SUPPORTING INFORMATION FOR:

Synthesis of the Sialic Acid (–)-KDN and Certain Epimers from (–)-3-Dehydroshikimic Acid or (–)-Quinic Acid

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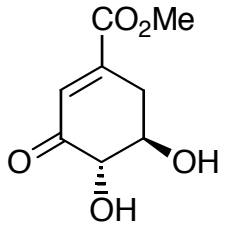
Experimental Procedures and Product Characterization

General Experimental:

Melting points were measured on a Reichert hot-stage microscope apparatus and are uncorrected. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Varian Inova 500 spectrometer operating at 500 MHz for proton and 126 MHz for carbon. In certain cases a Gemini 300 NMR spectrometer, operating at 300 MHz (for proton) and 75 MHz (for carbon), was employed. Spectra were acquired at 20 °C in deuterochloroform ($CDCl_3$) which had been filtered through basic alumina prior to use, or deuteromethanol (CD_3OD) or deuterium oxide (D_2O). Signals arising from the residual protio-forms of the solvent were used as the internal standard. Chemical shifts were recorded as δ values in parts per million (ppm). The assignments of signals observed in the various NMR spectra were often assisted by conducting DEPT, APT, homonuclear (^{1}H/^{1}H) correlation spectroscopy (gDQFCOSY), and/or heteronuclear (^{1}H/^{13}C) correlation spectroscopy (gHMQC or gHMBC) experiments. The term a-t refers to an apparent triplet. Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer. Samples were analysed as KBr disks (for solids) or as thin films on NaCl plates (for oils). Low resolution mass spectra were recorded on a Micromass–Waters LC-ZMD single quadrupole liquid chromatograph-MS or VG Quattro II triple quadrupole MS instrument using electrospray techniques in positive and/or negative ionization mode. Low resolution EI and FAB mass spectra were recorded on an AUTOSPEC spectrometer or a Kratos Analytical Concept ISQ instrument, the latter being located at the University of Tasmania. High resolution mass spectra were acquired by FAB methods on a Thermoquest Mat95XL instrument (located at CSIRO Molecular Science, Melbourne) or by EI methods on an AUTOSPEC instrument. Optical rotations were measured with a Perkin–Elmer 241 polarimeter at the sodium-D line (589 nm) and the concentrations (*c*) (g/100 mL) indicated using spectroscopic grade $CHCl_3$ unless otherwise specified. The measurements were carried out in a cell with a path length (l) of 1 dm. Specific rotations $[\alpha]_D$ (determined at the temperature indicated) were calculated using the equation $[\alpha]_D = 100.\alpha/(c.l)$ and are given in 10^{-1}.deg.cm^2.g^{-1}. Elemental analyses were performed by the Australian National University's Microanalytical Services Unit based at the Research School of Chemistry, Canberra, Australia. The unit cell parameters were recorded on a Nonius Kappa CCD instrument. Dichloromethane and chloroform were distilled from calcium hydride and THF and benzene were distilled, under nitrogen, from sodium benzophenone ketyl. Where necessary, reactions were performed under a nitrogen atmosphere.

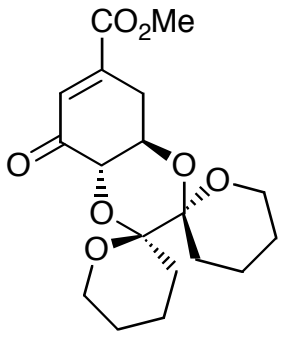
Methyl (4*S*,5*R*)-4,5-Dihydroxy-3-oxo-1-cyclohexene-1-carboxylate (5)



5

A solution of diazomethane in diethyl ether was added dropwise to a solution of (–)-3-dehydroshikimic acid **4** (3.0 g, 17 mmol) in CH_3OH (20 mL) at –15 °C until the yellow color remained. At this point a stream of nitrogen was blown over the reaction mixture to remove excess diazomethane then the solvent was removed under reduced pressure. The orange residue thus obtained was triturated with diethyl ether/CH_3OH (12 mL of a 5:1 v/v mixture) to yield the methyl ester **5** (2.5 g, 77%) as a colorless solid, mp 120–122 °C (lit.[1] mp 124–125 °C); ^{1}H NMR (300 MHz, CD_3OD) δ 6.71 (1H, d, H7, *J* 3.1), 4.07 (1H, d, H5, *J* 10.5), 3.87 (1H, ddd, H4, *J* 10.5, 9.3, 5.1), 3.83 (3H, s, OMe), 3.09 (1H, dd, H3, *J* 18.3, 5.1), 2.55 (1H, ddd, H3', *J* 18.3, 9.3, 3.1 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 200.6 (C), 167.2 (C), 147.3 (C), 132.1 (CH), 80.1 (CH), 72.3 (CH), 53.3 (CH_3), 34.3 (CH_2).

Compound 6



6

From 5:

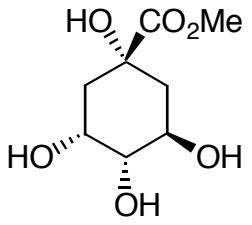
1(*S*)-(+)-Camphor-10-sulfonic acid (110 mg, 0.47 mmol) was added to a solution of diol **5** (800 mg, 4.3 mmol) and *bis*-dihydropyran (1.20 g, 7.2 mmol) in anhydrous $CHCl_3$ (60 mL) and the resulting mixture was heated at reflux for 48 h. After cooling the resulting solution was diluted with CH_2Cl_2 (20 mL), washed with $NaHCO_3$ (3 × 30 mL of a sat aq solution) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a brown oil. Subjection of this material to flash chromatography (1:3 v/v EtOAc/hexane elution) and concentration of the appropriate fractions (R_f 0.3) gave a pale-yellow oil which was triturated with ice-cold EtOAc to provide the dispiroketal **6** (1.20 g, 79%) as a colorless solid, mp 153–154 °C; $[\alpha]_D^{18}$ +45.7 (*c* 1.0 in $CHCl_3$).

From 9:[2]

Pyridinium chlorochromate (858 mg, 4.0 mmol) was added to a magnetically stirred mixture of compound **9** (370 mg, 0.99 mmol), 4Å molecular sieves (powdered, 740 mg) and pyridine (323 mg, 0.33 mL, 4.08 mmol) in CH_2Cl_2 (4 mL). The mixture was stirred at 18 °C for 24 h at which time TLC analysis (1:1 v/v EtOAc/hexane elution) showed an absence of starting material (R_f 0.2) and the formation of two products, **6** and **10** (R_f 0.6 and R_f 0.3, respectively). The reaction mixture was applied directly to a silica pad and eluted with EtOAc. The residue obtained upon concentration of the filtrate under reduced pressure was dissolved in CH_2Cl_2 (3 mL) and the resulting solution cooled to 0 °C, then treated with Hunig's base (384 mg, 0.517 mL, 2.97 mmol), DMAP (12 mg, 0.099 mmol) and acetic anhydride (152 mg, 0.140 mL,1.49 mmol). The reaction mixture was stirred overnight at ca. 18 °C, at which point TLC analysis (1:1 v/v EtOAc/hexane elution) indicated complete conversion of the more polar product (R_f 0.3) to the less polar one (R_f 0.6). Silica gel (0.5 g) was added to the reaction mixture which was then concentrated under reduced pressure to yield a pale-yellow powder. This was subjected to flash chromatography (short silica gel pad; 1:1 v/v EtOAc/hexane elution). Concentration of the appropriate fractions (R_f 0.6) yielded compound **6**, (235 mg, 67%) as a colorless solid, mp 153–154°C;

$[\alpha]_D^{18}$ +49.0 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (1H, d, H7, *J* 3.4), 4.34 (1H, d, H5, *J* 11.2), 4.16 (1H, ddd, H4, *J* 11.2, 10.7, 5.4), 3.85 (3H, s, OMe), 3.71–3.59 (4H, complex m, 2 × CH_2), 3.10 (1H, dd, H3, *J* 18.3, 5.4), 2.66 (1H, ddd, H3, *J* 18.3, 10.7, 3.4 Hz), 2.05–1.73 (4H, complex m, 2 × CH_2), 1.66–1.40 (8H, complex m, 4 × CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.7 (C), 166.0 (C), 144.5 (C), 132.8 (CH), 97.5 (C), 96.6 (C), 74.2 (CH), 66.4 (CH), 61.1 (CH_2), 60.8 (CH_2), 52.9 (CH_3), 30.4 (CH_2), 28.3(3) (CH_2), 28.2(5) (CH_2), 24.8 (CH_2, two signals superimposed), 17.9(3) (CH_2), 17.8(8) (CH_2); IR (NaCl, thin film) 2951, 2874, 1727, 1707, 1639, 1439, 1381, 1356, 1249, 1211, 1191, 1159, 1143, 1098, 1073, 1045, 994, 883, 736 cm^{-1}; MS (ESI+) *m/z* 375 ($M+Na^+$, 100%); Anal. Calcd for $C_{18}H_{24}O_7$: C 61.35, H 6.86. Found: C 60.90, H 7.15%.

Compound 8

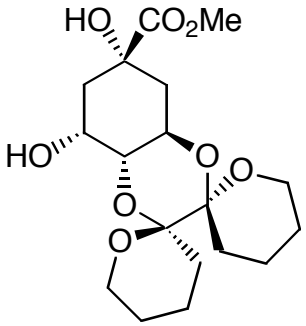


8

Methanolic HCl was generated by the dropwise addition of acetyl chloride (1.75 g, 1.6 mL, 22.3 mmol) to CH_3OH (35 mL) at 0°C. The resulting solution was transferred to a flask containing quinic acid **(7)** (2.00 g, 10.4 mmol) and the reaction mixture was stirred at reflux overnight. TLC analysis (1:7 v/v CH_3OH/EtOAc elution) after this time showed complete conversion of starting material (R_f 0.0) to product (R_f 0.2). As a result, the reaction mixture was filtered through a pad of Celite™ which was washed with CH_3OH (50 mL). Concentration of the combined filtrates under reduced pressure yielded a residue which was subjected to flash chromatography (short silica gel pad; 1:7 v/v CH_3OH/EtOAc elution). Concentration of the appropriate fractions (R_f 0.2) yielded compound **8**[3] (1.92 g, 90%) as colorless needles, mp 126–127 °C (lit.[3] mp 118°C); $[\alpha]_D^{19}$ –30.9 (*c* 1.86, CH_3OH) {lit.[4] $[\alpha]_D^{20}$ –31.6 (*c* 1.45, CH_3OH)}; ^{1}H NMR (500 MHz, CD_3OD) δ 4.07 (1H, m, H6), 3.98 (1H, ddd, H4, *J* 10.0, 8.5, 4.4), 3.72 (3H, s, OMe), 3.40 (1H, dd, H5, *J* 8.5, 2.8), 2.09 (1H, ddd, $H3_{eq}$, *J* 13.2, 4.4, 2.2), 2.06 (1H, dd, $H7_{ax}$, *J* 14.2, 3.2), 1.99 (1H, ddd, $H7_{eq}$, *J* 14.2, 4.4, 2.2), 1.86 (1H, dd, $H3_{ax}$, *J* 13.2, 10.0 Hz); ^{13}C NMR (125.7 MHz, CD_3OD) δ 175.9 (C), 76.8 (C), 76.5 (CH), 71.3 (CH), 68.1 (CH), 52.9 (CH_3), 41.9 (CH_2),

38.2 (CH_2); IR (NaCl, thin film) 3340, 1734, 1435, 1245, 1122, 1072 cm^{-1}; MS (ESI+) *m/z* 435 ($2M+Na^+$, 5%), 413 ($2M+H^+$, 5), 229 ($M+Na^+$, 100); Anal. Calcd for $C_8H_{14}O_6$: C, 46.60; H, 6.84. Found: C, 46.05; H, 7.24%.

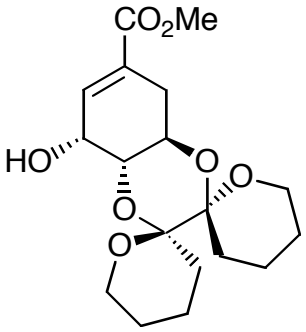
Compound 9



9

1(*S*)-(+)-Camphor-10-sulfonic acid (44 mg, 0.191 mmol) was added to a magnetically stirred solution of methyl quinate **8** (0.392 g, 1.91 mmol) and 2,2'-*bis*-dihydropyran (2,2'-*bis*-DHP) (475 mg, 2.86 mmol) in dry $CHCl_3$ (25 mL) and the resulting mixture was heated at reflux for 16 h. TLC analysis (1:1 v/v EtOAc/hexane elution) after this time revealed a mixture of products, with the major one appearing at R_f 0.2. The cooled reaction mixture was neutralized by the addition of Et_3N (100 μL) then concentrated under reduced pressure. The residue thus obtained was dissolved in $CHCl_3$, preadsorbed onto silica and subjected to flash chromatography (1:2 then 1:1 v/v EtOAc/hexane elution). Concentration of the appropriate fractions (R_f 0.2 in 1:1 v/v EtOAc/hexane) gave diol **9** (407 mg, 57%) as a colorless solid, mp 61–63 °C; $[\alpha]_D^{19}$ +75.1 (*c* 1.07, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 4.35 (1H, ddd, H4, *J* 12.2, 10.0, 4.6), 4.22 (1H, dd, H6, *J* 5.9, 2.9), 3.78 (3H, s, OMe), 3.68–3.63 (5H, complex m, H5, 2 × CH_2–O), 2.20 (1H, a-dt, $H7_{eq}$, *J* 15.1, 2.9), 2.14 (1H, ddd, $H3_{eq}$, *J* 12.7, 4.4, 2.9), 2.05 (1H, dd, $H7_{ax}$, *J* 15.1, 2.9), 1.94 (1H, a-t, $H3_{ax}$, *J* 12.2 Hz) 1.86–1.70 (4H, complex m, 2 × CH_2), 1.62–1.45 (8H, complex m, 4 × CH_2); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 174.3 (C), 97.6 (C), 75.8 (C), 71.9 (CH), 69.3 (CH), 61.6 (CH), 60.7 (CH_2), 60.6 (CH_2), 52.9 (CH_3), 38.7 (CH_2), 37.2 (CH_2), 28.6 (CH_2), 28.3 (CH_2), 24.9 (CH_2), 24.8 (CH_2), 18.0 (CH_2, two signals superimposed); IR (NaCl, thin film) 3468, 2947, 2873, 1735, 1437, 1352, 1240, 1210, 1161, 1136, 1072, 1044, 992, 972, 938 cm^{-1}; MS (ESI+) *m/z* 767 ($2M+Na^+$, 25%), 395 ($M+Na^+$, 100), 167 (10); Anal. Calcd for $C_{18}H_{28}O_8$: C, 58.05; H, 7.58. Found: C, 58.22; H, 7.72%.

Alcohol 11

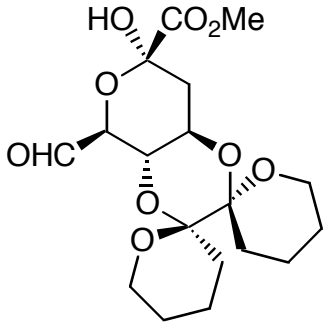


11

K-Selectride (0.90 mL of a 1 M solution in THF, 0.9 mmol) was added to a solution of enone **6** (263 mg, 0.75 mmol) in THF (6 mL) maintained at –78 °C under an atmosphere of nitrogen and the resulting mixture was stirred at –78 °C for 20 min. TLC analysis (1:2 v/v EtOAc/hexane elution) after this time showed residual staring material (R_f 0.4) and a new product (R_f 0.3). Additional K-Selectride (0.5 mL of a 1 M solution in THF, 0.5 mmol) was added and after 20 min TLC analysis (1:2 v/v EtOAc/hexane elution) showed complete conversion of the starting enone to product (R_f 0.3). NH_4Cl (10 mL of a sat aq solution) was then added and the mixture was warmed to ambient temperature. The mixture was partitioned between diethyl ether (30 mL) and H_2O (30 mL). The separated aqueous phase was extracted with diethyl ether (2 × 20 mL) and the combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a yellow oil. This material was dissolved in CH_3OH (12 mL) and silica gel (2.5 g) was added. The resulting mixture was stirred for 16 h at 18 °C and then the solvent was removed, under reduced pressure, to give the product adsorbed onto silica. Subjection of this material to flash chromatography (1:2 v/v EtOAc/hexane elution) and concentration of the appropriate fractions (R_f 0.3) gave the alcohol **11** (227 mg, 86%) as a colorless foam, $[\alpha]_D$ –0.9 (*c* 1.2 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (1H, dd, H7, *J* 5.1, 2.5), 4.38 (1H, a-t, H6, *J* ~4.8), 4.13 (1H, a-dt, H4, *J* 10.5, 5.9), 3.72 (3H, s, OMe), 3.70–3.55 (5H, complex m, H5, 2 × CH_2–O), 2.82 (1H, dd, H3, *J* 17.6, 5.9), 2.23 (1H, ddd, H3', *J* 17.6, 10.4, 2.8 Hz), 1.83–1.62 (4H, complex m, 2 × CH_2), 1.61–1.40 (8H, complex m, 4 × CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 (C), 135.1 (CH), 131.6 (C), 97.2 (C), 96.5 (C), 69.5 (CH), 64.9 (CH), 61.5 (CH), 60.8 (CH_2), 60.6 (CH_2), 52.0 (CH_3), 29.9 (CH_2), 28.5 (CH_2), 28.3 (CH_2), 24.9 (CH_2), 24.8 (CH_2), 17.9 (CH_2, two signals superimposed); IR (KBr) 3476, 2949, 2872, 1720, 1650, 1438, 1258, 1191, 1162, 1090, 1072, 1044, 994, 735 cm^{-1}; MS

(EI) *m/z* 354 ($M^{+\bullet}$, 12%), 323 (1), 296 (1), 254 (10), 225 (8), 167 (17), 154 (57), 101 (100), 95 (32), 83 (31); HRMS (EI) *m/z* calcd for $C_{18}H_{26}O_7$ $M^{+\bullet}$: 354.1679. Found: 354.1676.

