Supplementary Material (ESI) for Chemical Communications

Supporting Information

Glycosyl Tricyclic Orthoesters as Versatile Intermediates for the Preparation of Glycosyl Phosphate Building Blocks

Xinyu Liu, Reiko Wada, Siwarutt Boonyarattanakalin, Bastien Castagner and Peter H. Seeberger*

Laboratory for Organic Chemistry, Swiss Federal Institute of Technology (ETH) Zürich
Wolfgang-Pauli-Str. 10, HCI F315, 8093 Zürich, Switzerland.

General Information

All chemicals used were reagent grade and used as supplied except where noted. All reactions were performed in oven-dried glassware under an inert atmosphere unless noted otherwise. Reagent grade dichloromethane (CH_2Cl_2) was passed through activated neutral alumina column prior to use. Reagent grade N,N-dimethylformamide (DMF) and methanol (MeOH) were dried over activated molecular sieves prior to use. Pyridine, triethylamine and acetonitrile were distilled over CaH_2 prior to use. Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} plates (0.25mm). Compounds were visualized by UV irradiation or dipping the plate in a cerium sulfate-ammonium molybdate (CAM) solution. Flash column chromatography was carried out using forced flow of the indicated solvent on Fluka Kieselgel 60 (230-400 mesh).

^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Varian Mercury 300 (300 MHz), Varian Gemini 300 (300 MHz), Bruker DRX500 (500 MHz) in $CDCl_3$ with chemical shifts referenced to internal standards $CDCl_3$ (7.26 ppm ^{1}H, 77.0 ppm ^{13}C) unless otherwise stated. ^{31}P spectra are reported in δ value relative to H_3PO_4 (0.0 ppm) as an external reference. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; brs, broad singlet for ^{1}H NMR data. High-resolution mass spectral (HRMS) analyses were performed by the MS-service at the Laboratory for Organic Chemistry (LOC) at ETH Zürich. High-resolution MALDI and ESI mass spectra were run on an IonSpec Ultra instrument. IR spectra were recorded on a Perkin-Elmer 1600 FTIR spectrometer. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by the Microanalytical Laboratory of the LOC, ETH Zürich. The

automated synthesis was performed on an ABI 431A peptide synthesizer with a custom-made jacketed glass reaction vessel.

Preparation of Glycosyl Tricylic Orthoester via Acid-Catalyzed Intramolecular Trans-orthoesterification of Glycosyl 1,2-Orthoester

3,4-*O*-Benzyl α-D-mannopyranose 1,2,6-orthobenzoate (5a):

From mannosyl 1,2-orthoester **2a**. To a solution of **2a** [1] (195 mg, 0.65 mmol) in CH_3CN (4 mL) in the presence of activated 4Å MS (220 mg) was added CSA (35 mg, 0.15 mmol) at room temperature. The mixture was stirred for 12 h when additional amount of CSA (15 mg) was added. Further stirred for 12 h, the reaction was quenched by the addition of Et_3N (0.15 mL). Filtration through a pad of Celite, followed by removal of the solvents gave the crude tricyclic orthoester. This crude material was dissolved in DMF (4.5 mL), added BnBr (0.24 mL, 2.0 mmol) and NaH (48 mg, 2.0 mmol) at 0 °C. The mixture was gradually warmed up to room temperature during 12 h. Excess NaH was quenched by the addition of MeOH. Typical aqueous workup, followed by silica gel column chromatography gave **5a** (244 mg, 85%) as a white solid.

From mannosyl 1,2-orthoester **2b**. To a solution of **2b** [2] (440 mg, 1.34 mmol) in CH_3CN (8 mL) in the presence of activated 4Å MS (220 mg) was added CSA (35 mg, 0.15 mmol) at room temperature. The mixture was stirred for 12 h before quenched with Et_3N (0.13 mL). Filtration through a pad of Celite, followed by removal of the solvents gave the crude tricyclic orthoester. This crude material was dissolved in DMF (7.5 mL), added BnBr (0.5 mL, 4.20 mmol) and NaH (90 mg, 3.9 mmol) at 0 °C. The mixture was gradually warmed up to room temperature and the reaction completed after 3 h. Excess NaH was quenched by the addition of MeOH. Typical aqueous workup, followed by silica gel column chromatography gave **5a** (578 mg, 95%) as a white solid. R_f 0.40 (Hexanes/EtOAc = 4 : 1); $[\alpha]_D^{r.t.}$= +2.1 (*c* = 1.2, $CHCl_3$); m.p.=110–111 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74 (dd, *J* =12.9, 3.6 Hz, 1H), 3.77 (dd, *J* = 7.5, 2.4 Hz, 1H), 4.18 (d, *J* = 12.9 Hz, 1H), 4.21 (dd, *J* =7.5, 1.3 Hz, 1H), 4.24 (dd, *J* = 3.6, 1.3 Hz 1H), 4.64 (dd, *J* =7.5, 1.3 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.84 (app s, 2H), 5.86 (d, *J* = 5.7 Hz, 1H), 7.25-7.44 (m, 13H), 7.62-7.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.6,

72.4, 72.6,73.2, 74.5, 77.4, 79.3, 99.7, 121.9, 126.0, 127.8, 127.9, 128.0, 128.4, 128.5, 129.3, 137.1, 138.0; Anal. Calcd for $C_{27}H_{26}O_6$; C, 72.63; H, 5.87; Found: C, 72.48; H, 5.86.

3,4-*O*-Benzyl α-D-mannopyranose 1,2,6-orthoacetate (5b):

To a solution of **2d** [3] (500 mg, 1.91 mmol) in CH_3CN (10 mL) in the presence of activated 4Å MS (300 mg) was added CSA (44 mg, 0.19 mmol) at room temperature. The mixture was stirred for 12 h before quenched with Et_3N (0.20 mL). Filtration through a pad of Celite, followed by removal of the solvents gave the crude tricyclic orthoester. This crude material was dissolved in DMF (10 mL), added BnBr (0.68 mL, 5.70 mmol) and NaH (137 mg, 5.7 mmol, 60% in minerial oil) at 0 °C. The mixture was gradually warmed up to room temperature and the reaction completed after 3 h. Excess NaH was quenched by the addition of MeOH. Typical aqueous workup, followed by silica gel column chromatography gave **5b** (700 mg, 95%) as a colorless syrup. R_f 0.28 (Hexanes/EtOAc = 4 : 1); $[\alpha]_D^{r.t.}$= –8.1 (*c* = 7.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (s, 3H), 3.52 (dd, *J* =13.0, 3.3 Hz, 1H), 3.66 (dd, *J* = 7.5, 2.4 Hz, 1H), 3.98 (app d, *J* = 13.0 Hz, 1H), 4.04 (dd, *J* =7.5, 1.2 Hz, 1H), 4.06 (dd, *J* = 3.3, 1.2 Hz 1H), 4.45 (dd, *J* = 6.0, 2.4 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.76 (d, *J* = 12.0 Hz, 1H), 4.80 (app s, 2H), 5.68 (d, *J* = 6.0 Hz, 1H), 7.25-7.42 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 69.8, 72.4, 73.1, 73.8, 77.2, 79.1, 99.4, 122.9, 127.7, 127.8, 127.9, 128.3, 128.4, 137.9, 138.0; HRMS-MALDI (*m/z*): $[M+Na]^+$ calcd for $C_{22}H_{24}O_6$, 407.1471; Found: 407.1459.

3-*O*-Benzyl α-D-xylopyranose 1,2,4-orthoacetate (5c):

To a solution of **2e** [4] (348 mg, 1.50 mmol) in CH_3CN (40 mL) was added CSA (42 mg, 0.18 mmol) at room temperature. The mixture was stirred for 12 h before quenched with Et_3N (0.15 mL). Filtration through a pad of Celite, followed by removal of the solvents gave the crude tricyclic orthoester. Two-third portion of this crude material was dissolved in DMF (3 mL), added BnBr (0.13 mL, 1.1 mmol) and NaH (32 mg, 1.3 mmol, 60% in mineral oil) at 0 °C. The mixture was gradually warmed up to room temperature and the reaction completed after 5 h. Excess NaH was quenched by the addition of MeOH. Typical aqueous workup, followed by silica gel column chromatography gave **5c** (194 mg, 73%) as a syrup. R_f 0.53 (CH_2Cl_2/EtOAc = 1 : 1). $[\alpha]_D^{r.t.}$= +44.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63 (s, 3H), 3.91–3.96 (m,

1H), 4.12–4.19 (m, 3H), 4.35–4.39 (m, 1H), 4.58–4.71 (m, 2H), 5.75 (d, *J* = 4.8 Hz, 1 H), 7.28–7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3, 65.5, 69.9, 71.4, 72.2, 72.3, 97.9, 118.2, 127.7 (2x), 128.1, 128.5 (2x), 137.4; HRMS-MALDI (*m/z*): $[M+Na]^+$ Calcd for $C_{14}H_{16}O_5$, 287.0889; Found: 287.0880.

3-*O*-Benzyl α-D-xylopyranose 1,2,4-orthobenzoate (5d):

To a solution of **2f** [5] (2.65 g, 9.89 mmol) in CH_3CN (50 mL) was added silica gel (10 g, Fluka Kieselgel 50), and the mixture was stirred at room temperature for 12 h. The reaction mixture was filtered through a short pad of Celite and the solvent was removed in vacuo. Purification by silica gel chromatography gave tricyclic orthoester α-D-xylopyranose 1,2,4-orthobenzoate **(**1.33 g, 60%) as a colorless solid. R_f 0.31 (CH_2Cl_2/EtOAc = 1 : 1). $[\alpha]_D^{r.t.}$= +71.5 (*c* = 1.0, $CHCl_3$); m.p. = 145–147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (d, *J* = 10.2 Hz, 1H), 4.24-4.29 (m, 1H), 4.28 (dd, *J* = 12.0, 4.5 Hz, 1H), 4.44 (app d, *J* = 12.0 Hz, 1H), 4.49 (td, *J* = 4.5, 2.0 Hz, 1H), 4.57 (app dt, *J* = 4.5, 2.0 Hz, 1H), 5.96 (d, *J* = 4.8 Hz, 1H), 7.36-7.44 (m, 3H), 7.66-7.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 63.8, 65.9, 73.1, 74.5, 98.0, 117.7, 125.9, 128.1, 129.7, 133.5; Anal. Calcd for $C_{12}H_{12}O_5$; C, 61.02; H, 5.12; Found: C, 60.98; H, 5.05.

To a solution of α-D-xylopyranose 1,2,4-orthobenzoate (777 mg, 3.29 mmol) in DMF (12 mL) was added BnBr (0.78 mL, 6.58 mmol) and NaH (158 mg, 6.58 mmol, 60% in mineral oil) at 0 °C. The mixture was allowed to warm up to room temperature gradually and stirred overnight. Excess NaH was quenched by the addition of MeOH. Typical aqueous workup, followed by silica gel column chromatography gave **5d** (1.11 g, quant.) as a white solid. R_f 0.49 (Hexanes/EtOAc = 4 : 1). $[\alpha]_D^{rt}$ = +43.8 (*c* = 1.4, $CHCl_3$); m.p. = 54–55 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10-4.12 (m, 1H), 4.27 (dd, *J* = 12.0, 6.9 Hz, 1H), 4.34 (dd, *J* = 12.0, 1.0 Hz, 1H), 4.38 (td, *J* = 4.2, 2.4 Hz, 1H), 4.58 (dt, *J* = 4.8, 2.0 Hz, 1H), 4.67 (d, *J* = 12.1 Hz, 1H), 4.74 (d, *J* = 12.1 Hz, 1H), 5.94 (d, *J* = 5.1 Hz, 1H), 7.33-7.42 (m, 8H), 7.65-7.68 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 65.7, 70.0, 72.2, 72.4, 72.7, 98.1, 117.3, 127.8, 128.1, 128.2, 128.6, 129.8, 133.7, 137.4; Anal. Calcd for $C_{19}H_{18}O_5$; C, 69.93; H, 5.56; Found: C, 69.66; H, 5.57.

3,6-Di-*O*-benzyl α-D-glucopyranose 1,2,4-orthoacetate (5e):

To a solution of **2g** [6] (89.9 mg, 0.381 mmol) in acetonitrile (1.9 mL) was added 4Å AW 300 MS, and the mixture was stirred at 40 °C for 14 h, then at 60 °C for 3 h. The reaction mixture was

filtered through a short pad of Celite and the solvent was removed in vacuo. In a separate flask, NaH (116 mg, 60% in mineral oil) was washed with hexane twice and DMF (0.45 mL) was added. To this suspension of NaH in DMF was added the crude tricylic orthoester mixture in DMF (1 mL) at 0°C, and BnBr (345 μL, 2.9 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 13 h, and H_2O was added to quench the reaction. After extraction with diethyl ether, combined organic layer was washed with brine, and dried over magnesium sulfate. Filtration, evaporation, and purification by silica gel chromatography gave **5e** as a colorless syrup (73.0 mg, 50%). $[\alpha]_D^{rt}$ = +21.1 (*c* = 0.82, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63 (s, 3H), 3.72 (dd, *J* = 9.6, 7.8 Hz, 1H), 3.81 (dd, *J* = 9.6, 6.6 Hz, 1H), 3.97 (dt, *J* = 4.5 Hz, 1H), 4.26 (dd, *J* = 4.5, 2.1 Hz, 1H), 4.40 (dt, *J* = 4.8, 2.1 Hz, 1H), 4.48 (d, *J* = 12.3 Hz, 1H), 4.53 (brs, 2H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.65 (t, *J* = 6.9 Hz, 1H), 5.80 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4, 69.9, 71.1, 71.4, 72.0, 72.3, 73.2, 75.8, 97.8, 118.8, 127.5, 127.6, 127.7, 128.0, 128.3, 128.5, 137.2, 137.9; HRMS-MALDI (*m/z*): $[M+Na]^+$ Calcd for $C_{22}H_{24}O_6$, 407.1471; Found: 407.1467.

α-D-Glucopyranose 1,2,4-orthoacetate

α-D-Glucopyranose 1,2,4-orthoacetate can be purified with silica gel chromatography, before being subjected to benzylation conditions. Spectral data are as follows.

$[\alpha]_D^{r.t.}$= +110 (*c* = 0.5, MeOH); m.p. = 119-120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (s, 3H), 3.86 (dd, *J* = 12.0, 3.3 Hz, 1H), 4.02 (dd, *J* = 12.0, 4.2 Hz, 1H), 4.17 (d, *J* = 3.3 Hz, 1H), 4.28 (dd, *J* = 4.5, 2.1 Hz, 1H), 4.38 (dt, *J* = 4.8, 2.1 Hz, 1H), 4.59 (t, *J* = 3.6 Hz, 1H), 5.85 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3, 62.3, 63.8, 74.2, 75.1, 76.7, 97.6, 119.0; HRMS-ESI (*m/z*): $[M]^-$ calcd for $C_8H_{11}O_6$, 203.0556; Found: 203.0559.

Opening of Glycosyl Tricyclic Orthoester with Dibutyl Phosphate: General Procedure

To a solution of suitably protected glycosyl tricyclic orthoester (1.0 equiv) in either CH_2Cl_2 or CH_3CN was added freshly activated 4Å molecular sieves. The mixture was stirred for 15 min stirring at room temperature, before added dibutyl phosphate (6 equiv.) in one portion. After completion of the reaction (TLC analysis), the reaction was cooled to 0°C and triethylamine (10 equiv) was added. The solution was warmed to room temperature and filtered off through a pad

of Et_3N-deactivated silica gel. The resulting mixture was purified by flash silica column chromatography.

Dibutyl-(2-*O*-benzoyl-3,4-di-*O*-benzyl-α-D-mannopyranosyl) phosphate (6a):

General procedure with mannosyl tricyclic orthoester **5a** (51 mg, 0.11 mmol), dibutyl phosphate (136 μL, 0.68 mmol), 4Å MS (30 mg), CH_2Cl_2 (1.5 mL), room temperature, 24 h, gave **6a** (62 mg, 83%) as a colorless syrup. R_f 0.32 (Hexanes/EtOAc = 1:1); $[\alpha]_D^{r.t.}$ = +0.44 (*c* = 2.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92-0.98 (m, 6H), 1.35-1.49 (m, 4H), 1.63-1.73 (m, 4H), 2.16 (t, *J* = 6.9 Hz, 1H), 3.81-3.92 (m, 2H), 3.94-4.16 (m, 7H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.68 (d, *J* = 10.8 Hz, 1H), 4.80 (d, *J* = 11.7 Hz, 1H), 4.92 (d, *J* = 10.8 Hz, 1H), 5.42 (app t, *J* = 2.4 Hz, 1H), 5.77 (dd, *J* = 6.3, 2.0 Hz, 1H), 7.24-7.37 (m, 10H), 7.45-7.51 (m, 2H), 7.58-7.64 (m, 1H), 8.06-8.09 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 18.8, 32.3, 61.6, 68.1, 68.6, 71.9, 73.3, 73.9, 75.4, 77.3, 95.6, 127.7, 127.8, 127.9, 128.0, 128.3, 128.4, 128.5, 129.4, 129.9, 133.4, 137.6, 137.9, 165.1; ^{31}P NMR (121MHz, $CDCl_3$): δ -2.19. HRMS-MALDI (*m/z*): $[M+Na]^+$ Calcd for $C_{35}H_{45}O_{10}P$, 679.2643; Found: 679.2639.

