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Access to Antigens Related to Anthrose Using Pivotal Cyclic Sulfite/Sulfate Intermediates

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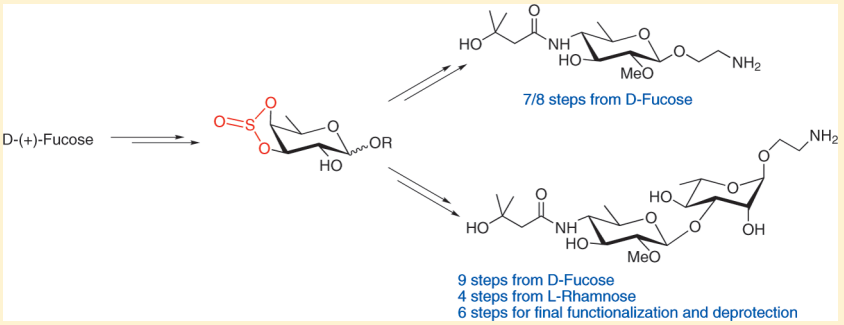
Supporting Information

ABSTRACT:



Anthrose is the upstream terminal unit of the tetrasaccharide side chain from a major glycoprotein of *Bacillus anthracis* exosporium and is part of important antigenic determinants. A novel entry to anthrose-containing antigens and precursors is described. The synthetic route, starting from D(+)-fucose, makes use of intermediates featuring a cyclic sulfite or sulfate function which serves successively as a protecting and a leaving group.

INTRODUCTION

Bacillus anthracis, the etiological agent of anthrax, is a spore-forming Gram positive bacterium. Because of the ease of production, storage, and dissemination of the spores as well as the high lethality that result from spore exposure, this pathogen has recently emerged as a potential biological weapon.[1] This has stimulated the development of effective detection methods and vaccines against this pathogen. The structure of a tetrasaccharide **1**, present as multiple copies on a glycoprotein (BclA) of *B. anthracis* exosporium,[2] has recently been disclosed. The terminal unit of this linear tetrasaccharide features a rare sugar, called anthrose, which, to date, has only been detected on *B. anthracis* and related Bacillus species (Figure 1).[3]

This unique feature has encouraged several laboratories, including ours, to prepare this tetrasaccharide and analogues by chemical synthesis[4−16] or purification from bacterial strains.[17] The tetrasaccharide as well as related fragments and analogues have been key in establishing that the anthrose unit is part of immunodominant antigenic determinants and that analogues featuring an intact or a slightly modified anthrose moiety could be used for detection or sufficed to induce the production of antibodies in detection kits or as immunogens for vaccination.[5,8,13,16−21]

We are interested in developing a glycoconjugate vaccine that might offer an improved alternative to, or complement, the lower than optimal vaccines currently marketed. The latter exploit the immunogenicity of only one virulence factor.[22] The

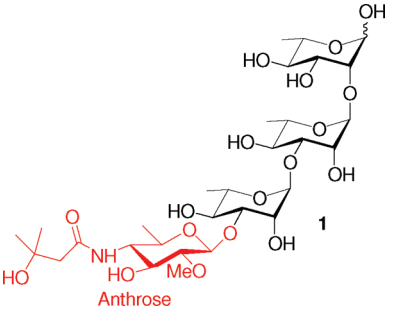


Figure 1. Structure of the anthrose-terminated tetrasaccharide **1** of *B. anthracis* surface glycoprotein, BclA.

development of such alternative glycoconjugate vaccines would necessitate the determination of whether tetrasaccharide **1** is fully required or truncated analogues comprising the anthrose moiety suffice to induce a memory immune response in addition to optimize synthetic access to anthrose-related immunogens. That implies the preparation of anthrose-related intermediates suitable for further glycosylation to rhamnosyl derivatives or coupling to protein carriers.

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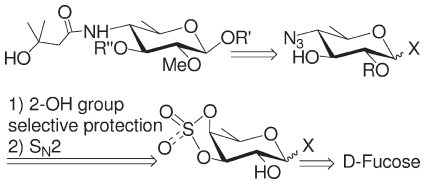
Scheme 1. Overall Route to Anthrose-Derivatives Based on a Dual Role Played by a Cyclic Sulfite



The anthrose moiety in tetrasaccharide **1** is a β-linked 6-deoxy-sugar, having a gluco configuration and displaying a 3-hydroxy-3-methylbutanamido side chain at C-4 and a methoxy at C-2. The most efficient syntheses of anthrose or derivatives thereof reported so far make use of either commercially available D(+)-galactose or D(+)-fucose as starting material and all rely on an S_N2-type reaction between a sulfonate and an azide to install the amide side chain with the correct configuration at C-4.[5,8,12,13,16,23] Whatever the starting sugar or the strategy envisaged, conventional and extensive protecting group (typically isopropylidene, stannylidene, or benzylidene) manipulations have been required in order to differentiate each hydroxyl group of the starting sugar ring.[5,8,12,13,16,23]

We thought to examine a strategy whereby a bis-functional group such as a cyclic sulfite (or sulfate) could serve first as a 3,4-diol protecting group in a D-fucose derivative, thereby allowing selective methylation or orthogonal protection of the remaining free 2-OH group and subsequently serve as a leaving group to enable the stereo- and regioselective introduction of an azido group and thus the anthrose side chain (Scheme 1). Upon adopting this strategy, our goal was ultimately to shorten and to improve the synthesis of anthrose-related antigens.

RESULTS AND DISCUSSION

Cyclic sulfites and sulfates have long been known as versatile electrophiles, and particularly as epoxide surrogates, in both noncarbohydrate and carbohydrate chemistry.[24,25] However, the substitution of cyclic sulfites (or sulfates) other than those involving the anomeric center or a primary hydroxyl group of a sugar has scarcely been studied despite its broad synthetic potential: To our knowledge, no attempt of substitution on a pyranoside 3,4-cyclic sulfate has been reported so far. On the other hand, Guiller et al. reported the preparation of some methyl 4-azido-α-D-arabinopyranosides from their corresponding 3,4-cyclic sulfites in high yields and complete regioselectivity.[26] However, when the same authors iterated the reaction on a (α-L-arabinopyranosyl)uracil derivative, the 3′-azido compound was the sole isolated product, in 50% yield, from a complex mixture in which they tentatively identified the presence of the 4′-azido regioisomer.[27] From these extremely limited results, we envisioned that the anomeric substituent plays an important role in controlling the nucleophilic attack either at the C-3 or C-4 site and that existing 1,3-diaxial interactions will strongly disfavor attack at the former site.[28]

Cyclic Sulfate/Sulfite Ring-Opening from β-Anomers. We nevertheless decided to test our strategy on a β-intermediate: Indeed, we reasoned that the anthrose-derived antigen targets would be more readily accessed if we could secure the required β-anomeric configuration at an early stage of the synthesis. Thus, D-(+)-fucose was reacted with thionyl diimidazole to afford the corresponding bis-cyclic sulfite **2** as a mixture of the four possible diastereomers. This mixture, either purified or crude, was next glycosylated with an excess of *N*-Cbz-ethanolamine, in the presence of a catalytic amount of ytterbium(III) trifluoromethanesulfonate according to the literature[29,30] so as to introduce the spacer-arm precursor required for future conjugation. The desired β-glycoside **3b** could not be separated from the unreacted alcohol acceptor, used in excess, by chromatographic purification. Moreover, the ratio of anomers varied with each experiment and up to 60% of the α-anomer **3a** was sometimes detected in the reaction mixture. Partial isomerization has already been observed in the past for sugar donors bearing electron-withdrawing substituents.[29] When a polar solvent such as dioxane and prolonged reaction times were used, we observed that the formation of the undesired isomer was favored. However, a set of standardized experimental conditions which limited isomerization to the unwanted isomer could not be established. To avoid obtaining such uncontrollable mixture, the cyclic sulfite **3b** (obtained as a 40/60 endo/exo mixture) was unambiguously synthesized by an alternative route via tri-*O*-acetyl-D-fucopyranose **4**[31] using Schmidt's trichloroacetimidate glycosylation[32] followed by Zemplèn deacetylation and then reaction with thionyl chloride (Scheme 2).

O-Methylation of the pure alcohol **3b**, or the crude glycosylation mixture, carried out using methyl iodide and silver(I) oxide, proceeded in almost quantitative yield. The cyclic sulfite survived these methylation conditions, and formation of any 2,3-oxirane byproduct did not occur. Attempts to accelerate the O-methylation rate by adding catalytic amount of dimethyl sulfide led to methylation of the carbamate nitrogen atom, an issue which was suggested by ESI monitoring of the reaction. On the other hand, the O-methylated derivative **5b** was easily separated from its corresponding α-anomer **5a**, or any *N*-Cbz-(2-methoxyethyl)-carbamic acid contaminant when the O-methylation was conducted on the crude glycosylation mixture.

The crucial nucleophilic substitution step was examined using **5b**, whose anomeric configuration was that of the anthrosyl residue featuring in BclA glycoprotein (see Figure 1). Treatment of the cyclic sulfite **5b** with sodium azide led, as expected, to ring-opening to give a 4:1 mixture of regioisomers in 66% isolated yield (Scheme 3). These were easily separable but the unwanted gulo isomer **6b** predominated. The stereochemistry of each regioisomer was evident from their proton NMR data: in particular, coupling constants ($J_{2,3}$ = 9.0 Hz, $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 9.5 Hz) are in full agreement with four H-2, H-3, H-4, and H-5 protons in a trans-diaxial relationship on a pyranose ring in the $^4C_1$ conformation for compound **6a**. For comparison, $J_{2,3}$ and $J_{3,4}$ coupling constants of compound **6b** were found equal to 3.8 and 3.7 Hz, respectively, and are compatible with a gulo configuration for this derivative.

The reaction was carried out on cyclic sulfite **5b** as a whole, which comprises a 60/40 mixture of both exo and endo isomers. The identity of each isomer was established on the basis of literature data[33] while the integration of the ^{1}H NMR signals corresponding to the H-3 exo, H-4 exo, H-3 endo, and H-4 endo protons, observed at 4.72, 4.68, 4.53, and 4.24 ppm, respectively, was used to determine the isomeric ratio. To check whether the ring-opening regioselectivity was sensitive to the stereochemical nature of the leaving group, part of **5b** was repurified by silica gel chromatography so that the reaction was iterated on either enriched endo-**5b** (endo/exo > 85:15) or exo-**5b** (exo/endo > 90:10) cyclic sulfites respectively. Whatever the mixture used,

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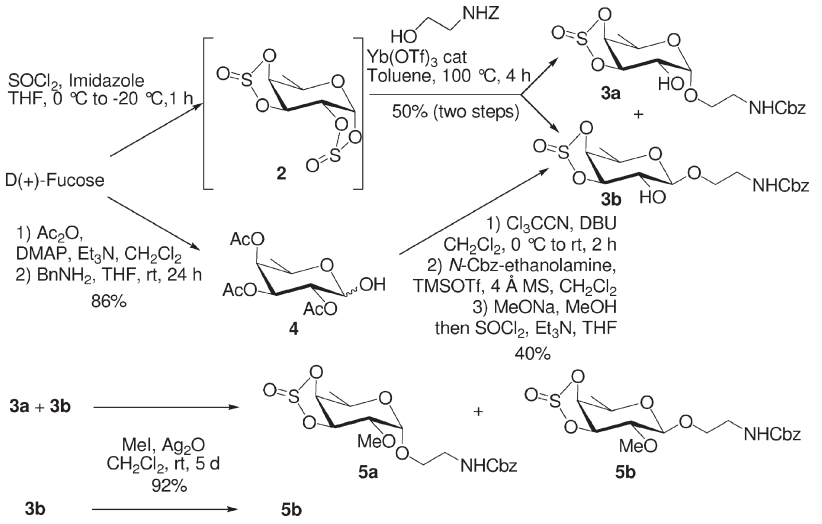
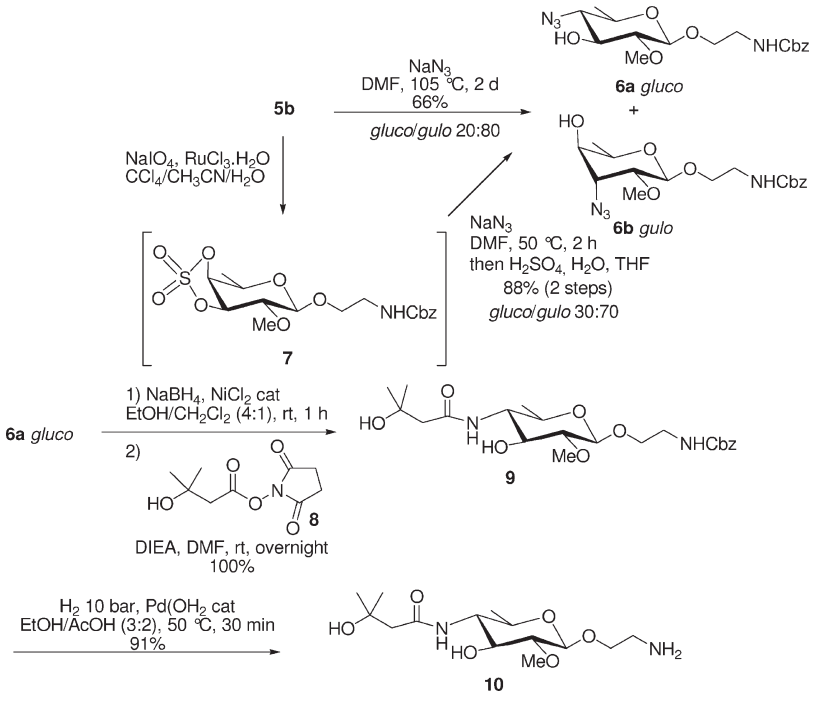
Scheme 2. Preparation of the Key 2-O-Methylated β-Glycosylated Cyclic Sulfite Intermediate



Scheme 3. Nucleophilic Substitution and Final Elaboration of the Anthrose-Related Antigen



identical ratios of products were obtained. However, a modest change in regioselectivity was observed upon using the alternative cyclic sulfate **7** which reacted smoothly to give the azides **6a**/**6b** 3:7 ratio and in a slightly improved yield.

The synthesis of a first target anthrose analogue **10** was achieved from pure **6a** upon reduction of the azido group, acylation of the formed amine function with the β-hydroxyisovaleric acid succinimidyl ester **8**, and subsequent removal of the benzyloxycarbonyl protective group by hydrogenation. Although the synthesis of an anthrose-related immunogen was realized in only seven or eight steps from D(+)-fucose, a route which is considerably shorter than any previously disclosed one (18 steps from D(+)-galactose in 4.6% yield),[13] the overall yield (11%) suffers from the poor regioselectively of the ring-opening step by azide. To further control this step, the strategy was thus revisited from α-glycoside precursors.

