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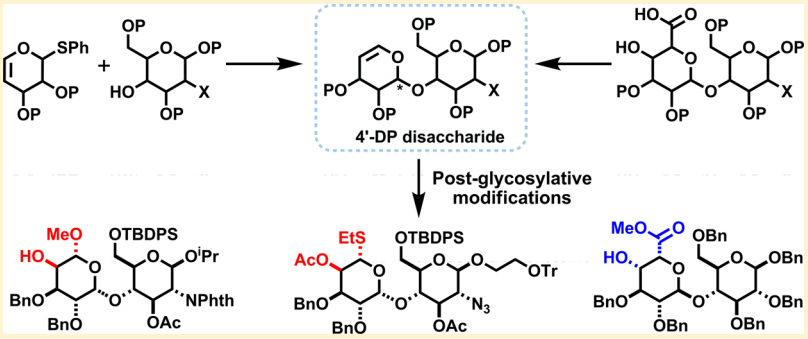
Synthesis and Reactivity of 4′-Deoxypentenosyl Disaccharides

Panuwat Padungros,[†] Ren-Hua Fan,[‡] Matthew D. Casselman, Gang Cheng, Hari R. Khatri, and Alexander Wei*

Department of Chemistry, Purdue University, 560 Oval Drive, West Lafayette, Indiana 47907-2084, United States

Supporting Information



ABSTRACT: 4-Deoxypentenosides (4-DPs) are versatile synthons for rare or higher-order pyranosides, and they provide an entry for structural diversification at the C5 position. Previous studies have shown that 4-DPs undergo stereocontrolled DMDO oxidation; subsequent epoxide ring-openings with various nucleophiles can proceed with both *anti* or *syn* selectivity. Here, we report the synthesis of α- and β-linked 4′-deoxypentenosyl (4′-DP) disaccharides, and we investigate their post-glycosylational C5′ additions using the DMDO oxidation/ring-opening sequence. The α-linked 4′-DP disaccharides were synthesized by coupling thiophenyl 4-DP donors with glycosyl acceptors using BSP/Tf_2O activation, whereas β-linked 4′-DP disaccharides were generated by the decarboxylative elimination of glucuronyl disaccharides under microwave conditions. Both α- and β-linked 4′-DP disaccharides could be epoxidized with high stereoselectivity using DMDO. In some cases, the α-epoxypentenosides could be successfully converted into terminal L-iduronic acids via the *syn* addition of 2-furylzinc bromide. These studies support a novel approach to oligosaccharide synthesis, in which the stereochemical configuration of the terminal 4′-DP unit is established at a post-glycosylative stage.

INTRODUCTION

The structural complexity of oligosaccharides and glycoconjugates is an integral part of their diverse biological activities, but it poses significant challenges in synthesis and the determination of structure−activity relationships. In particular, stereoselective glycosylation is vital for producing carbohydrate derivatives with specific biological activities. While many excellent methods have been developed for glycosyl coupling,[1−3] there are also numerous instances in which coupling efficiency or stereocontrol is compromised by subtle structural changes in the glycosyl donor or acceptor.[4−7] These issues can be particularly troublesome in the glycosyl coupling of advanced intermediates near the end of a multistep synthesis. One way around such obstacles is to install functional groups or stereocenters on terminal glycosides in "post-glycosylative" fashion (i.e., after formation of the glycosidic bond). Post-glycosylative modifications of oligosaccharides are relatively uncommon, due, in part, to the greater complexity of the substrate; however, the successful development of such reactions can lead to more efficient strategies for synthesizing complex carbohydrates and related derivatives for the reasons mentioned above.

Unsaturated pyranosides are promising intermediates for post-glycosylative modification. For example, 2,3-unsaturated pyranosides can be derived from glycals by Ferrier rearrangement under Lewis-acid conditions and then can be converted into various pyranoside derivatives by epoxidation, dihydroxylation, aziridination, or intramolecular cyclizations.[8−11] 2,3-Unsaturated pyranosides can also be synthesized de novo by the Pd-catalyzed acetalization of chiral pyranones followed by post-glycosylative reduction and dihydroxylation to produce three additional stereocenters in the newly formed hexose unit.[12,13] Similarly, 3,4-dideoxyhexenosides have been converted into *S*-linked disaccharides and glycoconjugates via epoxidation and S_N2 ring-opening.[14]

Previous efforts from our laboratories have focused on 4-deoxypentenosides (4-DPs) as a novel synthon for L-hexopyranosides or higher monosaccharides.[15−18] General methods for efficiently converting common D-pyranosides to L-hexose derivatives are relatively rare, although the synthetic opportunities have been recognized.[19,20] 4-DPs bear a strong resemblance to glycals, but they possess heteroatom sub-

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stituents at the anomeric position and an unsaturated C4−C5 bond. Like glycals, 4-DPs can be stereoselectively epoxidized using dimethyldioxirane (DMDO) into α- or β-epoxypyranosides, which are amenable to *anti*- or *syn*-selective ring-opening to generate novel pyranosides with rare or unnatural substituents at the C5 position. These earlier studies demonstrated that 4-DPs are versatile and robust synthons with predictable reactivity, and they encouraged us to examine their utility as advanced intermediates in the synthesis of complex carbohydrates.

In this work, we investigate methods for incorporating 4-DPs as terminal units in disaccharides to support a unique strategy for chain elongation at the nonreducing end. By this approach, the 4′-deoxypentenosyl (4′-DP) disaccharide can serve as a common intermediate for a structurally diverse set of disaccharides and their analogues, based on post-glycosylative modifications at a late stage of synthesis. For example, the pair of 4′-DP disaccharides shown in Figure 1 can produce terminal

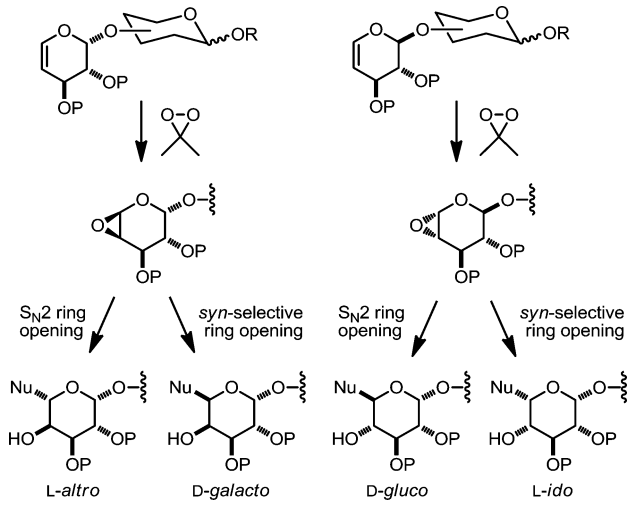


Figure 1. Post-glycosylative approach toward 1,4-linked disaccharides with diverse terminal sugars derived from 4′-deoxypentenosyl disaccharides.

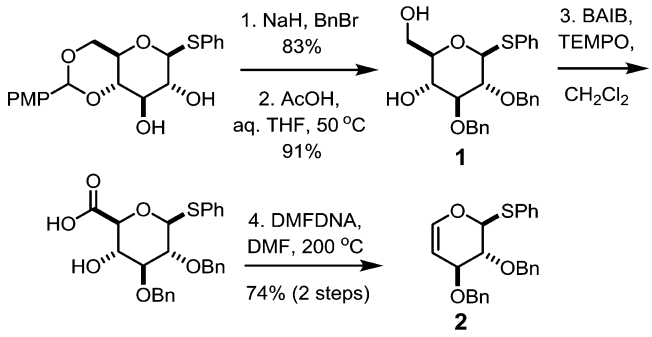
pyranosides with a D-*galacto*, L-*altro*, L-*ido*, or D-*gluco* configuration. In this study, we examined epoxide ring-opening conditions for the stereoselective installation of C5′ substituents on 1,4-linked 4′-DP disaccharides to evaluate the possibility of synthesizing higher-order saccharides using a post-glycosylational approach.

RESULTS AND DISCUSSION

Two synthetic routes to 4′-DP disaccharides were investigated: (i) the glycosyl coupling of 4-DP donors with pyranoside acceptors and (ii) the decarboxylative elimination of disaccharides with terminal glucuronic acid (GlcA) units. Each approach must address possible issues in cross-reactivity: the electron-rich enol ethers of the 4-DPs may react toward electrophilic agents and Brønsted or Lewis acids in glycosyl coupling and they must survive high reaction temperatures during decarboxylative elimination. For these reasons, we chose to develop thiophenyl 4-DPs as glycosyl donors, as the corresponding pyranosides are known for their thermal stability and tolerance to a variety of reaction conditions, particularly those involved in the cleavage of protecting groups. Thioglycosides can also be selectively activated by a broad range of thiophilic reagents,[1−3] several of which may be compatible with the enol ether moiety in 4-DPs.

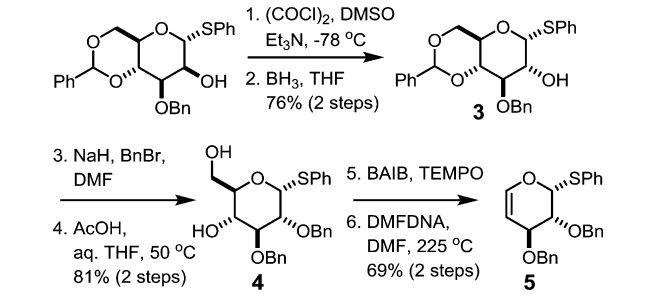
Synthesis of α-Linked 4′-DP Disaccharides. The synthesis of β-thiophenyl 4-DP donor **2** was achieved by converting thiophenyl 4,6-anisylidene-β-D-glucopyranoside[21] into diol **1** followed by chemoselective oxidation to glucuronic acid (GlcA) using bisacetoxyiodobenzene (BAIB) and catalytic (tetramethylpiperidin-1-yl)oxyl (TEMPO; Scheme 1).[22,23]

Scheme 1. Synthesis of β-Thiophenyl 4-DP Donor 2



BAIB/TEMPO oxidation is highly selective for primary alcohols and does not react with the anomeric sulfide.[22] The intermediate GlcA derivative was subjected without further purification to decarboxylative elimination using *N*,*N*-dimethylformamide dineopentyl acetal (DMFDNA) in DMF at 200 °C in a heavy-walled reaction vessel to provide 4-DP donor **2** in 74% overall yield from **1**. Thiophenyl 4-DP α-glucoside **5** was prepared from α-thiophenyl 3-*O*-benzyl-4,6-benzylidene mannopyranoside[24] in good overall yield by Swern oxidation and BH_3 reduction of the intermediate ketone into thiophenyl α-glucoside **3** followed by hydrolysis into 4,6-diol **4** and then oxidation by TEMPO/BAIB and decarboxylative elimination, as described above (Scheme 2).

Scheme 2. Synthesis of α-Thiophenyl 4-DP Donor 5



We next examined thiophenyl 4-DP donors **2** and **5** as glycosyl donors in the synthesis of 1,4-linked 4′-DP disaccharides (Table 1). Thioglycoside activation was achieved using the benzenesulfinyl piperidine/triflic anhydride (BSP/Tf_2O) conditions developed by Crich and co-workers,[25] using tri-*tert*-butylpyrimidine (TTBP) as a base, which we have previously found to be reliable and compatible with various protecting groups.[26] Indeed, electrophilic activation of the anomeric sulfide proceeded in each case without affecting the enol ether moiety, with yields comparable to that of standard thioglycoside donors (Table 1). In addition, the glycosyl couplings proceeded with uniformly high stereoselectivity: for example, the coupling of β-thiophenyl 4-DP donor **2** with

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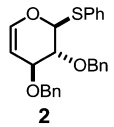
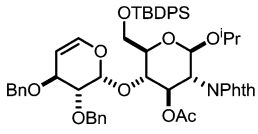
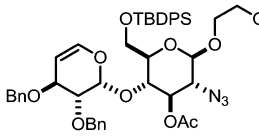
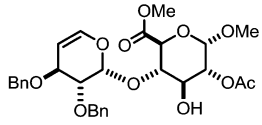
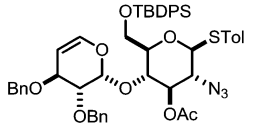
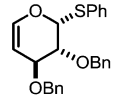
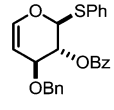
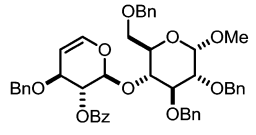
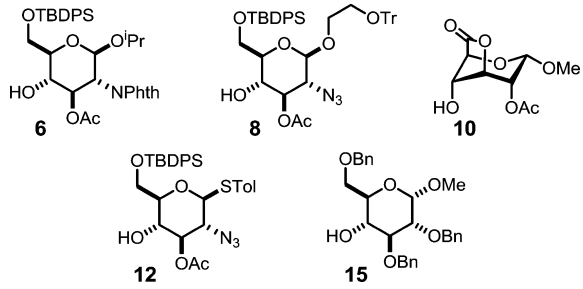
Table 1. Synthesis of 1,4-Linked 4′-DP Disaccharides by Glycosyl Coupling[a]

Entry	4-DP Donor	Acceptor	Coupling Product (yield)
1	 **2**	**6**	 **7** (75%)
2	**2**	**8**	 **9** (57%)
3	**2**	**10**	 **11** (62%, 2 steps)[b]
4	**2**	**12**	 **13** (60%)
5	 **5**	**6**	**7** (49%)
6	**5**	**8**	**9** (69%)
7	 **14**	**15**	 **16** (52%)



[a][Donor]$_i$ = 0.15 M, BSP (1.3 equiv), TTBP (1.6 equiv), 4 Å mol sieves, CH_2Cl_2. Coupling conditions: (i) Tf_2O (1.6 equiv), −78 °C, 45 min; (ii) acceptor (1.5−2.0 equiv) in CH_2Cl_2, −78 °C, 12 h; [Donor]$_f$ = 0.10 M. Quenching conditions: Et_3N, MeOH, −78 °C. [b]Isolated yield after saponification with MeOH.

glucosamine acceptors **6** and **8**, respectively, afforded 1,4-linked 4′-DP disaccharides **7** and **9** in 75 and 57% yields, with exclusive α selectivity in each case (entries 1 and 2). The α-selective glycosylation was supported by a strong NOE interaction between H1′ and H4 (Figure 2). Similarly, coupling of β-thiophenyl 4-DP donor **2** with bicyclic [3.2.1]-glucuronolactone **10**, an acceptor with a constrained $_4C^1$

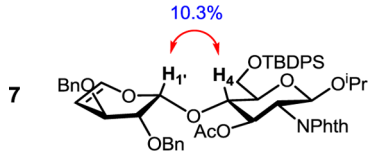


Figure 2. NOE interaction between H1′ and H4 in **7**.

conformation to lower steric encumbrance,[26] proceeded smoothly to provide α-1,4-linked 4′-DP disaccharide **11** after lactone ring-opening in 62% overall yield (entry 3).

