Published in final edited form as:

J Carbohydr Chem. 2012 January 1; 31(4-6): 353–370. doi:10.1080/07328303.2012.663431.

Synthesis of β -Glycosyl Amides from *N*-Glycosyl Dinitrobenzenesulfonamides

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Abstract

The *N*-glycosyl-2,4-dinitrobenzenesulfonamides were accessed via benzoyl-protected β -glycosyl azides. The azides were reduced with Adams' catalyst to the corresponding amines. The glycosylamines were sulfonated with 2,4-dinitrobenzenesulfonyl chloride to form *N*-glycosyl-2,4-dinitrobenzenesulfonamides in moderate yields. β -Glycosyl amides were then prepared in 67 – 81 % yields by treatment of the sulfonamides with thioacetic acid and cesium carbonate. The conversion of the glycosylsulfonamide to the glycosyl amide proceeded with high stereoselectivity.

Keywords

β -glycosyl amides; 2,4-dinitrobenzenesulfonamides; thioacids; Meisenheimer complex

INTRODUCTION

Glycosyl amide linkages are found in a variety of natural products. It is also notable that the glycosyl amide can be activated and used as a glycosyl donor.¹ A popular strategy for accessing the β -glycosyl amide linkage found in *N*-linked glycopeptide is the Lansbury aspartylation which involves the direct coupling of a glycosylamine to an activated aspartic acid on a protected peptide.² The intermediate glycosylamines are frequently accessed by the Kochetkov reaction³ or by deprotection of a sugar anomeric azide to access the amine.⁴ Aspartylations have also been performed using less active esters under microwave-mediated conditions.⁵ A limitation of the method is that the starting glycosylamines are relatively unstable⁶ and the hemiaminal is prone to mutarotation to give a mixture of anomers thus making stereocontrol difficult.⁷ Further, diglycosylamines have also been observed as by-products of glycosylamine forming reactions.^{8,9} Thus, methods for forming the β -glycosyl amide linkage which do not involve an anomeric amine can be considered advantageous. Several methods for improving this basic transformation have been explored; however, most are overly complex and have noted limitations.^{10,11} Alternative strategies to access the β -glycosyl amide include the use of the Staudinger reduction–acylation process,^{10,11} starting from β -glycosyl azides. However, anomerization remains a significant problem and mixtures of anomers are often obtained.^{12,13} These same azides have also been used in traceless Staudinger ligations using 2-diphenylphosphanyl-phenyl alkanoates. The diastereoselectivity of these reactions appears dependent on sugar protecting group.¹⁴ Glycosyl azides have also been reported to react with thioacids to yield the amide,¹⁵ while per-acylated sugars in the presence of methanesulfonic acid and nitrile form glycosyl amides via a Ritter-type reaction.¹⁶ Further, β -glycosyl isonitriles and carboxylic acids under the

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influence of microwaves react to afford formylated β -glycosyl amides.¹⁷ Thus, there have been sustained efforts to identify more stereoselective routes to generate β -glycosyl amides.

2,4-Dinitrobenzenesulfonyl chloride (dNBS-Cl) has been used to protect primary amines. The resulting 2,4-dinitrobenzenesulfonamides (dNBS) have in-turn been used to synthesize secondary amines and diamines by Fukuyama *et. al.*^{18,19} 2,4-Dinitrobenzenesulfonamides were later exploited to generate amides, thioamides, ureas, and thioureas proceeding through the *ipso* attack of various S and O nucleophiles on the sulfonamide to produce the Meisenheimer complex.^{20,21} In case of the reaction between thioacids and dNBS's, the sulfonamide nitrogen ultimately attacks a thioester on the disintegration of the Meisenheimer complex, Figure 1. Only recently, has this chemistry been taken up as a possible chemoselective approach to form peptide linkages,^{22,23,24} and neoglycoconjugates.²⁵ Our lab has reported that a β -glycosyl amide could be formed from the reaction between 2,4-dinitrobenzenesulfonyl β -N-glycosides and thioacids.²⁶ During the course of the study we found it notable that the reaction was fast and no alpha anomer was isolated. Herein we explore the scope of that reaction by examining several additional sugar congeners.

