Supplementary Information for "Cationic Poly-Amido-Saccharides: Stereochemically-defined, Enantiopure Polymers from Anionic Ring-opening Polymerization of an Amino-Sugar Monomer"

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Table of Contents

Supplementary Figures

Figure S1. Cycloaddition rates for protected glycals.

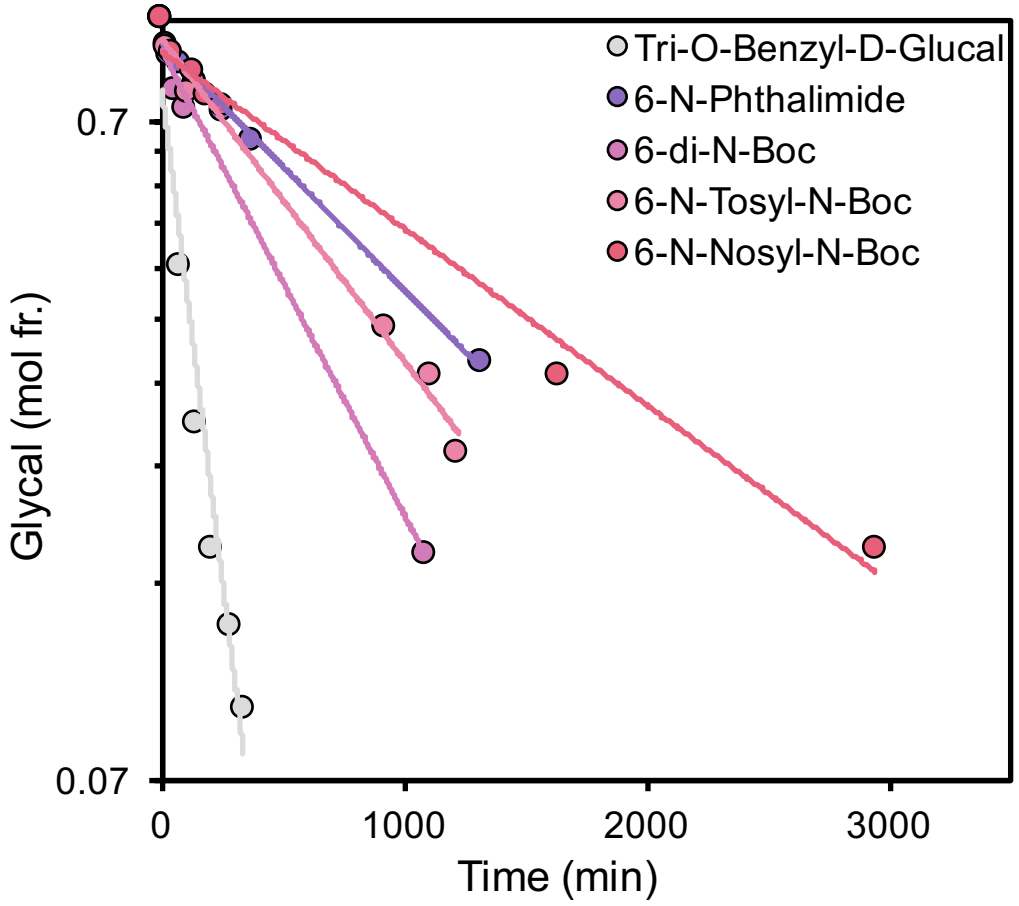
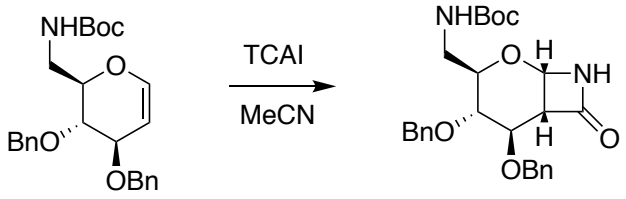


Figure S1. Reaction progress of [2+2] cycloaddition reactions between trichloroacetyl isocyanate (TCAI) and glycals over time. The mol fraction of glycal remaining is calculated by calculating the fractional integration of ^{1}H-NMR peaks corresponding to the glycal H1 peak, [2+2] product H1 peak, and [4+2] product H1 peak. Tri-O-Benzyl-D-Glucal: $R^2 = 0.96$, k = -0.00688 min^{-1}; 6-*N*-phthalimide: $R^2 = 0.99$, k = -0.000864 min^{-1}; 6-di-*N*-Boc: $R^2 = 0.99$, k = -0.00163 min^{-1}; 6-*N*-Tosyl-*N*-Boc: $R^2 = 0.99$, k = -0.00113 min^{-1}; Tri-O-Benzyl-D-Glucal: $R^2 = 0.96$, k = -0.00688 min^{-1}; 6-*N*-Nosyl-*N*-Boc: $R^2 = 0.99$, k = -0.000618 min^{-1}.

Figure S2. Cycloaddition of TCAI to 8.



8 n.r.

Figure S2. Attempted cycloaddition of TCAI with **8**. Side reaction occurred and no product was isolated.

Figure S3. Minimum energy structures of protected lactams.

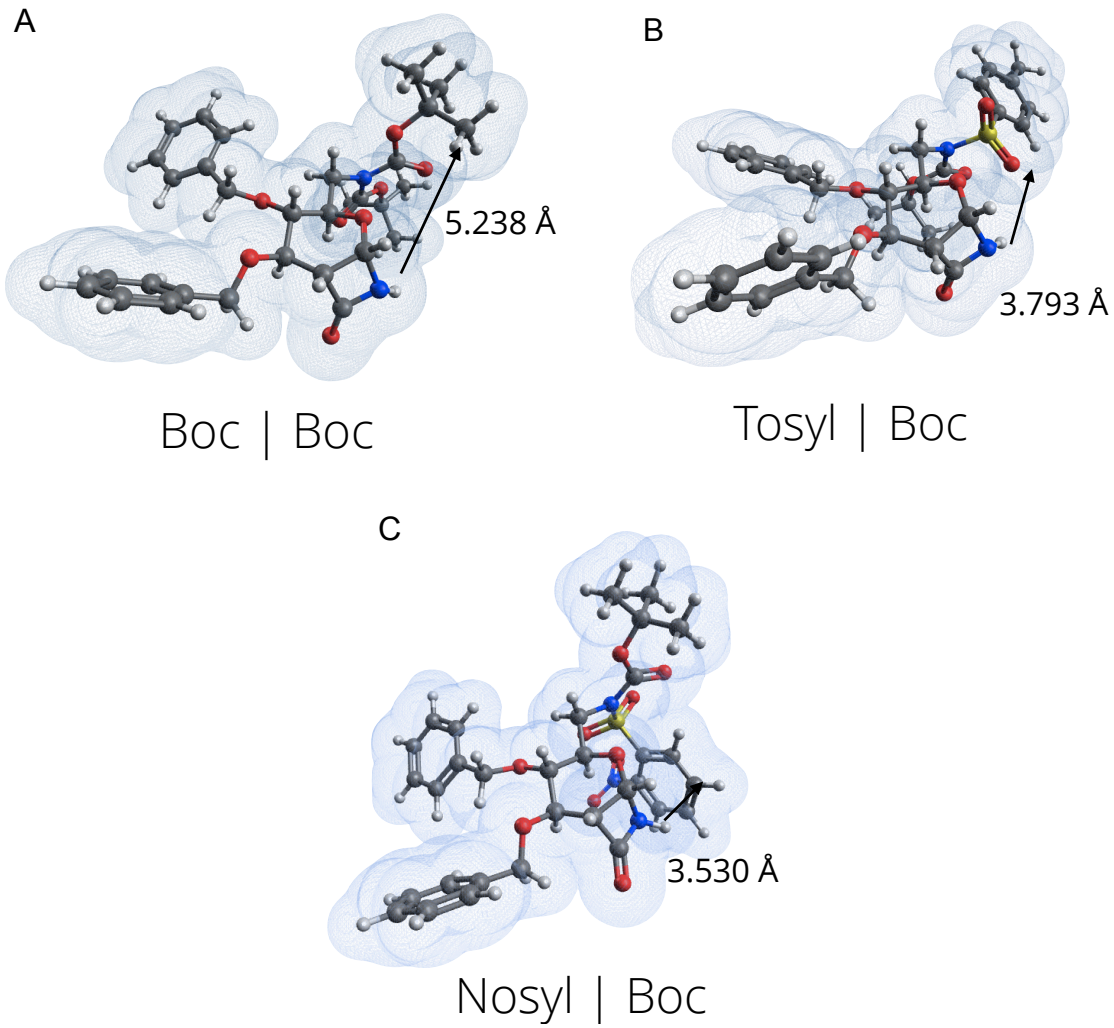


Figure S3. Comparison between minimum energy structures (B3LYP/6-31G(d)) of di-*N* protected lactam monomers **15**, **17**, and **19**. (A): 6-di-*N*-Boc protected monomer – the distance from lactam nitrogen proton to the nearest moiety in the forward path is 5.2 Å. (B): 6-*N*-Tosyl-*N*-Boc protected monomer – the distance from lactam nitrogen proton to the nearest moiety in the forward path is 3.8 Å. (C): 6-*N*-Nosyl-*N*-Boc protected monomer – the distance from lactam nitrogen proton to the nearest moiety in the forward path is 3.5 Å.

Figure S4. Polymerization kinetics raw data

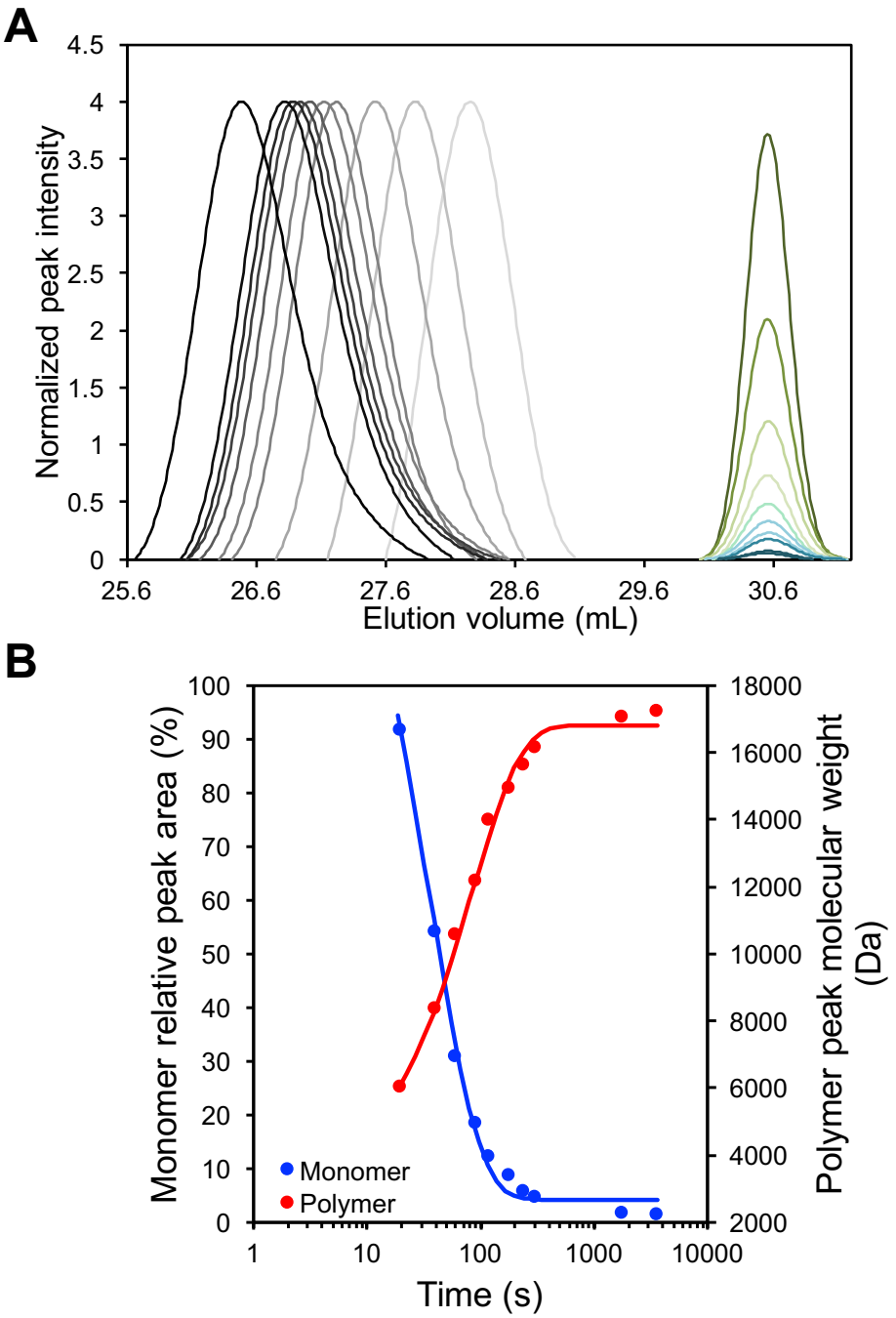


Figure S4. (A): Raw SEC chromatograms of polymerization kinetics study with monomer peak decreasing over time (green to blue) and polymer peak shifting to earlier retention time as polymerization proceeded (light grey to black). (B): Modeled data (exponential fit) of decreasing monomer peak area over time and increasing peak of polymer molecular weight distribution. Monomer: ($k = -0.027\ s^{-1}$); Polymer: ($k = -0.016\ s^{-1}$).

Figure S5. SEC buffer optimization

	Buffer A	Buffer B	Buffer C	Buffer D	Buffer E	Buffer F	Buffer G
pH	2.5	2.5	2.5	7.4	2.3	2.3	2.3
[G] (M)	0.2	0.2	0.2	0	0.1	0.1	0.05
[R] (M)	0.2	0.7	0.2	0.4	0	0	0
Methanol (%)	0	0	10	0	0	0	0
[AcOH] (M)	0	0	0	0	0.5	0.2	0.5
[NaAc] (M)	0	0	0	0	0	0	0
[Phosphate] (M)	0	0	0	0.2	0	0	0
total Ionic (M)	0.4	0.9	0.4	0.6	0.6	0.3	0.55
Start elution	45.8	47.1	46.1	-	45.7	45.5	44.4
Peak elution	50.6	53.1	51.8	-	51.1	50.1	48.7
Max elution	55.3	55.9	55.8	-	55.9	55.2	53.5
Elution time	9.5	8.8	9.7	-	10.2	9.7	9.1
PDI	1.48	1.35	1.37	-	1.35	1.26	1.23
	Buffer H	Buffer I	Buffer J	Buffer K	Buffer L	Buffer M	
pH	2.3	2.76	2.76	4.5	2.6	2.3	
[G] (M)	0.3	0.2	0.2	0	0	0.02	
[R] (M)	0	0	0	0	0	0	
Methanol (%)	0	9	0	0	0	0	
[AcOH] (M)	0.2	0	0	0.3	0.3	0.1	
[NaAc] (M)	0	0	0	0.2	0	0	
[Phosphate] (M)	0	0	0	0	0.2	0	
total Ionic (M)	0.5	0.2	0.2	0.5	0.5	0.12	
Start elution	45.1	46.2	45.5	-	45.9	44.15	
Peak elution	51.2	51.7	50.6	-	50	47.6	
Max elution	56.2	57.6	55.3	-	54.8	51.89	
Elution time	11.1	11.4	9.8	-	8.9	7.74	
PDI	1.37	1.63	1.28	-	1.25	1.16	

Figure S5. Buffer optimization of aqueous SEC characterization for **P2**. Buffers were freshly prepared and allowed to flow through the column at 0.5 mL/min for 24 hours to equilibriate the columns (PL aquagel OH 60 micron, 7.8 x 300 mm) and purge the refractive index reference cell. Molecular weight distributions were calculated using poly(2-vinylpyridine) reference standards.

Figure S6. ^{1}H-NMR spectra of AmPAS

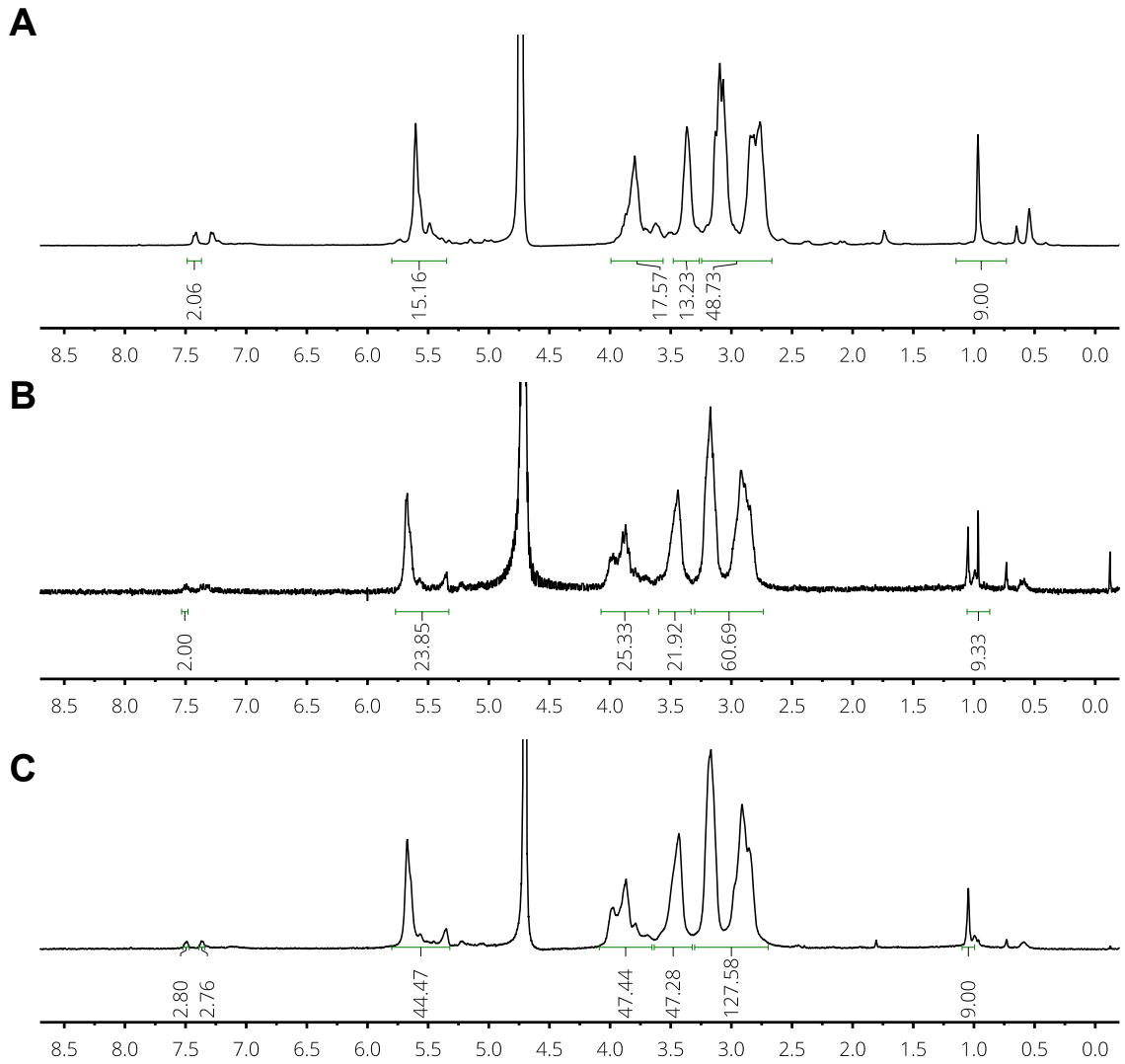


Figure S6. ^{1}H-NMR spectra (500 MHz, D_2O) and end group analysis of **P1-P3** comparing the integration of the peaks attributed to the polymer to those of the *t*-butylbenzoyl initiator (δ 7.5, 7.3, 1.0 ppm). (A): **P1**, degree of polymerization (DP) calculated: ~15; (B): **P2**, DP calculated: ~23; **P3**, DP calculated ~46.

Figure S7. Aqueous SEC traces of AmPAS

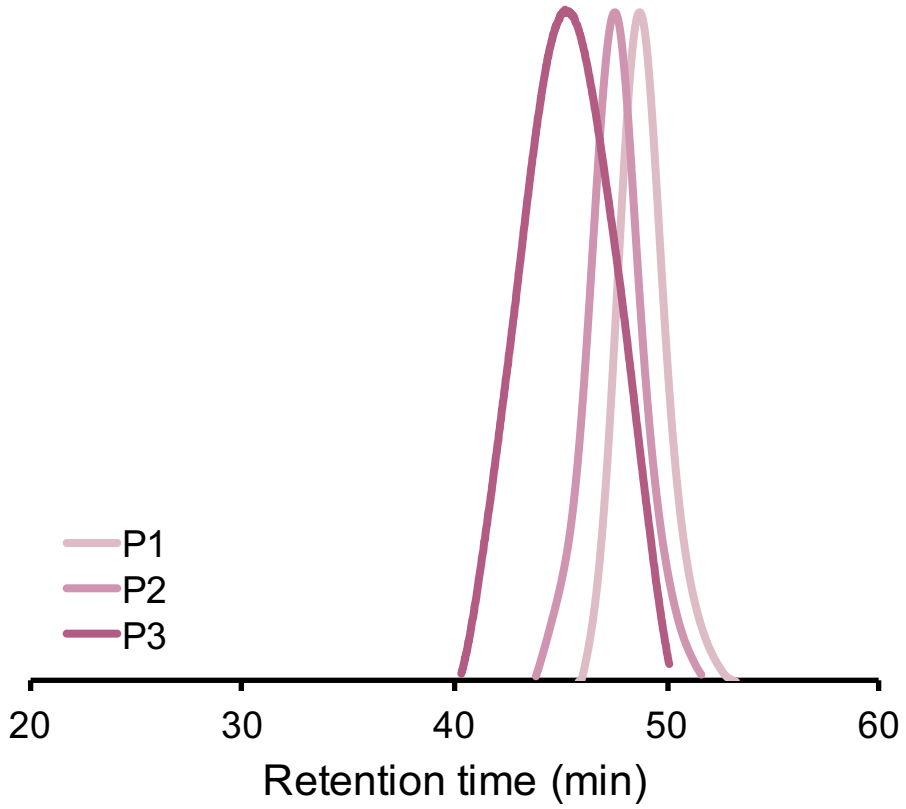


Figure S7. Aqueous GPC chromatograms (using Buffer M from **Figure S4**) of polymers **P1**-**P3**. Molecular weight data corresponding to traces found in **Table 3**.

