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A Stereochemical Surprise at the Late Stage of the Synthesis of Fully *N*-Differentiated Heparin Oligosaccharides Containing Amino, Acetamido, and *N*-Sulfonate Groups

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The glucosamine residues in heparin-like glycosaminoglycans have been found to exist as amines, acetamides, and *N*-sulfonates. To develop a completely general, modular synthesis of heparin, three degrees of orthogonal nitrogen protection are required. Reported herein is a strategy for the synthesis of fully *N*-differentiated heparin oligosaccharides in the context of target octasaccharide **1**, which contains an *N*-acetate, *N*-sulfonates, and a free amine. The protecting group scheme used in the synthesis blocked the *N*-acetate as a *N*-diacetate, the *N*-sulfonates as azido groups, and the amine as a *N*-CBz; free hydroxyls were masked as benzyl ethers and *O*-sulfonates as acetate esters. Disaccharide and tetrasaccharide modules were synthesized using this strategy; however, the union of tetrasaccharide trichloroacetimidate **4** with disaccharide acceptor **5** unexpectedly formed the undesired β-linked glycoside in addition to the α-linkage anticipated for iduronic acid nucleophiles, resulting in an inseparable 6:1 α/β mixture of products. Detailed studies into the basis for this unexpected result were conducted and are also reported.

Heparin-like glycosaminoglycans (HLGAGs) are a class of polysaccharides found protein-conjugated in the extracellular matrix and free in the circulatory system. HLGAGs are involved in an array of signaling functions, including regulation of the coagulation cascade, growth factor interactions, and viral entry into cells.[1] Heparin fractions isolated from animal sources are used clinically as anticoagulants,[2,3] and several synthetic analogues of heparin have been prepared as anticoagulant drug candidates.[4−7]

HLGAGs consist of alternating 1,2-anti-(1→4) linked uronic acid residues and α-(1→4)-linked glucosamine residues. The polysaccharides exist in a wide variety of *O*-and *N*-sulfonated as well as *N*-acetylated states with a high sequence variability. Due to both the high structural complexity and the difficulty of isolating homogeneous structures from natural sources, heparin is an ideal target for a modular synthetic method. Defined sequences of heparin are needed for biological study, and the ability to generate diverse libraries of heparin would greatly facilitate studies into the structure−activity relationship of HLGAGs. The direct study of heparin biochemistry and the development of HLGAG analytical techniques would benefit from the availability of defined sequences. No completely general method for the production of heparin oligosaccharides exists, and substantial synthetic challenges remain to be overcome.[8]

Recent reports describe fully differentiated monosaccharide building blocks for HLGAG synthesis.[9−15] Several sequences have been produced, including oligomers of the fibroblast growth factor (FGF) disaccharide repeat[16−22]

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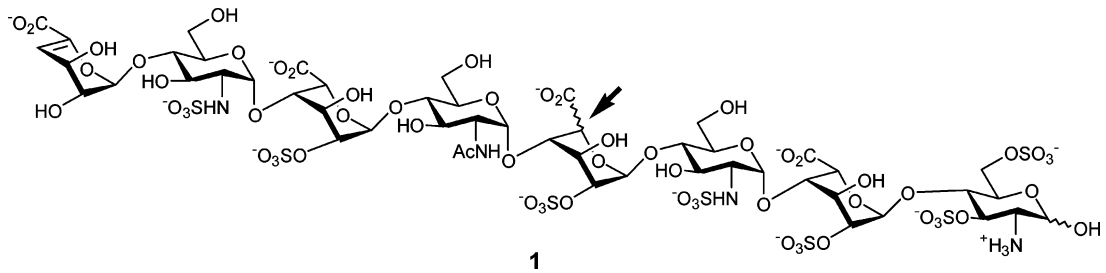

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FIGURE 1. Target structure as reported from sequencing studies.[33] The stereochemistry at the indicated site is unknown. Counterions after oligosaccharide purification are primarily sodium.

and several variants and analogues of the antithrombin III (ATIII) binding structure.[12,23−28] The amine group has been masked as an azide in most heparin syntheses to date, allowing access to only poly-*N*-sulfonated structures. One synthesis of the ATIII binding sequence included a nonreducing end GlcNAc residue, but the method used was not general and the use of the *N*-acetate as the protecting group resulted in poor coupling yields.[27]

2-Azidoglucosyl trichloroacetimidates or halides frequently serve as glycosylating agents to install α-glucosamine linkages. These reagents have shown high α-selectivity when coupled to the C4 hydroxyl group of iduronic acid but afford mixtures of products when coupled to glucuronic acid.[24,26,29] In our recent synthesis of a ATIII-binding hexasaccharide,[12] all α-glucosamine linkages were formed with complete selectivity during the assembly of disaccharide modules via glycosylation of conformationally constrained 1,2-*O*-isopropylidene-iduronic or glucuronic acids with 2-azidoglucosyl trichloroacetimidates.[30]

The HLGAG octasaccharide **1** is known to bind viral coat proteins on herpes simplex virus 1 (HSV-1) and is thought to be involved in viral cell entry.[31,32] On the basis of sequencing efforts that combine enzymatic degradation and mass spectrometry, two possible structures (Figure 1) have been proposed for the herpes-binding sequence.[33] The isolated structures contained 4,5-dehydrouronic acids at the nonreducing end and at the indicated site as a result of the degradation techniques used. The structure contains *N*-sulfonates, an *N*-acetate, and a free amine.

This report describes a strategy for the synthesis of *N*-differentiated heparin oligosaccharides en route to fully protected target **2** (Figure 2). Iduronic acid was selected arbitrarily in the two uronic acid positions of unknown stereochemistry to reduce the complexity of the synthetic target. As in previous heparin syntheses, *O*-sulfonates were masked as *O*-acetates, free hydroxyls as *O*-benzyl ethers, carboxylic acids as methyl esters, and *N*-sulfonates as azide groups.[12,16−27] An *N*-diacetate marked the position of *N*-acetate[34,35] while the free amine was masked as the benzyl carbamate (CBz). These protecting groups would allow for the deprotection and elaboration of **2** through a modification of previously established heparin deprotection protocols.[12,16,18,20,21,24−26,36] All *O*-acetates and methyl esters, as well as one of the *N*-diacetate amides, will be removed using LiOOH/NaOH. Selective reduction of the azides could be achieved by Staudinger, thiol, SmI_2, or a variety of other selective reduction chemistries.[37] Sulfonation of all hydroxyls and amines with $SO_3{\cdot}NEt_3$, followed by Pd/C reductive removal of benzyl ethers and the CBz carbamate, would reveal the fully deprotected and elaborated structure.

Results and Discussion

Fully protected octasaccharide **2** was the proposed target en route to the HSV-1 binding octasaccharide **1**. Retrosynthetic analysis of **2** revealed that two disaccharides (**3**, **5**) and one tetrasaccharide (**4**) would provide the key modules based on the assumption that 2-azido glucosamines can be coupled to iduronic acid residues with complete α-stereoselectivity.[7,12,16,17,30,38−42] Intermediates **3**−**5** can be readily assembled from five previously reported monosaccharide modules: iduronic acid derivatives **6**, **8**, and **9**[14] and $GlcN_3$ derivatives **7**[12] and **10**.

Synthesis of Nonreducing End Disaccahride Trichloroacetimidate 3. Disaccharide **3** was synthe-

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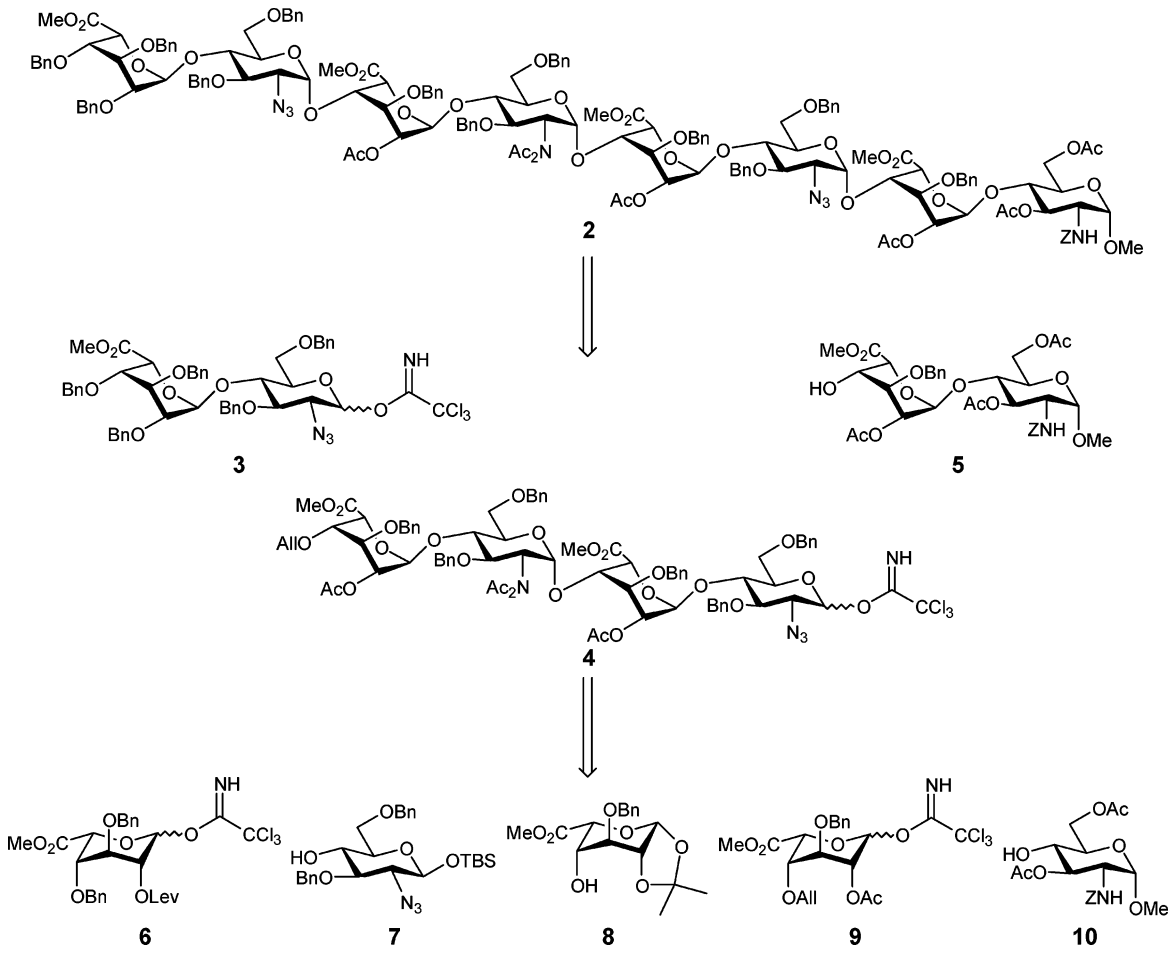
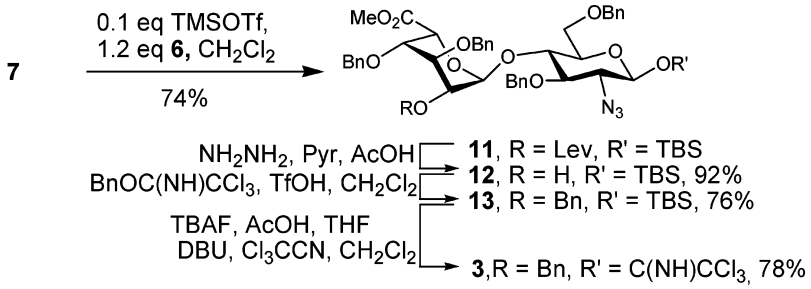


FIGURE 2. Retrosynthetic analysis.

SCHEME 1



sized by coupling iduronic acid trichloroacetimidate **6** and glucosamine azide **7** to yield the desired disaccharide **11** in 74% yield (Scheme 1). Removal of the levulinic (Lev) ester with hydrazine proceeded in 92% yield to give **12**. This product was converted to its benzyl ether **13** in 76% yield using benzyl trichloroacetimidate and trifluoromethanesulfonic acid (TfOH) activator. Cleavage of the anomeric silyl ether with TBAF/AcOH, followed by reaction with DBU/Cl_3CCN, yielded 78% of trichloroacetimidate disaccharide building block **3**.

Synthesis of Tetrasaccharide Trichloroacetimidate 4. Synthesis of the central tetrasaccharide **4** presented more of a challenge (Scheme 2). Iduronic acid donor **9** and $GlcN_3$ derivative **7** were coupled through TMSOTf activation in 88% yield. Conversion of the product disaccharide **14** into glycosyl trichloroacetimidate **15** was accomplished by cleavage of the TBDMS group followed by reaction with DBU/Cl_3CCN (96% yield for two steps). Union of **15** with iduronic acid derivative **8** afforded trisaccharide **16** with complete α-selectivity in 83% yield.