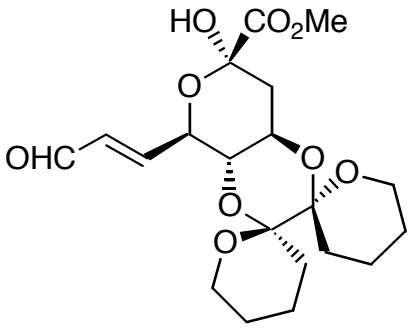
Aldehyde 12



12

A stream of ozone in oxygen was bubbled through a solution of the alcohol **11** (227 mg, 0.64 mmol) in CH_2Cl_2 (30 mL) maintained at –78 °C until the solution turned blue (~0.25 h). TLC analysis (2:1 v/v EtOAc/hexane elution) then showed an absence of starting alcohol (R_f 0.6) so the solution was purged with a stream of nitrogen then Me_2S (0.50 mL, >10 eq.) was added, together with silica gel (6 g). The resulting mixture was stirred at 18 °C for 16 h then concentrated under reduced pressure. The mixture thus obtained was subjected to rapid flash chromatography (short silica gel pad, 2:1 v/v EtOAc/hexane elution) to give, upon concentration of the appropriate fractions (R_f 0.14), the aldehyde **12** (155 mg, 63%) as a colorless foam, $[\alpha]_D^{21}$ +100.9 (*c* 0.81, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (1H, d, H7, *J* 0.9), 4.51 (1H, dd, H6, *J* 10.8, 0.9), 4.32 (1H, ddd, H4, *J* 12.3, 9.6, 4.8), 4.07 (1H, d, OH, *J* 1.8), 3.86 (3H, s, OMe), 3.83 (1H, m, H5), 3.74–3.65 (3H, complex m, 3 × CH_2–O), 3.54 (1H, m, 1 × CH_2–O), 2.27 (1H, ddd, H3, *J* 12.6, 12.3, 2.1), 2.06 (1H, dd, H3, *J* 12.6, 4.8 Hz), 1.85–1.41 (12H, complex m, 6 × CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.3 (CH), 169.3 (C), 97.6 (C), 97.4 (C), 95.5 (C), 75.1 (CH), 68.1 (CH), 64.2 (CH), 61.1 (CH_2), 60.9 (CH_2), 53.8 (CH_3), 35.0 (CH_2), 28.6 (CH_2), 28.5 (CH_2), 24.9 (CH_2), 24.8 (CH_2), 18.1 (CH_2), 18.0 (CH_2); IR (KBr) 3443, 2948, 2873, 1744, 1439, 1273, 1209, 1191, 1150, 1070, 1047, 988, 966, 899, 736 cm^{-1}; MS (ESI+) *m/z* 795 (2M+Na^+, 10%), 468 (M+2CH_3CN^+, 32), 450 (M+Na^++CH_3CN, 25), 427 (M+CH_3CN^+, 55), 409 (M+Na^+, 27), 167 (100); Anal. Calcd for $C_{18}H_{26}O_9$: C, 55.95; H, 6.78. Found: C, 56.20; H, 7.04%.

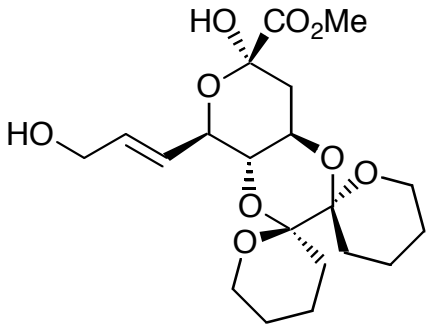
Aldehyde 13



13

The aldehyde **12** (155 mg, 0.40 mmol) was dissolved in CH_2Cl_2 (13 mL) containing AcOH (3 drops) and then (triphenylphosphoranylidene)acetaldehyde (128 mg, 0.42 mmol) was added. The resulting orange solution was stirred at 18 °C for 18 h after which time TLC analysis (2:1 v/v EtOAc/hexane elution) showed the formation of a new product (R_f 0.7). Silica gel (0.3 g) was added and the solvent then removed under reduced pressure. The residue thus obtained was subjected to flash chromatography (1:1 v/v EtOAc/hexane with 0.1% Et_3N elution) to give the aldehyde **13** (128 mg, 78%) as a colorless foam (R_f 0.6), $[\alpha]_D$ +137.7 (*c* 1.2 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (1H, d, H9, *J* 8.1), 6.90 (1H, dd, H7, *J* 15.9, 4.2), 6.39 (1H, ddd, H8, *J* 15.9, 8.1, 1.5), 4.74 (1H, ddd, H6, *J* 10.2, 4.2, 1.5), 4.29 (1H, ddd, H4, *J* 12.3, 9.3, 4.8), 4.12 (1H, m, OH), 3.84 (3H, s, OMe), 3.74–3.61 (3H, complex m), 3.52 (1H, a-t, H5, *J* ~9.9), 3.45 (1H, m), 2.27 (1H, a-dt, H3, *J* 12.3, 2.1), 2.07 (1H, dd, H3, *J* 12.3, 4.8 Hz), 1.85–1.45 (12H, complex m, 6 × CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.1 (CH), 169.5 (C), 151.4 (CH), 132.2 (CH), 97.6 (C), 97.2 (C), 95.4 (C), 71.0 (CH), 70.6 (CH), 64.4 (CH), 60.9 (CH_2, two signals superimposed), 53.6 (CH_3), 35.2 (CH_2), 28.6 (CH_2), 28.5 (CH_2), 24.9 (CH_2), 24.8 (CH_2), 18.2 (CH_2), 18.0 (CH_2); IR (KBr) 3369, 2948, 2872, 1752, 1690, 1439, 1272, 1209, 1191, 1151, 1071, 1046, 989, 935, 899 cm^{-1}; MS (EI) *m/z* 412 ($M^{+\bullet}$, 1%), 353 (2), 312 (2), 283 (9), 265 (13), 212 (18), 194 (14), 168 (39), 140 (47), 101 (100); HRMS (EI) *m/z* calcd for $C_{20}H_{28}O_9$ $M^{+\bullet}$: 412.1733. Found: 412.1737.

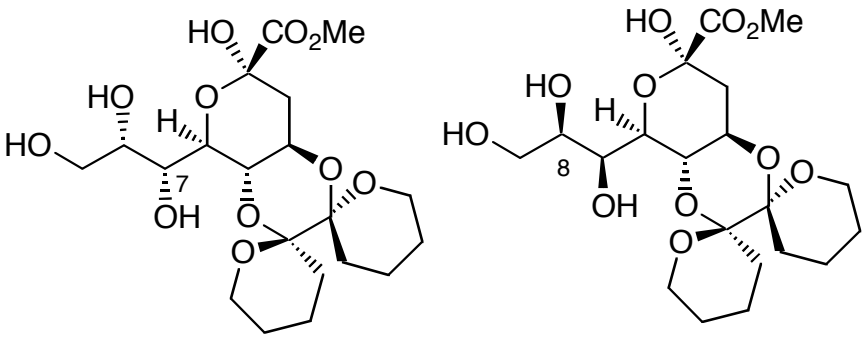
Allylic alcohol 14



14

$CeCl_3 \bullet 7H_2O$ (120 mg, 0.323 mmol) was added to a solution of aldehyde **13** (121 mg, 0.294 mmol) and 2,6-lutidine (157 mg, 171 μL, 1.47 mmol) in CH_2Cl_2/EtOH (5.4 mL of a 1:1 v/v mixture) maintained at ca. 18 °C. This mixture was then cooled to –78 °C, treated with $NaBH_4$ (33 mg, 0.881 mmol) in EtOH (0.87 mL) and stirring continued at –78 °C for 1 h. TLC analysis (1:2 v/v EtOAc/hexane elution) after this time showed the absence of starting material (R_f 0.3) and the presence of a new product (R_f 0.07). As a result acetone (0.8 mL) was added, the cooling bath was removed and the reaction mixture was poured into H_2O (40 mL). HCl (5 mL of a 1 M aq solution) was then added and the resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with NaCl (15 mL of a sat aq solution) then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography (1:1 v/v EtOAc/hexane with 0.5% NH_3 elution) and concentration of the appropriate fractions (R_f 0.2) gave allylic alcohol **14** (64 mg, 50%) as a colorless foam, $[\alpha]_D$ +128.6 (*c* 0.7 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (1H, dtd, H8, *J* 15.5, 5.4, 1.1), 5.77 (1H, tdd, H7, *J* 15.5, 6.3, 1.5), 4.47 (1H, ddd, H6, *J* 10.0, 6.3, 0.9), 4.23 (1H, ddd, H4, *J* 12.2, 9.7, 4.8), 4.16 (2H, m, H9, H9), 3.94 (1H, br s, OH), 3.83 (3H, s, OMe), 3.74–3.54 (4H, complex m, 2 × CH_2–O), 3.48 (1H, a-t, H5, *J* 9.7), 2.25 (1H, a-td, $H3_{ax}$, *J* 12.5, 1.5), 2.05 (1H, dd, $H3_{eq}$, *J* 12.5, 4.8 Hz), 1.85–1.40 (12H, complex m, 6 × CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0 (C), 133.1 (CH), 126.9 (CH), 97.3 (C), 97.1 (C), 95.3 (C), 72.0 (CH), 71.1 (CH), 64.3 (CH), 63.1 (CH_2), 60.8(3) (CH_2), 60.7(9) (CH_2), 53.5 (CH_3), 35.4 (CH_2), 28.6 (CH_2, two signals superimposed), 25.0(3) (CH_2), 24.9(8) (CH_2), 18.2 (CH_2), 18.1 (CH_2); IR (KBr) 3468, 2948, 2873, 1751, 1439, 1272, 1209, 1191, 1148, 1071, 1045, 990, 966, 731 cm^{-1}; MS (EI) *m*/*z* 414 ($M^{+\bullet}$, 0.5%), 356 (0.5), 315 (0.5), 283 (6), 196 (14), 183 (11), 168 (22), 167 (20), 155 (14), 101 (100), 83 (25); HRMS (EI) *m*/*z* calcd for $C_{20}H_{30}O_9$ $M^{+\bullet}$: 414.1890. Found: 414.1890.

Compounds 15 and 16



15 **16**

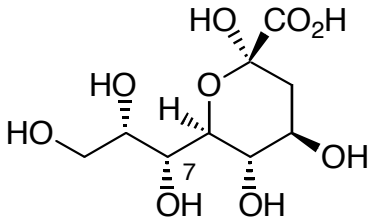
A magnetically stirred solution of alkene **14** (50 mg, 0.12 mmol) in acetone (3 mL) was treated with H_2O (0.3 mL) and NMO (28 mg, 0.24 mmol) then OsO_4 (4 drops of a 2.5 wt% solution in *t*-BuOH). The resulting mixture was stirred at ca. 18 °C under a nitrogen atmosphere for 4.5 h then a solution of $NaHSO_3$ (440 mg, 2.3 mmol) in H_2O (5 mL) was added. The resulting mixture was stirred at ca. 18 °C for 1.5 h then filtered through a pad of Florisil. The Florisil was washed with $CHCl_3$/*i*-PrOH (100 mL of a 3:1 v/v mixture) and the combined filtrates concentrated under reduced pressure to give a colorless oil. Subjection of this material to column chromatography (190:9:1 v/v/v $CHCl_3/CH_3OH$/AcOH elution) gave two fractions, A (R_f 0.4) and B (R_f 0.3).

Concentration of fraction A gave alcohol **15** (17 mg, 31%) as a colorless oil, $[\alpha]_D^{19}$ +100.0 (*c* 0.53, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD) δ 4.21 (1H, ddd, H4, *J* 12.2, 9.8, 4.9), 4.03 (1H, dd, H6, *J* 10.3, 3.4), 3.97 (1H, m), 3.88 (1H, a-t, *J* ~3.9), 3.86–3.58 (7H, complex m), 3.77 (3H, s, OMe), 2.05 (1H, dd, $H3_{eq}$ *J* 12.2, 4.9), 1.89 (1H, a-t, $H3_{ax}$, *J* 12.2 Hz), 1.82–1.63 (4H, complex m, 2 × CH_2), 1.62–1.46 (8H, complex m, 4 × CH_2); ^{13}C NMR (125.7 MHz, CD_3OD) δ 171.7 (C), 98.7 (C), 98.5 (C), 96.8 (C), 73.6 (CH), 72.8 (CH), 72.6 (CH), 70.3 (CH), 65.9 (CH), 63.8 (CH_2), 62.1 (CH_2), 61.7 (CH_2), 53.3 (CH_3), 37.2 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 26.0 (CH_2), 25.8 (CH_2), 19.4 (CH_2), 19.1 (CH_2); IR (NaCl) 3369, 2945, 1744, 1437, 1272, 1209, 1191, 1153, 1071, 1047, 988 cm^{-1}; MS (FAB+) *m/z* 471 ($M+Na^+$, 100%); HRMS (FAB) *m/z* calcd for $C_{20}H_{32}O_{11}Na$, ($M+Na^+$): 471.1842. Found: 471.1837.

Concentration of fraction B gave alcohol **16** (20 mg, 37%) as a colorless oil; $[\alpha]_D^{19}$ +88.2 (*c* 0.44, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD) δ 4.18 (1H, ddd, H4, *J* 12.2, 9.8, 4.9), 4.00 (1H, dd, H6, *J* 9.8, 1.5), 3.94 (1H, dd, *J* 11.2, 2.9), 3.91 (1H, dd, *J* 5.9, 1.5), 3.84 (1H, a-t, H5, *J* 9.8), 3.80–3.57 (6H, complex m), 3.78 (3H, s, OMe), 2.08 (1H, dd, $H3_{eq}$, *J*12.2, 4.9), 1.89 (1H, a-t, $H3_{ax}$, *J* 12.2 Hz), 1.82–1.66 (4H, complex m, 2 × CH_2), 1.61–1.45 (8H, complex m, 4 × CH_2); ^{13}C NMR (125.7 MHz, CD_3OD) δ 171.8 (C), 98.6 (C), 98.5 (C), 97.0 (C), 74.9 (CH), 73.5 (CH), 69.2 (CH), 68.0 (CH), 65.9

(CH), 63.8 (CH_2), 61.8 (CH_2), 61.7 (CH_2), 53.3 (CH_3), 37.2 (CH_2), 29.6 (CH_2, two signals superimposed), 26.9(9) (CH_2), 25.9(6) (CH_2), 19.3 (CH_2), 19.2 (CH_2); IR (NaCl) 3368, 2945, 1735, 1436, 1270, 1210, 1191, 1155, 1071, 1046, 989 cm^{-1}; MS (FAB+) *m/z* 471 ($M+Na^+$, 100%), 413 (10), 391 (25), 329 (40), 307 (92), 289 (48). HRMS (FAB) *m/z* calcd for $C_{20}H_{32}O_{11}Na$ ($M+Na^+$): 471.1842. Found: 471.1845.

