Regioselective and Stereoselective Cyclizations of Chloropolyols in Water: Rapid Synthesis of Hydroxytetrahydrofurans

*Baldip Kang, Stanley Chang, Shannon Decker, and Robert Britton**

Department of Chemistry, Simon Fraser University
8888 University Drive, Burnaby, B.C., Canada, V5A 1S6
E-mail: rbritton@sfu.ca

General

All reactions described were performed under an atmosphere of dry argon using oven dried glassware unless otherwise specified. Flash chromatography was carried out with 230-400 mesh silica gel (E. Merck, Silica Gel 60) following the technique described by Still.[i] Concentration and removal of trace solvents was done via a Buchi rotary evaporator using acetone-dry-ice condenser and a Welch vacuum pump.

Nuclear magnetic resonance (NMR) spectra were recorded using deuterochloroform ($CDCl_3$), deuteromethanol (CD_3OD) or deuterobenzene (C_6D_6) as the solvent. Signal positions (δ) are given in parts per million from tetramethylsilane (δ 0) and were measured relative to the signal of the solvent ($CDCl_3$: δ 7.26, ^1H NMR; δ 77.0, ^{13}C NMR; CH_3OD: δ 3.31, ^1H NMR; δ 49.0, ^{13}C NMR; C_6D_6: δ 7.16, ^1H NMR; δ 128.1, ^{13}C NMR). Coupling constants (*J* values) are given in Hertz (Hz) and are reported to the nearest 0.1 Hz. ^1H NMR spectral data are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet), number of protons, coupling constants, assignment (where possible). NMR spectra were recorded on a Bruker Avance 600 equipped with a QNP or TCI cryoprobe (600 MHz) or Bruker 400 (400 MHz). Assignments of ^1H and ^{13}C NMR spectra are based on analysis of ^1H-^1H COSY, HMBC, HMQC, TOCSY and 1D NOESY spectra.

High performance liquid chromatography (HPLC) analysis was performed on an Agilent 1200 HPLC, equipped with a variable wavelength UV-Vis detector and Chiracel OD-H chiral column (0.46 cm x 25 cm).

Infrared (IR) spectra were recorded on a MB-series Bomem/Hartman & Braun Fourier transform spectrophotometer with sodium chloride plates. Only selected, characteristic absorption data are provided for each compound.

Chemical ionization (CI) mass spectra were recorded on a Varian 4000 GC/MS/MS mass spectrometer. High resolution mass spectra were performed on an Agilent 6210 TOF LC/MS mass spectrometer.

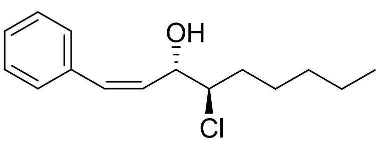
Optical rotation was measured on a Perkin Elmer Polarimeter 341 at 589 nm.

Microwave reactions were performed in either a Biotage Initiator 2.5 or a CEM Discover LabMate at 2.45 GHz.

General procedure for the cyclization of chloropolyols

The chlorodiol, chlorotriol, or chlorotetrol (0.1 mmol) was placed in a 10 mL vial, deionized water (1 mL) was added and the vial was sealed in a CEM Discover LabMate. The reaction mixture was then heated to 120 °C in a microwave (MW) (as monitored by a vertically focused IR temperature sensor) and maintained at this temperature for 20 minutes. After this time, the mixture was diluted with ethyl acetate (5 mL) washed with brine (5 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$) and concentrated. Purification of the crude material by flash chromatography afforded the desired tetrahydrofuran.

Preparation of (1*Z*,3*S**,4*R**)-4-chloro-1-phenylnon-1-en-3-ol (7)



To a cold (-78 °C), stirred solution of iodostyrene[ii] (115 mg, 0.50 mmol) in THF (10 mL) was added *n*-butyllithium (2.0 M soln. in hexane, 275 µL, 0.55 mmol). The resulting solution was stirred at -78 °C for 30 minutes. After this time, a solution of 2-chloroheptanal[vi] (82 mg, 0.55 mmol) in THF (1.0 mL) was then added in one portion at -78 °C and the resulting mixture was stirred for an additional 30 minutes. Saturated aqueous NH_4Cl (2 mL) was then added, the mixture was diluted with ethyl acetate (10 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$) and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes-ethyl acetate) afforded (1*Z*,3*S**,4*R**)-4-chloro-1-phenylnon-1-en-3-ol (**7**) (111 mg, 88%) as a clear oil.

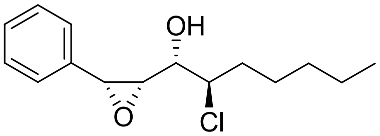
^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.37-7.35 (m, 4H), 7.29 (m, 1H), 6.76 (dd, 1H, J = 0.9, 11.4 Hz), 5.85 (dd, 1H, J = 9.0, 11.4 Hz), 4.63 (dddd, 1H, J = 0.9, 4.2, 7.8, 9.0 Hz), 4.11 (m, 1H), 2.22 (d, 1H, J = 7.8 Hz), 1.66 (m, 2H), 1.51 (m, 1H), 1.26 (m, 5H), 0.91 (t, 3H, J = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 136.3, 134.5, 134.2, 129.8, 128.7, 128.5, 128.4, 127.6, 70.1, 68.6, 33.6, 31.2, 26.2, 22.5, 14.0.

IR (neat): 3393, 2955, 2930, 2859 cm^{-1}

Exact mass calcd. for $C_{15}H_{20}Cl$: 235.1254 (M-H_2O); found: 235.1248 (M-H_2O).

Preparation of (1*S**,2*R**)-2-chloro-1-[(2'*S**,3'*R**)-3'-phenyloxiran-2-yl]heptan-1-ol (8)



To a solution of (1*Z*,3*S**,4*R**)-4-chloro-1-phenylnon-1-en-3-ol (**7**) (630 mg, 2.5 mmol) in dichloromethane (20 mL) was added *m*-chloroperoxybenzoic acid (77%, 1.68 g, 7.5 mmol). The resulting solution was stirred for 3 hours. Saturated aqueous sodium thiosulfate (10 mL) was then added, the mixture was diluted with dichloromethane (20 mL) and washed with a saturated aqueous solution of sodium bicarbonate, and the layers separated. The aqueous phase was extracted with dichloromethane (3 x 20 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$) and concentrated to provide a crude white solid. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes-ethyl acetate) afforded (1*S**,2*R**)-2-chloro-1-[(2*S**,3*R**)-3-phenyloxiran-2-yl]heptan-1-ol (**8**) (520 mg, 77%, 15:1 diastereomeric mixture) as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.38-7.30 (m, 5H), 4.27 (d, 1H, *J* = 4.2 Hz), 3.85 (ddd, 1H, *J* = 4.8, 7.2, 7.8 Hz), 3.46 (dd, 1H, *J* = 4.2, 7.8 Hz), 3.27 (m, 1H), 2.41 (d, 1H, *J* = 4.8 Hz), 1.50 (m, 2H), 1.41 (m, 1H), 1.26-1.04 (m, 5H), 0.84 (t, 3H, *J* = 7.2 Hz).

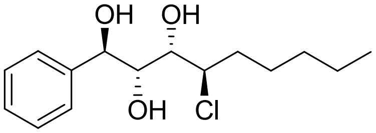
^{13}C NMR (150 MHz, $CDCl_3$) δ: 134.6, 128.3, 128.1, 126.2, 70.8, 64.9, 60.3, 58.8, 33.7, 31.1, 25.9, 22.3, 13.9.

IR (neat): 3420, 2956, 2930, 2860, 1457 cm^{-1}

Exact mass calcd. for $C_{15}H_{22}ClO_2$: 269.1303 (M+H); found: 269.1291 (M+H).

Preparation of (1*R**,2*R**,3*S**,4*R**)-4-chloro-1-phenylnonane-1,2,3-triol (9)

Method A



To a solution of (1*S**,2*R**)-2-chloro-1-[(2'*S**,3'*R**)-3'-phenyloxiran-2-yl]heptan-1-ol (**8**) (31 mg, 0.12 mmol) in trifluoroethanol (1.0 mL) was added 0.5 M aqueous sulfuric acid (1.0 mL, 0.50 mmol). The resulting solution was stirred for 40 hours. The mixture was then diluted with dichloromethane (10 mL), washed with water (10 mL) and the layers separated. The aqueous phase was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$) and concentrated to provide a crude white solid (as a 8:1 diastereomeric mixture). Purification of the crude product by flash chromatography (silica gel, 2:1 hexanes-ethyl acetate) afforded (1*R**,2*R**,3*S**,4*R**)-4-chloro-1-phenylnonane-1,2,3-triol (**9**) (22 mg, 67%) as a white solid (m.p. 144 °C)

Method B

To a solution of (1*Z*,3*S**,4*R**)-4-chloro-1-phenylnon-1-en-3-ol (**7**) (500 mg, 2.0 mmol) in acetone (18 mL) and water (12 mL) was added *N*-methylmorpholine *N*-oxide (351 mg, 3.0 mmol) and osmium tetroxide (5 mg, 0.02 mmol). The resulting solution was stirred for 24 hours. After this time, saturated aqueous sodium hydrosulfite (10 mL) was added, the mixture was filtered through a pad of Celite® and the cake washed with acetone (3 x 20 mL). The filtrate was neutralized to pH 7 with aqueous sulfuric acid, and the acetone was removed by rotary evaporation. The mixture was diluted with ethyl acetate (20 mL) and washed with brine (20 mL) and the layers separated. The aqueous phase was extracted with ethyl acetate (3 x 20 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$) and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 2:1 hexanes-ethyl acetate) afforded (1*R**,2*R**,3*S**,4*R**)-4-chloro-1-phenylnonane-1,2,3-triol (**9**) (450 mg, 79%) as a white solid (m.p. 144 °C).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.40-7.39 (m, 4H), 7.33 (m, 1H), 4.95 (d, 1H, *J* = 5.4 Hz), 4.15 (d, 1H, *J* = 5.4 Hz), 3.95 (ddd, 1H, *J* = 3.0, 7.8, 10.8 Hz), 3.82 (d, 1H, *J* = 7.8 Hz), 2.99 (s, 1H), 2.76 (s, 1H), 2.51 (s, 1H), 1.94 (m, 1H), 1.62-1.52 (m, 2H), 1.34-1.21 (m, 5H), 0.88 (t, 3H, *J* = 6.0 Hz).

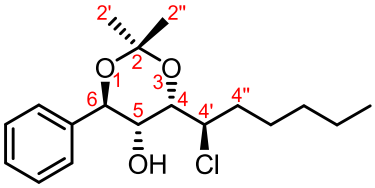
^{13}C NMR (150 MHz, $CDCl_3$) δ: 140.2, 128.9, 128.2, 126.2, 76.1, 72.62, 72.58, 63.1, 33.6, 31.3, 25.7, 22.5, 14.0.

IR (neat): 3549, 3365, 2955, 2926, 2861, 1455 cm^{-1}

Exact mass calcd. for $C_{15}H_{23}ClO_3Na$: 309.1233 (M+Na); found: 309.1231 (M+Na).

The relative stereochemistry of the newly formed carbinol stereocentres were determined by analysis of the ^{1}H and ^{13}C NMR spectra and 1D NOESY spectra recorded on the corresponding acetonide following the method reported by Rychnovsky.[iii]

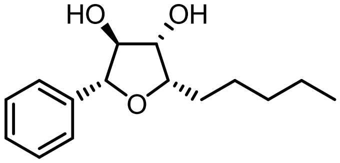
To a solution of (1*R**,2*R**,3*S**,4*R**)-4-chloro-1-phenylnonane-1,2,3-triol (**9**) (10 mg, 0.035 mmol) in dichloromethane (3 mL) was added 2,2-dimethoxypropane (17 µL, 0.14 mmol) and *p*-toluenesulfonic acid (1 mg, 0.005 mmol). The mixture was allowed to stir for 1 hour and then concentrated to give a crude yellow product. Purification of the crude product by flash chromatography (silica gel, 4:1 hexanes-ethyl acetate) afforded the corresponding acetonide.



^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.48 (d, 2H, *J* = 7.2 Hz), 7.37 (t, 2H, *J* = 7.2 Hz), 7.30 (d, 1H, J = 7.2 Hz), 4.57 (d, 1H, *J* = 7.2 Hz, H-6), 4.19 (ddd, 1H, *J* = 3.2, 5.6, 7.2 Hz, H-5), 4.14 (dt, 1H, *J* = 2.4, 9.6 Hz, H-4'), 3.92 (dd, 1H, *J* = 3.2, 9.6 Hz, H-4), 2.16 (d, 1H, *J* = 5.6 Hz, OH), 2.08 (m, 1H), 1.68 (m, 2H), 1.48 (s, 3H, H-2'), 1.42 (s, 3H, H-2"), 1.38-1.26 (m, 6H), 0.91 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 140.5, 128.5, 127.8, 126.3, 102.0 (C2), 75.3 (C6), 74.7 (C5), 73.9 (C4), 59.4 (C4'), 34.0 (C4"), 31.4, 25.2, 24.0 (C2"), 24.3 (C2'), 22.6, 14.0.

Preparation of (2*S**,3*S**,4*S**,5*R**)-2-pentyl-5-phenyltetrahydrofuran-3,4-diol (10)



(1*R**,2*R**,3*S**,4*R**)-4-chloro-1-phenylnonane-1,2,3-triol (**9**) (500 mg, 1.7 mmol) was placed in a 10 mL vial, deionized water (3 mL) was added and the vial was sealed in a CEM Discover LabMate. The reaction mixture was then heated to 120 °C (as monitored by a vertically focused IR temperature sensor) and maintained at this temperature for 20 minutes. After this time, the water was decanted off and the crude powder dried. Purification of the crude product by flash chromatography (silica gel, 2:1 hexanes-ethyl acetate) afforded (2*S**,3*S**,4*S**,5*R**)-2-pentyl-5-phenyltetrahydrofuran-3,4-diol (**10**) (390 mg, 91%) as a white solid (m.p. 122 °C).

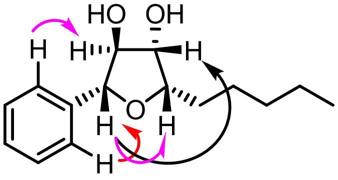
^{1}H NMR (600 MHz, CDCl$_3$) δ: 7.41 (d, 2H, *J* = 7.2 Hz), 7.35 (t, 2H, *J* = 7.2 Hz), 7.28 (t, 1H, *J* = 7.2 Hz), 4.62 (d, 1H, *J* = 4.2 Hz), 4.10-4.07 (m, 2H), 4.03 (ddd, 1H, *J* = 1.8, 4.2, 6.6 Hz), 2.21 (d, 1H, *J* = 4.2 Hz), 1.78 (m, 1H), 1.71 (m, 1H), 1.66 (d, 1H, *J* = 6.6 Hz), 1.53 (m, 1H), 1.43 (m, 1H), 1.40-1.32 (m, 4H), 0.91 (t, 3H, *J* = 6.6 Hz).

^{13}C NMR (150 MHz, CDCl$_3$) δ: 140.1, 128.6, 127.8, 126.0, 86.3, 85.4, 81.4, 79.3, 31.9, 28.5, 25.8, 22.5, 14.0.

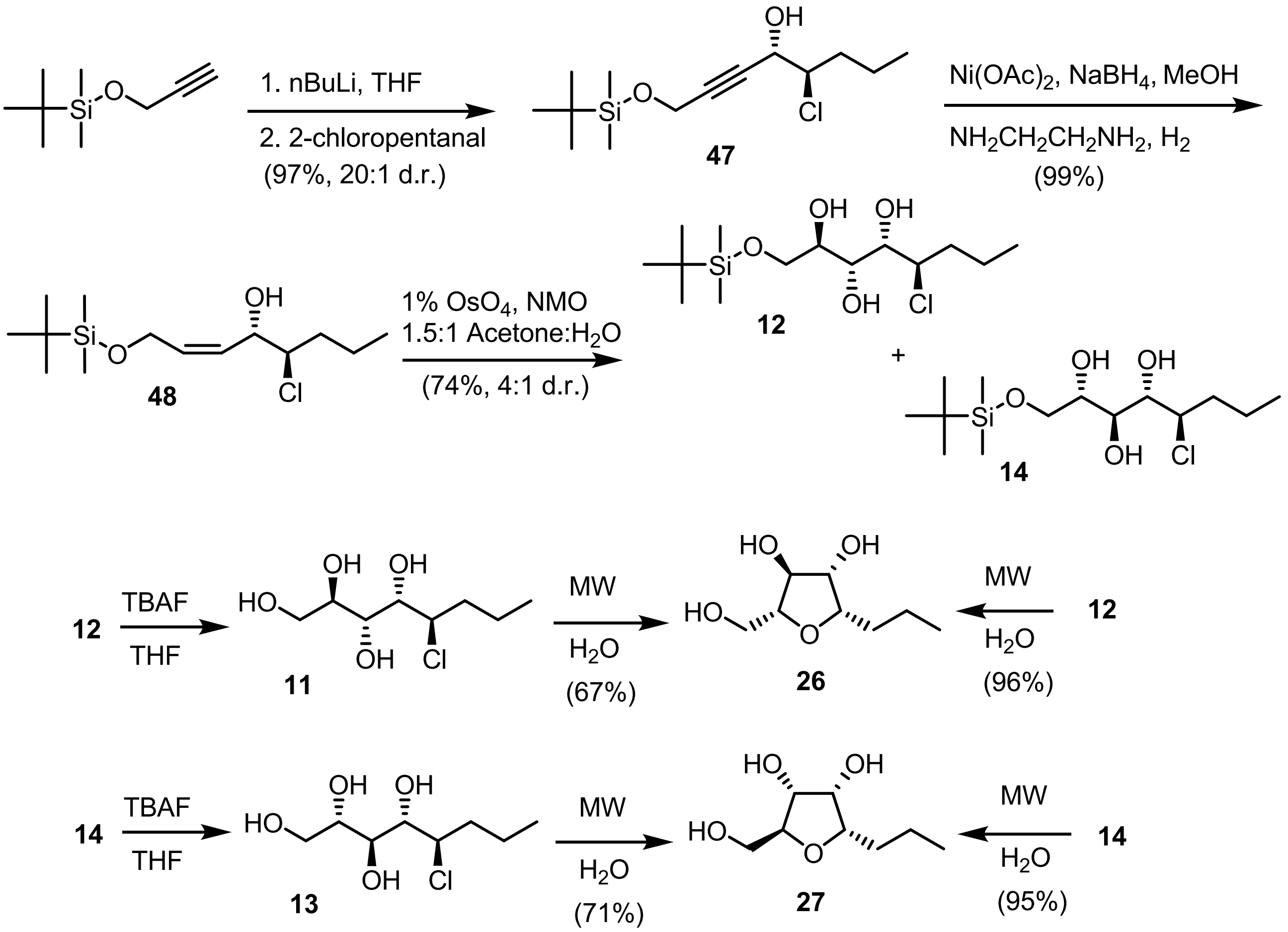
IR (neat): 3344, 3054, 2917, 2856, 1266 cm^{-1}

Exact mass calcd. for $C_{15}H_{22}O_3$: 251.1642 (M+H); found: 251.1657 (M+H).

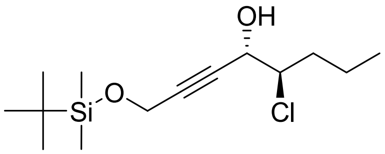
Key nOe correlations:



Scheme 1. Synthesis of tetrahydrofuranols **26** and **27**.



Preparation of (4*S**,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooct-2-yn-4-ol (47)



To a cold (-78 °C), stirred solution of *t*-butyldimethyl(prop-2-ynyloxy)silane[iv] (3.50 g, 20.5 mmol) in THF (100 mL) was added *n*-butyllithium (2.2 M soln. in hexane, 10.25 mL, 22.55 mmol). The resulting solution was stirred at -78 °C for 60 minutes. After this time, a solution of 2-chloropentanal[vi] (3.00 g, 24.6 mmol) in THF (10.0 mL) was added in one portion at -78 °C and the resulting mixture was stirred for an additional 60 minutes. Saturated aqueous NH_4Cl (10 mL) was then added, the mixture was diluted with diethyl ether (40 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 x 25 mL) and the combined organic phases were washed with brine (25 mL), dried ($MgSO_4$) and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 2:1 hexanes-ethyl acetate) afforded (4*S**,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooct-2-yn-4-ol (**47**) (5.78 g, 97%) as a white solid (m.p. 79 °C).

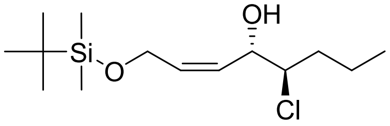
^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.54 (m, 1H), 4.36 (s, 2H), 4.03 (ddd, 1H, *J* = 4.2, 5.4, 7.8 Hz), 2.53 (d, 1H, *J* = 8.4 Hz), 1.80 (m, 2H), 1.61 (m, 1H), 1.42 (m, 1H), 0.94 (t, 3H, *J* = 7.2 Hz), 0.90 (s, 9H), 0.11 (s, 6H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 85.6, 81.3, 66.6, 66.2, 51.6, 35.6, 25.7, 19.7, 18.2, 13.5, -5.1.

IR (neat): 3382, 2971, 2129, 1433 cm^{-1}

Exact mass calcd. for $C_{14}H_{28}ClO_2Si$: 291.1547 (M+H); found: 291.1540 (M+H).

Preparation of (2*Z*,4*S**,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooct-2-en-4-ol (48)



To a cold (0 °C), stirred solution of nickel (II) acetate tetrahydrate (225 mg, 0.9 mmol) in methanol (18 mL) was added sodium borohydride (34 mg, 0.9 mmol) and the mixture was stirred for 5 minutes. To the resulting black solution was added ethylenediamine (120 µL, 1.8 mmol) and the mixture was stirred for an additional 5 minutes. After this time the reaction was placed under an atmosphere of H_2 and a solution of (4*S**,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooct-2-yn-4-ol (**47**) (3.50 g, 12 mmol) in methanol (6 mL) was introduced. This mixture was allowed to stir for 3 hours at room temperature under an atmosphere of H_2 (balloon). The reaction mixture was then filtered through Celite® and the filtrate was concentrated. Purification of the crude product by flash column chromatography (silica gel, 2:1 hexanes-ethyl acetate) afforded (2*Z*,4*S**,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooct-2-en-4-ol (**48**) (3.50 g, 99%) as a white solid (m.p. 75-77 °C).

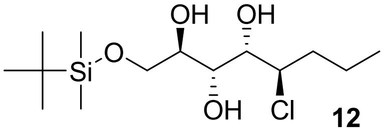
^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.75 (m, 1H), 5.61 (m, 1H), 4.52 (m, 1H), 4.30 (ddd, 1H, *J* = 1.6, 6.0, 14.0 Hz), 4.22 (ddd, 1H, *J* = 1.6, 6.0, 14.0 Hz), 3.99 (dt, 1H, *J* = 4.0, 8.0 Hz), 2.74 (d, 1H, *J* = 5.6 Hz), 1.76-1.56 (m, 3H), 1.39 (m, 1H), 0.91 (t, 3H, *J* = 7.2 Hz), 0.89 (s, 9H), 0.07 (s, 6H).

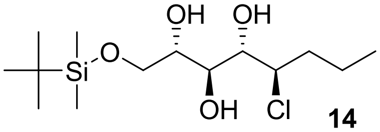
^{13}C NMR (100 MHz, $CDCl_3$) δ: 133.4, 128.9, 70.6, 67.5, 59.9, 35.2, 25.9, 19.7, 18.2, 13.5, -5.32, -5.34.

IR (neat): 3347, 3204, 2955, 2929, 2859, 1504, 1465, 1034 cm^{-1}

Exact mass calcd. for $C_{14}H_{30}ClO_2Si$: 293.1704 (M+H); found: 293.1707 (M+H).

Preparation of (2*R**,3*R**,4*S**,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooctane-2,3,4-triol (12) and (2*S**,3*S**,4*S**,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooctane-2,3,4-triol (14)


12


14

To a solution of (2*Z*,4*S**,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooct-2-en-4-ol (**48**) (1.2 mg, 4.1 mmol) in acetone (37 mL) and water (25 mL) was added *N*-methylmorpholine *N*-oxide (720 mg, 6.2 mmol) and osmium tetroxide (10 mg, 0.04 mmol). The resulting solution was stirred for 24 hours. After this time, saturated aqueous sodium hydrosulfite (20 mL) was added, the mixture was filtered through a pad of Celite® and the cake washed with acetone (3 x 20 mL). The filtrate was then neutralized to pH 7 with aqueous sulfuric acid and the acetone was removed by rotary evaporation. The mixture was diluted with ethyl acetate (30 mL) and washed with brine (20 mL), and the layers separated. The aqueous phase was extracted with ethyl acetate (3 x 30 mL) and the combined organic phases were washed with brine (25 mL), dried ($MgSO_4$) and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 3:1 to 2:1 hexanes-ethyl acetate) afforded (2*R**,3*R**,4*S**,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooctane-2,3,4-triol (**12**) (793 mg, 59%) as a white solid (m.p. 90-92 °C) and (2*S**,3*S**,4*S**,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooctane-2,3,4-triol (**14**) (196 mg, 15%) as a white solid (m.p. 89-90 °C).

Data for (**12**):
^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.05-3.99 (m, 2H), 3.85 (t, 1H, *J* = 6.8 Hz), 3.79-3.77 (m, 2H), 3.69 (dd, 1H, *J* = 5.2, 10.0 Hz), 3.36 (d, 1H, *J* = 6.4 Hz), 3.98 (d, 1H, *J* = 6.8 Hz), 2.93 (d, 1H, *J* = 5.2 Hz), 2.02 (m, 1H), 1.71-1.60 (m, 2H), 1.45 (m, 1H), 0.94 (t, 3H, *J* = 7.2 Hz), 0.90 (s, 9H), 0.10 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 73.1, 71.9, 70.7, 64.1, 62.7, 35.8, 25.8, 19.2, 18.2, 13.5, -5.5.

IR (neat): 3394, 3253, 2957, 2930, 2857, 1464, 1256 cm^{-1}

Exact mass calcd. for $C_{14}H_{32}ClO_4Si$: 327.1753 (M+H); found: 327.1760 (M+H).

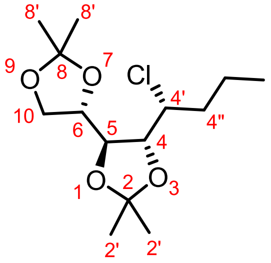
Data for (**14**):
^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.33 (dt, 1H, *J* = 3.2, 10.4 Hz), 3.92-3.80 (m, 5H), 4.53 (dd, 1H, *J* = 4.2, 8.0 Hz), 3.27 (s, 1H), 3.17 (s, 1H), 2.91 (s, 1H), 1.85 (m, 1H), 1.77 (m, 1H), 1.67 (m, 1H), 1.43 (m, 1H), 0.95 (t, 3H, *J* = 7.2 Hz), 0.91 (s, 9H), 0.11 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 76.9, 73.3, 71.5, 65.8, 64.9, 33.2, 25.8, 19.8, 18.2, 13.5, -5.6.

IR (neat): 3401, 3252, 2957, 2930, 2858, 1471, 1464, 1254 cm^{-1}

Exact mass calcd. for $C_{14}H_{32}ClO_4Si$: 327.1753 (M+H); found: 327.1760 (M+H).

The relative stereochemistry of the newly formed carbinol stereocenters in **14** were determined by analysis of the ^{1}H and ^{13}C NMR spectra and 1D NOESY spectra recorded on the corresponding acetonide following the method reported by Dana and Danechpajouh.[v]

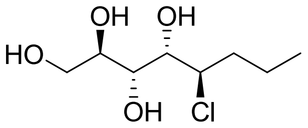


To a solution of (2*S**,3*S**,4*S**,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooctane-2,3,4-triol (**14**) (10 mg, 0.03 mmol) in dichloromethane (1 mL) was added 2,2-dimethoxypropane (15 µL, 0.12 mmol) and *p*-toluenesulfonic acid (1.1 mg, 0.006 mmol). The mixture was allowed to stir for 1 hour and then concentrated to give a crude yellow product. Purification of the crude product by flash chromatography (silica gel, 9:1 hexanes-ethyl acetate) afforded the corresponding bis-acetonide.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.28 (dd, 1H, *J* = 5.4, 7.8 Hz, H-4), 4.22 (ddd, 1H, *J* = 5.4, 7.8, 7.8 Hz, H-6), 4.15 (dd, 2H, *J* = 5.4, 7.8 Hz, H-5), 4.11 (ddd, 1H, *J* = 2.4, 7.8, 10.2 Hz, H-4’), 4.09 (dd, 1H, *J* = 5.4, 7.8 Hz, H-10), 3.93 (dd, 1H, *J* = 5.4, 7.8 Hz, H-10), 1.93 (m, 1H, H-4”), 1.74 (m, 1H, H-4”), 1.66 (m, 1H), 1.48 (m, 1H), 1.43 (s, 3H, H-8’) 1.42 (s, 3H, H-8’), 1.35 (s, 6H, H-2’), 0.96 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 109.8 (C2), 108.8 (C8), 80.8 (C4), 78.3 (C5), 73.2 (C6), 67.5 (C10), 59.0 (C4’), 36.8, 27.5 (C-8’), 26.6 (C8’), 25.5 (C2’), 25.4 (C2’), 18.8, 13.6.

Preparation of (2*R**,3*R**,4*S**,5*R**)-5-chlorooctane-1,2,3,4-tetrol (11)



To a solution of (2*R**,3*R**,4*S**,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooctane-2,3,4-triol (**12**) (98 mg, 0.30 mmol) in THF (6 mL) was added tetrabutylammonium fluoride (1.0 M solution in THF, 0.33 mL, 0.33 mmol). The resulting solution was stirred for 2 hours. Saturated aqueous ammonium chloride (2 mL) was then added, the mixture was diluted with ethyl acetate (20 mL) and the layers separated. The aqueous phase was extracted with ethyl acetate (3 x 20 mL) and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and concentrated to provide a crude white solid. Purification of the crude product by flash chromatography (silica gel, 5% methanol in ethyl acetate) afforded (2*R**,3*R**,4*S**,5*R**)-5-chlorooctane-1,2,3,4-tetrol (**11**) (50 mg, 78%) as a white solid (m.p. 162-163 °C).

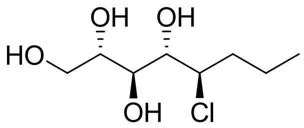
^{1}H NMR (400 MHz, CD_3OD) δ: 4.02 (dt, 1H, *J* = 2.4, 9.2 Hz), 3.93 (d, 1H, *J* = 7.6 Hz), 3.81 (m, 2H), 3.69-3.60 (m, 2H), 2.01 (m, 1H), 1.66 (m, 2H), 1.49 (m, 1H), 0.96 (t, 3H, *J* = 6.8 Hz).

^{13}C NMR (100 MHz, CD_3OD) δ: 74.1, 72.9, 71.4, 65.2, 63.0, 37.4, 20.3, 14.0.

IR (neat): 3395, 3388, 3210, 2950, 1464, 1254 cm^{-1}

Exact mass calcd. for $C_8H_{18}ClO_4$: 213.0888 (M+H); found: 213.0898 (M+H).

Preparation of (2*S**,3*S**,4*S**,5*R**)-5-chlorooctane-1,2,3,4-tetrol (13)



To a solution of (2*S**,3*S**,4*S**,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooctane-2,3,4-triol (**14**) (100 mg, 0.30 mmol) in THF (5 mL) was added tetrabutylammonium fluoride (1.0 M solution in THF, 0.33 mL, 0.33 mmol). The resulting solution was stirred for 3 hours. Saturated aqueous ammonium chloride (2 mL) was then added, the mixture was diluted with ethyl acetate (20 mL) and the layers separated. The aqueous phase was extracted with ethyl acetate (3 x 20 mL) and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and concentrated to provide a crude white solid. Purification of the crude product by flash chromatography (silica gel, 5% methanol in ethyl acetate) afforded (2*S**,3*S**,4*S**,5*R**)-5-chlorooctane-1,2,3,4-tetrol (**13**) (57 mg, 90%) as a white solid (m.p. 160-162 °C).

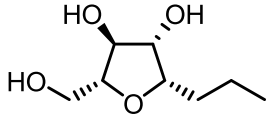
^{1}H NMR (400 MHz, CD_3OD) δ: 4.31 (dt, 1H, *J* = 4.4, 6.8 Hz), 4.21 (t, 1H, *J* = 4.4 Hz), 3.88 (dd, 2H, *J* = 6.8, 8.4 Hz), 3.67 (dd, 1H, *J* = 6.8, 8.0 Hz), 3.59 (dd, 1H, *J* = 3.6, 8.0 Hz), 1.63 (m, 2H), 1.42 (m, 2H), 0.96 (t, 3H, *J* = 6.8 Hz).

