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Supporting Information

Concise Synthesis of the Tricyclic Skeleton of Crotobarin and Crotogoudin via a Gold-catalyzed Cycloisomerization Reactions

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I. General considerations

Unless otherwise noted, all experiments were carried out under air atmosphere. Dichloromethane (DCM) was distilled over CaH_2. Toluene were distilled over sodium and tetrahydrofuran (THF) were distilled over Na-Kalloy. The other reagents and solvents were directly used from the supplier without further purification unless noted. Analytical thin-layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates (silica gel 60, F254, Merck). Visualization was achieved under a UV lamp (254 nm and 365 nm), and by developing the plates with phosphomolybdic acid in ethanol. Flash chromatography was performed using silica gel (200-300 mesh) with solvents distilled prior to use.

Proton NMR (^{1}H) were recorded at 400 MHz NMR or 300 MHz NMR spectrometer, Carbon NMR (^{13}C) at 100 MHz NMR spectrometer unless otherwise stated. For $CDCl_3$ solutions the chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvents; $CHCl_3$ δ H (7.26 ppm), TMS δ H (0.00 ppm) and $CDCl_3$ δ C (77.00 ppm). Coupling constants (*J*) are reported in Hertz (Hz). Data for ^{1}H NMR spectra are reported as follows: chemical shift (ppm, referenced to protium; s = singlet, d = doublet, t = triplet), coupling constant (Hz), and integration.

Infrared spectra were recorded with a thin layer of the product on a KBr disk and reported in frequency of absorption (cm^{-1}).

High resolution mass spectral (HRMS) data were obtained with an ionization mode of ESI.

The following abbreviations are used: PE: petroleum ether; EtOAc: ethyl acetate; DCM: dichloromethane; THF: tetrahydrofuran; Et_2O: diethyl ether.

Experimental procedure and physical data

General Procedure A for enol triflate formation:

To a solution of ketoester (1 equiv.) in THF at -78 ^{o}C was added a solution of KHMDS (0.5 N, 1 equiv.) in toluene dropwise. After 30 min, a solution of $PhNTf_2$ (1.1 equiv.) in THF was added dropwise via cannula to the the enolate solution. The reaction mixture was then allowed to warm to rt and stirred overnight. The THF was added to achieve a concentration of 0.1 M with respect to substrate. The reaction was quenched with sat. aqueous NH_4Cl and the layers were separated. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated. Silica gel chromatography (PE-EtOAc) gave a yellow oil, which was contaminated with PhNHTf. Further purification by thin-layer chromatography (PE-DCM, 1 : 1) obtained the enol triflate.

General Procedure B for Negishi coupling reaction Reactions:

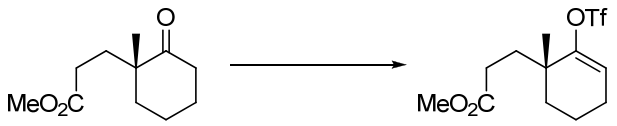
To a flame-dried flask backfilled with argon was added Mg particles (3 equiv.) and anhydrous $ZnCl_2$ (2 equiv.). After brief vacuum purging and backfilling the flask with argon, the metal was suspended in THF. To this suspension was added alkyl iodide (2 equiv.), and then heated to reflux. After 3 h, the reaction was cooled to room temperature, and a prepared solution of enol triflate (1 equiv.) in THF was added to the alkyl zinc solution via cannula. The THF was added to achieve a concentration of 0.1 M with respect to substrate. To this mixture was added $Pd(dppf)Cl_2$ (0.1 equiv.) and the reaction was sealed and heated to 75 ^{o}C for 4 h. After this time had elapsed, the reaction was cooled to room temperature and filtered over a Celite pad with copious washing with diethyl ether, the filtrate was evaporated and the crude product purified by flash column chromatography (PE-Et_2O) to afford 1,6-enyne ester.

General Procedure C for hydrolysis:

To a solution of 1,6-enyne ester (1 equiv.) in THF was added $LiOH{\cdot}H_2O$ (15 equiv.) followed by H_2O. The solvent (THF / H_2O = 3 : 1) was added to achieve a concentration of 0.15 M with respect to substrate. The mixture was stirred at room temperature for 16 h, then was acidified with 0.5 M HCl followed by extraction with ethyl acetate (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Purification by flash column chromatography (DCM-EtOAc) afforded 1,6-enyne acid.

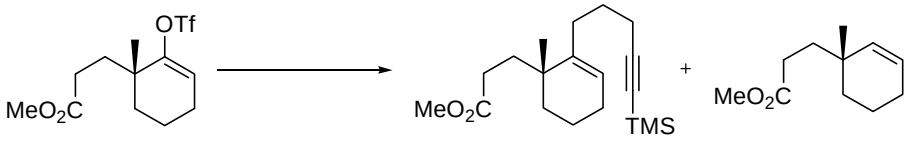
General Procedure D for gold-catalyzed 1,6-enyne cycloisomerization reaction:

To a solution of 1,6-enyne acid (1 equiv.) in dichloromethane was added a solution of $[Au(PPh_3)Cl]$ (0.05 equiv.) and AgOTf (0.05 equiv.) in dichloromethane and the resulting mixture was stirred for 1 h at room temperature. The dichloromethane was added to achieve a concentration of 0.05 M with respect to substrate. The reaction was filtered through a silica gel pad, the filtrate was evaporated. The residue was dissolved in diethyl ether and alkalified by 5% aqueous NaOH solution. The layers were separated, and the aqueous layer was extracted with diethyl ether (2 times). The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated under vacuum. The crude product purified by flash column chromatography (DCM-EtOAc) to afford the desired product.



7 **8**

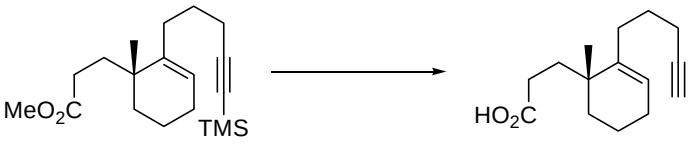
Compound 8: This compound was prepared according to General Procedure A using 1.98 g of compound **7**, 20 mL of KHMDS, and 3.91 g of $PhNTf_2$. Reaction was purified via Silica gel chromatography (PE-EtOAc, 6 : 1). Yield was 2.48g (75%) of the desired product as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (t, J = 4.0 Hz, 1 H), 3.67 (s, 3 H), 2.24-2.36 (m, 2 H), 2.12-2.21 (m, 2 H), 1.74-1.89 (m, 2 H), 1.59-1.61 (m, 3 H), 1.55 (m, 1 H), 1.15 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 154.2, 118.3(q, $J_{C\text{-}F}$ = 317.0 Hz), 117.6, 51.7, 37.7, 35.2, 33.2, 29.1, 24.7, 24.4, 18.2; IR (KBr) 2947, 2874, 1741, 1411, 1247, 1210, 1179, 1143, 1020, 888 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{17}F_3O_5SNa$ $(M + Na)^+$ 353.0641; found 353.0639.



8 **10** **11**

Compound 10: This compound was prepared according to General Procedure B using 365 mg of Mg particles, 1.36 g of $ZnCl_2$, 2.66 g of 1-Indo-5-trimethylsilyl-4-pentyne (**9**), 1.65 g of compound **8**, and 366 mg of $Pd(dppf)Cl_2$. Reaction was purified via flash column chromatography (PE-Et_2O, 100 : 1) to provide the desired product **10** (1.52g, 95%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43 (t, J = 3.6 Hz, 1 H), 3.66 (s, 3 H), 2.22-2.29 (m, 3 H), 2.13 (m, 1 H), 1.90-2.03 (m, 4 H), 1.79 (m, 1 H), 1.60-1.68 (m, 3 H), 1.47-1.59 (m, 3 H), 1.34 (m, 1 H), 1.01 (s, 3 H), 0.14 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 142.1, 122.5, 107.5, 84.7, 51.5, 37.0, 35.1, 34.6, 29.5, 29.4, 28.0, 26.3, 25.8, 19.9, 19.0, 0.14; IR (KBr) 2961, 2933, 2868, 2174, 1742, 1461, 1436, 1250, 844 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{32}O_2SiNa$ $(M + Na)^+$ 343.2064; found 343.2061.

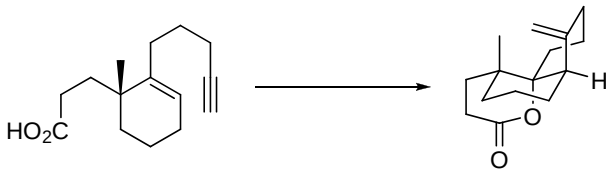
Compound 11 as a colorless oil**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61 (dt, J = 3.6, 10.4 Hz, 1 H), 5.33 (d, J = 10.4 Hz, 1 H), 3.64 (s, 3 H), 2.25-2.30 (m, 2 H), 1.88-1.93 (m, 2 H), 1.48-1.65 (m, 4 H), 1.44 (m, 1 H), 1.35 (m, 1 H), 0.94 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 135.4, 126.3, 51.5, 37.2, 34.3, 33.8, 29.4, 27.2, 25.0, 19.1; IR (KBr) 3012, 2931, 2866, 2838, 1741, 1435, 1370, 1198, 1169 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{11}H_{19}O_2$ $(M + H)^+$ 183.1377; found 183.1380.



10 **6**

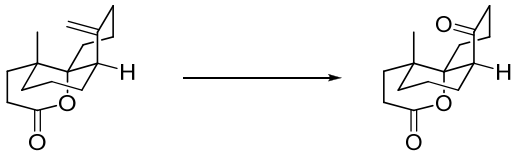
Compound 6: This compound was prepared according to General Procedure C using 1.52 g of compound **10**, and 2.99 g of $LiOH{\cdot}H_2O$. Reaction was purified via flash column chromatography (DCM-EtOAc, 60 : 1). Yield was 1.12 g (quantitative) of the desired product as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (brs, 1 H), 5.44 (t, J = 3.8 Hz, 1 H), 2.31 (m, 1 H),

2.13-2.22 (m, 3 H), 1.94-2.07(m ,5 H), 1.81 (m, 1 H), 1.60-1.71(m, 3 H), 1.47-1.60 (m, 3 H), 1.34 (m, 1 H), 1.02 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.9, 141.8, 122.7, 84.5, 68.4, 36.9, 35.1, 34.3, 29.6, 29.2, 27.7, 26.3, 25.8, 18.9, 18.4; IR (KBr) 3307, 2934, 2871, 2117, 1708, 1458, 1415, 1297, 1220 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{22}O_2Na$ $(M + Na)^+$ 257.1512; found 257.1503.



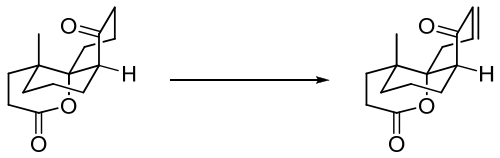
6 **5**

Compound 5: This compound was prepared according to General Procedure D using 1.44 g of compound **6**, 152 mg of [Au(PPh$_3$)Cl], and 79.2 mg of AgOTf. Reaction was purified via flash column chromatography (DCM-EtOAc, 80 : 1). Yield was 1.13g (70%) of the desired product as a white solid. MP 152-153 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (s, 1 H), 4.68 (s, 1 H), 2.51-2.60 (m, 4 H), 2.13-2.20 (m, 2 H), 1.81-1.91 (m, 2 H), 1.71-1.80 (m, 2 H), 1.58-1.65 (m, 4 H), 1.48-1.54 (m, 2 H), 1.22 (m, 1 H), 1.03 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 148.1, 110.2, 88.9, 49.4, 37.1, 34.5, 30.9, 29.0, 27.9, 26.6, 26.1, 22.5, 21.4, 20.1; IR (KBr) 3072, 2940, 2855, 1725, 1649, 1145, 984, 891 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{23}O_2$ $(M + H)^+$ 235.1693; found 235.1689.



5 **12**

Compound 12: A solution of compound **5** (1.01 g, 4.31 mmol) in methanol (86 mL), cooled at -78 °C, was subjected to a stream of O_2/O_3. Ozone treatment was terminated when the solutions assumed a blue color. Excess ozone was removed by a stream of oxygen. dimethyl sulfide (16 mL) was added. The mixture was stirred for 6 h at room temperature and then concentrated under vacuum. Purification by flash column chromatography afforded compound **12** (762 mg, 75%) as a white solid. MP 164-165 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.65 (m, 1 H), 2.53-2.60 (m, 2 H), 2.35-2.49 (m, 2 H), 2.28 (m, 1 H), 2.21 (m, 1 H), 2.08 (m, 1 H), 1.87-1.96 (m, 2 H), 1.81 (m, 1 H), 1.59-1.73 (m, 5 H), 1.26 (m, 1 H), 1.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.4, 169.4, 90.5, 56.2, 36.6, 35.9, 34.2, 29.2, 27.4, 26.3, 25.5, 22.4, 19.6, 19.1; IR (KBr) 2970, 2951, 2916, 1724, 1720, 1254, 1154, 1033 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{24}NO_3$ $(M + NH_4)^+$ 254.1751; found 254.1756.

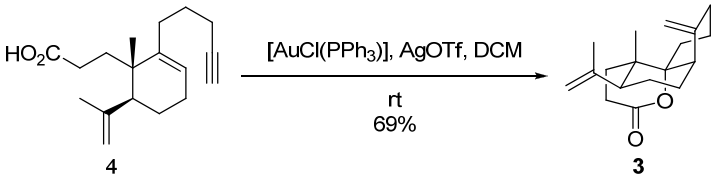


12 **13**

Compound 13: To a stirred solution of compound **12** (446 mg, 1.89 mmol) in EtOAc (38 mL) at 0 °C was added PhSeCl (726 mg, 3.78 mmol) and *p*-TsOH·H_2O (325 mg, 1.89 mmol). The reaction was stirred at the same temperature for 2.5 h, warmed to room temperature for 1.5 h,

and then diluted with DCM (35 mL), followed by addition of H_2O_2 (30%, 1.1 mL). Then stirring continued at room temperature for 50 min, and aqueous $CuSO_4$ (10%, 15 mL) was added. The resultant mixture was stirred for additional 20 min, diluted with water (50 mL), extracted with DCM (50 mL x 2). The combined organic phase was washed with saturated $Na_2S_2O_3$, 5% HCl and brine, dried over Na_2SO_4, and evaporated to give a residue, which was purified by a flash column chromatography (DCM-EtOAc, 40 : 1 → DCM-MeOH, 80 :1) to afford compound **13** (235 mg, 53%) as a white solid. MP 162-164 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 6.77 (m, 1 H), 6.03 (d, J = 10.1 Hz, 1 H), 2.64-2.77 (m, 2 H), 2.53-2.60 (m, 3 H), 2.37 (m, 1 H), 1.87 (d, J = 12.3, 1 H), 1.60 (s, 4 H), 1.26-1.40 (m, 2 H), 1.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0, 169.2, 144.2, 127.0, 88.5, 52.5, 36.5, 33.5, 30.0, 29.0, 26.6, 25.8, 21.0, 19.0; IR (KBr) 3047, 2968, 2948, 2923, 2864, 1726, 1668, 1283, 1147, 1034 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{18}O_3Na$ $(M + Na)^+$ 257.1148; found 257.1153.

Preparation of Substrate 3:

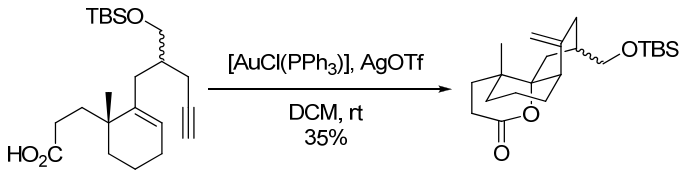


4 **3**

Compound 4: This compound was prepared in our laboratory. The desired product was obtained as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 11.4 (brs, 1 H), 5.52 (s, 1 H), 4.91 (s, 1 H), 4.69 (s, 1 H), 2.40 (m, 1 H), 2.14-2.28 (m, 3 H), 1.99-2.11 (m, 4 H), 1.90-1.99 (m, 2 H), 1.85 (m, 1 H), 1.77 (m, 1 H), 1.76 (s, 3 H), 1.61-1.73 (m, 3 H), 1.55 (m, 1 H), 0.97 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.7, 146.8, 141.2, 123.5, 114.0, 84.4, 68.5, 46.9, 41.5, 31.4, 29.5, 28.8, 27.9, 25.9, 24.3, 22.9, 22.8, 18.4; IR (KBr) 3306, 3068, 2932, 2117, 1708, 1459, 1376, 1248, 1290, 896 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{26}O_2Na$ $(M + Na)^+$ 297.1825; found 297.1828.

Compound 3: This Compound was prepared according to General Procedure D using 14.3 mg of compound **4**, 1.32 mg of [Au(PPh_3)Cl], and 0.67 mg of AgOTf. Reaction was purified via flash column chromatography (DCM-EtOAc, 80 : 1). Yield was 9.81 mg (69%) of the desired product as a white solid. MP 150-151 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 4.98 (s, 1 H), 4.94 (s, 1 H), 4.88 (s, 1 H), 4.75 (s, 1 H), 2.54-2.66 (m, 1 H), 2.44-2.54 (m, 2 H), 2.25-2.44 (m, 3 H), 2.11-2.23 (m, 1 H), 1.92-2.07 (m, 3 H), 1.66-1.88 (m, 5 H), 1.78 (s, 3 H), 1.43-1.55 (m, 1 H), 1.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 148.2, 146.1, 115.1, 108.2, 90.3, 46.3, 45.9, 39.3, 34.8, 34.3, 28.7, 26.0, 24.5, 24.2, 24.1, 23.4, 20.7; IR (KBr) 2954, 2924, 2852, 1737, 1463, 1377, 1245, 1109, 1050, 841 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{26}O_2Na$ $(M + Na)^+$ 297.1825; found 297.1824.

Preparation of Substrate 15:



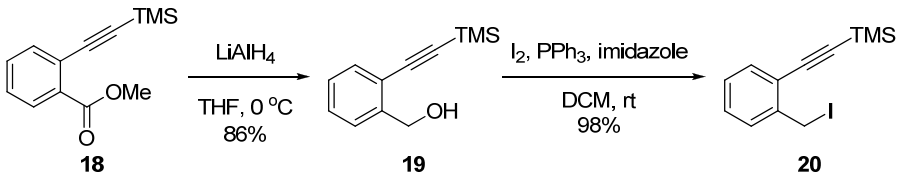
14 **15**

Compound 14: This compound was prepared in our laboratory. The diastereomers could not

be separated via column chromatography. Mixture of the two diastereomers was obtained as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.5 (brs, 1 H), 5.41-5.56 (m, 1 H), 5.48-5.69 (m, 2 H), 2.13-2.37 (m, 4 H), 1.86-2.08 (m, 6 H), 1.73-1.86 (m, 1 H), 1.45-1.71 (m, 3 H), 1.28-1.42 (m, 2 H), 0.98-1.06 (d, 3 H) , 89 (s, 9 H), 0.04 (d, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.7, 140.0, 123.9, 123.7, 83.1, 83.0, 77.3, 77.0, 76.7, 69.5, 69.4, 64.4, 64.3, 38.6, 38.5, 37.0, 36.9, 35.2, 35.1, 34.3, 34.2, 31.0, 29.5, 26.4, 26.3, 25.9, 19.8, 19.7, 18.9, 18.8, 18.3, 0.13, -5.4, -5.5; IR (KBr) 3310, 2956, 2930, 2857, 2156, 1711, 1464, 1250, 1216, 842, 760 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{22}H_{37}O_3Si$ $(M - H)^+$ 377.2517; found 377.2525.