Dibutyl-(2-*O*-acetyl-3,4-di-*O*-benzyl-α-D-mannopyranosyl) phosphate (6b):

General procedure with microwave irradiation at 120 °C, using mannose tricyclic orthoester **5b** (41 mg, 0.11 mmol), 4Å MS (50 mg), dibutyl phosphate (0.38 mL, 0.64 mmol), CH_3CN (4 mL), 5 min, gave **6b** as a colorless oil (38.2 mg, 60%), R_f 0.18 (Hexanes/EtOAc = 1:1); $[\alpha]_D^{r.t.}$ = +22.7 (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88–0.99 (m, 6H), 1.32–1.48 (m, 4H), 1.59–1.72 (m, 4H), 2.01 (brs, 1H), 2.15 (s, 3H), 3.73–3.91 (m, 4H), 3.95–4.13 (m, 5H), 4.48–4.77 (m, 3H), 4.88–4.95 (m, 1H), 5.42 (dd, *J* = 3.0, 2.4 Hz, 1H), 5.62 (dd, *J* = 6.2, 1.8 Hz, 1H), 7.27–7.38 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 18.7, 21.0, 32.2, 32.3, 61.6, 68.0, 68.1, 68.3, 72.0, 73.4, 73.7, 75.3, 77.1, 95.5, 95.6, 127.7 (2x), 127.9 (2x), 128.0 (2x), 128.3 (2x), 128.4 (2x), 137.5, 137.9, 169.7; ^{31}P NMR (121MHz, $CDCl_3$): δ –2.55; IR (film) ν_{max} 3372, 2961, 2875, 1748, 1456, 1368, 1233, 1029, 956 cm^{-1}; HRMS-MALDI (*m/z*): $[M+Na]^+$ Calcd for $C_{30}H_{43}O_{10}P$, 617.2486; Found: 617.2484.

Dibutyl-(2-*O*-acetyl-3-*O*-benzyl-α-D-xylopyranosyl) phosphate (6c):

General procedure with xylose tricyclic orthoester **5c** (51 mg, 0.19 mmol), dibutyl phosphate (0.23 mL, 1.16 mmol), 4Å MS (30 mg), CH_2Cl_2 (1 mL), room temperature, 24 h, gave **6c** as a colorless syrup (69 mg, 65%). R_f 0.22 (Hexanes/EtOAc = 1:1); $[\alpha]_D^{r.t.}$ = +63.2 (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89–1.00 (m, 6H), 1.32–1.49 (m, 4H), 1.60–1.74 (m, 4H), 2.05 (s, 3H), 2.32 (brs, 1H), 3.68–3.88 (m, 4H), 3.97–4.17 (m, 4H), 4.67–4.90 (m, 3H), 5.73 (dd, *J* = 6.6, 3.3 Hz, 1H), 7.23–7.41 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 13.5, 18.5, 18.5, 20.7, 32.0, 32.1, 63.0, 67.7, 67.8, 69.1, 72.2, 72.3, 74.9, 79.1, 94.5, 94.5, 127.6 (2x), 127.9, 128.5 (2x), 138.1, 169.9; ^{31}P NMR (121MHz, $CDCl_3$): δ –2.07; HRMS-MALDI (*m/z*): $[M+Na]^+$ Calcd for $C_{22}H_{35}O_9$, 497.1911; Found: 497.1918.

Dibutyl-(2-*O*-benzoyl-3-*O*-benzyl-α-D-xylopyranosyl) phosphate (6d):

General procedure with xylosyl tricyclic orthoester **5d** (56 mg, 0.17 mmol), dibutyl phosphate (204 μL, 1.03 mmol), 4Å MS (30 mg), CH_2Cl_2 (2.0 mL), room temperature, 24 h gave **6d** (82 mg, 90%) as a colorless solid. R_f 0.51 (Hexanes/EtOAc = 1:2); m.p. = 103–104 °C; $[\alpha]_D^{r.t.}$ = +80.7 (*c* = 2.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79–0.88 (m, 6H), 1.20–1.32 (m, 4H), 1.42–1.56 (m, 4H), 2.69 (s, 1H), 3.80–4.00 (m, 8H), 4.73 (d, *J* = 11.7 Hz, 1H), 4.85 (d, *J* = 11.7 Hz, 1H), 5.11 (app dt, *J* = 9.6, 3.3 Hz, 1H), 5.86 (dd, *J* = 6.9, 3.3 Hz, 1H), 7.23–7.27 (m, 5H), 7.42–7.46 (m, 2H), 7.56–7.61 (m, 1H), 8.03–8.06 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 18.6, 32.2, 63.2, 68.0, 69.6, 73.1, 75.4, 79.5, 94.9, 128.1, 128.2, 128.7, 129.5, 130.0, 133.7, 138.1, 165.9; ^{31}P NMR (121MHz, $CDCl_3$): δ –1.83; Anal. Calcd for $C_{27}H_{37}O_9P$; C, 60.44; H, 6.95; Found: C, 60.55; H, 6.75.

Dibutyl-(2-*O*-acetyl-3,4-di-*O*-benzyl-β-D-glucopyranosyl) phosphate (6e):

General procedure with glucosyl tricyclic orthoester **5e** (46 mg, 0.12 mmol), dibutyl phosphate (142 μL, 0.72 mmol), 4Å MS (23 mg), CH_3CN (1.2 mL), room temperature, 5 h gave **6e** (69 mg, 90%) as a colorless syrup. $[\alpha]_D^{r.t.}$ = +61.0 (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84-0.93 (m, 6H), 1.25-1.42 (m, 4H), 1.53-1.64 (m, 4H), 1.97 (s, 3H), 3.51-3.59 (m, 2H), 3.63-3.79 (m, 3H), 3.89-4.06 (m, 4H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.69 (d, *J* = 12.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 5.03 (app t, *J* = 9.0 Hz, 1H), 5.18 (app t, *J* = 7.2 Hz, 1H), 7.24-7.41 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 18.7, 20.9, 32.1, 68.0, 69.6, 71.3, 72.7, 73.6, 74.6, 75.0, 81.8, 96.5, 127.5, 127.7, 128.3, 128.4, 137.5, 138.0, 169.3; ^{31}P NMR (121MHz,

$CDCl_3$): δ -2.59; HRMS-MALDI (*m/z*): $[M+Na]^+$ Calcd for $C_{30}H_{43}O_{10}P$, 617.2492; Found: 617.2500.

Dibutyl 2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-(9-fluorenylmethoxycarbonyl)-α-D-manno pyranosyl phosphate (4a):

Following the general procedure for the selective opening of glycosyl tricyclic orthoester, mannosyl orthoester **5a** (131 mg, 0.29 mmol) was treated with dibutyl phosphate (291 μL, 1.47 mmol) in CH_2Cl_2 (3.0 mL) at room temperature for 24 h. To this mixture at 0 °C was added pyridine (0.47 mL, 5.8 mmol) and FmocCl (150 mg, 0.58 mmol). The mixture was stirred for 2 h before subjected to typical aqueous workup. The crude material was purified by silica gel column chromatography to give the target compound **4a** (236 mg, 85%) as a syrup. R_f 0.55 (Hexanes/EtOAc = 2 : 1). $[\alpha]_D^{rt}$ = +6.4 (*c* = 1.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92-0.98 (m, 6H), 1.36-1.50 (m, 4H), 1.65-1.73 (m, 4H), 4.00-4.21 (m, 7H), 4.27 (t, *J* = 7.5 Hz, 1H), 4.37-4.48 (m, 4H), 4.62 (d, *J* = 11.1 Hz, 1H), 4.64 (d, *J* = 10.8 Hz, 1H), 4.84 (d, *J* = 11.1 Hz, 1H), 4.94 (d, *J* = 10.8 Hz, 1H), 5.72 (app t, *J* = 2.4 Hz, 1H), 5.80 (dd, *J* = 6.3, 1.8 Hz, 1H), 7.26-7.45 (m, 15H), 7.52-7.65 (m, 3H), 7.78 (d, *J* = 7.2 Hz, 2H), 8.13 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 18.9, 32.4, 46.8, 66.4, 68.1, 68.3, 70.1, 71.5, 71.8, 73.1, 75.4, 77.3, 95.4, 120.0, 125.1, 127.2, 127.8-128.4, 129.4, 129.9, 133.4, 137.4, 137.6, 141.2, 143.1, 143.3, 155.0, 165.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ –2.23; Anal. Calcd for $C_{50}H_{55}O_{12}P$; C, 68.33; H, 6.31; Found: C, 68.23; H, 6.21.

Multigram synthesis of building block 5a from D-mannose (Scheme 3):

A solution of benzoyl chloride (193 mL, 1.665 mol) in pyridine (600 mL) was cooled to 0 °C in an ice-water bath. D-mannose (50 g, 0.278 mol) was added to the cooled reaction solution in small portions over a period of 30 min. The reaction mixture was allowed to warm to room temperature and the solution was kept stirring at room temperature for 12 h. The solvent was removed *in vacuo* and the residual material was extracted by EtOAc and 1 N HCl (aq.). The combined organic layer was washed with saturated $NaHCO_3$ (aq.) and concentrated *in vacuo*. The

crude product was recrystalized in hot EtOH to yield the perbenzoylated D-mannose as a white solid.

Perbenzoylated D-mannopyranoside (65.5 g, 99.32 mmol) was treated with acetic anhydride (14 mL, 150 mmol) and a solution of HBr in AcOH (100 mL of 33% solution, 579 mmol). The reaction was stirred at room temperature for 24 h, then poured in ice-cold water in a 500 mL separatory funnel, and extracted by CH_2Cl_2. The combined organic layer was concentrated *in vacuo* at room temperature to afford 1-bromo-2,3,4,6-*O*-benzoyl-α-D-mannopyranoside. The product obtained from this step was directly treated with 2,6-lutidine (46.27 mL, 397 mmol) and allyl alcohol (135 mL, 1986 mmol). The reaction was stirred at room temperature for 20 h and concentrated *in vacuo*. The crude product was co-evaporated with toluene (3x), dried under high vacuum for 12 h, dissolved in CH_2Cl_2, washed with water, and concentrated *in vacuo* to obtain a semi-solid product which was used in the next step without further purifications.

The following reactions were carried out in 15 to 50 mmol scales. The protected bicyclic orthoester crude product (ca 50 mmol) was dissolved in 1:1 THF/MeOH and treated with a freshly prepared solution of NaOMe in MeOH (metal Na in MeOH, 0.05 eq.) at reflux temperature for 8 h. The reaction mixture was concentrated *in vacuo*, re-dissoloved in CH_2Cl_2 and filtered to a silica gel plug to remove methyl benzoate. Without further purifications the triol-bicyclic orthoester crude product was dissolved in CH_3CN and treated with camphor sulfonic acid (0.15 eq.) and 4Å molecular sieves (1x the mass of the crude product) at room temperature for 24 h. The reaction mixture was neutralized by addition of Et_3N and filtered to remove 4Å molecular sieves and concentrated *in vacuo*. The tricyclic orthoester crude product was dissolved in DMF and cooled to 0 °C before BnBr (3 eq.) and NaH (3 eq.) were added to the solution consecutively. The reaction mixture was allowed to warm to room temperature and kept stirring at room temperature for 12 h. The reaction mixture was extracted with Et_2O and water and washed with brine. The combined organic layer was concentrated *in vacuo*, and recrystalized in EtOAc and hexanes to obtain the title compound as a white solid (70% - 80%).

Automated Modules:

Module A: The resin is washed 6 times with THF for 15 sec. each.

Module B: The resin is washed with DCM for 15 sec. followed by hexanes. Reapeated 6 times.

Module C: The resin is washed 6 times with DCM for 15 sec. each.

Module D: The building block (5 eq., 0.125 mmol in 1.0 mL DCM) is delivered to the reaction vessel containing the resin. The mixture is allowed to cool for 3 min. (with vortex for 30 sec. followed by standing for 30 sec.). TMSOTf (5 eq., 0.125 mmol, in 1.0 mL DCM) is added to the reaction vessel with vortex in two portions, with 2 min. interval. The reaction mixture is then left for 45 min. (with vortex for 30 sec. followed by standing for 30 sec.). After that time, the solution is drained and the resin is washed once with DCM.

Module E: The resin is submitted to piperidine (20% v/v in DMF, 2 mL) for 5 min. (with vortex for 30 sec., followed by standing for 30 sec.). After that time, the solution is drained and the resin is submitted to the same conditions twice.

Module F: The resin is washed 6 times with acetic acid (0.2 M in DCM) for 15 sec. each.

Automated synthesis of α(1-6) hexamannoside 7:

The octenediol resin (104 mg, 26 μmol) was loaded in the reaction vessel and the modules A, B, and C were performed at room temperature. The reaction vessel was cooled to -15ºC and modules D and C were performed. The reaction vessel was warmed to room temperature and modules A, C, E, C, F, A, B, and C were performed to complete the first cycle. This cycle was executed six times to furnish the resin-bound hexasaccharide. The resin was washed manually with alternating DCM and Methanol and dried under high vacuum overnight. The resin was swelled in 2 mL DCM and treated with 2 mg of Grubb's first generation catalyst. The flask was put under an atmosphere of ethylene and gently stirred overnight. The resin was washed six times with 2 mL of DCM. The washing solution was concentrated and loaded on a silica gel column. Elution with 20-30% ethyl acetate/hexanes furnished the desired hexamannoside **7** (57.5 mg, 80%). $[\alpha]_D^{rt}$ = +44.8 (*c* = 0.83, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18-8.07 (m, 12H), 7.55-7.47 (m, 18H), 7.35-7.09 (m, 60H), 5.85-5.72 (m, 6H), 5.65-5.64 (m, 1H), 5.11-4.70 (m, 19H), 4.58 (t, *J*=10.5 Hz, 2H), 4.46-4.32 (m, 9H), 4.13-3.38 (m, 34H), 2.18-2.06 (m, 2H), 1.69-1.57 (m, 2H), ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 165.6, 165.6, 165.5, 138.6, 138.5, 138.4, 138.0, 137.9, 137.7, 137.6, 137.6, 137.6, 133.3, 130.0, 129.9, 128.7, 128.6, 128.5, 128.4, 128.2, 128.2,

128.2, 128.1, 128.1, 127.7, 127.7, 127.4, 127.4, 127.3, 127.2, 127.2, 115.1, 98.5, 98.5, 98.4, 98.3, 98.2, 98.0, 78.7, 78.4, 78.3, 78.2, 78.0, 77.7, 77.3, 75.2, 75.1, 75.1, 74.2, 74.0, 73.8, 73.7, 72.1, 71.7, 71.4, 71.2, 71.0, 70.8, 69.1, 68.6, 68.4, 67.4, 66.1, 65.8, 65.5, 61.9, 30.3, 28.6; HRMS-MALDI (*m/z*): $[M+Na]^+$ Calcd for $C_{167}H_{166}O_{37}$, 2786.100; Found: 2786.092.

Reference:

[1] Hölemann, A.; Stocker, B. L.; Seeberger, P. H. *J. Org. Chem.* **2006**, *71*, 8071-8088.