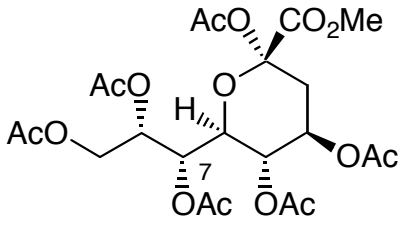
Compound 7-*epi*-3



7-*epi*-**3**

Compound **15** (11 mg, 0.025 mmol) was dissolved in TFA/H_2O (1.0 mL of a 95:5 v/v mixture) and the resulting solution was stirred at 18 °C for 24 h. ESMS (+ve and –ve ionization) analysis after this time suggested some starting material remained so the reaction mixture was concentrated under reduced pressure and the residue thus obtained was again treated with TFA/H_2O (1.0 mL of a 95:5 v/v mixture) at 18 °C for 16 h. The ensuing mixture was then concentrated under reduced pressure with toluene co-evaporation. The residue thus obtained was dissolved in H_2O (1.5 mL), treated with NaOH (50 μL of a 1 M aq solution), stirred at 18 °C for 2 h then diluted with H_2O (1 mL). Amberlite IR 120 (H^+) ion exchange resin was then added and after stirring for 0.25 h the reaction mixture was filtered (H_2O washes, 2 mL) and the filtrate concentrated under reduced pressure. The residue was dissolved in H_2O (0.5 mL) and applied to a C18 reverse-phase solid-phase extraction column (H_2O elution). Concentration of the appropriate fractions yielded sialic acid 7-*epi*-**3** (5 mg, 76%) as a light-yellow gum, ^1H NMR (500 MHz, D_2O) δ 4.00–3.94 (2H, complex m, H4, H8), 3.92 (1H, dd, H7, *J* 3.4, 2.9), 3.86 (1H, dd, H6, *J* 9.8, 3.4), 3.69 (1H, dd, H9, *J* 11.5, 4.9), 3.65 (1H, dd, H9', *J* 11.5, 7.1), 3.58 (1H, a-t, H5, *J* 9.5), 3.29 (1H, m, OH), 2.19 (1H, dd, $H3_{eq}$, *J* 12.5, 5.0), 1.81 (1H, a-t, $H3_{ax}$, *J* 12.5 Hz); ^{13}C NMR (150 MHz, D_2O/CD_3CN) δ 74.9, 72.7, 72.4, 71.7, 69.8, 63.7, 39.7 (signals due to C1 and C2 not observed).

Compound 17



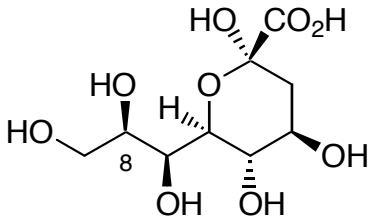
17

Compound **15** (9 mg, 0.020 mmol) was dissolved in TFA/H_2O (1.0 mL of a 95:5 v/v mixture) and the resulting solution was stirred at 18 °C for 24 h. ESMS (+ve and –ve ionization) analysis after this time suggested some starting material remained so the reaction mixture was concentrated under reduced pressure and the residue thus obtained was again treated with TFA/H_2O (1.0 mL of a 95:5 v/v mixture) at 18 °C for 16 h. The ensuing mixture was then concentrated under reduced pressure with toluene co-evaporation to yield sialic acid 7-*epi*-**3** which was used directly in the next step.

Thus, crude acid 7-*epi*-**3**, obtained as described immediately above, was dissolved in CH_3OH (1 mL) and the resulting solution treated with AG 50W-X8 (200–400 mesh, H^+ form, 10 mg) cation exchange resin. After stirring at 18 °C for 16 h, TLC analysis (60:30:3:5 v/v/v/v $CHCl_3$/CH_3OH/AcOH/H_2O elution) showed the formation of a new product (R_f 0.4). Consequently, the reaction mixture was filtered through a sintered funnel with CH_3OH washes (20 mL) and the combined filtrates concentrated under reduced pressure, with toluene co-evaporation, to give a light-yellow oil. This was treated directly with pyridine (0.5 mL), acetic anhydride (0.5 mL) and DMAP (4 mg) then the resulting solution was stirred at 18 °C for 18 h. TLC analysis (1:1 v/v EtOAc/hexane elution) after this time showed the formation of a new product (R_f 0.3). Concentration of the reaction mixture under reduced pressure, with toluene co-evaporation, gave a residue that was subjected to flash chromatography (1:2 v/v EtOAc/hexane elution). Concentration of the appropriate fractions (R_f 0.3, 1:1 v/v EtOAc/hexane) then gave compound **17** (6 mg, 56% over 3 steps) as a colorless glass, mp 43–45 °C; $[\alpha]_D^{18}$ +28.7 (*c* 0.23, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.44 (1H, a-dt, H8, *J* 6.3, 4.4,), 5.25 (1H, ddd, H4, *J* 11.2, 9.3, 4.9), 5.20 (1H, a-t, H5, *J* 9.3), 5.17 (1H, a-t, H7, *J* 3.9), 4.23 (1H, dd, H9, *J* 12.2, 4.4), 4.18 (1H, dd, H9', *J* 12.2, 6.3), 4.09 (1H, dd, H6, *J* 9.8, 3.9), 3.78 (3H, s, OMe), 2.55 (1H, dd, H3, *J* 13.7, 4.9 Hz), 2.14 (3H, s, CH_3CO), 2.10 (3H, s, CH_3CO), 2.08(2) (3H, s, CH_3CO), 2.07(7) (3H, s, CH_3CO), 2.05 (3H, s, CH_3CO), 2.03 (1H, m, H3', obscured), 2.02 (3H, s, CH_3CO); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.5

(C), 170.0(9) (C), 170.0(5) (C), 169.7 (C), 169.6 (C), 168.1 (C), 166.2 (C), 96.7 (C), 72.4 (CH), 69.6 (CH), 69.2 (CH), 68.7 (CH), 68.6 (CH), 62.4 (CH_2), 53.2 (CH_3), 35.3 (CH_2), 20.8(5) (CH_3), 20.8(3) (CH_3), 20.6(8) (CH_3), 20.6(5) (CH_3) (two signals obscured or overlapping); IR (NaCl, thin film) 2958, 1747, 1436, 1371, 1222, 1048, 1012, 939 cm^{-1}; MS (ESI+) 557 ($M+Na^+$, 100); HRMS (FAB) *m/z* calcd for $C_{22}H_{30}O_{15}Cs$ ($M+Cs^+$): 667.0634. Found: 667.0647.

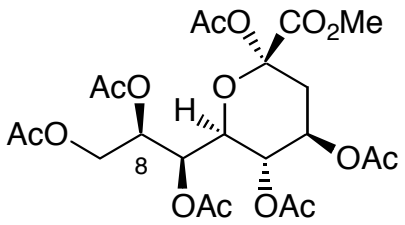
Compound 8-*epi*-3



8-*epi*-**3**

Compound **16** (9 mg, 0.020 mmol) was dissolved in TFA/H_2O (1.0 mL of a 95:5 v/v mixture) and the resulting solution was stirred at 18 °C for 24 h. ESMS (+ve and –ve ionization) analysis after this time suggested some starting material remained so the reaction mixture was concentrated under reduced pressure and the residue thus obtained was again treated with TFA/H_2O (1.0 mL of a 95:5 v/v mixture) at 18 °C for 16 h. Concentration of the ensuing mixture under reduced pressure, with toluene co-evaporation, yielded a light-yellow oil. This was dissolved in H_2O (1.5 mL), treated with NaOH (50 μL of a 1 M aq solution), stirred at 18 °C for 2 h then diluted with H_2O (1 mL). Amberlite IR 120 (H^+) ion exchange resin then was added and, after stirring for 0.25 h, the reaction mixture was filtered (H_2O washes, 2 mL) and the combined filtrates concentrated under reduced pressure. The residue thus obtained was dissolved in H_2O (0.5 mL) and applied to a C18 reverse-phase solid-phase extraction column (H_2O elution). Concentration of the appropriate fractions yielded sialic acid 8-*epi*-**3** (4 mg, 69%) as a light-yellow gum, ^1H NMR (500 MHz, D_2O) δ 3.96–3.89 (2H, complex m, H7, H4), 3.82 (1H, m, H8), 3.75 (1H, d, H6, *J* 9.5), 3.69 (1H, dd, H9, *J* 12.0, 3.0), 3.58 (1H, a-t, H5, *J* 9.5), 3.56 (1H, dd H9, *J* 12.0, 6.3), 2.18 (1H, dd, $H3_{eq}$, *J* 12.5, 4.9), 1.77 (1H, a-t, $H3_{ax}$, *J* 12.5 Hz); ^{13}C NMR (150 MHz, D_2O/CD_3CN) δ 74.2, 74.1, 71.4, 69.8, 69.5, 63.1, 40.0 (signals due to C1 and C2 not observed).

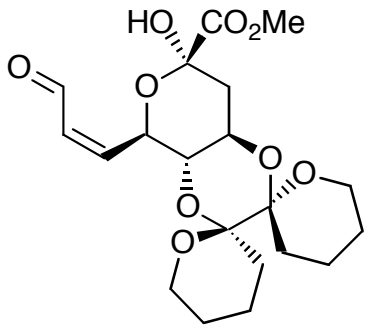
Compound 18



18

Compound **16** (7 mg, 0.016 mmol) was dissolved in TFA/H_2O (0.5 mL of a 95:5 v/v mixture) and the resulting solution was stirred at 18 °C for 24 h. TLC analysis (10% $CH_3OH/CHCl_3$) after this time showed an absence of starting material (R_f 0.25) and the formation of a new product (R_f 0.0). Concentration of the reaction mixture under reduced pressure with toluene co-evaporation yielded 8-*epi*-**3** as a light-yellow gum. This gum was dissolved in CH_3OH (1 mL) and the resulting solution treated with AG 50W-X8 (200–400 mesh, H^+ form, 10 mg) cation exchange resin at 18 °C for 16 h. TLC analysis (60:30:3:5 v/v/v/v $CHCl_3/CH_3OH/AcOH/H_2O$ elution) after this time showed the formation of a new product (R_f 0.3). Filtration through a sintered funnel with CH_3OH washes and concentration of the filtrates under reduced pressure, with toluene co-evaporation, gave a yellow oil which was treated with pyridine (0.5 mL), acetic anhydride (0.5 mL) and DMAP (4 mg). The resulting solution was stirred at 18 °C for 18 h, after which time TLC analysis (1:1 v/v EtOAc/hexane elution) showed the formation of a new product (R_f 0.3). The reaction mixture was concentrated under reduced pressure, again with toluene co-evaporation. The residue thus obtained was subjected to flash chromatography (1:1 v/v EtOAc/hexane elution) and concentration of the appropriate fractions (R_f 0.3, 1:1 v/v EtOAc/hexane) gave compound **18** (4 mg, 50% over 3 steps) as a colorless solid, mp 136–138 °C; $[\alpha]_D^{18}$ +12.0 (*c* 0.15, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.36–5.26 (3H, complex m, H4, H7, H8), 5.03 (1H, a-t, H5, *J* 10.3), 4.33 (1H, dd, H9, *J* 13.2, 2.4), 4.26 (1H, dd, H9', *J* 13.2, 4.4), 4.12 (1H, dd, H6, *J* 10.3, 2.4), 3.81 (3H, s, OMe), 2.62 (1H, dd, H3, *J* 13.7, 5.4 Hz), 2.17 (3H, s, CH_3CO), 2.10 (3H, s, CH_3CO), 2.09 (3H, s, CH_3CO), 2.08 (1H, m, H3', obscured), 2.04 (3H, s, CH_3CO), 2.02(1) (3H, s, CH_3CO), 2.01(5) (3H, s, CH_3CO); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.6 (C), 170.2 (C), 170.1 (C), 169.7(3) (C), 169.6(9) (C), 168.7 (C), 166.1 (C), 97.2 (C), 71.2 (CH), 70.8 (CH), 68.4 (CH), 67.5 (CH), 67.0 (CH), 62.4 (CH_2), 53.3 (CH_3), 35.6 (CH_2), 20.8 (CH_3), 20.7 (CH_3), 20.6 (CH_3) (three signals due to acetate methyl groups obscured or overlapping); IR (NaCl, thin film) 2924, 2854, 1748, 1441, 1371, 1228, 1112, 1055, 1011 cm^{-1}; MS (ESI+) 557 ($M+Na^+$, 100%), 497 (10). HRMS (FAB) *m/z* calcd for $C_{22}H_{30}O_{15}Cs$ ($M+Cs^+$): 667.0634. Found: 667.0612.

Compound 19



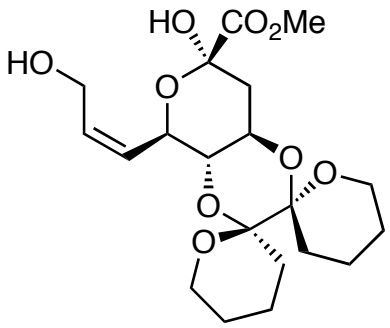
19

Compound **13** (69 mg, 0.168 mmol) was dissolved in dry, degassed benzene and the resulting solution irradiated at 300 nm (Rayonet reactor) for 2 h. TLC analysis (1:1 v/v EtOAc/hexane elution) after this time showed a mixture of starting material (R_f 0.3) and product (R_f 0.2), while ^{1}H NMR analysis showed a 1.2:1 ratio of compounds **13** and **19**. The reaction mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash chromatography (1:3 v/v EtOAc/hexane with 0.1% Et_3N elution) and thus affording two fractions, A (R_f 0.2) and B (R_f 0.3).

Concentration of fraction A gave compound **19** (29 mg, 42%) as a colorless foam, $[\alpha]_D$ +97.1 (*c* 0.93, CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6) δ 9.99 (1H, d, H9, *J* 8.1), 6.17 (1H, dd, H7, *J* 11.5, 7.4), 5.89 (1H, ddd, H8, *J* 11.5, 8.1, 1.4), 5.19 (1H, ddd, H6, *J* 10.2, 7.4, 1.4), 4.56 (1H, ddd, H4, *J* 12.2, 9.3, 4.8), 4.02 (1H, m, OH), 3.62 (1H, a-t, H5, J ~ 9.6), 3.65–3.35 (3H, complex m), 3.25 (1H, a-d, *J* 9.3), 3.20 (3H, s, OMe), 2.41 (1H, a-t, $H3_{ax}$, *J* 12.4), 2.15 (1H, dd, $H3_{eq}$, *J* 12.4, 4.8 Hz), 2.16–1.95 (2H, complex m), 1.88–1.05 (10H, complex m); ^{13}C NMR (75 MHz, C_6D_6) δ 191.0 (CH), 169.9 (C), 144.6 (CH), 132.4 (CH), 98.3 (C), 97.6 (C), 95.8 (C), 70.1 (CH), 69.1 (CH), 64.7 (CH), 60.8 (CH_2), 60.6 (CH_2), 52.8 (CH_3), 35.8 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 25.2 (CH_2), 25.0 (CH_2), 18.6 (CH_2), 18.4 (CH_2); IR (NaCl) 3436, 2927, 2873, 1752, 1686, 1439, 1272, 1210, 1191, 1147, 1086, 1070, 1047, 990, 965, 936, 898, 878 cm^{-1}; MS (ESI+) *m/z* 451 ($M+K^+$, 15%), 435 ($M+Na^+$, 100); HRMS (FAB) *m/z* calcd for $C_{20}H_{28}O_9Cs$ ($M+Cs^+$): 545.0788. Found: 545.0775.

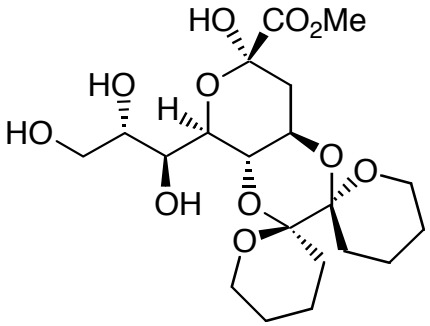
Concentration of fraction B gave starting material **13** (40 mg, 58% recovery) as a colorless foam and identical, in all respects, with authentic material.

