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Glycosyl Dithiocarbamates: β-Selective Couplings without Auxiliary Groups

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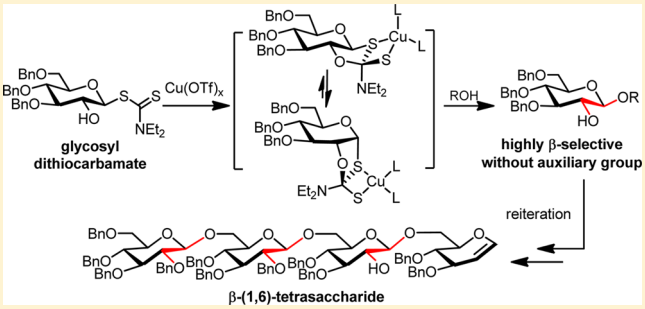
Supporting Information

ABSTRACT: In this article, we evaluate glycosyl dithiocarbamates (DTCs) with unprotected C2 hydroxyls as donors in β-linked oligosaccharide synthesis. We report a mild, one-pot conversion of glycals into β-glycosyl DTCs via DMDO oxidation with subsequent ring opening by DTC salts, which can be generated in situ from secondary amines and CS_2. Glycosyl DTCs are readily activated with Cu(I) or Cu(II) triflate at low temperatures and are amenable to reiterative synthesis strategies, as demonstrated by the efficient construction of a tri-β-1,6-linked tetrasaccharide. Glycosyl DTC couplings are highly β-selective despite the absence of a preexisting C2 auxiliary group. We provide evidence that the directing effect is mediated by the C2 hydroxyl itself via the putative formation of a cis-fused bicyclic intermediate.



INTRODUCTION

Thioglycosides are widely used as glycosyl donors in the synthesis of complex oligosaccharides because their stability, ease of activation, and flexibility in the tuning of glycosyl coupling conditions. Numerous thioglycosyl donors have been developed, resulting in both technological advances and mechanistic insights for glycosyl activation.[1] For example, thioglycosides are often orthogonal with respect to glycosyl donors that are activated by Lewis acids,[2] and their reactivities can be tuned to enable programmable one-pot oligosaccharide syntheses.[3] Thioglycosyl donors can also be activated at low temperatures to generate highly reactive glycosyl triflates followed by coupling with an acceptor.[4−7] However, thioglycosides are susceptible to side reactions, such as aglycon transfer or cross-reactivity between the thiophilic promoter and acceptor,[8] and the influence of protecting groups on donor reactivity (i.e., armed vs disarmed) can sometimes be counterproductive toward glycosyl coupling. Such limitations motivate the search for new glycosyl donors and activation conditions.

In this article, we evaluate glycosyl dithiocarbamates (DTCs) as activatible donors for glycoconjugate and oligosaccharide synthesis. We have recently described the in situ generation of glycosyl DTCs as intermediates in a modified version of glycal assembly;[9] here, we deliberately isolate glycosyl DTCs to understand their reactivities further. DTCs already have broad applicability in organic synthesis,[10] as ligands in coordination chemistry,[11] and for the functionalization of metal surfaces.[12−14] An especially appealing quality of DTCs is that many of them can be prepared in situ simply by adding amines to CS_2 in polar solvents.[15,16]

DTCs are excellent candidates for electrophilic activation based on their strong affinity for metals[11] and the relatively low oxidative potentials of thioamide species.[17,18] The latter is significant, as the activation barriers of thioglycosides and related species have been shown to correlate with their oxidative potentials.[19] Surprisingly, glycosyl DTCs have been largely overlooked as donors despite the use of closely related glycosyl thioimidates in carbohydrate synthesis.[1] This may be partly due to earlier challenges in the preparation of glycosyl DTCs by the nucleophilic substitution of glycosyl halides with DTC salts[20,21] or by the dehydrative substitution of lactols (hemiacetals) under phase-transfer conditions.[22] Furthermore, although glycosyl DTCs have been shown to produce disaccharides in good yield, the coupling conditions involve excess activating agent and offer limited stereocontrol. We find that glycosyl DTCs are efficiently prepared from glycals, and we demonstrate their use in the synthesis of oligosaccharides using mild Lewis acids.

A remarkable aspect of this study is that glycosyl DTCs are highly β-selective in the absence of predesignated auxiliary groups. β-Linked glycosides are typically formed using glycosyl donors with an acyl group at the C2 position (Figure 1, top). However, acylated glycosyl donors can have variable reactivity: in some cases, a 2-*O*-benzoate or pivaloate can enhance donor reactivity,[1,23] but in other cases, the electron-withdrawing nature of acyl groups can be deactivating.[24] Furthermore, donors with C2 acyl groups can form stabilized 1,2-dioxolenium intermediates whose ambident nature can give rise to competing orthoester byproducts, particularly when

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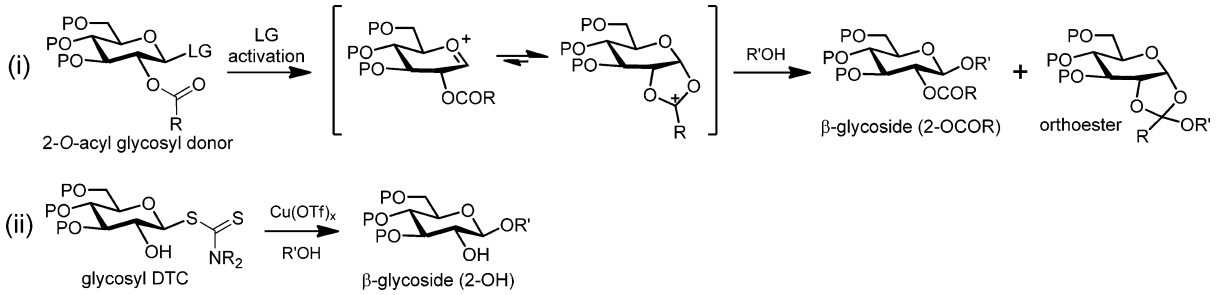


Figure 1. β-Selective glycosylation using (i) 2-*O*-acyl glycosyl donors (with potential formation of orthoester byproduct) or (ii) glycosyl dithiocarbamates with free C2 hydroxyls.

challenged with sterically hindered acceptors.[23,25] Such issues are neatly circumvented when using glycosyl DTCs (Figure 1, bottom). With regard to the basis for β-selectivity, we present a series of experiments to show that the C2 hydroxyl itself plays an essential directing role in β-glycoside formation.

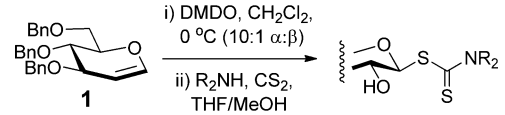
RESULTS AND DISCUSSION

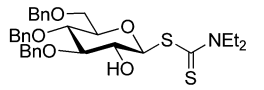
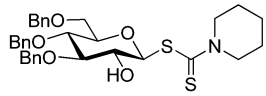
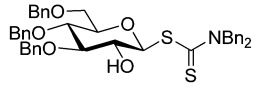
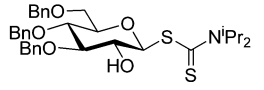
Synthesis and Characterization of Glycosyl Dithiocarbamates. At the outset, we presumed β-glycosyl DTCs could be readily prepared via S_N2 epoxide ring opening of α-epoxyglycals, which are in turn prepared selectively by treating glycals with dimethyldioxirane (DMDO).[23,26,27] In our previous studies with glycals and the closely related 4-deoxypentenosides, their corresponding epoxides reacted readily in THF with mildly basic nucleophiles such as thiolates.[26,27] However, initial attempts to treat tri-*O*-benzyl epoxyglucal **1** with Et_2DTC diethylammonium salt (prepared in situ from a 2:1 ratio of Et_2NH and CS_2) resulted in little to no glycosyl DTC formation. The addition of Lewis acids such as $LiClO_4$, which has been reported to catalyze epoxyglycal ring opening under aprotic conditions,[28] did not lead to significant improvements. However, epoxide ring openings with DTC salts in protic solvents proved to be highly effective. Thus, treatment of **1** with stoichiometric amounts of DMDO produced α-epoxyglycal with high stereoselectivity, with subsequent addition of various dialkyl-DTCs in MeOH giving β-glycosyl DTCs **2**–**5** in good to high overall yields (Table 1). The glycosyl DTCs were stable toward chromatographic separation and could be stored at −20 °C for months without any decomposition. ^{13}C NMR chemical-shift analysis indicated the anomeric (C1) and C=S carbonyl signals to be at 90–92 and 192–198 ppm; ^{1}H NMR analysis of diethyl-DTC glycoside **2** revealed the C1 methine proton to be notably downfield (δ 6.10 ppm; ^3J = 10 Hz), consistent with previous literature.[20]

Glycosyl *N*,*N*-diphenyl-DTC **6** was synthesized in a similar fashion except that a DTC lithium salt was generated from CS_2 and Ph_2NLi, with the latter prepared from diphenylamine with Li-dimsyl. Again, epoxide ring openings proceeded most efficiently when performed in a mixture of THF and MeOH (82% yield); other aprotic polar solvents produced glycosyl DTC **6** in lower yields (Table 2).[29] It is worth noting that epoxide ring openings with DTCs were also efficient in aqueous THF, but reactions in pure MeOH or other alcohols gave poorer results (entries 2 and 3). We did not observe significant amounts of solvolysis despite the well-established sensitivity of epoxyacetals to alcohols under mildly acidic conditions.[27,30]

The efficiency of epoxide ring opening under protic conditions can be attributed to the combination of the high nucleophilicity of DTC anion and the low activation barrier for reprotonation. The importance of protic solvents in epoxyglycal ring opening has been noted previously.[31] It is also worth mentioning that the α-mannosyl DTC (the expected ring-opening product from the minor β-epoxyglucal) is never observed; ^{1}H NMR analysis of the crude reaction mixture after

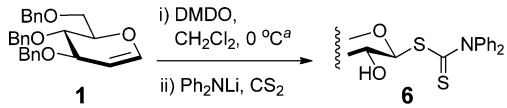
Table 1. One-Pot Synthesis of Glycosyl Dithiocarbamates from Glycals[a]



	**2**	87%
	**3**	89%
	**4**	83%
	**5**	52%

[a]Standard conditions: (i) DMDO (1.5 equiv), 0 °C, DCM; (ii) CS_2 (4 equiv), R_2NH (8 equiv), 4:1 THF/MeOH, 0 °C to rt; [rxn] = 0.1 M. Facioselectivity of epoxidation was 10:1 α/β. Isolated yield of β-glycosyl DTC.

Table 2. Synthesis of Glycosyl *N*,*N*-Diphenyl-DTC 6[a]



entry	solvent	yield[b]
1	THF/CH_3OH (1:2)	82%
2	THF/H_2O (1:2)	77%
3	CH_3OH[c]	65%
4	THF/CH_3CN (1:1)	37%
5	DMF	18%

[a]Standard conditions: (i) DMDO (1.5 equiv), 0 °C, DCM; (ii) CS_2 (4 equiv), Ph_2NLi (2 equiv), 0 °C to rt; [**1**] = 0.1 M. 10:1 α/β. [b]Isolated yield of β-glycosyl DTC. [c]Other alcohols (EtOH, *i*-PrOH, *t*BuOH) gave inferior results.

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DTC treatment revealed only β-glucosyl DTC without any trace of mannosyl DTC. This implies that the β-epoxide is unreactive to the DTC anion and decomposes upon workup, a form of chiral resolution favoring the α-epoxyglycal. The practical result is a clean isolation of β-glycosyl DTC products regardless of the facioselectivity of glycal epoxidation.[27,32]

Glycosyl DTC **2** was converted into tetra-*O*-benzylglucosyl DTC (**2a**), which produced high-quality crystals via slow evaporation of a toluene–hexanes solution at room temperature (Figure 2). X-ray crystallographic analysis revealed a $^4C_1$

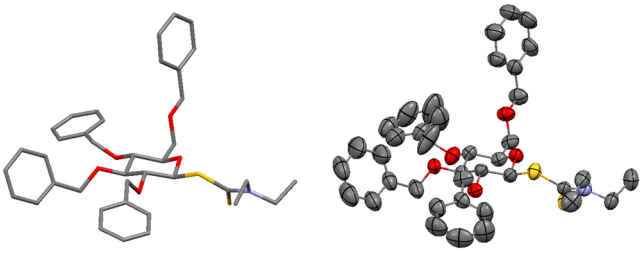
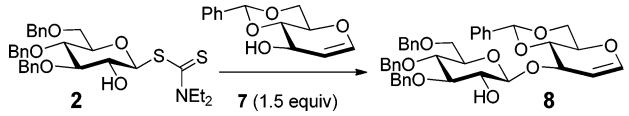


Figure 2. X-ray crystal structure of tetra-*O*-benzylglucosyl DTC (**2a**), displayed as a capped-stick model (left) with 50% ellipsoids (right).

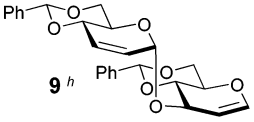
conformation with the dithiocarbamate adopting an exoanomeric (least sterically encumbered) conformation. The O5–C1–S bond angle (109.25°) is essentially that of a tetrahedral sp^3 carbon, with minimal torsional strain and no evidence of secondary interactions between the carbodithioate and the carbohydrate structure. We thus assume DTC activation to be driven by its affinity for the thiophilic agent.

Optimization of Glycosylation Conditions. The straightforward conversion of glycals into glycosyl DTC donors prompted us to investigate their coupling with glycal acceptors, inspired by the seminal studies by Danishefsky and coworkers.[33] Glycosyl coupling conditions were systematically screened using *N*,*N*-diethyl-DTC donor **2** and 4,6-benzylidene-protected acceptor **7** (Table 3). Standard Lewis acids such as TMSOTf did not produce disaccharide glycals at low temperatures, and warming the reaction to 0 °C resulted in decomposition of **2** (entry 1).[34] Thiophilic agents such as dimethylsulfonium triflate (DMTST)[20] gave complex mixtures, most likely because of the sensitivitiy of the enol ether moieties in the acceptor and product (entry 2). We then examined metal triflate salts, which have high affinity for the DTC group and low reactivity toward the enol ether functionality. Zn(OTf)$_2$ and AgOTf were previously used for glycosyl DTC activation,[22] but neither gave satisfactory results (entries 3 and 4). Fortunately, Cu^{II}(OTf)$_2$ proved to be highly effective and produced β-1,3-linked disaccharide **8** as the major product (entry 5). The highest and most reproducible yields were obtained by (i) sequential addition of acceptor **7** to preactivated donor **2** and (ii) using a weak base such as tri-*tert*-butylpyrimidine (TTBP). Couplings performed in the presence of stronger bases like Et$_2$N^{i}Pr (entry 6) required higher temperatures (0 °C) to reach completion, presumably because of coordination between the amine and Cu(OTf)$_2$. We note that Bronsted bases were not used in earlier reports involving glycosyl DTC or thioimidate activation.[1,20−22] However, in the absence of base, the coupling reaction was compromised by self-condensation of acceptor **7** into disaccharide **9** via Ferrier rearrangement (entry 7). Lastly, β selectivity was maximized by using 1:1 dichloroethane/dichloromethane (DCE/DCM) at −30 °C (entry 8), but more polar solvents such as acetonitrile

Table 3. Glycosyl Coupling of DTC Donor 2 and Glycal Acceptor 7



entry	react cond[a]	product / yield[c]	α:β ratio[g]
1	TMSOTf (no base)	decomposition[d]	---
2	DMTST, TTBP	trace amount[e]	---
3	Zn^{II}OTf$_2$, TTBP	no reaction[e]	---
4	Ag^{I}OTf, TTBP	43%	1:5
5	Cu^{II}OTf$_2$, TTBP	70%	1:5
6	Cu^{II}OTf$_2$, ^{i}PrNEt$_2$	61%[d]	1:4
7	Cu^{II}OTf$_2$ (no base)	41%[f]	1:5
8[b]	Cu^{II}OTf$_2$, TTBP	71%	1:9



[a]Standard conditions: [**2**] = 0.15 M; acceptor **7** (1.5 equiv), Lewis acid (2 equiv), base (2 equiv), 4 Å molecular sieves, DCM, −50 to −30 °C. [b]1:1 DCE/DCM. [c]Isolated yields. [d]Warmed to 0 °C. [e]Warmed to rt. [f]Disaccharide **9** was produced in 48% yield. [g]Determined by ^{1}H NMR signal integration. [h]Disaccharide **9** was isolated but not fully characterized; ^{1}H and ^{13}C NMR spectra are available in the Supporting Information.

or diethyl ether resulted in low yields. The basis for β selectivity will be discussed in a later section.

