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Glycosyl Disulfides: Novel Glycosylating Reagents with Flexible Aglycon Alteration

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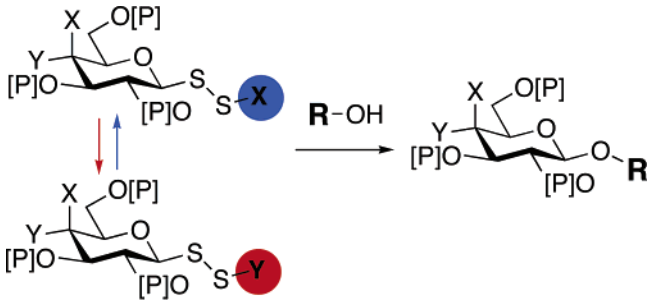
Received July 2, 2005



Glycosyl disulfides have been shown for the first time to be effective glycosyl donors. Glucosylation and galactosylation of a panel of representative alcohol acceptors allowed the formation of 28 simple glycosides, disaccharides, and glycoamino acids in yields of up to 90%. As well as providing a novel class of effective glycosyl donors, the ability to easily alter the nature of the aglycon and the ability to differently activate donors that differ only in their aglycon simply through altering conditions lends glycosyl disulfide donors to their use in latent−active reactivity tuning strategies.

Introduction

Oligosaccharides are vital components in biological systems, often attached to proteins on cell surfaces as key cell−cell interaction mediators that initiate a number of highly specific processes.[1,2] To achieve a better understanding of the subtlety of the often highly specific nature of these processes, there is a continuing need for access to precise oligosaccharide structures. Although many highly elegant and powerful approaches have been developed,[3−11] no generally applicable, selective, and hence easily automatable glycosylation method is yet available for the synthesis of oligosaccharides.[12,13] Development in this area therefore remains a vital challenge to glycoscience.[2] As part of the search for such a method, a number of glycosyl donor systems have been developed in which differences in their anomeric leaving groups have an often critical effect on their reactivity.[5] Two of the most powerful, thioglycosides[14] and glycosyl sulfoxides,[15] utilize sulfur at the anomeric center, and therefore, such donors are attractive in glycosylation strategies. Thioglycosides, such as **1** (see Figure 1), in particular, are one of the most popular donor systems.[14] Strategies for tuning[16] their reactivity, including the use of armed/disarmed donors,[17,18] latent−active donors,[5,19−21] or a bulky leaving group,[6,22] have culminated in elegant one-

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10.1021/jo051374j CCC: $30.25
Published on Web 10/25/2005

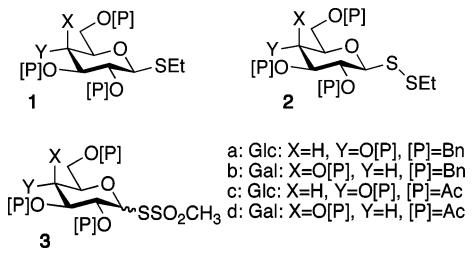

FIGURE 1. Generalized structures of core glycosyl donors and reagents used in this study.

pot glycosylation systems.[16,18,22−34] In many of these systems, the substituent on sulfur plays a key role in modulating activity[21,22] yet, once installed, is difficult to alter.

With the aim of extending the scope of glycosyl donor reagents with sulfur at the anomeric center, we have examined the use of glycosyl disulfides, such as **2**. It was anticipated that glycosyl disulfides would exhibit reactivities similar to those of their thioglycoside counterparts but would have the added advantage that the disulfide linkage could be readily cleaved and reformed. This would usefully allow the variable adjustment of the aglycon in reactivity tuning methods late in synthetic routes for enhanced strategic flexibility and contrasts with the typically early installation of the aglycon in thioglycoside syntheses.[5]

Despite this potential attraction, very little has been reported on the use of glycosyl disulfides as glycosyl donors, and prior to this study, little was known of their reactivity. Indeed, to the best of our knowledge, only one example of any activation of glycosyl disulfides as glycosyl donors had been demonstrated and it was for *N*- rather than *O*-glycoside formation.[35] Vasella and co-workers successfully activated [(2,3:5,6)-di-*O*-isopropylidene-1-thio-α-D-mannofuranosyl]methyl disulfide with bromine and trapped with aniline as an acceptor in this single, yet encouraging, example. The lack of scrutiny may be due to the paucity of efficient methods for the synthesis of glycosyl disulfides. Although the use of a large excess of aglycon thiol under oxidizing conditions can allow their formation,[36] this method is not compatible with the efficient use of sensitive, scarce, or expensive aglycon thiols or with solid-supported thiols. We now report the efficient preparation of glucosyl and galactosyl disulfides **2** and an investigation of their behavior in representative glycosylations. Part of this work has already been published in a short, initial communication.[37]

Results and Discussion

Synthesis of Novel Disulfides as Potential Glycosyl Donors. Representative ethyl disulfides **2a**−**d** were synthesized from the corresponding parent aldoses, as shown in Scheme 1 through the use of four corresponding methanethiosulfonates (MTS), **3**, as powerful mixed disulfide forming reagents.[38−41] Benzyl-protected bromides **5a,b** were obtained from tetrabenzylglucose **4a** and -galactose **4b**, respectively, by treatment with oxalyl bromide using the method of Bundle and co-workers.[42] Crude yields of **5a,b** were approximately quantitative, as judged by ^{1}H NMR. However, owing to their instability, the bromides were dried but not purified further before immediate use in subsequent reactions. Tetraacetylglucosyl bromide **5c** and tetraacetylgalactosyl bromide **5d** were prepared by reaction of pentaacetylglucose and -galactose, respectively, with HBr in AcOH, according to literature methods.[43]

Sodium methanethiosulfonate (NaMTS) for reaction with bromides **5** was prepared through direct reaction of sodium methanesulfinate with sulfur.[44] Having surveyed a range of alternative methods either for the preparation of NaMTS[38] or for the use of alternative MTS ion sources, such as KMTS,[45] we have found this method and source of $CH_3SO_2^-$ to be the most efficient, although different selectivities may be obtained with some alternative sources (vide infra). Heating the bromides **5a**−**d** with NaMTS in dioxan (for **3a,b**), ethanol (for **3c**), or toluene (under phase-transfer conditions for **3d**) furnished the corresponding methanethiosulfonates **3** in moderate to good yields. Many conditions were investigated, and optimal conditions are shown in Table 1 (see Supporting Information for further details of conditions).

Perbenzylated MTS reagents **3a,b** were obtained as β-enriched anomer mixtures; the level of β-stereoselectivity and yields were generally higher for gluco-MTS **3a** than for galacto-MTS **3b**. Pure samples of the anomers

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SCHEME 1

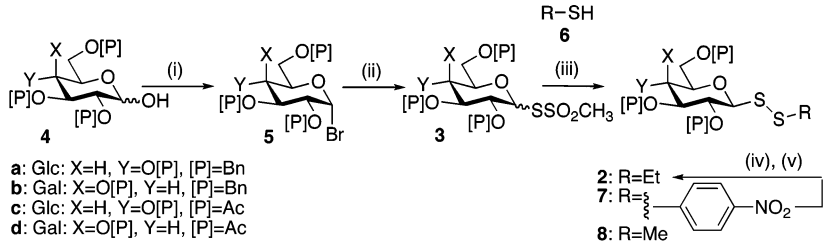
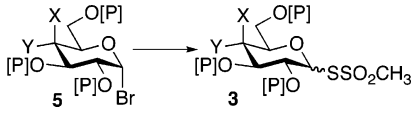


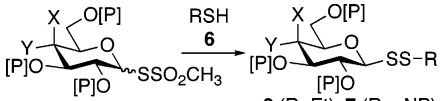
TABLE 1. Preparation of Methanethiosulfonates 3a−d



MTS product	solvent	method[b]	β:α ratio	yield (%)
3a	dioxane	A	7.5:1	76[a]
3a	dioxane	D	1:5.9	73[a]
3b	dioxane	A	4.5:1	62[a]
3c	EtOH	F	100:0	95
3d	toluene	G	100:0	80

[a] Over two steps from **4a,b**. [b] A: 70 °C, 15 h, split batch of 2 × ∼1 g, with NaMTS. D as for B: 0.5 g with ∼1 equiv of Bu_4NBr. F: 90 °C, 25 min with NaMTS. G: reflux, 75 min, 0.1 equiv of Bu_4NI. See Supporting Information and Experimental Section for further details of the effects of other conditions, B,C, and E.

TABLE 2. Preparation of Disulfides 2a−d and 7a from Methanethiosulfonates 3a−d



disulfide product	order of addition	yield (%)[a]
2a	inverse	79
2b	inverse	82
2c	normal[b]	65−74
2c	inverse	96
2d	inverse	82
7a	inverse	67

[a] Based on β-3. [b] Addition of **3** *to* **6**.

of **3a,b** could be obtained by column chromatography. However, it should be noted that advantageously even only β-enriched MTS mixtures under correct conditions react in an exclusively β-selective manner with thiols (vide infra), thereby allowing the ready formation of pure β-disulfide products without the need for obtaining pure β-MTS reagents. Carrying out the reaction of bromide **5a** with NaMTS in the presence of organic-soluble bromide source tetrabutylammonium bromide (Bu_4NBr) (conditions D) or the use of Bu_4MTS as an MTS source (conditions E, see Supporting Information) reversed stereoselectivity to give highly α-enriched **3a** (β:α = 1:4.2−1:5.9). Presumably, under these conditions, tetrabutylammonium serves as a solvating counterion for bromide that in turn is able to catalyze in situ anomerization of α-bromide **5a** to its β-anomer. More rapid reaction of this β-anomer with the MTS ion then leads to preferential α-MTS formation in a manner akin to that proposed for α-*O*-glycosides by Lemieux.[46] Although peracetylated gluco-MTS **3c** was most readily prepared according to our previously established methods through the reaction of NaMTS in EtOH at 90 °C,[41] this method proved low yielding in the preparation of corresponding peracetylated galacto-MTS **3d** and ethyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside was instead isolated as the major product. However, reaction of bromide **5d** in refluxing toluene in the presence of catalytic Bu_4NI as a solid-solution phase-transfer catalyst successfully yielded **3d** in 80% yield. The conformation of **3d** in $CDCl_3$ is consistent with a $^1C_4$ conformation and led to initial confusion over the anomeric configuration; C1−H1 coupling in $CDCl_3$ is also inconclusive[47] with a value of $^1J_{CH}$ = 165 Hz. However, in deuterated acetone, the expected $^4C_1$ conformation is observed and coupling constants consistent with a β-MTS were observed. The structure of **3d** was unequivocally determined to be the β-anomer by X-ray crystallography (Supporting Information); this also indicated a $^4C_1$ conformation in the solid state which is adopted by both symmetrically independent molecules. The observed formation of only β-anomers of the methanethiosulfonates **3c,d** with exclusive stereoselectivity is consistent with neighboring group participation of the C-2 acetate group.

To allow ready comparison with known ethyl thioglycoside glycosyl donors, ethyl glycosyl disulfides, **2**, were selected as model donor systems. The methanethiosulfonates **3a−d** reacted with Et_3N and ethanethiol (**6a**) to give the corresponding β-ethyl disulfides **2a−d** in good yields (Table 2). Initially, a solution of **3c** was added to a solution of ethanethiol at room temperature in one portion. This resulted in moderate yields (65−74%) of desired glycosyl donor **2c**. However, the best results were achieved by carrying out the reaction in dichloromethane at 0 °C and effecting dropwise addition of a dilute (∼0.04 M) solution of ethanethiol *to* **3c** ("inverse addition") over ∼30−40 min. The reaction was complete in 1 h to afford **2c** as a stable white solid in an improved and excellent yield of 96% (Scheme 1 and Table 2). Use of the same dilute solution conditions and inverse addition order also proved optimal for reactions of **3a,b,d**. In all cases, the anomeric configuration was unperturbed in the resulting ethyl disulfides **2a−d**. The structure of **2d** was further confirmed by X-ray crystallography (Supporting Informa-

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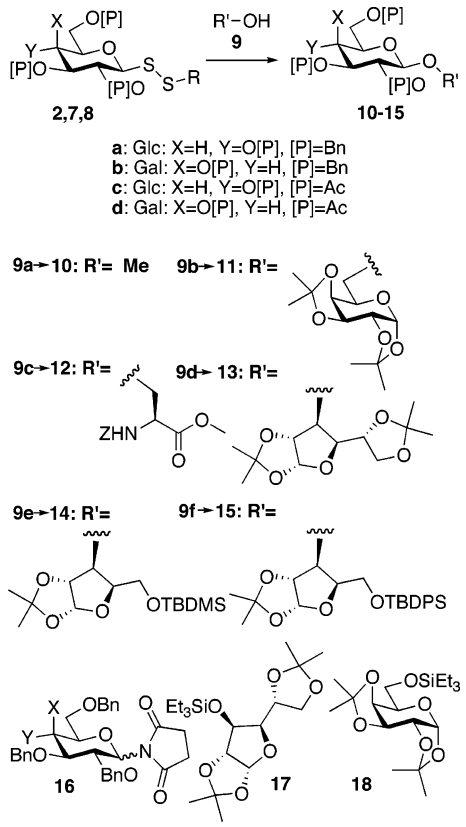
SCHEME 2



tion); the asymmetric unit comprises three molecules, all adopting essentially the same core conformation. Although perbenzylated glycomethanethiosulfonate, **3a**, could be obtained as its pure β-anomer, conveniently, the use of glycomethanethiosulfonate **3a** as a mixture of anomers (93% β, 7% α) also allowed the formation of pure β-ethyl disulfide **2a**. Thus, using short reaction times, complete reaction of only the β-anomers of **3a** or **3b** was achieved, thus rendering anomer separation unnecessary for **3a,b**. Indeed, chromatographic separation of the starting material recovered at this stage allowed the convenient isolation of pure samples of the unreacted α-anomers of **3a,b**. Presumably, 1,3-diaxial interactions render the α-anomer a poorer electrophile. To explore aglycon variation, an example of a latent glycosyl donor containing an electron deficient aglycon, the perbenzylated *p*-nitrophenyl (pNP) glucosyl disulfide **7a**, was also prepared, and again, this was readily achieved by reaction of the appropriate MTS **3a** with Et_3N and the corresponding thiol, *p*-nitrothiophenol **6b**.

Glycosylation Reactions Using Glycosyl Disulfides. To test the power of these novel disulfides **2a**−**d** and **7** as potential glycosyl donors, we evaluated their utility in the glycosylation of a representative panel of alcohol glycosyl acceptors, **9** (Scheme 2). These included simple alcohols, MeOH (**9a**), primary carbohydrate alcohols **9b** for disaccharide synthesis, a protected serine derivative **9c**,[48] and three more hindered secondary alcohol acceptors, **9d**−**f**. To test the compatibility of glycosylation conditions with a variety of potentially labile protecting groups, primary acetonide, secondary acetonide, Z, TBDMS, TBDPS, and COOMe groups were also variously incorporated into these acceptors. Moreover, our selection and construction of glycosyl disulfides **2a**−**d** and **7** as model systems was designed to test various donor properties that are often critical to their effectiveness:[7] (i) the effect of the protecting group (activating[17] ether Bn (**a,b**) vs deactivating ester Ac (**c,d**)), (ii) aglycon variation (active[17] SSEt **2** vs latent SSpNP **7**), and (iii) donor configuration (Glc (**a,c**) vs Gal (**b,d**)).