Compound 15: This compound was prepared according to General Procedure D using 19.2 mg of compound **14**, 1.21 mg of [Au(PPh_3)Cl], and 0.91 mg of AgOTf. Reaction was purified via flash column chromatography (DCM-EtOAc, 80 : 1). Yield was 35% (β : α = 2 : 1). The diastereomers could be separated via column chromatography (PE-EtOAc, 20 : 1). **The β-diastereomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80 (s, 1 H), 4.79 (s, 1 H), 3.75 (m, 1 H), 3.54 (m, 1 H), 2.45-2.59 (m, 3 H), 2.37 (m, 2 H), 2.20 (m, 1 H), 1.95-2.10 (m, 2 H), 1.56-1.80 (m, 7 H), 1.27-1.38 (s, 1 H), 1.03 (s, 3 H), 0.89 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 146.0, 111.4, 89.4, 66.7, 48.8, 37.0, 36.6, 34.5, 31.9, 30.7, 29.3, 28.5, 26.4, 26.0, 22.6, 19.8, 18.3, -5.3; IR (KBr) 2930, 2857, 1732, 1465, 1380, 1253, 1149, 1081, 1032, 839, 776 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{22}H_{38}O_3SiNa$ $(M + Na)^+$ 401.2482; found 401.2495. **The α-diastereomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (s, 1 H), 4.72 (s, 1 H), 3.46-3.55 (m, 2 H), 2.48-2.63 (m, 4 H), 2.06-2.23 (m, 3 H), 1.74 (d, J = 8.2 Hz, 2 H), 1.44-1.70 (m, 7 H), 1.04 (s, 3 H) , 0.90 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 147.7, 110.6, 89.2, 67.3, 49.2, 37.1, 35.3, 34.5, 32.0, 30.8, 29.1, 28.0, 26.6, 25.9, 22.5, 20.1, 18.3, -5.4; IR (KBr) 2925, 2853, 1725, 1465, 1381, 1247, 1145, 1080, 1041, 835, 774 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{22}H_{42}O_3SiN$ $(M + NH_4)^+$ 396.2929; found 369.2944.

Preparation of alkyl iodide 20:



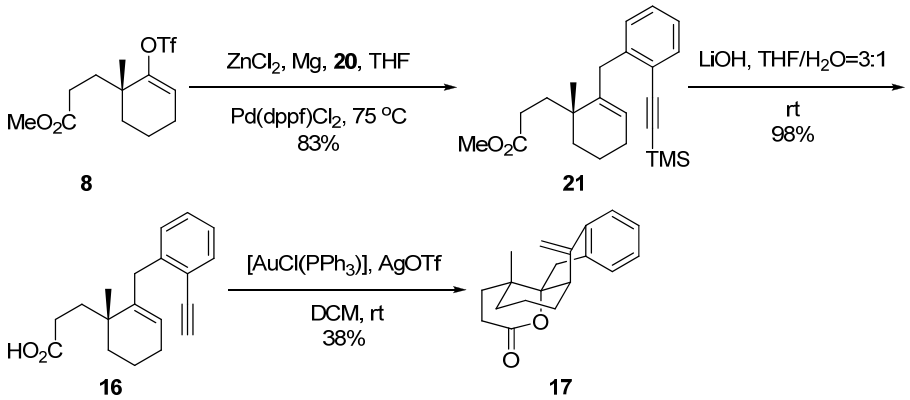
compound 18: Prepared according to a published procedure; spectral data were in agreement with literature values.[1]

Compound 19: A THF solution (5 mL) of lithium aluminum hydride (42.3 mg, 1.1 mmol) was cooled to 0 °C and a THF solution (5 mL) of compound **18** obtained above was added dropwise. After being stirred for 0.5 h at room temperature, the reaction was stopped by adding Na_2SO_4•$10H_2O$. After being stirred for another 1 h at room temperature, the crude material was filtered through a silica gel pad, and the resulting filtrate was concentrated in vacuo. Purification by flash column chromatography (PE-EA, 15 : 1) afforded compound **19** (177 mg, 86%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 0.9, 7.6 Hz, 1 H), 7.41 (d, J = 7.6 Hz, 1 H), 7.33 (dt, J = 1.2, 7.6 Hz, 1 H), 7.24 (dt, J = 1.2, 7.6 Hz, 1 H), 4.82 (d, J = 6.4 Hz, 2 H), 2.25 (t, J = 6.4 Hz, 1 H), 0.27 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 132.4, 128.9, 127.3, 127.2, 121.2, 102.6, 99.6, 64.1, -0.09; IR (KBr) 3345, 3067, 2959, 2899, 2155, 1480, 1450, 1041, 867, 843, 759 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{16}O_1SiNa$ $(M + Na)^+$ 227.0863; found

227.0859.

Compound 20: To a solution of Ph_3P (295 mg, 1.12 mmol) and imidazole (82.1 mg, 1.21 mmol) in CH_2Cl_2 (5 mL), I_2 (285 mg, 1.12 mmol) was added in portions, and the mixture was stirred vigorously at ambient temperature for 0.5 h. A solution of the compound **19** (177 mg, 0.86 mmol) in CH_2Cl_2 (5 mL) was added dropwise and the reaction was stirred for addition 1 h. Saturated sodium dithionite (5 mL) was added before further dilution with water (50 mL), the two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by a flash column chromatography (PE) to afford the compound **20** (276 mg, 98%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J =1.2, 7.4 Hz, 1 H), 7.39 (d, J = 1.2, 7.4 Hz, 1 H), 7.25 (dt, J = 1.6, 7.4 Hz, 1 H), 7.20 (dt, J = 1.6 Hz, 7.4, 1 H), 4.62 (s, 2 H), 0.32 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 132.7, 129.0, 128.9, 127.8, 122.5, 102.1, 101.4, 4.18, -0.11; IR (KBr) 3062, 3029, 2956, 2897, 2156, 1480, 1447, 1249, 872, 842, 752 cm^{-1}.

Preparation of Substrate 17:



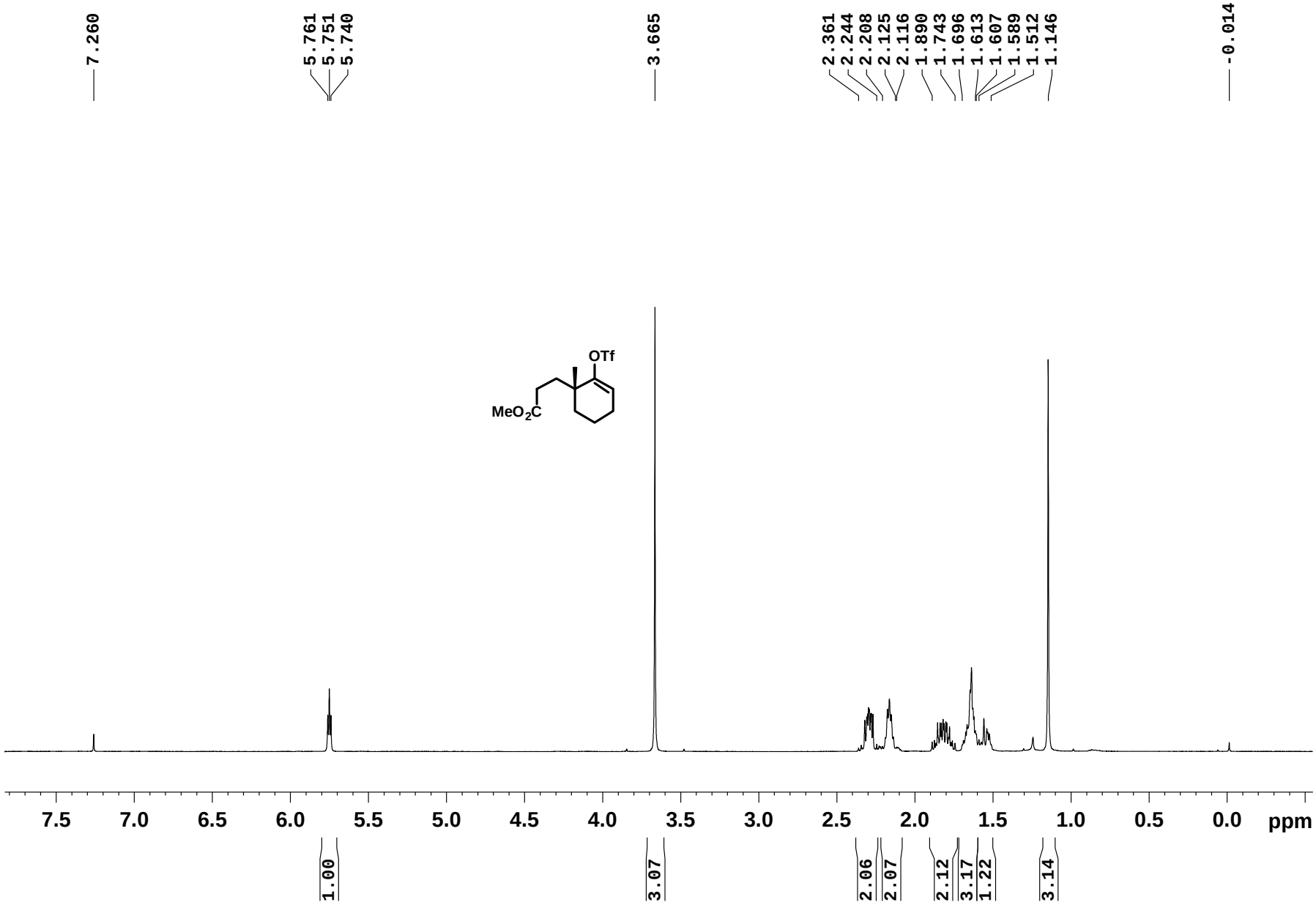
Compound 21: This compound was prepared according to General Procedure B using 32.1 mg of Mg particles, 119 mg of $ZnCl_2$, 276 mg of compound **20**, 145 mg of compound **8**, and 32.1 mg of Pd(dppf)Cl_2. Reaction was purified via flash column chromatography (PE-Et_2O, 100 : 1). Yield was 134 mg (83%) of the desired product as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 7.6 Hz, 1 H), 7.24 (t, J = 7.6 Hz, 1 H), 7.10-7.18 (m, 2 H), 4.94 (t, J = 3.7 Hz, 1 H), 3.67 (s, 3 H), 3.55 (dd, J = 1.2, 16 Hz, 1 H), 3.34 (dd, J = 1.2, 16 Hz, 1 H), 2.30 (m, 2 H), 1.84-1.99 (m, 3 H), 1.75 (m, 1 H) , 1.51-1.57 (m, 2 H), 1.37 (m, 1 H), 1.11 (s, 3 H), 0.28 (m, 1 H), 0.23 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 142.8, 141.7, 132.6, 130.1, 128.3, 125.7, 124.9, 123.4, 104.1, 97.1, 51.5, 37.0, 35.9, 35.1, 34.6, 29.6, 26.5, 25.9, 18.9, -0.03; IR (KBr) 2956, 2932, 2869, 2837, 2155, 1740, 1435, 1249, 870, 843, 759 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{32}O_2SiNa$ $(M + Na)^+$ 391.2064; found 391.2070.

Compound 16: This compound was prepared according to General Procedure C using 134 mg of compound **21**, and 227 mg of $LiOH{\cdot}H_2O$. Reaction was purified via flash column chromatography (DCM-EtOAc, 70 : 1). Yield was 99.4 mg (98%) of the desired product as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.35 (brs, 1 H), 7.47 (dd, J = 1.6, 8.4 Hz, 1 H), 7.28 (dt, J = 1.6, 8.4 Hz, 1 H), 7.08-7.18 (m, 2 H), 4.89 (s, 1 H), 3.48 (dd, J = 1.6, 16 Hz, 1 H), 3.40 (dd, J = 1.6, 16 Hz, 1 H), 3.20 (s, 1 H), 2.25-2.43 (m, 2 H), 1.96 (m, 1 H), 1.80-1.90 (s, 2 H), 1.73 (m, 1 H), 1.45-1.65 (m, 3 H), 1.36 (m, 1 H), 1.11 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

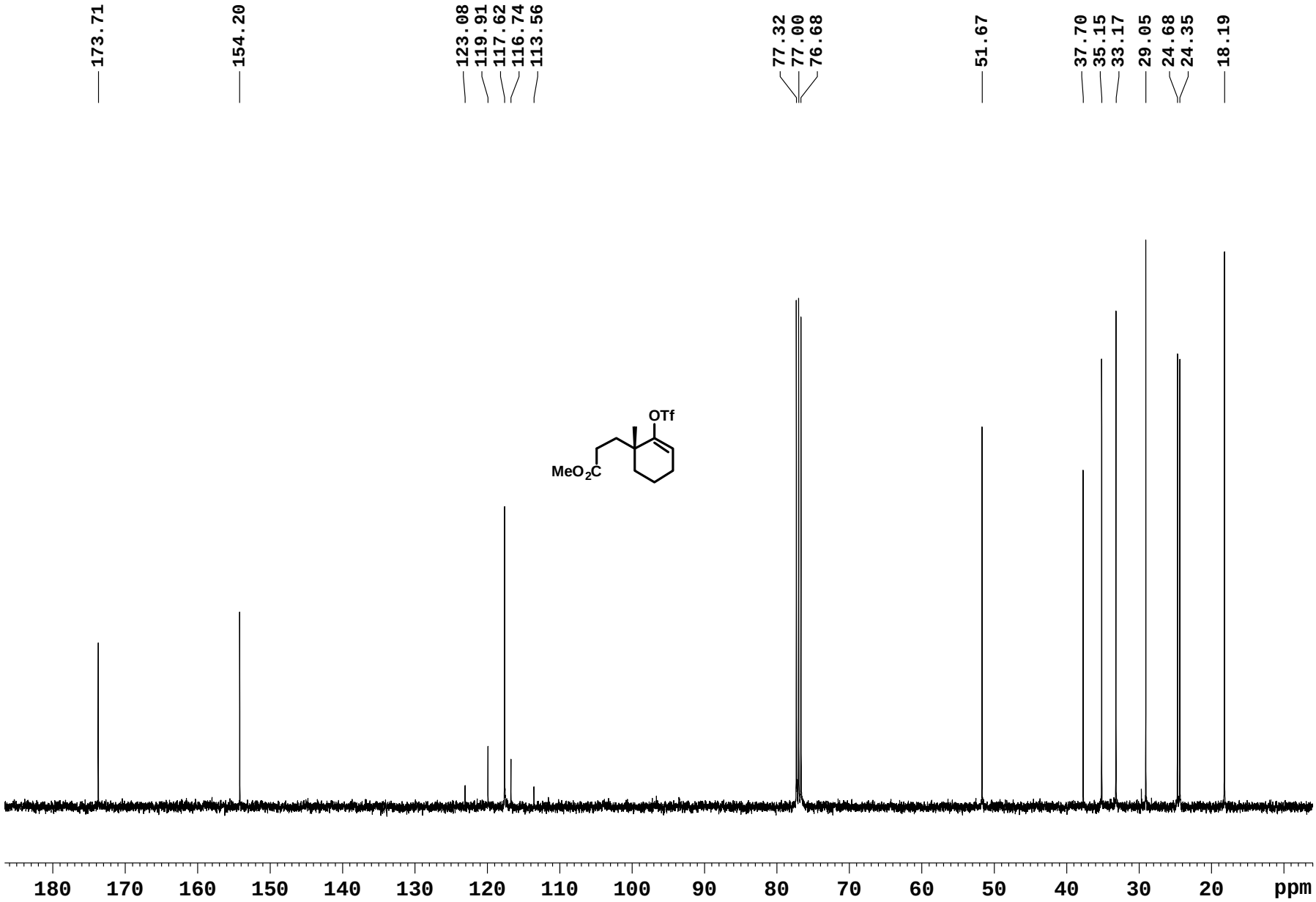
180.6, 143.0, 141.7, 132.8, 130.4, 128.6, 125.9, 125.1, 122.4, 82.6, 80.4, 37.0, 35.8, 35.1, 34.3, 29.5, 26.6, 25.9, 18.9; IR (KBr) 3295, 2930, 2102, 1736, 1707, 1447, 1374, 1245, 1047, 842, 759 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{21}O_2$ $(M - H)^+$ 281.1547; found 281.1544.

Compound 17: This compound was prepared according to General Procedure D using 16.8 mg of compound **16**, 1.52 mg of [Au(PPh_3)Cl], and 0.76 mg of AgOTf. Reaction was purified via flash column chromatography (DCM-EtOAc, 80 : 1). Yield was 6.33 mg (38%) of the desired product as a white solid. MP 157-158 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, J = 1.6, 8.0 Hz, 1 H), 7.12-7.22 (m, 2 H), 7.09 (dd, J = 0.8, 7.6 Hz, 1 H), 5.56 (s, 1 H), 5.03 (s, 1 H), 3.29 (d, J = 17.6 Hz, 1 H), 3.02 (d, J = 17.6 Hz, 1 H), 2.82 (dd, J = 2.8, 12.8 Hz, 1 H), 2.55-2.70 (m, 3 H), 1.64-1.78 (m, 3 H), 1.51-1.64 (m, 2 H), 1.31-1.48 (m, 2 H), 1.16 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 144.1, 132.1, 131.6, 129.3, 128.0, 126.3, 124.4, 111.0, 87.2, 48.3, 37.3, 34.3, 33.2, 32.2, 27.7, 26.4, 21.7, 20.2; IR (KBr) 2930, 2855, 1712, 1489, 1455, 1280, 1045, 1017, 898, 776, 746 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{23}O_2$ $(M + H)^+$ 283.1693; found 283.1694.

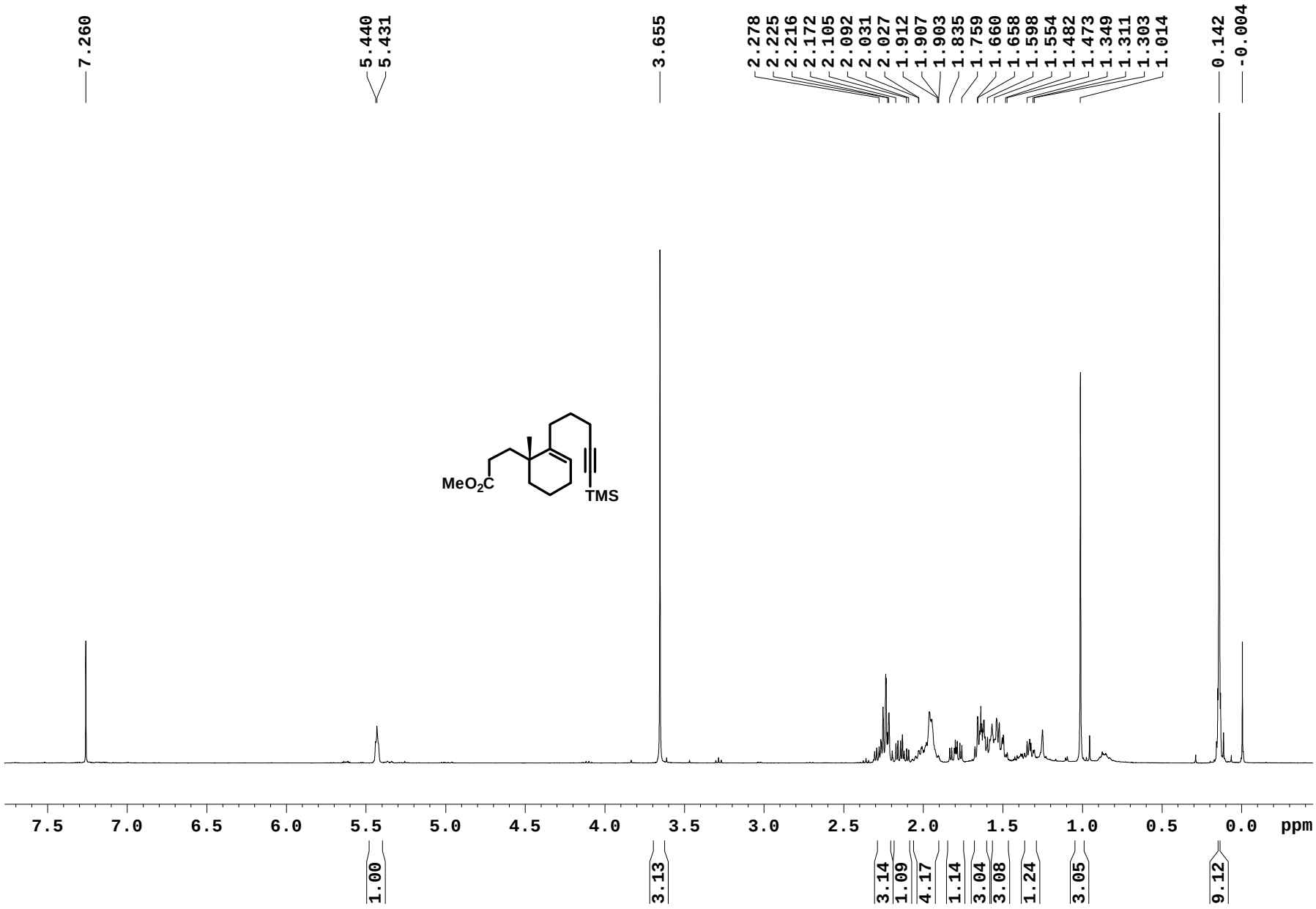
^{1}H-NMR of compound 8 (400 MHz, $CDCl_3$)



