

Formal Synthesis of Anti-Platelet Drug, Beraprost

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SUPPORTING INFORMATION

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S2– General information, materials

S3 –S12 Experimental procedures and spectroscopic data for the intermediates

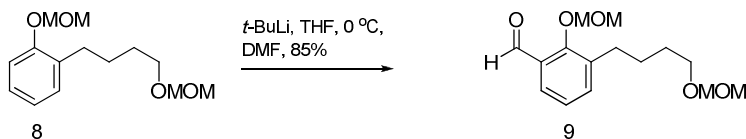
S13 –S38 Copies of ^1H and ^{13}C NMR spectra

General Experimental

All ^1H and ^{13}C NMR spectra were recorded in CDCl_3 solvent on a Varian Gemini 200, Bruker 300, Varian Unity 400 MHz spectrometer at ambient temperature, chemical shifts δ are in ppm on scale downfield from TMS, coupling constant J are in Hz. The signal patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; bs, broad singlet. IR spectra were recorded as neat thin films on Perkin-Elmer Infrared spectrophotometer with NaCl optics. Optical rotations were measured on JASCO DIP-370 digital polarimeter using a 2 mL cell with a 1 dm path length, the concentration c is given in g/100 mL. Mass spectra were obtained on Agilent technologies LC/MSD Trap SL spectrometer. HPLC was recorded on SHIMADZU HPLC using Chiralcel OD-H, Terra RP C18 250×4.6 mm, 5 μ column, water and acetonitrile as eluents. All the reagents and solvents were used without further purification unless specified otherwise. Technical grade ethyl acetate and petroleum ether used for column chromatography were distilled prior to use. Tetrahydrofuran (THF) and diethyl ether, when used as a solvent for reactions, were freshly distilled from sodium-benzophenone ketyl. Column chromatography was carried out using silica gel (60-120 mesh & 100-200 mesh) packed in glass columns. All reactions were performed under nitrogen atmosphere and in flame-dried or oven-dried glassware with magnetic stirring.

Experimental procedures

2-(Methoxymethoxy)-3-(4-(methoxymethoxy)butyl)benzaldehyde (**9**)



To a solution of MOM ether **8** (14.4 g, 56.6 mmol) in hexane (110 mL) at $0\text{ }^{\circ}\text{C}$ was added drop wise a solution of $t\text{-BuLi}$ (78.1 mL, 1 M in pentane, 78.2 mmol) at the same temperature. The mixture was stirred for 2 h, and a solution of DMF (7 g, 95.8 mmol) in THF (90 mL) was added drop wise. The reaction mixture was warmed to room temperature and stirred for an additional 12 h. After addition of water (20 mL) the mixture was evaporated to dryness. The residue was dissolved in water (30 mL) and extracted with CH_2Cl_2 (50 mL \times 2) to afford 1-(1,3-dioxabutyl)-2-(5,7-dioxaoctyl) benzaldehyde **9** (13.5g 85%) as an oil.

R_f (2:8, hexanes/EtOAc): 0.20;

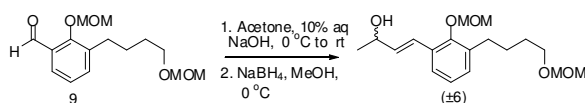
IR (neat): ν_{max} 3068, 2939, 2885, 1689, 1588, 1386, 1155, 1041, 953 cm^{-1} ;

^1H NMR (CDCl_3 , 300 MHz): δ 1.57-1.77 (m, 4H), 2.71 (t, $J = 7.5$ Hz, 2H), 3.32 (s, 3H), 3.52 (t, $J = 6.7$ Hz, 2H), 3.58 (s, 3H), 4.56 (s, 2H), 5.04 (s, 2H), 7.16 (t, $J = 7.55$ Hz, 1H), 7.42 (dd, $J = 7.55$ Hz, 1H), 7.66 (dd, $J = 7.55$ Hz, 1H), 10.21 (s, 1H);

^{13}C NMR (CDCl_3 , 75 MHz): δ 26.8, 29.4, 54.9, 57.6, 67.3, 96.2, 101.3, 124.5, 126.9, 129.6, 136.0, 136.4, 158.4, 190.5;

HRMS: Calcd for $\text{C}_{15}\text{H}_{22}\text{O}_5\text{Na}^+ [\text{M}+\text{Na}]^+$ 305.1359, found: 305.1357.

(*E*)-4-(2-(Methoxymethoxy)-3-(4-(methoxymethoxy)butyl)phenyl)but-3-en-2-ol (\pm 6)



To a solution of **9** (10 g, 34.5 mmol) in acetone (100 mL) at $0\text{ }^{\circ}\text{C}$ was added 10% aqueous NaOH solution (20 mL). The reaction mixture was warm to room temperature and stirred for 6 h before extraction. The solvent was evaporated to dryness, the residue dissolved in water (20 mL) and extracted with ether (50 mL \times 2). The combined organic layers dried over Na_2SO_4 to give ketone (9.93g, 88%) as a colorless liquid.

R_f (3:7, hexanes/EtOAc): 0.25;

IR (neat): ν_{max} 2939, 1670, 1450, 1360, 1219, 961, 772 cm^{-1} ;

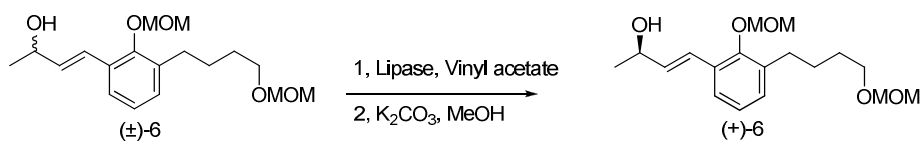
^1H NMR (CDCl_3 , 300 MHz): δ 1.67 (m, 4H), 2.36 (s, 3H), 2.68 (t, $J = 7.7$ Hz, 2H), 3.32 (s, 3H), 3.52 (t, $J = 6.2$ Hz, 2H), 3.61 (s, 3H), 4.5 (s, 2H), 4.9 (s, 2H), 6.62 (d, $J = 16.4$ Hz, 1H), 7.06 (t, $J = 7.5$ Hz, 1H), 7.22 (dd, $J = 7.3$ Hz, 1H), 7.85 (d, $J = 16.4$, 1H);

^{13}C NMR (CDCl_3 , 75 MHz): δ 26.7, 26.9, 29.3, 29.6, 54.7, 57.4, 67.1, 96.0, 100.4, 124.5, 127.6, 128.1, 132.1, 136.1, 139.0, 155.2, 198.1, 198.2;

MS (LC): m/z 344.9 $[\text{M}+\text{Na}]^+$.

NaBH_4 (1.1 g, 31 mmol) was added in portions at $0\text{ }^\circ\text{C}$ to a solution of the above ketone (10 g, 31 mmol) in CH_3OH (60 mL), after the mixture was stirred for 1 h at same temperature, completion of reaction was monitored by TLC. Methanol was removed in vacuum, the slurry was cooled to $0\text{ }^\circ\text{C}$, quenched with saturated aqueous solution of NH_4Cl (10 mL) and extracted with EtOAc (20 mL). Combined organic layers were washed with water, brine and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc, 7:3) to obtain product (\pm) **6** (9 g, 90%) as a thick oil.

(R)-(E)-4-(2-(Methoxymethoxy)-3-(4-(methoxymethoxy)butyl)phenyl)but-3-en-2-ol (+)-6



A mixture of (\pm) **6** (20 g) lipase (10 g) and vinyl acetate (20 mL) in *t*-butylmethyl ether (150 mL) was stirred at room temperature for 24 h. The residue obtained upon evaporation of the filtered reaction mixture was chromatographed using hexane/EtOAc, 8:2 as the eluent. The acetate **10** (10.19 g, 45%) and alcohol (–) **6** (11.3 g, 56.5%) were separated.

To complete the deacetylation K_2CO_3 (3.79 g, 27.5 mmol) was added to acetate **10** (10.19 g, 27.5 mmol) in MeOH (50 mL), the solution was stirred for 1 h at room temperature. It was then poured in saturated NH_4Cl solution (50 mL), extracted with EtOAc followed by drying with (MgSO_4) and concentration of combined organic layers *in vacuo*. Residue was purified by silica gel column chromatography (hexane/EtOAc, 7:3) to obtain (+) **6** (7.57 g, 85%) as an oil.

R_f (3:7, hexanes/EtOAc): 0.25;

Enantiomeric Excess was determined by chiral HPLC using Chiral Pak OD-H 250 x 4.6 mm, 5μ column with 12% isopropyl alcohol and 88% hexane as mobile phase. The eluent was monitored at 225 nm and retention times were observed at 9.2 and 11.1 min respectively.

$[\alpha]_{\text{D}}^{20} +3.15$ (c 2, CHCl_3);

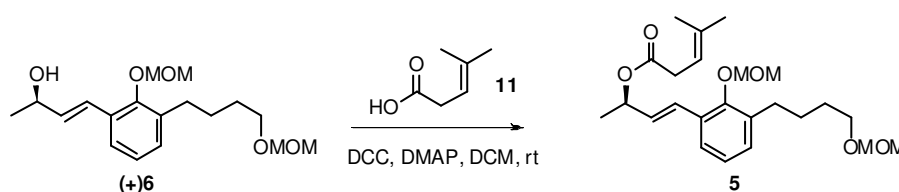
IR (neat): ν_{max} 3440, 2934, 2879, 1451, 1153, 973 cm^{-1} ;

^1H NMR (CDCl_3 , 300 MHz): δ 1.36 (d, $J = 6.0$ MHz, 3H), 1.68 (m, 4H), 2.29 (bs, 1H), 2.69 (t, $J = 7.5$ Hz, 2H), 3.34 (s, 2H), 3.54 (t, $J = 6.0$ MHz, 2H), 3.59 (s, 3H), 4.48 (m, $J = 6.0$ Hz, 1H), 4.62 (s, 2H), 4.93 (s, 2H), 6.23 (dd, $J = 15.8$ Hz, 1H), 6.84 (d, $J = 15.8$ Hz, 1H), 7.06 (m, $J = 7.5$ Hz, 2H), 7.32 (dd, $J = 7.5$ Hz, 1H);

^{13}C NMR (CDCl_3 , 75 MHz): δ 23.3, 27.0, 29.5, 29.9, 54.8, 57.3, 67.4, 68.6, 96.1, 99.8, 124.3, 124.4, 124.5, 129.1, 130.3, 134.9, 135.6, 153.4;

HRMS: Calcd for $\text{C}_{18}\text{H}_{28}\text{O}_5\text{Na}^+ [\text{M}+\text{Na}]^+$: 347.1829, found: 347.1853.

(*R*)-(*E*)-4-(2-(Methoxymethoxy)-3-(4-(methoxymethoxy)butyl)phenyl)but-3-en-2-yl-4-methylpent-3-enoate (5**)**



To a solution of **+6** (5 g, 15.4 mmol) in CH_2Cl_2 (150 mL) were added 4-methyl-3-pentenoic acid **11** (2.11 g, 18.5 mmol), DMAP (1.3 g, 10 mmol) and DCC (4.76 g, 23.1 mmol) at 0°C . The mixture was stirred for 10 h at room temperature followed by dilution with hexane. Generated white precipitate was removed by filtration through celite. The filtrate was concentrated and residue was purified by column chromatography on silica gel (hexane/EtOAc, 9:1), to give **5** (5.2 g, 80%) as an oil.

R_f (9:1, hexanes/EtOAc): 0.1;

$[\alpha]_D^{20} +37.7$ (c 2, CHCl_3);

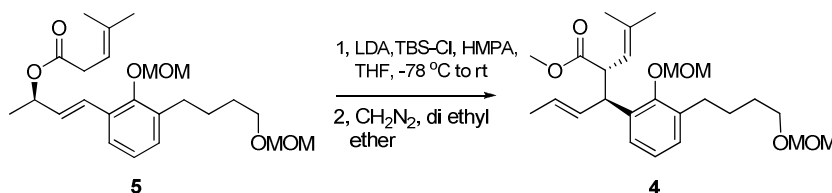
IR (neat): ν_{max} 2931, 1732, 1459, 1379, 772 cm^{-1} ;

^1H NMR (CDCl_3 , 300 MHz): δ 1.41 (d, $J = 6.4$ Hz, 3H), 1.64 (m, 7H), 1.75 (s, 3H), 2.67 (t, $J = 7.9$ Hz, 2H), 3.0 (d, $J = 7.1$ Hz, 2H), 3.3 (s, 3H), 3.51 (t, $J = 6.2$ Hz, 2H), 3.57 (s, 3H), 4.56 (s, 2H), 4.88 (m, $J = 6.6$ Hz, 2H), 5.3 (m, $J = 7.1$ Hz, 1H), 5.49 (m, $J = 6.6$ Hz, 1H), 6.1 (dd, $J = 16.0$ Hz, 1H), 6.82 (d, $J = 16.0$ Hz, 1H), 6.97 (t, $J = 7.5$ Hz, 1H), 7.04 (m, $J = 7.5$ Hz, 1H), 7.25 (m, $J = 7.7$ Hz, 1H);

^{13}C NMR (CDCl_3 , 75 MHz): δ 17.6, 19.9, 25.2, 26.8, 29.3, 29.6, 33.7, 54.6, 57.1, 67.2, 70.7, 96.0, 99.7, 115.7, 124.0, 124.3, 126.6, 129.3, 129.6, 129.7, 134.9, 135.5, 153.4, 171.1;

HRMS: Calcd for $\text{C}_{24}\text{H}_{36}\text{O}_6\text{Na}^+ [\text{M}+\text{Na}]^+$: 443.2404, found: 443.2405.

(2*R*,3*S*)-(E)-Methyl-3-(2-(methoxymethoxy)-3-((methoxymethoxy)butyl)phenyl)-2-(2-methylprop-1-enyl)hex-4-enoate (4)



To a stirred solution of **5** (420 mg, 1.00 mmol) in THF (40 mL) and HMPA (10 mL) was added TBSCl (300 mg, 2.00 mmol) in THF (5 mL). After the mixture was cooled to $-78\text{ }^{\circ}\text{C}$, LDA (4.1 mL, 0.5 M, in THF) was slowly added. The reaction mixture was slowly warmed to room temperature and stirred for 15 h. It was acidified to pH 2-3 with 1N HCl aqueous solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude acid **12** was taken to next step without purification. Acid **12** was dissolved into dry ether and treated with ethereal solution of diazomethane at $0\text{ }^{\circ}\text{C}$. After stirring the mixture for 0.5 h, aqueous NH_4Cl solution was added and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 8:2), to give **4** (338 mg, 78%) for two steps.

R_f (8:2, hexanes/EtOAc): 0.2;

Diastereomeric Excess was determined by HPLC using Waters Xterra RP column 250 x 4.6 mm, 5μ column with 70% acetonitrile and 30% water as mobile phase. The eluent was monitored at 225 nm and retention times were observed at 8.0 and 8.5 min respectively for 2 diastereomers.

$[\alpha]_{\text{D}}^{20} -2.4$ (c 2, CHCl_3);

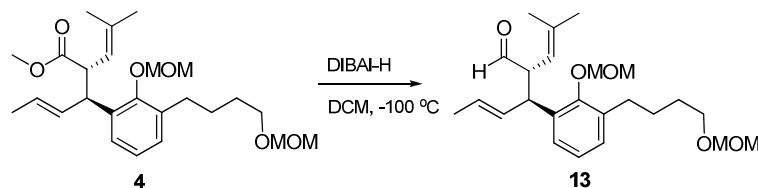
IR (neat): ν_{max} 2936, 1736, 1440, 1156, 972(cm^{-1});

^1H NMR (CDCl_3 , 300 MHz): δ 1.36 (s, 3H), 1.46 (s, 3H), 1.63 (m, 7H), 2.6 (m, 1H), 2.73 (m, 1H), 3.35 (s, 3H), 3.54 (t, $J = 5.6$ Hz, 3H), 3.65 (bs, 6H), 4.1 (t, $J = 8.1$ Hz, 1H), 4.6 (s, 2H), 4.91 (m, $J = 8.6$ Hz, 2H), 5.0 (d, $J = 9.8$, 1H), 5.58 (m, 2H), 7.0 (m, 3H);

^{13}C NMR (CDCl_3 , 75 MHz): 17.9, 25.5, 27.1, 29.5, 30.3, 44.1, 51.4, 51.6, 55.0, 57.3, 67.6, 96.3, 100.1, 120.7, 124.2, 125.9, 126.6, 127.9, 131.9, 135.1, 135.4, 154.1, 174.1;

HRMS: Calcd for $\text{C}_{25}\text{H}_{38}\text{O}_6\text{Na}^+ [\text{M}+\text{Na}]^+$: 445.2561, found: 445.2565.

