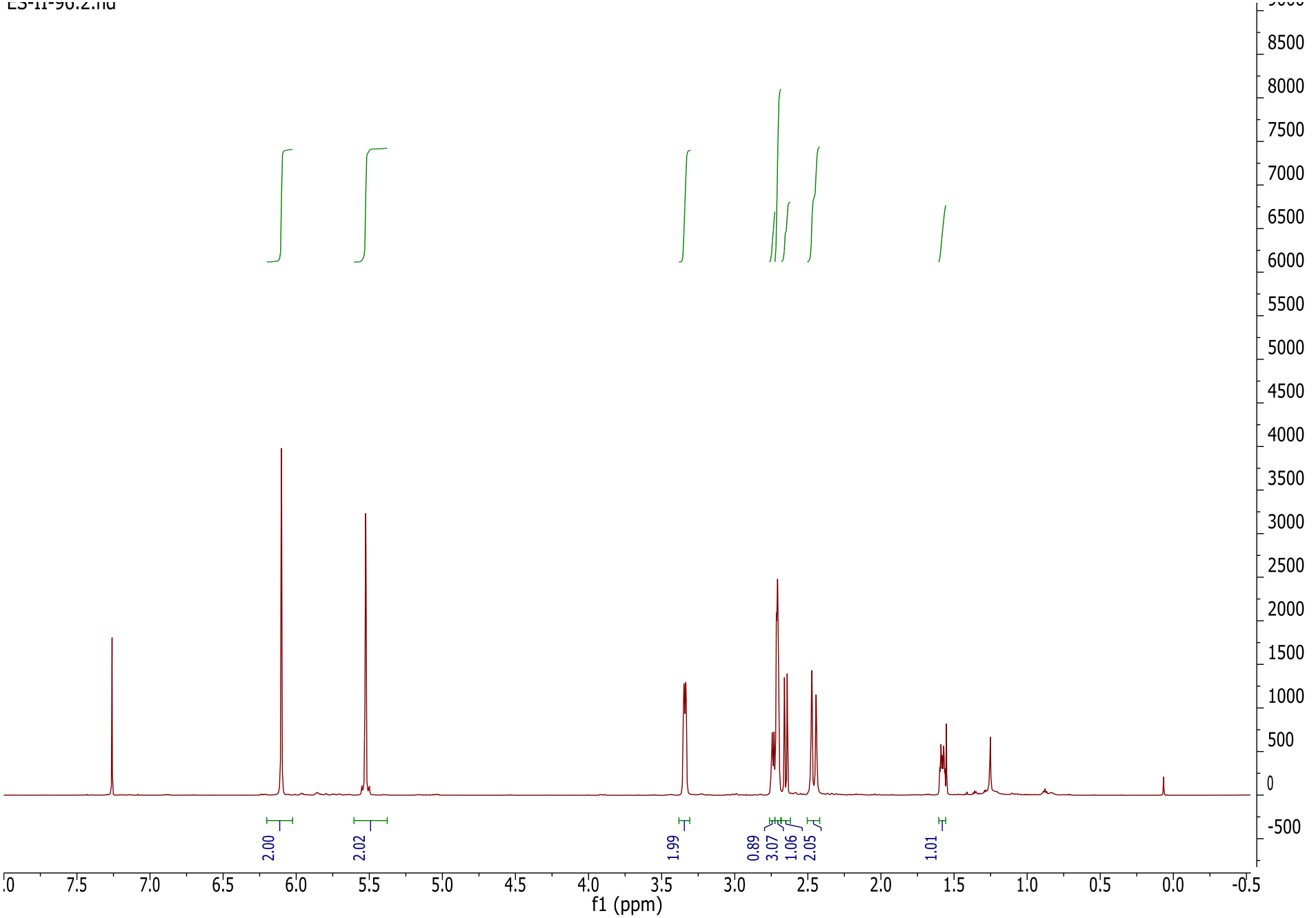

CN
CN
H
Pr
O


140.24
139.17
135.13
134.51
127.84
119.86
118.65
114.62
114.20
99.99
79.68
76.82
75.51
42.81
38.50
36.27
34.56
22.05
13.58
450
400
350
300
250
200
150
100
50
0
-50
f1 (ppm)

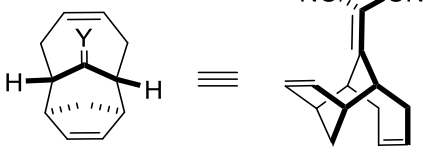
^{1}H NMR of **7a**



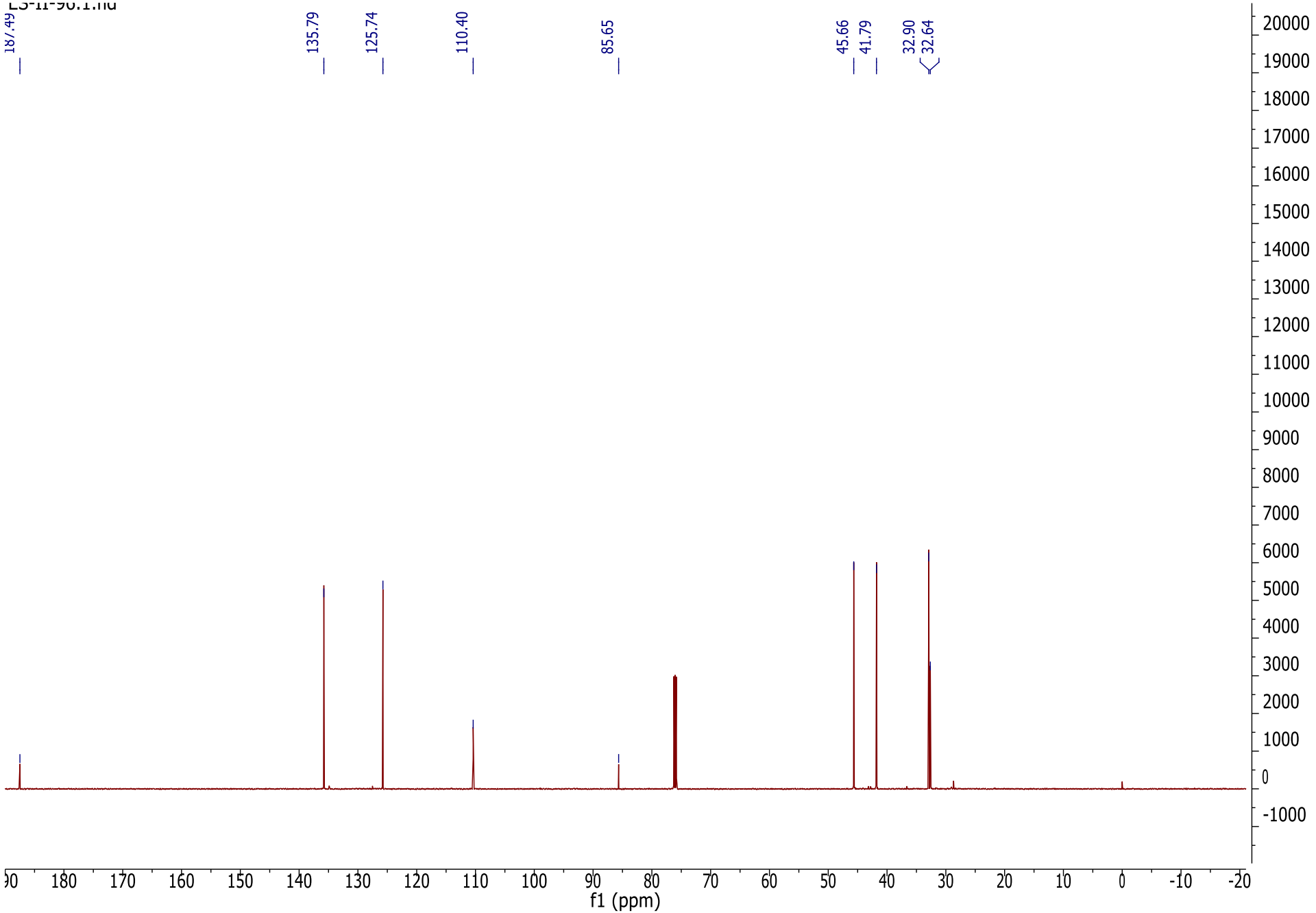
Y = $C(CN)_2$



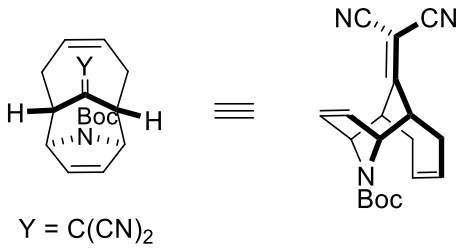
^{13}C NMR of **7a**



Y = $C(CN)_2$

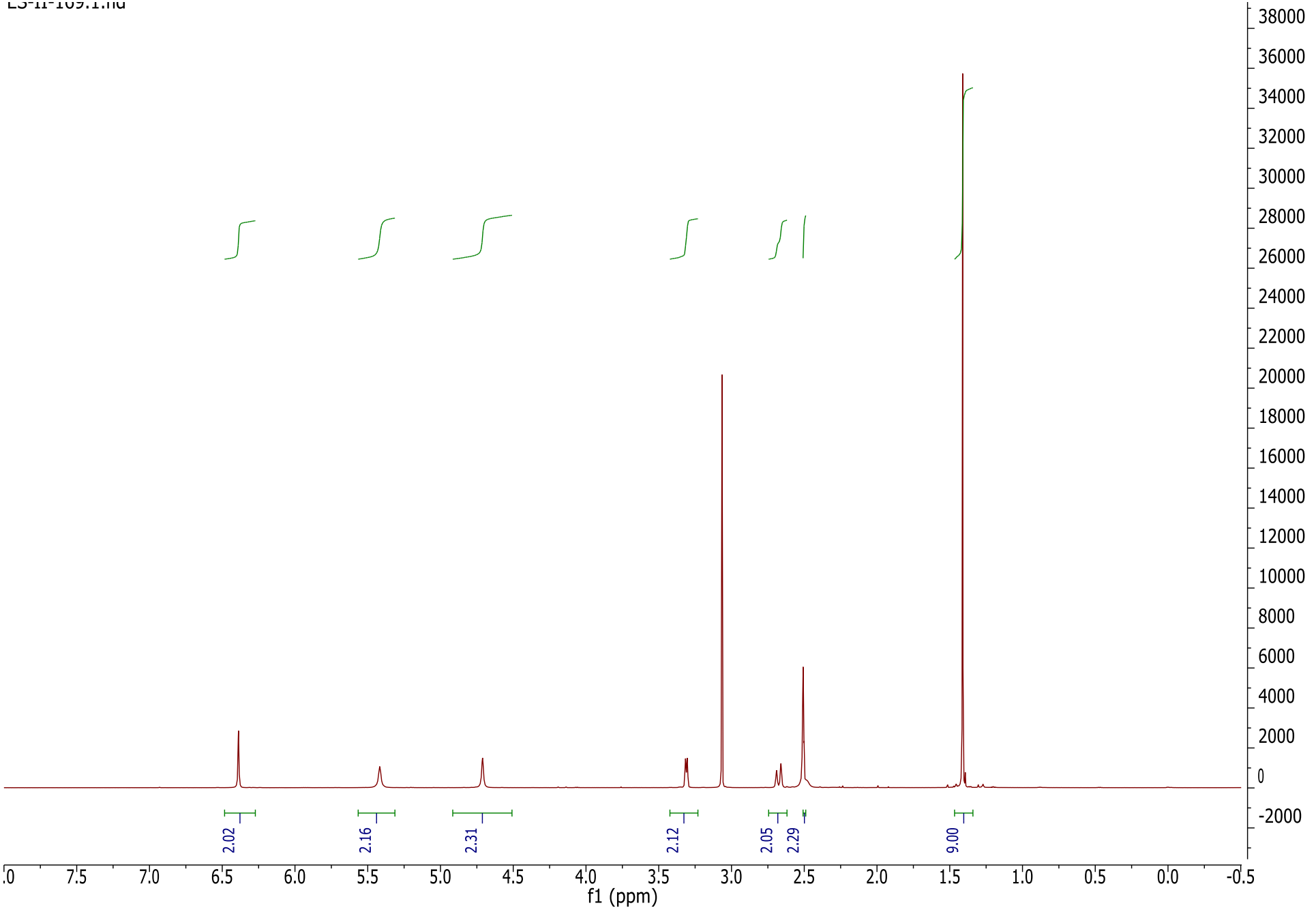


^{1}H NMR of **7b**

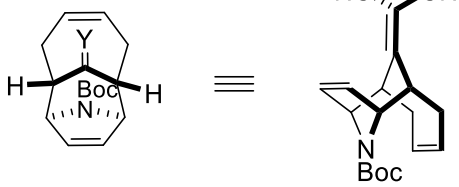


Y = $C(CN)_2$

≡

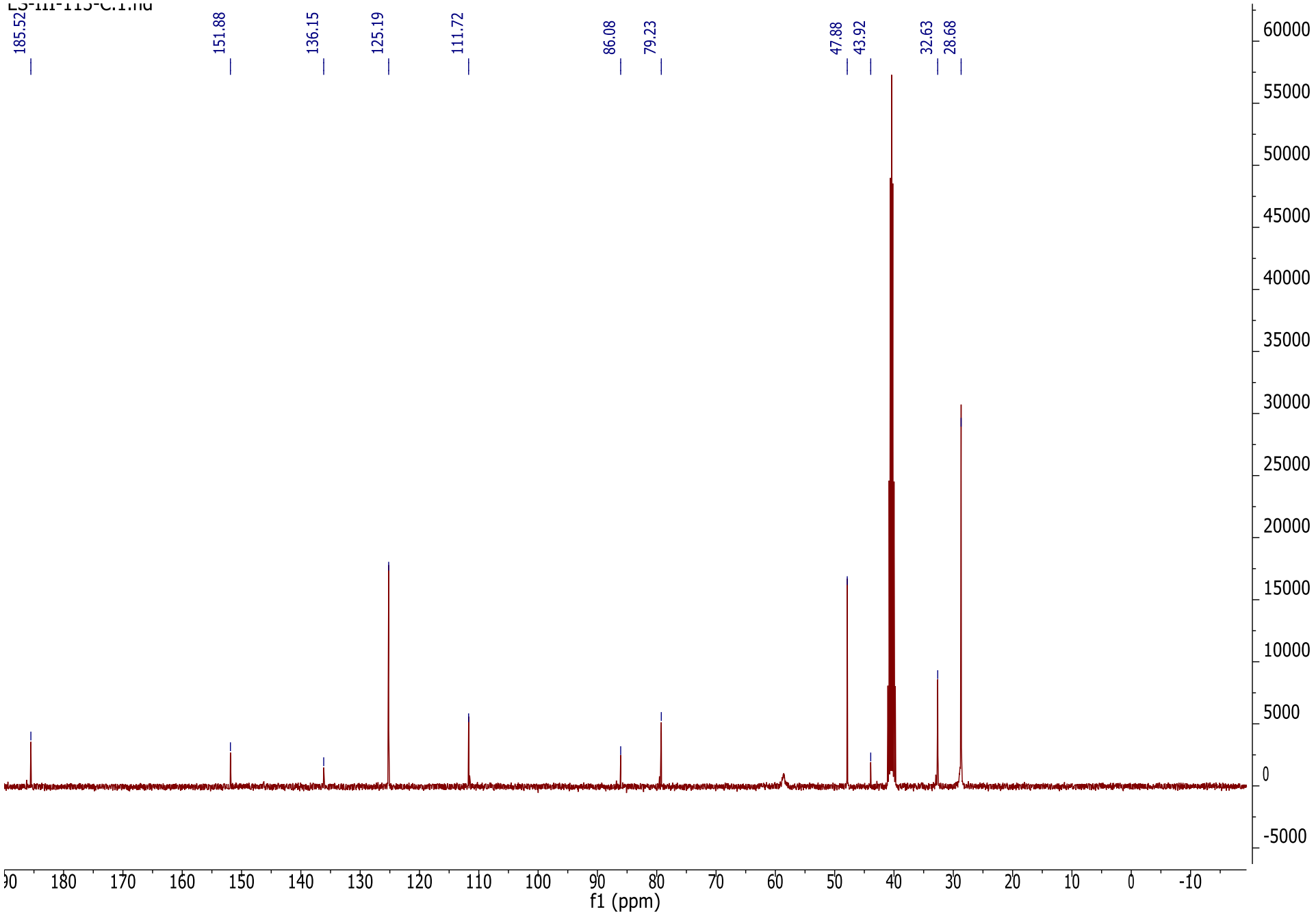


^{13}C NMR of **7b**

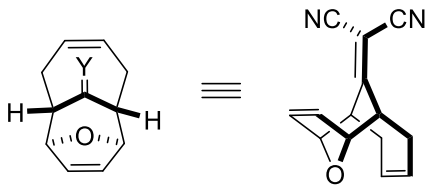


Y = $C(CN)_2$

≡

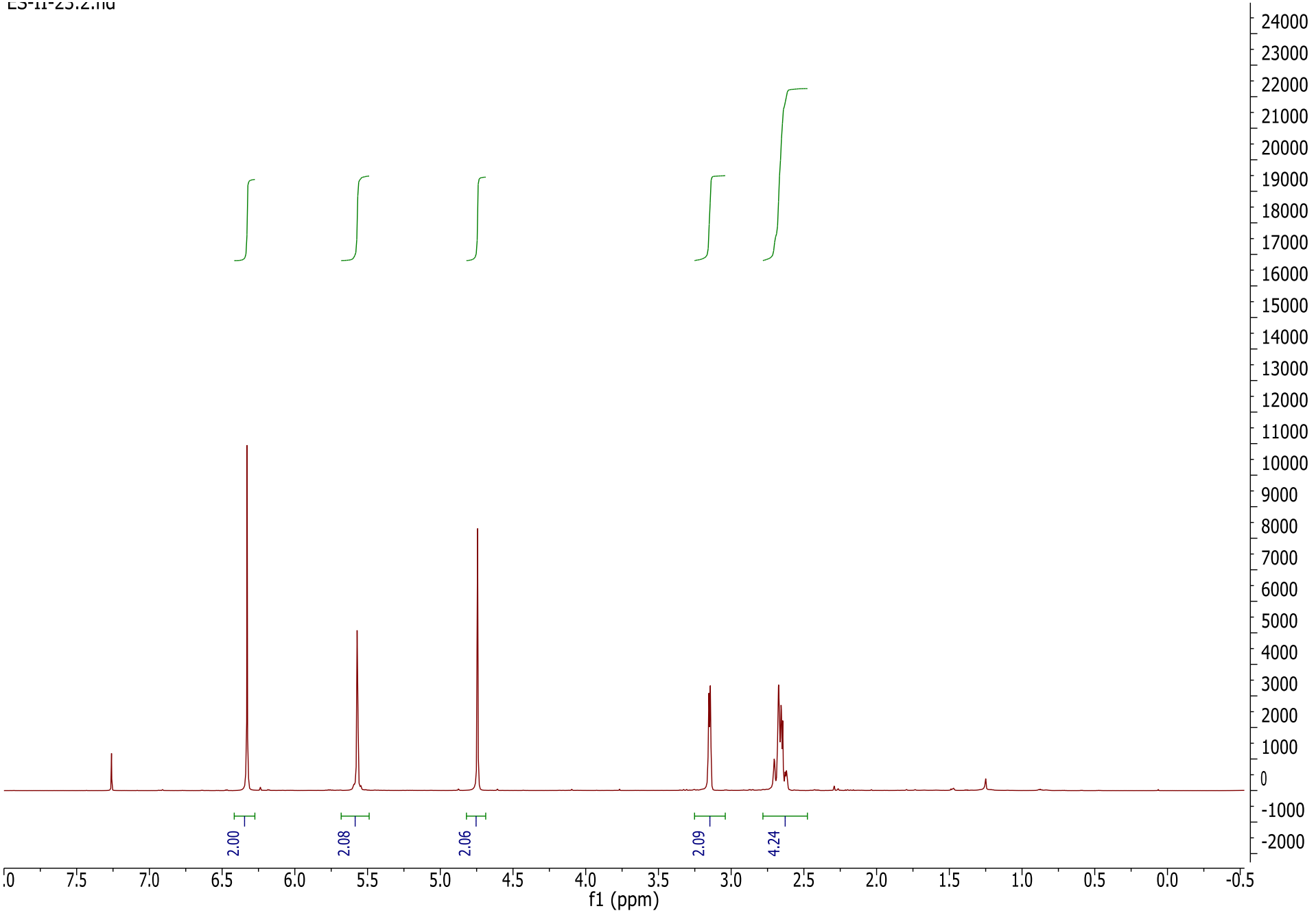


^{1}H NMR of **7c**

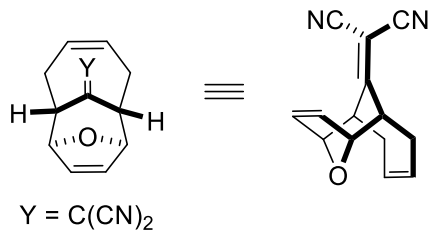


Y = $C(CN)_2$

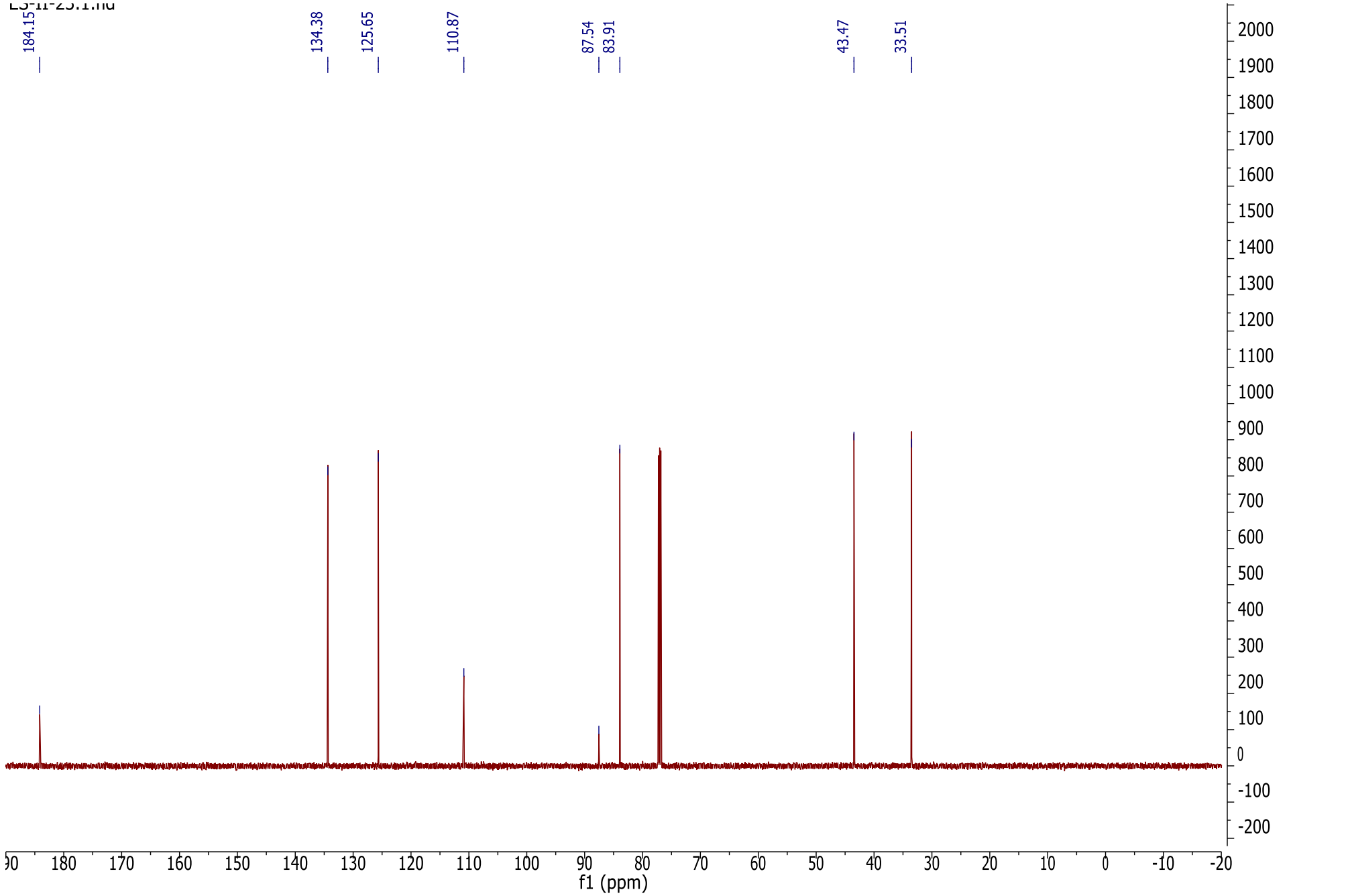
≡



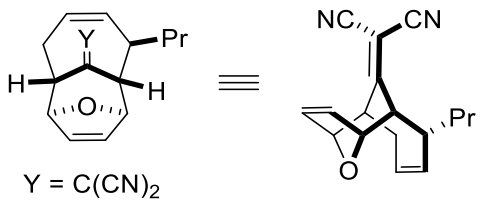
^{13}C NMR of **7c**


Y
H
H
O
Y = C(CN)2

NC
CN
O

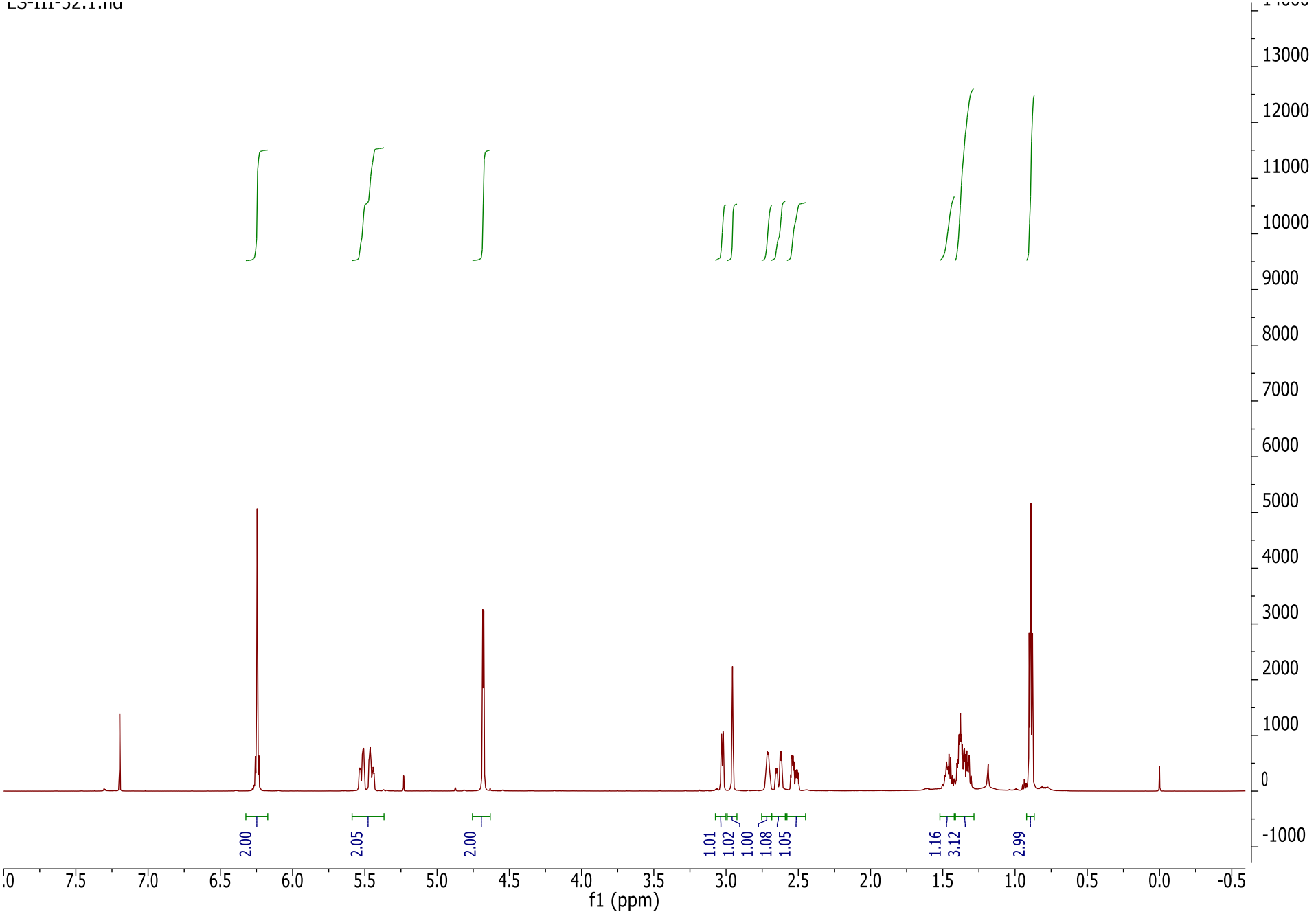

184.15
134.38
125.65
110.87
87.54
83.91
43.47
33.51
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

^{1}H NMR of **7e**

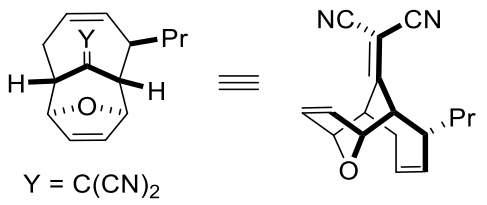

Y
Pr
H
H
O
Y = C(CN)2

≡

NC
CN
Pr
O

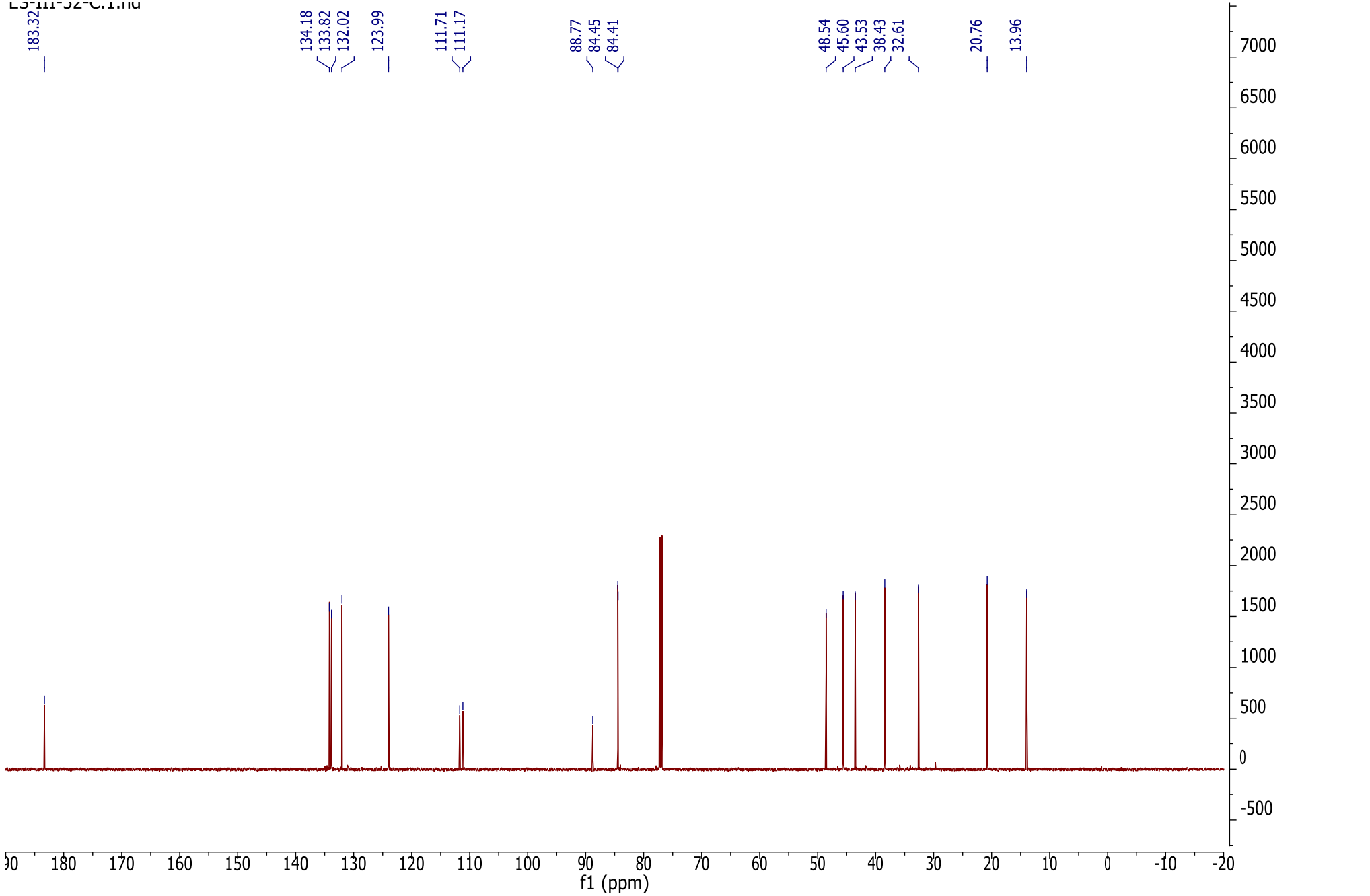

13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
2.00
2.05
2.00
1.01
1.02
1.00
1.08
1.05
1.16
3.12
2.99
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

^{13}C NMR of **7e**

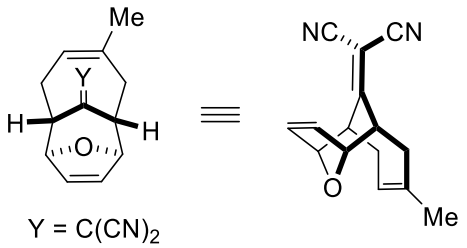

Y
Pr
H
H
O
Y = C(CN)2

≡

NC
CN
Pr
O

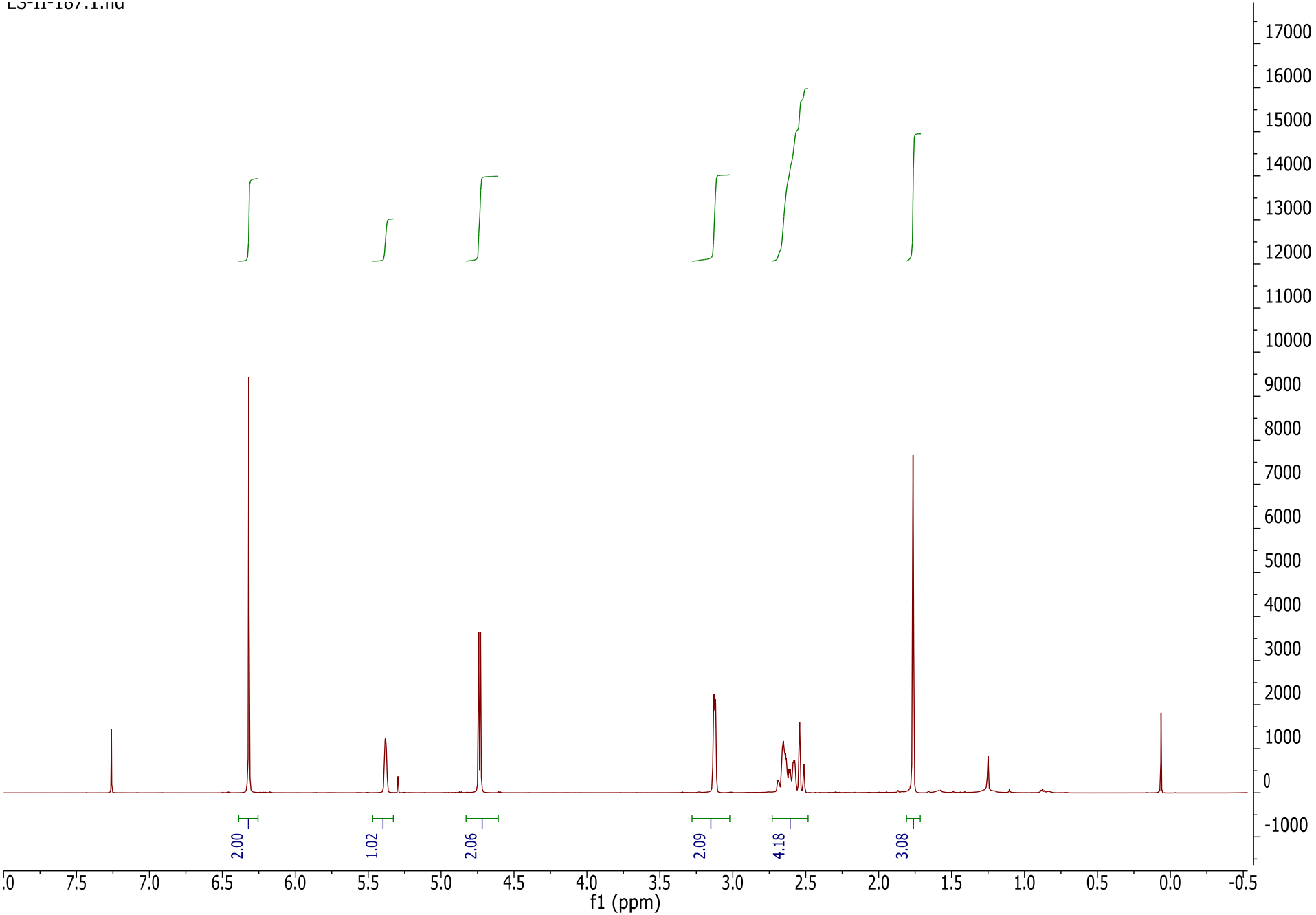

183.32
134.18
133.82
132.02
123.99
111.71
111.17
88.77
84.45
84.41
48.54
45.60
43.53
38.43
32.61
20.76
13.96
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