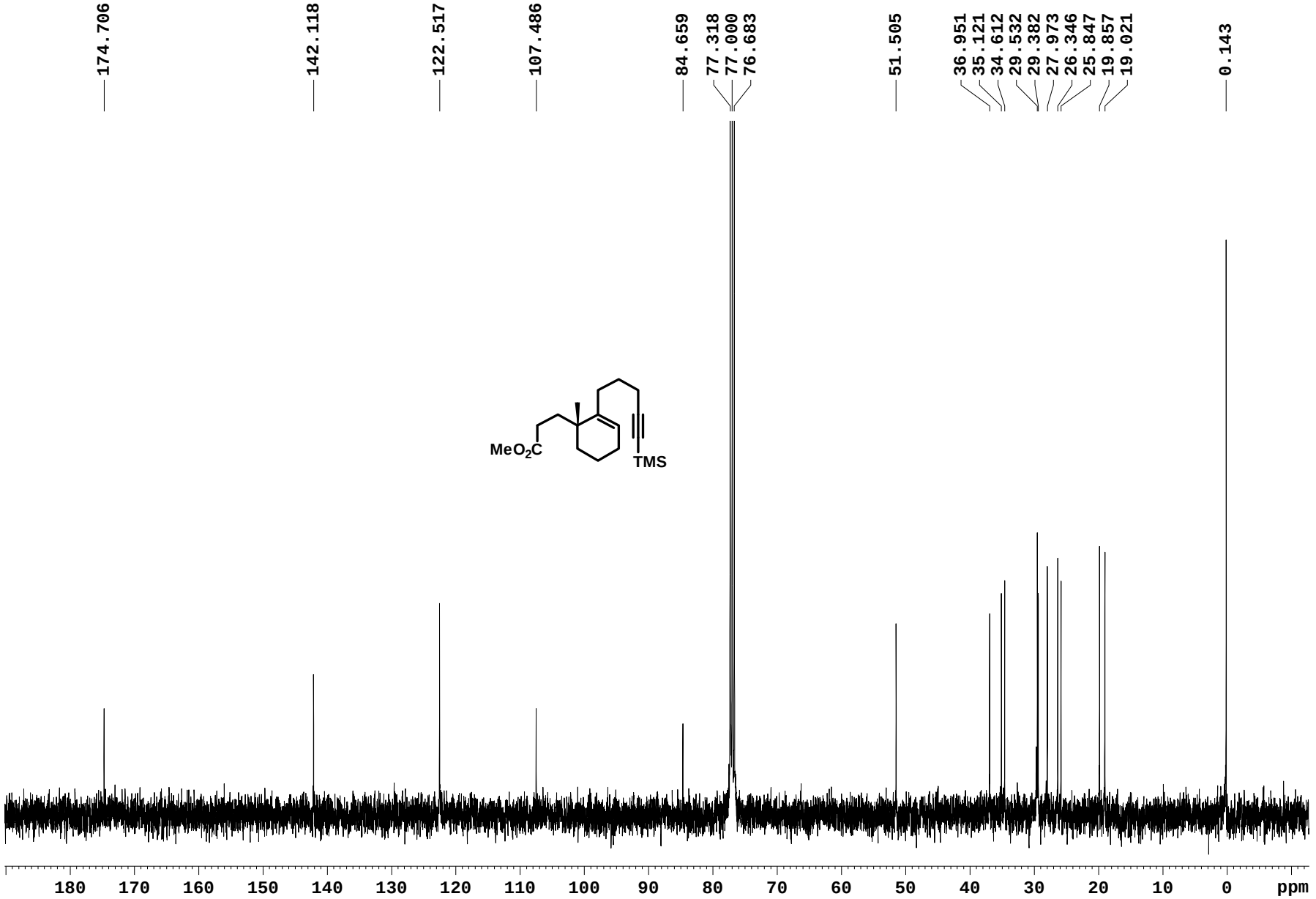
^{13}C-NMR of compound 8 (100 MHz, $CDCl_3$)



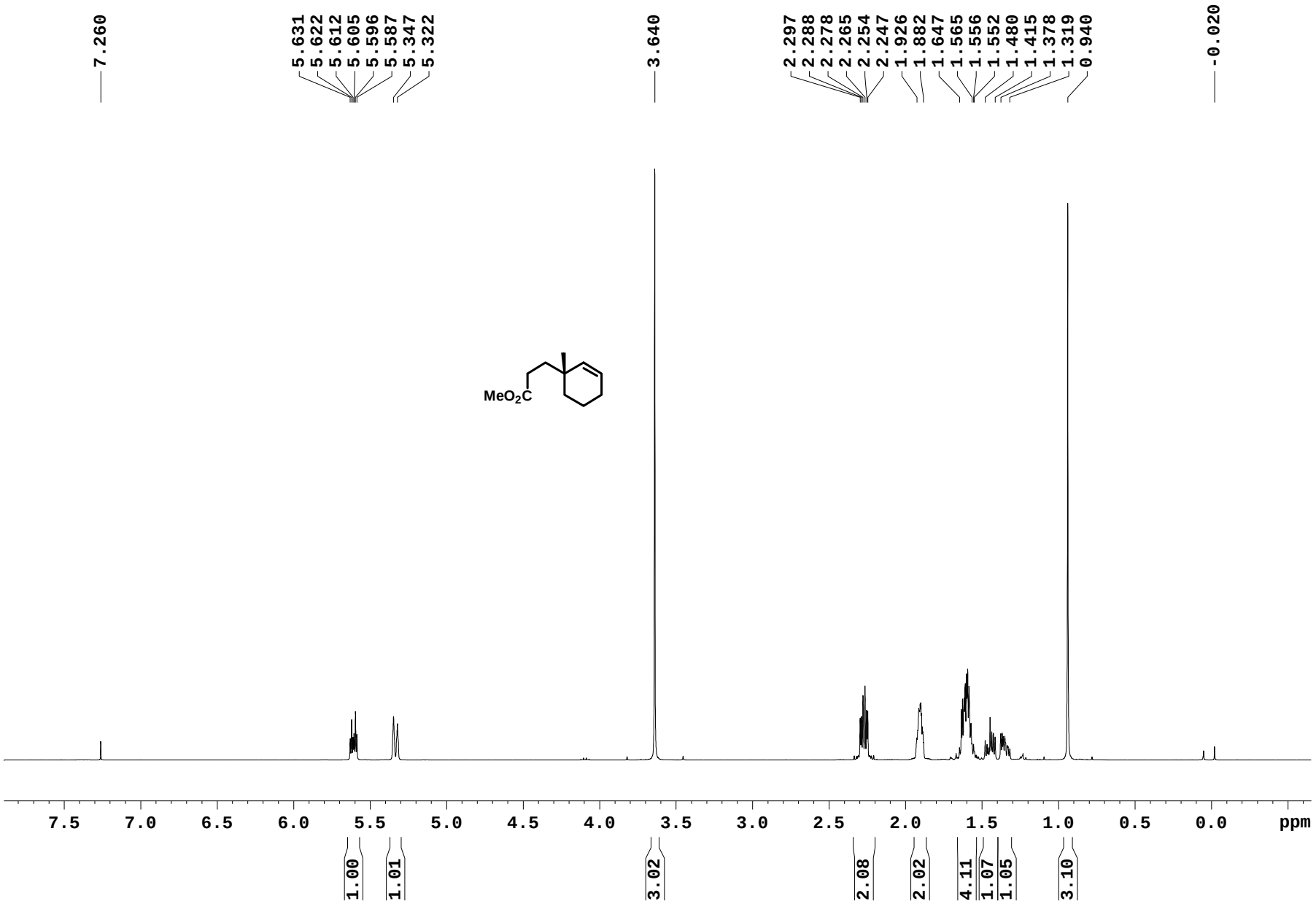
^{1}H-NMR of compound 10 (400 MHz, $CDCl_3$)



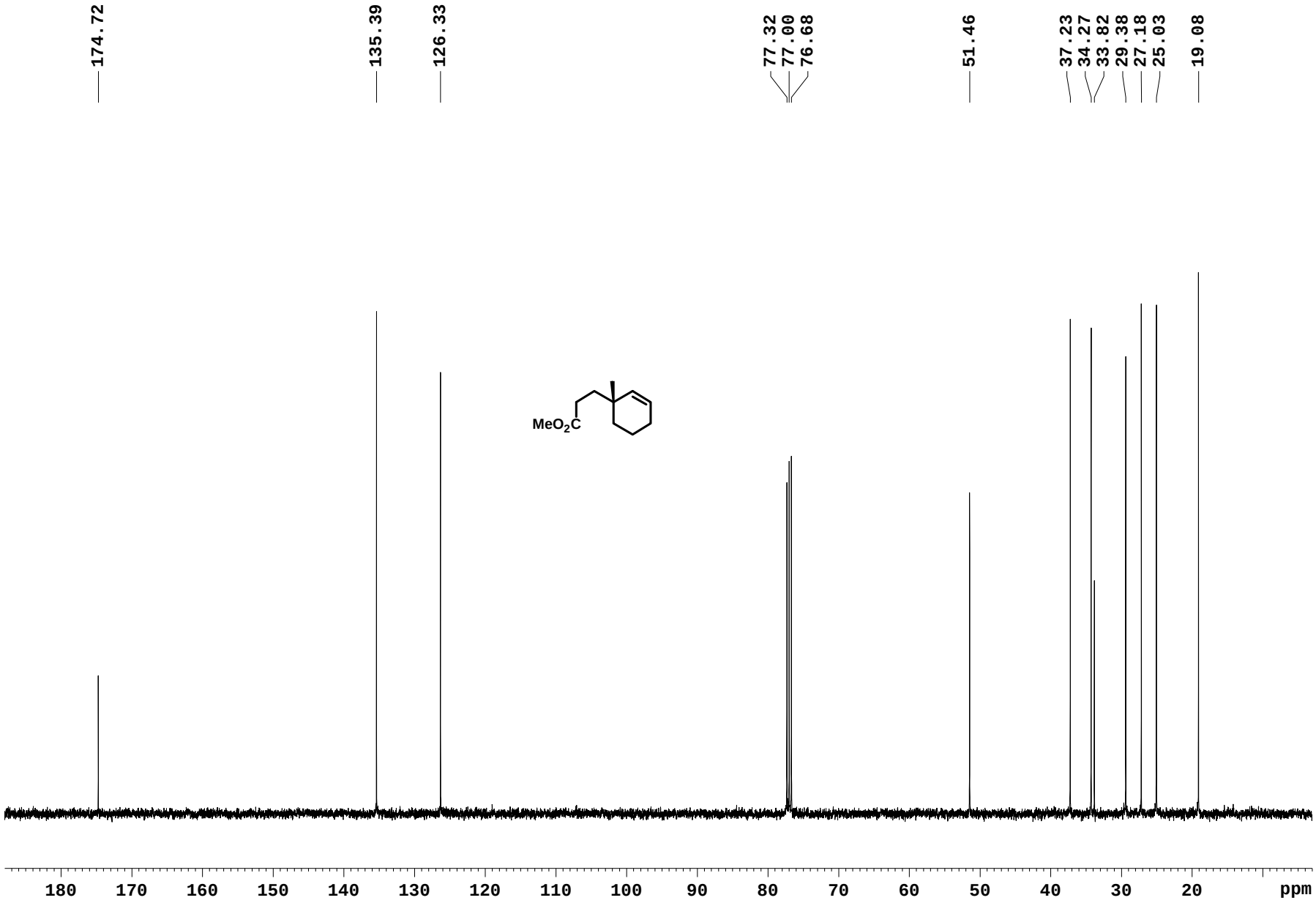
^{13}C-NMR of compound 10 (100 MHz, $CDCl_3$)



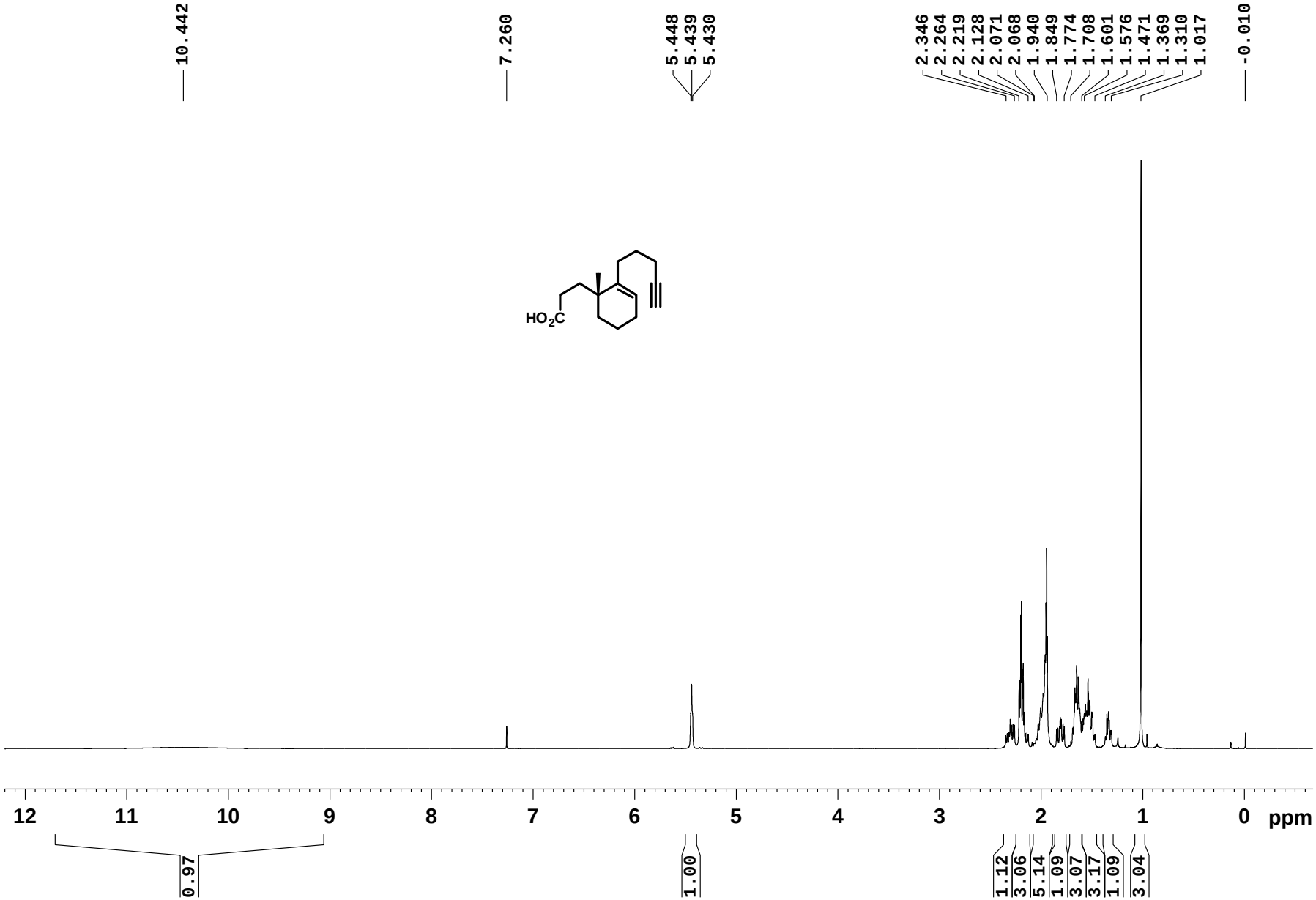
^{1}H-NMR of compound 11 (400 MHz, $CDCl_3$)



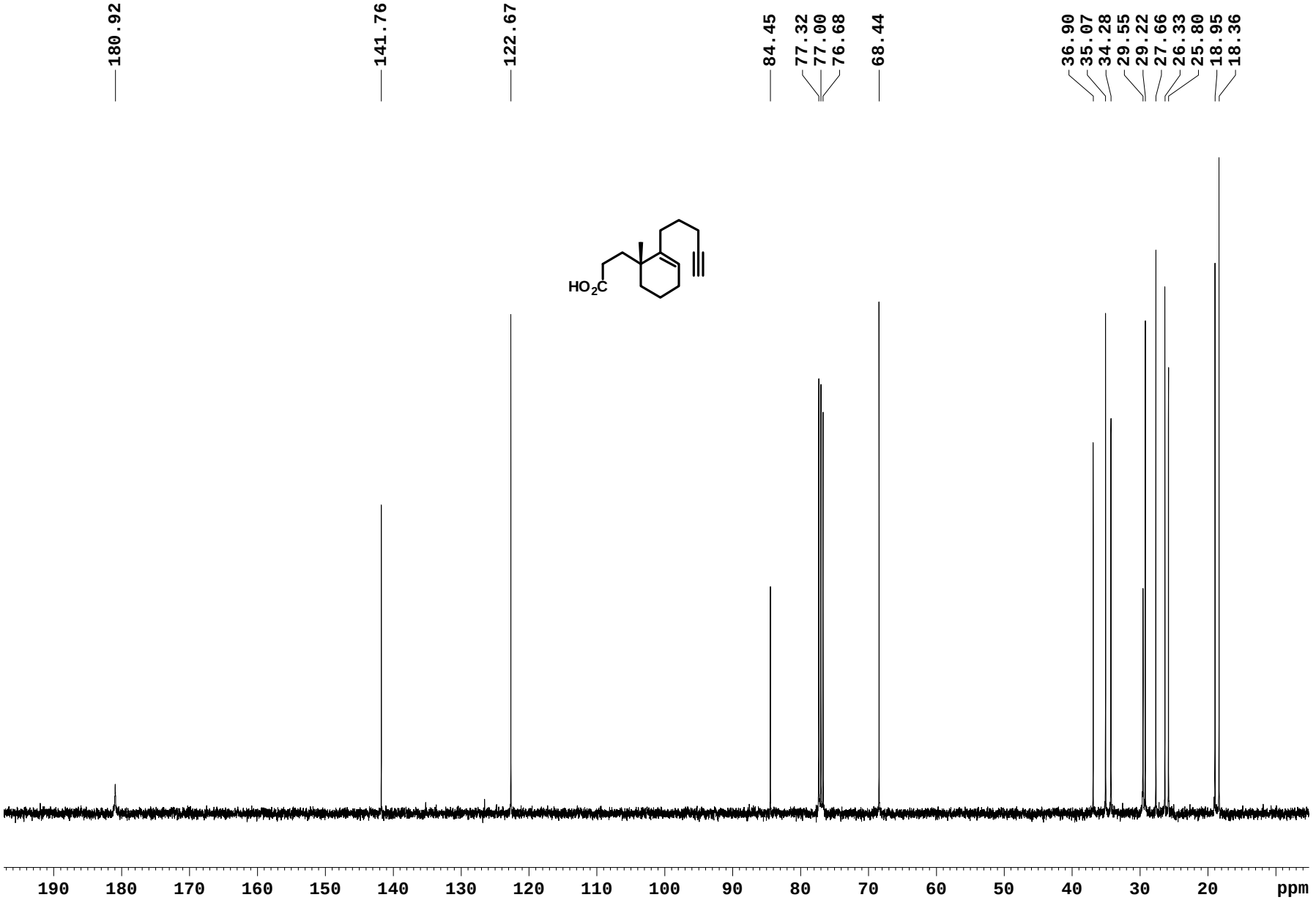
^{13}C-NMR of compound 11 (100 MHz, $CDCl_3$)