To determine if the oxidation state of Cu had any influence on glycosyl DTC activation, we also performed couplings with Cu^{I}OTf·(C$_6$H$_6$)$_{0.5}$, an air-sensitive metal salt.[35] Controlled addition of solid Cu^{I}OTf at low temperature to the reaction mixture produced similar results, often with slightly better isolated yields. Cu^{I}OTf was likewise compatible with acid-sensitive functional groups such as benzylidene acetals and enol ethers. We therefore used Cu^{I}OTf and Cu^{II}(OTf)$_2$ interchangeably for all subsequent glycosyl couplings.

To determine whether Cu(OTf)$_x$-mediated coupling could be influenced by the redox potential of the glycosyl DTC donor, we compared the efficiencies of coupling donors **2**–**6** with acceptor **7**. Donors **2**–**6** were chosen on the basis of an earlier electrochemical study that showed the redox potentials of *N*,*N*-disubstituted DTCs to be influenced by their substituents, with E^0 values (versus SCE) ranging from ca. −225 (for Ph$_2$-DTC) to −302 mV (for Et$_2$DTC).[36] These values suggested that glycosyl DTC **6** might be more reactive than **2**–**4** if electron transfer was involved. Instead, *N*,*N*-diphenyl DTC **6** was the least reactive donor, and unreacted donor was recovered after workup. This series implies that DTC activation is essentially driven by Lewis acid–base interactions (Table 4) and confirms Et$_2$-DTC derivative **2** to be the most efficient and most practical donor for glycosyl couplings.

One-Pot Cu(OTf)$_x$-Mediated Coupling with Glycals via Glycosyl Dithiocarbamates. Glycosyl DTC donor **2** was tested with a variety of acceptors and was found to produce β-

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Table 4. Donor Activity of Glycosyl DTCs 2−6[a]

glycosyl donor	yield[b]	α/β[c]
2 (R_2 = Et_2)	71%	1:9
3 (R_2 = -$(CH_2)_5$-)	58%	1:8
4 (R_2 = Bn_2)	61%	1:9
6 (R_2 = Ph_2)	47%[d]	1:8

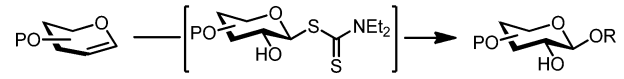
[a]Standard conditions: acceptor **7** (1.5 equiv), $Cu(OTf)_2$ (2 equiv), TTBP (2 equiv), 4 Å molecular sieves, 1:1 DCE/DCM, −50 to −30 °C; [rxn] = 0.1 M. [b]Isolated yields. [c]Determined by ^{1}H NMR signal integration. [d]Twenty-three percent of glycosyl DTC **6** was recovered.

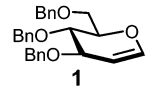
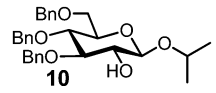
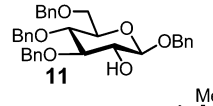
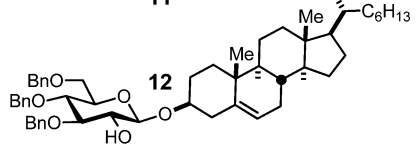
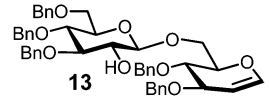
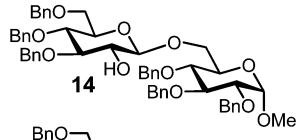
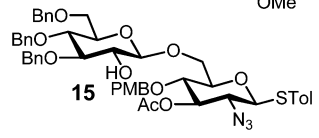
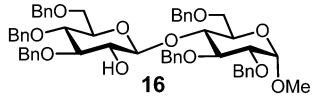
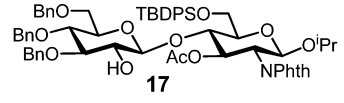
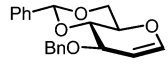
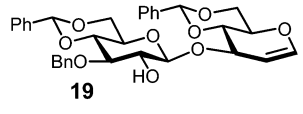
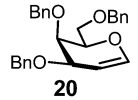
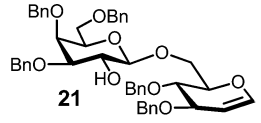
coupling products in good to high yields (Table 5, entries 1−8). The glycosyl DTC couplings were efficient with 1.2−1.5 equiv of acceptor and compatible with acid-sensitive functional groups. Importantly, the coupling procedure was simplified by performing three operations (DMDO oxidation, DTC ring opening, and glycosylation) in sequence without workup or chromatographic purification of the glycosyl DTC.[9] Thus, DMDO oxidation of glycal **1** was followed immediately by stoichiometric addition of diethyl-DTC salt in MeOH to afford the corresponding β-glycosyl DTC **2**, which was then dried by azeotropic distillation with toluene and subjected to $Cu(OTf)_x$-mediated glycosyl couplings under the optimized conditions above. This one-pot procedure produced β-glycosides such as **10**−**12**, β-1,6-linked disaccharides **13**−**15**, and β-1,4-linked disaccharides **16** and **17**, all with exclusive β selectivity.

We also evaluated $Cu(OTf)_x$-mediated coupling with 4,6-benzylidene-protected glucal **18** and galactal **20** (Table 5, entries 9 and 10). The DTC donor derived from **18** was combined with acceptor **7** but found to be significantly less reactive relative to **2** (cf. Table 3); the reaction was warmed to 0 °C before affording disaccharide **19** in 42% yield. The lower reactivity and yield can be attributed to the conformational constraint imposed by the 4,6-benzylidene acetal (to be discussed below). The DTC donor derived from galactal **20** was coupled with 3,4-di-*O*-benzyl glucal (**22**) to produce β-1,6-linked disaccharide **21** in 78% yield, albeit with moderate selectivity (β/α, 5:1). In these limiting cases, issues of reactivity and stereoselectivity are readily addressed by installing a C2 auxiliary such as a benzoate onto the glycosyl DTC donor, which guarantees β selectivity and improves the coupling yield by as much as 30%.[9]

Having established an efficient and β-selective glycosylation via in situ generation of glycosyl DTCs, we applied this methodology toward the reiterative synthesis of a β-1,6-linked tetrasaccharide (Scheme 1). First, glucal **1** was converted into **2** and coupled with acceptor **22** using CuOTf-mediated glycosylation to afford β-1,6-linked disaccharide **13** in 69% overall yield. The C2′ hydroxyl of **13** was then protected as benzyl ether **23** and subjected to DMDO oxidation and Et_2NH/CS_2 ring opening to yield glycosyl DTC **24** with >95% β selectivity. CuOTf-mediated glycosylation with a second round of **22** yielded β,β-linked trisaccharide **25** in 63% isolated yield along with 7% of the β,α-linked product. 2′-*O*-Benzylation of trisaccharide **25** afforded trisaccharide glycal **26** followed by in situ conversion into β-glycosyl DTC **27** and coupling with **22** to obtain β,β,β-linked tetrasaccharide **28** in 49% isolated yield as well as 10% of the β,β,α-linked product. Overall, the synthesis of tetrasaccharide **28** was accomplished in just 11 steps and 19% overall yield from glucal donor **1** and 4.5 equiv of glucal acceptor **22**.

Table 5. β-Selective Glycal Assembly via Glycosyl DTCs[a]



entry	glycal	product	yield[b]
1	 **1**	 **10**	71%[c]
2		 **11**	63%[c]
3		 **12**	76%[d,e]
4		 **13**	69%[d]
5		 **14**	71%[d]
6		 **15**	63%[d]
7		 **16**	48%
8		 **17**	56%
9	 **18**	 **19**	42%
10	 **20**	 **21**	78% (5:1 β:α)[e,f]

[a]Standard conditions: (i) DMDO (1.5 equiv), DCM, 0 °C; (ii) CS_2 (1.05 equiv), Et_2NH (2.1 equiv), 4:1 THF/MeOH, rt; (iii) $Cu(OTf)_2$ (2 equiv), TTBP (2 equiv), 4 Å molecular sieves, 1:1 DCE/DCM, −50 °C, then acceptor (1.5 equiv), −30 °C; [rxn] = 0.1 M. [b]Isolated yield of β isomer, unless stated otherwise. [c]Also isolated 9% of α isomer. [d]See ref 9. [e]$Cu^{I}OTf$ was used at −50 °C. [f]Ratio determined by ^{1}H NMR signal integration.

It should be noted that the C2′ protecting group in disaccharides **23** and **26** was important for high facioselectivity during epoxidation. DMDO oxidation of glycal **13** at −50 °C resulted in a 3:1 ratio of α- and β-epoxides, whereas epoxidation of **23** and **26** at −50 °C yielded the desired α-epoxyglycals in >20:1 α/β selectivity. We have observed similar

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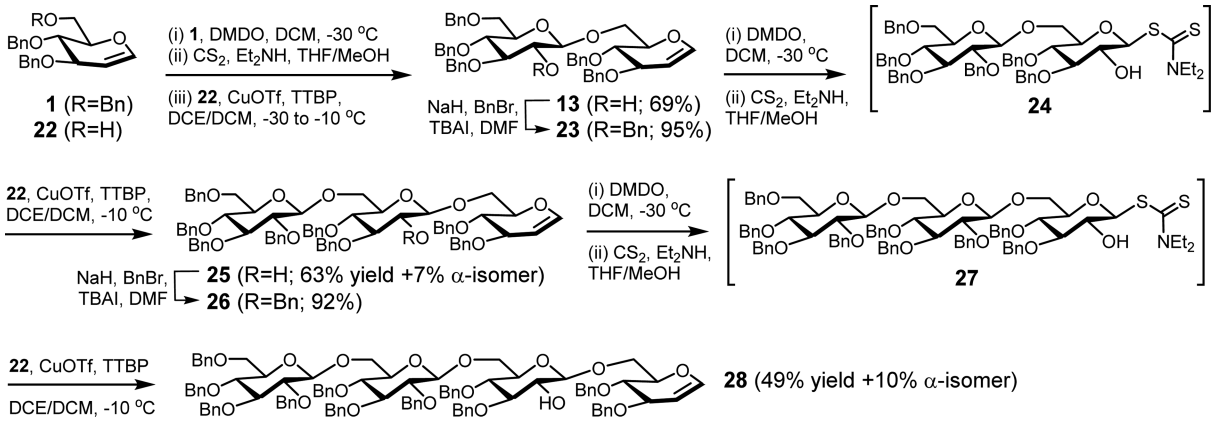
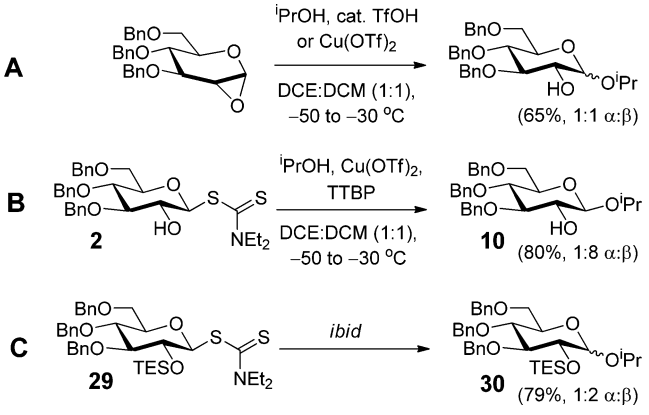
Scheme 1. Reiterative Synthesis of β-1,6-Linked Tetrasaccharide via Glycosyl DTC Intermediates



effects in the DMDO oxidation of a 4-deoxypentenosyl (4-DP) disaccharide having a remote hydroxyl group.[37]

Mechanistic Insights into β-Selective Glycosyl Couplings. The glycosyl DTC couplings proceed cleanly with high yields and β selectivities despite the presence of a free C2 hydroxyl on the donor. Moreover, oligomerization of the glycosyl donor is never observed. A survey of the literature reveals just a handful of examples on β-selective coupling of glycosyl donors with free C2 hydroxyls using either glycosyl phosphates or thioglycosides.[34,38] In the latter case, β selectivity was attributed to in situ generation of an α-oxonium intermediate (i.e., protonated epoxyglycal) followed by S_N2 ring opening at C1 to produce β-glycosides. However, one must also consider the conformational strain of placing the C2 hydroxyl of the glucopyranose in a pseudoaxial position prior to epoxide ring closure.[39,40] To test the putative α-oxonium intermediate, we treated an α-epoxyglucal and acceptor at low temperature with either TfOH or $Cu(OTf)_2$ (Scheme 2A). However, neither condition resulted in the selective formation of β-glycosides, allowing us to eliminate this as a possible intermediate.

Scheme 2. Control Experiments to Determine the Basis for Selective β-Glycosylation

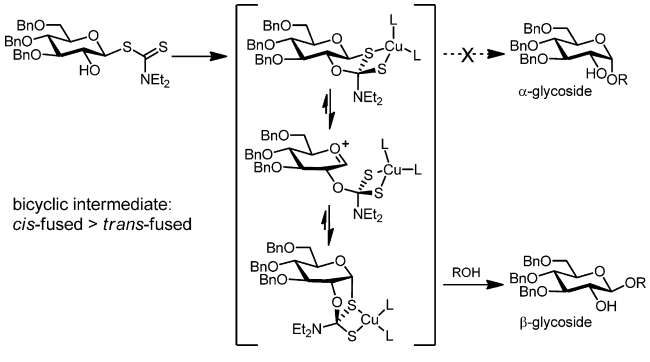


To determine whether the C2 hydroxyl was important for β-selective glycosylation, we compared donor **2** (with free C2 hydroxyl) with 2-*O*-triethylsilyl (TES) ether **29** using isopropanol and $Cu(OTf)_2$ for activation (Scheme 2B, C). As expected, glycosylation with **2** was highly β-selective and yielded β-isopropyl glucoside **10** as the major product, whereas glycosylation with **29** produced **30** in equally high yield but with poor stereoselectivity, suggesting an active role for the C2 hydroxyl in stereoselective coupling.

We also considered whether β selectivity could be attributed to S_N2-like reactivity of an α-glycosyl triflate intermediate, which is known to exist at low temperatures following glycosyl activation.[41−44] However, $Cu(OTf)_2$-mediated glycosylation of the 4,6-benzylidene-protected DTC donor derived from **18** produces β-coupling product exclusively and is also slow relative to unconstrained donor **2**, requiring temperatures up to 0 °C to reach completion (Table 5, entry 9). In addition, it has been shown that conformationally constrained donors with 4,6-benzylidene acetals favor α-glycoside formation, as the increased stability of the α-glycosyl triflate forces the coupling to proceed through the more reactive β-glycosyl triflate.[45] We thus rule out the intermediacy of an α-glycosyl triflate.

