Synthesis and Biological Evaluation of Hippolachnin A Analogs

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Supporting Information

Table of Contents:

General Information

Unless otherwise noted, reactions were performed in either oven (115 ºC)- or flame-dried glassware and under an atmosphere of nitrogen or argon employing standard Schleck techniques. Diethyl ether, tetrahydrofuran (THF), methylene chloride,

and toluene were purified by passage through columns of activated alumina under nitrogen (Grubbs apparatus). All work-up and purification procedures were carried out using reagent grade solvents and reagents. Flash column chromatography (FCC) was performed with 200–400 mesh silica gel (Sillicycle, P60). Thin layer chromatography (TLC) was performed on silica gel 60 F254 (EMD Chemicals Inc.). Room temperature is 23 °C. Infrared spectra were obtained using a Bruker Alpha ATR-IR. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400, Varian 500, or Bruker 600. Chemical shifts (δ) are reported in parts per million (ppm) relative to internal residual solvent peaks from indicated deuterated solvents. Coupling constants (*J*) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. Resonance multiplicities are defined as: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets. High Resolution Mass (HRMS) analysis was obtained using electro-spray ionization (ESI) were obtained on a ThermoScientific LTQ Orbitrap and the found mass represents an average of three, individual, direct infusions.

Reagents

1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate [abbreviated White's Catalyst] was purchased from Strem and used as received.

2-[2-(2-Propynyloxy)ethoxy]ethylamine was purchased from Ark Pharm and used as received.

Acetonitrile was purchased from Sigma-Aldrich and stored over activated 3Å molecular sieves.

***n*-Butanol** was purchased from Aldrich in a Sure-Seal bottle and used as received.

Chlorotrimethylsilane was purchased from Sigma-Aldrich and distilled over CaH_2 immediately prior to use.

(*R,R*)-(−)-*N,N′*-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamine [abbreviated Cr(Salen)Cl] was purchased from Strem and was used as received.

1,4-Dioxane was purchased from Sigma-Aldrich in a Sure-Seal bottle and used as received.

4-(dimethylamino)pyridine was purchased from Sigma-Aldrich and used as received

***N*-(3-Dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (EDC)** was purchased from Sigma-Aldrich and used as received.

Ethylene (99.9% purity) was purchased from Praxair and used as received.

Grubb's 1st generation catalyst was purchased from Sigma-Aldrich and stored in a dessicator and weighed out under air.

Potassium bis(trimethylsilyl)amide was purchased from Sigma-Aldrich and was used as received.

Palladium on carbon (5 % w/w) was purchased from Sigma-Aldrich and used as received.

***p*-benzoquinone** was purchased from Sigma-Aldrich and sublimed immediately prior to use.

Potassium carbonate was purchased from BDH and was used as received.

Quadricyclane was purchased from Exciton (Dayton, OH), was used as received and was stored at 0 °C under argon.

Rhodium on Alumina was purchased from Sigma-Aldrich and used as received

Sodium Carbonate was purchased from Sigma-Aldrich and used as received.

***tert*-butyl acetate** was purchased from Alfa Aesar and used as received.

***tert*-butyl lithium** was purchased from Sigma-Aldrich and used as received.

Titanium (IV) chloride was purchased from Sigma-Aldrich (neat) and used as received.

Trifluoroacetic acid was purchased from Oakwood and used as received.

Wood Total Synthesis of Hippolachnin A (1)

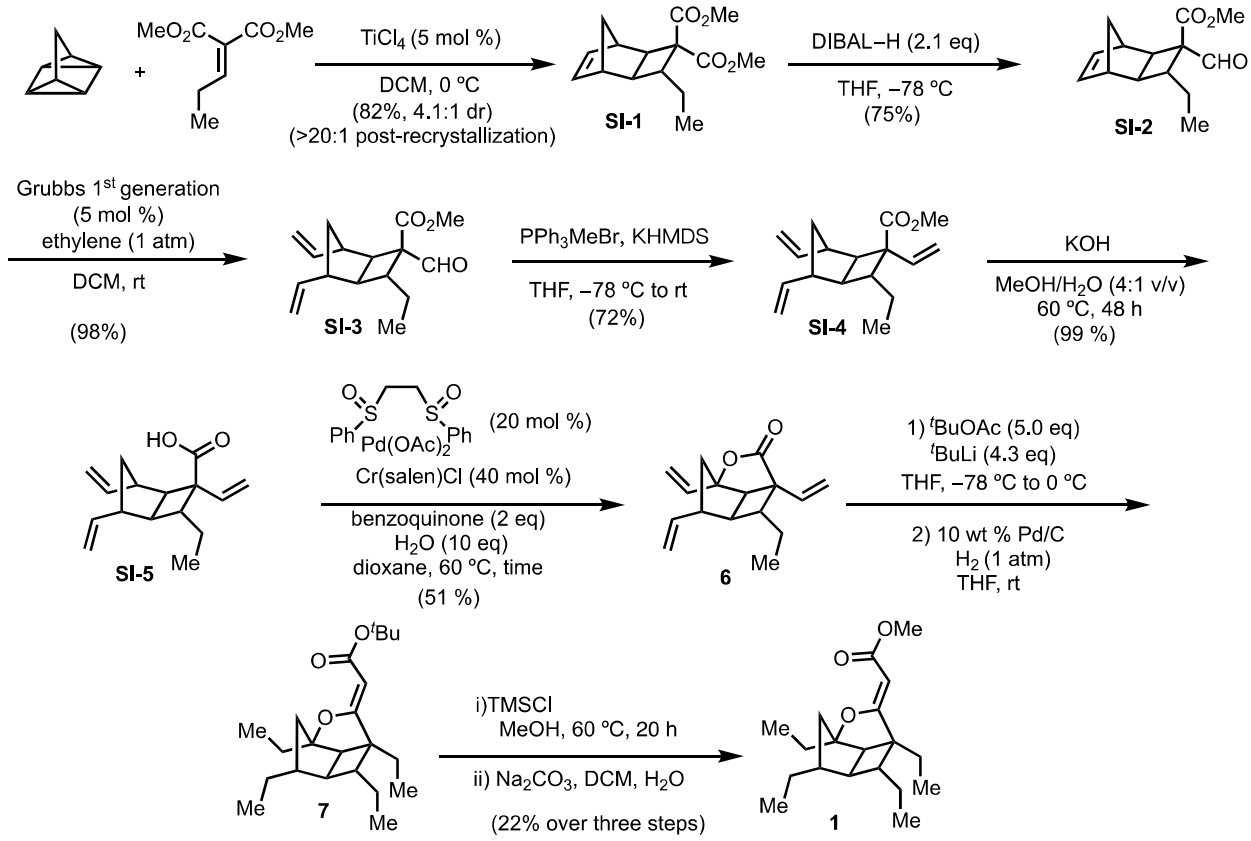


Figure S1. The Wood total synthesis of **1.**

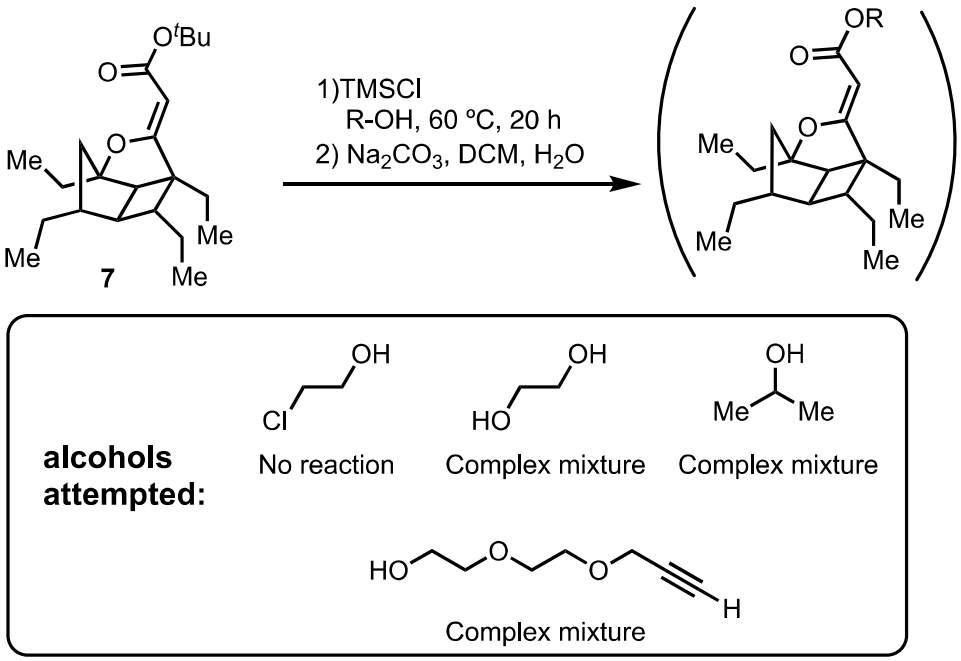
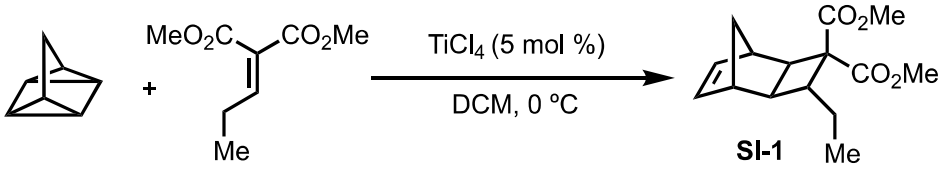


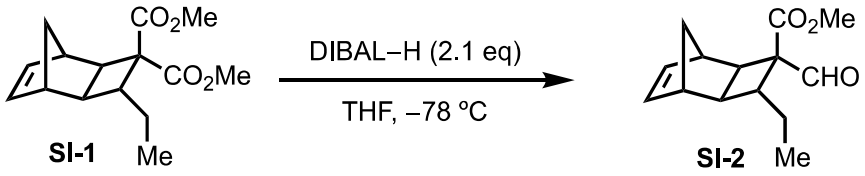
Figure S2. Unsuccessful substrates in the final transesterification step.

Experimental Procedures:

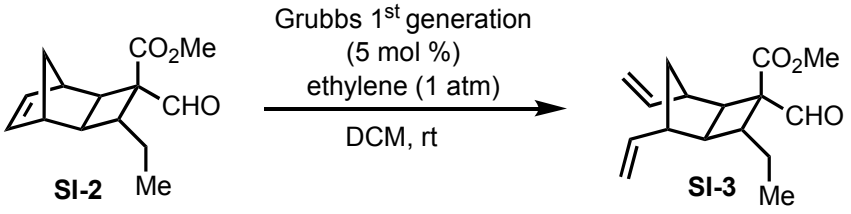


Dimethyl 4-ethyltricyclo[4.2.1.^{02,5}]non-7-ene-3,3-dicarboxylate (SI-1). Adapted from our previously described procedure:[S1] A stirred solution containing dimethyl 2-propylidenemalonate[S2] (12.05 g, 69.7 mmol) and quadricyclane (9.8 mL, 104.7 mmol) in DCM (35 mL) was cooled to 0 ºC before neat $TiCl_4$ (0.4 mL, 3.67 mmol) was added dropwise over 10 minutes. After stirring at 0 ºC for 1 hour, diethyl ether (30 mL) was added, followed by saturated aqueous NH_4Cl (30 mL). The layers were separated and the aqueous phase extracted with diethyl ether (3 x 40 mL). The combined organic phases were washed with saturated NH_4Cl (40 mL) and brine (40 mL) before being dried over $MgSO_4$. Volatiles were removed *in vacuo*. The resulting oil was purified by

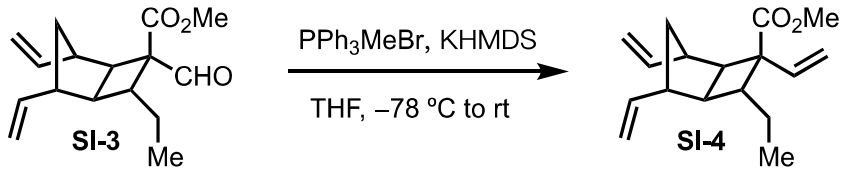
silica gel chromatography (hexanes–EtOAc = 98:2) to yield **SI-1** (13.21 g, 73%) as a colorless oil and as a 4.8:1 mixture of diastereomers. On standing at room temperature, **SI-1** began to partially solidify over the course of ca. 4 hours. Cold pentane (20 mL) was added and the residue decanted. The crystals were washed with cold pentane (2 x 5 mL) to give SI-1 in >25:1 dr. This process was repeated with the mother liquor twice to afford 3.01 g (17%) of **SI-1**. The spectral data of **SI-1** matched those reported previously.



Methyl 4-ethyl-3-formyltricyclo[4.2.1.02,5]non-7-ene-3-carboxylate (SI-2): Adapted from our previously described procedure:[S1] A stirred solution of **SI-1** (790 mg, 2.9 mmol) in methylene chloride (6 mL) was cooled to –78 ºC before DIBAL–H (6.2 mL, 1.0 M solution in hexanes), was added dropwise over 15 minutes. After 40 minutes at this temperature, acetone (6.0 mL) was added via syringe over 5 minutes, followed by diethyl ether (6.0 mL). The reaction was then removed from the cold bath and H_2O was (0.2 mL) added. The reaction was allowed to warm to 24 °C with vigorous stirring. Once at room temperature, 1M NaOH (0.2 mL) was added followed by H_2O (0.2 mL). The reaction as then stirred for 1 hour before being filtered over a pad of Celite, which was eluted with diethyl ether and concentrated. The resulting oil was purified by silica gel chromatography (hexanes–EtOAc = 98:2) to afford **SI-2** (520.5 mg, 75%) as a colorless oil. The spectral data of **SI-2** matched those reported previously.

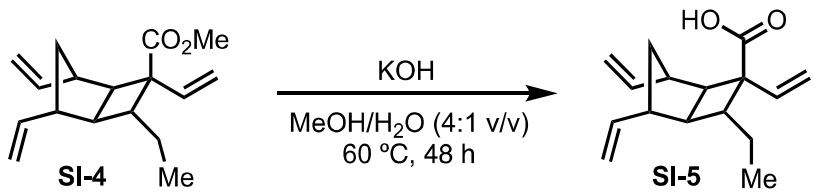


Methyl 7-ethyl-6-formyl-2,4-divinylbicyclo[3.2.0]heptane-6-carboxylate (SI-3). Adapted from our previously described procedure:[S1] A stirred solution of **SI-2** (1.05 g, 4.48 mmol) in methylene chloride (200 mL) was sparged with ethylene for 15 minutes before Grubbs 1st generation catalyst (68.5 mg, 0.89 mmol) was added in one portion under an atmosphere of ethylene. The reaction was let to stir for 1 hour under an atmosphere of ethylene before being concentrated. The resulting residue purified by silica gel chromatography (hexanes–EtOAc = 98:2) to give **SI-3** (1.07 g, 94%) as a colorless oil. The spectral data of **SI-3** matched those previously reported.

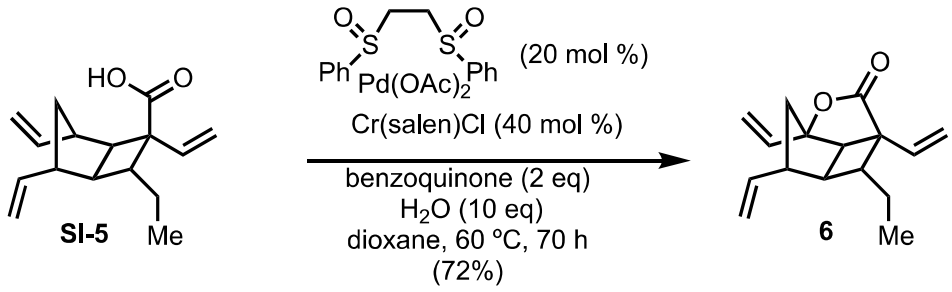


Methyl (7-ethyl-2,4,6-trivinylbicyclo[3.2.0]heptane-6-carboxylate (SI-4): Adapted from our previously described procedure:[S1] A slurry containing $PPh_3(Me)Br$ (1.61 g, 4.5 mmol) in THF (6 mL) was cooled to 0 ºC. KHMDS (9.0 mL, 0.5 M in PhMe) was added dropwise via syringe and the reaction allowed to warm to room temperature and stirred for 30 minutes before being cooled to –78 ºC. A solution of **SI-3** (1.07 g, 4.08 mmol) in

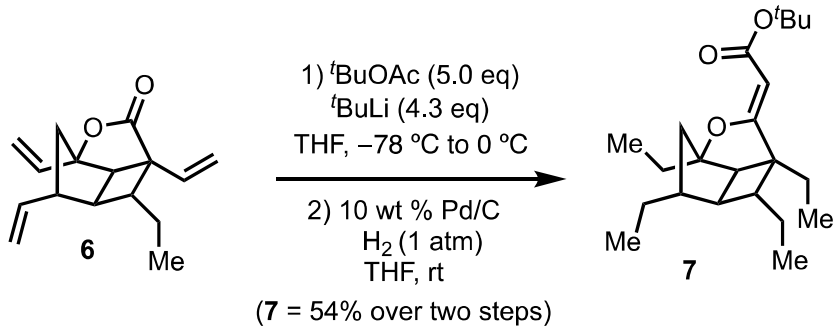
PhMe (4 mL) was added dropwise to this solution. The reaction was allowed to stir at –78 ºC for 1 hour before being warmed to 24 °C and stirred for 45 minutes before being quenched with saturated NH_4Cl (10 mL). The phases were separated and aqueous phase extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with sat. brine and dried over $MgSO_4$. The volatile material was removed in vacuo. The resulting oil purified by silica gel chromatography (hexanes–EtOAc = 100:0→85:15) to afford **SI-4** (838 mg, 79%) as a colorless oil. The spectra data of **SI-4** matched those previously reported.



7-ethyl-2,4,6-trivinylbicyclo[3.2.0]heptane-6-carboxylic acid (SI-5): Adapted from our previously described procedure:[S1] To a solution containing **SI-4** (838 mg, 3.23 mmol) in MeOH (4.5 mmol) was added 5 M KOH (2.2 mL) and heated to 60 ºC for 48 hours. The reaction was then cooled to room temperature and 5 mL diethyl ether added. The phase separated and organic phases washed with 1 M NaOH (3 x 2mL). The combined aqueous extracts were acidified to pH 1 with 6 M HCl, then extracted with diethyl ether (4 x 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (hexanes–EtOAc = 4:1) to give **SI-5** as a colorless microcrystalline solid. The spectral data of **SI-5** matched those previously reported.



Ethyl-2,3a,5a-trivinylhexahydro-4-oxacyclobuta[cd]pentalen-5(1H)-one (6): Adapted from our previously described procedure: [S1] Dioxane (15 mL) was added to a flask containing **SI-5** (490 mg, 1.99 mmol), White's Catalyst (184.2 mg, 0.368 mmol), Cr(salen)Cl (433 mg, 0.685 mmol), and *p*-benzoquinone (392 mg, 3.562 mmol) and the solution stirred under an atmosphere of argon. Deionized water (0.294 mL) was added via syringe and the reaction heated to 60 ºC for 70 hours. The reaction was then cooled to room temperature, diluted with diethyl ether (30 mL), washed sequentially with saturated aqueous sodium metabisulfite (20 mL), saturated aqueous sodium thiosulfate (20 mL) 1M HCl (20 mL, and saturated brine (20 mL). The organic layer was dried over MgSO4 and concentrated under vacuum. The cured residue was purified by silica gel chromatography (hexanes–EtOAc = 4:1) to afford **6** (350.4 mg, 72%) as a yellow oil, which solidified during storage at –20 ºC. The spectral data for **6** matched those previously reported.

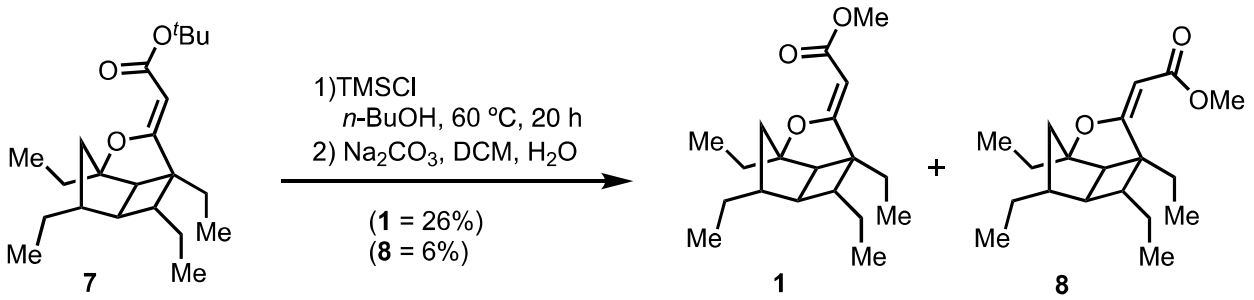


***Tert*-butyl (*Z*)-2-(1,2,3a,5a-tetraethylhexahydro-4-oxacyclobuta[cd]pentalen-5(1H)-ylidene)acetate (7)**: Adapted from our previously described procedure:[S1] A stock solution containing *tert*-butyl acetate (1.7 mL, 12.6 mmol, 0.63 M), THF (20.0 mL) and 4 Å molecular sieves (10 % w/v) was let to sit overnight. *Tert*-butyl lithium (2.65 mL, 1.3 M in pentane) was added to stirred solution of THF at – 78 ºC. A stock solution of tert-butyl acetate (6.4 mL, 0.63 M, 4.0 mmol) was added dropwise to the yellow solution and stirred for 15 minutes at –78 ºC. A solution containing lactone **6** (199 mg, 0.8 mmol) in THF (10 mL) was added dropwise to the colorless solution and at –78 ºC for 2 hours before being placed in an ice bath and stirring for an additional 2 hours. The reaction was quenched by addition of 6 M HCl (15 mL) and allowed to warm to room temperature before being diluted with diethyl ether (30 mL) and layers separated. The aqueous phase was extracted with diethyl either (2 x 20 mL) and the combined organic phases dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude NMR of this residue was pure enough to use in the next step (> 90 % purity by ^{1}H NMR) and indicated a ~1.0:1.3 mixture of Z/E isomers, respectively (**SI-6a** and **SI-6b**, respectively).

Palladium on carbon (28.0 mg, 5 wt % loading) was added to a solution of the crude material (175 mg, 0.53 mmol) in THF (10 mL). The reaction as stirred vigorously under a hydrogen atmosphere. After 2 hours, the suspension was filtered over a pad of Celite, which was eluted with diethyl ether (30 mL). The filtrate was concentrated under vacuum and the residue purified by silica gel chromatography (hexanes–EtOAc = 95:5) to give (*Z*)-**7** (97.9 mg, 54%) and (*E*)-**7** (71.5 mg) as colorless oils. (*E*)-**7** co-eluted with unknown and inseparable impurities.

For **SI-6a**/**SI-6b**: TLC (EtOAc–hexanes = 5:95): R_f = 0.36. ^{1}H NMR (600 MHz, Chloroform-*d*): δ 6.58 (dd, *J* = 17.4, 10.6 Hz, 1 H), 5.96 (ddd, *J* = 17.3, 10.9, 1.6 Hz, 2 H), 5.75 (td, *J* = 10.3, 5.4 Hz, 1 H), 5.40 (dd, *J* = 17.1, 1.2 Hz, 1 H), 5.29 (dd, *J* = 17.2, 1.3 Hz, 1 H), 5.22 (s, 1 H), 5.21 – 5.16 (m, 1 H), 5.14 – 4.98 (m, 4 H), 4.97 – 4.89 (m, 2 H), 4.60 (s, 1 H), 3.17 (d, *J* = 8.7 Hz, 1H), 3.10 (d, *J* = 8.7 Hz, 1 H), 2.96 – 2.78 (m, 1 H), 2.51 (dd, *J* = 13.9, 5.9 Hz, 1 H), 2.24 (dd, *J* = 13.6, 5.9 Hz, 1 H), 2.14 (dt, *J* = 11.7, 2.8 Hz, 1 H), 2.08 – 1.96 (m, 2 H), 1.93 – 1.85 (m, 1 H), 1.79 (t, *J* = 12.8 Hz, 1 H), 1.48 (d, *J* = 1.7 Hz, 5 H), 1.45 (s, 9 H), 0.88 (t, *J* = 7.3 Hz, 4 H), 0.82 (t, *J* = 7.3 Hz, 1 H). ^{13}C NMR (151 MHz, Chloroform-*d*): δ 181.3, 178.0, 166.5, 165.7, 140.0, 139.7, 137.9, 137.7, 136.3, 135.1, 115.3, 114.4, 114.3, 113.9, 113.8, 113.7, 101.2, 97.5, 89.7, 88.3, 78.7, 78.5, 57.8, 57.6, 54.5, 54.1, 51.3, 50.4, 49.8, 49.3, 48.0, 47.0, 46.1, 45.8, 28.4, 28.4, 24.7, 10.9, 10.8.

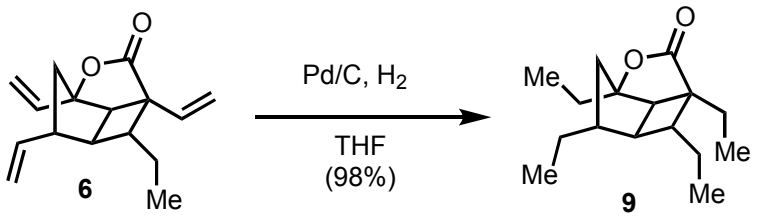
For (*Z*)-**7**: TLC (EtOAc–hexanes = 5:95): R_f = 0.16. ^{1}H NMR (600 MHz, Chloroform-*d*): δ 4.45 (s, 1 H), 2.57 (d, *J* = 8.2 Hz, 1 H), 2.42 (dd, *J* = 13.8, 6.5 Hz, 1 H), 2.04 – 1.95 (m, 1H), 1.90 – 1.57 (m, 5 H), 1.48 (s, 11 H), 1.43 – 1.19 (m, 3 H), 1.00 (t, *J* = 7.4 Hz, 3 H), 0.94 – 0.73 (m, 10 H). ^{13}C NMR (151 MHz, Chloroform-*d*): δ 180.0, 166.3, 103.7, 85.48, 78.2, 56.4, 52.6, 49.1, 47.3, 46.3, 45.1, 30.6, 28.5, 28.2, 24.5, 23.3, 12.9, 11.6, 9.7, 8.7. IR (thin film) cm^{-1} 2964, 2926, 1711, 1683, 1636, 1460, 1363, 1288, 1221, 1133, 962. HRMS calcd (found) for $C_{22}H_{36}NaO_3$ ($M+Na^+$): 371.2566 (371.2568)



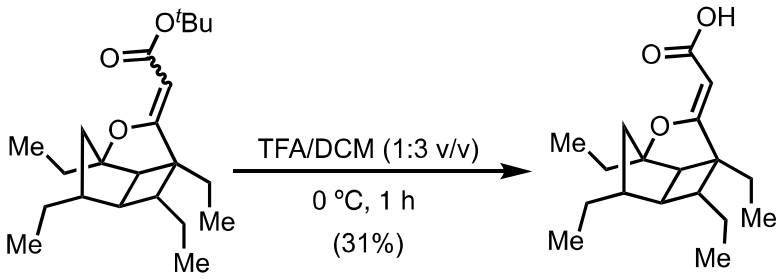
Hippolachnin A (1) and (E)-hippolachnin A (8): Adapted from our previously reported procedure: [S1] To a stirred solution of (*Z*)-**7** (45.0 mg, 0.13 mmol) in MeOH (6.5 mL) was added TMSCl (0.5 mL, 3.9 mmol) via syringe. The solution was heated to 60 ºC for 20 hours before being cooled to 24 °C. Solid sodium carbonate (450 mg, 4.2 mmol mmol) was added followed by deionized H_2O (0.75 mL), and methylene chloride (10 mL). The reaction was let to stir for 30 minutes at room temperature and $MgSO_4$ (ca. 1 g) added before filtering over a pad of Celite, which was eluted with methylene chloride (20 mL). Volatiles were removed under vacuum and the residue purified by silica gel chromatography (hexanes–EtOAc) = 95:5) to give **1** (13.1 mg, 28%) and **8** (19.8 mg). **8** was further purified by preparative HPLC (hexanes–EtOAc = 99:1, 10 mL/min, 10mm x 250 mm Sunfire silica preparative column 10 µM) to give **8** (2.8 mg, 6%) as a colorless oil and in >95% purity.

For **8**: TLC (EtOAc–hexanes = 5:95): R_f = 0.26. ^{1}H NMR (600 MHz, Chloroform-*d*): δ 5.22 (d, *J* = 0.5 Hz, 1 H), 3.62 (s, 3 H), 2.63 (d, *J* = 8.3 Hz, 1 H), 2.47 (ddd, *J* = 16.8, 14.3, 7.6 Hz, 1 H), 2.34 – 2.22 (m, 1 H), 2.18 (dd, *J* = 13.4, 6.0 Hz, 1 H), 2.00 – 1.92 (m, 3 H), 1.91 – 1.82 (m, 1 H), 1.79 (ddd, *J* = 8.5, 6.5, 2.1 Hz, 1 H), 1.69 – 1.59 (m, 1 H), 1.47 – 1.25 (m, 6 H), 0.98 (t, *J* = 7.5 Hz, 3 H), 0.95 – 0.87 (m, 6 H), 0.72 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (151 MHz, Chloroform-*d*): δ 184.9, 167.9, 100.7, 87.0, 56.8, 52.9, 50.4,

50.4, 47.1, 46.6, 45.7, 29.6, 28.0, 24.6, 21.8, 13.1, 11.6, 9.7, 9.0. IR (thin film) cm^{-1} 2964, 2921, 2365, 2342, 2133, 1968, 1708, 1622, 1110, 952. HRMS calcd (found) for $C_{19}H_{30}NaO_3$ ($M+Na^+$): 329.2093 (329.2100).

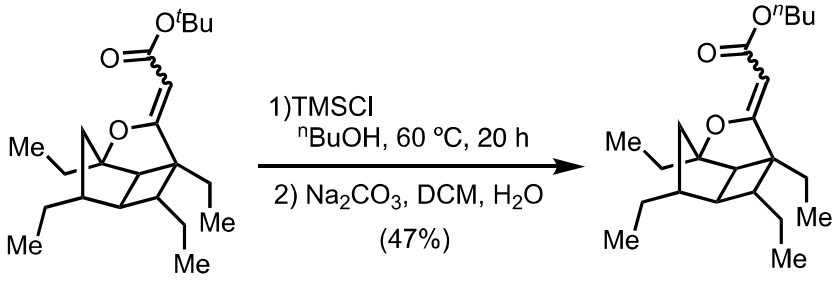


1,2,3a,5a-tetraethylhexahydro-4-oxacyclobuta[cd]pentalen-5(1H)-one (9): To a stirred solution of **6** (13.3 mg, 0.054 mmol) in THF (1.0 mL) was added palladium on carbon (1.8 mg, 5 wt % loading). The reaction was stirred under an atmosphere of hydrogen gas for 11 hours before being filtered over a pad of Celite, which was eluted with diethyl ether (10 mL). Volatiles were removed under vacuum to give **9** (13.1 mg, 98%) as a colorless oil. ^{1}H NMR (600 MHz, Chloroform-d): δ 2.71 (d, *J* = 8.4 Hz, 1 H), 2.63 (dtd, *J* = 15.5, 6.9, 3.9 Hz, 1H), 2.53 – 2.37 (m, 1 H), 2.33 (dd, *J* = 13.8, 6.4 Hz, 1 H), 2.02 (tt, *J* = 11.9, 6.0 Hz, 1 H), 1.95 – 1.73 (m, 3 H), 1.73 – 1.53 (m, 3 H), 1.47 – 1.23 (m, 6 H), 1.00 (t, *J* = 7.5 Hz, 3 H), 0.90 (t, *J* = 7.3 Hz, 3H), 0.82 (t, *J* = 7.4 Hz, 3 H). ^{13}C NMR (151 MHz, Chloroform-*d*): δ 182.3, 95.9, 51.7, 49.4, 49.2, 47.4, 46.5, 44.9, 30.9, 28.1, 24.6, 21.5, 13.0, 11.4, 9.1. IR (thin film) cm^{-1} 2595. 2929, 2874, 1757 1714, 1461, 1378, 1311, 1214, 1184, 1113, 970, 949, 741. HRMS calcd (found) for $C_{16}H_{26}NaO_2$ ($M+Na^+$): 273.1830 (273.1832).



(**7**, *E*/*Z* = 1:1.4) **10**

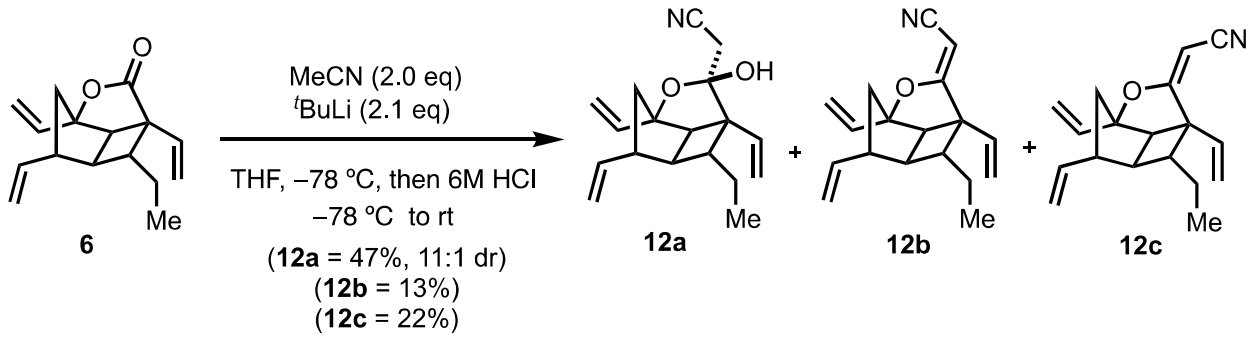
(Z)-1,2,3a,5a-tetraethylhexahydro-4-oxacyclobuta[cd]pentalen-5(1H)-ylidene)acetic acid (10): To a stirred solution of **7** (1:1.4 E/Z) (18.5 mg, 0.053 mmol) in methylene chloride (3 mL) at 0 ºC, trifluoroacetic acid (1 mL) was added dropwise. The solution was stirred at 0 ºC for 15 minutes before saturated aqueous $NaHCO_3$ (12 mL) was added dropwise. The suspension was diluted with methylene chloride (20 mL), the layers separated and the aqueous layer acidified with 1 % HCl until the pH reached ~2. The acidified aqueous layer was extracted with methylene chloride (3 x 10 mL) and the combined organic phases dried over $MgSO_4$ before being concentrated under vacuum. The crude residue was purified by silica gel chromatography (hexanes–EtOAc = 4:1) to give acid **10** (4.9 mg, 32 %) as a colorless microcrystalline solid. TLC (EtOAc–hexanes = 1:4): R_f = 0.20. ^{1}H NMR (600 MHz, Chloroform-*d*): δ 9.71 (s, 1 H), 4.70 (s, 1 H), 2.69 (d, *J* = 7.7 Hz, 1 H), 2.39 (dd, *J* = 14.1, 6.4 Hz, 1 H), 2.07 – 1.92 (m, 1 H), 1.89 – 1.60 (m, 6 H), 1.53 (dd, *J* = 14.2, 7.2 Hz, 1 H), 1.46 (dd, *J* = 14.0, 10.0 Hz, 1 H), 1.34 (ddt, *J* = 17.2, 13.6, 6.8 Hz, 2 H), 1.01 (t, *J* = 7.5 Hz, 3 H), 0.91 – 0.87 (m, 6H), 0.80 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (151 MHz, Chloroform-*d*): δ 179.3, 167.4, 106.3, 87.3, 55.8, 52.7, 49.8, 47.5, 46.1, 45.1, 30.5, 28.1, 24.4, 22.9, 12.9, 11.6, 9.6, 8.5. IR (thin film) cm^{-1} 3368, 2995, 2940, 2853, 1686, 1640, 1456, 1398, 1233, 1151, 1068, 993, 912, 772, 716. HRMS calcd (found) for $C_{18}H_{28}NaO_3$ ($M+Na^+$): 315.1936 (315.1936).



(**7**, *E*/*Z* = 1:1.4) **11**

Butyl (*Z*)-1,2,3a,5a-tetraethylhexahydro-4-oxacyclobuta[cd]pentalen-5(1H)-ylidene)acetate (11): To a stirred solution of (*Z*)-**7** (7.2 mg, 0.021 mmol) in *n*-BuOH (0.3 mL, 3.2 mmol) was added TMSCl (75 µL, 0.59 mmol) via syringe. The solution was heated to 60 ºC for 20 hours before being cooled to 24 °C. Solid sodium carbonate (68.0 mg, 0.62 mmol) was added followed by deionized H_2O (9 µL), and methylene chloride (1.5 mL). The reaction was let to stir for 30 minutes at room temperature and $MgSO_4$ (ca. 0.1 g) added before filtering over a pad of Celite, which was eluted with methylene chloride (20 mL). Volatiles were removed under vacuum and the residue purified by silica gel chromatography (hexanes–EtOAc) = 95:5) to give **11** (2.5 mg, 35%). TLC (EtOAc–hexanes = 5:95): R_f = 0.31. ^{1}H NMR (600 MHz, Chloroform-*d*): δ 4.55 (s, 1 H), 4.18 – 4.00 (m, 2 H), 2.58 (d, *J* = 8.2 Hz, 1 H), 2.42 (dd, *J* = 13.8, 6.5 Hz, 1 H), 2.06 – 1.94 (m, 1 H), 1.89 – 1.70 (m, 4 H), 1.71 – 1.58 (m, 4 H), 1.52 (dd, *J* = 14.1, 7.2 Hz, 1 H), 1.47 – 1.20 (m, 6 H), 1.02 (t, *J* = 7.4 Hz, 3 H), 0.93 (t, *J* = 7.4 Hz, 3 H), 0.87 (t, *J* = 7.3 Hz, 3 H), 0.80 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (151 MHz, Chloroform-*d*): δ 180.8, 103.9, 83.9, 62.90, 56.6, 52.8, 49.4, 47.4, 46.2, 45.1, 30.9, 30.8, 28.2, 24.6, 23.3, 19.3, 13.8, 12.9, 11.7, 9.6, 8.6. IR (thin film) cm^{-1} 2961, 2928, 2364, 1709, 1685, 1638, 1364,

1287, 1108, 991, 916, 805. HRMS calcd (found) for $C_{22}H_{36}NaO3$ ($M+Na^+$): 371.2566 (371.2560).



Acetonitrile addition to **6**: A solution of acetonitrile (9.4 µL, 0.164 mmol) in THF (6.8 mL) was cooled to –78 ºC and *tert*-butyl lithium (120 µL, 1.4 M in pentane, 0.172 mmol) was added dropwise. The solution was stirred for 30 minutes before a solution containing lactone **6** (20.0 mg, 0.082 mmol) in THF (1.5 mL) was added dropwise via syringe. The solution was stirred for 1 hour at –78 ºC before 1.0 mL of 6 M HCl was added and the slurry allowed to warm to room temperature. The solution was poured into sat NH_4Cl (20 mL) and extracted with EtOAc (3 x 20 mL) the combined organic phases washed with saturated brine (10 mL) and dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by silica gel chomotography (hexanes–EtOAc = 9:1) to give **12a** (11.0 mg, 47 %, 11:1 mixture of diastereomers), **12b** (2.8 mg, 13 %), and **12c** (4.8 mg, 22 %) as colorless oils.

For **12a**: TLC (EtOAc–hexanes = 1:9): R_f = 0.15. ^{1}H NMR (600 MHz, Chloroform-*d*): δ 6.14 – 5.98 (m, 2 H), 5.92 (ddd, *J* = 17.6, 10.7, 9.1 Hz, 1 H), 5.79 (dd, *J* = 17.3, 10.7 Hz, 1 H), 5.71 (dddd, *J* = 14.9, 10.1, 7.8, 4.8 Hz, 1 H), 5.52 – 5.28 (m, 2H), 5.25 (dd, *J* = 17.2, 1.4 Hz, 1 H), 5.19 – 5.14 (m, 1 H), 5.11 (dd, *J* = 10.9, 1.0 Hz, 1 H), 5.08 (dd, *J* = 10.8, 1.2 Hz, 1 H), 4.99 – 4.87 (m, 2 H), 3.51 – 3.35 (m, 1 H), 3.22 (d, *J* = 8.1 Hz, 1 H), 3.18 (d, *J* = 8.1 Hz, 1 H), 3.01 –

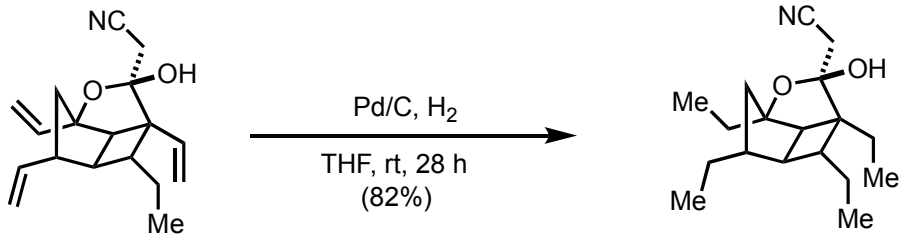
2.80 (m, 1 H), 2.79 (qd, *J* = 8.6, 7.9, 4.3 Hz, 1 H), 2.64 (s, 1 H), 2.51 – 2.42 (m, 1 H), 2.37 (dd, *J* = 14.3, 7.3 Hz, 1 H), 2.28 (dt, *J* = 10.7, 5.5 Hz, 2 H), 2.04 – 1.89 (m, 2 H), 1.69 (ddd, *J* = 18.5, 14.3, 8.8 Hz, 1 H), 1.56 – 1.48 (m, 1 H), 1.31 – 1.14 (m, 1H), 0.84 (t, *J* = 7.3 Hz, 3 H), 0.78 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*): δ 144.2, 141.6, 141.0, 141.0, 140.3, 135.6, 133.8, 133.2, 118.4, 117.3, 116.3, 116.1, 113.4, 113.1, 113.1, 113.0, 111.0, 106.3, 105.3, 95.5, 93.6, 59.6, 51.1, 51.0, 50.9, 49.6, 49.4, 47.8, 46.6, 46.0, 45.7, 39.7, 28.73 24.7, 24.8, 24.6, 11.6, 11.2. IR (thin film) cm^{-1} 3446, 2958, 2930, 2250, 1638, 1417, 1107, 1078, 1045, 995, 916, HRMS calcd (found) for $C_{18}H_{23}NaNO2$ (M+Na$^+$): 308.1626 (308.1622).

SI-6c: TLC (EtOAc–hexanes = 1:9): R_f = 0.35. ^{1}H NMR (600 MHz, Chloroform-d): δ 5.89 (ddd, *J* = 32.6, 17.2, 10.7 Hz, 2 H), 5.73 (ddd, *J* = 17.4, 10.2, 7.6 Hz, 1 H), 5.35 (d, *J* = 17.2 Hz, 1 H), 5.23 (d, *J* = 10.6 Hz, 1 H), 5.14 (d, *J* = 10.9 Hz, 1 H), 5.11 – 5.01 (m, 2 H), 4.96 (dd, *J* = 10.2, 1.4 Hz, 1 H), 4.06 (s, 1 H), 3.18 (d, *J* = 8.4 Hz, 1 H), 2.90 – 2.82 (m, 1 H), 2.45 (dd, *J* = 13.9, 6.2 Hz, 1 H), 2.06 – 1.93 (m, 2 H), 1.81 (dd, *J* = 13.9, 11.4 Hz, 1 H), 1.61 – 1.56 (m, 1 H), 1.27 – 1.19 (m, 1 H), 0.84 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (151 MHz, Chloroform-*d*): δ 183.4, 139.4, 137.0, 133.8, 117.1, 116.4, 114.7, 114.2, 101.6, 63.9, 56.9, 54.5, 52.1, 49.9, 46.9, 45.7, 24.9, 10.8. HRMS calcd (found) for $C_{18}H_{21}NNaO$ (M+Na$^+$): 290.1521 (290.1519).

For 12b: TLC (EtOAc–hexanes = 1:9): R_f = 0.35. ^{1}H NMR (600 MHz, Chloroform-d): δ 5.89 (ddd, *J* = 32.6, 17.2, 10.7 Hz, 2 H), 5.73 (ddd, *J* = 17.4, 10.2, 7.6 Hz, 1 H), 5.35 (d, *J* = 17.2 Hz, 1 H), 5.23 (d, *J* = 10.6 Hz, 1 H), 5.14 (d, *J* = 10.9 Hz, 1 H), 5.11 – 5.01 (m, 2 H), 4.96 (dd, *J* = 10.2, 1.4 Hz, 1 H), 4.06 (s, 1 H), 3.18 (d, *J* = 8.4 Hz, 1 H), 2.90 – 2.82 (m, 1 H), 2.45 (dd, *J* = 13.9, 6.2 Hz, 1 H), 2.06 – 1.93 (m, 2 H), 1.81 (dd, *J* = 13.9, 11.4 Hz, 1 H), 1.61 – 1.56 (m, 1 H), 1.27 – 1.19 (m, 1 H), 0.84 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR

(151 MHz, Chloroform-*d*): δ 183.4, 139.4, 137.0, 133.8, 117.1, 116.4, 114.7, 114.2, 101.6, 63.9, 56.9, 54.5, 52.1, 49.9, 46.9, 45.7, 24.9, 10.8. HRMS calcd (found) for $C_{18}H_{21}NNaO$ ($M+Na^+$): 290.1521 (290.1519)

For 12c (contains ca. 10 % **12b**)**:** TLC (EtOAc–hexanes = 1:9): R_f = 0.38 ^{1}H NMR (600 MHz, Chloroform-*d*): δ 6.46 (dd, *J* = 17.1, 10.5 Hz, 1 H), 5.94 (dd, *J* = 17.2, 10.9 Hz, 1 H), 5.74 (ddd, *J* = 17.3, 10.2, 7.4 Hz, 1 H), 5.34 – 5.22 (m, 2 H), 5.15 (dd, *J* = 10.9, 1.0 Hz, 1 H), 5.09 – 5.02 (m, 2 H), 4.98 (dt, *J* = 10.2, 1.3 Hz, 1 H), 4.63 (d, *J* = 0.5 Hz, 1 H), 3.21 (d, *J* = 8.6 Hz, 1 H), 2.82 (dq, *J* = 13.0, 6.7 Hz, 1 H), 2.33 – 2.26 (m, 1 H), 2.20 (ddd, *J* = 10.5, 5.5, 2.4 Hz, 1 H), 2.05 (ddd, *J* = 8.9, 6.7, 2.4 Hz, 1 H), 1.82 (dd, *J* = 13.8, 12.0 Hz, 1 H), 1.75 (dtd, *J* = 14.5, 7.2, 5.5 Hz, 1 H), 0.91 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (151 MHz, Chloroform-*d*): δ 185.2, 139.1, 136.9, 133.5, 118.0, 116.4, 114.7, 114.4, 100.6, 65.5, 58.0, 53.1, 52.6, 49.6, 47.4, 46.0, 25.0, 11.0. HRMS calcd (found) for $C_{18}H_{21}NNaO$ ($M+Na^+$): 290.1521 (290.151).