(2*R*,3*S*)-(E)-3-(2-(Methoxymethoxy)-3-(4-(methoxymethoxy)butyl)phenyl)-2-(2-methylprop-1-enyl)hex-4-enal (13)



A solution of **4** (434 mg, 1.00 mmol) in CH₂Cl₂ (5 mL) was cooled in ether / dry ice bath and treated drop wise with DIBAL-H (0.56 mL, 1 mmol, 25% in toluene). The reaction mixture was stirred at –100 °C for 1h and then quenched with saturated aqueous potassium sodium tartrate. The biphasic mixture was washed with CH₂Cl₂ (10 mL × 2). The combined organic layers washed with H₂O and brine, dried over (MgSO₄) and concentrated *in vacuo*, residue was purified by flash silica gel column chromatography (hexanes/EtOAc, 7:3) gives **13** (335 mg, 83%) as an oil.

R_f (7:3, hexanes/EtOAc): 0.3;

[α]_D²⁰ +2 (c 0.2, CHCl₃) ;

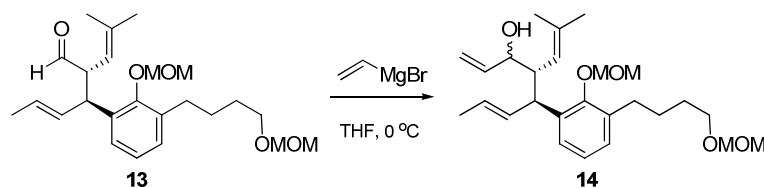
IR (neat): ν_{max} 2928, 1727, 1452, 1380, 1158, 971 cm⁻¹;

¹H NMR (CDCl₃, 300 MHz): δ 1.48 (s, 3H), 1.54 (s, 3H), 1.64 (m, *J* = 5.2 Hz, 7H), 2.59 (m, 1H), 2.72 (m, 1H), 3.35 (s, 3H), 3.54 (t, *J* = 6.0 Hz, 3H), 3.63 (s, 3H), 4.22 (t, *J* = 10.5 Hz, 1H), 4.6 (s, 2H), 4.8 (d, *J* = 9.0 Hz, 1H), 4.9 (m, *J* = 17.3 Hz, 2H), 5.5 (m, *J* = 6.7 Hz, 2H), 7 (m, 3H), 9.4 (d, *J* = 4.5 Hz, 1H);

¹³C NMR (CDCl₃, 75 MHz): δ 17.9, 18.4, 25.8, 27.1, 29.5, 30.2, 41.4, 55.0, 57.3, 57.5, 67.6, 96.3, 100.1, 117.2, 124.5, 126.3, 127.1, 128.1, 131.9, 135.5, 138.3, 153.9, 199.9 ;

HRMS: Calcd for C₂₄H₃₆O₅Na⁺ [M+Na]⁺: 427.2455, found: 427.2457.

(4*R*,5*S*)-(E)-5-(2-(Methoxymethoxy)-3-(4-(methoxymethoxy)butyl)phenyl)-4-(2-methylprop-1-enyl)octa-1,6-dien-3-ol (14)



To a solution of **13** (404 mg, 1.00 mmol) in dry THF (10 mL) was added vinyl magnesium bromide (1.9 mL, 1.0 M in THF, 2 mmol) at 0 °C slowly. The solution was stirred for an additional 1 h, quenched with saturated NH₄Cl solution and extracted with EtOAc twice. The

combined organic layers were dried over MgSO_4 and concentrated. The residue was purified by column chromatography on silica gel (hexanes/EtOAc, 7:3) to give **14** (302 mg, 75%) as a colorless liquid.

R_f (7:3, hexanes/EtOAc): 0.3;

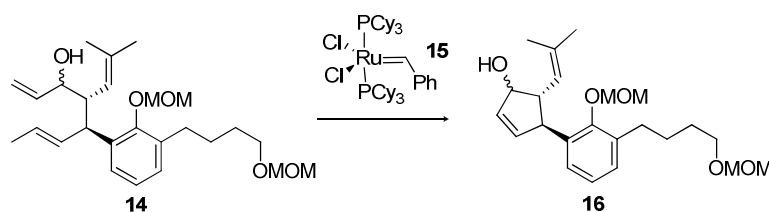
IR (neat): ν_{max} 3499, 3067, 2958, 2929, 2861, 1459, 1381, 1041, 974 cm^{-1} ;

^1H NMR (CDCl_3 , 300 MHz): δ 1.47-1.68 (m, 13H), 2.5-2.8 (m, 3H), 3.35 (s, 3H), 3.64 (t, J = 6.0 Hz, 2H), 3.99 (t, J = 9.8 Hz, 1H), 4.36 (b, 1H), 4.61 (s, 2H), 4.86-4.98 (m, 3H), 5.08 (dt, J = 10.7 Hz, 1H), 5.21 (dt, J = 17.3 Hz, 1H), 5.56-5.7 (m, 2H), 5.86 (m, 1H), 6.94-7.06 (m, 3H);

^{13}C NMR (CDCl_3 , 75 MHz): δ 18.0, 18.2, 25.7, 27.2, 29.5, 29.6, 30.4, 42.9, 49.3, 55.0, 57.3, 67.7, 73.6, 100.0, 114.2, 121.1, 124.1, 126.2, 126.6, 127.4, 133.8, 134.1, 135.4, 137.1, 140.5, 153.6;

HRMS: Calcd for $\text{C}_{25}\text{H}_{36}\text{O}_6\text{Na}^+ [\text{M}+\text{Na}]^+$: 455.2504, found: 455.2411.

(4*S*,5*R*)-4-(2-(Methoxymethoxy)-3-(4-(methoxymethoxy)butyl)phenyl)-5-(2-methylprop-1-enyl)cyclopent-2-enol (16**)**



To a solution of **14** (302 mg, 0.69 mmol) in CH_2Cl_2 (50 mL) was added first generation Grubbs catalyst **15** (28.7 mg, 0.03 mmol). The mixture was heated to reflux for 12 h and then cooled to room temperature. The volatiles were removed and residue was purified by flash silica gel column chromatography (hexanes/EtOAc, 6:4) to give **16** (0.207 mg, 76%) as an oil.

R_f (6:4, hexanes/EtOAc): 0.4;

IR (neat): ν_{max} 3458, 2930, 1729, 1456, 1380, 1155, 1041, 976 cm^{-1} ;

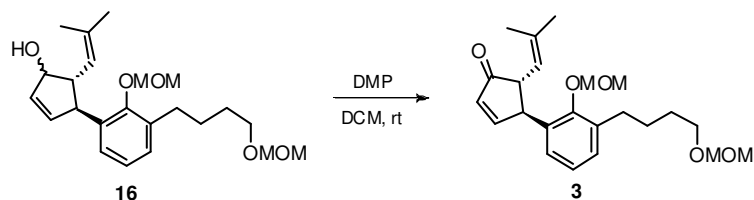
^1H NMR (CDCl_3 , 300 MHz): δ 1.57-1.89 (m, 20H), 2.11 (m, 2H), 2.58-2.81 (m, 6H), 3.2 (m, 1H), 3.36 (s, 7H), 3.56 (s, 1H), 3.97 (m, 2H), 4.62 (s, 11H), 4.8 (m, 2H), 4.9 (m, 2H), 4.98 (d, 1H), 5.27 (d, 1H), 5.78 (dt, J = 6.0 Hz, 1H), 5.93 (dt, J = 5.2 Hz, 1H), 6.9-7.15 (m, 5H), 7.22 (dd, J = 7.5 Hz, 1H);

^{13}C NMR (CDCl_3 , 75 MHz): δ 18.0, 18.2, 18.4, 25.8, 25.9, 27.1, 29.6, 30.2, 31.8, 32.8, 42.4, 49.8, 55.0, 55.2, 57.2, 58.5, 67.6, 79.2, 83.2, 96.3, 100.2, 100.3, 124.6, 124.7, 125.4, 125.6,

125.9, 126.8, 127.5, 128.2, 133.2, 134.2, 134.8, 135.2, 135.4, 136.8, 137.1, 137.7, 153.6, 154.0;

HRMS: Calcd for $C_{23}H_{34}O_5Na^+$ $[M+Na]^+$: 413.2303, found: 413.2311.

(4*S*,5*R*)-4-(2-(Methoxymethoxy)-3-(4-(methoxymethoxy)butyl)phenyl)-5-(2-methylprop-1-enyl)cyclopent-2-enone (3)



To a solution of **16** (0.218 mg, 0.53 mmol) in CH_2Cl_2 (2.5 mL), cooled to 0 °C, Dess-Martin periodinane (270 mg, 1.2 equiv, 0.63 mmol) was added. The reaction was allowed to warm room temperature, stirred for 1 h at rt, quenched with saturated $NaHCO_3$ solution (5 mL) and diluted with ether (10 mL). The white precipitate was removed by filtration through celite. The bi-phase mixture was separated and organic layer was washed with H_2O (10 mL). The organic layer was separated, dried over Na_2SO_4 , concentrated *in vacuo* and residue was subjected to column chromatography with (hexanes/EtOAc, 8:2) to give **3** (184 mg, 85%) as an oil.

R_f (8:2, hexanes/EtOAc): 0.4;

$[\alpha]_D^{20} +193$ (c 2.00, $CHCl_3$);

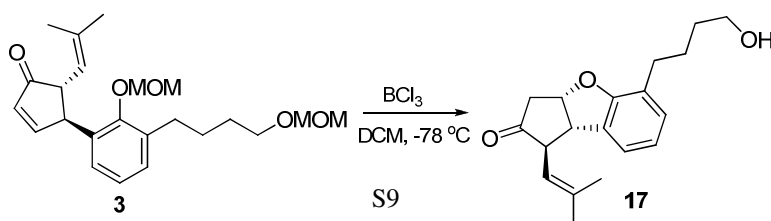
IR (neat): ν_{max} 2925, 2854, 1716, 1461, 1220, 772 cm^{-1} ;

1H NMR ($CDCl_3$, 300 MHz): δ 1.48 (s, 3H), 1.69 (m, 4H), 1.75 (s, 3H), 2.70 (m, $J = 6.7$ Hz, 2H), 3.18 (dd, $J = 9.2$ Hz 1H), 3.36 (s, 3H), 3.58 (m, 5H), 4.34 (d, $J = 2.4$ Hz, 1H), 4.63 (s, 2H), 4.83-4.99 (dd, $J = 5.4$ Hz, 2H) 5.11 (d, $J = 9.2$ Hz, 2H), 6.28-6.32 (dd, $J = 5.6$ Hz, 1H), 6.88 (m, $J = 7.3$ Hz, 1H), 7.09 (m, 1H), 7.57 (dd, $J = 5.6$ Hz, 1H);

^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.3, 25.6, 27.0, 29.5, 30.1, 48.2, 55.0, 55.6, 57.2, 67.5, 96.3, 100.4, 120.4, 125.0, 125.5, 129.0, 132.4, 134.2, 136.0, 153.7, 166.2, 210.9;

HRMS: Calcd for $C_{23}H_{32}O_5^+$ $[M+H]^+$: 389.2323, found: 389.2301.

(1*R*,3*aS*,8*bS*)-5-(4-Hydroxybutyl)-1-(2-methylprop-1-enyl)-3,3*a*-dihydro-1*H*-benzo[*b*]cyclopenta[*d*]furan-2(8*bH*)-one (17)



To a solution of **3** (388 mg, 1.00 mmol) in CH₂Cl₂ (10 mL), was added BCl₃ (3.9 mL, 1.0 M in CH₂Cl₂, 4 mmol) at –78 °C slowly. The solution was stirred for an additional 0.5 h at –78 °C and then quenched with saturated aqueous NaHCO₃. The organic layer was separated, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was subjected to column chromatography with (hexanes/EtOAc, 6:4) to give **17** (155 mg, 52%) as an yellow oil.

R_f (6:4, hexanes/EtOAc): 0.5;

[α]²⁰_D +67.5 (*c* 0.16, CHCl₃);

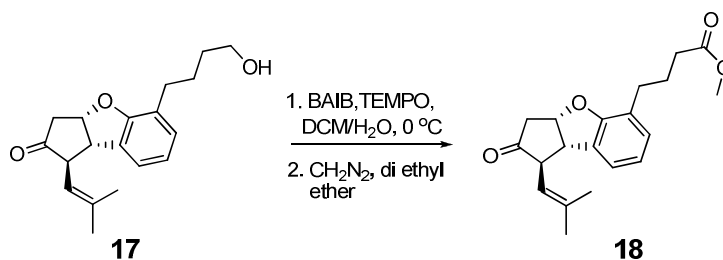
IR (neat): ν_{max} 3413, 2927, 2857, 1736, 1596, 1451, 1261, 1020, 770 cm⁻¹;

¹H NMR (CDCl₃, 300 MHz): δ 1.59 (s, 3H), 1.66 (m, 4H), 1.8 (s, 3H), 2.59 (m, 2H), 2.82 (m, 2H), 3.17 (t, *J* = 8.3 Hz, 1H), 3.60 (t, *J* = 8.3 Hz, 1H), 3.66 (t, *J* = 6.0 Hz, 2H), 5.03 (d, *J* = 8.3 Hz, 1H), 5.34 (m, 1H), 6.76 (t, *J* = 7.5 Hz, 1H), 6.96 (m, *J* = 7.5 Hz, 2H);

¹³C NMR (CDCl₃, 75 MHz): δ 18.6, 29.4, 32.3, 43.7, 50.7, 55.3, 62.7, 82.1, 121.0, 122.0, 124.6, 129.0, 130.0, 137.8, 157.3, 216.0;

HRMS: Calcd for C₁₈H₂₀O₄⁺ [M+H]⁺: 301.1434, found: 301.1443.

Methyl-4-((1R,3aS,8bS)-1-(2-methylprop-1-enyl)-2-oxo-2,3,3a,8b-tetrahydro-1H-benzo[b]cyclopenta[d]furan-5-yl)butanoate (18**)**



To a vigorously stirred solution of alcohol **17** (300 mg, 1 mmol) in CH₂Cl₂ (4 mL) and H₂O (2 mL) were added TEMPO (94 mg, 0.6 mmol) and BAIB (1.6 g, 5 mmol). Stirring was allowed until TLC indicated complete conversion of the starting material (3 h). The reaction mixture was quenched by the addition of saturated Na₂SO₃ solution (20 mL). The mixture was then extracted with EtOAc and combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude acid was taken to next step without purification. The intermediate acid was dissolved in dry ether and treated with ethereal solution of diazomethane at 0 °C. After stirring for 0.5 h, aqueous NH₄Cl solution was added and extracted with EtOAc. The combined organic layers dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexanes/EtOAc, 9:1) to give **18** (247 mg, 75%) as an oil.

R_f (9:1, hexanes/EtOAc): 0.2;

$[\alpha]_D^{20} +58.8$ (c 0.5, CHCl_3);

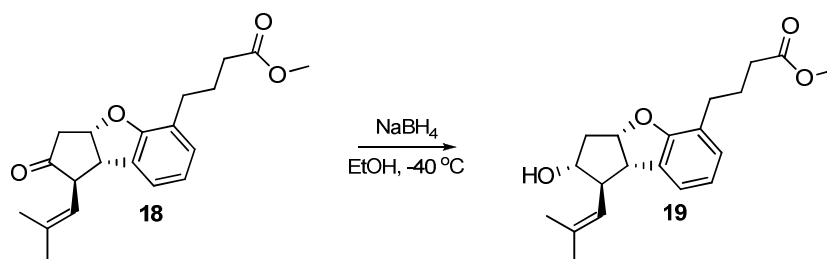
IR (neat): ν_{max} 2928, 2859, 1738, 1451, 1249, 1191 cm^{-1} ;

^1H NMR (CDCl_3 , 300 MHz): δ 1.59 (s, 3H), 1.80 (s, 3H), 1.96 (m, $J = 7.5$ Hz, 2H) 2.34 (t, $J = 8.3$ Hz, 2H), 2.58-2.65 (m, $J = 7.5$ Hz, 2H), 2.84 (m, 2H), 3.2 (t, $J = 8.3$ Hz, 1H), 3.63 (t, $J = 7.5$ Hz, 1H), 3.65 (s, 3H), 5.02 to 5.09 (m, $J = 9$ Hz, 1H), 5.32 to 5.39 (m, 1H), 6.80 (t, $J = 7.5$ Hz, 1H), 6.99 (t, $J = 8.3$ Hz, 2H);

^{13}C NMR (CDCl_3 , 75 MHz): δ 18.4, 24.7, 25.8, 29.1, 29.6, 33.4, 43.6, 50.7, 51.4, 55.3, 82.2, 96.0, 119.6, 121.0, 122.3, 123.6, 129.1, 130.2;

HRMS: Calcd for $\text{C}_{20}\text{H}_{25}\text{O}_4^+$ $[\text{M}+\text{H}]^+$: 329.747, found: 329.1777.