Figure S8. $^{1}H^{13}C$-HSQC of AmPAS

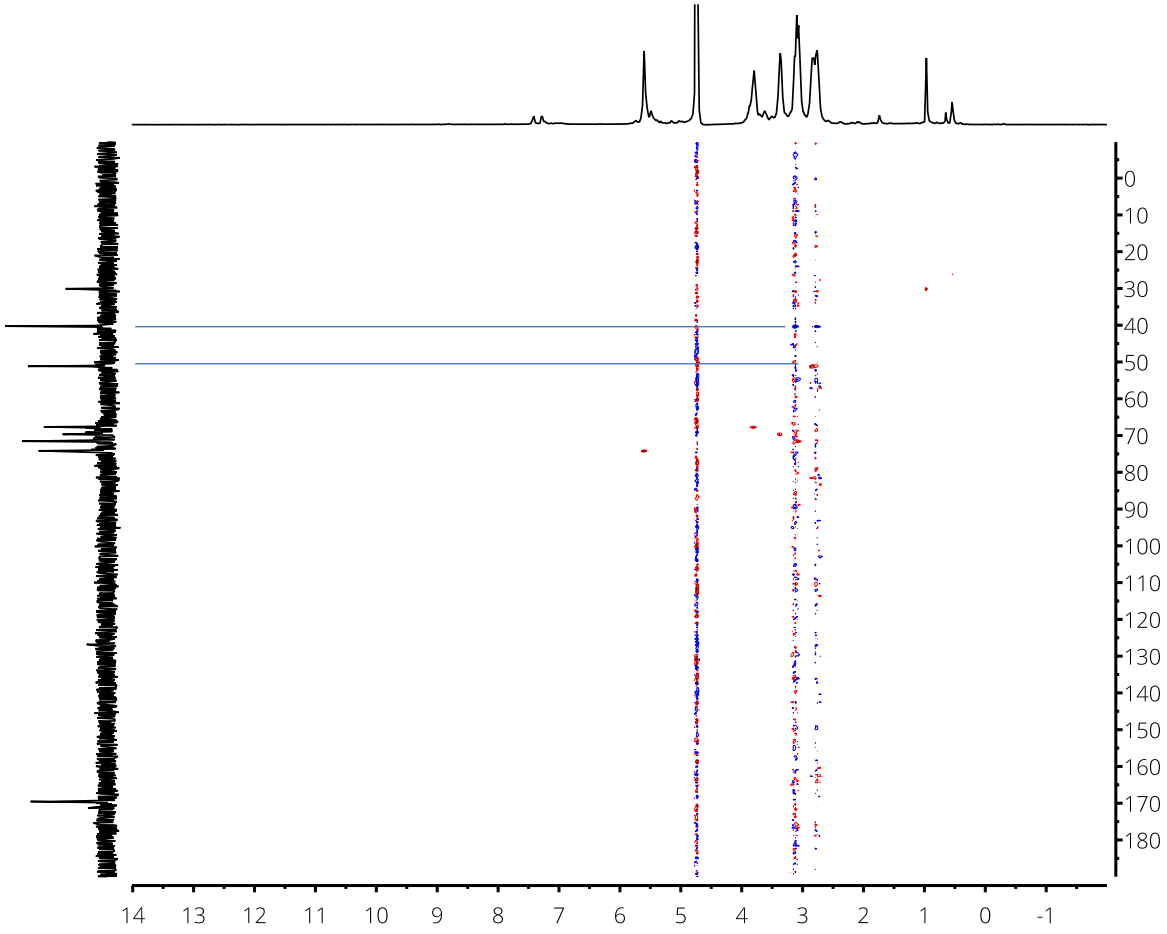


Figure S8. $^{1}H^{13}C$-HSQC spectra of **P1** (500 MHz, 126 MHz, D_2O). Cross-peaks corresponding to C2/H2 and C6/(H6-1, H6-2) have been highlighted with horizontal line.

Figure S9. ^{13}C-NMR spectra of AmPAS

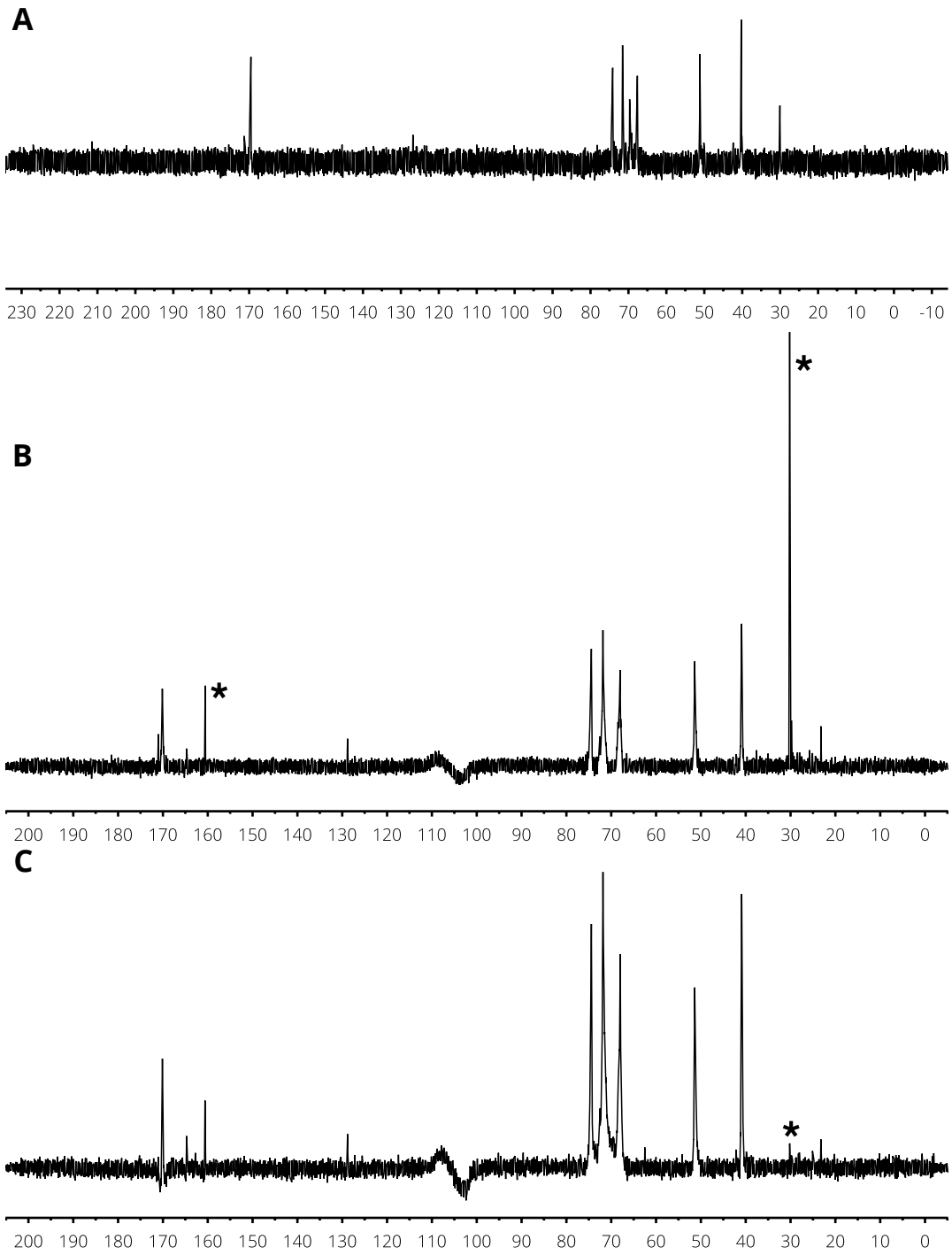


Figure S9. ^{13}C-NMR spectra (126 MHz, D_2O) of (A) **P1**, (B) **P2**, and (C) **P3**. * - residual acetone.

Figure S10. Colorimetric titration of P2 via Alizarin Yellow R / Thymol Blue

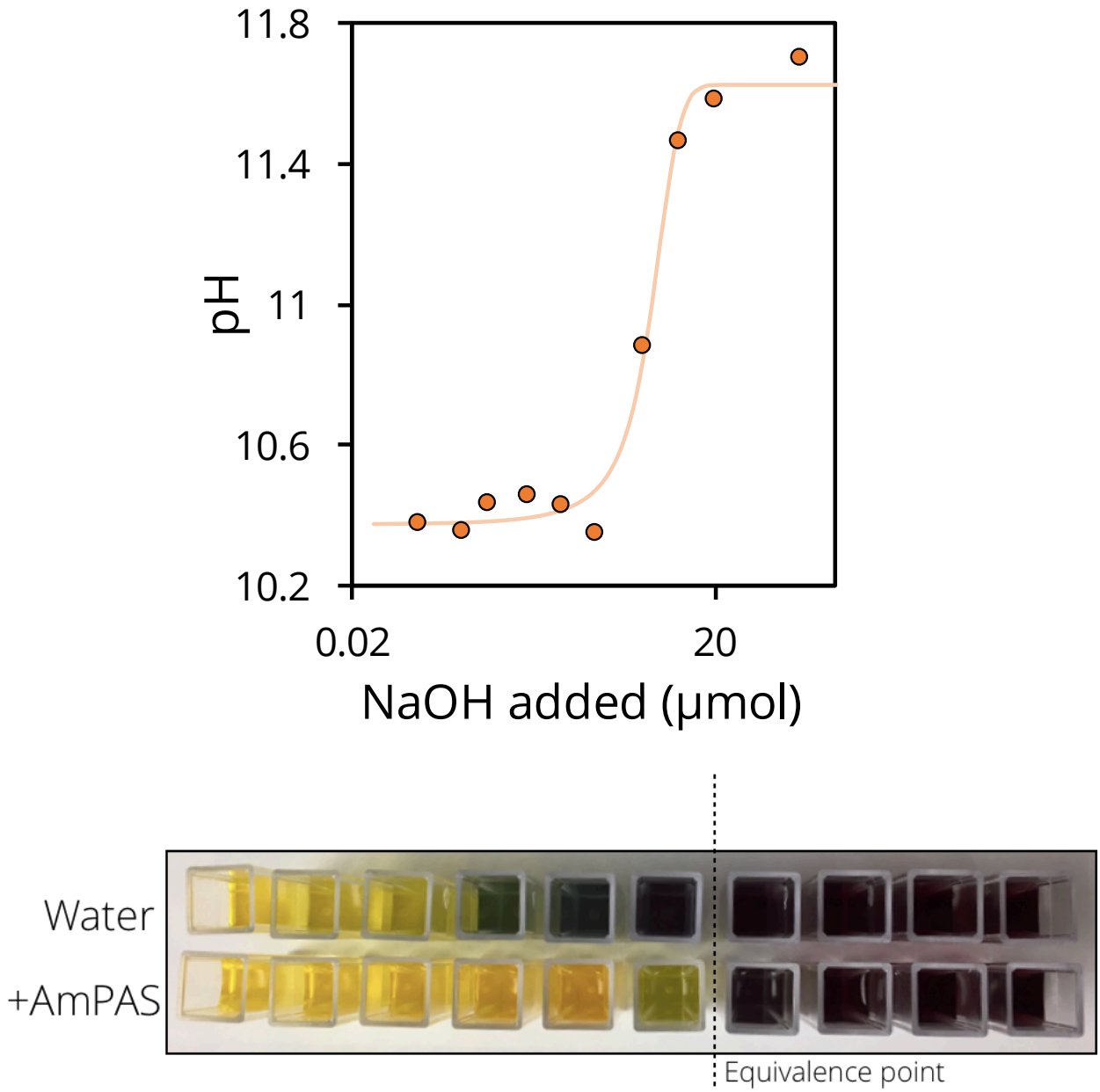


Figure S10. Titration of lyophilized AmPAS / HCl performed via adding NaOH to a solution of polymer with a combination of Alizarin Yellow R and Thymol Blue. The color-pH association was calculated by calibration curve and applied to the absorbance at 486 nm of the mixed dye solution. The pH data was fit to a 4 parameter Hill model to extract the equivalence point. The pKa (pH at half-equivalence point) was then calculated to be 10.54.

Figure S11. MALDI-TOF spectrum of P1

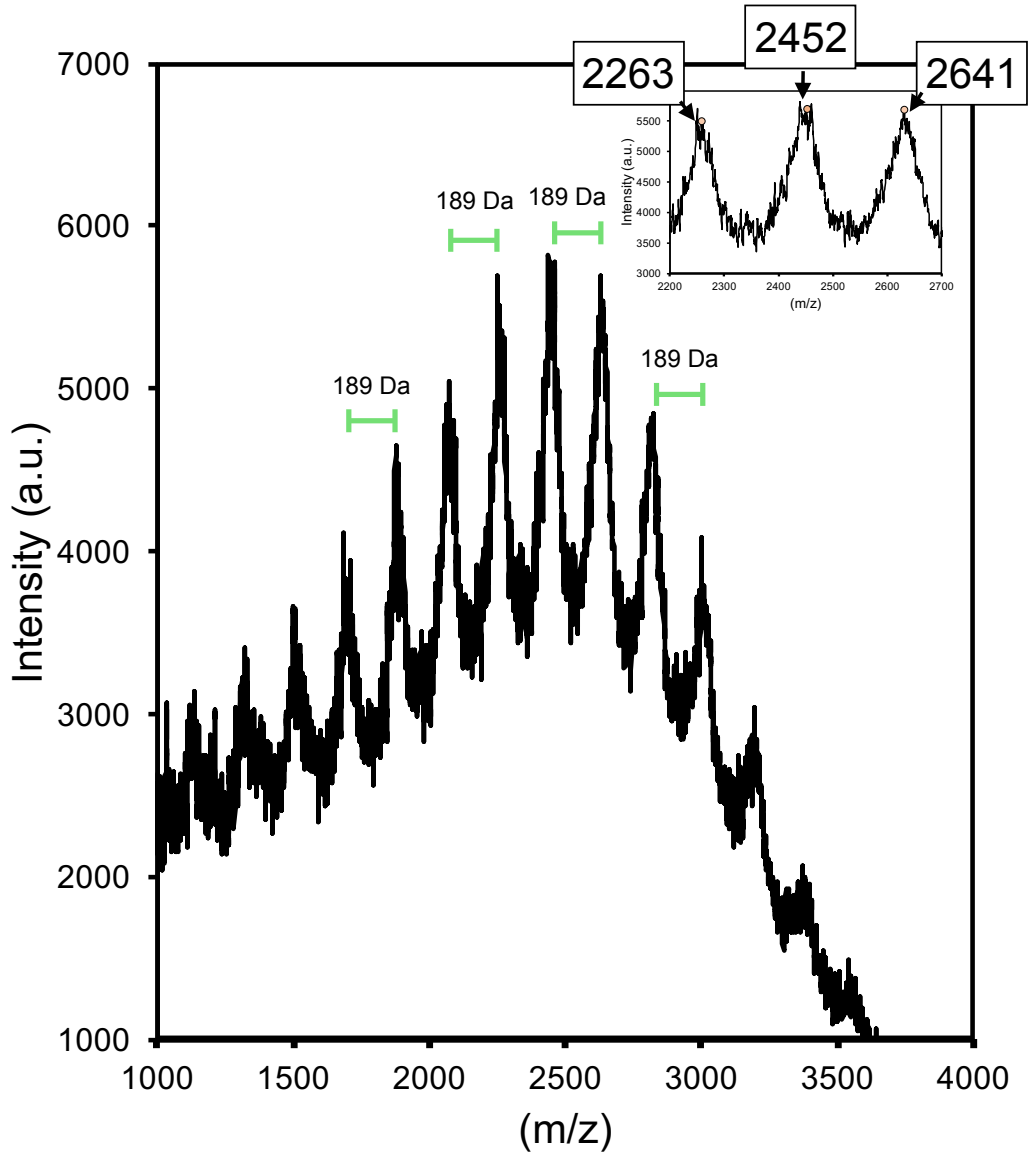


Figure S11. MALDI-TOF spectrum of **P1**. Peaks are uniformly spaced by 189 Da (protonated monomer). Inset shows zoomed in window of spectrum with peak m/z values highlighted.

Figure S12. IR spectra of protected and deprotected AmPAS (PB2'' – P2).

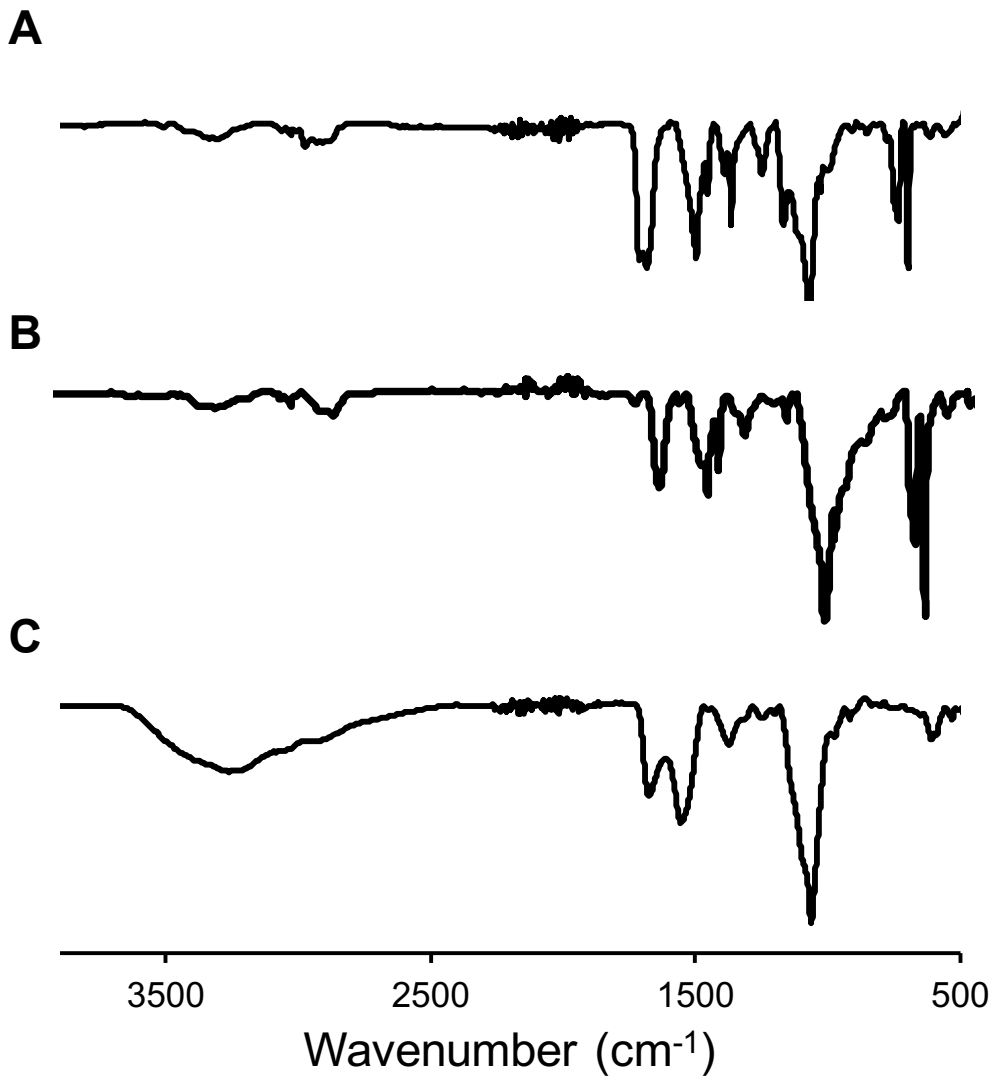


Figure S12. IR spectra obtained for: (A) **PB2''** (drop cast from CH_2Cl_2); (B) **PB2'** (drop cast from CH_2Cl_2); (C) **P2**.

