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Synthesis of *S*-Glycosyl Primary Sulfonamides

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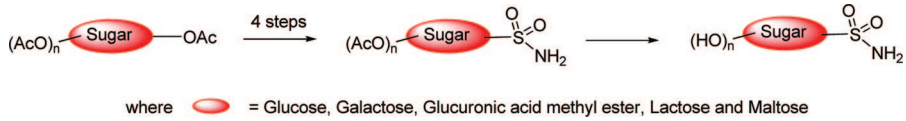


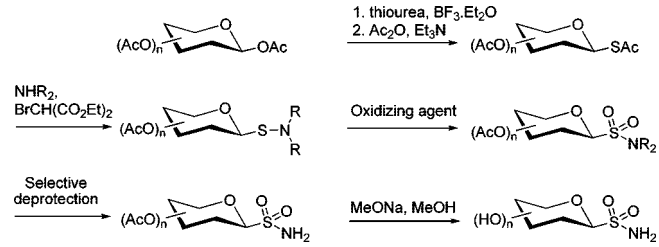
The synthesis of *S*-glycosyl sulfonamides wherein the primary sulfonamide functional group ($-SO_2NH_2$) is directly attached to the anomeric position of a carbohydrate moiety is reported. Our general approach consists of first introducing a thioacetate group at the anomeric center of a per-*O*-acetylated sugar derivative. From this follows formation of a glycosyl sulfenamide (sugar-SNR_2), oxidation of the sulfenamide to give a glycosyl N-protected sulfonamide (sugar-SO_2NR_2), and removal of the sulfonamide protecting (R) group to yield a primary sulfonamide at the anomeric center (sugar-SO_2NH_2). A variety of mono- and disaccharide derivatives were synthesized using this new methodology.

Introduction

The sulfonamide group has been proven to have remarkable utility in medicinal chemistry and features in the structure of a number of clinically relevant small molecules.[1] Almost all therapeutically used sulfonamides are aromatic (Ar-SO_2NH_2 or Ar-SO_2NHR).[2] To our knowledge, there are no reports of the synthesis of *S*-glycosyl sulfonamides wherein the primary sulfonamide functional group is linked directly to the anomeric position of a carbohydrate.

The synthesis of primary sulfonamides is typically achieved by the reaction of a substituted sulfonyl chloride with excess ammonia. Anomeric sulfonyl chlorides, in principle, could serve as precursors to anomeric sulfonamides. Recently, Knapp and co-workers[3] attempted the synthesis of anomeric sulfonyl chlorides with this task in mind. All conditions evaluated in this study resulted instead in the formation of anomeric chlorides as product rather than the desired anomeric sulfonyl chloride. It was proposed that although the anomeric sulfonyl chloride was likely to have formed it proved unstable toward loss of SO_2, rapidly converting into the chloride. The lack of stability of precursor anomeric sulfonyl chlorides eliminates this synthetic methodology as an avenue to anomeric sulfonamides. We now present a relatively simple procedure for the preparation of *S*-glycosyl primary sulfonamides. We expect anomeric sulfonamides, as new chemical entities, will prove to be a valuable species to investigate biological interactions and other parameters relevant to drug discovery.

SCHEME 1. Proposed Strategy To Synthesize *S*-Glycosyl Sulfonamides[a]



[a] R = sulfonamide protecting group. This general strategy is illustrated for a monosaccharide but is proposed to apply to a range of carbohydrate substrates.

Results and Discussion

Glycosyl sulfenamides (sugar-SNR_2) have been prepared and oxidized to glycosyl *N*,*N*-disubstituted sulfonamides (sugar-SO_2NR_2) by others.[4] We reasoned that this methodology may be exploited to generate *S*-glycosyl primary sulfonamides (sugar-SO_2NH_2) if an appropriate sulfonamide protecting group (R) could be employed throughout the synthesis. Our general approach, outlined in Scheme 1, consists of first introducing a

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(2) (a) Anand, N. *Burger's Medicinal Chemistry and Drug Discovery*, 5th ed.; Wollf, M. E., Ed.; John Wiley & Sons: New York, 1996; Vol. 2, p 527. (b) Supuran, C. T. *Nat. Rev. Drug Discovery* **2008**, *7*, 168.

(3) Knapp, S.; Darout, E.; Amorelli, B. *J. Org. Chem.* **2006**, *71*, 1380.

(4) (a) Owen, D. J.; von Itzstein, M. *Carbohydr. Res.* **2000**, *328*, 287. (b) Owen, D. J.; Davis, C. B.; Hartnell, R. D.; Madge, P. D.; Thomson, R. J.; Chong, A. K. J.; Coppel, R. L.; von Itzstein, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2274.

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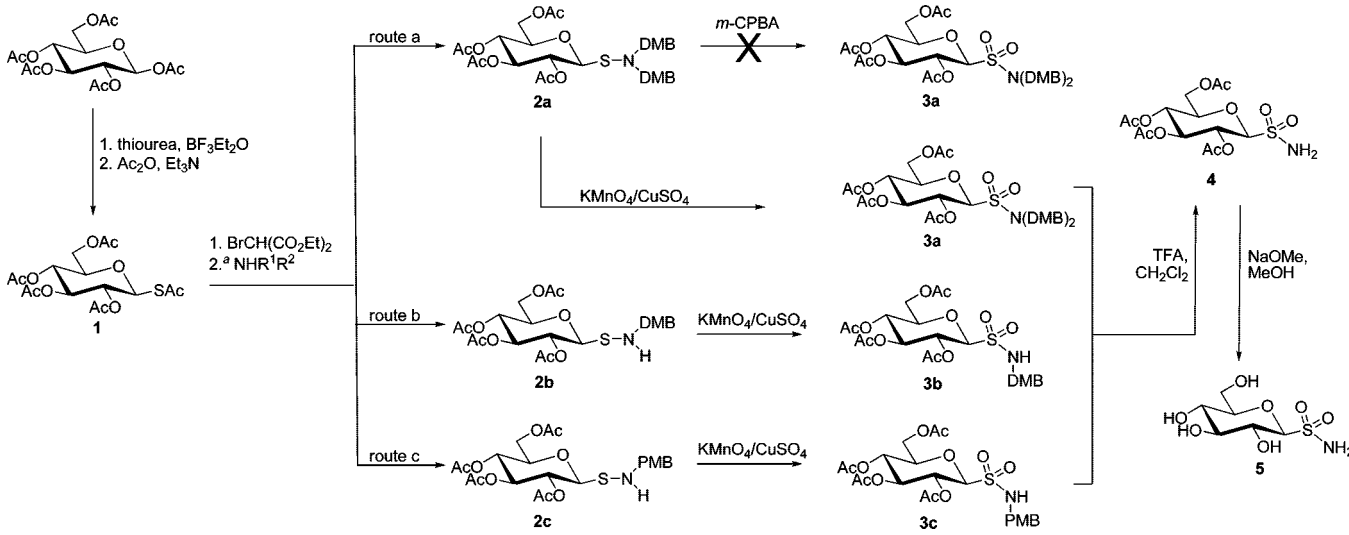
SCHEME 2. Synthesis of Sulfonamides 4 and 5 from Per-*O*-acetylated D-Glucose [a]