^{1}H NMR of **7f**

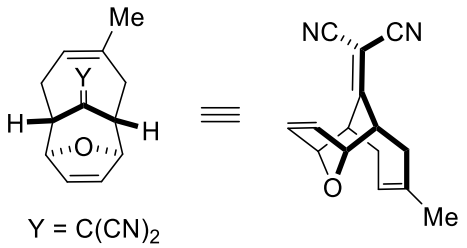

Me
Y
H
H
O
Y = C(CN)2

≡

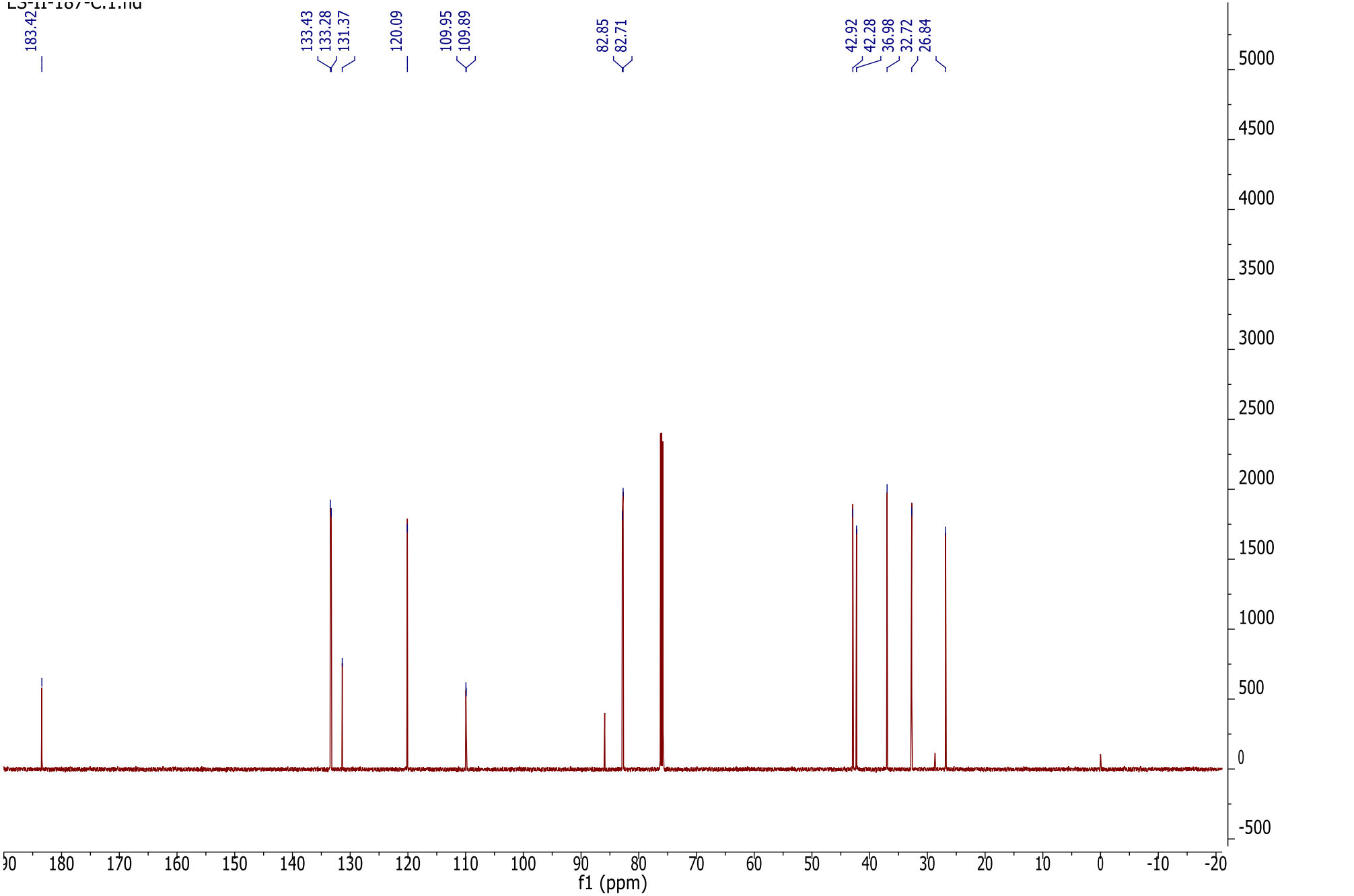
NC
CN
O
Me


17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
2.00
1.02
2.06
2.09
4.18
3.08
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
f1 (ppm)

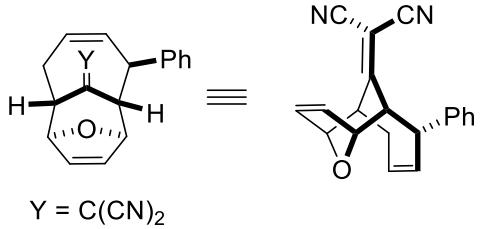
^{13}C NMR of **7f**


Me
Y
H
H
O
Y = C(CN)2

NC
CN
O
Me

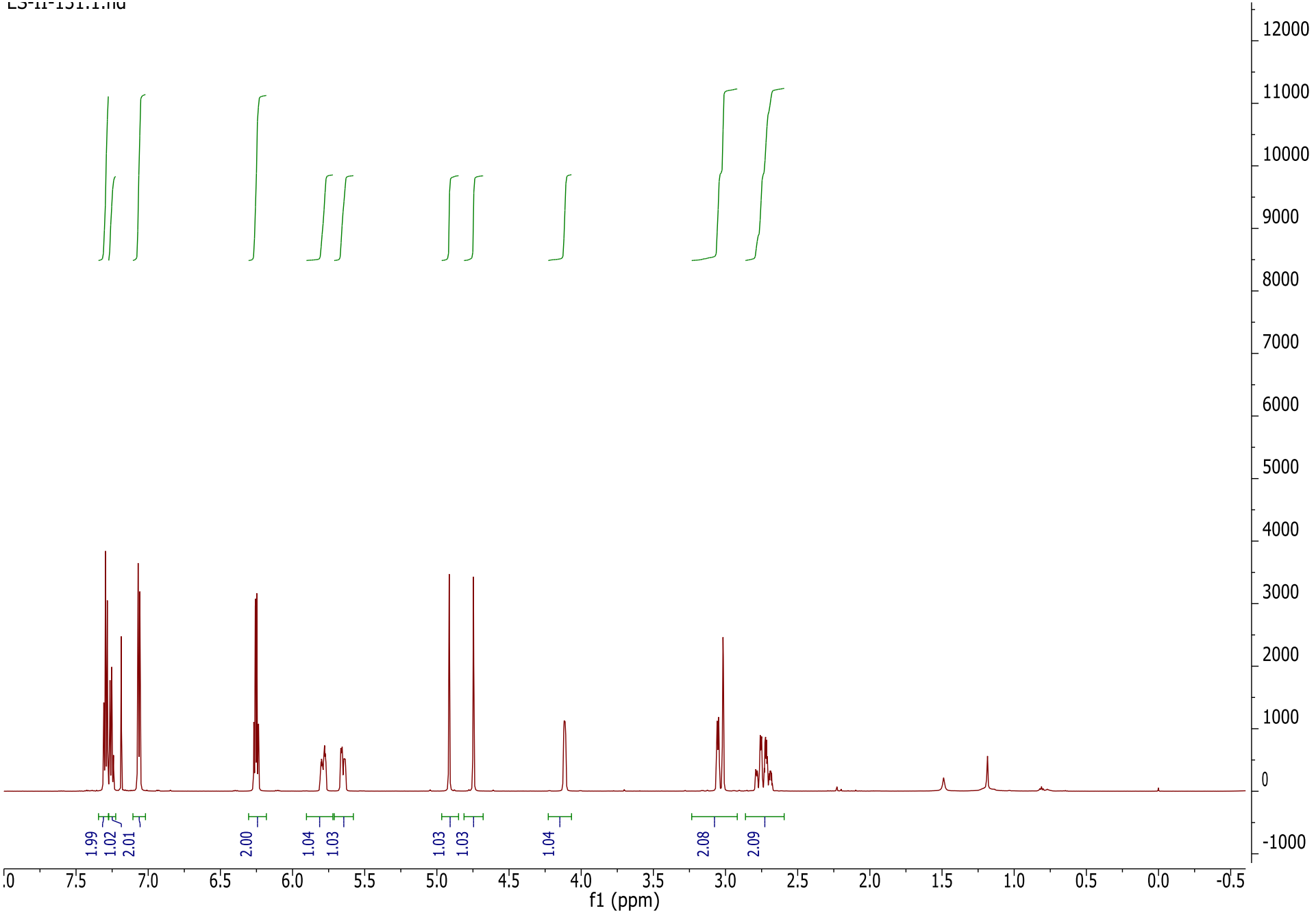

183.42
133.43
133.28
131.37
120.09
109.95
109.89
82.85
82.71
42.92
42.28
36.98
32.72
26.84
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

^{1}H NMR of **7g**

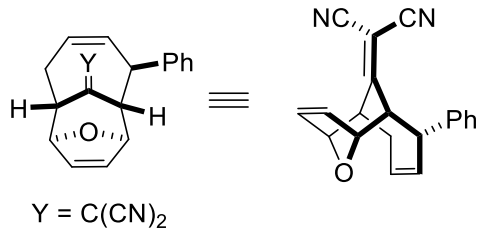


Y = $C(CN)_2$

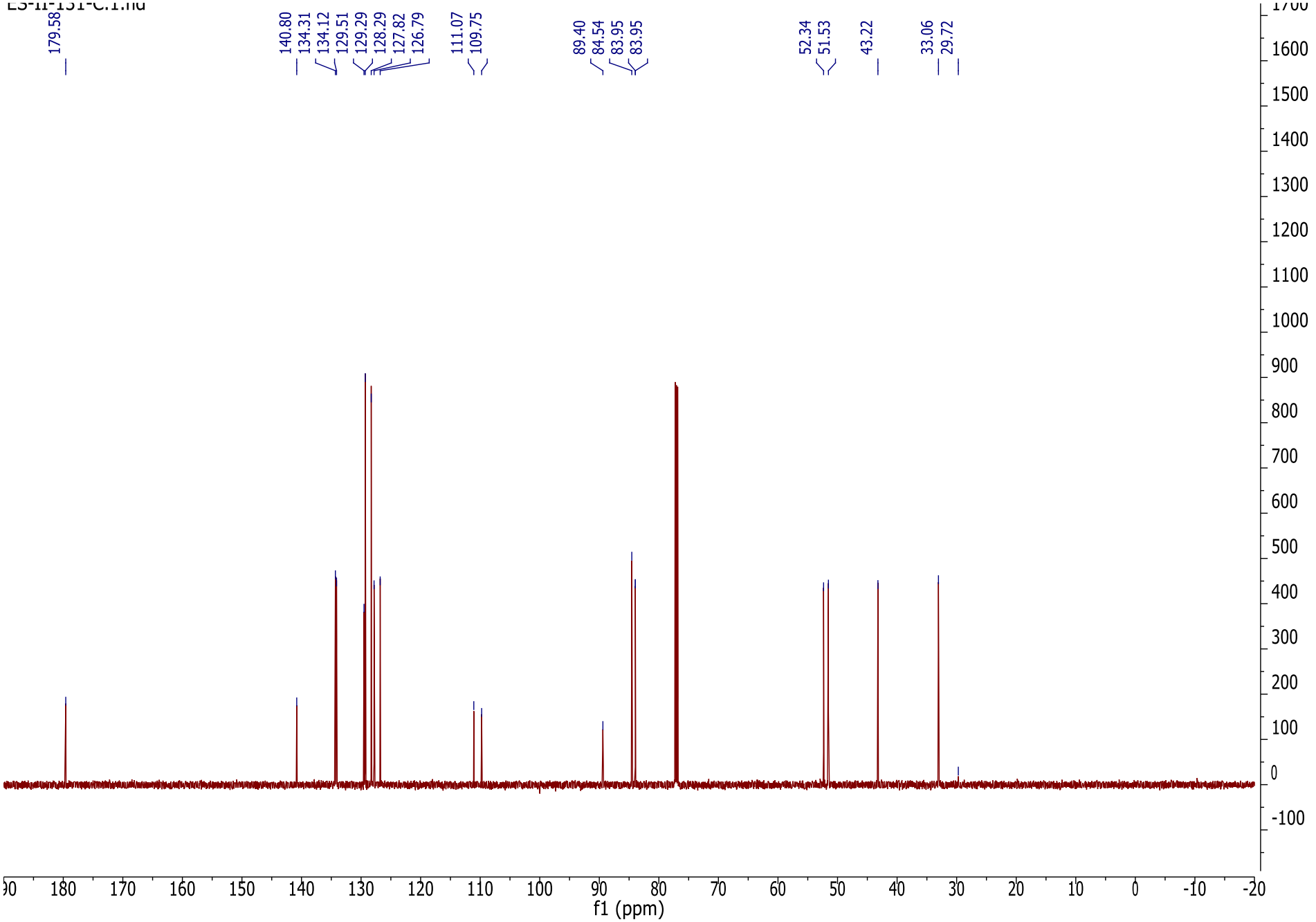
≡



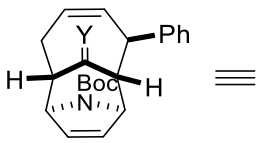
^{13}C NMR of **7g**


Y
Ph
H
H
O
Y = C(CN)2

NC
CN
Ph
O

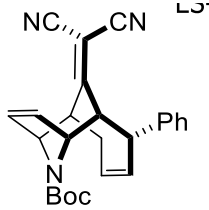

179.58
140.80
134.31
134.12
129.51
129.29
128.29
127.82
126.79
111.07
109.75
89.40
84.54
83.95
83.95
52.34
51.53
43.22
33.06
29.72
f1 (ppm)

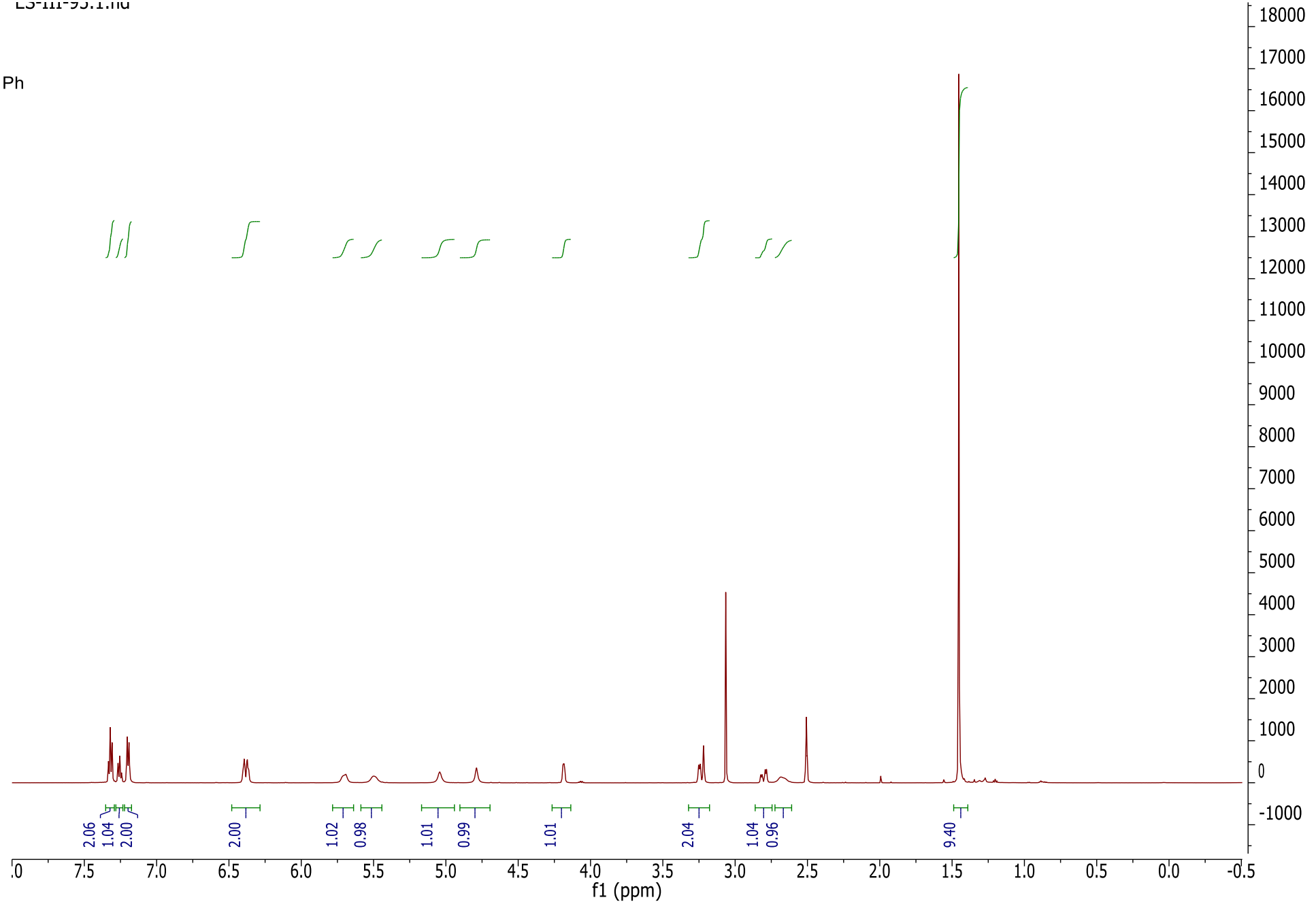
^{1}H NMR of **7h**



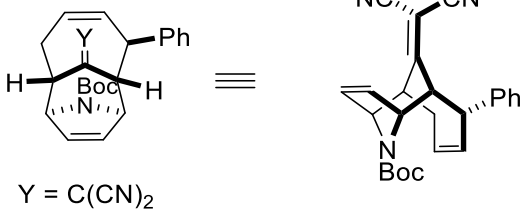
Y = $C(CN)_2$

≡

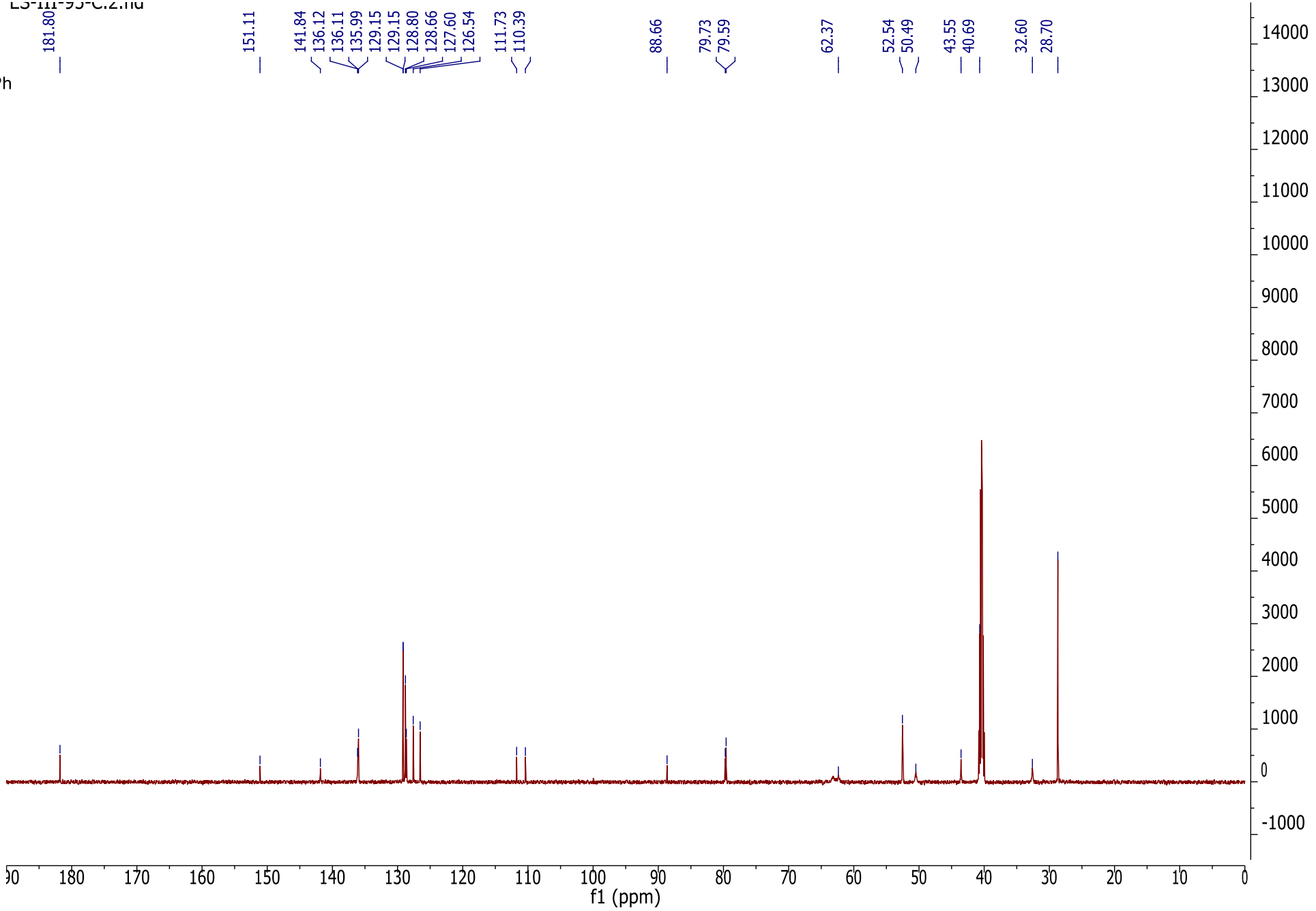




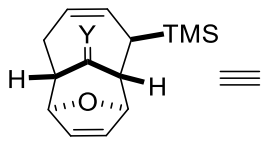
^{13}C NMR of **7h**



Y = $C(CN)_2$

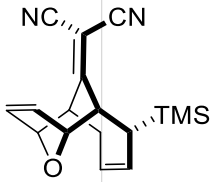


^{1}H NMR of **7k**

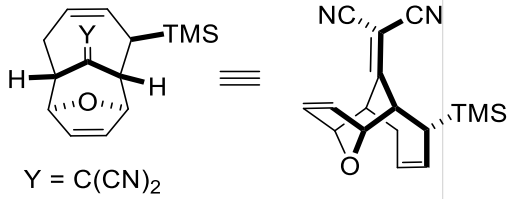


Y = $C(CN)_2$

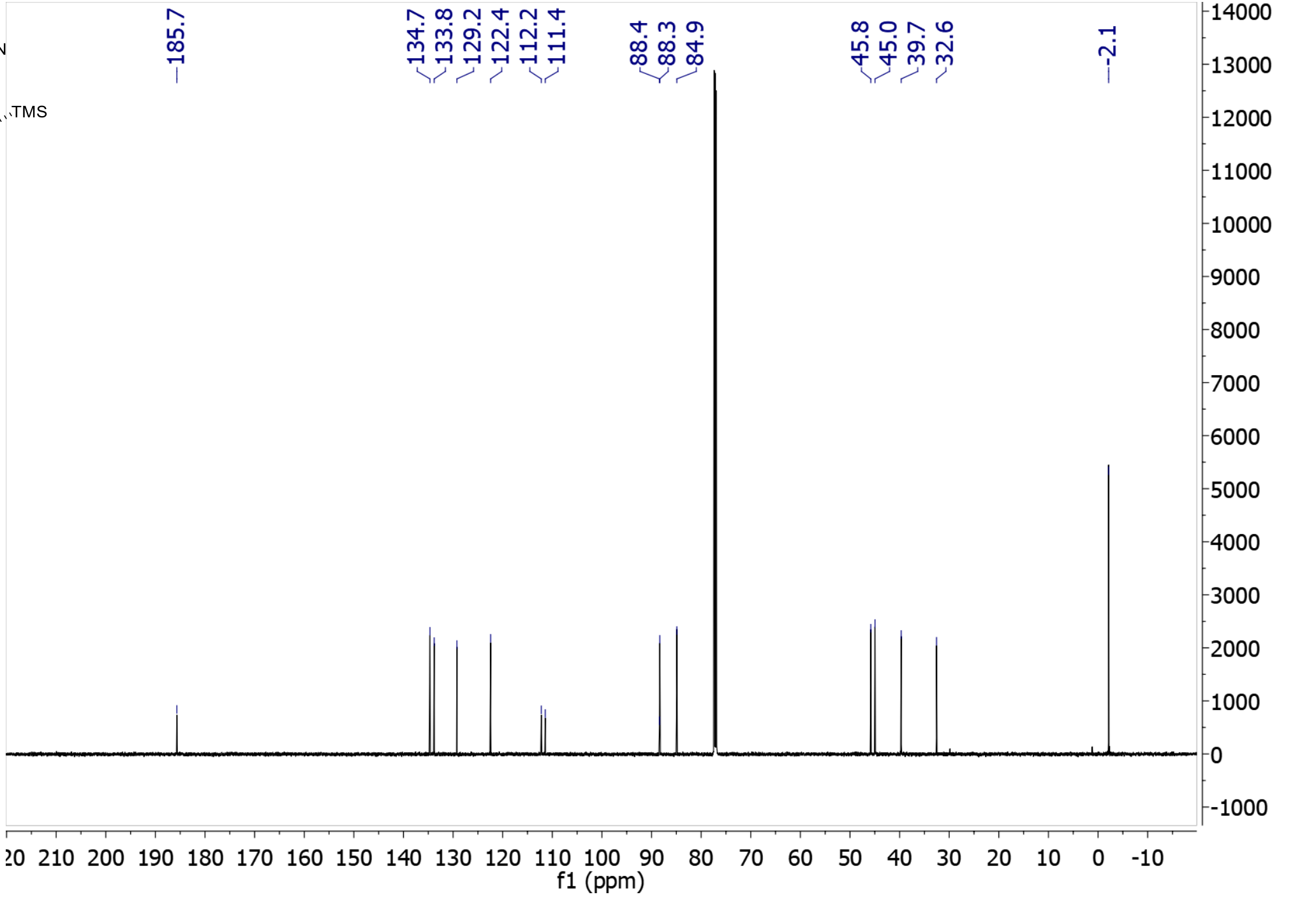
≡



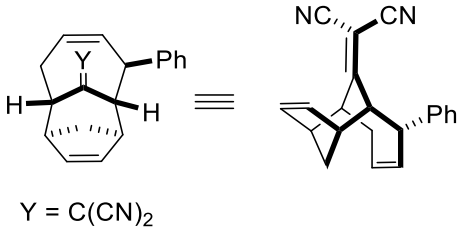
^{13}C NMR of **7k**


Y
TMS
H
H
O
Y = C(CN)2

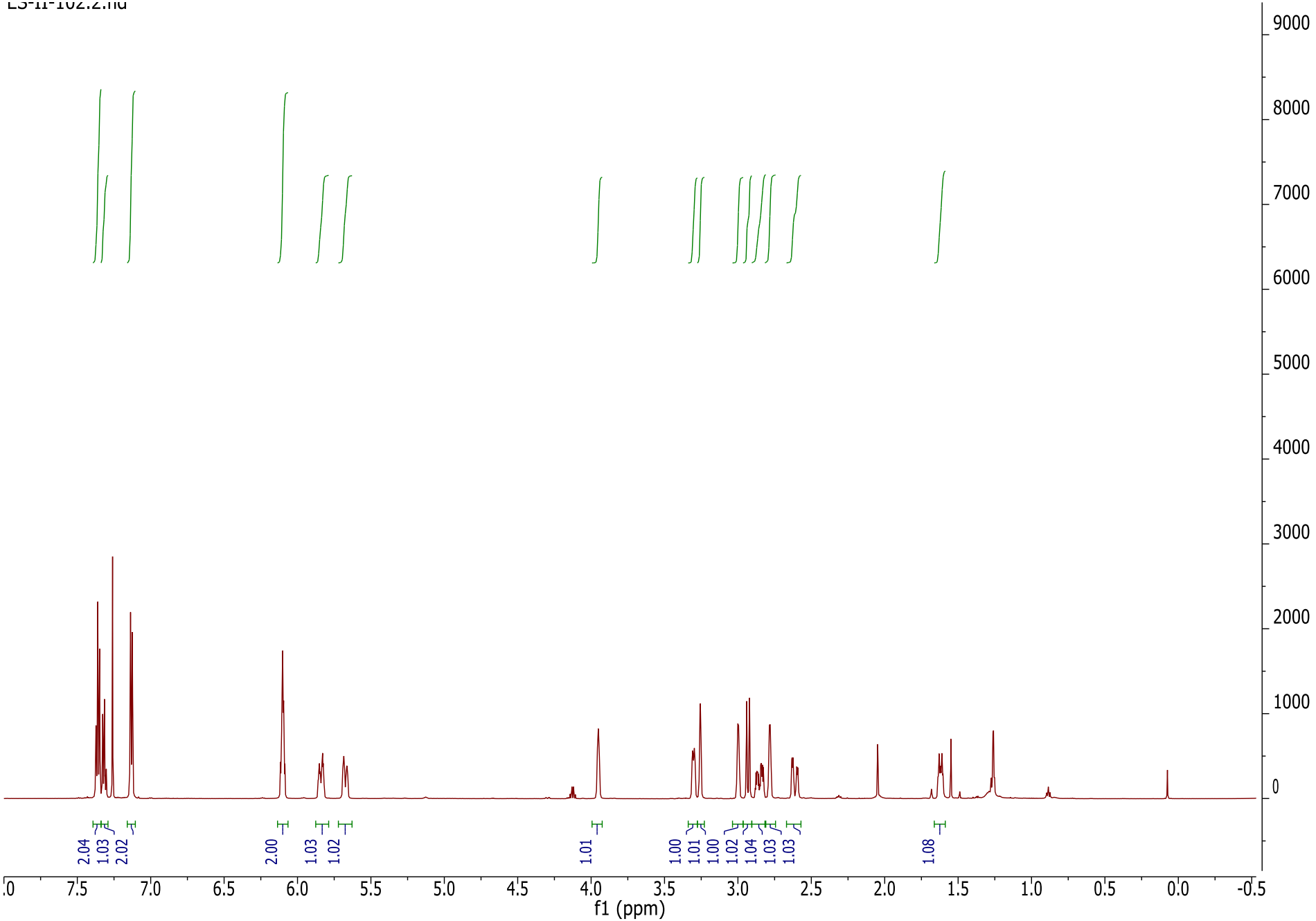
NC
CN
TMS
O


185.7
134.7
133.8
129.2
122.4
112.2
111.4
88.4
88.3
84.9
45.8
45.0
39.7
32.6
2.1
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

