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Synthesis of L-iduronic acid derivatives via [3.2.1] and [2.2.2] L-iduronic lactones from bulk glucose-derived cyanohydrin hydrolysis: A reversible conformationally-switched super-disarmed/re-armed lactone route to heparin disaccharides

Steen U. Hansen,[a] Charlotte E. Dalton,[a] Marek Baráth,[¶a] Glenn Kwan,[a] James Raftery,[b] Gordon C. Jayson,[c] Gavin J. Miller[a] and John M. Gardiner[a*]

[a]Manchester Institute of Biotechnology and the School of Chemistry, 131 Princess Street, The University of Manchester, Manchester M1 7DN, UK

[b]The School of Chemistry, The University of Manchester, Manchester M13 9PL, UK

[c]Institute of Cancer Sciences, Christie Hospital and University of Manchester, Wilmslow Road, Manchester M20 4BX, UK

* E-mail: gardiner@manchester.ac.uk

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ABSTRACT: L-Idofuranoside cyanohydrin **1** is converted on large scale into a mixture of L-IdoA methyl pyranosides and furanosides which is converged to provide short 2-step routes to bicyclic [3.2.1] or [2.2.2] L-iduronate lactones. The former is obtained via a 100 g-scale synthesis of 3-OBn L-IdoA. A two-step conversion of this mixture provides either pure anomer of the novel [2.2.2] L-iduronate thioglycoside lactones. Both [3.2.1] and [2.2.2] lactones are converted into GlcN-IdoA heparin precursor disaccharides. The [2.2.2] lactone enables a scalable 3-step route from **1** to a new type of highly disarmed *O*-4 iduronate thioglycoside which is an effective acceptor with glucoazide thioglycoside donors. The resulting new iduronic [2.2.2]-lactone disaccharides are readily re-armed by mild methanolysis to provide GlcN-IdoA thiophenyl disaccharide donors, intercepting their established utility for the assembly of both heparin- and heparan sulfate-like oligosaccharides. The [2.2.2] lactonization acts as a conformational switch to super-disarm iduronate components, reversible by lactone ring-opening. In addition, the separated 2,4-diacetates also pro-

vide short access to all four anomeric and ring size isomers of L-iduronic acid methyl glycosides, including the first syntheses of the parent idofuranosides. X-ray structures are reported for a [2.2.2] iduronate lactone and examples of both methyl L-idopyranoside and novel methyl-L-idofuranoside systems.

INTRODUCTION

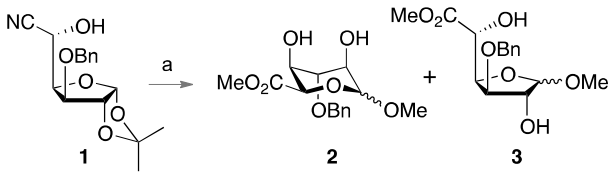
The heparin/heparan sulfate (H/HS) family of glycosaminoglycans (GAGs) are oligosaccharides with pervasive roles in regulating a wide range of signalling processes.[1] These poly/oligosaccharides are very heterogeneous, consisting of alternating D-glucosamine and uronic acid monomers, with significant variability in the N- and O-6 functionality of the D-GlcN unit, alongside incorporation of variable levels of D-glucuronic or L-iduronic acid. The diverse roles of such heterogeneous H/HS structures in many key host cell processes, as well as in many pathogen interactions, ensures that understanding their structure-specific effects is a major challenge in carbohydrate chemical biology.[1e,2] This is underpinned by enabling synthetic access to different backbones, controlling sequence, end groups and the diversity of funtionalization, and this has seen significant examples of strategies to deliver H/HS syntheses.[3] Access to mono- and disaccharide H/HS building blocks dominates the key upstream requirement for synthetic capacity to such oligosaccharides. Within this, access to derivatives of the rare L-iduronic acid and exploitation of their reactivity has been an area that has seen many elegant approaches,[4] and remains central to delivering improved and scalable syntheses of synthetic H/HS targets. Several H/HS syntheses have employed iditol, then including a late stage oxidation to the L-iduronic acid, post-glycosylation(s).[5] This has recently been exploited in the work of the Hung lab for synthesis of a large disaccharide library, where the late stage oxidation involves synthesis of an iduronic [2.2.2]-lactone.[6] To date, there has been no exploration of the synthesis and capabilities of iduronate lactones for the assembly of heparin-related disaccharide building blocks. Herein we report a new approach to herapin-like oligosaccharide synthesis which exploits reversible conformatinal control of arming/disarming iduronate thoglycoside functionality, and provides a short new route to such key disaccharides.

We have previously shown cyanohydrin **1** (accessible on kg scale)[7] to be a convenient starting material for access to various L-iduronic acid intermediates,[7,8] including thioglycosides, underpinning the large scale assembly of heparin-related oligosaccharides up to the 12-mer, and the synthesis of a low molecular weight heparin (LMWH)-like per-6-*O*-sulfated dodecasaccharide,[10] in which all synthesis directs through early incorporation of the iduronic caboxylic group.[9] We reported that cyanohydrin **1** was converted into a mixture of L-idopyranosides and L-idofuranosides, which were not separable (Scheme 1),[10] but which were converted into their diacetates to enable separation of the pyranosides, **2** from furanosides, **3**, with the former then elaborated for oligosaccharide synthesis.

However, there would be considerable value if the large scalability of the conversion of **1** into **2**+**3** were exploited to provide direct throughput to high value L-iduronic acid reagents, without the need for furanoside/pyranoside separation. This could provide short, large scale processes towards high value iduronate targets from bulk scale precursors. Additionally, the facility to develop new rea-

gents allowing for disaccharide syntheses *via* exploiting a new, conformationally-switched, disarming/re-arming anomeric reactivity of new iduronic acid derivatives would also be a valuable advance.

Scheme 1. Large scale conversion of L-ido cyanohydrin 1 into L-iduronate methyl glycosides mixture 2 + 3[a,10]



[a]Reagents and conditions: (a) AcCl, MeOH, 77%.

Herein we report short, scalable routes from the bulk crude **2**+**3** mixture to H/HS precursor disaccharides, which demonstrate a new disarmed (super-disarmed) L-IdoA acceptor lactone, which provides both convenient complete control of the acceptor protection (reversibly sequestering O2 through lactone formation) and access to thioglycoside H/HS disaccharides, using just one type of donor functionality and thus obviating the need for any anomeric interconversions. We also report separation of all four ring and anomeric isomers of **2** and **3**, demonstrating further synthetic utility for **1**, as a cheap and scalable precursor to a diversity of L-idopyranoses and L-idofuranoses.

■ RESULTS AND DISCUSSION

This work reports that the mixture of **2**+**3** can be employed to provide large scale access to new L-iduronic acid derivatives, specifically novel [3.2.1] and [2.2.2] lactones and the application of the latter in synthesis of heparin-related disaccharide reagents, contingent on discovery of the highly disarmed capabilites of [2.2.2] iduronate thioglycosides providing reversible conformationally-regulated reactivity.

These new strategies were based on two iduronic acid lactones, whose syntheses are mediated via the conformational promiscuity of the iduronic acid ring system. Both 1-OH and 2-OH of the iduronic acid system could form bridged lactones. Thus, free sugar derivatives of iduronic acid could lactonize either via the $^{1}C_{4}$ conformer (Route A, Figure 1) or an alternative 2,6-lactonization would be possible, but via the boat $B_{2,5}$ conformer (Route B, Figure 1) or closely-related $^{O}S_{2}$ skew-boat. Strategically, route **A** would directly protect O1 as a cyclic acyl whilst route **B** would instead selectively protect O2. It may be anticipated that the free sugar would proceed via the $^{1}C_{4}$ pathway (**A**), whilst replacing the anomeric hydroxyl (**B**) with a different group (e.g. SPh) would then only leave the possible lactonization pathway via the skew-boat. Of particular interest was the control of glycosylation reactivity of the thioglycoside [2.2.2] lactone.

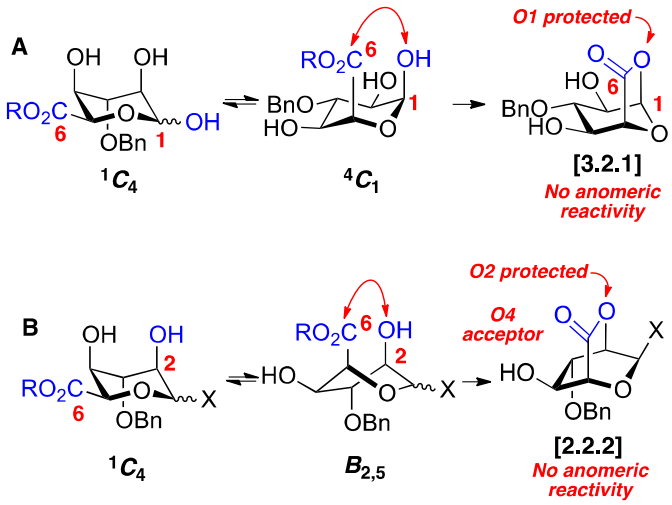
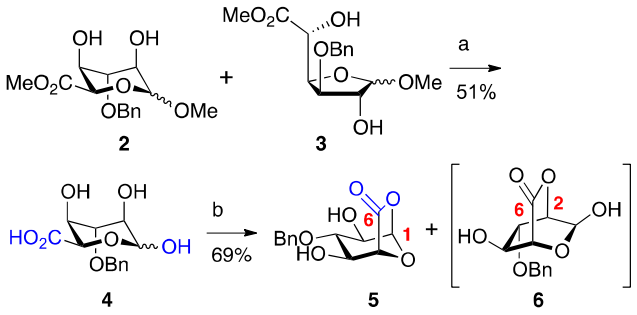


Figure 1. Conformationally-directed regioselective lactonization approaches to protected iduronate bicyclic lactones.

Thus, the mixture of **2**+**3** was saponified on large scale (>200 g), followed directly by acid hydrolysis of the methyl glycoside to afford 3-*O*-benzyl L-iduronic acid **4** (Scheme 2). This provides a practicable large scale 2-step process to afford 100 g batch access to L-iduronic acid derivative, **4**, requiring no purification or separation at the intermediate step, with the material isolated by precipitation and filtration. This offers a significant scale and process advantage over previous syntheses of parent L-iduronic acid derivatives.

Scheme 2. Large scale conversion of glycosides 2 and 3 into 3-OBn L-iduronic acid and derived lactones.[a]



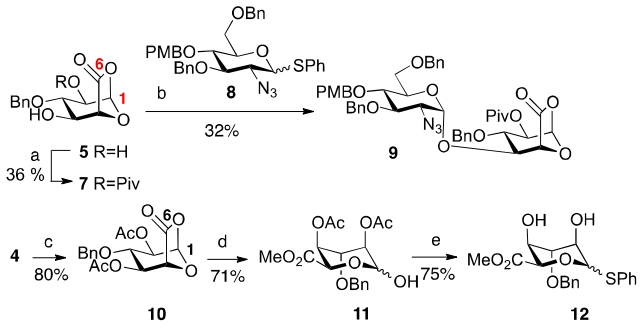
[a]Reagents and conditions: (a) (i) KOH, THF/MeOH/H_2O (ii) HCl, H_2O; (b) TsCl, Me-Imidazole, CH_3CN (additional 12% of **6**).

With a short and scalable access to **4** in hand, we then investigated methods to differentially protect groups within **4** through lactonization. This envisaged the temporary protection of the anomeric OH via a [3.2.1]-lactone (1,6-cyclization) or of the 2-OH via a [2.2.2]-lactone (1,6-cyclization; thereby de facto ensuring 4-OH as the only acceptor OH site). We reasoned that either lactone could be exploited for synthesis of new lactone O4 acceptors, but also then be elaborated to intercept (via ring-opening) L-iduronic mono- or disaccharide derivatives.

Reaction of **4** with TsCl in the presence of Me-imidazole converted **4** into the novel crystalline L-iduronate [3.2.1] lactone **5**, via cyclization of the 1-OH onto the intermediate tosylated carboxylate. The direction of lactonization was largely to the [3.2.1] outcome, with only small amounts of the alternative crystalline [2.2.2] lactone **6** isolated from the reaction mixture.

We investigated the regioselective protection of diol **5**, aiming to deliver a new O4 L-iduronic acceptor. Whilst benzoylation of **5** provided poor regioselectivity (7:5 of *O*-2 *vs O*-4), treatment of **5** with pivaloyl chloride afforded a better ratio (3:1) of the *O*-2/*O*-4 pivaloylated regioisomers, with the desired *O*-2 pivaloate **7** isolable by crystallisation on gram scale, making this a practicable process. (Scheme 3).

Scheme 3. Conversion of [3.2.1] iduronate lactone into disaccharide and L-iduronate thiophenyl glycoside[a]



[a]Reagents and conditions: (a) Piv-Cl, Me-Imidazole, THF, -15 ºC. (b) NIS, AgOTf, DCM. (c) (i) TsCl, Me-Imidazole, CH_3CN. (ii) Ac_2O, Me-Imidazole, MeCN. (d) MeOH, pyr. (e) (i) CCl_3CN, DBU, DCM. (ii) PhSH, TMSOTf, toluene. (iii) NaOMe, MeOH.[8]

The utility of lactone **7** as a glycosyl acceptor was evaluated *via* glycosylation with glucosamine-derived donor **8**.[8] The disaccharide product **9** was obtained as a pure α-anomer, though isolated in modest yield (32%), along with recovery of almost all the unreacted acceptor **7** and traces of a succinamide donor adduct. This indicated low acceptor capability for **7** with donor **8**, and provided an interesting addition to our prior reports using this donor, the trichloracetimidate and other modified L-IdoA acceptors, which had reported that L-iduronate ester and the 5-CN analogue are good acceptors, whilst the L-iduronamide performs even more poorly than **7**.[7,8] This provides further data that the nature of the C5 functionality strongly influences the reactivity of L-IdoA derivatives for O-4 glycosylations.

