Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

for

Angew. Chem. Int. Ed. 200460176

69451 Weinheim, Germany

Iterative One-Pot Oligosaccharide Synthesis

Xuefei Huang,[a]* Lijun Huang[a], Haishen Wang[b], and Xin-Shan Ye[b*]

[a]Department of Chemistry, University of Toledo, 2801 West Bancroft Street, MS 602, Toledo, Ohio 43606, USA
[b]The State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Xue Yuan Road #38, Beijing, China 100083

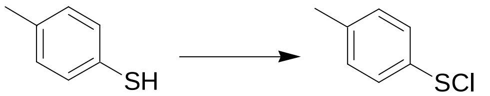
General Procedures. All reactions were carried out under argon or nitrogen with anhydrous solvents in flame-dried glassware, unless otherwise noted. All glycosylation reactions were performed in the presence of molecular sieves, which were flame-dried right before the reaction under high vacuum. Glycosylation solvents were freshly distilled before usage over drying agents (Et_2O with Na/benzophenone, CH_2Cl_2 with CaH_2). Chemicals used were reagent grade as supplied except where noted. Analytical thin-layer chromatography was performed using silica gel 60 F254 glass plates (EM Science); compound spots were visualized by UV light (254 nm) and/or by staining with a yellow solution containing $Ce(NH_4)_2(NO_3)_6$ (0.5 g) and $(NH_4)_6Mo_7O_{24}4H_2O$ (24.0 g) in 6% H_2SO_4 (500 mL). Flash column chromatography was performed on silica gel 60 (230-400 Mesh, EM Science). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian VXRS-400 or Inova-600 instrument and were referenced using TMS (0 ppm), residual $CHCl_3$ (δ ^{1}H-NMR 7.26 ppm, ^{13}C-NMR 77.0 ppm) or residual CD_2HOD (δ ^{1}H-NMR 3.30 ppm, ^{13}C-NMR 49.0 ppm). ESI mass spectra were recorded on ESQUIRE LC-MS operated in positive ion mode. High-resolution mass spectra were recorded on a Micromass electrospray Tof™ II (Micromass, Wythenshawe, UK) mass spectrometer equipped with an orthogonal electrospray source (Z-spray) operated in positive ion mode.

General Procedure for Chemoselective Glycosylation. After a mixture of donor (60 μmol), AgOTf (120 μmol) and MS-AW-300 (300 mg) in Et_2O (2 mL) was stirred at -60° C for 1h, *p*-toluene sulfenyl chloride (*p*-TolSCl) (60 μmol, 8.6 μL) was added via a micro-syringe. After five minutes when TLC indicated that donor was completely activated, a solution of the acceptor (54 μmol) in Et_2O or CH_2Cl_2 (0.5 mL) was added. The reaction mixture was stirred further for 15 minutes and warmed up to room temperature, followed by addition of triethylamine and filtration to remove all insoluble material. The filtrate was concentrated and the desired compound was purified by silica gel chromatography. Typical conditions for chromatography are silica gel / product ~ 2000 by weight with a flow rate of approximate 5 mL/min and a solvent gradient of R_f ~ 0.1 - 0.3.

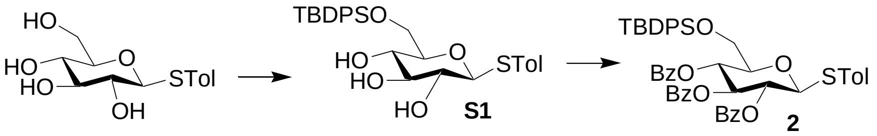
General Procedure for One-pot Synthesis. After a mixture of donor (60 μmol), AgOTf (240 μmol) and MS-AW-300 (300 mg) was stirred at -60° C for 1h, *p*-TolSCl (60 μmol, 8.6 μL) was added via a micro-syringe. After five minutes when TLC indicated that donor was completely activated, a solution of acceptor 1 (54 μmol) in Et_2O or CH_2Cl_2 (0.5 mL) was added. After 15 minutes, the reaction mixture was warmed to room temperature and stirred for 15 minutes before cooling back to -60° C. *p*-TolSCl (54 μmol, 7.5 μL) was added to the reaction mixture followed by a solution of acceptor 2 (49 μmol). The whole process was repeated until the addition of last acceptor. Et_2O was used as the glycosylation solvent unless otherwise specified. The reaction was quenched with triethylamine and all insoluble material was removed by filtration. The desired compound was purified by silica gel flash chromatography. Typical conditions for chromatography are silica gel / product ~ 2000 by weight with a flow rate of approximate 5 mL/min and a solvent gradient of R_f ~ 0.1 - 0.3.

In oligosaccharides containing glucose or galactose, stereochemistry of the glycosidic linkages are determined by the coupling constant $^3J(^1H, ^1H)$ between H1 and H2 protons. In mannosyl linkages, the stereochemistry is determined by $^1J(^{13}C, ^1H)$ between anomeric carbon and anomeric proton.[1]

Building blocks **1**, **3, 4, 7, 15, 21** and **22** were synthesized according to literature procedures.[2, 3]

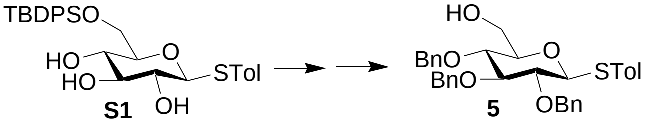


***p*-Toluene sulfenyl chloride**.[4] To a solution of 4-methylbenzenethiol (6.20g, 50 mmol) in anhydrous hexanes (25 mL) at 0° C was added sulfuryl chloride (4.8 mL, 60 mmol) over 10 minutes. The reaction was warmed to room temperature after one hour, and stirred at room temperature for one more hour. After removal of hexanes and excess sulfuryl chloride under vacuum, *p*-TolSCl (5.6 g, d=1.1, 70%) was obtained by vacuum distillation (50 ° C, 1 mmHg) using a short-path distillation apparatus as a red liquid. ^{1}H-NMR (399.95 MHz, $CDCl_3$) δ 2.40 (s, 3H), 7.20-7.25 (m, 2H), 7.60-7.65 (m, 2H).

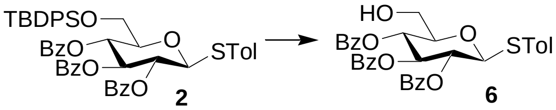


***p*-Tolyl-2,3,4-tri-*O*-benzoyl-6-*O*-^{t}butyldiphenylsilyl-1-thio-β-D-glucopyranoside (2).** A solution of *p*-tolyl-1-thio-β-D-glucopyranoside (4.0 g, 14.0 mmol),[3] imidazole (1.4 g, 20.6 mmol) and *tert*-butyldiphenylsilyl chloride (4.0 g, 14.5 mmol) in DMF (10 mL) was stirred at room temperature for 12 hours. Diethyl ether (30 mL) and sat. aqueous NH_4Cl solution (30 mL) were added. The organic layer was collected and purified by flash column chromatography to give the corresponding 6-*O-tert*-butyldiphenylsilyl ether **S1** (6.6 g, 90%) as a syrup.

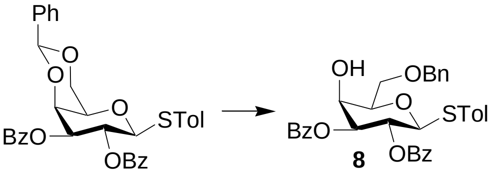
To a solution of **S1** (1.5 g, 2.9 mmol) and *N,N*-dimethylamino pyridine (0.35 g, 2. 9 mmol) in pyridine (5 mL) and CH_2Cl_2 (20 mL) was added benzoyl chloride (1.45 g, 10.3 mmol) at 0° C. The mixture was stirred overnight and was washed with 1N HCl (10 mL) three times. The organic layer was collected and the desired product **2** (1.72 g, 72%) was obtained as a white foam after flash chromatography. ^{1}H-NMR (399.95 MHz, $CDCl_3$) δ 1.04 (s, 9H), 2.32 (s, 3H), 3.80 – 3.93 (m, 3H), 4.96 (d, 1H, *J* = 9.6 Hz), 5.44 (t, 1H, *J* = 9.6 Hz), 5.61 (t, 1H, *J* = 9.6 Hz), 5.82 (t, 1H, *J* = 9.6 Hz), 7.02 – 7.08 (m, 2H), 7.13 – 7.95 (m, 27H); ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ 19.38, 21.43, 26.87, 62.98, 69.06, 70.95, 74.98, 79.66, 86.61, 127.84, 127.91, 128.41, 128.45, 128.87, 129.95, 129.99, 130.01, 130.10, 133.11, 133.14, 133.30, 133.42, 133.86, 135.75, 135.88, 138.65, 165.17, 165.28, 166.14; HRMS $C_{50}H_{48}NaO_8SSi$ [M + Na$^+$] calc. 859.2737 found 859.2740.



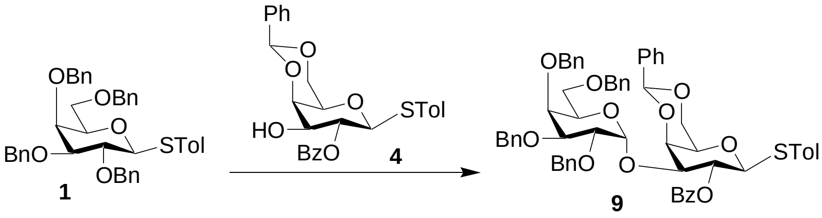
***p*-Tolyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (5).** To a solution of the 6-*O*-^{t}butyldiphenylsilyl ether **S1** (3 g, 5.7 mmol) in DMF (10 mL), 60% NaH (0.9 g, 22.5 mmol) was added at 0° C. The solution became very viscous and additional DMF (30 mL) was added followed by benzyl bromide (3.9 g, 22.8 mmol). The reaction mixture was stirred at room temperature overnight. Diethyl ether (60 mL) and sat. aqueous NH_4Cl solution (30 mL) were added. The organic layer was collected and purified by flash column chromatography to give the corresponding 2,3,4-tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl ether (3.2 g, 70%) as a syrup. The 2,3,4-tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl ether (2.2 g, 2.8 mmol) was dissolved in 1 M solution of tetrabutylammonium fluoride in THF (8 mL) and the mixture was stirred for four hours. Diethyl ether (30 mL) and sat. aqueous NH_4Cl solution (30 mL) were added. The organic layer was collected and purified by flash column chromatography to give the desired product **5** (1.36 g, 88%) as a white solid. ^{1}H-NMR (399.95 MHz, $CDCl_3$) δ 1.88 (t, 1H, J = 6.8 Hz), 3.34 – 3.43 (m, 1H), 3.48 (t, 1H, J = 9.2 Hz), 3.58 (t, 1H, J = 9.2 Hz), 3.68 – 3.78 (m, 2H), 3.84 – 3.91 (m, 1H), 4.63 – 4.70 (m, 2H), 4.78 (d, 1H, J = 10.4 Hz), 4.85 – 4.97 (m, 4H), 7.10 – 7.17 (m, 2H), 7.22 – 7.48 (m, 17H); ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ 21.38, 62.38, 75.36, 75.75, 76.06, 77.87, 79.51, 81.33, 86.81, 88.07, 128.00, 128.05, 128.22, 128.29, 128.47, 128.69, 128.72, 128.77, 129.71, 130.06, 132.89, 138.10, 138.21, 138.29, 138.58; HRMS $C_{34}H_{36}NaO_5S$ [M + Na$^+$] calc. 579.2181 found 579.2205.



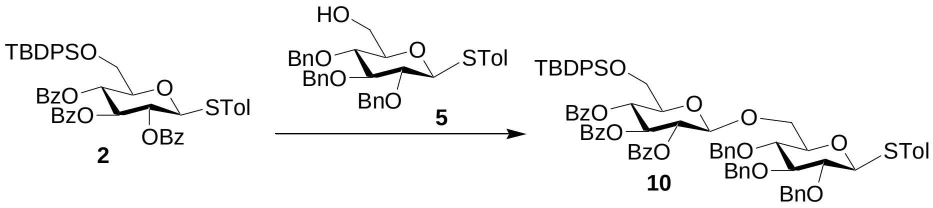
***p*-Tolyl-2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (6).** To a solution of **2** (1.45 g, 1.73 mmol) in 1 M solution of tetrabutylammonium fluoride in THF (7 mL) was added acetic acid until the pH of the solution was around 6. The reaction mixture was stirred at room temperature for 4 hours. Diethyl ether (10 mL) and sat. aqueous NH_4Cl solution (30 mL) were added. The organic layer was collected and purified by flash column chromatography to give the desired product **6** (1.1 g, 100%) as a white solid. ^{1}H-NMR (599.87 MHz, $CDCl_3$) δ 2.33 (s, 3H), 2.62 (dd, 1H, J = 5.4, 8.4 Hz), 3.76 (dt, 1H, J = 5.4, 12.6 Hz), 3.80-3.88 (m, 2H), 4.99 (d, 1H, J = 10.2 Hz), 5.45 (t, 1H, J = 9.6 Hz), 5.46 (t, 1H, J = 9.6 Hz), 5.92 (t, 1H, J = 9.6 Hz), 7.10 – 7.14 (m, 2H), 7.22 – 7.26 (m, 2H); 7.33 – 7.42 (m, 7H), 7.47 – 7.52 (m, 2H), 7.78 – 7.82 (m, 2H), 7.91 – 7.93 (m, 2H), 7.95 – 7.98 (m, 2H); ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ 21.44, 61.88, 69.56, 70.94, 74.44, 79.10, 86.49, 128.54, 128.66, 128.74, 129.96, 130.10, 130.15, 133.49, 133.57, 133.89, 134.01, 139.03, 165.30, 166.10; HRMS $C_{34}H_{30}NaO_8S$ [M + Na$^+$] calc. 621.1559 found 621.1600.