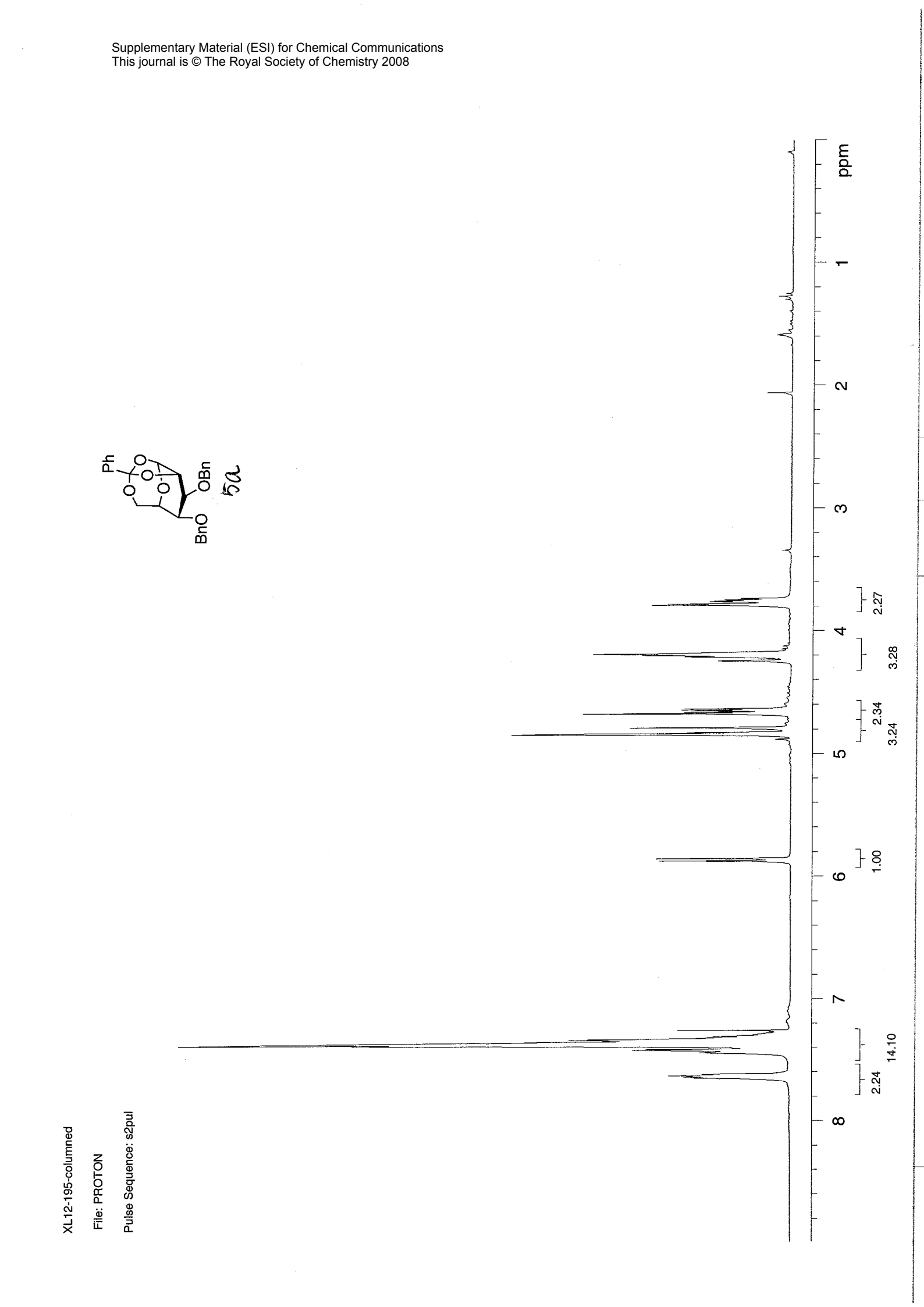
[2] Kwon, Y. U.; Soucy, R. L.; Snyder, D. A.; Seeberger, P. H. *Chem. Eur. J.* **2005**, *11*, 2493-2504.

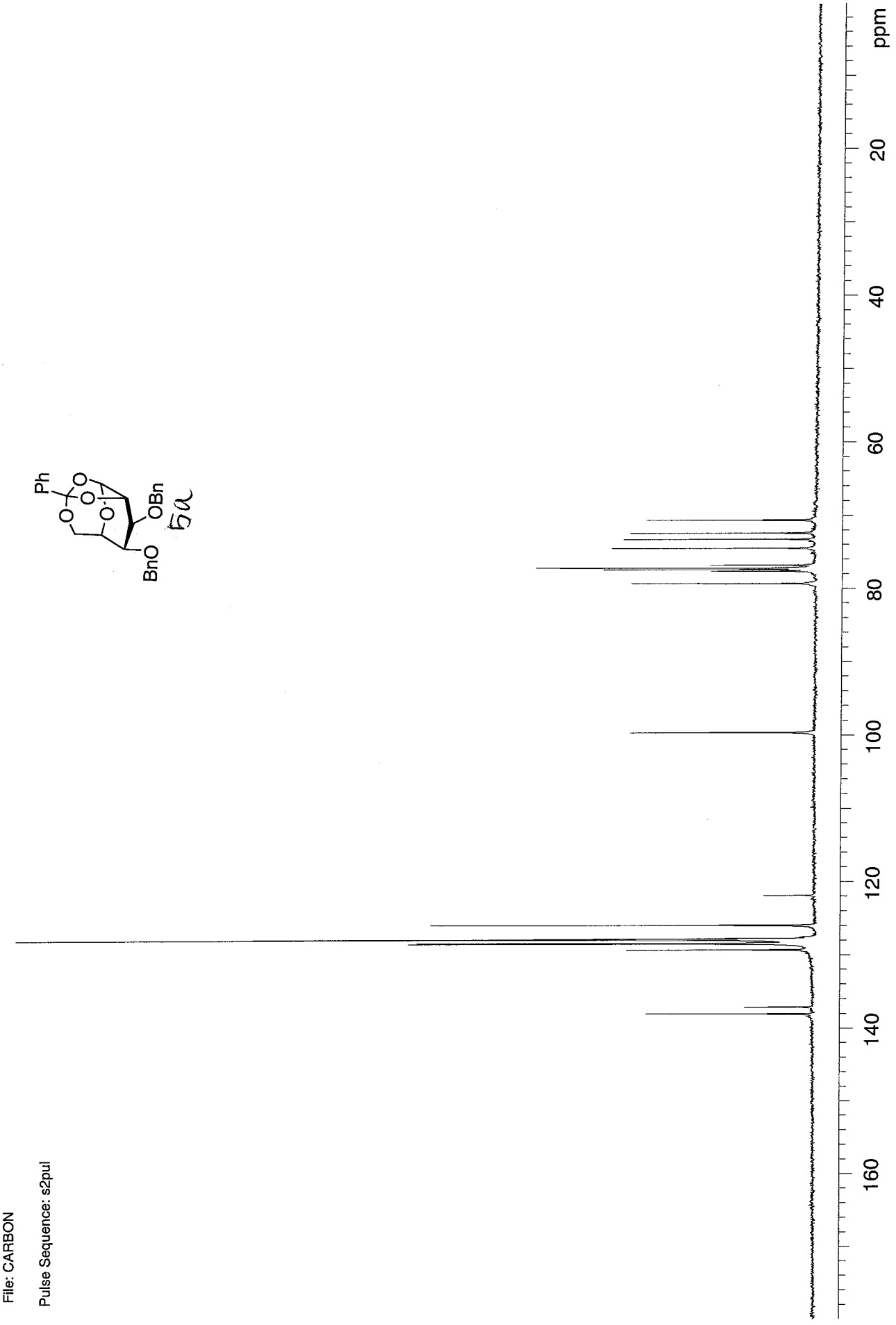
[3] (a) Paulsen, H.; Helpap, B. *Carbohydr. Res.* **1991**, *216*, 289-313; (b) Lindhorst, T. K. *J. Carbohydr. Chem.* **1997**, *16*, 237-243.

[4] Bochkov, A. F.; Voznyi, Y. V.; Chernetskii, V. N.; Dashunin, V. M.; Rodionov, A. V. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1975**, 420-423.

[5] Bochkov, A. F.; Obruchnikov, I. V.; Kochetkov, N. K. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1971**, 1291-1295.

[6] (a) Bakinovskii, L. V.; Bairamova, N. E.; Tsvetkov, Yu. E.; Betaneli, V. I. *Carbohydr. Res.* **1981**, *98*, 181-93; (b) Du, Y.; Zhang, M.; Kong, F. *J. Chem. Soc., Perkin Trans 1* **2001**, 2289-2293.

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60
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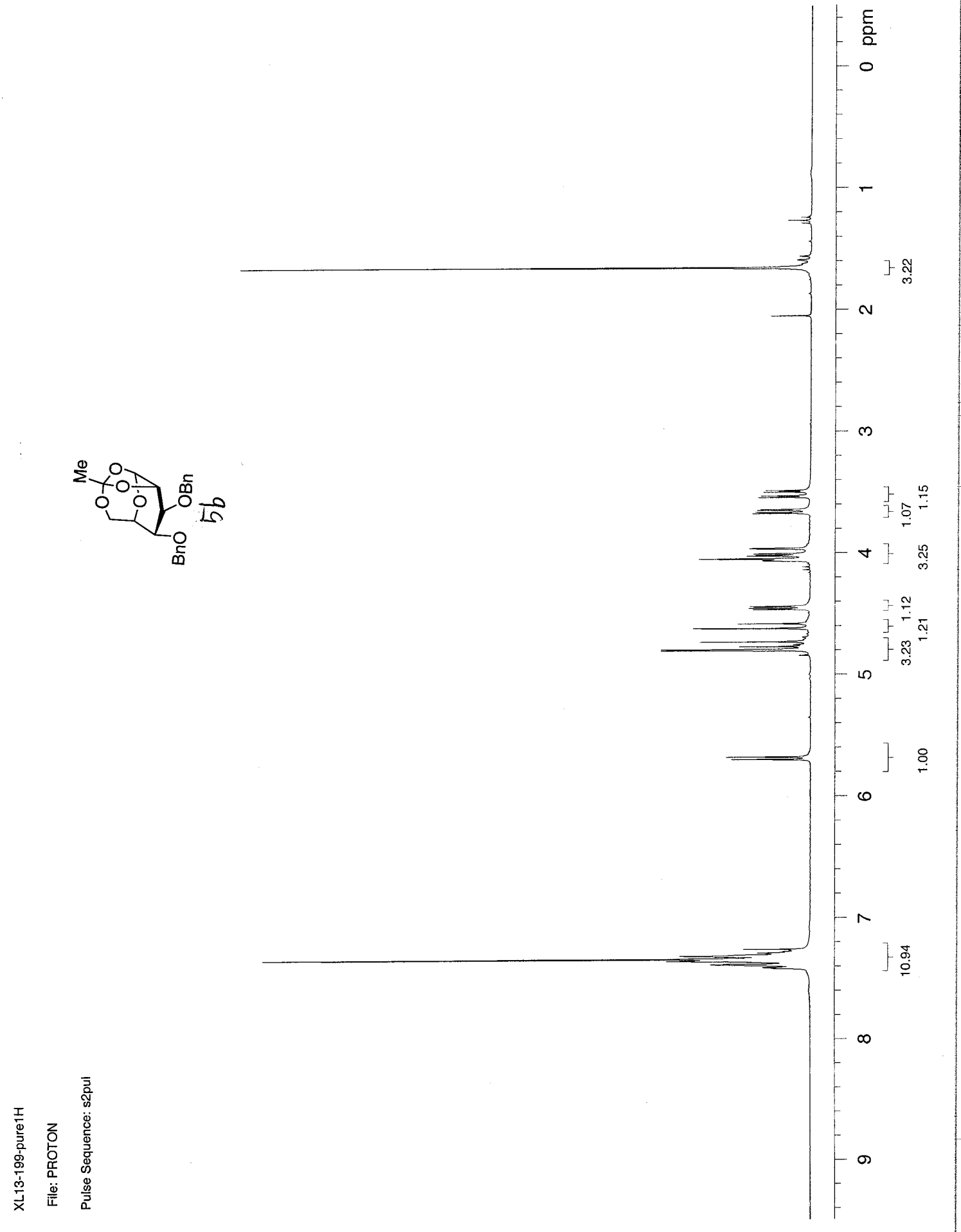