Figure S13. ^{1}H-NMR of protected AmPAS

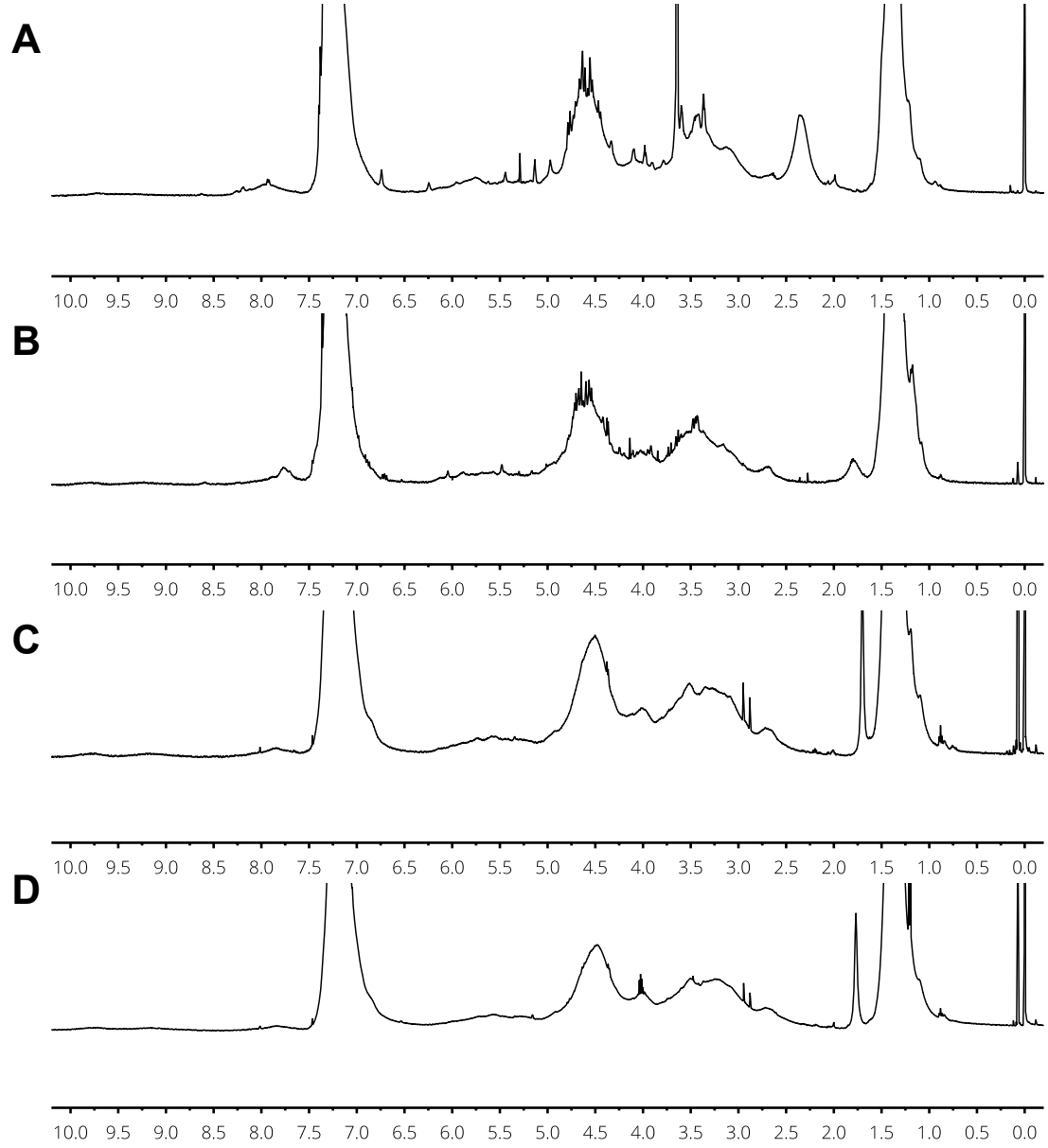


Figure S13. ^{1}H-NMR (500 MHz, $CDCl_3$) of: (A): **PB1''**; (B): **PB2''**; (C): **PB3''**; (D): **PB4''**

Figure S14. ^{13}C-NMR of PB1''

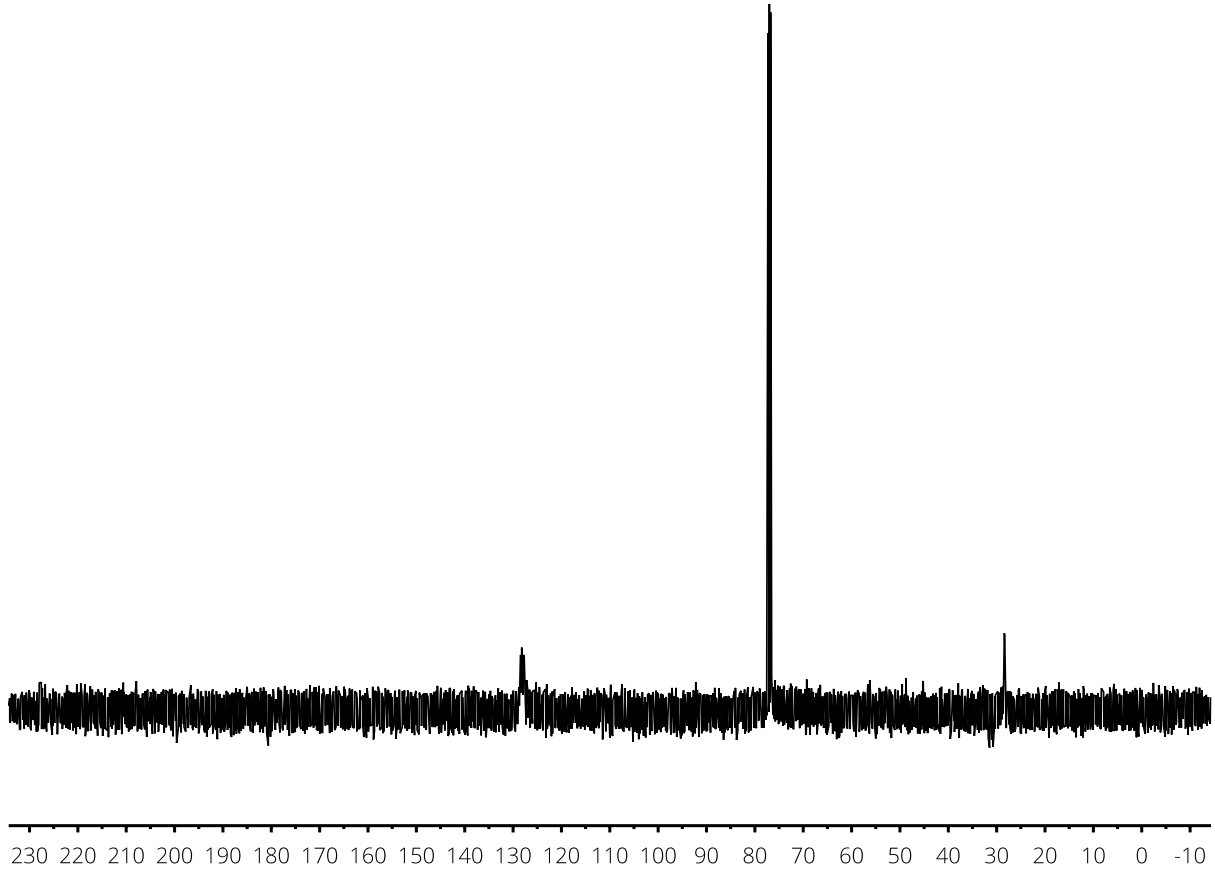


Figure S14. ^{13}C-NMR (126 MHz, $CDCl_3$) of **PB1''**

Figure S15. NMR spectra of PTS''

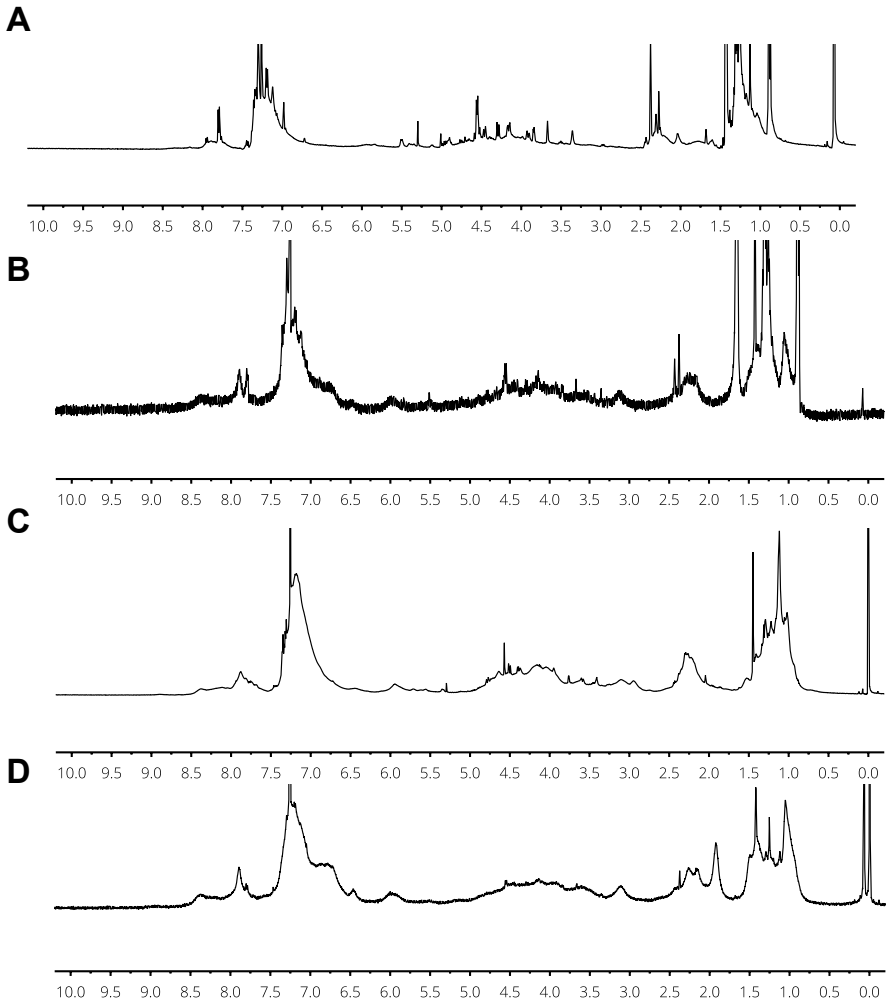


Figure S15. ^{1}H-NMR (500 MHz, $CDCl_3$) of: (A): **PTS1''**; (B): **PTS2''**; (C): **PTS3''**; (D): **PTS4''**

Figure S16. IR spectra of PTS''

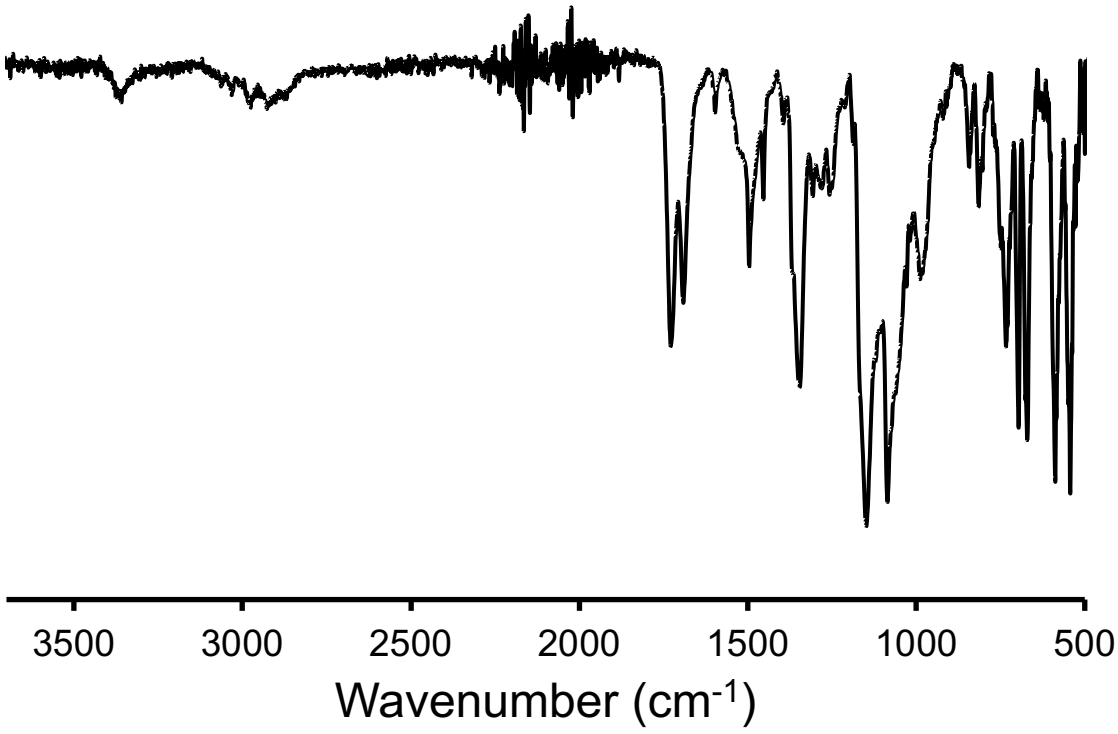


Figure S16. IR spectrum of **PTS2''** obtained via drop-casting (CH_2Cl_2) at 25 ºC

Materials and Methods

Materials and instrumentation

D-glucal was purchased from Carbosynth (San Diego, CA). 2-nitrobenzenesulfonamide was purchased from Chem-Impex (Wood Dale, IL). Trichloroacetyl isocyanate was purchased from TCI (Portland, OR). All other reagents and solvents were purchased from Millipore Sigma (Burlington, MA) or Thermo Fisher Scientific (Waltham, MA). Reactions were monitored by thin-layer chromatography (TLC) analysis, and stained by potassium permanganate or ninhydrin. All ^{1}H-NMR and ^{13}C-NMR spectra were taken with compounds dissolved in $CDCl_3$ [(D, 99.8%) + 0.05% V/V TMS + Silver foil] or CD_3CN (D, 99.8%) and the TMS (0 ppm) was used as an internal standard for ^{1}H-NMR spectra. Chemical shifts (δ) are recorded in ppm, coupling constants (J) are reported in Hz. Unless otherwise noted, all reactions were performed under an argon atmosphere using anhydrous solvents and oven-dried glassware and stir bars. Lyophilization was performed using a Virtis Benchtop 4K freeze dryer Model 4BT4K2L-105 at -40 ^{o}C. Small molecule ^{1}H NMR and ^{13}C NMR spectra and spectra of **P1** were recorded on a Varian INOVA 500MHz spectrometer. ^{1}H NMR, ^{13}C NMR, 1H1H-COSY, and 1H13C-HSQC spectra for **P2** and **P3** were performed on a Bruker AVANCE III HD spectrometer equipped with a cryogenically cooled multinuclear probe. Infrared spectroscopy (IR) was performed on a Nicolet FT-IR with a horizontal attenuated total reflectance (ATR) adapter plate. Specific optical rotations were determined at 25 ^{o}C using a Rudolph Autopol II polarimeter operating at 589 nm in a 50 mm pathlength cell.

Synthetic methods

*(**5**) 3,4-di-O-benzyl-6-O-(p-toluenesulfonyl)-D-glucal.* Prior to the reaction, p-toluenesulfonyl chloride (TsCl) was freshly recrystallized using a previously described method[1]. D-glucal (**1**) (5.00 g, 34.2 mmol) was dissolved in 20 mL of pyridine and cooled to 0 ºC. A solution of 1.1 eq of TsCl in 10 mL of DCM (7.20 g, 37.6 mmol) was added carefully dropwise via an addition funnel to avoid increasing the reaction temperature. The reaction was kept at 0 ºC and monitored for 4 hours or until the starting material had been consumed by TLC (permanganate stain). The reaction was poured into 300 mL of 1 M HCl and extracted 4 times with 50 mL of DCM. The combined organic extracts were washed once with 1 M HCl, twice with a saturated bicarbonate solution, brine, and dried over sodium sulfate before being evaporated to dryness. The crude product (**4**) was immediately dissolved in DMF (100 mL) and cooled to 0 ºC, followed by the addition of 2.8 eq of NaH (95.8 mmol, 2.30 g) split up into 4 portions of ~600 mg. The reaction mixture was allowed to warm to room temperature for 30 minutes before being cooled again down to 0 ºC. After an additional 30 minutes, 2.5 eq of BnBr (10.2 mL, 85.5 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature overnight before being poured into 500 mL of 0.1 M HCl, followed by extraction 4 times with 100 mL of diethyl ether. The combined organic extracts were washed with 0.1 M HCl, saturated sodium bicarbonate, brine, dried over sodium sulfate, and evaporated to dryness. The crude product was purified using column chromatography (9:1 hexanes:ethyl acetate) and fractions containing the product (determined by permanganate stain and UV on TLC stain) were collected and evaporated to dryness to yield the title compound (**5**) as a clear oil (34% yield, 5.6 g). $[\alpha]_{25}^{D}$ = +2.0 (0.2, CH_3OH). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.81 – 7.74 (m, 2H, Tosyl), 7.40 – 7.26 (m, Ar+Tosyl), 7.28 – 7.22 (m, 1H, Tosyl), 6.27 (dd, J = 6.1, 1.3 Hz, 1H, C1), 4.87 (dd, J = 6.2, 2.9 Hz, 1H, C2), 4.81 (d, J = 11.2 Hz, 1H, ArCH_2), 4.64

– 4.55 (m, 2H, ArC*H*$_2$), 4.51 (d, J = 11.7 Hz, 1H, ArC*H*$_2$), 4.36 (dd, J = 10.8, 5.4 Hz, 1H, H6), 4.26 (dd, J = 10.8, 2.6 Hz, 1H, H6), 4.17 – 4.05 (m, 2H, H3+H5), 3.74 (dd, J = 8.1, 5.8 Hz, 1H, H4), 2.43 (s, 2H, TosC*H*$_3$). ^{13}C NMR (126 MHz, Chloroform-d) δ 144.82 (C1) 144.04 (Tosyl), 138.01 (Tosyl), 138.28-127.71 (Ar), 99.97 (C2), 74.66 (C5), 74.44 (C3), 73.53 (C4), 73.26 (Ar*C*H$_2$), 70.35 (Ar*C*H$_2$), 68.02 (Ar*C*H$_2$), 21.65 (Tosyl). HRMS ESI+ TOF (*m/z*): [M+Na]$^+$ calcd for $C_{27}H_{28}O_6S$: 503.1499; found, 503.1519.

*(**6**) 3,4-di-O-benzyl-6-N-azido-6-deoxy-D-glucal*. To a stirring solution of compound **5** (500 mg, 1.04 mmol) in 100 mL of anhydrous DMSO was added 20 eq of NaN_3 (1.35 g, 20.8 mmol). The reaction mixture was heated to 55 ^{o}C overnight and, after completion, the reaction was allowed to cool and filtered. The solvent from the collected filtrate was removed by rotary evaporation and the crude solid was then dissolved in 300 mL of ethyl acetate and washed thoroughly with water, brine, and then dried over sodium sulfate before evaporating to dryness. The crude product was purified by column chromatography (95:5 hexanes:ethyl acetate) and fractions containing the product (permanganate stain and PPh_3/DCM followed by ninhydrin stain, TLC) were collected and evaporated to dryness to afford the product as a clear oil (86%, 314 mg). $[\alpha]_{25}^D$ = +51.0 (0.2, CH_3OH). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.39 – 7.26 (m, 10H, Ar), 6.41 (dd, J = 6.2, 1.4 Hz, 1H, H1), 4.96 – 4.86 (m, 2H, H2+ArC*H*$_2$), 4.68 (dd, J = 11.5, 9.4 Hz, 2H, ArC*H*$_2$), 4.57 (d, J = 11.6 Hz, 1H, ArC*H*$_2$), 4.23 (ddd, J = 6.2, 2.7, 1.4 Hz, 1H, H3), 4.02 (ddd, J = 8.7, 5.0, 3.8 Hz, 1H, H5), 3.78 (dd, J = 8.7, 6.2 Hz, 1H, H4), 3.62 – 3.52 (m, 2H, H6). ^{13}C NMR (126 MHz, Chloroform-d) δ 144.22 (C1), 138.06-127.77 (Ar), 100.36 (C2), 76.27 (C5), 75.57 (C3), 74.60 (C4), 73.83 (Ar*C*H$_2$), 70.51 (Ar*C*H$_2$), 50.84 (C6). HRMS ESI+ TOF (*m/z*): [M+Na]$^+$ calcd for $C_{20}H_{21}N_3O_3$: 374.1475; found, 374.1274.

*(**8**) 3,4-di-O-benzyl-6-N-boc-6-deoxy-D-glucal*. To a stirring solution of compound **6** (300 mg, 0.85 mol) in 50 mL of THF was added 10 eq of PPh_3 (2.24 g, 8.50 mmol) and 20 eq of water (310 µL, 17.0 mmol). The reaction mixture was monitored by TLC (ninhydrin, permanganate stains on TLC) and, after the starting material had been consumed, a 10% solution of H_2O_2 in water was added to the reaction to quench the reaction. The crude mixture was dissolved in 2 parts toluene followed by the addition of 3 parts diethyl ether and was kept at -20 ^oC to allow for crystallization of the PPh_3O. After filtration to remove the crystallized byproduct, the filtrate was evaporated to dryness and dissolved in 50 mL of THF. To this stirring solution was added 1.1 eq of Et_3N (130 µL, 0.935 mmol), 0.2 eq of DMAP (0.02 g, 0.16 mmol), and 1.1 eq of Boc_2O (0.20 g, 0.935 mmol) portionwise over 15 minutes. The reaction mixture was allowed to stir overnight at room temperature and the solvent was then removed by rotary evaporation. The crude product was dissolved in ethyl acetate and washed 3 times with 1 M HCl, once with a saturated bicarbonate solution, brine, dried over sodium sulfate, and evaporated to dryness. The crude product was purified by column chromatography (9:1 hexanes:ethyl acetate) and fractions containing the product (permanganate, ninhydrin on TLC) were collected and evaporated to dryness to yield the title compound as a clear oil. (Yield 82%, 0.30 g) $[\alpha]_{25}^{D}$ = -116.0 (0.1, CH_3OH). ^1H NMR (500 MHz, Chloroform-d) δ 7.40 – 7.26 (m, 10H, Ar), 6.37 (dd, J = 6.1, 1.3 Hz, 1H, H1), 4.91 (dd, J = 6.1, 2.7 Hz, 1H, H2), 4.82 (d, J = 11.2 Hz, 1H, ArCH_2), 4.73 – 4.62 (m, 2H, ArCH_2), 4.56 (d, J = 11.5 Hz, 1H, ArCH_2), 4.20 (ddd, J = 6.3, 2.7, 1.3 Hz, 1H, H3), 3.97 (dt, J = 8.5, 5.0 Hz, 1H, H5), 3.66 (dd, J = 8.4, 6.0 Hz, 1H, H4), 3.54 (dq, J = 8.1, 5.5, 3.8 Hz, 2H, H6), 1.45 (s, 9H, Boc). ^{13}C NMR (126 MHz, Chloroform-d) δ 155.75 (Boc), 144.23 (C1), 138.28-127.75 (Ar), 100.20 (C2),

79.33 (C5), 75.97 (C3), 75.92 (C4), 75.54-70.66 (Ar*C*H_2), 40.62 (C6), 28.39 (Boc). HRMS ESI+ TOF (*m/z*): $[M+Na]^+$ calcd for $C_{25}H_{31}NO_5$: 448.2094; found, 448.2095.