[a] Route a: $R^1 = R^2 =$ DMB. Route b: $R^1 =$ DMB, $R^2 =$ H. Route c: $R^1 =$ PMB, $R^2 =$ H.

thioacetate group at the anomeric center of the per-*O*-acetylated sugar derivative. From this follows formation of a glycosyl sulfenamide (sugar-SNR_2),[4a] oxidation of the sulfenamide to give a glycosyl N-protected sulfonamide (sugar-SO_2NR_2), and removal of the sulfonamide protecting (R) group to yield a primary sulfonamide at the anomeric center (sugar-SO_2NH_2). Thus the "R" protecting group must be readily introduced, be stable to oxidation conditions, and readily removed following oxidation so as to unmask the primary sulfonamide group. As a final step, the deprotection of the hydroxyls of the glycosyl moiety using standard Zemplen conditions[5] should give the fully deprotected target *S*-glycosyl sulfonamide.

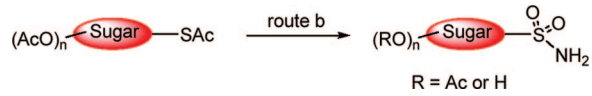
Given the prominence of the sulfonamide group in medicinal chemistry, there is a surprising paucity in the literature with regard to protecting group strategies for primary sulfonamides. A literature search revealed a small number of examples where the 2,4-dimethoxybenzyl (DMB) substituent had been employed as a protecting group for sulfonamides.[6] We commenced investigation of the DMB moiety as a protecting group with the synthesis of the *N*,*N*-$(DMB)_2$ glucosyl sulfenamide **2a**. Compound **2a** was prepared with high anomeric stereoselectivity from **1**, diethyl bromomalonate, and bis(2,4-dimethoxybenzyl)-amine as base (Scheme 2, route a).[4a] Oxidation of **2a** with *m*-CPBA led to a complex mixture of components, and we postulated that the byproduct (*m*-chlorobenzoic acid) of the reaction partially cleaves the acid-labile DMB groups.[7] Misra recently reported the rapid oxidation of thioglycosides to glycosyl sulfones using a combination of $KMnO_4$ and $CuSO_4 \cdot 5H_2O$ in acetonitrile and water.[8] These oxidative conditions are neutral, and Misra confirmed compatibility with several acid-labile hydroxyl protecting groups of sugar derivatives including benzylidene acetal, isopropylidene acetal, and TBDMS.[8] We were thus encouraged to investigate the capacity of this mild oxidative protocol to effect the oxidation of sulfenamide **2a** in the presence of our acid-labile protecting group. Gratifyingly, the oxidation proceeded smoothly, leading to the *N*,*N*-$(DMB)_2$-protected glucosyl sulfonamide **3a** (Scheme 2, route a). Next, the DMB groups of **3a** were removed using acidic conditions (10% TFA in CH_2Cl_2), and this reaction was complete after 2 h and delivered the target per-*O*-acetylated glucosyl sulfonamide **4**. Zemplen's conditions[5] were employed to remove the acetate groups of **4** to prepare the fully deprotected anomeric sulfonamide **5**. Sulfonamides **4** and **5** were spectroscopically characterized using 1D and 2D NMR (^1H, ^{13}C, gCOSY, gHSQC) and ESI HRMS. All characterization data were consistent with the target structures. A characteristic signal for the sulfonamide protons (SO_2NH_2) of **4** was observed at δ 5.01 ppm in $CDCl_3$ and δ 7.22 ppm in DMSO-d_6 and for **5** δ 6.69 ppm in DMSO-d_6.

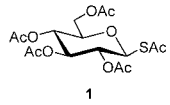
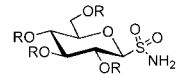
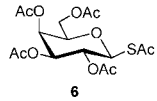
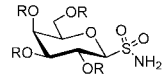
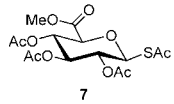
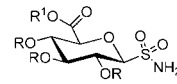
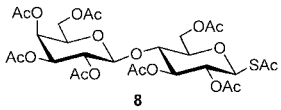
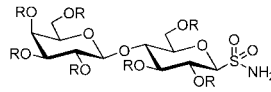
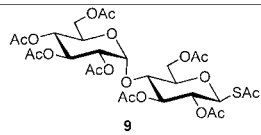
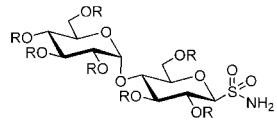
Although we had successfully synthesized the *S*-glucosyl primary sulfonamides **4** and **5**, we sought to further improve our synthesis. The *N*,*N*-$(DMB)_2$-protected compounds—sulfenamide **2a** and sulfonamide **3a**—proved highly sensitive on normal phase silica and were difficult to manipulate without substantial degradation during standard purification protocols. Even when the silica was preconditioned with 1% Et_3N, degradation occurred (including loss of the DMB group). Further to this, bis(2,4-dimethoxybenzyl)amine is not commercially available and required a two-step synthesis over 2 days using hazardous reagents. We therefore decided to investigate the utility of the primary amine derivatives 2,4-dimethoxybenzylamine and 4-methoxybenzylamine in our synthesis as these have the advantage of being readily available from commercial suppliers. We had a concern that these reagents, as primary amines, may cause undesirable O-deacetylation of the carbohydrate moiety;[4a] however, this was not observed. As a protecting group, the 4-methoxybenzyl substituent (PMB) should have intermediate stability toward acid-promoted removal compared to the more acid-labile DMB protecting group.