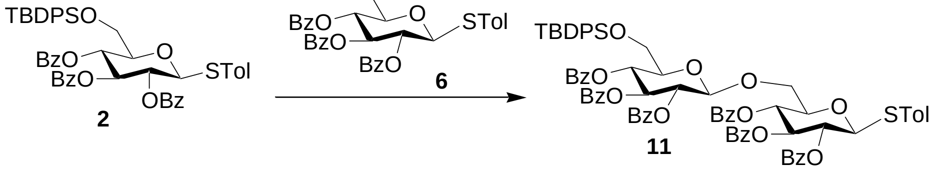
***p*-Tolyl-2,3-di-*O*-benzoyl-6-*O*-benzyl-1-thio-β-D-galactopyranoside (8).** A solution of *p*-tolyl-2,3-*O*-dibenzoyl-4,6-*O*-benzylidene-1-thio-β-D-galactopyranoside (0.1 g, 172 µmol)[3] and sodium cyanoborohydride (0.11 g, 1.7 mmol) in THF (2 mL) was stirred for one hour in the presence of MS-AW-300 (400 mg) at 0° C. A solution of 2 M hydrogen chloride in ether (1 mL) was added slowly until no more gas was evolved. The reaction mixture was further stirred for one hour and the solid was filtered off. CH_2Cl_2 (10 mL) was added to the filtrate followed by sat. aqueous $NaHCO_3$ (10 mL) solution. The organic layer was collected and **8** (0.09 g, 90%) was obtained after flash chromatography. ^{1}H-NMR (399.95 MHz, $CDCl_3$) δ 2.04(s 3H), 2.87 (d, 1H, J = 4.4 Hz), 3.57-3.59 (m, 3H), 4.38-4.43 (m, 1H), 4.57-4.64 (m, 2H), 4.88 (d, 1H, J = 10.0 Hz), 5.31 (dd, 1H, J = 3.2, 10.0 Hz), 5.77 (t, 1H, J = 10.0 Hz); ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ 21.43, 60.65, 68.28, 68.56, 69.89, 74.06, 75.88, 77.49, 87.07, 128.02, 128.10, 128.59, 128.64, 128.72, 129.37, 129.82, 129.89, 130.03, 130.10, 133.39, 133.59, 133.64, 137.89, 138.54, 165.51, 166.09; HRMS $C_{34}H_{32}NaO_7S$ [M + Na$^+$] calc. 607.1766 found 607.1732.



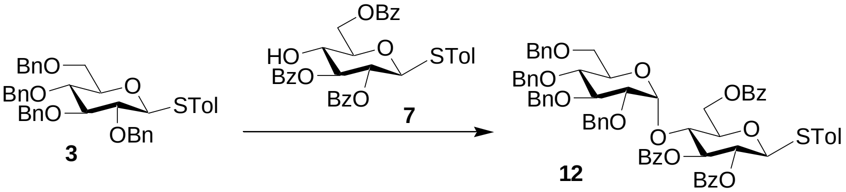
***p*-Tolyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-2-*O*-benzoyl-4,6-*O*-benzylidene-1-thio-β-D-galactopyranoside (9).** Compound **9** (38.0 mg, 36 μmol, 87 % yield) was prepared according to the general procedure for chemoselective glycosylation from donor **1** (30.0 mg, 46 μmol) and acceptor **4** (21 mg, 42 μmol). ^{1}H NMR (500 MHz, $CDCl_3$) : 7.96 (d, *J* = 8.0 Hz, 2H), 7.41-7.45 (m, 3H), 7.34 (d, *J* = 7.5 Hz, 2H), 7.02- 7.27 (m, 23H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 5.49 (t, *J* = 9.5 Hz, 1H), 5.32 (s, 1H), 4.98 (d, *J* = 3.0 Hz, 1H), 4.70 (d, *J* = 11.8 Hz, 1H), 4.65 (d, *J* = 9.5 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 11.5Hz, 1H), 4.39 (d, *J* = 11.5 Hz, 1H), 4.35 (d, *J* = 12.0 Hz, 1H), 4.24-4.31 (m, 4H), 4.18 (d, *J* = 12.0 Hz, 1H), 3.84- 3.94 (m, 3H), 3.74 (t, *J* = 6.0 Hz, 1H), 3.55 (d, *J* = 10.0 Hz, 1H), 3.34 (d, *J* = 13.0 Hz, 2H), 3.16 (m, 2H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) : 164.62, 138.80, 138.66, 138.54, 138.28, 138.08, 137.66, 134.16, 132.92, 130.07, 129.81, 129.46, 128.89, 128.29, 128.22, 128.14, 128.10, 128.06, 127.80, 127.66, 127.55, 127.46, 127.38, 127.30, 127.25, 126.55, 101.04, 94.64, 85.44, 78.59, 75.80, 75.53, 74.94, 74.57, 74.23, 73.12, 72.17, 71.80, 69.91, 69.84, 69.34, 68.98, 68.66, 21.25. TOF-MS [M + NH_4^+] calc. for $C_{61}H_{64}O_{11}SN$ 1018, found 1018.



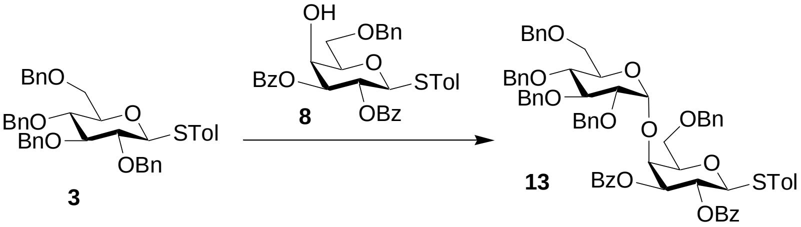
***p*-Tolyl-2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4-tri-*O*-benzoyl-6-*O*-^{t}butyldiphenylsilyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (10).** Compound **10** (42 mg, 34.7 μmol, 69 % yield) was prepared according to the general procedure for chemoselective glycosylation from donor **2** (42 mg, 50 μmol) and acceptor **5** (28 mg, 50 μmol). ^{1}H-NMR (399.95 MHz, $CDCl_3$) δ 1.04 (s, 9H), 2.34 (s, 3H), 3.37 (d, 1H, *J* = 9.2 Hz), 3.41 (d, 1H, *J* = 8.4 Hz), 3.45 (dd, 1H, *J* = 3.6, 10.0 Hz), 3.61 (t, 1H, *J* = 8.8 Hz), 3.76 – 3.88 (m, 4H), 4.18 (d, 1H, *J* = 11.2 Hz), 4.41 (d, 1H, *J* = 11.2 Hz), 4.52 (d, 1H, *J* = 10.0 Hz), 4.54 (d, 1H, *J* = 10.0 Hz), 4.65 (d, 1H, *J* = 10.0 Hz), 4.72 (d, 1H, *J* = 10.8 Hz), 4.82 (d, 1H, *J* = 7.6 Hz), 4.85 (d, 1H, *J* = 10.4 Hz), 4.89 (d, 1H, *J* = 7.6 Hz), 5.56 (dd, 1H, *J* = 8.0, 10.0 Hz), 5.65 (t, 1H, *J* = 9.6 Hz), 5.80 (t, 1H, *J* = 9.6 Hz), 7.08 – 7.90 (m, 44 H); ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ 19.41, 21.83, 26.91, 63.07, 67.88, 69.58, 72.41, 73.73, 75.00, 75.42, 75.52, 75.84, 77.64, 79.19, 80.67, 86.87, 87.88, 101.21, 127.88, 127.96, 128.04, 128.09, 128.43, 128.49, 128.53, 128.59, 128.64, 129.31, 129.53, 129.66, 129.82, 129.87, 129.90, 129.99, 130.01, 130.03, 130.13, 133.04, 133.22, 133.30, 133.38, 133.41, 135.74, 135.92, 138.15, 138.18, 138.40, 138.63, 165.24, 165.26, 166.15; HRMS $C_{77}H_{76}NaO_{13}SSi$ [M + Na^+] calc. 1291.4674 found 1291.4651.



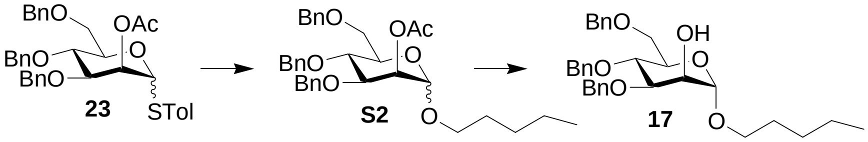
***p*-Tolyl-2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4-tri-*O*-benzoyl-6-*O*-^{t}butyldiphenylsilyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (11).** Compound **11** (37 mg, 28 μmol) was prepared according to the general procedure for chemoselective glycosylation from donor **2** (42 mg, 50 μmol) and acceptor **6** (25 mg, 42 µmol) in 67 % yield. ^{1}H-NMR (599.87 MHz, $CDCl_3$) δ 1.00(s, 9H), 2.34 (s, 3H), 3.76 – 3.84 (m, 4H), 3.89 (dd, 1H, *J* = 7.8, 12.0 Hz), 3.96 – 4.02 (m, 2H), 4.77 (d, 1H, *J* = 10.2 Hz), 4.97 (d, 1H, *J* = 8.4 Hz), 5.23 (t, 1H, *J* = 9.6 Hz), 5.32 (t, 1H, *J* = 9.6 Hz), 5.46 (dd, 1H, *J* = 7.8, 9.6 Hz), 5.59 (t, 1H, *J* = 9.6 Hz), 5.75 (t, 1H, *J* = 9.6 Hz), 5.80 (t, 1H, *J* = 9.6 Hz), 7.14 – 7.98 (m, 44 H); ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ 19.35, 21.46, 26.87, 62.85, 68.44, 69.43, 69.83, 70.77, 72.32, 73.60, 74.41, 75.42, 78.85, 86.23, 101.12, 127.74, 127.86, 127.89, 128.44, 128.48, 128.52, 158.57, 128.60, 128.63, 128.92, 129.09, 129.48, 128.56, 129.69, 129.83, 129.93, 130.01, 130.02, 130.08, 130.11, 130.18, 130.23, 133.10, 133.29, 133.34, 133.41, 133.45, 133.55, 133.67, 135.71, 135.85, 139.14, 165.18, 165.20, 165.47, 165.89, 166.08; HRMS $C_{77}H_{70}NaO_{16}SSi$ [M + Na^{+}] calc. 1333.4052 found 1333.4049.



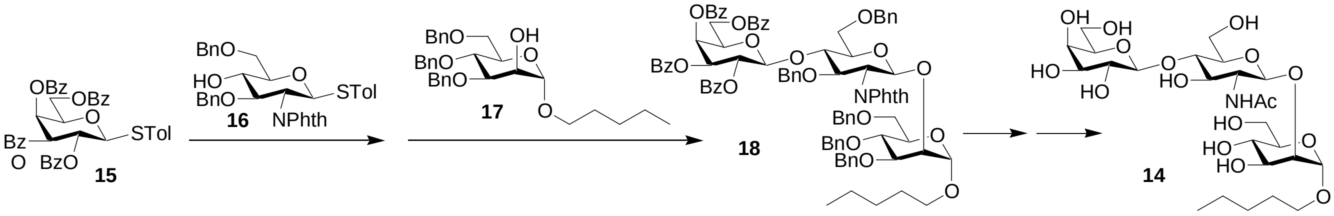
p-Tolyl-2,3,6-tri-O-benzoyl-4-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (12). Compound **12** (37 mg, 34 µmol) was prepared according to the general procedure for chemoselective glycosylation from donor **3** (36 mg, 56 µmol) and acceptor **7** (30 mg, 50 µmol) in 67 % yield. ^{1}H-NMR (599.87 MHz, $CDCl_3$) δ 2.23 (s, 3H), 3.21 (dd, 1H, *J* = 3.6, 10.2 Hz), 3.45 – 3.53 (m, 2H), 3.57 (dd, 1H, *J* = 3.6, 10.8 Hz), 3.77 (d, 1H, *J* = 12.6 Hz), 3.79 – 3.83 (m, 1H), 3.88 (t, 1H, *J* = 9.6 Hz), 3.88 – 3.93 (m, 1H), 4.06 (t, 1H, *J* = 9.6 Hz), 4.11 (d, 1H, *J* = 12.6 Hz), 4.30 (d, 1H, *J* = 12.0 Hz), 4.36 (d, 1H, *J* = 10.8 Hz), 4.47 (d, 1H, *J* = 12.0 Hz), 4.54 (dd, 1H, *J* = 4.8, 12.0 Hz), 4.66 – 4.71 (m, 2H), 4.72 (d, 1H, *J* = 10.8 Hz), 4.79 (d, 1H, *J* = 3.0 Hz), 4.86 (d, 1H, *J* = 10.2 Hz), 4.96 (dd, 1H, *J* = 1.8, 12.0 Hz), 5.39 (t, 1H, *J* = 9.6 Hz), 5.82 (t, 1H, *J* = 9.0 Hz), 6.84 – 6.88 (m, 2 H), 7.04 – 7.52 (m, 30 H), 7.61 – 7.65 (m, 1 H), 7.92 – 7.97 (m, 4 H), 8.01 – 8.04 (m, 2 H); ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ 21.40, 63.68, 68.42, 70.83, 72.02, 73.00, 73.69, 75.08, 75.57, 75.73, 77.01, 77.48, 77.80, 79.17, 81.61, 86.05, 100.13, 127.77, 127.85, 127.90, 127.94, 128.13, 128.17, 128.22, 128.43, 128.50, 128.54, 128.57, 128.64, 129.57, 129.77, 130.03, 130.09, 130.26, 133.17, 133.30, 133.44, 134.09, 138.04, 138.33, 138.54, 138.62, 138.91, 165.51, 165.76, 166.07; HRMS $C_{68}H_{64}NaO_{13}S$ [M + Na^{+}] calc. 1143.3965 found 1143.4037.