RESULTS AND DISCUSSION

We chose four monosaccharides D-glucose, D-galactose, D-mannose, D-arabinose, and a disaccharide D-maltose as a representative set of saccharides to explore the scope of the reaction between 2,4-dinitrobenzenesulfonyl β -N-glycosides and thioacids. Initially we began by selecting D-glucose and D-galactose and converting each into the corresponding β -glycosyl azide **1** and **2**, respectively.²⁷ Reduction of glycosyl azides was accomplished using Adams' catalyst to generate the respective glycosylamines. As free glycosylamines are prone to anomerization, the reduced glycosylamine was immediately subjected to sulfonation with dNBS-Cl in pyridine. The resulting per-*O*-acetylated- β -glycosyl-2,4-dinitrobenzenesulfonamides **3** and **4** were formed in 24–30 % yield, Table 1. Disappointed by the low yields, we attempted to modify the conditions to improve the yield, Table 2. Pd/C-H₂ in methanol and PtO₂-H₂ in either ethanol or ethyl acetate were used for the initial reduction steps. Solvents were kept anhydrous and there appeared to be no difference in the quality or dryness of the intermediate glycosylamine. The concentration of base pyridine was varied between neat solvent and 2.0 and 4.0 equivalents since we were concerned that high concentrations of base may lead to a competing deprotection reaction. The dNBS-Cl reagent was also varied between 1.5–2.5 equivalents and the use of catalytic DMAP was explored. No noticeable improvement in yield was achieved. Mass spectral analysis of the glycosylsulfonamide reaction mixtures suggested liability of acetyl groups under reaction conditions. ESI-MS showed m/z = 600.08 M+Na, 558, 516, 474 and 423 indicating a progressive loss of acetyl groups with intermediates appearing as sodium adducts. The apparent sensitivity of the acetyl group led us to examine other potential routes to access the glycosyl sulfonamides.

Various strategies to access the glycosylsulfonamides **3** and **4** were explored. Initially the dNBS-Cl was converted to 2,4-dinitrobenzenesulfonamide (**5**) in 78% yield by reacting with ammonium carbonate in a mixture of acetone-water (1:1), Scheme 2. We then prepared the 4-methylphenyl 2,3,4,6-tetra-*O*-acetyl- β -D-thioglucopyranoside (**7**) from α/β -D-glucose pentaacetate (**6**) and *p*-thiocresol in the presence of BF₃.OEt₂.^{28,29} We then attempted to glycosylate the sulfonamide **5** with thioglycoside **7** in the presence of 2,4,6-tri-*tert*-butylpyridine (TTBP), *N*-iodosuccinimide (NIS), and trimethylsilyl trifluoromethanesulfonate (TMSOTf).³⁰ To our surprise, this reaction failed. We attribute the lack of reactivity to the electron deficient sulfonamide **5** which is possibly a very poor nucleophile. We then converted pentaacetate **6** to 2,3,4,6-tetra-*O*-acetyl- α -D-glucopyranosyl

bromide (**8**), followed by reacting **8** with **5** in presence of Cs_2CO_3 to produce compound **3**. Cs_2CO_3 was deemed a sufficiently strong base, since the pK_a of the acidic sulfonamide NH was estimated to be 8.2 using Chemaxon software. Again no desired product was obtained. Peracetate **6** was directly reacted with **5** in presence of $\text{BF}_3 \cdot \text{OEt}_2$, in this case trace product was obtained according to mass spectral analysis of the crude reaction mixture; however, the yield was not synthetically useful. The various attempts were summarized in Scheme 1. We also accessed the known glucosylamine and treated it with the dNBS-Cl to access the sulfonamide free of protecting groups. The polar compound was difficult to handle and purify. Acetylation of this intermediate with acetic anhydride in pyridine resulted in an isolable pentaacetate which contained an N-acetyl group on the sulfonamide nitrogen (data not shown). It is possible that acylation using less basic conditions could yield a more direct route to our desired target.

At this point a less direct approach to access the glycosyl sulfonamides was considered. Benzoate protecting groups are reported to be less readily hydrolyzed in comparison to acetates, and the tendency for benzoate migration, in contrast to acetates, is not nearly as strong. Therefore, the β -glycosyl azides **1** and **2** were converted to their benzoyl protected congeners **12** and **13**, respectively (Table 3). These compounds were further subjected to reduction to the free amine using Adams' catalyst to produce intermediate glycosylamines followed by sulfonation reaction with dNBS-Cl. The desired β -glycosylsulfonamides **17** and **18**, were obtained in 44% and 48% yield, respectively. While these yields are still modest, they represented as significant improvement over the yields obtained from the acetate protected sugars. We had also considered that the improved yield may be a result of increased nucleophilicity of the anomeric amine when benzoates are present. However, the benzoyl group should be more withdrawing owing to the sp^2 centers of the phenyl ring. Supporting this notion is experimental evidence in the form of relative reactivity data comparing per-acetyl and per-benzoyl thioglucosides in model glycosylation reactions.³¹ The data reveals per-benzoyl as slightly more deactivating than per-acetyl. In addition, pK_a studies comparing per-acetylated and per-benzoylated 1-deoxynojirimycin derivatives show the benzoyl congener (pK_a 3.4) to be slightly more electron withdrawing than the acetate (pK_a 3.5).³² With this data in hand the 2,3,4,6-tetra-*O*-acetyl- β -D-mannopyranosyl azide (**9**), 2,3,4-tetra-*O*-acetyl- β -D-arabinopyranosyl azide (**10**), 2,3,6,2',3',6'-hepta-*O*-acetyl- β -maltosyl azide (**11**), were prepared using known procedures and converted to the corresponding benzyl-protected glycosyl azides **14**, **15**, and **16** in very good yields, Table 3.

