CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200700141

De Novo Synthesis of Uronic Acid Building Blocks for Assembly of Heparin Oligosaccharides

Alexander Adibekian, Pascal Bindschädler, Mattie S. M. Timmer, Christian Noti, Nina Schützenmeister, and Peter H. Seeberger*[a]

Abstract: An efficient de novo synthesis of uronic acid building blocks is described. The synthetic strategy relies on the stereoselective elongation of thioacetal protected dialdehydes **12a** and **17**. The dialdehydes are prepared from D-xylose, a cheap and commercially available source. A highly stereoselective $MgBr_2{\cdot}OEt_2$-mediated Mukaiyama aldol addition to C4-aldehyde **12a** is performed to obtain D-glucuronic acid building block **16**, whereas L-iduronic acid building block **22** is prepared by $MgBr_2{\cdot}OEt_2$-mediated cyanation of C5-aldehyde **17**. Synthesis of a heparin disaccharide demonstrates the utility of the de novo strategy for the assembly of glycosaminoglycan oligosaccharides.

Keywords: carbohydrates · de novo synthesis · heparin · oligosaccharides · uronic acids

Introduction

The chemical synthesis of oligosaccharides requires suitably protected monosaccharide building blocks that are traditionally synthesized from unprotected sugars through a series of protection and deprotection maneuvers.[1] One fundamental difficulty of this process is the differentiation of up to five chemically similar hydroxyl groups in hexoses that require temporary protecting groups as well as selective masking of the anomeric hydroxyl group. Consequently, protocols for the preparation of carbohydrate building blocks rely on up to 20 synthetic steps[1] making this process time consuming and expensive. Dissection of carbohydrate building blocks into linear fragments reduces the number of hydroxyl groups and avoids temporary protection of the anomeric hydroxyl. The de novo strategy is convergent and minimizes the number of synthetic steps. It is possible to prepare several structurally related carbohydrate building blocks from one common linear precursor by varying the conditions for the stereoselective construction of the carbon skeleton.

Intriguing strategies for the de novo synthesis of monosaccharides have been reported in the past two decades.[2] Sharpless and Masamune[3] reported the syntheses of eight different hexoses by asymmetric epoxidation. More recently, proline-catalyzed aldol reactions served to rapidly construct partially protected monosaccharides.[4] Still, none of these elegant approaches delivered carbohydrate building blocks suitable for the synthesis of oligosaccharides.

Heparin, a linear, highly sulfated polysaccharide and the most acidic naturally occurring biopolymer, is composed of α-1,4-linked repeating disaccharide units containing uronic acid and D-glucosamine (GlcN). The uronic acid monosaccharides are L-iduronic acid (IdoA) and less frequently (about 10%) D-glucuronic acid (GlcA). A typical heparin disaccharide bears O-sulfation at C2 of the uronic acid, at C6 and more rarely also at C3 of glucosamine. In addition, the glucosamine nitrogen can be sulfated or acetylated.[5] Heparin isolated from natural sources is very heterogeneous. Nevertheless, heparins play a key role in regulating the biological activity of several proteins in the coagulation cascade along with many other pathological processes including cell growth, virus entry, tumor metastasis and inflammatory processes.[6]

The modular assembly of heparins[7] requires large quantities of differentially protected monosaccharides. While the synthesis of D-glucosamine building blocks from cheap, commercially available D-glucosamine is straightforward,[8] the procurement of orthogonally protected uronic acids is the highest synthetic hurdle on the way to heparin oligosaccharides. The synthesis of IdoA building blocks represents an ex-

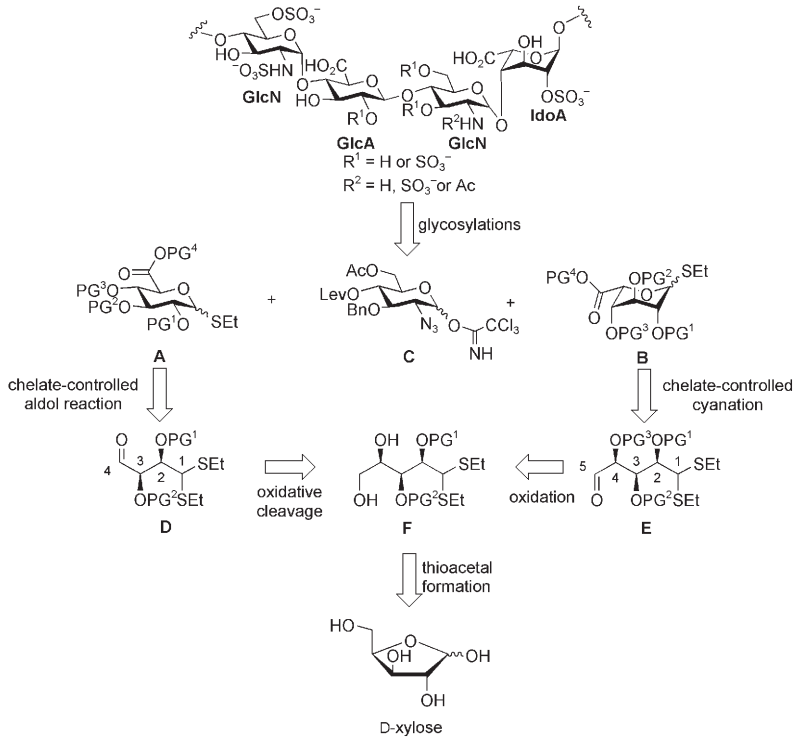
[a] A. Adibekian, P. Bindschädler, Dr. M. S. M. Timmer, C. Noti, N. Schützenmeister, Prof. Dr. P. H. Seeberger
Laboratory for Organic Chemistry
Swiss Federal Institute of Technology (ETH) Zürich
Wolfgang-Pauli-Strasse 10, HCI F312, 8093 Zürich (Switzerland)
Fax: (+41) 44-633-1235
E-mail: seeberger@org.chem.ethz.ch

Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.

traordinary challenge, since iduronic acid itself is not commercially available. Syntheses of iduronic acid building blocks from a variety of starting materials including idose,[9] glucose[10] and glycals,[11] have been developed. While L-idose is too expensive to serve as starting material, syntheses from alternative starting materials require the inversion of the C5 stereogenic center of a D-*gluco* configured sugar. Few methods employed for this inversion have shown complete selectivity for the desired configuration. Syntheses from idose to procure iduronic acid building blocks have been reported[9] but remain lengthy and involve several steps that produce multiple products. Although a plethora of other syntheses of glucuronic and iduronic acid building blocks is known,[8,12] no concise, stereoselective route to both orthogonally protected uronic acids from one common advanced intermediate has been reported to date.

Recently, we developed a de novo synthesis of fully functionalized uronic acids.[13] We used L-arabinose as the starting material for the synthesis of different C4 aldehydes that were elongated by Mukaiyama-type aldol reactions[14] to give uronic acid building blocks. While D-glucuronic acid was efficiently prepared in overall yield of 16%, the route to the L-iduronic acid, more abundant in heparin, yielded only 6% overall, due to low selectivity in the aldol addition step. Here, we report a selective and high yielding route to D-glucuronic acid and L-iduronic acid building blocks. The key steps are the diastereoselective elongations of two monoprotected dialdehydes that are both derived from D-xylose as a cheap, commercially available starting material. A C4 aldehyde is elongated by an aldol reaction to furnish glucuronic acid. Cyanation of a C5 aldehyde provides iduronic acid. The highly diastereoselective carbonyl additions were studied in detail and allowed us to postulate possible transition states. Finally, the synthetic utility of the new strategy is demonstrated by construction of a selectively O-sulfated and N-acetylated heparin disaccharide.

blocks: D-glucuronic acid **A**, L-iduronic acid **B** and D-glucosamine **C** (Scheme 1). A proper choice of protecting groups in the synthesis of uronic acid building blocks is of paramount importance for the control of glycosidation events and selective sulfations in the assembly of heparins.[7] Thus, we selected the pivaloyl group as the acyl group (PG^1) for anchimeric assistance to form selectively the desired *trans*-glycosidic bonds. In addition, pivaloate esters can be hydrolyzed in anticipation of O-sulfation[15] prior to cleavage of benzyl ethers that were chosen as permanent protecting groups (PG^2). For protection of carboxylic acids (PG^4) we planned to use methyl esters that can be removed together with other acyl groups. Finally, we decided to use levulinic esters[16] as temporary protecting groups PG^3 for the C4-hydroxyl groups on both building blocks, as Lev esters are orthogonal to all other masking groups.



Scheme 1. Retrosynthetic analysis of heparin oligosaccharides (P = protecting group; PG^1 = Piv, PG^2 = Bn, PG^3 = Lev, PG^4 = Me).

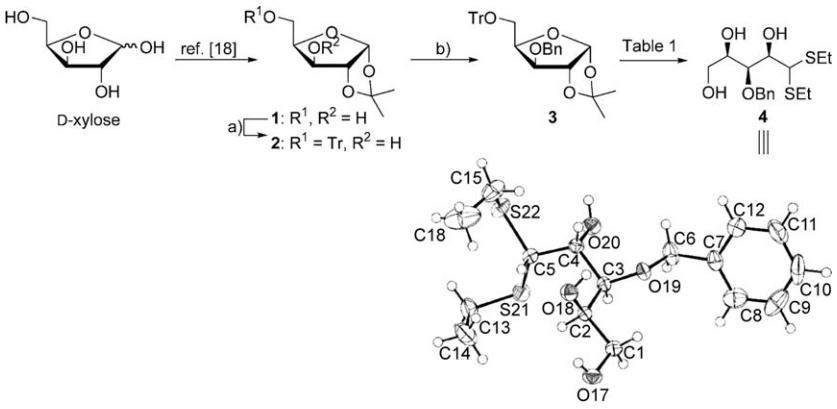
Results and Discussion

Synthetic strategy: Dissection of a model heparin oligosaccharide reveals three different monosaccharide building

IdoA and GlcA are epimers with respect to C5 in the pyranose ring. Therefore, our retrosynthetic analysis focused on means of introducing the C5 stereocenter at a late stage of the synthesis. Synthesis of common intermediate **F** would be followed by divergence to both targets. The pathway to the glucuronic acid building block relies on the oxidative cleavage of diol **F** to aldehyde **D**. A chelate-controlled 2,3-*anti*-selective aldol reaction,[17] C4 protection as levulinic ester and concluding cyclization will deliver D-*gluco*-thioglycoside **A**. En route to the iduronic acid building block, C5-aldehyde **E** will be prepared by oxidation of the primary hydroxyl of diol **F**. Subsequently, *syn*-selective chelate-controlled

cyanation, methanolysis of the nitrile via a Pinner reaction and final cyclization is expected to furnish the desired L-*ido*-configured thioglycoside **B**. Glucosamine building block **C** will be derived using previously established methods.[8d]

Synthesis of the building blocks: The first goal of our synthetic approach was the preparation of diol **F**, the key compound on the way to both uronic acids. Monoacetal **1** was readily available from D-xylose on hundreds of gram scale[18] (Scheme 2). Protection of the primary alcohol with triphenylchloromethane in pyridine proceeded smoothly to give alcohol **2**. Benzylation of the secondary hydroxyl with benzyl bromide, sodium hydride and catalytic amount of TBAI afforded fully protected D-xylofuranose **3** in quantitative yield over two steps.