p-Tolyl-6-O-benzyl-4-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-2,3-di-O-benzoyl-1-thio-β-D-galactopyranoside (13). Compound **13** (40 mg, 36 µmol, 65% yield) was prepared according to the general procedure for chemoselective glycosylation from donor **3** (40 mg, 62 µmol) and acceptor **8** (32 mg, 55 µmol). ^{1}H-NMR (599.87 MHz, $CDCl_3$) δ 2.11 (s, 3H), 2.85 (dd, 1H, *J* = 1.8, 11.4 Hz), 3.14 (dd, 1H, *J* = 1.8, 10.8 Hz), 3.51 (dd, 1H, *J* = 3.0, 9.6 Hz), 3.66 (t, 1H, *J* = 9.6 Hz), 3.75 (dd, 1H, *J* = 5.4, 9.0 Hz), 3.89 – 3.96 (m, 4H), 4.05 (d, 1H, *J* = 12.0 Hz), 4.33 (bs, 2H), 4.36 (d, 1H, *J* = 11.4 Hz), 4.38 (d, 1H, *J* = 11.4 Hz), 4.40 (d, 1H, *J* = 3.0 Hz), 4.61 (d, 1H, *J* = 11.4 Hz), 4.75 (d, 1H, *J* = 11.4 Hz), 4.79 (d, 1H, *J* = 11.4 Hz), 4.83 (d, 1H, *J* = 9.6 Hz), 4.85 (d, 1H, *J* = 10.8 Hz), 4.92 (d, 1H, *J* = 3.6 Hz), 5.30 (dd, 1H, *J* = 3.0, 10.2 Hz), 5.64 (d, 1H, *J* = 10.2 Hz), 6.98 – 7.02 (m, 2H), 7.08 – 7.95 (m, 37 H); ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ 21.32, 67.86, 68.19, 68.51, 71.30, 73.46, 73.61, 74.12, 75.04, 75.29, 75.45, 75.79, 77.93, 78.44, 80.45, 82.03, 86.31, 127.66, 127.91, 127.93, 127.95, 128.04, 128.10, 128.14, 128.25, 128.30, 128.39, 128.45, 128.56, 128.64, 128.78, 129.46, 129.80, 129.91, 129.94, 130.03, 130.25, 133.29, 133.44, 133.49, 134.13, 135.04, 137.68, 138.17, 138.18, 138.23, 138.63, 138.85, 139.08, 165.25, 166.21; HRMS $C_{68}H_{66}NaO_{12}S$ [M + Na$^+$] calc. 1129.4173 found 1129.4216.

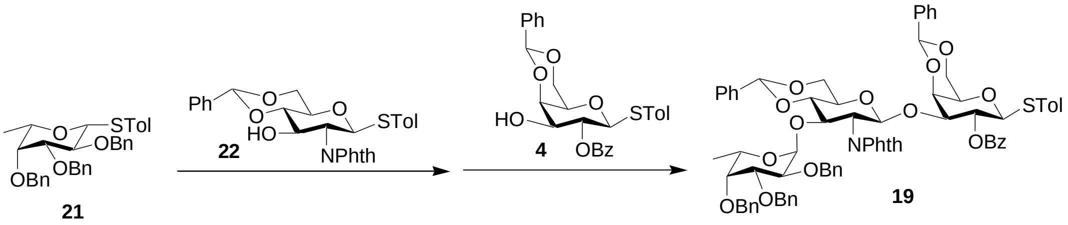


Pentyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (17). To a mixture of **23** (260 mg, 440 μmol), 1-pentanol (90 mg, 1.2 mmol), AgOTf (20 mg, 80 μmol) and MS-AW-300 in CH_2Cl_2 (10 mL) under nitrogen at 0 °C was added N-iodosuccinimide (137 mg, 600 μmol). After 1 hour, the reaction was quenched by addition of sat. aqueous $NaHCO_3$ solution (20 mL). The organic layer was collected and **S2** was obtained after flash chromatography as an α:β mixture. To a solution of **S2** in anhydrous methanol (5 mL) was added a solution of 30 % NaOMe in methanol (0.1 mL). The reaction mixture was stirred at room temperature for 2 hours. Amberlite IR120 was added until the solution became acidic. The resin was filtered off and **17** (160 mg, 71%) was obtained after flash chromatography separation of anomers (α : β ~ 4 : 1). ^{1}H-NMR (399.95 MHz, $CDCl_3$) δ 0.92 (t, *J* = 10.2 Hz, 3H), 1.25 – 1.40 (m, 4H), 1.58 (quin, *J* = 10.2 Hz, 2H), 2.53 (bs, 1H), 3.39-3.45 (m, 1H), 3.66-3.95 (m, 6H), 4.02-4.08 (m, 1H), 4.52 (d, 1H, *J* = 10.4 Hz), 4.56 (d, 1H, *J* = 12.4 Hz), 4.64-4.78 (m, 3H), 4.84 (d, *J* = 10.8 Hz, 1H), 4.92 (bs, 1H), 7.12-7.42 (m, 14H); ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ 14.31, 22.74, 28.57, 29.38, 68.02, 68.72, 69.23, 71.27, 72.22, 73.70, 74.67, 75.45, 80.60, 99.41, 127.79, 127.95, 128.09, 128.15, 128.26, 128.57, 128.62, 128.77, 138.27, 138.56; ESI-MS $C_{32}H_{40}NaO_6$ [M + Na$^+$] calc. 543.3 found 543.3.

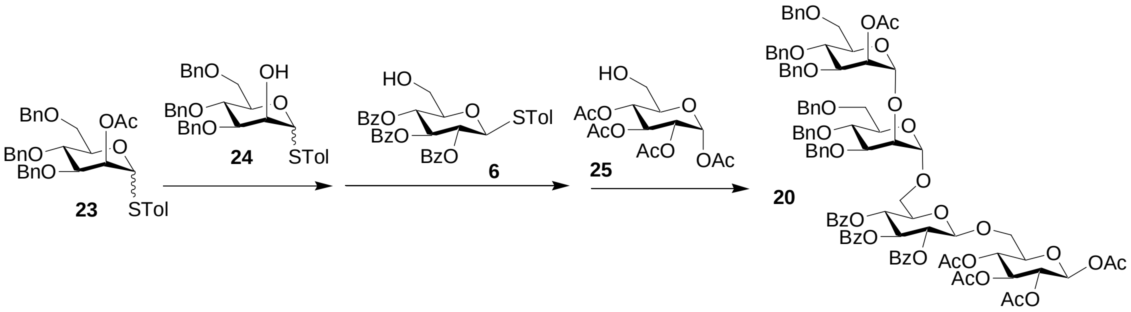


Pentyl-2-*O*-(2-deoxy-3,6-di-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-2-*N*-phthalimido-β-D-glucopyranosyl)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (18). Compound **18** (40 mg, 25.5 μmol, 54% yield) was synthesized according to the general procedure for one-pot synthesis from donor **15** (35 mg, 50 μmol), building block **16** (28 mg, 47 μmol), and **17** (28 mg, 54 μmol) using CH_2Cl_2 as a solvent. ^{1}H-NMR (599.87 MHz, $CDCl_3$) δ 0.80 (t, 3H, *J* = 7.2 Hz), 1.10 – 1.26 (m, 4H), 1.36 (quin, 2H, *J* = 7.2 Hz), 2.94 (dd, 1H, *J* = 6.6, 10.8 Hz), 3.11 (dt, 1H, *J* = 7.2, 9.0 Hz), 3.38 – 3.52 (m, 5H), 3.55 (d, 1H, *J* = 10.2 Hz), 3.70 – 3.76 (m, 2H), 3.94 – 4.08 (m, 4H), 4.22 – 4.43 (m, 8H), 4.65 (d, 1H, *J* = 12.0 Hz), 4.72 (d, 1H, *J* = 12.0 Hz), 4.73 (d, 1H, *J* = 12.0 Hz), 4.74 (d, 1H, *J* = 10.8 Hz), 4.98 – 5.02 (m, 2H), 5.17 (d, 1H, *J* = 7.8 Hz), 5.43 (dd, 1H, *J* = 3.6, 10.8 Hz), 5.79 (dd, 1H, *J* = 7.8, 10.8 Hz), 5.85 (d, 1H, *J* = 3.6 Hz), 6.78 – 6.82 (m, 2 H), 7.06 – 7.68 (m, 39H), 7.74 – 7.78 (m, 2H), 7.89 – 7.94 (m, 4H), 8.06 – 8.42 (m, 2H); ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ 14.20, 22.62, 28.41, 29.21, 55.77, 60.64, 61.97, 67.89, 68.32, 68.43, 70.24, 70.62, 70.83, 71.40, 71.92, 71.97, 73.08, 73.75, 73.87, 74.49, 74.94, 75.07, 76.80, 77.25, 78.03, 78.37, 97.16, 100.82, 123.32, 127.28, 127.49, 127.56, 127.64, 127.74, 127.98, 128.06, 128.12, 128.38, 128.45, 128.48, 128.52, 128.55, 128.61, 128.68, 129.17, 129.32, 129.71, 129.98, 130.06, 132.02, 133.47, 133.51, 133.68, 138.25, 138.69, 138.76, 138.81, 165.22, 165.53, 165.69, 166.26; HRMS $C_{94}H_{91}NNaO_{21}$ [M + Na$^+$] calc. 1952.5981 found 1952.5961.

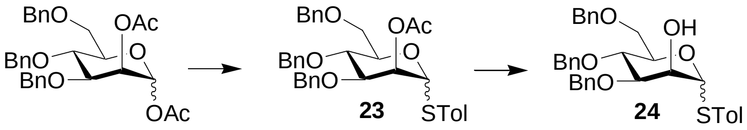
Pentyl-2-*O*-(2-*N*-acetamido-2-deoxy-4-*O*-β-D-galactopyranosyl-β-D-glucopyranosyl)-α-D-mannopyranoside (14). The mixture of trisaccharide **18** (16 mg, 8.27 μmol) and ethylenediamine (300 μL, 4.45 mmol) in EtOH (2 mL) was refluxing for 16 h at 105-110°C. The reaction mixture was concentrated in vaccum, and the residue was coevaporated with toluene (2x10 mL) and ethanol (2x5 mL). The crude product was redissolved in MeOH (1.5 mL) and acetic anhydride (300 μL) was added. After stirred for 6 h at rt, the resulting mixture was concentrated under reduced pressure and purified by flash column chromatography. The resulting partially deprotected trisaccharide was dissolved in 50% EtOH aqueous solution (2 mL), 10% Pd/C (40 mg) was added and the mixture was stirred for 40 h under hydrogen atmosphere at rt. After removal of the solvent, the crude product was purified by RP C-18 column with elution system 100% H_2O to 10% Methanol in H_2O to afford the trisaccharide **14** (3.6 mg, 70%). ^{1}H-NMR (599.87 MHz, CD_3OD) δ 0.90 (t, 3H, *J* = 7.2 Hz), 1.31 – 1.38 (m, 4H), 1.54 – 1.62 (m, 2H), 1.98 (s, 3H), 3.25 – 3.88 (m, 20H), 4.34 (d, 1H, *J* = 7.8 Hz), 4.44 (d, 1H, *J* = 8.4 Hz), 4.75 (d, 1H, *J* = 1.2 Hz); δ (399.95 MHz, D_2O) 0.69 (t, 3H, *J* = 6.8 Hz), 1.05 – 1.12 (m, 4H), 1.38 – 1.46 (m, 2H), 1.86 (s, 3H), 3.25 – 3.88 (m, 20H), 4.27 (d, 1H, *J* = 8.0 Hz), 4.38 (d, 1H, *J* = 7.6 Hz);^{13}C-NMR (150.8 MHz, CD_3OD) δ 13.18, 22.03, 22.37, 22.96, 28.41, 29.16, 55.35, 60.41, 61.33, 62.13, 67.53, 67.85, 69.11, 70.52, 71.38, 72.37, 73.61, 73.70, 75.42, 75.95, 77.74, 79.36, 97.38, 100.33, 103.90, 172.99; ESI-MS $C_{25}H_{45}NNaO_{16}$ [M + Na^+] calc. 638.3 found 638.2. All spectroscopic data are consistent with the structure assigned.[5]



***p*-Tolyl-2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-(4,6-*O*-benzylidene-3-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-2-deoxy-2-*N*-phthalimido-β-D-glucopyranosyl)-1-thio-β-D-galactopyranoside (19).** Compound **19** (45 mg, 35.3 μmol, 59% yield) was synthesized according to the general procedure for one-pot synthesis from donor **21** (40 mg, 74 μmol), building block **22** (32 mg, 64 μmol), and **4** (29 mg, 60 μmol). ^{1}H-NMR (599.87 MHz, $CDCl_3$) δ 0.81 (d, 3H, *J* = 6.6 Hz), 2.27 (s, 3H), 3.38 (d, 1H, *J* = 1.8 Hz), 3.52 – 3.65 (m, 6H), 3.79 (d, 1H, *J* = 9.6 Hz), 3.93 (q, 1H, *J* = 6.6 Hz), 4.01 – 4.08 (m, 3H), 4.23 (d, 1H, *J* = 11.4 Hz), 4.28 – 4.38 (m, 4H), 4.42 – 4.47 (m, 2H), 4.66 (d, 1H, *J* = 3.0 Hz), 4.68 (d, 1H, *J* = 9.6 Hz), 4.73 (d, 1H, *J* = 11.4 Hz), 5.31 (t, 1H, *J* = 9.6 Hz), 5.48 (s, 1H), 5.51 (s, 1H), 5.55 (d, 1H, *J* = 9.6 Hz), 6.88 – 6.92 (m, 2 H), 6.93 – 6.96 (m, 2 H), 7.08 – 7.50 (m, 32H), 7.62 – 7.66 (m, 2H); ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ 16.67, 21.46, 55.50, 66.27, 67.45, 68.77, 68.99, 69.37, 70.25, 72.62, 73.32, 74.88, 75.61, 76.28, 76.33, 78.13, 79.68, 80.06, 82.08, 86.02, 99.77, 100.16, 101.19, 101.33, 122.92, 126.19, 126.80, 127.49, 127.58, 127.66, 127.67, 127.71, 127.89, 128.01, 128.27, 128.38, 128.43, 128.49, 128.72, 129.68, 129.84, 129.86, 132.81, 133.45, 134.19, 137.21, 137.94, 138.26, 138.54, 138.71, 139.10, 164.55; HRMS $C_{75}H_{71}NNaO_{16}S$ [M + Na^+] calc. 1296.4391 found 1296.4384.