(9a) *6-O-tert-butyldimethylsilyl-D-glucal* was prepared as previously described. The crude product was purified by silica column chromatography (2:1 hexanes:ethyl acetate) and the combined fractions were evaporated to dryness to yield 6-O-*tert*-butyldimethylsilyl-D-glucal as a clear oil (yield 47%). Spectroscopic and mass characterization data matched those previously reported[2].

(9b) *6-O-triisopropylsilyl-D-glucal* was prepared as previously described. The crude product was purified by silica column chromatography (4:1 hexanes:ethyl acetate to 1:1 hexanes:ethyl acetate) and the combined fractions were evaporated to dryness to yield 6-O-triisopropylsilyl-D-glucal as a viscous, clear oil (yield 83%). Spectroscopic and mass characterization data matched those previously reported[2].

(9c) *6-O-tert-butyldiphenylsilyl-D-glucal* was prepared as previously described. The crude product was purified by silica column chromatography (3:1 hexanes:ethyl acetate) and the combined fractions were evaporated to dryness to yield 6-O-*tert*-butyldiphenylsilyl-D-glucal as a viscous, clear oil (yield 84%). Spectroscopic and mass characterization data matched those previously reported[2].

(10b) *3,4-di-O-benzyl-6-O-triisopropylsilyl-D-glucal* was prepared as previously described. The crude product was purified by silica column chromatography (19:1 hexanes:ethyl acetate to 17:1 hexanes:ethyl acetate) and the combined fractions were evaporated to dryness to yield 3,4-di-O-

benzyl-6-O-triisopropylsilyl-D-glucal as a clear oil (yield 63%). Spectroscopic and mass characterization data matched those previously reported[2].

(10c) *3,4-di-O-benzyl-6-O-tert-butyldiphenylsilyl-D-glucal* (3) was prepared as previously described. The crude product was purified by silica column chromatography (15:1 hexanes:ethyl acetate) and the combined fractions were evaporated to dryness to yield 3,4-di-O-benzyl-6-O-*tert*-butyldiphenylsilyl-D-glucal as a clear oil (yield 25%). Spectroscopic and mass characterization data matched those previously reported[2].

(11) *3,4-di-O-benzyl-D-glucal* was prepared as previously described. The crude product was purified by silica column chromatography (4:1 hexanes:ethyl acetate to 2:1 hexanes:ethyl acetate) and the combined fractions were evaporated to dryness to yield 3,4-di-O-benzyl-D-glucal as a clear oil that solidified into an amorphous white solid upon storage at -20 ^{o}C (yield 93%). Spectroscopic and mass characterization data matched those previously reported[3].

(12) *3,4-di-O-benzyl-6-N-phthalimido-6-deoxy-D-glucal*. Compound **11** (5.0 g, 13.8 mmol), was added to 1.0 eq of phthalimide (2.0 g, 13.8 mmol) and 1.1 eq of PPh_3 (4.0 g, 15.2 mmol) in 100 mL of THF and the stirring mixture was allowed to cool to 0 ^{o}C. Diethyl azodicarboxylate (40 wt% solution in toluene) (1.1 eq, 7.2 mL, 15.2 mmol) was added dropwise at a rate that allowed for immediate removal of yellow color in solution with each drop. The reaction mixture was allowed to warm to room temperature overnight and the solvent was then removed by rotary evaporation. The mixture was then dissolved in 2 parts toluene, followed by 3 parts diethyl ether to allow for crystallization of PPh_3O at -20 ^{o}C. The mixture was filtered and the solvent was

removed from the filtrate by rotary evaporation. The crude product was purified by column chromatography (2:1 hexanes:ethyl acetate) and fractions containing the product (permanganate stain, TLC) were collected and evaporated to dryness. The product, obtained as a yellow solid, was then dissolved in boiling isopropanol and poured into an Erlenmeyer flask and allowed to cool slowly at room temperature; additional isopropanol was added at this point, the flask was scratched, and then stored at -20 ^{o}C overnight. The resulting crystals were collected by filtration, dried in air, and then under vacuum to afford the title compound (**12**). (Yield 85%, 5.34 g) $[\alpha]_{25}^{D}$ = -21.0 (0.1, CH_3OH). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.84 (dd, J = 5.4, 3.0 Hz, 2H, Phth), 7.70 (dd, J = 5.5, 3.0 Hz, 2H, Phth), 7.39 – 7.25 (m, 10H, Ar), 6.34 (dd, J = 6.2, 1.2 Hz, 1H, H1), 4.96 (ddd, J = 6.2, 3.2, 0.6 Hz, 1H, H2), 4.85 (d, J = 11.7 Hz, 1H, ArCH_2), 4.75 (d, J = 11.7 Hz, 1H, ArCH_2), 4.66 (d, J = 11.7 Hz, 1H, ArCH_2), 4.53 (d, J = 11.6 Hz, 1H, ArCH_2), 4.37 (dddd, J = 9.7, 6.8, 3.0, 0.8 Hz, 1H, H3), 4.25 (dd, J = 14.2, 9.5 Hz, 1H, H6-1), 4.15 (ddt, J = 4.5, 3.3, 1.1 Hz, 1H, H4), 3.88 (dd, J = 14.3, 3.0 Hz, 1H, H6-2), 3.78 – 3.71 (m, 1H, H5). ^{13}C NMR (126 MHz, Chloroform-d) δ 168.20 (Phth*C*O), 144.17 (C1), 138.14 - 123.26 (Ar), 99.64 (C2), 75.38 (C5), 73.56 (C3), 73.48 (C4), 72.81 (Ar*C*H_2), 70.21 (Ar*C*H_2), 38.32 (C6). HRMS ESI+ TOF (*m/z*): $[M+Na]^+$ calcd for $C_{28}H_{25}NO_5$: 478.1625; found, 478.1643.

*(**14**) 3,4-di-O-benzyl-6-di-N,N-boc-6-deoxy-D-glucal*. To a stirring solution of compound **8** (200 mg, 0.47 mol) in 30 mL of MeCN at 0 ^{o}C was added 1.2 eq of DMAP (0.07 g, 0.56 mmol), and 2.2 eq of Boc_2O (0.230 g, 1.03 mmol) portionwise over 15 minutes. The reaction mixture was allowed to stir overnight at room temperature and the solvent was then removed by rotary evaporation. The crude product was dissolved in ethyl acetate and washed 3 times with 0.1 M HCl, once with a saturated bicarbonate solution, brine, dried over sodium sulfate, and evaporated to

dryness. The crude product was purified by column chromatography (9:1 hexanes:ethyl acetate) and fractions containing the product (permanganate, ninhydrin on TLC) were collected and evaporated to dryness to yield the title compound as a clear oil (Yield 89%, 0.22 g). $[\alpha]_{25}^{D}$ = -17.0 (0.2, CH_3OH). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.39 – 7.26 (m, 10H, Ar), 6.38 (dd, J = 6.2, 1.0 Hz, 1H, H1), 4.96 (dd, J = 6.2, 3.6 Hz, 1H, H2), 4.77 (d, J = 11.9 Hz, 1H, ArCH_2), 4.72 – 4.61 (m, 2H, ArCH_2), 4.50 (d, J = 11.7 Hz, 1H, ArCH_2), 4.38 – 4.30 (m, 1H, H3), 4.26 (dd, J = 14.5, 10.0 Hz, 1H, H6-1), 4.07 (td, J = 4.1, 3.5, 1.1 Hz, 1H, H4), 3.73 (dd, J = 14.5, 2.0 Hz, 1H, H6-2), 3.67 – 3.61 (m, 1H, H5), 1.50 (s, 18H). ^{13}C NMR (126 MHz, Chloroform-d) δ 152.66 (Boc), 144.40 (C1), 138.28-127.62 (Ar), 99.05 (C2), 75.19 (C5), 75.10 (C3), 72.54 (C4), 72.45 (ArCH_2), 70.12 (ArCH_2), 46.25 (C6), 28.04 (Boc). HRMS ESI+ TOF (*m/z*): $[M+Na]^+$ calcd for $C_{30}H_{39}NO_7$: 548.2619; found, 548.2620.

*(**16**) 3,4-di-O-benzyl-6-N-(4-toluenesulfonyl)-N-boc-6-deoxy-D-glucal*. Compound **11** (5.0 g, 13.8 mmol), was added to 1.0 eq of *N*-boc-4-toluenesulfonamide (3.7 g, 13.8 mmol) and 1.1 eq of PPh_3 (4.0 g, 15.2 mmol) in 100 mL of THF and the stirring mixture was allowed to cool to 0 °C. Diethyl azodicarboxylate (40 wt% solution in toluene) (1.1 eq, 7.2 mL, 15.2 mmol) was added dropwise at a rate that allowed for immediate removal of yellow color in solution with each drop. The reaction mixture was allowed to warm to room temperature overnight and the solvent was then removed by rotary evaporation. The mixture was then dissolved in 2 parts toluene, followed by 3 parts diethyl ether to allow for crystallization of PPh_3O at -20 °C. The mixture was filtered and the solvent was removed from the filtrate by rotary evaporation. The crude product was purified by column chromatography (7:1 hexanes:ethyl acetate) and fractions containing the product (permanganate stain, TLC) were collected and evaporated to dryness to yield the title compound

(**16**) as a pale, highly sticky and viscous oil (Yield 86%, 6.9 g). $[\alpha]_{25}^{D}$ = -12 (0.3, CH_3OH) ^1H NMR (500 MHz, Chloroform-d) δ 7.88 – 7.83 (m, 2H, Tosyl), 7.40 – 7.28 (m, 11H, Ar+Tosyl), 7.28 (s, 1H, Tosyl), 6.47 (dd, J = 6.2, 1.0 Hz, 1H, H1), 5.02 (ddd, J = 6.3, 3.8, 0.9 Hz, 1H, H2), 4.77 (d, J = 11.9 Hz, 1H, ArCH_2), 4.70 (d, J = 12.0 Hz, 1H, ArCH_2), 4.64 (d, J = 11.7 Hz, 1H, ArCH_2), 4.59 – 4.43 (m, 3H, ArCH_2+H6-1+H3), 4.05 (td, J = 3.9, 1.9 Hz, 1H, H4), 3.93 (dd, J = 14.7, 1.4 Hz, 1H, H6-2), 3.72 (ddd, J = 4.9, 3.9, 0.9 Hz, 1H, H5), 2.44 (s, 3H, Tosyl), 1.31 (s, 9H, Boc). ^{13}C NMR (126 MHz, Chloroform-d) δ 148.32 (Boc), 141.62 (C1), 135.65-125.11 (Ar+Tosyl), 96.63 (C2), 72.31 (C5), 72.10 (C3), 69.80 (ArCH_2), 69.00 (C4), 67.51 (ArCH_2), 43.65 (C6), 25.28 (Tosyl), 19.04 (Boc). HRMS ESI+ TOF (*m/z*): $[M+Na]^+$ calcd for $C_{32}H_{37}NO_7S$: 602.2188; found, 602.2166.

*(**17**) 1,2-β-lactam-3,4-di-O-benzyl-6-N-(4-toluenesulfonyl)-N-boc-6-deoxy-D-glucal*. Compound **16** (1.50 g, 2.59 mmol), was dissolved to 1 M in MeCN and cooled to 0 ºC. Trichloroacetyl isocyanate (4 eq, 1.30 mL, 10.4 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature. The reaction was monitored from 7-10 days by TLC (permanganate stain), or until the starting material was completely consumed. The reaction mixture was then cooled to -20 ºC with a water/methanol cooling bath, followed by the addition of 1.1 eq (to TCAI) of benzylamine (1.30 mL, 11.4 mmol) dissolved in 20 mL of acetonitrile dropwise by syringe pump over 1 hour. The reaction mixture was then allowed to warm to room temperature while monitoring; once its temperature reached ~0 ºC, a white precipitate was formed in a yellow solution. The mixture was filtered to remove the white precipitate and the flask and filtered solid were quickly triturated with hexanes before the residual acetonitrile could evaporate. The filtrate was then poured into 600 mL of 0.1 M HCl and extracted 4 times with ethyl acetate. The combined

organic extracts were washed 2 times with 0.1 M HCl, brine, dried over sodium sulfate, and evaporated to dryness. The crude product was purified by column chromatography (3:1 hexanes:ethyl acetate to 1:1 hexanes:ethyl acetate) and fractions containing the product (permanganate stain, TLC) were collected and evaporated to dryness to yield the title compound (**17**) as a pale foam. (Yield 45%, 0.726 g). $[\alpha]_{25}^{D}$ = +15 (0.1, CH_3OH). 1H NMR (500 MHz, Chloroform-d) δ 7.83 – 7.74 (m, 2H, Tosyl), 7.40 – 7.23 (m, 12H, Ar), 5.85 (d, J = 2.4 Hz, 1H, N*H*), 5.51 (d, J = 4.4 Hz, 1H, H1), 4.85 – 4.74 (m, 1H, ArCH_2), 4.75 – 4.63 (m, 1H, ArCH_2), 4.57 (dd, J = 11.7, 9.7 Hz, 2H, ArCH_2), 4.26 – 4.09 (m, 3H, H4+H5+H6-1), 4.05 (dd, J = 14.7, 9.5 Hz, 1H, H6-2), 3.51 (dd, J = 8.3, 6.2 Hz, 1H, H3), 3.44 (dt, J = 4.8, 2.6 Hz, 1H, H2), 2.43 (s, 3H, TosylCH_3), 1.30 (s, 9H, Boc). ^{13}C NMR (126 MHz, Chloroform-d) δ 166.62 (Lactam *C*O), 150.87 (Boc*C*O) 137.82-127.70 (Ar), 84.42, 77.21 (C5), 75.86 (C3), 75.84 (C1), 72.94 (Ar*C*H_2), 71.19 (Ar*C*H_2), 68.58 (C4), 54.69 (C2), 47.96 (C6), 27.82 (Boc), 21.60 (Tos*C*H_3). HRMS ESI+ TOF (*m/z*): $[M+Na]^+$ calcd for $C_{33}H_{38}N_2O_8S$: 645.2241; found, 645.2269.

*(**18**) 3,4-di-O-benzyl-6-N-(2-nitrobenzenesulfonyl)-N-boc-6-deoxy-D-glucal*. Compound **11** (5.0 g, 13.8 mmol), was added to 1.0 eq of *N*-boc-2-nitrobenzenesulfonamide (4.2 g, 13.8 mmol) and 1.1 eq of PPh_3 (4.0 g, 15.2 mmol) in 100 mL of THF and the stirring mixture was allowed to cool to 0 °C. Diethyl azodicarboxylate (40 wt% solution in toluene) (1.1 eq, 7.2 mL, 15.2 mmol) was added dropwise at a rate that allowed for immediate removal of yellow color in solution with each drop. The reaction mixture was allowed to warm to room temperature overnight and the solvent was then removed by rotary evaporation. The mixture was dissolved in 300 mL ethyl acetate and washed 3 times with 100 mL of 0.1 M NaOH, brine, dried over sodium sulfate, and evaporated to dryness. The crude product was purified by column chromatography (2:1 toluene:ethyl acetate)

and fractions containing the product (permanganate stain, TLC) were collected and evaporated to dryness to yield the title compound (**16**) as a pale, highly sticky and viscous oil (Yield 78%, 6.6 g). $[\alpha]_{25}^{D}$ = +1.0 (0.7, CH_3OH). ^1H NMR (500 MHz, Chloroform-d) δ 8.34 (dt, J = 6.2, 2.3 Hz, 1H, Nosyl), 7.79 – 7.66 (m, 3H, Nosyl), 7.34 (m, 10H, Ar), 6.51 – 6.46 (m, 1H, H1), 5.03 – 4.92 (m, 1H, H2), 4.79 (d, J = 11.8 Hz, 1H, ArCH_2), 4.72 – 4.65 (m, 2H, ArCH_2), 4.52 (d, J = 11.6 Hz, 1H, ArCH_2), 4.46 – 4.35 (m, 2H, H3+H6-1), 4.09 (t, J = 4.0 Hz, 1H, H4), 4.02 – 3.94 (m, 1H, H6-2), 3.70 (t, J = 4.7 Hz, 1H, H5), 1.32 (s, 9H, Boc). ^{13}C NMR (126 MHz, Chloroform-d) δ 150.21 (Boc*C*O), 147.71 (Nosyl), 144.39 (C1), 138.23-124.38 (Aryl+Nosyl), 99.14 (C2), 85.11, 74.80 (C5), 74.50 (C3), 72.53 (Ar*C*H_2), 72.18 (C4), 69.82 (Ar*C*H_2), 47.62 (C6), 27.92 (Boc). HRMS ESI+ TOF (*m/z*): $[M+Na]^+$ calcd for $C_{31}H_{34}N_2O_9S$: 633.1877; found, 633.1868.

*(**19**) 1,2-β-lactam-3,4-di-O-benzyl-6-N-(2-nitrobenzenesulfonyl)-N-boc-6-deoxy-D-glucal*. Compound **16** (6.1 g, 10 mmol), was dissolved to 1 M in MeCN (10 mL) and cooled to 0 ºC. Trichloroacetyl isocyanate (4 eq, 4.9 mL, 40 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature. The reaction was monitored from 7-10 days by TLC (permanganate stain), or until the starting material was completely consumed. The reaction mixture was then cooled to -20 ºC with a water/methanol cooling bath, followed by the addition of 1.1 eq (to TCAI) of benzylamine (4.8 mL, 43.9 mmol) dissolved in 20 mL of acetonitrile dropwise by syringe pump over 1 hour. The reaction mixture was then allowed to warm to room temperature while monitoring; once its temperature reached ~0 ºC, a white precipitate was formed in a yellow solution. The mixture was filtered to remove the white precipitate and the flask and filtered solid were quickly triturated with hexanes before the residual acetonitrile could evaporate. The filtrate was then poured into 600 mL of 0.1 M HCl and extracted 4 times with ethyl acetate.

The combined organic extracts were washed 2 times with 0.1 M HCl, brine, dried over sodium sulfate, and evaporated to dryness. The crude product was purified by column chromatography (2:1 hexanes:ethyl acetate to 1.5:1 hexanes:ethyl acetate to 1:1 hexanes:ethyl acetate) and fractions containing the product (permanganate stain, TLC) were collected and evaporated to dryness to yield the title compound (**17**) as a pale foam. (Yield 38%, 2.5 g). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.35 – 8.27 (m, 1H, Nosyl), 7.79 – 7.69 (m, 3H, Nosyl), 7.46 – 7.21 (m, 10H, Ar), 6.14 (d, J = 2.4 Hz, 1H, N*H*), 5.57 (d, J = 4.4 Hz, 1H, C1), 4.79 (d, J = 11.6 Hz, 1H, ArCH_2), 4.69 (d, J = 11.8 Hz, 1H, ArCH_2), 4.59 (dd, J = 28.1, 11.6 Hz, 2H, ArCH_2), 4.25 –4.07 (m, 3H, H4, H6-1, H3), 4.04 – 3.83 (m, 1H, H6-2), 3.53 – 3.42 (m, 2H, H5+H2), 1.30 (s, 9H, Boc). ^{13}C NMR (126 MHz, Chloroform-d) δ 166.88 (Lactam *C*O), 150.14 (Boc), 137.75-124.43 (Ar+Nosyl), 77.22 (C5), 76.18 (C3), 75.98 (C1), 73.14 (Ar*C*H$_2$), 71.17 (Ar*C*H$_2$), 68.24 (C4), 54.78 (C2), 49.00 (C6), 27.82 (Boc). LC/MS (*m/z*): $[M+Na]^+$ calcd for $C_{32}H_{35}N_3O_{10}S$: 676.2; found, 676.3.

*(**20**) 1,2-β-lactam-3,4-di-O-benzyl-6-N-boc-6-deoxy-D-glucal*. Compound **19** (3.40 g, 5.2 mmol), was dissolved to 0.2 M in MeCN and 1.2 eq of PhSh was added (640 μL, 6.2 mmol). The reaction mixture was cooled to 0 °C and 2.2 eq of K_2CO_3 (1.58 g, 11.4 mmol) was added. The reaction mixture was allowed to stir overnight and a strong orange color developed, followed by a yellow color. The mixture was filtered and the solvent was removed by rotary evaporation. The residue was then dissolved in ethyl acetate and washed three times with 0.1 M HCl, brine, dried over sodium sulfate, and evaporated to dryness. The crude product was purified by column chromatography (95:4:1 dichloromethane:acetone:methanol to 93:4:3 dichloromethane:acetone:methanol) and fractions containing the product (permanganate stain, TLC) were collected and evaporated to dryness to afford the title compound (**20**) as a white foam.