We also examined the coupling of thiophenyl 4-DP donors with thioglycoside acceptors, which would enable further glycoconjugation at the reducing end. β-Thiophenyl 4-DP **2** could be activated in the presence of thioglycoside acceptor **12** to produce α-1,4-linked thiophenyl 4′-DP disaccharide **13** in moderate yield, along with some unidentified byproducts (Table 1, entry 4). We attribute the reduction in yield to the variable reactivity of *S*-glycoside acceptors, which are known to be less nucleophilic than their *O*-glycosyl counterparts[4] and prone to aglycone transfer.[27−29]

To determine whether stereoselective glycosylation depended on the anomeric configuration of the 4-DP donor, glycosyl couplings were performed using α-thiophenyl 4-DP donor **5** and acceptors **6** and **8**, which, again, produced α-1,4-linked 4′-DP disaccharides **7** and **9** in good yields (Table 1, entries 5 and 6). We also investigated whether glycosylation could be directed by anchimeric assistance, and we found that glycosyl coupling of 2-*O*-Bz-protected donor **14** (prepared in a manner similar to that of **2**) and acceptor **15** produced exclusively β-linked disaccharide **16** (Table 1, entry 7). However, 2-*O*-Ac- and -Cbz- protected donors did not produce β-linked 4′-DP disaccharides in appreciable amounts and yielded only decomposition byproducts. The lower reactivity of these donors may be due to the disarming effect of the C2 acyl groups during thioglycosyl activation, permitting the 4-DP enol ether to compete for electrophiles. Earlier studies by Gin and co-workers have shown that the enol ether in glycals is activated by diphenylsulfonium triflate (Ph_2SO/Tf_2O).[30]

It is interesting to consider the electronic effect of nearby unsaturation on oxocarbenium formation. Typically, conjugation can be expected to provide resonance stabilization, but the π bond adjacent to the 4-DP oxocarbenium is not properly configured to participate in charge delocalization and may even destabilize the carbenium ion by removing electron density from the ring oxygen. These arguments are supported by density functional theory (DFT) calculations that compare the heats of formation (ΔH_f) of parent 3,4-dihydropyrylium **A** with conjugated isomer 5,6-dihydropyrylium **B**,[31] indicating an enthalpic difference of well over 10 kcal/mol (Table 2).[32] Similarly, DFT analysis using substituted dihydropyryliums **C** and **D** indicates an energy difference of over 20 kcal/mol. We note that the C1−O5 π^* orbital in 4-DP oxocarbenium **C** is delocalized relative to the saturated analogue (Figure 3); however, electron density of the C1 carbenium remains dominant, and its stabilization by the lone pairs on the C5 ring oxygen is reduced by their delocalization into the 2p orbitals of the adjacent π bond.

The analysis above suggests that the 4-DP oxocarbeniums generated from **2** and **5** are relatively short-lived and that glycosylation proceeds with kinetic control. It is unclear whether the high selectivities resulting in α-linked disaccharides can be attributed to a single factor: possiblilities include steric

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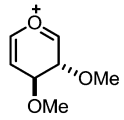
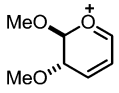
Table 2. Resonance Stabilization Energies for Conjugated Oxocarbenium Ions[a]

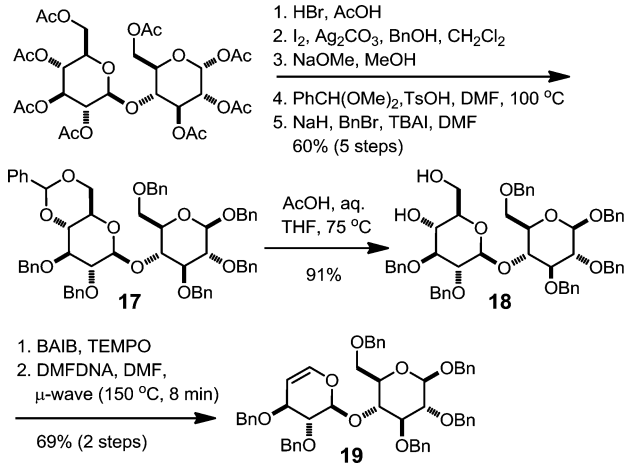
Compound[b]	Energy (a.u.)[c]	$\Delta\Delta H_f$ (kcal/mol)[d]
A 	−269.6669	
		12.3
B 	−269.6865	
C 	−498.7062[e]	
		22.9
D 	−498.7427[e]	

[a]Electronic structures optimized by DFT-B3LYP calculations (6-31+G(d,p)). [b]See ref 31 for atom numbering nomenclature. [c]Atomic units, in hartrees. [d]Resonance stabilization energies based on heats of formation. [e]Assumed $^3C_4$ or $^2C_3$ half-chair conformation with pseudoequatorial groups.

arguments favoring a nucleophilic approach to the α-face, stereoelectronic effects on oxocarbenium facioselectivity directed by transannular substituents,[33] or an S_N2-like mechanism via the formation of a β-glycosyl triflate.[34] With regard to the latter, a low-temperature NMR study was conducted in which BSP and 4-DP thioglycoside **2** were treated with Tf_2O at −60 °C and then slowly warmed to −30 °C prior to quenching with MeOH. ^{13}C NMR and COSY chemical shift analysis at −60 °C suggested the predominance of a single intermediate; however, coupling constant analysis did not confirm β-glycosyl triflate formation (see the Supporting Information).

Synthesis of β-Linked 4′-DP Disaccharides. As an alternative route to this class of compounds, we applied decarboxylative elimination toward β-1,4-linked disaccharides with terminal Glc units. Octa-*O*-acetyl cellobiose was converted into β-benzyl hepta-*O*-acetyl cellobiose using modified Koenigs–Knorr conditions[35] followed by standard protecting group manipulations to generate 4′,6′-benzylidene-protected cellobioside **17** in 60% yield over five steps (Scheme 3). Hydrolytic cleavage of the benzylidene acetal afforded 4′,6′-diol **18**, which was subjected to BAIB/TEMPO oxidation and decarboxylative elimination using DMFDNA and microwave heating (150 °C for 8 min) to generate β-1,4-linked 4′-DP disaccharide **19** in 63% yield over three steps. We found

Scheme 3. Synthesis of β-1,4-Linked 4′-DP Disaccharide 19



microwave conditions to be superior to conventional external heating: a 2 h immersion in an oil bath at 150 °C produced significant amounts of tetra-*O*-benzylglucose (13%), indicating decomposition of the 4-DP and cleavage of the 1,4-glycosidic bond.

We also synthesized an orthogonally protected 4′-DP disaccharide with a reducing-end glucosamine bearing structural relevance to heparan sulfate and other glycosaminoglycans.[26] The glycosyl donor was prepared from β-thiophenyl 4,6-anisylidene glucopyranoside[21] by treatment with Bu_2SnO in toluene with azeotropic distillation followed by regioselective 3-*O*-benzylation of the intermediate stannylidene acetal and 2-*O*-benzoylation to produce donor **20** in high overall yield (Scheme 4). The glycosyl acceptor was prepared from a known glucosamine derivative[36] in several steps: (i) deprotection of the C2 amine followed by its coversion to an azide by diazotransfer,[37] (ii) regioselective reductive cleavage of the anisylidene acetal using Bu_2BOTf and BH_3 at 0 °C to produce a 4-*O*-*p*-methoxybenzyl (PMB)-protected thioglucosamine,[38] (iii) protection of the C3 and C6 hydroxyls as SEM and TBDPS ethers, respectively, and (iv) oxidative cleavage of the 4-*O*-PMB ether to produce acceptor **21**.

Glycosyl coupling of **20** and **21** under BSP/Tf_2O conditions was initially attempted using the original protocol;[25] however, we were unable to isolate the desired 1,4-linked disaccharide, **22**. This is likely due to oxidation of the thioacetal moieties in acceptor **21** or product **22**. Thioglycoside acceptor **21** was completely consumed even when used in excess, consistent with previous reports on the use of thioglycosyl donors and acceptors using BSP/Tf_2O coupling.[39] After a systematic variation of reaction conditions, we found that (i) activation of donor **20** was complete after 30 min at −60 °C, (ii) glycosyl

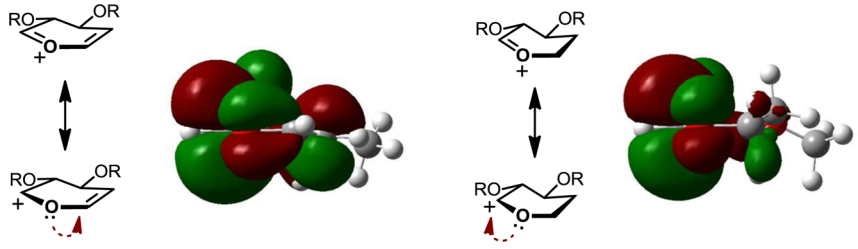


Figure 3. LUMO of "unsaturated" 4-DP oxocarbenium (left) and "saturated" dihydro analogue (right). The enol ether in the former affects the capacity of the O5 oxygen lone pair to stabilize the C1 carbenium.

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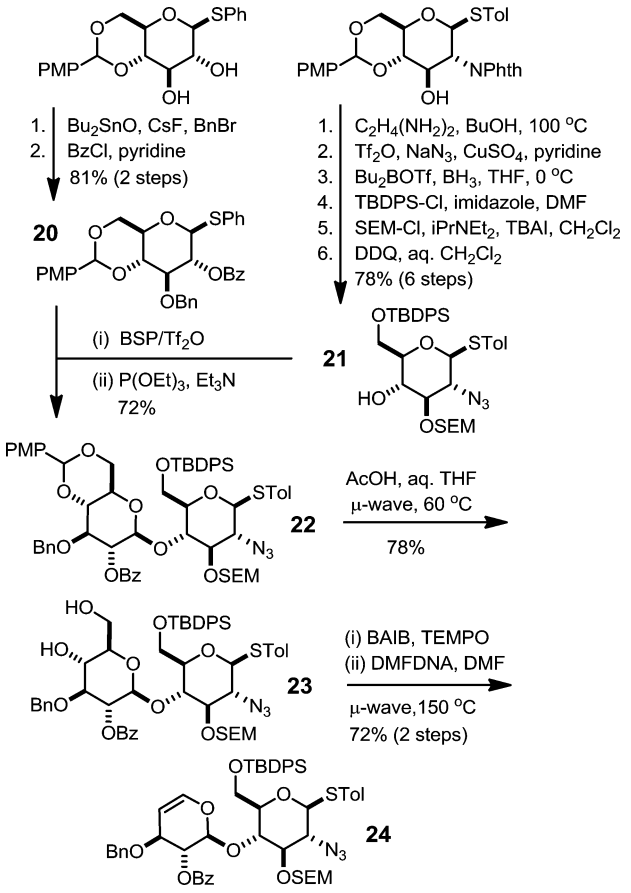
Scheme 4. Synthesis of β-1,4-Linked 4′-DP Disaccharide 24

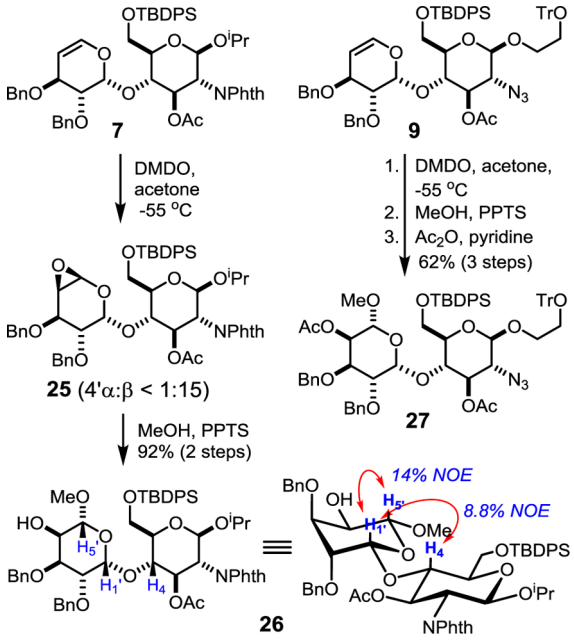


coupling was most effective when the thioglycoside acceptor was precooled before combining with the activated glycosyl donor at −60 °C with gradual warming to −20 °C, and (iii) the reaction was efficiently quenched by treatment with $P(OEt)_3$ and Et_3N precooled to −20 °C to prevent inadvertent oxidation of the thioglycoside product.[40] Optimization of this reaction sequence yielded thiotolyl disaccharide **22** in 72% yield and with exclusive β stereoselectivity.

Orthogonally protected, β-linked 4′-DP disaccharide **24** was obtained in good overall yield from coupling product **22** by hydrolysis of the 4′,6′-anisylidene acetal followed by C6′ oxidation and decarboxylative elimination using our standard procedure (see above). Acetal hydrolysis was initially carried out at 60 °C for 12 h under mildly acidic conditions (8:1:1 AcOH/THF/H_2O) to produce diol **23**, but it was accompanied by partial cleavage of the 3-*O*-SEM group. The latter reaction was suppressed by using microwave heating for 90 min, affording **23** in 78% isolated yield. The C6′ alcohol was regioselectively oxidized using BAIB/TEMPO conditions, and decarboxylative elimination of the corresponding GlcA derivative was achieved using microwave conditions to afford β-linked 4′-DP disaccharide **24** in 72% yield over two steps.

Stereoselective Epoxidation of 4′-DP Disaccharides. Post-glycosylative modifications of the 1,4-linked 4′-DP disaccharides were investigated by their conversion into 4′-epoxypyranosyl (EP) derivatives using dimethyldioxirane (DMDO) followed by treatment with various nucleophiles for the installation of C5′ substituents. DMDO oxidation of α-linked 4′-DP disaccharide **7** was carried out at −55 °C to achieve maximum stereoselectivity followed by concentration under reduced pressure to afford the 4′-EP derivative **25** in essentially quantitative yield with high β selectivity (Scheme 5).

Scheme 5. Post-Glycosylative Modification of α-1,4-Linked 4′-DP Disaccharides 7 and 9



Methanolysis of **25** yielded 1′,5′-bisacetal **26** as a single stereoisomer with a presumed L-*altro* configuration based on earlier studies,[15,16] which was subsequently confirmed by strong NOE interactions between H1′ and H5′. 4′-DP disaccharide **9** was also stereoselectively epoxidized by DMDO to a 4′β-EP derivative, which was subjected to S_N2 ring-opening by methanolysis to produce adduct **27**, again with L-*altro* stereochemistry.

The reactivity of 4′β-EP **25** was also tested with organozinc reagents (e.g., 2-thienylzinc bromide), which we have previously found to be effective for opening epoxyacetals with *syn* selectivity.[17] However, no C5′ adduct was observed; instead, the major side product was monosaccharide **6**, regenerated by cleavage of the 1,4-glycosidic bond. Remarkably, 4′β-EP **25** was unreactive toward other organometallic reagents, such as Et_2Zn, PhLi, and PhMgBr, and was even resistant to hydrolysis. The stability of epoxide **25** contrasts with that of epoxyacetals derived from other 4-DP and glycals, which react quite readily with nucleophiles in the presence of mild Lewis acids.[17,41−45]

With respect to β-linked 4′-DP disaccharides, compound **19** could be epoxidized by DMDO to produce 4α′-EP **28** with high facioselectivity (Scheme 6). Methanolysis generated a terminal pyranoside with D-*gluco* stereochemistry, as confirmed by 4′-*O*-acetylation and coupling constant analysis of **29** ($J_{4',5'}$ = 9.8 Hz). Epoxidation of 4′-DP disaccharide **24** was more complicated because of the competing oxidation of the thiotolyl glycoside: treatment with a stoichiometric amount of DMDO at −55 °C resulted in a 60:40 mixture of sulfoxide and sulfone without any C4′ epoxide formation. Doubling the amount of DMDO resulted in the exclusive production of glycosyl sulfone, and a third equivalent produced tolylsulfonyl 4α′-epoxy-disaccharide **30** with >20:1 selectivity. Epoxide ring-opening of 4α′-EP **30** with diethyldithiocarbamate[46] produced a C5′

