Supplementary Information

Deuterium-Isotope Study on the Reductive Ring Opening of Benzylidene Acetals

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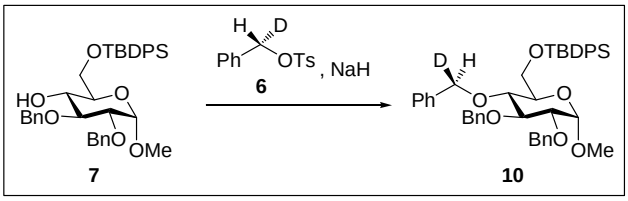
Table of Contents

A. General Procedures

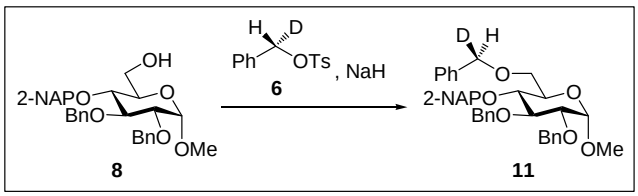
CH_2Cl_2 was purified and dried from a safe purification system filled with anhydrous Al_2O_3. Flash column chromatography was carried out on Silica Gel 60 (230–400 mesh, E. Merck). TLC was performed on pre-coated glass plates of Silica Gel 60 F254 (0.25 mm, E. Merck); detection was executed by spraying with a solution of $Ce(NH_4)_2(NO_3)_6$, $(NH_4)_6Mo_7O_{24}$, and H_2SO_4 in water and subsequent heating on a hot plate. The specific rotations are reported in 10^{-1} deg cm^2 g^{-1}. ^{1}H and ^{13}C NMR spectra were recorded using 400 MHz and 600 MHz spectrometers. Chemical shifts are in ppm from Me_4Si calibrated using the resonance of the residual proton and carbon of $CDCl_3$ (solvent). Proton peak assignments were performed using 2D NMR techniques (^{1}H-^{1}H COSY, HMQC and NOESY) and/or guided by the assignment of known undeuterated derivatives; the hydrogen multiplicity of carbon peaks were determined using DEPT experiments.

B. Synthesis of the Reference Compounds



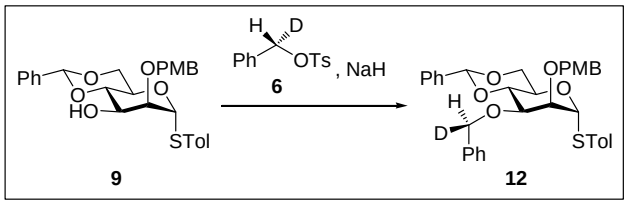
Methyl 4-*O*-(*R*)-benzyl-α-d$_1$-2,3-di-*O*-benzyl-6-*O*-*tert*-butydiphenylsilyl-α-D-gluco-pyranoside (10). A mixture of methyl 2,3-di-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-glucopyranoside **7** (120 mg, 0.196 mmol) and (*S*)-benzyl-α-d$_1$-4-methylbenzenesulfonate (**6**, 32.1 mg, 0.122 mmol) was stirred in *N*,*N*-dimethylformamide (DMF, 1 mL) and CH_2Cl_2 (1 mL) at room temperature under nitrogen atmosphere. The reaction flask was cooled to 0 °C, sodium hydride (60% dispersion in mineral oil, 14 mg, 0.35 mmol) was added to the mixture, and the reaction was gradually warmed up to room temperature. After stirring for 10 hours, Dowex® 50WX4-200 was added to quench the reaction, the whole mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure. The crude residue was purified by flash column chromatography (ethyl acetate/hexanes = 1/4, v/v) to obtain the product **10** (79 mg, 64%). $[\alpha]_D^{27}$ +10.0 (*c* 0.3 in $CHCl_3$); IR ($CHCl_3$) ν 3031, 2930, 1454, 1159, 1105, 822, 738, 700 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67–7.64 (4 H, m, Ar-H), 7.40–7.26 (16 H, m, Ar-H), 7.23–7.22 (3 H, m, Ar-H), 7.12–7.10 (2 H, m, Ar-H), 4.95, 4.81, (2 H, ABq, *J* = 10.7 Hz, PhC*H*$_2$), 4.80, 4.69

(2 H, ABq, *J* = 12.0 Hz, PhC*H*$_2$), 4.64 (1 H, d, *J* = 3.5 Hz, 1-H), 4.55 (1 H, s, PhC*H*D), 3.98 (1 H, t, *J* = 9.5 Hz, 3-H), 3.86–3.81 (2 H, m, 6-H$_a$, 6-H$_b$), 3.69–3.66 (1 H, m, 5-H), 3.58 (1 H, t, *J* = 9.5 Hz, 4-H), 3.53 (1 H, dd, *J* = 9.5, 3.5 Hz, 2-H), 3.35 (3 H, s, OC*H*$_3$), 1.01 (9 H, s, *t*-Bu); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.7 (C), 138.3 (C), 138.2 (C), 135.8 (CH), 135.6 (CH), 133.6 (C), 133.3 (C), 129.6 (CH), 129.5 (CH),128.4 (CH), 128.35 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 97.8 (CH), 82.3 (CH), 80.2 (CH), 77.8 (CH), 75.9 (CH_2), 74.9/74.7/74.6 (CHD), 73.3 (CH_2), 71.4 (CH), 62.9 (CH_2), 54.8 (CH_3), 26.8, (CH_3) 19.3 (C); HRMS [ESI, MNa^+] calcd for $C_{44}H_{49}DO_6SiNa$ 726.3337, found 726.3329.