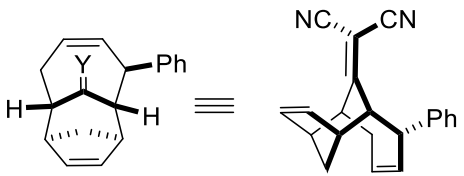
^{1}H NMR of **7l**



Y = $C(CN)_2$

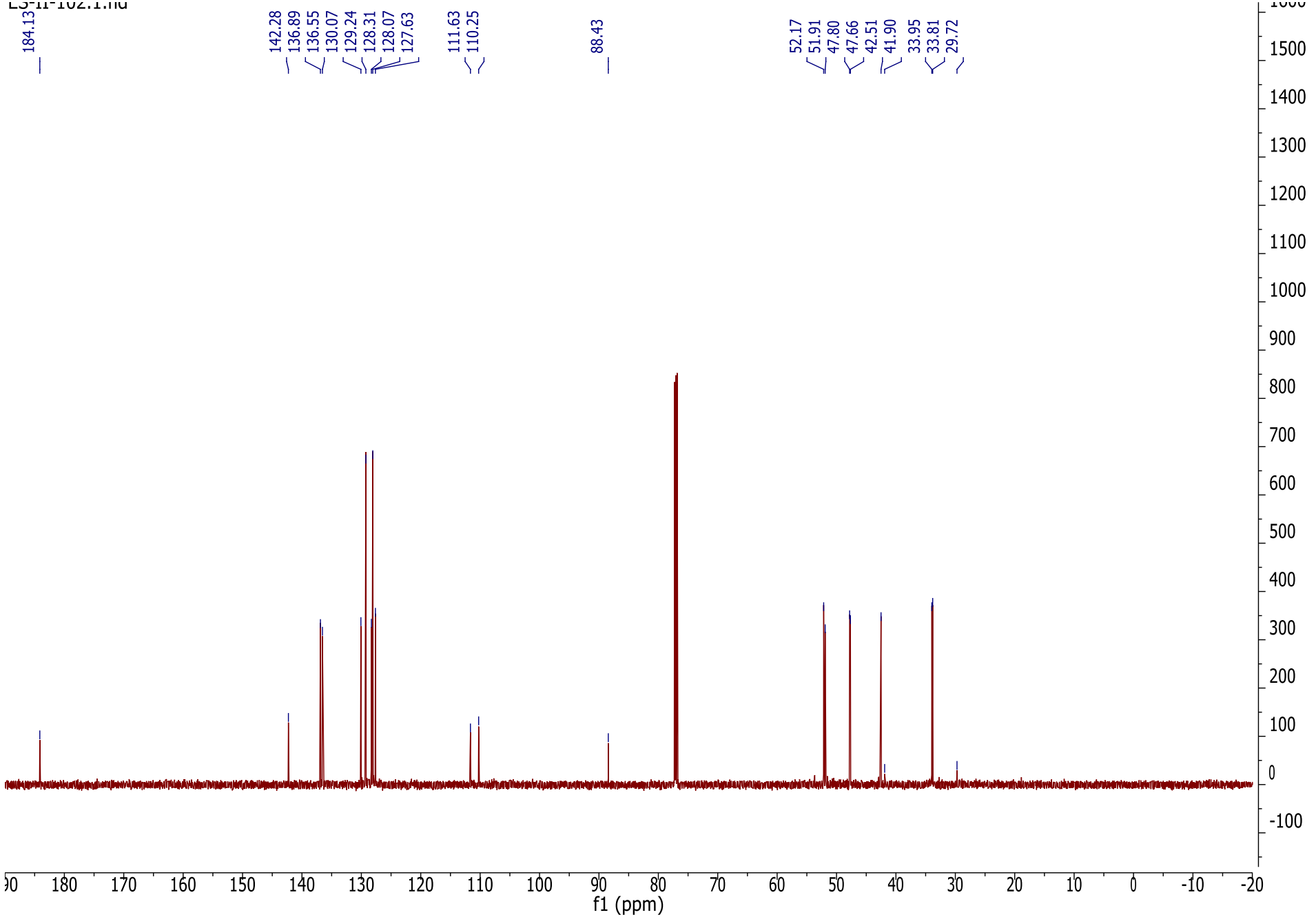


^{13}C NMR of **7l**

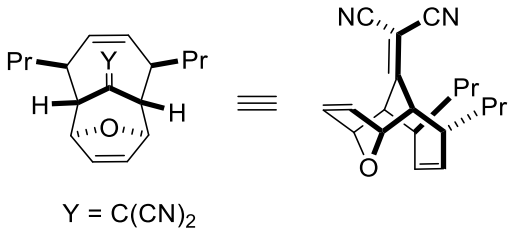


≡

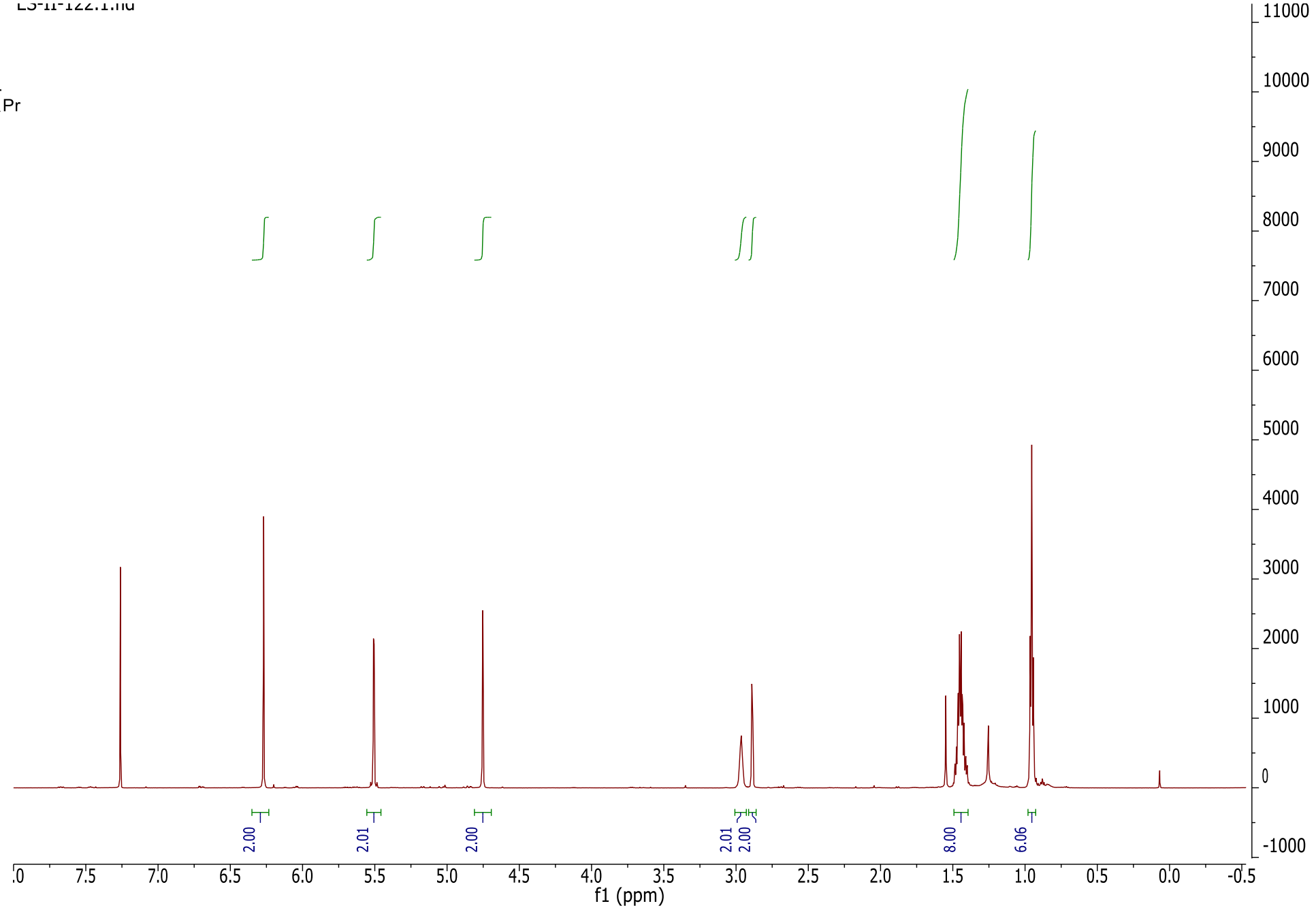
Y = $C(CN)_2$



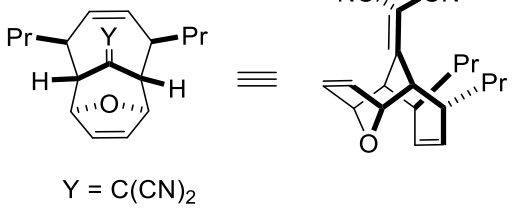
^{1}H NMR of **7n**



Y = $C(CN)_2$

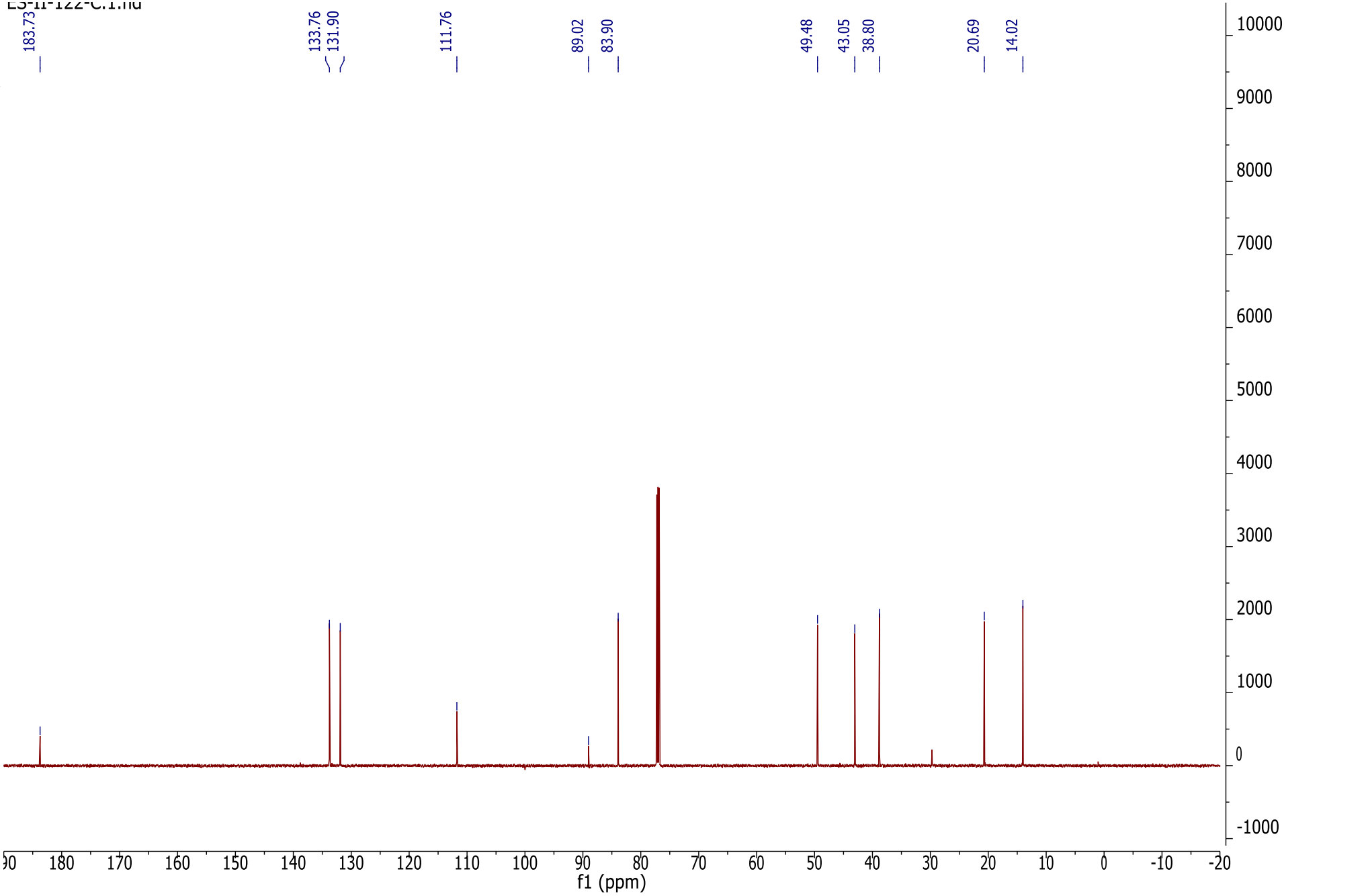


^{13}C NMR of **7n**

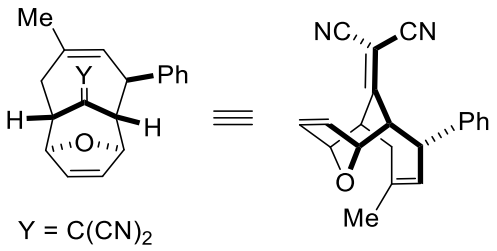


Y = $C(CN)_2$

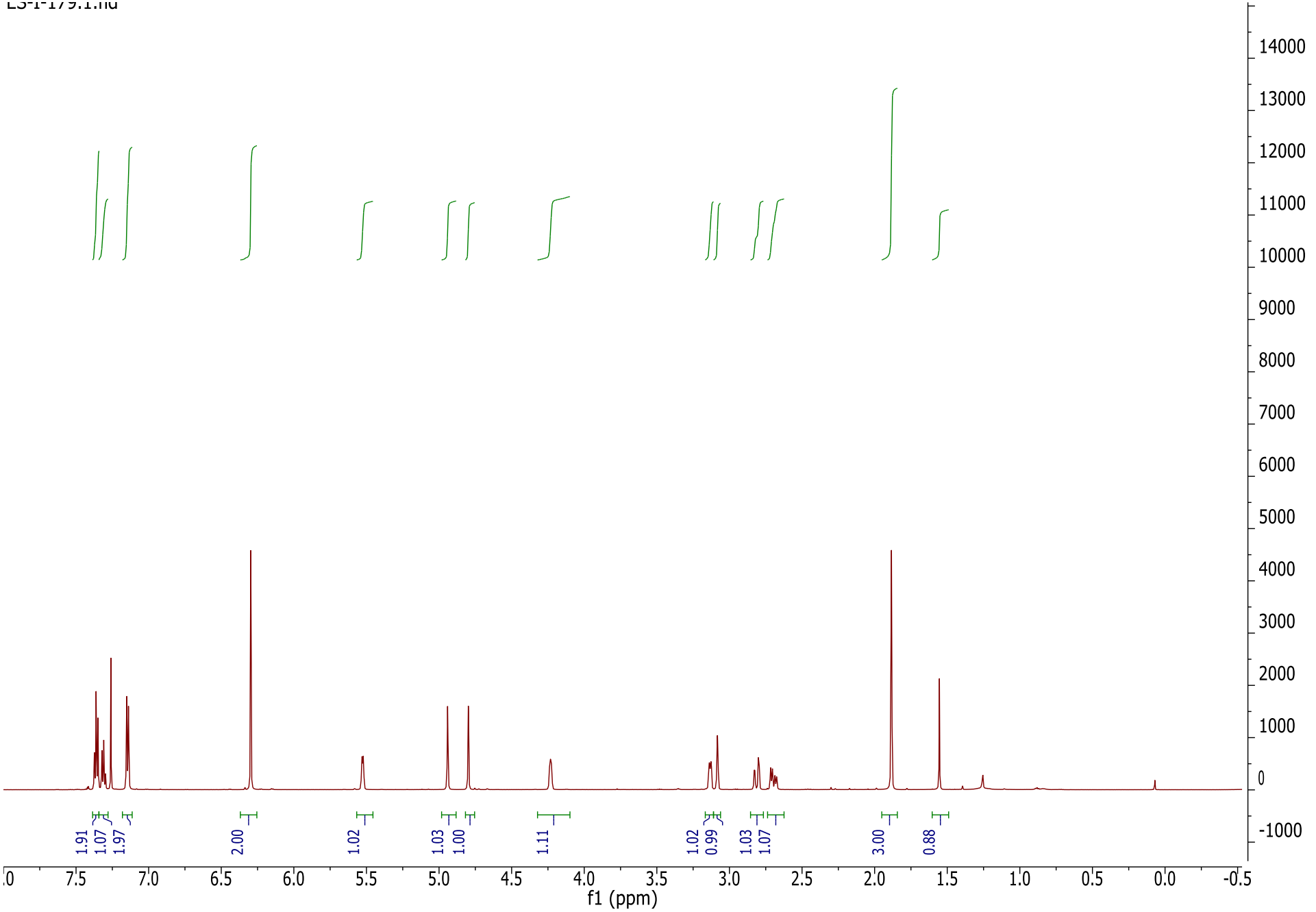
≡



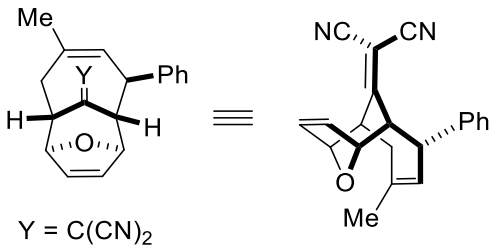
^{1}H NMR of **7o**


Me
Y
Ph
H
H
O
Y = C(CN)2

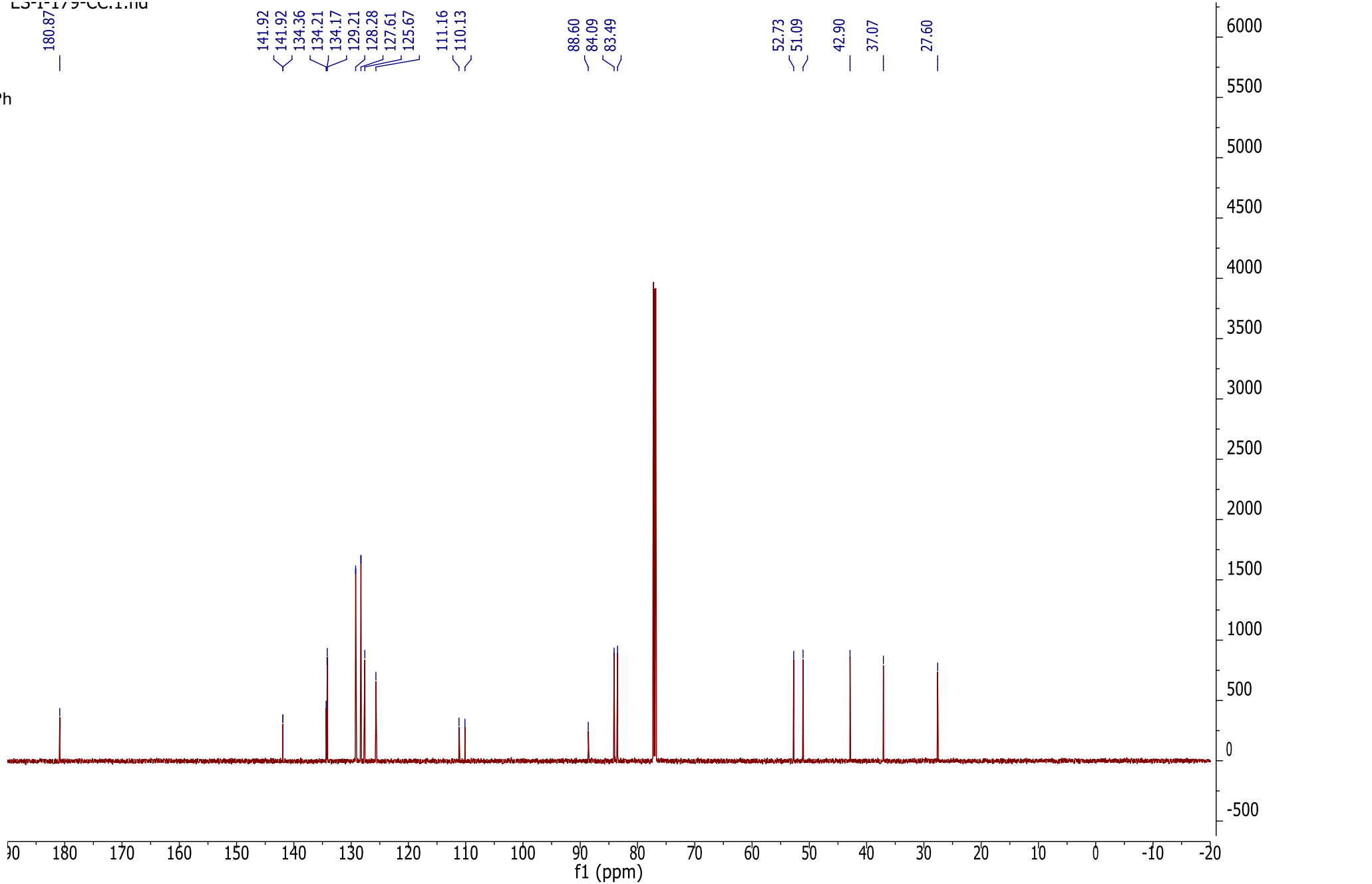
NC
CN
Ph
O
Me


14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
1.91
1.07
1.97
2.00
1.02
1.03
1.00
1.11
1.02
0.99
1.03
1.07
3.00
0.88
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
f1 (ppm)

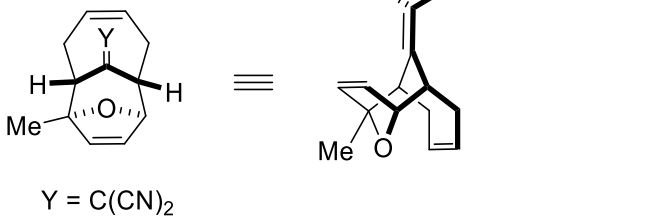
^{13}C NMR of **7o**


Me
Y
Ph
H
H
O
Y = C(CN)2

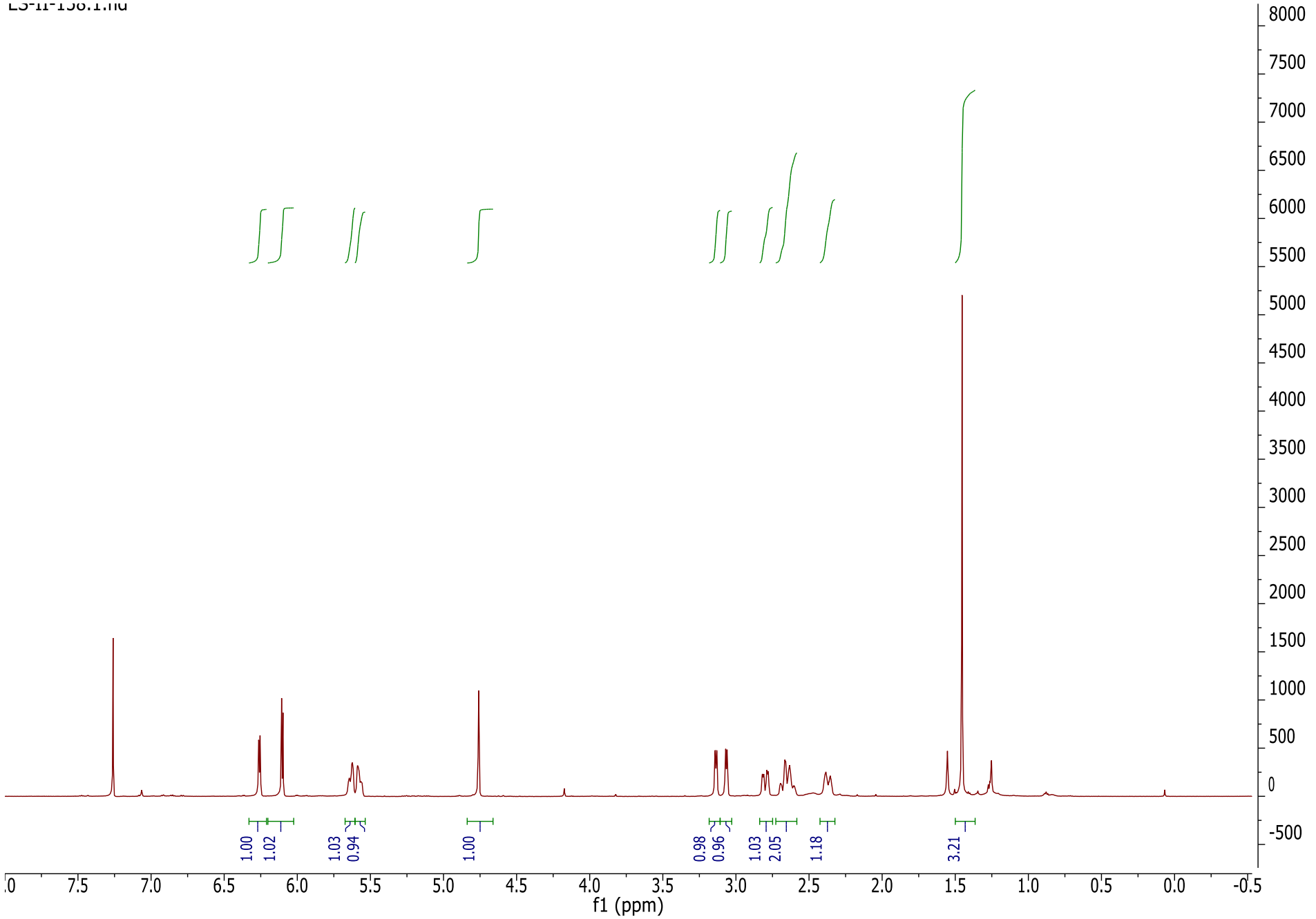
NC
CN
Ph
O
Me


180.87
141.92
141.92
134.36
134.21
134.17
129.21
128.28
127.61
125.67
111.16
110.13
88.60
84.09
83.49
52.73
51.09
42.90
37.07
27.60
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

