Thio-arylglycosides with Various Aglycon Para-Substituents, a Probe for Studying Chemical Glycosylation Reactions

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Supporting Information

Table of content

General Experimental Procedures. All reactions were carried out under 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 dried using a solvent purification system and used directly without further drying. When methanol was used as acceptor in glycosylation, it is pre-dried by molecular sieve 3A. Donors and acceptors **16** and **17** were azeotropically evaporated with toluene to remove residue moisture just before glycosylation. Chemicals used were reagent grade as supplied except where noted. HPLC solvents were all HPLC grade as supplied. Analytical thin-layer chromatography was performed using silica gel 60 F254 glass plates. Flash column chromatography was performed on silica gel 60 (230-400 Mesh, EM Science). Compound spots were visualized by UV light (254 nm) and 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). NMR spectra were referenced using Me_4Si (0 ppm), residual $CHCl_3$ (δ ^{1}H-NMR 7.26 ppm, ^{13}C-NMR 77.0 ppm). Peak assignments are based on ^{1}H-NMR, ^{1}H–^{1}H gCOSY and (or) ^{1}H–^{13}C gHMQC and ^{1}H–^{13}C gHMBC experiments.

Procedure for large scale competitive glycosylation for yield determination:

Methanol was pre-dried by molecular sieves 3Å overnight. Donors **10** and **1b** were dried under high vacuum overnight and azeotropically evaporated with toluene to remove any residue moisture. To a solution of donors **10** (80.5 mg, 0.177 mmol) and **1b** (160 mg, 0.177 mmol), methanol (36 μL, 0.885 mmol) in CH_2Cl_2 (17 mL), a solution of AgOTf (91 mg, 0.354 mmol) in acetonitrile (0.05 mL) was added under N_2. The mixture was stirred for 15 minutes and cooled down to -40^{o}C followed by addition of *p*-TolSCl (28 mg, 25 μL, 0.177 mmol). The reaction was stirred for 30 minutes from -40^{o}C to room temperature and quenched with several drops of triethylamine. CH_2Cl_2 (20 mL) was added and all insoluble material was filtered off. The filtrate was washed with saturated aqueous $NaHCO_3$ and dried over Na_2SO_4. Purification by flash chromatography gave unreacted donor **10** (23.1 mg), unreacted donor **1b** (103.4 mg), methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (41.6 mg, 0.115 mmol, 92% yield based on the amount of donor **10** consumed) and methyl-2,3,4-tri-*O*-benzoyl-6-*O*-*tert*-butyldiphenylsilyl-β-D-galactopyranoside (45.4 mg, 0.060 mmol, 94% yield based on the amount of donor **1b** consumed). **Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00-2.10 (m, 12H, 12 X COC$\underline{H}_3$), 3.40 (s, 3H, OC$\underline{H}_3$), 3.95-3.98 (m, 1H, H_5), 4.19-4.26 (m, 2H, H_6), 4.89 (t, 1H, J = 9.6 Hz, H_2), 4.95 (d, 1H, J = 9.6 Hz, H_1), 5.06 (t, H, J= 9.6 Hz, H_4), 5.47 (t, 1H, J= 9.6 Hz, H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8-21.0 (4 X CO$\underline{C}H_3$), 55.7 (O$\underline{C}H_3$), 62.1 (C_6), 67.3, 68.7, 70.3, 71.0, 97.0 (C_1), 169.4-171.0 ($\underline{C}OCH_3$); MS (ESI) *m*/*z*. calcd. for $C_{15}H_{22}NaO_{10}$ $[M + Na]^+$ 385.1; found 385.2; HRMS *m*/*z*. calcd. for $C_{15}H_{22}NaO_{10}$ $[M + Na]^+$ 385.1111; found 385.1123. **Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-*tert*-butyldiphenylsilyl-1-β-D-galactopyranoside** ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.99 (s, 9H, $(CH_3)_3$), 3.52 (s, 3H, OC$\underline{H}_3$), 3.82-3.84

(m, 2H, 2 X H_6), 4.06 (t, 1H, *J* = 7.0Hz, H_5), 4.66 (d, 1H, *J* = 7.0 Hz, H_1), 5.60-5.62 (dd, 1H, *J* = 10.8 Hz, 3.6 Hz, H_3), 5.67-5.70 (dd, 1H, *J* = 10.8, 7.0 Hz, H_2), 6.02 (d, 1H, *J* = 3.6 Hz, H_4), 7.09-7.11 (m, 2H), 7.22-7.25 (m, 2H), 7.35-7.49 (m, 12H), 7.64-7.66 (m, 2H), 7.77-7.79 (m, 2H), 7.93-7.95 (m, 2H), 8.00-8.01 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.2, 26.8, 29.9, 57.4, 61.5, 68.1, 70.2, 72.1, 74.0, 102.6, 127.8-130.2, 132.8-133.5, 135.7-135.8, 165.6-165.9; MS (ESI) *m*/*z* calcd. for $C_{44}H_{44}NaO_9Si$ $[M + Na]^+$767.3; found 767.5; HRMS *m*/*z* calcd. for $C_{44}H_{44}NaO_9Si$ $[M + Na]^+$767.2652; found 767.2670.

General procedure for competitive glycosylation and HPLC measurements:

Two donors of interest (0.05 mmol each) were dried together with a reference compound (50 mg) under high vacuum overnight. They were then dissolved in anhydrous CH_2Cl_2 (5 mL). Aliquots of this solution (1 mL each) were transferred to three pre-dried vials. The exact ratio of two donors in each vial was determined by HPLC analysis of an aliquot (10 μL) of the solution. Each vial was measured at least three times. Anhydrous MeOH (2.04 μL, 5 eq), acceptor **16** or acceptor **17** was then added to each vial followed by 0.5 M NIS solution in acetonitrile (20 μL) and 0.1 M TfOH in Et_2O (10 μL). The reactions were left at room temperature for 2 hours and quenched by triethylamine (20 μL). The reaction mixture was diluted with CH_2Cl_2 (2 mL), washed with saturated aqueous sodium thiosulfate solution containing 10% sodium hydrogen bicarbonate, dried over Na_2SO_4 and evaporated to dryness. The solid obtained was then dissolved in CH_2Cl_2 (1 mL). The concentration of remaining donors in each vial were determined by HPLC (~10 μL each injection; 3 injections for each vial). RRVs are calculated according to equation 1 as the average of all measurements. All HPLC analyses were performed using a HP 1050 series HPLC system with a SUPELCO normal phase analytical HPLC column (25 cm * 4.6 mm ID) with hexanes and ethyl acetate elution system and UV detection at 270 nm.

For glycosylations using the *p*-TolSCl/AgOTf promoter system, all procedures are the same as above except that 0.5 M AgOTf solution in acetonitrile (40 μL) and *p*-TolSCl (1.5 μL) were added to each vial instead of NIS and TfOH.

The absorbance increases in baselines of some chromatograms are due to change of solvent gradient. The peak areas were calculated with baseline correction. Therefore, the increases of baseline absorbance do not interfere with peak integrations.

Figure S1. Gal-Series **1a**-**1e** with Methanol as the Acceptor in CH_2Cl_2 (The RRV of building block **11** was set as 1).

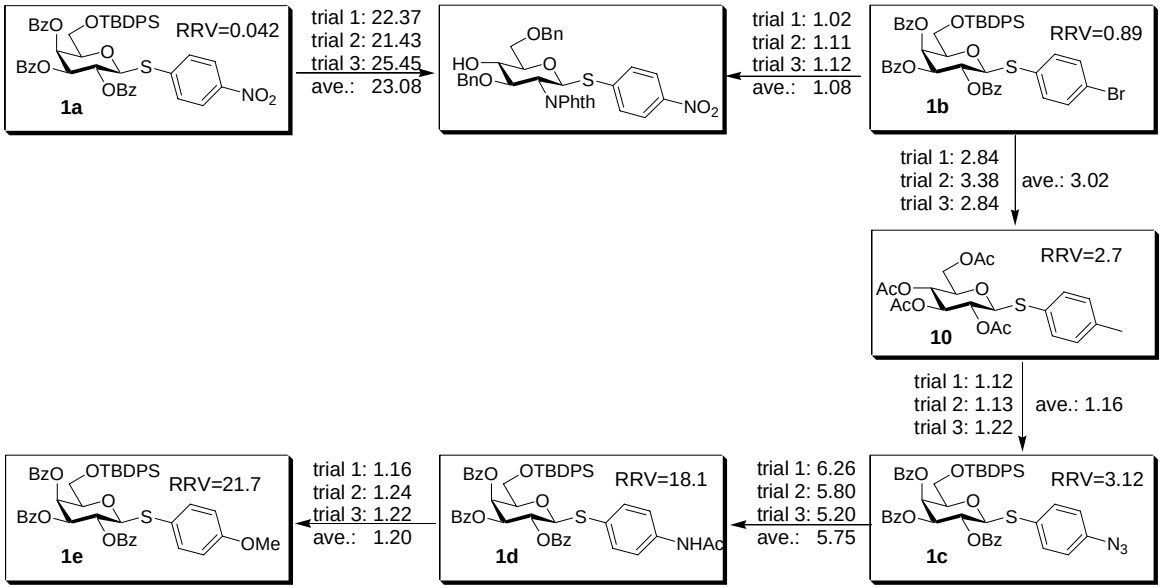


Figure S2. GlcN-series **2a**-**2e** with Methanol as the Acceptor in CH_2Cl_2 (The RRV of building block **11** was set as 1).

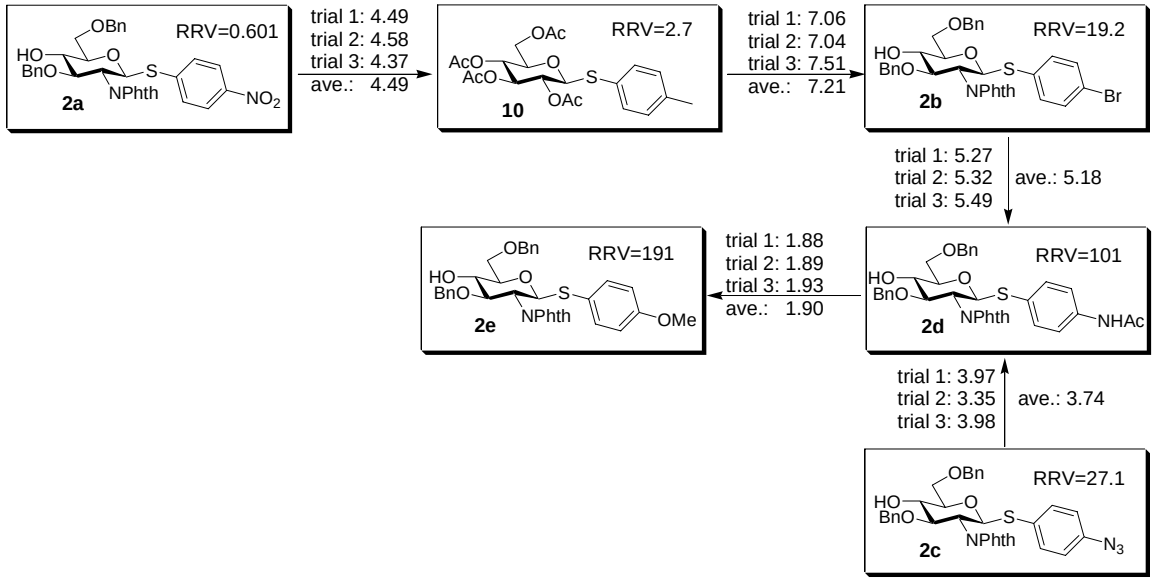
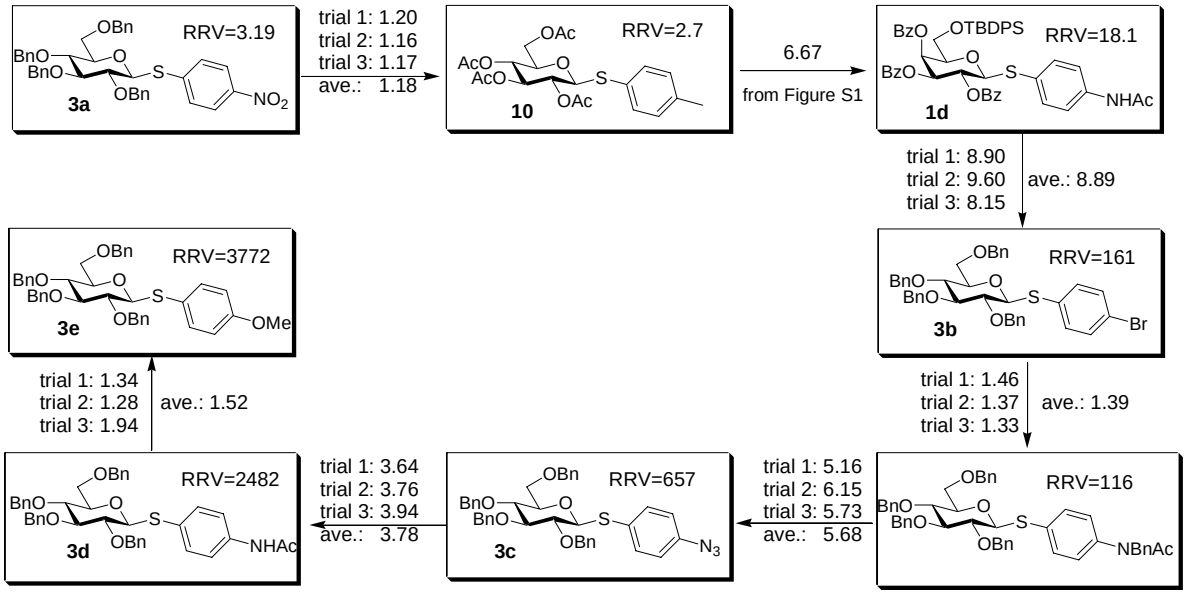
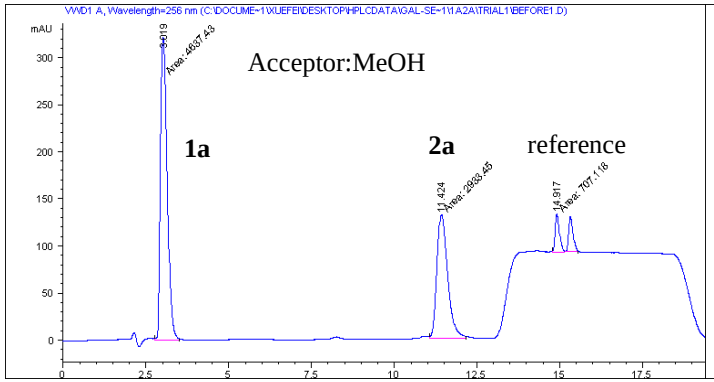


Figure S3. GlcBn-Series **3a**-**3e** with Methanol as the Acceptor in CH_2Cl_2 (The RRV of building block **11** was set as 1).



