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Exploring and Exploiting the Reactivity of Glucuronic Acid Donors

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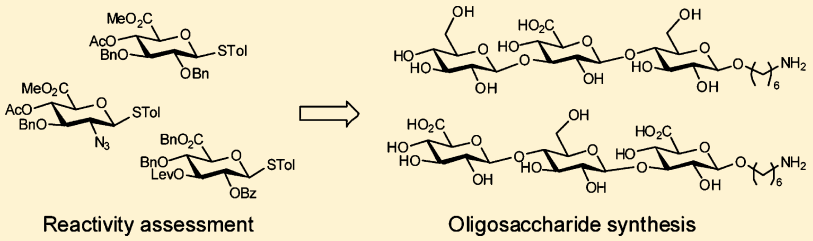
Supporting Information



ABSTRACT: The relative reactivity of glucuronic acid esters was established in a series of competition experiments, in which two thioglucoside and/or thioglucuronic acid ester donors competed for a limited amount of activator (NIS-TfOH). Although glucuronic acid esters are often considered to be of very low reactivity, the series of competition reactions revealed that the reactivity of the glucuronic acid esters studied is sufficient to provide productive glycosylation reactions. The latter is illustrated in the synthesis of two *Streptococcus pneumoniae* trisaccharides, in which the applicability of the two similarly protected frame-shifted thiodisaccharide donors, Glc-GlcA and GlcA-Glc, were compared. The Glc-GlcA disaccharide, featuring the glucuronic acid donor moiety, proved to be the most productive in the assembly of a protected *S. pneumoniae* trisaccharide.

INTRODUCTION

D-Glucuronic acid is a prime constituent of many biologically relevant poly- and oligosaccharides and glycoconjugates. For example, the human body uses glucuronylation as a key step in detoxification processes,[1] in which xenobiotic or endobiotic substances are rendered (more) water-soluble by the appendage of a glucuronic acid to allow secretion. Glucuronic acids are also frequently encountered on saponins, a very diverse class of glycosylated steroid- and triterpene-based compounds, forming the active ingredient of many traditional folk medicines.[2] The glycosaminoglycans (GAGs), a family of linear, anionic polysaccharides, which fulfill a plethora of biological functions,[3] are an important example of D-glucuronic acid containing polysaccharides. Furthermore, various bacterial capsular polysaccharides feature glucuronic acids as prominent contituents.[4] Because of their biological relevance, the synthesis of D-glucuronic acid containing oligosaccharides has received considerable attention.[5] For the preparation of glucuronic acid containing oligosaccharides, two strategies can be used. In a postglycosylation−oxidation approach, the oligosaccharide backbone is assembled with nonoxidized glucosyl building blocks and the introduction of the carboxylic acid moiety takes place at the oligosaccharide stage. In a preglycosylation−oxidation approach, the oligosaccharide is prepared using glucuronic acid building blocks. Because glucuronic acids are often considered to be unreactive glycosyl donors because of the presence of the electron-withdrawing carboxylic acid moiety, the postglycosylation−oxidation approach is usually favored over the alternate strategy.[5,6] The reactivity of a large number of thioglycoside donors[7] has been quantified by the groups of Ley,[8] Wong,[9] and Bols,[10] but the relative reactivity of thioglucuronic acid esters has never been explored.[11] The establishment of the relative reactivity of carbohydrate building blocks can not only pave the way for chemoselective glycosylation reaction sequences but also provides important insight into the glycosylation capacity of a given donor. We here present the establishment of the relative reactivity of glucuronic acid ester thiodonors in relation to the reactivity of a set of relevant thioglucosides. Guided by these results, glucuronic acid donors were probed for their use in the construction of *Streptococcus pneumoniae* type 3 di- and trisaccharides.

RESULTS AND DISCUSSION

We investigated the relative reactivity of three different thioglucuronic acid esters **1**, **2**, and **3**, in combination with the panel of thioglucosides (**4**−**7**) displayed in Table 1. Di-*O*-benzyl glucuronic acid ester **1** was studied as a model glucuronic acid ester having two "arming" benzyl protecting groups.[12] Azidoglucuronate (donor **2**) was used to investigate the effect of a strongly electron-withdrawing functionality on the reactivity. Glucuronic acid ester **3** was studied because it represents a potentially useful building block in the preparation of fragments of the *Streptococcus pneumoniae* type 3 capsular oligosaccharide (vide infra). Thioglucosides **4**−**7** were used as reference compounds because these represent commonly used glucosyl donors featuring arming (benzyl ethers), semidisarming (benzylidene acetal),[13] and disarming (benzoyl and acetyl esters) protecting groups. Wong and co-workers have quantified the

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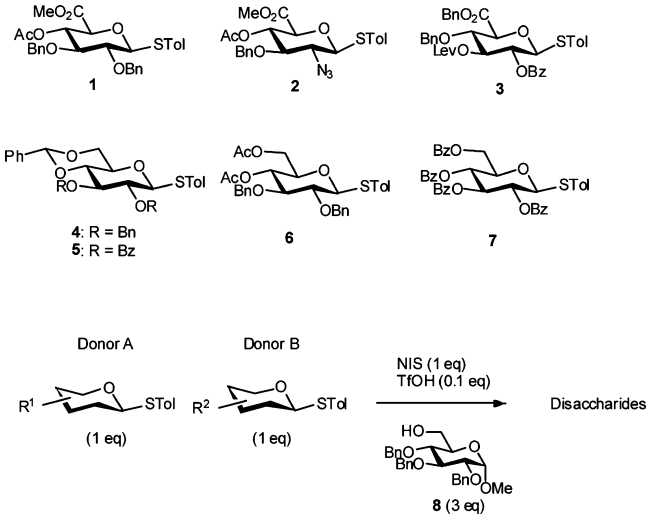
Table 1. Competing Donors in Glycosylation of 8



entry	donor A	donor B	product[a] ratio[b] donor A/donor B	yield (%)
1	**1**	**4**	1:1	90
2	**1**	**6**	1:8	87
3	**4**	**6**	1:8	84
4	**1**	**5**	2.3:1	90
5	**1**	**2**	1:0	95
6	**1**	**3**	9:1	89
7	**2**	**3**	0:1	84
8	**2**	7	1:0	94

[a]For structures of the disaccharides, see the Experimental Section. [b]Product ratio was determined by NMR of the disaccharide mixtures.

reactivity of a large series of *p*-methylphenylthio (*S*-tolyl)-glycosides using the NIS-TfOH promoter system.[9] To stay close to this system, we also employed *S*-Tol donors and the same activator. In our competition experiments (Table 1), two thioglucuronic acid esters and/or thioglycosides competed for a limited amount of activator (NIS, 1 equiv) in the presence of a catalytic amount of TfOH (0.1 equiv) and an excess of the model glycosyl acceptor methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **8** (3 equiv).[11] The ratio of formed disaccharides was established by NMR spectroscopy using the fraction of disaccharides, obtained after size-exclusion chromatography of the crude reaction mixtures. The results of these experiments are summarized in Table 1.

In the first competition reaction, glucuronic acid ester **1** competed with benzylidene-protected glucoside **4** leading to 1:1 mixture of the corresponding disaccharides (entry 1), indicating that the combined deactivating effect of the C-5 carboxylic acid ester and the C-4-*O*-acetate in **1** is similar to the disarming effect of the benzylidene group in **4**. The similar reactivity of glucuronic acid **1** and benzylidene glucoside **4** was confirmed in competition experiments, in which both donors competed separately with donor **6** (entry 2 and 3). Diacetyl donor **6** turned out to be eight times more reactive than both donor **1** and donor **4**. In line with expectations, the C-5 carboxylic acid ester reduces the reactivity of a glucosyl donor more than a CH_2OAc moiety at C-5 (entry 2).[14] The conformationally and electronically disarming 4,6-benzylidene group[13] in **4** reduces the glucosyl donor reactivity more than the two acetyls at the C-4 and C-6 position (entry 3). This is in line with the relative reactivity of the analogous mannosyl donors, on which we recently reported.[11] The introduction of stronger electron-withdrawing benzoyl groups at C-2 and C-3 of the 4,6-*O*-benzylidene glucoside leads to a donor (**5**) that is less reactive than glucuronic acid methyl ester **1** (entry 4). The introduction of an azide at C-2 of the glucuronic acid donor, as in **2**, significantly reduces the reactivity, as judged from entry 5, which shows that only the disaccharide derived from donor **1** was formed. The reactivity of glucuronic acid **3**, a building block to be used in the assembly of the *S. pneumoniae* oligomers, was assessed in competion experiments with both glucuronides **1** and **2**.[15] Donor **3** was less reactive than dibenzyl donor **1** and more reactive than **2** (entries 6 and 7). To establish the relative reactivity of the uronic acid donors with respect to a glucosyl donor of known reactivity, we competed the least reactive glucuronide, i.e. **2**, with tetra-*O*-benzoyl glucose donor **7**. Glucosyl donor **7** has a relative reactivity value (RRV) of 1.3, on a scale in which α-*S*-tolyl peracetylmannose has a RRV of 1 and β-*S*-tolyl perbenzylglucose a RRV of 2656, as established by Wong and co-workers.[9] In this competition reaction (entry 8), the 2-azidoglucuronic acid donor completely outcompeted the tetrabenzoyl glucosyl donor leading to the formation of the glucuronic acid derived disaccharide as the sole product in 94% yield. Taken together, these results show that, although the C-5 carboxylic acid ester has a disarming effect on glucosyl donor reactivity (Table 1, entry 2), glucuronic acids should not by definition be classified as highly unreactive donors, but placed in the continuum of reactivity among the 4,6-*O*-benzylidene glucosides.

We then explored the utility of monomeric and dimeric donor building blocks in the synthesis of *Streptococcus pneumoniae* type 3 oligosaccharides. *S. pneumoniae* is one of the most prevalent commensal Gram-positive pathogens, causing a variety of diseases such as bacteremia, otitis media, meningitis, and sepsis.[16] A tridecavalent capsular polysaccharide vaccine, licensed under the name of Prevnar/Prevenar-13, which is routinely administered to infants and young children, presents one of the most powerful weapons to prevent infections by this pathogen, and polyvalent vaccines providing protection against more *S. pneumoniae* serotypes are currently being introduced on the market.[17] To study the immune response to this type of vaccines and the virulence factors of the parent pathogen at the molecular level, well-defined oligo- or polysaccharide structures are valuable tools.[18] The anionic cellobiouronic acid polymer of *S. pneumoniae* type 3, built up from 1,3-linked [β-glucuronic acid-(1→4)-β-glucose] disaccharide repeats[19] is one of the prominent *S. pneumoniae* capsular polysaccharides. In the construction of fragments of this polysaccharide two types of linkages have to be installed: a β-glucuronic acid bond to the C-4-OH of a glucose acceptor and a β-glucosyl bond to a glucuronic acid C-3-OH. Although previous syntheses of this oligosaccharide have employed a postglycosylation oxidation approach to circumvent the assumed low reactivity of glucuronic acid building blocks,[20] the results described above indicate that the reactivity of glucuronic acid donors such as **3** is sufficient to be of use in the synthesis of oligosaccharides. We therefore investigated the construction of these bonds using both monomeric and dimeric glucuronic acid donor building blocks as described below.

First, the two relevant monomeric acceptors **10** and **14** were assembled as depicted in Scheme 1. Glucuronic acid donor **3** and *S*-tolyl glucose **12** were condensed with an azidohexanol spacer under the agency of NIS/TfOH to provide **9** and **13** in 85% and 80% yield, respectively. Delevulinoylation gave the two acceptor molecules **10** and **14** in 91% and 99% yield, respectively. The glycosylation of glucoside **12** (1 equiv) with glucuronic acid ester acceptor **10** (1.3 equiv) yielded disaccharide **11** in 62% yield.

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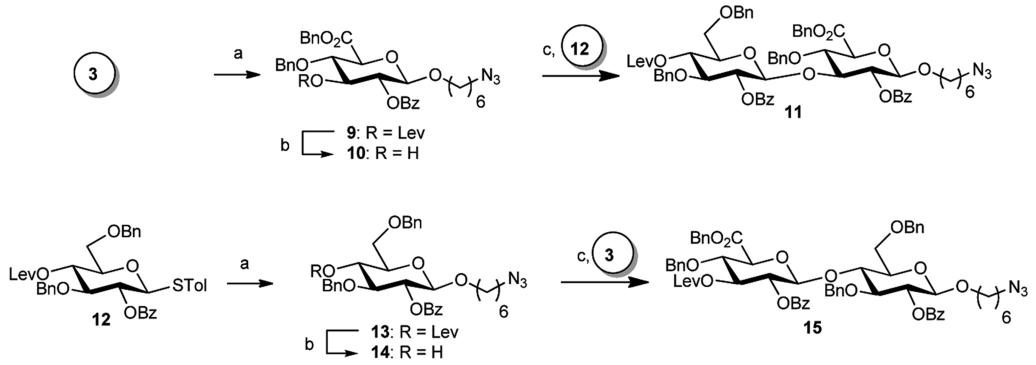
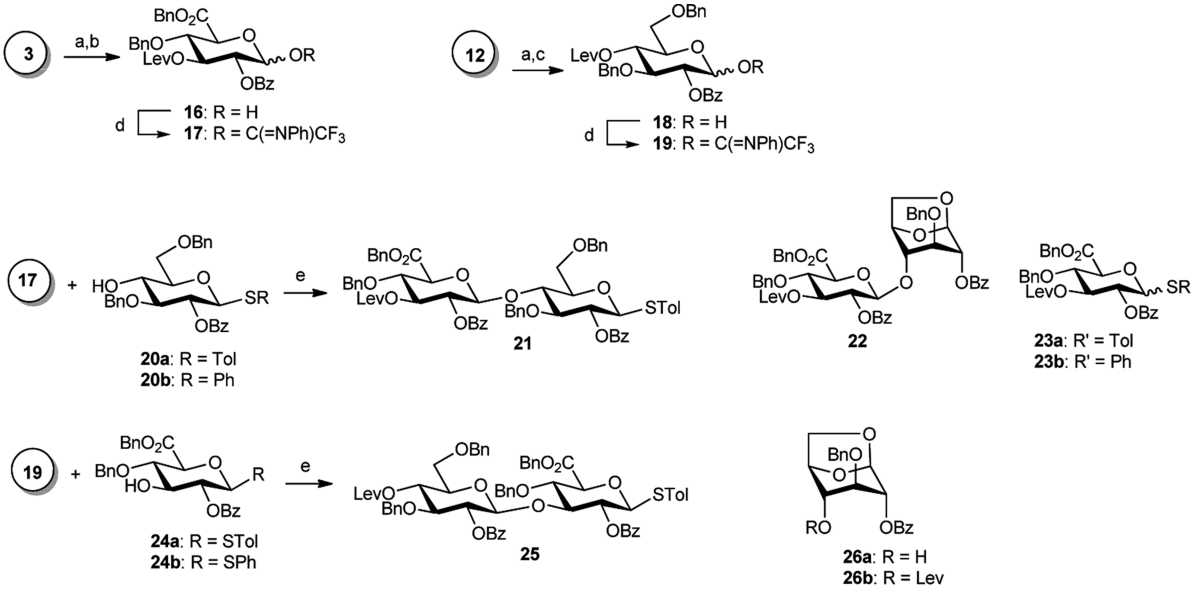
Scheme 1. Synthesis of Both Alternating Disaccharides[a]



[a]Reagents and conditions: (a) $HO(CH_2)_6N_3$, NIS, TfOH, DCM, 0 °C, **9**: 85%, **13**: 80%; (b) $NH_2NH_2{\cdot}H_2O$, pyridine/AcOH, **10**: 91%, **14**: 99%; (c) NIS, TfOH, DCM, 0 °C, **11**: 62%, **15**: 74%.

Scheme 2. Synthesis of the Dimeric Donors[a]



[a]Reagents and conditions: (a) NIS, TFA, DCM, 0 °C; (b) $NaHCO_3$ (aq, sat), **16**: 88%; (c) piperidine, **18**: 84%; (d) $ClC(=NPh)CF_3$, Cs_2CO_3, acetone, 0 °C, **17**: 83%, **19**: 68%; (e) TfOH, DCM, 0 °C, **21**: 12%, **25**: 0%.

Glucuronic acid ester donor **3** (1.3 equiv) was condensed with glucosyl acceptor **14** (1 equiv) to give the alternative disaccharide **15** in slightly higher yield (74%). These results show that the glucose donor–glucuronic acid acceptor combination does not outperform the glucuronic acid donor–glucose acceptor pair.

Next, we explored the applicability of dimer donors in the synthesis of two complementary trisaccharides. The required dimer donors **21** and **25** were synthesized in an orthogonal glycosylation reaction[7] between a *S*-tolyl acceptor and a trifluoro-*N*-phenylimidate donor,[21] in turn obtained from the thioglycoside precursor **3** or **12** (Scheme 2).[22] The preparation of imidate **17** started by substitution of the anomeric thio functionality in **3** for a trifluoroacetyl function using NIS and TFA in dry DCM.[23] Subsequent hydrolysis of the anomeric trifluoroacetate with aqueous $NaHCO_3$ led to hemiacetal **16** in 88%. These conditions, however, were not efficient for the hydrolysis of donor **12**, as a result of intramolecular benzoyl migration.[24] To prevent the formation of the anomeric benzoate, we cleaved the anomeric trifluoroacetate with piperidine, which yielded hemiacetal **18** in 84%. The hemiacetals **16** and **18** were converted into the corresponding *N*-phenyl trifluoroacetimidate donors **17**, and **19** in 83% and 68% yield, respectively. The *S*-tolyl acceptors **20a** and **24a** were obtained en route to donors **12** and **3**.

The condensation of glucuronic acid ester *N*-phenyl trifluoroacetimidate **17** (1.3 equiv) with acceptor **20a** (1 equiv) using a catalytic amount of TfOH in DCM only led to a modest yield of disaccharide **21** (12%). Increasing the concentration of the reaction (0.05 to 0.5 M) did not give an improved yield but led to formation of two major side products instead. Disaccharide **22**, featuring an anhydroglucose reducing end, and *S*-tolyl glucuronic acid ester **23a** were isolated in 29% and 10% yield, respectively. The formation of glucuronic acid ester **23a** can be explained by aglycon transfer from glucoside **20a** to the activated glucuronic acid donor (Scheme 3).[25] The activated glucoside, formed in this event, collapses via the formation of the 1,6-anhydro ring[26] into a glucosyl acceptor **26a**, with an accessible axial hydroxyl group. This 1,6-anhydro glucoside reacts with an activated glucuronic acid ester, leading to the formation of disaccharide **22**. To explore whether these side reactions were due to the nucleophilicity of the anomeric *S*-tolyl moiety in **20a**, we prepared acceptor **20b**, bearing the

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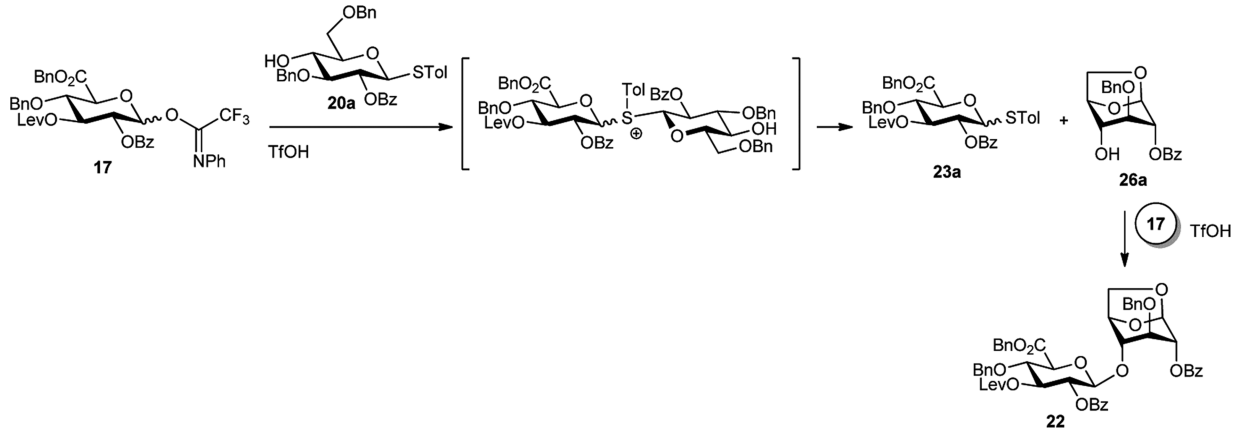
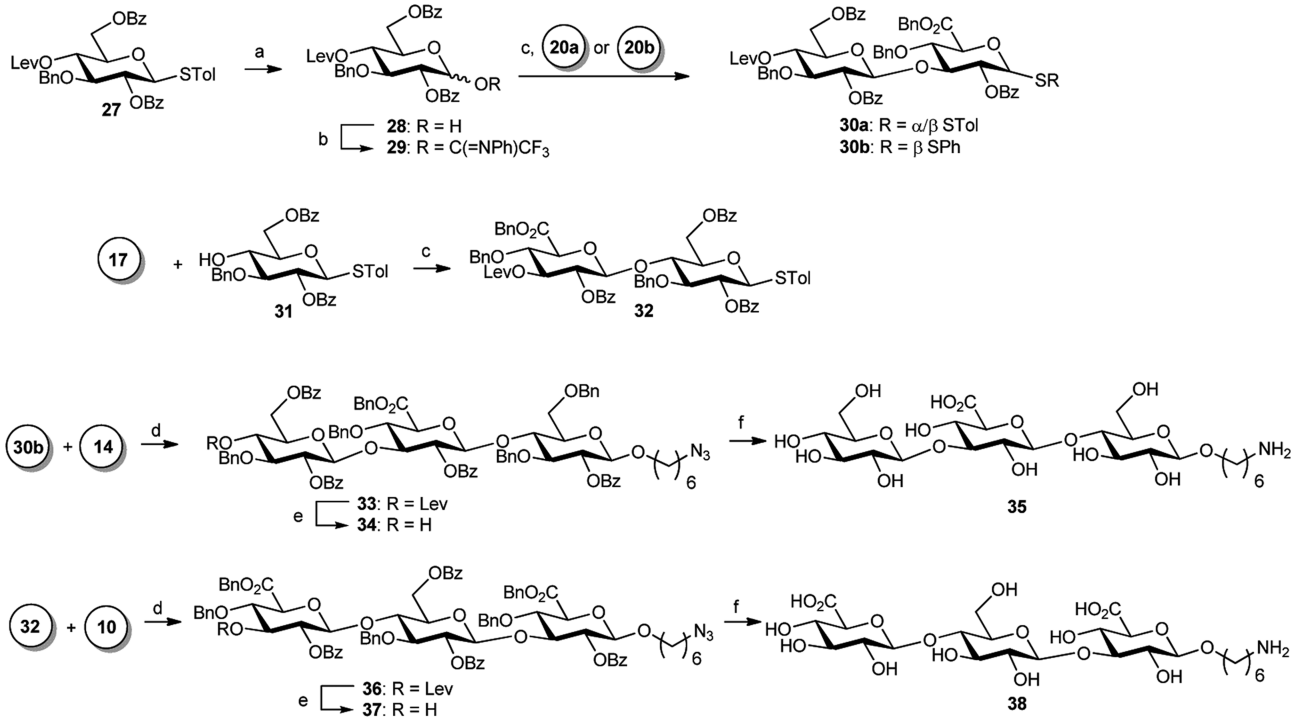
Scheme 3. Aglycon Transfer during the Condensation of Glucuronic Acid Donor 17 and Acceptor 20a



Scheme 4. Preparation of the Dimeric Donors and the Construction of the Trisaccharides[a]



[a]Reagents and conditions: (a) NIS, TFA, DCM, 0 °C, then piperidine, 85%; (b) ClC(=NPh)CF_3, Cs_2CO_3, acetone, 0 °C, 77%; (c) TfOH, DCM, 0 °C, **30a**: 51%, **30b**: 64%, **32**: 68%; (d) NIS, TfOH, DCM, 0 °C, **33**: 75%, **36**: 51%; (e) hydrazine acetate, pyridine/AcOH, **34**: 95%, **37**: 93%; (f) (i) KOH, dioxane/H_2O, (ii) H_2, Pd/C, ^{t}BuOH/H_2O, **35**: 44%/two steps; **38**: 28%/two steps.

somewhat less nucleophilic thiophenyl aglycon.[27] However, use of this thioglucosyl acceptor also resulted in aglycon transfer, yielding glucuronic acid ester **23b**, and disaccharide **22** (41% isolated yield). On the basis of these results, we reasoned that activation of donor **17** was not the problem but that acceptors **20a** and **20b** were simply too reactive. This was confirmed in the attempted synthesis of dimer **25** through the condensation of glycosyl *N*-phenyl trifluoroacetimidate **19** (1.3 equiv) and glucuronic acid ester acceptor **24a** (1 equiv) (Scheme 2). No disaccharide could be obtained from this reaction; instead, only anhydroglucoside **26b** was isolated in 34% yield.

In order to prevent these side reactions, we decided to downtune the donor reactivity of the *S*-tolyl glucosyl building block by replacing the C-6-*O*-benzyl for a more electron-withdrawing C-6-*O*-benzoyl group, resulting in donor **27**[28] and acceptor **31** (Scheme 4). The condensation of glucuronic acid imidate **17** with acceptor glucoside **31** yielded disaccharide **32** without any side products. Similarly, anhydroglucoside formation was prevented in the reaction between glucosyl imidate **29** (1 equiv) and glucuronic acid acceptor **20a** (1.3 equiv), which gave disaccharide **30a** in 51% yield. This disaccharide, however, was obtained as a mixture of α/β-thioglucuronides (α/β 1/5).[29] Anomerisation was not observed when glucuronic acid ester **20b**, having a somewhat less electron rich thiophenyl function,[26] was used. Dimer **30b** was uneventfully obtained from **29** (1.3 equiv) and **20b** (1 equiv) in 64% yield. Next, the disaccharide donors **30b** and **32** were used for the formation of trisaccharides **33** and **36**. Donor **30b**, having the glucuronic acid donor moiety (1 equiv) was coupled to spacer containing glucoside **14** (1.3 equiv), leading to the formation of trisaccharide **33** in 75% yield.

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The condensation of dimer **32** (1 equiv), featuring the glucosyl donor moiety, and acceptor **10** (1.3 equiv) led to the alternative trimer **36** in 54% yield. In line with the results obtained with the monomeric donors, the glucuronic acid donor−glucosyl acceptor combination performed better than the corresponding glucosyl donor−glucuronic acid acceptor couple, indicating that the former disaccharide donor is the building block of choice for the assembly of larger oligomers of *S. pneumoniae* type 3.

Finally, the obtained trisaccharides were deprotected as follows. First, the levulinyl group was removed from trisaccharide **33** and **36** by treatment with hydrazine acetate in a pyridine/AcOH mixture, yielding trisaccharides **34** and **37** in 95% and 93% yield, respectively. Then, the benzoyl esters and benzyl esters were saponified using KOH in dioxane/H_2O and the azido en benzyl protective groups were reduced with H_2 gas and Pd/C in a mixture of ^{t}BuOH and H_2O. The deprotected trisaccharides **35** and **38** were obtained in 44% and 28% yield over two steps, respectively.

CONCLUSION

In summary, we determined the relative reactivity of a set of thioglucuronic acid esters. From the established reactivities it has become apparent that the reactivity of glucuronic acid is not as low as often assumed. For example, 2,3-di-*O*-benzylglucuronic acid methyl ester **1** was shown to be of equal reactivity as 2,3-di-*O*-benzyl-4,6-*O*-benzylideneglucosyl donor **4**, and the least reactive glucuronide studied here, azidoglucuronic acid **2**, outcompeted tetrabenzoyl glucose **7** completely. In the construction of dimers and trimers of the capsular polysaccharide of *Streptococcus pneumoniae* type 3, the glycosylations involving the glucuronic acid donors proceeded well, paving the way for the preparation of larger oligomers.