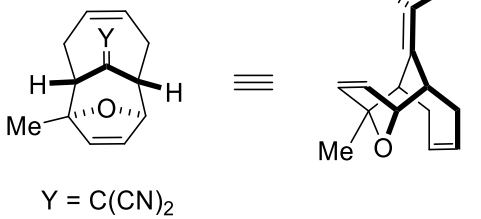
^{1}H NMR of **7d**



Y = $C(CN)_2$

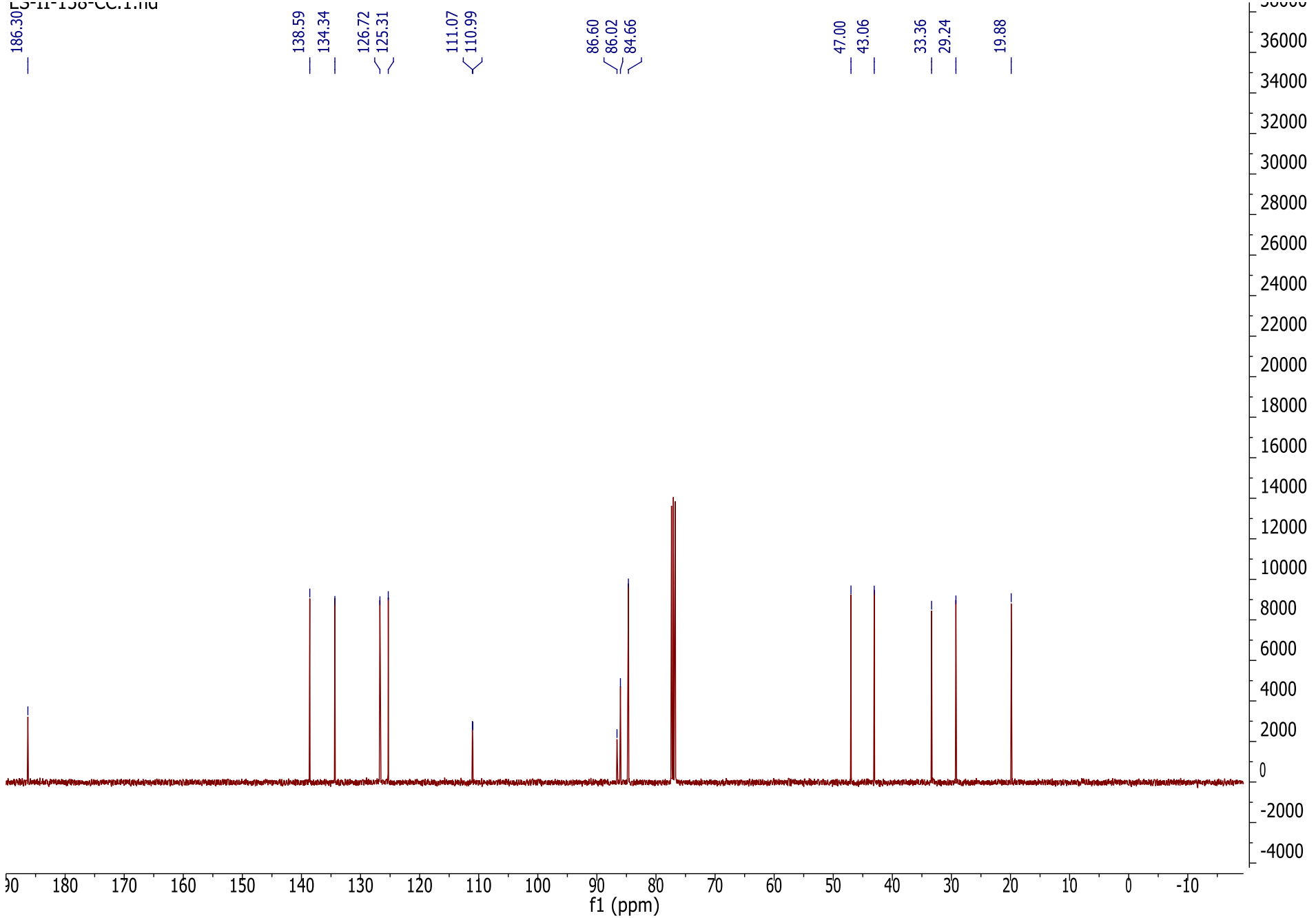


^{13}C NMR of **7d**

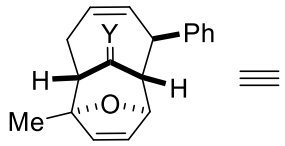


Y = $C(CN)_2$

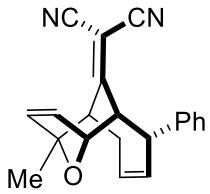
≡



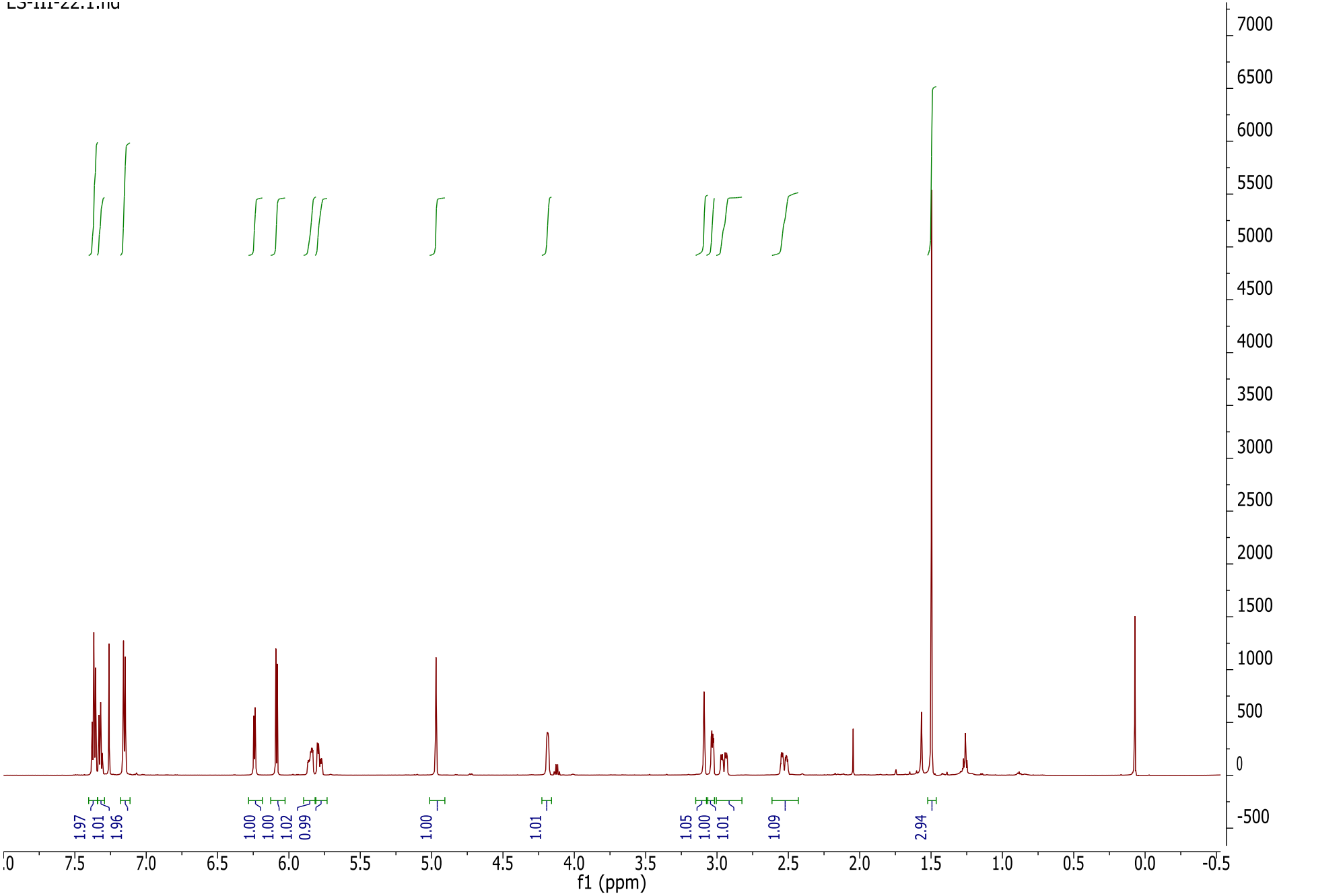
^{1}H NMR of **7i**



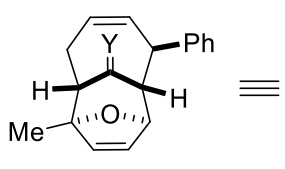
≡



Y = $C(CN)_2$

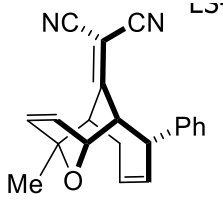


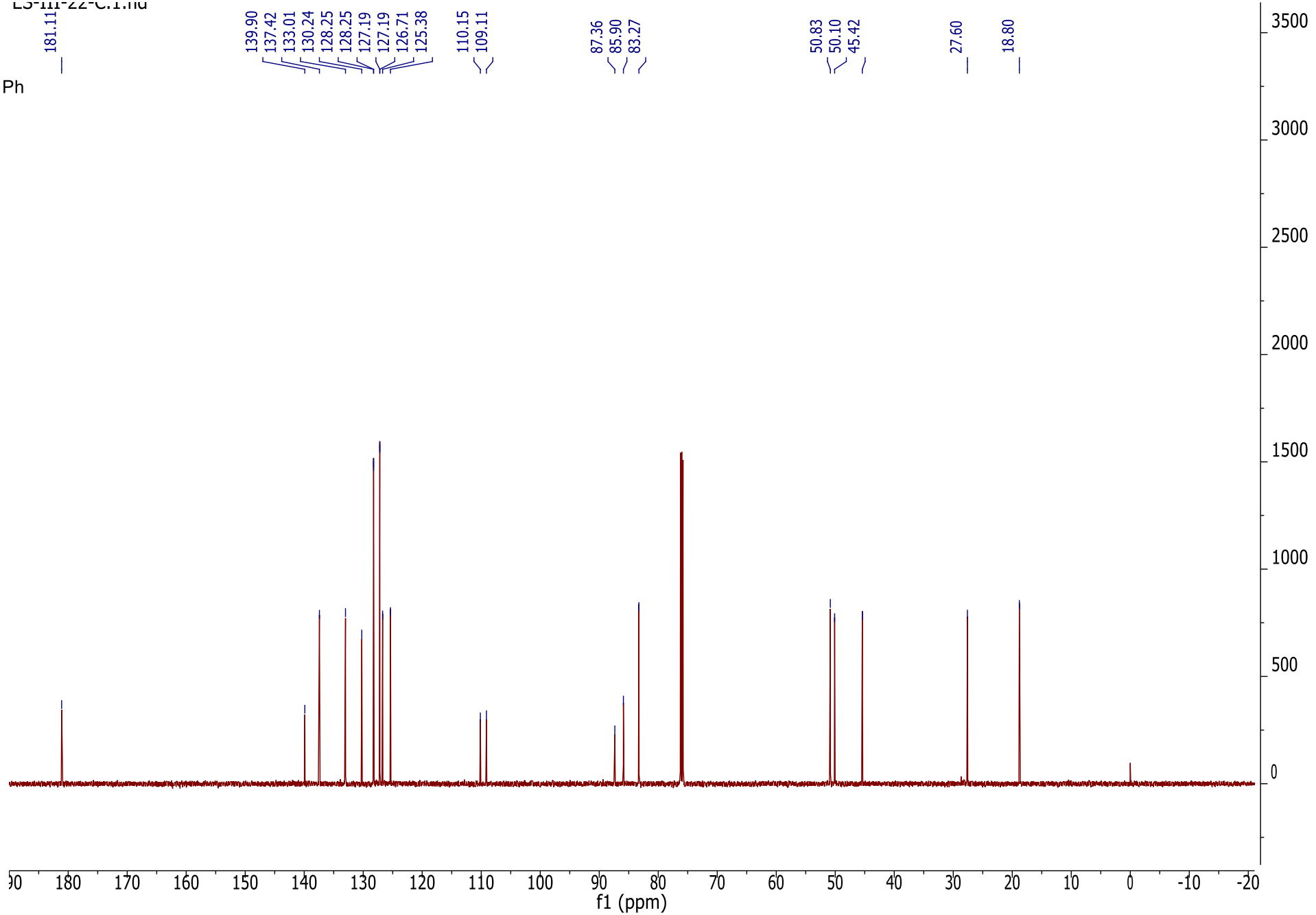
^{13}C NMR of **7i**



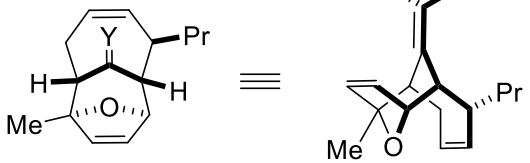
Y = $C(CN)_2$

≡



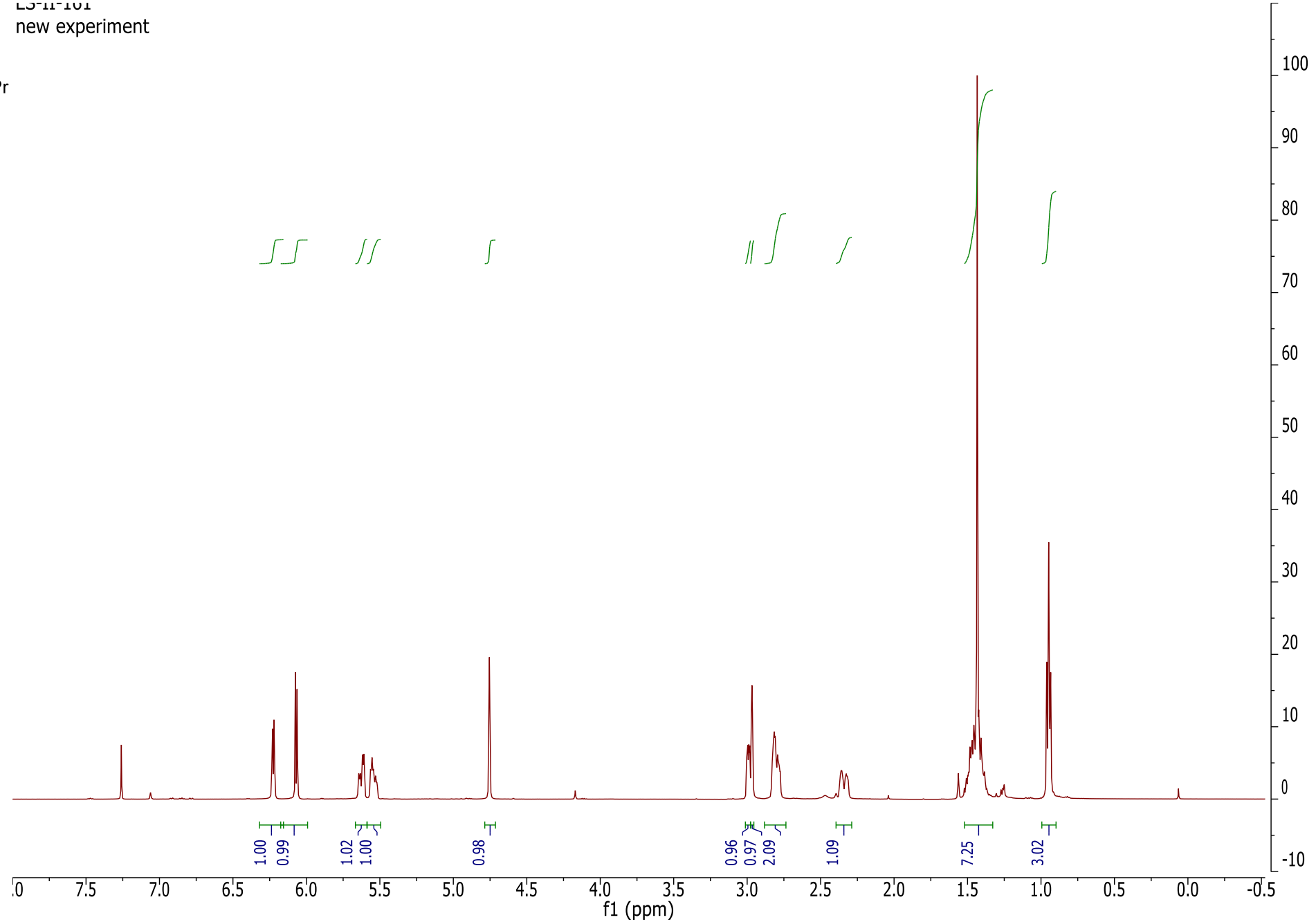


^{1}H NMR of **7j**

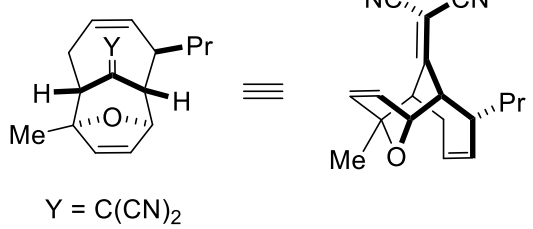


Y = $C(CN)_2$

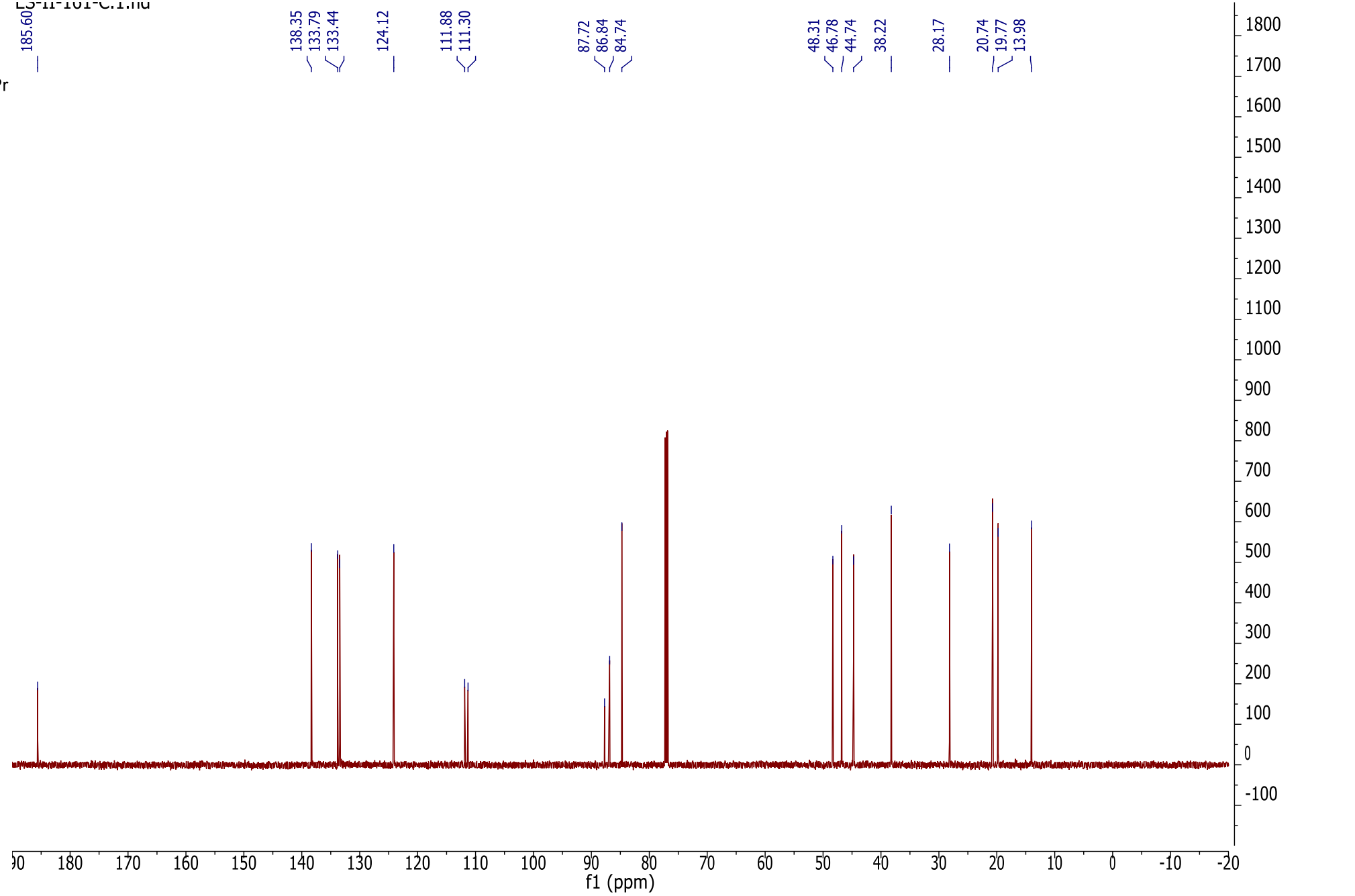
LS-H-101
new experiment



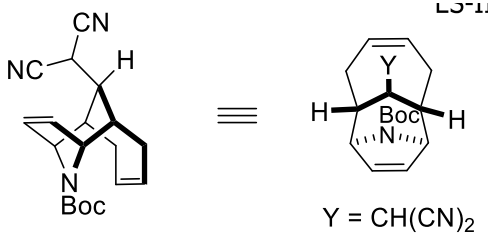
^{13}C NMR of **7j**


Y
Pr
H
H
Me
O
Y = C(CN)2

NC
CN
Pr
Me
O

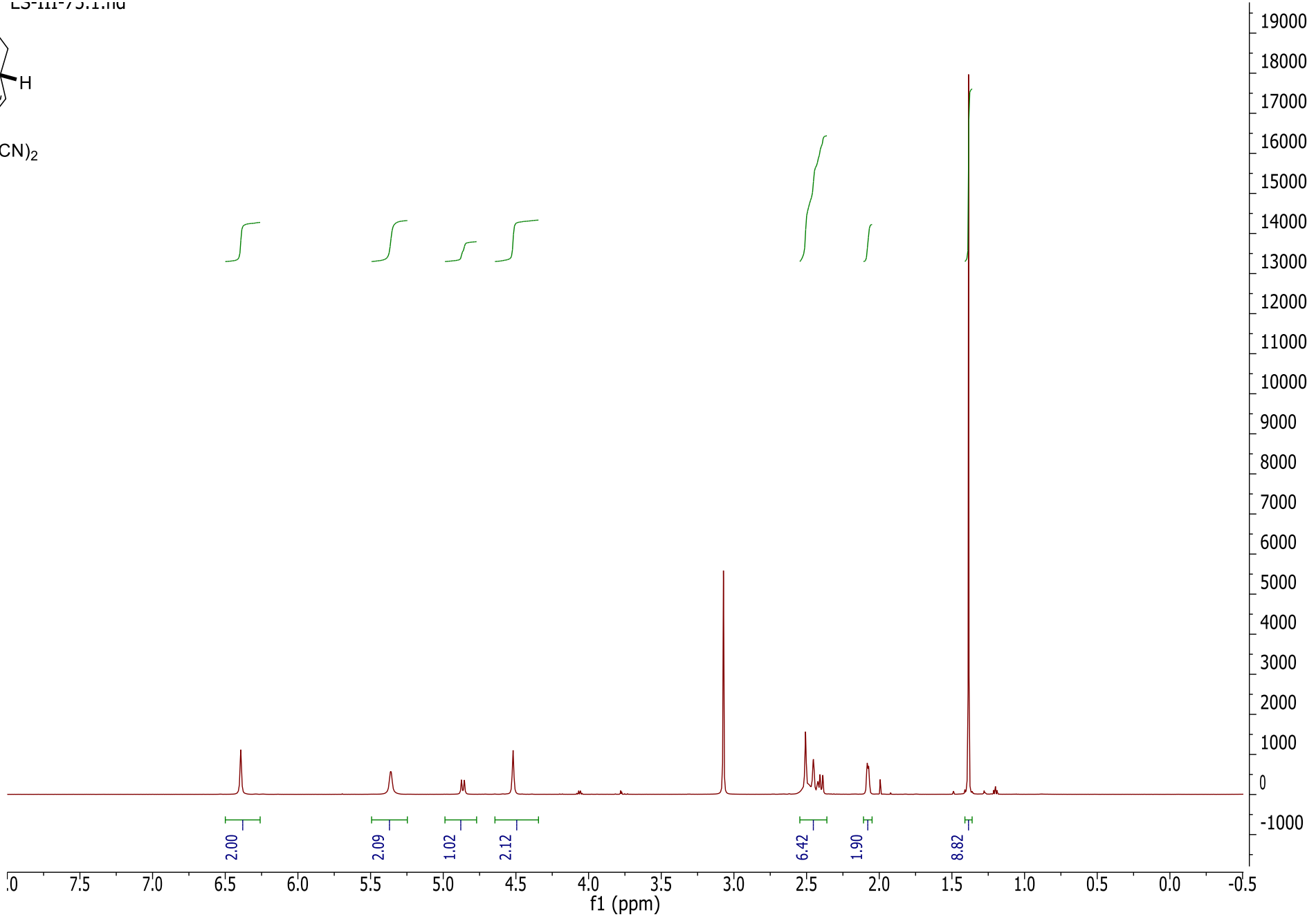

185.60
138.35
133.79
133.44
124.12
111.88
111.30
87.72
86.84
84.74
48.31
46.78
44.74
38.22
28.17
20.74
19.77
13.98
f1 (ppm)

^{1}H NMR of **10**

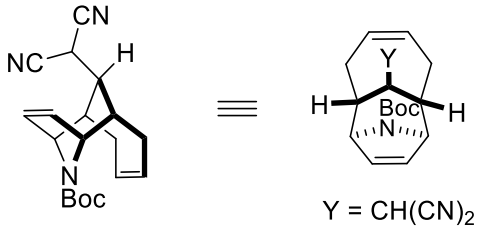


≡

Y = $CH(CN)_2$

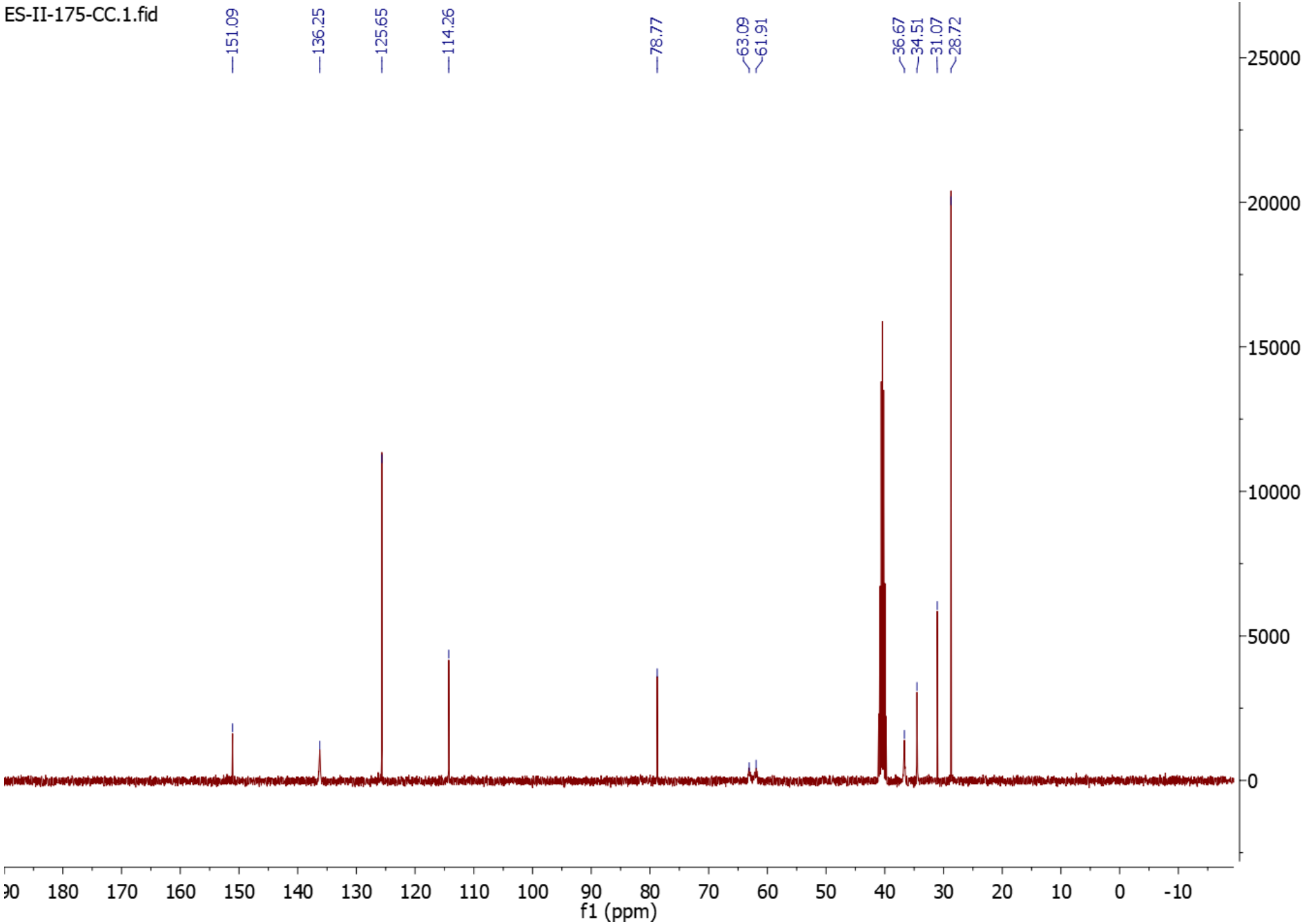


^{13}C NMR of **10**

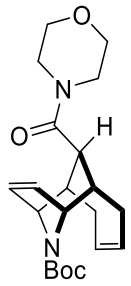


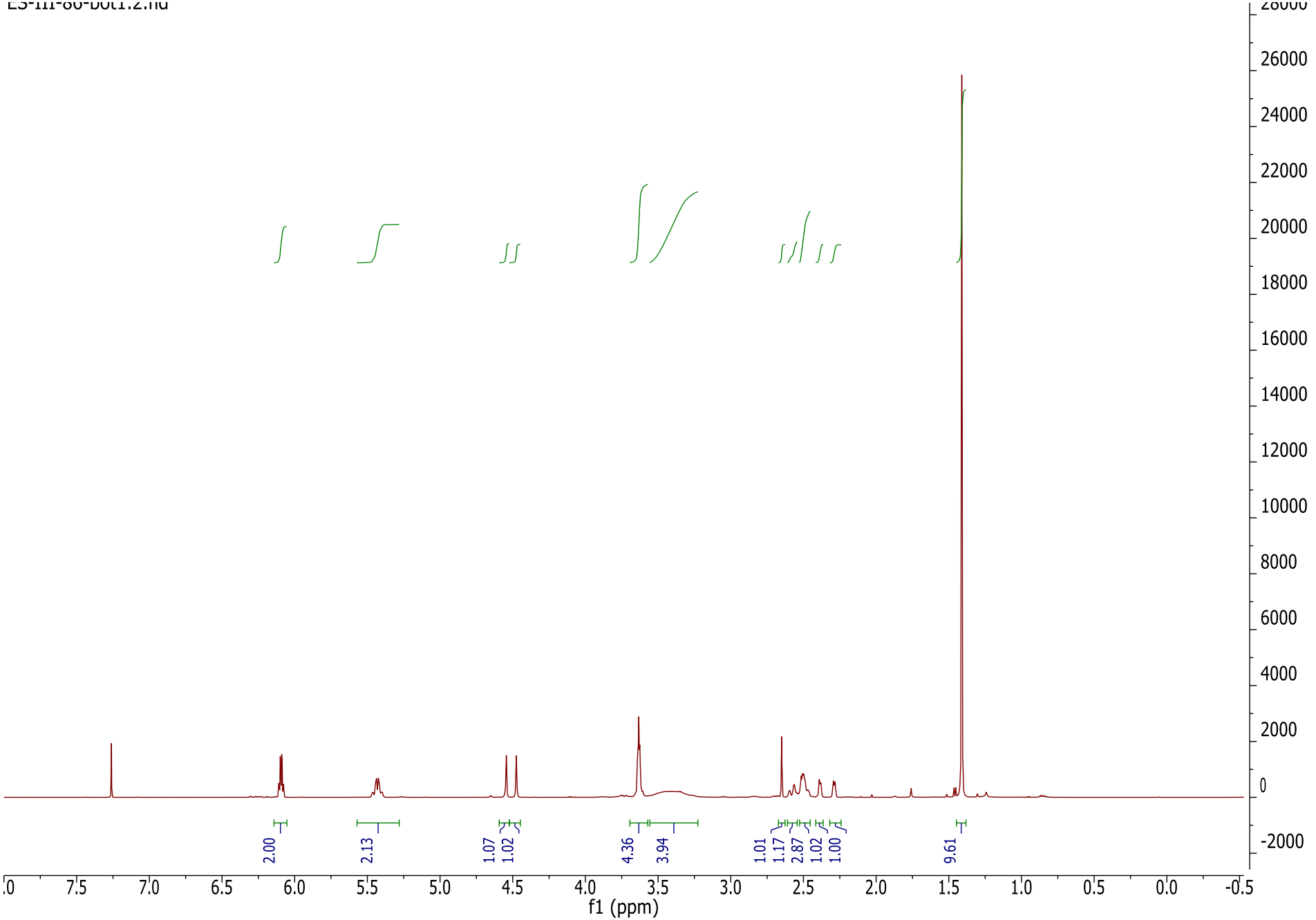
≡

Y = $CH(CN)_2$

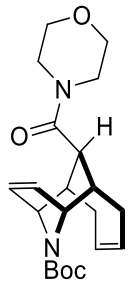


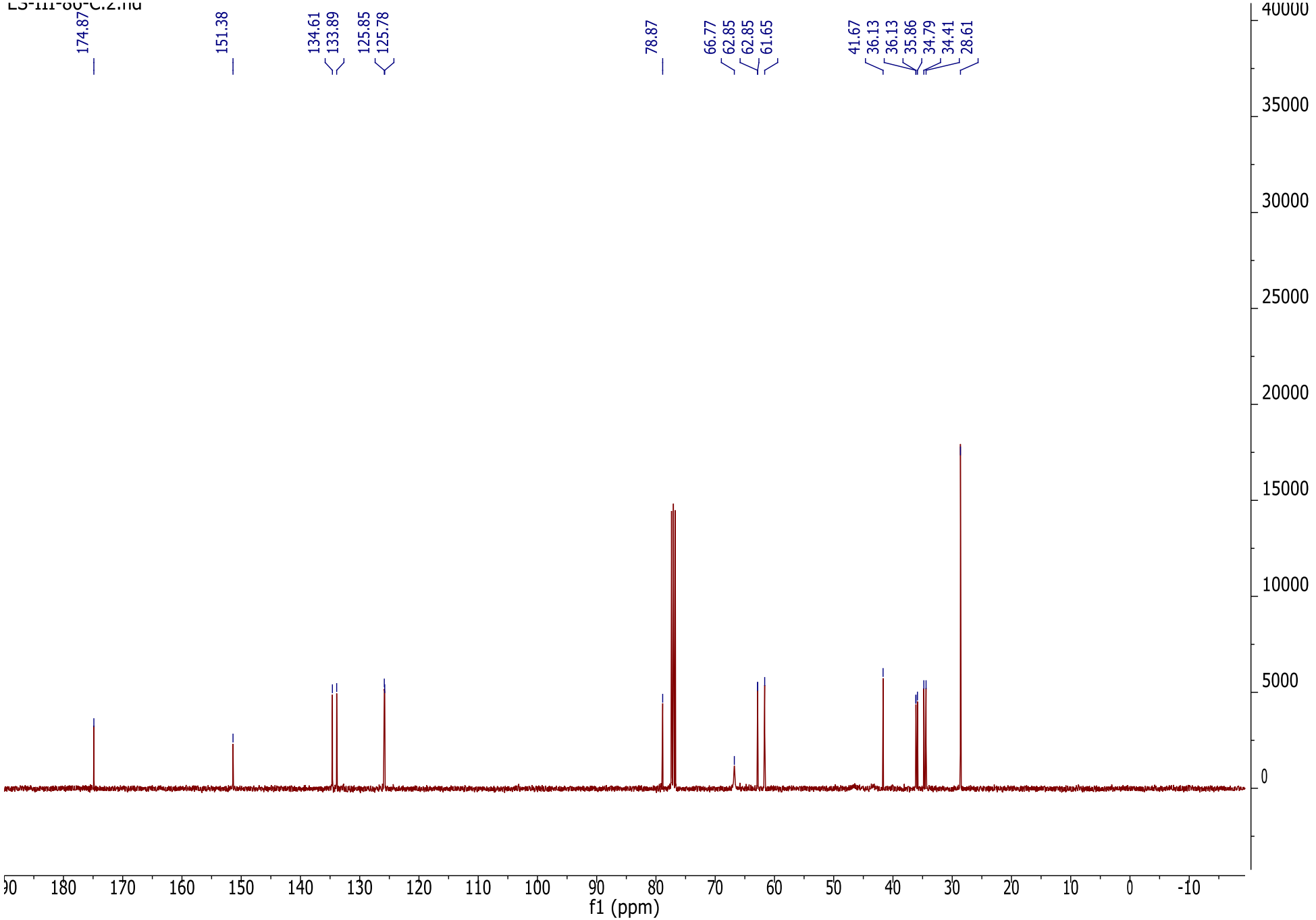
^{1}H NMR of **11a**


O
N
O
H
N
Boc

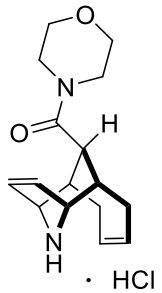

ES-III-80-b0t1.2.nd
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
2.00
2.13
1.07
1.02
4.36
3.94
1.01
1.17
2.87
1.02
1.00
9.61
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

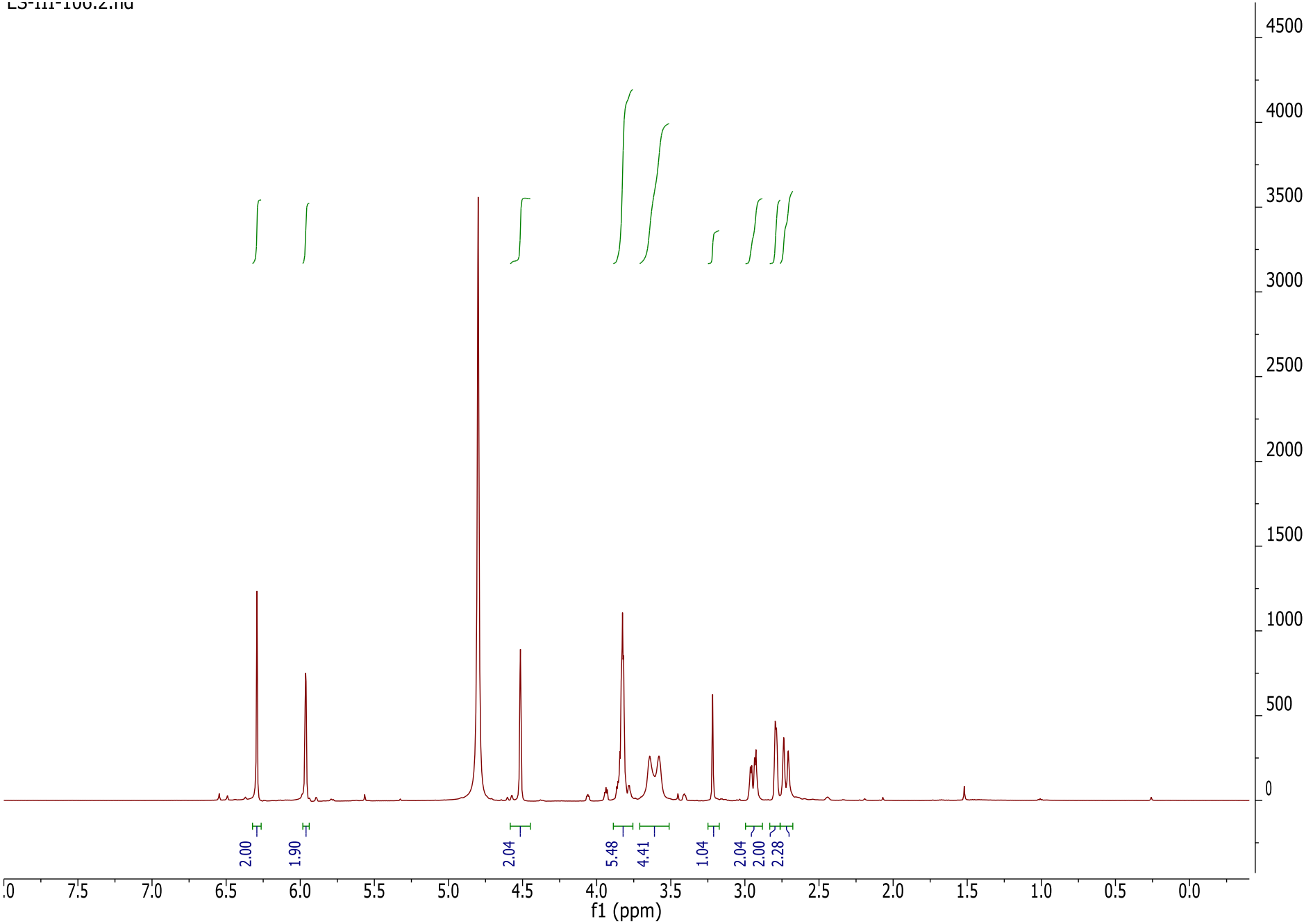
^{13}C NMR of **11a**



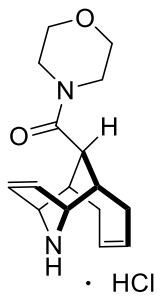


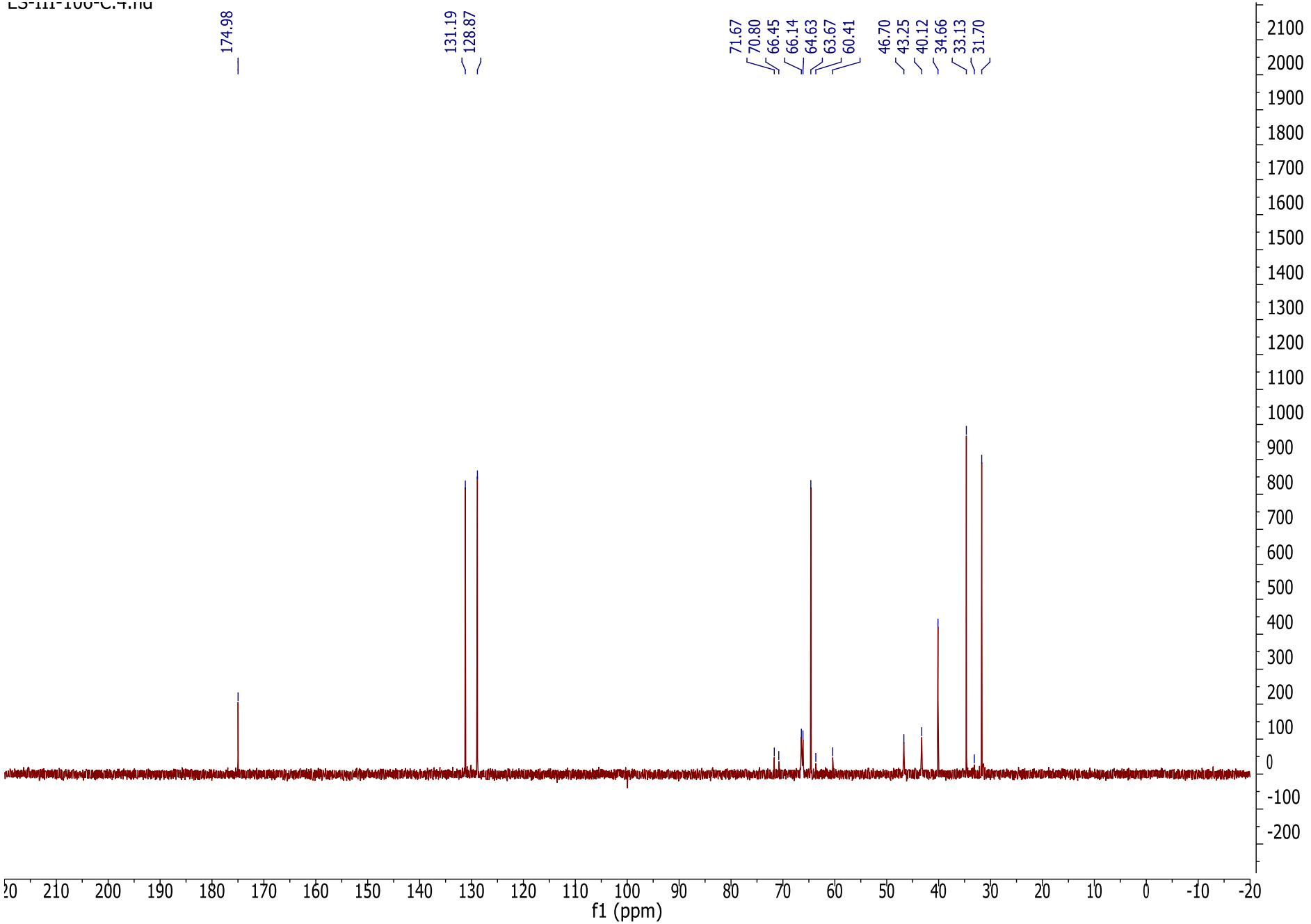
^{1}H NMR of **11b**


O
N
O
H
N
H
· HCl

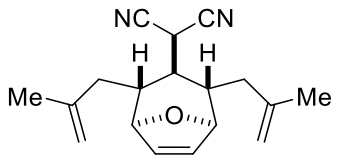

4500
4000
3500
3000
2500
2000
1500
1000
500
0
2.00
1.90
2.04
5.48
4.41
1.04
2.04
2.00
2.28
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

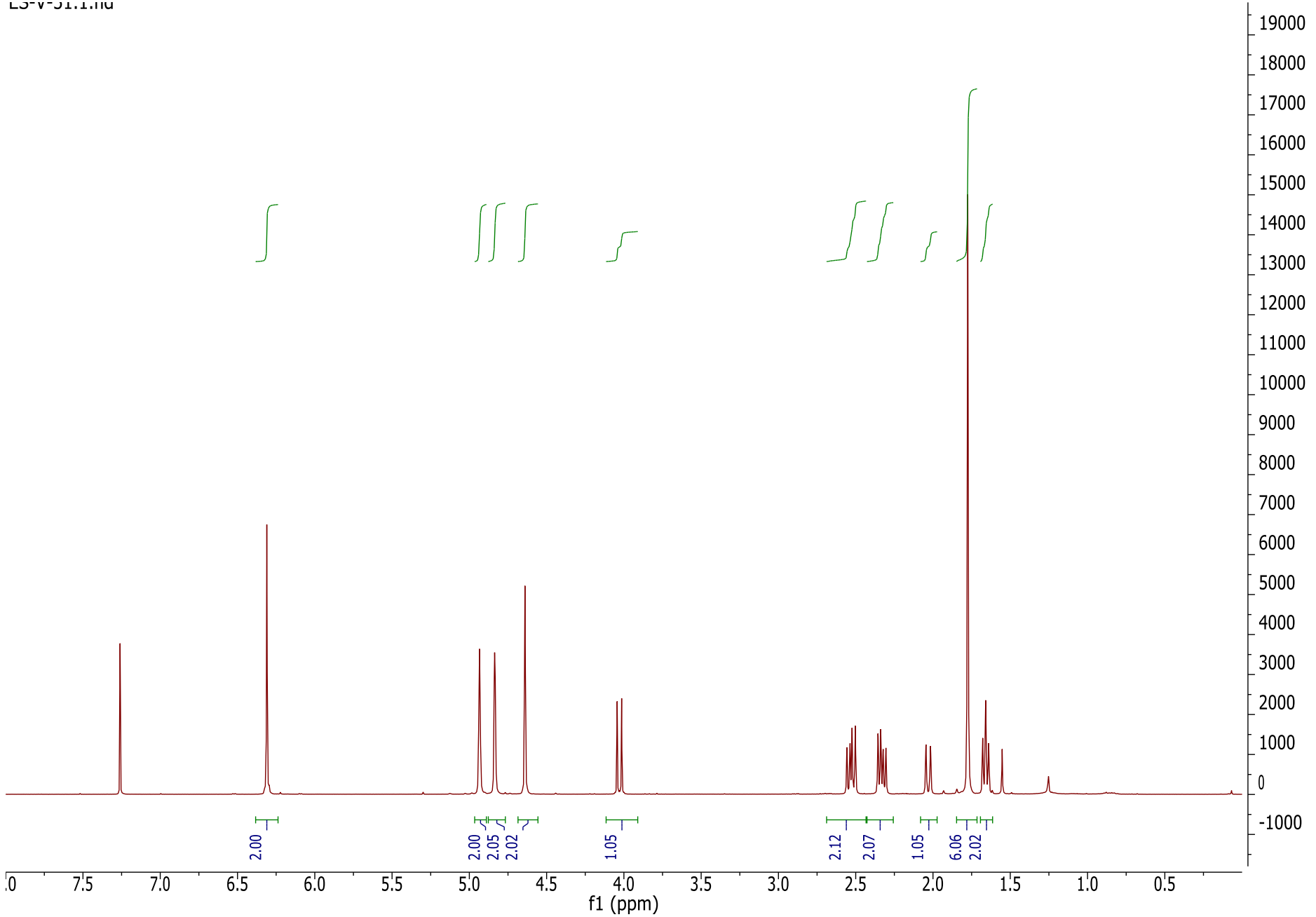
^{13}C NMR of **11b**



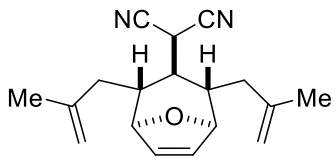


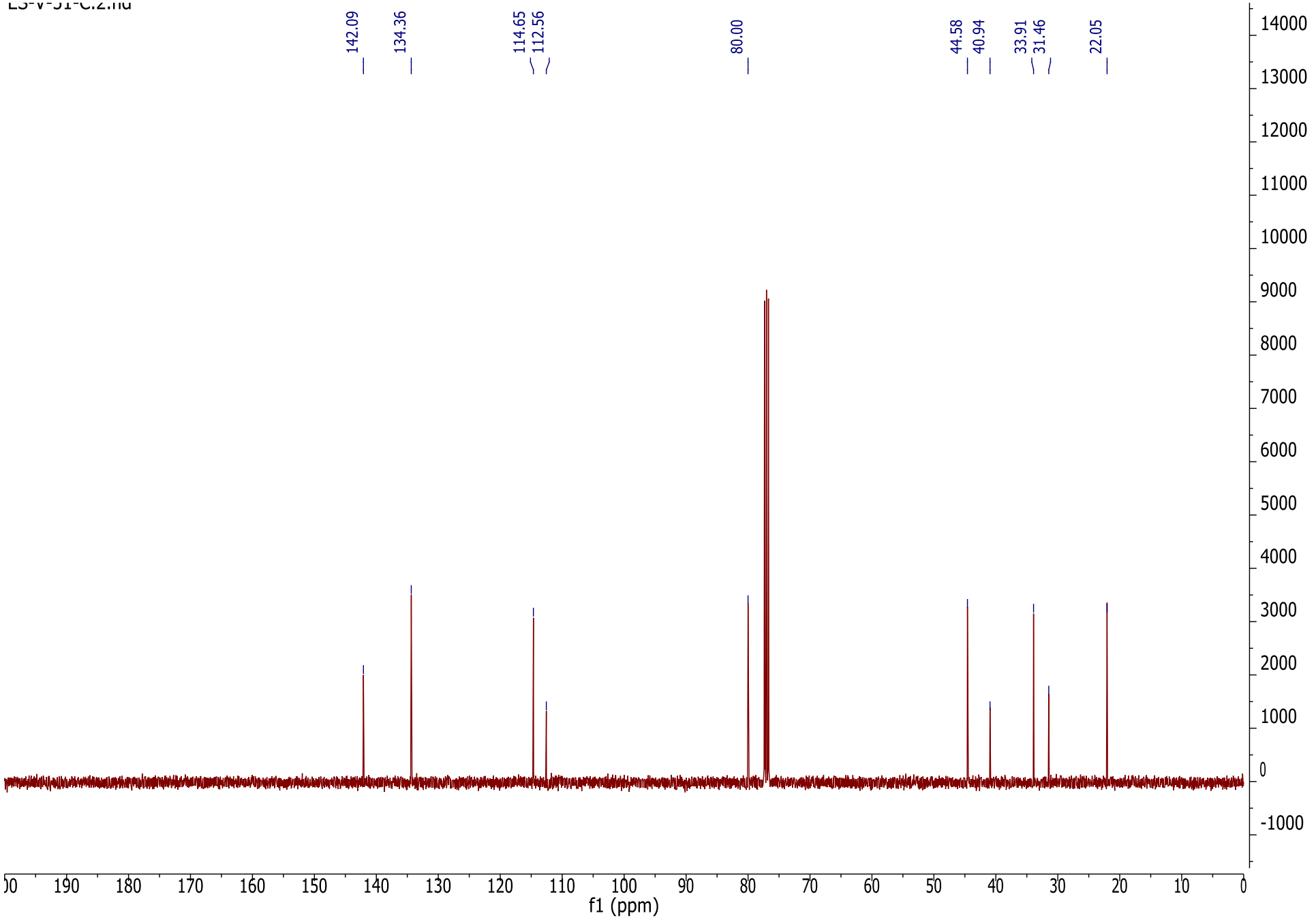
^{1}H NMR of **13a**


NC
CN
H
H
Me
Me
O

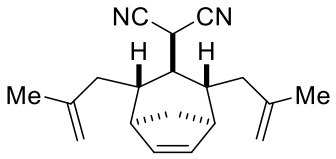

19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
2.00
2.00
2.05
2.02
1.05
2.12
2.07
1.05
6.06
2.02
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