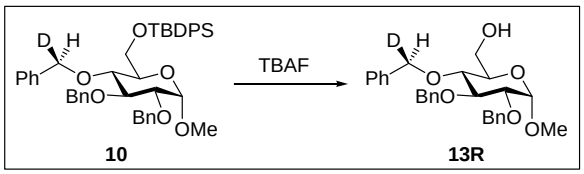


Methyl 6-*O*-(*R*)-benzyl-α-d$_1$-2,3-di-*O*-benzyl-4-*O*-(2-naphthylmethyl)-α-D-gluco-pyranoside (11). A mixture of methyl 2,3-di-*O*-benzyl-4-*O*-(2-naphthylmethyl)-α-D-glucopyranoside (**8**, 307 mg, 0.60 mmol) and tosylate **6** (188 mg, 0.72 mmol) was stirred in DMF (1 mL) and CH_2Cl_2 (1 mL) at room temperature under nitrogen atmosphere. The reaction flask was cooled to 0 °C, sodium hydride (60% dispersion in mineral oil, 48 mg, 1.19 mmol) was added to the mixture, and the reaction was gradually warmed up to room temperature. After stirring for 2 hours, Dowex® 50WX4-200 was added to quench the reaction, the whole mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure. The crude residue was purified by flash column chromatography (ethyl acetate/hexanes = 1/4, v/v) to afford the product **11** (275 mg, 78%). $[\alpha]_D^{26}$ +11.2 (*c* 1.1 in $CHCl_3$); IR ($CHCl_3$) ν 3030, 2923, 1453, 1274, 1160, 1049, 737, 698 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80–7.71 (22 H, m, Ar-H), 4.99, 4.83 (2 H, ABq, *J* = 10.8 Hz, ArC*H*$_2$), 4.95, 4.61 (2 H, ABq, *J* = 10.8 Hz, ArC*H*$_2$), 4.79, 4.66 (2 H, ABq, *J* = 12.0 Hz, ArC*H*$_2$), 4.63 (1 H, d, *J* = 3.6 Hz, 1-H), 4.41 (1 H, s, PhC*H*D), 4.00 (1 H, t, *J* = 9.3 Hz, 3-H), 3.77–3.71 (2 H, m, 5-H, 6-H$_a$), 3.68 (1 H, t, *J* = 9.3 Hz, 4-H), 3.64 (1 H, d, *J* = 9.0 Hz, 6-H$_b$), 3.58–3.55 (1 H, m, 2-H), 3.37 (3 H, s, OC*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.8 (C), 138.1 (C), 137.8 (C), 135.7 (C), 133.2 (C), 132.9 (C), 128.4 (CH), 128.38 (CH), 128.4 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.88 (CH), 127.7 (CH), 127.6 (CH), 127.56 (CH), 126.5 (CH), 126.0 (CH), 125.9 (CH), 125.8 (CH), 98.2 (CH) , 82.2 (CH),

79.8 (CH), 77.6 (CH), 75.7 (CH_2), 75.0 (CH_2), 73.4 (CH_2), 73.3/73.1/73.0 (CHD), 70.1 (CH), 68.4 (CH_2), 55.2 (CH_3); HRMS [ESI, MNa^+] calcd for $C_{39}H_{39}DO_6Na$ 628.2785, found 628.2779.

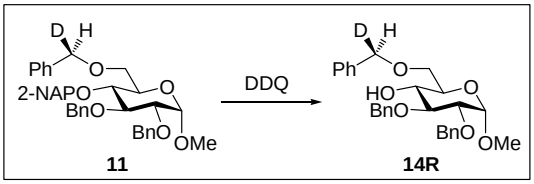


***p*-Methylphenyl 3-*O*-(*R*)-benzyl-α-d_1-4,6-*O*-benzylidene-2-*O*-(4-methoxybenzyl)-1-thio-α-D-mannopyranoside (12)**. A mixture of *p*-methylphenyl 4,6-*O*-benzylidene-2-*O*-(4-methoxylbenzyl)-1-thio-α-D-mannopyranoside (**9**, 138 mg, 0.279 mmol) and tosylate **6** (73.2 mg, 0.279 mmol) was stirred in DMF (1 mL) and CH_2Cl_2 (1 mL) at room temperature under nitrogen atmosphere. The reaction flask was cooled to 0 °C, sodium hydride (60% dispersion in mineral oil, 22.3 mg, 0.558 mmol) was added to the mixture, and the reaction was gradually warmed up to room temperature. After stirring for 3 hours, Dowex® 50WX4-200 was added to quench the reaction, the whole mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure. The crude residue was purified by flash column chromatography (ethyl acetate/hexanes = 1/4, v/v) to get the product **12** (141 mg, 86%). $[\alpha]_D^{27}$ +85.1 (*c* 0.5 in $CHCl_3$); IR ($CHCl_3$) ν 3032, 2900, 1612, 1514, 1454, 1249, 1100, 811, 698 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.51–7.49 (2 H, m, Ar-H), 7.38–7.23 (12 H, m, Ar-H), 7.09–7.08 (2 H, m, Ar-H), 6.84–6.82 (2 H, m, Ar-H), 5.62 (1 H, s, PhC*H*), 5.36 (1 H, s, 1-H), 4.63 (2 H, s, CH_2PhOMe), 4.60 (1 H, s, PhC*H*D), 4.27–4.25 (3 H, m, 5-H, 6-H_a), 4.21–4.19 (1 H, m, 4-H), 4.00 (1 H, s, 2-H), 3.94 (1 H, dd, *J* = 9.6, 3.4 Hz, 3-H), 3.86 (1 H, m, 6-H_b), 3.79 (3 H, s, OCH_3), 2.32 (3 H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.4 (C), 138.3 (C), 137.9 (C), 137.6 (C), 132.3 (CH), 129.9 (CH), 129.8 (CH), 128.8 (CH), 128.3 (CH), 128.2 (CH), 127.6 (CH), 127.58 (CH), 126.1 (CH), 113.8 (CH), 101.5 (CH), 87.5 (CH), 79.1 (CH), 77.4 (CH), 76.1 (CH), 72.8/72.7/72.5 (CHD), 72.6 (CH_2), 68.5 (CH_2), 65.4 (CH), 55.2 (CH_3), 21.1 (CH_3); HRMS [ESI, MNa^+] calcd for $C_{35}H_{35}DO_6SNa$ 608.2193, found 608.2199.



Methyl 4-*O*-(*R*)-benzyl-α-d$_1$-2,3-di-*O*-benzyl-α-D-glucopyranoside (13R).

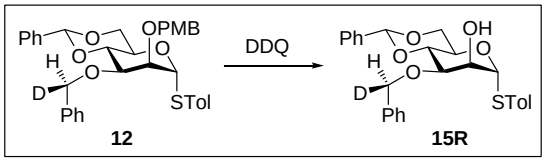
Compound **10** (61 mg, 86.7 μmol) was stirred in tetrahydrofuran (THF, 1 mL) at room temperature under nitrogen atmosphere. The reaction flask was cooled to 0 °C, and a 1 M solution of tetra-*n*-butylammonium fluoride (TBAF) in THF (2 mL, 2 mmol) was added to the mixture. After stirring for 16 hours, the whole mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure. The crude residue was purified by flash column chromatography (ethyl acetate/hexanes = 1/4, v/v) to acquire the 6-alcohol **13R** (38.3 mg, 95%). $[\alpha]_D^{27}$ +26.9 (*c* 1.2 in $CHCl_3$); IR ($CHCl_3$) ν 3467, 3031, 2926, 1453, 1356, 1091, 740, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.25 (15 H, m, Ar-H), 4.97 (1 H, d, *J* = 11.0 Hz, PhC*H*$_2$), 4.81 (1 H, d, *J* = 11.1 Hz, PhC*H*$_2$), 4.78 (1 H, d, *J* = 12.1 Hz, PhC*H*$_2$), 4.64 (1 H, d, *J* = 12.1 Hz, PhC*H*$_2$), 4.60 (1 H, s, PhC*H*D), 4.56 (1 H, d, *J* = 3.6 Hz, 1-H), 3.99 (1 H, t, *J* = 9.4 Hz, 3-H), 3.75 (1 H, ddd, *J* = 11.6, 5.4, 2.7 Hz, 6-H$_a$), 3.70–3.61 (2 H, m, 6-H$_b$, 5-H), 3.50 (1 H, dd, *J* = 9.6, 9.4 Hz, 4-H), 3.48 (1 H, dd, *J* = 9.4, 3.6 Hz, 2-H), 3.35 (3 H, s, OC*H*$_3$); HRMS [ESI, MNa^+] calcd for $C_{28}H_{31}DO_6Na$ 488.2159, found 488.2163.