EXPERIMENTAL SECTION

General Experimental Procedures. Chemical shifts (δ) are given in ppm relative to TMS as internal standard. All ^{13}C-APT spectra are proton decoupled. IR spectra are reported in cm^{-1}. Reactions were performed at rt unless stated otherwise and were followed by TLC analysis with detection by UV absorption (254 nm) where applicable and by spraying with 20% sulfuric acid in EtOH or with a solution of $(NH_4)_6Mo_7O_{24}\cdot H_2O$ (25 g L^{-1}), followed by charring at 150 °C. Flash column chromatography was performed on silica gel (0.04−0.063 nm) and size-exclusion chromatography (SEC) was performed on Sephadex LH-20. Experiments which required an inert atmosphere were carried out under dry argon. Dichloromethane (p.a.) was distilled over P_2O_5 prior to use. Molecular sieves (3 Å) were flame-dried before use.

General Procedure for the Competition Experiments. Donor A (0.1 mmol, 1 equiv), donor B (0.1 mmol, 1 equiv) and the acceptor (methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside, 3 equiv) were coevaporated with toluene (2×). DCM was refluxed with P_2O_5 and distilled before use. Freshly distilled DCM (4 mL, donor concentration 0.05 M), a Teflon stirrer bar, and activated (flame-dried) molecular sieves 3 Å were added, and the mixture was stirred under argon for 30 min at rt. NIS (1 equiv) was added, and the mixture was cooled to −40 °C. TfOH (0.1 equiv, 0.1 mL of a 0.1 M stock solution in distilled DCM) was added, and the mixture was allowed to warm to 0 °C in ∼3 h. Triethylamine (0.1 mL) was added, and the mixture was diluted with EtOAc, washed with satd aq $Na_2S_2O_3$ (1×) and satd aq NaCl (2×), dried over $MgSO_4$, and concentrated in vacuo. Elution over a Sephadex LH-20 (DCM/MeOH, 1/1, v/v) enabled isolation of the disaccharide products, which were analyzed with NMR spectroscopy. The yield of the disaccharide fraction and the ratio of the disaccharides were determined.

General Procedure for Glycosylations Using NIS/TfOH. The donor and acceptor glucosides and/or glucuronic acid esters were coevaporated with toluene (2×), dissolved in freshly distilled DCM, followed by addition of activated (flame-dried) molecular sieves 3 Å. The reaction mixture was stirred for 30 min, followed by addition of NIS (1.3 equiv relative to the donor). The reaction mixture was cooled to 0 °C, followed by addition of TfOH (0.1 equiv), and the reaction mixture was allowed to warm to rt. When TLC analysis showed completion, the reaction mixture was neutralized with TEA and quenched with $Na_2S_2O_3$ (aq, satd). The organic layer was isolated, dried over $MgSO_4$, filtered, and concentrated. Size-exclusion chromatography (DCM/MeOH, 1/1, v/v) and/or column chromatography resulted in the isolation of the products formed.

*Benzyl (6-Azidohexyl 4-O-benzyl-2-O-benzoyl-3-O-levulinyl-β-D-glucopyranosyluronate) (**9**).* Glucuronic acid ester **3** (410 mg, 0.6 mmol) and 6-azidohexanol (102 mg, 0.71 mmol, 1.18 equiv) were coevaporated with toluene (2×) and dissolved in freshly distilled DCM (24 mL, 0.03 M). Activated MS 3 Å were added, and the reaction mixture was stirred for 30 min, followed by addition of NIS (202 mg, 0.9 mmol, 1.5 equiv). The reaction mixture was cooled to 0 °C, followed by addition of TfOH (0.6 mL of a 0.1 M stock solution, 0.06 mmol, 0.1 equiv). The reaction mixture was allowed to warm to rt, and after 3 h, TLC analysis (PE/EtOAc 12/8, v/v) showed total conversion into a higher running spot. The reaction mixture was neutralized with TEA, quenched with $Na_2S_2O_3$ (aq, satd), and diluted with EtOAc, followed by separation of the layers. The organic layer was washed with $NaHCO_3$ (aq, satd) and brine, dried over $MgSO_4$, filtered, and concentrated. Column chromatography (PE/EtOAc 1/0 → 17:3) gave the title compound in 85% yield (358 mg, 0.51 mmol). $[\alpha]^{20}_D$: +24.2 (c = 0.7, DCM). IR (neat, cm^{-1}): 2940, 2862, 2097, 1746, 1724, 1454, 1360, 1315, 1265, 1215, 1179, 1153, 1096, 1070, 1028, 1001, 735, 712, 700. ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 7.99 (d, 2H, J = 7.6 Hz, H_{arom}), 7.57 (t, 1H, J = 7.6 Hz, H_{arom}), 7.46−7.42 (m, 2H, H_{arom}), 7.36−7.24 (m, 7H, H_{arom}), 7.18−7.14 (m, 3H, H_{arom}), 5.43 (t, 1H, J = 9.6 Hz, H-3), 5.25−5.18 (m, 3H, H-2, CH_2 CO_2Bn), 4.62 (d, 1H, J = 7.6 Hz, H-1), 5.54 (d, 1H, J = 11.2 Hz, C*H*HPh), 4.81 (d, 1H, CH*H*Ph), 4.01−4.013 (m, 2H, H-4, H-5), 3.90−3.85 (m, C*H*H $N_3(CH_2)_6OH$), 3.49−3.41 (CH*H* $N_3(CH_2)_6OH$), 3.04 (t, 2H, J = 7.2 Hz, $N_3(CH_2)_6OH$), 2.52−2.47 (m, 2H, CH_2 Lev), 2.40−2.35 (m, 2H, CH_2 Lev), 2.00 (s, 3H, CH_3 Lev), 1.50−1.45 (m, 2H, CH_2 $N_3(CH_2)_6OH$), 1.34−1.28 (m, 4H, 2 × CH_2 $N_3(CH_2)_6OH$), 1.28−1.15 (m, 2H, CH_2 $N_3(CH_2)_6OH$). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 205.9 (C=O Lev ketone), 171.9 (C=O Lev), 168.0 (C-6), 165.3 (C=O Bz), 137.6 (C_q C_{arom}), 135.0 (C_q C_{arom}), 133.4 (CH_{arom}), 129.9 (CH_{arom}), 129.5 (C_q C_{arom}), 129.2−128.0 (CH_{arom}), 125.4 (CH_{arom}), 101.4 (C-1), 77.6 (C-4 or C-5), 77.4 (C-4 or C-5), 74.2 (C-3), 72.0 (C-2), 70.2 (CH_2 $N_3(CH_2)_6OH$), 67.7 (CH_2 CO_2Bn), 51.3 (CH_2 $N_3(CH_2)_6OH$), 37.8 (CH_2 Lev), 29.2 (CH_2 $N_3(CH_2)_6OH$), 28.7 (CH_2 $N_3(CH_2)_6OH$), 28.0 (CH_2 Lev), 26.4 (CH_2 $N_3(CH_2)_6OH$), 25.5 (CH_2 $N_3(CH_2)_6OH$). HRMS: $[M + Na]^+$ calcd for $C_{38}H_{43}N_3O_{10}Na$ 724.28407, found 724.28369.

*Benzyl (6-Azidohexyl 2-O-benzoyl-4-O-benzyl-β-D-glucopyranosyluronate) (**10**).* Glucuronic acid ester **9** (211 mg, 0.3 mmol) was dissolved in a mixture of pyridine/AcOH (4/1, 6 mL), and hydrazine monohydrate (90 μL, 1.50 mmol, 5 equiv) was added. The reaction mixture was stirred for 2 h. The reaction mixture was diluted with EtOAc, washed with 1 M HCl and $NaHCO_3$ (aq, satd), dried over $MgSO_4$, filtered, and concentrated. Column chromatography (PE/EtOAc 9/1) gave the title compound as a transparent oil in 91% yield (165 mg, 0.27 mmol). $[\alpha]^{20}_D$: −1.5 (c = 1.6, DCM). IR (neat, cm^{-1}): 2932, 2884, 2860, 2095, 1732, 1601, 1497, 1454, 1396, 1362, 1315, 1267, 1215, 1177, 1098, 1069, 1028, 1009, 1001, 978, 908, 897, 750, 712, 698, 619. ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 8.04 (d, 2H, J = 7.6 Hz, H_{arom}), 7.58 (t, 1H, J = 7.2 Hz, H_{arom}), 7.45−7.22 (m, 10H, H_{arom}), 7.20−7.18 (m, 2H, H_{arom}), 5.25 (d, 1H, J = 12.4 Hz, C*H*HPh), 5.20 (d, 1H, J = 12.0 Hz, CH*H*Ph), 5.10 (t, 1H, J = 8.2 Hz, H-2), 4.70 (d, 1H, J = 11.2 Hz, C*H*HPh), 4.60 (d, 1H, J = 7.6 Hz, H-1), 5.54 (d, 1H, J = 11.2 Hz, CH*H*Ph), 4.02 (d, 1H, J = 8.8 Hz, H-5), 3.95−3.86 (m, 3H, H-3, H-4, C*H*H $N_3(CH_2)_6OH$), 3.48−3.23 (m, 1H, CH*H* $N_3(CH_2)_6OH$), 3.06 (t, 2H, J = 7.0 Hz, CH_2 $N_3(CH_2)_6OH$), 2.72 (bs, 1H, C-3-O*H*), 1.54−1.44 (m, 2H, CH_2 $N_3(CH_2)_6OH$), 1.35−1.13 (m, 6H, 3x CH_2 $N_3(CH_2)_6OH$). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 168.4 (C=O), 166.3 (C=O), 137.9 (C_q C_{arom}), 135.1 (C_q C_{arom}),

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133.6 (CH_{arom}), 130.0 (CH_{arom}), 129.6 (C_q C_{arom}), 128.7−128.1 (CH_{arom}), 101.2 (C-1), 79.8 (C-3 or C-4), 75.3 (C-3 or C-4), 75.0 (CH2 Bn), 74.7 (C-2 or C-5), 74.6 (C-2 or C-5), 70.1 (CH_2 $N_3(CH_2)_6OH$), 67.6 (CH_2 CO_2Bn), 51.3 (CH_2 $N_3(CH_2)_6OH$), 29.3 (CH_2 $N_3(CH_2)_6OH$), 28.7 (CH_2 $N_3(CH_2)_6OH$), 26.4 (CH_2 $N_3(CH_2)_6OH$), 25.5 (CH_2 $N_3(CH_2)_6OH$). HRMS: $[M + Na]^+$ calcd for $C_{33}H_{37}N_3O_8Na$ 626.24729, found 626.24673.

*Benzyl (6-Azidohexyl 2-O-benzoyl-4-O-benzyl-3-O-(2,6-di-O-benzoyl-3-O-benzyl-4-O-levulinyl-1-thio-β-D-glucopyranoside)-β-D-glucopyranosyluronate)) (**11**).* Glucuronic acid ester acceptor **10** (175 mg, 0.26 mmol, 1.3 equiv) and glucoside donor **12** (119 mg, 0.20 mmol, 1 equiv) were condensed according to the general procedure for glycosylations and yielded the title compound as a white solid in 62% yield (142 mg, 0.12 mmol). R_f: 0.29 (Tol/EtOAc 3/1). $[\alpha]_D$: +5.4 (c = 1, DCM). IR (neat, cm^{-1}): 2938, 2095, 1721, 1452, 1362, 1315, 1263, 1211, 1177, 1146, 1094, 1069, 1026, 1001, 737, 710, 700. ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 8.01 (d, 2H, J = 7.2 Hz, H_{arom}), 7.94 (d, 2H, J = 7.6 Hz, H_{arom}), 7.84 (d, 2H, J = 7.6 Hz, H_{arom}), 7.59−7.52 (m, 2H, H_{arom}), 7.50−7.30 (m, 7H, H_{arom}). 7.28−7.26 (m, 6H, H_{arom}), 7.17−7.10 (m, 7H, H_{arom}), 7.10−7.01 (m, 2H, H_{arom}), 5.33 (t, 1H, J = 8.8 Hz, H-2′), 5.21 (t, 1H, J = 9.6 Hz, H-2), 5.14−5.10 (m, 2H, CH_2 CO_2Bn), 4.98 (d, 1H, J = 10.8 Hz, C*H*HPh), 4.93 (d, 1H, J = 8.0 Hz, H-1′), 4.51−4.47 (m, 3H, CH_2 Bn, H-6), 4.46 (d, 1H, J = 6.0 Hz, H-1), 4.44 (d, 1H, J = 12.0 Hz, CH*H*Ph), 4.24−4.17 (m, 2H, H-6′, H-5′), 4.03 (t, 1H, J = 9.6 Hz, H-4), 3.98 (d, 1H, J = 8.8 Hz, H-5), 3.77−3.69 (m, 3H, H-3, H-3′, C*H*H CH_2 $N_3(CH_2)_6OH$), 3.23−3.18 (m, 1H, CH*H* CH_2 $N_3(CH_2)_6OH$), 3.04 (t, 2H, 7.2 Hz, CH_2 $N_3(CH_2)_6OH$), 2.65−2.60 (m, 2H, CH_2 Lev), 2.50−2.42 (m, 1H, C*H*H Lev), 2.38−2.32 (m, 1H, CH*H* Lev), 2.09 (s, 3H, CH_3 Lev), 1.30−1.22 (m, 4H, 2 × CH_2 $N_3(CH_2)_6OH$), 1.11−1.00 (m, 4H, 2 × CH_2 $N_3(CH_2)_6OH$). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 206.1 (C═O Lev ketone), 171.4 (C═O), 168.2 (C═O), 166.1 (C═O Bz), 165.0 (C═O), 164.4 (C═O), 138.0 (C_q C_{arom}), 137.4 (C_q C_{arom}), 135.1 (C_q C_{arom}), 133.5 (CH_{arom}), 133.0 (CH_{arom}), 129.9−129.8 (CH_{arom}), 129.7−129.5 (C_q C_{arom}), 128.6−127.11 (CH_{arom}), 100.5 (C-1), 100.2 (C-1′), 80.0 (C-3′), 76.6 (C-5′), 76.8 (C-4), 74.8 (CH_2 Bn), 74.5 (C-5), 74.1 (CH_2 Bn), 73.6 (C-4′), 73.3 (C-2′), 72.2 (C-3′), 70.5 (C-2), 69.3 (CH_2 $N_3(CH_2)_6OH$), 67.3 (CH_2 CO_2Bn), 63.0 (C-6′), 51.2 (CH_2 $N_3(CH_2)_6OH$), 37.8 (CH_2 Lev), 29.7 (CH_3 Lev), 28.9 (CH_2 $N_3(CH_2)_6OH$), 28.5 (CH_2 Lev), 27.8 (CH_2 $N_3(CH_2)_6OH$), 26.2 (CH_2 $N_3(CH_2)_6OH$), 25.2 (CH_2 $N_3(CH_2)_6OH$). HRMS: $[M + Na]^+$ calcd for $C_{65}H_{67}N_3O_{17}Na$ 1184.43627, found 1184.43563.

*6-Azidohexyl 2-O-Benzoyl-3,6-di-O-benzyl-4-O-levulinyl-β-D-glucopyranoside (**13**).* Glucoside donor **12** (654 mg, 1 mmol) and 6-azidohexanol (214 mg, 1.5 mmol, 1.5 equiv) were coevaporated with toluene (2×) and dissolved in freshly distilled DCM (4.0 mL, 0.25 M). Activated MS 3 Å were added, and the reaction mixture was stirred for 30 min, followed by addition of NIS (338 mg, 1.5 mmol, 1.5 equiv). The reaction mixture was cooled to −25 °C, followed by addition of TfOH (1 mL of 0.1 M stock solution, 0.1 mmol, 0.1 equiv). The reaction mixture was allowed to warm to rt. TLC analysis (PE/EtOAc 3/2, v/v) showed total consumption of the thioglucoside. The reaction mixture was quenched with TEA and $Na_2S_2O_3$ (aq, satd) and diluted with DCM, followed by separation of the layers. The organic layer was washed with $NaHCO_3$ (aq, satd) and brine, dried over $MgSO_4$, filtered, and concentrated. Column chromatography (PE/EtOAc 9/1 → 7/3) gave a mixture of the title compound and 6-azidohexanol. This mixture was dissolved in a mixture of pyridine/Ac_2O (1/1, 10 mL) and stirred overnight (acetylation of 6-azidohexanol). The reaction mixture was quenched with MeOH, diluted with EtOAc, washed with 2 M HCl, $NaHCO_3$ (aq, satd), dried over $MgSO_4$, filtered, and concentrated. Column chromatography (PE/EtOAc 9/1 → 3/1) gave the title compound as a transparent oil in 80% yield (550 mg, 0.80 mmol). $[\alpha]^{20}_D$: +16.0 (c = 1.1, DCM). IR (neat, cm^{-1}): 2936, 2862, 2095, 1721, 1452, 1362, 1314, 1267, 1206, 1177, 1148, 1094, 1069, 1026, 988, 970, 910, 748, 712 698. ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 8.03−8.01 (m, 2H, H_{arom}), 7.59 (t, 1H, J = 7.6 Hz, H_{arom}), 7.77−7.73 (m, 2H, H_{arom}), 7.35−7.26 (m, 5H, H_{arom}), 7.14−7.10 (m, 5H, H_{arom}), 5.30 (t, 1H, J = 9.2 Hz, H-2), 5.14 (t, 1H, J = 9.6 Hz, H-4), 4.60 (s, 2H, CH_2 Bn), 4.55 (s, 2H, CH_2 Bn), 5.54 (d, 1H, J = 8.0 Hz, H-1), 3.91−3.85 (m, 2H, H-3, C*H*H $N_3(CH_2)_6OH$), 3.70−3.58 (m, 3H, H-5, H-6), 3.47−3.41 (m, 1H, CH*H* $N_3(CH_2)_6OH$), 3.02 (t, 1H, J = 6.8 Hz, CH_2 $N_3(CH_2)_6OH$), 2.63−2.58 (m, 2H, CH_2 Lev), 2.43−2.36 (m, 2H, CH_2 Lev), 2.10 (s, 3H, CH_3 Lev), 1.50−1.44 (m, 2H, CH_2 $N_3(CH_2)_6$-OH), 1.31−1.15 (m, 6H, 3x CH_2 $N_3(CH_2)_6OH$). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 206.3 (C═O Lev ketone), 171.6 (C═O Lev), 165.0 (C═O Bz), 138.1 (C_q C_{arom}), 137.8 (C_q C_{arom}), 133.3 (CH_{arom}), 129.9 (C_q C_{arom}), 129.8 (CH_{arom}), 128.5−127.6 (CH_{arom}), 101.2 (C-1), 79.8 (C-3), 73.8 (CH_2 Bn), 76.7 (C-5), 76.6 (CH_2 Bn), 73.4 (C-2), 71.2 (C-4), 69.7 (CH_2 $N_3(CH_2)_6OH$), 69.7 (C-6), 51.2 (CH_2 $N_3(CH_2)_6OH$), 37.8 (CH_2 Lev), 29.8 (CH_3 Lev), 29.3 (CH_2 $N_3(CH_2)_6OH$), 29.3 (CH_2 $N_3(CH_2)_6OH$), 27.9 (CH_2 Lev), 26.3 (CH_2 $N_3(CH_2)_6OH$), 25.4 (CH_2 $N_3(CH_2)_6OH$). HRMS: $[M + Na]^+$ calcd for $C_{38}H_{45}N_3O_9Na$ 710.30480, found 710.30474.

*6-Azidohexyl 2-O-Benzoyl-3,6-di-O-benzyl-β-D-glucopyranoside (**14**).* Glucoside **13** (523 mg, 0.76 mmol) was dissolved in pyridine/AcOH (4/1, 15 mL) followed by addition of hydrazine monohydrate (0.22 mL, 3.8 mmol, 5 equiv). After 1 h, TLC analysis (PE/EtOAc 4/1, v/v) showed total conversion of the starting material. The reaction mixture was diluted with EtOAc, washed with 2 M HCl and $NaHCO_3$ (aq, satd), dried over $MgSO_4$, filtered, and concentratedd. Column chromatography (PE/EtOAc 7/3) gave the target compound in 99% yield (442 mg, 0.75 mmol). $[\alpha]^{20}_D$: +2.6 (c = 0.7, DCM). IR (neat, cm^{-1}): 2938, 2866, 2095, 1726, 1452, 1362, 1314, 1265, 1209, 1179, 1110, 1069, 1026, 984, 733, 698, 648. ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): ^1H NMR: 8.08−8.03 (m, 2H, H_{arom}), 7.60−7.57 (m, 1H, H_{arom}), 7.47−7.44 (m, 2H, H_{arom}), 7.37−7.18 (m, 10H, H_{arom}), 5.24 (t, 1H, J = 8.8 Hz, H-2), 4.73 (d, 1H, J = 11.6 Hz, C*H*HPh), 4.69 (d, 1H, J = 11.6 Hz, CH*H*Ph), 4.63 (d, 1H, J = 11.6 Hz, C*H*HPh), 4.58 (d, 1H, J = 11.6 Hz, CH*H*Ph), 4.50 (d, 1H, J = 8.0 Hz, H-1), 3.94−3.85 (m, 1H, C*H*H $N_3(CH_2)_6OH$), 3.84−3.73 (m, 3H, H-4, H-6), 3.68 (t, 1H, J = 9.2 Hz, H-3), 3.57−3.52 (m, 1H, H-5), 3.44−3.38 (m, CH*H* $N_3(CH_2)_6OH$), 3.01 (t, 1=2H, J = 6.8 Hz, CH_2 $N_3(CH_2)_6OH$), 1.52−1.41 (m, 2H, CH_2 $N_3(CH_2)_6OH$), 1.13−1.15 (m, 6H, 3x CH_2 $N_3(CH_2)_6OH$). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 165.2 (C═O Bz), 138.0 (C_q C_{arom}), 137.8 (C_q C_{arom}), 133.2 (CH_{arom}), 130.0 (C_q C_{arom}), 130.0−129.8 (CH_{arom}), 128.6−127.9 (CH_{arom}), 101.3 (C-1), 82.1 (C-3), 74.5 (CH_2 Bn), 74.2 (C-5), 73.8 (CH_2 Bn), 73.5 (C-2), 72.3 (C-4), 70.4 (C-6), 69.7 (CH_2 $N_3(CH_2)_6OH$), 51.2 (CH_2 $N_3(CH_2)_6OH$), 29.3 (CH_2 $N_3(CH_2)_6OH$), 28.6 (CH_2 $N_3(CH_2)_6OH$), 26.3 (CH_2 $N_3(CH_2)_6OH$), 25.5 (CH_2 $N_3(CH_2)_6OH$). HRMS: $[M + Na]^+$ calcd for $C_{55}H_{54}O_{13}Na$ 945.34566, found 945.34162.

*6-Azidohexyl 3,6-Di-O-benzyl-4-O-(benzyl (2-O-benzoyl-4-O-benzyl-3-O-levulinyl-β-D-glucopyranosyluronate))-2-O-benzoyl-1-thio-β-D-glucopyranoside (**15**).* Glucuronic acid ester donor **3** (151 mg, 0.22 mmol, 1.3 equiv) and glucoside acceptor **14** (100 mg, 0.17 mmol, 1 equiv) were glycosylated according to the general procedure for glycosylations and yielded disaccharide **16** in 74% yield (144 mg, 0.13 mmol) as a transparent oil, which crystallized on standing. R_f: 0.46 (PE/EtOAc 12/8, v/v). $[\alpha]_D$: +26.0 (c = 1, DCM). IR (neat, cm^{-1}): 2940, 2095, 1721, 1452, 1364, 1315, 1263, 1211, 1177, 1148, 1094, 1069, 1026, 1001, 735, 710, 700. ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 7.94−7.91 (m, 4H, H_{arom}), 7.58−7.54 (m, 2H, H_{arom}), 7.45−7.24 (m, 17H, H_{arom}), 7.15−7.14 (m, 4H, H_{arom}), 7.14−7.04 (m, 3H, H_{arom}), 5.31 (t, 1H, J = 9.2 Hz, H-3′), 5.23 (t, 1H, J = 10.0 Hz, H-2′), 5.17 (t, 1H, J = 8.8 Hz, H-2), 5.06 (d, 1H, J = 12.0 Hz, C*H*H CO_2Bn), 5.01 (d, 1H, J = 12.0 Hz, CH*H* CO_2Bn), 4.86 (d, 1H, J = 10.8 Hz, C*H*HPh), 4.84 (d, 1H, J = 7.2 Hz, H-1′), 4.64 (d, 1H, J = 12.0 Hz, C*H*HPh), 4.59 (d, 1H, J = 11.6 Hz, CH*H*Ph), 4.49 (d, 1H, J = 12.0 Hz, C*H*HPh), 4.49 (d, 1H, J = 12.4 Hz, CH*H*Ph), 4.37 (d, 1H, J = 11.2 Hz, CH*H*Ph), 4.34 (d, 1H, J = 8.4 Hz, H-1), 4.11 (t, 1H, J = 9.2 Hz, H-4), 4.00 (d, 1H, J = 9.6 Hz, H-4′), 3.89 (d, 1H, J = 9.6 Hz, H-5′), 3.80-.3.70 (m, 2H, H-3, CH*H* CH_2 $N_3(CH_2)_6OH$), 3.60 (dd, 1H, J = 3.6 Hz, J = 11.2 Hz, H-6), 3.49 (d, 1H, J = 10.4 Hz, H-6), 3.35−3.27 (m, 1H, CH*H* CH_2 $N_3(CH_2)_6OH$), 3.26−3.23 (m, 1H, H-5), 3.03−3.96 (m, 2H, CH_2 CH_2 $N_3(CH_2)_6OH$), 2.47−2.44 (m, 2H, CH_2 Lev), 2.34−2.31 (m, 2H, CH_2 Lev), 1.97 (s, 3H, CH_3 Lev), 1.50−1.28 (m, 2H, CH_2 CH_2 $N_3(CH_2)_6OH$), 1.28−1.26 (m, 2H, CH_2 $N_3(CH_2)_6OH$), 1.24−1.11 (m, 4H, 2 × CH_2 CH_2 $N_3(CH_2)_6OH$). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 205.5 (C═O Lev ketone), 171.5 (C═O, 167.5 (C═O),

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165.0 (C═O), 164.9 (C═O), 138.3 (C_q C_{arom}), 137.8 (C_q C_{arom}), 137.5 (C_q C_{arom}), 136.6 (C_q C_{arom}), 134.8 (C_q C_{arom}), 133.4 (CH_{arom}), 132.9 (CH_{arom}), 130.0 (C_q C_{arom}), 129.8−129.1 (CH_{arom}), 128.6 (C_q C_{arom}), 128.5−127.1 (CH_{arom}), 101.1 (C-1), 100.4 (C-1′), 80.2 (C-3), 77.6 (C-4′), 77.3 (C-4), 74.6 (C-5), 74.5 (CH_2 Bn), 74.5 (C-5′), 74.4 (CH_2 Bn), 74.0 (C-3′), 73.5 (CH_2 Bn), 73.1 (C-2), 72.2 (C-2′), 69.3 (CH_2 $N_3(CH_2)_6OH$), 67.5 (C-6), 67.4 (CH_2 CO_2Bn), 51.1 (CH_2 $N_3(CH_2)_6OH$), 37.7 (CH_2 Lev), 29.4 (CH_3 Lev), 29.1 (CH_2 $N_3(CH_2)_6OH$), 28.5 (CH_2 $N_3(CH_2)_6OH$), 27.8 (CH_2 $N_3(CH_2)_6OH$), 26.2 (CH_2 Lev), 25.3 (CH_2 $N_3(CH_2)_6OH$). HRMS: $[M + Na]^+$ calcd for $C_{65}H_{69}N_3O_{16}Na$ 1170.45700, found 1170.45688.