Donors **1a-1e**



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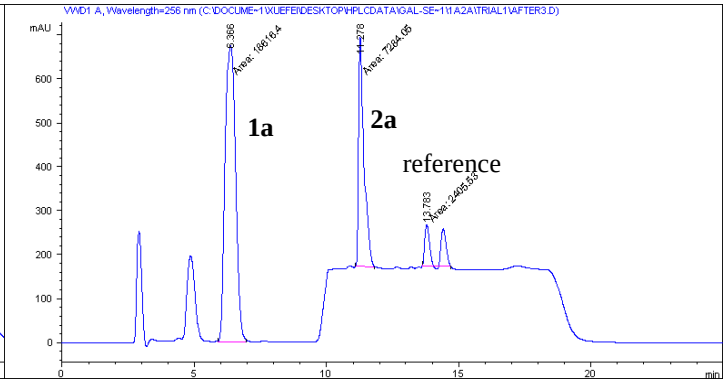

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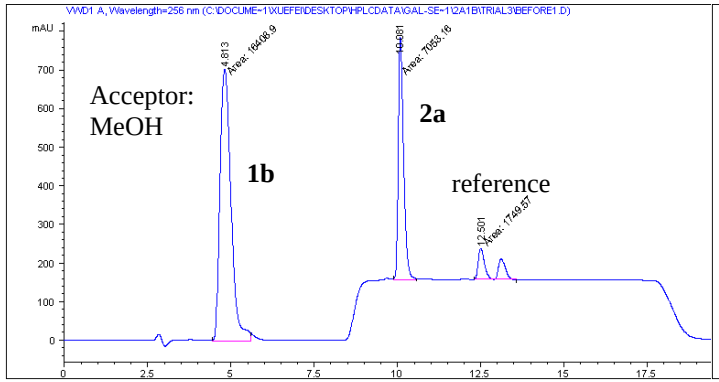

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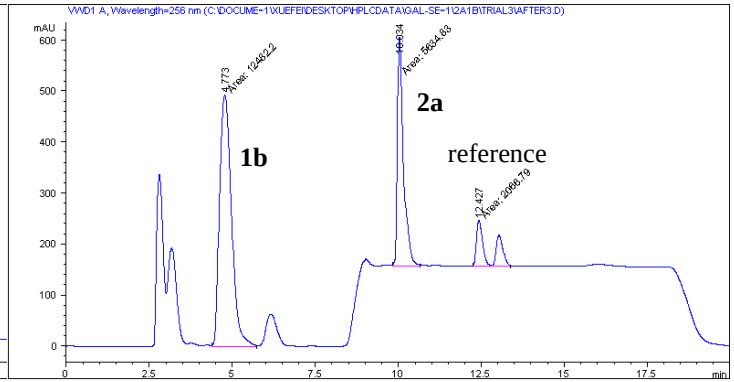

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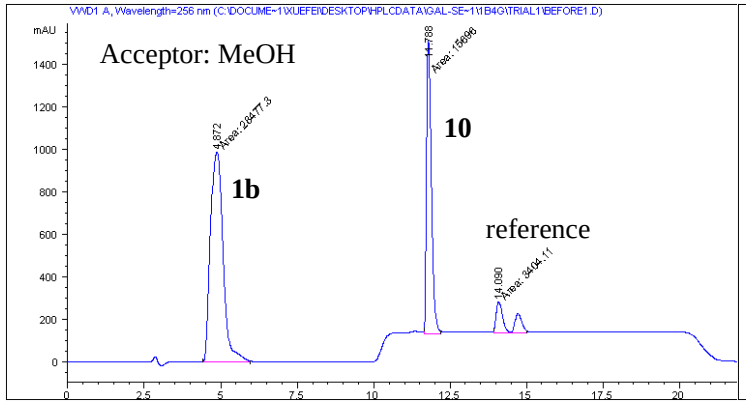

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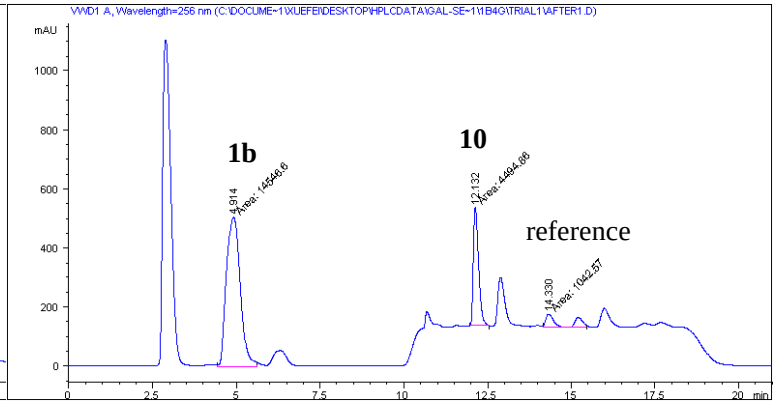

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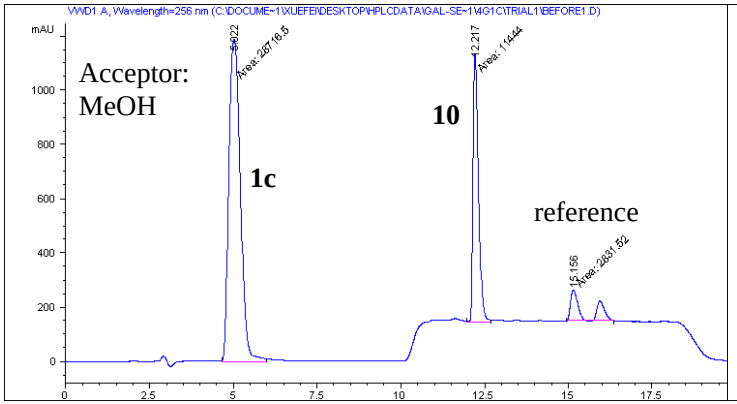

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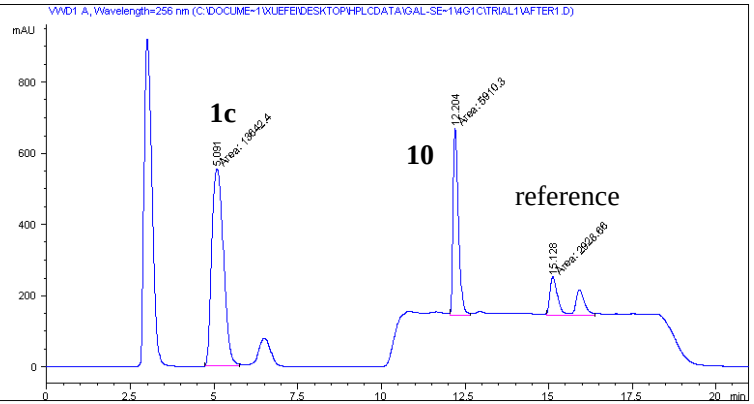

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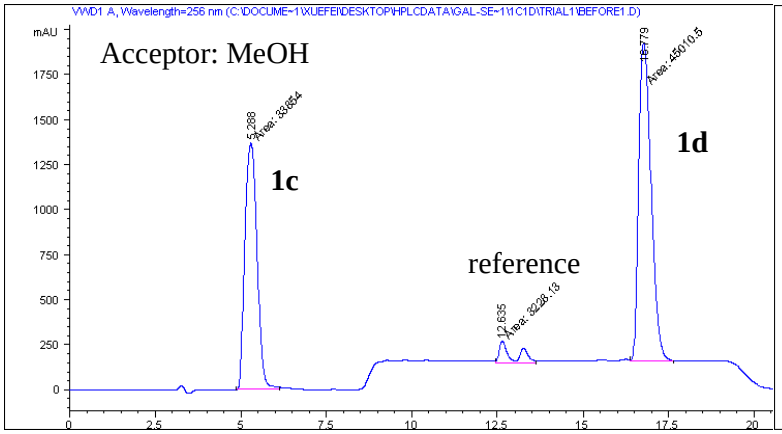

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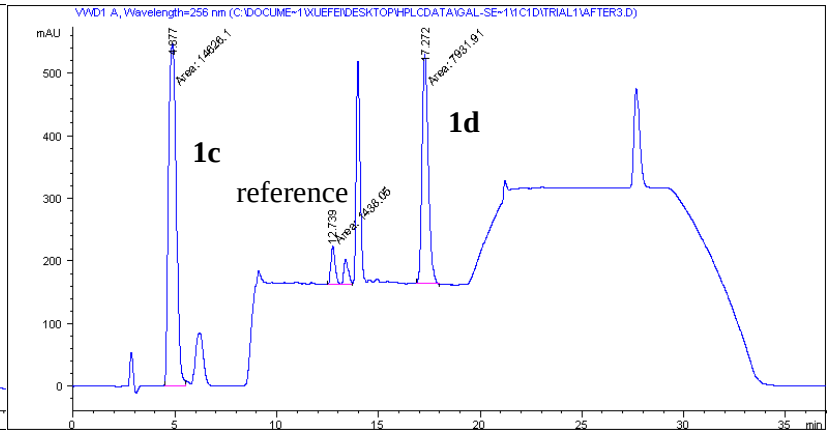

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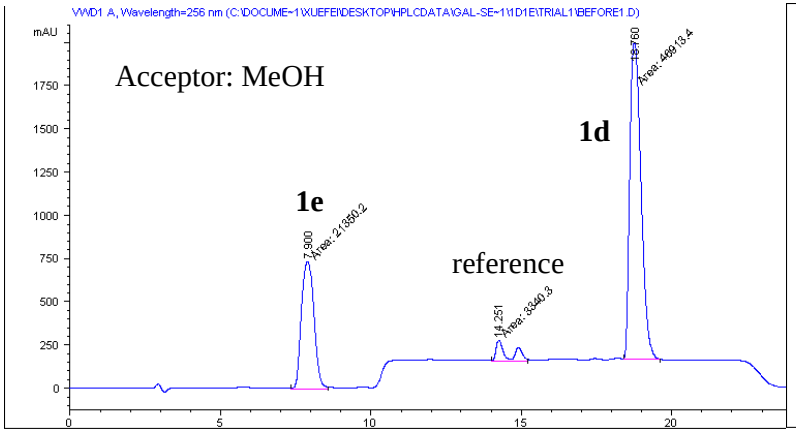

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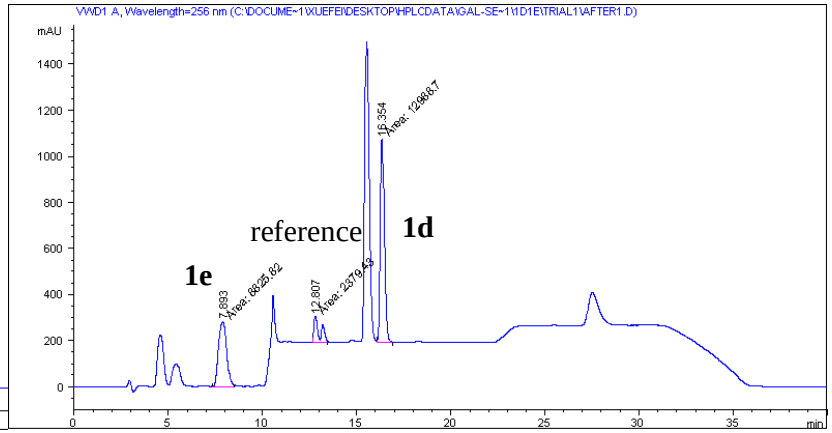
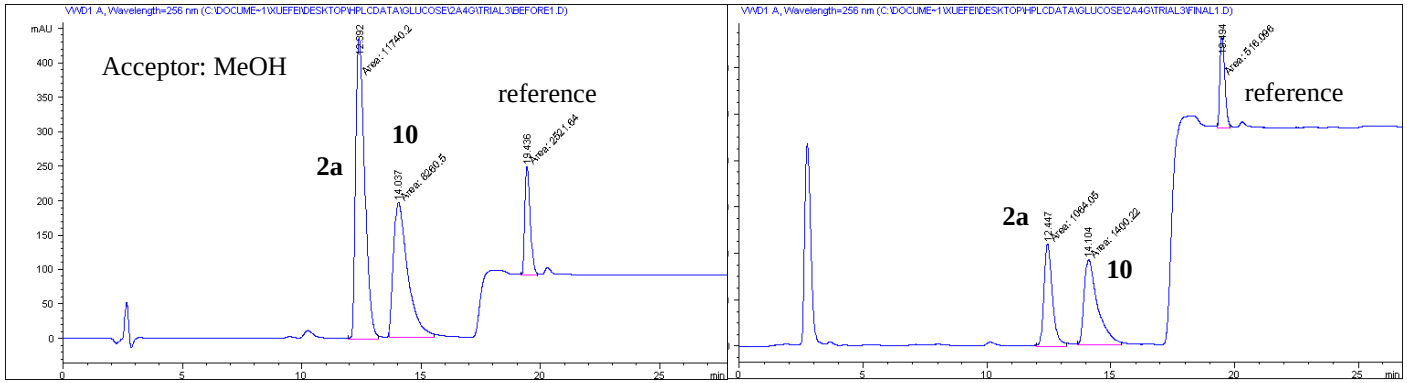