With a representative series of β -glycosyl azides, we envisioned converting each to the corresponding β -glycosyl sulfonamide. These sulfonamides would then be combined with a thioacid and the yield, reaction time, and propensity for anomerization determined. The overall reaction sequence is shown in Scheme 2. Thus, β -glycosyl azides **14**, **15** and **16** were treated with $\text{PtO}_2\text{-H}_2$ to form the corresponding glycosylamines followed by treatment with dNBS-Cl in pyridine with catalytic DMAP to form the sulfonamides **19**, **20** and **21**, respectively, in 43–45% yield, Table 4. β -Glycosyl sulfonamides **17–21** reacted smoothly with thioacetic acid in presence of Cs_2CO_3 to generate β -glucosyl amides **22–26**, respectively, in 67–81% yield. Reactions were complete in 20–30 minutes, Table 5, and the β -anomers appeared to be the exclusive products. Coupling constants for the $^3J_{\text{H-1,H-2}}$ and $^3J_{\text{H-1,NH}}$ for **23–26** were in the range of 9.0–9.6 Hz with the H-1 signals all appearing as an apparent triplets. The coupling constants for $^3J_{\text{H-1,H-2}}$ and $^3J_{\text{H-1,NH}}$ in the known β -glycosyl amides, such as 1-acetamido-1-deoxy-2,3,4,6-tetraacetyl- β -D-glucose, are also in the range of 9.0 Hz with H-1 appearing as an apparent triplet.³³ On the other hand, the coupling pattern of H-1 in α -glycosyl amides usually appears as a doublet of doublets in compounds with H-2 in the axial position.³⁴

In conclusion, we have shown that a variety β -glycosyl-2,4-dinitrobenzenesulfonamides could be accessed in moderate yields from the benzoyl-protected β -glycosyl azides. Some mutarotation of the glycosylamine during the conversion from per-*O*-acetylated glycosyl azides compounds to glycosyl-2,4-dinitrobenzenesulfonamides, (~5 – 10%) was usually observed. While considerable effort was required to manipulate the starting sugars into the β -glycosyl-sulfonamides, it is likely that more direct routes to these intermediates can be developed which would improve their utility of the strategy. The electron deficient sulfonamides reacted with thioacetic acid, rapidly, in good yield, and in high stereoselectively. Furthermore, it likely the β -glycosyl-2,4-dinitrobenzenesulfonamides behave similarly to *N*-alkyl 2,4-dinitrobenzenesulfonamides which suggest they could be used to access secondary glycosyl- amides, thioamides, ureas, thioureas, an potentially even guanidinium derivatives. Examples of these reactions would further expanding the usefulness of glycosyl-2,4-dinitrobenzenesulfonamides.

EXPERIMENTAL

General methods

The starting sugars D-glucose, D-galactose, D-mannose, D-arabinose, D-maltose and other fine chemicals were purchased from Acros Organics. Boron trifluoride diethyl etherate was from Sigma–Aldrich. The chemicals were used without further purification. All solvents were obtained from Fisher Scientific Co. Dichloromethane, which was dried and distilled following the standard procedures while pyridine, dimethyl sulfoxide, and dimethylformamide were stored over 4 Å molecular sieves. Silica (230–400 mesh) for flash column chromatography was obtained from Sorbent Technologies; precoated plates for thin-layer chromatography (TLC) were from E. Merck. TLCs (Silica Gel 60, F₂₅₄) were visualized under UV light, by charring (5% H₂SO₄–MeOH), or by use of a ninhydrin solution. Flash column chromatography was performed on silica gel (230–400 mesh) using solvents as received. ¹H NMR spectra were recorded either on a Varian VXR 400 MHz or an INOVA 600 MHz spectrometer in CDCl₃ using residual CHCl₃ as an internal reference. ¹³C NMR spectra were recorded at 100 MHz or 150 in CDCl₃ using the triplet centered at δ 77.0. ¹H-¹H gCOSY was performed on a 600 MHz spectrometer. High-resolution mass spectrometry (HRMS) was performed on a ESI-TOF mass spectrometer for *m/z* < 1000 for *m/z* > 1000 MALDI-TOF data was obtained .

General Procedures

Synthesis of 2,3,4,6-tetra-*O*-benzoyl- β -D-glucopyranosyl azide (12), 2,3,4,6-tetra-*O*-benzoyl- β -D-galactopyranosyl azide (13), 2,3,4,6-tetra-*O*-benzoyl- β -D-mannopyranosyl azide (14), 2,3,4-tri-*O*-benzoyl- β -D-arabinopyranosyl azide (15), and 2,3,6,2',3',6'-hepta-*O*-benzyl- β -maltosyl azide (16)—The starting materials 2,3,4,6-tetra-*O*-acetyl- β -D-glucosyl azide,²⁷ 2,3,4,6-tetra-*O*-acetyl- β -D-galactopyranosyl azide,²⁷ 2,3,4-tri-*O*-acetyl- β -D-arabinopyranosyl azide²⁷ and 2,3,6,2',3',6'-hepta-*O*-acetyl- β -maltosyl azide²⁷ were all prepared from a known literature procedure. The 2,3,4,6-tetra-*O*-acetyl- β -D-mannopyranosyl azide could not be prepared, in our hands using ref 27, however, we could access the know compound starting from the glycosyl chloride followed by displacement with tetrabutylammonium azide.³⁵ Once in hand, 2.0 g the respective per-*O*-acetylated- β -glycosyl azides was dissolved in 15 mL anhydrous methanol in a round bottom flask and stirred until complete dissolution under nitrogen atmosphere. A catalytic amount of sodium metal (ca. 25 mg) was added to the flask and the solution allowed to stir for about 1.0 h. The completion of reaction was monitored using TLC. On completion the solution was neutralized with Amberlite IR 120 H resin. The resin was filtered and rinsed with additional methanol followed by concentration of the filtrate to dryness on a rotary evaporator under reduced pressure. The products were dried under high