*Benzyl (2-O-Benzoyl-4-O-benzyl-3-O-levulinyl-α/β-D-glucopyranose)uronate (**16**).* Glucuronic acid ester **3** (3074 mg, 0.45 mmol) was dissolved in freshly distilled DCM (4.5 mL, 0.1M). The reaction mixture was cooled to 0 °C, followed by addition of NIS (111 mg, 0.50 mmol, 1.1 equiv) and TFA (38 μL, 0.50 mmol, 1.1 equiv). The reaction mixture was allowed to warm to rt, and after 30 min, TLC analysis (Tol/EtOAc 4/1, v/v) showed total conversion into a lower running spot. The reaction mixture was quenched by addition of $Na_2S_2O_3$ (aq, satd) and $NaHCO_3$ (aq, satd) and stirred for 30 min. Then the reaction mixture was diluted with DCM, followed by separation of the layers. The organic layer was dried over $MgSO_4$, filtered, and concentrated. Column chromatography (PE/EtOAc 1/0 → 6/4) gave hemiacetal **16** as a transparent oil and as anomeric mixture (α/β 4/1) in 88% yield (229 mg, 0.40 mmol). IR (neat, cm^{-1}): 3443, 1744, 1721, 1601, 1497, 1452, 1404, 1360, 1339, 1315, 1265, 1213, 1179, 1155, 1109, 1098, 1070, 1061, 1028, 986, 962, 908, 853, 750, 714, 698, 635, 621. α isomer: ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 8.01 (d, 2H, J = 7.6 Hz, H_{arom}), 7.44 (t, 1H, J = 5.2 Hz, H_{arom}), 7.41−7.22 (m, 10H, H_{arom}), 7.17−7.13 (m, 2H, H_{arom}), 5.78 (t, 1H, J = 10.0 Hz, H-3), 5.59 (d, 1H, J = 3.2 Hz, OH), 5.18 (s, 2H, CH_2 Bn ester), 5.02 (dd, 1H, J = 3.6 Hz, J = 10.0 Hz, H-2), 4.63 (d, 1H, J = 10.0 Hz, H-5), 4.53 (d, 1H, J = 11.2 Hz, C*H*HPh), 4.50 (d, 1H, J = 11.2 Hz, CH*H*Ph), 3.96 (t, 1H, J = 9.6 Hz, H-4), 3.62 (bs, OH), 2.54−2.48 (m, 2H, CH_2 Lev), 2.38−2.32 (m, 2H, CH_2 Lev), 1.99 (s, 3H, CH_3 Lev). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 206.0 (C═O Lev ketone), 171.8 (C═O Bn ester), 169.0 (C═O Lev), 165.8 (C═O Bz), 137.5 (C_q C_{arom}), 134.8 (C_q C_{arom}), 133.5 (CH_{arom}), 130.0 (CH_{arom}), 129.0 (CH_{arom}), 128.7 (C_q C_{arom}), 128.6−127.8 (CH_{arom}), 90.6 (C-1), 77.6 (C-4), 74.5 (CH_2 Bn ether), 71.8 (C-2), 71.2 (C-3), 70.2 (C-5), 67.5 (C-6), 37.7 (CH_2 Lev), 29.6 (CH_3 Lev), 27.9 (CH_2 Lev), 27.9 (CH_3 STol). HRMS: $[M + Na]^+$ calcd for $C_{32}H_{32}O_{10}Na$ 599.18877, found 599.18776.

*Benzyl (2-O-Benzoyl-4-O-benzyl-3-O-levulinyl-1-O-(N-phenyltrifluoroacetimidoyl)-α/β-D-glucopyranosyl)uronate (**17**).* Hemiacetal **16** (190 mg, 0.33 mmol) was dissolved in acetone (1.65 mL, 0.2 M), and the reaction mixture was cooled to 0 °C. To this mixture were added *N*-phenyl-2,2,2-trifluoroacetimidoyl chloride (0.1 mL, 0.66 mmol, 2 equiv) and Cs_2CO_3 (108 mg, 0.33 mmol, 1 equiv). The reaction mixture was allowed to warm to rt, and after 2 h, TLC analysis showed total conversion into a higher running spot (PE/EtOAc 12/8, v/v, R_f 0.55). The reaction mixture was filered over Celite and concentrated. Column chromatography (PE/EtOAc 1/0 → 6/4) gave the title compound as a transparent oil in 83% yield (α/β 3.4/1). IR (neat, cm^{-1}): 1746, 1719, 1452, 1404, 1358, 1317, 1263, 1209, 1153, 1107, 1096, 1070, 1040, 1028, 1003, 984, 908, 754, 739, 712, 696. α Isomer: ^1H NMR (50 °C, 400 MHz, $CDCl_3$, HH-COSY, HSQC): 8.00 (d, 2H, J = 7.6 Hz, H_{arom}), 7.59−7.50 (m, 2H, H_{arom}), 7.41−7.16 (m, 12H, H_{arom}), 7.11−7.07 (m, 3H, H_{arom}), 6.99 (t, 1H, J = 7.2 Hz, H_{arom}), 6.68 (bs, 1H, H-1), 5.81 (t, 1H, J = 10.0 Hz, H-3), 5.31 (dd, 1H, J = 2.4 Hz, J = 10.0 Hz, H-2), 5.23 (s, 2H, CH_2 Bn ester), 4.56−4.50 (m, 3H, H-5, CH_2 Bn ether), 4.08 (t, 1H, J = 9.6 Hz, H-4), 2.55−2.50 (m, 2H, CH_2 Lev), 2.42−2.38 (m, 2H, CH_2 Lev), 2.02 (s, 3H, CH_3 Lev). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 171.6 (C═O), 167.8 (C═O), 165.3 (C═O), 142.9 (C_q C_{arom}), 137.4 (C_q C_{arom}), 134.9 (C_q C_{arom}), 133.6 (CH_{arom}), 130.1 (CH_{arom}), 128.9 (C_q C_{arom}), 128.7−127.9 (CH_{arom}), 124.4 (CH_{arom}), 119.1 (CH_{arom}), 92.4 (C-1), 77.2 (C-4), 74.9 (CH_2 Bn ether), 72.8 (C-5), 71.3 (C-3), 70.4 (C-2), 67.8 (CH_2 Bn ester), 37.8 (CH_2 Lev), 29.4 (CH_3 Lev), 28.0 (CH_2 Lev). HRMS: $[M + Na]^+$ calcd for $C_{40}H_{36}F_3NO_{10}Na$ 770.21835, found 770.21895.

*2-O-Benzoyl-3,6-di-O-benzyl-4-O-levulinyl-α/β-D-glucopyranose (**18**).* Glucoside **11** (263 mg, 0.39 mmol) was dissolved in freshly distilled DCM (39.3 mL, 0.1 M). The reaction mixture was cooled to 0 °C, followed by addition of NIS (97 mg, 0.43 mmol, 1.1 equiv) and TFA (33 μL, 0.43 mmol, 1.1 equiv). The reaction mixture was allowed to warm to rt. After 3 h, piperidine (128 μL, 1.29 mmol, 3 equiv) was added, and the reaction mixture turned orange. The reaction was quenched by addition of $Na_2S_2O_3$ (aq, satd) and diluted with DCM, followed by separation of the layers. The organic layer was dried over $MgSO_4$, filtered, and concentrated. Column chromatography (PE/EtOAc 1/0 → 6/4) gave hemiacetal **18** as a transparent oil in 84% yield (186 mg, 0.33 mmol). IR (neat, cm^{-1}): 1717, 1452, 1404, 1362, 1271, 1207, 1177, 1153, 1098, 1067, 1026, 1001, 937, 914, 746, 712, 698. α Anomer: ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 8.05−8.03 (m, 2H, H_{arom}), 7.59−7.18 (m, 13H, H_{arom}), 5.52 (t, 1H, J = 3.2 Hz, H-1), 5.15−5.04 (m, 2H, H-2, H-4), 4.71 (d, 1H, J = 11.6 Hz, C*H*HPh), 4.63 (d, 1H, J = 11.6 Hz, CH*H*Ph), 4.50 (s, 2H, CH_2 Bn), 4.26−4.16 (m, 2H, H-3, H-5), 3.53−3.49 (m, 2H, H-6), 2.67−2.48 (m, 2H, CH_2 Lev), 2.44−2.23 (m, 2H, CH_2 Lev), 2.11 (s, 3H, CH_3 Lev). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 206.4 (C═O Lev ketone), 171.5 (C═O Lev), 165.6 (C═O Bz), 138.0 (C_q C_{arom}), 137.5 (C_q C_{arom}), 133.2 (CH_{arom}), 129.8 (CH_{arom}), 129.7 (CH_{arom}), 129.5 (C_q C_{arom}), 128.5−127.5 (CH_{arom}), 92.2 (C-1), 76.8 (C-3 or C-5), 74.7 (CH_2 Bn), 73.8 (C-2 or C-4), 73.4 (CH_2 Bn), 70.9 (C-2 or C-4), 69.0 (C-6), 68.5 (C-3 or C-5), 37.7 (CH_2 Lev), 29.7 (CH_3 Lev), 27.7 (CH_2 Lev). HRMS: $[M + Na]^+$ calcd for $C_{32}H_{34}O_9Na$ 585.20950, found 585.20905.

*2-O-Benzoyl-3,6-di-O-benzyl-4-O-levulinyl-1-O-(N-phenyltrifluoroacetimidoyl)-α/β-D-glucopyranoside (**19**).* Hemiacetal **18** (465 mg, 0.83 mmol) was dissolved in acetone (5.5 mL, 0.2 M), and the reaction mixture was cooled to 0 °C. To this mixture were added *N*-phenyl-2,2,2-trifluoroacetimidoyl chloride (0.25 mL, 1.66 mmol, 2 equiv) and Cs_2CO_3 (270 mg, 0.83 mmol, 1 equiv). The reaction mixture was allowed to warm to rt, and after 2 h, TLC analysis showed total conversion into a higher running spot (PE/EtOAc 12/8, v/v, R_f 0.50). The reaction mixture was filered over Celite and concentrated. Column chromatography (PE/EtOAc 1/0 → 7/3) gave the title compound as a transparent oil in 68% yield (α/β 9/1). IR (neat, cm^{-1}): 1717, 1364, 1315, 1265, 1207, 1152, 1119, 1098, 1070, 1026, 924, 885, 737, 712, 696. α Anomer ^1H NMR (50 °C, 400 MHz, $CDCl_3$, HH-COSY, HSQC): 8.02−7.99 (m, 2H, H_{arom}), 7.61−7.58 (m, 1H, H_{arom}), 7.47−7.43 (m, 3H, H_{arom}), 7.35−7.07 (m, 12H, H_{arom}), 7.00−6.96 (m, 2H, H_{arom}), 6.62 (bs, 1H, H-1), 6.43 (d, 2H, J = 7.6 Hz, H_{arom}), 5.36 (dd, 1H, J = 3.6 Hz, J = 10.0 Hz, H-2), 5.29 (t, 1H, J = 9.6 Hz, H-4), 4.73 (d, 1H, J = 11.6 Hz, C*H*HPh), 4.68 (d, 1H, J = 11.6 Hz, CH*H*Ph), 4.56 (d, 1H, J = 12.4 Hz, C*H*HPh), 4.53 (d, 1H, J = 12.0 Hz, CH*H*Ph), 4.22 (t, 1H, J = 9.6 Hz, H-3), 4.14−4.11 (m, 1H, H-5), 3.66−3.57 (m, 2H, H-6), 2.67−2.53 (m, 2H, CH_2 Lev), 2.50−2.35 (m, 2H, CH_2 Lev), 2.12 (s, 3H, CH_3 Lev). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 205.8 (C═O Lev ketone), 171.3 (C═O Lev ketone), 165.1 (C═O Bz), 143.1 (C_q C_{arom}), 138.0 (C_q C_{arom}), 133.5 (CH_{arom}), 129.8 (CH_{arom}), 129.3 (C_q C_{arom}),128.7−127.6 (CH_{arom}), 124.2 (CH_{arom}), 119.2 (CH_{arom}), 92.9 (C-1), 77.1 (C-3), 74.8 (CH_2 Bn), 73.7 (CH_2 Bn), 72.2 (C-2), 72.1 (C-5), 70.3 (C-4), 68.8 (C-6), 37.8 (CH_2 Lev), 29.6 (CH_3 Lev), 28.0 (CH_2 Lev). HRMS: $[M + Na]^+$ calcd for $C_{40}H_{38}F_3NO_9Na$ 756.23909, found 756.23982.

*p-Tolyl 3,6-Di-O-benzyl-4-O-(benzyl (2-O-benzoyl-4-O-benzyl-3-O-levulinyl-β-D-glucopyranosyluronate))-2-O-benzoyl-1-thio-β-D-glucopyranoside (**21**).* Donor **17** (256 mg, 0.34 mmol, 1.3 equiv) and acceptor **20** (151 mg, 0.26 mmol) were coevaporated with toluene (2×) and dissolved in freshly distilled DCM (6.8 mL, 0.05 M). Activated MS 3 Å were added, and the reaction mixture was stirred for 30 min. The reaction mixture was cooled to 0 °C, followed by addition of TfOH (0.2 mL of 0.1 M stock solution, 0.02 mmol, 0.1 equiv). The reaction mixture was allowed to warm to rt. After 4 h, TLC analysis (PE/EtOAc 12/8, v/v) showed disappearance of the acceptor. The reaction mixture was neutralized with TEA, diluted with DCM, washed with H_2O, dried over $MgSO_4$, filtered, and concentrated. A yellow oil was obtained, which was purified by SEC (DCM/MeOH 1/1), yielding disaccharide **37** in 12% yield (35 mg, 0.031 mmol). $[\alpha]^{20}_D$: +2.0 (c = 0.6, DCM).

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IR (neat, cm^{-1}): 2914, 2872, 1744, 1728, 1495, 1452, 1400, 1360, 1315, 1263, 1215, 1177, 1144, 1092, 1069, 1051, 1026, 1001, 910, 845, 810, 750, 710, 698. ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 7.95−7.92 (m, 4H, H_{arom}), 7.60−7.55 (m, 2H, H_{arom}), 7.45−7.25 (m, 19H, H_{arom}), 7.19−7.03 (m, 7H, H_{arom}), 6.95 (d, 2H, J = 7.6 Hz, H_{arom}), 5.33 (t, 1H, J = 9.2 Hz, H-3′), 5.23 (t, 1H, J = 9.6 Hz, H-2′), 5.16 (t, 1H, J = 9.6 Hz, H-2), 5.03 (d, 1H, J = 12.0 Hz, C*H*HPh), 4.96 (d, 1H, J = 12.0 Hz, CH*H*Ph), 4.87 (d, 1H, J = 8.4 Hz H-1′), 4.87 (d, 1H, J = 11.2 Hz, C*H*HPh), 4.58−4.53 (m, 3H, CH_2 Bn, H-1), 4.47 (s, 2H, CH_2 Bn), 4.35 (d, 1H, J = 12.0 Hz, CH*H*Ph), 4.11 (t, 1H, J = 9.6 Hz, H-4), 4.04 (t, 1H, J = 9.2 Hz, H-4′), 3.90 (d, 1H, J = 9.6 Hz, H-5′), 3.73 (t, 1H, J = 8.8 Hz, H-3), 3.61 (dd, 1H, J = 3.6 Hz, J = 11.6 Hz, H-6), 3.53 (d, 1H, J = 11.2 Hz, H-6), 3.28−3.25 (m, 1H, H-5), 2.46−2.44 (m, 2H, CH_2 Lev), 2.35−2.29 (m, 2H, CH_2 Lev), 2.24 (s, 3H, CH_3 STol), 1.97 (s, 3H, CH_3 Lev). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 205.6 (C═O Lev ketone), 171.6 (C═O), 167.5 (C═O Bz), 165.0 (C═O Bz), 138.2 (C_q C_{arom}), 138.1 (C_q C_{arom}), 137.9 (C_q C_{arom}), 137.5 (C_q C_{arom}), 134.8 (C_q C_{arom}), 133.4−133.0 (CH_{arom}), 130.0 (C_q C_{arom}), 129.8 (CH_{arom}), 129.5 (CH_{arom}), 129.0 (C_q C_{arom}), 128.6−127.2 (CH_{arom}), 100.5 (C-1′), 86.2 (C-1), 81.6 (C-3), 78.8 (C-5), 77.5 (C-4′), 77.1 (C-4), 74.8 (CH_2 Bn), 74.5 (CH_2 Bn), 74.5 (C-5′), 74.1 (C-3′), 73.5 (CH_2 Bn), 72.2 (C-2′), 71.9 (C-2), 67.6 (C-6), 67.5 (CH_2 CO_2*Bn*), 37.7 (CH_2 Lev), 29.5 (CH_3 Lev), 27.8 (CH_2 Lev), 21.1 (CH_3 STol). HRMS: $[M + Na]^+$ calcd for $C_{66}H_{62}O_{16}SNa$ 1165.36508, found 1165.36484.

*1,6-Anhydro-2-O-benzyl-4-O-(benzyl (2-O-benzoyl-4-O-benzyl-3-O-levulinyl-β-D-glucopyranosyluronate))-2-O-benzoyl-β-D-glucopyranoside (**22**).* Donor **17** (1.15 g mg, 1.54 mmol, 1.8 equiv) and acceptor **20** (491 mg, 0.86 mmol) were coevaporated with toluene (2×) and dissolved in freshly distilled DCM (1.72 mL, 0.5 M). Activated MS 3 Å were added, and the reaction mixture was stirred for 30 min. The reaction mixture was cooled to 0 °C, followed by addition of TfOH (0.14 μL, 0.154 mmol, 0.1 equiv). After 5 min, TLC analysis (PE/EtOAc 12/8, v/v) showed total conversion of the acceptor. The reaction mixture was neutralized with TEA, diluted, washed with H_2O, dried over $MgSO_4$, filtered, and concentrated. Column chromatography (PE/EtOAc 1/0 → 7/3), followed by SEC DCM/MeOH 1/1) gave the title compound as a clear oil in 10% yield (81 mg, 0.089 mmol). $[\alpha]^{20}_D$: −6.0 (c = 1, DCM). IR (neat, cm^{-1}): 1746, 1719, 1362, 1316, 1265, 1215, 1179, 1150, 1094, 1070, 1026, 1009, 1001, 750, 712, 698. ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 8.05 (d, 2H, J = 7.6 Hz, H_{arom}), 7.95 (d, 2H, J = 7.2 Hz, H_{arom}), 7.61−7.06 (m, 21H, H_{arom}), 5.45 (s, 1H, H-1), 5.37 (1, 1H, J = 8.4 Hz, H-3′), 5.26 (t, 1H, J = 9.6 Hz, H-2′), 5.06 (d, 1H, J = 12.0 Hz, C*H*HPh), 5.01 (d, 1H, J = 12.0 Hz, CH*H*Ph), 4.91 (s, 1H, H-2), 4.74 (d, 1H, J = 13.6 Hz, C*H*HPh), 4.71 (d, 1H, J = 7.6 Hz, H-1′), 4.54−4.44 (m, 4H, CH_2 Bn, CH*H*Ph, H-5), 3.99 (d, 1H, J = 7.6 Hz, H-6), 4.02−3.95 (m, 2H, H-4′, H-5′), 3.78 (s, 1H, H-3 or H-4), 3.74 (s, 1H, H-3 or H-4), 3.68 (t, 1H, J = 6.4 Hz, H-6), 2.52−2.40 (m, 2H, CH_2 Lev), 2.38−2.34 (m, 2H, CH_2 Lev), 2.18 (s, 3H, CH_3 Lev). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 205.7 (C═O Lev ketone), 171.7 (C═O), 167.3 (C═O), 165.7 (C═O), 165.1 (C═O), 137.7 (C_q C_{arom}), 137.4 (C_q C_{arom}), 134.7 (C_q C_{arom}), 133.3−133.2 (CH_{arom}), 131.9−129.3 (CH_{arom}), 128.8−128.5 (C_q C_{arom}), 128.5−127.5 (CH_{arom}), 100.2 (C-1′), 99.4 (C-1), 77.0 (C-4′ or C-5′), 76.9 (C-3 or C-4), 76.4 (C-3 or C-4), 74.7 (CH_2 Bn), 74.6 (C-4′ or C-5′), 74.1 (C-3), 73.6 (C-5), 72.4 (CH_2 Bn), 71.9 (C-2′), 68.9 (C-2), 67.5 (CH_2 Bn ester), 64.8 (C-6), 37.6 (CH_2 Lev), 29.6 (CH_3 Lev), 27.8 (CH_2 Lev). HRMS: $[M + Na]^+$ calcd for $C_{52}H_{50}O_{15}Na$ 937.30419, found 937.30413.

*Benzyl (Tolyl 2-O-benzoyl-4-O-benzyl-3-O-levulinyl-1-thio-α/β-D-glucopyranosyluronate) (**23a**).* The title compound was isolated during the glycosylation of glucuronic acid ester **17** with glucoside **20a** in 53% yield (341 mg, 0.46 mmol, α/β 1/3). IR (neat, cm^{-1}): 1744, 1721, 1493, 1452, 1402, 1358, 1315, 1263, 1206, 1177, 1153, 1090, 1069, 1026, 997, 972, 908, 847, 810, 735, 710, 696, 640. ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 8.05−8.00 (m, H_{arom}), 7.58−7.56 (m, H_{arom}), 7.47−7.14 (m, H_{arom}), 7.04−6.95 (m, H_{arom}), 5.89 (d, J = 5.6 Hz, H-1 α), 5.66 (t, J = 9.2 Hz, H-3 β), 5.42 (t, J = 9.2 Hz, H-3 β), 5.26 (dd, J = 4.8 Hz, J = 10.0 Hz, H-2 α), 5.21 (s, CH_2 Bn ester), 5.14 (t, J = 9.6 Hz, H-2 β), 5.00 (d, J = 9.2 Hz, H-5 α), 4.79 (d, J = 10.0 Hz, H-1 β), 4.95 (s, CH_2 Bn ether α), 5.54 (d, J = 11.2 Hz, C*H*HPh β), 4.49 (d, J = 11.2 Hz, CH*H*Ph β), 4.08 (d, J = 9.6 Hz, H-5 β), 4.04 (t, J = 9.2 Hz, H-4 α), 3.98 (t, J = 9.6 Hz, H-4 β), 2.59−2.26 (m, 2 × CH_2 Lev, CH_3 Lev), 2.02 (s, CH_3 Lev α), 1.98 (s, CH_3 Lev β). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 205.7 (C═O Lev ketone β), 205.6 (C═O Lev ketone α), 171.6 (C═O), 171.5 (C═O), 168.5 (C═O), 165.4 (C═O), 165.1 (C═O), 165.0 (C═O), 138.7−137.4 (C_q C_{arom}), 134.9 (C_q C_{arom}), 133.5−132.3 (CH_{arom}), 131.9 (CH_{arom}), 130.0−129.1 (CH_{arom}), 128.9−128.8 (C_q C_{arom}), 128.6−127.4 (CH_{arom}), 127.2 (C_q C_{arom}), 86.6 (C-1 β), 86.3 (C-1 α), 74.1 (C-5 β), 77.2 (C-4 α), 77.0 (C-4 β), 75.1 (C-3 β), 74.6 (CH_2 Bn β), 74.6 (CH_2 Bn α), 71.3 (C-3 α), 70.8 (C-2 α), 70.7 (C-5 α), 70.3 (C-2 β), 67.4 (CH_2 CO_2*Bn* β), 67.4 (CH_2 CO_2*Bn* α), 37.7 (CH_2 Lev), 29.5 (CH_3 Lev), 27.8 (CH_2 Lev), 21.0 (CH_3 STol). HRMS: $[M + Na]^+$ calcd for $C_{39}H_{38}O_9SNa$ 705.21287, found 705.21230.

*Benzyl (Phenyl 2-O-benzoyl-4-O-benzyl-3-O-levulinyl-1-thio-α/β-D-glucopyranosyluronate) (**23b**).* The title compound was isolated as a clear oil and as an anomeric mixture. IR (neat, cm^{-1}): 1744, 1721, 1404, 1358, 1315, 1265, 1207, 1179, 1155, 1092, 1070, 1026, 999, 972, 908, 733, 712, 698. ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 8.04−8.00 (m, 3H, H_{arom}), 7.59−7.57 (m, 1.6H, H_{arom}), 7.47−7.15 (m, 27.6H, H_{arom}), 5.97 (d, 1H, 0.4H, J = 5.6 Hz, H-1 α), 5.66 (t, 1H, J = 9.2 Hz, H-3 α), 5.43 (t, 1H, J = 9.2 Hz, H-3 β), 5.29−5.15 (m, 4.3H, H-2 α, CH_2 CO_2*Bn*, H-2 β), 4.97 (d, 1H, J = 9.6 Hz, H-5 α), 4.86 (d, 1H, J = 10.0 Hz, H-1β), 4.59 (s, 1H, CH_2 Bn α), 4.54 (d, 1H, J = C*H*HPh β), 5.50 (d, 1H, J = CH*H*Ph β), 4.10 (d, 1H, J = 9.6 Hz, H-5 β), 4.07−4.05 (m, 1.53H, H-4 α, H-4 β), 2.57−2.55 (m, 1H, C*H*H Lev), 2.46−2.32 (m, 5H, CH_2 Lev α and β), 2.03 (s, 1.36H, CH_3 Lev α), 1.97 (s, 2.85H, CH_3 Lev β). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 205.6 (C═O Lev ketone), 171.7 (C═O), 167.3 (C═O), 165.3 (C═O), 137.4 (C_q C_{arom}), 133.6−132.6 (CH_{arom}), 131.6 (C_q C_{arom}), 130.1−130.0 (CH_{arom}), 129.0 (C_q C_{arom}), 128.9−127.8 (CH_{arom}), 86.6 (C-1 α), 86.0 (C-1 β), 78.2 (C-5 β), 77.3 (C-4 α), 77.2 (C-4 β), 75.4 (C-3 β), 74.7 (CH_2 Bn β), 74.7 (CH_2 Bn α), 71.7 (C-3 α), 71.2 (C-2 α), 71.0 (C-5 α), 70.4 (C-2 β), 67.5 (CH_2 CO_2*Bn* β), 67.4 (CH_2 CO_2*Bn* α), 37.8 (CH_2 Lev α), 37.7 (CH_2 Lev β), 29.5 (CH_3 Lev), 27.9 (CH_2 Lev). HRMS: $[M + Na]^+$ calcd for $C_{38}H_{36}O_9SNa$ 691.19722, found 691.19684.