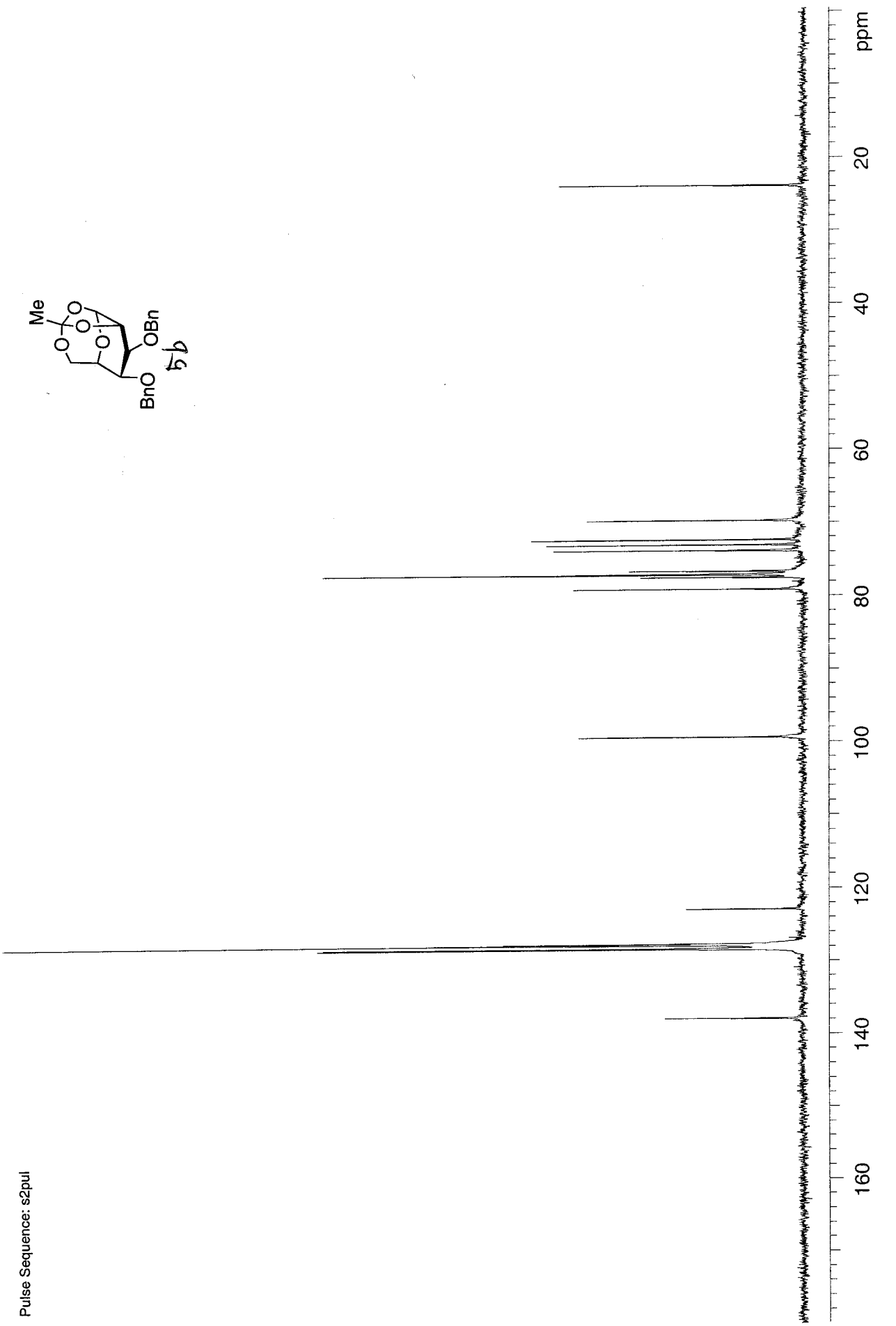

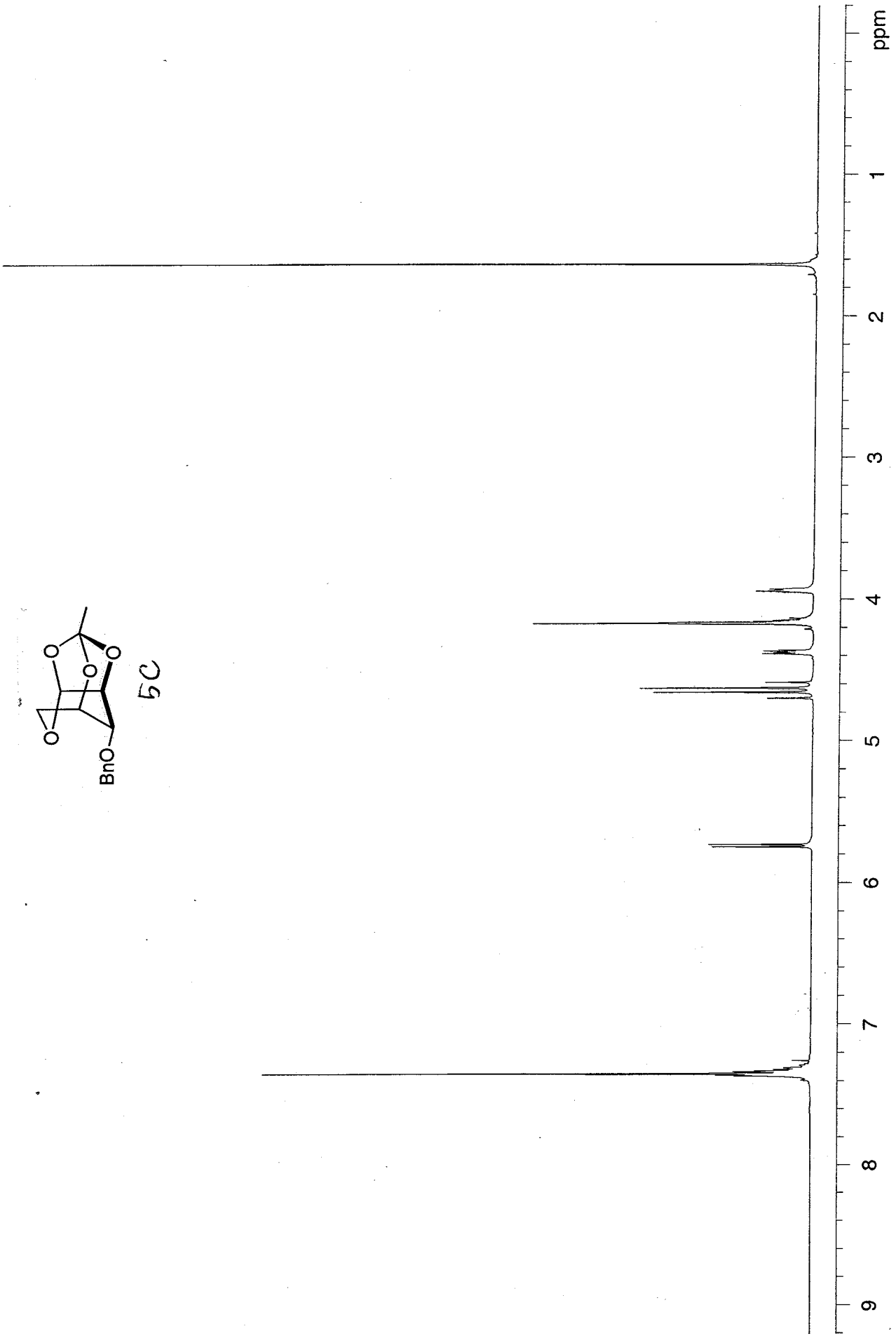

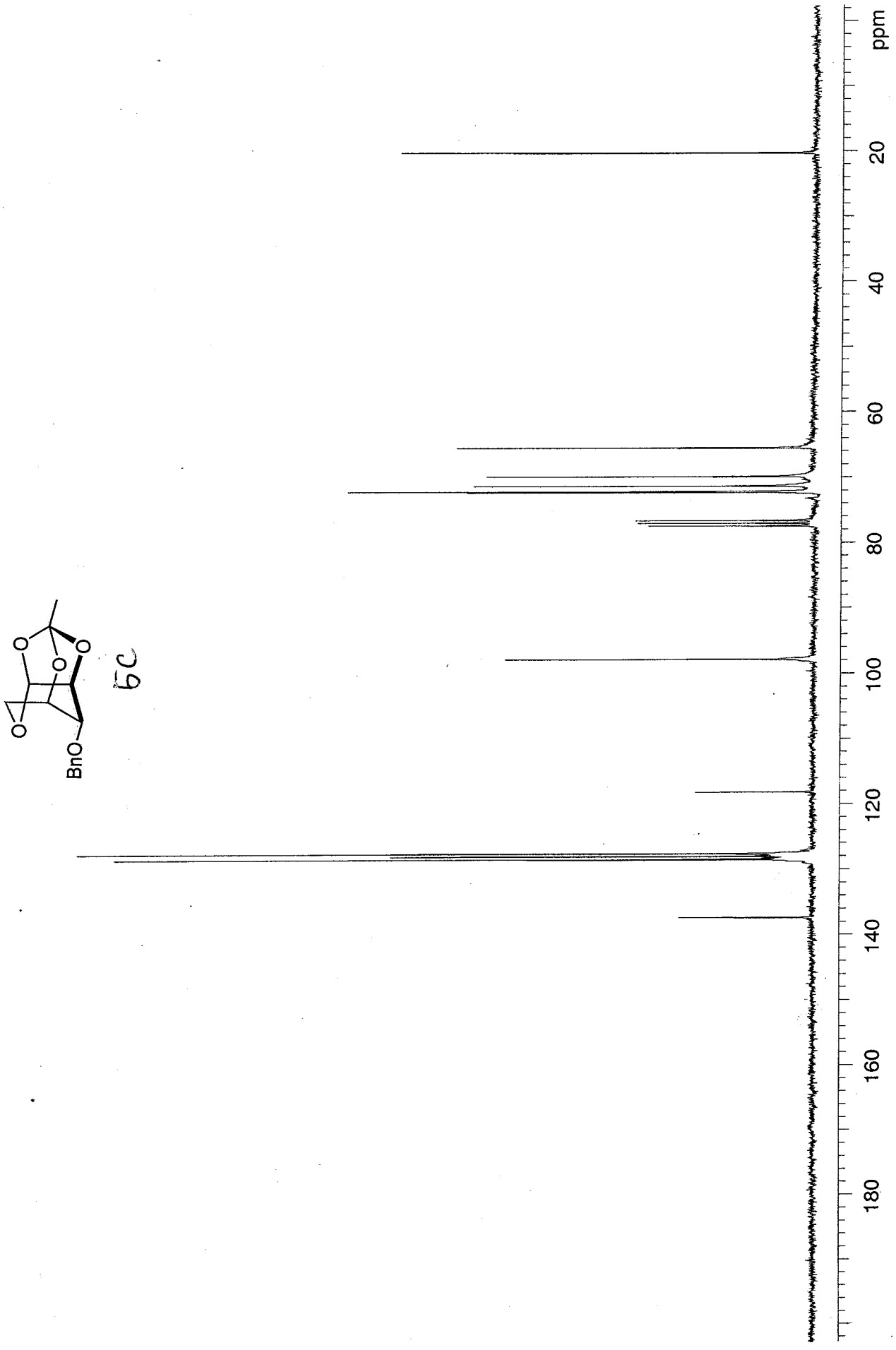

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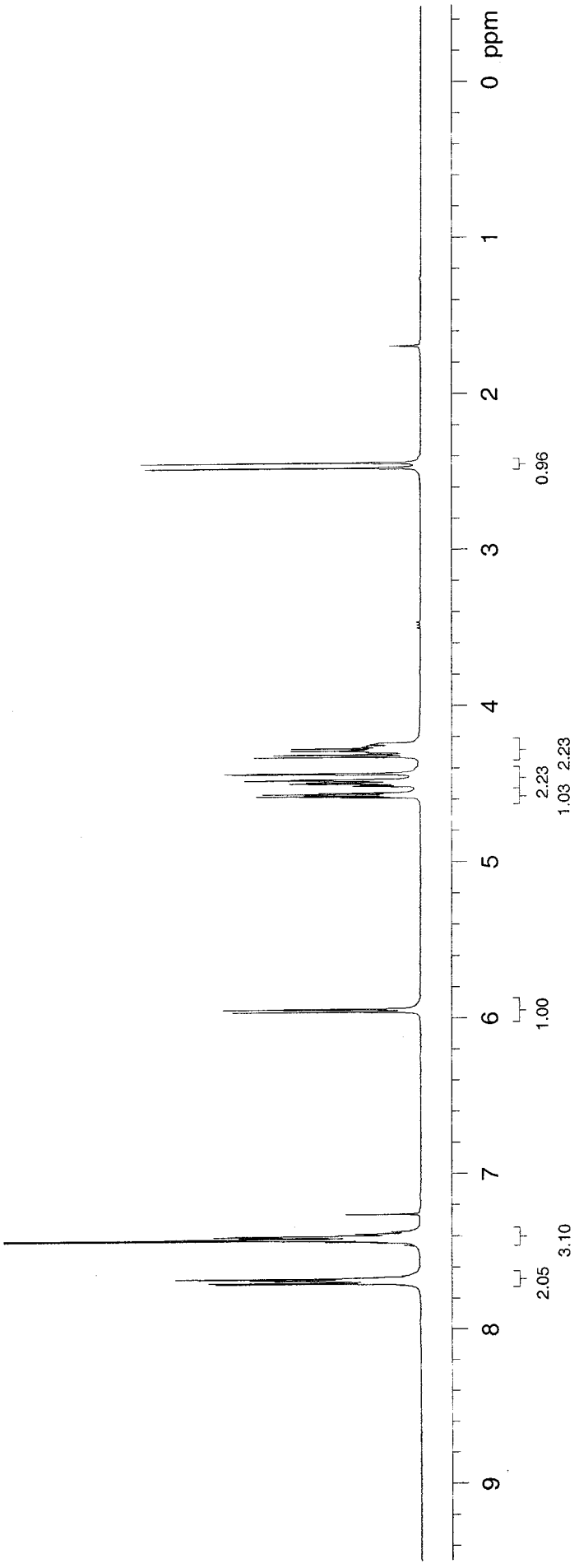

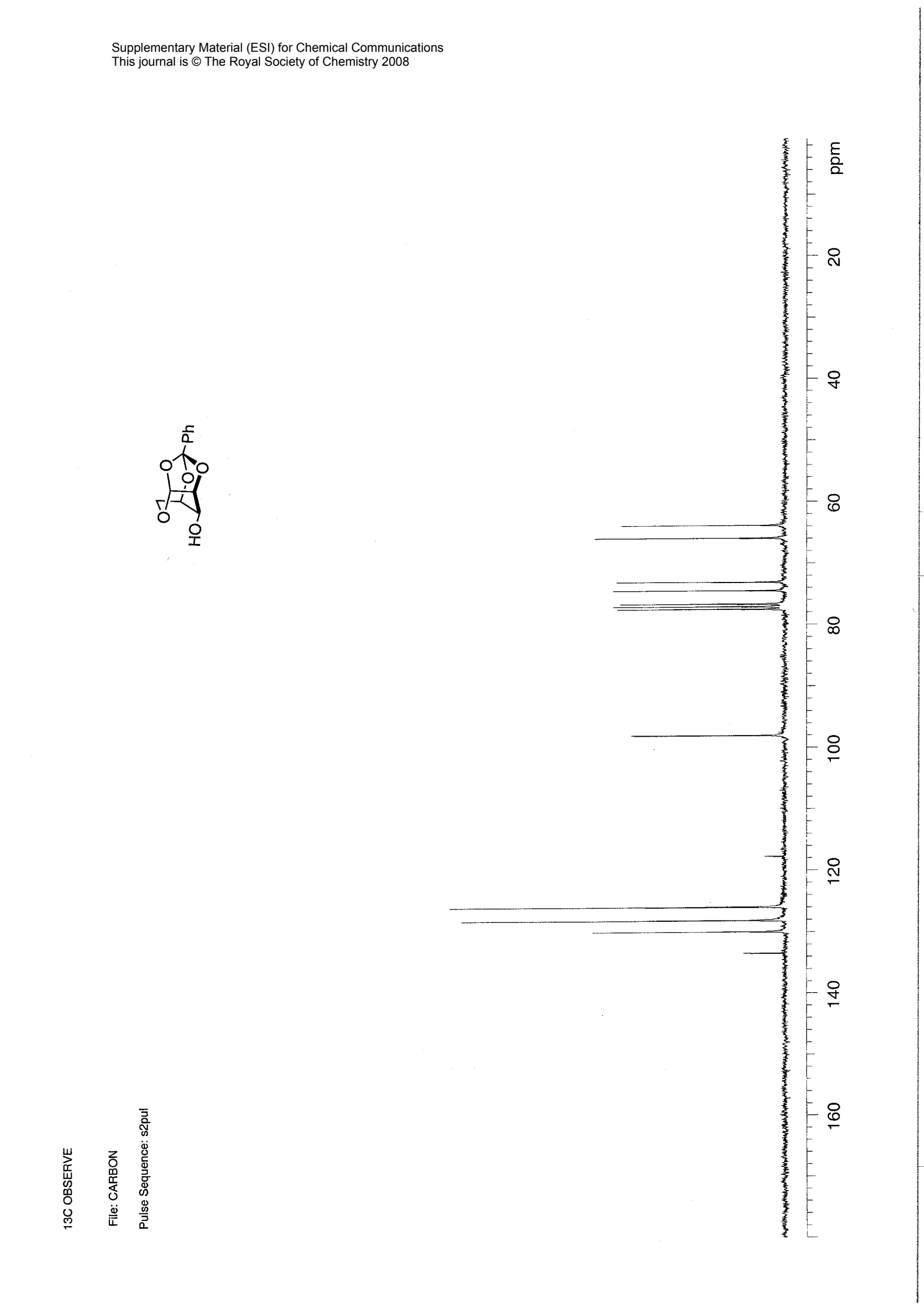

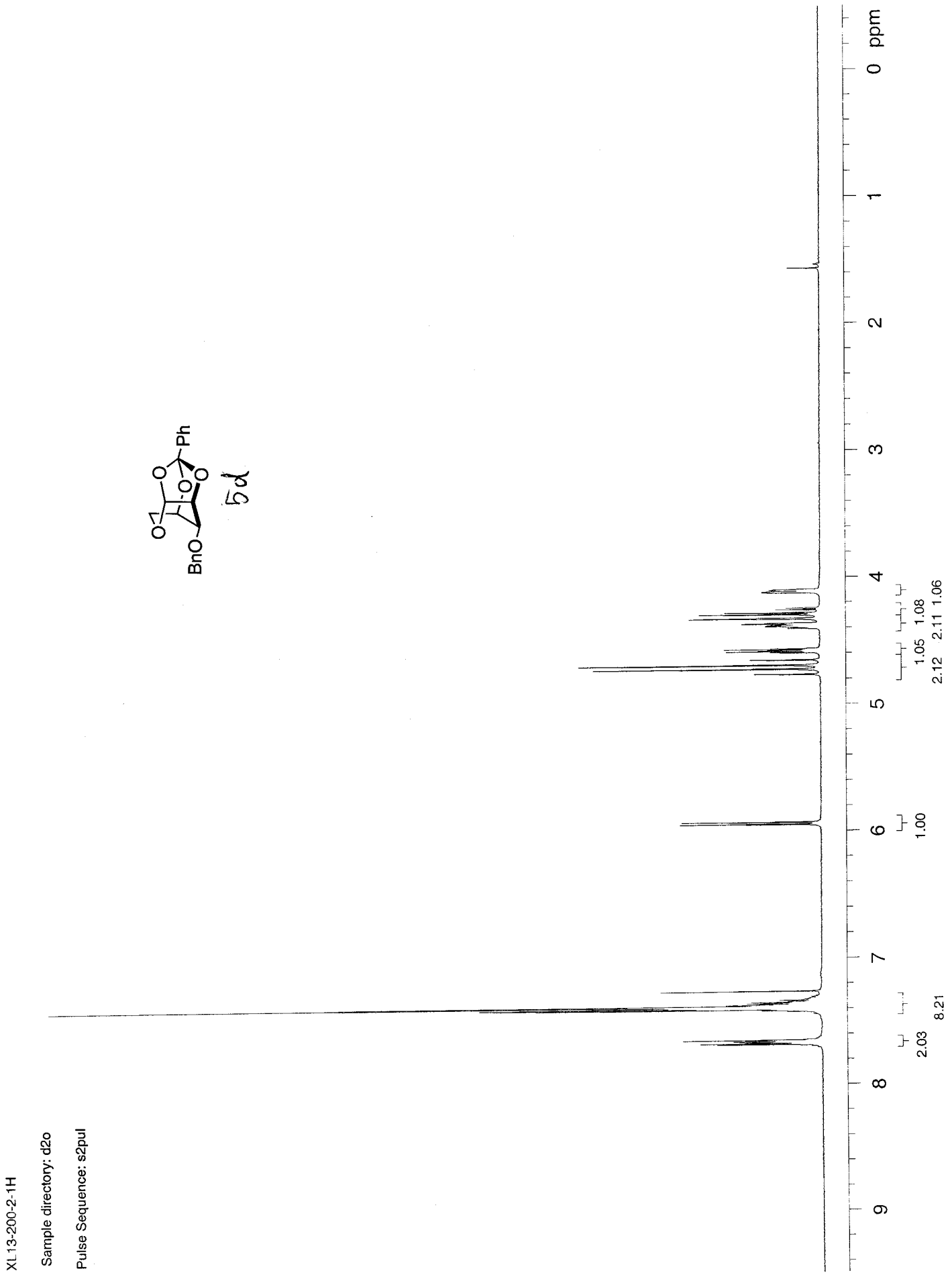
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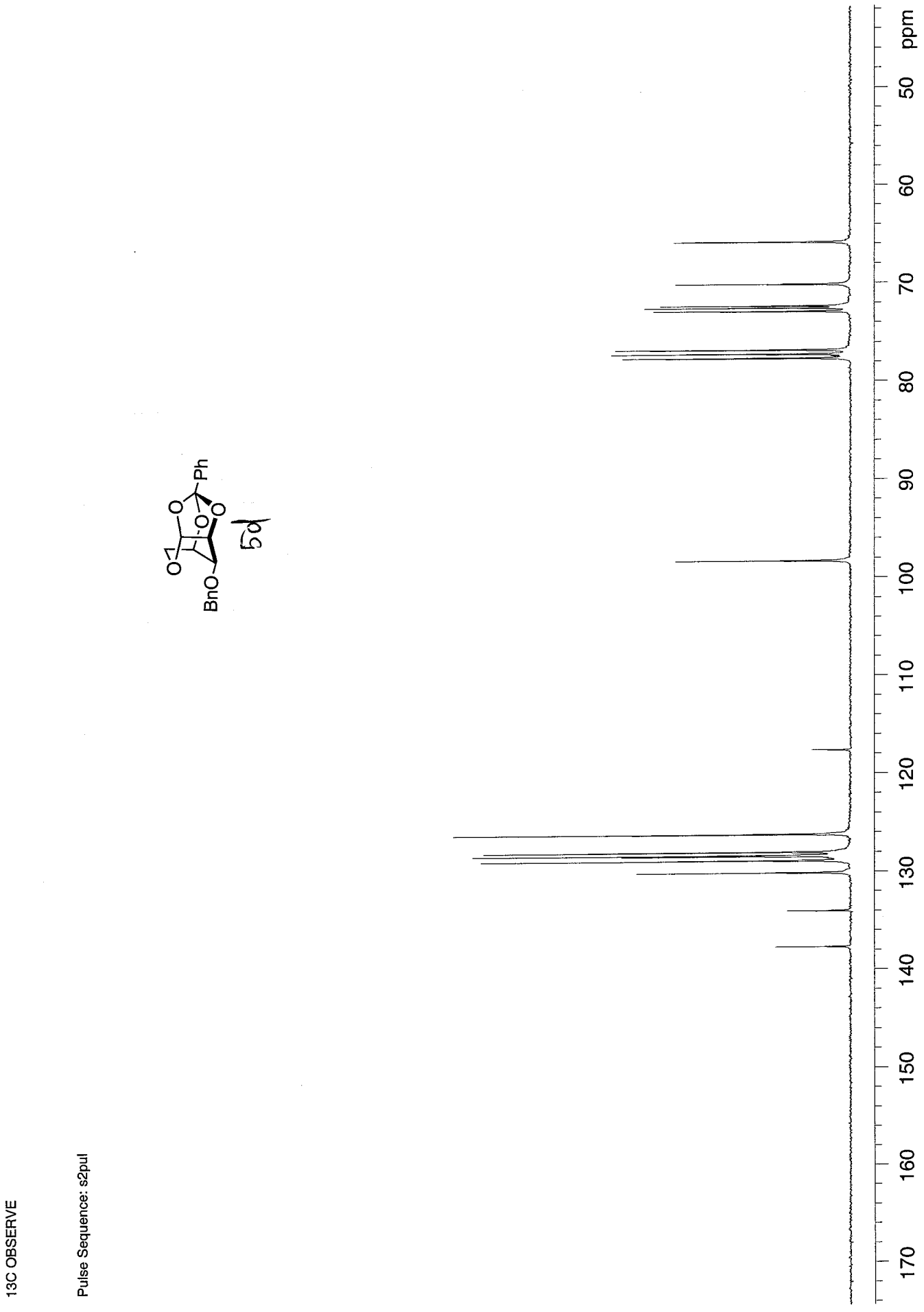
1.05
1.08
2.12
2.11
1.06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100
90
80
70
60
50
ppm