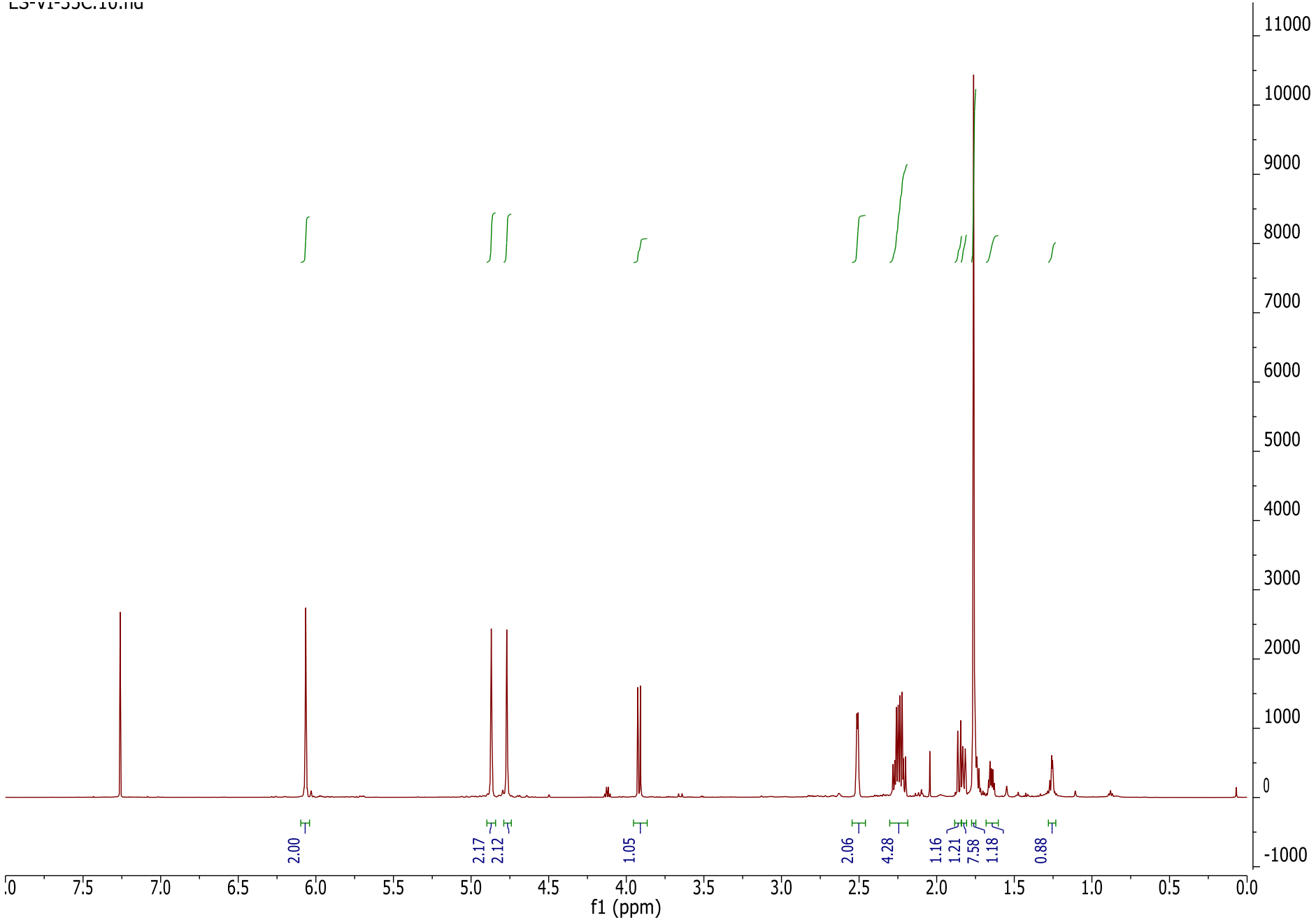
^{13}C NMR of **13a**



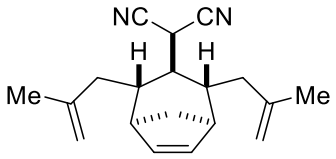


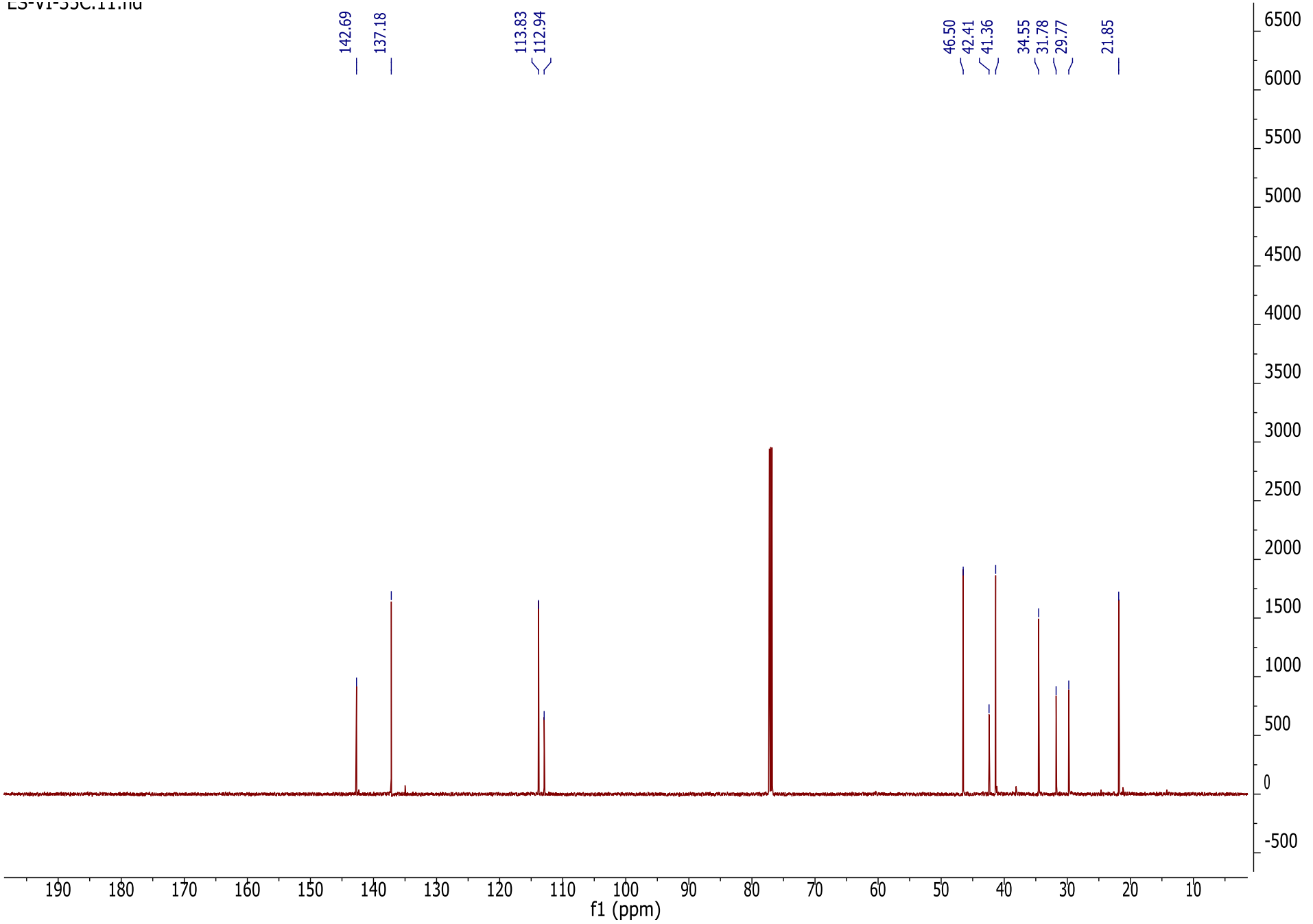
^{1}H NMR of **13b**


NC
CN
H
H
Me
Me

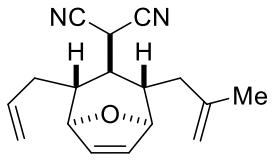

11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
2.00
2.17
2.12
1.05
2.06
4.28
1.16
1.21
7.58
1.18
0.88
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

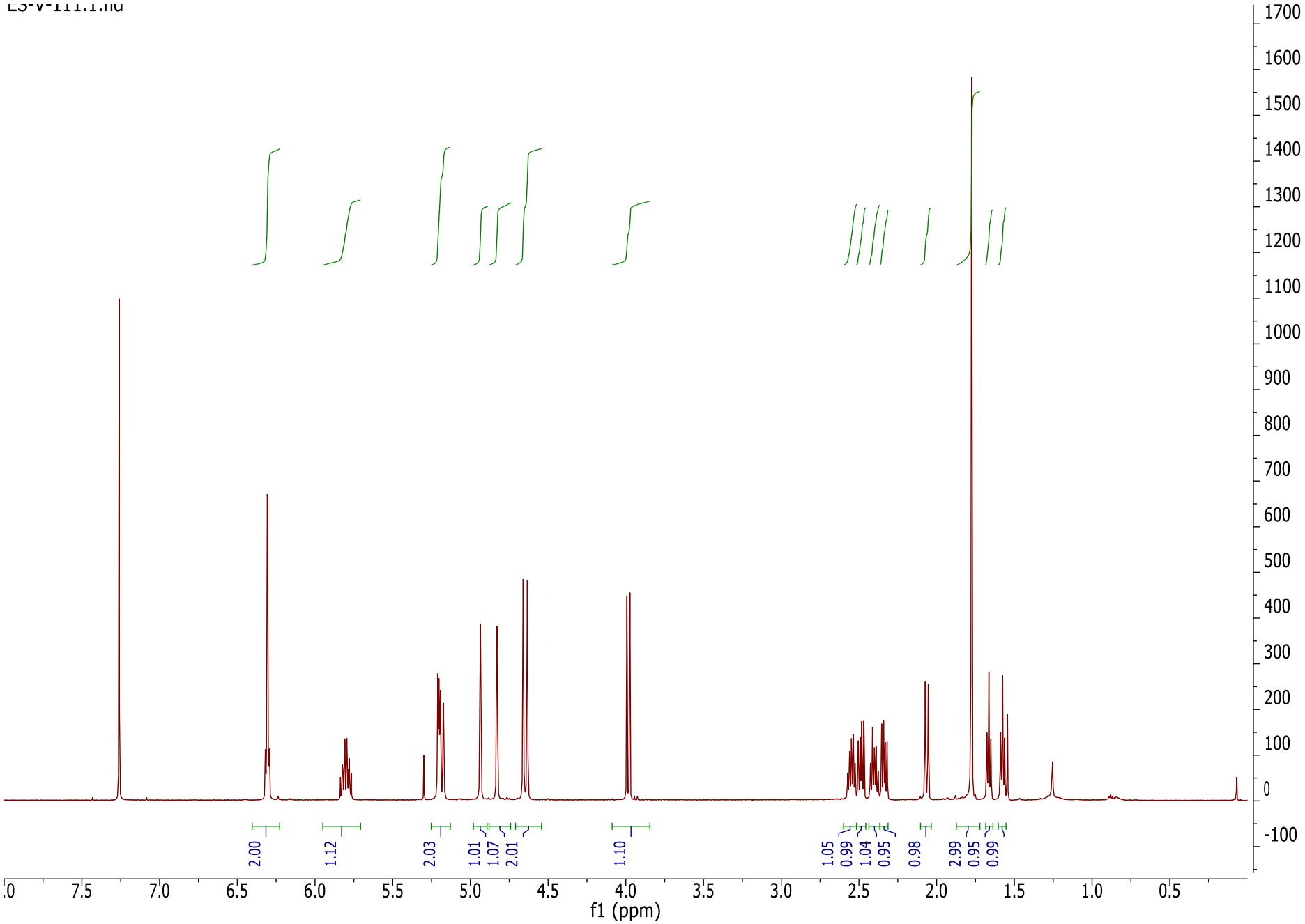
^{13}C NMR of **13b**



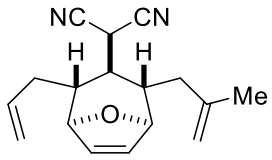


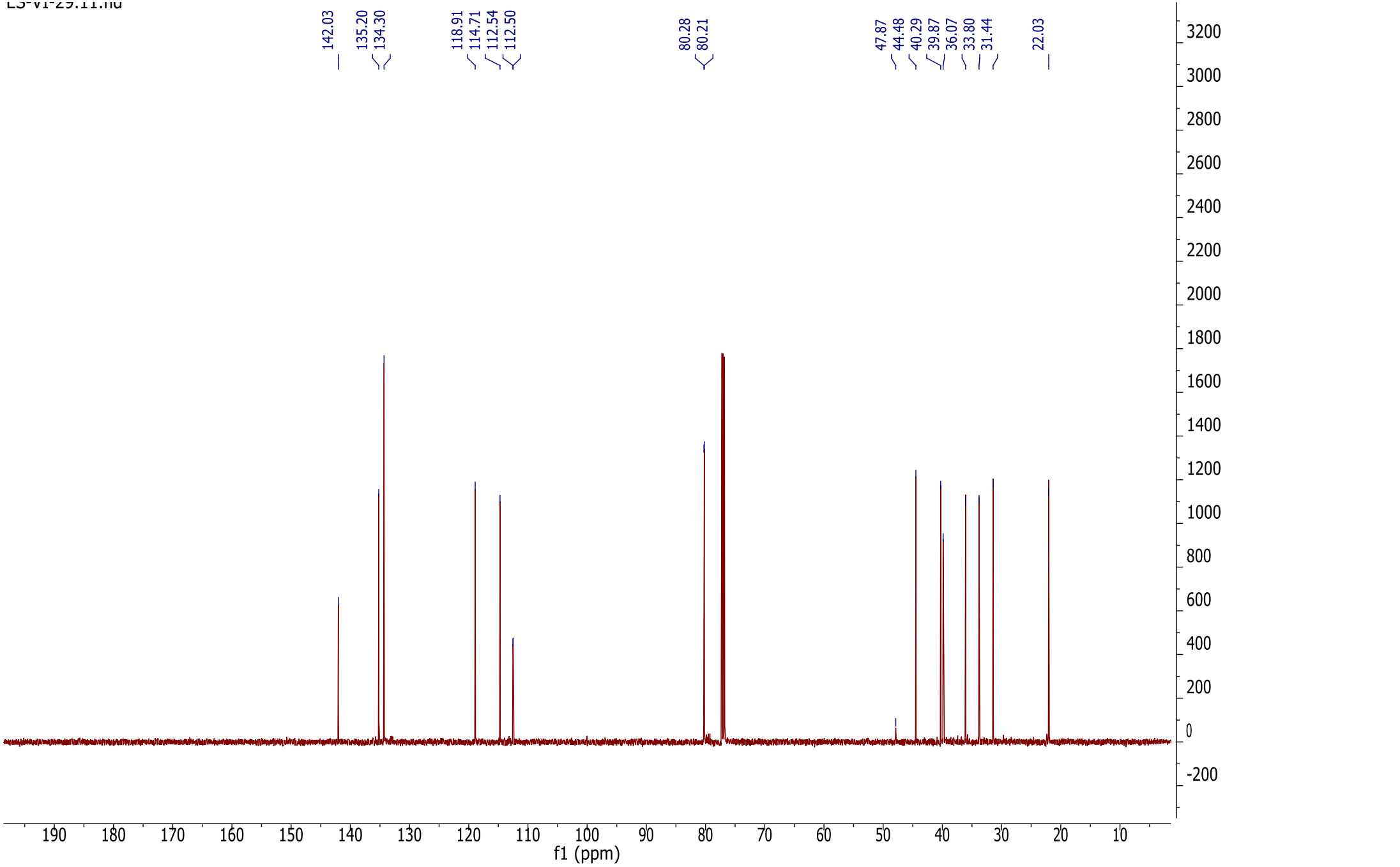
^{1}H NMR of **13c**


NC
CN
H
H
Me
O

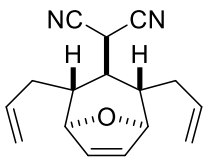

1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
2.00
1.12
2.03
1.01
1.07
2.01
1.10
1.05
0.99
1.04
0.95
0.98
2.99
0.95
0.99
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

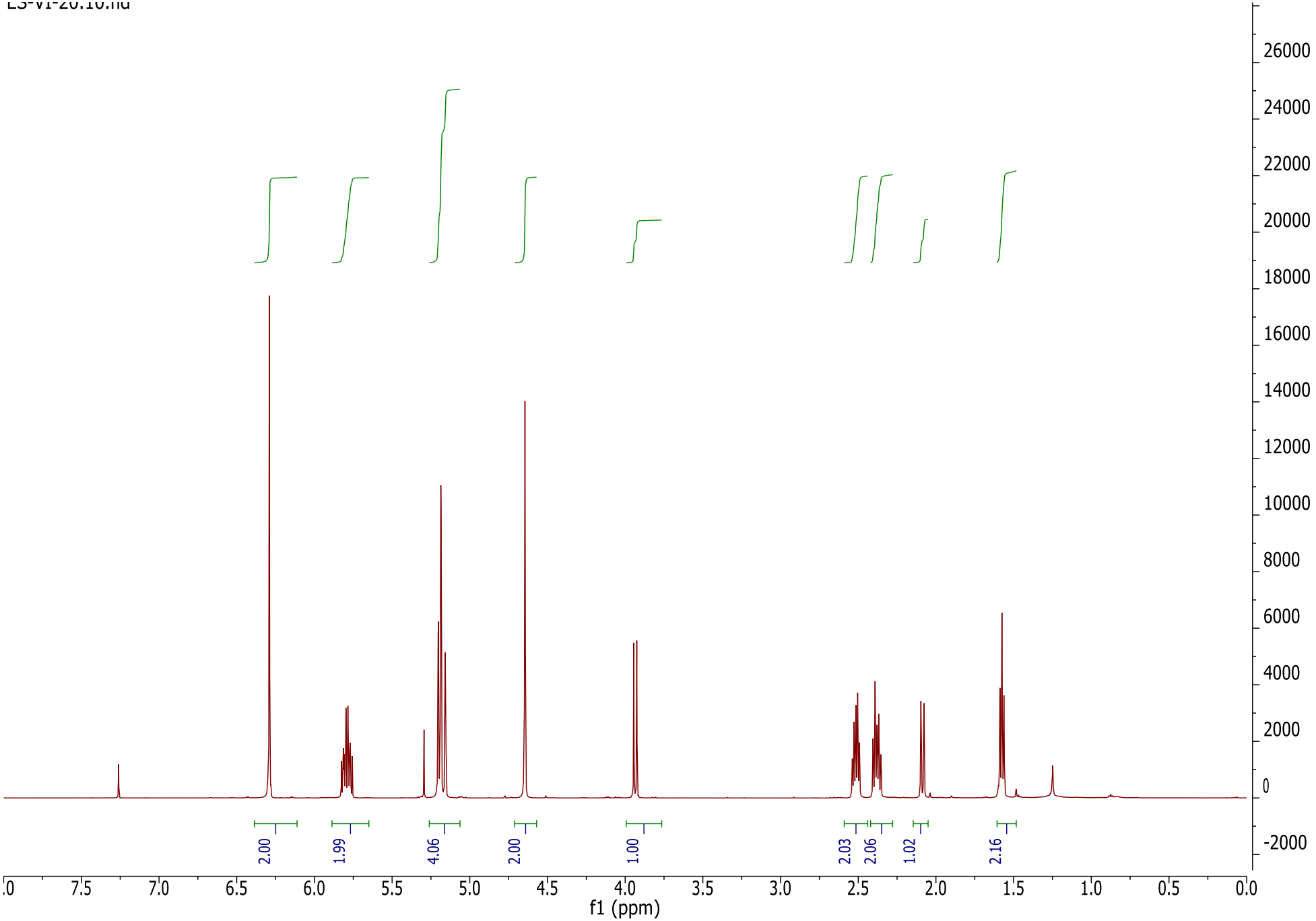
^{13}C NMR of **13c**



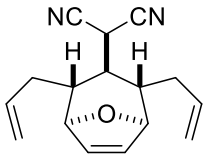


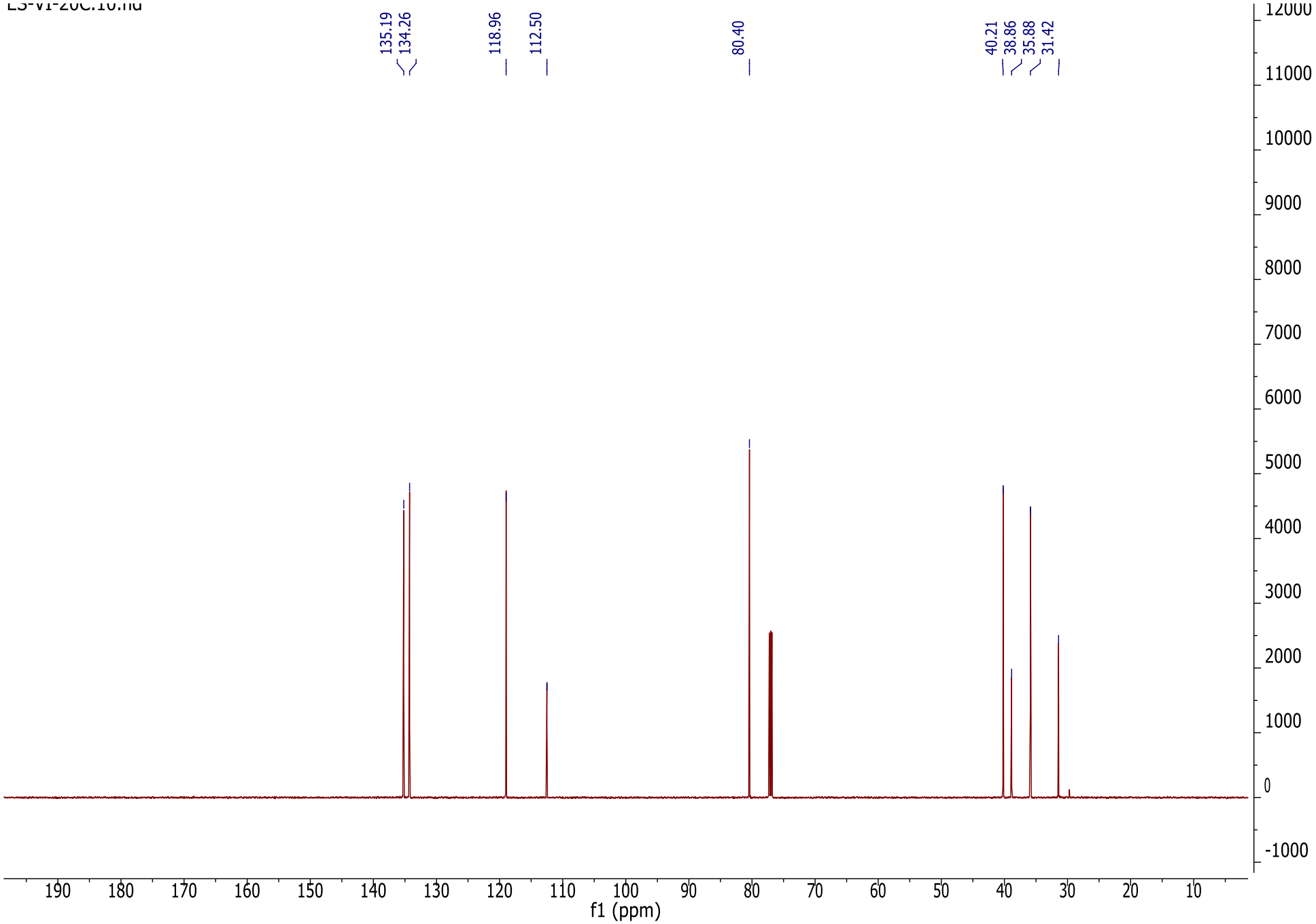
^{1}H NMR of **13d**


NC
CN
H
H
O

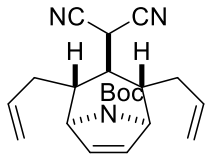

LS-VI-20.10.fid
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
2.00
1.99
4.06
2.00
1.00
2.03
2.06
1.02
2.16
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

^{13}C NMR of **13d**

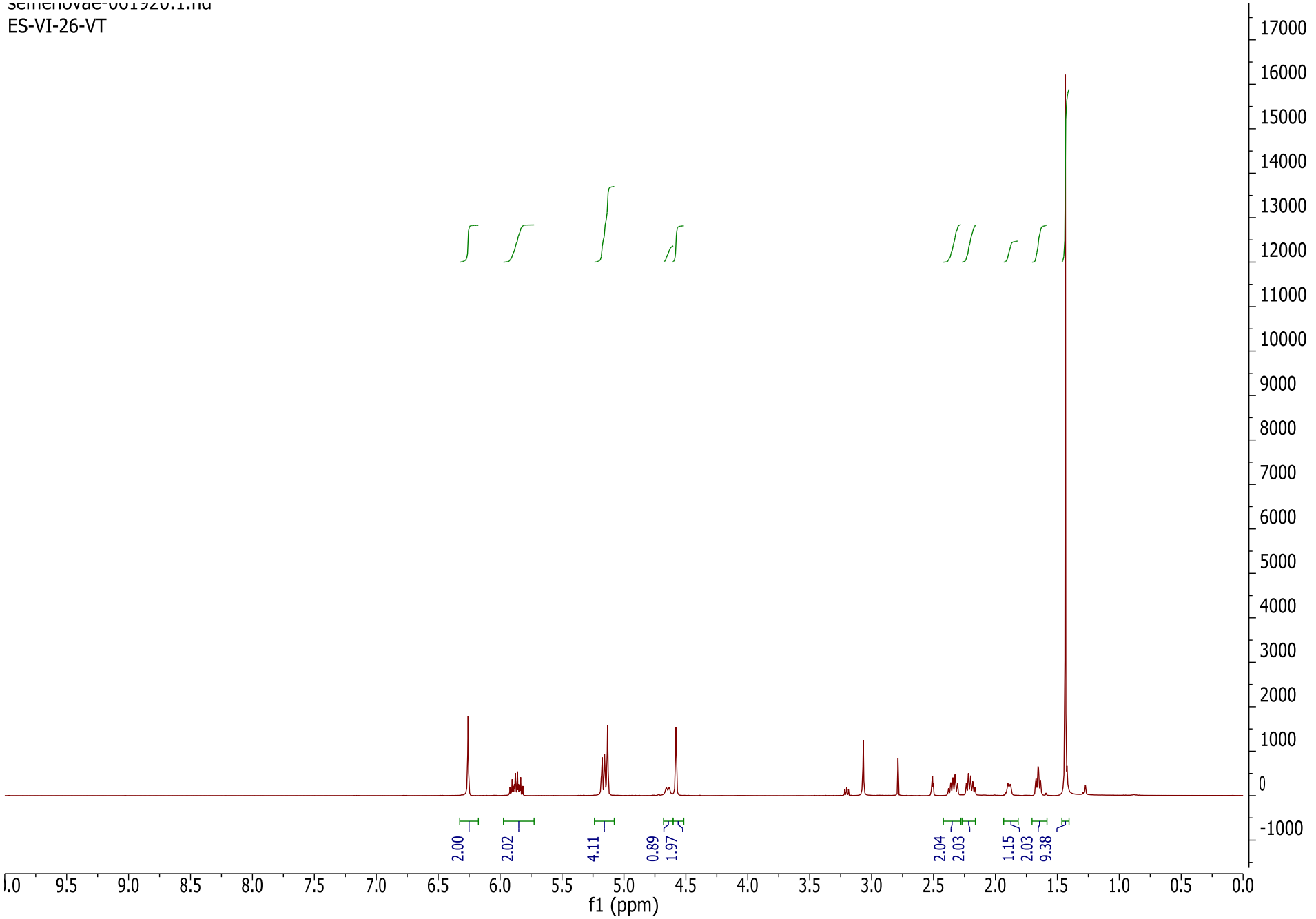




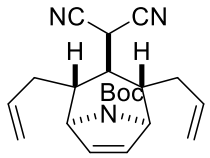
^{1}H NMR of **13e**



semenovae-001920.1.nd
ES-VI-26-VT



^{13}C NMR of **13e**

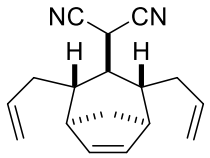


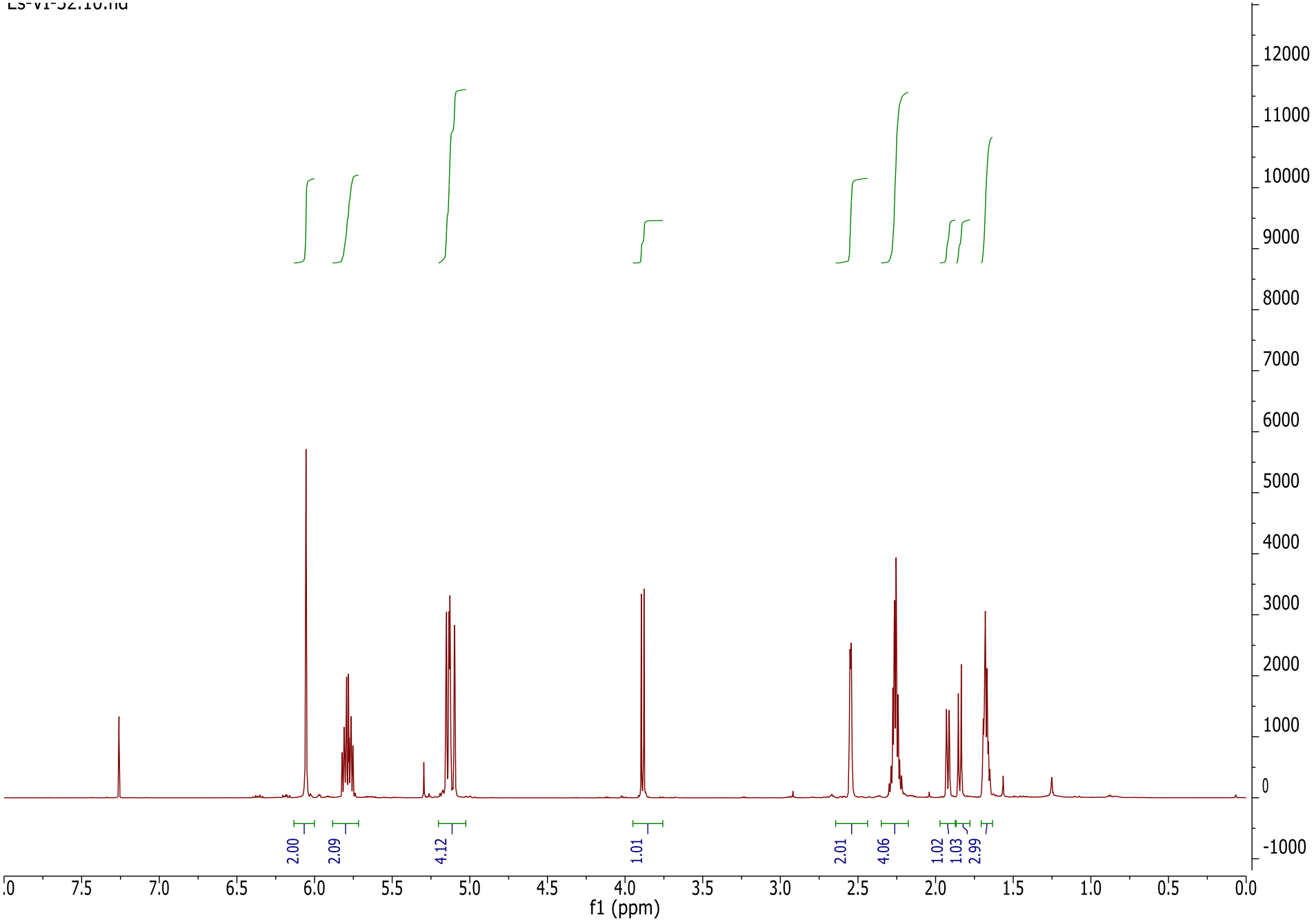
semenovae-001920.2.nd
ES-VI-26-VT

153.79
136.09
135.23
118.18
114.28
79.63
60.04
41.26
38.11
31.27
28.55

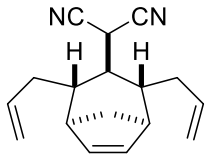
f1 (ppm)

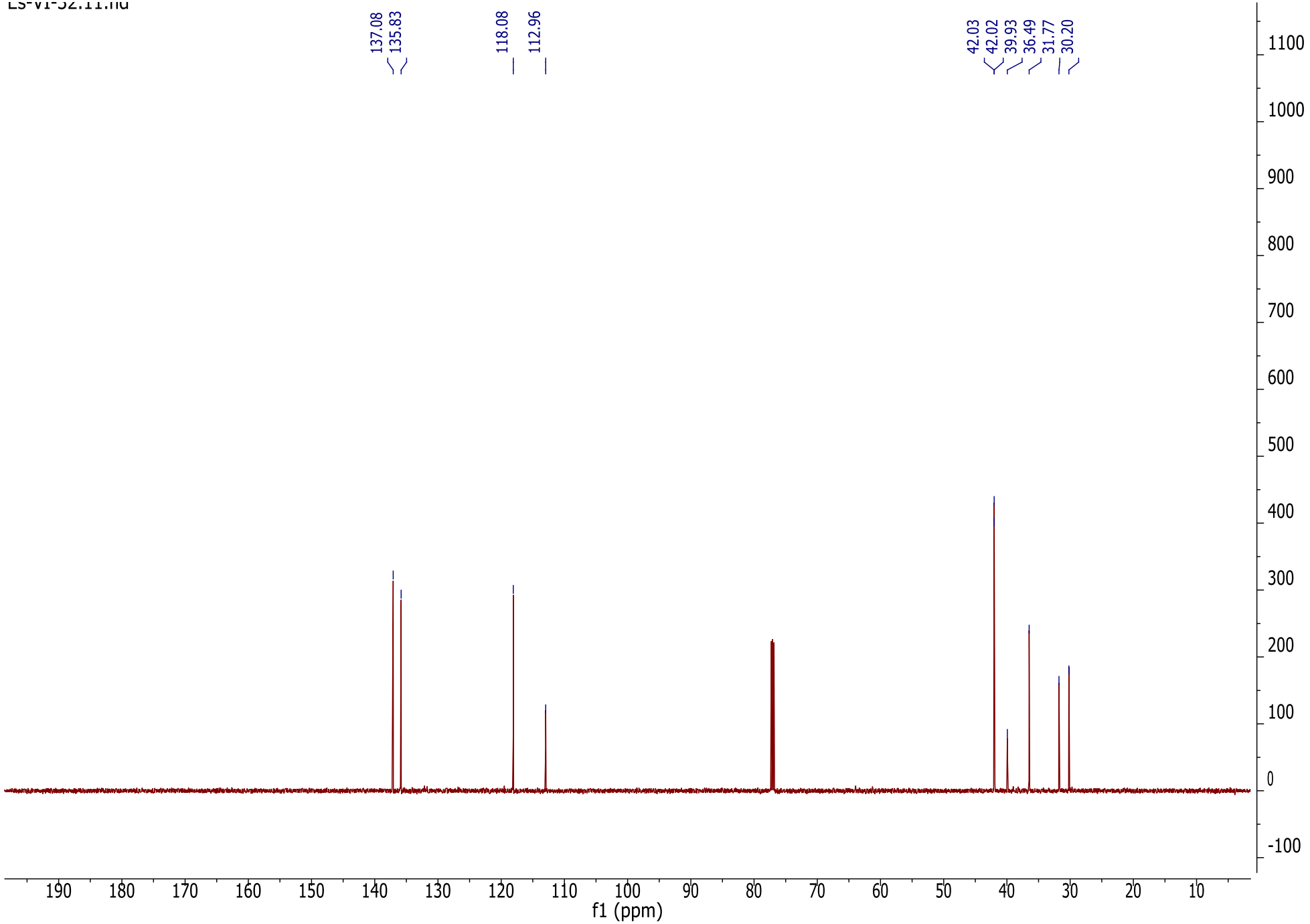
^{1}H NMR of **13f**


NC
CN
H
H

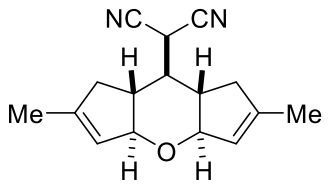

12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
2.00
2.09
4.12
1.01
2.01
4.06
1.02
1.03
2.99
.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