Methyl-4-((1R,2R,3aS,8bS)-2-hydroxy-1-(2-methylprop-1-enyl)-2,3,3a,8b-tetrahydro-1H-benzo[b]cyclopenta[d]furan-5-yl)butanoate (19)



NaBH_4 (23 mg, 0.62 mmol) was added in portions at -40 $^\circ\text{C}$ to a solution of ketone **18** (210 mg, 0.64 mmol) in EtOH (6 mL). After the mixture was stirred for 1 h, the reaction was quenched with saturated aqueous NH_4Cl (3 mL). Aqueous layer was extracted with ether twice, the combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexanes/EtOAc, 6:4) to give **19** (179 mg, 85%) as an oil.

R_f (6:4, hexanes/EtOAc): 0.3;

$[\alpha]_D^{20} +30.56$ (c 0.36, CHCl_3);

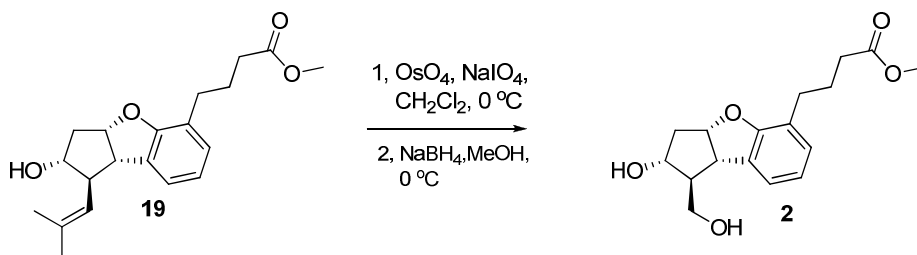
IR (neat): ν_{max} 3459, 2925, 2858, 1736, 1450, 1259, 1193 cm^{-1} ;

^1H NMR (CDCl_3 , 300 MHz): δ 1.66 (s, 3H), 1.79 (s, 3H), 1.85-2.10 (m, 3H), 2.33 (t, $J = 7.5$ Hz, 2H), 2.51-2.64 (m, $J = 7.5$ Hz, 3H), 2.74-2.84 (m, 1H), 3.4 (t, $J = 8.3$ Hz, 1H), 3.65 (s, 3H), 3.9 (bs, 1H), 5.06 (d, $J = 9.8$ Hz, 1H), 5.15 (m, 1H), 6.76 (t, $J = 7.5$ Hz, 1H), 6.96 (t, $J = 7.5$ Hz, 2H);

^{13}C NMR (CDCl_3 , 75 MHz): δ 18.5, 24.7, 25.9, 29.1, 33.3, 41.4, 51.4, 51.9, 55.0, 77.8, 85.2, 120.4, 122.0, 123.1, 125.1, 128.6, 130.2, 135.2, 157.1, 174.1;

HRMS: Calcd for $\text{C}_{20}\text{H}_{26}\text{O}_4\text{Na}^+$ $[\text{M}+\text{Na}]^+$: 353.1723, found: 353.1692.

Methyl-4-((1S,2R,3aS,8bS)-2-hydroxy-1-(hydroxymethyl)-2,3,3a,8b-tetrahydro-1H-benzo[b]cyclopenta[d]furan-5-yl)butanoate (2**)**



To a solution of compound **19** (330 mg, 1.00 mmol) in THF/H₂O (3:1, 8 mL) were added OsO₄ (5 mg, 0.02 equiv, 0.019 mmol), 2, 6-lutidine (0.23 mL, 2 equiv, 2 mmol) and NaIO₄ (852 mg, 4 equiv, 4mmol). The solution was stirred at 0 °C until completion (2 h), then quenched by addition of H₂O (10 mL) followed by the addition of CH₂Cl₂ (15 mL). The aqueous layer was extracted with CH₂Cl₂ twice and combined organic layer were dried over Na₂SO₄, filtered and concentrated *in vacuo*. Aldehyde (**20**) was unstable; which was used in the next reaction without further purification.

To a solution of the above aldehyde (330 mg, 1.08 mmol) in MeOH (10 mL) at 0 °C were added NaBH₄ (40 mg, 1.08 mmol). After the mixture was stirred for 10 min to complete the reaction, it was quenched with saturated NH₄Cl solution and aqueous layer was extracted with EtOAc twice. The combined organic layers dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (CHCl₃/CH₃OH, 9:1) to get **2** (205 mg, 67% two steps) as a solid.

R_f (9:1, CHCl₃/CH₃OH): 0.3;

Mp: 61.0-64.0 °C;

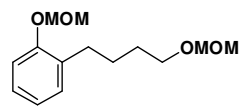
[α]_D²⁰ +22.3 (*c* 0.4, CHCl₃);

IR (neat): ν_{max} 3330, 2924, 2855, 1736, 1451, 1067, 1031, 772 cm⁻¹;

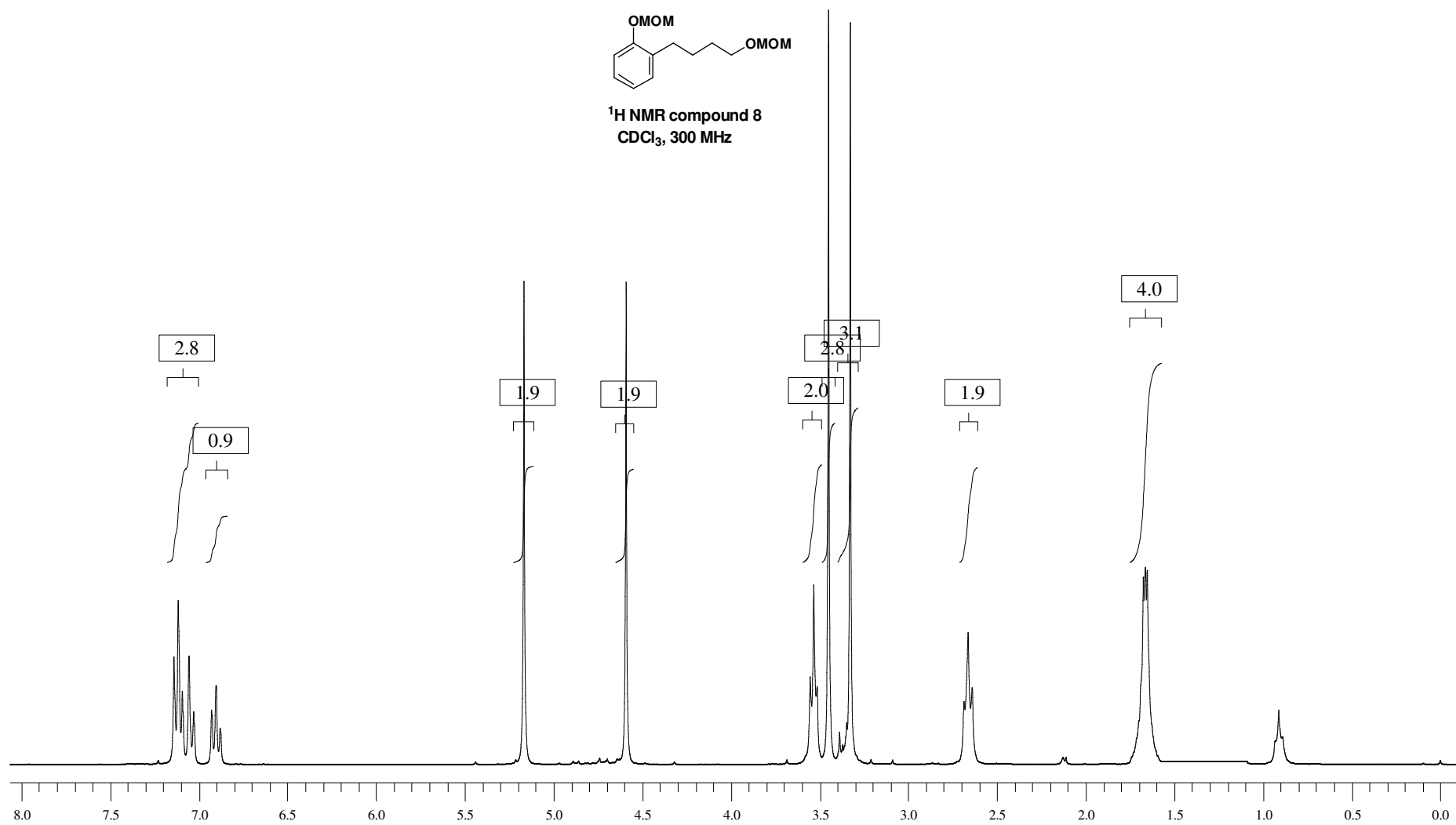
¹H NMR (CDCl₃, 500 MHz): δ 1.53-1.73 (bs, 2H), 1.87-2.08 (m, 3H), 2.12 (m, 1H), 2.32 (t, *J* = 7.7 Hz, 2H), 2.53-2.67 (m, 3H), 3.4 (t, *J* = 7.7 Hz, 1H), 3.64 (s, 3H), 3.78 (m, 1H), 3.92-3.98 (m, 1H), 4.08-4.16 (m, 1H), 5.09-5.16 (m, 1H), 6.78 (t, *J* = 7.7 Hz, 1H), 6.94 (d, *J* = 7.0 Hz, 1H), 7.01 (d, *J* = 7.7 Hz, 1H);

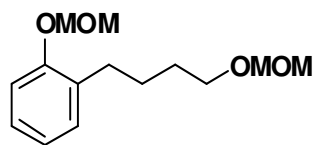
¹³C NMR (CDCl₃, 75 MHz): δ 24.7, 29.1, 33.3, 41.9, 47.4, 51.4, 56.7, 64.7, 85.3, 120.6, 122.0, 123.3, 128.2, 128.8, 130.1, 157.0, 174.1;

HRMS: Calcd for C₁₇H₂₂O₅Na⁺ [M+Na]⁺: 329.1463, found: 329.1428.