We propose that $Cu(OTf)_x$ activation of the glycosyl DTC promotes intramolecular addition of the C2 hydroxyl to form a bicyclic, trans-fused orthodithiocarbamate, which rapidly equilibrates via an oxocarbenium intermediate to a cis-fused bicyclic system with reduced torsional strain, accompanied by a stabilizing anomeric effect on the C−S axial bond (Scheme 3).[46] The activated orthodithiocarbamate is thus directed by the

Scheme 3. Proposed Mechanism for the β Selectivity of Activated Glycosyl Dithiocarbamates



neighboring C2 hydroxyl, allowing the acceptor to attack the exposed β-face for β-glycoside formation. We note that a similar equilibration may be possible for glycosyl phosphates and dithiophosphates.[34,47]

Additional evidence supporting the bicyclic orthodithiocarbamate intermediate was obtained by attempts to alkylate

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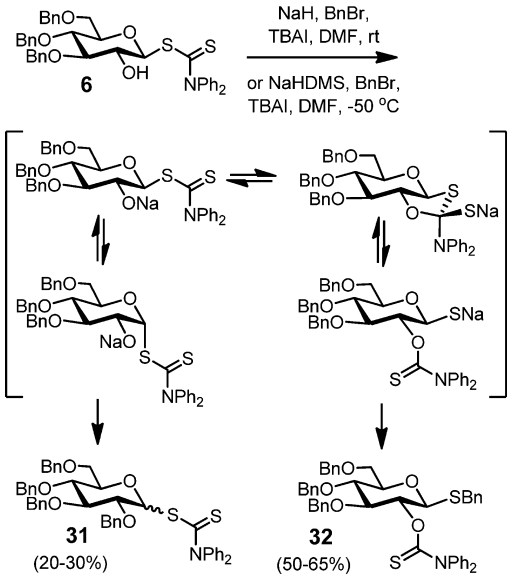
glycosyl DTC **6** under basic conditions. Exposure of **6** to NaH or NaHDMS and BnBr in DMF produced the desired 2-*O*-benzyl ether **31** in low yields along with major side product **32**, formed by the migration of the thiocarbamoyl unit to the C2 hydroxyl and *S*-benzylation at C1 (Scheme 4). This necessarily implies the facile formation of the bicyclic orthodithiocarbamate, which decomposes under anionic conditions to the C2 thiocarbamate and C1 thiolate prior to alkylation. A similar migration has been observed in attempts to alkylate glycosyl phosphoryldithioates, which produced a *S*-alkyl, 2-*O*-thiophosphoryl glycoside.[47]

Scheme 4. Thiocarbamoyl Migration in 6 via Bicyclic Orthodithiocarbamate Intermediate



The β-selective coupling was further investigated by low-temperature ^{13}C NMR experiments using CuOTf activation because of its diamagnetic character.[48] Glycosyl DTC **2** was treated at −50 °C with CuOTf·$(C_6H_6)_{0.5}$ in CD_2Cl_2 and minimal 2-butanone to produce a green heterogeneous mixture, which caused the disappearance of the thiocarbonyl signal (C7) at 190.7 ppm and a reduction or broadening of the remaining signals (Figure 3). Warming the solution to −10 °C resulted in additional changes: (i) the appearance of two new peaks at 111.0 and 111.7 ppm, (ii) the loss of signal at 89.1 ppm (C1) and the appearance of two new peaks at 97.2 and 97.5 ppm, and (iii) the loss of signals at 47.1 and 49.8 ppm (methylene carbons of Et_2DTC) and the appearance of four new peaks between 23−33 ppm. These signals can be ascribed to the formation of orthodithiocarbamates (C7 epimers). We also observe a minor signal at 197 ppm, suggesting the coexistence of a stabilized oxocarbenium species,[7,49−51] possibly generated by reversible ligand dissociation from the **2**−Cu complex.

A similar low-temperature ^{13}C NMR study was performed on tetra-*O*-benzylglucosyl DTC (**2a**). At −10 °C, new signals could again be observed, but these are not suggestive of the putative orthodithiocarbamate. Changes include the replacement of thiocarbonyl signal at 191.9 with two peaks at 197.2 and 193 ppm (the latter attributable to free CS_2), and the replacement of the C1 signal at 89.1 ppm with a new peak at δ 104.3 ppm (Figure 4). Although the latter value is close to the C1 chemical shift for glucosyl triflates,[44,45,49,52] such species are

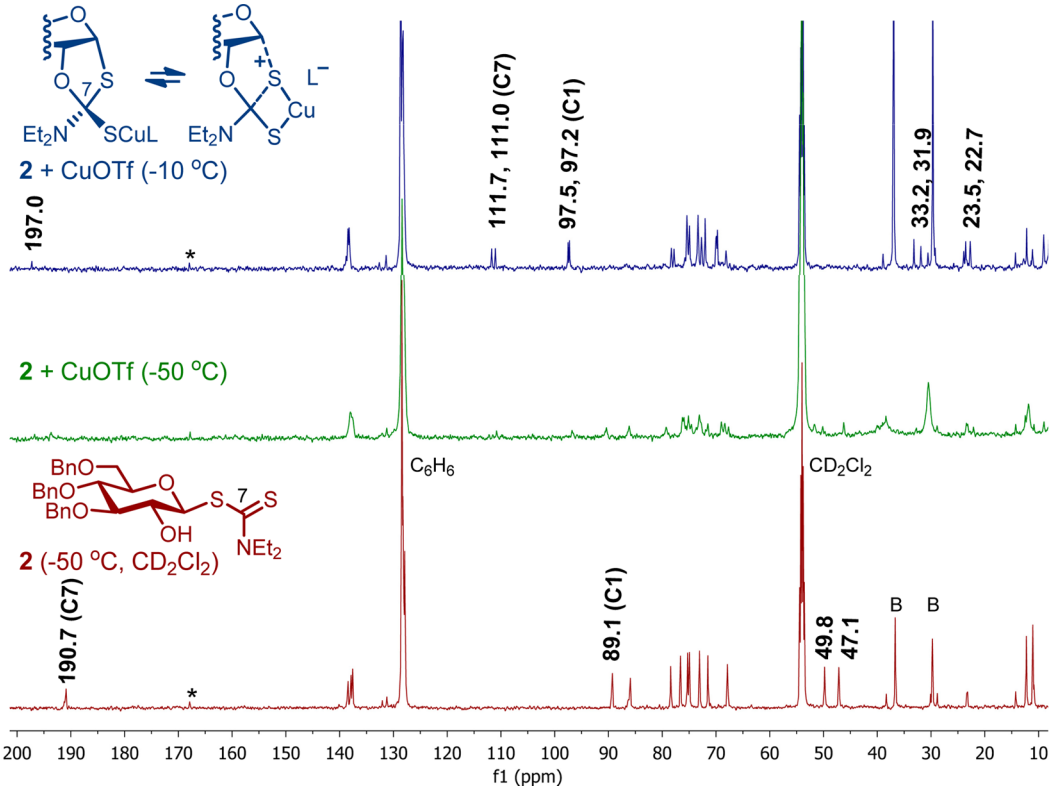


Figure 3. ^{13}C NMR analysis of glycosyl DTC activation using CuOTf·$(C_6H_6)_{0.5}$ with a small amount of 2-butanone (CD_2Cl_2, 125 MHz). Bottom, glycosyl DTC **2** at −50 °C; middle, **2** + CuOTf at −50 °C; and top, **2** + CuOTf at −10 °C. Butanone and impurity are marked with B and *, respectively.

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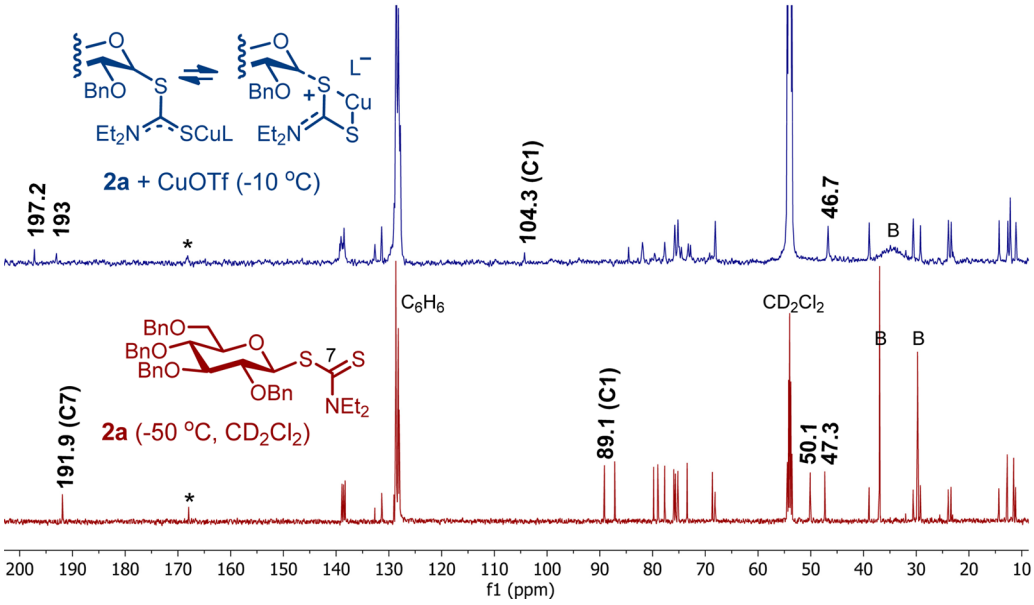

Figure 4. ^{13}C NMR analysis of glycosyl DTC−CuOTf complex using **2a** and CuOTf·$(C_6H_6)_{0.5}$ with a small amount of 2-butanone (CD_2Cl_2, 125 MHz). Bottom, glucosyl DTC **2a** at −50 °C; top, **2a** after treatment with CuOTf at −50 °C and warming to −10 °C. Butanone and impurity are marked with B and *, respectively.

known to decompose above −20 °C, whereas activated **2a** appeared to be stable at −10 °C. This indicates that glycosyl DTC−CuOTf complexes are more stable than glycosyl triflates but retain sufficient reactivity for efficient coupling (cf. Scheme 2).

CONCLUSIONS

Glycosyl dithiocarbamates can be prepared efficiently from glycals by in situ DMDO oxidation and DTC ring opening, enabling a one-pot glycosyl coupling with various acceptors. The Cu(OTf)$_x$-mediated glycosylations are highly β-selective despite the absence of a predesignated C2 acyl group for anchimeric assistance. We note that yields can be further improved by chromatography-free acylation of the glycosyl DTC donor prior to glycosyl coupling.[9] Glycosyl DTCs are useful in the reiterative assembly of β-linked oligosaccharides, as demonstrated by an 11-step synthesis of a 1,6-linked tetrasaccharide from glucal **1** in 19% overall yield. Control experiments and low-temperature NMR analysis suggest the involvement of a cis-fused bicyclic orthodithiocarbamate in the β-selective coupling.

EXPERIMENTAL SECTION

General Methods. All starting materials and reagents were obtained from commercial sources and used as received unless otherwise noted. All experiments were performed under an argon atmosphere unless otherwise specified. All solvents used were freshly distilled prior to use; 4 Å molecular sieves were flame-dried under reduced pressure. CuOTf·$(C_6H_6)_{0.5}$ was prepared according to literature procedures[35] and handled under anaerobic conditions. ^1H and ^{13}C NMR spectra were recorded on spectrometers operating at 300, 400, or 500 MHz and referenced to the solvent used (7.16 and 128.06 ppm for C_6D_6, 7.26 and 77.00 ppm for $CDCl_3$). FT-IR spectra were acquired using an attenuated total reflectance (ATR) module. Optical rotations were measured at room temperature with a polarimeter. Mass spectra were acquired using electrospray ionization. Silica gel chromatography was performed in hand-packed columns, and preparative TLC separations were performed with 0.5 mm silica-coated plates. TLC analysis was monitored with 0.25 mm silica-coated plates ($G60_{F254}$) and detected by UV absorption at 254 nm or by staining with *p*-anisaldehyde−sulfuric acid at 150 °C.

General Procedure for Epoxidations Using DMDO and in Situ Formation of Glycosyl DTCs. DMDO solutions were prepared according to our previous report.[27] In a typical procedure, a glycal (0.25 mmol) is dried by azeotropic distillation with toluene and dissolved in CH_2Cl_2 (ca. 0.3 M), treated at 0 °C with a precooled solution of DMDO (0.22 M in CH_2Cl_2, 1.5 equiv), and stirred for 1 h or until the starting material is completely consumed. The reaction mixture is carefully concentrated to dryness under reduced pressure, starting at −78 °C with gradual warming to rt over 1 h until a white solid is obtained. The crude α-epoxyglycal is dissolved in degassed THF (2 mL) and cooled to 0 °C. In parallel, a degassed solution of diethylamine (560 μL, 5.2 mmol) in MeOH (4.9 mL) is cooled to 0 °C under an argon atmosphere followed by dropwise addition of CS_2 (160 μL, 2.6 mmol) and stirring at rt for 30 min to obtain a pale yellow solution of Et_2DTC (0.53 M in MeOH). A portion of this stock (0.49 mL, 1.05 equiv) is added dropwise at 0 °C to the stirred epoxyglycal solution, which is then warmed to rt for 2.5 h. The reaction mixture is concentrated to dryness under reduced pressure and further dried by azeotropic distillation with toluene (3 × 2 mL). The glycosyl DTC can be used without further workup or purification.

Cu(OTf)$_x$-Mediated Glycosyl Couplings. In a typical procedure, the crude glycosyl DTC (0.25 mmol) is dried by azeotropic distillation with toluene, dissolved in degassed 1:1 DCE/DCM (1.7 mL), treated with TTBP (124 mg, 0.5 mmol) and activated 4 Å molecular sieves (200 mg), and stirred for 1 h at rt. The reaction mixture is cooled to −50 °C for 15 min, treated with anhydrous $Cu^{II}OTf_2$ (184 mg, 2 equiv) or $Cu^{I}OTf\cdot(C_6H_6)_{0.5}$ (126 mg, 2 equiv) in one portion, and stirred for 10 min, during which the color turns from pale yellow to brown to dark green. A solution of glycosyl acceptor in degassed 1:1 DCE/DCM (0.8 mL, 1.5 equiv) is cooled to −50 °C, added dropwise to the reaction mixture via cannula, stirred for 5 min, warmed to −30 °C over a period of 45 min, and stirred at −30 °C for an additional 12 h. The dark green reaction mixture is warmed to 10 °C over a period of 3 h, then quenched with a saturated $NaHCO_3$ solution with vigorous stirring for 15 min at rt. The yellow reaction mixture is then passed through a pad of Celite and washed with EtOAc (3 × 5 mL) prior to standard aqueous workup and purification by silica gel chromatography.

3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl 1-Diethyldithiocarbamate (2). Tri-*O*-benzyl glucal **1** (91 mg, 0.22 mmol) was subjected to

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DMDO oxidation at 0 °C for 1 h to provide α-epoxyglucal in quantitative yield (10:1, α/β). The crude epoxyglucal was subjected to DTC ring opening in THF with a freshly prepared solution of Et_2DTC (0.88 mmol, 0.5 M in MeOH) as described above. After workup, the pale yellow syrup was purified by silica gel chromatography (neutralized with 1% Et_3N) using a 5−40% EtOAc in hexanes gradient with 1% Et_3N, with mixed fractions separated by preparative TLC (30% EtOAc in hexanes with 1% Et_3N) to afford glycosyl DTC **2** as a colorless syrup (111 mg, 87%). ^{1}H NMR (500 MHz, C_6D_6): δ 7.39−7.05 (m, 15H), 6.15 (d, 1H, *J* = 10.4 Hz), 5.00 (d, 1H, *J* = 11.5 Hz), 4.89 (d, 1H, *J* = 11.5 Hz), 4.85 (d, 1H, *J* = 11.5 Hz), 4.63 (d, 1H, *J* = 11.5 Hz), 4.42 (d, 1H, *J* = 12.0 Hz), 4.25 (d, 1H, *J* = 12.0 Hz), 4.00 (dd, 1H, *J* = 9.0, 9.5 Hz), 3.92 (dd, 1H, *J* = 9.0, 9.5 Hz), 3.74−3.57 (m, 6H), 3.18−3.02 (m, 2H), 2.65 (br s, 1H), 0.96 (t, 3H, *J* = 7.0 Hz), 0.75 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, C_6D_6): δ 192.6, 139.7, 139.4, 139.0, 128.6, 128.5, 128.4, 128.2, 128.1, 127.8, 127.7, 127.6, 90.5, 87.6, 80.1, 77.8, 75.5, 74.8, 73.7, 73.5, 69.1, 49.7, 47.0, 12.6, 11.6. IR (thin film): 2869, 1502, 1451, 1413, 1354, 1261, 1202, 1067, 919, 746, 695 cm^{-1}. $[\alpha]_D^{25}$ = +23.0° (*c* 2.0, CH_2Cl_2). HRESI−MS: *m*/*z* calcd for $C_{32}H_{39}NO_5S_2Na$ [M + Na]$^+$, 604.2167; found, 604.2158. Compound **2** was also characterized as the 2-*O*-acetate by treatment with Ac_2O (1 mL) in pyridine (2 mL) at rt for 12 h followed by concentration and azeotropic distillation with toluene (3 × 1 mL). The ^{1}H NMR and pfg-COSY spectrum of 2-*O*-acetyl-**2** confirmed the β configuration ($J_{1,2}$ = 10.7 Hz).