Scheme 2. Synthesis of thioacetal **4**: a) TrCl, pyridine, quant.; b) BnBr, NaH, TBAI (cat.), DMF, quant.

At this stage, we investigated the one-pot Lewis acid mediated cleavage of the trityl protecting group and concomitant opening of the anomeric acetal **3** with ethane thiol as nucleophile to obtain monobenzylated thioacetal **4** (Table 1). Screening a variety of different Lewis acids and reaction conditions allowed access to triol **4** (Scheme 2) as the major product in moderate yield by using hard Lewis acids such as $SnCl_4$, $TiCl_4$ or $BF_3{\cdot}OEt_2$ and three equivalents of thiol (entries 1–3). An increased yield of 81% was observed by employing $BF_3{\cdot}OEt_2$ and six equivalents of EtSH (entry 4), as well as by careful controlling of reaction time. Gratifyingly, the use of mild Lewis acid $ZnBr_2$ and large excess of ethane thiol improved the yield further to give 91% of thioacetal **4** (entry 7). Unambiguous confirmation of the structure of **4** was based on the X-ray analysis of single crystals (CCDC-633131).[40]

In order to selectively introduce an acyl protecting group at the C2 hydroxyl, an acetonide was installed on triol **4** using thermodynamic conditions (Scheme 3). The dioxolane ring was formed selectively under agency of 15 mol% of *p*TsOH and acetone at room temperature to afford alcohol **5** in 93% yield. Subsequent protection of the free hydroxyl using pivaloyl chloride and DMAP furnished the fully protected thioacetal **6** in quantitative yield. After treatment with 75% acetic acid in water at 50°C, the desired diol **7**

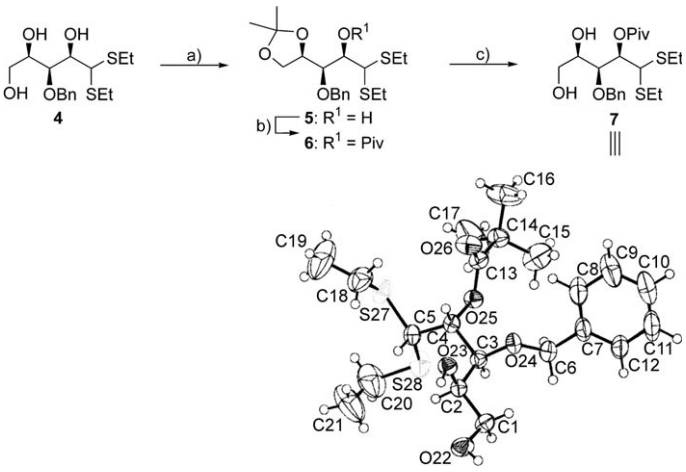
Table 1. Lewis acid mediated reaction of acetal **3** to form thioacetal **4**[a].

Entry	Lewis acid	equiv EtSH	Yield **4** [%][b]
1	$SnCl_4$	3	64
2	$TiCl_4$	3	37
3	$BF_3{\cdot}OEt_2$	3	70
4	$BF_3{\cdot}OEt_2$	6	81
5	$BF_3{\cdot}OEt_2$	20	67
6	$ZnCl_2$	20	85
7	$ZnBr_2$	20	91

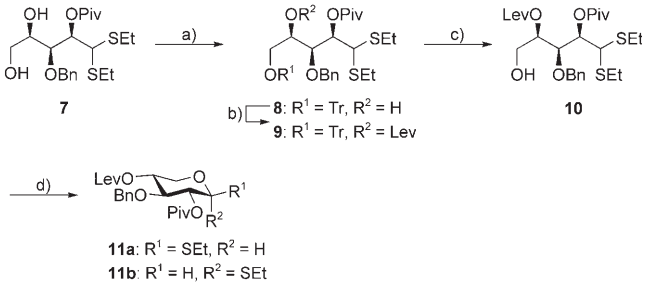
[a] All reactions were carried out in CH_2Cl_2 (0.3 M) at 0°C. [b] Isolated yield.

was obtained in quantitative yield. An X-ray structure of **7**[40] revealed that the pivaloyl group did not migrate during isopropylidene cleavage with acid.

We had planned for the *N*-iodosuccinimide-mediated cyclization of thioacetals[13] to be the final step in the synthesis of both uronic acid thioglycosides. The reaction was tested on a compound bearing both pivaloyl and levulinoyl protecting groups. For this purpose, the primary hydroxyl on diol **7** was selectively protected as triphenylmethyl ether (Scheme 4). The secondary hydroxyl was subjected to esterification conditions using levulinic acid, *N*,*N*′-diisopropyl carbodiimide (DIPC) and 4-dimethylaminopyridine (DMAP) to give ester **9** in quantitative yield over two steps. For the cleavage of triphenylmethyl ether, various acidic conditions were tested, since the levulinoyl group exhibited a tendency to migrate to the primary hydroxyl. Optimal reaction conditions employed TFA and triethylsilane in dichloromethane to afford primary alcohol **10** in 90% yield. Finally, the cyclization of thioacetal



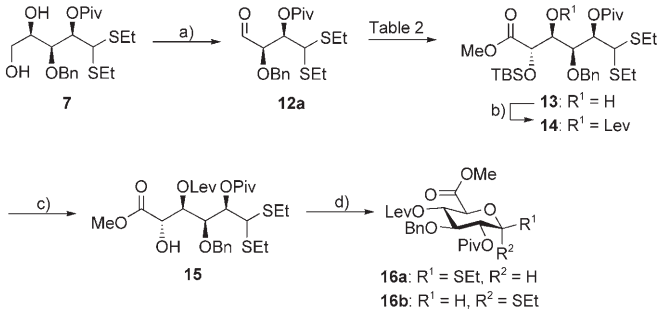
Scheme 3. Synthesis of diol **7**: a) *p*TsOH, acetone, 93%; b) PivCl, DMAP, CH_2Cl_2, 0°C, quant.; c) $AcOH/H_2O$, 50°C, quant.



Scheme 4. Synthesis of D-xylopyranose building block **11**: a) TrCl, pyridine, 90%; b) LevOH, DIPC, DMAP, CH_2Cl_2, quant.; c) TES, TFA, CH_2Cl_2, 90%; d) NIS, TFA, CH_2Cl_2, 0°C, 92% (α/β 1:1).

10 proceeded smoothly with *N*-iodosuccinimide (NIS) and one equivalent of TFA at 0°C to furnish orthogonally protected D-xylopyranose thioglycoside[19,20] **11** as a separable 1:1 mixture of α and β anomers in 92% yield. Building block **11** is useful[21] for the construction of β-glycosidic linkages found in the tetrasaccharide core of glycosaminoglycans linking xylose to the serine/threonine residues of the proteoglycan core protein.[22]

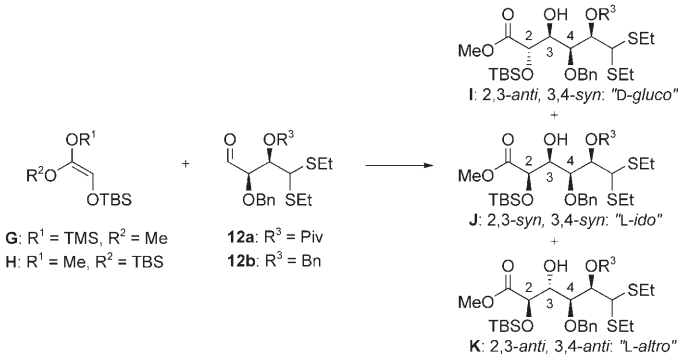
Next, we explored the route to the D-glucuronic acid building block. Oxidative cleavage of diol **7** with sodium periodate in a THF/water mixture afforded C4-aldehyde **12a** in 82% yield (Scheme 5). Aldehyde **12a** was purified by silica gel column chromatography and could be stored for days without significant decomposition.



Scheme 5. Synthesis of the D-glucuronic acid building block **16**: a) $NaIO_4$, H_2O/THF, 82%; b) LevOH, DIPC, DMAP, CH_2Cl_2, quant.; c) HF py, THF, quant.; d) NIS, TFA, CH_2Cl_2, 88% (α/β 1:1).

Now the stage was set for the chelation controlled Mukaiyama-type aldol addition to aldehyde **12a**. Yamamoto's ketene acetals[23] **G** and **H** were chosen as nucleophiles (Table 2), since they are equipped with an acid-cleavable TBS protecting group in the α-position. To identify optimal reaction conditions, the (*E*)-ketene acetal **G** was used in combination with aldehyde **12b** (entries 1–9), that is available in five steps from L-arabinose.[13] The use of $TiCl_4$ as activator led to the decomposition of the aldehyde even at low temperatures (entry 1). Aldol addition with non-chelating Lewis acid $BF_3{\cdot}OEt_2$ at 0°C (entry 3) was high yielding (93%), but three different diastereomers were formed in a 1:1:1 ratio. After conversion to the corresponding thioglycosides and analysis of the ^{1}H NMR coupling constants[13] the isomers were identified as the D-*gluco* (**I**), L-*ido* (**J**) and L-*altro* (**K**) configurations. The low selectivity is in agreement with recent results by Evans,[24] who reported the $BF_3{\cdot}OEt_2$-mediated addition of enol silanes to *syn*-α,β-bisalkoxy aldehydes. The absence of the D-*galacto* isomer can be explained assuming a sterically demanding *Si*,*Si* attack in a non-chelating, open transition state. Next, $ZnCl_2$ was used as a chelating Lewis acid (entries 5–7). The best selectivity was obtained at room temperature, giving **I** and **J** in a ratio of 10:4 and moderate yield of 66%. Use of $ZnCl_2$ at low temperatures improved yields but decreased selectivity (entries 6 and 7). The use of $MgBr_2{\cdot}OEt_2$ at −78°C led to exclusive formation of isomer **I** in quantitative yield. Interestingly, when the (*Z*)-ketene acetal **H** was used, the same result was obtained (entry 10). After applying these conditions to aldehyde **12a**, again only isomer **I** was formed in 85% yield (entry 11).