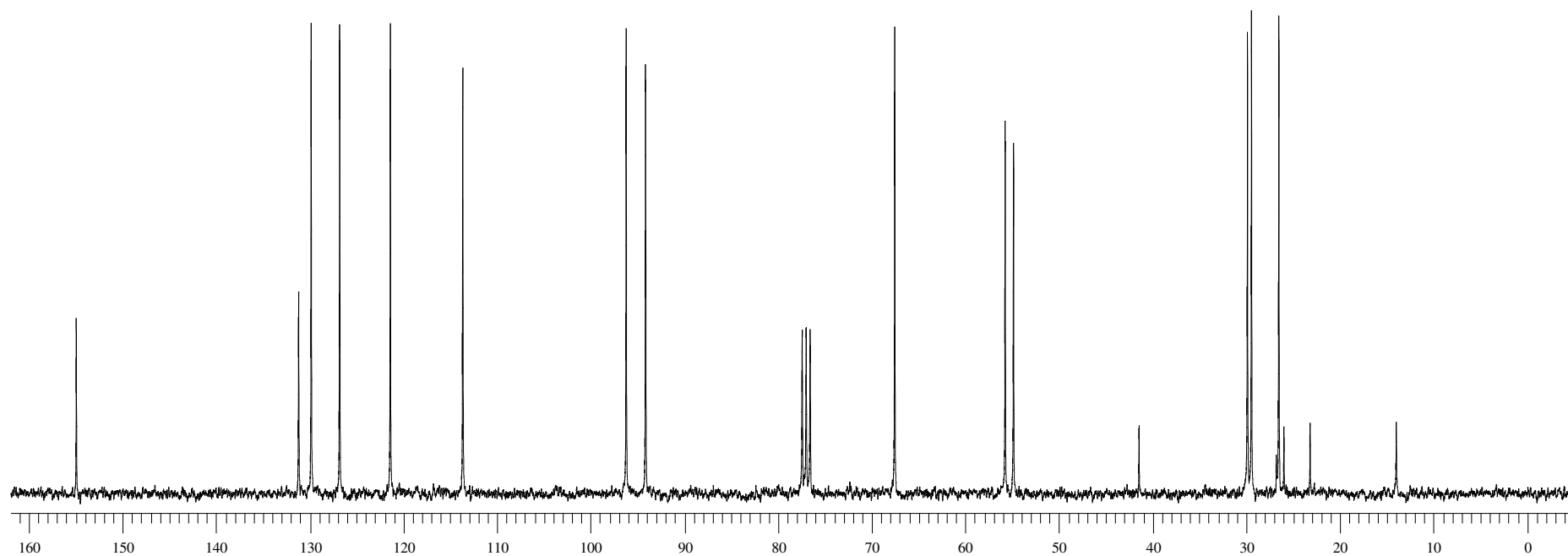


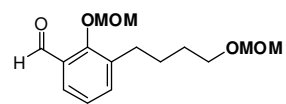
¹H NMR compound 8
CDCl₃, 300 MHz



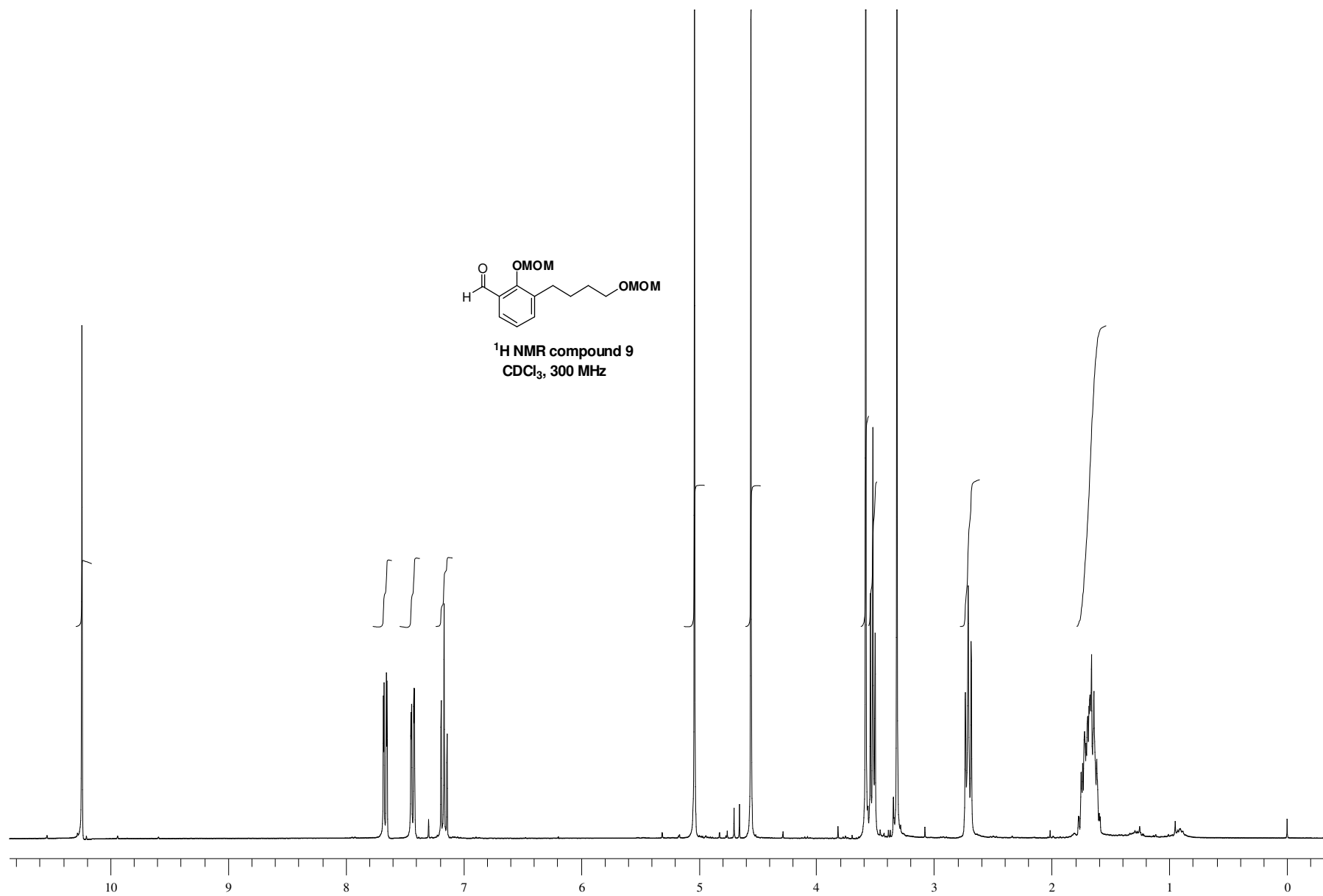


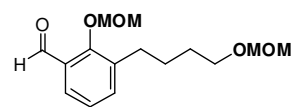
¹³C NMR compound 8
CDCl₃, 75 MHz





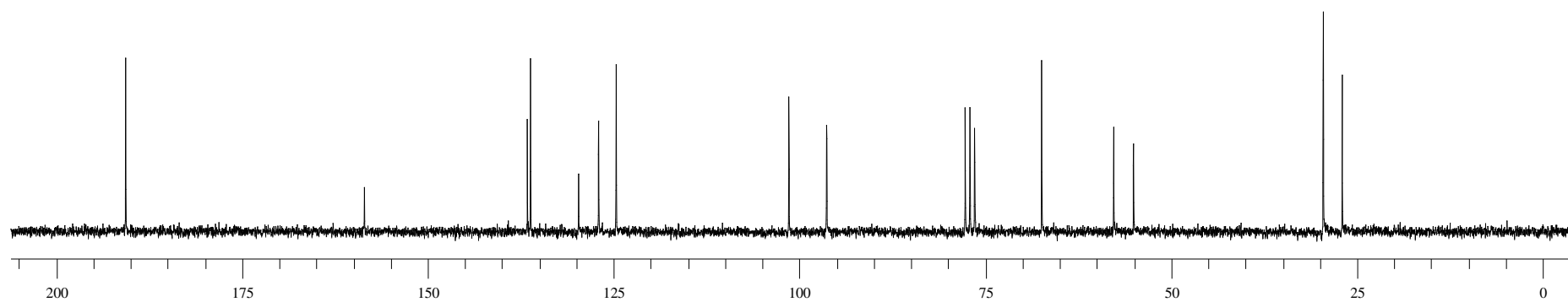
¹H NMR compound 9
CDCl₃, 300 MHz

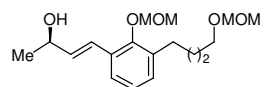




¹³C NMR compound 9

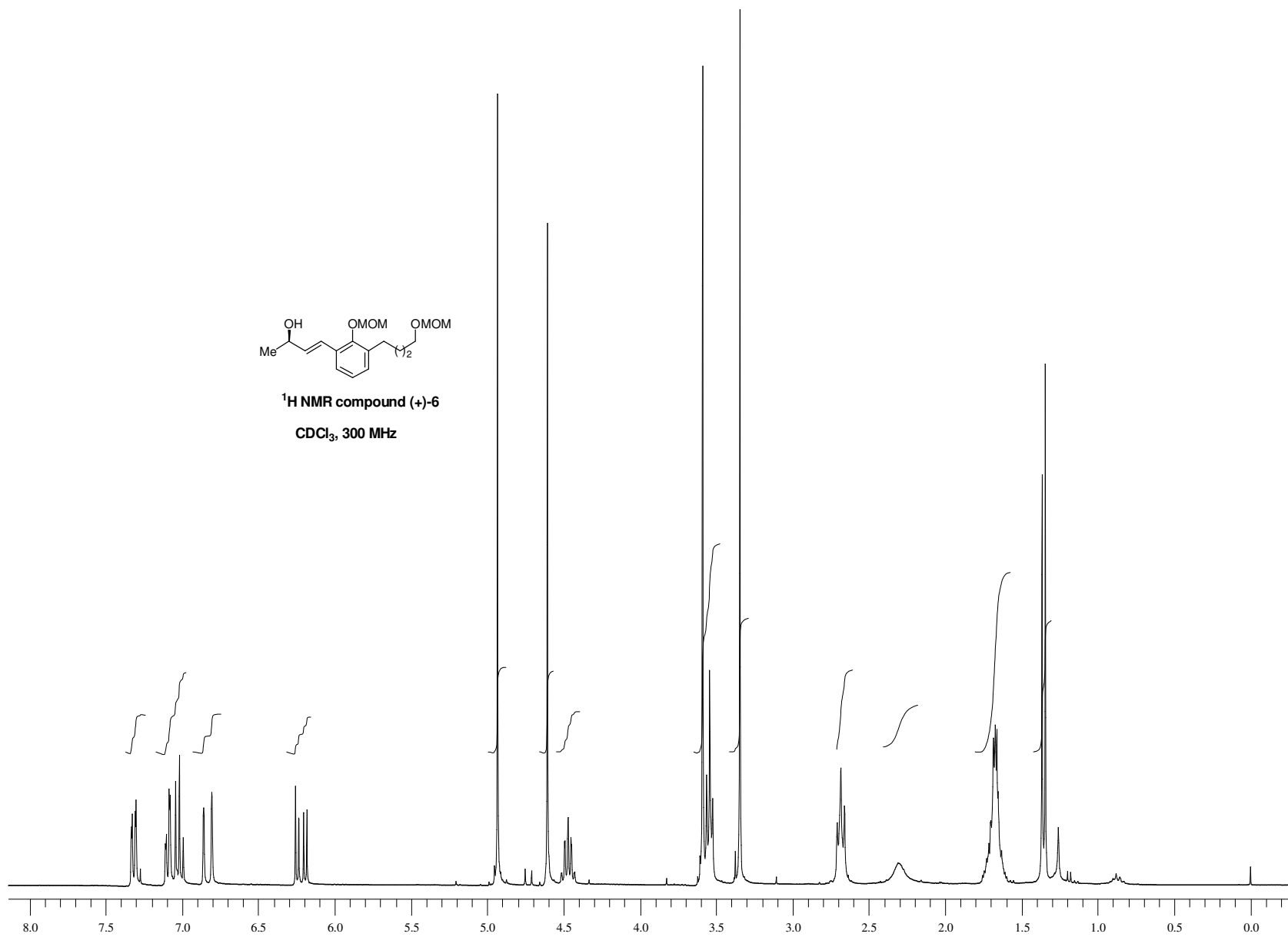
CDCl₃, 75 MHz

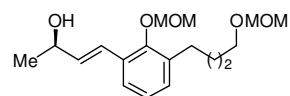




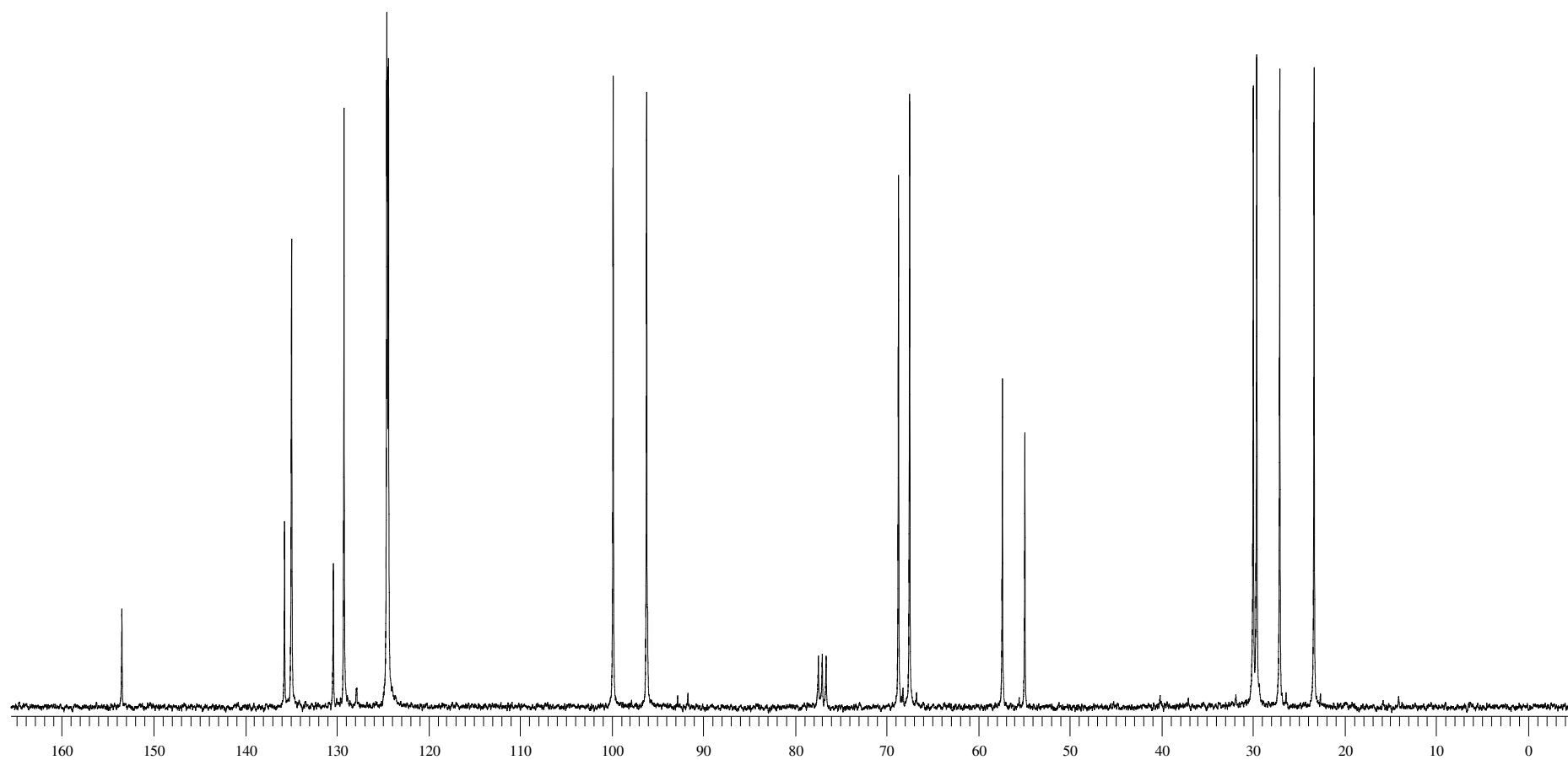
¹H NMR compound (+)-6

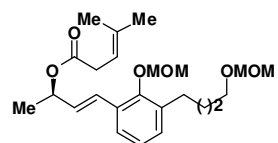
CDCl₃, 300 MHz



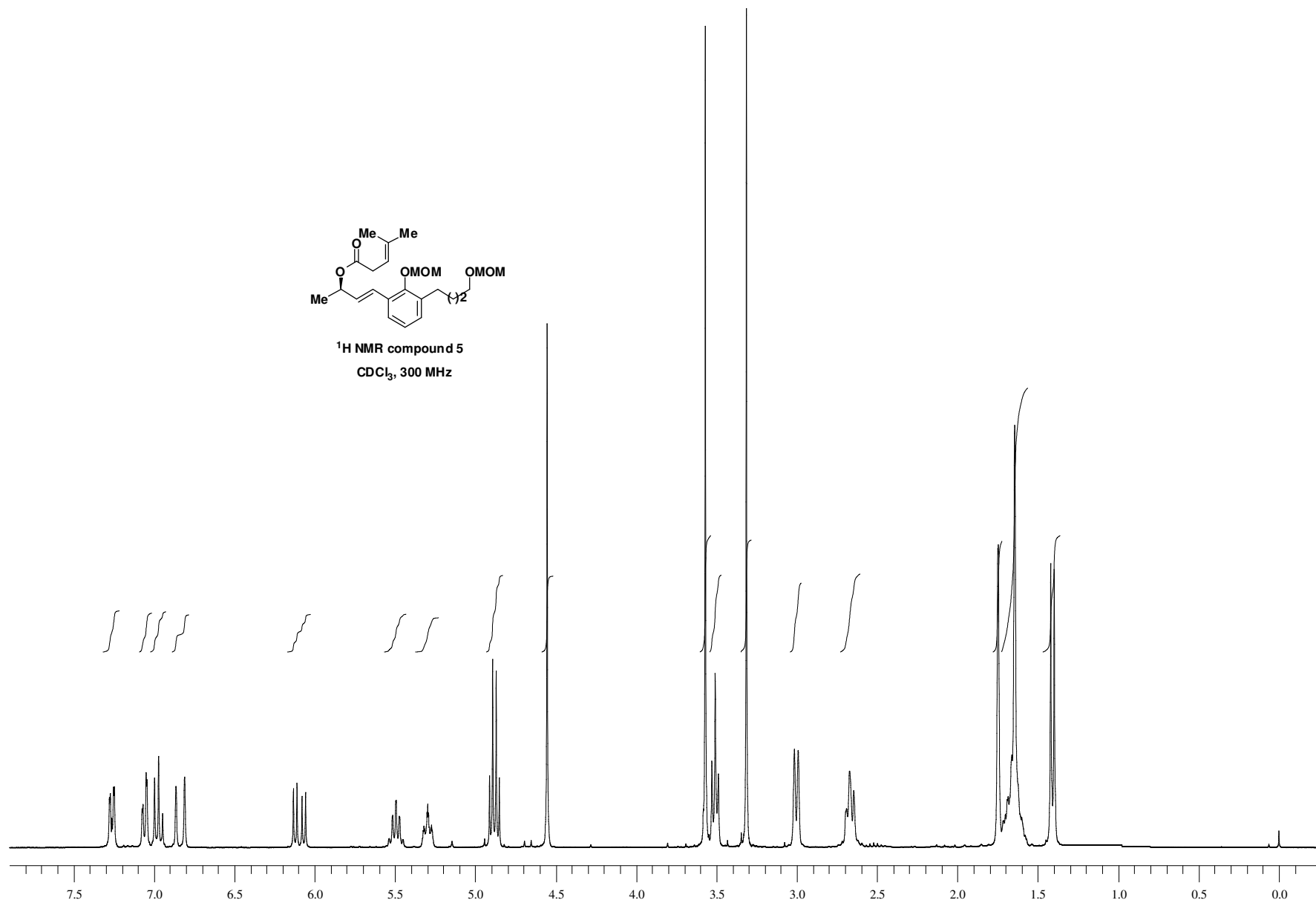


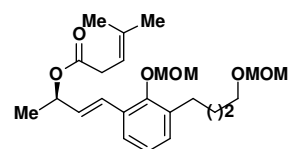
^{13}C NMR compound (+)-6
 CDCl_3 , 75 MHz