Luche reduction of Compound 19 – Formation of the Corresponding Allylic Alcohol



$CeCl_3$•$7H_2O$ (59 mg, 0.158 mmol) was added to a magnetically stirred solution of aldehyde **19** (59 mg, 0.143 mmol) and 2,6-lutidine (77 mg, 83 μL, 0.716 mmol) in CH_2Cl_2/EtOH (2.6 mL of a 1:1 mixture) maintained at ca. 18 °C. This mixture was then cooled to –78 °C and treated with $NaBH_4$ (16 mg, 0.430 mmol) in EtOH (0.43 mL). Stirring was continued at –78 °C for 1 h at which time TLC analysis (1:2 v/v EtOAc/hexane elution) showed an absence of starting material (R_f 0.3) and the presence of a product (R_f 0.1). Consequently acetone (0.5 mL) was added to the reaction mixture, the cooling bath was then removed and the reaction mixture poured into H_2O (40 mL). HCl (5 mL of a 1 M aq solution) was added and the resulting mixture extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with brine (1 × 15 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography (1:1 v/v EtOAc/hexane elution) and concentration of the appropriate fractions (R_f 0.2) under reduced pressure gave the title allylic alcohol (23 mg, 39%) as a clear, colorless oil, $[\alpha]_D^{18}$ +91.7 (*c* 0.90, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 (1H, m, H8), 5.54 (1H, m, H7), 4.88 (1H, ddd, H6, *J* 9.9, 8.3, 1.1), 4.30–4.08 (3H, complex m), 3.82 (3H, s, OMe), 3.80–3.55 (4H, complex m), 3.48 (1H, a-t, H5, *J* 9.8), 2.56 (1H, br s, OH), 2.24 (1H, a-t, $H3_{ax}$, *J* 12.5), 2.06 (1H, dd, $H3_{eq}$, *J* 12.5, 4.8 Hz), 1.82–1.42 (12H, complex m, 6 × CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0 (C), 133.7 (CH), 128.6 (CH), 97.8 (C), 97.1 (C), 95.4 (C), 70.3 (CH), 68.4 (CH), 64.2 (CH), 60.7 (CH_2), 58.7 (CH_2), 53.4 (CH_3), 35.3 (CH_2), 28.6 (CH_2), 28.2 (CH_2), 24.8 (CH_2), 24.7 (CH_2), 18.0 (CH_2) (two signals obscured or overlapping); IR (NaCl, thin film) 3468, 2947, 2874, 1751, 1439, 1272, 1209, 1191, 1151, 1071, 1046, 990, 937, 899, 877, 754 cm^{-1}; MS (ESI+) *m/z* 437 (M+Na^+, 100%); HRMS (FAB) *m/z* calcd for $C_{20}H_{30}O_9Cs$ (M+Cs^+): 547.0944. Found: 547.0926.

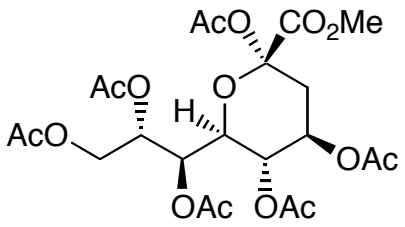
Compound 20



20

A magnetically stirred solution of the allylic alcohol derived from the Luche reduction of compound **19** (20 mg, 0.048 mmol) in acetone (1.5 mL) was treated with H_2O (0.15 mL) and NMO (11 mg, 0.096 mmol) then OsO_4 (2 drops of a 2.5 wt% solution in *t*-BuOH) was added and the ensuing mixture stirred at 18 °C under a nitrogen atmosphere for 16 h. TLC analysis (10% v/v $CH_3OH/CHCl_3$ elution) after this time showed residual starting material (R_f 0.6) and a major product spot (R_f 0.3). Consequently, additional NMO (11 mg, 0.096 mmol), OsO_4 (2 drops of a 2.5 wt% solution in *t*-BuOH) and THF (0.5 mL) were added and the reaction mixture then stirred at 18 °C for an additional 64 h. Further OsO_4 (1 drop of a 2.5 wt% solution in *t*-BuOH) and THF (0.5 mL) were added after this time and stirring was continued for another 16 h. After this time TLC analysis (10% $CH_3OH/CHCl_3$ elution) showed an absence of starting material (R_f 0.6). As a result, solid $Na_2S_2O_5$ (80 mg), H_2O (0.2 mL) and Florisil (0.2 g) were added and the resulting mixture was stirred at 18 °C for 4 h. Silica gel (0.2 g) was then added and the solvent removed under reduced pressure. Application of this material to flash chromatography (5% v/v $CH_3OH/CHCl_3$ containing 0.05% NH_3 elution) and concentration of the appropriate fraction (R_f 0.3, 10% v/v $CH_3OH/CHCl_3$) gave compound **20** (93 mg, 42%) as a clear, colorless oil, $[\alpha]_D^{17}$ +74.2 (*c* 0.52, CH_3OH); ^1H NMR (500 MHz, $CDCl_3$) δ 4.21 (1H, ddd, H4, *J* 12.2, 9.8, 4.9), 4.18 (1H, dd, H6, *J* 9.8, 1.5), 3.95–3.56 (9H, complex m), 3.78 (3H, s, OMe), 2.06 (1H, dd, $H3_{eq}$, *J* 12.7, 4.9), 1.91 (1H, a-t, $H3_{ax}$, *J* 12.7 Hz), 1.84–1.69 (4H, complex m, 2 × CH_2), 1.61–1.45 (8H, complex m, 4 × CH_2); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 172.1 (C), 98.5 (C, two signals superimposed), 97.1 (C), 72.2 (CH), 71.5 (CH), 69.2 (CH), 67.6 (CH), 66.2 (CH), 64.9 (CH_2), 61.8 (CH_2), 61.7 (CH_2), 53.3 (CH_3), 37.1 (CH_2), 29.6 (CH_2, two signals superimposed), 26.0 (CH_2, two signals superimposed), 19.3 (CH_2), 19.2 (CH_2); IR (NaCl, thin film) 3369, 2945, 2868, 1735, 1454, 1437, 1272, 1209, 1191, 1153, 1070, 1047, 989 cm^{-1}; MS (ESI+) *m/z* 471($M+Na^+$, 100%), 413 (25).

Compound 21



21

Compound **20** (9.3 mg, 0.021 mmol) was dissolved in TFA/H_2O (1.0 mL of a 95:5 v/v mixture) and the resulting solution was stirred at 18 °C for 24 h. ESMS (+ve and –ve ionization) analysis of the reaction mixture after this time suggested some starting material remained so the reaction mixture was concentrated under reduced pressure and the residue thus obtained was again treated with TFA/H_2O (1.0 mL of a 95:5 v/v mixture) at 18 °C for 16 h. Concentration of the ensuing oil under reduced pressure, with toluene co-evaporation, then yielded compound **3** which was used directly in the next step.

The sample of compound **3** obtained as described immediately above was dissolved in CH_3OH (1 mL) and the resulting solution treated with AG 50W-X8 (200–400 mesh, H^+ form, 10 mg) cation exchange resin at 18 °C for 16 h. TLC analysis (60:30:3:5 v/v/v/v $CHCl_3$/CH_3OH/AcOH/H_2O elution) after this time showed the formation of a new product (R_f 0.3). Filtration of the reaction mixture through a sintered funnel with CH_3OH washes and concentration of the combined filtrates under reduced pressure gave a residue which was treated directly with pyridine (0.5 mL), acetic anhydride (0.5 mL) and DMAP (4 mg). The resulting solution was stirred at 18 °C for 18 h at which time TLC analysis (1:1 v/v EtOAc/hexane elution) showed the formation of a new product (R_f 0.3). Concentration of the reaction mixture under reduced pressure, with toluene co-evaporation, gave a residue that was subjected to flash chromatography (1:2 v/v EtOAc/hexane elution). Concentration of the appropriate fractions (R_f 0.3, 1:1 v/v EtOAc/hexane) then gave the *ent*-KDN derivative **21** (4.6 mg, 42% over 3 steps) as a colorless solid, mp 100–102 °C (lit.[5] mp 100–104°C); $[\alpha]_D^{18}$ +26.2 (*c* 0.18, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.39 (1H, dd, H7, *J* 6.3, 2.4), 5.26 (1H, ddd, H4, *J* 11.7, 9.8, 5.4), 5.15 (1H, a-dt, H8, *J* 5.9, 2.4), 4.97 (1H, a-t, H5, *J* 9.8), 4.43 (1H, dd, H9, *J* 12.7, 2.4), 4.18 (1H, dd, H6, *J* 10.3, 2.4), 4.14 (1H, dd, H9', *J* 12.7, 5.9), 3.79 (3H, s, OMe), 2.62 (1H, dd, H3, *J* 13.7, 5.4 Hz), 2.15 (3H, s, CH_3CO), 2.11 (3H, s, CH_3CO), 2.07 (3H, s, CH_3CO), 2.07 (1H, m, H3', obscured), 2.04 (3H, s, CH_3CO), 2.02 (3H, s, CH_3CO), 2.01 (3H, s, CH_3CO); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.6 (C), 170.1 (C), 170.0 (C), 169.7 (C), 169.6 (C), 168.2 (C), 166.1 (C), 97.3 (C), 71.4 (CH), 70.2 (CH), 68.7 (CH), 67.3 (CH), 66.8 (CH),

61.8 (CH_2), 53.2 (CH_3), 35.4 (CH_2), 20.8(3) (CH_3), 20.7(5) (CH_3), 20.6 (CH_3) (three signals due to acetate methyl groups obscured or overlapping); IR (NaCl, thin film) 2959, 1749, 1436, 1371, 1224, 1169, 1113, 1052, 1012, 945, 819 cm^{-1}; MS (ESI+) *m/z* 557 ($M+Na^+$, 100%); HRMS (FAB) *m/z* calcd for $C_{22}H_{30}O_{15}Cs$ ($M+Cs^+$): 667.0634. Found: 667.0669.

References

1. Reddy, K. K.; Saady, M.; Falck, J. R.; Whited, G. *J. Org. Chem.* **1995**, *60*, 3385–3390.
2. For some closely related conversions see: (a) Shing, T.K.M.; Tang, Y. *J. Chem. Soc., Chem. Commun*. **1990**, 748–749. (b) Shing, T. K. M.; Tang, Y. *Tetrahedron* **1991**, *47*, 4571–4578. (c) Alves, C.; Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Tetrahedron* **1999**, *55*, 8443–8456.
3. Bianco, A.; Brufani, M.; Manna, F.; Melchioni, C. *Carbohydrate Res.* **2001**, *332*, 23–31.
4. Hiroya, K.; Ogasawara, K. *Chem. Commun*. **1998**, 2033–2034.
5. Banwell, M.; De Savi, C.; Watson, K. *Chem. Commun*. **1998**, 1189–1190.

nlh177f4pptCDCl3H1-30/10/03

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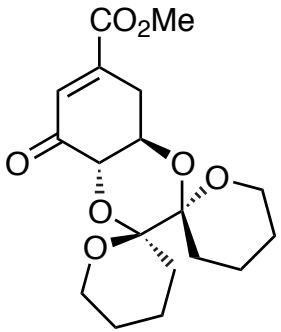
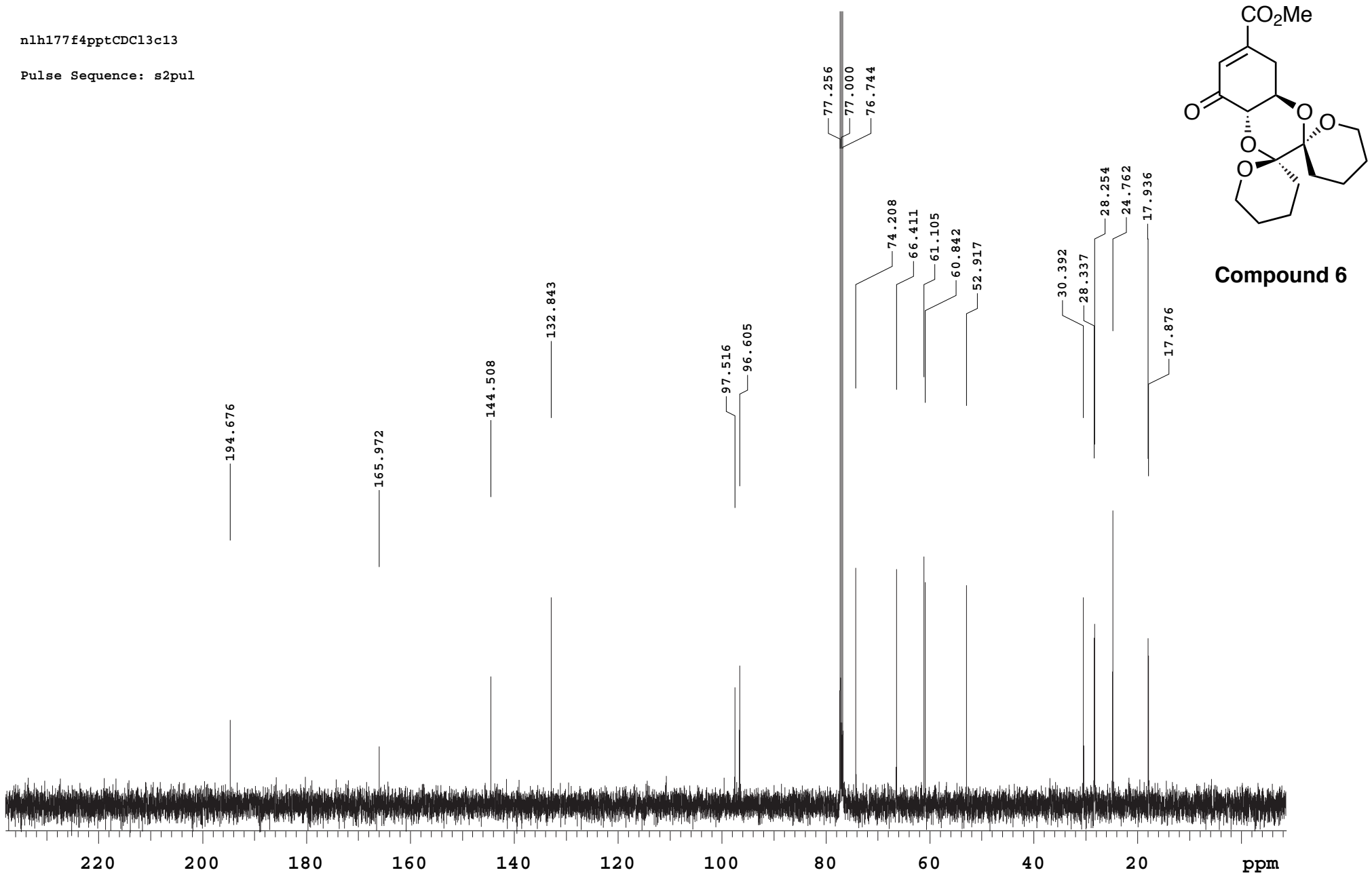


Compound 6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66.411
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60.842
52.917
30.392
28.337
28.254
24.762
17.936
17.876
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180
160
140
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Compound 6

nlh164f2pptCD3ODH1

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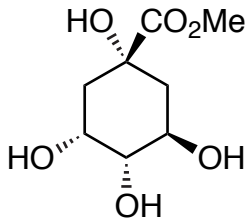

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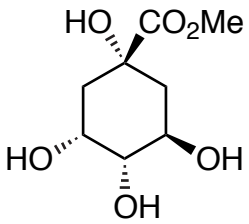

Compound 8

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49.000
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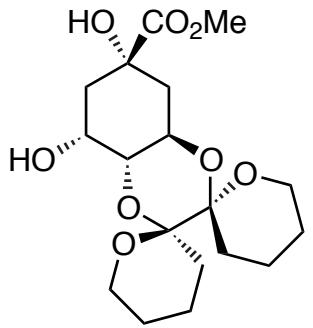

