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New Glucuronic Acid Donors for the Modular Synthesis of Heparan Sulfate Oligosaccharides**

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Electronic supplementary information (ESI) available: Experimental procedures for the preparation of compounds **21, **23**, **25**, **27**, **37**, **38** and ^{1}H, HSQC NMR spectra of synthetic compounds.

Abstract: Although hundreds of heparan sulfate (HS) binding proteins have been implicated in a myriad of physiological and pathological processes, very little information is known about ligand requirements for binding and mediating biological activities by these proteins. We report here a streamlined approach for the preparation of modular disaccharide building blocks that will facilitate the assembly of libraries of HS oligosaccharides for structure-activity relationship studies. In particular, we have found that glucuronic acid donors, which usually perform poorly in glycosylations, can give high yields of coupling product when the C-2 hydroxyl is protected with a permanent 4-acetoxy-2,2-dimethyl butanoyl- (PivOAc) or temporary levulinoyl (Lev) ester and the C-4 hydroxyl modified with a selectively removable 2-methylnaphthyl (Nap) ether. It has been shown that the PivOAc ester can be removed without affecting sulfate esters making it an ideal protecting group for HS oligosaccharide assembly. Iduronic acid donors exhibit more favorable glycosyl donating properties and a compound protected with a Lev ester at C-2 and an Fmoc function at the C-4 hydroxyl gave coupling products in high yield. The new donors avoid post-glycosylation oxidation and therefore allow the facile preparation of modular disaccharide building blocks.

Introduction

Glycosylaminoglycans (GAGs), such as heparin and heparan sulfate (HS), are naturally occurring polydisperse linear polysaccharides that are heavily *O*- and *N*-sulfated. The interaction between GAGs and proteins can cause profound physiological effects on hemostasis, lipid transport and adsorption, cell growth and migration and development. Binding of GAGs can result in the immobilization of proteins at their sites of production and in the matrix for future mobilization, regulation of enzyme activity, binding of ligands to their receptors and protection of proteins against degradation.[1-5] Alteration in GAG expression has been associated with disease and for example, significant changes in content of proteoglycans have been reported in the stroma surrounding tumors. GAGs are also employed by microbes for cell entry and inhibition of these interactions may provide new avenues for the development of antimicrobial agents.

Although many heparan sulfate-binding proteins have been identified, the oligosaccharide structure that mediates a particular interaction has been defined in only a very few cases.[6-8] This problem is mainly due to the structural complexity of HS, which in turn, arises from a complex biosynthetic pathway. To address this difficulty, we have developed a modular approach for the chemical synthesis of HS oligosaccharides whereby a set of disaccharide building blocks, which resemble the different disaccharide motifs found in HS, can repeatedly be used for the assembly of a wide range of sulfated oligosaccharides (Figure 1).[9-13] In this approach, levulinoyl esters (Lev)[14] are employed for the protection of hydroxyls that need sulfation. In HS, the C-3 and C-6 of glucosamine and C-2 hydroxyls of uronic acids can be sulfated and therefore depending on the sulfation pattern of a targeted disaccharide module, one or more of these positions are protected as Lev esters. In case the C-2 position of a disaccharide module does not need sulfation, an acetyl ester is employed as a permanent protecting group. An azido group is used as an amino-masking functionality because it does not perform neighboring group participation and therefore allows the introduction of α-glucosides.[15] The C-4' hydroxyl, which is required for extension, is protected as 9-fluorenylmethyl carbonate (Fmoc), and this protecting group can be removed using a hindered base such as Et_3N without affecting the Lev ester. On the other hand, the Lev group can be cleaved with hydrazine buffered with acetic acid and these conditions do not affect the Fmoc carbonate.[14] The anomeric center of the modular disaccharide building blocks is

protected with a TDS ether and this functionality can easily be removed by treatment with HF in pyridine to give a lactol, which in turn, can be converted into a leaving group for glycosylations with appropriate acceptors. Compared to conventional approaches,[16-25] a modular synthetic strategy makes it possible to rapidly assemble libraries of HS oligosaccharides for structure activity relationship studies.

Although modular assembly of HS oligosaccharide is very attractive,[9-13, 26-27] the preparation of the disaccharide building blocks is time consuming. In particular, glycosyl donors derived from uronic acid often perform poorly in glycosylations due to a low reactivity which is caused by the electron withdrawing carboxylic acid that destabilizes the oxacarbenium ion like transition state of glycosylations.[28-30] Therefore, it is common to employ a post-glycosylation oxidation approach in which an oligosaccharide is assembled followed by selective oxidation of the C-6 hydroxyl of glucosides or idosides to the corresponding carboxylic acid. Such an approach requires additional reaction steps of advanced intermediates reducing the overall efficiency of the process.

Here, we report a detailed examination of the influence of protecting group patterns of uronyl donors on glycosylation efficiencies that led to the identification of new modular disaccharide building blocks that can readily be prepared without a need for post-glycosylation oxidation.

Results and Discussion

It is well known that the nature of a C-2 ester of a glycosyl donor can have a profound influence on the outcome of glycosylations. In this respect, the use of pivaloyl esters at C-2 can suppress orthoester formation, however, the removal of this protecting group requires harsh conditions which may not be compatible with the presence of sulfate esters in large complex HS oligosaccharides.[31] The 4-acetoxy-2,2-dimethyl butanoyl (PivOAc) ester has the steric advantage of the pivaloyl group but can be removed under mild basic conditions by a relay mechanism.[32-33] Thus, we set out to prepare glycosyl donors **14**, **15** and **16** (Scheme 1) which carry at C-2 an acetyl-, Lev- or PivOAc ester, respectively, and examine their glycosyl donor properties in glycosylations with glycosyl acceptor **17** (Scheme 2). The glycosyl donors could readily be prepared starting from compound **1**, which has a free hydroxyl at C-2. Acetylation of **1** under standard conditions provided **2**, whereas treatment of the same compound with levulinic acid in

the presence of *N,N′*-Dicyclohexylcarbodiimide (DDC) and 4-dimethylaminopyridine (DMAP) gave compound **6**. PivOAc protected **4** could readily be prepared in a high yield by a reaction of **1** with 4-acetoxy-2,2-dimethyl butanoyl chloride in the presence of DMAP in pyridine. The benzylidene acetal of compounds **2-4** was removed to give diols **5-7**, respectively and the primary hydroxyl of these compounds was selectively oxidized using 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) in the presence of iodobenzene diacetate (BAIB) as the cooxidant.[34-36] The resulting carboxylic acids were protected as methyl esters using diazomethane to provide derivatives **8-10**. The C-4 hydroxyl of the latter compounds was protected as a Fmoc carbonate by treatment with FmocCl in pyridine to give compounds **11-13** in yields ranging form 76-87%. Removal of the anomeric TDS group of the fully protected compounds **11-13** with HF in pyridine and subsequent installation of an anomeric trichloroacetimidate[37] using trichloroacetonitrile and NaH in DCM provided the required glycosyl donors **14-16**, respectively. The latter reaction conditions did not affect the base labile Fmoc protecting group.

As expected, a triflic acid (TfOH) mediated glycosylation of trichloroacetimidate **14** with glycosyl acceptor **17** did not lead to the formation of disaccharide **18** and instead hydrolyzed donor and the corresponding trehalose were isolated (Scheme 2). A similar glycosylation with glycosyl donor **15**, having a Lev ester at C-2, provided the corresponding disaccharide **19** as only the β-anomer in a low yield of 27%. The use of PivOAc protected glycosyl donor **16** improved the outcome of the glycosylation, however, the corresponding disaccharide **20** was isolated in a disappointing yield of 36%.

In addition to the C-2 functionality of a glycosyl donor, other protecing groups may affect the outcome of glycosylations. We reasoned that the electron withdrawing carbonate at C-4 further reduces the reactivity of the glucuronic acid donors, which have low intrinsic glycosyl donating properties. Thus, replacement of this protecting group by a C-4 ether was expected to increase the anomeric reactivity which may lead to higher yields of glycosylation products. To test this hypothesis, glycosyl donors **21**, **23** and **25** were prepared (see SI) and examined in TfOH mediated glycosylations with glycosyl acceptor **17** (Scheme 3). Gratifyingly, the use of glycosyl donors **23** and **25** resulted in improved glycosylation outcomes and the disaccharides **24** and **26** were isolated as only the β-anomers in yields of 61% and 71%, respectively. The coupling with

glycosyl donor **21** to give disaccharide **22** was still low yielding (22%) due to the formation of a substantial quantity of trehalose.

The modular synthesis of heparan sulfate requires disaccharides having a removable protecting group at C-4 of the glucuronic moiety. Therefore, we examined the use of glycosyl donor **27** that has a 2-methylnaphthyl (Nap) ether at C-4, which can be removed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). As expected, coupling of **27** with glycosyl acceptor **28** provided disaccharide **29** in a yield of 88%. These results show that glucuronyl donors having an ether protecting group at C-4 and a Lev or PivOAc ester at C-2 perform well in glycosylations with 2-azido-2-deoxy glycosyl acceptors having a free C-4 hydroxyl.

Next, we examined whether a Lev ester can be selectively removed in the presence of a PivOAc ester to give an alcohol for selective sulfation. For this purpose, disaccharide **31** was prepared by a TfOH catalyzed glycosylation of glycosyl donor **27** with glycosyl acceptor **30** (Scheme 4). The latter disaccharide has a Lev ester at C-6 that allows the installation of a sulfate ester, and an anomeric *N*-(benzyl)benzyloxycarbonyl protected aminopentanol moiety, which after deprotection provides opportunities for conjugation chemistry. As designed, removal of the Lev ester of **31** by treatment with hydrazine acetate in a mixture of toluene and ethanol followed by sulfation of the resulting hydroxyl of **32** with pyridinium sulfur trioxide lead to the clean formation of monosulfate **33**. Importantly, these conditions did not affect the PivOAc ester. However, the latter protecting group and the acetyl and methyl esters of **33** could readily be saponified by a two-step procedure employing first LiOH in a mixture of hydrogen peroxide and THF and then sodium hydroxide in methanol to give partially deprotected **34**. The azido moiety of **34** was reduced with trimethyl phosphine in THF in the presence of NaOH[38-39] to give amine **34**, which was immediately acetylated to give **35**. Finally, the benzyl ethers and benzyloxycarbamate of **35** were removed by a two-step procedure[40] involving hydrogenation over Pd/C in a mixture of MeOH/H_2O which led to the removal of the spacer protecting groups followed by hydrogenation over $Pd(OH)_2$ which resulted in to removal of the benzyl and Nap ethers to give HS disaccharides **36**.

Next, we examined the use of iduronic acid donors for the preparation of modular disaccharides. Gratifyingly, the coupling of **37** with **30** in the presence of NIS and AgOTf gave, after removal of the Fmoc protecting group, disaccharide **38** in an overall yield of 70% (Scheme

5, see SI for experimental procedures). In this case, there was no need to protect the C-4 postion of the donor with and ether protecting group, highlighting the more favorable glycosyl donating properties of iduronic acid donors, which has also been observed by others.[39, 41-42] Disaccharide **38** was also prepared by a post-oxidation approach by coupling **39** with **30** to give disaccharide **40**, which was subject to EtSH, TsOH in DCM to give a diol. The primary alcohol of the latter compounds was selectively oxidized to and carboxylic acid which was protected as a methyl ester by treatment with diazomethane to give disaccharide **38**. The latter three chemical manipulations proceeded in an overall yield of 50% demonstrating the liabilities of a post-oxidation approach.