Cyclic Sulfate/Sulfite Ring-Opening from α-Anomers. With adoption of this alternative strategy, the anomeric substituent should ideally first serve to orient the 3,4-cyclic sulfite/sulfate ring-opening and further be activated in a glycosylation process. We sought to use glycosyl fluorides, but we anticipated that fluorine might be a too small substituent to exert an effective control of the ring-opening regioselectivity. We also did not investigate the use of α-thioglycosides because they are not as

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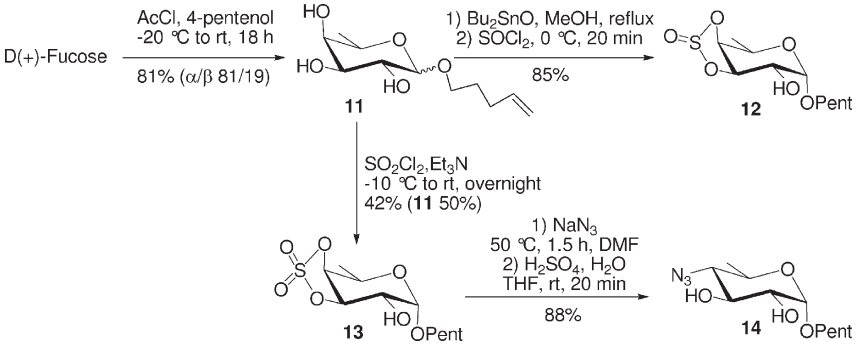
Scheme 4. Preliminary Cyclic Sulfite/Sulfate Formation and Reactivity Study



easily accessible as their corresponding β-anomers, although the latter appeared as valuable intermediates for the preparation of numerous anthrose-derived oligosaccharides.[8,10−13] We finally chose to test alkyl α-fucopyranosides, readily prepared under Fisher-type glycosylation conditions while enabling glycosylation either by direct activation or after being exchanged to a trichloroacetimidate or a halogen leaving group.[34] 4-Pentenyl D-fucopyranoside **11**[35] was prepared following Gin's conditions[36] in an α/β mixture (81:19) in 81% yield (Scheme 4).

This derivative was successively reacted with tributyltin oxide and thionyl chloride[33] to give the 3,4-cyclic sulfite **12** in 85% yield. Unfortunately, this intermediate did not react with sodium azide under reported conditions[26] (105 °C) (recovery of the starting material) and decomposed at more elevated temperature (135 °C). If some products of substitution were formed, we have been unable to detect them in the crude reaction mixture. It is likely that, in accordance with our initial hypothesis, attack at C-3 is prevented on account of the presence of the axial anomeric pentenyl group but that steric hindrance by the methyl group at C-5, not present in the arabinose series described in the literature,[26] suffices to block attack at C-4. We failed in preparing the more reactive 3,4-cyclic sulfate **13** via a stannylidene as for the preparation of compound **12**. Attempts to oxidize sulfite **12** into sulfate under Sharpless conditions proceeded with concomitant oxidation of the alkene function. This sulfate was therefore obtained directly from triol **11** upon treatment with sulfuryl chloride in 42% yield together with recovered starting material (50%): because hydroxyls at sites C-2 and C-3 of the pyranose were vicinal to an axial substituent, they probably possess close reactivity, accounting for the modest, less than 50% percent conversion. It is likely that the 3,4-cyclic sulfate can only be formed when the initial reaction takes place at the 3-OH (considering that the 4-OH is marginally reactive). Indeed, if the reaction first takes place at the concurrent 2-OH, it is likely that the resulting 2-chlorosulfonate cannot cyclize with the 3-OH which is in a trans-diequatorial relationship to give the 2,3-cyclic sulfate product and is too deactivated to react with a further equivalent of sulfuryl chloride, ending in a 3,4-cyclic sulfate. Finally, the 2-chlorosulfonate is apparently hydrolyzed back to the starting material during workup.[37] The preparation of an alkyl fucopyranoside 3,4-cyclic sulfite which could be oxidized into its corresponding sulfate without any further protective steps should circumvent this limiting step. Meanwhile, the key ring-opening was attempted on compound **13**. The 4-azido derivative **14**, having the gluco configuration, was isolated upon reaction with sodium azide at 50 °C as a unique product in 88% yield, a yield identical or even superior to that reported for the substitution of a trifluoromethanesulfonate leaving group.[5,8,9,12,13,16]

Encouraged by this result, the reaction sequence was iterated from methyl α-D-fucopyranoside **15**, whose anomeric substituent is stable toward oxidative experimental conditions. Methylation or acetylation of sulfite **16**, obtained from **15** in 86% yield as described above, gave intermediates **17** or **18** in 86% and 90% yields, respectively (Scheme 5).

These sulfites were oxidized under Sharpless conditions[38] to afford cyclic sulfates **19** and **20**. Key nucleophilic ring-opening using sodium azide at 50 °C in DMF followed by aqueous acid hydrolysis of the resulting acyclic sulfates afforded the 4-azido fucopyranosides **21** and **22** in 81% and 74% yields for this three-step sequence. Remarkably no trace of the gulo 3-azido regioisomers was detected in the reaction mixture. Treatment of compound **21** with benzyl bromide gave the corresponding 3-O-benzylated derivative **23** in 96% yields. The anomeric methyl group was then removed under acetolysis conditions[23] to give compound **24** in a 79:21 (α/β) anomeric mixture in 87% yield. Notably, this reaction was chemospecific and not accompanied by the removal of the benzyl protective group.[39] Deacetylation of **24** using sodium methoxide followed by treatment with trichloroacetonitrile gave the known trichloroacetimidate donor **25**[8] in 82% yield for the two steps. In parallel, compound **22** was either benzylated using benzyl trichloroacetimidate in the presence of a catalytic amount of triflic acid[40] or benzoylated to give **26** and **27** in 70% and quantitative yield, respectively. Acetolysis, followed by selective removal of the anomeric acetates and treatment with trichloroacetonitrile in the presence of DBU afforded trichloracetimidates, **32** and known **33**,[16] in 43% and 38% yields for the three steps, respectively.

The three anthrose-related donors **25**, **32**, and **33** have been synthesized in nine steps in 32%, 13%, and 22% yield, respectively. For comparison, donors **25** and **33** were previously obtained following conventional protection/deprotection steps both in either 12 or 13 steps from D(+)-galactose and 38[8] or 11%[16] overall yield, respectively.

Synthesis of a Disaccharide Related to Anthrax Tetrasaccharide. To fully demonstrate the efficiency of a synthetic approach based on the use of a cyclic sulfate, the synthesis of an anthrose-containing antigen disaccharide has been achieved using novel trichloroacetimidate **32** and a rhamnopyranoside acceptor (Scheme 6).

To this aim, *N*-Z-aminoethyl L-rhamnopyranoside **34**, obtained in a 5:1 (α/β) anomeric mixture upon *p*TsOH-catalyzed condensation of *N*-Cbz-aminoethanol onto L-rhamnose, was

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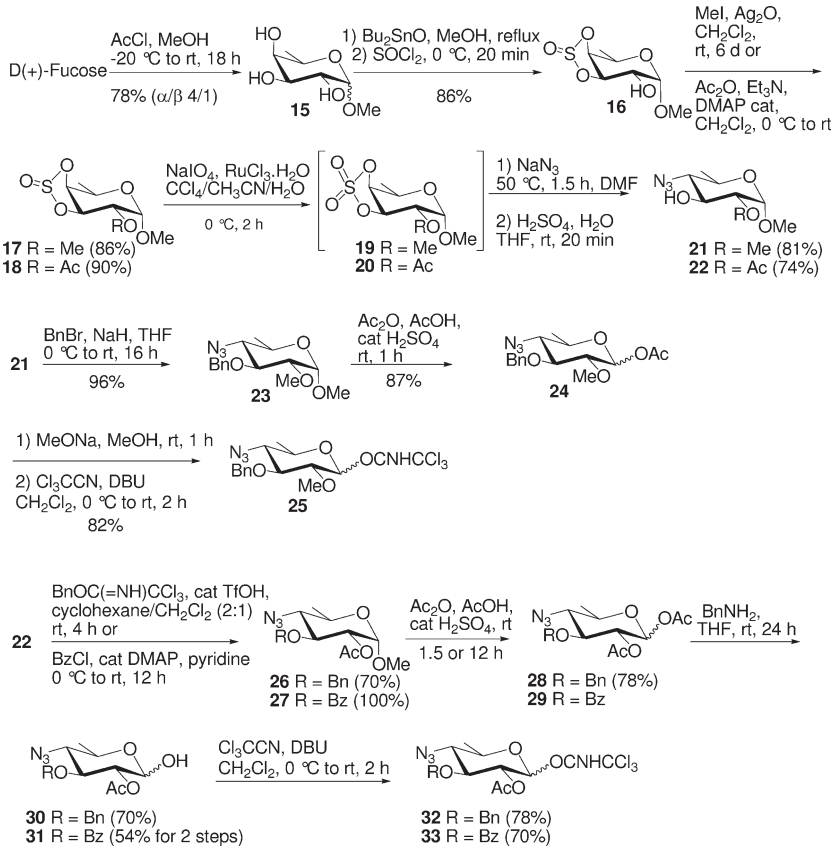
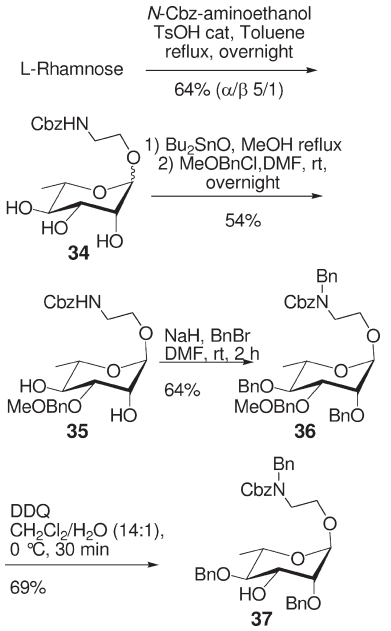
Scheme 5. Syntheses of Anthrose-Related Donors from Cyclic Sulfates



Scheme 6. Synthesis of Rhamnose-Derived Acceptor 37



converted to the 3-*O*-*p*-MeO-benzyl intermediate **35** by regioselective stannylene-mediated alkylation[41] in 28% yield for the two steps. Benzylation of the two remaining hydroxyls as well as the carbamate group gave intermediate **36**, whose selective deprotection using DDQ afforded acceptor **37** in 44% yield (two steps). Donor **32** was then reacted with acceptor **37** at −40 °C for 1 h in the presence of TMSOTf to afford disaccharide **38**, having the β-configuration, in 68% yield (Scheme 7). Zemplén deacetylation of compound **38** gave alcohol **39** which was further methylated by treatment with excess methyl iodide to give **40** (47% yield for the two steps). Hydride reduction of the azido group of intermediate **40**, followed by acylation using 3-hydroxy-3-methylbutanoic acid, preactivated with HOBt/HATU, rather than the succinimidyl ester **8** which proved insufficiently reactive, gave intermediate **41** in 55% yield. Disaccharide **42** was finally obtained after removal of the protecting groups by catalytic hydrogenation in 91% yield.

■ CONCLUSION

The synthetic potential of sugar-derived cyclic sulfite/sulfate, not involving primary or anomeric hydroxyls, has largely been overlooked. The approach reported herein relied on the unprecedented, sequential use of 3,4-cyclic sulfite/sulfates on pyranoses as protecting and leaving groups and was successfully applied to the preparation of several anthrose-related antigens and precursors. We have been able to demonstrate that the key nucleophilic ring-opening could be performed in the presence of various functionalities (alcohol, ether, and ester) but was sensitive to steric hindrance. In particular, an attack at the C-3 site is strongly favored by a β-configuration of the anomeric substituent whenever a cyclic sulfite or sulfate was used. While cyclic sulfites do not react, the reaction proceeds in very high yield and

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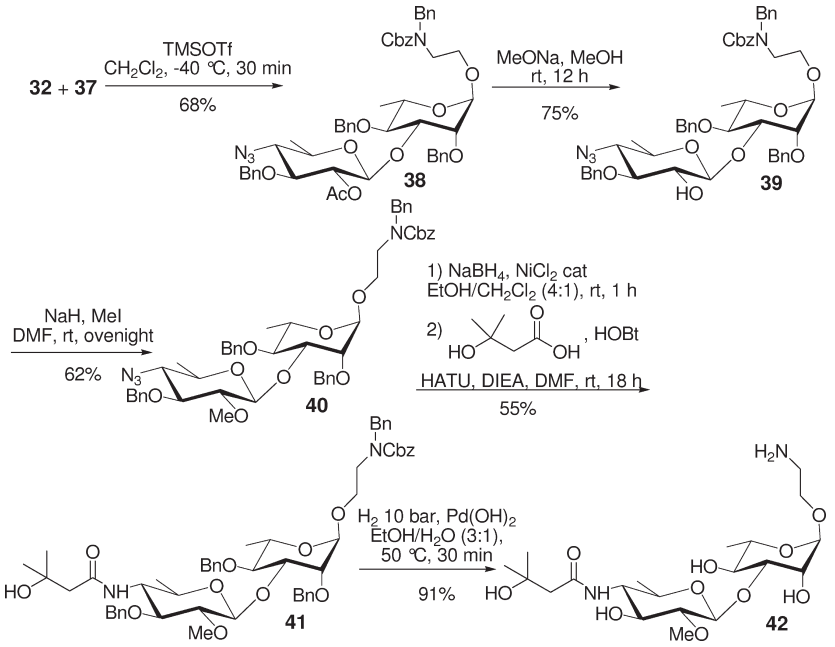
Scheme 7. Synthesis of an Anthrose-Derived Disaccharide



exclusively at the C-4 site when it was conducted on cyclic sulfates derived from α-glycopyranosides.

EXPERIMENTAL SECTION

General. All reactions were monitored by TLC on Kieselgel 60 F254. Detection was achieved by charring with vanillin. Silica gel (240−400 mesh) was used for chromatography. Optical rotation was measured with a digital polarimeter, using a sodium lamp (λ = 589 nm) at 20 °C. All NMR experiments were performed at 300.13 and 500.13 MHz on spectrometers equipped with a Z-gradient unit for pulsed-field gradient spectroscopy. Assignments were performed by stepwise identification using COSY, successive RELAY, HSQC, and HMBC experiments using standard pulse programs. Chemical shifts are given relative to external TMS with calibration involving the residual solvent signals. When D_2O was used, TMS was used as internal standard reference in a previous ^{13}C NMR experiment performed in the same experimental conditions. Low-resolution ESI mass spectra were obtained on a hybrid quadrupole/time-of-flight (Q-TOF) instrument, equipped with a pneumatically assisted electrospray (Z-spray) ion source. High-resolution mass spectra were recorded in positive mode on a TOF tandem hydrid mass spectrometer with EBETOF geometry. The compounds were individually dissolved in MeOH at a concentration of 10 μg cm^{-3} and then infused into the electrospray ion source at a flow rate of 10 mm^3 min^{-1} at 60 °C. The mass spectrometer was operated at 4 kV while scanning the magnet at a typical range of 4000−100 Da. The mass spectra were collected as continuum profile data. Accurate mass measurement was achieved using polyethylene glycol as internal reference with a resolving power set to a minimum of 10 000 (10% valley).