1,2,3,4-Tetra-*O*-acetyl-6-*O*-(6-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-α-D-mannopyranosyl)-2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl)-β-D-glucopyranoside (20). Compound **20** (40 mg, 23 μmol, 55% yield) was synthesized according to the general procedure for one-pot synthesis from donor **23** (32 mg, 52 μmol), building block **24** (26 mg, 47 μmol), **6** (25 mg, 42 μmol) and **25** (15 mg, 43 μmol). ^{1}H-NMR (599.87 MHz, $CDCl_3$) δ 1.91 (s, 3H), 1.92 (s, 3H), 1.97 (s, 3H), 1.98 (s, 3H), 2.10 (s, 3H), 3.46 – 3.92(m, 17H), 4.32 – 4.53 (m, 8H), 4.60 (d, 1H, *J* = 10.8 Hz), 4.68 (d, 1H, *J* = 12.0 Hz), 4.78 – 4.85 (m, 4H), 4.87 (t, 1H, *J* = 9.0 Hz), 4.93 (dd, 1H, *J* = 8.4, 9.6 Hz), 4.99 (d, 1H, *J* = 1.8 Hz), 5.10 (t, 1H, *J* = 9.6 Hz), 5.44 (dd, 1H, *J* = 7.8, 9.6 Hz), 5.46 – 5.49 (m, 1H), 5.50 (d, 1H, *J* = 9.6 Hz), 5.57 (d, 1H, *J* = 8.4 Hz), 5.80 (t, 1H, *J* = 9.6 Hz), 7.08 – 7.42 (m, 42 H), 7.48 – 7.52 (m, 1H), 7.78 – 7.82 (m, 2H), 7.87 – 7.90 (m, 2H), 7.96 – 8.02 (m, 2H); ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ 20.76, 20.91, 21.38, 66.93, 67.46, 68.80, 68.92, 69.05, 69.27, 70.40, 70.59, 71.83, 72.05, 72.08, 72.88, 73.16, 73.35, 73.57, 74.27, 74.47, 74.50, 74.89, 75.18, 75.24, 77.44, 78.33, 79.69, 91.80, 99.22, 99.76, 101.06, 127.56, 127.63, 127.70, 127.74, 127.77, 127.83, 127.99, 128.09, 128.30, 128.38, 128.45, 128.48, 128.52, 128.55, 128.64, 129.17, 129.26, 129.59, 129.98, 130.17, 133.33, 133.35, 133.49, 138.25, 138.55, 138.64, 138.71, 138.77, 138.87, 165.22, 165.36, 166.01, 168.94, 169.38, 169.61, 170.22, 170.32; $^1J(^{13}C-^1H)$: 166.4 Hz (δ 91.80 ppm, β linkage), 171.8 Hz (δ 99.22 ppm, α linkage), 172.3 Hz (δ 99.76 ppm, α linkage), 163.9 Hz (δ 101.06 ppm, β linkage);[1] HRMS $C_{97}H_{100}NaO_{29}$ [M + Na$^+$] calc. 1751.6248 found 1751.6301.



***p*-Tolyl-2-*O*-acetyl-3,4,6-tri-*O*-benzyl-1-thio-α/β-D-mannopyranoside (23).** To a solution of 1,2-*O*-diacetyl-3,4,6-tri-O-benzyl-α/β-D-mannopyranoside (0.7 g, 1.3 mmol)[6] and *p*-methylbenzenethiol (0.24 g, 1.9 mmol) in CH_2Cl_2 (10 mL) was added BF_3•Et_2O (0.25 mL, 1.9 mmol). After 1 hour, the reaction was quenched by addition of sat. aqueous $NaHCO_3$ solution (20 mL). The organic layer was collected and **23** (0.62 g, 80%) was obtained after flash chromatography as an α:β mixture (3 :1). ^{1}H-NMR (399.95 MHz, $CDCl_3$) δ α anomer 2.16 (s, 3H), 2.32 (s, 3H), 3.74 (dd, 1H, *J* = 1.6, 10.8 Hz), 3.88 (dd, 1H, *J* = 4.4, 10.8 Hz), 3.94-4.02 (m, 2H), 4.33-4.42 (m, 1H), 4.48 (d, 1H, *J* = 12.0 Hz), 4.53 (d, 1H, *J* = 10.4 Hz), 4.58 (d, 1H, *J* = 11.2 Hz), 4.68 (d, 1H, *J* = 12.0 Hz), 4.75 (d, 1H, *J* = 11.2 Hz), 4.90 (d, 1H, *J* = 11.2 Hz), 5.49 (d, 1H, *J* = 1.6 Hz), 5.63 (bs, 1H), 7.05 – 7.08 (m, 2H), 7.18 – 7.40 (m, 17H); β anomer 2.03 (s, 3H), 2.21 (s, 3H), 3.52 (ddd, 1H, *J* = 1.2, 6.0, 9.0 Hz), 3.65 (dd, 1H, *J* = 3.0, 9.0 Hz), 3.72 (dd, 1H, *J* = 1.2, 9.0 Hz), 5.78 (d, 1H, *J* = 3.6 Hz), 7.07 – 7.11 (m, 2H), 7.24 – 7.54 (m, 17H) ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ α anomer 21.38, 69.18, 70.59,72.16, 72.69, 73.62, 74.86, 75.52, 78.75, 86.90, 127.80, 127.94, 128.01, 128.14, 128.44, 128.54, 128.61, 128.73, 130.07, 132.56, 137.69, 138.13, 138.48, 138.55, 170.57; HRMS $C_{36}H_{38}NaO_6S$ [M + Na$^+$] calc. 621.2287 found 621.2245.

***p*-Tolyl-3,4,6-tri-*O*-benzyl-1-thio-α/β-D-mannopyranoside (24).** To a solution of **23** (0.30 g, 0.5 mmol) in anhydrous methanol (5 mL) was added a solution of 30 % NaOMe in methanol (0.1 mL). The reaction mixture was stirred at room temperature for 2 hours. Amberlite IR120 was added until the solution became acidic. The resin was filtered off and analytically pure **24** (0.28 g, 100%) was obtained. ^{1}H-NMR (399.95 MHz, $CDCl_3$) δ α anomer 2.31 (s, 3H), 2.69 (bs, 1H), 3.70 (dd, 1H, *J* = 1.6, 10.8 Hz), 3.81 (dd, 1H, *J* = 4.8, 10.8 Hz), 3.88-3.98 (m, 2H), 4.24-4.28 (m, 1H), 4.30-4.38 (m, 1H), 4.46 (d, 1H, *J* = 12.0 Hz), 4.54 (d, 1H, *J* = 10.8 Hz), 4.63 (d, 1H, *J* = 12.0 Hz), 4.69-4.76 (m, 2H), 4.85 (d, 1H, *J* = 11.2 Hz), 5.55 (bs, 1H), 7.04 – 7.08 (m, 2H), 7.18 – 7.40 (m, 17H); β anomer 2.31 (s, 3H), 2.66-2.70 (m, 1H), 3.48 (ddd, 1H, *J* = 1.2, 6.4, 9.6 Hz), 3.62 (dd, 1H, *J* = 3.2, 8.8 Hz), 3.72 (dd, 1H, *J* = 2.0, 10.8 Hz), 3.80-3.86 (m, 2H), 4.27-4.32 (m, 1H), 4.52-4.62 (m, 3H), 4.88 (d, 1H, *J* = 11.2 Hz), 4.72-4.78 (m, 2H), 4.88 (d, 1H, *J* = 11.2 Hz), 7.03 – 7.08 (m, 2H), 7.22 – 7.48 (m, 17H); ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ α anomer 21.37, 69.15, 70.07, 72.37, 72.46, 73.63, 74.80, 75.43, 80.53, 87.88, 127.76, 127.96, 128.09, 128.17, 128.22, 128.31, 128.53, 128.62, 128.85, 130.04, 132.46, 137.88, 137.90, 138.48; β anomer 21.36, 69.73, 70.13, 72.14, 73.75, 74.51, 75.49, 79.97, 83.01, 87.31, 127.75, 128.04, 128.23, 128.28, 128.36, 128.54, 128.65, 128.87, 129.96, 131.21, 131.93, 137.73, 138.32, 138.63. HRMS $C_{34}H_{36}NaO_5S$ [M + Na$^+$] calc. 579.2181 found 579.2159.

References:

[1] (a) K. Bock, C. Pedersen, *J. Chem. Soc. Perkin Trans. 2* **1974**, 293; (b) D. Crich, S. Sun, *Tetrahedron* **1998**, *54*, 8321.

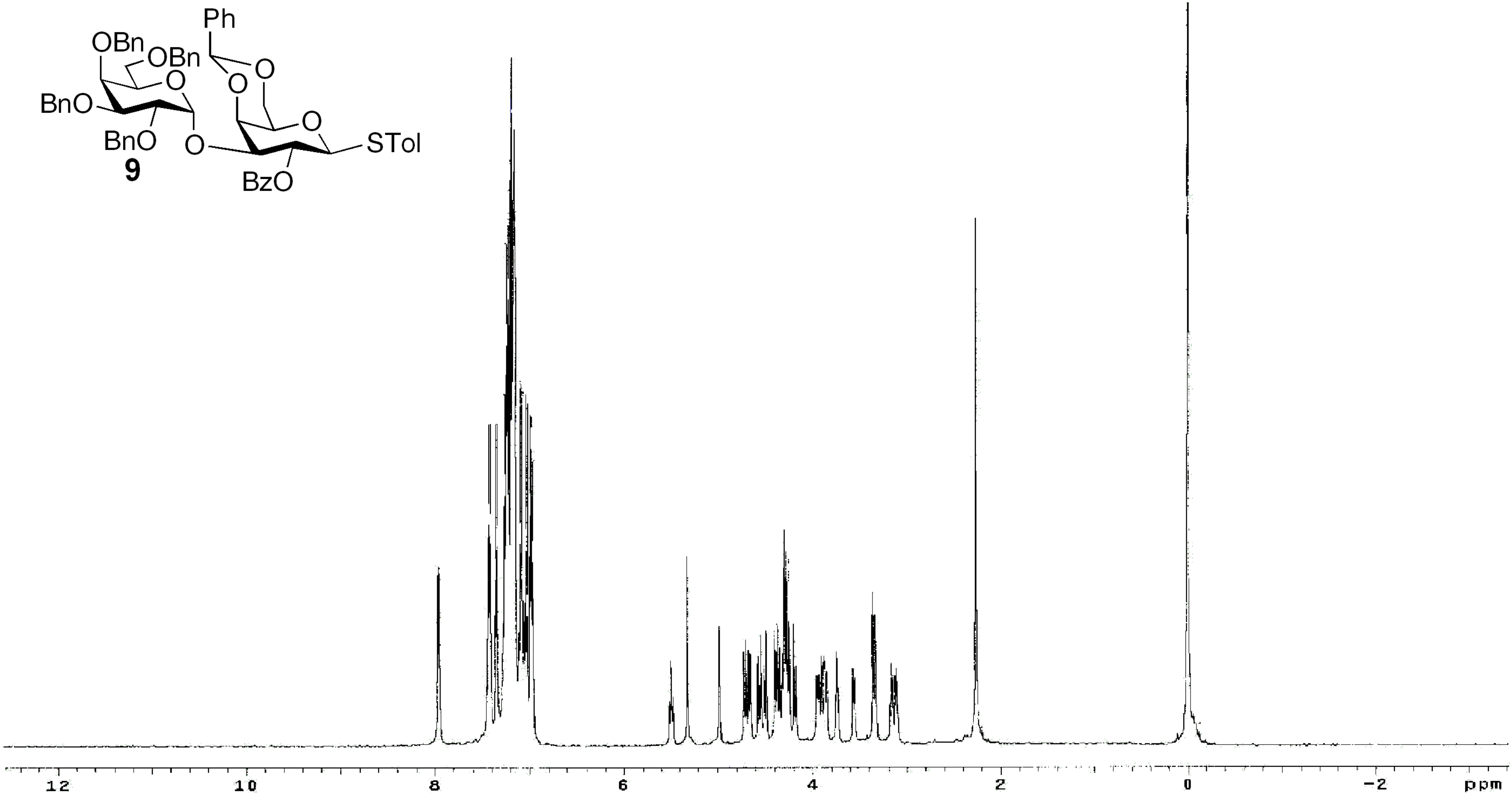
[2] O. Kanie, Y. Ito, T. Ogawa, *J. Am. Chem. Soc.* **1994**, *116*, 12073.