Conversion of the azide moiety in trisaccharide **16** to an *N*-acetate was accomplished in one pot and 84% yield by treatment with thiolacetic acid in pyridine.[43] Removal

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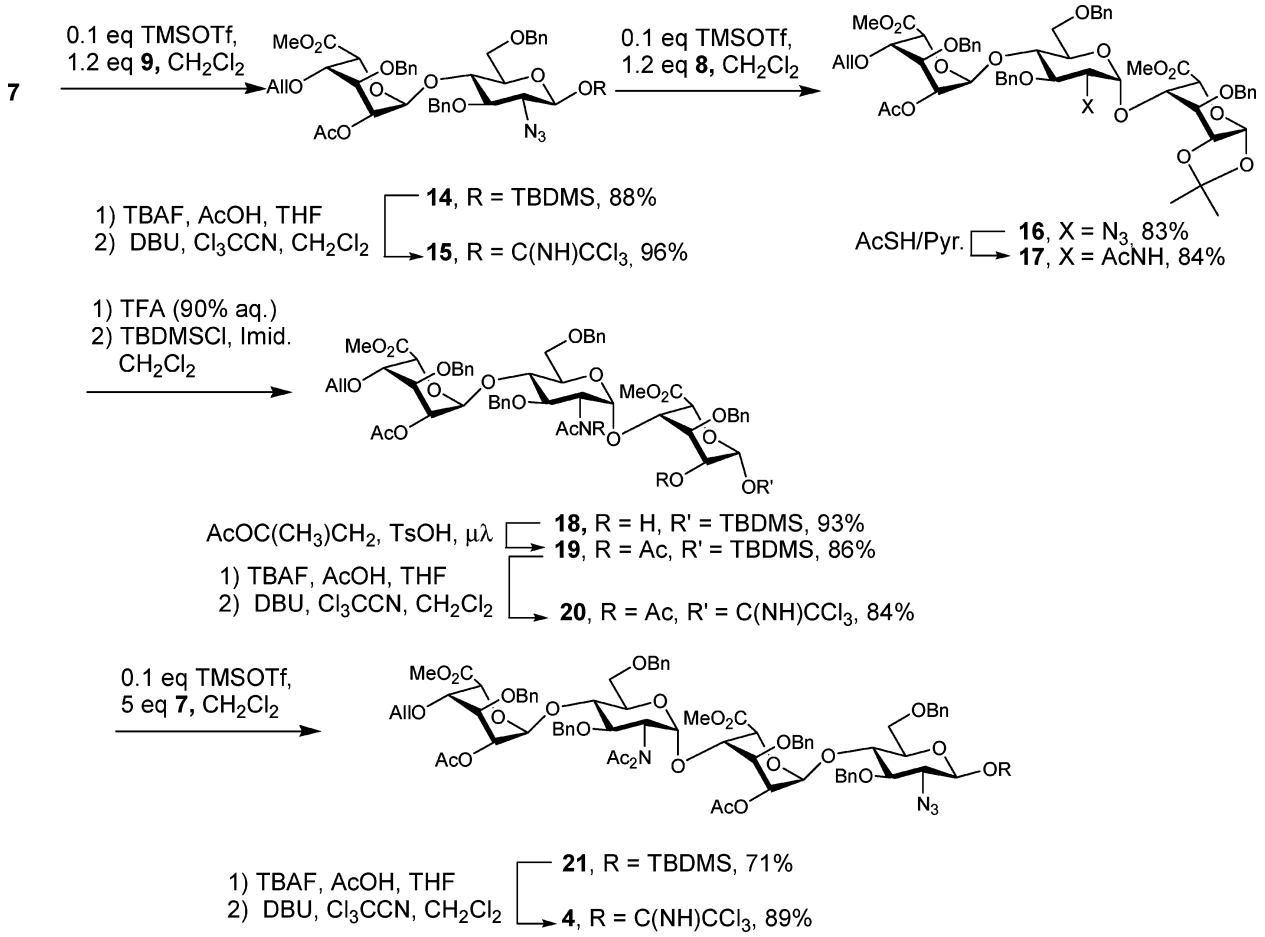
SCHEME 2



SCHEME 3

of the isopropylidene group from product trisaccharide **17** with trifluoroacetic acid followed by selective silyl ether formation at the anomeric hydroxyl group[38] furnished **18** in a 93% yield. Microwave irradiation of **18** in isopropenyl acetate with catalytic *p*-toluenesulfonic acid[35] simultaneously installed the desired *N*-diacetate and acetylated the free hydroxyl, forming **19** in 86% yield. This transformation could not be achieved under a variety of thermal conditions, with only poor yields of **19** achieved even after several days. Conversion of **19** to trisaccharide trichloroacetimidate building block **20** was achieved in 84% yield by cleavage of the TBDMS ether and reaction with DBU/Cl_3CCN.

Glycosylating agent **20** coupled only poorly with 2-azidoglucose **7** in the presence of catalytic TMSOTf, with mainly hydrolyzed trisaccharide lactol formed instead. Use of a large excess (5 equiv) of **7** resulted in a 71% conversion to **21**; most unreacted **7** could be recovered and recycled. Tetrasaccharide **21** was converted to glycosyl trichloroacetimidate **4** in 89% yield.

Synthesis of Reducing End Disaccharides 5 and 30. The reducing end disaccharide **5** was synthesized from known 2-*N*-CBz glucosamine **22** (Scheme 3).[44] Selective acetylation of the primary hydroxyl with acetyl chloride in 2,4,6-collidine afforded acceptor **10** in 82% yield.[45] Glucosamine **10** reacted with iduronic acid donor **9** under TMSOTf activation to form disaccharide **23** in highly variable yields. Close monitoring by TLC revealed that **10** was rapidly consumed to form ortho ester **24** that was identified by ^{1}H NMR (Figure 3). When left under reaction conditions for several hours, **24** rearranged to the desired disaccharide **23**. Rearrangement and hydrolysis of the ortho ester intermediate was highly

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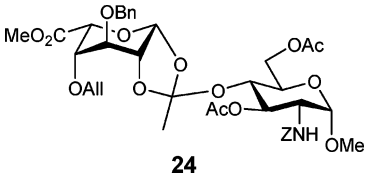

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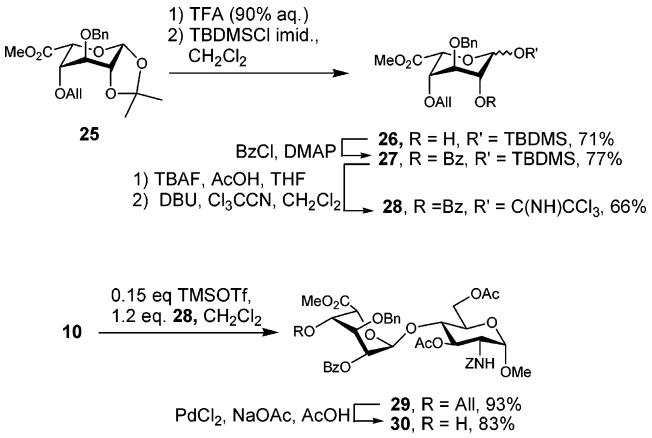
FIGURE 3. Ortho ester byproduct.

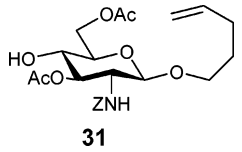
SCHEME 4



sensitive to the reaction conditions and resulted in the variability in yield of desired disaccharide **23**.

While sufficient quantities of **5** could be produced via $PdCl_2$-catalyzed allyl ether removal from disaccharide **23**, an alternate reducing end disaccharide was also prepared (Scheme 4). Synthesis of iduronic acid **28** followed established procedures,[14] with the exception of the use of a C-2 benzoate ester, which was included to reduce ortho ester formation. Glycosylating agent **28** reacted cleanly with the CBz glucosamine derivative **10** to give **29** in excellent yield. No ortho ester intermediate was observed. This disaccharide was treated with $PdCl_2$/NaOAc in acetic acid and water to afford disaccharide **30** in 83% yield.

The replacement of a C2 acetate to a C2 benzoate group dramatically improved the yield of this coupling reaction. Interestingly, glycosylating agent **9** containing a C2 acetate and the *N*-CBz glucosamine *n*-pentenyl glycoside **31** (Figure 4) coupled in high yield without the formation of ortho ester (data not shown). All other couplings of iduronic acid donors reported here proceed in good yields to 1-*O*-TBDMS ether β-glucosamines. On the basis of these and previous[12] observations, it appears that the stereoelectronics of α-glucosamine acceptors negatively influence the outcome of coupling reactions with uronic acid trichloroacetimidates, greatly favoring ortho ester



31

FIGURE 4. Glucosamine CBz acceptor.

formation. Use of a C2 benzoate protecting group can overcome this effect.

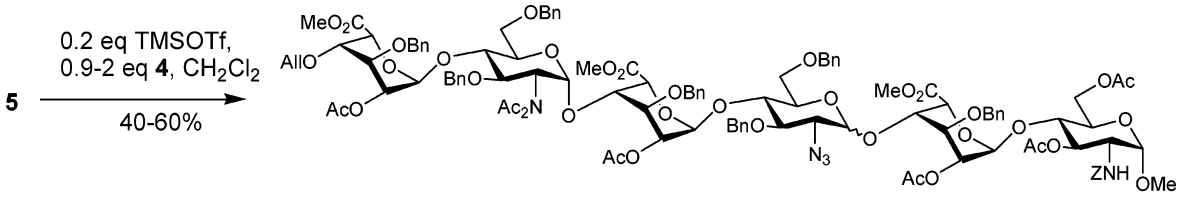
Attempted Block Coupling of Tetrasaccharide 4 with Reducing End Disaccharides 5 and 30. With compounds **3**, **4**, and **5** as well as alternate reducing end acceptor **30** in hand, assembly of the fully protected target **2** was attempted (Scheme 5). Coupling of **4** and **5** under TMSOTf activation proceeded in 59% yield when reacted at −40 °C in the presence of molecular sieves. Although the desired α-linked hexasaccharide **32** was obtained as the major product, it was contaminated with 17% of an inseparable impurity. Even after purification via normal- and reversed-phase silica gel HPLC and size-exclusion chromatography (Bio-rad Bio-Beads), some of the contaminant always remained.

Varying the reaction conditions for coupling **4** and **5** did not prevent formation of the minor product. Variation of reaction temperature (from −78 to 0 °C) and activator (TMSOTf and TBSOTf) affected the coupling yields, but the isolated product always contained the minor product (data not shown). Varying the polarity of the reaction solvent through addition of heptanes had no effect on the ratio of the products.

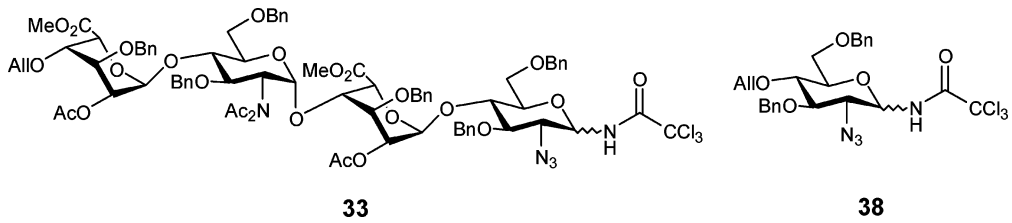
Removal of the allyl protecting group through treatment of the mixture with $PdCl_2$/NaOAc in acetic acid and water and further coupling with disaccharide **3** to form the octasaccharide **2** did not allow for the separation of the minor product at this later stage of the synthesis. Spectral data indicated that the major isomer did react as desired, but a minor product copurified at each step, suggesting that the contaminant reacted similarly. Finally, coupling of tetrasaccharide **4** with disaccharide **30** under the best conditions found for the coupling with **5** resulted in the formation of a 1:1 mixture of inseparable products (data not shown).

To identify the minor product contaminating **32**, possible reaction byproducts were systematically eliminated. Size-exclusion purification ruled out any decomposition products of **5**. Small amounts of hydrolyzed **4** were detected and separated from the products through silica gel chromatography. Tetrasaccharide **33**, formed by rearrangement of **4**, was also observed in the crude reaction mixture but could be readily separated from product **2** (Figure 5). Acetylation, *N*-diacetylation, and silylation to

SCHEME 5



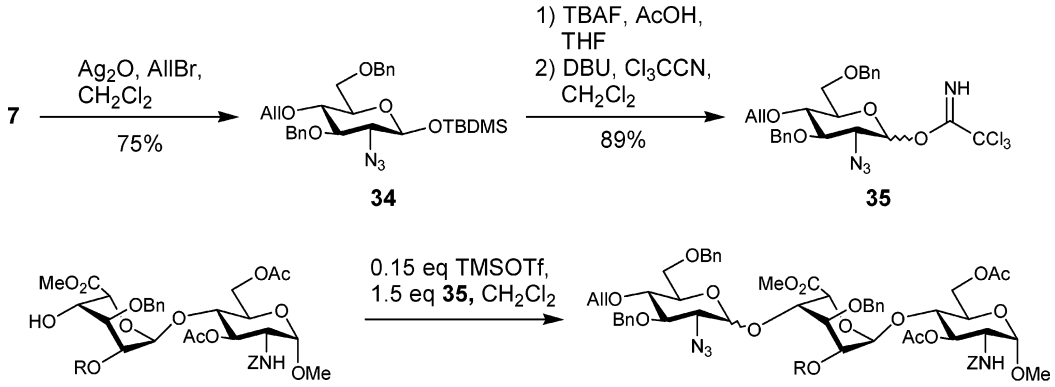
32, ~6:1 mixture of isomers



33 **38**

FIGURE 5. Rearranged glycosyl donors.

SCHEME 6



5, R = Ac
30, R = Bz

36, R = Ac, >20:1 α:β
37, R = Bz, 5:1 α:β

cap potentially rearranged tetrasaccharides containing a free hydroxyl group or an *N*-acetamide resulted in reisolated **32** that contained the same contaminant in an unchanged ratio.