^{13}C NMR (100 MHz, CD_3OD) δ: 84.9, 73.2, 72.9, 72.2, 70.9, 37.2, 19.6, 14.5.

IR (neat): 3407, 3399, 3300, 2960, 1477, 1199 cm^{-1}

Exact mass calcd. for $C_8H_{17}ClO_4Na$: 235.0708 (M+Na); found: 235.0716 (M+Na).

Preparation of (2*R**,3*S**,4*S**,5*S**)-2-(hydroxymethyl)-5-propyltetrahydrofuran-3,4-diol (26)



Tetrahydrofuranol **26** was synthesized following the "General Procedure for the Cyclization of Chloropolyols" (*see above*) from (2*R**,3*R**,4*S**,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooctane-2,3,4-triol (**12**) in 96% yield. Tetrahydrofuranol **26** was also synthesized following the "General Procedure for the Cyclization of Chloropolyols" (*see above*) from (2*R**,3*R**,4*S**,5*R**)-5-chlorooctane-1,2,3,4-tetrol (**11**) in 67% yield.

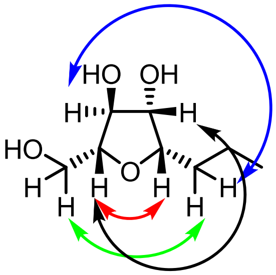
^{1}H NMR (600 MHz, CD_3OD) δ: 3.95 (m, 1H), 3.92 (ddd, 1H, *J* = 3.0, 6.6, 10.2 Hz), 3.78 (d, 1H, *J* = 3.0 Hz), 3.72 (m, 1H), 3.67 (dd, 1H, *J* = 4.2, 11.4 Hz), 3.63 (dd, 1H, *J* = 4.8, 11.4 Hz), 1.61 (dt, 2H, *J* = 6.6, 7.2 Hz), 1.42 (m, 2H), 0.96 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (100 MHz, CD_3OD) δ: 87.3, 82.8, 80.6, 78.8, 63.6, 31.7, 20.5, 14.6.

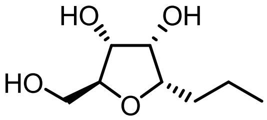
IR (neat): 3344, 2961, 2931, 2870, 1265, 1092, 1038, 738 cm^{-1}

Exact mass calcd. for $C_8H_{17}O_4$: 177.1121 (M+H); found: 177.1127 (M+H).

Key nOe correlations:



Preparation of (2*S**,3*R**,4*S**,5*S**)-2-(hydroxymethyl)-5-propyltetrahydrofuran-3,4-diol (27)



Tetrahydrofuranol **27** was synthesized following the "General Procedure for the Cyclization of Chloropolyols" (*see above*) from (2*S**,3*S**,4*S**,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooctane-2,3,4-triol (**14**) in 95% yield. Tetrahydrofuranol **27** was also synthesized following the "General Procedure for the Cyclization of Chloropolyols" (*see above*) from (2*S**,3*S**,4*S**,5*R**)-5-chlorooctane-1,2,3,4-tetrol (**13**) in 71% yield.

^{1}H NMR (600 MHz, CD_3OD) δ: 4.12 (dd, 1H, *J* = 4.2, 7.8 Hz), 3.97-3.92 (m, 2H), 3.79 (ddd, 1H, *J* = 3.0, 4.8, 7.8 Hz), 3.75 (dd, 1H, *J* = 3.0, 12.0 Hz), 3.58 (dd, 1H, *J* = 4.8, 12.0 Hz), 1.70-1.57 (m, 2H), 1.48-1.36 (m, 2H), 0.97 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, CD_3OD) δ: 82.8, 82.2, 73.9, 73.7, 63.3, 32.7, 20.1, 14.6.

IR (neat): 3380, 2960, 2932, 2873, 1265 cm^{-1}

Exact mass calcd. for $C_8H_{17}O_4$: 177.1121 (M+H); found: 177.1127 (M+H).

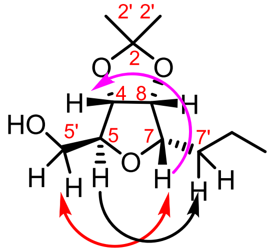
The relative configuration of **27** was determined by analysis of the ^{1}H and ^{13}C NMR spectra and 1D NOESY spectra recorded on the corresponding acetonide.

To a solution of (2*S**,3*R**,4*S**,5*S**)-2-(hydroxymethyl)-5-propyltetrahydrofuran-3,4-diol (**27**) (11 mg, 0.06 mmol) in dichloromethane (2 mL) was added 2,2-dimethoxypropane (31 μL, 0.25 mmol) and *p*-toluenesulfonic acid (2.4 mg, 0.012 mmol). The mixture was allowed to stir for 1 hour and then concentrated to give a crude yellow product. Purification of the crude product by flash chromatography (silica gel, 2:1 hexanes-ethyl acetate) afforded the corresponding acetonide.

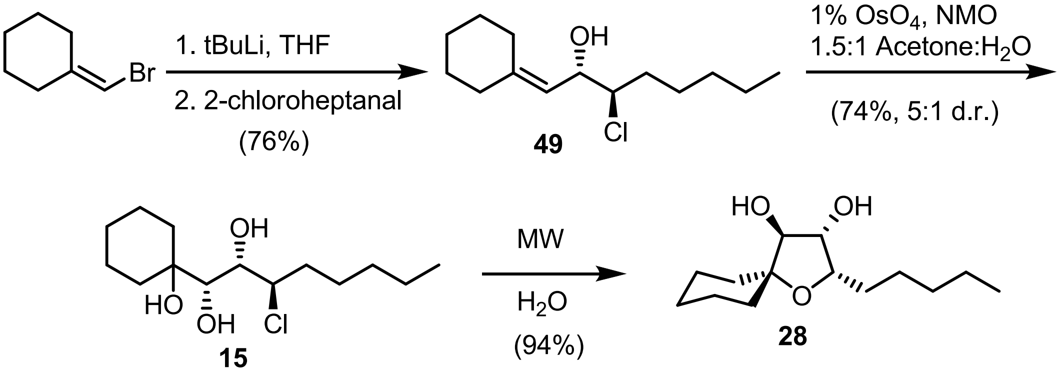
^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.62 (dd, 1H, *J* = 3.6, 6.0 Hz, H-8), 4.58 (dd, 1H, *J* = 1.2, 6.0 Hz, H-4), 4.11 (m, 1H, H-5), 3.87 (dt, 1H, *J* = 3.6, 6.6 Hz, H-7), 3.57 (m, 2H, H-5'), 1.92 (m, 1H, OH), 1.69 (m, 2H, H-7’), 1.50 (s, 3H, H-2’), 1.44 (m, 2H), 1.33 (s, 3H, H-2’), 0.96 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 112.5 (C2), 83.9 (C5), 82.4 (C4), 81.7 (C8), 80.6 (C7), 61.7 (C5’), 31.2 (C7’), 26.4 (C2’), 25.2 (C2’), 19.6, 14.4.

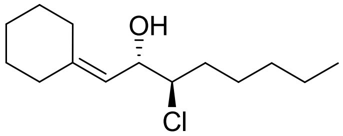
Key nOe coorelations:



Scheme 2. Synthesis of tetrahydrofuranol **28**.



Preparation of (2*S**,3*R**)-3-chloro-1-cyclohexylideneoctan-2-ol (49)



To a cold (-78 °C), stirred solution of bromomethylenecyclohexane (525 mg, 3.0 mmol) in THF (15 mL) was added *t*-butyllithium (1.8 M solution in pentanes, 3.5 mL, 6.3 mmol). The resulting solution was stirred at -78 °C for 60 minutes. After this time, a solution of (2*R**)-2-chloroheptanal[vi] (535 mg, 3.6 mmol) in THF (2.0 mL) was added in one portion at -78 °C and the resulting mixture was stirred for an additional 60 minutes. Saturated aqueous NH_4Cl (5 mL) was then added, the mixture was diluted with ethyl acetate (25 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 20 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$) and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 9:1 hexanes-ethyl acetate) afforded (2*S**,3*R**)-3-chloro-1-cyclohexylideneoctan-2-ol (**49**) (560 mg, 76%) as a clear oil.

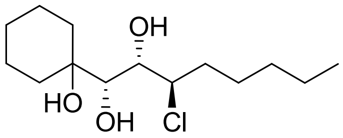
^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.25 (d, 1H, *J* = 8.4 Hz), 4.52 (dd, 1H, *J* = 4.0, 8.4 Hz), 4.03 (dt, 1H, *J* = 4.0, 9.2 Hz), 2.21-2.13 (m, 4H), 1.72-1.48 (m, 10H), 1.37-1.27 (m, 4H), 0.90 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 146.0, 119.3, 70.5, 69.0, 37.2, 33.2, 31.3, 29.8, 28.5, 27.9, 26.6, 26.3, 22.5, 14.0.

IR (neat): 3476, 3044, 2980, 1711, 1411 cm^{-1}

Exact mass calcd. for $C_{14}H_{25}ClONa$: 267.1486 (M+Na); found: 267.1487 (M+Na).

Preparation of (1*S**,2*S**,3*R**)-3-chloro-1-(1-hydroxycyclohexyl)octane-1,2-diol (15)



To a solution of (2*S**,3*R**)-3-chloro-1-cyclohexylideneoctan-2-ol (**49**) (350 mg, 1.4 mmol) in acetone (10 mL) and water (8 mL) was added *N*-methylmorpholine *N*-oxide (328 mg, 2.8 mmol) and osmium tetroxide (2.5 mg, 0.01 mmol). The resulting solution was stirred for 24 hours. After this time, saturated aqueous sodium hydrosulfite (5 mL) was then added, the mixture was filtered through a pad of Celite® and the cake was washed with acetone (3 x 15 mL). The filtrate was then neutralized to pH 7 with aqueous sulfuric acid, and the acetone was removed by rotary evaporation. The mixture was diluted with ethyl acetate (10 mL) and washed with brine (10 mL), and the layers separated. The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$) and concentrated to provide a crude yellow solid. Purification of the crude mixture by flash chromatography (silica gel, 3:1 hexanes-ethyl acetate) afforded (1*S**,2*S**,3*R**)-3-chloro-1-(1-hydroxycyclohexyl)octane-1,2-diol (**15**) (360 mg, 92%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.03 (dt, 1H, *J* = 2.8, 8.8 Hz), 3.91 (d, 1H, *J* = 8.8 Hz), 3.80 (m, 1H), 3.55 (s, 1H), 2.54 (s, 1H), 2.13 (s, 1H), 2.06 (m, 1H), 1.78 (m, 1H), 1.69-1.51 (m, 12H), 1.35-1.26 (m, 4H), 0.90 (t, 3H, *J* = 7.2 Hz).

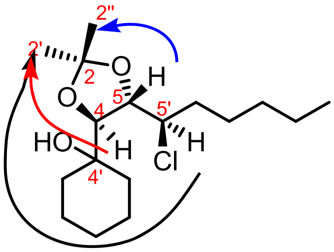
^{13}C NMR (100 MHz, $CDCl_3$) δ: 75.2, 73.5, 72.7, 63.0, 34.9, 33.6, 33.5, 31.4, 25.6, 25.5, 22.6, 21.6, 21.5, 14.0.

IR (neat): 3054, 2987, 2685, 2305, 1422, 1265 cm^{-1}

Exact mass calcd. for $C_{14}H_{27}ClO_3Na$: 301.1541 (M+Na); found: 301.1540 (M+Na).

The relative stereochemistry of the carbinol stereocentres were determined by analysis of the ^{1}H and ^{13}C NMR spectra from the corresponding acetonide using the method reported by Dana and Danechpajouh.[v]

To a solution of (1*S**,2*S**,3*R**)-3-chloro-1-(1-hydroxycyclohexyl)octane-1,2-diol (**15**) (12 mg, 0.05 mmol) in dichloromethane (2 mL) was added 2,2-dimethoxypropane (21 μL, 0.17 mmol) and *p*-toluenesulfonic acid (1 mg, 0.005 mmol). The mixture was allowed to stir for 1 hour and then concentrated to give a crude yellow product. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes-ethyl acetate) afforded the corresponding acetonide.

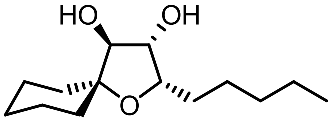


^{1}H NMR (600 MHz, CDCl$_3$) δ: 4.23 (dd, 1H, *J* = 5.4, 7.2 Hz, H-5), 3.94 (ddd, 1H, *J* = 2.4, 2.4, 7.2 Hz, H-5'), 3.90 (d, 1H, *J* = 5.4 Hz, H-4), 1.98 (m, 1H), 1.77-1.69 (m, 2H), 1.77-1.69 (m, 2H), 1.66-1.54 (m, 7H), 1.45 (s, 3H, H-2'), 1.40 (s, 3H, H-2''), 1.36-1.20 (m, 8H), 0.90 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, CDCl$_3$) δ: 110.1 (C2), 86.0 (C4), 80.3 (C5), 71.4 (C4'), 63.8 (C5'), 34.7, 33.6, 33.4, 31.2, 28.2 (C2'), 27.6 (C2''), 25.7, 25.6, 22.5, 21.42, 21.40, 14.0.

(2*S,3*S**,4*S**)-2-pentyl-1-oxaspiro[4.5]decane-3,4-diol (28)**

Tetrahydrofuranol **28** was synthesized following the "General Procedure for the Cyclization of Chloropolyols" (*see above*) from (1*S**,2*S**,3*R**)-3-chloro-1-(1-hydroxycyclohexyl)octane-1,2-diol (**15**) in 94% yield.



^{1}H NMR (400 MHz, CD$_3$OD) δ: 3.93 (m, 1H), 3.89 (m, 1H), 3.75 (d, 1H, *J* = 2.4 Hz), 1.69-1.35 (m, 18H), 0.92 (t, 3H, *J* = 7.2 Hz).

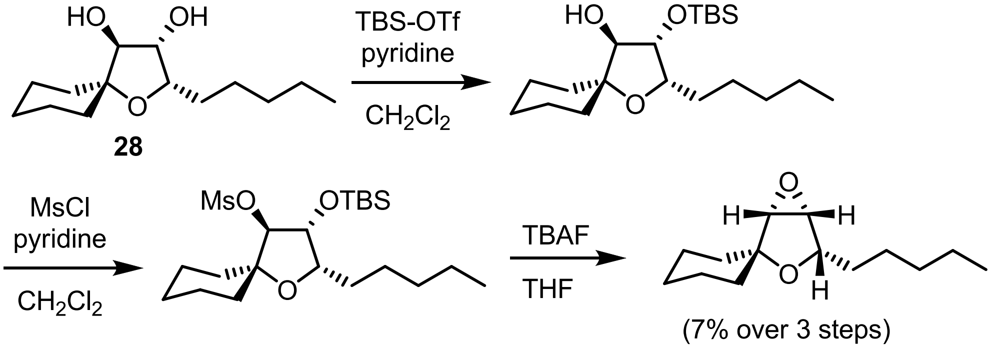
^{13}C NMR (100 MHz, CD$_3$OD) δ: 84.2, 83.8, 80.1, 79.5, 38.1, 33.2, 31.5, 30.5, 27.0, 26.8, 24.5, 23.9, 23.7, 14.4.

IR (neat): 3067, 2990, 2805, 2609, 1417 cm^{-1}

Exact mass calcd. for $C_{14}H_{27}O_3$: 243.1955 (M+H); found: 243.1963 (M+H).

The relative stereochemistry of the carbinol stereocentres were determined by analysis of the ^{1}H and ^{13}C NMR spectra and 1D NOESY spectra recorded on the corresponding epoxide.

Scheme 3. Synthesis of epoxide derived from tetrahydrofuranol **28**.

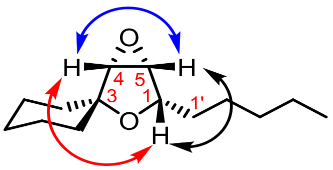


To a solution of (2*S**,3*S**,4*S**)-2-pentyl-1-oxaspiro[4.5]decane-3,4-diol (**28**) (20 mg, 0.08 mmol) in dichloromethane (2 mL) was added pyridine (12 µL, 0.16 mmol) and *t*-butyldimethylsilyl triflate (15 µL, 0.08 mmol). The mixture was allowed to stir for 1 hour and then concentrated to give a crude yellow product. Purification of the crude product by flash chromatography (silica gel, 7:1 hexanes-ethyl acetate) afforded (2*S**,3*S**,4*S**)-3-(tert-butyldimethylsilyloxy)-2-pentyl-1-oxaspiro[4.5]decan-4-ol which was then treated with methanesulfonyl chloride (12 µL, 0.16 mmol) and pyridine (12 µL, 0.16 mmol) in dichloromethane (2 mL). The mixture was allowed to stir for 10 minutes and concentrated to give a crude yellow product. Purification of the crude product by flash chromatography (silica gel, 8:1 hexanes-ethyl acetate) afforded (2*S**,3*R**,4*S**)-3-(tert-butyldimethylsilyloxy)-2-pentyl-1-oxaspiro[4.5]decan-4-yl methanesulfonate which was then treated with tetrabutylammonium fluoride (1.0 M solution in THF, 0.16 µL, 0.16 mmol) in THF (2 mL). The mixture was allowed to stir for 30 minutes and then concentrated to give a crude brown product. Purification of the crude product by flash chromatography (silica gel, 12:1 hexanes-ethyl acetate) afforded (1*R**,4*R**,5*R**)-4-pentyl-3,6-dioxaspiro[bicyclo[3.1.0]hexane-2,1'-cyclohexane] (1.1 mg, 7% over 3 steps).

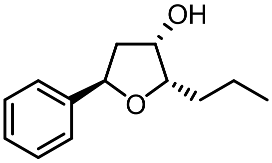
Data for epoxide:
^{1}H NMR (600 MHz, C_6D_6) δ: 3.56 (t, 1H, *J* = 6.6 Hz, H-1), 3.12 (d, 1H, *J* = 3.0 Hz, H-5), 3.08 (d, 1H, *J* = 3.0 Hz, H-4), 1.89 (m, 1H), 1.80 (m, 1H, H-1'), 1.70-1.63 (m, 3H), 1.67 (m, 1H), 1.43-1.14 (m, 6H), 1.35 (m, 1H), 1.25-1.20 (m, 5H), 0.85 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, C_6D_6) δ: 75.7 (C1), 60.3 (C4), 57.0 (C5), 32.3, 32.1, 31.8, 31.0 (C1'), 26.0, 25.9, 23.2, 22.82, 22.78, 22.5, 14.1.

Key nOe coorelations:



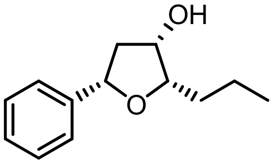
Preparation of (2*S**,3*S**,5*R**)-5-phenyl-2-propyltetrahydrofuran-3-ol (29)



Tetrahydrofuranol **29** was synthesized following the "General Procedure for the Cyclization of Chloropolyols" (*see above*) from (1*R**,3*S**,4*R**)-4-chloro-1-phenylheptan-1,3-diol[vi] (**16**) in 93% yield.

The ^{1}H and ^{13}C NMR spectra recorded on this material were identical to that reported in the literature.[vi]

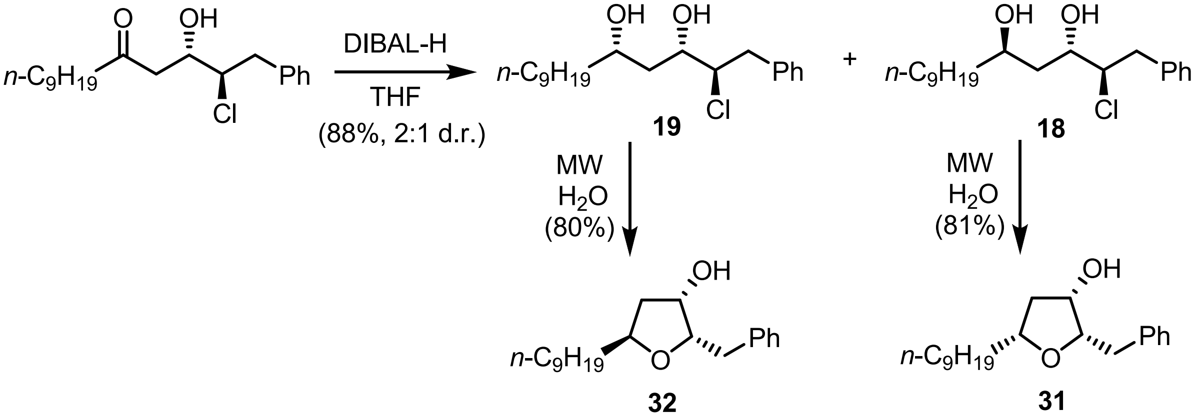
Preparation of (2*S**,3*S**,5*S**)-5-phenyl-2-propyltetrahydrofuran-3-ol (30)



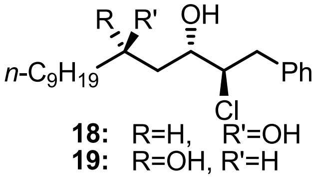
Tetrahydrofuranol **30** was synthesized following the "General Procedure for the Cyclization of Chloropolyols" (*see above*) from (1*S**,3*S**,4*R**)-4-chloro-1-phenylheptan-1,3-diol[vi] (**17**) in 82% yield.

The ^{1}H and ^{13}C NMR spectra recorded on this material were identical to that reported in the literature.[vi]

Scheme 4. Synthesis of tetrahydrofuranols **31** and **32**.



Preparation of (2*R,3*S**,5*S**)-2-chloro-1-phenyltetradecane-3,5-diol (19) and (2*R**,3*S**,5*R**)-2-chloro-1-phenyltetradecane-3,5-diol (18)**



To a cold (-78 °C), stirred solution of (2*R**,3*S**)-2-chloro-3-hydroxy-1-phenyltetradecan-5-one (169 mg, 0.5 mmol) in THF (10 mL) was added diisobutylaluminum hydride (1.0 M solution in hexanes, 1.25 mL, 1.25 mmol). The resulting solution was stirred at -78 °C for 4 hours. Aqueous HCl (1N) was then added, the mixture was diluted with ethyl acetate (20 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 15 mL) and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes-ethyl acetate) afforded (2*R**,3*S**,5*S**)-2-chloro-1-phenyltetradecane-3,5-diol (**19**) (101 mg, 59%) and its diastereomer (2*R**,3*S**,5*R**)-2-chloro-1-phenyltetradecane-3,5-diol (**18**) (49 mg, 29%) as clear oils.

Data for (**19**):
^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.36-7.27 (m, 5H), 4.11 (m, 1H), 4.00 (m, 1H), 3.89 (m, 1H), 3.26 (dd, 1H, *J* = 4.2, 14.4 Hz), 2.99 (dd, 1H, *J* = 9.0, 14.4 Hz), 2.94 (dd, 1H, 9.6, 14.4 Hz), 1.94 (m, 1H), 1.66 (m, 1H), 1.52 (m, 2H), 1.47-1.26 (m, 14H), 0.89 (t, 1H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 137.6, 129.4, 128.4, 126.7, 75.1, 72.7, 67.5, 39.5, 38.6, 38.2, 31.9, 29.54, 29.53, 29.51, 29.3, 25.6, 22.7, 14.1.

IR (neat): 3372, 2954, 2925, 2854, 1454, 1091, 700 cm^{-1}

Exact mass calcd. for $C_{20}H_{34}ClO_2$: 341.2247 (M+H); found: 341.2244 (M+H).

Data for (**18**):

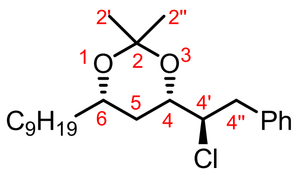
^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.36-7.27 (m, 5H), 4.11 (m, 1H), 4.00 (m, 1H), 3.89 (m, 1H), 3.26 (dd, 1H, *J* = 4.2, 14.4 Hz), 2.99 (dd, 1H, *J* = 9.0, 14.4 Hz), 2.94 (dd, 1H, 9.6, 14.4 Hz), 1.94 (m, 1H), 1.66 (m, 1H), 1.52 (m, 2H), 1.47-1.26 (m, 14H), 0.89 (t, 1H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 137.6, 129.4, 128.4, 126.7, 75.1, 72.7, 67.5, 39.5, 38.6, 38.2, 31.9, 29.54, 29.53, 29.51, 29.3, 25.6, 22.7, 14.1.

IR (neat): 3372, 2954, 2925, 2854, 1454, 1091, 700 cm^{-1}

Exact mass calcd. for $C_{20}H_{34}ClO_2$: 341.2247 (M+H); found: 341.2244 (M+H).

The relative stereochemistry of the newly formed carbinol stereocentre in **19** was determined by analysis of the ^{1}H and ^{13}C NMR spectra recorded on the corresponding acetonide following the method reported by Rychnovsky.[iii]

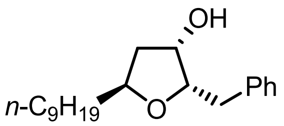


To a solution of (2*R**,3*S**,5*S**)-2-chloro-1-phenyltetradecane-3,5-diol (**19**) (10 mg, 0.03 mmol) in dichloromethane (1 mL) was added 2,2-dimethoxypropane (15 μL, 0.12 mmol) and *p*-toluenesulfonic acid (1.1 mg, 0.006 mmol). The mixture was allowed to stir for 1 hour and then concentrated to give a crude yellow product. Purification of the crude product by flash chromatography (silica gel, 10:1 hexanes-ethyl acetate) afforded the corresponding acetonide.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.32-7.25 (m, 5H), 3.92 (dt, 1H, *J* = 3.6, 7.8Hz, H-4'), 3.80 (m, 1H, H-6), 3.77 (m, 1H, H-4), .32 (dd, 1H, *J* = 3.6, 14.4 Hz, H-4"), 2.94 (dd, 1H, *J* = 7.8, 14.4 Hz, H-4"), 1.90 (dt, 1H, *J* = 2.4, 12.6 Hz, H-5), 1.53 (m, 1H, H-5), 1.44 (s, 3H, H-2'), 1.43 (s, 3H, H-2'), 1.39-1.15 (m, 16H), 0.88 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.5, 129.9, 128.1, 126.8, 99.0, 71.3 (C6), 68.9 (C4), 65.5 (C4'), 39.6 (C4"), 36.4, 34.3 (C5), 31.9, 30.1 (C2'), 29.57, 29.56, 29.53, 29.3, 24.9, 22.7, 20.0 (C2''), 14.2.

Preparation of (2*S**,3*S**,5*S**)-2-benzyl-5-nonyltetrahydrofuran-3-ol (32)



Tetrahydrofuranol **32** was synthesized following the "General Procedure for the Cyclization of Chloropolyols" (*see above*) from (2*R**,3*S**,5*S**)-2-chloro-1-phenyltetradecane-3,5-diol (**19**) in 80% yield.

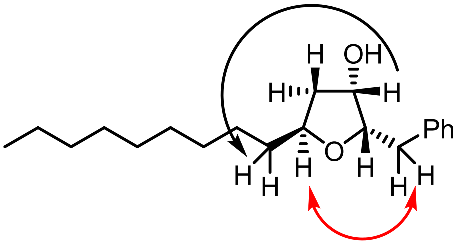
^{1}H NMR (600 MHz, CD_3OD) δ: 7.29 (d, 2H, *J* = 7.2 Hz), 7.25 (t, 2H, *J* = 7.2 Hz), 7.16 (t, 1H, *J* = 7.2 Hz), 4.25 (m, 1H), 4.12 (m, 1H), 4.00 (dt, 1H, *J* = 3.0, 7.2 Hz), 2.95 (dd, 1H, *J* = 6.6, 13.8 Hz), 2.84 (dd, 1H, *J* = 7.2, 13.8 Hz), 2.05 (dd, 1H, *J* = 6.0, 13.2 Hz), 1.71 (ddd, 1H, *J* = 4.8, 9.0, 13.2 Hz), 1.56 (m, 1H), 1.40 (m, 1H), 1.34-1.22 (m, 16H), 0.90 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, CD$_3$OD) δ: 140.5, 130.3, 129.2, 127.1, 84.7, 78.8, 73.6, 42.6, 37.3, 36.5, 33.1, 30.77, 30.75, 30.7, 30.5, 27.1, 23.7, 14.5.

IR (neat): 3501, 3028, 2925, 2854 cm^{-1}

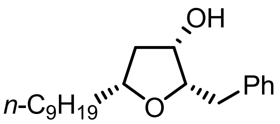
Exact mass calcd. for $C_{20}H_{33}O_2$: 305.2475 (M+H); found: 305.2477 (M+H).

Key nOe correlations:



Preparation of (2*S**,3*S**,5*R**)-2-benzyl-5-nonyltetrahydrofuran-3-ol (31)

Tetrahydrofuranol **31** was synthesized following the "General Procedure for the Cyclization of Chloropolyols" (*see above*) from (2*R**,3*S**,5*R**)-2-chloro-1-phenyltetradecane-3,5-diol (**18**) in 81% yield.



^{1}H NMR (600 MHz, CDCl$_3$) δ: 7.30-7.18 (m, 5H), 7.27-7.24 (m, 3H), 4.10 (m, 1H), 3.83-3.73 (m, 2H), 3.02 (d, 2H, *J* = 6.8Hz), 2.35 (ddd, 1H, *J* = 6.4, 8.2, 14.0 Hz), 1.77-1.63 (m, 1H), 1.55-1.50 (m, 2H, *J* = 9.8, 15.0 Hz), 1.46-1.38 (m, 1H), 1.81 (m, 1H), 1.76 (ddd, 1H, *J* = 2.4, 8.6, 15.0 Hz), 1.53-1.47 (m, 2H), 1.45-1.38 (m, 2H) 1.34-1.26 (m, 14H), 0.88 (t, 3H, *J* = 7.2 Hz).

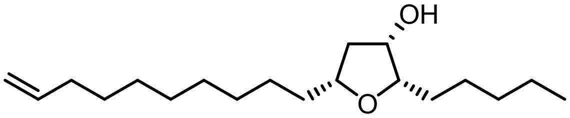
^{13}C NMR (150 MHz, CDCl$_3$) δ: 138.6, 129.2, 128.5, 126.3, 83.9, 77.9, 72.4, 41.6, 36.9, 35.1, 31.9, 29.64, 29.57, 29.55, 29.3, 26.2, 22.7, 14.1.

IR (neat): 3450, 2925, 2854, 1092 cm^{-1}

Exact mass calcd. for $C_{20}H_{33}O_2$: 305.2475 (M+H); found: 305.2481 (M+H).

Preparation of (2*S**,3*S**,5*R**)-2-pentyl-5-(dec-9-enyl)tetrahydrofuran-3-ol (33)

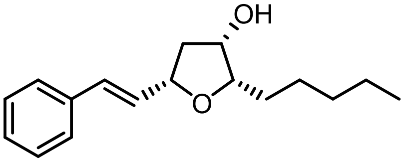
Tetrahydrofuranol **33** was synthesized following the "General Procedure for the Cyclization of Chloropolyols" (*see above*) from (6*R**,7*S**,9*R**)-6-chlorononadec-18-en-7,9-diol[vi] (**20**) in 87% yield.



The ^{1}H and ^{13}C NMR spectra recorded on this material were identical to that reported in the literature.[vi]

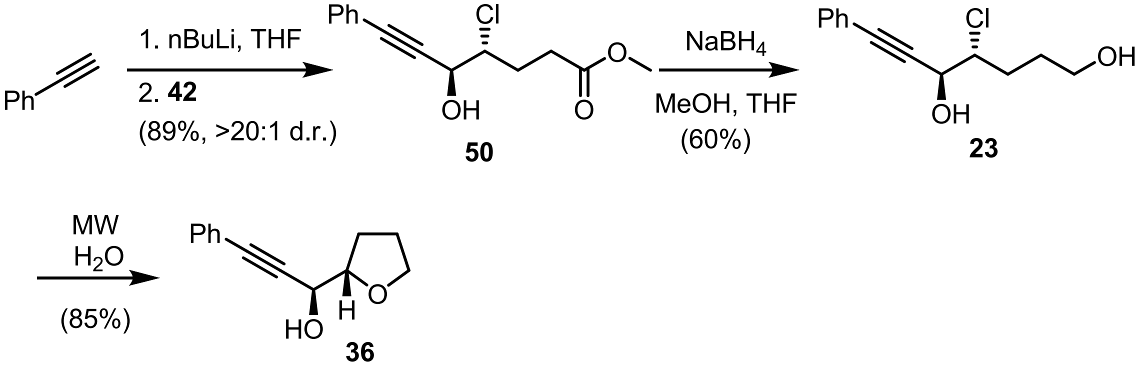
Preparation of (2*S**,3*S**,5*S**)-2-pentyl-5-styryl-tetrahydrofuran-3-ol (34)

Tetrahydrofuranol **34** was synthesized following the "General Procedure for the Cyclization of Chloropolyols" (*see above*) from (1*E*,3*S**,5*S**,6*R**)-6-chloro-1-phenylundec-1-en-3,5-diol[vi] (**21**) in 88% yield.