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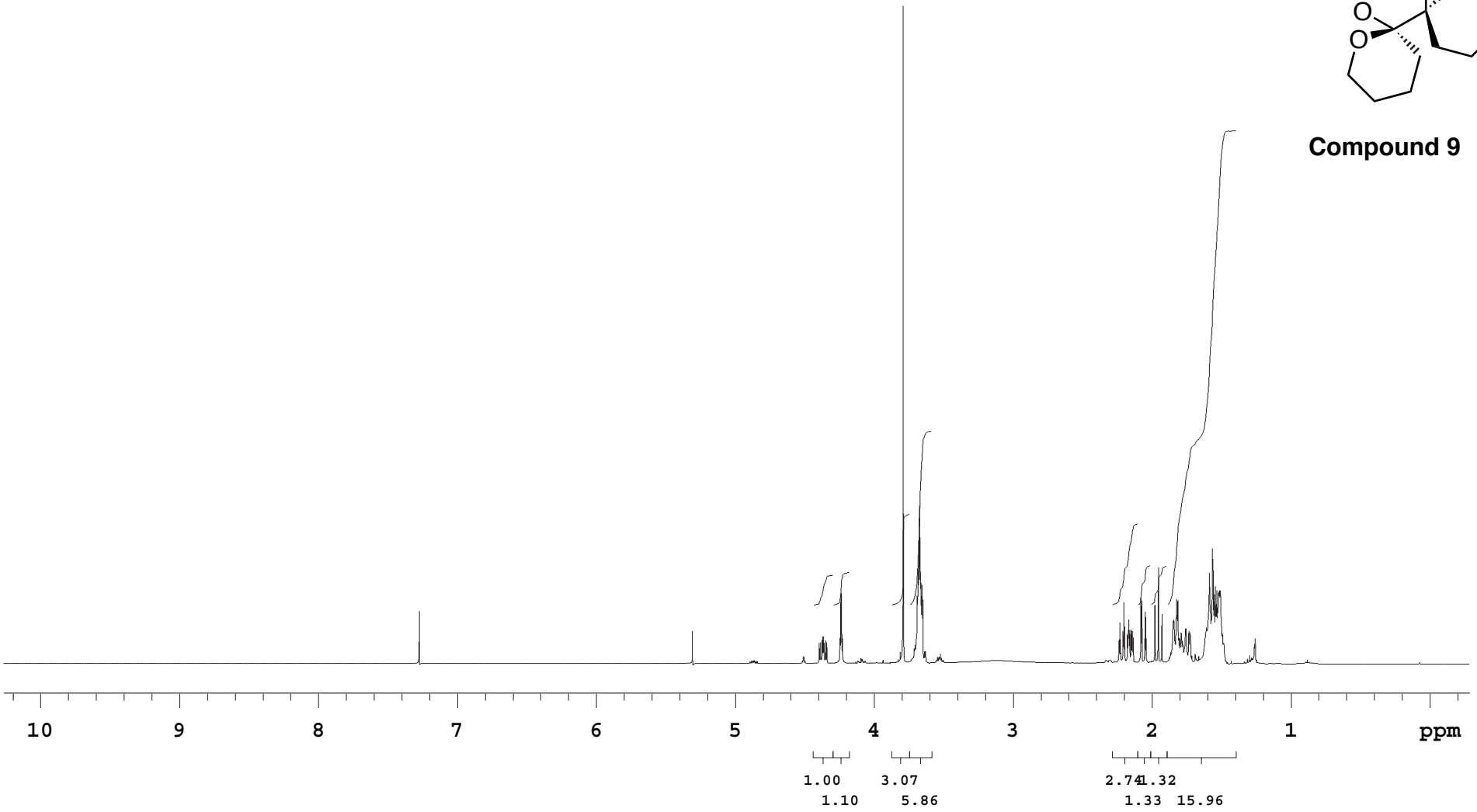

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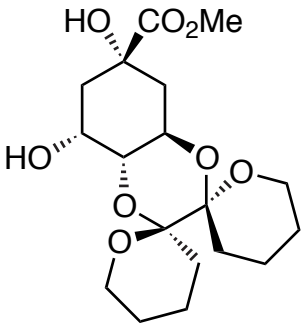

Compound 9

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60.721
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38.700
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28.631
28.352
24.875
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97.094

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nlh138f7-24CDCl3H1 300 MHz

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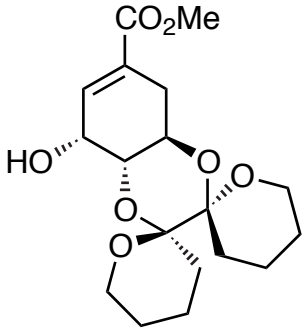

Compound 11

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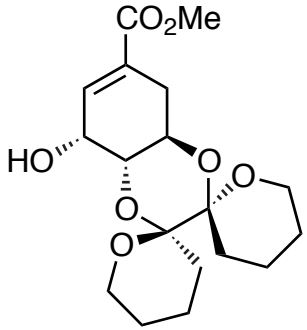

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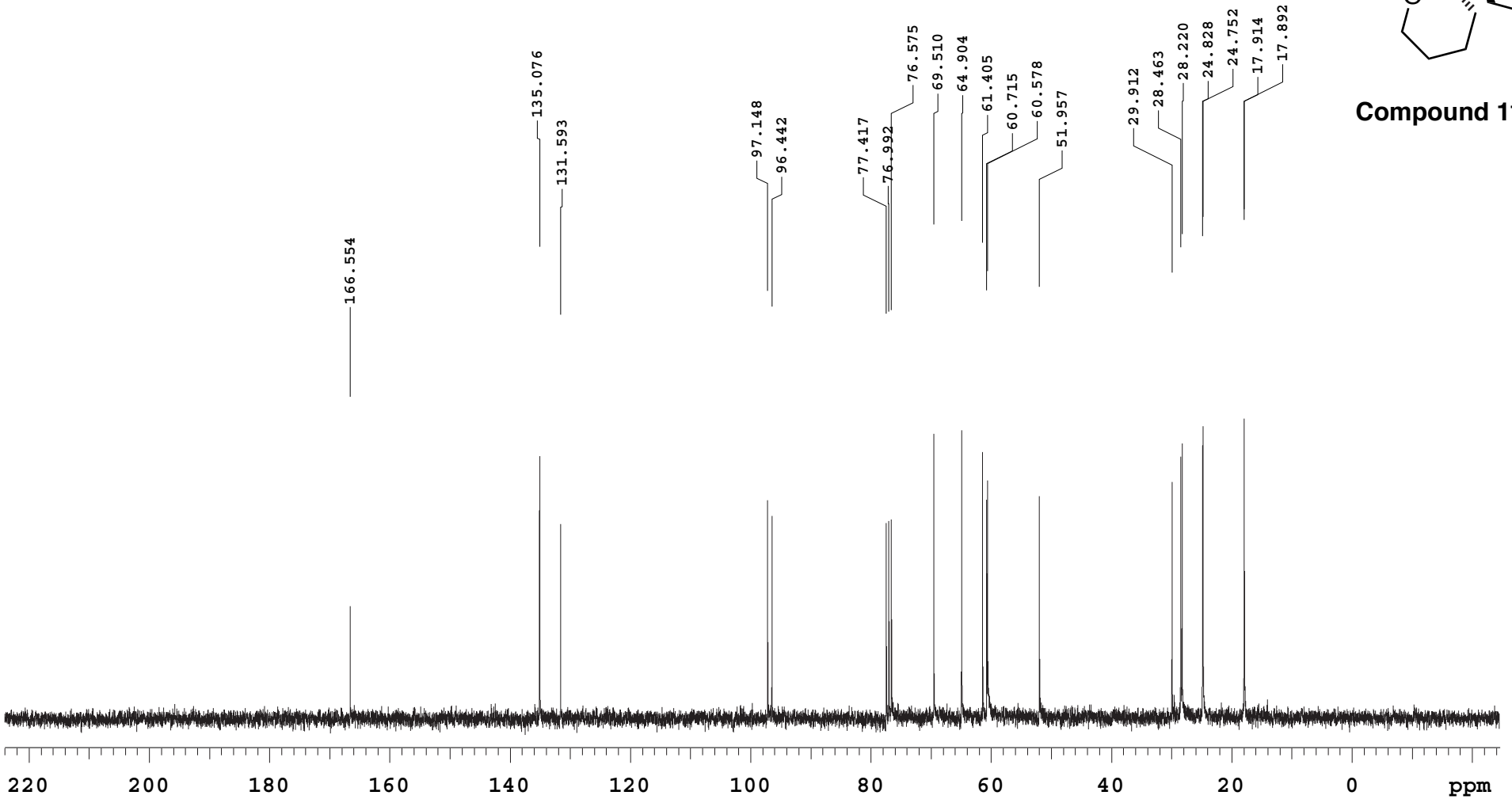

kj4-44-1-02-1H

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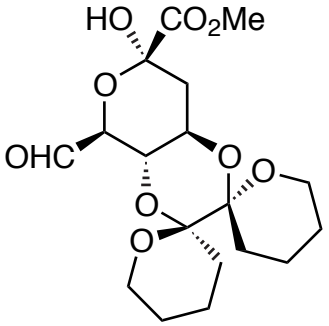

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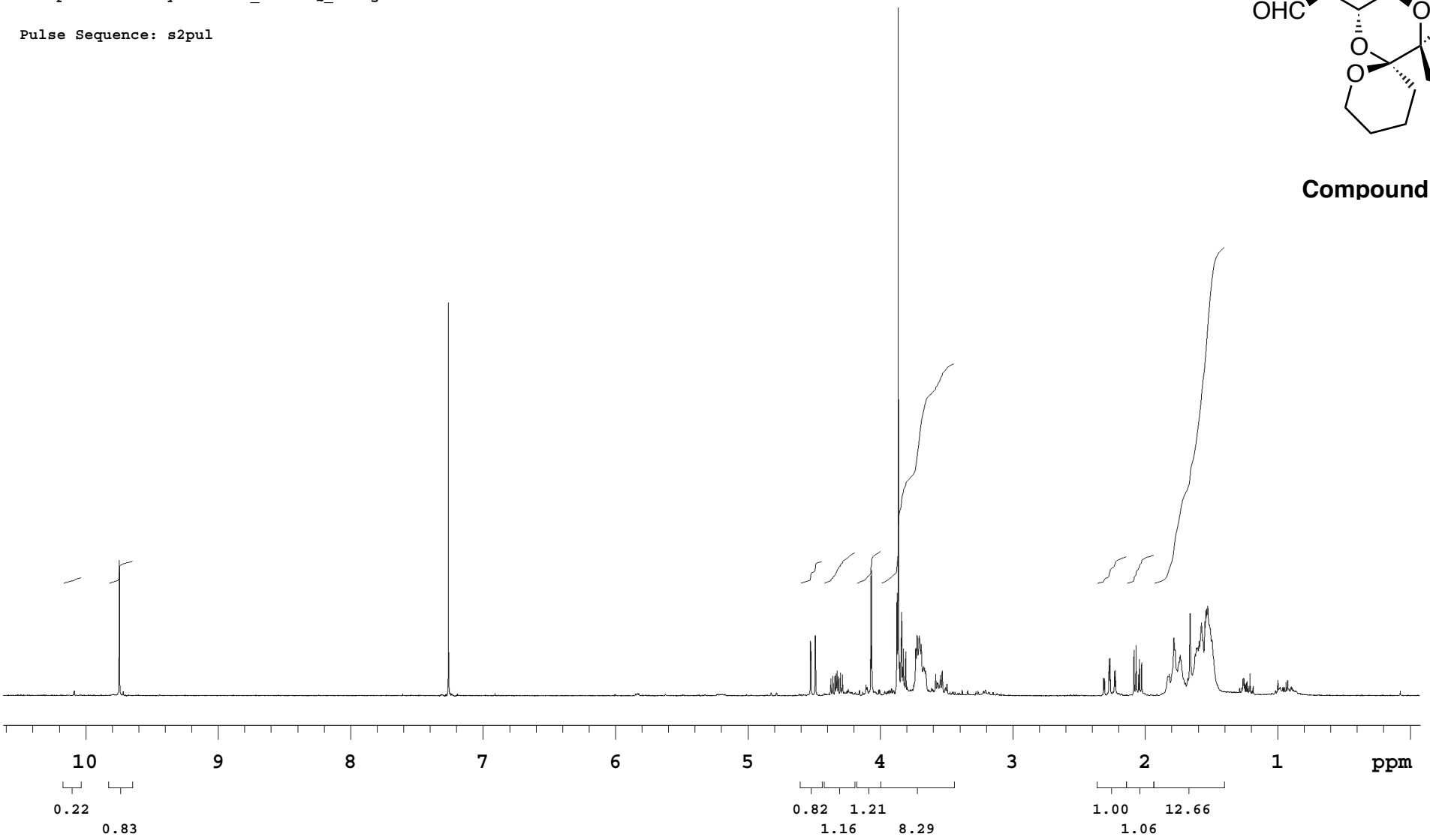

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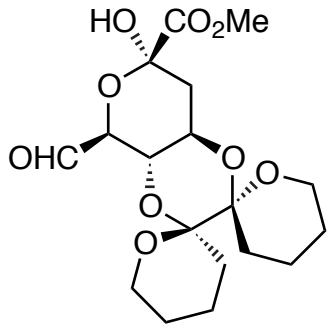

Compound 12

kj6de10-1H_300

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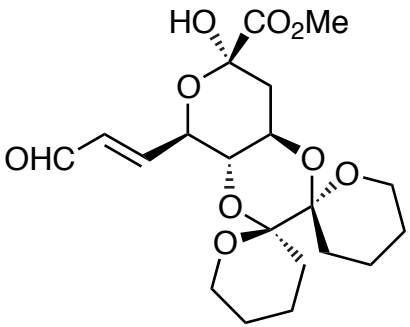

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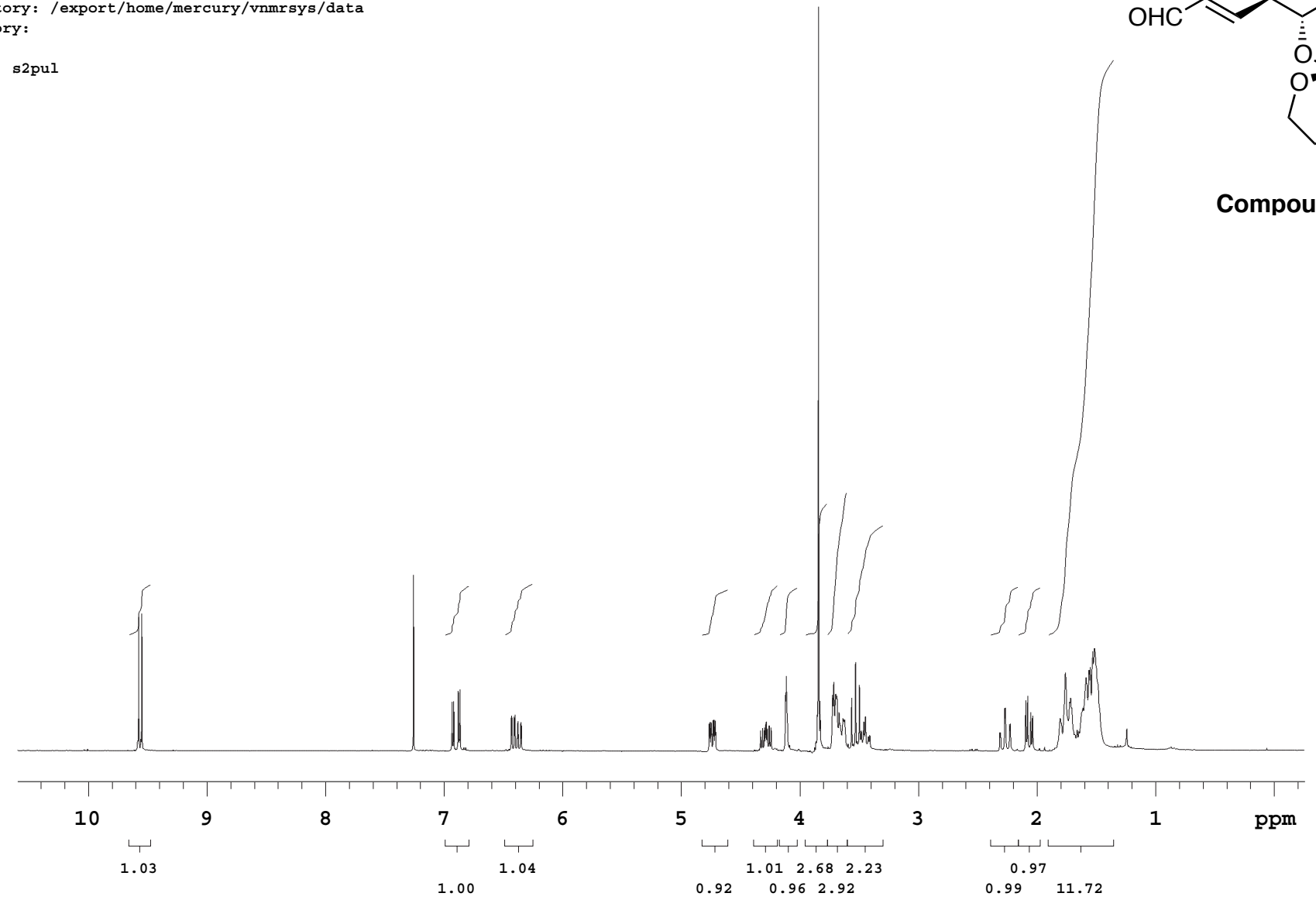