A. Glycosylation Using Iodonium-Source Activation. The utility of disulfides **2** as glycosyl donors was first tested by exploring the reactions of glucosyl disulfides **2a** and **2c** with diacetone galactose (**9b**) as a model acceptor using a series of activator systems based on iodonium-source reagents in dichloromethane (DCM) or acetonitrile (CH_3CN) as solvent (Scheme 2, Table 3). The selected activator systems (NIS, NIS/TfOH, NIS/TMSOTf, I_2, IBr, MeOTf, and NIS/TESOTf) have all been used previously in successful activations of thioglycosides.[7] This initial optimization survey (Table 3) revealed the use of 10 equiv NIS/0.5 equiv TESOTf in DCM as giving the best yields of the corresponding disaccharides **11a** and **11c** (entries 8 and 12). In all cases, the use of disarmed glycosyl donor **2c** gives substantially lower yields, up to 36% (entries 1−8), than armed donor **2a** (90%, entry 12), albeit with exclusive β-stereoselectivity by virtue of the participatory Ac substituent on O-2. Consistent with the disarmed and peracetylated nature of **2c**, moderate yields and acetyl migration side products were obtained under a variety of conditions. The mass balance of these reactions was made up of two major side products, 1,3,4,6-tetra-*O*-acetyl-α-D-glucose and an acetylated acceptor.[49,50] This indicated successful activation of the donor but subsequent acetyl migration. The disarmed nature of **2c** was further confirmed by the lack of reactivity with I_2[51] (entry 9) but the efficient conversion of **2c** to acetobromoglucose **5c** using IBr (entry 10). IBr has been previously shown to be capable of activating disarmed thioglycosides that cannot be activated under other conditions.[52]

Having established suitable activation conditions for glucosyl donors **2a,c**, we next probed their reactivity toward our panel of representative acceptors (Scheme 2).

We were pleased to find that under the optimal conditions elucidated for activation (10 equiv NIS, 0.5 equiv TESOTf, DCM, 0 °C), ethyl tetrabenzylglucosyl disulfide **2a** rapidly and smoothly gave methyl glucoside **10a** in an excellent 90% yield. Furthermore, reaction with more challenging acceptors **9b** and **9c** gave good yields of disaccharide **11a**[53] and glycopeptide **12a**[54] *O*-glucosides, respectively. Secondary alcohol acceptors proved more challenging. A yield of 56% of **13a** was obtained from **9d** through the inclusion of 1 equiv of the base tri-

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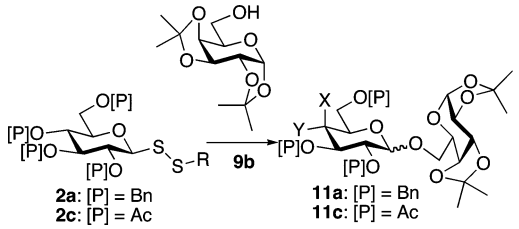
TABLE 3. Glycosylation Reactions to Explore Varying Donor and Iodonium-Activation Conditions Using 2a,c with Model Acceptor Diacetone Galactose (9b)



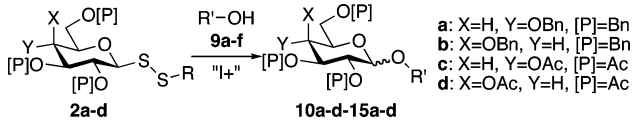
entry *N*	donor	activation conditions[a]	solvent	activator equiv	time (h)	temp (°C)	product	yield (%)	product *β*:α ratio
1	**2c**	NIS[b]	DCM	2.5	24	reflux	**11c**	18	100:0
2	**2c**	NIS, TfOH[c]	DCM	2.5	22	rt	**11c**	26	100:0
3	**2c**	NIS, TfOH[c]	CH_3CN	10	24	rt	**11c**	2	100:0
4	**2c**	NIS, TMSOTf[d]	DCM	10	4.5	rt	**11c**	30	100:0
5	**2c**	NIS, TMSOTf[d]	CH_3CN	10	6	rt	**11c**	16	100:0
6	**2c**	NIS, TESOTf	DCM	3	15	rt	**11c**	15	100:0
7	**2c**	NIS, TESOTf	DCM	5	24	rt	**11c**	34	100:0
8	**2c**	NIS, TESOTf[e]	DCM	10	2	rt	**11c**	36	100:0
9	**2c**	I_2	DCM	10	168	rt			
10	**2c**	IBr	DCM	3	30 min	rt	**5c**	82	0:100
11	**2a**	NIS, TESOTf[f]	DCM	3	1.5	0	**11a**	70	1:1
12	**2a**	NIS, TESOTf[g]	DCM	10	1	0	**11a**	90	9:14
13	**2a**	NIS, TESOTf[g]	DCM	10	40 min	0	**11a**	75	9:11

[a] 0.5 equiv of coactivator. [b] Activation method F in Experimental Section. [c] Activation method G in Experimental Section. [d] Activation method H in Experimental Section. [e] Activation method D in Experimental Section. [f] Activation method B in Experimental Section. [g] Activation method A in Experimental Section.

tert-butylpyrimidine (TTBP)[55] to minimize Lewis-acid-catalyzed acetonide deprotection of both the starting material **9d** and the product **13a**. Activation condition associated side products, succinimidyl glucoside derivative **16a** (21%) and the 3-*O*-triethyl silylated glucofuranoside **17** (23%), were also observed. Glycosylated succinimides, such as **16a**, have been observed previously in potent glycosylating systems[30] with hindered acceptors, and it is a testament to the electrophilicity of the intermediates generated that they are capable of glycosylating such a nonnucleophilic imide species. To further test the ability of **2a** to glycosylate other less-nucleophilic alcohol acceptors and to explore the compatibility of silyl ether protection, secondary alcohol acceptors, 5-*O*-*tert*-butyldimethylsilyl **9e**[56] and 5-*O*-*tert*-butyldiphenylsilyl-1,2-diisopropylidenexylose **9f** were tested. The disaccharide coupling product **14a** was obtained from **9e** in 77% yield and, remarkably, with exclusive α-stereoselectivity. From the more bulky acceptor **9f**, the glucosylated product **15a** was obtained in a lower 41% yield together with succinimide adduct **16a** (27%). Presumably, as for **9d**, because this acceptor is particularly sterically hindered, even succinimide can compete successfully as a nucleophile.

The glycosyl disulfide methodology was then tested for *galactosylation* of a range of acceptors using ethyl tetrabenzylgalactosyl donor **2b**. As has been observed for other galactosyl donors,[30] **2b** is more reactive than glucosyl donor **2a** and, as a result, the use of NIS/TESOTf as an activator proved much less satisfactory (yields of 31−56%), with significant quantities of the corresponding succinimide adduct **16b** being formed even with less-hindered primary alcohol acceptors **9a**−**c** (Table 4). Interestingly, slightly improved yields under these conditions were, in fact, obtained using secondary over primary hydroxyl acceptors: with diacetone glucose **9d** buffered

TABLE 4. Glycosylation Reactions Using Donors 2a−d and NIS/TESOTf Activation



entry *N*	donor	acceptor	activation method[a]	NIS equiv	product	yield (%)	product α:*β* ratio
1	**2a**	**9a**	A	10	**10a**	90	9:15
2	**2a**	**9b**	A	10	**11a**	90	9:14
3	**2a**	**9c**	A	10	**12a**	73	1:1
4	**2a**	**9d**	C	10	**13a**	56[b]	1.6:1
5	**2a**	**9e**	B	3	**14a**	77[c]	100:0
6	**2a**	**9f**	B	3	**15a**	41[d]	3.4:1
7	**2b**	**9a**	B	2	**10b**	44[e]	1:2.4
8	**2b**	**9b**	C	3	**11b**	39[f]	1.4:1
9	**2b**	**9c**	B	1.5	**12b**	31[g]	100:0
10	**2b**	**9d**	C	3	**13b**	34[h]	100:0
11	**2b**	**9e**	B	3	**14b**	54[i]	3.6:1
12	**2b**	**9f**	B	3	**15b**	56	5:1
13	**2c**	**9a**	D	10	**10c**	24	0:100
14	**2c**	**9b**	D	10	**11c**	36	0:100
15	**2c**	**9c**	D	10	**12c**	34	0:100
16	**2d**	**9b**	D	10	**11d**	43	0:100

[a] A: 10 equiv of NIS, 0.5 equiv TESOTf, DCM, 0 °C. B: as for A with 1.5−3 equiv of NIS. C: as for A with 1.5−10 equiv of NIS with TTBP. D: as for A at room temperature. [b] Also obtained 21% succinimidyl adduct **16a** and 23% triethyl silylated diacetone glucose **17**. [c] Also obtained 21% succinimidyl adduct **16a**. [d] Also obtained 27% succinimidyl adduct **16a**. [e] Also obtained 22% succinimidyl adduct **16b**. [f] Also obtained 27% succinimidyl adduct **16b** and 33% triethyl silylated diacetone galactose **18**. [g] Also obtained 16% succinimidyl adduct **16b**. [h] Also obtained 32% succinimidyl adduct **16b** and 36% triethylsilylated diacetone glucose **17**. [i] Also obtained 29% succinimidyl adduct **16b**.

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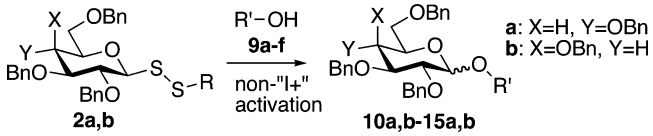
TABLE 5. Glycosylation Reactions Using Donors 2a,b with Noniodonium Lewis Activation Sources[a]



entry *N*	donor	acceptor	activator	activator equiv	product	yield (%)	product α:β ratio
1	**2a**	**9a**	DMTST	5	**10a**	78	1:2
2	**2a**	**9b**	DMTST	5	**11a**	76	1:1
3	**2a**	**9c**	DMTST	5	**12a**	73	1.7:1
4	**2a**	**9d**	DMTST	5	**13a**	23[b]	2.3:1
5	**2a**	**9d**	DMTST[c]	6	**13a**	39[d]	1.6:1
6	**2a**	**9f**	DMTST	6	**15a**	56	3:1
7	**2b**	**9a**	DMTST	5	**10b**	80	1:1.7
8	**2b**	**9b**	DMTST	5	**11b**	82	1.3:1
9	**2b**	**9c**	DMTST	5	**12b**	79	2:1
10	**2b**	**9d**	DMTST[c]	6	**13b**	56[e]	1.8:1
11	**2b**	**9f**	DMTST	4	**15b**	66	6.5:1
12	**2a**	**9b**	MeOTf	1–10			
13	**2a**	**9e**	DMTST[f]	5	**14a**	49	7:1
14	**2a**	**9e**	DMTST[f]	4	**14a**	61	6:1
15	**2a**	**9e**	DMTST[f]	3	**14a**	42	5:1
16	**2a**	**9b**	DMTST[f]	4	**11b**	80	1:1
17	**2a**	**9b**	DMTST[f]	3	**11b**	78	1:1
18	**2a**	**9d**	DMTST[f]	4	**13a**	76	1.6:1
19	**2b**	**9e**	DMTST[f]	4	**14b**	46	9:1
20	**2b**	**9d**	DMTST[f]	4	**13b**	69	2.5:1
21	**2a**	**9b**	NPCL/Tf_2O[g]	1	**11a**	75	1:1
22	**2b**	**9b**	NPCL/Tf_2O[g]	1	**11b**	65	1.3:1
23	**2a**	**9b**	Ph_2SO/Tf_2O[h]	1	**11a**	41	1:1
24	**2b**	**9b**	Ph_2SO/Tf_2O[h]	1	**11b**	20	1.4:1

[a] DMTST as the activator (method E). [b] Also obtained 23% monoacetone glucose deprotection side product. [c] Buffered by 1 equiv of TTBP. [d] Also obtained 27% glycosylated migration side product **19a**. [e] Also obtained 14% glycosylated migration side product **19b**. [f] Bufffered with 1.1 of equiv TTBP for every 1 equiv of DMTST. [g] 1.03 equiv of NPCL, 1.2 equiv of Tf_2O, and 1.3 of equiv TTBP for 45 min at 0 °C. [h] 1.03 equiv of Ph_2SO, 1.2 equiv of Tf_2O, and 1.3 equiv of TTBP for 2 h at 0 °C.

by 1 equiv of TTBP, the coupling product **13b** was formed in 34% yield (together with 32% succinimide adduct **16b** and 36% 3-*O*-triethylsilylated diacetone glucose **17**) and silylated acceptors **9e** and **9f** gave galactosylated products **14b** and **15b** in yields of 54% and 56% (with 29% and 32% **16b**), respectively.