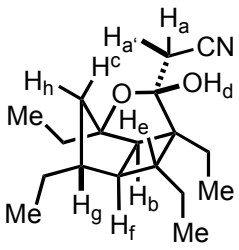


12a **13** (≥20:1 dr)

2-(1,2,3a,5a-tetraethy)l-5-hydroxyoctahydro-4-oxacyclobuta[cd]pentalen-5-yl)acetonitrile (13): To a stirred solution of **12a** (6.3 mg, 0.022 mmol) in THF (0.2 mL) was added palladium on carbon (0.3 mg, 10 wt %). The reaction was purged with nitrogen before being replaced with an atmosphere of hydrogen gas and stirred for 28 hours. The reaction was then filtered over Celite, which was eluted with EtOAc and

concentrated under vacuum. The crude residue was purified by silica gel chromatography (hexanes–EtOAc = 9:1) to give **13** (5.1 mg, 81%) as a colorless oil.

For **13**: TLC (EtOAc–hexanes = 1:9): R_f = 0.14. ^{1}H NMR (600 MHz, Chloroform-*d*): δ 2.85 (d, *J* = 16.4 Hz, 1 H), 2.67 (d, *J* = 16.4 Hz, 1 H), 2.61 (d, *J* = 7.4 Hz, 1 H), 2.38 (dd, *J* = 14.6, 8.0 Hz, 1 H), 2.28 (s, 1 H), 1.99 – 1.90 (m, 2 H), 1.90 – 1.76 (m, 3 H), 1.71 (dd, *J* = 14.5, 7.4 Hz, 1 H), 1.66 – 1.54 (m, 3 H), 1.51 – 1.39 (m, 2 H), 1.29 (dt, *J* = 13.4, 7.3 Hz, 1 H), 1.17 (dt, *J* = 13.3, 7.4 Hz, 1 H), 1.02 (t, *J* = 7.5 Hz, 3 H), 0.98 (t, *J* = 7.5 Hz, 3 H), 0.90 – 0.85 (m, 6 H). ^{13}C NMR (151 MHz, Chloroform-*d*): δ 117.0, 106.3, 98.5, 54.8, 53.5, 49.3, 46.8, 45.7, 45.3, 33.8, 28.9, 26.6, 23.8, 21.2, 12.5, 11.7, 11.3, 9.6. IR (thin film) cm^{-1} 3345, 2960, 2932, 2876, 2259, 1461, 1378, 1047. HRMS calcd (found) for $C_{18}H_{29N}NaO_2$ (M+Na$^+$): 314.2096 (314.2093).



Key ^{1}H-^{1}H nOe correlations

H_d ⟷ H_e
H_d ⟷ H_g
H_c ⟷ H_e
H_c ⟷ H_g
H_c ⟷ H_h
H_b ⟷ H_f

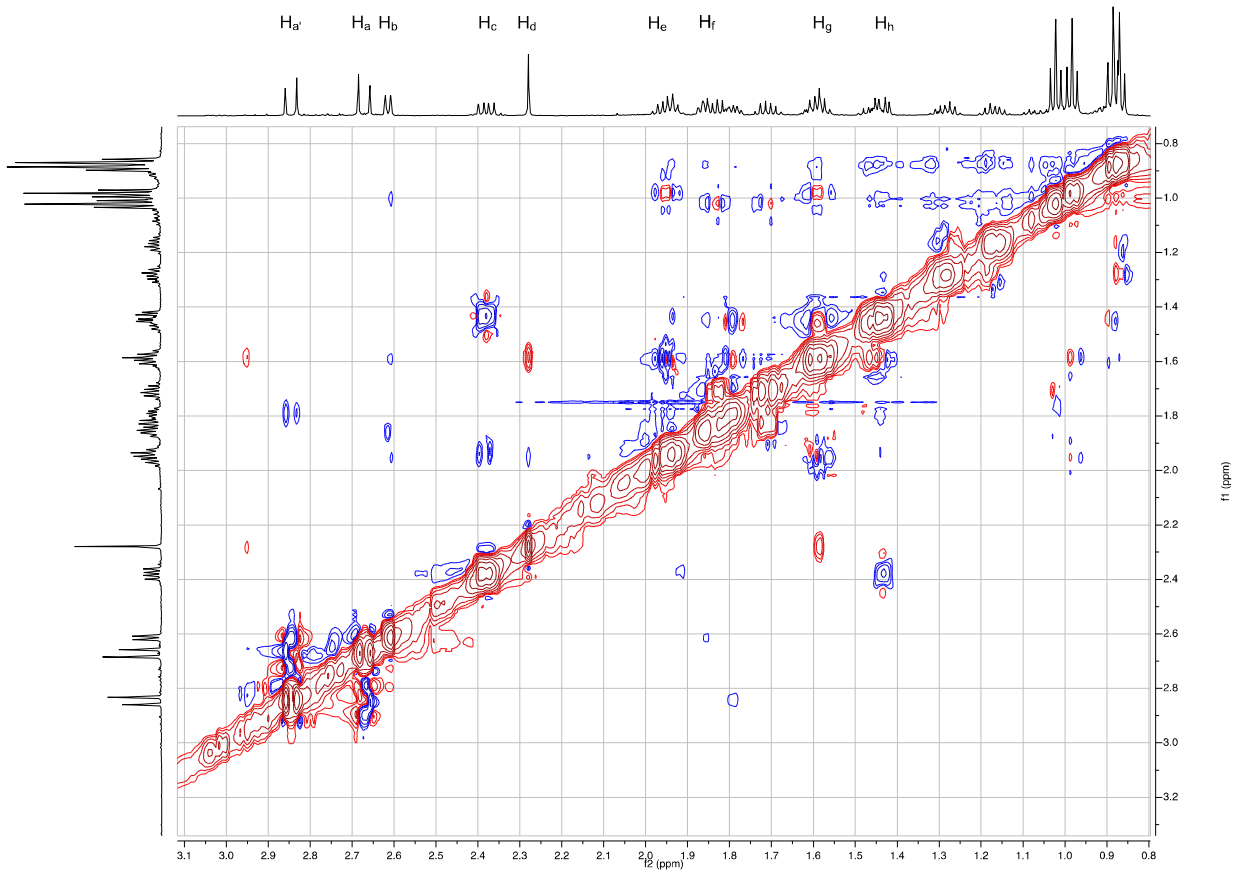
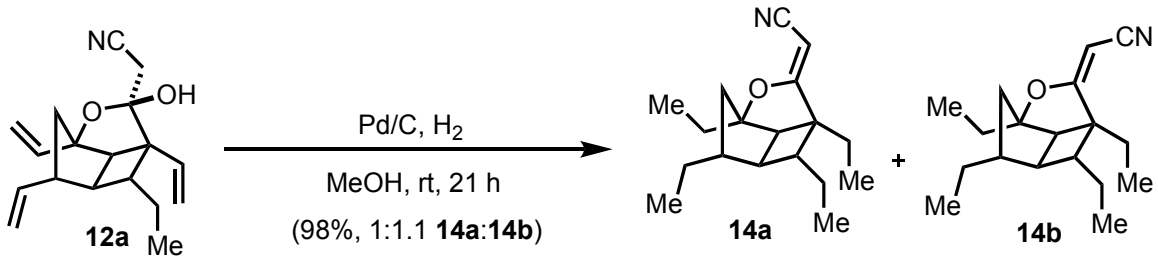


Figure S3. Selected nOe data and partial $^{1}H–^{1}H$ NOESY spectrum of hemiacetal **13**.

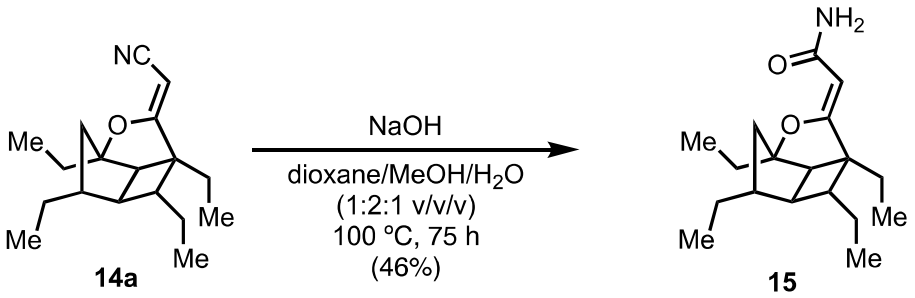


Hydrogenation of **12a** to **14a** and **14b:** To a stirred solution of **12a** (32.1 mg, 0.11 mmol) in THF (2.0 mL) was added palladium on carbon (3.2 mg, 10 wt %). The reaction was purged with nitrogen before being replaced with an atmosphere of hydrogen gas and stirred for 21 hours. The reaction was then filtered over Celite, which was eluted with

EtOAc and concentrated under vacuum. The crude residue was purified by silica gel chromatography (hexanes–EtOAc = 9:1) to give **14a** and **14b** (30.0 mg, 98%, **14a**:**14b** = 1.1:1) as colorless microcrystalline solids.

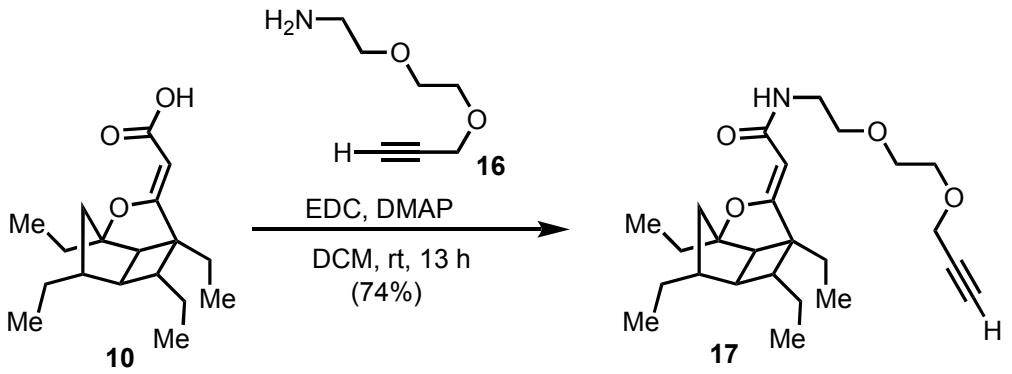
14a: 1H NMR: TLC (EtOAc–hexanes = 1:9): R_f = 0.35 ^{1}H NMR (600 MHz, Chloroform-*d*): δ 3.91 (s, 1 H), 2.66 (d, *J* = 7.8 Hz, 1 H), 2.38 (dd, *J* = 13.9, 6.5 Hz, 1 H), 2.04 – 1.91 (m, 1 H), 1.86 – 1.72 (m, 4 H), 1.71 – 1.59 (m, 1 H), 1.49 – 1.24 (m, 5 H), 1.00 (t, *J* = 7.4 Hz, 3 H), 0.91 – .086 (m, 6 H), 0.80 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (151 MHz, Chloroform-*d*): δ 185.2, 118.1, 104.3, 61.1, 55.8, 52.6, 50.6, 47.5, 46.1, 44.9, 30.5, 28.1, 24.5, 23.2, 12.9, 11.6, 9.4, 8.5. IR (thin film) cm^{-1} 3060, 3960, 2928, 2211, 1627, 1459, 1416, 1353, 1118, 990. 918. HRMS calcd (found) for $C_{18}H_{27}NNaO$ ($M+Na^+$): 296.1990 (290.1997)

14b (contains ca 10% **14a):** TLC (EtOAc–hexanes = 1:9): R_f = 0.39 ^{1}H NMR (600 MHz, Chloroform-d): δ 4.50 (s, 1 H), 3.90 (s, 1H, for **14a**), 2.65 (d, *J* = 8.4 Hz, 1 H), 2.38 (dd, *J* = 13.9, 6.5 Hz, 1 H), 2.28 – 2.14 (m, 2 H), 1.96 (dddd, *J* = 19.8, 12.2, 5.8, 3.6 Hz, 2 H), 1.89 – 1.76 (m, 3 H), 1.71 (dq, *J* = 14.7, 7.5 Hz, 1 H), 1.67 – 1.53 (m, 1 H), 1.47 – 1.24 (m, 5 H), 0.96 (dt, *J* = 10.5, 7.4 Hz, 6 H), 0.90 (t, *J* = 7.4 Hz, 3 H), 0.81 (t, *J* = 7.4 Hz, 3 H). ^{13}C NMR (151 MHz, Chloroform-*d*): δ 186.6, 118.3, 103.1, 63.6, 56.6, 52.0, 51.4, 47.3, 46.4, 45.2, 30.0, 28.0, 24.7, 22.1, 13.0, 11.7, 9.5, 8.6. IR (thin film) cm^{-1} 2962, 2926, 2876, 2290, 1630, 1461, 1357, 966, 937 for $C_{18}H_{27}NNaO$ ($M+Na^+$): 296.1990 (296.1994)



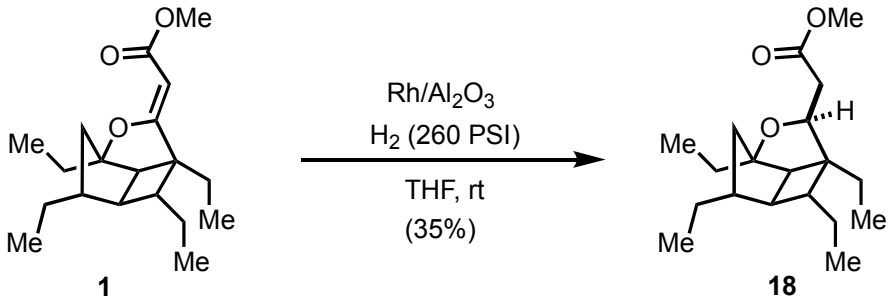
(Z)-1,2,3a,5a-tetraethylhexahydro-4-oxacyclobuta[cd]pentalen-5(1H)-ylidene)acetamide (15): To a 1 dram vial fitted with magnetic stirbar was added **14b** (11.2 mg, 0.041 mmol) and MeOH (150 µL) and 1,4-dioxane (200 µL). To this stirred solution was added 10 M NaOH (150 µL). The reaction was stirred at 100 ºC for 75 hours before being cooled to room temperature, poured into sat. aqueous brine, acidified to pH ~7 with 1 M HCl, and extracted with diethyl ether (3 x 5 mL). The combined extracted were dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified by silica gel chromatography (hexanes–EtOAc = 1:1) to give **15** (5.5 mg) as a colorless microcrystalline solid with minor aromatic impurities; this semi-pure material was further purified by preparative HPLC (100% EtOAc, 10 mL/min, 10 mm ID sunfire preparative HPLC column) to give **15** (5.2 mg, 46%) in > 90 % purity. TLC (EtOAc–hexanes = 1:3): R_f = 0.13. ^{1}H NMR (600 MHz, Chloroform-*d*): δ 6.99 (s, 1 H), 5.33 (s, 1 H), 4.59 (t, *J* = 1.4 Hz, 1 H), 2.63 (d, *J* = 8.1 Hz, 1 H), 2.33 (dd, *J* = 13.9, 6.5 Hz, 1 H), 2.03 – 1.94 (m, 1 H), 1.88 – 1.72 (m, 4 H), 1.70 – 1.61 (m, 2 H), 1.57 – 1.47 (m, 1 H), 1.43 (dd, *J* = 13.9, 10.0 Hz, 1 H), 1.40 – 1.29 (m, 3 H), 1.01 (t, *J* = 7.4 Hz, 3 H), 0.93 – 0.84 (m, 6 H), 0.79 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (151 MHz, Chloroform-*d*): δ 175.6, 169.7, 103.8, 90.2, 55.6, 52.7, 50.1, 47.5, 46.1, 45.4, 30.8, 28.1, 24.5, 23.1, 12.9, 11.7, 9.7, 8.6. IR (thin film) cm^{-1} 3464, 3185, 2951, 2925, 1650, 1591, 1460, 1406, 1314, 1078, 969, 934, 823. HRMS calcd (found) for $C_{18}H_{29N}NaO_2$ (M+Na$^+$): 314.2096

(314.2095).



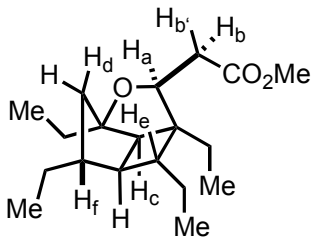
(*Z*)-N-(2-(2-(prop-2-yn-1-yloxy)ethoxy)ethyl)-2-1,2,3a,5a-tetraethylhexahydro-4-oxacyclobuta[cd]pentalen-5(1H)-ylidene)acetamide (17): To a 0.5 dram vial containing a magnetic stirbar was added **10** (2.5 mg, 0.0085 mmol) and **16** (1.7 mg, 0.0116 mmol), followed by methylene chloride (0.3 mL). To this stirred solution was added DMAP (2.6 mg, 0.0021 mmol), followed by EDC (3.5 mg, 0.0018 mmol). The mixture was stirred for 11 hours before the volatiles were removed under a stream of nitrogen. The reside was purified by silica gel chromatography (hexanes–EtOAc = 1:1) to give **17** (2.6 mg, 75%) as a colorless oil. TLC (EtOAc–hexanes = 1:1): R_f = 0.28. ^{1}H NMR (600 MHz, Chloroform-*d*): δ 7.47 (s, 1 H), 4.60 (s, 1 H), 4.20 (d, *J* = 2.4 Hz, 2 H), 3.72 – 3.65 (m, 4 H), 3.65 – 3.56 (m, 3 H), 3.55 – 3.48 (m, 1 H), 2.61 (d, *J* = 8.2 Hz, 1 H), 2.42 (t, *J* = 2.4 Hz, 1 H), 2.35 (dd, *J* = 13.8, 6.5 Hz, 1 H), 2.04 – 1.94 (m, 1 H), 1.88 – 1.77 (m, 3 H), 1.74 (s, 1 H), 1.68 – 1.61 (m, 2 H), 1.56 – 1.46 (m, 1 H), 1.41 (dd, *J* = 13.9, 9.9 Hz, 1 H), 1.38 – 1.28 (m, 3 H), 1.02 (t, *J* = 7.4 Hz, 3 H), 0.92 – 0.87 (m, 6 H), 0.78 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (151 MHz, Chloroform-*d*): δ 173.9, 167.6, 103.4, 90.83, 79.6, 74.5, 70.4, 70.1, 69.0, 58.4, 55.3, 52.8, 50.2, 47.6, 46.1, 45.3, 38.9, 30.9,

28.2, 24.5, 23.0, 12.9, 11.8, 9.7, 8.6. HRMS calcd (found) for $C_{25}H_{39}NaNNaO_4$ ($M+Na^+$): 440.2777 (440.2776).



Methyl 2-1,2,3a,5a-tetraethyloctahydro-4-oxacyclobuta[cd]pentalen-5-yl)acetate (18): To a solution of **1** (7.3 mg, 0.023 mmol) in THF (1.6 mL) was added Rhodium on alumina (7.2 mg). The vial was placed in a Parr reactor and stirred under an atmosphere of hydrogen gas (130 PSI). After 24 hours, UPLC analysis indicated ca. 30% conversion of **1.** At that point, the hydrogen pressure was increased to 260 PSI and the reaction stirred for an additional 24 hours before being filtered through a plug of Celite and concentrated under vacuum. Crude ^{1}H NMR analysis showed a 1:1.3 mixture of resonances corresponding to **1** and **18**, respectively. The crude reside was purified by silica gel chromatography (hexanes–EtOAc = 10:1) to give **18** (2.6 mg, 35%) as a colorless oil. TLC (EtOAc–hexanes = 1:10): R_f = 0.36. ^{1}H NMR (600 MHz, Chloroform-*d*): δ 4.17 (dd, *J* = 8.3, 4.2 Hz, 1 H), 3.68 (s, 3 H), 2.59 (dd, *J* = 15.5, 8.3 Hz, 1 H), 2.48 (d, J = 8.3 Hz, 1 H), 2.35 – 2.24 (m, 2 H), 2.04 – 1.96 (m, 1 H), 1.83 – 1.78 (m, 1 H), 1.78 – 1.72 (m, 1 H), 1.70 – 1.59 (m, 2 H), 1.47 – 1.38 (m, 2 H), 1.37 – 1.27 (m, 3 H), 1.24 – 1.16 (m, 1 H), 1.13 (dd, *J* = 13.8, 8.9 Hz, 1 H), 0.93 (t, *J* = 7.4 Hz, 3 H), 0.88 (t, *J* = 7.4 Hz, 3 H), 0.87 – 0.82 (m, 6 H). ^{13}C NMR (151 MHz, Chloroform-*d*): δ 172.4, 94.5,

77.6, 52.9, 51.6, 50.8, 49.1, 46.0, 45.5, 45.2, 34.1, 29.3, 29.2, 24.1, 20.2, 12.9, 12.2, 9.5, 8.8. IR (thin film) cm^{-1} 3959, 2921, 1744, 1461, 1379, 1305, 1160, 1055. HRMS calcd (found) for $C_{19}H_{32}NaO_3$ ($M+Na^+$): 331.2249 (331.2245).



18

Key ^1H-^1H nOe correlations

H_a	⟷	H_b
H_a	⟷	$H_{b'}$
H_e	⟷	$H_{b'}$
H_e	⟷	H_d
H_b	⟷	H_d
$H_{b'}$	⟷	H_d
$H_{b'}$	⟷	H_f
H_e	⟷	H_f

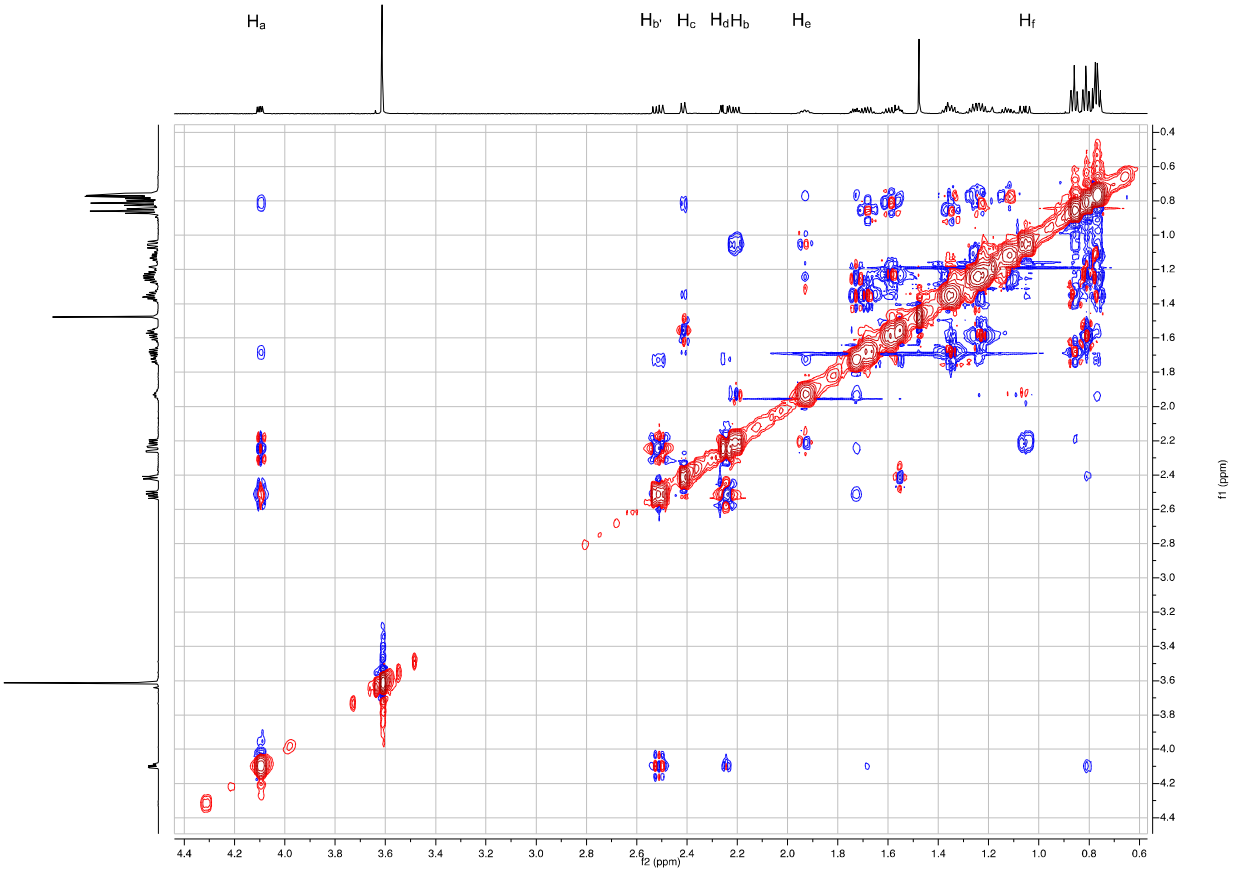
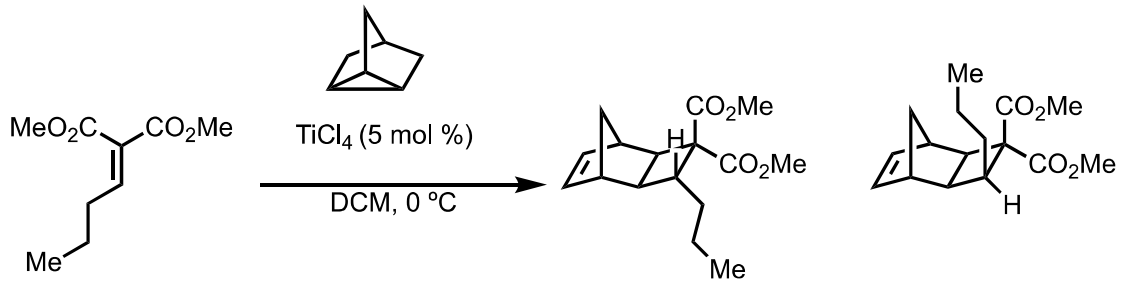


Figure S4. Selected nOe data and partial $^{1}H–^{1}H$ NOESY spectrum of ester **18**.

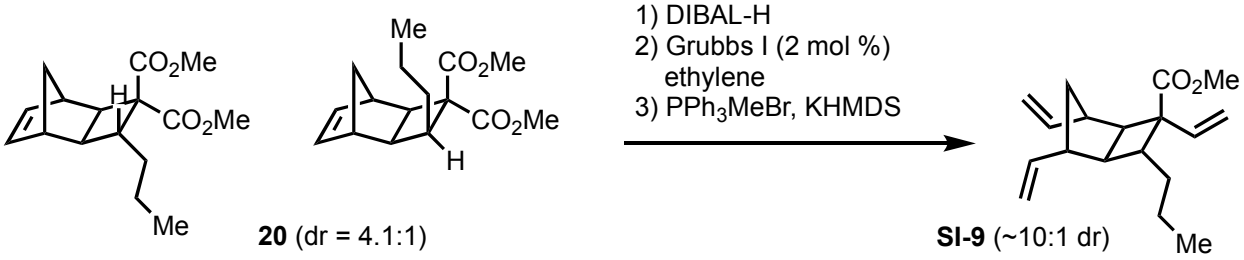
Synthesis of C10-propylhippolachnin A



19 **20** (dr = 4.1:1)

Dimethyl 4-propyltricyclo[4.2.1.02,5]non-7-ene-3,3-dicarboxylate (20): A solution containing **19**[S3] (1.40 g, 6.99 mmol) and quadricyclane (0.773 mg, 8.39 mmol) in DCM (60 mL) was stirred at 0 ºC. $TiCl_4$ (1.0 M in DCM, 349 µL, 0.349 mmol) was added to the stirred solution dropwise and the resulting black solution allowed to stir for 1 hour before being quenched with sat. aqueous NH_4Cl and warmed to 24 °C. The suspension was extracted with methylene chloride (3 x 50 mL) and the organic phases combined before being washed with sat. brine, dried over $MgSO_4$, and concentrated. The crude residue was purified by silica gel chromatography (hexanes–EtOAc = 9:1 → 1:1) to give **20** (1.12 g, 58%) as a 4.1:1 mixture of diastereomers. TLC (EtOAc–hexanes = 1:10): R_f = 0.43. ^{1}H NMR (600 MHz, Chloroform-*d*): δ 6.12 – 5.93 (m, 2.3 H). 3.77–3.70 (m, 8 H), 3.11 (s, 1 H), 2.87 (td, *J* = 9.6, 6.0 Hz, 1 H), 2.81 (s, 1 H), 2.71 (s, 1 H), 2.63 (d, *J* = 7.3 Hz, 1 H, major diastereomer), 2.56 (d, *J* = 7.0 Hz, 0.22 H, minor diastereomer), 2.40 (dt, *J* = 10.4, 5.3 Hz, 1 H), 2.08 (t, *J* = 8.2 Hz, 0.3 H), 1.92 – 1.77 (m, 1 H), 1.71 – 1.60 (m, 1 H), 1.55 – 1.43 (m, 2 H), 1.43 – 1.31 (m, 0.3 H), 1.31 – 1.14 (m, 3 H), 0.97 – 0.90 (m, 7 H). ^{13}C NMR (151 MHz, Chloroform-*d*): δ 173.6 (minor), 171.1 (major), 170.9 (major), 169.1 (minor), 137.6 (minor), 136.2 (major), 135.6 (major), 135.5 (minor), 54.2, 53.8, 52.9, 52.2, 52.1, 51.5, 44.5, 43.0, 42.4, 42.4, 41.8, 41.4, 41.3, 40.6, 40.2, 40.0, 39.5, 36.7, 33.2, 27.9, 21.8, 19.8, 14.2, 14.0. IR (thin film) cm^{-1} 2966, 1727, 1433, 1245, 1205,

1161, 1130, 1044, 711, 690. HRMS calcd (found) for $C_{16}H_{22}NaO_4$ ($M+Na^+$): 301.1416 (301.1411).



20 (dr = 4.1:1) **SI-9** (~10:1 dr)

Methyl 7-propyl-2,4,6-trivinylbicyclo[3.2.0]heptane-6-carboxylate (SI-9): A solution of **20** (1.95 g, 6.67 mmol) in methylene chloride (14 mL) was cooled to –78 ºC. DIBAL–H (1.0 M in PhMe, 14.0 mL, 14.0 mmol) was added dropwise to the cooled solution vis syringe over 10 minutes. The solution was stirred at this temperature for 55 minutes before acetone (12 mL) was added dropwise. The reaction was allowed to stir for 5 minutes before diethyl ether (12 mL) was added and stirred for 5 minutes. Water (0.4 mL) was then added and the reaction allowed to warm to 24 °C with vigorous stirring. Once at room temperature, 1M NaOH (0.4 mL) was added followed by H_2O (0.4 mL). The reaction as then stirred for 1 hour before being filtered over a pad of Celite, which was eluted with diethyl ether and concentrated. The resulting oil was purified by silica gel chromatography (hexanes–EtOAc = 98:2) to afford **SI-7** (1.00 g, 57%) as a colorless oil.

A stirred solution of **SI-7** (1.26 g, 5.08 mmol) in methylene chloride (180 mL) was sparged with ethylene for 15 minutes before Grubbs 1st generation catalyst (86.0 mg, 0.96 mmol) was added in one portion under an atmosphere of ethylene. The reaction was let to stir for 1 hour under an atmosphere of ethylene before being concentrated. The resulting residue purified by silica gel chromatography (hexanes–EtOAc = 98:2) to

give **SI-8** (1.19 g, 85%) as a colorless oil.

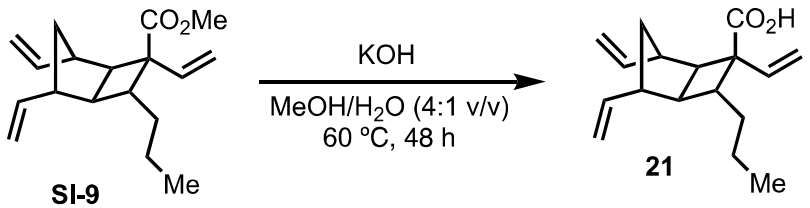
A slurry containing $PPh_3(Me)Br$ (3.32 g, 9.29 mmol) in THF (10 mL) was cooled to 0 ºC. KHMDS (18.9 mL, 0.5 M in PhMe) was added dropwise via syringe and the reaction allowed to warm to 24 °C and stirred for 30 minutes before being cooled to –78 ºC. A solution of **SI-8** (1.19 g, 4.31 mmol) in toluene (6 mL) was added dropwise to this solution. The reaction was allowed to stir at –78 ºC for 3 hours before being warmed to room temperature and stirred for 15 hours before being quenched with saturated NH_4Cl (10 mL). The phases were separated and aqueous phase extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with sat. brine and dried over $MgSO_4$. The volatile material was removed *in vacuo*. The resulting oil purified by silica gel chromatography (hexanes–EtOAc = 100:0→85:15) to afford **SI-9** (1.09 mg, 92%) as a colorless oil and in 7.3:1 dr.

For Methyl 3-formyl-4-propyltricyclo[4.2.1.02,5]non-7-ene-3-carboxylate (SI-7): TLC (EtOAc–hexanes = 2:98): R_f = 0.33. ^{1}H NMR (400 MHz, Chloroform-*d,* major diastereomer): δ 9.69 (s, 1 H), 6.14 – 5.83 (m, 2 H), 3.79 – 3.73 (m, 2 H), 2.92 – 2.85 (m, 1 H), 2.76 – 2.70 (m, 1 H), 2.50 (dd, *J* = 7.3, 1.3 Hz, 1 H), 2.48 – 2.38 (m, 1H), 1.64 (td, J = 6.2, 5.6, 1.4 Hz, 1H), 1.62 – 1.50 (m, 1H), 1.50 – 1.41 (m, 2H), 1.41 – 1.11 (m, 5 H), 0.91 – 0.88 (m, 3 H). HRMS calcd (found) for $C_{15}H_{20}NaO_3$ ($M+Na^+$): 271.1310 (271.1305)

For Methyl 6-formyl-7-propyl-2,4-divinylbicyclo[3.2.0]heptane-6-carboxylate (SI-8): TLC (EtOAc–hexanes = 2:98): R_f = 0.50. ^{1}H NMR (400 MHz, Chloroform-*d*): δ 9.82 (s, 1 H), 5.74 (ddd, *J* = 17.6, 9.8, 7.7 Hz, 2 H), 5.11 – 4.81 (m, 4 H), 3.75 (d, *J* = 2.7 Hz, 3

H), 3.13 – 2.88 (m, 2 H), 2.68 (dd, *J* = 12.1, 6.6 Hz, 1 H), 2.22 – 2.07 (m, 2 H), 1.54 – 1.38 (m, 2 H), 1.24 – 1.13 (m,1 H), 0.90 (t, *J* = 7.2 Hz, 3 H).

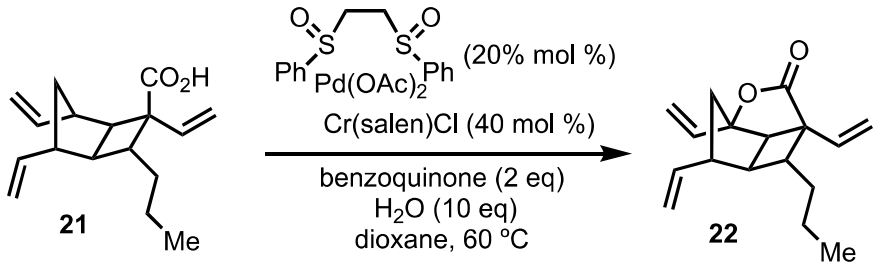
For Methyl 7-propyl-2,4,6-trivinylbicyclo[3.2.0]heptane-6-carboxylate (SI-9): TLC (EtOAc–hexanes = 2:98): R_f = 0.58. ^{1}H NMR (600 MHz, Chloroform-*d,* major diastereomer): δ 5.92 (dd, *J* = 17.5, 10.8 Hz, 1 H), 5.85 – 5.75 (m, 1 H), 5.70 (ddd, *J* = 17.2, 10.4, 7.8 Hz, 1 H), 5.24 (d, *J* = 10.7 Hz, 1 H), 5.12 (d, *J* = 17.4 Hz, 1 H), 5.02 – 4.79 (m, 4 H), 3.63 – 3.60 (m, 3H), 2.68 (td, J = 8.6, 6.0 Hz, 1 H), 2.65 – 2.57 (m, 1 H), 2.58 – 2.52 (m, 1 H), 2.46 (dqd, *J* = 17.2, 9.0, 8.0, 5.8 Hz, 1 H), 2.05 (dt, *J* = 12.5, 6.2 Hz, 1 H), 1.98 (td, *J* = 8.2, 3.7 Hz, 1 H), 1.46 – 1.33 (m, 2 H), 1.31 – 1.13 (m, 3 H), 0.90 – 0.83 (m, 3 H). ^{13}C NMR (101 MHz, Chloroform-*d*, major diastereomer): δ 194.2, 174.6, 142.1, 141.2, 136.9, 124.4, 115.2, 113.3, 112.7, 52.0, 51.1, 50.8, 50.2, 48.6, 47.3, 47.3, 42.8, 33.3, 20.6, 14.2. HRMS calcd (found) for $C_{18}H_{26}NaO_2$ ($M+Na^+$): 297.1830 (297.1829)



SI-9 **21**

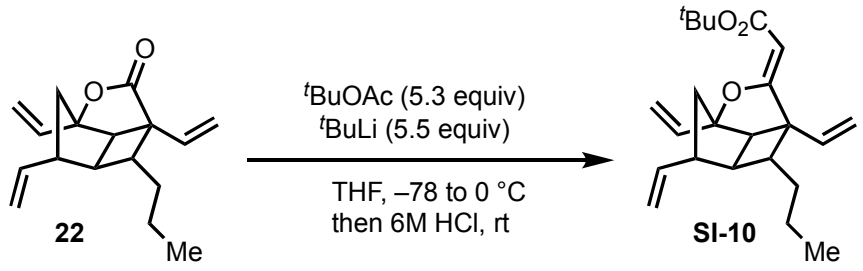
7-propyl-2,4,6-trivinylbicyclo[3.2.0]heptane-6-carboxylic acid (21): To a solution containing **SI-9** (265 mg, 0.97 mmol) in MeOH (1.3 mL) was added 5 M KOH (0.66 mL) and heated to 60 ºC for 47 hours. The reaction was then cooled to 24 °C and 3 mL diethyl ether added. The phase separated and organic phases washed with 1M NaOH (3 x 2 mL). The combined aqueous extracts were acidified to pH 1 with 6 M HCl, then extracted with diethyl ether (4 x 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by silica gel

chromatography (hexanes–EtOAc = 4:1) to give **21** (139 mg, 46 %) as a colorless microcrystalline solid and in >20:1 dr. TLC (EtOAc–hexanes = 1:4): R_f = 0.13. ^{1}H NMR (400 MHz, Chloroform-*d*): δ 5.99 (dd, *J* = 17.5, 10.8 Hz, 1 H), 5.88 (ddd, *J* = 17.2, 10.3, 6.8 Hz, 1 H), 5.74 (ddd, *J* = 17.1, 10.1, 7.8 Hz, 1 H), 5.36 – 5.21 (m, 2 H), 5.04 – 4.82 (m, 4 H), 2.77 (ddd, J = 12.7, 9.4, 6.3 Hz, 1 H), 2.68 (td, *J* = 8.6, 5.9 Hz, 1 H), 2.57 (t, *J* = 8.5 Hz, 1 H), 2.49 (dd, *J* = 7.4, 3.7 Hz, 1 H), 2.11 (dt, *J* = 12.6, 6.2 Hz, 1 H), 2.02 (td, *J* = 8.3, 3.8 Hz, 1 H), 1.53 – 1.35 (m, 2 H), 1.35 – 1.13 (m, 2 H), 0.89 (t, *J* = 7.1 Hz, 3 H). HRMS calcd (found) for $C_{17}H_{24}NaO_2$ (M–Na^+): 283.1674 (283.1670).



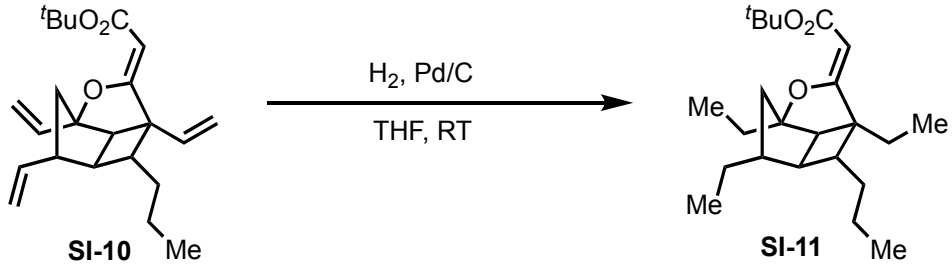
1-propyl-2,3a,5a-trivinylhexahydro-4-oxacyclobuta[cd]pentalen-5(1H)-one (22): Dioxane (5.4 mL) was added to a flask containing **21** (139 mg, 0.53 mmol), White's Catalyst (55.0 mg, 0.11 mmol), Cr(salen)Cl (136 mg, 0.176 mmol), and benzoquinone (115 mg, 1.06 mmol) and the solution stirred under an atmosphere of argon. Deionized water (0.091 mL) was added via syringe and the reaction heated to 60 ºC for 72 hours. The reaction was then cooled to room temperature, diluted with diethyl ether (10 mL), washed sequentially with saturated aqueous sodium metabisulfite (10 mL), saturated aqueous sodium thiosulfate (10 mL) 1M HCl (10 mL, and saturated brine (10 mL). The organic layer was dried over MgSO4 and concentrated under vacuum. The cured residue was purified by silica gel chromatography (hexanes–EtOAc = 4:1) to afford **21** 52.3 mg, 38%) as a yellow oil. TLC (EtOAc–hexanes = 1:3): R_f = 0.50. ^{1}H NMR (400

MHz, Chloroform-*d*): δ 5.96 (ddd, *J* = 36.5, 17.3, 10.7 Hz, 2 H), 5.75 (ddd, *J* = 17.4, 10.1, 7.6 Hz, 1 H), 5.41 – 5.22 (m, 2 H), 5.19 – 4.91 (m, 4 H), 3.20 (d, *J* = 8.7 Hz, 1 H), 2.88 (dq, *J* = 12.9, 6.5 Hz, 1 H), 2.35 (dd, *J* = 13.8, 6.1 Hz, 1 H), 2.25 (dq, *J* = 7.8, 2.6 Hz, 1 H), 2.10 (ddd, *J* = 8.9, 6.1, 2.9 Hz, 1 H), 1.80 (dd, *J* = 13.8, 11.7 Hz, 1 H), 1.48 (ddd, *J* = 9.3, 6.9, 5.2 Hz, 1 H), 1.38 – 1.09 (m, 3 H), 0.88 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR (101 MHz, Chloroform-*d*): δ 179.5, 139.4, 137.3, 132.6, 116.9, 114.7, 114.4, 93.6, 52.9, 49.9, 49.5, 49.4, 47.1, 46.3, 34.0, 19.4, 13.8. IR (thin film) cm^{-1} 3110, 2985, 2919, 1750, 1639, 1605, 1510, 1417, 1221, 1155, 989, 925, 820. HRMS calcd (found) for $C_{17}H_{22}NaO_2$ (M+Na$^+$): 281.1517 (281.1513)



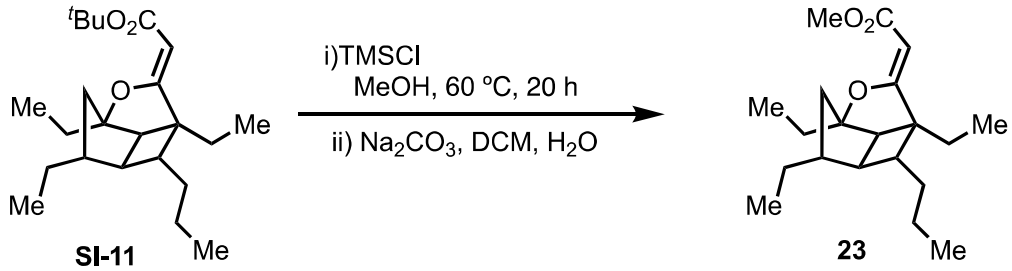
Tert-butyl (Z)-2-(1-propyl-2,3a,5a-trivinylhexahydro)-4-oxacyclobuta[cd]pentalen-5(1H)-ylidene)acetate (SI-10): A stock solution containing *tert*-butyl acetate (1.7 mL, 12.6 mmol, 0.63 M), THF (20.0 mL) and 4 Å molecular sieves (10 % w/v) was let to sit overnight. *Tert*-butyl lithium (0.5 mL, 1.7 M in pentane) was added to stirred solution of THF (3.3 mL) at – 78 ºC. A stock solution of *tert*-butyl acetate (1.29 mL, 0.63 M) was added dropwise to the yellow solution and stirred for 15 minutes at –78 ºC. A solution containing lactone **22** (43.6 mg, 0.17 mmol) in THF (3 mL) was added dropwise to the colorless solution and at –78 ºC for 2 hours before being placed in an ice bath and stirring for an additional 2 hours. The reaction was quenched by addition of 6 M HCl (15 mL) and allowed to warm to 24 °C before being diluted with diethyl ether (30 mL) and

layers separated. The aqueous phase was extracted with diethyl either (2 x 20 mL) and the combined organic phases dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was purified by silica gel chromatography (hexanes–EtOAc = 100:0 → 94:6) to give **SI-10** (27.8 mg, 46%) as a colorless oil and as a single diastereomer. TLC (EtOAc–hexanes = 1:9): R_f = 0.40. ^{1}H NMR (600 MHz, Chloroform-*d*): δ 5.94 (ddd, *J* = 17.2, 15.1, 10.7 Hz, 2 H), 5.73 (ddd, *J* = 17.4, 10.2, 7.6 Hz, 1 H), 5.39 (dd, *J* = 17.2, 1.2 Hz, 1 H), 5.18 (dd, *J* = 10.6, 1.1 Hz, 1 H), 5.09 (dd, *J* = 10.8, 1.2 Hz, 1 H), 5.06 – 4.97 (m, 2 H), 4.92 (ddd, *J* = 10.2, 1.6, 1.0 Hz, 1 H), 4.59 (s, 1 H), 3.10 (d, *J* = 8.7 Hz, 1 H), 2.96 – 2.86 (m, 1 H), 2.50 (dd, *J* = 13.8, 6.3 Hz, 1 H), 2.12 (ddd, *J* = 10.4, 5.2, 3.2 Hz, 1 H), 1.98 (ddd, *J* = 8.8, 5.8, 3.2 Hz, 1 H), 1.78 (dd, *J* = 13.8, 11.3 Hz, 1 H), 1.48 (s, 9 H), 1.33 – 1.11 (m, 2 H), 0.87 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (151 MHz, Chloroform-*d*): δ 178.1, 165.7, 140.1, 137.7, 135.1, 115.3, 114.3, 113.7, 101.2, 88.2, 78.7, 57.5, 52.5, 50.4, 49.8, 47.0, 45.9, 34.2, 28.4, 19.6, 14.0. IR (thin film) cm^{-1} 3095, 3961, 3928, 2364, 1709, 1635, 1638, 164, 1225, 1139, 991, 915, 805. HRMS calcd (found) for $C_{23}H_{32}NaO_3$ ($M–Na^+$): 379.2249 (379.2248).