2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl 1-Diethyldithiocarbamate (2-*O*-acetyl 2). ^{1}H NMR (500 MHz, C_6D_6): δ 7.25 (dd, 6H, *J* = 7.6, 9.5 Hz), 7.22−7.02 (m, 9H), 6.30 (d, 1H, *J* = 10.7 Hz), 5.72 (t, 1H, *J* = 10.7 Hz), 4.72 (dd, 2H, *J* = 9.0, 11.5 Hz), 4.62 (d, 1H, *J* = 11.7 Hz), 4.55 (d, 1H, *J* = 11.4 Hz), 4.41 (d, 1H, *J* = 11.9 Hz), 4.24 (d, 1H, *J* = 11.9 Hz), 3.89 (m, 1H), 3.80−3.74 (m, 2H), 3.72 (m, 1H), 3.70−3.58 (m, 2H), 3.53 (dt, 1H, *J* = 13.9, 7.0 Hz), 3.00 (q, 2H, *J* = 7.0 Hz), 1.64 (s, 3H), 0.90 (t, 3H, *J* = 7.0 Hz), 0.66 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (120 MHz, C_6D_6): δ 192.1, 169.4, 139.3, 139.2, 139.0, 128.6, 128.5, 128.4, 128.3, 128.1, 128.1, 127.9, 127.8, 127.7, 127.7, 127.6, 88.5, 85.6, 80.2, 78.1, 75.4, 74.8, 73.5, 71.2, 69.0, 49.6, 46.7, 20.6, 12.8, 11.5. IR (thin film): 2876, 1745, 1492, 1458, 1413, 1359, 1268, 1231, 1206, 1149, 1061, 917, 823, 746, 701 cm^{-1}. $[\alpha]_D^{25}$ = +30.9° (*c* 3.8, CH_2Cl_2).

2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl 1-Diethyldithiocarbamate (2a). Glycosyl DTC **2** (273 mg, 0.47 mmol) was disolved in DMF (5.8 mL), cooled to −50 °C under argon, and then treated with BnBr (280 μL, 2.35 mmol). A 0.6 M solution of NaHMDS in toluene (1.6 mL, 0.94 mmol) was added dropwise to the reaction mixture, and the mixture was stirred at −50 °C for 5 min. The reaction mixture was allowed to warm to room temperature over a period of 2 h, quenched at 0 °C with saturated NH_4Cl (10 mL), and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with H_2O (3 × 10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. After workup, the yellow syrup was purified by silica gel chromatography (neutralized with 1% Et_3N) using a 5−60% EtOAc in hexanes gradient with 1% Et_3N to afford glycosyl DTC **2a** as a colorless syrup (259 mg, 82%). ^{1}H NMR (500 MHz, C_6D_6): δ 7.47−6.91 (m, 20H), 6.46 (d, 1H, *J* = 10.1 Hz), 4.88 (d, 1H, *J* = 11.4 Hz), 4.86−4.80 (m, 2H), 4.79 (s, 2H), 4.68 (d, 1H, *J* = 11.4 Hz), 4.42 (d, 1H, *J* = 11.9 Hz), 4.24 (d, 1H, *J* = 11.9 Hz), 4.00 (ddd, 1H, *J* = 2.4, 6.5, 9.2), 3.84−3.79 (m, 2H), 3.78−3.56 (m, 5H), 3.13 (dt, 1H, *J* = 7.2, 14.4 Hz), 3.01 (dt, 1H, *J* = 7.2, 14.7 Hz), 0.96 (t, 3H, *J* = 7.0 Hz), 0.72 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (125 MHz, C_6D_6): δ 192.3, 139.3, 139.2, 138.9, 138.8, 128.3, 128.2, 127.8, 127.6, 127.4, 89.5, 87.3, 80.3, 79.7, 78.0, 75.5, 75.0, 74.6, 73.3, 68.9, 49.4, 46.5, 12.4, 11.4. IR (thin film): 2931, 2866, 1489, 1454, 1417, 1356, 1269, 1207, 1090, 1070, 916, 829, 735, 698 cm^{-1}. $[\alpha]_D^{25}$ = +21.3° (*c* 0.3, CH_2Cl_2). HRESI−MS: *m*/*z* calcd for $C_{39}H_{46}NO_5S_2$ [M + H]$^+$, 672.2817; found, 672.2812.

3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl 1-Piperidinyldithiocarbamate (3). Tri-*O*-benzyl glucal **1** (95 mg, 0.23 mmol) was subjected to DMDO oxidation at 0 °C for 1 h to produce α-epoxyglucal in quantitative yield followed by DTC ring opening with piperidinyl-DTC (0.92 mmol, 0.5 M in MeOH) as described above. The reaction mixture was concentrated and purified by silica gel chromatography using a 5−50% EtOAc in hexanes gradient with 1% Et_3N to afford glycosyl DTC **3** as a colorless syrup (121 mg, 89%). ^{1}H NMR (500 MHz, C_6D_6): δ 7.38 (d, 2H, *J* = 7.5 Hz), 7.28−7.07 (m, 13H), 6.20 (d, 1H, *J* = 10.3 Hz), 5.02 (d, 1H, *J* = 11.5 Hz), 4.87 (t, 2H, *J* = 10.6 Hz), 4.64 (d, 1H, *J* = 11.4 Hz), 4.43 (d, 1H, *J* = 12.0 Hz), 4.26 (d, 1H, *J* = 12.0 Hz), 4.05 (t, 2H, *J* = 9.5 Hz), 3.94 (t, 2H, *J* = 9.1 Hz), 3.78−3.67 (m, 4H), 3.43−3.18 (m, 2H), 2.71 (br s, 1H), 1.16 (br s, 2H), 0.98 (br s, 4H). ^{13}C NMR (125 MHz, C_6D_6): δ 192.2, 139.5, 139.2, 139.0, 138.8, 138.4, 136.7, 135.0, 128.3, 128.2, 128.0, 127.9, 127.8, 127.6, 90.3, 87.3, 79.9, 77.6, 75.2, 74.5, 73.4, 73.3, 69.0, 52.6, 51.1, 25.6, 25.0, 23.8. IR (thin film): 2941, 2852, 1480, 1421, 1362, 1244, 1222, 1067, 738, 691 cm^{-1}. $[\alpha]_D^{25}$ = +30.6° (*c* 2.0, CH_2Cl_2). HRESI−MS: *m*/*z* calcd for $C_{33}H_{39}NO_5S_2Na$ [M + Na]$^+$, 616.2167; found, 616.2160. Compound **3** was also characterized as the 2-*O*-acetate by treatment with Ac_2O (1 mL) in pyridine (2 mL) as described above. The ^{1}H NMR and pfg-COSY spectrum of 2-*O*-acetyl-**3** confirmed the β configuration ($J_{1,2}$ = 10.8 Hz).

2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl 1-Piperidinyldithiocarbamate (2-*O*-acetyl 3). ^{1}H NMR (400 MHz, C_6D_6): δ 7.47−6.83 (m, 15H), 6.38 (d, 1H, *J* = 10.8 Hz), 5.78 (dd, 1H, *J* = 10.8, 8.9 Hz), 4.74 (dd, 2H, *J* = 8.8, 11.6 Hz), 4.63 (d, 1H, *J* = 11.7 Hz), 4.56 (d, 1H, *J* = 11.4 Hz), 4.42 (d, 1H, *J* = 12.0 Hz), 4.25 (d, 1H, *J* = 11.9 Hz), 4.07 (m, 1H), 3.93 (t, 1H, *J* = 9.3 Hz), 3.82−3.73 (m, 2H), 3.72 (d, 1H, *J* = 1.7 Hz), 3.68 (dd, 1H, *J* = 3.2, 11.2 Hz), 3.23 (t, 1H, *J* = 11.4 Hz), 3.09 (d, 1H, *J* = 14.6 Hz), 1.66 (s, 3H), 1.22−0.99 (m, 3H), 0.99−0.59 (m, 4H).

3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl 1-Dibenzyldithiocarbamate (4). Tri-*O*-benzyl glucal **1** (95 mg, 0.23 mmol) was subjected to DMDO oxidation at 0 °C for 1 h to provide α-epoxyglucal in quantitative yield followed by DTC ring opening in THF with Bn_2DTC (0.92 mmol, 0.5 M solution in MeOH) as described above. The pale yellow syrup was concentrated and purified by silica gel chromatography using a 5−50% EtOAc in hexanes gradient with 1% Et_3N to afford glycosyl DTC **4** as a colorless syrup (135 mg, 83%). ^{1}H NMR (500 MHz, C_6D_6): δ 7.34 (d, 2H, *J* = 7.3 Hz), 7.28−7.26 (m, 3H), 7.23 (d, 2H, *J* = 7.3 Hz), 7.20−6.98 (m, 16H), 6.93 (d, 2H, *J* = 6.5 Hz), 6.15 (d, 1H, *J* = 10.3 Hz), 5.29 (d, 1H, *J* = 14.8 Hz), 5.17 (d, 1H, *J* = 14.8 Hz), 4.91 (d, 1H, *J* = 11.5 Hz), 4.86 (d, 1H, *J* = 11.4 Hz), 4.81 (d, 1H, *J* = 11.5 Hz), 4.62 (d, 1H, *J* = 11.0 Hz), 4.61−4.52 (m, 2H), 4.42 (d, 1H, *J* = 11.9 Hz), 4.27 (d, 1H, *J* = 11.9 Hz), 3.90 (t, 1H, *J* = 9.2 Hz), 3.82 (dd, 1H, *J* = 8.6, 10.3 Hz), 3.78−3.60 (m, 4H), 3.58 (br s, 1H). ^{13}C NMR (125 MHz, C_6D_6): δ 196.7, 139.4, 139.2, 138.8, 135.7, 128.9, 128.7, 128.3, 128.3, 128.2, 128.1, 127.9, 127.4, 127.0, 91.2, 87.1, 80.0, 77.5, 75.1, 74.5, 73.2, 73.2, 68.8, 56.4, 54.1. IR (thin film): 2928, 1506, 1451, 1404, 1341, 1219, 1079, 746, 700 cm^{-1}. $[\alpha]_D^{25}$ = +36° (*c* 1.0, CH_2Cl_2). HRESI−MS: *m*/*z* calcd for $C_{42}H_{43}NO_5S_2Na$ [M + Na]$^+$, 728.2480; found, 728.2474. Compound **4** was also characterized as the 2-*O*-acetate by treatment with Ac_2O (1 mL) in pyridine (2 mL) at rt for 12 h as described above. The ^{1}H NMR and pfg-COSY spectrum of 2-*O*-acetyl-**4** confirmed the β configuration ($J_{1,2}$ = 10.5 Hz).

2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl 1-Dibenzyldithiocarbamate (2-*O*-acetyl 4). ^{1}H NMR (500 MHz, C_6D_6): δ 7.45−6.71 (m, 25H), 6.30 (d, 1H, *J* = 10.5 Hz), 5.70 (dd, 1H, *J* = 9.0, 10.5 Hz), 5.30 (d, 1H, *J* = 14.9 Hz), 5.15 (d, 1H, *J* = 14.9 Hz), 4.73 (dd, 2H, *J* = 8.3, 11.6 Hz), 4.63 (d, 1H, *J* = 11.7 Hz), 4.58−4.50 (m, 2H), 4.51−4.42 (m, 2H), 4.32 (d, 1H, *J* = 12.0 Hz), 3.87 (t, 1H, *J* = 9.3 Hz), 3.84−3.73 (m, 3H), 3.68 (dd, 1H, *J* = 3.8, 11.4 Hz), 1.61 (s, 3H).

3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl 1-Diisopropyldithiocarbamate (5). Tri-*O*-benzyl glucal **1** (29 mg, 0.07 mmol) was subjected to DMDO oxidation at 0 °C for 1 h to provide α-epoxyglucal in quantitative yield followed by DTC ring opening in THF with (*i*-Pr)$_2$DTC (0.28 mmol, 0.5 M in MeOH) as described above. The pale yellow syrup was concentrated and purified by silica gel chromatography using a 5−30% EtOAc in hexanes gradient with 1% Et_3N; mixed fractions were separated by preparative TLC (15% EtOAc in hexanes with 1% Et_3N) to afford glycosyl DTC **5** as a pale yellow syrup (22 mg, 52%). ^{1}H NMR (500 MHz, C_6D_6): δ 7.36 (d,

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2H, J = 7.5 Hz), 7.27−7.19 (m, 4H), 7.18−7.05 (s, 9H), 4.99 (d, 1H, J = 11.5 Hz), 4.87 (d, 1H, J = 11.4 Hz), 4.83 (d, 1H, J = 11.5 Hz), 4.62 (d, 1H, J = 11.4 Hz), 4.39 (d, 1H, J = 11.9 Hz), 4.23 (d, 1H, J = 11.9 Hz), 4.03 (br s, 1H), 3.91 (t, 1H, J = 9.4 Hz), 3.74−3.61 (m, 5H), 2.67 (br s, 1H), 1.70−0.67 (m, 14H). ^{13}C NMR (100 MHz, C_6D_6): δ 139.7, 139.5, 139.0, 128.6, 128.5, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 87.6, 80.1, 77.8, 75.4, 74.8, 73.7, 73.6, 73.4, 69.1, 19.7. IR (thin film): 2869, 1455, 1379, 1298, 1198, 1063, 700 cm^{-1}. $[\alpha]_D^{25}$ = +22.2° (c 1.5, CH_2Cl_2). HRESI−MS: m/z calcd for $C_{34}H_{44}NO_5S_2$ $[M + H]^+$, 610.2661; found, 610.2673. Compound **5** was also characterized as the 2-*O*-acetate by treatment with Ac_2O (1 mL) in pyridine (2 mL) at rt for 12 h as described above. The ^{1}H NMR and pfg-COSY spectrum of 2-*O*-acetyl **5** confirmed the β configuration ($J_{1,2}$ = 9.7 Hz).

2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl 1-Diisopropyldithiocarbamate (2-*O*-acetyl 5). ^{1}H NMR (500 MHz, C_6D_6): δ 7.26 (t, 5H, J = 7.8 Hz), 7.22−7.01 (m, 10H), 6.43 (d, 1H, J = 10.5 Hz), 5.76 (t, 1H, J = 9.7 Hz), 4.73 (dd, 2H, J = 9.0, 11.5 Hz), 4.62 (d, 1H, J = 11.7 Hz), 4.55 (d, 1H, J = 11.4 Hz), 4.40 (d, 1H, J = 11.9 Hz), 4.25 (d, 1H, J = 11.9 Hz), 3.89 (t, 1H, J = 9.3 Hz), 3.81−3.69 (m, 3H), 3.65 (dd, 1H, J = 3.4, 11.2 Hz), 1.65 (s, 3H), 1.68−0.39 (m, 12H). ^{13}C NMR (100 MHz, C_6D_6): δ 169.4, 139.3, 139.2, 139.1, 128.6, 128.5, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 85.7, 80.2, 78.2, 75.4, 74.8, 73.4, 68.9, 20.7, 19.6.