Preparation of 2-[(*N*-Benzyloxycarbonyl)amino]ethyl 3,4-Cyclic Sulfite-6-deoxy-2-*O*-methyl-α-D-galacto-pyranoside (5a) and 2-(*N*-Benzyloxycarbonyl)aminoethyl 3,4-Cyclic Sulfite-6-deoxy-2-*O*-methyl-β-D-galactopyranoside (5b) via 1,2:3,4-Bis-cyclic Sulfite-6-deoxy-β-D-galactopyranose (2). To a solution of imidazole (1.25 g, 19 mmol) in anhydrous THF (7.5 mL) was added thionyl chloride (0.8 mL, 12.2 mmol) dropwise at 0 °C. The reaction mixture was stirred under argon for 30 min and was then cooled to −20 °C. D(+)-fucose (500 mg, 3 mmol) was then added in one portion. The reaction mixture was stirred at this temperature under argon for 2 h. The reaction mixture was then concentrated, and the residue was diluted in CH_2Cl_2 (50 mL) and washed by aqueous 1 M HCl (2 × 25 mL) and water (25 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give crude compound **2** which was used in the next step without purification.

A solution of crude **2** (554 mg), $Yb(OTf)_3$ (135 mg, 0.21 mmol), and 4 Å molecular sieves in anhydrous toluene (7.5 mL) was stirred under Ar for 30 min. 2-[(*N*-Benzyloxycarbonyl)amino]ethanol (1.27 g, 6.4 mmol) was then added, and the mixture was heated at 100 °C for 4 h. The reaction mixture was then diluted in EtOAc (80 mL) and washed successively with aqueous 1 M HCl (2 × 25 mL), saturated aqueous $NaHCO_3$, and brine (25 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated under vacuum. The crude reaction mixture was purified by flash chromatography on silica gel using cyclohexane/ethyl acetate (1:1) to give **3b** in a mixture with a two-fold excess of 2-[(*N*-benzyloxycarbonyl)amino]ethanol, and, depending on the experiments, its α-anomer **3a**.

In a typical example, a 6:4 mixture of compounds **3a**/**3b** with 2-[(*N*-benzyloxycarbonyl)amino]ethanol (1.56 g) was dissolved in dry CH_2Cl_2 (50 mL), and silver(I) oxide (2.6 g, 32.4 mmol) was added. The reaction mixture was stirred at rt for 1 h. Iodomethane (4.03 mL, 64.8 mmol) was then added dropwise, and the reaction mixture was stirred at rt for 5 d. Silver(I) oxide was filtered trough a Celite pad, and the filtrate was concentrated. The residue was purified by flash chromatography using cyclohexane/ethyl acetate (7:3) as eluent to give **5a** (329 mg) and **5b** (220 mg) as pale yellow oils. (**5a**): 20/80 endo/exo mixture; R_f 0.35 (cyclohexane/ethyl acetate 1:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.30 (m, 5 H endo and 5 H exo), 5.55 (br s, H endo and H exo), 5.27 (m, 2 H endo and 2 H exo), 4.91 (dd, J = 5.4 and 8.2 Hz, 1 H exo), 4.91 (d, J = 3.8 Hz, 1 H endo), 4.86 (d, J = 3.5 Hz, 1 H exo), 4.77 (dd, J = 5.4 and 2.3 Hz, 1 H exo), 4.67 (dd, J = 5.5 and 8.2 Hz, 1 H endo), 4.35−4.22 (m, 2 H endo and 2 H exo), 4.21−4.07 (m, 1 H endo), 4.02 (dd, J = 3.8 and 8.8 Hz, 1 H endo), 3.84−3.72 (m, 1 H endo and 1 H

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exo), 3.58−3.33 (m, 2 H endo and 2 H exo), 3.47 (s, 3 H exo), 3.51 (s, 3 H endo), 3.16 (dd, J = 3.5 and 8.2 Hz, 1 H exo), 1.37 (d, J = 6.6 Hz, 3 H endo) 1.36 (d, J = 6.6 Hz, 3 H exo); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4 (C endo and C exo), 136.6, 128.5, 128.2, 128.1 (6 C endo and 6 C exo), 97.1 (C endo), 96.6 (C exo), 83.9 (C endo), 81.2 (C exo), 80.1 (C endo), 78.9 (C exo), 78.1 (C endo and C exo), 67.9 (C endo and C exo), 66.6 (C endo and C exo), 62.8 (C endo), 61.9 (C exo), 59.3 (C endo), 58.8 (C exo), 40.7 (C endo and C exo), 16.3 (C endo and C exo). HR-ESI-MS m/z Calcd for $C_{17}H_{23}NO_8S$ 402.1223 $[M + H]^+$. Found 402.1217.

See below for the description of **5b**.

2-[(*N*-Benzyloxycarbonyl)amino]ethyl 3,4-Cyclic Sulfite-6-deoxy-β-D-galactopyranoside (3b). To a solution of **4**[31] (2.0 g, 6.8 mmol) and trichloroacetonitrile (15 mL, 150 mmol) in CH_2Cl_2 (20 mL) was added DBU (0.252 mL, 1.6 mmol) dropwise at 0 °C. The mixture was then strirred at rt for 2 h and then filtered trough a Celite pad. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel using 2% Et_3N in cyclohexane/ethyl acetate (7:3) as eluent to give 2,3,4-tri-*O*-acetyl-6-deoxy-β-D-galactopyranosyl trichloroacetimidate[42] (2.5 g, 84%) as a pale yellow oil as a mixture of α/β (9/1) anomers. (α-anomer) R_f 0.72 (cyclohexane/ethyl acetate 1:1); ESI-MS m/z 457 $[M + Na]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (s, 1 H), 6.59 (d, J = 3.5 Hz, 1 H), 5.51−5.35 (m, 3 H), 4.43−4.37 (br q, J = 6.6 Hz, 1 H), 2.22, 2.05, and 2.04 (3 s, 3 × 3 H), 1.15 (d, $J_{6,5}$ = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4−170.0 (3 × C), 161.1, 93.9, 77.2, 70.5, 67.9, 66.9, 67.5, 20.7−20.6 (3 × C), 15.9. A solution of the trichloroacetimidate (2.2 g, 5.1 mmol), 2-[(*N*-benzyloxycarbonyl)amino]ethanol (1.9 g, 10.2 mmol) and 4 Å molecular sieves (500 mg) in dry CH_2Cl_2 (30 mL) was stirred for 15 min at rt. The mixture was cooled to 0 °C, and a solution of TMSOTf in CH_2Cl_2 (0.1 N, 60 μL) was added dropwise. After being stirred for 2 h, the reaction mixture was quenched with Et_3N, diluted in CH_2Cl_2, and then washed with saturated aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography using cyclohexane/ethyl acetate (7:3) as eluent to give the 2-[(*N*-benzyloxycarbonyl)amino]ethyl 2,3,4-tri-*O*-acetyl-6-deoxy-β-D-galactopyranoside (1.2 g, 55%) as a pale yellow oil. R_f 0.65 (cyclohexane/ethyl acetate 1:1); $[\alpha]_D$ +8 (c 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29−7.21 (m, 5 H), 5.43−5.35 (m, 1 H), 5.15−5.02 (m, 2 H), 5.00 (s, 2 H), 4.93 (dd, J = 3.7 and 10.5 Hz, 1 H), 4.35 (d, J = 7.9 Hz, 1 H), 3.82−3.75 (m, 1 H), 3.71 (m, 1 H), 3.60−3.58 (m, 1 H), 3.39−3.17 (m, 2 H), 2.06, 1.93, and 1.88 (3 s, 3 × 3 H), 1.11 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 170.0, and 169.6 (3 × C), 156.3, 136.6−128.0 (6 C), 101.1, 71.1, 70.1, 69.1, 69.0, 68.9, 66.5, 40.7, 20.5 (3 × C), 15.9. HR-ESI-MS m/z Calcd for $C_{22}H_{29}NO_{10}$ 490.1689 $[M + Na]^+$, Found 490.1680. 2-[(*N*-Benzyloxycarbonyl)amino]ethyl 2,3,4-tri-*O*-acetyl-6-deoxy-β-D-galactopyranoside (1.2 g, 2.8 mmol) was treated by a 0.2 M methanolic NaOMe solution (42 mL, 8.4 mmol) for 1 h at rt. The reaction mixture was then neutralized by resin Amberlite 120 H^+. The resin was filtered off, and the filtrate was concentrated in vacuo. The crude residue was dissolved in THF (10 mL) at 0 °C. Et_3N (1 mL) was added to the reaction mixture, followed by dropwise addition of thionyl chloride (530 μL, 3.6 mmol). The reaction mixture was warmed to rt and stirred for 2 h. The mixture was then diluted with $CHCl_3$ and washed with water and brine. The organic layer was dried over anhydrous $NaSO_4$ and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography on silica gel using cyclohexane/ethyl acetate (4:6) as eluent to give **3b** (944 mg, 87% over two steps) as an 40/60 endo/exo mixture as pale yellow oil. R_f 0.65 (cyclohexane/ethyl acetate 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.30 (m, 5 H endo and 5 H exo), 5.98 and 5.91 (2 br s, 1 H endo and 1 H exo), 5.06 (s, 2 H endo and 2 H exo), 4.72 (dd, J = 7.6 and 5.3 Hz, 1 H exo), 4.68 (dd, J = 5.3 and 1.5 Hz, 1 H exo), 4.53 (dd, J = 7.6 and 5.7 Hz, 1 H endo), 4.24 (dd, J = 5.7 and 1.5 Hz, 1 H endo), 4.16 (d, J = 7.6 Hz, 1 H endo and 1 H exo), 3.95−3.82 (m, 2 H exo and 1 H endo), 3.77 (q, J = 6.6 Hz, 1 H endo), 3.64−3.51 (m, 1 H endo and 1 H exo), 3.50−3.23 (m, 3 H endo and 3 H exo), 1.41 and 1.38 (2 d, J = 6.6 Hz, 3 H endo and 3 H exo); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0 (C endo and C exo), 136.4−128.0 (6 C endo and 6 C exo), 102.7 and 101.8 (C endo and C exo), 83.9 (C endo), 83.8 (C exo), 82.7 (C endo), 76.1 (C exo), 72.8 (C endo and C exo), 69.4 (C endo and C exo), 67.9 (C exo), 67.3 (C endo), 66.8 (C endo and C exo), 40.9 (C endo and C exo), 16.7 (C endo and C exo); HR-ESI-MS m/z Calcd for $C_{16}H_{21}NO_8S$ 410.0886 $[M + Na]^+$, Found 410.0894.

2-[(*N*-Benzyloxycarbonyl)amino]ethyl 3,4-Cyclic Sulfite-6-deoxy-2-*O*-methyl-β-D-galactopyranoside (5b). To a solution of **3b** (944 mg, 2.6 mmol) in dry CH_2Cl_2 (50 mL) was added silver(I) oxide (2.8 g, 7.8 mmol). The reaction mixture was stirred at rt for 1 h. Iodomethane (1.5 mL, 26 mmol) was then added dropwise, and the reaction mixture was stirred at rt for 5 days. Silver(I) oxide was filtered through a Celite pad, and the filtrate was concentrated. The residue was purified by flash chromatography using cyclohexane/ethyl acetate (7:3) as eluent to give **5b** as a 40/60 endo/exo mixture as a pale yellow oil (962 mg, 92%). R_f 0.26 (cyclohexane/ethyl acetate 5:5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.29 (m, 5 H endo and 5 H exo), 5.48 (br s, 1 H endo), 5.41 (br s, 1 H exo), 5.12 (s, 2 H endo and 2 H exo), 4.80 (dd, J = 5.5 and 1.8 Hz, 1 H exo), 4.76 (dd, J = 6.7 and 5.7 Hz, 1 H exo), 4.53 (dd, J = 7.6 and 5.7 Hz, 1 H endo), 4.36 (dd, J = 5.9 and 1.7 Hz, 1 H endo), 4.25 (d, J = 7.9 Hz, 1 H exo), 4.24 (d, J = 7.9 Hz, 1 H endo), 4.02 (dq, J = 1.8 and 6.6 Hz, 1 H exo), 3.94−3.80 (m, 2 H endo and 2 H exo), 3.77−3.72 (m, 1 H endo and 1 H exo), 3.60 (s, 3 H endo), 3.56 (s, 3 H exo), 3.46−3.43 (m, 2 H endo and 2 H exo), 1.46 (d, J = 6.6 Hz, 3 H endo and 3 H exo,); ^{13}C NMR (75 MHz, CDCl3) δ 156.5 and 156.4 (C endo and C exo), 136.6 (C endo and C exo), 128.5, 128.1, and 128.0 (5 C endo and 5 C exo), 103.0 (C endo), 102.1 (C exo), 83.9 (C endo), 83.5 (C exo), 82.8 (C endo), 81.6 (C exo and C endo), 76.8 (C exo), 69.3 (C exo and C endo), 67.4 (C endo), 67.2 (C exo), 66.7 (C exo), 66.6 (C endo), 60.3 (C exo and C endo), 41.1 (C exo and C endo), 16.7 (C exo and C endo); IR (selected data) (ν) 3357 (NH), 1709 (CO), 1517 (NH), 1210 (SO); HR-ESIMS m/z Calcd for $C_{17}H_{24}NO_8S$ $[M + H]^+$: 402.1223. Found 402.1233.

Preparation of 2-[(*N*-Benzyloxycarbonyl)amino]ethyl 4-Azido-4,6-dideoxy-2-*O*-methyl-β-D-glucopyranoside (6a) and 2-[(*N*-Benzyloxycarbonyl)amino]ethyl 3-Azido-3,6-dideoxy-2-*O*-methyl-β-D-gulopyranoside (6b) from Sulfite 5b. A mixture of **5b** (733 mg, 1.8 mmol) and NaN_3 (900 mg, 3.6 mmol) in dry DMF (10 mL) was stirred for 2 d at 105 °C. The solvent was then removed under vacuum. The residue was dissolved in EtOAc (200 mL) and washed with water (2 × 100 mL) and brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography using cyclohexane/ethyl acetate (1:1) as eluent to give **6a** (76 mg, 13%) as a white solid and **6b** (361 mg, 53%) as a yellow oil, in a 20/80 ratio.