After Reaction

Donors **2a-2e**



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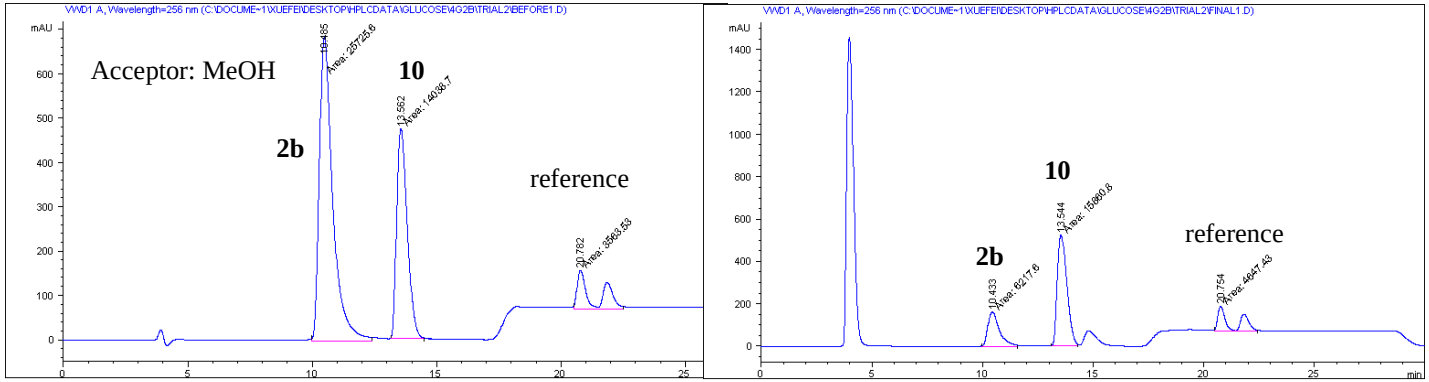

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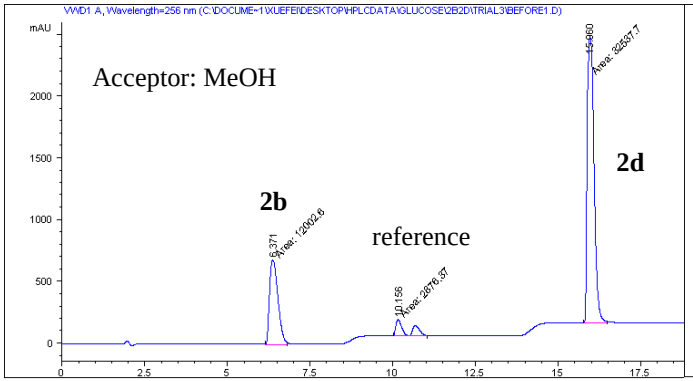

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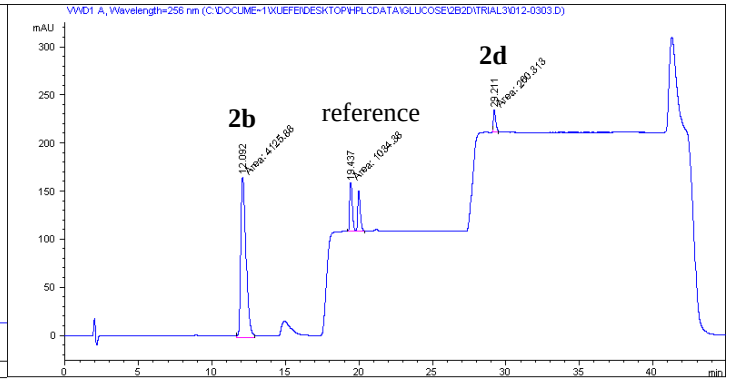

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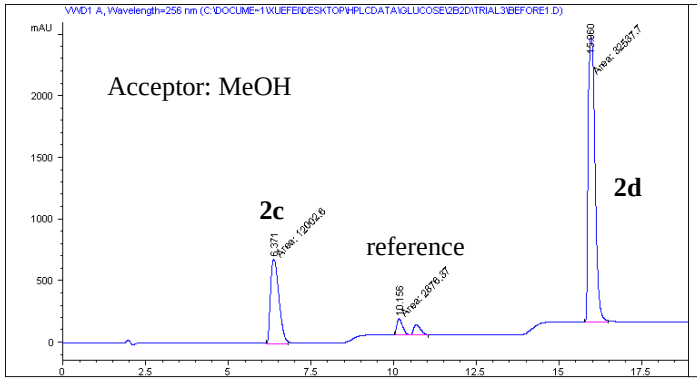

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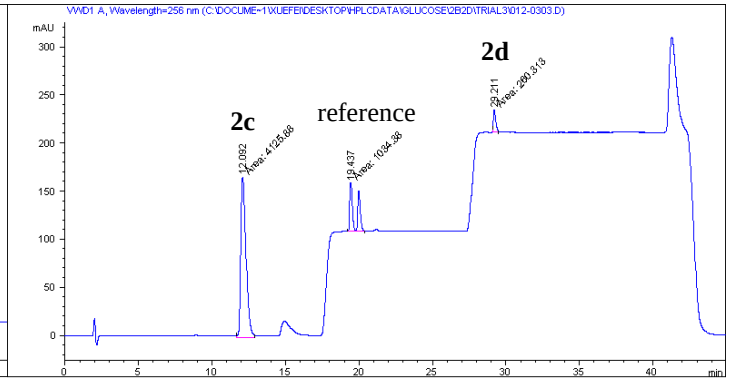

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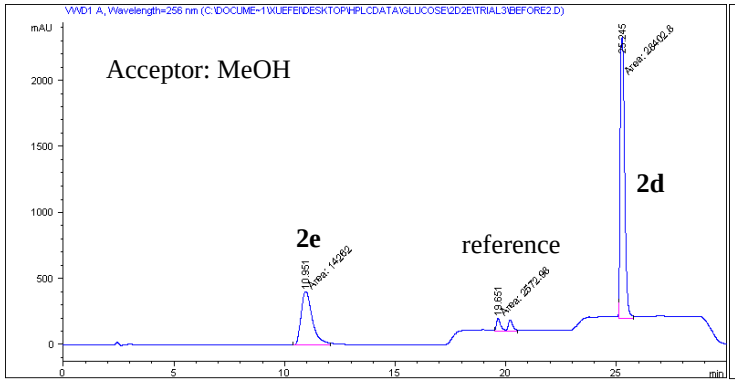

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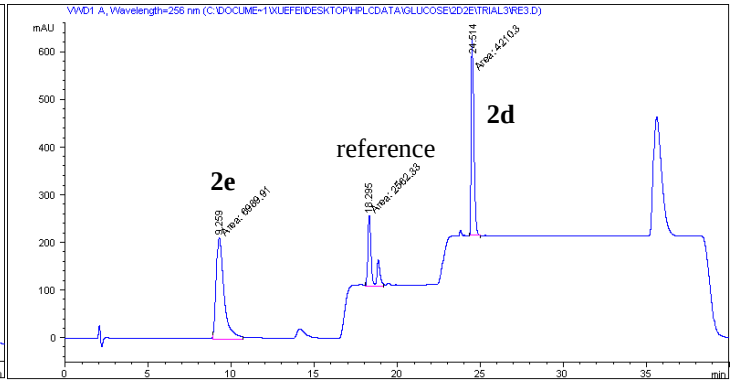
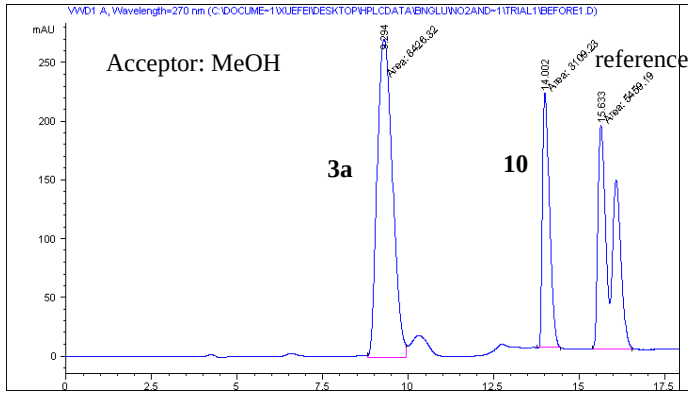


After Reaction

Donors **3a-3e**



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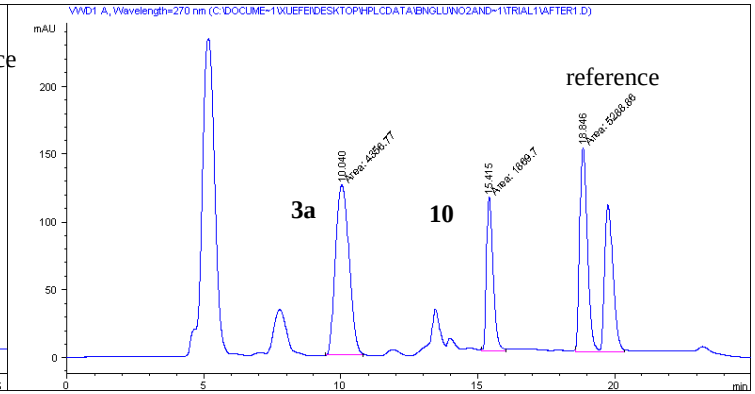

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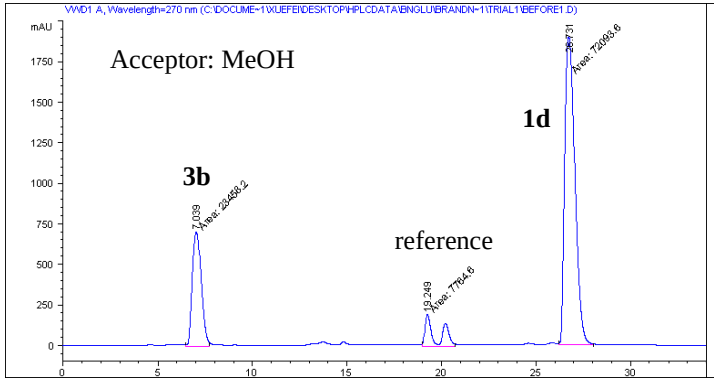

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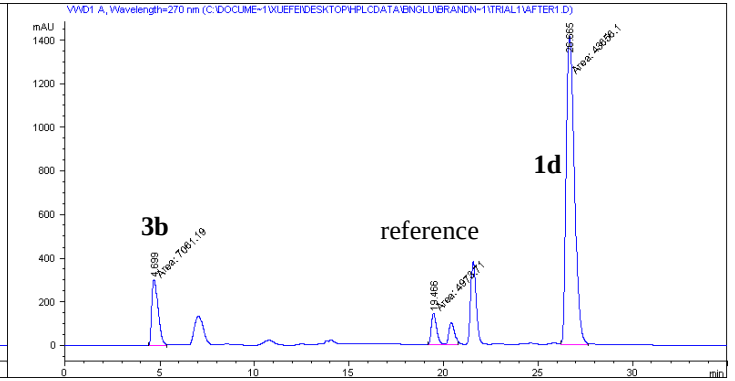

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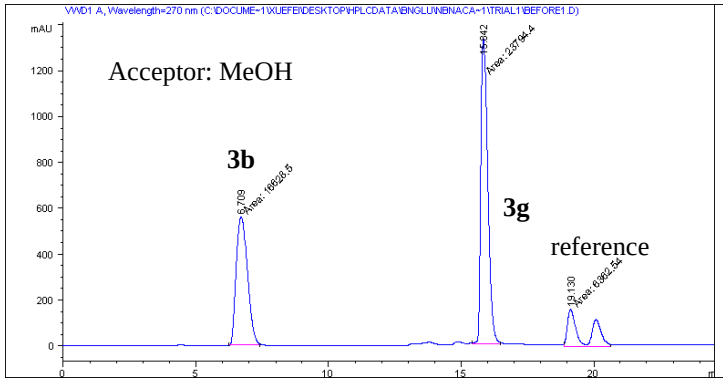

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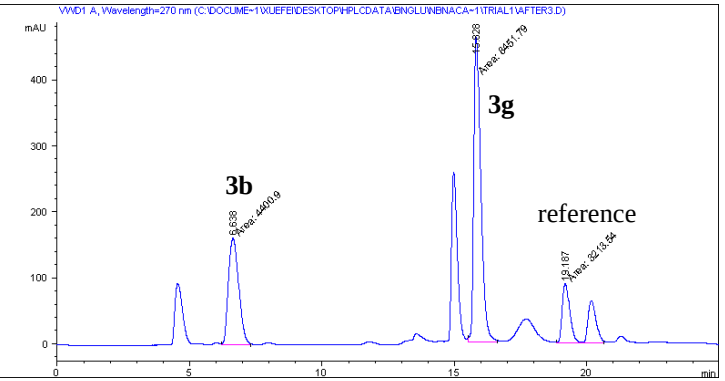

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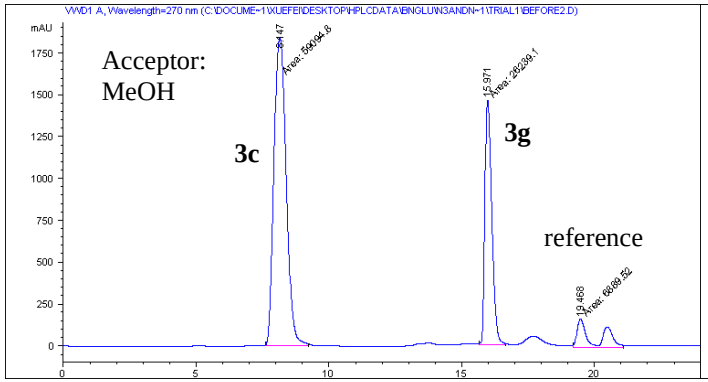

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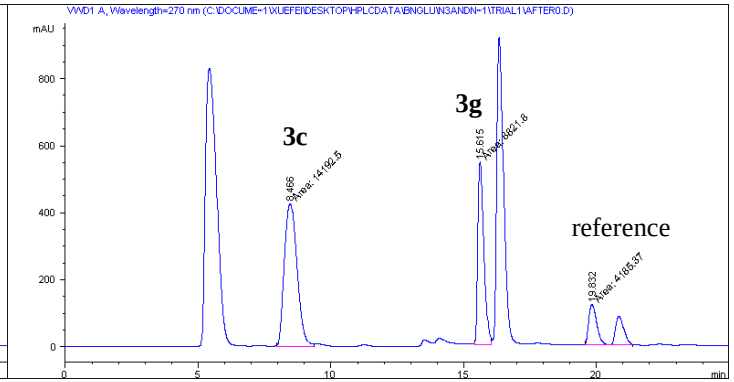