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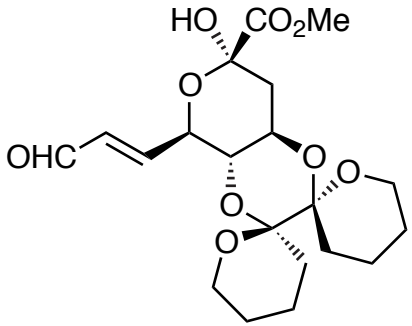

Compound 13

nlh21f22-29CDCl3H1

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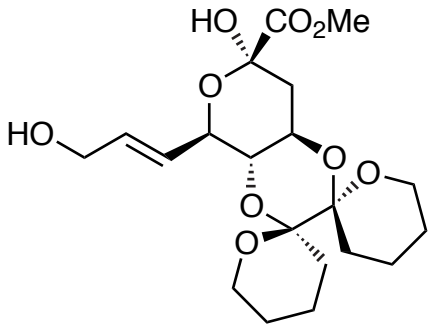
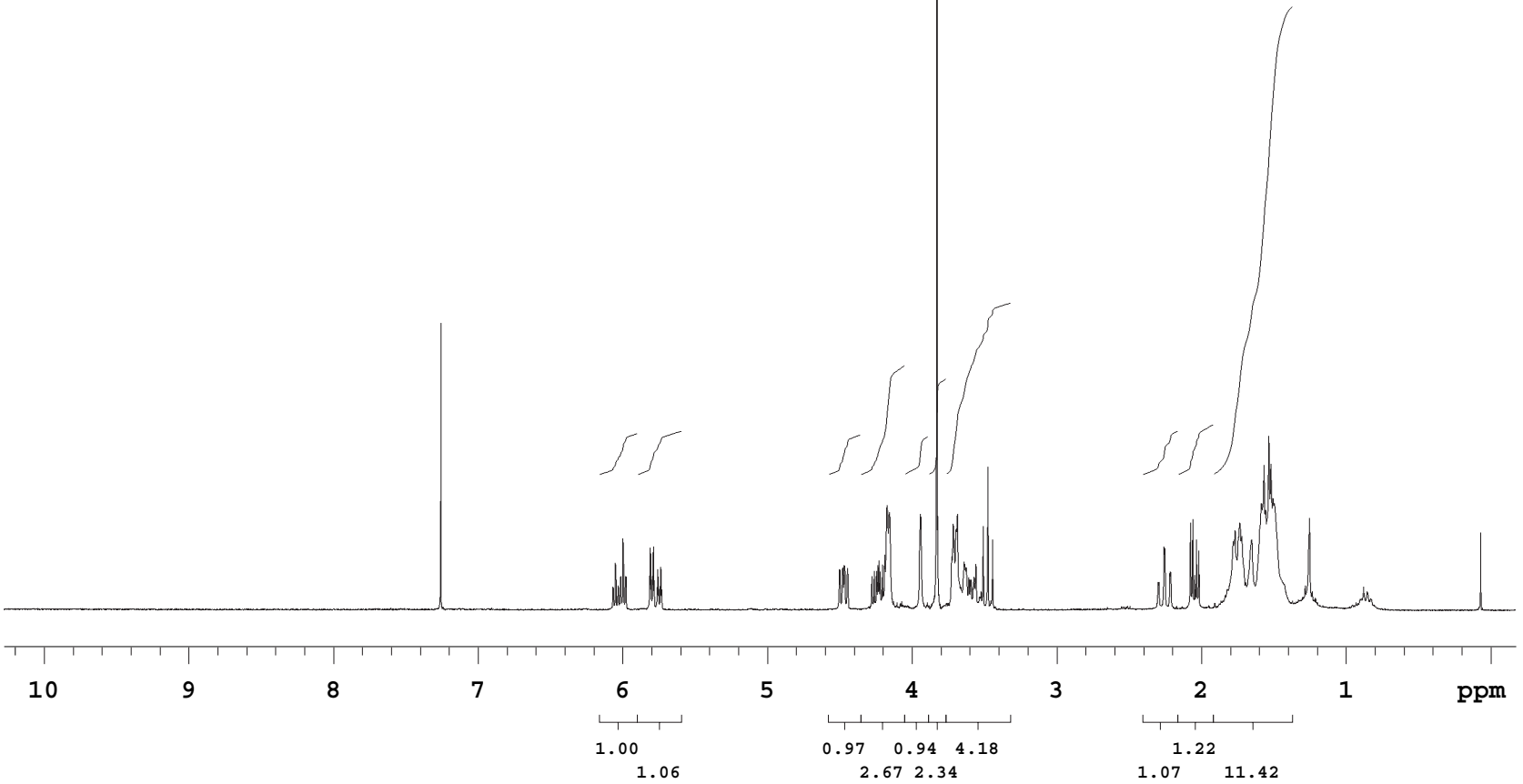
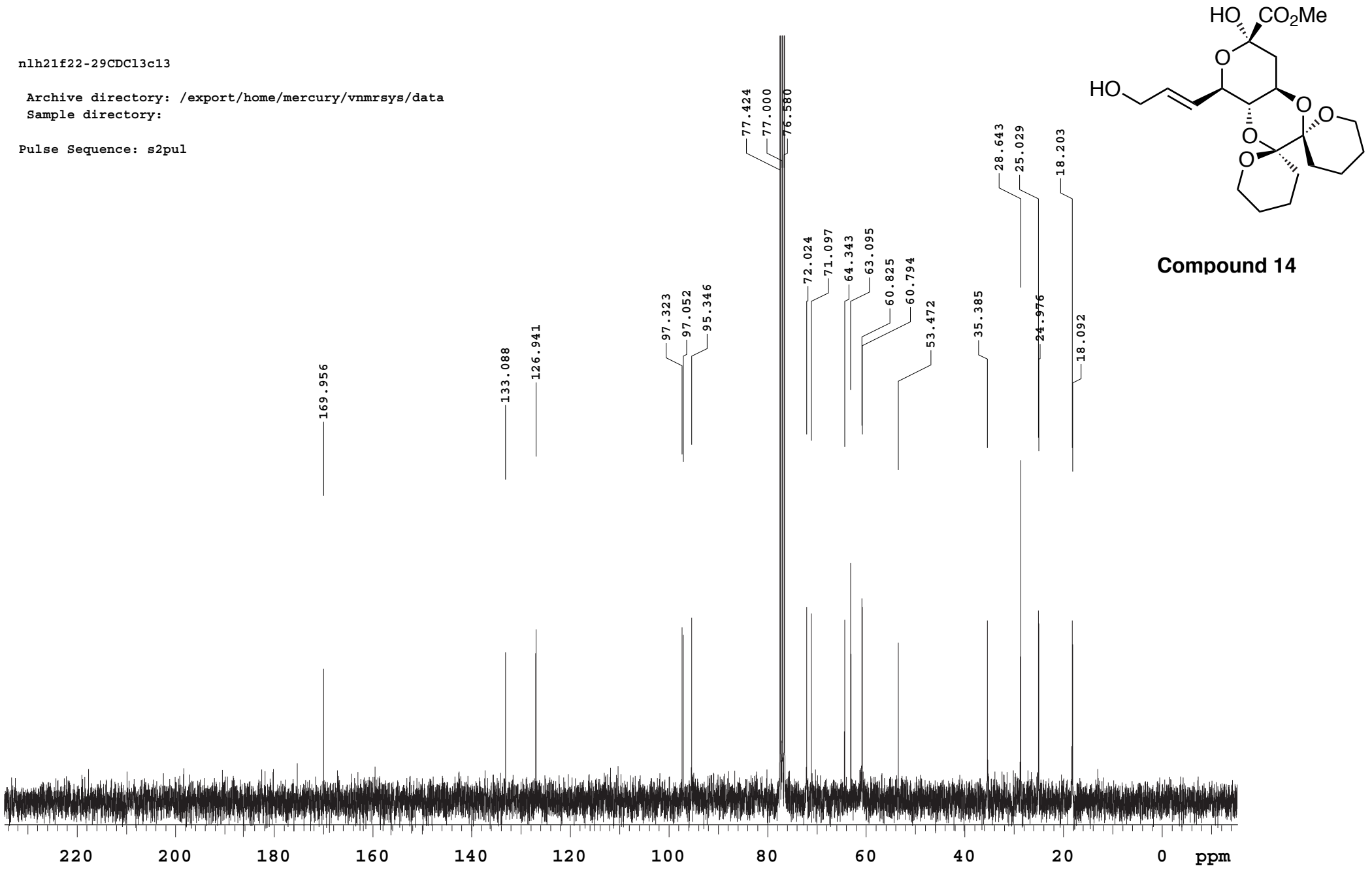


Compound 14

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24.976
18.203
18.092
97.323
97.052
95.346
169.956
133.088
126.941
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200
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160
140
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100
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60
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Compound 14

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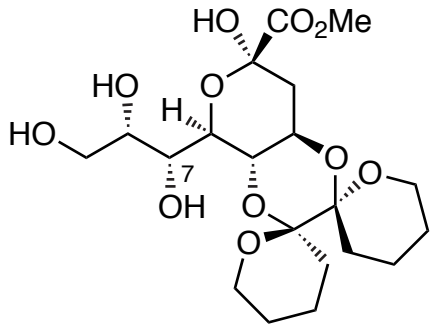

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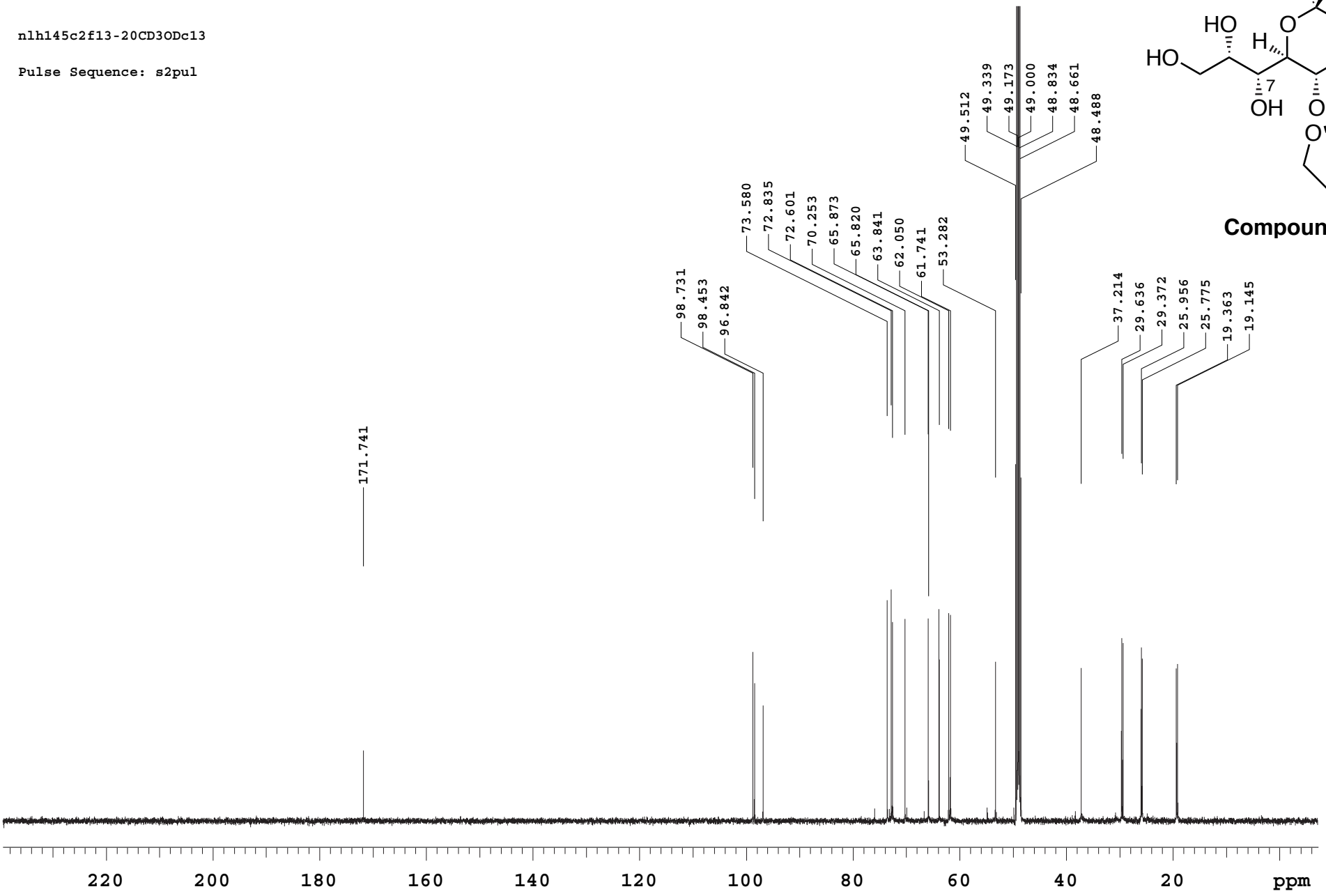
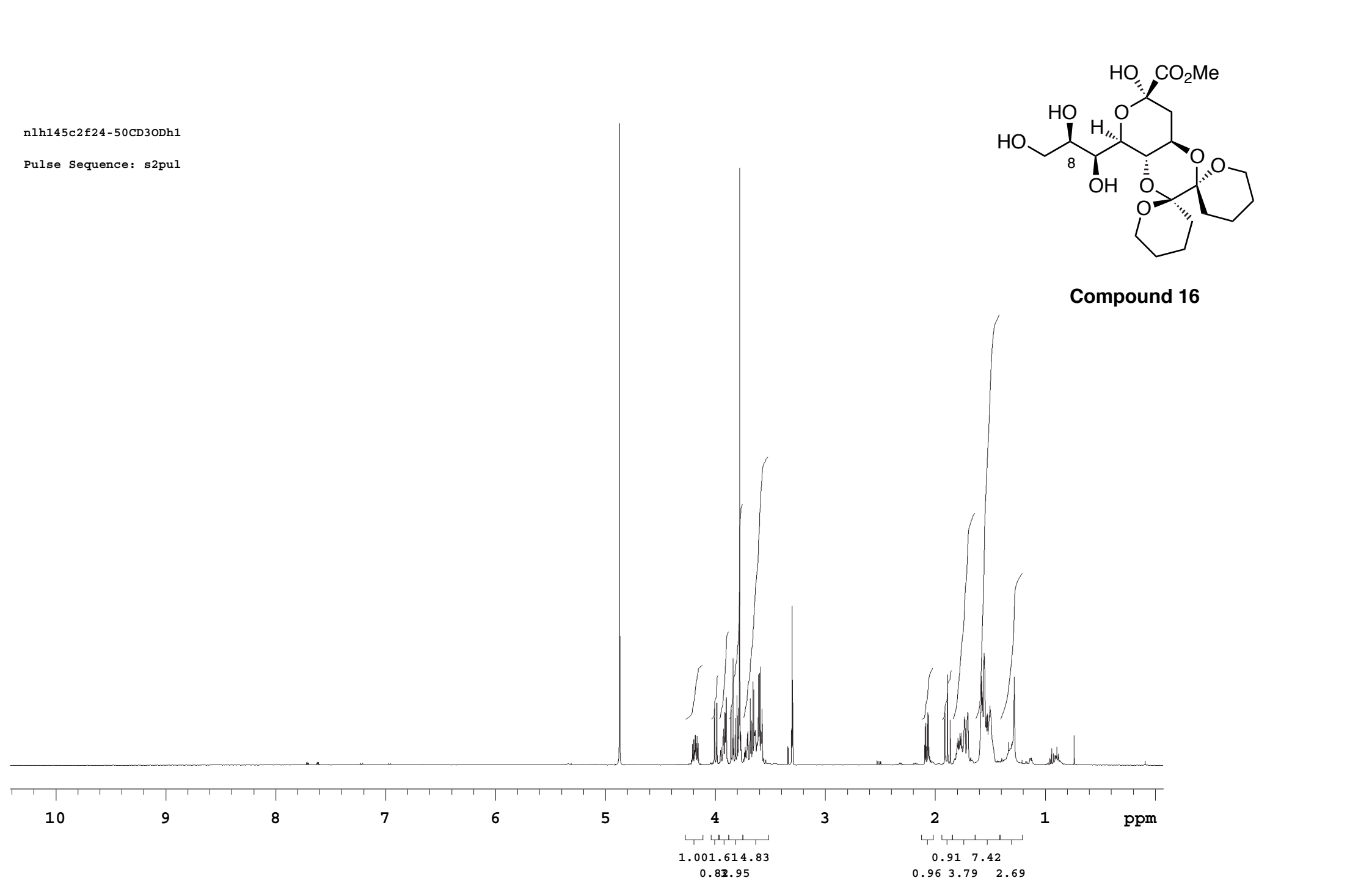