11 **14R**

Methyl 6-*O*-(*R*)-benzyl-α-d$_1$-2,3-di-*O*-benzyl-α-D-glucopyranoside (14R).

Compound **11** (256 mg, 0.433 mmol) was stirred in CH_2Cl_2 (9 mL) and water (0.5 mL) at room temperature. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 294 mg, 1.30 mmol) was added to the mixture three times, one equivalent at a time, in half-hour intervals. After 4 hours, the mixture was filtered, and ethyl acetate and saturated $NaHCO_{3(aq)}$ was added. The organic layer was collected and evaporated under reduced pressure. The crude residue was purified by flash column chromatography (ethyl acetate/hexanes = 1/4, v/v) to afford the 4-alcohol **14R** (191 mg, 95%). $[\alpha]_D^{29}$ +26.3 (*c* 1.1 in $CHCl_3$); IR ($CHCl_3$) ν 3467, 3031, 2920, 1496, 1452, 1276, 1055, 738, 698 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35–7.25 (15 H, m, Ar-H), 4.99, 4.72 (2 H, ABq, *J* = 11.4 Hz, PhC*H*$_2$), 4.76, 4.65 (2 H, ABq, *J* = 12.1 Hz, PhC*H*$_2$), 4.62 (1 H, d, *J* = 3.2 Hz, 1-H), 4.51 (1 H, s, PhC*H*D), 3.77 (1 H, t, *J* = 9.3 Hz, 3-H), 3.70–3.65 (3 H, m, 5-H, 6-H$_a$, 6-H$_b$), 3.59 (1 H, td, *J* = 9.3, 2.0, Hz, 4-H), 3.52 (1 H, dd, *J* = 9.3, 3.3, Hz, 2-H), 3.37 (3 H, s, OC*H*$_3$), 2.30 (1 H, d, *J* = 2.0 Hz, 4-O*H*); HRMS [ESI, MNa^+] calcd for $C_{28}H_{31}DO_6Na$ 488.2159, found 488.2162.



***p*-Methylphenyl 3-*O*-(*R*)-benzyl-α-d$_1$-4,6-*O*-benzylidene-1-thio-α-D-manno-pyranoside (15R)**. Compound **12** (76.2 mg, 0.13 mmol) was stirred in CH_2Cl_2 (2.74 mL) and water (0.15 mL) at room temperature. DDQ (60 mg, 0.26 mmol) was added to the mixture twice, one equivalent at a time, in half-hour interval. After 4 hours, the mixture was filtered, and ethyl acetate and saturated $NaHCO_{3(aq)}$ was added. The organic layer was collected and evaporated under reduced pressure. The crude residue was purified by flash column chromatography (ethyl acetate/hexanes = 1/3, v/v) to get the 2-alcohol **15R** (56 mg, 93%). $[\alpha]_D^{27}$ +209.9 (*c* 1.2 in $CHCl_3$); IR ($CHCl_3$) ν 3459, 3033, 2899, 1493, 1453, 1210, 1099, 1018, 749, 698 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53–7.49 (2 H, m, Ar-H), 7.40–7.30 (10 H, m, Ar-H), 7.11 (2 H, d, *J* = 8.0 Hz, Ar-H), 5.61 (1 H, s, PhC*H*), 5.51 (1 H, s, 1-H), 4.72 (1 H, s, PhC*H*D), 4.34 (1 H, td, *J* = 9.6, 4.9 Hz, 5-H), 4.27 (1 H, dd, *J* = 3.4, 1.0 Hz, 2-H), 4.20 (1 H, dd, *J* = 10.3, 4.9 Hz, 6-H$_a$), 4.16 (1 H, t, *J* = 9.6 Hz, 4-H), 3.95 (1 H, dd, *J* = 9.6, 3.4 Hz, 3-H), 3.84 (1 H, m, 6-H$_b$), 2.84 (1 H, br s, 2-O*H*), 2.32 (3 H, s, C*H*$_3$); HRMS [ESI, MNa$^+$] calcd for $C_{27}H_{27}DO_5SNa$ 488.1618, found 488.1613.

C. Representative Procedures for Benzylidene Ring Opening

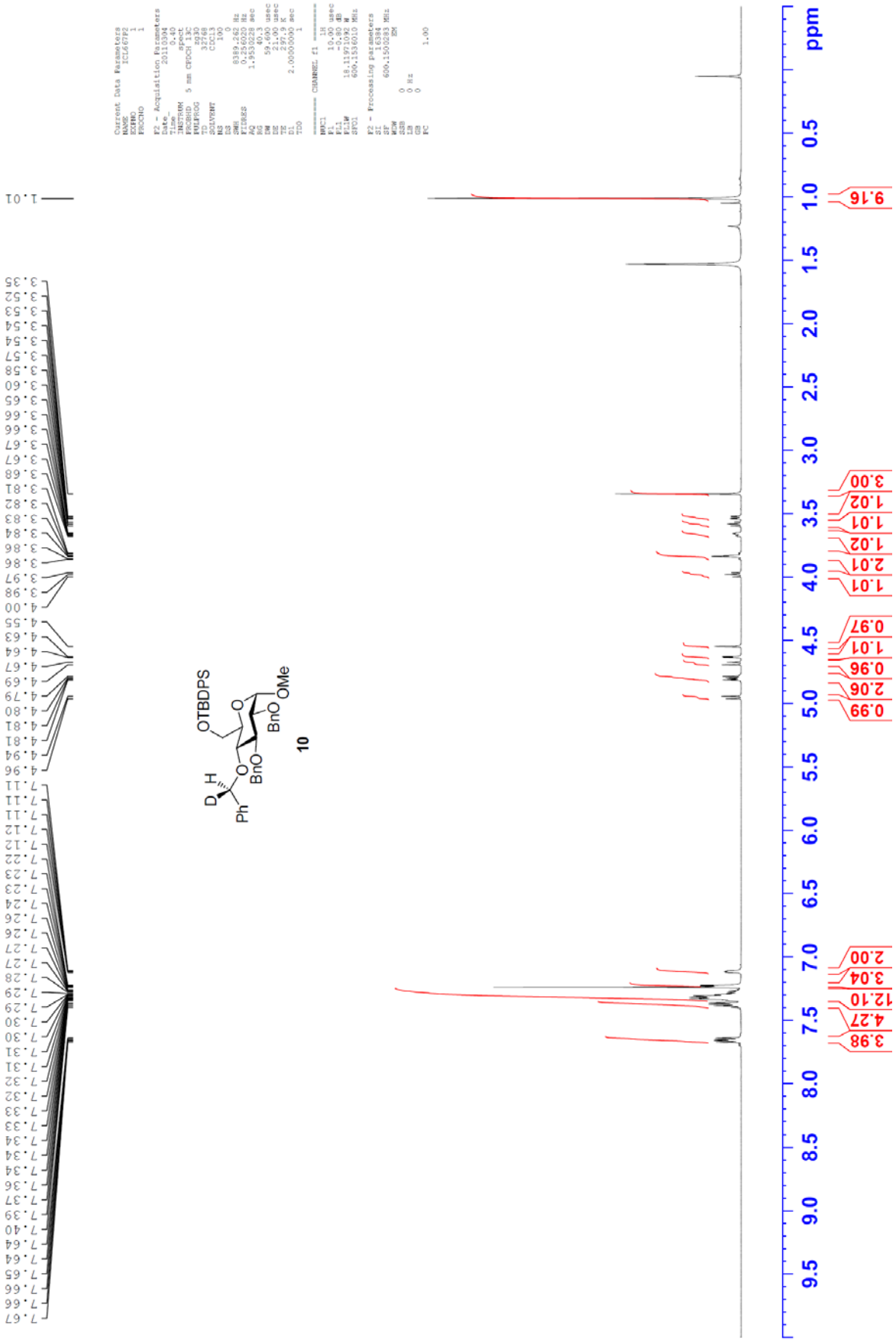
6-*O*-Ring opening by AlD_3. $AlCl_3$ (14.4 mg, 0.108 mmol) and $LiAlD_4$ (13.7 mg, 0.325 mmol) were mixed in ice-cold Et_2O (1 mL). A solution of compound **1** (50 mg, 0.108 mmol) in CH_2Cl_2 (1 mL) was added 5 minutes later and the reaction was allowed to warm up to room temperature. After 90 minutes of reaction, ethyl acetate (1 mL) was added followed by a few drops of water. The mixture was diluted with ethyl acetate, washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (ethyl acetate/hexanes = 1/2, v/v) to obtain the target 6-alcohol(s) (44 mg, 88%).