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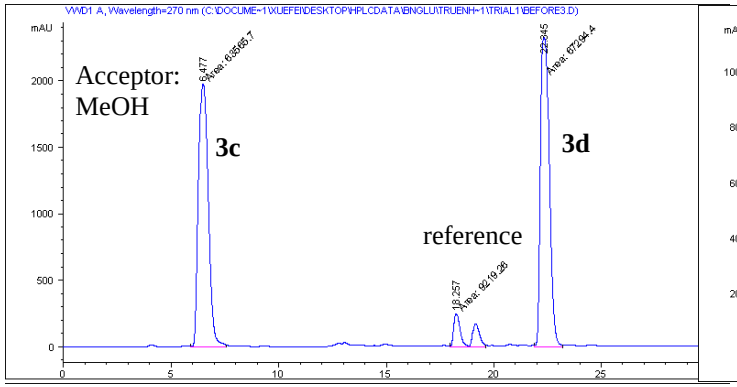

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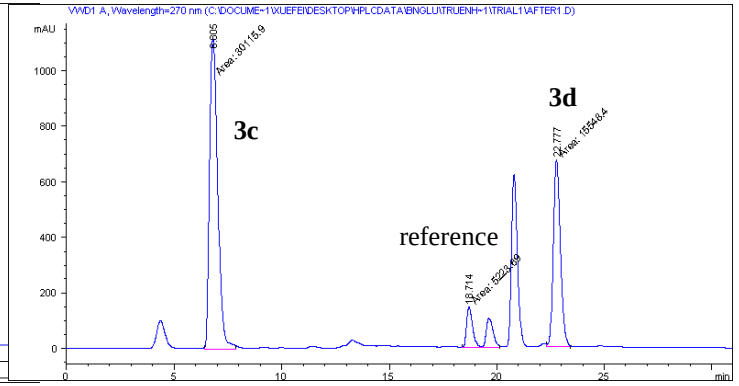

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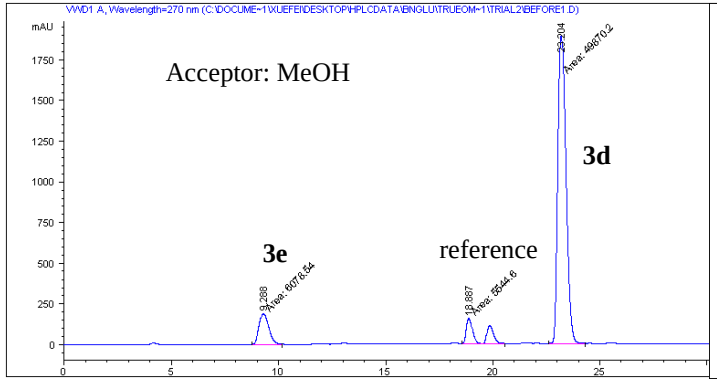

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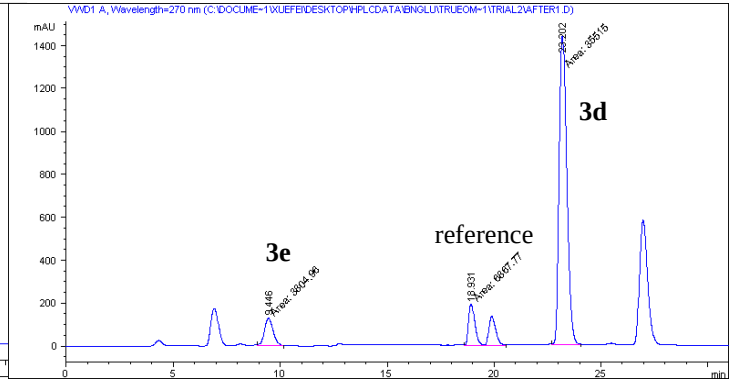
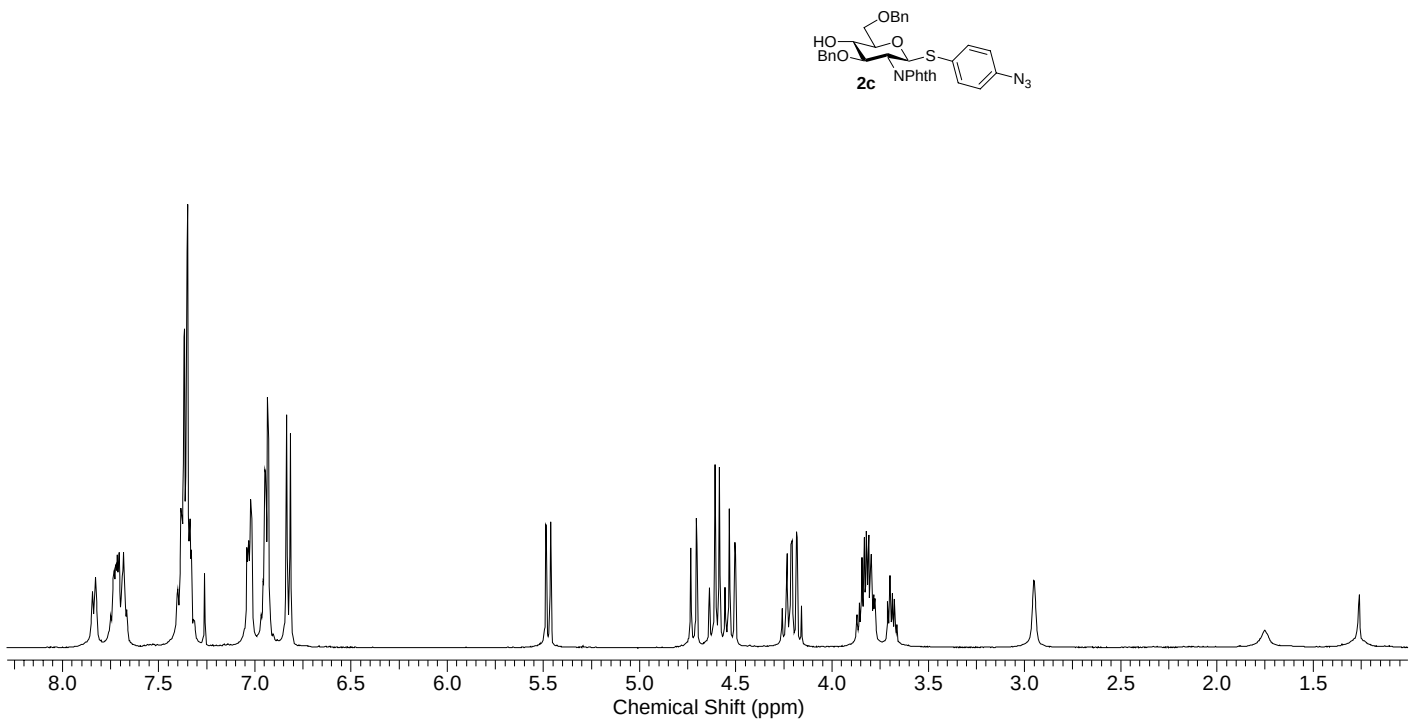
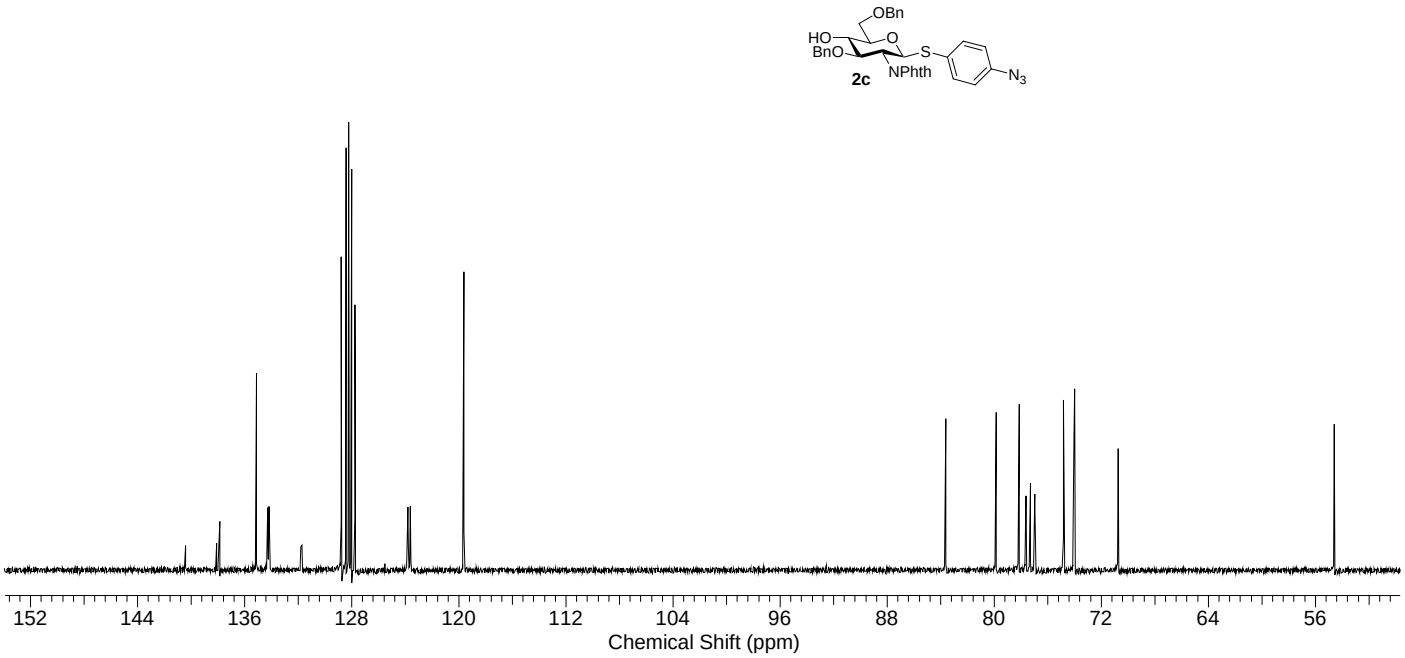