In conclusion, we have developed a new procedure for the preparation of modular disaccharide building blocks for the synthesis of HS-oligosaccharides using glucuronic acid donors and therefore commonly employed late stage oxidation steps to make such compounds can be avoided. Particularly, it has been found that a glucuronic acid donor protected at C-2 with a permanent PivOAc or temporary Lev ester and an ether protecting group at C-4 can provide modular disaccharides in high yield. Our previous studies have shown that such building blocks are ideally suited for the preparation of libraries of HS oligosaccharides.[12, 43] Previous attempts to improve the yield of glycosylation of glucuronic acid donors for HS oligosaccharide synthesis have focus on increasing the reactivity of the glycosyl acceptor and for example, protection of the C-2 amine of the glycosyl acceptor as a 2,2,2-trichlorocarbonylamino (Troc) moiety led to a significantly higher yield of coupling product compared to the use of a similar acceptor having an azido group at C-2.[44] Removal of the Troc moiety was, however, problematic and led to a low yield of product. Another successful example of the use of a glucuronic acid donor involved a glycosylation with an acceptor locked in $^{1}C_{4}$ conformation by formation of a 1,6-anhydro-bridge.[27] Opening of the anhydro-bridge requires, however, strong acidic conditions that may compromise the preparation of modular building blocks. Methylation of hydroxyls of glucuronic acid donors also appears to improve the yield of glycosylation but such an approach can only provide HS-oligosaccharide analogs.[45]

Experimental

General procedures. ^{1}H and ^{13}C (data from HSQC) NMR spectra were recorded on Varian Mercury 300 MHz, Varian INOVA 500 MHz, 600 MHz or 800 MHz spectrometers. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS) as the internal standard. NMR data is presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, m = multiplet and/or multiple resonances), coupling constant in Hertz (Hz), integration. All NMR signals were assigned on the basis of ^{1}H NMR, COSY and HSQC experiments. Mass spectra were recorded on an ABISciex 5800 MALDi-TOF-TOF or Shimadzu LCMS-IT-TOF mass spectrometer. The matrix used was 2, 5-dihydroxy-benzoic acid (DHB). TLC-analysis was performed on Silica gel 60 F254 (EMD Chemicals inc.) with detection by UV-absorption (254 nm) when applicable, and by spraying with a solution of $(NH_4)_6Mo_7O_{24}.H_2O$ (25 g/L) in 5% sulfuric acid in ethanol followed by charring. CH_2Cl_2 was freshly distilled from calcium hydride under nitrogen prior to use. Acid washed molecular sieves (4Å) were flame activated *in vacuo*. All reactions were carried out under an argon atmosphere.

General procedure for glycosylations. Glycosyl donor (1.2 equiv based on acceptor) and acceptor (1.0 equiv) were combined in a flask, co-evaporated with toluene (3 × 3 mL), and dissolved in DCM to maintain a concentration of 0.02 M (based on donor). Powdered freshly activated 4 Å molecular sieves (weight of sieves equal to the combined weight of donor and acceptor) were added, and the mixture was stirred for 30 min at ambient temperature and then cooled to -30 °C. TfOH (0.1 equiv unless otherwise specified) was added to the mixture, and stirring was continued until TLC indicated disappearance of glycosyl donor. The reaction mixture was allowed to warm to 5 °C and then quenched by the addition of DTBMP. The mixture was filtered, the filtrate was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography using a gradient of hexane /EtOAc (6/1 → 3/1, v/v) to give pure product.

General procedure for benzylidene acetal cleavage. A solution of monosaccharide in a mixture of DCM:TFA:H_2O (0.06 M, 10/1/0.1, v/v/v) was stirred at ambient temperature for 30 min. The reaction mixture was concentrated *in vacuo*, and the residue was coevaporated with

toluene followed by purification using silica gel column chromatography using a gradient of hexanes and EtOAc to give product.

General procedure for TEMPO/BAIB-mediated oxidation and esterification by diazomethane. To a vigorously stirred solution of the diol (0.3 M solution) in a mixture of DCM:H_2O (2/1, v/v) was added TEMPO (0.2 equiv) and BAIB (2.5 equiv). Stirring was continued until TLC indicated complete conversion of the starting material to a spot of lower Rf. The reaction mixture was quenched by the addition of aqueous $Na_2S_2O_3$ (10%, 10 mL). The mixture was extracted with EtOAc (2 × 10 mL), and the combined aqueous layers were back-extracted with EtOAc (10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the filtrate was concentrated *in vacuo*. The oily residue was dissolved in THF (0.1 M) and treated with an excess of freshly prepared ethereal solution of diazomethane until the reaction mixture stayed yellow. The excess diazomethane was quenched by the addition of AcOH until the reaction mixture became colorless. The mixture was concentrated *in vacuo* and coevaporated with toluene, and the residue was purified by silica gel column chromatography using a gradient of hexanes and EtOAc to yield a methyl ester.

General procedure for synthesis of Fmoc-protected monosaccharides. To a solution of monosaccharide (0.03 M) in DCM at 0 °C was added 9-fluorenylmethoxycarbonyl chloride (10 equiv) and DMAP (0.01 equiv). The reaction mixture was brought to room temperature, and stirring was continued until TLC indicated complete consumption of the starting material (~2 h). After quenching the reaction with MeOH (50 μL), the mixture was diluted with DCM (50 mL) and washed with saturated aqueous sodium bicarbonate (2 × 50 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$), filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography using a gradient of hexanes and EtOAc to yield Fmoc carbonate-protected monosaccharide.

General procedure for preparation of trichloroacetimidates. Monosaccharide was dissolved in THF (0.05 M) followed by the addition of HF·pyridine (100 equiv). After stirring for 18 h, the

reaction mixture was diluted with DCM (50 mL) and washed with water (50 mL), saturated aqueous sodium bicarbonate (50 mL), and brine (50 mL). The organic phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was chromatographed over silica gel using a gradient of hexanes and EtOAc to give pure lactol. To a solution of the lactol in DCM (0.05 M) was added trichloroacetonitrile (5 eq.) and NaH (60%, 1 eq.). After stirring at room temperature for 1.5 h, the reaction mixture was concentrated *in vacuo*. The residue was chromatographed over silica gel using a mixture of hexanes and EtOAc containing 0.01% pyridine to yield a trichloroacetimidate donor, which was used directly for glycosylations.

Dimethylthexylsilyl 2-*O*-acetyl-3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (**2**). A solution of compound **1** (1.20 g, 2.40 mmol) in a mixture of pyridine and acetic anhydride (4/1, v/v, 0.2 M) was stirred for 2 h at ambient temperature. The reaction mixture was co-evaporated with toluene under reduced pressure and the residue was purified by silica gel column chromatography using a gradient of hexanes/EtOAc (3/1 → 2/1, v/v) to give compound **2** as oil (1.12 g, 87%). ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.57 – 7.25 (m, 10H, C*H* Aromatic), 5.57 (s, 1H, C*H* benzylidene), 4.97 (dd, *J* = 9.2, 7.6 Hz, 1H, H-2), 4.86 (d, *J* = 12.2 Hz, 1H, C*H*HBn), 4.73 – 4.61 (m, 2H, H-1, CH*H*Bn), 4.31 (dd, *J* = 10.5, 5.0 Hz, 1H, H-6a), 3.80 (m, 2H, H-6b, H-4), 3.69 (t, *J* = 9.2 Hz, 1H, H-3), 3.43 (td, *J* = 9.8, 5.0 Hz, 1H, H-5), 1.98 (s, 3H, COC*H*$_3$),1.57-1.53(m, 1H, C*H*$(CH_3)_2$) 0.93 – 0.68 (m, 12H, C(C*H*$_3)_2$ and CH(C*H*$_3)_2$), 0.14 (s, 3H, SiC*H*$_3$), 0.12 (s, 3H, SiC*H*$_3$). ^{13}C NMR (201 MHz, $CDCl_3$) δ 126.5, 131.4, 131.0, 129.0, 128.2, 126.0, 102.2, 97.2, 82.1, 78.9, 75.3, 73.7, 69.5, 69.1, 67.0, 63.4, 21.9, 21.5, 21.1, 20.6, -0.8, -1.9. HRMS: m/z: calcd for $C_{30}H_{42}O_7SiNa$: 565.2597; found: 565.2605 $[M+Na]^+$.

Dimethylthexylsilyl 2-*O*-levulinoyl-3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (**3**). A suspension of DCC (1.20 g, 6.0 mmol) and DMAP (12 mg, 0.09 mmol) in DCM (5 mL) was added to a solution of compound **1** (1.00 g, 1.99 mmol) and levulinic acid (0.46 g, 3.99 mmol) in DCM (5 mL) at 0 ^{o}C. After stirring for 2 h at ambient temperature, TLC analysis (hexanes/EtOAc, 7/3, v/v) indicated consumption of the starting material. The mixture was filtered over pad of celite and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using a gradient of hexanes/EtOAc (4/1 → 2/1,

v/v) to give compound **3** as oil (1.07 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.08 (m, 10H, C*H* Aromatic), 5.44 (s, 1H, C*H* benzylidene), 4.85 (dd, *J* = 8.8, 7.5 Hz, 1H, H-2), 4.73 (d, *J* = 12.1 Hz, 1H, C*H*HBn), 4.62 – 4.51 (m, 2H, H-1, CH*H*Bn), 4.18 (dd, *J* = 10.5, 5.0 Hz, 1H, H-6a), 3.73 – 3.53 (m, 3H, H-3, H-5, H-6b), 3.32 (dt, *J* = 9.4, 4.8 Hz, 1H, H-4), 2.66 – 2.34 (m, 4H, 2xCH_2 Lev), 2.04 (s, 3H, CH_3 Lev), 1.55 – 1.41 (m, 1H, C*H*$(CH_3)_2$), 0.76 – 0.67 (m, 12H, C(CH_3)$_2$ and CH(CH_3)$_2$), 0.02 (s, 3H, SiCH_3), 0.00 (s, 3H, SiCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.0, 128.5, 128.4, 128.3, 128.2, 101.8, 96.5, 82.0, 78.7, 75.6, 74.2, 69.0, 66.5, 38.0, 34.1, 30.1, 28.1, 19.0, -1.8, -1.7. HRMS: m/z: calcd for $C_{33}H_{46}O_8SiNa$: 621.2860; found: 621.2869 $[M+Na]^+$.

Dimethylthexylsilyl 2-*O*-(4-acetoxy-2,2-dimethylbunoate)-3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (**4**). To a stirring solution of compound **1** (2.70 g, 5.34 mmol) in pyridine (18 mL), DMAP (0.70 g, 5.54 mmol) and 4-acetoxy-2,2-dimethyl butanoyl chloride (1 mL, 10.67 mmol) was added at 0 ^{o}C. After stirring for 4 h at ambient temperature, TLC analysis (hexanes/EtOAc, 70/30, v/v) indicated the consumption of the starting material. The reaction mixture was diluted with EtOAc (30 mL) and washed with aqueous $NaHCO_3$ (10%), H_2O, brine. The combined organic layers were dried ($MgSO_4$), filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using a gradient of hexanes/EtOAc (4/1 → 2/1, v/v) to obtain compound **4** as oil (3.0 g, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51– 7.20 (m, 10H, C*H* Aromatic), 5.56 (s, 1H, C*H* benzylidene), 5.02 (dd, *J* = 8.8, 7.2, 1.3 Hz, 1H, H-2), 4.92 (d, *J* = 11.6 Hz, 1H, C*H*HBn), 4.81 (d, *J* = 7.1 Hz, 1H, H-1), 4.63 (d, *J* = 11.7 Hz, 1H, CH*H*Bn), 4.32 (t, *J* = 10.5 Hz, 1H, H-4), 4.07 (t, *J* = 7.2 Hz, 2H, CH_2 PivOAc), 3.88 – 3.73 (m, 3H, H-3, H-6a, H-6b), 3.49 (m, 1H, H-5), 1.97 (d, *J* = 1.3 Hz, 3H, CH_3 PivOAc), 1.85 (t, *J* = 7.4 Hz, 2H, CH_2 PivOAc), 1.62 (m, *J* = 6.8 Hz, 1H, C*H*$(CH_3)_2$), 1.18 (t, *J* = 2.6 Hz, 6H, 2xCH_3 PivOAc), 0.92 – 0.80 (m, 12H, C(CH_3)$_2$ and CH(CH_3)$_2$), 0.20 – 0.11 (m, 6H, Si(CH_3)$_2$). ^{13}C NMR (151 MHz, $CDCl_3$) δ 129.7, 129.1, 128.0, 127.5, 124.9, 101.8, 96.4, 81.3, 79.5, 74.0, 73.8, 73.7, 69.2, 68.3, 66.1, 62.2, 38.6, 34.6, 24.7, 21.5, 19.2. HRMS: m/z: calcd for $C_{36}H_{52}O_9SiNa$: 679.3278; found: 679.3289 $[M+Na]^+$.