3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl 1-Diphenyldithiocarbamate (6). Tri-*O*-benzyl glucal **1** (31 mg, 0.075 mmol) was subjected to DMDO oxidation at 0 °C for 1 h to provide α-epoxyglucal (10:1 α:β) in quantitative yield followed by DTC ring opening in THF with Li-$(Ph)_2$DTC (0.15 mmol) dissolved in MeOH. The pale yellow syrup was purified by silica gel chromatography using a 5−50% EtOAc in hexanes gradient with 1% Et_3N; mixed fractions were separated by preparative TLC (20% EtOAc in hexanes with 1% Et_3N) to afford glycosyl DTC **6** as a colorless solid (42 mg, 82%). ^{1}H NMR (500 MHz, C_6D_6): δ 7.30 (d, 2H, J = 7.5 Hz), 7.23 (d, 2H, J = 7.4 Hz), 7.21 (d, 2H, J = 7.5 Hz), 7.19−7.05 (m, 13H), 7.00 (dd, 4H, J = 9.5, 10 Hz), 6.91 (dd, 2H, J = 7.5, 9.5 Hz), 5.99 (d, 1H, J = 10.1 Hz), 4.84 (dd, 2H, J = 11.0, 11.5 Hz), 4.77 (d, 1H, J = 11.5 Hz), 4.60 (d, 1H, J = 11.4 Hz), 4.40 (d, 1H, J = 11.9 Hz), 4.21 (d, 1H, J = 11.9 Hz), 3.85 (dd, 1H, J = 11.0, 11.5 Hz), 3.73−3.63 (m, 4H), 3.59 (dd, 1H, J = 10.5, 11.0 Hz), 1.96 (br s, 1H). ^{13}C NMR (100 MHz, C_6D_6): δ 198.3, 139.6, 139.4, 138.9, 129.7, 128.6, 128.5, 128.5, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 127.6, 90.7, 87.4, 79.9, 77.7, 75.3, 74.7, 73.5, 72.9, 69.1. IR (thin film): 2877, 1590, 1489, 1455, 1353, 1041, 755, 700 cm^{-1}. $[\alpha]_D^{25}$ = +11.3° (c 0.4, CH_2Cl_2). HRESI−MS: m/z calcd for $C_{40}H_{39}NO_5S_2Na$ $[M + Na]^+$, 700.2167; found, 700.2159. Product **6** was also characterized as the 2-*O*-acetate by treatment with Ac_2O (1 mL) in pyridine (2 mL) at rt for 12 h as described above. The ^{1}H NMR and pfg-COSY spectrum of 2-*O*-acetyl-**6** confirmed the β configuration ($J_{1,2}$ = 10.5 Hz).

2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl 1-Diphenyldithiocarbamate (2-*O*-acetyl 6). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30−7.04 (m, 30H), 5.53 (d, 1H, J = 10.5 Hz), 5.03 (t, 1H, J = 10.5 Hz), 4.69 (d, 1H, J = 11.1 Hz), 4.65 (d, 1H, J = 10.2 Hz), 4.57 (d, 1H, J = 10.4 Hz), 4.55(d, 1H, J = 12.0 Hz), 4.43(d, 1H, J = 9.0 Hz), 4.39 (d, 1H, J = 10.2 Hz), 3.71−3.60 (m, 4H), 3.53 (m, 1H), 1.79 (s, 3H).

3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl-(1→3)-4,6-*O*-Benzylidene-D-glucal (8).[53] Glycosyl DTC **2** (58 mg, 0.1 mmol) was subjected to Cu$(OTf)_2$-mediated glycosylation with glucal acceptor **7** (35 mg, 0.15 mmol) as previously described with a slight modification: glucal acceptor **7** was added into the reaction mixture in 1:1 DCE/DCM without precooling because of its limited solubility. After workup, the crude mixture was passed through a plug of silica gel (neutralized with 1% Et_3N) packed on a fritted funnel and eluted with 2% EtOAc in toluene with 1% Et_3N to remove nonpolar byproducts followed by EtOAc to collect the product, which was concentrated to dryness. The pale yellow syrup was purified by preparative TLC (10% EtOAc in toluene with 1% Et_3N and then 15% EtOAc in toluene with 1% Et_3N) to afford an inseparable mixture of 1,3-linked disaccharide glucals as a colorless syrup (47 mg, 70% α/β 1:9). The α/β ratio was determined by the peak integration of the 2′-*O*-acetyl derivative. The diastereomeric mixture was recrystallized with 5% benzene in hexanes at −20 °C to afford pure β-1,3-linked disaccharide glucal **8** as a white solid. ^{1}H NMR (500 MHz, C_6D_6): δ 7.56 (d, 1H, J = 7.2 Hz), 7.37 (d, 1H, J = 7.3 Hz), 7.29 (d, 1H, J = 7.3 Hz), 7.23 (d, 1H, J = 7.2 Hz), 7.19−7.07 (m, 16H), 6.10 (dd, 1H, J = 1.2, 6.1 Hz), 5.31 (s, 1H), 5.06 (d, 1H, J = 11.5 Hz), 4.89 (d, 1H, J = 11.3 Hz), 4.86 (dd, 1H, J = 1.9, 6.1 Hz), 4.80 (d, 1H, J = 11.5 Hz), 4.64 (d, 1H, J = 7.6 Hz), 4.57 (d, 1H, J = 11.4 Hz), 4.53 (d, 1H, J = 8.0 Hz), 4.42 (d, 2H, J = 4.2 Hz), 4.10 (dd, 1H, J = 5.2, 10.4), 3.99 (dd, 1H, J = 7.7, 10.2 Hz), 3.77 (t, 1H, J = 8.4 Hz), 3.73−3.57 (m, 5H), 3.48 (t, 1H, J = 10.4 Hz), 3.40 (dt, 1H, J = 10.0, 3.5 Hz), 2.76 (s, 1H). ^{13}C NMR (125 MHz, C_6D_6): δ 144.7, 139.8, 139.3, 139.1, 137.9, 129.2, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.1, 128.0, 127.9, 127.7, 127.7, 127.6, 126.8, 102.8, 101.8, 101.4, 84.8, 78.5, 77.8, 76.0, 75.0, 75.0, 74.4, 73.6, 71.6, 69.4, 69.3, 68.4. IR (thin film): 3515, 2522, 2862, 1646, 1498, 1453, 1359, 1229, 1104, 1064, 755, 701 cm^{-1}. $[\alpha]_D^{25}$ −18.2° (c 0.9, CH_2Cl_2). HRESI−MS: m/z calcd for $C_{40}H_{42}O_9Na$ $[M + Na]^+$, 689.2727; found, 689.2737. Product **8** was also characterized as the 2-*O*-acetate; the ^{1}H NMR and pfg-COSY spectrum of 2-*O*-acetyl-**8** confirmed the β configuration ($J_{1,2}$ = 8.5 Hz).

2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl-(1→3)-4,6-*O*-benzylidene-D-glucal (2′-*O*-acetyl 8). ^{1}H NMR (500 MHz, C_6D_6): δ 7.62 (d, 2H, J = 7.3 Hz), 7.29 (t, 4H, J = 8.1 Hz), 7.19−7.02 (m, 14H), 6.07 (dd, 1H, J = 1.5, 6.0 Hz), 5.45 (t, 1H, J = 8.5 Hz), 5.33 (s, 1H), 4.74−4.57 (m, 5H), 4.53 (dt, 1H, J = 7.0, 2.0 Hz), 4.44 (m, 1H), 4.42 (s, 2H), 4.11 (dd, 1H, J = 5.1, 10.4 Hz), 4.03 (dd, 1H, J = 7.3, 10.3 Hz), 3.69 (dt, 1H, J = 5.0, 10.2 Hz), 3.65 (dd, 1H, J = 1.9, 11.0 Hz), 3.62−3.53 (m, 3H), 3.48 (t, 1H, J = 10.4 Hz), 3.42 (m, 1H), 1.71 (s, 3H).

Isopropyl 3,4,6-Tri-*O*-benzyl-β-D-glucopyranoside (10). Tri-*O*-benzyl glucal **1** (104 mg, 0.25 mmol) was subjected to DMDO oxidation at 0 °C for 1 h followed by DTC ring opening as previously described. The crude glycosyl DTC **2** was then subjected to Cu$(OTf)_2$-mediated glycosylation with i-PrOH (29 μL, 0.38 mmol) as described in the general procedure. After workup, the crude mixture was passed through a plug of silica gel (neutralized with 1% Et_3N) packed on a fritted funnel and eluted with 1% EtOAc in toluene with 1% Et_3N to remove nonpolar byproducts followed by EtOAc with 1% Et_3N to collect the product mixture. The pale yellow syrup was concentrated and repurified by silica gel chromatography using a 5−20% EtOAc in hexanes gradient with 1% Et_3N to afford β-i-Pr glucoside **10** as a colorless syrup (87 mg, 71%) and α-i-Pr glucoside **10′** as a crystalline solid (11 mg, 9%). Major isomer **10**: ^{1}H NMR (500 MHz, C_6D_6): δ 7.42 (d, 2H, J = 7.4 Hz), 7.30 (d, 2H, J = 7.5 Hz), 7.24 (d, 2H, J = 7.4 Hz), 7.18−7.16 (m, 6H), 7.13−7.05 (m, 3H), 5.13 (t, 1H, J = 9.9 Hz), 4.92 (d, 1H, J = 11.3 Hz), 4.89 (d, 1H, J = 11.6 Hz), 4.55 (d, 1H, J = 11.3 Hz), 4.47 (d, 1H, J = 12.5 Hz), 4.42 (d, 1H, J = 12.5 Hz), 4.22 (d, 1H, J = 7.2 Hz), 3.86 (dt, 1H, J = 12.3, 6.2 Hz), 3.74−3.61 (m, 5H), 3.41 (m, 1H), 2.41 (br s, 1H), 1.21 (d, 3H, J = 6.2 Hz), 1.01 (d, 3H, J = 6.1 Hz). ^{13}C NMR (125 MHz, C_6D_6): δ 140.1, 139.7, 139.4, 128.9, 128.9, 128.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.0, 128.0, 102.1, 85.3, 78.4, 76.0, 75.4, 73.8, 71.9, 69.9, 24.2, 22.4. IR (thin film): 3468, 2898, 1464, 1362, 1109, 1054, 738, 700 cm^{-1}. $[\alpha]_D^{25}$ = −8.0° (c 3.5, CH_2Cl_2). HRESI−MS: m/z calcd for $C_{30}H_{36}O_6Na$ $[M + Na]^+$, 515.2410; found, 515.2417. Major isomer **10** was also characterized as the 2-*O*-acetate; ^{1}H NMR and pfg-COSY confirmed the β configuration ($J_{1,2}$ = 8.6 Hz).

Isopropyl 2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (2-*O*-acetyl 10). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40−6.96 (m, 15H), 4.88 (t, 1H, J = 8.6 Hz), 4.72 (d, 2H, J = 11.4 Hz), 4.63−4.42 (m, 4H), 4.32 (d, 1H, $J_{1,2}$ = 8.0 Hz), 3.83 (q, 1H, J = 6.1 Hz), 3.72−3.50 (m, 4H), 3.41 (m, 1H), 1.89 (s, 3H), 1.16 (d, 3H, J = 6.2 Hz), 1.04 (d, 3H, J = 6.1 Hz).

Isopropyl 3,4,6-Tri-*O*-benzyl-α-D-glucopyranoside (10′).[54] ^{1}H NMR (500 MHz, C_6D_6): δ 7.41 (d, 2H, J = 7.4 Hz), 7.30 (d, 2H, J = 7.5 Hz), 7.26 (d, 2H, J = 7.3 Hz), 7.18−7.07 (m, 9H), 5.02 (d, 1H, J = 11.4 Hz), 4.95 (d, 1H, J = 11.2 Hz), 4.85 (d, 1H, J = 4.0 Hz), 4.78 (d, 1H, J = 11.4 Hz), 4.60 (d, 1H, J = 11.2 Hz), 4.45 (d, 1H, J = 12.2 Hz), 4.38 (d, 1H, J = 12.2 Hz), 4.05 (ddd, 1H, J = 1.7, 4.5, 10.0 Hz), 3.87 (t, 1H, J = 9.0 Hz), 3.78 (dr, 1H, J = 4.0, 9.6 Hz), 3.75−3.68

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(m, 3H), 3.66 (dd, 1H, J = 1.8, 10.7 Hz), 1.88 (d, 1H, J = 9.9 Hz), 1.09 (d, 3H, J = 6.2 Hz), 0.90 (d, 3H, J = 6.1 Hz). ^{13}C NMR (125 MHz, C_6D_6): δ 139.8, 139.4, 139.1, 128.6, 128.5, 128.3, 128.2, 128.0, 128.0, 127.9, 127.7, 127.6, 127.6, 97.6, 84.4, 78.1, 75.4, 75.1, 73.7, 73.5, 71.5, 70.6, 69.6, 23.4, 21.7. IR (thin film): 3497, 2917, 2857, 1500, 1458, 1363, 1330, 1129, 1074, 1025, 741, 702 cm^{-1}. $[\alpha]_D^{25}$ = +77.1° (c 1.5, CH_2Cl_2). HRESI−MS: m/z calcd for $C_{30}H_{36}O_6Na$ $[M + Na]^+$, 515.2410; found, 515.2418.

Benzyl 3,4,6-Tri-*O*-benzyl-β-D-glucopyranoside (11).[55] Tri-*O*-benzyl glucal **1** (104 mg, 0.25 mmol) was subjected to DMDO oxidation at 0 °C for 1 h followed by DTC ring opening as previously described. The crude glycosyl DTC **2** was subjected to $Cu(OTf)_2$-mediated glycosylation with benzyl alcohol (39 μL, 0.38 mmol) as described in the general procedure. After workup, the crude mixture was passed through a plug of silica gel (neutralized with 1% Et_3N) packed on a fritted funnel and eluted with 0.5% EtOAc in toluene with 1% Et_3N to remove byproducts followed by EtOAc with 1% Et_3N to collect the product mixture. The pale yellow syrup was concentrated and repurified by silica gel chromatography using a 5−30% EtOAc in hexanes gradient with 1% Et_3N to afford β-benzyl glucoside **11** as a crystalliine solid (85 mg, 63%) and α-benzyl glucoside **11′** as a crystalline solid (12 mg, 9%). Major isomer **11**: ^{1}H NMR (500 MHz, C_6D_6): δ 7.39 (d, 2H, J = 7.8 Hz), 7.34−7.27 (m, 4H), 7.26−7.22 (m, 2H), 7.21−7.13 (m, 8H), 7.13−7.07 (m, 4H), 5.05 (d, 1H, J = 11.5 Hz), 4.90 (d, 1H, J = 11.3 Hz), 4.86 (d, 1H, J = 11.9 Hz), 4.82 (d, 1H, J = 11.5 Hz), 4.55 (d, 1H, J = 11.3 Hz), 4.45 (dd, 2H, J = 5.6, 12.0 Hz), 4.40 (d, 1H, J = 12.2 Hz), 4.24 (d, 1H, J = 7.7 Hz), 3.76−3.67 (m, 4H), 3.59 (t, 1H, J = 8.9 Hz), 3.37 (ddd, 1H, J = 2.6, 4.0, 9.7 Hz), 2.09 (br s, 1H). ^{13}C NMR (125 MHz, C_6D_6): δ 139.7, 139.4, 139.0, 138.1, 128.7, 128.6, 128.5, 128.5, 128.4, 128.3, 128.1, 127.9, 127.7, 127.7, 102.3, 84.9, 78.0, 75.7, 75.7, 75.1, 75.0, 73.6, 71.0, 69.5. IR (thin film): 3481, 2873, 1502, 1455, 1358, 1117, 1058, 695 cm^{-1}. $[\alpha]_D^{25}$ = −18.0° (c 1.0, CH_2Cl_2). HRESI−MS: m/z calcd for $C_{34}H_{36}O_6Na$ $[M + Na]^+$, 563.2410; found, 563.2407. Product **11** was also characterized as the 2-*O*-acetate; ^{1}H NMR and pfg-COSY confirmed a β configuration ($J_{1,2}$ = 9.2 Hz).