Tert-butyl (Z)-2-((2,3a,5a-triethyl-1-propylhexahydro)-4-oxacyclobuta[cd]pentalen-5(1H)-ylidene)acetate (SI-11): To a stirred solution of **SI-10** (25.0 mg 0.070 mmol) in

THF (2.4 mL) was added palladium on carbon (2.2 mg, 10 wt % loading). The reaction was purged with nitrogen before being replaced with an atmosphere of hydrogen gas and stirred for 15 hours. The reaction was then filtered over Celite, which was eluted with diethyl ether and concentrated under vacuum. The crude residue was purified by silica gel chromatography (hexanes–EtOAc = 100:0 → 94:6) to give **SI-11** (12.0 mg, 47%) as a colorless oil. TLC (EtOAc–hexanes = 1:9): R_f = 0.40. ^{1}H NMR (600 MHz, Chloroform-*d*): δ 4.44 (d, *J* = 0.9 Hz, 1 H), 2.57 (d, *J* = 8.2 Hz, 1 H), 2.42 (dd, *J* = 13.8, 6.5 Hz, 1 H), 2.02 – 1.87 (m, 2 H), 1.87 – 1.63 (m, 4 H), 1.47 (s, 9 H), 1.44 – 1.22 (m, 5 H), 0.99 (t, *J* = 7.4 Hz, 3 H), 0.95 – 0.83 (m, 69 H), 0.83 – 0.75 (m, 3 H). ^{13}C NMR (101 MHz, Chloroform-*d*): δ 179.9, 166.3, 103.7, 85.4, 78.3, 56.3, 50.5, 49.1, 47.3, 46.5, 45.1, 33.9, 30.7, 28.5, 28.3, 23.3, 20.3, 14.3, 12.9, 9.7, 8.7. HRMS calcd (found) for $C_{23}H_{32}NaO_3$ ($M+Na^+$): 385.2719 (385.2715).



Methyl (*Z*)-2-(2,3a,5a-triethyl-1-propylhexahydro-4-oxacyclobuta[cd]pentalen-5(1H)-ylidene)acetate (23): To a stirred solution of **SI-11** (12.0 mg, 0.033 mmol) in MeOH (1.5 mL) was added TMSCl (75 µL, 0.59 mmol) via syringe. The solution was heated to 60 ºC for 20 hours before being cooled to room temperature. Solid sodium carbonate (98 mg, 0.92 mmol) was added followed by deionized H_2O (19 µL), and methylene chloride (3 mL). The reaction was let to stir for 30 minutes at 24 °C and

$MgSO_4$ (ca. 0.5 g) added before filtering over a pad of Celite, which was eluted with methylene chloride (10 mL). Volatiles were removed under vacuum and the residue purified by silica gel chromatography (hexanes–EtOAc) = 100:0 → 9:1) to give **23** (2.0 mg, 20%) as a colorless oil. TLC (EtOAc–hexanes = 1:9): R_f = 0.19. ^{1}H NMR (600 MHz, Chloroform-*d*): δ 4.55 (s, 1 H), 3.66 (s, 3 H), 2.59 (d, *J* = 8.3 Hz, 1 H), 2.43 (dd, *J* = 13.8, 6.5 Hz, 1 H), 2.03 – 1.94 (m, 1 H), 1.91 (dt, *J* = 10.7, 4.4 Hz, 1 H), 1.88 – 1.71 (m, 3 H), 1.66 (ddd, *J* = 14.0, 7.5, 1.1 Hz, 1 H), 1.51 (dt, *J* = 14.2, 7.1 Hz, 1 H), 1.44 – 1.38 (m, 1 H), 1.37 – 1.13 (m, 4 H), 1.01 (td, *J* = 7.5, 1.1 Hz, 3 H), 0.94 – 0.82 (m, 6 H), 0.79 (t, J = 7.4 Hz, 3 H). ^{13}C NMR (151 MHz, Chloroform-*d*): δ 181.0, 167.2, 104.1, 83.4, 56.4, 50.7, 50.4, 49.3, 47.4, 46.5, 45.0, 33.9, 30.8, 28.3, 23.2, 20.38, 14.2, 12.9, 9.6, 8.6. HRMS calcd (found) for $C_{20}H_{32}NaO_3$ ($M–Na^+$): 343.2249 (343.2244).

Biological Testing Methods and Data

All biological testing data was performed by CO-ADD (University of Queensland, Australia). Below are the methods provided by CO-ADD:

Sample Preparation:

Samples were prepared in DMSO to a final testing concentration of 32 µg/mL or 20 µM and serially diluted 1:2 fold for 8 times. Each sample concentration was prepared in 384-well plates, non-binding surface plate (NBS; Corning 3640) for each bacterial/fungal strain, tissue-culture treated (TC-treated; Corning 3712/3764) black for mammalian cell types and polypropylene 384-well (PP; Corning 3657) for haemolysis assays, all in duplicate (n=2), and keeping the final DMSO concentration to a maximum

of 0.5%. All the sample preparation was done using liquid handling robots.

Antibacterial Assay:

All bacteria were cultured in Cation-adjusted Mueller Hinton broth (CAMHB) at 37 °C overnight. A sample of each culture was then diluted 40-fold in fresh broth and incubated at 37 °C for 1.5–3 h. The resultant mid-log phase cultures were diluted (CFU/mL measured by OD600), then added to each well of the compound containing plates, giving a cell density of 5 x 10^5 CFU/mL and a total volume of 50 µL. All the plates were covered and incubated at 37 °C for 18 h without shaking.

Inhibition of bacterial growth was determined measuring absorbance at 600 nm (OD600), using a Tecan M1000 Pro monochromator plate reader. The percentage of growth inhibition was calculated for each well, using the negative control (media only) and positive control (bacteria without inhibitors) on the same plate as references.

The percentage of growth inhibition was calculated for each well, using the negative control (media only) and positive control (bacteria without inhibitors) on the same plate. The MIC was determined as the lowest concentration at which the growth was fully inhibited, defined by an inhibition ≥ 80%. In addition, the maximal percentage of growth inhibition is reported as DMax, indicating any compounds with partial activity.

Antifungal Assay:

Fungi strains were cultured for 3 days on Yeast Extract-Peptone Dextrose (YPD) agar at 30 °C. A yeast suspension of 1 x 106 to 5 x 106 CFU/mL (as determined by OD530) was prepared from five colonies. The suspension was subsequently diluted and added to each well of the compound-containing plates giving a final cell density of fungi

suspension of 2.5 x 10^3 CFU/mL and a total volume of 50 µL. All plates were covered and incubated at 35 °C for 36 h without shaking.

Growth inhibition of C. albicans was determined measuring absorbance at 630 nm (OD630), while the growth inhibition of C. neoformans was determined measuring the difference in absorbance between 600 and 570 nm (OD600-570), after the addition of resazurin (0.001% final concentration) and incubation at 35 °C for 2 h. The absorbance was measured using a Biotek Multiflo Synergy HTX plate reader.

In both cases, the percentage of growth inhibition was calculated for each well, using the negative control (media only) and positive control (fungi without inhibitors) on the same plate. The MIC was determined as the lowest concentration at which the growth was fully inhibited, defined by an inhibition ≥ 80% for C. albicans and an inhibition ≥ 70% for C. neoformans. Due to a higher variance in growth and inhibition, a lower threshold was applied to the data for C. neoformans. In addition, the maximal percentage of growth inhibition is reported as DMax, indicating any compounds with marginal activity.

Cytotoxicity Assay:

HEK293 cells were counted manually in a Neubauer haemocytometer and then plated in the 384-well plates containing the compounds to give a density of 5000 cells/well in a final volume of 50 µL. DMEM supplemented with 10% FBS was used as growth media and the cells were incubated together with the compounds for 20 h at 37 °C in 5% CO2.

Cytotoxicity (or cell viability) was measured by fluorescence, ex: 560/10 nm, em: 590/10 nm (F560/590), after addition of 5 µL of 25 µg/mL resazurin (2.3 µg/mL final

concentration) and after incubation for further 3 h at 37 °C in 5% CO_2. The fluorescence intensity was measured using a Tecan M1000 Pro monochromator plate reader, using automatic gain calculation.

CC50 (concentration at 50% cytotoxicity) were calculated by curve fitting the inhibition values vs. log(concentration) using a sigmoidal dose-response function, with variable fitting values for bottom, top and slope. In addition, the maximal percentage of cytotoxicity is reported as DMax, indicating any compounds with partial cytotoxicity.

The curve fitting was implemented using Pipeline Pilot's dose-response component, resulting in similar values to curve fitting tools such as GraphPad's Prism and IDBS's XlFit. Any value with > indicate sample with no activity (low DMax value) or samples with CC50 values above the maximum tested concentration (higher DMax value).

Haemolysis assay:

Human whole blood was washed three times with 3 volumes of 0.9% NaCl and then resuspended in same to a concentration of 0.5 x 108 cells/mL, as determined by manual cell count in a Neubauer haemocytometer. The washed cells were then added to the 384-well compound-containing plates for a final volume of 50 µL. After a 10 min shake on a plate shaker the plates were then incubated for 1 h at 37 °C. After incubation, the plates were centrifuged at 1000g for 10 min to pellet cells and debris, 25 µL of the supernatant was then transferred to a polystyrene 384-well assay plate.

Haemolysis was determined by measuring the supernatant absorbance at 405 mm (OD405). The absorbance was measured using a Tecan M1000 Pro monochromator plate reader.

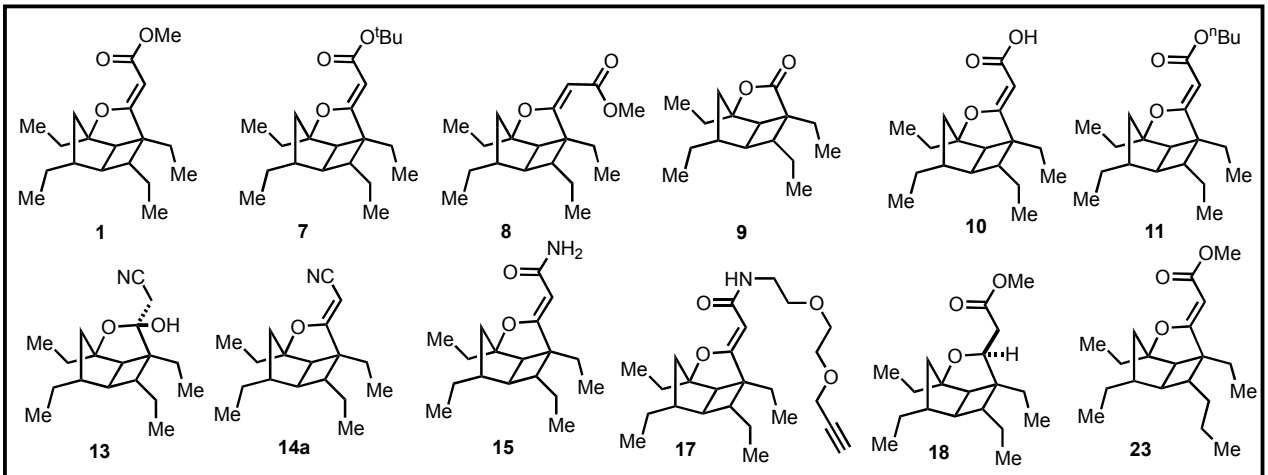
HC10 and HC50 (concentration at 10% and 50% haemolysis, respectively) were calculated by curve fitting the inhibition values vs. log(concentration) using a sigmoidal dose-response function with variable fitting values for top, bottom and slope. In addition, the maximal percentage of haemolysis is reported as DMax, indicating any compounds with partial haemolysis.

The curve fitting was implemented using Pipeline Pilot's dose-response component, resulting in similar values to curve fitting tools such as GraphPad's Prism and IDBS's XlFit. Any value with > indicate sample with no activity (low DMax value) or samples with HC10 values above the maximum tested concentration (higher DMax value).

Biological testing data quality control:

Colistin and Vancomycin were used as positive bacterial inhibitor standards for Gram- negative and Gram-positive bacteria, respectively. Fluconazole was used as a positive fungal inhibitor standard for C. albicans and C. neoformans. Tamoxifen was used as a positive cytotoxicity standard. Melittin was used as a positive heamolytic standard.

Each antibiotic standard was provided in 4 concentrations, with 2 above and 2 below its MIC or CC50 value, and plated into the first 8 wells of column 23 of the 384-well NBS plates. Tamoxifen and melittin was used in 8 concentrations in 2 fold serial dilutions with 50 µg/mL highest concentration.



	Cryptococcus neoformans		*Candida albicans*		*Staphylococcus aureus*		*Escheria coli*		*Acinobacter baumannii*	
	MIC (mg/mL)	DMax (%)	MIC	DMax	MIC	DMax	MIC	DMax	MIC	DMax
1	>32	41.1	>32	13.7	>32	7.6	>32	<5	>32	10.2
7	>32	32.1	>32	5.3	>32	29.2	>32	<5	>32	6.3
8	>32	22.4	>32	20.1	>32	18.1	>32	<5	>32	11.4
9	>32	37.0	>32	35.3	>32	30.1	>32	<5	>32	8.5
10	>32	29.0	>32	4.8	>32	16.5	>32	<5	>32	11.2
11	>32	24.1	>32	11.0	>32	12.0	>32	<5	>32	11.5
13	>32	47.8	>32	8.7	>32	<5	>32	<5	>32	12.6
14a	>32	27.3	>32	11.0	>32	10.6	>32	<5	>32	1.6
15	>32	43.8	>32	8.7	>32	15.1	>32	<5	>32	<5
17	>32	27.9	>32	30.6	>32	25.5	>32	<5	>32	36.8
18	>32	24.1	>32	5.7	>32	14.5	>32	<5	>32	12.6
23	>32	33.2	>32	10.3	>32	21.3	>32	<5	>32	11.7

	Pseudomonas aeruginosa		*Klebsiella pneumoniae*		Human embryonic kidney cells (HEK-293)		Human red blood cells	
	MIC (mg/mL)	DMax (%)	MIC	DMax	MIC	DMax	MIC	DMax
1	>32	19.4	>32	8.0	>32	72.6	>32	8.5
7	>32	24.7	>32	7.5	>32	58	>32	2.3
8	>32	21.4	>32	9.7	>32	28	>32	2.3
9	>32	23.5	>32	9.8	>32	17.7	>32	2.5
10	>32	29.0	>32	11.5	>32	18.1	>32	3.5
11	>32	19.3	>32	9.6	>32	11.3	>32	3.2
13	>32	36.8	>32	11.6	>32	44.6	>32	1.8
14a	>32	43.8	>32	7.3	>32	10.0	>32	2.0
15	>32	48.7	>32	8.4	>32	20.2	>32	20.7
17	>32	35.8	>32	11.5	14.2	95.4	>32	3.1
18	>32	27.2	>32	10.3	>32	25.5	>32	2.5
23	>32	24.6	>32	12.2	>32	32.1	>32	3.1

Figure S5: Summary of biological testing data for **1** and all synthesized analogs.

References:

S1): McCallum, M. E.; Rasik, C. M.; Wood, J. L.; Brown, M. K. *J. Am. Chem. Soc*. **2016**, *138*, 2437.

S2) John, J.; Hopf, H. *Eur. J. Org. Chem*. **2013**, 5, 841–845.

S3) Cardillo, G, Gentilucci, L.; Gianotti, M.; Perciaccante, R.; Tolomelli, A. *J. Org. Chem.* **2001,** *66*, 8657.

Scans of NMR spectra for new compounds

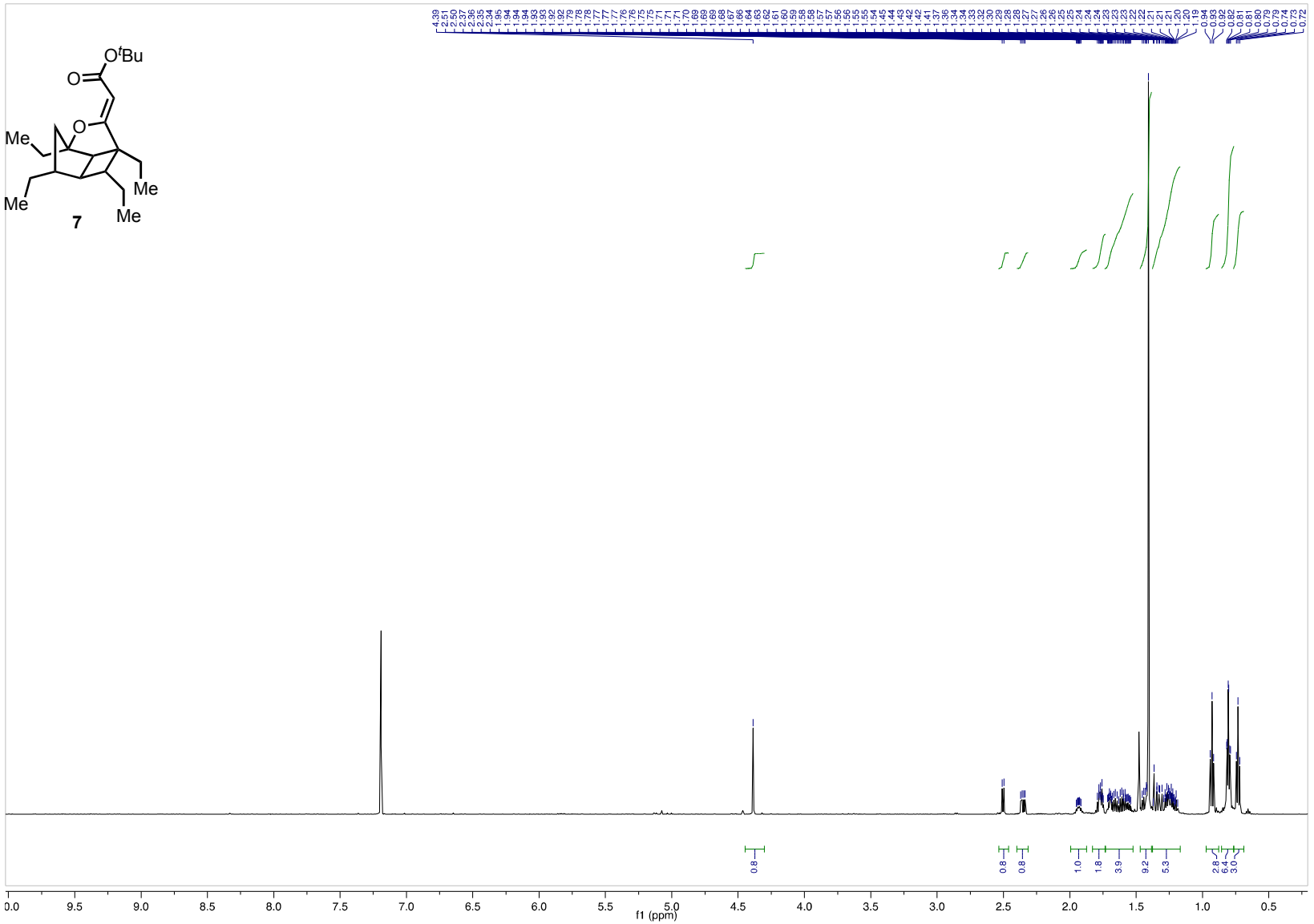


Figure S6: ^{1}H NMR (600 MHz, chloroform, *d*), **7**

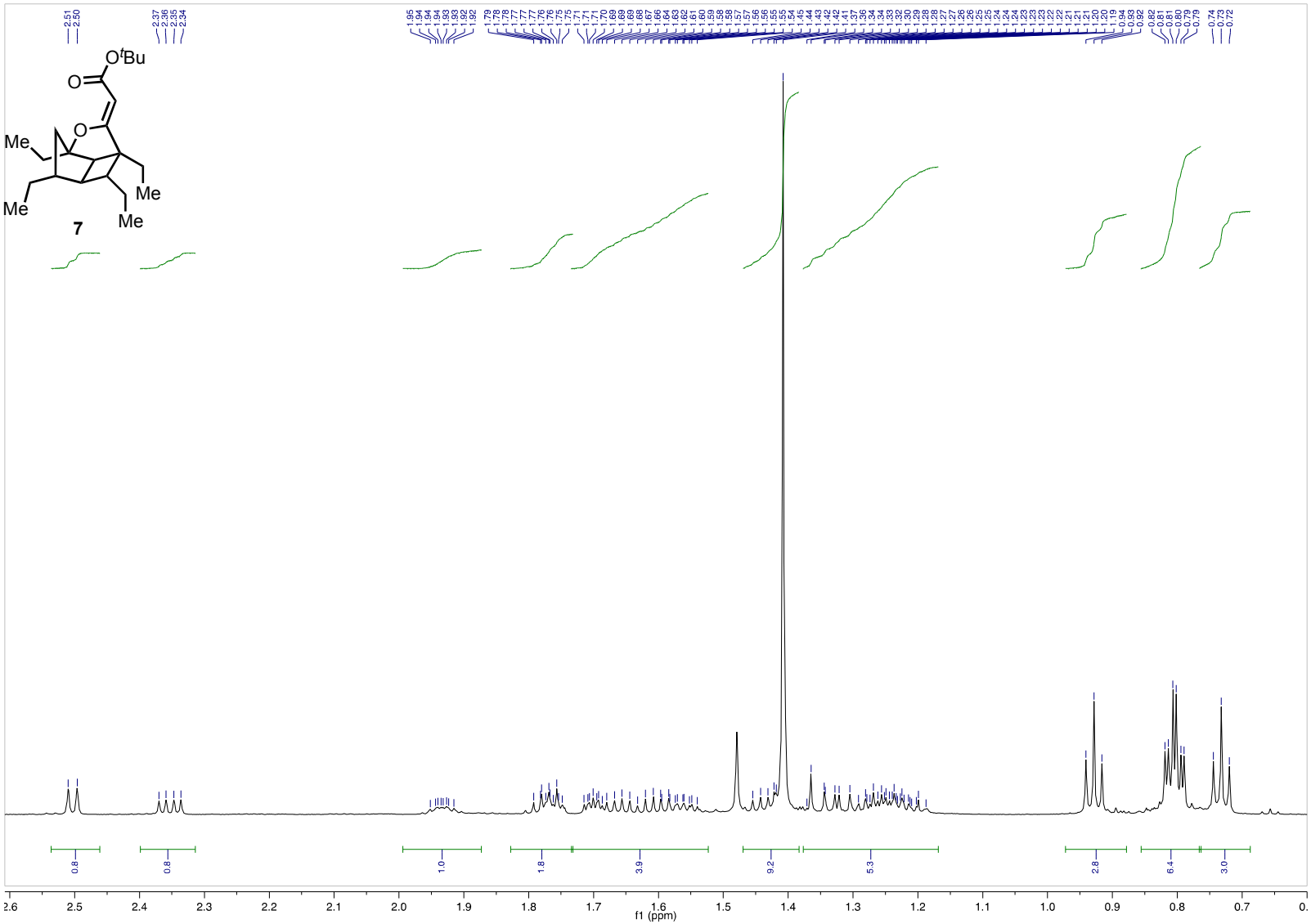


Figure S7: ^{1}H NMR (600 MHz, chloroform, *d*), **7** (inset).

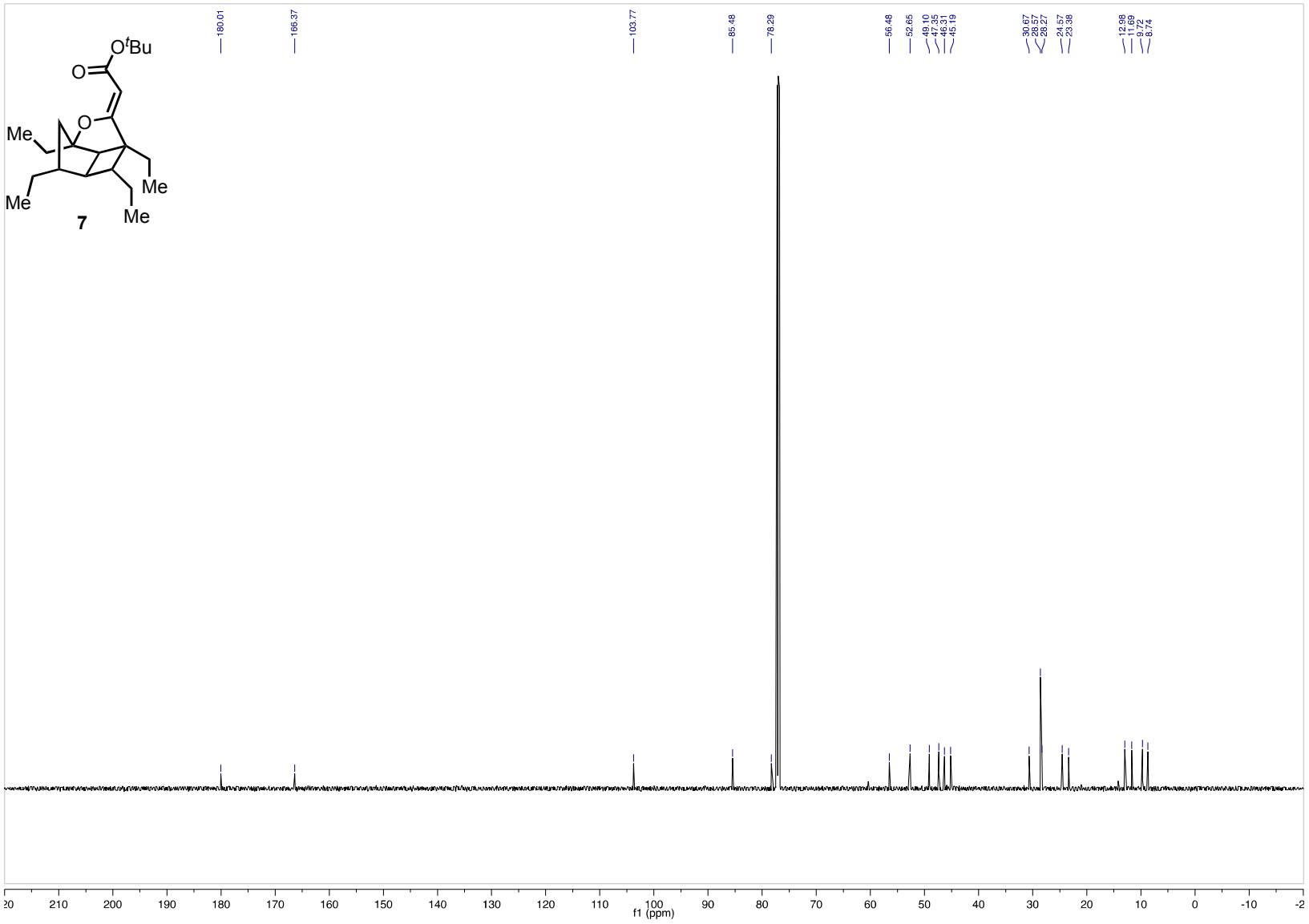


Figure S8: ^{13}C NMR (151 MHz, chloroform, *d*), **7**

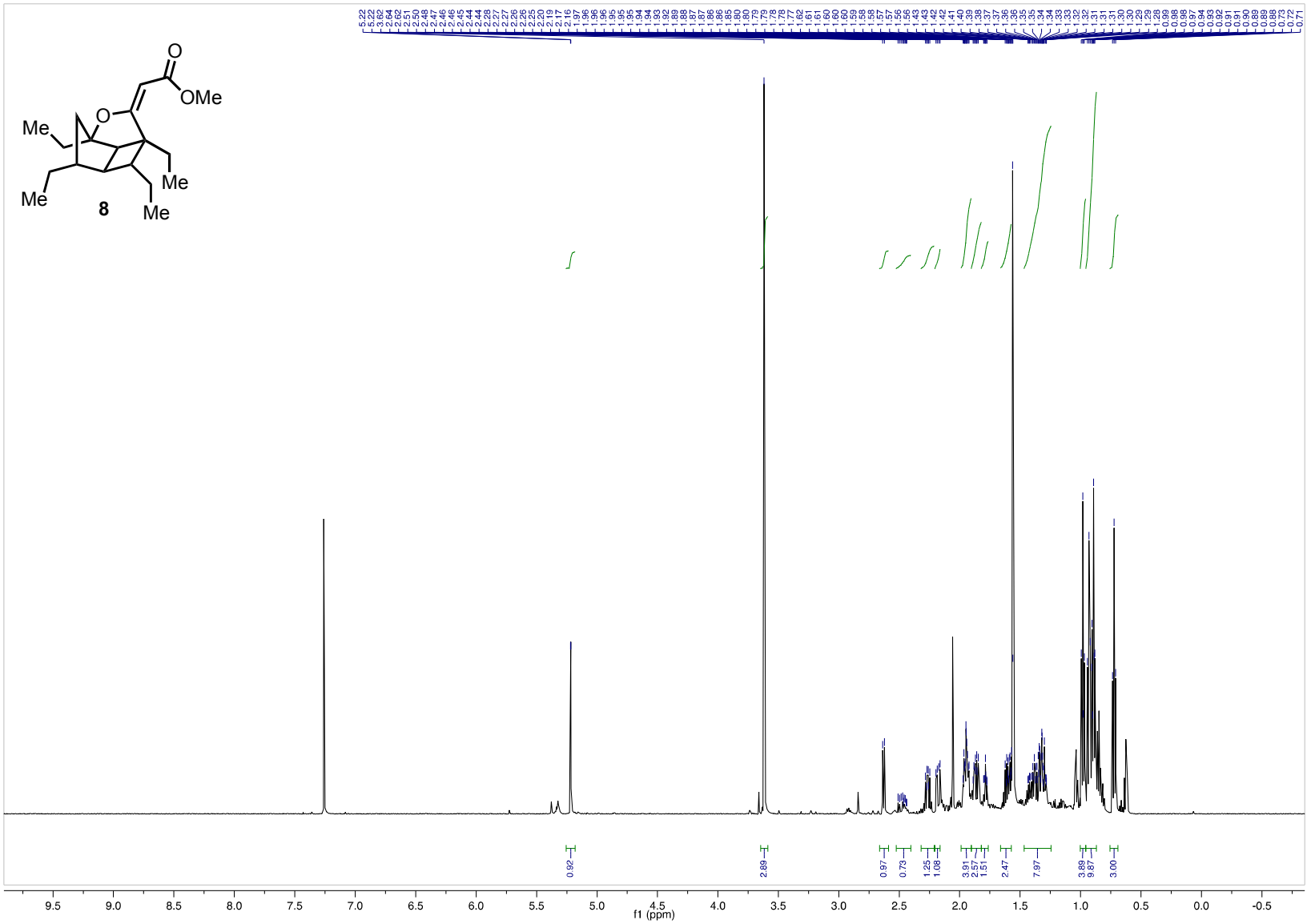


Figure S9: ^{1}H NMR (600 MHz, chloroform, *d*), **8**.

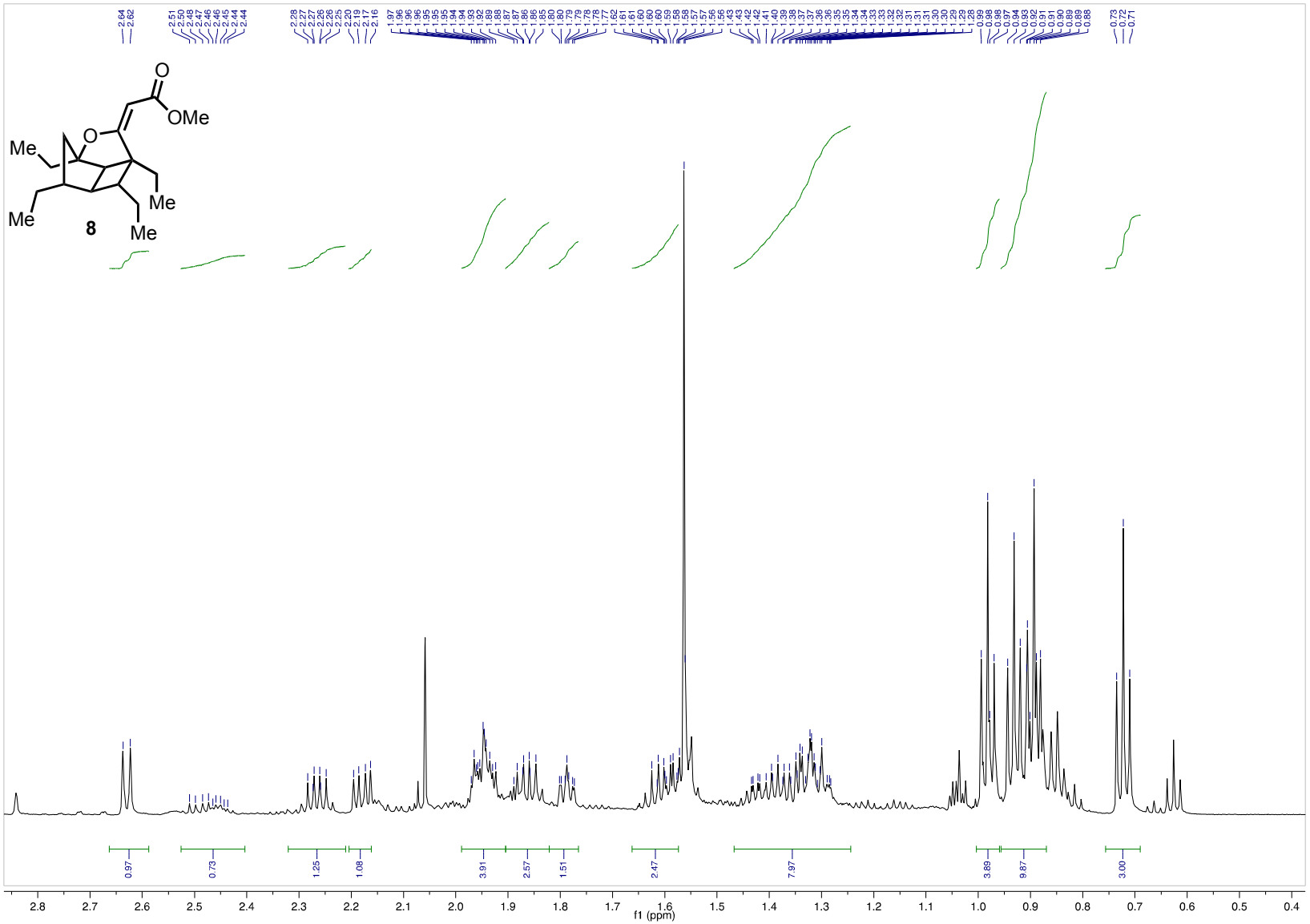


Figure S10: ^{1}H NMR (600 MHz, chloroform, *d*), **8** (inset).

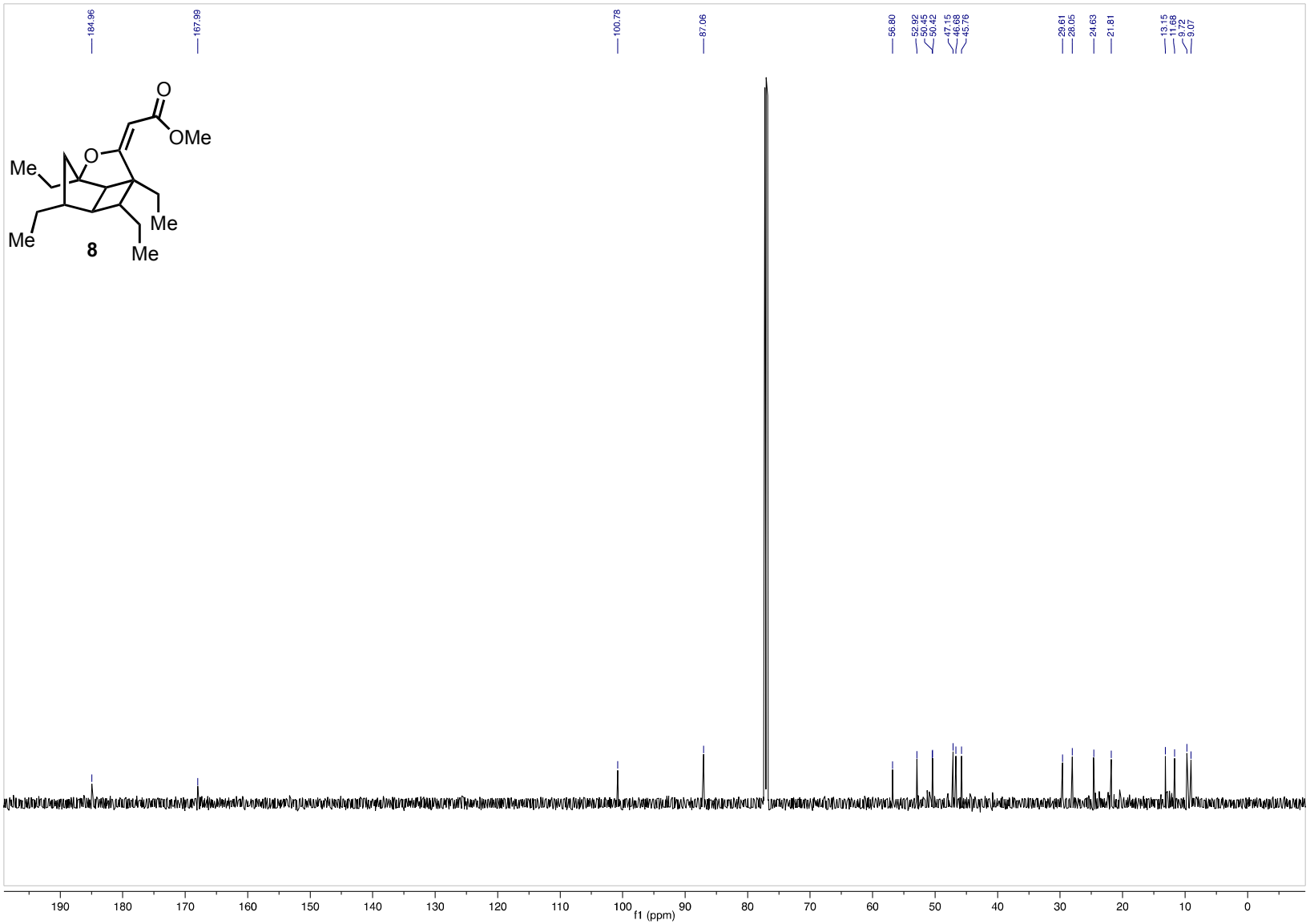


Figure S11: ^{13}C NMR (151 MHz, chloroform, *d*), **8** (inset).

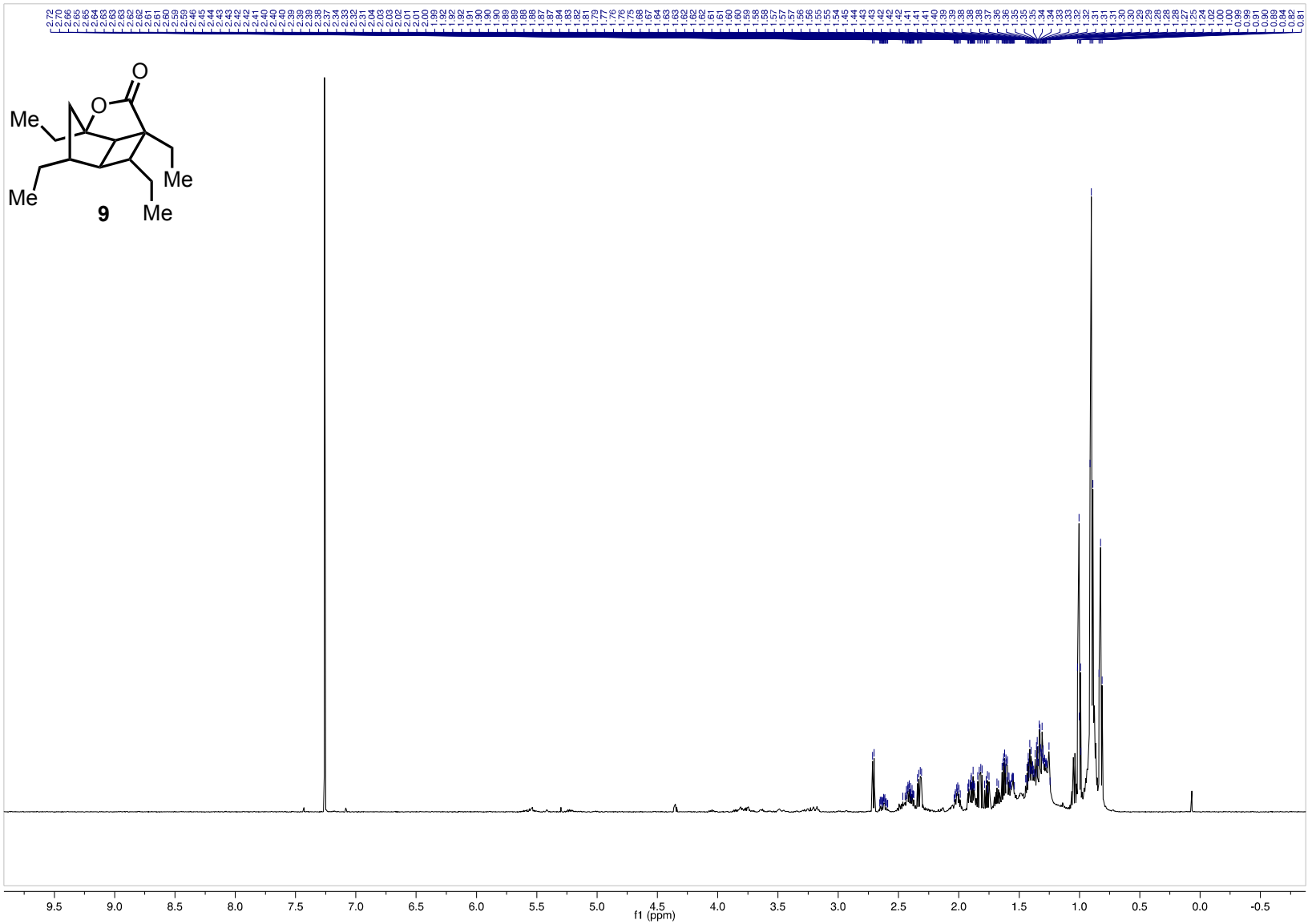


Figure S12: ^{1}H NMR (600 MHz, chloroform, *d*), **9**.

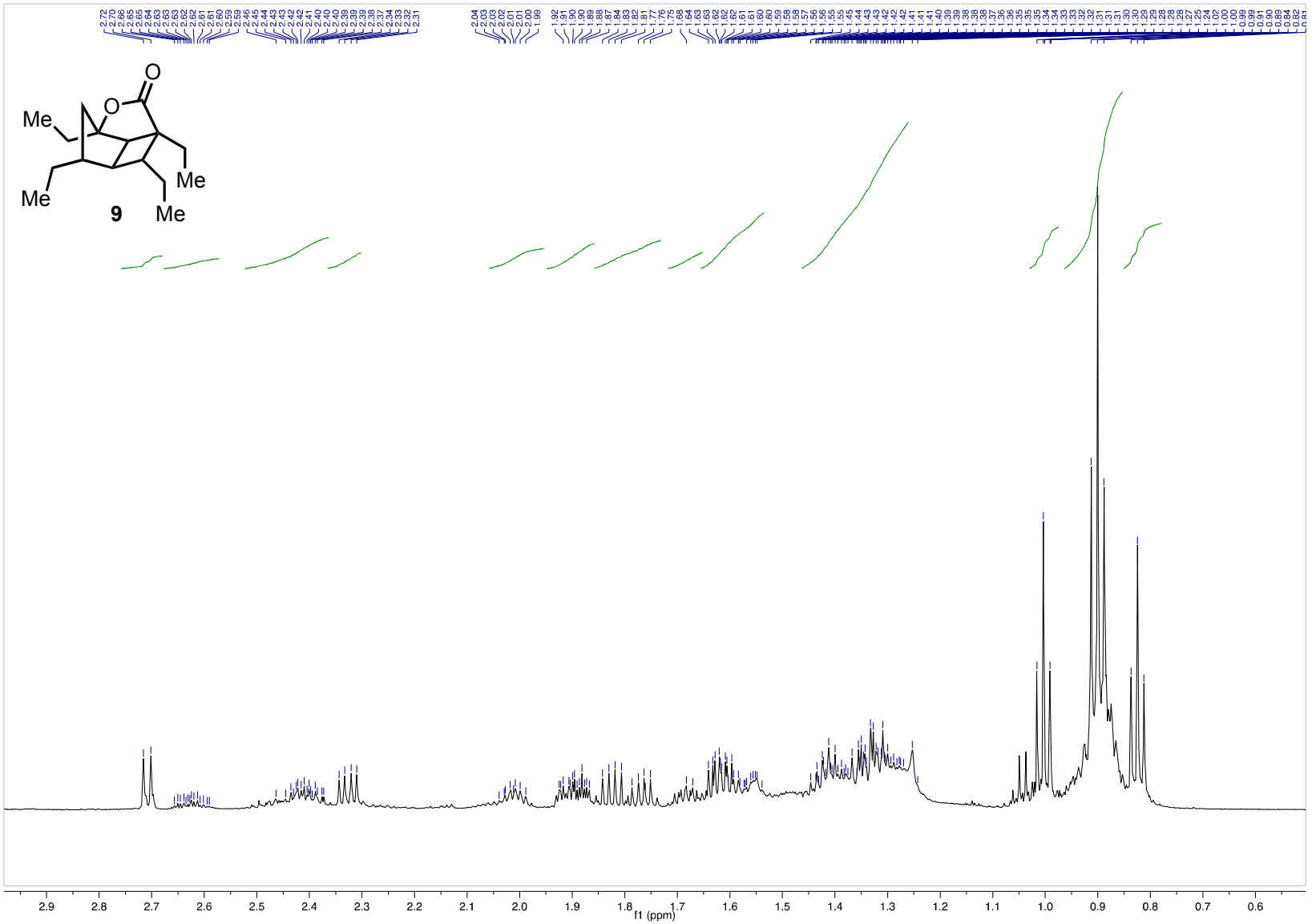


Figure S13: ^{1}H NMR (600 MHz, chloroform, *d*), **9** (inset).