(Yield 75%, 1.83 g). $[\alpha]_{25}^{D}$ = +3.4 (0.4, CH_3OH). ^{1}H NMR (500 MHz, Acetonitrile-d3) δ 7.60 – 7.19 (m, 10H, Ar), 6.70 (s, 1H, N*H*), 5.44 (d, J = 4.5 Hz, 1H, H1), 5.30 (s, 1H, N*H*Boc), 4.68 (dd, J = 19.8, 11.4 Hz, 2H, ArCH_2), 4.54 (t, J = 11.0 Hz, 2H, ArCH_2), 4.00 (dd, J = 5.3, 2.7 Hz, 1H, H3), 3.89 (q, J = 6.5, 5.7 Hz, 1H, H4), 3.52 – 3.48 (m, 1H, H2), 3.44 (dd, J = 8.1, 5.4 Hz, 1H, H5), 3.41 – 3.23 (m, 2H, H6), 1.42 (s, 9H, Boc). ^{13}C NMR (126 MHz, Acetonitrile-d3) δ 166.61 (Lactam *C*O), 138.38 (Boc *C*O), 128.73 – 127.16 (Ar), 76.63 (C5), 75.60 (C1), 75.37 (C3), 72.57 (Ar*C*H_2), 70.43 (Ar*C*H_2), 68.93 (C2), 53.55 (C6), 27.62 (Boc). HRMS ESI+ TOF (*m/z*): $[M+Na]^+$ calcd for $C_{26}H_{32}N_2O_6$: 491.2153; found, 491.2157.

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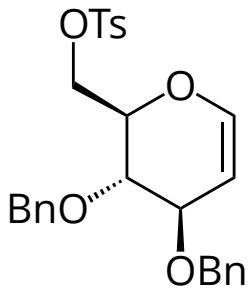
Small molecule spectroscopic data.

*(**5**) 3,4-di-O-benzyl-6-O-(p-toluenesulfonyl)-D-glucal.*



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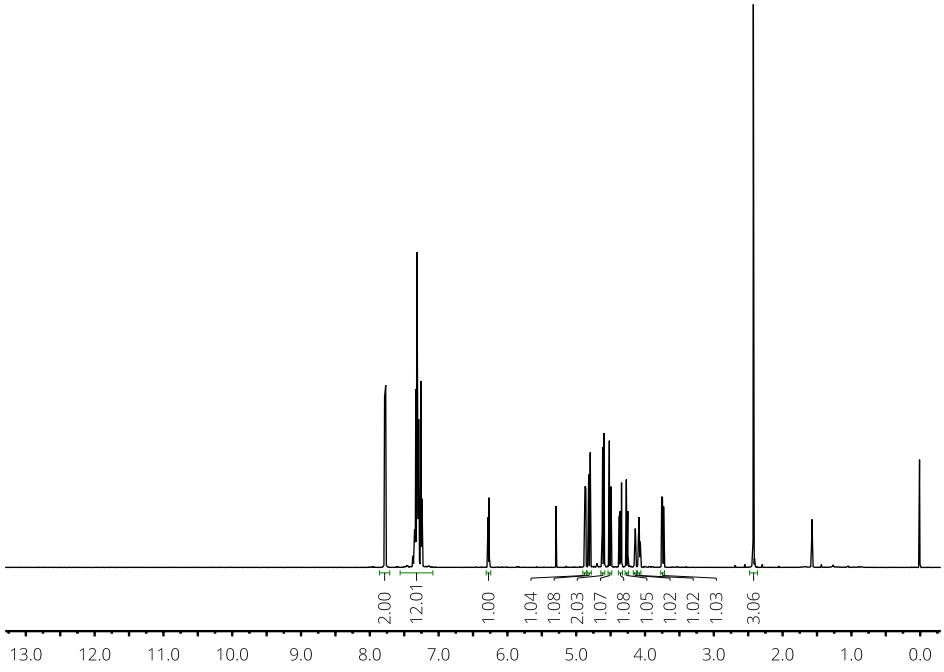

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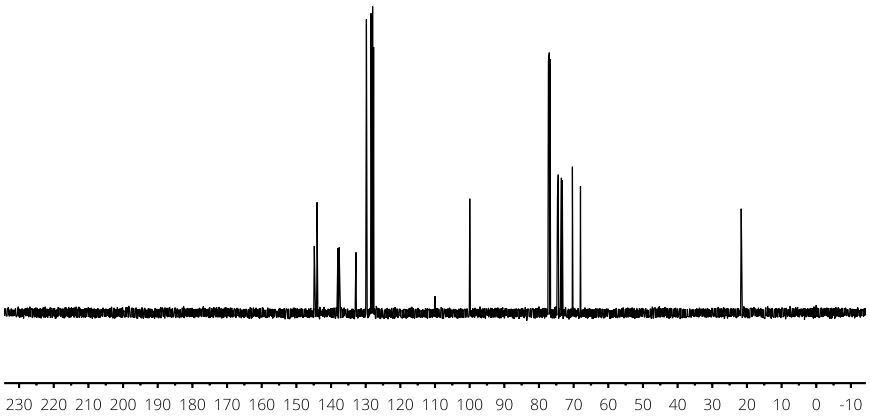

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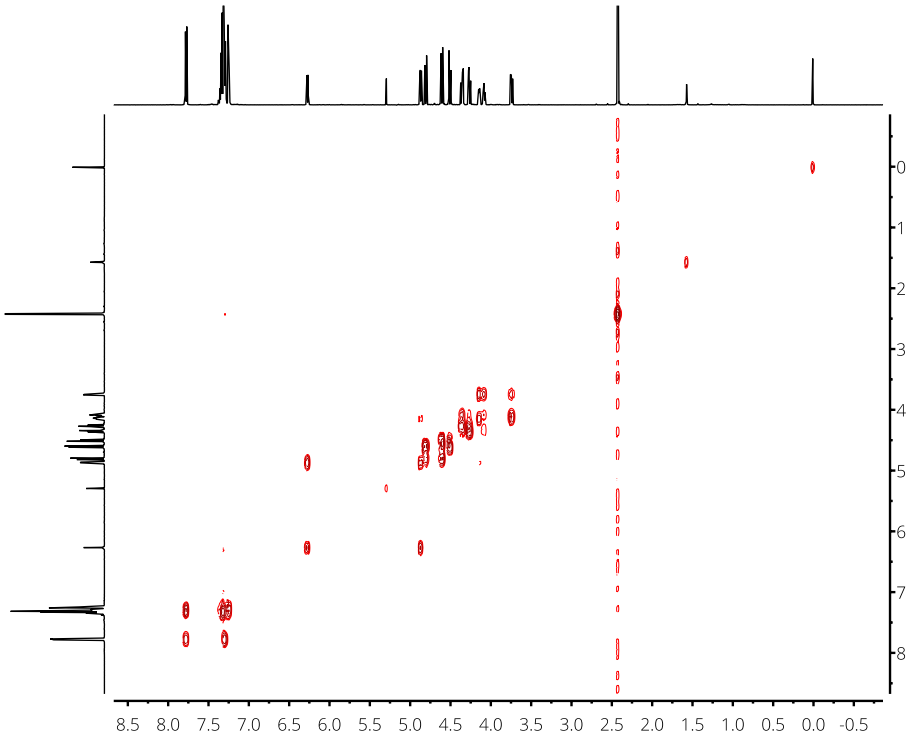

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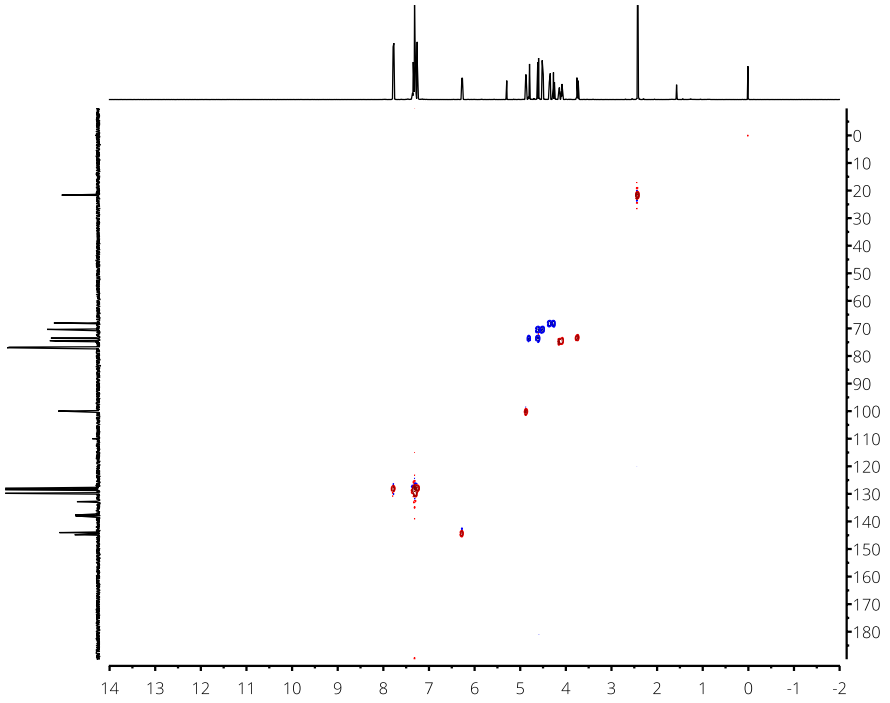
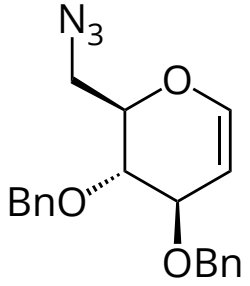


*(**6**) 3,4-di-O-benzyl-6-N-azido-6-deoxy-D-glucal.*



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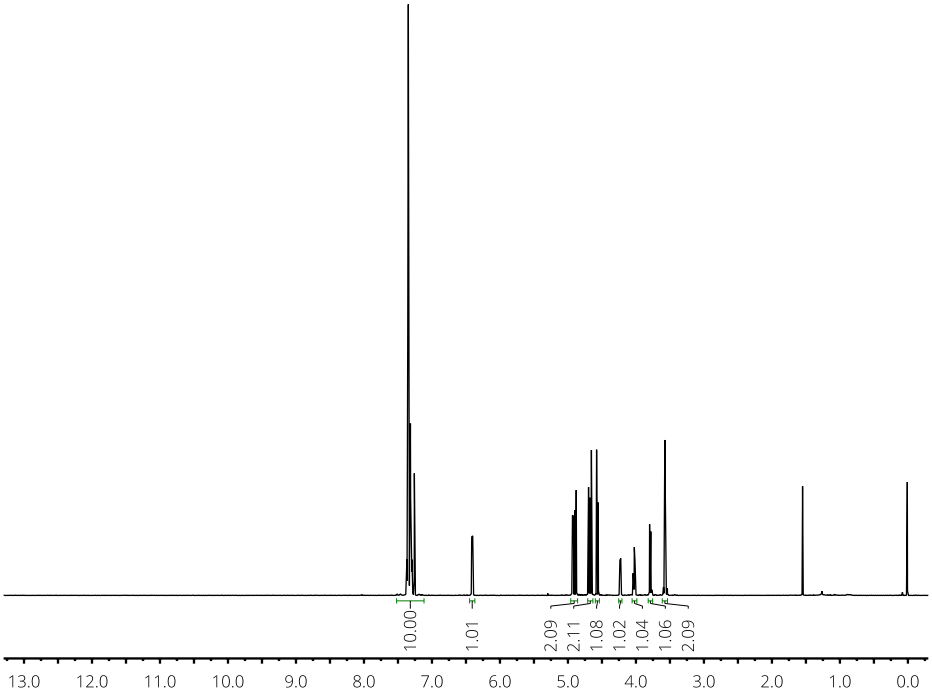

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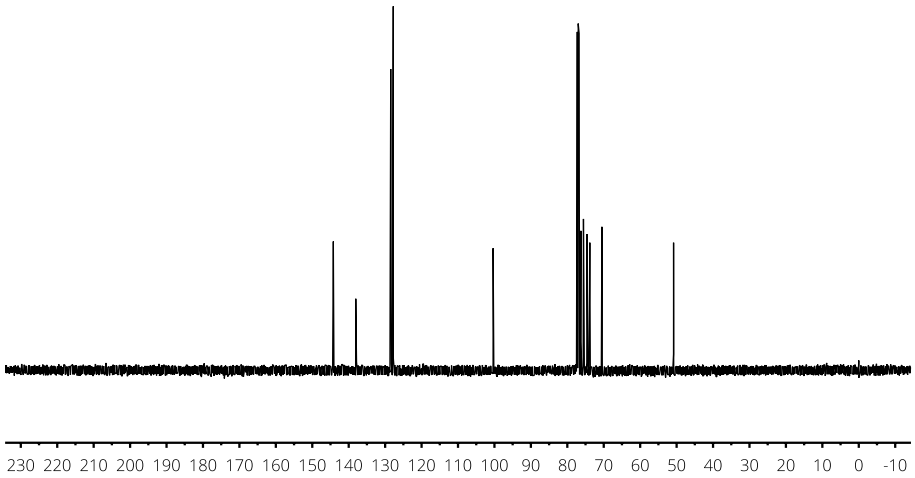

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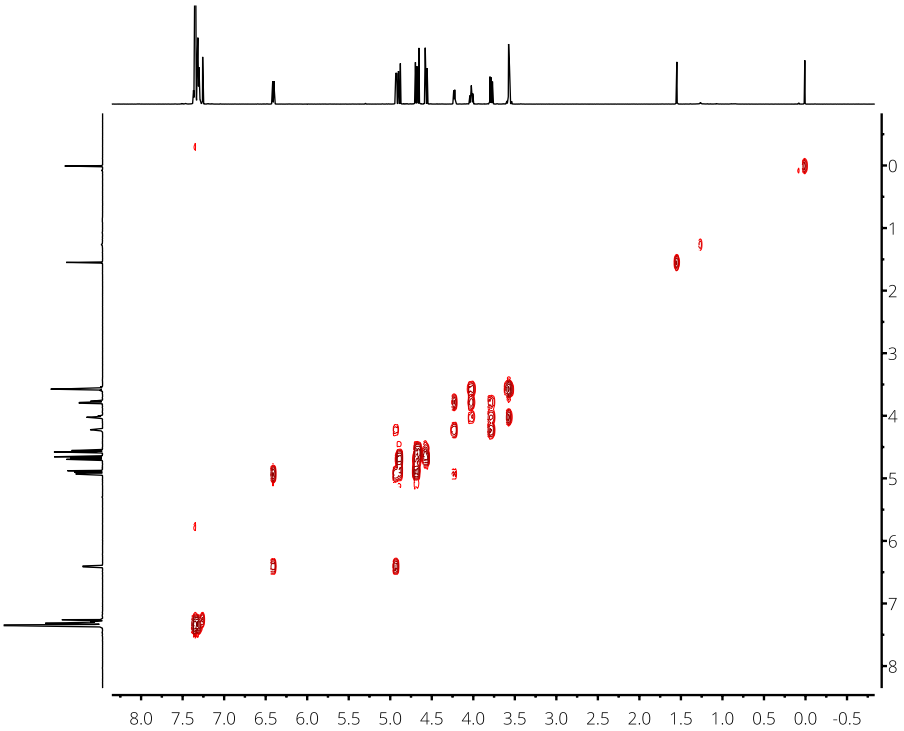

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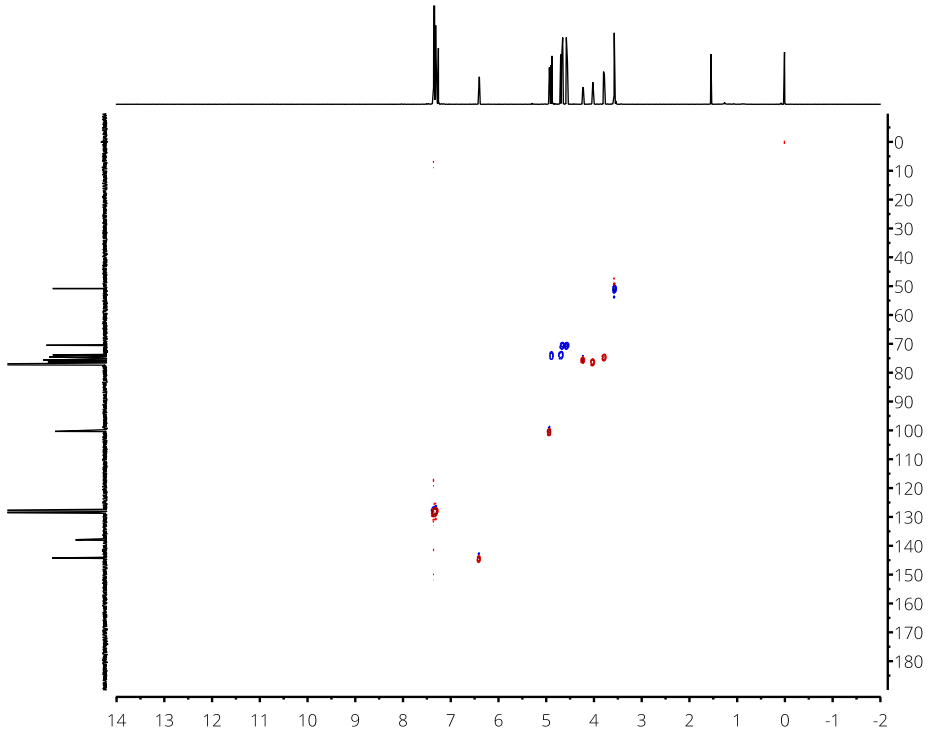
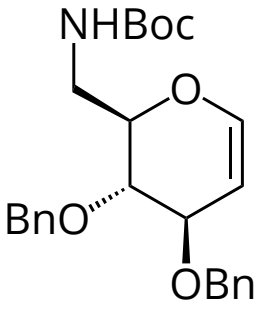


(8) *3,4-di-O-benzyl-6-N-boc-6-deoxy-D-glucal.*



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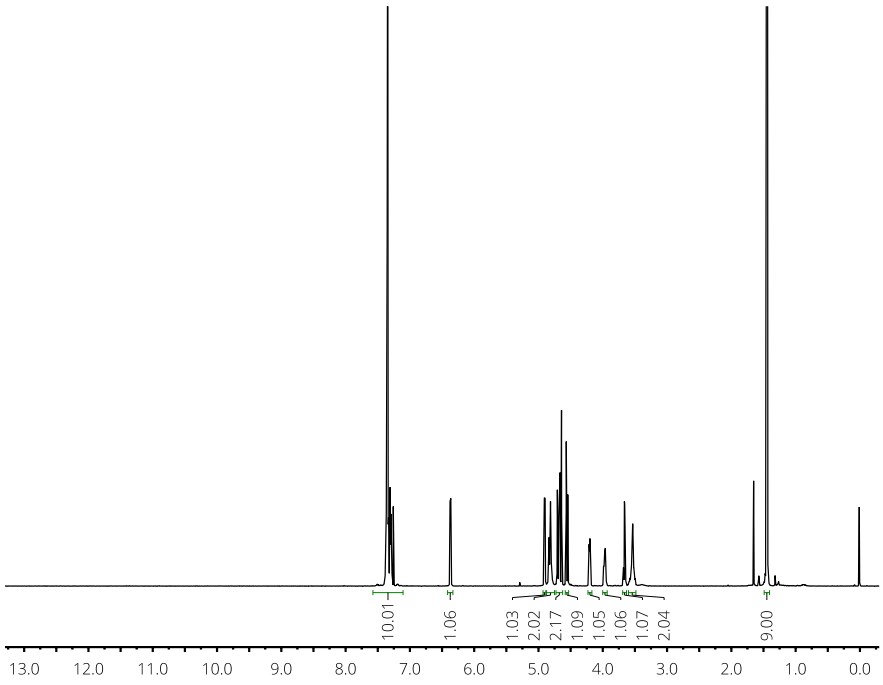