On the basis of these observations, the minor product was likely an isomer of the desired hexasaccharide. Two major possibilities exist: either acceptor **5** rearranged under the reaction conditions to result in 1→2-linked hexasaccharide or an α/*β* mixture of 1→4-linked isomers was being produced. Treatment of acceptors **5** and **30** under coupling conditions in the absence of a glycosylating agent resulted exclusively in the reisolation of unchanged starting materials. Thus, the formation of 1→2-linked regioisomer hexasaccharide could be ruled out. In direct contrast to previous reports,[7,12,16−17,30,38−42] the coupling of a 2-azido glucosamine donor and the C4 hydroxyl group of iduronic acid seemed to produce an anomeric mixture of products.

Examination of Model Trisaccharides 36 and 37. Since a detailed NMR analysis of the hexasaccharide mixture was difficult due to the large number of overlapping signals, a simplified model system was devised (Scheme 6). Allylation of **7** using silver oxide and allyl bromide furnished glucosamine **34** in 75% yield. Conversion of **34** to trichloroacetimidate **35** was achieved in 89% yield. Reaction of monosaccharide trichloroacetimidate **35** with **5** and **30** yielded trisaccharides **36** and **37**, respectively. The structure of rearranged glycosylating agent **38** (Figure 5) was confirmed by 2-D NMR experiments. Trisaccharide **36** contained less than 5% of a contaminating product, while trisaccharide **37** was isolated as a 5:1 mixture. Detailed analysis of **37** of by NMR and mass spectrometry identified an apparent mixture of trisaccharide isomers. Carbon−proton correlation spectroscopy (HSQC, Figure 6) showed that one anomeric cross-peak of the minor isomer was consistent with a *β*-GlcN_3 anomeric cross-peak.[46−48]

These observation indicate that the erosion of anomeric selectivity is dependent both on the size of the glycosylating agent and on the exact nature of the nucleophile. The conformation of uronic acid acceptors has a profound influence on the anomeric selectivity of couplings involving such monomers,[30] whereby the $^1C_4$ conformation normally adopted by iduronic acid derivatives overwhelmingly favors α-products. This selectivity has also been observed for oligosaccharides containing an iduronic acid at the nonreducing end.

In the case described here, we hypothesize the selectivity is eroded due to an altered conformation of the iduronic acid. The 2-*N*-CBz glucosamine residue connected to the anomeric position of the iduronic acid is the major difference between acceptor **5** and previously described, α-selective iduronic acid disaccharide acceptors. The nitrogen protecting group used to differentiate the glucosamine may be responsible for loss of selectivity in the union of **4** and **5**. Presumably the iduronic acid acceptor is forced out of the $^1C_4$ conformation that appears to allow 2-azido glucosyl trichloroacetimidates to react with complete α-selectivity. The loss of selectivity was apparently exacerbated by the change of the C2 protecting group from acetate to the sterically bulkier benzoate. The C2 substituent is placed axial when the

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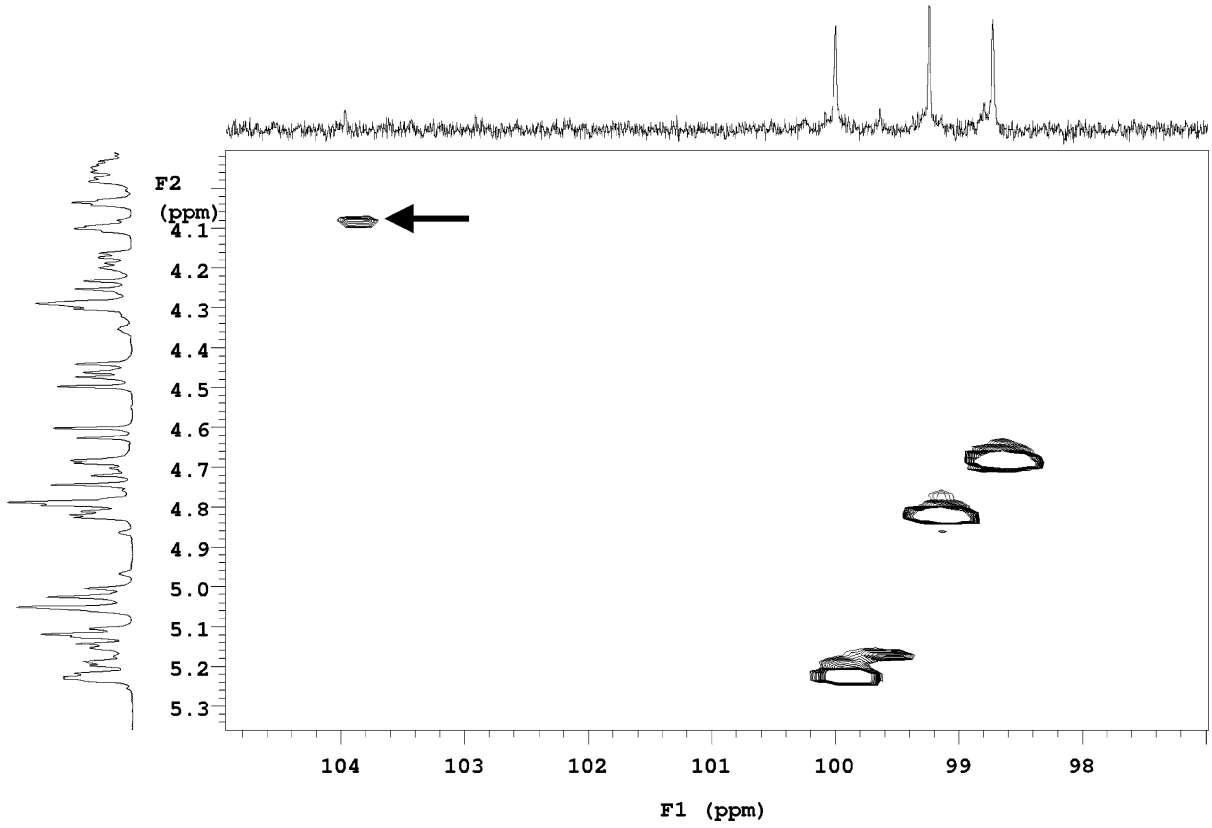

FIGURE 6. HSQC spectrum of the anomeric region of trisaccharide **37**. The indicated cross-peak arises from the minor isomer and is consistent with a β-glucosamine H1−C1 cross-peak.

sugar ring is in the $^1C_4$ conformation; thus, larger susbstituents likely favor the $^4C_1$ conformation.

Due to the loss of selectivity in this block coupling, and the difficulties encountered with purification, it was judged that the proposed strategy was not useful for producing the target octasaccharide. It is becoming increasingly clear that the coupling of larger oligosaccharide building blocks in the synthesis of heparin-like glycosaminoglycans is greatly influenced by the conformation of the nucleophile. The loss of selectivity in these couplings is a significant obstacle to the general synthesis of HLGAGs. A systematic reevaluation of the protecting group and anomeric leaving group chemistries used in heparin synthesis will greatly facilitate further work on the assembly of larger structures using the modular approach.

Experimental Section

***tert*-Butyldimethylsilyl (Methyl 3,4-di-*O*-benzyl-2-*O*-levonuyl-α-L-idopyranosiduronate)-(1→4)-2-azido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (11).** Trichloroacetimidate **6**[14] (220 mg, 0.349 mmol) and monosaccharide **7**[12] (145 mg, 0.29 mmol) were coevaporated three times with anhydrous toluene. The compounds were dissolved in anhydrous CH_2Cl_2 (3 mL) under N_2 and cooled to −15 °C. Trimethylsilyl trifluoromethanesulfonate (7.5 μL, 0.042 mmol) was added, and the reaction mixture was stirred for 45 min. The reaction was quenched by addition of NEt_3 (0.2 mL), and the solvent was removed under reduced pressure. Flash chromatography on silica (hexanes/ethyl acetate 17:3) afforded recovered **7** (13 mg, 0.026 mmol, 9%). Further elution (hexanes/ethyl acetate 3:1) yielded **11** (208 mg, 0.215 mmol, 74%) as a clear oil: R_f 0.13 (hexanes/ethyl acetate 3:1); $[\alpha]^{24}_D$ −28.3, c = 0.9; IR (thin film, NaCl plates) 2928, 2110, 1745, 1739, 1721 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22−7.39 (m, 20H), 5.31 (d, J = 3.6 Hz, 1H), 4.91 (t, J = 3.6 Hz, 1H), 4.81 (d, J = 3.6 Hz, 1H), 4.69−4.75 (m, 3H), 4.43−4.60 (m, 6H), 4.02 (t, J = 9.3 Hz, 1H), 3.87 (t, J = 4.1, 1H), 3.81 (t, J = 3.9 Hz, 1H), 3.70−3.71 (m, 2H), 3.44 (s, 3H), 3.38 (m, 1H), 3.35 (d^2, J = 7.5 Hz, 10 Hz, 1H), 3.26 (t, J = 4.5 Hz, 1H), 2.63 (m, 2H), 2.46 (m, 2H), 2.12 (s, 3H), 0.94 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.4, 172.1, 169.8, 138.5, 138.4, 137.9, 137.8, 128.6, 128.5, 128.4, 128.3, 128.1, 128.07, 128.04, 128.0, 127.7, 127.6, 127.4, 97.8, 97.4, 81.0, 75.4, 75.0, 74.9, 74.7, 73.6, 73.4, 73.6, 73.4, 72.9, 72.7, 69.6, 69.3, 68.8, 68.4, 51.9, 37.9, 30.0, 28.1, 25.8, 10.2, −4.0, −5.0; ESI MS ($C_{52}H_{65}N_3O_{13}$-Si) m/z (M + Na$^+$) calcd 990.4179, obsd 990.4145.

***tert*-Butyldimethylsilyl (Methyl 3,4-di-*O*-benzyl-α-L-idopyranosiduronate)-(1→4)-2-azido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (12).** Disaccharide **11** (176 mg, 0.182 mmol) was dissolved in pyridine (550 μL) and acetic acid (360 μL). Hydrazine hydrate (44 μL, 0.91 mmol) was added, and the reaction mixture was stirred for 1 h. The reaction was quenched by addition of acetone (5 mL) and the mixture stirred for 30 min. The solution was poured into ethyl acetate (50 mL) and washed with 1 N HCl, brine, and saturated $NaHCO_3$. The organic phase was dried over $MgSO_4$, and solvent was removed under reduced pressure. Flash chromatography on silica (hexanes/ethyl acetate 17:3) afforded **12** (145 mg, 0.167 mmol, 92%) as a clear oil: R_f 0.21 (hexanes/ethyl acetate 3:1); $[\alpha]^{24}_D$ −47.6, c = 0.8; IR (thin film, NaCl plates) 3495, 2929, 2857, 2109, 1776, 1742, 839 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21−7.4 (m, 20H), 5.23 (d, J = 1.5 Hz, 1H), 4.90 (d, J = 2.3 Hz, 1H), 4.45−4.71 (m, 9H), 3.98 (ψt, J = 9.4 1H), 3.83−3.87 (m, 2H), 3.67−3.72 (m, 3H), 3.43 (d, J = 10.9 Hz, 1H), 3.35−3.4 (m, 2H), 3.36 (s, 3H), 3.22 (ψt, J = 9.5 Hz, 1H), 0.94 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 138.5, 138.1, 137.9, 136.9, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 127.9, 127.4, 101.1, 97.6, 81.2, 75.5, 75.0, 74.3,

73.3, 73.2, 72.3, 68.9, 68.2, 67.2, 52.0, 25.7, 18.2, −4.0, −5.0; ESI MS ($C_{47}H_{59}N_3O_{11}Si$) *m/z* (M + Na^+) calcd 892.3811, obsd 892.3829.