6-*O*-Ring opening by BD_3•THF. BF_3•Et_2O (292 μL, 2.3 mmol) was added to a suspension of $NaBD_4$ (72 mg, 1.72 mmol) in THF (0.7 mL) at room temperature. After overnight stirring, compound **1** (106 mg, 0.23 mmol) and copper(II) trifluoromethanesulfonate ($Cu(OTf)_2$, 4.2 mg, 12 μmol) were sequentially added. The reaction was allowed to proceed for 7 hours and, then, quenched with methanol and Et_3N.

The resulting mixture was filtered through Celite, concentrated under reduced pressure, and purified by flash column chromatography (ethyl acetate/hexanes = 1/2, v/v) to get the target 6-alcohol(s) (65.5 mg, 62%).

4-*O*-Ring opening by Et_3SiD. Et_3SiD (37 μL, 0.234 mmol) was added to a solution of compound **1** (54.1 mg, 0.117 mmol) in CH_3CN (0.5 mL) at room temperature under nitrogen atmosphere. The reaction flask was immersed in an ice-bath, $Cu(OTf)_2$ (0.4 mg, 1 μmol) was added to the mixture, and the resulting solution was gradually warmed up to room temperature. After stirring for 30 minutes, the mixture was diluted with ethyl acetate and, after 1 hour of stirring, the resulting mixture was washed by saturated $NaHCO_{3(aq)}$, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification of the residue *via* flash column chromatography (ethyl acetate/hexanes = 1/2) provided the target 4-alcohol(s) (35.4 mg, 65%).