2-[(*N*-Benzyloxycarbonyl)amino]ethyl 4-Azido-4,6-dideoxy-2-*O*-methyl-β-D-glucopyranoside (6a) and 2-[(*N*-Benzyloxycarbonyl)amino]ethyl 3-Azido-3,6-dideoxy-2-*O*-methyl-β-D-gulopyranoside (6b). To **5b** (962 mg, 2.4 mmol) was added a cold solution of CCl_4 (7 mL) and CH_3CN (7 mL). The mixture was cooled to 0 °C, and cold water was added (10 mL). $RuCl_3 \cdot H_2O$ (276 mg, 1.2 mmol) and $NaIO_4$ (1.0 g, 4.8 mmol) were added in one portion, and the reaction mixture was stirred vigorously at 0 °C. After the mixture was stirred 2 h at this temperature, diethyl ether (200 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (100 mL), and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum to give **7**. This material is used in the next

step without any further purification. A mixture of crude **7** and NaN_3 (1.2 g, 4.8 mmol) in dry DMF (10 mL) was stirred for 2 h at 60 °C. The solvent was then removed in vacuo. The residue was suspended in dry THF (20 mL), and concd H_2SO_4 (117 μL) and water (42 μL) were added and the mixture was stirred at rt for 1 h. The reaction mixture was then quenched by sodium bicarbonate in excess and stirred for 20 min. The mixture was then concentrated under vacuum, and the residue was purified by flash chromatography using cyclohexane/ethyl acetate (6:4) to give a mixture of **6a** (240 mg, 26%) as a white solid and **6b** (561 mg, 61%) as a pale yellow oil, in a 30/70 ratio. (**6a**): R_f (cyclohexane/ethyl acetate 5:5) 0.36; $[\alpha]_D$ +12 (*c* 1.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.35 (m, 5 H), 5.36 (br s, 1 H), 5.14 (s, 2 H), 4.25 (d, *J* = 7.9 Hz, 1 H), 3.95−3.82 (m, 1 H), 3.82−3.72 (m, 1 H), 3.61 (s, 3 H), 3.55 (br dd, *J* = 9.0 and 9.5 Hz, 1 H), 3.50−3.42 (m, 2 H), 3.30−3.19 (m, 1 H), 3.11 (br t, *J* = 9.5 Hz, 1 H), 3.01 (dd, *J* = 7.9 and 9.0 Hz, 1 H), 2.96 (br s, 1 H), 1.36 (d, *J* = 6.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 136.5, 128.5, 128.2, 103.2, 83.3, 75.2, 70.7, 69.4, 67.1, 66.8, 60.4, 41.2, 18.3; IR (selected data) ν 3307 (NH), 2932, 2924, 2912 (OH), 2121 (N_3), 1684 (CO), 1274 (OH); HR-ESIMS: *m*/*z* Calcd for $C_{17}H_{24}N_4O_6$ $[M + H]^+$: 381.1774. Found 381.1766. (**6b**): R_f (cyclohexane:EtOAc 5:5) 0.26; $[\alpha]_D$ + 4 (*c* 2.7, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.39−7.29 (m, 5 H), 5.48 (br s, 1 H), 5.14 (s, 2 H), 4.63 (d, *J* = 7.8 Hz, 1 H), 4.17 (dd, *J* = 3.8 and 3.7 Hz, 1 H), 3.94−3.87 (m, 2 H), 3.76−3.80 (m, 1 H), 3.53 (s, 3 H), 3.59−3.51 (m, 1 H), 3.49−3.41 (m, 2 H), 3.46 (dd, *J* = 7.8 and 3.8 Hz, 1 H), 1.24 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 136.6, 128.0, 128.1, 101.3, 77.5, 71.0, 69.6, 68.9, 66.7, 62.3, 41.2, 15.7; HR-ESIMS: *m*/*z* Calcd for $C_{17}H_{24}N_4O_6$ $[M + H]^+$: 381.1774. Found 381.1782.

β-Hydroxyisovaleric Acid Succinimidyl Ester (8). To a solution of β-hydroxyisovaleric acid (1.0 g, 9.8 mmol) in CH_2Cl_2 (10 mL) were added *N*-hydroxysuccinimide (1.1 g, 9.8 mmol) and EDC (1.9 g, 9.8 mmol). The reaction mixture was stirred at rt for 2 h and was then concentrated in vacuo. The residue was then purified by flash chromatography using cyclohexane/ethyl acetate (5:5) as eluent to provide **8** (1.6 g, 77%) as a white solid. R_f 0.24 (cyclohexane/ethyl acetate 1:1); ^1H NMR (300 MHz, $CDCl_3$) δ 3.21 (s, 1 H), 2.63 (br s, 4 H), 2.57 (s, 2 H), 1.18 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9 (2 × C), 166.4, 69.2, 44.5, 28.9 (2 C), 25.4 (2 C).

2-[(*N*-Benzyloxycarbonyl)amino]ethyl 4,6-Dideoxy-4-(3-hydroxy-3-methylbutanamido)-2-*O*-methyl-β-D-glucopyranoside (9). To a solution of **6a** (240 mg, 0.6 mmol) in a mixture of dry CH_2Cl_2 (9 mL) and EtOH (42 mL) were added sodium borohydride (45 mg, 1.2 mmol) and a catalytic amount of $NiCl_2 \cdot 6H_2O$. The reaction mixture was stirred at rt for 1 h and was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (200 mL). The organic layer was washed with water (2 × 100 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide 2-[(*N*-benzyloxycarbonyl)amino]ethanol 4-amino-4,6-dideoxy-2-*O*-methyl-β-D-glucopyranoside which was used in the next step without purification. The crude was dissolved in dry CH_3CN (10 mL), and **8** (30 mg, 0.5 mmol) and DIEA (297 μL, 1.2 mmol) were added. The reaction mixture was stirred under argon at rt for 4 h and was then concentrated under reduced pressure. The residue was purified by flash chromatography using ethyl acetate/MeOH (95:5) as eluent to provide **9** (272 mg, quantitative over two steps) as a white solid. R_f 0.14 (cyclohexane/ethyl acetate 1:9); $[\alpha]_D$ +17 (*c* 1.0, $CHCl_3$) [lit.[13] $[\alpha]_D$ +16 (*c* 0.13, $CHCl_3$)]; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.30 (m, 5 H), 6.63 (d, *J* = 8.5 Hz, 1 H), 5.55−5.47 (m, 1 H), 5.12 (s, 2 H), 4.29 (d, *J* = 7.9 Hz, 1 H), 3.92−3.63 (m, 3 H), 3.59 (s, 3 H), 3.56−3.41 (m, 4 H), 3.03 (dd, *J* = 7.9 and 8.8 Hz, 1 H), 2.41 (s, 2 H), 1.32 (s, 3 H), 1.31 (s, 3 H), 1.27 (s, 3 H, *J* = 6.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 156.5, 136.5−128.1 (6 C), 103.2, 83.8, 74.1, 70.8, 70.0, 69.3, 66.7, 60.8, 57.0, 48.6, 41.2, 29.8, 29.2, 18.0; HR-ESI-MS *m*/*z* Calcd for $C_{22}H_{35}N_2O_8$ 455.2393 $[M + H]^+$; Found 455.2405 $[M + H]^+$.

2-Aminoethyl 4,6-Dideoxy-4-(3-hydroxy-3-methylbutanamido)-2-*O*-methyl-β-D-glucopyranoside (10). Compound **9** (20 mg, 0.04 mmol) in a 3:2 mixture of EtOH/AcOH (4 mL) was deprotected under 10 bar H_2 using catalytic $Pd(OH)_2$ at 50 °C. After 30 min, the reaction mixture was concentrated in vacuo. The residue was dissolved in H_2O (10 mL) and was washed with CH_2Cl_2 (7 mL). The organic layer was extracted by water (5 × 5 mL). The aqueous phases were combined and concentrated under vacuum. The crude was then purified on cation exchange resin (AG MP-50 Resin, analytical grade 100−200 mesh) to give **10** (12 mg, 91%) as a yellow solid after lyophilization. $[\alpha]_D$ +19 (*c* 0.1, H_2O) [lit.[13] $[\alpha]_D$ +17 (*c* 0.17, H_2O)]; ^1H NMR (300 MHz, $CDCl_3$) δ 4.52 (d, *J* = 8.0 Hz, 1 H), 4.02−3.98 (m, 1 H), 3.88−3.84 (m, 1 H), 3.64−3.56 (m, 1 H), 3.15 (br t, *J* = 8.0 Hz, 1 H), 3.08 (br t, *J* = 8.3 Hz, 2 H), 2.47 (s, 2 H), 1.27 (s, 3 H), 1.24 (s, 3 H), 1.17 (d, *J* = 5.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 109.9, 101.8, 83.1, 73.6, 72.9, 70.9, 70.2, 66.6, 60.1, 56.5, 48.9, 39.5, 28.2, 28.1, 16.9; HR-ESIMS: *m*/*z* Calcd for $C_{14}H_{28}N_2O_6$ $[M + H]^+$: 321.2026. Found 321.2023.

4-Penten-1-yl D-Fucopyranoside (11). D-(+)-Fucose (2 g, 12.2 mmol, 1.0 equiv) was added to a stirred mixture of 4-pentenol (11.3 mL, 110 mmol, 9.0 equiv) and acetyl chloride (0.8 mL, 12.2 mmol, 1.0 equiv) cooled at −10 °C. The reaction mixture was stirred for 18 h at rt before $NaHCO_3$ was added and was then concentrated under reduced pressure. The crude residue was purified by flash column chromatography using ethyl acetate as eluent to afford **11** (2.27 g, 81%) as an α/β (81:19) mixture. α-anomer: R_f 0.17 (ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$) δ 5.89−5.74 (m, 1 H), 5.08−4.92 (m, 2 H), 4.83 (d, *J* = 3.3 Hz, 1 H), 3.83−3.42 (m, 6 H), 2.18−2.06 (m, 2 H), 1.80−1.66 (m, 2 H), 1.26 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, CD_3OD) δ 138.0, 115.0, 98.7, 72.1, 71.3, 69.0, 67.6, 66.0, 30.3, 28.7, 16.2; HR-ESI-MS *m*/*z* Calcd for $C_{11}H_{20}O_5$ 255.1208 $[M + Na]^+$; Found 255.1206.

4-Penten-1-yl 3,4-Cyclic Sulfite-α-D-fucopyranoside (12). A mixture of 4-pentenyl D-fucopyranoside (1.6 g, 6.9 mmol) and dibutyl oxide (1.88 g, 7.6 mmol) was refluxed in dry MeOH (40 mL) under stirring for 5 h. The cleared reaction mixture was then concentrated under reduced pressure for 2 h and then diluted with CH_2Cl_2 (20 mL). Thionyl chloride (505 μL, 6.9 mmol) was next added dropwise to the reaction vessel cooled at 0 °C. The reaction mixture was stirred for 20 min at rt before $NaHCO_3$ was added and was then concentrated under reduced pressure. The crude residue was purified by flash chromatography using cyclohexane/ethyl acetate (8:2) as eluent to give compound **12** (1.63 g, 85%). R_f 0.49 (cyclohexane/ethyl acetate 7:3); major isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 5.89−5.76 (m, 1 H, H-10), 5.10−5.00 (m, 2 H, H-11), 4.91−4.85 (m, 2 H), 4.82 (d, *J* = 3.9 Hz,1 H), 4.40−4.29 (m, 1 H), 3.82−3.73 (m, 2 H), 3.63 (br s, 1 H), 3.56−3.47 (m, 2 H), 2.20−2.10 (m, 2 H), 1.81−1.69 (m, 2 H), 1.42 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 115.2, 97.6, 81.8, 78.3, 69.7, 68.1, 62.1, 30.3, 28.5, 16.3; HR-ESI-MS *m*/*z* Calcd for $C_{11}H_{18}O_6S$ 301.0722 $[M + Na]^+$; Found 301.0718.

4-Penten-1-yl 3,4-Cyclic Sulfate-α-D-fucopyranoside (13). Sulfuryl chloride (1 M in CH_2Cl_2, 5.2 mL, 5.2 mmol) was added dropwise at −10 °C to a mixture of 4-pentenyl D-fucopyranoside (600 mg, 2.6 mmol) and Et_3N (1.44 mL, 10.8 mmol) in dry CH_2Cl_2 (20 mL) under Ar. The reaction mixture was stirred at rt overnight, diluted with CH_2Cl_2, and successively washed with H_2O, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduce pressure. The crude residue was purified by flash chromatography using cyclohexane/ethyl acetate (8:2) and then ethyl acetate as eluent to give compound **13** (319 mg, 42%) and then **12** (300 mg). R_f 0.68 (cyclohexane/ethyl acetate 5:5); $[\alpha]_D$ +135.2 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.88−5.72 (m, 1 H), 5.07−5.80 (m, 5 H), 4.22−4.12 (m, 2 H), 3.77−3.70 (m, 1 H), 3.8−3.73 (m, 1 H), 2.96 (br s, 1 H), 3.56−3.47 (m, 2 H), 2.18−2.10 (m, 2 H), 1.78−1.69 (m, 2 H), 1.38 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR

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(75 MHz, $CDCl_3$) δ 137.8, 115.2, 97.8, 84.8, 82.8, 68.4, 67.7, 62.3, 30.1, 28.3, 15.9; HR-ESI-MS m/z Calcd for $C_{11}H_{18}O_7S$ 317.0671 $[M + Na]^+$; Found 317.0683.

4-Penten-1-yl 4-Azido-4,6-dideoxy-α-D-glucopyranoside (14). A mixture of **13** (250 mg, 0.85 mmol) and NaN_3 (110 mg, 1.7 mmol) in dry DMF (2 mL) was stirred for 1.5 h at 50 °C. The solvent was then removed in vacuo. The residue was suspended in dry THF (4 mL), concd H_2SO_4 (45 μL, 0.85 mmol) and water (16 μL, 0.85 mmol) were added, and the mixture was stirred at rt for 20 min. The reaction mixture was then quenched by sodium bicarbonate in excess and stirred for 20 min. The mixture was then concentrated under vacuum, and the residue was purified by flash chromatography using cyclohexane/ethyl acetate (7.5:2.5 then 6:4) as eluent to give **14** (160 mg, 88%) as a white oil. R_f 0.28 (cyclohexane/ethyl acetate 7:3); $[\alpha]_D$ +176.4 (*c* 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 5.89−5.76 (m, 1 H), 5.0.9−4.99 (m, 2 H), 4.82 (d, *J* = 3.8 Hz, 1 H), 3.82−3.68 (m, 2 H), 3.66−3.55 (m, 2 H), 3.51−344 (m, 1 H), 3.05 (t, *J* = 9.7 Hz, 1 H), 2.81 (br s, 1 H), 2.20−2.09 (m, 2 H), 1.79−1.68 (m, 2 H), 1.31 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 115.2, 98.0, 73.5, 72.7, 67.7 (2 C-4), 66.3, 30.3, 28.6, 18.2; HR-ESIMS: m/z Calcd for $C_{11}H_{19}N_3O_4$ $[M + Na]^+$: 280.1273. Found 280.1286.