After Reaction

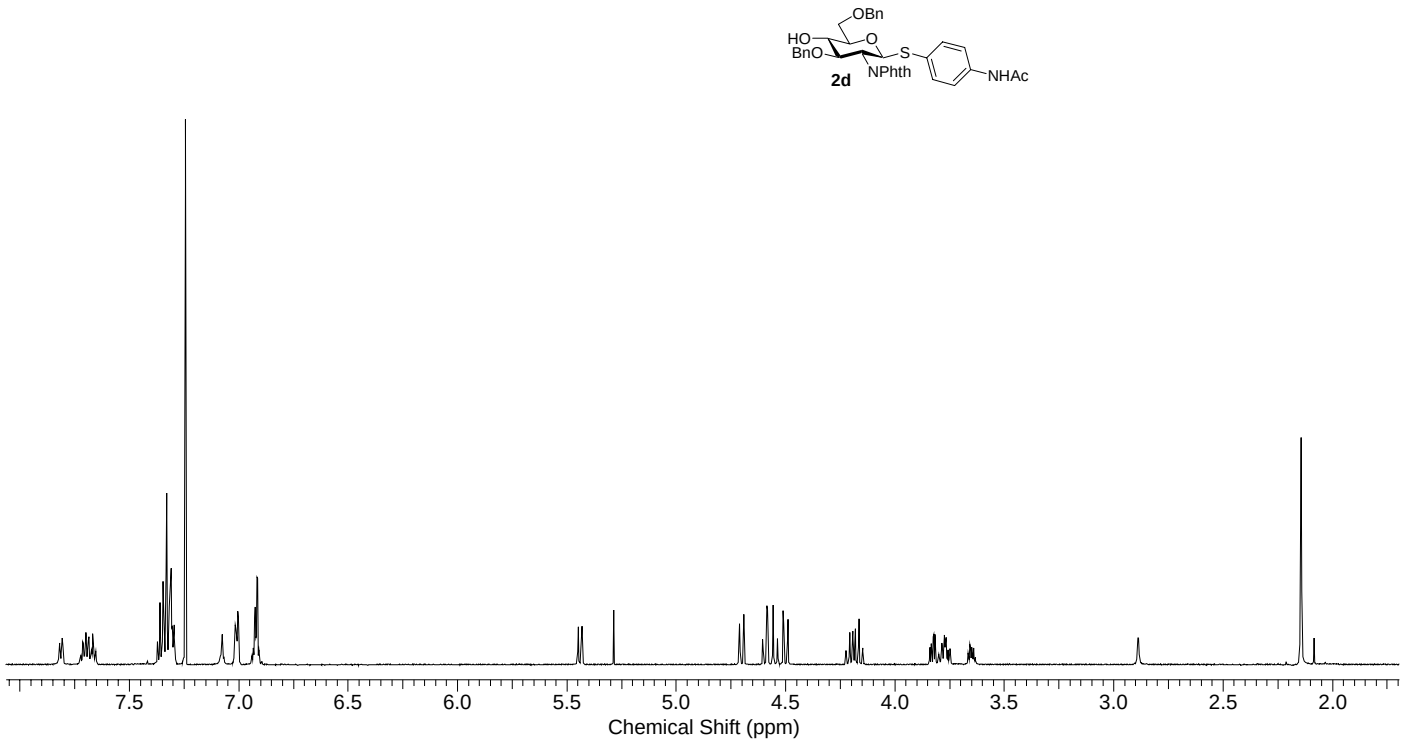
^{1}H-NMR (400 MHz, $CDCl_3$) of **2c**



^{13}C-NMR (100 MHz, $CDCl_3$) of **2c**



^{1}H-NMR (400 MHz, $CDCl_3$) of **2d**



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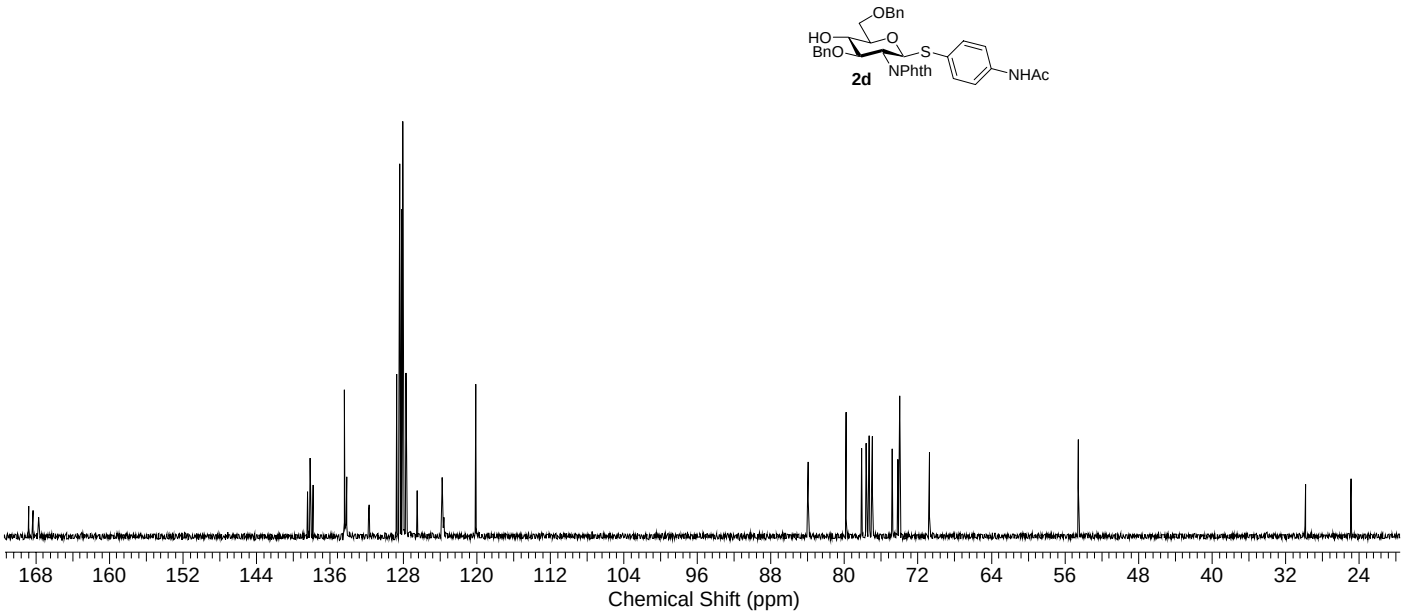
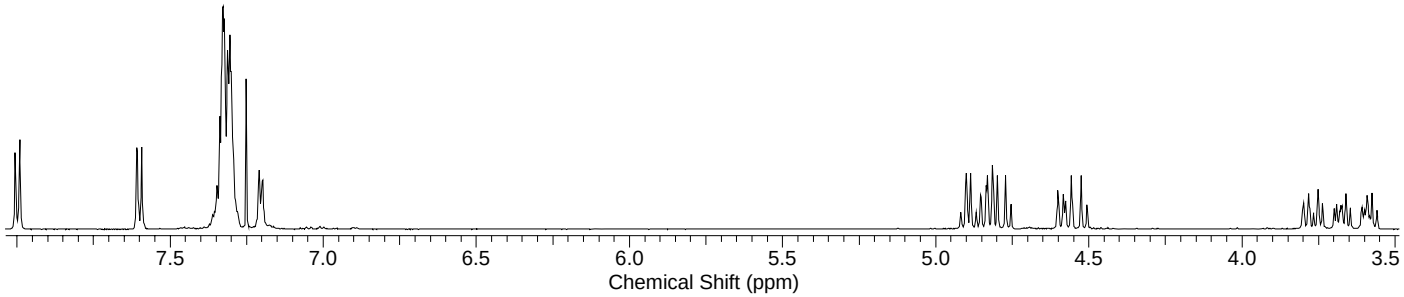


^{1}H-NMR (600 MHz, $CDCl_3$) of **3a**



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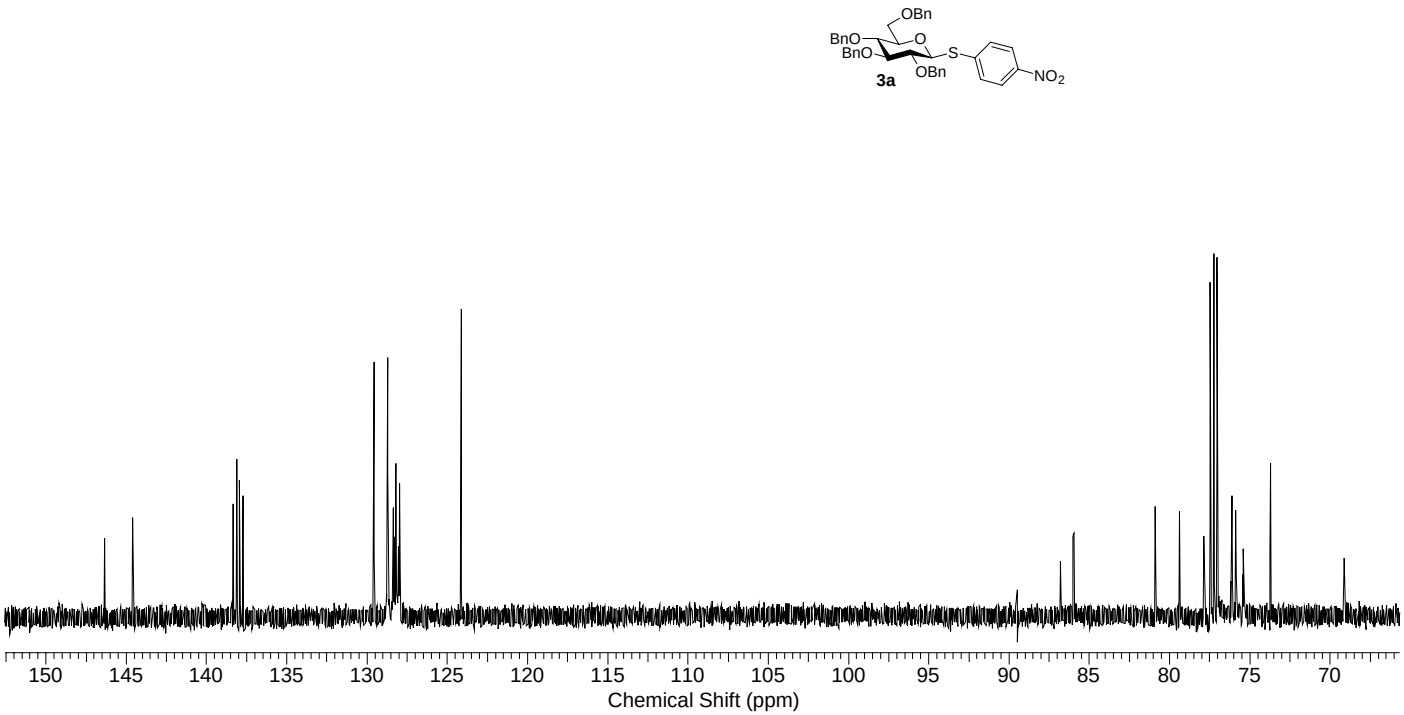
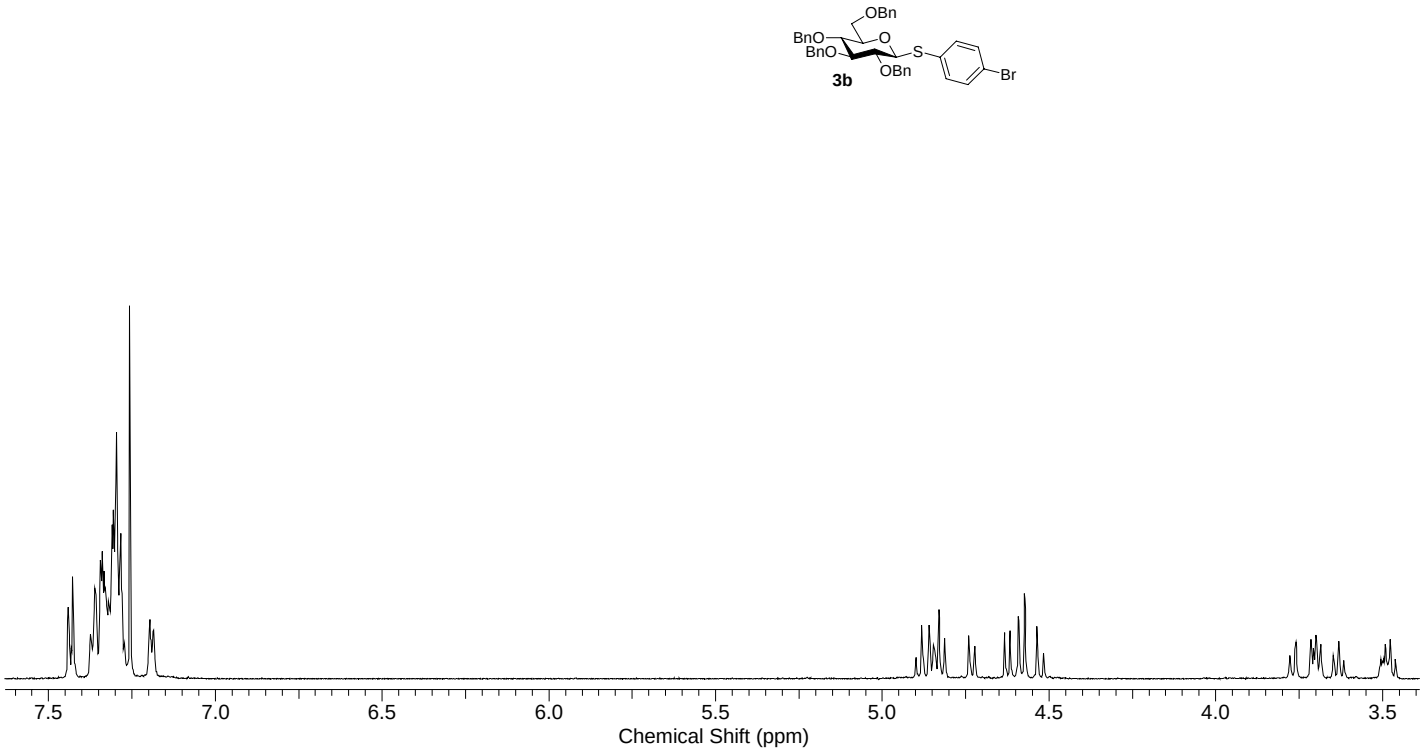
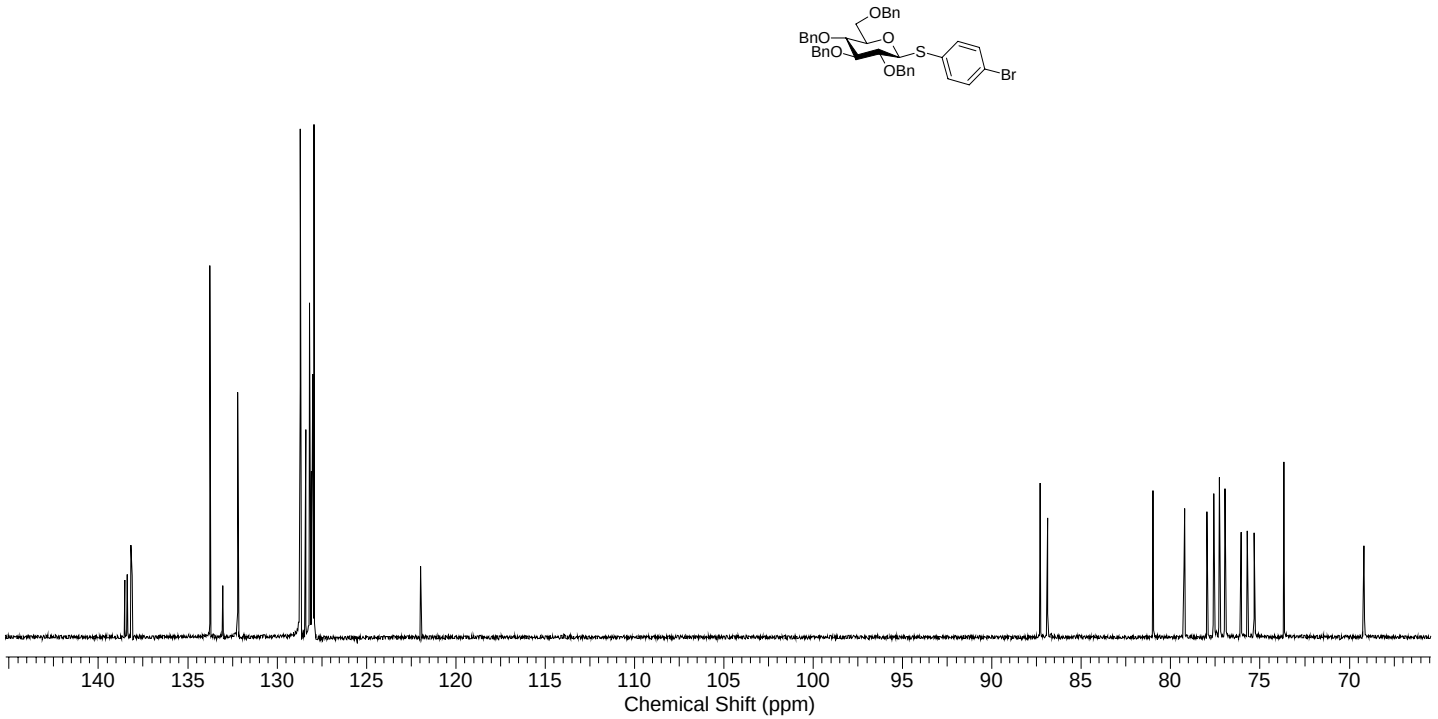