LOC ETHZ NMR Mercury-vx 300MHz Nr.5 09/05/06 15:34:35 USER:preiko GROUP:seeber SAMPLE:rw050906_5

STANDARD 1H OBSERVE

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Ambient temperature
User: preiko
Mercury-300BB "gem5oc"

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8 repetitions
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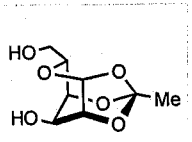
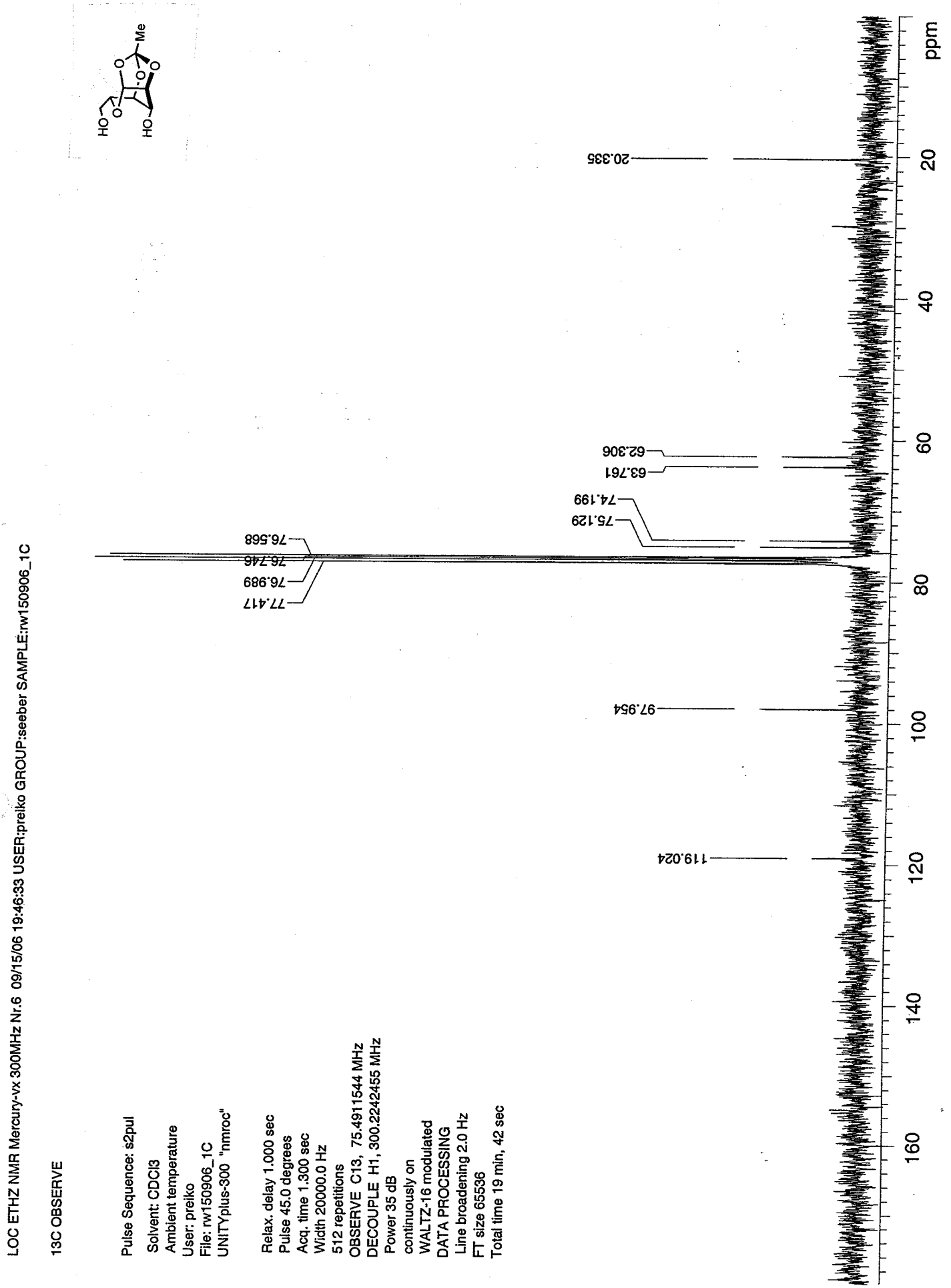
FT size 32768
Total time 0 min, 25 sec

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Solvent: CDCl3
Ambient temperature
User: preiko
File: rw150906_1C
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Pulse 45.0 degrees
Acq. time 1.300 sec
Width 20000.0 Hz
512 repetitions
OBSERVE C13, 75.4911544 MHz
DECOUPLE H1, 300.2242455 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 19 min, 42 sec
HO
HO
Me
O
O
O
O
O
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74.199
75.129
76.568
76.746
76.989
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ppm
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40
60
80
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120
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STANDARD 1H OBSERVE

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Mercury-300BB "gem5oc"

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Pulse 56.2 degrees
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DATA PROCESSING
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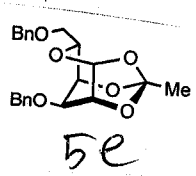
Total time 0 min, 25 sec



5e

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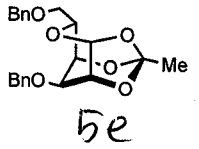
13C OBSERVE



5e

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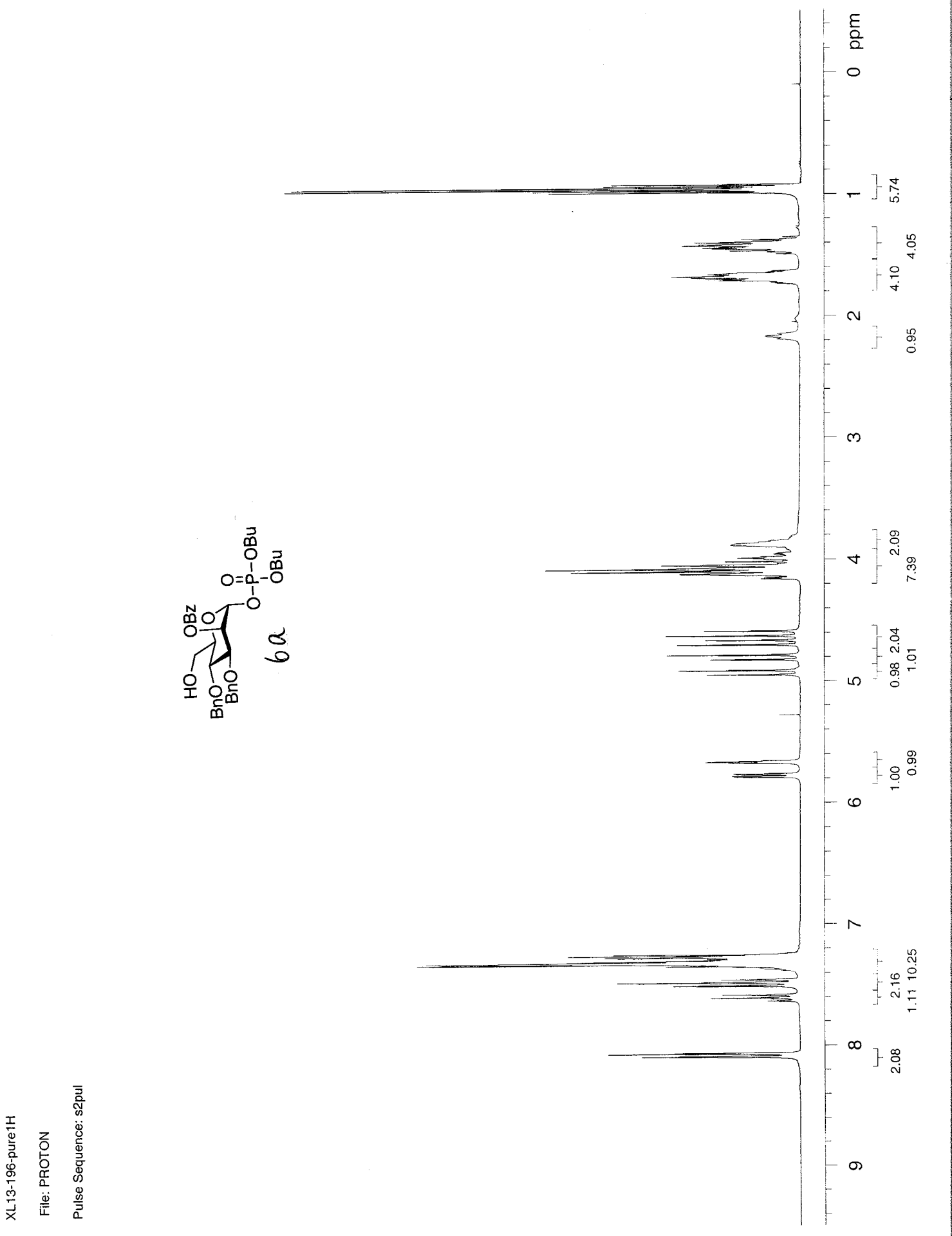

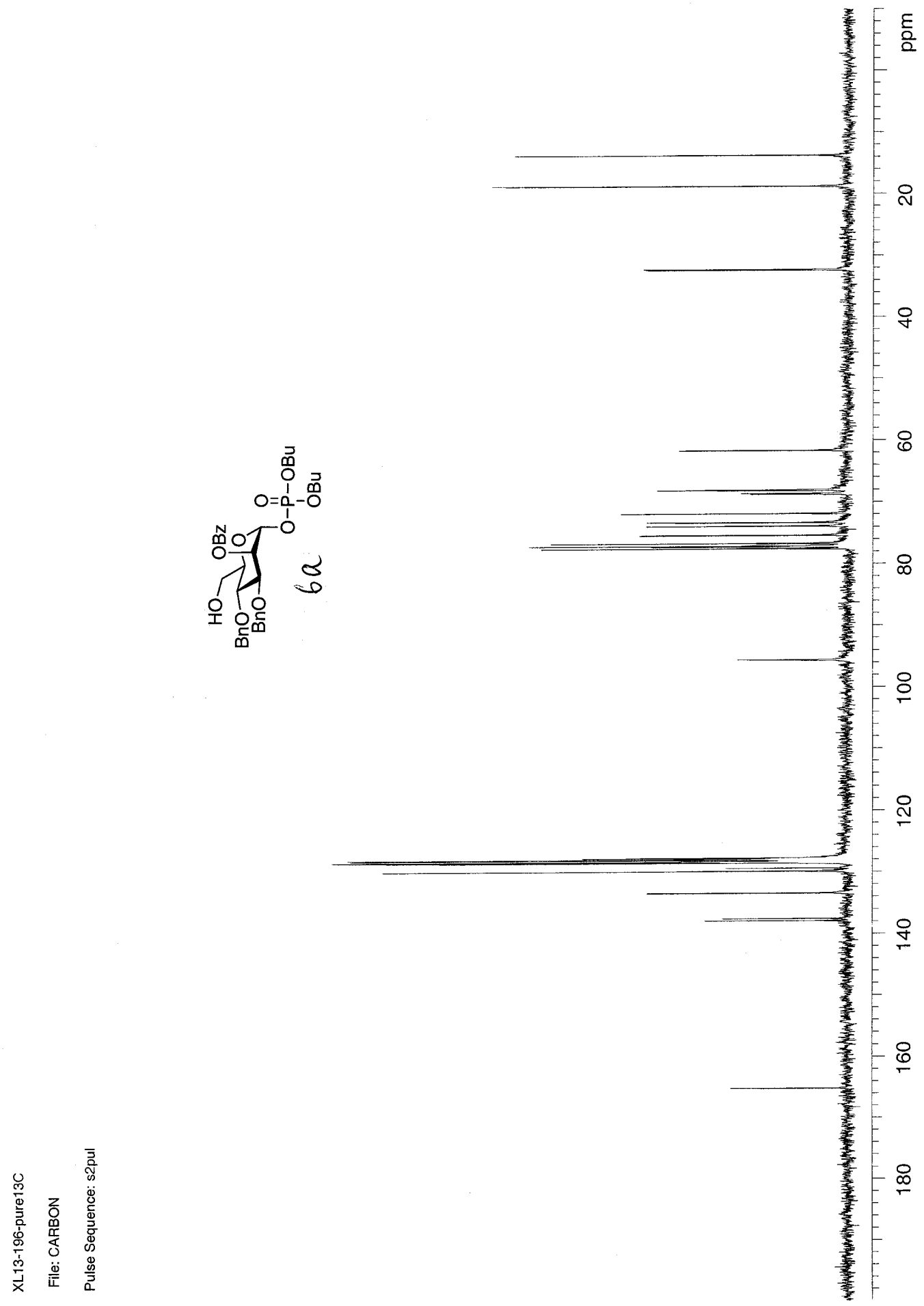
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XL13-196-pure31P

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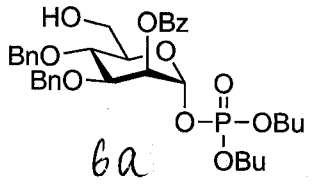