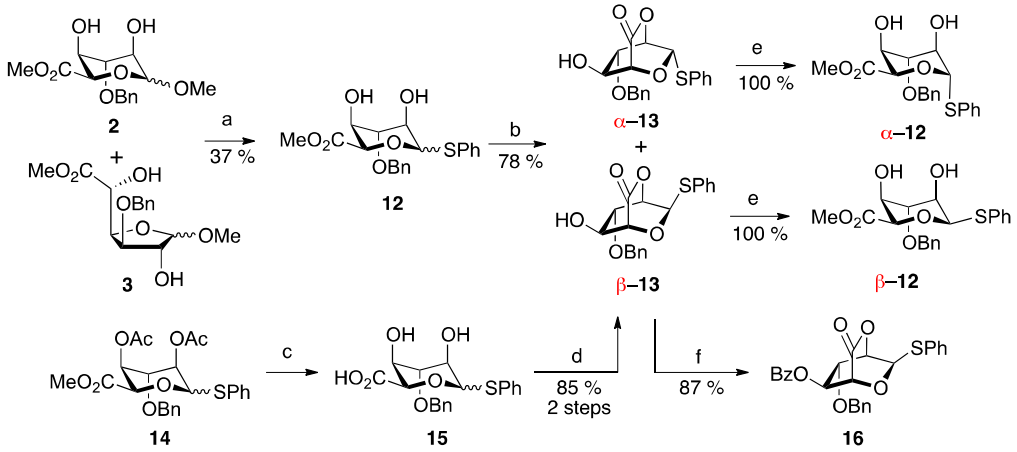
Conversion of **5** into known L-idopyranosides with donor funtionality requires opening of the lactone. The 1,6-lactone is attractive as a new construct as this offers a temporary protection of the anomeric hydroxyl, the utlility of such protection demonstrated by conversion of **4** into iduronates **11** and thence **12** (Scheme 3). Thus, **4** provided 80% yield of a 2,4-*O*-diacetylated derivative **10** in a single pot-process and on 40 g scale (along with formation of about 10% of diacylated 2,6-lactone **6**), with subsequent methanoloysis of the lactone affording L-iduronate derivative **11** (Scheme 3). Iduronate **11** was separable from the residual material and unreacted diacylated derivative of 2,6-lactone **6**. Iduronate **11** could be converted into L-IdoA thiolglycoside donor **12**, a previously described[8] key precursor for the L-iduronate unit employed in our syntheses of a diversity of longer heparanoids.

Whilst [3.2.1] lactone **5** was thus shown to be converted into the key thioglycoside iduronate **12** in only 4 steps from the feedstock mixture of glycosides **2** and **3** (22% overall yield), we also established that this iduronate methyl glycoside mixture **2**+**3** could be directly converged into **12** in just one step (Scheme 4). Under typical thioglycosylation conditions, **2**+**3** was converted directly into **12**, and though only isolated in modest yield (37%, α/β 1:3), this achieves the same conversion in one step and competitive overall yields.

No evidence of thiophenyl furanosides, nor any methyl furanoside starting material was observed. Our previously reported iodine-based work-up (oxidizing residual thiophenol) was also successful here, in facilitating a simple extraction suitable on scale.

Although evaluation of a range of changes to reaction conditions and reagents did not lead to further yield optimization, this synthesis now provides by far the shortest route described to such key L-iduronate thioglycosides, replacing multiple step routes by a one–pot conversion of **2**+**3** into **12**.

Scheme 4. Convergent conversion of iduronic pyranoside/furanoside mixture into anomerically pure [2.2.2] L-iduronic lactones and their opening to anomerically-pure iduronic thioglycosides[a]



[a]Reagents and conditions: (a) (i) PhSH, $BF_3{\cdot}OEt_2$, DCM. (ii) I_2, $NaHCO_3$. (b) $(Bu_3Sn)_2O$, toluene. (c) KOH, THF/MeOH/H_2O. (d) TsCl, Me-imidazole, CH_3CN. (e) Et_3N, MeOH, 1.5 h. (f) BzCl, pyridine, DCM.

The use of tin reagents to deliver regioselective protections is a common strategy in carbohydrate synthesis.[11] The dibutyl tin-oxide-mediated *O*-2 benzoylation of **12** is the approach we and others have previously employed.[8] We report here that a second type of L-iduronate lactone can be efficiently prepared from thioglycoside **12**, thereby differentiating O-2 *vs* O-4 functionalization by temporary protection of O-2 through lactonization. Thus, we found that **12** can be converted into the [2.2.2] lactone system **13** via cyclo-transesterification in two ways. Firstly, by directly heating **12** with bis(tributyltin) oxide (stannyl oxide-mediated cyclization of an OTDS glycoside analogue of **12** was reported previously).[3d] However, we also found that conversion to the 2,4-diacetate α/β–**14** and then complete ester hydrolysis, followed by tosylation-mediated lactonization of the resulting diol acid α/β–**15** provided a se-

cond route to thioglycoside lactones of type α/β–**13**. The use of iduronate lactones as synthetic building blocks has been very limited. The use of a 1-OTDS glycoside iduronate [2.2.2] lactone as an acceptor employed for synthesis of a heparin-related disaccharide was reported by Martin-Lomas *et al*,[3d] providing valuable precedent for the use here of the thioglycosidic [2.2.2] system as an acceptor. However, this prior report required subsequent conversion of the glycosidic ether into a donor functionality and is thus not related to modifying reactivity characteristics with a single anomeric group. Whereas inclusion of the thioglycosidic lactone reported here could, we reasoned, if the lactone were suitably disarmed with respect to gluco-thioglycosides, directly provide donor-ready heparin disaccharides without changing the anomeric group.

At this stage, the anomers of L-iduronate lactone **13** could be separated to provide multi-gram quantities of the pure thioglycoside anomers α–**13** and β–**13** (~1:3). The anomers of these novel lactones offer separability advantages on larger scale compared to monocyclic thioglycosides such as **12** and **14**.The β-anomer was 4-*O*-benzoylated providing crystalline material β–**16**, for which an X-ray structure determination was obtained (Figure 2. Unit Cell see Supplementary Data).[12]

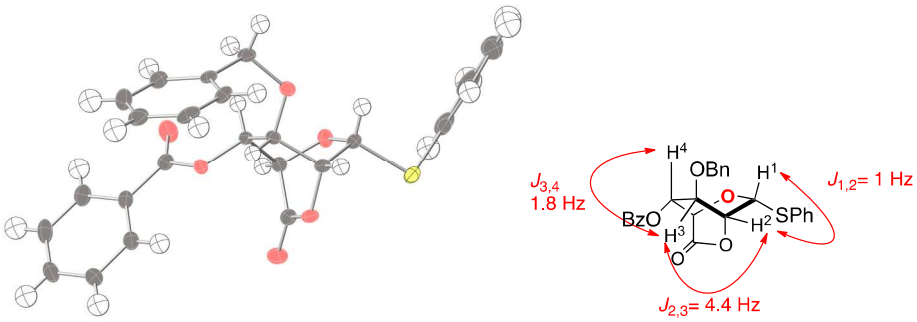


Figure 2. X-Ray Structure of [2.2.2] lactone β-**16** and ^{1}H solution state ^{3}J NMR coupling constants (400 MHz). [H5 not shown: $J_{4,5}$=4.4Hz]. The ^{1}H spectrum also shows ^{4}J couplings for H2-H5 of 0.4-0.9 Hz.

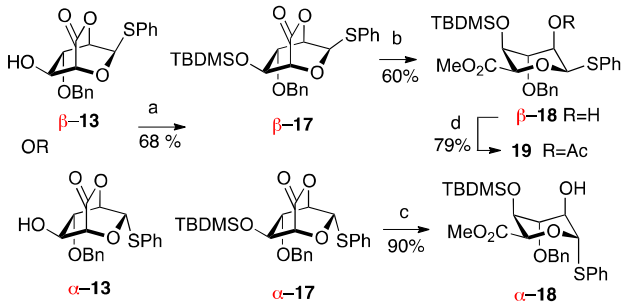
We next evaluated the methanoloysis of α–**13** and β–**13** to regenerate a free 2-OH and concurrently install the iduronate methyl ester, thereby providing anomerically pure quantities of 2,4-diol **12**. This proceeded in essentially quantitative yields for both anomers within 1.5 h at room temperature (Scheme 4). This thereby provides an alternative and scalable route to these anomerially pure methyl iduronate thioglycosides, α– and β–**12**, offering valuable process advantages. The differential protection of O-2 in these systems has been exploited previously for the synthesis of iduronate acceptors for heparin fragment syntheses by us and others (*vide supra*) and this de facto provides routes to both anomeric series of these.

Formation of a [2.2.2] lactone provides concurrent protection of O-2 and the carboxylate, leaving O-4 uniquely free which could provide two further possible advantages for the synthesis of heparin-related building blocks. Firstly, the selective protection of O-2 *via* lactone formation could enable specific protection of O-4, where re-opening the lactone would then provide differential functionalization of O-2 and O-4 (i.e. for donor iduronate thioglycosides). Secondly, the potential use of the [2.2.2] system as a glycosyl acceptor in coupling with D-glucosamine donors, with subsequent lactone opening *after* formation of disaccharide systems, would provide a useful addition to the use of lactone systems. Most significantly, were the thioglycoside relative reactivity suitably differ-

entiated from monocyclic thioglycoside glucosyl donors, then such lactones could be employed as a conformationally-controlled disarming/re-arming switch.

To evaluate the first of these approaches, for monosaccharide iduronate manipulations, the free 4-OH of α– and β–**13** was protected as its TBDMS ether, affording α– or β–**17**, respectively. The same methanolysis conditions effective in the esterolytic opening of **13** were evaluated. We observed that the methanolysis which had been equivalently facile on either anomer of **13**, showed notable kinetic differences between the two anomers of **17**, with a 4-OTBDMS installed. Thus, whilst methanolysis opening of α–**17** to α–**18** was complete in 18 h at room temperature, the same conditions led to little conversion for β–**17** to β–**18**, for which a prolonged reaction time (~72 h) was required to effect the same ring opening (Scheme 5).

Scheme 5. Protection and ring opening of anomers of [2.2.2] iduronic lactones[a]



[a]Reagents and conditions: (a) TBDMSCl, ImH, DCM. (b) MeOH, Et_3N, 72 h, r.t. (c) MeOH, Et_3N, 16 h, r.t. (d) DMAP, Ac_2O. pyr., DCM.

This large difference in rate of esterolysis of α– and β–**17**, and the dramatic difference to the behavior of the 4-OH analogues, we rationalize is at least in part due to the steric effects of two large substituents (SPh and OTBDMS) which hinder attack from either face of the ester carbonyl (Figure 3). The ring opened β–**18** was also a notably poor substrate for *O*-2 benzoylation (also supportive of a steric crowding at O2), but was efficiently acylated to **19**. These ring-opened iduronates **18** are only five steps from our large-scale feedstock cyanohydrin **1** and thus offer considerable scope for further diversification to various anomerically-pure, fully-differentiated new and known iduronic acid derivatives.

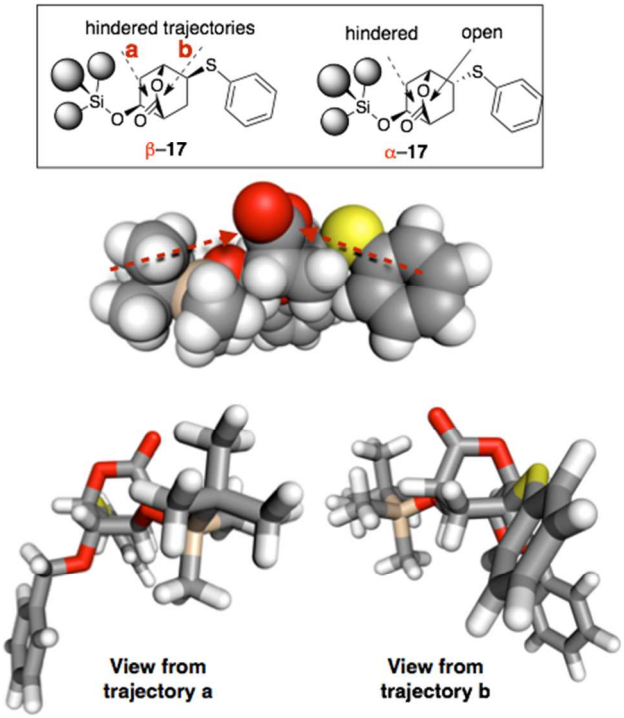


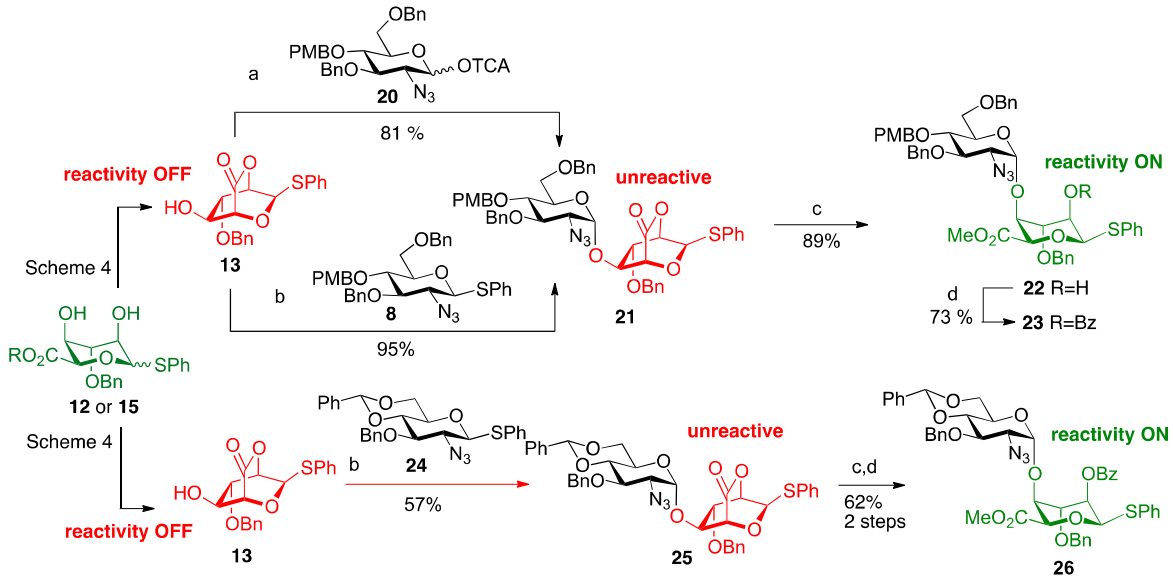
Figure 3. Esterolysis of β–**17** is considerably slower than α–**17**, rationalized on the basis of steric hindrance of both carbonyl faces in β-**17**.

The second utlilization of [2.2.2] lactone **13** demonstrates its capability as an effective acceptor for reaction with glucoazide donors to afford disaccharides suitable for oligosaccharide synthesis.. Thus, β–**13** was reacted with 2-azido gluco trichloroacetimidate **20**[8] to provide novel lactone-disaccharide **21** in good yield and with high anomeric selectivity (Scheme 6). Whilst this parallels the precedent for the 1-OTDS analogue of **13**,[3d] significantly, we found that the lactone thioglycoside is sufficiently disarmed that it can also be converted to disaccharide **21** using the 2-azido thioglycoside donor **8** in excellent yield (6:1 α:β). This yield was notably higher using toluene (90%) rather than DCM (60%).