2-*O*-Ring opening by AlD_3. $AlCl_3$ (17.5 mg, 0.131 mmol) and $LiAlD_4$ (15 mg, 0.394 mmol) were mixed in Et_2O (4 mL) at 0 °C. After 15 minutes, this mixture was added to an ice-cooled stirring solution of compound **16** (243 mg, 0.525 mmol) in CH_2Cl_2/Et_2O (2/1, 12 mL). The ice-water bath was removed and the reaction was allowed to warm up to room temperature. Ethyl acetate (10 mL) was added 5 hours later and the solution was washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (ethyl acetate/hexanes = 1/4, v/v) to obtain the target 2-alcohol(s) (179 mg, 73%).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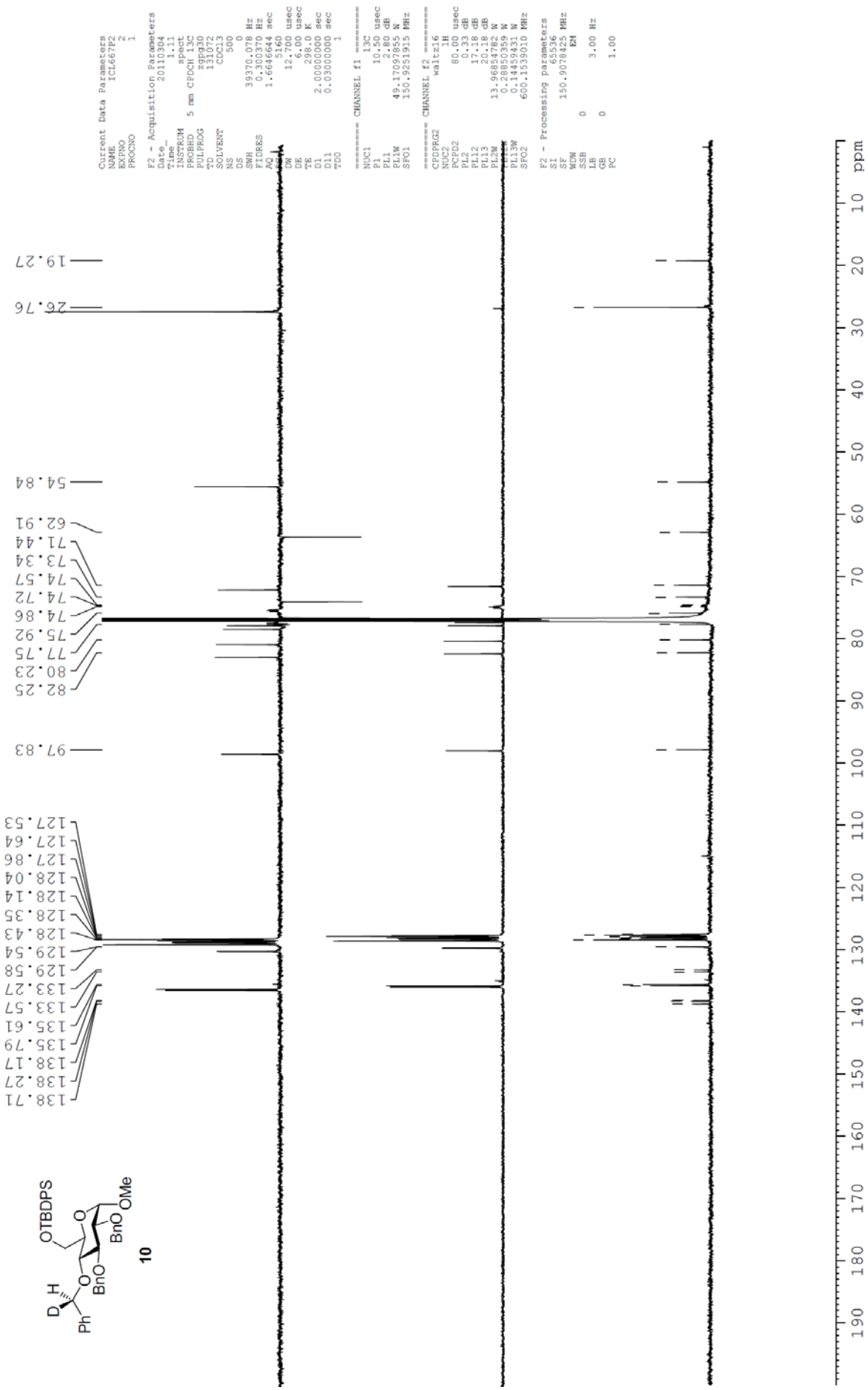