*1,6-Anhydro-2-O-benzoyl-3-O-benzyl-4-O-levulinyl-β-D-glucopyranoside (**26b**).* The title compound was isolated as a transparent oil (185 mg, 0.41 mmol, 34% yield with respect to the donor **19**). $[\alpha]^{20}_D$: +30.9 (c = 3.6, DCM). IR (neat, cm^{-1}): 1717, 1362, 1337, 1315, 1265, 1207, 1179, 1148, 1109, 1098, 1070, 1047, 1026, 1009, 1001, 932, 903, 885, 733, 712, 700, 617. ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 8.11−8.00 (m, 2H, H_{arom}), 7.59−7.57 (m, 1H, H_{arom}), 7.49−7.44 (m, 2H, H_{arom}), 7.38−7.11 (m, 5H, H_{arom}), 5.60 (s, 1H, H-1), 5.00 (s, 1H, H-2 or H-4), 4.84 (s, 1H, H-5), 4.83 (d, 1H, J = 11.2 Hz, C*H*HPh), 4.69 (d, 1H, J = 11.2 Hz, CH*H*Ph), 4.65 (d, 1H, J = 5.2 Hz, H-2 or H-4), 4.25 (d, 1H, J = 7.2 Hz, H-6), 3.80 (t, 1H, J = 6.8 Hz, H-6), 3.65 (d, 1H, H-3), 2.79−2.54 (m, 4H, 2 × CH_2 Lev), 2.11 (s, 3H, CH_3 Lev). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 206.1 (C═O Lev ketone), 171.9 (C═O), 165.3 (C═O), 137.4 (C_q C_{arom}), 133.4 (CH_{arom}), 129.7 (CH_{arom}), 129.4 (C_q C_{arom}), 128.4−127.5 (CH_{arom}), 99.5 (C-1), 75.6 (C-3), 73.6 (C-2 or C-4), 72.3 (CH_2 Bn), 71.0 (C-5), 69.3 (C-2 or C-4), 65.1 (C-6), 37.7 (CH_2 Lev), 29.6 (CH_3 Lev), 28.0 (CH_2 Lev). HRMS: $[M + Na]^+$ calcd for $C_{25}H_{28}O_7Na$: 463.17272, found 463.17281.

*2,6-Di-O-benzoyl-3-O-benzyl-4-O-levulinyl-α/β-D-glucopyranose (**28**).* Glucoside **27** (1.23 g, 1.80 mmol) was dissolved in DCM (18 mL, 0.1 M), and the reaction mixture was cooled to 0 °C. NIS (445 mg, 1.98 mmol, 1.1 equiv) and TFA (152 μL, 1.98 mmol) were added, and the reaction mixture was allowed to warm to rt. After 3 h, the reaction mixture was cooled to 0 °C, followed by addition of piperidine (535 μL, 5.40 mmol, 3 equiv). The reaction mixture was allowed to warm to rt, and TLC analysis (PE/EtOAc 12/8, v/v) showed total conversion into a lower running spot. The reaction mixture was quenched with $Na_2S_2O_3$ (aq, satd), diluted with DCM, followed by separation of the layers. The organic layer was washed with 1 M HCl, $NaHCO_3$ (aq, satd), dried over $MgSO_4$, filtered, and concentrated. The yellow oil obtained was purified by column chromatography (PE/EtOAc 1/0 → 6/4) yielding the title

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compound as a transparent oil in 85% yield (882 mg, 1.53 mmol). IR (neat, cm^{-1}): 3412, 1719, 1601, 1452, 1362, 1315, 1267, 1207, 1177, 1152, 1110, 1098, 1069, 1049, 1026, 989, 972, 937, 764, 750, 712, 689. α anomer: ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 8.08−8.01 (m, 5H, H_{arom}), 7.60−7.53 (m, 2H, H_{arom}), 7.48−7.26 (m, 4H, H_{arom}), 7.21−7.18 (m, 4H, H_{arom}), 5.59 (t, 1H, J = 3.6 Hz, H-1), 5.31 (t, 1H, J = 9.2 Hz, H-4), 5.13 (dd, 1H, J = 3.2 Hz, J = 10.0 Hz, H-2), 4.76 (d, 1H, J = 11.6 Hz, C*H*HPh), 4.69 (d, 1H, J = 11.6 Hz, CH*H*Ph), 4.57 (d, 1H, J = 10.0 Hz, H-6), 4.38−4.31 (m, 2H, H-5, H-6), 4.28 (t, 1H, J = 9.6 Hz, H-3), 3.31 (d, 1H, J = 3.2 Hz, OH), 2.70−2.64 (m, 2H, CH_2 Lev), 2.57−2.35 (m, 2H, CH_2 Lev), 2.11 (s, 3H, CH_3 Lev). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 206.3 (C═O ketone), 171.5 (C═O Lev), 166.4 (C═O Bz), 165.7 (C═O Bz), 138.0 (C_q C_{arom}), 133.6−133.1 (CH_{arom}), 129.9 (CH_{arom}), 129.8 (C_q C_{arom}), 129.4−127.6 (CH_{arom}), 90.4 (C-1), 76.9 (C-3), 75.0 (CH_2 Bn), 73.9 (C-2), 70.4 (C-4), 67.9 (C-5), 62.6 (C-6), 37.8 (CH_2 Lev), 29.7 (CH_3 Lev), 27.9 (CH_2 Lev). HRMS: $[M + Na]^+$ calcd for $C_{32}H_{32}O_{10}Na$ 599.18877, found 599.18785.

*2,6-Di-O-benzoyl-3-O-benzyl-4-O-levulinyl-1-O-(N-phenyltrifluoroacetimidoyl)-α/β-D-glucopyranoside (**29**).* Hemiacetal **28** (149 mg, 0.26 mmol) was dissolved in acetone (2.6 mL, 0.1 M), and the reaction mixture was cooled to 0 °C. To this mixture were added *N*-phenyl-2,2,2-trifluoroacetimidoyl chloride (80 μL, 0.52 mmol, 2 equiv) and Cs_2CO_3 (85 mg, 0.26 mmol, 1 equiv). The reaction mixture was allowed to warm to rt, and after 2 h, TLC analysis showed total conversion into a higher running spot (PE/EtOAc 12/8, v/v, R_f 0.76). The reaction mixture was filered over Celite and concentrated. Column chromatography (PE/EtOAc 1/0 → 6/4) gave the title compound as a transparent oil in 77% yield (α/β: 8/1). IR (neat, cm^{-1}): 1717, 1452, 1364, 1315, 1265, 1207, 1152, 1109, 1098, 1069, 1026, 926, 908, 895, 773, 735, 710, 696, 633, 617. α anomer: ^1H NMR (50 °C, 400 MHz, $CDCl_3$, HH-COSY, HSQC): ^1H NMR: 8.07−7.93 (m, 4H, H_{arom}), 7.60−7.23 (m, 7H, H_{arom}), 7.19−6.96 (m, 8H, H_{arom}), 6.59 (bs, 1H, H-1), 6.45−6.43 (m, 1H, H_{arom}), 5.39−5.31 (m, 2H, H-2, H-4), 4.722 (s, 2H, CH_2 Bn), 5.54 (d, 1H, J = 12.0 Hz, H-6), 4.39 (dd, 1H, J = 5.2 Hz, J = 12.4 Hz, H-6), 4.28−4.24 (m, 2H, H-3, H-5), 2.69−2.44 (m, 4H, 2 × CH_2 Lev), 2.08 (s, 3H, CH_3 Lev). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 205.4 (C═O Lev ketone), 171.3 (C═O Lev), 166.1 (C═O Bz), 165.2 (C═O Bz), 143.0 (C_q C_{arom}), 137.9 (C_q C_{arom}), 133.5 (CH_{arom}), 133.3 (CH_{arom}), 133.0 (CH_{arom}), 130.1 (C_q C_{arom}), 129.9 (CH_{arom}), 129.8 (C_q C_{arom}), 129.4−127.7 (CH_{arom}), 124.4 (CH_{arom}), 119.2 (CH_{arom}), 93.0 (C-1), 77.2 (C-3 or C-5), 75.0 (CH_2 Bn), 72.3 (C-2), 71.1 (C-3 or C-5), 70.1 (C-4), 62.6 (C-6), 37.9 (CH_2 Lev), 29.4 (CH_3 Lev), 28.1 (CH_2 Lev). HRMS: $[M + Na]^+$ calcd for $C_{40}H_{36}F_3NO_{10}Na$ 770.21835, found 770.21854.

*Benzyl (Tolyl 2-O-benzoyl-4-O-benzyl-3-O-(3,6-di-O-benzyl-2-O-benzoyl-4-O-levulinyl-1-thio-β-D-glucopyranosyl)-α/β-D-glucopyranosyluronate)) (**30a**).* Glucoside donor **29** (88 mg, 0.12 mmol) and glucuronic acid acceptor **20a** (90 mg, 0.15 mmol, 1.3 equiv) were coevaporated with toluene (2×) and dissolved in freshly distilled DCM (1.2 mL, 0.1 M), followed by addition of activated MS 3 Å. The reaction mixture was stirred for 30 min and then cooled to 0 °C. TfOH (120 μL of 0.1 M stock solution, 0.012 mmol, 0.1 equiv) and the reaction mixture were allowed to warm to rt. After 15 min, TLC analysis (PE/EtOAc 12/8, v/v) showed total consumption of the donor. The reaction mixture was neutralized with TEA, diluted with DCM, washed with H_2O, dried over $MgSO_4$, filtered, and concentrated. Size-exclusion chromatography (DCM/MeOH 1/1) gave the disaccharide **33** as a transparent oil in 51% yield (69 mg, 0.06 mmol). IR (neat, cm^{-1}): 2920, 1719, 1601, 1493, 1452, 1402, 1632, 1315, 1263, 1209, 1177, 1148, 1092, 1067, 1026, 1001, 910, 845, 810, 737, 710, 698, 662, 637. The identification was based on NMR analysis (400 MHz, $CDCl_3$, HSQC): **33*α*** 5.76 (d, J = 4.8 Hz, H-1), **33*β*** 4.59 (d, J = 9.6 Hz, H-1). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): **33*α*** 84.7 (C-1), **33*β*** 87.5 (C-1). HRMS: $[M + Na]^+$ calcd for $C_{66}H_{62}O_{16}SNa$ 1165.36508, found 1165.36444.

*Benzyl (Phenyl 2-O-benzoyl-4-O-benzyl-3-O-(2,6-di-O-benzoyl-3-O-benzyl-4-O-levulinyl-β-D-glucopyranoside)-1-thio-β-D-glucopyranosyluronate)) (**30b**).* Glucoside donor **29** (593 mg, 0.79 mmol, 1.3 equiv) and glucuronic acid ester acceptor **20b** (354 mg, 0.61 mmol) were coevaporated with toluene (2×) and dissolved in freshly distilled DCM (6.1 mL, 0.1 M), followed by addition of activated MS 3 Å. The reaction mixture was stirred for 30 min and then cooled to 0 °C. TfOH (305 μL of 0.2 M stock solution, 0.061 mmol, 0.1 equiv) was added, and the reaction mixture was allowed to warm to rt. After 15 min, TLC analysis (PE/EtOAc 12/8, v/v) showed total consumption of the acceptor. The reaction mixture was neutralized with TEA, diluted with DCM, washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated. Column chromatography (PE/EtOAc 1/0 → 1/1) followed by SEC gave disaccharide **34** as a colorless oil in 64% yield (444 mg, 0.39 mmol). $[\alpha]^{20}_D$: +19.2 (c = 1, DCM). IR (neat, cm^{-1}): 1719, 1452, 1362, 1315, 1263, 1204, 1177, 1148, 1090, 1067, 1026, 991, 972, 910, 845, 933, 698, 638, 617. ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 8.01 (d, 2H, J = 7.6 Hz, H_{arom}), 7.96 (d, 2H, J = 7.2 Hz, H_{arom}), 7.92 (d, 2H, J = 7.6 Hz, H_{arom}), 7.67−7.65 (m, 1H, H_{arom}), 7.59−7.57 (m, 1H, H_{arom}), 7.54−7.50 (m, 2H, H_{arom}), 7.45−7.35 (m, 3H, H_{arom}), 7.33−7.23 (m, 10H, H_{arom}), 7.19−7.08 (m, 11H, H_{arom}), 7.00−6.98 (m, 2H, H_{arom}), 5.31 (t, 1H, J = 8.8 Hz, H-2′), 5.22 (t, 1H, J = 8.8 Hz, H-2), 5.19 (t, 1H, J = 9.2 Hz, H-4′), 5.13 (d, 1H, J = 12.8 Hz, C*H*H CO_2Bn), 5.09 (d, 1H, J = 12.8 Hz, CH*H* CO_2Bn), 4.98 (d, 1H, J = 11.2 Hz, C*H*HPh), 4.86 (d, 1H, J = 8.0 Hz, H-1′), 4.67 (d, 1H, J = 10.0 Hz, H-1), 4.51 (d, 1H, J = 10.8 Hz, CH*H*Ph), 4.51−4.47 (m, 1H, H-6′), 4.44 (s, 2H, CH_2 Bn), 4.24 (t, 1H, J = 8.8 Hz, H-3), 4.21 (dd, 1H, J = 6.0 Hz, J = 12.4 Hz, H-6′), 3.99 (t, 1H, J = 9.2 Hz, H-4), 3.90 (d, 1H, J = 9.6 Hz, H-5), 3.74−3.69 (m, 1H, H-5′), 3.62 (t, 1H, J = 9.2 Hz, H-3′), 2.62−2.58 (m, 2H, CH_2 Lev), 2.50−2.38 (m, 1H, C*H*H Lev), 2.38−2.29 (m, 1H, CH*H* Lev), 2.07 (s, 3H, CH_3 Lev). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 206.0 (C═O Lev ketone), 171.3 (C═O), 167.2 (C═O, 166.0 (C═O), 165.0 (C═O), 164.3 (C═O0, 137.9 (C_q C_{arom}), 137.3 (C_q C_{arom}), 135.0 (C_q C_{arom}), 133.5 (CH_{arom}, 133.0 (CH_{arom}), 132.9 (C_q C_{arom}), 132.1 (CH_{arom}), 129.8 (CH_{arom}), 129.7 (CH_{arom}), 129.7 (CH_{arom}), 129.4−129.3 (C_q C_{arom}), 128.8−127.4 (CH_{arom}), 100.4 (C-1′), 87.2 (C-1), 80.3 (C-3), 79.8 (C-3′), 78.1 (C-5), 76.7 (C-4), 74.9 (CH_2 Bn), 74.0 (CH_2 Bn), 73.3 (C-2′), 72.3 (C-2), 72.2 (C-3′), 70.5 (C-4′), 67.2 (CH_2 CO_2Bn), 63.0 (C-6′), 37.7 (CH_2 Lev), 29.6 (CH_3 Lev), 27.7 (CH_2 Lev). HRMS: $[M + Na]^+$ calcd for $C_{65}H_{60}O_{16}SNa$ 1151.34943, found 1151.34865.

*Tolyl 3-O-Benzyl-4-O-(benzyl (2-O-benzoyl-4-O-benzyl-3-O-levulinyl-β-D-glucopyranosyluronate))-2,6-di-O-benzoyl-1-thio-β-D-glucopyranoside (**32**).* Glucuronic acid ester donor **17** (260 mg, 0.35 mmol, 1 equiv) and glucoside acceptor **31** (275 mg, 0.46 mmol, 1.3 equiv) were coevaporated with toluene (2×) and dissolved in freshly distilled DCM (3.5 mL, 0.1 M). Activated MS 3 Å were added, and the reaction mixture was stirred for 30 min. The reaction mixture was cooled to 0 °C, followed by addition of TfOH (175 μL of 0.2 M stock solution, 0.035 mmol, 0.1 equiv). The reaction mixture was allowed to warm to rt. After 10 min, TLC analysis (Tol/EtOAc 16/4, v/v) showed total consumption of the donor. The reaction mixture was neutralized with TEA, diluted with DCM, washed with H_2O, dried over $MgSO_4$, filtered, and concentrated, yielding a yellow oil. Column chromatography (PE/EtOAc 1/0 → 6/4) followed by SEC (MeOH/DCM 1/1) gave the title compound as a white solid in 68% yield (274 mg, 0.24 mmol). $[\alpha]^{20}_D$: + 20.6 (c = 1.6, DCM). IR (neat, cm^{-1}): 1724, 1452, 1400, 1360, 1315, 1263, 1215, 1177, 1144, 1092, 1069, 1051, 1026, 980, 737, 710, 700. ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 7.99−7.95 (m, 4H, H_{arom}), 7.88 (d, 2H, J = 7.6 Hz, H_{arom}), 7.59−7.51 (m, 2H, H_{arom}), 7.45−7.33 (m, 7H, H_{arom}), 7.28−7.14 (m, 10H, H_{arom}), 7.12−7.05 (m, 7H, H_{arom}), 6.78 (d, 2H, J = 8.0 Hz, H_{arom}), 5.37 (t, 1H, J = 9.2 Hz, H-3′), 5.30 (t, 1H, J = 9.6 Hz, H-2′), 5.13 (t, 1H, J = 9.6 Hz, H-2), 5.05 (d, 1H, J = 12.0 Hz, C*H*HPh), 4.97 (d, 1H, J = 12.0 Hz, CH*H*Ph), 4.90 (d, 1H, J = 7.6 Hz, H-1′), 4.89 (d, 1H, J = 11.6 Hz, C*H*HPh), 4.64−4.53 (m, 2H, CH*H*Ph, H-6), 4.48 (d, 1H, J = 11.2 Hz, C*H*HPh), 4.44 (d, 1H, J = 11.2 Hz, CH*H*Ph), 4.29 (dd, 1H, J = 4.4 Hz, J = 12.0 Hz, H-6), 4.05−4.00 (m, 2H, H-4, H-4′), 3.96 (d, 1H, J = 9.6 Hz, H-5′), 3.82 (t, 1H, J = 8.8 Hz, H-3), 3.56−3.53 (m, 1H, H-5), 2.56−2.32 (m, 4H, 2 × CH_2 Lev), 2.16 (s, 3H, CH_3 STol), 1.95 (s, 3H, CH_3 STol). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 205.6 (C═O Lev ketone), 171.5 (C═O), 167.3 (C═O), 165.6 (C═O), 165.0 (C═O), 164.9 (C═O), 138.1 (C_q C_{arom}), 137.8 (C_q C_{arom}), 137.2 (C_q C_{arom}), 134.7 (C_q C_{arom}), 134.0 (CH_{arom}), 133.9

(CH_{arom}), 133.4 (CH_{arom}), 133.0 (CH_{arom}), 129.8−127.8 (CH_{arom}), 127.5 (C_q C_{arom}), 127.3 (CH_{arom}), 100.9 (C-1′), 85.6 (C-1), 81.7 (C-3), 77.8 (C-4 or C-4′), 77.3 (C-4 or C-4′), 76.7 (C-5), 75.0 (CH_2 Bn), 74.6 (C-5′), 74.6 (CH_2 Bn), 73.8 (C-3′), 72.2 (C-2′), 71.7 (C-2), 67.5 (CH_2 CO_2Bn), 62.3 (C-6), 37.6 (CH_2 Lev), 29.4 (CH_3 Lev), 27.8 (CH_2 Lev), 21.0 (CH_3 STol). HRMS: $[M + Na]^+$ calcd for $C_{66}H_{62}O_{16}SNa$ 1165.36508, found 1165.36540.

*6-Azidohexyl 2-O-Benzoyl-3,6-di-O-benzyl-4-O-[benzyl (2-O-benzoyl-4-O-benzyl-3-[2,6-di-O-benzoyl-3-O-benzyl-4-O-levulinyl-β-D-glucopyranosyl]-β-D-glucopyranosyluronate)]-β-D-glucopyranoside (**33**).* Disaccharide **30b** (102 mg, 0.09 mmol) and acceptor glucoside **13** (69 mg, 0.117 mmol, 1.3 equiv) were glycosylated according to the general procedure for glycosylations using NIS/TfOH. Trisaccharide **37** was obtained as a transparent oil in 75% yield (108 mg, 0.067 mmol). R_f: 0.49 (Tol/EtOAc 4/1, v/v). $[\alpha]^{20}_D$: + 11.0 (c = 1, DCM, cm^{-1}). IR (neat): 2872, 2095, 1722, 1452, 1418, 1402, 1362, 1315, 1263, 1209, 1177, 1140, 1092, 1069, 1026, 1001, 910, 847, 733, 700, 638, 617. ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC): 7.99 (d, 2H, J = 7.2 Hz, H_{arom}), 7.88 (d, 2H, J = 7.2 Hz, H_{arom}), 7.75 (d, 3H, J = 7.2 Hz, H_{arom}), 7.74−7.57 (m, 1H, H_{arom}), 7.56−6.96 (m, 37H, H_{arom}), 5.30 (t, 1H, J = 9.2 Hz, H-2″), 5.21−5.16 (m, 2H, H-4″, H-2), 5.11 (t, 1H, J = 9.2 Hz, H-2′), 4.97 (d, 1H, J = 11.2 Hz, C*H*HPh), 4.96 (d, 1H, J = 12.0 Hz, C*H*H CO_2Bn), 4.91 (d, 1H, J = 12.0 Hz, CH*H* CO_2Bn), 4.79 (d, 1H, J = 10.4 Hz, CH*H*Ph), 4.77 (d, 1H, J = 7.6 Hz, H-1″), 4.65 (d, 1H, J = 8.0 Hz, H-1), 4.57 (d, 1H, C*H*HPh), 4.51 (dd, 1H, J = 2.8 Hz, J = 12.0 Hz, H-6″), 4.47 (d, 2H, J = 10.8 Hz, CH_2 Bn), 4.43 (s, 2H, CH_2 Bn), 4.25 (d, 1H, J = 8.0 Hz, H-1′), 4.24−4.17 (m, 2H, CH*H*Ph, H-6″), 4.06 (t, 1H, J = 8.8 Hz, H-3), 3.98 (t, 2H, J = 8.4 Hz, H-4, H-4′), 3.86 (d, 1H, J = 9.2 Hz, H-5′), 3.78 (dt, 1H, J = 3.2, J = 9.6 Hz, H-5″), 3.73−3.65 (m, 1H, C*H*H $N_3(CH_2)_6OH$), 3.65−3.59 (m, 2H, H-3″, H-3′), 3.43 (dd, 1H, J = 3.6 Hz, J = 11.2 Hz, H-6), 4.44 (d, 1H, J = 11.2 Hz, H-6), 3.33−3.21 (m, 1H, CH*H* $N_3(CH_2)_6OH$), 3.04−3.02 (m, 1H, H-5), 3.00−2.95 (m, 2H, CH_2 $N_3(CH_2)_6OH$), 2.65−2.60 (m, 2H, CH_2 Lev), 2.45−2.44 (m, 1H, C*H*H Lev), 2.38−2.32 (m, 1H, CH*H* Lev), 2.08 (s, 3H, CH_3 Lev), 1.50−1.20 (m, 4H, 2 × CH_2 $N_3(CH_2)_6OH$), 1.19−1.05 (m, 4H, 2 × CH_2 $N_3(CH_2)_6OH$). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC): 206.2 (C═O Lev ketone), 171.4 (C═O), 167.5 (C═O), 166.3 (C═O), 165.0 (C═O), 165.0 (C═O), 163.9 (C═O), 138.4 (C_q C_{arom}), 138.1 (C_q C_{arom}), 137.4 (C_q C_{arom}), 135.0 (C_q C_{arom}), 133.5−132.9 (CH_{arom}), 130.1 (C_q C_{arom}), 130.0−129.2 (CH_{arom}), 128.7 (C_q C_{arom}), 128.6 (C_q C_{arom}), 128.5 (C_q C_{arom}), 128.4−127.1 (CH_{arom}), 101.1 (C-1′), 100.9 (C-1″), 100.4 (C-1), 80.3 (C-3′), 80.0 (C-3″), 79.9 (C-3), 77.5 (C-4 or C-4′), 77.1 (C-4 or C-4′), 75.0 (CH_2 Bn), 74.8 (C-5′), 74.7 (C-5), 74.6 (CH_2 Bn), 74.0 (CH_2 Bn), 73.8 (C-2), 73.5 (CH_2 Bn), 73.4 (C-2″), 73.1 (C-2′), 72.3 (C-5″), 70.6 (C-4″),69.3 (CH_2 $N_3(CH_2)_6OH$), 67.4 (CH_2 CO_2Bn), 67.3 (C-6), 63.2 (C-6″), 51.2 (CH_2 $N_3(CH_2)_6OH$), 37.8 (CH_2 Lev), 29.7 (CH_3 Lev), 29.2 (CH_2 Lev), 28.6 (CH_2 $N_3(CH_2)_6OH$), 27.8 (CH_2 $N_3(CH_2)_6OH$), 26.2 (CH_2 $N_3(CH_2)_6OH$), 26.3 (CH_2 $N_3(CH_2)_6OH$), 25.4 (CH_2 $N_3(CH_2)_6OH$). HRMS: $[M + Na]^+$ calcd for $C_{92}H_{93}N_3O_{23}Na$ 1630.60921, found 1630.60872.

*6-Azidohexyl 2-O-Benzoyl-3,6-di-O-benzyl-4-O-[benzyl (2-O-benzoyl-4-O-benzyl-3-[2,6-di-O-benzoyl-3-O-benzyl-β-D-glucopyranosyl]-β-D-glucopyranosyluronate)]-β-D-glucopyranoside (**34**).* Trisaccharide **33** (82 mg, 0.051 mmol) was dissolved in a mixture of pyridine/AcOH (4/1, 0.51 mL, 0.1 M), and the reaction mixture was cooled to 0 °C. Hydrazine acetate (24 mg, 0.26 mmol, 5 equiv) was added, and the reaction mixture was allowed to warm to rt. After 15 min, TLC analysis (Tol./EtOAc 4/1) showed total conversion into a higher running spot (R_f 0.5). The reaction mixture was cooled to 0 °C, quenched with acetone, diluted with EtOAc, washed with 1 M HCl and $NaHCO_3$ (aq, satd), dried over $MgSO_4$, filtered, and concentrated. Column chromatography (PE/EtOAc 1/0 → 6/4) gave the title compound as a colorless oil in 95% yield (73 mg, 0.048 mmol). $[\alpha]^{20}_D$: + 16.7 (c = 0.86, DCM). IR (neat, cm^{-1}): 3065, 3034, 2928, 2869, 2253, 2099, 1728, 1603, 1497, 1452, 1418, 1362, 1315, 1265, 1213 1179, 1157, 1086, 1069, 1026, 905, 849. ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC): 8.00 (d, 2H, J = 7.2 Hz, H_{arom}), 4.94 (d, 2H, J = 7.2 Hz, H_{arom}), 7.92−7.78 (m, 3H, H_{arom}), 7.58−7.51 (m, 1H, H_{arom}), 7.51−7.40 (m, 5H, H_{arom}), 7.40−6.97 (m, 33H, H_{arom}), 5.23−5.16 (m, 2H, H-2, H-2″), 5.13 (t, 1H, J = 9.2 Hz, H-2′), 5.03 (d, 1H, J = 11.2 Hz, CH*H*Ph), 4.94 (d, 1H, C*H*H CO_2Bn), 4.88 (d, 1H, CH*H* CO_2Bn), 4.78 (d, 1H, J = 11.6 Hz, C*H*HPh), 4.76 (d, 1H, J = 8.0 Hz, H-1″), 4.69 (d, 1H, J = 8.0 Hz, H-1), 4.67−4.54 (m, 4H, H-6″, CH_2Ph), 4.54−4.45 (m, 4H, 2 × CH_2Ph), 4.25 (d, 1H, J = 10.0 Hz, H-5″), 4.25 (d, 1H, J = 8.0 Hz, H-1′), 4.12 (t, 1H, J = 8.8 Hz, H-3), 4.02−3.95 (m, 2H, H-4′, H-4), 3.90 (d, 1H, J = 9.6 Hz, H-5′), 3.91−3.55 (m, 3H, C*H*H $N_3(CH_2)_6OH$, H-4″, H-3′), 3.46 (dd, 1H, J = 3.2 Hz, J = 8.0 Hz, H-6^a), 3.41 (t, 1H, J = 9.2 Hz, H-3″), 3.30 (d, 1H, J = 10.0 Hz, H-6^b), 3.28−3.24 (m, 1H, CH*H* $N_3(CH_2)_6OH$), 3.08−3.05 (m, 1H, H-5), 3.0 (dt, 2H, J = 2.0 Hz, J = 6.8 Hz, CH_2 $N_3(CH_2)_6OH$), 2.81 (d, 1H, J = 3.2 Hz, O*H*), 1.58−1.26 (m, 4H, 2 × CH_2 $N_3(CH_2)_6OH$), 1.16−1.09 (m,4H, 2 × CH_2 $N_3(CH_2)_6OH$). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC): 167.5 (C═O CO_2Bn), 167.2 (C═O Bz), 165.2 (C═O Bz), 164.9 (C═O Bz), 163.8 (C═O Bz), 138.4−137.5 (C_q C_{arom}), 134.9 (C_q C_{arom}), 133.6−132.9 (CH_{arom}), 130.1 (C_q C_{arom}), 130.0−129.7 (CH_{arom}), 129.7−129.6 (C_q C_{arom}),129.3−127.0 (CH_{arom}), 101.3 (C-1′), 100.9 (C-1″), 100.4 (C-1), 82.0 (C-3″), 80.3 (C-3′), 79.7 (C-3), 77.5 (C-4), 77.3 (C-4′), 74.8 (CH_2 Bn), 74.8 (C-5′), 74.8 (CH_2 Bn), 74.7 (C-5), 74.6 (CH_2 Bn), 74.1 (C-3′), 73.9 (C-2 and C-5″), 73.5 (CH_2 Bn), 73.4 (C-2″), 73.1 (C-2′), 70.3 (C-4″), 69.3 (CH_2 $N_3(CH_2)_6OH$), 67.4 (C-6), 67.3 (CH_2 CO_2Bn), 63.5 (C-6″), 51.1 (CH_2 $N_3(CH_2)_6OH$), 29.1 (CH_2 $N_3(CH_2)_6OH$), 28.5 (CH_2 $N_3(CH_2)_6OH$), 26.2 (CH_2 $N_3(CH_2)_6OH$), 25.3 (CH_2 $N_3(CH_2)_6OH$). HRMS: $[M + Na]^+$ calcd for $C_{87}H_{87}N_3O_{21}Na$ 1532.57243, found 1532.57327.