Compound 15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8
OH
O
O
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O
Compound 16
10
9
8
7
6
5
4
3
2
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ppm
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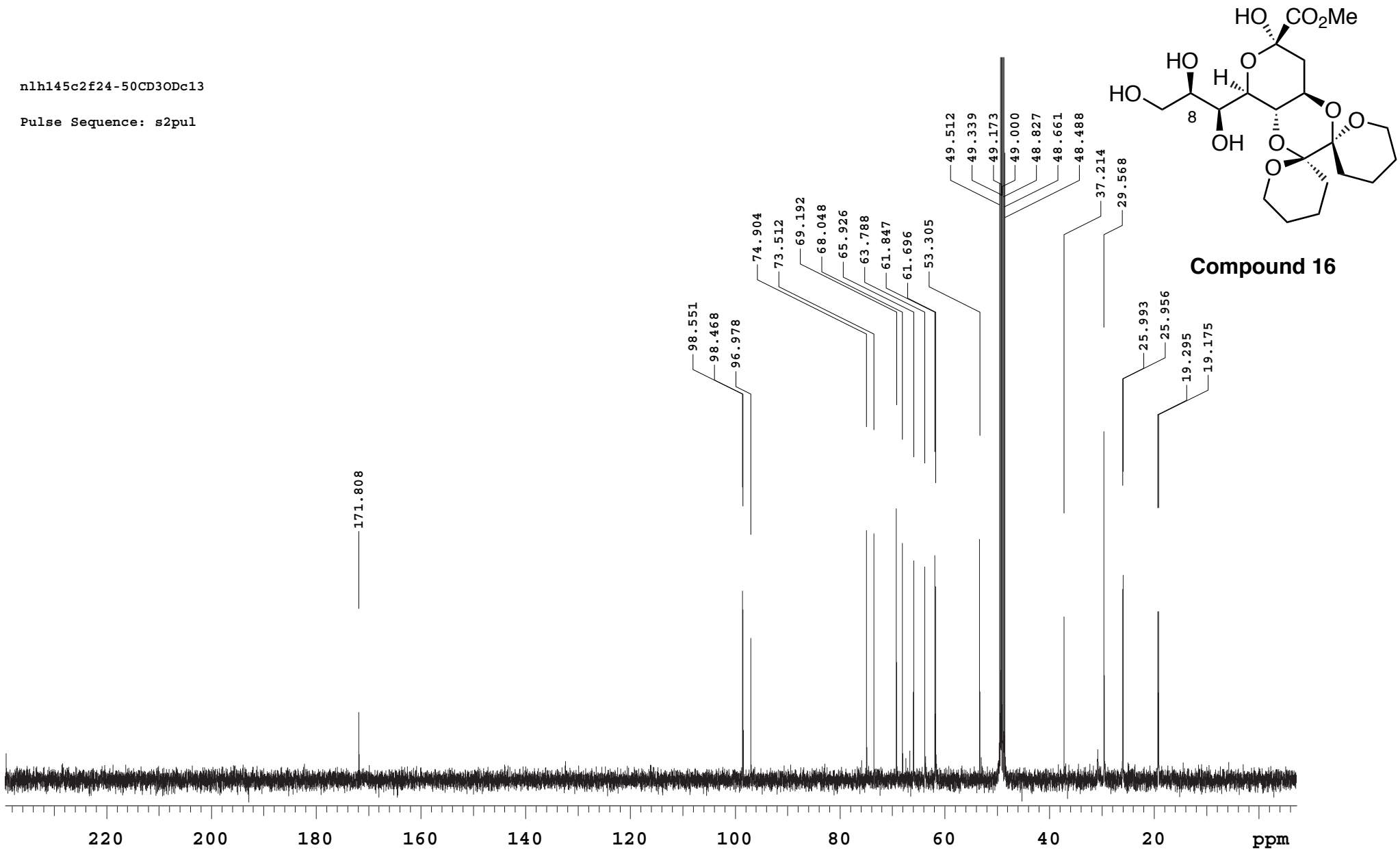
0.83 2.95
0.91 7.42
0.96 3.79 2.69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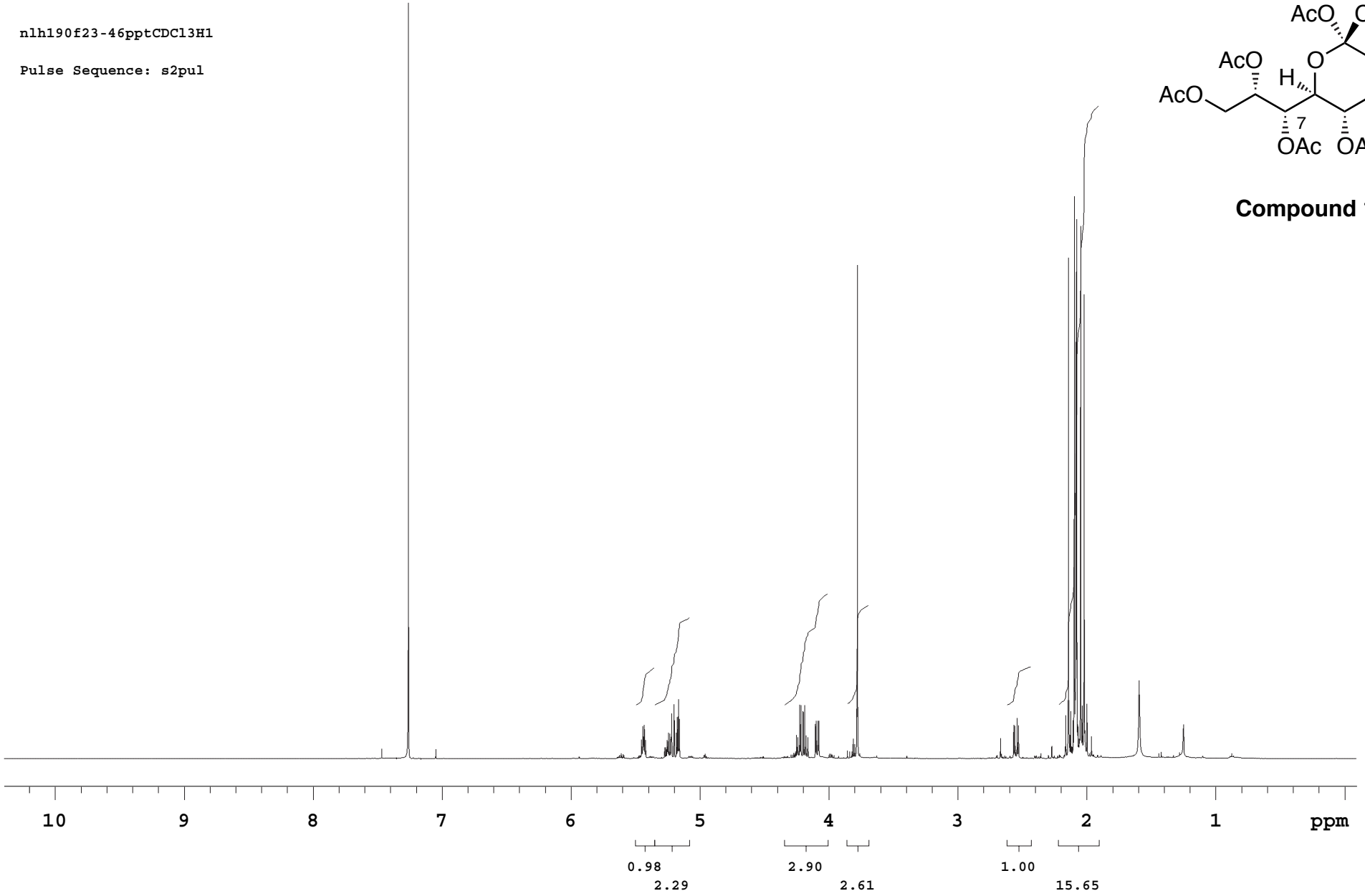
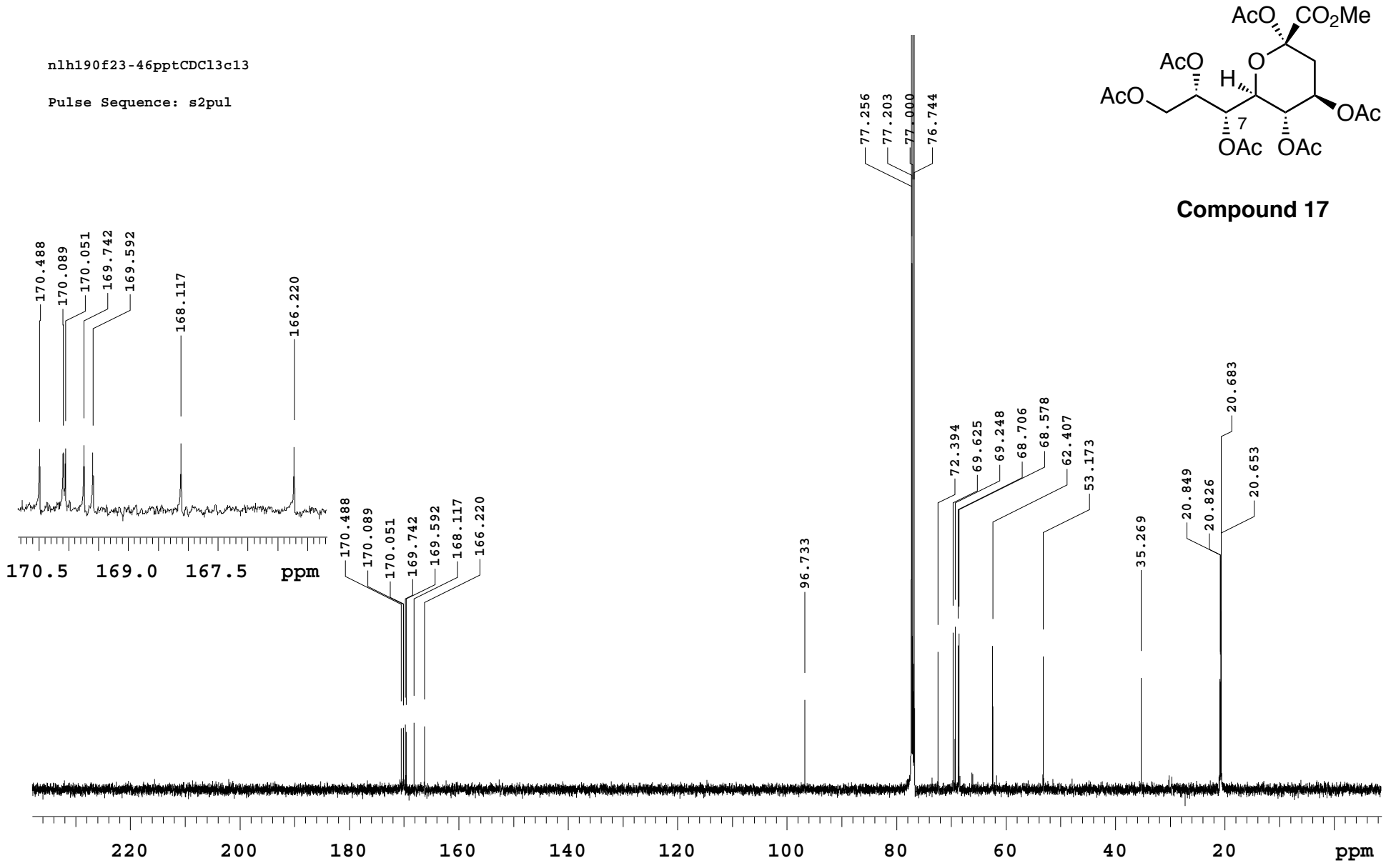
CO2Me
HO
O
H
HO
8
OH
O
O
O
O
Compound 16
49.512
49.339
49.173
49.000
48.827
48.661
48.488
37.214
29.568
74.904
73.512
69.192
68.048
65.926
63.788
61.847
61.696
53.305
98.551
98.468
96.978
25.993
25.956
19.295
19.175
171.808
220
200
180
160
140
120
100
80
60
40
20
ppm


nlh190f23-46pptCDCl3H1
Pulse Sequence: s2pul
10
9
8
7
6
5
4
3
2
1
ppm
0.98
2.29
2.90
2.61
1.00
15.65

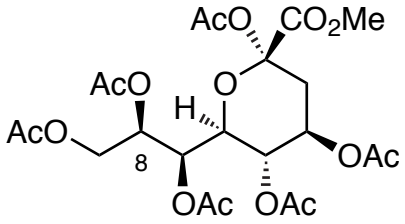
AcO
CO2Me
AcO
O
H
AcO
OAc
7
OAc
OAc

Compound 17

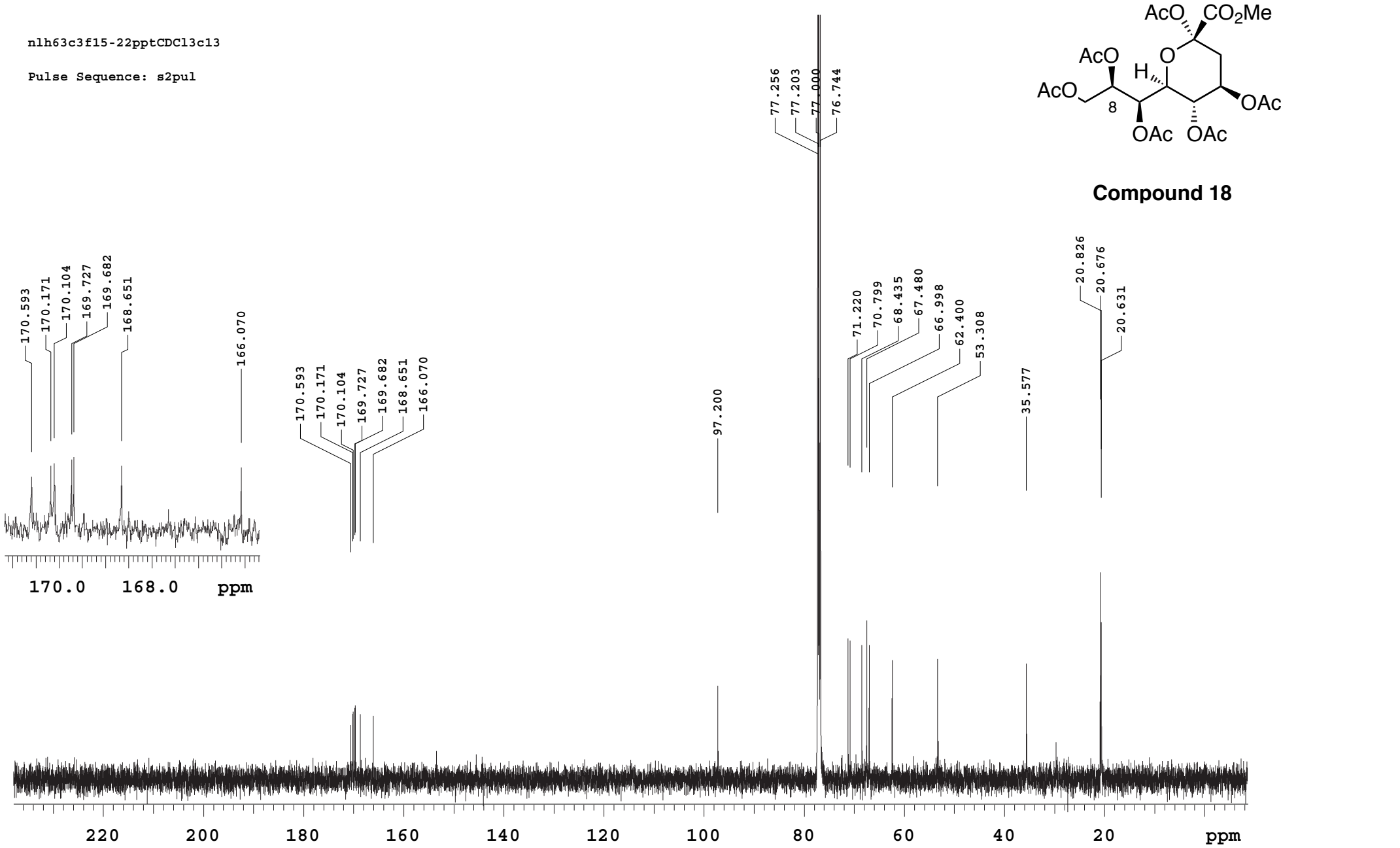

nlh190f23-46pptCDCl3c13
Pulse Sequence: s2pul
AcO
CO2Me
AcO
O
H
AcO
OAc
7
OAc
OAc
Compound 17
77.256
77.203
77.000
76.744
170.488
170.089
170.051
169.742
169.592
168.117
166.220
72.394
69.625
69.248
68.706
68.578
62.407
53.173
96.733
35.269
20.849
20.826
20.683
20.653
170.5
169.0
167.5
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