Table 2. Mukaiyama-type aldol reactions with aldehydes **12a** and **12b**.[a]



Entry	Enol ether	Aldehyde	Lewis acid	*T* [°C]	**I**/**J**/**K** [%][b]
1	**G**	**12b**	$TiCl_4$	−78	–[c]
2	**G**	**12b**	$BF_3{\cdot}OEt_2$	RT	1:1:1 (74)
3	**G**	**12b**	$BF_3{\cdot}OEt_2$	0	1:1:1 (93)
4	**G**	**12b**	$BF_3{\cdot}OEt_2$	−78	–[d]
5	**G**	**12b**	$ZnCl_2$	RT	10:4:– (66)
6	**G**	**12b**	$ZnCl_2$	0	10:5:– (72)
7	**G**	**12b**	$ZnCl_2$	−78	10:7:– (87)
8	**G**	**12b**	$MgBr_2{\cdot}OEt_2$[e]	0	10:2:– (99)
9	**G**	**12b**	$MgBr_2{\cdot}OEt_2$[e]	−78	1:–:– (98)
10	**H**	**12b**	$MgBr_2{\cdot}OEt_2$[e]	−78	1:–:– (96)
11	**G**	**12a**	$MgBr_2{\cdot}OEt_2$[e]	−78	1:–:– (85)

[a] All reactions were carried out with 1.5 equiv of ketene acetal and 1.5 equiv of Lewis acid in toluene (0.2 M). [b] Isolated yields. [c] Decomposition of the aldehyde was observed. [d] No reaction was observed. [e] Excess $MgBr_2{\cdot}OEt_2$ (3 equiv) was used due to its low solubility in toluene.

Transmetallation of both enol silanes[25] to magnesium enolate would enable formation of a cyclic transition state and explain the high selectivity of these transformations. To investigate this mechanistic assumption, both ketene acetals were treated with $MgBr_2{\cdot}OEt_2$ in [D_8]toluene at −78°C. Even after warming to room temperature neither changes in ^{1}H NMR signals of both nucleophiles nor appearance of characteristic ^{1}H NMR signals of TMS-Br or TBS-Br were observed. Based on these results we exclude the possibility of transmetallation and assume that the $MgBr_2{\cdot}OEt_2$-medi-

ated[26] Mukaiyama aldol reaction between ketene acetal **G** or **H** and aldehyde **12a** or **12b** proceeds via an open transition state, where $MgBr_2$ chelates the formyl oxygen and the benzyloxy oxygen of the aldehyde (Figure 1). The nature of the protecting group on oxygen at C3 plays a minor role in this process, as both aldehydes react in a similar way. The *Si* attack on the aldehyde is prohibited by the bulky rest R on C2 of the aldehyde. The face selectivity on nucleophiles is determined by steric repulsion between the bromide ligands on magnesium and bulky substituents of ketene acetals **G** and **H**. According to Heathcock,[27] this repulsion is minimized in synclinal transition structures **TS1** and **TS2**, as well as in antiperiplanar transition structures **TS3** and **TS4**. Both **TS3** and **TS4** are disfavored compared with **TS1** and **TS2**, since increased steric repulsion is caused by a sterically demanding substituent R. The topological rule for preferred *gauche* relationship of the donor and acceptor π systems in a variety of C,C-bond forming reactions proposed by Seebach[28] additionally favors **TS1** and **TS2**. Thus, the D-*gluco* diastereomer is formed with high selectivity using both ketene acetals.

Aldol product **13** was masked as the corresponding levulinoyl ester (Scheme 5). The silyl ether was cleaved under mild conditions using HF·pyridine in THF to furnish the C5-alcohol **15** in quantitative yield over two steps. Finally, NIS-mediated thioacetal cyclization led to the formation of the desired D-glucuronic acid thioglycoside **16** as a separable 1:1 mixture of both anomers in 88% yield. At this stage, the NOE correlations served to confirm the D-*gluco* configuration on β-thioglycoside **16a** (Figure 2). 1-Thio D-glucuronic

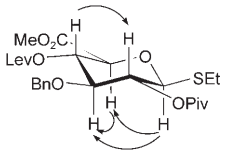


Figure 2. Diagnostic NOE correlations for donor **16a**.

acids have recently been demonstrated to be efficient glycosylating agents in the assembly of glycosaminoglycans.[8f]

The next target in our synthetic endeavor was the L-iduronic acid building block. We planned to prepare a C5 aldehyde and elongate it via a cyanation reaction (Scheme 6). A number of procedures for the oxidation of alcohol **10** to aldehyde **17** were tested, but all failed either due to oxidation of the sulfur or epimerization of the aldehyde during the reaction. Finally, we found that a mild procedure based on DMSO in combination with sulfur trioxide pyridine complex and DIPEA, known as the Parikh–Doering oxidation,[29] gave the desired aldehyde **17** in excellent yield of 94%.

Next, the chelate-controlled cyanation of aldehyde **17** was explored. Chelating halide salts in combination with trimethylsilyl cyanide as a safe source of cyanide[30] were used to selectively obtain the L-*ido*-configured product. The most interesting results of this investigation are summarized in Table 3. The mixtures of D-*gluco*- and L-*ido* diastereomers were separated and analyzed after cleavage of the levulinoyl protecting group, as partial migration took place during the cyanation. No product was obtained when hard Lewis acids such as BF_3·OEt_2 or $TiCl_4$ were used, since rapid decomposition of the aldehyde occured even at −78°C (entries 1 and 2). Use of $CuBr_2$ at −20°C gave a mixture of cyanohydrins with a slight preference for the isomer **18a** in 82% yield (entry 4). It was possible to determine the relative configuration of cyanohydrin **18a** by X-ray analysis[40] to confirm the desired L-*ido* configuration (Figure 3). When ZnI_2 was used, cyanation of the levulinoyl ketone as side reaction resulted in low yields of 32–57% (entries 5–7). Again, use of $MgBr_2$·OEt_2 as chelating activator[30,31] proved to be the method of choice and furnished the L-*ido* isomer with 8:1 diastereoselectivity and 82% yield at 0°C (entry 9). The *syn*-preference of this transformation is in accordance with Reetz' model for chelate-controlled additions of cyanosilanes to aldehydes.[30,32]

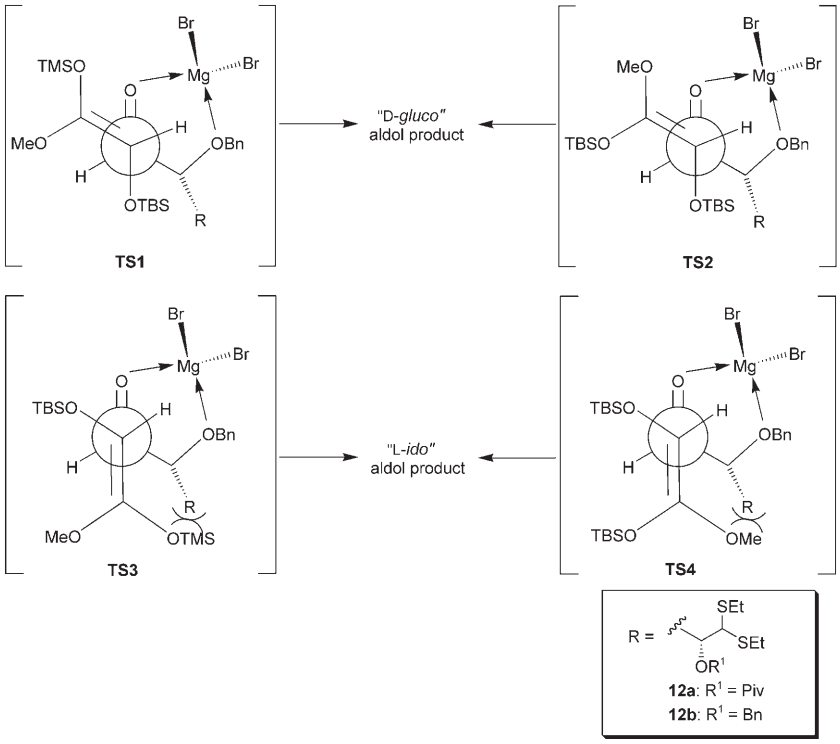
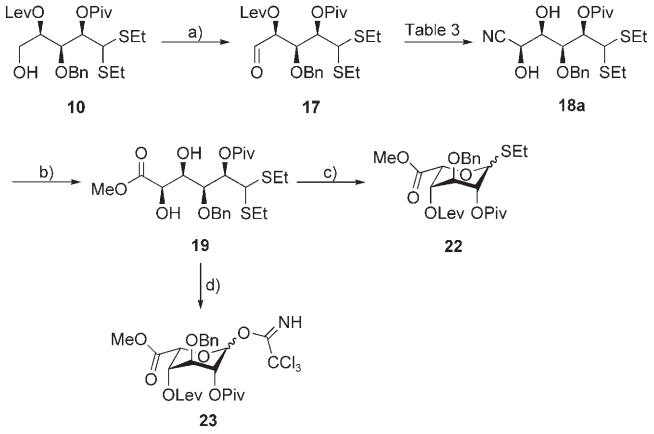
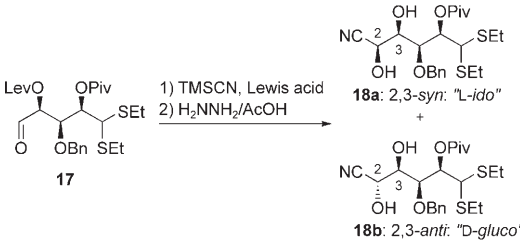


Figure 1. Possible transition states for $MgBr_2$·OEt_2-mediated aldol reaction.