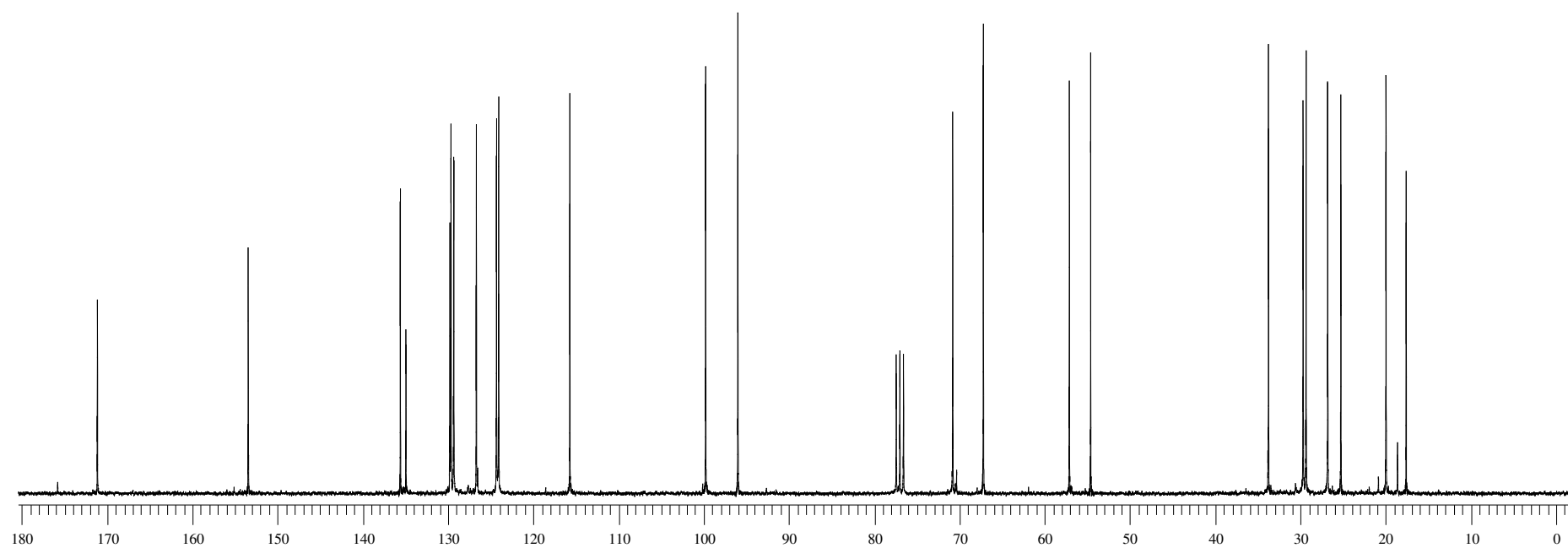


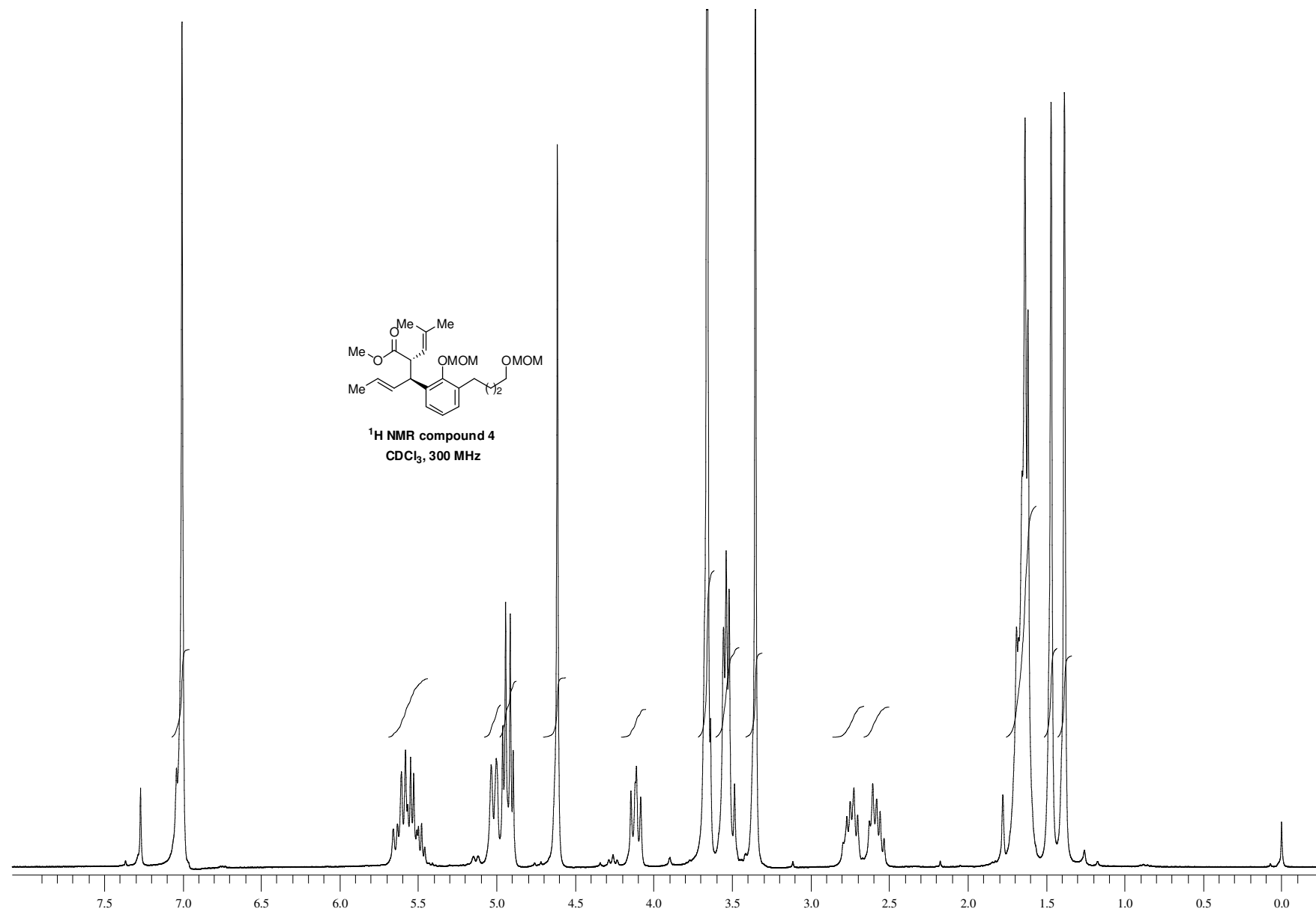
¹H NMR compound 5
CDCl₃, 300 MHz

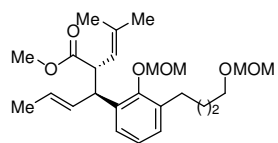




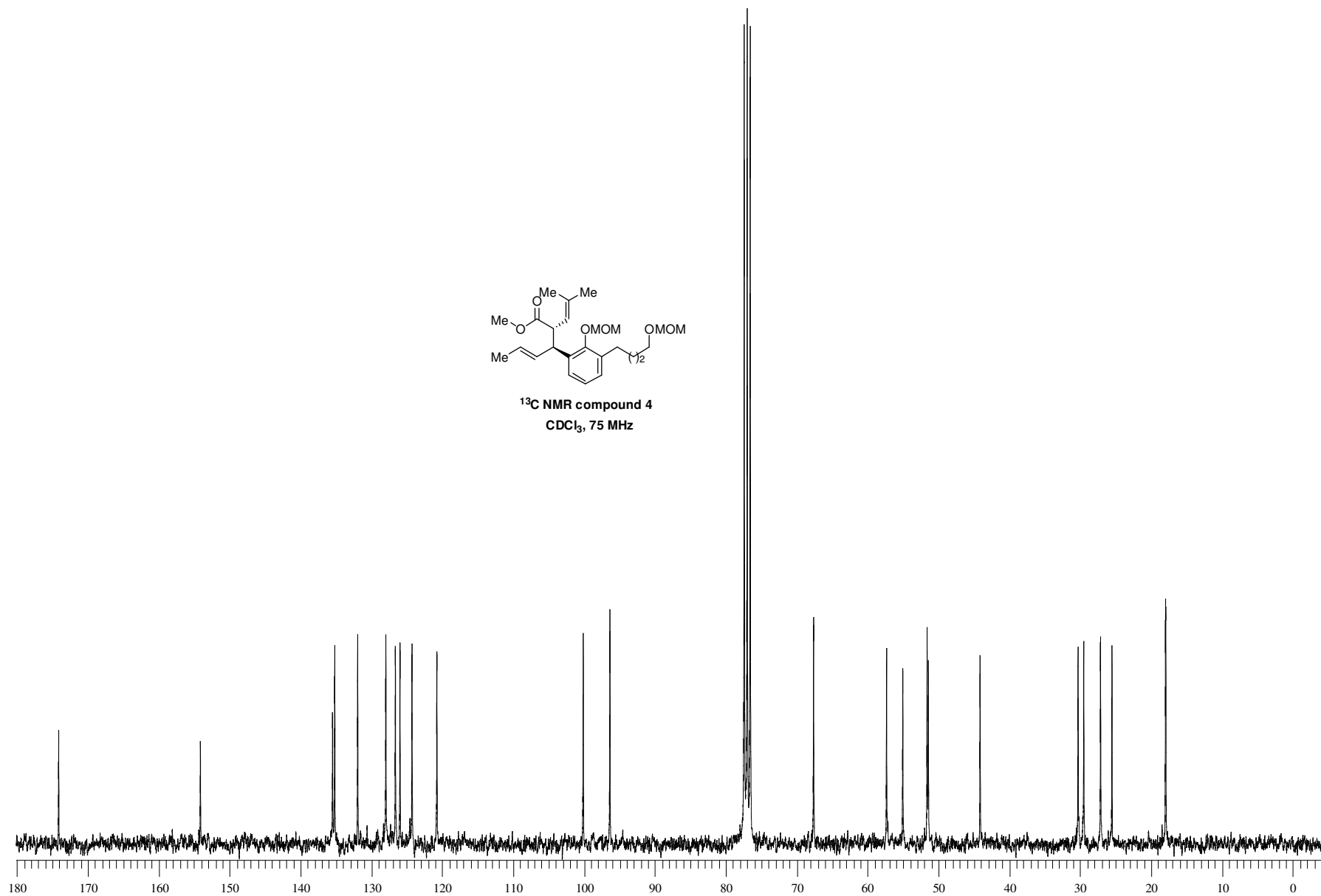
^{13}C NMR compound 5
 CDCl_3 , 75 MHz

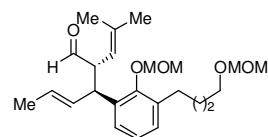




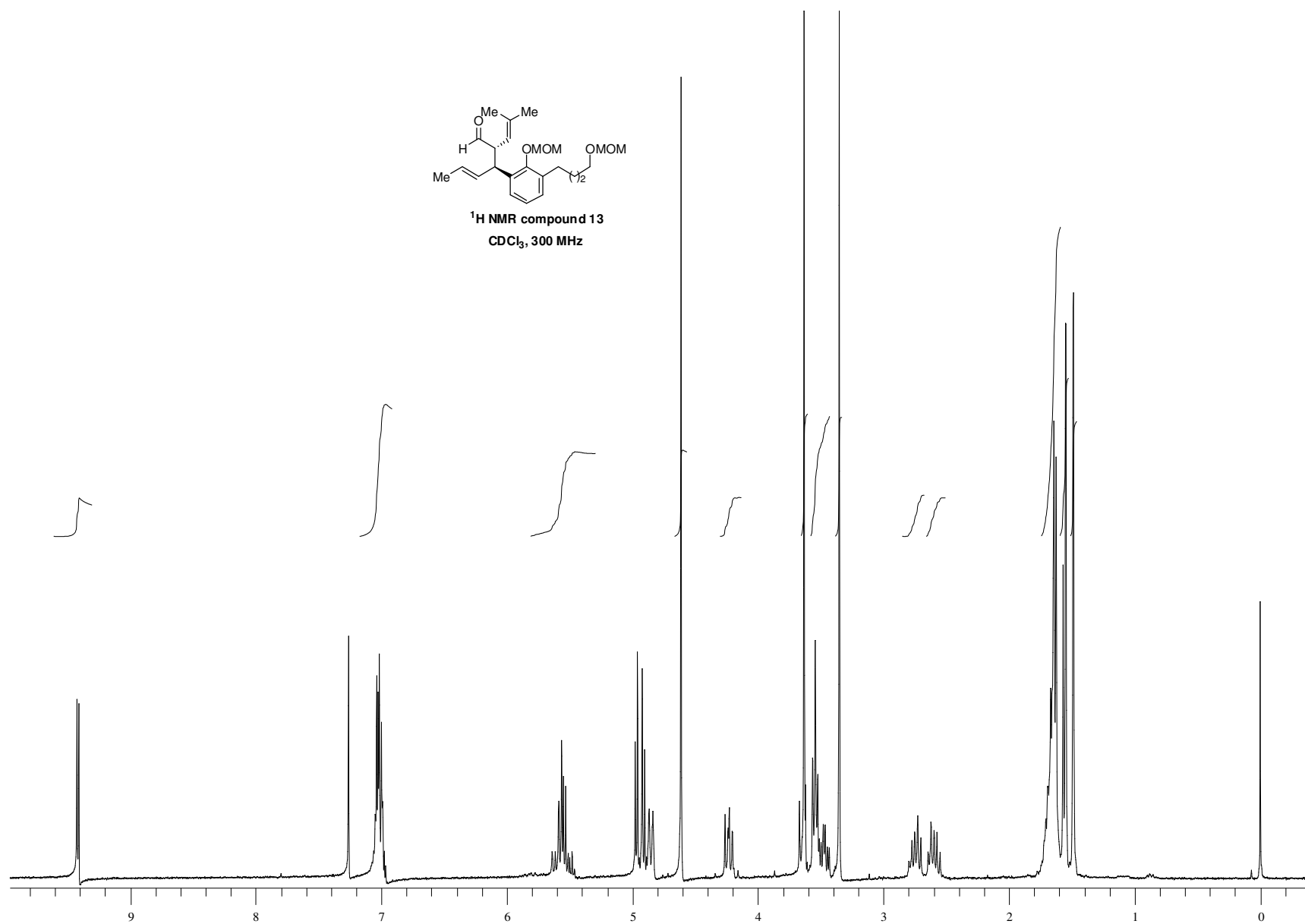


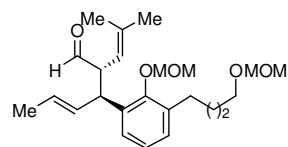
^{13}C NMR compound 4
 CDCl_3 , 75 MHz



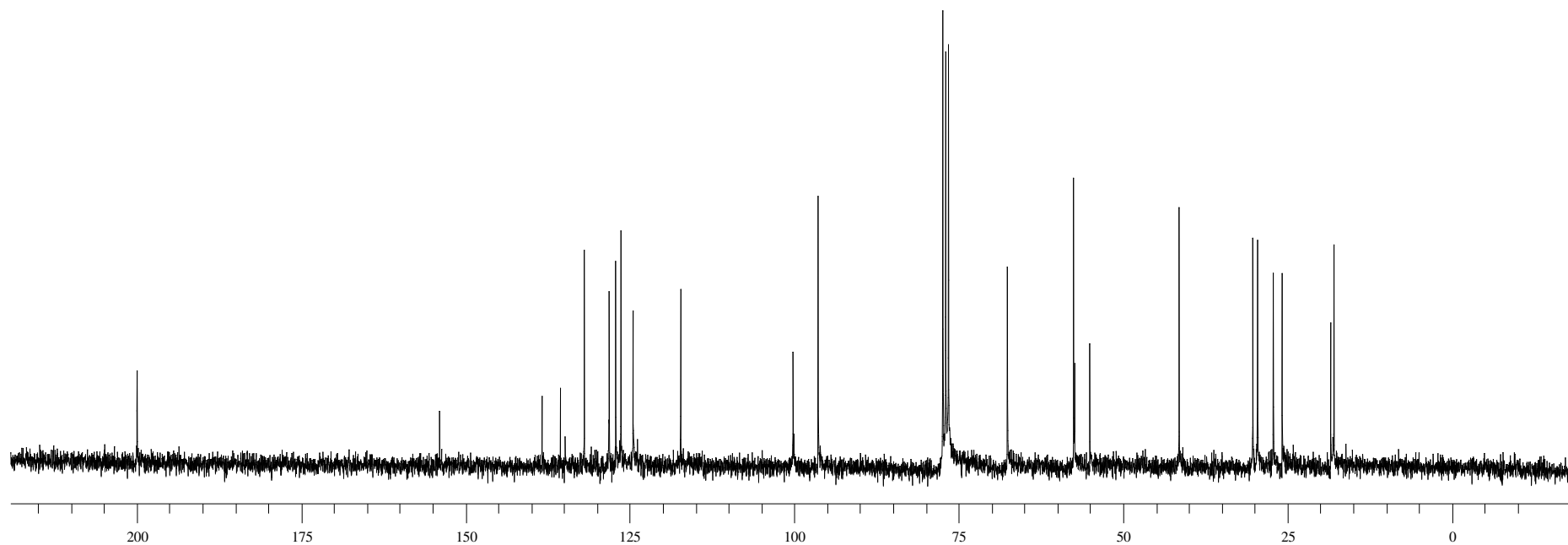