Benzyl 2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (2-*O*-acetyl 11). ^{1}H NMR (500 MHz, C_6D_6): δ 7.30 (t, 5H, J = 7.4 Hz), 7.25−7.00 (m, 15H), 5.54 (dd, 1H, $J_{2,3}$ = 8.0, $J_{1,2}$ = 9.2 Hz), 4.86 (d, 1H, J = 12.4 Hz), 4.71 (dd, 2H, J = 7.8, 11.3 Hz), 4.64 (d, 1H, J = 11.6 Hz), 4.53 (d, 1H, J = 12.4 Hz), 4.45 (t, 3H, J = 11.5 Hz), 4.39 (m, 1H), 3.72−3.60 (m, 3H), 3.57 (t, 1H, J = 8.6 Hz), 3.41 (m, 1H), 1.69 (s, 3H).

Benzyl 3,4,6-Tri-*O*-benzyl-α-D-glucopyranoside (11′).[56] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40−7.23 (m, 18H), 7.13 (dd, 2H, J = 2.8, 6.6 Hz), 4.93 (d, 1H, J = 3.6 Hz), 4.82 (dd, 2H, J = 2.6, 10.9 Hz), 4.75 (d, 1H, J = 11.7 Hz), 4.64 (d, 1H, J = 12.0 Hz), 4.58−4.43 (m, 3H), 3.86−3.56 (m, 7H), 2.10 (d, 1H, J = 8.8 Hz). Product **11′** was also characterized as the 2-*O*-acetate; ^{1}H NMR and pfg-COSY confirmed the α configuration ($J_{1,2}$ = 3.7 Hz).

Benzyl 2-*O*-Acetyl-3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (2-*O*-acetyl 11′). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55−6.96 (m, 20H), 5.11 (d, 1H, J = 3.7 Hz), 4.89 (dd, 1H, J = 3.7, 10.1 Hz), 4.85−4.78 (m, 2H), 4.73−4.62 (m, 2H), 4.56−4.44 (m, 3H), 4.06 (t, 1H, J = 8.7 Hz), 3.86 (dq, 1H, J = 10.1, 1.8 Hz), 3.79−3.68 (m, 2H), 3.62 (dd, 2H, J = 1.9, 10.7 Hz), 2.00 (s, 3H).

Methyl 3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (16). Tri-*O*-benzyl glucal **1** (83 mg, 0.2 mmol) was subjected to DMDO oxidation at 0 °C for 1 h followed by DTC ring opening as previously described. The crude glycosyl DTC **2** was subjected to $Cu(OTf)_2$-mediated glycosylation with methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (139 mg, 0.3 mmol) as described in the general procedure to yield the desired 1,4-linked disaccharide. After workup, the crude mixture was passed through a plug of silica gel (neutralized with 1% Et_3N) packed on a fritted funnel and eluted with 2% EtOAc in toluene with 1% Et_3N to remove byproducts followed by EtOAc with 1% Et_3N to collect the product mixture. The pale yellow syrup was concentrated and repurified by silica gel chromatography using a 5−30% EtOAc in hexanes gradient with 1% Et_3N to afford 1,4-β-linked disaccharide **16** as a colorless syrup (86 mg, 48%). ^{1}H NMR (500 MHz, C_6D_6): δ 7.49 (d, 2H, J = 7.6 Hz), 7.41 (d, 2H, J = 7.5 Hz), 7.36 (d, 2H, J = 7.5 Hz), 7.26−7.05 (m, 24H), 5.31 (d, 1H, J = 11.5 Hz), 5.10 (d, 1H, J = 12.0 Hz), 5.05 (d, 1H, J = 11.5 Hz), 4.89 (dd, 1H, J = 7.5, 11.5 Hz), 4.74 (d, 1H, J = 8.0 Hz), 4.63−4.21 (m, 8H), 4.04 (dd, 1H, J = 9.5 Hz), 4.04 (dd, 1H, J = 3.0, 11.0 Hz), 3.90 (br s, 1H), 3.82−3.75 (m, 2H), 3.70 (dd, 1H, J = 1.5, 11.0 Hz), 3.63 (t, 2H, J = 9.0 Hz), 3.59 (dd, 1H, J = 4.0, 11.0 Hz), 3.55 (d, 1H, J = 9.5 Hz), 3.52 (dd, 1H, J = 3.5, 8.5 Hz), 3.39 (d, 1H, J = 9.5 Hz), 3.31 (d, 1H, J = 2.5 Hz), 3.13 (s, 3H), 3.03 (s, 1H). ^{13}C NMR (125 MHz, C_6D_6): δ 140.2, 139.6, 139.2, 138.9, 138.4, 128.5, 128.3, 128.2, 128.1, 127.9, 127.4, 127.3, 127.0, 103.5, 98.3, 84.9, 80.7, 80.4, 77.6, 77.5, 75.9, 75.7, 74.9, 74.7, 73.5, 73.3, 73.0, 70.3, 69.1, 68.9, 54.8. IR (thin film): 3466, 2919, 1725, 1501, 1455, 1365, 1274, 1107, 1061, 741, 704 cm^{-1}. $[\alpha]_D^{25}$ = +34.0° (c 2.0, CH_2Cl_2). HRESI−MS: m/z calcd for $C_{55}H_{60}O_{11}Na$ $[M + Na]^+$, 919.4033; found, 919.4038. Product **16** was also characterized as the 2′-*O*-acetate; ^{1}H NMR and pfg-COSY confirmed the β configuration ($J_{1',2'}$ = 9.4 Hz).

Methyl 2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (2′-*O*-acetyl 16). ^{1}H NMR (500 MHz, C_6D_6): δ 7.48 (d, 2H, J = 7.4 Hz), 7.35 (d, 2H, J = 7.4 Hz), 7.32 (d, 2H, J = 7.2 Hz), 7.28 (d, 2H, J = 7.6 Hz), 7.24 (d, 2H, J = 7.1 Hz), 7.21−7.00 (m, 20H), 5.46 (t, 1H, J = 9.4 Hz), 5.27 (d, 1H, J = 11.9 Hz), 4.95 (d, 1H, J = 11.9 Hz), 4.88 (d, 1H, J = 8.0 Hz), 4.74 (d, 1H, J = 11.6 Hz), 4.70−4.53 (m, 5H), 4.51−4.39 (m, 5H), 4.32−4.20 (m, 2H), 3.98−3.94 (m, 2H), 3.71 (dd, 1H, J = 2.5, 9.5 Hz), 3.69 (d, 1H, J = 6.8 Hz), 3.66 (dd, 1H, J = 1.5, 11.0 Hz), 3.59−3.51 (m, 3H), 3.42 (dd, 1H, J = 3.4, 8.9 Hz), 3.12 (s, 3H), 1.69 (s, 3H).

Isopropyl 3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl-(1→4)-3-*O*-acetyl-6-*O*-*tert*-butyl-diphenylsilyl-2-phthalimido-β-D-glucopyranoside (17). Tri-*O*-benzyl glucal **1** (42 mg, 0.1 mmol) was subjected to DMDO oxidation at 0 °C for 1 h and then subjected to DTC ring opening as previously described. The crude glycosyl DTC **2** was subjected to $Cu(OTf)_2$-mediated glycosylation with the acceptor (76 mg, 0.12 mmol) as described in the general procedure. After workup, the crude mixture was passed through a plug of silica gel (neutralized with 1% Et_3N) packed on a fritted funnel and eluted with 2% EtOAc in toluene with 1% Et_3N to remove byproducts followed by EtOAc with 1% Et_3N to collect the product mixture. The pale yellow syrup was concentrated and repurified by preparative TLC (30% EtOAc in hexanes with 1% Et_3N and then 40% EtOAc in hexanes with 1% Et_3N) to afford 1,4-β-linked disaccharide **17** as a colorless syrup (60 mg, 56%). ^{1}H NMR (500 MHz, C_6D_6): δ 7.99 (dd, 2H, J = 1.3, 8.0 Hz), 7.94 (d, 2H, J = 6.8 Hz), 7.53 (d, 1H, J = 6.3 Hz), 7.46 (d, 1H, J = 6.4 Hz), 7.43 (d, 2H, J = 7.5 Hz), 7.33−7.04 (m, 19H), 6.90−6.74 (m, 2H), 6.34 (t, 1H, J = 10.8 Hz), 5.84 (d, 1H, J = 8.4 Hz), 5.11 (d, 1H, J = 11.6 Hz), 4.92 (d, 2H, J = 11.4 Hz), 4.83 (dd, 1H, J = 8.5, 10.8 Hz), 4.75 (d, 1H, J = 7.6 Hz), 4.57 (d, 1H, J = 11.3 Hz), 4.39 (t, 1H, J = 9.4 Hz), 4.27 (d, 2H, J = 11.9 Hz), 4.19 (d, 1H, J = 11.9 Hz), 4.12 − 3.95 (m, 2H), 3.77 (t, 1H, J = 9.2 Hz), 3.73 − 3.46 (m, 7H), 1.88 (s, 3H), 1.20 (d, 3H, J = 6.2 Hz), 1.17 (s, 9H), 0.97 (d, 3H, J = 6.1 Hz). ^{13}C NMR (125 MHz, C_6D_6): δ 139.7, 139.4, 139.0, 138.1, 128.7, 128.6, 128.5, 128.5, 128.4, 128.3, 128.1, 127.9, 127.7, 127.7, 102.3, 84.9, 78.0, 75.7, 75.7, 75.1, 75.0, 73.6, 70.9, 69.5. IR (thin film): 3432, 2936, 1722, 1384, 1229, 1117, 1041, 763, 695 cm^{-1}. $[\alpha]_D^{25}$ = +20.9° (c 1.0, CH_2Cl_2). HR-MALDI−MS: m/z calcd for $C_{62}H_{69}NO_{13}SiNa$ $[M + Na]^+$, 1086.4434; found, 1086.4458. Product **17** was also characterized as the 2′-*O*-acetate; ^{1}H NMR and pfg-COSY confirmed the β configuration ($J_{1',2'}$ = 8.6 Hz).

Isopropyl 2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl-(1→4)-3-*O*-acetyl-6-*O*-*tert*-butyldiphenylsilyl-2-phthalimido-β-D-glucopyranoside (2′-*O*-acetyl 17). ^{1}H NMR (500 MHz, C_6D_6): δ 7.97 (d, 2H, J = 8.0 Hz), 7.87 (d, 2H, J = 8.0 Hz), 7.56 (d, 1H, J = 6.7 Hz), 7.47 (d, 1H, J = 6.8 Hz), 7.35 (d, 3H, J = 7.2 Hz), 7.31 (d, 3H, J = 7.5 Hz), 7.30−7.04 (m, 15H), 6.88−6.76 (m, 2H), 6.28 (t, 1H, J = 10.7 Hz), 5.74 (d, 1H, J = 8.5 Hz), 5.39 (t, 1H, J = 8.6 Hz), 4.93 (d, 1H, $J_{1,2}$ = 8.1 Hz), 4.79 (dd, 2H, J = 6.3, 15.3 Hz), 4.68 (d, 2H, J = 11.3 Hz), 4.45 (d, 1H, J = 11.3 Hz), 4.36 (t, 1H, J = 9.5 Hz), 4.26 (d, 1H, J = 11.8 Hz), 4.18 (d, 1H, J = 11.8 Hz), 4.03 (dd, 1H, J = 2.8, 11.3

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Hz), 3.97 (dt, 1H, J = 12.4, 6.2 Hz), 3.88 (d, 1H, J = 10.7 Hz), 3.70−3.58 (m, 5H), 3.51 (m, 1H), 1.85 (s, 3H), 1.62 (s, 3H), 1.19 (d, 3H, J = 6.2 Hz), 1.14 (s, 9H), 0.98 (d, 3H, J = 6.1 Hz).

3-*O*-Benzyl-4,6-*O*-benzylidene-β-D-glucopyranosyl-(1→3)-4,6-*O*-benzylidene-D-glucal (19). 4,6-Benzylidene glucal **18** (49 mg, 0.15 mmol) was subjected to DMDO oxidation at 0 °C for 1 h followed by DTC ring opening as previously described. The crude DTC glycosyl donor was subjected to $Cu(OTf)_2$-mediated glycosylation with 4,6-benzylidene glucal **7** (54 mg, 0.23 mmol) as described in the general procedure except that acceptor **7** was added to the reaction mixture without precooling because of its low solubility. After workup, the crude mixture was passed through a plug of silica gel (neutralized with 1% Et_3N) packed on a fritted funnel and eluted with 2% EtOAc in toluene with 1% Et_3N to remove byproducts followed by EtOAc with 1% Et_3N to collect the product mixture. The pale yellow solid was concentrated and repurified by preparative TLC (5% EtOAc in DCE with 1% Et_3N and then 10% EtOAc in DCE with 1% Et_3N) to afford 1,3-β-linked disaccharide glucal **19** as a white solid (36 mg, 42%). ^{1}H NMR (500 MHz, 1:1 C_6D_6/$CDCl_3$): δ 7.56−7.39 (m, 5H), 7.31 (d, 3H, J = 6.9 Hz), 7.20−7.09 (m, 7H), 6.40 (dd, 1H, J = 2, 6.5 Hz), 5.62 (s, 1H), 5.54 (s, 1H), 4.94 (d, 1H, J = 12.0 Hz), 4.86 (dd, 1H, J = 1.9, 6.1 Hz), 4.79 (d, 1H, J = 12.0 Hz), 4.63 (d, 1H, J = 7.5 Hz), 4.60 (d, 1H, J = 7.0 Hz), 4.38 (dd, 1H, J = 5.0, 10.5 Hz), 4.24 (dd, 1H, J = 5.0, 10.5 Hz), 4.02 (dt, 1H, J = 5.2, 10.3 Hz), 4.02 (t, 1H, J = 7.5 Hz), 3.94 (dt, 1H, J = 5.0, 10.0 Hz), 3.85 (t, 1H, J = 10 Hz), 3.77 (t, 1H, J = 10 Hz), 3.71−3.61 (m, 3H), 3.39 (m, 1H), 2.57 (s, 1H). ^{13}C NMR (125 MHz, 1:1 C_6D_6/$CDCl_3$): δ 145.1, 139.2, 138.1, 137.7, 129.4, 129.1, 128.6, 128.4, 128.3, 128.1, 127.9, 126.5, 102.0, 101.8, 101.5, 81.6, 80.5, 78.4, 74.6, 74.4, 73.1, 69.2, 69.0, 68.4, 67.0. IR (thin film): 2923, 1645, 1451, 1362, 1235, 1100, 1016, 695 cm^{-1}. $[\alpha]_D^{25}$ = −18.0° (*c* 0.7, CH_2Cl_2). HRESI−MS: *m*/*z* calcd for $C_{33}H_{34}O_9Na$ $[M + Na]^+$, 597.2101; found, 597.2107. Product **19** was also characterized as the 2′-*O*-benzoate; ^{1}H NMR and pfg-COSY of 2′-*O*-benzoyl **19** confirmed the β configuration ($J_{1',2'}$ = 7.8 Hz).

2-*O*-Benzoyl-3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranosyl-(1→3)-4,6-*O*-benzylidene-D-glucal (2′-*O*-benzoyl 19). ^{1}H NMR (500 MHz, 5:2 C_6D_6/$CDCl_3$): δ 8.00−7.97 (m, 2H), 7.46 (d, 2H, J = 7.6 Hz), 7.42 (d, 2H, J = 7.7 Hz), 7.29−7.03 (m, 11H), 7.02−6.83 (m, 3H), 5.89 (d, 1H, J = 6.2 Hz), 5.45 (t, 1H, J = 7.8 Hz), 5.21 (d, 2H, J = 4.2 Hz), 4.75 (d, 1H, J = 12.3 Hz), 4.64 (d, 1H, J = 12.2 Hz), 4.57 (d, 1H, J = 7.7 Hz), 4.43 (dd, 1H, J = 1.2, 6.2 Hz), 4.32 (d, 1H, J = 7.3 Hz), 4.13 (dd, 1H, J = 4.9, 10.4 Hz), 4.07 (dd, 1H, J = 5.1, 10.5 Hz), 3.76 (dd, 1H, J = 7.4, 10.2 Hz), 3.70 (t, 1H, J = 8.7 Hz), 3.67 (t, 1H, J = 9.0 Hz), 3.61 (dt, 1H, J = 10.3, 5.2 Hz), 3.56 (t, 1H, J = 10.2 Hz), 3.44 (t, 1H, J = 10.3 Hz), 3.27 (dt, 1H, J = 5.0, 9.4 Hz).