Methyl 3,4-Cyclic Sulfite-α-D-fucopyranoside (16). To a solution of methyl D-fucopyranoside **15** (2.5 g, 14.2 mmol) in dry MeOH (75 mL) was added dibutyltin oxide (3.5 g, 14.2 mmol). The mixture was heated to reflux under inert atmosphere for 6 h and was then evaporated to dryness. The residue was dried under vacuum for 2 h and was then dissolved in dry CH_2Cl_2 (100 mL). Thionyl chloride (1.1 mL, 14.2 mmol) diluted in CH_2Cl_2 (10 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 1 h under inert atmosphere at rt and was evaporated in vacuo. The crude residue was purified by flash chromatography using cyclohexane/ethyl acetate (5:5) as eluent to give compound **16** (2.7 g, 86%). R_f 0.48 (cyclohexane/ethyl acetate 1:1); ^1H NMR (300 MHz, $CDCl_3$) (major isomer) δ 4.82 (dd, *J* = 7.7 and 7.6 Hz, 1 H), 4.79 (dd, *J* = 7.6 and 2.2 Hz, 1 H), 4.63 (d, *J* = 3.7 Hz, 1 H), 3.24 (dq, 1 H, *J* = 2.2 and 6.5 Hz, 1 H), 3.52−3.48 (m, 1 H), 3.37 (s, 3 H), 3.30 (d, *J* = 7.3 Hz, 1 H), 1.35 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 99.0, 82.0, 78.3, 69.9, 61.7, 55.8, 16.3; HR-ESIMS: m/z Calcd for $C_7H_{12}O_6S$ $[M + Na]^+$: 247.0252. Found 247.0250.

Methyl 3,4-Cyclic Sulfite-2-*O*-methyl-α-D-fucopyranoside (17). Alcohol **16** (943 mg, 4.21 mmol) was dissolved in dry CH_2Cl_2 (10 mL), and silver(I) oxide (2.44 g, 10.5 mmol) was added. The reaction mixture was stirred at rt for 1 h. Iodomethane (2.62 mL, 42.1 mmol) was then added dropwise, and the reaction mixture was stirred at rt for 5 d. Silver(I) oxide was filtered through a Celite pad, and the filtrate was concentrated. The residue was purified by flash chromatography using cyclohexane/ethyl acetate (7:3) as eluent to give **17** (824 mg, 82%). R_f 0.52 (cyclohexane/ethyl acetate 1:1); ^1H NMR (300 MHz, $CDCl_3$) (major isomer) δ 4.85−4.65 (m, 3 H), 4.22−4.15 (m, 1 H), 3.40 (s, 3 H), 3.31 (s, 3 H), 3.08 (dd, *J* = 3.1 and 8.1 Hz, 1 H), 1.30 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 97.1, 81.3, 78.6, 78.0, 61.3, 58.7, 55.6, 16.2; HR-ESIMS: m/z Calcd for $C_8H_{14}O_6S$ $[M + Na]^+$: 261.0419. Found 261.0409.

Methyl 2-*O*-Acetyl-3,4-cyclic Sulfite-α-D-fucopyranoside (18). To a solution of compound **16** (2.4 g, 10.7 mmol) in CH_2Cl_2 (50 mL) at 0 °C were successively added Ac_2O (3.0 mL, 32.1 mmol), Et_3N (1.52 mL, 10.7 mmol), and DMAP (144 mg, 1.07 mmol). The reaction mixture was warmed up to rt and was stirred for 2 h. The mixture was then diluted in CH_2Cl_2 and was washed by saturated aq $KHSO_4$, saturated aq $NaHCO_3$, and water. The organic phase was then dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was then purified by flash chromatography using cyclohexane/ethyl acetate (8:2) as eluent to give acetate **18** (2.56 g, 90%) as a white solid. R_f 0.72 (cyclohexane/ethyl acetate 4:6); ^1H NMR (300 MHz, $CDCl_3$) δ 4.88 (dd, *J* = 8.6 and 5.1 Hz, 1 H), 4.76 (dd, *J* = 5.2 and 2.4 Hz, 1 H), 4.67 (d, *J* = 3.6 Hz, 1 H), 4.51 (dd, *J* = 3.6 and 8.6 Hz, 1 H), 4.17 (dq, *J* = 2.4 and 6.6 Hz, 1 H), 3.24 (s, 3 H), 1.98 (s, 3 H), 1.28 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 96.3, 78.3, 77.9, 71.0, 61.2, 55.2, 20.2, 15.8; HR-ESIMS: m/z Calcd for $C_9H_{14}NaO_7S$ $[M + Na^+]$: 289.0358. Found 289.0344.

Methyl 2-*O*-Acetyl-3,4-*O*-cyclic Sulfate-α-D-fucopyranoside (20). To compound **18** (1.85 g, 6.9 mmol) was added a cold solution of CCl_4 (15 mL) and CH_3CN (15 mL). The mixture was cooled to 0 °C, and cold water was added (20 mL). $RuCl_3 \cdot H_2O$ (10 mg, 0.7 mmol) and $NaIO_4$ (2.8 g, 13.8 mmol) were added in one portion, and the reaction mixture was stirred vigorously at 0 °C. After the mixture was stirred for 2 h at this temperature, diethyl ether was added and the layers were separated. The aqueous layer was extracted with diethyl ether, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum to give crude sulfate **20**. An aliquot of this material was purified for characterization by flash chromatography using cyclohexane/ethyl acetate (8:2) as eluent. R_f 0.57 (cyclohexane/ethyl acetate 6:4); $[\alpha]_D$ = +129.6 (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.25 (dd, *J* = 3.5 and 8.4 Hz, 1 H), 5.08 (dd, *J* = 8.4 and 5.0 Hz, 1 H), 5.06 (dd, *J* = 5.0 and 2.0 Hz, 1 H), 5.00 (d, *J* = 3.5 Hz, 1 H), 4.20 (dq, *J* = 2.0 and 6.8 Hz, 1 H), 3.41 (s, 3 H), 2.17 (s, 3 H), 1.43 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 96.6, 82.3, 81.0, 69.3, 61.9, 56.0, 20.7, 15.8; HR-ESIMS: m/z Calcd for $C_9H_{14}O_8S$ $[M + Na]^+$: 305.0296. Found 305.0307.

Methyl 4-Azido-4,6-dideoxy-2-*O*-methyl-α-D-glucopyranoside (21). To cyclic sulfite **17** (800 mg, 3.36 mmol) was added a cold solution of CCl_4 (10 mL) and CH_3CN (10 mL). The mixture was cooled to 0 °C, and cold water was added (15 mL). $RuCl_3 \cdot H_2O$ (10.7 mg, 0.05 mmol) and $NaIO_4$ (1.44 g, 6.72 mmol) were added in one portion, and the reaction mixture was stirred vigorously at 0 °C. After the mixture was stirred for 2 h at this temperature, diethyl ether was added and the layers were separated. The aqueous layer was extracted with diethyl ether, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum to give sulfate **19**. This material is used in the next step without any further purification. A mixture of crude **19** and NaN_3 (437 mg, 6.72 mmol) in dry DMF (8 mL) was stirred for 2 h at 50 °C. The solvent was then removed in vacuo. The residue was suspended in dry THF (5 mL), concd H_2SO_4 (176 μL, 3.36 mmol) and water (62 μL, 3.36 mmol) were added, and the mixture was stirred at rt for 1 h. The reaction mixture was then quenched by $NaHCO_3$ in excess and stirred for 20 min. The mixture was then concentrated under vacuum, and the residue was purified by flash chromatography using cyclohexane/ethyl acetate (6:4) as eluent to give azide **21** (592 mg, 81% over two steps) as a white solid. R_f 0.38 (cyclohexane/ethyl acetate 1:1); $[\alpha]_D$ +164.5 (*c* 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 4.82 (d, *J* = 3.5 Hz, 1 H), 3.81 (dt, *J* = 9.5 and 3.3 Hz, 1 H, H-3), 3.69 (d, *J* = 3.3 Hz, 1 H), 3.50−3.42 (m, 1 H), 3.41 (s, 3 H), 3.30 (s, 3 H), 3.12 (dd, *J* = 3.5 and 9.5 Hz, 1 H), 2.97 (t, *J* = 9.5 Hz, 1 H), 1.20 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 96.7, 81.4, 71.5, 67.8, 65.7, 58.2, 55.1, 18.2; HR-ESIMS: m/z Calcd for $C_8H_{15}N_3O_4$ $[M + Na]^+$: 240.0963. Found 240.0960.

Methyl 2-*O*-Acetyl-4-azido-4,6-dideoxy-α-D-glucopyranoside (22). To crude compound **20** in dry DMF (20 mL) was added NaN_3 (897 mg, 13.8 mmol). The reaction mixture was stirred for 2 h at 50 °C. The solvent was then removed in vacuo. The residue was suspended in dry THF (15 mL), H_2SO_4 (350 μL) and water (120 μL) were added, and the mixture was stirred at rt for 1 h. The reaction mixture was then quenched by $NaHCO_3$ in excess and stirred for 20 min. The mixture was then concentrated in vacuo, and the residue was purified by flash chromatography using cyclohexane/ethyl acetate (6:4) as eluent to give azide **22** (1.25 g, 74% over two steps) as a white solid. R_f 0.68 (cyclohexane/ethyl acetate 4:6); $[\alpha]_D$ = +152.6 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.82 (d, *J* = 3.5 Hz, 1 H), 4.70 (dd, *J* = 3.5 and 9.9 Hz, 1 H), 3.96 (br t, *J* = 10.0 Hz, 1 H), 3.58 (dq, *J* = 6.2 and

9.9 Hz, 1H), 3.38 (s, 3 H), 3.37 (br s, 1 H), 3.11 (t, J = 9.9 Hz, 1 H), 2.14 (s, 3 H), 1.30 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 96.8, 76.7, 70.3, 68.4, 65.8, 55.2, 20.9, 18.1; HR-ESIMS: m/z Calcd for $C_9H_{15}N_3O_5$ $[M + Na]^+$: 268.0909. Found 268.0915.

Methyl 4-Azido-3-*O*-benzyl-4,6-dideoxy-2-*O*-methyl-α-D-glucopyranoside (23). To a solution of alcohol **21** (460 mg, 2.13 mmol) in dry THF (5 mL) was added NaH (110 mg 6% in oil, 2.77 mmol) under Ar at 0 °C. After a period of 10 min, BnBr (306 μL, 4.26 mmol) was added and the reaction mixture stirred overnight at rt. The reaction mixture was then quenched by aqueous saturated NH_4Cl in excess and stirred for 2 min. The mixture was then concentrated under vacuum, and the residue was purified by flash chromatography using cyclohexane/ethyl acetate (1:0 to 8:2) as eluent to give compound **23** (633 mg, 96%) as an oil. R_f 0.38 (cyclohexane/ethyl acetate 9:1); $[\alpha]_D$ +180.6 (c 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.27 (m, 5 H), 4.92 (d, J = 10.7 Hz, 1 H), 4.80 (d, J = 10.7 Hz, 1 H), 4.80 (d, J = 3.5 Hz, 1 H), 3.79 (t, J = 9.6 Hz, 1 H), 3.65−3.52 (m, 1 H), 3.52 (s, 3 H), 3.42 (s, 3 H), 3.35 (dd, J = 3.5 and 9.6 Hz, 1 H), 3.11 (t, J = 9.6 Hz, 1 H), 1.32 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 128.4 (2 C), 128.3 (2 C), 127.8, 97.3, 82.4, 79.8, 75.4, 67.9, 65.9, 58.9, 55.2, 18.4; HR-ESIMS: m/z Calcd for $C_{15}H_{21}N_3O_4$ $[M + Na]^+$: 330.1418. Found 330.1430.

1-Acetyl-4-azido-3-*O*-benzyl-4,6-dideoxy-2-*O*-methyl-D-glucopyranose (24). A solution of methyl glycoside **23** (600 mg, 1.95 mmol) in $Ac_2O/AcOH/H_2SO_4$ (2.7:0.472:0.011 mL) was stirred at rt for 1.5 h. The reaction mixture was then quenched by $NaHCO_3$ in excess, diluted in H_2O, and extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography using cyclohexane/ethyl acetate (9:1) as eluent to give compound **24** (570 mg, 87%) in a 79:21 α/β mixture as an oil. R_f 0.59 (cyclohexane/ethyl acetate 8:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.27 (m, 5 H), 6.35 (d, J = 3.6 Hz, 1 Hα), 5.53 (d, J = 8.2 Hz, 1 Hβ), 4.95 (d, J = 10.8 Hz, 1 Hα), 4.91 (d, J = 10.8 Hz, 1 Hβ), 4.84 (d, J = 10.8 Hz, 1 Hβ), 4.82 (d, J = 10.8 Hz, 1 Hα), 3.76 (t, J = 9.5 Hz, 1 Hα), 3.74−3.65 (m, 1 Hα), 3.57 (s, 3 H, CH_3β), 3.51 (t, J = 9.4 Hz, 1 Hβ), 3.46 (s, 3 Hα), 3.42 (dd, J = 3.6 and 9.5 Hz, 1 Hα), 3.32−3.41 (m, 1 Hβ), 3.29 (dd, J = 8.2 and 9.4 Hz, 1 Hβ), 3.18 (t, J = 9.5 Hz, 1 Hα), 3.16 (t, J = 9.4 Hz, 1 Hβ), 1.34 (d, J = 6.2 Hz, 3 Hβ), 1.34 (d, J = 6.2 Hz, 3 Hα); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2 (Cα), 169.1 (Cβ), 138.2 (Cα), 138.0 (Cβ), 128.4 (2 Cα), 128.3 (2 Cβ), 128.2 (2 Cα), 128.2 (2 Cβ), 128.0 (Cβ), 127.9 (Cα), 93.8 (Cβ), 89.1 (Cα), 83.1 (Cβ), 82.7 (Cβ), 81.4 (Cα), 79.5 (Cα), 75.5 (Cβ), 75.4 (Cα), 71.3 (Cβ), 68.5 (Cα), 67.2 (Cα), 60.6 (Cβ), 58.8 (Cα), 20.9 (Cα and Cβ), 18.5 (Cα), 18.3 (Cβ); HR-ESIMS: m/z Calcd for $C_{16}H_{21}N_3O_5$ $[M + Na]^+$: 358.1389. Found 358.1379.