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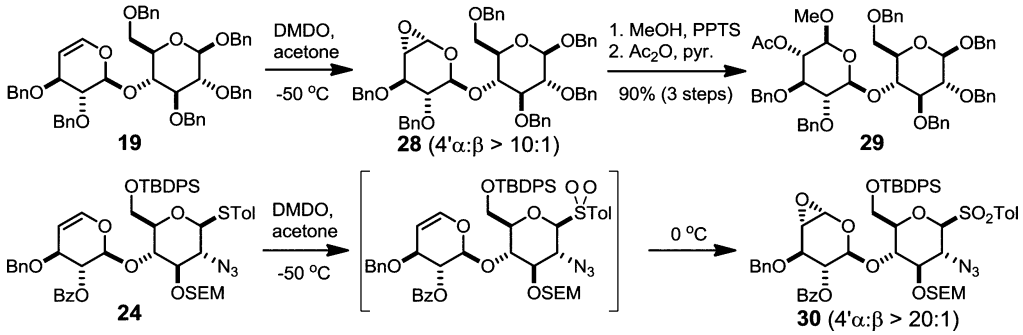
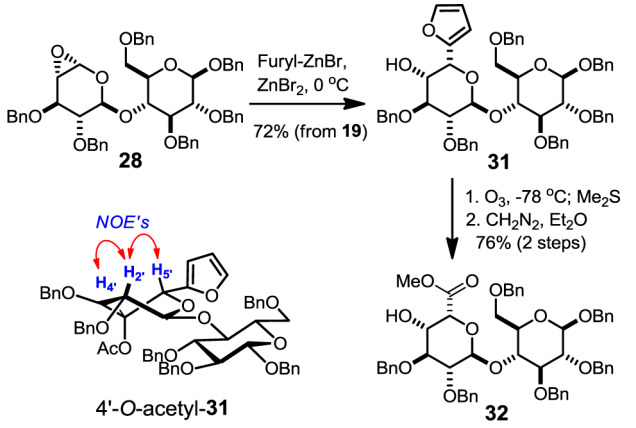
Scheme 6. Post-Glycosylative Modification of β-1,4-Linked 4′-DP Disaccharides



adduct with D-*gluco* configuration ($J_{4',5'}$ = 10 Hz), confirming the epoxide stereochemistry. It should be noted that the facioselectivity of DMDO oxidation for all 4′-DP disaccharides follows an empirical "majority rule", in which the oxygen is delivered to the face opposite to two out of three substituents on the pyranoside, as established previously for 4-DP monosaccharides.[16,18]

4′α-EP **28** was more reactive than 4′β-EP **25** toward organozinc nucleophiles (Scheme 7). Treatment of **28** with 2-furyl-ZnBr in THF in the presence of excess $ZnBr_2$ afforded disaccharide **31** with a 5′-*C*-furyl substituent in 72% yield.[17] The L-*ido* configuration was confirmed by a sizable NOE interaction between H2′ and H5′ of the 4′-*O*-acetate of **31**, supported by small coupling constants within the ring consistent with conformationally flexible idopyranosides.[17] Ozonolysis of 5′-*C*-furyl disaccharide **31** produced a carboxylic acid, with CH_2N_2 treatment producing terminal L-iduronic acid methyl ester **32** in high overall yield.

Scheme 7. Synthesis of L-Idopyranosides by *syn*-Selective C5′ Addition



Similar to **25**, 4′-EP disaccharide **28** did not react with organometallic nucleophiles (furyl-M, where M = Li, Cu, or BF_3K) that might otherwise produce pyranosides with D-*gluco* configuration under S_N2 conditions. Attempts to perform epoxide ring-openings with these nucleophiles in the presence of Lewis acids such as $BF_3{\cdot}Et_2O$ or with heterogeneous catalysts such as Montmorillonite K10 resulted in complex mixtures or hydrolysis of the epoxyacetal upon aqueous workup. Furthermore, tolylsulfonyl 4′α-EP disaccharide **30** was found to be unreactive toward 2-furylzinc bromide even at room temperature and could be recovered intact after aqueous workup. The poor reactivity of these 4′-EP disaccharides, relative to that observed in our earlier studies with 4-EP monosaccharides,[15−18] suggests that the electronic character of the reducing-end glycoside has a significant influence on the reactivity of the terminal 4′-epoxide.

In summary, 4′-DP disaccharides have been synthesized by glycosyl couplings with thiophenyl 4-DP donors and by the decarboxylative elimination of disaccharides with terminal GlcA units. The first approach is useful for the stereoselective synthesis of α-1,4-linked 4′-DP disaccharides, whereas the second provides an efficient route to β-1,4-linked 4′-DP derivatives. Both α- and β-1,4-linked 4′-DP disaccharides are amenable to stereoselective DMDO oxidation, which produces 4′β- and 4′α-epoxypentenosides, respectively. These undergo facile S_N2 ring-opening when treated with standard nucleophiles, but they are more selective in their reactivity with organometallic reagents. The addition of furyl-ZnBr to 4′α-EP disaccharide **28** proceeds in *syn*-selective fashion and can be converted into a terminal L-iduronic acid unit. These results support the development of post-glycosylative approaches toward the divergent synthesis of carbohydrates with structurally variable C5′ units. Lastly, it is worth noting that the 4′-EP disaccharides are stable intermediates and may warrant further investigation as novel inhibitors of cell-surface lectins and protein receptors under physiological conditions.

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; $ZnBr_2$ was freshly sublimed under reduced pressure, Tf_2O was freshly distilled from P_2O_5, and 4 Å mol sieves were flame-dried under reduced pressure. Microwave reactions were performed in a CEM Discover with customized tubes and an internal temperature probe. ^1H and ^{13}C NMR spectra were recorded on spectrometers operating at 300, 400, or 500 MHz and are 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. High-resolution mass spectra were acquired using electrospray ionization mode with a time-of-flight detector. 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.

Preparation of 2-Furyllithium (0.5 M in THF). A solution of freshly distilled furan (0.9 mL, 12.4 mmol) was diluted with degassed THF (2.8 mL), cooled to −78 °C, and then treated with *n*-BuLi (1.18 mL of a 2.1 M solution in hexanes). After stirring for 10 min at −78 °C, the reaction mixture was stirred at 0 °C for 30 min and then at rt

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for an additional 1.5 h to afford the 2-furyllithium solution as a clear, pale yellow solution.

Preparation of 2-Furylzinc Bromide (0.1 M in THF). A solution of 2-furyllithium (1.8 mL, 0.9 mmol) was cooled to −78 °C and then treated with $ZnBr_2$ (510 mg, 2.3 mmol) dissolved in THF (7.2 mL). After stirring for 10 min at −78 °C, the reaction mixture was stirred at 0 °C for 30 min prior to use.

General Procedure for Glycosylations Using BSP and Tf_2O. In a typical reaction, thiophenyl 4-DP donor (0.15 mmol) and BSP (0.20 mmol) were azeotroped separately with toluene (3 × 3 mL) and dried under reduced pressure for 1 h. The dried thiophenyl 4-DP donor was combined with BSP, TTBP (0.24 mmol), and 4 Å mol sieves (120 mg), dissolved in CH_2Cl_2 (1 mL), and stirred at rt for 1 h. The solution was cooled to −60 °C, stirred for 30 min, and then treated dropwise with freshly distilled Tf_2O (0.24 mmol) over 5 min. The resulting bright-orange solution was cooled to −78 °C, stirred for 45 min until the glycosyl donor was completely consumed, and then treated with a solution of precooled acceptor in CH_2Cl_2 (−78 °C, 0.23 mmol in 0.5 mL). The reaction mixtures was stirred at −78 °C for 12 h and then slowly warmed to 0 °C over a period of 4 h. The pale orange solution was quenched with Et_3N (0.75 mmol) and MeOH (1 mL) and then stirred for another 15 min at 0 °C before warming to rt for 30 min. The reaction mixture was cooled again to 0 °C, quenched with saturated $NaHCO_3$ (5 mL), and then stirred vigorously for 30 min at rt. The suspension was filtered through Celite and then extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure prior to silica gel chromatography.

General Procedure for Epoxidations Using DMDO. DMDO solutions were prepared according to our previous report.[18] In a typical reaction, 4′-DP disaccharide (0.15 mmol) in CH_2Cl_2 (0.3 mL) was cooled to −55 °C and treated with a precooled solution of DMDO (2.9 mL of a 0.08 M solution in acetone) or acetone-free DMDO (1.2 mL of a 0.2 M solution in CH_2Cl_2). The reaction mixture was stirred at −55 °C (unless otherwise stated) for 12−36 h to achieve maximum stereoselectivity and then concentrated under reduced pressure at −55 °C for 20 min to remove excess DMDO. The reaction mixture was warmed to 0 °C and then further concentrated under reduced pressure at that temperature for 30 min prior to warming to rt. The 4′-epoxypyranosyl disaccharide was used immediately without further purification.

DFT Calculations. Structures were subjected to energy minimization using Gaussian03 (B3LYP/6-31+G(d,p)), starting from idealized half-chair conformations. Tables of atomic coordinates and absolute energies are provided in the Supporting Information.

Thiophenyl 2,3-Di-*O*-benzyl-*β*-D-glucopyranoside (1). Thiophenyl-4,6-*O*-*p*-methoxybenzylidene-*β*-D-glucopyranoside (2.0 g, 5.128 mmol) was dissolved in DMF (20 mL) and cooled to 0 °C. NaH (4.1 g, 102.56 mmol) was added followed by the addition of benzyl bromide (6.1 mL, 51.28 mmol). The reaction mixture was allowed to warm to rt over 4 h and was then quenched with saturated aqueous NH_4Cl, extracted with CH_2Cl_2, and concentrated. The residue was purified by silica gel chromatography using a 5−11% EtOAc in hexanes gradient to afford 2.42 g of dibenzylated product.

Thiophenyl-4,6-*O*-*p*-methoxybenzylidene-2,3-di-*O*-benzyl-*β*-D-glucopyranoside (2.42 g, 4.246 mmol) was dissolved in 8:1:1 AcOH/H_2O/THF (50 mL) and heated at 45 °C for 12 h. The reaction was concentrated under reduced pressure, and the residue was purified by silica gel chromatography using a 5−20% EtOAc in hexanes gradient to afford thiophenyl 2,3-di-*O*-benzyl-*β*-D-glucopyranoside (1.746 g, 91%). The ^{1}H NMR spectral data for **1** matched well with that in the literature.[47]

Thiophenyl 2,3-Di-*O*-benzyl-4-deoxy-*β*-pent-4-enopyranoside (2). Diol **1** (1.00 g, 2.212 mmol) was dissolved in 2:1 CH_2Cl_2/H_2O at rt. TEMPO (69 mg, 0.442 mmol) and BAIB (2.137 g, 6.626 mmol) were added sequentially, and the reaction was stirred for 2.5 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$, extracted with $CHCl_3$ (4 × 500 mL), and concentrated. The residue was purified via silica gel chromatography using a 10−50% EtOAc in hexanes gradient with 1% AcOH to afford 876 mg of the corresponding carboxylic acid.

The carboxylic acid (200 mg, 0.429 mmol) was dissolved in DMF (1 mL) in a sealed microwave tube. DMFDNA (597 μL, 2.146 mmol) was added, and the reaction was heated under microwave conditions at 225 °C for 2.5 min. The reaction was concentrated under vacuum, and the residue was purified via silica gel chromatography to afford 4-DP **2** as an oil (107 mg, 54% over 2 steps). ^{1}H NMR (400 MHz, C_6D_6): δ 7.65 (d, J = 7.7 Hz, 2H), 7.42 (d, J = 7.5 Hz, 2H), 7.32−6.97 (m, 11H), 6.34 (d, J = 6.4 Hz, 1H), 5.77 (d, J = 3.6 Hz, 1H), 5.00 (t, J = 5.3 Hz, 1H), 4.52 (d, J = 12.0 Hz, 1H), 4.44 (dd, J = 2.7, 11.5 Hz, 2H), 4.34 (d, J = 11.8 Hz, 1H), 4.11 (d, J = 3.4 Hz, 1H), 3.96 (t, J = 3.5 Hz, 1H). ^{13}C NMR (100 MHz, C_6D_6): δ 142.8, 138.7, 138.1, 136.6, 131.1, 128.8, 128.22, 128.18, 126.9, 100.5, 83.8, 76.1, 71.8, 70.3, 69.8. IR: 3063, 3031, 1649, 1584, 1453, 1241, 1203, 1068, 956, 738, 696 cm^{-1}. $[\alpha]_D^{25}$ = −118.2° (c 1.0, CH_2Cl_2). HRESI-MS: m/z calcd for $C_{25}H_{24}O_3SNa$ [M + Na]$^+$, 427.1338; found, 427.1363.

Thiophenyl 3-*O*-Benzyl-4,6-*O*-benzylidene-*α*-D-glucopyranoside (3). Thiophenyl 3-*O*-benzyl-4,6-*O*-benzylidene-*α*-D-mannopyranoside (22.5 mg, 0.05 mmol) was oxidized under Swern conditions. Oxalyl chloride (35 μL, 0.4 mmol) was dissolved in CH_2Cl_2 (2 mL), cooled to −78 °C, treated dropwise with DMSO (50 μL, 0.7 mmol), and stirred for 10 min. The C2 alcohol was dissolved in CH_2Cl_2 (1 mL) and added to the reaction mixture, which was then stirred at −78 °C for 30 min. Triethylamine (111 μL, 0.8 mmol) was added, and the reaction was warmed to 0 °C and stirred for 10 min. The reaction was diluted with CH_2Cl_2 (50 mL), quenched with saturated aqueous NH_4Cl, washed with brine, dried over Na_2SO_4, concentrated, and purified by silica gel chromatography using 11% EtOAc in hexanes to afford 18 mg of the intermediate C2 ketone.

The ketone was dissolved in THF (1 mL) and cooled to 0 °C. BH_3 (0.2 mL of a 1 M THF solution) was added dropwise, and the reaction mixture was stirred for 4 h, quenched with triethylamine (0.5 mL) and methanol (5 mL) at 0 °C, concentrated, and purified by column chromatography to afford partially protected glucopyranoside **3** as an oil (15 mg, 76% over 2 steps). ^{1}H NMR (500 MHz, C_6D_6): δ 7.62 (m, 2H), 7.39 (m, 2H), 7.32 (m, 2H), 7.16−7.02 (m, 6H), 7.00−6.92 (m, 3H), 5.52 (d, J = 5.4 Hz, 1H), 5.30 (s, 1H), 4.95 (d, J = 11.7 Hz, 1H), 4.64 (d, J = 11.8 Hz, 1H), 4.50 (dt, J = 5.0, 9.9 Hz, 1H), 4.08 (dd, J = 4.9, 10.2 Hz, 1H), 3.91 (dt, J = 5.1, 10.0 Hz, 1H), 3.83 (t, J = 9.2 Hz, 1H), 3.49 (t, J = 9.3 Hz, 1H), 3.45 (t, J = 10.2 Hz, 1H) 2.25 (, J = 5.0 Hz, 1H). ^{13}C NMR (125 MHz, C_6D_6): δ 139.0, 138.1, 134.4, 132.2, 129.0, 128.9, 128.40, 128.36, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.3, 126.4, 101.5, 90.4, 82.2, 79.6, 74.7, 72.4 68.6, 64.3. IR: 3380, 3062, 2903, 1450, 1371, 1078, 1027, 1000, 741, 696 cm^{-1}. $[\alpha]_D^{25}$ = +263.8° (c 1.0, CH_2Cl_2). HRESI-MS: m/z calcd for $C_{26}H_{27}O_5S$ [M + H]$^+$, 451.1574; found, 451.1562.