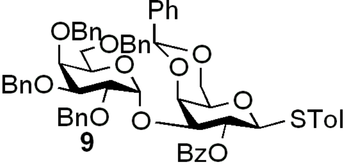
[3] Z. Zhang, I. R. Ollman, X.-S. Ye, R. Wischnat, T. Baasov, C.-H. Wong, *J. Am. Chem. Soc.* **1999**, *121*, 734.

[4] A. G. M. Barrett, D. Dhanak, G. G. Graboski, S. J. Taylor, *Org. Syn. Coll. Vol.*, *8*, 550.

[5] O. J. Plante, E. R. Palmacci, P. H. Seeberger, *Science* **2001**, *291*, 1523.

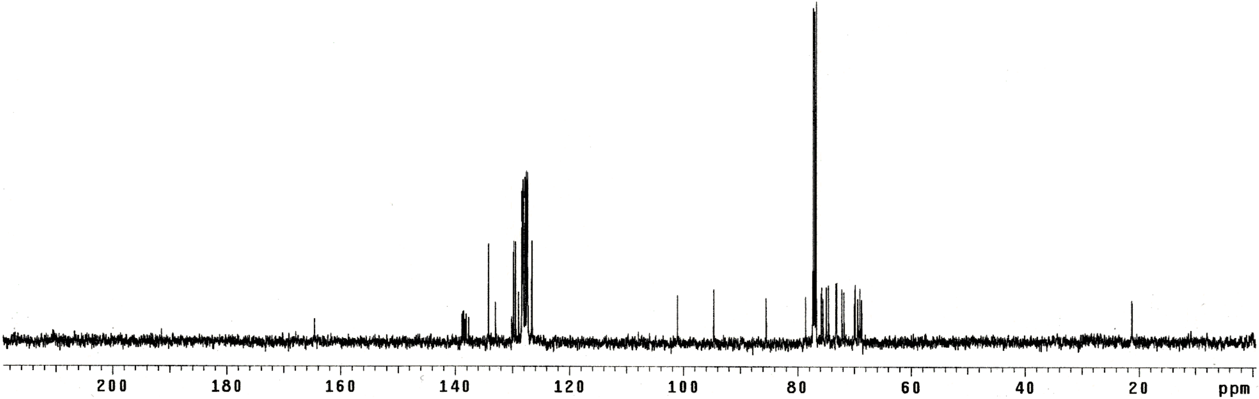
[6] C. S. Callam, T. L. Lowary, *J. Org. Chem.* **2001**, *66*, 8961.