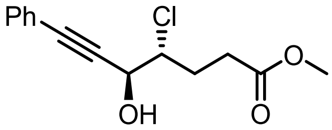


The ^{1}H and ^{13}C NMR spectra recorded on this material were identical to that reported in the literature.[vi]

Scheme 5. Synthesis of tetrahydrofuran **36**.



Preparation of methyl (4*R**,5*S**)-4-chloro-5-hydroxy-7-phenylhept-6-ynoate (50)



To a cold (-78 °C), stirred solution of phenylacetylene (204 mg, 2.0 mmol) in THF (10 mL) was added *n*-butyllithium (2.5 M soln. in hexane, 880 μL, 2.2 mmol). The resulting solution was stirred at -78 °C for 30 minutes. After this time, a solution of methyl (4*R**)-4-chloro-5-oxopentanoate (**42**) (395 mg, 2.4 mmol) in THF (1.0 mL) was then added in one portion at -78 °C and the resulting mixture was stirred for an additional 30 minutes. Saturated aqueous NH_4Cl (5 mL) was then added, the mixture was diluted with ethyl acetate (20 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 15 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$) and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 3:1 to 2.5:1 hexanes-ethyl acetate) afforded methyl (4*R**,5*S**)-4-chloro-5-hydroxy-7-phenylhept-6-ynoate (**50**) (474 mg, 89%, 15:1 diastereomeric mixture) as a clear oil.

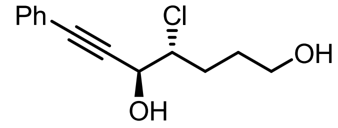
^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.46 (d, 2H, *J* = 7.2 Hz), 7.35-7.29 (m, 3H), 4.77 (dd, 1H, *J* = 3.6, 8.4 Hz), 4.21 (dt, 1H, *J* = 3.6, 10.2 Hz), 3.70 (s, 3H), 2.70-2.52 (m, 3H), 2.34 (m, 1H), 2.15 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.4, 132.4, 128.8, 128.4, 122.3, 87.0, 85.7, 66.8, 52.3, 30.9, 29.0.

IR (neat): 3452, 2953, 2926, 2232, 1737, 1441 cm^{-1}

Exact mass calcd. for $C_{14}H_{16}ClO_3$: 267.0782 (M+H); found: 267.0793 (M+H).

Preparation of (4*R**,5*S**)-4-chloro-7-phenylhept-6-yne-1,5-diol (23)



To a solution of methyl (4*R**,5*S**)-4-chloro-5-hydroxy-7-phenylhept-6-ynoate (**50**) (70 mg, 0.25 mmol) in THF (5 mL) and methanol (1.0 mL) was added sodium borohydride (100 mg, 2.5 mmol). The resulting solution was stirred for 18 hours. Saturated aqueous ammonium chloride (2 mL) was then added, the mixture was diluted with ethyl acetate (10 mL) and the layers separated. The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and concentrated to provide a crude white solid. Purification of the crude product by flash chromatography (silica gel, 2:3 hexanes-ethyl acetate) afforded (4*R**,5*S**)-4-chloro-7-phenylhept-6-yne-1,5-diol (**23**) (35 mg, 60%) as a clear oil.

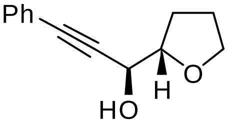
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47-7.45 (m, 2H), 7.34-7.30 (m, 3H), 4.76 (dd, 1H, *J* = 4.0, 7.6 Hz), 4.16 (dt, 1H, *J* = 4.0, 9.6 Hz), 3.72 (t, 2H, *J* = 6.0 Hz), 2.82 (d, 1H, *J* = 7.6 Hz), 2.09 (m, 1H), 1.93 (m, 2H), 1.73 (m, 1H).

^{13}C NMR (100 MHz, CD_3OD) δ: 131.9, 128.8, 128.4, 122.0, 86.9, 85.6, 66.7, 62.2, 30.1, 29.5.

IR (neat): 3503, 3433, 3329, 2955, 2857, 2201, 1401 cm^{-1}

Exact mass calcd. for $C_{13}H_{15}O_2Na$: 261.0653 (M+Na); found: 261.0661 (M+Na).

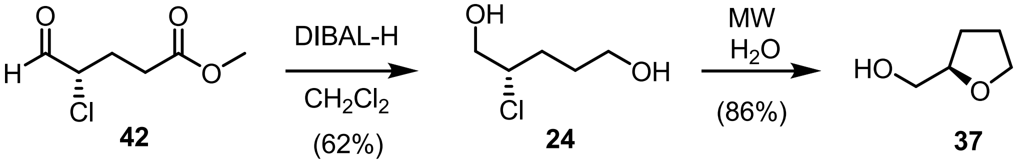
Preparation of (*S**)-3-phenyl-1-((*S*)-tetrahydrofuran-2-yl)prop-2-yn-1-ol (36)



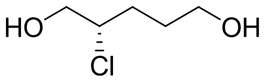
Tetrahydrofuranol **36** was synthesized following the "General Procedure for the Cyclization of Chloropolyols" (*see above*) from (4*R**,5*S**)-4-chloro-7-phenylhept-6-yne-1,5-diol (**23**) in 85% yield.

The ^{1}H and ^{13}C NMR spectra recorded on this material were identical to that reported in the literature.[vii]

Scheme 6. Synthesis of tetrahydrofuran **37**.



Preparation of (2*S**)-2-chloropentane-1,5-diol (24)



To a cold (0 °C), stirred solution of methyl (4*S**)-4-chloro-5-oxopentanoate (**42**) (329 mg, 2.0 mmol) in dichloromethane (25 mL) was added diisobutylaluminum hydride (1.0 M solution in dichloromethane, 12.5 mL, 12.5 mmol). The resulting solution was stirred for 2 hours at 0 °C. To this solution was added aqueous HCl (1.0 M, 2.0 mL) the mixture was diluted with dichloromethane (10 mL) and the layers separated. The aqueous phase was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and concentrated to provide a yellow oil. Purification of the crude product by flash chromatography (silica gel, 1:2 to 0:1 hexanes-ethyl acetate) afforded (2*S**)-2-chloropentane-1,5-diol (**24**) (170 mg, 62%) as a clear oil.

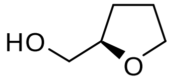
^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.08 (m, 1H), 3.81 (m, 1H), 3.73-3.67 (m, 3H), 2.05 (dd, 1H, *J* = 5.6, 7.6 Hz), 1.99-1.68 (m, 5H), 1.34 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 67.0, 64.9, 62.2, 30.6, 29.3.

IR (neat): 3345, 2951, 2879, 1722, 1444, 1057 cm^{-1}

Exact mass calcd. for $C_5H_{12}ClO_2$: 139.0520 (M+H); found: 139.0525 (M+H).

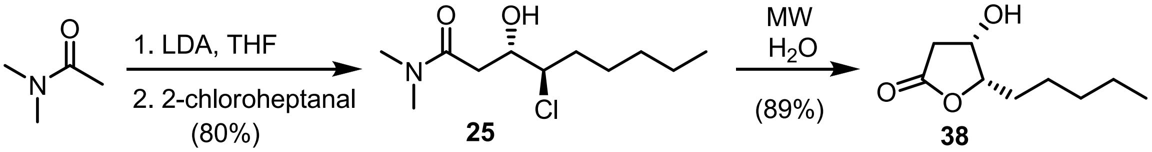
Preparation of (*R**)-(tetrahydrofuran-2-yl)methanol (37)



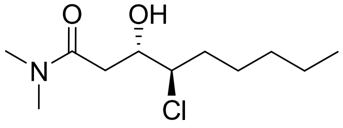
Tetrahydrofuranol **37** was synthesized following the "General Procedure for the Cyclization of Chloropolyols" (*see above*) from (2*R**)-2-chloropentane-1,5-diol (**24**) in 86% yield.

The ^{1}H and ^{13}C NMR spectra recorded on this material were identical to that reported in the literature.[viii]

Scheme 7. Synthesis of lactone **38**.



Preparation of (3*S**,4*R**)-4-chloro-3-hydroxy-*N*,*N*-dimethylnonanamide (25)



To a cold (0 °C), stirred solution of diisopropyl amine (617 µL, 4.4 mmol) in THF (20 mL) was added *n*-butyllithium (2.5 M soln. in hexane, 1.8 mL, 4.4 mmol) and the resulting mixture was stirred for 30 minutes. After this time, the slightly yellow solution was cooled to -78 °C and *N*,*N*-dimethylacetamide (372 µL, 4.0 mmol) was added in one portion. The reaction mixture was stirred for 30 minutes, a solution of 2-chloroheptanal[vi] (713 mg, 4.8 mmol) in THF (2.0 mL) was then added in one portion at -78 °C and the resulting mixture was stirred for an additional 30 minutes. Saturated aqueous NH_4Cl (10 mL) was then added, the mixture was diluted with ethyl acetate (20 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 15 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$) and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 3:2 to 1:2 hexanes-ethyl acetate) afforded (3*S**,4*R**)-4-chloro-3-hydroxy-*N*,*N*-dimethylnonanamide (**25**) (760 mg, 80%) as a white solid (m.p. 54-55 °C).

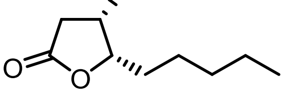
^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.80 (d, 1H, *J* = 4.4 Hz), 4.00 (m, 1H), 3.93 (m, 1H), 3.03 (s, 3H), 2.97 (s, 3H), 2.76 (dd, 1H, J = 2.8, 16.4 Hz), 2.64 (dd, 1H, *J* = 7.8, 16.4 Hz), 2.02 (m, 1H), 1.71-1.60 (m, 2H), 1.44-1.27 (m, 6H), 0.90 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.4, 71.7, 65.7, 37.2, 35.23, 35.19, 34.2, 31.3, 25.9, 22.5, 14.0.

IR (neat): 3347, 2961, 2874, 2772, 2447, 1771, 1709, 1643, 1467, 1171 cm^{-1}

Exact mass calcd. for $C_{11}H_{23}ClNO_2$: 236.1412 (M+H); found: 236.1404 (M+H).

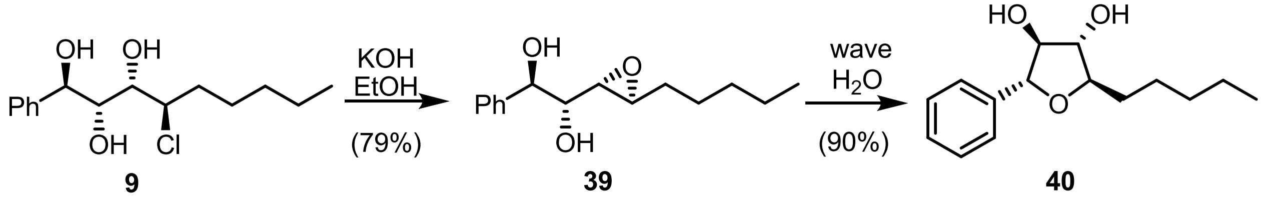
Preparation of (4*S**,5*S**)-4-hydroxy-5-pentyldihydrofuran-2(3*H*)-one (38)



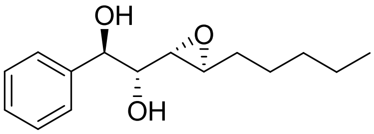
Tetrahydrofuranol **38** was synthesized following the "General Procedure for the Cyclization of Chloropolyols" (*see above*) from (3*S**,4*R**)-4-chloro-3-hydroxy-*N*,*N*-dimethylnonanamide (**25**) in 1:1 water:methanol at 80 °C to give the product in 89% yield.

The ^{1}H and ^{13}C NMR spectra recorded on this material were identical to that reported in the literature.[ix]

Scheme 8. Synthesis of tetrahydrofuranol **40**.



Preparation of (1*R**,2*R**)-1-((2*S**,3*S**)-3-pentyloxiran-2-yl)-2-phenylethane-1,2-diol (39)



To a solution of (1*R**,2*R**,3*S**,4*R**)-4-chloro-1-phenylnonane-1,2,3-triol (**9**) (35 mg, 0.12 mmol) in ethanol (0.7 mL) was added potassium hydroxide (0.2 M, 1.2 mL, 0.24 mmol). The resulting solution was stirred for 30 minutes. The mixture was then diluted with pentane (10 mL), washed with water (10 mL) and the layers separated. The aqueous phase was extracted with pentane (3 x 10 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$) and concentrated to provide a crude white solid. Purification of the crude product by flash chromatography (silica gel, 7:3 hexanes-ethyl acetate) afforded (1*R**,2*R**)-1-((2*S**,3*S**)-3-pentyloxiran-2-yl)-2-phenylethane-1,2-diol (**39**) (24 mg, 79%) as a white solid.

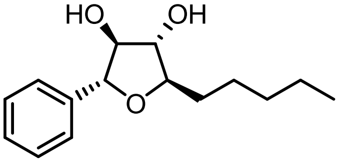
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28-7.15 (m, 5H), 4.79 (m, 1H), 3.54 (m, 1H), 3.05 (d, 1H, *J* = 2.8 Hz), 2.87 (m, 1H), 2.80 (dd, 1H, *J* = 2.8, 5.2 Hz), 2.50 (ddd, 1H, *J* = 2.8, 5.2, 7.6 Hz), 1.27-1.19 (m, 2H), 1.16-1.05 (m, 6H), 0.84 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.8, 128.4, 127.8, 126.1, 75.4, 74.7, 57.8, 57.0, 31.5, 31.3, 25.2, 22.5, 13.9.

IR (neat): 3509, 3308, 2997, 2902, 1534, 1437 cm^{-1}

Exact mass calcd. for $C_{15}H_{23}O_3$: 251.1642 (M+H); found: 251.1636 (M+H).

(2*R**,3*S**,4*S**,5*R**)-2-pentyl-5-phenyltetrahydrofuran-3,4-diol (40)



Tetrahydrofuranol **40** was synthesized following the "General Procedure for the Cyclization of Chloropolyols" (*see above*) from (1*R**,2*R**)-1-((2*S**,3*S**)-3-pentyloxiran-2-yl)-2-phenylethane-1,2-diol (**39**) in 90% yield.

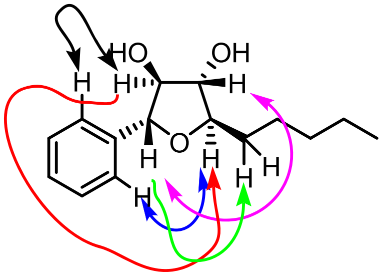
^{1}H NMR (600 MHz, C_6D_6) δ: 7.46 (d, 2H, *J* = 7.8 Hz), 7.20 (t, 2H, *J* = 7.8 Hz), 7.11 (t, 1H, *J* = 7.8 Hz), 4.73 (d, 1H, *J* = 7.2 Hz), 3.96 (m, 1H), 3.78 (t, 1H, *J* = 7.2 Hz), 3.71 (t, 1H, *J* = 7.2 Hz), 1.70-1.58 (m, 7H), 1.43 (m, 1H), 1.28 (t, 3H, *J* = 7.2 Hz), 0.55 (s, 1H).

^{13}C NMR (150 MHz, C_6D_6) δ: 142.1, 128.7, 128.3, 126.2, 85.1, 83.1, 82.7, 82.4, 34.3, 32.3, 25.8, 23.0, 14.3.

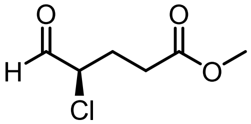
IR (neat): 3347, 2919, 2856, 1455, 1266, 1008 cm^{-1}

Exact mass calcd. for C15H22O3: 251.1642 (M+H); found: 251.1654 (M+H).

Key nOe coorelations:



Preparation of (*R*)-methyl 4-chloro-5-oxopentanoate (42)



To a cold (10 °C), stirred solution of (2*S*,5*R*)-2-*tert*-butyl-3,5,dimethylimidazolidin-4-one trifluoroacetate (**46**) (105 mg, 0.4 mmol) in acetonitrile (30 mL) was added water (75 µL, 4.1 mmol), lithium chloride (120 mg, 2.8 mmol), copper (II) trifluoroacetate hydrate (270 mg, 0.9 mmol), sodium persulfate (450 mg, 1.8 mmol). The resulting solution was stirred at 10 °C for 5 minutes. After this time, a solution of methyl 5-oxopentanoate (**41**) (240 mg, 1.8 mmol) in acetonitrile (1.0 mL) was then added in one portion at 10 °C and the resulting mixture was stirred for an additional 4 hours. Water (10 mL) was then added, the mixture was diluted with ethyl acetate (20 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 15 mL) and the combined organic phases were washed with brine (3 x 15 mL), dried ($MgSO_4$) and concentrated to provide (*R*)-methyl 4-chloro-5-oxopentanoate (**42**) (271 mg, 88%) as clear oil which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.48 (d, 1H, *J* = 1.6 Hz), 4.32 (ddd, 1H, *J* = 1.6, 5.2, 8.0 Hz), 3.65 (s, 3H), 2.51 (m, 2H), 2.34 (m, 1H), 2.05 (m, 1H).

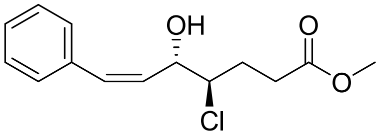
^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.3, 172.4, 62.6, 51.7, 29.5, 26.8.

IR (neat): 2955, 2849, 1732, 1439, 1250, 1174 cm^{-1}

Exact mass calcd. for $C_6H_{10}ClO_3$: 165.0318 (M+H); found: 165.0312 (M+H).

$[\alpha]_D^{25}$: 24.3° (c = 1.0, EtOH)

Preparation of methyl (4*R*,5*S*,6*Z*)-4-chloro-5-hydroxy-7-phenylhept-6-enoate (44)



To a cold (-78 °C), stirred solution of iodostyrene[ii] (50 mg, 0.22 mmol) in THF (5 mL) was added *n*-butyllithium (2.1 M soln. in hexane, 109 µL, 0.24 mmol). The resulting solution was stirred at -78 °C for 30 minutes. After this time, a solution of methyl (4*R*)-4-chloro-5-oxopentanoate (**42**) (40 mg, 0.24 mmol) in THF (0.5 mL) was added in one portion at -78 °C and the resulting mixture was stirred for an additional 30 minutes. Saturated aqueous NH_4Cl (1 mL) was then added, the mixture was diluted with ethyl acetate (10 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$) and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes-ethyl acetate) afforded methyl (4*R*,5*S*,6*Z*)-4-chloro-5-hydroxy-7-phenylhept-6-enoate (**44**) (51 mg, 88%, 13:1 diastereomeric mixture) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37-7.27 (m, 5H), 6.77 (d, 1H, *J* = 11.4 Hz), 5.83 (dd, 1H, *J* = 9.2, 11.4 Hz), 4.64 (m, 1H), 4.14 (m, 1H), 3.66 (s, 3H), 2.56 (m, 1H), 2.47 (m, 1H), 2.32 (d, 1H, *J* = 6.8 Hz), 2.10 (m, 1H), 1.98 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.2, 136.1, 134.8, 128.7, 128.5, 128.3, 127.7, 70.2, 66.8, 51.7, 30.7, 28.5.

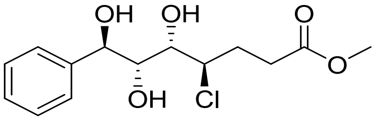
IR (neat): 3536, 3080, 3007, 2965, 2920, 2884, 1723, 1441, 1093 cm^{-1}

Exact mass calcd. for $C_{14}H_{18}ClO_3$: 269.0944 (M+H); found: 269.0963 (M+H).

$[\alpha]_D^{25}$: -16.4° (c = 0.7, EtOH)

The enantiomeric excess of (**44**) was determined to be 91% by chiral HPLC analysis. Injection volume: 10 µL (5 mg/mL solution); Solvent: 95:5 Hexane:Methanol; Flow rate: 1 mL/min; Wavelength: 254 nm; Retention time = 20.3 min (4*S*, 5*R* isomer), 25.4 min (4*R*, 5*S* isomer).

Preparation of methyl (4*R*,5*S*,6*R*,7*R*)-4-chloro-5,6,7-trihydroxy-7-phenylheptanoate (45)



To a solution of methyl (4*R*,5*S*,6*Z*)-4-chloro-5-hydroxy-7-phenylhept-6-enoate (**44**) (269 mg, 1.0 mmol) in acetone (5 mL) and water (3 mL) was added *N*-methylmorpholine *N*-oxide (176 mg, 1.5 mmol) and osmium tetroxide (2.5 mg, 0.01 mmol). The resulting solution was stirred for 3 hours. After this time, saturated aqueous sodium hydrosulfite (5 mL) was added, the mixture was filtered through a pad of Celite® and the cake washed with acetone (3 x 15 mL). The filtrate was then neutralized to pH 7 with aqueous sulfuric acid, and the acetone was removed by rotary evaporation.

The mixture was diluted with ethyl acetate (10 mL) and washed with brine (10 mL), and the layers separated. The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$) and concentrated to provide a crude yellow solid. Purification of the 8:1 diastereomeric mixture by flash chromatography (silica gel, 1:2 hexanes-ethyl acetate) afforded methyl (4*R*,5*S*,6*R*,7*R*)-4-chloro-5,6,7-trihydroxy-7-phenylheptanoate (**45**) (222 mg, 74%) as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.3-7.29 (m, 5H), 4.9 (dd, 1H, *J* = 4.8, 4.8 Hz), 4.13 (dd, 1H, *J* = 6.0, 6.0 Hz), 4.07 (dt, 1H, *J* = 3.0, 7.8 Hz), 3.75-3.70 (m, 2H), 3.64 (s, 3H), 3.34 (d, 1H, *J* = 4.2 Hz), 2.80 (m, 1H), 2.58 (m, 1H), 2.46 (m, 1H), 2.35 (m, 1H), 1.96 (m, 1H), 1.82 (s, 1H).

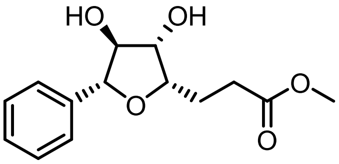
^{13}C NMR (150 MHz, $CDCl_3$) δ: 174.3, 140.6, 128.6, 127.9, 126.1, 76.0, 72.7, 72.5, 60.6, 51.8, 30.0, 28.5.

IR (neat): 3535, 3409, 2928, 1729, 1609, 1414, 1087 cm^{-1}

Exact mass calcd. for $C_{14}H_{20}ClO_5$: 303.0994 (M+H); found: 303.0992 (M+H).

$[\alpha]_D^{25}$: 11.1° (c = 0.7, EtOH)

Preparation of (+)-Goniothalesdiol (1)



To a 10 mL microwave vial with (4*R*,5*S*,6*R*,7*R*)-4-chloro-5,6,7-trihydroxy-7-phenylheptanoate (**45**) (50 mg, 0.16 mmol) was added methanol (1.6 mL) and the vial was sealed in a CEM Discover LabMate microwave. The reaction mixture was then heated to 120 °C (as monitored by a vertically focused IR temperature sensor) and maintained at this temperature for 60 minutes. After this time, the mixture was diluted with ethyl acetate (5 mL) and washed with brine (5 mL), and the layers separated. The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$) and concentrated to provide a crude product. Purification of the crude product by flash chromatography (silica gel, 2:1 hexanes-ethyl acetate) afforded (+)-goniothalesdiol (**1**) (39 mg, 92%) as a clear oil.[x]

Data for a 50 mg/mL solution:

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.42 (d, 2H, *J* = 7.2 Hz), 7.35 (t, 2H, *J* = 7.2 Hz), 7.29 (d, 1H, *J* = 7.2 Hz), 4.61 (d, 1H, *J* = 4.8 Hz), 4.03-4.12 (m, 3H), 3.70 (s, 3H), 2.63 (m, 1H), 2.55-2.47 (m, 2H), 2.28 (d, 1H, *J* = 4.0 Hz), 2.18-2.03 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 174.8, 140.0, 128.6, 127.8, 126.2, 85.6, 85.0, 80.3, 78.9, 51.9, 30.6, 24.0.

Data for a 10 mg/mL solution:

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 (d, 2H, *J* = 7.2 Hz), 7.34 (t, 2H, *J* = 7.2 Hz), 7.26 (d, 1H, *J* = 7.2 Hz), 4.59 (d, 1H, *J* = 4.8 Hz), 4.02-4.10 (m, 3H), 3.68 (s, 3H), 2.62 (m, 1H), 2.54-2.44 (m, 2H), 2.28 (d, 1H, *J* = 4.0 Hz), 2.18-2.00 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.8, 140.0, 128.7, 127.9, 126.2, 86.2, 85.3, 80.7, 78.9, 51.9, 30.6, 23.8.

IR (neat): 3449, 2954, 2952, 2929, 1736, 1449, 1417 cm^{-1}

Exact mass calcd. for $C_{14}H_{19}O_5$: 267.1227 (M+H); found: 267.1227 (M+H).

$[\alpha]_D^{25}$: +7.2° (c = 0.2, EtOH)[xi]

References

[i] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

[ii] Stamos, D. P.; Taylor, A. G.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 8647-8650.

[iii] Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945-948.

[iv] Harvey, D. F.; Neil, D. A. *Tetrahedron* **1993**, *49*, 2145-2150.

[v] Dana, G.; Danechpajouh, H. *Bull. Soc. Chim. Fr.* **1980**, *II*, 395-399.

[vi] Kang, B.; Mowat, J.; Pinter, T.; Britton, R. *Org. Lett.* **2009**, *11*, 1717-1720.

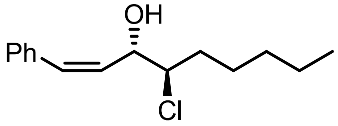
[vii] Karakhanov, R. A.; Vartanyan, M. M.; Solov'eva, T. Yu.; Lapuka, L. F. *Chem. Heterocyc. Compd.* **1983**, *19*, 1263-1266.

[viii] Alajarin, R.; Vaquero, J. J.; Alvarez-Builla, J.; Pastor, M.; Sunkel, C.; Fau de Casa-Juana, M.; Priego, J.; Statkow, P. R.; Sanz-Aparicio, J.; Fonseca, I. *J. Med. Chem.* **1995**, *38*, 2830-2841.

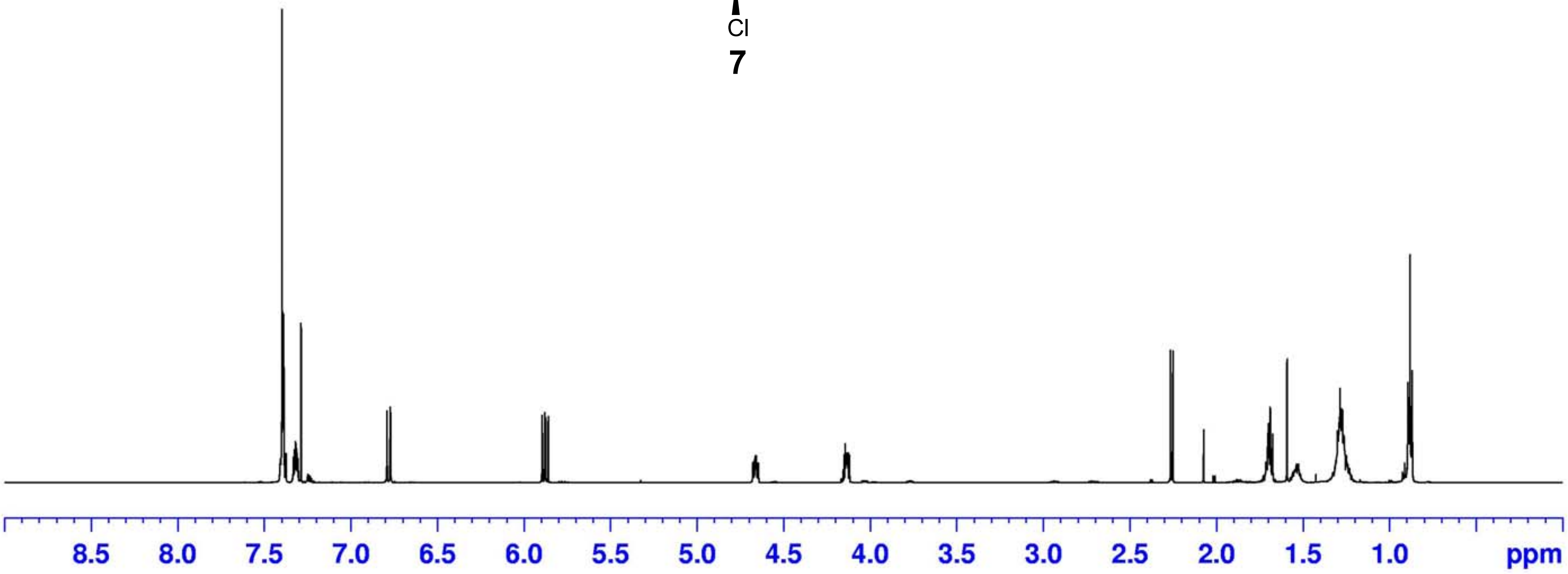
[ix] Takahata, H.; Uchida, Y.; Momose, T. *J. Org. Chem.* **1995**, *60*, 5628-5633.

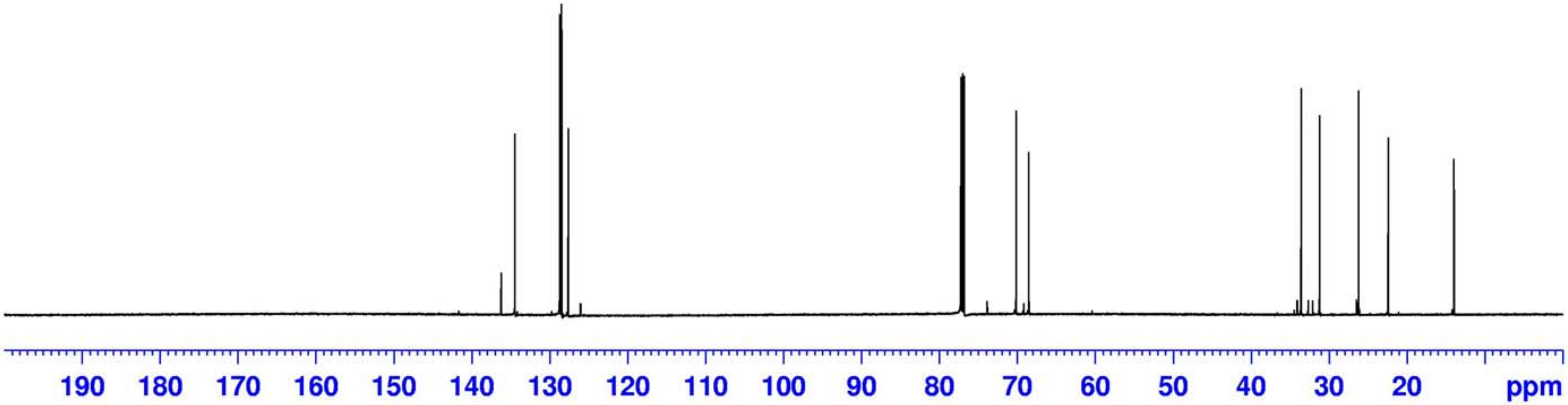
[x] Certain resonances in the ^{13}C NMR spectrum of **(+)-1** recorded in $CDCl_3$ were found to shift slightly depending on concentration. The ^{13}C NMR spectrum of a 0.01M solution of **(+)-1** was identical to that reported for both natural and synthetic goniothalesdiol.

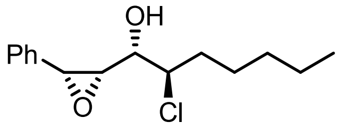
[xi] Lit. $[\alpha]_D^{25}$: +7.5° (c = 0.23, EtOH); Cao, S. –G.; Wu, X. –H; Sim, K. –Y.; Tan, B. K. H.; Pereira, J. T.; Goh, S. –H. *Tetrahedron* **1998**, *10*, 2143-2148.