Thiophenyl 2,3-Di-*O*-benzyl-*α*-D-glucopyranoside (4). C2 alcohol **3** (575 mg, 1.278 mmol) was dissolved in DMF (10 mL) and cooled to 0 °C. NaH (204 mg, 5.112 mmol) was added followed by the addition of benzyl bromide (760 μL, 6.389 mmol). The reaction was warmed to rt with stirring over 12 h, quenched with saturated aqueous NH_4Cl, extracted with CH_2Cl_2, and concentrated. The residue was purified by silica gel chromatography using a 10−33% EtOAc in hexanes gradient to afford 607 mg of C2 benzyl ether. This intermediate (587 mg, 1.087 mmol) was dissolved in 8:1:1 AcOH/H_2O/THF (10 mL), heated at 50 °C for 12 h, concentrated under reduced pressure, and purified by silica gel chromatography using a 20−50% EtOAc in hexanes gradient to afford 4,6-diol **4** as an oil (447 mg, 81% over 2 steps). ^{1}H NMR (500 MHz, C_6D_6): δ 7.54 (dd, J = 1.3, 8.3 Hz, 2H), 7.38 (d, J = 7.3 Hz, 2H), 7.31 (d, J = 7.3 Hz, 2H), 7.19−7.01 (m, 9H), 5.66 (d, J = 5.4 Hz, 1H), 4.99 (d, J = 11.7 Hz, 1H), 4.65 (d, J = 11.7 Hz, 1H), 4.59 (d, J = 11.5 Hz, 1H), 4.36 (d, J = 2.7 Hz, 1H), 4.34 (d, J = 4.6 Hz, 1H), 3.88 (t, J = 9.2 Hz, 1H), 3.79 (t, J = 4.8 Hz, 2H), 3.76 (dd, J = 5.4, 9.5 Hz, 1H), 3.62 (dt, J = 2.4, 9.5 Hz, 1H), 2.14 (d, J = 3.7 Hz, 1H), 1.48 (t, J = 6.4 Hz, 1H). ^{13}C NMR (125 MHz, C_6D_6): δ 139.3, 138.2, 134.6, 132.4, 129.8, 129.1, 129.0, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 127.6, 127.3, 86.9, 81.9, 80.0, 75.1, 72.4, 71.9, 70.8, 62.5. IR: 3404, 3062, 2872, 1453, 1115, 1057,

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739, 697 cm^{-1}. $[\alpha]_D^{25}$ = +123.0° (*c* 1.0, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{26}H_{32}NO_5S$ $[M + NH_4]^+$, 470.1996; found, 470.2016.

Thiophenyl 2,3-Di-*O*-benzyl-4-deoxy-α-pent-4-enopyranoside (5). Diol **4** (200 mg, 0.442 mmol) was dissolved in 2:1 CH_2Cl_2/H_2O at rt. TEMPO (13.8 mg, 0.088 mmol) and BAIB (427 mg, 1.326 mmol) were added sequentially, and the reaction was stirred for 3 h, quenched with saturated aqueous $Na_2S_2O_3$, extracted with EtOAc (3 × 250 mL), and concentrated. The residue was purified by silica gel chromatography using a 33−66% EtOAc in hexanes gradient with 1% AcOH to afford 182 mg of the corresponding carboxylic acid.

The carboxylic acid (162 mg, 0.348 mmol) was dissolved in DMF (4 mL) in a sealed microwave tube. DMFDNA (484 μL, 1.738 mmol) was added, and the reaction mixture was heated under microwave conditions at 225 °C for 2.5 min. The reaction was concentrated under vacuum, and the residue was purified via silica gel chromatography to afford 4-DP **5** as an oil (107 mg, 69% over 2 steps). ^1H NMR (400 MHz, C_6D_6): δ 7.59 (d, *J* = 6.8 Hz, 2H), 7.36 (d, *J* = 7.2 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 2H), 7.24−7.09 (m, 7H), 7.07−6.95 (m, 2H), 6.30 (d, *J* = 6.1 Hz, 1H), 5.70 (d, *J* = 2.3 Hz, 1H), 4.94−4.85 (m, 1H), 4.51 (d, *J* = 2.2 Hz, 1H), 4.51 (s, 2H), 4.42 (dd, *J* = 8.1, 12.0 Hz, 2H), 4.11 (d, *J* = 2.6 Hz, 2H). ^{13}C NMR (100 MHz, C_6D_6): δ 144.0, 138.7, 138.1, 135.1, 131.4, 128.9, 128.2, 127.6, 127.0, 100.6, 85.0, 77.2, 72.4, 70.6, 70.3. IR: 3063, 3029, 2869, 1644, 1454, 1231, 1092, 1055, 1026, 737, 697 cm^{-1}. $[\alpha]_D^{25}$ = +167.3° (*c* 1.0, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{25}H_{25}O_3S$ $[M + H]^+$, 405.1519; found, 405.1501.

Isopropyl 3-*O*-Acetyl-4-*O*-(2′,3′-di-*O*-benzyl-4′-deoxy-α-pent-4′-enopyranosyl)-6-*O*-*tert*-butyldiphenylsilyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (7). Thiophenyl 4-DP donor **2** (50 mg, 0.12 mmol) was coupled with acceptor **6**[46] (145 mg, 0.23 mmol) under BSP/Tf_2O conditions (see above). BSP (34 mg, 0.16 mmol), TTBP (49 mg, 0.20 mmol), and 4 Å mol sieves (100 mg) were dispersed in CH_2Cl_2 (0.8 mL), cooled to −78 °C, treated with Tf_2O (34 μL, 0.20 mmol), and stirred for 45 min prior to treatment with a solution of **6** in CH_2Cl_2 (0.4 mL, cooled to −78 °C). The reaction mixture was stirred at −78 °C for 12 h, warmed slowly to 0 °C over a period of 4 h, and quenched with workup according to the general procedure. The product was purified by silica gel chromatography using a 5−10% EtOAc in hexanes gradient with 1% Et_3N to yield 4′-DP disaccharide **7** as a yellow oil (84 mg, 75%). ^1H NMR (500 MHz, C_6D_6): δ 7.93 (dd, *J* = 1.6, 8.0 Hz, 2H), 7.85 (dd, *J* = 2.0, 7.4 Hz, 2H), 7.56 (m, 1H), 7.48 (m, 1H), 7.45−7.41 (m, 2H), 7.38−7.33 (m, 2H), 7.31−7.06 (m, 12H), 6.85−6.78 (m, 2H), 6.25 (dd, *J* = 9.0, 10.7 Hz, 1H), 6.04 (dd, *J* = 1.2, 6.2 Hz, 1H), 5.68 (d, *J* = 8.4 Hz, 1H), 5.39 (br s, 1H), 4.75 (dd, *J* = 8.5, 10.7 Hz, 1H), 4.69 (dd, *J* = 4.0, 6.2 Hz, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.56−4.48 (m, 3H), 4.30 (t, *J* = 9.4 Hz, 1H), 4.09 (d, *J* = 11.0 Hz, 1H), 4.03 (dd, *J* = 1.6, 10.8 Hz, 1H), 3.98 (t, *J* = 4.6 Hz, 1H), 3.90 (sep, *J* = 6.2 Hz, 1H), 3.59 (m, 1H), 3.36 (ddd, *J* = 1.7, 3.4, 9.9 Hz, 1H), 1.68 (s, 3H), 1.18 (s, 9H), 1.15 (d, *J* = 6.2 Hz, 3H), 0.93 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (125 MHz, C_6D_6): δ 169.5, 167.8, 167.4, 142.1, 139.4, 138.4, 135.9, 135.5, 134.0, 133.4, 133.1, 133.1, 131.9, 131.6, 129.5, 128.7, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.0, 122.8, 122.8, 100.5, 96.4, 75.7, 75.2, 71.9, 70.8, 70.1, 62.3, 55.9, 26.6, 23.1, 21.2, 20.2, 19.1. IR: 3069, 2931, 2858, 1750, 1738, 1387, 1225, 1113, 1038, 702 cm^{-1}. $[\alpha]_D^{25}$ = +68.5° (*c* 1.0, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{54}H_{63}N_2O_{11}Si$ $[M + NH_4]^+$, 943.4196; found, 943.4172.

2-Ethoxytrityl 3-*O*-Acetyl-2-azido-4-*O*-(2′,3′-di-*O*-benzyl-4′-deoxy-α-pent-4′-enopyranosyl)-6-*O*-*tert*-butyldiphenylsilyl-2-deoxy-β-D-glucopyranoside (9). Thiophenyl 4-DP donor **2** (20 mg, 0.05 mmol) was coupled with acceptor **8** (76 mg, 0.099 mmol) using BSP/Tf_2O conditions (see the general procedure). After work up, the product was purified by silica gel chromatography using a 5−10% EtOAc in hexanes gradient with 1% Et_3N to yield 4′-DP disaccharide **9** (33 mg, 57%). ^1H NMR (400 MHz, C_6D_6): δ 7.99 (ddd, *J* = 1.5, 3.1, 6.5 Hz, 4H), 7.70 (d, *J* = 8.5 Hz, 6H), 7.45 (d, *J* = 6.8 Hz, 2H), 7.37−7.17 (m, 23H), 6.17 (d, *J* = 6.1 Hz, 1H), 5.40 (dd, *J* = 9.2, 10.5 Hz, 1H), 5.24 (s, 1H), 4.97−4.76 (m, 2H), 4.69 (d, *J* = 12.0 Hz, 1H), 4.41 (d, *J* = 11.6 Hz, 1H), 4.33 (d, *J* = 11.5 Hz, 1H), 4.18 (dd, *J* = 3.4, 7.3 Hz, 2H), 4.14−4.04 (m, 3H), 4.00 (t, *J* = 9.5 Hz, 1H), 3.93−3.80 (m, 1H), 3.61−3.50 (m, 1H), 3.44 (t, *J* = 4.9 Hz, 2H), 3.39 (dd, *J* = 8.0, 10.5 Hz, 1H), 3.16 (ddd, *J* = 2.0, 4.4, 9.7 Hz, 1H), 1.76 (s, 3H), 1.26 (s, 9H). ^{13}C NMR (100 MHz, C_6D_6): δ 169.2, 144.3, 142.8, 138.7, 138.5, 135.9, 135.7, 134.0, 133.5, 129.6, 129.6, 128.9, 128.2, 128.1, 127.8, 127.2, 126.9, 108.6, 101.3, 100.6, 99.4, 86.8, 76.0, 75.3, 75.1, 74.1, 73.4, 72.4, 70.2, 68.6, 64.4, 62.9, 62.5, 29.8, 26.6, 20.3, 19.3. IR: 3062, 2919, 2851, 2111, 1753, 1643, 1221, 1112, 1051, 700 cm^{-1}. $[\alpha]_D^{25}$ = +29.5° (*c* 1.0, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{64}H_{67}N_3O_{10}SiNa$ $[M + Na]^+$, 1088.4488; found, 1088.4505.

Methyl (Methyl 2-*O*-acetyl-4-*O*-(2′,3′-di-*O*-benzyl-4′-deoxy-α-pent-4′-enopyranosyl)-α-D-glucopyranosiduronate (11). Thiophenyl 4-DP donor **2** (33 mg, 0.08 mmol) was coupled with acceptor **10**[26] (25 mg, 0.11 mmol) using BSP/Tf_2O conditions (see the general procedure). After work up, the product was treated with MeOH (1 mL) to produce the desired GlcA methyl ester, which was purified by silica gel chromatography using a 5−10% EtOAc in hexanes gradient with 1% Et_3N to yield 4′-DP disaccharide **11** (28 mg, 62% over 2 steps). ^1H NMR (400 MHz, C_6D_6): δ 7.35−7.01 (m, 10H), 5.98 (d, *J* = 6.3 Hz, 1H), 5.21−5.10 (m, 2H), 5.03 (d, *J* = 3.6 Hz, 1H), 4.83 (dd, *J* = 2.2, 6.5 Hz, 1H), 4.66−4.53 (m, 2H), 4.53−4.37 (m, 4H), 4.10 (t, *J* = 9.4 Hz, 1H), 3.96 (s, 1H), 3.81 (dd, *J* = 2.8, 8.1 Hz, 1H), 3.50 (s, 3H), 2.98 (s, 3H), 2.13 (s, 1H), 1.69 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6): δ 169.8, 168.4, 140.2, 138.8, 137.6, 128.4, 128.2, 128.1, 108.6, 101.8, 100.5, 97.6, 82.6, 77.4, 73.9, 73.3, 72.6, 71.0, 70.9, 70.3, 54.8, 51.5, 20.0. IR: 3472, 2937, 1748, 1650, 1497, 1454, 1372, 1234, 1197, 1136, 1100, 1049, 928, 741, 699 cm^{-1}. $[\alpha]_D^{25}$ = +114.2° (*c* 0.5, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{29}H_{34}O_{11}Na$ $[M + Na]^+$, 581.1993; found, 581.2022.

Thiotolyl 3-*O*-Acetyl-2-azido-4-*O*-(2′,3′-di-*O*-benzyl-4′-deoxy-α-pent-4′-enopyranosyl)-6-*O*-*tert*-butyldiphenylsilyl-2-deoxy-β-D-glucopyranoside (13). Thiophenyl 4-DP donor **2** (28 mg, 0.069 mmol) was coupled with acceptor **12**[46] (94 mg, 0.139 mmol) using BSP/Tf_2O conditions (see the general procedure). After work up, the product was purified by silica gel chromatography using 5% EtOAc in hexanes with 1% Et_3N to yield 4′-DP disaccharide **13** (36 mg, 60%). ^1H NMR (500 MHz, C_6D_6): δ 8.01 (t, *J* = 8.3 Hz, 4H), 7.67 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 7.4 Hz, 2H), 7.33−7.29 (m, 4H), 7.25 (t, *J* = 7.2 Hz, 2H), 7.22−7.12 (m, 6H), 7.11−7.05 (m, 2H), 6.86 (d, *J* = 8.0 Hz, 2H) 6.06 (d, *J* = 5.9 Hz, 1H), 5.31 (t, *J* = 9.6 Hz, 1H), 5.09 (d, *J* = 1.7 Hz, 1H), 4.78−4.71 (m, 2H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.33 (d, *J* = 11.6 Hz, 1H), 4.25 (d, *J* = 11.7 Hz, 1H), 4.16 (d, *J* = 10.1 Hz, 1H), 4.06 (d, *J* = 2.9 Hz, 2H), 3.97 (d, *J* = 5.4 Hz, 1H), 3.82 (t, *J* = 9.5 Hz, 1H), 3.76 (dt, *J* = 1.1, 4.9 Hz, 1H), 3.16 (t, *J* = 10.0 Hz, 1H), 2.98 (dt, *J* = 9.7, 3.5 Hz, 1H), 1.99 (s, 3H), 1.64 (s, 3H), 1.24 (s, 9H). ^{13}C NMR (100 MHz, C_6D_6): δ 169.1, 142.8, 138.7, 138.4, 138.2, 135.9, 135.8, 133.9, 133.7, 133.5, 129.73, 129.65, 128.2, 108.6, 100.4, 99.3, 85.8, 79.4, 76.0, 75.8, 74.5, 73.4, 72.4, 70.1, 63.0, 62.5, 29.8, 26.7, 20.6, 20.2, 19.2. IR: 3068, 2928, 2857, 2110, 1755, 1643, 1216, 1112, 1051, 809, 701 cm^{-1}. $[\alpha]_D^{25}$ = +31.8° (*c* 1.0, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{50}H_{59}N_4O_8SSi$ $[M + NH_4]^+$, 903.3817; found, 903.3809.

Thiophenyl 2-*O*-Benzoyl-3-*O*-benzyl-4-deoxy-β-pent-4-enopyranoside (14). 4,6-Anisylidene-protected glucopyranoside **20**[46] (85 mg, 0.14 mmol) was dissolved in 8:1:1 AcOH/THF/H_2O (5 mL) and heated at 70 °C in an oil bath for 3 h. After cooling to rt, the solution was concentrated, azeotroped with toluene to remove residual AcOH, redissolved in EtOAc, washed with brine, dried over Na_2SO_4, and concentrated to a white solid. The residue was purified by silica gel chromatography using a 20−100% EtOAc in hexanes gradient to afford the corresponding 4,6-diol as a white crystalline solid (66 mg, 96%). The diol was subjected to TEMPO/BAIB oxidation and workup conditions described in the synthesis of compound **2** and was purified by silica gel chromatography using 5% EtOAc in hexanes with 1% Et_3N to yield thiophenyl 4-DP **14** as white solid; mp 92−95 °C (28 mg, 47% over 2 steps). ^1H NMR (400 MHz, C_6D_6): δ 8.09 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 7.5 Hz, 2H), 7.25−6.90 (m, 11H), 6.32 (d, *J* = 6.4 Hz, 1H), 5.90 (d, *J* = 1.6 Hz, 1H), 5.76 (d, *J* = 1.2 Hz, 1H), 4.98 (t, *J* = 12 Hz, 1H), 4.67 (d, *J* = 12.4 Hz, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 3.87 (m, 1H). ^{13}C NMR (100 MHz, C_6D_6): δ 165.0, 142.9, 138.59, 138.58, 136.3, 133.1, 131.5, 129.9, 129.0, 128.4, 128.1, 127.82, 127.75, 127.6, 127.3, 100.9, 83.4, 70.2, 68.3. IR: 3072, 2886, 1722, 1649, 1265,

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1070, 711, 677 cm^{-1}. $[\alpha]_D^{25} = -201°$ (*c* 0.46, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{25}H_{22}O_4SNa$ $[M + Na]^+$, 441.1136; found, 441.1131.