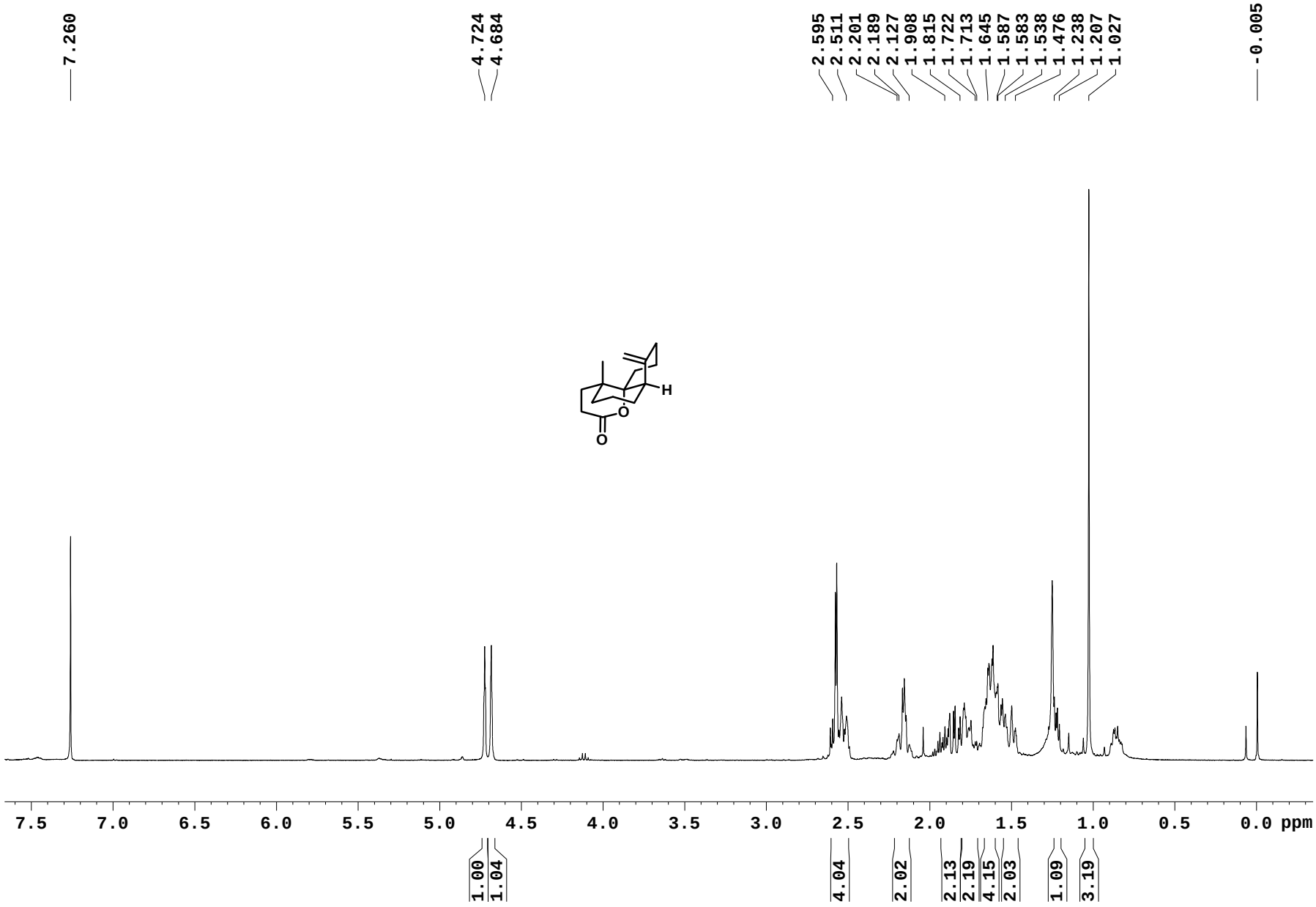
^{1}H-NMR of compound 6 (400 MHz, $CDCl_3$)



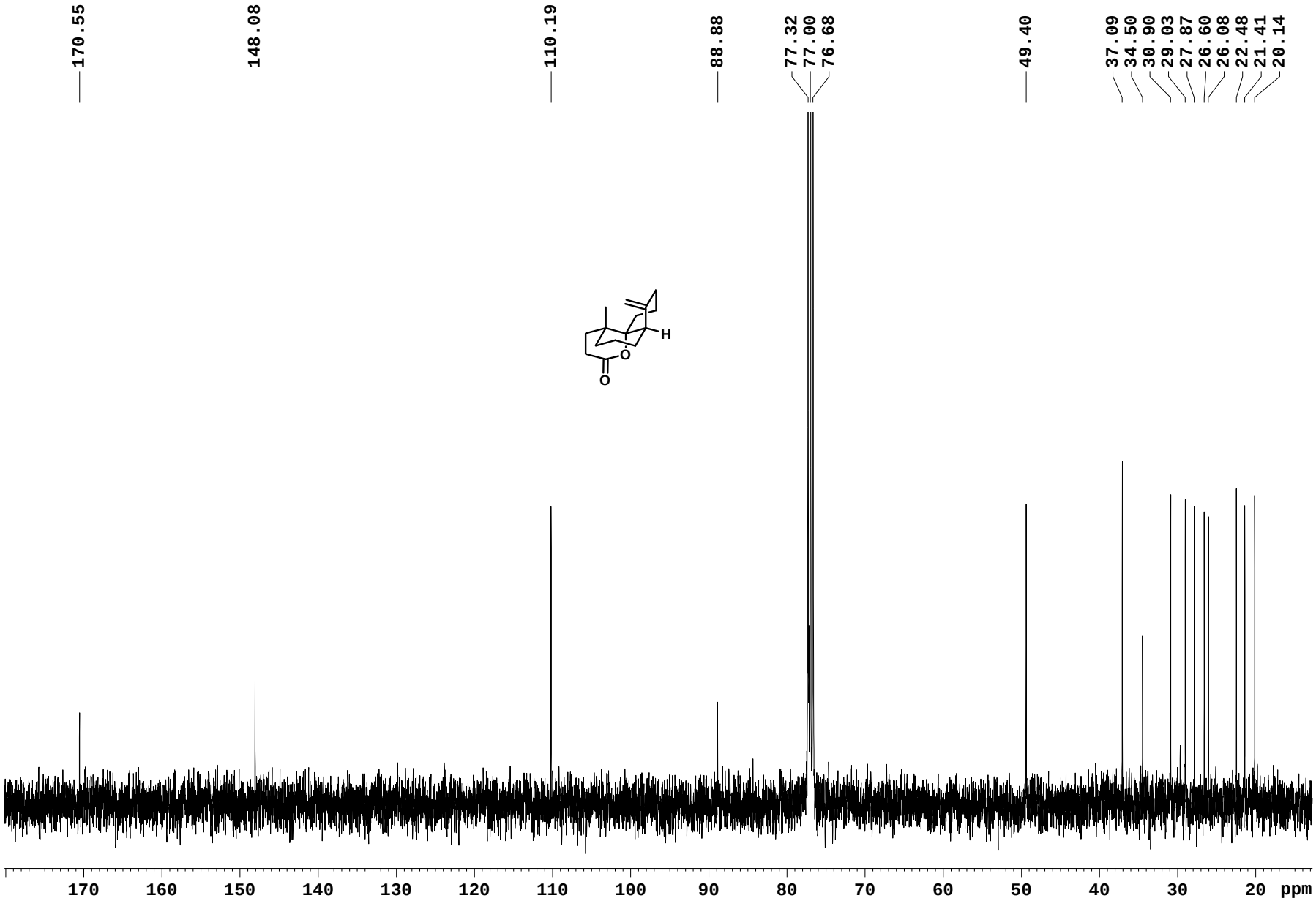
^{13}C-NMR of compound 6 (100 MHz, $CDCl_3$)



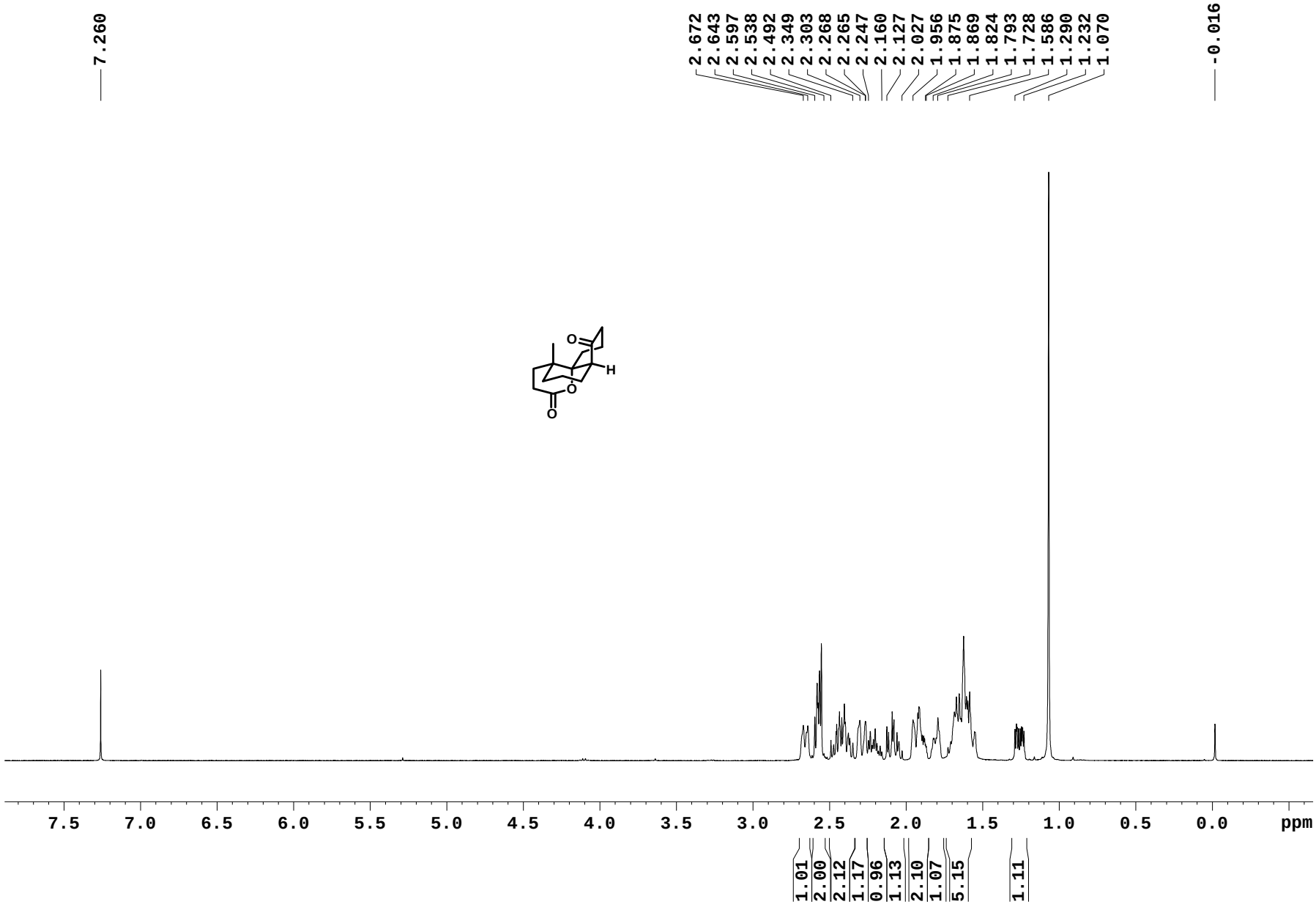
^{1}H-NMR of compound 5 (400 MHz, $CDCl_3$)



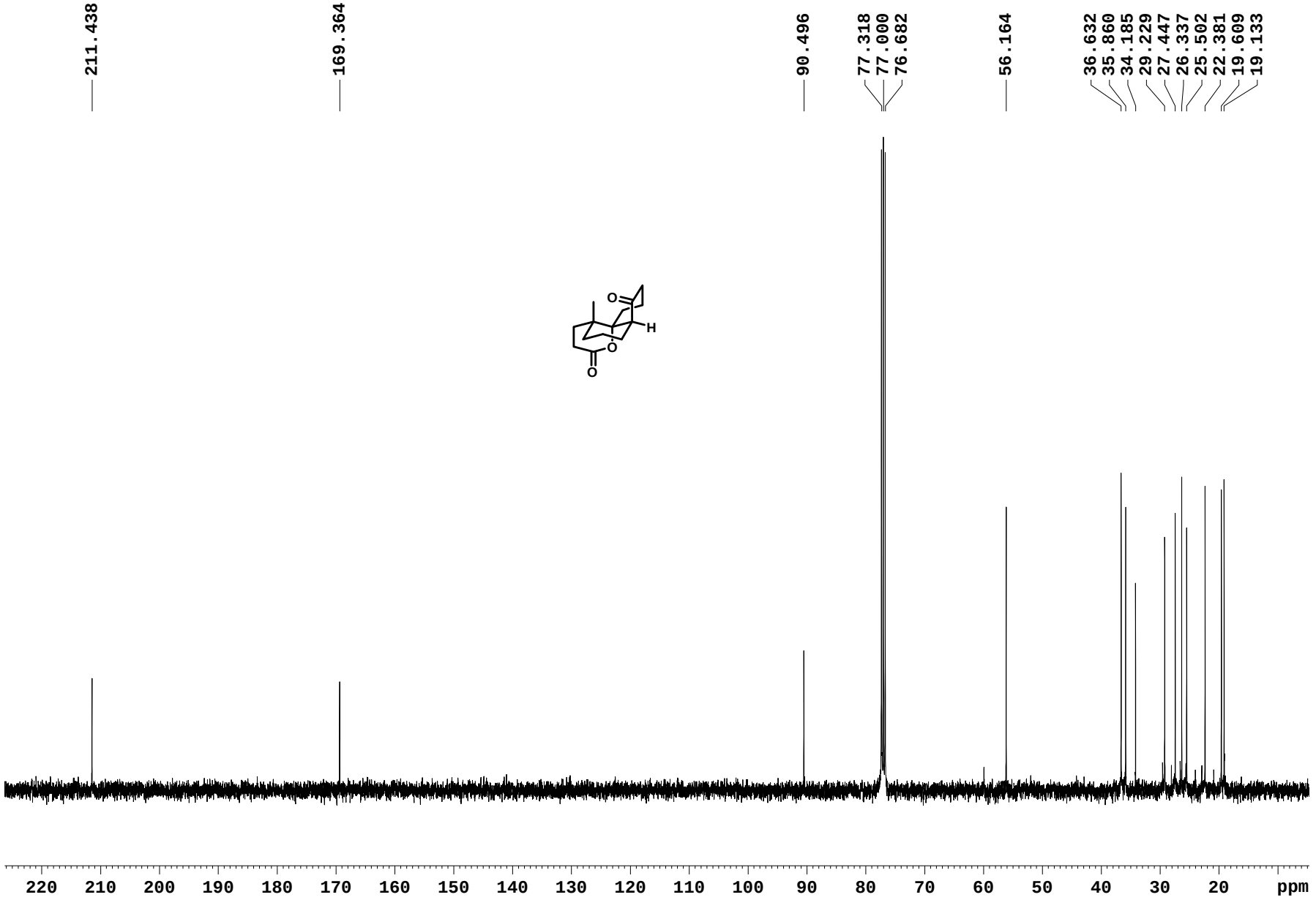
^{13}C-NMR of compound 5 (100 MHz, $CDCl_3$)



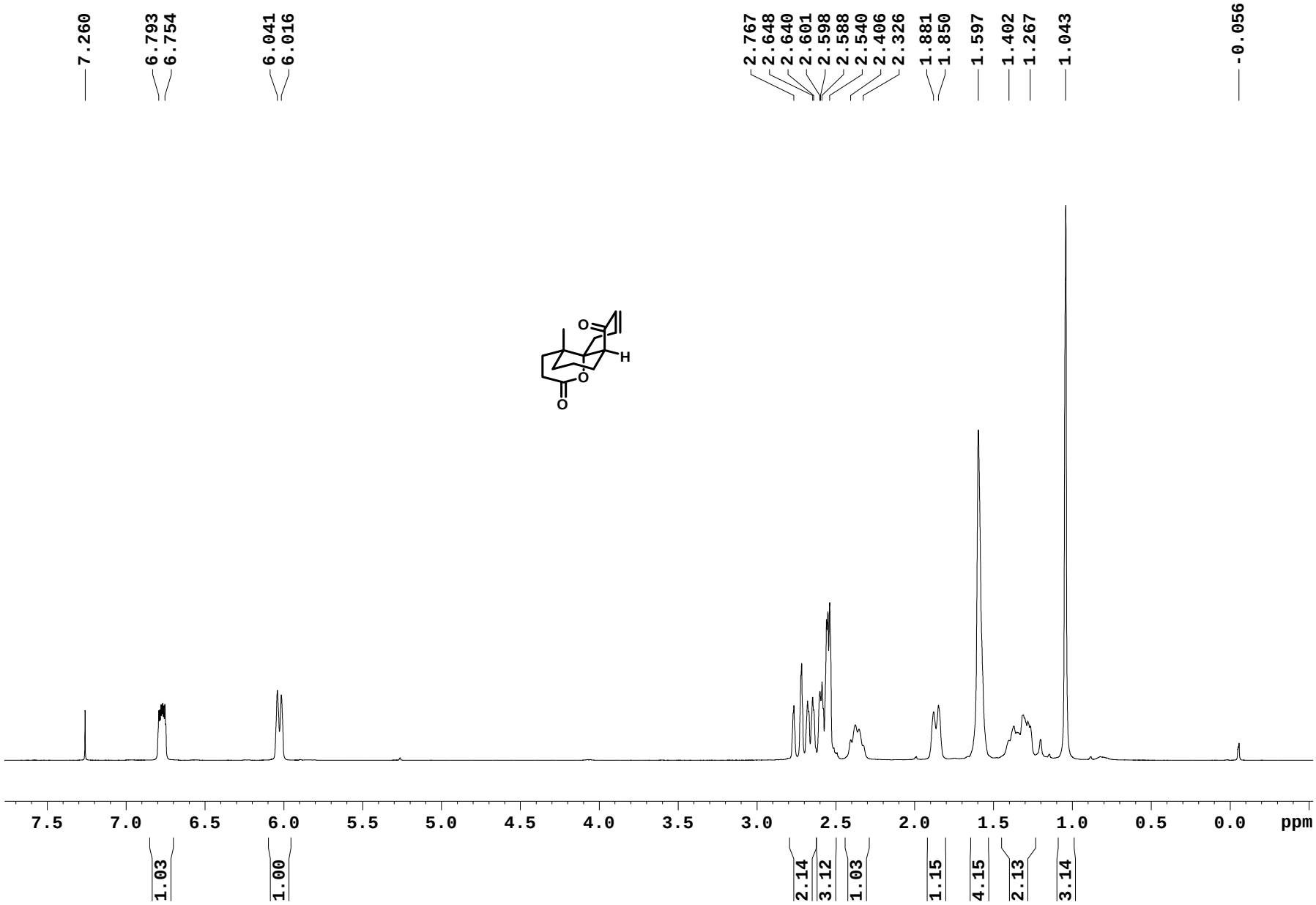
^{1}H-NMR of compound 12 (400 MHz, $CDCl_3$)



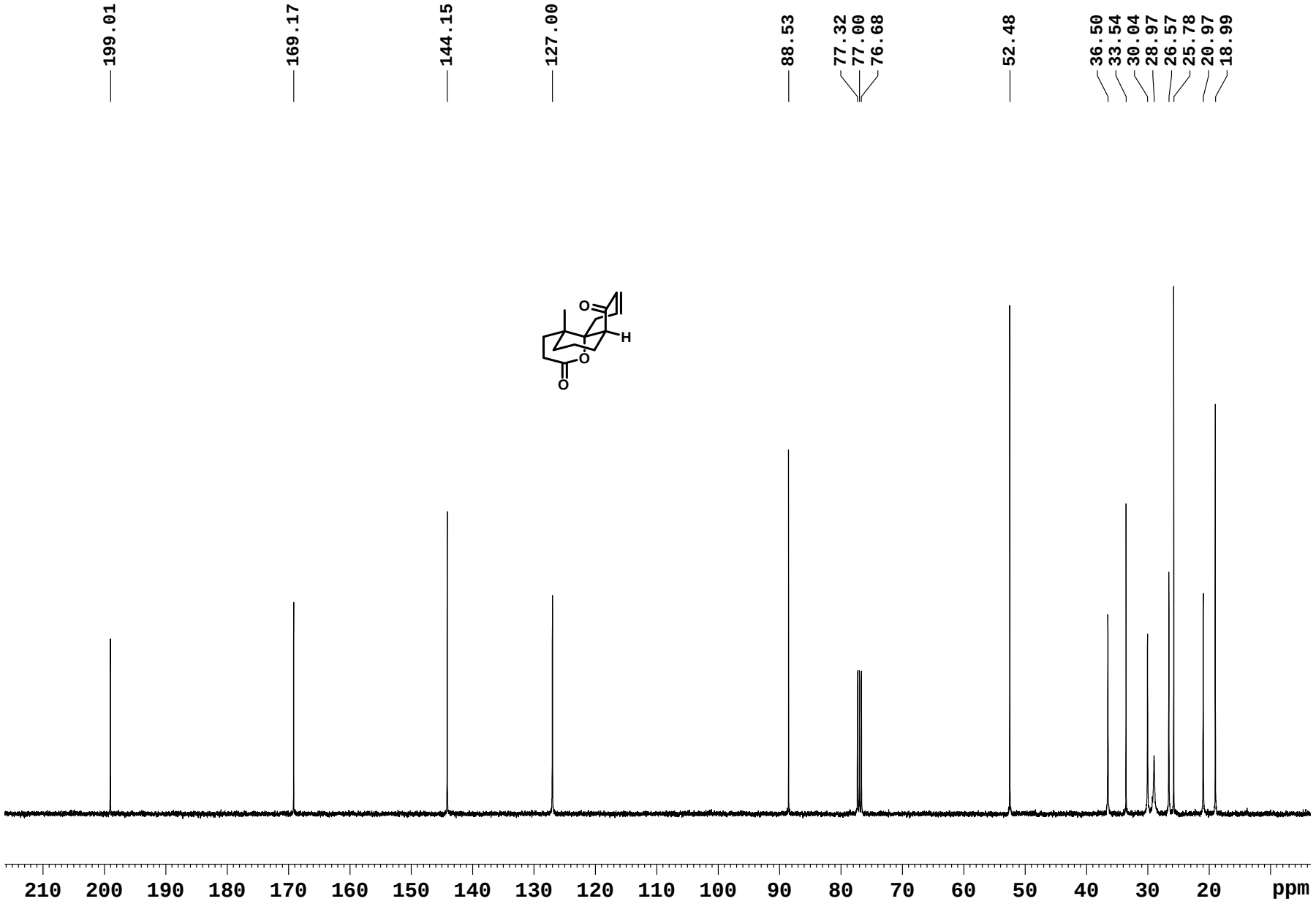
^{13}C-NMR of compound 12 (100 MHz, $CDCl_3$)