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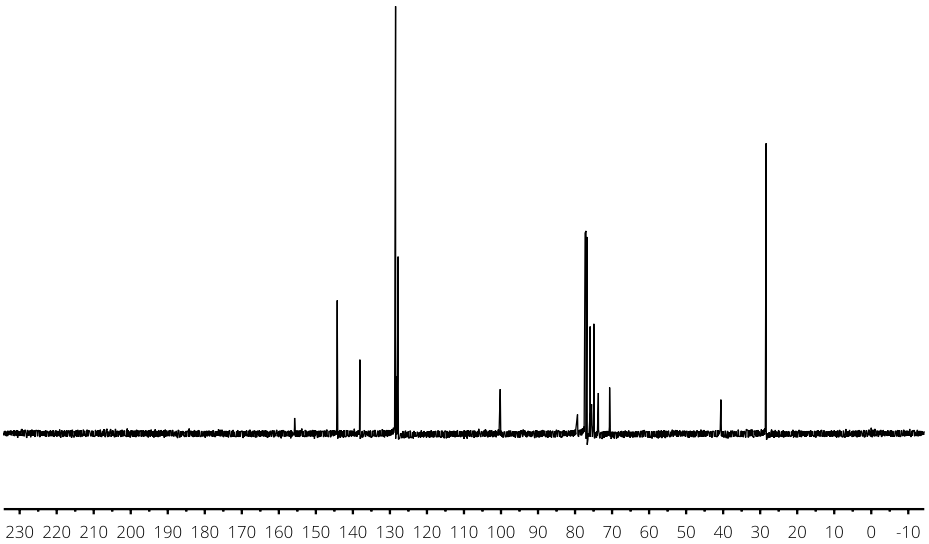
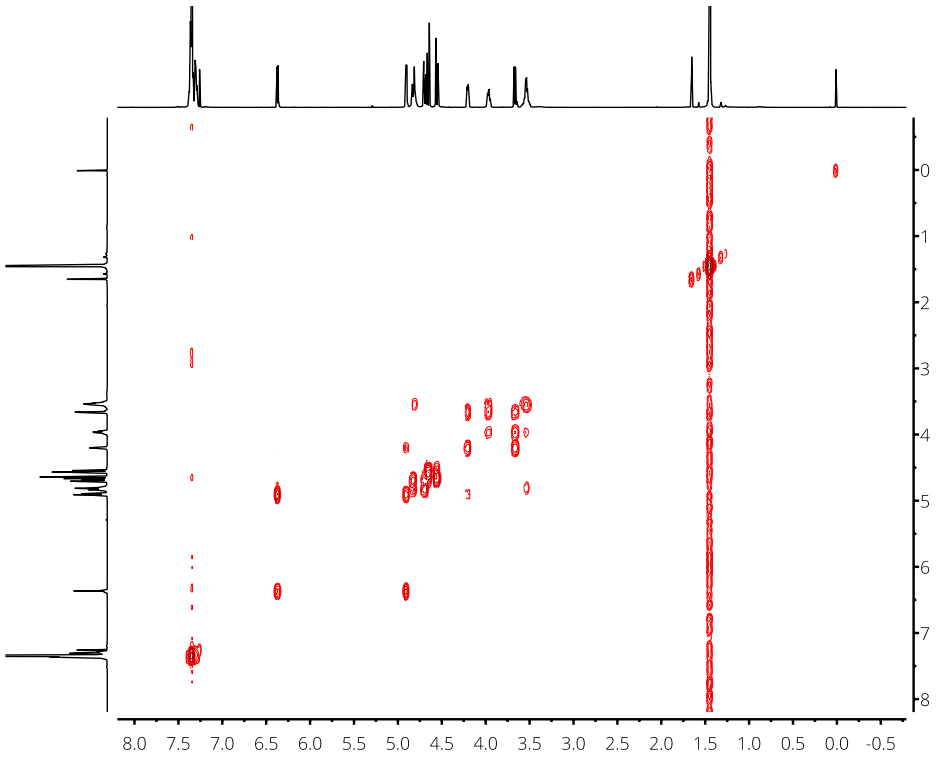
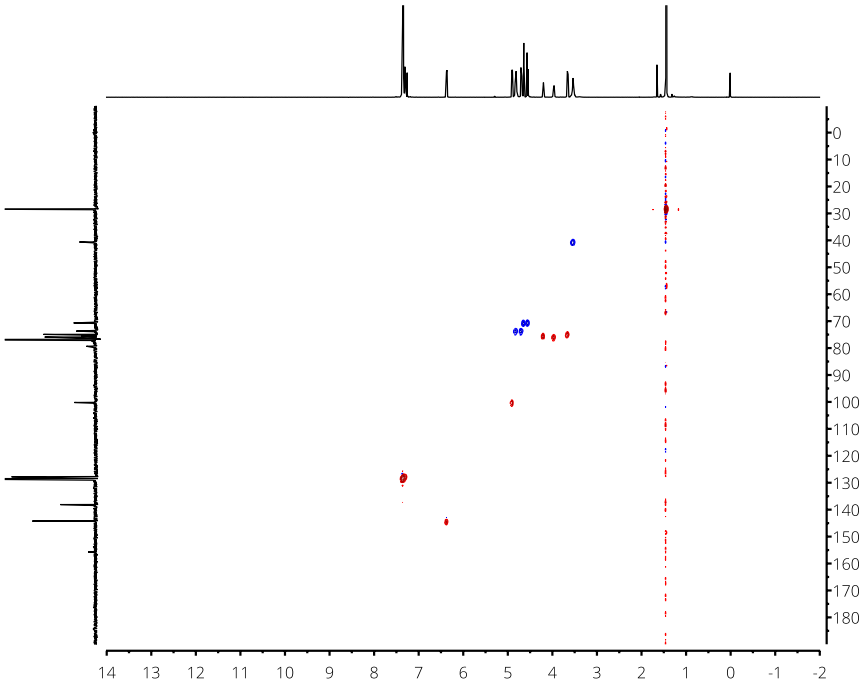


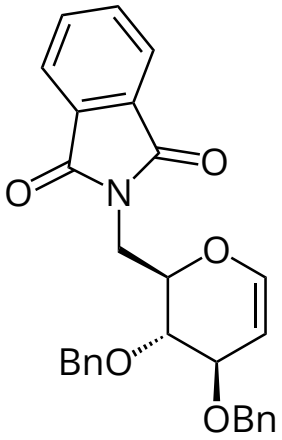
($^{1}H^{1}H$-COSY, 500 MHz, $CDCl_3$)



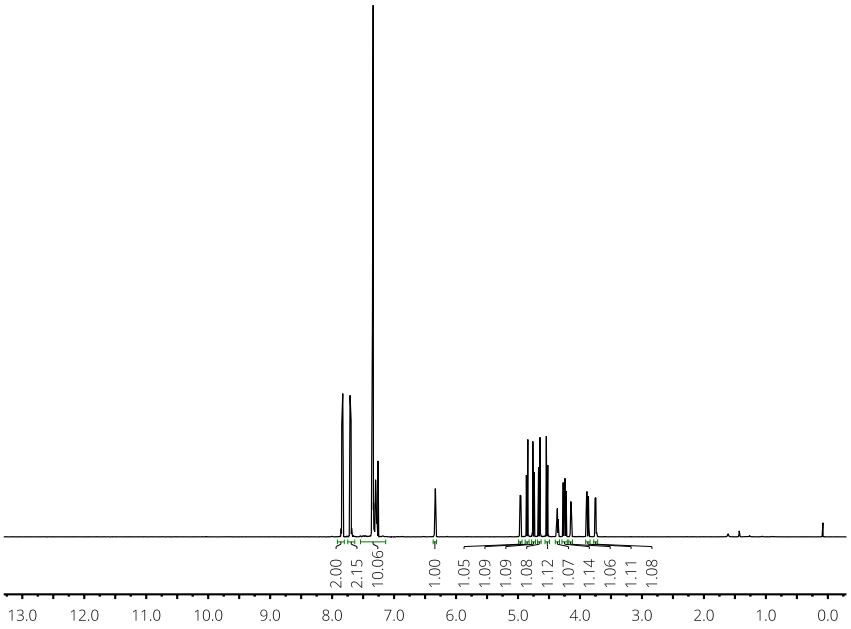
($^{1}H^{13}C$-HSQC, 500 MHz, 126 MHz $CDCl_3$)



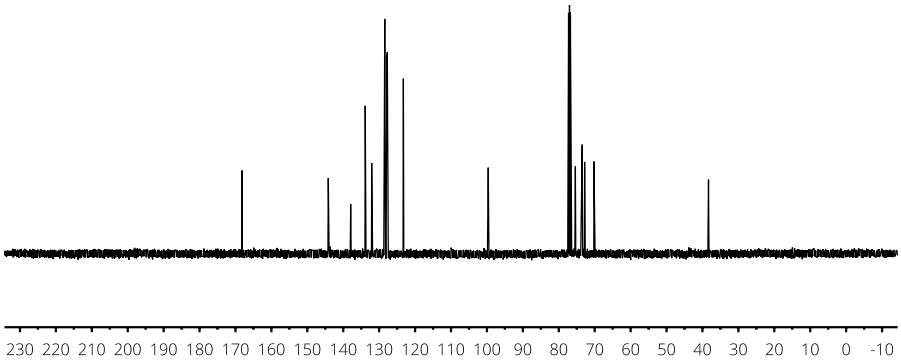
*(**12**) 3,4-di-O-benzyl-6-N-phthalimido-6-deoxy-D-glucal.*



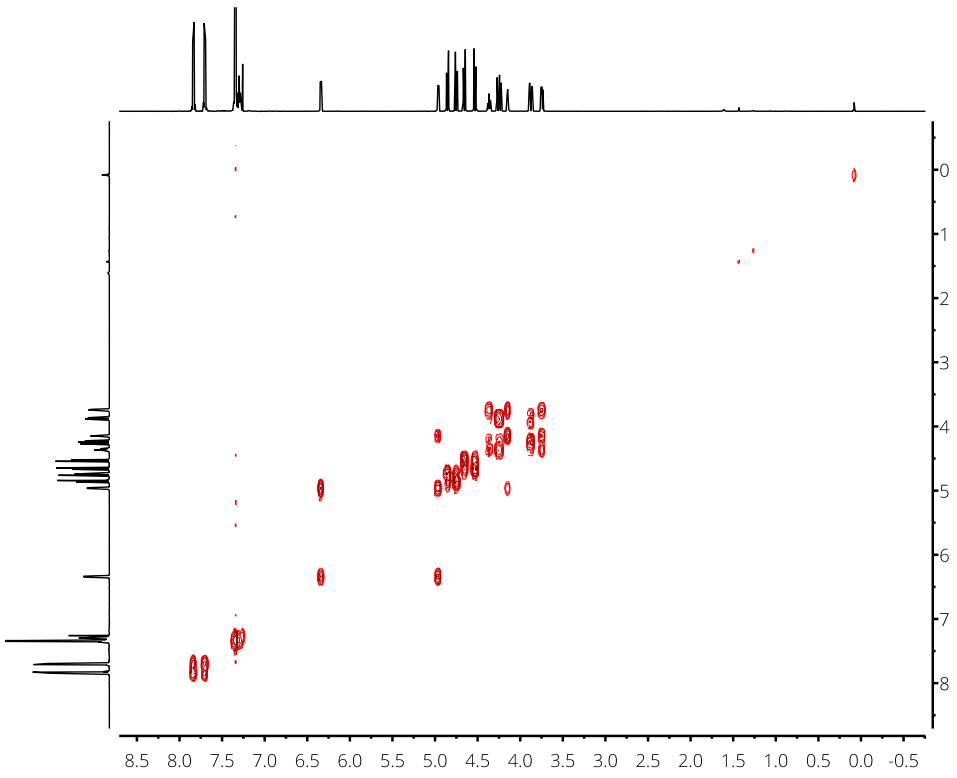
(^{1}H-NMR, 500 MHz, $CDCl_3$)



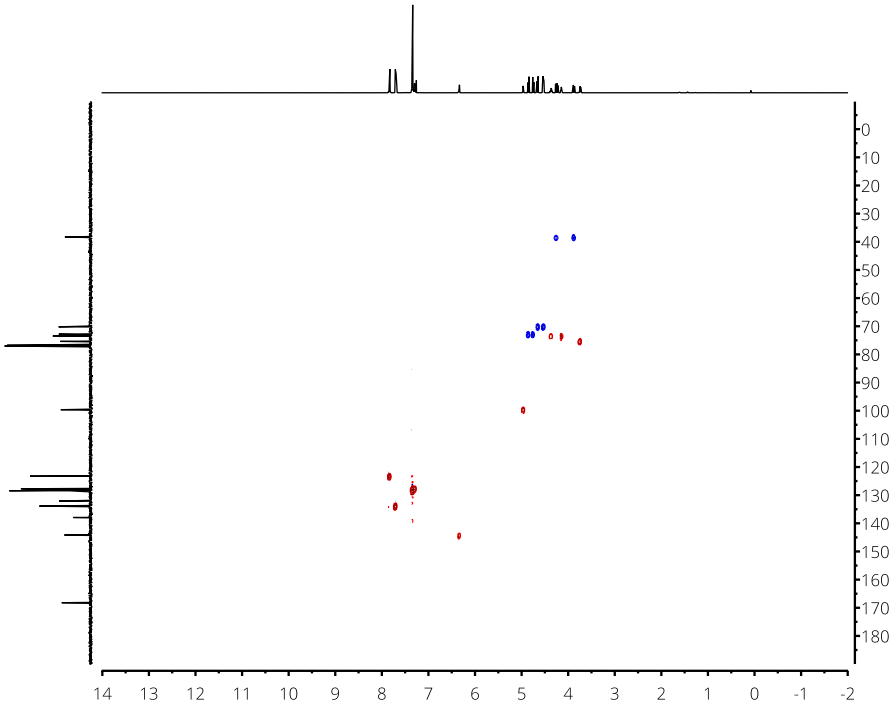
(^{13}C-NMR, 126 MHz, $CDCl_3$)



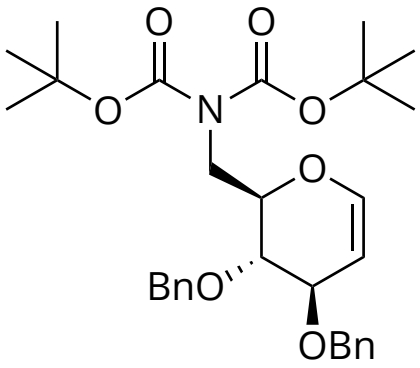
(^{1}H^{1}H-COSY, 500 MHz, $CDCl_3$)



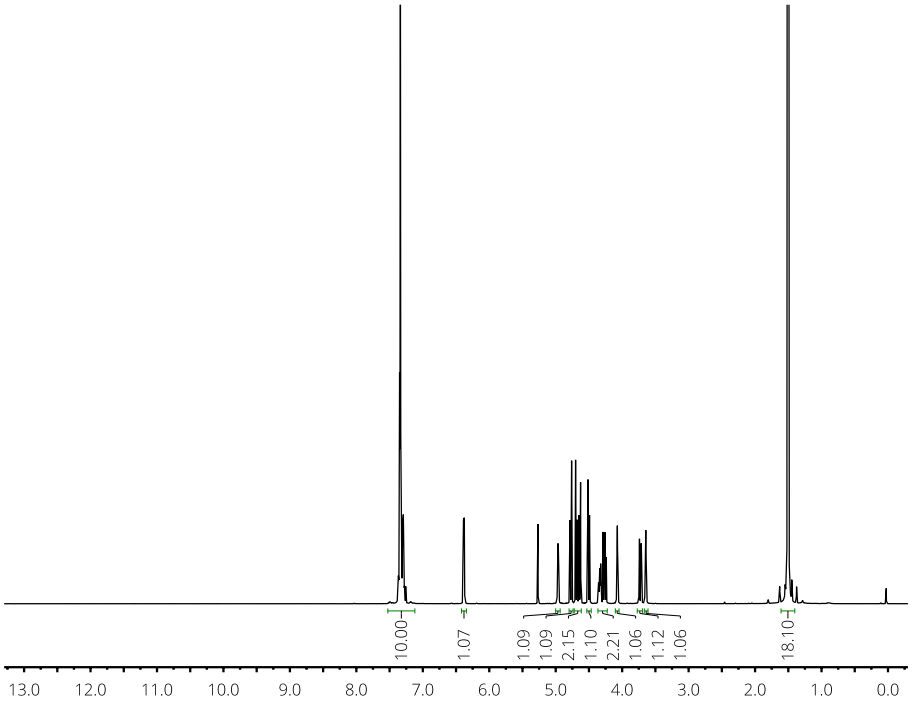
($^{1}H^{13}C$-HSQC, 500 MHz, 126 MHz $CDCl_3$)



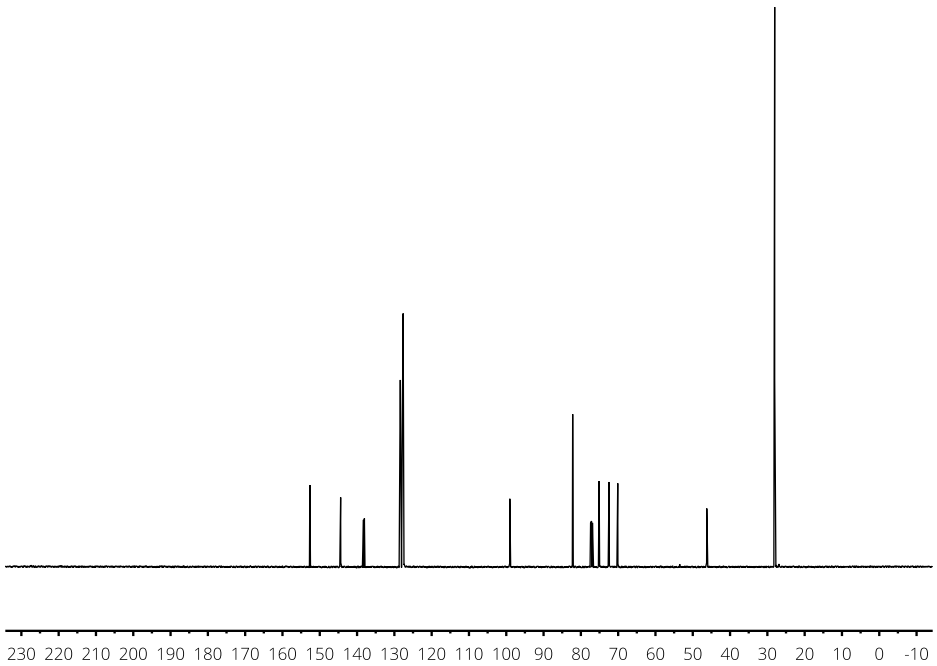
(14) *3,4-di-O-benzyl-6-di-N,N-boc-6-deoxy-D-glucal.*



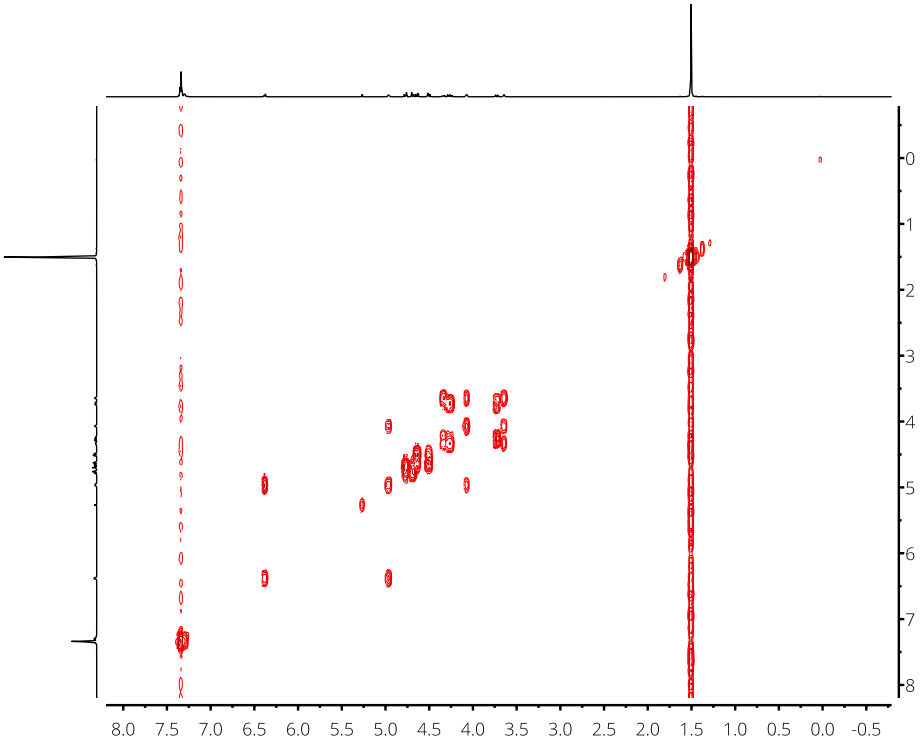
(^{1}H-NMR, 500 MHz, $CDCl_3$)



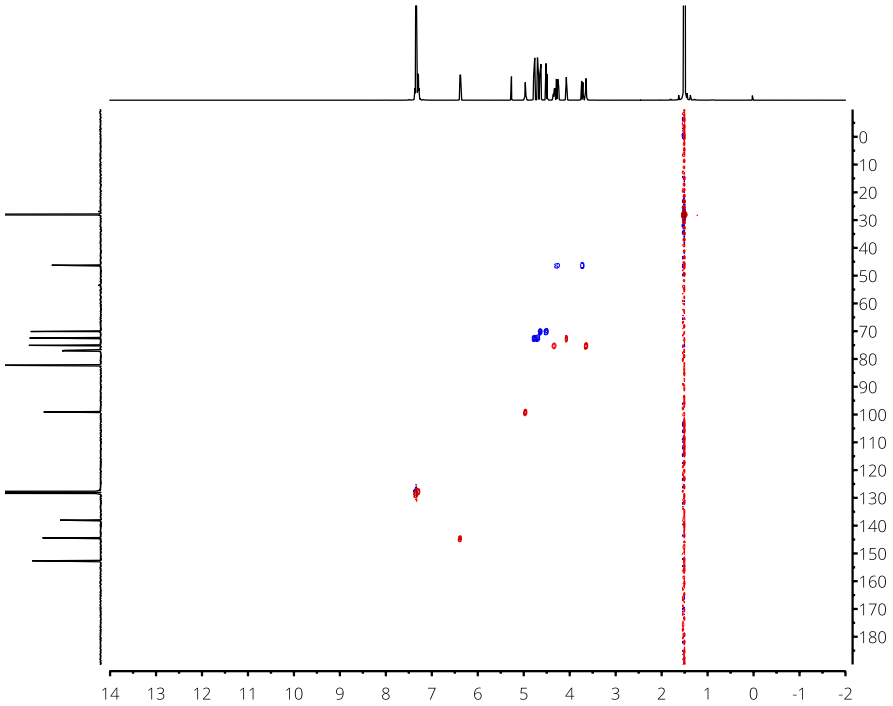
(^{13}C-NMR, 126 MHz, $CDCl_3$)