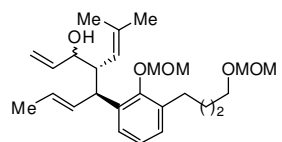
¹H NMR compound 13
CDCl₃, 300 MHz



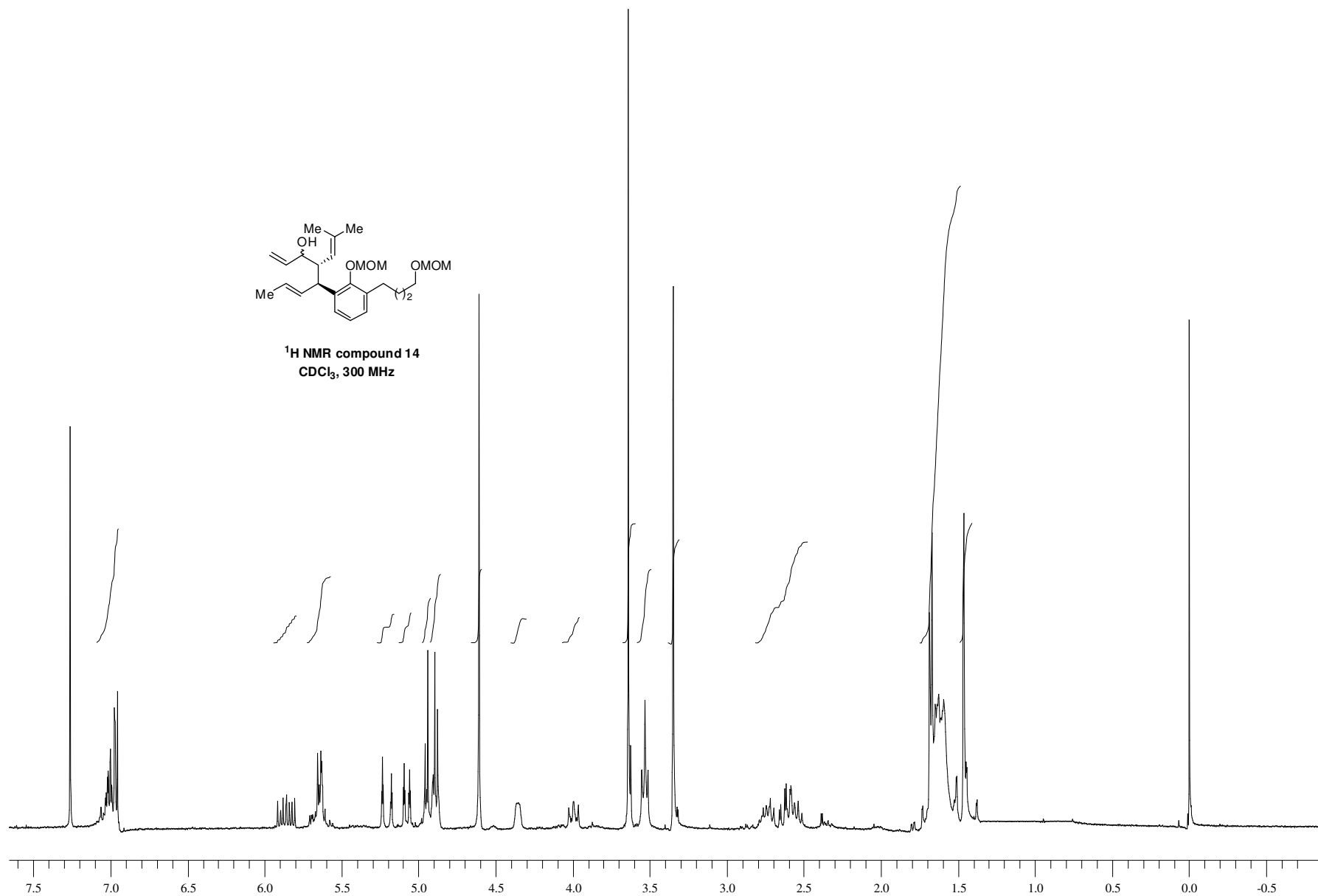


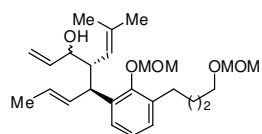
¹³C NMR compound 13
CDCl₃, 75 MHz



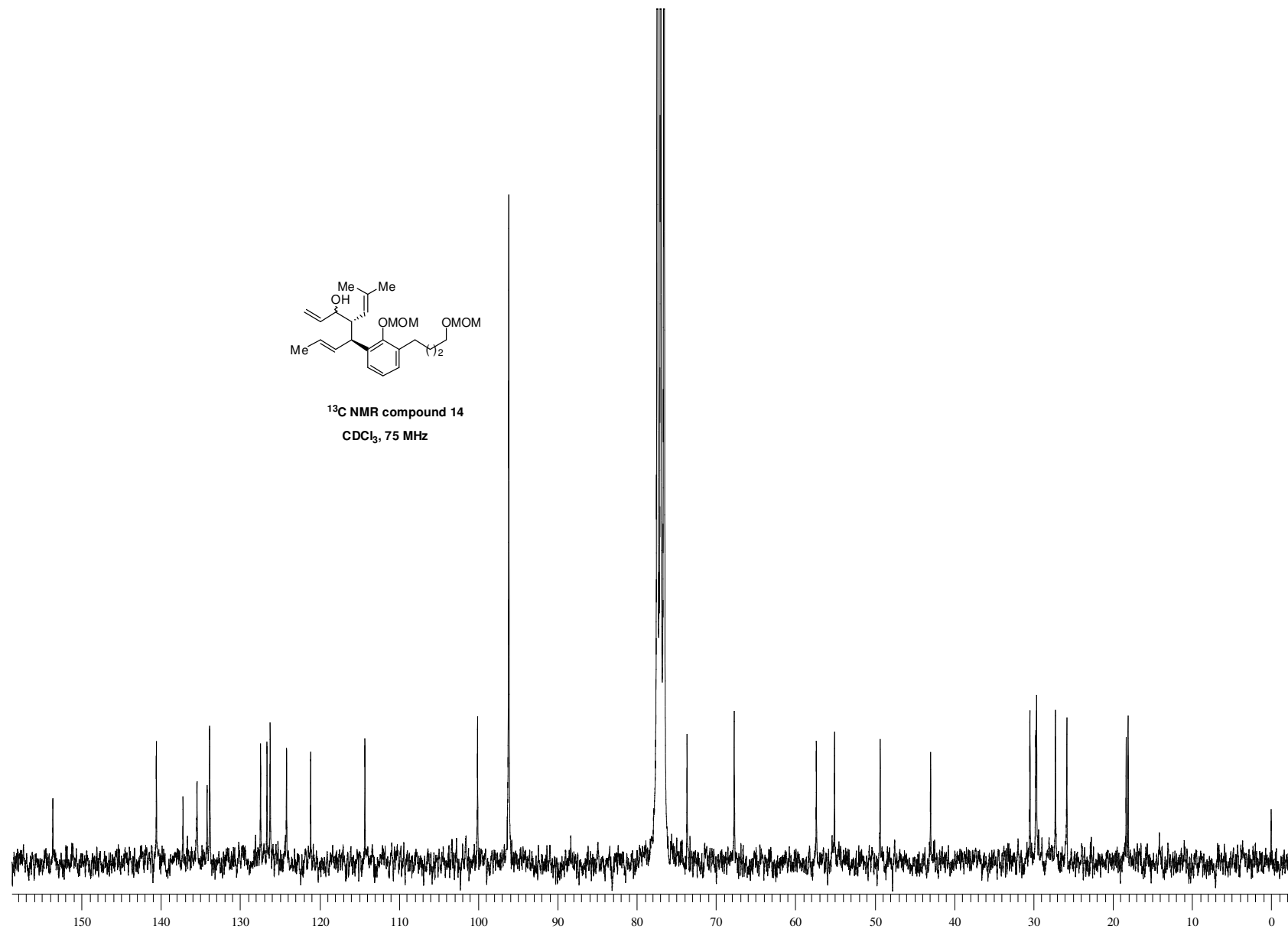


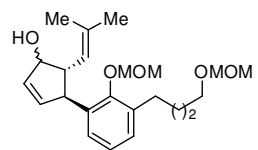
¹H NMR compound 14
CDCl₃, 300 MHz



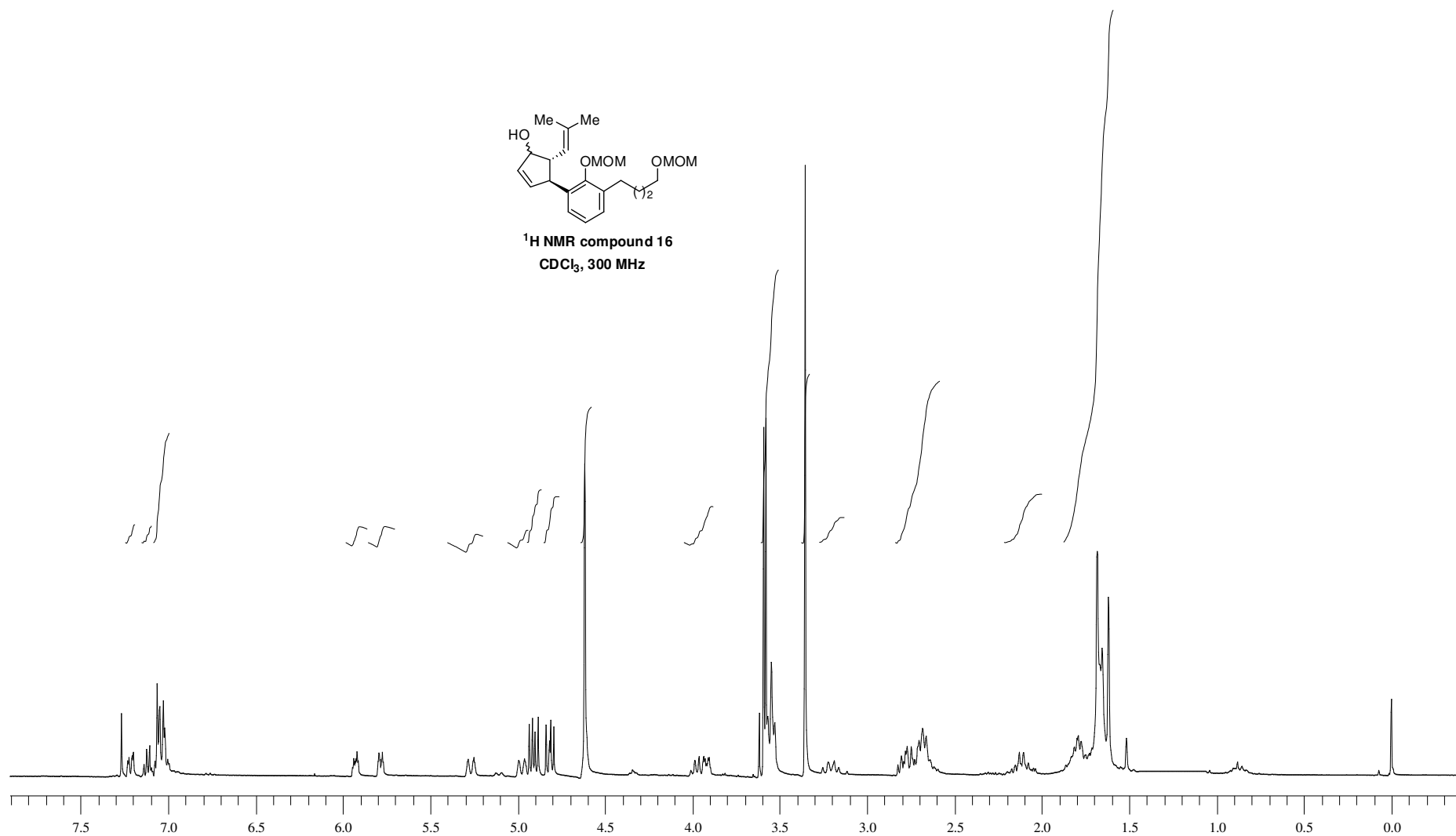


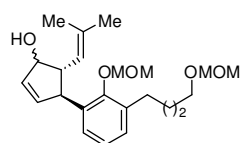
^{13}C NMR compound 14
 CDCl_3 , 75 MHz





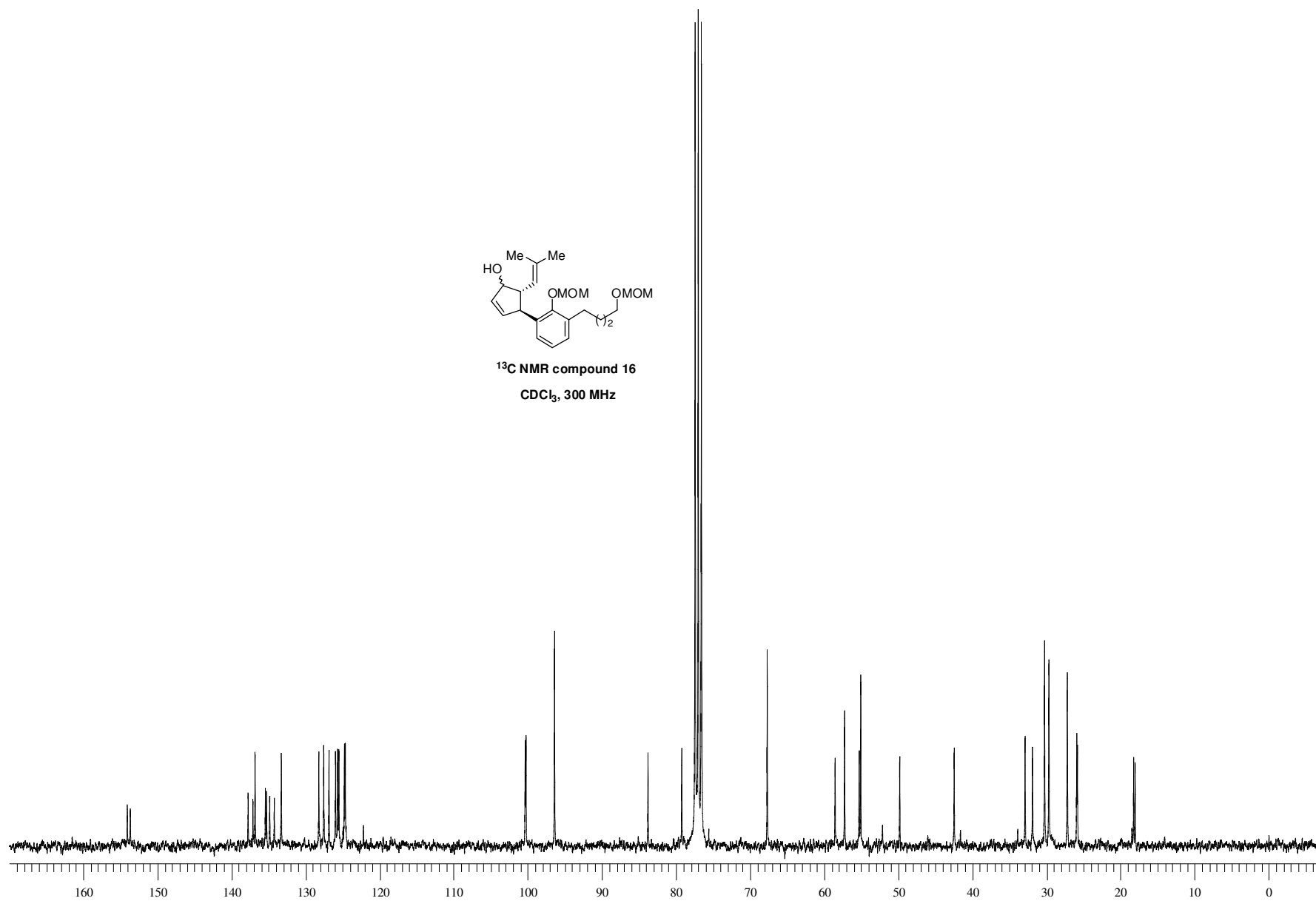