Methyl 2,3,6-Tri-*O*-benzyl-4-*O*-(2′-*O*-benzoyl-3′-*O*-benzyl-4′-deoxy-β-pent-4′-enopyranosyl)-α-D-glucopyranoside (16). Thiophenyl 4-DP donor **14** (55 mg, 0.13 mmol) was coupled with methyl 2,3,6-tri-*O*-benzyl-α-glucoside **15**[46] (80 mg, 0.17 mmol) using BSP/Tf_2O conditions (see the general procedure) and quenched with $P(OEt)_3$ (45 μL, 0.26 mmol) and Et_3N (100 μL, 0.75 mmol) precooled to −60 °C. After work up, the product was purified by silica gel chromatography using a 5−50% EtOAc in hexanes gradient with 1% Et_3N to yield 4′-DP disaccharide **16** as a colorless gel (53 mg, 52%). ^1H NMR (500 MHz, C_6D_6): δ 8.06 (d, *J* = 7.4 Hz, 2H), 7.49 (d, *J* = 7.5 Hz, 2H), 7.36 (d, *J* = 7.3 Hz, 2H), 7.30 (d, *J* = 7.4 Hz, 2H), 7.23−7.17 (m, 4H), 7.13−6.95 (m, 13H), 6.21 (dd, *J* = 1.2, 6.4 Hz, 1H), 5.84 (t, *J* = 3.2 Hz, 1H), 5.69 (d, *J* = 3.8 Hz, 1H), 5.20 (d, *J* = 11.5 Hz, 1H), 5.02 (d, *J* = 11.5 Hz, 1H), 4.82 (m, 1H), 4.59 (d, *J* = 3.5 Hz, 1H), 4.54 (d, *J* = 5.4 Hz, 2H), 4.51 (d, *J* = 6.3 Hz, 1H), 4.48 (br s, 1H), 4.44 (br s, 1H), 4.40 (m, 1H), 4.34 (t, *J* = 9.5 Hz, 1H), 4.22 (t, *J* = 9.3 Hz, 1H), 4.00 (d, *J* = 3.7 Hz, 1H), 3.92 (dd, *J* = 3.4, 11.0 Hz, 1H), 3.82 (dt, *J* = 9.6, 2.6 Hz, 1H), 3.58 (dd, *J* = 1.8, 10.9 Hz, 1H), 3.51 (dd, *J* = 3.6, 9.5 Hz, 1H), 3.04 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6): δ 165.1, 142.8, 140.2, 127.9, 127.7, 127.4, 100.2, 98.1, 96.96, 96.95, 80.6, 79.9, 77.5, 75.0, 73.2, 72.8, 70.4, 70.2, 69.7, 68.7, 54.5. IR: 3030, 2924, 1724, 1651, 1601, 1453, 1265, 1107, 1028, 912, 799, 698 cm^{-1}. $[\alpha]_D^{25}$ = +65.1° (*c* 3.5, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{47}H_{48}O_{10}Na$ $[M + Na]^+$, 795.3140; found, 795.3168.

Benzyl 2,3,6-Tri-*O*-benzyl-4-*O*-(2′,3′-di-*O*-benzyl-4′,6′-*O*-benzylidene-β-D-glucopyranosyl)-β-D-glucopyranoside (17). A solution of cellobiose octaacetate (10.2 g, 15 mmol) in CH_2Cl_2 (150 mL) was cooled to 0 °C and then treated dropwise with a solution of 30% HBr in AcOH (30 mL) over a period of 60 min. The progress of the reaction was monitored by TLC until no starting material remained. The resulting clear yellow mixture was then slowly poured into a beaker with ice and neutralized with 1 M NaOH followed by saturated $NaHCO_3$ (30 mL) with stirring at rt for 12 h. The crude product was extracted with CH_2Cl_2 (3 × 30 mL), washed with brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure to afford the α-glycosyl bromide as a white solid. This intermediate was dried by azeotropic distillation with toluene, mixed with 4 Å mol sieves (2 g), and redissolved in CH_2Cl_2 (150 mL). After stirring for 30 min at rt, the reaction mixture was treated with benzyl alcohol (7.7 mL, 75 mmol), Ag_2CO_3 (8.3 g, 30 mmol), and I_2 (191 mg, 2.10 mmol) and stirred at rt for 12 h protected from light. The reaction mixture was passed through Celite, quenched with saturated $NaHCO_3$ (150 mL), washed with brine (150 mL), dried over Na_2SO_4, concentrated under reduced pressure, and then recrystallized from EtOAc/hexanes to afford benzyl β-cellobioside heptaacetate as a white solid, mp 175−177 °C (8.14 mg, 75%).

A solution of benzyl hepta-*O*-acetyl-β-cellobioside (2.4 g, 3.30 mmol) in 1:1 CH_2Cl_2/MeOH (20 mL) was treated at 0 °C with NaOMe (3.3 mL of a 1.0 M solution in MeOH) and stirred for 15 min. The ice bath was removed, and the mixture was stirred at rt for 1 h, diluted with MeOH (5 mL), neutralized with activated H^+ resin, filtered, washed with MeOH, and concentrated to a white solid. The crude benzyl β-cellobioside (1.42 g, 3.30 mmol) was redissolved in DMF (47 mL) and then treated with benzaldehyde dimethyl acetal (1.48 mL, 9.86 mmol) and *p*-TsOH (312 mg, 1.64 mmol). The reaction mixture was stirred at rt for 1 h, stirred at 100 °C for 4 h, and quenched at rt with Et_3N (1 mL) with stirring for 1 h. The solution containing the 4′,6′-benzylidene-protected cellobioside was then treated with benzyl bromide (5.5 mL, 46.02 mmol) and TBAI (604 mg, 1.64 mmol), cooled to 0 °C under argon, and then treated with a 60% dispersion of NaH in mineral oil (2.76 g, 69.03 mmol), added in portions. The resulting suspension was stirred at rt for 12 h, diluted with Et_2O (30 mL), quenched at 0 °C with saturated NH_4Cl (30 mL), and extracted with Et_2O. The combined organic phase was washed with H_2O (3 × 30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was recrystallized with EtOAc/hexanes to afford cellobioside intermediate **17** as a white solid, mp 153−156 °C (2.56 g, 80% yield over 3 steps). ^1H NMR (500 MHz, C_6D_6): δ 7.57 (d, *J* = 7.2 Hz, 2H), 7.52 (d, *J* = 7.3 Hz, 2H), 7.44−7.32 (m, 9H), 7.32−7.04 (m, 22H), 5.24 (s, 1H), 5.16 (d, *J* = 11.1 Hz, 1H), 5.01 (dd, *J* = 9.4, 11.6 Hz, 2H), 4.92 (dd, *J* = 3.1, 11.7 Hz, 2H), 4.87 (d, *J* = 3.5 Hz, 2H), 4.84 (d, *J* = 7.6 Hz, 1H), 4.80 (d, *J* = 5.6 Hz, 1H), 4.72 (d, *J* = 7.8 Hz, 1H), 4.60 (d, *J* = 12.2 Hz, 1H), 4.50 (dd, *J* = 10.5, 12.1 Hz, 2H), 4.34 (d, *J* = 12.1 Hz, 1H), 4.27 (t, *J* = 9.5 Hz, 1H), 4.04 (dd, *J* = 4.9, 10.3 Hz, 1H), 3.99 (dd, *J* = 3.8, 10.9 Hz, 1H), 3.75−3.60 (m, 4H), 3.50 (dt, *J* = 2.9, 9.3 Hz, 2H), 3.37 (t, *J* = 10.2 Hz, 1H), 3.29 (dd, *J* = 2.3, 9.8 Hz, 1H), 3.16 (dt, *J* = 4.9, 9.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.0, 138.5, 138.3, 138.1, 137.5, 137.4, 128.9, 128.6, 128.3, 128.23, 128.18, 128.1, 128.0, 127.9, 127.82, 127.75, 127.7, 127.6, 127.5, 127.44, 127.37, 126.0, 102.7, 102.4, 101.0, 82.8, 82.5, 81.7, 81.6, 81.1, 77.3, 77.0, 76.8, 76.7, 75.4, 75.0, 74.9, 73.2, 70.9, 68.7, 67.9, 65.7. IR: 2890, 1497, 1358, 1096, 1020, 746, 695 cm^{-1}. $[\alpha]_D^{25}$ = −8.9° (*c* 2.1, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{61}H_{62}O_{11}Na$ $[M + Na]^+$, 993.4190; found, 993.4200.

Benzyl 2,3,6-Tri-*O*-benzyl-4-*O*-(2′,3′-di-*O*-benzyl-β-D-glucopyranosyl)-β-D-glucopyranoside (18). 4′,6′-Benzylidene-protected disaccharide **17** (3.29 g, 3.43 mmol) was dissolved in 8:1:1 AcOH/H_2O/THF (36 mL) and heated at 75 °C for 7 h. After cooling to 0 °C, the clear solution was quenched by dropwise addition of Et_3N (3.6 mL), concentrated under reduced pressure, and dried by azeotropic distillation with toluene (3 × 5 mL). The crude syrup consisting of 4′,6′-diol **15** and trace amounts of 6′-*O*-acetyl disaccharide byproduct was redissolved in CH_3OH (36 mL), treated with K_2CO_3 (1 g), and stirred at rt for 12 h. The reaction mixture was then concentrated to dryness, redissolved in EtOAc (20 mL), and quenched with saturated NH_4Cl (20 mL) to produce a yellowish precipitate. This was washed with hexanes (20 mL) and filtered to afford 4′,6′-diol **18** as white solid, mp 110−112 °C (2.76 g, 91%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.53−7.10 (m, 30H), 4.96 (d, 2H, *J* = 11.9 Hz), 4.89 (d, 2H, *J* = 8.7 Hz), 4.83 (d, 2H, *J* = 10.9 Hz), 4.77 (d, 1H, *J* = 2.9 Hz), 4.73 (d, 1H, *J* = 2.8 Hz), 4.70−4.61 (m, 3H), 4.52−4.38 (m, 3H), 4.00−3.88 (m, 1H), 3.82 (dd, 1H, *J* = 3.8, 10.9 Hz), 3.71 (d, 1H, *J* = 10.0 Hz), 3.62 (dd, 1H, *J* = 2.7, 11.8 Hz), 3.52 (t, 2H, *J* = 7.1 Hz), 3.47−3.28 (m, 5H), 3.07 (ddd, 1H, *J* = 3.3, 5.4, 9.0 Hz), 2.16 (s, 1H), 1.70 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.9, 138.4, 138.2, 138.0, 137.4, 128.5, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.59, 127.55, 127.5, 127.4, 127.3, 102.4, 84.2, 82.6, 82.3, 81.6, 77.3, 77.2, 77.0, 76.7, 76.6, 75.2, 75.0, 74.9, 74.7, 73.2, 70.8, 70.6, 67.9, 62.2. IR: 2894, 1514, 1447, 1366, 1054, 738, 691 cm^{-1}. $[\alpha]_D^{25}$ = −5.9° (*c* 2.4, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{54}H_{58}O_{11}Na$ $[M + Na]^+$, 905.3877; found, 905.3886.

Benzyl 2,3,6-Tri-*O*-benzyl-4-*O*-(2′,3′-di-*O*-benzyl-4′-deoxy-β-pent-4′-enopyranosyl)-β-D-glucopyranoside (19). A solution of 4′,6′-diol **18** (1.20 g, 1.36 mmol) in 2:1 CH_2Cl_2/H_2O (6.8 mL) was treated with TEMPO (42 mg, 0.27 mmol) and BAIB (2.2 g, 6.94 mmol). The reaction mixture was stirred vigorously for 3 h at rt and then quenched with a saturated $Na_2S_2O_3$ solution upon completion, as determined by TLC. The reaction mixture was extracted with EtOAc (3 × 20 mL), washed with brine (20 mL), dried over Na_2SO_4, and then concentrated under reduced pressure to afford the crude carboxylic acid as a foam, which was used without further purification.

Synthesis of 4′-DP Disaccharide 19 under Microwave Heating Conditions. The crude carboxylic acid was dissolved in degassed anhydrous DMF (12 mL) in a microwave tube under argon, treated with DMFDNA (1.9 mL, 6.80 mmol), sealed in a microwave reactor, and heated at 150 °C for 8 min. The dark-brown solution was cooled to rt, concentrated under reduced pressure, and then dried by azeotropic distillation with toluene (3 × 10 mL). The residue was purified by silica gel chromatography using a 5−30% EtOAc in hexanes gradient with 1% Et_3N to afford the desired 4′-DP disaccharide **19** (783 mg, 69% over 2 steps) as a colorless gel. ^1H NMR (500 MHz, C_6D_6): δ 7.52 (d, *J* = 7.5 Hz, 2H), 7.36−7.26 (m, 10H), 7.22 (t, *J* = 7.5 Hz, 2H), 7.19−7.06 (m, 16H), 6.05 (dd, *J* = 1.4, 6.1 Hz, 1H), 5.22 (d, *J* = 7.4 Hz, 1H), 5.18 (d, *J* = 11.1 Hz, 1H), 4.97 (dd, *J* = 11.0, 11.4 Hz, 2H), 4.88 (d, *J* = 12.2 Hz, 1H), 4.79−4.72 (m, 2H), 4.71−4.65 (m, 2H), 4.56 (d, *J* = 12.1 Hz, 1H), 4.50−4.42 (m, 4H), 4.38 (t, *J* = 12.4 Hz, 1H), 4.21 (m, 1H), 4.13 (ddd, *J* = 1.4, 2.7, 6.3 Hz, 1H), 3.90 (dd, *J* = 4.0, 11.0 Hz, 1H), 3.81 (dd, *J* = 6.2, 7.4 Hz, 1H), 3.70 (dd, *J* = 1.8, 11.1 Hz, 1H), 3.64 (m, 2H), 3.28 (ddd, *J* = 1.8,

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4.1, 10.0 Hz, 1H). ^{13}C NMR (75 MHz, C_6D_6): δ 142.5, 140.1, 139.5, 139.4, 139.1, 138.9, 138.3, 128.6, 128.4, 128.1, 127.9, 127.7, 127.6, 127.4, 103.0, 101.6, 101.5, 83.1, 82.4, 79.3, 78.3, 76.0, 75.6, 75.5, 75.0, 74.3, 73.5, 70.9, 68.6. IR: 3245, 2877, 2367, 1658, 1510, 1455, 1362, 1101, 1050, 763, 695 cm^{-1}. $[\alpha]_D^{25}$ = +10.2° (*c* 1.9, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{53}H_{54}O_9Na$ $[M + Na]^+$, 857.3666; found, 857.3674.

Synthesis of 4′-DP Disaccharide 19 Using External Heating. The crude carboxylic acid was dissolved in degassed anhydrous DMF (12 mL) in a thick-walled reaction vessel under argon, treated with DMFDNA (1.9 mL, 6.80 mmol), and heated at 150 °C for 1 h. The dark-brown solution was cooled to rt, concentrated under reduced pressure, and dried by azeotropic distillation with toluene (3 × 10 mL). The residue was purified by silica gel chromatography using a 5−30% EtOAc in hexanes gradient with 1% Et_3N to afford the desired disaccharide 4′-DP disaccharide **19** (544 mg, 48% over 2 steps) as well as benzyl 2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (95 mg, 13%) as a byproduct.