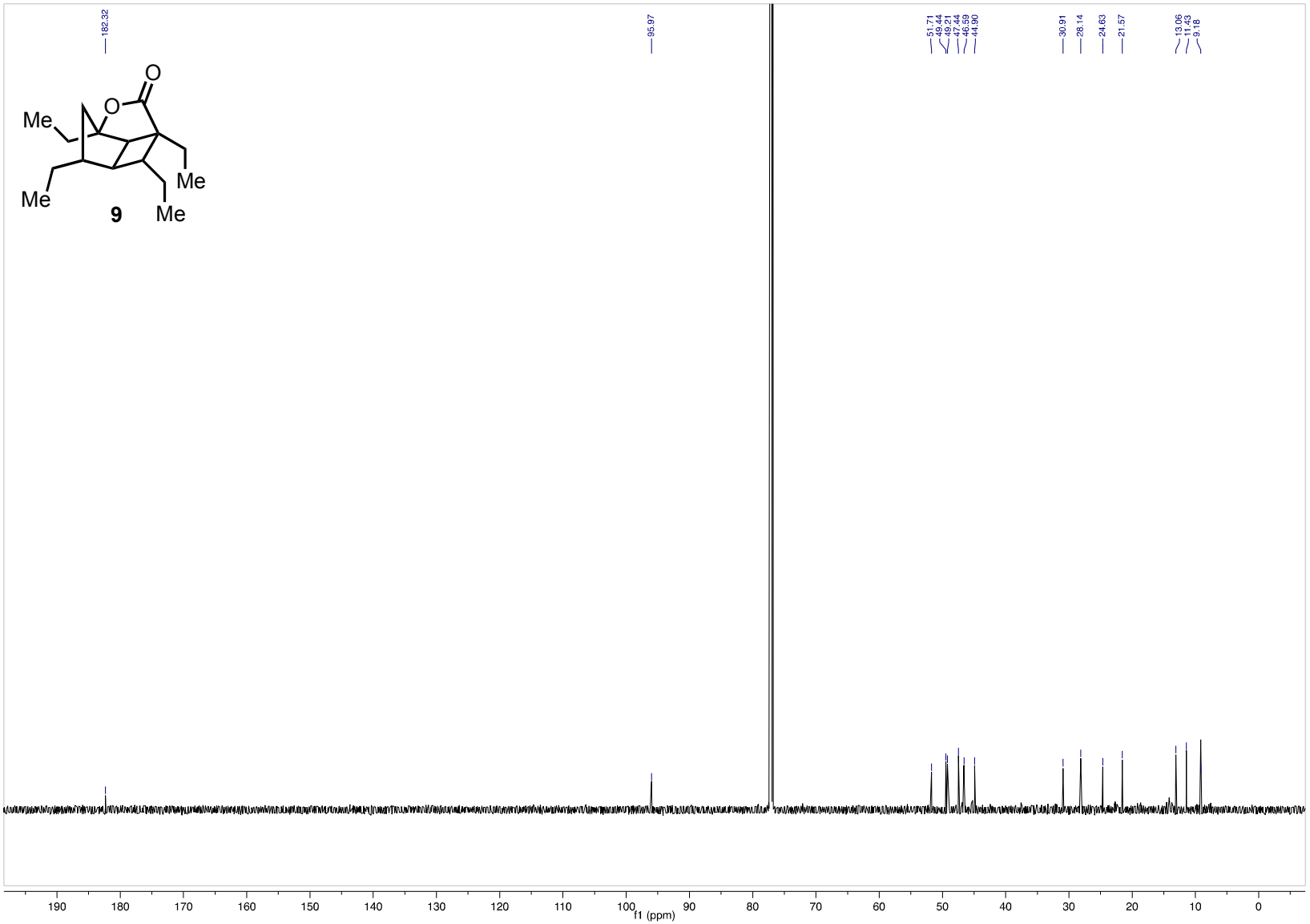


Figure S14: ^{13}C NMR (151 MHz, chloroform, *d*), **9** (inset).

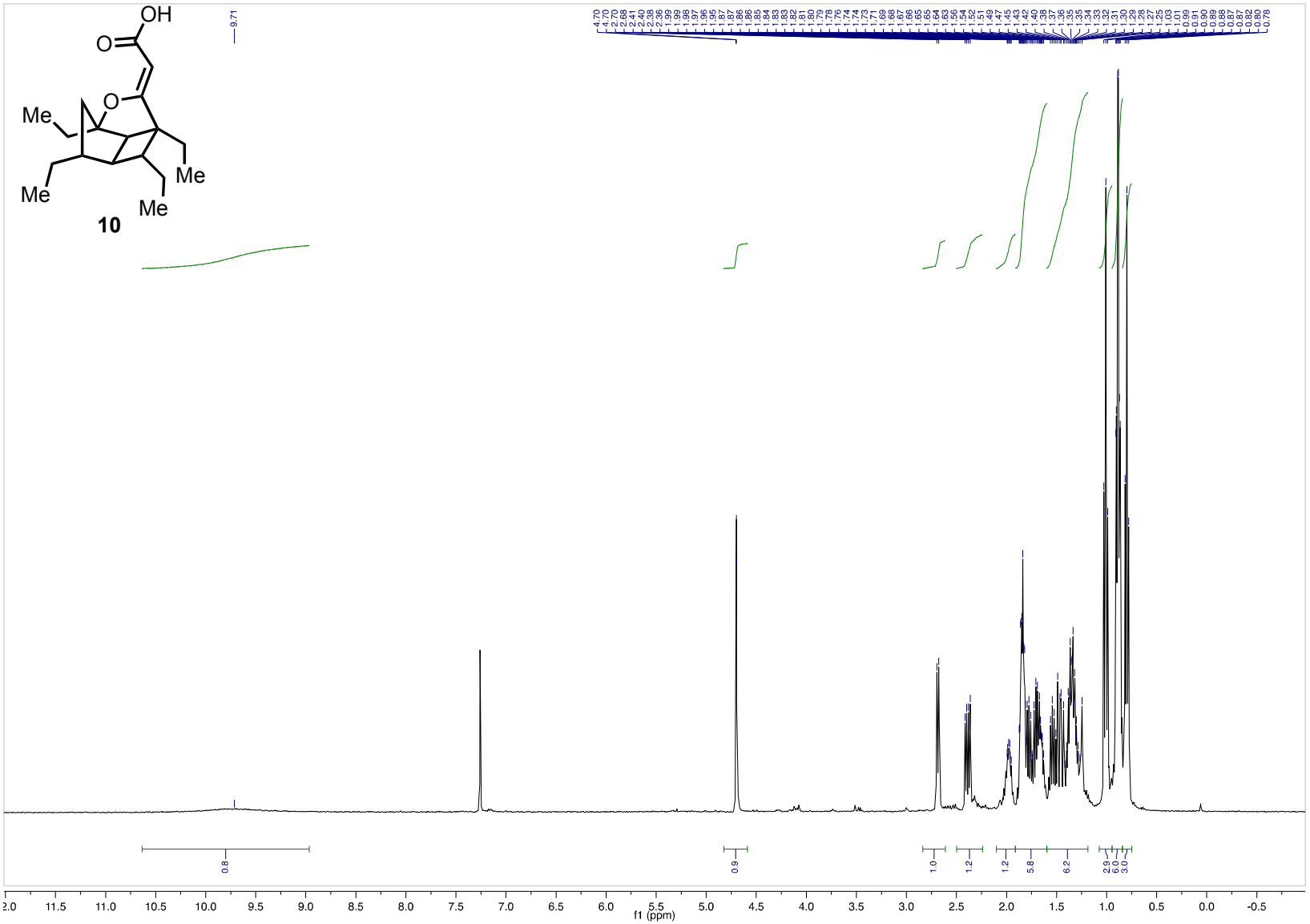


Figure S15: ^{1}H NMR (600 MHz, chloroform, *d*), **10**.

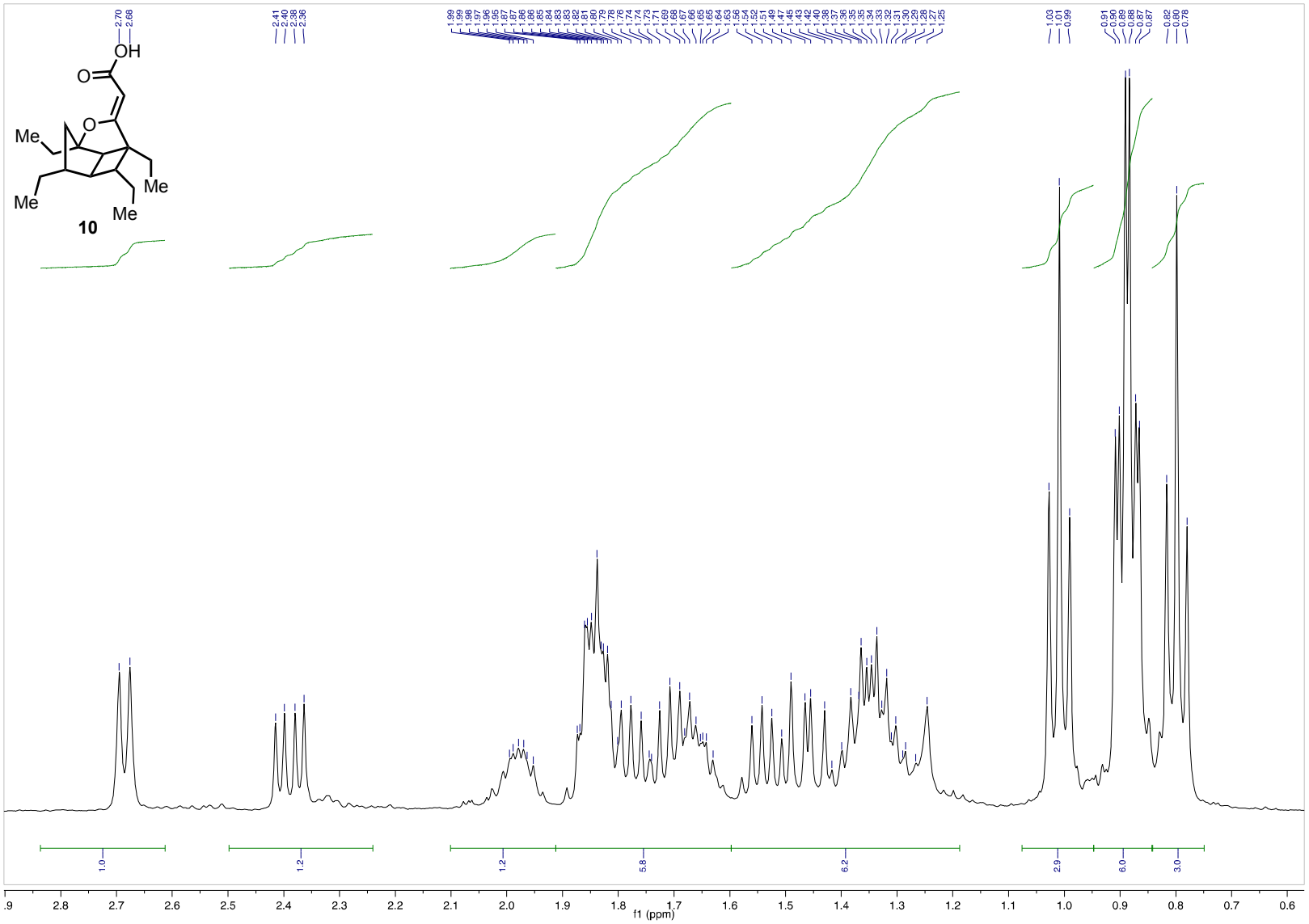


Figure S16: ^{1}H NMR (600 MHz, chloroform, *d*), **10** (inset).

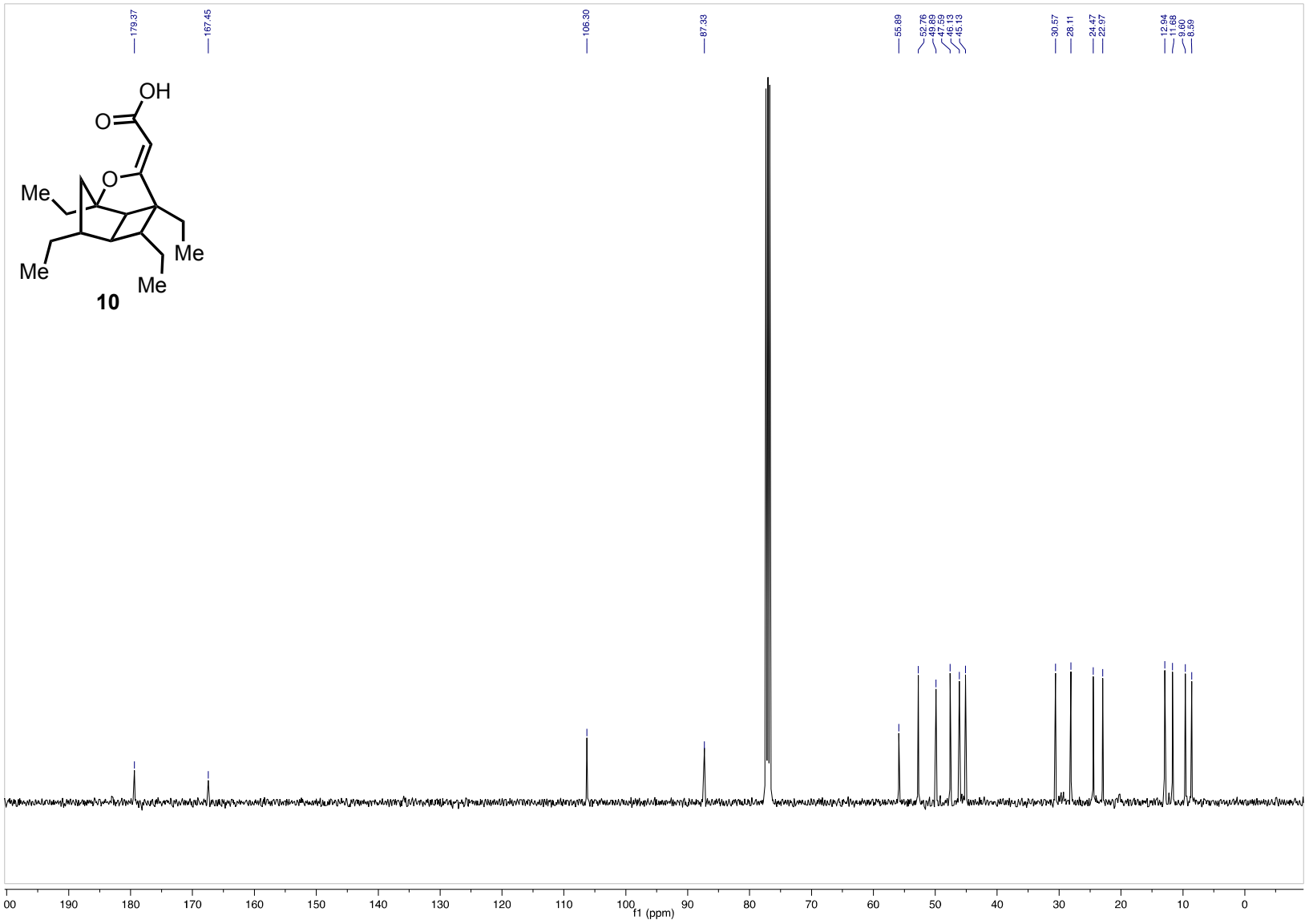


Figure S17: ^{13}C NMR (151 MHz, chloroform, *d*), **10**.

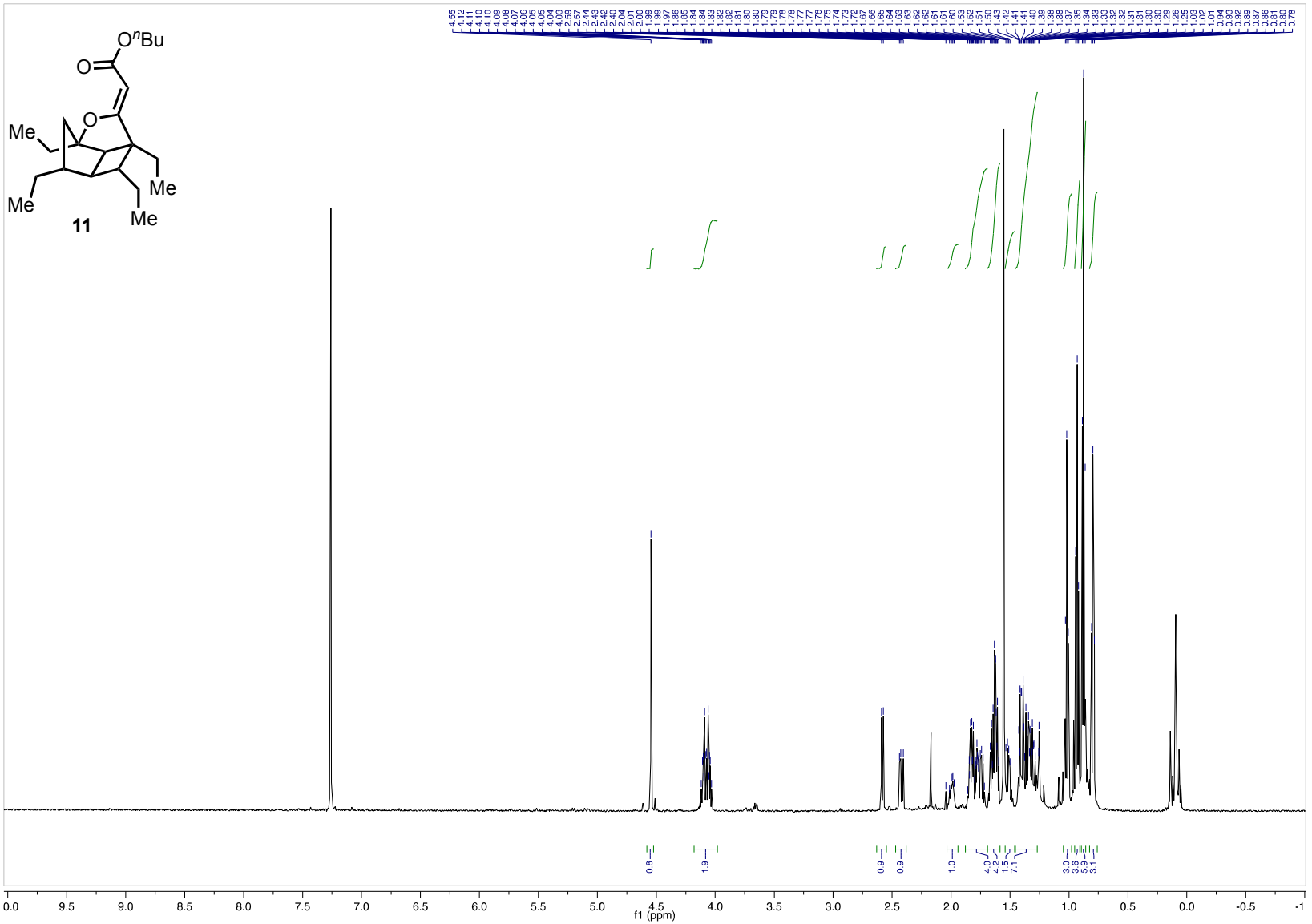


Figure S18: ^{1}H NMR (600 MHz, chloroform-*d*), **11**.

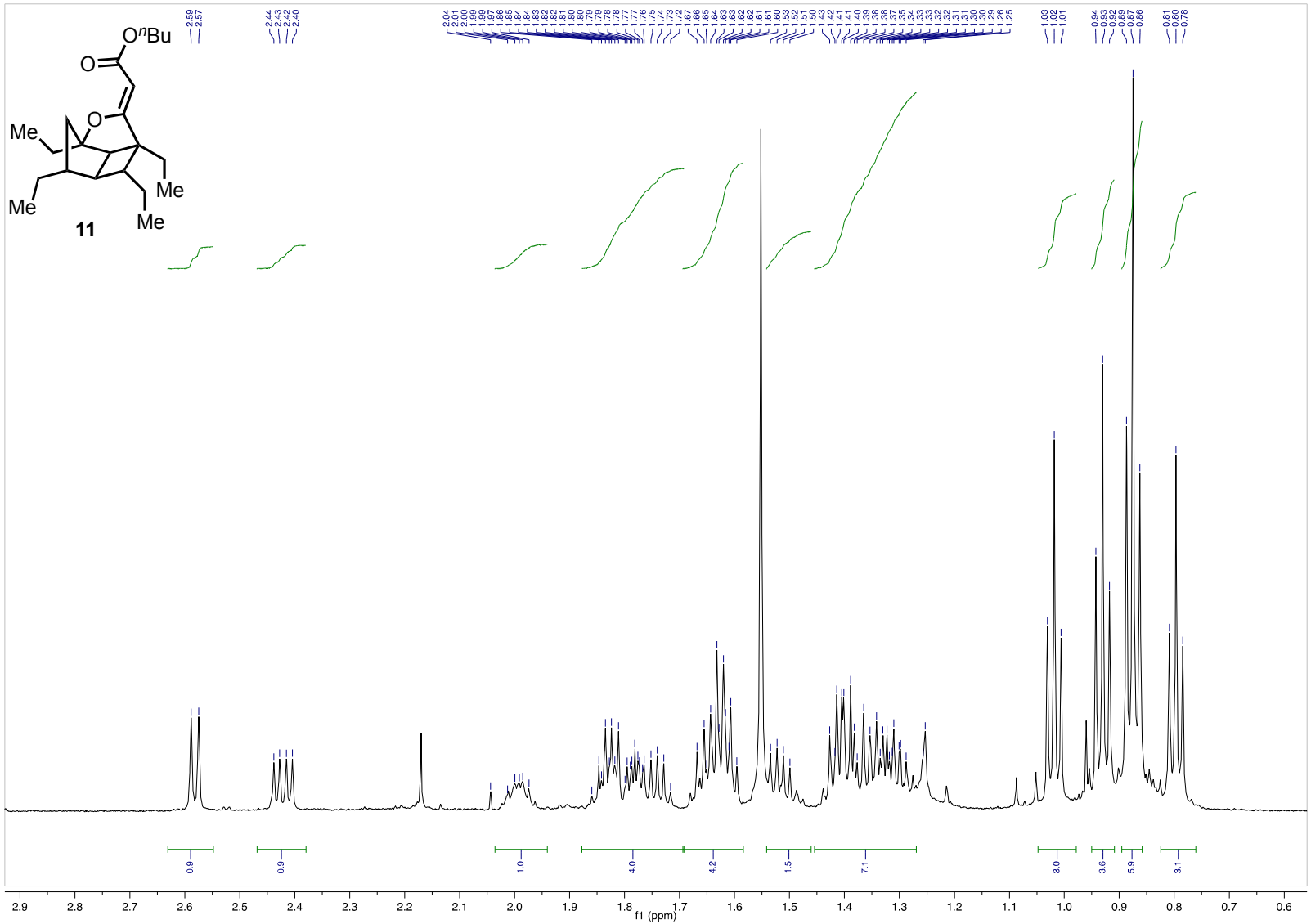


Figure S19: ^{1}H NMR (600 MHz, chloroform-*d*), **11** (inset).

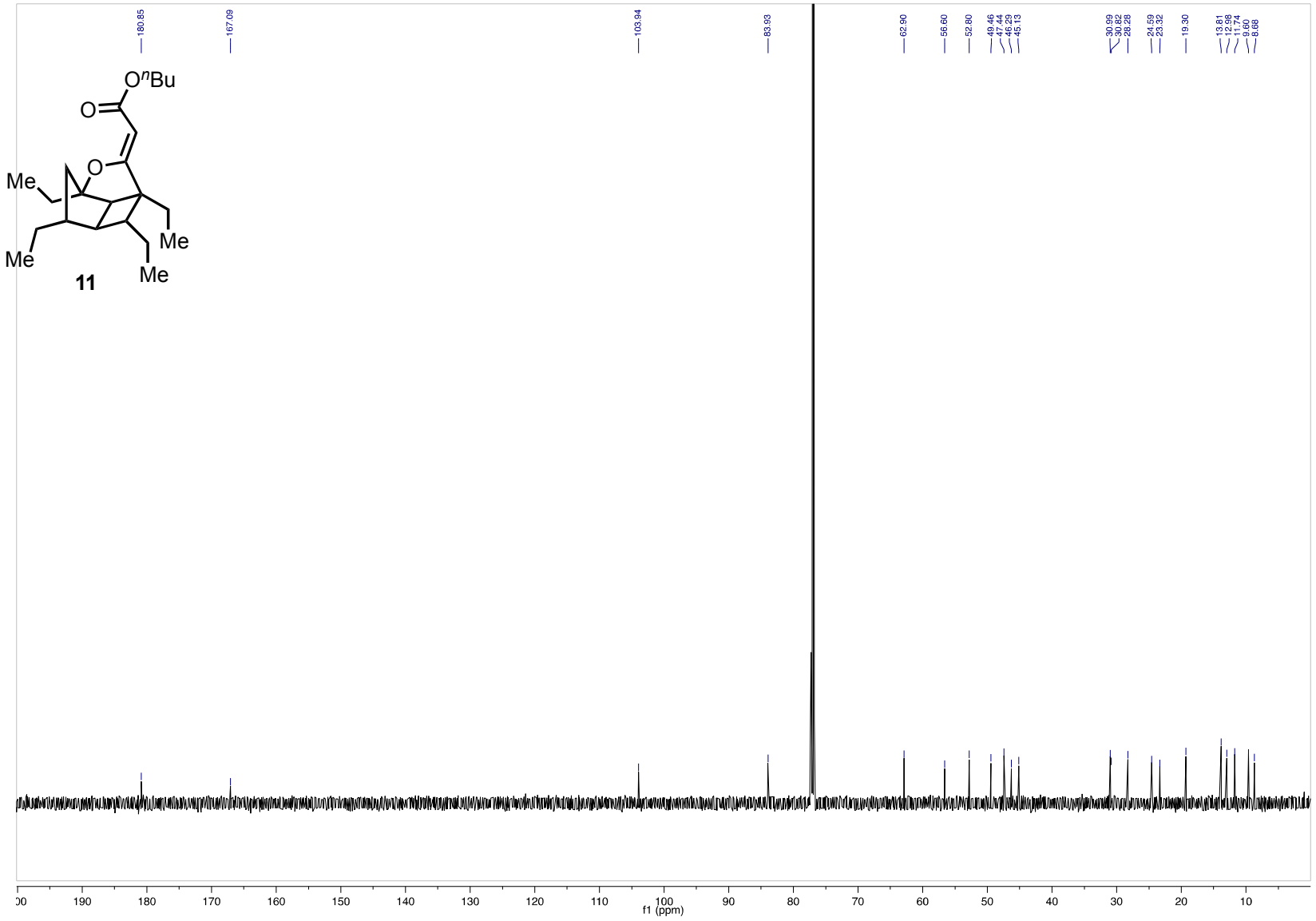


Figure S20: ^{13}C NMR (151 MHz, chloroform-*d*), **11** (inset).

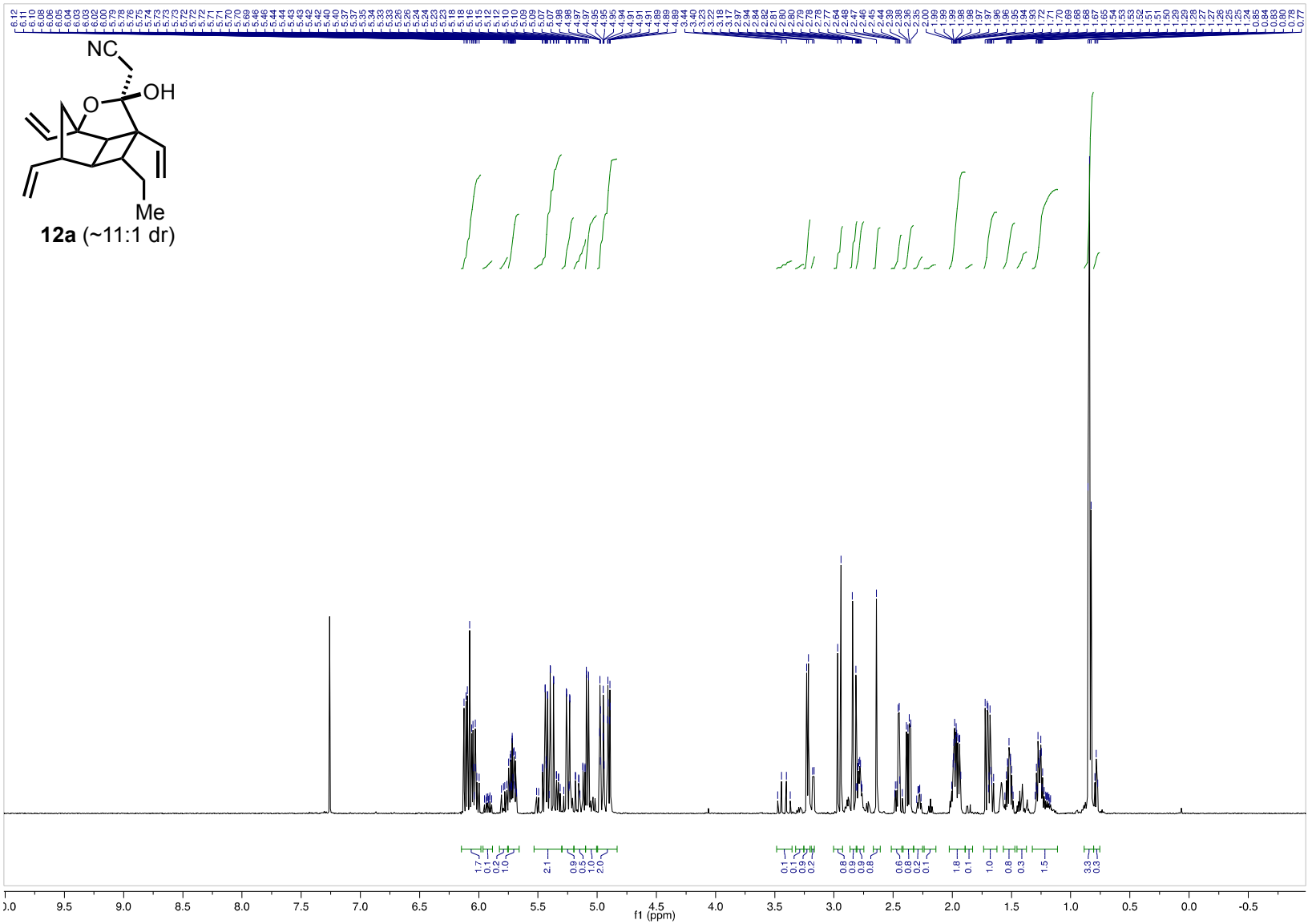


Figure S21: ^{1}H NMR (600 MHz, chloroform-*d*), **12a**.

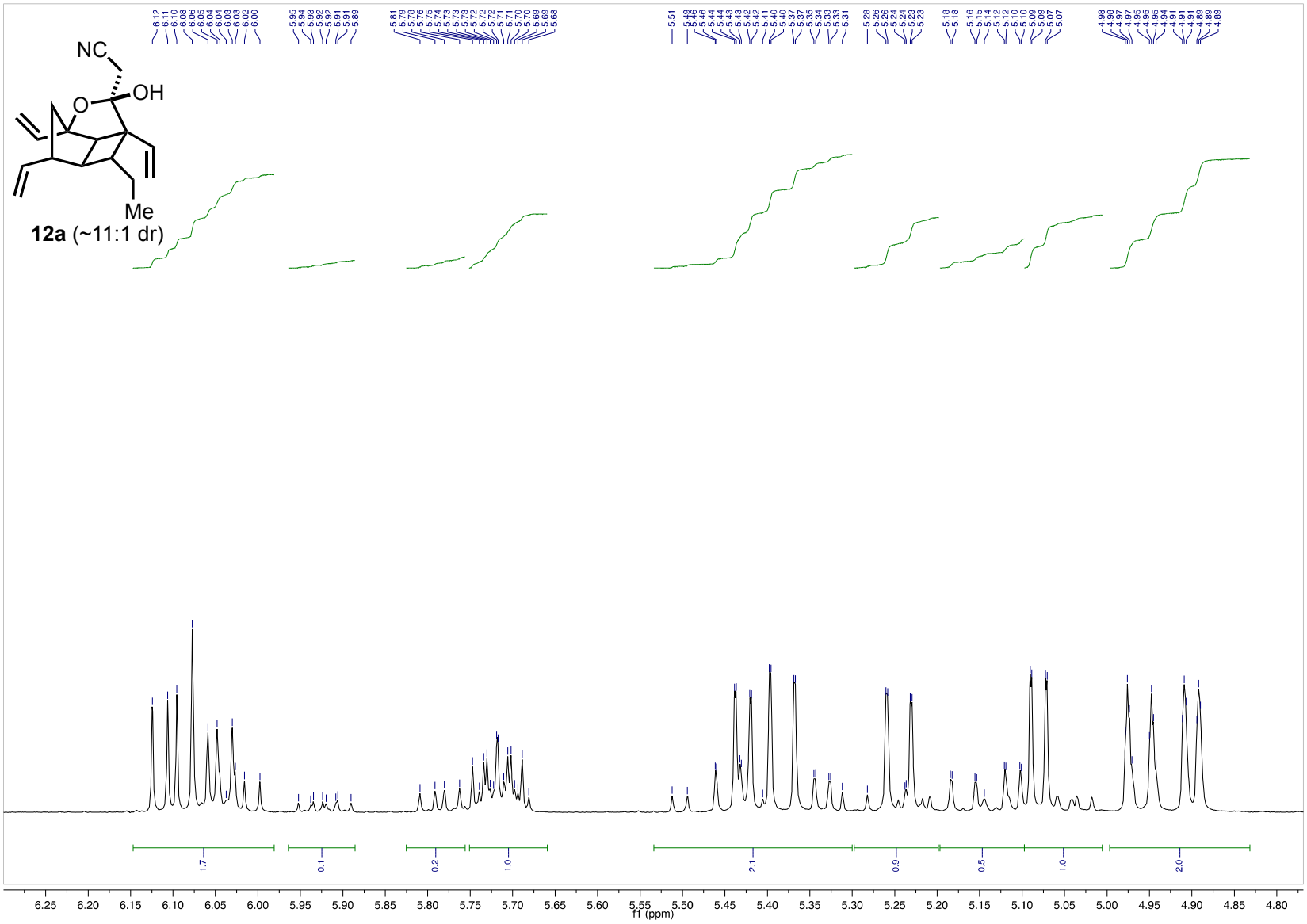


Figure S22: ^{1}H NMR (600 MHz, chloroform-*d*), **12a** (inset).

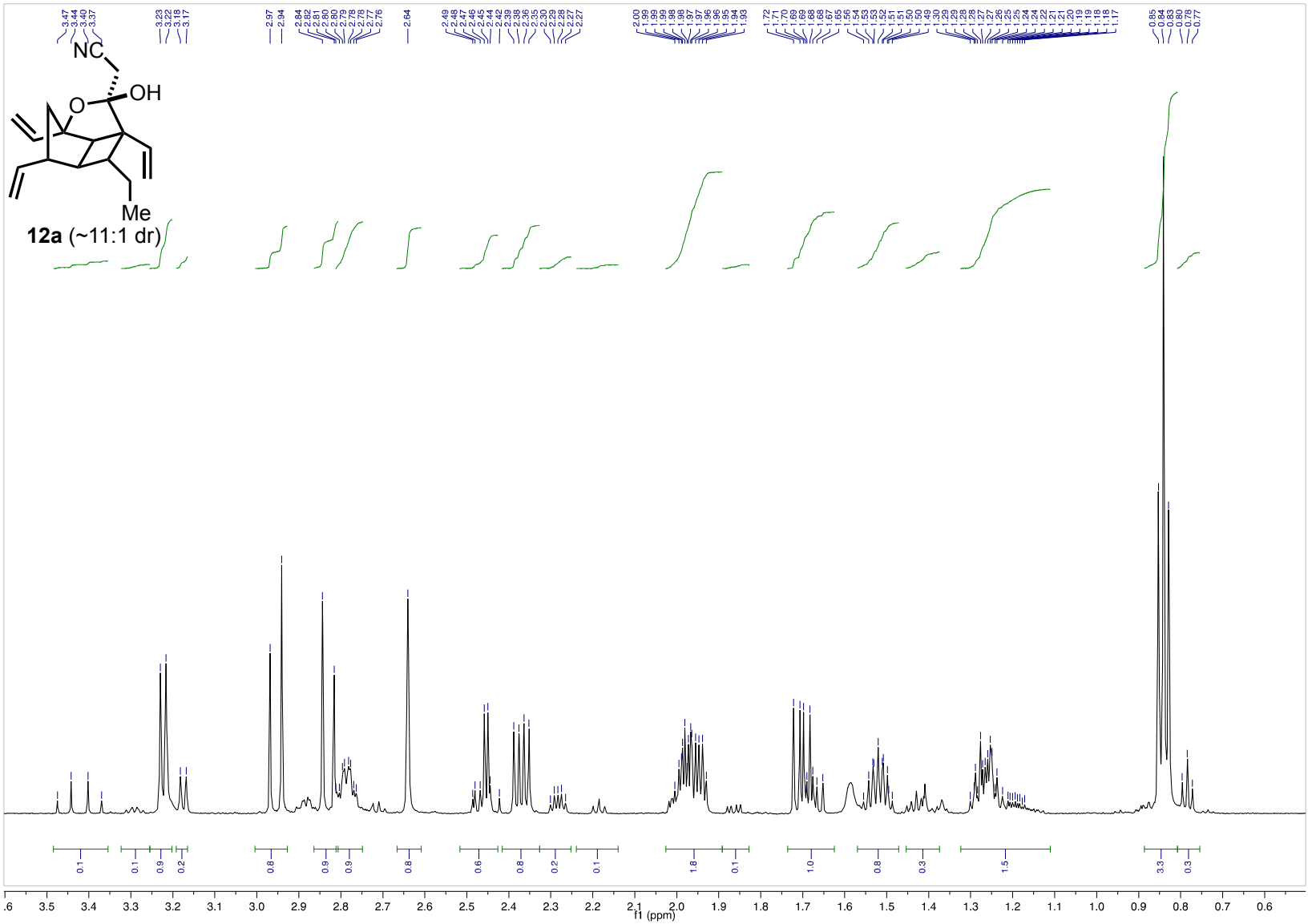


Figure S23: ^{1}H NMR (600 MHz, chloroform-*d*), **12a** (inset).

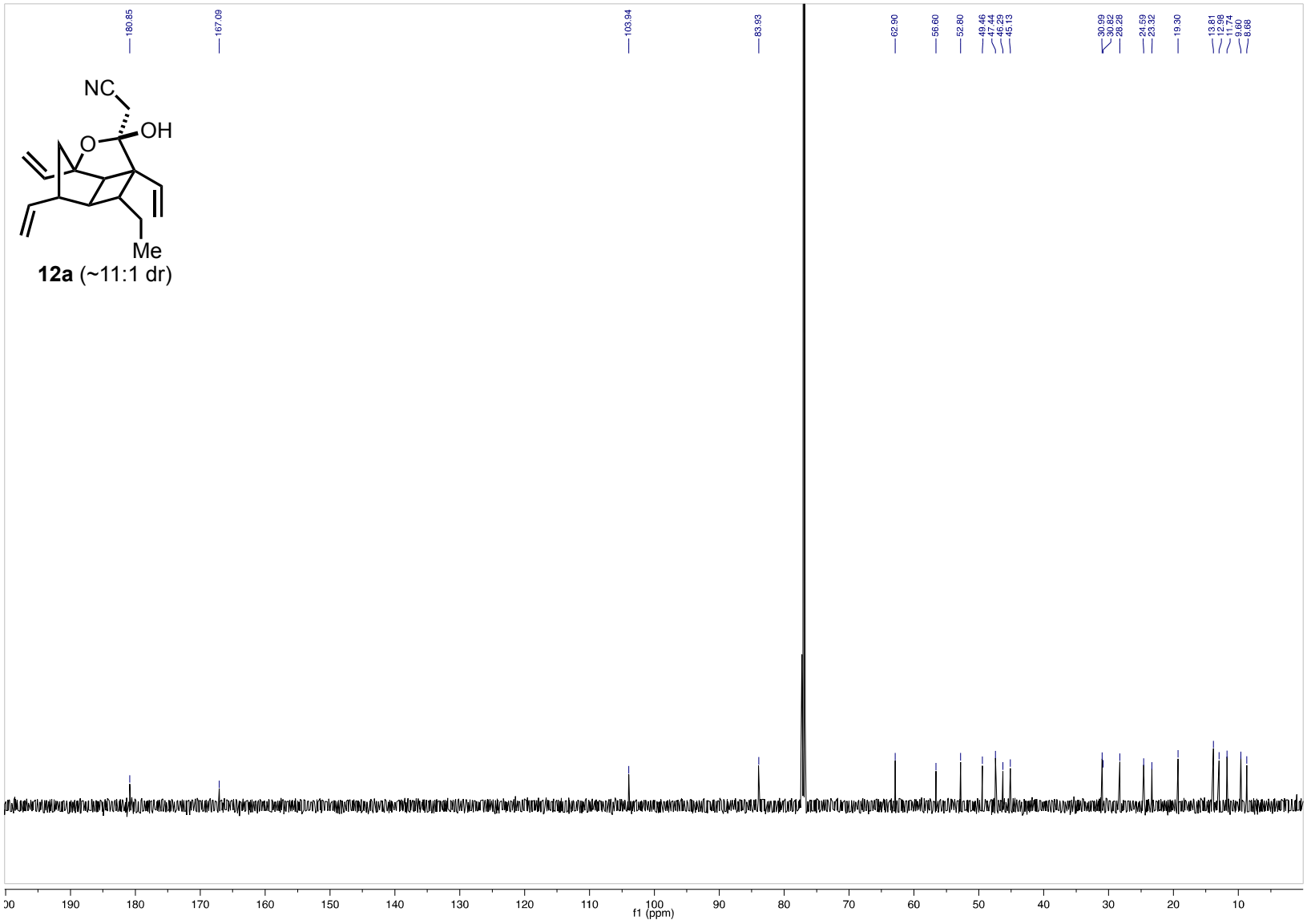


Figure S24: ^{13}C NMR (151 MHz, chloroform-*d*), **12a**.

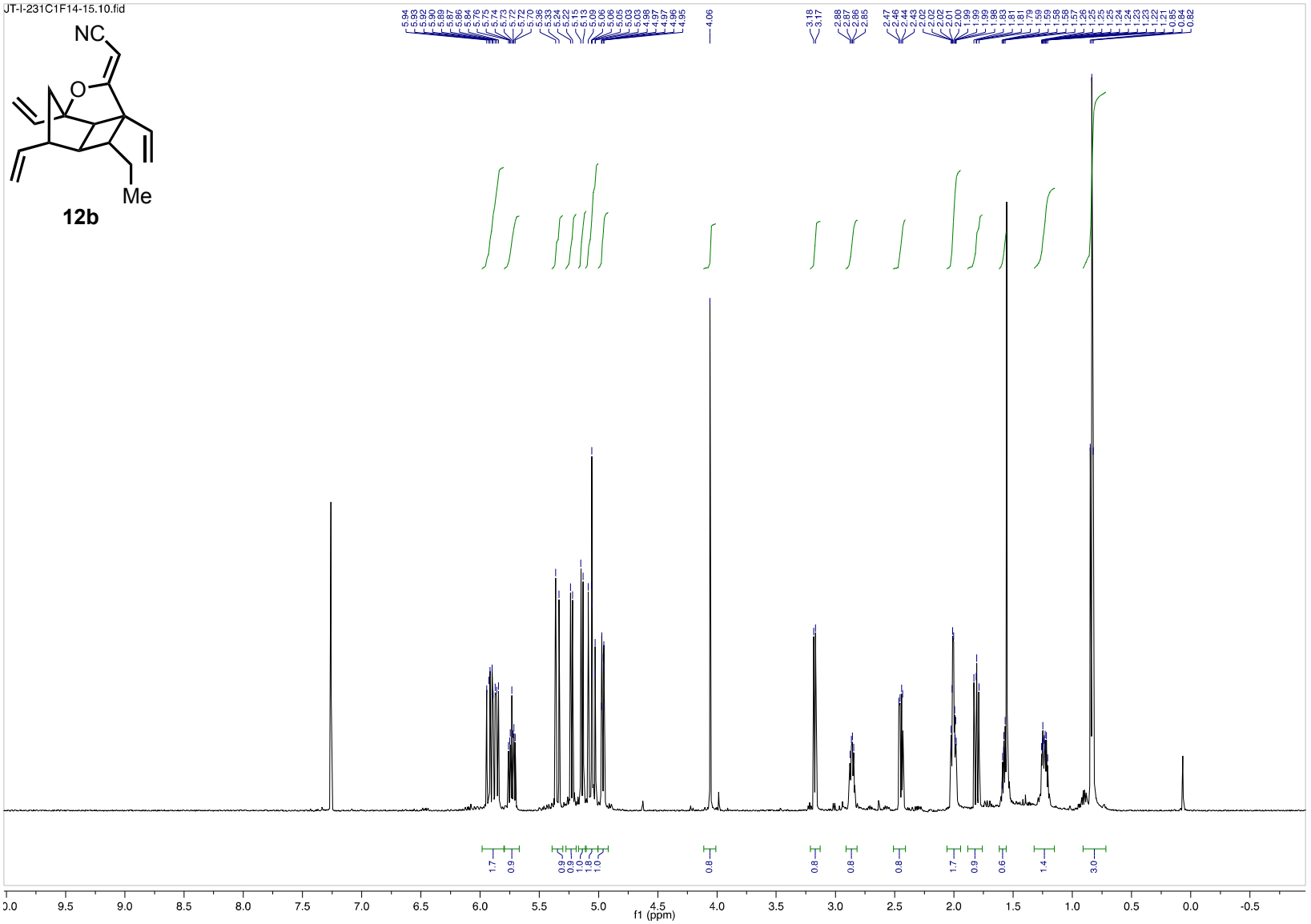


Figure S25: ^{1}H NMR (600 MHz, chloroform-*d*), **12b**.

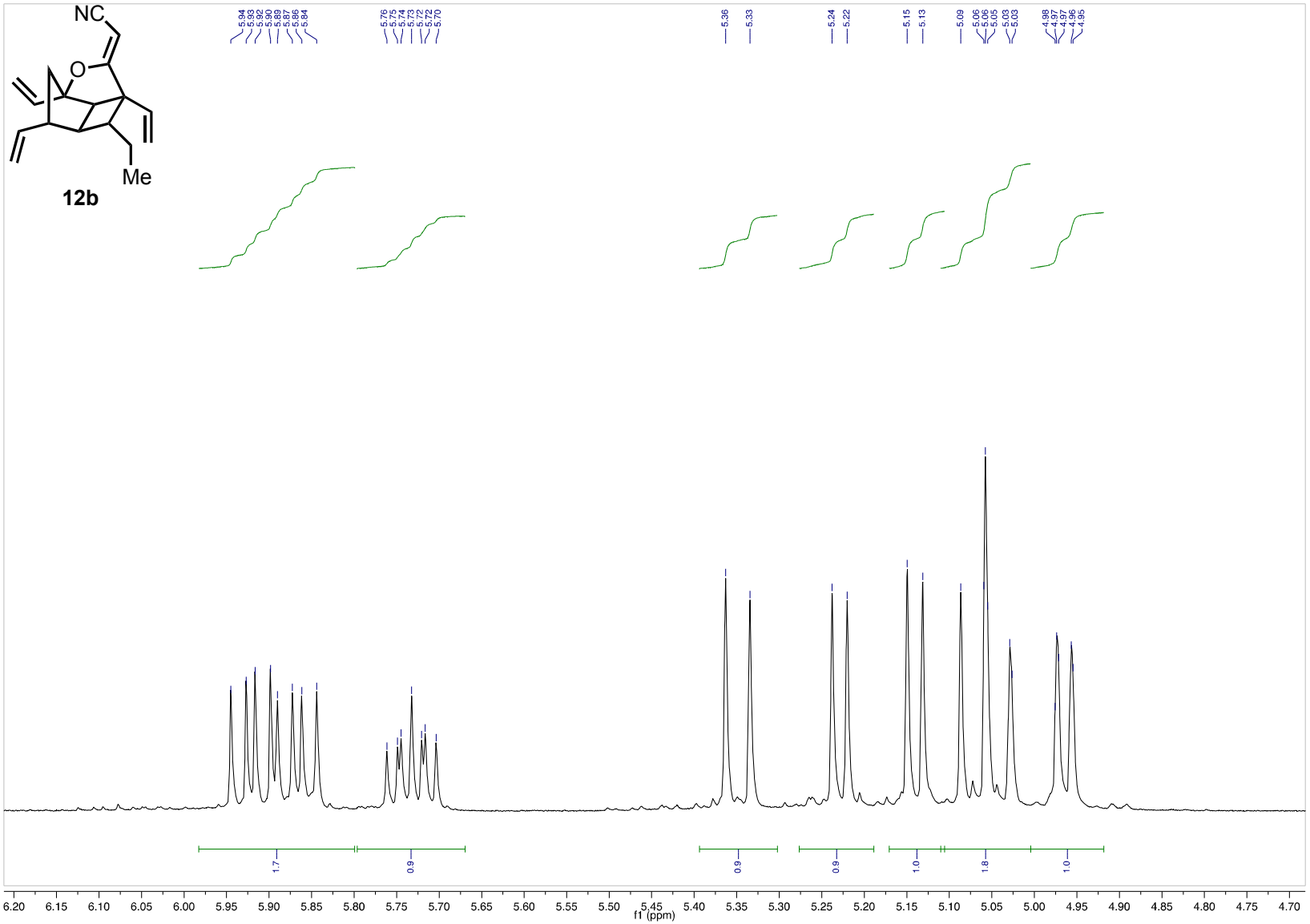


Figure S26: ^{1}H NMR (600 MHz, chloroform-*d*), **12b** (inset).