Finally, the disarmed[17] peracetylated donors **2c** and **2d** were also evaluated against several compounds of the panel of glycosyl acceptors under conditions of NIS-mediated activation. Only low yields (24–43%), albeit with expected exclusive β-stereoselectivity, were observed throughout (Table 4). As above, acetyl migration side products were also observed.[46,50]

B. Minimizing Succinimidyl Adduct Formation: Use of Alternative Noniodonium Activators. The high levels (in some cases up to 32%) of succinimidyl glucoside adducts in **16** prompted us to explore alternative activation methods devoid of such potentially competing nucleophiles. Dimethylthiosulfonium triflate (DMTST) has, like NIS/TESOTf, been established as an effective activator for armed thioglycosides.[58,59] It is typically less reactive than NIS/TESOTf but has the advantage of not producing unwanted byproducts (namely succinimidyl adducts). By use of 5–6 equiv of DMTST as activators, both armed donors **2a** and **2b** underwent glycosylation with all the primary alcohol acceptors **9a–c** in good yields (73–82%, Table 5) to give glycosides, disaccharides, and glycoamino acids **10–12a–c**. With the secondary alcohol acceptor diacetone glucose **9d**, however, even when buffered with 1 equiv of TTBP, the coupling products **13a** and **13b** were formed from **2a** and **2b**, respectively, in moderate yields of 39 and 56%, respectively. These reactions of **9d** were contaminated by isomeric byproducts in yields of 27 and 14% that were not the same as those formed using NIS/TESOTf. From the glucosylation of **9d** using **2a**, ^{13}C NMR resonances at 100.81 and 100.95 of a side product obtained in 27% yield were characteristic of a dimethylacetal carbon in a dioxan ring.[60,61] This indicated that rearrangement of **9d** to give **19a**, as illustrated in Scheme 3, had taken place in this case. Acetonide rearrangement reactions of **9d** using O-6 as a nucleophile rather than OH-3 to give rearranged products in which the 5,6-dioxolane ring has opened and reclosed with the 3-OH to form a dioxan ring (Scheme 3) have been used as a general approach to primary 6-halo-6-deoxyglucosides,[62–64] and acetonides may act as nucleophiles in intramolecular ether formation.[65] However, to the best of our knowledge, this

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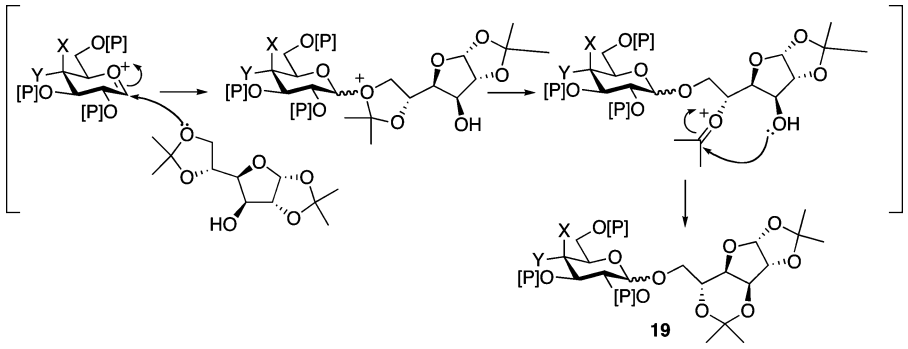
SCHEME 3



rearrangement has not, until now, been used as a strategy for accessing 6-*O*-glycosylated glucosides with perbenzylated donors, although isolated examples have been observed in low yield in Koenigs−Knorr glucosylations with peracetylated donors.[61,66] We are currently investigating this interesting and potentially useful rearrangement further.

With secondary alcohol acceptor **9e** as an acceptor, extensive silyl migration occurred leading to a mixture of coupling products arising from intra- and intermolecular migration of the TBDMS group. Such migrations are known to occur in the presence of certain Lewis acids.[67] However, with less labile *tert*-butyldi*phenyl*silylated **9f** as an acceptor, donors **2a** and **2b** gave the coupling products **15a** and **15b** in fair yields of 56 and 66%, respectively, without associated migration.

To reduce the migration that had been observed and thus increase the efficiency of glycosyl disulfide donors with testing acceptors such as **9d,e**, addition of base TTBP and reduced levels of the DTMST activator were investigated (entries 13−20, Table 5). Interestingly, a survey of the literature for activations of thioglycoside donors using DMTST reveals a disparity in the numbers of equivalents typically employed ranging from 2 to 12 equiv, with 4 equiv being most frequently employed.[68−74] Testing acceptor **9e**, which had failed to react successfully, previously gave improved yields with **2a** when treated with 3−5 equiv of DMTST (Table 5, entries 13−15); 4 equiv proved optimal. Similarly, 4 equiv proved optimal for glucosylation of **9b,d**, with the latter being formed in a dramatically improved yield (76% cf. 39%). In general, the use of fewer equivalents of DMTST gave rise to slower reactions. Although, with more nucleophilic acceptors, such as **9b**, the use of only 3 equiv of DMTST proved possible with only a marginally reduced yield (entry 17) and reaction times were greatly prolonged (18 h cf. 1 h for 4 equiv). Application of these conditions to galactosylation of **9b,d** with **2b** (entries 19 and 20) also proved successful.

Comparisons of other noniodonium-source activators and an assessment of the effect of varying the level of a given activator were also conducted. The use of triflic anhydride in conjunction with diphenylsulfoxide[75] and *N*-(phenylthio)-ϵ-caprolactam (NPCL)[76] has been recently revealed. However, using these alternative promoters, we observed reduced yields only (Table 5, entries 21−24).

The nature of the cleavage products from the activation of this novel class of donors has also intrigued us. Although, in most cases, a mixture of aglycone-associated products was isolated, making definitive accounting of all mass balance difficult, these products strongly suggested the formation of methyl polysulfides, presumably as the product of a further reaction of released disulfides and sulfenyliodides; in some cases, mass spectrometry suggests that polysulfide species with degrees of polymerization (dp) as high as dp = 10 are observed.

Competition Reactions. Having established effective conditions for the glycosylation of a range of representative acceptors, we investigated the utility of glycosyl disulfide donors in potential latent−active[19,21] reactivity tuning[18] strategies through aglycon variation.

A. Comparison of the Reactivities of 2a and 1a. Initially, ethyl glucosyl disulfide, **2a**, was compared with the corresponding thioglucoside **1a**. Thus, 1 equiv of **2a**, 1 equiv of **1a** (prepared by a literature procedure[77]), and 4 equiv of representative acceptor diacetone galactose **9b** were treated with 6 equiv of DMTST at 0 °C, followed by warming to room temperature, under the successful conditions established previously for glycosylations with DMTST. Activation with NIS/TESOTf under these conditions was considered too rapid to be monitored effectively by high-pressure liquid chromatography (HPLC) and was plagued by succinimidyl side product formation. After 10 min, HPLC indicated all of thioglucoside **1a** had reacted whereas disulfide **2a** remained. From this competition reaction, the disaccharide coupling product **11a** was obtained in 85% yield based on 1 equiv of donor **1a**, slightly higher than the yield of 75−80% obtained in

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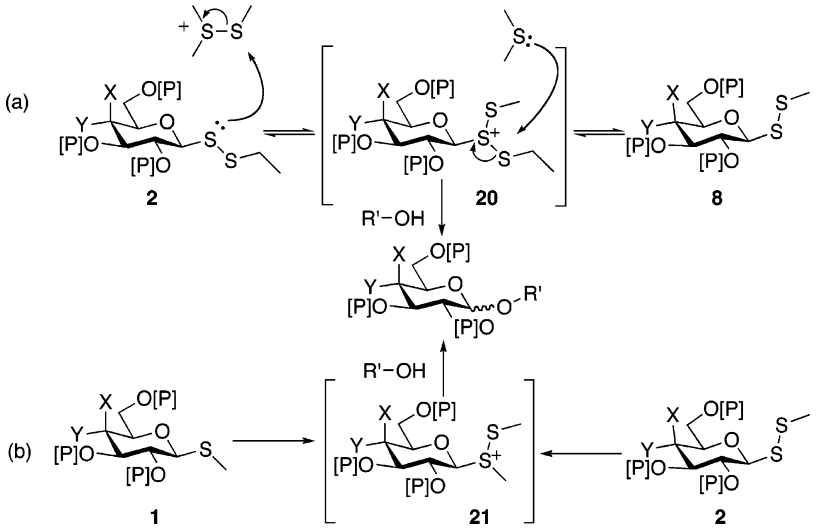
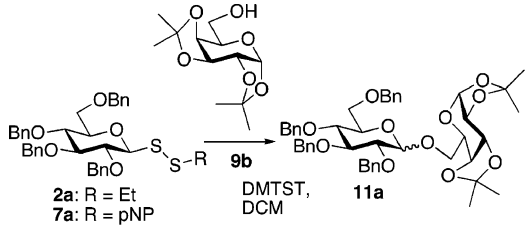
SCHEME 4



control, noncompetition reactions of **1a** with **9b** in the absence of **2a** under the same conditions. The unreacted glycosyl disulfide donor was also recovered, in 69% yield. Interestingly, this consisted of an inseparable mixture of unreacted ethyl disulfide **2a** (22% recovery) and the methyl disulfide **8a** (47%). These results show that, contrary to earlier predictions,[37] the disulfide **2a** is markedly less reactive than its counterpart thioglucoside **1a**. Recovery of the methyl disulfide **8a** may be explained by the activation preequilibria with DMTST shown in Scheme 4a via dithiosulfonium **20**. This role of DMTST as a source of "MeS^+" also suggests the likely formation of thiosulfoniums, such as **21** (Scheme 4b), similar to dithiosulfonium **20** (Scheme 4a) in DMTST activation of thioglycosides. This, in turn, highlights the potentially common intermediacy of thiosulfoniums (e.g., **21**) both in the activation of thioglycosides (e.g., methyl thioglycosides **22**), known successful donors,[14] by DMTST and in the activation of glycosyl disulfides (e.g., **8** or **2**) by a source of "Me^+". However, despite this mechanistic indication, treatment of **8** or **2a** with 1−10 equiv of MeOTf gave no reaction (entry 12, Table 5).

B. Comparison of the Reactivities of 2a and 7a. It has been shown previously that partially protected thioglycosides in which *p*-nitrophenyl is the aglycon group are sufficiently unreactive as donors to be used instead as acceptors. These may then be activated under more strenuous conditions and therefore may, in effect, be considered to be so-called latent donors[19,21] whose reactivity and hence function may be tuned by activation conditions. To explore the potential of glycosyl disufides in this regard, a competition reaction was therefore carried out to compare the reactivity of ethyl disulfide **2a** with corresponding *p*-nitrophenyl disulfide **7a**. This tested whether the *p*-nitrophenyl disulfide group could be used as a leaving group in an analogous acceptor/latent donor molecule strategy. As before, 1 equiv of **2a**, 1 equiv of **7a**, and 4 equiv of diacetone galactose **9b** were treated with 6 equiv of DMTST at 0 °C, followed by warming to room temperature. After 20 min, HPLC indicated that all the disulfide **2a** had reacted whereas disulfide **7a** largely remained. From the reaction, 74% of unreacted **7a** was recovered, as well as the coupling product **11a** in 87% yield. Given this highly promising indication of differences in reactivity based only on aglycon variation, further glycosylation reactions with DMTST and diacetone galactose **9b** were carried out using **2a** and **7a** separately to find mild activating conditions under which **2a** reacted completely but **7a** did not and more strenuous activating conditions under which **7a** reacted completely. The results are shown in Table 6.

TABLE 6. Temperature-Tuned Glycosylation Reactions of Active 2a and Latent 7a with Diacetone Galactose 9b and DMTST[a]



entry *N*	donor	reaction time (h)	temp (°C)	yield (%)[a] coupled	recovered donor	recovered acceptor
1	**2a**	5	−10	80		
2	**2a**	4	0	78		
3	**7a**	5	−10	6	80	94
4	**7a**	4	0	16	60	50
5	**7a**	20 min	0 → 20	16	58	70
6	**7a**	20 h	0 → 20	70		

[a] 5 equiv of DMTST (method E).

Pleasingly, these results indicated that a suitably protected sugar bearing a *p*-nitrophenyl disulfide group on the anomeric carbon was poorly active (entry 3, Table 6) and could be used as an acceptor/latent donor at −10 °C with a short reaction time and as a donor at room temperature with a longer reaction time (entry 6, Table 6). Importantly, under the same −10 °C mild conditions, **2a** gave 80% disaccharide coupling product (entry 1, Table 6).

The recovery of methyl *p*-nitrophenyl disulfide **23** from the glycosylation of **7a** (entry 6) may arise either through direct transfer of −SMe from the thiophilic Lewis acid activator DMTST, through transfer of −Me to the proximal, anomeric sulfur, or through post activation disulfide

scrambling of released disulfide and/or trisulfide products. The second possibility seems less likely given that methyl triflate, a powerful Me^+ donor, was found to be inactive when tested as an activator for glycosyl disulfides (entry 12, Table 5).

Finally, although these results confirmed that the *p*-nitrophenyl disulfide could be converted from a latent into an active donor by simply altering temperature and reaction time, the feasibility of chemically converting the latent *p*-nitrophenyl disulfide group in **7a** into the active ethyl group to give **2a** was also demonstrated. The disulfide **7a** was cleaved by PBu_3 in a 6:3:1 mixture of chloroform/dioxan/water[78] to give the thiol **24**[79] in 95% yield that was then reacted with ethyl methanethiosulfonate[80] and Et_3N in dichloromethane to give disulfide **2a** in 74% overall yield (Scheme 1).

Conclusions

Glycosyl disulfides have been shown for the first time to be effective glycosyl donors. Glucosylation and galactosylation of a panel of representative alcohol acceptors allowed the formation of simple glycosides, disaccharides, and glycoamino acids in yields of up to 90%. Although NIS/TESOTf proved to be an effective activator for armed glucosyl donors with good nucleophiles, the succinimide side product competed as a nucleophile with poorer nucleophiles such as secondary alcohol acceptors and even with armed galactosyl donors. DMTST proved to be a more effective activator that allowed generally efficient glycosylation of this useful novel class of tunable glycosyl donors. It should be noted that these glycosylation reactions were intentionally optimized to be compatible with relatively mild reaction conditions (typically room temperature unlike many glycosylations that require, in some cases, significant cooling). Improved yields were possible in some glycosyl disulfide systems through the use of much lower temperatures; however, these are incompatible with our longer-term goals of readily translated methods for solid-phase and oligosaccharide assembly. Although the preparative route from, e.g., precursor acetate to donor, is slightly longer for glycosyl disulfides than for, e.g., thioglycosides, the overall yields can be similarly efficient (up to 91% in this work) and such donors can be readily accessed on a gram scale. Advantageously, we have shown here that, once a given donor aglycon unit has been installed, it may be easily switched in only two steps to an alternative aglycon with differing reactivity. We believe this additional switching ability combined with effective relative glycosylation reactivities holds great promise in novel reactivity tuning strategies.

Experimental Section

Sodium Methanethiosulfonate.[44,81] Method A. Sodium sulfide nonahydrate (72.1 g, 0.3 mol) was dissolved in water (80 mL) with gentle heating to about 60 °C. The solution was cooled to 0−5 °C in an ice bath with stirring. Freshly distilled methanesulfonyl chloride (23.3 mL, 34.5 g, 0.3 mol) was added dropwise over 1 h. The mixture turned yellow, then orange-brown, and finally colorless. Some sulfur was precipitated. The mixture was heated under reflux for 18 h and then cooled. At this stage, the reaction mixture was brown. The solution was evaporated on a high-vacuum rotary evaporator giving a white solid. The solid was dried for 24 h in a vacuum desiccator over calcium chloride, ground with a pestle and mortar, and replaced in the vacuum desiccator for an additional 24 h. The white solid was extracted with dry ethanol (ca. 15 × 100 mL), and the slurry was filtered after each extraction. The filtrate was evaporated down to a thick slurry of precipitated sodium methanethiosulfonate which was collected by filtration. The filtrate thus obtained was evaporated further and refiltered. Sodium methanethiosulfonate (32.5 g, 87%) was obtained as white crystals.