nlh63c3f15-22pptshimCDCl3H1

Pulse Sequence: s2pul

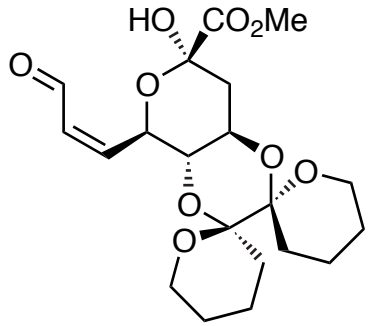


Compound 18

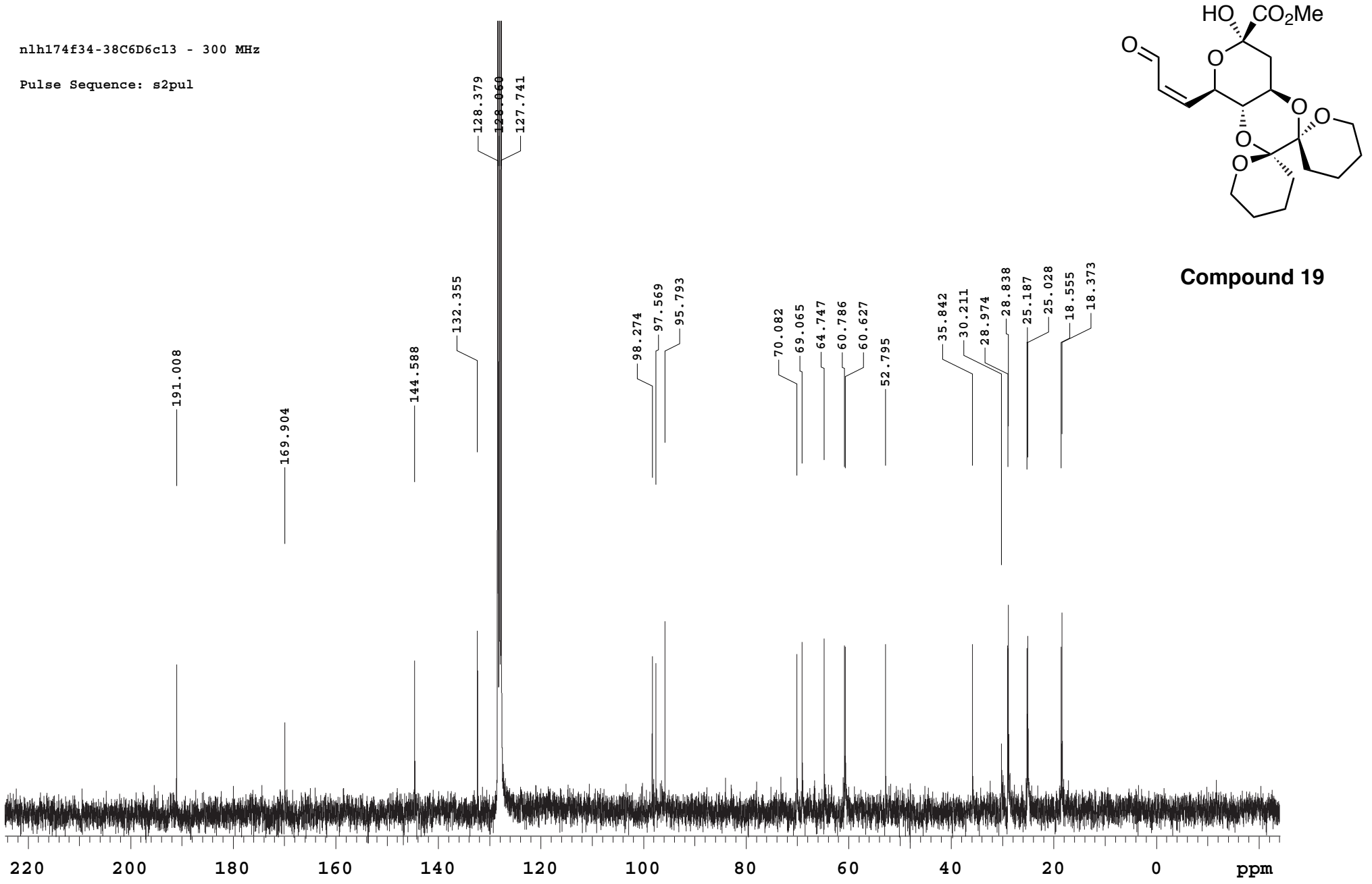

nlh63c3f15-22pptCDCl3c13
Pulse Sequence: s2pul
AcO
CO2Me
AcO
O
H
AcO
8
OAc
OAc
OAc
Compound 18
77.256
77.203
77.000
76.744
170.593
170.171
170.104
169.727
169.682
168.651
166.070
97.200
71.220
70.799
68.435
67.480
66.998
62.400
53.308
35.577
20.826
20.676
20.631
170.0
168.0
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

nlh174f34-48C6D6H1 300 MHz

Pulse Sequence: s2pul

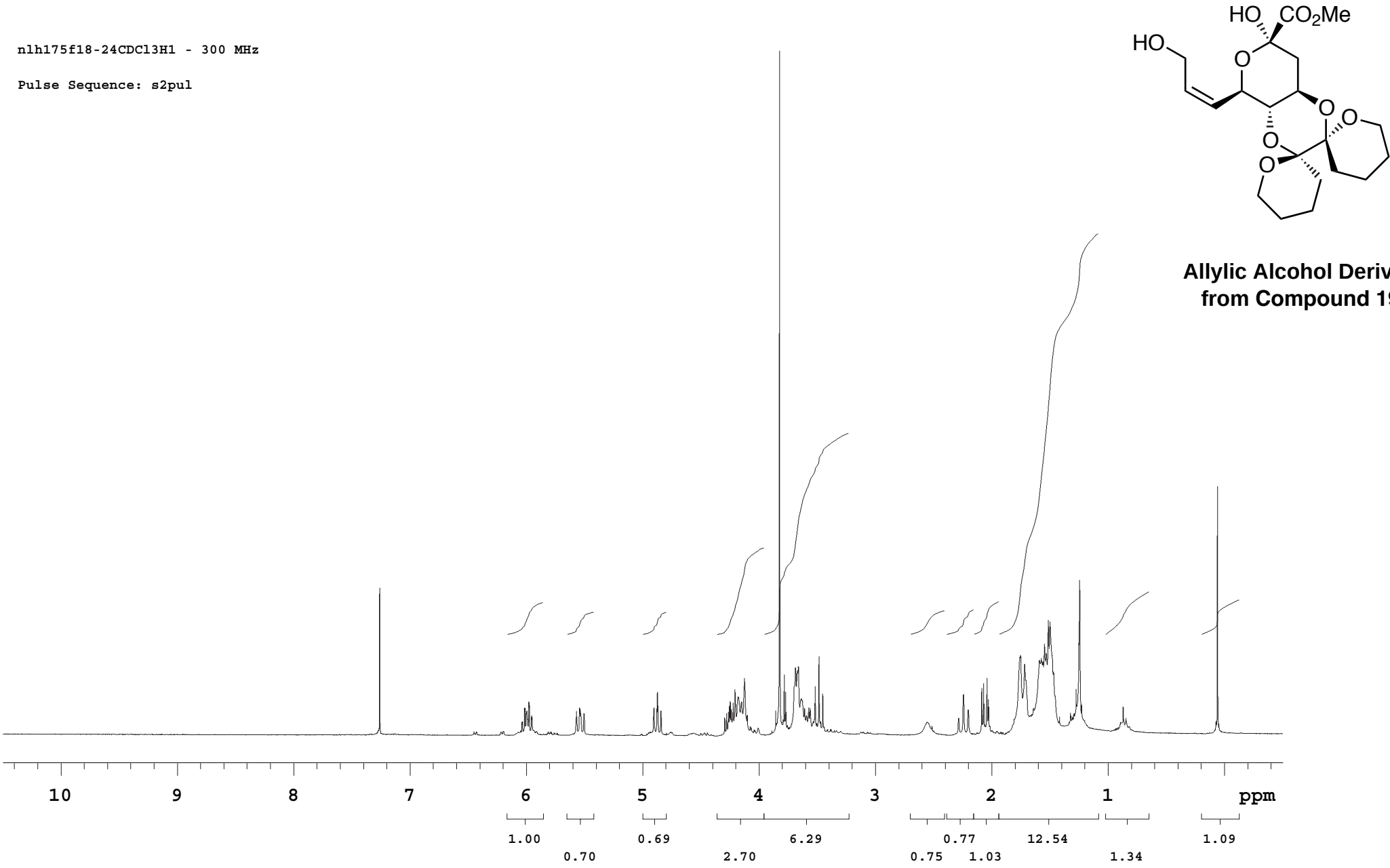


Compound 19


nlh174f34-38C6D6c13 - 300 MHz
Pulse Sequence: s2pul
128.379
128.060
127.741
191.008
169.904
144.588
132.355
98.274
97.569
95.793
70.082
69.065
64.747
60.786
60.627
52.795
35.842
30.211
28.974
28.838
25.187
25.028
18.555
18.373
220
200
180
160
140
120
100
80
60
40
20
0
ppm

HO
CO2Me
O
O
O
O
O
O

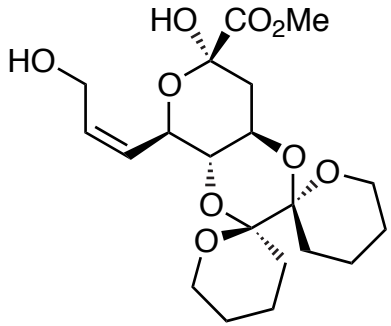
Compound 19



Allylic Alcohol Derived from Compound 19

nlh175f18-24CDCl3c13-15/10/03 300 MHz

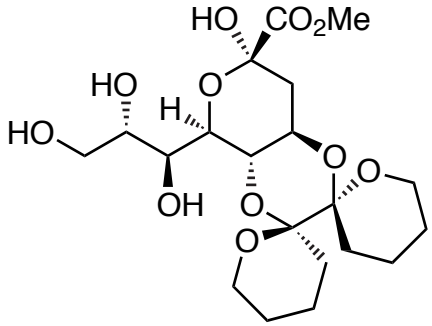
Pulse Sequence: s2pul



Allylic Alcohol Derived from Compound 19

nlh176c2f6c3f11-27CD3ODH1500

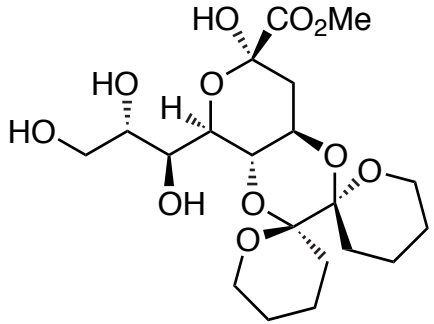
Pulse Sequence: s2pul



Compound 20

nlh176c2c3CD3ODc13

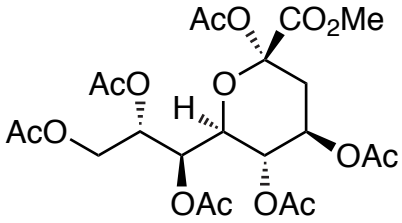
Pulse Sequence: s2pul



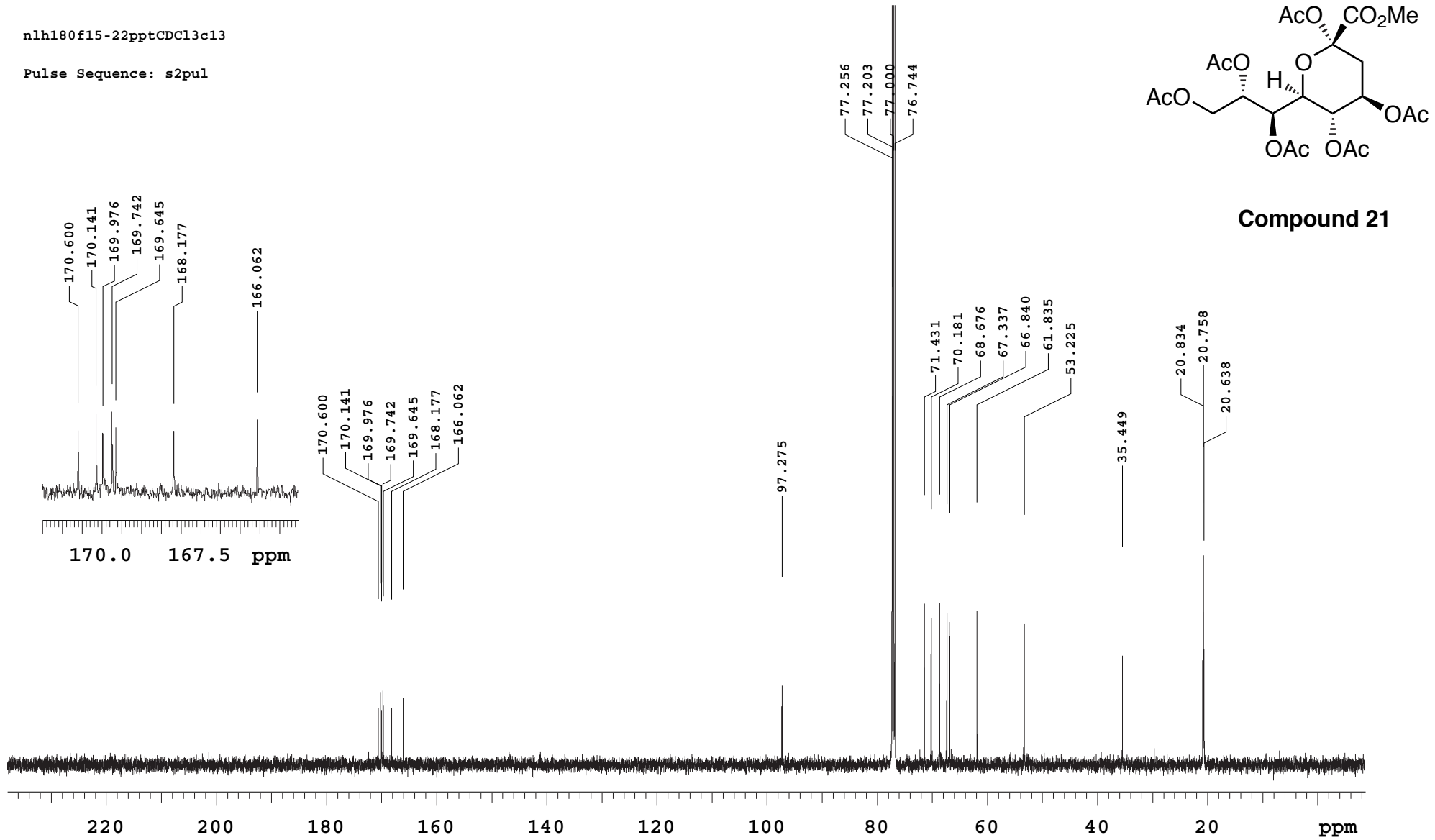
Compound 20

nlh180f15-22pptCDCl3H1

Pulse Sequence: s2pul



Compound 21


nlh180f15-22pptCDCl3c13
Pulse Sequence: s2pul
AcO
CO2Me
AcO
O
H
AcO
OAc
OAc
OAc
Compound 21
77.256
77.203
77.000
76.744
71.431
70.181
68.676
67.337
66.840
61.835
53.225
35.449
20.834
20.758
20.638
97.275
170.600
170.141
169.976
169.742
169.645
168.177
166.062
170.0
167.5
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm