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Synthesis and Scalable Conversion of L-Iduronamides to Heparin-Related Di- and Tetrasaccharides

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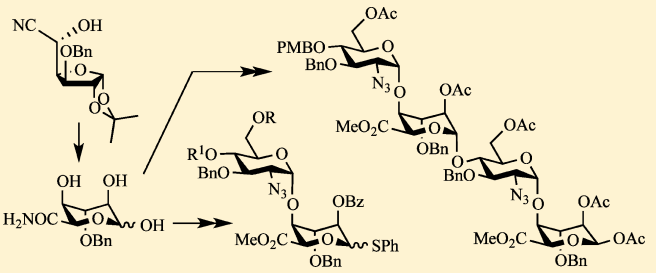
Supporting Information

ABSTRACT: A diastereomerically pure cyanohydrin, preparable on kilogram scale, is efficiently converted in one step into a novel L-iduronamide. A new regioselective acylation of this iduronamide and a new mild amide hydrolysis method mediated by amyl nitrite enables short, scalable syntheses of an L-iduronate diacetate C-4 acceptor, and also L-iduronate C-4 acceptor thioglycosides. Efficient conversions of these to a range of heparin-related gluco-ido disaccharide building blocks (various C-4 protection options) including efficient multigram access to key heparin-building block ido-thioglycoside donors are described. A 1-OAc disaccharide is converted into a heparin-related tetrasaccharide, via divergence to both acceptor and donor disaccharides. X-ray and NMR data of the 1,2-diacetyl iduronate methyl ester and the analogous iduronamide show that while both adopt $^{1}C_{4}$ conformations in solution, the iduronate ester adopts the $^{4}C_{1}$ conformation in solid state. An X-ray structure is also reported for the novel, $^{4}C_{1}$-conformationally locked bicyclic 1,6-anhydro iduronate lactone along with an X-ray structures of a novel distorted $^{4}C_{1}$ iduronate 4,6-lactone. Deuterium labeling also provides mechanistic insight into the formation of lactone products during the novel amyl nitrite-mediated hydrolysis of iduronamide into the parent iduronic acid functionality.



INTRODUCTION

Heparin/heparan sulfate (H/HS) are linear highly sulfated glycosaminoglycan (GAG) 1,4-linked polysaccharides consisting of repeating disaccharide units of D-glucosamine and either L-iduronic acid or D-glucuronic acid. They play critical roles through binding to a wide range of proteins,[1] offering considerable potential for development of therapeutic agents.[2,3] The complex heterogeneity of natural HS oligosaccharides means that defining the roles of specific HS sequences is best addressed through the synthesis of structurally defined oligosaccharide sequences, also underpinning provision of designed sequences for potential therapeutic applications. Biological evidence implicates L-iduronic containing domains and the number/location of sulfates as key to effects on a number of fibroblast growth factors (FGFs).[4] Synthesis of heparin-related oligosaccharides requires access to component L-ido-monosaccharides with suitable C-4 and C-1 functionalization to enable introduction of the necessary α1,4-glycosidic linkages. L-Iduronic acid is a rare sugar and not readily available in commercial quantities, so there have been considerable efforts directed at syntheses delivering suitably functionalized iduronic acid derivatives.[5] As L-iduronic acid is the C-5 epimer of D-glucuronic acid, a majority of stereoselective routes have involved inversion of the C-5 stereochemistry of D-sugar precursors, in some cases with subsequent oxidation of intermediate L-idose derivatives.[5d−j] Low temperature addition of tris-(phenylthio)methyllithium (a carboxylate surrogate)[6] to a C-5 aldehyde has also provided stereoselective introduction of the L-stereochemistry.[7] Oxidation of L-iditose components in oligosaccharides has also been employed.[8]

We previously reported a large scale (kg)[9] stereoselective route to cyanohydrin **1**, introducing the key C-5 stereocenter relevant to L-iduronic acid via a highly diastereoselective cyanohydrin reaction.[10] We reported the conversion of **1** into 1,2-*O*-isopropylidine iduronate acceptors and demonstrated synthesis of various heparin-related (GlcN-Ido) disaccharides with this 1,2-*O*-protection in place. Such a strategy has been employed in several heparan sulfate-related saccharide syntheses.

RESULTS AND DISCUSSION

Our interests have been in developing new routes to iduronate building blocks that are short but also viable for economic, larger scale synthesis, as there remains a need for scalable routes to diverse iduronates.

We now report alternative elaborations of cyanohydrin **1** in 3−5 steps to provide new routes to several other key iduronate building blocks bearing free C-4 hydroxyl acceptor functionalities. These routes provide significantly improved access to

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these valuable building blocks, underpinned by important new methods for the regioselective acylation of novel iduronamide intermediates and for carboxamide to ester conversion.

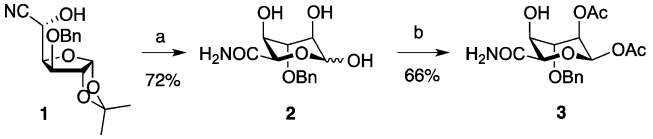
The use of a variety of alternate strategies to obtain important L-ido acceptors, including thioglycosides, via this new approach is reported. These scalable entries to such L-iduronic glycosyl donors were required for scaled syntheses of HS-related disaccharide building blocks, specifically to access larger, structurally defined HS mimetics on sufficient scales for in vivo evaluations.

Thus, with cyanohydrin **1** available on very large scale, we evaluated a range of methods for direct elaboration of **1** into idopyranosides. Three key methodology developments underpinned this new approach.

A number of methods are available for conversion of nitriles to carboxylic derivatives, including strong base or acid-catalyzed hydrolysis, basic peroxide catalysis, enzymatic hydrolysis, Pt-catalyzed hydration and acid catalyzed alcoholysis.[11] As the cyanohydrin **1** epimerises under mildy basic conditions and scalability was a key issue, none of the above approaches were feasible. In the case of acid-catalyzed methanolysis (Pinner reaction), a mixture of methyl furanosides and pyranosides were anticipated that would limit further elaboration into suitably protected donors at the reducing end.

Hydrolysis using strongly acidic conditions was initially discarded as incompatible with saccharides. However, it was found that acid-catalyzed reaction of **1** using 30% aq HCl did, in this case, effect nitrile hydration (no hydrolysis to the acid was observed) and concurrent acetal hydrolysis leading directly to isolation of the amide pyranoside **2** in 72% yield (Scheme 1).

Scheme 1. Nitrile Hydration and Regioselective Acylation[a]



[a]Reagents: (a) HCl, 30% aq; (b) Ac_2O, DMAP, CH_2Cl_2.

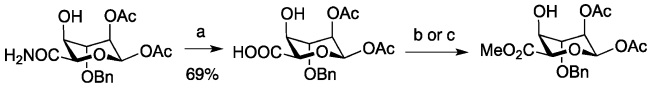
It was unexpected that **2** would be stable under such concentrated acidic conditions; however, it was observed that extending the reaction time or heating did drastically reduce the yield of the reaction. This necessitated the development of an endothermic workup using saturated bicarbonate solution to quench the acid. The polar product **2** could be extracted with THF from the resulting brine solution, thus avoiding evaporation of large volumes of aqueous brine. It was also found that the product **2** could be purified by precipitation making the reaction feasible on larger scale.

Peracylation of L-iduronic acid derivatives is known to be less selective than observed with D-sugars, with respect to the isolated pyranoside:furanoside ratio, unless low temperature and extended reaction times are used.[7b,12] So it was a key discovery that iduronamide **2** underwent regioselective 1,2-di-*O*-acetylation (or 1,2-di-*O*-benzoylation) by employing acylation conditions using only 1−2 mol % of DMAP and no other base. Thus, the 6-carboxyamide L-iduronic system **2** could be converted into diacetate **3** in 66% yield. Critically the product could be isolated by crystallization in a yield of 43%, making the reaction viable on large scale. The remaining mixture containing triacetylated pyranose and furanose products could be recycled by acid-catalyzed deprotection to give **2**.[13] As far as we are aware 1,2-di-*O*-regioselective acetylation has not previously been observed in such pyranose systems.

This thus provides an efficient and scalable two step route from cyanohydrin **1** to novel carboxamido iduronic analogue **3**, suitably functionalized as a potential acceptor for glycosylation itself but, critically, as a suitable precursor to iduronate esters as key reagents toward HS-related oligosaccharide synthesis.

The next challenge was thus converting the primary amide functionality of **3** into the ester functionality of iduronate targets for oligosaccharide syntheses. There are a wide range of synthetic tools available to interchange between different carboxylic acid derivatives. Indirect transformation via the carboxylic acid, using classical acid or base catalysis, is complicated by the lability of the acetate groups under both acidic and basic conditions. The direct transformation of primary amides to esters has been described using the dimethyl acetal of DMF,[14] Meerwein's reagent[15] or acid-catalyzed alcoholysis[16] or by two step procedures involving conversion of amide NH_2 to pyrrole or di-Boc leaving groups followed by base-catalyzed hydrolysis/alcoholysis,[17] but again these reaction conditions were not compatible with the protecting groups in our case. Nitrosyl type reagents, such as NOCl, $NOBF_4$, N_2O_4, N_2O_5 and BuONO (combined with HCl gas) have been used.[18] Indeed dinitrogen tetroxide is reported to convert a primary amide to the carboxylic acid on an acetylated D-glucuronic derivative.[19] However, the highly toxic and corrosive nature of gaseous N_2O_4 made us dismiss the use of this reagent as unsuitable to deploy on large scale. Investigating nontoxic, readily available alternative reagents with similar properties, we explored the use of isopentyl nitrite (amyl nitrite). Satisfyingly, this less reactive nitrite did convert amide **3** to the acid **4** in 69% yield, when heated to 80−100 °C in neat acetic acid (Scheme 2). This third key development is, as far as we know, a new milder method for the selective conversion of a primary amide to a carboxylic acid.

Scheme 2. Isopentyl Nitrite Catalyzed Hydrolysis of Primary Amides and Esterification[a]



[a]Reagents: (a) Isopentyl nitrite, AcOH; (b) MeI, $KHCO_3$, DMF, 60% (2 steps from **3**); (c) DMF·DMA, DCM, 84%.

Elaboration to the iduronate ester **5** was effected through subsequent methylation using either the dimethyl acetal of DMF or a preferred alkylation with methyl iodide[20] (Scheme 2). The acid **4** was not crystalline, so to avoid column chromatography purification on scale, the crude product could be directly converted into **5** using a small excess of the alkylating agent. To quench traces of the highly toxic methyl iodide an excess of potassium acetate was added. The ester **5** could be purified by crystallization making the overall process from cyanohydrin **1** to 1,2-di-*O*-acetyl iduronate **5** truly scalable, avoiding all chromatograhy.

This provides a new methodology for the conversion of amides to esters, efficiently illustrated by this synthesis of iduronate acceptor **5** (previously reported as a mixture of anomers[21]) in 60% yield over 2 steps. This mild amide-to-ester chemistry offers considerable synthetic value underpinning the

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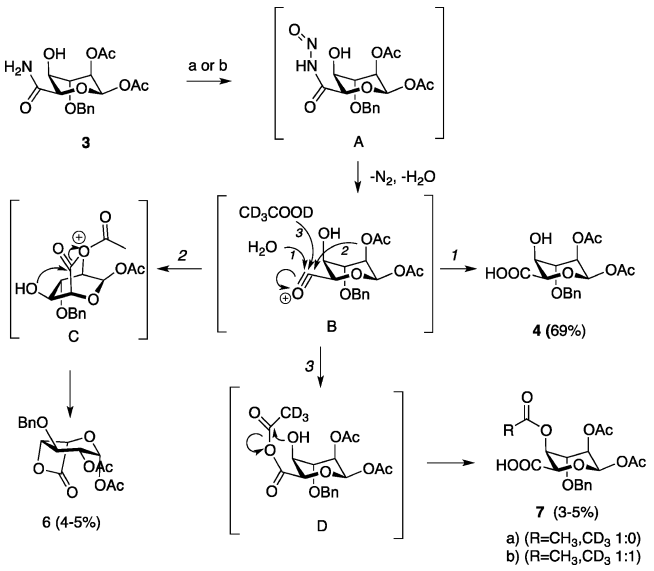
viable exploitation of iduronamide intermediate **2** for the synthesis of a number of iduronic acid derivatives on scale.

Interestingly, while the hydrolysis of **3** with isopentyl nitrite gave a good yield of the acid **4** (69%), two side-products, lactone **6** and triacetate acid **7** (Scheme 3), were reproducibly

Scheme 3. Mechanism of Isopentyl Nitrite-Promoted Amide Hydrolysis[a]



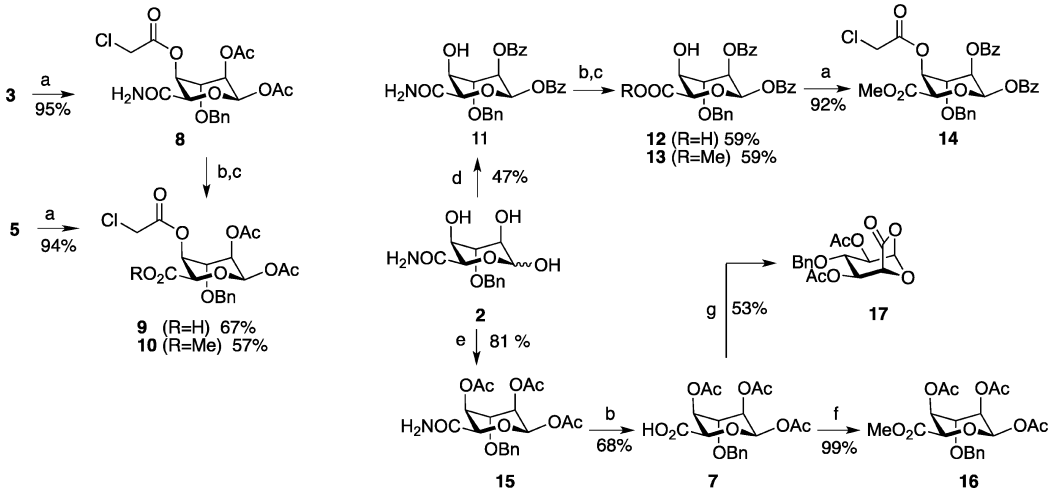
[a]Reagents: (a) Isopentylnitrite, CH_3COOH; (b) isopentylnitrite, CD_3COOD.

obtained, each in ca. 3−5% yield. The mechanism of this hydrolysis is anticipated to proceed via the nitroso intermediate **A**, which loses water and N_2 to give the highly reactive acylium intermediate **B**. If water then acts as the external nucleophile, the predominant product carboxylic acid **4** will be formed (path 1). However, this reactive onium ion could be intercepted by a competing internal or alternative external nucleophile. While such reaction using C-4 is clasically disfavored (4-*exo*-dig), the C-2 acetate oxygen could act as an internal nucleophile leading to intermediate C (related analogues of which we have prepared independently), with a subsequent 4-*exo*-trig process leading to the isolated 4,6-lactone **6**. Steric considerations are central to the viability of this proposed pathway, and a ring flip from the favored (deduced from NMR data) $^1C_4$ chair form to the $^0S_2$ skew boat form brings the C-2 acetate close enough in space to the depicted acylium intermediate, enabling pathway 2 to proceed via intermediate **C**. An alternative reaction pathway to deliver the second observed byproduct **7** is external nucleophilic attack from the acetic acid solvent on the acylium ion **B** giving anhydride intermediate **D** (path 3). This is then set up for intramolecular acyl transfer via a 6-membered ring to furnish **7**.

To provide some further insight into these proposed mechanisms, distinguishing between the intramolecular pathway 2 and the intermolecular pathways, experiments were performed using deuterated acetic acid-d_4 as the solvent under the same reaction conditions. Indeed, we observed the same lactone **6** was formed, supporting the intramolecular acyl transfer mechanism, giving rise to this novel lactone. However, a mixture of deuterated and nondeuterated product **7** was observed.[22] If the reaction proceeded via pathway 3 only, we were expecting to see fully deuterated acyl incorporation at C-4. This outcome is consistent with some reaction via pathway 3, but the observation of mixed label incorporation suggests alternative pathway(s), which acylate **4** with unlabeled acetate. This must derive from the starting material acetyl groups (in the reaction with only acetic acid-d_4 solvent) and could arise from direct acylation from an intermeidate acylium (akin to path 3), or other processes leading to acetic acid-d_4 forming a mixed anhydride from acetate byproduct. Noting that total material recovery of **4**, **6** and **7** is around 80%, there is mass balance to account for this via other pathways, but without isolation of further byproduct the exact source for this unlabeled acylation pathway is not conclusive.

With this new, scalable access to differentiated iduronates **3** and **5**, suitable as *acceptors* for glycosylations, our attention turned to their elaboration into suitable monosaccharide *donors*. Thioglycosides are well established as effective glycosyl donors and have advantages in relation to compability with most

Scheme 4. Elaboration of Iduronamide and Iduronates[a]



[a]Reagents: (a) $ClCH_2COCl$, pyridine; (b) isopentyl nitrite, AcOH; (c) DMF·DMA, CH_2Cl_2; (d) Bz_2O, DMAP, THF; (e) Ac_2O, DMAP, pyridine, CH_2Cl_2; (f) MeI, $KHCO_3$, DMF; (g) TMSOTf, DCM.

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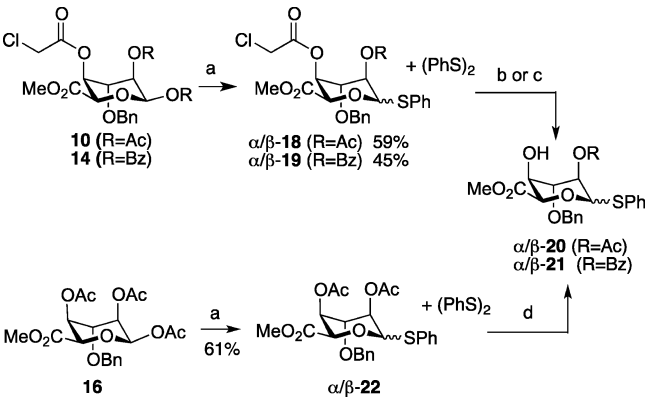
protecting group manipulations and stability, compared with many other glycosyl donors. There are several reported syntheses of L-iduronate thioglycosides. Thioglycoside **20** (see Scheme 5) or its *t*-butyl ester analogue have been previously prepared from an iditol thioglycoside precursor via a late-stage oxidation of C-6.[23−25] These approaches employ C-5 inversion through the C-5, C-6 epoxide derived from a 1,2-isopropylidine glucofuranoside. A different strategy for iduronate thioglycosides routes through a D-xlyose-derived dithioacetal, affording a iduronate thioethyl glycoside with a free C-4 hydroxyl in 14 steps overall from D-xylose.[26]

Consequently, elaboration of the novel iduronamide **3** into iduronate thioglycosides was a key aim. To approach this from intermediate **3**, which has the differentation of the C-4 hydroxyl embedded within it, protection of C-4 with chloroacetate was employed to provide **8** (Scheme 4). In this case, esterolysis was completed using DMF·DMA to yield ester **10** via the carboxylate **9**. While this reagent was able to effect the necessary conversion, yields were less reliable than the use of methyl iodide (for carboxylate methylation), but the reagent was preferred in this case as we observed that using methyl iodide alkylation on chloroacetate modified derivatives such as **9** efficiently produced iodoacetate products.[27]

Amidotriol **2** also underwent regiocontrolled 1,2-di-*O*-benzoylation using the same conditions effective for diacylation, affording 1,2-di-*O*-benzoate **11** (Scheme 4). This approach also illustrates an alternative sequence of amide to ester conversion, followed by C-4 hydroxyl protection, affording **14** (with the parallel chemistry converting diacetate **5** into the C-4-chloroacetate **10**). Additionally, amido triol **2** was peracylated by standard conditions using pyridine as base, yielding the triacetyl iduronamide **15** in good yield (81%). This then provided a further substrate to illustrate application of the isopentyl nitrite-based amide hydrolysis, in this case with methyl iodide methylation yielding the known triacetyl iduronate[17] via the acid **7**. This provides a scalable alternative method to provide **16**, a valuable iduronate intermediate that has been used as a key starting point for several syntheses of HS oligosaccharides. When the acid **7** was subjected to standard conditions for forming thioglycosides, none of the expected product was observed. Instead an intramolecular reaction of the carboxylate formed the 1,6-lactone **17**, isolated in a reasonable yield of 53% using TMSOTf catalysis.

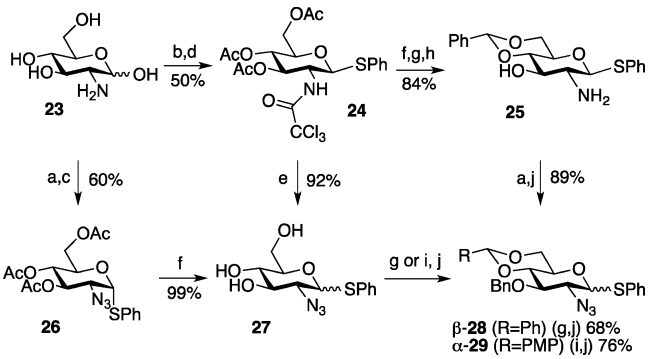
With fully protected L-iduronate derivatives **10**, **14** and **16** available on large scale, our attention turned to the aforementioned thioglycoside donors. The C-4-chloroacetyl protected iduronates **10** and **14** were converted into thiophenyl glycoside donors **18** and **19**, respectively, under standard conditions using borontrifluoride etherate and thiophenol (Scheme 5). One of the main drawbacks of thioglycoside synthesis, which has prevented its use on large scale, is the toxicity and obnoxious odors encountered when handling thiol reagents. This inspired us to another key development in making such thioiduronate donors accessible on larger scale. We observed a valuable modification for the workup of this reaction, whereby the initial inclusion of I_2 (oxidizing any remaining thiophenol to its disulfide) in the aqueous $NaHCO_3$ workup solution, followed by addition of $Na_2S_2O_3$ to remove any remaining I_2, provided a reliable method for removing the excess malodorous thiophenol. The iodine can be directly added to the extraction during workup, as its consumption can be visually monitored within seconds of shaking the extraction funnel. This provides a simple method for the efficient and practially facile removal of all traces of thiols during the workup, without affecting the thioglycoside. This is a valuable practical discovery, and the methodology has been utilized successfully for other similar processes within our laboratory, for example, in the large scale synthesis of glucoazide thioglycoside **24** (Scheme 6).

Scheme 5. Synthesis of Iduronate Thioglycosides[a]



[a]Reagents: (a) (1) PhSH, $BF_3.OEt_2$, DCM, (2) I_2, $NaHCO_3$; (b) $BnNH_2$, Et_2O (69% for **20**, 68% for **21**); (c) thiourea, ethanol (80% for **20**); (d) (1) NaOMe, MeOH, (2) Bu_2SnO, MeOH, (3) BzCl, 1,4-dioxane (55%, 3 steps).

Scheme 6. Synthesis of 4,6-*O*-Benzylidine Thioglucosides[a]



[a]Reagents: (a) (1) K_2CO_3, MeOH, imidazole-1-sulfonyl azide, $Cu^{II}SO_4$, (2) Ac_2O, pyridine; (b) (1) CCl_3COCl, NEt_3, MeOH, (2) Ac_2O, pyridine; (c) PhSH, $BF_3{\cdot}Et_2O$, DCM; (d) PhSH, TMSOTf, DCM; (e) K_2CO_3, MeOH, then imidazole-1-sulfonyl azide, $Cu^{II}SO_4$, MeOH; (f) NaOMe, MeOH; (g) $PhCH(OMe)_2$, TsOH, MeCN; (h) KOH, THF/MeOH/H_2O; (i) $PMB(OMe)_2$, CSA, THF; (j) BnBr, NaH, DMF.

The C-4-chloroacetate protecting group could be selectively removed with either benzylamine or thiourea, providing C-4 acceptor thioglycosides **20** and **21**, in good yields. Alternatively, **21** was also accessed by conversion of triacetate **16** into thioglycoside **22** followed by deacetylation, and finally regioselective C-2-benzoylation using dibutyltin oxide and benzoyl chloride as described previously.[28] This provides two routes for the conversion of novel iduronamide **2** into the known thioglycoside **20**, in 6 steps via C-4-chloroacetate protection or in 5 steps via the iduronamide triacetate **15** (in this case using tin acetal chemistry, which is less suited for large scale).

To summarize the overall approach, novel L-iduronamide **2** can, efficiently and on large scale, be converted into

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Table 1. NMR Data for Ring Protons in Diacetylated L-Iduronic Acid Derivatives (^{1}H, 400 MHz, $CDCl_3$)

cpd	H_1	$J_{1,2}$	H_2	$J_{2,3}$	H_3	$J_{3,4}$	H_4	$J_{4,5}$	H_5
17	5.90	2.1	5.02	8.2	3.95	8.2	5.05	4.6	4.59
6	6.27	2.6	5.14	10.0	4.30	2.2	4.84	6.7	5.33
3	6.07	1.6	5.12	3.2	3.89	3.2	4.18	1.6	4.57
5	6.07	1.6	5.15	3.2,[a] 1.2	3.85	3.2	3.99	2.0	4.71

[a] $J_{2,4}$ W-coupling observed. Proton shifts in ppm; coupling constants in Hz.

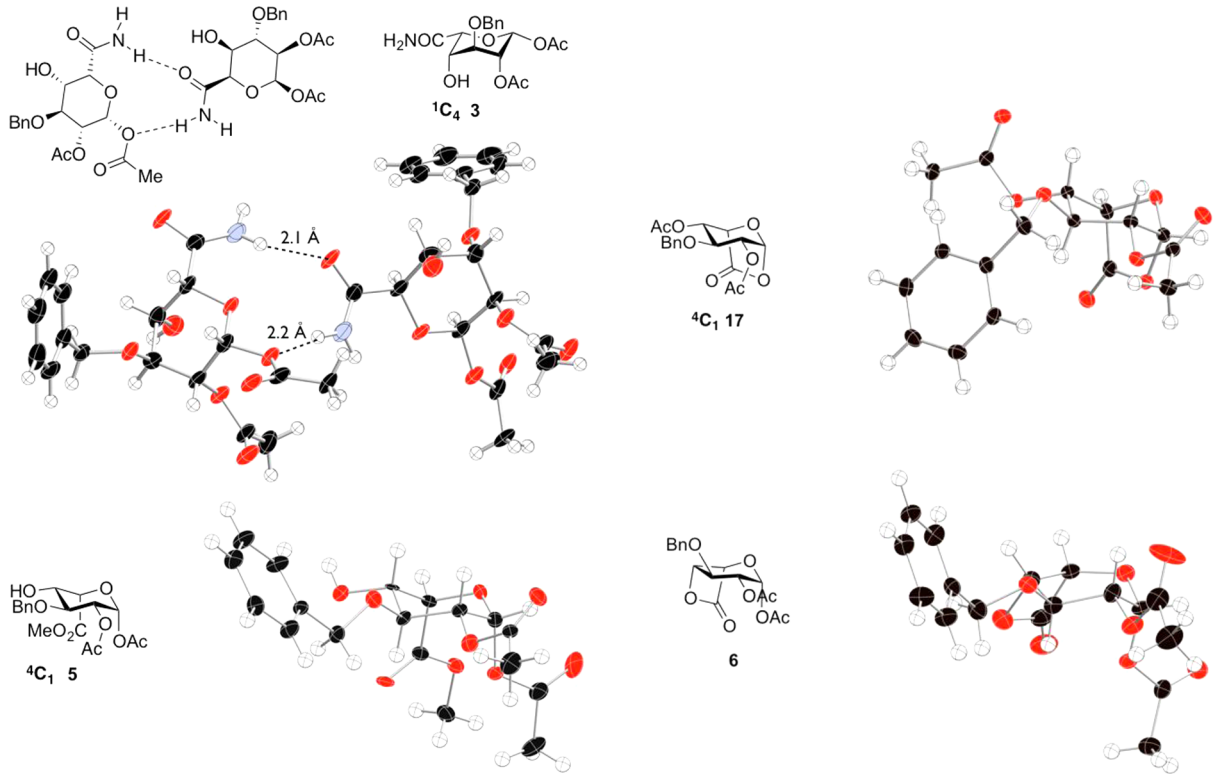

Figure 1. X-ray structures of iduronate **5**, iduronamide **3**, and lactones **17** and **6**.[33]

thioglycoside iduronates of type **18** in 6 steps from cyanohydrin **1** (15% overall yield) and 10 steps (12% overall yield) from commercial diacetone-D-glucose. This compares with alternative syntheses to compounds of type **18** in 14 steps from commerial D-xylose (routing via an alternative cyanohydrin intermediate)[26] or in 9 steps starting from diacetone-D-glucose (via a late stage oxidation of C-6).[25]

L-Iduronic acid is a pyranose sugar that, in contrast to most other pyranoses, in solution is in equilibrium between the main conformations $^1C_4$, $^2S_0$ and $^4C_1$. This conformational flexibility is believed significant in the context of the binding of heparinoid oligosaccharides to proteins, although there is evidence of a relatively small overall impact on oligosaccharide shape.[29] The energy barrier between the different conformations is low and dependent on subtle variations in substitution patterns in the monosaccharide,[30] while the conformational array of oligosaccharides is likely perturbed by the other components of the oligosaccharide, including other sulfation sites.[31] Locked derivatives of L-iduronic acid have been used for studying different conformations and, in certain cases, shown to enhance binding to proteins.[32] The versatility of outcomes from the different inter/intramolecular reactions (Scheme 3) led to an intriguing conformational diversity across the monocyclic iduronate and iduronamide and the bicyclic lactones **6** and **17**. We thus pursued a more detailed study of the conformations of the novel diacetate derivatives **3** and **5** and locked lactones **6** and **17** in both solid phase (X-ray) and solution phase (NMR).

NMR data for the ring protons of the diacetates **3** and **5** and lactones **6** and **17** (Table 1) show that the diacetates **3** and **5** have small and similar J values <4 Hz, which corresponds to a $^1C_4$ conformational preference, with ring protons in equatorial positions (except H-5). Additionally, a rare $J_{2,4}$ W-coupling of 1.2 Hz was seen for **5**, which would only be observed in the $^1C_4$ conformation. For lactone **17** the $J_{2,3}$ and $J_{3,4}$ values of 8.2 Hz were in good agreement with the locked $^4C_1$ conformation, as H-2, H-3 and H-4 would be expected to have an axial orientation. The $J_{3,4}$ value of 2.2 Hz for **6** and the relatively large $J_{2,3}$ value of 10.0 Hz are closely consistent with predicted values for the 4,6-lactone structure **6**.

To compare the solution structures, particularly of the monocyclic conformationally flexible iduronic derivatives, with those in the solid state and to confirm the structure of **6**, we obtained single crystal X-ray structures of diacetates **3** and **5** and lactones **6** and **17** (Figure 1).

Interestingly, we found that while amide **3** adopted the expected $^1C_4$ conformation, as observed in solution, ester **5** in the solid state assumed a $^4C_1$ conformation. For amide **3** the crystal packing showed evident hydrogen bonding involving unsymmetrical dimers with one amide as an H-bond acceptor and donor, interacting with the C-2 acyl (sp^3) oxygen and

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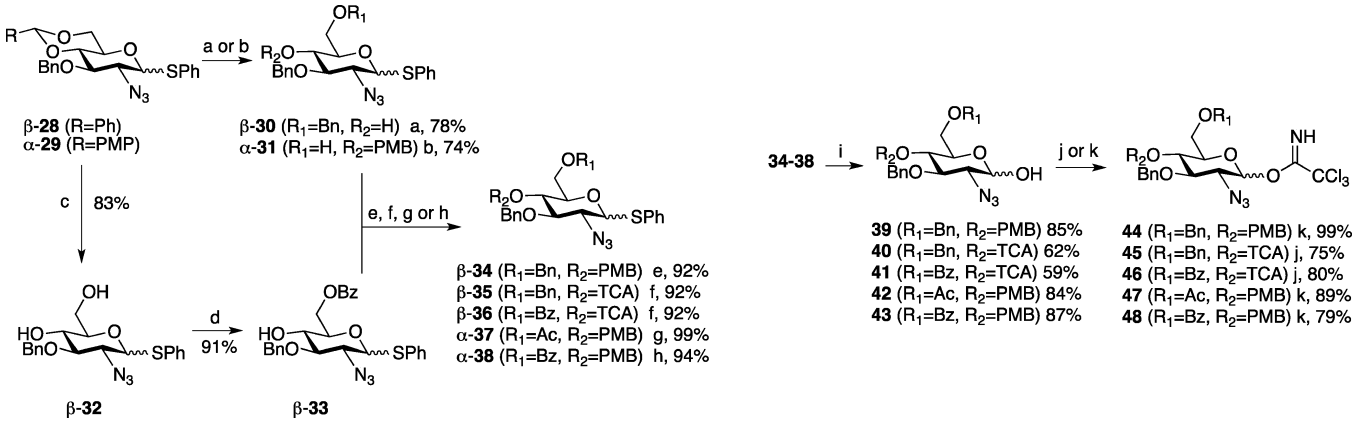
Scheme 7. Synthesis of C-6, C-4-Differentiated Thioglycoside and Trichloroacetimidate Glucoazides[a]



[a]Reagents: (a) Et_3SiH, $BF_3{\cdot}Et_2O$, DCM; (b) Bu_2BOTf, $BH_3{\cdot}THF$; (c) 60% aq AcOH; (d) BzCl, Et_3N, DCM; (e) NaH, PMBCl, THF; (f) Cl_3CCOCl, Et_3N, DCM; (g) Ac_2O, pyridine, DMAP, DCM; (h) BzCl, pyridine, DMAP, DCM; (i) NBS, Me_2CO; (j) Cl_3CCN, NaH, DCM; (k) Cl_3CCN, DBU, DCM.

amide NH of the other iduronate unit. These dimers pack as a C_2-symmetric pair in the unit cell (see the Supporting Information). This could account for the difference in solid state structures found between **3** and **5** and may have relevance to the role of solvation and H-bonding in effecting conformational changes in L-iduronic acid derivatives. The conformationally locked lactone **17** adopted a $^4C_1$ conformation in the solid state, validating the solution state data. Additionally, the X-ray structure of **6** confimed the identity of an interesting 4,6-bridged lactone species, in which C3−C4−C5 are essentially coplanar, and provides a new example of conformational constraint within the iduronate family.[34]

With scalable access to the acetate and thioglycoside iduronates **5**, **20** and **21**, and the novel iduronamide **3** established, demonstrating their utility in the synthesis of HS related disaccharide building blocks was investigated.

Concomitant with this we also required a scalable synthesis of the appropriate 2-azido glucoside donors, specifically with variable C-6 hydroxyl protection, to provide a diversity of disaccharide variants for oligosaccharide syntheses. To deliver this we evaluated an alternative to the traditional triflic azide method for conversion of 2-amino glucosides into 2-azido derivatives,[35] in large part due to scalability issues. We thus explored the use of the diazo-transfer reagent imidazole-1-sulfonyl azide, which had been shown to covert glucosamine to its 2-azido derivative.[36] The major improvement developed here involved a one pot *O*-/*N*-acyl deprotection and diazo transfer and additionally the demonstration of three alternative entry points for installing the crucial azido moiety at C-2 during the synthesis of glucosamines **26** and **28** (Scheme 6). First, a synthesis of 3,4,6-tetraacetyl-2-trichloroacetate thioglycoside **24**[37] was carried out in good yield (Scheme 6), importantly affording the desired material as a single *β*-anomeric product, thus avoiding any chromatographic isomer separation issues. This large scale synthesis (>140 g of **24** was prepared in a single batch) was also assisted by application of the iodine workup described above for the iduronate thioglycoside syntheses (**18** and **19**).

To access the required 2-azido thioglycoside **27**,[38] thioglycoside **24** was treated with K_2CO_3 in MeOH at 60 °C followed by addition of imidazole-1-sulfonyl azide and $Cu^{II}SO_4$ at room temperature to furnish **27** in excellent yield (92%) in one step. This reaction could be performed on scale (100 g) and needed no further purification after workup (following removal of the imidazole byproduct with an acidic aqueous wash). This offers a significant practical improvement for synthesis of this commonly employed valuable intermediate precursor to 2-aminoglucoside containing targets. Intermediate **27** was then elaborated into benzylidine derivative **28**.[39]

Alternatively, azido transfer could be deferred by converting **24** into known 2-amino derivative **25**[40] using standard deacylation conditions, followed by benzylidene formation and base-catalyzed hydrolysis of the trichloroacetamide moiety (100 g). Aminoglucoside **25** was thus amenable to the above-mentioned azido transfer chemistry, followed by benzylation to afford an alternative entry to benzylidine **28**.

Additionally, 4-*O*-*p*-methoxybenzylidine (PMB) donor **29** was obtained through a route involving introduction of the azide at C-2 as the first step (completing three different points for utilizing this diazo transfer step), a reaction that also proved efficiently scalable (Scheme 6). Thus, direct azidation of glucosamine **23** was effected using imidazole-1-sulfonyl azide, followed by acylation giving **26**[41] in 94% yield over two steps.[36] Further elaborations into the equivalent PMP-benzylidene donor **29** involved deacetylation with NaOMe, PMP benzylidene formation and benzylation.[42] Importantly most of these steps yielded crystalline products allowing ready purification on large scales.

Benzylidine acetals **28** and **29** then served as precursors to azido thioglycoside donors **34**−**38** bearing different C-4 and C-6 protecting groups patterns (Scheme 7). Selective opening of benzylidene **28** using triethylsilane/$BF_3{\cdot}OEt_2$ gave the C-6-benzyl derivative **30**. Similar selective opening of PMP benzylidene **29** using $^nBu_2BOTf/BH_3{\cdot}THF$ gave the C-4-PMB derivative **31**. Benzylidene **28** could also be hydrolyzed to yield **32**, followed by selective benzoylation giving novel derivative **33**. The C-4 hydroxyl of **30** and **33** were then protected to give either the PMB benzyl ether **34** or the novel trichloroacetate esters **35** and **36**. The C-6 hydroxyl of **31** was protected as either the acetate ester **37** or novel benzoate ester **38**. Finally, thioglycosides **34**−**38** were converted to their trichloroacetimidate donors **44**−**48** in a two step process using standard conditions. Generally the yields were high for the NBS promoted hydrolysis of **34**−**38** (to **39**−**43**[43]) except for C-4-trichloroacetyl (TCA) derivatives **40** and **41**. The trichlor-

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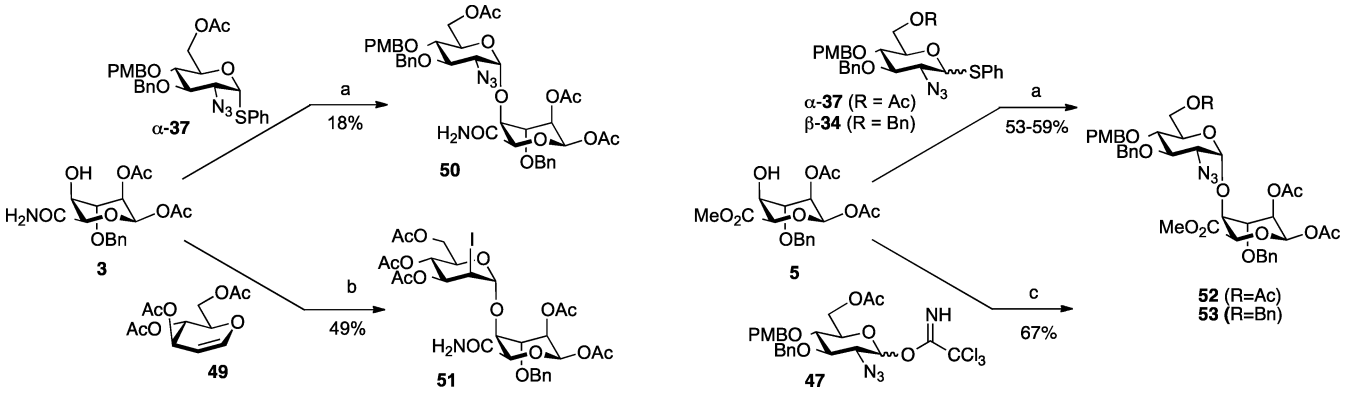
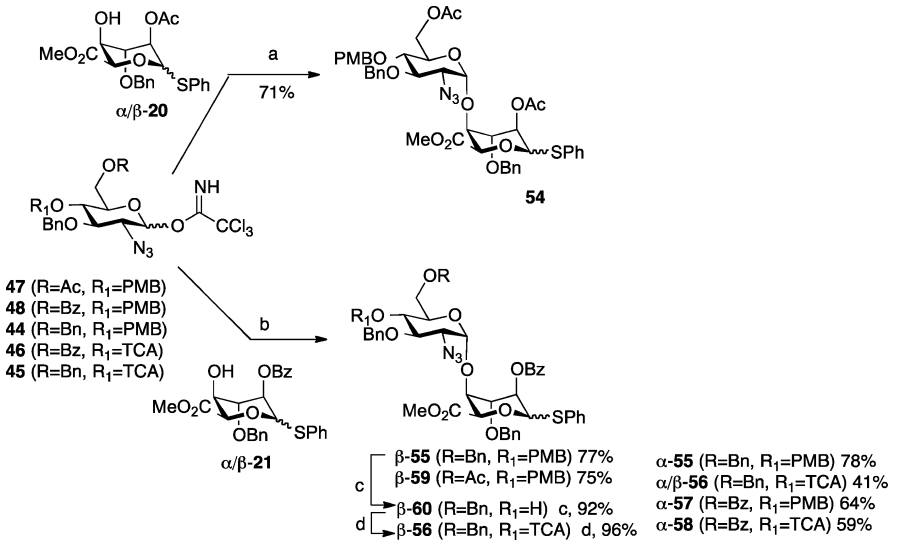
Scheme 8. Exploring L-Ido Acceptor Reactivity with Different Types of Donors[a]



[a]Reagents: (a) NIS, AgOTf, DCM; (b) I_2, CH_3CN; (c) TMSOTf, DCM.

Scheme 9. Synthesis of Various C-4, C-6 Differentiated Glc-Ido Thioglycosides[a]



[a]Reagents: (a) *α*/*β*-**20**,TMSOTf, DCM; (b) *α*-**21** or *β*-**21**,TMSOTf, DCM; (c) CAN, CH_3CN/H_2O; (d) CCl_3COCl, pyridine, DCM.

oacetimidate donors **44**−**48** were also formed in high yields using CCl_3CN and either DBU or NaH as the base.

With scalable access to various 2-azidoglucoside donors established, application to disaccharide synthesis was undertaken. Utilizing our entry to the novel iduronamides reported here, we sought to assess their utility as acceptors in glycosylation reactions. While we have previously observed that amide-containing 1,2-*O*-acetonide-protected ido acceptors function less efficiently than their analogous esters,[10] the use of the amide reported here, without that conformational locking group, would provide a useful comparitor to indicate if the reactivity difference is more general, but conversely may also provide access to new amide-containing iduronate disaccharide analogues. Reaction of iduronamide diacetate acceptor **3** with donor **37** led to the novel disaccharide **50** but only in poor yield (18%) (Scheme 8).

In parallel, reactivity of iduronamide acceptor **3** with triacyl glucal **49** under iodine-mediation did afford better yields of the 2-iodo *α*-linked disaccharide **51** (it was noted that the iodine promotion only worked when it was added directly as a solid to the solution of reactants also containing powdered molecular sieves). It was anticipated that disaccharide **51** could be converted to an azido gluco derivative by S_N2 substitution with azide. Several attempts failed and only produced elimination products that have been observed previously in similar *α*-iodomannosides.[44] Though these reactions do thus demonstrate that iduronamide **3** can be employed as an acceptor to provide novel amido mimetics of HS-related disaccharide building blocks (**50** and **51**), the modest yields consolidate the proposal[10] that these idoamides are less reactive as acceptors than the corresponding iduronate esters.

The acceptor **5** has the advantage of being compatible with many types of donors as the C-1 acetate is not reactive under most glycosylation conditions. As such, **5** was employed for the synthesis of the differentially C-6-protected disaccharides **52** and **53**, obtained using either thioglycoside donors (**37** and **34**) or the corresponding trichloroacetimidate **47**. The yields obtained were not that high, indicating that the acceptor C-4 hydroxyl was not strongly reactive as a nucleophile, and unreacted acceptor could be recovered from the product mixture. The C-6 acyl-protected donors gave high *α* selectivity, while the C-6 benzyl donor was less selective (ca. *α*/*β* 6:1). The disaccharides **52** and **53** serve as precursors for either selective removal of the C-4 terminal protecting group to generate a disaccharide acceptor or selective C-1 manipulation into a more active donor function (see Scheme 10).

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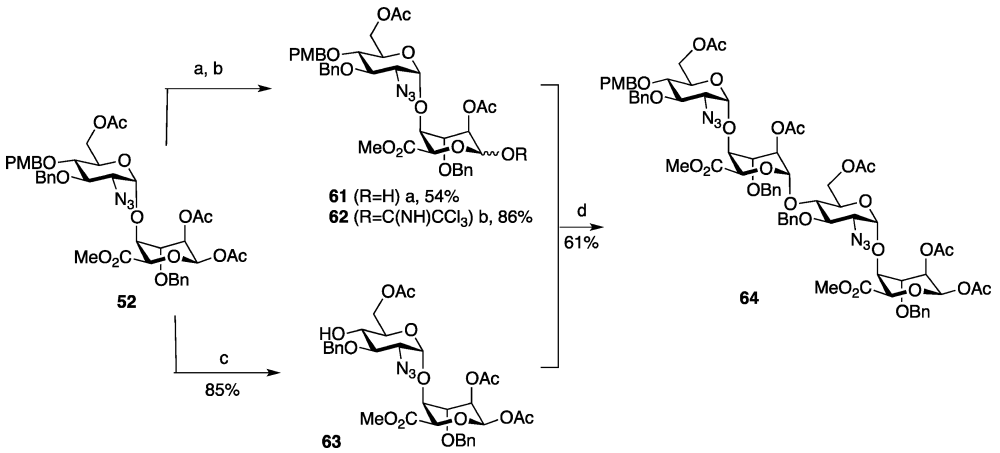
Scheme 10. Iterative Elongation to Tetrasaccharide[a]



[a]Reagents: (a) $BnNH_2$, Et_2O; (b) CCl_3CN, DBU, DCM; (c) DDQ, DCM/H_2O; (d) TMSOTf, DCM.

Alongside synthesis of 1,2-*O*-diacetate iduronate-containing disaccharides (Scheme 8), the iduronate thioglycosides **20** and **21** were also employed as acceptors for the construction of a range of differentially protected Glc-Ido thioglycoside disaccharides (Scheme 9). Thus, glucoazide trichloracetimidates **44**−**48**, bearing variable C-4 and C-6 protection, were reacted with **20** and **21** to provide an array of Glc-Ido thioglycoside disaccharides **55**−**59** in yields highly dependent on the donor. The C-6 acyl donors **47** and **48** generally gave good yields and selective formation of α-glycosides, while the C-6 *O*-benzyl donors **44**−**46** gave modest to high yields and $\alpha\beta$-mixtures. The yields using donors **44**−**46** also depended on a slow reverse addition of excess donor at low temperatures. Because of the modest yield obtained with donor **45**, an alternative method to access disaccharide **56** was investigated. A two-step deprotection of PMB derivative β-**55** with high purity CAN to give **60**, followed by reprotection with trichloroacetyl chloride, provided β-**56** in high yield (87% two steps).

Because of the modest yield obtained with donor **45**, an alternative method to access the disaccharide **56** was investigated. A two-step deprotection of PMB derivative β-**55**, with high purity CAN to give **60**, followed by reprotection with trichloroacetyl chloride provided β-**56** in high yield (87% two steps). Overall, this thus provides a matrix of Glc-Ido disaccharide thioglycosides, bearing differentiated C-6 protection (acyl groups, or benzyl protection), ultimately allowing correlating deprotections/reactions of Glc-C-6 with L-ido C-2 or orthogonal to it, but also with different C-4 protection options, to provide a range of different orthogonal options for C-4 deprotections of these disaccharides or of derived longer saccharides following their use as thioglycoside donors. Moreover, as this is underpinned by our improved scalable syntheses of both the L-ido and D-glucosamine monosaccharide precursors, access to these disaccharides can now be routinely and readily achieved on multigram scales.

With the capacity to generate scalable access to a diversity of thioglycoside disaccharides in hand, we also wished to demonstrate that the use of the C-4 *O*-PMB protection in 1,2-di-*O*-acetate protected disaccharide **52** would facilitate access to further saccharide homologation without involving thioglycoside donors. Thus, **52** was converted into a donor disaccharide in two steps, via selective C-1 deacylation and conversion of the resulting C-1 hydroxyl into its C-1 *O*-trichloroacetimidate derivative **62** (Scheme 10). The selective C-1 deacetylation did not go to completion, and extending the reaction time led to product degradation. Thus it was decided that the optimal process involved partial deprotection to **61** (54%) and recovery of starting material **52** (39%), which was then utilized for C-4 deprotection with DDQ to acceptor disaccharide **63**. Donor **62** and acceptor **63** were then reacted to afford the novel HS-component tetrasaccharide **64** in good yield. This illustrates a convenient use of disaccharide **52** to function as a sole disaccharide building building block for the provision of acceptor and donor modules to access higher oligosaccharide sequences, which could be further extended to longer sequences. Such protecting group combinations have previously been successfully elaborated into oligosaccharde components bearing sulfates on the gluco N and C-6, and L-ido C-2 positions.[5d]

CONCLUSIONS

This synthesis provides a scalable access to a diversity of disaccharides suitable as both donor and acceptor species to elaborate further to heparin-related oligosaccharides. The chemistry is underpinned by the novel and scalable synthesis of L-iduronamides and accesses iduronate building blocks through the application of a novel and mild amide to ester conversion to provide L-iduronate methyl esters. Additionally, a new mild method for removal of thiols with iodine from reaction mixtures has made thioglycosides available on large scale. This facilitates routine access to multigram scale syntheses of these disaccharides, bearing a range of different C-6 and C-4 protection group combinations, which afford valuable applications in the selection of chemistry for further oligosaccharide synthesis and options for programmability of different site-specific modifications of ultimate HS-related oligosaccharides. An illustrative application to a tetrasaccharide is also provided. In addition, structural studies have provided interesting examples of iduronate conformational promiscuity as a function of the nature of the C-6 group, with carboxylate and carboxamides adopting different solid-state conformations, as well as conformationally locked lactone derivatives. Mechanistic studies using deuterium labeling have also provided insight into the mechanism for the novel isopentyl nitrite-mediated mild hydrolysis of primary amides to carboxylic acids.

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EXPERIMENTAL SECTION

3-*O*-Benzyl-L-idopyranuronamide (2). To L-ido cyanohydrin **1** (75.7 g, 0.248 mol) was added THF (120 mL) and 36% HCl (600 mL) at 0 °C. The mixture was stirred for 4 h at rt. The solution was neutralized by slow addition to aqueous $NaHCO_3$ (600 g in 500 mL water). The resulting aqueous brine phase was then extracted 5 times with THF (800 mL, 500 mL, 3 × 300 mL). The organic phase was dried with $MgSO_4$, filtered and evaporated to yield an oil. Stirring this crude oil with $CHCl_3$ (400 mL) overnight and filtering off the resulting solid gave L-idopyranose amide **2** (50.9 g, 0.18 mol, 72%) as a powder (mixture of anomers). An alternative method for purification on smaller scale involved column chromatography of the crude material, using $CHCl_3$/MeOH 10:1: R_f 0.11 ($CHCl_3$/MeOH 10:1); ^{1}H NMR (400 MHz; DMSO-d_6) for major anomer of mixture δ 7.40−7.29 (m, 5H), 6.90 (brs, 1H, N*H*), 6.79 (d, J = 7.9 Hz, 1H, O*H*), 5.12 (d, J = 6.7 Hz, 1H, O*H*), 4.86 (d, J = 8.8 Hz, 1H, O*H*), 4.85 (dd, J = 8.0, 0.8 Hz, 1H, H-1), 4.63 (s, 2H, CH_2Ph), 4.10 (d, J = 1.4 Hz, 1H, H-5), 3.89 (dt, J = 8.6, 1.5 Hz, 1H, H-2), 3.71 (t, J = 3.1 Hz, 1H, H-3), 3.62−3.59 (m, 1H, H-4); ^{13}C NMR (100 MHz; DMSO-d_6) δ 171.2, 138.1, 128.3, 127.6, 127.5, 93.0, 76.5, 75.0, 70.9, 68.1, 66.3; HRMS (TOF-ES$^+$) m/z calcd for $C_{13}H_{18}NO_6$ [M + H]$^+$ 284.1129, found 284.1133; Elemental analysis calcd (%) for $C_{13}H_{17}NO_6$, C 55.12, H 6.05, N 4.94, found C 55.25, H 6.17, N 4.78.

1,2-Di-*O*-acetyl-3-*O*-benzyl-β-L-idopyranuronamide (3). To the powdered L-ido amide **2** (103.2 g, 0.36 mol) was added dichloromethane (900 mL), and the solution cooled to 0 °C in an icebath. Acetic anhydride (81 mL, 0.86 mol) and DMAP (0.45 g, 3.7 mmol) were then added. The cooling was removed, and the mixture stirred for 5 h at room temperature. The reaction was quenched with EtOH (10 mL), and solvents removed in vacuo. The crude product was extracted with EtOAc (1.2 L), washed with water (800 mL) and saturated aqueous $NaHCO_3$ (800 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated. The product was crystallized by dissolving in EtOAc (800 mL) and adding hexane (500 mL). The precipitated solid was filtered after 1 day yielding 3 (57.0 g, 43%) as a white powder. The filtrate containing a mixture of triacetylated furanoside and pyranoside byproduct and more diacetylated pyranoside could be purified by flash column chromatography using EtOAc as eluent. This gave 12% of the triacetylated pyranoside (**12**), 15% triacetylated furanoside and another batch of **3** to give the total yield of **3** (87.5 g, 0.24 mol, 66%). The residual mixture of triacylated pyranoside and furanoside, with some unseparated diacetate, could be recycled as described below: R_f 0.21 (EtOAc); mp 148−152 °C; $[\alpha]_D^{20}$ = +69.2 (c = 0.83, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.37−7.29 (m, 5H), 6.47 (brs, 1H, N*H*), 5.70 (brs, 1H, N*H*), 6.07 (d, J = 1.6 Hz, 1H, H-1), 5.12 (m, 5.13−5.11, 1H, H-2), 4.67 (s, 2H, CH_2Ph), 4.56 (s, 1H, H-5), 4.18 (brd, J = 10.3 Hz, 1H, H-4), 3.89 (t, J = 3.2 Hz, 1H, H-3), 2.08 (d, J = 11.2 Hz, 1H), 2.17 (s, 3H, CH_3), 2.13 (s, 3H, CH_3). ^{13}C NMR (100 MHz; $CDCl_3$) δ 170.9, 169.5, 168.6, 136.8, 128.6, 128.3, 127.9, 90.4, 76.1, 74.8, 72.7, 67.2, 66.3, 21.0, 20.9; HRMS (TOF-ES$^+$) m/z calcd for $C_{17}H_{21}NO_8Na$ [M + Na]$^+$ 390.1159, found 390.1156; Elemental analysis calcd (%) for $C_{17}H_{21}NO_8$, C 55.58, H 5.76, N 3.81, found C 55.19, H 5.79, N 3.68.

Recycling Acetylated L-Iduronamide Products to Reform 2. To a mixture of di- and triacetylated L-iduronamide pyranose and furanose (132.4 g, ∼0.32 mol) was added THF (650 mL) and HCl 4 M (650 mL), and the mixture was stirred for 24 h. The reaction mixture was poured slowly (foaming) onto solid $NaHCO_3$ with stirring, and the brine-like aqueous phase extracted with THF (3 × 500 mL). The combined organic phases were dried ($MgSO_4$), filtered, and solvent evaporated. This gave the crude 3-*O*-benzyl-L-iduronamide triol (85 g, 93%).

1,2-Di-*O*-acetyl-3-*O*-benzyl-β-L-idopyranuronic acid (4). To the amide **3** (4.55 g, 12.4 mmol) was added acetic acid (100 mL) and then isoamyl nitrite (4.3 mL, 37.2 mmol). The flask was fitted with a condenser, and the mixture was heated for 4 h to 100 °C under N_2. The solution was evaporated and then coevaporated with toluene (2 × 100 mL). The crude product was purified by flash column chromatography (EtOAc/hexane, 2:1 containing 1% formic acid), yielding **4** (3.14 g, 8.5 mmol, 69%) as an oil: R_f 0.06 (EtOAc/hexane 2:1 + 1% HCOOH); $[\alpha]_D^{20}$ = +44.5 (c = 0.82, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.32 (m, 5H, Ph), 6.08 (d, J = 1.6 Hz, 1H, H-1), 5.16−5.14 (m, 1H, H-2), 4.74 (d, J = 2.0 Hz, 1H, H-5), 4.71 (d, J = 11.6 Hz, 1H, CH_2Ph), 4.67 (d, J = 12.0 Hz, 1H, CH_2Ph), 4.07−4.05 (m, 1H, H-4), 3.88 (t, J = 3.6 Hz, 1H, H-3), 2.14 (s, 3H, COCH_3), 2.10 (s, 3H, COCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 169.3, 168.6, 136.5, 128.6, 128.3, 127.9, 90.0, 74.8, 74.7, 72.8, 67.4, 66.7, 20.8, 20.7; HRMS (TOF-ES$^+$) m/z calcd for $C_{17}H_{19}O_9$ [M + H]$^+$ 367.1029, found 367.1032.

Methyl 1,2-Di-*O*-acetyl-3-*O*-benzyl-β-L-idopyranuronate (5).[21] *Method A.* To the acid **4** (1.73 g, 4.70 mmol) was added dry DCM (25 mL), and then dimethylformamide dimethylacetal (DMF·DMA) was added dropwise over 40 min (0.7 mL, 4.93 mmol) at 0 °C . The mixture was left for 5 h at room temperature under a N_2 atmosphere. The reaction was quenched by addition of AcOH, solvents removed in vacuo, and the residue purified by flash column chromatography (EtOAc/hexane, 1:1), yielding **5** (1.50 g, 3.9 mmol, 84%) as a white foam. The product could be crystallized by dissolving in EtOAc and adding hexane (1:3 v/v) giving white needles.

Method B. The amide **3** was converted to the acid **4**, and then the crude product used directly to prepare the ester **5**. To the diacetylated L-ido amide **3** (53.0 g, 0.144 mol) was added acetic acid (1 L) and isoamyl nitrite (77 mL, 0.577 mol), and the mixture was heated for 6 h to 90 °C under N_2. The solvents were removed, and the residue azeotroped with toluene (3 × 500 mL) yielding crude **4**. To this reside was added anhydrous DMF (400 mL), potassium hydrogencarbonate (14.5 g, 0.144 mol) and methyliodide (9.0 mL, 0.144 mol) under N_2. The mixture was vigorously stirred for 16 h. Potassium acetate (10 g, 0.102 mol) was added to quench excess methyliodide, and the mixture stirred for another 8 h. The solution was then extracted with DCM (1 L) and washed with water (4 × 500 mL) to remove DMF from the organic phase. After extraction, the organic phase was dried ($MgSO_4$), filtered, evaporated, and the residue purified by flash column chromatography (EtOAc/hexane, 1:2 to 1:1). This yielded **5** (33.0 g, 86.0, mmol 60%) as a syrup. The product could be crystallized by dissolving in diethylether and cooling to 0 °C followed by filtration yielding pure **5** as a white powder: R_f 0.18 (EtOAc/hexane 1:1); mp 77−78 °C; $[\alpha]_D^{20}$ = +39.2 (c = 0.93, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.30 (m, 5H, Ph), 6.07 (d, J = 1.6 Hz, 1H, H-1), 5.15 (ddd, J = 3.2 Hz, 1.6 Hz, 1.2 Hz, 1H, H-2), 4.71 (d, J = 2.0 Hz, 1H, H-5), 4.70 (d, J = 11.6 Hz, 1H, CH_2Ph), 4.65 (d, J = 11.6 Hz, 1H, CH_2Ph), 4.01−3.98 (m, 1H, H_4), 3.85 (t, J = 3.2 Hz, 1H, H-3), 3.80 (s, 3H, C(O)OCH_3), 2.92 (d, J = 12.4 Hz, 1H, O*H*), 2.13 (s, 3H, COCH_3), 2.09 (s, 3H, COCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 168.4, 168.2, 136.6, 128.6, 128.2, 127.8, 90.1, 75.3, 74.7, 72.6, 67.5, 66.8, 52.4, 20.8, 20.7; HRMS (TOF-ES$^+$) m/z calcd for $C_{18}H_{26}O_9N$ [M + NH_4]$^+$ 400.1608, found 400.1611; Elemental analysis calcd (%) for $C_{18}H_{22}O_9$, C 56.54, H 5.80, found C 56.65, H 5.75.

Method B Employing CD_3CO_2D. To the amide **3** (136 mg, 0.37 mmol) was added deuterated acetic acid-d_4 (1 mL) and then isoamyl nitrite (0.2 mL, 1.5 mmol). The mixture was heated for 6 h to 90 °C under a N_2 atmosphere. The solution was evaporated and then coevaporated with toluene (2 × 10 mL). The crude product was purified by flash column chromatography (EtOAc/hexane gradient 1:3 then 1:1 containing 1% formic acid). This yielded **4** (94 mg, 69%), along with **6** (5 mg, 4%), **7** as a 1:1 mixture of 4-*O*-CH_3CO- and 4-*O*-CD_3CO- (4 mg, 3%).

1,2-Di-*O*-acetyl-3-*O*-benzyl-β-L-idopyranurono-4,6-lactone (6). This compound was isolated from the amide hydrolysis/esterification (**3** to **5**, method B) reaction as a byproduct using flash column chromatography (EtOAc/hexane, 1:3). This yielded **6** (2.8 g, 8.0 mmol, 5%): R_f 0.28 (EtOAc/hexane 1:3); mp 88−90 °C; $[\alpha]_D^{20}$ = +99.8 (c = 0.49, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.42−7.33 (m, 5H, Ph), 6.27 (d, J = 2.6 Hz, 1H, H-1), 5.33 (d, J = 6.7 Hz, 1H, H-5), 5.14 (dd, J = 10.0, 2.6 Hz, 1H, H-2), 4.84 (dd, J = 6.7, 2.2 Hz, 1H, H-4), 4.82 (d, J = 12.0 Hz, 1H, CH_2Ph), 4.66 (d, J = 12.0 Hz, 1H, CH_2Ph), 4.30 (dd, J = 10.0, 2.2 Hz, 1H, H-3), 2.12 (s, 3H, COCH_3), 2.09 (s, 3H, COCH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 169.8, 168.8,

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168.7, 136.8, 128.6, 128.3, 127.8, 89.4, 76.8, 76.2, 75.3, 72.5, 69.1, 20.7, 20.5; MS-MALDI m/z = 373 $[M + Na]^+$; HRMS (FTMS-NSI$^+$) m/z calcd for $C_{17}H_{18}O_8Na$ $[M+Na]^+$ 373.0899, found 373.0902; Elemental analysis calcd (%) for $C_{17}H_{18}O_8$, C 58.28, H 5.18, found C 58.61, H 5.13.

1,2-Di-*O*-acetyl-3-*O*-benzyl-4-*O*-chloroacetyl-β-L-idopyranuronamide (8). To the diacetylated L-ido amide **3** (4.57 g, 12.45 mmol) was added dry dichloromethane (80 mL), pyridine (1.6 mL, 19.7 mmol), and chloroacetyl chloride (1.4 mL, 17.6 mmol) dropwise over 15 min, and the mixture was stirred for a further 90 min under N_2. The reaction mixture was then extracted with dichloromethane (300 mL), washed with 1% HCl (200 mL) and saturated aqueous $NaHCO_3$ (200 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash column chromatography (EtOAc/Hexane 1:1), yielding **8** (5.25 g, 11.8 mmol, 95%) as a white solid. The product was recrystallized by dissolving in EtOAc and adding hexane (1:2 v/v) to give white needles: R_f 0.37 (EtOAc/hexane 2:1); mp 124−126 °C; $[\alpha]_D^{20}$ = +45.3 (c = 0.87, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.39−7.34 (m, 5H, Ph), 6.54 (brs, 1H, N*H*), 6.09 (d, J = 1.8 Hz, 1H, H-1), 6.06 (brs, 1H, N*H*), 5.38−5.34 (m, 1H, H-4), 5.07 (dd, J = 2.9, 1.8 Hz, 1H, H-2), 4.80 (d, J = 11.6 Hz, 1H, C*H*$_2$Ph), 4.73 (d, J = 11.6 Hz, 1H, C*H*$_2$Ph), 4.71 (d, J = 2.0 Hz, 1H, H-5), 4.08 (d, J = 14.8 Hz, 1H, C*H*$_2$Cl), 4.01 (d, J = 14.8 Hz, 1H, C*H*$_2$Cl), 4.00 (t, J = 2.8 Hz, 1H, H$_3$), 2.15 (s, 6H, 2 x COC*H*$_3$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 169.7, 168.9, 168.5, 166.3, 136.4, 128.7, 128.4, 128.0, 90.1, 74.0, 73.1, 72.6, 67.8, 66.2, 40.5, 20.91, 20.83; HRMS (TOF-ES$^+$) m/z calcd for $C_{19}H_{22}ClNO_9Na$ $[M + Na]^+$ 466.0881, found 466.0886; Elemental analysis calcd (%) for $C_{19}H_{22}ClNO_9$, C 51.42, H 5.00, N 3.16, found C 51.30, H 4.98, N 3.08.

1,2-Di-*O*-acetyl-3-*O*-benzyl-4-*O*-chloroacetyl-β-L-idopyranuronic acid (9). To the amide **8** (551 mg, 1.24 mmol) was added acetic acid (6 mL) and isoamyl nitrite (0.67 mL, 4.96 mmol). The mixture was heated for 5 h to 90 °C under N_2, solvents were removed, coevaporated with toluene (2 × 20 mL), and the residue was purified by flash column chromatography (EtOAc/hexane, 1:1 containing 1% formic acid). This yielded **9** (372 mg, 0.84 mmol, 67%) as an oil: R_f 0.10 (EtOAc/hexane 1:1 + 1% HCOOH); $[\alpha]_D^{20}$ = +28.9 (c = 0.88, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.54 (brs, 1H, CO_2H), 7.41−7.36 (m, 5H, Ph), 6.12 (d, J = 1.7 Hz, 1H, H-1), 5.25−5.23 (m, 1H, H-4), 5.10 (m, 1H, H-2), 4.88 (d, J = 2.1 Hz, 1H, H-5), 4.78 (m, 2H, C*H*$_2$Ph), 4.10, (d, J = 14.8 Hz, 1H, C*H*$_2$Cl), 4.02 (d, J = 14.8 Hz, 1H, C*H*$_2$Cl), 4.02 (t, J = 2.8 Hz, 1H, H-3), 2.14 (s, 6H, 2 x COC*H*$_3$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 170.1, 169.9, 168.7, 166.5, 136.3, 129.1, 128.7, 128.5, 128.3, 128.0, 89.9, 73.3, 72.7, 72.6, 68.3, 65.8, 40.4, 20.8, 20.8; HRMS (TOF-ES$^-$) m/z calcd for $C_{19}H_{20}ClO_{10}$ $[M-H^+]$ 443.0750, found 443.0767.

Methyl 1,2-Di-*O*-acetyl-3-*O*-benzyl-4-*O*-chloroacetyl-β-L-idopyranuronate (10). To the acid **9** (2.03 g, 4.57 mmol) was added dry DCM (30 mL) and then *N*,*N*-dimethylformamide dimethyl acetal (0.65 mL, 4.57 mmol) dropwise over 5 min. The mixture was stirred for 1 h at room temperature under N_2. The reaction was quenched with AcOH (0.5 mL), solvents evaporated, and the residue purified by flash column chromatography (EtOAc/hexane, 1:2) yielding **10** (1.19 g, 2.59 mmol, 57%) as a white solid. The product could be crystallized by dissolving in EtOAc and adding hexane (1:3 v/v) giving white needles: R_f 0.18 (EtOAc/hexane 1:2); mp 143−145 °C; $[\alpha]_D^{20}$ = +16.3 (c = 0.60, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.34−7.25 (m, 5H, Ph), 6.02 (d, J = 1.8 Hz, 1H, H-1), 5.15−5.14 (m, 1H, H-4), 5.00−4.98 (m, 1H, H-2), 4.75 (d, J = 2.0 Hz, 1H, H-5), 4.69 (d, J = 12.0 Hz, 2H, C*H*$_2$Ph), 3.97, (d, J = 14.8 Hz, 1H, C*H*$_2$Cl), 3.91 (d, J = 14.8 Hz, 1H, C*H*$_2$Cl), 3.91 (t, J = 2.8 Hz, 1H, H-3), 3.72 (s, 3H, C(O)OC*H*$_3$), 2.06 (s, 6H, 2 x COC*H*$_3$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 169.9, 168.5, 167.0, 166.4, 136.4, 128.7, 128.5, 128.0, 89.9, 73.2, 73.0, 72.8, 68.6, 65.8, 52.8, 40.4, 20.92, 20.84; HRMS (TOF-ES$^+$) m/z calcd for $C_{20}H_{23}ClO_{10}Na$ $[M + Na]^+$ 481.0877, found 481.0882; Elemental analysis calcd (%) for $C_{20}H_{23}ClO_{10}$, C 52.35, H 5.05, found C 52.34, H 4.99.

1,2-Di-*O*-benzoyl-3-*O*-benzyl-β-L-idopyranuronamide (11). To the powdered L-ido amide **2** (10.7 g, 37.8 mmol) was added CH_2Cl_2 (100 mL), THF (100 mL) and then benzoic anhydride (18.8 g, 83.1 mmol) and DMAP (230 mg, 1.90 mmol). The mixture was stirred for 3 h, and more benzoic anhydride (4.4 g, 19.4 mmol) was added. After 5 h the solvents were removed, and the residue extracted with EtOAc (500 mL), washed with 1% HCl (300 mL) and saturated aqueous $NaHCO_3$ (300 mL). The organic phase was dried ($MgSO_4$) filtered, evaporated, and flash column chromatography (EtOAc/Hexane, 3:2) yielded **11** (8.68 g, 17.6 mmol, 47%) as a white powder. The product could be recrystallized by dissolving in EtOAc and adding hexane: R_f 0.31 (EtOAc/hexane 2:1); mp 79−80 °C; $[\alpha]_D^{20}$ = +56.3 (c = 0.55, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.12−8.09 (m, 2H, Ar*H*), 7.97−7.94 (m, 2H, Ar*H*), 7.65−7.55 (m, 2H, Ar*H*), 7.52−7.47 (m, 2H, Ar*H*), 7.42−7.31 (m, 7H, Ar*H*), 6.60 (d, J = 2.9 Hz, 1H, *NH*), 6.43 (d, J = 1.6 Hz, 1H, H-1), 6.18 (d, J = 2.9 Hz, 1H, N*H*), 5.53 (dd, J = 3.6, 1.6 Hz, 1H, H-2), 4.80 (s, 2H, C*H*$_2$Ph), 4.73 (d, J = 2.1 Hz, 1H, H-5), 4.34 (dd, J = 3.6, 2.1 Hz, 1H, H-4), 4.16 (t, J = 3.6 Hz, 1H, H-3), 3.11 (s, 1H, O*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ 171.1, 165.4, 164.3, 136.9, 133.8, 133.7, 130.0, 129.9, 129.2, 128.7, 128.6, 128.6, 128.3, 128.0, 91.1, 75.9, 75.4, 73.0, 68.0, 66.8; HRMS (TOF-ES$^+$) m/z calcd for $C_{27}H_{25}NO_8Na$ $[M + Na]^+$ 514.1478, found 514.1482.

1,2-Di-*O*-benzoyl-3-*O*-benzyl-β-L-idopyranuronic acid (12). To the dibenzoylated L-ido amide **11** (15.0 g, 30.5 mmol) was added acetic acid (200 mL) and isoamyl nitrite (20 mL, 150 mmol). The mixture was heated to 90 °C for 5 h under N_2. The solvents were removed and coevaporated with toluene (2 × 200 mL) and flash column chromatography (EtOAc/Hexane 1:1 containing 1% HCOOH) yielded **12** (8.86 g, 18.0 mmol, 59%) as an oil: R_f 0.27 (EtOAc/hexane 2:1 + 1% HCOOH); $[\alpha]_D^{20}$ = +43.0 (c = 0.67, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.08−8.05 (m, 2H, Ar*H*), 7.95−7.92 (m, 2H, Ar*H*), 7.63−7.59 (m, 1H, Ar*H*), 7.56−7.52 (m, 1H, Ar*H*), 7.50−7.46 (m, 2H, Ar*H*), 7.40−7.34 (m, 7H, Ar*H*), 6.45 (d, J = 1.8 Hz, 1H, H$_1$), 5.52 (ddd, J = 3.8, 1.7, 0.9 Hz, 1H, H-2), 4.85−4.77 (m, 3H, C*H*$_2$Ph, H-5), 4.19−4.17 (m, 1H, H-4), 4.15 (t, J = 3.8 Hz, 1H, H-3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 172.5, 165.5, 164.4, 136.9, 134.0, 130.3, 130.1, 129.1, 129.0, 128.8, 128.7, 128.6, 128.2, 128.0, 91.1, 75.3, 74.8, 73.4, 68.1, 68.0; HRMS (TOF-ES$^+$) m/z calcd for $C_{27}H_{24}O_9Na$ $[M + Na]^+$ 515.1318, found 515.1322).

Methyl 1,2-Di-*O*-benzoyl-3-*O*-benzyl-β-L-idopyranuronate (13). To the dibenzoylated L-ido acid **12** (8.70 g, 17.7 mmol) was added dry dichloromethane (150 mL), and the mixture cooled to 0 °C in an ice-bath. *N*,*N*-Dimethylformamide dimethyl acetal (2.2 mL, 17.7 mmol) was added dropwise over 15 min. Cooling was removed, and the reaction stirred for 7 h under N_2. Solvents were then evaporated, and purification of the residue by flash column chromatography (EtOAc/Hexane, 1:2) yielded pure **13** (5.25 g, 10.3 mmol, 59%) as an oil: R_f 0.24 (EtOAc/hexane 1:2); $[\alpha]_D^{20}$ = +37.5 (c = 0.84, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.09−8.06 (m, 2H, Ar*H*), 7.98−7.95 (m, 2H, Ar*H*), 7.66−7.55 (m, 2H, Ar*H*), 7.51−7.47 (m, 2H, Ar*H*), 7.42−7.33 (m, 7H, Ar*H*), 6.49 (d, J = 2.0 Hz, 1H, H-1), 5.53 (ddd, J = 4.2, 1.9, 0.9 Hz, 1H, H-2), 4.89−4.81 (m, 3H, C*H*$_2$Ph, H-5), 4.21−4.15 (m, 2H, H-3, H-4), 3.74 (s, 3H, CO_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 169.1, 165.3, 164.1, 136.9, 133.8, 130.1, 129.9, 129.1, 128.7, 128.7, 128.6, 128.5, 128.3, 128.0, 91.0, 75.3, 74.8, 73.3, 68.4, 68.3, 52.6; HRMS (TOF-ES$^+$) m/z calcd for $C_{28}H_{26}O_9Na$ $[M + Na]^+$ 529.1469, found 529.1467; Elemental analysis calcd (%) for $C_{28}H_{26}O_9$, C 66.40, H 5.17, found C 66.30, H 5.17.

Methyl 1,2-Di-*O*-benzoyl-3-*O*-benzyl-4-*O*-chloroacetyl-β-L-idopyranuronate (14). To the dibenzoylated L-ido ester **13** (3.0 g, 5.93 mmol) was added dry dichloromethane (50 mL), pyridine (1.0 mL, 12.3 mmol) and chloroacetyl chloride (0.9 mL, 11.3 mmol). The mixture was stirred for 90 min under N_2, extracted with dichloromethane (200 mL), the organics washed with 1% HCl (200 mL) and saturated $NaHCO_3$ (200 mL). The organic phase was dried ($MgSO_4$), filtered, and solvents removed in vacuo. Purification of the crude residue by flash column chromatography (EtOAc/Hexane 1:3) yielded **14** (3.18 g, 5.45 mmol, 92%) as a white foam: R_f 0.43 (EtOAc/hexane 1:2); $[\alpha]_D^{20}$ = +32.5 (c = 0.57, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.09−8.02 (m, 2H, Ar*H*), 7.87−7.85 (m, 2H, Ar*H*), 7.57−7.51 (m, 1H, Ar*H*), 7.47−7.36 (m, 3H, Ar*H*), 7.36−7.22 (m, 7H, Ar*H*), 6.37 (d, J = 1.6 Hz, 1H, H-1), 5.37−5.35 (m, 1H, H-2), 5.27−

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5.24 (m, 1H, H-4), 4.90 (d, J = 2.1 Hz, 1H, H-5), 4.77 (s, 2H, CH_2Ph), 4.12 (t, J = 3.2 Hz, 1H, H-3), 3.84 (d, J = 14.9 Hz, 1H, CH_2Cl), 3.73−3.67 (m, 4H, CH_2Cl, CO_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 167.2, 166.5, 165.5, 164.2, 136.5, 133.8, 133.7, 130.1, 130.0, 129.2, 128.7, 128.6, 128.4, 128.4, 128.0, 90.7, 73.4, 73.1, 73.0, 68.8, 66.8, 52.8, 40.3; HRMS (TOF-ES$^+$) m/z calcd for $C_{30}H_{31}ClO_{10}N$ [M + NH_4]$^+$ 600.1631, found 600.1633; Elemental analysis calcd (%) for $C_{30}H_{27}ClO_{10}$, C 61.81, H 4.67, found C 61.64, H 4.63.

1,2,4-Tri-*O*-acetyl-3-*O*-benzyl-β-L-idopyranuronamide (15). To the amide triol **2** (19.5 g, 0.069 mol) was added dichloromethane (300 mL), and the mixture cooled to 0 °C in an ice-bath. Acetic anhydride (23 mL, 0.241 mol) and 4-(dimethylamino)pyridine (168 mg, 1.38 mmol) were added. The insoluble starting material was gradually consumed while being vigorously stirred for 4 h, slowly warming to room temperature. Pyridine (22 mL, 0.276 mol) was added and stirred for another 16 h. The solvents were removed, and the residue azeoptroped twice with toluene (2 × 200 mL). The crude product was purified by column chromatography using EtOAc/hexane (2:1) as eluent, yielding triacetylated L-ido amide **15** (22.7 g, 55.5 mmol 81%) as a white solid. The product was recrystallized by dissolving in EtOAc (600 mL) and adding hexane (600 mL) yielding white needles of pure **15** (19.4 g, 47.4 mmol, 69%): R_f 0.25 (EtOAc/hexane 2:1); mp 201−202 °C; $[\alpha]_D^{20}$ = +58.9 (c = 0.53, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.31 (m, 5H, Ph), 6.52 (brs, 1H, CONH_2), 6.06 (d, J = 1.5 Hz, 1H, H_1), 5.88 (brs, 1H, CONH_2), 5.26 (s, 1H, H-4), 5.02 (s, 1H, H-2), 4.78 (d, J = 11.7 Hz, 1H, CH_2Ph), 4.69 (d, J = 12.3 Hz, 1H, CH_2Ph), 4.66 (s, 1H, H-5), 3.97 (t, J = 2.7 Hz, 1H, H-3), 2.13 (s, 3H, $COCH_3$), 2.12 (s, 3H, $COCH_3$), 2.03 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 169.5, 169.1, 168.4, 136.6, 128.5, 128.2, 127.9, 90.0, 74.2, 72.9, 72.6, 66.5, 66.3, 20.8, 20.7, 20.6; HRMS (TOF-ES$^+$) m/z calcd for $C_{19}H_{23}NO_9Na$ [M + Na]$^+$ 432.1265, found 432.1266; Elemental analysis calcd (%) for $C_{19}H_{23}NO_9$, C 55.74, H 5.66, N 3.42, found C 55.78, H 5.81, N 3.32.

1,2,4-Tri-*O*-acetyl-3-*O*-benzyl-β-L-idopyranuronic acid (7). To the triacetylated L-ido amide **15** (19.3 g, 47.2 mmol) was added acetic acid (200 mL) and isoamyl nitrite (25 mL, 189 mmol). The mixture was heated to 90 °C for 5 h under N_2, solvents removed in vacuo and coevaporated with toluene (2 × 200 mL). Purification of the residue by flash column chromatography (EtOAc/Hexane 2:1 containing 1% HCOOH) yielded **7** (13.1 g, 32 mmol, 68%) as a solid. The solid was recrystallized by dissolving in EtOAc (200 mL) and adding hexane (400 mL) to yield a white solid (9.75 g): R_f 0.07 (EtOAc/hexane 2:1 + 1% HCOOH); mp 150−151 °C; $[\alpha]_D^{20}$ = +38.3 (c = 0.72, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.32 (m, 5H, Ph), 6.09 (d, J = 1.6 Hz, 1H, H-1), 5.17−5.15 (m, 1H, H-4), 5.04−5.02 (m, 1H, H-2), 4.82 (d, J = 2.0 Hz, 1H, H-5), 4.76 (d, J = 11.6 Hz, 1H, CH_2Ph), 4.72 (d, J = 11.6 Hz, 1H, CH_2Ph), 3.97 (t, J = 2.8 Hz, 1H, H-3), 2.11 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 2.04 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 169.9, 169.8, 168.6, 136.4, 128.6, 128.3, 127.9, 89.8, 73.0, 72.8, 72.6, 66.8, 65.9, 20.7, 20.7, 20.6; HRMS (FTMS-NSI$^+$) m/z calcd for $C_{19}H_{22}O_{10}Na$ [M + Na]$^+$ 433.1105, found 433.1099.

Methyl 1,2,4-Tri-*O*-acetyl-3-*O*-benzyl-β-L-idopyranuronate (16). To the L-ido acid **7** (112 mg, 0.27 mmol) was added dry DMF (1 mL), $KHCO_3$ (28 mg, 0.27 mmol) and then iodomethane (25 μL, 0.40 mmol). The mixture was stirred for 24 h under N_2, solvents removed in vacuo, and the residue extracted with DCM (25 mL), and H_2O (25 mL), the organic phase was dried ($MgSO_4$), filtered and evaporated. Purification by flash column chromatography using (EtOAc/hexane (1:1) yielded **16** (113 mg, 0.27 mmol, 99%) as a white solid. The product could be recrystallized using ether. Data for this compound matched those previously reported.[5g]

2,4-Di-*O*-acetyl-3-*O*-benzyl-β-L-idopyranurono-1,6-lactone (17). To the acid **7** (13.3 g, 32.5 mmol) was added dry DCM (100 mL) and then trimethylsilyl trifluoromethanesulfonate (TMSOTf) (1.2 mL, 9.74 mmol). The mixture was stirred for 30 h at room temperature under N_2, after which time the reaction was quenched with pyridine, solvents removed, and the residue purified by flash column chromatography (EtOAc/hexane, 1:2), yielding **17** (6.01 g, 17.0 mmol, 53%) as a white solid. The product could be recrystallized by dissolving in EtOAc and adding hexane (1:3 v/v): R_f 0.34 (EtOAc/hexane 1:3); mp 107−108 °C; $[\alpha]_D^{20}$ = +87.9 (c = 0.66, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.39−7.26 (m, 5H, ArH), 5.90 (d, J = 2.1 Hz, 1H, H-1), 5.05 (dd, J = 8.2, 4.6 Hz, 1H, H-4), 5.01 (dd, J = 8.2, 2.1 Hz, 1H, H-2), 4.73−4.66 (m, 2H, CH_2Ph), 4.59 (d, J = 4.6 Hz, 1H, H-5), 3.95 (t, J = 8.2 Hz, 1H, H-3), 2.09 (s, 3H, $COCH_3$), 2.08 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 170.0, 169.9, 168.5, 137.4, 128.6, 128.1, 127.7, 100.3, 75.1, 73.2, 69.9, 69.1, 20.7; MS-MALDI m/z = 351 [M + H]$^+$; HRMS (FTMS-NSI$^+$) m/z calcd for $C_{17}H_{19}O_8$ [M + H]$^+$ 351.1074, found 351.1075; Elemental analysis calcd (%) for $C_{17}H_{18}O_8$, C 58.28, H 5.18, found C 58.54, H 5.30.

Methyl (Phenyl 2-*O*-acetyl-3-*O*-benzyl-4-*O*-chloroacetyl-1-thio-β-L-idopyranoside)uronate (18). To the L-ido ester **10** (3.72 g, 8.12 mmol) was added dry dichloromethane (70 mL), borontrifluoride diethyl etherate (5.1 mL, 40.6 mmol) and thiophenol (0.91 mL, 8.93 mmol). The mixture was stirred for 21 h under N_2 and was then quenched by adding to a mixture of saturated $NaHCO_3$ (200 mL) and dichloromethane (150 mL) with stirring. To this mixture was added iodine until a dark red color persisted, indicating all remaining thiophenol had been oxidized to diphenyldisulfide, thus removing all odor from the product mixture. The excess of iodine was reduced to iodide by adding enough sodium thiosulfate solution (10% aq) until the dark red color disappeared. The organic phase was separated, dried ($MgSO_4$), filtered and evaporated. Purification by flash column chromatography (EtOAc/Hexane 1:4) yielded **16** (2.43 g, 4.77 mmol, 59%, α/β 3:1) as an oil. Starting material **10** (0.52 g, 14%) was recovered: R_f 0.42 (EtOAc/hexane 1:2); See the Supporting Information for copies of ^{1}H and ^{13}C NMR spectra; HRMS (TOF-ES$^+$) m/z calcd for $C_{24}H_{25}ClO_8SNa$ [M + Na]$^+$ 531.0856, found 531.0870.

Methyl (Phenyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-chloroacetyl-1-thio-L-idopyranoside) uronate (19). To the L-ido ester **14** (3.1 g, 5.32 mmol) was added dry dichloromethane (50 mL), thiophenol (0.84 mL, 7.23 mmol) and borontrifluoride diethyl etherate (2.4 mL, 16.7 mmol), and the mixture was stirred 15 h under N_2 and was then quenched by adding to a mixture of saturated $NaHCO_3$ (200 mL) and dichloromethane (150 mL) with stirring. To this mixture was added iodine until a dark red color persisted, indicating all remaining thiophenol had been oxidized to diphenyldisulfide, thus removing all odors from the product mixture. The excess of iodine was reduced to iodide by adding sodium thiosulfate solution (10% aq) dropwise until the dark red color disappeared. The organic phase was separated, dried ($MgSO_4$), filtered and evaporated, and purification by flash column chromatography (EtOAc/Hexane 1:4) yielded **19** (1.36 g, 45%, 2.39 mmol, α/β 3:1) as an oil, along with recovery of starting material (0.95 g, 31%). **19α**: R_f 0.18 (EtOAc/hexane 1:5); $[\alpha]_D^{20}$ = −64.1 (c = 0.57, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.00−7.95 (m, 2H, ArH), 7.53−7.42 (m, 3H, ArH), 7.42−7.16 (m, 10H, ArH), 5.71 (s, 1H, H-1), 5.44 (d, J = 2.0 Hz, 1H, H-5), 5.37 (dd, J = 2.6, 1.2 Hz, 1H, H-2), 5.29−5.27 (m, 1H, H-4), 4.86 (d, J = 11.7 Hz, 1H, CH_2Ph), 4.72 (d, J = 11.8 Hz, 1H, CH_2Ph), 3.95−3.92 (m, 1H, H-3), 3.83 (d, J = 14.9 Hz, 1H, CH_2Cl), 3.77−3.69 (m, 4H, CH_2Cl, CO_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 168.4, 166.4, 165.1, 136.7, 135.3, 133.8, 131.3, 129.9, 129.1, 129.1, 128.6, 128.5, 128.2, 127.8, 127.7, 86.5, 73.0, 71.3, 69.4, 68.6, 66.7, 52.8, 40.3; HRMS (TOF-ES$^+$) m/z calcd for $C_{29}H_{27}ClO_8SNa$ [M + Na]$^+$ 593.1007, found 593.1005; Elemental analysis calcd (%) for $C_{29}H_{27}ClO_8S$, C 61.00, H 4.77, found C 60.70, H 4.82.

Methyl (Phenyl 2-*O*-acetyl-3-*O*-benzyl-1-thio-L-idopyranoside) uronate (20). *Method A.* To the L-ido thioglycoside **18** (0.65 g, 1.28 mmol) was added diethylether (6 mL), and this solution cooled to 0 °C with an ice-bath. Benzylamine (0.4 mL, 3.83 mmol) was then added, and the mixture stirred for 1 h at 0 °C. The reaction was extracted with EtOAc (100 mL) and 1 M HCl (100 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and solvents removed. Purification of the residue by flash column chromatography (EtOAc/Hexane 1:1) yielded **20** (382 mg, 0.88 mmol, 69%, α/β 2:1) as an oil.

Method B. To the L-ido thioglycoside **18** (92 mg, 0.18 mmol) was added ethanol (5 mL), thiourea (20 mg, 0.27 mmol), sodium hydrogencarbonate (30 mg, 0.36 mmol), and the mixture was heated

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to 70 °C with stirring for 3 h. The reaction was extracted with dichloromethane (50 mL), and the organics washed with water (50 mL). The organic phase was separated, dried ($MgSO_4$) filtered and evaporated. Purification by flash column chromatography (EtOAc/Hexane 1:2) yielded **20** (69 mg, 0.16 mmol, 80%, α/β 2:1) as an oil. ***20α***: R_f 0.10 (EtOAc/hexane 1:2); $[\alpha]_D^{20}$ = −110.7 (c = 0.61, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.46−7.40 (m, 2H, Ar*H*), 7.36−7.15 (m, 8H, Ar*H*), 5.49 (s, 1H, H-1), 5.26 (d, J = 1.7 Hz, 1H, H-5), 5.20 (dd, J = 2.7, 1.3 Hz, 1H, H-2), 4.76 (d, J = 11.9 Hz, 1H, C*H*$_2$Ph), 4.56 (d, J = 11.9 Hz, 1H, C*H*$_2$Ph), 4.03−4.00 (m, 1H, H-4), 3.75 (s, 3H, C(O)OC*H*$_3$), 3.70−3.67 (td, J = 2.7, 1.2 Hz, 1H, H-3), 2.65 (brs, 1H, O*H*), 2.00 (s, 3H, COC*H*$_3$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 169.5, 169.0, 136.8, 135.6, 131.1, 129.1, 128.5, 128.1, 127.8, 127.6, 86.6, 73.1, 72.3, 69.0, 68.6, 68.2, 52.4, 20.9; MS-MALDI m/z = 450 [M + NH_4]$^+$; HRMS (FTMS-NSI$^+$) m/z calcd for $C_{22}H_{28}NO_7S$ [M + NH_4]$^+$ 450.1587, found 450.1587.

Methyl (Phenyl 2-*O*-benzoyl-3-*O*-benzyl-1-thio-L-idopyranoside) uronate (21).[28] To the L-ido thioglycoside **19** (2.71 g, 4.76 mmol) was added diethylether (25 mL) and benzylamine (1.1 mL, 14.3 mmol). After stirring for 3 h the reaction was extracted with EtOAc (100 mL) and HCl aq (1M, 100 mL). The organic phase was separated, dried ($MgSO_4$), filtered and evaporated. The crude material was purified by flash column chromatography (EtOAc/Hexane 1:3). This yielded **21** (1.59 g, 3.21 mmol, 68%, $\alpha\beta$ 3:1) as an oil. Repeated flash column chromatography allowed separation of the anomers.

***β*-21**: R_f 0.35 (EtOAc/hexane 1:2); $[\alpha]_D^{20}$ = +55.2 (c = 0.37, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.21 (d, J = 8.1 Hz, 2H, Ar*H*), 7.74−7.65 (m, 3H, Ar*H*), 7.58 (t, J = 7.5 Hz, 2H, Ar*H*), 7.51−7.37 (m, 8H, Ar*H*), 5.54 (d, J = 0.9 Hz, 1H, H-1), 5.44 (s, 1H, H-5), 4.92 (d, J = 11.8 Hz, 1H, C*H*$_2$Ph), 4.84 (d, J = 11.8 Hz, 1H, C*H*$_2$Ph), 4.75 (s, 1H, H-4), 4.17−4.15 (m, 2H, H-2, H-3), 3.95 (s, 3H, C(O)OC*H*$_3$), 2.69 (brs, 1H, O*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ 169.2, 165.8, 137.4, 134.2, 132.0, 130.4, 129.5, 129.1, 129.0, 128.7, 128.3, 128.2, 85.8, 76.8, 74.9, 73.2, 70.8, 67.9, 52.9.

***α*-21**: R_f 0.32 (EtOAc/hexane 1:2); $[\alpha]_D^{20}$ = −86.7 (c = 1.09, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.03−8.00 (m, 2H, Ar*H*), 7.62−7.56 (m, 3H, Ar*H*), 7.48−7.30 (m, 10H, Ar*H*), 5.79 (s, 1H, H-1), 5.55 (dd, J = 2.7, 1.3 Hz, 1H, H-2), 5.46 (d, J = 1.6 Hz, 1H, H-5), 4.95 (d, J = 11.8 Hz, 1H, C*H*$_2$Ph), 4.74 (d, J = 11.8 Hz, 1H, C*H*$_2$Ph), 4.21 (s, 1H, H4), 3.99 (td, J = 3.0, 1.3 Hz, 1H, H-3), 3.86 (s, 3H, C(O)OC*H*$_3$), 2.92 (s, 1H, O*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ 169.7, 137.0, 133.9, 131.4, 129.8, 129.2, 128.8, 128.7, 128.6, 128.2, 127.8, 127.7, 86.9, 73.5, 72.5, 69.7, 69.1, 68.3, 52; HRMS (TOF-ES$^+$) m/z calcd for $C_{27}H_{26}O_7Na$ [M+Na]$^+$ 517.1297, found 517.1294.

Methyl (Phenyl 2,4-Di-*O*-acetyl-3-*O*-benzyl-1-thio-L-idopyranoside) uronate (22).[28] To the L-ido ester **16** (18.0 g, 42.5 mmol) was added dry dichloromethane (300 mL), thiophenol (6.7 mL, 63.7 mmol) and borontrifluoride diethyl etherate (28 mL, 212 mmol), and the mixture was stirred for 16 h under N_2. The reaction was quenched by adding to a mixture of saturated aqueous $NaHCO_3$ (800 mL) and dichloromethane (500 mL) with stirring. To this mixture was added iodine until a dark red color persisted, indicating all remaining thiophenol had been oxidized to diphenyldisulfide, thus removing all odor from the product mixture. The excess of iodine was reduced to iodide by adding sodium thiosulfate solution (10% aq) dropwise until the dark red color disappeared. The organic phase was separated, dried ($MgSO_4$), filtered, and solvents removed. Purification by flash column chromatography (EtOAc/Hexane 1:2) yielded **22** (12.2 g, 44.4 mmol, 61%, $\alpha\beta$ 2:1) as an oil, along with recovered starting material (1.38 g, 8%): HRMS (FTMS-NSI$^+$) m/z calcd for $C_{24}H_{27}O_8S$ [M + H]$^+$ 475.1421, found 475.1407. ***α*-22**: R_f 0.09 (EtOAc/hexane 1:3); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.55−7.25 (m, 10H, Ph), 5.68−5.67 (m, 1H, H-4), 5.42 (d, J = 2.0 Hz, 1H, H-1), 5.24−5.23 (m, 1H, H-2), 5.18−5.17 (m, 1H, H-5), 4.82 (d, J = 10.0 Hz, 2H, C*H*$_2$Ph), 3.90−3.89 (m, 1H, H-3), 3.81 (s, 3H, OC*H*$_3$), 2.07 (s, 3H, COC*H*$_3$), 2.06 (s, 3H, COC*H*$_3$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 169.8, 169.6, 168.7, 136.9, 135.7, 130.9, 129.1, 128.6, 128.1, 127.7, 127.4, 86.1, 72.7, 71.3, 68.6, 67.9, 67.0, 52.6, 20.9, 20.7.

***β*-22**: R_f 0.11 (EtOAc/hexane 1:3); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.59−7.15 (m, 10H, Ph), 5.20−5.18 (m, 2H, H-1, H-4), 5.12−5.11 (m, 1H, H-2), 4.74 (s, 2H, C*H*$_2$Ph), 4.62 (d, J = 1.5 Hz, 1H, H-5), 3.93 (t, J = 0.7 Hz, 1H, H-3), 3.80 (s, 3H, OC*H*$_3$), 2.13 (s, 3H, COC*H*$_3$), 2.06 (s, 3H, COC*H*$_3$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 170.3, 170.1, 168.1, 137.1, 134.2, 132.3, 129.3, 128.9, 128.6, 128.5, 128.2, 128.2, 125.6, 85.0, 74.6, 73.2, 72.5, 69.3, 67.1, 52.9, 21.1, 21.0.

Phenyl 3,4,6-Tri-*O*-acetyl-2-deoxy-l-thio-2-trichloroacetamido-*β*-D-glucopyranoside (24). 1. D-Glucosamine·HCl (86.4 g, 401 mmol) was suspended in MeOH (1.0 L) at room temperature. Et_3N (112.0 mL, 802 mmol, 2.0 equiv) was added, and the suspension cooled to 0 °C. Trichloroacetyl chloride (45.0 mL, 401 mmol, 1.0 equiv) was then added dropwise. The suspension was warmed to room temperature and stirred for 5 days. The reaction was filtered through a plug of Celite, washing with MeOH, and the solvent removed in vacuo. The crude residue was dissolved in pyridine (800 mL) and cooled to 0 °C. Ac_2O (300 mL) was added dropwise, and the solution allowed to warm to room temperature and stirred for 16 h. The reaction was filtered through a Celite plug, and solvent removed in vacuo, including coevaporation with toluene (3 × 350 mL). The crude material was taken in EtOAc (450 mL) and washed with 1 M HCl (5 × 100 mL), saturated aqueous $NaHCO_3$ (3 × 200 mL), saturated aqueous NaCl (1 × 200 mL), dried ($MgSO_4$), and solvent removed in vacuo to reveal 175.0 g of a brown solid. This was recrystallized from EtOH (1.2 L) to give 71.0 g of product (alpha anomer only). The liquors were reduced in volume in vacuo to produce a second crop of material, 38.0 g (1:1, α/β mixture). Finally the liquors were evaporated to dryness and purified on a short silica plug (eluting with diethyl ether/DCM, 5/95) to give another 30.3 g of product (4:6, α/β mixture) and an overall yield of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-trichloroacetamido-*β*-D-glucopyranose (139.0 g, 282 mmol, 70%). Data for this compound matched those previously reported.[45,46]

2. To 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-trichloroacetamido-*β*-D-glucopyranose (184.4 g, 374 mmol) dissolved in dry DCM (900 mL) at room temperature under nitrogen was added PhSH (50.0 mL, 486 mmol, 1.3 equiv) and (dropwise) TMSOTf (68.0 mL, 374 mmol, 1.0 equiv). The resulting dark red solution was stirred at room temperature for 18 h and then poured onto a vigorously stirred solution of aqueous $NaHCO_3$ (70.0 g in 60 mL H_2O) and stirred for 30 min. I_2 (32.2 g, 131 mmol, 0.35 equiv) was then added, and the solution stirred vigorously for another 30 min. $Na_2S_2O_3$ (41.4 g, 262 mmol, 0.70 equiv) was added, and stirring continued for a final 30 min. The layers were separated, and the aqueous extracted with DCM (1 × 200 mL). The organics were combined, dried ($MgSO_4$), and solvent removed in vacuo afforded crude **24** (220.0 g) as a dark brown solid, which was then recrystallized from hexane/EtOAc (350 mL, 1:1), filtered and washed with cold hexane:EtOAc (150 mL, 2:1) to yield **24** (135.0 g, 67%) as a tan solid. The liquors were stripped and passed through a silica plug (eluting with hexane:EtOAc, 5:1 then 2:1), and solvent removed in vacuo to give a brown solid, recrystallization of which (hexane:EtOAc, 60 mL:120 mL) gave a second batch of **24** (11.6 g, 5%) as a faint tan solid. Overall yield of **24** (146.4 g, 269 mmol, 72%). Data collected for **24** matched those previously reported.[37]

Phenyl 4,6-*O*-Benzylidene-1-thio-*β*-D-glucosaminopyranoside (25). 1. To **24** (101.2 g, 0.186 mol) was added dry MeOH (1 L) and Sodium (0.3 g, 0.013 mol). The mixture was stirred overnight under N_2. Then the reaction was quenched by adding Amberlite strongly acidic resin (3 g) and stirring another 30 min. After filtration and evaporation of solvent phenyl 1-thio-2-trichloroacetamide-*β*-D-glucosaminopyranoside (77.7 g, 0.186 mol, 100%) was obtained in high enough purity to be used in the next step. Data collected matched those previously reported.[47]

2. To phenyl 1-thio-2-trichloroacetamide-*β*-D-glucosaminopyranoside (140.7 g, 0.337 mol) was added dry THF (800 mL), benzaldehyde dimethyl acetal (67 mL, 0.404 mol) and camphorsulfonic acid (4.2 g, 0.017 mol). To the reaction flask was fitted a Dean−Stark collector and condenser. The mixture was heated to mild reflux allowing slow removal of the THF/MeOH azeotrope (100 mL over 2 h). After 2 h the reaction was quenched by addition of NEt_3 (5 mL), and the solvent evaporated. The crude was extracted with EtOAc (1 L)/aq $NaHCO_3$(sat) (1 L), organic phase dried ($MgSO_4$), filtered and

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evaporated. The white solid obtained was recrystallized by dissolving in THF/EtOAc and excess hexane added. This was repeated twice with filtrates to yield phenyl 4,6-*O*-benzylidene-1-thio-2-trichloroacetamide-*β*-D-glucosaminopyranoside (143.7 g, 0.284 mol, 84% over 2 steps). Data collected matched those previously reported.[47] See the Supporting Information for copies of ^{1}H and ^{13}C NMR spectra.

3. To phenyl 4,6-*O*-benzylidene-1-thio-2-trichloroacetamido-*β*-D-glucosaminopyranoside (10.2 g, 20.2 mmol) was added THF (65 mL), MeOH (15 mL) and water (15 mL). Then KOH (3.4 g, 60.7 mmol) in 15 mL water was added with vigorous stirring. After 2 h, brine (200 mL) and THF (150 mL) were added. A gel was formed that could be removed by filtration. The aqueous brine layer was then again extracted with THF (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated. To the crude mixture was added THF (200 mL), the material filtered again and evaporated to yield **25** (7.2 g, 20.0 mmol, 99%) as a white solid. The product could be recrystallized from hot MeOH (300 mL), which upon cooling gave a white cotton-like solid.

3. (Large scale): To phenyl 4,6-*O*-benzylidene-1-thio-2-trichloroacetamido-*β*-D-glucosaminopyranoside (108.3 g, 0.214 mol) was added THF (600 mL), MeOH (150 mL) and water (150 mL). Then was added KOH (36 g, 0.642 mol) in 150 mL of water over 15 min. After 3 h the remixture was extracted with brine (1 L) and THF (1 L, 2 × 500 mL). The combined organic layers were dried with $MgSO_4$, filtered and evaporated. To the crude mixture was added THF (2 L), filtered again and evaporated to give a crude yield of **25** (90.8 g) as a white solid. The product could be recrystallized from hot MeOH (1.5 L), which upon cooling gave a white cotton like solid (33.4 g). The filtrate was evaporated and purified by filtering through a short layer (5 cm) of silica gel in a 1 L funnel using first EtOAc and then EtOAc/MeOH 10:1 also containing NEt_3 1%. This yielded another batch of **25** (29.6 g) and gave a combined yield (63.0 g, 0.175 mol, 82%). Data for **25** matched those reported.[40]

Phenyl 2-Azido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-*α*-D-glucopyranoside (26). D-Glucosamine hydrochloride (24.1 g, 0.112 mol), imidazole-1-sulfonyl azide hydrochloride [**WARNING:** this material is potentially explosive and should be handled with due caution][36] (28.1 g, 0.134 mol), copper sulfate pentahydrate (250 mg, 0.96 mmol) and potassium carbonate (38.0 g, 0.275 mol) were combined and then dissolved in MeOH (500 mL). This mixture was stirred 4 h at room temperature. The solution was filtered, solvent evaporated and then azeotroped with toluene (3 × 300 mL). The crude solid was dissolved in pyridine (100 mL) whereupon significant amounts of insoluble salts were observed. Acetic anhydride (84 mL, 0.90 mol) was added to the solution cooled in an icebath, and the reaction mixture stirred overnight at room temperature. The mixture was concentrated in vacuo and azeotroped with toluene (2 × 300 mL). The residue was then diluted with EtOAc (35 mL), washed with water (15 mL), the organic layer dried ($MgSO_4$), and solvents removed in vacuo. Purification of this residue by flash column chromatography (EtOAc/hexane gradient 1:3 and then 1:2) afforded 1,3,4,6-tetra-*O*-acetyl-2-azido-2-deoxy-*α̃*D-glucopyranoside (39.1 g, 0.105 mol, 94%) as a yellow solid. It could be recrystallized from hot EtOH. Data collected matched those previously reported.[41] To a solution of 1,3,4,6-tetra-*O*-acetyl-2-azido-2-deoxy-*α̃*D-glucose (37.3 g, 0.100 mmol) in dry DCM (300 mL), under anhydrous conditions, was added thiophenol (15.0 mL, 0.147 mol) and TMSOTf (5.4 mL, 0.030 mol). The reaction mixture was stirred under N_2 at room temperature for 6 days. Then the reaction was quenched with NEt_3 (5 mL), and solvent evaporated. Flash column chromatography (EtOAc/hexane 1:3) gave **26** (27.1 g, 64.0 mmol, 64%) along with starting material (8.0 g, 21% recovery). The product was recrystallized from hot ethanol. Data collected for **26** matched those previously reported.[48]

Phenyl 2-Azido-2-deoxy-1-thio-D-glucopyranoside (27). ***β*-27**: Triacetate **24** (100.0 g, 184 mmol) was suspended in MeOH (900 mL) at room temperature. K_2CO_3 (127.0 g, 920 mmol, 5.0 equiv) in H_2O (100 mL) was added, and the mixture heated at 60 °C for 18 h. The reaction was cooled, filtered and washed with MeOH (300 mL). To this solution was then added further K_2CO_3 (26.7 g, 193 mmol, 1.05 equiv). The diazo transfer reagent imidazole-1-sulfonyl azide hydrochloride[36] (40.4 g, 193 mmol, 1.05 equiv) was then added in four portions over 40 min followed by $Cu^{II}SO_4$ (459 mg, 1.8 mmol, 0.01 equiv). The suspension was stirred for 2 h at room temperature. The reaction was filtered, and MeOH removed in vacuo. H_2O (200 mL) was added, and the pH adjusted to 3 with 1 M HCl. The aqueous phase was extracted with EtOAc (3 × 300 mL), and the combined organics washed with saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried ($MgSO_4$), and solvent removed in vacuo to reveal the required azido-triol ***β*-27** (50.3 g, 169 mmol, 92%) as a pale yellow solid. Data collected for ***β*-27** matched reported data.[41]

***α*-27**: To **26** (16.8 g, 0.040 mol) was added dry MeOH (200 mL) and sodium (0.1 g, 4.3 mmol). The mixture was stirred 90 min under N_2. Then the reaction was quenched by adding Amberlite strongly acidic resin (1 g) and stirring another 30 min. After filtration and evaporation of solvent ***α*-27** (11.6 g, 39.0 mmol, 100%) was obtained in high enough purity to be used in the next step. Data collected for ***α*-27** matched those reported.[38]

Phenyl 2-Azido-4,6-*O*-benzylidene-3-*O*-benzyl-2-deoxy-1-thio-*β*-D-glucopyranoside (*β*-28). *Method A.* Triol **27** (110.0 g, 370 mmol) was dissolved in MeCN (1100 mL) at ambient temprature and benzaldehyde dimethylacetal (66.6 mL, 444 mmol, 1.2 equiv) and *p*-TsOH (3.2 g, 19 mmol, 0.05 equiv) added, and the reaction stirred for 72 h. To the reaction mixture was added Et_3N (5 mL), and the solvents removed in vacuo. The residue was recrystallized from propan-2-ol (1.1 L), affording pure benzylidine acetal (94.8 g, 66%). The reduced mother liquors were purified through a short silica plug (eluting with hexane/EtOAc, 9/3, 3/1) to provide, when combined with the recrystallized material, the required benzylidine acetal (104.8 g, 272 mmol, 78%). To this 3-OH intermediate (48 g, 125 mmol) dissolved in THF (500 mL) at ambient temperature was added NaH (5.5 g, 138 mmol, 1.1 equiv) over 30 min, and the reaction stirred for 1 h. Benzyl bromide (16.4 mL, 138 mmol, 1.1 equiv) was then added, and the mixture heated at 50 °C for 3 h, over which period a precipitate formed. The reaction was cooled and quenched by addition of water (5 mL), the solvents removed in vacuo, and the residue taken up into ethyl acetate (300 mL) and water (200 mL), the organics separated, washed with brine (100 mL), dried ($MgSO_4$), and solvents removed in vacuo to yield a tan solid. Recrystallization from ethyl acetate:hexane, and washing the resulting product with neat hexane, yielded ***β*-28** as a tan solid (51.7 g, 109 mmol, 87%).

Method B. To **25** (7.4 g, 20.6 mmol) was added THF (20 mL), MeOH (80 mL), K_2CO_3 (4.27 g, 30.9 mmol), imidazole-1-sulfonyl azide hydrochloride (5.18 g, 24.7 mmol) and $CuSO_4{\cdot}5H_2O$ (52 mg, 0.21 mmol). The mixture was stirred for 5 h and extracted with DCM (200 mL) and H_2O (2 × 200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. After evaporation of solvent the crude was purified by flash column chromatography using EtOAc/Hexane 1:4 as the eluent. This yielded phenyl 2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-*β*-D-glucopyranoside (7.45 g, 0.019 mmol, 94%) as a white solid.

(**Large scale**): **1.** To **25** (43.5 g, 0.121 mol) was added MeOH (700 mL), K_2CO_3 (25 g, 0.18 mol), imidazole-1-sulfonyl azide hydrochloride (30.3 g, 0.145 mol) and $CuSO_4{\cdot}5H_2O$ (150 mg, 0.60 mmol). The mixture was stirred for 16 h, and more reagents added (K_2CO_3 (5 g, 0.036 mol), imidazole-1-sulfonyl azide hydrochloride (6.0 g, 0.024 mol) and $CuSO_4{\cdot}5H_2O$ (30 mg, 0.12 mmol)). After another 2 h the solvent was evaporated, and the crude extracted with EtOAc (1.5 L) and H_2O (1 L). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude was purified by filtering through a short layer (3 cm) of silica gel in a 1 L funnel using first DCM and then DCM/EtOAc 20:1). The product was further purified by crystallization. It was dissolved in the minimum amount of EtOAc (230 mL) and adding hexane (800 mL). This yielded phenyl 2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-*β*-D-glucopyranoside (33.1 g, 0.86 mmol, 70%) as a white solid.

2. To phenyl 2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-*β*-D-glucopyranoside (36.0 g, 0.094 mol) was added dry THF (350 mL), benzyl bromide (12.2 mL, 0.103 mol), and then NaH (60% in mineral oil) (4.1 g, 0.103 mol) was added in portions over 60 min (**NOTE**: Exothermic reaction and hydrogen liberated) while being kept under

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N_2. The mixture was then heated to 50 °C for 12 h. The reaction (at room temperature) was quenched by careful addition of MeOH (25 mL) followed by water (5 mL). The solvent (containing precipitated NaBr) was evaporated and extracted with DCM (500 mL)/H_2O (500 mL) and brine (300 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude was purified by eluting through a short layer (5 cm) of silica gel in a 1 L funnel using DCM. This yielded **β-28** (42.4 g, 0.089 mol, 95%). Data collected for the intermediate benzylidine acetal and **β-28** matched those previously reported.[17]

Phenyl 2-Azido-3-*O*-benzyl-2-deoxy-4,6-*O*-*p*-methoxybenzylidene-1-thio-α-D-glucopyranoside (α-29). 1. To **α-27** (15.2 g, 0.051 mol) was added dry CH_3CN (160 mL), anisaldehyde dimethyl acetal (11.2 mL, 0.061 mol) and camphorsulfonic acid (777 mg, 2.55 mmol). After stirring 16 h the reaction was quenched by addition of NEt_3 (1 mL), and the solvent evaporated. The crude was extracted with DCM (300 mL)/aq $NaHCO_3$(sat) (300 mL), organic phase dried ($MgSO_4$), filtered and evaporated. The product was purified by flash column chromatography (EtOAc/hexane 1:3 containing 10% DCM) yielding Phenyl 2-azido-2-deoxy-4,6-*O*-*p*-methoxybenzylidene-1-thio-α-D-glucopyranoside (20.2 g, 48.7 mmol, 90%) as a white solid. It could be recrystallized by dissolving in minimum amount EtOAc and adding 4 times the volume hexane.[42]

2. To phenyl 2-azido-2-deoxy-4,6-*O*-*p*-methoxybenzylidene-1-thio-α-D-glucopyranoside (20.3 g, 0.049 mol) was added dry DMF (150 mL), benzyl bromide (6.5 mL, 0.054 mol) and then NaH (60% in mineral oil) (2.36 g, 0.059 mol) was added in 3 portions over 30 min (**NOTE**: Exothermic reaction and gas liberated) while being kept under N_2. The mixture was stirred for 5 h. The reaction (at room temperature) was quenched by careful addition of EtOH (1 mL) followed by water (150 mL). At this stage heavy precipitation was observed, and the solid was filtered off and washed with water (3 × 100 mL) and hexane (3 × 100 mL). After drying in the air the residue was recrystallized from hot EtOH (1 L) to yield **α-29** (20.7 g, 0.041 mol, 84%) as a white solid. Data collected matched those previously reported.[42]

Phenyl 2-Azido-2-deoxy-3,6-*O*-dibenzyl-1-thio-β-D-glucopyranoside (β-30). To **β-28** (18.0 g, 0.038 mol) was added dry DCM (200 mL), while keeping under N_2 and cooled to 0 °C using an icebath. Then first triethylsilane (18.2 mL, 0.114 mol) was added followed by $BF_3{\cdot}OEt_2$ (14.5 mL, 0.114 mol) over 5 min. The mixture was stirred at 0 °C for 4 h and then quenched by pouring into sat. $NaHCO_3$ (400 mL) and DCM (200 mL) (**NOTE**: Gas liberated). The phases were separated, the organic layer dried ($MgSO_4$), filtered and evaporated. The crude was purified by flash column chromatography (EtOAc/hexane gradient 1:4, 1:3, 1:0) to yield **β-30** (14.1 g, 0.030 mol, 84%). Starting material was also recovered (2.2 g, 12%), and two more polar products identified as phenyl 2-azido-3-*O*-benzyl-4-*O*-benzyl-2-deoxy-1-thio-β-D-glucopyranoside (0.40 g, 2%) and phenyl 2-azido-3-*O*-benzyl-2-deoxy-1-thio-β-D-glucopyranoside (0.99 g, 7%). Data collected matched those previously reported.[38]

Phenyl 2-Azido-3-*O*-benzyl-2-deoxy-4-*O*-*p*-methoxybenzyl-1-thio-α-D-glucopyranoside (α-31). Derivative **α-29** (16.7 g, 0.033 mol) was dissolved in 1 M $BH_3{\cdot}$THF in THF (100 mL, 0.10 mmol) cooled to 0 °C. Then 1 M Bu_2BOTf in DCM (34 mL, 0.034 mol) was added over 40 min, and the reaction mixture stirred a further 1 h before being quenched with triethylamine (5 mL), followed by slow addition of methanol (**NOTE**: Hydrogen being liberated). The solvents were evaporated and then azeotroped with methanol (2 × 100 mL) to remove borate esters. The residue was purified by flash column chromatography (EtOAc/hexane 1:3) to yield **α-31** (12.48 g, 0.025 mol, 74%) as a clear gum. Data collected matched those previously reported.[42]

Phenyl 2-Azido-3-*O*-benzyl-2-deoxy-1-thio-β-D-glucopyranoside (β-32).[24] Benzylidine glucoside **β-28** (43.3 g, 91.0 mmol) was suspended in 60% aq AcOH (400 mL). The suspension was then heated to 100 °C whereupon the substrate went into solution. The reaction temperature was maintained at 100 °C for 3 h, cooled and then cautiously poured onto a solution of aqueous $NaHCO_3$ (400 g in 1 L H_2O). The solution was then extracted with EtOAc (3 × 200 mL), the organics combined, dried ($MgSO_4$), and solvent removed in vacuo to yield the crude material as a yellow oil. This was purified on a silica plug (eluting with EtOAc/hexane, 3/1, 1/1) to yield **β-32** (29.8 g, 77.0 mmol, 83%) as a white solid. Data recorded for this compound matched those in the literature.[24]

Phenyl 2-Azido-6-*O*-benzoyl-3-*O*-benzyl-2-deoxy-1-thio-β-D-glucopyranoside (β-33). Glucoside diol **β-32** (3.30 g, 8.5 mmol) was dissolved in dry DCM (30 mL) at room temperature under N_2. Et_3N (1.3 mL, 9.4 mmol, 1.1 equiv) was added, and the solution cooled to 0 °C. BzCl (987 μL, 8.5 mmol, 1.0 equiv) was added, and the reaction warmed to room temperature over 30 min. The reaction was poured onto 1 M HCl (50 mL), and the layers separated. The organics were washed with saturated aqueous $NaHCO_3$ (20 mL), saturated aqueous NaCl (20 mL), dried ($MgSO_4$), and solvent removed in vacuo to provide a white solid. This was slurried in Et_2O and filtered to give **β-33** (3.81 g, 7.8 mmol, 91%) as a fluffy white solid: $[\alpha]_D^{20}$ = −50.0 (*c* = 0.07, DCM); mp 152−155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10−8.07 (m, 2H, Ar*H*), 7.67−7.59 (m, 3H, Ar*H*), 7.52−7.48 (m, 2H, Ar*H*), 7.41−7.26 (m, 6H, Ar*H*), 7.21−7.17 (m, 2H, Ar*H*), 4.94 (d, *J* = 10.9 Hz, 1H, CH_2Ph), 4.84 (d, *J* = 10.9 Hz, 1H, CH_2Ph), 4.75 (dd, *J* = 12.2, 3.9 Hz, 1H, H-6), 4.60 (dd, *J* = 12.2, 2.1 Hz, 1H, H-6′), 4.49 (d, *J* = 9.6 Hz, 1H, H-1), 3.59 (ddd, *J* = 9.7, 3.9, 2.1 Hz, 1H, H-5), 3.52 (ddd, *J* = 9.6, 8.9, 3.4 Hz, 1H, H-4), 3.42 (dd, *J* = 9.6, 8.9 Hz, 1H, H-3), 3.31 (t, *J* = 9.6, 8.9 Hz, 1H, H-2), 2.82 (d, *J* = 3.4, 1H, O*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ 168.8, 139.4, 135.7, 135.3, 132.4, 131.6, 131.2, 130.7, 130.5, 130.3, 130.3, 130.11, 130.1, 87.6, 86.0, 79.7, 77.5, 71.5, 66.2, 65.0; ES MS *m*/*z* 514 [M + Na]$^+$; HRMS (TOF-ES$^+$) *m*/*z* calcd for $C_{26}H_{25}N_3O_5SNa$ [M + Na]$^+$ 514.1408, found 514.1400.

Phenyl 2-Azido-2-deoxy-3,6-di-*O*-benzyl-4-*O*-*p*-methoxybenzyl-1-thio-β-D-glucopyranoside (β-34). To **β-30** (25.2 g, 0.053 mol) was added dry THF (300 mL), *p*-methoxybenzyl chloride (11.5 mL, 0.085 mol), and then NaH (60% in mineral oil) (3.1 g, 0.078 mol) was added in portions over 60 min (**NOTE**: Exothermic reaction and gas liberated) while being kept under N_2. The mixture was then heated to 60 °C for 36 h. The reaction (at room temperature) was quenched by careful addition of MeOH (25 mL) followed by water (5 mL). The solvent (containing precipitated NaCl) was evaporated and extracted with DCM (500 mL)/H_2O (500 mL) and brine (300 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The product was purified by flash column chromatography (EtOAc/hexane gradient 1:6, 1:4) yielding **β-34** (29.3 g, 0.049 mol, 93%). Data collected matched those previously reported.[38]

Phenyl 2-Azido-2-deoxy-3,6-di-*O*-benzyl-4-*O*-trichloroacetyl-1-thio-β-D-glucopyranoside (β-35). Glucoside **β-30** (17.2 g, 36.0 mmol) was dissolved in dry DCM (150 mL) at room temperature under N_2. Et_3N (5.30 mL, 38.0 mmol, 1.05 equiv) was added, and the solution cooled to 0 °C. Trichloroacetyl chloride (4.23 mL, 38.0 mmol, 1.05 equiv) was added, and the pale yellow solution stirred at room temperature for 2 h. The reaction was then poured onto 1 M HCl (100 mL), and the layers separated. The organics were washed with saturated aqueous $NaHCO_3$ (50 mL), saturated aqueous NaCl (50 mL), dried ($MgSO_4$), and solvent removed in vacuo to give the crude as a yellow gum. This was purified by passage through a short plug of silica gel, eluting with hexane/EtOAc, 15/1 to give **β-35** (20.8 g, 33.4 mmol, 92%) as a yellow solid: ^{1}H NMR (400 MHz; $CDCl_3$) δ ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.52−7.47 (m, 2H, Ar*H*), 7.31−7.13 (m, 13H, Ar*H*), 5.07 (t, *J* = 9.6 Hz, 1H, H-4), 4.71 (d, *J* = 10.4 Hz, 1H, CH_2Ph), 4.64 (d, *J* = 10.4 Hz, 1H, CH_2Ph), 4.46 (s, 2H, CH_2Ph), 4.39 (d, *J* = 10.1 Hz, 1H, H-1), 3.63 (ddd, *J* = 10.4, 4.9, 2.7 Hz, 1H, H-5), 3.58−3.50 (m, 3H, H-3, H-6, H-6′), 3.35 (dd, *J* = 10.0, 9.4 Hz, 1H, H-2). ^{13}C NMR (100 MHz; $CDCl_3$) δ 160.6, 137.6, 136.9, 133.8, 130.5, 129.2, 128.7, 128.6, 128.5, 128.2, 128.0, 127.8, 89.6, 86.2, 82.1, 77.0, 75.8, 75.0, 73.7, 68.5, 64.8; MS ES$^+$ *m*/*z* 644 [M + Na]$^+$; HRMS (TOF-ES$^+$) *m*/*z* calcd for $C_{28}H_{26}N_3O_5NaSCl_3$ [M + Na]$^+$ 644.0551, found 644.0545.

Phenyl 2-Azido-6-*O*-benzoyl-3-*O*-benzyl-2-deoxy-1-thio-4-trichloroacetyl-β-D-glucopyranoside (β-36). To **β-33** (24.8 g, 50.5 mmol) dissolved in dry DCM (250 mL) at room temperature under N_2 was added Et_3N (7.40 mL, 53.0 mmol, 1.05 equiv) and

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trichloroacetyl chloride (5.90 mL, 53.0 mmol, 1.05 equiv), and the pale yellow solution stirred at room temperature for 5 h. The reaction was then poured onto 1 M HCl (100 mL), and the layers separated. The organics were washed with saturated aqueous $NaHCO_3$ (50 mL), saturated aqueous NaCl (50 mL), dried ($MgSO_4$), and solvent removed in vacuo to give the crude as a brittle yellow solid. This was slurried in Et_2O and filtered to give phenyl-2-azido-6-*O*-benzoyl-3-*O*-benzyl-2-deoxy-1-thio-4-trichloroacetyl-*β*-D-glucopyranoside (24.3 g) as a white solid. The remaining liquors were purified by silica gel flash chromatography (eluting with hexane/EtOAc, 8/1) to give a further 5.2 g of product as a white solid, providing ***β*-36** (29.5 g, 46.3 mmol, 92%): $[\alpha]_D^{20}$ = −37.6 (*c* = 0.06, DCM); mp 117−119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.00−7.97 (m, 2H, Ar*H*), 7.57−7.53 (m, 1H, Ar*H*), 7.48−7.39 (m, 4H, Ar*H*), 7.29−7.16 (m, 6H, Ar*H*), 7.06−7.01 (m, 2H, Ar*H*), 5.15 (t, *J* = 9.7 Hz, 1H, H-4), 4.77−4.66 (m, 3H, C*H*$_2$Ph, H-6′), 4.42 (d, *J* = 10.1 Hz, 1H, H-1), 4.25 (dd, *J* = 12.5, 4.3, 1H, H-6), 3.84 (ddd, *J* = 9.7, 4.3, 2.1 Hz, 1H), 3.63 (t, *J* = 9.3 Hz, 1H, H-3), 3.36 (dd, *J* = 10.1, 9.7 Hz, 1H, H-2); ^{13}C NMR (100 MHz; $CDCl_3$) *δ* 165.9, 160.7, 136.6, 134.5, 133.5, 129.9, 129.6, 129.4, 129.1, 129.0, 128.7, 128.6, 128.37, 128.2, 89.4, 85.9, 81.9, 76.1, 75.5, 74.2, 64.6, 61.9; ES MS *m*/*z* 658/660 $[M + Na]^+$; HRMS (TOF-ES$^+$) *m*/*z* calcd for $C_{28}H_{24}N_3O_6SCl_3Na$ $[M + Na^+]$ 658.0344, found 658.0328.

Phenyl 6-*O*-Acetyl-2-azido-3-*O*-benzyl-2-deoxy-1-thio-4-*p*-methoxybenzyl-*α*-D-glucopyranoside (*α*-37).[42] To a stirred solution of ***α*-31** (6.7 g, 13.12 mmol) in dry DCM (75 mL) and pyridine (2.1 mL) at 0 °C was added dropwise acetic anhydride (1.9 mL, 19.8 mmol) followed by catalytic amount of *N*,*N*-dimethylaminopyridine. The cooling was removed and stirred for another 2 h. Then solvents were evaporated, and the residue was diluted with DCM (250 mL) and washed with $NaHCO_3$ and brine. The product was purified by flash column chromatography (EtOAc/hexane 1:4) yielding ***α*-37** (10.7 g, 99%): MS ES$^+$ $[M + Na]^+$ *m*/*z* 571.1. See the Supporting Information for copies of ^{1}H and ^{13}C NMR spectra.

Phenyl 2-Azido-6-*O*-benzoyl-3-*O*-benzyl-2-deoxy-1-thio-4-*O*-*p*-methoxybenzyl-*α*-D-glucopyranoside (*α*-38). To a stirred solution of ***α*-31** (8.5 g, 0.017 mol) in dry DCM (100 mL) and pyridine (1.5 mL, 0.018 mol) was added dropwise benzoyl chloride (2.2 mL, 0.018 mol) followed by catalytic amount of *N*,*N*-dimethylamino pyridine (42 mg, 0.34 mmol). The mixture was stirred for 4 h, more DCM (200 mL) added, extracted with water (300 mL) and sat. $NaHCO_3$ (200 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated. The white solid obtained could be recrystallized by dissolving in minimum amount EtOAc (50 mL) and hexane added (250 mL) yielding ***α*-38** (9.6 g, 94%) as large white needles: mp = 115−116 °C; $[\alpha]_D^{20}$ = +163.0° (*c* = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 7.97−7.94 (m, 2H, aromatic), 7.59−7.55 (m, 1H, Ar*H*), 7.49−7.32 (m, 9H, Ar*H*), 7.23−7.18 (m, 5H, Ar*H*), 6.84−6.80 (m, 2H, Ar*H*), 5.61 (d, 1H, H-1, *J* = 5.2 Hz), 4.98 (d, 1H, benzylic CH^a, *J* = 10.4 Hz), 4.93 (d, 1H, benzylic CH^b, *J* = 10.4 Hz), 4.84 (d, 1H, H-6a, *J* = 10.4 Hz), 4.59−4.54 (m, 2H, H-5, H-6b), 4.52−4.47 (m, 2H), 3.98 (dd, 1H, H-2, *J* = 5.2, 10.0 Hz), 3.89 (dd, 1H, H-3, *J* = 8.4, 10.0 Hz), 3.74 (s, 3H), 3.68 (dd, 1H, H$_4$, *J* = 8.4, 9.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 166.1, 159.5, 137.6, 133.0, 132.5, 129.8, 129.7, 129.2, 128.6, 128.1, 128.0, 127.9, 114.0, 87.1, 81.7, 77.6, 75.8, 74.8, 72.5, 70.3, 64.1, 63.2, 55.2; HRMS (TOF-ES$^+$) *m*/*z* calcd for $C_{34}H_{33}N_3O_6SNa$ $[M + Na^+]$ 634.1988, found 634.1980; Elemental analysis calcd (%) for $C_{34}H_{33}N_3O_6S$, C 66.76, H 5.44, N 6.87, found C 66.37, H 5.79, N 6.86.

2-Azido-3,6-di-*O*-benzyl-2-deoxy-4-*O*-*p*-methoxybenzyl-*α̃β*-D-glucopyranose (39).[43a] To ***β*-34** (20.1 g, 0.034 mol) was added acetone (600 mL), and the mixture was cooled to 0 °C in an icebath. Then was added *N*-bromosuccinimide (6.0 g, 0.034 mol), and the mixture was stirred for 30 min. The reaction was quenched by addition of saturated $NaHCO_3$ solution (15 mL), the acetone evaporated and DCM (300 mL), and water (300 mL) added. The organic phase was separated, dried ($MgSO_4$), filtered and evaporated. The crude was purified using flash column chromatography (EtOAc/hexane 1:3), followed by recrystallization by dissolving in EtOAc (50 mL) and adding hexane (300 mL). This yielded the product **39** (14.5 g, 0.029 mmol, 85%) as a white solid: MS ES $[M + Na]^+$ *m*/*z* 528. See the Supporting Information for copies of ^{1}H and ^{13}C NMR spectra.

2-Azido-3,6-di-*O*-benzyl-2-deoxy-4-trichloroacetyl-*α̃β*-D-glucopyranose (40). To ***β*-35** (11.66 g, 18.7 mmol) was added acetone (300 mL), and the mixture cooled to 0 °C in an icebath. *N*-bromosuccinimide (3.5 g, 19.4 mmol) was then added. After 40 min another portion of *N*-bromosuccinimide (1.26 g, 7.0 mmol) was added. After 2 h the solvent was evaporated, and the mixture extracted with DCM (200 mL) and water (200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude mixture was purified by flash column chromatography using EtOAc/hexane (1:4) as the eluent to yield **40** (8.89 g, 16.7 mmol, 89%) as a white solid. The product could be recrystallized by dissolving in minimum amount of EtOAc and adding 4 times the volume of hexane giving a white cotton like solid: R_f 0.24 (EtOAc/hexane 1:3); mp 131−132 °C; MS ES $[M + Na]^+$ *m*/*z* 552.0; HRMS (FTMS-NSI$^+$) *m*/*z* calcd for $C_{22}H_{22}N_3O_6Cl_3Na$ $[M + Na]^+$ 552.0467, found 554.0462. See the Supporting Information for copies of ^{1}H and ^{13}C NMR spectra.

2-Azido-6-*O*-benzoyl-3-*O*-benzyl-2-deoxy-4-trichloroacetyl-*α̃β*-D-glucopyranose (41). To ***β*-36** (15.0 g, 24.0 mmol) dissolved in Me_2CO (160 mL) at room temperature was added NBS (6.4 g, 36.0 mmol, 1.5 equiv), and the pale yellow solution stirred for 2 h at room temperature. TLC analysis (hexane/EtOAc, 3:1) showed the reaction to be incomplete, and further NBS (1.0 equiv) was added, and stirring continued for another 2 h. Saturated aqueous $NaHCO_3$ (4 mL) was added, and the solvents removed in vacuo. The crude residue was taken up in EtOAc (100 mL) and washed with saturated aqueous $NaHCO_3$ (50 mL), dried ($MgSO_4$), solvents removed in vacuo, and the residue purified by silica gel flash chromatography (eluting with hexane/EtOAc, 5:1 → 3:1) to give the intermediate 1-OH glucoazide, **41** (7.6 g, 14.0 mmol, 59%) as a yellow gum which was used immediately: MS ES$^+$ *m*/*z* 566 $[M + Na]^+$; HRMS (FTMS-NSI$^+$) *m*/*z* calcd for $C_{22}H_{24}N_4O_7SCl_3$ $[M + NH_4]^+$ 561.0705, found 561.0706. See the Supporting Information for copy of ^{1}H NMR spectrum.

6-*O*-Acetyl-2-azido-3-*O*-benzyl-2-deoxy-4-*p*-methoxybenzyl-*α̃β*-D-glucopyranose (42).[43b] To ***α*-37** (7.0 g, 12.7 mmol) was added acetone (85 mL), and the mixture was cooled to 0 °C in an ice bath. Then was added *N*-bromosuccinimide (2.38 g, 13.4 mmol), and the mixture was stirred for 30 min. The reaction was quenched by addition of saturated $NaHCO_3$ solution (5 mL), the acetone evaporated, and DCM (200 mL) and water (200 mL) added. The organic phase was separated, dried ($MgSO_4$), filtered and evaporated. The crude was purified using flash column chromatography (EtOAc/hexane 1:3). This yielded the product **42** (4.87 g, 10.7 mmol, 84%) as a white solid. The product could be recrystallized by dissolving in minimum amount of EtOAc and adding 5 times the volume of hexane: MS ES $[M + Na]^+$ *m*/*z* 480. See the Supporting Information for copies of ^{1}H and ^{13}C NMR spectra.

2-Azido-6-*O*-benzoyl-3-*O*-benzyl-2-deoxy-4-*O*-*p*-methoxybenzyl-*α̃β*-D-glucopyranose (43). To a solution of ***α*-38** (1.5 g, 2.45 mmol) in acetone (20 mL) at 0 °C was added NBS (437 mg, 2.46 mmol), and the solution was left stirring at 0 °C for 40 min and then quenched with saturated $NaHCO_3$ solution followed by evaporation of solvents. The crude was redissolved into DCM (100 mL) and was washed with saturated aqueous $NaHCO_3$ and brine. The organics were dried ($MgSO_4$), filtered and evaporated in vacuo to yield a yellow gum, which was purified by column chromatography (hexane:EtOAc, 3:1) to give the intermediate **43** as a white powder (1.10 g, 2.12 mmol, 87%): HRMS (TOF-ES$^+$) *m*/*z* calcd for $C_{28}H_{29}N_3O_7Na$ $[M + Na^+]$ 542.1898, found 542.1909. See the Supporting Information for copies of ^{1}H and ^{13}C NMR spectra.

2-Azido-3,6-di-*O*-benzyl-2-deoxy-4-*O*-*p*-methoxybenzyl-1-*O*-trichloroacetimidate-*α̃β*-D-glucopyranoside (44).[43a] The derivative **39** (8.46 g, 16.7 mmol) was dissolved in dry DCM (100 mL) and to this was added trichloroacetonitrile (8.5 mL, 85 mmol) and DBU (0.12 mL, 0.84 mmol) while being kept under N_2. The mixture was stirred 90 min, solvents were then evaporated, and the product immediately purified by flash column chromatography (EtOAc/hexane 1:3 + 1% triethylamine) to yield **44** (10.8 g, 16.6 mmol, 99%) as sticky oil. This compound was used immediately for glycosylation.

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2-Azido-3,6-di-*O*-benzyl-2-deoxy-4-*O*-trichloroacetyl-1-*O*-trichloroacetimidate-α̃β-D-glucopyranoside (45). To **40** (8.52 g, 16.0 mmol) was added dry DCM (100 mL), CCl_3CN (8 mL, 80 mmol) and sodium hydride 60% (64 mg, 1.6 mmol). The solution was stirred for 45 min, the solvent was evaporated and purified by flash column chromatography using EtOAc/hexane (1:6 + 1% NEt_3) as the eluent. This yielded **45** (8.10 g, 12.0 mmol, 75%) as a white solid: MS ES^+ *m/z* 566 $[M + Na]^+$; HRMS (FTMS-NSI$^+$) *m/z* calcd for $C_{24}H_{22}N_4O_6Cl_6Na$ $[M + Na]^+$ 694.9563, found 694.9559. See the Supporting Information for copy of ^1H NMR spectrum.

2-Azido-6-*O*-benzoyl-3-*O*-benzyl-2-deoxy-4-*O*-trichloroacetyl-1-*O*-trichloroacetimidate-α̃β-D-glucopyranoside (46). The intermediate **41** (5.4 g, 9.9 mmol) was dissolved in dry DCM (50 mL) under N_2. Trichloroacetonitrile (5.0 mL, 50.0 mmol, 5.0 equiv) and NaH (40 mg, 0.1 mmol, 0.1 equiv) were added, and the reaction stirred for 1.5 h. Solvent was removed in vacuo, and the crude brown solid slurried in hexane/EtOAc, 5/1 and filtered. This gave the β-anomer of **46** (2.29 g). The remaining liquors were purified by silica gel flash chromatography (hexane/EtOAc, 5:1 +1% Et_3N) to give the α-anomer (3.17 g), affording a total yield for **46** (5.46 g, 7.9 mmol, 80%). For **β-46**: ^1H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H, N*H*), 8.07 (d, *J* = 8.4 Hz, 2H, ArH), 7.60 (t, *J* = 7.4 Hz, 1H, ArH), 7.48 (t, *J* = 7.4 Hz, 2H, ArH), 7.40−7.33 (m, 5H, ArH), 5.77 (d, *J* = 8.4 Hz, 1H, H_1), 5.42 (dd, *J* = 9.6 Hz, 1H, H_4), 4.91 (d, *J* = 10.6 Hz, 1H, C*H*$_2$Ph), 4.81 (d, *J* = 10.6 Hz, 1H, C*H*$_2$Ph), 4.66 (dd, *J* = 12.6, 2.3 Hz, 1H, $H_{6'}$), 4.42 (dd, *J* = 12.6, 4.5 Hz, 1H, H_6), 4.08 (ddd, *J* = 9.6, 4.5, 2.3 Hz, 1H, H_5), 3.89 (dd, *J* = 8.4, 9.6 Hz, 1H, H_2), 3.78 (dd, *J* = 9.6 Hz, 1H, H_3); For **α-46**: ^1H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H, N*H*), 8.06−8.02 (m, 2H, ArH), 7.62−7.58 (m, 1H, ArH), 7.49−7.45 (m, 2H, ArH), 7.40−7.32 (m, 6H, ArH), 6.53 (d, *J* = 3.6 Hz, 1H, H_1), 5.47 (dd, *J* = 10.1, 9.4 Hz, 1H), 4.91−4.84 (m, 2H, C*H*$_2$Ph), 4.66−4.62 (m, 1H), 4.43−4.36 (m, 2H), 4.19 (t, *J* = 9.7 Hz, 1H), 3.89 (dd, *J* = 10.0, 3.6 Hz, 1H, H_2).

6-*O*-Acetyl-2-azido-3-*O*-benzyl-2-deoxy-4-*p*-methoxybenzyl-α̃β-D-glucopyranose (47). The derivative **42**[43b] (182 mg, 0.398 mmol) was dissolved in dry DCM (3 mL), and to this was added trichloroacetonitrile (0.2 mL, 1.99 mmol) and DBU (0.05 mL, 0.04 mmol) while being kept under N_2. The mixture was stirred 3 h, and solvents were then evaporated, and the product immediately purified by flash column chromatography (EtOAc/hexane 1:3 + 1% triethylamine) to yield **47** (213 mg, 0.35 mmol, 89%) as a sticky oil. This compound was used immediately for glycosylation.

2-Azido-6-*O*-benzoyl-3-*O*-benzyl-2-deoxy-4-*O*-*p*-methoxybenzyl-1-*O*-trichloroacetimidate-α̃β-D-glucopyranoside (48). The derivative **43** (3.26 g, 6.28 mmol) was dissolved in DCM (20 mL), and to this was added trichloroacetonitrile (3.78 mL, 37.68 mmol) and DBU (4 drops). The mixture was stirred at rt for 2 h, solvents were then evaporated, and the product immediately purified by column chromatography (3:1 hexane:ethyl acetate +1% triethylamine) to yield **48** (3.27 g, 4.93 mmol, 79%) as a mixture of anomers: ^1H NMR α-anomer ($CDCl_3$, 400 MHz) δ 8.72 (s, 1H, NH), 7.98−7.95 (m, 2H, Ar*H*), 7.92−7.54 (m, 1H, Ar*H*), 7.45−7.36 (m, 7H, Ar*H*), 7.21−7.19 (m, 2H, Ar*H*), 6.80−6.78 (m, 2H, Ar*H*), 6.42 (d, 1H, H_1, *J* = 3.6 Hz), 5.00−4.94 (dd, 2H, *J* = 10.4, 14.0 Hz), 4.82 (d, 1H, *J* = 10.4 Hz), 4.57 (d, 1H, *J* = 10.4 Hz), 4.54−4.45 (m, 2H, C_6, CH_2), 4.18−4.14 (m, 1H, H_5), 4.14−4.07 (m, 2H), 3.81−3.76 (dd, 1H, H_3), 3.72 (s, 3H); ^1H NMR β anomer ($CDCl_3$, 400 MHz) δ 8.70 (s, 1H, NH), 8.00−7.97 (m, 2H, Ar*H*), 7.85−7.54 (m, 1H, Ar*H*), 7.43−7.35 (m, 7H, Ar*H*), 7.18−7.16 (m, 2H, Ar*H*), 6.79−6.77 (m, 2H, Ar*H*), 5.64 (d, 1H, H_1, *J* = 8.4 Hz), 4.97−4.87 (dd, 2H, *J* = 10.8, 2.6 Hz), 4.79 (d, 1H, *J* = 10.8 Hz), 4.55 (d, 1H, *J* = 10.8 Hz), 4.56−4.44 (m, 2H, C_6, CH_2), 3.75−3.70 (m, 3H, H_2, H_3, H_4), 3.72 (s, 3H), 3.62−3.57 (m, 1H, H_5).

6-*O*-Acetyl-2-azido-3-*O*-benzyl-2-deoxy-4-*O*-*p*-methoxybenzyl-α-D-glucopyranosyl-(1−4)-1,2-di-*O*-acetyl-3-*O*-benzyl-β-L-idopyranuronamide (50). To the thioglycoside azido donor **α-37** (262 mg, 0.49 mmol) and the iduronic amide acceptor **3** (149 mg, 0.41 mmol) was added dry DCM (3 mL). The solution was cooled to 0 °C, and activated powdered molecular sieves 4 Å (150 mg) added. After 10 min, NIS (328 mg, 1.48 mmol) was added followed by a catalytic amount of AgOTf after another 5 min. The mixture was stirred 3 h at room temperature (the solution slowly becomes dark red from the iodine formed), and then another catalytic amount of AgOTf added. After a total of 4 h the reaction was quenched by pouring into a mixture of saturated $NaHCO_3$ (20 mL), sodium thiosulfate 10% aq (3 mL) and DCM (20 mL). The two phase mixture was shaken until the iodine color disappeared, filtered to separate the powdered molecular sieves and then extracted with DCM (2 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered and evaporated, and purification by flash column chromatography (EtOAc/hexane, 1:1, then a second column using DCM/EtOAc 4:1) yielded **50** (60 mg, 0.07 mmol, 18%) as a white foam: R_f 0.27 (EtOAc/hexane 1:1); $[\alpha]_D^{20}$ = +68.0 (*c* = 0.57, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.31 (m, 10H, Ph), 7.18 (d, *J* = 8.8 Hz, 2H, PMP), 6.84 (d, *J* = 8.8 Hz, 2H, PMP), 6.54 (d, *J* = 3.6 Hz, 1H, CON*H*$_2$), 6.03 (d, *J* = 1.6 Hz, 1H, H-1), 5.65 (d, *J* = 3.6 Hz, 1H, CON*H*$_2$), 5.05−5.04 (m, 1H, H-2), 4.88−4.65 (m, 4H, C*H*$_2$Ph), 4.79 (d, *J* = 3.6 Hz, 1H, H′-1), 4.73 (d, *J* = 10.8 Hz, 1H, C*H*$_2$PMP), 4.57 (d, *J* = 2.0 Hz, 1H, H-5), 4.49 (d, *J* = 10.8 Hz, 1H, C*H*$_2$PMP), 4.28 (dd, *J* = 12.4 Hz, *J* = 2.0 Hz, 1H, H′-6a), 4.20 (dd, *J* = 12.4 Hz, *J* = 3.6 Hz, 1H, H′-6b), 4.14 (m, 1H, H-4), 4.01 (t, *J* = 2.4 Hz, 1H, H-3), 3.94 (dt, *J* = 10.0 Hz, *J* = 2.8 Hz 1H, H′-5), 3.85 (dd, *J* = 10.0 Hz, *J* = 8.8 Hz, 1H, H′-3), 3.79 (s, 3H, PhOC*H*$_3$), 3.51 (dd, *J* = 10.0 Hz, *J* = 9.2 Hz, 1H, H′-4), 3.33 (dd, *J* = 10.4 Hz, *J* = 3.6 Hz, 1H, H′-2), 2.20 (s, 3H, COC*H*$_3$), 2.13 (s, 3H, COC*H*$_3$), 2.03 (s, 3H, COC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.5, 169.7, 168.6, 159.4, 137.6, 136.4, 129.7, 129.5, 128.6, 128.5, 128.3, 127.9, 127.9, 127.9, 113.8, 96.0, 90.2, 80.0, 77.2, 75.4, 74.5, 72.7, 71.3, 70.0, 69.6, 66.2, 63.4, 62.5, 55.2, 20.9, 20.8, 20.7; HRMS (TOF-ES$^+$) *m/z* calcd for $C_{40}H_{50}N_4O_{14}N$ $[M + NH_4]^+$ 824.3354, found 824.3356.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-iodo-α-D-mannopyranosyl-(1−4)-1,2-di-*O*-acetyl-3-*O*-benzyl-β-L-idopyranuronamide (51). To 3,4,6-tri-*O*-acetyl-D-glucal **49** (370 mg, 1.25 mmol) and the iduronic amide acceptor **3** (367 mg, 1.00 mmol) was added dry CH_3CN (8 mL) and powdered molecular sieves 4 Å (500 mg). The solution was kept under an inert N_2 atmosphere, and iodine (480 mg, 1.89 mmol) added as a solid. The mixture was stirred for 1 h, and the reaction was quenched by pouring into a mixture of saturated aqueous $NaHCO_3$ (50 mL) containing sodium thiosulfate and DCM (50 mL). The two-phase mixture was filtered to separate the powdered molecular sieves and then extracted with DCM (2 × 25 mL). The combined organic phase was dried ($MgSO_4$), filtered, evaporated, and purification by flash column chromatography using EtOAc/hexane 2:1 as the eluent yielded **51** (363 mg, 0.47 mmol, 48%) as a white foam: R_f 0.20 (EtOAc/hexane 2:1); $[\alpha]_D^{20}$ = 40.3 (*c* = 0.76, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.29 (m, 5H, Ph), 6.61 (d, *J* = 3.2 Hz, 1H, CON*H*$_2$), 6.03 (d, *J* = 1.6 Hz, 1H, H-1), 5.78 (d, *J* = 3.2 Hz, 1H, CON*H*$_2$), 5.34 (t, *J* = 10.0 Hz, 1H, H′-4), 5.19 (s, 1H, H′-1), 5.09−5.08 (m, 1H, H-2), 4.69 (d, *J* = 11.6 Hz, 1H, C*H*$_2$Ph), 4.65 (d, *J* = 11.6 Hz, 1H, C*H*$_2$Ph), 4.58 (d, *J* = 2.0 Hz, 1H, H-5), 4.47 (t, *J* = 4.4 Hz, 1H, H′-3) 4.45−4.42 (m, 1H, H′-2). 4.20−4.19 (m, 1H, H-4), 4.19−4.11 (m, 2H, H′-5), 3.95 (t, *J* = 2.8 Hz, 1H, H-3), 2.15 (s, 3H, COC*H*$_3$), 2.12 (s, 3H, COC*H*$_3$), 2.10 (s, 3H, COC*H*$_3$), 2.05 (s, 3H, COC*H*$_3$), 2.03 (s, 3H, COC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 169.8, 169.8, 169.4, 168.5, 136.2, 128.6, 128.4, 127.7, 98.3, 89.8, 74.9, 73.0, 70.8, 69.7, 68.9, 68.3, 66.6, 65.9, 61.8, 28.6, 20.8, 20.7, 20.7, 20.7, 20.6; HRMS (TOF-ES$^+$) *m/z* calcd for $C_{29}H_{36}INO_{15}Na$ $[M + Na]^+$ 788.1022, found 788.1011.

6-*O*-Acetyl-2-azido-3-*O*-benzyl-2-deoxy-4-*O*-*p*-methoxybenzyl-α-D-glucopyranosyl-(1−4)-methyl 1,2-di-*O*-acetyl-3-*O*-benzyl-β-L-idopyranuronate (52). *Method A.* To trichloroacetimidate azido donor **47** (2.22 g, 3.69 mmol) and iduronic ester acceptor **5** (1.21 g, 3.17 mmol) was added dry toluene, and this was then evaporated (twice). The residue was dried under high vacuum for 1 h, and while being kept under argon, dry DCM (20 mL) was added. The solution was cooled to −25 °C using a 65:35 mixture of $^iPrOH/H_2O$/dry ice bath, and then TMSOTf (7 μL, 0.039 mmol) was added dropwise. The mixture was kept at this temperature for 1 h and then quenched with two drops of NEt_3. The solvent was evaporated, and the residue purified by flash column chromatography (first EtOAc/hexane 1:2, followed by a second column using DCM/EtOAc 20:1,

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which separates CCl_3CONH_2), yielding **52** (1.74 g, 2.11 mmol, 67%) as a white foam, along with recovery of acceptor **5** (0.28 g, 23%).

Method B. To thioglycoside azido donor **α-37** (388 mg, 0.72 mmol) and iduronic ester acceptor **5** (211 mg, 0.55 mmol) was added dry DCM (3 mL). The solution was cooled to 0 °C, and activated powdered molecular sieves 4 Å (250 mg) were added. After 10 min, NIS (373 mg, 1.66 mmol) was added, followed by a catalytic amount of AgOTf after another 5 min. The mixture was stirred for 15 min (the solution became dark red from the iodine formed) and quenched by pouring into a mixture of saturated $NaHCO_3$ (40 mL) containing sodium thiosulfate and DCM (40 mL). The two phase mixture was filtered to separate the powdered molecular sieves and then extracted with DCM (2 × 20 mL). The combined organic phase was dried ($MgSO_4$), filtered, evaporated, and purification by flash column chromatography (EtOAc/hexane 1:2) yielded **52** (269 mg, 0.33 mmol, 59%) as a white foam, along with recovery of acceptor **5** (78 mg, 37%): R_f 0.15 (EtOAc/hexane 1:2); $[\alpha]_D^{20}$ = +37.1 (c = 0.56, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.32 (m, 10H, Ph), 7.16 (d, J = 8.8 Hz, 2H, PMP), 6.84 (d, J = 8.8 Hz, 2H, PMP), 6.06 (d, J = 2.0 Hz, 1H, H-1), 5.06−5.05 (m, 1H, H-2), 4.84−4.75 (m, 4H, CH_2Ph), 4.75 (d, J = 3.6 Hz, 1H, H′-1), 4.69 (d, J = 10.8 Hz, 1H, CH_2PMP), 4.68 (d, J = 2.0 Hz, 1H, H-5), 4.49 (d, J = 10.8 Hz, 1H, CH_2PMP), 4.28 (dd, J = 12.4 Hz, J = 2.0 Hz, 1H, H′-6a), 4.16 (dd, J = 12.4 Hz, J = 3.6 Hz, 1H, H′-6b), 4.08 (t, J = 3.2 Hz, 1H, H-3), 3.99 (t, J = 2.4 Hz, 1H, H-4), 3.86−3.80 (m, 2H, H′-3, H′-5), 3.80 (s, 3H, PhOCH_3), 3.77 (s, 3H, COOCH_3), 3.50 (dd, J = 10.4 Hz, J = 9.2 Hz, 1H, H′-4), 3.36 (dd, J = 10.4 Hz, J = 3.2 Hz, 1H, H′-2), 2.16 (s, 3H, COCH_3), 2.12 (s, 3H, COCH_3), 2.02 (s, 3H, COCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.5, 168.7, 167.9, 159.3, 137.4, 136.6, 129.6, 129.3, 128.6, 128.5, 128.3, 128.0, 127.9, 113.8, 97.6, 90.2, 83.2, 80.2, 75.4, 74.4, 73.0, 73.0, 72.5, 70.0, 66.3, 63.5, 62.2, 55.2, 52.5, 20.8, 20.7, 20.7; HRMS (TOF-ES$^+$) m/z calcd for $C_{41}H_{47}N_3O_{15}Na$ [M + Na^+] 844.2905, found 844.2898; Elemental analysis calcd (%) for $C_{41}H_{47}N_3O_{15}$, C 59.92, H 5.76, N 5.11, found C 60.13, H 5.73, N 5.08.

2-Azido-3,6-di-*O*-benzyl-2-deoxy-4-*O*-*p*-methoxybenzyl-α-D-glucopyranosyl-(1−4)-methyl-1,2-di-*O*-acetyl-3-*O*-benzyl-β-L-idopyranuronate (53). To thioglycoside azido donor **β-34** (3.70 g, 6.20 mmol) and iduronic ester acceptor **5** (1.97 g, 5.16 mmol) was added dry DCM (30 mL). The solution was cooled to 0 °C, and activated powdered molecular sieves 4 Å (1.5 g) were added. After 10 min, NIS (2.32 g, 10.3 mmol) was added followed by a catalytic amount of AgOTf (13 mg, 0.062 mmol) after another 5 min. The mixture was stirred for 30 min (the solution becomes dark red from the iodine formed), and more AgOTf (13 mg, 0.062 mmol) added. After stirring for 2 h at 0 °C the reaction was quenched by pouring into a mixture of saturated $NaHCO_3$ (40 mL) containing sodium thiosulfate and DCM (40 mL). The two phase mixture was filtered, extracted with DCM (2 × 20 mL), and the combined organic phases dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash column chromatography (EtOAc/hexane, 1:2) yielding **53** (2.38 g, 2.74 mmol, 53%, α/β 6:1) as a white foam, along with recovery of acceptor **5** (0.77 g (39%): R_f 0.23 (EtOAc/hexane 1:2); $[\alpha]_D^{20}$ = +19.7 (c = 1.06, CH_2Cl_2); See the Supporting Information for copies of ^{1}H and ^{13}C NMR spectra; HRMS (TOF-ES$^+$) m/z calcd for $C_{46}H_{55}O_{14}N_4$ [M + NH_4^+] 887.3715, found 887.3726.

Methyl (Phenyl 4-*O*-(6-*O*-Acetyl-2-azido-3-*O*-benzyl-2-deoxy-4-*O*-*p*-methoxybenzyl-α-D-glucopyranosyl)-2-*O*-acetyl-3-*O*-benzyl-1-thio-α-L-idopyranoside)-uronate (54). To the trichloroacetimidate azido donor **47** (1.03 g, 1.71 mmol) and the iduronic ester acceptor **α-20** (363 mg, 0.84 mmol) was added dry toluene and evaporated twice. The residue was dried under high vacuum for 1 h, and while being kept under nitrogen, dry DCM (5 mL) was added. The solution was cooled to 0 °C using an ice-bath, TMSOTf (3 μL, 0.016 mmol) was added, and the mixture was kept at this temperature for 30 min and then quenched with two drops of NEt_3. The solvent was evaporated, and flash column chromatography (EtOAc/hexane 1:3) yielded **54** (519 mg, 0.60 mmol, 71%) as a white foam: R_f 0.16 (EtOAc/hexane 1:3); $[\alpha]_D^{20}$ = −5.3 (c = 0.70, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.49−7.43 (m, 2H, Ph), 7.37−7.23 (m, 13H, Ph), 7.15−7.09 (m, 2H, 2H, PMP), 6.83−6.77 (m, 2H, PMP), 5.58 (s, 1H, H_1), 5.23 (d, J = 2.9 Hz, 1H, H_5), 5.13−5.11 (m, 1H, H_2), 4.82 (d, J = 3.6 Hz, $H_{1'}$), 4.81 (d, J = 11.7 Hz, 1H, CH_2Ar), 4.80−4.74 (m, 2H, CH_2Ar), 4.70 (d, J = 10.8 Hz, 1H, CH_2Ar), 4.65 (d, J = 11.7 Hz, 1H, CH_2Ar), 4.46 (d, J = 10.8 Hz, 1H, CH_2Ar), 4.26 (dd, J = 12.2, 2.1 Hz, 1H, $H_{6''}$), 4.13 (dd, J = 12.2, 3.7 Hz, 1H, $H_{6'}$), 4.07 (t, J = 2.9 Hz, 1H, H_4), 3.94 (t, J = 2.9 Hz, 1H, H_3), 3.85−3.77 (m, 2H, $H_{3'}$, $H_{5'}$), 3.75 (s, 3H, PhOCH_3), 3.74 (s, 3H, COOCH_3), 3.47 (t, J = 9.2 Hz, 1H, $H_{4'}$), 3.29 (dd, J = 10.3, 3.6 Hz, 1H, $H_{2'}$), 2.07 (s, 3H, COCH_3), 1.97 (s, 3H, COCH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 170.6, 170.2, 169.3, 159.3, 137.5, 137.0, 135.2, 131.3, 129.8, 129.4, 129.1, 128.6, 128.1, 128.0, 127.9, 127.5, 113.8, 97.4, 86.2, 80.2, 75.5, 74.5, 73.2, 72.8, 71.7, 70.0, 68.8, 68.6, 63.5, 62.4, 55.3, 52.4, 21.0, 20.8; HRMS (TOF-ES$^+$) m/z calcd for $C_{45}H_{49}N_3O_{13}SNa$ [M + Na^+] 894.2883, found 894.2894; Elemental analysis calcd (%) for $C_{45}H_{49}N_3O_{13}S$, C 61.99, H 5.66, N 4.82, found C 61.60, H 5.68, N 4.85.

Methyl (Phenyl 4-*O*-(2-azido-3,6-di-*O*-benzyl-2-deoxy-4-*O*-*p*-methoxybenzyl-α-D-glucopyranosyl)-2-*O*-benzoyl-3-*O*-benzyl-1-thio-L-idopyranoside)-uronate (α-55 and β-55). α-55: To iduronic ester acceptor **α-21** (5.90 g, 11.9 mmol) was added dry toluene, and the solvent evaporated twice. The residue was dried under the high vacuum for 2 h, and while being kept under nitrogen, dry DCM (70 mL) was added. The solution was cooled to −30 °C using a 65:35 mixture of ^{i}PrOH/H_2O in a dry ice bath, and TMSOTf (22 μL, 0.016 mmol) was added to the acceptor solution. To the trichloroacetimidate azido donor **44** (9.35 g, 14.4 mmol) was added dry toluene, and the solvent evaporated twice. The residue was dissolved in dry DCM (10 mL) and added dropwise via a gastight syringe over 1 h to the acceptor solution, while the reaction mixture temperature was maintained at −30 °C. After another 15 min the reaction was quenched with two drops of NEt_3. The solvent was evaporated, and flash column chromatography [EtOAc/hexane, 1:4 and then a second column using DCM/EtOAc, 20:1 (to remove CCl_3CONH_2)] yielded **α-55** (9.21 g, 9.4 mmol, 78%) as a white foam, along with recovered acceptor **21** (1.10 g, 19%): R_f 0.34 (EtOAc/hexane 1:3); $[\alpha]_D^{20}$ = −52.0 (c = 0.57, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.16−8.14 (m, 2H, Ph), 7.63−7.52 (m, 4H, Ph), 7.46−7.42 (m, 2H, Ph), 7.41−7.22 (m, 15H, Ph), 7.17−7.13 (m, 2H, Ph), 7.13−7.07 (m, 2H, Ph), 6.91−6.85 (m, 2H, Ph), 5.82 (s, 1H, H_1), 5.49−5.47 (brs, 1H, H_2), 5.42 (d, J = 2.0 Hz, 1H, H_5), 5.04 (d, J = 11.7 Hz, 1H, CH_2Ar), 4.82 (d, J = 11.7 Hz, 1H, CH_2Ar), 4.81 (d, J = 2.8 Hz, 1H, $H_{1'}$), 4.66 (d, J = 12.0 Hz, 1H, CH_2Ar), 4.60 (d, J = 10.4 Hz, 1H, CH_2Ar), 4.52 (d, J = 12.0 Hz, 1H, CH_2Ar), 4.44 (d, J = 10.4 Hz, 1H, CH_2Ar), 4.27 (td, J = 2.9, 1.0 Hz, 1H, H_3), 4.15−4.12 (m, 2H, H_4, CH_2Ar), 3.96−3.88 (m, 2H, $H_{5'}$, CH_2Ar), 3.88−3.86 (m, 1H, $H_{6'}$), 3.86 (s, 3H, PhOCH_3), 3.80 (s, 3H, COOCH_3), 3.76−3.67 (m, 2H, $H_{6''}$, $H_{4'}$), 3.51 (t, J = 9.6 Hz, 1H, $H_{3'}$), 3.30 (dd, J = 10.3, 3.5 Hz, 1H, $H_{2'}$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 169.2, 165.5, 159.2, 137.9, 137.8, 137.1, 135.5, 133.3, 131.5, 130.6, 130.1, 129.5, 129.4, 129.1, 128.9, 128.5, 128.4, 128.3, 128.1, 128.1, 127.8, 127.7, 127.6, 127.6, 113.6, 100.6, 87.0, 80.2, 74.5, 74.4, 73.6, 72.8, 72.5, 71.8, 69.2, 68.4, 67.8, 63.8, 55.4, 52.4; MS-MALDI m/z = 999 [M + NH_4]$^+$; HRMS (FTMS-NSI$^+$) m/z calcd for $C_{55}H_{55}O_{12}N_3SNH_4$ [M + NH_4]$^+$ 999.3845, found 999.3854; [isotope pattern in the Supporting Information].

β-55: To iduronic ester acceptor **β-21** (6.90 g, 13.9 mmol) was twice added dry toluene, and the solvent evaporated. The residue was dried under high vacuum for 2 h, and while being kept under nitrogen, dry DCM (100 mL) was added. The solution was cooled to −30 °C using a 65:35 mixture of ^{i}PrOH/H_2O and a dry ice bath, and TMSOTf (25 μL, 0.016 mmol) was then added. To the trichloroacetimidate azido donor **44** (10.50 g, 16.2 mmol) was added twice dry toluene, and the solvent evaporated. The residue was dissolved in dry DCM (20 mL) and added dropwise via a gastight syringe over 90 min to the acceptor solution, while the reaction mixture was maintained at −30 °C. After another 15 min the reaction was quenched with two drops of NEt_3, solvents were removed in vacuo, and flash column chromatography (EtOAc/hexane, 1:4 as the eluent and then a second column using DCM/EtOAc, 20:1) yielded **β-55** (10.50 g, 10.7 mmol, 77%) as a white foam, along with recovered acceptor **21** (0.99 g, 14%):

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R_f 0.31 (EtOAc/hexane 1:3); $[\alpha]_D^{20}$ = +28.9 (*c* = 0.60, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.26−8.24 (m, 2H. Ph), 7.63−7.58 (m, 2H, Ph), 7.44−7.28 (m, 19H, Ph), 7.14−7.06 (m, 4H, Ph), 6.92−6.84 (m, 2H, Ph), 5.34 (d, *J* = 1.9 Hz, 1H, H_1), 5.31 (t, *J* = 1.7 Hz, 1H, H_2), 4.92 (d, *J* = 11.6 Hz, 1H, CH_2Ar), 4.82 (d, *J* = 11.6 Hz, 1H, CH_2Ar), 4.72 (d, *J* = 3.5 Hz, 1H, $H_{1'}$), 4.66 (d, *J* = 12.0 Hz, 1H, CH_2Ar), 4.61−4.59 (m, 2H, CH_2Ar, H_5),4.51 (d, *J* = 12.0 Hz, 1H, CH_2Ar), 4.43 (d, *J* = 10.5 Hz, 1H, CH_2Ar), 4.36 (t, *J* = 2.6 Hz, 1H, H_3), 4.06 (s, 1H, H_4), 4.04 (d, *J* = 10.7 Hz, 1H, CH_2Ar), 3.97−3.93 (m, 2H, $H_{5'}$, $H_{6'}$), 3.88−3.82 (m, 4H, $H_{6''}$, PhOCH_3), 3.79 (s, 3H, COOCH_3), 3.75 (d, *J* = 10.7 Hz, 1H, CH_2Ar), 3.67 (t, *J* = 9.5 Hz, 1H, $H_{4'}$), 3.46 (t, *J* = 9.5 Hz, 1H, $H_{3'}$), 3.27 (dd, *J* = 9.5, 3.5 Hz, 1H, H_2); ^{13}C NMR (100 MHz; $CDCl_3$) δ 168.5, 166.1, 159.2, 137.9, 137.9, 137.0, 134.9, 133.3, 131.2, 130.6, 130.2, 129.5, 129.4, 129.0, 128.9, 128.6, 128.2, 128.3, 128.3, 128.2, 128.1, 127.7, 127.6, 127.5, 113.6, 100.1, 85.9, 80.2, 75.7, 75.6, 74.5, 74.4, 73.6, 73.2, 73.0, 71.7, 70.0, 63.8, 55.4, 52.4; HRMS (FTMS-NSI$^+$) *m*/*z* calcd for $C_{55}H_{55}O_{12}N_3SNH_4$ $[M + NH_4]^+$ 999.3850, found 999.3848; Elemental analysis calcd (%) for $C_{55}H_{55}N_3O_{12}S$, C 67.26, H 5.64, N 4.28, found C 67.38, H 5.77, N 4.14.

Methyl [Phenyl 4-*O*-(2-azido-3,6-*O*-dibenzyl-2-deoxy-4-*O*-trichloroacetyl-*α*-D-glucopyranosyl)-2-*O*-benzoyl-3-*O*-benzyl-1-thio-L-ido-pyranoside] uronate (*α*-56 and *β*-56). *Method A.* To a 1:2 α/β mixture of ido acceptor **21** (4.92 g, 9.94 mmol) was added dry toluene, and the mixture was evaporated twice. The residue was dried on the high vacuum for 2 h, and while being kept under nitrogen, dry DCM (70 mL) was added. The solution was cooled to −30 °C using a 65:35 mixture of ^{i}PrOH/H_2O and dry ice bath. To the trichloroacetimidate azido donor **45** (8.05 g, 11.9 mmol) was added dry toluene, and the mixture was evaporated twice. Then TMSOTf (72 μL, 0.39 mmol) was added to the acceptor solution, the donor was dissolved in dry DCM (10 mL) and added dropwise via a gastight syringe over 1 h while the reaction mixture was maintained at −30 °C. After another 15 min the reaction was quenched with two drops of NEt_3. The solvent was evaporated, and product purified by flash column chromatography (EtOAc/hexane 1:4 as the eluent and then a second column using DCM) yielding ***α*/*β*-56** (4.11 g, 4.08 mmol, 41%) as a white foam. Also 2.04 g (41%) of acceptor **21** was recovered. For analysis, the α/β anomers could be separated by flash column chromatography (EtOAc/hexane, 1:5).

***α*-56**: R_f 0.13 (EtOAc/hexane 1:4); $[\alpha]_D^{20}$ = −28.6 (*c* = 0.47, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.23 (d, *J* = 8.2 Hz, 2H, Ph), 7.59−7.52 (m, 4H, Ph), 7.50−7.42 (m, 5H, Ph), 7.39−7.28 (m, 12H, Ph), 7.06 (d, *J* = 7.9 Hz, 2H, Ph), 5.89 (s, 1H, H_1), 5.47 (d, *J* = 2.0 Hz, 1H, H_5), 5.46−5.42 (m, 1H, H_2), 5.30 (dd, *J* = 10.2, 9.4 Hz, 1H, $H_{4'}$), 5.06 (d, *J* = 11.7 Hz, 1H, CH_2Ar), 4.83 (d, *J* = 11.7 Hz, 1H, CH_2Ar), 4.69 (d, *J* = 3.7 Hz, 1H, $H_{1'}$), 4.54 (d, *J* = 11.9 Hz, 1H, CH_2Ar), 4.47 (d, *J* = 11.9 Hz, 1H, CH_2Ar), 4.31 (td, *J* = 2.7, 1.0 Hz, 1H, H_3), 4.05−4.02 (m, 2H, $H_{5'}$, H_4), 3.99 (d, *J* = 10.2 Hz, 1H, CH_2Ar), 3.78 (s, 3H, COOCH_3), 3.72 (d, *J* = 10.2 Hz, 1H, CH_2Ar), 3.65 (dd, *J* = 11.0, 2.6 Hz, 1H, $H_{6'}$), 3.58−3.50 (m, 2H, $H_{3'}$, $H_{6''}$), 3.40 (dd, *J* = 10.1, 3.6 Hz, 1H, $H_{2'}$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 169.4, 165.5, 160.2, 137.3, 137.0, 136.8, 135.4, 133.5, 131.2, 130.0, 129.8, 129.2, 128.8, 128.5, 128.4, 128.3, 128.3, 128.3, 128.1, 127.9, 127.8, 127.6, 100.2, 89.7, 87.0, 77.9, 77.6, 77.4, 74.9, 74.7, 73.8, 72.8, 71.4, 69.5, 69.2, 68.3, 67.1, 63.5, 52.5; MS-MALDI *m*/*z* = 1025 $[M + NH_4]^+$; HRMS (FTMS-NSI$^+$) *m*/*z* calcd for $C_{49}H_{50}O_{12}N_4SCl_3$ $[M + NH_4]^+$ 1023.2207, found 1023.2216; [isotope pattern in the Supporting Information]; Elemental analysis calcd (%) for $C_{49}H_{46}Cl_3N_3O_{12}S$, C 58.42, H 4.60, N 4.17, found C 58.22, H 4.92, N 4.07.

***β*-56**: R_f 0.07 (EtOAc/hexane 1:4); $[\alpha]_D^{20}$ = +56.1 (*c* = 0.59, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.24−8.18 (m, 2H, Ph), 7.50−7.14 (m, 21H, Ph), 7.00−6.89 (m, 2H, Ph), 5.23 (d, *J* = 1.8 Hz, 1H, H_1), 5.19−5.13 (m, 2H, H_2, $H_{4'}$), 4.81 (d, *J* = 11.7 Hz, 1H, CH_2Ar), 4.70 (d, *J* = 11.7 Hz, 1H, CH_2Ar), 4.52 (d, *J* = 1.7 Hz, 1H, H_5), 4.48 (d, *J* = 3.6 Hz, 1H, $H_{1'}$), 4.43 (d, *J* = 11.9 Hz, 1H, CH_2Ar), 4.35 (d, *J* = 11.9 Hz, 1H, CH_2Ar), 4.26 (t, *J* = 2.5 Hz, 1H, H_3), 3.90 (d, *J* = 10.4 Hz, 1H, CH_2Ar), 3.89−3.83 (m, 2H, H_4, $H_{5'}$), 3.66 (s, 3H, COOCH_3), 3.56 (d, *J* = 10.4 Hz, 1H, CH_2Ar), 3.54−3.50 (m, 1H, $H_{6'}$), 3.46 (d, *J* = 9.6 Hz, 1H, $H_{3'}$), 3.40 (dd, *J* = 11.0, 2.6 Hz, 1H, $H_{6''}$), 3.28 (dd, *J* = 10.1, 3.6 Hz, 1H, H_2); ^{13}C NMR (100 MHz; $CDCl_3$) δ 168.6, 166.2, 160.2, 137.3, 136.8, 136.8, 134.7, 133.5, 131.2, 130.1, 129.9, 129.1, 128.8, 128.6, 128.5, 128.4, 128.42, 128.33, 128.18, 127.8, 127.7, 99.5, 89.8, 86.0, 77.9, 76.2, 75.8, 74.9, 74.8, 73.8, 73.0, 72.2, 70.2, 69.2, 67.3, 63.6, 52.4.

Method B. The disaccharide ***β*-60** (640 mg, 0.74 mmol) was dissolved in dry DCM (10 mL), cooled to 0 °C in an icebath, and then dry pyridine (0.18 mL, 2.22 mmol) and trichloroacetyl chloride (0.13 mL, 1.11 mmol) was added. The solution was stirred for 90 min. The solution was then extracted with DCM (50 mL) and water (50 mL), dried ($MgSO_4$), filtered and evaporated. The crude was purified using flash column chromatography (EtOAc/hexane 1:4). This yielded the product ***β*-56** (718 mg, 0.71 mmol, 96%) as a white foam.

Methyl [Phenyl 4-*O*-(2-azido-3-*O*-benzyl-6-*O*-benzoyl-4-*O*-*p*-methoxybenzyl-*α*-D-glucopyranosyl)-2-*O*-benzoyl-3-*O*-benzyl-1-thio-*α*-L-ido-pyranoside] uronate (*α̃*57). Acceptor ***α*-21** (1.88 g, 3.8 mmol) was dissolved in DCM (20 mL) in anhydrous conditions under N_2, this solution was cooled to −20 °C, and TMSOTf (∼6 μL) was added. A dropwise addition of the donor trichloroacetimidate **48** (3.27 g, 4.9 mmol predissolved in DCM (10 mL)) was then added to a reaction mixture over 30 min. The solution was stirred for 30 min at which point only starting materials were observed (TLC), and pH ∼ 7. A further portion of TMSOTf (20 μL) was added, and the mixture stirred for a further 40 min when the reaction was deemed complete (TLC). The reaction was quenched with triethylamine (1 mL), solvents were removed in vacuo, and purification by flash chromatography (hexane:EtOAc, 5:1 → 3:1 gradient, followed by 40:1 → 30:1 DCM:EtOAc, to remove the trichloroacetamide) yielded ***α̃*57** as a white foam (2.43 g, 2.44 mmol, 64%): $[\alpha]_D^{20}$ = +57° (*c* = 0.30, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23−8.20 (m, 2H, Ar*H*), 7.96−7.94 (m, 2H, Ar*H*), 7.59−7.52 (m, 4H, Ar*H*), 7.42−7.28 (m, 17H, Ar*H*), 7.16−7.10 (m, 4H, Ar*H*), 6.81−6.78 (m, 2H, Ar*H*), 5.29 (d, 1H, IdoA H_5, *J* = 2.0 Hz), 5.25 (br s, 1H, IdoA H_1), 4.87 (d, 1H, IdoA Benzyl CH_a, *J* = 11.2 Hz), 4.76 (d, 1H, IdoA Benzyl CH_b, *J* = 11.6 Hz), 4.68 (d, 1H, GlcN H_1, *J* = 3.6 Hz), 4.67−4.63 (m, 1H, GlcN H_{6a}), 4.64 (d, 1H, PMB CH_a, *J* = 10.4 Hz), 4.55 (d, 1H, IdoA H_4, *J* = 1.2 Hz), 4.52−4.48 (dd, 1H, GlcN H_{6b}, *J* = 2.4 Hz, 12.0 Hz), 4.47 (d, 1H, PMB CH_b, *J* = 10.8 Hz), 4.32 (dd, 1H, IdoA H_2, *J* = 2.4 Hz), 4.14−4.11 (m, 1H, GlcN H_5), 4.05 (br s, 1H, IdoA H_3), 3.97 (d, 1H, GlcN Benzyl CH_a, *J* = 10.4 Hz), 3.79 (s, 3H, IdoA methyl ester CH_3), 3.75 (d, 1H, GlcN Benzyl CH_b, *J* = 10.8 Hz), 3.73 (s, 3H, PMB OMe), 3.57 (dd, 1H, GlcN H_4, *J* = 8.8 Hz), 3.48 (dd, 1H, GlcN H_3, *J* = 10.0 Hz), 3.20 (dd, 1H, GlcN H_2, *J* = 3.6 Hz, 10.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 166.1, 159.3, 137.6, 137.0, 133.3, 133.1, 131.3, 130.2, 129.76, 129.71, 129.62, 129.07, 128.94, 128.60, 128.46, 128.43, 128.40, 128.32, 128.19, 128.12, 127.99, 127.95, 127.7, 113.8, 99.6, 86.0, 80.3, 77.3, 76.9, 75.5, 74.7, 74.5, 73.0, 70.1, 63.8, 62.6, 55.2, 52.5; Low res MS (ES$^+$) 1018.6 [M + Na]; HRMS (TOF-ES$^+$) *m*/*z* calcd. for $C_{55}H_{52}O_{13}N_3SNa$ $[M + Na]^+$ 1018.3197, found 1018.3182.

Methyl [Phenyl 4-*O*-(2-azido-3-*O*-benzyl-6-*O*-benzoyl-4-*O*-trichloroacetyl-*α*-D-glucopyranosyl)-2-*O*-benzoyl-3-*O*-benzyl-1-thio-*α*-L-ido-pyranoside] uronate (*α*-58). Iduronate acceptor ***α*-21** (3.3 g, 6.6 mmol) was dissolved in dry DCM (40 mL) under N_2. The reaction solution was cooled to −30 °C, and TMSOTf (72 μL, 0.39 mmol, 0.06 equiv) added. The solution color changed to pale yellow (pH = 3). To this solution was added dropwise **46** (5.46 g, 7.9 mmol, 1.2 equiv) dissolved in dry DCM (50 mL). Stirring was continued for 2 h at −30 °C, and the reaction then allowed to warm to room temperature, Et_3N (100 μL) was added, and the solvents removed in vacuo to give a brown gum. This material was purified by flash chromatography (hexane/EtOAc, 5:1 → 2:1) to give ***α*-58** (4.03 g, 3.95 mmol, 60%) as a pale yellow foam along with recovery of unreacted ***α*-21** (1.21 g): $[\alpha]_D$ (*c* = 0.11, DCM) +0.20; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01−7.98 (m, 2H, Ar−H), 7.82−7.79 (m, 2H, Ar−H), 7.36−7.01 (m, 19H, Ar−H), 6.81−6.77 (m, 2H, Ar−H), 5.64 (d, *J* = 2.5, 1H, H1′), 5.22 (d, *J* = 1.9, 1H, H5′), 5.20−5.19 (m, 1H, H2′), 5.02 (t, *J* = 9.7, 1H, H4), 4.82 (d, *J* = 11.8, 1H), 4.58 (d, *J* = 12.0, 1H), 4.62 (d, *J* = 12.8, 1.0, 1H, $H6_A$), 4.45 (d, *J* = 3.7, 1H, H1), 4.08−4.06 (m, 1H, H3′), 4.04−3.97 (m, 2H, H5+$H6_B$), 3.80 (s, 1H, H4′), 3.67−3.63 (m, 4H), 3.40 (d, *J* = 10.1, 1H), 3.31 (t, *J* = 9.6, 1H, H2), 3.15 (dd, *J* = 10.0, 3.6, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 165.9,

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165.5, 160.5, 137.0, 136.5, 135.3, 133.6, 133.3, 131.4, 130.0, 129.8, 129.5, 129.2, 128.9, 128.6, 128.5, 128.5, 128.3, 128.3, 128.1, 127.9, 127.8, 100.5, 89.5, 87.2, 78.4, 77.9, 74.8, 74.5, 72.8, 71.4, 69.5, 68.4, 68.2, 63.7, 61.2, 52.7; MS m/z 1044.10 $(M + Na)^+$; HRMS (TOF-ES$^+$) m/z calcd for $C_{49}H_{48}Cl_3N_4O_{13}S$ $[M + NH_4]^+$ 1037.1999, found 1037.2000.

Methyl (Phenyl 4-*O*-(6-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-4-*O*-*p*-methoxybenzyl-α-D-glucopyranosyl)-2-*O*-benzoyl-3-*O*-benzyl-1-thio-β-L-idopyranoside)-uronate (β59). To iduronic ester acceptor **α/β-21** (2.85 g, 5.76 mmol) and trichloroacetimidate donor **47** (4.7 g, 7.77 mmol) was added dry toluene, and this solvent evaporated twice. The residue was dried on under high vacuum for 2 h, and while being kept under nitrogen, dry DCM (65 mL) was added. The solution was cooled to −30 °C using a 65:35 mixture of ^{i}PrOH/H_2O in dry ice, TMSOTf (15 μL, 0.08 mmol) was added, and after 30 min the reaction was quenched with two drops of NEt_3. The solvent was evaporated and flash column chromatography (EtOAc/hexane 2:9) yielded **β̃59** (4.0 g, 4.28 mmol, 75%) as a white foam: R_f 0.14 (EtOAc/hexane 1:3); ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.12 (d, J = 8.0 Hz, 2H, Ph), 7.48 (d, J = 7.7 Hz, 2H, Ph), 7.31−7.15 (m, 14H, Ph), 7.08 (d, J = 8.3 Hz, 2H, Ph), 7.01 (d, J = 7.3 Hz, 2H, Ph), 6.79 (d, J = 8.2 Hz, 2H, Ph), 5.20 (s, 1H, H_1), 5.16 (s, 1H, H_2), 4.78 (d, J = 11.6 Hz, 1H, CH_2Ar), 4.68 (d, J = 11.6 Hz, 1H, CH_2Ar), 4.56 (d, J = 3.3 Hz, 1H, $H_{1'}$), 4.51 (d, J = 10.5 Hz, 1H, CH_2Ar), 4.45 (s, 1H, H_5), 4.34−4.19 (m, 4H, CH_2Ar, H_3, $H_{6'}$, $H_{6''}$), 3.93−3.86 (m, 3H, CH_2Ar, H_4, $H_{3'}$), 3.71 (s, 3H, COOCH_3), 3.70 (s, 3H, PhOCH_3), 3.66 (d, J = 10.6 Hz, 1H, CH_2Ar), 3.34 (t, J = 8.1 Hz, 2H, $H_{3'}$, H4$_{''}$), 3.08 (dd, J = 9.5, 3.0 Hz, 1H, H_2), 1.91 (s, 3H, C(O)CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 171.0, 168.9, 166.5, 159.8, 138.2, 137.4, 135.1, 131.7, 130.6, 130.4, 130.1, 130.0, 129.4, 129.3, 129.0, 128.7, 128.7, 128.6, 128.2, 128.1, 128.0, 114.2, 100.1, 86.4, 80.6, 76.0, 75.9, 74.9, 74.9, 73.2, 73.3, 70.5, 70.4, 64.2, 62.7, 55.7, 52.9, 21.3; HRMS (TOF-ES$^+$) m/z calcd for $C_{50}H_{51}N_3O_{13}SNa$ $[M + Na^+]$ 956.3035, found 956.3025.

Methyl [Phenyl 4-*O*-(2-azido-3,6-*O*-dibenzyl-α-D-glucopyranosyl)-2-*O*-benzoyl-3-*O*-benzyl-1-thio-β̃L-ido-pyranoside] uronate (β-60). To **β-55** (370 mg, 0.377 mmol) was added CH_3CN (8 mL) and water (0.8 mL) followed by ammonium cerium(IV) nitrate (>99.99%) (439 mg, 0.801 mmol). The orange solution was stirred for 90 min, more CAN was added (80 mg, 0.146 mmol), and the mixture stirred for another 1 h. The solution was then extracted with DCM (2 × 100 mL) and water (100 mL), dried ($MgSO_4$), filtered and evaporated. The crude product was purified using flash column chromatography (EtOAc/hexane, 1:3) to yield the product **β-60** (325 mg, 92%) as a white foam: R_f 0.18 (EtOAc/hexane 1:3); $[\alpha]_D^{20}$ = +41.8 (c = 0.46, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.32−8.26 (m, 2H, Ph), 7.65−7.58 (m, 2H, Ph), 7.55−7.26 (m, 19H, Ph), 7.21−7.12 (m, 2H, Ph), 5.34 (d, J = 1.9 Hz, 1H, H_1), 5.32−5.26 (brs, 1H, H_2), 4.91 (d, J = 11.6 Hz, 1H, CH_2Ar), 4.80 (d, J = 11.6 Hz, 1H, CH_2Ar), 4.67−4.54 (m, 4H, CH_2Ar, H_5, $H_{1'}$), 4.35 (t, J = 2.6 Hz, 1H, H_3), 4.13 (d, J = 10.8 Hz, 1H, CH_2Ar), 4.04 (brs, 1H, H_4), 3.93−3.84 (m, 2H, CH_2Ar, H_5), 3.82 (dd, J = 10.3, 3.3 Hz, 1H, $H_{6'}$), 3.76 (s, 3H, COOCH_3), 3.70−3.62 (m, 2H, $H_{4'}$, $H_{6''}$), 3.39 (t, J = 10.2 Hz, 1H, $H_{3'}$), 3.18 (dd, J = 10.2, 3.5 Hz, 1H, $H_{2'}$), 2.54 (s, 1H, OH); ^{13}C NMR (100 MHz; $CDCl_3$) δ 168.5, 166.2, 138.1, 137.7, 137.0, 134.8, 133.4, 131.2, 130.3, 129.7, 129.1, 128.8, 128.6, 128.4, 128.3, 128.35, 128.2, 127.9, 127.8, 127.7, 127.6, 99.4, 86.0, 80.0, 75.7, 75.1, 74.7, 73.7, 72.9, 72.8, 72.6, 70.4, 70.1, 69.5, 63.2, 52.3; MS ES m/z = 884.9 $[M + Na]^+$; HRMS (FTMS-NSI$^+$) calcd for $C_{47}H_{47}O_{11}N_3SNa$ $[M + Na]^+$ 884.2824, found 884.2808.

6-*O*-Acetyl-2-azido-3-*O*-benzyl-2-deoxy-4-*O*-*p*-methoxybenzyl-α-D-glucopyranosyl-(1−4)-methyl-2-*O*-acetyl-3-*O*-benzyl-L-idopyranuronate (61). To the disaccharide **52** (1.63 g, 1.98 mmol) was added diethyl ether (30 mL), the mixture was cooled to 0 °C, and benzylamine (1.0 mL, 8.9 mmol) added. The solution was stirred for 3 h at 0 °C and then extracted with EtOAc (2 × 50 mL) and 1 M HCl (50 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (50 mL), dried ($MgSO_4$), filtered and evaporated. Purification by flash column chromatography (EtOAc/hexane 1:1) yielded the intermediate free 1-OH disaccharide (838 mg, 1.01 mmol, 54%) as a white foam, along with recovered starting materal **52** (638 mg, 39%): R_f 0.28 (EtOAc/hexane 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.32 (m, 10H, Ph), 7.17 (d, J = 8.8 Hz, 2H, PMP), 6.85 (d, J = 8.8 Hz, 2H, PMP), 5.34−5.32 (m, 1H, H-2a), 5.15−5.13 (m, 1H, H-2b), 4.90−4.49 (m, 9H, CH_2Ph, CH_2PMP, H′-1, H-1, H-5), 4.32−3.81 (m, 6H, H-3, H-4, H′-3, H′-5, H′-6a, H′-6b), 3.80 (s, 3H, PhOCH_3), 3.78 (s, 3H, COOCH_3), 3.54−3.48 (m, 1H, H′-4), 3.36−3.30 (m, 1H, H′-2), 2.17 (s, 3H, COCH_3), 2.11 (s, 3H, COCH_3), 2.02 (s, 3H, COCH_3); HRMS (TOF-ES$^+$) m/z calcd for for $C_{39}H_{45}N_3O_{14}Na$ $[M + Na]^+$ 802.2799, found 802.2783; Elemental analysis calcd (%) for $C_{39}H_{45}N_3O_{14}$, C 60.07, H 5.82, N 5.39, found C 60.24, H 5.83, N 5.29.

6-*O*-Acetyl-2-azido-3-*O*-benzyl-2-deoxy-4-*O*-*p*-methoxybenzyl-α-D-glucopyranosyl-(1−4)-methyl-2-*O*-acetyl-3-*O*-benzyl-1-*O*-trichloroacetimidate-α̃β-L-idopyranuronate (62). To the intermediate 1-OH disaccharide **61** (781 mg, 1.00 mmol) was added dry DCM (10 mL), CCl_3CN (0.7 mL, 7.0 mmol) and DBU (0.01 mL, 0.07 mmol). The solution was stirred for 90 min, and the mixture was evaporated and purified by flash column chromatography (EtOAc/hexane 1:2 containing 1% NEt_3 as the eluent) yielding (796 mg, 0.86 mmol, 86%) of disaccharide donor **62** as an oil, which was used directly for the synthesis of tetrasaccharide **64**.

6-*O*-Acetyl-2-azido-3-*O*-benzyl-2-deoxy-α-D-glucopyranosyl-(1−4)-methyl-1,2-di-*O*-acetyl-3-*O*-benzyl-β-L-idopyranuronate (63). To disaccharide **52** (370 mg, 0.45 mmol) was added DCM and H_2O (5 mL/0.1 mL) followed by DDQ (150 mg, 0.68 mmol). The solution was stirred for 1 h, and another portion of DDQ (20 mg) was added. After a total of 90 min the mixture was evaporated and purified by flash column chromatography (EtOAc/hexane 2:3) yielding **63** (268 mg, 0.38 mmol, 85%) as a white foam: R_f 0.14 (EtOAc/hexane 2:3); $[\alpha]_D^{20}$ = +32.1 (c = 0.68, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.32 (m, 10H, Ph), 6.06 (d, J = 2.0 Hz, 1H, H-1), 5.07−5.06 (m, 1H, H-2), 4.87−4.75 (m, 6H, CH_2Ph, H′-1, H-5), 4.56 (dd, J = 12.8 Hz, J = 3.2 Hz, 1H, H′-6a), 4.13 (dd, J = 12.8 Hz, J = 2.0 Hz, 1H, H′-6b), 4.07 (t, J = 3.2 Hz, 1H, H-3), 4.00 (t, J = 2.4 Hz, 1H, H-4), 3.78 (s, 3H, COOCH_3), 3.75−3.68 (m, 2H, H′-3, H′-5), 3.42 (dt, J = 10.0 Hz, J = 3.6 Hz, 1H, H′-4), 3.30 (dd, J = 10.0 Hz, J = 3.6 Hz, 1H, H′-2), 2.96 (d, J = 3.6 Hz, 1H, OH), 2.17 (s, 3H, COCH_3), 2.12 (s, 3H, COCH_3), 2.10 (s, 3H, COCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 170.5, 168.7, 168.0, 137.6, 136.6, 128.6, 128.3, 128.1, 128.1, 127.9, 97.8, 90.2, 79.1, 75.2, 74.4, 73.1, 72.9, 72.5, 71.0, 70.3, 66.1, 62.9, 62.5, 52.4, 20.8, 20.8, 20.8; HRMS (TOF-ES$^+$) m/z calcd for $C_{33}H_{39}N_3O_{14}Na$ $[M + Na^+]$ 724.2330, found 724.2321; Elemental analysis calcd (%) for $C_{33}H_{39}N_3O_{14}$, C 56.49, H 5.60, N 5.99, found C 56.64, H 5.61, N 5.86.

6-*O*-Acetyl-2-azido-3-*O*-benzyl-2-deoxy-4-*O*-*p*-methoxybenzyl-α-D-glucopyranosyl-(1−4)-methyl-2-*O*-acetyl-3-*O*-benzyl-α-L-idopyranosyluronate-(1−4)-6-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-4-*O*-*p*-methoxybenzyl-α-D-glucopyranosyl-(1−4)-methyl-2-*O*-acetyl-3-*O*-benzyl-β-L-idopyranosyluronate (64). To donor **62** (458 mg, 0.49 mmol) and disaccharide acceptor **63** (268 mg, 0.38 mmol) was added dry toluene, which was evaporated (two cycles). Then, while the flask was kept under N_2, dry DCM (5 mL) was added, and the mixture cooled to −30 °C using a 70:30 mixture of ^{i}PrOH/H_2O and dry ice. TMSOTf (5 μL, 0.027 mmol) was added dropwise, and the mixture was kept at this temperature for 2 h and then quenched with two drops of NEt_3. The solvent was evaporated, and flash column chromatography (EtOAc/hexane 2:3) yielded **64** (340 mg, 0.23 mmol, 61%) as a white foam, along with recovery of acceptor **63** (64 mg, 24%): R_f 0.17 (EtOAc/hexane 2:3); $[\alpha]_D^{20}$ = +37.6 (c = 0.76, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.30 (m, 20H, Ph), 7.18 (d, J = 8.4 Hz, 2H, PMP), 6.85 (d, J = 8.8 Hz, 2H, PMP), 6.05 (d, J = 2.0 Hz, 1H, H-1), 5.28 (d, J = 4.8 Hz, 1H, H″-1), 5.05−5.04 (m, 1H, H-2), 5.02 (d, J = 3.6 Hz, 1H, H‴-1), 4.90−4.89 (m, 1H, H″-2), 4.88−4.48 (m, 13H, CH_2Ph, CH_2PMP, H′-1, H-5, H″-5), 4.39 (dd, J = 12.4 Hz, J = 1.6 Hz, 1H, H′-6a), 4.24−4.20 (m, 3H, H′-6b, H‴-6a, H‴-6b), 4.05 (t, J = 3.2 Hz, 1H, H-3), 4.02 (dd, J = 6.0 Hz, J = 4.8 Hz, 1H, H″-4), 3.98 (t, J = 2.0 Hz, 1H, H-4), 3.93 (t, J = 6.0 Hz, 1H, H″-3), 3.88−3.68 (m, 5H, H′-3, H′-4, H′-5, H‴-3, H‴-5), 3.80 (s, 3H, PhOCH_3), 3.73 (s, 3H, COOCH_3), 3.58 (s, 3H, COOCH_3), 3.51 (dd, J = 9.6 Hz, J = 8.8 Hz, 1H, H‴-4), 3.37 (dd, J = 10.4 Hz, J = 3.2 Hz, 1H, H′-2), 3.24 (dd, J = 10.4 Hz, J = 3.2 Hz, 1H, H‴-2), 2.14 (s, 3H, COCH_3), 2.12 (s, 3H, COCH_3), 2.12 (s, 3H,

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$COCH_3$), 2.07 (s, 3H, $COCH_3$), 1.97 (s, 3H, $COCH_3$); MS-MALDI m/z = 1480 $[M + NH_4]^+$; HRMS (FTMS-NSI$^+$) m/z calcd for $C_{72}H_{86}O_{27}N_7$ $[M + NH_4]^+$ 1480.5566, found 1480.5587 [isotope pattern in the Supporting Information].

■ ASSOCIATED CONTENT

Supporting Information

General experimental methods, copies of ^1H and ^{13}C NMR, COSY and HMQC spectra for new compounds, and mass spectra for oligosaccharide **64**. CIF data files for the X-ray analyses of **3**, **5**, **6** and **17**. Unit cell ORTEP for amide **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

[§]These authors contributed significantly to the synthetic experimental work and contributed to the research planning and manuscript preparation. Experimental design and planning and primary contributions to the iduronate development chemistry by SUH; work on glucosides (and scale work) additionally contributed by GJM along with major contribution to the manuscript, experimental and supporting data analysis and interpretation of iduronates and glucosides. MB and KB contributions to iduronate development and saccharide synthesis methods. X-ray data analyses were obtained by MH and JR. EA and GCJ were involved in overall oligosaccharide target selection.

Notes

The authors declare no competing financial interest.

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