Sulfenamides **2b** (*NH*-DMB) and **2c** (*NH*-PMB) were synthesized from **1** similarly to **2a** (Scheme 2, routes b and c, respectively). As observed for **2a**, compound **2b** was also unstable on normal phase silica preconditioned with 1% Et_3N and so was instead semipurified on C18 reverse phase silica to remove excess amine reagent. The PMB compound **2c** was more

(5) Zemplen, G. *Ber. Deutsch. Chem. Ges.* **1926**, *59*, 1254.
(6) (a) Hill, B.; Liu, Y.; Taylor, S. D. *Org. Lett.* **2004**, *6*, 4285. (b) Hill, B.; Ahmed, V.; Bates, D.; Taylor, S. D. *J. Org. Chem.* **2006**, *71*, 8190. (c) Navidpour, L.; Lu, W.; Taylor, S. D. *Org. Lett.* **2006**, *8*, 5617. (d) Chen, L.; Gao, G.; Bonnac, L.; Wilson, D. J.; Bennett, E. M.; Jayaram, H. N.; Pankiewicz, K. W. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3152.
(7) Kocienski, P. J. *Protecting Groups*, 2nd ed.; Thieme: Stuttgart, 2000.
(8) Agnihotri, G.; Misra, A. K. *Carbohydr. Res.* **2006**, *341*, 275.

TABLE 1. Synthesized *S*-Glycosyl Sulfonamides



Thioacetate	Compound	Yield (%)
 **1**		**4** (R=Ac) **5** (R=H)	10[a] 100[b]
 **6**		**10** (R=Ac) **14** (R=H)	24[a] 100[b]
 **7**		**11** (R=Ac, R[1]=Me) **15** (R= R[1]=H)	18[a] 59[c]
 **8**		**12** (R=Ac) **16** (R=H)	31[a] 55[b]
 **9**		**13** (R=Ac) **17** (R=H)	45[a] 59[b]

[a] Yield (%) over three steps from thioacetate. [b] Yield (%) for Zemplen deprotection. [c] Yield (%) for deprotection using sodium hydroxide.

stable to chromatography on normal phase silica (conditioned with 1% Et_3N), consistent with the reduced lability of this protecting group toward an acidic environment. Compounds **2b** and **2c** were oxidized to the sulfonamides **3b** and **3c**, respectively, applying our previously used neutral oxidation conditions ($KMnO_4/CuSO_4 \cdot 5H_2O$). A small amount of protecting group loss was observed during these reactions; however, oxidation predominates, leading to a relatively clean reaction mixture that required only an aqueous workup followed by purification on reverse phase silica (C18). The deprotection of **3b** and **3c** to remove the DMB and PMB groups was then achieved by stirring with a solution of TFA in CH_2Cl_2 at room temperature to generate the primary sulfonamide **4**. Deprotection of **3b** was complete in 2 h (25% TFA, yield 10% over three steps from thioacetate **1**), while deprotection of **3c** required 2 days (50% TFA, yield 26% over three steps from thioacetate **1**).

Each of the three sulfonamide protecting groups, $(DMB)_2$, DMB, and PMB, allowed the successful transformation of thioacetate **1** to the primary sulfonamide **4** through the combination of neutral oxidizing conditions followed by acid-catalyzed selective deprotection. The ready availability of the starting amines for routes b and c is an advantage; however, the ease of removal of the DMB group compared to the PMB group brings us to conclude that DMB (route b) is the most practical protecting group to facilitate the synthesis of anomeric sulfonamides for our substrates. Although not strictly a one-pot synthesis, the use of intermediates **2b** and **3b** in a semipurified form following rapid chromatography on reverse phase silica (C18 SPE cartridges) proved highly effective and made the overall transformation of glycosyl thioacetate to anomeric sulfonamide a relatively succinct synthetic procedure.

Having the reaction conditions to form anomeric primary sulfonamides established on the D-glucose moiety (to prepare **4** and **5**), we then applied our methodology to a variety of mono- (D-galactose, D-glucuronic acid) and disaccharide (maltose, lactose) derivatives (Table 1). Glycosyl thioacetates **6**−**9** were synthesized from per-*O*-acetylated sugars using thiourea and boron trifluoroetherate in yields ranging from 47 to 79%.[9] The corresponding sulfenamides were prepared from 2,4-dimethoxybenzyl amine similarly to **2b** and were used in the next step following semipurification on reverse phase silica (C18). Oxidation of sulfenamides as before ($KMnO_4/CuSO_4 \cdot 5H_2O$) followed by deprotection of the DMB group with 25% TFA in CH_2Cl_2 for 2 h gave the target anomeric primary sulfonamides **10**−**13** (18−45% yields over three steps). Next, Zemplen's conditions[5] were applied to remove the acetate groups of compounds **10**, **12**, and **13**, while NaOH (0.07 M) was used to deprotect both the hydroxyl and carboxylic acid groups of the glucuronic acid derivative **11**. The fully deprotected anomeric sulfonamide compounds **14**−**17** were obtained in good to high yields (Table 1).

Conclusions

In conclusion, we have developed a relatively simple and general procedure for the synthesis of *S*-glycosyl primary sulfonamides starting from per-*O*-acetylated sugar derivatives. Our approach has been to optimize reaction transformations

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appropriate for the protecting group requirements leading to the anomeric sulfonamide. We also propose that the DMB group is a viable sulfonamide protecting group provided neutral reaction conditions are employed.