Method B.[44] A mixture of sodium methanesulfinate (10 g, 98 mmol) and sulfur (3.14 g, 98 mmol) in dry methanol (1.2 L) was heated to reflux. After 20 min, the sulfur had dissolved and the reaction was stopped. The solvent was removed under reduced pressure, and the off-white residue was triturated with dry ethanol. The remaining solvent was removed in vacuo, affording the product as a pale yellow solid (10.04 g, 76%): mp 273−274 °C (lit.[81] 272−273 °C); ^{1}H NMR (200 MHz, D_2O) δ 3.24 (s, SC*H*$_3$);[44] ^{13}C NMR (400 MHz, D_2O) δ 54.9 (CH_3); MS−ES$^+$ *m/z* (%) 156 (100) (M^+ + Na).

Tetrabutylammonium Methanethiosulfonate. Sodium methanethiosulfonate (0.3 g, 2.4 mmol) and tetrabutylammonium bromide (0.772 g, 2.4 mmol) were stirred in dry acetone (5 mL) under nitrogen at room temperature for 18 h. The suspension was filtered, and the filtrate was evaporated to give an oil, which was taken up in dried chloroform (10 mL) and refiltered. The filtrate was reevaporated to give tetrabutylammonium methanethiosulfonate as a colorless oil (0.81 g, 95%) which began to crystallize under vacuum: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.95 (t, 12H, C*H*$_3$CH$_2$, *J* = 7.1 Hz), 1.35−1.75 (m, 16H, CH$_3$C*H*$_2$), 3.25−3.4 (m, 11H, SC*H*$_3$, NC*H*$_2$).

General Procedure for Bromides 5a,b.[42] Tetrabenzyl-glucose or -galactose, **4a** or **4b** (2 g, 3.7 mmol), was dissolved in a mixture of dry dichloromethane (12 mL) and dry DMF (0.8 mL) under argon. Oxalyl bromide (6 mL, 2 M in DMF, 12 mmol) was added via a syringe very carefully over 5−10 min to the stirred solution. The reaction mixture foamed. Stirring was continued for 1 h. At the end of this time, the ^{1}H NMR spectrum of a small aliquot showed complete conversion of the starting material into product. The solvent was removed in vacuo, and the residue was taken up in dichloromethane (50 mL). The dichloromethane solution was washed with saturated aqueous sodium bicarbonate (2 × 20 mL) to render it alkaline, with water (20 mL), with and brine (20 mL). The dichloromethane solution was dried ($MgSO_4$) and evaporated. The residue was taken up in toluene (30 mL) and reevaporated under high vacuum. This procedure was repeated to give **5a** or **5b** as a yellow-brown oil in approximately quantitative yield. They were used without purification either immediately or after storage for up to 15 h in a deep freeze. The procedure gave the same results on larger (4 g) scales.

Data for 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide **5a**:[42,82] ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 3.57 (dd, 1H, H-2, *J*(H-1,H-2) = 3.5 Hz, *J*(H-2,H-3) = 9.1 Hz), 3.68 (dd, 1H, H-6, *J*(H-6, H-5) = 2.1 Hz, *J*(H-6,H-6′) = 11.0 Hz), 3.79−3.84 (m, 2H, H-4, H-6′), 4.07 (t, 1H, H-3, *J* = 9.1 Hz), 4.07−4.11 (m, 1H, H-5), 4.47−4.62 (m, 3H, PhC*H*$_2$), 4.74 (s, 2H, PhC*H*$_2$), 4.84−4.89 (m, 2H, PhC*H*$_2$), 5.10 (d, 1H, PhC*H*′, *J* = 11.1 Hz), 6.46 (d, 1H, H-1, *J*(H-1,H-2) = 3.7 Hz), 7.15−7.40 (m, 20H, Ar−*H*); ^{13}C NMR (125.7 MHz, $CDCl_3$, HSQC) δ 67.5 (C-6), 72.8 (C-5), 73.5 (PhCH_2), 75.2 (PhCH_2), 75.8 (PhCH_2), 76.0 (PhCH_2), 79.6 (C-2), 82.1 (C-3), 91.9 (C-1), 127.8−128.4 (Ar−*C*H), 137.3−138.2 (Ar−*C*) (30C).

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General Procedures for Methanethiosulfonates 3a,b. Method A. The crude bromide **5a** or **5b** (ca. 2.28 g, 3.7 mmol) was divided into two roughly equal portions. They were placed under argon, and a portion of sodium methanethiosulfonate (total 1.48 g, 11.04 mmol) was added to each portion followed by dry dioxan (7.5 mL) (total 15 mL). The mixtures were stirred thoroughly and then heated to 70 °C for 15 h. They were combined, filtered, and evaporated to give a yellow oil which was then purified by flash column chromatography on silica gel (hexane/ethyl acetate 8:2).

Method B. The procedure described in method A was repeated but as a single batch using bromide **5a** or **5b** (ca. 4.5 g, 7.2 mmol), sodium methanethiosulfonate (2.96 g, 22.08 mmol), and dry dioxan (30 mL).

Method C. The procedure described in method A was repeated but as a single batch using bromide **5a** or **5b** (0.136 g, 0.225 mmol), sodium methanethiosulfonate (0.110 g, 0.820 mmol), and dry dioxan (2 mL).

Method D. The procedure described in method B was repeated using the bromide **5a** (ca. 0.59 g, ca. 0.91 mmol), sodium methanethiosulfonate (0.3 g, 2.4 mmol), and anhydrous dioxan (4 mL). Tetrabutylammonium bromide (0.297 g, 0.925 mmol) was also placed in the reaction flask with the bromide **5a** before the dioxan was added. **3a** was obtained in 73% yield (β:α = 1:5.9).

Method E. Bromide **5a** (ca. 0.56 g, ca. 0.86 mmol) was placed under nitrogen, and a solution of tetrabutylammonium methanethiosulfonate (ca. 0.81 g, ca. 2.2 mmol) in anhydrous dioxan (4 mL) was added. The mixture was heated with stirring at 70 °C for 15 h. Workup as described in method A furnished **3a** in 73% yield (β:α = 1:4.2).

2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl Methanethiosulfonate 3a. 3a was prepared using methods A, B, and C as a mixture of anomers in yields of 76% (β:α = 7.5:1), 78% (β:α = 6.2:1), and 70% (β:α = 93:7), respectively. The mixed product could be further purified by column chromatography (hexane/ethyl acetate 9:1) to afford pure 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl methanethiosulfonate **3a** as a white crystalline solid: mp 135−137 °C; $[\alpha]^{23}_D$ −6.9 (*c* 1, $CHCl_3$); IR (Nujol) 3028 (Ar C−H), 1325, 1130 (S−SO_2) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY) δ 3.36 (s, 3H, SC*H*$_3$), 3.60 (dd, 1H, H-6, *J*(H-6,H-6′) = 10.0 Hz, *J*(H-6,H-5) = 2.4 Hz), 3.45 (m, 4H, H-2, H-4, H-5, H-6′), 3.78 (pt, 1H, H-3, *J* = 8.6 Hz), 4.49 (d, 1H, PhC*H*H′, *J* = 11.6 Hz), 4.51 (d, 1H, PhC*H*H′, *J* = 10.4 Hz), 4.58 (d, 1H, PhC*H*H′, *J* = 10.8 Hz), 4.74 (d, 1H, PhCH*H*′, *J* = 10.4 Hz), 4.78 (d, 1H, PhCH*H*′, *J* = 10.8 Hz), 4.85 (d, 1H, PhC*H*H′, *J* = 10.8 Hz), 4.88 (d, 1H, PhCH*H*′, *J* = 11.2 Hz), 4.93 (d, 1H, PhCH*H*′, *J* = 10.8 Hz), 5.12 (d, 1H, H-1, *J*(H-1,H-2) = 10.0 Hz), 7.19−7.22, 7.31−7.37 (m, 20H, Ar−*H*); ^{13}C NMR (100 MHz, $CDCl_3$, APT) δ 52.9 (*C*H$_3$), 68.7 (C-6), 72.3 (Ph*C*H$_2$), 73.1 (Ph*C*H$_2$), 73.2 (Ph*C*H$_2$), 73.5 (Ph*C*H$_2$), 78.3 (C-5), 78.8 (C-2), 79.3 (C-4), 86.4 (C-3), 87.5 (C-1), 127.7−128.6 (16 × Ar−*C*H), 137.0, 137.5, 137.6, 138.0 (Ar−*C*); MS−ES$^+$ *m/z* (%) 652 (100) ($M^+ + NH_4$), 657 (98) (M^+ + Na); HRMS−ES calcd for $C_{35}H_{38}O_7S_2NH_4$ ($M^+ + NH_4$) 652.2403, found 652.2408.

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl Methanethiosulfonate 3c.[41] A mixture of **5c** (0.800 g, 1.9 mmol) and sodium methanethiosulfonate (0.390 g, 2.9 mmol) in ethanol (7 mL) was stirred at 90 °C under nitrogen. The reaction was followed on thin-layer chromatography (TLC) (ethyl acetate/hexane 9:11) which revealed conversion of starting material (R_f = 0.3) into product (R_f = 0.2). After 25 min, the resulting suspension was cooled, and the solvent was removed in vacuo. The residue was triturated with ether and dried to afford **3c** as a white solid (0.800 g, 95%): mp 148−151 °C (lit.[41] mp 151−152 °C); $[\alpha]^{22}_D$ −22 (*c* 1.0, $CHCl_3$) (lit.[41] $[\alpha]^{27}_D$ −19 (*c* 1.24, $CHCl_3$); IR (KBr, disk) 1742 (C=O), 1331, 1139 (S−SO_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.02, 2.06, 2.07, 2.09 (4 × s, 12H, OAc), 3.45 (s, 3H, SC*H*$_3$), 3.84 (ddd, 1H, H-5, *J*(H-5,H-4) = 9.9 Hz, *J*(H-5,H-6) = 5.8 Hz, *J*(H-5,H-6′) = 2.2 Hz), 4.10 (dd, 1H, H-6, *J*(H-6,H-6′) = 12.4 Hz, *J*(H-6,H-5) = 5.8 Hz), 4.33 (dd, 1H, H-6′, *J*(H-6′,H-6) = 12.4 Hz, *J*(H-6′,H-5) = 2.2 Hz), 5.06 (t, 1H, H-4, *J* = 9.7 Hz), 5.08 (dd, 1H, H-2, *J*(H-2,H-1) = 10.2 Hz, *J*(H-2,H-3) = 9.2 Hz), 5.26 (d, 1H, H-1, *J*(H-1,H-2) = 10.2 Hz), 5.31 (t, 1H, H-3, *J* = 9.2 Hz); MS−ES$^+$ *m/z* (%) 465 (100) (M^+ + Na).

General Procedure for Disulfide Syntheses for 2a−d. Methanethiosulfonate **3** (β-anomer or β-enriched) was dissolved in dry dichloromethane (15 mL). Triethylamine (221 μL, 1.59 mmol) was added, and the resulting solution was cooled to 0 °C. A dilute solution of ethanethiol (39.7 mL, 0.04 M, 1.59 mmol) was added dropwise with stirring over 40 min. The reaction mixture was allowed to warm to room temperature and was stirred for 2 h. Volatile materials were removed in vacuo, and the residue was purified by column chromatography. Elution with hexane/ethyl acetate 9:1 furnished **2.** Further elution with hexane/ethyl acetate 7:3 allowed isolation of pure samples of the unreacted α-anomer of **3** in the cases of **3a** and **3b**.

Ethyl 2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl Disulfide 2a. 3a (1.25 g, estimated β-content 1.59 mmol) gave β-**2a** (0.78 g, 79% based on β-3a) as a white solid: mp 62−64 °C; $[\alpha]^{25}_D$ −80.0 (*c* 3.0, CH_3OH); IR (KBr, disk) 3024 (Ar C−H), 2980, 2927, 2899, 2868, 2789 (C−H), 1953, 1864, 1818 (weak, Ar C−C) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, COSY) δ 1.33 (t, 3H, SCH_2CH_3, *J* = 7.8 Hz), 2.88 (m, 2H, SCH_2CH_3), 3.53 (ddd, 1H, H-5, *J*(H-5,H-4) = 9.5 Hz, *J*(H-5,H-6) = 4.0 Hz, *J*(H-5,H-6′) = 2.0 Hz), 3.72 (pd, 1H, H-6, *J*(H-6,H-6′) = 9.0 Hz), 3.74−3.77 (m, 2H, H-2, H-4), 3.78 (pd, 1H, H-6′, *J*(H-6′,H-6) = 9.0 Hz), 3.84 (t, 1H, H-3, *J* = 8.7 Hz), 4.48 (d, 1H, H-1, *J*(H-1,H-2) = 9.5 Hz), 4.58 (d, 1H, PhCHH′, *J* = 12.0 Hz), 4.63 (d, 1H, PhCHH′, *J* = 12.0 Hz), 4.65 (d, 1H, PhCHH′, *J* = 10.6 Hz), 4.83 (d, 1H, PhCHH′, *J* = 10.5 Hz), 4.89 (d, 1H, PhCHH′, *J* = 10.7 Hz), 4.92 (d, 1H, PhCHH′, *J* = 10.3 Hz), 4.92 (d, 1H, PhCHH′, *J* = 10.8 Hz), 4.98 (d, 1H, PhCHH′, *J* = 10.8 Hz), 7.22−7.40 (m, 20H, Ar−H); ^{13}C NMR (125 MHz, $CDCl_3$, HSQC) δ 14.3 (SCH_2CH_3), 34.2 (SCH_2CH_3), 69.3, 73.7, 79.4, 79.8, 86.9, (C-2,3,4,5,6), 90.1 (C-1); MS−ES$^+$ *m/z* (%) 639 (3) (M^+ + Na); HRMS−ES calcd for $C_{36}H_{40}O_5S_2NH_4$ ($M^+ + NH_4$) 634.2661, found 634.2661. Anal. Calcd for $C_{36}H_{40}O_5S_2$: C, 70.10; H, 6.54. Found: C, 70.06; H, 6.67.