4-Azido-3-*O*-benzyl-4,6-dideoxy-2-*O*-methyl-D-glucopyranosyl Trichloroacetimidate (25).[8]**.** To a solution of **24** (570 mg, 1.70 mmol) in MeOH (5 mL) was added sodium methoxide (110 mg, 2.04 mmol) at rt. The reaction mixture was stirred for 20 min and then concentrated under reduced pressure. The crude residue was dissolved in CH_2Cl_2 (5.2 mL). To this solution were added trichloroacetonitrile (3.61 mL, 37.4 mmol) and DBU (54 μL, 0.39 mmol) dropwise at 0 °C. The mixture was then stirred at rt for 2 h and then concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 2% Et_3N in cyclohexane/ethyl acetate (9:1) as eluent to give **25** (558 mg, 82%) as a pale yellow oil as a mixture of α/β (63/37) anomers. R_f 0.79 (cyclohexane/ethyl acetate 7:3); ESI-MS: m/z 459 $[M + Na]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (s, 1 Hβ), 8.68 (s, 1 Hα), 7.47−7.28 (m, 10 H), 6.52 (d, J = 3.3 Hz, 1 Hα), 5.70 (d, $J_{1\beta,2\beta}$ = 8.2 Hz, 1 Hβ), 4.99 (d, J = 10.7 Hz, 1 Hα), 4.97 (d, J = 10.8 Hz, 1 Hβ), 4.89 (d, J = 10.8 Hz, 1 Hβ), 4.87 (d, J = 10.7 Hz, 1 Hα), 3.89 (t, J = 9.5 Hz, 1 H-3α), 3.74−3.65 (m, 1 Hα), 3.68 (s, 3 Hβ), 3.61−3.39 (m, 4 H, 1 Hα, 3 Hβ), 3.25 (t, J = 9.3 Hz, 1 Hβ), 3.24 (t, J = 9.5 Hz, 1 Hα), 1.41 (d, J = 6.4 Hz, 3 Hβ), 1.37 (d, J = 6.4 Hz, 3 Hα); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3 (Cα and Cβ), 138.0 (Cα and Cβ),128.6 (2 Cα), 128.4 (2 Cβ), 128.2 (2 Cα), 128.0 (2 Cβ), 127.9 (Cα and Cβ), 97.9 (Cβ), 93.5 (Cα), 83.3 (Cβ), 82.7 (Cβ), 81.8 (Cα), 79.0 (Cα), 77.6 (Cα and Cβ), 75.4 (Cβ), 75.6 (Cα), 71.5 (Cβ), 69.0 (Cα), 67.2 (Cα and Cβ), 60.9 (Cβ), 58.8 (Cα), 18.6 (Cα), 18.5 (Cβ).

Methyl 2-*O*-Acetyl-4-azido-3-*O*-benzyl-4,6-dideoxy-α-D-glucopyranoside (26). To a solution of alcohol **22** (500 mg, 2.04 mmol) and benzyl trichloroacetimidate (570 μL, 3.06 mmol) in a mixture of dry cyclohexane/CH_2Cl_2 (2:1) (21 mL) was added trifluoromethanesulfonic acid (100 μL) under Ar at rt. The reaction mixture was stirred for 2.5 h at rt. The reaction mixture was then filtered through a Celite pad and the filtrate washed with 5% aq $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure, and the resulting crude residue was purified by flash chromatography using cyclohexane/ethyl acetate (9:1) as eluent to give compound **26** (478 mg, 70%) as an oil. R_f 0.64 (cyclohexane/ethyl acetate 7:3); $[\alpha]_D$ +148.3 (c 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.21 (m, 5 H), 4.91−4.85 (m, 3 H), 4.77 (d, J = 11.2 Hz, 1 H), 3.91 (t, J = 9.4 Hz, 1 H-3), 3.65−3.52 (m, 1 H), 3.38 (s, 3 H), 3.35 (dd, J = 3.5 and 9.4 Hz, 1 H), 3.21 (t, J = 9.4 Hz, 1 H), 2.06 (s, 3 H), 1.32 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 138.0, 128.4 (2 C), 127.8 (4 C), 97.0, 78.3, 75.4, 73.7, 68.0, 65.9, 55.2, 20.7, 16.0; HR-ESIMS: m/z Calcd for $C_{16}H_{21}N_3O_5$ $[M + Na]^+$: 358.1374. Found 358.1379.

Methyl 2-*O*-Acetyl-4-azido-3-*O*-benzoyl-4,6-dideoxy-α-D-glucopyranoside (27). To a solution of compound **22** (612 mg, 2.55 mmol) in pyridine (25 mL) at 0 °C was added benzoyl chloride (0.35 mL, 5.10 mmol). The reaction mixture was stirred at rt for 12 h and was then quenched by addition of MeOH. The solvent was evaporated in vacuo, and the residue was dissolved in EtOAc and washed with brine. The organic phase was dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography using cyclohexane/ethyl acetate (6:4) as eluent to give ester **27** (890 mg, quantitative) as a white solid. R_f 0.82 (cyclohexane/ethyl acetate 4:6); $[\alpha]_D$ = +154 (c 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11−7.26 (m, 5 H), 5.66 (t, J = 10.0 Hz, 1 H), 5.00 (dd, J = 3.5 and 10.0 Hz, 1 H), 4.84 (d, J = 3.4 Hz, 1 H), 3.73 (dq, J = 10.0 and 6.2 Hz, 1 H), 3.34 (s, 3 H, OCH_3), 3.31 (t, J = 10.0 Hz, 1 H), 1.88 (s, 3 H), 1.32 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 165.4, 133.4, 129.8, 128.5 (6 C), 96.9, 71.2, 71.0, 66.3, 65.9, 55.2, 20.6, 18.1; HR-ESIMS: m/z Calcd for $C_{16}H_{19}N_3O_6$ $[M + Na]^+$: 372,1172. Found 372.0956.

4-Azido-3-*O*-benzyl-1,2-di-*O*-acetyl-4,6-dideoxy-D-glucopyranoside (28). A solution of methyl glycoside **26** (360 mg, 1.07 mmol) in $Ac_2O/AcOH/H_2SO_4$ (1.41:0.246:0.016 mL) was stirred at rt for 1.5 h. ant then was neutralized upon addition of $NaHCO_3$ at 0 °C. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was dried (Na_2SO_4), filtered, and purified by by flash chromatography using cyclohexane/ethyl acetate (9:1) as eluent to give ester **28** (316 mg, 78%) as a white solid. R_f 0.80 (cyclohexane/ethyl acetate 7:3); α anomer ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.25 (m, 5 H), 6.26 (d, J = 3.7 Hz, 1 H), 5.04 (dd, J = 3.7 and 9.8 Hz, 1 H-2), 4.89 (d, J = 11.2 Hz, 1 H), 4.77 (d, J = 11.2 Hz, 1 H), 3.88 (t, J = 9.8 Hz, 1 H), 3.74 (dq, J = 9.8 and 6.2 Hz, 1 H), 3.24 (t, J = 9.8 Hz, 1 H), 2.15 (s, 3 H), 1.99 (s, 3 H), 1.35 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 169.0, 137.7, 128.5 (2 C), 128.2, 127.9 (2 C), 89.6, 78.0, 75.3, 72.0, 68.9, 67.4, 20.9, 20.6, 18.4; HR-ESIMS: m/z Calcd for $C_{17}H_{21}N_3O_6$ $[M + Na]^+$: 386.1337. Found 386.1328.

2-*O*-Acetyl-4-azido-3-*O*-benzyl-4,6-dideoxy-D-glucopyranose (30). To a solution of compound **28** (242 mg, 0.67 mmol) in dry THF (3 mL) was added benzylamine (80 μL, 0.73 mmol). The reaction mixture was stirred at rt under inert atmosphere overnight and then quenched with 1 N aq HCl. The solvent was evaporated under reduced pressure, and the crude residue was purified by flash chromatography

using cyclohexane/ethyl acetate (7:3) as eluent to provide compound **30** (180 mg, 84%) as a white solid. R_f 0.45 (cyclohexane/ethyl acetate 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.30 (m, 5 H), 5.38 (d, J = 3.6 Hz, 1 H), 4.87 (d, J = 11.2 Hz, 1 H), 4.86 (dd, J = 3.6 and 9.8 Hz, 1 H), 4.77 (d, J = 11.2 Hz, 1 H), 3.96 (t, 1 H, J = 9.8 Hz, 1 H), 3.94−3.85 (m, 1 H), 3.21 (t, 1 H, J = 9.8 Hz, 1 H), 2.08 (s, 3 H), 1.34 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 137.7, 128.5 (2 C), 128.2, 127.9 (2 C), 90.3, 77.8, 75.4, 73.9, 68.0, 66.1, 20.9, 20.9, 18.4; HR-ESIMS: m/z Calcd for $C_{15}H_{19}N_3O_5$ [M + Na]$^+$: 344.1219. Found 344.1222.

2-*O*-Acetyl-4-azido-3-*O*-benzoyl-4,6-dideoxy-D-glucopyranose (31).[16] A solution of compound **27** (880 mg, 2.5 mmol) in Ac_2O/AcOH/H_2SO_4 (14 mL, 14:4:0.1) was stirred at rt for 12 h. NaOAc trihydrate (300 mg) was then added and the solvent was evaporated in vacuo. The residue was dissolved in ethyl acetate and was washed with saturated aq $NaHCO_3$ and brine. The organic phase was then dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue **29** was used in the next step without any further purification. R_f 0.41 (cyclohexane/ethyl acetate 4:6); ESIMS m/z 399.8 [M + Na]$^+$. To a solution of crude residue **29** in dry THF (5 mL) was added benzylamine (300 μL, 2.8 mmol). The reaction mixture was stirred at rt under inert atmosphere for 12 h and then quenched with 38% HCl. The solvent was evaporated under reduced pressure, and the crude residue was purified by flash chromatography using cyclohexane/ethyl acetate (8:2) as eluent to provide compound **31** (461 mg, 54% over two steps) as a mixture of anomers (α/β 60/40), as a white solid. R_f 0.49 and 0.35 (cyclohexane/ethyl acetate 7:3); ESIMS m/z 358.1 [M + Na]$^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10−7.44 (m, 5 H), 5.74 (t, J = 10.0 Hz, 1 Hα), 5.46−5.39 (m, 1 Hα and 1 Hβ), 5.04 (dd, J = 3.6 and 10.0 Hz, 1 Hα), 4.97 (dd, J = 8.2 Hz, J = 10.0 Hz, 1 Hβ), 4.76 (t, J = 8.2 Hz, 1 Hβ), 4.08 (dq, J = 10.0 and 6.2 Hz, 1 Hα), 3.75 (d, J = 8.2 Hz, 1 Hβ), 3.75 (dq, J = 10.0 and 6.2 Hz, 1 Hβ), 3.40 (t, J = 10.0 Hz, 1 Hα), 3.34 (t, J = 10.0 Hz, 1 Hβ), 1.98 (s, 3 Hβ), 1.97 (s, 3 Hα), 1.44 (d, J = 6.2 Hz, 3 Hβ), 1.37 (d, J = 6.2 Hz, 3 Hα); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2 and 170.4 (Cα and Cβ), 165.8 (Cα and Cβ), 133.7, 133.5, 129.9, 128.6 (6 Cα and 6 Cβ), 95.3 (Cβ), 90.5 (Cα); 73.9 (Cβ), 73.4 (Cβ), 71.7 (Cα), 71.3 (Cβ), 70.8 (Cα), 66.5 (Cβ), 66.2 (2 Cα), 20.8 (Cα and Cβ), 18.5 (Cβ), 18.4 (Cα).

2-*O*-Acetyl-4-azido-3-*O*-benzyl-4,6-dideoxy-D-glucopyranosyl Trichloroacetimidate (32). To a solution of **30** (160 mg, 0.50 mmol) in CH_2Cl_2 (2 mL) were added trichloroacetonitrile (1.10 mL, 11 mmol) and DBU (17 μL, 0.12 mmol) dropwise at 0 °C. The mixture was then stirred at rt for 2 h and then concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 2% Et_3N in cyclohexane/ethyl acetate (8:2) as eluent to give **32** (180 mg, 78%) as a pale yellow oil as a mixture of α/β (70/30) anomers. R_f 0.60 (cyclohexane/ethyl acetate 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (s, 1 Hβ), 8.66 (s, 1 Hα), 7.40−7.23 (m, 10 H), 6.48 (d, J = 3.6 Hz, 1 Hα), 5.75 (d, J = 8.3 Hz, 1 Hβ), 5.32 (dd, J = 8.3 and 9.5 Hz, 1 Hβ), 5.07 (dd, J = 3.6 and 9.8 Hz, 1 Hα), 4.92 (d, J = 11.2 Hz, 1 Hα), 4.77 (d, J = 11.6 Hz, 1 Hβ), 4.81 (d, J = 10.7 Hz, 1 Hα), 4.77 (d, J = 10.8 Hz, 1 Hβ), 4.01 (t, J = 9.5 Hz, 1 H-3α), 3.91−3.80 (m, 1 Hα), 3.68 (s, 3 Hβ), 3.56−3.47 (m, 1 Hβ), 3.35 (t, J = 9.5 Hz, 1 Hβ), 3.32 (t, J = 9.5 Hz, 1 Hα), 1.99 and 1.98 (2 s, 3 Hα and 3 Hβ), 1.45 (d, J = 6.2 Hz, 3 Hβ), 1.37 (d, J = 6.2 Hz, 3 Hα); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9 (Cα), 169.0 (Cβ), 161.2 (Cβ), 160.8 (Cα), 137.6 (Cα), 137.5 (Cβ), 128.5−128.0 (5 Cα and 5 Cβ), 95.8 (Cβ), 93.6 (Cα), 81.1 (Cβ), 77.6 (Cα and Cβ), 77.5 (Cα), 75.3 (Cα), 74.9 (Cβ), 73.1 (Cα), 72.0 (Cβ), 71.9 (Cβ), 69.2 (Cα), 67.3 (Cα and Cβ), 20.8 (Cβ), 20.6 (Cα), 18.5 (Cα and Cβ); HR-ESIMS: m/z Calcd for $C_{17}H_{19}Cl_3N_4O_5$ [M + Na]$^+$: 487.0316. Found 487.0319.