*6-Aminohexyl 4-O-(3-O-(β-D-Glucopyranosyl)-β-D-glucopyranosyluronic acid)-β-D-glucopyranoside (**35**).* Trisaccharide **34** (66 mg, 43.7 μmol) was dissolved in dioxane (874 μL, 0.05 M) followed by addition of KOH (0.5 M KOH in H_2O, 1.05 mL, 0.52 mmol, 12 equiv). After the mixture was stirred overnight, more KOH was added portionwise (52 μL, 0.26 mmol, 6 equiv, then 26 μL, 0.13 mmol, 3 equiv). After 6 days, LCMS analysis confirmed that the esters were saponified. The reaction mixture was neutralized with H^+ Amberlite, filtered, and concentrated. Size-exclusion chromatography (DCM/MeOH 1/1) gave a white solid, which was dissolved in H_2O/^{t}BuOH mixture (1/2, v/v, 486 μL, 0.09 M). A drop of 1 M HCl (aq) was added followed by addition of Pd/C. The reaction mixture was purged with H_2 gas and stirred overnight. The reaction mixture was filtered over a Whatman filter and concentrated. The obtained residue was subjected to gel filtration (HW-40, 0.15 M NH_4HCO_3 in H_2O) and subsequent lyophilization. The deprotected trimer was obtained as a white solid in 44% yield over two steps (12 mg, 19.4 μmol). ^1H NMR (600 MHz, $CDCl_3$, HH-COSY, HSQC, TOCSY, HMBC): 4.75 (d, 1H, J = 7.8 Hz, H-1″), 4.49 (d, 1H, J = 7.8 Hz, H-1′), 3.93 (d, 1H, J = 11.4 Hz, H-6^a″), 3.91−3.77 (m, 2H, H-6^a, CH*H* $N_3(CH_2)_6OH$), 3.77−3.72 (m, 3H, H-5, H-3′, H-6^b″), 3.67 (dd, 1H, J = 6.0 Hz, J = 12.4 Hz, H-6^b), 3.67−3.63 (m, 1H, C*H*H $N_3(CH_2)_6OH$), 3.61−3.54 (m, 4H, H-3, H-4, H-4′, H-5′), 5.53 (t, 1H, J = 9.0 Hz, H-2), 3.47 (t, 1H, J = 9.6 Hz, H-3″), 3.45−3.40 (m, 1H, H-5″), 3.35 (t, 1H, J = 9.6 Hz, H-4″), 3.30 (t, 1H, J = 9.0 Hz, H-2″), 3.24 (t, 1H, J = 9.0 Hz, H-2), 2.94 (t, 2H, J = 7.8 Hz, CH_2 $N_3(CH_2)_6OH$), 1.64−1.59 (m, 4H, 2 × CH_2 $N_3(CH_2)_6OH$), 1.37−1.36 (m, 4H, 2 × CH_2 $N_3(CH_2)_6OH$). ^{13}C NMR (150 MHz, $CDCl_3$, HH-COSY, HSQC, TOCSY, HMBC): 176.3 (C═O), 103.5 (C-1″), 103.0 (C-1′), 102.9 (C-1), 83.5 (C-5), 79.8 (C-4 or C-4′ or C-5′), 77.0 (C-5″), 76.7 (C-3′), 76.5 (C-3″), 75.7 (C-4 or C-4′ or C-5′), 75.3 (C-3), 74.4 (C-2″), 74.1 (C-2′), 73.8 (C-2), 71.4 (CH_2 $N_3(CH_2)_6$-OH), 71.2 (C-4 or C-4′ or C-5′), 70.5 (C-4″), 61.7 (C-6″), 61.0 (C-6), 40.3 (CH_2 $N_3(CH_2)_6OH$), 29.4 (CH_2 $N_3(CH_2)_6OH$), 27.6 (CH_2 $N_3(CH_2)_6OH$), 26.2 (CH_2 $N_3(CH_2)_6OH$), 25.5 (CH_2 $N_3(CH_2)_6$-OH). HRMS: $[M + H]^+$ calcd for $C_{24}H_{44}NO_{17}$ 618.26038, found 618.26016.

*Benzyl (6-Azidohexyl 2-O-benzoyl-4-O-benzyl-3-O-[2,6-di-O-benzoyl-3-O-benzyl-4-O-[benzyl (2-O-benzoyl-4-O-benzyl-3-O-levulinyl-β-D-glucopyranosyluronate)]-β-D-glucopyranosyl]-β-D-glucopyranosyluronate) (**36**).* Disaccharide **32** (90 mg, 0.08 mmol) and glucuronic acid ester acceptor **10** (61 mg, 0.10 mmol, 1.3 equiv) were condensed according to the general procedure for glycosylations using NIS/TfOH. The title compound was isolated as a white solid in 54% yield. R_f 0.36 (PE/EtOAc 13/7). $[\alpha]^{20}_D$: +6.1 (c = 1, DCM). IR (neat, cm^{-1}): 2095, 1728, 1452, 1362, 1315, 1261, 1215, 1177, 1142, 1094,

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1069, 1026, 978, 910, 750, 710, 698. ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC): 8.00−7.88 (m, 2H, H_{arom}),7.86−7.76 (m, 4H, H_{arom}), 7.61−7.56 (m, 2H, H_{arom}), 7.48−7.35 (m, 11H, H_{arom}), 7.28−7.09 (m, 15H, H_{arom}), 7.08−7.01 (m, 8H, H_{arom}), 7.08−6.95 (m, 3H, H_{arom}), 5.33−5.20 (m, 3H, H-3″, H-2′, H-2″), 5.10−5.03 (m, 3H, H-2, CH_2 CO_2Bn), 5.02 (d, 1H, J = 12.4 Hz, C*H*H CO_2Bn), 4.94 (d, 1H, J = 12.4 Hz, CH*H* CO_2Bn), 4.85 (d, 1H, J = 11.2 Hz, C*H*HPh), 4.82 (d, 1H, J = 8.0 Hz, H-1′), 4.76 (d, 1H, J = 10.8 Hz, CH*H*Ph), 4.76 (d, 1H, J = 8.0 Hz, H-1″), 4.53 (d, 1H, J = 11.6 Hz, H-6), 4.48−4.34 (m, 4H, 2 × CH_2 Bn), 4.35 (d, 1H, J = 7.6 Hz, H-1), 4.19 (dd, 1H, J = 4.4 Hz, J = 12.0 Hz, H-6), 4.12 (t, 1H, J = 8.0 Hz, H-3), 4.05 (t, 1H, J = 8.8 Hz, H-4′), 3.97 (t, 1H, J = 9.2 Hz, H-4″), 3.93 (t, 1H, J = 8.4 Hz, H-4), 3.88 (d, 1H, J = 8.4 Hz, H-5 or H-5″), 3.84 (d, 1H, J = 9.6 Hz, H-5 or H-5″), 3.71−3.64 (m, 2H, H-3, C*H*H $N_3(CH_2)_6OH$), 3.49−3.47 (m, 1H, H-5′), 3.20-.3.14 (m, 1H, CH*H* $N_3(CH_2)_6OH$), 3.02 (t, 2H, J = 6.8 Hz, CH_2 $N_3(CH_2)_6OH$), 2.47−2.38 (m, 2H, CH_2 Lev), 2.36−2.23 (m, 2H, CH_2 Lev), 1.97 (s, 3H, CH_3 Lev), 1.26−1.17 (m, 4H, 2 × CH_2 $N_3(CH_2)_6OH$), 1.14−0.96 (m, 4H, 2 × CH_2 $N_3(CH_2)_6OH$). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC): 205.6 (C═O Lev ketone), 171.5 (C═O), 168.2 (C═O), 167.3 (C═O), 165.6 (C═O), 165.1 (C═O), 164.4 (C═O), 137.9 (C_q C_{arom}), 137.8 (C_q C_{arom}), 137.2 (C_q C_{arom}), 135.0 (C_q C_{arom}), 134.6 (C_q C_{arom}), 133.4 (CH_{arom}), 133.1 (CH_{arom}), 132.9 (CH_{arom}), 129.9 (C_q C_{arom}), 129.8 (C_q C_{arom}), 129.7−127.2 (CH_{arom}), 100.8 (C-1″), 100.5 (C-1), 99.7 (C-1′), 80.7 (C-3′), 79.1 (C-3), 77.8 (C-4′), 77.3 (C-4″), 76.9 (C-4), 74.7 (CH_2 Bn), 74.6 (CH_2 Bn), 74.6 (CH_2 Bn), 74.5 (C-5 or C-5″), 74.4 (C-5 or C-5″), 73.9 (C-3″), 73.5 (C-2), 73.3 (C-2′), 72.6 (C-5′), 72.1 (C-2″), 69.3 (CH_2 $N_3(CH_2)_6OH$), 67.5 (CH_2 CO_2Bn), 67.2 (CH_2 CO_2Bn), 62.4 (C-6′), 51.2 (CH_2 $N_3(CH_2)_6OH$), 37.6 (CH_2 Lev), 29.5 (CH_3 Lev), 28.9 (CH_2 $N_3(CH_2)_6OH$), 28.5 (CH_2 Lev), 27.8 (CH_2 $N_3(CH_2)_6OH$), 26.1 (CH_2 $N_3(CH_2)_6OH$), 25.2 (CH_2 $N_3(CH_2)_6OH$). HRMS: $[M + Na]^+$ calcd for $C_{92}H_{91}N_3O_{24}Na$ 1644.58847, found 1644.58818.

*Benzyl (6-Azidohexyl 2-O-benzoyl-4-O-benzyl-3-O-[2,6-di-O-benzoyl-3-O-benzyl-4-O-[benzyl (2-O-benzoyl-4-O-benzyl-β-D-glucopyranosyluronate)]-β-D-glucopyranosyl]-β-D-glucopyranosyluronate) (**37**).* Trisaccharide **36** (24 mg, 0.015 mmol) was dissolved in a mixture of pyridine/AcOH (4/1, 300 μL, 0.05 M), and the resulting mixture was cooled to 0 °C. Hydrazine acetate (7 mg, 0.075 mmol, 5 equiv) was added, and the reaction mixture was allowed to warm to rt. After 30 min, TLC analysis (PE/EtOAc 12/8) showed total conversion into a slightly higher running spot (R_f 0.82). The reaction mixture was cooled to 0 °C and quenched with acetone. The reaction mixture was diluted with EtOAc, washed with 1 M HCl and $NaHCO_3$ (aq, satd), dried over $MgSO_4$, filtered, and concentrated. Column chromatography (PE/EtOAc 1/0 → 7/3) gave the title compound as an transparent oil which crystallized on standing in 93% yield (21 mg, 0.014 mmol). $[\alpha]^{20}_D$: +16.2 (c = 0.4, DCM). IR (neat, cm^{-1}): 3696, 303, 2986, 2307, 1732, 1603, 1558, 1452, 1421, 1398, 1373, 1263, 1217, 1179, 1157, 1096, 1070, 1028, 1001, 986, 949, 895. ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC): 8.09 (d, 2H, J = 7.8 Hz, H_{arom}), 7.91−7.86 (m, 4H, H_{arom}), 7.75 (d, 2H, J = 8.4 Hz, H_{arom}), 7.55−7.11 (m, 29 H, H_{arom}), 7.05−6.95 (m, 8H, H_{arom}), 5.25 (t, 1H, J = 8.8 Hz, H-2′), 5.15 (t, 1H, J = 8.8 Hz, H-2″), 5.04 (t, 1H, J = 8.8 Hz, H-2), 5.02 (s, 2H, CH_2 CO_2Bn), 5.01 (d, 1H, J = 12.0 Hz, C*H*HPh CO_2Bn), 4.96 (d, 1H, J = 12.0 Hz, CH*H*Ph CO_2Bn), 4.89 (d, 1H, J = 11.2 Hz, CH*H*Ph), 4.81 (d, 1H, J = 10.4 Hz, C*H*HPh), 4.81 (d, 1H, J = 8.4 Hz, H-1′), 4.69 (d, 1H, J = 7.6 Hz, H-1″), 4.54 (d, 1H, J = 11.2 Hz, CH*H*Ph), 4.49−4.44 (m, 3H, H-6^a, 2 × C*H*HPh), 4.43 (d, 1H, J = 11.6 Hz, CH*H*Ph), 4.40 (d, 1H, J = 8.4 Hz, H-1), 4.33 (dd, 1H, J = 4.8 Hz, J = 11.6 Hz, H-6^b), 4.10 (t, 1H, J = 9.6 Hz, H-3), 4.08 (t, 1H, J = 9.6 Hz, H-4′), 3.95 (t, 1H, J = 10.0 Hz, H-4), 3.92 (d, 1H, J = 10.8 Hz, H-5), 3.80−3.68 (m, 4H, H-3″, H-4″, H-5″, C*H*H $N_3(CH_2)_6OH$), 3.63 (t, 1H, J = 8.8 Hz, H-3′), 3.49−3.46 (m, 1H, H-5′), 3.21−3.15 (m, 1H, CH*H* $N_3(CH_2)_6OH$), 3.02 (t, 2H, J = 6.8 Hz, CH_2 $N_3(CH_2)_6OH$), 1.28−1.24 (m, 4H, 2 × CH_2 $N_3(CH_2)_6OH$), 1.23−1.08 (m, 4H, 2 × CH_2 spacer). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC): 168.1 (C═O CO_2Bn), 167.6 (C═O CO_2Bn), 165.8 (C═O Bz or CO_2Bn), 165.7 (C═O or CO_2Bn), 165.1 (C═O Bz), 164.4 (C═O Bz), 138.0−137.5 (C_q C_{arom}), 135.0−134.8 (C_q C_{arom}), 133.5−132.8 (CH_{arom}), 130.0−129.4 (CH_{arom}), 128.9−128.7 (C_q C_{arom}), 128.6−127.2 (CH_{arom}), 100.8 (C-1″), 100.5 (C-1), 100.0 (C-1′), 80.6 (C-3′), 79.6 (C-3″), 79.4 (C-3), 77.8 (C-4′), 76.9 (C-4), 74.9 (CH_2 Bn), 74.9 (C-4″), 74.8 (CH_2 Bn), 74.6 (CH_2 Bn), 74.5 (C-5 and C-5″), 74.1 (C-2″), 73.5 (C-2), 73.2 (C-2′), 72.8 (C-5), 69.3 (CH_2 $N_3(CH_2)_6OH$), 67.4 (CH_2 CO_2Bn), 67.2 (CH_2 CO_2Bn), 62.6 (C-6′), 51.2 (CH_2 $N_3(CH_2)_6OH$), 28.9 (CH_2 $N_3(CH_2)_6OH$), 28.5 (CH_2 $N_3(CH_2)_6OH$), 26.2 (CH_2 $N_3(CH_2)_6OH$), 25.2 (CH_2 $N_3(CH_2)_6OH$). HRMS: $[M + Na]^+$ calcd for $C_{87}H_{85}N_3O_{22}Na$ 1546.55169, found 1546.55288.

*6-Aminohexyl 3-O-(4-O-(β-D-Glucopyranosyluronic acid)-β-D-glucopyranosyl)-β-D-glucopyranosyluronic Acid (**38**).* Trisaccharide **37** (61 mg, 40 μmol) was dissolved in dioxane (800 μL, 0.05 M) followed by addition of KOH (0.5 M KOH in H_2O, 0.96 mL, 0.48 mmol, 12 equiv). After the mixture was stirred overnight, more KOH was added portionwise (48 μL, 0.26 mmol, 6 equiv, then 24 μL, 0.13 mmol, 3 equiv, then 24 μL, 0.13 mmol, 3 equiv). After 6 days, LCMS analysis confirmed that the esters were saponified. The reaction mixture was neutralized with H^+ Amberlite, filtered, and concentrated. Size-exclusion chromatography (DCM/MeOH 1/1) gave a white solid, which was dissolved in H_2O/^{t}BuOH mixture (1/2, v/v, 500 μL, 0.08 M). A drop of 1 M HCl (aq) was added followed by addition of Pd/C. The reaction mixture was purged with H_2 gas and stirred overnight. The reaction mixture was filtered over a Whatman filter and concentrated. The obtained residue was subjected to gel filtration (HW-40, 0.15 M NH_4HCO_3 in H_2O) and subsequent lyophilization. The deprotected trimer was obtained as a fine white powder in 28% yield over two steps (7 mg, 11 μmol). ^{1}H NMR (600 MHz, D_2O, 283 K, HH-COSY, HSQC, HMBC): 4.77 (d, 1H, J = 7.8 Hz, H-1′), 4.46 (d, 1H, J = 8.4 Hz, H-1″), 4.44 (d, 1H, J = 7.8 Hz, H-1), 3.94 (d, 1H, J = 11.4 Hz, H-6^a), 3.90−3.80 (m, 1H, CH*H* $N_3(CH_2)_6OH$), 3.77−3.68 (m, 4H, H-3, H-4′, H-5, H-6$^{b\prime}$), 3.65−3.62 (m, 2H, H-3″, C*H*H $N_3(CH_2)_6OH$), 3.60−3.55 (m, 2H, H-5′, H-5″), 3.48−3.44 (m, 3H, H-2, H-3′, H-4), 3.35−3.31 (m, 2H, H-2′, H-2″), 2.94 (t, 2H, J = 7.2 Hz, CH_2 $N_3(CH_2)_6OH$), 1.6−1.58 (m, 4H, 2 × CH_2 $N_3(CH_2)_6OH$), 1.37−1.36 (m, 4H, 2 × CH_2 $N_3(CH_2)_6OH$). ^{13}C NMR (150 MHz, D_2O, HH-COSY, HSQC, HMBC): 176.7 (C═O), 176.6 (C═O), 103.4 (C-1′), 103.3 (C-1″), 102.9 (C-1), 84.3 (C-3 or C-4′), 79.9 (C-5′ or C-5″), 77.2 (C-5), 76.8 (C-3 or C-4′), 76.2 (C-2 or C-3′), 75.8 (C-5′ or C-5″), 75.1 (C-3″), 74.1 (C-2″), 73.9 (C-4), 76.9 (C-2′), 72.7 (C-2 or C-3′), 71.7 (CH_2 $N_3(CH_2)_6OH$), 71.2 (C-4″), 61.0 (C-6), 40.4 (CH_2 $N_3(CH_2)_6OH$), 29.4 (CH_2 $N_3(CH_2)_6OH$), 27.6 (CH_2 $N_3(CH_2)_6OH$), 26.1 (CH_2 $N_3(CH_2)_6OH$), 25.4 (CH_2 $N_3(CH_2)_6OH$). HRMS: $[M + Na]^+$ calcd for $C_{24}H_{41}NO_{18}Na$ 654.22158, found 654.22136.

*Methyl (p-Tolyl 2,3-di-O-benzyl-1-thio-β-D-glucopyranosyluronate) (**40**).* Glucoside **39**[30] (1.0 g, 2.14 mmol) was dissolved in a mixture of DCM/H_2O (2/1, 10.7 mL, 0.2 M) (Scheme 5). The reaction mixture was cooled to 0 °C, followed by addition of BAIB (1.72 g, 5.35 mmol, 2.5 equiv) and TEMPO (67 mg, 0.43 mmol, 0.2 equiv), The reaction mixture was allowed to warm to rt, and after 2 h, TLC analysis (PE/EtOAc 1/1, v/v) showed total conversion of the starting material. The reaction mixture was quenched by addition of $Na_2S_2O_3$ (aq, satd), followed by separation of the layers. The aqueous layer was extracted with EtOAc (2×), and the combined organic layers were dried over $MgSO_4$, filtered, concentrated, and coevaporated with toluene. The yellow oil obtained was dissolved in DMF (10.7 mL, 0.2 M) followed by addition of MeI (0.4 mL, 6.42 mmol, 3 equiv) and K_2CO_3 (0.89 g 6.42 mmol, 3 equiv). After 30 min, TLC analysis (PE/EtOAc 1/1, v/v) showed total conversion of the glucuronic acid. The reaction mixture was quenched with MeOH, diluted with DCM, washed with with brine, dried over $MgSO_4$, filtered, and concentrated. Column chromatography (PE/EtOAc 1/0 → 6/4) gave the target compound in 69% yield over two steps (0.73 g, 1.48 mmol). $[\alpha]^{20}_D$: −38.8 (c = 1, DCM). IR (neat, cm^{-1}): 2870, 1746, 1493, 1454, 1439, 1398, 1356, 1279, 1265, 1238, 1209, 1175, 1130, 1059, 1018, 986, 908, 839, 808, 733, 696, 633, 615, 604. ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 7.47 (d, 2H, J = 8.0 Hz, H_{arom}), 7.41−7.28 (m, 10H, H_{arom}), 7.11 (d, 2H, J = 8.0 Hz, H_{arom}), 4.88 (d, 1H, J = 10.8 Hz, C*H*HPh), 4.85 (m, 2H, CH_2 Bn), 4.74 (d, 1H, J = 10.4 Hz, CH*H*Ph), 4.63 (d, 1H, J = 9.6 Hz, H-1), 3.88 (t, 1H, J = 8.8 Hz, H-4), 3.82−3.80 (m, 4H, H-5, OCH_3), 3.57 (t, 1H, J = 8.8 Hz, H-3), 3.45 (t, 1H, J = 9.2 Hz, H-2), 2.93 (bs, 1H, O*H*), 2.33 (s, 3H, CH_3 STol). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY,

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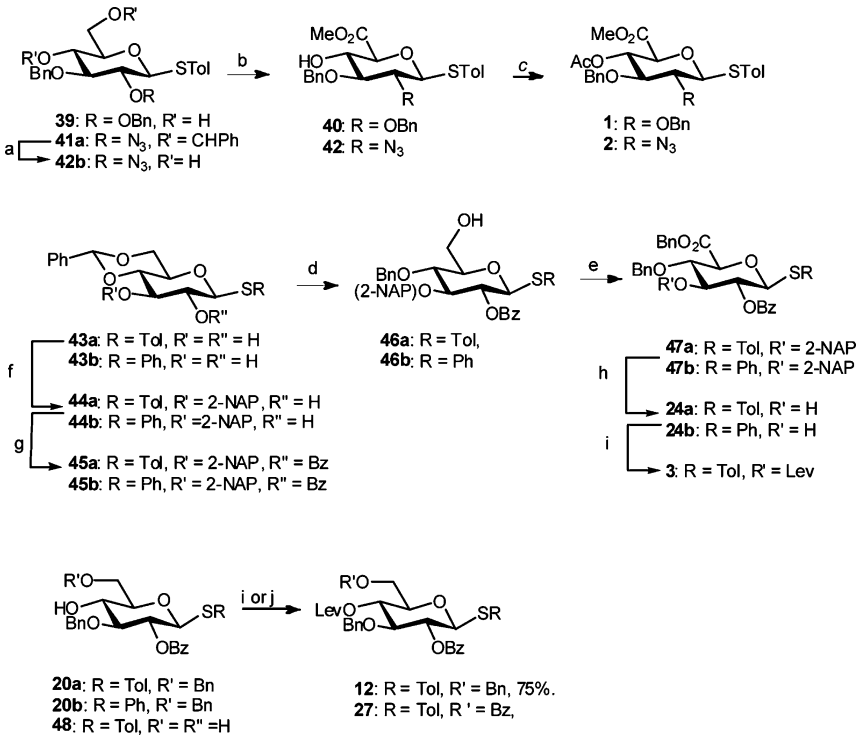
Scheme 5. Synthesis of Thioglycosides 1, 2, 3, 12, and 27[a]



[a]Reagents and conditions: (a) *p*TsOH, MeOH (used without further purification); (b) (i) TEMPO, BAIB, DCM/H_2O, (ii) MeI, K_2CO_3, DMF, **40**: 67%/two steps, **42**: 61%/three steps; (c) (i) Ac_2O, Pyr, **1**: 78%, **2**: 82%; (d) BH_3·THF, $Cu(OTf)_2$, DCM, **46a**: 66%, **46b**: 66%; (e) (i) TEMPO, BAIB, DCM/H_2O, (ii) BnBr, K_2CO_3, DMF, **47a**: 17%/two steps, **47b**: 56%/two steps.; (f) (i) Bu_2SnO, Tol, (ii) NAP-Br, CsF, DMF, **44a**: 65%, **44b**: 60%; (g) BzCl, Pyr, **45a**: 80%, **45b**: 84%; (h) DDQ, DCM/H_2O, **24a**: 68%, **24b**: 97%; (i) LevOH, DMAP, DCM, **3**: 78%, **12**: 75%; (j) (i) Bu_2SnO, Tol, (ii) BzBr, Tol, (iii) LevOH, DIC, DMAP, DCM, **27**: 75%/three steps.

HSQC): 169.4 (C=O CO_2Me), 138.0 (C_q C_{arom}), 137.7 (C_q C_{arom}), 132.7 (CH_{arom}), 129.6 (CH_{arom}), 129.1 (C_q C_{arom}), 128.4–127.7 (CH_{arom}), 88.5 (C-1), 85.1 (C-3), 79.5 (C-2), 77.4 (C-5), 75.5 (CH_2 Bn), 75.3 (CH_2 Bn), 71.7 (C-4), 52.6 (OCH_3), 21.0 (CH_3 STol). HRMS: $[M + Na]^+$ calcd for $C_{28}H_{30}O_6SNa$ 517.16553, found 517.16477.