This reactivity control provides a critical addition to the utility of such a lactone acceptor, exploiting the disarmed nature of the lactone thioglycoside to provide access directly to thioglycoside donor disaccharides via such lactone-OFF to opened-ON glycosylation donor capability. Methanolysis of the lactone of disaccharide **21** provided novel disaccharide **22** (under slightly stronger basic conditions for this β–lactone opening, cf. Scheme 5) which was then *O*-2 benzoylated to provide GlcN-IdoA thioglycoside disaccharide **23**, previously prepared by non-lactone intermediates[13] and suitable for direct use in established oligosaccharide homologations.[9]

In addition, lactone **13** was also a viable acceptor reacting with 4,6-benzylidine-protected 2-azido thioglycoside donor **24** to give lactone disaccharide **25**. This lactone also underwent similar methanolysis and benzoylation to afford a second example disaccharide thioglycoside **26**, similarly intercepting our recently reported non-lactone route.[13]

Scheme 6. [2.2.2] Iduronic lactone as disarmed thioglycoside acceptor for HS disaccharide synthesis via post-glycosylation lactone esterolysis[a]



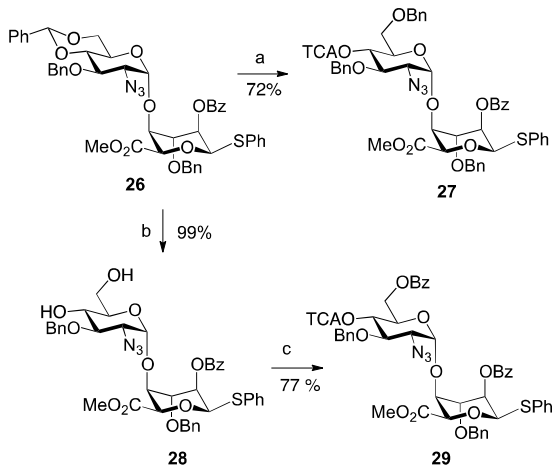
[a]Reagents and conditions: (a) TMSOTf, DCM. (b) NIS, AgOTf, toluene. (c) NaOMe, MeOH, (d) BzCl, Me-Imidazole, DCM.

Bicyclization has been previously employed in L-IdoA units to influence the stereocontrol of the glycosidation using these as an *acceptor*.[3d,7] However, here, as we have already established previously that the analogous monocyclic iduronates act as effective donors for highly stereoselective glycosylations, the current work provides a new conformationally-controlled on/off regulation of iduronate thioglycoside donor capability.

This is strategically significant as it now enables synthetic approaches to diverse longer H/HS targets with all glycosylations being effected using shelf-stable thiophenyl glycosides of both the D-GlcN and L-IdoA components. Since we report here multigram scale 2-step access to pure **13** from the crude glycoside mixture **2**+**3**, overall this provides a useful route to key heparin disaccharide donors in only 5 steps from **2**+**3**, and 6 steps from bulk cyanohydrin **1**.

Disaccharide **23** contains a 6-OBn protecting group, which, in our prior syntheses enabled the introduction of a 6-OH into the final oligosaccharide target.[9] Disaccharide **26** was also converted into the analogous 4-*O*TCA/6-*O*-Bn disaccharide **27** (Scheme 7) and also its 6-OBz analogue **29**, via diol **28**. We also included 6-OBz in previous deacasaccride synthesis to programme per-6-*O*-sulfation.[10] Thus, benzylidine-protected **26** provides a divergent route to disaccharides whose *O*-6 protection programmes towards either 6-OH or 6-OSO_3Na oligosaccharides, and thus either of the O6 modifications seen in heparin- or heparan sulfate structures.

Scheme 7. Synthesis of β–thioglycoside GlcN-IdoA heparin-related disaccharides[a]



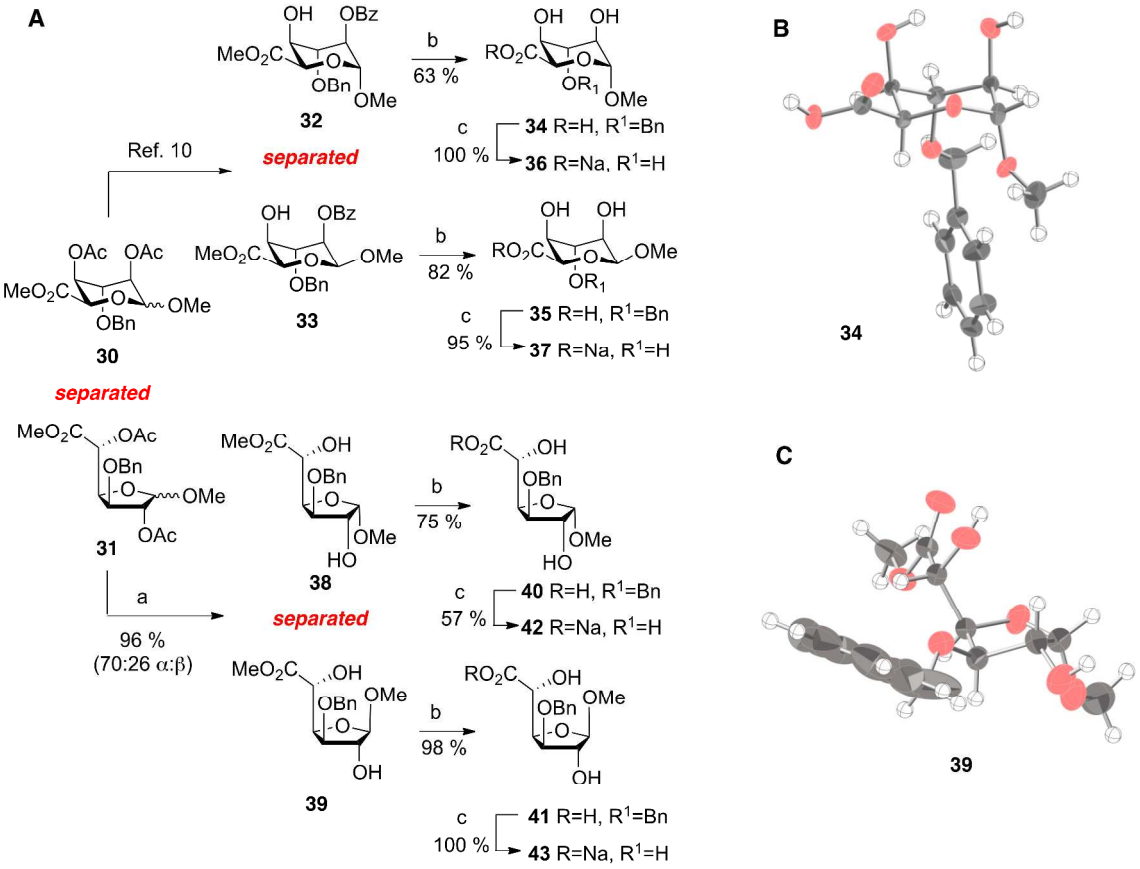
[a]Reagents and conditions: (a) (i) Et_3SiH, $BF_3{\cdot}OEt_2$, DCM. (ii) pyridine, CCl_3COCl. DCM (b) EtSH, *p*-Toluenesulfonic acid (cat.), DCM. (c) BzCl, pyridine, DCM then CCl_3COCl.[8]

In summary, this work provides a number of significant process advantages in demonstrating that a bulk mixture of L-iduronate glycosides **2**+**3** can be converged to important monosaccharide iduronates, but also provides a new approach to fully differentiate O-2 and O-4, concurrent with a new conformational-regulator which de-activates the thioglycosides as a donor. The impact of this on synthetic design for oligosaccharide synthesis is significant, enabling introduction of all glycosidic bonds by thioglycoside couplings, with no need to interconvert any anomeric groups. The interception of previously-exploited disaccharides providing thereby a formal total synthetic approach to heparin-like and heparin-sulfate like oligosaccharides, based on use of thiophenyl glycoside couplings alone.

Having previously only separated the pyranoside/furanoside mixture **2**+**3** as anomeric mixtures of their diacetates,[10] we also wished to illustrate that this mixture could also provide a practicable route to all four ring size/anomeric parent iduronic acid glycosides. Thus, the previously separated diacetates of the pyranosides and furanosides were elaborated as shown in Scheme 8A. The pyranoside anomers were separated (as we previously described[10]) as their 2-*O*-benzoates **32** and **33**, with subsequent hydrolysis and hydrogenolysis then affording the pure known α– and β–idopyranosides **36** and **37**, respectively. In the case of the furanosides, diols **38** and **39** proved separable directly, and were then also similarly elaborated to their novel parent idofuranoside glycosides **42** and **43**. This thus employs the **2**+**3** mixture for a convenient divergence/separation approach to afford all four ring and anomeric isomers of L-iduronic acid methyl glycosides. This is particularly notable in providing the first syntheses of the previously unknown furanosides of this important hexoside.

Additionally, we obtained X-ray structures for examples of each ring size, as shown in Scheme 8b. The pyranoside **34** adopts a $^1C_4$ chair in the crystal (Scheme 8B), consistent with evidence from NMR data for previous derivatives,[8] whilst the previously unknown furanoside **39** adopts a $^2T_3$ conformation (Scheme 8C).

Scheme 8. Synthesis of all four iduronic methyl pyranosides and furanosides and X-ray structures of example idofuranoside and idopyranoside[a]



(**A**) [a]Reagents and conditions: (a) NaOMe, MeOH. (b) aq. KOH (1 equiv. 0.4 or 0.6 M), THF/MeOH (2:1). (c) H_2, $Pd(OH)_2$/C.

(**B**) ORTEP of idopryanoside **34**[12]; (**C**) ORTEP of idofuranoside **39**.[12]

■ CONCLUSIONS

This work reports that the crude hydrolysis products from L-idocyanohydrin **1** – available on multi-hundred gram scales - can be conveniently re-converged to elaborated L-idopyranosides. This is a valuable process advantage providing short routes for large batch scale synthesis from inexpensive feedstocks. Particularly, this mixture is converted via an idopyranoside thioglycoside into a new [2.2.2] thioglycoside L-ido lactone. This concurrently protects the carboxylate and O-2, leaving the key O-4 glycosylation site free. This lactone can be prepared on multi-gram scales, and we show that it can act directly as an effective acceptor for the synthesis of GlcN-IdoA disaccharides. This lactone is substantively disarmed relative to other thioglycosides and varied glucoazide thioglycosides can be employed as donors, with subsequent near-quantitative opening of the lactone in the derived disaccharide, re-arming the ido thioglycoside via ring-opening, thereby providing short access to several heparin-related disaccharide thioglycoside donors. These disaccharides have already been shown to be key units for assembling long synthetic heparin-related oligosaccha-

rides and are now available in 4 or 6 steps directly from the crude glycoside mixture **2**+**3**, which is preparable on 200 g batch scales. This route from a bulk glycoside mixture (**2**+**3**) via a novel lactone advances the practicability of total synthesis of a range of highly important H/HS oligosaccharides by significantly reducing the number of steps for, and with enhanced scalability of, the synthesis of such important units, underpinned by our introduction of a new type of conformational control of anomeric reactivity in such building blocks. Additionally, the **2**+**3** mixture is shown to be a precursor to provide short access (4 or 5 steps) to all the possible iduronic acid methyl glycosides in both pyranoside and furanoside forms, affording the first synthesis of parent idofuranosides.

■ EXPERIMENTAL SECTION

3-*O*-Benzyl-β-L-idopyranuronic acid 4

Crude **2/3** (210 g, 0.673 mol) was dissolved in a mixture of THF/MeOH (800 mL 3:1 v:v) and KOH (37.8 g, 0.674 mol) dissolved in H_2O (300 mL) added over 30 min (exothermic reaction). The reaction mixture was stirred for another 90 min. and then evaporated. To the crude carboxylate product was added H_2O (860 mL) and conc. HCl (140 mL) with stirring and then heated to 100 °C for 1 h. The acidic solution was treated with solid $NaHCO_3$ (88.3 g) until pH ~ 3, water was evaporated, the product redissolved in THF (1 L) using sonication, salts filtered off and washed with THF (5x300 mL). The organic fractions were combined and solvent removed in vacuo to give crude **4** (154 g). Purification was achieved by resuspending the crude in a $CHCl_3$/MeOH (600 mL/30 mL) mixture followed by sonication and filtration of the fine precipitate. This yielded **4** (97.1 g, 51%) as a white powder. R_f 0.03 (EtOAc + 1% HCOOH); ^{1}H NMR (400 MHz; CD_3SOCD_3) δ 12.73-12.53 (broad s, 1H, COO*H*), 7.39-7.26 (m, 5H, Ph), 6.79-6.68 (broad s, 1H, O*H*), 5.17-5.10 (broad s, 1H, O*H*), 4.82-4.80 (m, 1H, H-1), 4.64-4.62 (m, 2H, CH_2Ph), 4.30 (d, J = 1.6 Hz, 1H, H-5), 3.88-3.85 (m, 1H, H-4), 3.71 (t, J = 3.2 Hz, 1H, H-3), 3.60-3.58 (m, 1H, H-2); ^{13}C NMR (101 MHz; CD_3SOCD_3) δ 170.5, 138.2, 128.4, 127.7, 127.6, 92.9, 76.7, 73.8, 71.1, 67.9, 67.3; HRMS (TOF ES$^-$) calcd for $C_{13}H_{15}O_7$ [M-H]$^-$: 283.0823, found: 283.0816; Elemental analysis calcd (%) for $C_{13}H_{16}O_7$: C 54.93, H 5.67; found C 54.81, H 5.71.

3-*O*-Benzyl-β-L-idopyranurono-1,6-lactone 5+6

Iduronic acid **4** (27.9 g, 0.098 mol) was dissolved in dry CH_3CN (300 mL) and cooled to 0 °C in an ice bath. 1-Methylimidazole (7.8 mL, 0.098 mol) was then added and after 15 min tosyl chloride (16.9 g, 0.088 mol) added in portions over 30 min. The reaction mixture was stirred for another 1 h and another portion of 1-methylimidazole (7.8 mL, 0.098 mol) added over 10 min. The mixture was stirred another 1 h and the solvent evaporated. The crude was purified by silica gel flash column chromatography (dry loaded, EtOAc/hexane 1:1 to 1:0 v:v) to give a mixture of 1,6- and 2,6-lactone products (9:1, estimated from ^{1}H NMR). Further purification of the 1,6-lactone was achieved by crystallization (dissolved in EtOAc and two times volume hexane then added) yielding **5** (16.8 g, 69%) as white needles. R_f 0.31 (EtOAc/hexane 1:1 v:v); mp 159-161 °C; $[\alpha]_D^{20}$ = +99.3 (c = 0.35, acetone); ^{1}H NMR (400 MHz; CD_3COCD_3) δ 7.41-7.23 (m, 5H, Ph), 5.77 (d, J = 2.1 Hz, 1H, H-1), 5.09 (d, J = 4.9 Hz, 1H, O*H*-4), 4.99 (d, J = 6.5 Hz, 1H, O*H*-2), 4.91 (d, J = 11.6 Hz, 1H), 4.87 (d, J = 11.6 Hz, 1H), 4.39 (d, J = 4.6 Hz, 1H, H-5), 3.98 (dt, J = 8.4, 4.7 Hz, 1H, H-4), 3.85 (ddd, J = 7.9, 6.4, 2.1 Hz, 1H, H-2), 3.57 (t, J = 8.4 Hz, 1H, H-3); ^{13}C NMR (101 MHz; CD_3COCD_3) δ 170.7, 140.1, 128.9, 128.4, 128.1, 104.7, 84.7, 75.4, 73.7, 73.4, 70.7; HRMS (TOF ES$^+$)

calcd for $C_{13}H_{14}NaO_6$ $[M+Na]^+$: 289.0683, found: 289.0680. The ido 2,6-lactone **6** was isolated from the above mixture of lactones by careful column chromatography (EtOAc/hexane 1:2 v:v) followed by crystallization (dissolved in EtOAc and enough hexane added until the solution begins to appear cloudy) yielding **6** (1.5 g, 5.6 mmol, 12%) as long needles. mp 154-156 °C; $[\alpha]_D^{20}$ = +79.7 (*c* = 0.68, acetone); ^{1}H NMR (400 MHz; CD_3COCD_3) δ 7.42-7.31 (m, 5H, Ph), 6.12 (broad s, 1H, OH), 5.49 (s, 1H, H-1), 5.10 (broad s, 1H, OH), 4.80-4.70 (m, 2H, C*H*$_2$Ph), 4.78 (dt, *J* = 4.4, 0.8 Hz, 1H, H-2), 4.18 (dd, *J* = 4.1, 0.5 Hz, 1H, H-5), 4.16 (dd, *J* = 4.0, 2.2 Hz, 1H, H-4), 3.87 (dd, *J* = 4.2, 2.1 Hz, 1H, H-3); ^{13}C NMR (101 MHz; CD_3COCD_3) δ 169.1, 138.6, 129.2, 128.6, 88.7, 80.0, 76.6, 73.4, 72.5, 72.1; HRMS (TOF ES$^+$) calcd for $C_{13}H_{15}O_6$ $[M+H]^+$: 267.0864, found: 267.0860.

2-*O*-Pivaloyl-3-*O*-benzyl-β-L-idopyranurono-1,6-lactone 7

Lactone **5** (16.8 g, 0.063 mol) was dissolved in dry THF (200 mL) and cooled to -15 °C. 1-Methylimidazole (5.0 mL, 0.063 mol) was then added followed by pivaloyl chloride (7.77 mL, 0.063 mol). The mixture was stirred 1 h and the solvent removed *in vacuo*. The crude product was purified by silica gel flash column chromatography (dry loaded, EtOAc/hexane 1:2 to 1:1 v:v). From NMR it was determined to be a mixture of O2-/O4-pivaloate products (3:1). Pure O2-pivaloate regioisomer was isolated by crystallization (dissolved in EtOAc and three times volume of hexane added) yielding **7** (8.0 g, 36%) as a white powder. R_f 0.22 (EtOAc/hexane 1:3 v:v); mp 201-203 °C; $[\alpha]_D^{20}$ = +130.2 (*c* = 0.27, acetone); ^{1}H NMR (400 MHz; CD_3COCD_3) δ 7.35-7.26 (m, 5H, Ph), 5.92 (d, *J* = 2.0 Hz, 1H, H-1), 5.36 (d, *J* = 4.9 Hz, 1H, O*H*), 4.94 (dd, *J* = 8.8, 2 Hz, 1H, H-2), 4.91 (d, J = 11.2 Hz, 1H, C*H*$_2$Ph), 4.71 (d, J = 11.2 Hz, 1H, C*H*$_2$Ph) 4.51 (d, *J* = 4.7 Hz, 1H, H-5), 4.13 (dt, *J* = 8.4, 4.7 Hz, 1H, H-4), 3.78 (t, *J* = 8.4 Hz, 1H, H-3), 1.21 (s, 9H); ^{13}C NMR (101 MHz; CD_3COCD_3) δ 177.8, 170.0, 139.3, 128.9, 128.3, 128.3, 101.1, 81.4, 75.5, 73.5, 73.3, 70.8, 39.3, 27.2; HRMS (TOF ES$^+$) calcd for $C_{18}H_{22}NaO_7$ $[M+Na]^+$: 373.1258, found: 373.1269.

2-Azido-3,6-di-*O*-benzyl-2-deoxy-4-*O*-*p*-methoxybenzyl-α-D-glucopyranosyl-(1⟶4)-2-*O*-pivaloyl-3-*O*-benzyl-β-L-idopyranurono-1,6-lactone 9

Acceptor lactone **7** (350 mg, 1.0 mmol) and thioglycoside donor **8** (656 mg, 1.1 mmol) were dissolved in dry DCM (10 mL) under N_2. Freshly activated 4Å powdered molecular sieves (300 mg) were added and the solution kept at RT. After 10 min NIS (742 mg, 3.0 mmol) was added, and after another 10 min AgOTf (12 mg, 0.05 mmol) was added. The suspension changed colour from pale yellow to deep purple, was stirred for 15 min and then quenched into a separating funnel containing a mixture of DCM (30 mL), saturated aqueous $NaHCO_3$ (20 mL) and $Na_2S_2O_3$ (10 mL, 10% aqueous). After shaking until the iodine colour was removed, the suspension was filtered through a short pad of Celite® washing with water and DCM. The layers were separated and the aqueous extracted with DCM (30 mL). The organic layers were combined, dried ($MgSO_4$) and solvent removed *in vacuo*. The crude product was purified by silica gel flash column chromatography (EtOAc/hexane 1:2) to give **9 (**274 mg, 32%) as a white foam. **7** (249 mg, 71%) was also recovered. R_f 0.35 (EtOAc/hexane 1:3); $[\alpha]_D^{20}$ = +48.8 (*c* = 1.15, CH_2Cl_2); 7.42-7.28 (18 H, m, Ph), 7.15 (2 H, d, *J* = 8.7 Hz, PMB), 6.87 (2 H, d, *J* = 8.7 Hz, PMB), 5.87 (1 H, d, *J* = 2.1 Hz, H-1), 5.18 (1 H, d, *J* 3.9, H'-1), 5.07 (1 H, d, *J* = 10.6 Hz, C*H*$_2$Ph), 4.97 (2 H, m, C*H*$_2$Ph, H-2), 4.91 (1 H, d, 10.4 Hz, C*H*$_2$Ph), 4.85 (1 H, d, *J* = 3.9 Hz, H-5), 4.79 (1 H, d, *J* = 10.7 Hz, C*H*$_2$Ph), 4.71 (1 H, d, *J* = 10.6 Hz, C*H*$_2$Ph), 4.63 (1 H, d, *J* = 12.1, C*H*$_2$Ph), 4.53 (2 H, dd, *J* =11.4, 3.5, C*H*$_2$Ph), 4.33 (1 H, dt, *J* = 10.1, 3.2, H'-5'), 4.00-3.95 (3 H, m, H-3, H'-3, H-4), 3.85-3.82 (3 H,

s, PMB OCH_3), 3.74 (2 H, d, J = 3.4 Hz, H'-$6_{a/b}$), 3.68 (1 H, dd, J = 9.9, 9.1 Hz, H'-4), 3.59 (1 H, dd, J = 10.3, 3.8 Hz, H-2'), 1.28 (10 H, s, C(CH_3)$_3$). ^{13}C NMR (100 MHz; $CDCl_3$) δ 177.8, 169.3, 159.4, 137.8, 137.72, 129.6, 128.5, 128.2, 128.0, 127.9, 127.8, 127.7, 113.9, 100.7, 100.1, 80.3, 79.0, 78.6, 78.0, 77.5, 77.2, 76.9, 75.8, 75.6, 74.6, 73.5, 73.5, 71.5, 70.9, 68.6, 63.9, 55.3, 38.9, 27.1; HRMS (TOF ES$^+$) calcd for $C_{46}H_{51}N_3NaO_{12}$ $[M+Na]^+$: 860.3365, found: 860.3361.

Methyl 2,4-di-*O*-acetyl-3-*O*-benzyl-α/β-L-idopyranuronate 10

Iduronic acid **4** (40.9 g, 0.144 mol) was dissolved in dry CH_3CN (500 mL) and cooled to 0 °C in an ice bath. 1-Methylimidazole (11.5 mL, 0.144 mol) was then added and after 5 min tosyl chloride (24.9 g, 0.130 mol) added in one portion. The reaction mixture was stirred for 90 min and another portion of 1-methylimidazole (11.5 mL, 0.144 mol) added over 10 min. The mixture was stirred another 1 h, acetic anhydride (30 mL, 0.317 mol) added, left over night and the solvent evaporated. The crude was extracted with DCM (600 mL)/ H_2O (2 x 500 mL) and $NaHCO_3$ (sat.) /brine (1:1, 500 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated. The crude mixture was purified by silica gel flash column chromatography (toluene/acetone 20:1 to 10:1 v:v). Further purification could be achieved by crystallization (dissolved in EtOAc and three times volume hexane added) yielding **10** (40.4 g, 80%) as white plates. Analytical data matched those previously reported.[8]

Methyl 2,4-di-*O*-acetyl-3-*O*-benzyl-α/β-L-idopyranuronate 11

The lactone mixture **10** (40.4 g, 0.115 mol, 9:1) was dissolved in MeOH (500 mL), pyridine (5 mL) added and heated to 50 °C for 12 h. After evaporation of solvents the crude was purified using silica flash column chromatography (EtOAc/hexane, 1:1 v:v). This yielded **11** (39.4 g, 89%, α/β 2:1) as an oil. Also unreacted diacylated 2,6-lactone (4.07 g, 10%) was isolated. R_f 0.10 (EtOAc/hexane 1:1 v:v); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.35-7.26 (m, 5H, Ph), 5.32-5.31 (m, 0.6H, H-1α), 5.19 (t, J = 2.6 Hz, 0.6H, H-4α), 5.16 (d, J = 1.7 Hz, 0.3H, H-1β), 5.12-5.10 (m, 0.3H, H-4β), 5.02 (d, J = 2.3 Hz, 0.6H, H-5α), 4.90-4.88 (m, 0.3H, H-2β), 4.82-4.81 (m, 0.6H, H-2α), 4.78-4.70 (m, 2H, CH_2Ph), 4.66 (d, J = 2.0 Hz, 0.3H, H-5β), 3.95 (t, J = 2.9 Hz, 0.3H, H-3β), 3.88 (dt, J = 3.0, 1.3 Hz, 0.6H, H-3α), 3.75 (s, 2H, COOCH_3), 3.73 (s, 1H, COOCH_3), 2.08 (s, 1H, CH_3CO), 2.02 (s, 2H, CH_3CO), 2.01 (s, 2H, CH_3CO), 1.99 (s, 1H, CH_3CO); ^{13}C NMR (101 MHz; $CDCl_3$) δ 170.3, 169.9, 169.7, 169.7, 169.0, 168.2, 149.3, 136.8, 136.5, 128.6, 128.6, 128.5, 128.4, 128.2, 128.0, 127.8, 123.9, 92.9, 92.0, 73.1, 73.0, 72.8, 72.5, 71.8, 68.0, 67.2, 67.1, 67.0, 65.7, 52.6, 20.9, 20.8, 20.7, 20.6; HRMS (TOF ES$^+$) calcd for $C_{18}H_{22}NaO_9$ $[M+Na]^+$: 405.1156, found: 405.1152.

Diacylated **6***: R_f* 0.23 (EtOAc/hexane 1:3). $[\alpha]_D^{20}$ = +51.4 (c = 0.55, CH_2Cl_2). ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.36-7.28 (m, 5H, Ph), 6.40 (d, J = 1.2 Hz, 1H, H-1), 5.13 (ddd, J = 4.4, 1.7, 0.6 Hz, 1H, H-4), 4.77-4.58 (m, 3H, H-2, CH_2Ph), 4.47 (d, J = 4.1 Hz, 1H, H-5), 3.92 (dd, J = 4.4, 1.8 Hz, 1H, H-3), 2.10 (s, 3H, COCH_3), 2.04 (s, 3H, COCH_3). ^{13}C NMR (101 MHz; $CDCl_3$) δ 169.5, 169.1, 166.1, 136.2, 128.8, 128.6, 128.2, 87.8, 75.4, 74.1, 72.7, 71.0, 69.4, 21.0, 20.6. HRMS (TOF ES$^+$) calcd for $C_{17}H_{18}O_8Na$ $[M+Na]^+$: 373.0894, found: 373.0888.

Methyl (3-*O*-benzyl-1-thiophenyl-α,β-L-idopyranoside) uronate 12

The methyl furanoside/pyranoside mixture **2+3** (89.0 g, 0.285 mol) was dissolved in DCM (1.8 L), powdered molecular sieves 4Å (93 g) and thiophenol (34 mL, 0.33 mol) added. To the vigorously stirred mixture was added $BF_3{\cdot}OEt_2$ (105 mL, 0.86 mol) and left for 45 min.

The reaction mixture was slowly poured into a 5 L beaker with saturated aqueous $NaHCO_3$ (300 g in 1.8 L H_2O) with stirring (**NOTE**: Heavy foaming observed). To the stirred mixture was added iodine until the dark red colour persisted (**NOTE**: this converts thiophenol into diphenyl disulfide thus removing the excess of the odorous toxic reagent). To remove the excess iodine a small amount of $Na_2S_2O_3$ (10% aqueous) was added. The organic layer was separated, dried ($MgSO_4$) and solvent removed *in vacuo*. The crude was purified by silica gel flash column chromatography (EtOAc/hexane gradient 1:2 to 1:1 v:v) to give **12 (**41.5 g, 37%, α/β 1:3) as a viscous oil. Also starting material pyranoside (8.2 g, 9 %) could be recovered. Analytical data matched those previously reported.[3d]

Lactone **α,β-13** was also converted into **α,β-12** by methanolysis on 1g scale (MeOH (20 mL), Et_3N (0.05 mL) for 2 h, removal of solvents and crystallization from EtOAc:hexane (30 mL, 1:2, v:v)).