***tert*-Butyldimethylsilyl (Methyl 2,3,4-tri-*O*-benzyl-α-L-idopyranosiduronate)-(1→4)-2-azido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (13).** Disaccharide **12** (125 mg, 0.144 mmol) was coevaporated three times with anhydrous toluene and dissolved in anhydrous hexanes (1.4 mL) and a minimum amount of anhydrous CH_2Cl_2 to dissolve the compound. Benzyl trichloroacetimidate (54 μL, 0.288 mmol) was added, followed by one drop (∼1 μL) of triflic acid. After 90 min, the solution was filtered to remove the precipitated trichloroacetamide, and the solvent was removed under reduced pressure. Flash chromatography on silica (hexanes/ethyl acetate 9:1) yielded **13** (105 mg, 0.109 mmol, 76%) as a clear oil: R_f 0.53 (hexanes/ethyl acetate 3:1); $[\alpha]^{24}_D$ −20.1, *c* = 0.7; IR (thin film, NaCl plates) 2928, 2110, 1741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24−7.37 (m, 25H, aryl H), 5.40 (d, $^3J_{H1-H2}$ = 6.4, 1H, IdoA H1), 4.85 (d, ^2J = 10.7 Hz, 1H, benzyl CH_2), 4.73 (d, ^2J = 11.2 Hz, 1H, benzyl CH_2), 4.72 (m, 1H, benzyl CH_2), 4.71 (m, 1H, benzyl CH_2), 4.70 (m, 1H, benzyl CH_2), 4.68 (d, ^2J = 11.5 Hz, 1H, benzyl CH_2), 4.64 (d, ^2J = 11.6 Hz, 1H, benzyl CH_2), 4.60 (d, ^2J = 11.6 Hz, 1H, benzyl CH_2), 4.58 (d, $^3J_{H4-H5}$ = 5.8, 1H, IdoA H4), 4.54 (d, ^2J = 12.4 Hz, 1H, benzyl CH_2), 4.47 (d, $^3J_{H1-H2}$ = 7.4 Hz, 1H, $GlcN_3$ H1), 4.45 (d, ^2J = 12.4 Hz, 1H, benzyl CH_2), 3.98 (m, 1H, $GlcN_3$ H4), 3.96 (m, 1H, IdoA H3), 3.81 (d², $^3J_{H3-H4}$ = 7.4, $^3J_{H4-H5}$ = 5.8, 1H, IdoA H4), 3.71 (d², ^2J = 10.7 Hz, $^3J_{H5-H6}$ = 4.3 Hz, 1H, $GlcN_3$ H6), 3.66 (d², ^2J = 10.7 Hz, $^3J_{H5-H6'}$ = 1.7 Hz, 1H, $GlcN_3$ H6′), 3.53 (s, 3H, OCH_3), 3.37 (d², $^3J_{H1-H2}$ = 6.4, $^3J_{H2-H3}$ = 7.5, 1H, IdoA H2), 3.34 (m, 1H, $GlcN_3$ H5), 3.31 (m, 1H $GlcN_3$ H2), 3.29 (m, 1H, $GlcN_3$ H3), 0.95 (s, 9H, TBS *tert*-butyl), 0.16 (s, 3H, TBS methyl), 0.14 (s, 3H, TBS methyl); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0 (IdoA C6), 138.6 (benzyl quat), 138.5 (benzyl quat), 138.4 (benzyl quat), 137.9 (benzyl quat), 128.6 (aromatic C), 128.55 (aromatic C), 128.5 (aromatic C), 128.4 (aromatic C), 128.3 (aromatic C), 128.25 (aromatic C), 128.15 (aromatic C), 128.1 (aromatic C), 128.05 (aromatic C), 128.0 (aromatic C), 127.9 (aromatic C), 127.8 (aromatic C), 127.7 (aromatic C), 127.65 (aromatic C), 127.5 (aromatic C), 100.0 (IdoA C1), 97.3 ($GlcN_3$ C1), 81.1 ($GlcN_3$ C2), 80.6 (IdoA C2), 79.0 (IdoA C3), 77.2 (IdoA C4), 75.9 ($GlcN_3$ C4), 75.5 ($GlcN_3$ C3), 75.0 (benzyl CH_2), 74.9 (benzyl CH_2), 74.6 (benzyl CH_2), 73.4 (benzyl CH_2), 73.35 (benzyl CH_2), 72.0 (IdoA C5), 68.6 ($GlcN_3$ C51), 68.3 ($GlcN_3$ C6), 52.0 (OCH_3), 25.8 (TBS *tert*-butyl CH_3), 18.2 (TBS *tert*-butyl quat), −4.0 (TBS methyl CH_3), −5.0 (TBS methyl CH_3); ESI MS ($C_{54}H_{65}N_3O_{11}Si$) *m/z* (M + Na^+) calcd 982.4281, obsd 982.4250.

Methyl 2,3,4-Tri-*O*-benzyl-α-L-idopyranosiduronate-(1→4)-2-azido-3,6-di-*O*-benzyl-2-deoxy-D-glucopyranoside Trichloroacetimidate (3). Disaccharide **13** (30 mg, 31 μmol) was coevaporated three times with anhydrous toluene and dissolved in anhydrous THF (500 μL). The solution was cooled to 0 °C, and acetic acid (2 μL, 35 μmol) was added followed by TBAF (34 μL, 1.0 M in THF). After 1 h, the reaction was poured into ethyl acetate (100 mL) and washed twice with brine. The organic phase was dried over $MgSO_4$, and the solvent was removed under reduced pressure.

The residue was coevaporated three times with anhydrous toluene and dissolved in anhydrous CH_2Cl_2 (500 μL) under N_2. The solution was cooled to 0 °C, and trichloroacetonitrile (47 μL, 0.47 mmol) and DBU (0.5 μL, 3 μmol) were added. The reaction mixture was stirred for 30 min and then allowed to warm to room temperature. The solvent was evaporated, and the residue was purified by flash chromatography on silica (toluene/ethyl acetate 9:1) afforded **3** (24 mg, 24 μmol, 78%, 1.5:1 α/β) as a yellow oil: R_f 0.57, 0.63 (hexanes/ethyl acetate 2:1); IR (thin film, NaCl plates) 3030, 2918, 2112, 1761, 1739, 1674 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.70 (s, 0.4H), 8.69 (s, 0.6H), 7.12−7.39 (m, 25H), 6.38 (d, *J* = 3.5 Hz, 0.6H), 5.6 (d, *J* = 8.4 Hz, 0.4H), 5.44−5.50 (m, 1H), 5.03 (d, *J* = 10.3 Hz, 0.6H), 4.92 (d, *J* = 10.7 Hz, 0.4 H), 4.70−4.78 (m, 5H), 4.63−4.67 (m, 2H), 4.51−4.6 (m, 2H), 4.47 (d, *J* = 12.2 Hz, 0.4H), 4.42 (d, *J* = 12.0 Hz, 0.6H), 4.24 (t, *J* = 9.6 Hz, 0.6H), 4.13 (t, *J* = 9.3 Hz, 0.4 H), 3.91−4.04 (m, 3H), 3.76−3.84 (m, 2H), 3.65−3.71 (m, 1H), 3.35−3.56 (m 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 170.5, 161.8, 161.3, 139.0, 138.9, 138.85, 138.8, 138.75, 138.7, 138.6, 138.35, 138.30, 129.6, 129.4, 129.15, 129.11, 129.1, 129.07, 129.05, 129.03, 128.9, 128.89, 128.87, 128.85, 128.65, 128.63, 128.60, 128.58, 128.57, 128.55, 128.4, 128.35, 128.1, 100.6, 100.5, 97.4, 15.5, 91.7, 81.75, 81.7, 81.0, 79.9, 79.6, 78.8, 78.1, 77.0, 76.4, 75.9, 75.85, 75.8, 75.7, 75.4, 75.35, 75.1, 74.4, 74.0, 73.9, 73.8, 72.7, 68.0, 67.8, 65.9, 63.1, 52.5, 52.4; MS ($C_{50}H_{51}Cl_3N_4O_{11}$) *m/z* (M + Na^+) calcd 1011.2518, obsd 1011.2507.

***tert*-Butyldimethylsilyl (Methyl 2-*O*-acetyl-4-*O*-allyl-3-*O*-benzyl-α-L-idopyranosiduronate)-(1→4)-2-azido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (14).** Trichloroacetimidate **9**[14] (62 mg, 0.118 mmol) and monosaccharide **7**[12] (40 mg, 0.079 mmol) were combined and coevaporated three times with anhydrous toluene. The mixture was dissolved in anhydrous CH_2Cl_2 (1 mL) under N_2 and cooled to −15 °C. Trimethylsilyl trifluoromethanesulfonate (130 μL of a 0.1 M solution in CH_2Cl_2) was added and the reaction mixture stirred for 30 min at reduced temperature and then allowed to warm to room temperature over 30 min. The reaction was quenched with NEt_3 (0.2 mL), and the solvent was removed under reduced pressure. Flash chromatography on silica (hexanes/ethyl acetate 17:3) afforded **14** (60 mg, 0.070 mmol, 88%) as a clear oil: R_f 0.28 (hexanes/ethyl acetate 3:1); $[\alpha]^{24}_D$ −35.3, *c* = 0.62; IR (thin film, NaCl plates) 2926, 2110, 1764, 1741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24−7.39 (m, 15H, aromatics), 5.76 (m, 1H, allyl OCH_2CH=CH_2), 5.30 (d, $^3J_{H1-H2}$ = 3.5 Hz, 1H, IdoA H1), 5.17 (d³, *J* = 17.4, 3 Hz, ^4J = 1.6 Hz, 1H, allyl OCH_2HCH=CHH), 5.13 (d³, *J* = 10.4, 3 Hz, ^4J = 1.1 Hz), 4.89 (ψt, *J* = 3.8 Hz, 1H, IdoA H2), 4.79 (d, $^3J_{H5-H4}$ = 3.8 Hz, 1H, IdoA H5), 4.76 (d, ^2J = 11.1 Hz, 1H, $GlcN_3O3$ benzyl CH_2), 4.73 (d, ^2J = 11.7 Hz, 1H, IdoA O3 benzyl CH_2), 4.71 (d, ^2J = 11.1 Hz, 1H, $GlcN_3O3$ benzyl CH_2), 4.68 (d, ^2J = 11.7 Hz, 1H, IdoA O3 benzyl CH_2), 4.60 (d, ^2J = 12.3 Hz, 1H, $GlcN_3O6$ benzyl CH_2), 4.55 (d, ^2J = 12.3 Hz, 1H, $GlcN_3O6$ benzyl CH_2), 4.49 (d, $^3J_{H1-H2}$ = 7.5 Hz, 1H $GlcN_3$ H1), 3.99 (m, 1H, allyl $OCHHCH$=CH_2), 3.98 (m, 1H, $GlcN_3$ H4), 3.93 (d²ψt, *J* = 1.4 Hz, 5.8 Hz, 12.8 Hz, 1H, allyl $OCHHCH$=CH_2), 3.84 (ψt, *J* = 4.6 Hz, 1H, IdoA H3), 3.74 (ψt, *J* = 4.2, 1H, IdoA H4), 3.68 (m, 2H, $GlcN_3$ H6), 3.51 (s, 3H, $-OCH_3$), 3.37 (m, 1H, $GlcN_3$ H5), 3.35 (m, 1H $GlcN_3$ H2), 3.27 (d², ^3J = 9 Hz, 9.8 Hz, $GlcN_3$ H3), 1.99 (s, 3H, acetate CH_3), 0.96 (s, 9H, TBDMS *tert*-butyl), 0.16 (s, 3H, TBDMS methyl), 0.14 (s, 3H, TBDMS methyl); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3 (acetate carbonyl), 169.8 (IdoA C6), 138.5 ($GlcN_3$ O3 benzyl CH_2), 138.3 ($GlcN_3O6$ benzyl quat), 137.9 (IdoA O3 benzyl quat), 134.4 (allyl OCH_2CH=CH_2), 128.6 (aromatic C), 128.5 (aromatic C), 128.3 (aromatic C), 128.1 (aromatic C), 128.05 (aromatic C), 127.8 (aromatic C), 127.7 (aromatic C), 127.6 (aromatic C), 127.5 (aromatic C), 117.6 (allyl OCH_2CH=CH_2), 98.0 (IdoA C1), 97.4 ($GlcN_3$ C1), 81.1 ($GlcN_3$ C3), 75.4 ($GlcN_3$ C5), 75.1 ($GlcN_3$ C4), 75.1 (IdoA C4), 74.8 ($GlcN_3$ O3 benzyl CH_2), 73.9 (IdoA C3), 73.5 ($GlcN_3$-O6 benzyl CH_2), 73.1 (IdoA O3 benzyl CH_2), 71.8 (allyl OCH_2-CH=CH_2), 69.7 (IdoA C5), 69.4 (IdoA C2), 68.8 ($GlcN_3$ C2), 68.5 ($GlcN_3$ C6), 52.0 (OCH_3), 25.8 (TBDMS *tert*-butyl CH_3), 21.2 (acetate CH_3), 18.2 (TBDMS *t*-butyl quat), −4.0 (TBDMS methyl), −5.0 (TBDMS methyl); ESI MS ($C_{45}H_{59}N_3O_{12}Si$) *m/z* (M + Na^+) calcd 884.3760, obsd 884.3756.

Methyl (2-*O*-Acetyl-4-*O*-allyl-3-*O*-benzyl-α-L-idopyranosid)uronate-(1→4)-2-azido-3,6-di-*O*-benzyl-2-deoxy-D-glucopyranoside Trichloroacetimidate (15). Disaccharide **14** (960 mg, 1.11 mmol) was coevaporated three times with anhydrous toluene and dissolved in anhydrous THF (10 mL). The solution was cooled to 0 °C, and acetic acid (71 μL, 1.23 mmol) was added followed by TBAF (1.0 M in THF, 1.23 mL). After 45 min, the reaction was poured into saturated NH_4Cl, and the aqueous phase was extracted with ethyl acetate (3 ×

150 mL). The organic phases were combined and dried over $MgSO_4$, and the solvent was removed under reduced pressure.