OH
Ph
Cl

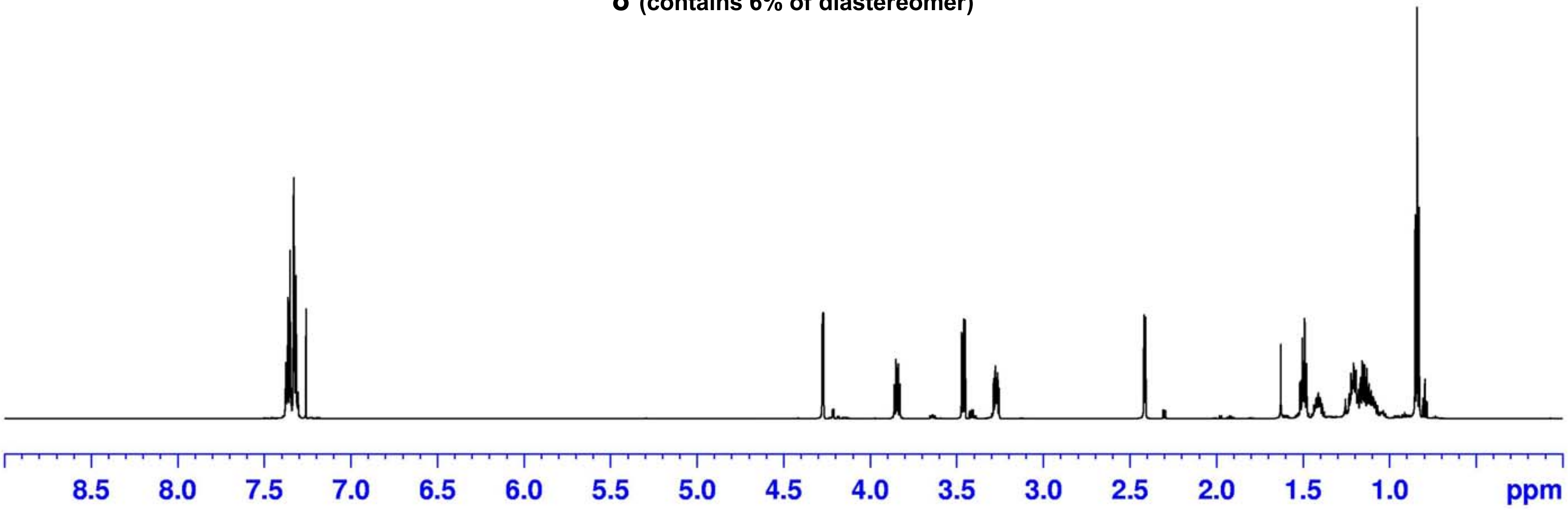
7

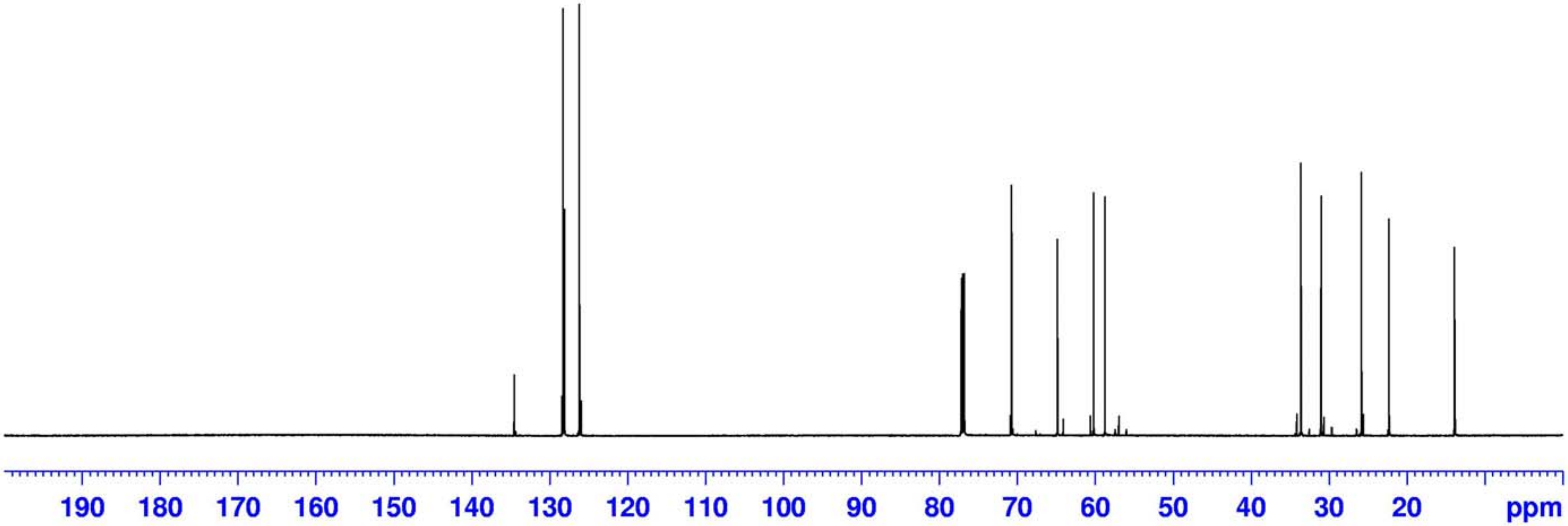

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

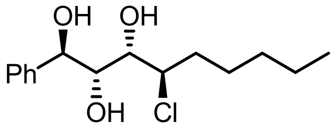

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm



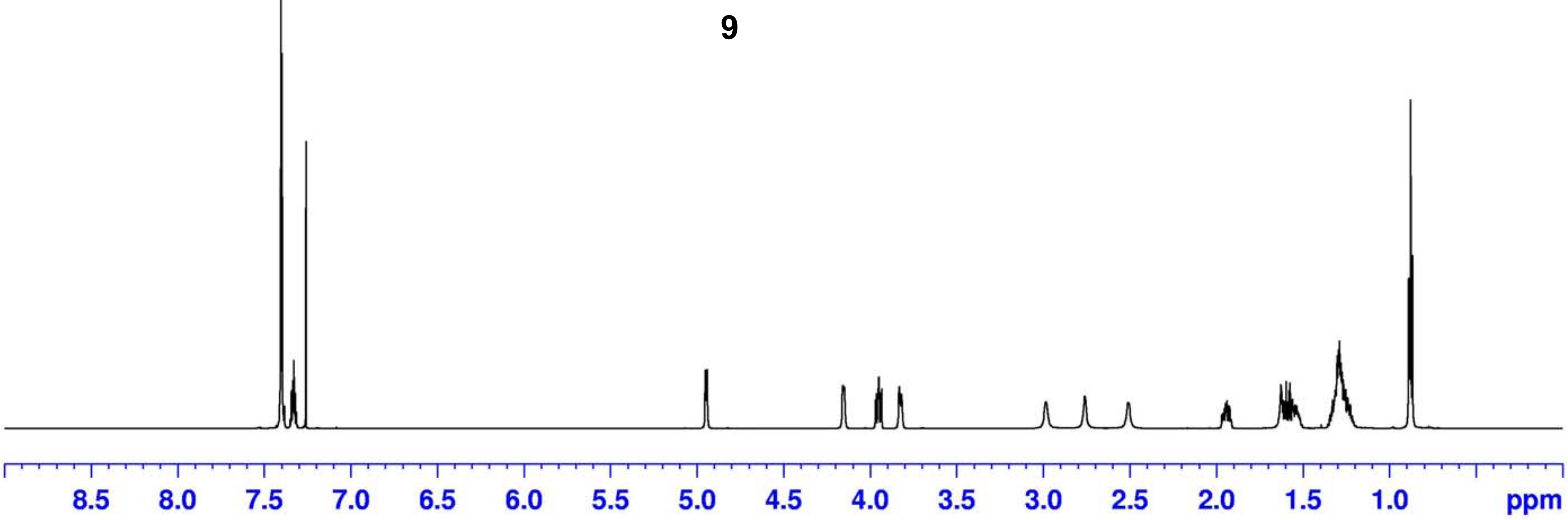
8 **(contains 6% of diastereomer)**

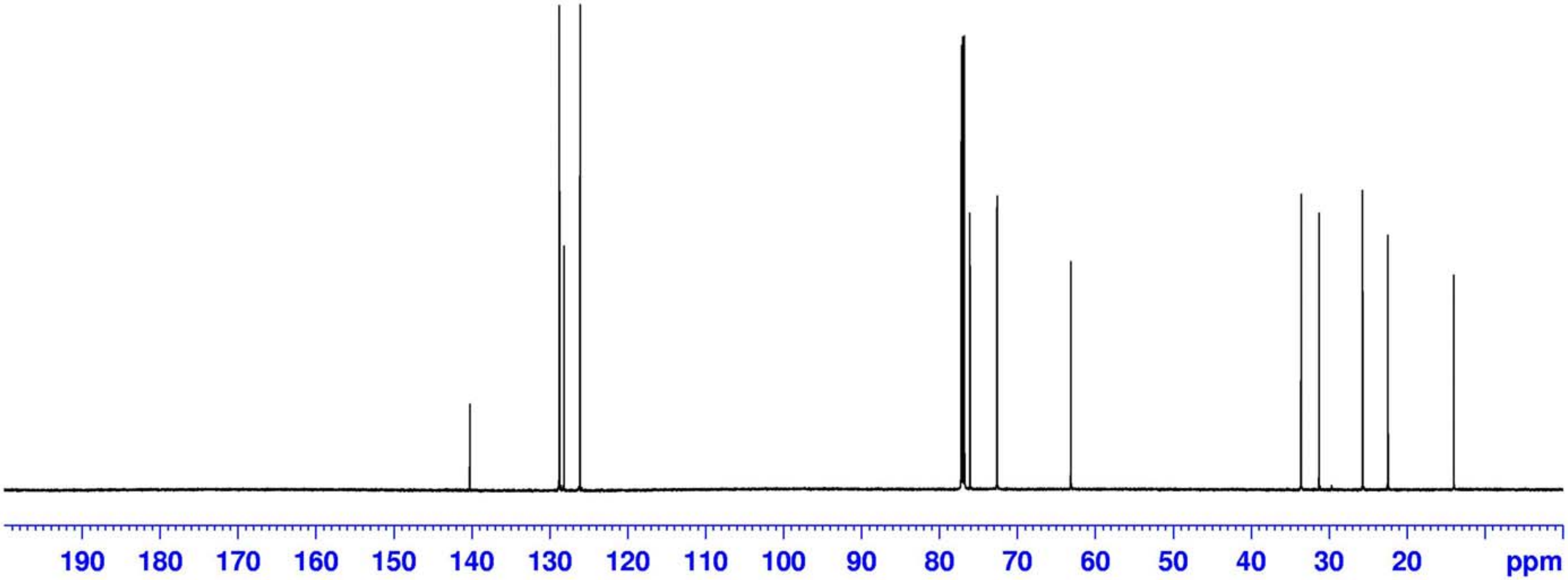


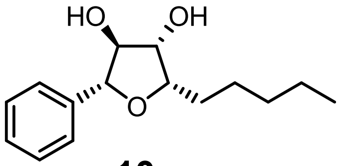



OH
OH
Ph
OH
Cl

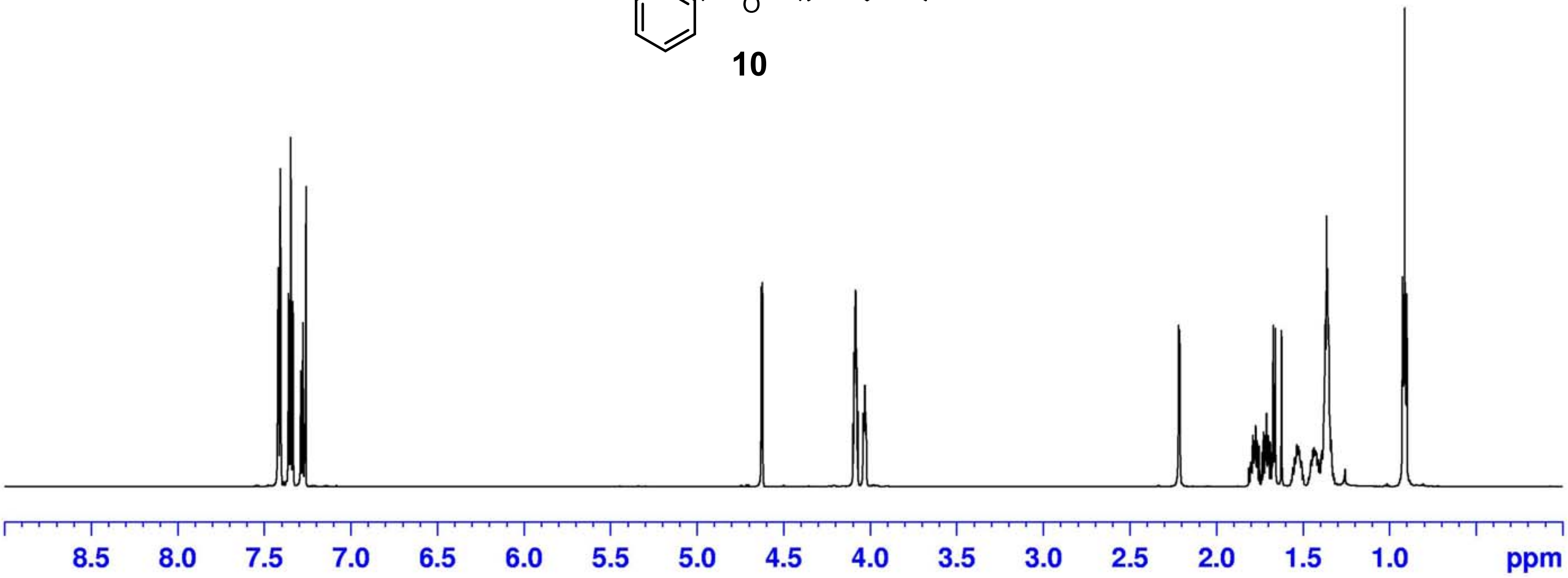
9

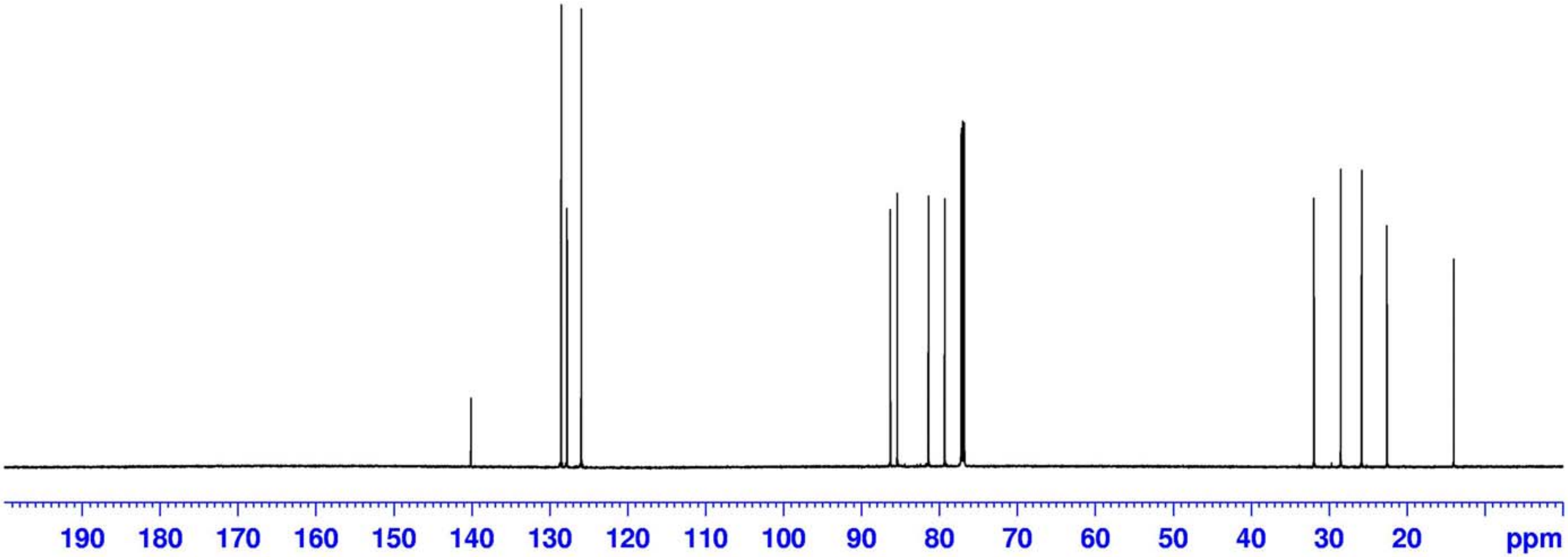

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

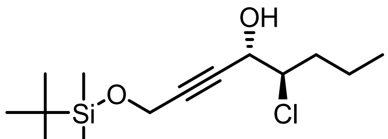

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


HO
OH
O

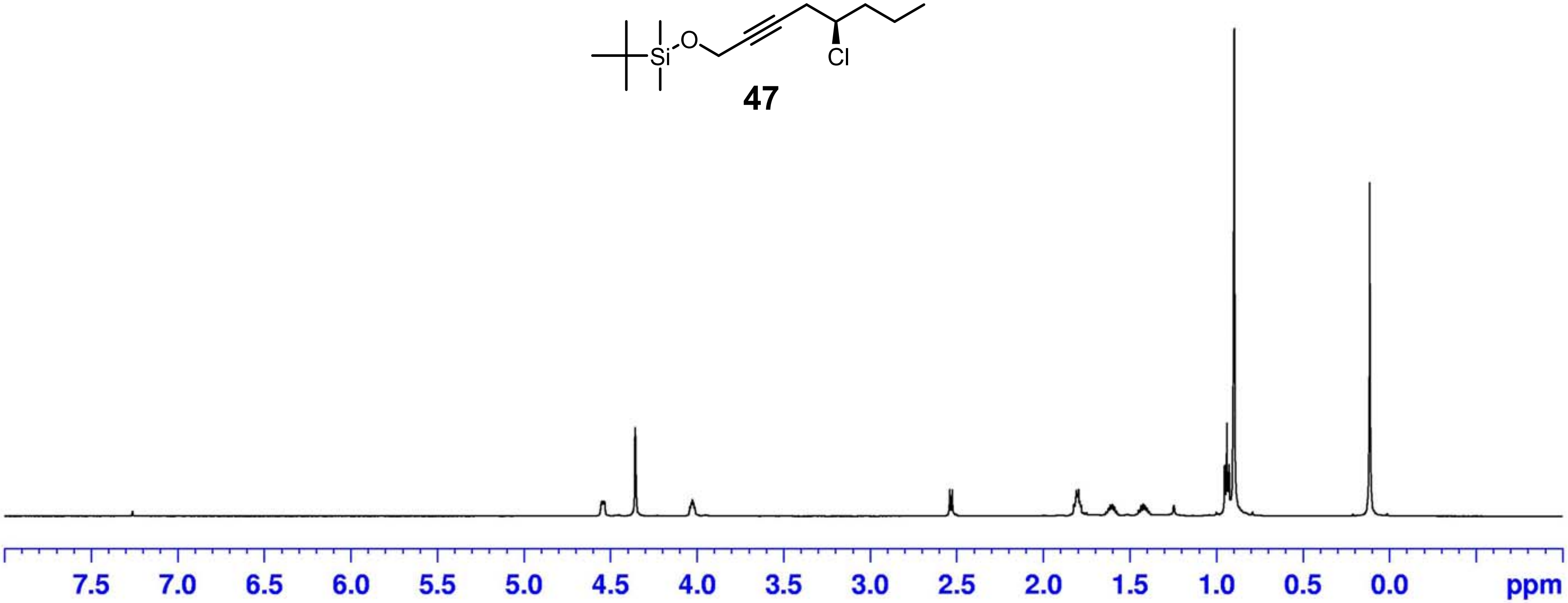
10

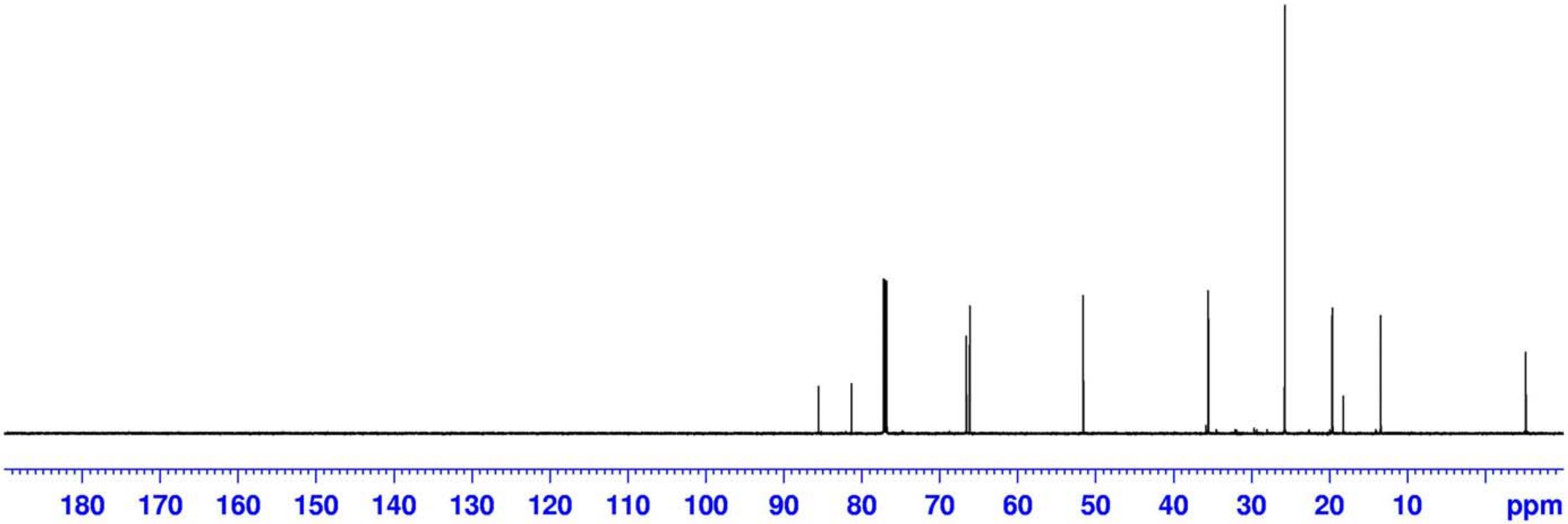

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

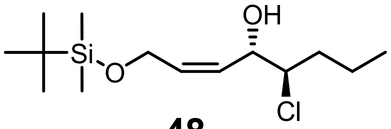

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


OH
Si
O
Cl

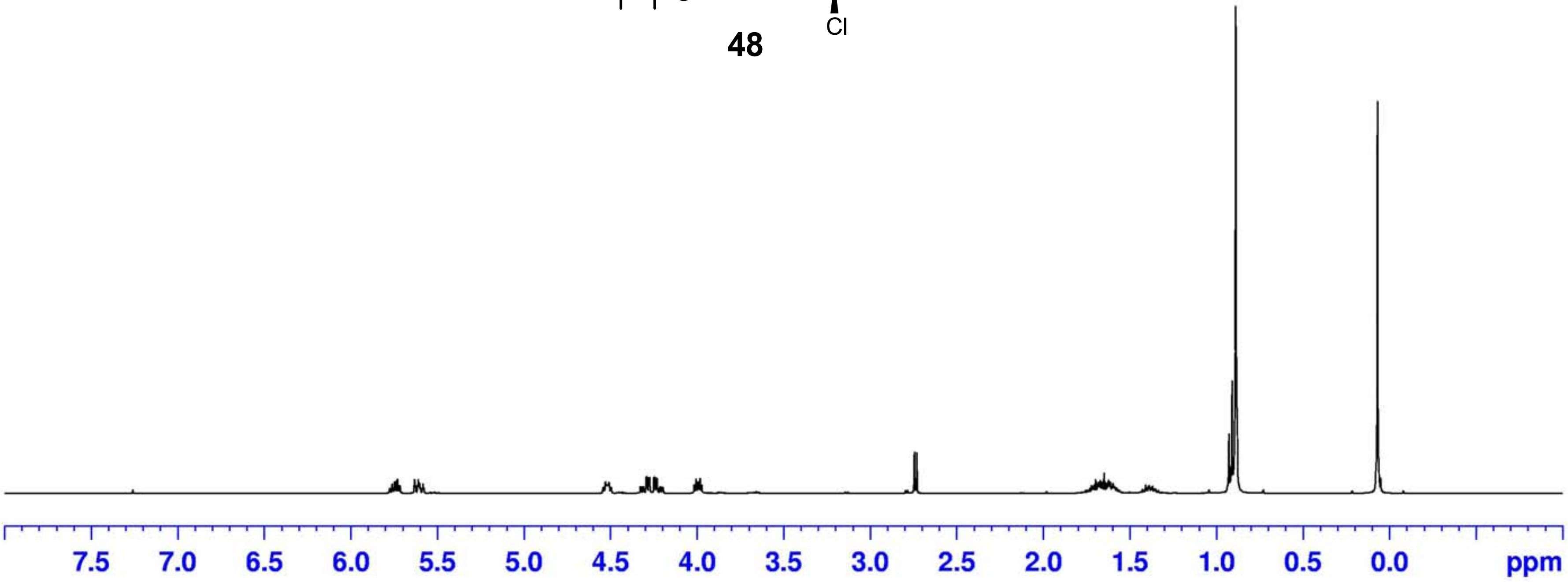
47

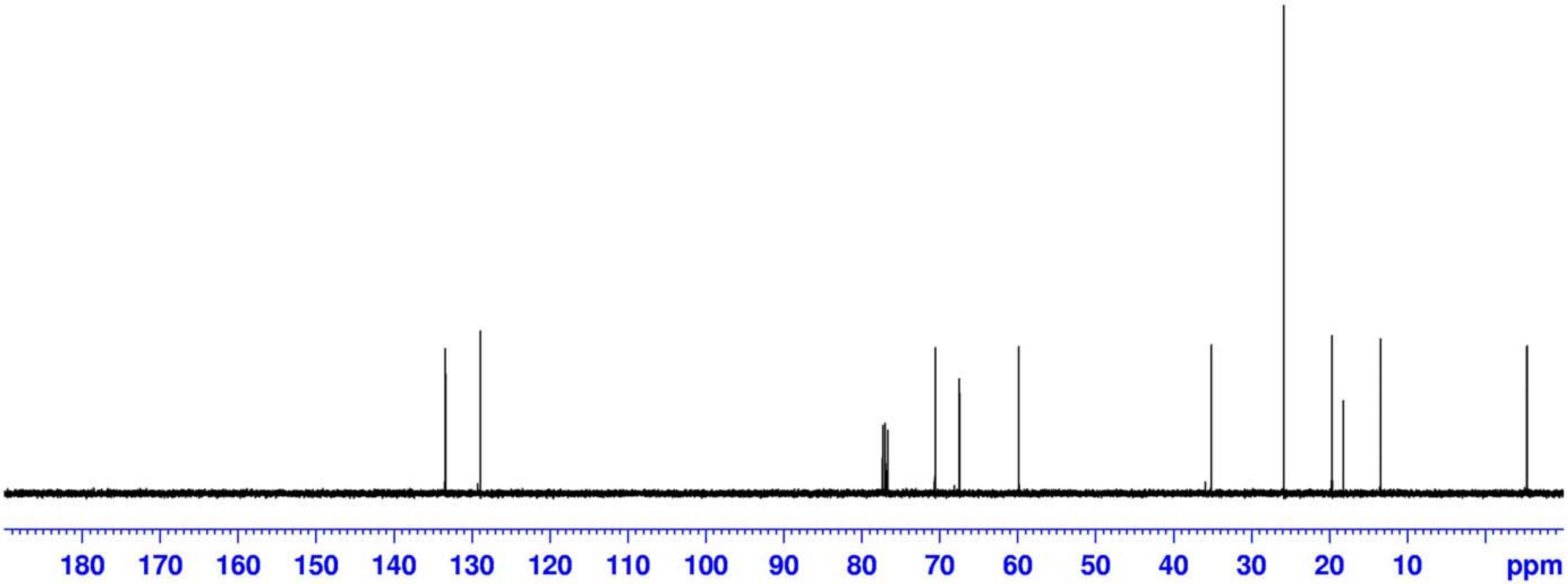

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

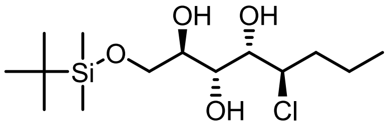

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


OH
Si
O
Cl