Experimental Section

***N*,*N*-Bis(2,4-dimethoxybenzyl)-1-*S*-(2,3,4,6-tetra-*O*-acetyl)-D-glucopyranosylsulfenamide (2a).** To a solution of thioacetate derivative **1** (1.21 g, 2.98 mmol, 1.0 equiv) in anhydrous MeOH (60 mL) under argon was added diethyl bromomalonate (1.2 mL, 7.13 mmol, 2.4 equiv). The solution was stirred at rt for 20 min, and then bis(2,4-dimethoxybenzyl)amine (3.79 g, 11.9 mmol, 4.0 equiv) was added. The reaction mixture was stirred overnight at rt, after which a precipitate was formed. The precipitate was collected by filtration and washed with MeOH to afford the title compound **2a** as a white solid (1.60 g, 2.35 mmol, 79%): $R_f = 0.47$ (1:1 EtOAc/hexane); mp = 143−144 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ = 7.16 (d, J = 8.5 Hz, 2H, H_{arom}), 6.48 (m, 4H, H_{arom}), 5.32 (t, J = 9.5 Hz, 1H, H-3), 5.21 (d, J = 10.0 Hz, 1H, H-1), 4.86 (t, J = 9.5 Hz, 1H, H-4), 4.65 (t, J = 10.0 Hz, 1H, H-2), 4.14 (dd, J = 6.0, 12.5 Hz, 1H, H-6a), 4.06 (m, 1H, H-5), 4.02 (m, 1H, H-6b), 3.99 (m, 4H, NCH_2), 3.74, 3.70 (2 × s, 12H, OCH_3), 2.01, 1.97, 1.94, 1.83 (4 × s, 12H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY; LRMS (ESI$^+$) m/z = 680 [M + H]$^+$, 702 [M + Na]$^+$.

***N*-(2,4-Dimethoxybenzyl)-1-*S*-(2,3,4,6-tetra-*O*-acetyl)-D-glucopyranosylsulfenamide (2b).** The title compound was synthesized from thioacetate **1** (300 mg, 0.74 mmol, 1.0 equiv), diethylbromomalonate (0.30 mL, 1.78 mmol, 2.4 equiv), and 2,4-dimethoxybenzylamine (0.42 mL, 2.80 mmol, 3.8 equiv) using the procedure described for compound **2a**. The crude product was semipurified on reverse phase silica (C-18 prepacked cartridge, 5 g sorbent) with a gradient of H_2O/MeOH. The title compound eluted over four fractions (40−70% MeOH) and was obtained as a yellow oil (265 mg, 0.50 mmol, 68%): R_f = 0.57 (1:1 EtOAc/hexane); ^{1}H NMR (500 MHz, DMSO-d_6) δ = 7.13 (d, J = 8.0 Hz, 1H, H_{arom}), 6.53 (d, J = 2.5 Hz, 1H, H_{arom}), 6.46 (dd, J = 2.5, 8.5 Hz, 1H, H_{arom}), 5.35 (t, J = 9.5 Hz, 1H, H-3), 5.00 (t, J = 10.0 Hz, 1H, H-2), 4.89 (t, J = 9.5 Hz, 1H, H-4), 4.69 (t, J = 10.0 Hz, 1H, H-1), 4.06 (m, 4H, H-6a, H-6b, NCH_2), 3.98 (m, 1H, H-5), 3.79, 3.75 (2 × s, 6H, OCH_3), 2.00, 1.99, 1.97, 1.96 (4 × s, 12H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY; LRMS (ESI$^+$) m/z = 530 [M + H]$^+$, 552 [M + Na]$^+$.

***N*,*N*-Bis(2,4-dimethoxybenzyl)-1-*S*-(2,3,4,6-tetra-*O*-acetyl)-D-glucopyranosylsulfonamide (3a).** A finely ground mixture of the catalytic oxidative system ($KMnO_4$/$CuSO_4 \cdot 5H_2O$; 1:1; w/w; 2.4 g, 6.3:4.0 equiv) was dissolved in H_2O (5 mL) and added to a solution of sulfenamide **2a** (825 mg, 1.21 mmol, 1.0 equiv) in acetonitrile (15 mL). The reaction was stirred at rt for 1.5 h, after which the acetonitrile was evaporated under reduced pressure and the remaining aqueous residue extracted with EtOAc (×1). The organic phase was washed with brine (×2), and aqueous extracts were back extracted with EtOAc (×2). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (2:3 EtOAc/hexane, 1% Et_3N) affording the title compound as a yellow oil (150 mg, 0.21 mmol, 17%): R_f = 0.32 (1:1 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.18 (m, 2H, H_{arom}), 6.38 (dd, J = 2.5, 8.0 Hz, 2H, H_{arom}), 6.35 (d, J = 2.5 Hz, 2H, H_{arom}), 5.34 (t, J = 9.5 Hz, 1H, H-2), 5.13 (t, J = 9.5 Hz, 1H, H-3), 4.97 (t, J = 10.0 Hz, 1H, H-4), 4.51 (d, J = 16.0 Hz, 2H, NCH_2), 4.29 (d, J = 10.0 Hz, 1H, H-1), 4.20 (d, J = 16.0 Hz, 2H, NCH_2), 3.99 (dd, J = 5.5, 10.0 Hz, 1H, H-6a), 3.94 (dd, J = 2.5, 10.0 Hz, 1H, H-6b), 3.74, 3.69 (2 × s, 12H, OCH_3), 3.53 (m, 1H, H-5), 2.00, 1.95, 1.94, 1.93 (4 × s, 12H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY; LRMS (ESI$^+$) m/z = 734 [M + Na]$^+$; HRMS (ESI) calcd for $C_{32}H_{41}N_1O_{15}SNa^+$ 734.2089, found 734.2085.