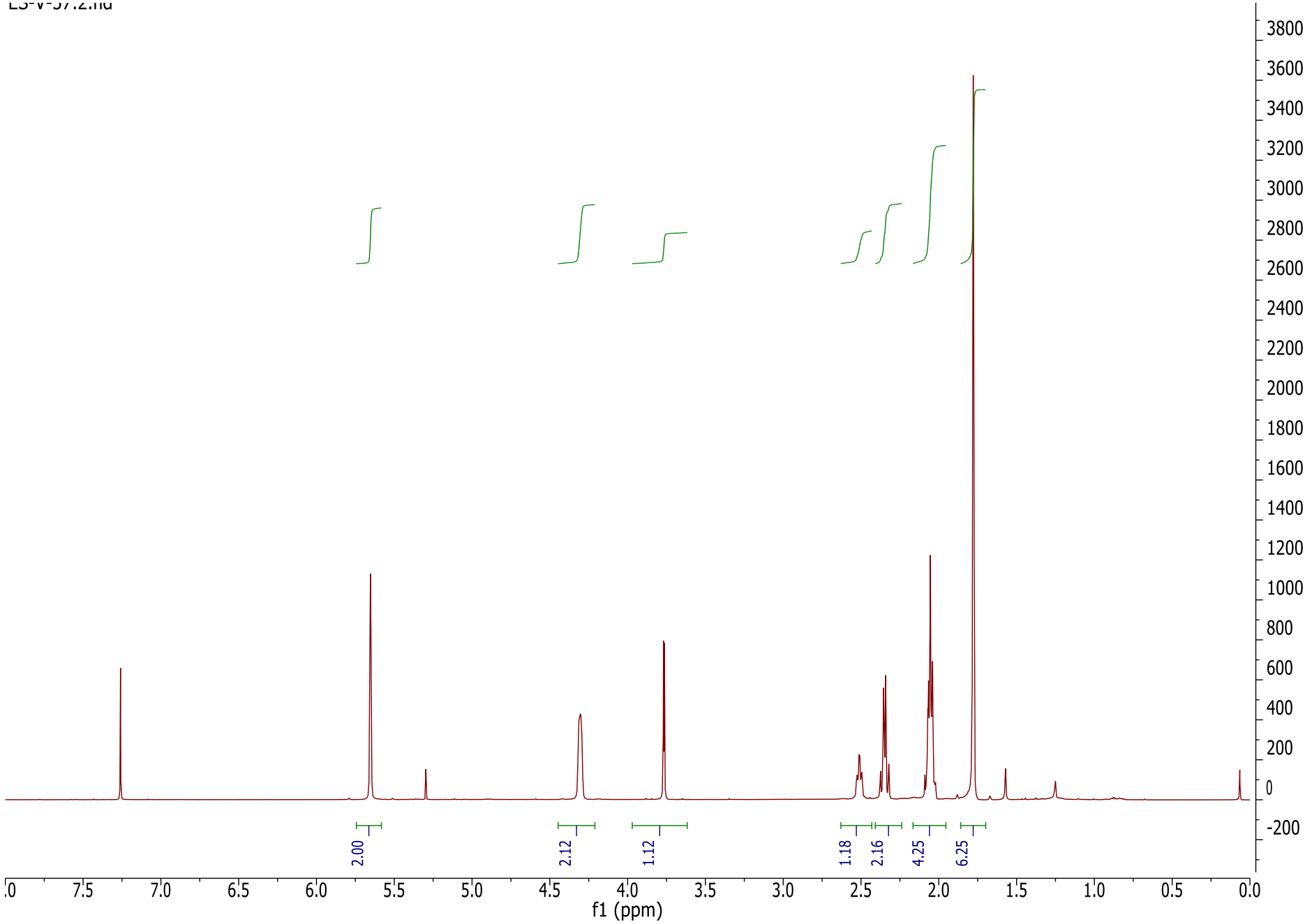
^{13}C NMR of **13f**



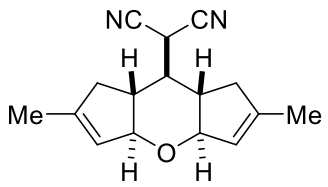


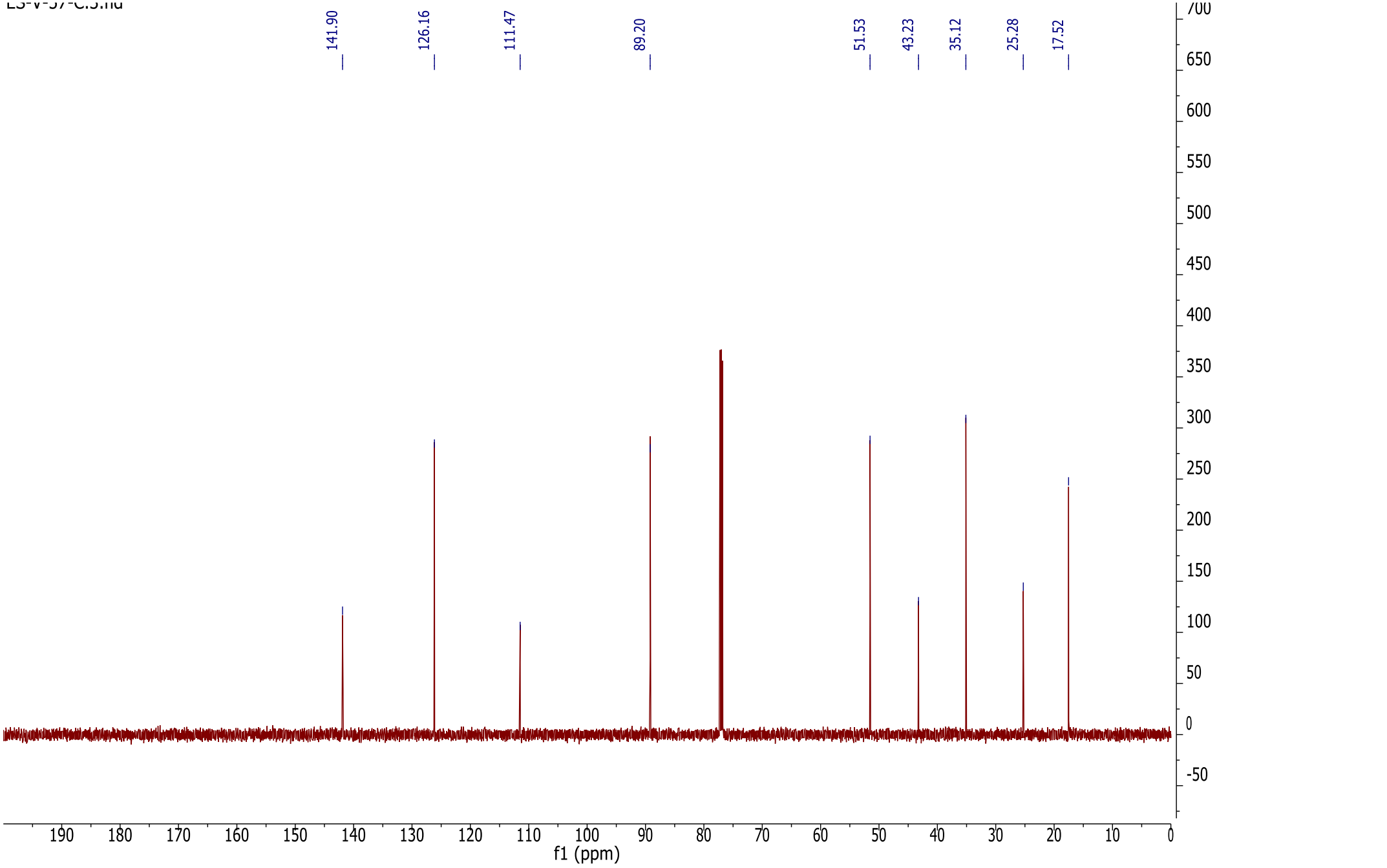
^{1}H NMR of **14a**


NC
CN
H
H
Me
Me
O
H
H

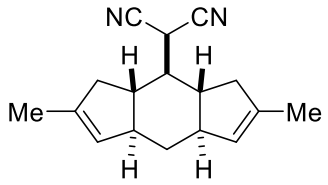

3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
2.00
2.12
1.12
1.18
2.16
4.25
6.25
.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

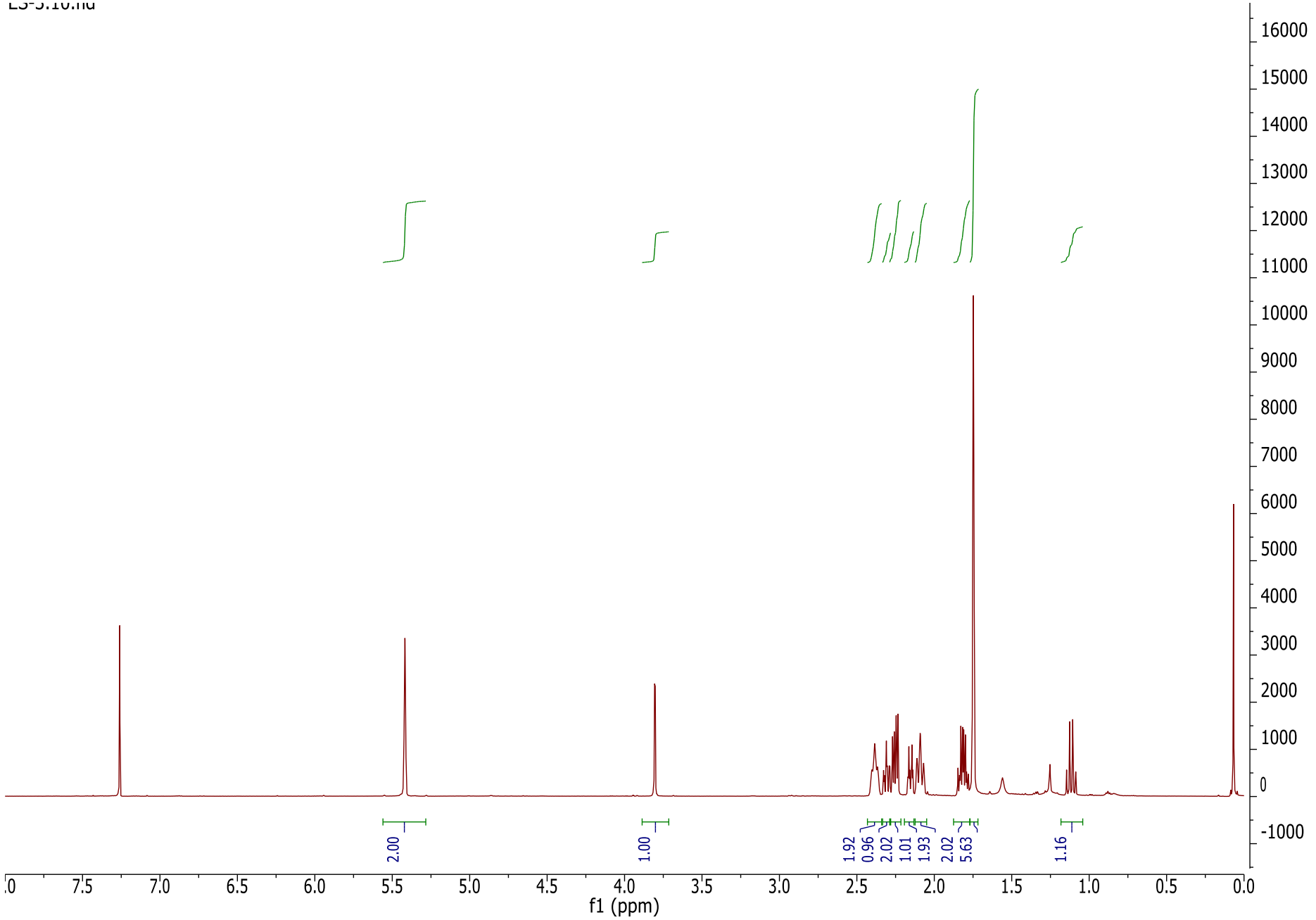
^{13}C NMR of **14a**



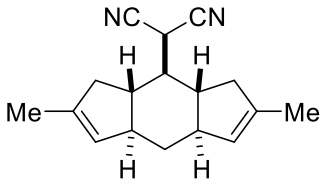


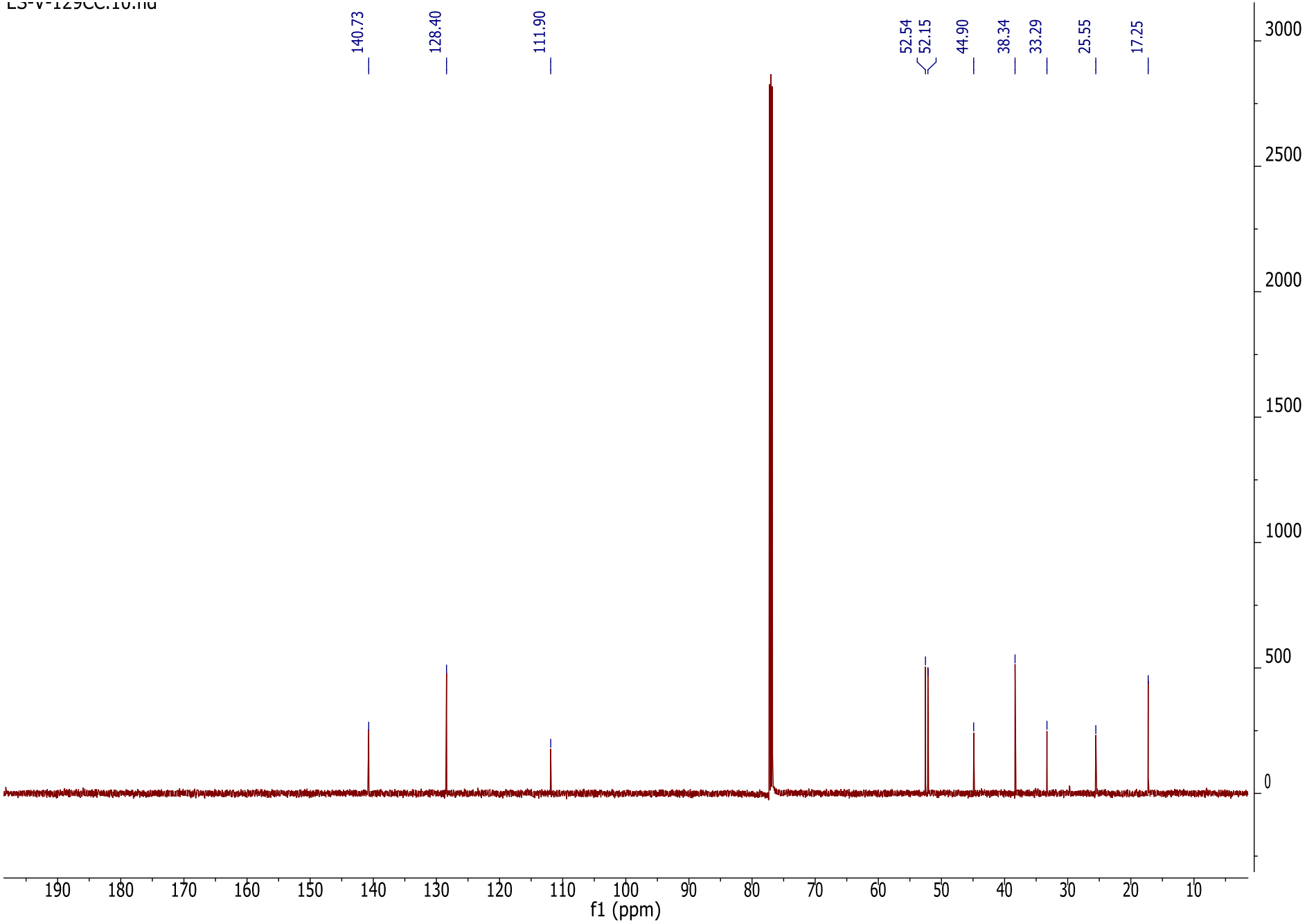
^{1}H NMR of **14b**


NC
CN
H
H
Me
Me
H
H

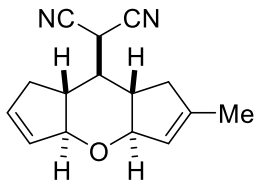

16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
2.00
1.00
1.92
0.96
2.02
1.01
1.93
2.02
5.63
1.16
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

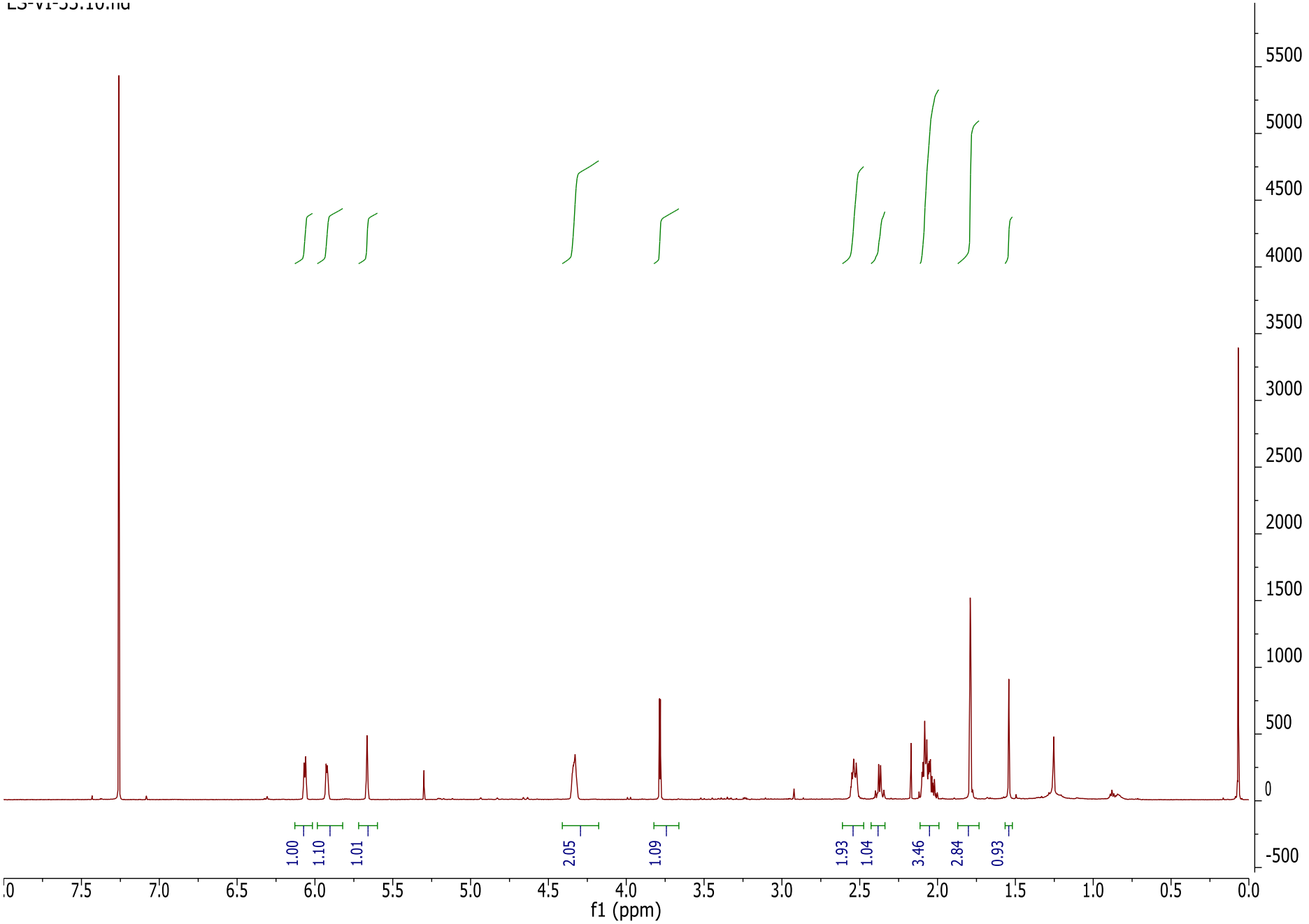
^{13}C NMR of **14b**



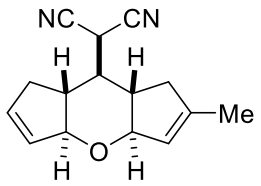


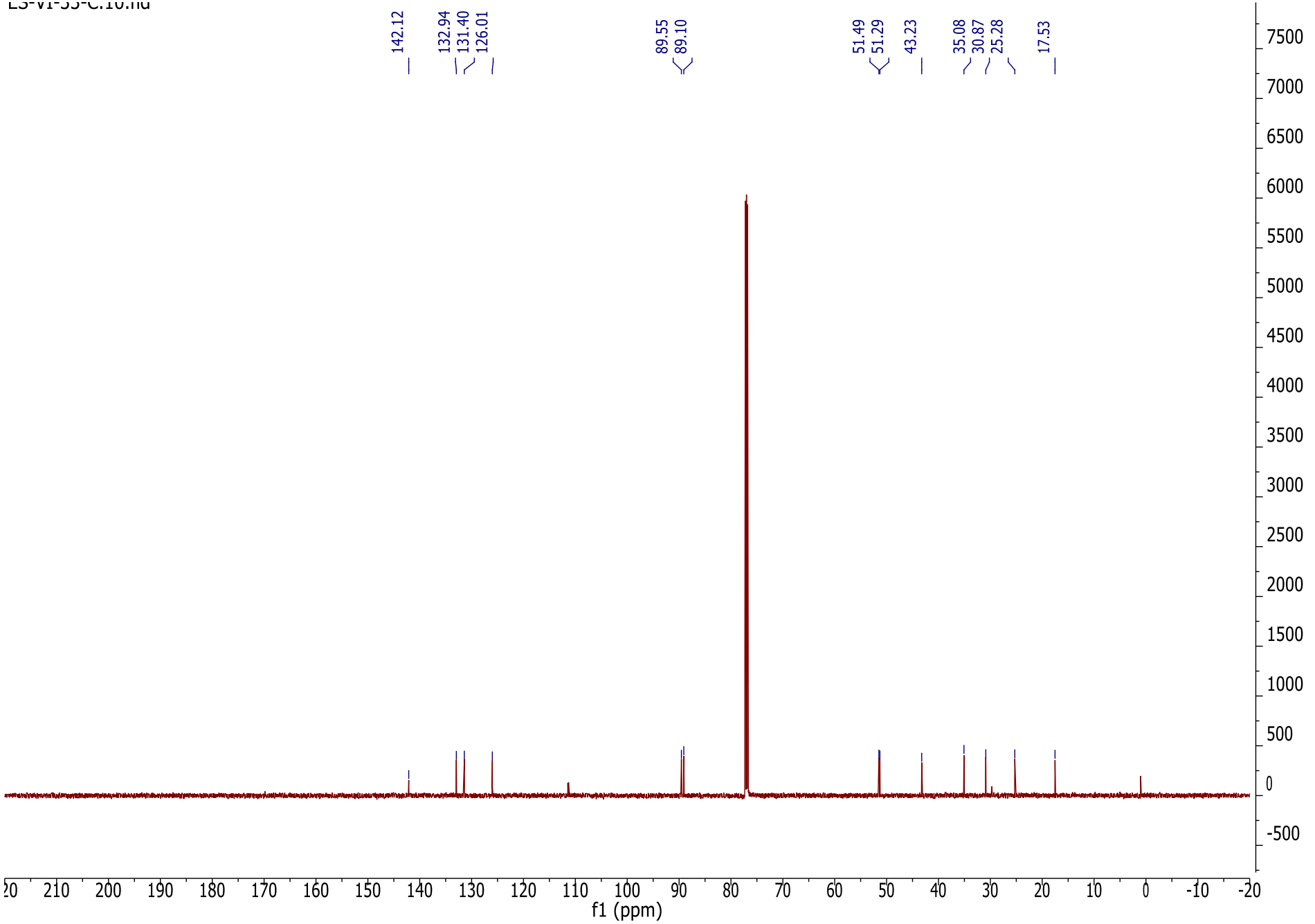
^{1}H NMR of **14c**


NC
CN
H
H
Me
O
H
H

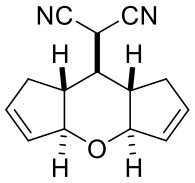

5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
1.00
1.10
1.01
2.05
1.09
1.93
1.04
3.46
2.84
0.93
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

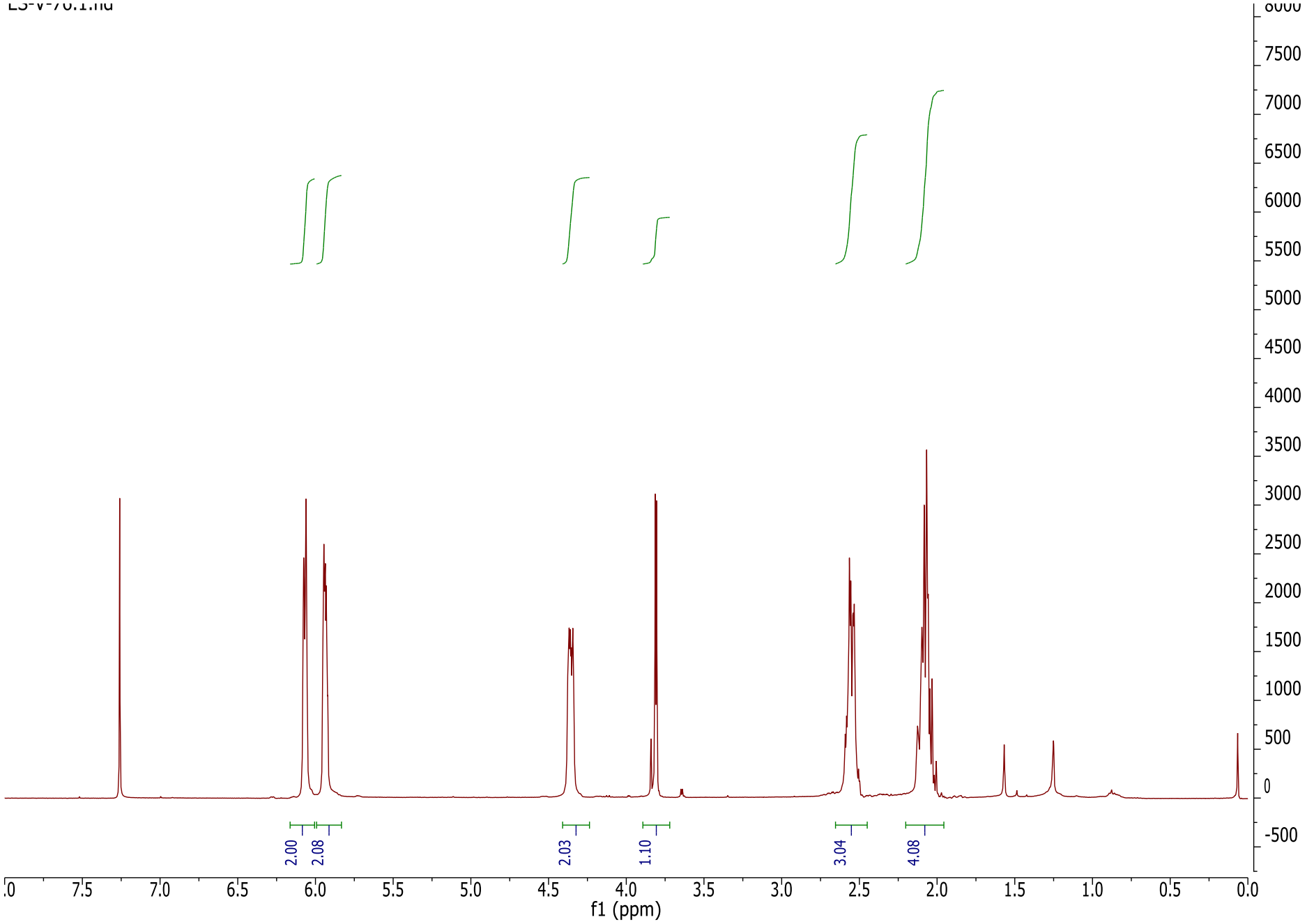
^{13}C NMR of **14c**



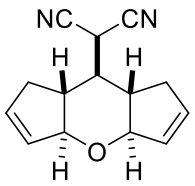


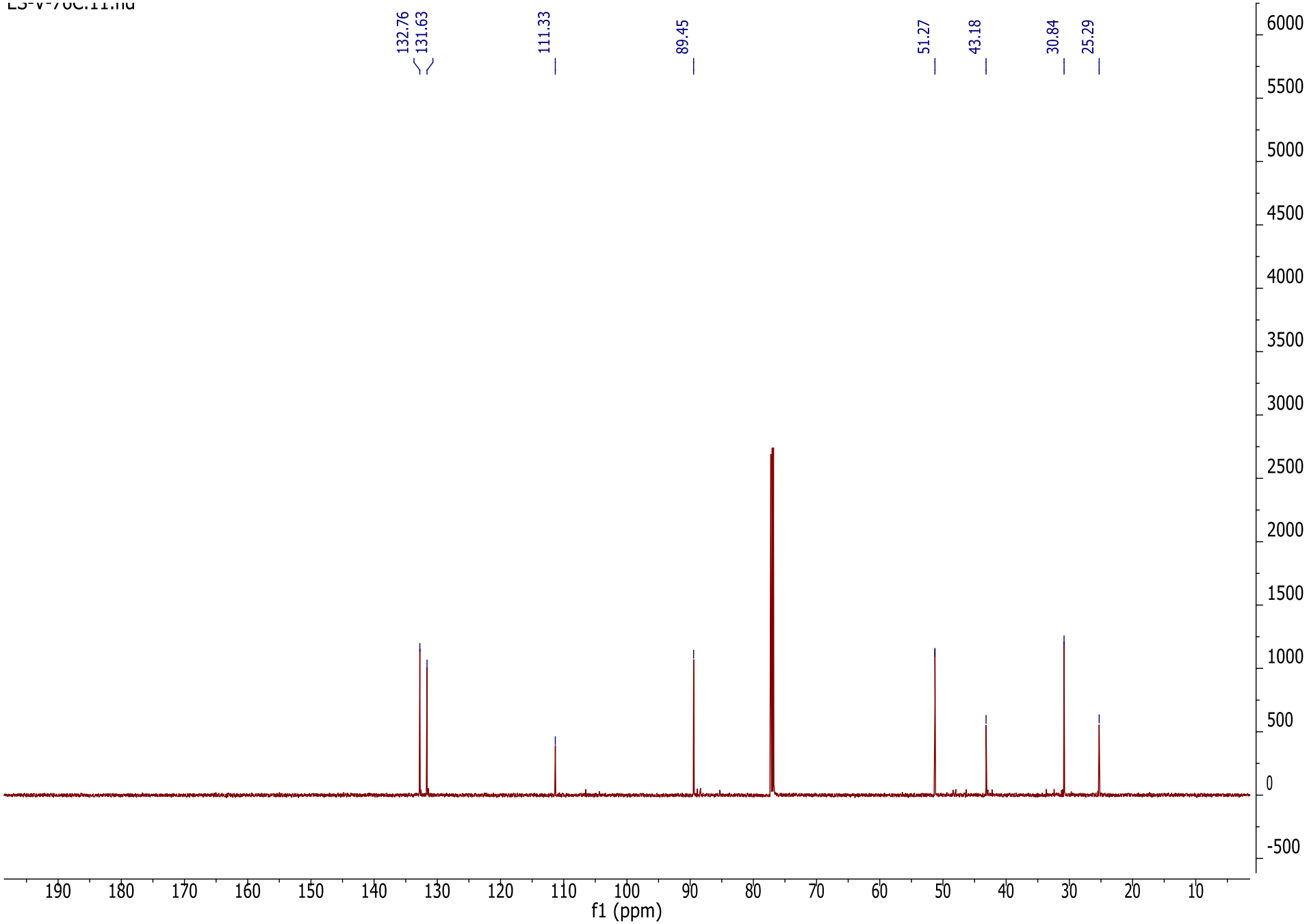
^{1}H NMR of **14d**



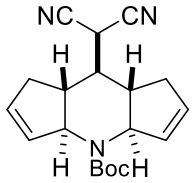


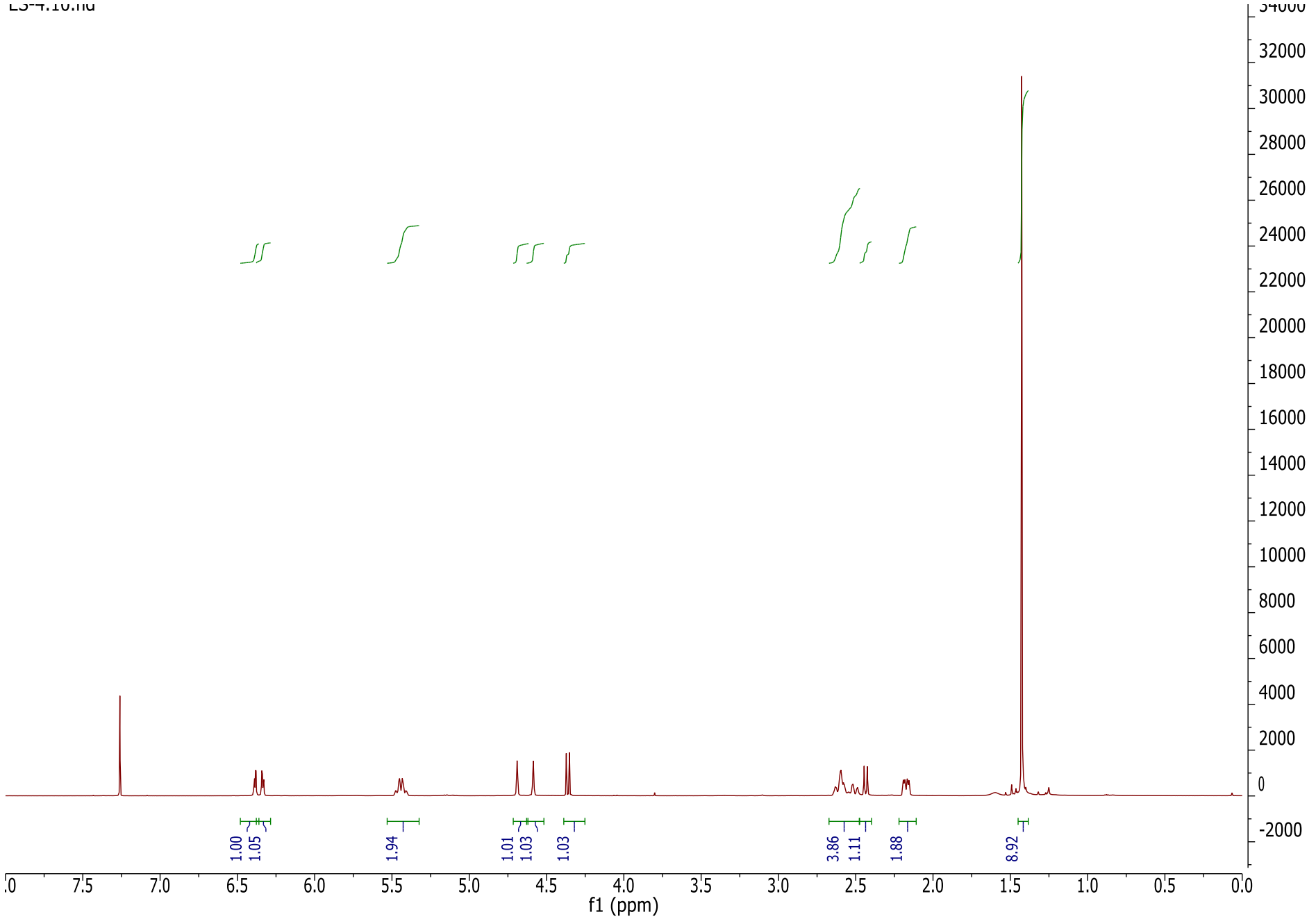
^{13}C NMR of **14d**



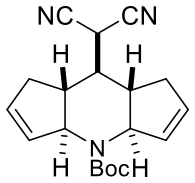


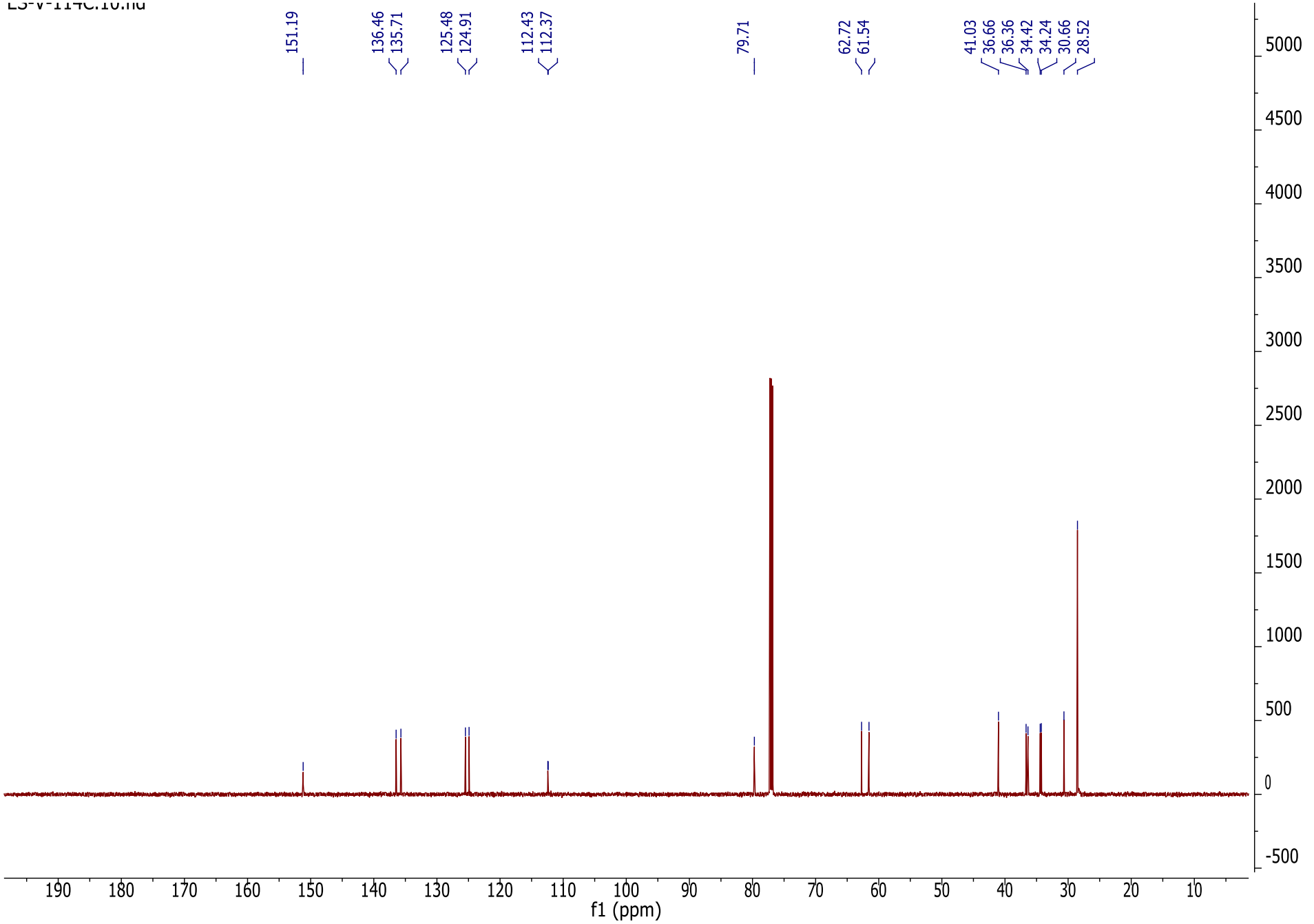
^{1}H NMR of **14e**


NC
CN
H
H
N
H
BocH

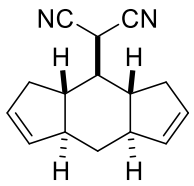

32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
1.00
1.05
1.94
1.01
1.03
1.03
3.86
1.11
1.88
8.92
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