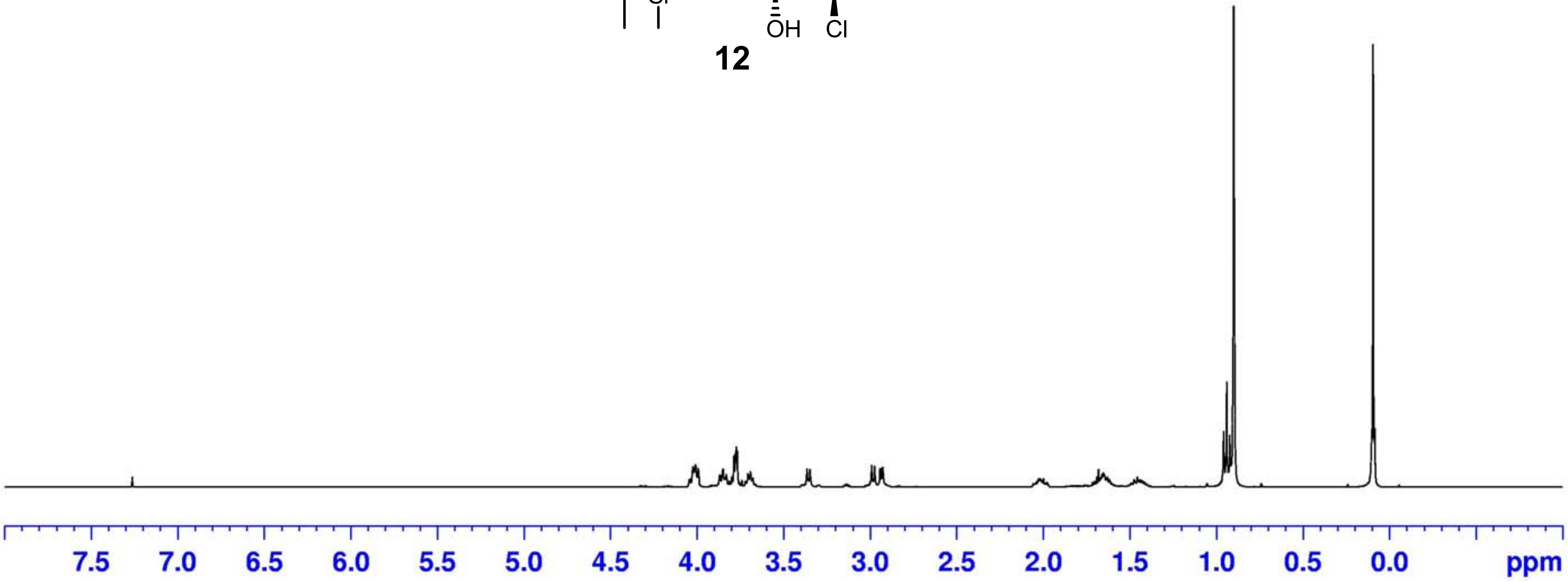
48

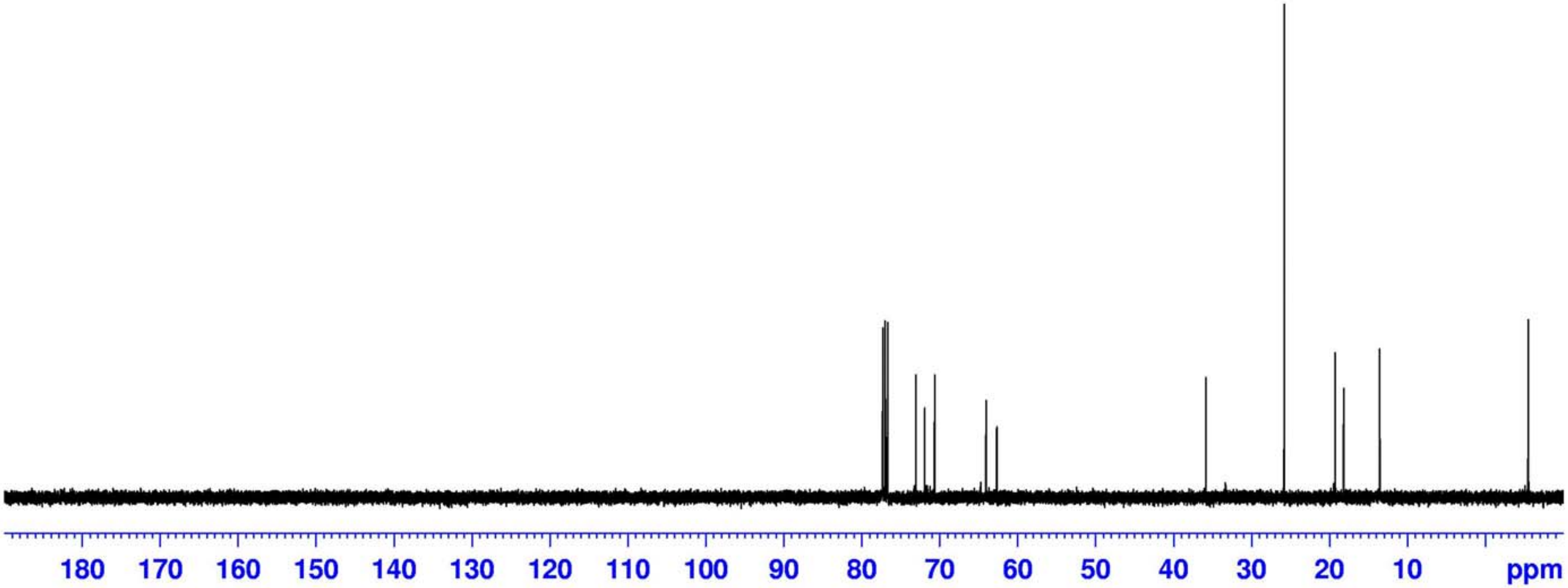

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

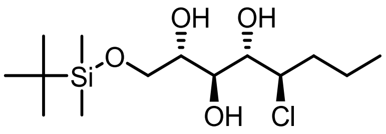

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


OH
OH
Si
O
OH
Cl

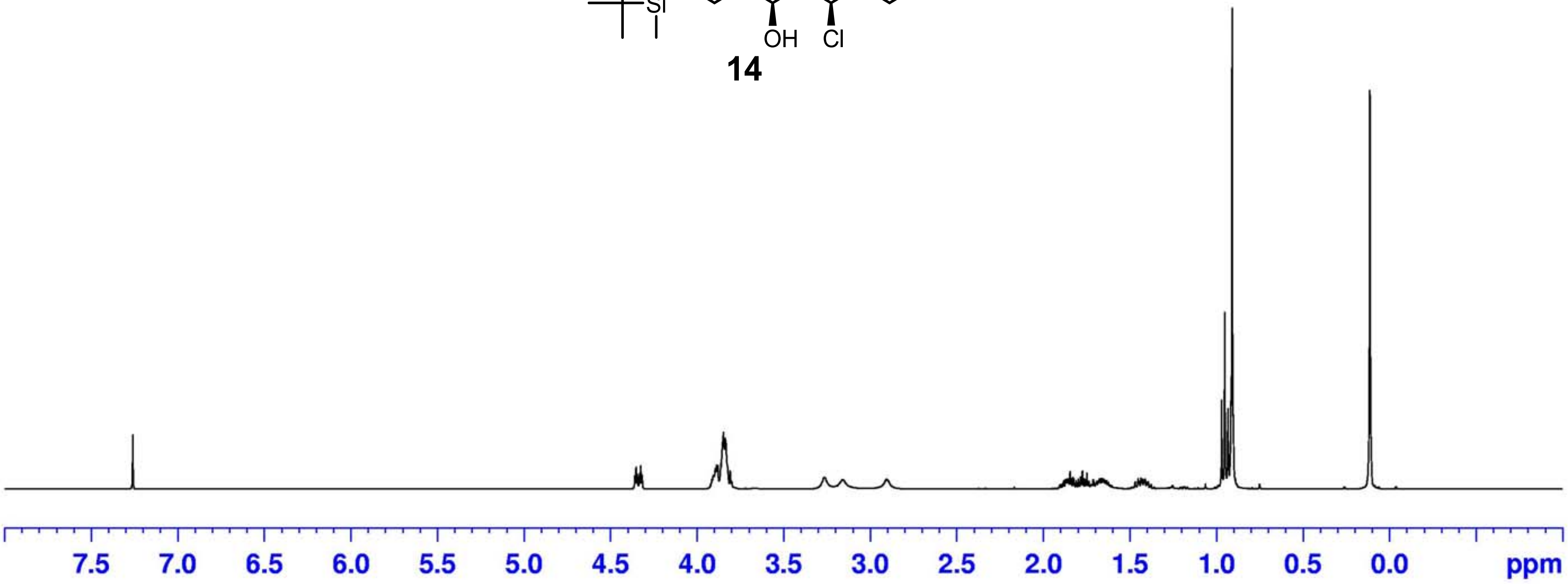
12

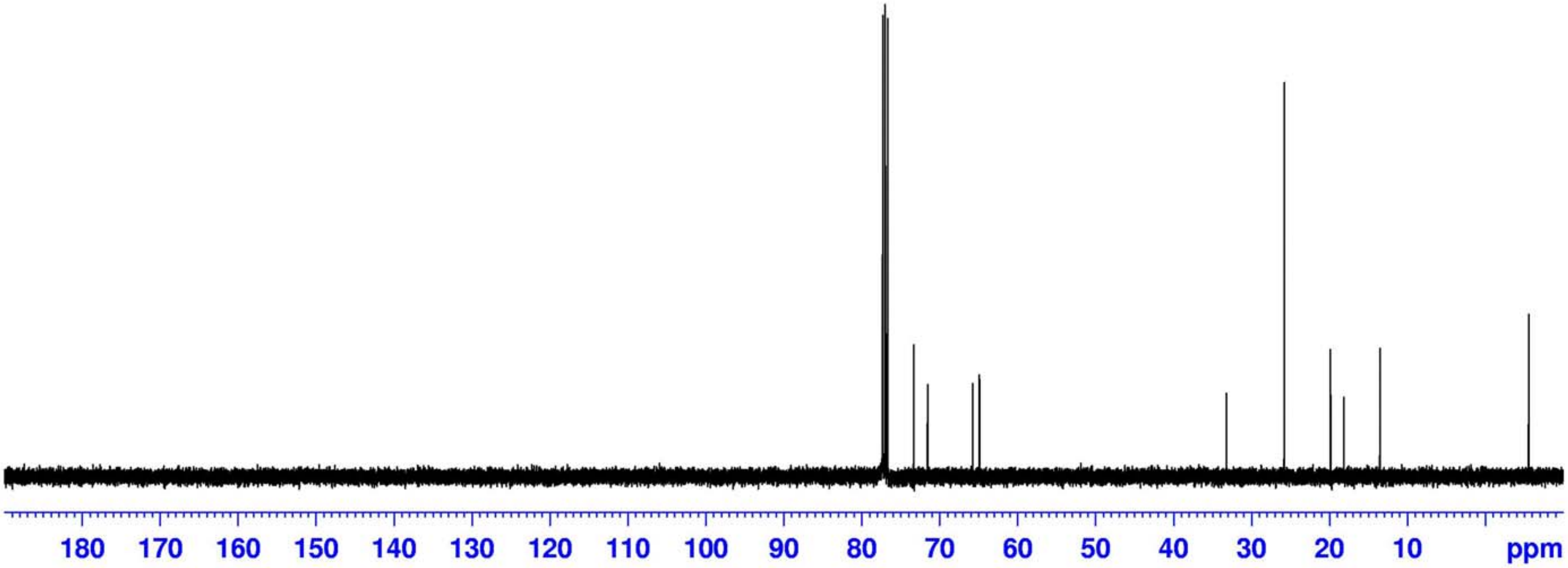

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

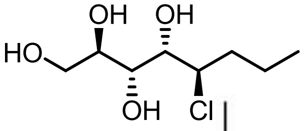

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


OH
OH
Si
O
OH
Cl

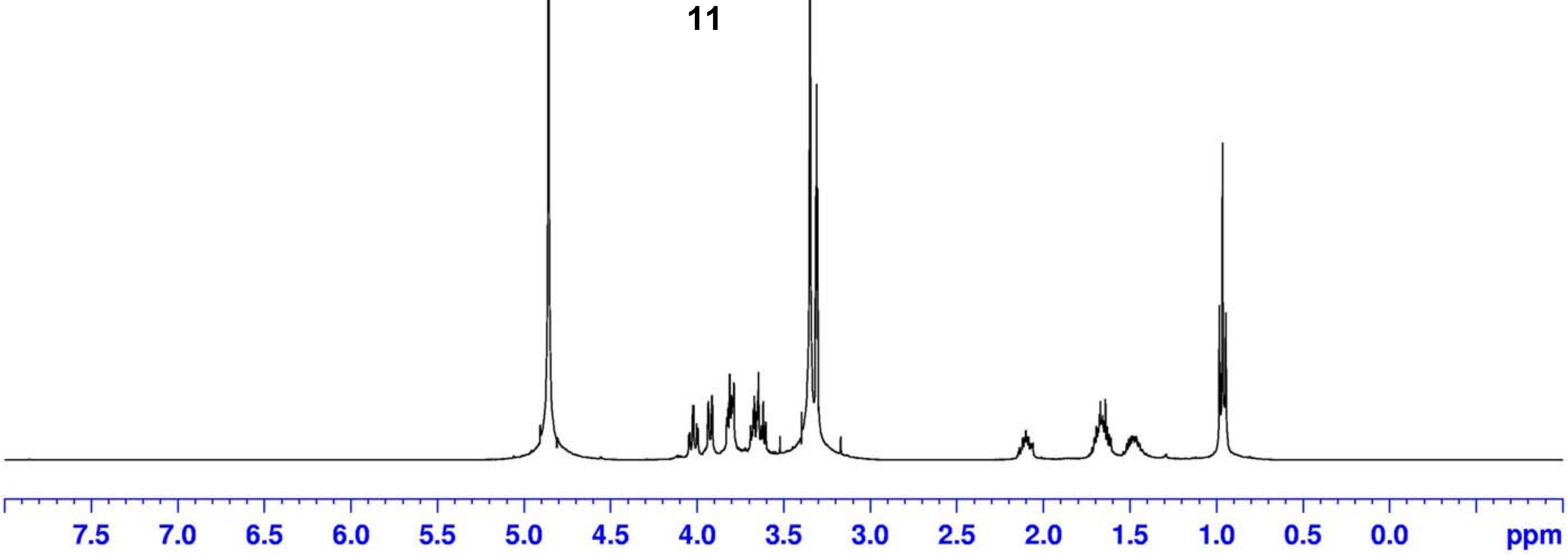
14

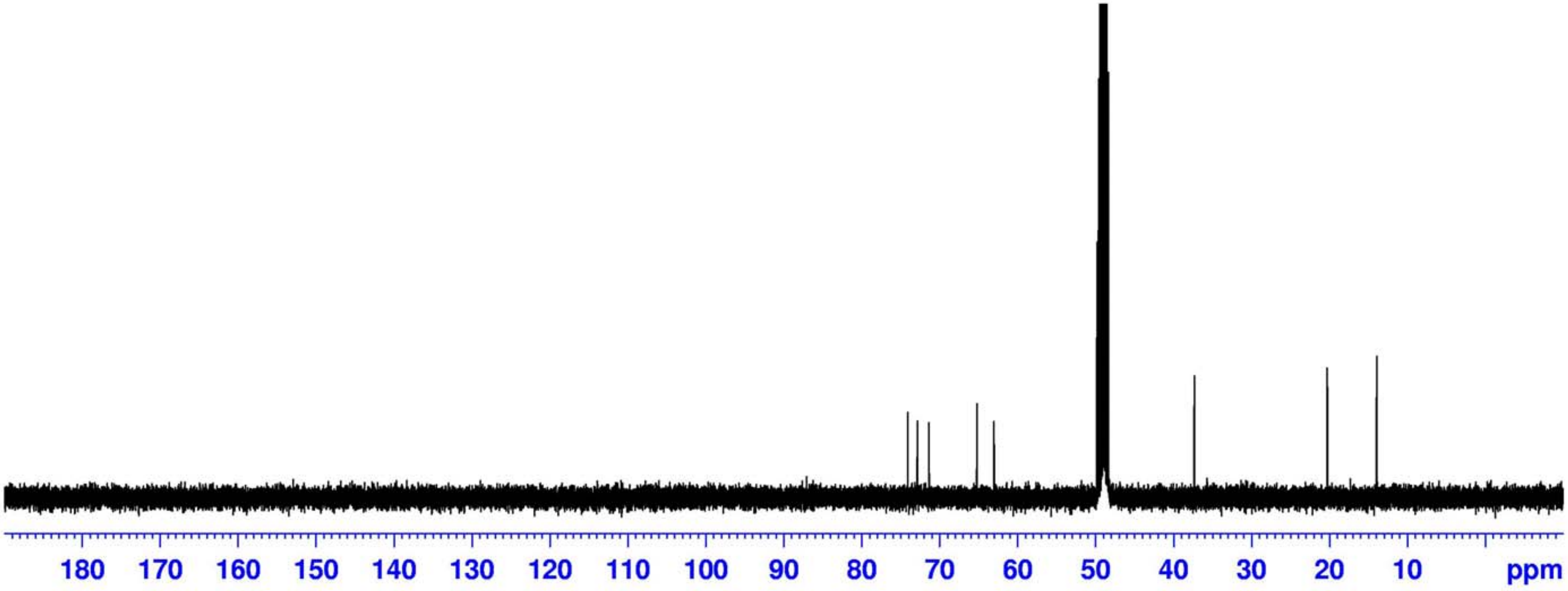

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

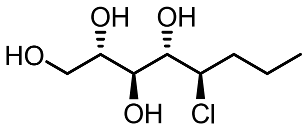

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


OH
OH
HO
OH
Cl

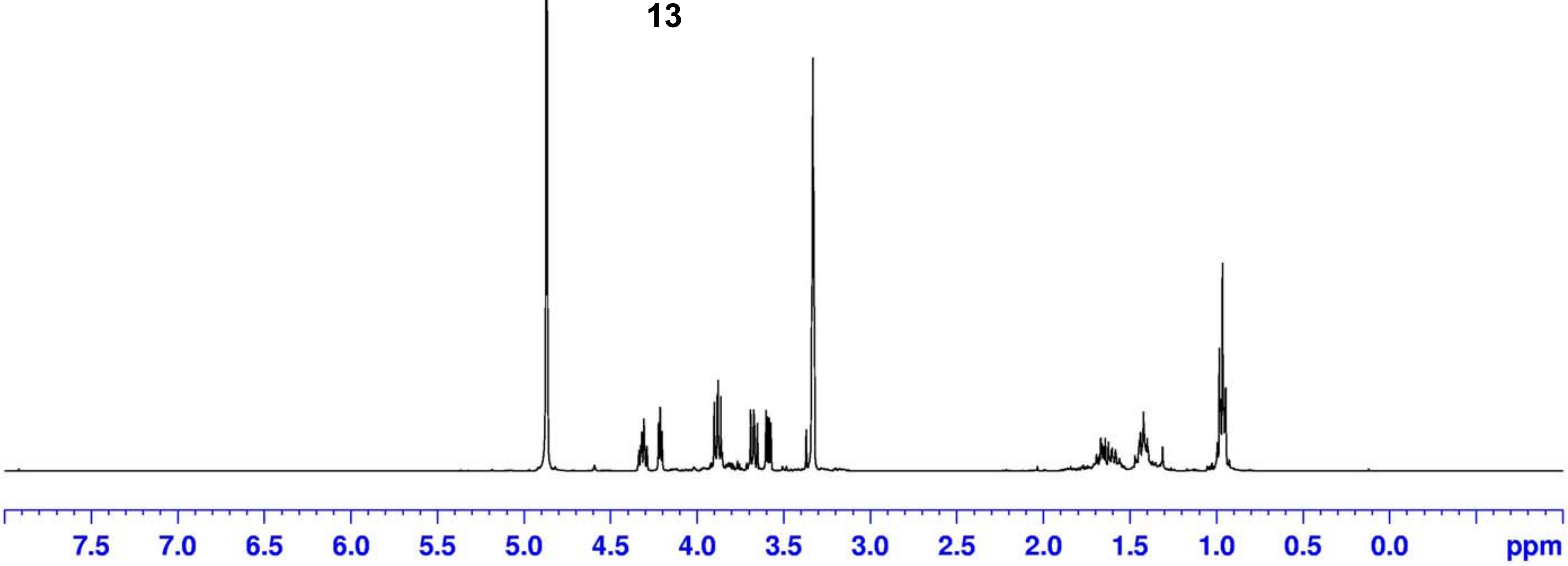
11

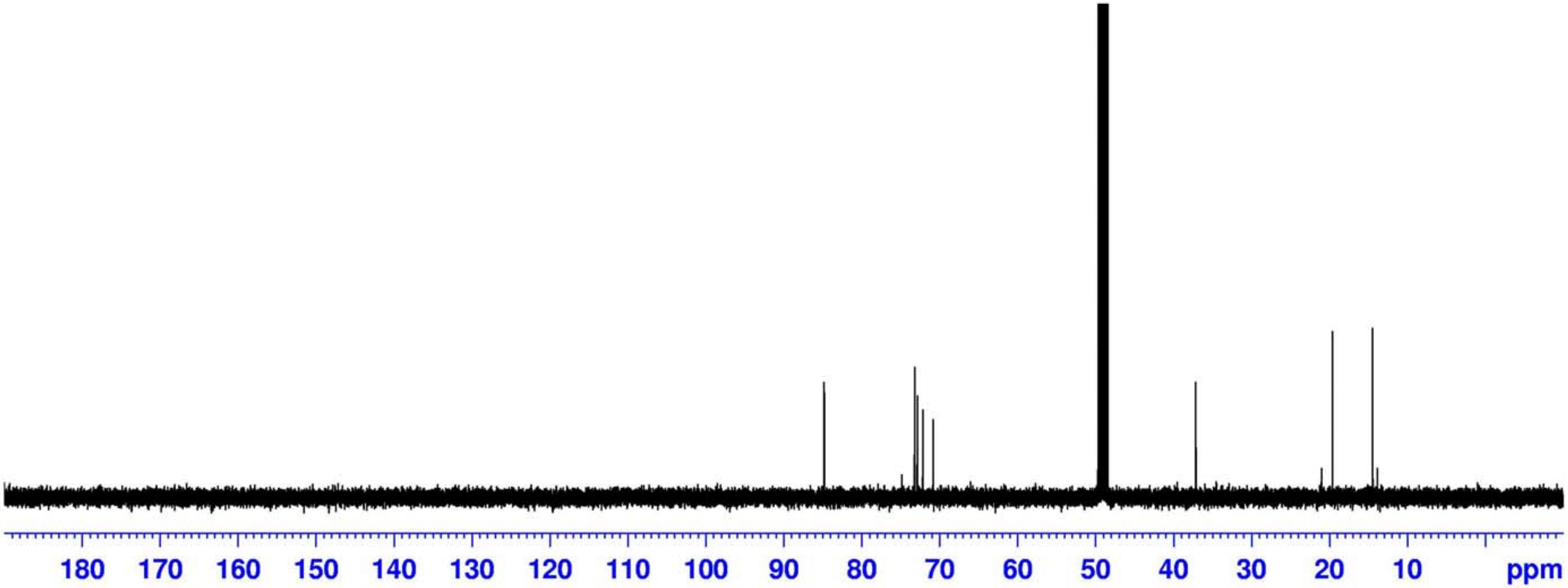

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

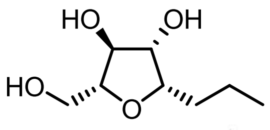

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


OH
OH
HO
OH
Cl

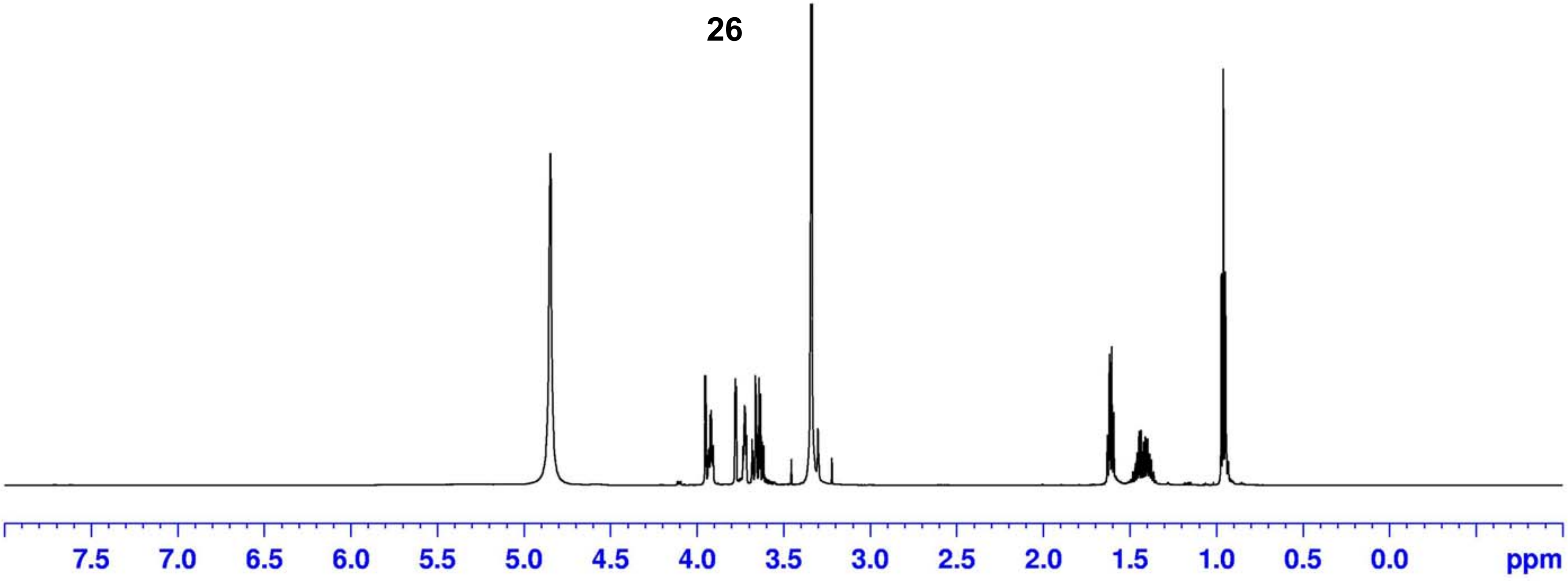
13

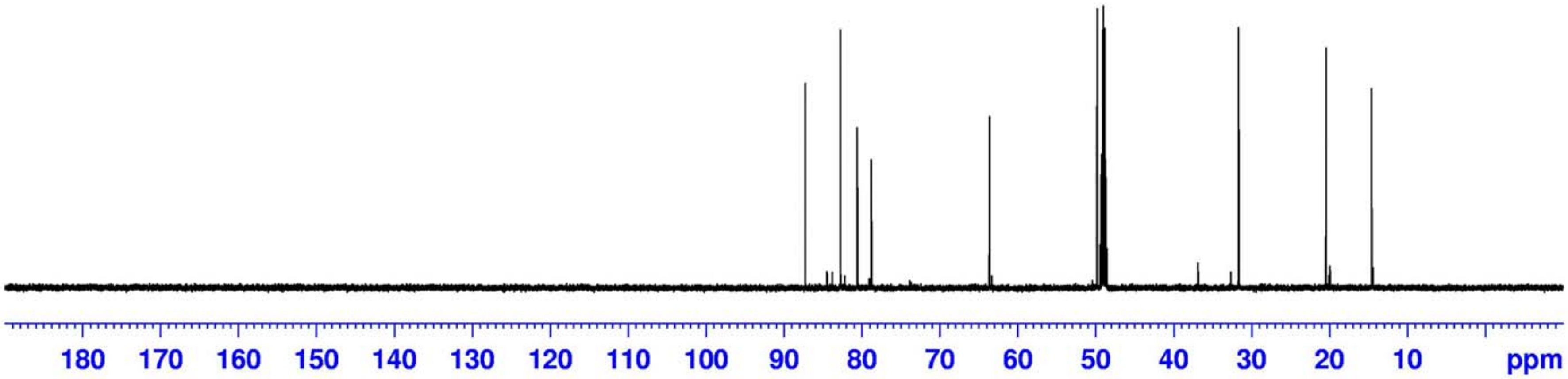

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

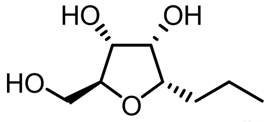