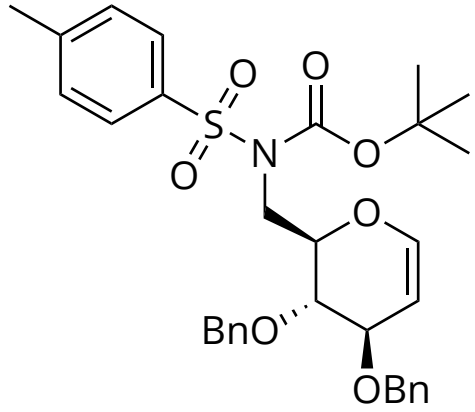
($^{1}H^{1}H$-COSY, 500 MHz, $CDCl_3$)



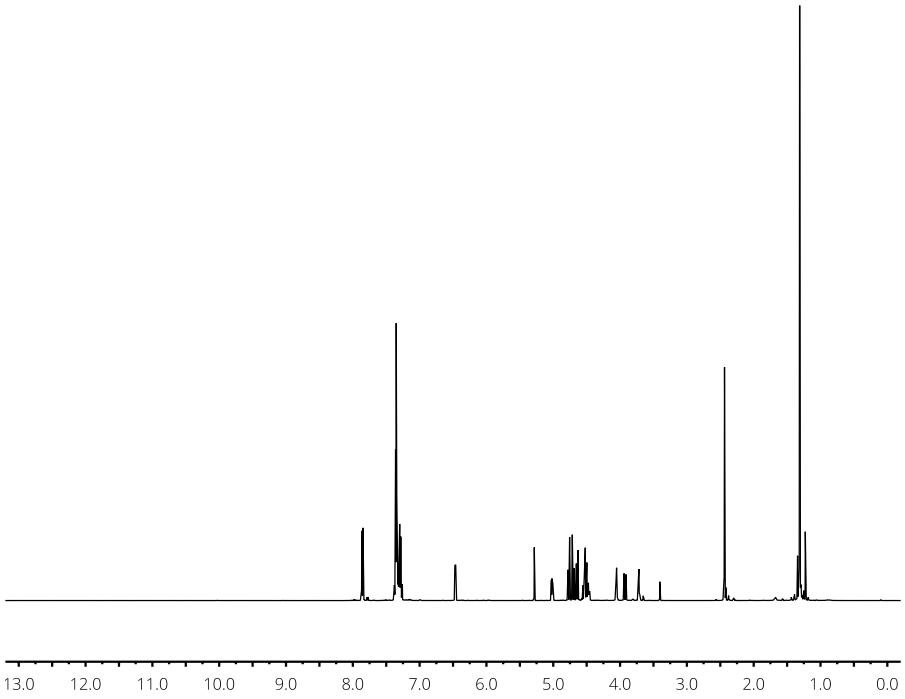
($^{1}H^{13}C$-HSQC, 500 MHz, 126 MHz $CDCl_3$)



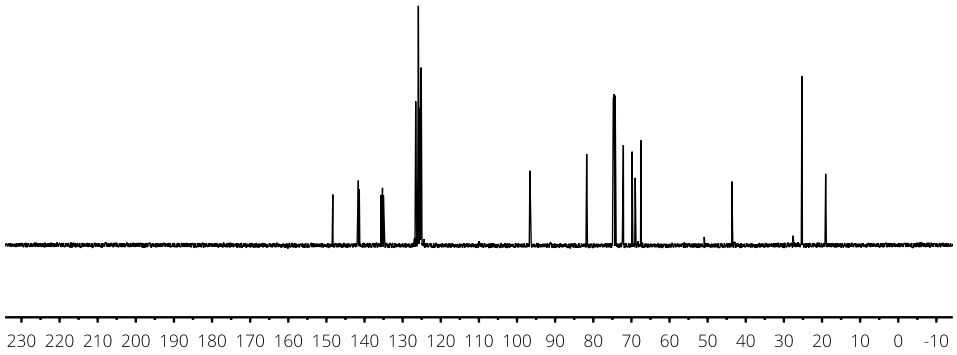
(16) *3,4-di-O-benzyl-6-N-(4-toluenesulfonyl)-N-boc-6-deoxy-D-glucal*



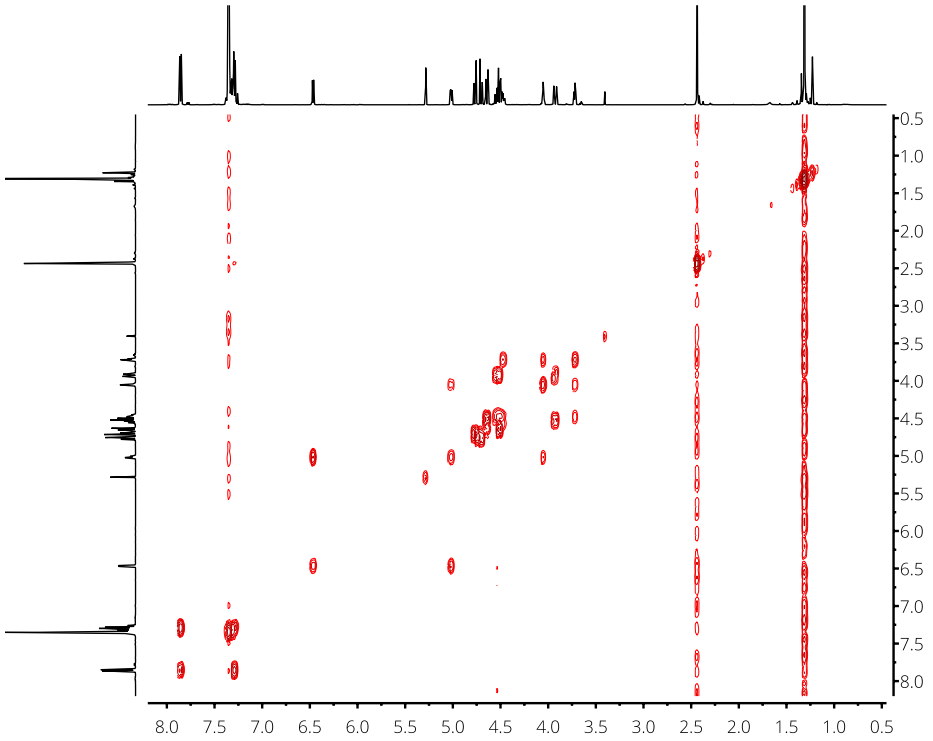
(^{1}H-NMR, 500 MHz, $CDCl_3$)



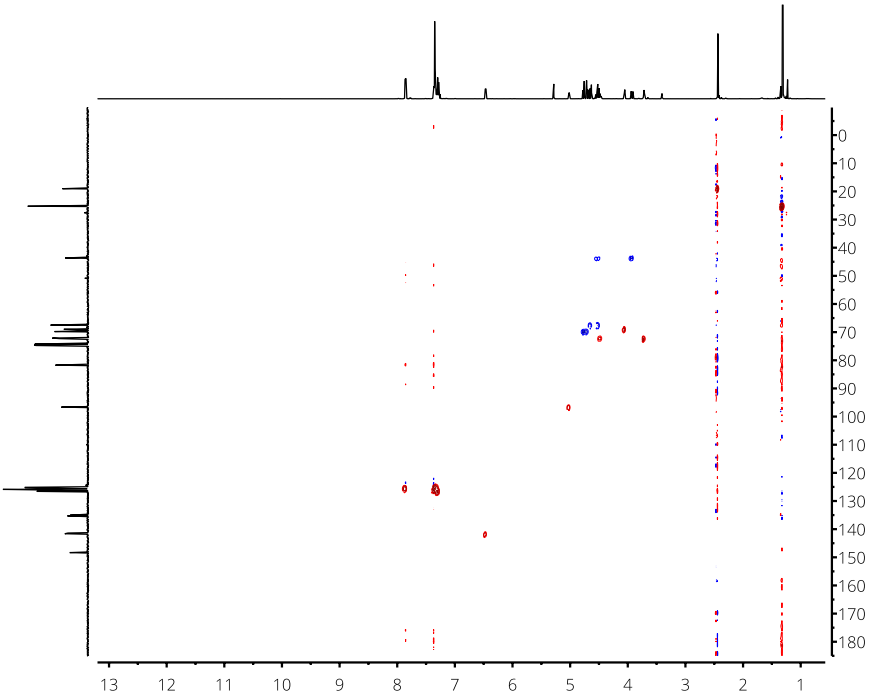
(^{13}C-NMR, 126 MHz, $CDCl_3$)



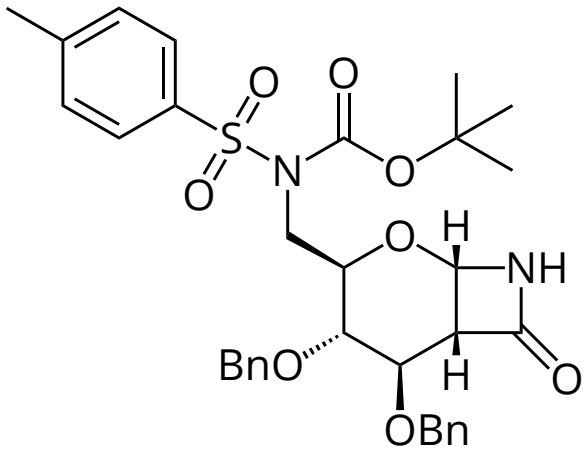
(^{1}H^{1}H-COSY, 500 MHz, $CDCl_3$)



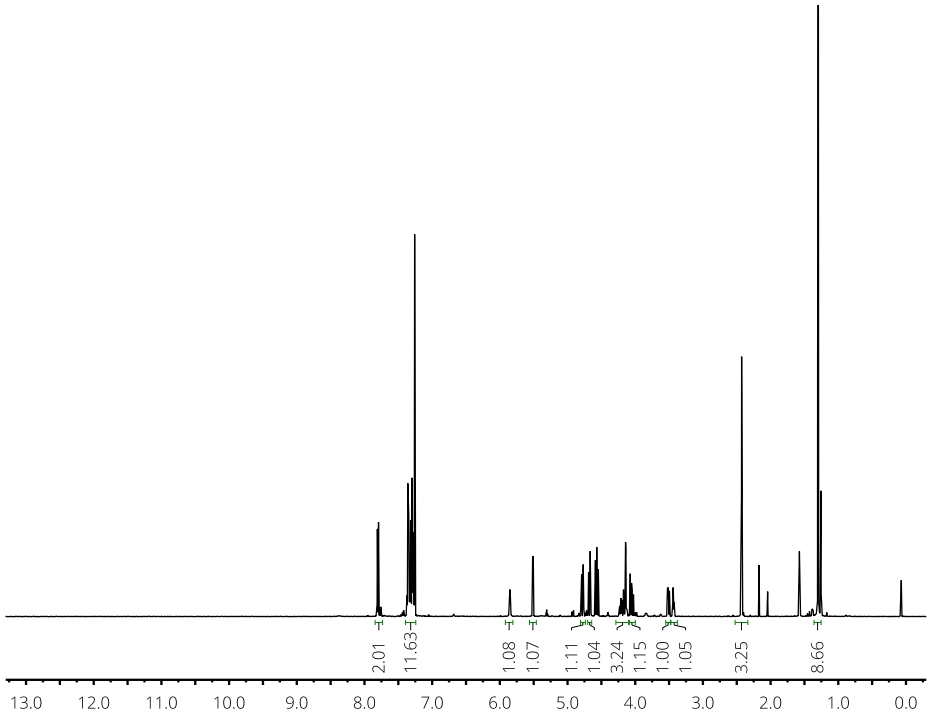
($^{1}H^{13}C$-HSQC, 500 MHz, 126 MHz $CDCl_3$)



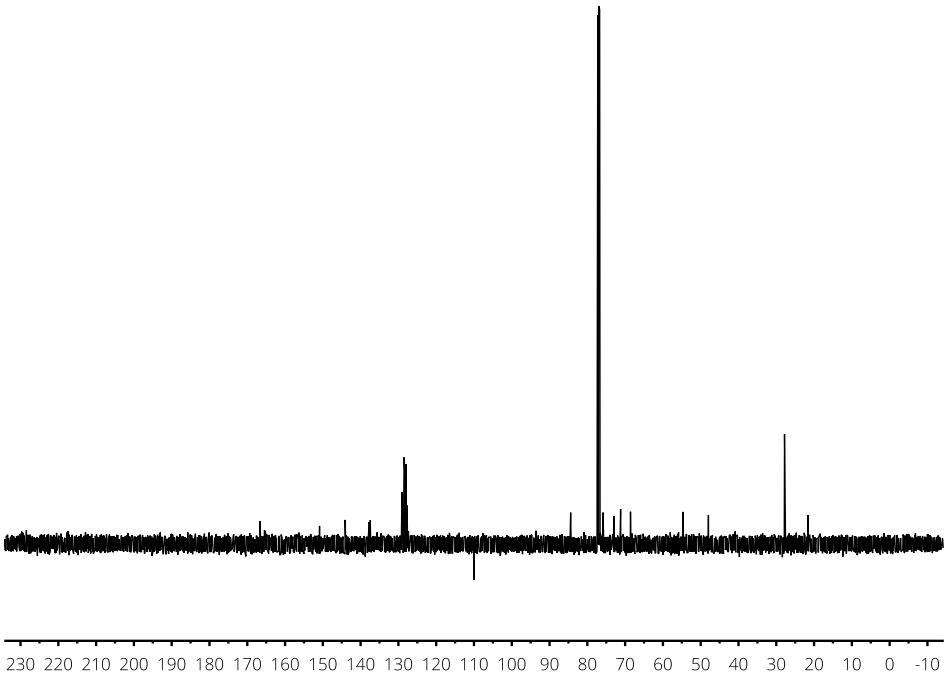
*(**17**) 1,2-β-lactam-3,4-di-O-benzyl-6-N-(4-toluenesulfonyl)-N-boc-6-deoxy-D-glucal.*



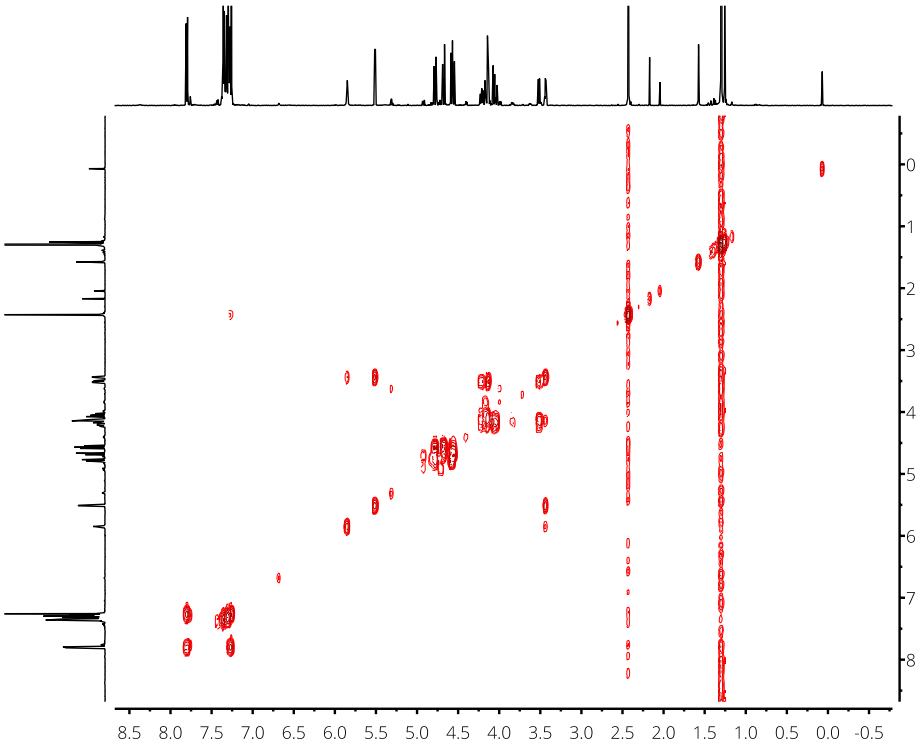
(^{1}H-NMR, 500 MHz, $CDCl_3$)



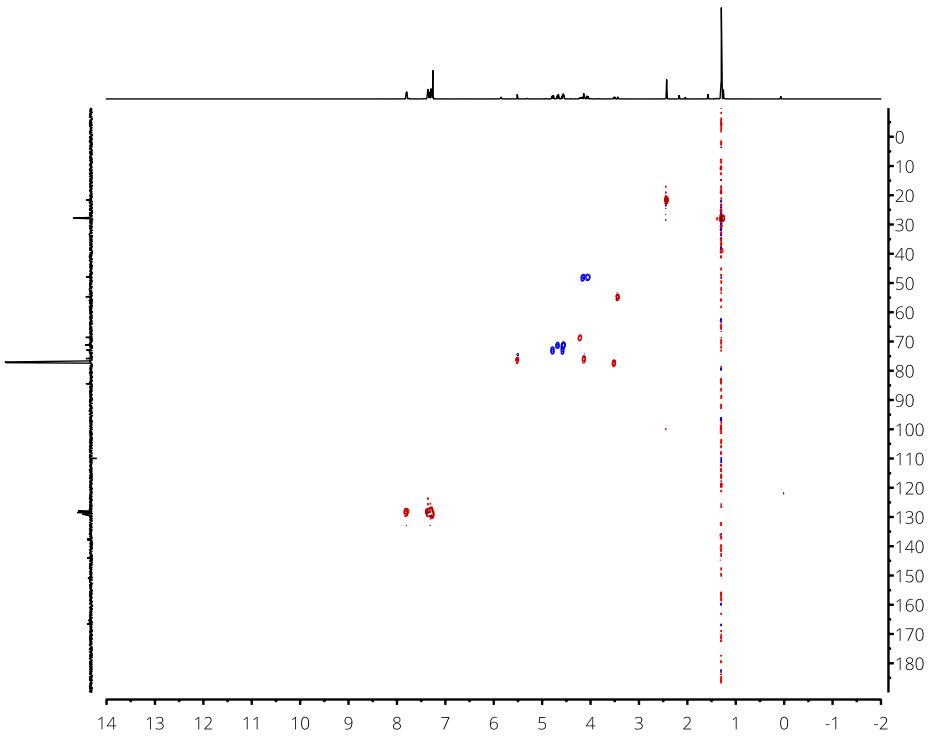
(^{13}C-NMR, 126 MHz, $CDCl_3$)



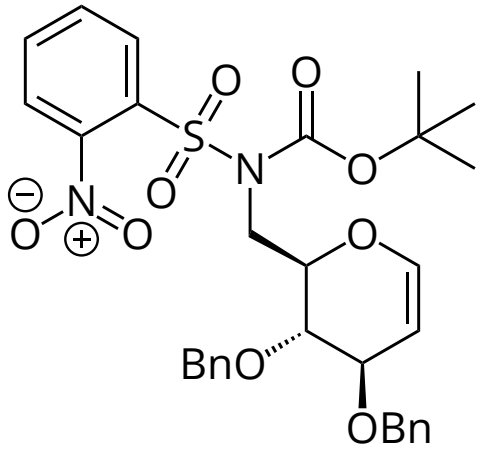
($^{1}H^{1}H$-COSY, 500 MHz, $CDCl_3$)



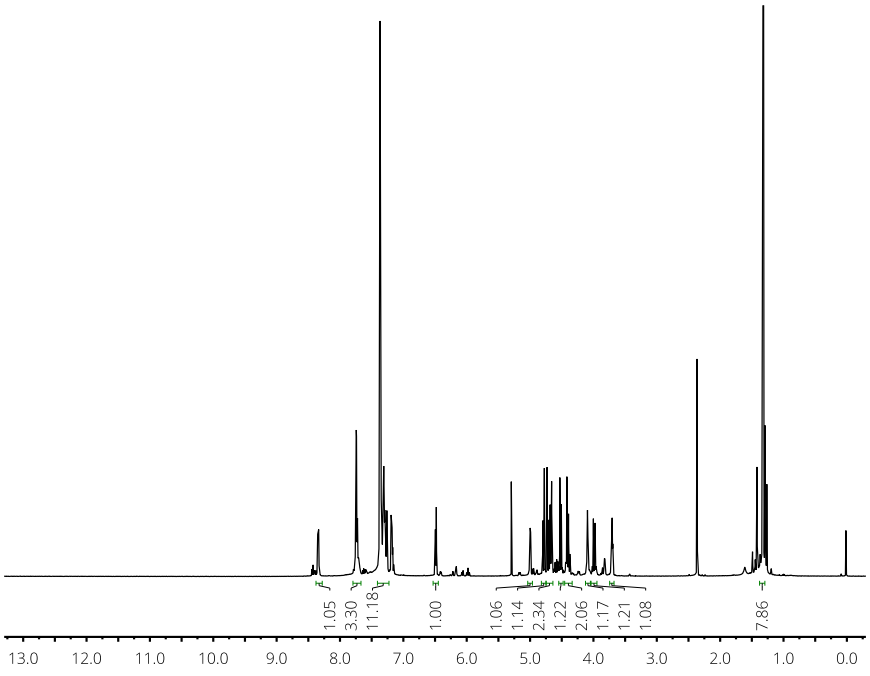
($^{1}H^{13}C$-HSQC, 500 MHz, 126 MHz $CDCl_3$)



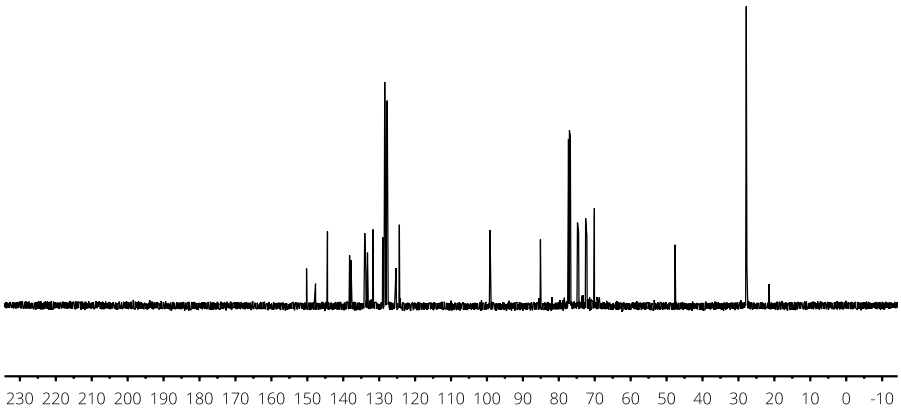
(18) 3,4-di-O-benzyl-6-N-(2-nitrobenzenesulfonyl)-N-boc-6-deoxy-D-glucal.