Dimethylthexylsilyl 2-*O*-acetyl-3-*O*-benzyl-β-D-glucopyranoside (5). Compound **5** (710 mg, 77%) was prepared according to the general procedure for benzylidene acetal cleavage starting from compound **2** (1.10 g, 2.03 mmol). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.23 (m, 5H, C*H* Aromatic), 4.93 (t, *J* = 9.5 Hz, 1H, H-2), 4.74 (d, *J* = 11.6 Hz, 1H, C*H*HBn), 4.70 – 4.61 (m, 2H, H-1, CH*H*Bn), 3.89 – 3.81 (d, *J* = 10.5 Hz, 1H, H-6a), 3.74 (d, *J* = 10.5 Hz, 1H, H-6b), 3.68 (t, *J* = 9.3 Hz, 1H, H-4), 3.51 (t, *J* = 9.2 Hz, 1H, H-3), 3.30-3.35 (m, 1H, H-5), 1.99 (s, 3H, COCH_3), 1.57-1.50(m, 1H, C*H*$(CH_3)_2$), 0.95-0.70 (m, 12H, C(CH_3)$_2$ and CH(CH_3)$_2$), 0.15 (s, 3H, SiCH_3), 0.13 (s, 3H, SiCH_3). ^{13}C NMR (151 MHz, $CDCl_3$) δ 127.7, 96.1, 82.5, 75.1, 74.6, 74.3, 70.6, 62.6, 34.0, 21.1, 19.3, 18.6, -2.4, -2.5. HRMS: m/z: calcd for $C_{23}H_{38}O_7SiNa$: 477.2284; found: 477.2290 $[M+Na]^+$.

Dimethylthexylsilyl 2-*O*-levulinoyl-3-*O*-benzyl-β-D-glucopyranoside (6). Compound **5** (690 mg, 81%) was prepared according to the general procedure for benzylidene acetal cleavage starting from compound **3** (1.00 g, 1.67 mmol). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.25 (m, 5H, C*H* Aromatic), 4.93 (t, *J* = 9.5 Hz, 1H, H-2), 4.81 (d, *J* = 11.8 Hz, 1H, CH*H*Bn), 4.71 – 4.61 (m, 2H, H-1, C*H*HBn), 3.87-3.74 (m, 2H, H-6), 3.66 (t, *J* = 9.3 Hz, 1H, H-4), 3.51 (t, *J* = 9.3 Hz, 1H, H-3), 3.37 (m, 1H, H-5), 2.80-2.46 (m, 4H, CH_2 Lev), 2.17 (s, 3H, COCH_3), 1.63-1.57 (m, 1H, C*H*$(CH_3)_2$), 0.88 – 0.80 (m, 12H, C(CH_3)$_2$ and CH(CH_3)$_2$), 0.15 (s, 3H, SiCH_3), 0.13 (s, 3H, SiCH_3). ^{13}C NMR (151 MHz, $CDCl_3$) δ 128.0, 95.8, 82.6, 75.1, 74.2, 70.6, 62.7, 42.2, 37.7, 29.8, 27.9, 25.0, 23.4, 19.8, 18.4, -1.8, -3.3. HRMS: m/z: calcd for $C_{26}H_{42}O_8SiNa$: 533.2547; found: 533.2555$[M+Na]^+$.

Dimethylthexylsilyl 2-*O*-(4-acetoxy-2,2-dimethylbunoate)-3-*O*-benzyl-β-D-glucopyranoside (**7**). EtSH (1.70 g, 27.42 mmol) and TsOH (0.55 g, 2.75 mmol) were added to a stirred solution of compound **4** (3.00 g, 4.57 mmol) in DCM (10 mL). After stirring at ambient temperature for 1 h, TLC analysis (hexane/EtOAc, 75/25, v/v) indicated the complete consumption of the starting material. The reaction mixture was quenched with Et_3N and was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using a gradient of hexanes/EtOAc (3/1 → 2/1, v/v) to give compound **7** as oil (2.00 g, 77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.26 (m, 5H, C*H* Aromatic), 4.99 (t, *J* = 9.5 Hz, 1H, H-2), 4.81 – 4.74 (m, 2H,

CH*H*Bn, H-1), 4.64 (d, *J* = 11.6 Hz, 1H, C*H*HBn), 4.14 (t, *J* = 7.4 Hz, 2H, CH_2 PivOAc), 3.88 (dd, *J* = 11.8, 4.1 Hz, 1H, H-6a), 3.82 – 3.69 (m, 2H, H-6b, H-3), 3.57 (t, *J* = 9.2 Hz, 1H, H-4), 3.40 (m, 1H, H-5), 2.01 (s, 3H, CH_3 PivOAc), 1.97 – 1.88 (m, 2H, CH_2 PivOAc), 1.69 – 1.55 (m, 1H, C*H*(CH_3)$_2$), 1.30 – 1.23 (m, 6H, 2xCH_3 PivOAc), 0.92 – 0.82 (m, 12H, C(CH_3)$_2$ and CH(CH_3)$_2$), 0.14 (s, 3H, SiCH_3), 0.12 (s, 3H, SiCH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 129.0, 128.0, 126.4, 96.2, 83.1, 75.2, 74.6, 73.8, 73.8, 70.5, 62.7, 62.7, 61.3, 50.6, 38.0, 33.5, 26.7, 25.2, 22.9, 21.1, 20.7, 19.5, 18.5. HRMS: m/z: calcd for $C_{29}H_{48}O_9SiNa$: 591.2965; found: 591.2969 $[M+Na]^+$.

Dimethylthexylsilyl *O*-methyl-2-*O*-acetyl-3-*O*-benzyl-β-D-glucupyranosyluronate (**8**). Compound **8** (581 mg, 77%) was prepared according to the general procedure from compound **15** (0.71 g, 1.56 mmol) using TEMPO (49 mg, 0.31 mmol), BAIB (1.26 g, 3.90 mmol) and freshly prepared solution of diazomethane in Et_2O (2 mL). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.24 (m, 5H, C*H* Aromatic), 4.93 (t, *J* = 9.6 Hz, 1H, H-2), 4.83 (d, *J* = 11.8 Hz, 1H, C*H*HBn), 4.72 (d, *J* = 11.8 Hz, 1H, C*H*HBn), 4.67 (d, *J* = 7.6 Hz, 1H, H-1), 4.00 (t, *J* = 9.8 Hz, 1H, H-4), 3.86 – 3.79 (m, 4H, H-5, CO_2CH_3), 3.53 (t, *J* = 9.6 Hz, 1H, H-3), 1.97 (s, 3H, COCH_3), 1.64 – 1.55 (m, 1H, C*H*(CH_3)$_2$), 0.93 – 0.79 (m, 12H C(CH_3)$_2$ and CH(CH_3)$_2$), 0.17 (s, 3H, SiCH_3), 0.13 (s, 3H, SiCH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 128.0, 96.2, 81.1, 74.3, 73.9, 72.2, 52.7, 33.9, 20.9, 19.8, 15.5, 14.3, -2.8, -3.3. HRMS: m/z: calcd for $C_{24}H_{38}O_8SiNa$: 505.2234; found: 505.2240 $[M+Na]^+$.

Dimethylthexylsilyl *O*-methyl-2-*O*-levulinoyl-3-*O*-benzyl-β-D-glucupyranosyluronate (**9**). Compound **9** (498 mg, 68%) was prepared according to the general procedure from compound **6** (0.69 g, 1.35 mmol) using TEMPO (42 mg, 0.27 mmol), BAIB (1.08 g, 3.38 mmol) and freshly prepared solution of diazomethane in Et_2O (2 mL).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 – 7.10 (m, 5H, C*H* Aromatic), 4.80 (dd, *J* = 9.5, 7.5 Hz, 1H, H-4), 4.72 – 4.57 (m, 2H, C*H*HBn, CH*H*Bn), 4.54 (d, *J* = 7.6 Hz, 1H, H-1), 3.85 (dd, *J* = 9.8 Hz, 1H, H-4), 3.69 (m, 4H, H-5, CO_2CH_3), 3.40 (t, *J* = 9.5 Hz, 1H, H-3), 2.68 – 2.26 (m, 4H, 2xCH_2 Lev), 2.02 (s, 3H, CH_3 Lev), 1.44 (q, *J* = 6.9 Hz, 1H, C*H*(CH_3)$_2$), 0.76 – 0.59 (m, 12H, C(CH_3)$_2$ and CH(CH_3)$_2$), 0.03 (s, 3H, Si(CH_3)$_2$), 0.01 (s, 3H, Si(CH_3)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.5, 96.3, 81.4, 74.6, 74.4, 74.2, 72.2, 54.1,

38.1, 34.1, 30.2, 28.1, 20.1, 0.8. HRMS: m/z: calcd for $C_{27}H_{42}O_9SiNa$: 561.2496; found: 561.2502 $[M+Na]^+$.

Dimethylthexylsilyl *O*-methyl-2-*O*-(4-acetoxy-2,2-dimethylbunoate)-3-*O*-benzyl-β-D-glucopyranosyluronate (10). Compound **10** (1.10 g, 88%) was prepared according to the general procedure from compound **7** (0.71 g, 1.56 mmol) using TEMPO (66 mg, 0.42 mmol), BAIB (1.69 g, 5.28 mmol) and freshly prepared solution of diazomethane in Et_2O (4 mL). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 – 7.08 (m, 10H, C*H* Aromatic), 4.83 (t, *J* = 9.3, 1H, H-3), 4.74 (d, *J* = 11.5 Hz, 1H, CH*H*Bn), 4.62 (d, *J* = 7.3 Hz, 1H, H-1), 4.54 (d, *J* = 11.5 Hz, 1H, C*H*HBn), 3.99 – 3.86 (m, 3H, H-4, CH_2 PivOAc), 3.70 (d, 4H, H-5, CO_2CH_3), 3.46 (t, *J* = 9.0 Hz, 1H, H-3), 1.83 (s, 3H, CH_3 PivOAc,), 1.53 – 1.43 (m, 1H, C*H*$(CH_3)_2$), 1.05 (s, 6H, 2xCH_3 PivOAc), 0.75 – 0.66 (m, 12H, C(C$H_3)_2$ and CH(C$H_3)_2$), 0.04 (s, 3H, SiCH_3), 0.02 (s, 3H, SiCH_3).^{13}C NMR (126 MHz, $CDCl_3$) δ 128.6, 128.5, 127.5, 128.8, 127.8, 96.4, 74.2, 74.1, 74.1, 61.6, 72.1, 74.1, 52.9, 81.8, 21.2, 38.3, 34.0, 25.4, 18.7, 20.7, 20.2, -1.8, -2.7. HRMS: m/z: calcd for $C_{27}H_{42}O_9SiNa$: 619.2914; found: 619.2924 $[M+Na]^+$.

Dimethylthexylsilyl *O*-Methyl-2-*O*-acetyl-3-*O*-benzyl-4-*O*-(9-fluorenylmethoxycarbonyl)-β-D-glucupyranosyluronate (11). Compound **11** (784 mg, 94%) was prepared according to the general procedure from compound **8** (570 mg, 1.18 mmol) using Fmoc-Cl (1.22 g, 4.72 mmol) and DMAP (14 mg, 0.12 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (t, *J* = 6.8 Hz, 2H, C*H* Aromatic), 7.63 (dd, *J* = 10.6, 7.4 Hz, 2H, C*H* Aromatic), 7.41 (m, 3H, C*H* Aromatic), 7.36 – 7.29 (m, 5H, C*H* Aromatic), 5.15 (t, *J* = 9.6 Hz, 1H, H-4), 5.06 (dd, *J* = 9.4, 7.3 Hz, 1H, H-2), 4.75 – 4.67 (m, 2H, H-1, CH*H*Bn), 4.60 (d, *J* = 11.8 Hz, 1H, C*H*HBn), 4.47 (dd, *J* = 10.5, 7.1 Hz, 1H, CH*H* Fmoc), 4.37 (dd, *J* = 10.7, 7.5 Hz, 1H, C*H*H Fmoc), 4.26 (t, *J* = 7.3 Hz, 1H, CH_2CH Fmoc), 4.06 (t, *J* = 9.8 Hz, 1H, H-4), 3.75 (m, 4H, H-5, CO_2CH_3), 3.68 (t, *J* = 9.8 Hz, H-3), 1.98 (s, 3H, COCH_3), 1.63 (m, 1H, C*H*$(CH_3)_2$), 1.00 – 0.82 (m, 12H, C(C$H_3)_2$ and CH(C$H_3)_2$), 0.20 (s, 3H, SiCH_3), 0.16 (s, 3H, SiCH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 119.8, 125.0, 127.7, 127.0, 128.0, 127.7, 75.0, 73.7, 95.8, 73.8, 73.8, 70.2, 70.3, 46.6, 72.3, 79.1, 53.8, 52.7, 20.9, 29.6, 18.6, 19.9, 0.2. HRMS: m/z: calcd for $C_{39}H_{48}O_{10}SiNa$: 727.2914; found: 727.2920 $[M+Na]^+$.

Dimethylthexylsilyl *O*-methyl-2-*O*-levulinoyl-3-*O*-benzyl-4-*O*-(9-fluorenylmethoxycarbonyl)-β-D-glucupyranosyluronate (12). Compound **12** (490 mg, 87%). was prepared according to the general procedure from compound **9** (400 mg, 0.75 mmol) using Fmoc-Cl (1.20 g, 4.48 mmol) and DMAP (10 mg, 0.07 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 – 7.70 (m, 2H, C*H* Aromatic), 7.65 – 7.55 (m, 2H, C*H* Aromatic), 7.39 (dd, *J* = 7.7, 3.8 Hz, 2H, C*H* Aromatic), 7.33 – 7.18 (m, 5H, C*H* Aromatic), 5.19 – 5.08 (t, *J* = 9.4 Hz, 1H, H-4), 5.04 (t, *J* = 9.1, 7.5, 1.0 Hz, 1H, H-2), 4.75 – 4.68 (m, 1H, H-1), 4.70 – 4.58 (m, 2H, CH*H*Bn, C*H*HBn), 4.44 (m, 1H, C*H*H Fmoc), 4.34 (m, 1H, CH*H* Fmoc), 4.28 – 4.19 (m, 1H, CH_2CH Fmoc),), 4.03 (m, 1H, H-5), 3.81 – 3.71 (t, *J* = 7.5 Hz, H-3), 3.69 (s, 3H, CO_2CH_3), 2.78 – 2.41 (m, 4H, 2xCH_2 Lev), 2.16 (s, 3H, CH_3 Lev), 1.67 – 1.49 (m, 1H, C*H*$(CH_3)_2$), 0.92 – 0.75 (m, 12H, C(CH_3)$_2$ and CH(CH_3)$_2$), 0.16 (dd, *J* = 11.4, 1.0 Hz, 6H, Si(CH_3)$_2$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 127.2, 125.2, 120.7, 95.9, 79.3, 75.0, 74.4, 74.0, 72.4, 70.4, 52.4, 46.7, 37.8, 34.0, 29.8, 28.0, 18.5, 19.9, 1.1. HRMS: m/z: calcd for $C_{42}H_{52}O_{11}SiNa$: 783.3177; found: 783.3189 $[M+Na]^+$.

Dimethylthexylsilyl *O*-methyl-2-*O*-(4-acetoxy-2,2dimethylbunoate)-3-*O*-benzyl-4-*O*-(9-fluorenylmethoxycarbonyl)-β-D-glucupyranosyluronate (13). Compound **13** (0.31 g, 76%) was prepared according to the general procedure from compound **8** (570 mg, 1.18 mmol) using FmocCl (780 mg, 3.02 mmol) and DMAP (6.0 mg, 0.05 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 – 7.74 (m, 3H, C*H* Aromatic), 7.72 – 7.42 (m, 7H, C*H* Aromatic), 7.55 – 7.29 (m, 4H, C*H* Aromatic), 5.24 (t, *J* = 9.6 Hz, 1H, H-4), 5.11 (dd, *J* = 8.7, 6.9 Hz, 1H, H-2), 4.84 (d, *J* = 6.9 Hz, 1H, H-1), 4.74 – 4.62 (m, 2H, C*H*HBn, CH*H*Bn), 4.52 – 4.37 (m, 1H, CH*H* Fmoc), 4.36 – 4.18 (m, 2H, C*H*H Fmoc, C*H* Fmoc), 4.16 – 4.06 (m, 3H, CH_2 PivOAc), 3.87 (t, *J* = 9.1 Hz, 1H, H-3), 3.71 (s, 3H, CO_2CH_3), 2.00 (s, 3H, CH_3 PivOAc), 1.89 (t, *J* = 7.4 Hz, 3H, CH_3 PivOAc), 1.59 (s, 1H, CH(CH_3)$_2$), 1.22 (s, 6H, 2xCH_3 PivOAc), 0.91 – 0.85 (m, 12H, C(CH_3)$_2$ and CH(CH_3)$_2$), 0.25 – 0.16 (m, 6H, Si(CH_3)$_2$).^{13}C NMR (151 MHz, $CDCl_3$) δ 128.0, 127.7, 125.1, 120.1, 158.4, 95.9, 79.4, 74.6, 73.8, 73.2, 72.1, 70.3, 61.1, 52.5, 46.4, 38.0, 33.7, 29.4, 25.1, 20.7, 19.5, -9.7. HRMS: m/z: calcd for $C_{45}H_{58}NaO_{12}Si$: 841.3595; found: 841.3603 $[M+Na]^+$.

Dimethylthexylsilyl *O*-(methyl-2-*O*-levulinoyl-3-*O*-benzyl-4-*O*-(9-fluorenylmethoxycarbonyl)-β-D-glucupyranosyluronate)-(1→4)-*O*-2-deoxy-2-azido-3-*O*-benzyl-6-*O*-acetyl-β-D-glucopyranoside (19). Compound **19** (19 mg, 27%) was prepared according to the general glycosylation procedure from compound **15** (60 mg, 0.08 mmol) and **17** (31 mg, 0.07 mmol) catalyzed by TfOH (1.0 µl, 0.01 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (t, *J* = 7.2 Hz, 2H, CH Aromatic), 7.60 – 7.54 (m, 2H, C*H* Aromatic), 7.43 – 7.18 (m, 16H, C*H* Aromatic), 5.04 (d, *J* = 19.1, 9.6 Hz, 2H, H-2′, H-4′), 4.97 (d, *J* = 11.6 Hz, 1H, C*H*H*Bn*), 4.80 (d, *J* = 11.6 Hz, 1H, *CH*H*Bn*), 4.67 – 4.57 (m, 3H, C*H*H*Bn* , *CH*H*Bn* , H-1′), 4.49 (d, *J* = 7.7 Hz, 1H, H-1), 4.44 – 4.37 (m, 1H, H-6a), 4.31 (dd, *J* = 10.5, 7.5 Hz, 2H, CH_2 Fmoc), 4.20 (t, *J* = 7.1 Hz, 1H, C*H* Fmoc), 4.12 (dd, *J* = 11.8, 6.1 Hz, 1H, H-6b), 3.85 (d, *J* = 9.8 Hz, 1H, H-5′), 3.76 – 3.66 (m, 2H, H-3′, H-4′), 3.58 (dd, *J* = 14.1, 7.8 Hz, 1H, H-5), 3.47 (s, 3H, CO_2CH_3), 3.43 – 3.37 (m, 1H, H-3), 3.29 (dd, *J* = 9.8, 7.8 Hz, 1H, H-2), 2.79 – 2.70 (m, 1H, CH_2 Lev), 2.68 – 2.51 (m, 3H, CH_2 Lev), 2.41 – 2.33 (m, 1H, CH_2 Lev), 2.15 (s, 3H, CH_3 Lev), 2.08 (d, *J* = 9.7 Hz, 3H, COCH_3), 1.64 (dt, *J* = 13.8, 6.8 Hz, 1H, C*H*$(CH_3)_2$), 0.88 (m, 12H, C(CH_3)$_2$ and CH(CH_3)$_2$), 0.28 – 0.09 (m, 6H, Si(CH_3)$_2$). ^{13}C NMR (126 MHz, CDCl3) δ 128.6, 128.0, 127.5, 125.3, 120.4, 101.3, 97.0, 81.27, 79.7, 79.0, 75.3, 75.1, 74.7, 74.6, 73.0, 72.8, 72.7, 70.7, 70.7, 52.9, 63.0, 46.8, 69.0, 68.9, 30.0, 21.1, 20.2, 18.7. HRMS: m/z: calcd for $C_{57}H_{69}N_3O_{16}SiNa$: 1102.4345; found: 1102.4355 $[M+Na]^+$

Dimethylthexylsilyl *O*-(methyl-2-*O*-(4-acetoxy-2,2-dimethylbunoate)-3-*O*-benzyl-4-*O*-(9-fluorenylmethoxycarbonyl)-β-D-glucupyranosyluronate)-(1→4)-*O*-2-deoxy-2-azido-3-*O*-benzyl-6-*O*-acetyl-β-D-glucopyranoside (20). Compound **20** (28 mg, 36%) was prepared according to the general glycosylation procedure from compound **16** (70 mg, 0.08 mmol) and **17** (33 mg, 0.07 mmol) catalyzed by TfOH (1.0 µl, 0.01 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 – 7.73 (m, 2H, C*H* Aromatic), 7.62 – 7.54 (m, 2H, C*H* Aromatic), 7.47 – 7.18 (m, 15H, C*H* Aromatic), 5.22 – 5.10 (m, 2H, H-4′, H-2′), 5.02 (d, *J* = 11.2 Hz, 1H, C*H*H*Bn*), 4.80 (d, *J* = 11.5 Hz, 1H, *CH*H*Bn*), 4.73 – 4.60 (m, 3H, H-1′, CH_2 Fmoc), 4.53 (d, *J* = 7.5 Hz, 1H, H-1), 4.42 (dd, *J* = 10.4, 7.1 Hz, 1H, H-6a), 4.34 (dd, *J* = 11.8, 1.8 Hz, 1H, C*H*H*Bn*), 4.28 (dd, *J* = 10.4, 7.6 Hz, 1H, H-6b), 4.25 – 4.17 (m, 2H, *CH*H*Bn* , C*H* Fmoc), 4.12 – 3.96 (m, 3H, CH_2 PivOAc, H-5′), 3.82 (m, *J* = 9.1, 5.5 Hz, 2H, H-3′, H-4), 3.57 (s, 3H, CO_2CH_3), 3.51 (dd, *J* = 8.4, 4.0 Hz, 1H, H-

5), 3.43 (t, *J* = 9.1 Hz, 1H, H-3), 3.32 (dd, *J* = 10.0, 7.6 Hz, 1H, H-2), 2.11 (s, 3H, C*H*$_3$ PivOAc), 2.04 – 1.98 (m, 3H, COC*H*$_3$), 1.88 (dd, *J* = 14.7, 7.7 Hz, 2H, C*H*$_2$ PivOAc), 1.75 – 1.61 (m, 1H, C*H*(CH$_3$)$_2$), 1.23 – 1.14 (m, 6H, 2 X C*H*$_3$ PivOAc), 0.94 – 0.86 (m, 12H, C(C*H*$_3$)$_2$ and CH(C*H*$_3$)$_2$), 0.18 (s, 3H, SiC*H*$_3$), 0.16 (s, 3H, SiC*H*$_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 128.2, 127.9, 128.3, 127.7, 127.2, 127.1, 125.1, 120.5, 120.0, 99.9, 96.7, 80.6, 79.4, 76.8, 75.0, 74.7, 73.7, 72.8, 72.5, 72.3, 70.5, 68.5, 62.6, 62.6, 61.2, 46.6, 53.2, 52.7, 38.2, 33.9, 29.7, 25.3, 24.9, 20.8, 20.9, 20.0, 19.9, 18.4, -3.2. HRMS: m/z: calcd for $C_{60}H_{75}N_3O_{17}SiNa$: 1160.4763; found: 1160.4770 $[M+Na]^+$.

Dimethylthexylsilyl *O*-(methyl-2-*O*-acetyl-3,4-*O*-benzyl-β-D-glucupyranosyluronate)-(1→4)-*O*-2-deoxy-2-azido-3-*O*-benzyl-6-*O*-acetyl-β-D-glucopyranoside (22). Compound **22** (16 mg, 22%) was prepared according to the general glycosylation procedure from compound **21** (55 mg, 0.10 mmol) and **17** (38 mg, 0.13 mmol) catalyzed by TfOH (1.0 µl, 0.01 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.17 (m, 15H, C*H* Aromatic), 5.05 – 4.99 (m, 1H, H-2′), 4.95 (d, *J* = 11.2 Hz, 1H, C*H*HBn), 4.78 (d, *J* = 11.5 Hz, 1H, CH*H*Bn), 4.72 (d, *J* = 11.0 Hz, 2H, C*H*HBn, CH*H*Bn), 4.63 (d, *J* = 11.5 Hz, 1H, C*H*HBn), 4.60 – 4.55 (m, 2H, CH*H*Bn, H-1′), 4.45 (d, *J* = 7.7 Hz, 1H, H-1), 4.38 (dd, *J* = 11.6, 1.9 Hz, 1H, H-6a), 4.08 (dd, *J* = 11.6, 6.4 Hz, 1H, H-6b), 3.91 (t, *J* = 9.1 Hz, 1H, H-4′), 3.84 (d, *J* = 9.5 Hz, 1H, H-5′), 3.70 – 3.59 (m, 2H, H-4, H-3′), 3.53 (s, 3H, CO_2C*H*$_3$), 3.43 (d, *J* = 6.9 Hz, 1H, H-4), 3.38 – 3.31 (m, 1H, H-3), 3.27 (dd, *J* = 9.8, 7.7 Hz, 1H, H-2), 2.10 – 2.02 (s, 3H, COC*H*$_3$), 1.94 (s, 3H, COC*H*$_3$), 1.71 – 1.59 (m, 1H, C*H*(CH$_2$)$_3$), 0.93 – 0.82 (m, 12H, C(C*H*$_3$)$_2$ and CH(C*H*$_3$)$_2$), 0.19 (s, 3H, SiC*H*$_3$), 0.15 (s, 3H, SiC*H*$_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 129.0, 128.8, 128.5, 128.4, 127.9, 127.7, 127.6, 127.5, 101.3, 96.7, 81.9, 80.9, 79.3, 78.48, 75.6, 75.1, 75.0, 74.5, 73.0, 72.7, 68.6, 63.3, 62.5, 62.5, 52.4, 33.9, 29.7, 20.8, 20.8, 20.3, 20.25, 19.9, 19.3, 18.5, 18.4, 17.9. HRMS: m/z: calcd for $C_{46}H_{61}N_3O_{13}SiNa$: 914.3871; found: 914.3879 $[M+Na]^+$.

Dimethylthexylsilyl *O*-(methyl-2-*O*-levulinoyl-3,4-*O*-benzyl-β-D-glucupyranosyluronate)-(1→4)-*O*-2-deoxy-2-azido-3-*O*-benzyl-6-*O*-acetyl-β-D-glucopyranoside (24). Compound **24** (76 mg, 61%) was prepared according to the general glycosylation procedure from compound **23** (100 mg, 0.16 mmol) and **17** (63 mg, 0.13 mmol) catalyzed by TfOH (1.5 µl, 0.016 mmol). ^{1}H

NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.17 (m, 15H, C*H* Aromatic), 5.06 – 4.99 (m, 1H, H-2′), 4.96 (d, *J* = 11.1 Hz, 1H, C*H*HBn), 4.80 – 4.64 (m, 4H, CH_2 Bn), 4.57 (dd, *J* = 9.4, 3.4 Hz, 2H, CH*H*Bn, H-1′), 4.48 (d, *J* = 7.7 Hz, 1H, H-1), 4.42 (dd, *J* = 11.7, 1.8 Hz, 1H, H-6a), 4.14 (dd, *J* = 11.8, 5.9 Hz, 1H, H-6b), 3.94 – 3.88 (m, 1H, H-4′), 3.85 (d, *J* = 9.5 Hz, 1H, H-5′), 3.68 (dt, *J* = 17.8, 9.3 Hz, 2H, H-4′, H-5′), 3.59 – 3.50 (m, 4H, H-5, COOCH_3), 3.39 – 3.32 (m, 1H, H-3), 3.27 (dd, *J* = 9.8, 7.8 Hz, 1H, H-2), 2.79 – 2.69 (m, 1H, CH_2 Lev), 2.66 – 2.50 (m, 2H, CH_2 Lev), 2.36 – 2.27 (m, 1H, CH_2 Lev), 2.15 (s, 3H, CH_3 Lev), 2.06 (s, 3H, COCH_3), 1.63 (td, *J* = 13.7, 6.9 Hz, 1H, C*H*$(CH_3)_2$), 0.93 – 0.82 (m, 12H, C(CH_3)$_2$ and CH(CH_3)$_2$), 0.19 (s, 3H, SiCH_3), 0.15 (s, 3H, SiCH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 128.7, 128.6, 128.3, 128.2, 128.1, 128.0, 127.4, 127.3, 127.2, 127.1, 101.5, 97.0, 82.2, 81.2, 79.5, 78.5, 75.3, 75.2, 74.8, 73.6, 72.8, 68.8, 62.9, 62.9, 52.7, 37.8, 34.0, 29.9, 20.8, 20.1, 18.4, -2.1, -3.1. HRMS: m/z: calcd for $C_{49}H_{65}N_3O_{14}SiNa$: 970.4134; found: 970.4137 $[M+Na]^+$.

Dimethylthexylsilyl *O*-(methyl-2-*O*-(4-acetoxy-2,2-dimethylbunoate)-3,4-*O*-benzyl-β-D-glucupyranosyluronate)-(1→4)-*O*-2-deoxy-2-azido-3-*O*-benzyl-6-*O*-acetyl-β-D-glucopyranoside (26). Compound **26** (95 mg, 71%) was prepared according to the general procedure from compound **25** (109 mg, 0.16 mmol) and compound **17** (63 mg, 0.13 mmol) catalyzed by TfOH (1.4 µl, 0.01 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 6.96 (m, 15H, C*H* Aromatic), 4.98 – 4.89 (t, *J* = 9.3 Hz, 1H, H-2′), 4.82 (d, *J* = 10.8 Hz, 1H, *CH*HBn), 4.64 (d, *J* = 11.4 Hz, 1H, *C*H*HBn*), 4.59 – 4.40 (m, 5H, CH_2 Bn, H-1′), 4.35 (d, *J* = 7.7 Hz, 1H, H-1), 4.17 (dd, *J* = 11.7, 1.8 Hz, 1H, H-6a), 4.03 (dd, *J* = 11.8, 5.9 Hz, 1H, H-6b), 3.86 (dd, *J* = 16.5, 8.2 Hz, 3H, H-4′, CH_2 PivOAc), 3.76 (d, *J* = 9.3 Hz, 1H, H-5′), 3.68 (dd, *J* = 9.8, 8.7 Hz, 1H, H-4), 3.53 (t, *J* = 8.6 Hz, 1H, H-3′), 3.45 (s, 3H, CO_2CH_3), 3.36 – 3.29 (m, 1H, H-5), 3.24 – 3.17 (t, *J* = 9.3 Hz,1H, H-3), 3.12 (m, *J* = 9.9, 7.7 Hz, 1H, H-2), 1.92 (d, *J* = 5.6 Hz, 3H, CH_3 PivOAc), 1.82 (s, 3H, COCH_3), 1.77 – 1.63 (m, 2H, CH_2 PivOAc), 1.50 (dd, *J* = 20.6, 13.7 Hz, 1H, C*H*$(CH_3)_2$), 1.00 (d, *J* = 12.6 Hz, 6H, 2 X CH_3 PivOAc), 0.72 (dd, *J* = 14.4, 7.5 Hz, 12H, C(CH_3)$_2$ and CH(CH_3)$_2$), 0.09 – 0.05 (m, 6H, Si(CH_3)$_2$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 128.6, 128.4, 128.5, 128.5, 128.1, 127.9, 127.8, 127.7, 127.3, 127.2, 100.2, 96.9, 82.0, 80.8, 79.5, 76.5, 75.5, 75.0, 74.8, 73.3, 72.8, 68.7, 62.9, 61.5, 52.8, 38.5, 34.2, 31.1, 21.2, 25.2, 20.9, 20.2, 18.6, -3.0, -1.9. HRMS: m/z: calcd for $C_{52}H_{71}N_3O_{15}SiNa$: 1028.4552; found: 1028.4560 $[M+Na]^+$.

Dimethylthexylsilyl *O*-(methyl-2-*O*-(4-acetoxy-2,2-dimethylbunoate)-3-*O*-benzyl-4-*O*-(2-methyl-napthyl)-β-D-glucupyranosyluronate)-(1→4)-*O*-2-deoxy-2-azido-3-*O*-benzyl-6-*O*-levulinoyl-β-D-glucopyranoside (29). Compound **29** (88 mg, 85%) was prepared according to the general glycosylation procedure from compound **27** (83 mg, 0.11 mmol) and compound **28** (50 mg, 0.09 mmol) catalyzed by TfOH (1.0 µl, 0.01 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 – 7.73 (m, 2H, C*H* Aromatic), 7.62 (d, *J* = 14.7 Hz, 1H, C*H* Aromatic), 7.51 – 7.15 (m, 13H, C*H* Aromatic), 5.20 – 5.10 (t, , *J* = 9.7 Hz, 1H, H-2′), 5.03 (dt, *J* = 14.9, 5.3 Hz, 1H, *CH*H*Bn*), 4.84 (t, *J* = 12.3 Hz, 2H, CH*H* napthylidene, *C*H*HBn*), 4.80 – 4.67 (m, 3H, C*H*H napthylidene, C*H*HBn , H-1′), 4.56 – 4.50 (d, *J* = 9.3 Hz, 1H, H-1), 4.36 – 4.22 (m, 2H, H-$6_{a,}$, H-6_b), 4.15 – 4.00 (m, 2H, H-5′, H-4′), 3.95 – 3.85 (m, 2H, H-3′, H-4), 3.57 (s, 3H, COOCH_3), 3.52 – 3.46 (m, 1H, H-5), 3.40 – 3.26 (m, 2H, H-3, H-2), 2.90 – 2.71 (m, 2H, CH_2 Lev), 2.69 – 2.53 (m, 2H, CH_2 Lev), 2.24 – 2.19 (s, 3H, CH_3 Lev), 1.99 (s, 3H, COCH_3), 1.95 – 1.83 (m, 2H, CH_2 PivOAc), 1.59 (m, 1*H*, C*H*(CH_3)$_2$), 1.20 (dd, *J* = 3.5, 1.3 Hz, 6H, 2xCH_3 PivOAc), 0.91 (d, 12H, C(CH_3)$_2$ and CH(CH_3)$_2$), 0.24 – 0.13 (m, 6H, Si(CH_3)$_2$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 129.0, 128.8, 128.3, 128.2, 128.0, 127.7, 127.5, 127.1, 126.6, 126.1, 125.7, 125.3, 99.9, 96.7, 81.7, 80.6, 79.6, 79.4, 79.3, 76.0, 75.4, 73.1, 75.4, 74.7, 74.5, 72.5, 68.4, 62.6, 61.3, 52.5, 51.9, 38.4, 37.9, 34.0, 30.3, 29.7, 28.0, 25.9, 25.3, 21.6, 20.9, 19.9, 18.2, 2.0. HRMS: m/z: calcd for $C_{59}H_{77}N_3O_{16}SiNa$: 1134.4971; found: 1134.4977 $[M+Na]^+$.

***N*-(Benzyl)-benzyloxycarbonyl-5-aminopentyl-*O*-(methyl-2-*O*-(4-acetoxy-2,2-dimethylbunoate)-3-*O*-benzyl-4-*O*-(2-methyl-napthyl)-β-D-glucupyranosyluronate)-(1→4)-*O*-2-deoxy-2-azido-3-*O*-benzyl-6-*O*-levulinoyl-α-D-glucopyranoside (31).** Compound compound **31** (152 mg, 64%) was prepared according to the general glycosylation procedure from compound **27** (164 mg, 0.22 mmol) and compound **30** (130 mg, 0.19 mmol) catalyzed by TfOH (6.0 µl, 0.07 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 – 7.74 (m, 3H, C*H* Aromatic), 7.64 (s, 1H, C*H* Aromatic), 7.53 – 7.43 (m, 3H, C*H* Aromatic), 7.42 – 7.16 (m, 20H, C*H* Aromatic), 5.28 – 5.14 (m, 4H, CH_2 Cbz, H-2′, C*H*HNAP), 4.93 – 4.65 (m, 7H, C*H*HNAP, 2 × CH_2Bn, H-1′, H-1), 4.58 – 4.49 (m, 2H, NCH_2Bn), 4.46 – 4.39 (m, 1H, H-6a), 4.25 (dd, *J* = 14.6, 10.5 Hz, 2H, H-6b, H-5′), 4.08 (dt, *J* = 15.6, 8.4 Hz, 3H, H-4′, CH_2 PivOAc), 4.02 – 3.87 (m, 3H,

H-4, H-3′, H-3), 3.85 – 3.77 (m, 1H, H-5), 3.73 – 3.57 (m, 1H, OC*H*H Linker), 3.53 (s, 3H, CO_2CH_3), 3.49 – 3.17 (m, 4H, OC*H*H Linker, CH_2N Linker, H-2), 2.94 – 2.83 (m, 1H, CH_2 Lev), 2.79 – 2.50 (m, 3H, CH_2 Lev), 2.22 (s, 3H, CH_3 Lev), 1.98 (s, 3H, CH_3 PivOAc), 1.90 (d, J = 6.9 Hz, 2H, CH_2 PivOAc), 1.70 – 1.47 (m, 4H, 2x CH_2 Linker), 1.41 – 1.25 (m, 2H, CH_2 Linker). ^{13}C NMR (126 MHz, $CDCl_3$) δ 128.3, 128.1, 127.9, 127.8, 127.5, 127.4, 127.3, 126.7, 125.9, 125.8, 100.2, 97.7, 81.7, 79.6, 77.8, 76.6, 75.4, 74.7, 74.6, 74.5, 74.5, 73.3, 68.6, 68.3, 67.8, 67.2, 62.8, 62.5, 61.2, 60.0, 52.5, 50.8, 50.4, 47.0, 46.4, 38.3, 38.0, 30.0, 29.1, 28.5, 28.0, 25.4, 23.9, 23.4, 21.0. HRMS: m/z: calcd for $C_{71}H_{82}N_4O_{18}Na$: 1301.5522; found: 1301.5532 $[M+Na]^+$.

***N*-(Benzyl)-benzyloxycarbonyl-5-aminopentyl-*O*-(methyl-2-*O*-(4-acetoxy-2,2-dimethylbunoate)-3-*O*-benzyl-4-*O*-(2-methyl-napthyl)-β-D-glucupyranosyluronate)-(1→4)--*O*-2-deoxy-2-azido-3-*O*-benzyl-α-D-glucopyranoside (32).** Hydrazine acetate (10 mg, 0.10 mmol) was added to a solution of compound **31** (90 mg, 0.07 mmol) in a mixture of ethanol and toluene (2/1, v/v, 2 mL) and the reaction mixture was stirred at ambient temperature for 2 h. TLC analysis (hexanes/EtOAc, 80/20, v/v) showed complete consumption of the starting material. The reaction mixture was diluted with DCM (10 mL), washed with water and brine. The organic layer was dried ($MgSO_4$), filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using a gradient of toluene/EtOAc (4/1→ 3/1, v/v) to give compound **32** as oil (70 mg, 85%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 – 7.73 (m, 3H, C*H* Aromatic), 7.61 (s, 1H, C*H* Aromatic), 7.49 – 7.40 (m, 4H, C*H* Aromatic), 7.40 – 7.20 (m, 18H, C*H* Aromatic), 7.17 (d, J = 7.2 Hz, 1H, C*H* Aromatic), 5.23 – 5.09 (m, 4H, CH_2 Cbz, H-2′, C*H*HNAP), 4.88 – 4.62 (m, 7H, C*H*HNAP, C*H*HBn, CH*H*Bn, H-1′, H-1), 4.50 (d, J = 11.8 Hz, 2H, NCH_2Bn), 4.15 – 3.98 (m, 5H, CH_2 PivOAc, H-6a, H-5′, H-4′), 3.97 – 3.87 (m, 2H, H-4, H-3′), 3.85 – 3.70 (m, 2H, H-6b, H-3), 3.66 – 3.55 (m, 3H, OC*H*H Linker, H-5), 3.53 (s, 3H, COOCH_3), 3.43 – 3.13 (m, 4H, OCH*H* Linker, NCH_2Bn, H-2), 2.00 (d, J = 5.5 Hz, 3H, CH_3 PivOAc), 1.86 (t, J = 7.4 Hz, 2H, CH_2 PivOAc), 1.70 – 1.45 (m, 4H, 2x CH_2 Linker), 1.41 – 1.23 (m, 2H, CH_2 Linker). ^{13}C NMR (126 MHz, $CDCl_3$) δ 128.2, 128.1, 127.9, 127.7, 127.5, 127.2, 126.7, 125.9, 125.8, 100.4, 97.8, 81.8, 79.8, 77.0, 76.6, 75.1, 74.8, 74.7, 74.6, 73.2, 70.9, 68.2,

68.1, 67.1, 62.9, 61.2, 61.0, 54.8, 52.5, 51.0, 50.4, 46.4, 38.2, 28.9, 25.4, 23.9, 23.3, 20.9. HRMS: m/z: calcd for $C_{66}H_{76}N_4O_{16}Na$: 1203.5154; found: 1203.5160 $[M+Na]^+$.

***N*-(Benzyl)-benzyloxycarbonyl-5-aminopentyl-*O*-(methyl-2-*O*-(4-acetoxy-2,2-dimethylbunoate)-3-*O*-benzyl-4-*O*-(2-methyl-napthyl)-β-D-glucupyranosyluronate)-(1→4)-*O*-2-deoxy-2-azido-3-*O*-benzyl-6-*O*-sulfonato-β-D-glucopyranoside sodium salt (33).** Sulfur trioxide pyridine complex (68 mg, 0.06 mmol) was added to a solution of the compound **32** (55 mg 0.35 mmol,) in DMF (6 mL) and the resulting mixture was stirred for 2 h at ambient temperature. TLC analysis ($CHCl_3/CH_3OH$, 9/1, v/v) indicated complete consumption of starting material. $NaHCO_3$ (58 mg, 0.69 mmol) was added to the reaction mixture and it was continued to stir for additional 10 min. The crude mixture was filtered through a syringe filter and concentrated under reduced pressure (bath temperature 20 ^oC). The residue was passed through a column of iatrobeads using a gradient of $CHCl_3/CH_3OH$ (97/3 → 90/10, v/v). The fractions containing product were concentrated under reduced pressure (bath temperature 20 °C), and the residue was immediately passed through a column of Biorad resin (Na^+, 0.6 × 5 cm, CH_3OH), providing compound **33** as an amorphous powder (57 mg, 77%). ^1H NMR (500 MHz, CD_3OD) δ 7.85 – 7.80 (m, 1H, C*H* Aromatic), 7.78 (dd, *J* = 7.2, 3.5 Hz, 2H, C*H* Aromatic), 7.67 (d, *J* = 1.5 Hz, 1H, C*H* Aromatic), 7.50 – 7.19 (m, 24H, C*H* Aromatic), 5.25 – 5.03 (m, 5H, H-1′, H-2′, CH_2 Cbz, C*H*HNAP), 4.87 (s, 4H, 4 x CH_2Bn, H-1), 4.64 – 4.57 (m, 1H, C*H*HNAP), 4.54 (d, *J* = 4.2 Hz, 2H, NCH_2Bn), 4.40 (d, *J* = 10.8 Hz, 1H, H-6a), 4.28 (d, *J* = 9.2 Hz, 1H, H-5′), 4.17 (s, 1H, H-6b), 4.12 – 3.96 (m, 5H, CH_2 PivOAc, H-4, H-3′, H-4′, OCH*H* Linker), 3.88 – 3.65 (m, 2H, H-3, H-5), 3.58 (s, 3H, CO_2CH_3), 3.40 -3.20 (m, 4H, H-2, OCH_2 Linker, NCH_2 Linker), 1.95 (s, 3H, CH_3 PivOAc), 1.88 (t, J= 6.7 Hz, 2H, CH_2 PivOAc), 1.60 – 1.50 (m, 4H, 2 x CH_2 Linker), 1.43 – 1.27 (m, 2H, CH_2 Linker). ^{13}C NMR (126 MHz, CD_3OD) δ 128.1, 127.6, 127.5, 127.3, 125.8, 98.7, 97.6, 80.9, 77.2, 75.9, 74.7, 74.6, 74.4, 74.3, 74.0, 69.6, 66.4, 64.9, 64.6, 61.7, 61.0, 51.3, 49.7, 47.7, 46.0, 43.5, 38.5, 28.3, 23.6, 18.9. ESI MS: m/z: calcd for $C_{66}H_{75}N_4O_{19}S$: 1259.4746; found: 1259.4740 $[M-Na]^-$.

***N*-(Benzyl)-benzyloxycarbonyl-5-aminopentyl-*O*-(methyl-3-*O*-benzyl-4-*O*-(2-methyl-napthyl)-β-D-glucupyranosyluronate)-(1→4)-*O*-2-deoxy-2-azido-3-*O*-benzyl-6-*O*-sulfonato-**

α-D-glucopyranoside disodium salt (34). A premixed solution of aqueous H_2O_2 (50%, 110 µL, 3.90 mmol) and 1 M LiOH (1.90 mL, 1.90 mmol) were added to a solution of compound **33** (50 mg, 0.04 mmol) in THF (4 mL). The resulting mixture was stirred at ambient temperature for 8 h. An aqueous solution of NaOH (0.50 mL, 4 N) was added to the mixture (pH 14). The reaction mixture was stirred for additional 18 h at ambient temperature. The mixture was then treated with AcOH (pH 8-8.5), and concentrated under reduced pressure (bath temperature 20 °C). The residue was vortexed with water and purified by C18 column using a gradient of H_2O/CH_3OH (9/1 → 7/3, v/v). The appropriate fractions were concentrated under reduced pressure (bath temperature 20 °C), and the residue was passed through a column of Biorad resin (Na^+, 0.6 × 5 cm, CH_3OH) to obtain compound **34** as powder (37 mg, 84%). ^{1}NMR (500 MHz, CD_3OD) δ 7.83 – 7.79 (m, 1H, C*H* Aromatic), 7.79 – 7.72 (m, 3H, C*H* Aromatic), 7.54 – 7.50 (m, 2H, C*H* Aromatic), 7.50 – 7.38 (m, 5H, C*H* Aromatic), 7.37 – 7.18 (m, 15H, C*H* Aromatic), 5.27 – 5.13 (m, 3H, CH_2 Cbz, C*H*HNAP), 4.97 (dd, *J* = 17.3, 11.1 Hz, 2H, 2 x C*H*HBn), 4.90 -4.80 (m, 4H, 2 x C*H*HBn, H-1, H-1′), 4.69 (d, *J* = 11.3 Hz, 1H, C*H*HNAP), 4.60 – 4.50 (m, 3H, NCH_2Ph, H-6a), 4.35 (d, *J* = 11.0 Hz, 1H, H-6b), 3.99 – 3.86 (m, 5H, H-4′, H-5′, H-3, H-4, H-5), 3.70 -3.63 (m, 2H, OCH*H* Linker, H-3′), 3.55 (dd, *J* = 9.2, 7.8 Hz, 1H, H-2′), 3.48 – 3.38 (m, 1H, OCH*H* Linker), 3.36 -3.00 (m, 3H, CH_2N Linker, H-2), 1.65-1.50 (m, 4H, 2 x CH_2 Linker), 1.46 – 1.28 (m, 2H, CH_2 Linker). ^{13}C NMR (126 MHz, CD_3OD) δ 128.6, 128.5, 127.9, 127.6, 127.3, 127.2, 127.1, 127.0, 126.1, 125.9,125.3, 103.6, 97.5, 84.5, 80.7, 79.5, 77.9, 77.8, 74.9, 74.5, 74.4, 74.1, 69.7, 69.6, 67.4, 67.0, 65.9, 62.6, 51.5, 50.0, 48.0, 46.4, 28.2, 27.9, 27.3, 22.9. ESI MS: m/z: calcd for $C_{65}H_{73}N_4O_{19}S$: 1245.4590; found: 1245.4585 $[M-2Na+H]^-$.

***N*-(Benzyl)-benzyloxycarbonyl-5-aminopentyl-*O*-3-*O*-benzyl-4-*O*-(2-methyl-napthyl)-β-D-glucupyranosyluronate)-(1→4)-*O*-2-deoxy-2-acetamido-3-*O*-benzyl-6-*O*-sulfonato-α-D-glucopyranoside disodium salt (35).** Aqueous NaOH (0.1 M, 367 µL, 0.04 mmol) and PMe_3 in THF (1 M, 92 µL, 0.09 mmol) were added to a stirred solution of compound **34** (20 mg, 0.02 mmol) in THF (2 mL) at ambient temperature. After stirring for 3 h, TLC analysis (EtOAc/Pyr./AcOH/H_2O, 8/5/3/1) showed complete consumption of the starting material. The mixture was then treated with AcOH (pH 8-8.5), and was concentrated under reduced pressure (bath temperature 20 °C). The residue was vortexed with water and purified by C18 column

using a gradient of H_2O/CH_3OH (9/1 → 5/5, v/v). The appropriate fractions were concentrated under reduced pressure (bath temperature 20 °C), and the residue was passed through a column of Biorad resin (Na^+, 0.6 × 5 cm, CH_3OH) to give an intermediate amine as a powder (14 mg). Acetic anhydride (15 µL, 0. 13 mmol) was added to a solution of the amine (14 mg, 0.01 mmol) in CH_3OH (1 mL) and Et_3N (27 µL, 0.26 mmol) at 0 °C. After stirring for 1 h at ambient temperature, the mixture was co-evaporated with toluene under reduced pressure (bath temperature 20 °C). The residue was purified by a C18 column using a gradient of H_2O/CH_3OH (9/1 → 7/3, v/v). The appropriate fractions were concentrated under reduced pressure (bath temperature 20 °C), and the residue was passed through a column of Biorad resin (Na^+, 0.6 × 5 cm, CH_3OH) to give compound **35** as oil (12 mg, 83%). ^{1}H NMR (500 MHz, CD_3OD) δ 7.89 – 7.12 (m, 26H, C*H* Aromatic), 5.18 – 4.99 (m, 3H, CH*H*NAP, CH_2Bn), 5.00 – 4.91 (dd, *J* = 36.4, 17.1 Hz, 1H, C*H*HBn), 4.99 – 4.72 (m, 2H, H-1, C*H*HNAP), 4.69 (d, *J* = 17.4 Hz, 1H, H-1′), 4.61 (d, *J* = 11.2 Hz, 1H, C*H*HBn), 4.54 (s, 2H, CH_2Cbz), 4.51 – 4.41 (m, 1H, H-6a), 4.31 – 4.20 (m, 1H, H-6b), 4.08 (m, 1H, H-2), 3.92 – 3.66 (m, 5H, H-3, H-4, H-5, H-4′, H-5′), 3.66 – 3.54 (m, 2H, H-3′, OC*H*H Linker), 3.50 (t, *J* = 6.0 Hz, 1H, H-2′), 3.38 – 3.29 (m, 3H, OC*H*H Linker, CH_2N Linker,), 1.96 – 1.67 (m, 3H, COCH_3), 1.67 – 1.14 (m, 4H, 2 x CH_2 Linker), 1.41 – 0.93 (m, 2H, CH_2 Linker). ^{13}C NMR (126 MHz, CD_3OD) δ 127.9, 127.2, 127.2, 126.8, 125.5, 103.5, 97.1, 84.6, 80.5, 77.8, 77.2, 75.0, 74.8, 74.7, 74.6, 74.3, 74.2, 74.2, 74.0, 70.1, 69.6, 68.3, 67.5, 67.1, 66.3, 66.2, 52.8, 50.1, 48.5, 48.0, 46.5, 29.4, 28.0, 23.0, 21.2. ESI MS: m/z: calcd for $C_{67}H_{77}N_2O_{20}S$: 1261.4790; found: 1261.4783 $[M-2Na+H]^-$.

5-aminopentyl-*O*-β-D-glucupyranosyluronate-(1→4)-*O*-2-deoxy-2-acetamido-6-*O*-sulfonato-α-D-glucopyranoside disodium salt (36): A suspension of Pd/C (10%, 15 mg) was added to a solution of compound **35** (10.0 mg, 0.01 mmol) in a mixture of $CH_3OH/H_2O/CH_3CO_2H$ (1/1/0.01, v/v/v, 3 mL). The reaction mixture was stirred for 12 h under an atmosphere of hydrogen and then filtered through a PTFE syringe filter (0.2 mm, 13 mm), washed with a mixture of CH_3OH and H_2O (1/1, v/v, 2 mL), and the solvents were concentrated under reduced pressure. The residue was dissolved in a mixture of distilled water/CH_3CO_2H (1/0.01, v/v, 3 mL), and $Pd(OH)_2$ on carbon (Degussa type, 20%, 15 mg) was added. The mixture was stirred for 12 h under an atmosphere of hydrogen and then filtered through a PTFE

syringe filter. The residue was washed with H_2O (2 mL) and after freeze drying the filtrate, the residue was dissolved in H_2O and passed through a column of Biorad resin (Na^+, 0.6 × 2.5 cm, H_2O). The appropriate fractions were freeze dried to give compound **36** as white solid (3.9 mg, 86%). ^{1}H NMR (500 MHz, D_2O) δ 4.79 (d, *J* = 3.4 Hz, 1H, H-1), 4.48 (d, *J* = 6.2 Hz, 1H, H-1′), 4.35 (dd, *J* = 11.2, 2.0 Hz, 1H, H-6a), 4.17 (m, 1H, H-6b), 4.03 – 3.92 (m, 1H, H-5), 3.85 – 3.78 (m, 2H, H-2, H-3), 3.71 – 3.52 (m, 3H, H-4, H-4′, OC*H*H Linker), 3.48 – 3.35 (m, 3H, H-3′, H-5′, OC*H*H Linker), 3.24 (t, *J* = 3.4 Hz, 1H, H-2′), 2.98 – 2.86 (t, *J* = 7.7 Hz, 2H, CH_2N Linker), 1.97 – 1.90 (s, 3H, COCH_3), 1.68 – 1.47 (m, 4H, 2 x CH_2 Linker), 1.42 – 1.30 (m, 2H, CH_2 Linker). ^{13}C NMR (126 MHz, D_2O) δ 102.3, 96.4, 79.5, 75.7, 75.3, 73.0, 71.7, 69.4, 68.6, 68.0, 66.8, 53.2, 39.4, 28.0, 21.9, 26.2, 22.3. ESI MS: m/z: calcd for $C_{19}H_{33}N_2O_{15}S$: 561.1607; found: 561.1600 $[M-2Na+H]^-$.