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


HO
OH
HO
O

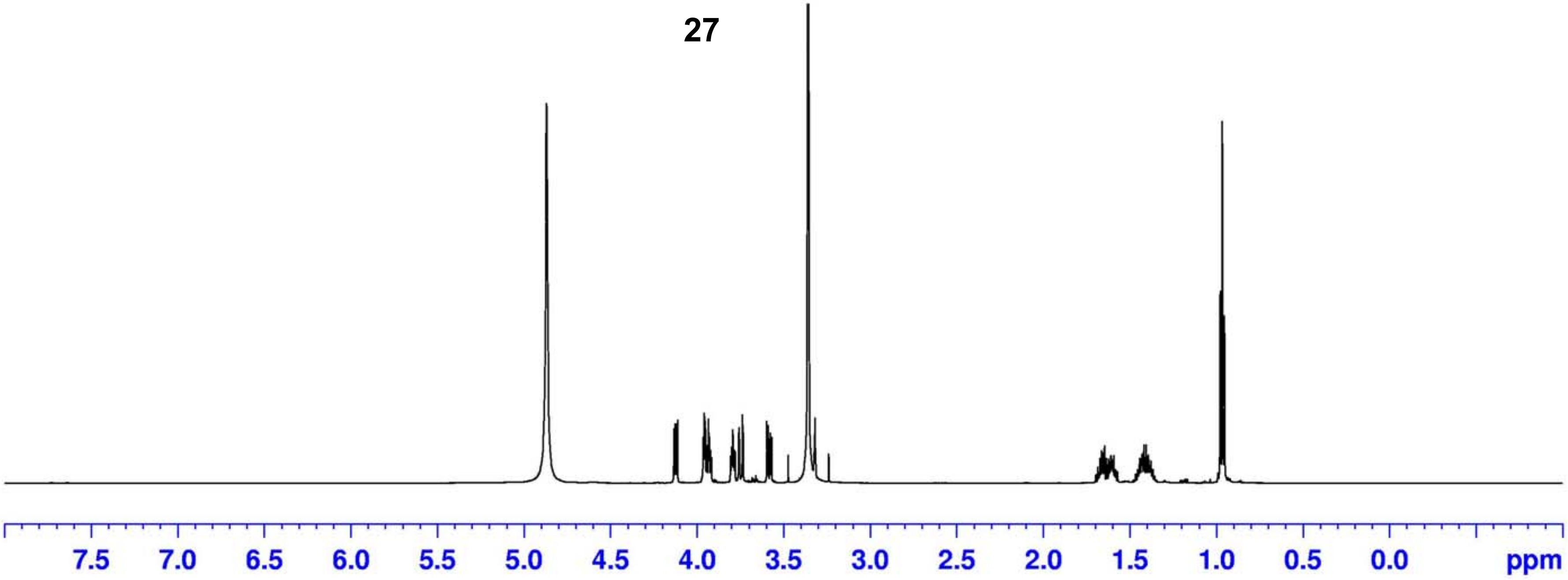
26

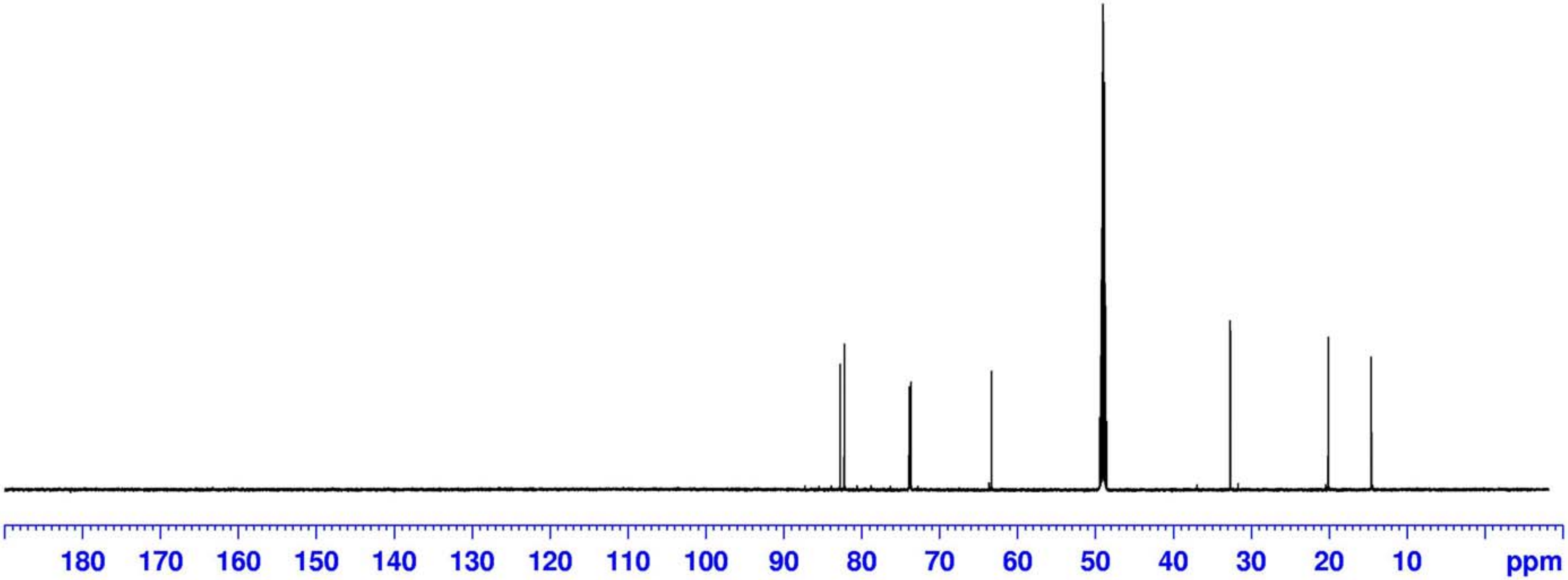

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

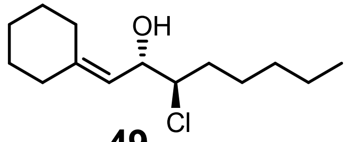

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


HO
OH
HO
O

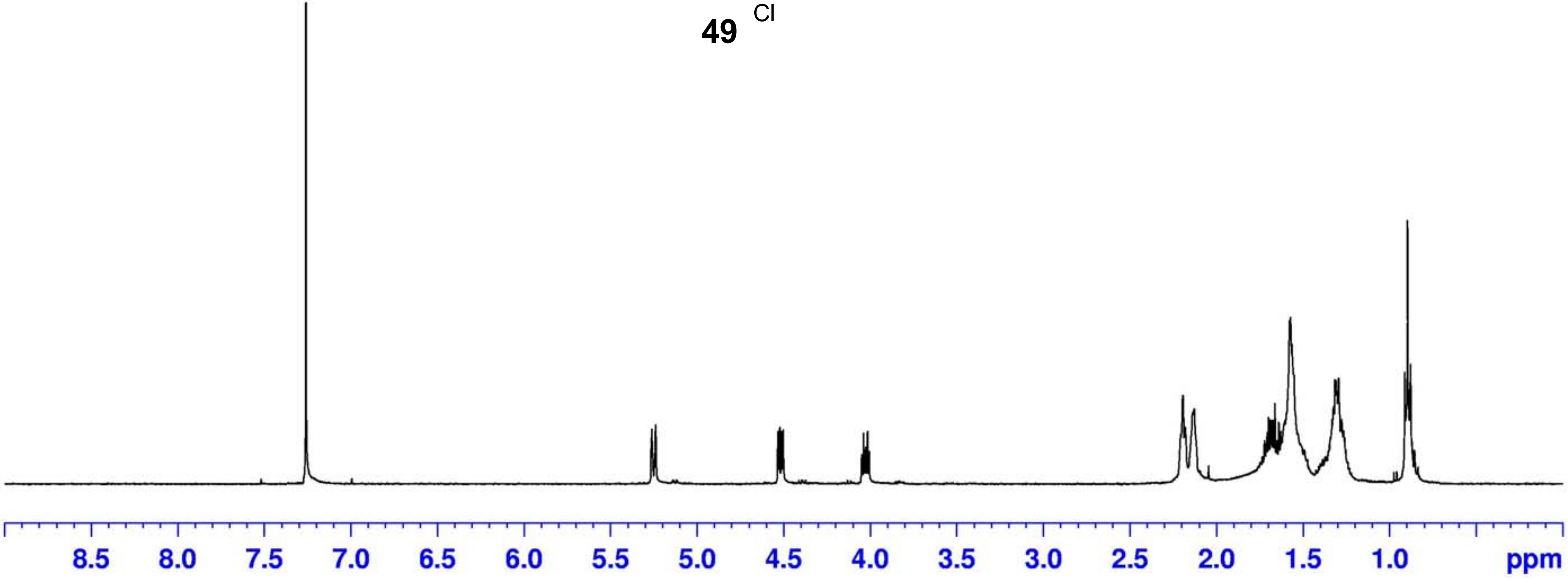
27

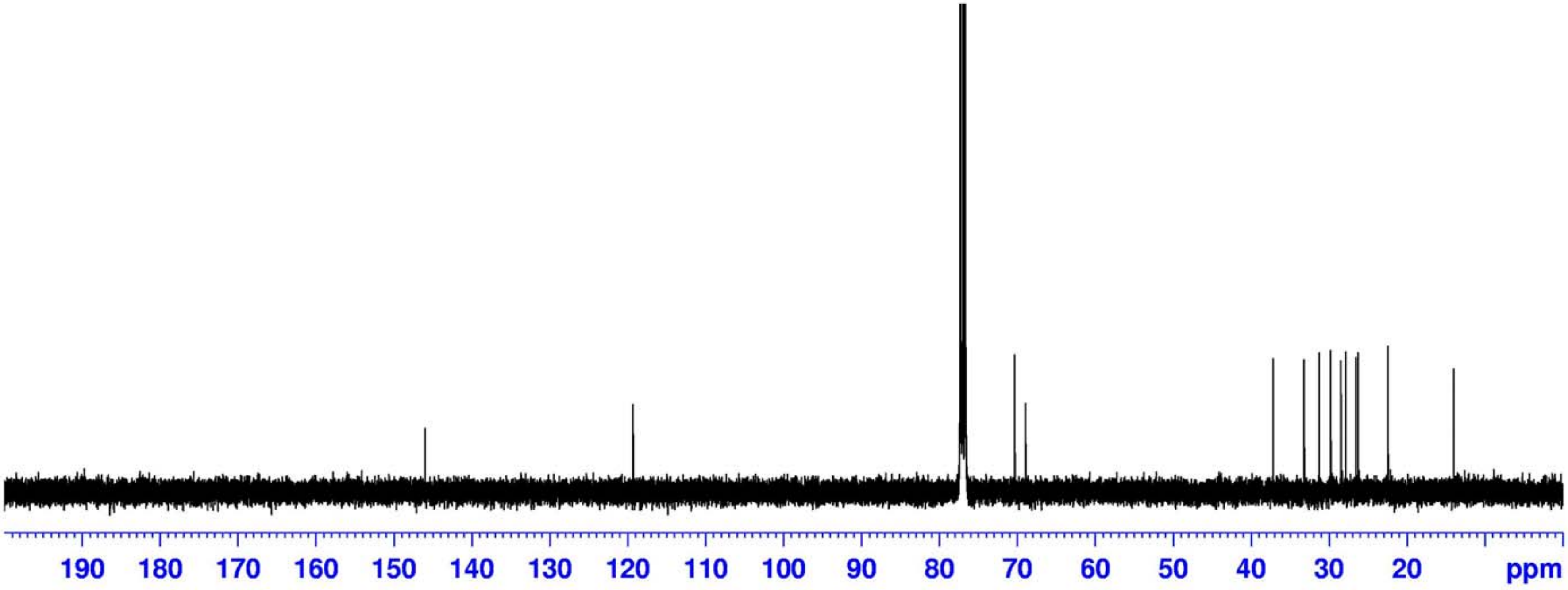

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

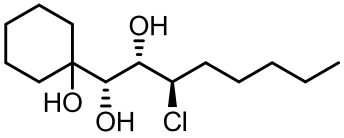

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


OH
Cl

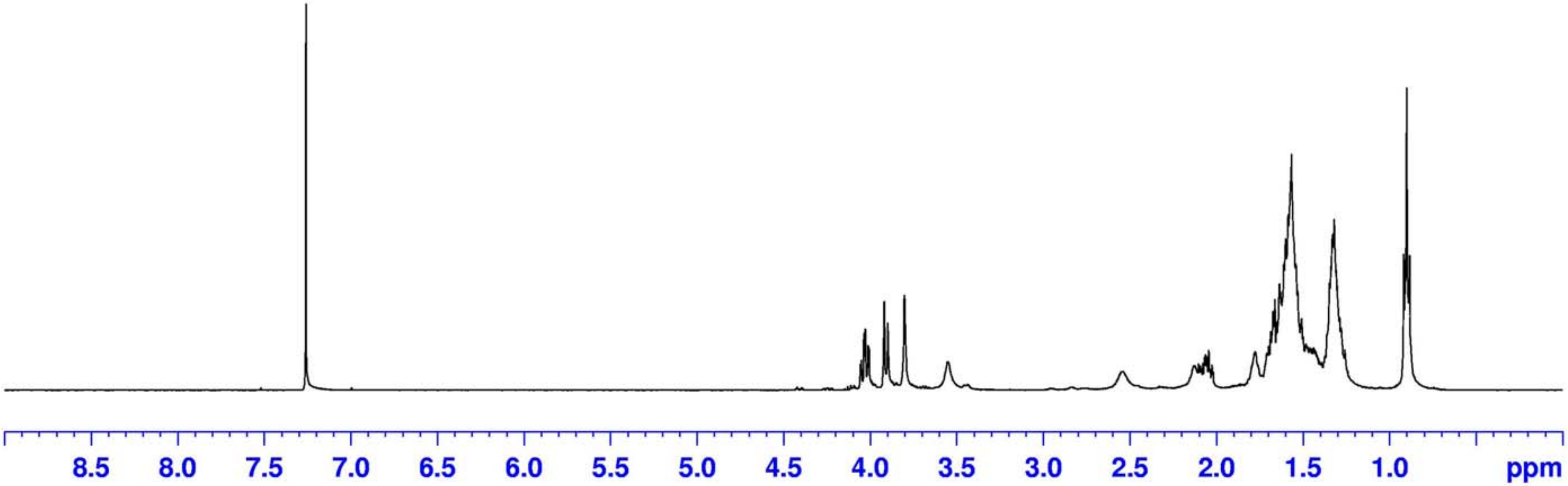
49

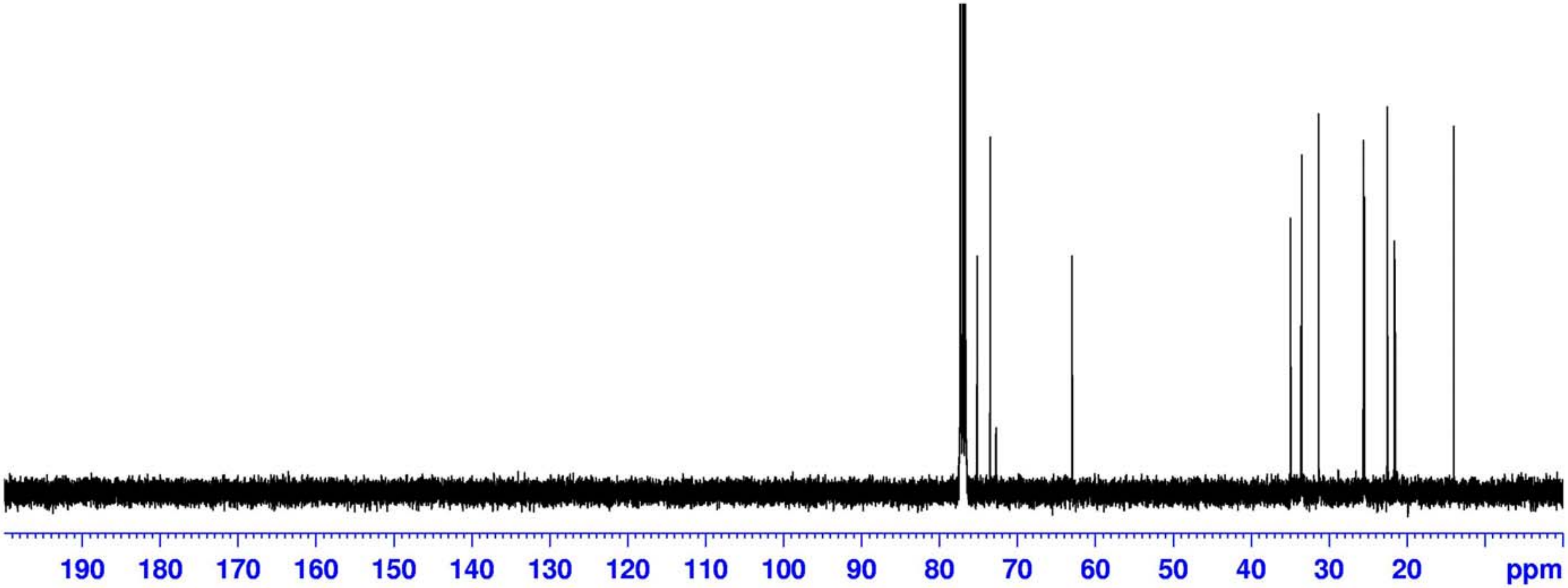

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

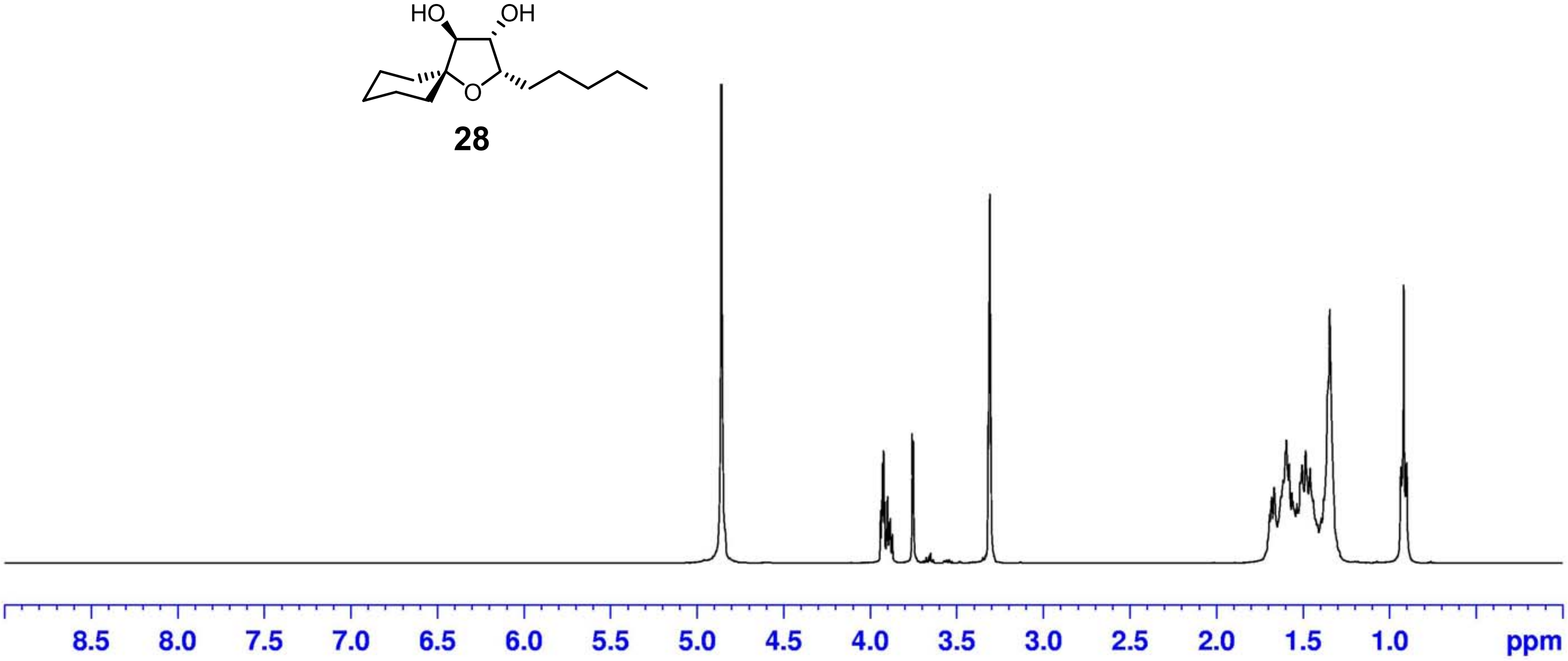

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


OH
HO
OH
Cl

15

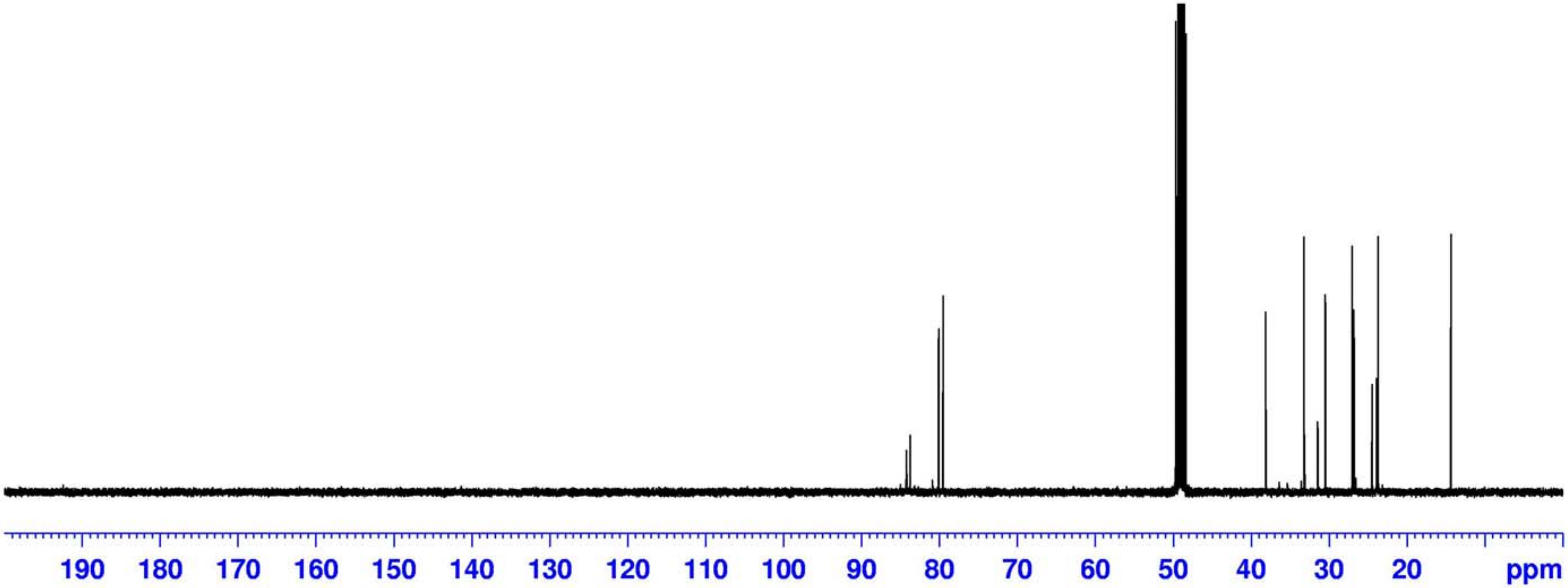

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

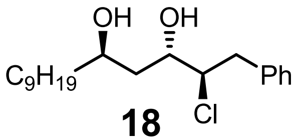


28

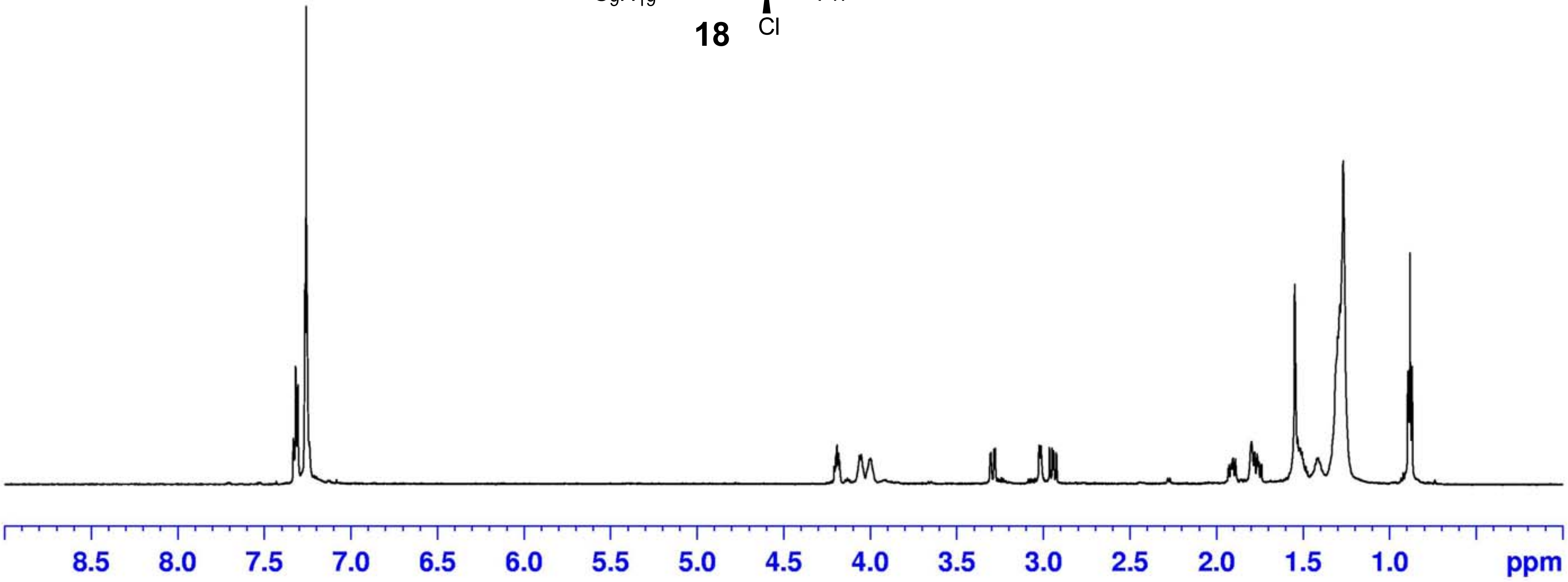
HO
OH
O
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

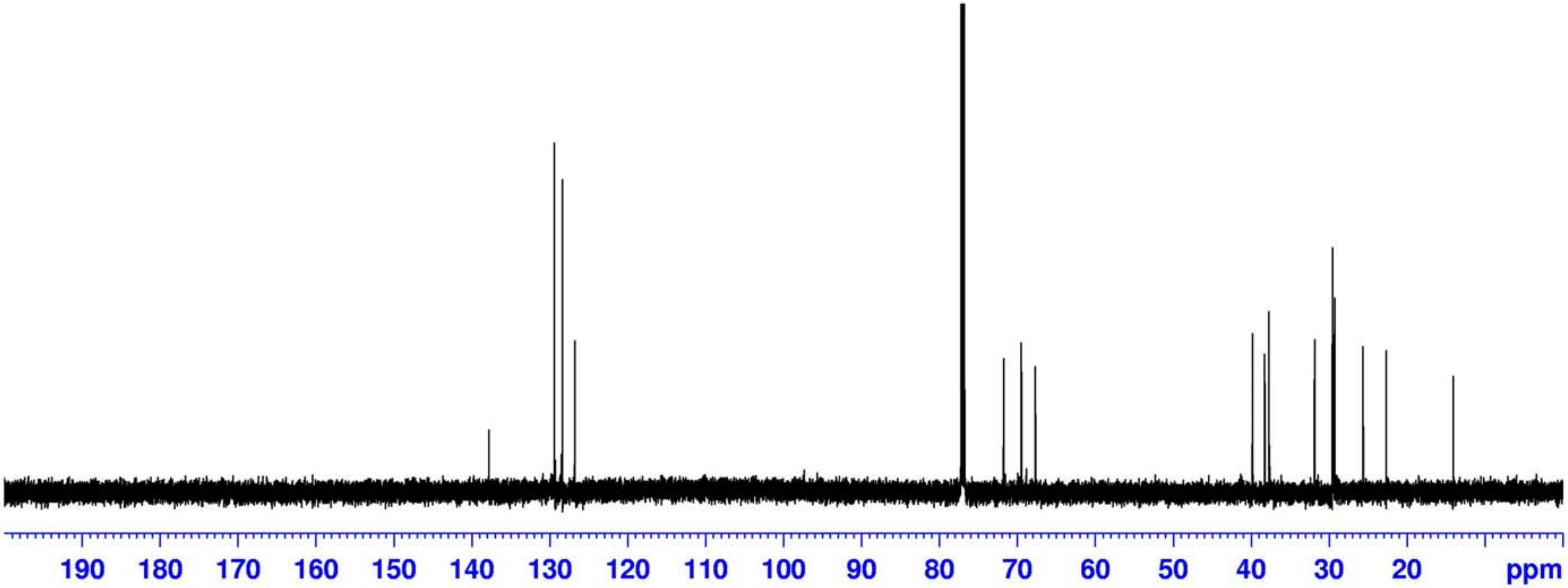


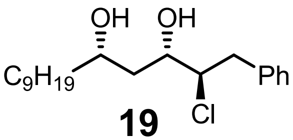
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