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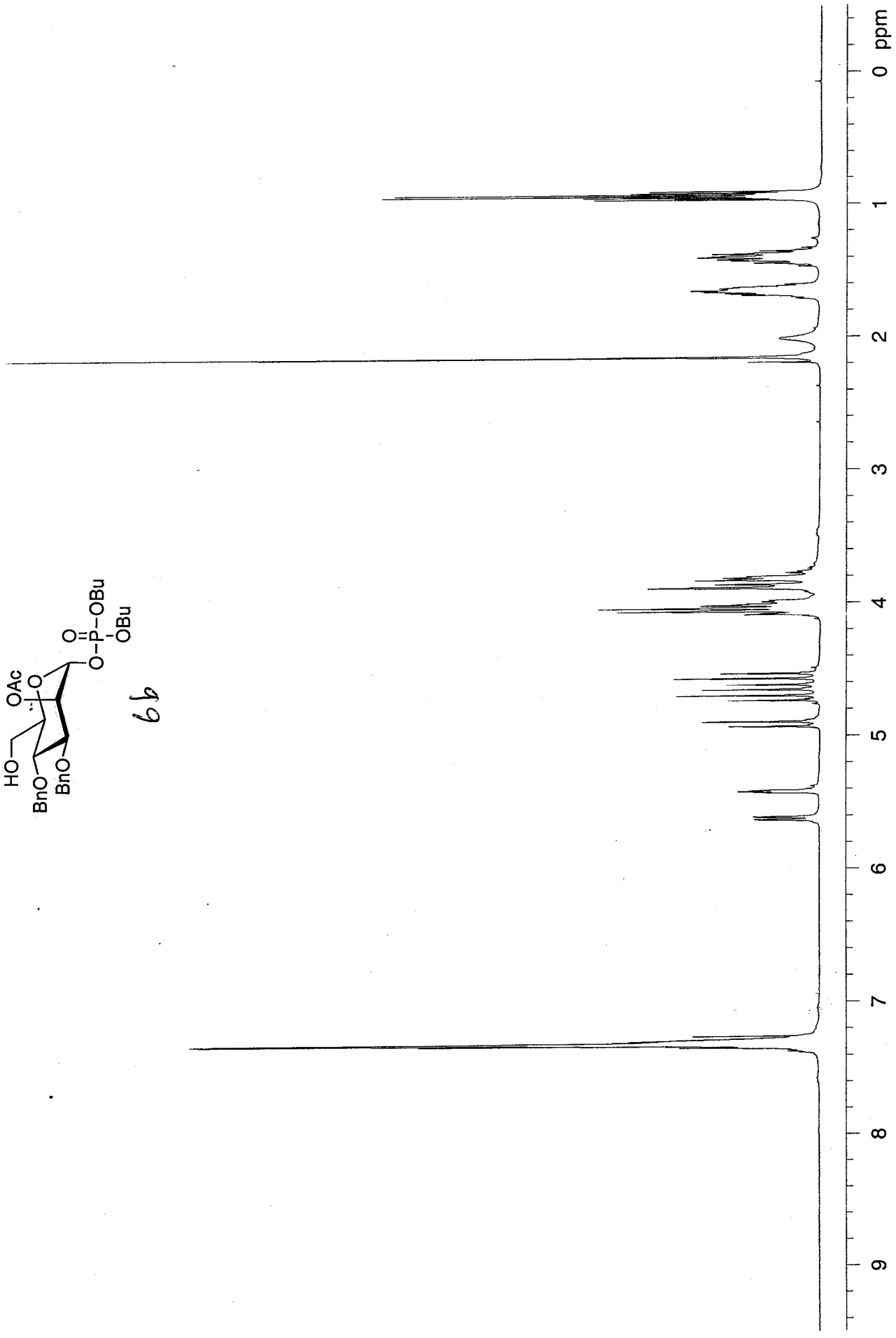

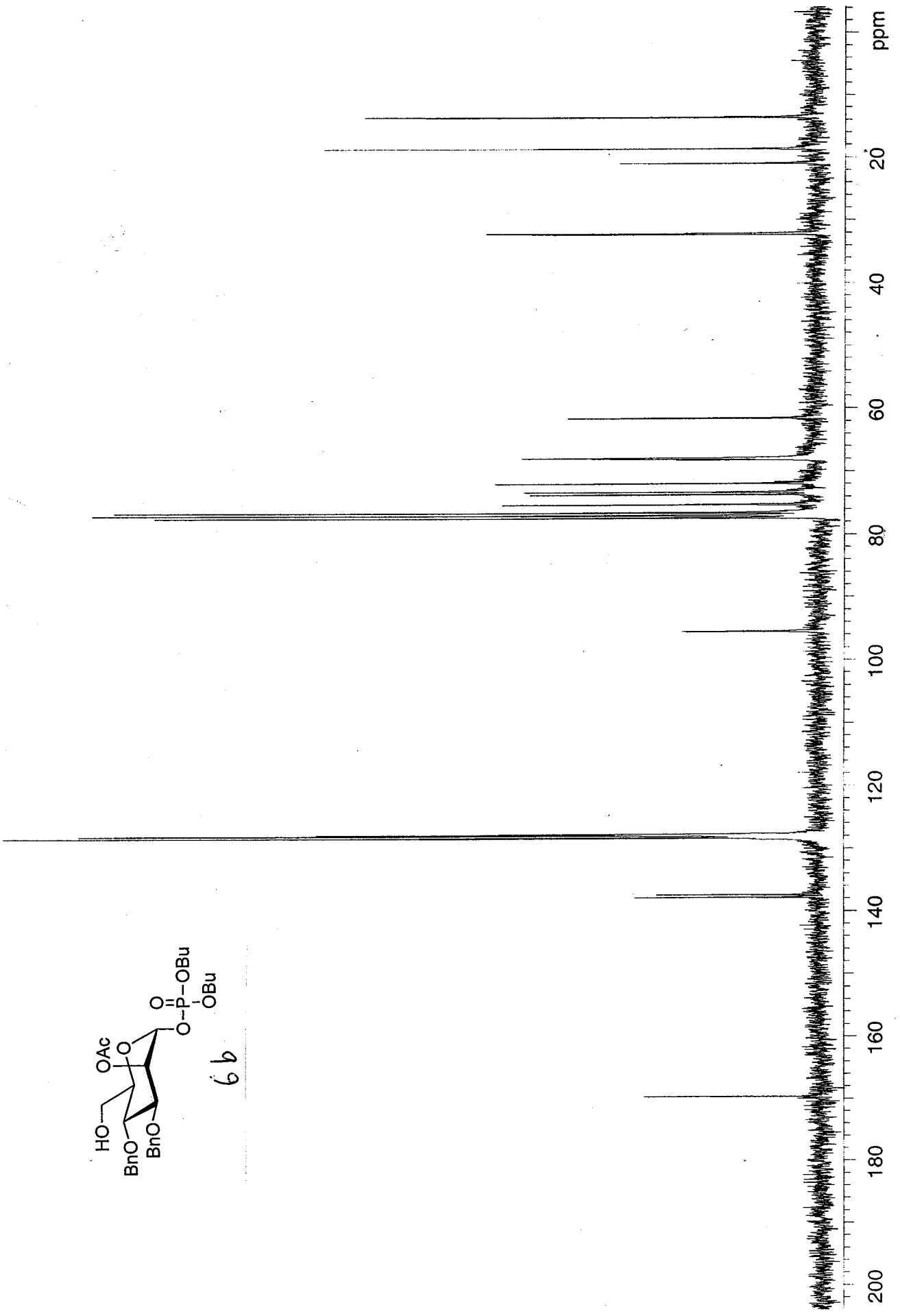

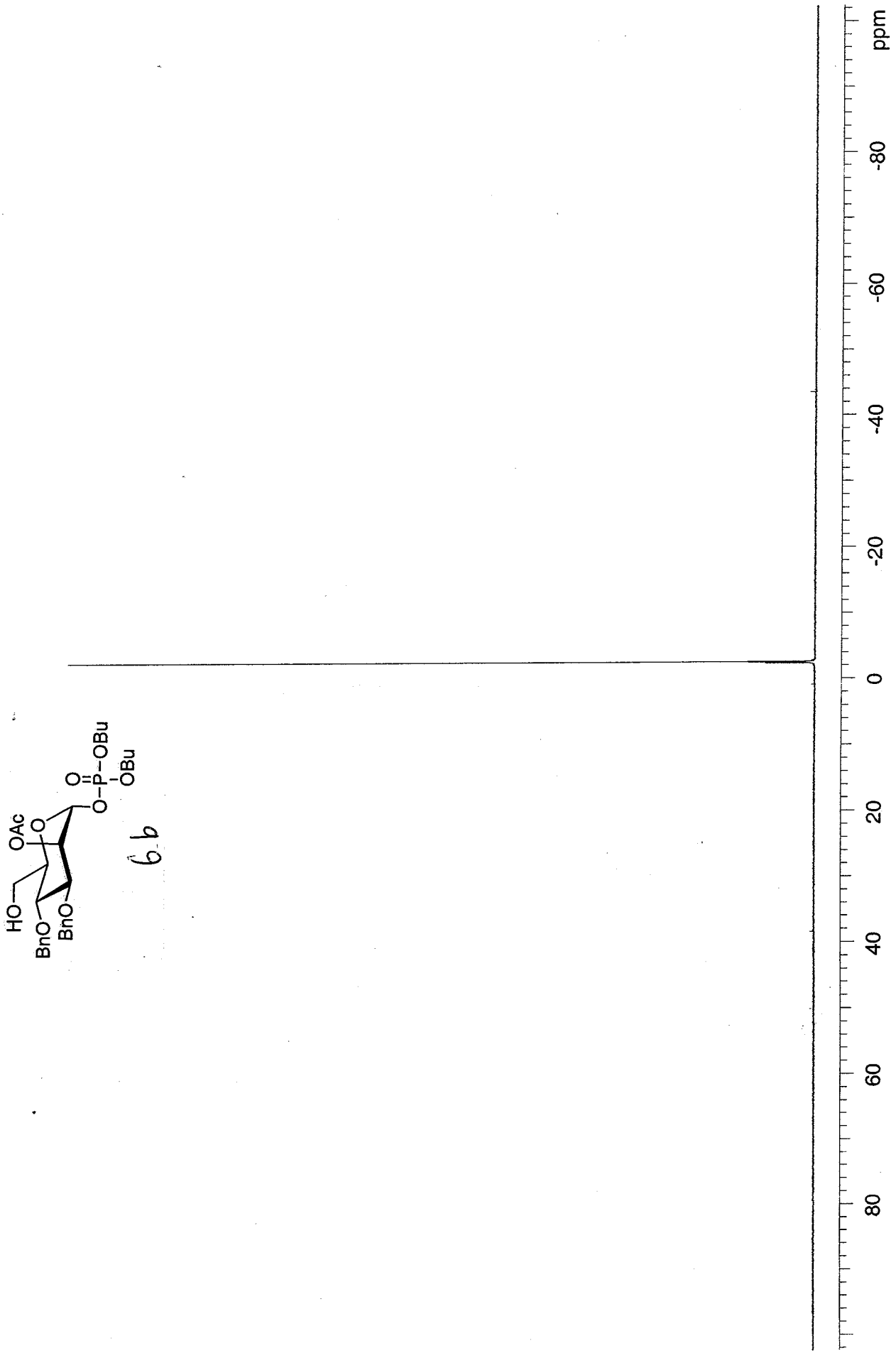

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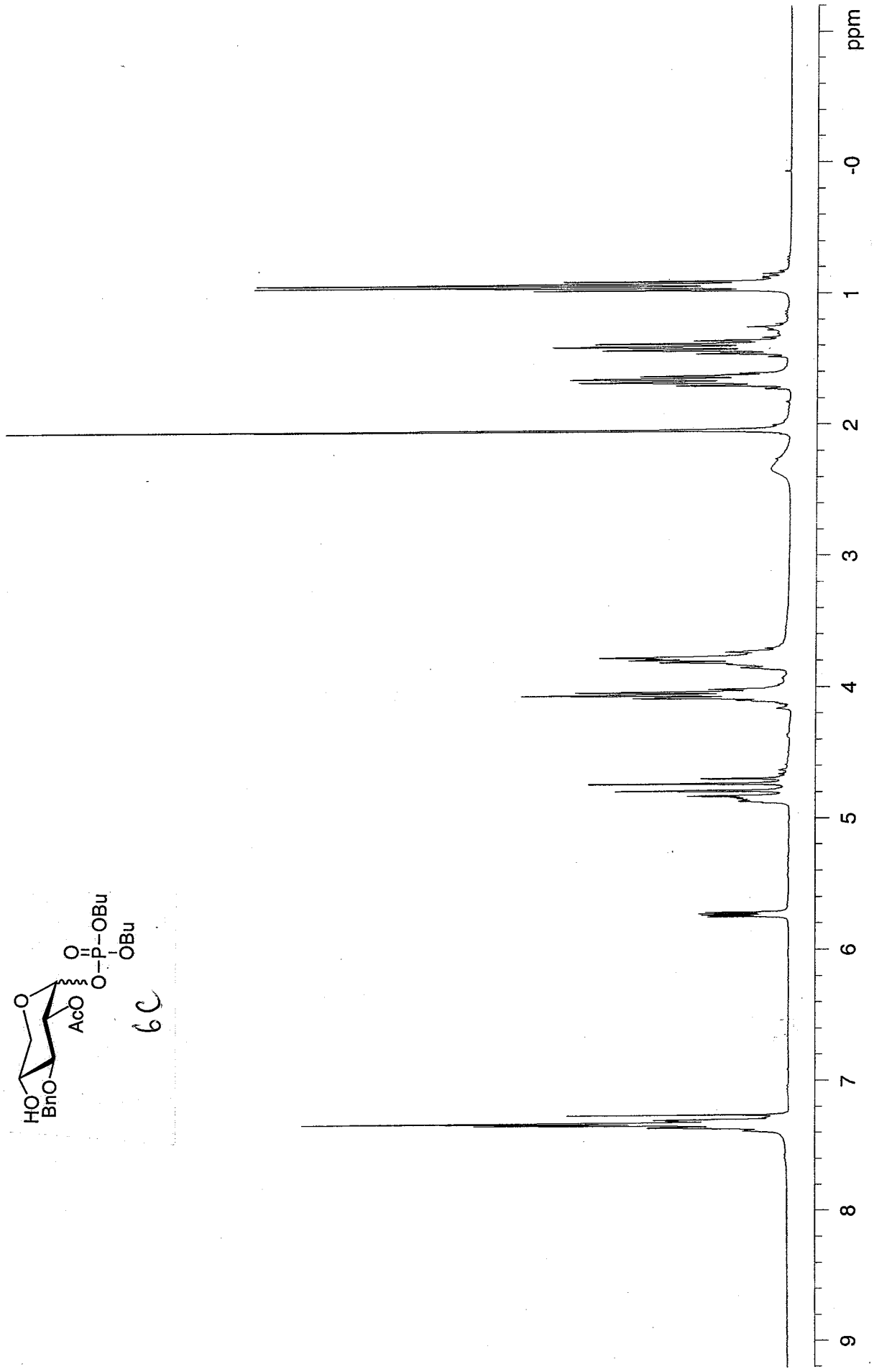