Thiophenyl 2-*O*-Benzoyl-3-*O*-benzyl-4,6-*O*-*p*-methoxybenzylidene-β-D-glucopyranoside (20). 4,6-Anisylidene-protected β-thiophenyl glucoside (5.46 g, 14 mmol) was dissolved in toluene (140 mL), treated with Bu_2SnO (5.23 g, 21 mmol), and heated under reflux for 4 h with water continuously removed by a Dean−Stark trap. The reaction mixture was cooled to rt after completion (with observation of stannylene acetal intermediate by TLC), concentrated to dryness under reduced pressure, and then redissolved in DMF (90 mL). The reaction mixture was treated with benzyl bromide (5 mL, 42 mmol) and CsF (6.38 g, 42 mmol), stirred at rt for 12 h, quenched at 0 °C with saturated $NaHCO_3$ (50 mL), and extracted with EtOAc (3 × 50 mL). The combined organic phase was washed with brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was recrystallized with EtOAc/hexanes to afford the desired 3-*O*-benzyl ether as a white solid, mp 139−141 °C (5.23 g). The mother liquor was concentrated to dryness and purified by silica gel chromatography using a 5−30% EtOAc in hexanes gradient with 1% Et_3N to afford additional product (5.71 g total, 85% overall).

Thiophenyl 3-*O*-benzyl-4,6-*O*-*p*-anisylidene glucoside (1.2 g, 2.50 mmol) was dissolved in pyridine (18 mL), cooled to 10 °C, treated with benzoyl chloride (0.88 mL, 7.50 mmol), and stirred at rt for 12 h. The reaction mixture was then diluted and extracted with CH_2Cl_2 (3 × 20 mL), washed with brine (20 mL), dried over Na_2SO_4, and then concentrated under reduced pressure. The crude residue was recrystallized from EtOAc in hexanes at −20 °C for 12 h to afford the desired 2-*O*-benzoate **20** as white solid, mp 205−208 °C (1.4 g, 96%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (d, 2H, *J* = 7.3 Hz), 7.61 (t, 1H, *J* = 7.4 Hz), 7.53−7.37 (m, 6H), 7.36−7.21 (m, 4H), 7.19−7.01 (m, 4H), 6.92 (d, 2H, *J* = 8.7 Hz), 5.57 (s, 1H), 5.29 (dd, 1H, *J* = 8.5, 10.0 Hz), 4.85 (d, 1H, *J* = 10.1 Hz), 4.80 (d, 1H, *J* = 11.9 Hz), 4.66 (d, 1H, *J* = 11.9 Hz), 4.40 (dd, 1H, *J* = 5.0, 10.5 Hz), 3.96−3.71 (m, 5H), 3.56 (m, 1H), 1.55 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.1, 160.2, 137.8, 133.3, 133.0, 132.3, 130.0, 129.9, 129.7, 129.0, 128.5, 128.3, 128.2, 127.7, 127.4, 113.7, 101.3, 87.1, 81.5, 79.4, 77.4, 77.2, 76.9, 74.3, 72.0, 70.7, 68.6, 55.4. IR: 1729, 1611, 1514, 1274, 1177, 1109, 1067, 1012, 991, 822, 712 cm^{-1}. $[\alpha]_D^{25}$ = +34.0° (*c* 1.1, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{34}H_{32}O_7SNa$ $[M + Na]^+$, 607.1766; found, 607.1761.

Thiotolyl 2-Azido-6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-3-*O*-(2-(trimethylsilyl)-ethoxymethyl)-β-D-glucopyranoside (21). Thiotolyl 4,6-*O*-*p*-anisylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside[26] (7.5 g, 14.1 mmol) was dissolved in *n*-BuOH (140 mL), treated with ethylenediamine (19 mL, 282 mmol), and stirred at 100 °C in a sealed vessel for 12 h. The reaction mixture was cooled to rt and transferred to a round-bottomed flask followed by azeotropic removal of all volatiles with toluene (3 × 50 mL) to afford the crude glucosamine as a yellow solid. This was redissolved in pyridine (70 mL), treated with $CuSO_4 \cdot 5H_2O$ (1.75 g, 7 mmol) and Et_3N (4 mL, 28 mmol), and cooled to 0 °C.

The reaction mixture was treated dropwise with freshly prepared TfN_3 in CH_2Cl_2[36,48] (1.7 M solution in CH_2Cl_2, 21 mL, 36 mmol) and then stirred from 0 °C to rt. After 24 h, the mixture was concentrated to dryness and azeotroped with toluene (3 × 30 mL). ***(Caution: large amounts of concentrated TfN_3 may be potentially explosive!)*** The crude product was redissolved in CH_2Cl_2 (100 mL), washed with saturated $NaHCO_3$ (3 × 50 mL), dried with Na_2SO_4, concentrated, and purified by silica gel chromatography using a 5−50% EtOAc in hexanes gradient with 1% Et_3N to afford the desired C2 azide as a white solid, mp 105−108 °C (5.93 g, 98% over 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, 2H, *J* = 8.1 Hz), 7.38 (d, 2H, *J* = 8.7 Hz), 7.23−7.11 (m, 2H), 6.89 (d, 2H, *J* = 8.7 Hz), 5.48 (s, 1H), 4.48 (d, 1H, *J* = 10.1 Hz), 4.35 (dd, 1H, *J* = 4.1, 10.6 Hz), 3.80 (s, 3H), 3.79−3.70 (m, 1H), 3.52−3.37 (m, 2H), 3.31 (t, 1H, *J* = 10.1 Hz), 2.72 (d, 1H, *J* = 2.7 Hz), 2.37 (s, 3H), 1.57 (s, 1H).

The 4,6-anisylidene-protected pyranoside (3.01 g, 7.0 mmol) was dried by azeotropic distillation with toluene, treated with TTBP (1.90 g, 7.7 mmol), and cooled to 0 °C followed by dropwise addition of BH_3 (70 mL of a 1 M solution in THF). The clear solution was cooled to −10 °C for 10 min, treated with Bu_2BOTf (7.7 mL of a 1 M solution in CH_2Cl_2), and stirred at 0 °C for 12 h. The reaction mixture was cooled to −10 °C and quenched by dropwise addition of Et_3N (10 mL) and MeOH (50 mL) until the effervescence ceased. The cooling bath was removed, and the reaction mixture was warmed to rt for 30 min and then concentrated to dryness. The residue was purified by silica gel chromatography using a 5−50% EtOAc in hexanes gradient with 1% Et_3N to afford the desired 4-*O*-PMB ether (3,6-diol) as a colorless syrup (2.95 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (d, 2H, *J* = 8.1 Hz), 7.25 (m, 2H), 7.15 (m, 2H), 6.88 (d, 2H, *J* = 8.5 Hz), 4.65 (s, 2H), 4.40 (dd, 1H, *J* = 0.7, 10.1 Hz), 3.90 (m, 1H), 3.80 (s, 3H), 3.75 (m, 1H), 3.58 (t, 1H, *J* = 8.9 Hz), 3.39 (t, 1H, *J* = 9.1 Hz), 3.31 (ddd, 1H, *J* = 2.4, 4.2, 9.6 Hz), 3.21 (m, 1H), 2.58 (br s, 1H), 2.35 (s, 3H), 1.97 (br s, 1H).

A solution of the 3,6-diol (2.89 g, 6.70 mmol) in DMF (20 mL) was treated with imidazole (1.37 g, 20.1 mmol) and cooled to 0 °C followed by the dropwise addition of TBDPS-Cl (3.44 mL, 13.4 mmol). The reaction was stirred at rt for 12 h, cooled to 0 °C, quenched with saturated NH_4Cl, and extracted with Et_2O. The organic extracts were washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography using a 5−40% EtOAc in hexanes gradient with 1% Et_3N to afford the desired 6-*O*-TBDPS ether as a colorless syrup (4.28 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (m, 2H), 7.73 (m, 2H), 7.53 (d, 2H, *J* = 8.1 Hz), 7.40−7.33 (m, 6H), 7.04 (d, 4H, *J* = 8.4 Hz), 6.78 (d, 2H, *J* = 8.7 Hz), 4.97 (d, 1H, *J* = 6.4 Hz), 4.87 (d, 1H, *J* = 6.4 Hz), 4.67 (d, 1H, *J* = 10.3 Hz), 4.58 (d, 1H, *J* = 10.3 Hz), 4.38 (d, 1H, *J* = 10.1 Hz), 3.99 (dd, 1H, *J* = 1.6, 11.4), 3.94−3.85 (m, 1H), 3.82 (m, 1H), 3.79 (s, 3H), 3.73−3.59 (m, 2H), 3.53 (t, 1H, *J* = 9.2 Hz), 3.34−3.18 (m, 2H), 2.32 (s, 3H), 1.10 (s, 9H), 0.96 (t, 2H, *J* = 8.7 Hz), 0.00 (s, 9H).

The intermediate above (4.28 g, 6.23 mmol) was dried by azeotropic distillation with toluene, redissolved in CH_2Cl_2 (62 mL), and treated with TBAI (1.14 g, 3.1 mmol) and SEM-Cl (8.9 mL, 50 mmol). The reaction mixture was cooled to 0 °C, treated with $(iPr)_2NEt$ (9.8 mL, 56 mmol), and stirred for 12 h at 40 °C. The dark-yellow mixture was quenched with saturated $NaHCO_3$ (50 mL), stirred at rt for 1 h, and then extracted with EtOAc. The organic extracts were washed with brine (50 mL), dried over Na_2SO_4, concentrated, and purified by silica gel chromatography using a 5−30% EtOAc in hexanes gradient with 1% Et_3N to afford the 3-*O*-SEM ether as a colorless syrup (4.9 g, 99%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (m, 2H), 7.74 (m, 2H), 7.53 (d, 2H, *J* = 8.1 Hz), 7.40−7.33 (m, 6H), 7.04 (d, 4H, *J* = 8.4 Hz), 6.78 (d, 2H, *J* = 8.7 Hz), 4.97 (d, 1H, *J* = 6.4 Hz), 4.87 (d, 1H, *J* = 6.4 Hz), 4.67 (d, 1H, *J* = 10.3 Hz), 4.58 (d, 1H, *J* = 10.3 Hz), 4.38 (d, 1H, *J* = 10.1 Hz), 3.99 (dd, 1H, *J* = 1.6, 11.4 Hz), 3.90 (m, 1H), 3.82 (m, 1H), 3.79 (s, 3H), 3.73−3.59 (m, 2H), 3.53 (t, 1H, *J* = 9.2 Hz), 3.34−3.18 (m, 2H), 2.32 (s, 3H), 1.10 (s, 9H), 0.96 (t, 2H, *J* = 8.7 Hz), 0.01 (s, 9H).

The orthogonally protected glucosamine (2.75 g, 3.44 mmol) was redissolved in CH_2Cl_2 (90 mL) and H_2O (9 mL) and then treated with DDQ (1.68 g, 6.88 mmol) at rt. The reaction mixture was stirred vigorously for 2.5 h, diluted with H_2O (20 mL), and quenched with saturated $NaHCO_3$ (30 mL) and saturated $Na_2S_2O_3$ (60 mL). The

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reaction mixture was stirred at rt for another 30 min and then extracted with CH_2Cl_2. The organic layers were washed with brine (20 mL), dried over Na_2SO_4, and then concentrated and purified by silica gel chromatography using a 1−10% EtOAc in toluene gradient with 1% Et_3N to yield glucosamine acceptor **21** as a colorless syrup (2.21 g, 94%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, 4H, J = 6.4 Hz), 7.52 (d, 2H, J = 8.1 Hz), 7.45−7.33 (m, 6H), 7.05 (d, 2H, J = 8.0 Hz), 4.92 (d, 1H, J = 7.2 Hz), 4.75 (d, 1H, J = 7.2 Hz), 4.47 (s, 1H), 4.37 (d, 1H, J = 9.6 Hz), 4.02 (dd, 1H, J = 2.1, 11.1 Hz), 3.93 (dd, 1H, J = 4.5, 11.1 Hz), 3.84 (m, 1H), 3.63−3.51 (m, 2H), 3.35 (ddd, 1H, J = 2.4, 4.5, 7.2 Hz), 3.33−3.26 (m, 2H), 2.31 (s, 3H), 1.07 (s, 9H), 0.97 (m, 2H), 0.01 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.5, 135.8, 134.1, 133.52, 133.48, 129.9, 129.7, 127.81, 127.78, 127.5, 96.7, 88.7, 85.9, 80.5, 77.4, 77.2, 76.9, 68.7, 66.7, 63.4, 26.9, 21.3, 19.5, 18.2. IR: 3393, 2964, 2885, 2111, 1427, 1277, 1257, 1112, 1078, 1010, 868, 826, 755, 701 cm^{-1}. $[\alpha]_D^{25}$ = −55.1° (c 2.2, CH_2Cl_2). HRESI-MS: m/z calcd for $C_{35}H_{49}N_3O_5SSi_2Na$ $[M + Na]^+$, 702.2829; found, 702.2838.

Thiotolyl 2-Azido-4-*O*-(3′-*O*-benzyl-2′-*O*-benzoyl-4′,6′-*O*-*p*-methoxybenzylidene-*β*-D-glucopyranosyl)-6-*O*-*tert*-butyldiphenylsilyl-2-deoxy-3-*O*-(2-(trimethylsilyl)ethoxymethyl)-*β*-D-glucopyranoside (22). Glycosyl donor **20** (264 mg, 0.45 mmol) was coupled with acceptor **21** (428 mg, 0.63 mmol) under BSP/Tf_2O conditions (see the general procedure). Donor **20** and BSP (104 mg, 0.50 mmol) were azeotroped separately with toluene, dried under reduced pressure for 1 h, combined with TTBP (223 mg, 0.90 mmol) and 4 Å mol sieves (360 mg) in CH_2Cl_2 (3.0 mL), and stirred at rt for 1 h. The solution was cooled to −60 °C under Ar, stirred for 30 min, and then treated dropwise with freshly distilled Tf_2O (92 μL, 0.54 mmol) over 5 min. The bright-orange solution was stirred at −60 °C for 30 min until glycosyl donor **20** was completely consumed and then treated with a precooled (−60 °C) solution of glycosyl acceptor **21** in 1.5 mL of CH_2Cl_2. The reaction mixture was stirred at −60 °C for 1 h and then slowly warmed to −20 °C over a period of 4 h. The pale orange solution was quenched with precooled $P(OEt)_3$ (93 μL, 0.54 mmol) and Et_3N (310 μL, 2.25 mmol), stirred for 15 min, warmed to rt over 30 min, quenched at 0 °C with saturated $NaHCO_3$ (5 mL), and stirred vigorously for 30 min at rt. The suspension was filtered through Celite and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and then concentrated under reduced pressure. The crude residue was purified by silica gel chromatography using a 5−25% EtOAc gradient in hexanes with 1% Et_3N to afford the desired 1,4-β-linked disaccharide **22** as a white foamy solid (374 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (dd, 4H, J = 8.0, 12.4 Hz), 7.61 (m, 2H), 7.50−7.34 (m, 5H), 7.31 (t, 3H, J = 7.4 Hz), 7.27−7.15 (m, 6H), 7.13−7.03 (m, 4H), 6.96 (dd, 4H, J = 8.4, 13.3 Hz), 5.56 (s, 1H), 5.20 (t, 1H, J = 8.6 Hz), 4.99 (d, 1H, J = 6.9 Hz), 4.93 (d, 1H, J = 8.1 Hz), 4.87 (d, 1H, J = 6.9 Hz), 4.82 (d, 1H, J = 12.3 Hz), 4.68 (d, 1H, J = 12.3 Hz), 4.39 (dd, 1H, J = 5.0, 10.5 Hz), 4.24 (d, 1H, J = 10.1 Hz), 4.10 (t, 1H, J = 9.4 Hz), 3.83 (s, 3H), 3.81−3.59 (m, 5H), 3.54 (t, 1H, J = 9.3 Hz), 3.36 (dt, 1H, J = 9.7, 5.0 Hz), 3.20 (t, 1H, J = 9.8 Hz), 2.96 (d, 1H, J = 9.7 Hz), 2.28 (s, 3H), 1.09 (s, 9H), 1.05−0.93 (m, 4H), 0.03 (s, 9H). ^{13}C NMR (125 MHz, C_6D_6): δ 164.7, 160.6, 138.8, 138.5, 136.3, 135.9, 134.4, 134.0, 133.2, 132.6, 130.51, 130.48, 130.3, 130.2, 130.0, 128.7, 128.54, 128.48, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 113.9, 101.6, 100.7, 97.1, 86.3, 82.2, 79.7, 79.0, 78.5, 75.3, 74.0, 73.9, 68.8, 66.8, 66.2, 65.1, 61.3, 54.8, 27.0, 21.0, 19.6, 18.6, −1.2. IR: 2953, 2865, 2118, 1742, 1523, 1430, 1379, 1257, 1105, 987, 839, 712 cm^{-1}. $[\alpha]_D^{25}$ = +14.2° (c 1.3, CH_2Cl_2). HRESI-MS: m/z calcd for $C_{63}H_{76}N_3O_{12}SSi_2$ $[M + H]^+$, 1154.4689; found, 1154.4650.