The residue was coevaporated three times with anhydrous toluene and dissolved in anhydrous CH_2Cl_2 (10 mL) under N_2. The solution was cooled to 0 °C and trichloroacetonitrile (1.7 mL, 16.7 mmol) and DBU (32 μL, 0.22 mmol) was added. The reaction mixture was stirred for 30 min and then allowed to warm to room temperature. The solvent was evaporated, and the residue was purified by flash chromatography on silica (hexanes/ethyl acetate 3:1) to afford **15** (950 mg, 1.07 mmol, 96%, 2:1 β:α) as a yellow oil: R_f 0.14 (hexanes/ethyl acetate 3:1); IR (thin film, NaCl plates) 3338, 3031, 2876, 2113, 1745, 1739, 1675 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.70 (s, 0.67H), 8.69 (s, 0.33H), 7.24−7.38 (m, 15H), 6.40 (d, J = 3.5 Hz, 0.33H), 5.74−5.79 (m, 1H), 5.60 (d, J = 8.3 Hz, 0.67H), 5.35−5.37 (m, 1H), 5.17−5.21 (m, 2H), 4.51−4.94 (m, 8H), 4.2 (t, J = 4.4, 0.33 H), 4.12 (t, 0.66H), 3.83−4.02 (m, 4H), 3.63−3.78 (m, 4H), 3.41−3.59 (m, 2H), 3.52 (s, 2H), 3.51 (s, 1H), 1.97 (s, 2H), 1.96 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 170.19, 169.8, 161.2, 160.9, 138.2, 138.1, 138.0, 137.98, 137.95, 137.92, 134.4, 134.3, 128.66, 128.65, 128.57, 128.48, 128.39, 128.33, 128.18, 128.15, 128.1, 127.98, 127.9, 127.87, 127.77, 127.71, 127.63, 127.6, 117.73, 117.67, 97.9, 96.9, 95.0, 90.7, 78.5, 76.3, 75.3, 75.17, 75.15, 75.0, 75.9, 74.5, 74.2, 74.0, 73.6, 73.5, 73.3, 73.2, 71.95, 71.9, 70.2, 69.9, 69.7, 69.5, 67.8, 67.7, 65.7, 63.1, 52.1, 52.0, 21.22, 21.20; ESI MS ($C_{41}H_{45}Cl_3N_4O_{12}$) m/z ($M + Na^+$) calcd 913.1992, obsd 913.1996.

Methyl [Methyl (2-*O*-acetyl-4-*O*-allyl-3-*O*-benzyl-α-L-idopyranosid)uronate-(1→4)-2-azido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside-(1→4)-3-*O*-benzyl-1,2-isopropylidine-β-L-idopyranosid]uronate (16). Trichloroacetimidate **15** (950 mg, 1.07 mmol) and monosaccharide **8**[12,30] (433 mg, 1.28 mmol) were combined and coevaporated three times with anhydrous toluene. The mixture was dissolved in anhydrous CH_2Cl_2 (10 mL) under N_2 and cooled to −25 °C, freshly activated 4 Å molecular sieves (1 g) were added, and the reaction mixture was stirred for 30 min. Trimethylsilyl trifluoromethanesulfonate (25 μL, 0.107 mmol) was added, and the reaction mixture was stirred for 90 min at reduced temperature. The reaction was quenched with NEt_3 (1 mL), and the solvent was removed under reduced pressure. Flash chromatography on silica (toluene/ethyl acetate 10:1 → 20:3) afforded **16** (940 mg, 0.88 mmol, 83%) as a clear oil: R_f 0.23 (hexanes/ethyl acetate 2:1); $[\alpha]^{24}_D$ −12.5, c = 1.2; IR (thin film, NaCl plates) 2932, 2108, 1765, 1741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24−7.29 (m, 20H), 5.75−5.81 (m, 1H), 5.35 (d, J = 4.9 Hz, 1H), 5.32 (d, J = 2.5 Hz, 1H), 5.19 (d^3, J = 1.6, 3.2, 17.2 Hz, 1H), 5.13 (d^3, J = 1.2, 2.8, 10.4 Hz, 1H), 4.86−4.89 (m, 3H), 4.65−4.74 (m, 6H), 4.61 (d, J = 12.2 Hz, 1H), 4.51 (d, J = 12 Hz, 1H), 4.40 d, J = 1.4 Hz, 1H), 4.19 (t, J = 2.3 Hz, 1H), 3.95−4.08 (m, 5H), 3.86 (t, J = 6 Hz, 1H), 3.70−3.77 (m, 4H), 3.64 (s, 3H), 3.61 (d^2, J = 1.9, 11.1 Hz, 1H), 3.51 (s, 3H), 3.43 (d^2, J = 3.3, 10.3 Hz, 1H), 1.96 (s, 3H), 1.58 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 161.2, 138.3, 138.15, 138.1, 137.2, 134.4, 128.8, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 128.05, 128.0, 127.9, 127.8, 127.5, 117.7, 112.3, 98.3, 97.9, 97.1, 78.3, 75.9, 75.45, 75.4, 75.2, 74.9, 73.6, 73.4, 73.0, 72.8, 72.1, 71.8, 71.4, 70.8, 70.6, 67.5, 63.7, 52.5, 52.0, 28.2, 26.3, 21.2; ESI MS ($C_{56}H_{65}N_3O_{18}$) m/z ($M + Na^+$) calcd 1090.4155, obsd 1090.4123.

Methyl [Methyl (2-*O*-acetyl-4-*O*-allyl-3-*O*-benzyl-α-L-idopyranosid)uronate-(1→4)-2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside-(1→4)-3-*O*-benzyl-1,2-isopropylidine-β-L-idopyranosid]uronate (17). Trisaccharide **16** (940 mg, 0.88 mmol) was coevaporated three times with anhydrous toluene. The compound was dissolved in anhydrous pyridine (9 mL) under N_2 and cooled to 0 °C. Thiolacetic acid (9 mL) was added and the cooling bath removed. The reaction mixture was stirred for 12 h, and the solvent was removed under reduced pressure. Flash chromatography on silica (hexanes/ethyl acetate 7:3) eluted the side products. Further elution (hexanes/ethyl acetate 1:1) afforded **17** (800 mg, 0.74 mmol, 84%): R_f 0.31 (hexanes/ethyl acetate 1:2); $[\alpha]^{24}_D$ −1.3, c = 1.03; IR (thin film, NaCl plates) 3030, 2931, 1767, 1739, 1682 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.16−7.41 (m, 20H), 6.53 (d, J = 9.7 Hz, 1H), 5.74 (m, 1H), 5.36 (d, J = 2.3 Hz, 1H), 5.30 (d, J = 3.6 Hz, 1H), 5.16 (d^3, J = 1.6, 3.3, 17.2 Hz, 1H), 5.10 (d^3, J = 1.3, 3.3, 10.4 Hz, 1H), 4.89 (t, J = 4 Hz, 1H), 4.66−4.74 (m, 6H), 4.57−4.6 (m, 3H), 4.48 (d, J = 1.4 Hz, 1H), 4.38 (d, J = 11.5 Hz, 1H), 4.36 (dt, J = 3.7, 10.5 Hz, 1H), 4.08 (t, J = 9.5 Hz, 2H), 3.93−3.99 (m, 4H), 3.88 (t, J = 2.2 Hz, 1H), 3.83 (t, J = 4.8 Hz, 1H), 3.76 (m, 1H), 3.68 (m, 1H), 3.67 (s, 3H), 3.60 (d^2, J = 2.3, 11 Hz, 1H), 3.52−3.56 (m, 1H), 3.47 (s, 3H), 3.43 (d^2, J = 9.3, 10.5 Hz), 1.93 (s, 3H), 1.8 (s, 3H), 1.55 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 170.15, 169.8, 169.1, 138.9, 138.2, 138.0, 136.6, 134.5, 129.0, 128.7, 128.65, 128.5, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.0, 117.5, 112.3, 98.0, 97.7, 96.6, 79.4, 75.3, 75.25, 75.2, 74.7, 74.0, 73.6, 73.25, 73.2, 72.2, 71.9, 71.5, 71.4, 71.35, 69.6, 69.4, 68.1, 52.7, 52.3, 52.0, 28.6, 26.4, 23.1, 21.2; ESI MS ($C_{58}H_{69}NO_{19}$) m/z ($M + Na^+$) calcd 1106.4356, obsd 1106.4328.

***tert*-Butyldimethysilyl Methyl [Methyl (2-*O*-acetyl-4-*O*-allyl-3-*O*-benzyl-α-L-idopyranosid)uronate-(1→4)-2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside-(1→4)-3-*O*-benzyl-β-L-idopyranosid]uronate (18).** Trisaccharide **17** (1.66 g, 1.53 mmol) was dissolved in TFA (90% aq, 30 mL) and stirred for 20 min. The solvent was removed under reduced pressure and the residue coevaporated five times with anhydrous toluene. The crude material was dissolved in anhydrous CH_2Cl_2 (4 mL) and cooled to −25 °C under N_2. TBDMSCl (347 mg, 2.3 mmol) and imidazole (417 mg, 6.12 mmol) were added, and the reaction mixture was stirred for 16 h at −5 °C. Methanol (1 mL) was added and the mixture stirred for 15 min and poured into ethyl acetate (300 mL). The organic phase was washed with 1 N HCl, brine, and saturated $NaHCO_3$. The organic phase was dried over $MgSO_4$, and solvent was removed under reduced pressure. Flash chromatography on silica (hexanes/ethyl acetate 1:1) afforded **18** (1.65 g, 1.43 mmol, 93%) as a clear oil (15:1 β/α). Characterization data is reported for the β isomer only: R_f 0.28 (hexanes/ethyl acetate 1:2); IR (thin film, NaCl plates) 3336, 3031, 2858, 1767, 1739, 1674 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.19−7.41 (m, 20H), 6.71 (d, J = 9.6 Hz, 1H); 5.7−5.78 (m, 1H), 5.26 (d, J = 3.5 Hz, 1H), 5.14 (d^3, J = 17.1, 3.2, 1.6 Hz, 1H), 5.09 (d^3, J = 10.3, 2.9, 1.2 Hz, 1H), 5.02 (d, J = 1.3 Hz, 1H), 4.85 (t, J = 4 Hz, 1H), 4.76 (d, J = 3.8 Hz, 1H), 4.67−4.73 (m, 4H), 4.62 (d, J = 11.6 Hz, 1H), 4.51−4.57 (m, 4H), 4.45 (d, J = 11.6 Hz, 1H), 4.27−4.32 (m, 1H), 4.05 (t, J = 9.5 Hz, 1H), 3.88−3.93 (m, 3H), 3.80 (t, J = 4.8 Hz, 1H), 3.74−3.77 (m, 2H), 3.70 (t, J = 4.3 Hz, 1H), 3.67 (s, 3H), 3.53−3.67 (m, 4H), 3.48 (s, 3H), 2.68 (s, 1H), 1.94 (s, 3H), 1.73 (s, 3H), 0.96 (s, 9H), 0.24 (s, 3H), 0.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 170.1, 169.8, 168.9, 138.9, 138.2, 138.0, 136.9, 134.4, 128.9, 128.65, 128.6, 128.4, 128.16, 128.15, 128.0, 127.9, 127.85, 127.75, 127.6, 127.1, 117.5, 98.0, 97.7, 93.8, 78.3, 75.3, 75.1, 74.4, 74.0, 73.7, 73.5, 73.4, 73.1, 73.0, 72.1, 71.8, 71.7, 69.5, 69.4, 68.7, 68.2, 52.5, 52.2, 51.9, 25.9, 23.1, 21.1, 18.4, −3.9, −5.2; ESI MS ($C_{61}H_{79}NO_{14}Si$) m/z ($M + Na^+$) calcd 1180.4908, obsd 1180.4883.

***tert*-Butyldimethysilyl Methyl [Methyl (2-*O*-acetyl-4-*O*-allyl-3-*O*-benzyl-α-L-idopyranosid)uronate-(1→4)-2-*N*-acetylacetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside-(1→4)-2-*O*-acetyl-3-*O*-benzyl-β-L-idopyranosid]uronate (19).** Trisaccharide **18** (1.66 g, 1.42 mmol) was coevaporated three times with anhydrous toluene and dissolved in isopropenyl acetate (15 mL) under N_2. *p*-Toluenesulfonic acid (700 μL, 0.1 M in DMF) was added and the mixture irradiated in a CEM Discover Series Microwave for 5 h at 30 W, 90 °C max. The reaction was poured into ethyl acetate (100 mL) and washed with saturated $NaHCO_3$. The organic phase was dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography on silica (hexanes/ethyl acetate 7:3) afforded **19** (1.52 g, 1.22 mmol, 86%) as a clear oil: R_f 0.38 (hexanes/ethyl acetate 1:1);

$[\alpha]^{24}_D$ +52.9, c = 0.91; IR (thin film, NaCl plates) 2952, 1741, 1675 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.12−7.39 (m, 20H), 5.74 (m, 1H), 5.34 (d, J = 3.4 Hz, 1H), 5.16 (m, 1H), 5.10 (m, 1H), 5.02 (d, J = 1.9 Hz, 1H), 5.01 (d, J = 3.8 Hz, 1H), 4.99 (m, 1H), 4.92 (ψt, 1H), 4.78 (d, J = 11.5 Hz, 1H), 4.67−4.75 (m, 4H), 4.52−4.62 (m, 5H), 4.45 (d, J = 1.8, 1H), 4.33 (d^2, J = 4.0, 11 Hz, 1H), 3.91−4.03 (m, 6H), 3.85 (ψt, 1H), 3.75 (s, 3H), 3.67−3.74 (m, 3H), 3.49 (s, 3H), 2.20 (s, 6H), 2.03 (s, 3H), 1.98 (s, 3H), 0.87 (s, 9H), 0.14 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 170.3, 170.0, 169.9, 168.8, 139.2, 138.03, 137.97, 137.2, 134.4, 128.8, 128.7, 128.5, 128.4, 128.24, 128.19, 128.06, 127.95, 127.87, 127.2, 127.1, 117.7, 98.0, 95.7, 93.6, 77.5, 76.3, 75.5, 74.7, 73.7, 73.4, 73.1, 72.9, 72.4, 72.3, 71.9, 70.4, 70.2, 70.0, 67.9, 67.7, 59.8, 52.4, 52.0, 26.8, 25.7, 21.2, 21.0, 18.0, −3.9, −5.4; ESI MS ($C_{65}H_{83}NO_{21}Si$) m/z (M + Na^+) calcd 1264.5119, obsd 1264.5082.