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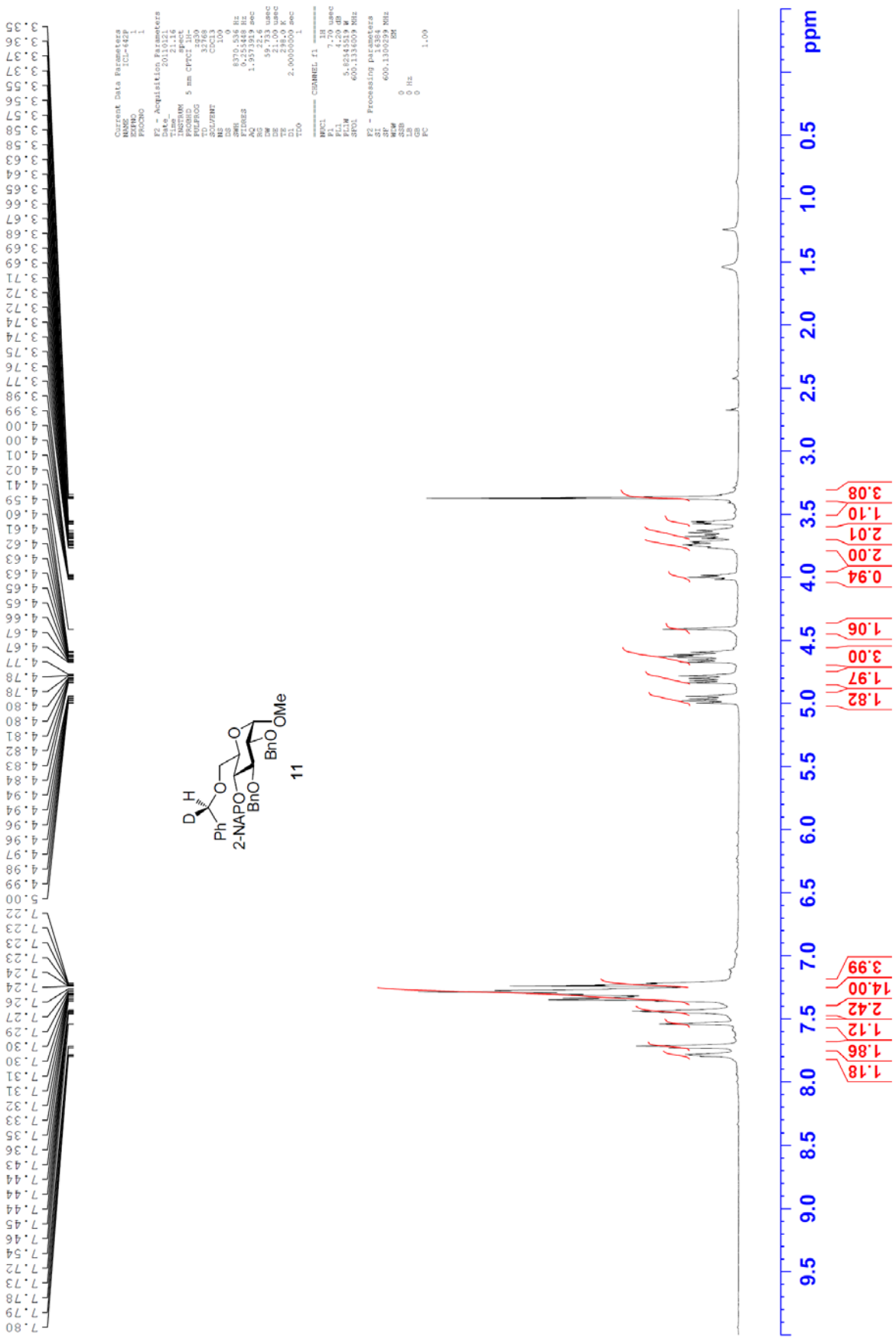
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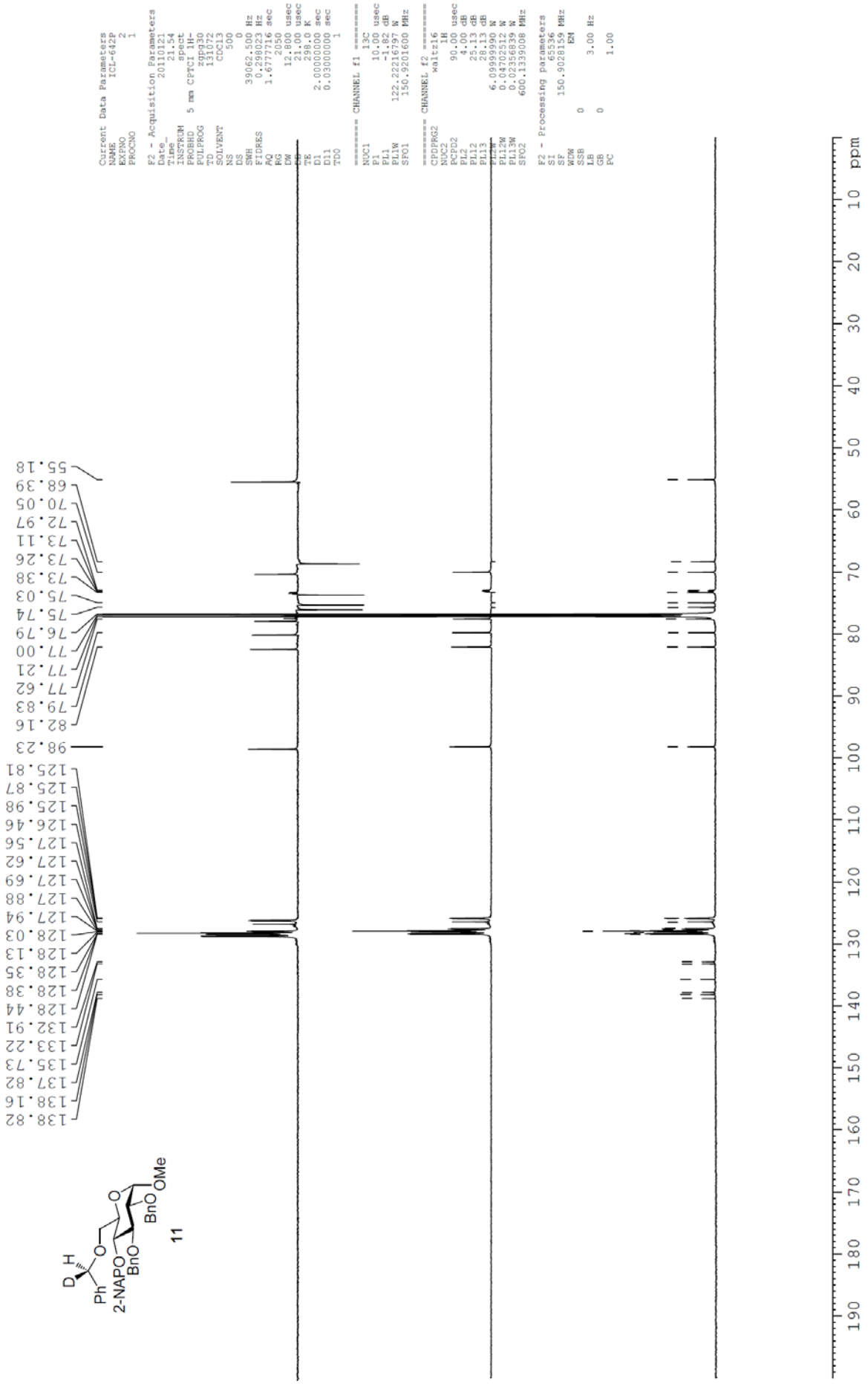
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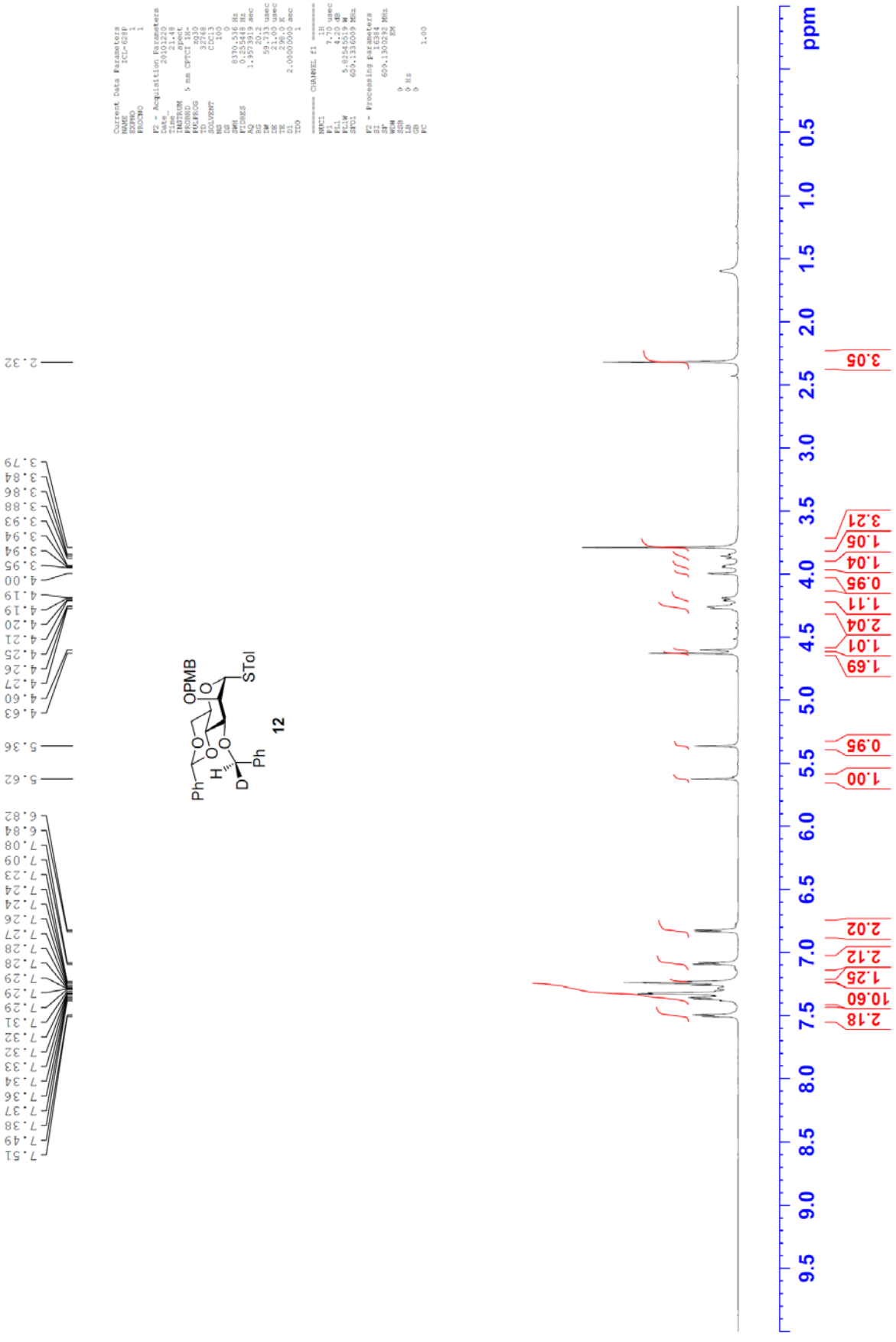