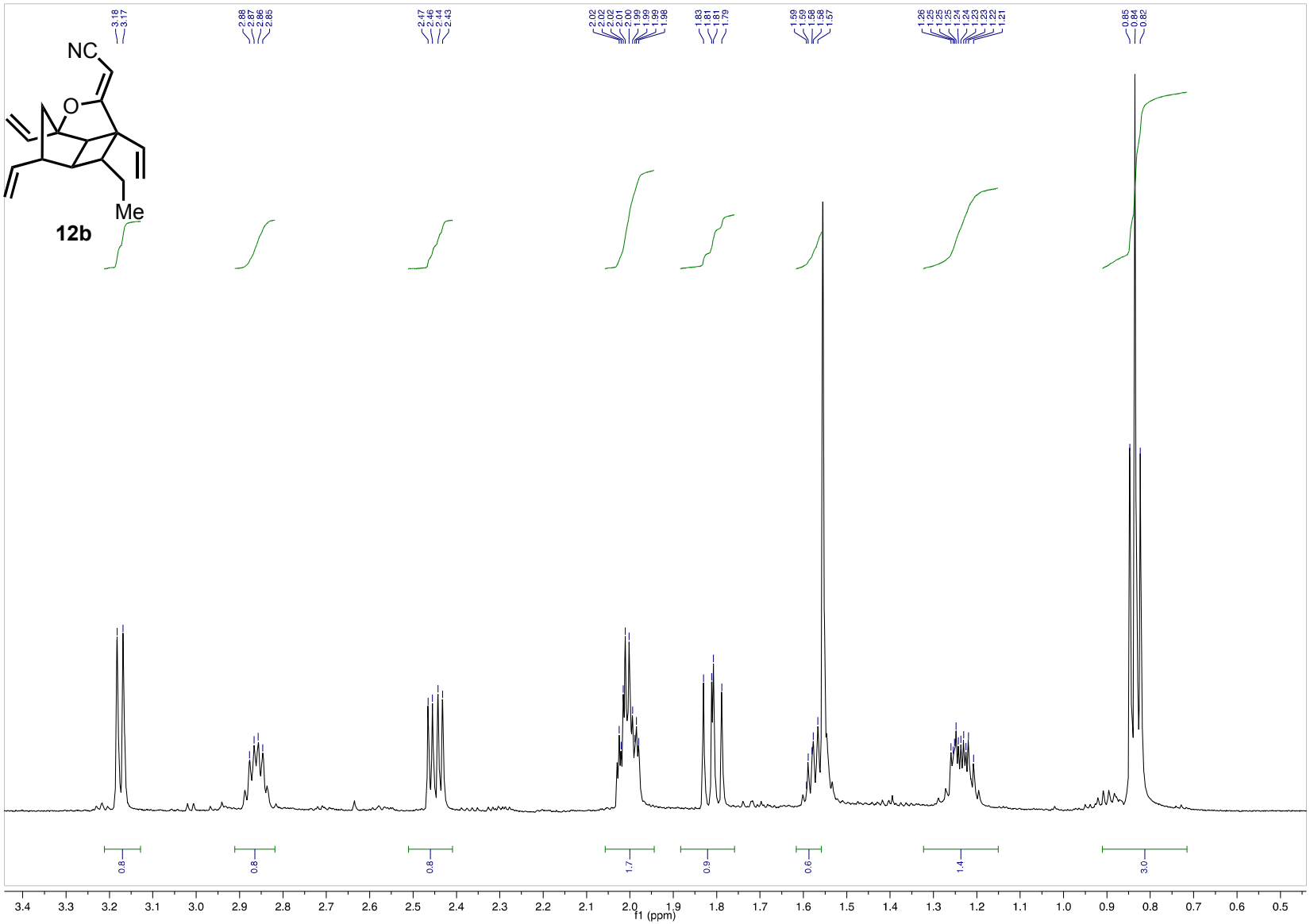


Figure S27: ^{1}H NMR (600 MHz, chloroform-*d*), **12b** (inset).

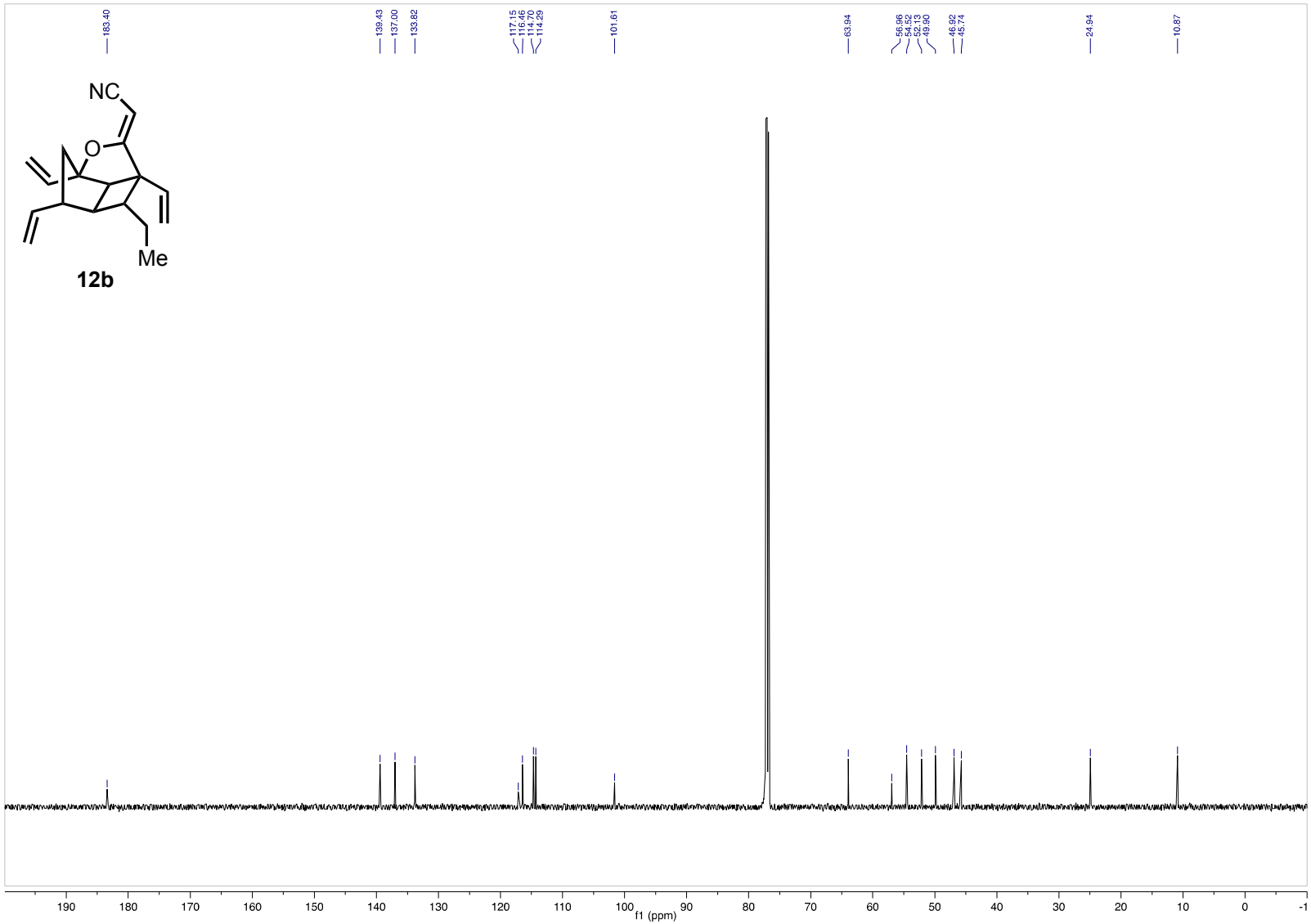


Figure S28: ^{13}C NMR (151 MHz, chloroform-*d*), **12b**.

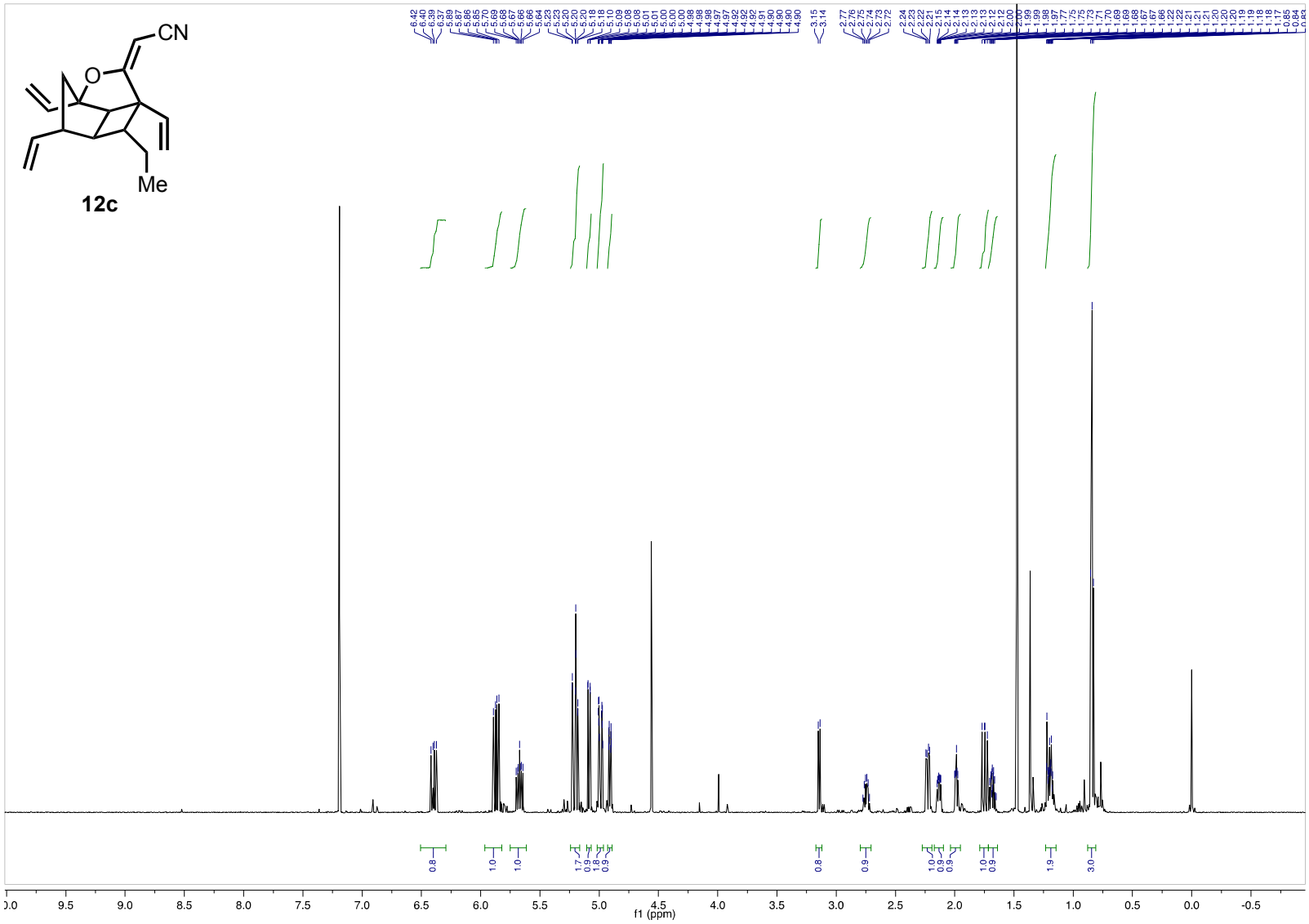


Figure S29: ^{1}H NMR (600 MHz, chloroform-*d*), **12c**.

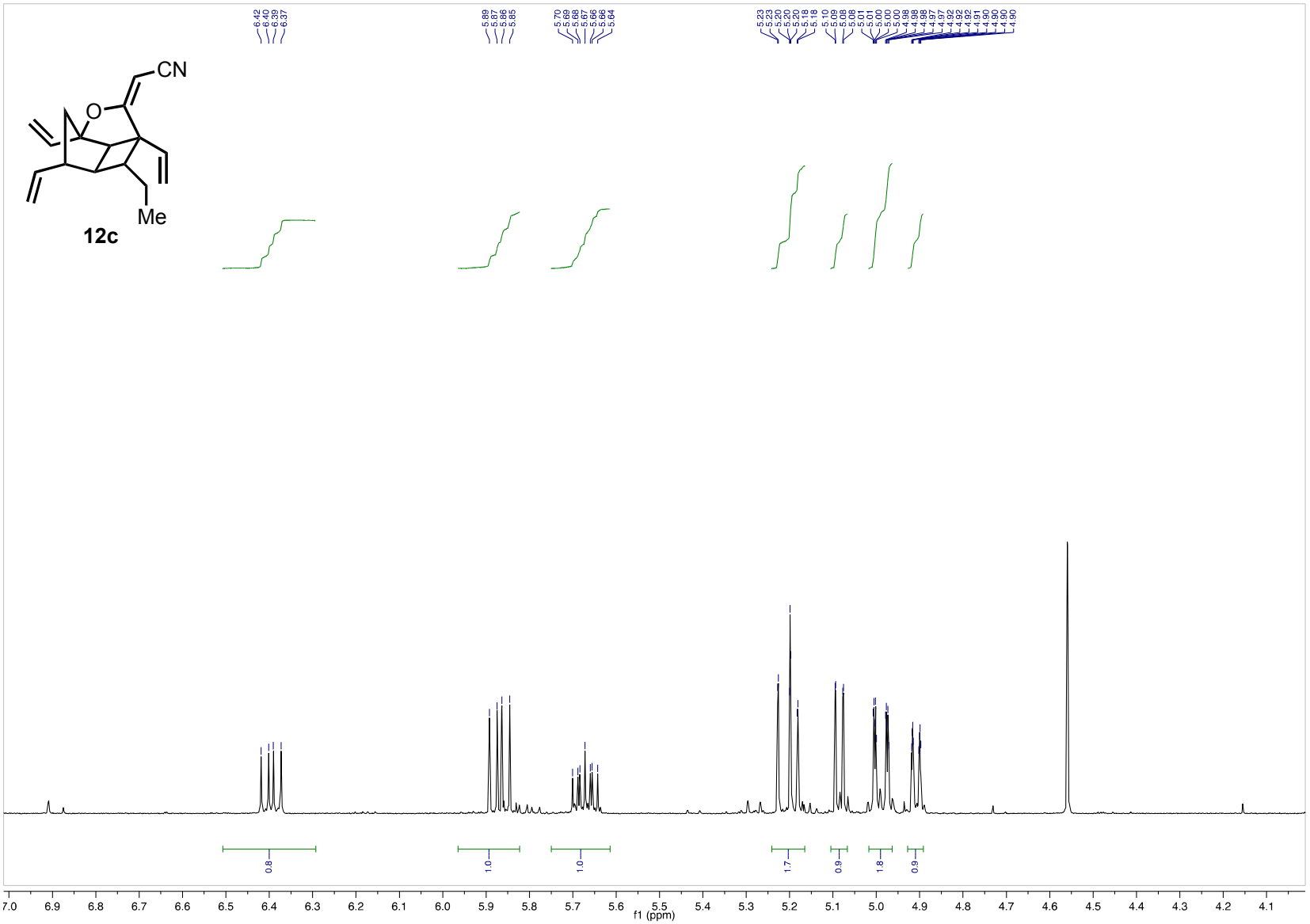


Figure S30: ^{1}H NMR (600 MHz, chloroform-*d*), **12c** (inset).

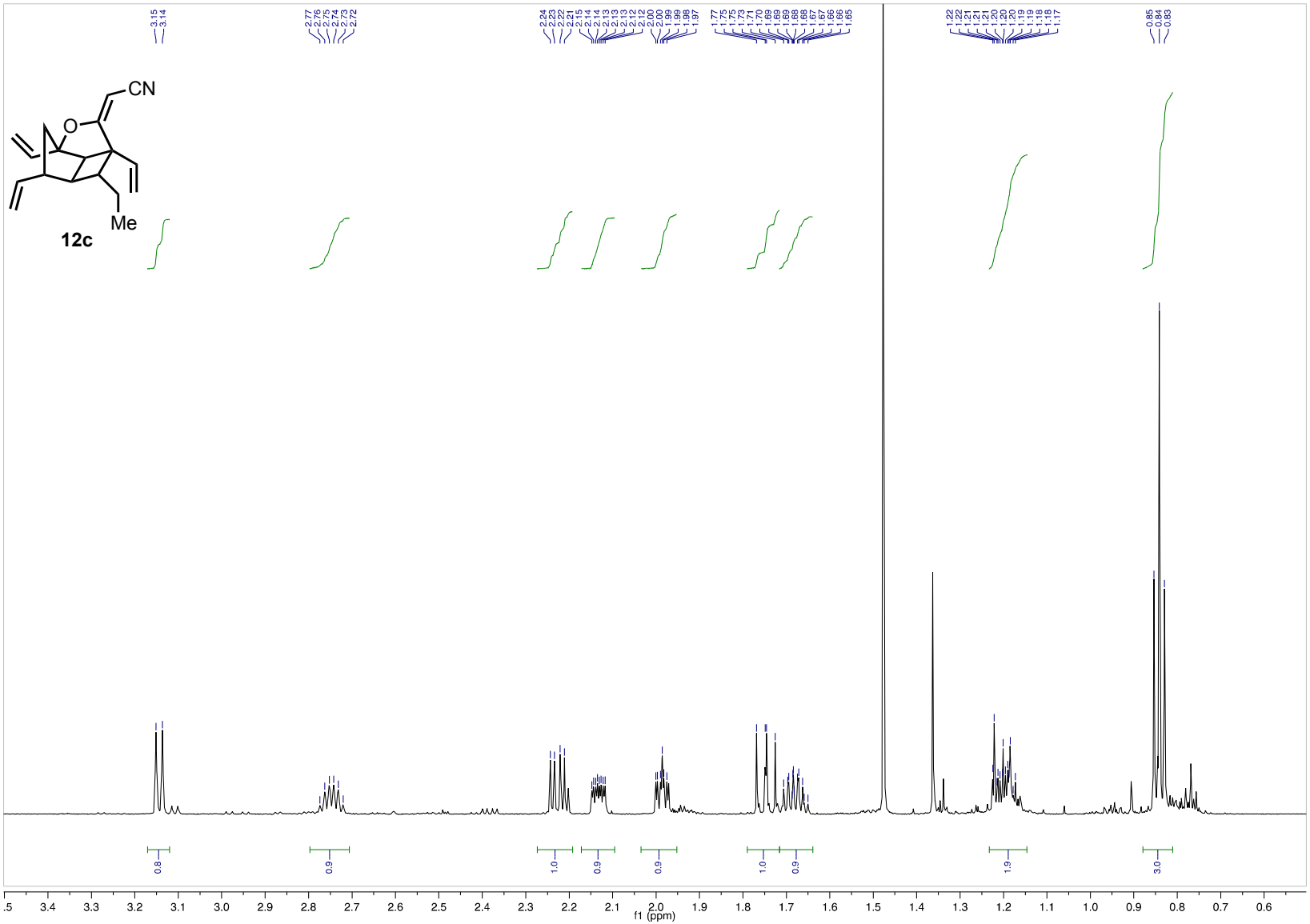


Figure S31: ^{1}H NMR (600 MHz, chloroform-*d*), **12c** (inset).

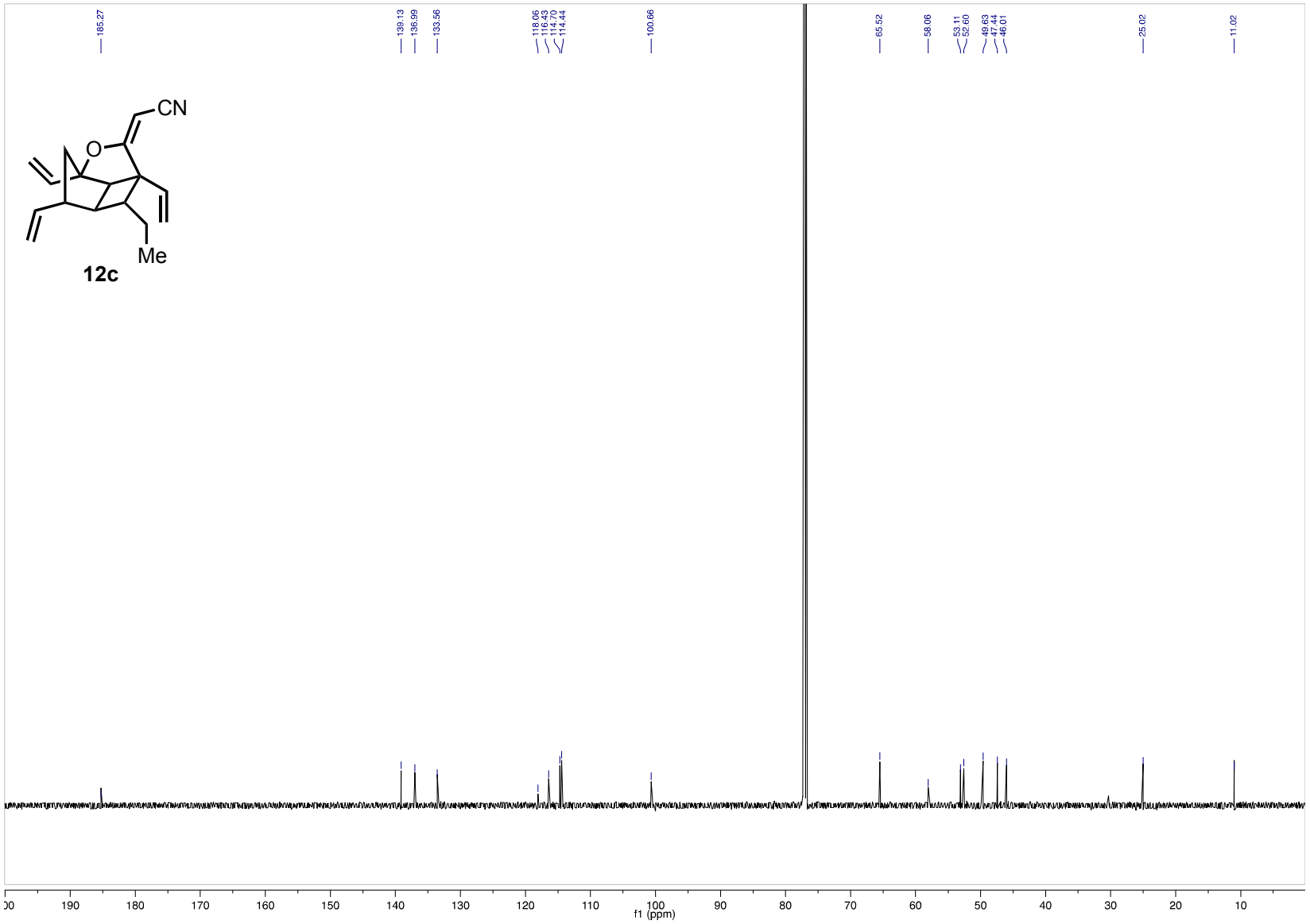


Figure S32: ^{13}C NMR (151 MHz, chloroform-*d*), **12c**.

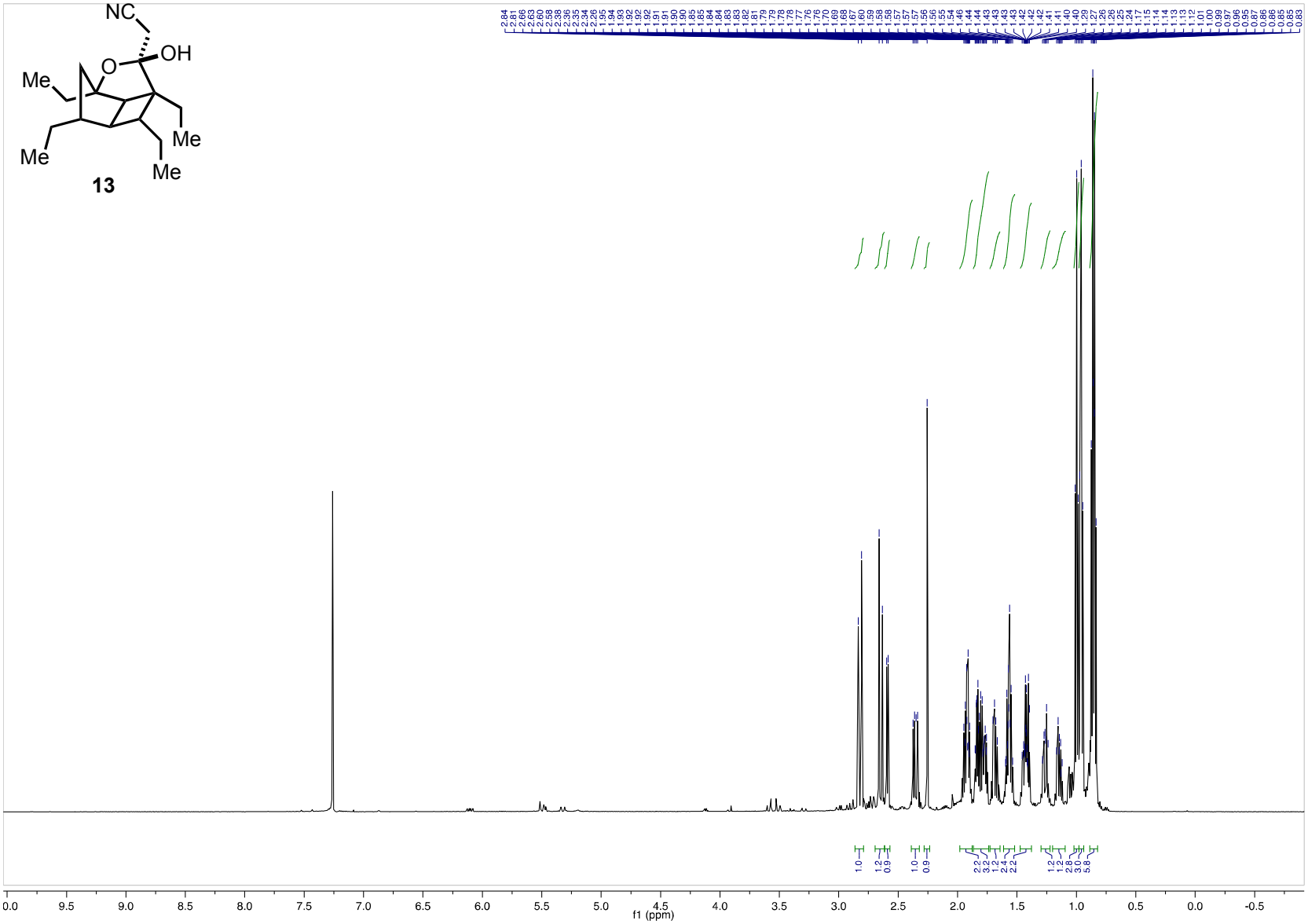


Figure S33: ^{1}H NMR (600 MHz, chloroform-*d*), **13**.

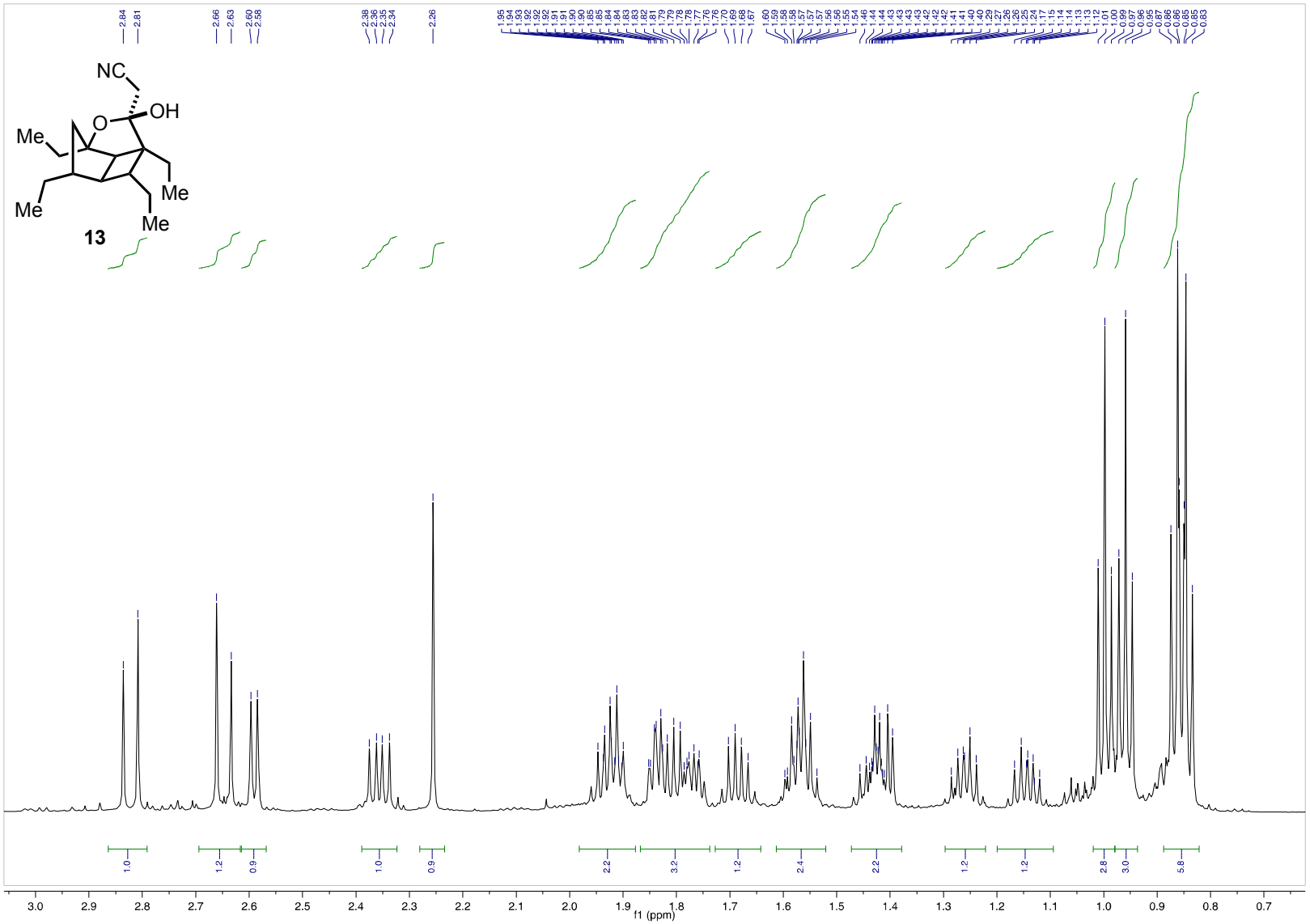


Figure S34: ^{1}H NMR (600 MHz, chloroform-*d*), **13** (inset).

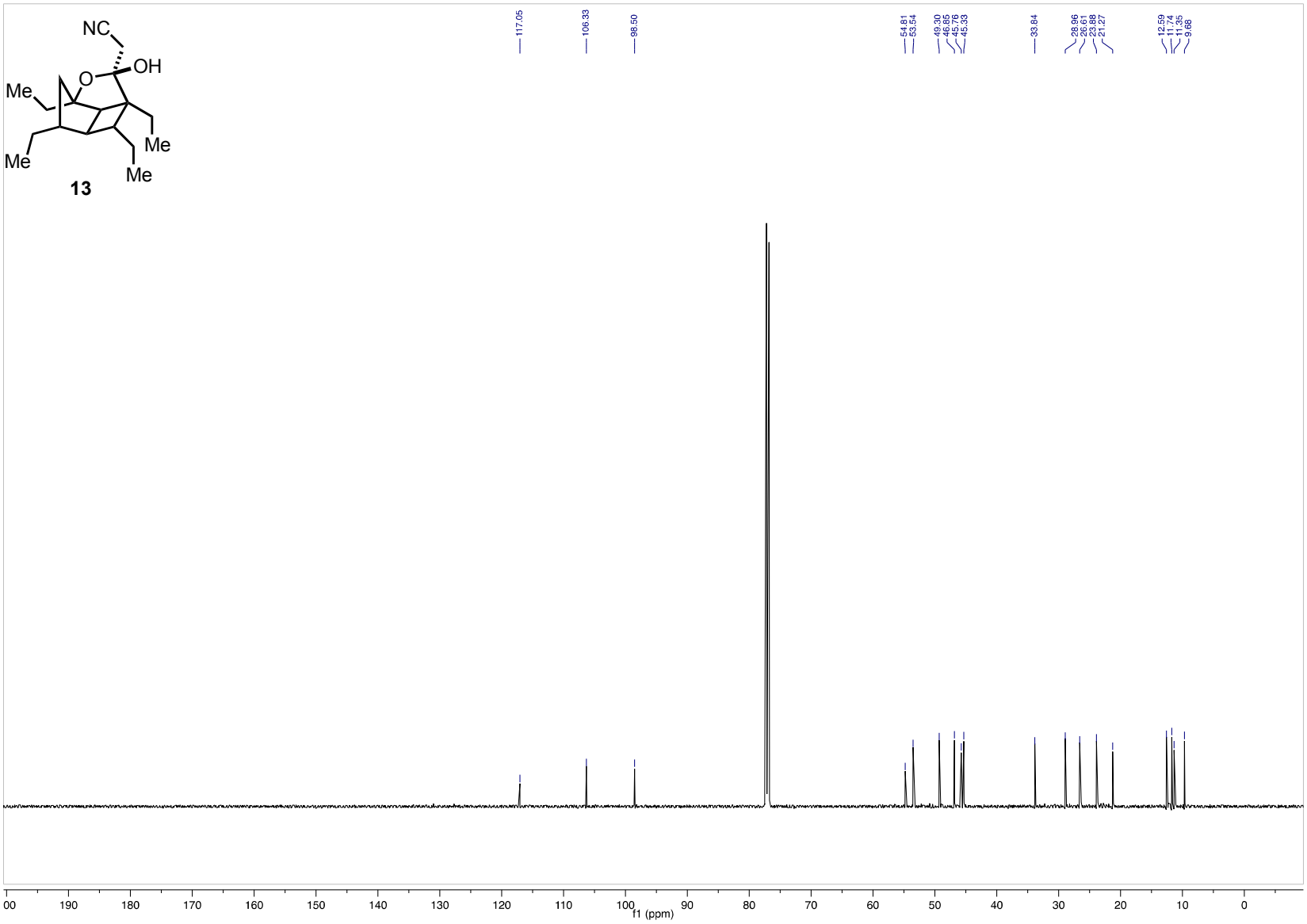


Figure S35: ^{13}C NMR (151 MHz, chloroform-*d*), **13**.

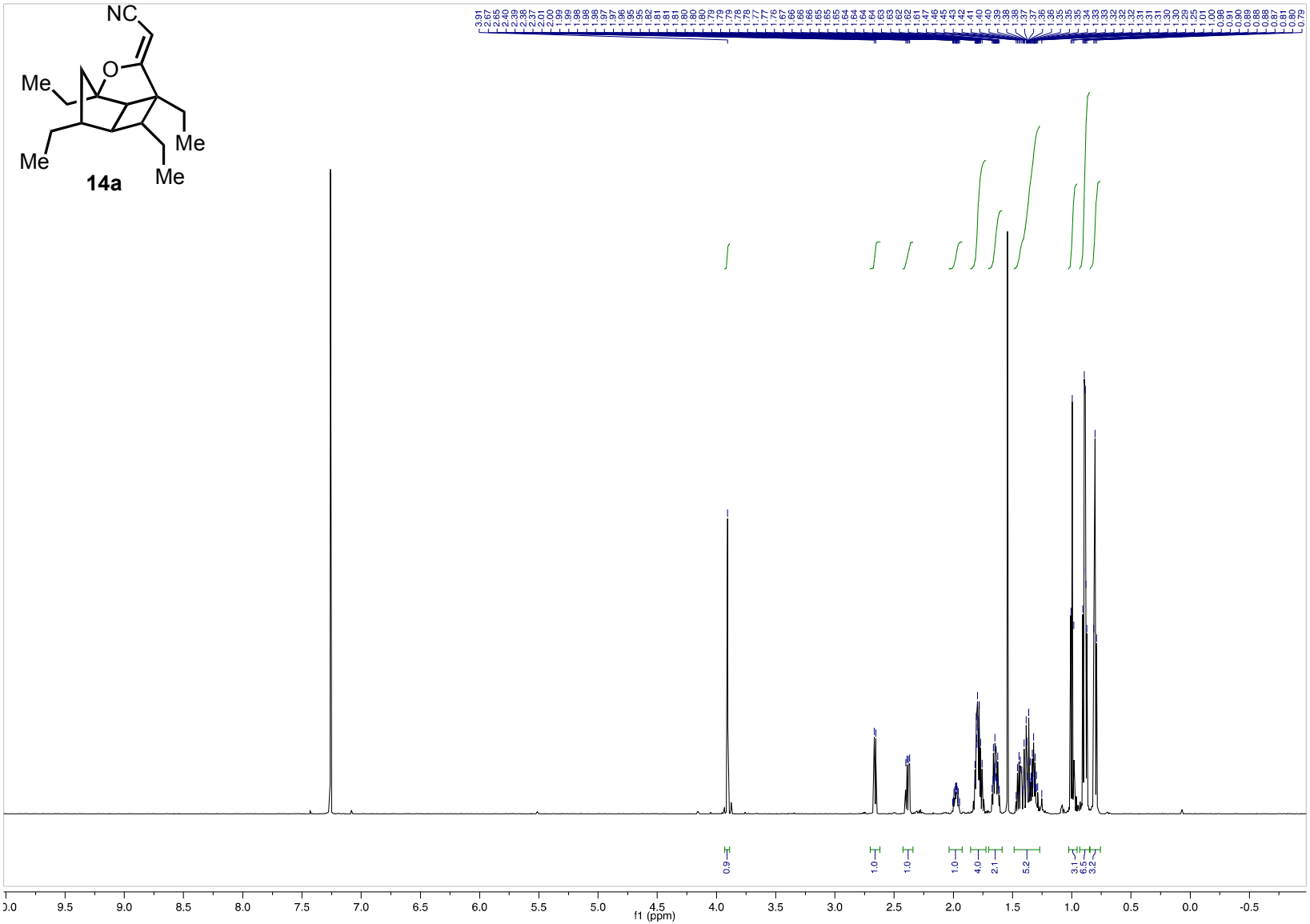


Figure S36: ^{1}H NMR (600 MHz, chloroform-*d*), **14a** (inset).

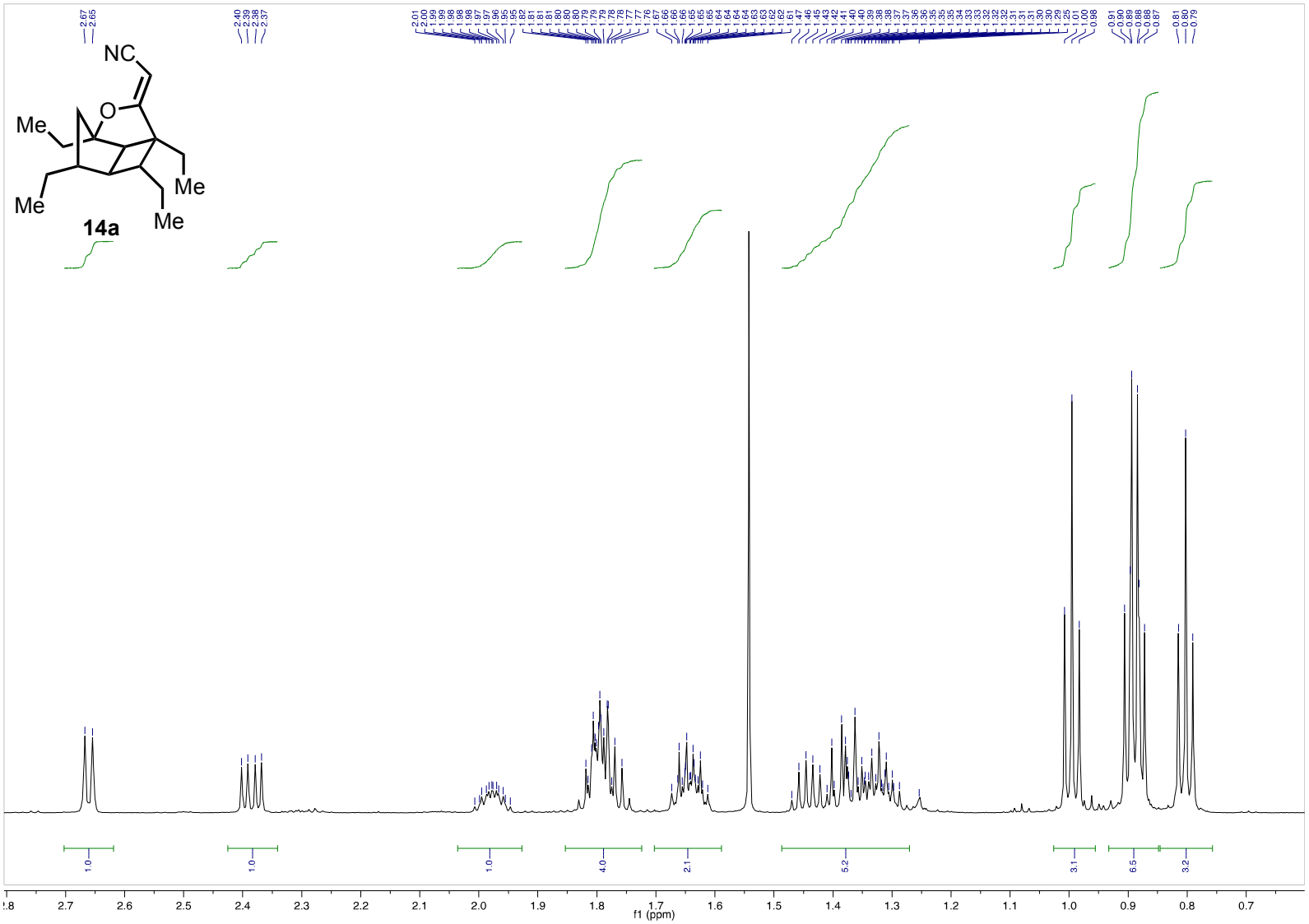


Figure S37: ^{1}H NMR (600 MHz, chloroform-*d*), **14a** (inset).

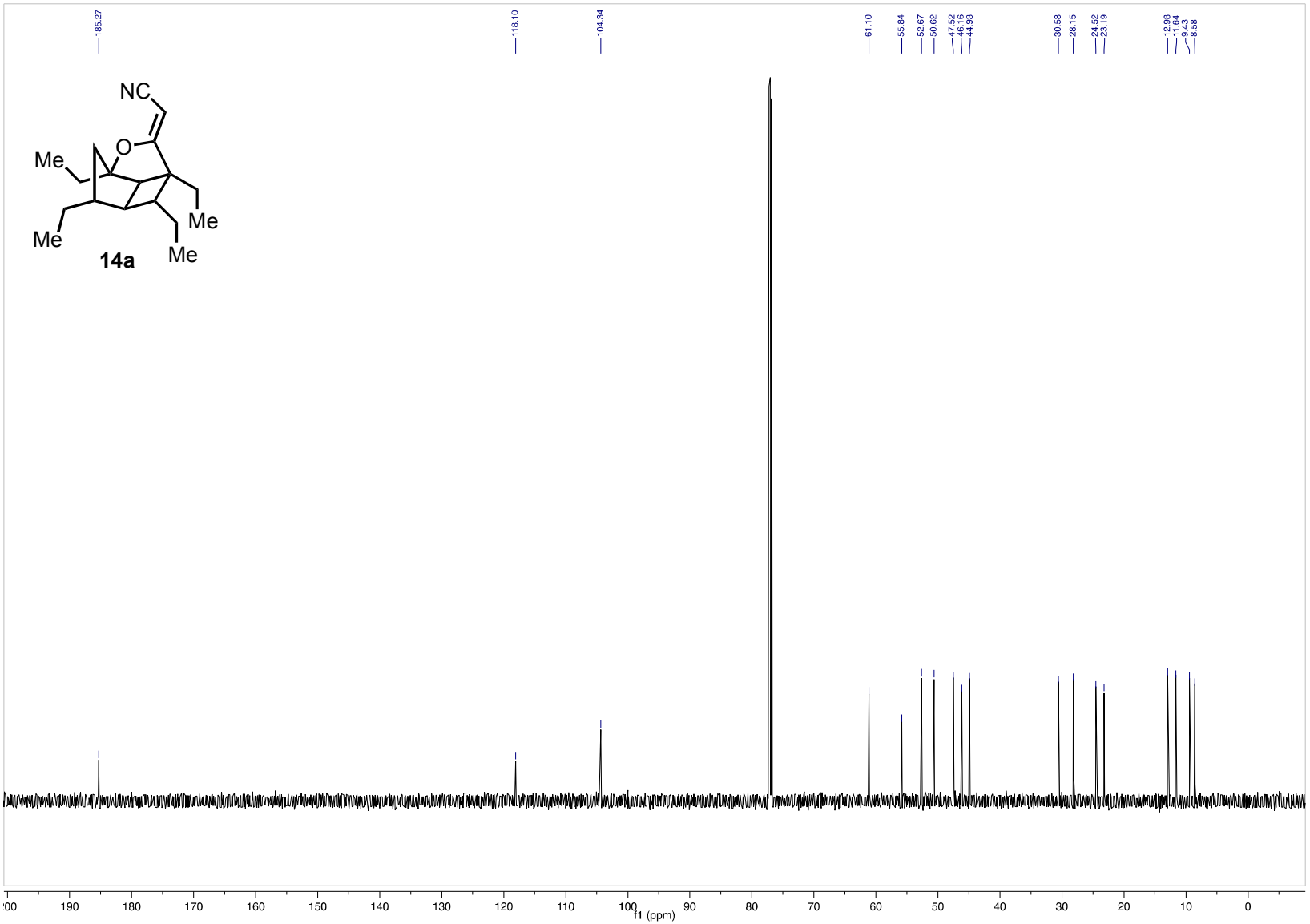


Figure S38: ^{13}C NMR (151 MHz, chloroform-*d*), **14a**.