***N*-(2,4-Dimethoxybenzyl)-1-*S*-(2,3,4,6-tetra-*O*-acetyl)-D-glucopyranosylsulfonamide (3b).** The title compound was synthesized from sulfenamide **2b** (3.54 g, 6.68 mmol, 1.0 equiv) with the procedure described for compound **3a**. After washing, the crude yellow oil obtained was used without purification: R_f = 0.31 (1:1 EtOAc/hexane); LRMS (ESI$^+$) m/z 584 [M + Na]$^+$; HRMS (ESI) calcd for $C_{23}H_{31}N_1O_{13}SNa^+$ 584.1408, found 584.1411.

***N*-(4-Methoxybenzyl)-1-*S*-(2,3,4,6-tetra-*O*-acetyl)-D-glucopyranosylsulfonamide (3c).** To a solution of thioacetate derivative **1** (307 mg; 0.76 mmol, 1.0 equiv) in anhydrous MeOH (15 mL) under argon was added diethyl bromomalonate (0.3 mL, 1.78 mmol, 2.3 equiv). The solution was stirred at rt for 20 min, and then 4-methoxybenzylamine (0.50 mL, 3.85 mmol, 5.1 equiv) was added. The reaction mixture was stirred overnight at rt. The mixture was concentrated, then purified by flash chromatography (2:3 EtOAc/hexane, R_f = 0.38). A yellow oil (313 mg, 0.63 mmol, 83%) was obtained. Oxidation of the sulfenamide occurred as described for the preparation of compound **3a** using catalytic system ($KMnO_4$/$CuSO_4 \cdot 5H_2O$; 1:1; w/w; 1.0 g, 4.2:2.6 equiv) in CH_3CN/H_2O (5:1, 180 mL). The crude mixture was semipurified on reverse phase silica (C-18 prepacked cartridge, 5 g sorbent) eluted with a gradient of H_2O/MeOH. Elution of sulfonamide **3c** occurred over five fractions (60−100% MeOH): R_f = 0.37 (1:1 EtOAc/hexane); LRMS (ESI$^+$) m/z 554 [M + Na]$^+$.

1-*S*-(2,3,4,6-Tetra-*O*-acetyl)-D-glucopyranosylsulfonamide (4). The crude mixture of the protected sulfonamide **3b** was dissolved in a solution of 25% trifluoroacetic acid (TFA) in CH_2Cl_2 (24 mL) and stirred 2 h at rt. Solvent and TFA were evaporated under reduced pressure, and the remaining residue was diluted with CH_2Cl_2 (150 mL) and washed with brine (×3). The aqueous extracts were back extracted with CH_2Cl_2 (×2), and then all organic extracts were combined, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by flash chromatography with solid addition (99:1 CH_2Cl_2/MeOH) to afford the title sulfonamide **4** as a colorless solid (372 mg, 0.90 mmol, 14% over two steps from **2b**): R_f = 0.26 (1:1 EtOAc/hexane); mp = 210−211 °C; $[\alpha]^{25}_D$ = −6 (c = 1.0, chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.36 (d, J = 9.5 Hz, 1H, H-3), 5.33 (d, J = 9.5 Hz, 1H, H-2), 5.14 (t, J = 9.5 Hz, 1H, H-4), 4.96 (br s, 2H, NH_2), 4.38 (d, J = 9.0 Hz, 1H, H-1), 4.37 (dd, J = 5.0, 12.5 Hz, 1H, H-6a), 4.18 (dd, J = 2.5, 12.5 Hz, 1H, H-6b), 3.87 (ddd, J = 2.5, 5.0, 10.5, 1H, H-5), 2.11, 2.10, 2.06, 2.04 (4 × s, 12H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 170.9, 170.6, 169.9, 169.4 (O*C*OCH$_3$), 87.5 (C-1), 76.7 (C-5), 72.7 (C-3), 68.2 (C-2), 67.9 (C-4), 61.6 (C-6), 20.7, 20.6, 20.5 (2C) (OCO*C*H$_3$), assignments were confirmed by ^{1}H−^{13}C HSQC; LRMS (ESI$^+$) m/z = 434 [M + Na]$^+$; LRMS (ESI$^-$) m/z = 410 [M − H]$^-$; HRMS (ESI) calcd for $C_{14}H_{21}N_1O_{11}SNa^+$ 434.0728, found 434.0708.

1-*S*-D-Glucopyranosylsulfonamide (5). General Procedure 1. Fully deprotected compound **5** was prepared by treating a solution of the per-*O*-acetylated compound **4** (191 mg, 0.46 mmol, 1.0 equiv) in anhydrous MeOH (15 mL) at 0 °C with methanolic sodium methoxide (25% w/v, 1 mL, 1.0 equiv), final pH = 14. The reaction was warmed to rt and left to stir until full deprotection was evident by TLC (∼2 h). The solution was neutralized with Amberlite IR-120 [H$^+$], filtered, and the resin washed several times with methanol. The solvent was evaporated under reduced pressure and lyophilized to dryness to furnish the title sulfonamide **5** as a slightly yellow hygroscopic solid (113 mg, 0.46 mmol, ∼100%) which was pure by ^{1}H NMR: R_f = 0.1 (9:1 CH_3CN/H_2O); mp = 63−64 °C; $[\alpha]^{25}_D$ = + 5 (c = 0.9, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ = 6.69 (br s, 2H, NH_2), 5.11 (m, 1H, OH), 5.05 (d, J = 5.0 Hz, 1H, OH), 5.02 (d, J = 5.5 Hz, 1H, OH), 4.47 (m, 1H, OH), 4.05 (d, J = 9.5 Hz, H-1), 3.68 (m, 1H, H-6a), 3.45 (m, 2H, H-6b, H-2), 3.25 (m, 2H, H-5, H-3), 3.05 (m, 1H, H-4), assignments were confirmed by ^{1}H−^{1}H gCOSY; ^{13}C NMR (125 MHz, DMSO-d_6) δ = 90.5 (C-1), 81.3 (C-5), 77.3 (C-3), 70.6 (C-2), 69.6 (C-4), 61.2 (C-6) assignments were confirmed by ^{1}H−^{13}C HSQC; LRMS

(ESI$^+$) m/z = 266 [M + Na]$^+$; HRMS (ESI) calcd for $C_6H_{13}N_1O_7SNa^+$ 266.0305, found 266.0309.