Methyl [Methyl (2-*O*-acetyl-4-*O*-allyl-3-*O*-benzyl-α-L-idopyranosid)uronate-(1→4)-2-*N*-acetylacetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside-(1→4)-2-*O*-acetyl-3-*O*-benzyl-L-idopyranosid]uronate Trichloroacetimidate (20). Trisaccharide **19** (325 mg, 0.262 mmol) was coevaporated three times with anhydrous toluene and dissolved in anhydrous THF (2.5 mL). The solution was cooled to 0 °C, and acetic acid (22.5 μL, 0.39 mmol) was added followed by TBAF (1.0 M in THF, 290 μL). After 80 min, the reaction was poured into saturated NH_4Cl and extracted with ethyl acetate (3 × 200 mL). The organic phase was dried over $MgSO_4$, and the solvent was removed under reduced pressure.

The residue was coevaporated three times with anhydrous toluene and dissolved in anhydrous CH_2Cl_2 (2.5 mL) under N_2. The solution was cooled to 0 °C and trichloroacetonitrile (394 μL, 3.93 mmol) and DBU (7.4 μL, 0.052 mmol) added. The reaction mixture was stirred for 60 min and then allowed to warm to room temperature. The solvent was evaporated, and the residue was purified by flash chromatography on silica (elutant toluene/ethyl acetate 3:1) to afford **20** (281 mg, 0.22 mmol, 84%, 4:1 mixture of isomers) as a yellow oil: R_f 0.27, 0.33 (hexanes/ethyl acetate 1:1); IR (thin film, NaCl plates) 3447, 1739, 1674, 1650 cm^{-1}; ESI MS ($C_{61}H_{69}Cl_3N_2O_{21}$) m/z (M + Na^+) calcd 1293.3351, obsd 1293.3347.

***tert*-Butyldimethylsilyl (Methyl [methyl (2-*O*-acetyl-4-*O*-allyl-3-*O*-benzyl-α-L-idopyranosid)uronate-(1→4)-2-*N*-acetylacetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside-(1→4)-2-*O*-acetyl-3-*O*-benzyl-α-L-idopyranosid]uronate-(1→4))-2-azido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (21).** Trichloroacetimidate **20** (288 mg, 0.226 mmol) and **7** (565 mg, 1.13 mmol) were combined and coevaporated three times with anhydrous toluene. The mixture was dissolved in CH_2Cl_2 (2.25 mL) under N_2 and cooled to −25 °C. Trimethylsilyl trifluoromethanesulfonate (4 μL, 0.023 mmol) was added and the reaction mixture stirred for 1.5 h at reduced temperature. The reaction was quenched with NEt_3 (0.1 mL), and the solvent was removed under reduced pressure. Flash chromatography on silica (hexanes/ethyl acetate 9:1) eluted unreacted **7** (480 mg, 0.96 mmol). Further elution (hexanes/ethyl acetate 7:3) afforded **21** (259 mg, 0.16 mmol, 71%) as a clear oil: R_f 0.37 (hexanes/ethyl acetate 1:1); $[\alpha]^{24}_D$ +6.22, c = 1.05; IR (thin film, NaCl plates) 2952, 2111, 1756, 1741, 1675 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.13−7.4 (m, 30H), 5.72−5.79 (m, 1H), 5.36 (d, J = 4.8 Hz, 1H), 5.16−5.2 (m, 2H), 5.12 (d^2, J = 1.5, 10.5 Hz, 1H), 5.05 (d, J = 3.8 Hz, 1H), 4.88−4.93 (m, 2H), 4.47−4.78 (m, 10H), 4.37 (d^2, J = 3.7, 11.1 Hz, 1H), 3.93−4.06 (m, 5H), 3.86−3.90 (m, 2H), 3.77−3.80 (m, 1H), 3.63−3.74 (m, 5H), 3.50 (s, 3H), 3.47 (s, 3H), 3.32−3.37 (m, 2H), 3.24 (ψt, 1H), 2.14 (s, 6H), 1.97 (s, 3H), 1.94 (s, 3H), 0.94 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 170.0, 169.91, 169.9, 169.2, 138.9, 138.4, 138.3, 138.08, 138.03, 137.6, 134.3, 128.7, 128.6, 128.55, 128.5, 128.3, 128.2, 128.15, 128.08, 128.05, 127.9, 127.85, 127.8, 127.7, 127.67, 127.66, 127.5, 127.2, 127.15, 117.75, 98.13, 98.1, 97.4, 96.7, 81.1, 76.7, 76.3, 75.7, 75.4, 75.0, 74.8, 74.7, 73.7, 73.5, 73.4, 73.2, 72.8, 72.0, 71.8, 71.7, 71.2, 70.7, 70.6, 69.0, 68.9, 68.8, 68.4, 67.7, 58.9, 52.1, 52.0, 26.7, 25.8, 21.1, 21.0, 18.1, −4.0, −5.0; ESI MS ($C_{85}H_{104}N_4O_{25}Si$) m/z (M + Na^+) calcd 1631.6651, obsd 1631.6701.

Methyl [Methyl (2-*O*-acetyl-4-*O*-allyl-3-*O*-benzyl-α-L-idopyranosid)uronate-(1→4)-2-*N*-acetylacetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside-(1→4)-2-*O*-acetyl-3-*O*-benzyl-α-L-idopyranosid]uronate-(1→4))-2-azido-3,6-di-*O*-benzyl-2-deoxy-D-glucopyranoside Trichloroacetimidate (4). Tetrasaccharide **21** (251 mg, 0.156 mmol) was coevaporated three times with anhydrous toluene and dissolved in anhydrous THF (1.5 mL). The solution was cooled to 0 °C, and acetic acid (10.2 μL, 0.18 mmol) was added followed by TBAF (1.0 M in THF, 172 μL). After 30 min, the reaction was poured into saturated NH_4Cl and extracted three times with ethyl acetate. The organic phase was dried over $MgSO_4$, and the solvent was removed under reduced pressure.

The residue was coevaporated three times with anhydrous toluene and dissolved in anhydrous CH_2Cl_2 (1.5 mL) under N_2. The solution was cooled to 0 °C, and trichloroacetonitrile (226 μL, 2.25 mmol) and DBU (4.3 μL, 0.03 mmol) were added. The reaction mixture was stirred for 45 min and then allowed to warm to room temperature. The solvent was evaporated, and the residue was purified by flash chromatography on silica (elutant toluene/ethyl acetate 7:3) to afford **4** (228 mg, 0.139 mmol, 89%, 6:1 mixture of isomers) as a yellow oil: R_f 0.3, 0.375 (hexanes/ethyl acetate 3:2); IR (thin film, NaCl plates) 2926, 2112, 1739, 1675 cm^{-1}; ESI MS ($C_{81}H_{90}Cl_3N_5O_{25}$) m/z (M + Na^+) calcd 1660.4883, obsd 1660.4913.

Methyl 2-Benzyloxycarbonylamino-2-deoxy-3,6-di-*O*-acetyl-α-D-glucopyranoside (10). Compound **22**[43] was coevaporated twice with anhydrous toluene and dissolved in 2,4,6-collidine (7 mL, distilled from CaH). The mixture was cooled to −40 °C, and acetyl chloride (270 μL, 3.78 mmol) was added. The reaction mixture was stirred overnight under N_2 at −40 °C. Water (1 mL) was added, and the reaction warmed to room temperature and poured into ethyl acetate (600 mL). The organic phase was washed with 1 N HCl, brine, and saturated $NaHCO_3$ and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography on silica (hexanes/ethyl acetate7:3) afforded **17** (1.17 g, 82%) as a glassy solid: R_f 0.19 (hexanes/ethyl acetate 1:1); $[\alpha]^{24}_D$ +55.2, c = 1.26; mp = 98.0−99.5 °C; IR (thin film, NaCl plates) 3434, 2956, 1739, 1710, 1520 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30−7.36 (m, 5H, CBz aromatic), 5.17 (d, $^3J_{H2-NH}$ =10 Hz, 1H, carbamate NH), 5.13 (d, ^2J = 12.3 Hz, 1H Cbz CH_2), 5.06 (d^2, $^3J_{H3-H4}$ = 9.4 Hz, $^3J_{H2-H3}$ = 10.5 Hz, 1H, H3), 5.02 (d, ^2J = 12.3 Hz, 1H, Cbz CH_2), 4.71 (d, $^3J_{H1-H2}$ = 3.6 Hz, 1H, H1), 4.44 (d^2, $^3J_{H5-H6}$ = 4.4 Hz, $^2J_{H6=H6'}$ = 12.2 Hz, 1H, H6), 4.29 (d^2, $^3J_{H5-H6'}$ = 2.2 Hz, $^2J_{H6=H6'}$ = 12.2 Hz, 1H, H6′), 3.95 (dψt, $^3J_{H1-H2}$ = 3.6 Hz, J = 10.3 Hz, 1H, H2), 3.77 (d^3, $^3J_{H5-H6'}$ = 2.2 Hz, $^3J_{H5-H6}$ = 4.4 Hz, $^3J_{H4-H5}$ = 10 Hz, 1H, H5), 3.57 (ψt, J = 9.4 Hz, 1H, H4), 3.38 (s, 3H, OCH_3), 3.17 (s (b), 1H, OH), 2.11 (s, 3H, 3-*O*-acetate CH_3), 1.94 (s, 6H, 3-*O*-acetate CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2 (6-*O*-acetate carbonyl), 171.6 (3-*O*-acetate carbonyl), 156.1 (CBz carbonyl), 136.4 (CBz phenyl quaternary), 128.7 (aromatic C), 128.3 (aromatic C), 128.2 (aromatic C), 98.8 (C1), 74.1 (C3), 70.0 (C5), 68.8 (C4), 67.0 (CBz CH_2), 63.1 (C6), 55.4 (OCH_3), 53.7 (C2), 21.0 (3-*O*-acetate CH_3), 20.9 (6-*O*-acetate CH_3); ESI MS ($C_{19}H_{25}NO_9$) m/z (M + Na^+) calcd 434.1422, obsd 434.1420.

Methyl Methyl 2-*O*-Acetyl-4-*O*-allyl-3-*O*-benzyl-α-L-idopyranosiduronate-(1→4)-3,6-di-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranoside (23). Glycosyl trichloroacetimidate **9** (243 mg, 0.46 mmol) and monosaccharide **10** (136 mg, 0.33 mmol) were combined and coevaporated three times with anhydrous toluene. The mixture was dissolved in anhydrous CH_2Cl_2 (5 mL) under N_2 and cooled to −15 °C. Trimethylsilyl trifluoromethanesulfonate (8 μL, 46 μmol) was added, and the mixture was stirred for 3 h at low temperature. The cooling bath was removed, and the reaction mixture was stirred for an additional 3 h at room temperature, followed by quenching with NEt_3 (0.5 mL). The solvent was

removed under reduced pressure. Flash chromatography on silica (hexanes/ethyl acetate 7:3) afforded **23** (143 mg, 0.195 mmol, 59%): R_f 0.26 (hexanes/ethyl acetate 1:1); $[\alpha]^{24}_D$ +5.75, $c = 1.4$; IR (thin film, NaCl plates) 1739, 1516 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 72.7−7.37 (m, 10H), 5.69−5.76 (m, 1H), 5.19 (d^2, J = 9 Hz, 10.6 Hz, 1H), 5.10−5.15 (m, 3H), 4.99−5.04 (m, 3H), 4.75−4.77 (m, 2H), 4.72 (d, J = 12.2 Hz, 1H), 4.70 (d, J = 3.6 Hz, 1H), 4.62 (d J = 12.2 Hz, 1H), 4.28 (d, J = 2.8 Hz, 2H), 3.79−3.99 (m, 5H), 3.78 (s, 3H), 3.74 (m, 2H), 3.36 (s, 3H), 2.13 (s, 3H), 2.06 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 171.1, 170.3, 169.8, 156.1, 137.8, 136.5,134.2, 128.7, 128.6, 128.4, 128.3, 128.0, 127.8, 118.0, 99.6, 98.7, 76.2, 74.5, 72.7, 72.5, 72.1, 71.8, 69.8, 68.8, 68.7, 67.1, 62.4, 55.5, 54.2, 52.3, 21.3, 21.1, 21.0; ESI MS ($C_{38}H_{47}NO_{16}$) m/z (M + Na^+) calcd 796.2793, obsd 796.2750.