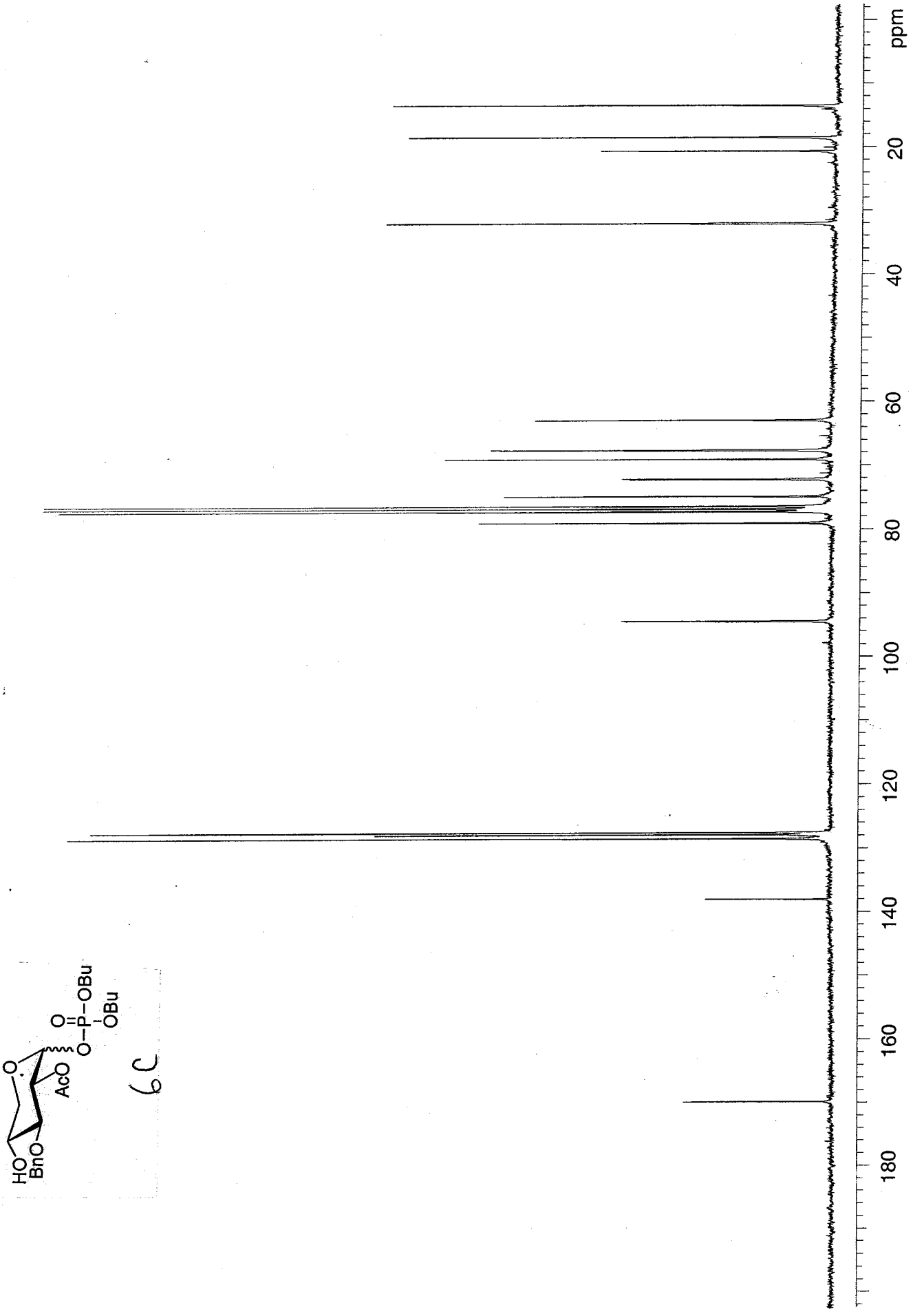

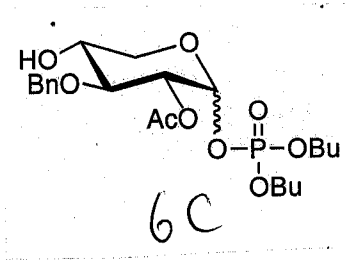

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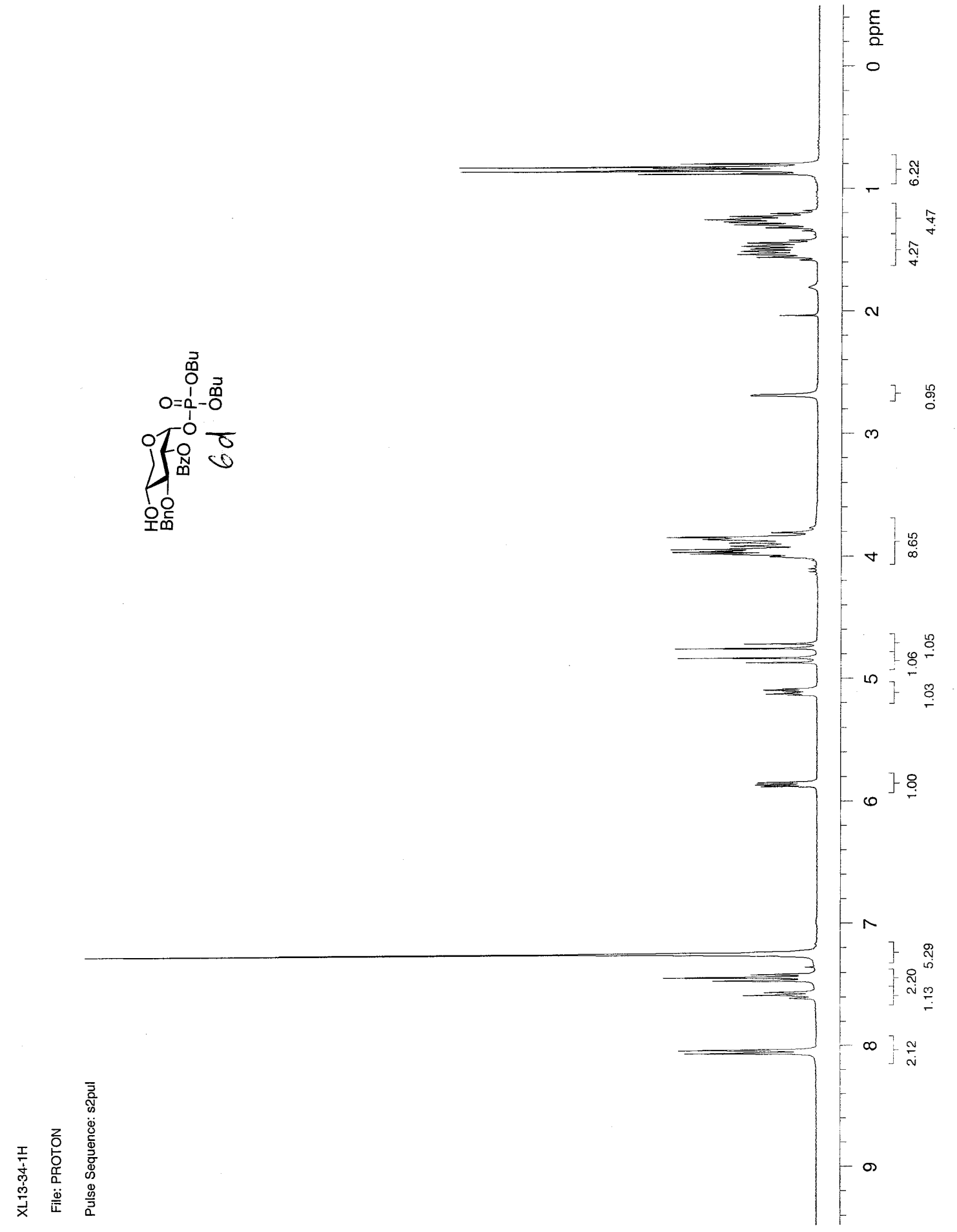

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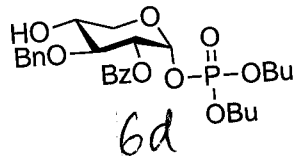

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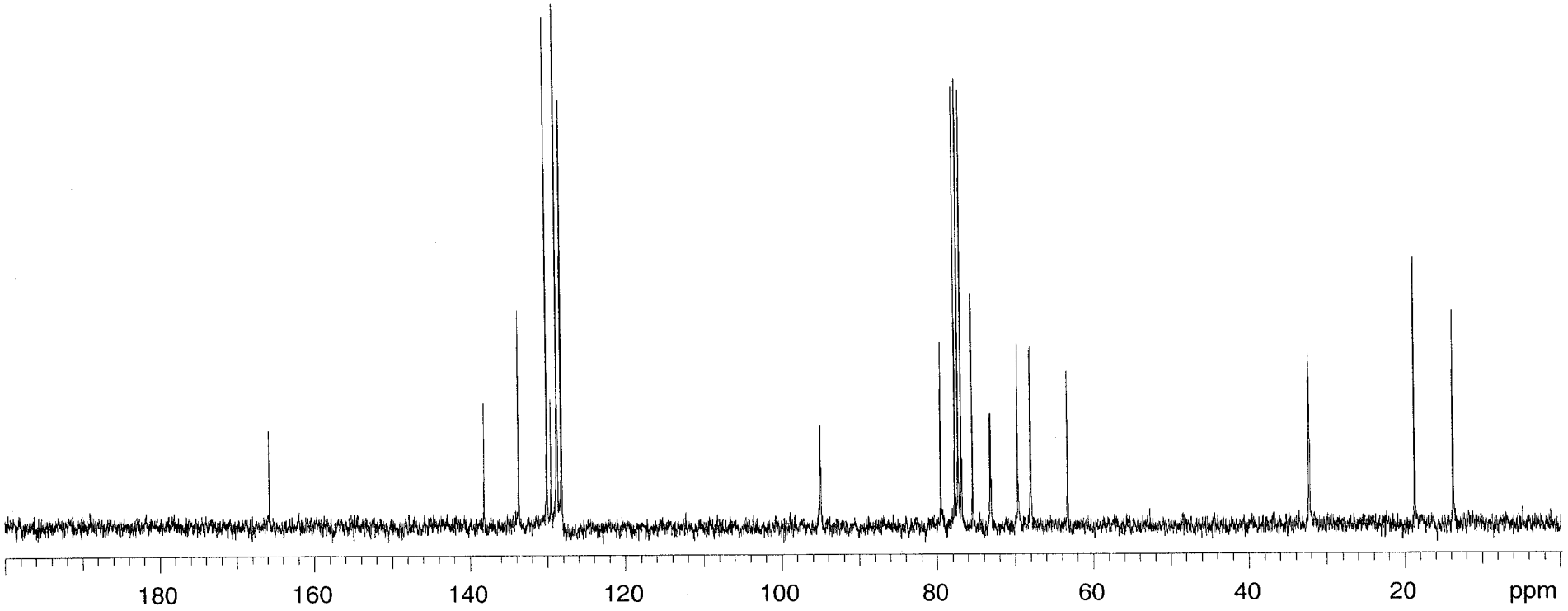

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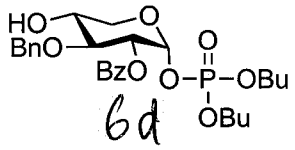
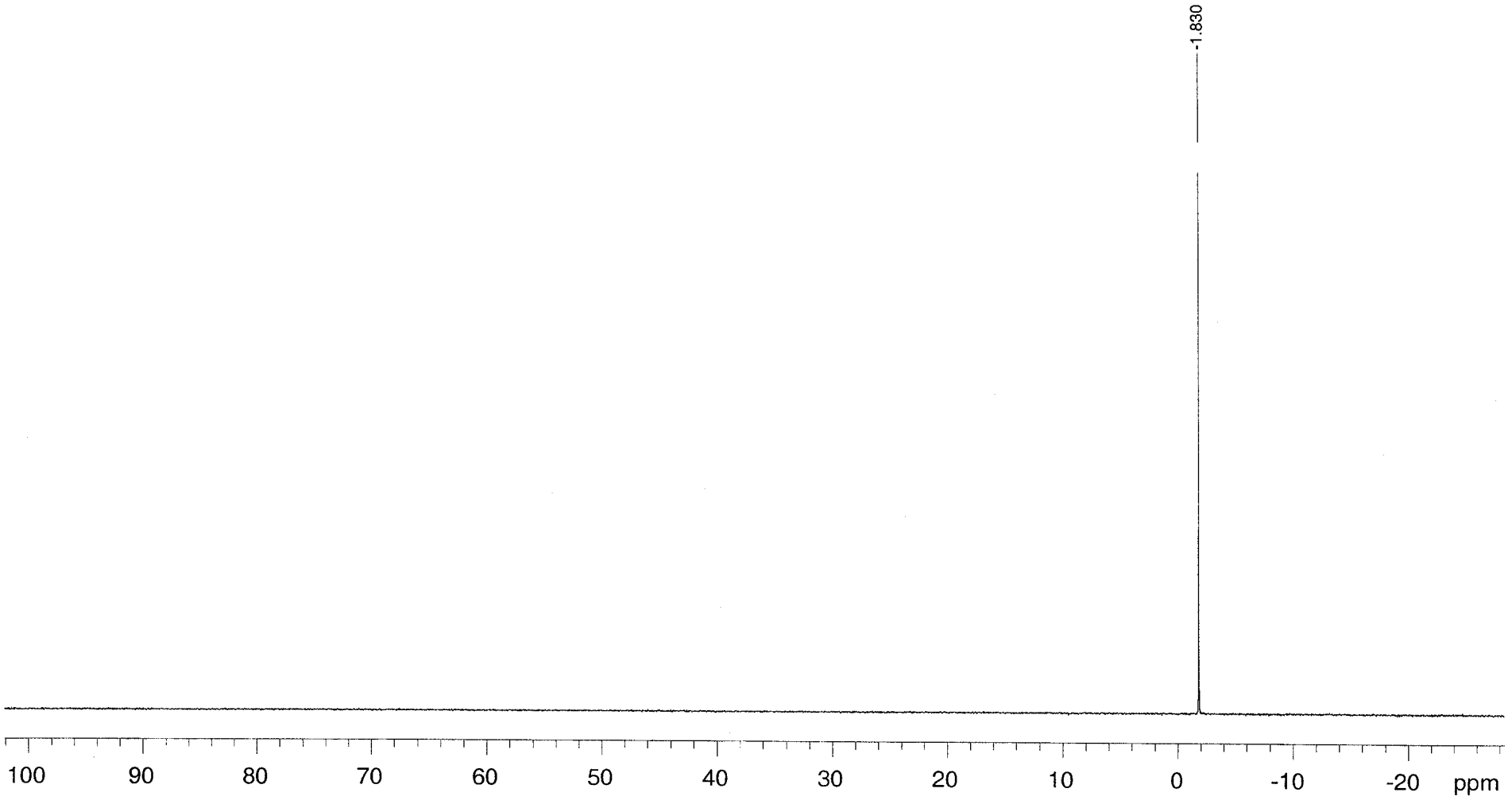
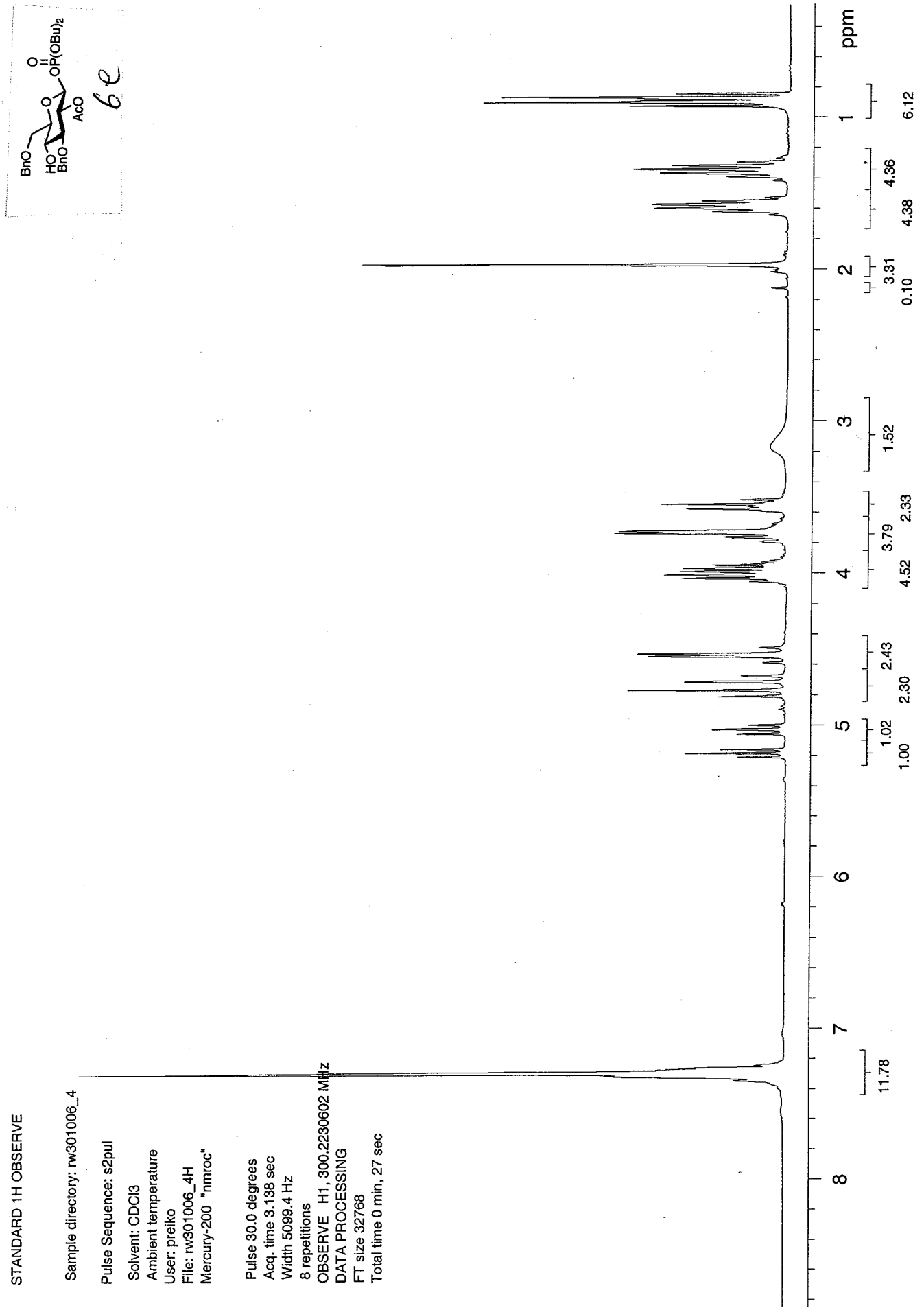
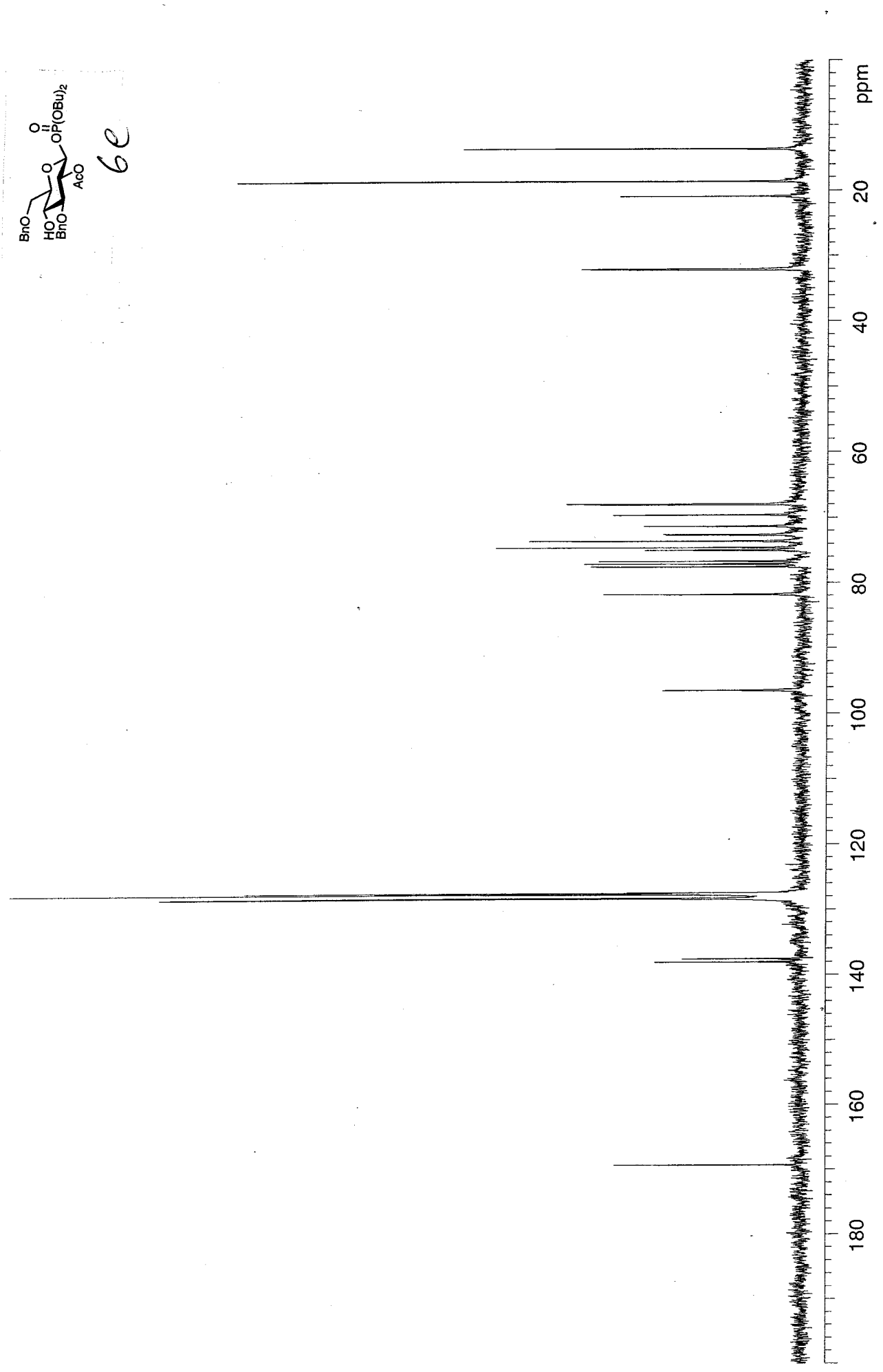