Methyl (3-*O*-benzyl-1-thiophenyl-β-L-idopyranoside) uronate β–12

From **β–18**: TBDMS protected iduronate **β–18** (114 mg, 0.23 mmol) was dissolved in dry THF (2 mL) and the solution cooled to 0 °C. Tetrabutylammonium fluoride solution (250 µL, 1 M in THF) was added dropwise and the reaction stirred at 0 °C for 30 min. The solvents were removed and the crude product purified by silica gel flash column chromatography (hexane/ethyl acetate 1:1 v:v) to afford **β–12** as a yellow oil (61 mg, 0.16 mmol, 70%).

From **β–13**: Lactone **β–13** (104 mg) was stirred in MeOH (2 mL), Et_3N (0.04 mL, 1 eq.) for 1.5 h, removal of solvents and chromatography isolating **β–12**. R_f 0.38 (1:1 EtOAc/hexane); $[\alpha]_D^{20}$ = +37.9 (c = 0.10, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): 7.56–7.54 (2 H, m, Ar*H*), 7.34–7.26 (8 H, m, Ar*H*), 5.20 (1 H, d, *J* = 1.1 Hz, H-1), 4.63 (1 H, d, *J* = 11.2 Hz, C*H*$_2$Ph), 4.59 (1 H, d, *J* = 12.1 Hz, C*H*$_2$Ph), 4.53 (1 H, d, *J* = 1.3 Hz, H-5), 4.15 (1 H, dt, *J* = 3.0, 1.4 Hz, H-4), 4.01–4.00 (1 H, m, H-2), 3.95 (1 H, t, *J* = 3.2 Hz, H-3), 3.82 (3 H, s, CO_2CH_3); δ_c (100 MHz, $CDCl_3$): δ 169.8 (C=O), 137.4 (Ar C), 134.3 (Ar C), 131.6 (Ar CH), 129.2 (Ar CH), 128.8 (Ar CH), 128.3 (Ar CH), 127.9 (Ar CH), 127.7 (Ar CH), 87.2 (C-1), 76.2 (C-5), 75.5 (C-3), 72.7 (CH_2Ph), 69.7 (C-2), 67.6 (C-4), 52.8 (CH_3); HRMS calcd for $C_{20}H_{26}O_6SN$ $[M+NH_4]^+$: 408.1475, found 408.1472.

Methyl (phenyl 3-*O*-benzyl-1-thiophenyl-α-L-idopyranoside) uronate α–12

From **α–18**: Prepared as **β–12**, R_f 0.44 (EtOAc/hexane 1:1); $[\alpha]_D^{20}$ = –226.8 (*c* = 0.55, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.54-7.52 (m, 2 H, Ph), 7.45-7.25 (m, 8 H, Ph), 5.59 (s, 1H, H-1), 5.25 (d, *J* = 1.5 Hz, 1 H, H-5), 4.79 (d, *J* = 11.9 Hz, 1 H, C*H*$_2$Ph), 4.64 (d, *J* = 11.9 Hz, 1 H, C*H*$_2$Ph), 4.20-4.17 (m, 2 H, H-2, H-4), 3.84 (td, *J* = 3.3, 0.9 Hz, 1 H, H-3), 3.82 (s, 3 H, COOC*H*$_3$); ^{13}C NMR (101 MHz; $CDCl_3$) δ 170.7, 137.4, 136.3, 130.9, 129.0, 128.6, 128.0, 127.7, 127.3, 89.4, 74.4, 72.4, 68.9, 68.8, 68.5, 52.6; HRMS (TOF ES$^+$) calcd for $C_{20}H_{26}O_6SN$ $[M+NH_4]^+$: 408.1475, found: 408.1472. Data collected matched those previously reported (ref 3d titles as **β**).[3d]

From **α–13**: Lactone **α–13** (76 mg) was stirred in MeOH (2 mL), Et_3N (0.04 mL, 1 eq.) for 1.5 h, removal of solvents and crystallization from EtOAc:hexane (1:3) providing **α–12**.

3-*O*-Benzyl-1-thiophenyl-α/β-L-idopyranoside urono-2,6-lactone 13

Method A – 2 steps) Step 1: The thioglycoside diacetate **14** (12.0 g, 25.3 mmol) was dissolved in THF / MeOH (130 mL 10:3 v:v), cooled to 0 °C and KOH (4.33 g, 77.1 mmol) dissolved in H_2O (80 mL) added. After stirring for 2 h, the reaction was extracted with EtOAc (300 mL)/ HCl 0.3 M (300 mL) and the organic phase dried ($MgSO_4$), filtered and evaporated. The crude was purified using silica gel flash column chromatography (EtOAc/hexane, 1:1 v:v + 1% HCOOH). This yielded intermediate iduronic acid thioglycoside **15** (9.1 g, 95%, α/β 1:3) as a foam. HRMS (ES^+) calcd for $C_{19}H_{20}NaSO_6$ $[M+Na]^+$: 399.0873, found: 399.0875. The α/β-anomers could not be separated and were used as such for the next step.

Step 2: The iduronic acid thioglycoside mixture **15** (9.5 g, 25.3 mmol) was dissolved in dry DCM (200 mL), cooled to 0 °C, 1-methylimidazole (2.11 mL, 26.6 mmol) and after 5 min., tosyl chloride (5.05 g, 26.5 mmol) added in one portion. The reaction mixture was stirred for 1 h and another portion of 1-methylimidazole (2.12 mL, 26.7 mmol) added over 10 min. After stirring for 3 h, the reaction was extracted with DCM (300 mL)/ H_2O (2 x 200 mL) and the organic phase dried ($MgSO_4$), filtered and evaporated. The crude was purified using silica gel flash column chromatography (toluene/acetone 30:1 to 20:1) separating the α/β-anomers. This yielded **α–13** (2.2 g, 22%) and **β–13** (6.1 g, 68%) as white solids after crystallization (dissolved in EtOAc and 4 times volume of hexane).

Method B) The thioglycoside diol mixture **12** (1.20 g, 3.08 mmol) was dissolved in toluene (50 mL) and $(Bu_3Sn)_2O$ (0.80 mL, 1.54 mmol) added. The reaction mixture was heated to reflux for 3 h, solvent evaporated and the crude was purified using silica flash column chromatography (EtOAc/hexane 1:3). This yielded **13** (0.86 g, 78%, α/β 1:3). **α–13**: R_f 0.25 (EtOAc/hexane 1:3); mp 112-113 °C; $[\alpha]_D^{20}$ = -236.7 (c = 0.55, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.54-7.28 (m, 10H, Ph), 5.50 (dd, J = 2.0, 1.6 Hz, 1H, H-3), 4.98-4.96 (m, 1H, H-2), 4.81 (d, J = 11.6 Hz, CH_2Ph), 4.72 (d, J = 11.6 Hz, CH_2Ph), 4.43 (t, J = 3.6 Hz, 1H, H-4), 4.31 (d, J = 3.7 Hz, 1H, H-5), 3.90 (dt, J = 3.5, 1.4 Hz, 1H, H-3), 3.18-3.14 (broad s, 1H, OH); ^{13}C NMR (101 MHz; $CDCl_3$) δ 168.4, 136.8, 135.6, 131.2, 129.4, 128.7, 128.4, 128.1, 127.9, 83.1, 80.5, 74.7, 72.5, 71.9, 71.2; MS (TOF ES^+) calcd for $C_{19}H_{18}NaO_5S$ $[M+Na]^+$: 381.0768, found: 381.0769; **β–13**: R_f 0.19 (EtOAc/hexane 1:3); mp 77-78°C; $[\alpha]_D^{20}$ = +149.8 (c = 0.56, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.52-7.30 (m, 10H, Ph), 5.70 (d, J = 0.8 Hz, 1H, H-1), 4.88 (d, J = 4.2 Hz, 1H, H-2), 4.73-4.58 (m, 2H, CH_2Ph), 4.35 (d, J = 4.2 Hz, 1H, H-5), 4.22-4.20 (m, 1H, H-4), 3.87 (dd, J = 4.2, 1.8 Hz, 1H, H-3), 3.19-3.15 (broad s, 1H, OH); ^{13}C NMR (101 MHz; $CDCl_3$) δ 168.7, 136.7, 132.7, 132.5, 129.3, 128.8, 128.5, 128.2, 128.1, 80.9, 79.1, 77.0, 72.5, 71.8, 71.5; HRMS (TOF ES^+) calcd for $C_{19}H_{18}NaO_5S$ $[M+Na]^+$: 381.0768, found: 381.0769.

4-*O*-Benzoyl-3-*O*-benzyl-1-thiophenyl-β-L-idopyranoside urono-2,6-lactone 16

The thiolactone **13** (1.03 g, 2.88 mmol) was dissolved in dry DCM (10 mL), pyridine (0.30 mL, 3.74 mmol) and benzoyl chloride (0.40 mL, 3.46 mmol) added. After stirring 4 h the reaction was extracted with DCM (100 mL)/H_2O (100 mL) and $NaHCO_3$ sat. (50 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated. The crude was purified using silica flash column chromatography (EtOAc/hexane 1:3 v:v). This yielded **16** (1.15 g, 87%) as cubic crystals after crystallization (dissolved in EtOAc and 4 times volume of hexane). R_f 0.32 (EtOAc/hexane 1:4 v:v); mp 122-123 °C; $[\alpha]_D^{20}$ = +166.2 (c = 0.66, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.94-7.91 (m, 2H, Bz), 7.58-7.24 (m, 13H, Ph), 5.80 (d, J = 1.0 Hz, 1H, H-1), 5.39 (ddd, J = 4.4, 1.8, 0.8 Hz, 1H, H-4), 4.89 (dt, J = 4.4, 0.9 Hz, 1H, H-2), 4.79 (d, J = 11.8 Hz, 1H), 4.59 (d, J = 11.8 Hz, 1H), 4.52 (dd, J = 4.4, 0.4 Hz, 1H, H-5), 4.00 (ddd, J = 4.4, 1.8, 0.6 Hz, 1H, H-3);

^{13}C NMR (101 MHz; $CDCl_3$) δ 166.5, 164.7, 136.3, 134.1, 132.6, 132.5, 130.0, 129.3, 128.8, 128.7, 128.59, 128.4, 128.3, 128.2, 81.5, 76.8, 76.5, 72.7, 71.9, 69.2; HRMS (TOF ES$^+$) calcd for $C_{26}H_{22}NaO_6S$ $[M+Na]^+$: 485.1029, found: 485.1030.

3-*O*-Benzyl-4-*O*-*t*-butyldimethylsilyl-1-thiophenyl-β-L-idopyranoside urono-2,6-lactone β–17. Lactone β–**13** (3.01 g, 8.41 mmol), was dissolved in dry DCM (50 mL), imidazole (858 mg, 1.5 eq., 12.60 mmol) and TBDSMCl (1.65 g, 1.3 eq., 10.9 mmol) were added and the reaction mixture was stirred overnight. Imidazole (170 mg, 0.3 eq., 2.50 mmol) and TBDSMCl (250 mg, 0.2 eq., 1.65 mmol) were added and the reaction mixture was stirred overnight. The crude product was extracted with DCM (300 mL)/ H_2O (2 x 150 mL), the organic phase was dried ($MgSO_4$), filtered and evaporated. Column chromatography of the crude product (5:1 hexane/EtOAc) yielded β–**17** as a yellow oil (2.70 g, 5.72 mmol, 68%). R_f 0.47 (EtOAc/hexane 1:7); $[\alpha]_D^{20}$ = +92.5 (*c* = 0.40, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.51-7.49 (2 H, m, Bz), 7.38-7.26 (8 H, m, Ph), 5.66 (1 H, d, *J* = 0.8 Hz, H-1), 4.84 (1 H, d, *J* = 4.2 Hz, H-2), 4.65 (1 H, d, *J* = 11.7, C*H*$_2$Ph), 4.56 (1 H, d, *J* = 11.7, C*H*$_2$Ph), 4.19 (1 H, d, *J* = 4.4 Hz, H-5), 4.14 (1 H, ddd, *J* = 4.0, 1.2, 0.7 Hz, H-4), 3.84 (1 H, ddd, *J* = 4.2, 1.8, 0.4 Hz, H-3), 0.87 (9 H, s, OSiC*(CH$_3$)$_3$*), 0.10 (6 H, s, OSi*(CH$_3$)$_2$*); ^{13}C NMR (101 MHz; $CDCl_3$) δ 167.0, 136.7, 132.6, 129.3, 128.9, 128.6, 128.1, 128.0, 81.0, 80.7, 76.3, 72.8, 72.7, 72.2, 25.6, 17.9, -4.5, -4.8; HRMS (TOF ES$^+$) calcd for $C_{25}H_{36}O_5SSiN$ $[M+NH_4]^+$: 490.2078, found: 490.2067.

3-*O*-Benzyl-4-*O*-*t*-butyldimethylsilyl-1-thiophenyl-α-L-idopyranoside urono-2,6-lactone α–17. Prepared as **β–17** (6.8g scale). R_f 0.43 (EtOAc/hexane 1:7 v:v); $[\alpha]_D^{20}$ = –153.4 (*c* = 0.90, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.51-7.48 (2 H, m, Bz), 7.43-7.30 (8 H, m, Ph), 5.48 (1 H, t, *J* = 1.6 Hz, H-1), 4.97 (1 H, ddd, *J* 3.5, 2.1, 0.6 Hz, H-2), 4.82 (1 H, d, *J* = 11.6 Hz, C*H*$_2$Ph), 4.64 (1 H, d, *J* = 11.6 Hz, C*H*$_2$Ph), 4.37 (1 H, ddd, *J* = 3.9, 3.1, 0.6 Hz, H-4), 4.19 (1 H, d, *J* = 3.9 Hz, H-5), 3.86 (1 H, td, *J* = 3.3, 1.4 Hz, H-3), 0.86 (9 H, s, OSiC*(CH$_3$)$_3$*), 0.11 (6 H, d, *J* = 6.3 Hz, OSi*(CH$_3$)$_2$*); ^{13}C NMR (101 MHz; $CDCl_3$) δ 167.2, 136.5, 135.7, 131.0, 129.3, 128.6, 128.3, 128.2, 127.8, 83.3, 81.5, 74.0, 72.5, 72.4, 72.3, 25.5, 17.8, -4.73, -4.88; HRMS (TOF ES$^+$) calcd for $C_{25}H_{36}O_5SSiN$ $[M+NH_4]^+$: 490.2078, found: 490.2064.

Methyl (3-*O*-benzyl-4-*O*-*t*-butyldimethylsilyl-1-thiophenyl-β-L-idopyranoside) uronate β–**18.** Lactone β–**17** (2.70 g, 5.70 mmol) was dissolved in MeOH (30 mL), Et_3N (790 µL, 1 eq., 5.70 mmol) added and the reaction mixture stirred at RT for 72 h. Et_3N (790 µL, 1 eq., 5.70 mmol) was added and the reaction stirred for another 3 h. The solvent was removed and the crude product purified by column chromatography (hexane/ethyl acetate 7:1 v:v) to afford β–**18** as a clear solid (1.73 g, 3.41 mmol, 60%) along with recovered starting material (500 mg, 1.06 mmol, 19%). R_f 0.30 (EtOAc/hexane 1:7 v:v); $[\alpha]_D^{20}$ = +52.9 (*c* = 0.90, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.57-7.55 (2 H, m, Bz), 7.37-7.29 (8 H, m, Ph), 5.19 (1 H, d, *J* = 1.1 Hz, H-1), 4.68 (1 H, d, *J* = 12.0 Hz, C*H*$_2$Ph), 4.58-4.55 (2 H, m, C*H*$_2$Ph, H-5), 4.12 (1 H, t, *J* = 1.6 Hz, H-4), 3.94-3.93 (1 H, m, H-2), 3.81 (3 H, s, COOC*H*$_3$), 3.75 (1 H, t, 3.2 Hz, H-3), 0.86 (9 H, s, OSiC*(CH$_3$)$_3$*), -0.01 (6 H, d, *J* = 3.1 Hz, OSi*(CH$_3$)$_2$*); ^{13}C NMR (101 MHz; $CDCl_3$) δ 169.2, 137.1, 135.7, 130.7, 128.9, 128.7, 128.4, 128.0, 127.0, 87.5, 77.4, 77.1, 76.8, 76.5, 75.4, 72.4, 69.8, 69.0, 52.3, 25.6, 17.9, -4.9, -5.4; HRMS (TOF ES$^+$) calcd for $C_{26}H_{40}O_6SSiN$ $[M+NH_4]^+$: 522.2340, found: 522.2328.

Methyl (3-*O*-benzyl-4-*O*-*t*-butyldimethylsilyl-1-thiophenyl-α-L-idopyranoside) uronate α–**18.** Lactone α–**17** (15 mg, 40 μmol) was dissolved in MeOH (2 mL), Et_3N (5 μL, 1 eq., 40 μmol) added and the reaction mixture stirred for 18 h. The solvent was removed and the crude product purified by column chromatography (7:1 hexane/ethyl acetate) to afford α–**18** as a clear solid (17 mg, 36 μmol, 90%).R_f 0.38 (EtOAc/hexane 1:7); $[\alpha]_D^{20} = -131.9$ (c = 0.85, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.53-7.50 (2 H, m, Bz), 7.42-7.30 (7 H, m, Ph), 7.23 (1 H, m, Ph), 5.66 (1 H, s, H-1), 5.28 (1 H, d, J = 1.5 Hz, H-5), 4.84 (1 H, d, J = 12.2 Hz, CH_2Ph), 4.56 (1 H, d, J = 12.2 Hz, CH_2Ph), 4.18-4.17 (1 H, m, H-4), 4.06-4.05 (1 H, m, H-2), 3.79 (3 H, s, COOCH_3), 3.66 (1 H, t, J = 2.8 Hz, H-3), 0.83 (9 H, s, OSiC$(CH_3)_3$), -0.02 (6 H, d, J = 7.4 Hz, OSi$(CH_3)_2$); ^{13}C NMR (101 MHz; $CDCl_3$) δ 169.8, 137.3, 136.6, 130.7, 129.0, 128.6, 128.2, 127.9, 127.1, 89.7, 74.0, 72.2, 69.9, 69.1, 68.9, 52.3, 25.5, 17.8, -4.8, -5.6; HRMS (TOF ES$^+$) $C_{26}H_{40}O_6SSiN$ $[M+NH_4]^+$: 522.2340, found: 522.2329.

Methyl (2-*O*-acetyl-3-*O*-benzyl-4-*O*-*t*-butyldimethylsilyl-1-thiophenyl-β-L-idopyranoside) uronate β–**19**: Iduronate β–**18** (104 mg, 0.21 mmol) was dissolved in dry CH_2Cl_2 (5 mL), pyridine (25 μL, 0.31 mmol) and DMAP (10 mg, 0.10 mmol) were added, Ac_2O (60 μL, 0.63 mmol) was added dropwise and the reaction mixture stirred ar RT for 72 h. EtOH (2 mL) was added, the solvents were removed and the resulting oil purified by column chromatography (6:1 hexane/EtOAc) to afford **19** as a clear oil (91 mg, 0.17 mmol, 79%). R_f = 0.28 (EtOAc/hexane 1:7); $[\alpha]_D^{20} = +22.8$ (c = 0.55, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.46 (2 H, dt, J = 6.4, 1.7 Hz, Bz), 7.27-7.15 (10 H, m, Ph), 5.05 (1 H, d, J = 1.8, H-1), 4.98 (1 H, dt, J = 3.0, 1.3 Hz, H-5), 4.66 (1 H, d, J = 12.1 Hz, CH_2Ph), 4.51 (1 H, d, J = 12.1 Hz, CH_2Ph), 4.37 (1 H, d, J = 1.8 Hz, H-2), 3.87 (1 H, dt, J = 3.0, 1.3 Hz, H-3), 3.70 (3 H, s, COOCH_3), 3.59 (1 H, t, J = 2.6 Hz, H-4), 2.02 (3 H, s, COCH_3), 0.70 (9 H, s, OSiC$(CH_3)_3$), -0.21 (3 H, s, OSi$(CH_3)_2$), -0.32 (3 H, s, OSi$(CH_3)_2$); ^{13}C NMR (101 MHz; $CDCl_3$) δ 171.2, 169.5, 137.4, 135.4, 131.6, 131.1, 129.3, 129.0, 128.8, 128.7, 128.3, 127.8, 85.2, 74.6, 72.7, 69.8, 68.3, 52.6, 26.0, 21.4, 18.3, -4.3, -5.3; HRMS (TOF ES$^+$) $C_{28}H_{42}O_7SSiN$ $[M+NH_4]^+$: 564.2446, found: 564.2440.

2-Azido-3,6-di-*O*-benzyl-2-deoxy-4-*O*-*p*-methoxybenzyl-α-D-glucopyranosyl-(1→4)-(phenyl 3-*O*-benzyl-1-thio-β-L-idopyranoside) urono-2,6-lactone 21

Acceptor thioglycoside **β-13** (2.72 g, 7.59 mmol) and thioglycoside donor **20** (5.62 g, 9.41 mmol) were dissolved in dry toluene (50 mL) under N_2. Freshly activated 4Å powdered molecular sieves (2.7 g) were added and the solution cooled to 0 °C in an ice bath. After 10 min NIS (4.21 g, 18.7 mmol) was added, and after another 10 min AgOTf (38 mg, 0.15 mmol) was added. The suspension changed colour from pale yellow to deep red, was stirred for 30 min and more AgOTf (13 mg, 0.05 mmol) added. After another 30 min the reaction was quenched into a separating funnel containing a mixture of CH_2Cl_2 (300 mL), saturated aqueous $NaHCO_3$ (200 mL) and $Na_2S_2O_3$ (40 mL, 10% aqueous). After shaking until the iodine colour was removed the suspension was filtered through a short pad of Celite® washing with water and CH_2Cl_2. The layers were separated and the aqueous extracted with DCM (30 mL). The organic layers were combined, dried ($MgSO_4$) and solvent removed *in vacuo*. The crude was purified by silica gel flash column chromatography (EtOAc/hexane 1:5 to 1:4 v:v) to give **21 (**5.20 g, 81%) as a white foam. The β-anomer product (0.90 g, 14 %) was also isolated. R_f 0.15 (EtOAc/hexane 1:4 v:v); $[\alpha]_D^{20}$ = +132.5 (c = 0.28, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.57-7.32 (m, 20H, Ph), 7.11 (d, J = 8.8 Hz, 2H, PMB), 6.86 (d, J = 8.8 Hz, 2H, PMB), 5.75 (d, J = 0.8 Hz, 1H, H^A-1), 5.04 (d, J = 3.8 Hz, 1H, H^B-1), 4.96 (d, J = 10.7 Hz, 1H, CH_2Ph), 4.91-4.87 (m, 2H, H^A-5, CH_2Ph), 4.77 (d, J = 12.0 Hz, 1H, CH_2Ph), 4.74 (d, J = 2.4 Hz, 1H, H^A-2), 4.71-4.66 (m, 3H, CH_2Ph), 4.54-4.49 (m, 2H, CH_2Ph), 4.11 (dd, J = 3.9,

2.4 Hz, 1H, H^A-4), 4.03 (dd, *J* = 4.0, 2.4 Hz, 1H, H^A-3), 3.93-3.76 (m, 5H, H^B-3, H^B-4, H^B-5, H^B-6_{ab}), 3.82 (s, 3H, PhOCH_3), 3.45 (dd, *J* = 10.2, 3.7 Hz, 1H, H^B-2); ^{13}C NMR (101 MHz; $CDCl_3$) δ 167.0, 159.3, 137.9, 137.8, 136.5, 132.7, 132.5, 130.0, 129.5, 129.3, 128.8, 128.6, 128.5, 128.2, 128.1, 128.0, 128.0, 127.8, 113.8, 100.4, 81.1, 81.0, 79.7, 77.8, 77.6, 76.5, 75.5, 74.6, 73.6, 72.4, 71.9, 70.4, 68.0, 63.2, 55.3; HRMS (TOF ES$^+$) calcd for $C_{47}H_{47}N_3NaO_{10}S$ $[M+Na]^+$: 868.2875, found: 868.2836.

Methyl 2-azido-3,6-di-*O*-benzyl-2-deoxy-4-*O*-*p*-methoxybenzyl-α-D-glucopyranosyl-(1⟶4)-(phenyl 3-*O*-benzyl-2-*O*-benzoyl-1-thio-β-L-idopyranoside) uronate 23

To **21** (4.40 g, 5.21 mmol) was added dry MeOH/DCM (60 mL 1:1 v:v) and a catalytic amount of NaOMe (25% in MeOH, 0.1 mL) while kept under N_2. The mixture was stirred for 6 h, quenched by addition of AcOH (0.1 mL) and solvent evaporated. The crude was extracted with DCM (200 mL)/H_2O (200 mL) and $NaHCO_3$ sat. (200 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated. The crude was purified by silica gel flash column chromatography (EtOAc/hexane 1:4 to 1:3 v:v) to yield disaccharide **22** (4.05 g, 89%) as a white foam. R_f 0.22 (EtOAc/hexane 1:3 v:v); $[\alpha]_D^{20}$ = +98.6 (*c* = 1.4, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.62-7.28 (m, 20H, Ph), 7.09 (d, *J* = 8.8 Hz, 2H, PMB), 6.85 (d, *J* = 8.8 Hz, 2H, PMB), 5.22 (d, *J* = 1.1 Hz, 1H, H^A-1), 5.10 (d, *J* = 3.8 Hz, 1H, H^B-1), 4.89-4.47 (m, 9H, H^A-5, 4xCH_2Ph), 4.28-4.27 (m, 1H, H^A-4), 4.05-4.02 (m, 2H, H^A-2, H^A-3), 4.02-3.59 (m, 6H, H^B-2, H^B-3, H^B-4, H^B-5, H^B-6_{ab}), 3.82 (s, 3H, PhOCH_3), 3.81 (s, 3H, COOCH_3); ^{13}C NMR (101 MHz; $CDCl_3$) δ 169.2, 159.2, 137.75, 137.7, 136.8, 135.4, 132.2, 130.9, 130.3, 129.2, 129.0, 129.0, 129.0, 128.7, 128.6, 128.6, 128.5, 128.5, 128.4, 128.2, 128.1, 128.0, 128.0, 127.9, 127.8, 127.2, 113.7, 94.7, 87.8, 81.2, 77.2, 75.9, 75.4, 74.4, 73.6, 72.7, 71.9, 71.6, 70.4, 69.3, 67.7, 63.6, 55.3, 52.7; HRMS (TOF ES$^+$) calcd for $C_{48}H_{51}N_3NaO_{11}S$ $[M+Na]^+$: 900.3137, found: 900.3144. The 2-OH disaccharide intermediate **22** (7.92 g, 9.03 mmol) was dissolved in dry CH_2Cl_2 (100 mL), 1-methylimidazole (1.07 mL, 13.5 mmol) and benzoyl chloride (1.36 mL, 11.7 mmol) were added. After stirring 8 h the reaction was extracted with DCM (300 mL)/H_2O (300 mL) and washed with brine (100 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated. The crude was purified using silica flash column chromatography (EtOAc/hexane 1:4 v:v). This yielded **23** (6.43 g, 73%) as a white foam. Analytical data matched those previously reported.[8]

2-Azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranosyl-(1⟶4)-(phenyl 3-*O*-benzyl-1-thio-β-L-idopyranoside) urono-2,6-lactone 25

Acceptor thioglycoside **13** (3.68 g, 10.3 mmol) and thioglycoside donor **24** (6.66 g, 14.0 mmol) was dissolved in dry DCM (50 mL) under N_2. Freshly activated 4Å powdered molecular sieves (2.7 g) were added and the solution cooled to 0 °C in an icebath. After 10 min. NIS (4.53 g, 20.1 mmol) was added, and after another 10 min. AgOTf (65 mg, 0.26 mmol) was added. The suspension changed colour from pale yellow to deep red, was stirred for 1 h, more AgOTf (62 mg, 0.25 mmol) added. After another 1 h the reaction was quenched into a separating funnel containing a mixture of CH_2Cl_2 (300 mL), saturated aqueous $NaHCO_3$ (250 mL) and $Na_2S_2O_3$ (50 mL, 10% aqueous). After shaking until the iodine colour was removed, the suspension was filtered through a short pad of Celite®, washing with water and CH_2Cl_2. The layers were separated and the aqueous extracted with CH_2Cl_2 (50 mL). The organic layers were combined, dried ($MgSO_4$) and solvent removed *in vacuo*. The crude was purified by silica gel flash column chromatography (EtOAc/hexane 1:5 to 1:4 to 1:3 v:v) to give **25 (**4.20 g, 57%) as white needles after crystallization (dissolved in EtOAc and 3 times the volume of hexane added). R_f 0.14

(EtOAc/hexane 1:4 v:v); mp 143-144 °C; $[\alpha]_D^{20}$ = +109.2 (*c* = 0.45, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.53-7.32 (m, 20H, Ph), 5.71 (d, *J* = 0.8 Hz, 1H, H^A-1), 5.56 (s, 1H, O_2CH), 4.98 (d, *J* = 11.0 Hz, 1H, CH_2Ph), 4.91 (d, *J* = 3.9 Hz, 1H, H^B-1), 4.87 (d, *J* = 4.2 Hz, 1H, H^A-2), 4.79 (d, *J* = 11.0 Hz, 1H, CH_2Ph), 4.75 (d, *J* = 11.8 Hz, 1H, CH_2Ph), 4.66 (d, *J* = 11.8 Hz, 1H, CH_2Ph), 4.53 (d, *J* = 4.0 Hz, 1H, H^A-5), 4.43 (dd, *J* = 10.1, 4.9 Hz, 1H, H^B-6_a), 4.08 (dd, *J* = 4.0, 2.3 Hz, 1H, H^A-4), 4.02-3.96 (m, 2H, H^B-3, H^A-4), 3.87 (dt, *J* = 9.9, 4.9 Hz, 1H, H^B-5), 3.73-3.67 (m, 2H, H^B-4, H^B-6_b), 3.41 (dd, *J* = 10.0, 3.9 Hz, 1H, H^B-2); ^{13}C NMR (101 MHz; $CDCl_3$) δ 166.7, 137.8, 137.2, 136.5, 132.6, 132.6, 129.3, 129.1, 128.8, 128.6, 128.5, 128.3, 128.3, 128.2, 128.0, 126.2, 101.5, 100.3, 82.3, 81.1, 81.0, 77.7, 76.5, 76.0, 75.2, 72.5, 70.5, 68.5, 63.8, 62.8; HRMS (TOF ES$^+$) calcd for $C_{39}H_{37}N_3NaO_9S$ $[M+Na]^+$: 746.2143, found: 746.2124.

Methyl 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranosyl-(1⟶4)-(phenyl-2-*O*-benzoyl-3-*O*-benzyl-1-thio-β-L-idopyranoside) uronate 26

To **25** (3.49 g, 4.83 mmol) was added dry MeOH/ CH_2Cl_2 (90 mL, 8:1 v:v) and a catalytic amount NaOMe (25% in MeOH, 0.3 mL) while kept under N_2. The mixture was stirred 2 h, quenched by addition of AcOH (0.1 mL) and solvent evaporated. The crude was extracted with CH_2Cl_2 (300 mL)/H_2O (200 mL) and $NaHCO_3$ sat. (200 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated. The crude was purified by silica gel flash column chromatography (EtOAc/hexane 1:4 to 1:3 v:v) to yield intermediate 2-OH disaccharide (2.92 g, 80%) as white needles after crystallization (dissolved in EtOAc and hexane 4 times the volume added). R_f 0.26 (EtOAc/hexane 1:3 v:v); mp 197-198 °C; $[\alpha]_D^{20}$ = +78.3 (*c* = 0.26, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.61-7.24 (m, 20H, Ph), 5.54 (s, 1H, PhCHO_2), 5.19 (d, *J* = 1.4 Hz, 1H, H^A-1), 4.94-4.90 (m, 2H, CH_2Ph, H^B-1), 4.78 (d, *J* = 10.6 Hz, 1H, CH_2Ph), 4.69-4.61 (m, 3H, H^A-5, 2xCH_2Ph), 4.29 (dd, *J* = 10.1, 4.7 Hz, 1H, H^B-6_a), 4.21-4.20 (m, 1H, H^A-4), 4.08-4.01 (m, 2H, H^A-2, H^B-4), 3.95 (t, *J* = 2.8 Hz, 1H, H^A-3), 3.89 (s, 3H, COOCH_3), 3.74-3.56 (m, 4H, H^B-2, H^B-3, H^B-5, H^B-6_b); ^{13}C NMR (101 MHz; $CDCl_3$) δ 169.1, 137.7, 137.2, 136.8, 135.4, 131.1, 129.2, 129.0, 128.8, 128.5, 128.4, 128.3, 128.0, 127.8, 127.3, 126.1, 101.6, 95.3, 88.1, 81.9, 78.0, 75.5, 75.2, 72.6, 72.2, 71.1, 69.2, 68.3, 63.4, 63.0, 53.0; HRMS (TOF ES$^+$) calcd for $C_{40}H_{42}N_3O_{10}S$ $[M+H]^+$: 756.2586, found: 756.2587.

The intermediate 2-OH disaccharide (2.83 g, 3.74 mmol) was dissolved in dry DCM (50 mL), 1-methylimidazole (0.44 mL, 5.61 mmol) and benzoyl chloride (0.57 mL, 4.86 mmol) added. After stirring 12 h the reaction was extracted with DCM (200 mL)/H_2O (200 mL) and brine (100 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated. The crude was purified using silica flash column chromatography (EtOAc/hexane 1:4 v:v). This yielded **26** (2.48 g, 77%) as white needles after crystallization (dissolved in EtOAc and hexane 4 times the volume added). R_f 0.11 (EtOAc/hexane 1:4 v:v). mp 172-173 °C; $[\alpha]_D^{20}$ = +4.2 (*c* = 0.35, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.28-8.26 (m, 2H, Bz), 7.63-7.09 (m, 23H, Ph), 5.51 (s, 1H, PhCHO_2), 5.34 (d, *J* = 1.8 Hz, 1H, H^A-1), 5.31-5.29 (m, 1H, H^A-2), 4.90 (d, *J* = 11.6 Hz, 1H, CH_2Ph), 4.80 (d, *J* = 11.6 Hz, 1H, CH_2Ph), 4.63 (d, *J* = 3.7 Hz, 1H, H^B-1), 4.60 (d, *J* = 1.5 Hz, 1H, H^A-5), 4.39 (dd, *J* = 10.1, 4.9 Hz, 1H, H^B-6_a), 4.35 (t, *J* = 2.5 Hz, 1H, H^A-3), 4.29 (d, *J* = 10.6 Hz, 1H, CH_2Ph), 4.08-4.02 (m, 2H, H^A-4, H^B-5), 3.84 (s, 3H, COOCH_3), 3.76-3.73 (m, 1H, CH_2Ph), 3.64 (t, *J* = 10.2 Hz, 1H, H^B-6_b), 3.57-3.49 (m, 2H, H^B-3, H^B-4), 3.23 (dd, *J* = 9.5, 3.6 Hz, 1H, H^B-2); ^{13}C NMR (101 MHz; $CDCl_3$) δ 168.7, 166.2, 137.9, 137.6, 137.0, 134.7, 133.3, 131.4, 130.2, 129.7, 129.1, 129.1, 128.9, 128.6, 128.4, 128.3, 128.0, 127.8, 127.7, 126.2, 101.4, 99.9, 85.9, 82.3, 77.0, 75.7, 75.5, 74.8, 73.0, 70.1, 68.5, 63.5, 63.2, 52.5; HRMS (TOF ES$^+$) calcd for $C_{47}H_{45}N_3NaO_{11}S$ $[M+Na]^+$: 882.2668, found: 882.2631.

Methyl 2-azido-3,6-di-*O*-benzyl-2-deoxy-4-*O*-trichloroacetyl-α-D-glucopyranosyl-(1⟶4)-(phenyl-2-*O*-benzoyl-3-*O*-benzyl-1-thio-β-L-idopyranoside) uronate 27

The disaccharide **26** (777 mg, 0.902 mmol) was dissolved in dry CH_2Cl_2 (8 mL), cooled to 0 °C, triethylsilane (0.29 mL, 1.80 mmol) and borontrifluoride etherate (0.22 mL, 1.80 mmol) added. After stirring 2 h more reagents, triethylsilane (0.29 mL, 1.80 mmol) and borontrifluoride etherate (0.22 mL, 1.80 mmol) added and stirred another 2 h. The reaction was extracted with CH_2Cl_2 (50 mL)/ $NaHCO_3$ sat. (50 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated. The crude was purified using silica flash column chromatography (EtOAc/hexane 1:3 v:v). This yielded **27** (583 mg, 75%) as a foam. Also starting material **26** (80 mg, 10%) and the 4,6-di-OH product (99 mg, 14%) were isolated from the column. Analytical data for this compound and the subsequent 4-OH acylation step (with trichloroacetyl chloride) are as reported previously.[8]

Methyl 2-azido-3-*O*-benzyl-2-deoxy-α-D-glucopyranosyl-(1⟶4)-(phenyl-2-*O*-benzoyl-3-*O*-benzyl-1-thio-β-L-idopyranoside) uronate 28

The disaccharide **26** (740 mg, 0.859 mmol) was dissolved in dry CH_2Cl_2 (10 mL), EtSH (0.6 mL, 8.6 mmol) and *p*-toluenesulfonic acid (20 mg, 0.086 mmol) added. After stirring 90 min. the reaction was quenched with NEt_3 (5 drops) and solvents removed. The reaction was extracted with CH_2Cl_2 (50 mL)/$NaHCO_3$ sat. (50 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated. The crude was purified using silica flash column chromatography (EtOAc/hexane 1:1 v:v). This yielded **28** (662 mg, 99%) as a foam. R_f 0.15 (EtOAc/hexane 1:1); $[\alpha]_D^{20}$ = +67.0 (*c* = 0.40, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.29-8.27 (m, 2H, Bz), 7.60-7.09 (m, 18H, Ph), 5.31 (d, *J* = 1.9 Hz, 1H, H^A-1), 5.26-5.25 (m, 1H, H^A-2), 4.91-4.77 (m, 2H, CH_2Ph), 4.57 (d, *J* = 3.6 Hz, 1H, H^B-1), 4.56 (d, *J* = 1.5 Hz, 1H, H^A-5), 4.33 (t, *J* = 2.5 Hz, 1H, H^A-3), 4.01-4.00 (m, 1H, H^A-4), 3.96 (d, *J* = 10.9 Hz, 1H, CH_2Ph), 3.86 (d, *J* = 10.8 Hz, CH_2Ph), , 3.83-3.75 (m, 3H, H^B-5, H^B-6_{ab}), 3.81 (s, 3H, COOCH_3), 3.43 (dt, *J* = 9.3, 4.2 Hz, 1H, H^B-4), 3.43 (dd, *J* = 10.0, 8.8 Hz, 1H, H^B-3), 3.09 (dd, *J* = 10.1, 3.6 Hz, 1H, H^B-2), 2.65 (d, *J* = 4.3 Hz, 1H, 4-O*H*), 2.49 (t, *J* = 5.7 Hz, 1H, 6-O*H*); ^{13}C NMR (101 MHz; $CDCl_3$) δ 169.0, 166.3, 137.9, 137.0, 134.6, 133.5, 131.5, 130.3, 129.8, 129.2, 128.9, 128.7, 128.5, 128.5, 128.4, 127.9, 127.8, 99.5, 86.2, 80.3, 75.7, 75.4, 74.8, 73.0, 72.8, 72.7, 71.3, 70.2, 63.4, 62.3, 52.7; HRMS (TOF ES^+) calcd for $C_{40}H_{42}N_3O_{11}S$ $[M+H]^+$: 772.2535, found: 772.2532.

Methyl 2-azido-3-*O*-benzyl-6-*O*-benzoyl-2-deoxy-4-*O*-trichloroacetyl-α-D-glucopyranosyl-(1⟶4)-(phenyl 3-*O*-benzyl-2-*O*-benzoyl-1-thio-β-L-idopyranoside) uronate 29

The disaccharide **28** (600 mg, 0.776 mmol) was dissolved in dry DCM (10 mL), pyridine (0.16 mL, 1.94 mmol) and benzoyl chloride (99 µL, 0.854 mmol) added. After stirring 3 h trichloroacetyl chloride (104 µL, 0.931 mmol) was added and left overnight. The reaction was extracted with DCM (50 mL)/ H_2O (50 mL) and $NaHCO_3$ sat. (20 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated. The crude was purified using silica flash column chromatography (EtOAc/hexane 1:4). This yielded **29** (606 mg, 77%) as a foam. Also the di-4,6-*O*-trichloroacetyl product 113 mg (14%) and the 6-*O*-benzoyl-4-OH product 55 mg (8%) were isolated from the column. R_f 0.13 (EtOAc/hexane 1:4); $[\alpha]_D^{20}$ = +108.6 (*c* = 0.21, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.27-8.25 (m, 2H, Bz), 7.98-7.96 (m, 2H, Bz), 7.53-6.94 (m, 21H, Ph), 5.27 (d, *J* = 1.9 Hz, 1H, H^A-1), 5.21-5.16 (m, 2H, H^A-2, H^B-4), 4.84 (d, *J* = 11.7 Hz, 1H, CH_2Ph), 4.76-4.71 (m,

2H, H^B-6_a, CH_2Ph), 4.56 (d, *J* = 1.6 Hz, 1H, H^A-5), 4.54 (d, *J* = 3.7 Hz, 1H, H^B-1), 4.31 (t, *J* = 2.5 Hz, 1H, H^A-3), 4.20-4.15 (m, 2H, H^B-5, H^B-6_b), 3.89-3.86 (m, 2H, H^B-4, CH_2Ph), 3.81 (s, 3H, COOCH_3), 3.57 (d, *J* = 10.1 Hz, 1H, CH_2Ph), 3.52 (t, *J* = 9.6 Hz, 1H, H^B-3), 3.30 (dd, *J* = 10.0, 3.6 Hz, 1H, H^B-2); ^{13}C NMR (101 MHz; $CDCl_3$) δ 168.6, 166.2, 166.1, 160.6, 136.9, 136.7, 134.7, 133.6, 133.3, 131.2, 130.2, 130.0, 129.9, 129.6, 129.2, 129.0, 128.7, 128.6, 128.5, 128.1, 128.0, 127.8, 99.9, 89.6, 86.1, 77.9, 77.4, 76.8, 75.8, 75.0, 74.5, 73.1, 72.4, 70.4, 68.5, 63.8, 61.4, 52.7; HRMS (FT MS) calcd for $C_{49}H_{48}Cl_3N_4O_{13}S$ $[M+NH_4]^+$: 1037.1999, found: 1037.1999.