Pure α-**3a** was also isolated in the chromatographic procedure as a white crystalline solid: mp 130−133 °C; $[\alpha]^{23.8}_D$ +146.7 (*c* 1, $CHCl_3$); IR (KBr, disk) 3087, 3063, 3028, 3002 (Ar C−H), 2917, 2868, 2809 (C−H), 1322, 1130 (S−SO_2) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, COSY) δ 3.30 (s, 3H, C*H*$_3$), 3.51 (t, 1H, H-4, *J* = 9.4 Hz), 3.59 (t, 1H, H-3, *J* = 8.8 Hz), 3.63 (dd, 1H, H-6′, *J*(H-6′,H-5) = 5.7 Hz, *J*(H-6′,H-6) = 10.1 Hz), 3.70 (dd, 1H, H-6, *J*(H-6,H-5) = 2.0 Hz, *J*(H-6,H-6′) = 10.4 Hz), 3.95 (dd, 1H, H-2, *J*(H-2,H-1) = 5.7 Hz, *J*(H-2,H-3) = 9.5 Hz), 4.10 (ddd, 1H, H-5, *J*(H-5,H-6) = 1.8 Hz, *J*(H-5,H-6′) = 5.9 Hz, *J*(H-5,H-4) = 10.2 Hz), 4.46 (d, 1H, PhC*H*H′, *J* = 11.3 Hz), 4.49 (d, 1H, PhC*H*H′, *J* = 12.0 Hz), 4.52 (d, 1H, PhCH*H*′, *J* = 12.0 Hz), 4.61 (d, 1H, PhC*H*H′, *J* = 11.3 Hz), 4.75 (d, 1H, PhC*H*H′, *J* = 11.3 Hz), 4.78 (d, 1H, PhCH*H*′, *J* = 11.3 Hz), 4.84 (d, 1H, PhCH*H*′, *J* = 11.3 Hz), 4.93 (d, 1H, PhCH*H*′, *J* = 11.3 Hz), 6.25 (d, 1H, H-1, *J*(H-1,H-2) = 5.7 Hz), 7.15−7.19, 7.26−7.39 (m, 20H, Ar-*H*); ^{13}C NMR (125 MHz, $CDCl_3$, HSQC) δ 52.1 (*C*H$_3$), 68.9 (C-6), 72.3 (Ph*C*H$_2$), 73.1 (C-5), 73.5 (Ph*C*H$_2$), 75.2 (Ph*C*H$_2$), 75.7 (Ph*C*H$_2$), 76.7 (C-4), 78.3 (C-2), 82.3 (C-3), 90.0 (C-1), 127.86, 127.89, 127.93, 127.97, 128.18, 128.25, 128.42, 128.46, 128.56 (Ar-*C*H), 136.66, 137.38, 137.57, 138.06 (Ar-*C*). MS-ES$^+$ *m/z* (%): 1291.2 (15) ($2M^+$ + Na), 657.1 (100) (M^+ + Na); HRMS−ES calcd for $C_{35}H_{38}O_7S_2NH_4$ ($M^+ + NH_4$) 652.2403, found 652.2407. Anal. Calcd for $C_{35}H_{38}O_7S_2$: C, 66.22; H, 6.03. Found: C, 66.41; H, 6.07.

Ethyl 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl Disulfide 2c. 3c (1.0 g, 2.2 mmol) gave β-**2c** (0.930 g, 96%) as a white solid: mp 100−102 °C; $[\alpha]^{24}_D$ −178 (*c* 1.0, CH_3OH); IR (KBr, disk) 3031 (C−H), 1728 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, COSY) δ 1.30 (t, 3H, SCH_2CH_3, *J* = 7.2 Hz), 2.00, 2.03, 2.04, 2.07 (4 × s, 12H, OAc), 2.79 (m, 2H, SCH_2CH_3), 3.73 (ddd, 1H, H-5, *J*(H-5,H-4) = 7.8 Hz, *J*(H-5,H-6) = 4.8 Hz, *J*(H-5,H-

6′) = 2.4 Hz), 4.15 (dd, 1H, H-6, *J*(H-6,H-6′) = 12.3 Hz, *J*(H-6,H-5) = 2.4 Hz), 4.22 (dd, 1H, H-6′, *J*(H-6′,H-6) = 12.3 Hz, *J*(H-6′,H-5) = 4.8 Hz), 4.51 (pt, 1H, H-2), 5.09 (m, 1H, H-4), 5.25 (d, 1H, H-1, *J*(H-1, H-2) = 8.4 Hz), 5.24 (pt, 1H, H-3); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT, HMQC) δ 14.2 (SCH_2CH_3), 20.5, 20.6, 20.7 × 2 (CH_3CO), 34.0 (SCH_2CH_3), 62.0 (C-6), 68.0 (C-4), 69.1 (C-2), 73.8 (C-3), 75.9 (C-5), 88.0 (C-1), 169.2, 169.4, 170.3, 170.6 (C=O); MS−ES$^+$ *m/z* (%) 871 (10) ($2M^+$ + Na), 447 (100) (M^+ + Na); HRMS−ES calcd for $C_{16}H_{24}O_9S_2H$ $[M+H]^+$ 425.0940, found 425.0936. Anal. Calcd for $C_{16}H_{24}O_9S_2$: C, 45.27; H, 5.70. Found: C, 45.57; H, 5.86.

***p*-Nitrophenyl 2,3,4,6-Tetra-*O*-benzyl-α,β-D-glucopyranosyl Disulfide 7a.** The methanethiosulfonate **3a** (0.11 g, estimated β-content 0.10 mmol) was placed under nitrogen, and a solution of triethylamine (12.5 μL, 0.09 mmol) in distilled dichloromethane (2 mL) was added. The mixture was stirred and cooled to 0 °C in an ice bath. A solution of *p*-nitrothiophenol (0.014 g, 0.09 mmol) in dichloromethane (8 mL) was added dropwise over 1 h. With each drop, a bright orange coloration appeared transiently. At the end of the addition, the solution was very pale yellow. All volatile materials were removed in vacuo leaving an orange oil. The oil was purified by column chromatography on silica gel using hexane/ethyl acetate 9:1 giving **7a** (0.047 g, 73%) (β:α = 9:1). Further chromatographic purification gave pure β-**7a** as a pale yellow solid (67%): mp 104.5−105.5 °C; $[\alpha]^{23.7}_D$ −182.2 (*c* 1, $CHCl_3$); IR (KBr, disk) 3027 (ArC−H), 2900 (C−H), 1515, 1340 (NO_2) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, COSY) δ 3.37−3.41 (m, 1H, H-5), 3.49−3.65 (m, 4 H, H-3, H-4, H-6, H-6′), 3.65 (t, 1H, H-2, *J* = 8.7 Hz), 4.29 (d, 1H, PhC*H*H′, *J* = 11.9 Hz), 4.33 (d, 1H, PhCH*H*′, *J* = 11.9 Hz), 4.44 (d, 1H, H-1, *J*(H-1, H-2) = 8.7 Hz), 4.48 (d, 1H, PhC*H*H′, *J* = 10.8 Hz), 4.72 (d, 1H, PhCH*H*′, *J* = 10.8 Hz), 4.76 (d, 1H, PhC*H*H′, *J* = 10.4 Hz), 4.80 (d, 1H, PhCH*H*′, *J* = 10.4 Hz), 4.81 (d, 1H, PhC*H*H′, *J* = 10.9 Hz), 4.84 (d, 1H, PhCH*H*′, *J* = 10.9 Hz), 7.05−7.31 (m, 20H, Ar-*H*), 7.65 (d, 2H, *o*-$C_6H_4NO_2$, *J* = 8.8 Hz), 7.87 (d, 2H, *m*-$C_6H_4NO_2$, *J* = 8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, HSQC) δ 68.8 (C-6), 73.5 (Ph*C*H_2), 75.1 (Ph*C*H_2), 75.6 (Ph*C*H_2), 75.8 (Ph*C*H_2), 77.4 (C-3), 79.3 (C-5), 79.8 (C-4 or C-2), 86.5 (C-4 or C-2), 89.5 (C-1), 123.5, 126.91, 127.44, 127.68, 127.76, 127.85, 127.90, 128.07, 128.13, 128.35, 128.41, 128.47, 128.49 (Ar-*C*H), 137.50, 137.70, 137.74, 138.14, 146.20, 146.72 (Ar-*C*); MS−ES$^+$ *m/z* (%) 732.3 (100) (M^+ + Na); HRMS−ES calcd for $C_{40}H_{39}NO_7S_2NH_4$ (M^+ + NH_4) 727.2512, found 727.2509.

General Procedures for Glycosylations with Disulfides 2. Method A. The disulfide **2** (0.081 mmol), NIS (10 equiv), the acceptor **9** (1 equiv), and activated powdered 4 Å molecular sieves (0.15 g) were stirred in dry dichloromethane (3 mL) under argon at room temperature for 1 h and then cooled to 0 °C. TESOTf (0.5 equiv) was added. The mixture was stirred at 0 °C until TLC (hexane/ethyl acetate 8:2 and 6:4) showed the disappearance of all starting materials. It was then diluted with dichloromethane (15 mL), washed with aqueous sodium thiosulfate (2 × 15 mL), saturated aqueous sodium bicarbonate (15 mL), water (15 mL), and brine (15 mL), and dried ($MgSO_4$). Evaporation gave the crude product, which was purified by column chromatography on silica gel using hexane/ethyl acetate mixtures.

Method B. The disulfide **2** (0.081 mmol), NIS (1.5−3 equiv), the acceptor **9** (1 equiv), and activated powdered 4 Å molecular sieves (0.15 g) were stirred in dry dichloromethane (3 mL) under argon at room temperature for 1 h and then cooled to 0 °C. TESOTf (0.5 equiv) was added. The mixture was allowed to warm to room temperature and was stirred until TLC (hexane/ethyl acetate 8:2 and 6:4) showed the disappearance of all starting materials. It was then diluted with dichloromethane (15 mL), washed with aqueous sodium thiosulfate (2 × 15 mL), saturated aqueous sodium bicarbonate (15 mL), water (15 mL), and brine (15 mL), and dried ($MgSO_4$). Evaporation gave the crude product, which was purified by column chromatography on silica gel using hexane/ethyl acetate mixtures.

Method C. The disulfide **2** (0.081 mmol), NIS (1.5−10 equiv), the acceptor **9** (1 equiv), TTBP (1 equiv), and activated powdered 4 Å molecular sieves (0.15 g) were stirred in dry dichloromethane (3 mL) under argon at room temperature for 1 h and then cooled to 0 °C. TESOTf (0.5 equiv) was added. The mixture was allowed to warm to room temperature and was stirred until TLC (hexane/ethyl acetate 8:2 and 6:4) showed the disappearance of all starting materials. It was then diluted with dichloromethane (15 mL), washed with aqueous sodium thiosulfate (2 × 15 mL), saturated aqueous sodium bicarbonate (15 mL), water (15 mL), and brine (15 mL), and dried ($MgSO_4$). Evaporation gave the crude product, which was purified by column chromatography on silica gel using hexane/ethyl acetate mixtures.

Method D. The disulfide **2** (0.081 mmol), NIS (10 equiv), the acceptor **9** (1 equiv), and activated powdered 4 Å molecular sieves (0.15 g) were stirred in dry dichloromethane (3 mL) under argon at room temperature for 1 h. TESOTf (0.5 equiv) was added. The mixture was stirred until TLC (hexane/ethyl acetate 3:2) showed the disappearance of all starting materials. It was then diluted with dichloromethane (15 mL), washed with aqueous sodium thiosulfate (2 × 15 mL), saturated aqueous sodium bicarbonate (15 mL), water (15 mL), and brine (15 mL), and dried ($MgSO_4$). Evaporation gave the crude product, which was purified by column chromatography on silica gel using hexane/ethyl acetate mixtures.

Method E. The disulfide **2** (0.081 mmol), the acceptor **9** (1 equiv), and activated powdered 4 Å molecular sieves (0.15 g) were stirred in dry dichloromethane (3 mL) under argon at room temperature for 1 h and then cooled to 0 °C. A freshly prepared solution of DMTST[58,59] (3,4,5, or 6 equiv) was added. The mixture was allowed to warm to room temperature and was stirred until TLC (hexane/ethyl acetate 8:2 and 6:4) showed the disappearance of all starting materials. It was then diluted with dichloromethane (15 mL), washed with saturated aqueous sodium bicarbonate (15 mL), water (15 mL), and brine (15 mL), and dried ($MgSO_4$). Evaporation gave the crude product, which was purified by column chromatography on silica gel using hexane/ethyl acetate mixtures.

Method F. The disulfide **2** (0.23 mmol) and the acceptor **9** (1 equiv) were refluxed with molecular sieves (4 Å beads, 200 mg) in dichloromethane (4 mL) under nitrogen. After 20 min, *N*-iodosuccinimide (2.5 equiv) was added. The reaction was followed by TLC (hexane/ethyl acetate 3:2) to show consumption of starting materials. Solids were removed by filtration, and the filtrate was diluted with dichloromethane (50 mL), washed with aqueous sodium thiosulfate (20 mL), and dried (Na_2SO_4). The solvent was removed in vacuo, and the crude product was purified by column chromatography (hexane/ethyl acetate mixtures).

Method G. The disulfide **2** (0.23 mmol) and the acceptor **9** (1 equiv) with molecular sieves (4 Å beads, 200 mg) were stirred in dichloromethane (6 mL), or acetonitrile (6 mL) was stirred under argon at room temperature. To this was added *N*-iodosuccinimide (2.5 equiv) and a solution of trifluoromethanesulfonic acid in dichloromethane (0.15 M, 1 mL). The reaction was followed by TLC (hexane/ethyl acetate 3:2) to show consumption of starting materials. Solids were removed by filtration, and the filtrate was diluted with dichloromethane (50 mL), washed with aqueous sodium thiosulfate (20 mL) and saturated sodium bicarbonate solution (2 × 20 mL), and dried (Na_2SO_4). If acetonitrile was used, then this was removed first in vacuo. The solvent was removed in vacuo, and the crude product was purified by column chromatography (hexane/ethyl acetate, mixtures).

Method H.[83] The disulfide **2** (0.18 mmol) and the acceptor **9** (1 equiv) with molecular sieves (3 Å beads, 100 mg) were stirred in dry dichloromethane (5 mL), or acetonitrile (5 mL) was stirred under argon at room temperature. After 2 h, *N*-iodosuccinimide (10 equiv) and trimethylsilyltrifluoro-

(83) Demchenko, A.; Stauch, T.; Boons, G.-J. *Synlett* **1997**, 818.

methanesulfonate (0.5 equiv) were added. The reaction was followed by TLC (hexane/ethyl acetate 3:2) to show consumption of starting materials. Solids were removed by filtration and the filtrate was diluted with dichloromethane (50 mL), washed with aqueous sodium thiosulfate (20 mL) and water (3 × 20 mL), and dried (Na_2SO_4). If acetonitrile was used, then this was removed first in vacuo. The solvent was removed in vacuo, and the crude product was purified by column chromatography (hexane/ethyl acetate, mixtures).

In Situ Preparation of DMTST.[58,59] Dimethyl disulfide (36 μL, 0.40 mmol) was added to a stirred solution of methyl triflate (45 μL, 0.40 mmol) in dry dichloromethane (1 mL) at 0 °C. The mixture was then stirred at room temperature for 2−3 h and used immediately.