1-*S*-(2,3,4,6-Tetra-*O*-acetyl)-D-galactopyranosylsulfonamide (10). General Procedure 2. The title compound was synthesized over three steps from thioacetate derivative **6**. First, the intermediate sulfenamide was prepared from thioacetate **6** (4.00 g, 9.84 mmol, 1.0 equiv), diethyl bromomalonate (0.30 mL, 1.78 mmol, 2.4 equiv), and 2,4-dimethoxybenzylamine (0.42 mL, 2.80 mmol, 3.8 equiv) using the procedure described for the preparation of compound **2a**. This intermediate was semipurified on reverse phase silica (C-18 prepacked cartridge, 5 g sorbent) using a gradient of H_2O/MeOH and eluted over three fractions (60−80% MeOH) to give a yellow oil. This sulfenamide intermediate was immediately submitted to oxidation using the procedure described for preparation of compound **3a** to afford the N-protected sulfonamide intermediate which was used without purification: R_f = 0.29 (1:1 EtOAc/hexane). Removal of the DMB protecting group was achieved as described for compound **4**. The yellow oil obtained was purified by flash chromatography (1:1 EtOAc/hexane) to afford the title sulfonamide **10** (980 mg, 2.38 mmol, 24% over three steps): R_f = 0.22 (1:1 EtOAc/hexane); $[\alpha]^{25}_D$ = + 5 (c = 1.1, chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.50 (t, J = 9.5 Hz, 1H, H-2), 5.49 (t, J = 9.5 Hz, 1H, H-3), 5.19 (dd, J = 3.0, 10.0 Hz, 1H, H-4), 5.03 (br s, 2H, NH_2), 4.39 (d, J = 10.0 Hz, 1H, H-1), 4.24 (m, 1H, H-6a), 4.16 (m, 1H, H-5), 4.11 (m, 1H, H-6b), 2.19, 2.11, 2.07, 2.02 (4 × s, 12H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 171.3, 170.5, 170.1, 169.9 (O*C*OCH$_3$), 88.1 (C-1), 75.6 (C-5), 70.8 (C-4), 67.1 (C-3), 65.6 (C-2), 61.1 (C-6), 20.7, 20.5 (2C), 20.4 (OCO*C*H$_3$), assignments were confirmed by ^{1}H−^{13}C HSQC; LRMS (ESI$^+$) m/z = 434 [M + Na]$^+$; LRMS (ESI$^-$) m/z = 410 [M − H]$^+$; HRMS (ESI) calcd for $C_{14}H_{21}N_1O_{11}SNa^+$ 434.0728, found 434.0706.

Methyl 1-*S*-(2,3,4,6-Tetra-*O*-acetyl)-D-glucopyranuronylsulfonamide (11). The title compound was obtained from thioacetate **7** (2.94 g, 7.49 mmol, 1.0 equiv) as described in general procedure 2 and obtained as a light yellow solid (542 mg, 1.36 mmol, 18% over 3 steps): R_f = 0.41 (2:1 EtOAc/hexane); mp = 200−202 °C; $[\alpha]^{25}_D$ = −13 (c = 0.8, chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.41 (t, J = 9.5 Hz, 1H, H-3), 5.35 (t, J = 9.5 Hz, 1H, H-2), 5.24 (t, J = 9.5 Hz, 1H, H-4), 5.13 (br s, 2H, NH_2), 4.41 (d, J = 10.0 Hz, 1H, H-1), 4.18 (d, J = 9.5 Hz, 1H, H-5), 3.77 (s, 3H, OCH_3), 2.10, 2.05 (2 × s, 9H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 171.1, 169.8, 169.5, 166.7 (O*C*OCH$_3$), 87.1 (C-1), 76.2 (C-5), 72.0 (C-3), 69.3 (C-4), 68.1 (C-2), 53.4 (CO_2CH_3), 20.9, 20.7, 20.6 (OCO*C*H$_3$), assignments were confirmed by ^{1}H−^{13}C HSQC; LRMS (ESI$^+$) m/z = 420 [M + Na]$^+$; LRMS (ESI$^-$) m/z = 396 [M − H]$^+$; HRMS (ESI) calcd for $C_{13}H_{19}N_1O_{11}SNa^+$ 420.0571, found 420.0580.

(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-1,2,3,6-tetra-*O*-acetyl-1-thio-β-D- glucopyranosylsulfonamide (12). The title compound was obtained from thioacetate **8** (4.36 g, 6.28 mmol, 1.0 equiv) as described in general procedure 2 and obtained as a light orange solid (1.35 g, 1.93 mmol, 31%): R_f = 0.23 (3:2 EtOAc/hexane); mp = 103−105 °C; $[\alpha]^{25}_D$ = −12 (c = 1.1, chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.37 (d, J = 3.0 Hz, 1H, H-4′), 5.32 (t, J = 9.0 Hz, 1H, H-3), 5.27 (t, J = 9.5 Hz, 1H, H-2), 5.12 (dd, J = 8.0, 10.5 Hz, 1H, H-2′), 4.98 (dd, J = 3.5, 10.5 Hz, 1H, H-3′), 4.96 (br s, 2H, NH_2), 4.54 (dd, J = 1.5, 12.5 Hz, 1H, H-6a), 4.51 (d, J = 7.5 Hz, 1H, H-1′), 4.37 (d, J = 10.0 Hz, 1H, H-1), 4.20 (dd, J = 4.0, 12.5 Hz, 1H, H-6b), 4.16 (dd, J = 6.5, 11.5 Hz, 1H, H-6a′), 4.09 (dd, J = 7.5, 11.0 Hz, 1H, H-6b′), 3.89 (m, 1H, H-5′), 3.86 (t, J = 9.5 Hz, 1H, H-4), 3.79 (m, 1H, H-5), 2.17, 2.14, 2.08 (6H), 2.07, 2.06, 1.98 (6 × s, 21H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 170.9, 170.7, 170.6, 170.3, 170.2, 169.7, 169.2 (O*C*OCH$_3$), 101.2 (C-1′), 87.6 (C-1), 77.6 (C-5), 75.7 (C-4), 72.8 (C-3), 71.1 (C-3′), 71.1 (C-5′), 69.3 (C-2′), 68.5 (C-2), 66.8 (C-4′), 61.7 (C-6), 61.0 (C-6′), 21.0, 20.9 (2C), 20.8 (2C), 20.7 (2C) (OCO*C*H$_3$), assignments were confirmed by ^{1}H−^{13}C HSQC; LRMS (ESI$^+$) m/z = 722 [M + Na]$^+$; LRMS (ESI$^-$) m/z = 697 [M − H]$^-$; HRMS (ESI) calcd for $C_{26}H_{37}N_1O_{19}SNa^+$ 722.1573, found 722.1541.