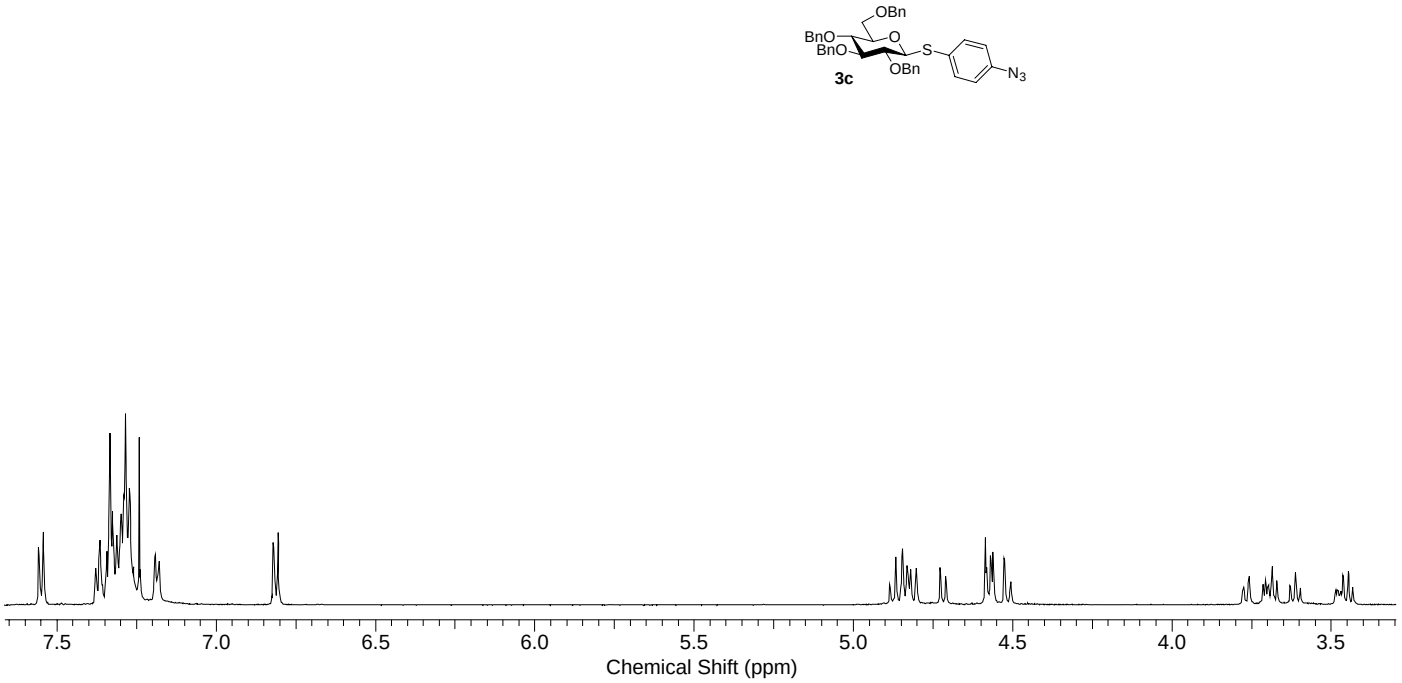
^{1}H-NMR (600 MHz, $CDCl_3$) of **3b**



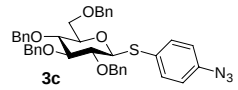
^{13}C-NMR (150 MHz, $CDCl_3$) of **3b**



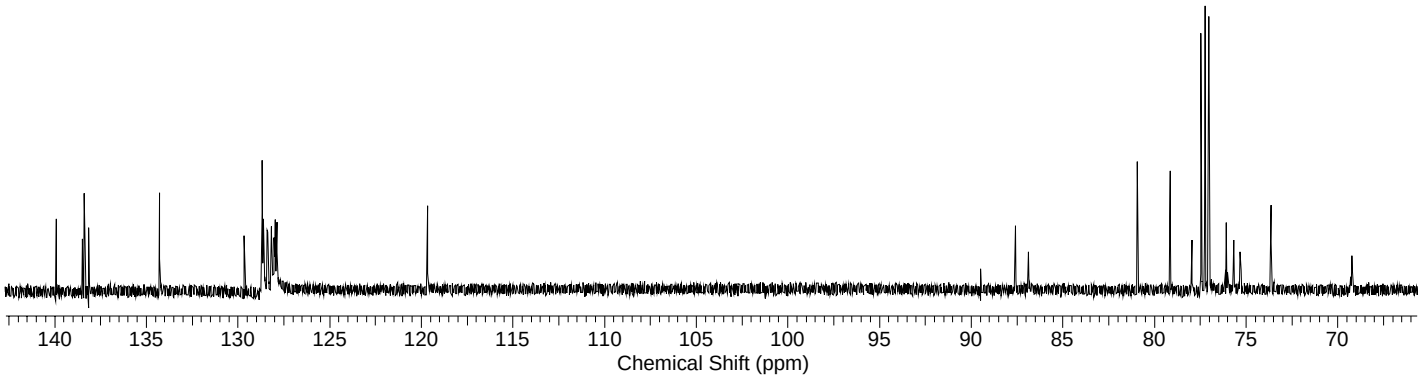
^{1}H-NMR (600 MHz, $CDCl_3$) of **3c**



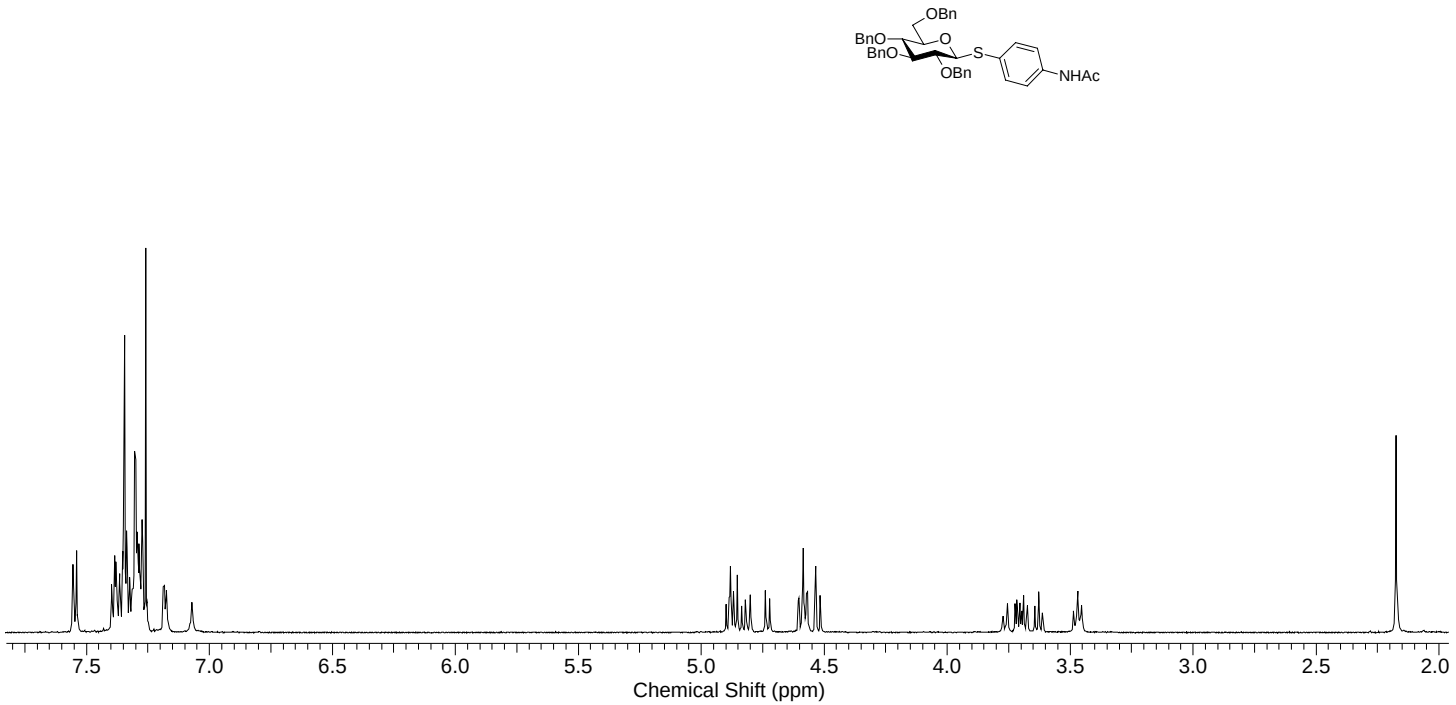
^{13}C-NMR (150 MHz, $CDCl_3$) of **3c**



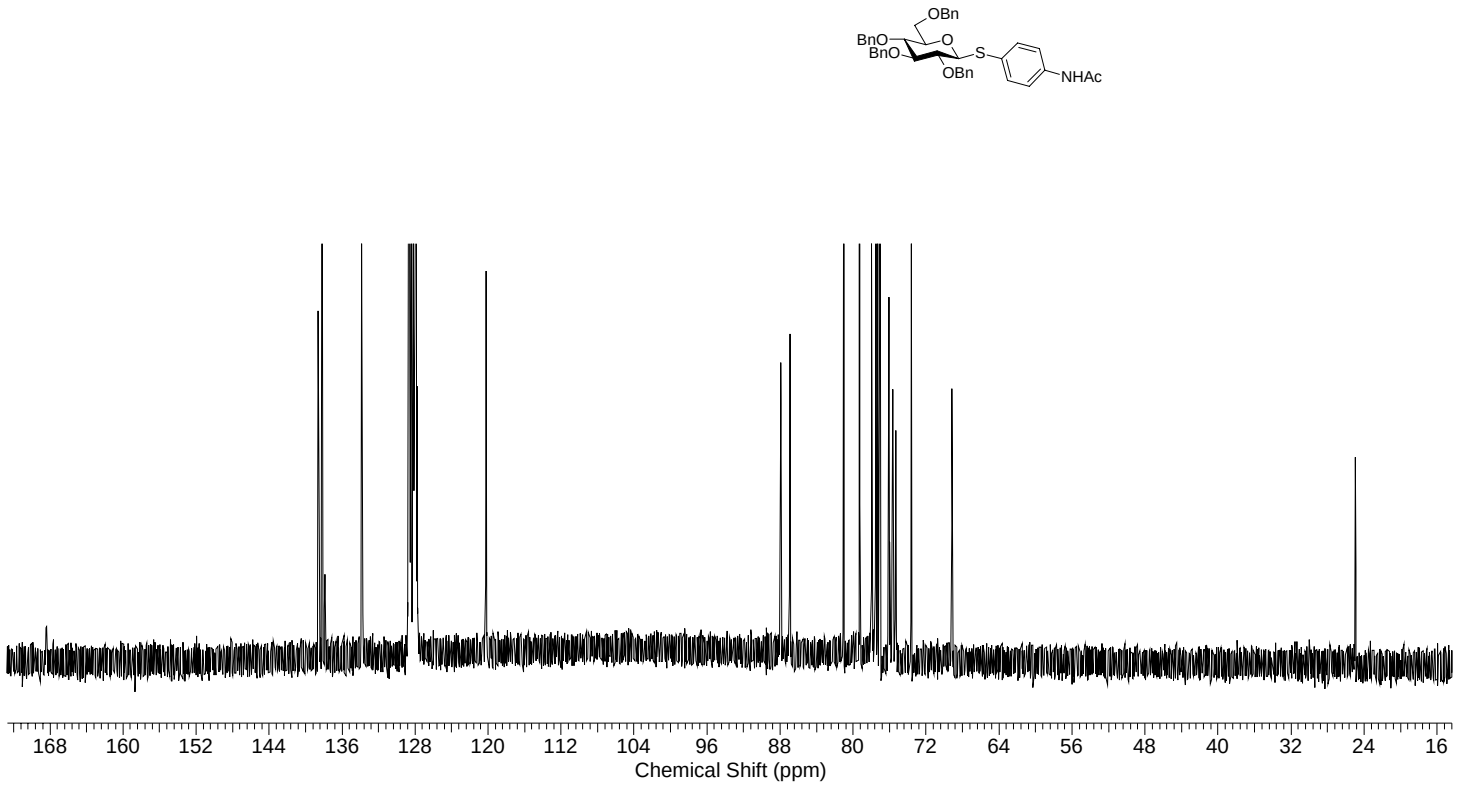
3c



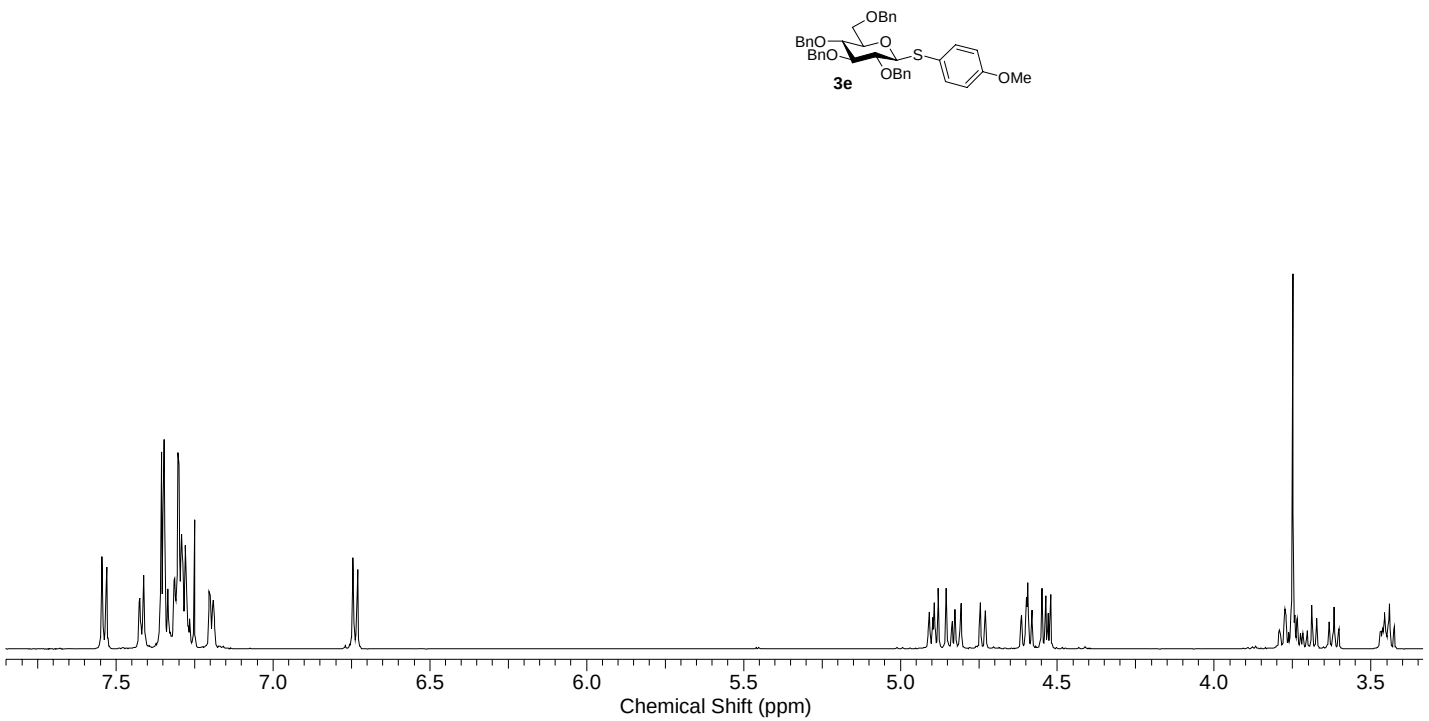
^{1}H-NMR (600 MHz, $CDCl_3$) of **3d**



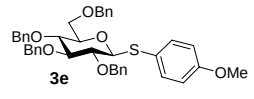
^{13}C-NMR (150 MHz, $CDCl_3$) of **3d**