Scheme 6. Synthesis of L-iduronic acid building blocks **21** and **22**: a) SO_3·Py, DMSO, DIPEA, 94%; b) AcCl, MeOH, toluene, 70%; c) 1) LevOH, DIPC, DMAP, CH_2Cl_2, 0°C; 2) NIS, CH_2Cl_2, 80% over two steps (α/β 1:1); d) 1) LevOH, DIPC, DMAP, CH_2Cl_2, 0°C; 2) BTI, aq. $NaHCO_3$, CH_3CN; then TFA, 50°C; 3) Cl_3CCN, DBU, CH_2Cl_2, 77% over three steps (α/β 1:1).

Table 3. Cyanation–deprotection sequence with aldehyde **17**.[a]



Entry	Lewis acid	T [°C]	**18a**/**18b** (Yield/%)[b]
1	BF_3·OEt_2	−78	–[c]
2	$TiCl_4$	−78	–[c]
3	$CuBr_2$	RT	2:1 (87)
4	$CuBr_2$	−20	3:1 (82)
5	ZnI_2	RT	5:1 (32)[d]
6	ZnI_2	−20	8:1 (57)[d]
7	ZnI_2[e]	−20	8:1 (52)[d]
8	$MgBr_2$·OEt_2[g]	RT	6:1 (84)
9	$MgBr_2$·OEt_2[g]	0	8:1 (82)
10	$MgBr_2$·OEt_2[g]	−20	–[f]

[a] All reactions were carried out with 1.1 equiv of TMSCN and 1.2 equiv of Lewis acid in CH_2Cl_2 (0.1 M). The diastereomeric ratio was determined after removal of the partially migrated levulinoyl protecting group. [b] Isolated yields. [c] Decomposition of the aldehyde was observed. [d] Cyanation of the levulinoyl ketone was observed. [e] 3 equiv of Lewis acid were used. [f] No reaction was observed. [g] Excess $MgBr_2$·OEt_2 (3 equiv) was used due to its low solubility in CH_2Cl_2.

Nitrile **18a** readily underwent the Pinner reaction (Scheme 6) when treated with an excess of hydrochloric acid in toluene and methanol as the nucleophile.[33] Subsequent hydrolysis furnished methyl ester **19** in 70% yield. The NIS-mediated cyclization of diol **19** delivered exclusively the β-furanose form of L-iduronic acid (Scheme 7). Serendipitously, protection with levulinic acid at 0°C gave selectively the 4-*O*-Lev thioacetal, that was cyclized with NIS in CH_2Cl_2 to furnish L-iduronic acid thioglycoside **22** in 80% yield over two steps. Known[34] trichloroacetimidate **23** was prepared as

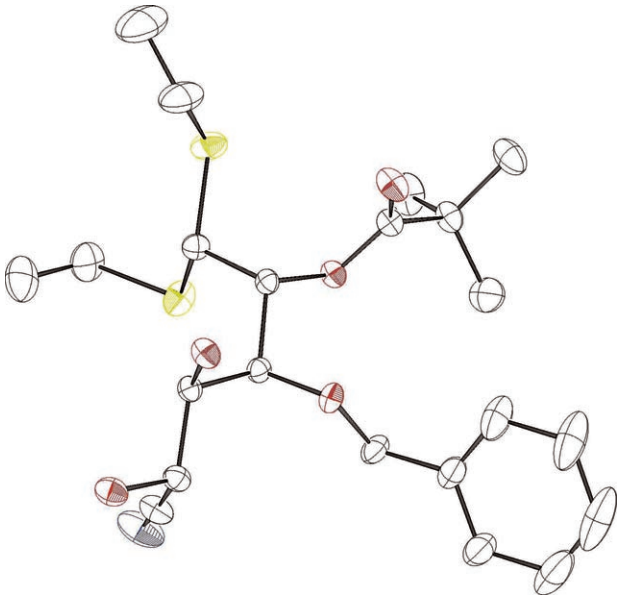
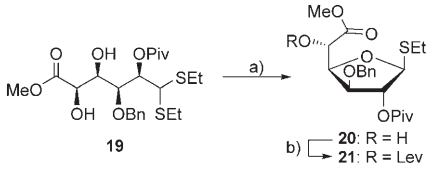


Figure 3. ORTEP plot of cyanohydrin **18a**.

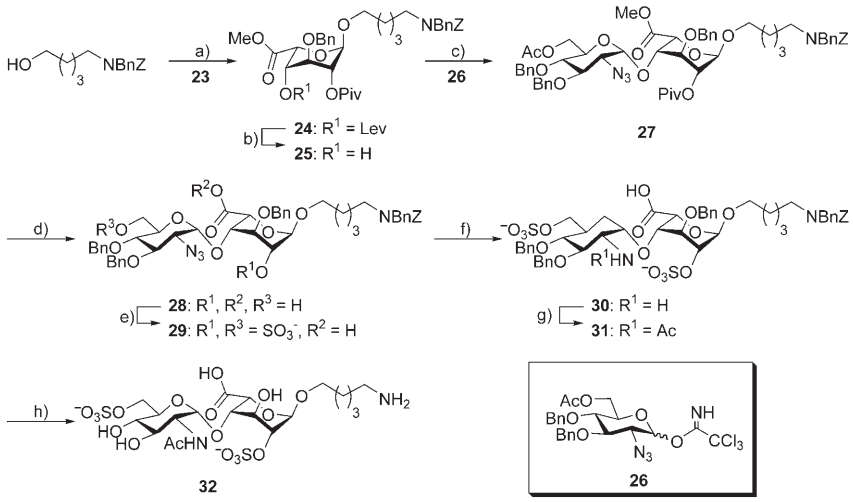


Scheme 7. Cyclization and protection of diol **19** to β-L-iduronic acid furanose **20**: a) NIS, CH_2Cl_2, 81%; b) LevOH, DIPC, DMAP, CH_2Cl_2, 0°C, 88%.

an alternative glycosylating agent in 77% yield using Stork's dethioacetalization with bis(trifluoroacetoxy)iodobenzene (BTI)[35] followed by the reaction of the formed hemiacetal with DBU and trichloroacetonitrile.

Synthesis of a heparin disaccharide: We applied the methodology described here to the synthesis of O-sulfated and N-acetylated heparin disaccharide **32** (Scheme 8). In the first step the IdoA building block was coupled with a linker bearing a protected amine group in the terminal position. This modification allows, after the sulfation and global deprotection, for the immobilization of the disaccharide on a glass slide to prepare heparin arrays.[36] An *N*-(benzyl)benzyloxycarbonylamino linker was selected, for its compatibility with oligosaccharide assembly.[37] Glycosidation of IdoA building block **23** with *N*-(benzyl)benzyloxycarbonyl-5-amino-pentane-1-ol catalyzed by TMSOTf in CH_2Cl_2 at −20°C followed by cleavage of the levulinoyl group furnished alcohol **25**.[36b] Coupling with 2-azidoglucopyranose building block[8d] **26** using these conditions afforded disaccharide **27** in 81% yield and complete α-selectivity for the newly constructed glycosidic linkage. With the fully protected heparin disaccharide in hand, we laid out the deprotection strategy. Saponification removes the acyl protecting groups on IdoA and GlcN as well as hydrolyzes the methyl ester. O-Sulfation

places sulfate groups on position 2 of iduronic acid and position 6 of glucosamine. The azide is reduced via a Staudinger reaction before N-acetylation. Finally, hydrogenolysis will remove all permanent protection from the desired heparin disaccharide. Treatment of **27** with lithium hydroperoxide followed by addition of an aqueous solution of KOH and MeOH afforded the partially protected disaccharide **28** in 85% yield. O-Sulfation was conducted with SO_3·Et_3N in DMF at 55°C[38] and furnished double sulfated compound **29** in 82% yield. The azido group was reduced using PMe_3 in THF[39] to give amine **30** in 87% yield. Subsequent N-acetylation gave **31** quantitatively. Finally, hydrogenolytic cleavage of the benzyl and benzyloxycarbonyl groups furnished the selectively sulfated heparin disaccharide **32** in quantitative yield.



Scheme 8. Assembly and sulfation of heparin disaccharide **32**: a) TMSOTf (cat.), CH_2Cl_2, −20°C, 76% (α/β 95:5); b) H_2NNH_2·H_2O, Py/AcOH, CH_2Cl_2, 96%; c) **25**, TMSOTf (cat.), CH_2Cl_2, −25°C, 4 Å MS, 81%; d) LiOH, H_2O_2; KOH, MeOH, 85%; e) SO_3·Et_3N, DMF, 55°C, 82%; f) PMe_3, THF, NaOH, 87%; g) Ac_2O, Et_3N, MeOH, quant.; h) H_2, Pd/C, quant.

Conclusion

In summary, we developed a de novo synthesis for D-glucuronic- and L-iduronic acid building blocks. Common intermediate **7** was obtained from D-xylose **1** in six steps and 85% yield. From this diol precursor, D-xylose thioglycoside **11** was afforded in four steps via a NIS-mediated cyclization in 75% yield. D-Glucuronic acid **16** was prepared in five steps and 61% yield, including a highly selective $MgBr_2$·OEt_2-mediated aldol addition as key transformation. $MgBr_2$·OEt_2-mediated cyanation and subsequent Pinner reaction served as key steps to synthesize L-iduronic acid **22** in eight steps and 30% yield. All transformations could be performed on a multigram scale without noticeable loss of yield or selectivity. The synthetic utility of the iduronic acid building block was demonstrated by construction of an O-sulfated and N-acetylated heparin disaccharide **32**.

The chemistry presented here offers a convenient and high-yielding route for the preparation of suitably protected building blocks of D-xylose as well as D-glucuronic and L-iduronic acids from a readily available common intermediate. Our de novo synthesis is based on the use of linear synthetic intermediates, thus no anomeric protection is necessary and α/β mixtures of anomers are not formed during the synthesis. The de novo synthesis of further carbohydrate building blocks is currently under investigation und will be reported in due course.

Experimental Section

General information: All chemicals used were reagent grade and used as supplied except where noted. Dichloromethane (CH_2Cl_2), toluene and tetrahydrofuran (THF) were purified by a Cycle-Tainer Solvent Delivery System. Pyridine and triethylamine were distilled over CaH_2 prior to use. Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} plates (0.25 mm). Compounds were visualized by UV irradiation or dipping the plate in an anisaldehyde solution followed by heating. Flash column chromatography was carried out using forced flow of the indicated solvent on Fluka Kieselgel 60 (230–400 mesh). Gel filtration chromatography was carried out using Sephadex LH-20 from Amersham Biosciences.