3,4,6-Tri-*O*-benzyl-β-D-galactopyranosyl-(1→6)-3,4-di-*O*-benzyl-D-glucal (21). Tri-*O*-benzyl galactal **20** (64 mg, 0.15 mmol) was subjected to DMDO oxidation at −50 °C for 12 h to provide α-epoxygalactal (20:1 α/β) in quantitative yield. We note that DMDO oxidation of galactal **20** at 0 °C caused significant overoxidation, as identified by an aldehyde proton signal at δ 9.6 ppm in ^{1}H NMR and by additional UV-active byproducts. The α-epoxygalactal was subjected to DTC ring opening as previously described; the crude DTC donor was then subjected to CuOTf-mediated glycosylation with 3,4-di-*O*-benzyl-D-glucal **22** (75 mg, 0.23 mmol) as described in the general procedure. After workup, the pale yellow syrup was purified by silica gel chromatography using a 2−7% EtOAc in toluene gradient with 1% Et_3N to afford an inseparable mixture of 1,6-linked disaccharide glucals as a colorless syrup (92 mg, 78%; α/β 1:5); the α/β ratio was determined by NMR peak integration of the 2′-*O*-acetyl derivatives. These were separated by preparative TLC (10% EtOAc in toluene with 1% Et_3N) to afford 2′-*O*-acetyl-β-disaccharide **21** ($J_{1,2}$ = 9.3 Hz) as the major product and 2′-*O*-acetyl-α-disaccharide **21′** ($J_{1',2'}$ = 3.7 Hz) as the minor product.

2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→6)-3,4-di-*O*-benzyl-D-glucal (major isomer, 2′-*O*-acetyl 21). ^{1}H NMR (500 MHz, C_6D_6): δ 7.30−7.05 (m, 25H), 6.25 (d, 1H, J = 6.2 Hz), 5.93 (t, 1H, J = 9.3 Hz), 4.92 (d, 1H, J = 11.6 Hz), 4.73 (d, 1H, J = 11.7 Hz), 4.70 (dd, 1H, J = 3.0, 6.0 Hz), 4.63 (d, 1H, J = 11.5 Hz), 4.52 (d, 1H, J = 11.5 Hz), 4.43 (d, 1H, J = 8.0 Hz), 4.39 (dd, 2H, J = 4.0, 12.5 Hz), 4.31 (d, 1H, J = 12.0 Hz), 4.26−4.28 (m, 4H), 4.13 (m, 1H), 4.07 (br s, 1H), 3.99 (dd, 1H, J = 5.5, 11.0 Hz), 3.90 (t, 1H, J = 7.0 Hz), 3.86 (br s, 1H), 3.70 (t, 1H, J = 8.0 Hz), 3.56 (dd, 1H, J = 5.5, 9.0 Hz), 3.38 (t, 1H, J = 6.5 Hz), 3.33 (dd, 1H, J = 2.5, 10.0 Hz), 1.81 (s, 3H). ^{13}C NMR (125 MHz, C_6D_6): δ 169.0, 144.8, 139.3, 138.8, 138.8, 128.7, 128.6, 128.6, 128.5, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.5, 102.2, 100.0, 81.0, 76.8, 75.2, 74.8, 74.6, 74.0, 73.6, 73.4, 73.2, 71.9, 71.4, 70.2, 68.9, 67.5, 20.9. IR (thin film): 3371, 2877, 1763, 1645, 1510, 1455, 1358, 1253, 1071, 734, 691 cm^{-1}. $[\alpha]_D^{25}$ = +4.9° (*c* 0.9, CH_2Cl_2). HRESI−MS: *m*/*z* calcd for $C_{49}H_{52}O_{10}Na$ $[M + Na]^+$, 823.3458; found, 823.3466.

2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α-D-galactopyranosyl-(1→6)-3,4-di-*O*-benzyl-D-glucal (minor isomer, 2′-*O*-acetyl 21′). ^{1}H NMR (500 MHz, C_6D_6): δ 7.35−7.06 (m, 25H), 6.18 (dd, 1H, J = 0.7, 6.1 Hz), 5.84 (dd, 1H, J = 3.7, 10.5 Hz), 5.52 (d, 1H, J = 3.7 Hz), 5.00 (d, 1H, J = 11.5 Hz), 4.83 (d, 1H, J = 11.4 Hz), 4.67−4.64 (m, 2H), 4.57 (d, 1H, J = 11.5 Hz), 4.47−4.40 (m, 3H), 4.33−4.24 (m, 4H), 4.10−4.08 (m, 2H), 4.04 (dd, 1H, J = 4.3, 12.0 Hz), 3.96−3.93 (m, 2H), 3.79 (t, 1H, J = 7.7 Hz), 3.75 (dd, 1H, J = 1.5, 12.9 Hz), 3.69 (dd, 1H, J = 5.7, 13.5 Hz), 1.85 (s, 3H). ^{13}C NMR (125 MHz, C_6D_6): δ 169.9, 144.6, 139.4, 139.2, 139.2, 138.9, 128.6, 128.5, 128.3, 128.1, 127.8, 127.5, 100.3, 97.8, 77.4, 77.1, 76.1, 75.2, 75.1, 73.8, 73.6, 72.4, 71.7, 70.5, 70.1, 69.4, 66.3, 20.9. IR (thin film): 2936, 2848, 1738, 1502, 1447, 1362, 1244, 1113, 1063, 750, 695 cm^{-1}. $[\alpha]_D^{25}$ = +39° (*c* 0.6, CH_2Cl_2). HRESI−MS: *m*/*z* calcd for $C_{49}H_{52}O_{10}Na$ $[M + Na]^+$, 823.3458; found, 823.3462.

2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-3,4-di-*O*-benzyl-D-glucal (23). 1,6-β-Linked disaccharide **13** (1.65 g, 2.1 mmol) and TBAI (214 mg, 0.6 mmol) were dissolved in DMF (29 mL), cooled to 0 °C under argon, and treated with BnBr (500 μL, 4.2 mmol) and a 60% dispersion of NaH in mineral oil (336 mg, 8.4 mmol). The reaction was stirred at rt for 12 h, quenched at 0 °C with saturated NH_4Cl (25 mL), and extracted with Et_2O (3 × 25 mL). The combined organic extracts were washed with H_2O (3 × 25 mL) and brine (25 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography using a 5−20% EtOAc−hexanes gradient with 1% Et_3N to afford the corresponding benzyl ether **23** as a white solid (1.83 g, 95%). ^{1}H NMR (400 MHz, C_6D_6): δ 7.45−7.06 (m, 30H), 6.30 (d, 1H, J = 6.0 Hz), 5.16 (d, 1H, J = 11.2 Hz), 5.01 (d, 1H, J = 11.2 Hz), 4.86 (d, 1H, J = 11.4 Hz), 4.83 (d, 1H, J = 11.4 Hz), 4.79 (d, 1H, J = 11.3 Hz), 4.74 (dd, 1H, J = 2.8, 6.2 Hz), 4.72 (d, 1H, J = 12.2 Hz), 4.58 (t, 1H, J = 12.6 Hz), 4.48 (d, 1H, J = 12.2 Hz), 4.44−4.39 (m, 3H), 4.36 (dd, 1H, J = 2.0, 11.2 Hz), 4.31 (m, 1H), 4.19 (t, 1H, J = 5.9 Hz), 4.12 (br s, 1H), 3.96 (dd, 1H, J = 5.8, 11.3 Hz), 3.93 (d, 1H, J = 5.9 Hz), 3.75−3.61 (m, 5H), 3.32 (dt, 1H, J = 9.5, 2.5 Hz), 2.11 (br s, 1H). ^{13}C NMR (100 MHz, C_6D_6): δ 144.4, 139.2, 139.1, 139.0, 139.0, 138.8, 138.7, 128.2, 128.1, 127.9, 127.7, 127.6, 127.4, 127.3, 104.2, 99.8, 84.7, 82.2, 77.9, 76.6, 75.2, 75.1, 74.7, 74.6, 74.5, 73.2, 73.0, 70.0, 69.0, 68.2. IR (thin film): 2884, 1651, 1502, 1349, 1109, 1066, 752, 697 cm^{-1}. $[\alpha]_D^{25}$ = +17.4° (*c* 0.5, CH_2Cl_2). HRESI−MS: *m*/*z* calcd for $C_{54}H_{56}O_9Na$ $[M + Na]^+$, 871.3822; found, 871.3804.

2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-3,4-di-*O*-benzyl-β-D-glucopyranosyl-(1→6)-3,4-di-*O*-benzyl-D-glucal (25). Disaccharide glucal **23** (604 mg, 0.71 mmol) was subjected to DMDO oxidation at −50 °C for 12 h to produce α-epoxyglucal (20:1, α/β) in quantitative yield followed by DTC ring opening as previously described. The crude glycosyl DTC donor was then subjected to CuOTf-mediated glycosylation with 3,4-di-*O*-benzyl glucal **22** (278 mg, 0.85 mmol) as described in the general procedure. After workup, the pale yellow syrup was purified by silica gel chromatography using a 5−20% EtOAc gradient in hexanes with 1% Et_3N; the mixed fractions were further separated by preparative TLC (15% EtOAc in hexanes with 1% Et_3N) to afford β,β-1,6-linked trisaccharide glucal **25** as a white solid (537 mg, 63%) and β,α-1,6-linked trisaccharide glucal **25′** as a minor product (56 mg, 7%). Major β,β-isomer **25**: ^{1}H NMR (500 MHz, C_6D_6): δ 7.53−7.15 (m, 40H), 6.38 (d, 1H, J = 6.5 Hz), 5.18 (dd, 2H, J = 6.0, 11.5 Hz), 5.10 (d, 1H, J = 11.5 Hz), 4.97−4.86 (m, 6H), 4.82 (dd, 1H, J = 4.2, 6.0 Hz), 4.75 (d, 1H, J = 12.0 Hz), 4.67 (dd, 2H, J = 6.0, 11.5 Hz), 4.63 (d, 1H, J = 7.5 Hz), 4.59 (d, 1H, J =

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12.5 Hz), 4.54 (d, 1H, J = 5.5 Hz), 4.51 (d, 1H, J = 7.0 Hz), 4.42−4.40 (m, 3H), 4.35 (d, 1H, J = 8.0 Hz), 4.21 (m, 1H), 4.16 (dt, 1H, J = 2.0, 6.0 Hz), 3.98−3.93 (m, 2H), 3.91−3.68 (m, 8H), 3.57 (t, 1H, J = 7.0 Hz), 3.47 (m, 1H), 3.48 (dd, 1H, J = 7.0, 14.0 Hz), 2.71 (br s, 1H). ^{13}C NMR (100 MHz, C_6D_6): δ 144.64, 139.7, 139.3, 139.2, 139.1, 139.0, 128.6, 128.5, 128.5, 128.3, 128.1, 127.9, 127.8, 127.6, 104.6, 103.8, 100.4, 85.2, 84.9, 82.6, 78.4, 76.8, 75.7, 75.6, 75.4, 75.1, 75.0, 74.9, 73.6, 73.6, 70.4. IR (thin film): 2920, 1645, 1506, 1459, 1345, 1063, 733, 700 cm^{-1}. $[\alpha]_D^{25}$ = +13.4° (c 0.5, CH_2Cl_2). HRESI−MS: m/z calcd for $C_{74}H_{78}O_{14}Na$ $[M + Na]^+$, 1213.5289; found, 1213.5292. Minor β,α-isomer **25′**: ^{1}H NMR (500 MHz, C_6D_6): δ 7.50−7.04 (m, 40H), 6.21 (d, 1H, J = 8.5 Hz), 5.12 (d, 1H, J = 11.5 Hz), 4.98 (dd, 2H, J = 9.0, 10.0 Hz), 4.89−4.72 (m, 7H), 4.70 (dd, 1H, J = 2.5, 6.0 Hz), 4.64−4.61 (t, 2H, J = 9.5 Hz), 4.56 (d, 1H, J = 11.5 Hz), 4.48 (d, 1H, J = 12.0 Hz), 4.44−4.40 (m, 3H), 4.33 (d, 1H, J = 9.5 Hz), 4.28 (d, 1H, J = 11.5 Hz), 4.12 (dd, 2H, J = 3.0, 8.0 Hz), 4.06 (dd, 1H, J = 5.0, 11.0 Hz), 3.96 (m, 1H), 3.94−3.87 (m, 2H), 3.82 (dt, 1H, J = 4.0, 9.5 Hz), 3.73−3.65 (m, 7H), 3.60 (t, 1H, J = 8.5 Hz), 3.35 (dt, 1H, J = 2.5, 9.5 Hz), 2.05 (d, 1H, J = 9.5 Hz). ^{13}C NMR (125 MHz, C_6D_6): δ 144.7, 139.6, 139.5, 139.3, 139.1, 139.0, 129.2, 128.7, 128.5, 128.3, 128.1, 127.8, 109.5, 104.5, 85.2, 82.6, 78.4, 78.2, 75.6, 74.9, 74.7, 74.1, 73.6, 71.3, 71.1, 70.4, 69.4, 69.0, 30.2. IR (thin film): 3966, 2911, 1648, 1498, 1458, 1362, 1081, 1027, 741, 704 cm^{-1}. $[\alpha]_D^{25}$ = +23.0° (c 0.8, CH_2Cl_2). HRESI−MS: m/z calcd for $C_{74}H_{78}O_{14}Na$ $[M + Na]^+$, 1213.5289; found, 1213.5321. Trisaccharide glycal **25** was also characterized as the 2′-*O*-acetate; ^{1}H NMR and pfg-COSY confirmed the β configuration ($J_{1',2'}$ = 8.2 Hz).

2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2-*O*-acetyl-3,4-di-*O*-benzyl-β-D-glucopyranosyl-(1→6)-3,4-di-*O*-benzyl-D-glucal (2′-*O*-acetyl 25). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65−6.78 (m, 40H), 6.28 (d, 1H, J = 6.2 Hz), 5.50 (t, 1H, J = 8.2 Hz), 5.04 (t, 1H, J = 11.6 Hz), 4.92−4.58 (m, 15H), 4.55 (d, 1H, J = 12.0 Hz), 4.46 (d, 1H, J = 12.2 Hz), 4.39 (d, 1H, J = 7.8 Hz), 4.31 (d, 1H, J = 12.2 Hz), 4.26 (d, 1H, J = 11.3 Hz), 4.01−4.07 (m, 2H), 3.91−3.87 (m, 2H), 3.81−3.74 (m, 5H), 3.64−3.54 (m, 3H), 3.53−3.45 (m, 2H), 1.72 (s, 3H).