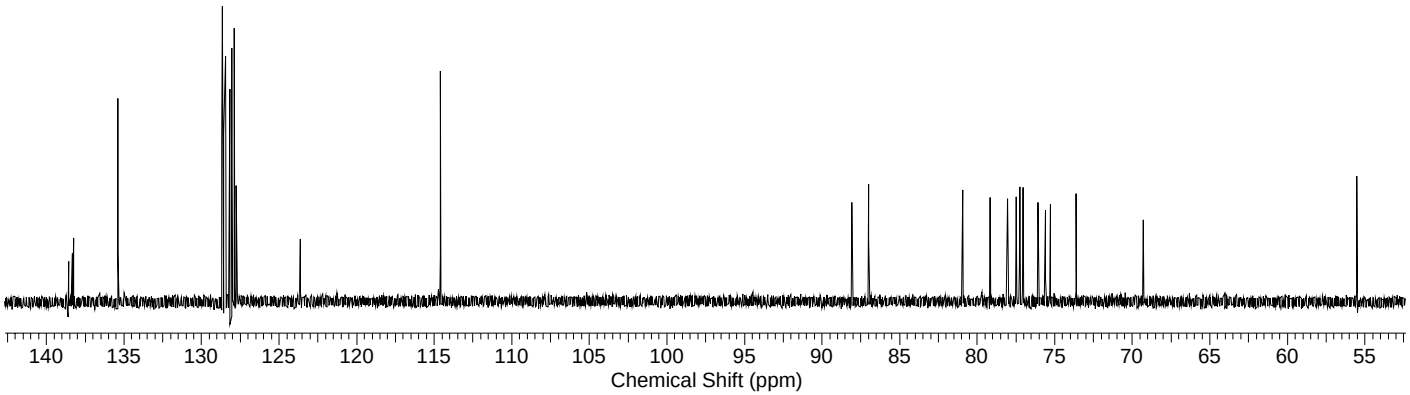


^{1}H-NMR (600 MHz, $CDCl_3$) of **3e**

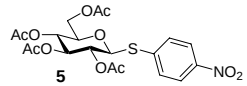


^{13}C-NMR (150 MHz, $CDCl_3$) of **3e**

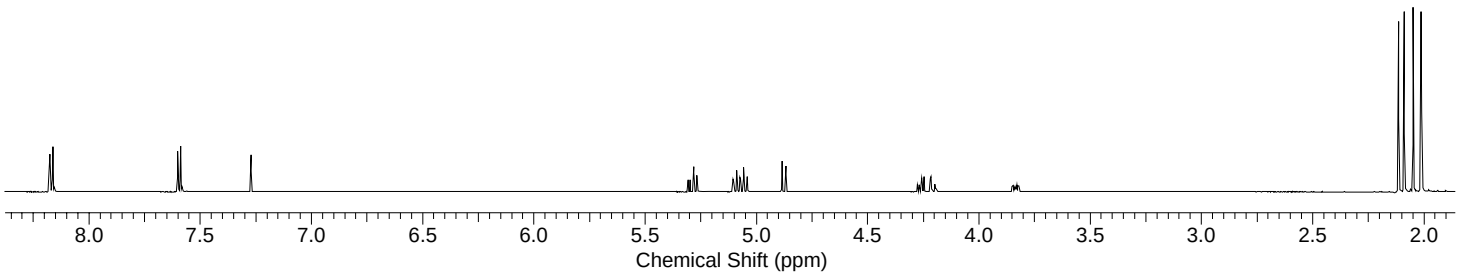




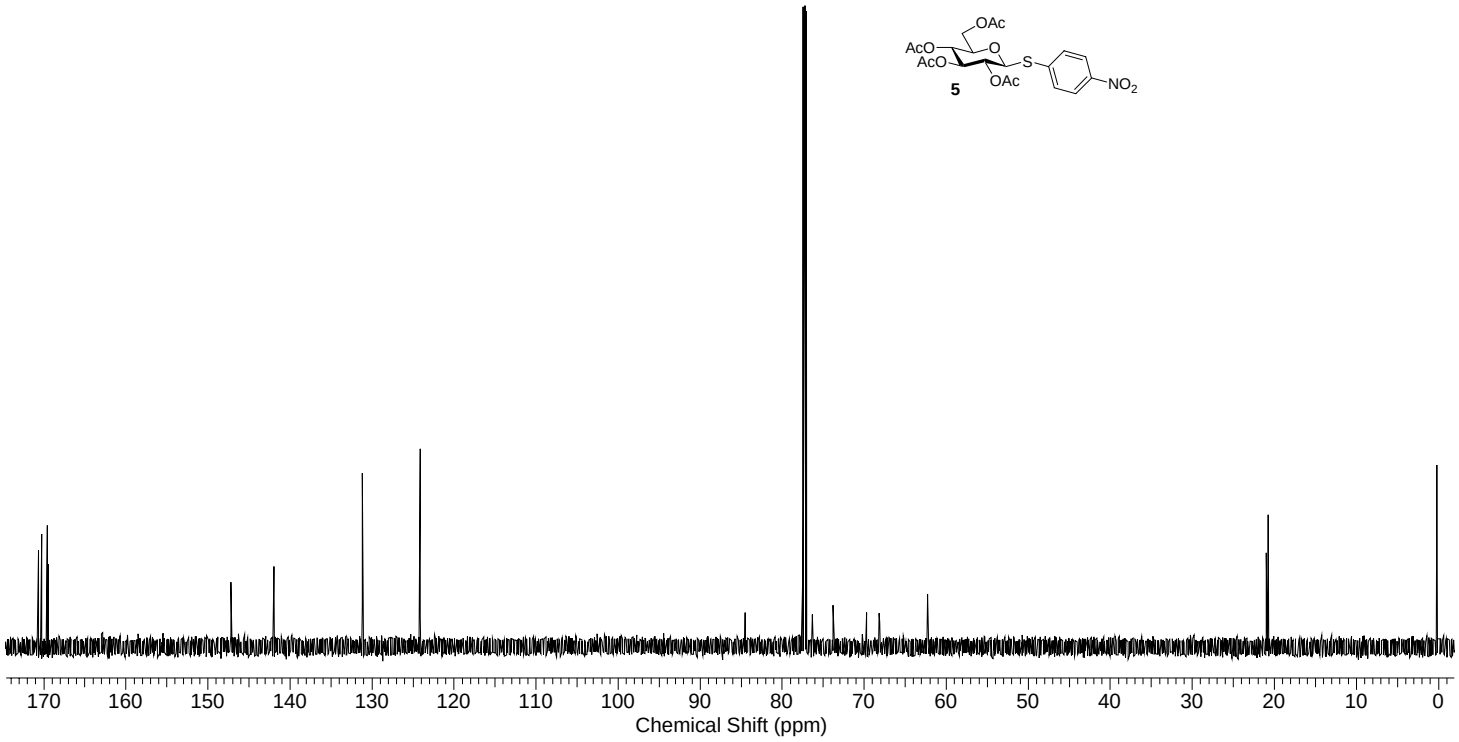
^{1}H-NMR (600 MHz, $CDCl_3$) of **5**



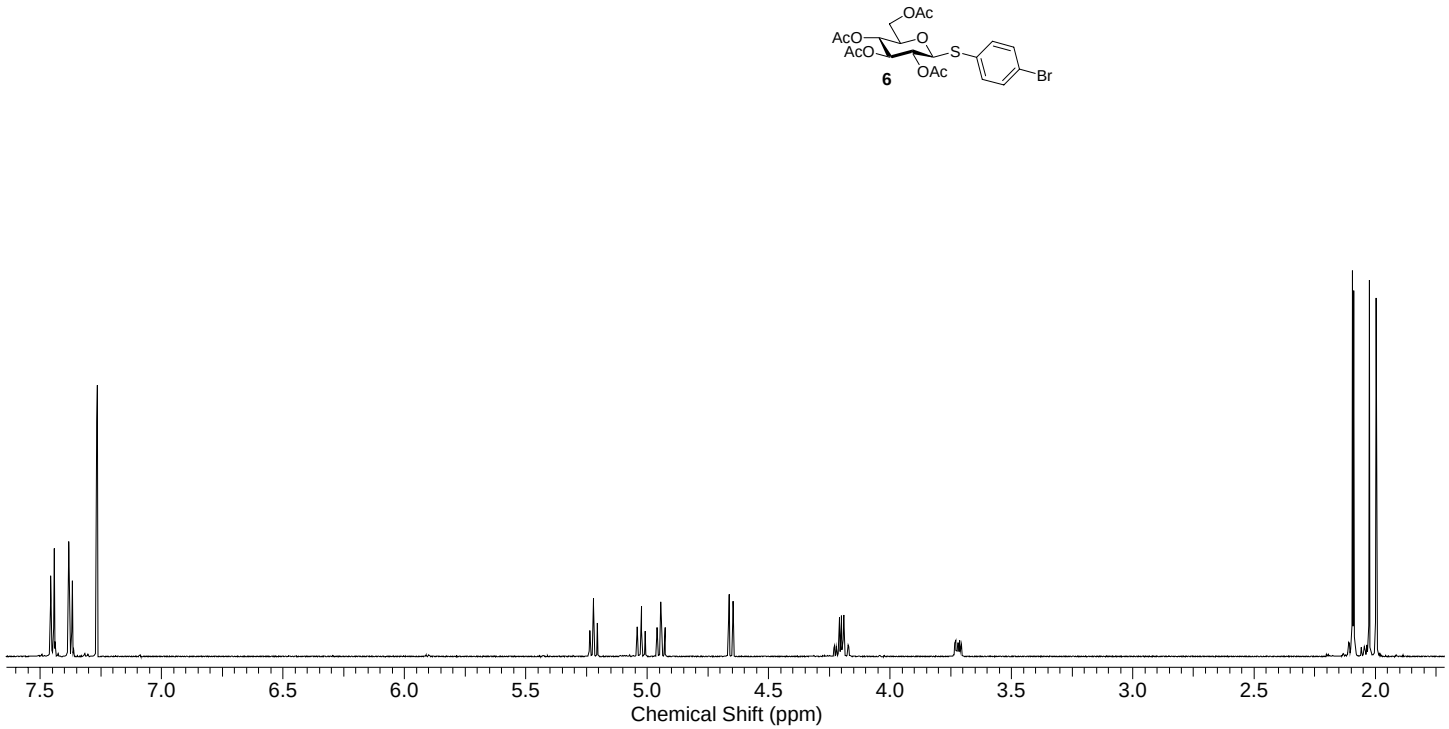
5



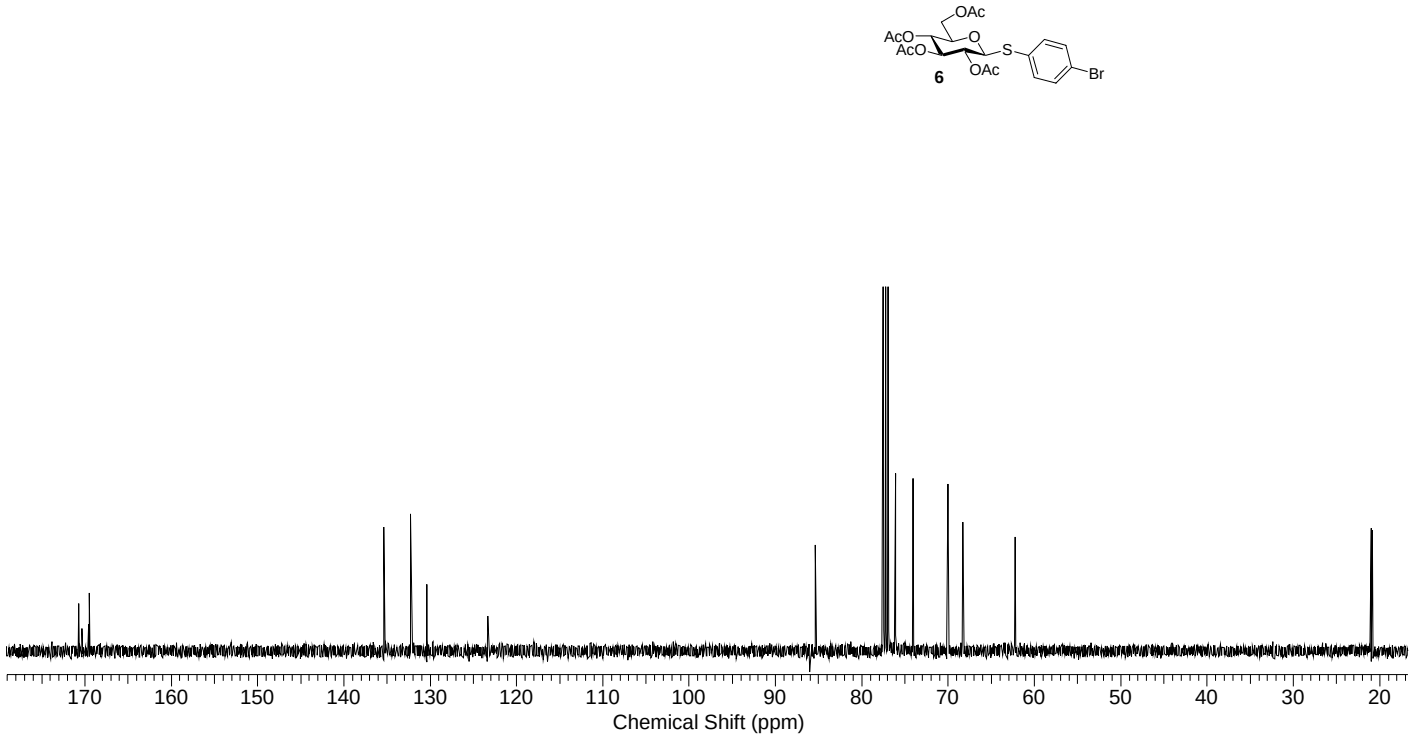
^{13}C-NMR (150 MHz, $CDCl_3$) of **5**