Thiotolyl 2-Azido-4-*O*-(2′-*O*-benzoyl-3′-*O*-benzyl-*β*-D-glucopyranosyl)-6-*O*-*tert*-butyldiphenylsilyl-2-deoxy-3-*O*-(2-(trimethylsilyl)ethoxymethyl)-*β*-D-glucopyranoside (23). A solution of disaccharide **22** (1.26 g, 1.09 mmol) in 8:1:1 AcOH/THF/H_2O (11 mL) was heated at 60 °C in a microwave reactor for 90 min, cooled to rt, and extracted twice with Et_2O. The organic layers were washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by silica gel chromatography using a 5−40% EtOAc gradient in hexanes with 0.5% Et_3N to afford desired 4′,6′ diol **23** as a white foamy solid (880 mg, 78%) as well as a partially deprotected byproduct (cleavage of 3-*O*-SEM ether; 160 mg, 16%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (m, 4H), 7.65 (m, 2H), 7.58−7.32 (m, 9H), 7.32−7.06 (m, 7H), 6.99 (d, 2H, J = 7.8 Hz), 5.23−5.09 (m, 2H), 4.90 (d, 1H, J = 8.0 Hz), 4.81 (d, 1H, J = 4.6 Hz), 4.67 (q, 2H, J = 11.6 Hz), 4.19 (d, 1H, J = 10.2 Hz), 4.12 (t, 1H, J = 9.4 Hz), 3.95 (dd, 1H, J = 2.9, 12.3 Hz), 3.93−3.76 (m, 4H), 3.75−3.62 (m, 3H), 3.55 (t, 1H, J = 9.3 Hz), 3.41 (t, 1H, J = 9.1 Hz), 3.31 (dt, 1H, J = 9.8, 3.2 Hz), 3.25 (t, 1H, J = 10.0 Hz), 2.98 (d, 1H, J = 10.0 Hz), 2.67 (br s, 1H), 2.29 (s, 3H), 1.11 (s, 9H), 1.01 (t, 2H, J = 10.0 Hz), 0.01 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 138.6, 137.8, 135.8, 135.5, 134.4, 133.6, 133.1, 132.1, 130.0, 129.8, 129.7, 129.5, 128.9, 128.4, 127.9, 127.8, 127.7, 126.6, 99.9, 96.3, 85.4, 82.5, 78.9, 78.7, 77.2, 77.1, 76.9, 76.6, 75.2, 75.1, 74.5, 73.6, 69.6, 67.5, 63.6, 60.9, 60.7, 26.9, 21.1, 19.3, 18.0, −0.1, −1.6. HRESI-MS: m/z calcd for $C_{55}H_{69}N_3O_{11}SSi_2Na$ $[M + Na]^+$, 1058.4089; found, 1058.4068.

Thiotolyl 2-Azido-4-*O*-(2′-*O*-benzoyl-3′-*O*-benzyl-4′-deoxy-*β*-pent-4′-enopyranosyl)-6-*O*-*tert*-butyldiphenylsilyl-2-deoxy-3-*O*-(2-(trimethylsilyl)ethoxymethyl)-*β*-D-glucopyranoside (24). A solution of disaccharide **23** (850 mg, 0.82 mmol) in 2:1 CH_2Cl_2/H_2O (17 mL) was treated with BAIB (793 mg, 2.46 mmol) and TEMPO (51 mg, 0.33 mmol). The bright-orange suspension was stirred vigorously for 50 min, cooled to 0 °C, quenched with $Na_2S_2O_3$ (20 mL), adjusted to pH 4−5, and then extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated to dryness.

A portion of the crude GlcA disaccharide (250 mg, 0.24 mmol) was azeotroped with toluene (2 mL), redissolved in degassed DMF (5 mL), treated with DMFDNA (334 μL, 1.20 mmol), and heated at 150 °C in a microwave reactor for 90 min. The reaction mixture was cooled to rt and extracted with Et_2O, and the organic layers were washed with brine (5 mL), dried over Na_2SO_4, concentrated, and purified by silica gel chromatography using a 5−20% EtOAc gradient in hexanes with 0.5% Et_3N to afford the desired 4′-DP disaccharide **24** as a colorless oil (583 mg, 72%). ^{1}H NMR (500 MHz, C_6D_6): δ 8.02 (t, J = 8.8 Hz, 4H), 7.85−7.77 (m, 2H), 7.59 (d, J = 8.1 Hz, 2H), 7.32 (t, J = 7.6 Hz, 4H), 7.25−7.03 (m, 8H), 6.99 (t, J = 7.7 Hz, 2H), 6.78 (d, J = 7.8 Hz, 2H), 6.31 (d, J = 6.5 Hz, 1H), 5.84 (t, J = 4.5 Hz, 1H), 5.79 (d, J = 5.0 Hz, 1H), 5.37 (d, J = 7.1 Hz, 1H), 5.01 (d, J = 7.1 Hz, 1H), 4.86 (dd, J = 3.7, 6.4 Hz, 1H), 4.53 (q, J = 12.2 Hz, 2H), 4.33 (t, J = 9.5 Hz, 1H), 4.19−4.09 (m, 2H), 4.06 (d, J = 10.2 Hz, 1H), 3.79 (br s, 1H), 3.79−3.71 (m, 2H), 3.58 (t, J = 9.4 Hz, 1H), 3.30 (t, J = 9.9 Hz, 1H), 2.50 (dd, J = 1.9, 9.6 Hz, 1H), 1.94 (s, 3H), 1.19 (m, 2H), 1.16 (s, 9H), 0.08 (s, 9H). ^{13}C NMR (125 MHz, C_6D_6): δ 165.1, 143.0, 138.9, 138.4, 136.4, 136.0, 134.1, 133.7, 133.4, 132.7, 130.3, 130.2, 130.15, 130.0, 128.7, 128.65, 128.6, 128.3, 128.2, 128.1, 127.9, 127.9, 127.8, 101.3, 97.6, 97.2, 86.9, 79.5, 79.4, 75.3, 71.2, 70.5, 70.4, 66.1, 65.3, 62.0, 27.1, 21.0, 19.5, 18.5, −1.2. IR: 2949, 2109, 1742, 1274, 1009, 1050, 856, 695 cm^{-1}. $[\alpha]_D^{25}$ = −6.0° (c 0.5, CH_2Cl_2). HRESI-MS: m/z calcd for $C_{54}H_{65}N_3O_9SSi_2Na$ $[M + Na]^+$, 1010.3878; found, 1010.3894.

Isopropyl 3-*O*-Acetyl-4-*O*-(2′,3′-di-*O*-benzyl-4′*β*-epoxyglucopyranosyl)-6-*O*-*tert*-butyldiphenylsilyl-2-deoxy-2-phthalimido-*β*-D-glucopyranoside (25). 4′-DP disaccharide **7** (25 mg, 0.027 mmol) was dissolved in CH_2Cl_2 (0.2 mL), cooled to −55 °C, treated with precooled DMDO (0.5 mL of a 0.08 M solution in acetone), and stirred for 36 h at −55 °C followed by a low-temperature workup as previously described to yield the corresponding 4′β-epoxypyranosyl disaccharide **25** as a colorless syrup (26 mg, quantitative yield, <1:15 α/β). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (m, 8H), 7.36−7.11 (m, 16H), 5.81 (t, J = 8.7 Hz, 1H), 5.46 (d, J = 8.1 Hz, 1H), 4.84 (d, J = 2.1 Hz, 1H), 4.64 (m, 4H), 4.16 (t, J = 9.0 Hz, 1H), 4.06 (d, J = 3.0 Hz, 1H), 3.96−3.78 (m, 5H), 3.70 (m, 1H), 3.60 (dd, J = 2.4, 8.7 Hz, 1H), 2.62 (t, J = 2.4 Hz, 1H), 1.55 (s, 3H), 1.19 (d, J = 6.0 Hz, 3H), 1.01 (s, 9H), 0.93 (d, J = 5.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 168.0, 167.7, 138.1, 137.6, 135.7, 134.2, 134.0, 133.2, 131.6, 131.3, 129.8, 129.5, 128.4, 128.3, 127.6, 123.4, 99.0, 96.5, 75.9, 75.2, 74.4, 74.0, 73.8, 73.2, 72.7, 72.3, 63.2, 55.5, 53.3, 29.6, 26.6, 23.3, 21.9, 20.4, 19.1. ESI-MS: m/z for $C_{54}H_{59}NO_{12}SiNa$ $[M + Na]^+$: 964. This compound was not submitted for HRESI-MS analysis because of its limited stability.

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Isopropyl 3-*O*-Acetyl-4-*O*-(2′,3′-di-*O*-benzyl-5′*R*-methoxy-α-pyranosyl)-6-*O*-*tert*-butyldiphenylsilyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (26). A solution of 4′β-epoxypyranosyl disaccharide **25** (15 mg, 0.016 mmol) in MeOH (2 mL) was treated with pyridinium *p*-toluenesulfonate (PPTS, 0.5 mg, 0.003 mmol) at rt. The reaction mixture was stirred at rt for 3 h, quenched with saturated aqueous $NaHCO_3$, and then extracted with CH_2Cl_2 (3 × 25 mL) followed by a standard workup. The residue was purified by silica gel chromatography using a 10% EtOAc in hexanes gradient with 1% Et_3N to yield 1′,5′-bisacetal disaccharide **26** with L-*altro* configuration as a yellow oil (14 mg, 92%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (m, 2H), 7.73 (ddd, *J* = 2.3, 4.6, 8.0 Hz, 4H), 7.68 (dd, *J* = 1.4, 7.9 Hz, 2H), 7.46−7.20 (m, 16H), 5.86 (dd, *J* = 9.2, 10.9 Hz, 1H), 5.45 (d, *J* = 8.4 Hz, 1H), 4.80 (d, *J* = 12.2 Hz, 1H), 4.66 (br s, 1H), 4.54 (d, *J* = 12.2 Hz, 1H), 4.45 (d, *J* = 11.6 Hz, 1H), 4.34 (d, *J* = 11.6 Hz, 1H), 4.27 (dd, *J* = 8.4, 10.9 Hz, 1H), 4.19−4.06 (m, 2H), 3.99 (dd, *J* = 1.6, 11.4 Hz, 1H), 3.93 (sep, *J* = 6.2 Hz, 1H), 3.87−3.80 (m, 2H), 3.68 (d, *J* = 3.0 Hz, 1H), 3.58 (s, 3H), 3.56 (s, 1H), 3.10 (dd, *J* = 3.0, 9.8 Hz, 1H), 2.30 (s, 1H), 1.96 (s, 3H), 1.21 (d, *J* = 6.2 Hz, 3H), 1.10 (s, 9H), 0.95 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 168.0, 167.7, 138.1, 137.4, 135.6, 135.6, 134.1, 133.8, 133.5, 131.5, 129.5, 129.4, 128.4, 128.2, 127.9, 127.8, 127.54, 127.49, 123.4, 100.0, 98.4, 96.1, 76.0, 75.7, 74.7, 73.9, 73.54, 73.48, 71.7, 69.1, 63.7, 56.0, 55.3, 29.6, 26.7, 23.2, 21.7, 20.4, 19.3. $[\alpha]_D^{25}$ = +20.4° (*c* 0.25, CH_2Cl_2). IR: 3229, 3069, 2930, 2857, 1750, 1719, 1649, 1607, 1497, 1455, 1387, 1334, 1228, 1113, 1059, 1037, 918, 875, 824, 743, 702, 663 cm^{-1}. HRESI-MS: *m*/*z* calcd for $C_{55}H_{63}NO_{13}SiNa$ [M + Na]$^+$, 996.3961; found, 996.3929.

2-Ethoxytrityl 3-*O*-Acetyl-2-azido-4-*O*-(4′-*O*-acetyl-2′,3′-di-*O*-benzyl-5′*R*-methoxy-α-pyranosyl)-6-*O*-*tert*-butyldiphenylsilyl-2-deoxy-β-D-glucopyranoside (27). 4′-DP disaccharide **9** (12 mg, 0.011 mmol) was dissolved in CH_2Cl_2 (0.5 mL), cooled to −30 °C, and then treated with precooled DMDO (0.8 mL of a 0.04 M solution in acetone) for 6 h followed by a low-temperature workup as previously described to yield the corresponding 4′β-epoxypyranosyl disaccharide. This was redissolved in MeOH (1 mL) and treated with PPTS (2 mg) at rt with stirring overnight. The reaction was concentrated and treated with Ac_2O (0.5 mL) and pyridine (0.5 mL) at rt overnight. The residue was purified by preparative TLC using 20% EtOAc in hexanes to yield ring-opened product **27** as a colorless oil (8 mg, 62% over 3 steps). ^{1}H NMR (500 MHz, C_6D_6): δ 7.91−7.89 (m, 4H), 7.67−7.65 (m, 6H), 7.46 (d, *J* = 7.2 Hz, 1H), 7.31−7.00 (m, 24H), 5.58 (dd, *J* = 3.2, 6.7 Hz, 1H), 5.31 (m, 1H), 5.15 (d, *J* = 1.0 Hz, 1H), 4.86 (dd, *J* = 1.8, 3.4 Hz, 2H), 4.68 (d, *J* = 12.2 Hz, 1H), 4.42 (dd, *J* = 1.5, 9.9 Hz, 1H), 4.35 (d, *J* = 11.5 Hz, 1H), 4.24 (d, *J* = 11.4 Hz, 1H), 4.17 (d, *J* = 8.0 Hz, 1H), 4.12−4.06 (m, 3H), 3.76 (dd, *J* = 1.5, 5.5 Hz, 1H), 3.65−3.57 (m, 2H), 3.44−3.40 (m, 3H), 3.33 (m, 1H), 3.08 (s, 3H), 1.69 (s, 3H), 1.64 (s, 3H), 1.2 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.74, 169.71, 143.8, 138.1, 137.4, 135.7, 135.5, 133.8, 133.2, 129.5, 129.4, 128.6, 128.3, 128.2, 127.9, 127.8, 127.7, 127.5, 126.9, 101.2, 98.6, 98.0, 86.5, 75.8, 75.6, 75.3, 74.7, 74.3, 73.9, 73.3, 70.5, 70.0, 68.6, 64.1, 63.0, 62.7, 55.3, 45.7, 30.2, 26.7, 20.9, 20.7, 19.3, 8.5. IR: 3244, 3032, 2931, 2857, 2112, 1751, 1589, 1491, 1450, 1426, 1366, 1321, 1227, 1113, 1057, 1029, 919, 745, 702 cm^{-1}. $[\alpha]_D^{25}$ = −25.3° (*c* 0.4, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{67}H_{73}N_3O_{13}SiNa$ [M + Na]$^+$, 1178.4805; found, 1178.4777.