Methyl (Methyl 2-*O*-acetyl-3-*O*-benzyl-α-L-idopyranosiduronate)-(1→4)-3,6-di-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranoside (5). Disaccharide **23** (140 mg, 0.19 mmol) and sodium acetate (600 mg) were combined and dissolved in acetic acid (2.6 mL) and water (150 μL). $PdCl_2$ (202 mg, 1.14 mmol) was added, and the reaction mixture was stirred for 9 h. Palladium black precipitated from solution over the course of the reaction. The reaction mixture was poured into saturated $NaHCO_3$ (200 mL), and the aqueous layer was extracted with ethyl acetate (3 × 200 mL). The combined organic phases were dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography on silica (1:1 hexanes/ethyl acetate) afforded **5** (113 mg, 0.16 mmol, 86%) as a clear oil: R_f 0.38 (hexanes/ethyl acetate 1:3); $[\alpha]^{24}_D$ +17.5, $c = 0.99$; IR (thin film, NaCl plates) 3447, 2955, 1743, 1521 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29−7.38 (m, 10H, aromatic H), 5.21 (d^2, ^3J = 9.0, 10.6 Hz, 1H, GlcN H3), 5.13 (d, ^2J = 12.2 Hz, 1H, CBz CH_2), 5.03 (d, ^2J = 12.2 Hz, 1H, CBz CH_2), 4.98 (d, $^3J_{H2-NH}$ = 10 Hz, 1H, CBz NH), 4.94 (s, 1H, IdoA H1), 4.83 (d, $^3J_{H5-H4}$ = 1.9 Hz, 1H, IdoA H5), 4.81, (s, 1H, IdoA H2), 4.71 (d, ^2J = 12.6, 1H 3-*O*-benzyl CH_2), 4.70 (d, $^3J_{H1-H2}$ = 3.9 Hz, 1H, GlcN H1), 4.62 (d, ^2J = 12.2, 1H 3-*O*-benzyl CH_2), 4.31 (d^2, $^2J_{H6-H6'}$ = 12.3 Hz, $^3J_{H6-H5}$ = 3.3 Hz, 1H, GlcN H6), 4.25 (d^2, $^2J_{H6-H6'}$ = 12.3 Hz, $^3J_{H6'-H5}$ = 1.8 Hz, 1H, GlcN H6′), 3.96 (m, 1H, IdoA H4), 3.92 (m, 1H, GlcN H2), 3.80 (s, 3H, methyl ester CH_3), 3.82 (m, 1H, GlcN H4), 3.75 (m, 1H, GlcN H5), 3.68 (ψt, 1H), 3.36 (s, 3H, methyl glycoside CH_3), 2.65 (d, $^3J_{H4-OH}$ = 11.7 Hz), 2.13 (s, 3H, 3-*O*-acetate CH_3), 2.10 (s, 3H, 2-*O*-acetate CH_3), 1.93 (s, 3H, 3-*O*-acetate CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5 (3-*O*-acetate carbonyl), 171.1 (6-*O*-acetate carbonyl), 169.6 (IdoA C6), 169.3 (2-*O*-acetate carbonyl), 156.0 (CBz carbonyl), 137.5 (benzyl quat), 136.5 (CBz quat), 128.7 (aromatic C), 128.6 (aromatic C), 128.4 (aromatic C), 128.3 (aromatic C), 128.1 (aromatic C), 127.6 (aromatic C), 99.8 (IdoA C1), 98.7 (GlcN C1), 77.0 (GlcN C4), 74.0 (IdoA C3), 72.3 (GlcN C3), 71.9 (benzyl CH_2), 68.8 (IdoA C5), 68.7 (GlcN C5), 68.0 (IdoA C4), 67.3 (IdoA C2), 67.1 (CBz CH_2), 62.3 (GlcN C6), 55.6 (methyl glycoside CH_3), 54.2 (GlcN C2), 52.5 (methyl ester CH_3), 21.2 (2-*O*-acetate CH_3), 21.05 (6-*O*-acetate CH_3), 20.9 (3-*O*-acetate CH_3); ESI MS ($C_{35}H_{43}NO_{16}$) m/z (M + Na^+) calcd 756.2474, obsd 756.2443.

Methyl (*tert*-Butyldimethylsilyl 4-*O*-allyl-3-*O*-benzyl-L-idopyranosid)uronate (26). Monosaccharide **25**[14] (200 mg, 0.529 mmol) was dissolved in TFA (90% aq, 5 mL) and stirred for 30 min. The solvent was removed under reduced pressure and the residue coevaporated five times with toluene. The crude material was dissolved in CH_2Cl_2 (500 μL) and cooled to −25 °C under N_2. TBDMS-Cl (120 mg, 0.794 mmol) and imidazole (144 mg, 2.12 mmol) were added, and the reaction mixture was stirred for 16 h at −25 °C. Methanol (1 mL) was added, and the mixture was stirred for 30 min and then diluted into ethyl acetate. The organic phase was washed with 1 N HCl, brine, and saturated aq $NaHCO_3$. The organic phase was dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash silica gel column chromatography (hexanes/ethyl acetate 85:15) afforded **26** (170 mg, 0.376 mmol, 71%) as a clear oil (6:1 mixture of isomers): R_f 0.37 (hexanes/ethyl acetate 3:1); IR (thin film, NaCl plate) 3519, 2929, 2858, 1770, 1739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) major isomer δ 7.31−7.40 (m, 5H), 5.72−5.80 (m, 1H), 5.14−5.18 (m, 2H), 5.03 (d, J = 0.8 Hz, 1H), 4.64 (d, J = 12 Hz, 1H), 4.60 (d, J = 12 Hz, 1H), 4.52 (d, J = 1.7 Hz, 1H), 4.04 (d^2, J = 5.9, 12.6 Hz, 1H), 3.89−3.93 (m, 2H), 3.78 (s, 3H), 3.76 (s, 1H), 3.63−3.65 (m, 1H), 3.04 (d, J = 10.1 Hz, 1H), 0.93 (s, 9H), 0.19 (s, 3H), 0.16 (s, 3H), minor isomer δ 5.32 (s, 1H), 4.92 (d, J = 1.8 Hz, 1H), 3.81 (s, 3H), 3.40 (d, J = 10 Hz, 1H), 0.87 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) major isomer δ 169.4, 137.5, 133.9, 128.8, 128.3, 127.9, 116.6, 94.7, 74.3, 74.0, 73.7, 72.5, 72.0, 68.8, 52.3, 26.0, 18.4, −3.9, −4.8, minor isomer δ 170.5, 138.0, 133.6, 128.7, 128.3, 127.6, 118.5, 96.4, 74.4, 72.8, 72.1, 71.7, 67.4, 67.3, 52.4, 25.7, 18.0; ESI MS ($C_{23}H_{36}O_7Si$) m/z (M + Na^+) calcd 475.2123, obsd 475.2143.

Methyl (*tert*-Butyldimethylsilyl 4-*O*-allyl-2-*O*-benzoyl-3-*O*-benzyl-L-idopyranosid)uronate (27). Compound **26** (488 mg, 1.08 mmol) was coevaporated three times with toluene and dissolved in CH_2Cl_2 (10 mL). DMAP (13.5 mg, 0.11 mmol) and benzoyl chloride (250 μL, 2.16 mmol) were added, and the reaction mixture was stirred overnight under N_2 with exclusion of light. The reaction mixture was poured into ethyl acetate (200 mL) and washed with 1 N HCl, brine, and saturated aq $NaHCO_3$. The organic phase was dried over $MgSO_4$ and, filtered, and the solvent was removed under reduced pressure. Flash silica gel column chromatography (hexanes/ethyl acetate 9:1) afforded **27** (464 mg, 0.833 mmol, 77%, 3:1 mixture of isomers) as a clear oil: R_f 0.33 (hexanes/ethyl acetate 85:15); IR (thin film, NaCl plate) 2929, 2857, 1772, 1723 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, J = 7.9 Hz, 1.5H), 8.06 (s, J = 8.1 Hz, 0.5H), 7.53−7.58 (m, 1H), 7.30−7.43 (m, 7H), 5.64−5.80 (m, 1H), 5.48 (s, 0.25H), 5.01−5.23 (m, 4H), 4.93 (d, J = 2.9 Hz, 0.25H), 4.80−4.82 (m, 1H), 4.67−4.71 (m, 1H), 4.58 (s, 0.75H), 4.04 (m, 1H), 3.89−3.95 (m, 2H), 3.75−3.80 (m, 4.5 H), 0.87 (s, 2.25H), 0.82 (s, 6.75H), 0.13 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) major isomer δ 169.4, 166.5, 137.5, 134.5, 133.1, 130.3, 128.7, 128.45, 128.4, 128.3, 128.1, 117.6, 93.4, 74.3, 73.6, 73.0, 72.9, 71.6, 68.2, 52.3, 25.8, 18.1, −3.7, −5.0; minor isomer δ 170.6, 165.9, 138.0, 134.4, 133.4, 130.4, 130.2, 129.9, 128.5, 128.35, 127.9, 117.4, 93.5, 75.1, 73.2, 72.6, 71.7, 70.0, 69.1, 52.35, 25.7, 18.04, −4.4, −5.4; ESI MS ($C_{30}H_{40}O_8Si$) m/z (M + Na^+) calcd 579.2385, obsd 579.2369.

Methyl 4-*O*-Allyl-2-*O*-benzoyl-3-*O*-benzyl-L-idopyranosiduronate Trichloroacetimidate (28). Monosaccharide **27** (303 mg, 0.544 mmol) was coevaporated three times with toluene and dissolved in THF (5 mL). The solution was cooled to 0 °C, and acetic acid (37.5 μL, 0.653 mmol) was added followed by TBAF (1.0 M in THF, 600 μL). After 30 min, the reaction was poured into ethyl acetate (100 mL) and washed twice with brine. The organic phase was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure.

The residue was coevaporated three times with toluene and dissolved in CH_2Cl_2 (4 mL) under N_2. The solution was cooled to 0 °C, and trichloroacetonitrile (820 μL, 8.16 mmol) and DBU (15 μL, 0.1 mmol) were added. The reaction mixture was stirred for 30 min, allowed to warm to room temperature, and stirred for an additional 1.5 h. The solvent was evaporated, and the residue was purified by flash silica gel column chromatography (silica quenched with 1% NEt_3 in toluene, eluted with toluene/ethyl acetate 19:1) afforded **28** (210 mg, 0.36 mmol, 66%, 3:1 mixture of isomers) as a yellow oil: R_f 0.3 (hexanes/ethyl acetate 85:15); IR (thin film, NaCl plate) 1723, 1621 cm^{-1}; ESI MS ($C_{26}H_{26}Cl_3NO_8$) m/z (M + Na^+) calcd 608.0616, obsd 608.0717.

Methyl Methyl 2-*O*-Benzoyl-3-*O*-benzyl-α-L-idopyranosiduronate-(1→4)-3,6-di-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranoside (30). Trichloroacetimidate **28** (210 mg, 0.358 mmol) and monosaccharide **10** (98 mg, 0.238 mmol) were combined and coevaporated three times with anhydrous toluene. The sugars were dissolved in anhydrous

CH_2Cl_2 (2.5 mL) under N_2 and cooled to −15 °C. Trimethylsilyl trifluoromethanesulfonate (6.5 μL, 36 μmol) was added, and the mixture was stirred for 1 h, allowed to warm to room temperature, and stirred for an additional 30 min. The reaction was quenched by addition of NEt_3 (0.5 mL), and the solvent was removed under reduced pressure. Flash chromatography on silica (hexanes/ethyl acetate 65:35) afforded **29** (185 mg, 0.22 mmol, 93%).

Disaccharide **29** (34 mg, 40.7 μmol) and sodium acetate (40 mg) were combined and dissolved in acetic acid (455 μL) and water (25 μL). $PdCl_2$ (42 mg, 0.24 mmol) was added, and the reaction mixture was stirred for 8 h. Palladium black precipitated from the solution over the course of the reaction. The reaction mixture was poured into saturated $NaHCO_3$ (50 mL), and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography on silica (4:1 toluene/ethyl acetate) afforded **30** (27 mg, 33.9 μmol, 83%) as a clear oil: R_f 0.19 (hexanes/ethyl acetate 1:1); $[\alpha]^{24}_D$ +26.0, c = 0.75; IR (thin film, NaCl plates) 3421, 1740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 7.4 Hz, 2H), 7.61 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.27−7.38 (m, 10H), 5.24 (d^2, J = 9.3, 10.4 Hz, 1H), 5.13 (ψt, 2H), 4.99−5.04 (m, 3H), 4.90 (d, J = 1.6 Hz, 1H), 4.77 (d, J = 12.1 Hz, 1H), 4.70 (d, J = 3.5 Hz, 1H), 4.66 (d, J = 12.1 Hz, 1H), 4.38 (d^2, J = 3.3, 12.3 Hz, 1H), 4.31 (d, J = 10.0 Hz, 1H), 4.04 (d, J = 11.4 Hz, 1H), 3.79−3.87 (m, 4H), 3.81 (s, 3H), 3.37 (s, 3H), 2.70 (d, J = 11.6 Hz, 1H), 2.13 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 171.0, 169.6, 165.1, 156.0, 137.6, 136.4, 134.0, 129.9, 128.9, 128.8, 128.75, 128.7, 128.6, 128.3, 128.2, 128.0, 127.6, 99.8, 98.6, 77.5, 77.0, 74.4, 72.3, 72.1, 68.8, 68.6, 68.1, 68.0, 67.5, 62.3, 55.5, 54.2, 52.4, 21.0, 20.8; ESI MS ($C_{40}H_{45}NO_8$) m/z (M + Na^+) calcd 818.2636, obsd 818.2561.