9

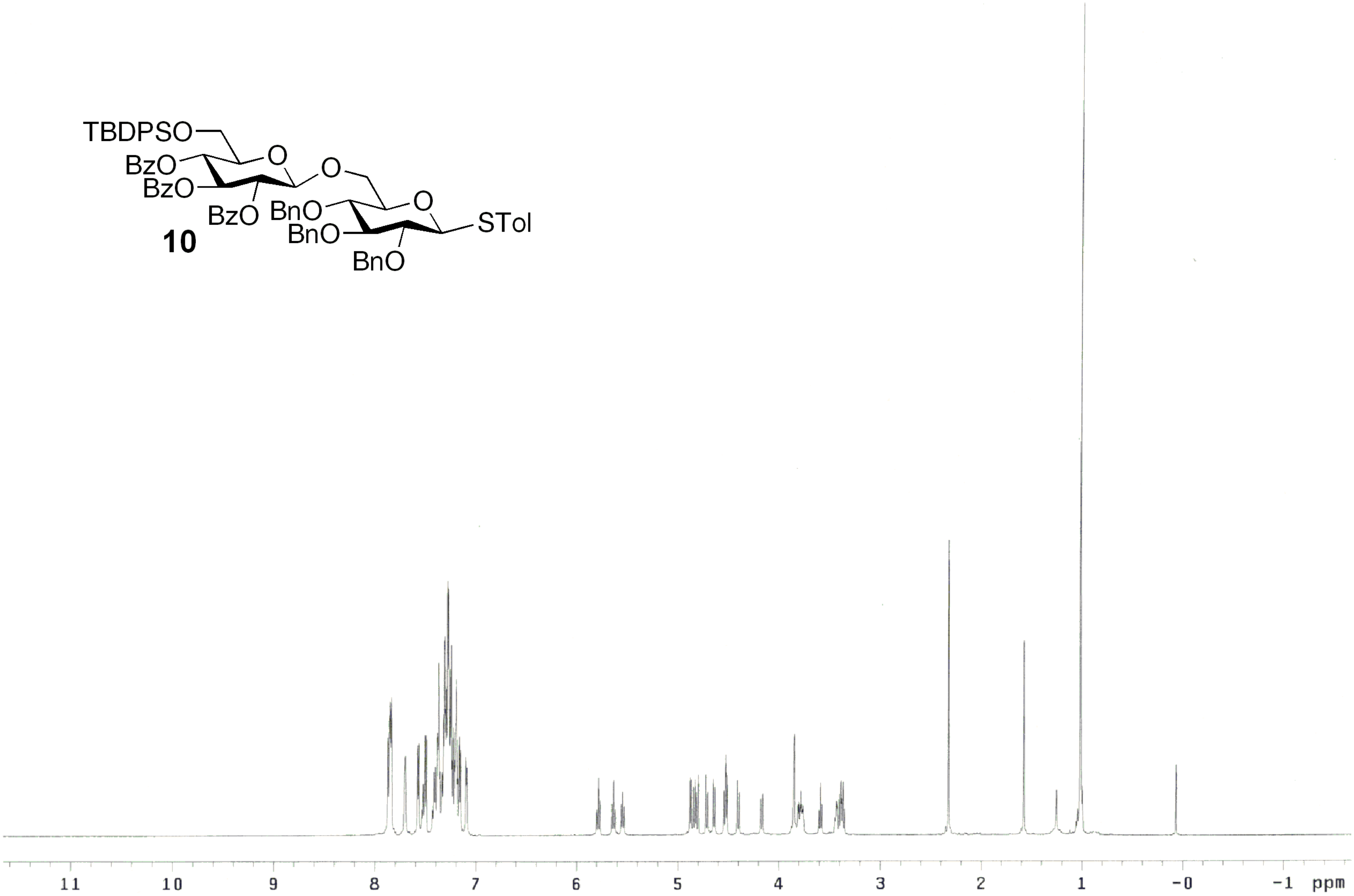


9

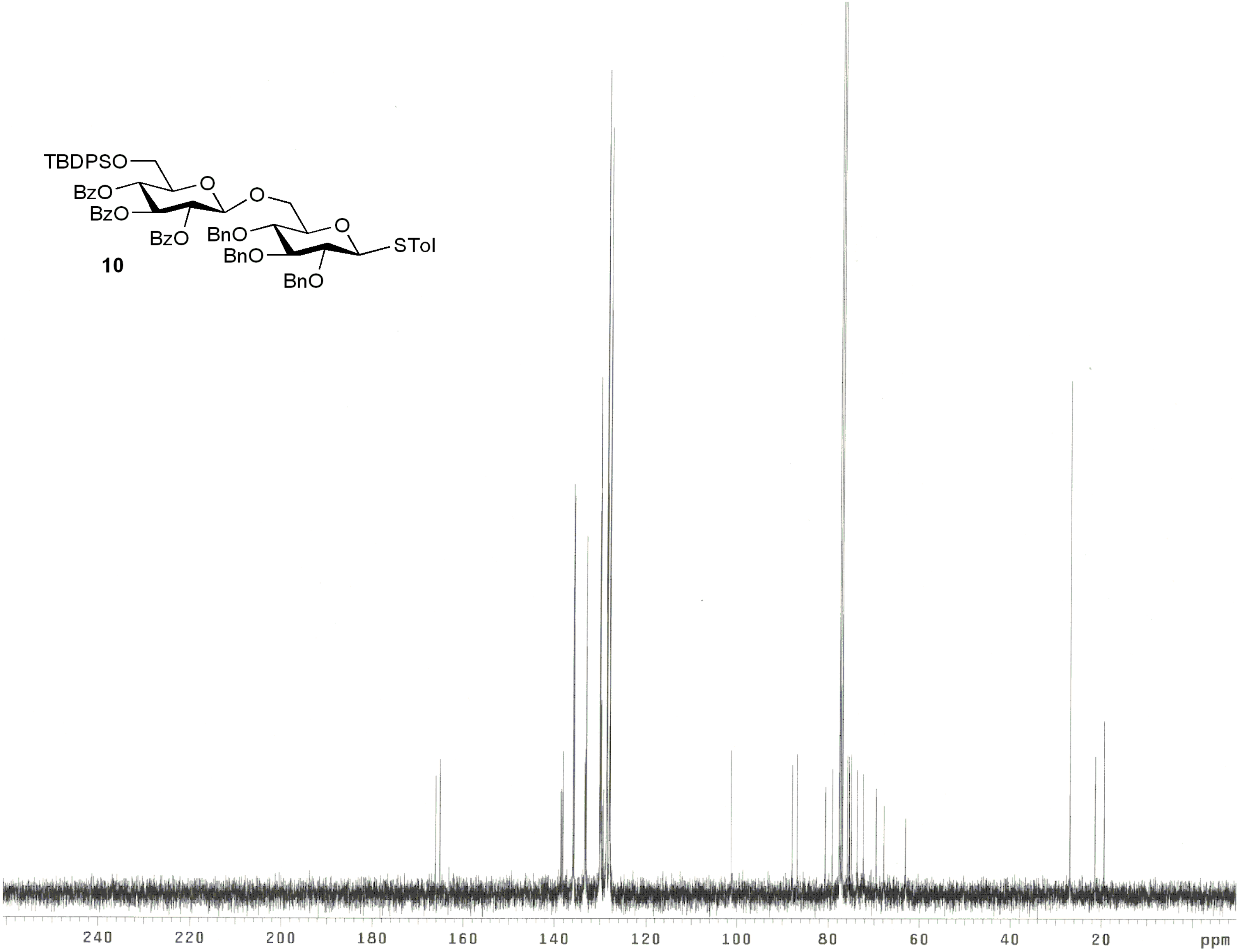
Ph
OBn
OBn
BnO
BnO
O
O
O
O
O
STol
BzO



200
180
160
140
120
100
80
60
40
20
ppm

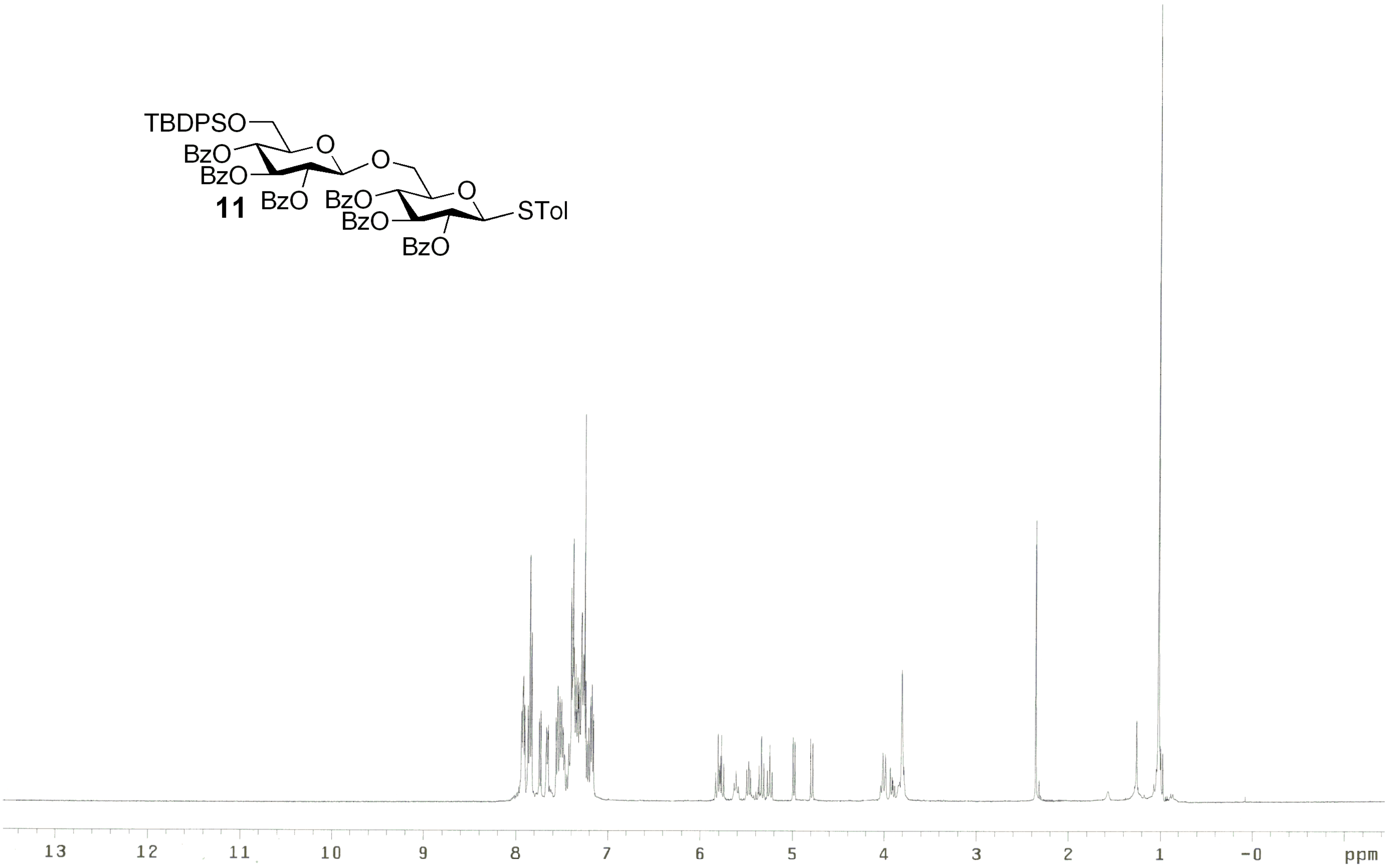


10

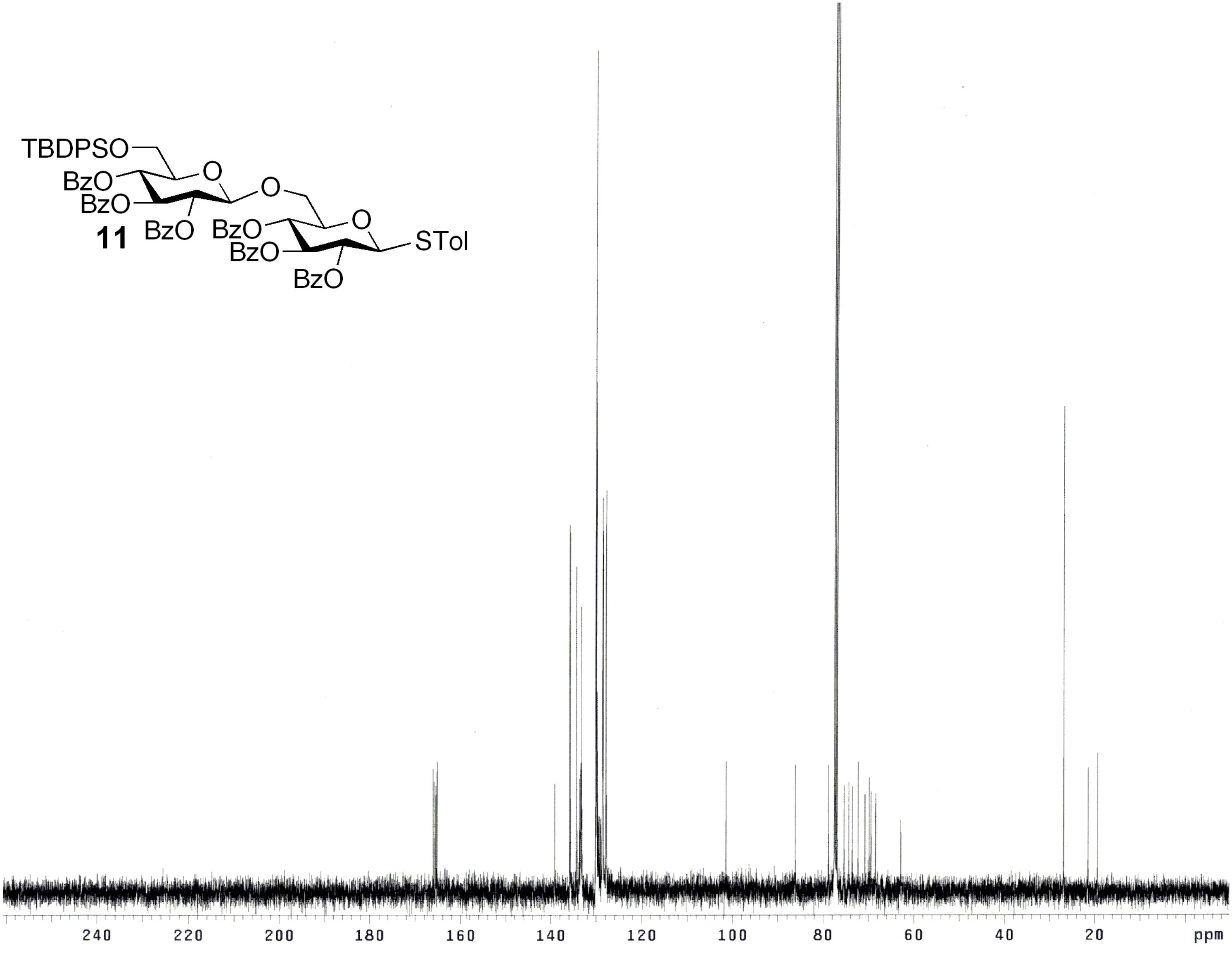

TBDPSO
BzO
BzO
BzO
O
O
BnO
BnO
BnO
O
STol

10

240
220
200
180
160
140
120
100
80
60
40
20
ppm

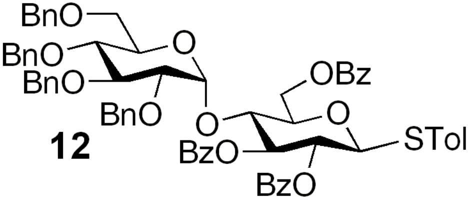
TBDPSO
BzO
BzO
BzO
O
O
BzO
BzO
BzO
O
STol
13
12
11
10
9
8
7
6
5
4
3
2
1
-0
ppm

11

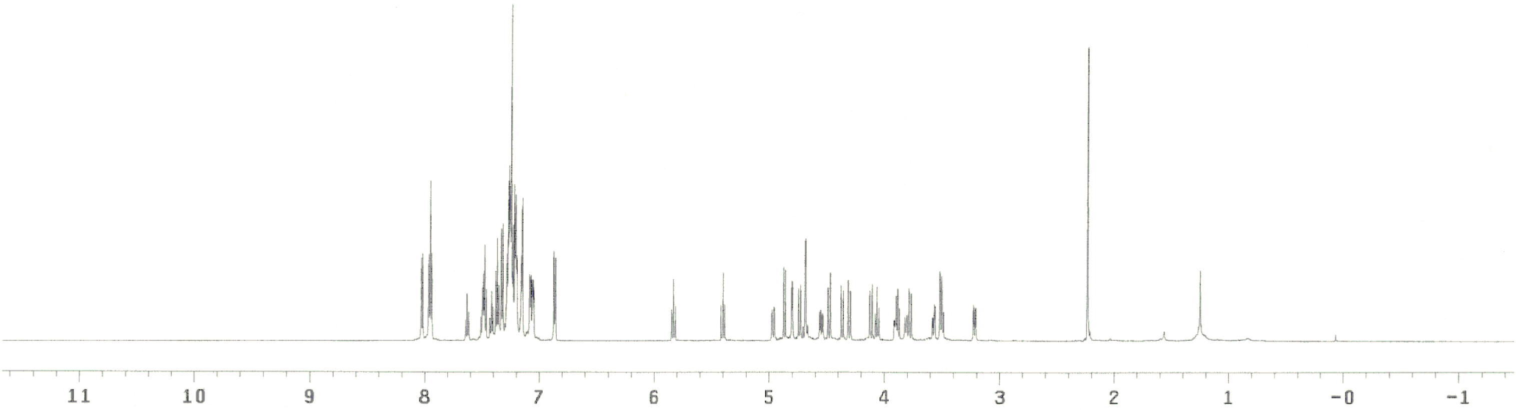


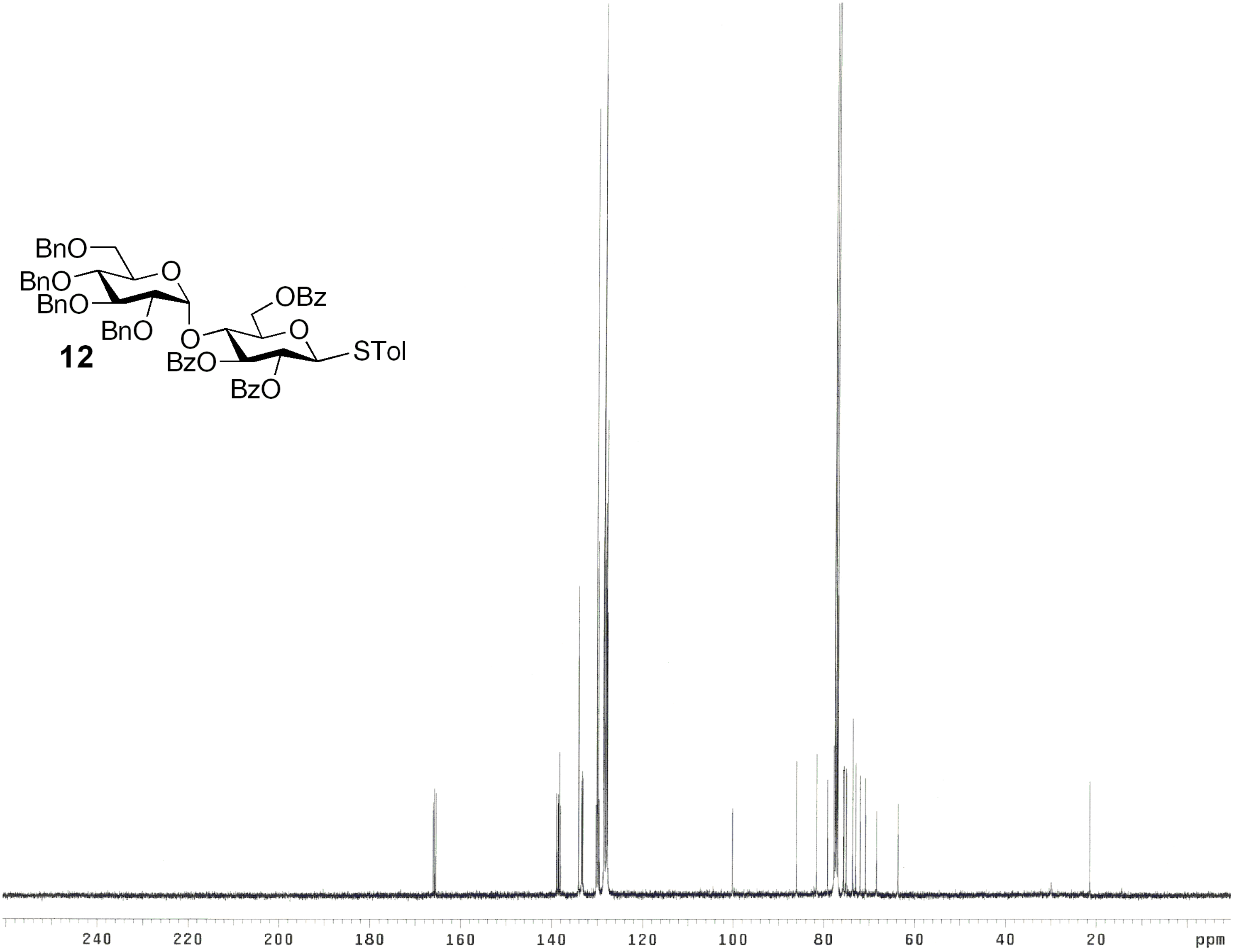
11

TBDPSO
BzO
BzO
BzO
O
O
BzO
BzO
BzO
O
STol
240
220
200
180
160
140
120
100
80
60
40
20
ppm