OH
OH
C9H19
Ph
Cl

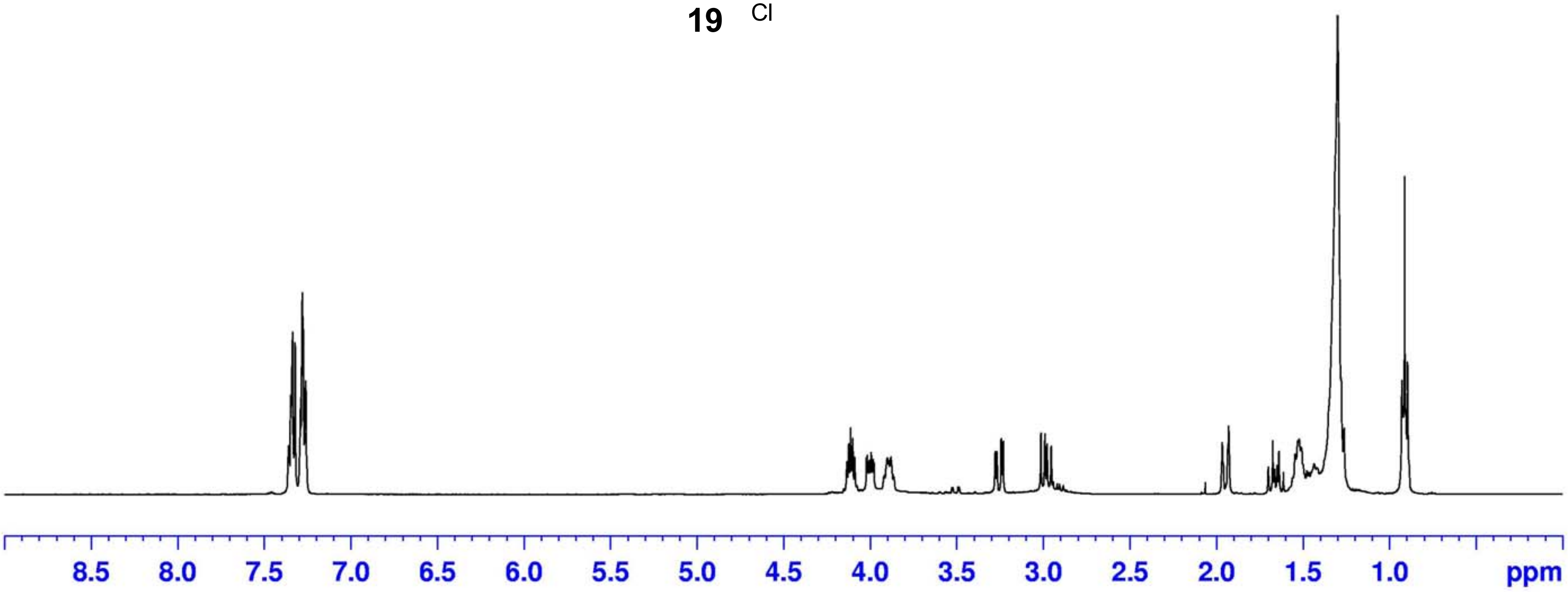
18

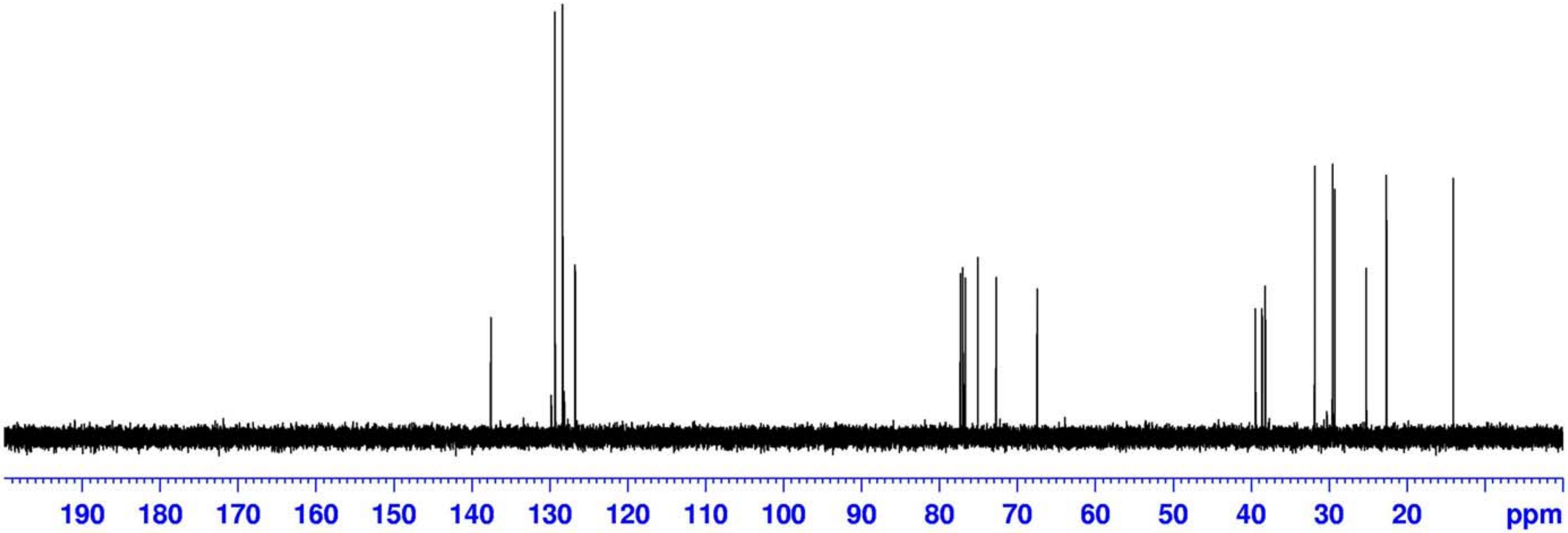

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

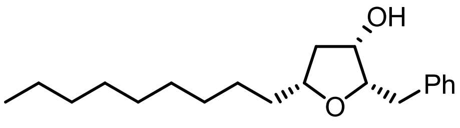

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


OH
OH
C9H19
Ph
Cl

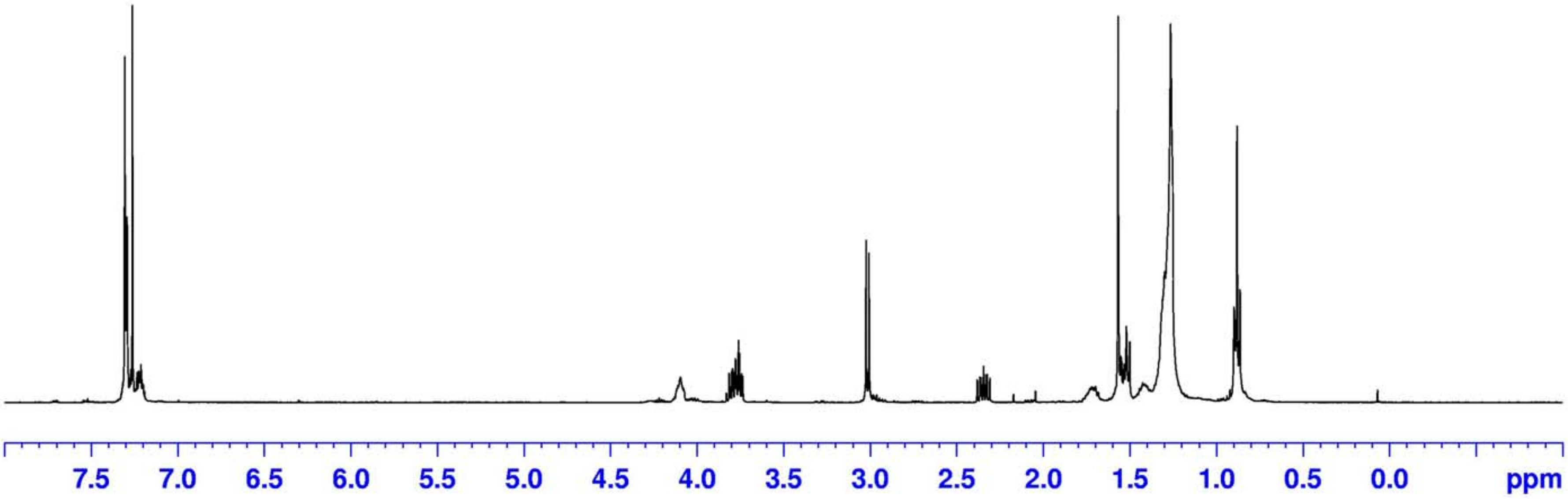
19

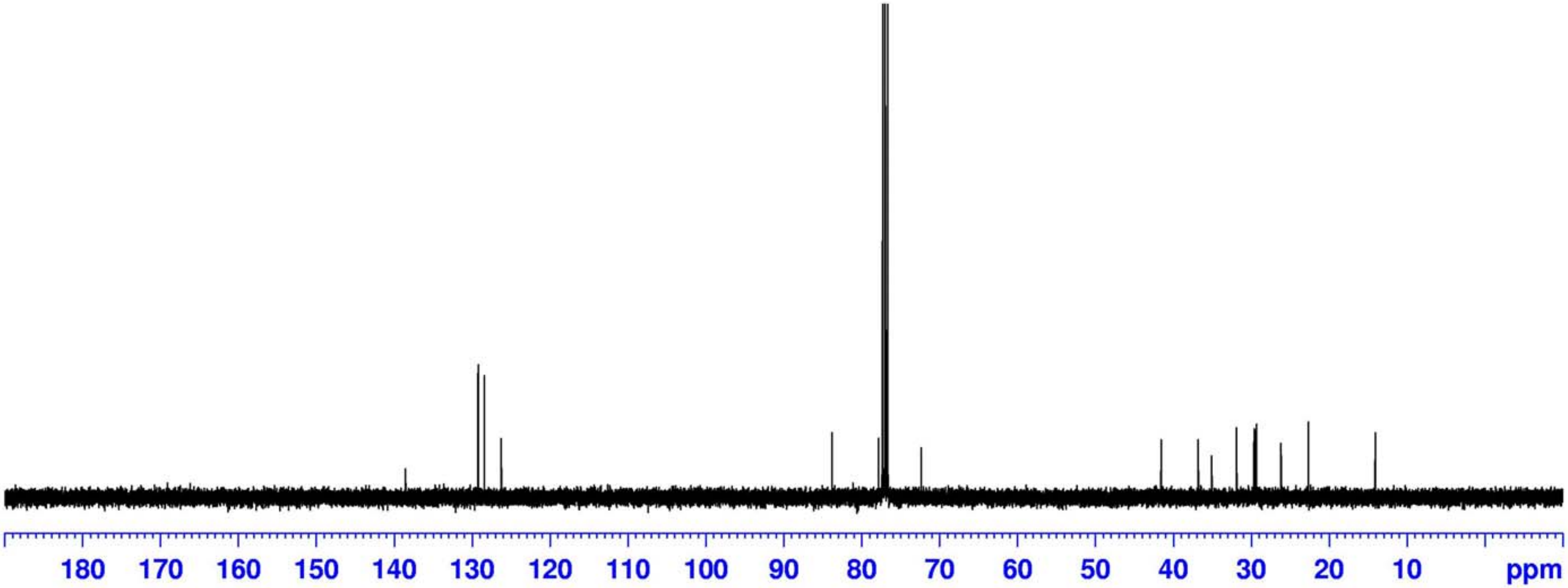

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

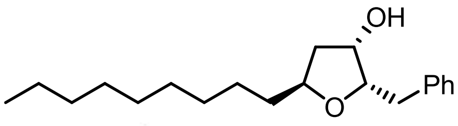

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


OH
O
Ph

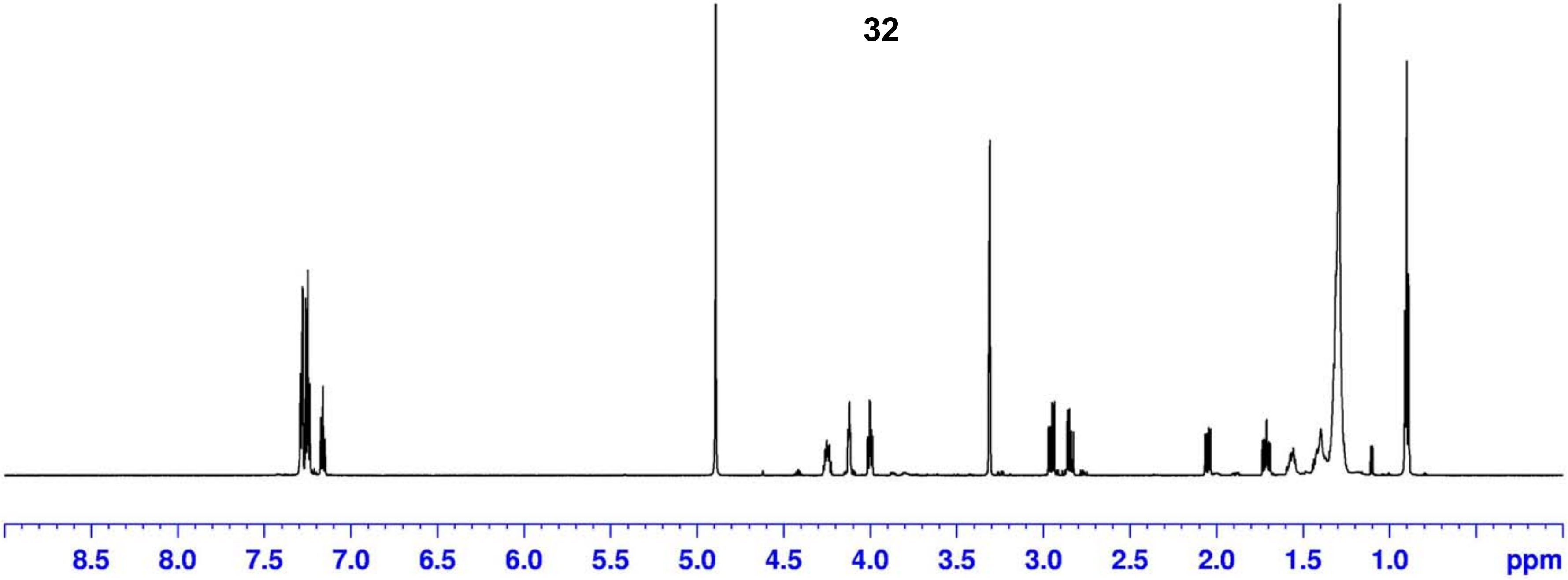
31

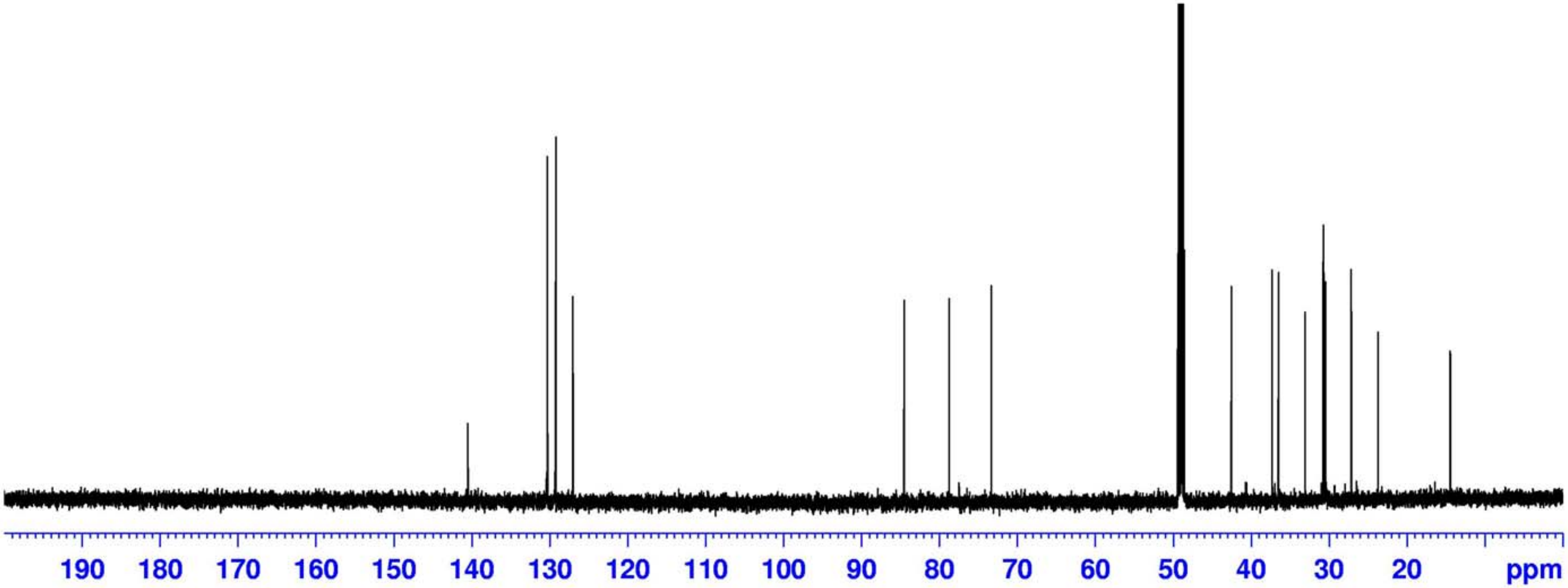

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

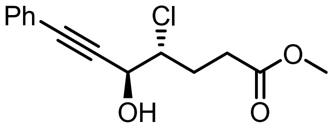

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


OH
O
Ph

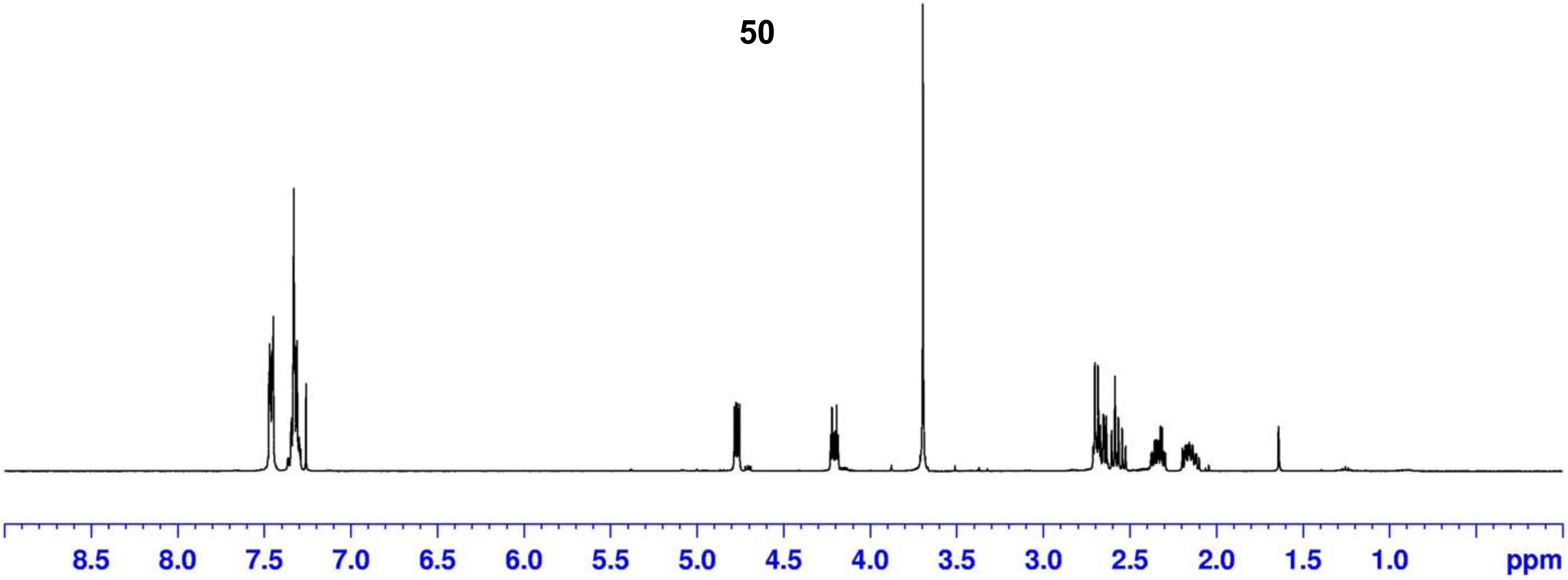
32

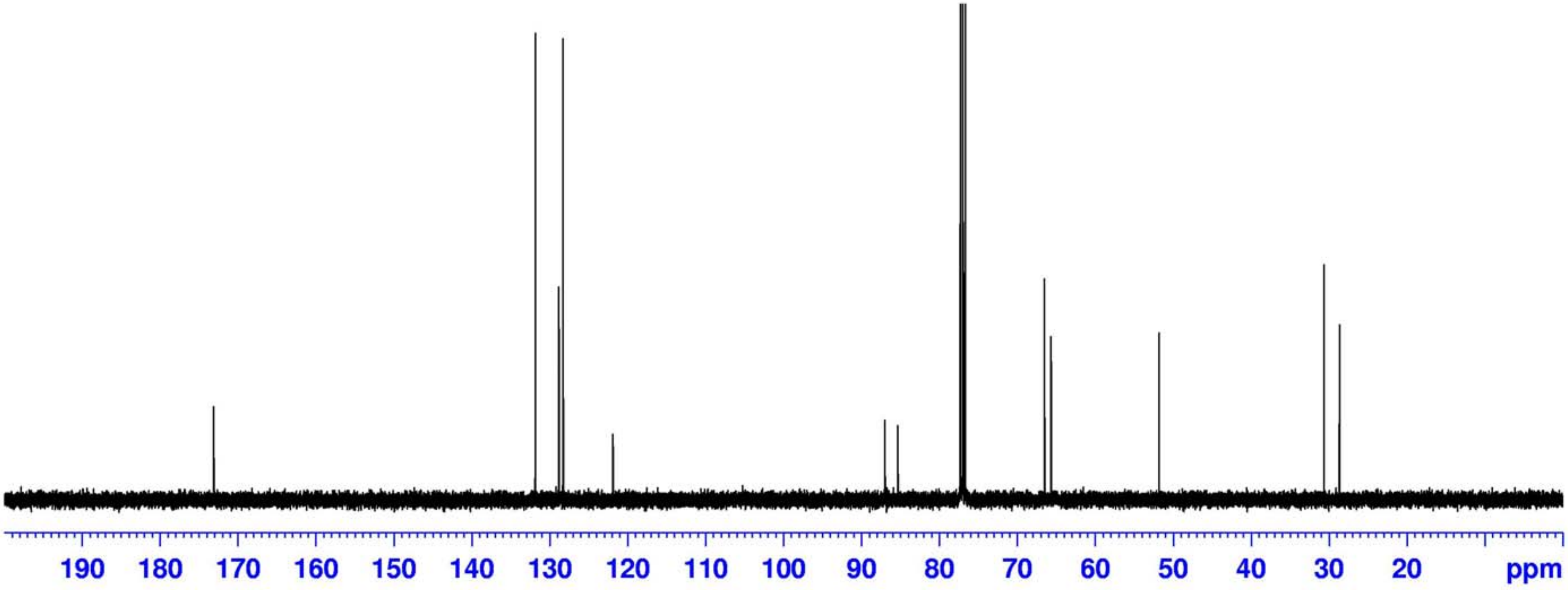

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

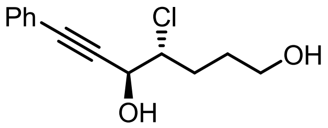

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


Ph
Cl
OH
O
O

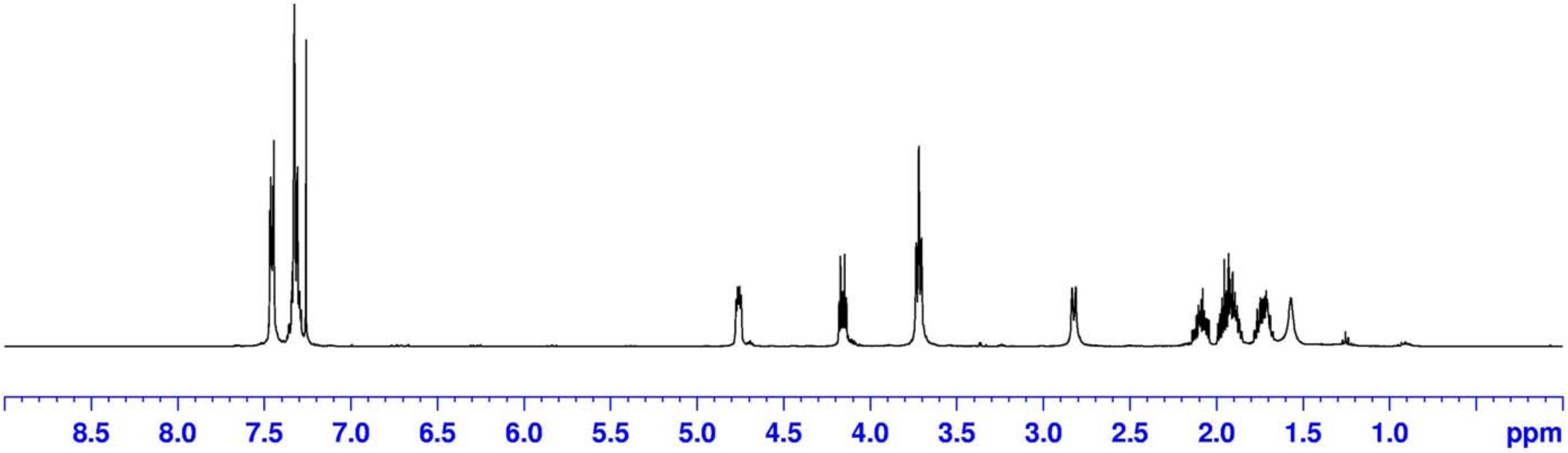
50

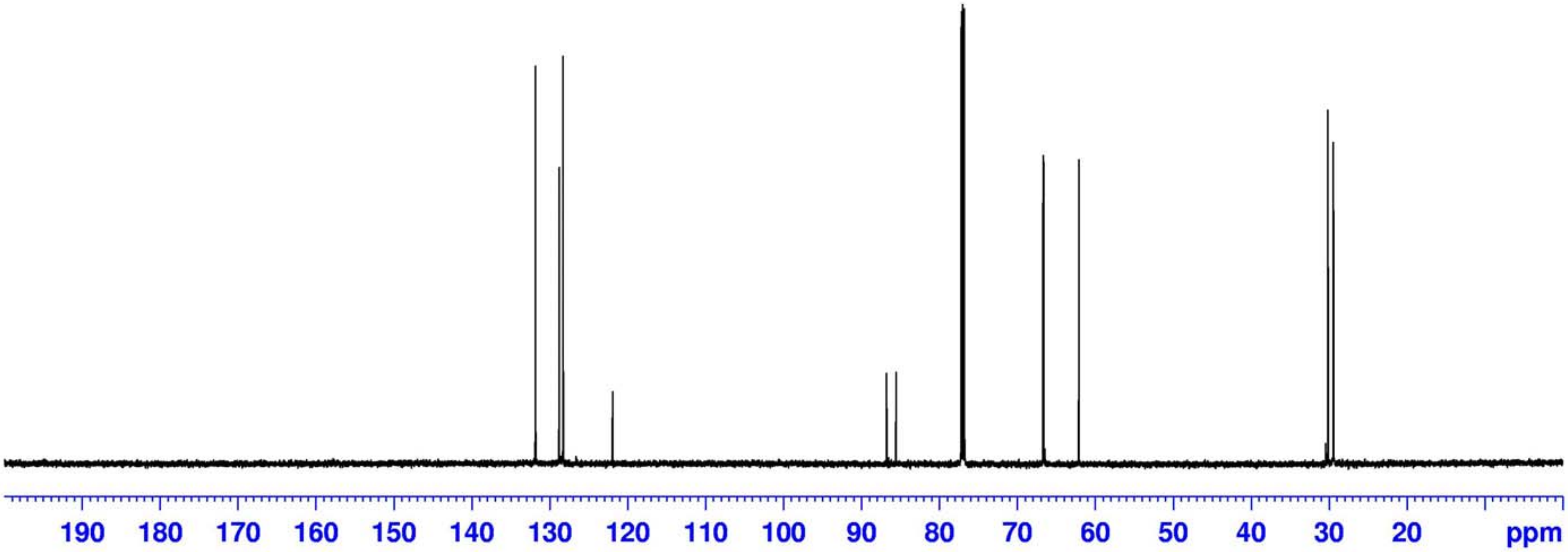

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

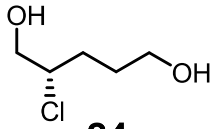

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


Ph
Cl
OH
OH

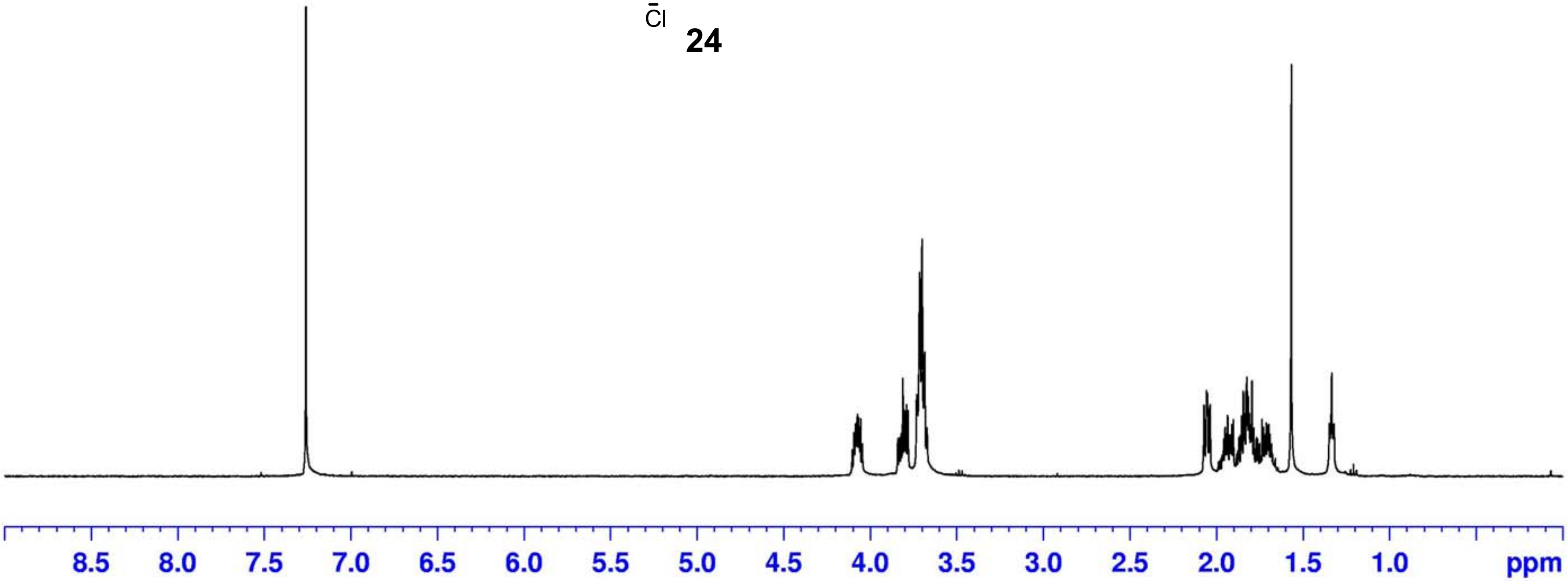
23

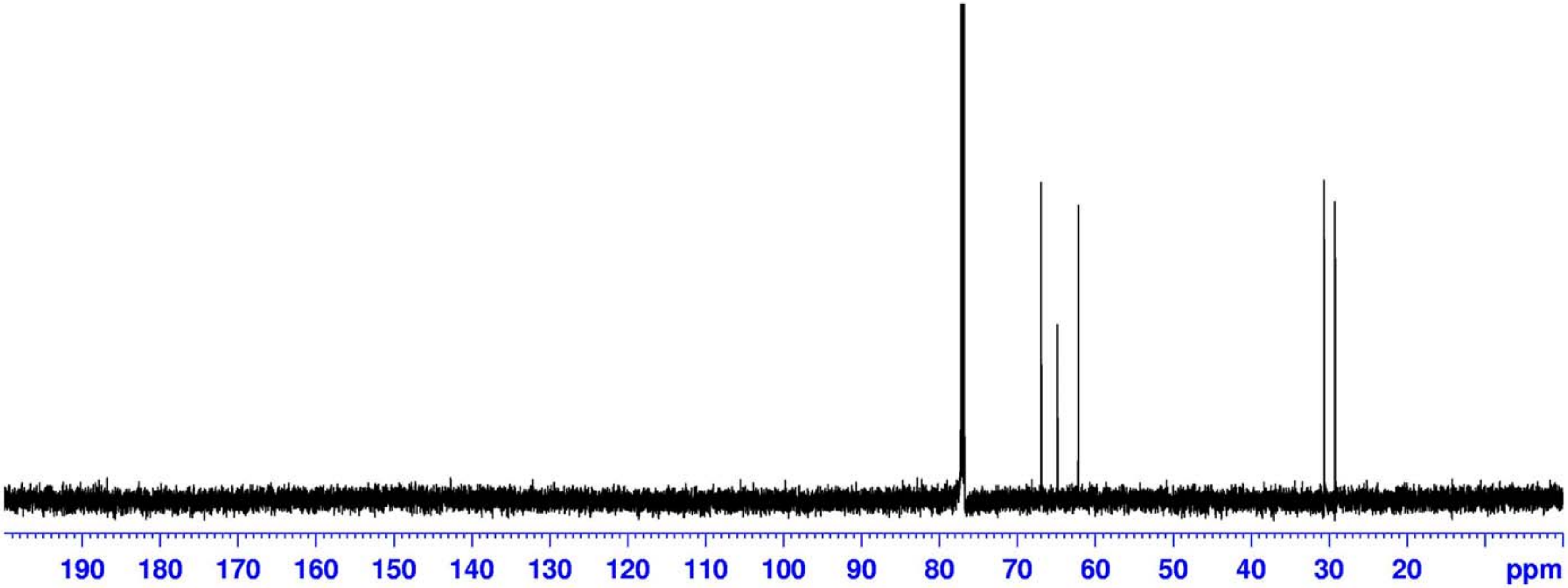

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

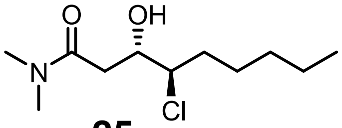

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


OH
OH
Cl

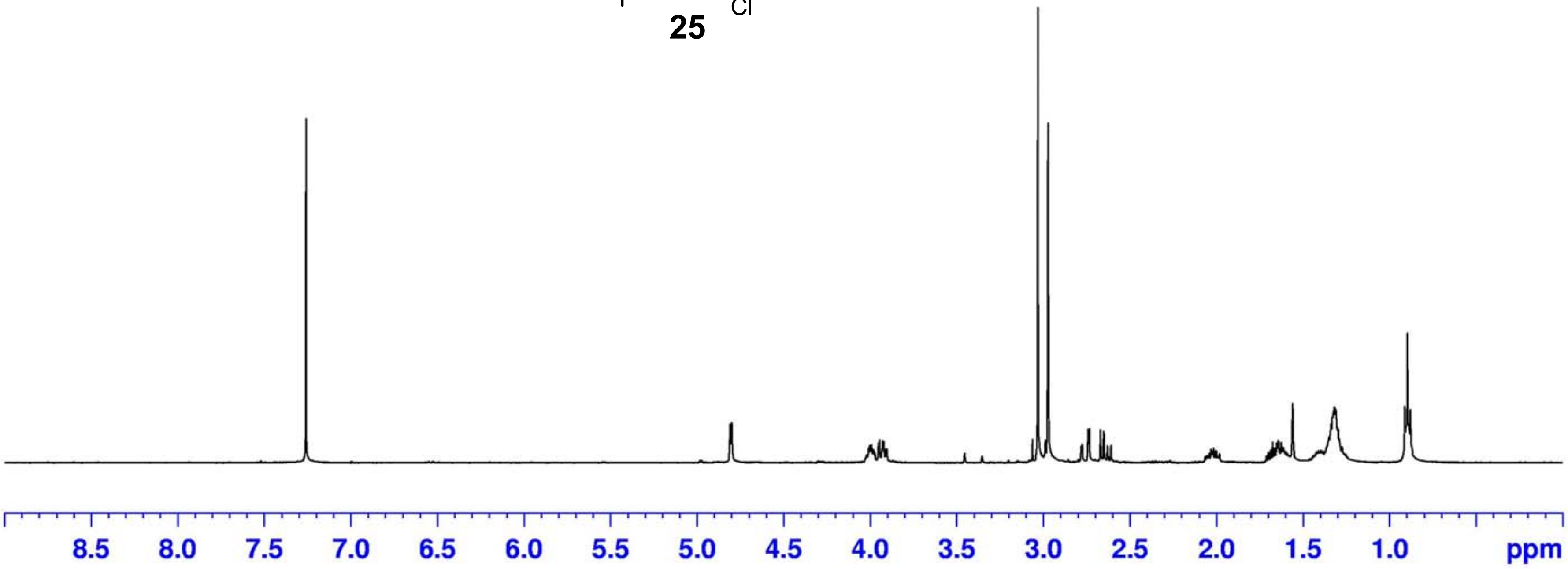
24

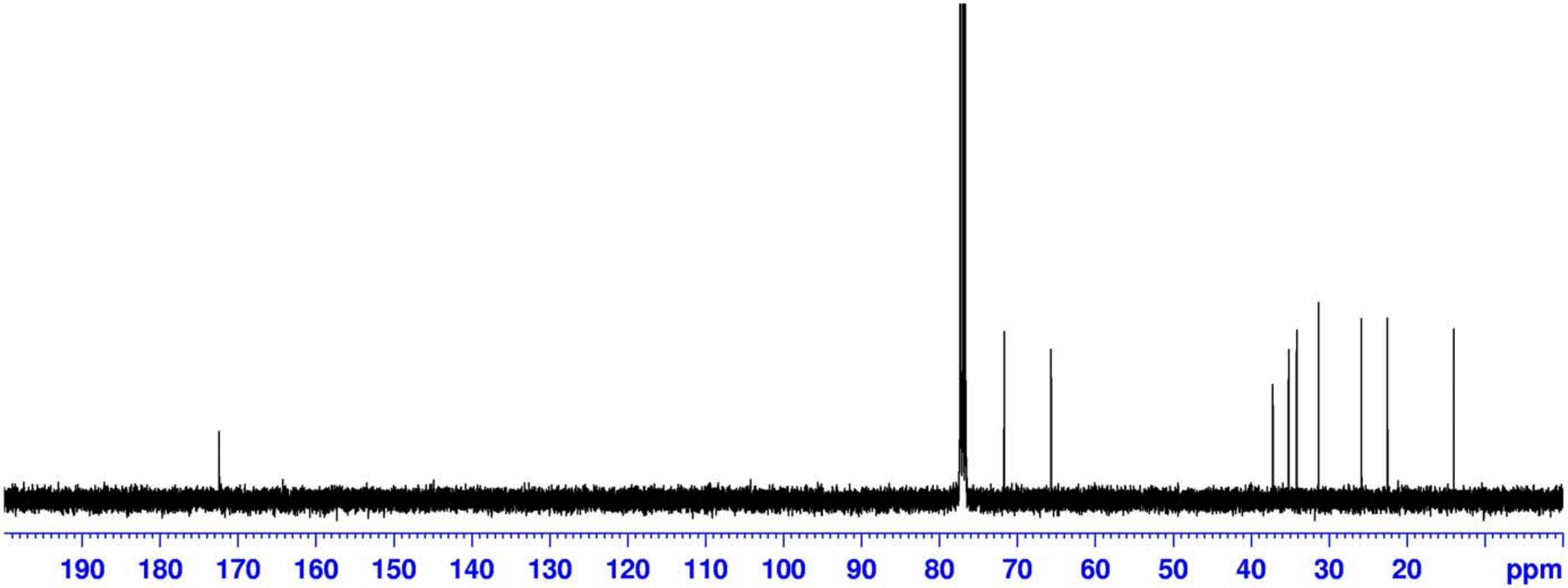