Methyl (p-Tolyl 4-O-acetyl-2,3-di-O-benzyl-1-thio-β-D-glucopyranosyluronate) (1). Glucuronic acid methyl ester **40** (264 mg, 0.53 mmol) was dissolved in pyridine (1.8 mL, 0.3 M). The reaction mixture was cooled to 0 °C, followed by addition of acetic anhydride (0.15 mL, 1.60 mmol, 3 equiv). After 15 min, TLC analysis (PE/EtOAc 1/1, v/v) showed total conversion into a higher running spot. The reaction mixture was quenched with MeOH, diluted with EtOAc, washed with 1 M HCl, $NaHCO_3$ (aq, satd), dried over $MgSO_4$, filtered, and concentrated. Column chromatography (PE/EtOAc 1/0 → 8/2) gave the title compound as a white solid in quantitative yield (286 mg, 0.53 mmol). $[\alpha]^{20}_D$: + 21.2 (*c* = 1, DCM). IR (neat, cm^{-1}): 2874, 1753, 1732, 1495, 1454, 1435, 1369, 1356, 1310, 1234, 1206, 1179, 1121, 1090, 1078, 1045, 1028, 1018, 986, 962, 947, 899, 820, 806, 743, 698, 671, 646, 629, 617. ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 7.49 (d, 2H, *J* = 7.6 Hz, H_{arom}), 7.40–7.7.22 (m, 10H, H_{arom}), 7.12 (d, 2H, *J* = 8.0 Hz, H_{arom}), 5.11 (t, 1H, *J* = 9.6 Hz, H-4), 4.87 (d, 1H, *J* = 10.0 Hz, C*H*HPh), 4.79 (d, 1H, *J* = 11.6 Hz, CH*H*Ph), 4.69 (d, 1H, *J* = 10.8 Hz, C*H*HPh), 4.66 (d, 1H, *J* = 11.6 Hz, CH*H*Ph), 4.57 (d, 1H, *J* = 9.6 Hz, H-1), 3.88 (d, 1H, *J* = 10.0 Hz, H-5), 3.73 (s, 3H, CO_2CH_3), 3.67 (t, 1H, *J* = 9.2 Hz, H-3), 3.52 (t, 1H, *J* = 9.6 Hz, H-2), 2.33 (s, 3H, CH_3 STol), 1.91 (s, 3H, CH_3 Ac). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 169.5 (C=O), 167.6 (C=O), 138.3 (C_q C_{arom}), 137.9 (C_q C_{arom}), 137.8 (C_q C_{arom}), 133.2–132.8 (CH_{arom}), 129.8 (CH_{arom}), 129.6 (C_q C_{arom}), 128.6–127.7 (CH_{arom}), 87.9 (C-1), 83.3 (C-3), 79.7 (C-2), 76.3 (C-5), 75.4 (CH_2 Bn), 75.2 (CH_2 Bn), 69.3 (C-4), 52.7 (OCH_3), 21.1 (CH_3 STol), 20.6 (CH_3 Ac). HRMS: $[M + Na]^+$ calcd for $C_{30}H_{32}O_7SNa$ 559.17610, found 559.17561.

Methyl (p-Tolyl 2-azido-3-O-benzyl-2-O-deoxy-1-thio-β-D-glucopyranosyluronate) (42). Glucosamine **41**[31] (2.83 g, 5.78 mmol) was suspended in MeOH (19.3 mL, 0.3 M), and a catalytic amount of *p*-TsOH was added. After 4 h, TLC analysis showed total conversion into a lower running spot (PE/EtOAc 3/1, v/v, R_f 0.2). The reaction mixture was neutralized with TEA and concentrated. The residue was dissolved in EtOAc and washed with H_2O (2×), dried over $MgSO_4$, filtered, and concentrated. Crude ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 7.41 (d, 2H, *J* = 8.0 Hz, H_{arom}), 7.35–7.25 (m, 5H, H_{arom}), 7.09 (d, 2H, *J* = 8.0 Hz, H_{arom}), 4.86 (d, 1H, *J* = 10.8 Hz, C*H*HPh), 4.76 (d, 1H, *J* = 11.2 Hz, CH*H*Ph), 4.35 (d, 1H, *J* = 10.0 Hz, H-1), 3.81 (d, 1H, *J* = 11.6 Hz, H-6), 3.71 (d, 1H, *J* = 11.6 Hz, H-6), 3.51 (t, 1H, *J* = 8.8 Hz, H-3), 3.44 (d, 1H, *J* = 3.6 Hz, C-3-O*H*), 3.29 (t, 1H, *J* = 9.2 Hz, H-4), 3.26–3.21 (m, 2H, H-2, H-5), 2.95 (bs, 1H, C-6-O*H*), 2.30 (s, 3H, CH_3 STol). Crude ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 138.6 (C_q C_{arom}), 137.6 (C_q C_{arom}), 133.6 (CH_{arom}), 129.7 (CH_{arom}), 128.4 (CH_{arom}), 128.0 (CH_{arom}), 127.1 (C_q C_{arom}), 86.2 (C-1), 84.4 (C-4), 79.3 (C-2), 75.3 (CH_2 Bn), 69.8 (C-3), 64.5 (C-5), 61.8 (C-6), 21.0 (CH_3 STol). The crude residue was dissolved in a mixture of DCM/H_2O (2/1, 28.9 mL, 0.2M). The reaction mixture was cooled to 0 °C and BAIB (4.66 g, 14.45 mmol, 2.5 equiv) and TEMPO (181 mg, 1.16 mmol, 0.2 equiv) were added.[8] After 2 h., TLC analysis (PE/EtOAc 1/1, v/v) showed total consumption of the starting material. The reaction mixture was quenched by addition of $Na_2S_2O_3$ (aq, satd) and $NaHCO_3$ (aq, satd). The reaction mixture was extracted with EtOAc (2×) and the combined organic layers were dried over $MgSO_4$, filtered, concentrated, and coconcentrated with toluene. The obtained yellow oil was dissolved in DMF (29.0 mL, 0.2M), followed by addition of methyl iodide (1.08 mL, 17.34 mmol, 3 equiv) and K_2CO_3 (2.4 g, 17.34 mmol, 3 equiv). After 20 min, TLC analysis (PE/EtOAc 1/1, v/v) showed total conversion of the glucuronate. The reaction mixture was quenched by addition of MeOH and extracted with Et_2O (2×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Column chromatography (PE/EtOAc 1/0 → 1/1) gave the title compound in 61% yield over 3 steps (1.51 g, 3.51 mmol).

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$[\alpha]^{20}_D$: + 82.8 (c = 1, DCM). IR (neat, cm^{-1}): 2874, 2108, 1744, 1493, 1454, 1439, 1379, 1354, 1267, 1236, 1207, 1175, 1065, 1018, 957, 908, 837, 810, 737, 698, 677, 617. ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 7.46 (d, 2H, J = 7.6 Hz, H_{arom}), 7.37−7.25 (m, 5H, H_{arom}), 7.11 (d, 2H, J = 8.0 Hz, H_{arom}), 4.88 (d, 1H, J = 10.8 Hz, C*H*HPh), 4.82 (d, 1H, J = 10.8 Hz, CH*H*Ph), 4.35 (d, 1H, J = 10.0 Hz, H-1), 3.78−3.75 (m, 5H, H-4, H-5, OCH_3), 3.38 (t, 1H, J = 8.4 Hz, H-3), 3.26 (t, 1H, J = 9.6 Hz, H-2), 2.31 (s, 3H, CH_3 STol). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 168.9 (C═O), 138.6 (C_q C_{arom}), 137.3 (C_q C_{arom}), 133.9 (CH_{arom}), 129.4 (CH_{arom}), 128.1 (CH_{arom}), 127.8 (CH_{arom}), 127.6 (CH_{arom}), 126.2 (C_q C_{arom}), 86.2 (C-1), 83.2 (C-3), 77.3 (C-4 or C-5), 75.1 (CH_2 Bn), 71.3 (C-4 or C-5), 63.6 (C-2), 60.0 (C-6), 52.4 (OCH_3), 20.7 (CH_3 STol). HRMS: [M + Na]$^+$ calcd for $C_{21}H_{23}N_3O_5SNa$ 452.12506, found 452.12362.

*Methyl (p-Tolyl 4-O-acetyl-2-azido-3-O-benzyl-2-O-deoxy-1-thio-β-D-glucopyranosyluronate) (**2**).* Azide glucuronate **42** (1.07 g, 2.50 mmol) was dissolved in pyridine (8.33 mL, 0.3 M). The reaction mixture was cooled to 0 °C, and acetic anhydride (1.0 mL, 10.58 mmol, 4.2 equiv) was added. After 15 min, TLC analysis (PE/EtOAc 1/1, v/v) showed total conversion of the starting material. The reaction mixture was quenched by subsequent addition of MeOH and H_2O, diluted with EtOAc, washed with 1 M HCl and $NaHCO_3$ (aq, satd), dried over $MgSO_4$, filtered, and concentrated yielding the target compound as a colorless oil in 82% (0.97 g, 2.1 mmol). $[\alpha]^{20}_D$: −10.7 (c = 1.5, DCM). IR (neat, cm^{-1}): 2108, 1746, 1356, 1277, 1233, 1213, 1186, 1163, 1126 1111, 1074, 1053, 1007, 986, 955, 903, 841, 812, 752, 698, 677, 650. ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 7.51 (d, 2H, J = 7.6 Hz, H_{arom}), 7.34−7.24 (m, 6H, H_{arom}), 7.19−7.15 (m, 2H, H_{arom}), 5.00 (t, 1H, J = 9.6 Hz, H-4), 4.80 (d, 1H, J = 11.2 Hz, C*H*HPh), 4.66 (d, 1H, J = 10.8 Hz, CH*H*Ph), 4.36 (d, 1H, J = 10.4 Hz, H-1), 3.87 (d, 1H, J = 10.0 Hz, H-5), 3.74 (s, 3H, OCH_3), 3.53 (t, 1H, J = 9.2 Hz, H-3), 3.45 (t, 1H, J = 9.6 Hz, H-2), 2.36 (s, 3H, CH_3 STol), 1.94 (s, 3H, CH_3 Ac). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 134.7 (CH_{arom}), 130.0 (CH_{arom}), 128.5 (CH_{arom}), 128.1 (CH_{arom}), 128.0 (CH_{arom}), 86.0 (C-1), 81.8 (C-3), 76.3 (C-5), 75.5 (CH_2 Bn), 70.8 (C-4), 63.9 (C-2), 52.8 (OCH_3), 21.2 (CH_3 STol), 20.6 (CH_3 Ac). [M + Na]$^+$ calcd for $C_{23}H_{25}N_3O_6SNa$: 494.13563, found 494.13521.

*Tolyl 4,6-O-Benzylidene-3-O-(naphthalen-2-ylmethyl)-1-thio-β-D-glucopyranoside (**44a**):.*[32] Compound **44a** was prepared as described for compound **44b**, starting with **43a** (5.0 g, 13.35 mmol) in 65% yield (4.47 g, 8.68 mmol) over two steps.

*Phenyl 4,6-O-Benzylidene-3-O-(naphthalen-2-ylmethyl)-1-thio-β-D-glucopyranoside (**44b**).* To a suspension of **43b** (7.2 g, 20.0 mmol) in toluene (70 mL, 0.3 M) was added dibutyltin oxide (5.0 g, 20.0 mmol, 1.0 equiv), and the mixture was heated to reflux for 3 h, during which the mixture became clear. The orange-brown solution was concentrated in vacuo. The crude tin ketal was dissolved in *N*,*N*-dimethylformamide (100 mL, 0.2 M), and 2-(bromomethyl)-naphthalene (5.3 g, 24.0 mmol, 1.2 equiv) and cesium fluoride (4.0 g, 26.0 mmol, 1.3 equiv) were added. After TLC analysis (toluene/EtOAc, 4:1 v/v) indicated completion of the reaction, the mixture was washed twice with water and once with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was crystallized from EtOAc/Et_2O to give the product as a white solid in 60% yield (6.0 g, 12.0 mmol). $[\alpha]_D$: −26.8 (c = 1, CH_2Cl_2). IR (neat): 3375, 3061, 3034, 2990, 2955, 2922, 2901, 2889, 2872, 2855, 1719, 1599, 1551, 1449, 1441, 1398, 1368, 1342, 1317, 1304, 1271, 1240, 1213, 1194, 1165, 1132, 1088, 1067, 1024, 1007, 991, 968, 934, 918, 889, 876, 853, 833, 812. ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ: 7.82−7.78 (m, 3H, CH arom), 7.74−7.72 (m, 1H, CH arom), 7.56−7.31 (m, 13H, CH arom), 5.58 (s, 1H, C*H* benzylidene), 5.10 (d, 1H, J_{gem} = 11.6 Hz, ArC*H*H NAP), 4.96 (d, 1H, J_{gem} = 12.0 Hz, ArCH*H* NAP), 4.62 (d, 1H, $J_{1,2}$ = 10.0 Hz, H-1), 4.39 (dd, 1H, $J_{6a,5}$ = 4.8 Hz, $J_{6a,6b}$ = 10.4 Hz, H-6a), 3.82 (t, 1H, $J_{6b,5}$ = $J_{6b,6a}$ = 10.0 Hz, H-6b), 3.77−3.66 (m, 2H, H-3, H-4), 3.58−3.47 (m, 2H, H-2, H-5), 2.57 (d, 1H, $J_{2\text{-}OH,2}$ = 2.0 Hz, 2-O*H*). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ: 137.3, 135.7 (C_q arom), 133.3 (CH arom), 131.4 (C_q arom), 128.5, 128.4, 128.1, 127.8, 127.1, 126.2, 126.1 (CH arom), 101.5 (CH benzylidene), 88.7 (C-1), 81.6, 81.2 (C-3, C-4), 75.0 ($ArCH_2$ NAP), 72.5 (C-2), 70.9 (C-5), 68.8 (C-6). HRMS: calcd for $[C_{30}H_{28}O_5S + NH_4]^+$ 518.19957, found 518.19942. Mp: 176 °C.

*Tolyl 2-O-Benzoyl-4,6-O-benzylidene-3-O-(naphthalen-2-ylmethyl)-1-thio-β-D-glucopyranoside (**45a**).* Compound **45a**[32] was prepared as described for compound **45b**, starting with **44a** (2.83 g, 5.49 mmol) in 80% yield (2.70 g, 4.37 mmol).

*Phenyl 2-O-Benzoyl-4,6-O-benzylidene-3-O-(naphthalen-2-ylmethyl)-1-thio-β-D-glucopyranoside (**45b**).* To a stirred solution of **44b** (5.1 g, 10.1 mmol) in pyridine/CH_2Cl_2 (1:1 v/v, 50 mL, 0.2 M) at 0 °C, was added benzoyl chloride (1.3 mL, 11.1 mmol, 1.1 equiv) and a catalytic amount of DMAP. The mixture was stirred at room temperature until TLC (toluene/EtOAc, 3:1, v/v) indicated complete consumption of the starting material. The reaction was quenched with MeOH, the mixture diluted with EtOAc. The organic phase was washed with aq 1 M HCl (2×), once with H_2O, and once with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Crystallization from MeOH gave the title compound as a white solid in 84% yield (8.5 mmol, 5.1 g). $[\alpha]_D$: +28.6 (c = 1, CH_2Cl_2). IR (neat): 3063, 2945, 2880, 1715, 1599, 1584, 1479, 1450, 1412, 1385, 1364, 1315, 1263, 1246, 1213, 1167, 1115, 1094, 1082, 1059, 1026, 991, 962, 935, 918, 905, 860, 835. ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ: 7.95 (d, 2H, J_{vic} = 7.2 Hz, CH arom), 7.67 (d, 1H, J_{vic} = 7.2 Hz, CH arom), 7.60−7.51 (m, 5H, CH arom), 7.46−7.35 (m, 10H, CH arom), 7.33−7.21 (m, 3H, CH arom), 7.19 (d, 1H, J_{vic} = 8.4 Hz, CH arom), 5.63 (s, 1H, C*H* benzylidene), 4.96 (d, 1H, J_{gem} = 12.0 Hz, ArC*H*H NAP), 4.83 (d, 1H, J_{gem} = 12.8 Hz, ArCH*H* NAP), 4.82 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1), 4.42 (dd, 1H, $J_{6a,5}$ = 4.8 Hz, $J_{6a,6b}$ = 10.6 Hz, H-6a), 3.93 (t, 1H, $J_{4,3}$ = $J_{4,5}$ = 9.2 Hz, H-4), 3.88−3.83 (m, 2H, H-3, H-6b), 3.57 (dt, 1H, $J_{5,4}$ = $J_{5,6b}$ = 9.6 Hz, $J_{5,6a}$ = 4.8 Hz, H-5). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ: 165.2 (C═O Bz), 137.3, 135.3, 133.3, 133.2 (C_q arom), 133.1, 133.0 (CH arom), 132.3 (C_q arom), 130.0 (CH arom), 129.9 (C_q arom), 129.3−125.9 (CH arom), 101.5 (CH benzylidene), 87.2 (C-1), 81.7 (C-4), 79.2 (C-3), 74.4 ($ArCH_2$ NAP), 72.1 (C-2), 70.7 (C-5), 68.8 (C-6). HRMS: calcd for $[C_{37}H_{32}O_6S + NH_4]^+$ 622.22578, found 622.22589. Mp: 179 °C.

*Phenyl 2-O-Benzoyl-4-O-benzyl-3-O-(naphthalen-2-ylmethyl)-1-thio-β-D-glucopyranoside (**46a**).* Glucoside **46a**[32] was prepared as described for glucoside **46b**, starting from **45a** (2.56 g 4.13 mmol), in 66% yield (1.64 g, 2.71 mmol).

*Phenyl 2-O-Benzoyl-4-O-benzyl-3-O-(naphthalen-2-ylmethyl)-1-thio-β-D-glucopyranoside (**46b**).* To a stirred solution of glycoside **45b** (3.0 g, 5 mmol) in dichloromethane (25 mL, 0.2 M) were added BH_3−THF (1 M in THF, 25 mmol, 5 equiv) and $Cu(OTf)_2$ (0.09 g, 0.25 mmol, 0.05 equiv) at 0 °C. After TLC analysis (toluene/EtOAc, 9:1 v/v) indicated complete conversion of the starting material, the mixture was quenched with NEt_3 (14 mL) and MeOH (20 mL). The mixture was filtered over a pad of Celite, concentrated, and coevaporated with methanol. Column chromatography (toluene/EtOAc, 49:1 → 19:1) gave the compound as a white solid in 66% yield (2.0 g, 3.3 mmol). $[\alpha]_D$: 56.2 (c = 1, CH_2Cl_2). IR (neat): 3516, 3059, 3026, 2947, 2916, 2862, 1717, 1684, 1601, 1584, 1479, 1452, 1439, 1404, 1360, 1325, 1288, 1261, 1209, 1180, 1153, 1113, 1101, 1086, 1069, 1030, 1018, 993, 966, 949, 930, 903, 889, 880, 858, 820. ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ: 7.95 (d, 2H, J_{vic} = 8.4 Hz, CH arom), 7.68−7.66 (m, 1H, CH arom), 7.61−7.58 (m, 1H, CH arom), 7.56−7.50 (m, 3H CH arom), 7.43−7.21 (m, 15H CH arom), 5.28 (dd, 1H, $J_{2,1}$ = 10.0 Hz, $J_{2,3}$ = 9.2 Hz, H-2), 4.93−4.87 (m, 2H, 2× ArC*H*H), 4.82 (d, 1H, $J_{1,2}$ = 10.0 Hz, H-1), 4.80 (d, 1H, J_{gem} = 11.2 Hz, ArC*H*H), 4.69 (d, 1H, J_{gem} = 11.2 Hz, ArCH*H*), 3.96−3.91 (m, 1H, H-6a), 3.91 (t, 1H, $J_{3,2}$ = $J_{3,4}$ = 9.2 Hz, H-3), 3.78−3.72 (m, 1H, H-6b), 3.73 (t, 1H, $J_{4,3}$ = $J_{4,5}$ = 9.4 Hz, H-4), 3.54−3.50 (m, 1H, H-5), 1.92 (t, 1H, $J_{6\text{-}OH,6}$ = 6.8 Hz, 6-O*H*). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ: 165.4 (C═O Bz), 137.9, 135.2 C_q arom), 133.4 (CH arom), 133.2, 133.0, 132.7 (C_q arom), 132.6, 129.9 (CH arom), 129.8 (C_q arom), 128.7, 128.5, 128.3, 128.2, 128.2, 128.0, 127.8, 127.0, 126.2, 126.1, 126.0 (CH arom), 86.3 (C-1), 84.0 (C-3), 79.7 (C-5), 77.8 (C-4), 75.5, 75.4 (2× $ArCH_2$), 75.5 (C-2), 62.2 (C-6). HRMS: calcd for $[C_{37}H_{34}O_6S + NH_4]^+$ 624.24144, found 624.24156.

*Benzyl (Tolyl 2-O-benzoyl-4-O-benzyl-3-O-naphthylmethyl-1-thio-β-D-glucopyranosyluronate) (**47a**).* Glucoside **46a** (1.47 g,

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2.37 mmol) was dissolved in DCM/H_2O (2/1, 11.8 mL, 0.2 M) and chilled to 0 °C. To this reaction mixture were added BAIB (1.91 g, 5.93 mmol, 2.5 equiv) and TEMPO (74 mg, 0.47 mmol, 0.2 equiv), and the reaction mixture was allowed to warm to rt. After 1 h, TLC analysis (PE/EtOAc 3/1 + 1% AcOH, v/v) showed total conversion into a lower running spot. The reaction mixture was quenched with $Na_2S_2O_3$ (aq, satd) and stirred for 30 min. Then, the reaction mixture was diluted with DCM, washed with brine, dried over $MgSO_4$, filtered, concentrated, and coevaporated with toluene. An orange oil was obtained, which was dissolved in DMF (11.84 mL, 0.2 M), followed by addition of BnBr (0.56 mL, 4.74 mmol, 2 equiv) and K_2CO_3 (0.66 g, 4.74 mmol, 2 equiv). TLC analysis showed total conversion into a higher running spot (PE/EtOAc 1/1, v/v, R_f 0.48). The reaction mixture was quenched with MeOH, diluted with DCM, washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated. A yellow solid was obtained, which was purified by column chromatography (PE/EtOAc 1/0 → 8/2) yielding the title compound as a white solid in 17% over two steps (0.31 g, 0.43 mmol). $[\alpha]^{20}_D$: +18.6 (c = 1, DCM). IR (neat, cm^{-1}): 1728, 1452, 1398, 1352, 1315, 1263, 1204, 1175, 1144, 1090, 1069, 1026, 972, 955, 812, 750, 710, 698. ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 7.94 (d, 2H, J = 7.6 Hz, H_{arom}), 7.66−7.49 (m, 16H, H_{arom}), 7.47−7.06 (m, 6H, H_{arom}), 7.10 (d, 2H, J = 8.0 Hz, H_{arom}), 5.24 (t, 1H, J = 9.6 Hz, H-2), 5.20 (m, 2H, CH_2 CO_2Bn), 4.88 (d, 1H, J = 10.8 Hz, C*H*HAr), 4.79−4.68 (m, 2H, CH_2Ar, H-1), 4.53 (d, 1H, J = 10.0 Hz, CH*H*Ar), 4.11 (d, 1H, J = 9.6 Hz, H-5), 3.97 (t, 1H, J = 9.6 Hz, H-4), 3.87 (t, 1H, J = 8.8 Hz, H-3), 2.30 (s, 3H, CH_3 STol). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 167.7 (C═O), 164.9 (C═O), 138.4 (C_q C_{arom}), 137.5 (C_q C_{arom}), 135.0−133.1 (CH_{arom}), 133.0 (C_q C_{arom}), 129.7−125.7 (CH_{arom}), 86.9 (C-1), 83.1 (C-3), 79.2 (C-4), 78.3 (C-5), 75.3 (CH_2Ar), 75.0 (CH_2Ar), 71.6 (C-2), 67.3 (CH_2 CO_2Bn), 21.1 (CH_3 STol). HRMS: $[M + Na]^+$ calcd for $C_{45}H_{40}O_7SNa$ 747.23870, found 747.23875.

*Phenyl 2-O-Benzoyl-4-O-benzyl-3-O-(naphthalen-2-methyl)-1-thio-β-D-glucopyranosiduronate (**47b**).* Glucuronic acid esters **47b** was prepared from **46b** (1.8 g, 3.0 mmol) as described for glucuronic acid ester **47a** in 56% yield (1.19 g, 1.68 mmol). $[\alpha]_D$: +30.6 (c = 1, CH_2Cl_2). IR (neat): 3059, 3026, 2967, 2955, 2907, 2862, 2853, 1742, 1713, 1601, 1584, 1495, 1476, 1454, 1389, 1391, 1360, 1327, 1315, 1285, 1260, 1211, 1194, 1169, 1157, 1113, 1070, 1020, 1003, 953, 924,899, 862, 849, 824, 804. ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ: 7.93 (d, 2H, J_{vic} = 7.2 Hz, CH arom), 7.65 (m, 1H, CH arom), 7.59−6.99 (m, 24H, CH arom), 5.28 (t, 1H, $J_{2,1}$ = $J_{2,3}$ = 9.4 Hz, H-2), 4.86 (d, 1H, J_{gem} = 11.2 Hz, ArC*H*H), 4.80−4.72 (m, 3H, H-1, 2× $ArCH_2$), 4.54 (d, 1H, J_{gem} = 10.8 Hz, ArCHH_2), 4.07 (d, 1H, $J_{5,4}$ = 9.6 Hz, H-5), 3.99 (t, 1H, $J_{4,3}$ = $J_{4,5}$ = 9.2 Hz, H-4), 3.88 (t, 1H, $J_{3,2}$ = $J_{3,4}$ = 8.8 Hz, H-3).^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ: 167.7 (C═O C-6), 165.0 (C═O Bz), 137.6, 135.1, 134.9 (C_q arom), 133.2, 133.1 (CH arom), 132.0 (C_q arom), 129.8, 129.8 (CH arom), 129.6 (C_q arom), 128.9, 128.9, 128.6, 128.6, 128.5, 128.5, 128.4, 128.4, 128.2, 128.2, 127.9, 127.9, 127.6, 126.9, 126.0, 125.9, 125.8 (CH arom), 86.9 (C-1), 83.1 (C-3), 79.3 (C-4), 78.4 (C-5), 75.4, 75.1 ($ArCH_2$), 71.7 (C-2), 67.5 ($PhCH_2$ Bn ester). HRMS: calcd for $[C_{44}H_{38}O_7S + Na]^+$ 733.22305, found 733.22300.