6d



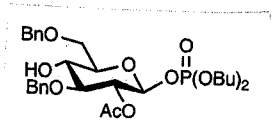

LOC ETHZ NMR Mercury-vx 300MHz Nr.6 10/30/06 18:13:26 USER:preiko GROUP:seeber SAMPLE:rw301006_4
STANDARD 1H OBSERVE
Sample directory: rw301006_4
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: preiko
File: rw301006_4H
Mercury-200 "nmroc"
Pulse 30.0 degrees
Acq. time 3.138 sec
Width 5099.4 Hz
8 repetitions
OBSERVE H1, 300.2230602 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 27 sec
BnO
HO
BnO
AcO
OP(OBu)2
6e
ppm
11.78
1.02
2.43
1.52
3.79
2.33
4.52
2.30
1.00
3.31
0.10
4.36
4.38
6.12



LOC ETHZ NMR Mercury-vx 300MHz Nr.6 03/27/07 11:01:38 USER:preiko GROUP:seeber SAMPLE:rw301006_4

LOC ETHZ NMR Mercury-vx 300MHz Nr.6 10/30/06 18:05:51 USER:preiko GROUP:seeber SAMPLE:rw301006_4

P-31 STANDARD PARAMETERS
PHOSPHATE REGION

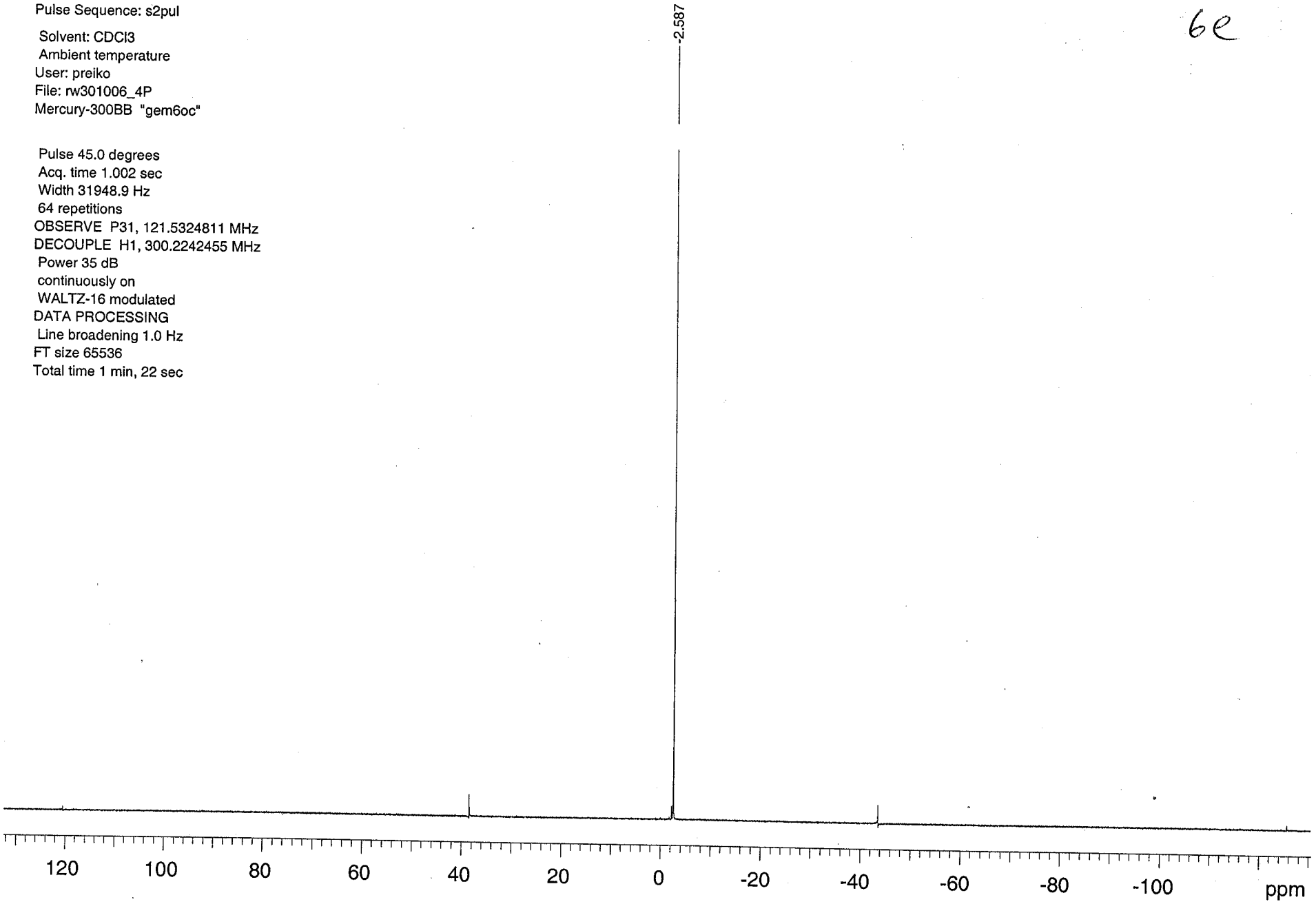


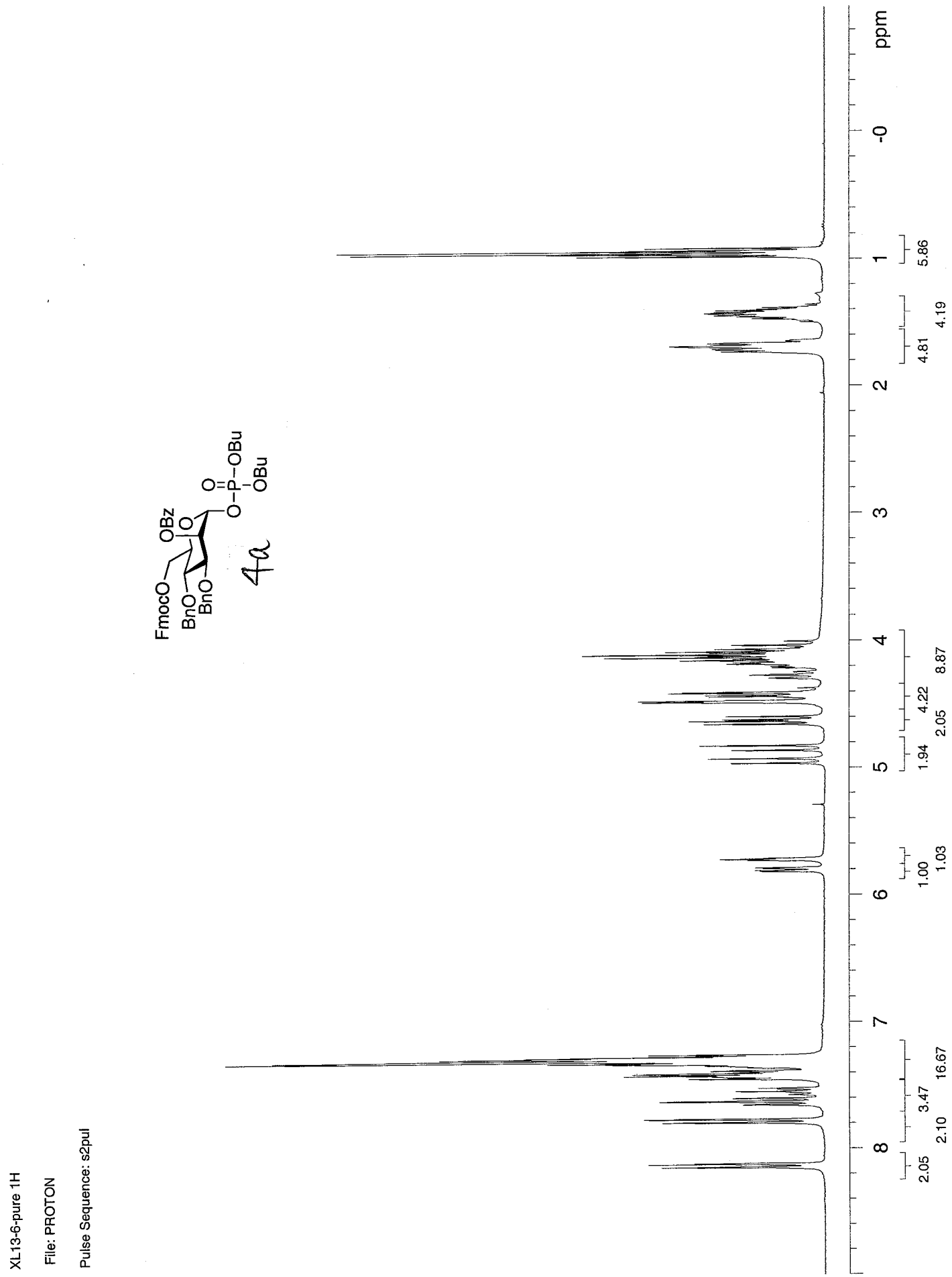
6e

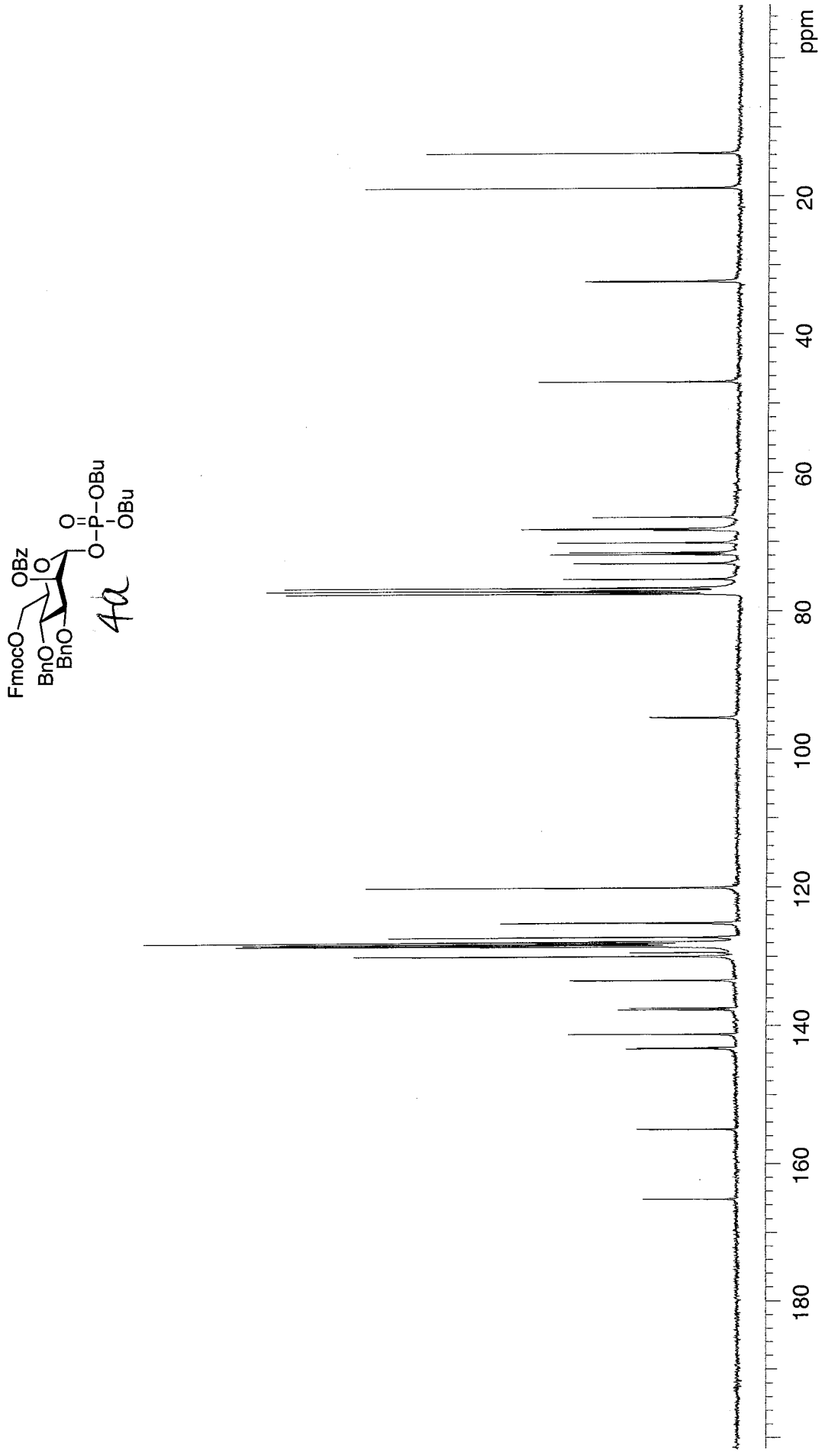
Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
User: preiko
File: rw301006_4P
Mercury-300BB "gem6oc"

Pulse 45.0 degrees
Acq. time 1.002 sec
Width 31948.9 Hz
64 repetitions
OBSERVE P31, 121.5324811 MHz
DECOUPLE H1, 300.2242455 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 1 min, 22 sec




XL13-6-pure 1H
File: PROTON
Pulse Sequence: s2pul
FmocO
BnO
BnO
OBz
O
O
O=P–OBu
OBu
4a
ppm
8
7
6
5
4
3
2
1
-0
2.05
2.10
3.47
16.67
1.00
1.03
1.94
4.22
2.05
8.87
4.81
4.19
5.86



XL13-6-pure 31P

File: PHOSPHORUS

Pulse Sequence: s2pul