Methyl 2,3,4,6-Tetra-*O*-benzyl-α*β*-D-glucopyranoside (10a). Using method A, a reaction time of 1 h, **2a** (0.080 g, 0.13 mmol), and **9a** (4 μL, 0.13 mmol) gave **10a** (0.065 g, 90%) and TLC conversion (EtOAc/hexane 4:1); R_f = 0.5 → 0,2,0.3 as a mixture of anomers (α:β = 9:15) after column chromatography (hexane/ethyl acetate 9:1). The spectroscopic and analytical data were in agreement with those reported in the literature.[84,85] Additional column chromatography (dichloromethane/ethyl acetate 20:1) furnished a pure sample of the β-anomer as a colorless oil: $[\alpha]^{23}_D$ +12.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, COSY) δ 3.45 (pt, 1H, H-2, *J* = 8.3 Hz), 3.45−3.50 (m, 1H, H-5), 3.59 (s, 3H, OC*H*$_3$), 3.60 (pt, 1H, H-4, *J* = 9.0 Hz), 3.66 (pt, 1H, H-3, *J* = 8.7 Hz), 3.70 (dd, 1H, H-6, *J*(H-6,H-6′) = 11.0 Hz, *J*(H-6,H-5) = 5.0 Hz), 3.77 (dd, 1H, H-6′, *J*(H-6′,H-6) = 11.0 Hz, *J*(H-6′,H-5) = 2.0 Hz), 4.32 (d, 1H, H-1, *J*(H-1,H-2) = 7.5 Hz), 4.54 (d, 1H, PhC*H*H′, *J* = 10.5 Hz), 4.57 (d, 1H, PhC*H*H′, *J* = 12.5 Hz), 4.63 (d, 1H, PhC*H*H′, *J* = 12.0 Hz), 4.72 (d, 1H, PhC*H*H′, *J* = 11.0 Hz), 4.80 (d, 1H, PhC*H*H′, *J* = 11.0 Hz), 4.83 (d, 1H, PhC*H*H′, *J* = 10.5 Hz), 4.93 (d, 1H, PhC*H*H′, *J* = 11.0 Hz), 4.94 (d, 1H, PhC*H*H′, *J* = 10.5 Hz), 7.15−7.17, 7.27−7.36 (m, 20H, Ar-*H*); MS−ES$^+$ *m/z* (%) 577 (100) (M^+ + Na).

Using method E, a reaction time of 2 h, **2a** (0.05 g, 0.081 mmol), and **9a** (23 μL, 0.81 mmol) gave **10a** (α:β = 1:2) (0.036 g, 78%).

1,2:3,4-Di-*O*-isopropylidene-6-*O*-(2,3,4,6-tetra-O-benzyl-α*β*-D-glucopyranosyl)-α-D-galactopyranose (11a). Using method A, a reaction time of 40 min, **2a** (0.080 g, 0.13 mmol), and **9b** (0.034 g, 0.13 mmol) gave **11a** (0.076 g, 75%) and TLC conversion (ethyl acetate/hexane 2:3); R_f = 0.3 → 0.6 as a mixture of anomers (α:β = 9:11) after column chromatography (hexane/ethyl acetate 8:2). Additional column chromatography (dichloromethane/ethyl acetate 20:1) furnished a pure sample of the β-anomer as a colorless oil: ^{1}H NMR (300 MHz, C_6D_6) δ 1.02, 1.12, 1.44, 1.47 (4 × s, 12H, CH_3), 3.29 (ddd, 1H, H-5′, *J*(H-5′,H-4) = 9.3 Hz, *J*(H-5′,H-6) = 3.9 Hz, *J*(H-5′,H-6′) = 2.1 Hz), 3.60 (dd, 1H, H-2′, *J*(H-2′,H-1′) = 5.7 Hz, *J*(H-2′,H-3′) = 3.6 Hz), 3.64 (dd, 1H, H-6′b, *J*(H-6′b,H-6′a) = 11.6 Hz, *J*(H-6′b,H-5′) = 2.1 Hz), 3.74 (dd, 1H, H-3′, *J*(H-3′,H-2′) = 11.4 Hz, *J*(H-3′,H-4′) = 9.0 Hz), 3.90 (dd, 1H, H-6b, *J*(H-6b,H-6a) = 7.8 Hz, *J*(H-6b,H-5) = 1.5 Hz), 4.03 (dd, 1H, H-3, *J*(H-3,H-2) = 10.6 Hz, *J*(H-3,H-4) = 7.6 Hz), 4.16 (dd, 1H, H-4, *J*(H-4,H-5) = 4.8 Hz, *J*(H-4,H-3) = 2.4 Hz), 4.24 (ddd, 1H, H-5, *J*(H-5,H-4) = 7.5 Hz, *J*(H-5,H-6a) = 4.5 Hz, *J*(H-5,H-6b) = 1.8 Hz), 4.43 (dd, 1H, H-6a, *J*(H-6a,H-6b) = 7.8 Hz, *J*(H-6a,H-5) = 2.1 Hz), 4.50 (dd, 1H, H-6′a, *J*(H-6′a,H-6′b) = 7.5 Hz, *J*(H-6′a,H-5′) = 1.8 Hz), 4.51 (d, 1H, H-1′, *J*(H-1′,H-2′) = 11.0 Hz), 4.38, 4.46, 4.50, 4.81, 4.86, 4.90, 5.06 (8 × d, 8H, $PhCH_2$), 5.55 (d, 1H, H-1, *J*(H-1,H-2) = 4.8 Hz), 7.07−7.61 (m, 20H, Ar−H); MS−ES$^+$ *m/z* (%) 805 (45) (M^+ + Na). The spectroscopic and analytical data were in agreement with those reported in the literature.[53,84]

Using method E with 5 equiv of DMTST, a reaction time of 30 min, **2a** (0.05 g, 0.081 mmol), and **9b** (0.021 g, 0.081 mmol) gave **11a** (α:β = 1:1) (0.048 g, 76%). Using method E with 4 equiv of DMTST and 4.4 equiv of TTBP, a reaction time of 1 h, **2a** (0.04 g, 0.065 mmol), and **9b** (0.015 g, 0.065 mmol) gave **11a** (α:β = 1:1) (0.041 g, 80%).

***N*-(Benzyloxycarbonyl)-*O*-(2,3,4,6-tetra-*O*-benzyl-α*β*-D-glucopyranosyl)-L-serine Methyl Ester (12a).** Using method A, a reaction time of 1.5 h, **2a** (0.117 g, 0.19 mmol), and **9c**[48] (0.048 g, 0.19 mmol) gave **12a** (0.042 g, 73%) and TLC conversion (ethyl acetate /hexane 2:3); R_f = 0.7 → 0.3,0.4 as a mixture of anomers (α:β = 1:1) after column chromatography (hexane/ethyl acetate 8:2) as a clear oil. Additional column chromatography (hexane/ethyl acetate 8:2) furnished a pure sample of α-**12a** as a colorless oil: IR (thin film) 3339 (C−H), 2918 (N−H), 1725 (br, C=O, amide I), 1512 (amide II), 737−668 (ArCH) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 3.53 (dd, 1H, H-2, *J*(H-2,H-3) = 9.6 Hz, *J*(H-2,H-1) = 4.0 Hz), 3.61 (dd, 1H, C*H*H′CH, *J* = 14.0 Hz, *J* = 4.4 Hz), 3.62 (pt, 1H, H-4, *J* = 6.0 Hz), 3.70 (s, 3H, OC*H*$_3$), 3.81 (m, 1H, H-5), 3.83 (dd, 1H, H-6, *J*(H-6,H-6′) = 10.8 Hz, *J*(H-6,H-5) = 3.6 Hz), 3.85 (m, 1H, CH*H*′CH), 3.89 (pt, 1H, H-3, *J* = 9.4 Hz), 4.13 (dd, 1H, H-6′, *J*(H-6′,H-6) = 10.6 Hz, *J*(H-6′,H-5) = 3.2 Hz), 4.41 (d, 1H, PhCHH, *J* = 12.0 Hz), 4.46 (d, 1H, PhCHH, *J* = 10.8 Hz), 4.52 (d, 1H, PhCHH, *J* = 10.8 Hz), 4.53 (m, 1H, CH_2C*H*), 4.59 (d, 1H, PhCHH, *J* = 11.6 Hz), 4.70 (d, 1H, PhCHH, *J* = 12.0 Hz), 4.74 (d, 1H, H-1, *J*(H-1,H-2) = 3.6 Hz), 4.79 (d, 1H, PhCHH, *J* = 10.8 Hz), 4.81 (d, 1H, PhCHH, *J* = 10.8 Hz), 4.93 (d, 1H, PhCHH, *J* = 11.2 Hz), 5.11 (s, 2H, PhC*H*$_2$), 6.03 (d, 1H, NH, *J* = 9.2 Hz), 7.28−7.42 (m, 25H, Ar-*H*); MS−ES$^+$ *m/z* (%) 798 (100) (M^+ + Na). The spectroscopic and analytical data were in agreement with those reported in the literature.[54,84]

Using method E, a reaction time of 1.5 h, **2a** (0.05 g, 0.081 mmol), and **9c** (0.020 g, 0.081 mmol) gave **12a** (α:β = 1.7:1) (0.047 g, 73%).

1,2:3,4-Di-*O*-isopropylidene-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α*β*-D-glucopyranosyl)-α-D-glucopyranose (13a). Using method C, a reaction time of 21 h, **2a** (0.05 g, 0.081 mmol), **9d** (0.021 g, 0.081 mmol), and NIS (0.18 g, 0.81 mmol) gave **13a** (α:β = 1.7:1) (0.036 g, 56%) after column chromatography (hexane/ethyl acetate 8:2). Repeated column chromatography furnished pure samples of the α- and β-anomers as colorless oils. Data for α-**13a**: $[\alpha]^{26}_D$ +43.8 (*c* 0.55, $CHCl_3$); IR (thin film) 3087, 3063, 3030 (Ar C−H), 2986, 2932 (C−H) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16, 1.18, 1.34, 1.41 (4 × s, 12H, C*H*$_3$), 3.49 (dd, 1H, H-2′, *J*(H-2′,H-1′) = 3.5 Hz, *J*(H-2′,H-3′) = 9.8 Hz), 3.54 (t, 1H, H-4′, *J* = 9.5 Hz), 3.61−3.67 (m, 2H, H-6′), 3.70−3.75 (m, 1H, H-5′), 3.87 (t, 1H, H-3′, *J* = 9.3 Hz), 3.95−4.01 (m, 2H, H-6), 4.06 (dd, 1H, H-4, *J*(H-4,H-3) = 2.8 Hz, *J*(H-4,H-5) = 8.2 Hz), 4.16 (d, 1H, H-3, *J*(H-3,H-4) = 2.8 Hz), 4.38 (d, 1H, PhC*H*H′, *J* = 10.7 Hz), 4.39−4.44 (m, 1H, H-5), 4.42 (d, 1H, PhC*H*H′, *J* = 12.1 Hz), 4.55 (d, 1H, PhCH*H*′, *J* = 12.1 Hz), 4.59 (d, 1H, H-2, *J*(H-2,H-1) = 3.6 Hz), 4.63 (d, 1H, PhC*H*H′, *J* = 11.8 Hz), 4.68 (d, 1H, PhCH*H*′, *J* = 11.9 Hz), 4.73 (d, 1H, PhCH*H*′, *J* = 10.8 Hz), 4.77 (d, 1H, PhC*H*H′, *J* = 10.5 Hz), 4.89 (d, 1H, PhCH*H*′, *J* = 11.1 Hz), 5.18 (d, 1H, H-1′, *J*(H-1′,H-2′) = 3.5 Hz), 5.80 (d, 1H, H-1, *J*(H-1,H-2) = 3.6 Hz), 7.03−7.30 (m, 20H, Ar-*H*); ^{13}C NMR (125 MHz, $CDCl_3$, HSQC) δ 25.5, 26.1, 26.8, 27.0 (*C*H$_3$), 67.0 (C-6), 68.5 (C-6′), 71.2 (C-5′), 72.3 (C-5), 73.0 (Ph*C*H$_2$), 73.5 (Ph*C*H$_2$), 75.3 (Ph*C*H$_2$), 75.6 (Ph*C*H$_2$), 77.6 (C-4′), 79.9 (C-2′), 80.6 (C-3), 81.2 (C-4), 81.5 (C-3′), 83.7 (C-2), 97.9 (C-1′), 105.2 (C-1), 109.0, 111.8 ((CH$_3$)$_2$*C*), 127.55, 127.59, 127.69, 127.74, 127.87, 127.93, 128.02, 128.06, 128.38, 128.39, 128.45 (Ar-*C*H), 137.80, 137.91, 138.13, 138.62 (Ar-*C*), MS−ES$^+$ *m/z* (%) 805.3 (100) (M^+ + Na). Data for β-**13a**: $[\alpha]^{26.1}_D$ +7.9 (*c* 0.5, $CHCl_3$); IR (thin film) 3063, 3030 (Ar C−H), 2985 (C−H) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.31 (t, 1H, H-2′, *J*(H-2′,H-1′) = 8.3 Hz), 3.34−3.38 (m, 1H, H-5′), 3.55−3.58 (m, 2H, H-3′, H-4′), 3.64 (d, 2H, H-6′, *J*(H-6′,H-5′) = 2.9 Hz), 4.00 (d, 2H, H-6, *J*(H-6,H-5) = 6.2 Hz), 4.27 (d, 1H, H-3, *J*(H-3,H-4) = 3.1 Hz), 4.31 (dd, 1H, H-4, *J*(H-4,H-5) = 4.4 Hz, *J*(H-4,H-3) = 2.8 Hz), 4.37 (dt, 1H, H-5, *J*(H-5,H-6) = 6.2 Hz, *J*(H-5,H-4) = 4.6 Hz), 4.39 (d, 1H, H-1′, *J* = 7.9 Hz), 4.42 (d, 1H, H-2, *J*(H-2,H-1) = 3.8 Hz), 4.48 (d, 1H,

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PhC*H*H′, J = 12.3 Hz), 4.51 (d, 1H, PhC*H*H′, J = 12.1 Hz), 4.55 (d, 1H, PhCH*H*′, J = 12.0 Hz), 4.66 (s, 2H, PhCH_2), 4.74 (d, 1H, PhCH*H*′, J = 10.8 Hz), 4.75 (d, 1H, PhC*H*H′, J = 11.00 Hz), 4.83 (d, 1H, PhCH*H*′, J = 11.00 Hz), 5.70 (d, 1H, H-1, J(H-1,H-2) = 3.8 Hz), 7.03−7.14, 7.16−7.33 (m, 20H, Ar-*H*); ^{13}C NMR (125 MHz, $CDCl_3$, HSQC) δ 25.3, 26.1, 26.5, 26.7 (*C*H_3), 65.8 (C-6), 68.5 (C-6′), 73.5 (Ph*C*H_2), 73.6 (C-5), 75.0 (Ph*C*H_2), 75.1 (Ph*C*H_2), 75.4 (Ph*C*H_2), 75.7 (C-5′), 77.6 (C-3′ or C-4′), 80.2 (C-3 and C-4), 82.1 (C-2′), 82.6 (C-2), 84.6 (C-3′ or C-4′), 101.3 (C-1′), 105.1 (C-1), 108.5, 111.8 ((CH$_3$)$_2$*C*), 127.89, 127.92, 128.01, 128.09, 128.29, 128.64, 128.66, 128.69, 128.74 (Ar-*C*H), 138.23, 138.37, 138.45, 138.70 (Ar-*C*); MS−ES$^+$ *m/z* (%) 805.3 (100) (M$^+$ + Na), 503.2 (95). The spectroscopic and analytical data were in agreement with those reported in the literature.[84,86]

A byproduct, the succinimidyl adduct **16a** (0.011 g, 21%), was also obtained as a colorless oil consisting of an inseparable mixture of anomers: $[\alpha]^{23.6}_D$ +23.2 (*c* 1, $CHCl_3$); IR (thin film) 3062, 3028 (Ar C−H), 2927, 2867 (C−H), 1715 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$ COSY, assignments made for the major, β-anomer) δ 2.49−2.54 (m, 4 H, (CH_2)$_2$), 3.54−3.65 (m, 3H, H-4, H-6, H-6′), 3.92 (dd, 1H, H-2, J(H-2,H-1) = 7.4 Hz, J(H-2,H-3) = 9.0 Hz), 4.08 (ddd, 1H, H-5, J = 2.2 Hz, J = 3.5 Hz, J = 10.0 Hz), 4.36−4.58 (m, 5 H, PhCH_2), 4.55 (t, 1H, H-3, J = 9.1 Hz), 4.72−4.87 (m, 3H, PhCH_2), 5.95 (d, 1H, H-1, J(H-1,H-2) = 7.5 Hz), 7.06−7.27 (m, 20H, Ar-*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1 (*C*H$_2$)$_2$), 68.8 (C-6), 73.3 (Ph*C*H_2), 73.4 (Ph*C*H_2), 74.5 (C-3), 75.2 (Ph*C*H_2), 75.9 (C-1), 75.9 (C-5), 77.3 (C-4), 78.4 (C-2), 83.1, 127.43−128.39 (Ar-*C*H), 137.44, 137.86, 138.39, 138.82 (Ar-*C*), 177.6 (C=O); MS−ES$^+$ *m/z* (%) 1266.6 (10) (2M$^+$ + Na), 644.7 (100) (M$^+$ + Na); HRMS−ES calcd for $C_{38}H_{39}NO_7NH_4$ (M$^+$ + NH_4) 639.3065, found 639.3061.