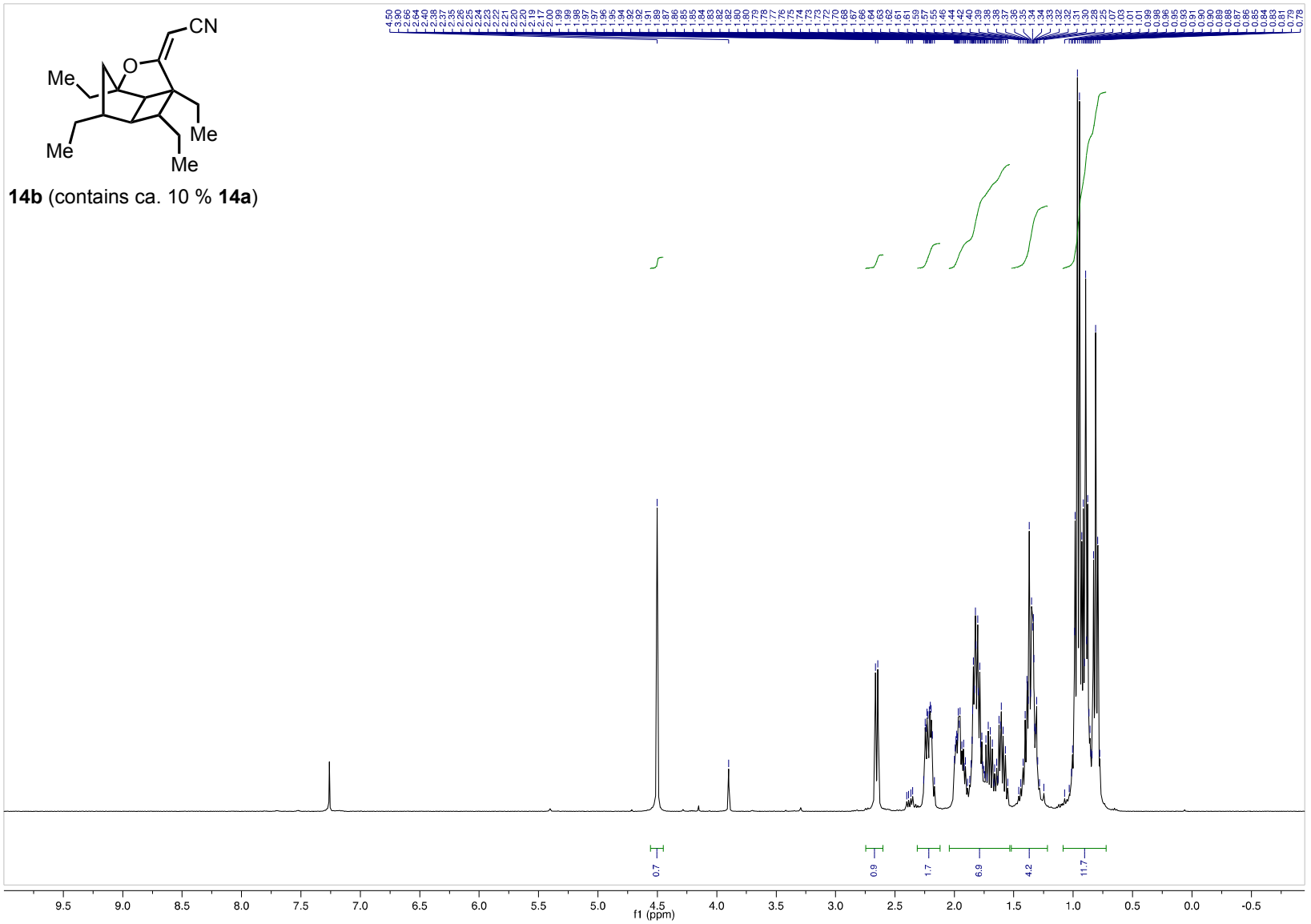


Figure S39: ^{1}H NMR (600 MHz, chloroform-*d*), **14b**.

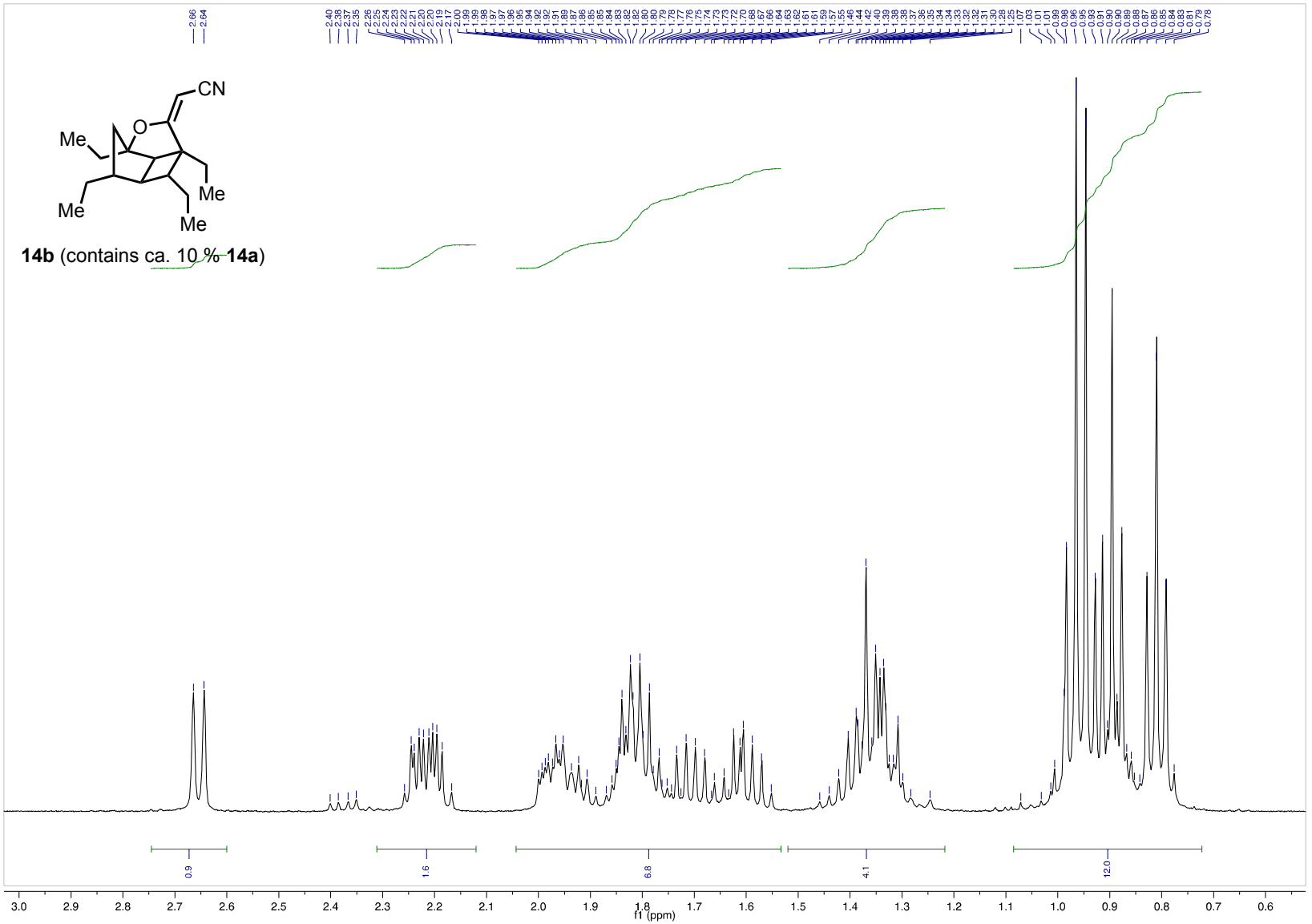


Figure S40: ^{1}H NMR (600 MHz, chloroform-*d*), **14b** (inset).

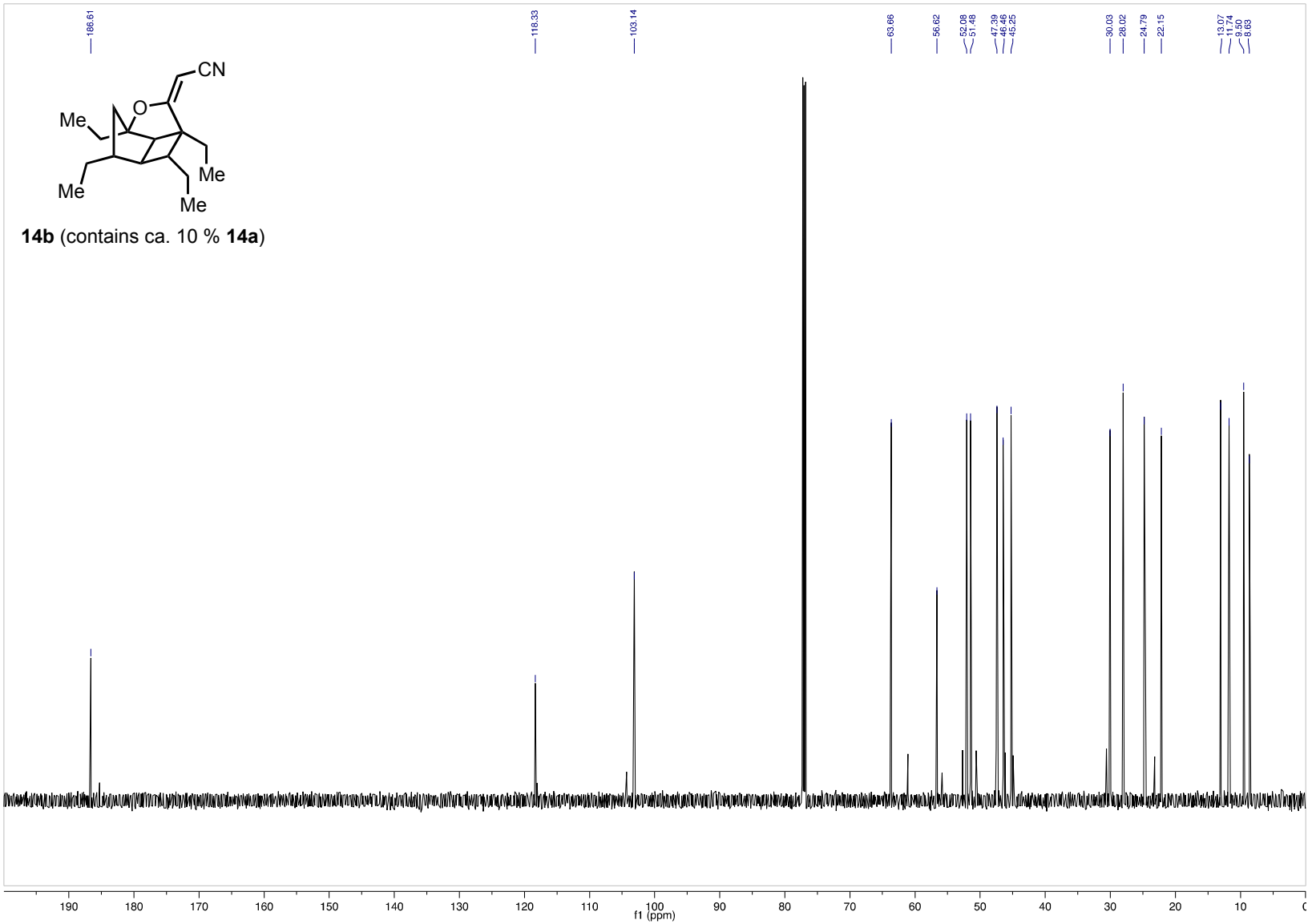


Figure S41: ^{13}C NMR (151 MHz, chloroform-*d*), **14b**.

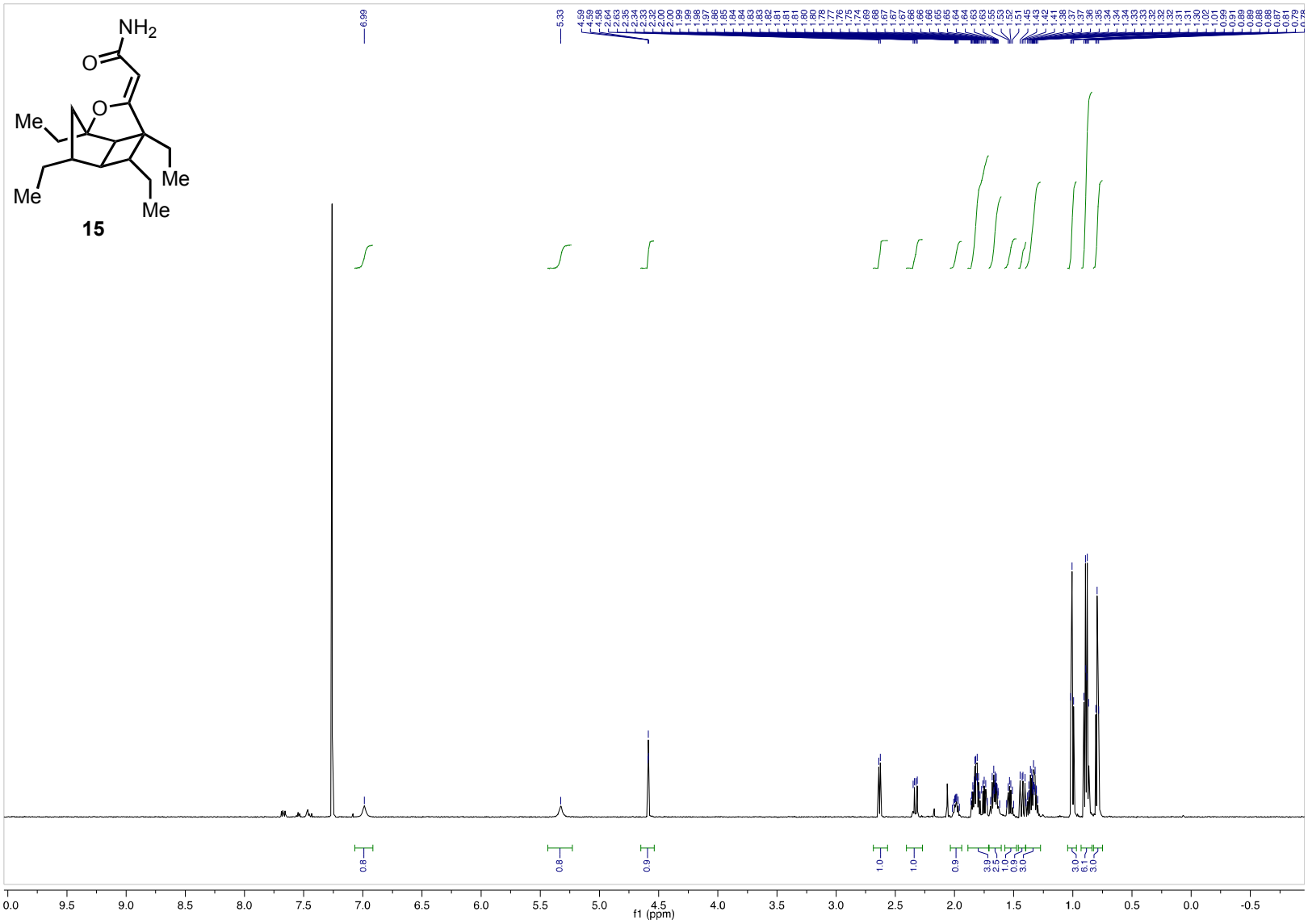


Figure S42: ^{1}H NMR (600 MHz, chloroform-*d*), **15**.

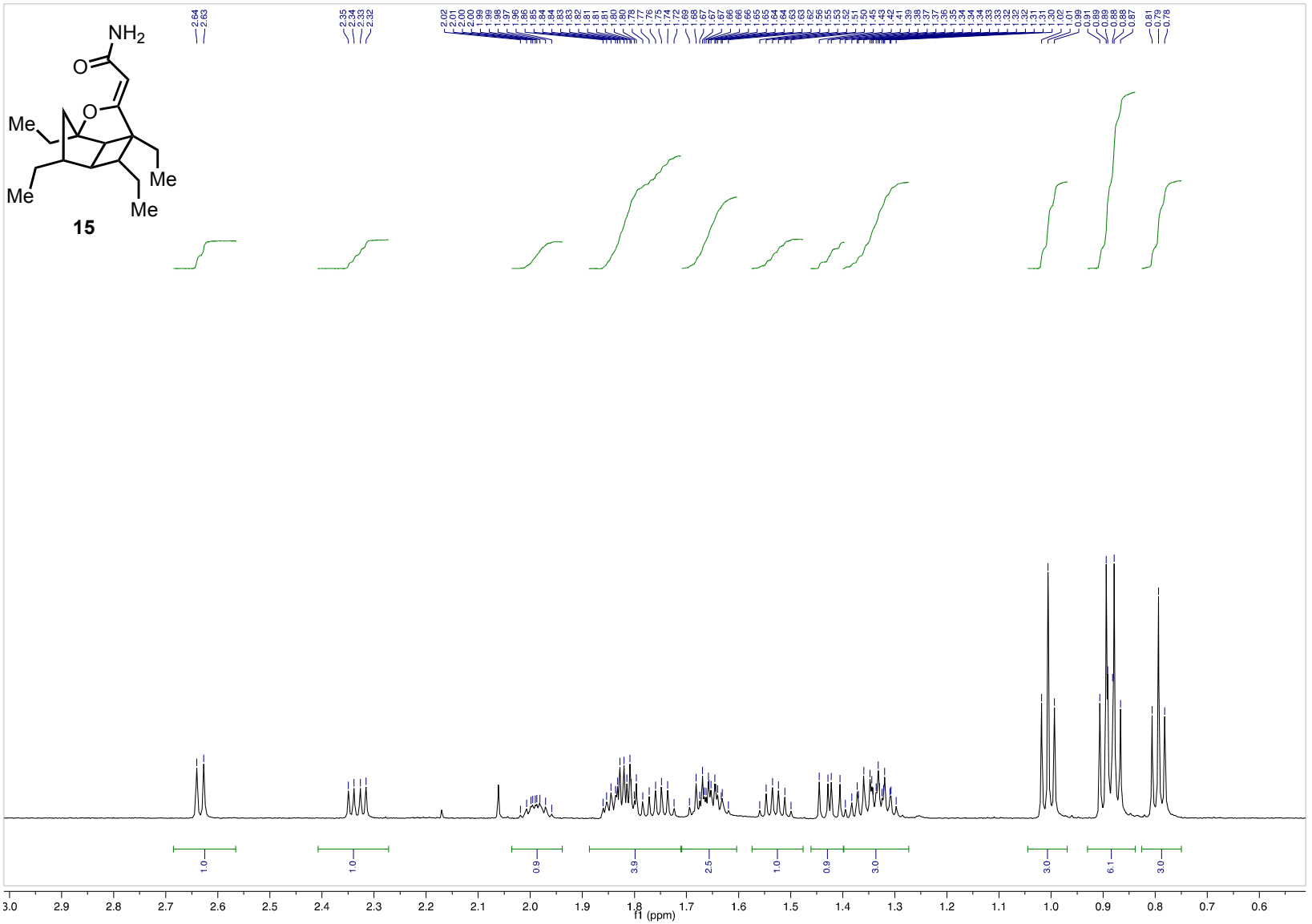


Figure S43: ^{1}H NMR (600 MHz, chloroform-*d*), **15** (inset).

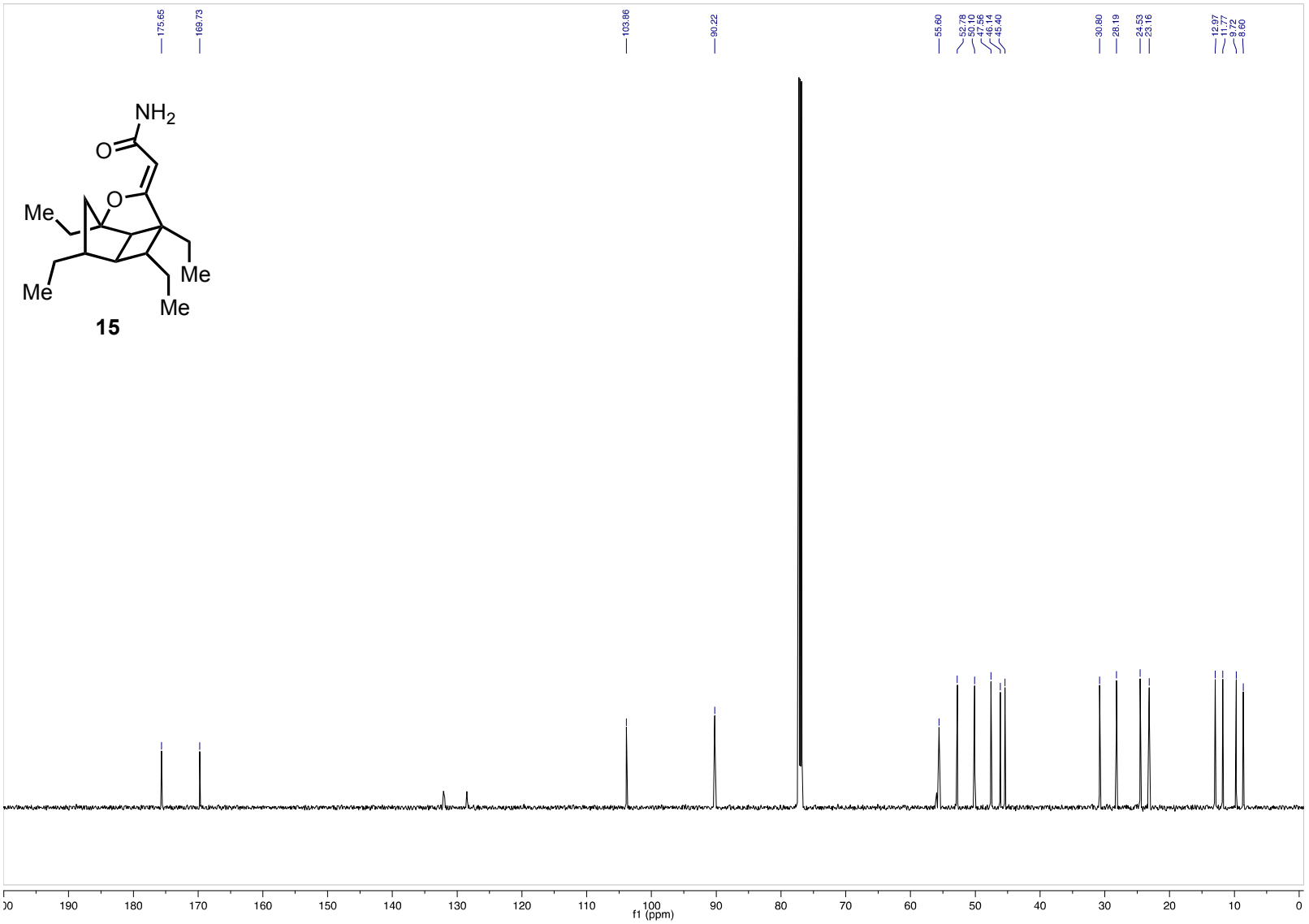


Figure S44: ^{13}C NMR (151 MHz, chloroform-*d*), **15**.

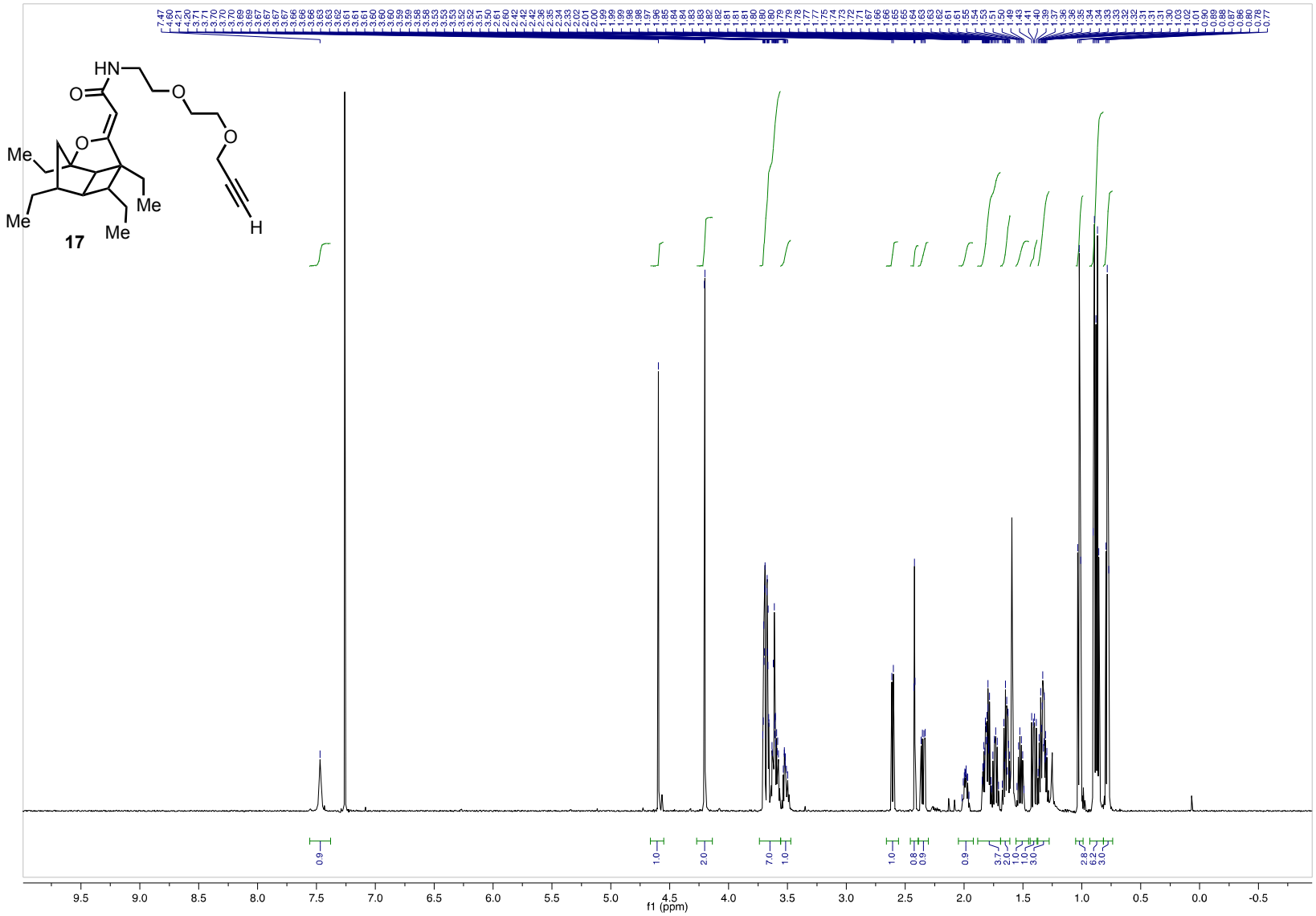


Figure S45: ^{1}H NMR (600 MHz, chloroform-*d*), **17**.

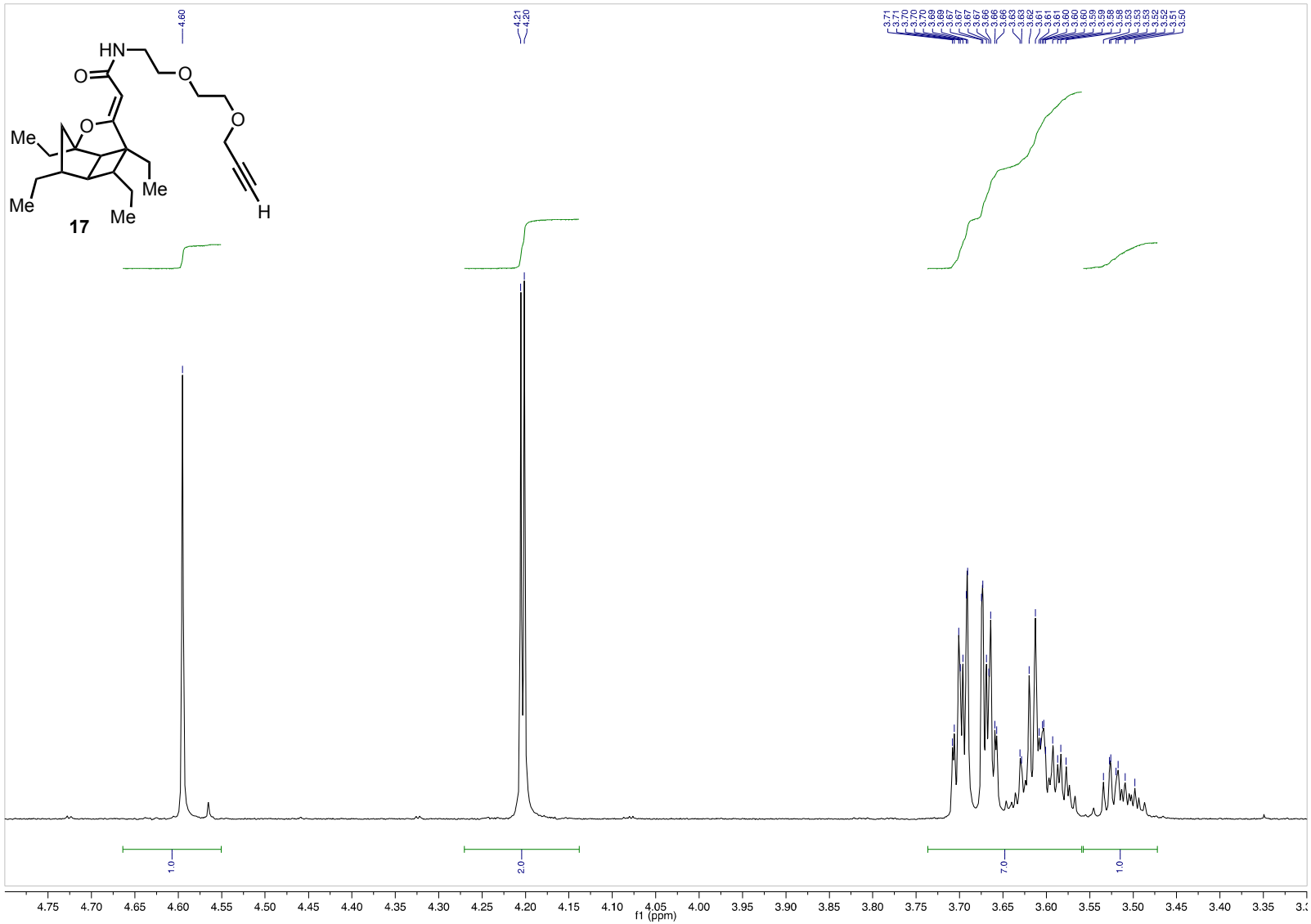


Figure S46: ^{1}H NMR (600 MHz, chloroform-*d*), **17** (inset).

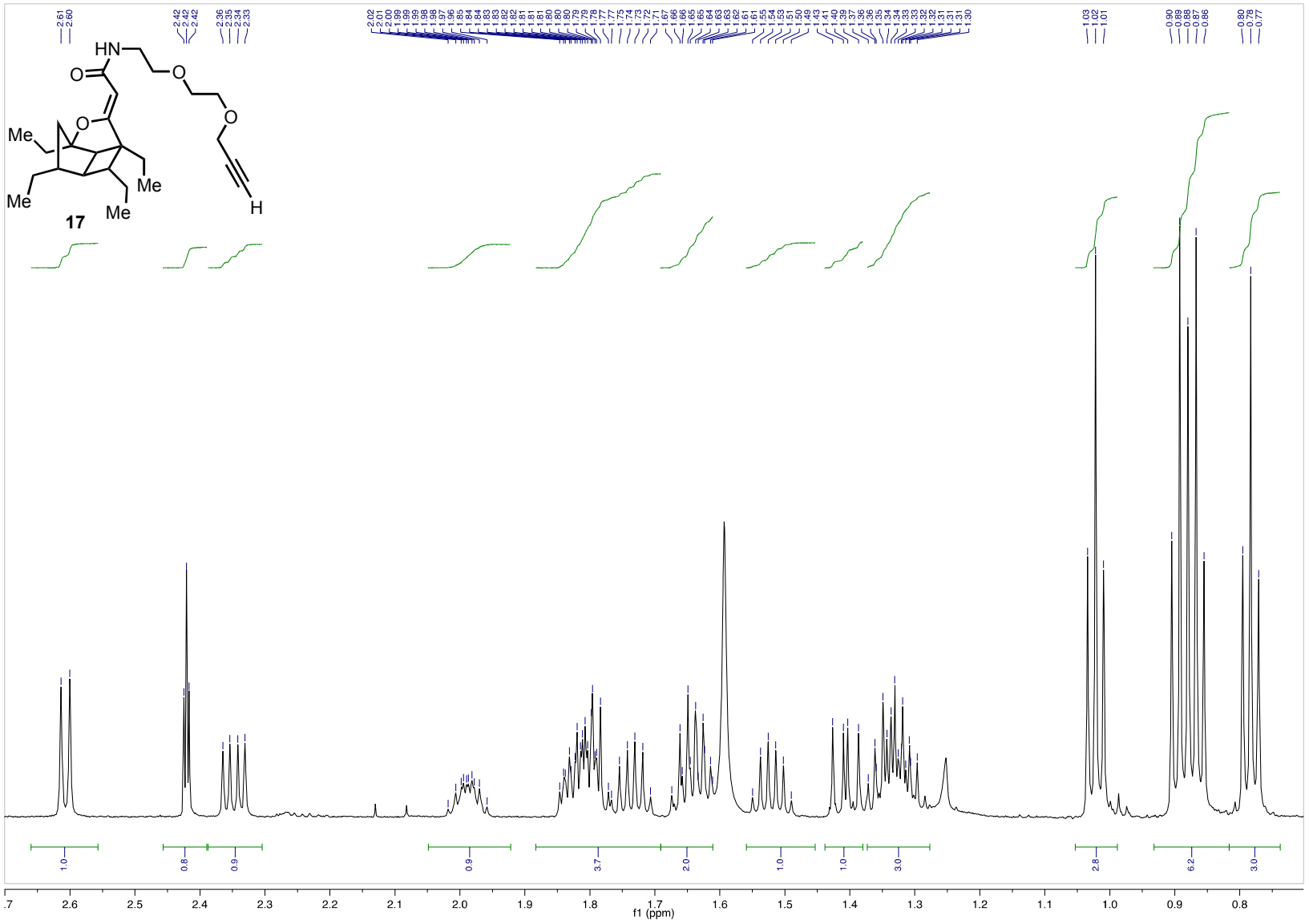


Figure S47: ^{1}H NMR (600 MHz, chloroform-*d*), **17** (inset).

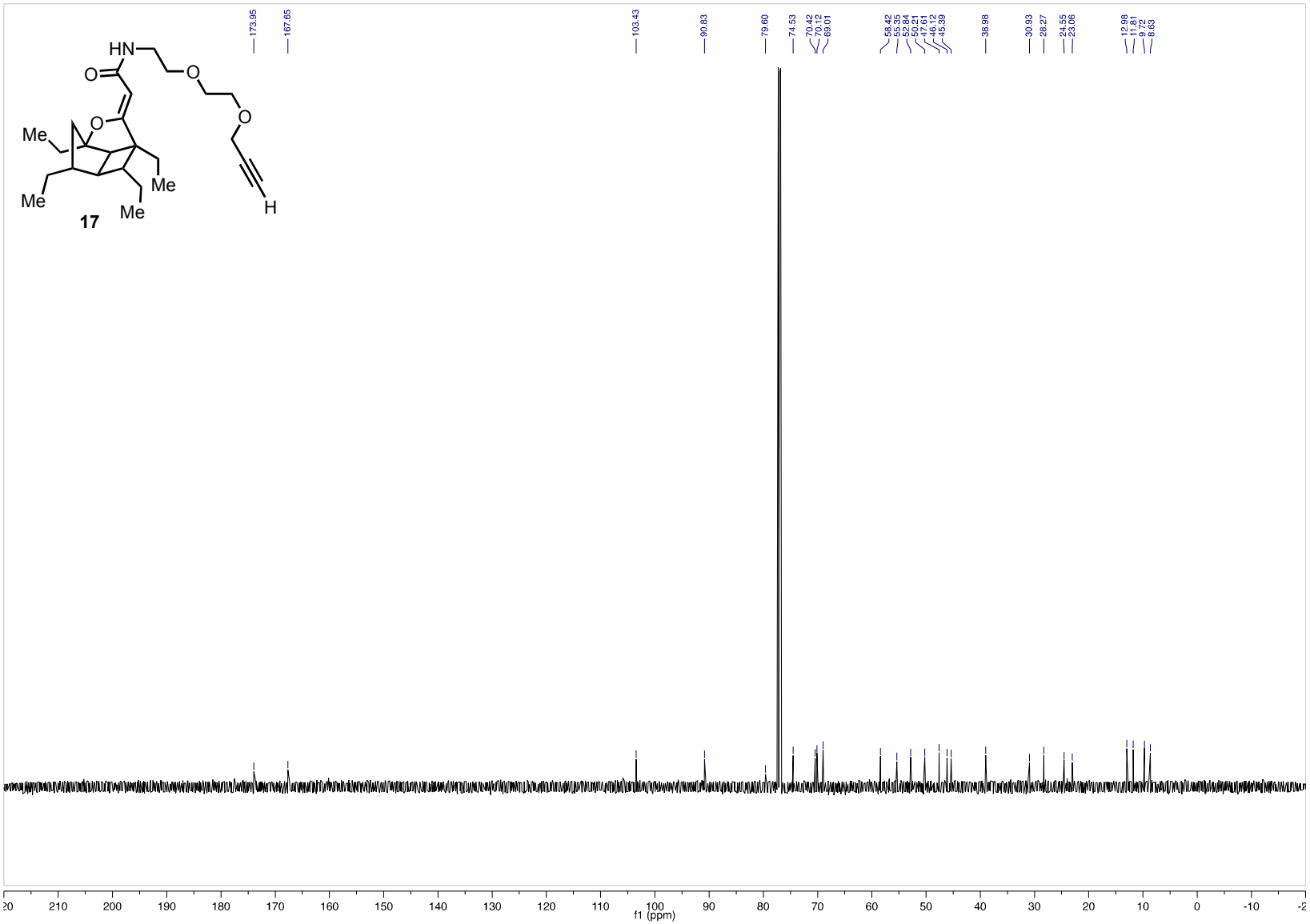


Figure S48: ^{13}C NMR (151 MHz, chloroform-*d*), **17**.

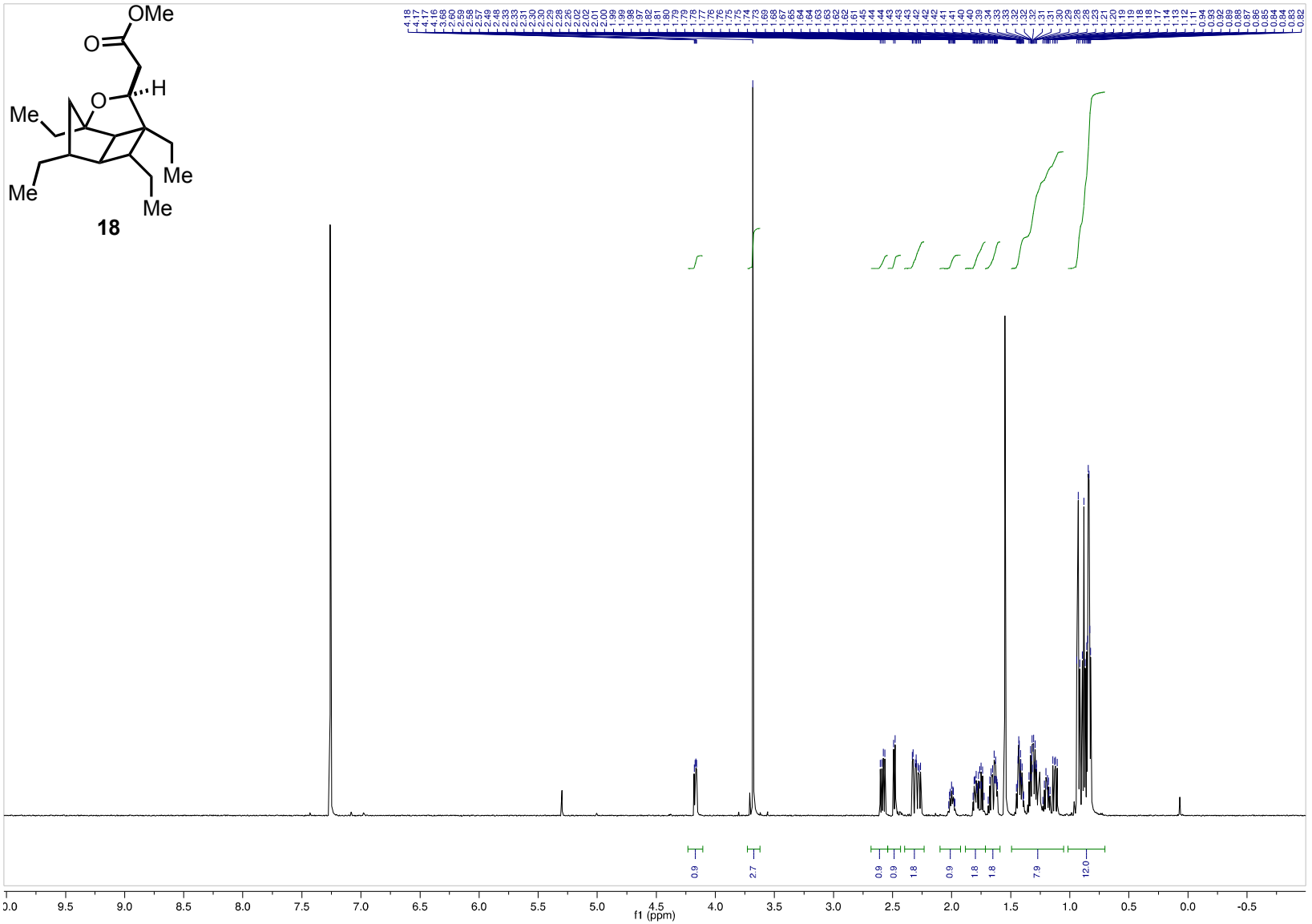


Figure S49: ^{1}H NMR (600 MHz, chloroform-*d*), **18**.

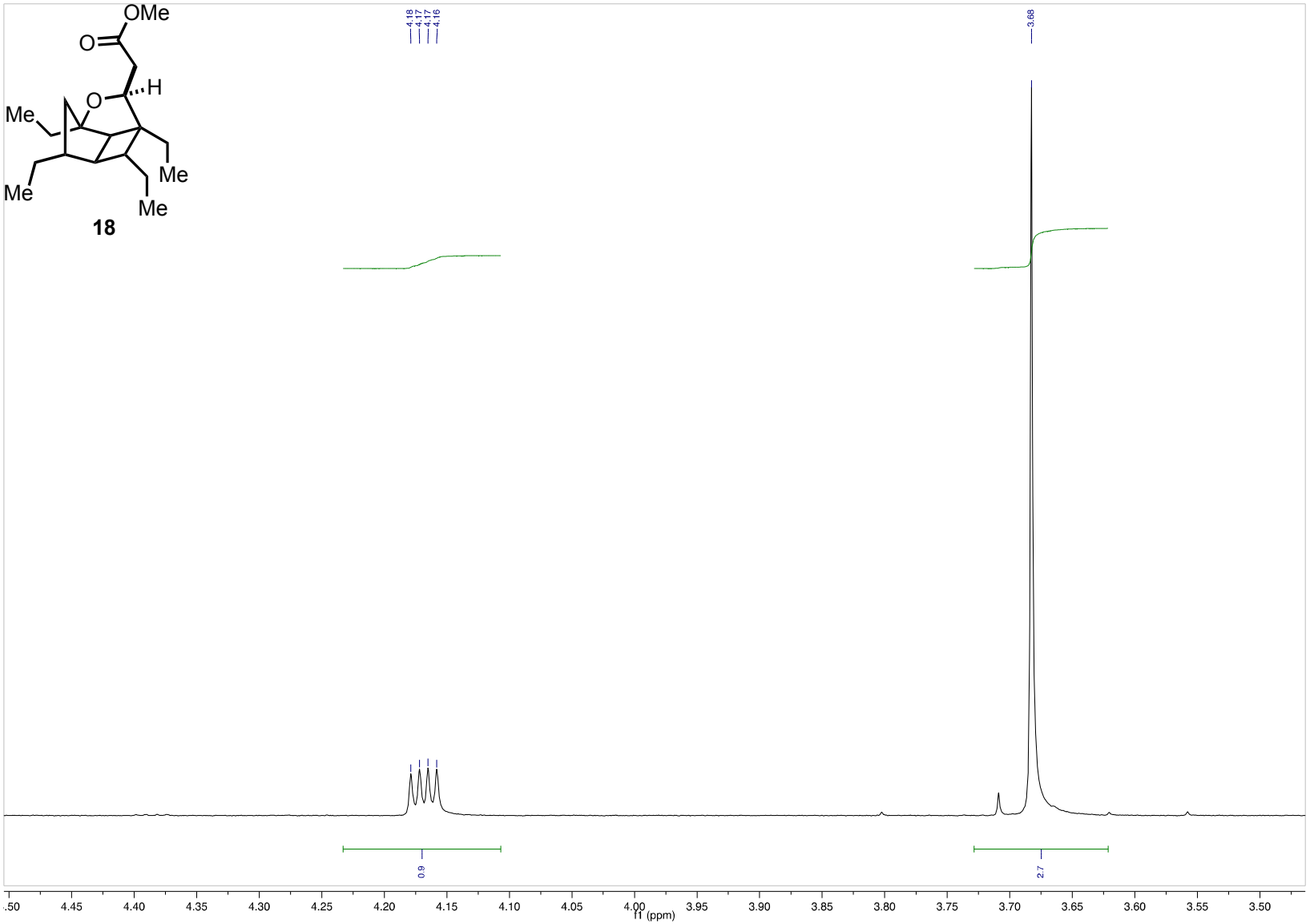


Figure S50: ^{1}H NMR (600 MHz, chloroform-*d*), **18** (inset).