Benzyl 2,3,6-Tri-*O*-benzyl-4-*O*-(2′,3′-di-*O*-benzyl-4′α-epoxypyranosyl)-β-D-glucopyranoside (28). 4′-DP disaccharide **19** (209 mg, 0.25 mmol) was dissolved in CH_2Cl_2 (0.6 mL), cooled to −55 °C, treated with precooled DMDO (1.9 mL of a 0.2 M solution in CH_2Cl_2), and stirred for 12 h at −55 °C followed by a low-temperature workup as previously described to yield the corresponding 4′α-epoxypyranosyl disaccharide **28** as a colorless syrup (213 mg, quantitative, 10:1 α/β). The crude epoxide was used without further purification. ^{1}H NMR (300 MHz, acetone-d_6): δ 7.53−7.32 (m, 30H), 5.13 (d, 1H, *J* = 10.9 Hz), 5.07 (d, 1H, *J* = 7.5 Hz), 5.04−4.74 (m, 10H), 4.72−4.47 (m, 3H), 4.06−3.93 (m, 3H), 3.85−3.56 (m, 3H), 3.56−3.41 (m, 2H), 3.22 (d, 1H, *J* = 2.3 Hz).

Benzyl 2,3,6-Tri-*O*-benzyl-4-*O*-(4′-*O*-acetyl-2′,3′-di-*O*-benzyl-5′*S*-methoxy-β-pyranosyl)-β-D-glucopyranoside (29). A solution of 4′α-epoxypyranosyl disaccharide **28** (14 mg, 0.016 mmol) in MeOH (1 mL) was treated with PPTS (2 mg, 0.008 mmol) at rt. The reaction mixture was stirred at rt for 12 h, quenched with saturated aqueous $NaHCO_3$, and then extracted with CH_2Cl_2 (3 × 5 mL) followed by a standard workup. The residue was purified by preparative TLC using 10% EtOAc in toluene with 1% Et_3N to yield a 1′,5′-bisacetal disaccharide with D-*gluco* configuration as a colorless oil (13 mg, 92%). This product (10 mg, 0.011 mmol) was dissolved in pyridine (1 mL) and Ac_2O (0.5 mL) at 0 °C, warmed to rt, and stirred for 12 h. The mixture was concentrated to dryness and then purified by preparative TLC using 5% EtOAc in toluene with 1% Et_3N to yield 1′,5′-bisacetal disaccharide **29** as a colorless oil (10 mg, 98%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48−7.10 (m, 30H), 4.95 (m, 4H), 4.70−4.54 (m, 6H), 4.54−4.44 (m, 2H), 4.42−4.33 (m, 2H), 4.01 (dd, 1H, *J* = 1.1, 7.8 Hz), 3.91 (t, 1H, *J* = 9.3 Hz), 3.80 (dd, 1H, *J* = 3.6, 11.0 Hz), 3.62 (dd, 1H, *J* = 1.8, 10.8 Hz), 3.54−3.45 (m, 2H), 3.43−3.35 (m, 2H), 3.36−3.29 (m, 1H), 3.23 (ddd, 1H, *J* = 1.7, 3.4, 9.8 Hz), 3.17 (s, 3H), 1.89 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.6, 138.7, 138.5, 138.1, 137.4, 128.4, 128.33, 128.26, 128.15, 128.0, 127.9, 127.80, 127.76, 127.7, 127.6, 127.4, 127.3, 102.4, 98.9, 98.0, 82.6, 82.2, 81.8, 80.1, 75.5, 74.94, 74.85, 74.8, 73.2, 72.8, 70.9, 67.8, 56.1, 29.6, 20.9. IR: 3062, 3031, 2921, 2853, 1751, 1497, 1454, 1364, 1234, 1091, 1049, 1029, 912, 833, 800, 737, 699 cm^{-1}. $[\alpha]_D^{25}$ = −10.0° (*c* 0.25, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{56}H_{60}O_{12}Na$ [M + Na]$^+$, 947.3977; found, 947.3992.

Tolylsulfonyl 2-Azido-4-*O*-(2′-*O*-benzoyl-3′-*O*-benzyl-4′α-epoxypyranosyl)-6-*O*-*tert*-butyldiphenylsilyl-2-deoxy-3-*O*-(2-(trimethylsilyl)ethoxymethyl)-β-D-glucopyranoside (30). 4′-DP disaccharide **24** (16 mg, 0.016 mmol) was dissolved in CH_2Cl_2 (0.2 mL), cooled to 0 °C, treated with precooled DMDO (0.25 mL of a 0.2 M solution in CH_2Cl_2), and stirred for 12 h at 0 °C followed by a low-temperature workup as previously described to yield 4′α-epoxypyranosyl disaccharide **30** as a colorless syrup (17 mg, quantitative yield, 20:1 α/β). The crude epoxide was used without further purification. ^{1}H NMR (400 MHz, C_6D_6): δ 8.05−7.84 (m, 10H), 7.54 (t, 4H, *J* = 7.6 Hz), 7.35−6.91 (m, 8H), 6.65 (d, 2H, *J* = 7.9 Hz), 5.51 (t, 1H, *J* = 6.2 Hz), 5.41 (d, 1H, *J* = 6.5 Hz), 5.19 (d, 1H, *J* = 6.5 Hz), 4.98 (d, 1H, *J* = 6.6 Hz), 4.74 (d, 1H, *J* = 2.0 Hz), 4.51−4.23 (m, 2H), 4.17 (t, 1H, *J* = 9.5 Hz), 4.11−3.97 (m, 2H), 3.87−3.68 (m, 3H), 3.59 (dd, 1H, *J* = 1.9, 12.1 Hz), 3.44 (t, 1H, *J* = 9.2 Hz), 3.31 (t, 1H, *J* = 9.8 Hz), 2.84 (d, 1H, *J* = 2.4 Hz), 2.36 (d, 1H, *J* = 9.4 Hz), 1.77 (s, 3H), 1.32−0.93 (m, 11H), 0.08 (s, 9H).

Benzyl 2,3,6-Tri-*O*-benzyl-4-*O*-(2′,3′-di-*O*-benzyl-5′*R*-furyl-β-pyranosyl)-β-D-glucopyranoside (31). A 0.1 M solution of 2-furylzinc bromide in THF (3.0 mL) was cooled to −78 °C and then treated dropwise with a precooled solution of epoxide **28** (128 mg, 0.15 mmol) in THF (1.5 mL) via cannula addition. The reaction mixture was stirred for 10 min at −78 °C, transferred to an ice bath, and allowed to warm gradually from 0 °C to rt over 12 h. The reaction mixture was cooled to 0 °C, quenched with saturated NH_4Cl (5 mL), extracted with EtOAc (3 × 10 mL), washed with brine (10 mL), dried over Na_2SO_4, and then concentrated under reduced pressure. The crude mixture was passed through a plug of silica gel neutralized with 1% Et_3N using 20% EtOAc in hexanes with 1% Et_3N followed by preparative TLC (developed once with 3% acetone in benzene and then again with 5% acetone in benzene with 1% Et_3N) to afford 5′-*C*-furyl adduct **31** as a colorless syrup (99 mg, 72%). ^{1}H NMR (500 MHz, C_6D_6): δ 7.44 (d, 2H, *J* = 7.2 Hz), 7.37−7.00 (m, 31H), 6.61 (d, 1H, *J* = 3.3 Hz), 6.07 (m, 1H), 5.65 (d, 1H, *J* = 2.3 Hz), 5.48 (d, 1H, *J* = 2.4 Hz), 5.13 (d, 1H, *J* = 10.9 Hz), 5.00 (d, 1H, *J* = 10.9 Hz), 4.99 (d, 1H, *J* = 11.3 Hz), 4.86 (d, 1H, *J* = 12.1 Hz), 4.67 (d, 1H, *J* = 11.3 Hz), 4.52 (d, 1H, *J* = 12.3 Hz), 4.48−4.37 (m, 4H), 4.34 (d, 2H, *J* = 4.1 Hz), 4.22 (t, 1H, *J* = 9.2 Hz), 4.11 (d, 1H, *J* = 9.7 Hz), 3.95 (t, 1H, *J* = 4.3 Hz), 3.79 (dd, 1H, *J* = 3.9, 11.1 Hz), 3.75−3.56 (m, 3H), 3.28 (d, 1H, *J* = 9.5 Hz), 3.13 (d, 1H, *J* = 10.0 Hz). ^{13}C NMR (125 MHz, C_6D_6): δ 152.8, 142.0, 139.9, 139.4, 139.0, 138.8, 138.3, 138.0, 128.7, 128.6, 128.5, 128.4, 128.34, 128.25, 128.2, 128.12, 128.06, 128.0, 127.9, 127.73, 127.66, 127.6, 127.5, 127.3, 110.5, 109.5, 103.0, 99.3, 83.4, 82.9, 76.9, 76.4, 76.0, 75.5, 75.3, 75.0, 74.9, 73.6, 73.0, 72.9, 70.8, 69.1, 66.7. IR: 2924, 1734, 1506, 1447, 1354, 1274, 1067, 742, 695

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cm^{-1}. $[\alpha]_D^{25}$ = −8.0° (*c* 1.2, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{57}H_{62}NO_{11}$ $[M + NH_4]^+$, 936.4323; found, 936.4297.

To confirm the stereochemical assignment of **31**, this product was treated with Ac_2O (1 mL) in pyridine (2 mL) at rt for 12 h and then concentrated to dryness followed by azeotropic distillation with toluene (3 × 1 mL) to afford 4′-*O*-acetyl **31**. ^{1}H NMR and pfg-COSY confirmed the L-*ido* configuration of this compound. ^{1}H NMR (500 MHz, C_6D_6): δ 7.55 (d, 2H, *J* = 7.2 Hz), 7.43−6.99 (m, 30H), 6.93 (m, 1H), 6.16 (d, 1H, *J* = 3.0 Hz), 5.90 (m, 1H), 5.60−5.47 (m, 2H), 5.33 (d, 1H, *J* = 5.9 Hz), 5.13 (d, 1H, *J* = 10.9 Hz), 4.97 (dd, 1H, *J* = 3.2, 11.1 Hz), 4.91−4.49 (m, 6H), 4.43 (m, 3H), 4.37 (t, 1H, *J* = 7.5 Hz), 4.19 (m, 1H), 3.87 (dd, 1H, *J* = 3.8, 11.1 Hz), 3.62 (m, 4H), 3.28 (d, 1H, *J* = 9.9 Hz), 1.49 (s, 3H). ^{13}C NMR (125 MHz, C_6D_6): δ 169.7, 151.2, 142.8, 139.9, 139.6, 139.2, 139.1, 138.9, 138.4, 128.61, 128.56, 128.4, 128.35, 128.3, 128.1, 128.0, 127.9, 127.6, 127.54, 127.50, 110.5, 110.4, 103.0, 99.8, 83.1, 82.6, 81.3, 78.4, 76.6, 75.7, 75.5, 75.0, 74.63, 74.56, 73.5, 71.9, 70.8, 68.6, 66.7, 20.4. IR: 2936, 1750, 1510, 1451, 1358, 1244, 1101, 1046, 746, 691 cm^{-1}. $[\alpha]_D^{25}$ = −14.8° (*c* 0.5, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{59}H_{60}O_{12}Na$ $[M + Na]^+$, 983.3983; found, 983.3969.

Benzyl 2,3,6-Tri-*O*-benzyl-4-*O*-(methyl (2′,3′-di-*O*-benzyl-β-L-iduronato)-β-D-glucopyranoside (32). 5′-*C*-Furyl disaccharide **30** (57 mg, 0.06 mmol) was dissolved in 1:1 CH_2Cl_2/MeOH (3 mL), cooled to −78 °C and then treated with ozone for 40 s. The solution turned a bright-blue and was immediately flushed with N_2; TLC analysis indicated complete consumption of the starting material. The reaction mixture was then treated with dimethyl sulfide (300 μL) and warmed to rt with stirring over a period of 12 h. The reaction mixture was concentrated under vacuum to obtain the corresponding L-iduronsyl disaccharide.

The crude carboxylic acid was redissolved in DMF (1 mL), cooled to 0 °C, treated with several drops of freshly prepared CH_2N_2 in Et_2O, and stirred at 0 °C for 1 h to ensure complete methylation. Diazomethane was generated by treating *N*-methyl *N*′-nitro(*N*-nitroso)guanidine (46 mg, 0.31 mmol) in 4:1 Et_2O/H_2O (2.5 mL) with the dropwise addition of aqueous KOH at 0 °C (0.25 mL of a 5 M solution) to produce a bright-yellow Et_2O solution; the mixture was stirred at 0 °C for another 30 min prior to use. The reaction mixture was then quenched with acetic acid (1 mL) at 0 °C, washed with water, extracted with Et_2O (3 × 10 mL), washed with brine (10 mL), dried over Na_2SO_4, and then concentrated under reduced pressure to a yellow syrup. The product was purified by preparative TLC by developing twice with 20% EtOAc in toluene containing 1% Et_3N to afford methyl ester **32** as an amorphous, colorless solid (41 mg, 76%). ^{1}H NMR (500 MHz, C_6D_6): δ 7.48 (d, 2H, *J* = 7.3 Hz), 7.34−7.02 (m, 28H), 5.55 (s, 1H), 5.26 (d, 1H, *J* = 2.1 Hz), 5.03 (d, 2H, *J* = 2.8 Hz), 4.98 (d, 2H, *J* = 11.3 Hz), 4.85 (d, 1H, *J* = 12.2 Hz), 4.63 (d, 1H, *J* = 11.3 Hz), 4.57−4.38 (m, 5H), 4.36−4.31 (m, 2H), 4.25−4.19 (m, 2H), 3.83 (t, 1H, *J* = 3.5 Hz), 3.68−3.52 (m, 6H), 3.28 (s, 3H), 3.19 (dt, 1H, *J* = 9.2, 2.7 Hz). ^{13}C NMR (125 MHz, C_6D_6): δ 170.0, 139.6, 139.3, 138.9, 138.5, 138.3, 137.7, 128.9, 128.8, 128.7, 128.64, 128.58, 128.44, 128.35, 128.3, 128.1, 127.9, 127.6, 127.5, 127.3, 103.1, 98.7, 83.2, 82.8, 75.6, 75.5, 75.0, 74.9, 74.4, 73.7, 72.5, 72.4, 70.9, 69.7, 69.2, 68.7, 51.4. IR: 2936, 1738, 1464, 1371, 1269, 1210, 1096, 1067, 746, 691 cm^{-1}. $[\alpha]_D^{25}$ = −11.4° (*c* 1.0, CH_2Cl_2). HRESI-MS: *m*/*z* calcd for $C_{55}H_{58}O_{12}Na$ $[M + Na]^+$, 933.3826; found, 933.3842.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H, ^{13}C, DEPT-135, and pfg-COSY NMR spectra for most of the enumerated compounds and select derivatives; table of atomic coordinates and absolute energies for **A**−**D** derived from DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: alexwei@purdue.edu.

Present Addresses

†(P.P.) Department of Chemistry, Faculty of Science, Chulalongkorn University, 254 Phayathai Road, Pathumwan, Bangkok 10330, Thailand.

‡(R.-H.F.) Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China.

Notes

The authors declare no competing financial interest.

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(31) The numbering for pyrans differs from that for pyranosides: atom 1 is reserved for the ring oxygen and atom 2, for the carbon closest to a *sp*3 center.
(32) Comparisons with 2,5-dihydropyrylium (unconjugated isomer) also indicate that the enol ether of **A** has a relatively destabilizing effect on the oxocarbenium ion ($\Delta\Delta H_f$ = +2.0 kcal/mol), whereas the alkene in **B** provides significant resonance stabilization ($\Delta\Delta H_f$ = −10.3 kcal/mol).
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