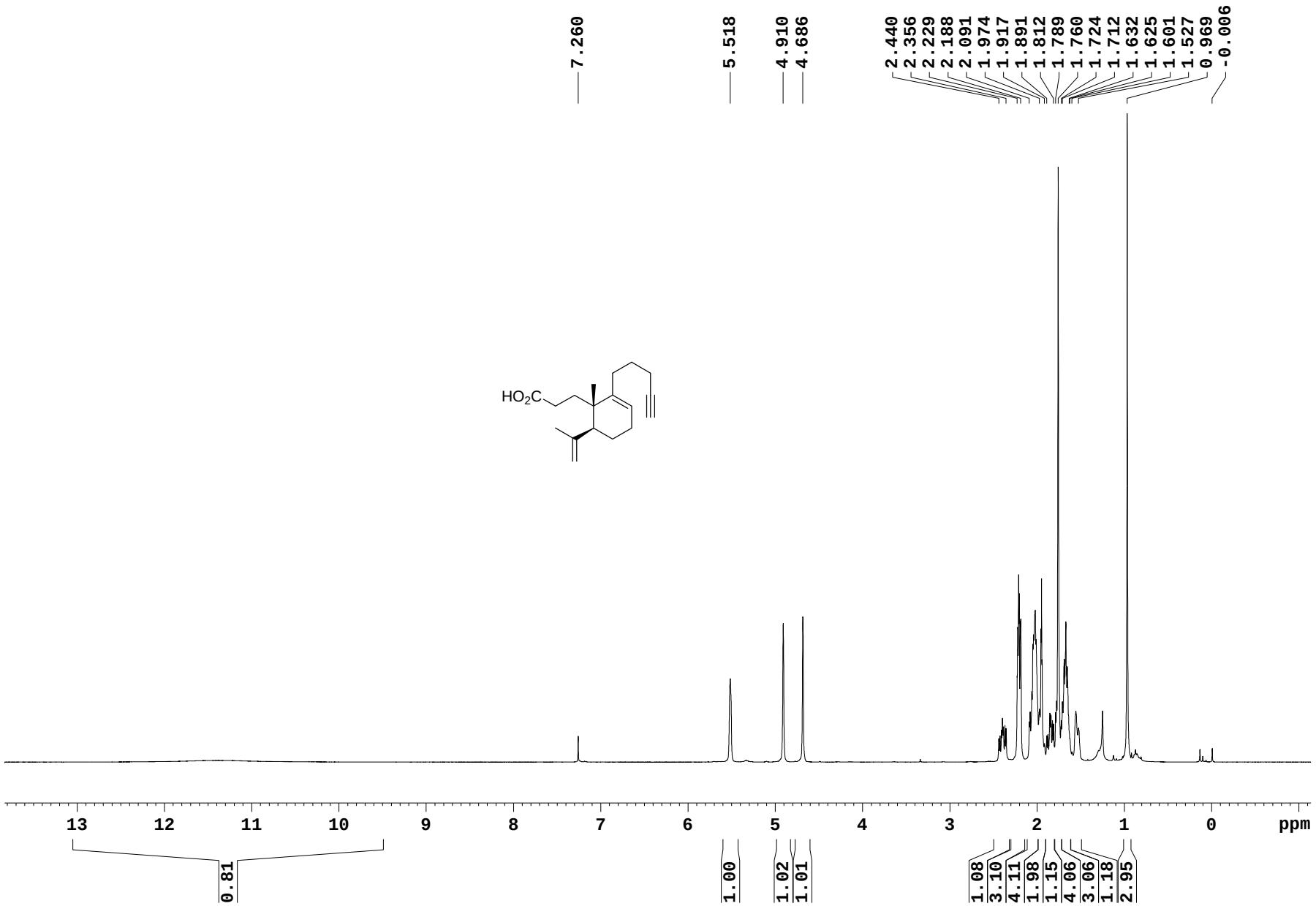
^{1}H-NMR of compound 13 (400 MHz, $CDCl_3$)



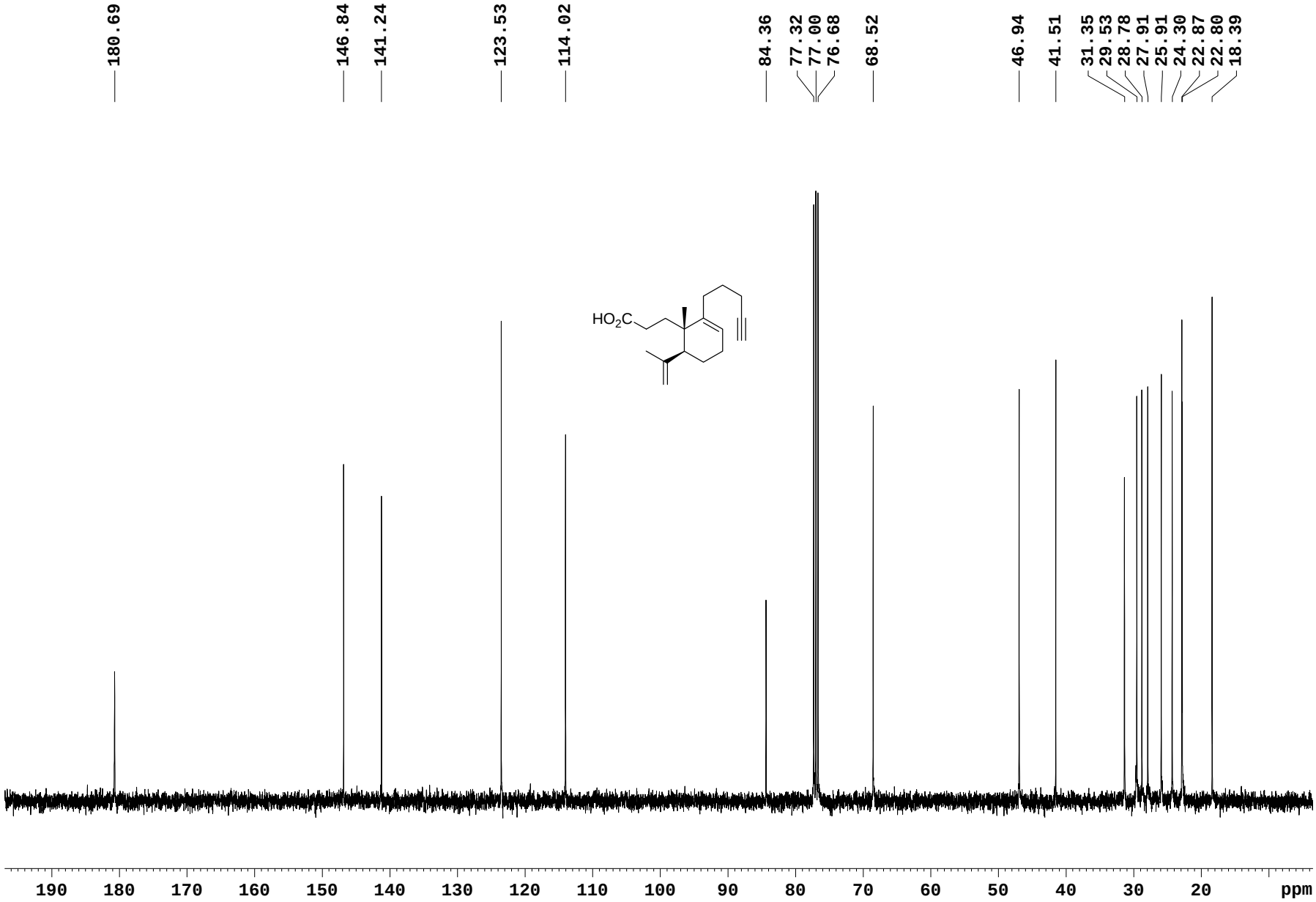
^{13}C-NMR of compound 13 (100 MHz, $CDCl_3$)



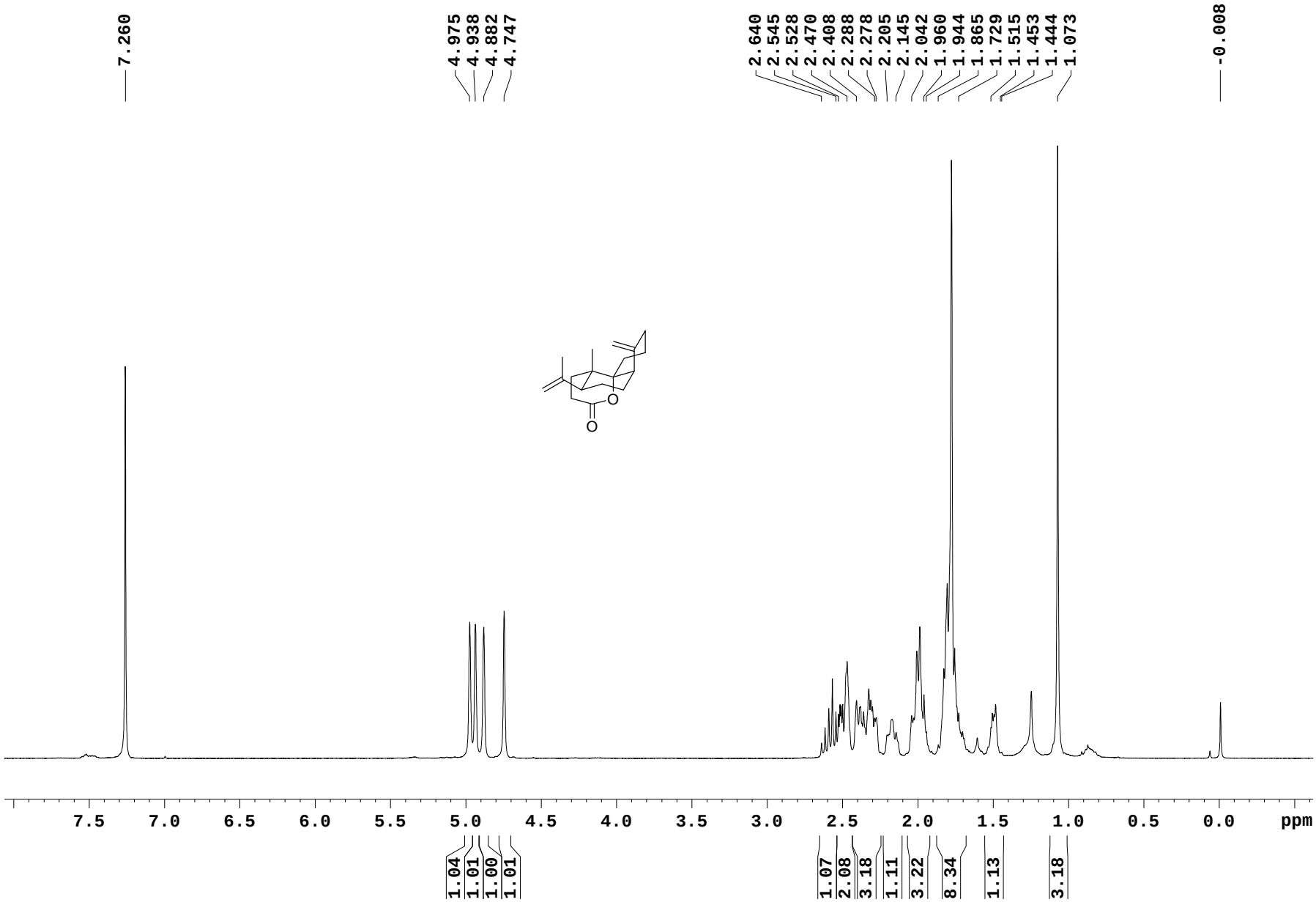
^{1}H-NMR of compound 4 (400 MHz, $CDCl_3$)



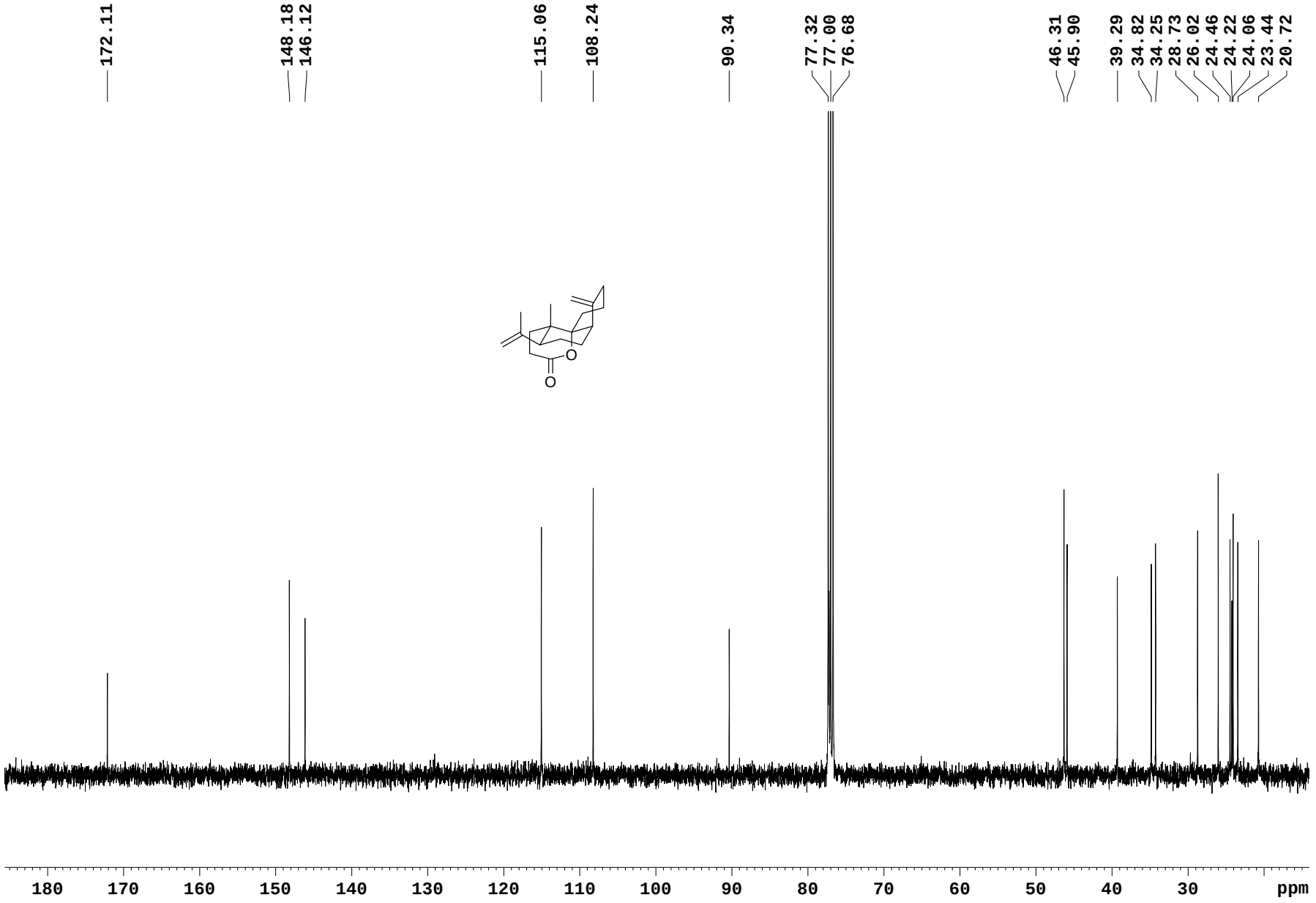
^{13}C-NMR of compound 4 (100 MHz, $CDCl_3$)



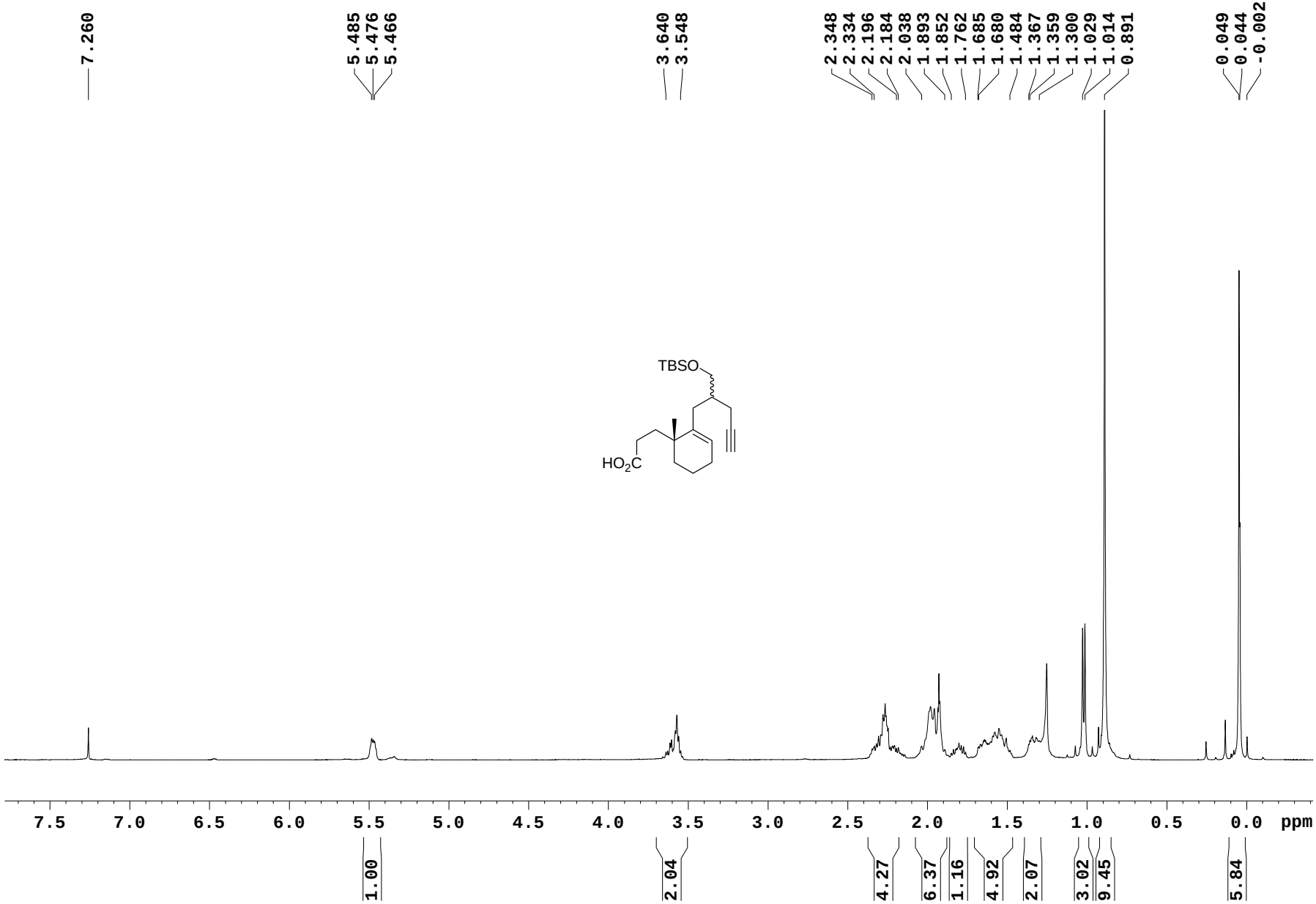
^{1}H-NMR of compound 3 (400 MHz, $CDCl_3$)