Using method E with 4 equiv of DMTST and 4.4 equiv of TTBP, a reaction time of 18 h, **2a** (0.04 g, 0.065 mmol), and **9d** (0.015 g, 0.065 mmol) gave **13a** (α:β = 1.6:1) (0.039 g, 76%).

1,2-Di-*O*-isopropylidene-5-*O*-*tert*-butyldimethylsilyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α*β*-D-glucopyranosyl)-α-D-xylofuranose (14a). Using method B, a reaction time of 22 h, **2a** (0.05 g, 0.081 mmol), **9e** (0.024 g, 0.081 mmol), and NIS (0.054 g, 0.243 mmol) gave, after column chromatography with hexane/ethyl acetate 8:2, **14a** (α-anomer only) as a colorless oil which slowly solidified to give white crystals (0.052 g, 77%): mp 105−108 °C; $[\alpha]^{27.1}_D$ +24.5 (*c* 0.85, $CHCl_3$); IR (thin film) 3087, 3063, 3030 (Ar C−H), 2951, 2928, 2883, 2856 (C−H) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, COSY) δ 0.00, 0.026 (2 × s, 6H, (CH_3)$_2$Si), 0.84 (s, 9H, (CH_3)$_3$C), 1.19, 1.45 (2 × s, 6H, (CH_3)$_2$C), 3.50 (dd, 1H, H-2′, J(H-2′,H-1′) = 3.4 Hz, J(H-2′,H-3′) = 9.7 Hz), 3.56 (t, 1H, H-4′, J = 9.5 Hz), 3.62−3.70 (m, 2H, H-6′), 3.75−3.80 (m, 1H, H-5′), 3.82 (dd, 1H, H-5a, J(H-5a,H-4) = 5.3 Hz, J(H-5a,H-5b) = 10.5 Hz), 3.90 (t, 1H, H-3′, J = 9.4 Hz), 4.03 (dd, 1H, H-5b, J(H-5b,H-4) = 7.5 Hz, J(H-5b,H-5a) = 10.6 Hz), 4.15−4.17 (m, 1H, H-3), 4.17−4.21 (m, 1H, H-4), 4.42 (d, 1H, PhC*H*H′, J = 10.8 Hz), 4.45 (d, 1H, PhC*H*H′, J = 12.1 Hz), 4.57 (d, 1H, PhCH*H*′, J = 12.1 Hz), 4.63 (d, 1H, PhC*H*H′, J = 12.5 Hz), 4.65 (d, 1H, H-2, J(H-2,H-1) = 3.7 Hz), 4.69 (d, 1H, PhCH*H*′, J = 12.0 Hz), 4.75 (d, 1H, PhC*H*H′, J = 11.0 Hz), 4.79 (d, 1H, PhCH*H*′, J = 10.6 Hz), 4.90 (d, 1H, PhCH*H*′, J = 10.9 Hz), 5.07 (d, 1H, H-1′, J(H-1′,H-2′) = 3.4 Hz), 5.84 (d, 1H, H-1, J(H-1,H-2) = 3.5 Hz), 7.07−7.14, 7.20−7.31 (m, 20H, Ar-*H*); ^{13}C NMR (125 MHz, $CDCl_3$, HSQC) δ −5.28, −5.15 ((*C*H$_3$)Si), 18.2 ((CH$_3$)$_3$*C*Si), 25.9 ((*C*H$_3$)$_3$CSi), 26.2, 26.8 ((*C*H$_3$)$_2$C), 59.9 (C-5), 68.5 (C-6′), 71.1 (C-5′), 73.0 (Ph*C*H_2), 73.5 (Ph*C*H_2), 75.2 (Ph*C*H_2), 75.6 (Ph*C*H_2), 77.6 (C-4′), 79.9 (C-2′), 80.7 (C-3), 81.0 (C-4), 81.5 (C-3′), 83.4 (C-2), 98.1 (C-1′), 105.9 (C-1), 111.6 ((CH$_3$)$_2$*C*), 127.56, 127.67, 127.69, 127.71, 127.80, 127.89, 127.92, 127.98, 128.00, 128.32, 128.36, 128.38, 128.42, 128.44 (Ar-*C*H), 137.83, 137.99, 138.12, 138.67 (Ar-*C*); MS−ES$^+$ *m/z* (%) 894.4 (100) (M$^+$ + Na); HRMS−ES calcd for $C_{48}H_{62}O_{10}SiNa$ (M$^+$ + Na) 849.4010, found 849.4001. Anal. Calcd for $C_{48}H_{62}O_{10}Si$: C, 69.70; H, 7.56. Found: C, 69.45; H, 7.61. **16a** (0.011 g, 21%) was also obtained.

Using method E with 4 equiv of DMTST and 4.4 equiv of TTBP, a reaction time of 18 h, **2a** (0.04 g, 0.065 mmol), and **9e** (0.02 g, 0.065 mmol) gave **14a** (α:β = 6:1) (0.033 g, 61%).

1,2-Di-*O*-isopropylidene-5-*O*-*tert*-butyldiphenylsilyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α*β*-D-glucopyranosyl)-α-D-xylofuranose (15a). Using method B, a reaction time of 18 h, **2a** (0.05 g, 0.081 mmol), **9f** (0.034 g, 0.081 mmol), and NIS (0.054 g, 0.243 mmol) gave, after column chromatography (hexane/ethyl acetate 9:1), **15a** (0.032 g, 41%) as a colorless oil consisting of an inseparable mixture of anomers (α:β = 3.4:1): $[\alpha]^{26.9}_D$ +14.05 (*c* 1, $CHCl_3$); IR (thin film) 3087, 3065, 3030 (Ar C−H), 2930, 2891, 2857 (C−H) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.05, 1.07 (2 × s, 9H, (CH_3)$_3$C), 1.22, 1.27, 1.40, 1.52 (4 × s, 6H, (CH_3)$_2$C), 3.29−4.96 (m, ca. 19H), 5.08 (d, H$_\alpha$-1′, J(H$_\alpha$-1′,H$_\alpha$-2′) = 3.3 Hz), 5.75 (d, H$_\beta$-1, J(H$_\beta$-1,H$_\beta$-2) = 3.9 Hz), 5.87 (d, H$_\alpha$-1, J(H$_\alpha$-1,H$_\alpha$-2) = 3.7 Hz), 7.09−7.48, 7.60−7.77 (m, 30H, Ar-*H*). ^{1}H NMR (500 MHz, $CDCl_3$, assignments were made for the ring protons of the individual isomers using two-dimensional COSY, HSQC, and TOCSY experiments) α-**15a**: δ 3.43 (dd, 1H, H-2′, J(H-2′,H-1′) = 3.5 Hz, J(H-2′,H-3′) = 9.7 Hz), 3.49 (dd, 1H, H-4′, J(H-4′,H-3′) = 9.2 Hz, J(H-4′,H-5′) = 9.8 Hz), 3.61 (m, 2H, H-6a′, H-6b′), 3.71 (m, 1H, H-5′), 3.80 (dd, 1H, H-3′, J = 9.2 Hz, J = 9.3 Hz), 3.89 (dd, 1H, H-5a, J = 3.6 Hz, J = 8.9 Hz), 4.07 (m, 1H, H-5b), 4.09 (m, 1H, H-3), 4.11 (m, 1H, H-4), 4.60 (d, 1H, H-2, J(H-2,H-1) = 3.6 Hz), 4.99 (d, 1H, H-1′, J(H-1′,H-2′) = 3.3 Hz), 5.78 (d, 1H, H-1, J(H-1,H-2) = 3.7 Hz). β-**15a**: δ 3.25 (dd, 1H, H-2′, J = 7.9 Hz, J = 8.9 Hz), 3.35 (m, 1H, H-4′), 3.56 (m, 4 H, H-3′, H-5′, H-6a′, H-6b′), 3.85 (dd, 1H, H-5a, J(H-5a,H-4) = 5.9 Hz, J(H-5a,H-5b) = 10.6 Hz), 3.94 (dd, 1H, H-5b, J(H-5b,H-4) = 6.2 Hz, J(H-5b,H-5a) = 10.6 Hz), 4.32 (m, 1H, H-4), 4.36 (m, 1H, H-3), 4.41 (d, 1H, H-1′, J(H-1′,H-2′) = 7.8 Hz), 4.49 (d, 1H, H-2, J(H-2,H-1) = 3.8 Hz), 5.66 (d, 1H, H-1, J(H-1,H-2) = 3.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, HSQC, assignable signals) δ 19.1 ((CH$_3$)$_3$*C*Si), 26.1−26.9 ((*C*H$_3$)$_2$C, (*C*H$_3$)$_3$CSi), 68.6 (C$_\alpha$-6′), 68.9 (C$_\beta$-6′), 71.2 (C$_\alpha$-5′), 72.8−75.6 (Ph*C*H_2), 77.5 (C$_\alpha$-4′), 77.7 (C$_\beta$-5′), 79.1 (C$_\beta$-3), 79.7 (C$_\alpha$-2′), 80.6 (C$_\alpha$-3), 80.7 (C$_\beta$-4), 81.0 (C$_\alpha$-4), 81.5 (C$_\alpha$-3′ and C$_\alpha$-5), 81.7 (C$_\beta$-2′), 82.1 (C$_\beta$-2), 83.3 (C$_\alpha$-2), 84.6 (C$_\beta$-3′), 98.1 (C$_\alpha$-1′), 100.8 (C$_\beta$-1′), 104.8 (C$_\beta$-1), 104.9 (C$_\alpha$-1), 115.6 ((CH$_3$)$_2$*C*), 127.5−133.5 (Ar-*C*H), 135.4−138.6 (Ar-*C*); MS−ES$^+$ *m/z* (%) 973.5 (100) (M$^+$ + Na); HRMS−ES calcd for $C_{58}H_{66}O_{10}SiNH_4$ (M$^+$ + NH_4) 968.4764, found 968.4774. **16a** (0.014 g, 27%) was also obtained.

Using method E, a reaction time of 27 h, **2a** (0.05 g, 0.081 mmol), and **9f** (0.034 g, 0.081 mmol) gave **15a** (α:β = 3:1) (0.044 g, 56%).

Methyl 2,3,4,6-Tetra-*O*-acetyl-*β*-D-glucopyranoside (10c). Using method D, a reaction time of 15 min, **2c** (0.080 g, 0.19 mmol), and **9a** (6 μL, 0.19 mmol) gave **10c** (β-anomer only) and TLC conversion (hexane/EtOAc 3:2; R_f = 0.3 → 0.2) (0.031 g, 24%) after column chromatography (hexane/ethyl acetate 1:1); IR (thin film) 3352 (C−H), 1730 (C=O) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.00, 2.02, 2.04, 2.05 (4 × s, 12H, OAc), 3.50 (s, 3H, OCH_3), 3.64−3.74 (m, 2H), 4.42 (d, 1H, H-1, J(H-1,H-2) = 8.0 Hz), 4.14 (dd, 1H, H-6, J(H-6,H-6′) = 12.2 Hz, J(H-6,H-5) = 2.4 Hz), 4.28 (dd, 1H, H-6′, J(H-6′,H-6) = 12.2 Hz, J(H-6′,H-5) = 4.5 Hz), 4.94−5.21 (m, 2H); MS-ES$^+$ *m/z* (%) 701 (6) (2M$^+$ + Na), 484 (100), 385 (2) (M$^+$ + Na). The spectroscopic and analytical data were in agreement with those reported in the literature.[87,88]

1,2:3,4-Di-*O*-isopropylidene-6-*O*-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)-α-D-galactopyranose (11c). Using method D, a reaction time of 2 h, **2c** (0.10 g, 0.23 mmol), and **9b** (0.061 g, 0.23 mmol) gave **11c** (β-anomer only) (0.05 g, 36%) after column chromatography (hexane/ethyl acetate 1:1). The spectroscopic and analytical data were in agreement with those reported in the literature:[89] mp 138−142 °C (lit.[90] 140−141 °C); $[\alpha]^{21}_D$ −35 (*c* 2.25, CH_3OH) (lit.[91] $[\alpha]^{27}_D$ −53 (*c* 1.05, $CHCl_3$)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30, 1.42, 1.48 (3 × s, 12H, CH_3), 1.98, 2.00, 2.05, 2. 05 (4 × s, 12H, OAc), 3.66 (dd,

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1H, H-6b, *J*(H-6b,H-6a) = 11.4 Hz, *J*(H-6b,H-5) = 7.2 Hz), 3.68 (m, 1H, H-5′), 3.91 (m, 1H, H-5), 4.00 (dd, 1H, H-6a, *J*(H-6a,H-6b) = 11.4 Hz, *J*(H-6a,H-5) = 3.3 Hz), 4.11 (m, 1H, H-6b′), 4.16 (dd, 1H, H-4, *J*(H-4,H-3) = 7.8 Hz, *J*(H-4,H-5) =1.9 Hz), 4.23 (pd, 1H, H-6a′), 4.27 (dd, 1H, H-2, *J*(H-2,H-3) = 5.1 Hz, *J*(H-2,H-1) = 2.4 Hz), 4.56 (dd, 1H, H-3, *J*(H-3,H-2) = 8.1 Hz, *J*(H-3,H-4) = 2.4 Hz), 4.60 (d, 1H, H-1, *J*(H-1,H-2) = 8.1 Hz), 4.98 (dd, 1H, H-2′, *J*(H-2′,H-3′) = 9.6 Hz, *J*(H-2′,H-1′) = 7.8 Hz), 5.06 (pt, 1H, H-3′), 5.20 (pt, 1H, H-4′), 5.48 (d, 1H, H-1, *J*(H-1,H-2) = 4.8 Hz); MS−ES$^+$ *m/z* (%) 613 (100) (M^+ + Na); HRMS−ES calcd for $C_{26}H_{38}O_{15}Na$ (M^+ + Na) 613.2108, found 613.2109.