^1H and ^{13}C NMR spectra were recorded on a Varian VXR-300 (300 MHz) or Bruker DRX500 (500 MHz) spectrometer. High-resolution mass spectra (MALDI-HRMS) were performed by the MS-service at the Laboratory for Organic Chemistry (ETH Zürich). ESI MS were run on an Agilent 1100 Series LC/MSD instrument. IR spectra were recorded on a Perkin-Elmer 1600 FTIR spectrometer. Optical rotations were measured using a Perkin-Elmer 241 polarimeter.

1,2-*O*-Isopropylidene-5-*O*-triphenylmethyl-α-D-xylofuranoside (2): Triphenylmethyl chloride (30 g, 107.69 mmol) was added at 0°C to a solution of diol **1** (18.6 g, 97.9 mmol) in pyridine (150 mL). The mixture was stirred at room temperature for 12 h and the solvent was removed in vacuo. The residue was purified by flash chromatography (hexanes/ethyl acetate 2:1) to give **2** (44.7 g, quant.) as a white foam. R_f = 0.4 (hexanes/ethyl acetate 3:7); $[\alpha]_D^{RT}$ = 54.4 (c = 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.57–7.19 (m, 15H), 6.04 (d, J = 3.7 Hz, 1H), 4.55 (d, J = 3.7 Hz, 1H), 4.38–4.23 (m, 2H), 3.58 (m, 2H), 3.30 (br s, 1H), 1.55 (s, 3H), 1.36 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.2, 128.4, 128.0, 127.2, 111.5, 104.9, 87.5, 85.1, 78.6, 76.2, 61.9, 27.0, 26.3 ppm; IR (thin film on NaCl): $\tilde{\nu}$ = 3458, 3008, 1491, 1448, 1263, 1074, 908 cm^{-1}; MALDI-HRMS: m/z: calcd for $C_{27}H_{28}O_5Na$: 455.1829, found: 455.1833 $[M+Na]^+$.

1,2-*O*-Isopropylidene-3-*O*-benzyl-5-*O*-triphenylmethyl-α-D-xylofuranoside (3): Alcohol **2** (14.8 g, 34.2 mmol) was dissolved in DMF (100 mL) and cooled to 0°C. Sodium hydride (1.5 g, 60% in oil, 37.6 mmol), benzyl bromide (4.5 mL, 37.6 mmol) and TBAI (cat.) were added and the mixture was allowed to stir at room temperature for 12 h. The reaction was quenched with sat. aq. NH_4Cl and concentrated in vacuo. The residue was taken in ethyl acetate, washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by flash chromatography (hexanes/ethyl acetate 20:1 → 10:1) to give **3**

(18.5 g, quant.) as a pale yellow oil. R_f = 0.7 (hexanes/ethyl acetate 3:7); $[\alpha]_D^{RT} = -26.8$ ($c = 1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56–7.11 (m, 20H), 5.97 (d, $J = 3.8$ Hz, 1H), 4.68–4.59 (m, 2H), 4.53–4.43 (m, 2H), 4.07 (d, $J = 3.1$ Hz, 1H), 3.63 (dd, $J = 9.3$, 5.8 Hz, 1H), 3.38 (dd, $J = 9.3$, 6.8 Hz, 1H), 1.59 (s, 3H), 1.38 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.8, 137.4, 128.7, 128.3, 127.7, 127.6, 127.5, 126.9, 111.6, 86.9, 82.5, 79.5, 72.0, 61.4, 27.0, 26.4 ppm; IR (thin film on NaCl): $\tilde{\nu} = 3007$, 1731, 1448, 1346, 1163, 1077, 1010, 899, 859 cm^{-1}; MALDI-HRMS: m/z: calcd for $C_{34}H_{34}O_5Na$: 545.2298, found: 545.2304 $[M+Na]^+$.

3-*O*-Benzyl-D-xylose di(ethylthio)acetal (4): Acetonide **3** (314 mg, 0.6 mmol) was dissolved in CH_2Cl_2 (2.4 mL) and cooled to 0°C. EtSH (0.75 mL, 12 mmol) and $ZnBr_2$ (676 mg, 3 mmol) were added and the mixture was stirred at 0°C for 75 min. The reaction was quenched by adding 5% aq. ammonium hydroxide and the resulting slurry was diluted with CH_2Cl_2 and 1M aq. HCl. The phases were separated and the aqueous layer extracted with CH_2Cl_2 (2×). The combined organic layers were dried over $MgSO_4$, concentrated and purified by flash chromatography (cyclohexane/ethyl acetate 7:3 → pure ethyl acetate) to afford **4** (189 mg, 91%) as a colorless oil. R_f = 0.5 (ethyl acetate); $[\alpha]_D^{RT} = 27.3$ ($c = 1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.27 (m, 5H), 4.79 (d, $J = 11.3$ Hz, 1H), 4.72 (d, $J = 11.3$ Hz, 1H), 4.07 (dd, $J = 4.8$, 2.5 Hz, 1H), 4.04 (d, $J = 7.7$ Hz, 1H), 3.95–3.77 (m, 3H), 3.72–3.59 (m, 1H), 3.39 (d, $J = 4.8$ Hz, 1H), 2.90 (d, $J = 5.8$ Hz, 1H), 2.83 (dd, $J = 8.3$, 4.5 Hz, 1H), 2.77–2.55 (m, 4H), 1.22 (t, $J = 7.4$, 3H), 1.21 ppm (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.9, 128.4, 128.1, 127.8, 78.4, 74.5, 71.9, 70.9, 62.9, 55.4, 25.2, 24.4, 14.6, 14.5 ppm; IR (thin film on NaCl): $\tilde{\nu} = 3451$, 3007, 2930, 1454, 1391, 1264, 1091, 1052, 876 cm^{-1}; MALDI-HRMS: m/z: calcd for $C_{16}H_{26}O_4S_2Na$: 369.1165, found: 369.1159 $[M+Na]^+$.

3-*O*-Benzyl-4,5-*O*-isopropylidene-D-xylose di(ethylthio)acetal (5): *p*TsOH (422 mg, 2.22 mmol) was added to a solution of triol **4** (5.12 g, 14.78 mmol) in acetone (100 mL). The mixture was stirred at room temperature for 12 h and the reaction was quenched with sat. aq. $NaHCO_3$. The suspension was filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexanes/ethyl acetate 10:1) to give **5** (5.31 g, 93%) as a colorless oil. R_f = 0.7 (hexanes/ethyl acetate 3:2); $[\alpha]_D^{RT} = 49.3$ ($c = 1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.19 (m, 5H), 4.94 (d, $J = 11.3$ Hz, 1H), 4.72 (d, $J = 11.3$ Hz, 1H), 4.52–4.41 (m, 1H), 4.06 (dd, $J = 8.1$, 6.4 Hz, 1H), 3.99 (d, $J = 8.2$ Hz, 1H), 3.94 (dd, $J = 7.0$, 2.0 Hz, 1H), 3.75 (d, $J = 7.9$ Hz, 1H), 3.47 (ddd, $J = 7.9$, 5.6, 2.1 Hz, 1H), 3.14 (d, $J = 5.6$ Hz, 1H), 2.72–2.54 (m, 4H), 1.45 (s, 3H), 1.37 (s, 3H), 1.23 (t, $J = 7.4$, 3H), 1.20 ppm (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.3, 128.2, 128.1, 127.6, 109.3, 78.7, 77.7, 74.1, 72.3, 66.0, 55.5, 26.8, 25.7, 25.1, 24.2, 14.7, 14.5 ppm; IR (thin film on NaCl): $\tilde{\nu} = 3007$, 2930, 1454, 1381, 1248, 1075, 852 cm^{-1}; MALDI-HRMS: m/z: calcd for $C_{19}H_{30}O_4S_2Na$: 409.1478, found: 409.1471 $[M+Na]^+$.

2-*O*-Pivaloyl-3-*O*-benzyl-4,5-*O*-isopropylidene-D-xylose di(ethylthio)acetal (6): Alcohol **5** (20 g, 51.7 mmol) was dissolved in CH_2Cl_2 (250 mL) and cooled to 0°C. Pivaloyl chloride (8.5 mL, 69 mmol) was added dropwise, followed by portionwise addition of DMAP (12.8 g, 103.5 mmol). After stirring at 0°C for 60 min sat. aq. NH_4Cl (50 mL) was added and the phases were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by silica gel chromatography (hexanes/ethyl acetate 5:1) to give **6** (26.2 g, quant.) as a colorless oil. R_f = 0.8 (hexanes/ethyl acetate 7:3); $[\alpha]_D^{RT} = -15.4$ ($c = 1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.20 (m, 5H), 5.13 (dd, $J = 7.3$, 3.6 Hz, 1H), 4.90 (d, $J = 11.7$ Hz, 1H), 4.72 (d, $J = 11.7$ Hz, 1H), 4.23 (t, $J = 7.2$, 1H), 4.16 (d, $J = 7.3$ Hz, 1H), 4.05 (dd, $J = 6.9$, 3.6 Hz, 1H), 3.97 (dd, $J = 8.5$, 6.4 Hz, 1H), 3.76 (dd, $J = 8.5$, 7.3 Hz, 1H), 2.76–2.50 (m, 4H), 1.44 (s, 3H), 1.34 (s, 3H), 1.26–1.17 ppm (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.1, 138.5, 128.1, 127.4, 127.3, 109.3, 78.8, 77.2, 74.3, 72.7, 65.9, 51.9, 39.1, 27.4, 26.6, 25.5, 24.8, 24.5, 14.5, 14.2 ppm; IR (thin film on NaCl): $\tilde{\nu} = 2976$, 1723, 1479, 1372, 1278, 1155, 1067, 854 cm^{-1}; MALDI-HRMS: m/z: calcd for $C_{24}H_{38}O_5S_2Na$: 493.2058, found: 493.2061 $[M+Na]^+$.