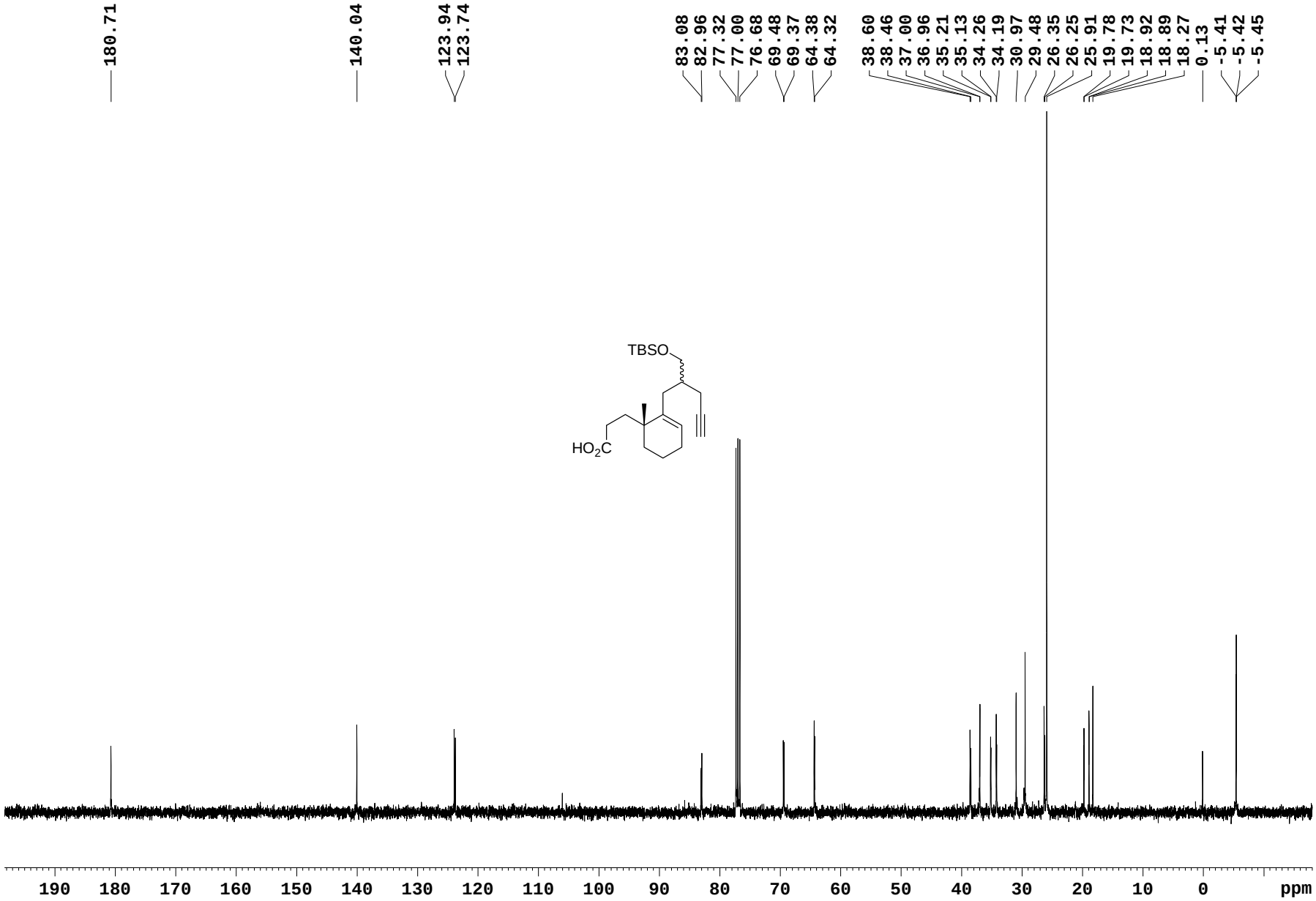
^{13}C-NMR of compound 3 (100 MHz, $CDCl_3$)



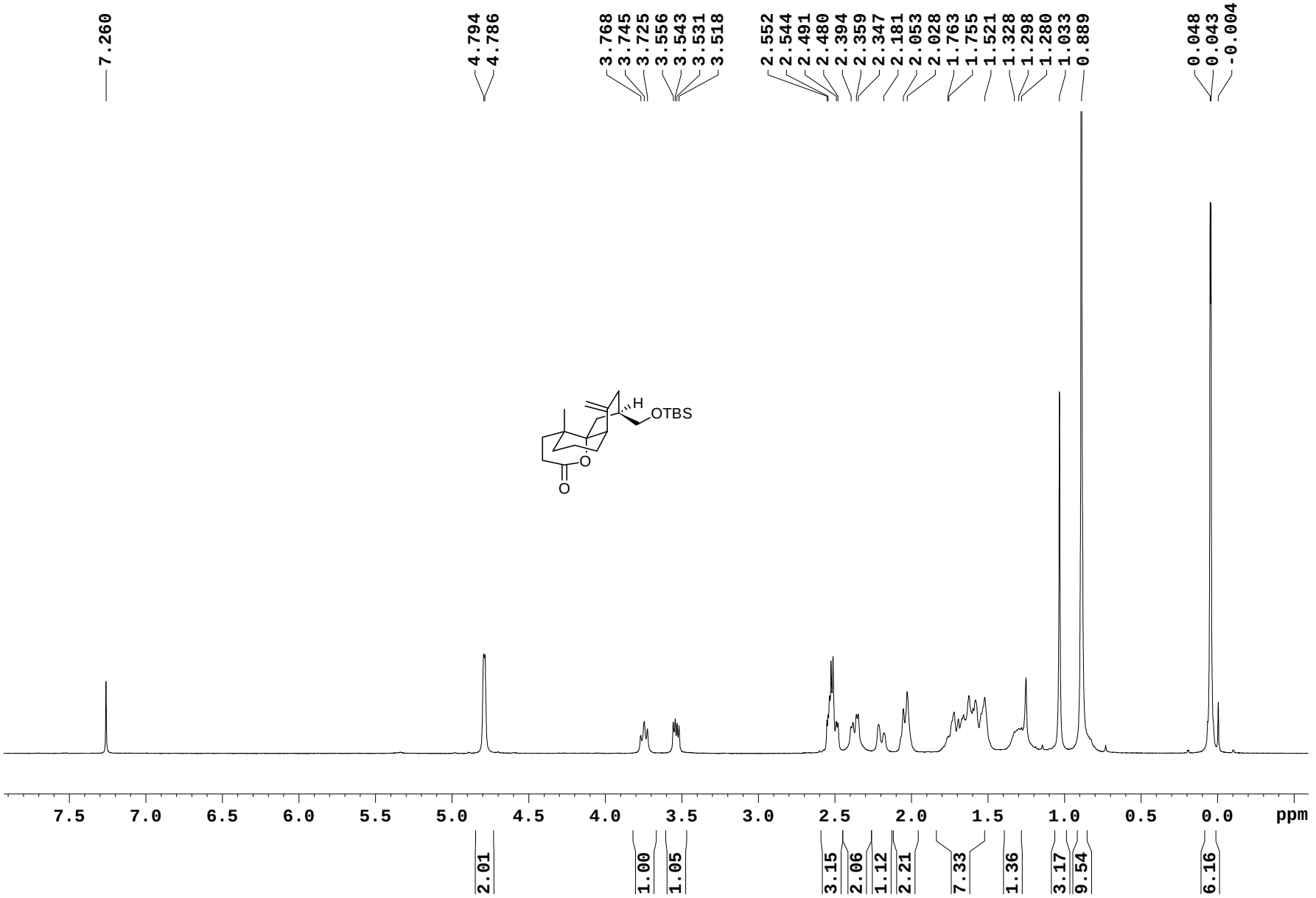
^{1}H-NMR of compound 14 (400 MHz, $CDCl_3$)



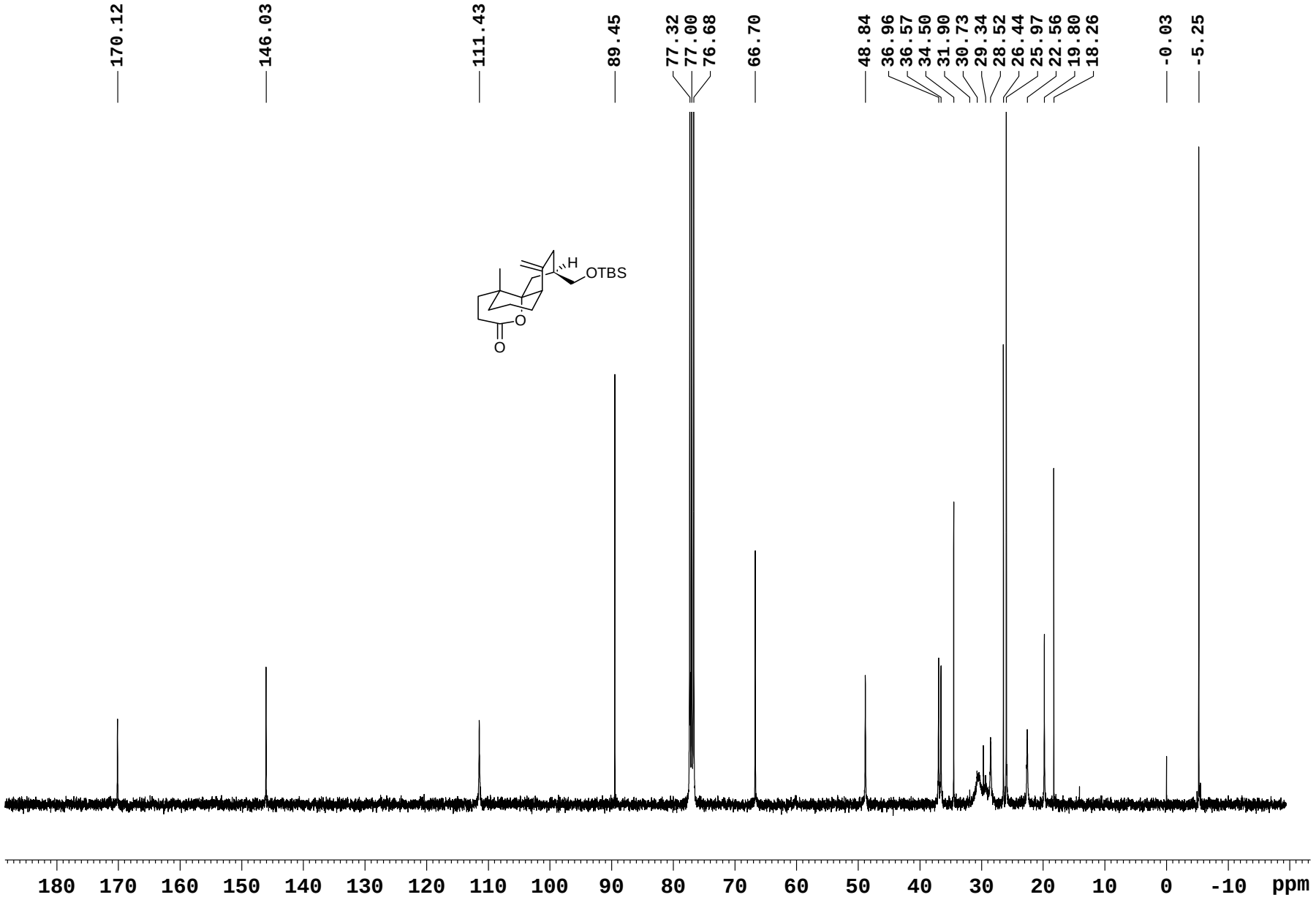
^{13}C-NMR of compound 14 (100 MHz, $CDCl_3$)



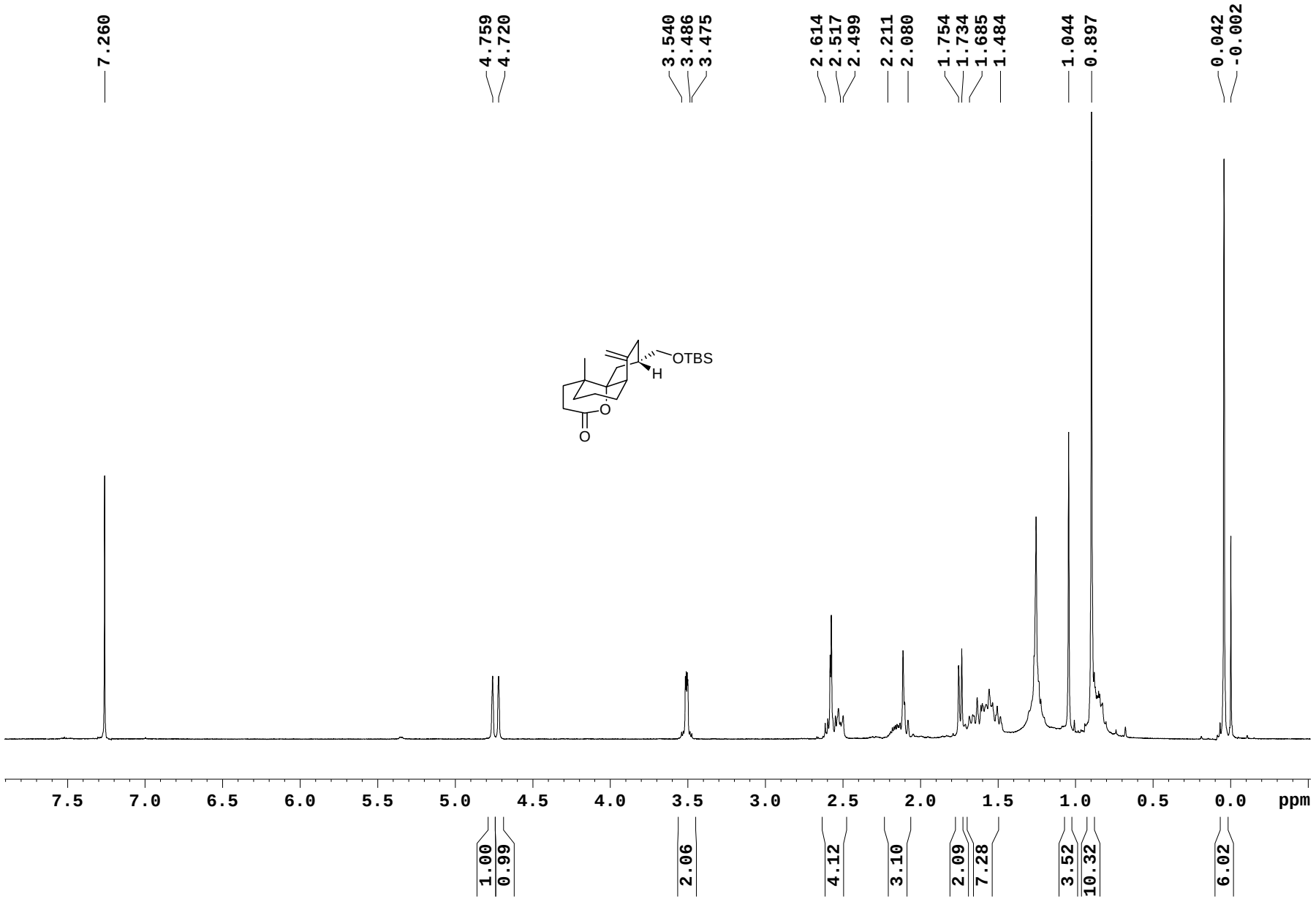
^{1}H-NMR of compound 15 (The β-diastereomer) (400 MHz, $CDCl_3$)



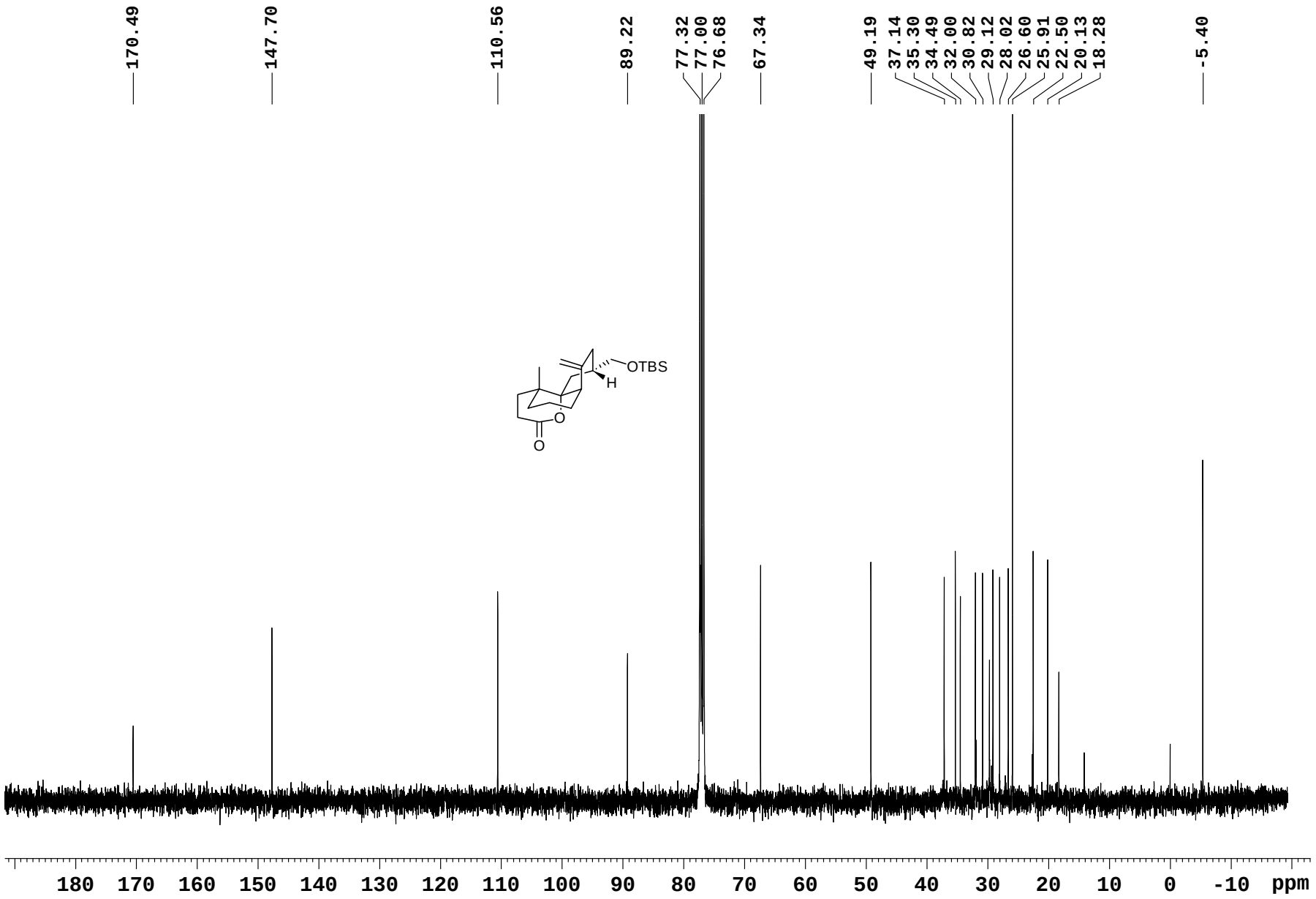
^{13}C-NMR of compound 15 (The β-diastereomer) (100 MHz, $CDCl_3$)