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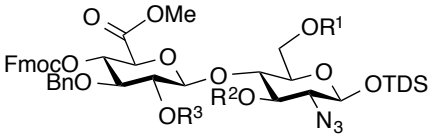
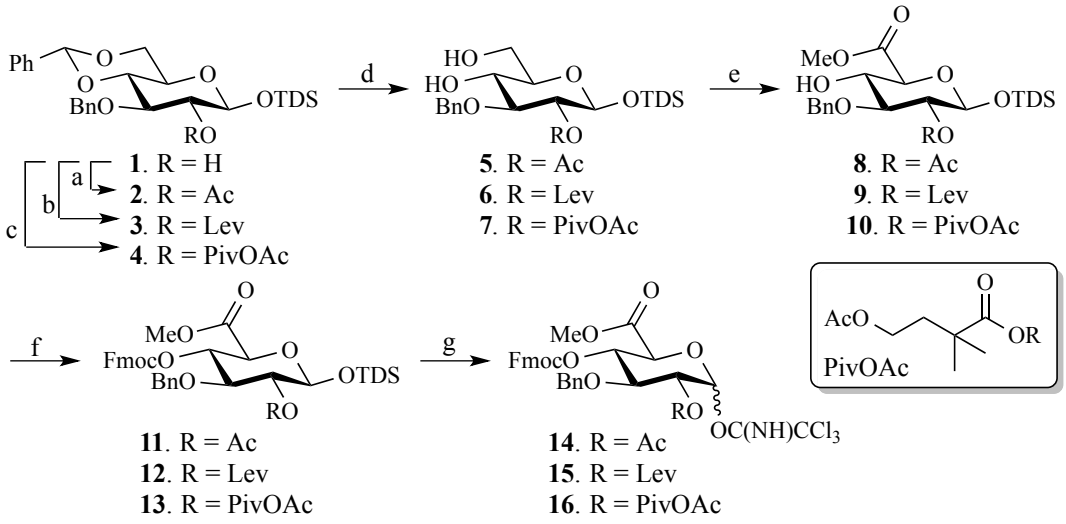


Sulfated	Unsulfated
R^1 = Lev	R^1 = Ac
R^2 = Lev	R^2 = Bn
R^3 = Lev	R^3 = Ac

Figure 1. Orthogonal protecting groups for disaccharide building blocks.



1. R = H
2. R = Ac
3. R = Lev
4. R = PivOAc

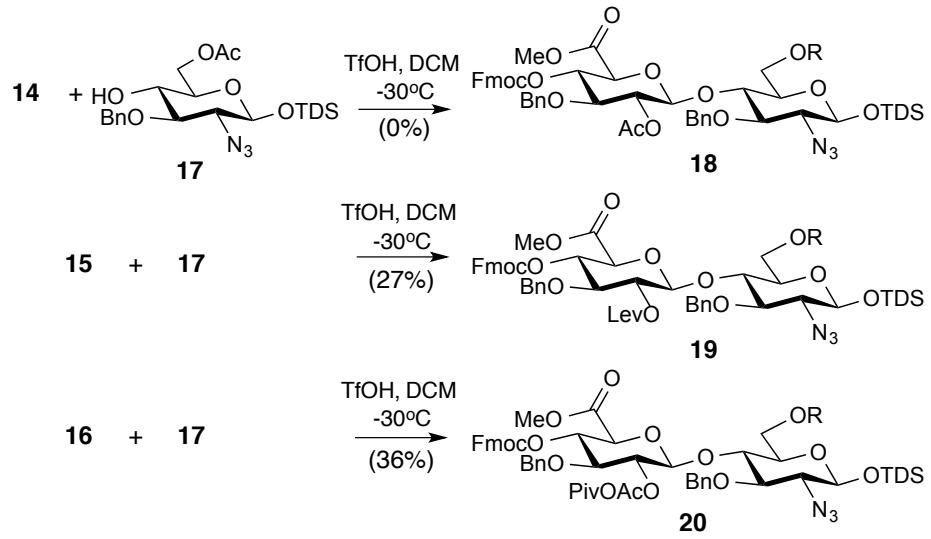
5. R = Ac
6. R = Lev
7. R = PivOAc

8. R = Ac
9. R = Lev
10. R = PivOAc

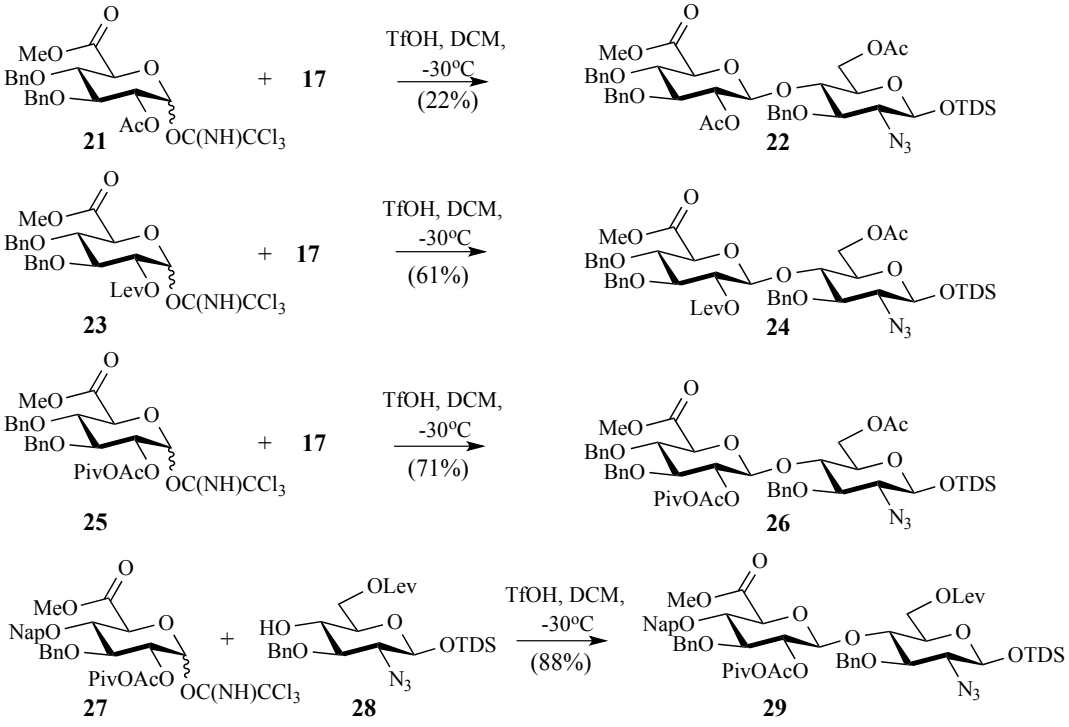
11. R = Ac
12. R = Lev
13. R = PivOAc

14. R = Ac
15. R = Lev
16. R = PivOAc

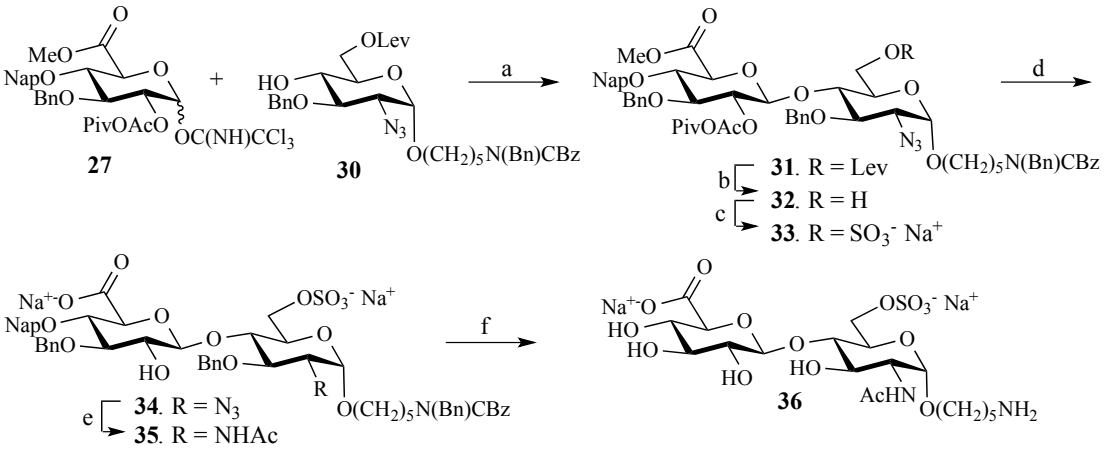
Scheme 1. Chemical synthesis of differently protected glucuronyl donors. Reagents and conditions: a) Ac_2O, pyridine (87%); b) levulinic acid, DCC, DMAP, CH_2Cl_2 (90%); c) PivOAcCl, DMAP, pyridine (86%); d) $CF_3C(O)OH$, CH_2Cl_2 (**5**, 77%, **6**, 81%), or EtSH, TsOH, DCM (**7**, 77%), e) TEMPO, BIAB, CH_2Cl_2, H_2O then CH_2N_2, Et_2O (**8**, 77%, **9**, 68%, **10**, 88%); f) FmocCl, DMAP, pyridine, (**11**, 94%, **12**, 87%, **13**, 76%); g) HF.pyridine, THF then Cl_3CCN, NaH, DCM.



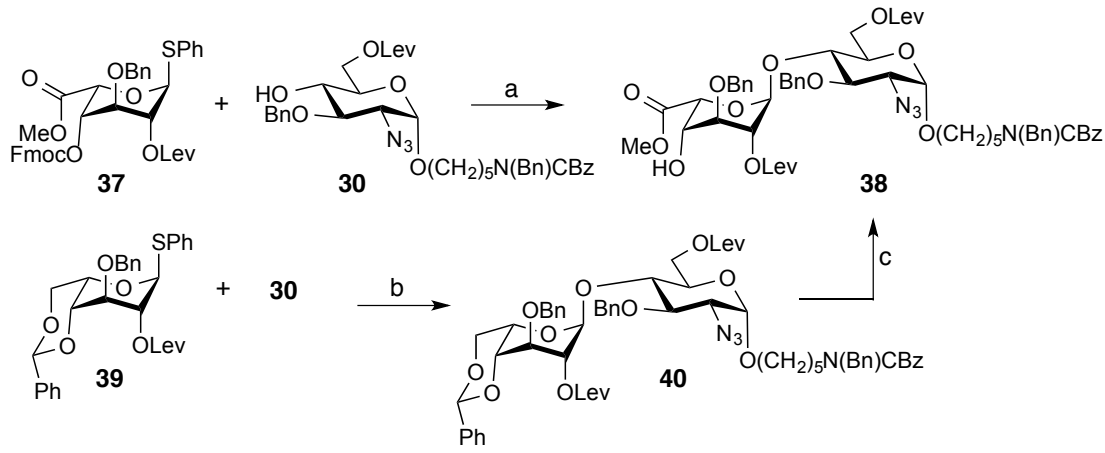
Scheme 2. Chemical glycosylations using uronyl donors.



Scheme 3. Improved glucuronyl donors.



Scheme 4. Deprotection and sulfation. Reagents and conditions: a) TfOH, DCM, -30ºC (64%); b) H_2NHH_2 AcOH, toluene/EtOH (65%); c) Pyr.SO_3, DMF (77%); d) LiOH, H_2O_2, THF then NaOH, MeOH (84%); e) PMe_3, THF, NaOH then Ac_2O; MeOH (83%); f) Pd/C, H_2 then $Pd(OH)_2$ (86%).



Scheme 5. Reagents and conditions: a) NIS, AgOTf, DCM, 0ºC, then Et_3N in DCM (70%, two-steps); b) NIS, AgOTf, DCM, 0ºC, (85%,); c) EtSH, TsOH, DCM, then TEMPO, BIAB, CH_2Cl_2, H_2O then CH_2N_2, Et_2O (50%, three-steps).

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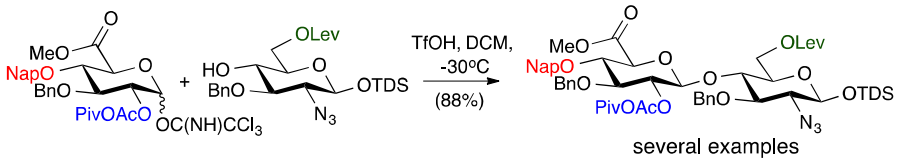

A streamlined approach has been developed for the preparation of modular disaccharide building blocks for the assembly of libraries of HS oligosaccharides that avoids post-glycosylation oxidation.