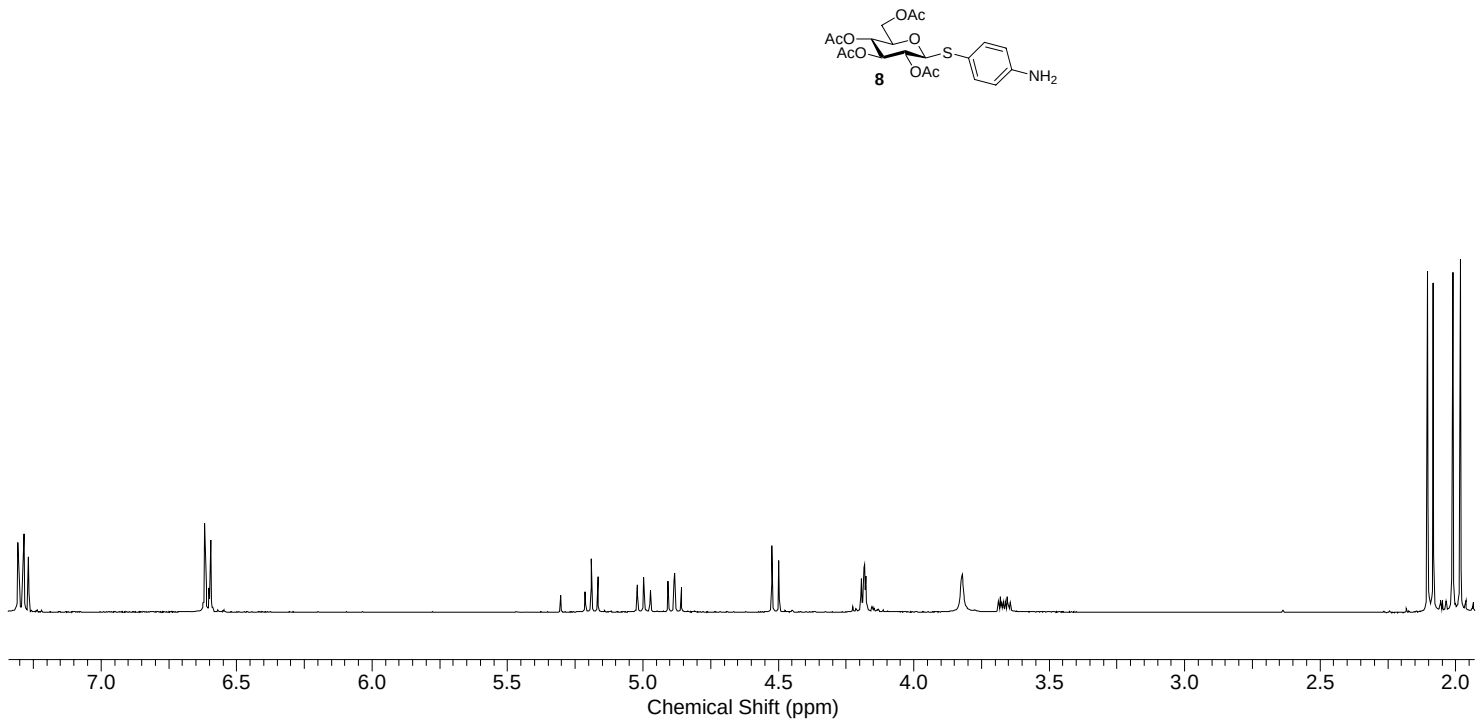
^{1}H-NMR (600 MHz, $CDCl_3$) of **6**



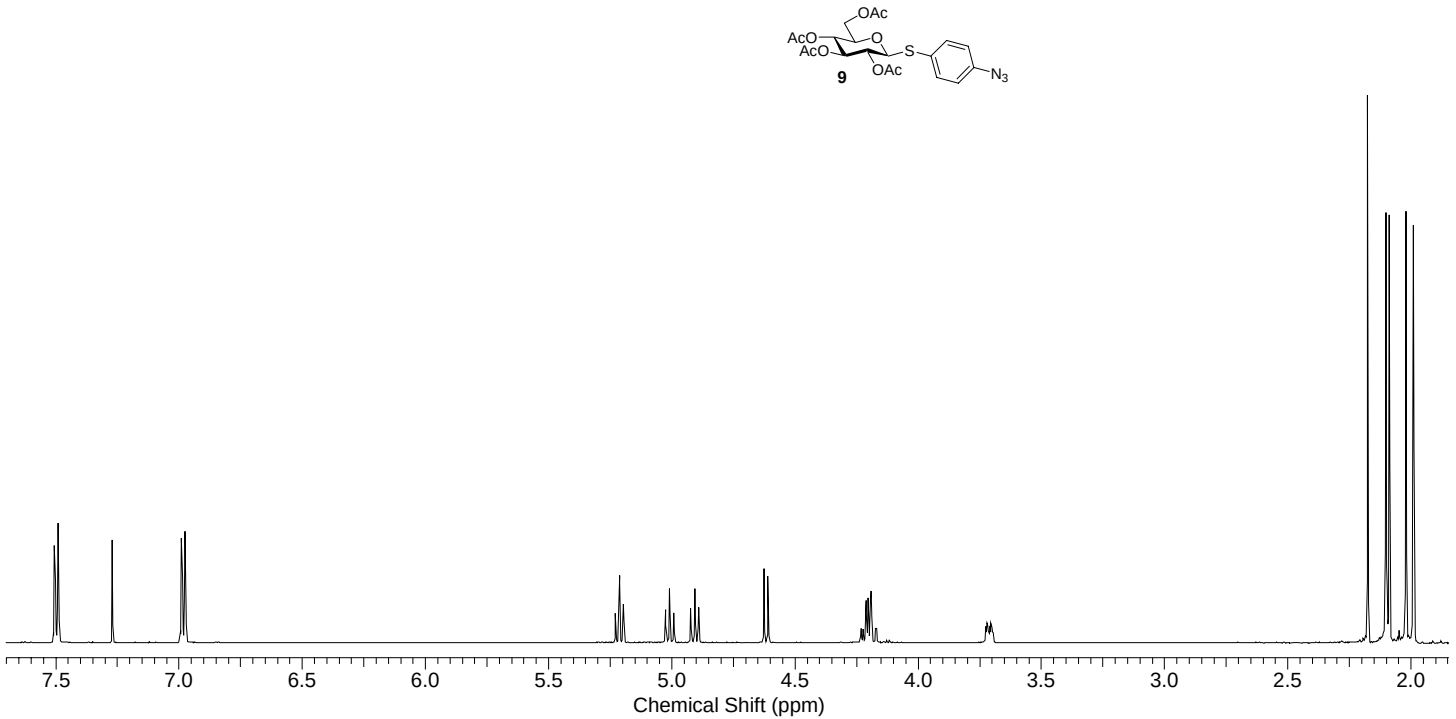
^{13}C-NMR (150 MHz, $CDCl_3$) of **6**



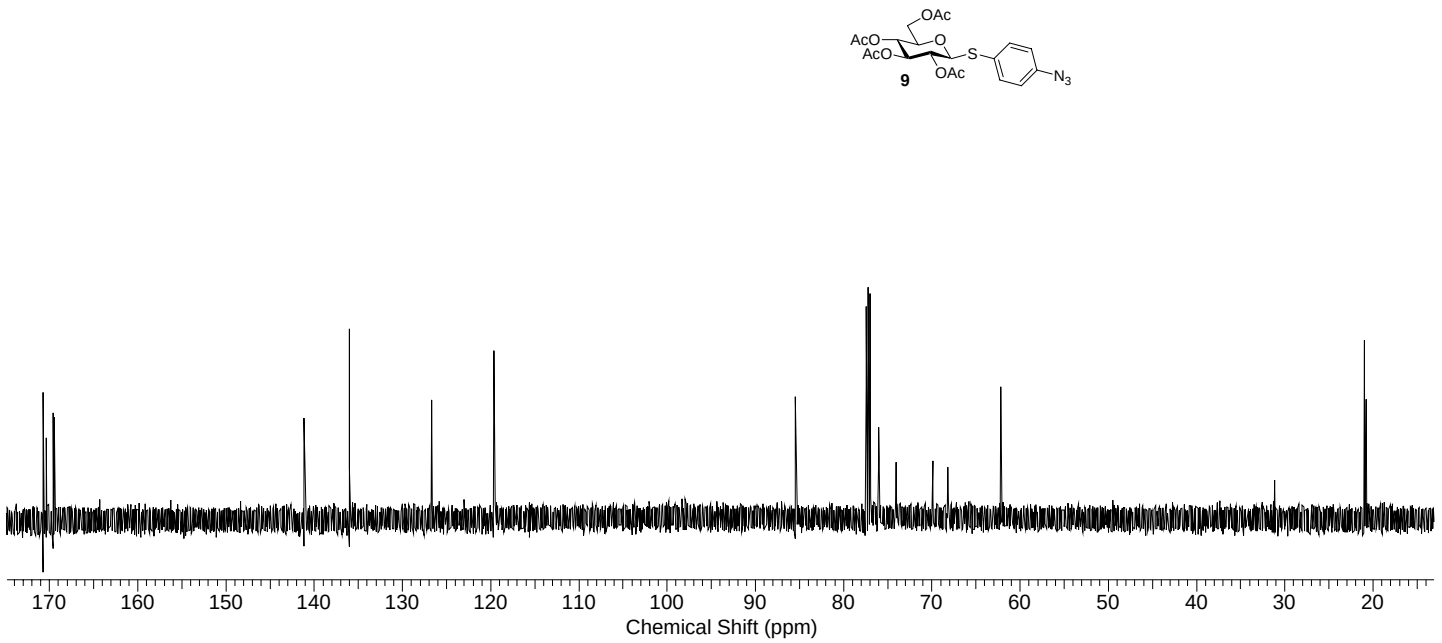
^{1}H-NMR (400 MHz, $CDCl_3$) of **8**



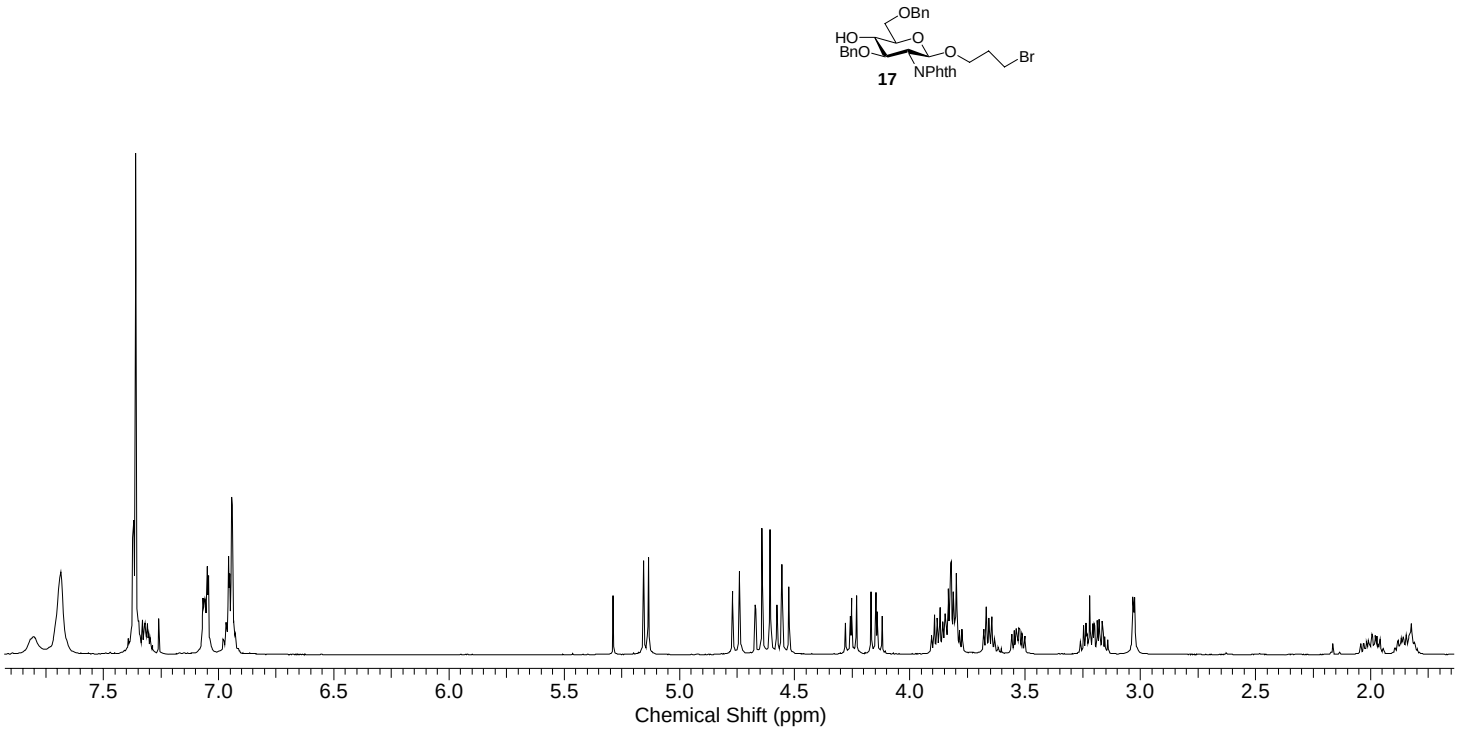
^{1}H-NMR (600 MHz, $CDCl_3$) of **9**



^{13}C-NMR (150 MHz, $CDCl_3$) of **9**



^{1}H-NMR (400 MHz, $CDCl_3$) of **17**



^{13}C-NMR (100 MHz, $CDCl_3$) of **17**