2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl-(1→6)-3,4-di-*O*-benzyl-D-glucal (26). Trisaccharide glucal **25** (186 mg, 0.16 mmol) and TBAI (12 mg, 0.03 mmol) were dissolved in DMF (1.6 mL), cooled to 0 °C under argon, and then treated with BnBr (38 μL, 0.32 mmol) and a 60% dispersion of NaH in mineral oil (13 mg, 0.31 mmol). The ice bath was removed, and the reaction mixture was stirred at rt for 12 h, quenched at 0 °C with saturated NH_4Cl (3 mL), and extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with H_2O (3 × 10 mL) and brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting foamy solid was recrystallized with Et_2O in hexanes to afford benzyl ether **26** as white crystals (184 mg, 92% yield). ^{1}H NMR (500 MHz, C_6D_6): δ 7.45−7.06 (m, 45H), 6.31 (d, 1H, J = 6.0 Hz), 5.17 (d, 1H, J = 11.0 Hz), 5.12 (d, 1H, J = 11.0 Hz), 5.00 (d, 2H, J = 11.5 Hz), 4.87−4.77 (m, 6H), 4.74 (d, 1H, J = 5.0 Hz), 4.67 (d, 1H, J = 12.0 Hz), 4.61−4.54 (m, 4H), 4.50 (d, 1H, J = 12.0 Hz), 4.45−4.38 (m, 4H), 4.33 (d, 1H, J = 11.5 Hz), 4.29 (d, 1H, J = 12.0 Hz), 4.13 (m, 1H), 4.09 (br s, 1H), 3.93 (dd, 1H, J = 5.5, 11.0 Hz), 3.89 (t, 1H, J = 7.0 Hz), 3.80 (dd, 1H, J = 6.0, 11.0 Hz), 3.75−3.59 (m, 8H), 3.46 (m, 1H), 3.40 (m, 1H). ^{13}C NMR (125 MHz, C_6D_6): δ 144.8, 139.6, 139.5, 139.4, 139.3, 139.2, 139.0, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.7, 104.6, 104.3, 100.2, 85.2, 85.1, 82.7, 78.6, 78.4, 76.8, 75.6, 75.5, 75.3, 75.1, 74.9, 74.8, 73.6, 73.4, 70.3, 69.5, 68.9, 68.4. IR (thin film): 2915, 1510, 1451, 1366, 1075, 733, 695 cm^{-1}. $[\alpha]_D^{25}$ = +18.0° (c 2.0, CH_2Cl_2). ESI−MS: m/z for $C_{81}H_{84}O_{14}Na$ $[M + Na]^+$, 1304.07.

2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl-(1→6)-3,4-di-*O*-benzyl-β-D-glucopyranosyl-(1→6)-3,4-di-*O*-benzyl-D-glucal (28). Trisaccharide glycal **26** (111 mg, 0.087 mmol) was subjected to DMDO oxidation at −50 °C for 12 h to produce α-epoxyglucal (20:1, α/β) in quantitative yield followed by DTC ring opening as previously described. The crude glycosyl DTC donor was subjected to CuOTf-mediated glycosylation with 3,4-di-*O*-benzyl glucal **22** (42 mg, 0.13 mmol) as described in the general procedure. After workup, the crude mixture was passed through a plug of silica gel (neutralized with 1% Et_3N) packed on a fritted funnel and eluted with 2% EtOAc in toluene with 1% Et_3N to remove byproducts followed by EtOAc with 1% Et_3N to collect the product mixture. The residue was repurified by silica gel chromatography using a 0−30% EtOAc−hexanes gradient with 1% Et_3N to afford the desired β,β,β-1,6-linked tetrasaccharide **28** as a white solid (68 mg, 49%) and β,β,α-1,6-linked tetrasaccharide **28′** as a minor product (14 mg, 10%). Major β,β,β-isomer **28**: ^{1}H NMR (500 MHz, C_6D_6): δ 7.60−6.91 (m, 55H), 6.28 (d, 1H, J = 5.9 Hz), 5.18−5.03 (m, 4H), 5.00 (dd, 2H, J = 3.8, 11.3 Hz), 4.90−4.75 (m, 6H), 4.76−4.66 (m, 2H), 4.63−4.20 (m, 14H), 4.14 (d, 1H, J = 6.6 Hz), 4.05 (m, 1H), 3.93 (t, 1H, J = 7.5 Hz), 3.90−3.50 (m, 16H), 3.43−3.37 (m, 2H), 1.04 (t, 1H, J = 7.1 Hz). ^{13}C NMR (125 MHz, C_6D6) δ 144.7, 139.7, 139.5, 139.4, 139.3, 139.3, 139.2, 139.0, 128.7, 128.6, 18.6, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.9, 127.7, 127.7, 127.6, 104.7, 103.7, 100.4, 85.2, 85.2, 84.9, 82.8, 82.7, 78.7, 78.4, 78.1, 76.9, 76.0, 75.6, 75.5, 75.4, 75.3, 75.1, 75.1, 75.0, 74.9, 74.8, 73.7, 73.6, 70.5, 69.5, 69.2, 68.9, 68.4. IR (thin film): 2924, 1717, 1464, 1274, 1058, 809, 738, 695 cm^{-1}. $[\alpha]_D^{25}$ = +5.8° (c 0.6, CH_2Cl_2). ESI−MS: m/z for $C_{101}H_{106}O_{19}Na$ $[M + Na]^+$, 1646.60. Minor β,β,α-isomer **28′**: ^{1}H NMR (500 MHz, C_6D_6): δ 7.67−6.81 (m, 55H), 6.21 (d, 1H, J = 6.0 Hz), 5.12 (t, 2H, J = 10.7 Hz), 5.01 (d, 2H, J = 11.2 Hz), 4.96 (d, 2H, J = 10.3 Hz), 4.91 (d, 1H, J = 3.6 Hz), 4.90−4.71 (m, 7H), 4.71−4.61 (m, 3H), 4.60−4.45 (m, 4H), 4.43 (d, 2H, J = 11.8 Hz), 4.39−4.24 (m, 3H), 4.13 (m, 1H), 4.11−4.03 (m, 2H), 3.98−3.89 (m, 3H), 3.86−3.82 (m, 3H), 3.79−3.58 (m, 12H), 3.48 (ddd, 1H, J = 2.0, 5.6, 9.6 Hz), 3.38 (dt, 1H, J = 9.9, 3.1 Hz), 2.15 (d, 1H, J = 9.2 Hz). ^{13}C NMR (125 MHz, C_6D_6): δ 144.7, 139.7, 139.6, 139.5, 139.5, 139.4, 139.3, 139.0, 128.7, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.7, 127.6, 104.8, 104.3, 100.4, 99.7, 85.2, 85.2, 83.7, 82.7, 82.7, 78.6, 78.3, 78.1, 76.6, 76.1, 75.6, 75.4, 75.3, 75.0, 74.9, 74.8, 74.7, 73.9, 73.6, 71.4, 70.4, 69.4, 69.0, 66.7. IR (thin film): 2898, 1746, 1497, 1451, 1362, 1236, 1101, 1046, 742, 683 cm^{-1}. $[\alpha]_D^{25}$ = +8.9° (c 1.3, CH_2Cl_2). ESI−MS: m/z for $C_{101}H_{106}O_{19}Na$ $[M + Na]^+$, 1647. Tetrasaccharide glycals **28** and **28′** were also characterized as 2′-*O*-acetates; ^{1}H NMR and pfg-COSY confirmed the β configuration of **28** ($J_{1',2'}$ = 9.5 Hz) and the α configuration of **28′** ($J_{1',2'}$ = 3.6 Hz).

2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2-*O*-acetyl-3,4-di-*O*-benzyl-β-D-glucopyranosyl-(1→6)-3,4-di-*O*-benzyl-D-glucal (2-*O*-acetyl 28). ^{1}H NMR (500 MHz, C_6D_6): δ 7.73−6.64 (m, 55H), 6.38 (dd, 1H, J = 1.4, 6.2 Hz), 5.56 (dd, 1H, J = 8.0, 9.5 Hz), 5.31−5.01 (m, 3H), 5.01−4.83 (m, 8H), 4.83−4.30 (m, 18H), 4.21−4.16 (m, 2H), 4.05−3.62 (m, 14H), 3.63−3.40 (m, 3H), 1.80 (s, 3H).

2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2-*O*-acetyl-3,4-di-*O*-benzyl-α-D-glucopyranosyl-(1→6)-3,4-di-*O*-benzyl-D-glucal (2-*O*-acetyl 28′). ^{1}H NMR (500 MHz, C_6D_6): δ 7.52−6.96 (m, 55H), 6.14 (dd, 1H, J = 1.3, 6.1 Hz), 5.49 (d, 1H, J = 3.6 Hz), 5.23 (dd, 1H, J = 3.5, 10.1 Hz), 5.13 (d, 2H, J = 11.4 Hz), 5.01 (d, 2H, J = 11.2 Hz), 4.92 (d, 1H, J = 11.6 Hz), 4.89−4.71 (m, 12H), 4.69−4.23 (m, 15H), 4.18 (ddd, 1H, J = 1.8, 5.1, 10.1 Hz), 4.10 (dt, 1H, J = 6.6, 1.8 Hz), 4.06−3.95 (m, 2H), 3.86 (dd, 1H, J = 5.9, 11.4 Hz), 3.83−3.58 (m, 16H), 3.54 (ddd, 1H, J = 1.9, 5.9, 9.7 Hz), 3.39 (dt, 1H, J = 9.8, 3.2 Hz), 1.80 (s, 3H).

3,4,6-Tri-*O*-benzyl-2-*O*-triethylsilyl-β-D-glucopyranosyl 1-diethyldithiocarbamate (29). Glycosyl DTC **2** (116 mg, 0.2 mmol) and imidazole (48 mg, 0.7 mmol) were disolved in THF (2 mL), cooled to 0 °C under argon, and treated with TESCl (170 μL, 1 mmol). The reaction mixture was stirred at room temperature for 12 h, quenched at 0 °C with saturated $NaHCO_3$ (10 mL), and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. After workup, the yellow syrup was purified by silica gel chromatography (neutralized with 1% Et_3N) using a 20−50% EtOAc in hexanes gradient with 1% Et_3N to afford 2-*O*-triethylsilyl glycosyl DTC **29** as a colorless syrup (115 mg, 83%). ^{1}H NMR (500 MHz, C_6D_6): δ 7.35 (d, 2H, J = 7.5 Hz), 7.23 (d, 2H, J = 7.5 Hz), 7.20−7.02 (m, 11H), 6.22 (d, 1H, J = 10.1 Hz), 5.01 (d, 1H, J = 11.8

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Hz), 4.82 (d, 1H, J = 11.8 Hz), 4.73 (d, 1H, J = 11.2 Hz), 4.64 (d, 1H, J = 11.2 Hz), 4.40 (d, 1H, J = 11.9 Hz), 4.21 (d, 1H, J = 11.9 Hz), 4.13 (dd, 1H, J = 8.4, 10.0 Hz), 4.00 (t, 1H, J = 9.5 Hz), 3.77−3.62 (m, 6H), 3.29 (m, 1H), 3.09 (m, 1H), 1.01 (t, 9H, J = 8.0 Hz), 0.99−0.96 (m, 3H), 0.81 (t, 3H, J = 7.0 Hz), 0.73 (q, 6H, J = 7.8 Hz). ^{13}C NMR (125 MHz, C_6D_6): δ 192.9, 140.0, 139.5, 139.3, 128.8, 128.8, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9, 127.7, 127.3, 91.8, 88.4, 80.2, 79.1, 75.7, 75.0, 73.9, 73.7, 69.4, 49.9, 46.9, 13.0, 11.9, 7.7, 6.3. IR (thin film): 2936, 2874, 1489, 1458, 1416, 1351, 1263, 1203, 1143, 1070, 1016, 922, 800, 732, 692 cm^{-1}. $[\alpha]_D^{25}$ = +7.2° (c 0.9, CH_2Cl_2). HRESI−MS: m/z calcd for $C_{38}H_{53}NO_5S_2SiNa$ $[M + Na]^+$, 718.3032; found, 718.3039.

Isopropyl 3,4,6-Tri-*O*-benzyl-2-*O*-triethylsilyl-β-D-glucopyranoside (30). 2-*O*-Triethylsilyl glycosyl DTC **29** (35 mg, 0.05 mmol) was subjected to $Cu(OTf)_2$-mediated glycosylation with *i*-PrOH (8 μL, 0.1 mmol) as described in the general procedure. After workup, the crude mixture was passed through a plug of silica gel (neutralized with 1% Et_3N) packed on a fritted funnel and eluted with 2% EtOAc in toluene with 1% Et_3N to remove byproducts followed by EtOAc with 1% Et_3N to collect the product mixture. The pale yellow syrup was concentrated and repurified by preparative TLC (5% EtOAc−hexanes with 1% Et_3N) to afford β-*i*-Pr glucoside **30** as a colorless syrup (16 mg, 53%) and α-*i*-Pr glucoside **30′** as a colorless syrup (8 mg, 26%). Major isomer **30**: ^{1}H NMR (500 MHz, C_6D_6): δ 7.41 (d, 2H, J = 7.7 Hz), 7.30 (d, 2H, J = 7.6 Hz), 5.01 (d, 1H, J = 12.0 Hz), 4.96 (d, 1H, J = 12.0 Hz), 4.79 (d, 1H, J = 12.0 Hz), 4.79 (d, 1H, J = 11.9 Hz), 4.54 (d, 1H, J = 11.0 Hz), 4.46 (d, 1H, J = 12.0 Hz), 4.40 (d, 1H, J = 12.0 Hz), 4.32 (d, 1H, J = 7.5 Hz), 4.04 (q, 1H, J = 6.0 Hz), 3.79 (d, 1H, J = 8.5 Hz), 3.72 (d, 1H, J = 9.5 Hz), 3.69−3.68 (m, 2H), 3.59 (t, 1H, J = 9.0 Hz), 3.40 (dt, 1H, J = 3.0, 10.0 Hz), 1.26 (d, 3H, J = 6.0 Hz), 1.12 (d, 3H, J = 6.0 Hz), 1.08 (t, 9H, J = 8.0 Hz), 0.80 (q, 6H, J = 8.0 Hz). ^{13}C NMR (125 MHz, C_6D_6): δ 139.5, 139.0, 138.8, 128.3, 128.3, 128.1, 128.0, 127.8, 127.6, 127.5, 127.1, 101.1, 86.4, 78.6, 75.9, 75.4, 75.2, 74.7, 73.3, 70.0, 69.3, 23.7, 21.2, 7.11, 5.50, 1.19. IR (thin film): 2877, 1506, 1354, 1117, 1063, 695 cm^{-1}. $[\alpha]_D^{25}$ = −21.4° (c 0.7, CH_2Cl_2). HRESI−MS: m/z calcd for $C_{36}H_{50}O_6SiNa$ $[M + Na]^+$, 629.3269; found, 629.3258. Minor isomer **30′**: ^{1}H NMR (500 MHz, C_6D_6): δ 7.37 (d, 2H, J = 7.1 Hz), 7.32 (d, 2H, J = 7.1 Hz), 7.23−7.07 (m, 11H), 5.00 (d, 1H, J = 12.0 Hz), 4.97−4.94 (m, 2H), 4.86 (d, 1H, J = 11.5 Hz), 4.64 (d, 1H, J = 11.0 Hz), 4.48 (d, 1H, J = 12.5 Hz), 4.40 (d, 1H, J = 12.0 Hz), 4.21 (t, 1H, J = 9.0 Hz), 4.18 (ddd, 1H, J = 1.5, 4.0, 10.0 Hz), 3.91−3.84 (m, 3H), 3.81 (dd, 1H, J = 4.0, 10.5 Hz), 3.70 (dd, 1H, J = 2.0, 10.5 Hz), 1.22 (d, 3H, J = 6.5 Hz), 1.14 (d, 3H, J = 6.0 Hz), 0.98 (t, 9H, J = 7.5 Hz), 0.62 (dd, 3H, J = 1.0, 7.5 Hz), 0.59 (dd, 3H, J = 2.0, 8.5 Hz). ^{13}C NMR (125 MHz, C_6D6): δ 140.3, 139.8, 139.5, 128.9, 128.8, 128.7, 128.6, 128.4, 128.2, 127.8, 127.7, 98.8, 83.5, 79.3, 76.0, 75.5, 74.9, 73.9, 71.8, 70.9, 70.1, 24.0, 22.2, 7.5, 5.8. IR (thin film): 2907, 1510, 1455, 1371, 1168, 1105, 999, 742, 691 cm^{-1}. $[\alpha]_D^{25}$ = +21.8° (c 0.5, CH_2Cl_2). HRESI−MS: m/z calcd for $C_{36}H_{50}O_6SiNa$ $[M + Na]^+$, 629.3274; found, 629.3285.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H, ^{13}C, DEPT-135, and pfg-COSY NMR spectra for all enumerated compounds; ^{1}H NMR spectra for selected 2-*O*-acetate and epoxide derivatives; and crystallographic information framework (CIF) file for compound **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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