2-*O*-Pivaloyl-3-*O*-benzyl-D-xylose di(ethylthio)acetal (7): Acetonide **6** (21.8 g, 46.3 mmol) was dissolved in 50% aq. AcOH (500 mL). The mixture was allowed to stir at 50°C for 3 h. The solvent was removed in vacuo and the residue was coevaporated twice with toluene. The resulting colorless oil **7** (19.9 g, quant.) was analytically pure and was used for the next step without further purification. R_f = 0.5 (hexanes/ethyl acetate 2:3); $[\alpha]_D^{RT} = -34.8$ ($c = 1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.22 (m, 5H), 5.49 (dd, $J = 6.2$, 4.5 Hz, 1H), 4.77 (d, $J = 11.4$ Hz, 1H), 4.60 (d, $J = 11.4$ Hz, 1H), 4.09 (d, $J = 4.5$ Hz, 1H), 4.02 (dd, $J = 6.2$, 3.7 Hz, 1H), 3.79 (dd, $J = 8.9$, 5.0 Hz, 1H), 3.65–3.53 (m, 2H), 2.81–2.58 (m, 4H), 1.30–1.19 ppm (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.6, 137.6, 128.4, 127.8, 127.6, 79.0, 74.8, 73.8, 71.5, 63.7, 51.7, 39.2, 27.5, 25.6, 25.4, 14.4 ppm; IR (thin film on NaCl): $\tilde{\nu} = 3559$, 2973, 1726, 1479, 1278, 1151 cm^{-1}; MALDI-HRMS: m/z: calcd for $C_{21}H_{34}O_5S_2Na$: 453.1740, found: 453.1748 $[M+Na]^+$.

2-*O*-Pivaloyl-3-*O*-benzyl-5-*O*-triphenylmethyl-D-xylose di(ethylthio)acetal (8): Triphenylmethyl chloride (16.7 g, 60 mmol) was added portionwise at 0°C to a solution of diol **7** (17.3 g, 40.2 mmol) in pyridine (200 mL). The mixture was stirred at room temperature for 24 h and the solvent was removed in vacuo. The residue was purified by flash chromatography (hexanes/ethyl acetate 20:1 → 6:1) to give **8** (24.3 g, 90%) as a pale yellow foam. R_f = 0.7 (hexanes/ethyl acetate 3:7); $[\alpha]_D^{RT} = -8.9$ ($c = 1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.11 (m, 20H), 5.70 (dd, $J = 7.0$, 4.0 Hz, 1H), 4.76 (d, $J = 11.1$ Hz, 1H), 4.51–4.42 (m, 2H), 4.27 (d, $J = 4.0$ Hz, 1H), 4.25–4.17 (m, 1H), 3.52 (dd, $J = 8.9$, 5.5 Hz, 1H), 3.22 (d, $J = 8.4$ Hz, 1H), 3.02–2.82 (m, 2H), 2.80–2.71 (m, 2H), 1.50–1.32 ppm (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.4, 146.9, 143.7, 128.6, 127.8, 127.2, 86.9, 82.1, 78.4, 75.1, 74.0, 70.5, 64.1, 39.2, 27.6, 26.0, 25.6, 14.8, 14.6 ppm; IR (thin film on NaCl): $\tilde{\nu} = 3007$, 1724, 1448, 1363, 1277, 1152, 1077, 632 cm^{-1}; MALDI-HRMS: m/z: calcd for $C_{40}H_{48}O_5S_2Na$: 695.2835, found: 695.2828 $[M+Na]^+$.

2-*O*-Pivaloyl-3-*O*-benzyl-4-*O*-levulinoyl-5-*O*-triphenylmethyl-D-xylose di(ethylthio)acetal (9): Levulinic acid (6.79 g, 58.5 mmol) was dissolved in CH_2Cl_2 (500 mL), followed by the addition of DMAP (7.15 g, 58.5 mmol). The mixture was cooled to 0°C and *N*,*N*′-diisopropyl carbodiimide (DIPC) (9.23 mL, 5.85 mmol) was added. After 10 min alcohol **8** (26.5 g, 39 mmol) in CH_2Cl_2 (40 mL) was added dropwise. The mixture was stirred at room temperature for 4 h. After dilution with CH_2Cl_2 (100 mL) the mixture was washed with sat. aq. NH_4Cl and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by silica gel chromatography (hexanes/ethyl acetate 4:1) to give **9** (2.96 g, quant.) as a white foam. R_f = 0.5 (hexanes/ethyl acetate 3:7); $[\alpha]_D^{RT} = -15.2$ ($c = 1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.10 (m, 20H), 5.35–5.28 (m, 1H), 5.23 (d, $J = 5.6$ Hz, 1H), 4.70 (d, $J = 11.5$ Hz, 1H), 4.57–4.49 (m, 2H), 4.06 (d, $J = 5.4$ Hz, 1H), 3.23 (m, 2H), 2.81–2.47 (m, 8H), 2.13 (s, 3H), 1.28 (t, $J = 7.4$ Hz, 3H), 1.22–1.12 ppm (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.8, 177.2, 172.1, 138.4, 128.1, 127.2, 127.0, 76.9, 75.0, 74.4, 72.4, 61.0, 52.0, 39.1, 37.8, 28.2, 27.5, 25.9, 25.1, 25.0, 18.2, 14.3 ppm; IR (thin film on NaCl): $\tilde{\nu} = 3007$, 1727, 1490, 1448, 1279, 1152, 1075, 1032, 899, 632 cm^{-1}; MALDI-HRMS: m/z: calcd for $C_{45}H_{54}O_7S_2Na$: 793.3203, found: 793.3194 $[M+Na]^+$.

2-*O*-Pivaloyl-3-*O*-benzyl-4-*O*-levulinoyl-D-xylose di(ethylthio)acetal (10): Compound **9** (3.5 g, 4.54 mmol) was dissolved in CH_2Cl_2 (200 mL) and cooled to 0°C. Triethylsilane (14.5 mL, 91 mmol) was added, followed by dropwise addition of trifluoroacetic acid (13.5 mL, 182 mmol). After 5 min the solution was adjusted to pH 5 by careful addition of sat. aq. $NaHCO_3$. The organic layer was separated, washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by silica gel chromatography (hexanes/ethyl acetate 3:1 → 2:3) to give **10** (2.16 g, 90%) as a colorless oil. R_f = 0.6 (hexanes/ethyl acetate 2:3); $[\alpha]_D^{RT} = -20.3$ ($c = 1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.20 (m, 5H), 5.33 (d, $J = 5.5$ Hz, 1H), 5.10 (t, $J = 4.7$, 4.4 Hz, 1H), 4.77 (d, $J = 11.7$ Hz, 1H), 4.67 (d, $J = 11.7$ Hz, 1H), 4.34 (d, $J = 5.3$ Hz, 1H), 4.04 (d, $J = 5.8$ Hz, 1H), 3.72–3.67 (m, 2H), 2.82–2.35 (m, 8H), 2.13 (s, 3H), 1.28–1.15 ppm (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.9, 177.4, 172.4, 138.0, 128.2, 127.5, 127.2, 77.0, 74.7, 74.6, 72.5, 61.4, 52.0, 39.1, 38.1, 29.9, 29.8, 28.3, 27.4, 25.1, 25.0, 14.5, 14.4 ppm; IR (thin film on NaCl): $\tilde{\nu} = 2973$, 1722, 1479, 1367, 1152, 1152, 1048 cm^{-1}; MALDI-

HRMS: *m/z*: calcd for $C_{26}H_{40}O_7S_2Na$: 551.2108, found: 551.2104 $[M+Na]^+$.

Ethyl 2-*O*-pivaloyl-3-*O*-benzyl-4-*O*-levulinoyl-α/β-D-xylopyranoside (11): A solution of alcohol **10** (110 mg, 208 μmol) in CH_2Cl_2 (4.2 mL) was treated with TFA (15.5 μL, 208 μmol) and NIS (51.5 mg, 229 μmol), stirred for 5 min at room temperature and cooled to 0 °C. The reaction was quenched by dropwise additon of saturated aqueous sodium thiosulfate solution (4.2 mL) and stirred for further 5 min at 0 °C. Saturated aqueous $NaHCO_3$ (0.8 mL) was added and the mixture was allowed to warm to room temperature. After diluting with CH_2Cl_2, the phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography (hexanes/ethyl acetate 1:1) to afford **11** (90 mg, 92 %, as a pale yellow oil) as 1:1 α/β mixture.

β Anomer (11a): R_f = 0.5 (hexanes/ethyl acetate 2:3); $[\alpha]_D^{RT}=-9.7$ ($c=1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.23 (m, 5H), 5.05 (d, $J=7.2$ Hz, 1H), 4.93 (dd, $J=7.6$, 4.5 Hz, 1H), 4.71 (d, $J=11.6$ Hz, 1H), 4.64 (d, $J=11.7$ Hz, 1H), 4.60 (d, $J=7.3$ Hz, 1H), 4.28 (dd, $J=11.8$, 4.5 Hz, 1H), 3.70 (d, $J=7.2$ Hz, 1H), 3.36 (dd, $J=11.9$, 7.7 Hz, 1H), 2.77–2.37 (m, 6H), 2.17 (s, 3H), 1.30–1.19 ppm (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.0, 176.6, 171.7, 137.8, 128.3, 128.2, 127.6, 127.4, 127.3, 83.5, 78.5, 73.6, 70.2, 70.1, 64.2, 38.8, 37.8, 29.9, 29.8, 29.7, 27.8, 27.1, 24.5, 14.9 ppm; IR (thin film on NaCl): $\tilde{\nu}$=2970, 2930, 1721, 1456, 1429, 1363, 1265, 1153, 1070 cm^{-1}; MALDI-HRMS: *m/z*: calcd for $C_{19}H_{28}O_5SNa$: 489.1918, found: 489.1916 $[M+Na]^+$.

α Anomer (11b): R_f = 0.7 (hexanes/ethyl acetate 2:3); $[\alpha]_D^{RT}=23.1$ ($c=1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.23 (m, 5H), 5.44 (d, $J=4.7$ Hz, 1H), 4.98–4.84 (m, 2H), 4.76 (d, $J=11.5$ Hz, 1H), 4.66 (d, $J=11.6$ Hz, 1H), 4.01–3.77 (m, 3H), 2.76–2.36 (m, 6H), 2.17 (s, 3H), 1.32–1.18 ppm (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.9, 177.2, 171.7, 137.8, 128.3, 128.2, 127.6, 127.4, 127.3, 83.5, 81.8, 74.4, 73.6, 72.1, 70.4, 60.7, 38.8, 37.8, 29.9, 29.8, 29.7, 27.9, 27.2, 24.5, 14.9 ppm; IR (thin film on NaCl): $\tilde{\nu}$=2929, 1721, 1602, 1456, 1429, 1363, 1280, 1153, 1028, 909 cm^{-1}; MALDI-HRMS: *m/z*: calcd for $C_{19}H_{28}O_5SNa$: 489.1918, found: 489.1916 $[M+Na]^+$.