2-*O*-Acetyl-4-azido-3-*O*-benzoyl-4,6-dideoxy-D-glucopyranosyl Trichloroacetimidate (33).[16] To a solution of **31** (923 mg, 2.7 mmol) in CH_2Cl_2 (5 mL) were added trichloroacetonitrile (5.4 mL, 54 mmol) and DBU (100 μL, 0.7 mmol) dropwise at 0 °C. The mixture was then stirred at rt for 2 h and then concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 2% Et_3N in cyclohexane/ethyl acetate (8:2) as eluent to give **33** (906 mg, 70%) as a pale yellow oil as a mixture of α/β (15/1) anomers. R_f 0.55 (cyclohexane/ethyl acetate 7:3); ESI-MS m/z 501.0 [M + Na]$^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ (α isomer) 8.68 (s, 1 Hα), 8.04−7.37 (m, 5 H) 6.50 (d, J = 3.7 Hz, 1 H), 5.79 (t, J = 10.1 Hz, 1 H), 5.24 (dd, J = 3.7 and 10.1 Hz,1 H), 4.01 (dq, J = 6.0 and 10.1 Hz, 1 H), 3.46 (t, J = 10.1 Hz, 1 H), 1.88 (s, 3 H), 1.40 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 165.4, 160.9, 133.6 (2 C), 129.6 (2 C), 128.6 (2 C), 93.3, 71.9, 70.2, 69.1, 65.8, 20.4, 18.3.

2-[(*N*-Benzyloxycarbonyl)amino]ethyl L-Rhamnopyranoside (34). To a mixture of L-rhamnose (10.0 g, 61 mmol) and 2-[(*N*-benzyloxycarbonyl)amino]ethanol (17.0 g, 102 mmol) in toluene (100 mL) was added a catalytic amount of *p*-toluenesulfonic acid (200 mg, 1.2 mmol), and the mixture was heated to reflux overnight. The reaction mixture was cooled, neutralized with Et_3N, and then concentrated in vacuo. The residue was purified by flash chromatography on silica gel using CH_2Cl_2−MeOH (98:2) as eluent to give a 5/1 mixture of *N*-(benzyloxycarbonyl)aminoethyl L-rhamnopyranoside **34** (12.8 g, 64%) as a 5/1 α/β anomeric mixture, as a pale yellow oil. R_f 0.22 (α) and 0.29 (β) (CH_2Cl_2:MeOH 9:1); ^{1}H NMR (300 MHz, MeOD) δ (α isomer) 7.38−7.31 (m, 5 H), 5.10 (br s, 2 H), 4.71 (d, J = 1.8 Hz, 1 H), 3.85 (dd, J = 1.8 and 3.6 Hz, 1 H), 3.79−3.72 (m, 1 H), 3.70 (dd, J = 3.6 and 9.5 Hz, 1 H-3), 3.65−3.58 (m, 1 H), 3.54−3.47 (m, 1 H), 3.41 (t, 1H, J = 9.5 Hz, 1 H), 3.37−3.32 (m, 2 H), 1.28 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, MeOD) δ (α isomer) 157.6, 136.9, 128.1, 127.6, 127.4, 100.3, 72.6, 71.1, 70.8, 68.5, 66.1, 66.0, 40.3, 16.7; HR-MS (ESI) m/z Calcd for $C_{16}H_{23}NO_7$ [M + Na]$^+$: 364.1383. Found 364.1378.

2-[(*N*-Benzyloxycarbonyl)amino]ethyl 3-*O*-(3-Methoxy)-benzyl-α-L-rhamnopyranoside (35). A suspension of compound **34** (852 mg, 2.5 mmol) and dibutyltin oxide (622 mg, 2.5 mmol) were heated at relux in dry MeOH (26 mL) for 5 h, evaporated under reduced pressure, and further dried in vacuo for 2 h. To the crude residue diluted in dry DMF (7 mL) was added *p*-methoxybenzyl bromide (420 μL, 3 mmol). After 5 h, the reaction mixture was concentrated under reduced pressure, and the crude residue was purified by flash chromatography on silica gel using cyclohexane/ethyl acetate 4:6 to 3:7 as eluent to give compound **35** (600 mg, 54%). R_f 0.2 (cyclohexane/ethyl acetate 4:6); $[\alpha]_D$ = −21.3 (c 0.5, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.31 (m, 5 H), 7.28 (d, J = 8.8 Hz, 2 H), 6.87 (d, J = 8.8 Hz, 2 H), 5.34 (br s, 1 H), 5.12 (br s, 2 H), 4.78 (br s, 1 H), 4.59−4.54 (d, 1 H, J = 11.2 Hz, 1 H), 4.50−4.49 (d, J = 11.2 Hz, 1 H), 3.95 (br s, 1 H), 3.78 (s, 3 H), 3.79−3.53 (m, 4 H), 3.53−3.30 (m, 3 H), 1.28 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 156.5, 144.0 (2 C), 136.5, 129.9, 129.7 (2 C), 128.6 (2 C), 128.2 (2 C), 99.6, 79.4, 71.5 (2 C), 68.3, 67.9, 66.8, 66.7, 55.3, 40.8, 17.7; HR-MS (ESI) m/z Calcd for $C_{24}H_{31}NO_8$ [M + Na]$^+$: 484.1947. Found 484.1942.

2-[(*N,N'*-Benzyl-benzyloxycarbonyl)amino]ethyl 2,4-Di-*O*-benzyl-3-*O*-(3-methoxy)benzyl-α-L-rhamnopyranoside (36). To a solution of **35** (580 mg, 1.3 mmol) in DMF (20 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 301 mg, 7.6 mmol) followed by dropwise addition of benzyl bromide (540 μL, 4.5 mmol). The reaction mixture was stirred at rt for 2 h, and the excess of NaH was neutralized by dropwise addition of MeOH (5 mL) at 0 °C. The mixture was concentrated in vacuo, and the residue was purified by flash chromatography using (cyclohexane/ethyl acetate 9:1) as eluent to give compound **36** (610 mg, 64%) as a pale yellow oil and mixture of conformers. R_f 0.33 (cyclohexane/ethyl acetate 8:2); $[\alpha]_D$ = −15.6 (c 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48−6.88 (m, 24 H), 5.26−5.23 (m, 2 H), 5.03 (d, J = 11.0 Hz, 41 H), 4.85−4.79 and 4.73−4.69 (m, 4 H), 4.65−4.47 (m, 4 H), 3.89−3.80 (m, 2 H), 3.78 (s, 3 H), 3.76−3.74 (m, 1 H), 3.72−3.64 (m, 2 H), 3.62−3.54 (m, 1 H),

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3.52−3.35 (m, 2 H), 1.38−1.34 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3 and 156.0 (1 C), 159.0, 138.6, 138.3, 137.7, 136.5, 130.4, 129.4, 129.1, 128.4, 128.2, 127.8, 127.7, 127.5, 127.3, 127.2, 127.1, 113.7, 98.0 and 97.7 (1 C), 80.3, 79.2, 75.2, 74.9, 72.7, 71.5, 68.1, 67.2, 65.7 and 65.2 (1 C), 55.0, 51.6, and 51.4 (1 C), 46.7 and 45.7 (1 C), 17.9; HR-MS (ESI) m/z Calcd for $C_{45}H_{49}NO_8$ $[M + Na]^+$: 754.3356. Found 754.3331.

2-[(*N,N*′-Benzyl-benzyloxycarbonyl)amino]ethyl 2,4-Di-*O*-benzyl-α-L-rhamnopyranoside (37). To a solution of derivative **36** (610 mg, 0.83 mmol) in a mixture of CH_2Cl_2 (14 mL) and H_2O (1 mL) was added DDQ (216 mg, 1.91 mmol) at 0 °C. After the mixture was stirred 30 min at this temperature, the reaction mixture was warmed to rt and stirred overnight. The mixture was then diluted with CH_2Cl_2 and quenched with Na_2CO_3. The layers were separated, and the organic phase was washed with satd aq Na_2CO_3, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was then purified by flash chromatography on silica gel using (cyclohexane/ethyl acetate 8:2) as eluent to provide alcohol **37** (350 mg, 69%) as a colorless oil (mixture of conformers). R_f 0.52 (cyclohexane/ethyl acetate 7:3); $[\alpha]_D$ = −4.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.18 (m, 20 H), 5.21−5.19 (m, 2 H), 4.91 (d, *J* = 10.9 Hz, 1 H), 4.83 (br s, 0.5 H), 4.75−4.49 (m, 5.5 H), 3.92−3.89 (m, 1 H), 3.85−3.73 (m, 1 H), 3.73−3.51 (m, 2 H), 3.65 (dd, *J* = 1.5 and 3.7 Hz, 1 H), 3.51−3.34 (m, 2 H), 3.32 (t, 1 H, *J* = 9.2 Hz, 1 H), 2.24 (br s, 1 H), 1.37−1.23 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6 and 156.4 (1 C), 138.6, 137.8, 136.7, 131.0, 128.5, 128.1, 128.0, 127.9, 127.8, 127.3, 97.2 and 96.8 (1 C), 82.3, 78.6, 75.2, 73.2 and 73.1 (1 C), 71.7, 67.4 (2 C), 66.0 and 65.5 (1 C), 51.8 and 51.7 (1 C), 46.8 and 46.0 (1 C), 18.1; HR-MS (ESI) m/z Calcd for $C_{37}H_{41}NO_7$ $[M + Na]^+$: 634.2781. Found 634.2780.

2-[(*N,N*-Benzyl-benzyloxycarbonyl)amino]ethyl *O*-(2-*O*-Acetyl-4-azido-3-*O*-benzyl-4,6-dideoxy-α-D-glucopyranosyl)-(1→3)-2,4-di-*O*-benzyl-α-L-rhamnopyranoside (38). To a solution of trichloroacetimide **32** (230 mg, 0.49 mmol), alcohol **37** (253 mg, 0.41 mmol), and 4 Å molecular sieves (200 mg) in dry CH_2Cl_2 (10 mL) under inert atmosphere at −40 °C was added TMSOTf (52 μL, 0.29 mmol). After the mixture was stirred 30 min at this temperature, the reaction mixture was neutralized by Et_3N and filtered. The filtrate was washed with water, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography using cyclohexane/ethyl acetate (8:2) as eluent to give disaccharide **38** (257 mg, 68%) as a white powder (mixture of conformers). R_f 0.54 (cyclohexane/ethyl acetate 7:3); $[\alpha]_D$ = −2.4 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.15 (m, 25 H), 5.24−5.21 (m, 2 H), 5.18 (dd, *J* = 7.9 and 9.5 Hz, 1 H), 4.90−4.83 (m, 3 H), 4.80−4.50 (m, 7 H), 4.10−4.01 (m, 1 H), 3.86−3.82 (m, 1 H), 3.82−3.17 (m, 7 H), 3.15−3.04 (m, 2 H), 1.86 (s, 3 H), 1.32−1.27 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 156.5, and 156.1 (1 C), 138.7, 138.3, 137.8, 137.7, 137.4, 136.6, 128.6, 128.5, 128.2, 128.1, 128.0, 127.8, 127.5, 127.2, 101.3, 98.8 and 98.7 (1 C), 81.4, 80.3, 79.5 and 79.4 (1 C), 78.0, 74.9 (2 C), 73.4 (2 C), 70.7, 68.1, 67.7, 67.3, 65.8 and 65.6 (1 C), 51.6 and 51.5 (1 C), 46.6 and 45.6 (1 C), 20.9, 18.4, 17.9; HR-MS (ESI) m/z Calcd for $C_{52}H_{58}N_4O_{11}$ $[M + Na]^+$: 937.4000. Found 937.3981.

2-[(*N,N*′-Benzyl-benzyloxycarbonyl)amino]ethyl *O*-(4-Azido-3-*O*-benzyl-4,6-dideoxy-α-D-glucopyranosyl)-(1→3)-2,4-di-*O*-benzyl-α-L-rhamnopyranoside (39). Compound **38** (257 g, 0.28 mmol) was treated by NaOMe (0.2 M solution in MeOH) (2.8 mL, 0.56 mmol) for 12 h at rt. The reaction mixture was then neutralized by resin Amberlite IR120 H^+. The resin was filtered off, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography on silica gel using cyclohexane/ethyl acetate (8:2) as eluent to give alcohol **39** (187 mg, 75%) as a white powder (mixture of conformers). R_f 0.48 (cyclohexane/ethyl acetate 7:3); $[\alpha]_D$ = +4 (*c* 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48−7.20 (m, 25 H), 5.19−5.16 (m, 2 H), 4.93 (d, *J* = 10.9 Hz, 1 H), 4.90−4.83 (m, 3 H), 4.75−4.39 (m, 6 H), 4.04−3.95 (m, 1 H), 3.80 (dd, *J* = 1.9 and 3.0 Hz, 1 H), 3.77−3.30 (m, 8 H), 3.13 (t, *J* = 9.6 Hz, 1 H), 3.25−3.10 (m, 1 H), 2.69 (br s, 1 H), 1.35−1.25 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5 and 156.3 (1 C), 138.6, 138.1, 138.0, 137.8, 136.6, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.8, 127.6, 127.5, 127.3, 104.0, 98.7 and 98.5 (1 C), 82.3, 80.6, 80.1, 77.7, 75.7, 75.5, 74.9, 73.4, 70.8, 68.3, 67.4, 67.2, 65.8 and 65.6 (1 C), 51.6, 46.7 and 45.7 (1 C), 18.7 and 18.2 (1 C); HR-MS (ESI) m/z Calcd for $C_{50}H_{56}N_4O_{10}$ $[M + Na]^+$: 895.3894. Found 895.3871.

2-[(*N,N*′-Benzyl-benzyloxycarbonyl)amino]ethyl *O*-(4-Azido-3-*O*-benzyl-4,6-dideoxy-2-*O*-methyl-α-D-glucopyranosyl)-(1→3)-2,4-di-*O*-benzyl-α-L-rhamnopyranoside (40). To a solution of alcohol **39** (185 mg, 0.21 mmol) in DMF was added NaH (60% dispersion in mineral oil, 12 mg, 0.31 mmol) at 0 °C, followed by dropwise addition of MeI (44 μL, 0.72 mmol). The reaction mixture was stirred at rt overnight, and the excess of NaH was neutralized by dropwise addition of methanol (20 mL) at 0 °C. The mixture was then evaporated to dryness, and the residue was purified by flash chromatography on silica gel using cyclohexane/ethyl acetate (9:1) as eluent to give compound **40** (118 mg, 62%) as a colorless oil (mixture of conformers). R_f 0.56 (cyclohexane/ethyl acetate 8:2); $[\alpha]_D$ = +2.7 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.05 (m, 25 H), 5.08−5.06 (m, 2 H), 4.92 (d, *J* = 10.6 Hz, 1 H), 4.83 (d, *J* = 10.6 Hz, 1 H), 4.73 (d, *J* = 10.6 Hz, 2 H), 4.67−4.34 (m, 6 H), 3.98−3.90 (m, 1 H), 3.71 (dd, *J* = 1.8 and 3.1 Hz, 1 H), 3.58 (s, 3 H), 3.77−3.30 (m, 3 H), 3.49−3.20 (m, 4 H), 3.07 (t, *J* = 8.4 Hz, 1 H), 3.04−2.99 (m, 2 H), 1.22−1.14 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5 and 156.2 (1 C), 137.8, 136.7, 128.7, 128.5, 128.4, 128.3, 128.0, 127.9, 127.6, 103.7, 98.8 and 98.7 (1 C), 84.9, 82.8, 80.8, 78.8, 78.6, 75.5, 75.0, 72.9, 70.3, 68.1, 67.8, 67.4, 66.0 and 65.8 (1 C), 60.9, 51.7 and 51.6 (1 C), 46.7 and 45.7 (1 C), 18.6, 18.0; HR-MS (ESI) m/z Calcd for $C_{51}H_{58}N_4O_{10}$ $[M + Na]^+$: 909.4051. Found 909.4058.