*Benzyl (Tolyl 2-O-benzoyl-4-O-benzyl-1-thio-β-D-glucopyranosyluronate) (**24a**).* Glucuronic acid ester **47a** (0.68 g, 0.94 mmol) was dissolved in a mixture of DCM/H_2O (4/1, 9.4 mL, 0.1 M), and the reaction mixture was cooled to 0 °C. DDQ (427 mg, 1.88 mmol, 2 equiv) was added, and the reaction mixture was allowed to warm to rt. After 3 h, TLC analysis (PE/EtOAc 12/8, v/v) showed total conversion into a lower running spot. The reaction mixture was diluted with DCM, washed with $Na_2S_2O_3$ (aq, satd), dried over $MgSO_4$, filtered, and concentrated. Column chromatography PE/EtOAc 1/0 → 7/3) gave the title compound a clear oil in 68% yield (438 mg, 0.64 mmol). $[\alpha]^{20}_D$: −21.0 (c = 1, DCM). IR (neat, cm^{-1}): 3466, 3065, 3032, 2953, 2920, 2872, 1728, 1601, 1493, 1452, 1398, 1356, 1315, 1263, 1198, 1175, 1092, 1070, 1026, 997, 908, 845, 808, 750, 710, 698, 636. ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 8.09 (d, 2H, J = 8.0 Hz, H_{arom}), 7.59−7.57 (t, 1H, J = 8.0 Hz, H_{arom}), 7.47−7.43 (m, 2H, H_{arom}), 7.37−7.18 (m, 12H, H_{arom}), 7.02 (d, 2H, J = 8.0 Hz, H_{arom}), 5.21 (s, 2H, CH_2 CO_2Bn), 4.98 (t, 1H, J = 9.6 Hz, H-2), 4.73 (d, 1H, J = 9.6 Hz, H-1), 4.69 (d, 1H, J = 11.2 Hz, C*H*HPh), 4.54 (d, 1H, J = 11.2 Hz, CH*H*Ph), 3.99 (d, 1H, J = 9.6 Hz, H-5), 3.90 (dt, 1H, J = 3.6 Hz, J = 8.8 Hz, H-3), 3.79 (t, 1H, J = 9.2 Hz, H-4), 2.79 (d, 1H, J = 3.6 Hz, OH), 2.30 (s, 3H, CH_3 STol). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 167.7, (C═O), 166.1 (C═O), 138.6 (C_q C_{arom}), 137.7 (C_q C_{arom}), 135.0 (C_q C_{arom}), 133.9 (CH_{arom}), 133.5 (CH_{arom}), 130.0 (CH_{arom}), 129.6 (CH_{arom}), 129.3 (C_q C_{arom}), 128.6−127.9 (CH_{arom}), 127.4 (C_q C_{arom}), 86.2 (C-1), 79.3 (C-4), 78.0 (C-5), 76.6 (C-3), 74.8 (CH_2 Bn ether), 72.6 (C-2), 67.3 (CH_2 CO_2Bn), 21.1 (CH_3 STol). HRMS: $[M + Na]^+$ calcd for $C_{34}H_{32}O_7SNa$ 607.17610, found 607.17534.

*Benzyl (Phenyl 2-O-benzoyl-4-O-benzyl-1-thio-β-D-glucopyranoside) uronate (**24b**).* Glucuronic acid esters **24b** was prepared from **47b** (1.0 g, 1.40 mmol) as described for glucuronic acid ester **24a** in 97% yield (0.78 g, 1.36 mmol). $[\alpha]_D$: −14.0 (c = 1, CH_2Cl_2). IR (neat): 3576, 3063, 3028, 2911, 1740, 1715, 1601, 1584, 1497, 1481, 1452, 1439, 1391, 1362, 1329, 1315, 1296, 1258, 1225, 1213, 1169, 1113, 1067, 1026, 999, 949, 926, 891, 847, 827, 804. ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ: 8.07 (d, 2H, J_{vic} = 7.2 Hz, CH arom), 7.59 (t, 1H, J_{vic} = 7.4 Hz, CH arom), 7.44−7.37 (m, 4H, CH arom), 7.36−7.33 (m, 5H, CH arom), 7.32−7.16 (m, 8H, CH arom), 5.22 (s, 2H,), 5.02 (t, 1H, $J_{2,1}$ = $J_{2,3}$ = 8.8 Hz, H-2), 4.81 (d, 1H, $J_{1,2}$ = 10.0 Hz, H-1), 4.69 (d, 1H, J_{gem} = 11.2 Hz, PhC*H*H Bn), 4.56 (d, 1H, J_{gem} = 11.2 Hz, PhCH*H* Bn), 4.02 (d, 1H, $J_{5,4}$ = 9.6 Hz, H-5), 3.93 (dt, 1H, $J_{3,2}$ = $J_{3,4}$ = 8.8 Hz, $J_{3,3\text{-}OH}$ = 2.0 Hz, H-3), 3.83 (t, 1H, $J_{4,3}$ = $J_{4,5}$ = 9.2 Hz, H-4), 2.72 (d, 1H, $J_{3\text{-}OH,3H}$ = 2.8 Hz, 3-O*H*). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC) δ: 167.9 (C═O C-6), 166.3 (C═O Bz), 137.9, 135.2 (C_q arom), 133.7, 133.4 (CH arom), 131.7 (C_q arom), 130.2 (CH arom), 129.5 (C_q arom), 129.1, 128.8, 128.7, 128.7, 128.6, 128.6, 128.5, 128.1 (CH arom), 86.3 (C-1), 79.5 (C-4), 78.2 (C-5), 76.8 (C-3), 75.1 (CH_2 Bn), 72.8 (C-2), 67.6 (CH_2 Bn ester). HRMS: calcd for $[C_{33}H_{30}O_7S + Na]^+$ 593.16045; found 593.16005.

*Benzyl (Tolyl 2-O-benzoyl-4-O-benzyl-3-levulinyl-1-thio-β-D-glucopyranosyluronate) (**3**).* Glucuronic acid ester **24a** (0.44 g, 0.75 mmol) was dissolved in DCM (7.5 mL, 0.1 M) followed by subsequent addition of LevOH (98 μL, 0.97 mmol, 1.3 equiv), DIC (114 μL, 0.97 mmol, 1.3 equiv), and DMAP (cat.). After 30 min, TLC analysis showed total conversion into a lower running spot (PE/EtOAc 12/8, v/v, R_f 0.48). The reaction mixture was filtered, diluted with EtOAc, washed with 1 M HCl, $NaHCO_3$ (aq, satd), dried over $MgSO_4$, filtered, and concentrated. Column chromatography (PE/EtOAc 1/0 → 7/3) gave the title compound as a white solid in 78% yield (398 mg, 0.58 mmol). $[\alpha]^{20}_D$: 1.56 (c = 5.6, DCM). IR (neat, cm^{-1}): 1742, 1719, 1452, 1402, 1360, 1315, 1263, 1206, 1177, 1155, 1090, 1069, 1026, 997, 970, 910, 847, 808, 750, 712, 698. ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 8.05 (d, 2H, J = 7.6 Hz, H_{arom}), 7.57 (t, 1H, J = 7.6 Hz, H_{arom}), 7.46−7.42 (m, 2H, H_{arom}), 7.36−7.21 (m, 10H, H_{arom}), 7.16−7.14 (m, 2H, H_{arom}), 7.02 (d, 2H, J = 8.0 Hz, H_{arom}), 5.43 (t, 1H, J = 9.2 Hz, H-3), 5.20 (s, 2H, CH_2 Bn ester), 5.14 (t, 1H, J = 9.6 Hz, H-2), 4.79 (d, 1H, J = 10.0 Hz, H-1), 4.54 (d, 1H, J = 11.2 Hz, C*H*HPh), 4.49 (d, 1H, J = 11.2 Hz, CH*H*Ph), 4.08 (d, 1H, J = 10.0 Hz, H-5), 3.98 (t, 1H, J = 9.6 Hz, H-3), 2.50−2.40 (m, 2H, CH_2 Lev), 2.39−2.25 (CH_2 Lev), 1.97 (s, 3H, CH_3 Lev). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 205.6 (C═O Lev ketone), 171.6 (C═O), 167.2 (C═O), 165.0 (C═O), 138.6 (C_q C_{arom}), 137.3 (C_q C_{arom}), 134.8 (C_q C_{arom}), 133.7 (CH_{arom}), 133.3 (CH_{arom}), 129.8 (CH_{arom}), 129.6 (CH_{arom}), 129.1 (C_q C_{arom}),128.5−127.7 (CH_{arom}), 127.4 (C_q C_{arom})„ 86.5 (C-1), 78.1 (C-5), 77.0 (C-4), 75.3 (C-3), 74.6 (CH_2 Bn ether), 70.2 (C-2), 67.4 (CH_2 Bn ester), 37.5 (CH_2 Lev), 29.4 (CH_3 Lev), 29.7 (CH_2 Lev), 21.1 (CH_3 STol). HRMS: $[M + K]^+$ calcd for $C_{39}H_{38}O_9SK$ 721.18681, found 721.18661.

*p-Tolyl 2-O-Benzoyl-3,6-di-O-benzyl-4-levulinyl-1-thio-β-D-glucopyranoside (**12**).* Glucoside **20a** (1.14 g, 1.99 mmol) was dissolved in DCM (10.0 mL, 0.2 M) followed by subsequent addition of LevOH (301 μL, 2.99 mmol, 1.5 equiv), DIC (319 μL, 2.99 mmol, 1.5 equiv), and a catalytic amount of DMAP. After 10 min, TLC analysis (PE/EtOAc 3/1, v/v) showed total conversion of the starting material into a lower running spot. The reaction mixture was filtered, diluted with EtOAc, washed with 1 M HCl, $NaHCO_3$ (aq, satd), dried over $MgSO_4$, filtered, and concentrated. Column chromatography (PE/EtOAc 1/0 → 7/3)

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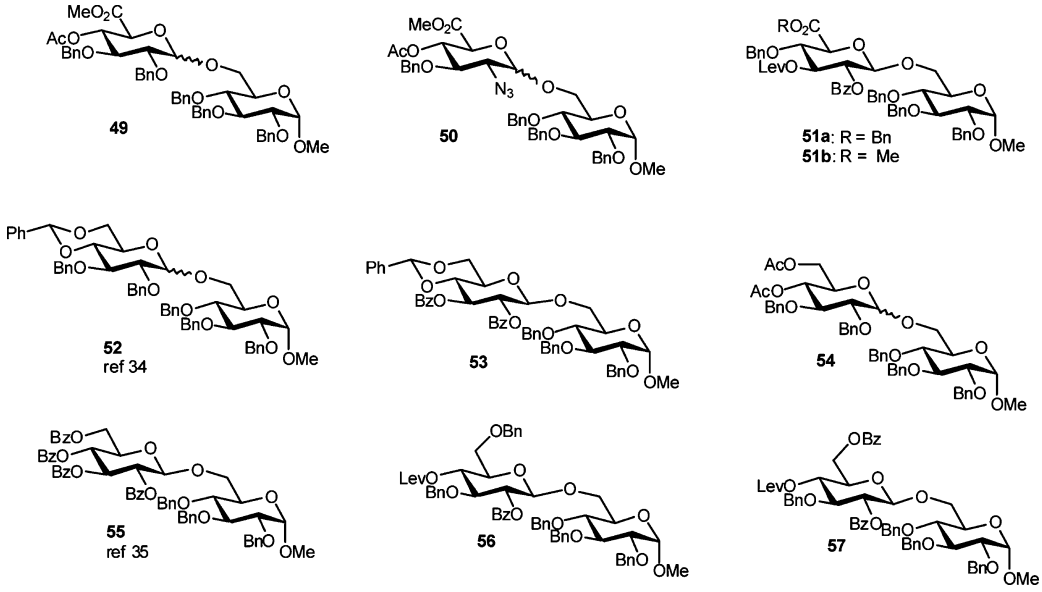
Chart 1. Overview of the Disaccharides



gave the title compound in 75% yield (1.0 g, 1.50 mmol). $[\alpha]_D$: + 23.1 (c = 0.3, DCM). IR (neat, cm^{-1}): 2864, 1740, 1717, 1495, 1452, 1418, 1400, 1362, 1317, 1287, 1260, 1213, 1179, 1153, 1112, 1090, 1063, 1040, 1028, 1007, 982, 964, 932, 908, 883, 843, 820, 804, 748,, 708, 694, 685, 619. ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 8.05 (d, 2H, J = 7.6 Hz, H_{arom}), 7.57−7.55 (m, 1H, H_{arom}), 7.46−7.42 (m, 2H, H_{arom}), 7.38−7.22 (m, 7H, H_{arom}), 7.19−7.11 (m, 5H, H_{arom}), 7.98 (d, 2H, J = 7.6 Hz, H_{arom}), 5.29 (t, 1H, J = 9.6 Hz, H-2), 5.11 (t, 1H, J = 9.6 Hz, H-4), 4.78 (d, 1H, J = 10.0 Hz, H-1), 4.57 (s, 2H, CH_2 Bn), 4.53 (s, 2H, CH_2 Bn), 3.89 (t, 1H, J = 9.2 Hz, H-3), 3.72−3.60 (m, 3H, H-5, H-6), 2.71−2.51 (m, 2H, CH_2 Lev), 2.47−2.31 (m, 2H, CH_2 Lev), 2.26 (s, 3H, CH_3 STol), 2.10 (s, 3H, CH_3 Lev). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 206.1 (C═O Lev ketone), 171.3 (C═O Lev), 164.8 (C═O Bz), 138.0 (C_q C_{arom}), 137.9 (C_q C_{arom}), 137.4 (C_q C_{arom}), 133.1 (CH_{arom}), 132.8 (CH_{arom}), 129.7 (CH_{arom}), 129.5 (CH_{arom}), 129.4 (C_q C_{arom}), 128.7 (C_q C_{arom}), 127.3−127.4 (CH_{arom}), 86.3 (C-1), 81.3 (C-3), 77.7 (C-5), 74.0 (CH_2 Bn), 73.3 (CH_2 Bn), 72.0 (C-2), 70.7 (C-4), 69.5 (C-6), 37.6 (CH_2 Lev), 29.5 (CH_3 Lev), 27.7 (CH_2 Lev), 20.9 (CH_3 STol). HRMS: $[M + Na]^+$ calcd for $C_{39}H_{40}O_8SNa$: 691.23361, found 691.23359.

*p-Tolyl 2,6-O-benzoyl-3-O-benzyl-1-thio-β-D-glucopyranoside (**27**).* Glucoside **48**[33] (2.40 g, 4.86 mmol) was suspended in toluene (16.2 mL, 0.3 M) followed by addition of Bu_2SnO (1.21 g, 4.86 mmol, 1 equiv). The reaction mixture was heated to reflux and stirred for 3 h. A clear reaction mixture was obtained, which was concentrated and coevaporated with toluene, yielding a transparent oil. The oil obtained was dissolved in toluene (16.2 mL, 0.3 M) followed by addition of BzCl (622 μL, 5.35 mmol, 1.1 equiv). After 3 h, TLC analysis (PE/EtOAc 1/1, v/v) showed total conversion into higher running spot. The reaction mixture was diluted with EtOAc, washed with H_2O, dried over $MgSO_4$, filtered, and concentrated. The white residue was dissolved in DCM (24.3 mL, 0.2 M) followed by addition of DIC (0.74 mL, 6.32 mmol, 1.3 equiv), LevOH (0.22 mL, 2.17 mmol, 1.3 equiv), and DMAP (cat.). After 1 h, TLC analysis showed total conversion into a lower running spot (PE/EtOAc 12/8, v/v, R_f 0.33). The reaction mixture was filtered, diluted with DCM, washed with 1 M HCl and $NaHCO_3$ (aq, satd), dried over $MgSO_4$, filtered, and concentrated. Column chromatography (PE/EtOAc 1/0 → 6/4) gave the title compound as a white solid in 75% yield (2.52 g, 3.65 mmol). $[\alpha]_D$: + 14.2 (c = 1, DCM). IR (neat, cm^{-1}): 1742, 1717, 1493, 1450, 1402, 1377, 1364, 1315, 1261, 1233, 1204, 1175, 1157, 1123, 1111, 1084, 1067, 1038, 1028, 976, 964, 914, 804, 750, 710, 700, 687. ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 8.08−8.04 (m, 4H, H_{arom}), 7.61−7.57 (m, 2H, H_{arom}), 7.61−7.57 (m, 2H, H_{arom}), 7.48−7.44 (m, 4H, H_{arom}), 7.43−7.31 (m, 2H, H_{arom}), 7.24−7.10 (m, 5H, H_{arom}), 6.83 (d, 2H, J = 8.0 Hz, H_{arom}), 5.28 (t, 1H, J = 9.2 Hz, H-2), 5.23 (t, 1H, J = 9.6 Hz, H-4), 4.77 (d, 1H, J = 10.0 Hz, H-1), 4.64 (dd, 1H, J = 2.4 Hz, J = 12.4 Hz, H-6), 4.61 (d, 1H, J = 10.8 Hz, C*H*HPh), 4.58 (d, 1H, J = 11.6 Hz, CH*H*Ph), 4.35 (dd, 1H, J = 6.0 Hz, J = 12.4 Hz, H-6), 3.93 (t, 1H, J = 9.2 Hz, H-3), 3.88−3.84 (m, 1H, H-5), 2.73−2.59 (m, 2H, CH_2 Lev), 2.57−2.51 (m, 1H, C*H*H Lev), 2.50−2.37 (m, 1H, CH*H* Lev), 2.20 (s, 3H, CH_3 STol), 2.10 (s, 3H, CH_3 Lev). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 206.0 (C═O Lev ketone), 171.3 (C═O Lev), 165.9 (C═O Bz), 164.8 (C═O Bz), 138.1 (C_q C_{arom}), 137.3 (C_q C_{arom}), 133.7−133.0 (CH_{arom}), 129.7 (CH_{arom}), 129.7 (CH_{arom}), 129.5 (C_q C_{arom}), 129.5 (CH_{arom}), 129.4 (CH_{arom}), 128.3 (CH_{arom}), 128.2 (CH_{arom}), 128.1 (C_q C_{arom}), 128.0 (CH_{arom}), 127.8 (CH_{arom}), 127.5 (CH_{arom}), 86.1 (C-1), 81.2 (C-3), 76.1 (C-5), 74.3 (CH_2 Bn), 71.9 (C-2), 70.1 (C-4), 62.8 (C-6), 37.6 (CH_2 Lev), 29.5 (CH_3 Lev), 27.7 (CH_2 Lev), 20.9 (CH_3 STol). HRMS: $[M + H]^+$ calcd for $C_{32}H_{31}O_9H$ calcd 560.20408, found 560.19972.

*Methyl 2,3,4-Tri-O-benzyl-6-O-(methyl 4-O-acetyl-2,3-di-O-benzyl-α/β-D-glucopyranosyluronate)-α-D-glucopyranoside (**49**).* The title compound was isolated as a white solid (Chart 1). IR (neat, cm^{-1}): 2920, 2909, 2872, 1748, 1454, 1362, 1292, 1265, 1231, 1156, 1138, 1090, 1047, 1028, 908, 733, 696. ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 7.90 (d, 2H, J = 7.2 Hz, H_{arom}), 7.43 (t, 1H, J = 7.2 Hz, H_{arom}), 7.35−7.22 (m, 23H, H_{arom}), 7.15−7.13 (m, 2H, H_{arom}), 7.03−7.01 (m, 2H, H_{arom}), 5.40 (dd, 1H, J = 3.6 Hz, J = 9.2 Hz, H-3′), 5.27 (t, 1H, J = 9.6 Hz, H-2′), 5.19 (s, 2H, CH_2 Bn ester), 4.88 (d, 1H, J = 12.4 Hz, C*H*HPh), 4.72 (d, 1H, J = 10.8 Hz, CH*H*Ph), 4.63 (d, 1H, J = 8.0 Hz, H-1′), 4.58 (d, 1H, J = 12.0 Hz, C*H*HPh), 4.55−4.47 (m, 2H, CH_2 Bn), 4.46 (d, 1H, J = 3.2 Hz, H-1), 4.25 (d, 1H, J = 11.2 Hz, CH*H*Ph), 4.08 (d, 1H, J = 9.2 Hz, H-6), 4.05−4.02 (m, 2H, H-4′, H-5′), 3.86 (t, 1H, J = 9.2 Hz, H-3), 3.69−3.63 (m, 2H, H-5, H-6), 3.40 (dd, 1H, J = 3.6 Hz, J = 9.6 Hz, H-2), 3.32 (t, 1H, J = 9.6 Hz, H-4), 3.17 (s, 3H, OCH_3), 2.52−2.41 (m, 2H, CH_2 Lev), 2.38−2.27 (m, 2H, CH_2 Lev), 1.98 (s, 3H, CH_3 Lev). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 205.7 (C═O Lev ketone), 171.8 (C═O), 167.5 (C═O), 165.0 (C═O), 138.7 (C_q C_{arom}), 138.1 (C_q C_{arom}), 138.0 (C_q C_{arom}), 137.4 (C_q C_{arom}), 134.9 (C_q C_{arom}), 133.2 (CH_{arom}), 129.8 (CH_{arom}), 129.2 (C_q C_{arom}), 128.6−127.5 (CH_{arom}), 101.3 (C-1′), 97.8 (C-1), 81.8 (C-3), 79.7 (C-2), 77.2 (C-4, C-4′, C-5′), 75.5 (CH_2 Bn), 74.7 (CH_2 Bn), 74.7 (CH_2 Bn), 74.1 (C-3′), 73.3 (CH_2 Bn), 71.7 (C-2′), 69.4 (C-5), 68.4 (C-6), 67.5 (CH_2 Bn ester), 54.9 (OCH_3), 37.7 (CH_2 Lev), 29.5 (CH_3 Lev), 27.9 (CH_2 Lev). HRMS: $[M + Na]^+$ calcd for $C_{44}H_{49}O_{12}Na$ 770.32968, found 770.33962.

*Methyl 2,3,4-Tri-O-benzyl-6-O-(methyl 3-O-acetyl-2-azido-2-deoxy-3-O-benzyl-α/β-D-glucopyranosyluronate)-α-D-glucopyranoside (**50**).* The title compound was isolated as a clear oil and as an

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anomeric mixture (α/β: 1/7.7). IR (neat, cm^{-1}): 2112, 1748, 1265, 1229, 1161, 1136, 1086, 1047, 1029, 908, 733, 696. ^1H NMR β anomer (400 MHz, $CDCl_3$, HH-COSY, HSQC): 7.37−7.26 (m, 20H, H_{arom}), 5.09 (t, 1H, J = 9.6 Hz, H-4′), 4.99 (d, 1H, J = 10.8 Hz, C*H*HPh), 4.93 (d, 1H, J = 11.2 Hz, CH*H*Ph), 4.85−4.77 (m, 3H, C*H*HPh, CH_2Ph), 4.69−4.61 (m, 3H, CH*H*Ph, CH_2Ph), 4.60 (d, 1H, J = 3.6 Hz, H-1), 4.18 (d, 1H, J = 8.0 Hz, H-1′), 4.10 (dd, 1H, J = 1.6 Hz, J = 10.8 Hz, H-6), 4.00 (t, 1H, J = 9.2 Hz, H-4), 3.82−3.80 (m, 1H, H-5), 4.76 (d, 1H, J = 10.0 Hz, H-5′), 3.67 (s, 3H, CO_2*Me*), 3.66−3.64 (m, 1H, H-6), 3.57−3.48 (m, 3H, H-2, H-2′, H-3), 3.43 (t, 1H, J = 9.6 Hz, H-3′, 3.37 (s, 3H, CH_3 Ac), 1.96 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 169.4 (C═O), 167.3 (C═O), 138.7−137.4 (C_q C_{arom}), 128.4−127.6 (CH_{arom}), 102.0 (C-1′), 98.1 (C-1), 82.0 (C-4), 79.8 (C-3′), 77.7 (C-2′, C-2, C-3), 75.7 (CH_2 Bn), 75.1 (CH_2 Bn), 74.8 (CH_2 Bn), 73.4 (CH_2 Bn), 72.8 (C-5), 70.9 (C-4′), 69.7 (C-5), 68.8 (C-6), 65.4 (C-2, C-2′, C-3), 55.2 (OCH_3), 52.7 (CO_2*Me*), 20.6 (CH_3 Ac). HRMS: $[M + Na]^+$ calcd for $C_{48}H_{51}O_{10}Na$ 810.33744, found 810.32286.

Methyl 2,3,4-Tri-O-benzyl-6-O-(benzyl 2-O-benzoyl-4-O-benzyl-3-O-levulinyl-β-D-glucopyranosyluronate)-α-D-glucopyranoside (***51a***). The title compound was isolated as a white solid. $[\alpha]_D$: + 0.8 (c = 0.8, DCM). IR (neat, cm^{-1}): 2918, 1744, 1454, 1360, 1265, 1213, 1177, 1155, 1092, 1070, 1028, 999, 735, 712, 698. ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 7.91−7.89 (m, 2H, H_{arom}), 7.43 (t, 1H, J = 7.2 Hz, H_{arom}), 7.35−7.22 (m, 23H, H_{arom}), 7.15−7.03 (m, 2H, H_{arom}), 7.02−7.01 (m, 2H, H_{arom}), 5.40 (t, 1H, J = 9.2 Hz, H-3′), 5.27 (t, 1H, J = 9.6 Hz, H-2′), 5.19 (s, 2H, CH_2 Bn ester), 4.88 (d, 1H, J = 10.8 Hz, C*H*HPh), 4.72 (d, 1H, J = 12.4 Hz, CH*H*Ph), 4.68 (d, 1H, J = 10.8 Hz, C*H*HPh), 4.63 (d, 1H, J = 8.0 Hz, H-1′), 4.58 (d, 1H, J = 12.0 Hz, CH*H*Ph), 4.55−4.47 (m, 3H, CH_2Ph, C*H*HPh), 4.46 (d, 1H, J = 3.2 Hz, H-1), 4.25 (d, 1H, J = 11.2 Hz, CH*H*Ph), 4.08 (d, 1H, J = 9.2 Hz, H-6′), 4.05−3.95 (m, 2H, H-4′, H-5′), 3.86 (t, 1H, J = 9.2 Hz, H-3), 3.69−3.63 (m, 2H, H-5, H-6), 3.40 (dd, 1H, J = 3.6 Hz, J = 9.6 Hz, H-2), 3.53 (t, 1H, J = 9.6 Hz, H-4), 3.17 (s, 3H, OCH_3), 2.51−2.41 (m, 2H, CH_2 Lev), 2.38−2.24 (m, 2H, CH_2 Lev), 1.98 (s, 3H, CH_3 Lev). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 205.7 (C═O Lev ketone), 171.8 (C═O), 167.5 (C═O), 165.0 (C═O), 138.7 (C_q C_{arom}), 138.1 (C_q C_{arom}), 138.0 (C_q C_{arom}), 137.4 (C_q C_{arom}), 134.9 (C_q C_{arom}), 133.2 (CH_{arom}), 129.8 (CH_{arom}), 129.2 (C_q C_{arom}), 128.6−127.5 (CH_{arom}), 101.3 (C-1′), 97.8 (C-1), 81.8 (C-3), 79.7 (C-2), 77.2 (C-4, C-4′, C-5′), 75.5 (CH_2 Bn), 74.7 (CH_2 Bn), 74.7 (CH_2 Bn), 74.1 (C-3′), 73.3 (CH_2 Bn), 71.7 (C-2′), 69.4 (C-5), 68.4 (C-6), 67.5 (CH_2 Bn ester), 54.9 (OCH_3), 37.7 (CH_2 Lev), 29.5 (CH_3 Lev), 27.9 (CH_2 Lev). HRMS: $[M + Na]^+$ calcd for $C_{55}H_{54}O_{13}Na$ 945.34566, found 945.34717.