¹H NMR compound 16
CDCl₃, 300 MHz

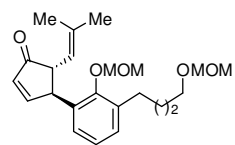




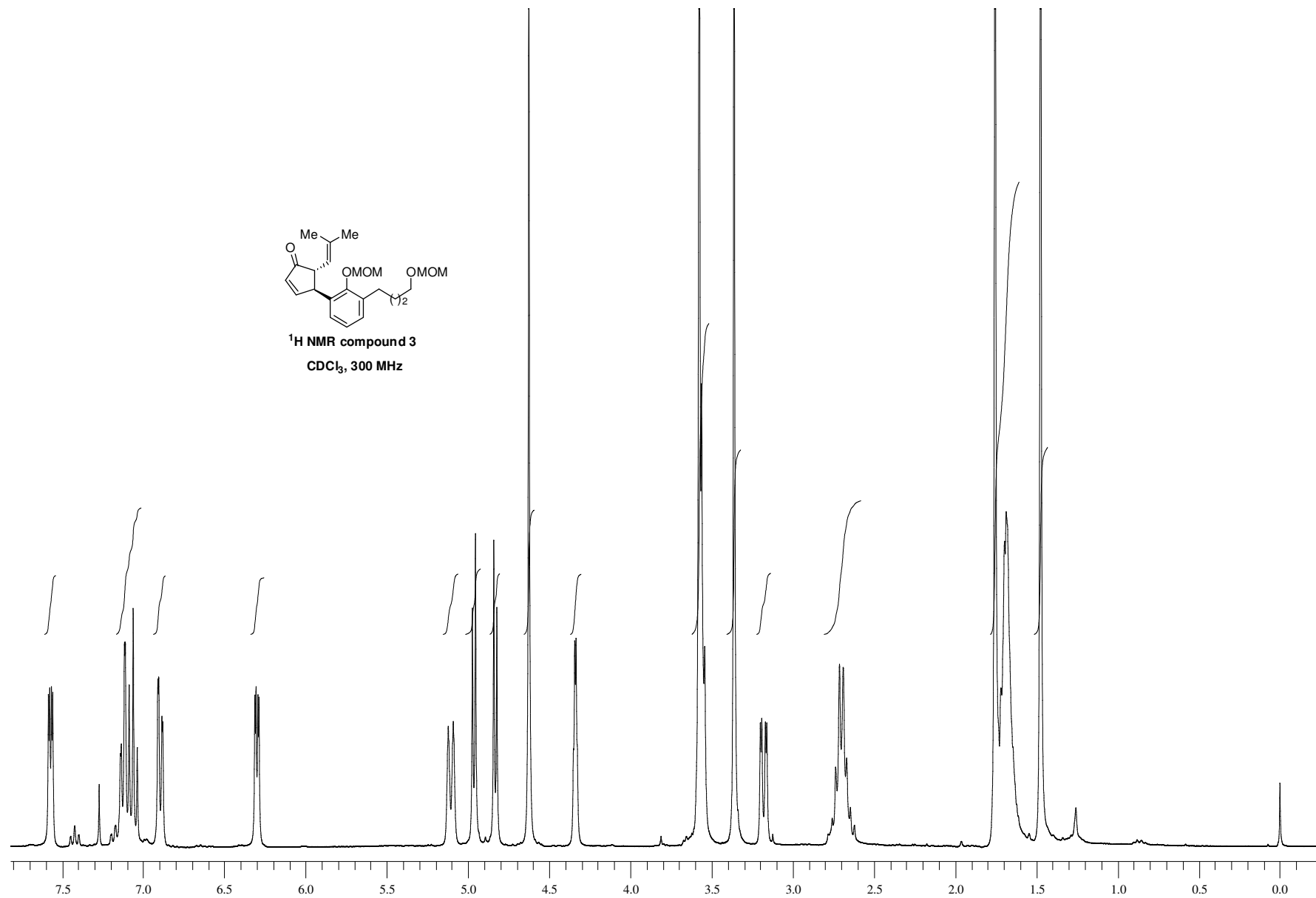
¹³C NMR compound 16

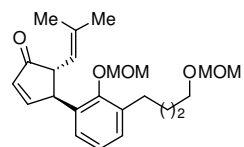
CDCl₃, 300 MHz



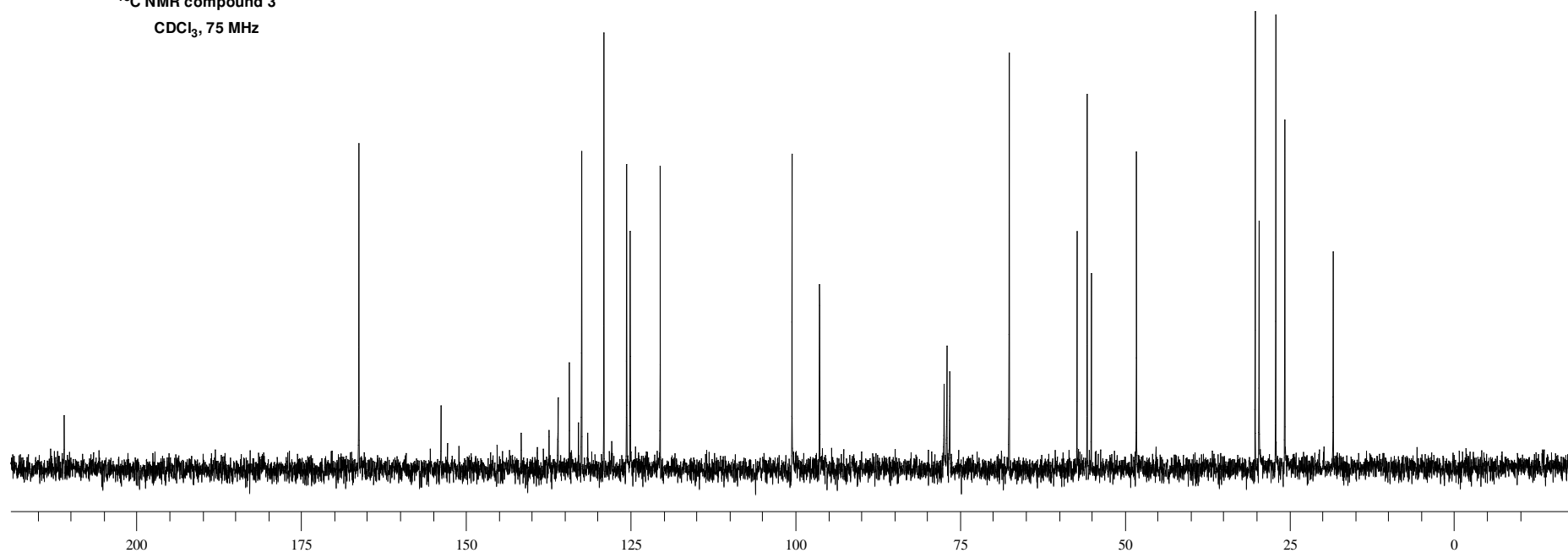


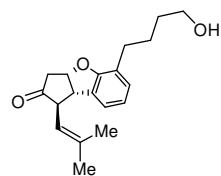
¹H NMR compound 3
CDCl₃, 300 MHz



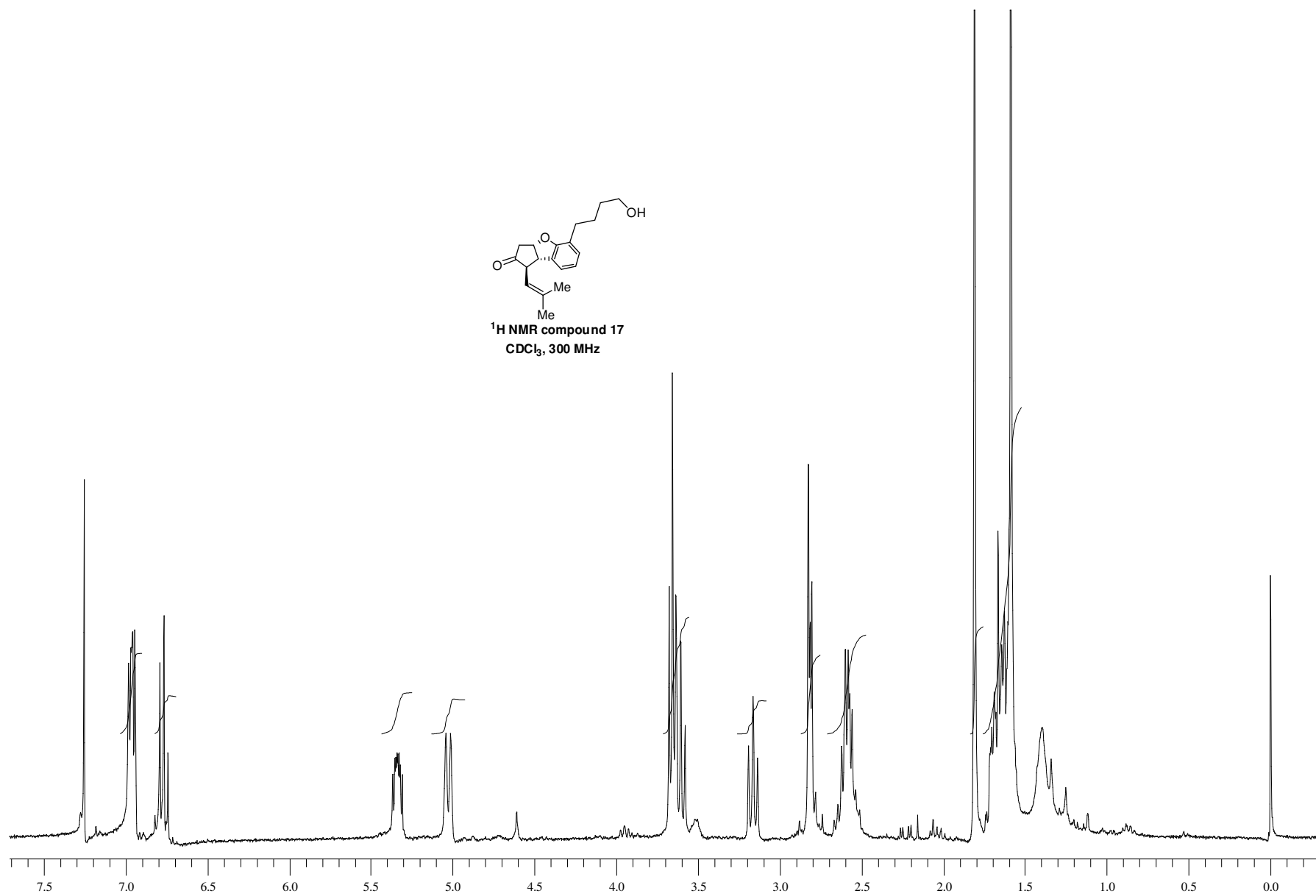


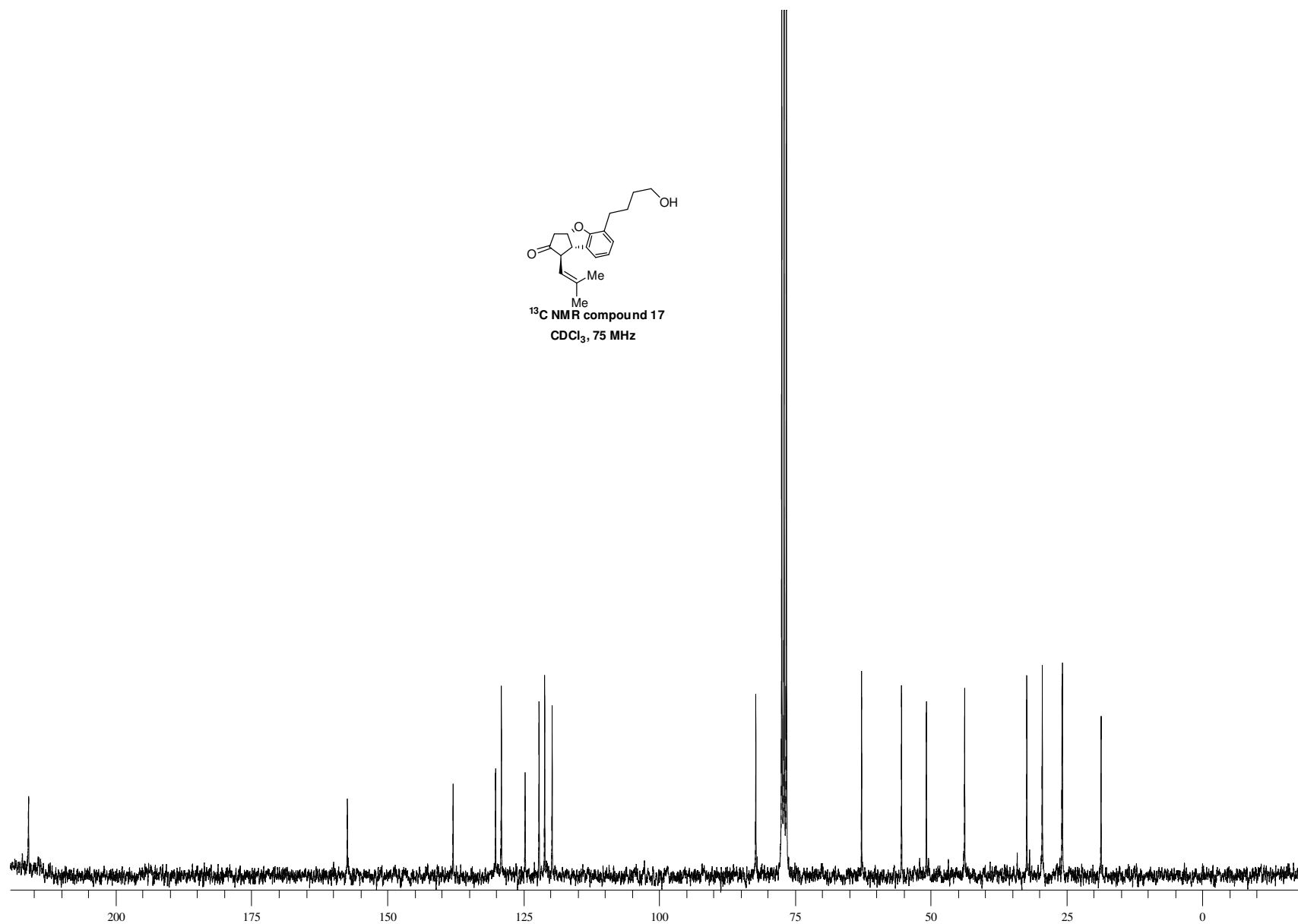
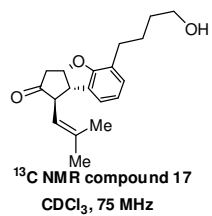
^{13}C NMR compound 3
 CDCl_3 , 75 MHz