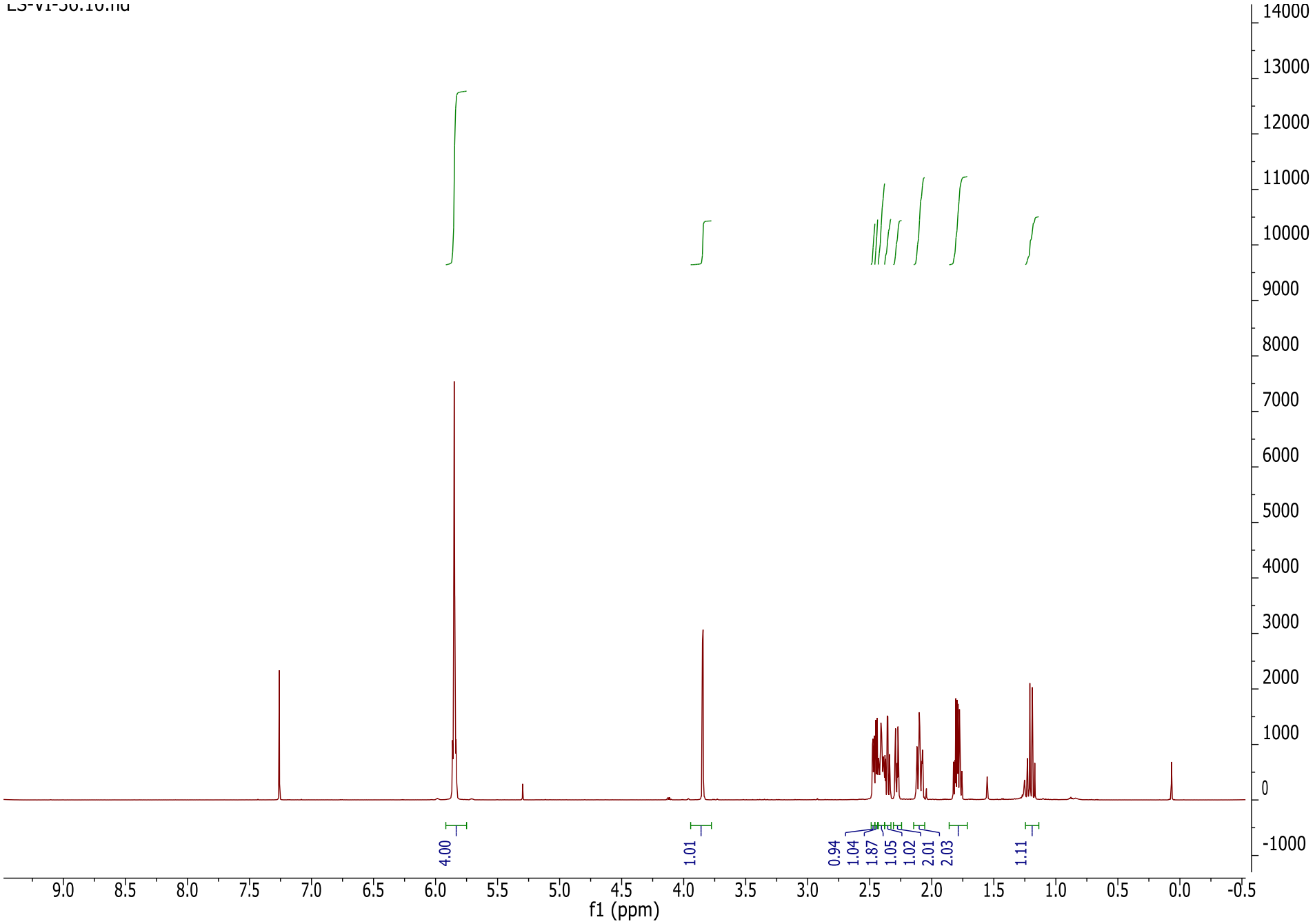
^{13}C NMR of **14e**



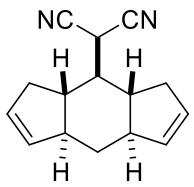


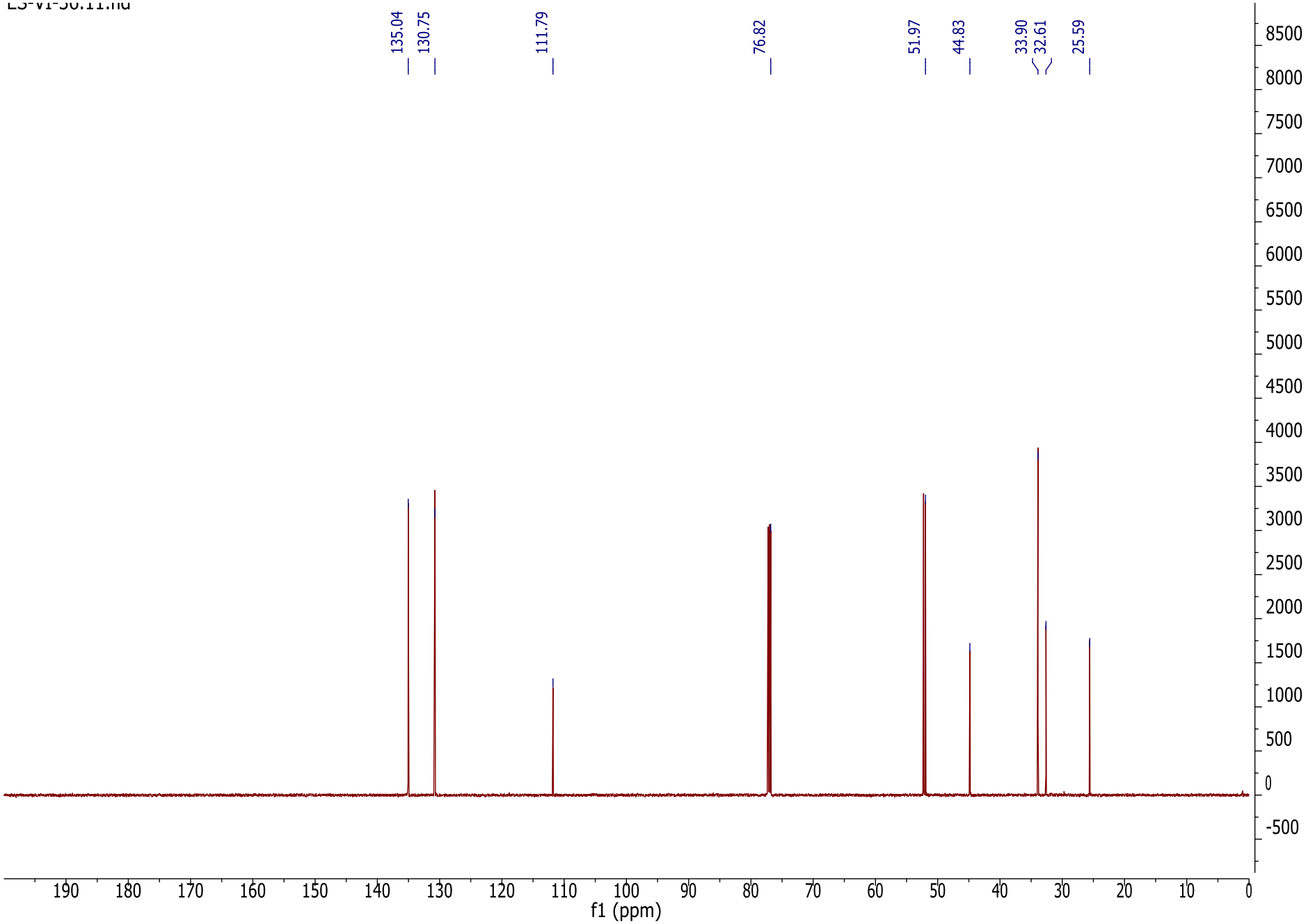
^{1}H NMR of **14f**


NC
CN
H
H
H
H

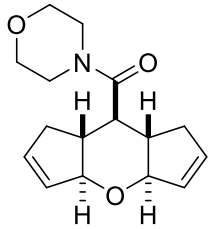

14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
4.00
1.01
0.94
1.04
1.87
1.05
1.02
2.01
2.03
1.11
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

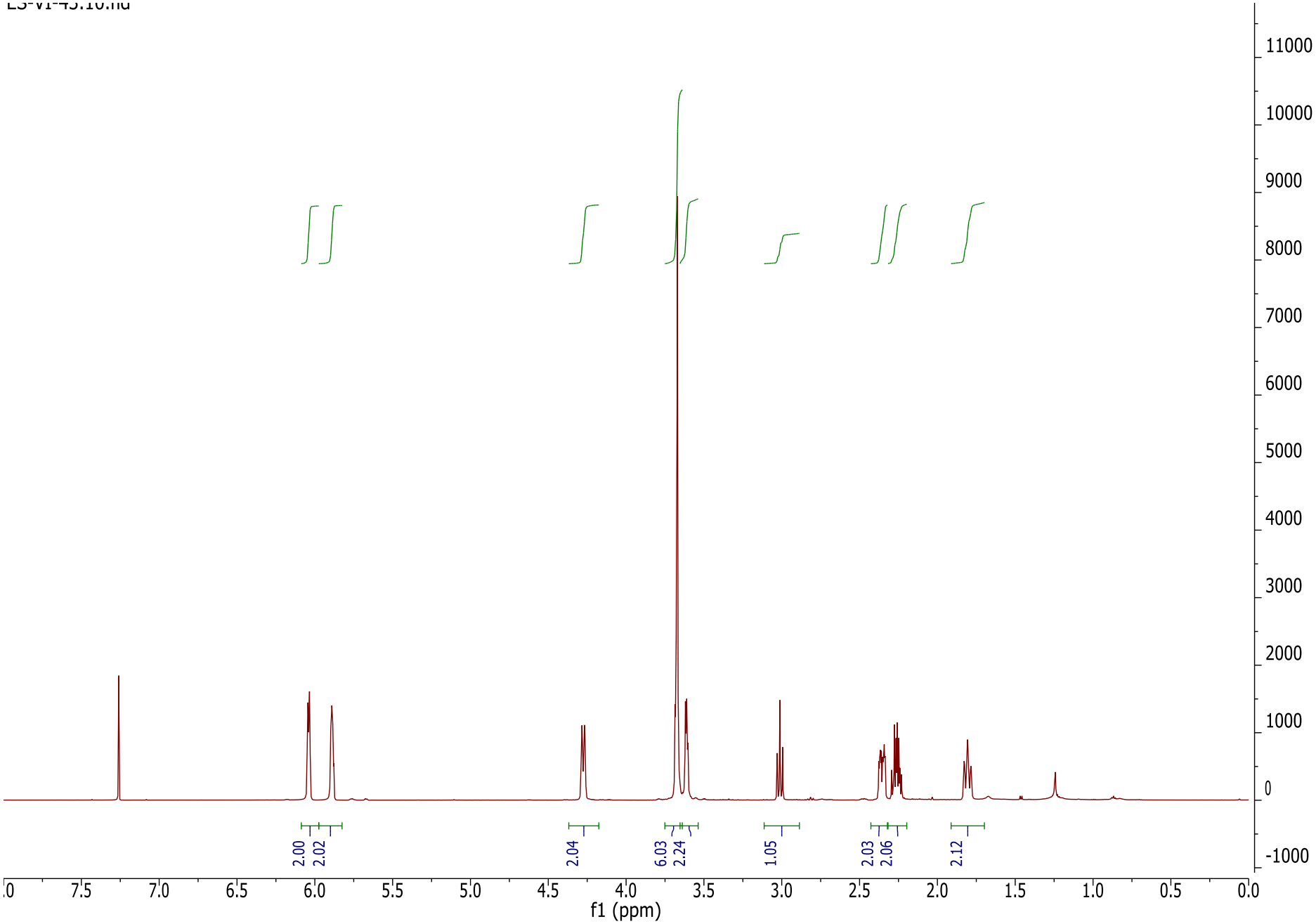
^{13}C NMR of **14f**



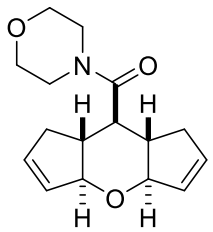


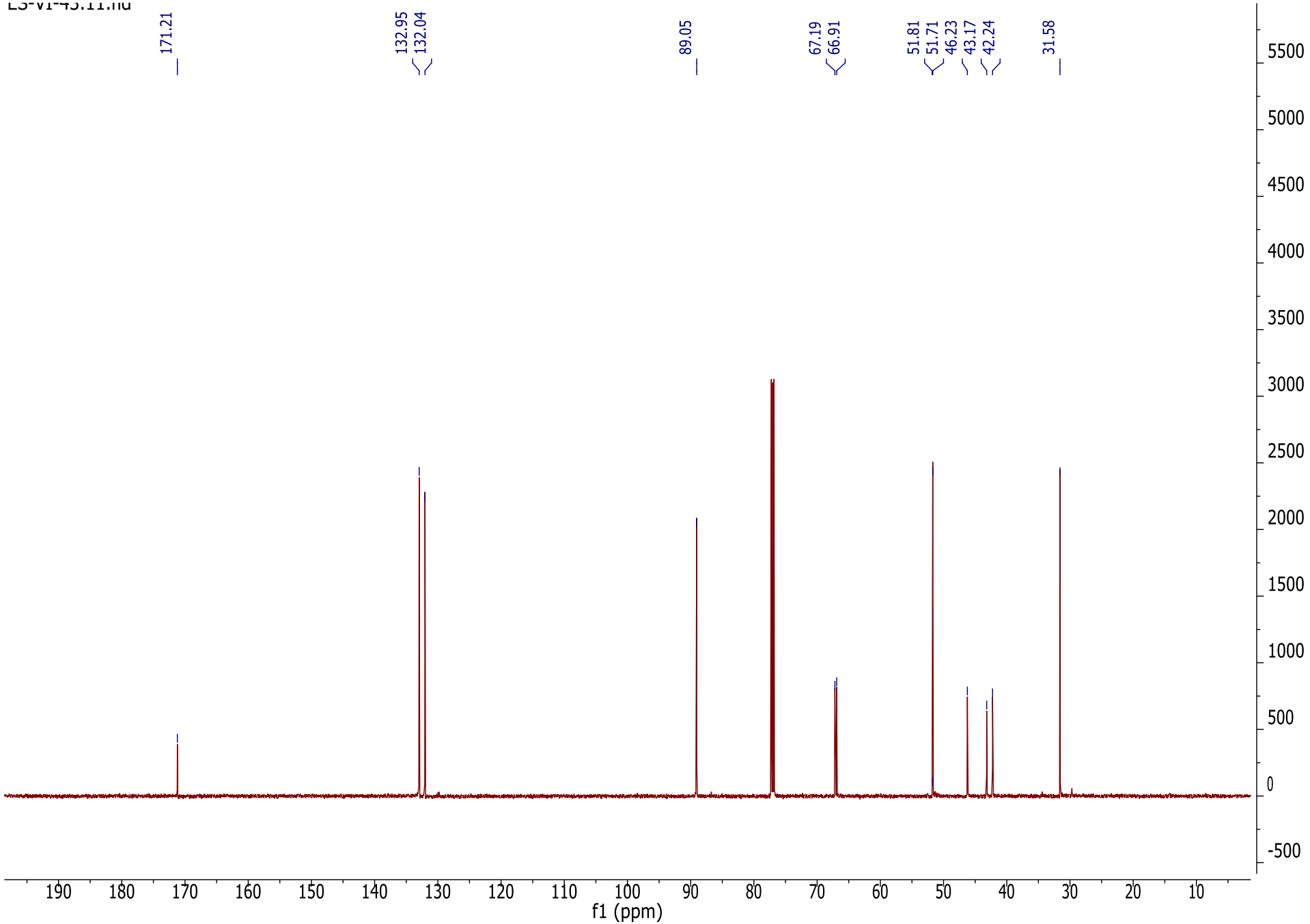
^{1}H NMR of **15**

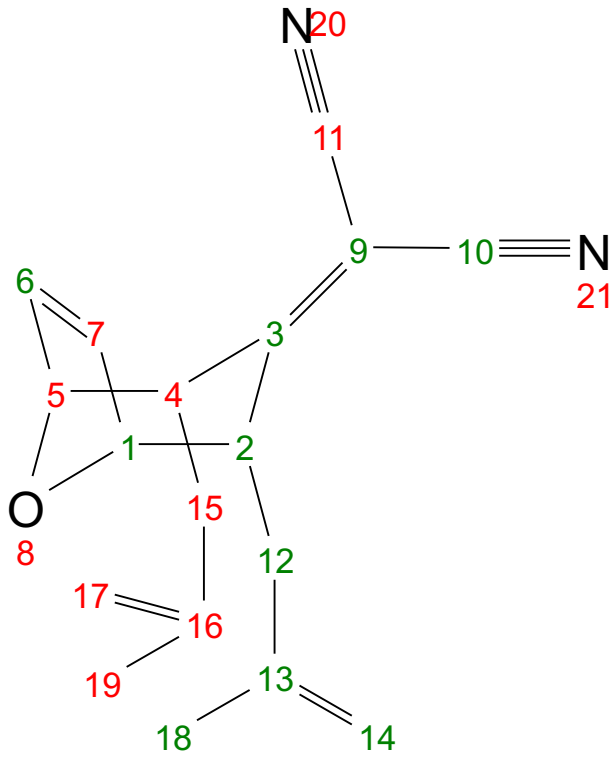

O
N
O
H
H
H
O
H


11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
2.00
2.02
2.04
6.03
2.24
1.05
2.03
2.06
2.12
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
f1 (ppm)

^{13}C NMR of **14f**





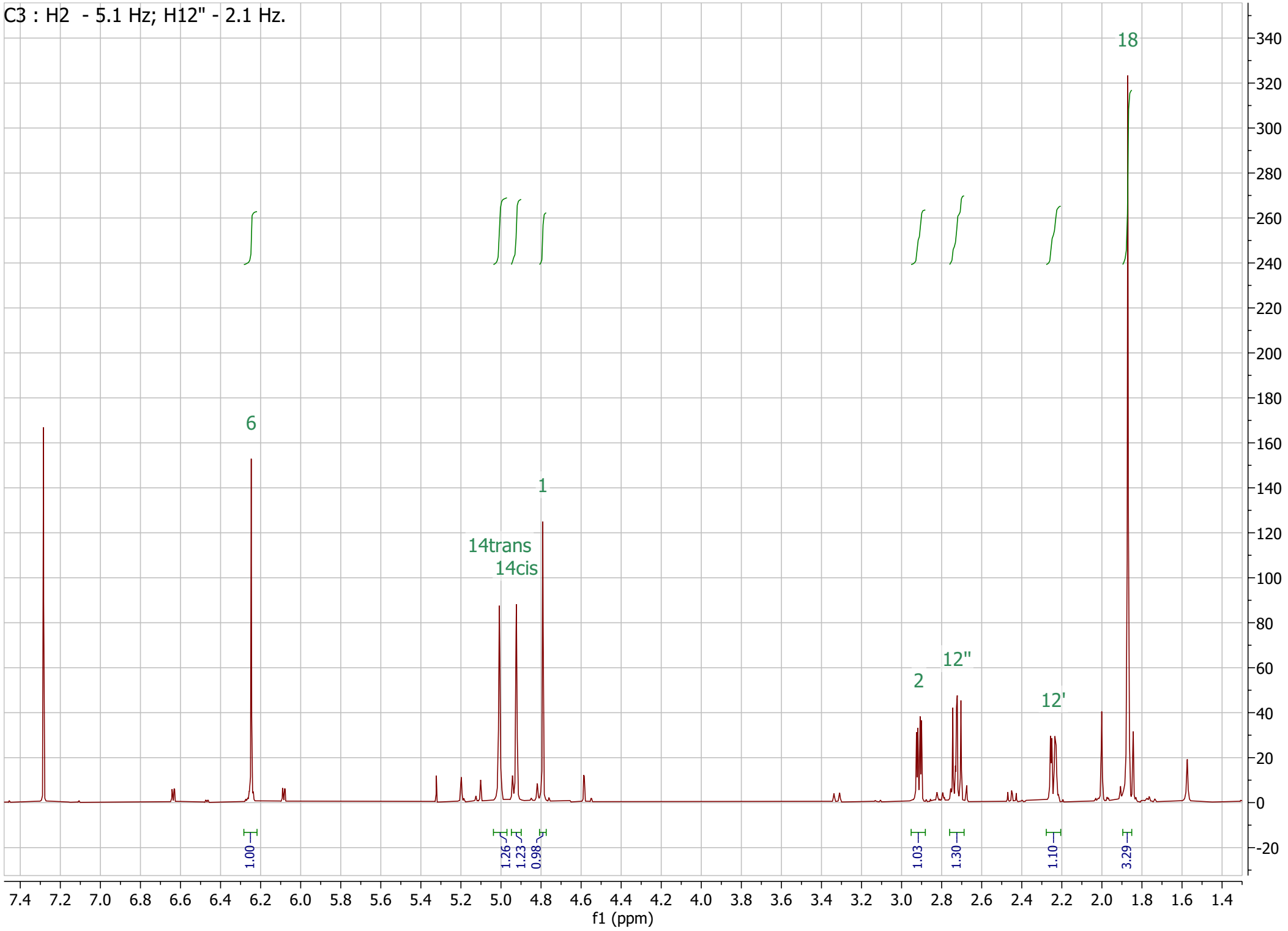


Atom	δ (ppm)	Atom	δ (ppm)
1 C	78.55	13 C	140.84
H	4.79	14 C	115.41
2 C	43.71	Hcis (to C12)	4.92
H	2.91	Htrans (to C12)	5.01
3 C	186.49	15 C	
4 C		H2	
H		16 C	
5 C		17 C	
H		H2	
6 C	133.58	18 C	21.86
H	6.25	H3	1.87
7 C		19 C	
H		H3	
8 O		20 N	
9 C	90.00	21 N	
10 C	111.10		
11 C			
12 C	42.07		
H'	2.24		
H''	2.72		

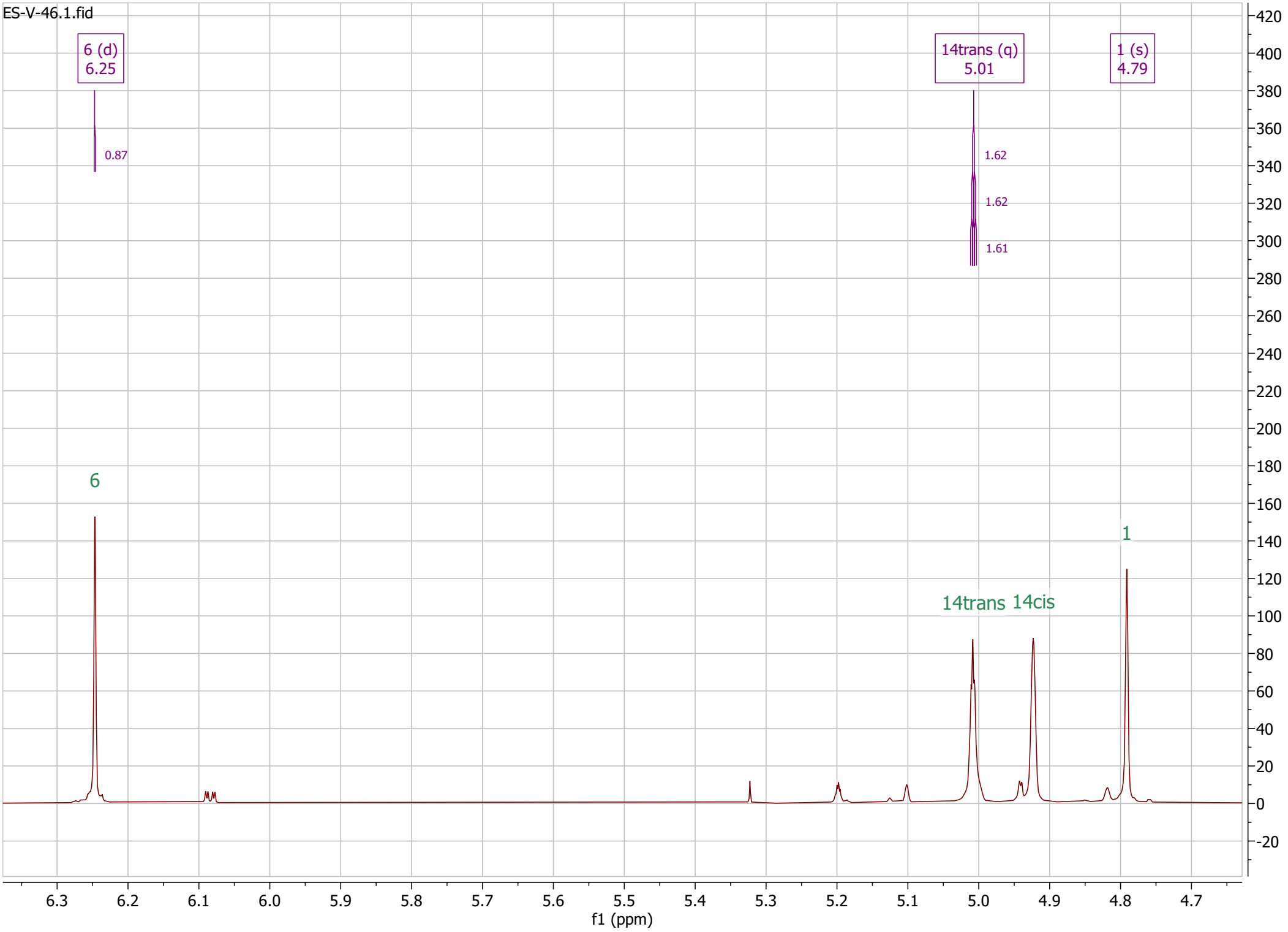
J (Hz)	H12'	H12"	C1
H2	4.0	10.9	0.0
C1	5.8	3.7	
C3	3.1	2.0	
C14	5.4	5.8	
C18	2.7	5.1	

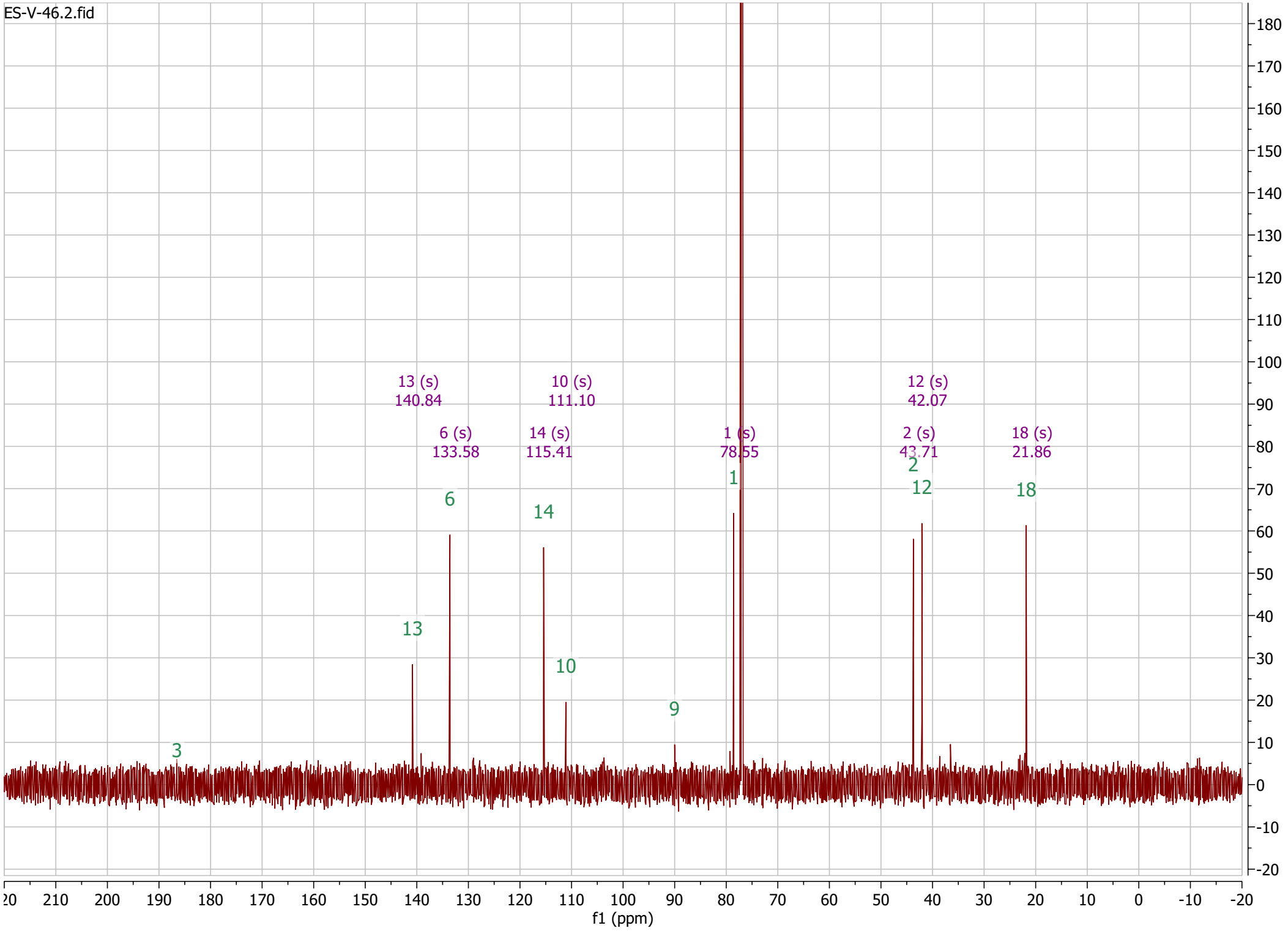
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.25 (d, J = 0.9 Hz, 1H), 5.01 (q, J = 1.6 Hz, 1H), 4.95 – 4.89 (m, 1H), 4.79 (s, 1H), 2.91 (dd, J = 10.9, 4.0 Hz, 1H), 2.72 (dd, J = 13.4, 11.0 Hz, 1H), 2.24 (dd, J = 13.1, 4.0 Hz, 1H), 1.87 (s, 1H).

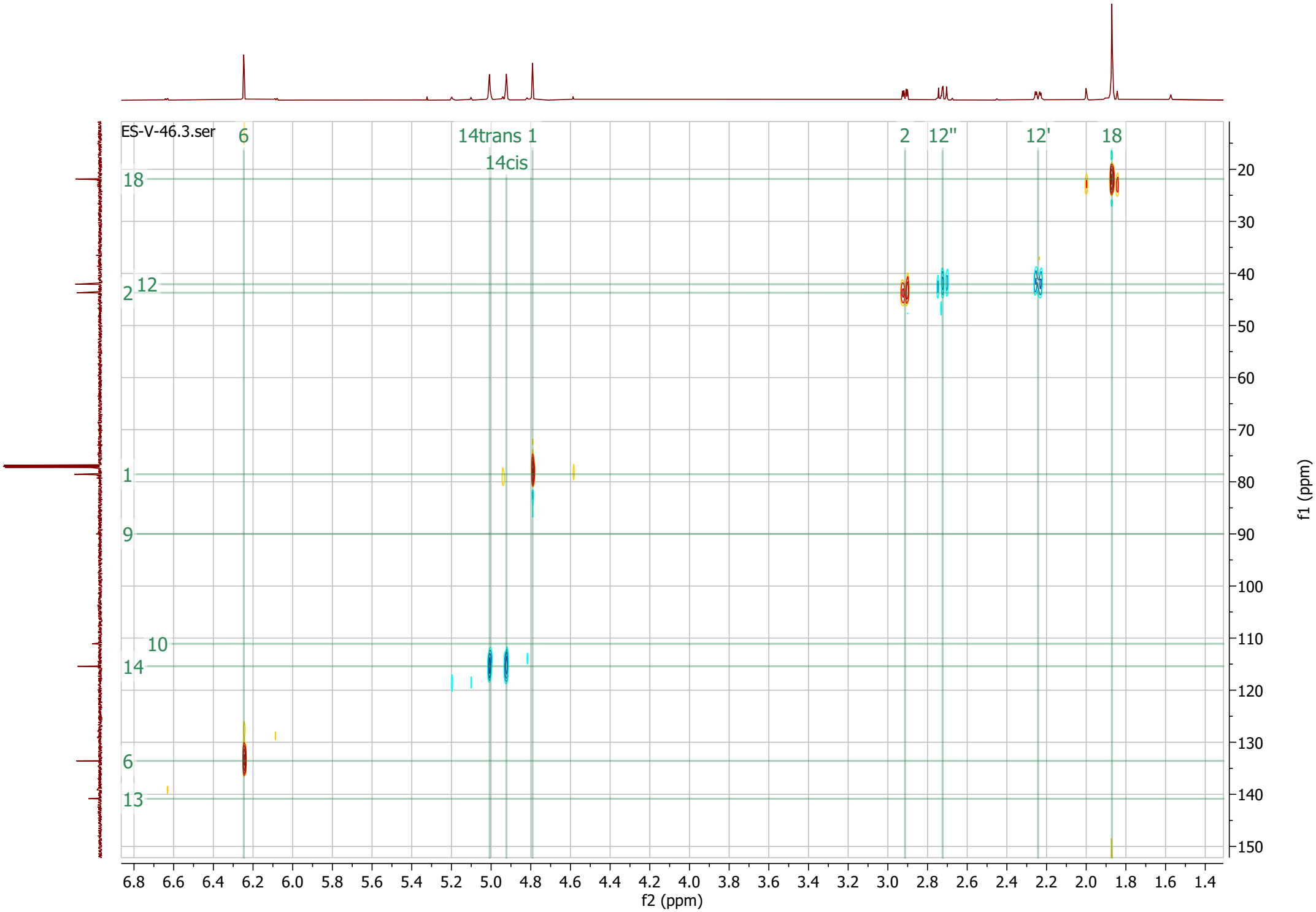
^{13}C NMR (151 MHz, $CDCl_3$) δ 186.49, 140.84, 133.58, 115.41, 111.10, 9,00, 78.55, 43.71, 42.07, 21.86.