(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl)-(1→4)-1,2,3,6-tetra-*O*-acetyl-1-thio-β-D- glucopyranosylsulfonamide (13). The title compound was obtained from thioacetate **9** (3.89 g, 5.60 mmol, 1.0 equiv) as described in general procedure 2 and obtained as a light orange solid (1.76 g, 2.52 mmol, 45%): R_f = 0.25 (3:2 EtOAc/hexane); mp = 96−98 °C; $[\alpha]^{25}_D$ = + 57 (c = 1.3, chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.41 (t, J = 9.0 Hz, 1H, H-3), 5.41 (d, J = 3.5 Hz, 1H, H-1′), 5.37 (t, J = 10.0 Hz, 1H, H-3′), 5.19 (t, J = 9.5 Hz, 1H, H-2), 5.07 (t, J = 10.0 Hz, 1H, H-4′), 4.95 (br s, 2H, NH_2), 4.87 (dd, J = 4.0, 10.5 Hz, 1H, H-2′), 4.55 (dd, J = 2.5, 12.5 Hz, 1H, H-6a), 4.43 (d, J = 9.5 Hz, 1H, H-1), 4.32 (dd, J = 4.5, 12.5 Hz, 1H, H-6b), 4.24 (dd, J = 4.0, 12.5 Hz, 1H, H-6a′), 4.08 (dd, J = 2.5, 12.5 Hz, 1H, H-6b′), 4.044 (t, J = 9.0 Hz, 1H, H-4), 3.96 (m, 1H, H-5′), 3.85 (m, 1H, H-5), 2.16, 2.11, 2.07, 2.06, 2.05, 2.04, 2.02 (7 × s, 21H, OCOCH_3), assignments were confirmed by ^{1}H−^{1}H gCOSY; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 170.7 (3C), 170.6, 170.0, 169.9, 169.5 (O*C*OCH$_3$), 96.0 (C-1′), 87.3 (C-1), 77.1 (C-5), 75.0 (C-3), 72.6 (C-4), 70.2 (C-2′), 69.3 (C-3′), 68.9 (C-5′), 68.8 (C-2), 68.2 (C-4′), 62.4 (C-6), 61.7 (C-6′), 20.9 (2C), 20.7 (3C), 20.6 (2C) (OCO*C*H$_3$), assignments were confirmed by ^{1}H−^{13}C HSQC; LRMS (ESI$^+$) m/z = 722 [M + Na]$^+$; LRMS (ESI$^-$) m/z = 697 [M − H]$^-$; HRMS (ESI) calcd for $C_{26}H_{37}N_1O_{19}SNa^+$ 722.1573, found 722.1541.

1-*S*-D-Galactopyranosylsulfonamide (14). The title compound was prepared from **10** (295 mg, 0.72 mmol) as described in general procedure 1 (except the reaction was maintained overnight at 50 °C). The lyophilized compound was obtained as an orange hygroscopic solid (174 mg, 0.72 mmol, ∼100%): R_f = 0.46 (8:2 CH_3CN/H_2O); mp = 58−59 °C; $[\alpha]^{25}_D$ = + 11 (c = 1.2, MeOH); ^{1}H NMR (400 MHz, D_2O) δ = 4.49 (d, J = 9.6 Hz, H-1), 4.06 (d, J = 3.2 Hz, 1H, H-4), 4.04 (t, J = 9.2 Hz, 1H, H-2), 3.72−3.64 (m, 3H, H-5, H-6a, H-6b), 3.62 (dd, J = 3.6, 9.6 Hz, 1H, H-3), assignments were confirmed by ^{1}H−^{1}H gCOSY; ^{13}C NMR (125 MHz, DMSO-d_6) δ = 91.3 (C-1), 79.8 (C-5), 73.9 (C-3), 68.1 (C-4), 67.5 (C-2), 60.5 (C-6), assignments were confirmed by ^{1}H−^{13}C HSQC; LRMS (ESI$^+$) m/z = 266 [M + Na]$^+$; LRMS (ESI$^-$) m/z = 242 [M − H]$^-$; HRMS (ESI) calcd for $C_6H_{13}N_1O_7SNa^+$ 266.0305, found 266.0310.