2-*O*-Benzyl-3-*O*-pivaloyl-L-*threo*-dialdose di(ethylthio)acetal (12a): $NaIO_4$ (39 mg, 0.18 mmol) in H_2O (0.5 mL) was added to a solution of diol (71 mg, 0.16 mmol) in THF (2 mL) at room temperature. After stirring for 2 h, the mixture was diluted with hexanes (20 mL) and washed with sat. aq. $NaHCO_3$ and brine. The phases were separated and the organic layer was dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by silica gel chromatography (hexanes/ethyl acetate 9:1) to give **12a** as pale yellow oil (52 mg, 82 %). R_f = 0.8 (hexanes/ethyl acetate 7:3); $[\alpha]_D^{RT}=-4.3$ ($c=1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.70 (d, $J=0.8$ Hz, 1H), 7.41–7.29 (m, 5H), 5.39 (dd, $J=6.5$, 4.2 Hz, 1H), 4.79 (d, $J=11.5$ Hz, 1H), 4.65 (d, $J=11.5$ Hz, 1H), 4.33 (dd, $J=4.2$, 0.8 Hz, 1H), 4.19 (d, $J=6.5$ Hz, 1H), 2.75–2.53 (m, 4H), 1.29–1.18 ppm (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.6, 177.2, 137.0, 128.4, 128.0, 127.9, 82.1, 73.7, 73.6, 51.1, 38.9, 27.1, 25.0, 24.9, 14.2, 14.0 ppm; IR (thin film on NaCl): $\tilde{\nu}$=2975, 2931, 2873, 1732, 1479, 1455, 1398, 1369, 1278, 1145, 1051 cm^{-1}; MALDI-HRMS: *m/z*: calcd for $C_{16}H_{26}O_4S_2H$: 399.1658, found: 399.1658 $[M+H]^+$.

Methyl 2-*O*-pivaloyl-3-*O*-benzyl-5-*O*-*tert*-butyldimethylsilyl-D-glucuronate di(ethylthio)acetal (13): Ketene acetal **G** (62 mg, 0.23 mmol) was dissolved in toluene (1.2 mL) and $MgBr_2{\cdot}OEt_2$ (116 mg, 0.45 mmol) was added. The solution was stirred for 15 min at room temperature and cooled to −78 °C. Aldehyde **12a** (60 mg, 0.15 mmol) in CH_2Cl_2 (1.2 mL) was added dropwise and stirred for 4 h at −78 °C. The solution was warmed to room temperature and stirred for another 2 h. The mixture was diluted with CH_2Cl_2 (20 mL), washed with sat. aq. $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by silica gel chromatography (hexanes/ethyl acetate 9:1) and gave aldol product **13** (77 mg, 85 %) as colorless oil. R_f = 0.5 (hexanes/ethyl acetate 4:1); $[\alpha]_D^{RT}=-28.3$ ($c=1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (m, 5H), 5.49 (dd, $J=6.1$, 4.8 Hz, 1H), 4.79 (d, $J=11.4$ Hz, 1H), 4.72 (d, $J=11.4$ Hz, 1H), 4.28 (d, $J=7.0$ Hz, 1H), 4.22 (dd, $J=6.2$, 2.2 Hz, 1H), 4.06 (d, $J=4.8$ Hz, 1H), 3.89 (ddd, $J=9.1$, 7.0, 2.1 Hz, 1H), 3.75 (s, 3H), 2.88–2.53 (m, 4H), 1.28–1.20 (m, 15H), 0.96–0.87 (m, 9H), 0.07–0.05 ppm (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.4, 172.1, 137.9, 128.2, 127.4, 126.8, 74.6, 73.7, 73.4, 73.1, 52.0, 51.9, 51.9, 51.8, 39.1, 27.4, 25.7, 25.8, 25.6, 25.2, 18.2, 14.3, −4.8, −5.1 ppm; IR (thin film on NaCl): $\tilde{\nu}$=3556, 3008, 2956, 2951, 2859, 1729, 1602, 1455, 1397, 1363, 1260, 1150, 840 cm^{-1}; MALDI-HRMS m/z calcd for $C_{29}H_{50}O_7S_2SiNa$: 625.2659, found: 625.2649 $[M+Na]^+$.

Methyl 2-*O*-pivaloyl-3-*O*-benzyl-4-*O*-levulinoyl-5-*O*-*tert*-butyldimethylsilyl-D-glucuronate di(ethylthio)acetal (14): LevOH (13 mg, 0.11 mmol) was dissolved in CH_2Cl_2 (0.4 mL) and DMAP (13 mg, 0.11 mmol) was added and stirred for 15 min. The reaction was cooled to 0 °C, DIPC (14 mg, 0.11 mmol) and alcohol **13** (43 mg, 0.07 mmol) in CH_2Cl_2 (1 mL) were added and stirred for 20 h at room temperature. The solution was diluted with CH_2Cl_2 (20 mL), washed with sat. NH_4Cl and brine, and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel chromatography (CH_2Cl_2) to give **14** (52 mg, quant.) as a pale yellow oil (52 mg, quant.). R_f = 0.3 (hexanes/ethyl acetate 4:1); $[\alpha]_D^{RT}=-10.4$ ($c=1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.20 (m, 5H), 5.36 (dd, $J=6.1$, 4.8 Hz, 1H), 5.21 (dd, $J=6.1$, 4.8 Hz, 1H), 4.79 (d, $J=11.9$ Hz, 1H), 4.70 (d, $J=11.9$ Hz, 1H), 4.55 (dd, $J=5.9$, 4.8 Hz, 1H), 4.48 (d, $J=4.8$ Hz, 1H), 4.14 (d, $J=6.2$ Hz, 1H), 3.73 (s, 3H), 2.81–2.34 (m, 8H), 2.12 (s, 3H), 1.34–1.15 (m, 15H), 0.97–0.79 (m, 9H), 0.07 (s, 3H), 0.06 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.9, 177.2, 171.5, 170.7, 138.4, 128.1, 127.1, 126.4, 77.4, 77.0, 76.6, 76.2, 74.6, 74.4, 72.2, 71.6, 52.2, 52.0, 39.1, 37.9, 29.8, 28.0, 27.4, 25.7, 25.0, 24.8, 23.6, 18.2, 14.3, −4.8, −5.2 ppm; IR (thin film on NaCl): $\tilde{\nu}$=3011, 2972, 2030, 1720, 1523, 1456, 1363, 1157, 1081, 929, 840 cm^{-1}; MALDI-HRMS: *m/z*: calcd for $C_{34}H_{56}O_9S_2SiNa$: 723.3027, found: 723.3034 $[M+Na]^+$.

Methyl 2-*O*-pivaloyl-3-*O*-benzyl-4-*O*-levulinoyl-D-glucuronate di(ethylthio)acetal (15): Silyl ether **14** (217 mg, 0.31 mmol) was dissolved in THF (3 mL) and HF·pyridine complex (55 μL, 0.62 mmol) was added dropwise. The solution was stirred for 12 h at room temperature, cooled to 0 °C and quenched with sat. aq. $NaHCO_3$. The mixture was diluted with ethyl acetate (20 mL), washed with sat. aq. $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by silica gel chromatography (hexanes/ethyl acetate 1:1) to give alcohol **15** (181 mg, quant.) as colorless oil. R_f = 0.8 (ethyl acetate); $[\alpha]_D^{RT}=-11.3$ ($c=1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5H), 5.44 (dd, $J=6.2$, 5.0 Hz, 1H), 5.27 (dd, $J=5.9$, 4.8 Hz, 1H), 4.77 (d, $J=11.4$ Hz, 1H), 4.71 (d, $J=11.4$ Hz, 1H), 4.44 (dd, $J=6.2$, 4.8 Hz, 1H), 4.36 (dd, $J=7.5$, 5.9 Hz, 1H), 3.98 (d, $J=5.0$ Hz, 1H), 3.76 (s, 3H), 3.25 (d, $J=7.5$ Hz, 1H), 2.83–2.43 (m, 8H), 2.17 (s, 3H), 1.32–1.17 ppm (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.5, 177.7, 172.8, 172.5, 138.1, 128.5, 127.7, 127.4, 77.1, 73.6, 75.3, 72.9, 69.5, 51.8, 39.3, 37.8, 29.9, 28.1, 27.5, 25.5, 25.2, 14.4 ppm; IR (thin film on NaCl): $\tilde{\nu}$=3690, 2929, 1733, 1602, 1456, 1374, 1277, 1151 cm^{-1}; MALDI-HRMS: *m/z*: calcd for $C_{28}H_{42}O_9S_2Na$: 609.2163, found: 609.2169 $[M+Na]^+$.

Methyl (ethyl 2-*O*-pivaloyl-3-*O*-benzyl-4-*O*-levulinoyl-1-thio-α/β-D-glucopyranosid)uronate (16): A solution of alcohol **15** (63 mg, 107 μmol) in CH_2Cl_2 (1 mL) was treated with TFA (8 μL, 107 μmol) and NIS (27 mg, 118 μmol), stirred for 5 min at room temperature and cooled to 0 °C. The reaction was quenched by dropwise additon of sat. aq. sodium thiosulfate solution (4.2 mL) and stirred for further 5 min at 0 °C. Sat. aq. $NaHCO_3$ was added to adjust pH 5 and the mixture was allowed to warm to room temperature. After diluting with CH_2Cl_2, the phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography (hexanes/ethyl acetate 4:1) to afford **15** (49 mg, 88 %, as a pale yellow oil) as 1:1 α/β mixture.

β Anomer (16a): R_f = 0.6 (hexanes/ethyl acetate 1:1); $[\alpha]_D^{RT}=25.4$ ($c=0.5$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.20 (m, 5H), 5.27–5.11 (m, 2H), 4.67 (d, $J=11.4$ Hz, 1H), 4.62 (d, $J=11.5$ Hz, 1H), 4.46 (d, $J=10.0$ Hz, 1H), 3.97 (d, $J=9.9$ Hz, 1H), 3.81 (d, $J=9.2$ Hz, 1H), 3.73 (s, 3H), 2.84–2.30 (m, 6H), 2.15 (s, 3H), 1.32–1.16 ppm (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.8, 176.4, 171.1, 167.3, 137.6, 128.2, 127.6, 127.3, 83.6, 81.0, 77.1, 74.0, 71.0, 70.2, 52.7, 38.6, 37.6, 29.6, 27.5, 27.0, 23.6, 14.6 ppm; IR (thin film on NaCl): $\tilde{\nu}$=3662, 3036, 2923, 1744, 1600, 1456, 1364, 1282, 1149, 1092 cm^{-1}; MALDI-HRMS: *m/z*: calcd for $C_{26}H_{36}O_9SNa$: 524.2080, found: 524.2072 $[M+Na]^+$.