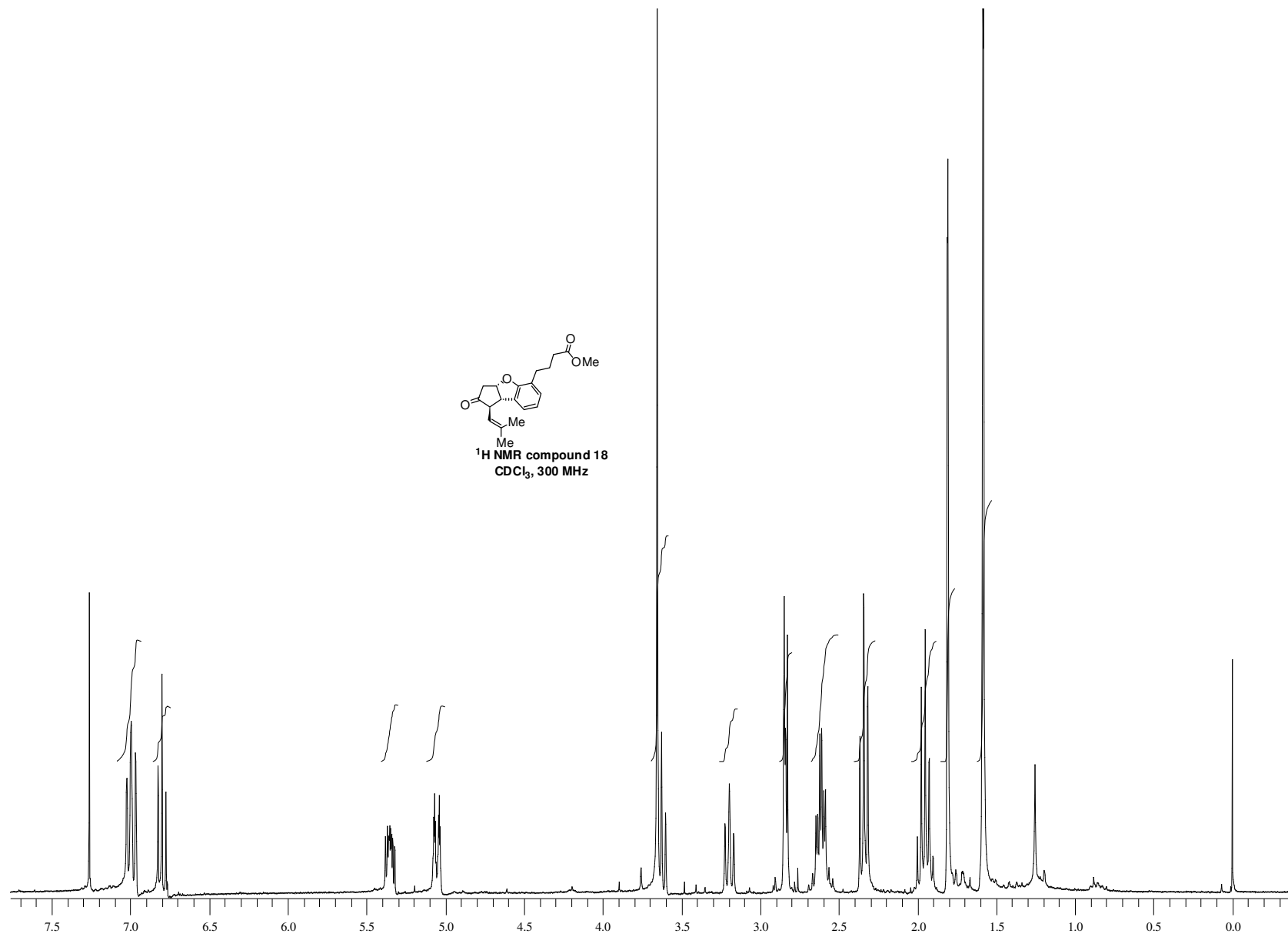


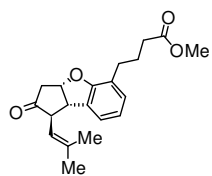


¹H NMR compound 17
CDCl₃, 300 MHz

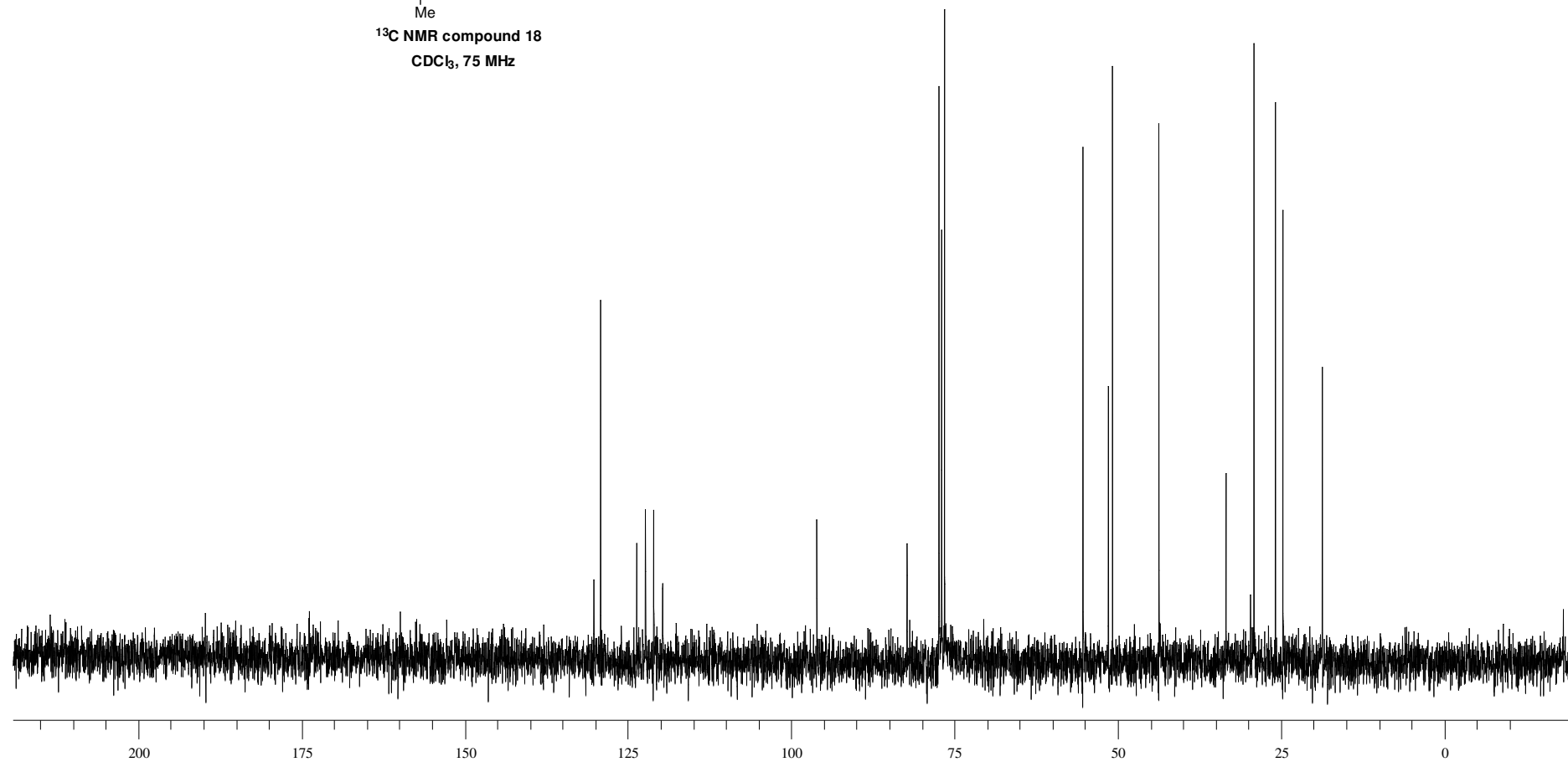


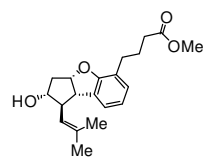




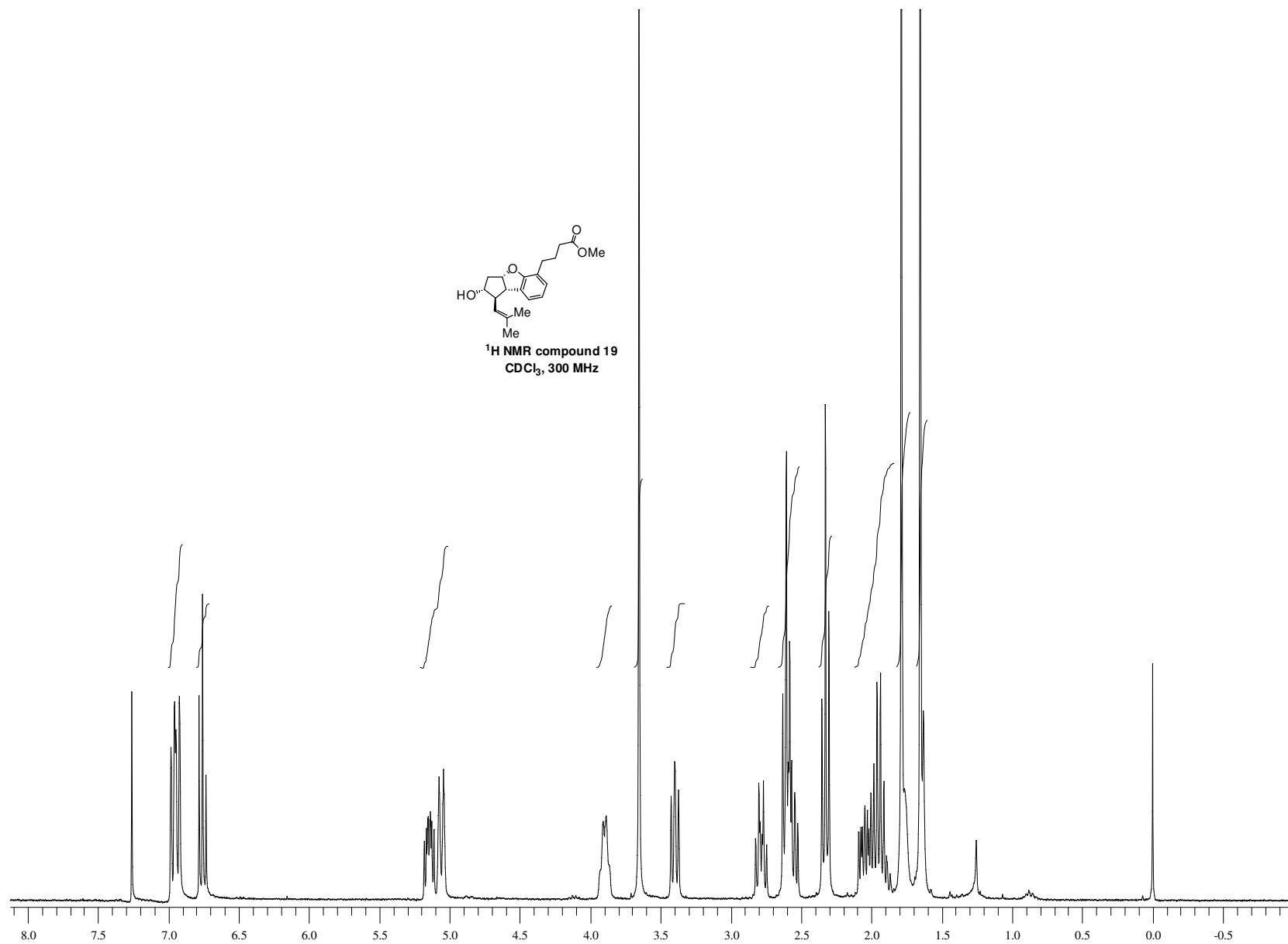


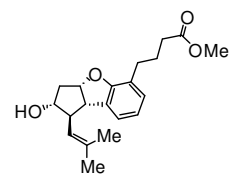
^{13}C NMR compound 18
 CDCl_3 , 75 MHz



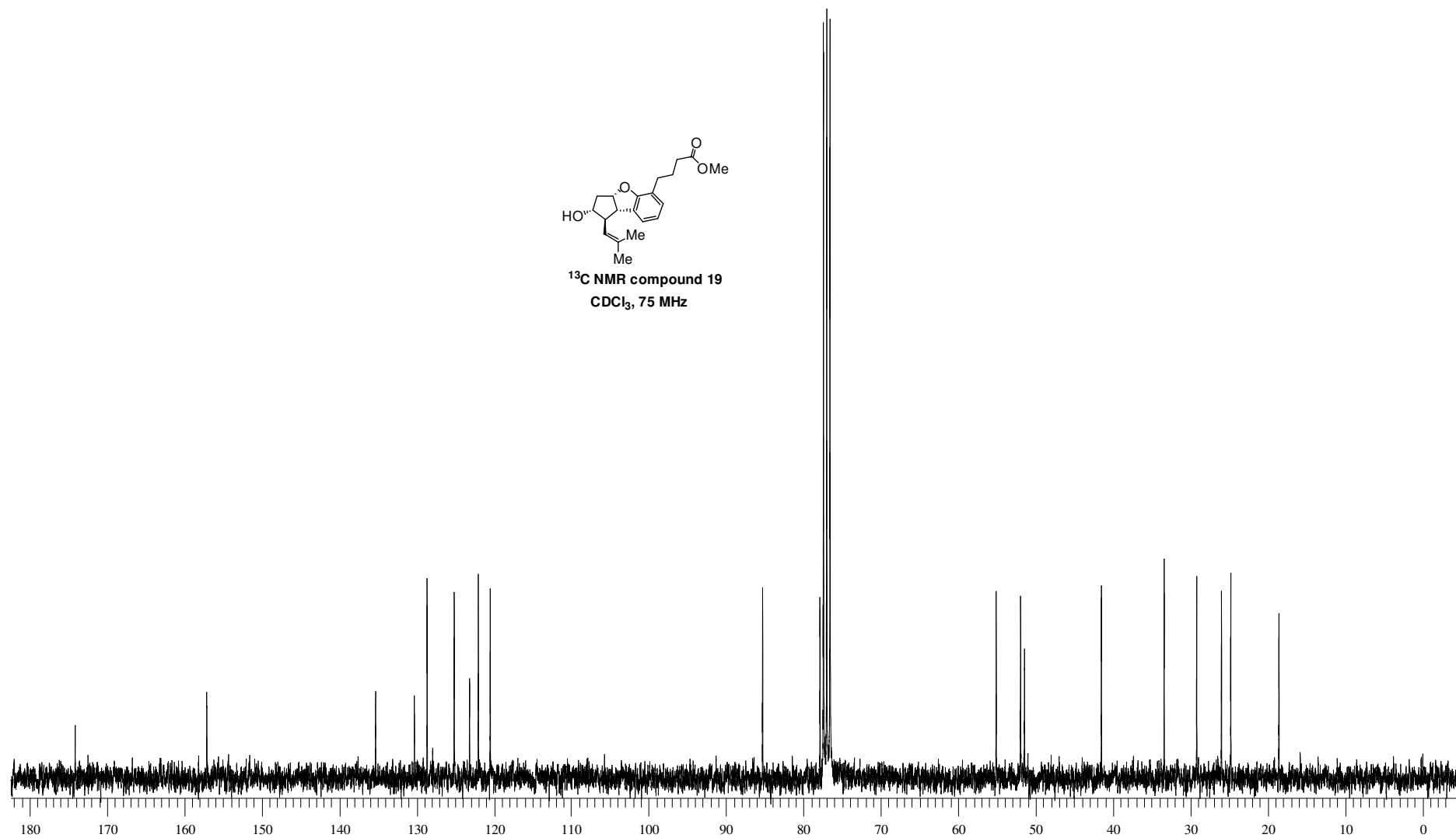


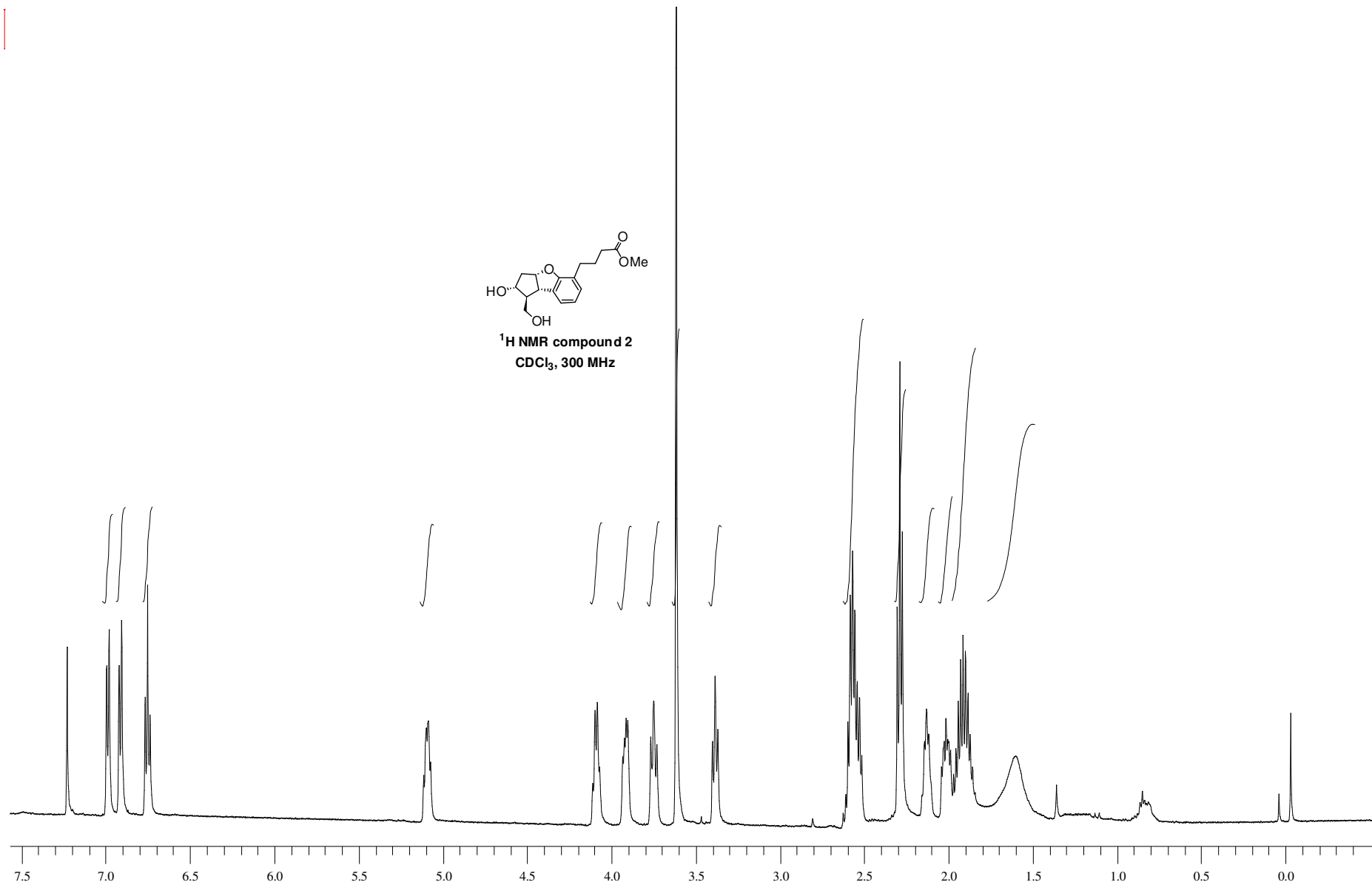
¹H NMR compound 19
CDCl₃, 300 MHz

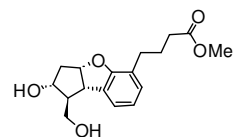




^{13}C NMR compound 19
 CDCl_3 , 75 MHz







^{13}C NMR compound 2
 CDCl_3 , 75 MHz