Methyl 1-*S*-D-Glucopyranuronylsulfonamide (15). To a solution of **11** (173 mg, 0.44 mmol, 1 equiv) in MeOH/H_2O (1:4, 7.5 mL) was added NaOH (20 mg, 0.50 mmol, 1.1 equiv). The reaction was stirred for 5 h at 0 °C then neutralized with Amberlite resin IR-120 H$^+$, filtered, evaporated, and the residue purified by flash chromatography with solid addition (8:2 CH_3CN/H_2O). Acetonitrile was evaporated from fractions containing the title compound, and the remaining aqueous solution was filtered (0.42 μm syringe filter) and lyophilized to dryness to furnish the title sulfonamide **15** as a white solid (66 mg, 0.26 mmol, 59%): mp = 109−111 °C; $[\alpha]^{25}_D$ = −18 (c = 1.1, MeOH); ^{1}H NMR (400 MHz, D_2O) δ = 4.59 (d, J = 9.6 Hz, H-1), 4.07 (d, J = 9.2 Hz, 1H, H-5), 3.87 (t, J = 9.2 Hz, 1H, H-2), 3.71 (t, J = 9.2 Hz, 1H, H-3), 3.66 (t, J = 9.2 Hz, 1H, H-4), assignments were confirmed by ^{1}H−^{1}H gCOSY; ^{13}C NMR (125 MHz, DMSO-d_6) δ = 170.2 (CO_2H), 90.6 (C-1), 78.7, 76.8, 71.2, 70.6 (C-5, C-2, C-3, C-4); LRMS (ESI$^+$) m/z = 280 [M + Na]$^+$; HRMS (ESI) calcd for $C_6H_{11}N_1O_8SNa^+$ 280.0098, found 280.0112.

β-D-Galactopyranosyl-(1→4)-1-thio-β-D-glucopyranosylsulfonamide (16). The title compound was prepared from **12** (462 mg, 0.66 mmol) as described in general procedure 1 and obtained as an orange solid following purification by flash chromatography with solid addition (85:15 CH_3CN/H_2O). Acetonitrile was evaporated from fractions containing the title compound, and the remaining aqueous solution was filtered (0.42 μm syringe filter) and lyophilized to dryness to furnish the title sulfonamide **16** as a white solid (144 mg, 0.36 mmol, 55%): R_f = 0.32 (8:2 CH_3CN/

H_2O); mp = 138−139 °C; $[\alpha]^{25}_D$ = + 13 (*c* = 1.0, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ = 6.71 (br s, 2H, N*H*$_2$), 5.21 (m, 1H, O*H*), 5.06 (d, *J* = 4.0 Hz, 1H, O*H*), 4.79 (d, *J* = 1.0 Hz, 1H, O*H*), 4.76 (m, 1H, O*H*), 4.63 (t, *J* = 5.0 Hz, 1H, O*H*), 4.52 (t, *J* = 6.5 Hz, O*H*), 4.48 (d, *J* = 4.5 Hz, 1H, O*H*), 4.20 (d, *J* = 7.5 Hz, 1H, H-1′), 4.13 (d, *J* = 9.5 Hz, 1H, H-1), 3.80 (m, 1H), 3.62−3.43 (m, 11H, H-2, H-2′, H-3, H-3′, H-4, H-4′, H-5, H-5′, H-6a, H-6a′, H-6b, H-6b′), assignments were confirmed by ^{1}H−^{1}H gCOSY; ^{13}C NMR (125 MHz, DMSO-d_6) δ = 103.7 (C-1′), 90.0 (C-1), 79.9 (C-4), 78.9 (C-3′), 75.5, 75.4 (C-5, C-5′), 73.2 (C-3), 70.5 (2C) (C-2, C-2′), 68.1 (C-4′), 60.5, 60.4 (C-6, C-6′), assignments were confirmed by ^{1}H−^{13}C HSQC; LRMS (ESI$^+$) *m*/*z* = 428 [M + Na]$^+$, 833 [2 M + Na]$^+$; HRMS (ESI) calcd for $C_{12}H_{23}N_1O_{12}SNa^+$ 428.0833, found 428.0836.

α-D-Glucopyranosyl-(1→4)-1-thio-β-D-glucopyranosylsulfonamide (17). The title compound was prepared from **13** (605 mg, 0.86 mmol) as described in general procedure 1 and obtained as an orange solid following purification by flash chromatography with solid addition (85:15 CH_3CN/H_2O). Acetonitrile was evaporated from fractions containing the title compound, and the remaining aqueous solution was filtered (0.42 μm syringe filter) and lyophilized to dryness to furnish the title sulfonamide **17** as a white solid (207 mg, 0.51 mmol, 59%): R_f = 0.34 (8:2 CH_3CN/H_2O); mp = 127−128 °C; $[\alpha]^{25}_D$ = + 79 (*c* = 0.9, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ = 6.74 (br s, 2H, N*H*$_2$), 5.63 (d, *J* = 3.0 Hz, 1H, O*H*), 5.40 (d, *J* = 6.0 Hz, 1H, O*H*), 5.13 (d, *J* = 5.5 Hz, 1H, O*H*), 5.04 (d, *J* = 4.0 Hz, 1H, O*H*), 4.88 (d, *J* = 5.5 Hz, 1H, O*H*), 4.85 (d, *J* = 4.5 Hz, 1H, O*H*), 4.52−4.46 (m, 2H, O*H*, H-1′), 4.12 (d, *J* = 9.0 Hz, 1H, H-1), 3.74 (m, 1H), 4.63−3.34 (m, 9H, H-2, H-2′, H-3, H-3′, H-4, H-4′, H-6a, H-6a′, H-6b, H-6b′), 3.23 (m, 1H, H-5), 3.23 (m, 1H, H-5′), assignments were confirmed by ^{1}H−^{1}H gCOSY; ^{13}C NMR (125 MHz, DMSO-d_6) δ = 100.7 (C-1′), 90.2 (C-1, C-1′), 79.9 (C-4), 78.9 (C-3′), 75.5, 75.4 (C-5, C-5′), 73.2 (C-3), 70.5 (2C) (C-2, C-2′), 68.1 (C-4′), 60.5, 60.4 (C-6, C-6′), assignments were confirmed by ^{1}H−^{13}C HSQC; LRMS (ESI$^+$) *m*/*z* = 423 [M + NH_4]$^+$, 428 [M + Na]$^+$; LRMS (ESI$^-$) *m*/*z* = 404 [M − H]$^-$, 440 [M + Cl]$^-$; HRMS (ESI) calcd for $C_{12}H_{23}N_1O_{12}SNa^+$ 428.0833, found 428.0823.

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Supporting Information Available: Detailed experimental procedures, characterization data, and copies of ^{1}H and ^{13}C spectra of new compounds **4**, **5**, and **10**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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