vacuum and used in the next step without further purification. The polyols were dissolved in 10 mL of anhydrous pyridine under N₂ atmosphere, and cooled to 0 °C. Benzoyl chloride (1.5 equiv. per -OH) was added dropwise to the stirred solution. After addition of benzoyl chloride was complete the reaction mixtures were brought to room temperature and stirred for a time respective to each compound, Table 3. Completion of the reactions was monitored by TLC. After completion 2–3 mL methanol was added to quench residual benzoyl chloride. The solutions were diluted with toluene, evaporated to dryness and purified by flash column chromatography on silica gel using 20% ethyl acetate in toluene as an eluent. The 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl azide (**12**),^{36,37} 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl azide (**13**),³⁸ and 2,3,4,6-tetra-*O*-benzoyl-β-D-mannopyranosyl azide (**14**)³⁷ are reported.

Synthesis of *N*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-2,4-dinitrobenzenesulfonamide (17), *N*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-2,4-dinitrobenzenesulfonamide (18), *N*-(2,3,4,6-tetra-*O*-benzoyl-β-D-mannopyranosyl)-2,4-dinitrobenzenesulfonamide (19), *N*-(2,3,4-tetra-*O*-benzoyl-β-D-arabinopyranosyl)-2,4-dinitrobenzenesulfonamide (20), and *N*-(2,3,6,2',3',6'-hepta-*O*-benzyl-β-maltosyl)-2,4-dinitrobenzenesulfonamide (21)—1.5 g of Per-*O*-benzoylated-β-glycosyl azide was dissolved in 10 mL of anhydrous ethyl acetate and transferred to a reaction flask containing platinum oxide (0.17 equiv). The solution was placed under 1 atm of H₂ atmosphere and allowed to stir according to the respective times shown in Table 4. Completion of the reaction was monitored by TLC. The reaction was worked up by filtering through a bed of Celite® 545 in a sintered glass funnel. The filtrate was concentrated by rotatory evaporation under reduced pressure. The concentrated glycosyl amines were used in the sulfonation without further purification. Crude per-*O*-benzoylated-β-glycosylamine was dissolved in 15 mL of anhydrous pyridine with a catalytic amount of DMAP under an N₂ atmosphere. 2,4-Dinitrobenzenesulfonyl chloride (1.5 equiv.) was added to the solution and the reaction was allowed to stir for the respective time as shown in Table 4. Completion of the reaction was monitored with TLC. The reaction was worked up by diluting with 50 mL of ice cold water and followed by extraction with 3 × 50 mL-portions of ethyl acetate. The organic layers were combined and washed successively with saturated NaHCO₃ and brine. It was dried over anhydrous Na₂SO₄. The solution was concentrated by rotatory evaporation under reduced pressure. These products were purified by flash column chromatography using silica gel using 25% acetone in hexanes as an eluent.

Synthesis of *N*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl) acetamide (22), *N*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl) acetamide (23), *N*-(2,3,4,6-tetra-*O*-benzoyl-β-D-mannopyranosyl) acetamide (24), *N*-(2,3,4-tetra-*O*-benzoyl-β-D-arabinopyranosyl) acetamide (25), and *N*-(2,3,6,2',3',6'-hepta-*O*-benzyl-β-maltosyl) acetamide (26)—To a suspension of cesium carbonate (2 equiv.) in 10 mL of anhydrous was added thioacetic acid (2 equiv.). The mixture was stirred for 10 min at room temperature under N₂ atmosphere before addition of 300 mg of *N*-glycosyl 2,4-dinitrobenzenesulfonamide. The resulting solution was further stirred for the time given in Table 5, respectively. Completion of the reaction was monitored by TLC. After completion, the reaction was worked up by diluting with EtOAc and washing the organic layer with saturated aqueous NH₄Cl followed by brine. The organic layer was dried over anhydrous Na₂SO₄, and concentrated under reduced pressure by rotatory evaporator. The product was purified by flash column chromatography on silica gel using 30% acetone in hexanes as an eluent. The physical data for *N*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl) acetamide (**22**) matches the previously reported data.¹⁵

Spectral data

^1H NMR and ^{13}C NMR spectra for known compounds that matched the data reported in the cited references. Data for new compounds is reported below.