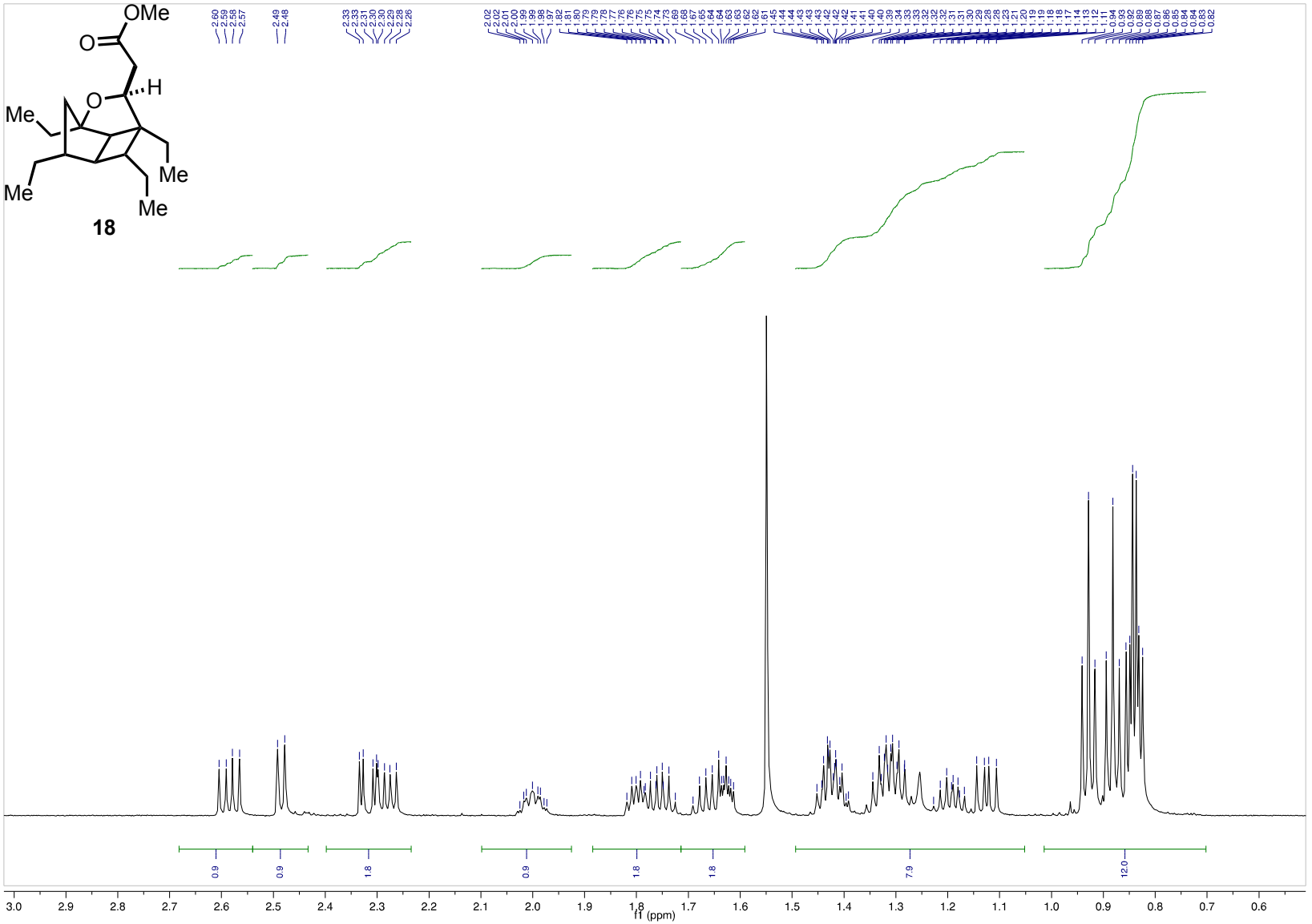


Figure S51: ^{1}H NMR (600 MHz, chloroform-*d*), **18** (inset).

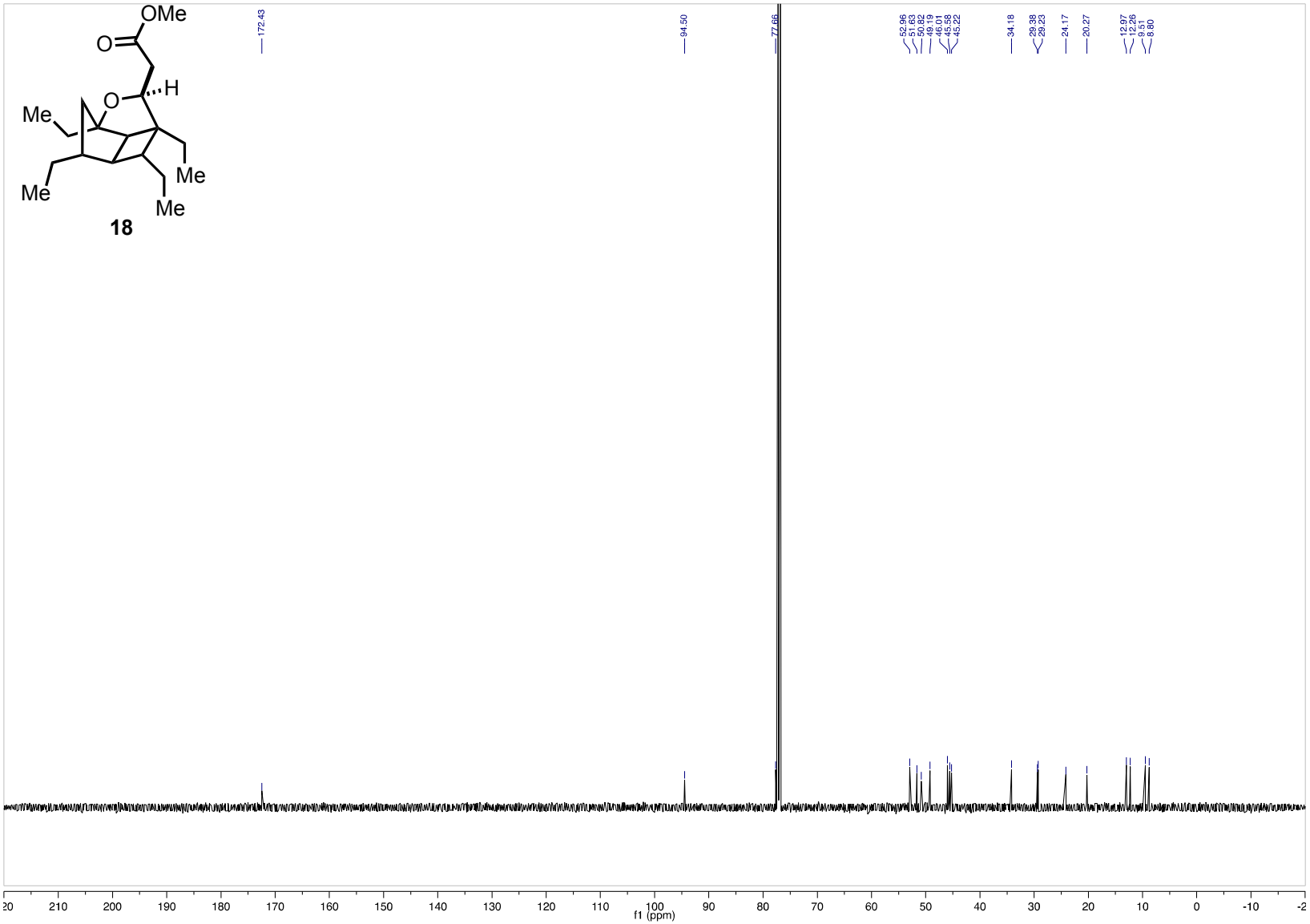


Figure S52: ^{13}C NMR (151 MHz, chloroform-*d*), **18**.

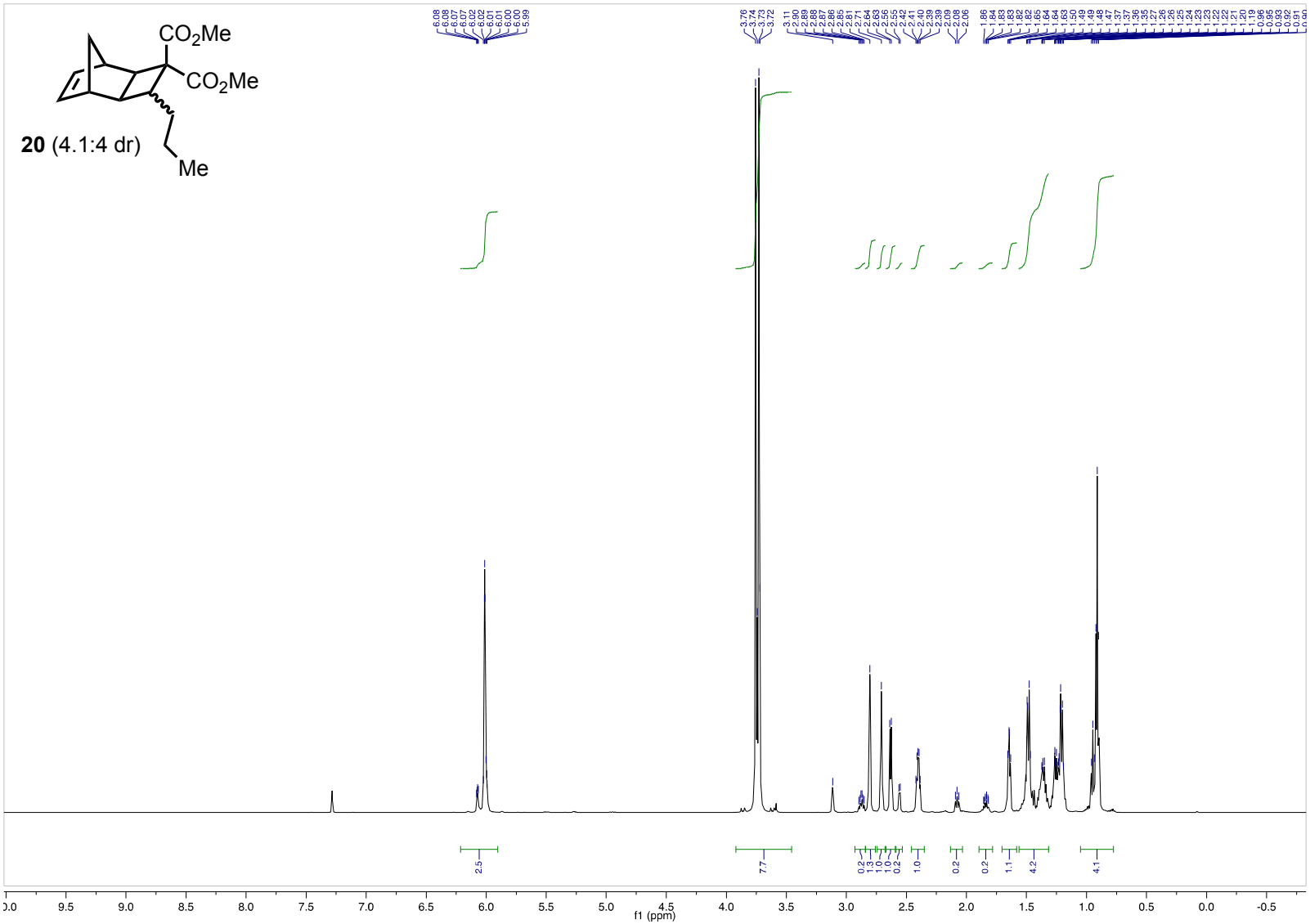


Figure S53: ^{1}H NMR (600 MHz, chloroform-*d*), **20**.

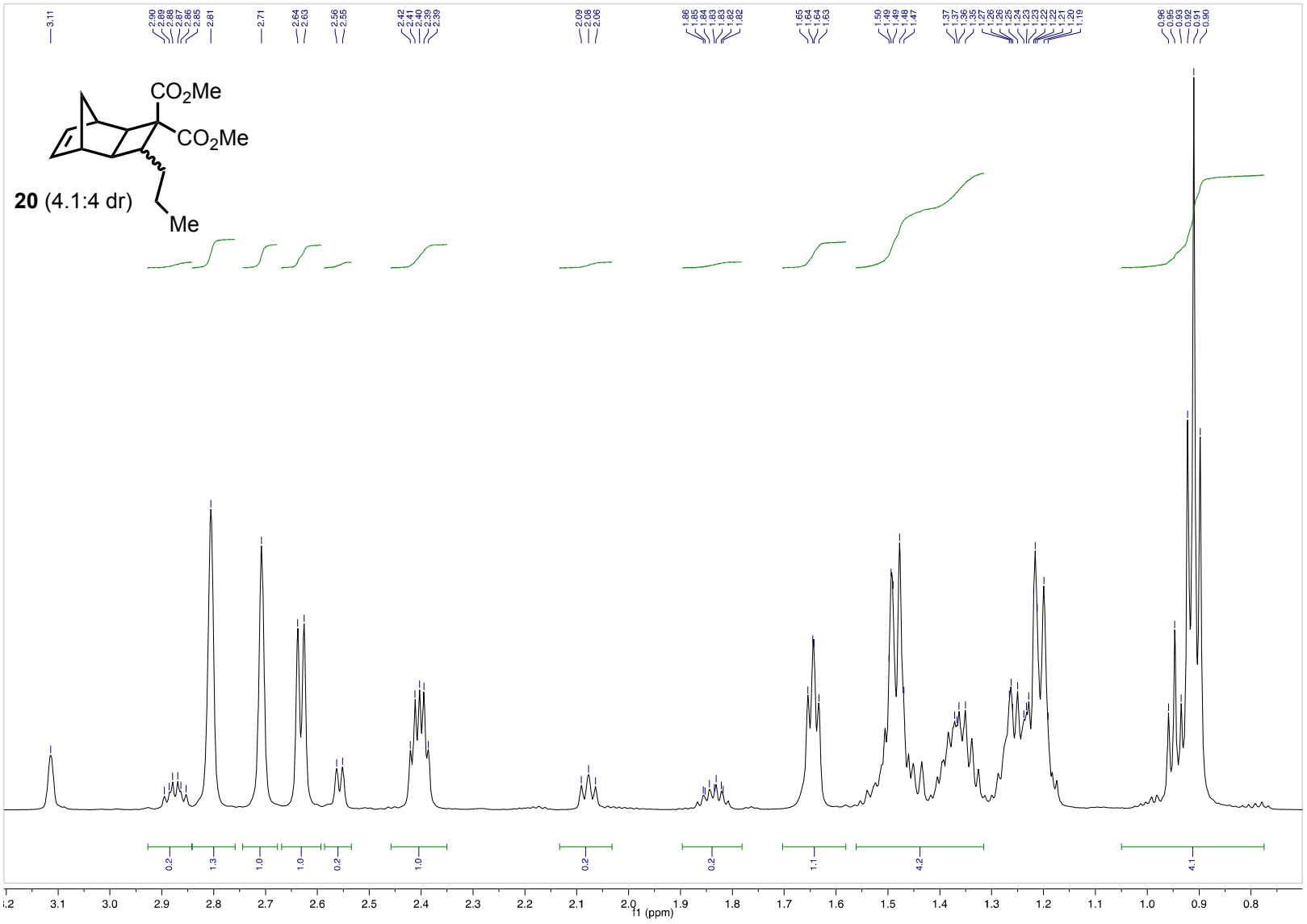


Figure S54: ^{1}H NMR (600 MHz, chloroform-*d*), **20** (inset).

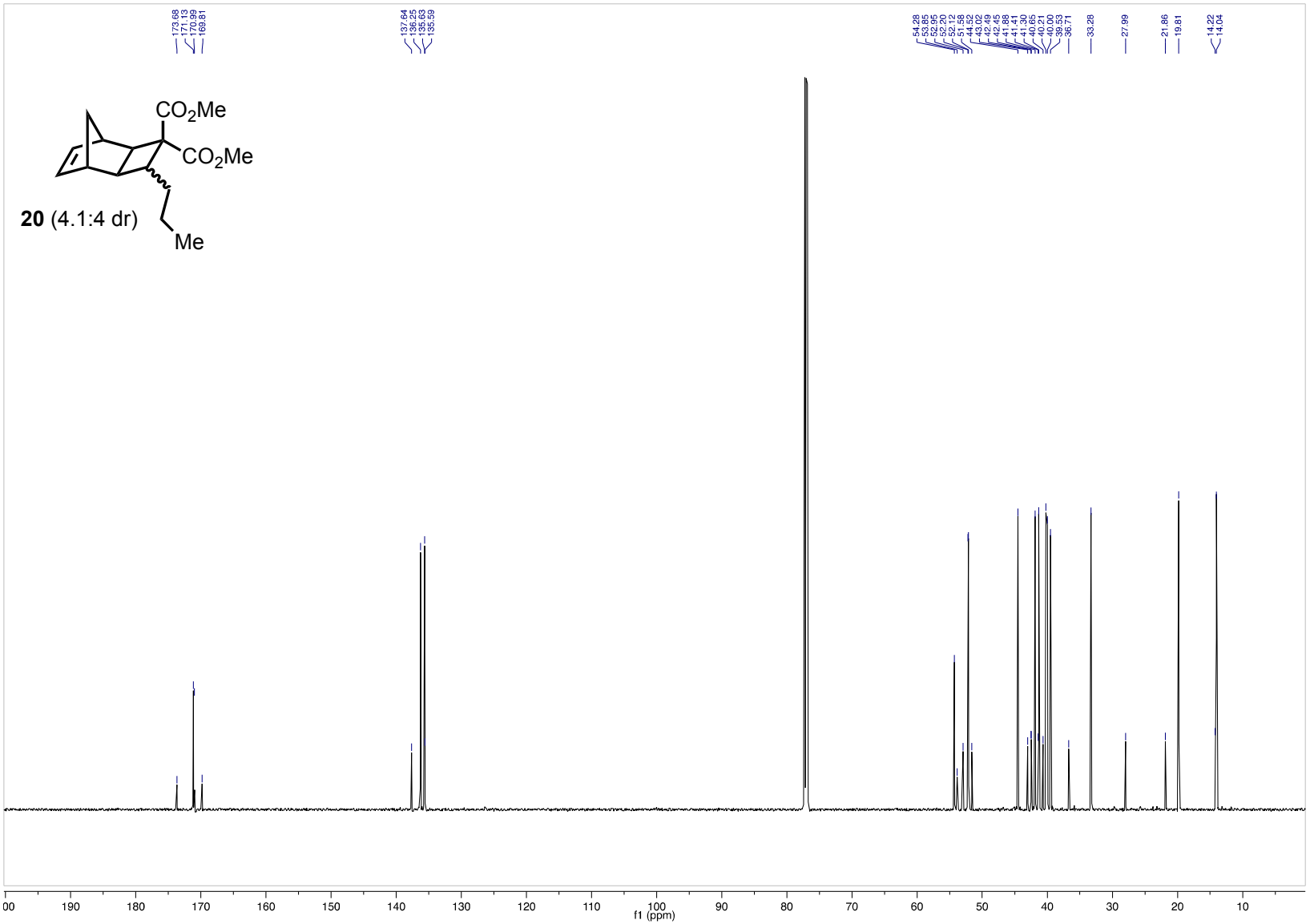


Figure S55: ^{13}C NMR (151 MHz, chloroform-*d*), **20**.

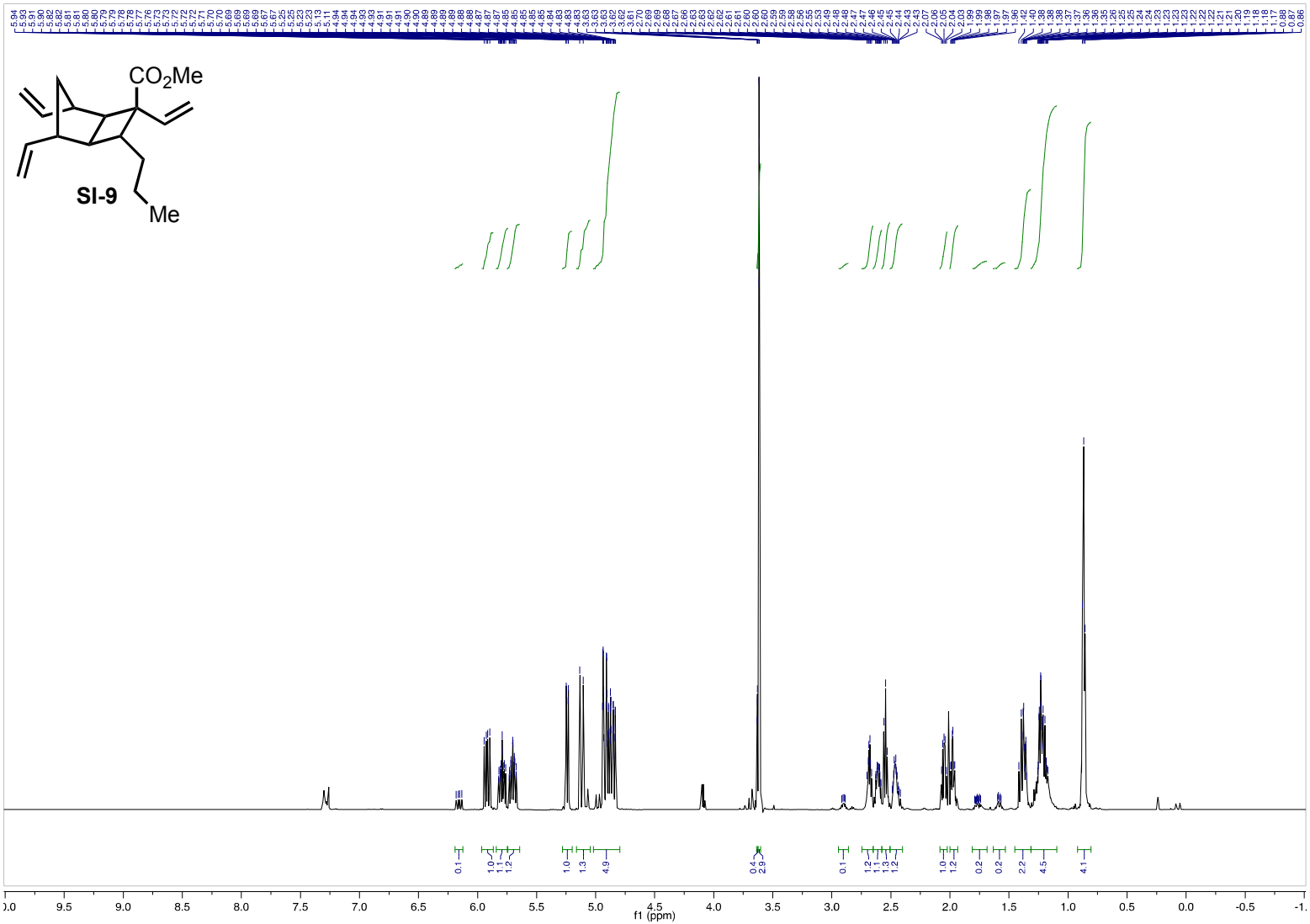


Figure S56: ^{1}H NMR (600 MHz, chloroform-*d*), **Si-9**.

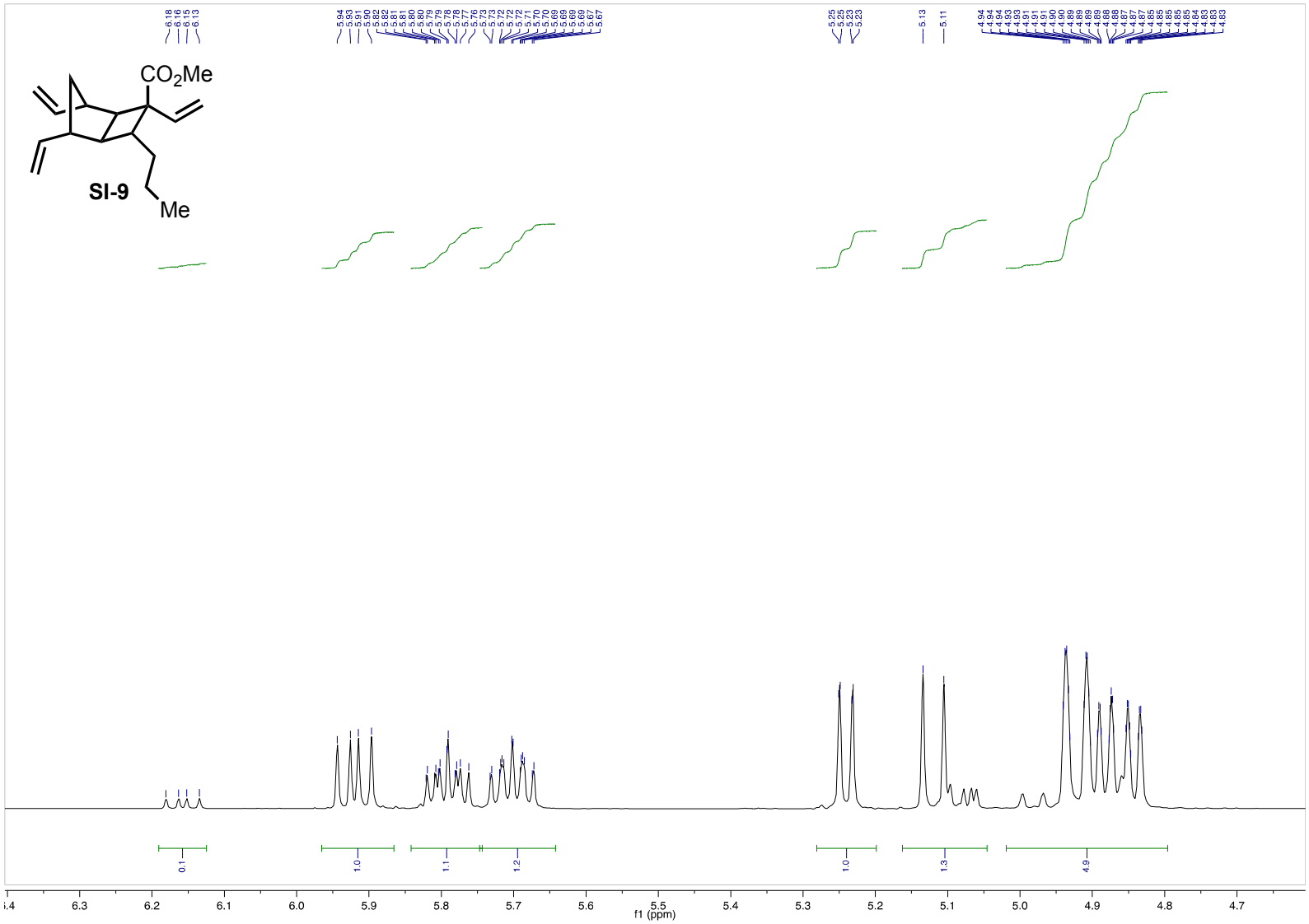


Figure S57: ^{1}H NMR (600 MHz, chloroform-*d*), **Si-9** (inset).

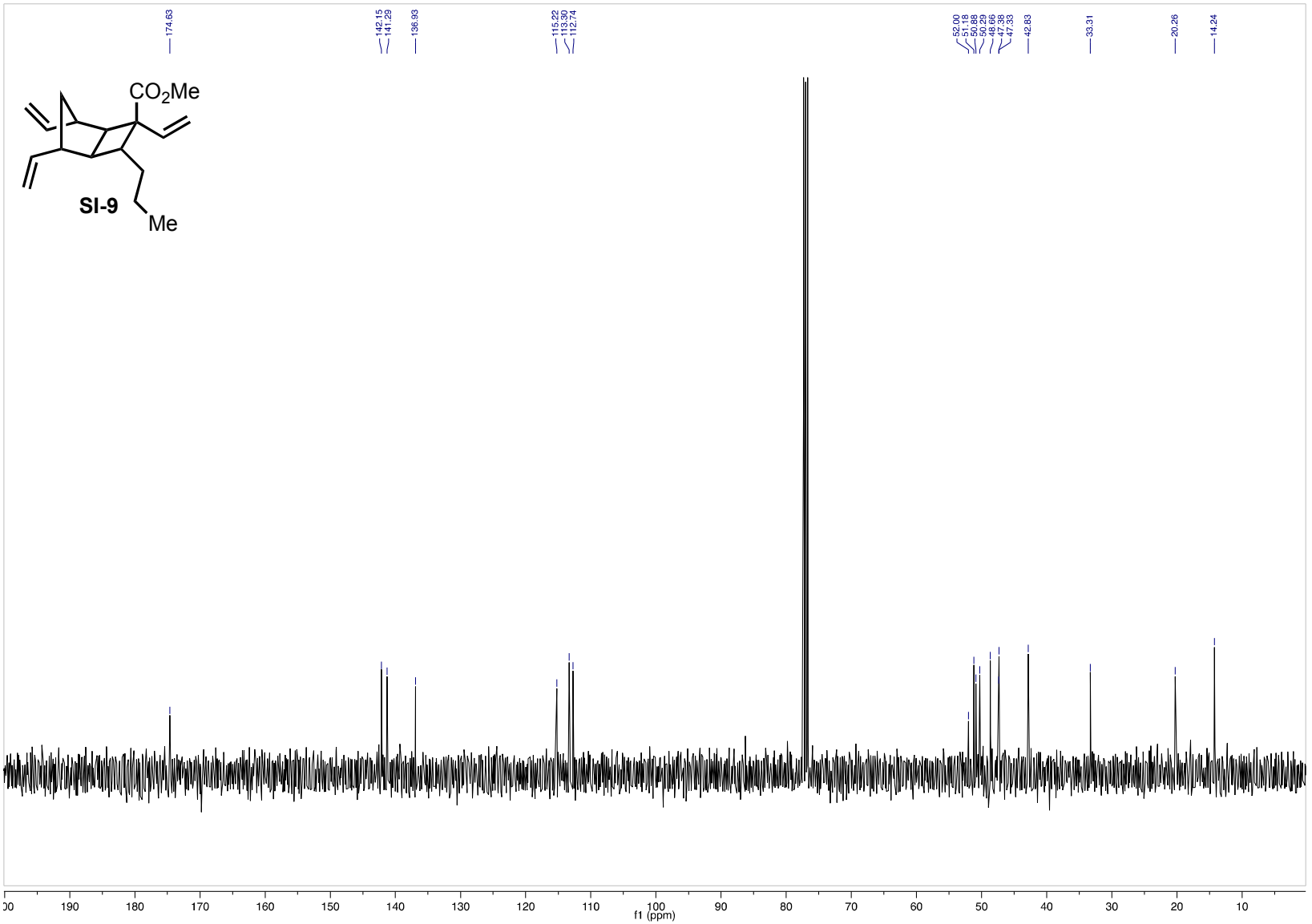


Figure S58: ^{13}C NMR (151 MHz, chloroform-*d*), **Si-9**.

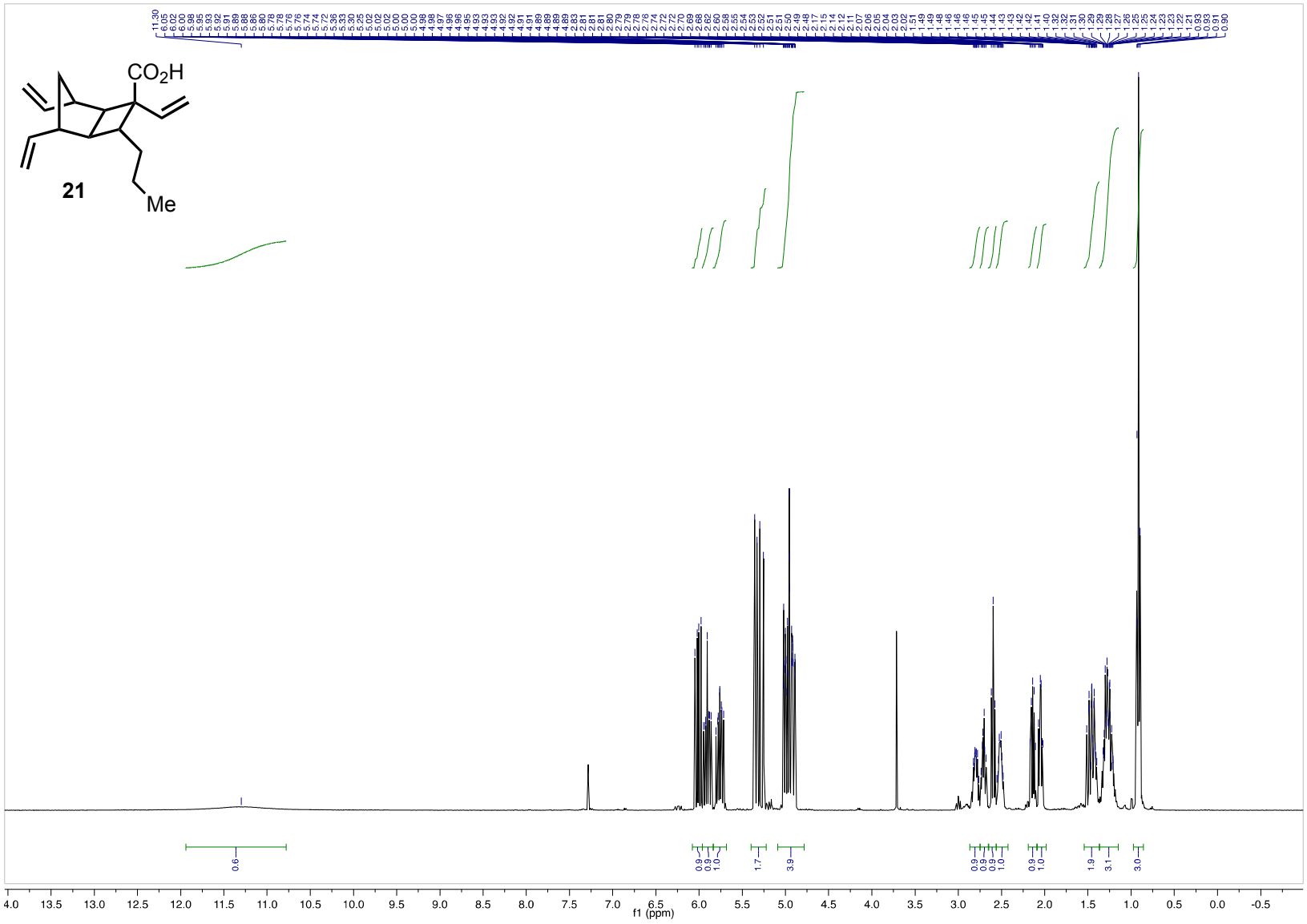


Figure S59: ^{1}H NMR (600 MHz, chloroform-*d*), **21**.

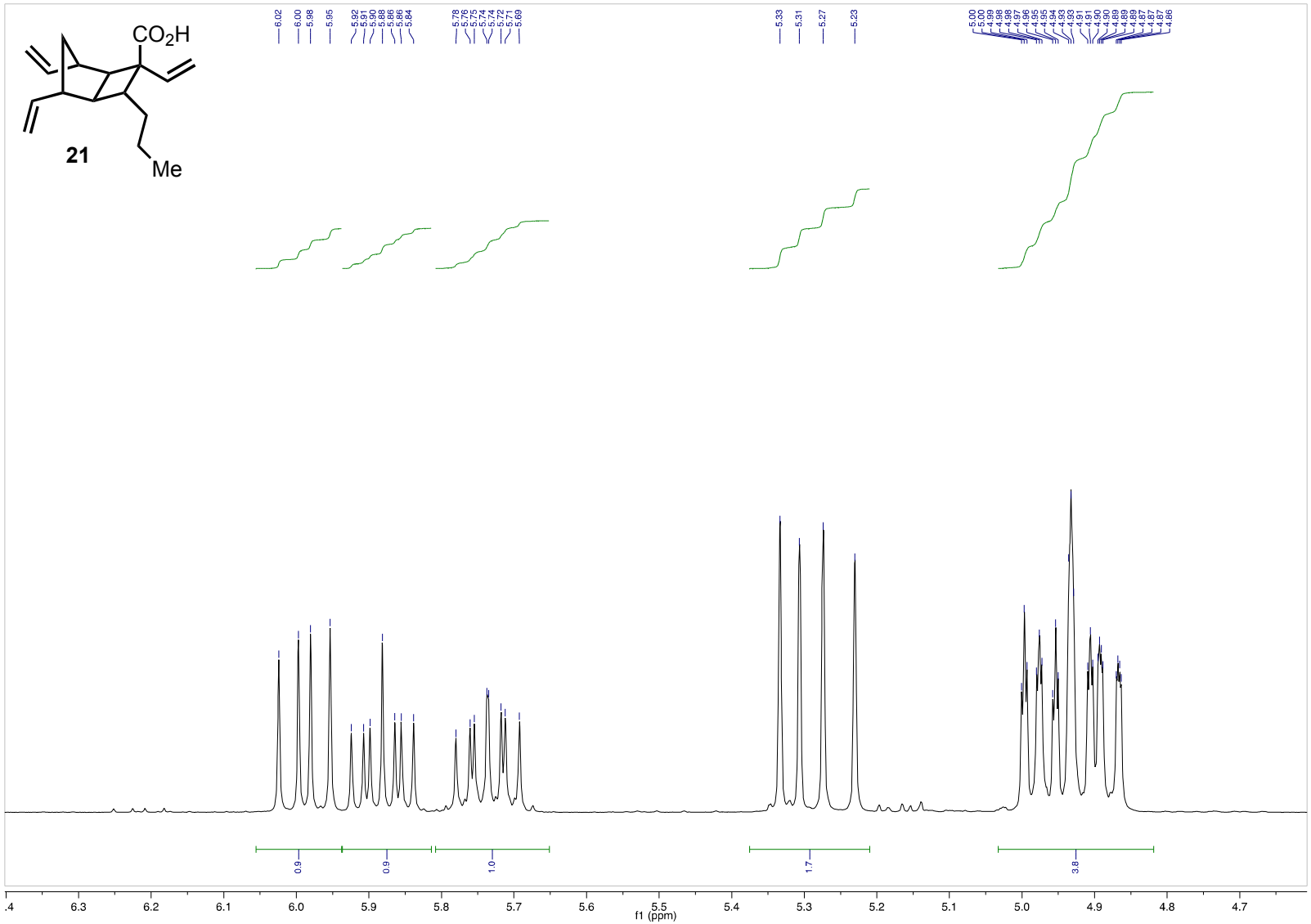


Figure S60: ^{1}H NMR (600 MHz, chloroform-*d*), **21** (inset).

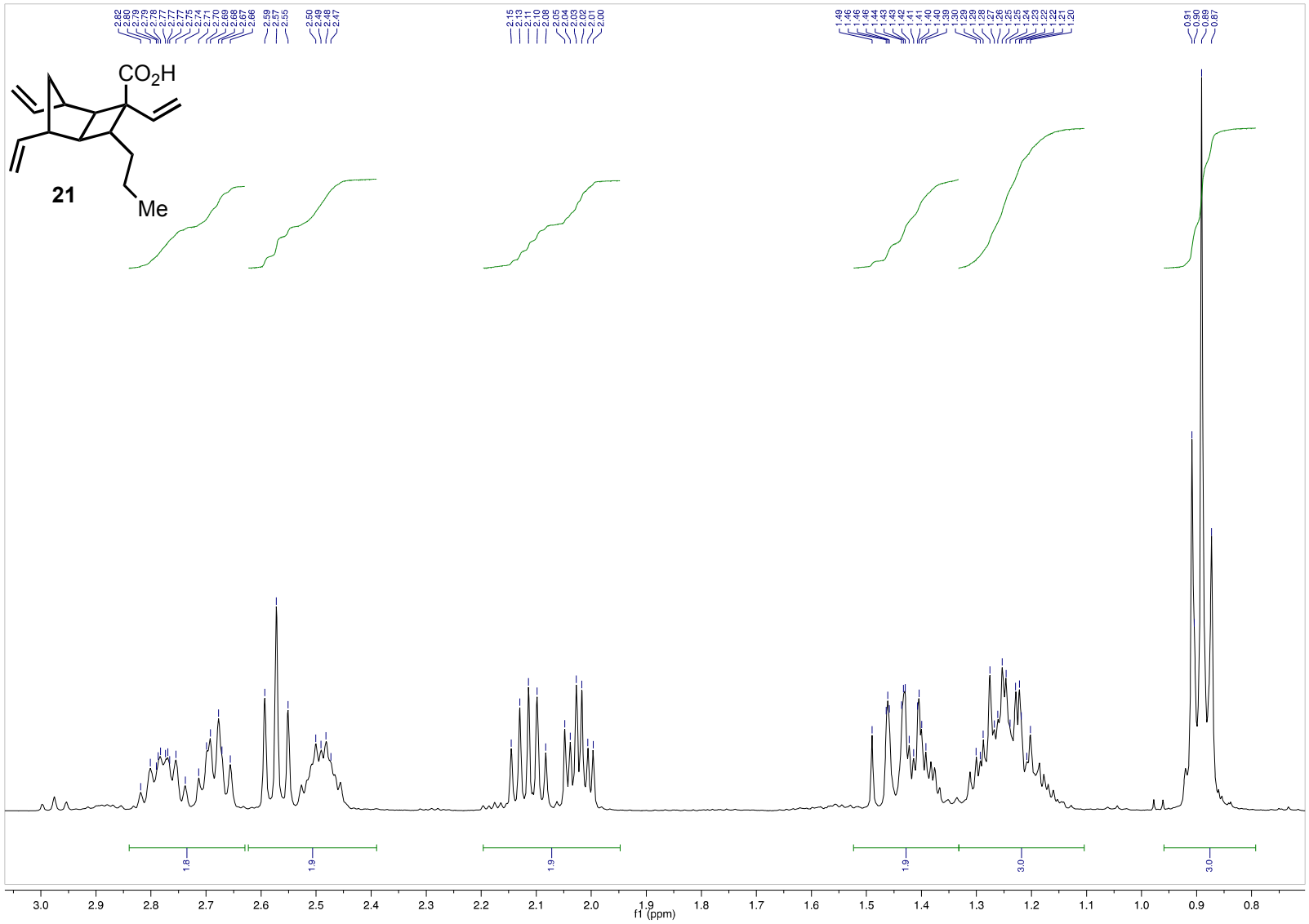


Figure S61: ^{1}H NMR (600 MHz, chloroform-*d*), **21** (inset).

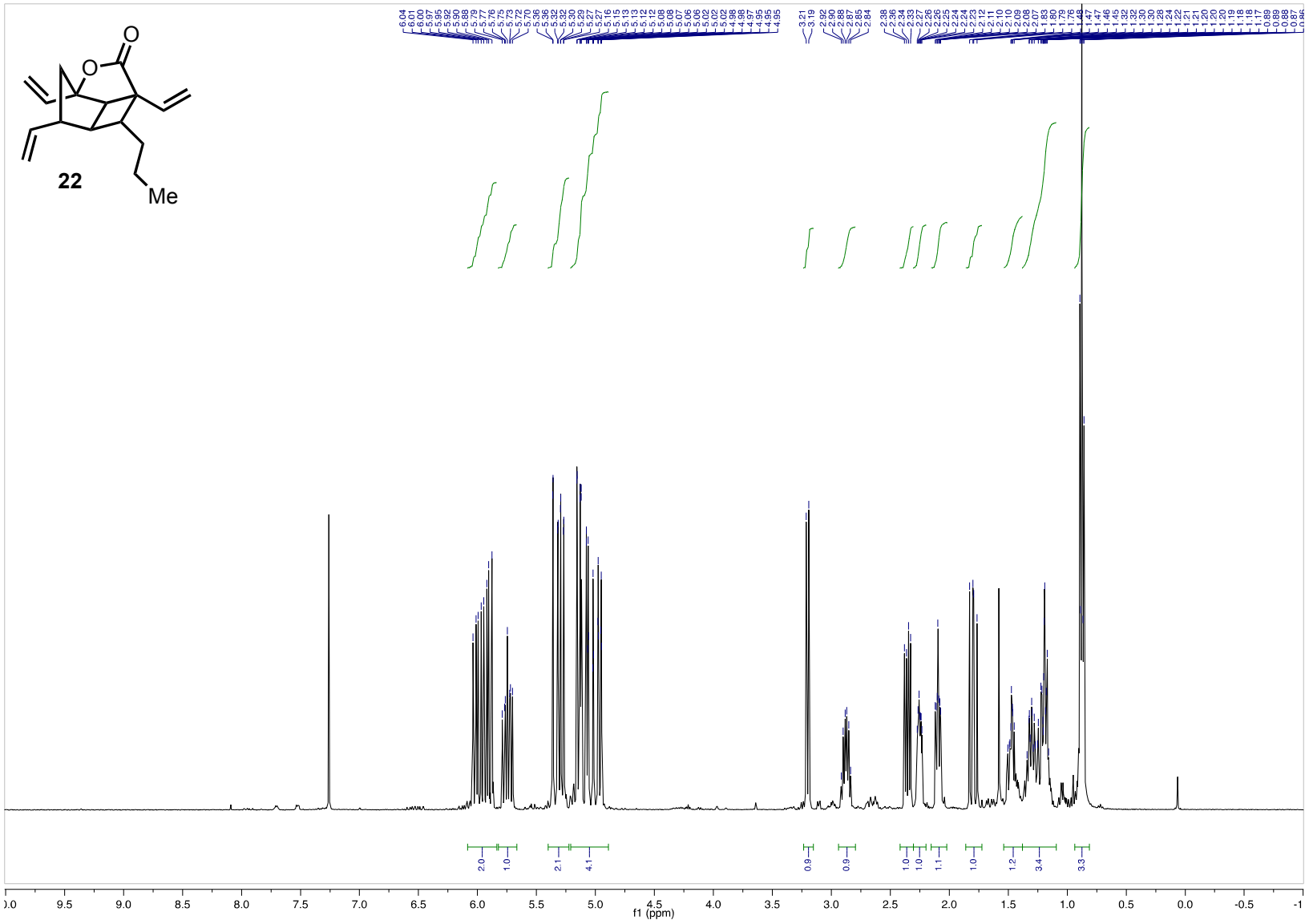


Figure S62: ^{1}H NMR (600 MHz, chloroform-*d*), **22**.

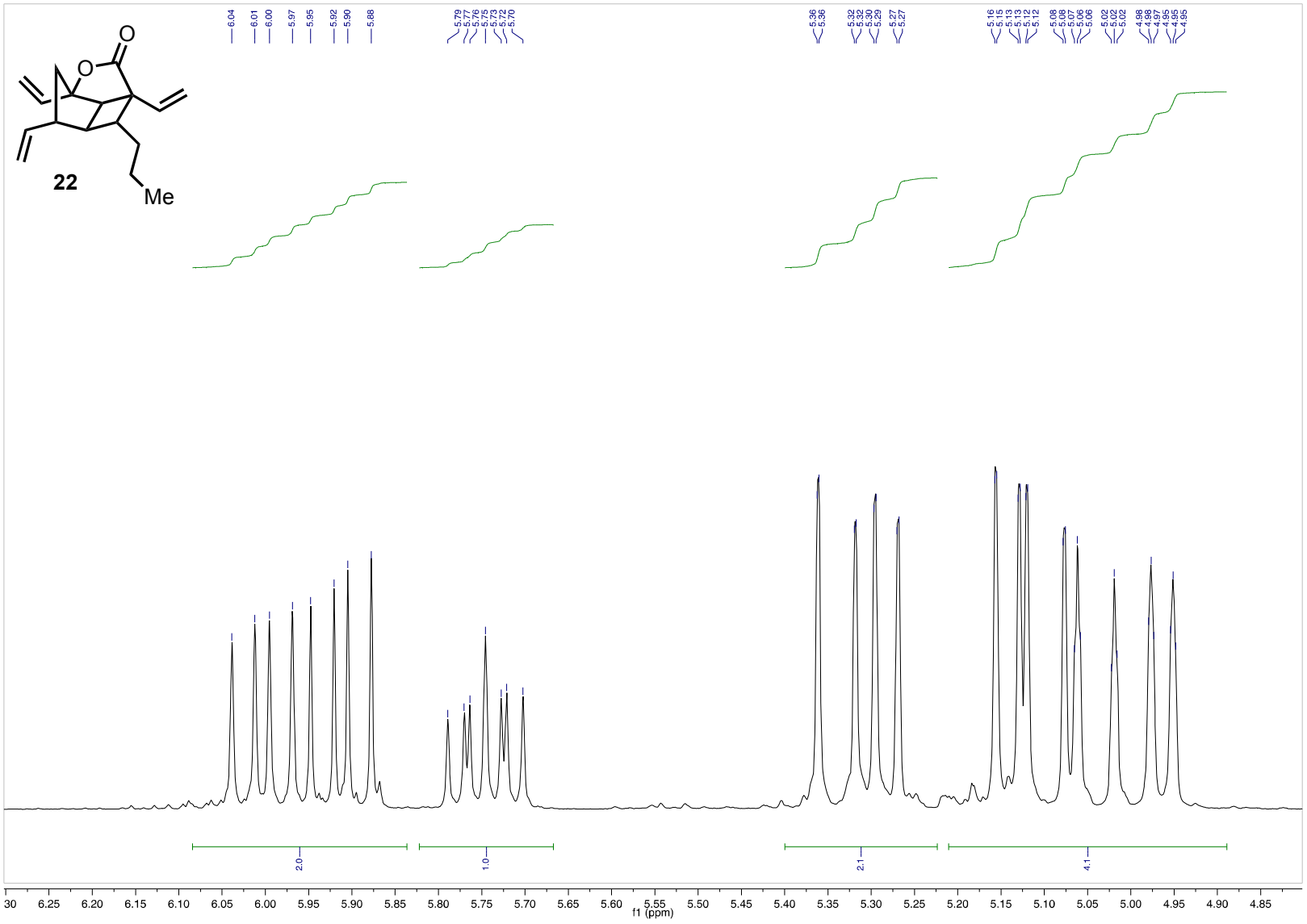


Figure S63: ^{1}H NMR (600 MHz, chloroform-*d*), **22** (inset).