Methyl (methyl 3-*O*-benzyl-α,β-L-idofuranoside) uronate 38 and **39**

The diacetylated α,β-furanoside mixture **31**[10] (5.37 g, 13.6 mmol) was dissolved in dry MeOH (50 mL) and a catalytic amount of sodium added. After 90 min the solution was quenched by addition of Amberlite® IR 120 H^+ resin (0.5 g) and stirred for 15 min. The resin was filtered off and solvent removed *in vacuo* to give the crude material as a clear oil. This was purified by silica gel flash chromatography (EtOAc/Hexane 2:3) to give **39** (1.13 g, 3.94 mmol, 26%) and **38** □□□□□□□, 9.3 mmol, 70%) as oils. Further purification of **38** was achieved by crystallization (dissolved in EtOAc and added 4 times volume hexane) to yield transparent needles. **39**: R_f = 0.36 (EtOAc/hexane 3:2); $[\alpha]_D^{20}$ = +2.00 (*c* = 0.55 CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.29-7.21 (m, 5H, Ph), 4.69 (d, *J* = 2.8 Hz, 1H, H-1), 4.66 (d, *J* = 12.1 Hz, 1H, CH_2Ph), 4.56 (d, *J* = 12.1 Hz, 1H, CH_2Ph), 4.53 (dd, *J* = 7.6, 2.0 Hz, 1H, H-4), 4.38 (dt, *J* = 5.2, 2.8 Hz, 1H, H-2), 4.27 (dd, *J* = 10.0, 2.0 Hz, 1H, H-5), 4.10 (dd, *J* = 7.6, 6.0 Hz, 1H, H-3), 3.84 (d, *J* = 10.0 Hz, 1H, O*H*), 3.68 (s, 3H, COOCH_3), 3.33 (s, 3H, OCH_3), 3.13 (d, *J* = 5.2 Hz, 1H, O*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ 172.9, 137.6, 128.6, 128.0, 127.8, 109.7, 83.9, 81.4, 80.1, 73.0, 70.2, 56.2, 52.4; MS (ESI^+) *m/z* calcd for $C_{15}H_{21}O_7$ $[M+H]^+$ 313.1282, found 313.1279. **38**: R_f = 0.24 (EtOAc/hexane 3:2 v:v); Mp 85-86 °C; $[\alpha]_D^{20}$ = +125.6 (*c* = 0.29, CH_2Cl_2). ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.28-7.21 (m, 5H, Ph), 4.84 (d, *J* = 4.8 Hz, 1H, H-1), 4.81 (d, *J* = 12.0 Hz, 1H, CH_2Ph), 4.59 (d, *J* = 12.0 Hz, 1H, CH_2Ph), 4.43 (dd, *J* = 7.6, 1.6 Hz, 1H, H-4), 4.38-4.33 (m, 2H, H-2, H-5), 4.12 (t, *J* = 7.2 Hz, 1H, H-3), 3.71 (s, 3H, COOCH_3), 3.35 (s, 3H, OCH_3), 3.18 (d, *J* = 5.6 Hz, 1H, O*H*), 2.65 (d, *J* = 9.2 Hz, 1H, O*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ 172.8, 137.6, 128.5, 127.9, 127.7, 101.5, 82.8, 77.9, 76.6, 72.5, 69.9, 55.8, 52.7; HRMS (ESI^+) *m/z* calcd for $C_{15}H_{20}NaO_7$ $[M+Na]^+$ 335.1101, found 335.1100; Elemental analysis calcd (%) for $C_{15}H_{20}O_7$: C 57.69, H 6.45; found C 57.52, H 6.32.

Methyl 3-*O*-benzyl-α-L-idopyranoside uronic acid 34

Monosaccharide **32** (283 mg, 0.70 mmol) was dissolved in THF / MeOH (4 mL, 3:1 v:v). The solution was cooled to 0 °C and KOH (107 mg, 2.09 mmol) in H_2O (1 mL) was added dropwise. The solution was stirred for 2 h at this temperature. The reaction was extracted with EtOAc (2 x 15 mL) and HCl (0.1 M, 15 mL) and then dried (Na_2SO_4), filtered and solvent removed *in vacuo* to give the crude material. This was purified by crystallization from EtOAc/hexane (dissolved in 15 mL EtOAc and hexane 15 mL added) to give **34** (130 mg, 0.44 mmol, 63%) as transparent needles. $[\alpha]_D^{20}$ = -71.7 (*c* = 0.32, acetone); ^{1}H NMR (400 MHz; MeOD) δ 7.41-7.30 (m, 5H, Ph), 4.97 (brs, 2H, O*H*), 4.80-4.79 (m, 1H, H-1), 4.72 (d, *J* = 11.8 Hz, 1H, CH_2Ph), 4.66-4.64 (m, 2H, CH_2Ph, H-5), 4.06 (dddd, *J* = 3.6, 1.3, 1.1, 0.9 Hz, 1H, H-4), 3.73 (ddd, *J* = 3.9, 2.4, 1.3 Hz, 1H, H-2), 3.69 (td, *J* = 3.9, 0.9 Hz, 1H, H-3), 3.44 (s, 3H, OCH_3). Other analytical data matched those previously reported by the group.[14]

Methyl 3-*O*-benzyl-β-L-idopyranoside uronic acid 35

Monosaccharide **33** (333 mg, 0.82 mmol) was dissolved in THF / MeOH (3 mL, 2:1 v:v). The solution was cooled to 0 °C and KOH (96 mg, 1.72 mmol) in H_2O (1 mL) was added dropwise. The solution was stirred for 4 h at this temperature. The reaction was extracted with EtOAc (2 x 20 mL) and HCl (0.1 M, 15 mL) and then dried (Na_2SO_4), filtered and solvent removed *in vacuo* to give the crude material. This was purified by silica gel flash chromatography (EtOAc/Hexane 1:1 + 1% HCOOH) to yield **35** (200 mg, 0.67 mmol, 82%) as an oil. R_f = 0.11 (EtOAc/hexane 1:1 + 1% HCOOH); $[\alpha]_D^{20}$ = +78.6 (*c* = 0.29, CH_2Cl_2); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.41-7.25 (m, 5H, Ph), 4.76 (d, *J* = 0.8 Hz, 1H, H-1), 4.70 (d, *J* = 11.7 Hz, 1H, C*H*$_2$Ph), 4.63 (d, *J* = 11.7 Hz, 1H, C*H*$_2$Ph), 4.57 (d, *J* = 1.6 Hz, 1H, H-5), 4.14-4.12 (m, 1H, H-4), 3.98 (t, *J* = 3.4 Hz, 1H, H-3), 3.89-3.87 (m, 1H, H-2), 3.63 (s, 3H, OC*H*$_3$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 172.1, 137.4, 128.6, 128.1, 127.8, 99.8, 75.8, 74.4, 72.5, 68.0, 67.5, 57.2; HRMS (ESI$^+$) *m/z* calcd for $C_{14}H_{22}O_7N_1$ $[M+NH_4]^+$ 316.1391, found 316.1388; IR ν_{max} 3422, 2901, 1733, 1454, 1215, 1043 cm^{-1}.

Methyl α-L-idopyranoside uronate sodium salt 36

Compound **36** was prepared analogously to compound **37** and analyzed as reported previously.[15]

Methyl β-L-idopyranoside uronate sodium salt 37

Monosaccharide **35** (113 mg, 0.38 mmol) was ion exchanged with Amberlite® IRC 86 Na^+ to give the sodium salt and then dissolved in MeOH/H_2O (0.5 mL/4 mL). To the flask was attached a 3-way tap and purged with N_2, 10-20% $Pd(OH)_2$/C (64 mg) was added and the system purged with H_2. Vigorous stirring having a balloon with H_2 attached (1 atm.) was continued for 8 h. The suspension was then filtered through Celite® and solvents removed *in vacuo* to afford **37** (83 mg, 0.36 mmol, 95%) as a clear glass. Analytical data matched those previously reported.[15]

Methyl 3-*O*-benzyl-α-L-idofuranoside uronate sodium salt 40

Monosaccharide **37** (98 mg, 0.31 mmol) was dissolved in THF (1 mL) and MeOH (0.5 mL). The solution was cooled to 0 °C and KOH (18 mg, 0.31 mmol) in H_2O (0.5 mL) was added dropwise. The solution was stirred for 2 h at this temperature. The reaction was extracted with EtOAc (2 x 15 mL) and HCl (0.1 M) (15 mL) and then dried (Na_2SO_4), filtered and solvent removed *in vacuo* to give the crude material. This was purified by silica gel flash chromatography (EtOAc/Hexane 1:1 + 1% HCOOH) followed by ion exchange with Amberlite® IRC 86 Na^+ to give the sodium salt **40** (97 mg, 0.33 mmol, 98%) as an oil. R_f = 0.11 (EtOAc/hexane 2:1 + 1% HCOOH); $[\alpha]_D^{20}$ = +133.0 (*c* = 0.20, MeOH); ^{1}H NMR (400 MHz; CD_3OD) δ 7.41-7.25 (m, 5H, Ph), 4.83-4.67 (m, 3H, H-1, C*H*$_2$Ph), 4.55 (dd, *J* = 7.6, 1.6 Hz, 1H, H-4), 4.41 (dd, *J* = 7.6, 4.8 Hz, 1H, H-2), 4.28-4.24 (m, 2H, H-3, H-5), 3.38 (s, 3H, OC*H*$_3$); ^{13}C NMR (100 MHz; CD_3OD): δ 177.3, 139.5, 129.4, 128.8, 128.7, 102.9, 83.5, 79.3, 77.2, 73.9, 71.2, 55.6; MS (ESI$^+$) *m/z* calcd for $C_{14}H_{22}O_7N_1$ $[M+NH_4]^+$ 316.1391, found 316.1389.

Methyl 3-*O*-benzyl-β-L-idofuranoside uronate sodium salt 41

Monosaccharide **39** (125 mg, 0.40 mmol) was dissolved in THF (1 mL) and MeOH (0.5 mL). The solution was cooled to 0 °C and KOH (22 mg, 0.40 mmol) in H_2O (1 mL) was added dropwise. The solution was stirred for 2 h at this temperature. The reaction was extracted with EtOAc (2 x 15 mL) and HCl (0.1 M) (15 mL) and then dried ($MgSO_4$), filtered and solvent removed *in vacuo* to give the crude material. This was purified by silica gel flash chromatography (EtOAc/Hexane 1:1 + 1% HCOOH) followed by ion exchange with Amberlite®

IRC 86 Na^+ to give the sodium salt **41** (96 mg, 0.32 mmol, 75%) as an oil. R_f = 0.28 (EtOAc + 1% HCOOH); $[\alpha]_D^{20}$ = -34.7 (*c* = 0.43, MeOH); ^{1}H NMR (400 MHz; CD_3OD) δ 7.39-7.25 (m, 5H, Ph), 4.76 (d, *J* = 2.0 Hz, 1H, H-1), 4.72 (d, *J* = 11.7 Hz, 1H, C*H*$_2$Ph), 4.65 (dd, *J* = 6.8, 3.6 Hz, 1H, H-4), 4.60 (d, *J* = 11.7 Hz, 1H, C*H*$_2$Ph), 4.30 (dd, *J* = 4.2, 2.0 Hz, 1H, H-2), 4.24 (d, *J* = 3.6 Hz, 1H, H-5), 4.12 (dd, *J* = 6.8, 4.4 Hz, 1H, H-3), 3.40 (s, 3H, OC*H*$_3$); ^{13}C NMR (100 MHz; CD_3OD) δ 176.2, 139.2, 129.3, 129.0, 128.8, 111.1, 85.4, 82.9, 80.0, 73.7, 71.7, 56.3; HRMS (ESI^-) *m/z* calcd for $C_{14}H_{18}O_7Na$ $[M+Na]^+$ 321.0945, found 321.0941.

Methyl α-L-idofuranoside uronate sodium salt 42

Monosaccharide **40** (25 mg, 91 μmol) was dissolved in H_2O (3 mL). To the flask was attached a 3-way tap and purged with N_2, 10-20% $Pd(OH)_2/C$ (70 mg) was added and the system purged with H_2. Vigorous stirring having a balloon with H_2 attached (1 atm) was continued for 12 h. The suspension was then filtered through Celite® and solvents removed *in vacuo* to provide **42** (12 mg, 52 μmol, 57%) as a clear glass. R_f = 0.09 (EtOAc); $[\alpha]_D^{20}$ = +1.65 (*c* = 0.75, H_2O); ^{1}H NMR (400 MHz; D_2O) δ 4.84 (d, *J* = 4.7 Hz, 1H, H-1), 4.42 (dd, *J* = 7.5, 2.4 Hz, 1H, H-4), 4.29 (t, *J* = 7.5 Hz, 1H, H-3), 4.19 (d, *J* = 2.4 Hz, 1H, H-5), 4.15 (dd, *J* = 7.5, 4.7 Hz, 1H, H-2), 3.33 (s, 3H, OC*H*$_3$); ^{13}C NMR (100 MHz; D_2O) δ 101.6, 78.8, 75.7, 74.3, 70.0, 55.5; HRMS (ESI^-) *m/z* calcd for $C_7H_{11}O_7$ $[M-Na]^-$ 207.0510, found 207.0508.

Methyl β-L-idofuranoside uronate sodium salt 43

Monosaccharide **41** (23 mg, 63 μmol) was dissolved in H_2O (3 mL). To the flask was attached a 3-way tap and purged with N_2, 10-20% $Pd(OH)_2/C$ (20 mg) and $NaHCO_3$ (25 mg, 0.30 mmol) was added and the system purged with H_2. Vigorous stirring having a balloon with H_2 attached (1 atm) was continued for 8 h. The suspension was then filtered through Celite® and solvents removed *in vacuo* to reveal **43** (15 mg, 65 μmol, quant.) as a clear glass. R_f = 0.06 (EtOAc); $[\alpha]_D^{20}$ = -3.30 (*c* = 1.0, H_2O); ^{1}H NMR (400 MHz; D_2O) δ 4.84 (d, *J* = 1.5 Hz, 1H, H-1), 4.37 (t, *J* = 5.6 Hz, 1H, H-3), 4.21 (dd, *J* = 5.6, 3.0 Hz, 1H, H-4), 4.18-4.15 (m, 2H, H-5, H-2), 3.38 (s, 3H, OC*H*$_3$); ^{13}C NMR (100 MHz; D_2O) δ 171.1, 108.5, 83.7, 79.4, 75.6, 71.7, 55.5; HRMS (ESI^-) *m/z* calcd for $C_7H_{11}O_7$ $[M-Na]^-$ 207.0510, found 207.0513.

■ AUTHOR INFORMATION

Corresponding Author

* Tel: (+44) 161 306 4530. E-mail: gardiner@manchester.ac.uk

Present Addresses

†¶ Present address: Institute of Chemistry, Centre of Glycomics, Dubravska Cesta 9, 845 38 Bratislava, Slovakia.

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■ SUPPORTING INFORMATION

Copies of ^{1}H and ^{13}C NMR, COSY and HMQC spectra for new compounds, and mass spectra. This material is available free of charge via the Internet at http://pubs.acs.org. CIF files for X-ray structures are available free from the CCDC.[12]

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