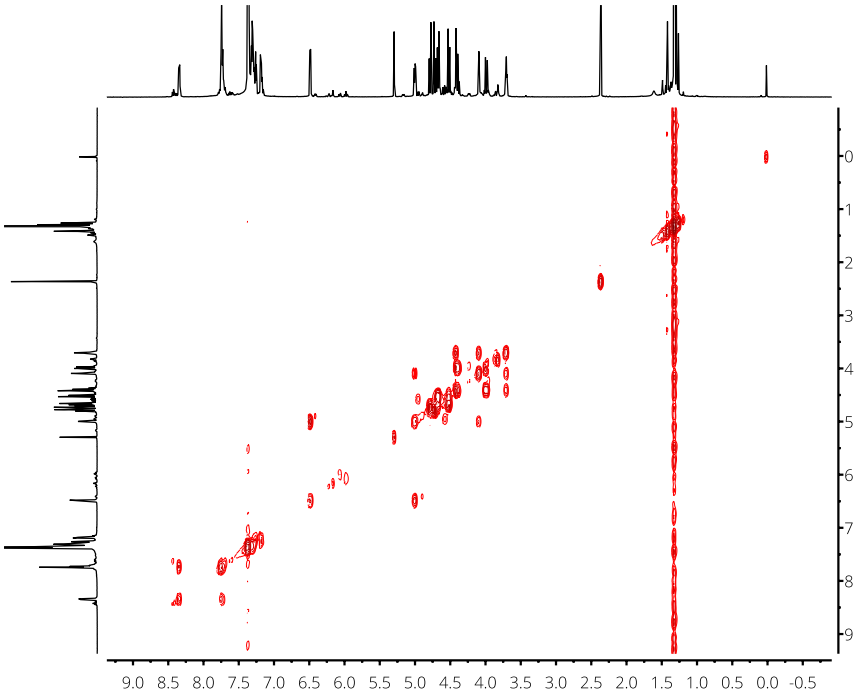
(^{1}H-NMR, 500 MHz, $CDCl_3$)



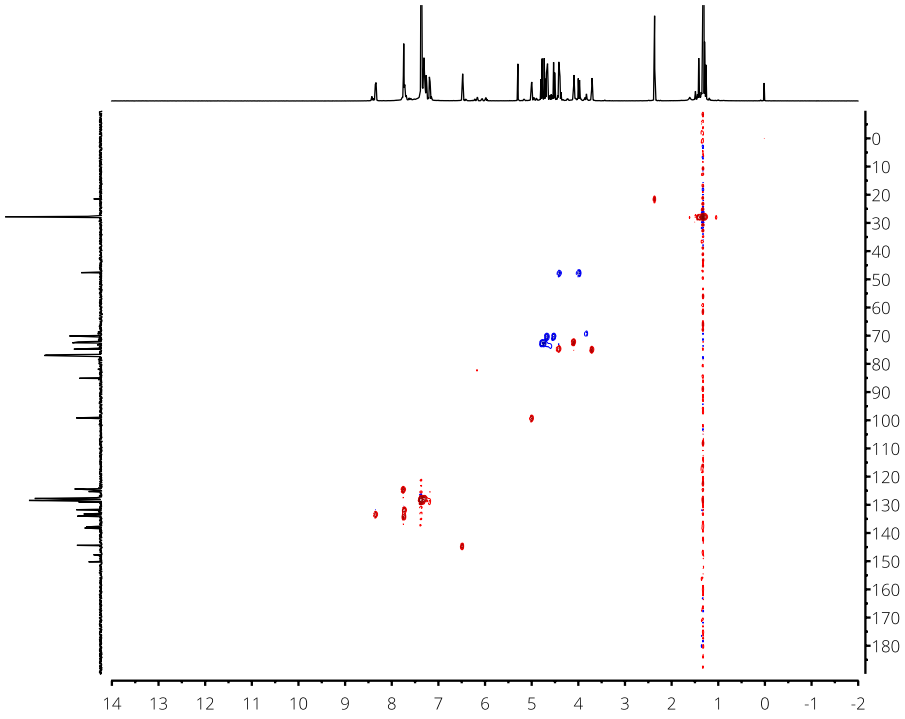
(^{13}C-NMR, 126 MHz, $CDCl_3$)



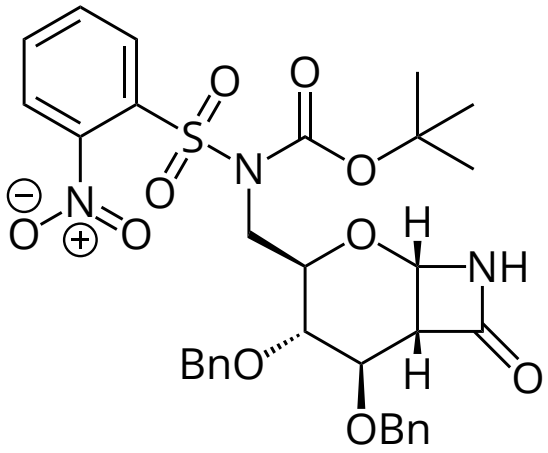
(^{1}H^{1}H-COSY, 500 MHz, $CDCl_3$)



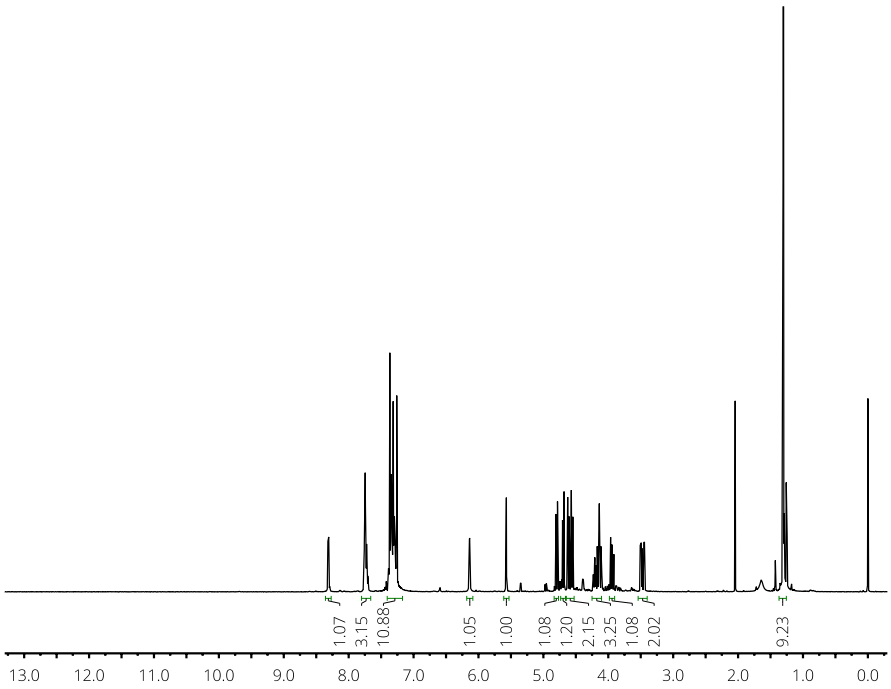
($^{1}H^{13}C$-HSQC, 500 MHz, 126 MHz $CDCl_3$)



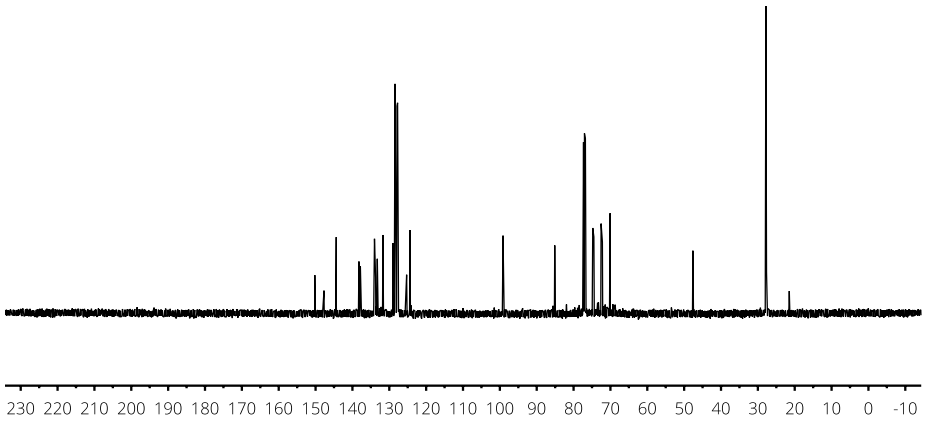
(19) *1,2-β-lactam-3,4-di-O-benzyl-6-N-(2-nitrobenzenesulfonyl)-N-boc-6-deoxy-D-glucal*



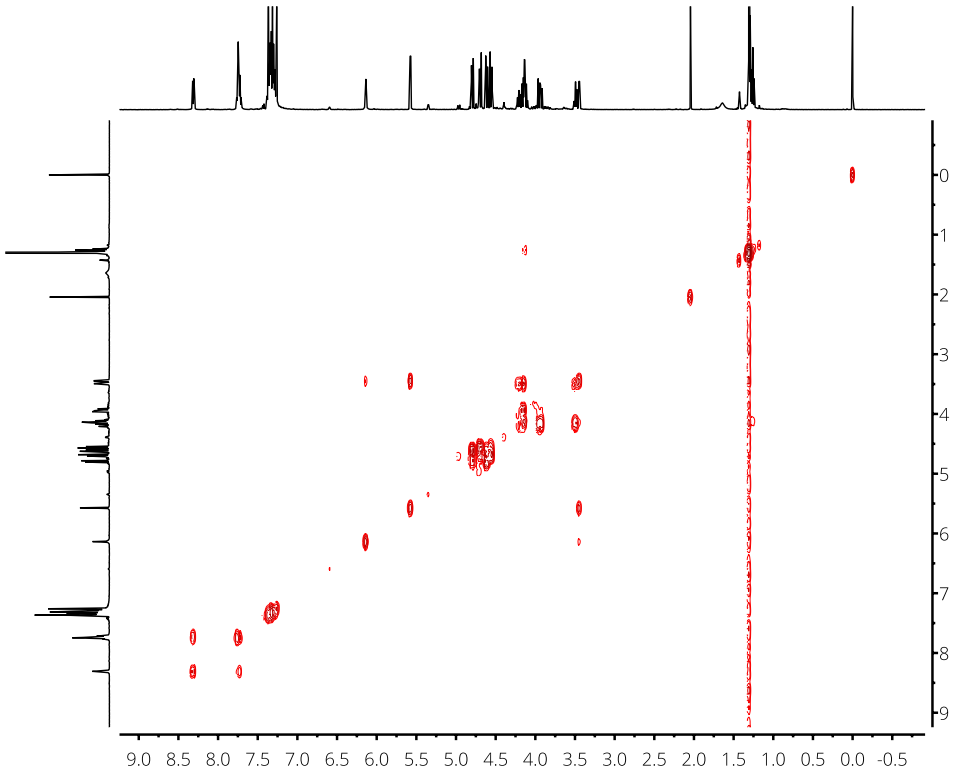
(^{1}H-NMR, 500 MHz, $CDCl_3$)



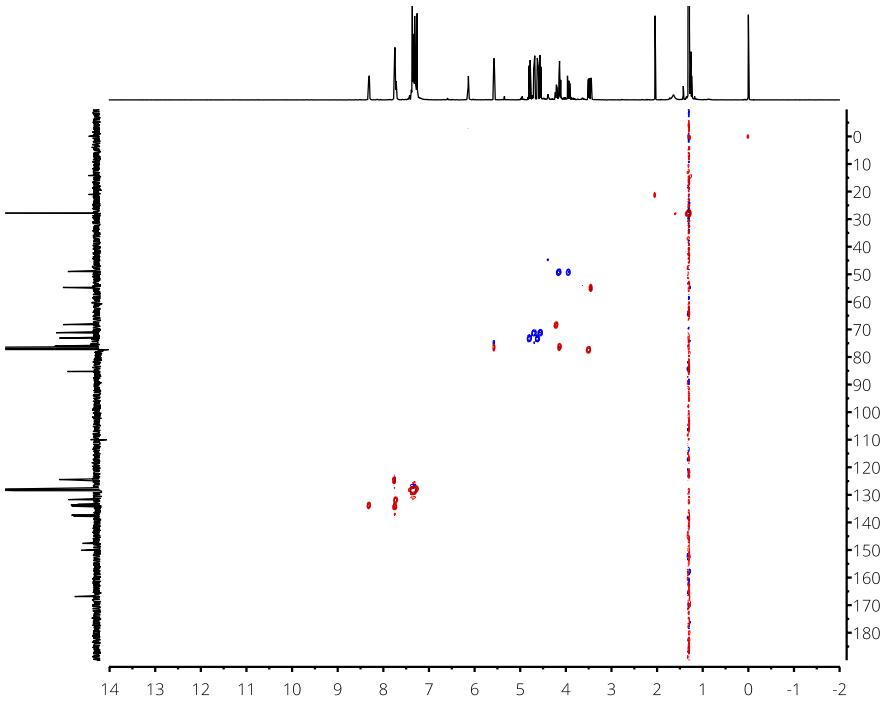
(^{13}C-NMR, 126 MHz, $CDCl_3$)



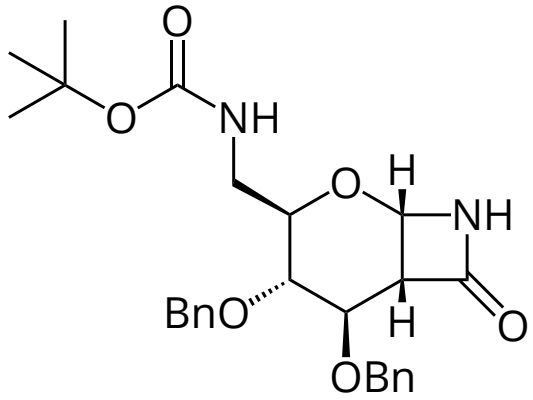
($^{1}H^{1}H$-COSY, 500 MHz, $CDCl_3$)



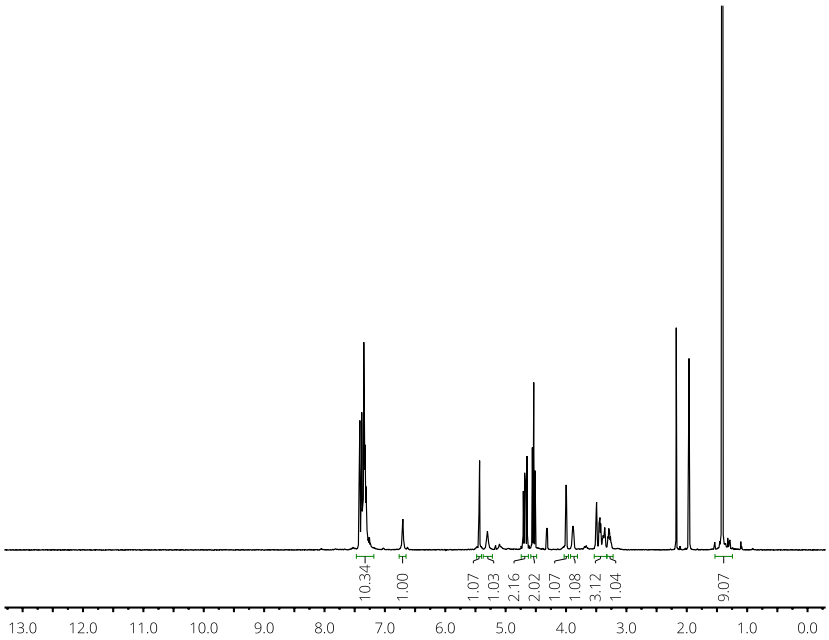
($^{1}H^{13}C$-HSQC, 500 MHz, 126 MHz $CDCl_3$)



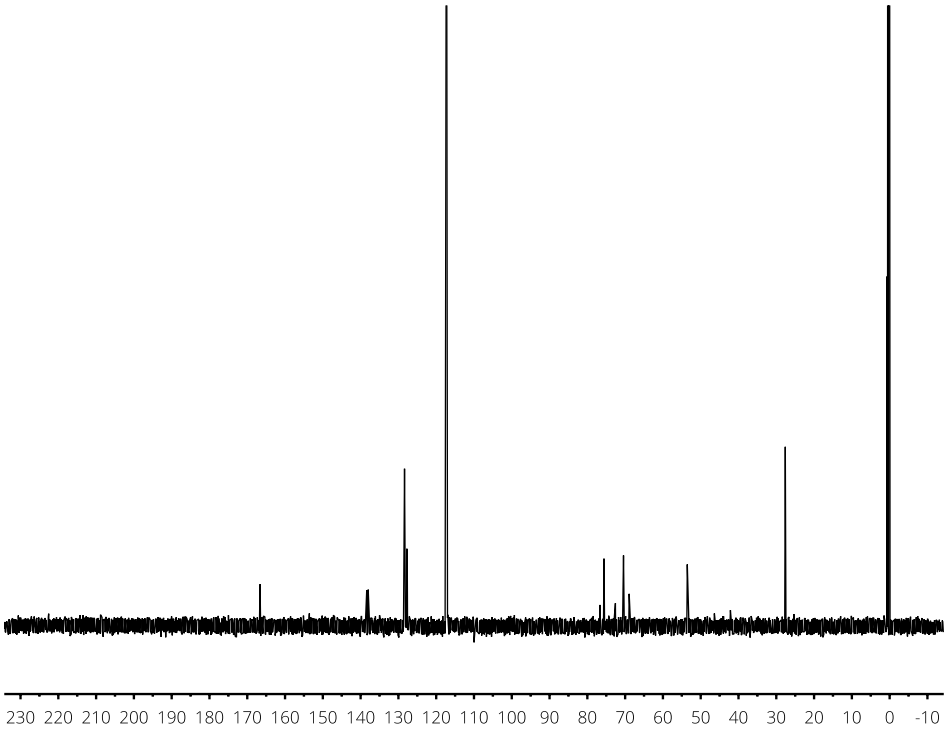
*(**20**) 1,2-β-lactam-3,4-di-O-benzyl-6-N-boc-6-deoxy-D-glucal.*



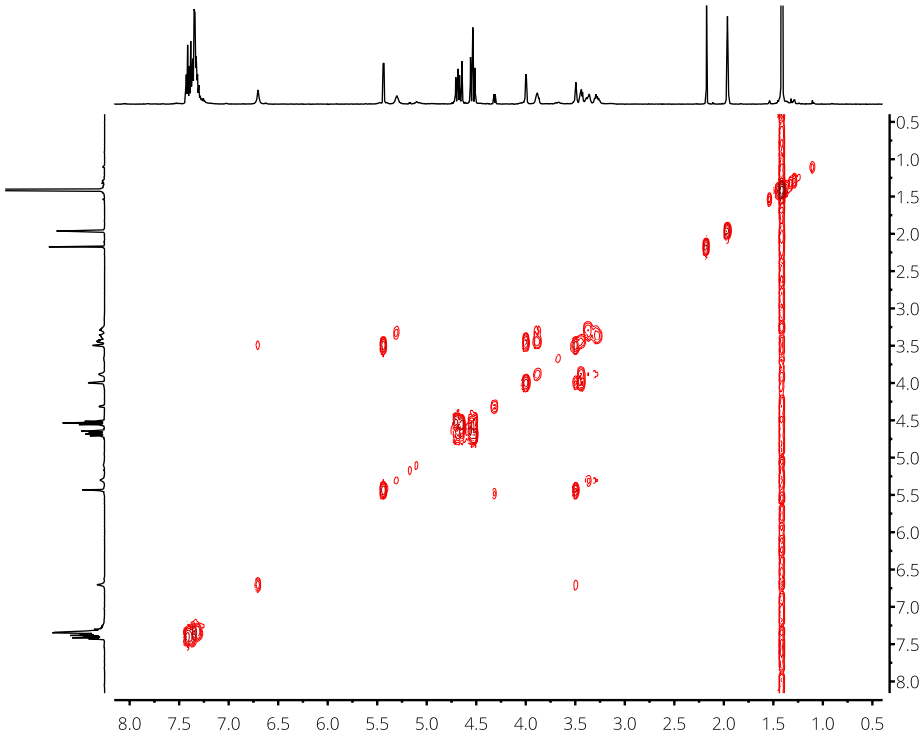
(^{1}H-NMR, 500 MHz, CD_3CN)



(^{13}C-NMR, 126 MHz, CD_3CN)



(^{1}H^{1}H-COSY, 500 MHz, CD_3CN)



($^{1}H^{13}C$-HSQC, 500 MHz, 126 MHz CD_3CN)