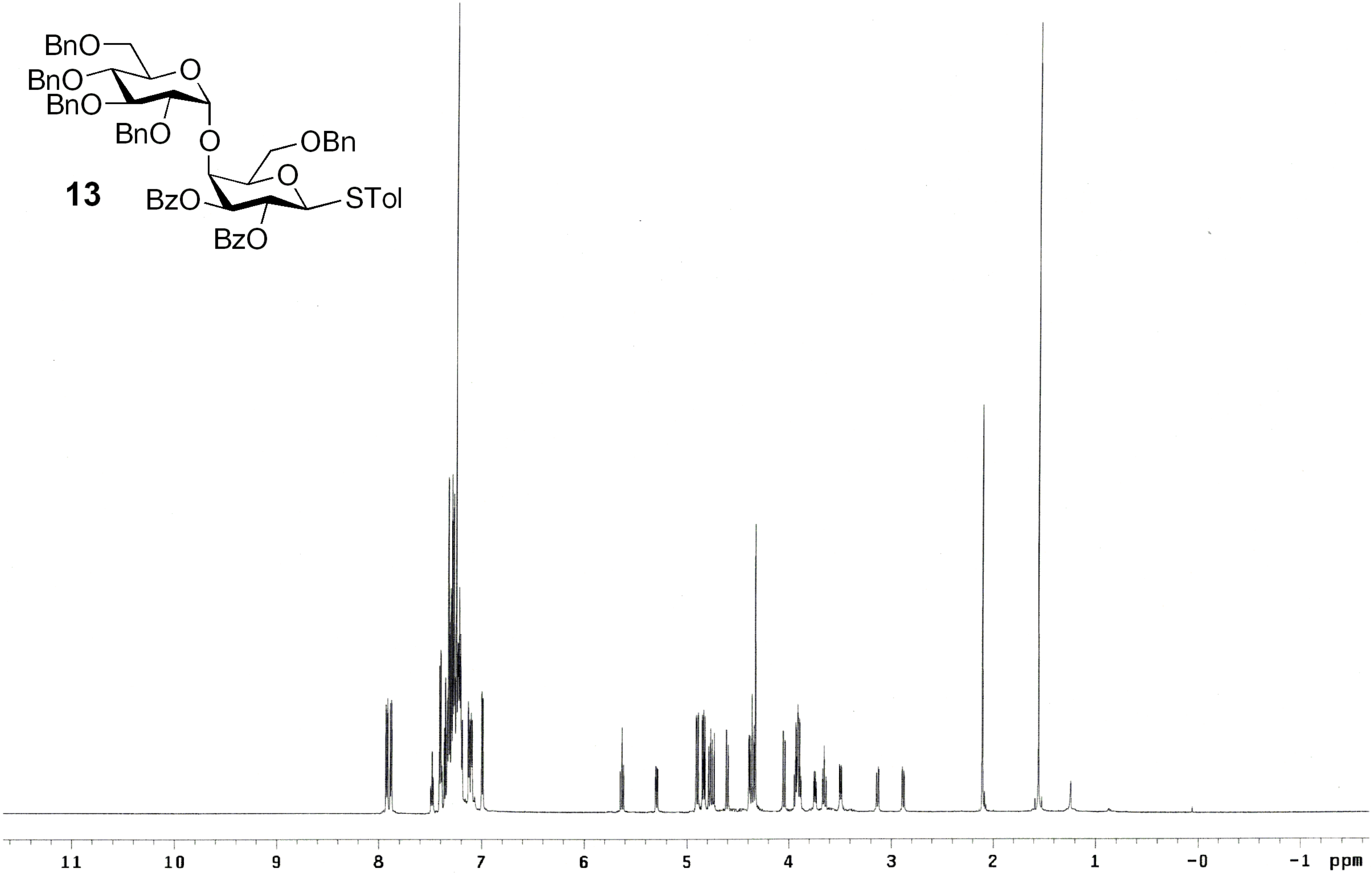
12



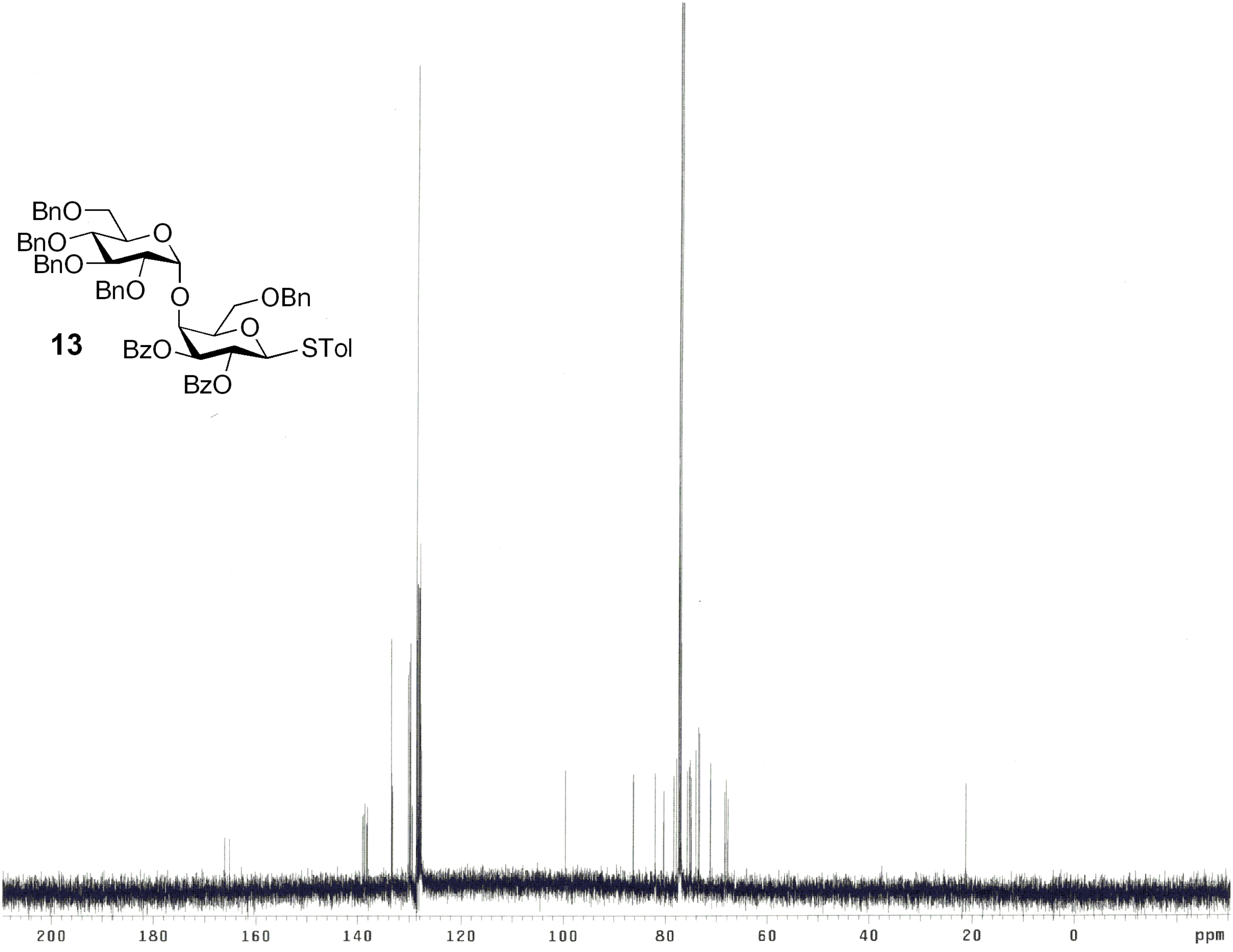


12

BnO
BnO
BnO
BnO
O
O
OBz
O
STol
BzO
BzO
240
220
200
180
160
140
120
100
80
60
40
20
ppm