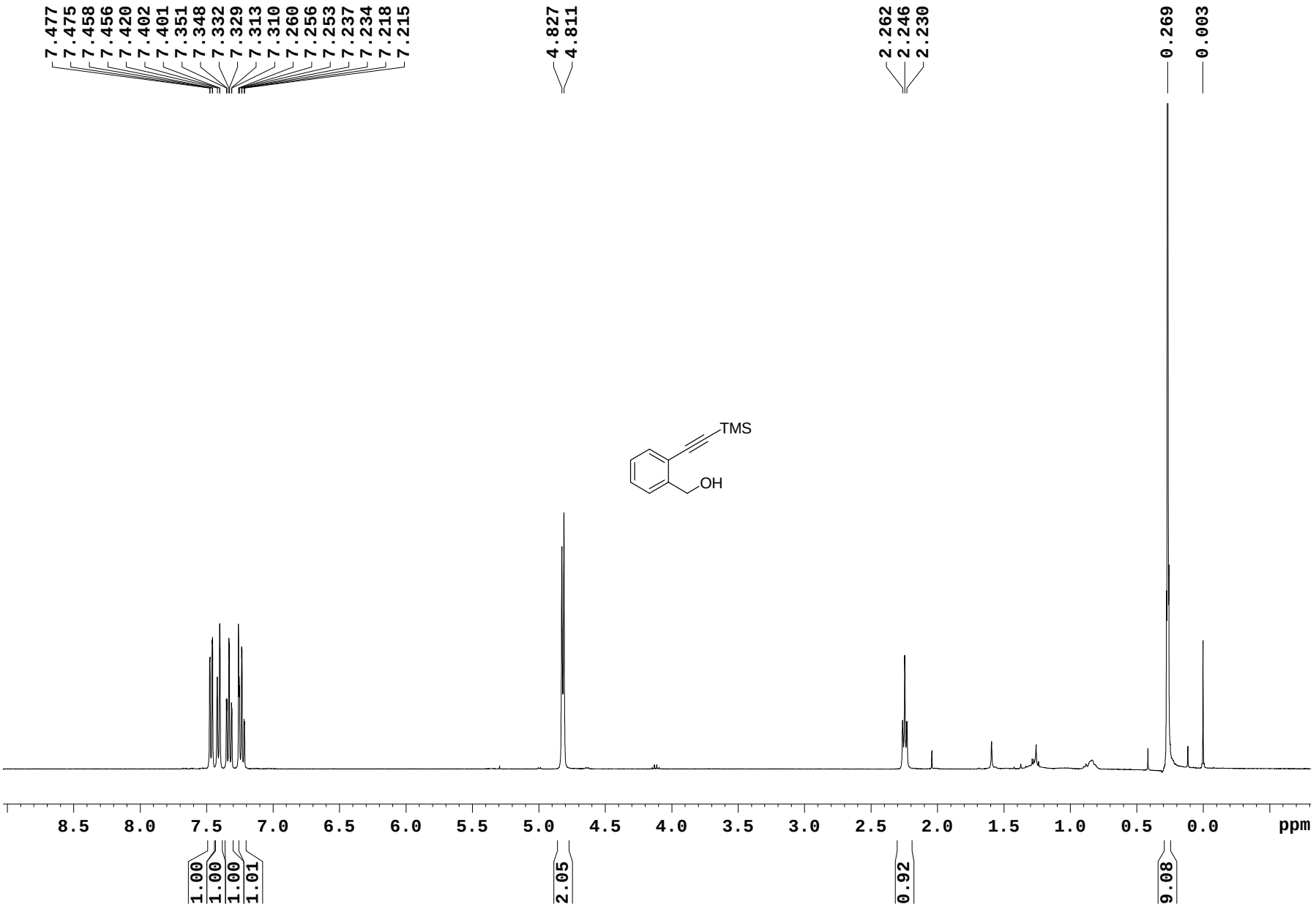
^{1}H-NMR of compound 15 (The α-diastereomer) (400 MHz, $CDCl_3$)



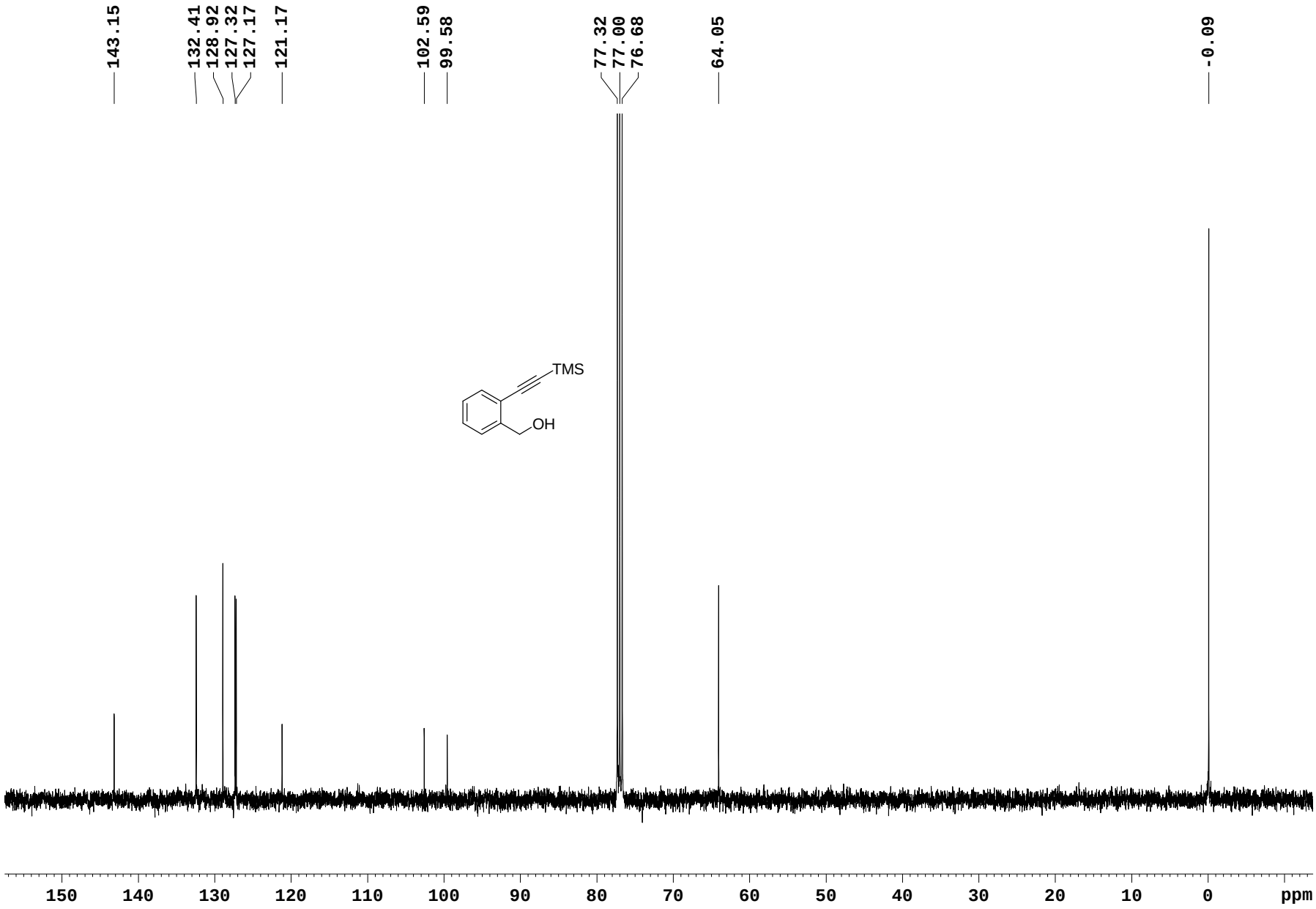
^{13}C-NMR of compound 15 (The *α*-diastereomer) (100 MHz, $CDCl_3$)



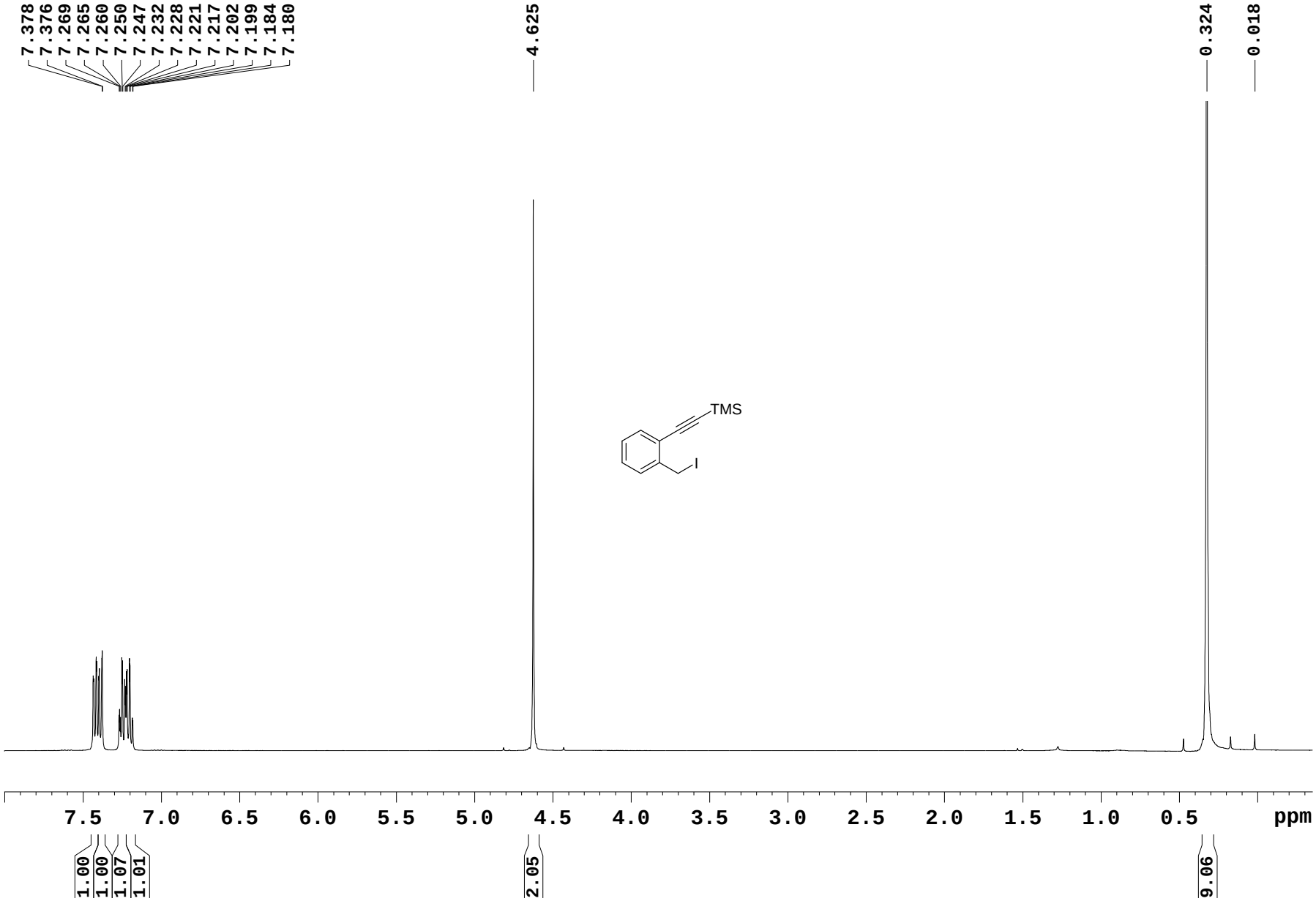
^{1}H-NMR of compound 19 (400 MHz, $CDCl_3$)



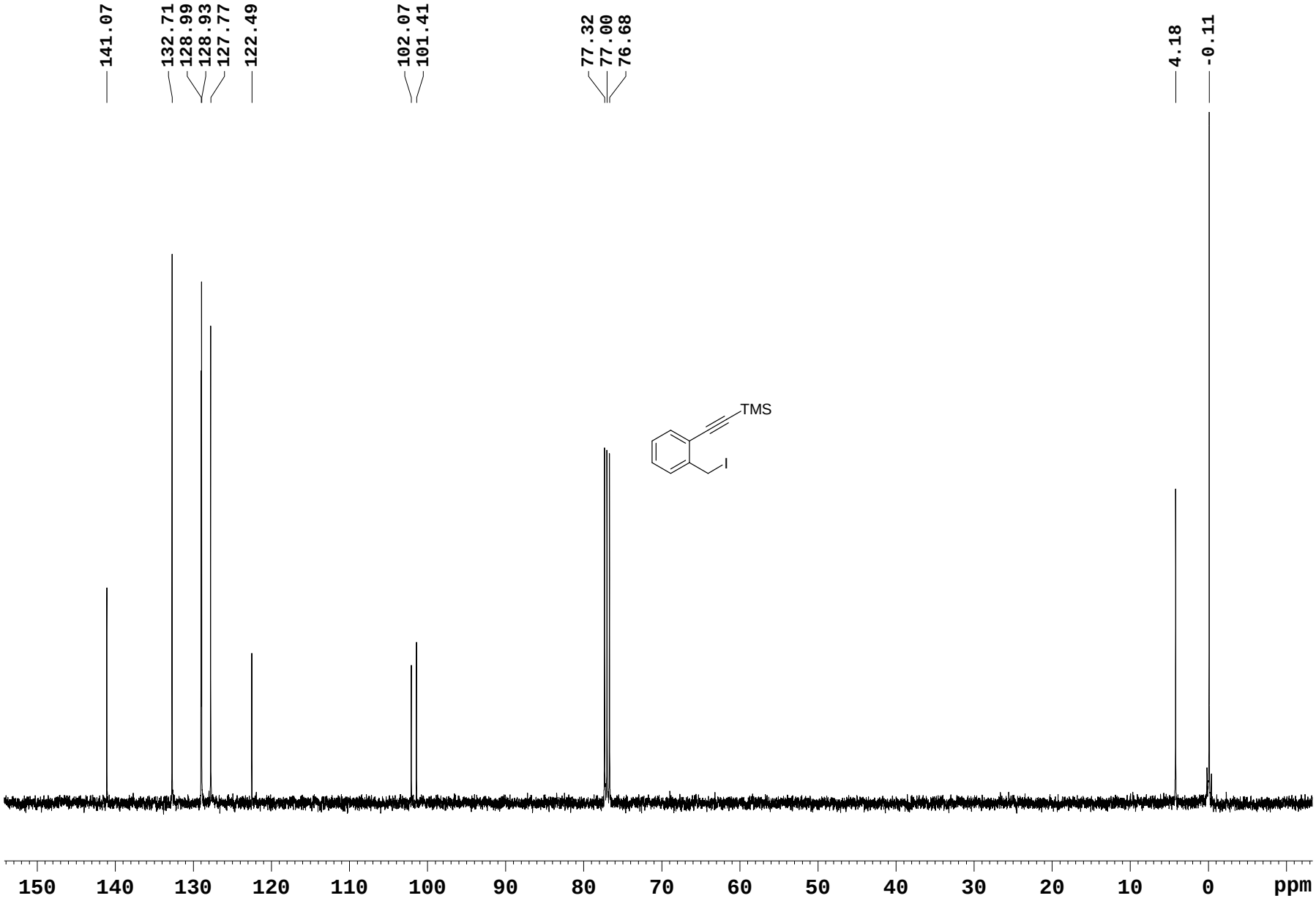
^{13}C-NMR of compound 19 (100 MHz, $CDCl_3$)



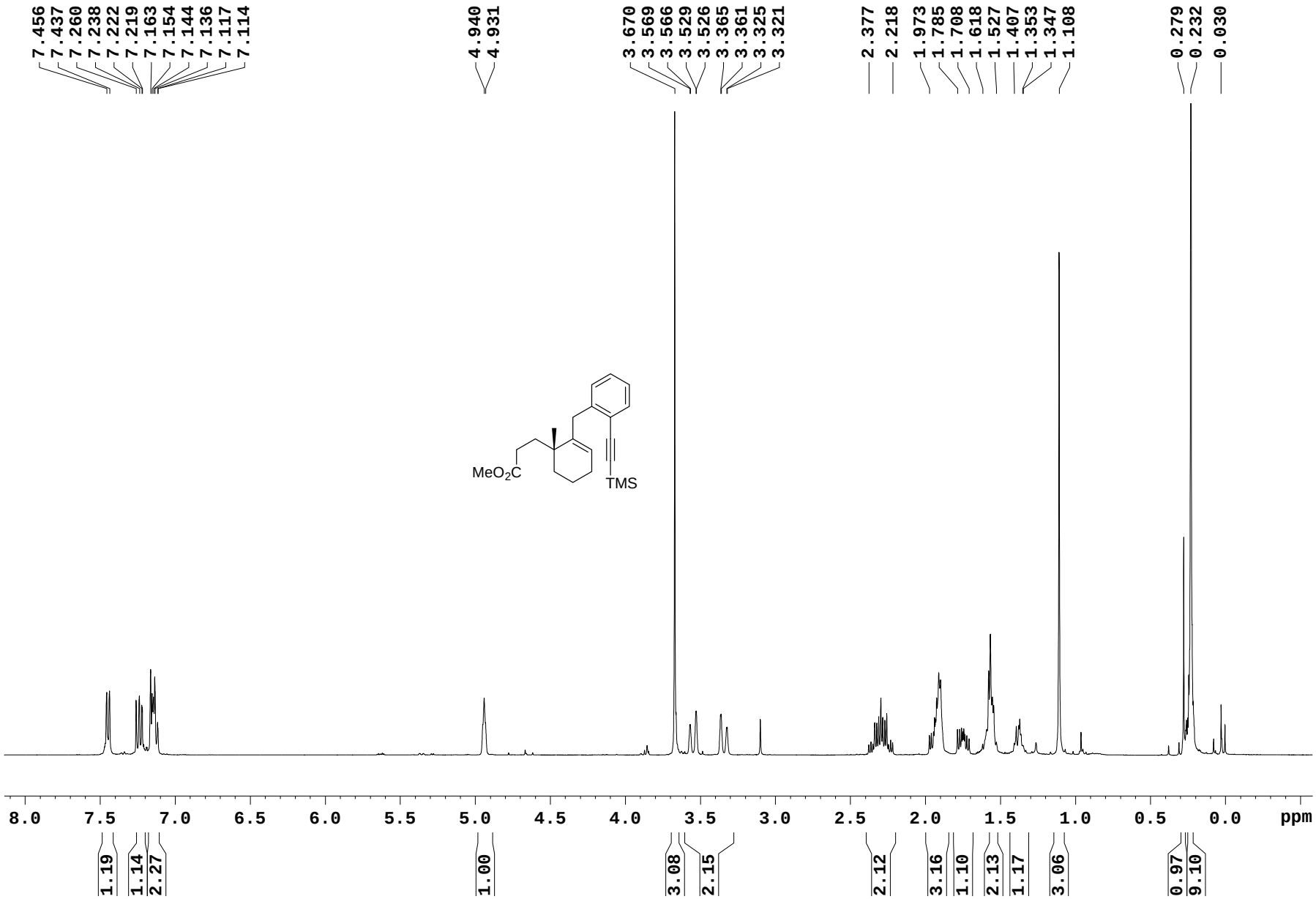
^{1}H-NMR of compound 20 (400 MHz, $CDCl_3$)



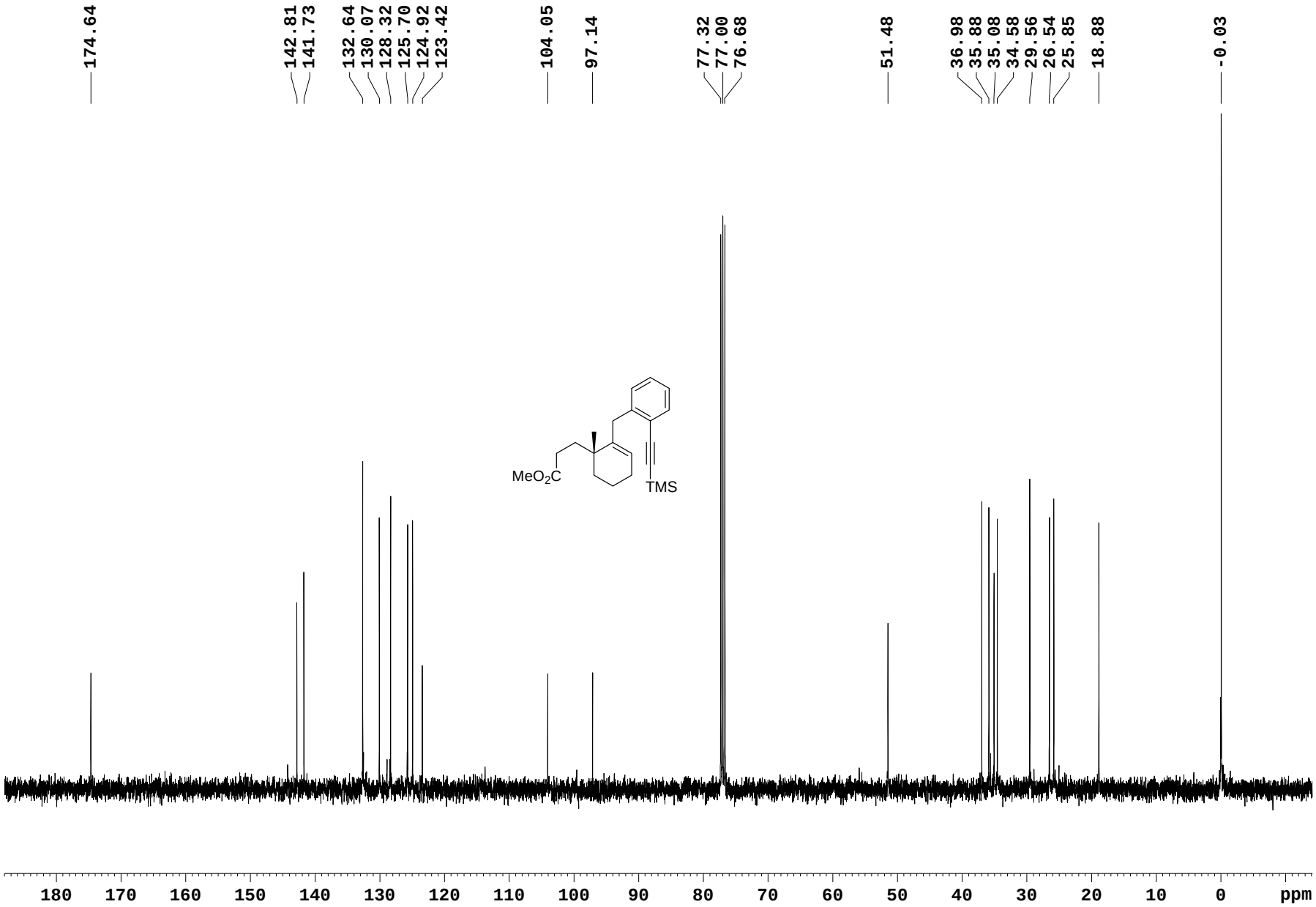
^{13}C-NMR of compound 20 (100 MHz, $CDCl_3$)