2,3,4-tetra-O-benzoyl- β -D-arabinopyranosyl azide (15)—Colorless solid. ^1H NMR (600 MHz, CDCl_3): δ 8.14 - 7.27 (m, 15H, aromatic), 5.74 (m, 1H, H-4), 5.72 (s, 1H, H-3), 5.64 (dd, 1H, $J=3.6\text{ Hz}$, 9.6 Hz, H-2), 4.97 (d, 1H, $J=6.0\text{ Hz}$, H-1), 4.42 (dd, 1H, $J=3.0\text{ Hz}$, 13.2 Hz, H-5), 4.03 (d, 1H, $J=13.2\text{ Hz}$, H-5'). ^{13}C NMR (100 MHz, CDCl_3): δ 165.7 - 165.38 (3C, carbonyl), 133.9 - 128.61 (18C, aromatic), 88.28 (1C, C-1), 70.9 - 65.59 (4C, ring carbon). HRMS: m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{26}\text{H}_{21}\text{N}_3\text{O}_7\text{Na}$ is 510.1277, found 510.1290.

2,3,6,2',3',6'-hepta-O-benzyl- β -maltosyl azide (16)—Colorless solid. ^1H NMR (600 MHz, CDCl_3): δ 8.11 - 7.16 (m, 35H, aromatic), 6.08 (t, 1H, $J=9.9\text{ Hz}$, H-3'), 5.78 (t, 1H, $J=9.3\text{ Hz}$, H-3), 5.75 (d, 1H, $J=4.2\text{ Hz}$, H-1'), 5.66 (t, 1H, $J=9.9\text{ Hz}$, H-4'), 5.27 (dd, 1H, $J=8.7\text{ Hz}$, 9.3 Hz, H-2), 5.24 (dd, 1H, $J=3.9\text{ Hz}$, 10.5 Hz, H-2'), 4.94 (dd, 1H, $J=2.1\text{ Hz}$, 12.3 Hz, H-6_b), 4.91 (d, 1H, $J=8.4\text{ Hz}$, H-1), 4.77 (dd, 1H, $J=3.9\text{ Hz}$, 12.3 Hz, H-6_a), 4.51 (t, 1H, $J=9.3\text{ Hz}$, H-4), 4.45 (m, 1H, H-5'), 4.40 (dd, 1H, $J=3.0\text{ Hz}$, 12.0 Hz, H-6' _a), 4.27 (dd, 1H, $J=3.6\text{ Hz}$, 12.0 Hz, H-6' _b), 4.18 (m, 1H, H-5). ^{13}C NMR (100 MHz, CDCl_3): δ 166.31 - 165.09 (7C, carbonyl), 133.75 - 125.48 (42C, aromatic), 96.67 (1C, C-1'), 88.06 (1C, C-1), 75.15 - 62.65 (10C, ring carbon). MALDI: m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{61}\text{H}_{49}\text{N}_3\text{O}_{17}$ is 1095.31, found 1118.341.

N-(2,3,4,6-tetra-O-benzoyl- β -D-glucopyranosyl)-2,4-dinitrobenzenesulfonamide (17)—Yellow solid. ^1H NMR (600 MHz, CDCl_3): δ 8.40 - 7.23 (m, 23H, aromatic), 6.02 (t, 1H, $J=9.6\text{ Hz}$, H-3), 5.64 (t, 1H, $J=9.9\text{ Hz}$, H-4), 5.46 (t, 1H, $J=9.3\text{ Hz}$, H-2), 5.29 (d, 1H, $J=9.0\text{ Hz}$, H-1), 4.48 (d, 1H, $J=9.6\text{ Hz}$, H-6'), 4.23 - 4.19 (m, 2H, H-5, H-6). ^{13}C NMR (100 MHz, CDCl_3): δ 166.23 - 165.21 (4C, carbonyl), 149.76 - 120.81 (30C, aromatic), 83.81 (1C, C-1), 74.24 - 62.10 (5C, ring carbon). HRMS: m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{40}\text{H}_{31}\text{N}_3\text{O}_{15}\text{SNa}$ is 848.1374, found 848.1343.

N-(2,3,4,6-tetra-O-benzoyl- β -D-galactopyranosyl)-2,4-dinitrobenzenesulfonamide (18)—Yellow solid. ^1H NMR (600 MHz, CDCl_3): δ 8.38 - 7.21 (m, 23H, aromatic), 6.89 (d, 1H, $J=9.6\text{ Hz}$, NH), 6.00 (d, 1H, $J=3.6\text{ Hz}$, H-4), 5.79 (dd, 1H, $J=3.0\text{ Hz}$, 10.2 Hz, H-3), 5.72 (t, 1H, $J=9.6\text{ Hz}$, H-2), 5.27 (d, 1H, $J=9.0\text{ Hz}$, H-1), 4.46 (m, 1H, H-5), 4.28 (dd, 1H, $J=2.7\text{ Hz}$, 9.3 Hz, H-6), 4.12 (dd, 1H, $J=7.2\text{ Hz}$, 14.4 Hz, H-6'). ^{13}C NMR (100 MHz, CDCl_3): δ 166.22 - 165.48 (4C, carbonyl), 149.60 - 120.77 (30C, aromatic), 84.03 (1C, C-1), 73.63 - 60.62 (5C, ring carbon). HRMS: m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{40}\text{H}_{31}\text{N}_3\text{O}_{15}\text{SNa}$ is 848.1374, found 848.1349.