Methyl 2,3,4-Tri-O-benzyl-6-O-(methyl 4-O-benzyl-2-O-benzoyl-3-O-levulinyl-β-D-glucopyranosyluronate)-α-D-glucopyranoside (***51b***). The title compound was isolated as a transparent oil. $[\alpha]_D$: +3.6 (c = 1.2, DCM). IR (neat, cm^{-1}): 2913, 1748, 1452, 1404, 1358, 1315, 1265, 1225, 1202, 1175, 1155, 1092, 1070, 1028, 1001, 910, 933, 912, 698. ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 7.90 (d, 2H, H_{arom}), 7.46 (t, 1H, J = 7.6 Hz, H_{arom}), 7.34−7.23 (m, 20H, H_{arom}), 7.05−7.02 (m, 2H, H_{arom}), 5.42 (t, 1H, J = 8.8 Hz, H-3′), 5.26 (t, 1H, J = 9.6 Hz, H-2′), 4.88 (d, 1H, J = 10.8 Hz, C*H*HPh), 4.72 (d, 1H, J = 12.0 Hz, CH*H*Ph), 4.68 (d, 1H, J = 11.2 Hz, C*H*HPh), 4.65−4.62 (m, 3H, CH*H*Ph, C*H*HPh, H-1′), 4.58 (d, 1H, J = 12.0 Hz, CH*H*Ph), 4.50 (d, 1H, J = 10.8 Hz, C*H*HPh), 4.59 (d, 1H, J = 3.6 Hz, H-1), 4.27 (d, 1H, J = 11.2 Hz, CH*H*Ph), 4.09−4.06 (m, 1H, H-6), 4.03−3.98 (m, 2H, H-4′, H-5′), 3.86 (t, 1H, J = 9.2 Hz, H-3), 3.73 (s, 3H, CO_2*Me*), 3.69−3.63 (m, 1H, H-6), 3.40 (dd, 1H, J = 3.2 Hz, J = 9.6 Hz, H-2), 3.32 (t, 1H, J = 9.6 Hz, H-4), 3.17 (s, 3H, OCH_3), 2.54−2.46 (m, 2H, CH_2 Lev), 2.44−2.38 (m, 2H, CH_2 Lev), 2.00 (s, 3H, CH_3 Lev). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 205.6 (C═O Lev ketone), 171.8 (C═O), 168.1 (C═O, 165.0 (C═O), 138.7 (C_q C_{arom}), 138.1 (C_q C_{arom}), 138.1 (C_q C_{arom}), 133.2 (CH_{arom}), 129.8 (CH_{arom}), 129.3 (C_q C_{arom}), 128.4−127.5 (CH_{arom}), 101.3 (C-1′), 97.8 (C-1), 81.8 (C-3), 79.7 (C-2′), 77.4 (C-4), 77.2 (C-5′), 75.5 (CH_2 Bn), 74.7 (CH_2 Bn), 74.7 (CH_2 Bn), 74.5 (C-4′), 74.2 (C-3′), 73.3 (CH_2 Bn0, 71.7 (C-2′), 69.5 (C-5′), 68.5 (C-6), 54.9 (OCH_3), 52.6 (CO_2*Me*), 37.7 (CH_2 Lev), 29.5 (CH_3 Lev), 27.9 (CH_2 Lev). HRMS: $[M + Na]^+$ calcd for $C_{54}H_{58}O_{15}Na$ 969.36679, found 969.36717.

Methyl 2,3,4-Tri-O-benzyl-6-O-(2,3-di-O-benzyl-4,6-O-benzylidene-β-D-glucopyranosyl)-α-D-glucopyranoside (***52***).[34] The title compound was isolated a white solid. IR (neat, cm^{-1}): 2924, 2914, 2868, 1454, 1364, 1314, 1265, 1209, 1157, 1134, 1086, 1070, 1049, 1028, 999, 912, 820, 733, 696, 678. ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): diagnostic peaks: 5.55 (s, 1H, C*H*Ph β), 5.53 (s, 1.51H, C*H*Ph α), 4.93 (d, 1.13H, J = 3.2 Hz, H-1′ $\beta\alpha$), 4.32 (dd, 1.14H, J = 5.2 Hz, J = 10.0 Hz, H-6′ β), 4.21 (dd, 1.61H, J = 5.2 Hz, J = 10.0 Hz, H-6′ α).

Methyl 2,3,4-Tri-O-benzyl-6-O-(4,6-O-benzylidene-2,3-di-O-benzoyl-β-D-glucopyranosyl)-α-D-glucopyranoside (***53***). The title compound was isolated as a white solid. $[\alpha]_D$: +12.0 (c = 1, DCM). IR (neat): 2930, 1728, 1452, 1362, 1315, 1265, 1209, 1179, 1159, 1090, 1069, 1053, 1026, 999, 914, 853, 733, 696. ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 7.93 (d, 2H, J = 6.8 Hz, H_{arom}), 7.90 (d, 2H, J = 7.2 Hz, H_{arom}), 7.46−7.37 (m, 5H, H_{arom}), 7.35−7.17 (m, 19H, H_{arom}), 7.01−6.99 (m, 2H, H_{arom}), 5.77 (t, 1H, J = 9.6 Hz, H-3′), 5.54 (t, 1H, J = 9.2 Hz, H-2′), 5.52 (s, 1H, C*H*Ph), 4.89 (d, 1H, J = 10.8 Hz, C*H*HPh0, 4.78 (d, 1H, J = 7.6 Hz, H-1′), 4.75 (d, 1H, J = 12.0 Hz, CH*H*Ph), 4.68 (d, 1H, J = 11.2 Hz, C*H*HPh), 4.65 (d, 1H, J = 9.6 Hz, CH*H*Ph), 4.50 (d, 1H, J = 3.2 Hz, H-1), 4.45 (d, 1H, J = 10.8 Jz. C*H*HPh), 4.41 (dd, 1H, J = 5.2 Hz, J = 10.4 Hz, H-6′), 4.23 (d, 1H, J = 11.2 Hz, CH*H*Ph), 4.12 (d, 1H, J = 9.6 Hz, H-6), 3.96−3.82 (m, 3H, H-6′, H-3, H-4′), 3.75−3.62 (m, 3H, H-6, H-4, H-5′), 3.44 (dd, 1H, J = 3.2 Hz, J = 9.6 Hz, H-2), 3.39−3.36 (m, 1H, H-5), 3.23 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 165.6 (C═O Bz), 165.0 (C═O Bz), 138.7 (C_q C_{arom}), 138.1 (C_q C_{arom}), 138.1 (C_q C_{arom}), 136.9 (C_q C_{arom}), 136.7 (C_q C_{arom}), 133.4−133.0 (CH_{arom}), 129.9−129.0 (CH_{arom}), 128.7 (C_q C_{arom}), 128.4 (C_q C_{arom}), 128.4 (C_q C_{arom}), 128.3−127.4 (CH_{arom}), 126.1−125.1 (CH_{arom}), 101.6 (C-1), 101.4 (CHPh), 98.0 (C-1′), 81.8 (C-3′ or C-4′), 79.4 (C-2), 78.6 (C-3′ or C-4′), 77.3 (C-5), 75.5 (CH_2 Bn), 74.7 (CH_2 Bn), 73.3 (CH_2 Bn), 72.3 (C-2′), 72.0 (C-3′), 69.4 (C-4), 68.5 (C-6′), 68.3 (C-6), 66.6 (C-5′), 55.0 (OCH_3). HRMS: $[M + Na]^+$ calcd for $C_{55}H_{54}O_{13}Na$ 945.34566, found 945.34537.

Methyl 2,3,4-Tri-O-benzyl-6-O-(4,6-di-O-acetyl-2,3-di-O-benzyl-α/β-D-glucopyranosyl)-α-D-glucopyranoside (***54***). The title compound was isolated as a clear oil and as an anomeric mixture (α/β: 1/1.2). IR (neat): 2930, 2907, 2872, 1744, 1497, 1454, 1362, 1329, 1265, 1237, 1194, 1157, 1136, 1090, 1044, 1028, 910, 845, 822, 733, 696, 635, 604. ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): Diagnostic peaks: 4.35 (d, 1H, J = 7.2 Hz, H-1β), 3.36 (2.68H OCH_3 α), 3.33 (3.07H OCH_3 β). HRMS: $[M + Na]^+$ calcd for $C_{52}H_{58}O_{13}Na$ 913.37696, found 913.37733.

Methyl 2,3,4-Tri-O-benzyl-6-O-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)-α-D-glucopyranoside (***55***):.[35] The title compound was isolated as a white solid. ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 7.99 (d, 2H, J = 7.2 Hz, H_{arom}), 7.89 (m, 4H, H_{arom}), 7.82 (d, 2H, H_{arom}), 7.53−7.46 (m, 2H, H_{arom}), 7.42−7.19 (m, 25H, H_{arom}), 7.05 (m, 2H, H_{arom}), 5.90 (t, 1H, J = 9.6 Hz, H-3′), 5.68 (t, 1H, J = 9.6 Hz, H-4′), 5.60 (t, 1H, J = 9.6 Hz, H-2′), 4.89 (d, 1H, J = 11.2 Hz, C*H*HPh), 4.82 (d, 1H, J = 7.6 Hz, H-1′), 4.73 (d, 1H, J = 12.4 Hz, CH*H*Ph), 4.68 (d, 1H, J = 10.8 Hz, C*H*HPh), 4.63−4.58 (m, 2H, CH*H*Ph, H-6), 4.54−4.48 (m, 3H, H-1, H-6, C*H*HPh), 4.28 (d, 1H, J = 11.2 Hz, CH*H*Ph), 4.16−4.09 (m, 2H, H-6′, H-5′), 3.88 (t, 1H, J = 9.2 Hz, H-3), 3.76−3.67 (m, 2H, H-5, H-6′), 3.44−3.35 (m, 2H, H-2, H-4), 3.21 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 166.1 (C═O Bz), 165.8 (C═O Bz), 165.1 (C═O Bz), 164.9 (C═O), 138.7 (C_q C_{arom}), 138.1 (C_q C_{arom}), 138.1 (C_q C_{arom}), 133.4 (CH_{arom}), 133.2 (CH_{arom}), 133.1 (CH_{arom}), 129.8 (CH_{arom}), 129.7 (CH_{arom}), 129.7 (C_q C_{arom}), 129.5 (C_q C_{arom}), 129.1 (C_q C_{arom}), 128.7−127.4 (CH_{arom}), 101.3 (C-1′), 97.9 (C-1), 81.8 (C-3), 79.7 (C-2), 77.3 (C-4), 75.5 (CH_2 Bn), 74.7 (CH_2 Bn), 73.3 (CH_2 Bn), 72.8 (C-3′), 72.1 (C-5′), 71.7 (C-2′), 69.7 (C-4′), 69.4 (C-5), 68.2 (C-6), 63.2 (C-6′), 55.0 (OCH_3).

Methyl 2,3,4-Tri-O-benzyl-6-O-(2-O-benzoyl-3,6-di-O-benzyl-4-levulinyl-β-D-glucopyranosyl)-β-D-glucopyranoside (***56***). The title compound was isolated as a transparent oil, which crystallized on standing. $[\alpha]_D$: + 23.6 (c = 0.9, DCM). IR (neat, cm^{-1}): 2874, 1721,

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1452, 1362, 1315, 1265, 1207, 1152, 1092, 1061, 1028, 912, 935, 696. ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 7.92 (d, 1H, J = 6.4 Hz, H_{arom}), 7.46−7.43 (m, 1H, H_{arom}), 7.32−7.21(m, 15H, H_{arom}), 7.14−7.13 (m, 5H, H_{arom}), 6.99−6.97 (m, 2H, H_{arom}), 5.39 (t, 1H, J = 9.6 Hz, H-2′), 5.12 (t, 1H, J = 9.2 Hz, H-4′), 4.87 (d, 1H, J = 11.2 Hz, CHHPh), 4.73 (d, 1H, J = 12.0 Hz, CHHPh), 4.65 (d, 1H, CHHPh), 4.60−4.53 (m, 6H, 2 × CH_2 Bn, CHHPh, H-1′), 4.49 (d, 1H, J = 3.6 Hz, H-1), 4.41 (d, 1H, J = 10.8 Hz, CHHPh), 4.23 (d, 1H, J = 11.2 Hz, CHHPh), 4.13 (d, 1H, J = 12.4 Hz, H-6), 3.91−3.84 (m, 2H, H-3, H-3′), 3.69−3.62 (m, 4H, H-6, H-5, H-6′, H-5′), 3.44 (dd, 1H, J = 3.6 Hz, J = 9.6 Hz, H-2), 3.38 (t, 1H, J = 9.2 Hz, H-4), 3.20 (s, 3H, OCH_3), 2.61−2.57 (m, 2H, CH_2 Lev), 2.41−2.36 (m, CH_2 Lev), 2.11 (s, 3H, CH_3 Lev). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 206.1 (C═O Lev ketone), 171.5 (C═O), 164.7 (C═O Bz), 138.8−137.6 (C_q C_{arom}), 133.0 (CH_{arom}), 129.7 (CH_{arom}), 129.5 (C_q C_{arom}), 128.4−127.3 (CH_{arom}), 101.0 (C-1′), 97.9 (C-1), 81.8 (C-3 or C-3′), 79.8 (C-3 or C-3′), 79.6 (C-2), 77.2 (C-4), 75.4 (CH_2 Bn), 74.5 (CH_2 Bn), 73.7 (C-5′), 73.6 (CH_2 Bn),73.5 (CH_2 Bn), 73.3 (CH_2 Bn), 72.2 (C-2′), 71.1 (C-4′), 69.7 (C-6′), 69.3 (C-5), 67.9 (C-6), 54.9 (OCH_3), 37.6 (CH_2 Lev), 29.7 (CH_3 Lev), 27.8 (CH_2 Lev). HRMS: $[M + Na]^+$ calcd for $C_{60}H_{64}O_{14}Na$ 1031.41883, found 1031.41796.

*Methyl 2,3,4-Tri-O-benzyl-6-O-(2,6-di-O-benzoyl-3-O-benzyl-4-levulinyl-β-D-glucopyranosyl)-β-D-glucopyranoside (**57**).* The title compound was isolated as an transparent oil, which crystallized on standing. $[\alpha]_D$: + 17.4 (c = 1, DCM). IR (neat, cm^{-1}): 3057, 2928, 1719, 1452, 1420, 1362, 1315, 1263, 120, 1177, 1152, 1092, 1069, 1026, 1013, 912, 897, 731, 698. ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): 8.05 (d, 2H, J = 8.4 Hz, H_{arom}), 7.93 (d, 2H, J = 8.4 Hz, H_{arom}), 7.54 (t, 1H, J = 7.6 Hz, H_{arom}), 7.46−7.40 (m, 3H, H_{arom}), 7.32−7.22 (m, 16H, H_{arom}), 7.21−7.14 (m, 4H, H_{arom}), 7.00−6.98 (m, 2H, H_{arom}), 5.42 (t, 1H, J = 9.6 Hz, H-2′), 5.28 (t, 1H, J = 9.6 Hz, H-4′), 4.86 (d, 1H, J = 11.2 Hz, CHHPh), 4.71 (d, 1H, J = 12.0 Hz, CHHPh), 4.65 (d, 1H, J = 11.2 Hz, CHHPh), 4.60−4.57 (m, 3H, H-1′, CH_2Ph), 4.56−4.53 (m, 2H, CHHPh, H-6′), 4.47 (d, 1H, J = 3.6 Hz, H-1), 4.41 (d, 1H, J = 11.2 Hz, H-6′), 4.36 (dd, 1H, J = 5.6 Hz, J = 11.2 Hz, H-6′), 4.22 (d, 1H, J = 11.2 Hz, CHHPh), 4.08 (d, 1H, J = 8.8 Hz, H-6), 3.90 (t, 1H, J = 9.6 Hz, H-3′), 3.84 (t, 1H, J = 9.6 Hz, H-3), 3.81−3.77 (m, 1H, H-5′), 3.68−3.63 (m, 2H, H-5, H-6), 3.41 (dd, 1H, J = 3.6 Hz, J = 9.6 Hz, H-2), 3.33 (t, 1H, J = 9.6 Hz, H-4), 3.18 (s, 3H, OCH_3), 2.67−2.59 (m, 2H, CH_2 Lev), 2.51−2.45 (m, 2H, CH_2 Lev), 2.11 (s, 3H, CH_3 Lev). ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): 206.2 (C═O Lev ketone), 171.5 (C═O Lev), 166.2 (C═O Bz), 164.8 (C═O Bz), 138.9 (C_q C_{arom}), 138.2 (C_q C_{arom}), 138.2 (C_q C_{arom}), 137.6 (C_q C_{arom}), 133.1 (CH_{arom}), 129.9 (CH_{arom}), 129.8 (C_q C_{arom}), 129.6 (C_q C_{arom}), 128.4−127.4 (CH_{arom}), 101.3 (C-1′), 97.9 (C-1), 81.9 (C-3), 79.8 (C-3′), 79.7 (C-2), 77.1 (C-4), 75.5 (CH_2 Bn), 74.6 (CH_2 Bn), 73.9 (CH_2 Bn), 73.4 (CH_2 Bn), 73.2 (C-2′), 72.3 (C-5′), 70.5 (C-4′), 69.3 (C-5), 68.1 (C-6), 63.1 (C-6′), 55.0 (OCH_3), 37.8 (CH_2 Lev), 29.7 (CH_3 Lev), 27.9 (CH_2 Lev). HRMS: $[M + Na]^+$ calcd for $C_{60}H_{62}O_{15}Na$ 1045.39809, found 1045.39751.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR, H−H COSY NMR, HSQC NMR, and ^{13}C APT NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) (a) Shipkova, M.; Wieland, E. *Clin. Chim. Acta* **2005**, *358*, 2−23. (b) Shipkova, M.; Armstrong, V. W.; Oellerich, M.; Wieland, E. *Ther. Drug. Monit.* **2003**, *25*, 1−16. (c) Stachulski, A. V.; Harding, J. R.; Lindon, J. C.; Maggs, J. L.; Park, B. K.; Wilson, I. D. *J. Med. Chem.* **2006**, *49*, 6931−6945. (d) Stachulski, A. V.; Jenkins, G. N. *Nat. Prod. Rep.* **1998**, *15*, 173−186. (e) Kaspersen, F. M.; Van Boeckel, C. A. A. *Xenobiotica* **1987**, *17*, 1451−1471.

(2) (a) Vincken, J.-P.; Heng, L.; Groot, A. D.; Gruppen, H. *Phytochemistry* **2007**, *68*, 275−297. (b) Hostettmann, K.; Marston, A. *Saponins*; Cambridge University Press: Cambridge, 1995. (c) Yu, B.; Sun, J. S. *Chem. Asian J.* **2009**, *4*, 642−654. (d) Yu, B.; Zhang, Y. C.; Tang, P. P. *Eur. J. Org. Chem.* **2007**, 5145−5161.

(3) (a) Spillmann, D.; Lindahl, U. *Curr. Opin. Struct. Biol.* **1994**, *4*, 677−682. (b) Capila, I.; Linhardt, R. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 391−412.

(4) (a) Griffiths, A. J.; Davies, D. B. *Carbohydr. Pol.* **1991**, *14*, 241−279. (b) Griffiths, A. J.; Davies, D. B. *Carbohydr. Pol.* **1991**, *14*, 339−365.

(5) (a) van den Bos, L. J.; Codée, J. D. C.; Litjens, R. E. J. N.; Dinkelaar, J.; Overkleeft, H. S.; van der Marel, G. A. *Eur. J. Org. Chem.* **2007**, 3963−3976. (b) Codée, J. D. C.; Christina, A. E.; Walvoort, M. T. C.; Overkleeft, H. S.; van der Marel, G. A. *Top. Curr. Chem.* **2011**, *301*, 253−289. (c) Wadouachi, A.; Kovensky, J. *Molecules* **2011**, *16*, 3933−3968.

(6) For some recent examples, see: (a) Wang, Z.; Xy, Y.; Yang, B.; Tiruchinapally, G.; Sun, B.; Liu, R.; Dulaney, S.; Liu, J.; Huang, X. *Chem.—Eur. J.* **2010**, *16*, 8365−8375. (b) Zeng, Y.; Wang, Z.; Whitfield, D.; Huang, X. *J. Org. Chem.* **2008**, *73*, 7952−7962. (c) Wu, X. Y.; Cui, L. N.; Lipinski, T.; Bundle, D. R. *Chem.—Eur. J.* **2010**, *16*, 3476−3488. (d) Polat, T.; Wong, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 12795−12800.

(7) (a) Codée, J. D. C.; Litjens, R. E. J. N.; van den Bos, L. J.; Overkleeft, H. S.; van der Marel, G. A. *Chem. Soc. Rev.* **2005**, *34*, 769−782. (b) Wang, Y.; Ye, X.-S.; Zhang, L.-H. *Org. Biomol. Chem.* **2007**, *5*, 2189−2200.

(8) Douglas, N. L.; Ley, S. V.; Lücking, U.; Warriner, S. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 51−65.

(9) (a) Zhang, Z. Y.; Ollmann, I. R.; Ye, X. S.; Wischna, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734−753. (b) Koeller, K. M.; Wong, C.-H. *Chem. Rev.* **2000**, *100*, 4465−4493. (c) Ritter, T. K.; Mong, K. K. T.; Liu, H. T.; Nakatani, T.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4657−4660. (d) Lee, J.-C.; Greenberg, W. A.; Wong, C.-H. *Nat. Prot.* **2006**, *1*, 3143−3152. (e) Wu, C.-Y.; Wong, C.-H. *Top. Curr. Chem.* **2011**, *301*, 223−252.

(10) Pedersen, C. M.; Marinescu, L. G.; Bols, M. *Chem. Commun.* **2008**, 2465−2467.

(11) For the establishment of relative reactivities of mannuronic acids, see: Walvoort, M. T. C.; de Witte, W.; van Dijk, J.; Dinkelaar, J.; Lodder, G.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *Org. Lett.* **2011**, *13* (16), 4360−4363.

(12) (a) Mootoo, D. R.; Konradson, P.; Ududong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583−5584. (b) Fraser-Reid, B.; Wu, Z.; Ududong, U.; Ottoson, H. *J. Org. Chem.* **1990**, *55*, 6068−6070. (c) Fraser-Reid, B.; Cristóbal-López, J. *Top. Curr. Chem.* **2011**, *301*, 1−30.

(13) (a) Fraser-Reid, B.; Wu, Z.; Webster Andrews, C.; Skowronski, E. *J. Am. Chem. Soc.* **1991**, *113*, 1434−1435. (b) Jensen, H. H.; Nordstrøm, M.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126*, 9205−9213.

(14) (a) Schmidt, R. R.; Grundler, G. *Synthesis* **1981**, 885−887. (b) Schmidt, R. R.; Stumpp, M.; Michel, J. *Tetrahedron Lett.* **1982**, *23*, 405−408. (c) Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331−1334.

(15) The effect of the nature of the ester (methyl versus benzyl) on the reactivity of the glucuronyl donor was found to be very small: the methyl ester was 1.3 times more reactive than the benzyl ester (1.3:1, 94% yield).

(16) Nair, H.; Nokes, D. J.; Gessner, B. D.; Dherani, M.; Madhi, S. A.; Singleton, R. J.; O'Brien, K. L.; Roca, A.; Wright, P. F.; Bruce, N.;

Chandran, A.; Theodoratou, E.; Sutanto, A.; Sedyaningsih, E. R.; Ngama, M.; Munywoki, P. K.; Kartasasmita, C.; Simões, E. A.; Rudan, I.; Weber, M. W.; Campbell, H. *Lancet* **2009**, *12* (374), 893−902.
(17) (a) Rennels, M. B.; Edwards, K. M.; Keyserling, H. L.; Reisinger, K. S.; Hogerman, D. A.; Madore, D. V.; Chang, I.; Paradiso, P. R.; Malinoski, F. J.; Kimura, A. *Pediatrics* **1998**, *101*, 604−611. (b) Duggan, S. T. *Drugs* **2010**, *70*, 1973−1986.
(18) (a) Riedmann, E. M. *Human Vaccines* **2011**, *7* (7), 716−716. (b) Yeh, S. H.; Gurtman, A.; Hurley, D. C.; Block, S. L.; Schwartz, R. H.; Patterson, S.; Jansen, K. U.; Love, J.; Gruber, W. C.; Emini, E. A.; Scott, D. A. *Pediatrics* **2010**, *126* (3), E493−e505.
(19) (a) Hotchkiss, R. D.; Goebel, W. F. *J. Biol. Chem.* **1937**, *121*, 195−203. (b) Reeves, R. E.; Goebel, W. F. *J. Biol. Chem.* **1941**, *139*, 511−519.
(20) (a) Lefeber, D. J.; Kamerling, J. P.; Vliegenthart, J. F. G. *Chem.—Eur. J.* **2001**, *7* (20), 441−4421. (b) Lefeber, D. J.; Arévalo, E. A.; Kamerling, J. P.; Vliegenthart, J. F. G. *Can. J. Chem.* **2002**, *80*, 76−81.
(21) (a) Yu, B.; Tao, H. *Tetrahedron Lett.* **2001**, *42*, 2405−2407. (b) Yu, B.; Sun, J. *Chem. Commun.* **2010**, *46*, 4668−4679.
(22) A chemoselective glycosylation with donor **12** and acceptor **24a** proved to be unproductive due to formation of anhydroglucoside **26b**.
(23) Dinkelaar, J.; Witte, M. D.; van den Bos, L. J.; Overkleeft, H. S.; van der Marel, G. A. *Carbohydr. Res.* **2006**, *341*, 1723−1729.
(24) Ensley, H. E.; Yu, H. *Tetrahedron Lett.* **2003**, *44*, 9363−9366.
(25) See, for example: (a) Codée, J. D. C.; Stubba, B.; Schiattarella, M.; Overkleeft, H. S.; van Boeckel, C. A. A.; van Boom, J. H.; van der Marel, G. A. *J. Am. Chem. Soc.* **2005**, *127*, 3767−3773. (b) Geurtsen, R.; Boons, G. J. *Tetrahedron Lett.* **2002**, *43*, 9429−9431. (c) Li, Z.; Gildersleeve, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 11612−11619, and references cited therein.
(26) Malysheva, N. N.; Torgov, V. I.; Klimov, E. M.; Kochetkov, N. K. *Russ. Chem. Bull.* **1974**, *23*, 2075−2077.
(27) (a) Lahmann, M.; Oscarson, S. *Can. J. Chem.* **2002**, *80*, 889−903. (b) Shiao, T. C.; Roy, R. *Top. Curr. Chem.* **2011**, *301*, 69−108.
(28) The reactivity difference between the C-6-*O*-benzyl donor **12** and C-6-*O*-benzoyl glucoside **27** was established in two competition reactions in which both donors competed with donor **4** as described above. Donor **12** turned out to be 19 times more reactive than donor **4**, where donor **27** was 3-fold less reactive than this thioglycoside.
(29) The anomerization of thio-glycosides in the presence of Lewis acids has been reported before. See, for example: (a) Connolly, D. T.; Roseman, S.; Lee, Y. C. *Carb. Res.* **1980**, *87*, 227−239. (b) Satoh, H.; Manabe, S.; Ito, Y.; Lüthi, H. P.; Laino, T.; Hutter, J. *J. Am. Chem. Soc.* **2011**, *133*, 5610−5619.
(30) Lu, L.-D.; Schie, C.-R.; Kulkarni, S. S.; Pan, G.-R.; Lu, X.-A.; Hung, S.-C. *Org. Lett.* **2006**, *8*, 5995−5998.
(31) Mong, T.K.-K.; Huang, Y.; Wong, C.-H. *J. Org. Chem.* **2003**, *68*, 2135−2142.
(32) Wang, C.-C.; Kulkarni, S. S.; Lee, J.-C.; Luo, S.-Y.; Hung, S.-C. *Nat. Prot.* **2008**, *3*, 97−113.
(33) Tüley, P.; Wong, C.-H. *J. Am. Chem. Soc.* **2007**, *129* (42), 12795−12800.
(34) Tanaka, H.; Sakamoto, H.; Sano, A.; Nakamura, S.; Nakajima, M.; Hashimoto, S *Chem. Commun.* **1999**, *13*, 1259−1260.
(35) Kamat, M. N.; Meo, C. D.; Demchenko, A. V. *J. Org. Chem.* **2007**, *72*, 6947−6955.