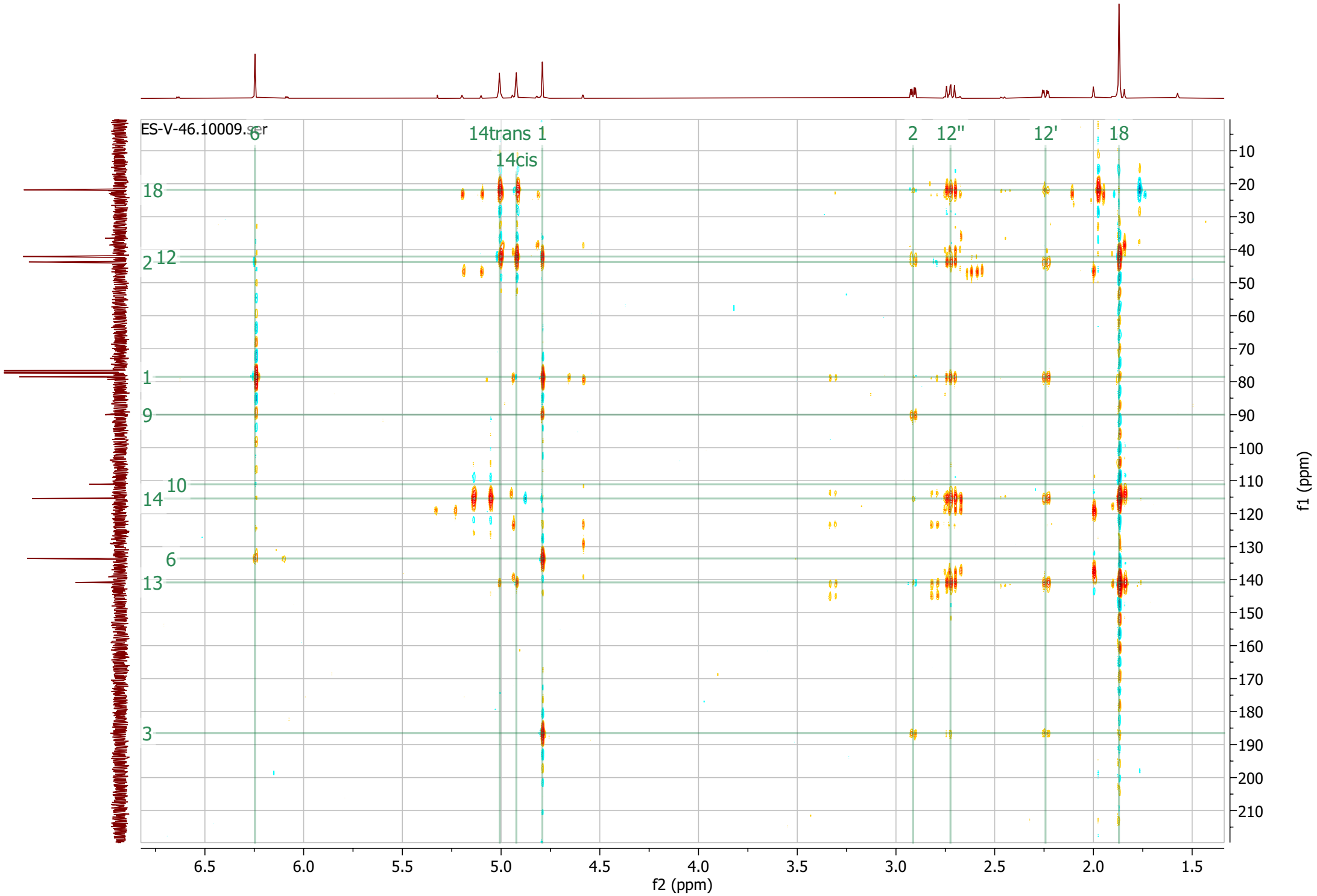

C3 : H2 - 5.1 Hz; H12" - 2.1 Hz.
18
6
1
14trans
14cis
2
12"
12'
1.00
1.26
1.23
0.98
1.03
1.30
1.10
3.29
f1 (ppm)

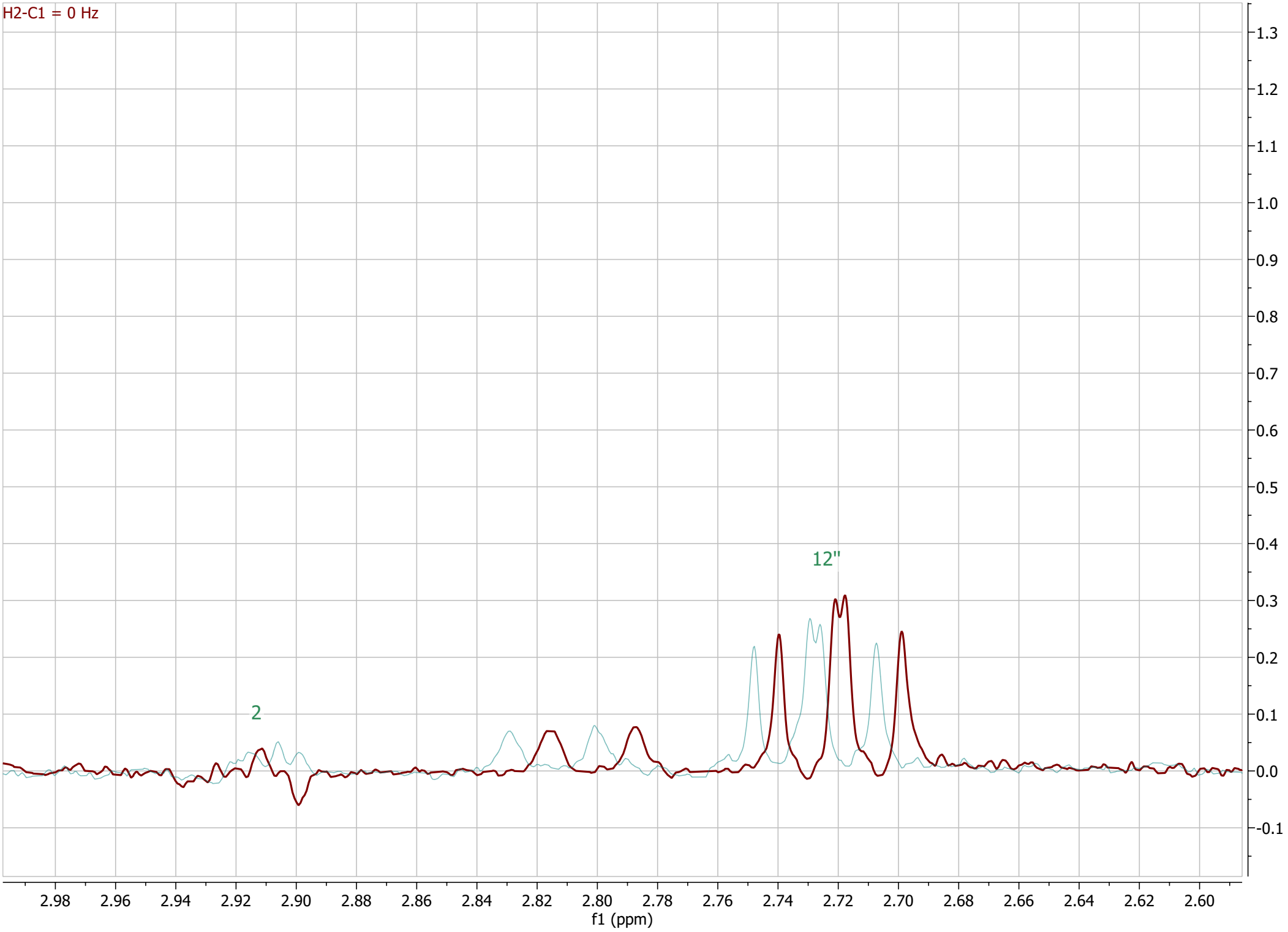

ES-V-46.1.fid
2 (dd)
2.91
10.89
3.98
12" (dd)
2.72
13.40
10.98
12' (dd)
2.24
13.05
4.03
2
12"
12'
f1 (ppm)

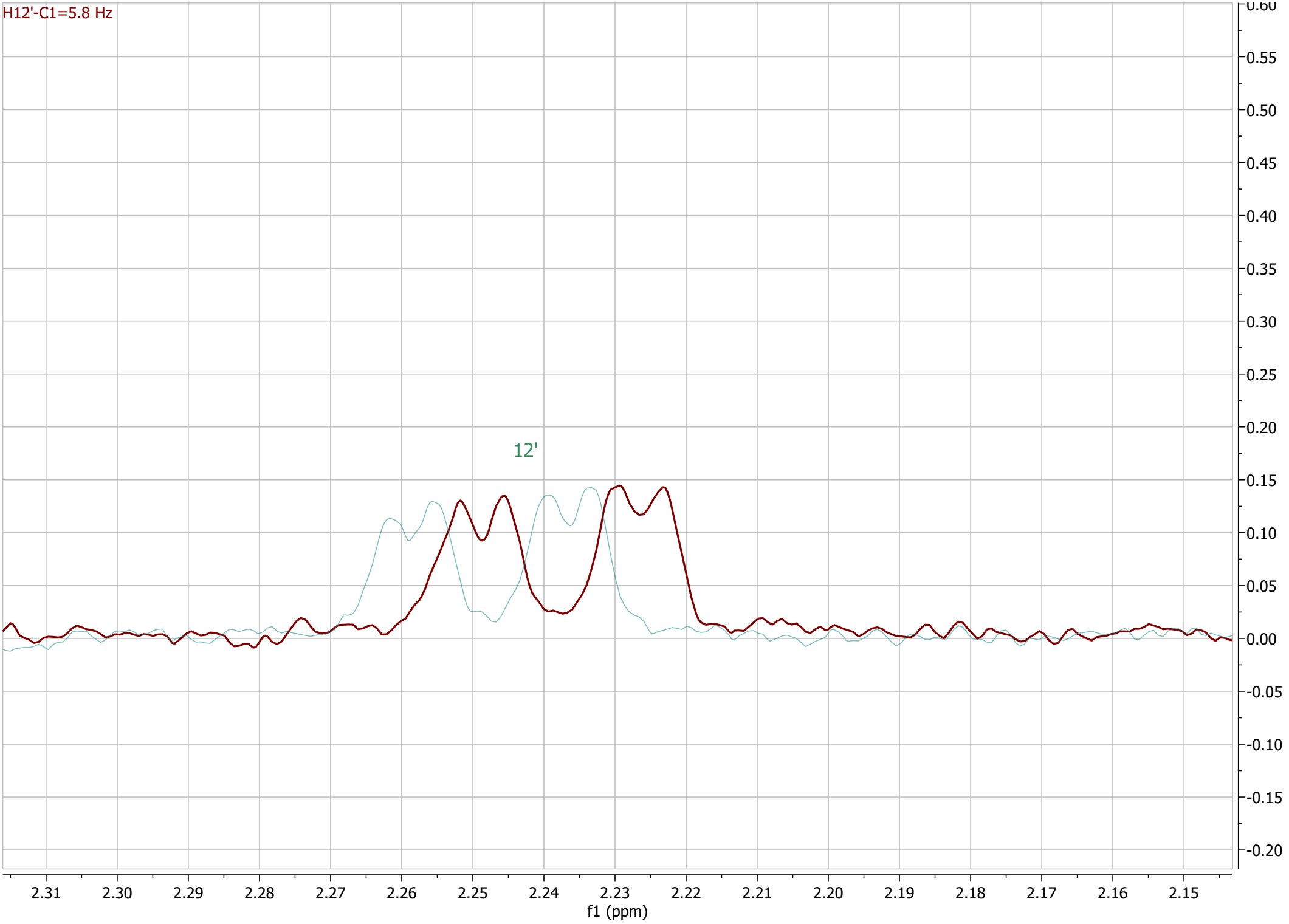

ES-V-46.1.fid
6 (d)
6.25
0.87
14trans (q)
5.01
1.62
1.62
1.61
1 (s)
4.79
6
14trans 14cis
1
f1 (ppm)

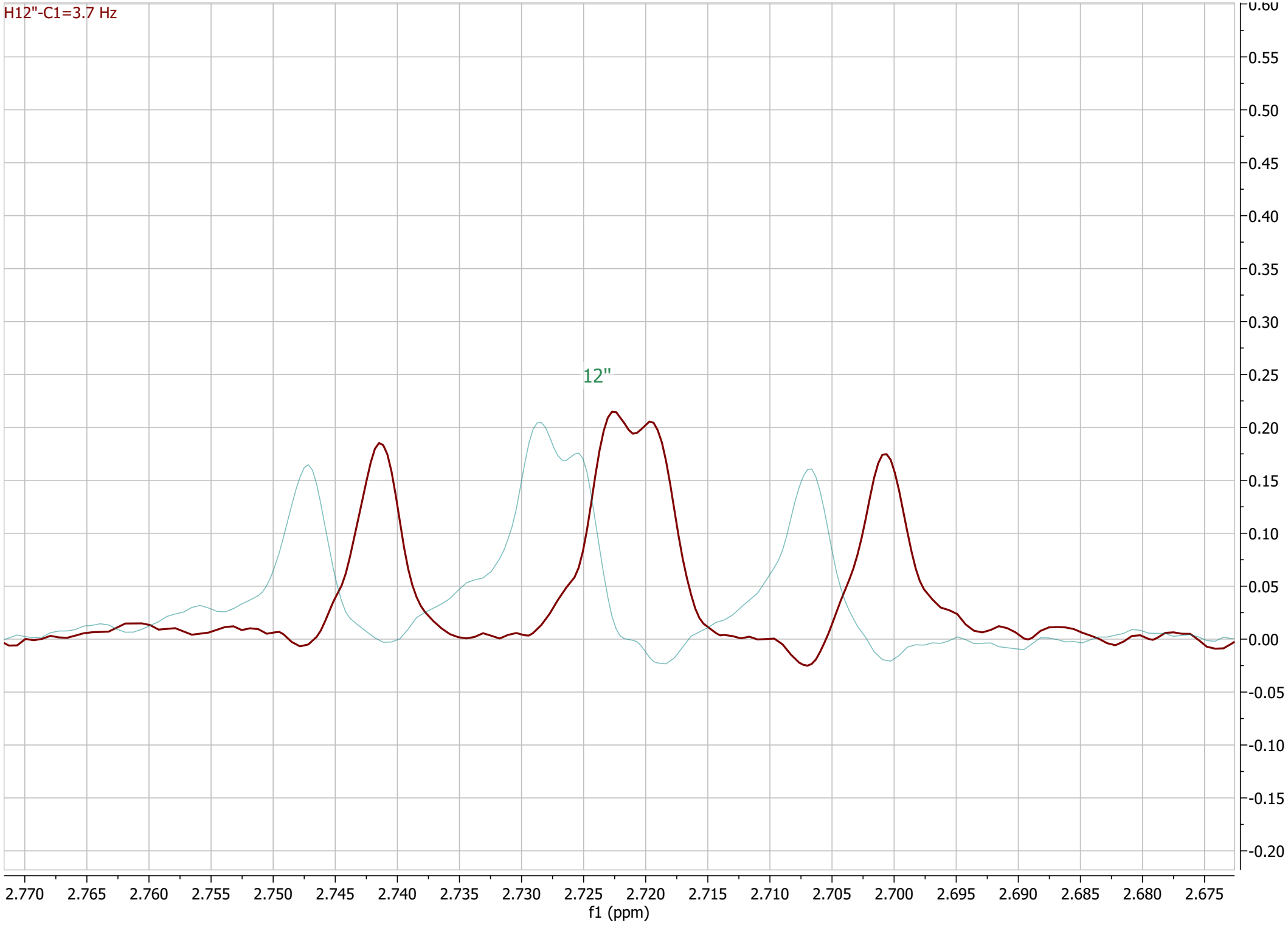

ES-V-46.2.fid
13 (s)
140.84
6 (s)
133.58
10 (s)
111.10
14 (s)
115.41
1 (s)
78.55
12 (s)
42.07
2 (s)
43.71
18 (s)
21.86
3
13
6
14
10
9
1
2
12
18
f1 (ppm)

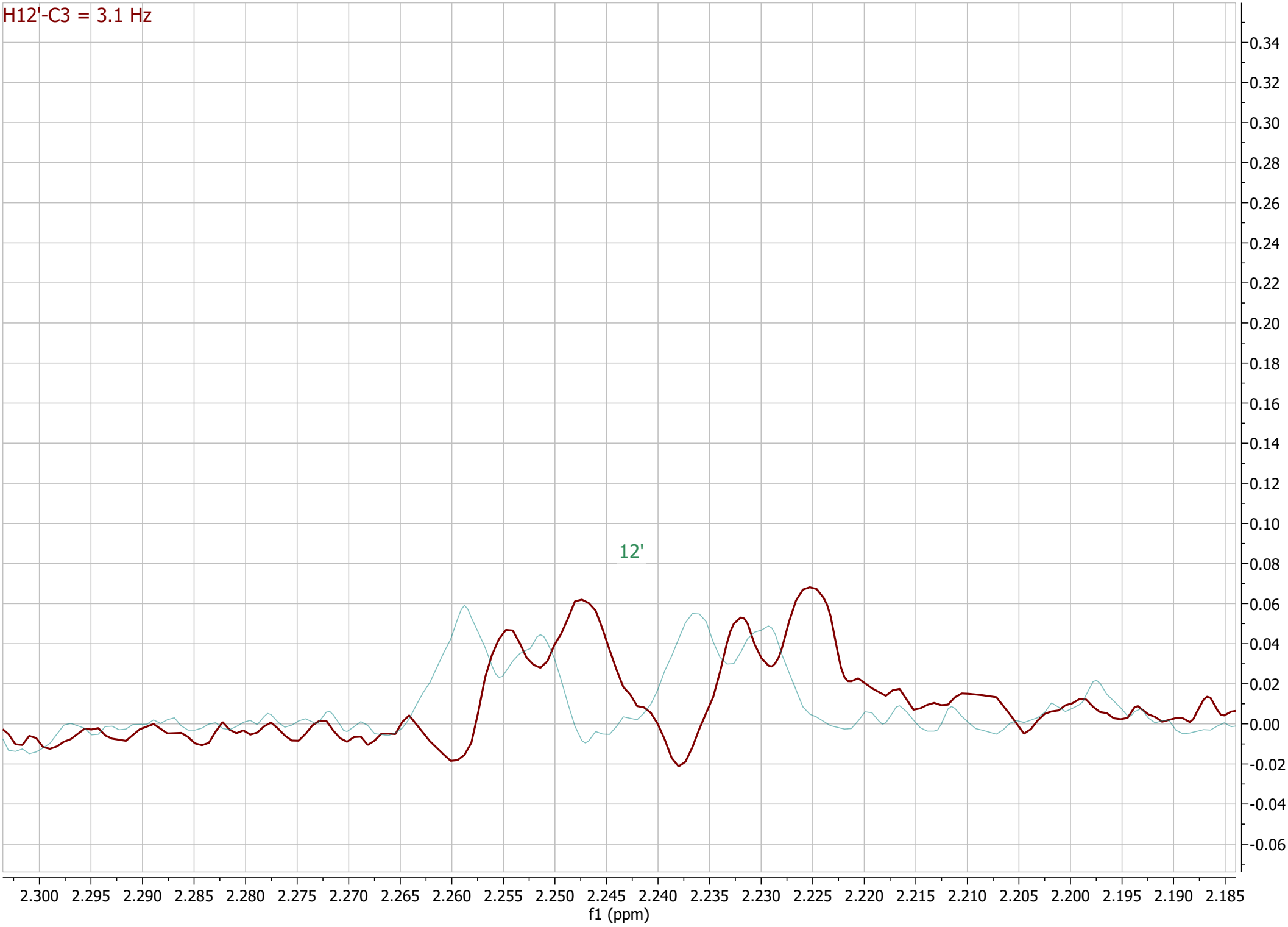

ES-V-46.3.ser
6
14trans
14cis
1
2
12"
12'
18
18
2
12
1
9
10
14
6
13
f2 (ppm)
f1 (ppm)

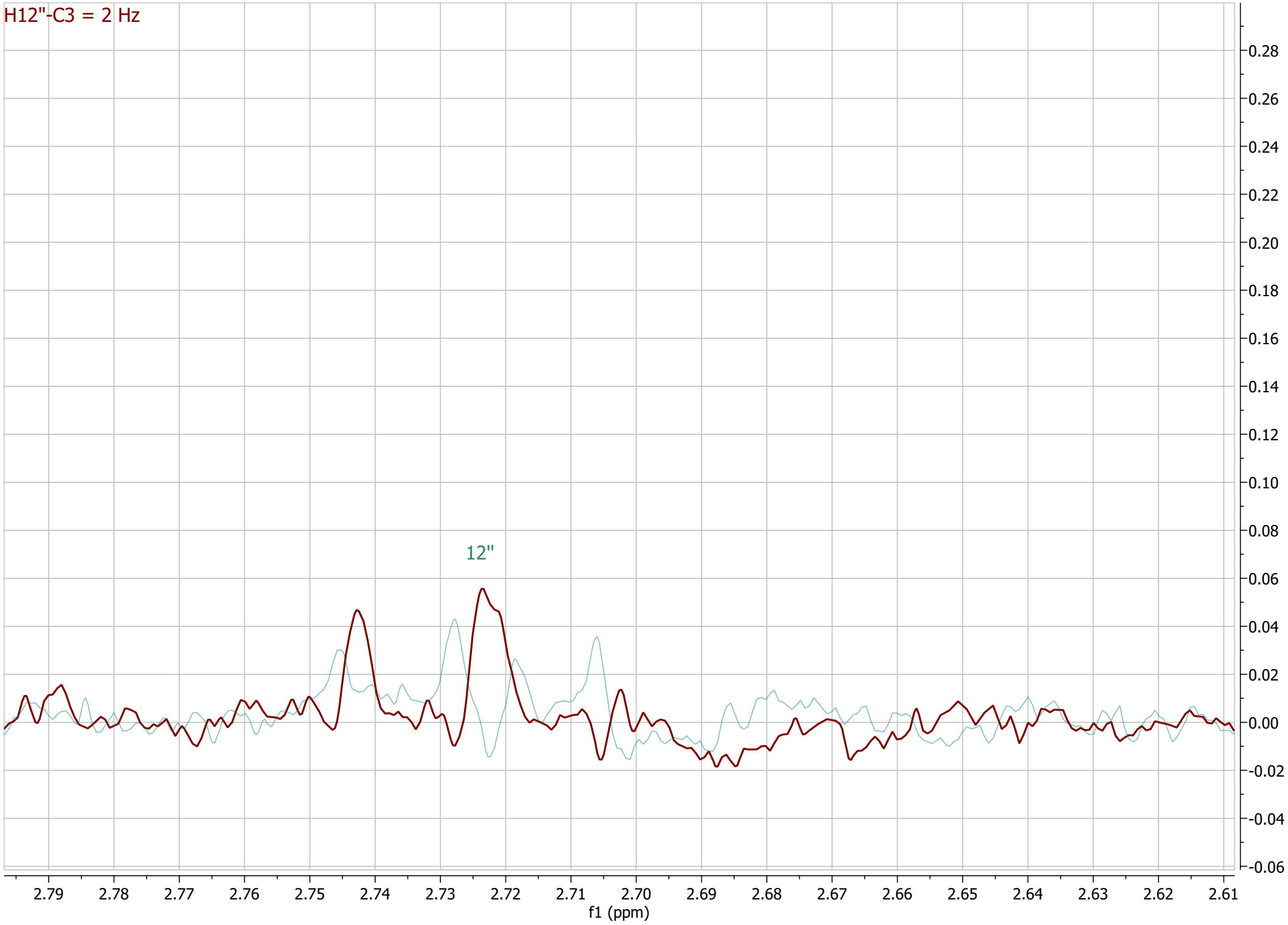

ES-V-46.10009.ser
6
14trans 1
14cis
2
12"
12'
18
18
2 12
1
9
10
14
6
13
3
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f2 (ppm)
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
f1 (ppm)

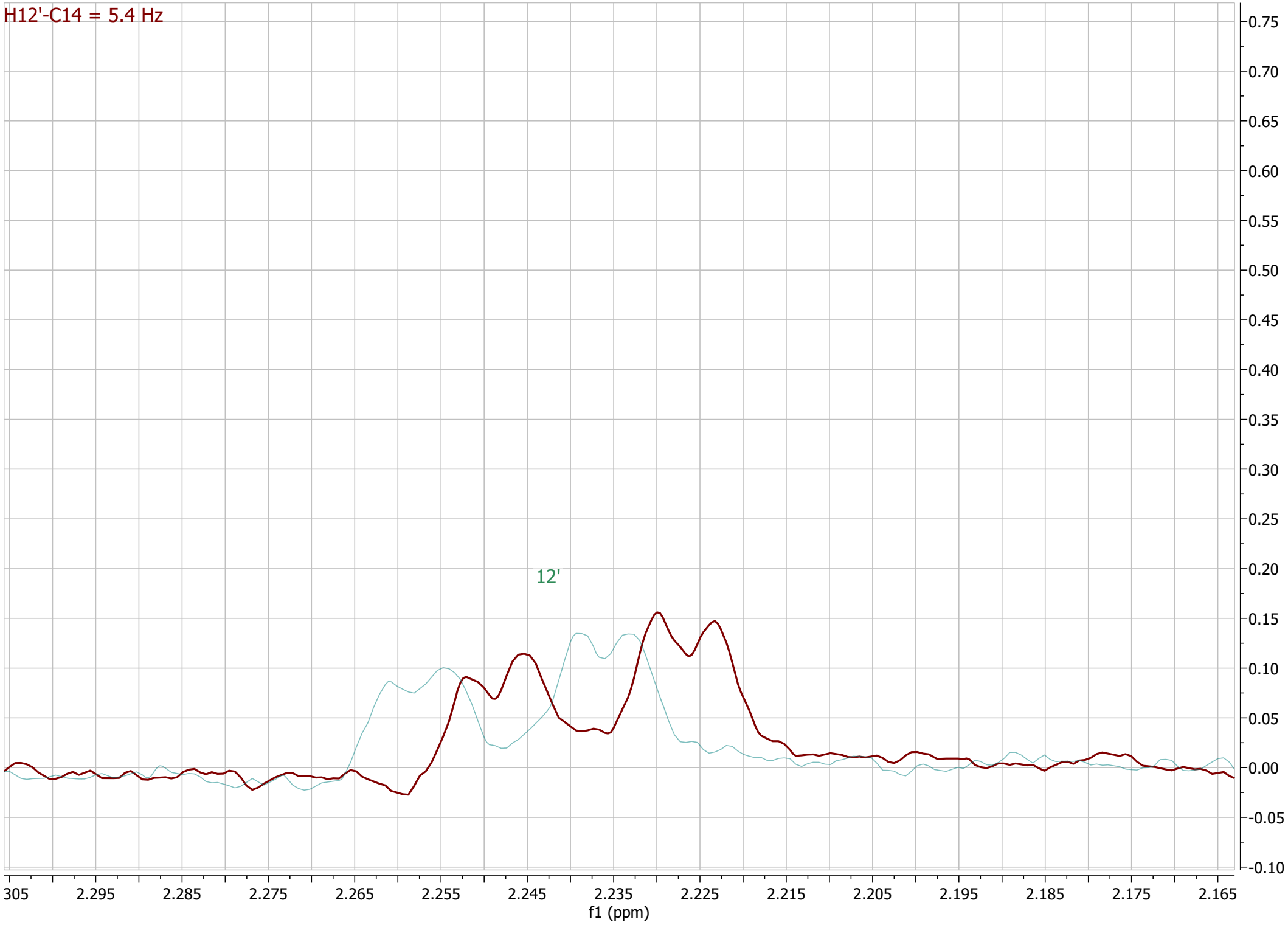

H2-C1 = 0 Hz
2
12"
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
2.98
2.96
2.94
2.92
2.90
2.88
2.86
2.84
2.82
2.80
2.78
2.76
2.74
2.72
2.70
2.68
2.66
2.64
2.62
2.60
f1 (ppm)

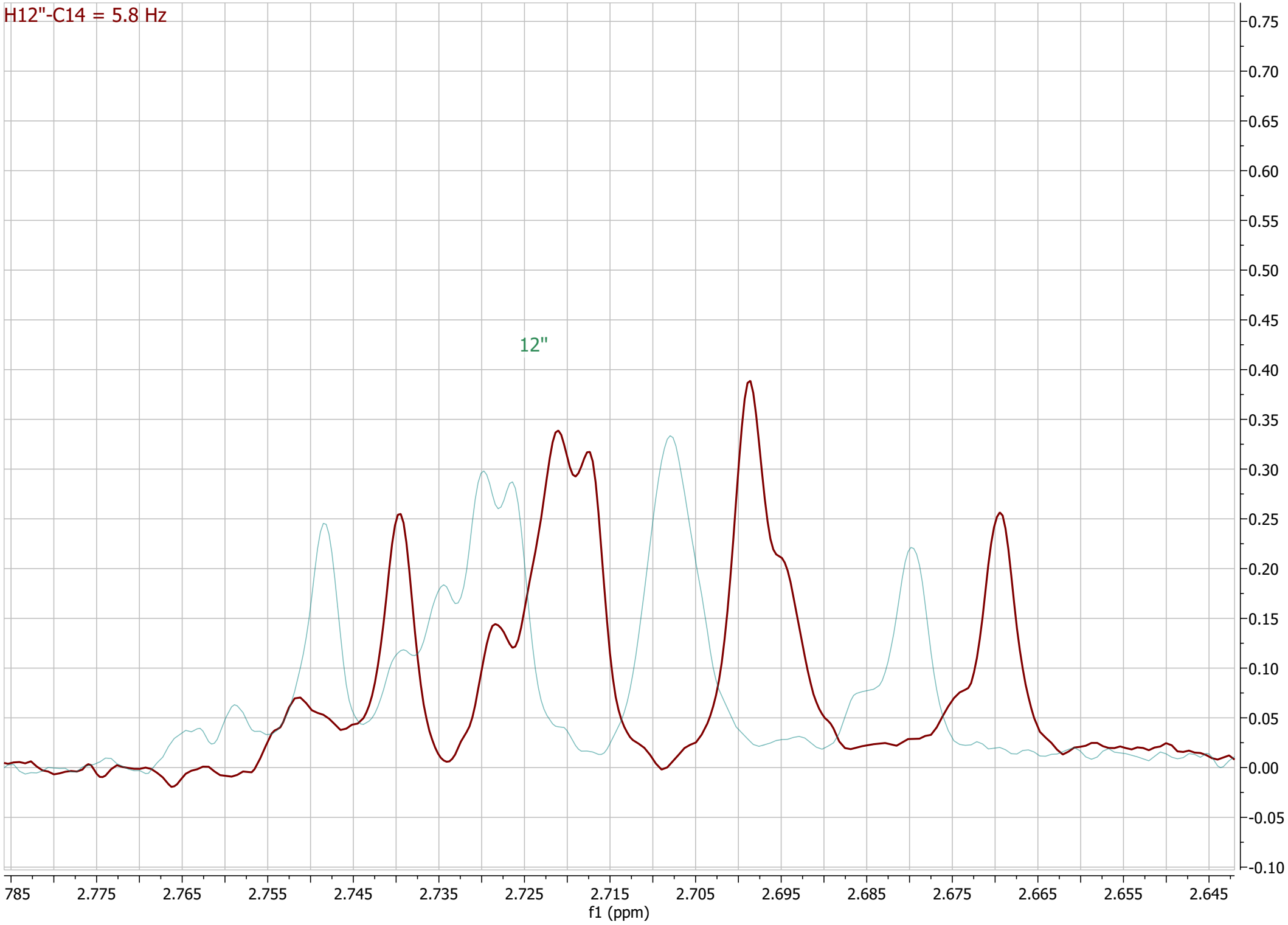

H12'-C1=5.8 Hz
12'
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
-0.10
-0.15
-0.20
2.31
2.30
2.29
2.28
2.27
2.26
2.25
2.24
2.23
2.22
2.21
2.20
2.19
2.18
2.17
2.16
2.15
f1 (ppm)

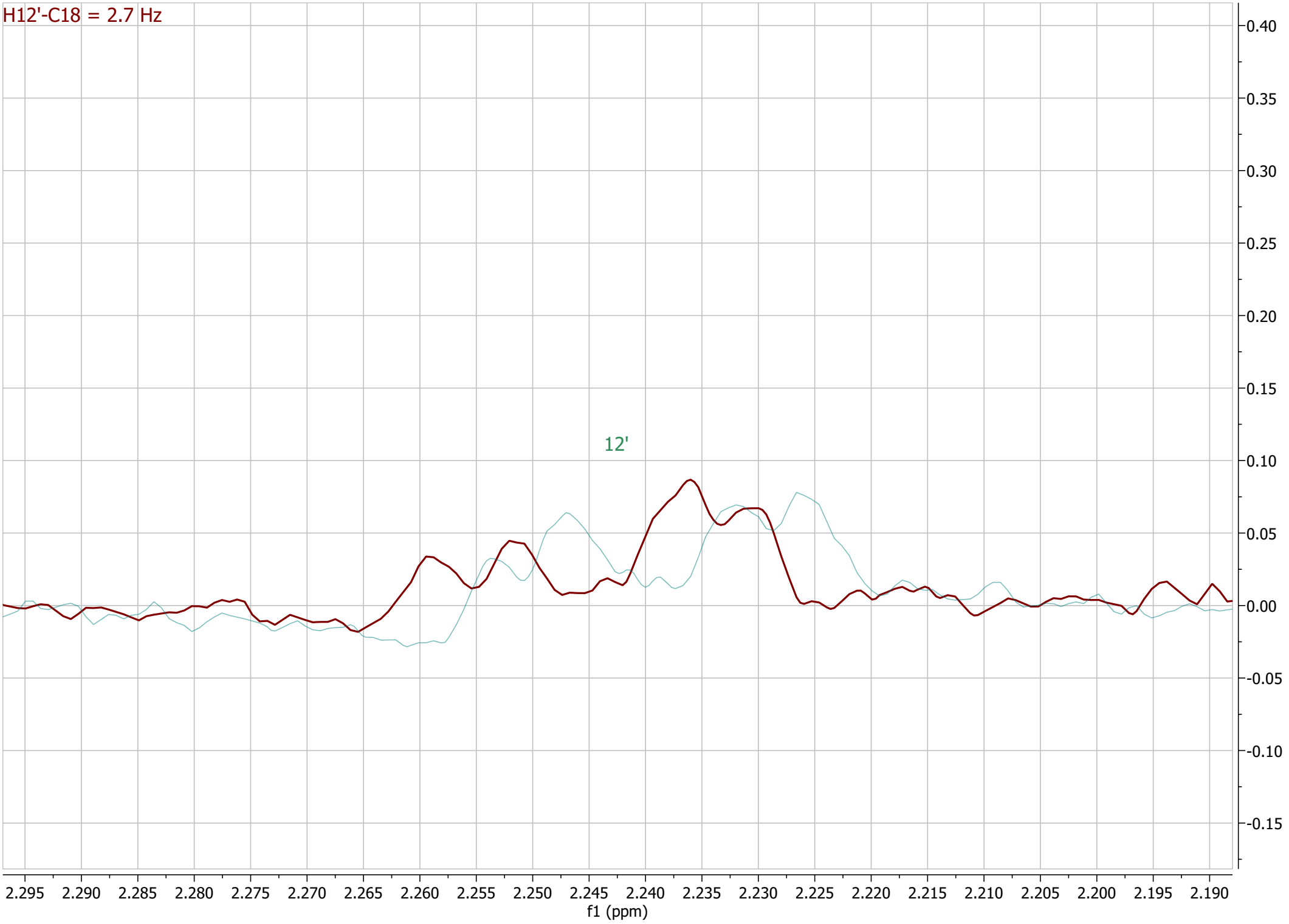

H12"-C1=3.7 Hz
12"
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
-0.10
-0.15
-0.20
2.770
2.765
2.760
2.755
2.750
2.745
2.740
2.735
2.730
2.725
2.720
2.715
2.710
2.705
2.700
2.695
2.690
2.685
2.680
2.675
f1 (ppm)

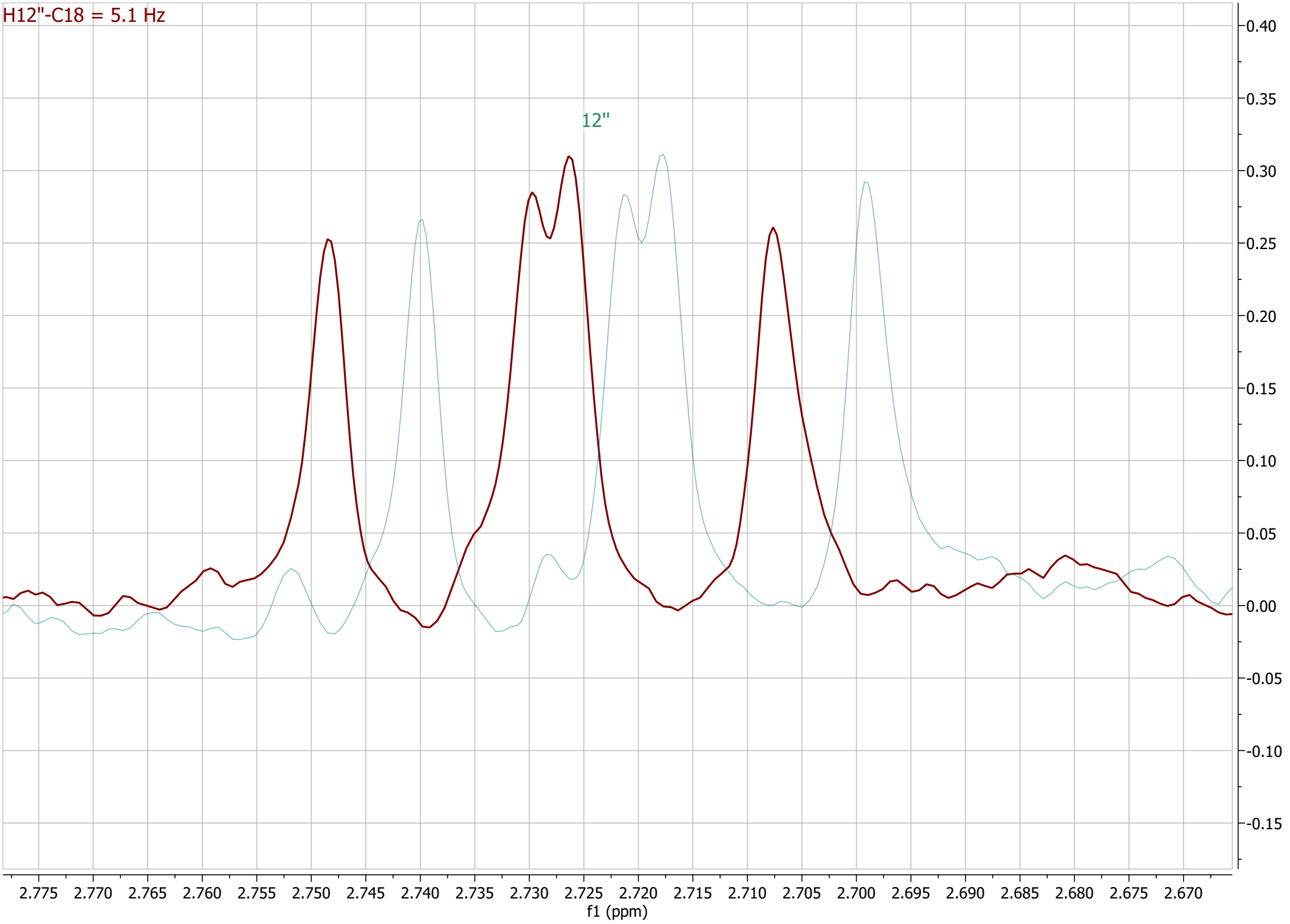

H12'-C3 = 3.1 Hz
12'
0.34
0.32
0.30
0.28
0.26
0.24
0.22
0.20
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
-0.02
-0.04
-0.06
2.300 2.295 2.290 2.285 2.280 2.275 2.270 2.265 2.260 2.255 2.250 2.245 2.240 2.235 2.230 2.225 2.220 2.215 2.210 2.205 2.200 2.195 2.190 2.185
f1 (ppm)


H12"-C3 = 2 Hz
12"
0.28
0.26
0.24
0.22
0.20
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
-0.02
-0.04
-0.06
2.79
2.78
2.77
2.76
2.75
2.74
2.73
2.72
2.71
2.70
2.69
2.68
2.67
2.66
2.65
2.64
2.63
2.62
2.61
f1 (ppm)


H12'-C14 = 5.4 Hz
12'
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
-0.10
305
2.295
2.285
2.275
2.265
2.255
2.245
2.235
2.225
2.215
2.205
2.195
2.185
2.175
2.165
f1 (ppm)


H12"-C14 = 5.8 Hz
12"
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
-0.10
785
2.775
2.765
2.755
2.745
2.735
2.725
2.715
2.705
2.695
2.685
2.675
2.665
2.655
2.645
f1 (ppm)


H12'-C18 = 2.7 Hz
12'
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
-0.10
-0.15
2.295
2.290
2.285
2.280
2.275
2.270
2.265
2.260
2.255
2.250
2.245
2.240
2.235
2.230
2.225
2.220
2.215
2.210
2.205
2.200
2.195
2.190
f1 (ppm)


H12"-C18 = 5.1 Hz
12"
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
-0.10
-0.15
2.775
2.770
2.765
2.760
2.755
2.750
2.745
2.740
2.735
2.730
2.725
2.720
2.715
2.710
2.705
2.700
2.695
2.690
2.685
2.680
2.675
2.670
f1 (ppm)