N-(2,3,4,6-tetra-O-benzoyl- β -D-mannopyranosyl)-2,4-dinitrobenzenesulfonamide (19)—Yellow solid. ^1H NMR (600 MHz, CDCl_3): δ 8.57 - 7.27 (m, 23H, aromatic), 6.85 (d, 1H, $J=9.6\text{ Hz}$, NH), 5.98 (s, 1H, H-2), 5.94 (t, 1H, $J=10.2\text{ Hz}$, H-4), 5.67 (t, 1H, $J=10.2\text{ Hz}$, H-3), 5.53 (d, 1H, $J=10.2\text{ Hz}$, H-1), 4.43 (d, 1H, $J=12.0\text{ Hz}$, H-6), 4.08 (d, 1H, $J=8.4\text{ Hz}$, H-5), 3.99 (d, 1H, $J=11.4\text{ Hz}$, H-6'). ^{13}C NMR (100 MHz, CDCl_3): δ 165.57 - 165.31 (4C, carbonyl), 150.13 - 121.28 (30C, aromatic), 81.46 (1C, C-1), 74.10 - 61.21 (5C, ring carbon). HRMS: m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{40}\text{H}_{31}\text{N}_3\text{O}_{15}\text{SNa}$ is 848.1374, found 848.1364.

N-(2,3,4-tetra-O-benzoyl- β -D-arabinopyranosyl)-2,4-dinitrobenzenesulfonamide (20)—Pale yellow solid. ^1H NMR (600 MHz, CDCl_3): δ 8.40 - 7.25 (m, 18H, aromatic), 6.98 (s, 1H, NH), 5.72 (s, 1H, H-3), 5.71 (s, 1H, H-2), 5.68 (s, 1H, H-4), 5.10 (d, 1H, $J=6.6\text{ Hz}$, H-1), 4.18 (d, 1H, $J=13.8\text{ Hz}$, H-5), 3.95 (d, 1H, $J=13.8\text{ Hz}$, H-5'). ^{13}C NMR (100 MHz,

CDCl₃): δ 165.9 - 165.54 (3C, carbonyl), 149.7 - 120.85 (24C, aromatic), 84.34 (1C, C-1), 71.02 - 66.34 (4C, ring carbon). HRMS: m/z [M+Na]⁺ calcd for C₃₂H₂₅N₃O₁₃SNa is 714.1006, found 714.1006.

***N*-(2,3,6,2',3',6'-hepta-*O*-benzyl- β -maltosyl)-2,4-dinitrobenzenesulfonamide (21)**

—Yellow solid. ¹H NMR (600 MHz, CDCl₃): δ 8.37 - 7.17 (m, 38H, aromatic), 6.85 (s, 1H, NH), 6.06 (t, 1H, J = 10.2 Hz, H-3'), 5.86 (t, 1H, J = 9.3 Hz, H-3), 5.76 (d, 1H, J = 3.6 Hz, H-1'), 5.65 (t, 1H, J = 9.9 Hz, H-4'), 5.24 (d, 1H, J = 3.6 Hz, H-2'), 5.23 (d, 1H, J = 4.2 Hz, H-2), 5.19 (d, 1H, J = 6.6 Hz, H-1), 4.71 (d, 1H, J = 10.8 Hz, H-6_a), 4.49 (dd, 1H, J = 3.3 Hz, 12.3 Hz, H-6_b), 4.45 (dd, 1H, J = 3.0 Hz, 12.0 Hz, H-6'_b), 4.39 (m, 2H, H-5', H-4), 4.27 (dd, 1H, J = 3.6 Hz, 12.0 Hz, H-6'_a), 4.07 (m, 1H, H-5). ¹³C NMR (100 MHz, CDCl₃): δ 166.29 - 164.97 (7C, carbonyl), 149.77 - 120.82 (48C, aromatic), 96.76 (1C, C-1'), 83.43 (1C, C-1), 74.89 - 62.34 (10C, ring carbons). MALDI: m/z [M+Na]⁺ calcd for C₆₇H₅₃N₃O₂₃S is 1299.28, found 1322.237.