Using method F, a reaction time of 24 h, **2c** (0.10 g, 0.23 mmol), and **9b** (0.061 g, 0.23 mmol) gave **11c** (β-anomer only) (0.026 g, 18%) after column chromatography (hexane/ethyl acetate 1:1).

Using method G in DCM, a reaction time of 22 h, **2c** (0.10 g, 0.23 mmol), and **9b** (0.061 g, 0.23 mmol) gave **11c** (β-anomer only) (0.036 g, 26%) after column chromatography (hexane/ethyl acetate 1:1).

Using method G in CH_3CN, a reaction time of 22 h, **2c** (0.10 g, 0.23 mmol), and **9b** (0.061 g, 0.23 mmol) gave **11c** (β-anomer only) (2 mg, 2%) after column chromatography (hexane/ethyl acetate 1:1).

Using method H in DCM, a reaction time of 22 h, **2c** (80 mg, 0.18 mmol), and **9b** (0.050 g, 0.18 mmol) gave **11c** (β-anomer only) (0.032 g, 30%) after column chromatography (hexane/ethyl acetate 1:1).

Using method H in CH_3CN, a reaction time of 22 h, **2c** (0.10 g, 0.23 mmol), and **9b** (0.061 g, 0.23 mmol) gave **11c** (β-anomer only) (0.022 g, 16%) after column chromatography (hexane/ethyl acetate 1:1).

***N*-(Benzyloxycarbonyl)-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-L-serine Methyl Ester (12c).** Using method D, a reaction time of 24 h, **2d** (0.090 g, 0.21 mmol), and **9c**[48] (0.054 g, 0.21 mmol) gave **12c** (β-anomer only) (0.042 g, 34%) after column chromatography with hexane/ethyl acetate 1:1. The spectroscopic and analytical data were in agreement with those reported in the literature:[92] IR (thin film) 3352 (C−H), 2955 (N−H), 1745 (C=O), 1653 (amide I), 1522 (amide II) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY) δ 1.99, 2.02, 2.07 (4 × s, 12H, OAc), 3.62 (ddd, 1H, H-5, *J*(H-5,H-4) = 9.6 Hz, *J*(H-5,H-6) = 4.8 Hz, *J*(H-5,H-6′) = 2.8 Hz), 3.76 (s, 3H, OC*H*$_3$), 3.88 (dd, 1H, C*H*H′CH, *J*(H,H′) = 10.6 Hz, *J* = 3.4 Hz), 4.10 (dd, 1H, H-6, *J*(H-6,H-6′) = 12.0 Hz, *J*(H-6,H-5) = 2.4 Hz), 4.24 (m, 2H, H-6′, CH*H*′CH), 4.48 (d, 1H, H-1, *J*(H-1,H-2) = 8.0 Hz), 4.93 (dd, 1H, H-2, *J*(H-2,H-3) = 9.2 Hz, *J*(H-2,H-1) = 8.0 Hz), 5.05 (pt, 1H, H-4, *J* = 9.6 Hz), 5.13 (m, 3H, CH_2CH, $PhCH_2$), 5.16 (pt, 1H, H-3, *J* = 8.8 Hz), 5.57 (d, 1H, NH, *J* = 7.6 Hz), 7.31−7.37 (m, 5H, Ar-*H*); MS-ES$^+$ *m/z* (%) 276 (100) (ZSerOMe$^+$ + Na), 606 (32) (M^+ + Na).

Competition Reaction Between 1a and 2a. 1a (0.047 g, 0.081 mmol), **2a** (0.05 g, 0.081 mmol), and activated powdered 4 Å molecular sieves (0.15 g) were placed under argon, and a solution of **9b** (0.084 g, 0.34 mmol) in dry dichloromethane (2 mL) was added. The mixture was stirred at room temperature for 1 h and then cooled to 0 °C. A solution of freshly prepared DMTST (from dimethyl disulfide (43 μL, 0.48 mmol) and methyl triflate (54 μL, 0.48 mmol)) in dry dichloromethane (1 mL) was added. The ice bath was removed, and the reaction mixture was allowed to warm to room temperature. After 10 min, HPLC indicated that **1a** had reacted completely but that **2a** remained. After 1 h, the HPLC trace was little changed so the reaction mixture was diluted with dichloromethane (15 mL), washed with saturated aqueous sodium bicarbonate (15 mL), water (15 mL), and brine (15 mL), and dried ($MgSO_4$). Evaporation, followed by column chromatography (hexane/ethyl acetate 8:2 to 1:1) furnished 0.034 g of a mixture of **2a** (22%) and **8a** (47%) as a white solid: selected ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, SCH_2CH_3 in **2a**, *J* = 7.5 Hz), 2.44 (s, SCH_3 in **8a**), 2.71−2.83 (m, SCH_2CH_3 in **2a**); selected ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.30 (SCH_2CH_3 in **2a**), 24.76 (s, SCH_3 in **8a**), 34.09 (SCH_2CH_3 in **2a**), 89.70, 89.75 (C-1 in **2a** and **8a**); MS−ES$^+$ *m/z* (%) 639.7 (15) (M^+(**2a**) + Na), 625.6 (100) (M^+(**8a**) + Na). **11a** (0.05 g, 85% based on quantity of **1a** used) and unreacted **9b** (0.036 g) were also obtained.

Competition Reaction Between 2a and 7a. 2a (0.05 g, 0.081 mmol), **7a** (0.057 g, 0.081 mmol), and activated powdered 4 Å molecular sieves (0.15 g) were placed under argon. A solution of **9b** (0.084 g, 0.34 mmol) in dry dichloromethane (2 mL) was added. The mixture was stirred at room temperature for 1 h, and a sample was removed and analyzed by HPLC. The reaction mixture was then cooled to 0 °C. A solution of freshly prepared DMTST (from dimethyl disulfide (43 μL, 0.48 mmol) and methyl triflate (54 μL, 0.48 mmol)) in dry dichloromethane (1 mL) was added. The ice bath was removed, and the reaction mixture was allowed to warm to room temperature. After 20 min, HPLC showed that **2a** had reacted completely but that some **7a** remained. After 2 h, there was no further change and the reaction mixture was diluted with dichloromethane (15 mL), washed with saturated aqueous sodium bicarbonate (15 mL), water (15 mL), and brine (15 mL), and dried ($MgSO_4$). Evaporation, followed by column chromatography (hexane/ethyl acetate 17:3, then 8:2, then 11:9), furnished unreacted **7a** (0.035 g, 74%), **11a** (0.045 g, 87% based on quantity of **2a** used), and unreacted **9b** (0.028 g).

Reactivity Testing Experiments with 2a (Table 6). A. 2a (0.05 g, 0.081 mmol) and activated powdered 4 Å molecular sieves (0.15 g) were placed under argon, and a solution of **9b** (0.021 g, 0.081 mmol) in dry dichloromethane (2 mL) was added. The mixture was stirred at room temperature for 1 h and then cooled to 0 °C. A solution of freshly prepared DMTST (from dimethyl disulfide (43 μL, 0.48 mmol) and methyl triflate (54 μL, 0.48 mmol)) in dry dichloromethane (1 mL) was added. The reaction mixture was stirred at 0 °C and monitored by TLC (hexane/ethyl acetate 8:2 and 6:4). After 4 h, TLC showed complete consumption of starting materials so the reaction mixture was diluted with dichloromethane (15 mL), washed with saturated aqueous sodium bicarbonate (15 mL), water (15 mL), and brine (15 mL), and dried ($MgSO_4$). Evaporation, followed by column chromatography using hexane/ethyl acetate 8:2, furnished **11a** (0.050 g, 78%).

B. The procedure described in A was repeated at −10 °C. In this case, TLC showed complete consumption of starting materials after 5 h. **11a** (0.051 g, 80%) was obtained.

Reactivity Testing Experiments with 7a (Table 6). A. 7a (0.055 g, 0.078 mmol) and activated powdered 4 Å molecular sieves (0.15 g) were placed under argon. A solution of **9b** (0.020 g, 0.078 mmol) in dry dichloromethane (2 mL) was added. The mixture was stirred at room temperature for 1 h and then cooled to 0 °C. A solution of freshly prepared DMTST (from dimethyl disulfide (43 μL, 0.48 mmol) and methyl triflate (54 μL, 0.48 mmol)) in dry dichloromethane (1 mL) was added. The ice bath was removed, and the reaction mixture was allowed to warm to room temperature. The reaction was monitored by TLC (hexane/ethyl acetate 8:2 and 6:4). After 20 h, TLC showed complete consumption of starting materials. The reaction mixture was diluted with dichloromethane (15 mL), washed with saturated aqueous sodium bicarbonate (15 mL), water (15 mL), and brine (15 mL), and dried ($MgSO_4$). Evaporation, followed by column chromatography using hexane/ethyl acetate 8.5:1.5, furnished **11a** (0.043 g, 70%) and methyl *p*-nitrophenyl disulfide (0.015 g, 95%) as a yellow solid: mp 36−38 °C (lit.[93] 42.9−44.3 °C); ^1H NMR (200 MHz, $CDCl_3$) δ 2.48 (s, 3H, C*H*$_3$), 7.65 (d, 2H, ArC-*H*, *J* = 9.2 Hz),

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8.20 (d, 2H, ArC-*H*, J = 9.0 Hz). The spectroscopic and analytical data were in agreement with those reported in the literature.[93]

B. 7a (0.055 g, 0.078 mmol) and activated powdered 4 Å molecular sieves (0.15 g) were placed under argon. A solution of **9b** (0.020 g, 0.078 mmol) in dry dichloromethane (2 mL) was added. The mixture was stirred at room temperature for 1 h and then cooled to 0 °C. A solution of freshly prepared DMTST (from dimethyl disulfide (43 μL, 0.48 mmol) and methyl triflate (54 μL, 0.48 mmol)) in dry dichloromethane (1 mL) was added. The ice bath was removed, and the reaction mixture was allowed to warm to room temperature over 20 min. It was then worked up as described in A. Evaporation, followed by column chromatography using hexane/ethyl acetate 8.5:1.5 furnished unreacted **7a** (0.032 g, 58%), **11a** (0.010 g, 16%), and unreacted **9b** (0.014 g, 70%).

C. 7a (0.055 g, 0.078 mmol) and activated powdered 4 Å molecular sieves (0.15 g) were placed under argon. A solution of **9b** (0.020 g, 0.078 mmol) in dry dichloromethane (2 mL) was added. The mixture was stirred at room temperature for 1 h and then cooled to 0 °C. A solution of freshly prepared DMTST (from dimethyl disulfide (43 μL, 0.48 mmol) and methyl triflate (54 μL, 0.48 mmol)) in dry dichloromethane (1 mL) was added. The reaction mixture was stirred at 0 °C for 4 h. It was then worked up as described in A. Evaporation, followed by column chromatography using hexane/ethyl acetate 8.5:1.5, furnished unreacted **7a** (0.033 g, 60%), **11a** (0.010 g, 16%), and unreacted **9b** (0.010 g, 50%).

D. The procedure described in C was repeated but with a reaction temperature of −10 °C and a reaction time of 5 h. Column chromatography of the crude product furnished unreacted **7a** (0.044 g, 80%), **11a** (0.004 g, 6%), and unreacted **9b** (0.019 g, 94%).

Conversion of 7a into 2a. 7a (0.023 g, 0.032 mmol) was dissolved in a mixture of chloroform (0.6 mL), dioxan (0.3 mL), and water (0.1 mL) under nitrogen. Nitrogen was bubbled through the solution for 30 min. Tributylphosphine (11.9 μL, 0.048 mmol) was added. The reaction mixture immediately became deep orange but faded rapidly to yellow. After 5 min, TLC (hexane/ethyl acetate 7:3) showed complete consumption of starting material. The solution was evaporated, and the residue was purified by rapid column chromatography using hexane/ethyl acetate 9:1 to furnish thiol **24** (0.017 g, 95%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.24 (d, 1H, SH, J = 8.3 Hz), 3.24−3.71 (m, 6H), 4.35−4.92 (m, 9H), 7.02−7.34 (m, 20H, Ar-*H*). **24** (0.017 g, 0.030 mmol) was then immediately dissolved in dichloromethane (1.5 mL) and added dropwise to a stirred solution of ethyl methanethiosulfonate **17**[80] (0.004 g, 0.035 mmol) and triethylamine (4.2 μL, 0.030 mmol) in dichloromethane (0.5 mL) at 0 °C under nitrogen. The ice bath was removed, and the reaction mixture was allowed to warm to room temperature. After 1 h, TLC (hexane/ethyl acetate 8:2) indicated complete consumption of **24**. The reaction mixture was evaporated, and the residue was purified by column chromatography using hexane/ethyl acetate 9:1, furnishing **2a** (0.014 g, 74%).

Ethyl Methanethiosulfonate.[80] Ethyl bromide (1.8 mL, 24 mmol) was added to a stirred suspension of sodium methanethiosulfonate (0.5 g, 4.0 mmol) in dry ethanol (5 mL) under argon. The reaction mixture was heated to 50 °C for 8 h and then cooled. The ethanol was evaporated, and the residue was stirred with dichloromethane (20 mL) and then filtered. The filtrate was evaporated. Column chromatography of the residue using hexane/ethyl acetate 8:2 gave the title product (0.498 g, 89%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.47 (t, 3H, SCH_2CH_3, J = 7.5 Hz), 3.22 (q, 2H, SCH_2CH_3, J = 7.3 Hz), 3.34 (s, 3H, SCH_3).

Acknowledgment. We thank Justin Marston and Dr. Andrew Cowley for technical assistance, Professor J. Grant Buchanan for helpful discussions, the EPSRC UK (S.J.W. and D.P.G.), the HEFCE UK (A.L.H.), the Daphne Jackson Trust for a fellowship funded by the Royal Commission for the Exhibition of 1851 (E.J.G.), and the University of Oxford (P.M.R. and D.P.G.) for funding.

Supporting Information Available: General experimental, experimental details for the D-galacto donor series, spectra of reported compounds, and crystallographic information files (CIF) for 2d and 3d. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051374J

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