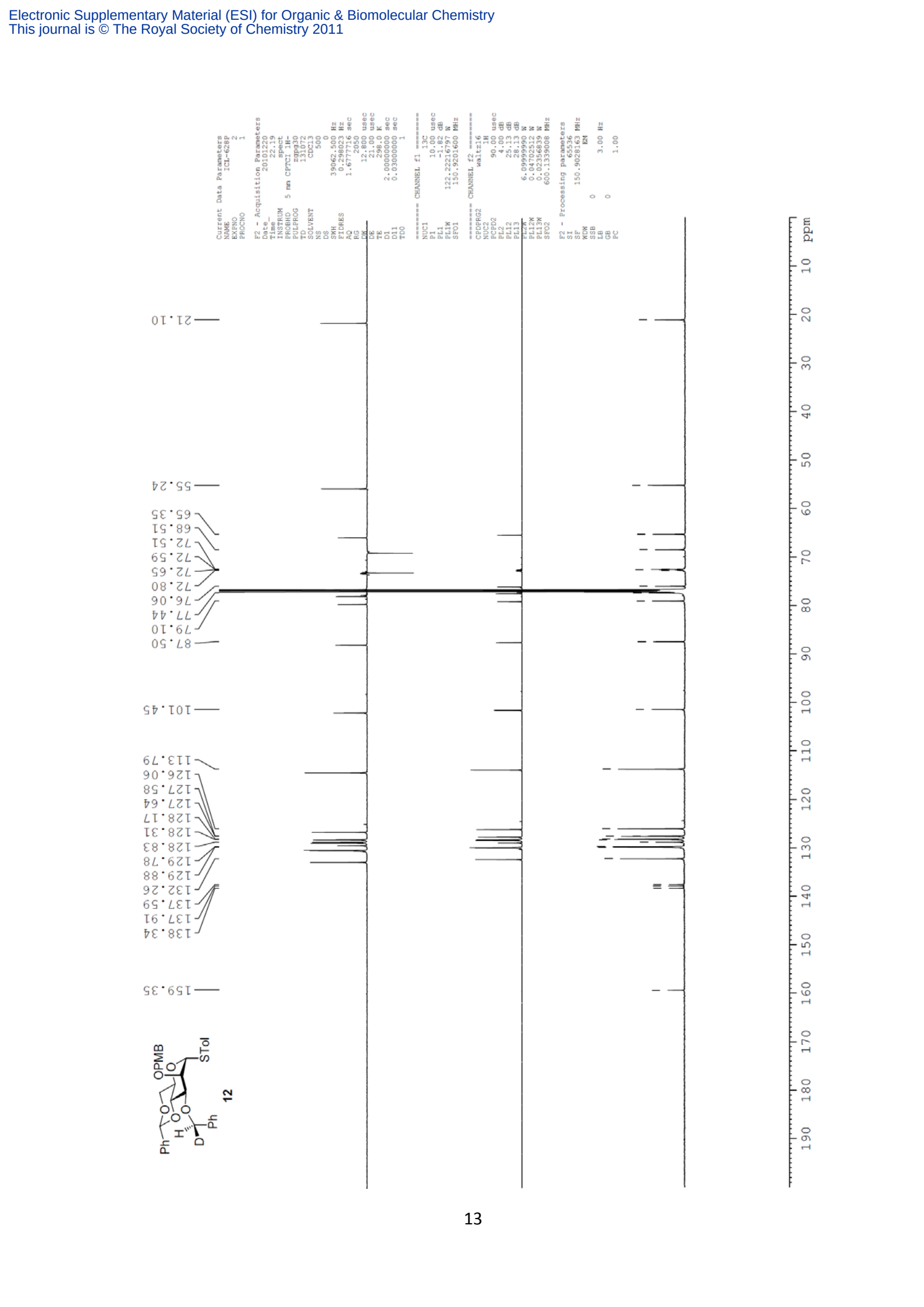
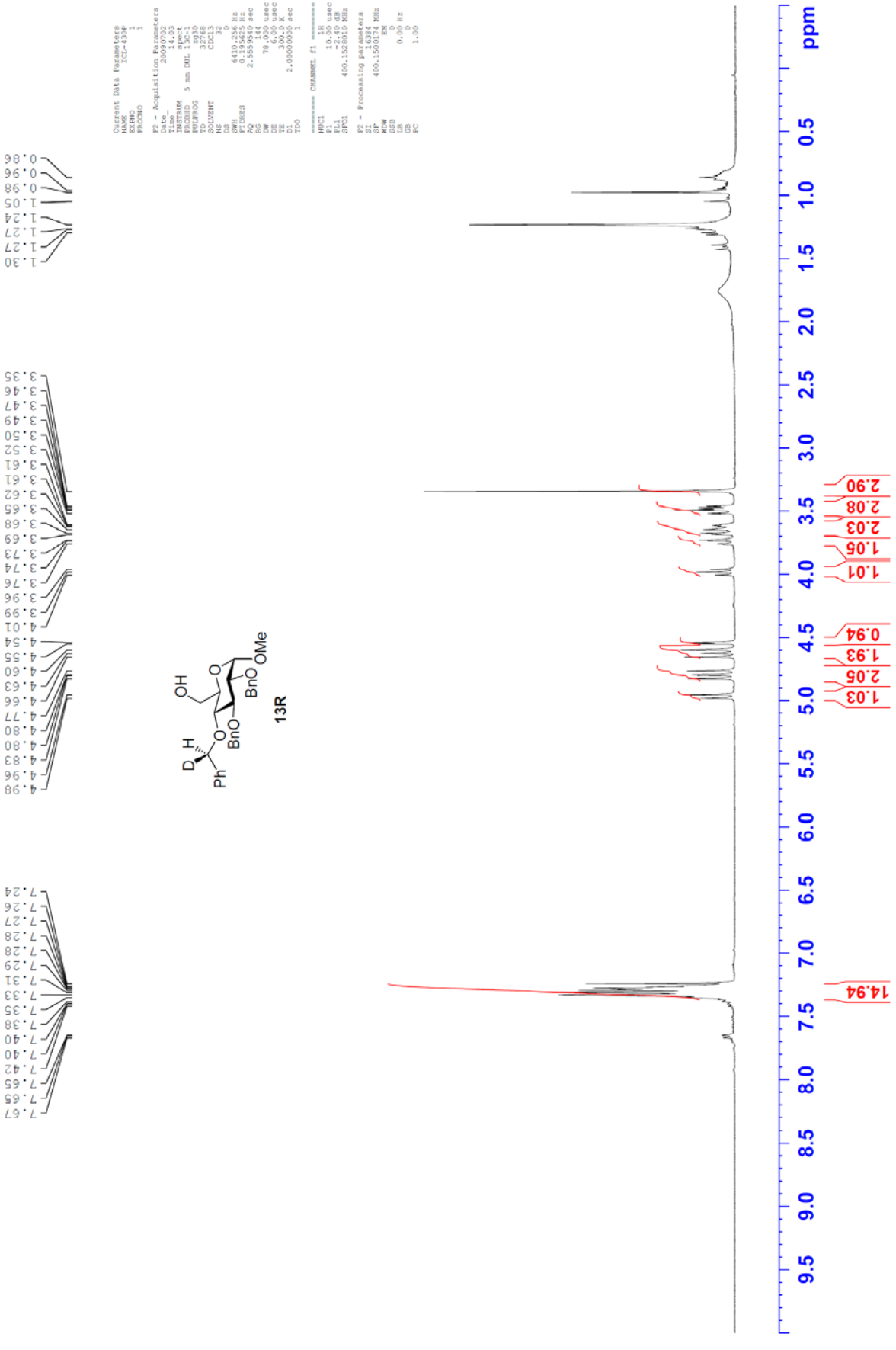
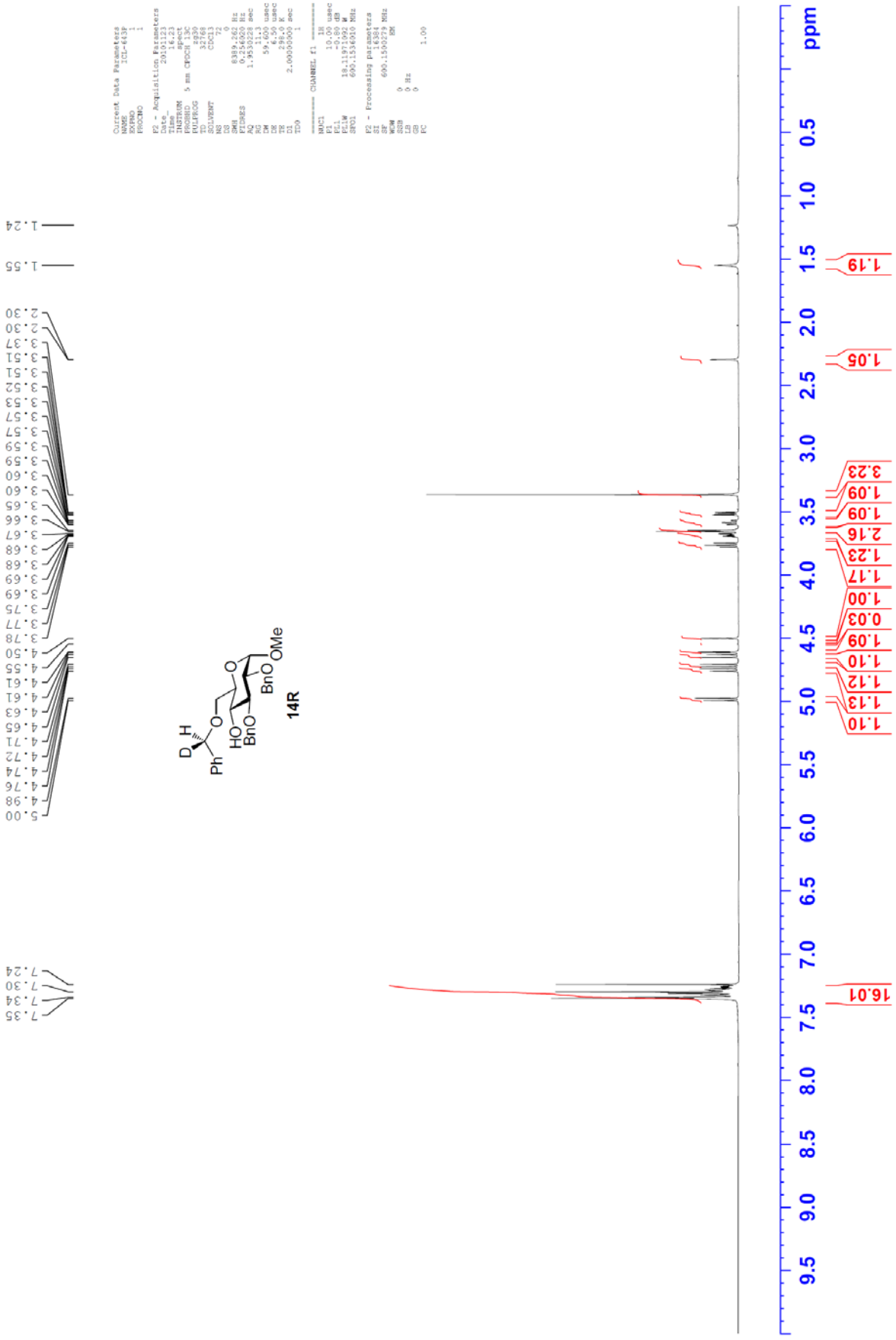
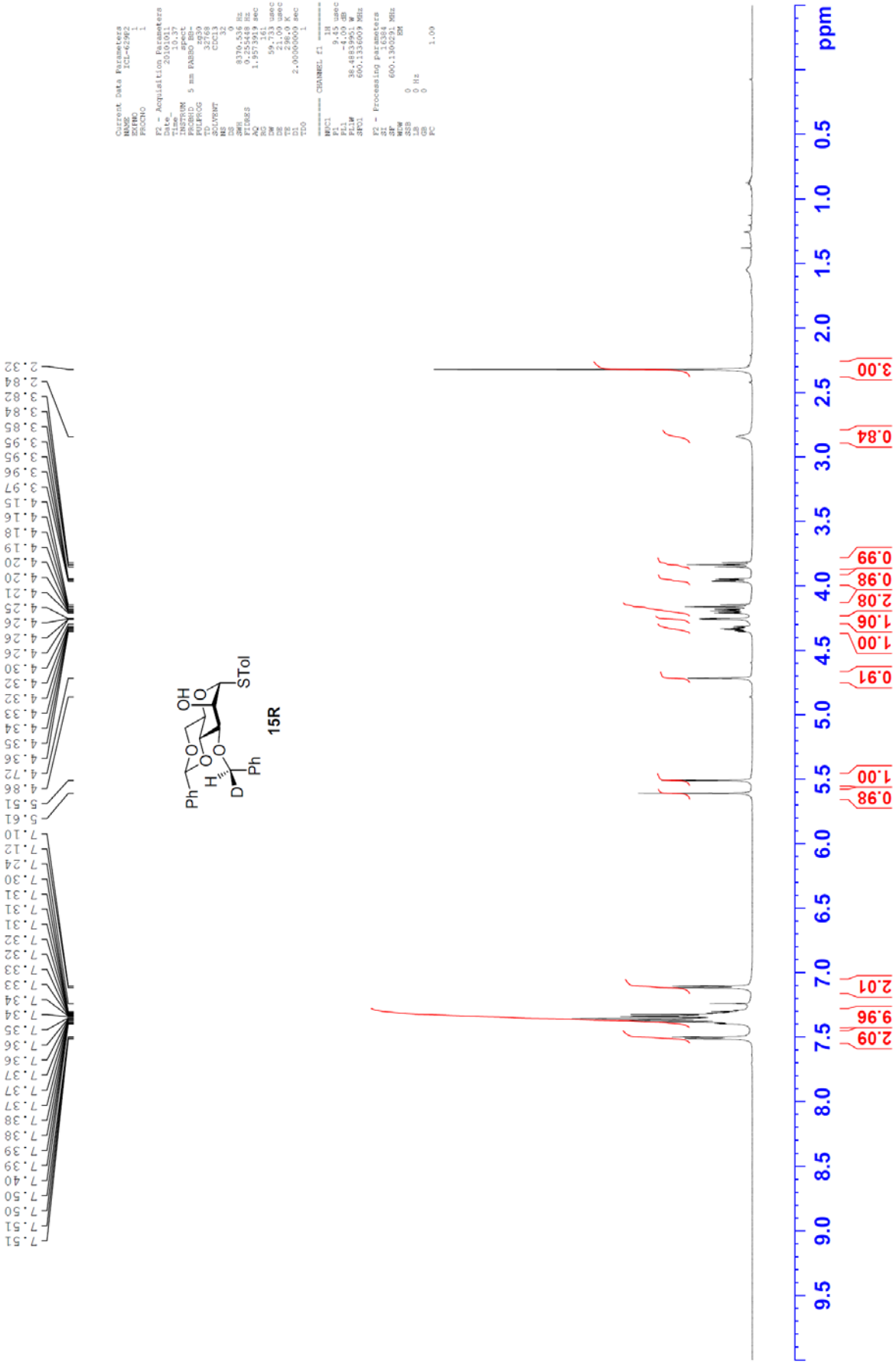

OPMB
STol
Ph
Ph
D
H
12
ppm




13R
OH
BnO
OMe
BnO
D
H
Ph
ppm
14.94
2.90
2.08
2.03
1.05
1.01
0.94
1.93
2.05
1.03


14R
BnO
OMe
HO
BnO
Ph
D H
ppm


15R
STol
OH
Ph
Ph
D
H
ppm