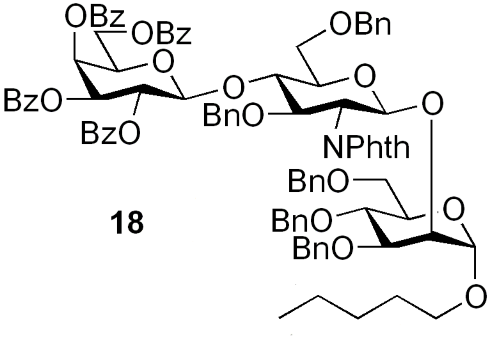


13

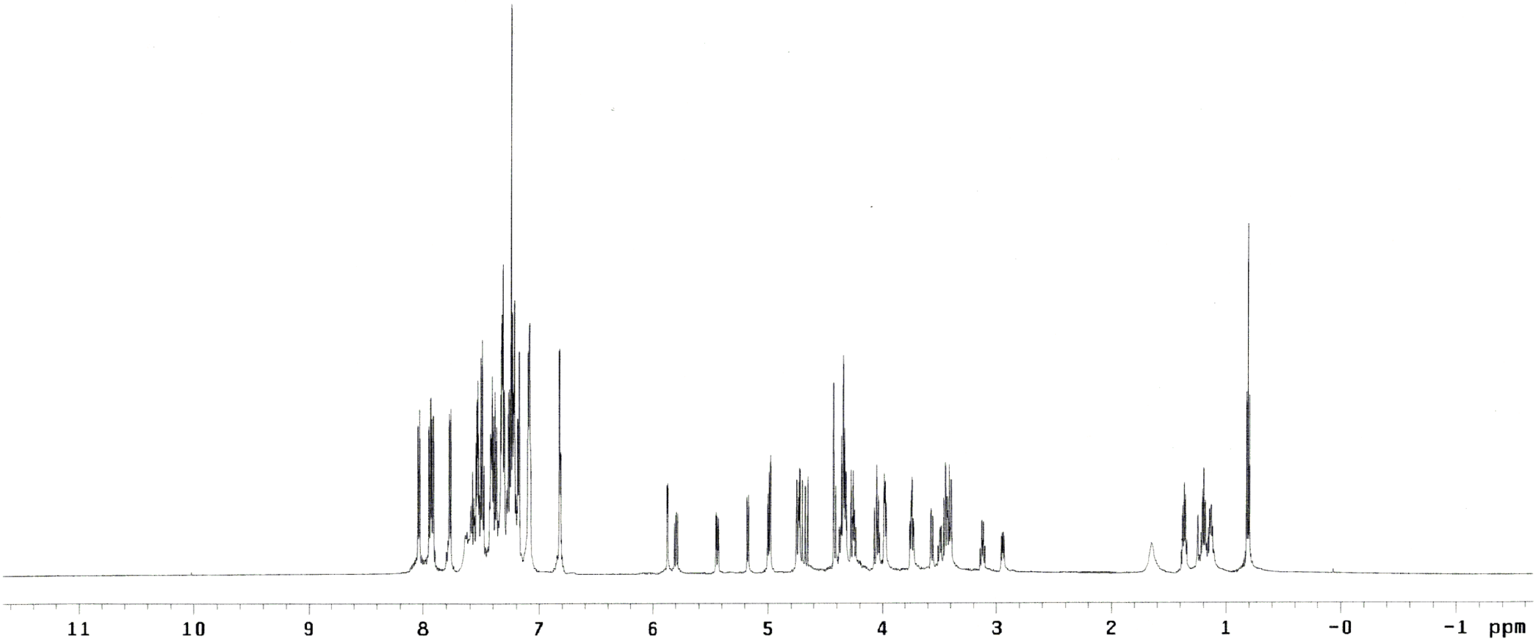


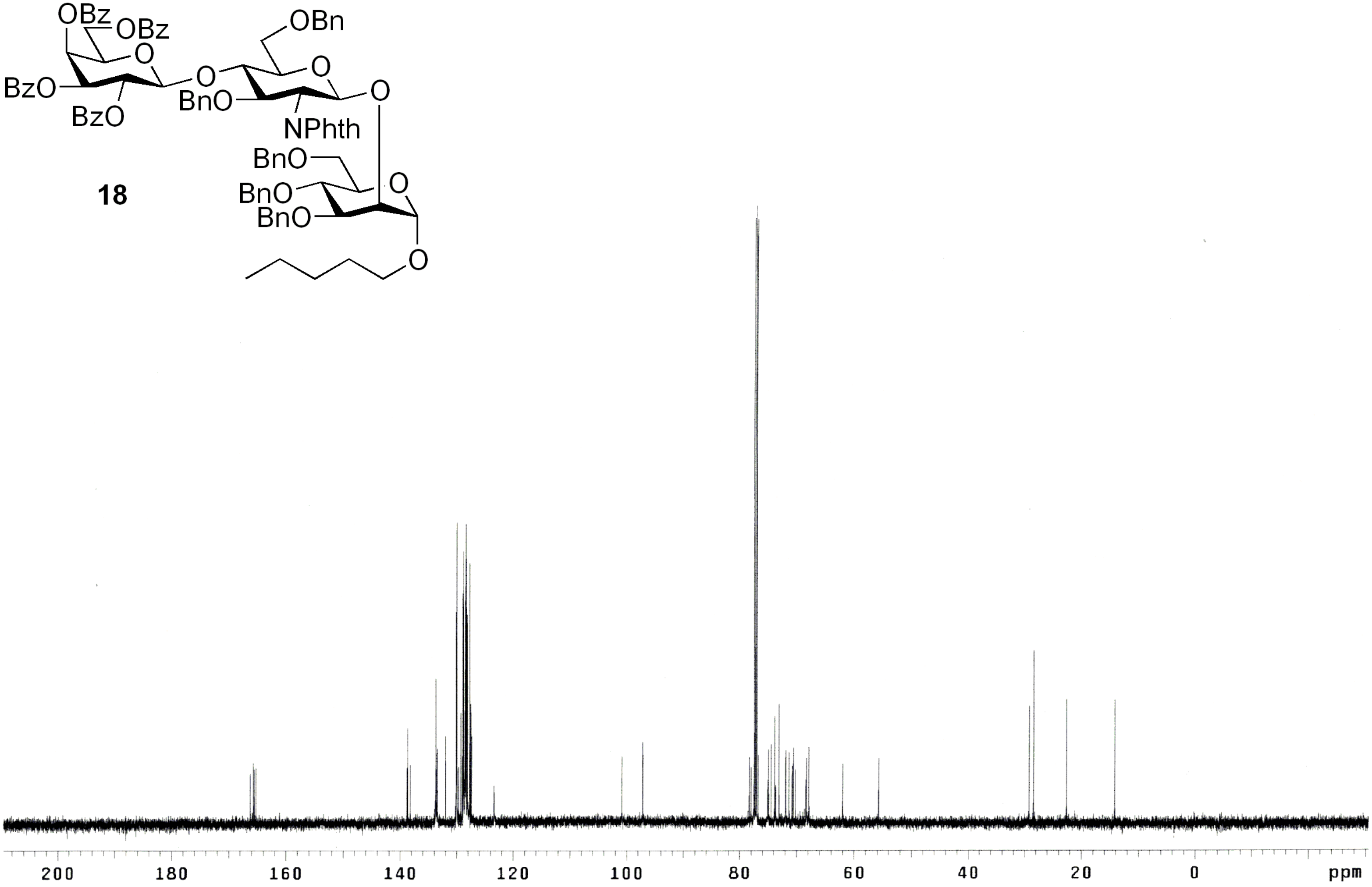
13

BnO
BnO
BnO
BnO
O
O
OBn
O
BzO
STol
BzO
200
180
160
140
120
100
80
60
40
20
0
ppm


OBz
OBz
BzO
BzO
OBn
O
O
BnO
O
NPhth
BnO
BnO
O
BnO
O

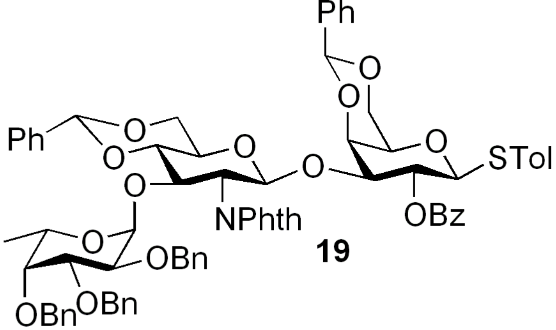
18


11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm

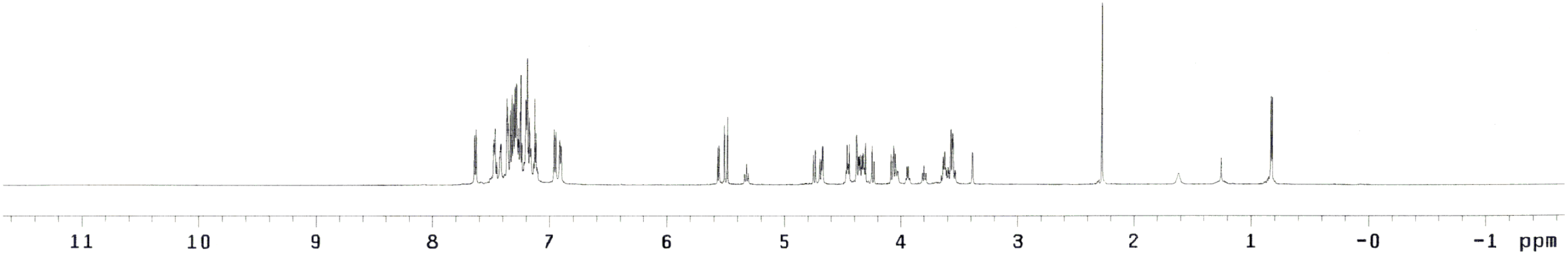


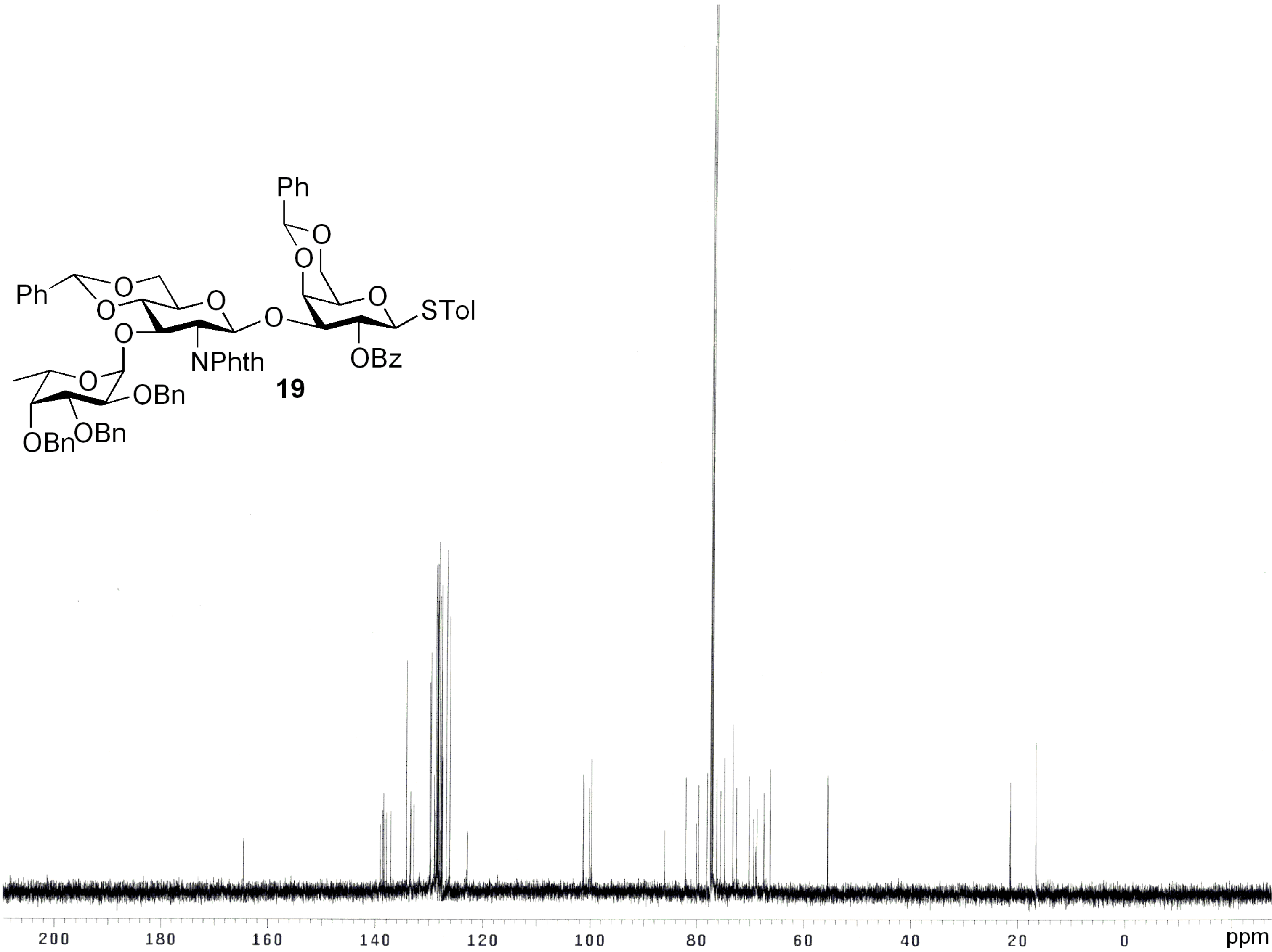
18

OBz
OBz
O
BzO
BzO
O
OBn
O
BnO
NPhth
O
BnO
O
BnO
BnO
O
200
180
160
140
120
100
80
60
40
20
0
ppm


Ph
O
O
Ph
O
O
O
O
STol
O
O
NPhth
OBz
O
OBn
OBnOBn

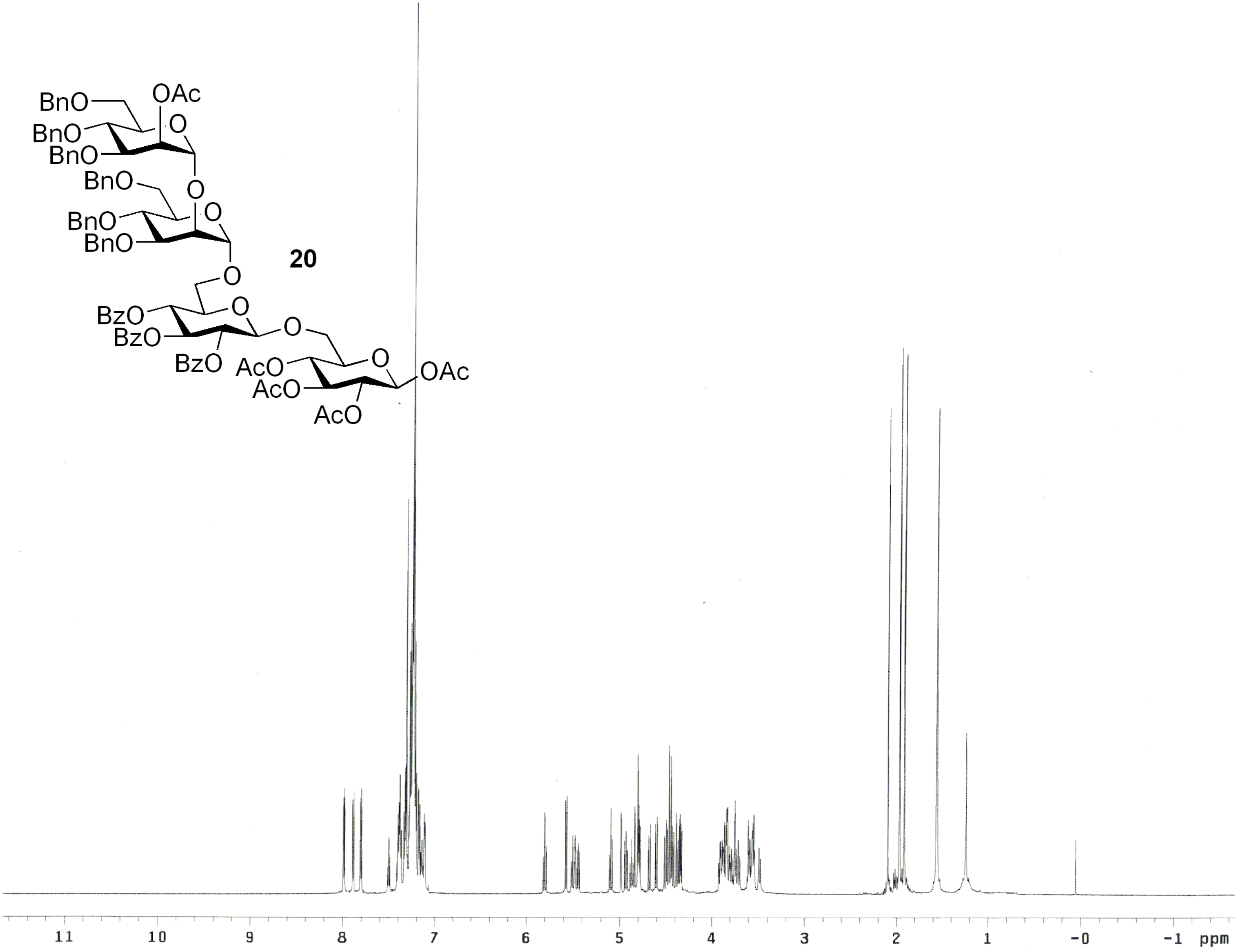
19

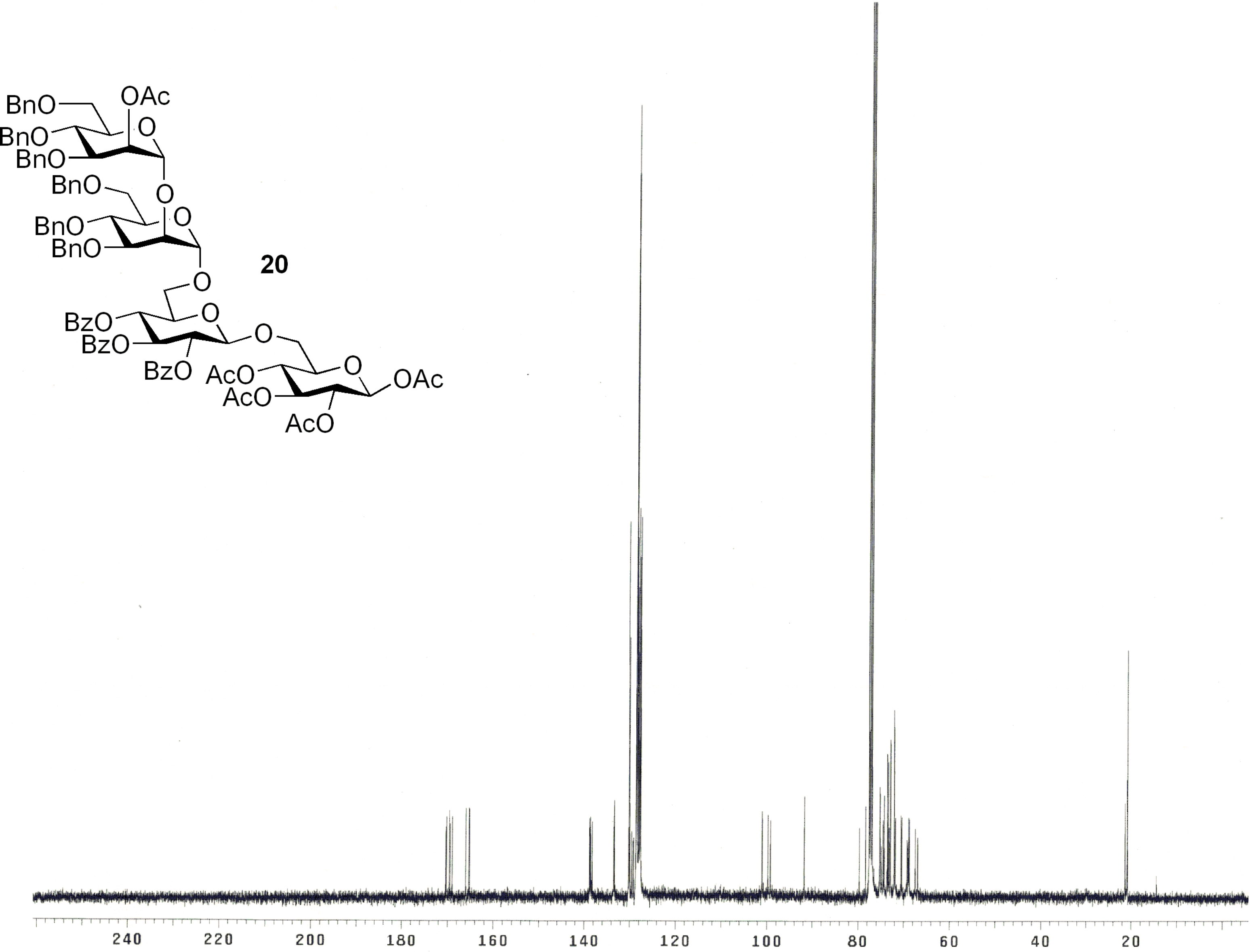

11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm


Ph
O
O
Ph
O
O
O
O
O
STol
O
NPhth
OBz
O
OBn
OBn
OBn
200
180
160
140
120
100
80
60
40
20
0
ppm

19

20


BnO
OAc
O
BnO
BnO
BnO
O
O
BnO
BnO
O
BzO
O
BzO
O
BzO
AcO
O
OAc
AcO
AcO
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm



20

BnO
BnO
BnO
OAc
O
BnO
O
BnO
BnO
O
O
BzO
BzO
BzO
O
O
AcO
AcO
AcO
OAc
240
220
200
180
160
140
120
100
80
60
40
20