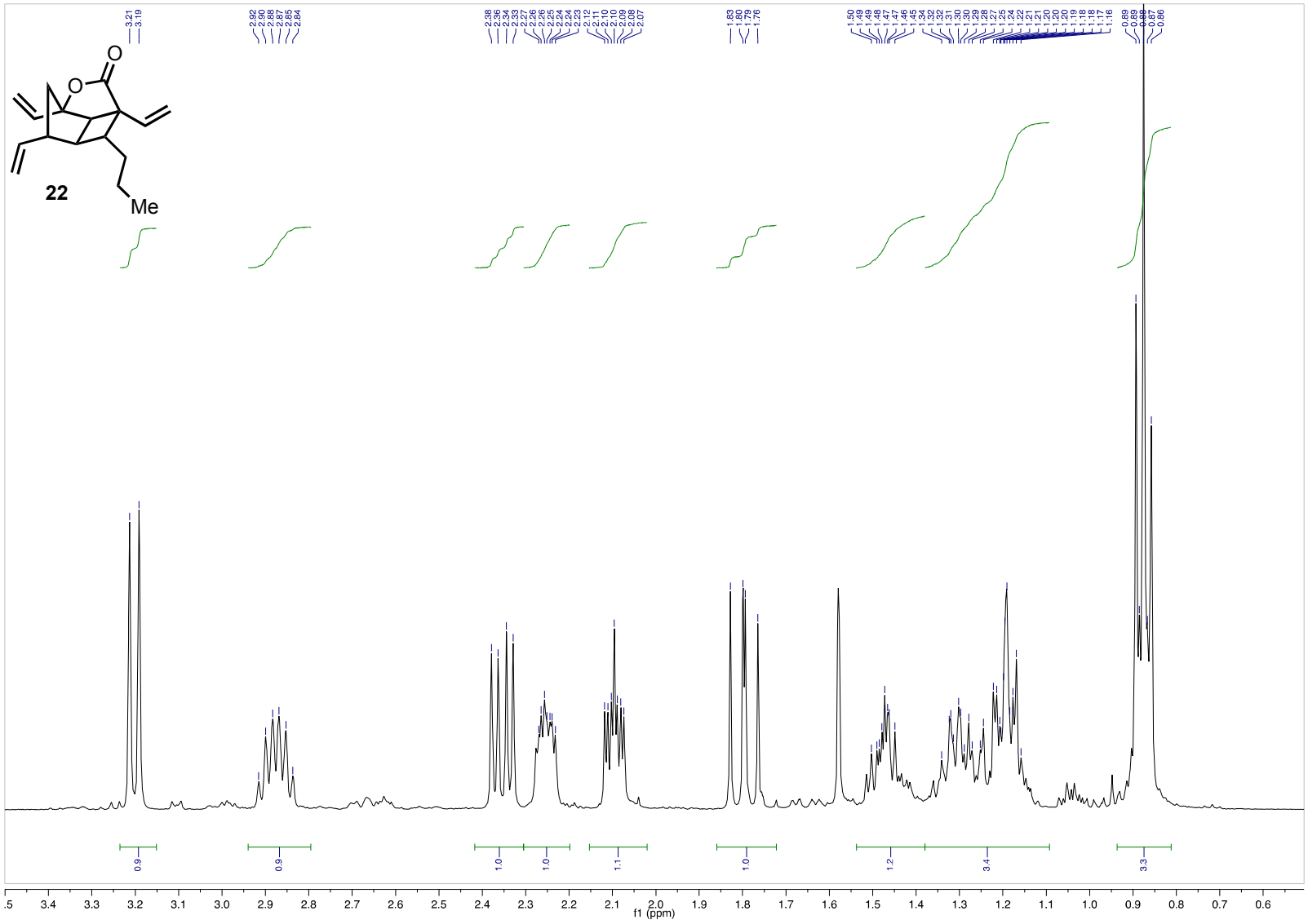


Figure S64: ^{1}H NMR (600 MHz, chloroform-*d*), **22** (inset).

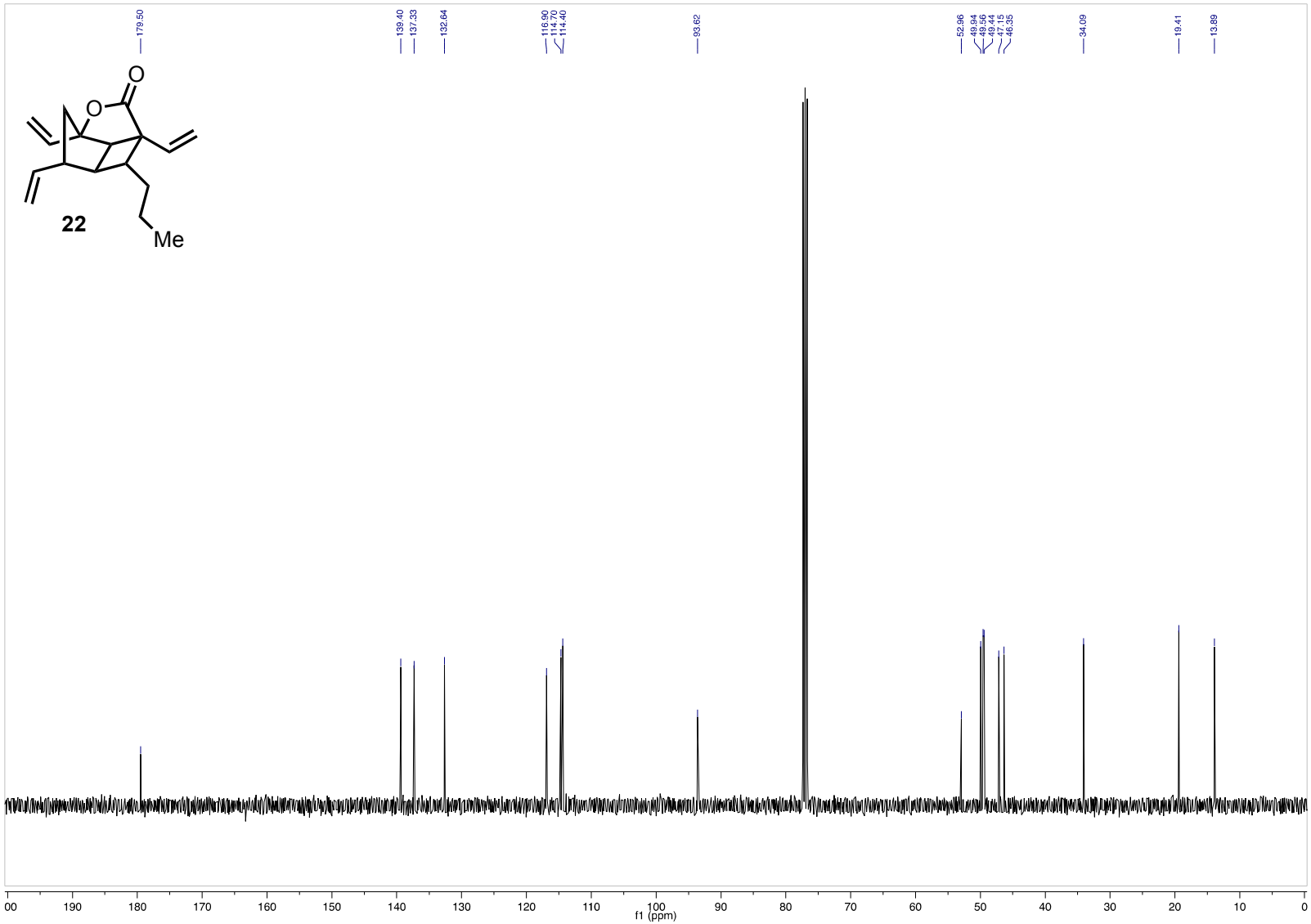


Figure S65: ^{13}C NMR (151 MHz, chloroform-*d*), **22**.

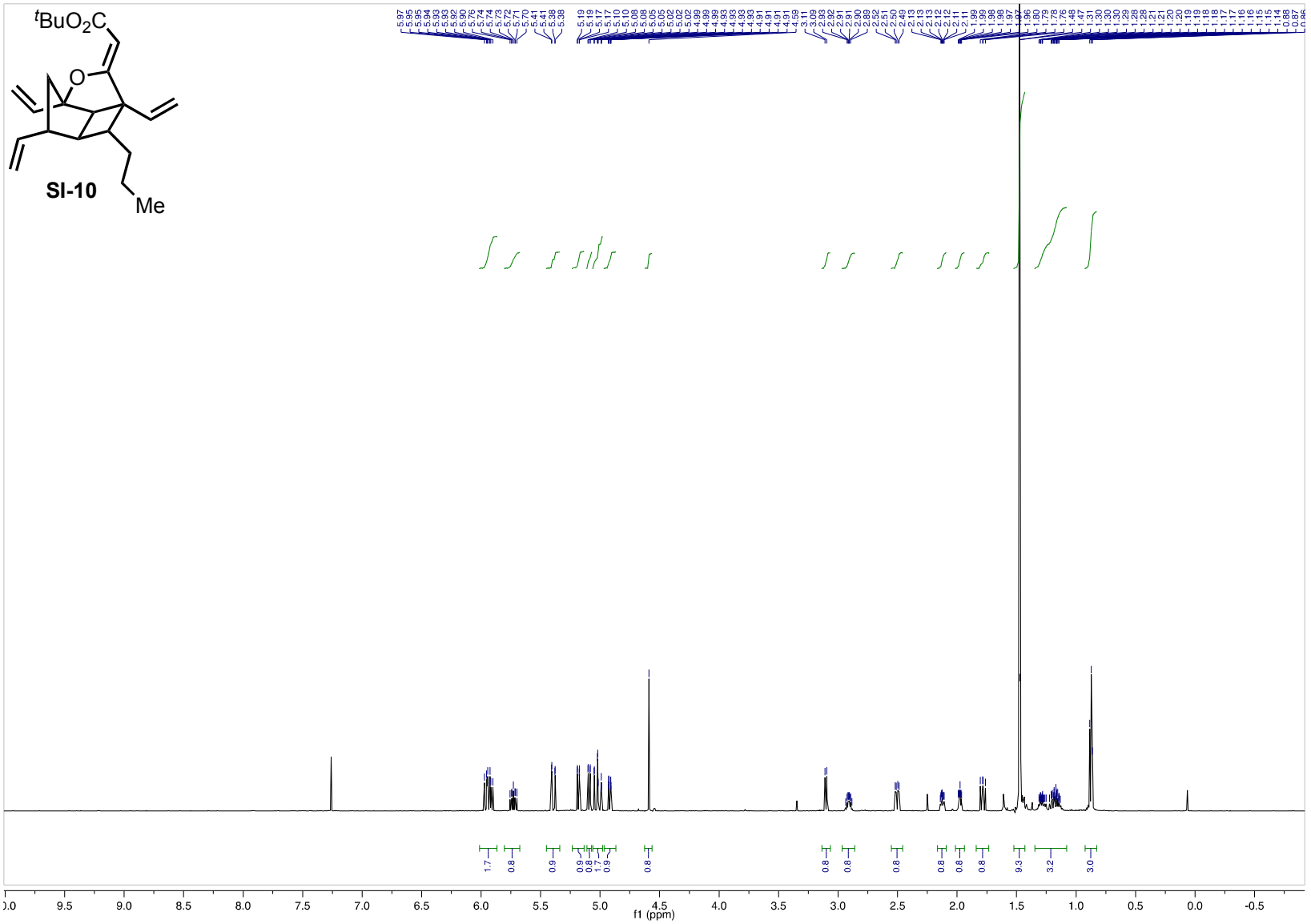


Figure S66: ^{1}H NMR (600 MHz, chloroform-*d*), **Si-10**.

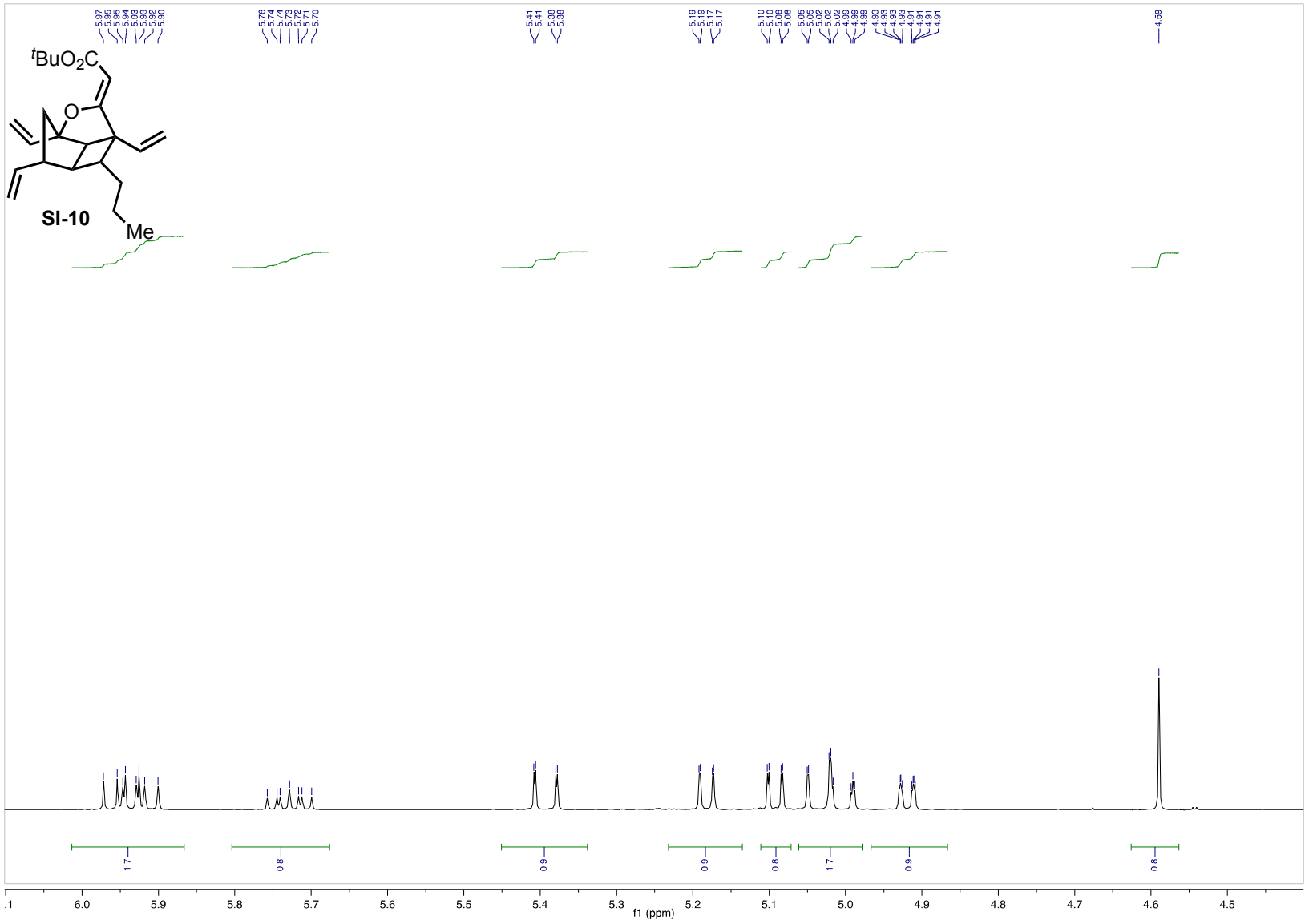


Figure S67: ^{1}H NMR (600 MHz, chloroform-*d*), **Si-10** (inset).

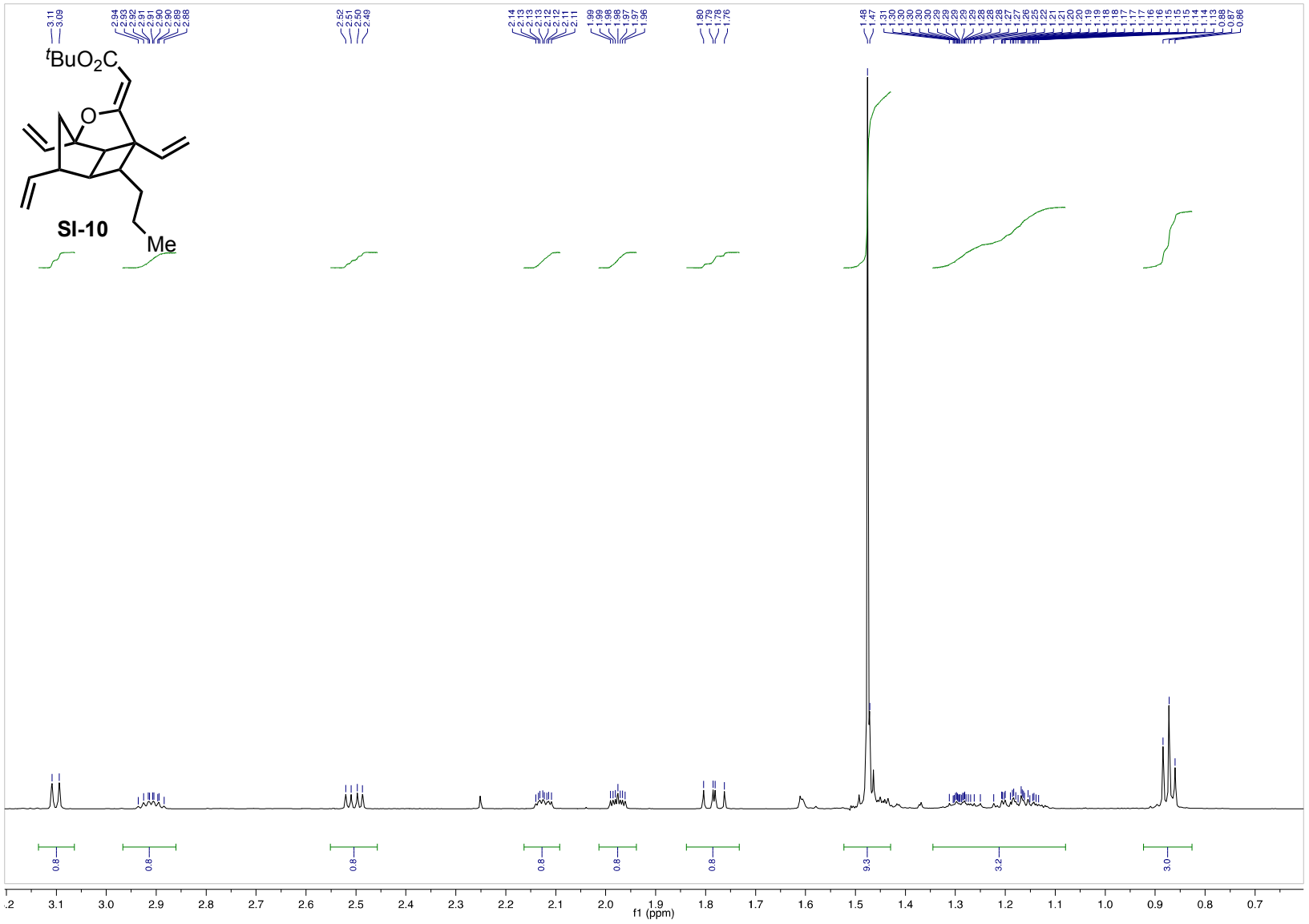


Figure S68: ^{1}H NMR (600 MHz, chloroform-*d*), **Si-10** (inset).

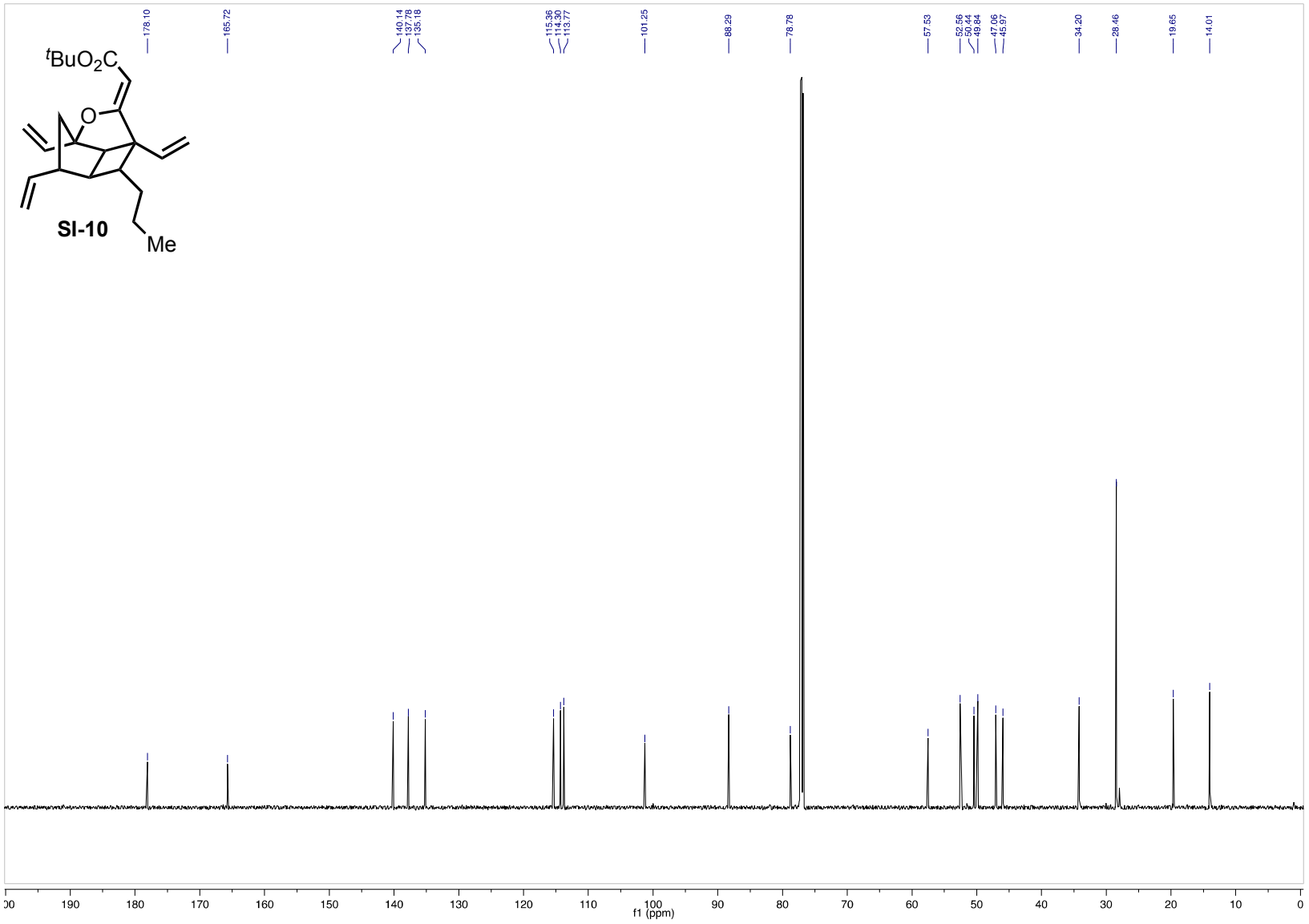


Figure S69: ^{13}C NMR (151 MHz, chloroform-*d*), **Si-10**.

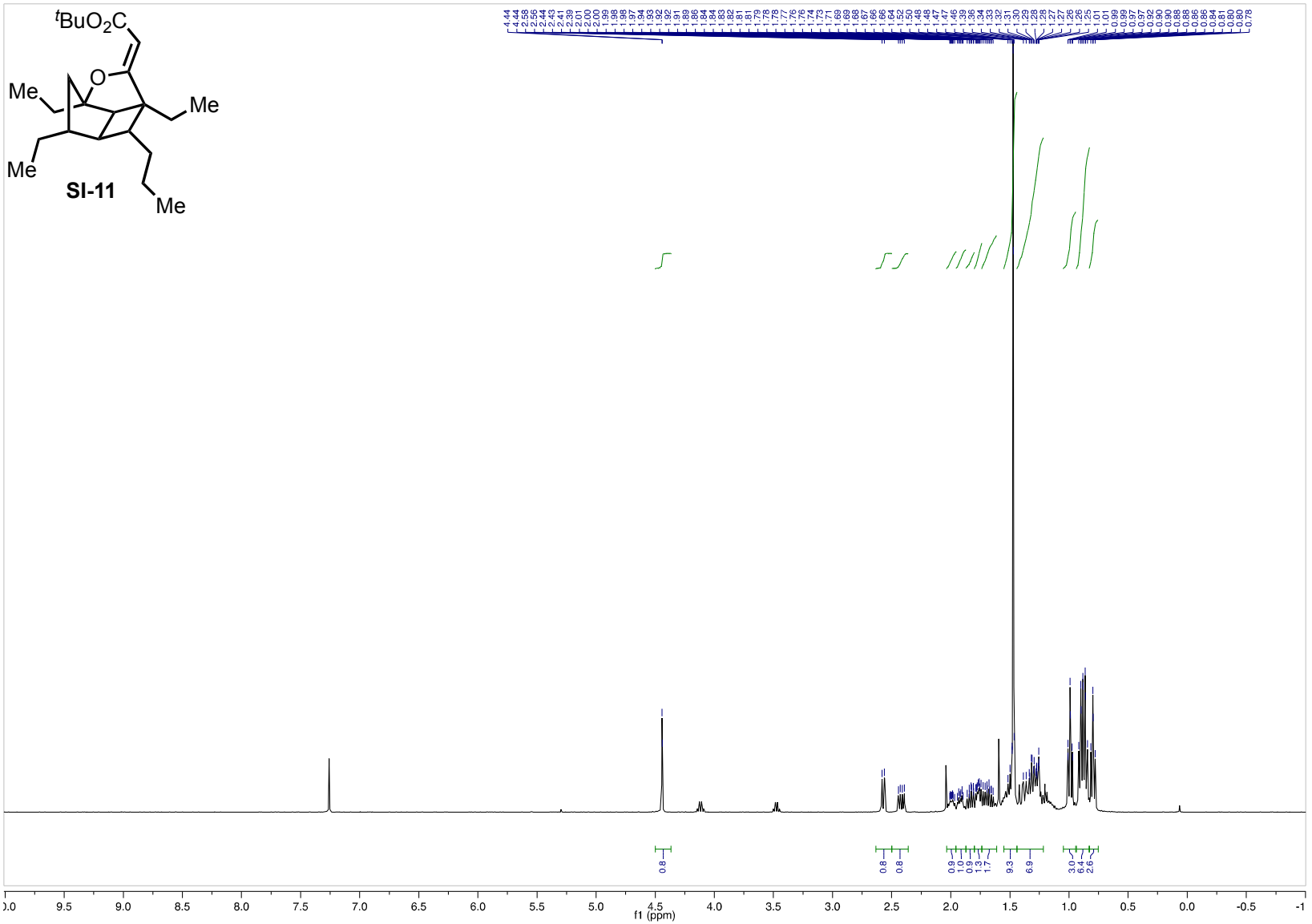


Figure S70: ^{1}H NMR (600 MHz, chloroform-*d*), **Si-11**.

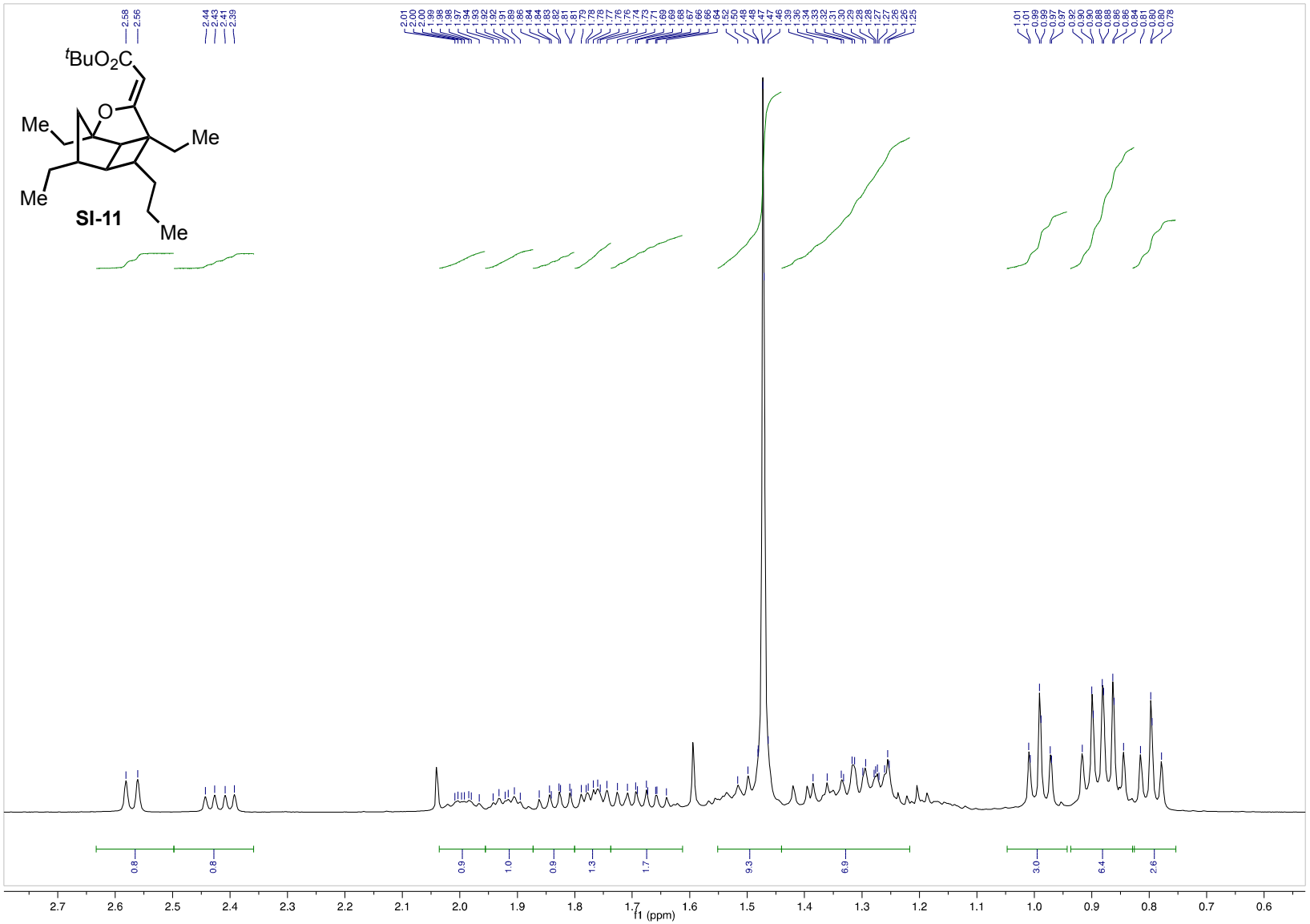


Figure S71: ^{1}H NMR (600 MHz, chloroform-*d*), **SI-11** (inset).

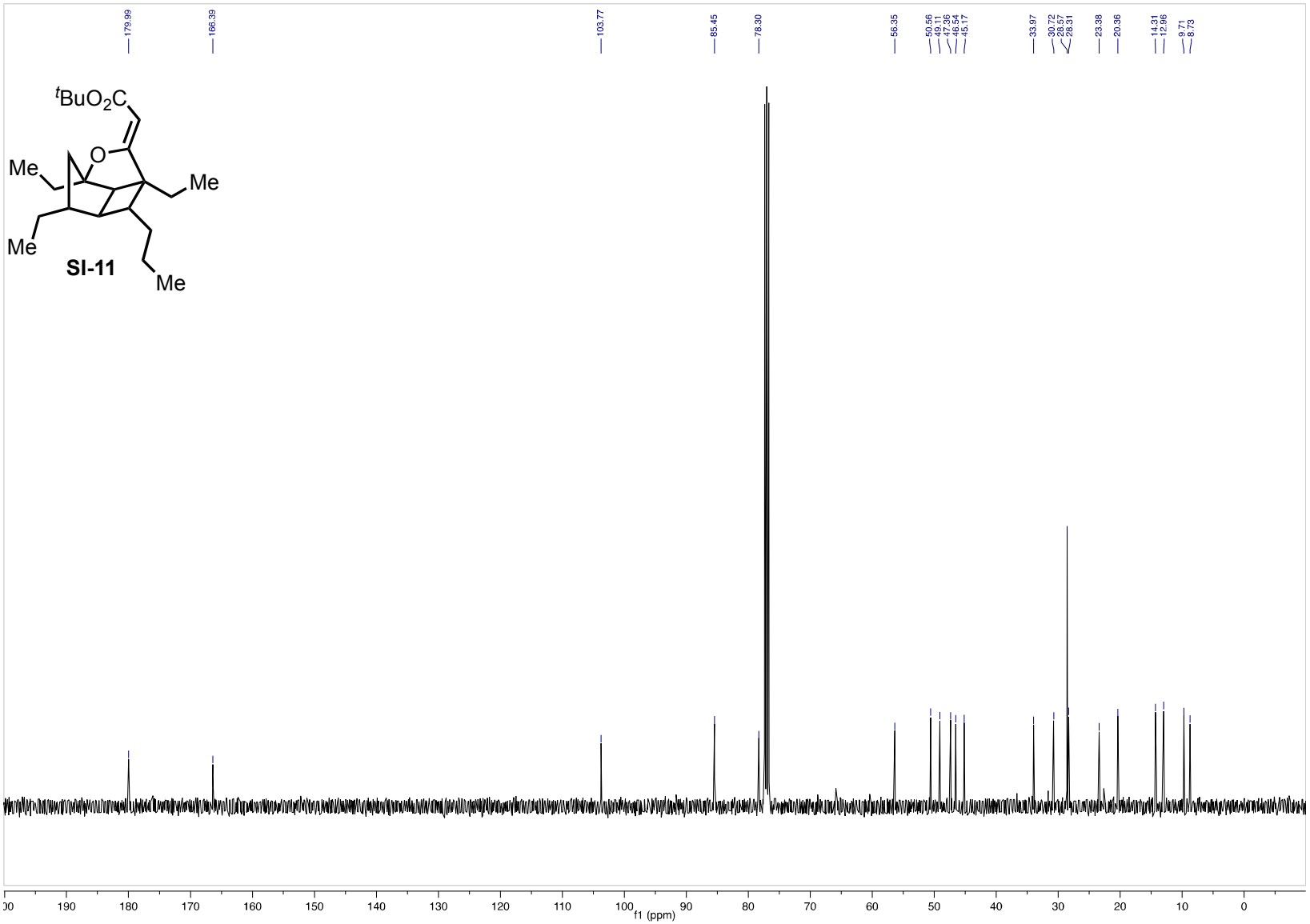


Figure S72: ^{13}C NMR (151 MHz, chloroform-*d*), **SI-11**.

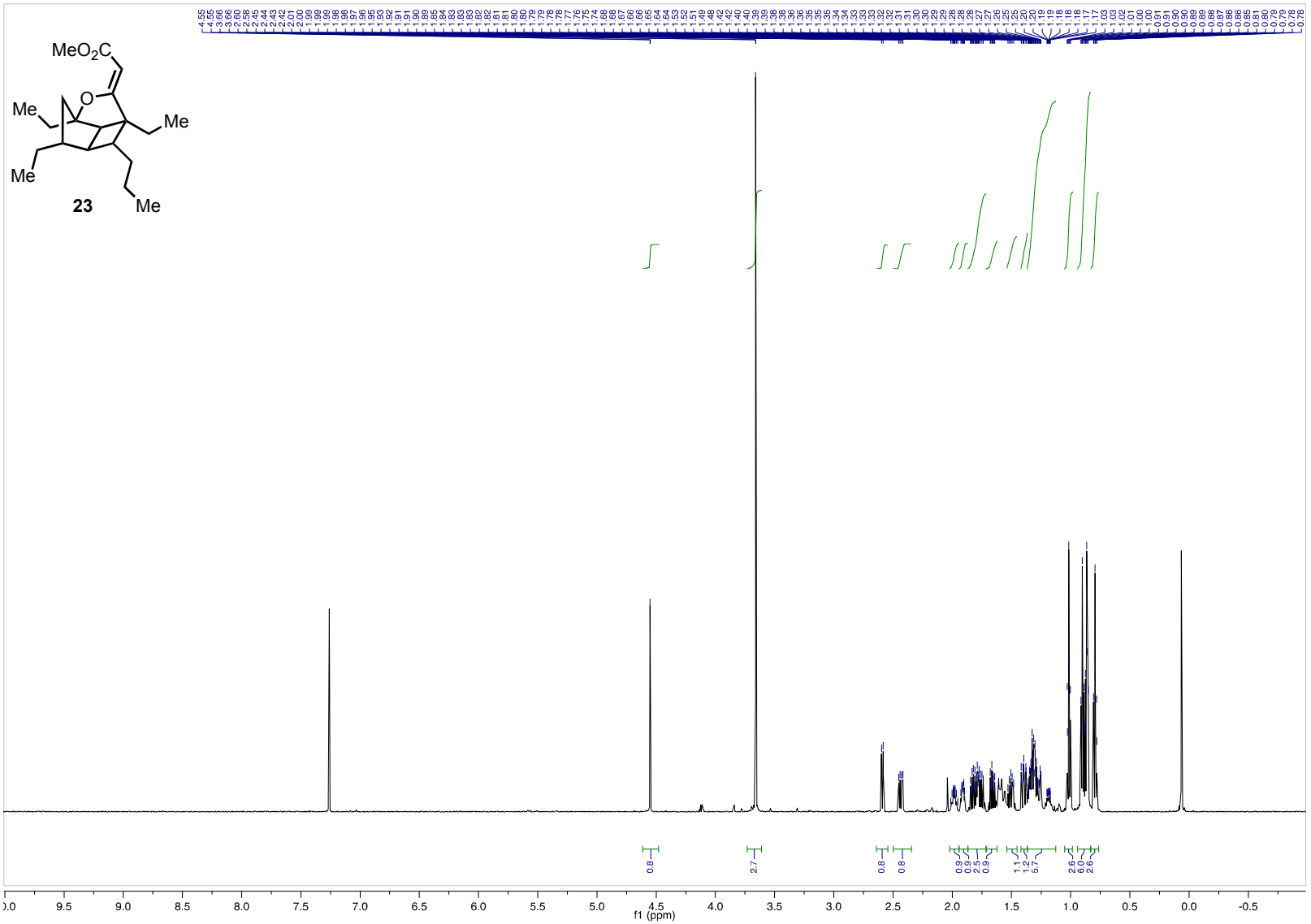


Figure S73: ^{1}H NMR (600 MHz, chloroform-*d*), **23**.

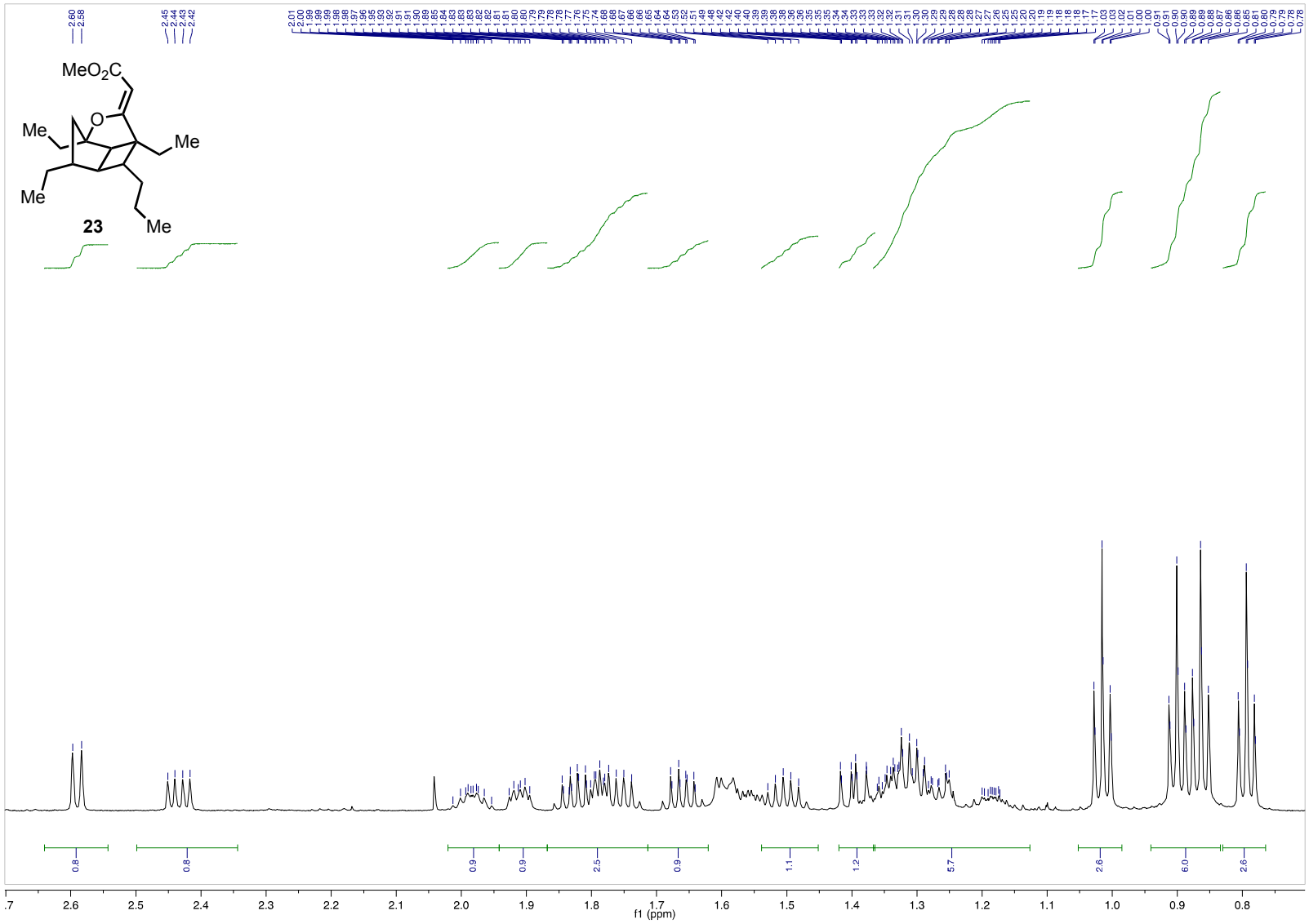


Figure S73: ^{1}H NMR (600 MHz, chloroform-*d*), **23** (inset).

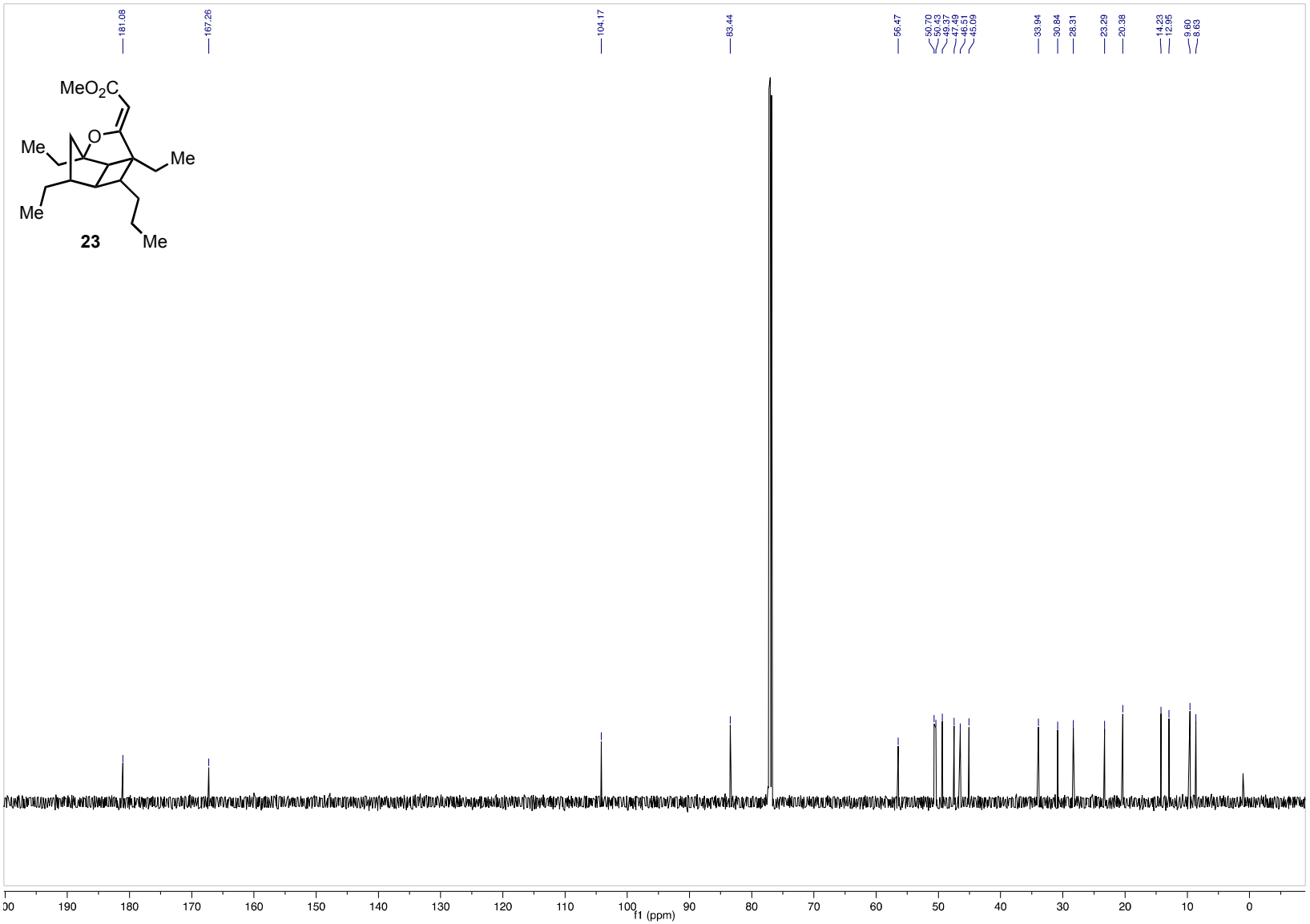


Figure S74: ^{13}C NMR (151 MHz, chloroform-*d*), **23**.