2-[(*N,N*′-Benzyl-benzyloxycarbonyl)amino]ethyl *O*-[3-*O*-Benzyl-4-(3-hydroxy-3-methylbutanamido)-4,6-dideoxy-2-*O*-methyl-α-D-glucopyranosyl]-(1→3)-2,4-di-*O*-benzyl-α-L-rhamnopyranoside (41). To a solution of azide 40 (118 mg, 0.13 mmol) in a mixture of CH_2Cl_2 (2.5 mL) and EtOH (10 mL) were added sodium borohydride (8 mg, 0.21 mmol) and a catalytic amount of $NiCl_2 \cdot 6H_2O$. The reaction mixture was stirred at rt for 1 h and then was concentrated in vacuo. The residue was dissolved in CH_2Cl_2. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to provide an amine intermediate which was used in the next step without purification. R_f 0.29 (cyclohexane/ethyl acetate 7:3); MS (ESI) m/z 883.4 $[M + Na]^+$. To a solution of crude amine (112 mg, 0.13 mmol) in dry DMF (10 mL) was added dropwise 3-hydroxy-3-methylbutanoic acid (20 μL, 0.16 mmol), followed by HOBt (22 mg, 0.16 mmol), by HATU (63 mg, 0.16 mmol), and then by DIPEA (27 μL, 0.16 mmol). The reaction mixture was stirred under argon at rt for 18 h, diluted with CH_2Cl_2, and washed with satd aq $NaHCO_3$ and water. The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using cyclohexane/ethyl acetate (6:4) as eluent to provide intermediate **41** (57 mg, 55% over two steps) as a colorless oil (mixture of conformers). R_f 0.42 (cyclohexane/ethyl acetate 5:5); $[\alpha]_D$ = +32.2 (*c* 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.04 (m, 25 H), 5.71 (br s, 1 H), 5.08−5.06 (m, 2 H), 4.93 (d, *J* = 10.3 Hz, 1 H), 4.79 (m, *J* = 11.6 Hz, 1 H), 4.77 (d, *J* = 10.6 Hz, 2 H) 4.67−4.36 (m, 7 H), 3.98−3.91 (m, 1 H), 3.79−3.49 (m, 6 H), 3.58 (s, 3 H), 3.49−3.10 (m, 6 H), 2.18−2.04 (m, 2 H), 1.28−1.18 (m, 3 H), 1.14 (s, 3 H), 1.12 (s, 3 H), 1.07−1.02 (br d, *J* = 4.0 Hz 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 156.5, 138.8, 138.6, 138.5, 137.7, 136.6, 129.6, 128.6, 128.5, 128.4, 128.3, 127.9, 127.8, 127.6, 103.9, 98.9, and 98.7 (1 C), 85.0, 80.6, 80.3, 79.2 and 79.1 (1 C), 78.5, 74.9, 73.9, 73.6, 70.9, 69.5, 68.2, 67.3, 65.9, and 65.8 (1 C), 60.7, 51.7 and 51.6 (1 C), 47.8,

46.6, and 45.7 (1 C), 29.5 and 29.4 (1 C), 18.2, 18.0; HR-MS (ESI) *m*/*z* Calcd for $C_{56}H_{68}N_2O_{12}$ $[M + Na]^+$: 983.4670. Found 983.4656.

2-Aminoethyl *O*-[4,6-Dideoxy-4-(3-hydroxy-3-methylbutanamido)-2-*O*-methyl-α-D-glucopyranosyl]-(1→3)-α-L-rhamnopyranoside (42). Compound **41** (57 mg, 0.06 mmol) in EtOH/AcOH (6 mL/2 mL) was treated with a catalytic amount of a $Pd(OH)_2$ under 10 bar of hydrogen at 50 °C for 30 min. The reaction mixture was then concentrated in vacuo. The residue was dissolved in H_2O (10 mL) and was washed with CH_2Cl_2 (2 × 5 mL). The organic layer was extracted with water (5 × 10 mL). The aqueous phases were combined and concentrated under vacuum. The crude was then purified by RP-HPLC [on an C18 5 μm (250 × 22 mm) column, with detection at 215 nm, at a 22 mL/min flow rate and a gradient of 0% B during 5 min, 0 to 100% solvent B over 25 min, 100% B, 5 min (eluent A: 0.05% TFA in H_2O; eluent B: 0.05% TFA in CH_3CN:H_2O 60:40)] to give compound **42** (11 mg, 91%) as a white solid after lyophilization. $[\alpha]_D$ = +6 (*c* 0.3, $CHCl_3$); ^1H NMR (600 MHz, D_2O) δ 4.85 (d, *J* = 1.7 Hz, 1 H), 4.77 (d, *J* = 8.0 Hz, 1 H), 4.20 (dd, *J* = 1.8 and 3.1 Hz, 1 H), 4.01−3.97 (m, 1 H), 3.95 (dd, *J* = 3.1 and 9.2 Hz, 1 H), 3.75−3.69 (m, 2 H), 3.66−3.62 (m, 2 H) 3.65 (s, 3 H), 3.59−3.53 (m, 2 H), 3.32−3.24 (m, 1 H), 3.23−3.21 (m, 1 H), 3.15 (dd, *J* = 8.0 and 9.2 Hz, 1 H), 2.41 (d, *J* = 13.4 Hz, 1 H), 2.39 (d, *J* = 13.4 Hz, 1 H), 1.33 (s, 3 H), 1.33 (d, *J* = 6.2 Hz, 1 H), 1.32 (s, 3 H), 1.16 (d, *J* = 5.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 103.6, 99.7, 83.3, 79.3, 72.7, 71.2, 70.8, 70.2, 69.7, 69.0, 63.3, 60.0, 56.6, 48.9, 39.0, 28.3, 28.1, 17.1, 16.6; HR-ESIMS: *m*/*z* Calcd for $C_{20}H_{38}N_2O_{10}$ $[M + H]^+$: 467.2605. Found 467.2590.

■ ASSOCIATED CONTENT

Supporting Information. Spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) Borio, L.; Frank, D.; Mani, V.; Chiriboga, C.; Pollanen, M.; Ripple, M.; Ali, S.; DiAngelo, C.; Lee, J.; Arden, J.; Titus, J.; Fowler, D.; O'Toole, T.; Masur, H.; Bartlett, J.; Inglesby, T. *JAMA, J. Am. Med. Assoc.* **2001**, *286*, 2554–2559.

(2) Daubenspeck, J. M.; Zeng, H.; Chen, P.; Dong, S.; Steichen, C. T.; Krishna, N. R.; Pritchard, D. G.; Turnbough, C. L., Jr. *J. Biol. Chem.* **2004**, *279*, 30945–30953.

(3) Dong, S.; McPherson, S. A.; Tan, L.; Chesnokova, O. N.; Turnbough, C. L., Jr.; Pritchard, D. G. *J. Bacteriol.* **2008**, *190*, 2350–2359.

(4) Saksena, R.; Adamo, R.; Kovàč, P. *Carbohydr. Res.* **2005**, *340*, 1591–1600.

(5) Werz, D. B.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 6315–6318.

(6) Adamo, R.; Saksena, R.; Kovàč, P. *Carbohydr. Res.* **2005**, *340*, 2579–2582.

(7) Saksena, R.; Adamo, R.; Kovàč, P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 615–617.

(8) Mehta, A. S.; Saile, E.; Zhong, W.; Buskas, T.; Carlson, R.; Kannenberg, E.; Reed, Y.; Quinn, C. P.; Boons, G.-J. *Chem., Eur. J.* **2006**, *12*, 9136–9149.

(9) Werz, D. B.; Adibekian, A.; Seeberger, P. H. *Eur. J. Org. Chem.* **2007**, 1976–1982.

(10) Saksena, R.; Adamo, R.; Kovàč, P. *Bioorg. Med. Chem.* **2007**, *15*, 4283–4310.

(11) Saksena, R.; Adamo, R.; Kovàč, P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 615–617.

(12) Crich, D.; Vinogradova, O. *J. Org. Chem.* **2007**, *72*, 6513–6520.

(13) Dhenin, S. G. Y.; Moreau, V.; Morel, N.; Nevers, M.-C.; Volland, H.; Créminon, C.; Djedaïni-Pilard, F. *Carbohydr. Res.* **2008**, *343*, 2101–2110.

(14) Guo, H.; O'Doherty, G. A. *Angew. Chem.* **2007**, *46*, 5206–5208.

(15) Guo, H.; O'Doherty, G. A. *J. Org. Chem.* **2008**, *73*, 5211–5220.

(16) Dhenin, S. G. Y.; Moreau, V.; Nevers, M.-C.; Créminon, C.; Djedaïni-Pilard, F. *Org. Biomol. Chem.* **2009**, *7*, 5184–5199.

(17) Kubler-Kielb, J.; Vinogradov, E.; Hu, H.; Leppla, S. H.; Robbins, J. B.; Schneerson, R. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 8709–8712.

(18) Tamborrini, M.; Werz, D. B.; Frey, J.; Pluschke, G.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 6581–6582.

(19) Wang, D.; Caroll, G. T.; Turro, N. J.; Koberstein, J. T.; Kovàč, P.; Saksena, R.; Adamo, R.; Herzenberg, L. A.; Herzenberg, L. A.; Steinman, L. *Proteomics* **2007**, *7*, 180–184.

(20) Parthasarathy, N.; Saksena, R.; Kovàč, P.; DeShazer, D.; Peacock, S. J.; Wuthiekanun, V.; Heine, H. S.; Friedlander, A. M.; Cote, C. K.; Welkos, S. L.; Adamovucz, J. J.; Bavari, S.; Waag, D. M. *Carbohydr. Res.* **2008**, *343*, 2783–2788.

(21) Tamborrini, M.; Oberli, M. A.; Werz, D. B.; Schürch, N.; Frey, J.; Seeberger, P. H.; Pluschke, G. *J. Appl. Microbiol.* **2009**, *106*, 1618–1628.

(22) Cybulski, R. J., Jr.; Snaz, P.; O'Brien, A. D. *Mol. Aspects Med.* **2009**, *30*, 490–502.

(23) Hou, S.; Kovàč, P. *Eur. J. Org. Chem.* **2008**, 1947–1952.

(24) (a) Lohray, B. B. *Synthesis* **1992**, 1035–1052. (b) Moon, H. R.; Kim, H. O.; Chun, M. W.; Jeong, L. S. *J. Org. Chem.* **1999**, *64*, 4733–4741.

(25) (a) Byun, H.-S.; He, L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7071–7091. (b) Fuentes, J.; Angulo, M.; Pradera, M. A. *J. Org. Chem.* **2002**, *67*, 2577–2587.

(26) Guiller, A.; Gagnieu, C. H.; Pacheco, H. *Tetrahedron Lett.* **1985**, *26*, 6343–6344.

(27) Gagnieu, C. H.; Guiller, A.; Pacheco, H. *Carbohydr. Res.* **1988**, *180*, 223–231.

(28) For a representative example of anomeric controlled nucleophilic substitution, see: Grandjean, C.; Lukacs, G. *J. Carbohydr. Chem.*, **1996**, *15*, 831−855.

(29) Sanders, W. J.; Kiessling, L. L. *Tetrahedron Lett.* **1994**, *35*, 7335–7338.

(30) Sanders, W. J.; Manning, D. D.; Koeller, K. M.; Kiessling, L. L. *Tetrahedron* **1997**, *53*, 16391–16422.

(31) Kajihara, Y.; Endo, T.; Ogasawara, H.; Kodama, H.; Hashimoto, H. *Carbohydr. Res.* **1995**, *269*, 273–294.

(32) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21–123.

(33) Guiller, A.; Gagnieu, C. H.; Pacheco, H. *Tetrahedron Lett.* **1985**, *26*, 6067–6070.

(34) For some representative examples, see: (a) Fraser-Reid, B.; Udodong, U. E.; Wu, Z.; Ottosson, H.; Meritt, R. J.; Rao, S. C.; Roberts, C.; Madsen, R. *Synlett* **1992**, 927–942. (b) Hotha, S.; Kashyap, S. *J. Am. Chem. Soc.* **2006**, *128*, 9620–9621. (c) Kuroiwa, Y.; Sekine, M.; Tomono, S.; Takahashi, D.; Toshima, K. *Tetrahedron Lett.* **2010**, *51*, 6294–6297. (d) Wang, Y.; Zhang, X.; Wang, P. *Org. Biomol. Chem.* **2010**, *8*, 4322–4328.

(35) Given the a priori facile access to alkyl cyclic sulfite α-D-fucopyranosides, the substitution was not tested on intermediate **5b** as a model compound.

(36) Kim, Y.-J.; Wang, P.; Navarro-Villalobos, M.; Rohde, B. D.; DerryBerry, J. M.; Gin, D. Y. *J. Am. Chem. Soc.* **2006**, *128*, 11906–11915.
(37) For comparison, that the 3,4-cyclic sulfite could be prepared from thionyl chloride in an almost quantitative yield under the same conditions underscores the deactivating effect of a postulated 2-chlorosulfonate intermediate.
(38) (a) Sharpless, K. B.; Carlsen, H. J.; Katsuki, T.; Martin, V. S. *J. Org. Chem.* **1981**, *46*, 3936–3938. (b) Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 655–659.
(39) Elchert, B.; Li, J.; Wang, J.; Hui, Y.; Rai, R.; Ptak, R.; Ward, P.; Takemoto, J. Y.; Bensaci, M.; Chang, C.—W. T. *J. Org. Chem.* **2004**, *69*, 1513–1523.
(40) Iversen, T.; Bundle, D. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240–1241.
(41) Banaszek, A.; Zaitsev, V. *Tetrahedron: Asymmetry* **2004**, *15*, 299–306.
(42) Liu, M.; Yu, B.; Wu, X.; Hui, Y.; Fung, K.-P. *Carbohydr. Res.* **2000**, *329*, 745–754.