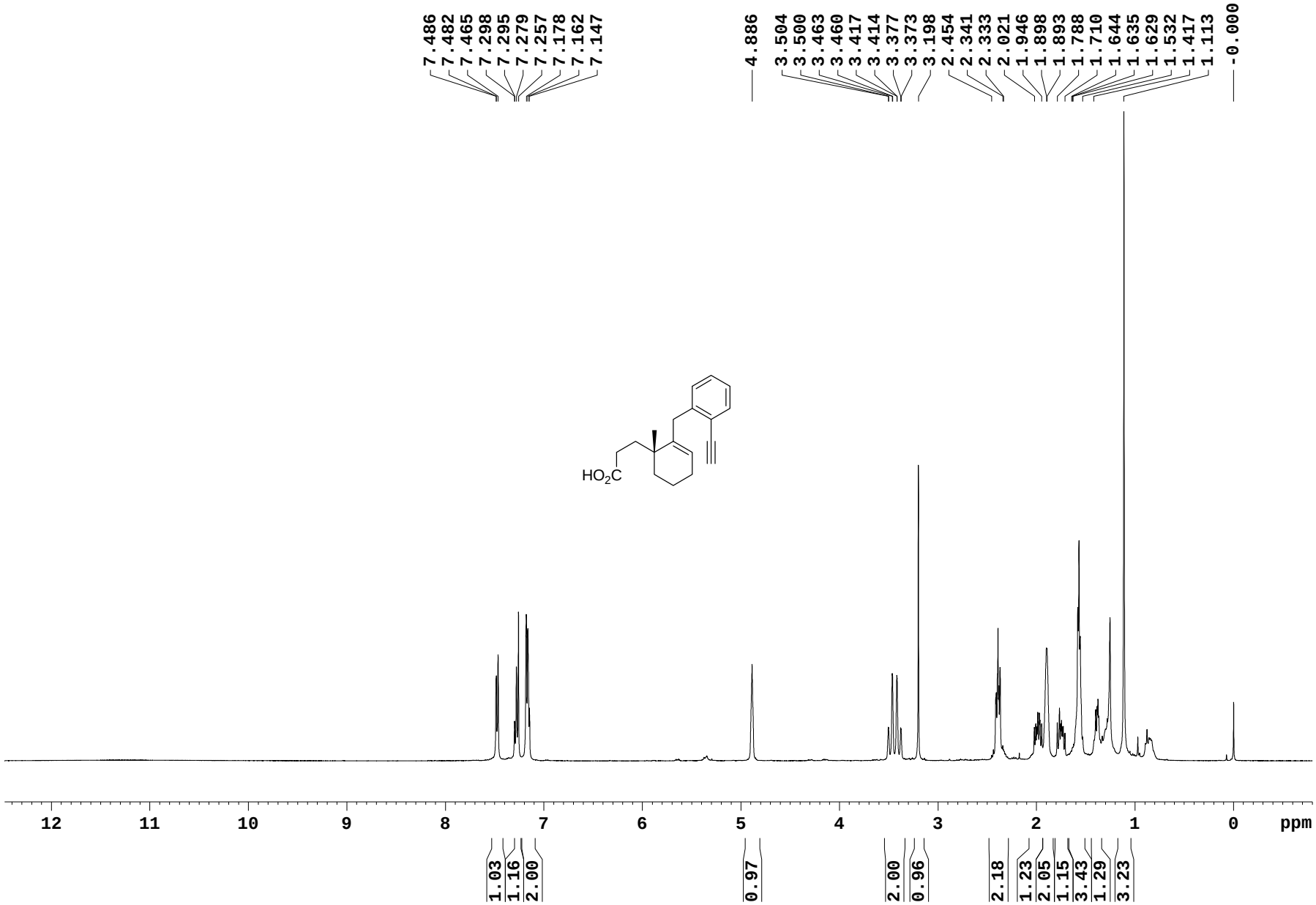
^{1}H-NMR of compound 21 (400 MHz, $CDCl_3$)



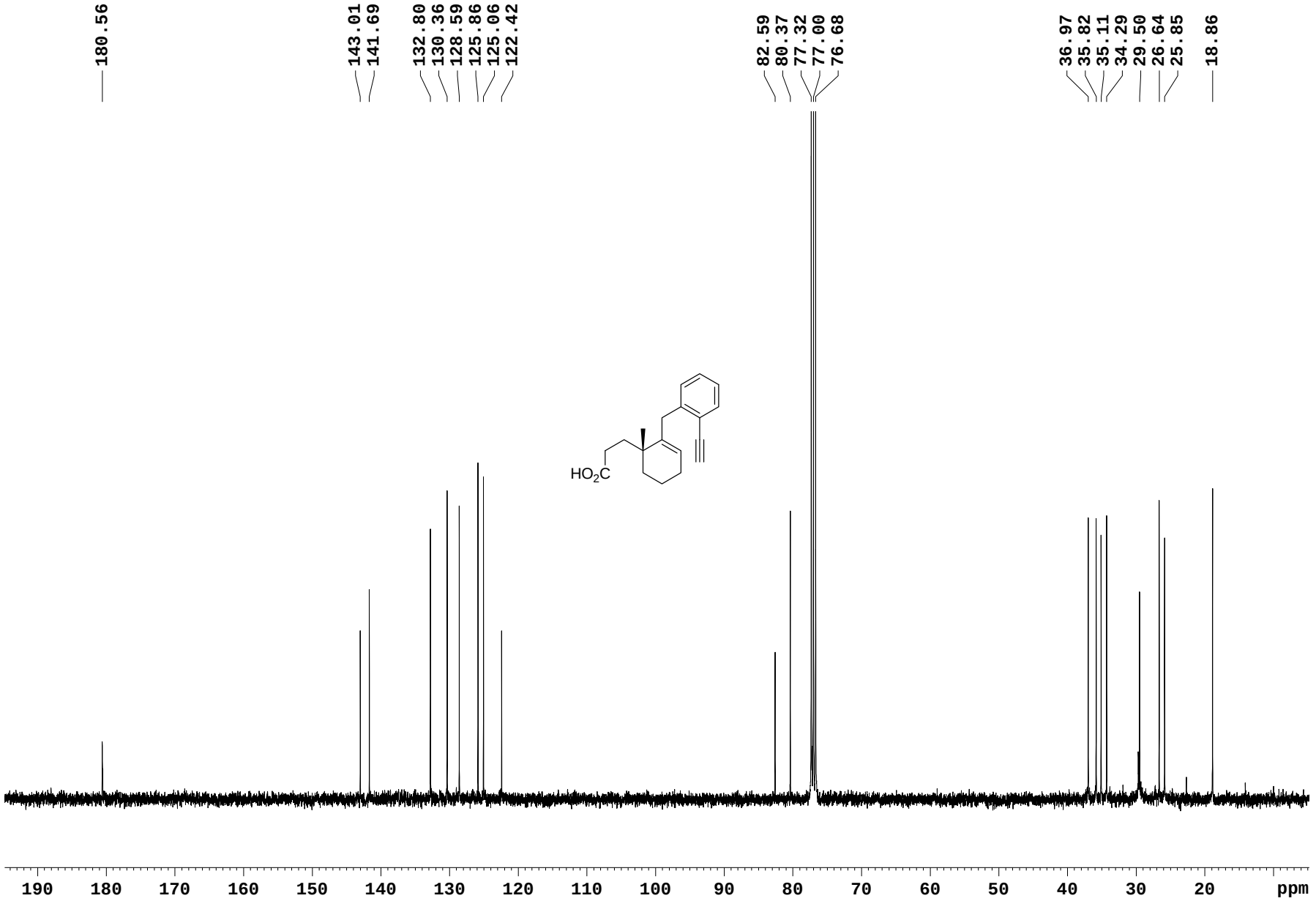
^{13}C-NMR of compound 21 (100 MHz, $CDCl_3$)



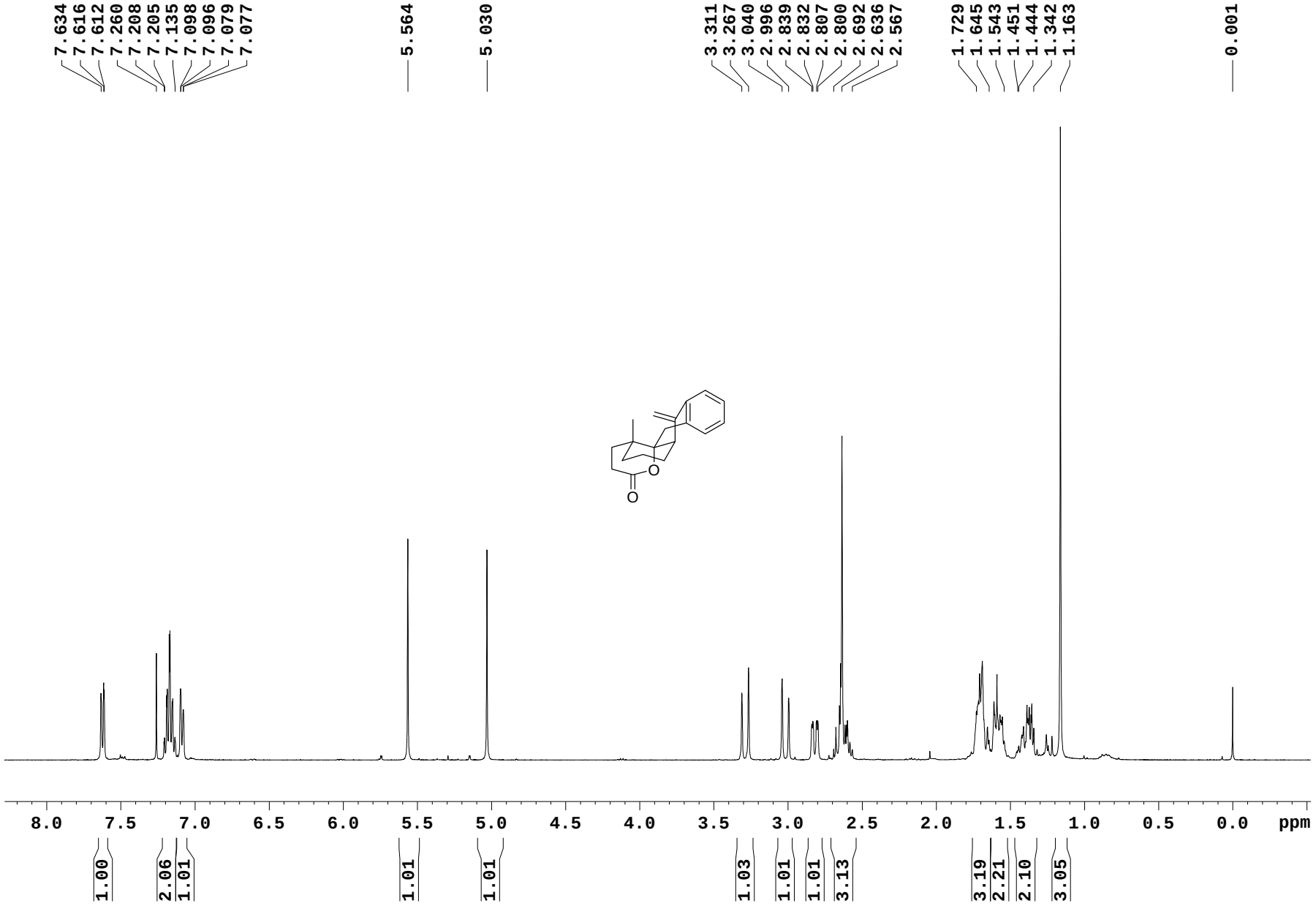
^{1}H-NMR of compound 16 (400 MHz, $CDCl_3$)



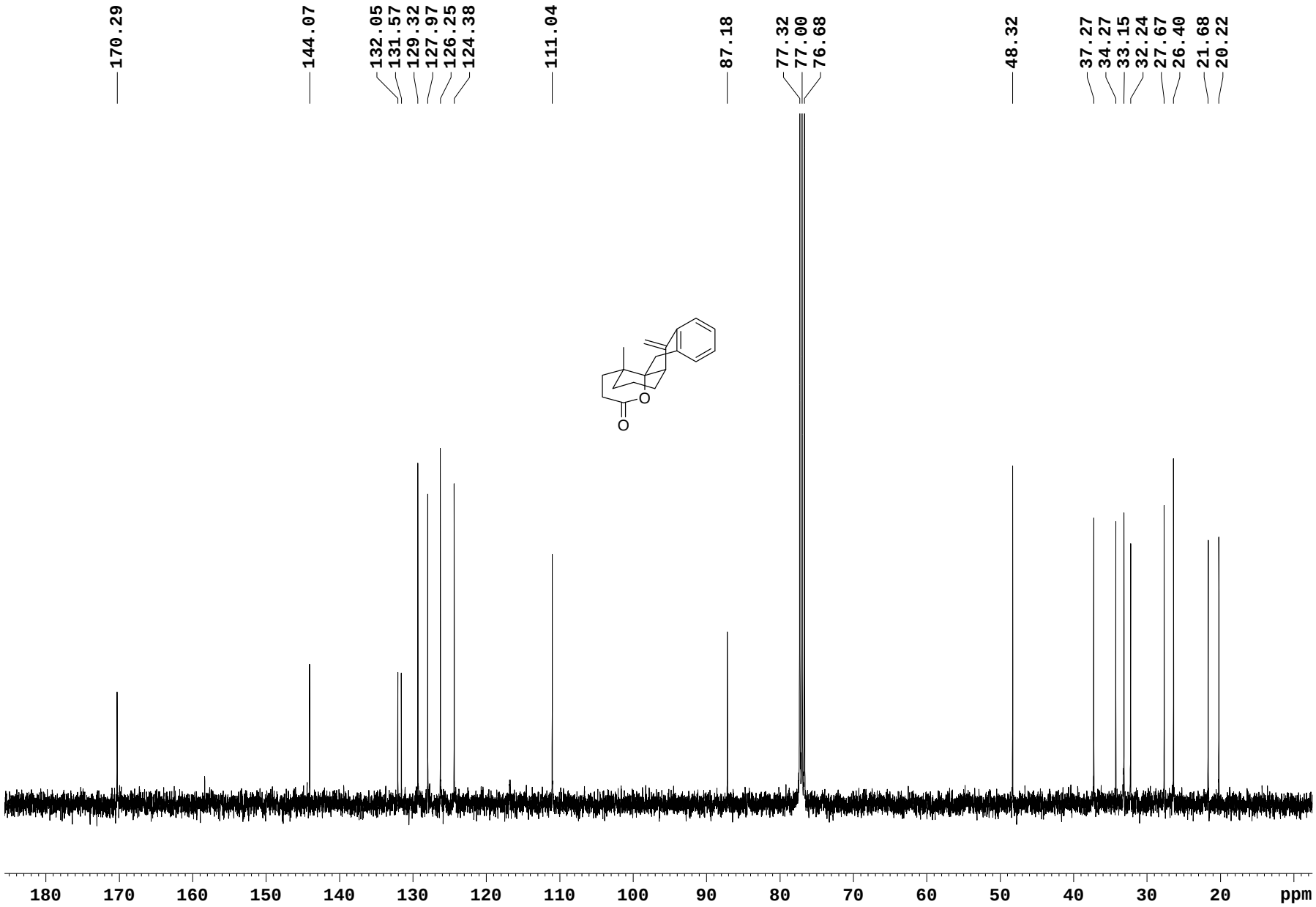
^{13}C-NMR of compound 16 (100 MHz, $CDCl_3$)



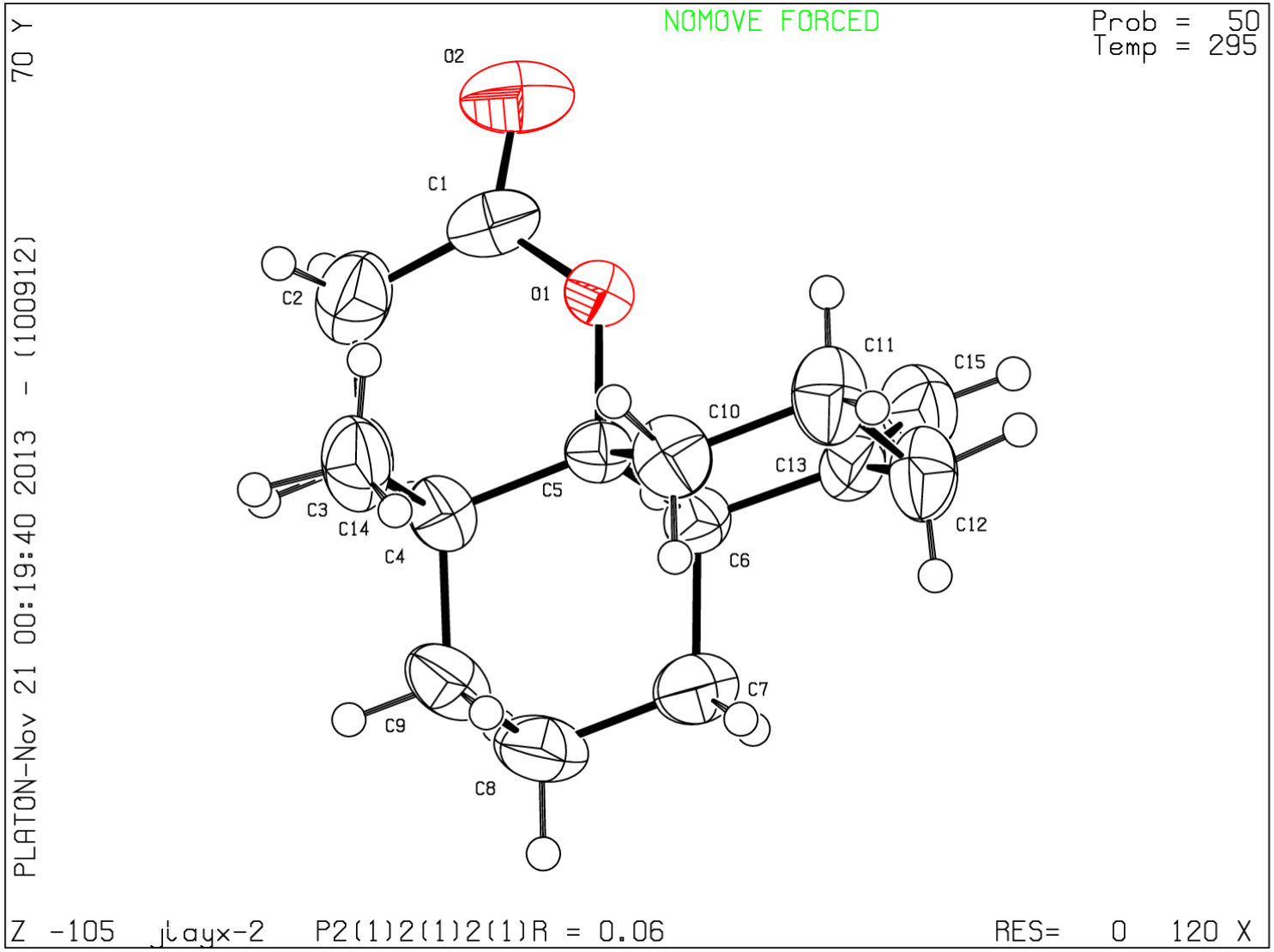
^{1}H-NMR of compound 17 (400 MHz, $CDCl_3$)



^{13}C-NMR of compound 17 (100 MHz, $CDCl_3$)



ORTEP drawing of 5



References

1 D. A. Offermann, J. E. McKendrick, J. J. P. Sejberg, B. Mo, M. D. Holdom, B. A. Helm, R. J. Leatherbarrow, A. J. Beavil, B. J. Sutton, and A. C. Spivey, *J. Org. Chem.*, 2012, **77**, 3197.