***N*-(2,3,4,6-tetra-*O*-benzoyl- β -D-galactopyranosyl) acetamide (23)**—Pale yellow

solid. ¹H NMR (600 MHz, CDCl₃): δ 8.08 - 7.23 (m, 20H, aromatic), 6.65 (d, 1H, J = 8.4 Hz, NH), 6.05 (m, 1H, H-4), 5.81 (dd, 1H, J = 3.3 Hz, 9.9 Hz, H-3), 5.65 (t, 1H, J = 9.9 Hz, H-2), 5.60 (t, 1H, J = 9.0 Hz, H-1), 4.63 (dd, 1H, J = 6.6 Hz, 10.8 Hz, H-6), 4.48 (t, 1H, J = 13.2 Hz, H-5), 4.39 (dd, 1H, J = 6.9 Hz, 11.1 Hz, H-6'), 1.99 (s, 1H, -CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 170.59 (1C, amide carbonyl), 167.26 - 165.54 (4C, carbonyl), 134.10 - 128.50 (m, 24C, aromatic), 79.09 (1C, C-1), 73.12 - 62.07 (5C, ring carbon), 23.64 (1C, -CH₃). HRMS: m/z [M+Na]⁺ calcd for C₃₆H₃₁NO₁₀Na is 660.1846, found 660.1862.

***N*-(2,3,4,6-tetra-*O*-benzoyl- β -D-mannopyranosyl) acetamide (24)**—Pale yellow

solid. ¹H NMR (600 MHz, CDCl₃): δ 8.14 - 7.24 (m, 20H, aromatic), 6.42 (d, 1H, J = 9.6 Hz, NH), 6.08 (t, 1H, J = 10.2 Hz, H-4), 5.86 (d, 1H, J = 9.6 Hz, H-1), 5.85 (d, 1H, J = 2.4 Hz, H-2), 5.68 (dd, 1H, J = 3.0 Hz, 10.2 Hz, H-3), 4.72 (dd, 1H, J = 2.1 Hz, 12.3 Hz, H-6'), 4.47 (dd, 1H, J = 3.9 Hz, 12.3 Hz, H-6), 4.26 (m, 1H, H-5), 1.99 (s, 1H, -CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 169.59 (1C, amide carbonyl), 166.27 - 165.46 (4C, carbonyl), 134.11 - 128.49 (m, 24C, aromatic), 76.59 (1C, C-1), 74.28 - 62.86 (5C, ring carbon), 23.54 (1C, -CH₃). HRMS: m/z [M+Na]⁺ calcd for C₃₆H₃₁NO₁₀Na is 660.1846, found 660.1829.

***N*-(2,3,4-tetra-*O*-benzoyl- β -D-arabinopyranosyl) acetamide (25)**—Pale yellow

solid. ¹H NMR (600 MHz, CDCl₃): δ 8.09 - 7.26 (m, 15H, aromatic), 6.75 (d, 1H, J = 9.6 Hz, NH), 5.77 (d, 1H, J = 3.6 Hz, H-3), 5.75 (s, 1H, H-4), 5.68 (t, 1H, J = 9.3 Hz, H-2), 5.47 (t, 1H, J = 9.0 Hz, H-1), 4.27 (d, 1H, J = 13.2 Hz, H-5_{equatorial}), 4.05 (d, 1H, J = 13.8 Hz, H-5_{axial}), 1.98 (s, 1H, -CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 170.76 (1C, amide carbonyl), 167.2 - 165.5 (3C, carbonyl), 134.01 - 128.51 (18C, aromatic), 79.38 (1C, C-1), 71.5 - 66.4 (4C, ring carbon), 23.7 (1C, -CH₃). HRMS: m/z [M+Na]⁺ calcd for C₂₈H₂₅NO₈Na is 526.1478, found 526.1495.

***N*-(2,3,6,2',3',6'-hepta-*O*-benzyl- β -maltosyl) acetamide (26)**—Yellow solid. ¹H

NMR (600 MHz, CDCl₃): δ 8.10 - 7.18 (m, 35H, aromatic), 6.49 (d, 1H, J = 9.0 Hz, NH), 6.07 (t, 1H, J = 10.2 Hz, H-3'), 5.91 (t, 1H, J = 9.3 Hz, H-3), 5.75 (d, 1H, J = 3.0 Hz, H-1'), 5.66 (t, 1H, J = 9.6 Hz, H-4'), 5.52 (t, 1H, J = 9.3 Hz, H-1), 5.25 (dd, 1H, J = 3.0 Hz, 10.2 Hz, H-2'), 5.18 (t, 1H, J = 9.6 Hz, H-2), 4.88 (d, 1H, J = 12.0 Hz, H-6_a), 4.75 (d, 1H, J = 9.6 Hz, H-6_b), 4.50 (t, 1H, J = 9.3 Hz, H-4), 4.38 (m, 2H, H-5', H-6'_b), 4.20 (m, 2H, H-5, H-6'_a). ¹³C NMR (100 MHz, CDCl₃): δ 170.54 - 164.95 (7C, carbonyl), 133.96 - 128.23 (42C, aromatic), 96.51 (1C, C-1'), 78.48 (1C, C-1), 75.09 - 62.53 (10C, ring carbon). MALDI: m/z [M+Na]⁺ calcd for C₆₃H₅₃NO₁₈ is 1111.33, found 1134.305.

Acknowledgments

This work was supported in part by a grant to SJS by the National Institutes of Health (GM094734).

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Figure 1.
Mechanism of amide formation.

Scheme 1.

a. Synthesis of 2,4-dinitrobenzenesulfonamide (**5**), b. Alternative route explored to access glycosyl sulfonamide **3**.