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

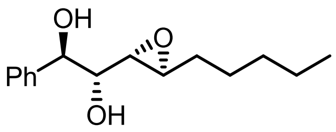

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


O
OH
N
Cl

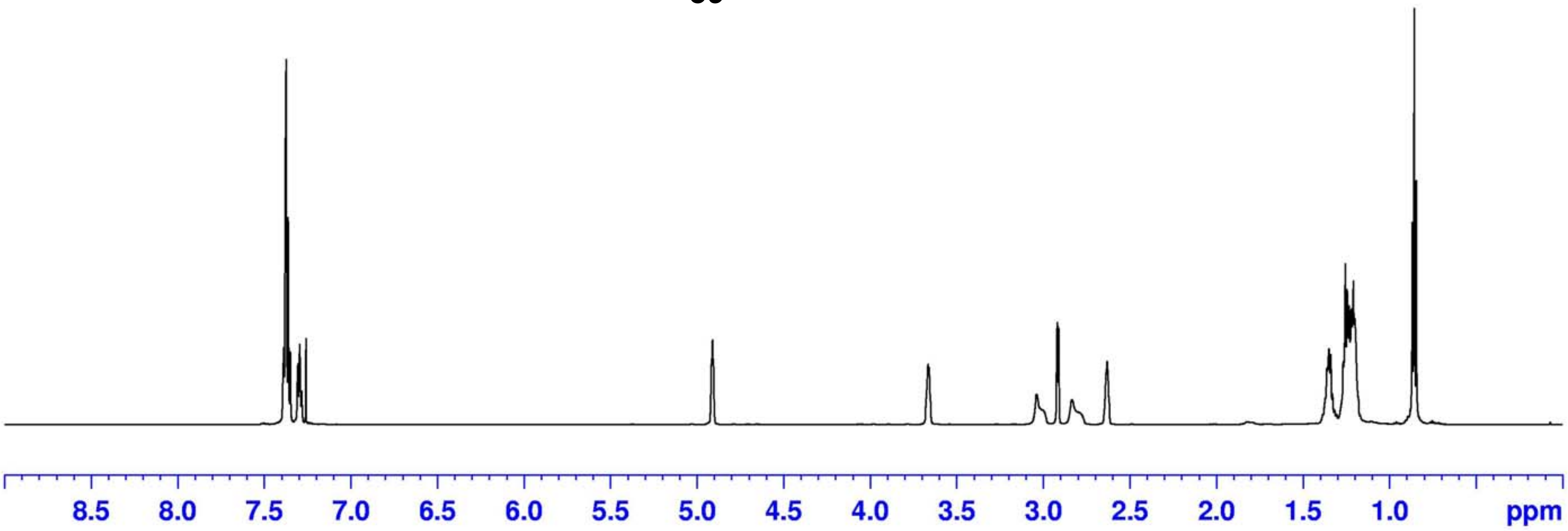
25

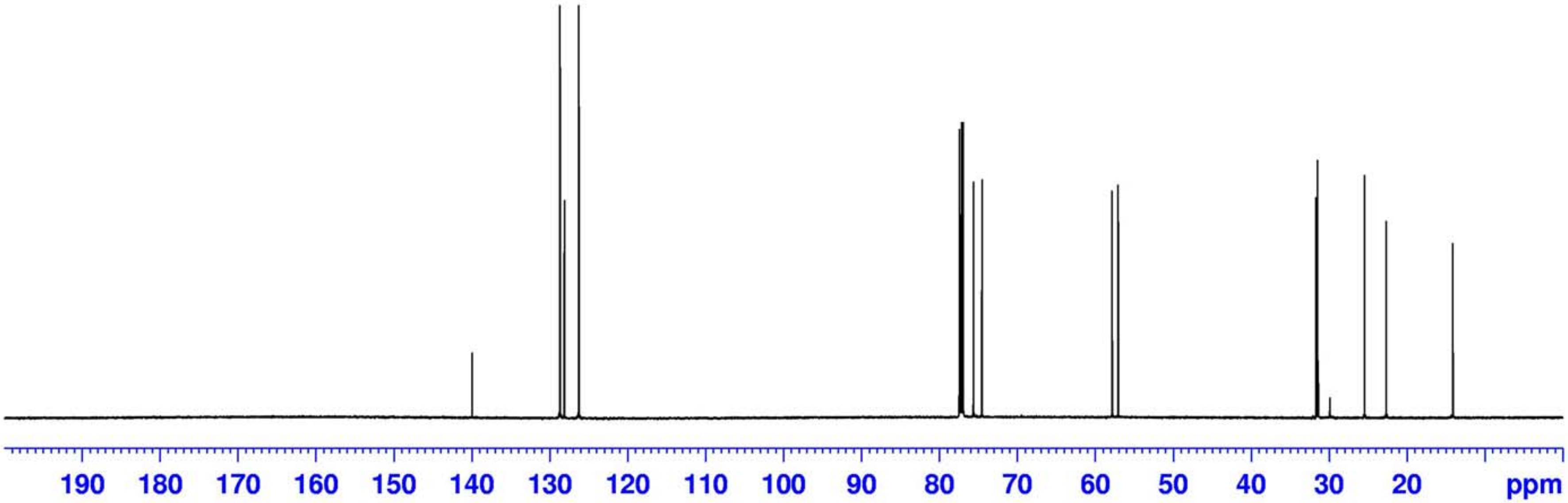

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

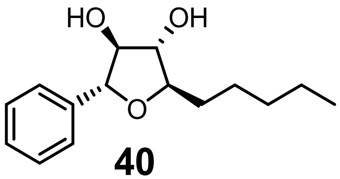

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


OH
O
Ph
OH

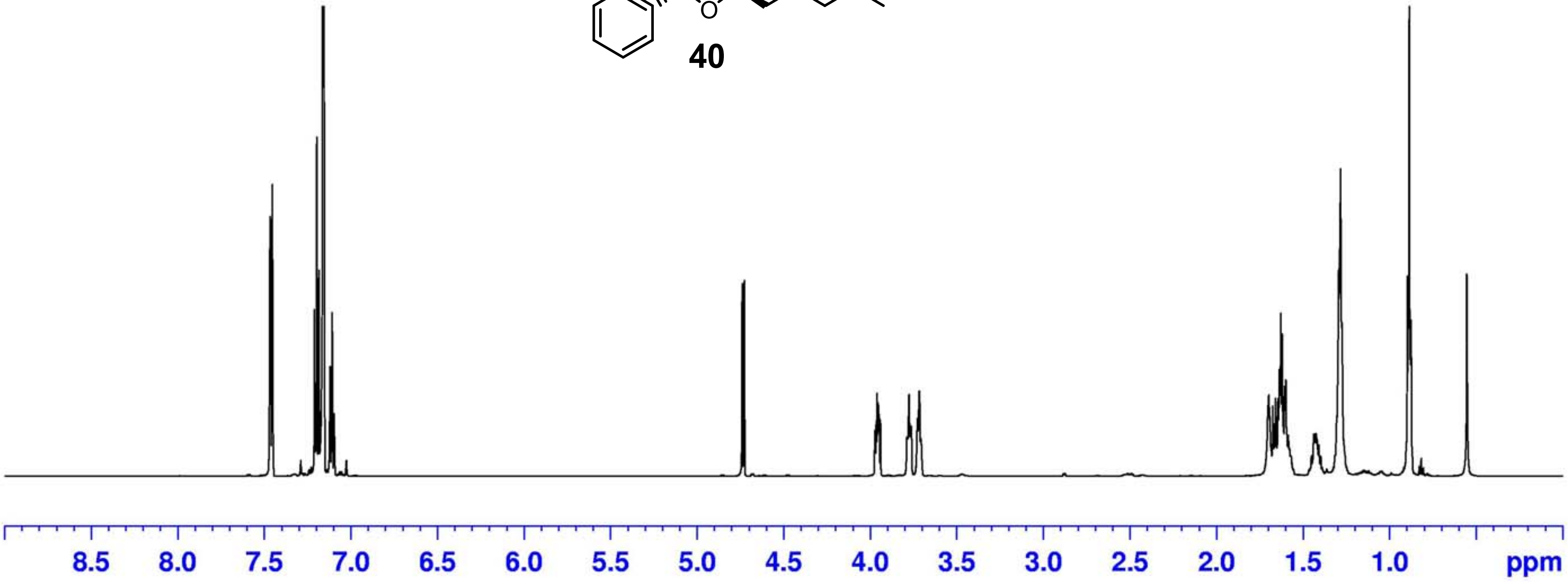
39

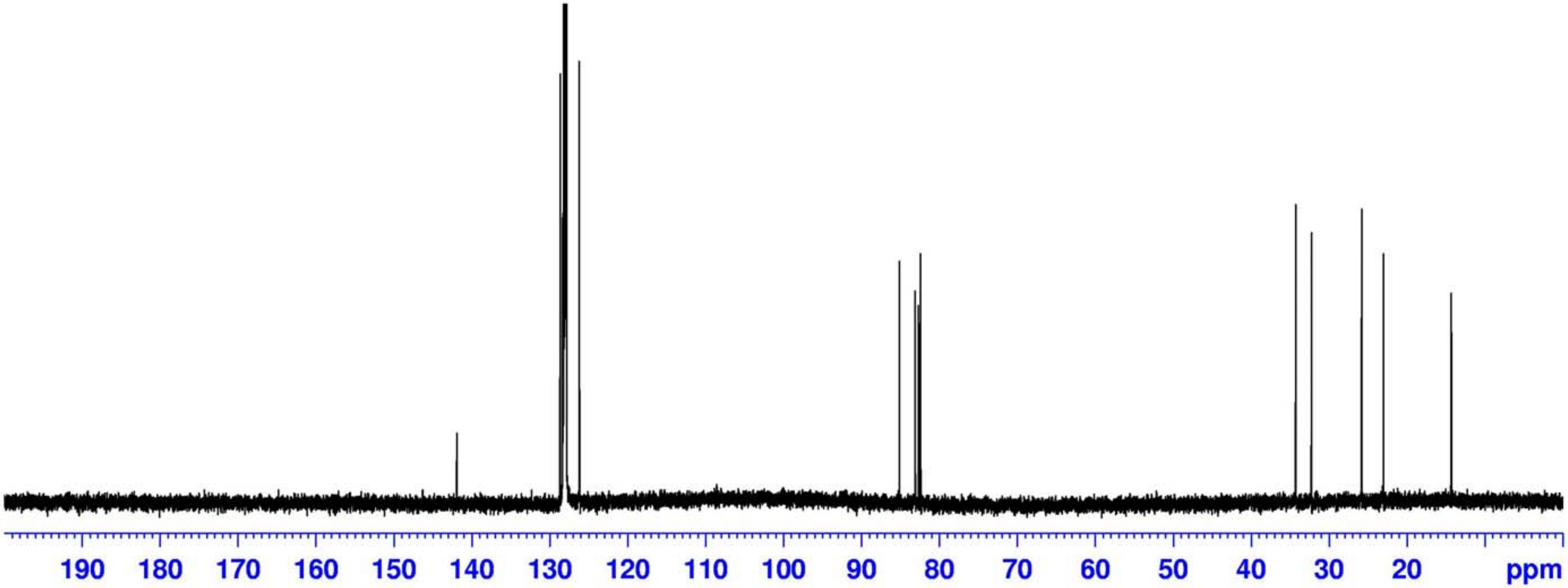

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

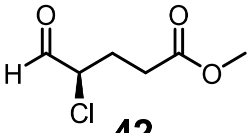

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


HO
OH
O

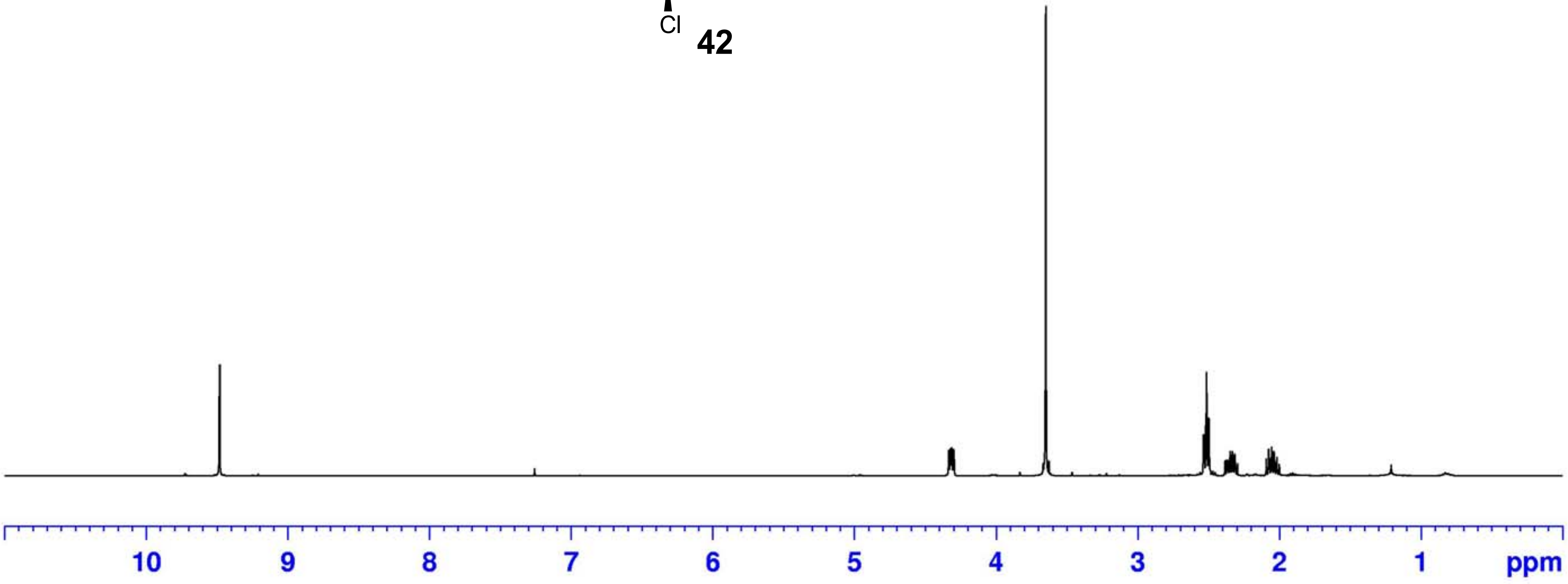
40

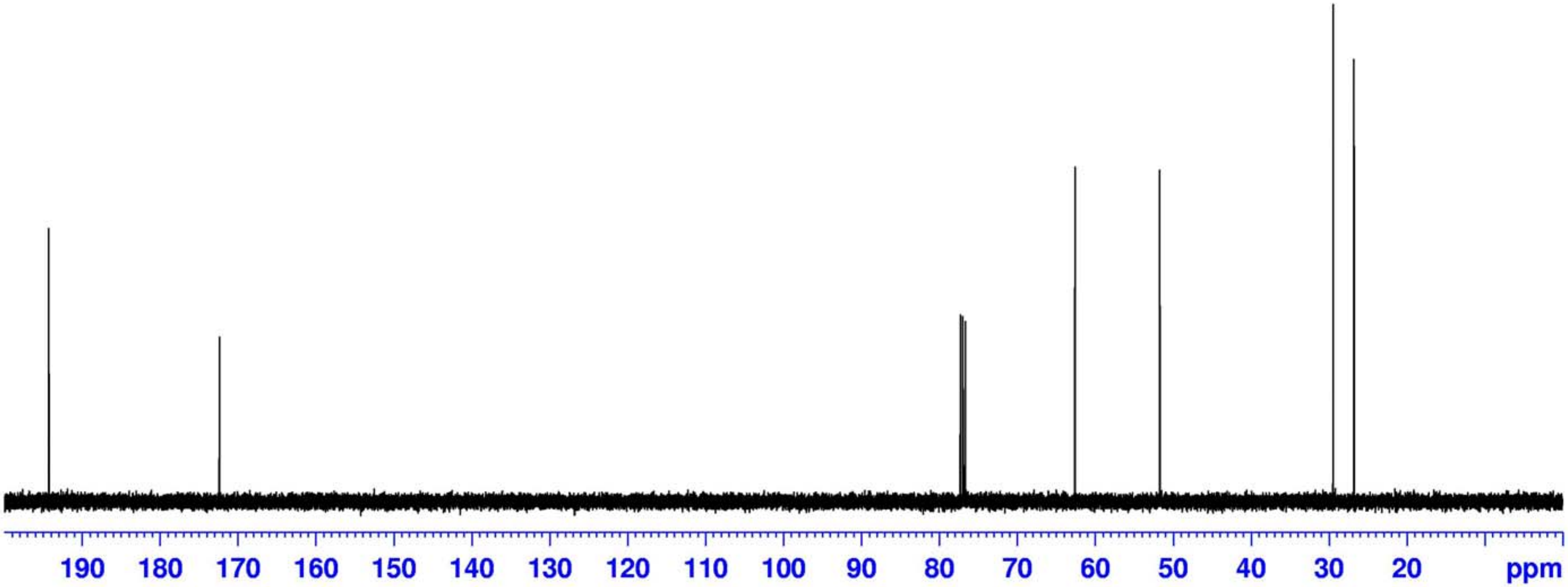

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

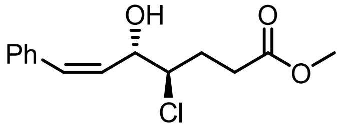

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


O
O
H
O
Cl

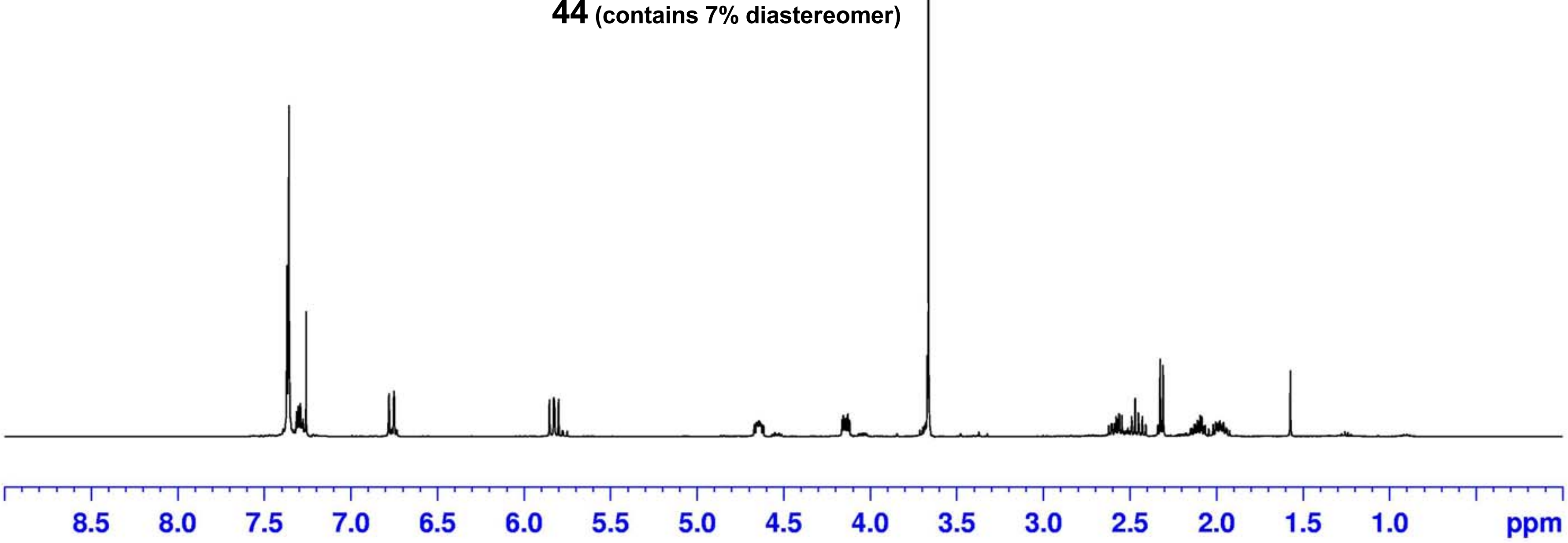
42

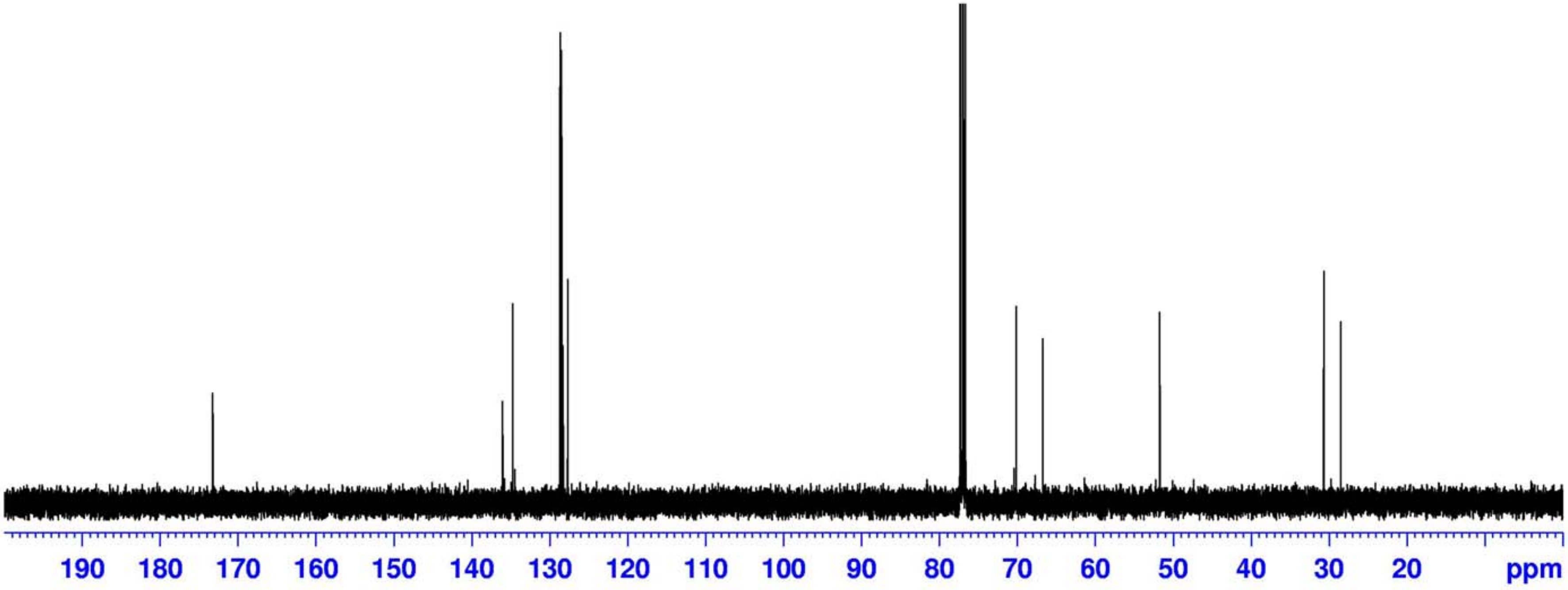

10
9
8
7
6
5
4
3
2
1
ppm

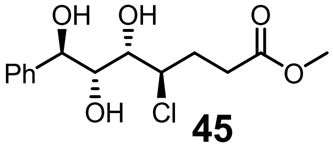

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm



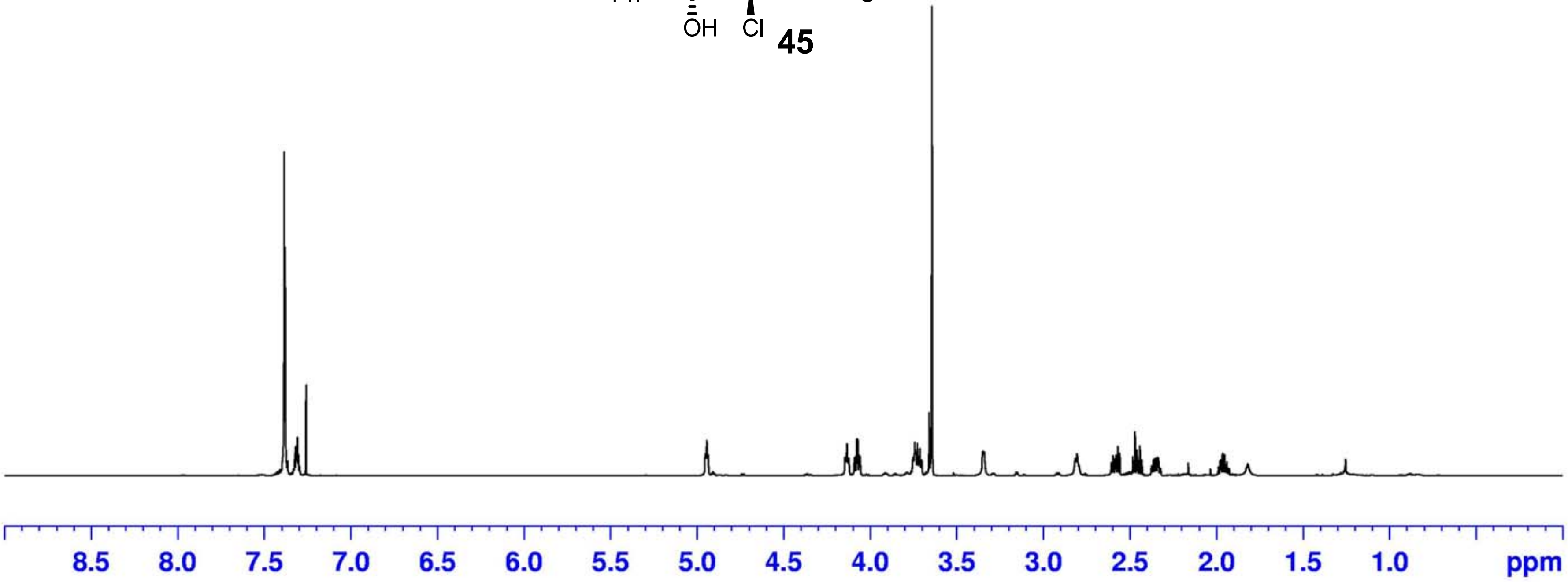
44 (contains 7% diastereomer)

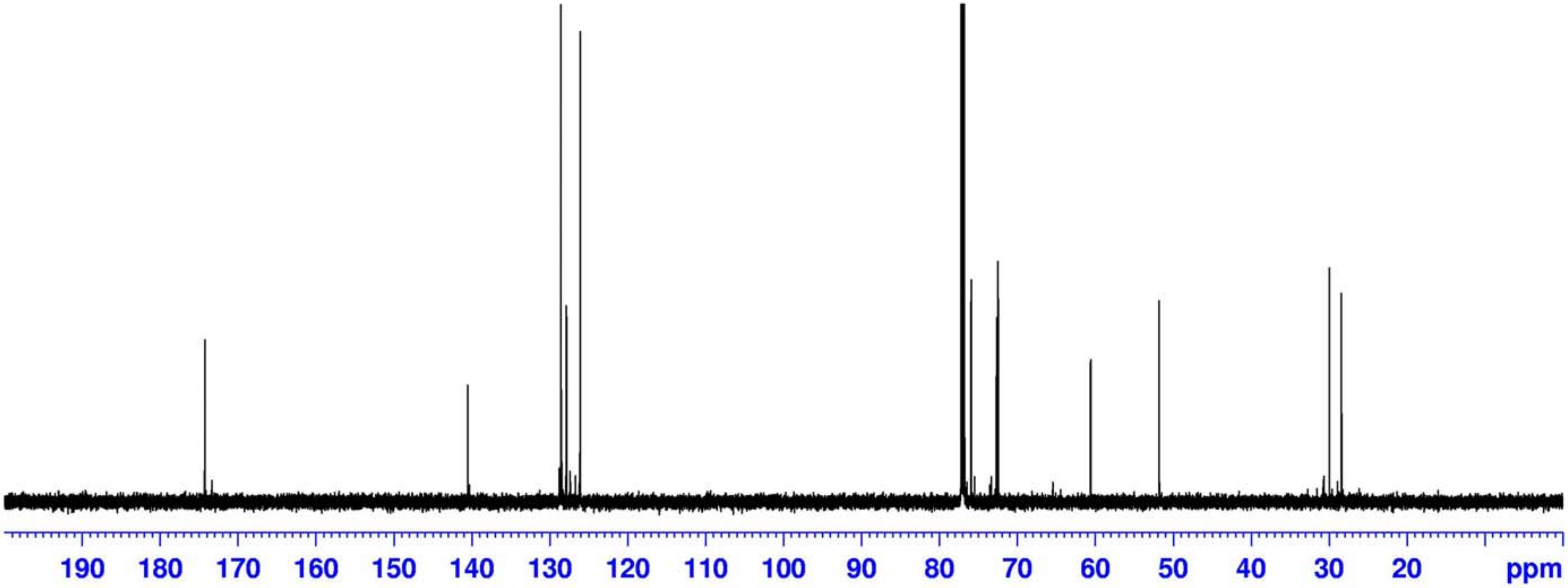


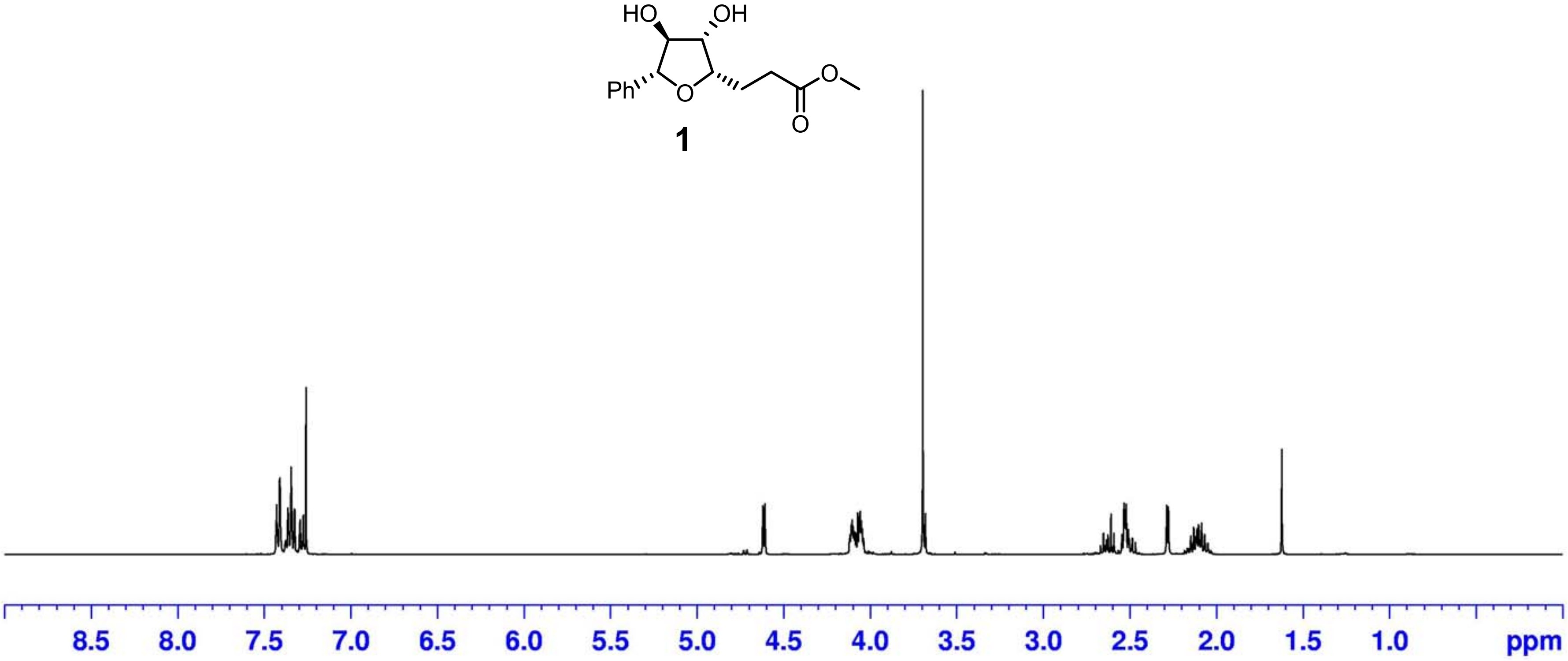



OH
OH
O
Ph
O
OH
Cl

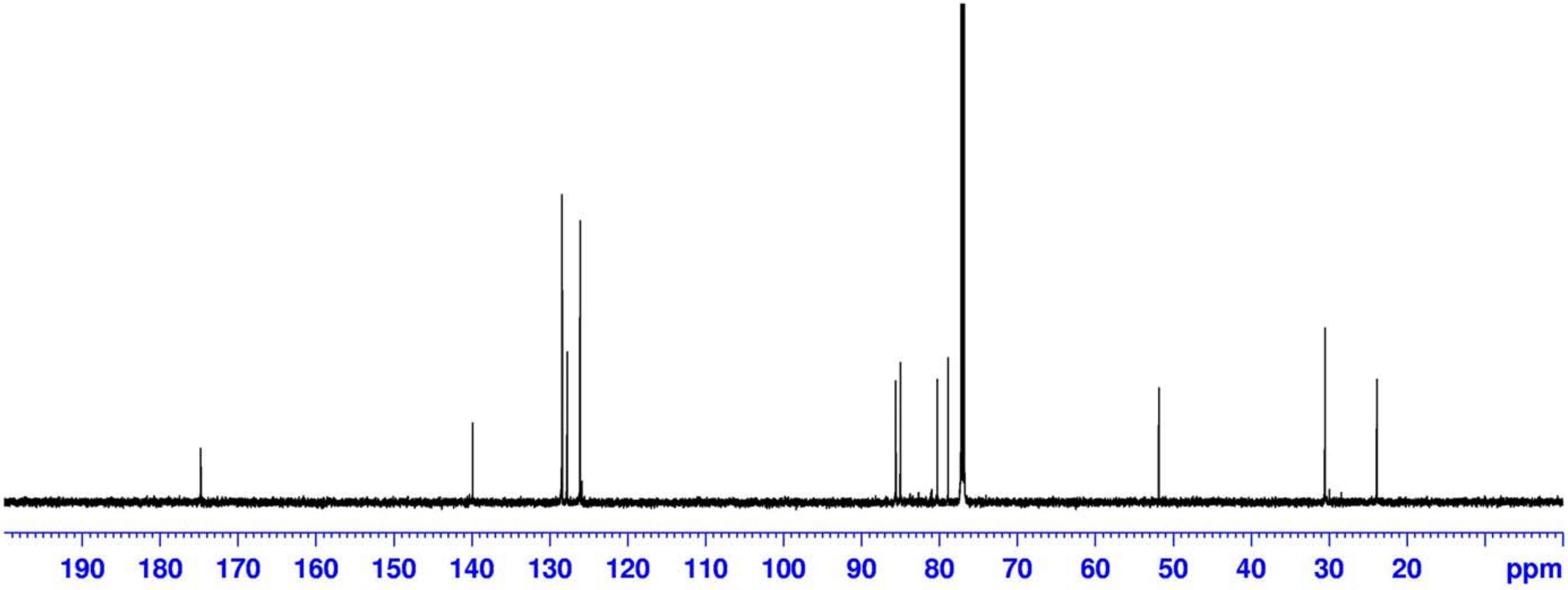
45


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

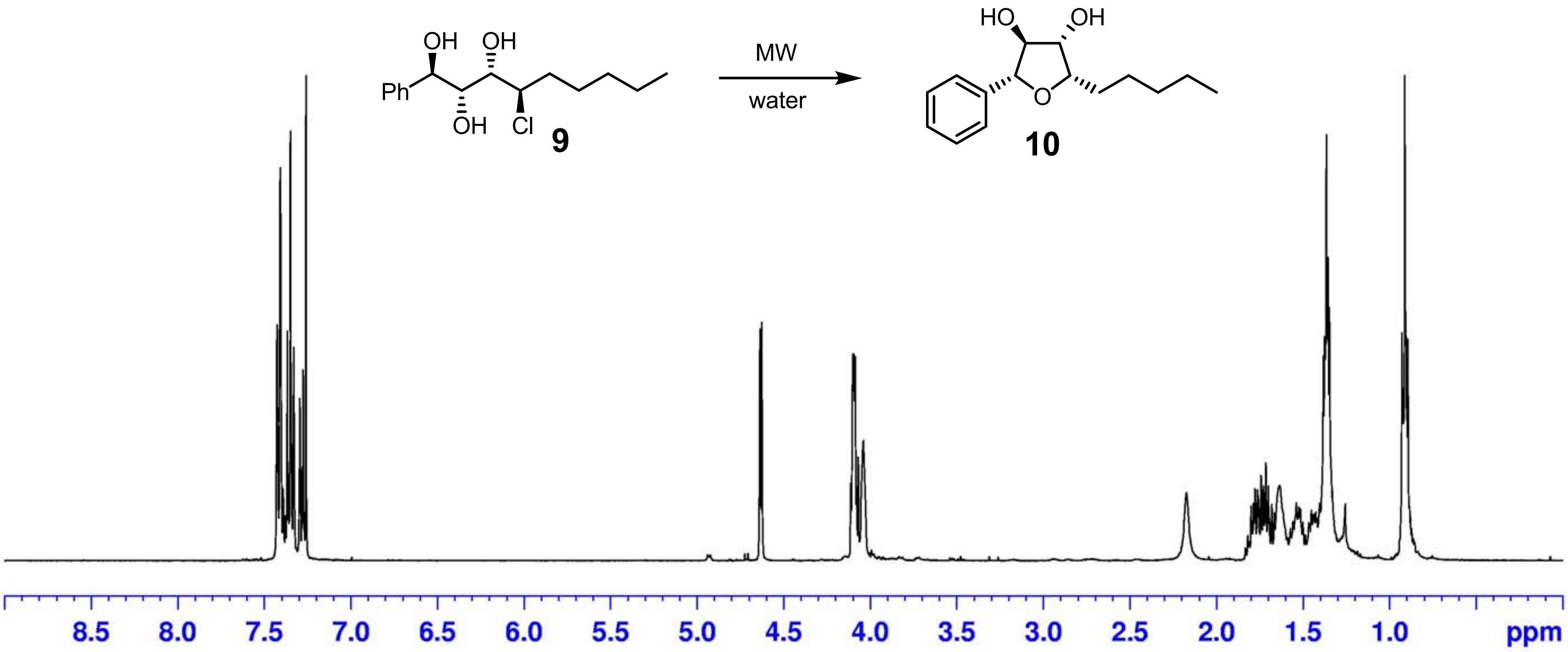

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


HO
OH
Ph
O
O
O
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

1


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

crude spectra



crude spectra