Methyl [Methyl (methyl [methyl (2-*O*-acetyl-4-*O*-allyl-3-*O*-benzyl-α-L-idopyranosid)uronate-(1→4)-2-*N*-acetyl-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside-(1→4)-2-*O*-acetyl-3-*O*-benzyl-α-L-idopyranosid]uronate-(1→4))-2-azido-3,6-di-*O*-benzyl-2-deoxy-D-glucopyranoside-(1→4)-2-*O*-acetyl-3-*O*-benzyl-α-L-idopyranosid)uronate]-(1→4)-3,6-di-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranoside (32). In a typical trial, tetrasaccharide **4** (145 mg, 88 μmol) and disaccharide **5** (71 mg, 97 μmol) were combined and coevaporated three times with anhydrous toluene. The sugars were dissolved in anhydrous CH_2Cl_2 (1 mL) under N_2 and cooled to −40 °C, 4 Å molecular sieves (300 mg) were added, and the reaction mixture was stirred for 30 min. Trimethylsilyl trifluoromethanesulfonate (1.6 μL, 9 μmol) was added, and the mixture was stirred for 1 h. The reaction was quenched by addition of NEt_3 (0.1 mL), and the solvent was removed under reduced pressure. Flash chromatography on silica (hexanes/ethyl acetate 60:40) eluted first a low polarity fraction (61 mg) which contained primarily **33** as a 1:1 α/β mixture, followed by a fraction containing **32**. Further elution (hexanes/ethyl acetate 40:60) afforded recovered **5** (37 mg). The product-containing fraction was further purified by size-exclusion chromatography on Biorad Biobeads, 1x cross-linking (40 cm × 2.5 cm, toluene elutant), to yield **32** (104 mg, 47 μmol, 53%) as a 6:1 α/β mixture: ^1H NMR (500 MHz, $CDCl_3$) major isomer characteristic peaks δ 5.72−5.79 (m, 1H, allyl C*H*=CH_2), 3.62 (s, 3H, methyl ester), 3.50 (s, 3H, methyl ester), 3.49 (s, 3H, methyl ester), 3.36 (s, 3H, methyl glycoside), 2.13 (s, 3H, acetate), 2.12 (s, 6H, NAc_2), 2.07 (s, 3H, acetate), 1.94 (s, 3H, acetate), 1.92 (s, 3H, acetate), 1.87 (s, 3H, acetate); ESI MS ($C_{114}H_{131}N_5O_{40}$) m/z (M + Na^+) calcd 2232.8263, obsd 2232.8263.

***tert*-Butyldimethylsilyl 4-*O*-Allyl-2-azido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (34).** Compound **7**[12] (140 mg, 0.28 mmol) was coevaporated three times with anhydrous toluene and dissolved in CH_2Cl_2 (1.5 mL). Freshly activated 4 Å molecular sieves (300 mg) and allyl bromide (114 μL, 1.4 mmol) were added, and the reaction mixture was stirred for 30 min. Silver(I) oxide (227 mg, 0.98 mmol) was added, light was excluded, and the reaction mixture was stirred for 40 h. The mixture was filtered through Celite, concentrated, and purified via flash column chromatography on silica (elutant 50:1 hexanes/ethyl acetate) to yield **34** (114 mg, 0.21 mmol, 75%) as a clear oil: R_f 0.38 (hexanes/ethyl acetate 10:1); $[\alpha]^{24}_D$ −3.57, c = 1.15; IR (thin film, NaCl plates) 2929, 2858, 2110 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28−7.42 (m, 10H), 5.82−5.90 (m, 1H), 5.21 (d^3, J = 1.6, 3.3, 17.2 Hz, 1H), 5.14 (dψt, J = 10.4, 1.7 Hz, 1H), 4.86 (d, J = 10.9 Hz, 1H), 4.79 (d, J = 10.9 Hz, 1H), 4.64 (d, J = 12 Hz, 1H), 4.58 (d, J = 12 Hz, 1H), 4.51−4.52 (m, 1H), 4.27−2.31 (m, 1H), 4.07−4.11 (m, 1H), 3.70 (m, 2H), 3.49−3.52 (m, 1H), 3.38−3.41 (m, 1H), 3.31−3.36 (m, 2H), 0.97 (s, 9H), 0.20 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 138.3, 134.8, 128.6, 128.5, 128.3, 128.0, 127.8, 127.79, 117.2, 97.4, 83.0, 77.8, 75.6, 75.3, 74.0, 73.7, 69.0, 68.8, 25.8, 18.2, −4.0, −5.0; ESI MS ($C_{29}H_{41}Cl_3N_3O_5Si$) m/z (M + Na^+) calcd 562.2708, obsd 562.2681.

4-*O*-Allyl-2-azido-3,6-di-*O*-benzyl-2-deoxy-D-glucopyranoside Trichloroacetimidate (35). Monosaccharide **34** (155 mg, 0.287 mmol) was coevaporated three times with toluene and dissolved in THF (2.5 mL). The solution was cooled to 0 °C, and acetic acid (18 μL, 0.313 mmol) was added followed by TBAF (1.0 M in THF, 299 μL). After 30 min, the reaction was poured into saturated NH_4Cl and extracted four times with CH_2Cl_2. The organic phases were combined, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure.

The residue was coevaporated three times with toluene and dissolved in CH_2Cl_2 (2.5 mL) under N_2. The solution was cooled to 0 °C, and trichloroacetonitrile (409 μL, 4.08 mmol) and DBU (7.5 μL, 0.054 mmol) were added. The reaction mixture was stirred for 30 min, allowed to warm to room temperature, and stirred for an additional 30 min. The solvent was evaporated, and the residue was purified by flash silica gel column chromatography (hexanes/ethyl acetate 9:1) afforded **35** (133 mg, 0.23 mmol, 81%,~3:2 α/β mixture) as a yellow oil: R_f 0.2, 0.3 (hexanes/ethyl acetate 85:15); IR (thin film, NaCl plates) 3340, 2868, 2112, 1675 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.75 (s, 0.4H), 8.72 (s, 0.6H), 7.27−7.43 (m, 10H), 6.42 (d, J = 3.4 Hz, 0.6H), 5.83−5.86 (m, 1H), 5.62 (d, J = 8.4 Hz, 0.4H), 5.14−5.23 (m, 2H), 4.87−4.94 (m, 2H), 4.64 (d, J = 11.4 Hz, 1H), 4.50−4.57 (m, 1H), 4.27−4.30 (m, 1H), 3.95−4.09 (m, 2.4H), 3.50−3.79 (m, 5.6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3, 160.9, 138.1, 137.95, 137.8, 134.5, 134.4, 128.7, 128.65, 128.6, 128.5, 128.4, 128.3, 128.2, 128.13, 128.1, 128.05, 128.0, 127.9, 117.6, 117.4, 96.9, 95.1, 91.1, 89.5, 83.0, 80.0, 77.6, 77.0, 76.3, 75.8, 75.7, 74.2, 74.0, 73.75, 73.7, 73.6, 68.0, 67.5, 65.8, 63.0; ESI MS ($C_{25}H_{27}Cl_3N_4O_5$) m/z (M + Na^+) calcd 591.0945, obsd 591.0939.

Methyl [Methyl (4-*O*-allyl-2-azido-3,6-di-*O*-benzyl-2-deoxy-D-glucopyranoside 2-*O*-acetyl-3-*O*-benzyl-α-L-idopyranosid)uronate]-(1→4)-3,6-di-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranoside (36) Trichloroacetimidate **35** (30 mg, 52 μmol) and disaccharide **5** (19 mg, 26 μmol) were combined and coevaporated three times with anhydrous toluene. The sugars were dissolved in anhydrous CH_2Cl_2 (1 mL) under N_2 and cooled to −40 °C, 4 Å molecular sieves (90 mg) were added, and the reaction mixture was stirred for 30 min. Trimethylsilyl trifluoromethanesulfonate (1 μL) was added, and the mixture was stirred for 2 h. The reaction was quenched by addition of NEt_3 (0.1 mL), and the solvent was removed under reduced pressure. Flash chromatography on silica (hexanes/ethyl acetate 90:10) eluted **38** (22.6 mg, 39 μmol) as a 1:1 α/β mixture. Further elution (hexanes/ethyl acetate 70:30) afforded **36** (9 mg) as a ~20:1 α/β mixture. Characterization data is reported for the major isomer only: IR (thin film, NaCl plates) cm^{-1} 2936, 2108, 1741.5, 15.14; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31−7.42 (m, 20H), 5.73−5.82 (m, 1H), 4.99−5.24 (m, 8H), 4.93 (d, J = 2.3 Hz, 1H), 4.62−4.86 (m, 10H), 4.51 (d, J = 12.1 Hz, 1H), 4.20−4.33 (m, 4H), 3.56−4.05 (m, 15H), 3.71 (s, 3H), 3.34 (s, 3H), 3.24 (m, 2H), 2.12 (s,

3H), 2.08 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 171.0, 170.2, 169.5, 150.1, 137.94, 137.93, 137.6, 136.5, 134.8, 128.7, 128.68, 128.64, 128.6, 128.5, 128.4, 128.3, 128.14, 128.11, 128.05, 128.0, 127.8, 127.7, 116.5, 99.5, 98.8, 97.3, 79.9, 77.8, 76.4, 75.5, 73.7, 73.69, 73.0, 72.4, 72.2, 72.1, 71.6, 69.0, 68.7, 68.2, 67.9, 67.1, 63.3, 62.3, 55.6, 54.3, 52.3, 21.1, 21.0, 20.9; ESI MS ($C_{61}H_{69}Cl_3N_2O_{21}$) *m*/*z* ($M + Na^+$) calcd 1163.4325, obsd 1163.4331.

Methyl [Methyl (4-*O*-allyl-2-azido-3,6-di-*O*-benzyl-2-deoxy-D-glucopyranoside 2-*O*-benzoyl-3-*O*-benzyl-α-L-idopyranosid)uronate]-(1→4)-3,6-di-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranoside (37) Trichloroacetimidate **35** (13 mg, 23 μmol) and disaccharide **30** (9 mg, 11 μmol) were combined and coevaporated three times with anhydrous toluene. The sugars were dissolved in anhydrous CH_2Cl_2 (500 μL) under N_2 and cooled to −40 °C, 4 Å molecular sieves (40 mg) were added, and the reaction mixture was stirred for 30 min. Trimethylsilyl trifluoromethanesulfonate (1 μL) was added, and the mixture was stirred for 2 h. The reaction was quenched by addition of NEt_3 (0.1 mL), and the solvent was removed under reduced pressure. Flash chromatography on silica (hexanes/ethyl acetate 90:10) eluted **38** (8 mg) as a 1:1 α/β mixture. Further elution (hexanes/ethyl acetate 70:30) afforded **37** (9 mg, 68%). Characterization data is reported for major isomer only: IR (thin film, NaCl plates) 3032, 2928, 2110, 1767, 1742, 1723 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) characteristic peaks δ 8.13 (d, J = 8.1 Hz, 2H, benzoate), 7.52 (ψt, 1H, benzoate), 7.45 (ψt, 2H, benzoate), 5.77−5.85 (m, 1H, allyl C*H*═CH_2), 3.75 (s, 3H, methyl ester), 3.35 (s, 3H, methyl glycoside), 2.06 (s, 3H, acetate), 1.90 (s, 3H, acetate); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 170.8, 169.5, 165.7, 156.1, 138.2, 137.9, 137.7, 136.5, 134.9, 133.6, 133.5, 130.2, 129.9, 129.6, 128.9, 128.7, 128.6, 128.5, 128.41, 128.28, 128.23, 128.13, 128.0, 127.92, 127.84, 127.6, 116.6, 99.9, 99.1, 98.6, 80.2, 77.5, 76.6, 75.2, 74.7, 73.8, 73.7, 72.9, 72.1, 69.4, 69.3, 68.8, 68.0, 67.1 63.6, 63.4, 55.6, 54.3, 52.3, 21.0, 20.9; ESI MS ($C_{61}H_{69}Cl_3N_2O_{21}$) *m*/*z* ($M + Na^+$) calcd 1225.4481, obsd 1225.4477.

***N*-(4-*O*-Allyl-2-azido-3,6-di-*O*-benzyl-2-deoxy-D-glucopyranoside) Trichloroacetamide (38)** This compound was isolated as a byproduct from the synthesis of **36** and **37** and isolated as a 3:2 mixture of anomers: R_f 0.23, 0.29 (hexanes/ethyl acetate 85:15); IR (thin film, NaCl plates) 3333, 3065, 2917, 2866, 2713, 1709, 1705 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−7.41 (m, 10H), 7.13 (d, J = 9.1 Hz, 0.6H), 7.01 (d, J = 6.5 Hz, 0.4H), 5.75−5.87 (m, 1H), 5.64 (ψt, 0.4H), 5.13−5.23 (m, 2H), 4.85−4.98 (m, 2.6H), 4.63−4.67 (m, 1H), 4.50−4.53 (m, 1H), 4.22−4.27 (m, 1H), 4.01−4.09 (m, 1H), 3.87−3.90 (m, 0.4H), 3.42−3.73 (m, 5.6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 161.9, 137.8, 137.6, 137.3, 134.4, 134.2, 128.8, 128.7, 128.61, 128.6, 128.5, 128.45, 128.4, 128.3, 128.2, 128.15, 128.1, 128.0, 117.9, 117.3, 83.9, 81.2, 80.5, 77.5, 77.1, 70.0, 76.0, 75.9, 74.0, 73.95, 73.8, 72.7, 67.9, 67.8, 65.8, 61.7; ESI MS ($C_{25}H_{27}Cl_3N_4O_5$) *m*/*z* ($M + Na^+$) calcd 591.0945, obsd 591.0942.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for all compounds not previously reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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