Scheme 2.

^a Synthetic route to access β -glycosyl amides from per-*O*-acetylated β -D- glucosyl, galactosyl, arabinosyl, mannosyl, and maltosyl azide.

^aReagents and conditions: a. NaOMe, 1 h, rt.; b. BzCl, pyridine, 12 – 14 h, 0°C - rt., (87 – 93% over 2-steps), c. PtO₂, H₂, EtOAc, 1.5 h, rt.; d. dNBS-Cl, pyridine, DMAP (cat.), 30 – 60 mins, rt., (43 – 48% over 2-steps); e. Thioacetic acid, Cs₂CO₃, DMF, 20 – 30 mins, rt., (67 – 81%).

Table 1

Preparation of *N*-2,4-Dinitrobenzenesulfonamide from Glycosyl Azides via Glycosylamines

Azides	<i>N</i> -dNBS glycosides	Yield
<p>1</p>	<p>3</p>	24%
<p>2</p>	<p>4</p>	27-30%

Table 2
Conditions for Reduction/Sulfonation of Per-*O*-acetylated Glycosyl Azide **1** and **2**

Entry	Compound	Reagents	Solvent	Temperature	Time	Yield ^a
a	1	Pd/C, H ₂	MeOH	rt	40 mins	24%
		dNBS-Cl, (1.5 eq.), N ₂	Pyridine	rt	3.0 h	
b	1	PtO ₂ , H ₂	EtOH	rt	2 h	25%
		dNBS-Cl (1.5 eq.), N ₂	Pyridine	0°C - rt	3.5 h	
c	1	PtO ₂ , H ₂	EtOH	rt	1.5 h	27%
		dNBS-Cl (1.5 eq.), N ₂ , DMAP (cat.)	Pyridine (2.0 eq.), CH ₂ Cl	0°C - rt	2.5 h	
d	1	PtO ₂ , H ₂	EtOAc	rt	1.5	24%
		dNBS-Cl (2.5 eq.), N ₂	Pyridine (4.0 eq.), CH ₂ Cl	0°C - rt	3.0 h	
e	2	Pd/C, H ₂	MeOH	rt	30 mins	24%
		dNBS-Cl (1.5 eq.), N ₂	Pyridine	rt	3.5 h	
f	2	PtO ₂ , H ₂	EtOH	rt	1.5 h	30%
		dNBS-Cl (1.5 eq.), N ₂	Pyridine	0°C - rt	3.5 h	
g	2	PtO ₂ , H ₂	EtOH	rt	1.5 h	26%
		dNBS-Cl (1.5 eq.), N ₂ , DMAP (cat.)	Pyridine (4.0 eq.), CH ₂ Cl	0°C - rt	3.0 h	
h	2	PtO ₂ , H ₂	EtOAc	rt	1.5 h	28%
		dNBS-Cl (2.5 eq.), N ₂	Pyridine	0°C - rt	2.5 h	

^aCombined yields over 2-step reaction.

Table 3Synthesis of per-*O*-Benzoylated Glycosyl Azides from Per-*O*-acetylated Glycosyl Azides

$\text{AcO} \begin{array}{c} \diagup \text{O} \diagdown \\ \text{N}_3 \end{array} \xrightarrow[2. \text{BzCl, Py, 0}^\circ\text{C} - \text{rt}]{1. \text{NaOMe, MeOH, rt}} \text{BzO} \begin{array}{c} \diagup \text{O} \diagdown \\ \text{N}_3 \end{array}$			
Peracetate	Perbenzoate	Time in h (Step)	Yield
1		(1) 1.5 (2) 14.5	(1) 98% (2) 93%
2		(1) 1.5 (2) 14.0	(1) 98% (2) 92%
(1) 1.0 (2) 15.0	(1) 100% (2) 89%
(1) 1.0 (2) 14.0	(1) 100% (2) 92%
(1) 1.5 (2) 14.5	(1) 98% (2) 87%

Table 4Formation of *N*-dNBS Glycoside from Per-*O*-benzoylated Glycosyl Azide

Perbenzoate	<i>N</i> -dNBS glycoside	Time in h (Step)	Yield
12		(1) 1.5 (2) 1.0	(1) 98% (2) 44%
13		(1) 1.5 (2) 1.0	(1) 98% (2) 48%
14		(1) 2.0 (2) 0.75	(1) 100% (2) 45%
15		(1) 1.0 (2) 0.5	(1) 97% (2) 45%
16		(1) 1.5 (2) 1.5	(1) 98% (2) 43%

Table 5Formation of Per-*O*-benzoylated Glycosylamides from Per-*O*-benzoylated Glycosyl Sulfonamide

<i>N</i> -dNBS glycoside	<i>N</i> -glycosylamide	Yield
17	<p style="text-align: center;">22</p>	67%
18	<p style="text-align: center;">23</p>	68%
19	<p style="text-align: center;">24</p>	81%
20	<p style="text-align: center;">25</p>	73%
21	<p style="text-align: center;">26</p>	67%