α Anomer (16b): R_f = 0.7 (hexanes/ethyl acetate 1:1); $[\alpha]_D^{RT} = -1.4$ (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29 (m, 5H), 5.75 (d, J = 4.8 Hz, 1H), 5.21 (d, J = 7.7 Hz, 1H), 4.99 (dd, J = 8.1, 4.8 Hz, 1H), 4.74 (d, J = 11.4 Hz, 1H), 4.68 (d, J = 7.9 Hz, 1H), 4.64 (d, J = 11.5 Hz, 1H), 3.88 (d, J = 7.8 Hz, 1H), 3.69 (s, 3H), 2.72–2.36 (m, 6H), 2.17 (s, 3H), 1.32–1.22 ppm (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.9, 177.2, 171.5, 168.4, 137.5, 128.3, 127.7, 127.4, 80.6, 77.1, 71.4, 70.0, 52.6, 38.6, 37.5, 29.8, 29.6, 27.6, 27.0, 24.5, 14.8 ppm; IR (thin film on NaCl): $\tilde{\nu}$ = 3670, 2922, 1730, 1656, 1433, 1364, 1280, 1158 cm^{-1}; MALDI-HRMS: m/z: calcd for $C_{26}H_{36}O_9SNa$: 524.2080, found: 524.2072 $[M+Na]^+$.

2-*O*-Levulinoyl-3-*O*-benzyl-4-*O*-pivaloyl-D-*xylo*-dialdose di(ethylthio)acetal (17): SO_3·Py complex (1.12 g, 7.0 mmol) was added to a solution of alcohol **10** (930 mg, 1.76 mmol) in CH_2Cl_2 (18 mL) at 0 °C, followed by the addition of DIPEA (2.1 mL, 12.3 mmol). The mixture was stirred for 5 min and dimethyl sulfoxide (1.7 mL, 24.6 mmol) was added dropwise. After stirring at 0 °C for 15 min, the solution was diluted with CH_2Cl_2 (100 mL) and brine (25 mL) was added. The phases were separated and the organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash chromatography (hexanes/ethyl acetate 5:1) to give **17** (871 mg, 94%) as a yellow oil. R_f = 0.4 (hexanes/ethyl acetate 7:3); $[\alpha]_D^{RT} = 3.7$ (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.52 (s, 1H), 7.38–7.24 (m, 5H), 5.41 (d, J = 5.5 Hz, 1H), 5.28 (d, J = 4.6 Hz, 1H), 4.75 (d, J = 11.3 Hz, 1H), 4.66 (d, J = 11.1 Hz, 1H), 4.61–4.57 (m, 1H), 4.00 (d, J = 5.7 Hz, 1H), 2.91–2.54 (m, 8H), 2.18 (s, 3H), 1.29–1.17 ppm (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.9, 195.9, 176.8, 171.7, 137.1, 128.3, 127.9, 127.6, 77.4, 76.3, 74.6, 72.0, 51.6, 39.1, 37.9, 29.8, 27.8, 27.4, 25.4, 25.2, 14.4, 14.3 ppm; IR (thin film on NaCl): $\tilde{\nu}$ = 3008, 1736, 1455, 1366, 1275, 1147 cm^{-1}; MALDI-HRMS: m/z: calcd for $C_{26}H_{38}O_7S_2Na$: 549.1951, found: 549.1946 $[M+Na]^+$.

4-*O*-Benzyl-5-*O*-pivaloyl-6,6-di(ethylthio)-L-idonitrile (18a) and 4-*O*-benzyl-5-*O*-pivaloyl-6,6-di(ethylthio)-D-gluconitrile (18b): Aldehyde **17** (1.49 g, 2.84 mmol) was dissolved in CH_2Cl_2 (28 mL) and cooled to 0 °C. $MgBr_2$·OEt_2 (2.93 g, 11.36 mmol) was added and the mixtute was stirred vigorously for 5 min. Then trimethylsilyl cyanide (416 μL, 3.12 mmol) was added dropwise over 10 min. The mixture was warmed to room temperature overnight before it was quenched with brine. The solution was diluted with CH_2Cl_2 (100 mL), washed with brine and dried over $MgSO_4$. After concentration, the residue was filtered through silica gel (hexanes/ethyl acetate 2:1) and concentrated again. The resulting yellow oil was dissolved in CH_2Cl_2 (28 mL). Hydrazine acetate (314 mg, 3.41 mmol) in MeOH (28 mL) was added dropwise and the mixture was stirred for 12 h at room temperature. The solvent was removed in vacuo and two nitriles were separated by silica gel chromatography (hexanes/ethyl acetate 10:1 → 5:1) to give **18a** (943 mg, 73%) as a yellow solid and **18b** (117 mg, 9%) as a yellow oil.

Nitrile (18a): R_f = 0.7 (hexanes/ethyl acetate 1:1); $[\alpha]_D^{RT} = -35.2$ (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.27 (m, 5H), 5.46 (dd, J = 5.9, 4.4 Hz, 1H), 4.81 (d, J = 11.3 Hz, 1H), 4.66 (d, J = 11.4 Hz, 1H), 4.50 (d, J = 5.7 Hz, 1H), 4.18 (dd, J = 5.9, 3.8 Hz, 1H), 4.06 (d, J = 4.4 Hz, 1H), 3.96 (dd, J = 5.7, 3.7 Hz, 1H), 2.84–2.55 (m, 4H), 1.33–1.17 ppm (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.1, 136.9, 128.6, 128.1, 127.8, 117.9, 77.2, 75.0, 73.8, 72.1, 62.3, 51.2, 39.1, 27.2, 25.4, 25.3, 14.2, 14.0 ppm; IR (thin film on NaCl): $\tilde{\nu}$ = 3553, 2977, 1729, 1479, 1397, 1264, 1148 cm^{-1}; MALDI-HRMS: m/z: calcd for $C_{22}H_{33}NO_5S_2Na$: 478.1692, found: 478.1682 $[M+Na]^+$.

Nitrile (18b): R_f = 0.8 (hexanes/ethyl acetate 1:1); $[\alpha]_D^{RT} = 17.1$ (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.26 (m, 5H), 5.50 (dd, J = 6.5, 4.1 Hz, 1H), 4.81 (d, J = 11.2 Hz, 1H), 4.66 (d, J = 11.3 Hz, 1H), 4.37 (d, J = 7.3 Hz, 1H), 4.22 (dd, J = 6.5, 2.6 Hz, 1H), 4.06 (d, J = 4.1 Hz, 1H), 3.97 (dd, J = 7.3, 2.7 Hz, 1H), 2.88–2.53 (m, 4H), 1.36–1.12 ppm (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.0, 137.1, 128.6, 128.2, 127.9, 118.9, 74.9, 74.0, 71.4, 62.9, 51.2, 39.1, 27.2, 25.6, 25.4, 14.2, 14.1 ppm; IR (thin film on NaCl): $\tilde{\nu}$ = 3555, 2975, 1728, 1479, 1397, 1277, 1148, 1072 cm^{-1}; MALDI-HRMS: m/z: calcd for $C_{22}H_{33}NO_5S_2Na$: 478.1692, found: 478.1684 $[M+Na]^+$.

Methyl 2-*O*-pivaloyl-3-*O*-benzyl-L-iduronate di(ethylthio)acetal (19): MeOH (1.16 mL) was added at 0 °C to a mixture of nitrile **18** (230 mg, 0.51 mmol) in toluene (5 mL) and silica gel (1.16 g), followed by dropwise addition of acetyl chloride (0.41 mL). The mixture was warmed to room temperature, stirred for 20 h and cooled again to 0 °C. Water (5 mL) was added dropwise at 0 °C, and the mixture was warmed to room temperature overnight. The reaction was quenched by addition of sat. aq. $NaHCO_3$, the phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash chromatography (cyclohexane/ethyl acetate 1:1) to give **19** (173 mg, 70%) as a colorless oil. R_f = 0.7 (hexanes/ethyl acetate 1:1); $[\alpha]_D^{RT} = -29.7$ (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.27 (m, 5H), 5.43 (dd, J = 5.7, 4.9 Hz, 1H), 4.84 (d, J = 11.3 Hz, 1H), 4.71 (d, J = 11.2 Hz, 1H), 4.30 (dd, J = 5.3, 2.8 Hz, 1H), 4.25 (d, J = 5.1 Hz, 1H), 4.14 (d, J = 6.1 Hz, 1H), 4.07 (ddd, J = 8.1, 5.6, 2.8 Hz, 1H), 3.66 (s, 3H), 3.10 (d, J = 5.4 Hz, 1H), 2.80–2.57 (m, 4H), 1.59 (br s, 1H), 1.31–1.20 ppm (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.5, 173.1, 137.8, 128.3, 127.6, 127.5, 78.6, 74.8, 73.1, 72.4, 70.7, 52.8, 51.8, 39.2, 27.4, 25.0, 14.4, 14.3 ppm; IR (thin film on NaCl): $\tilde{\nu}$ = 3544, 2972, 1731, 1429, 1367, 1277, 1148 cm^{-1}; MALDI-HRMS: m/z: calcd for $C_{23}H_{36}O_7S_2Na$: 511.1795, found: 511.1787 $[M+Na]^+$.

Methyl (ethyl 2-*O*-pivaloyl-3-*O*-benzyl-1-thio-β-L-idofuranosyl)uronate (20): A solution of diol **19** (136 mg, 278 μmol) in CH_2Cl_2 (5.6 mL) at room temperature was treated with NIS (75 mg, 334 μmol) and stirred for 15 min at room temperature. The reaction was quenched by the addition of sat. aq. sodium thiosulfate solution (10 mL), stirred for 10 min at room temperature, then diluted with CH_2Cl_2. The organic layer was separated, washed with brine and dried over $MgSO_4$. After concentration, the residue was purified by flash chromatography (cyclohexane/ethyl acetate 17:3 → 4:1) to afford **20** (96 mg, 81%) as a pale yellow oil. R_f = 0.5 (cyclohexanes/ethyl acetate 3:2); $[\alpha]_D^{RT} = 113.3$ (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 5H), 5.71 (d, J = 5.6 Hz, 1H), 5.37 (t, J = 5.3 Hz, 1H), 4.77 (d, J = 12.1 Hz, 1H), 4.59 (d, J = 11.8 Hz, 1H), 4.56 (dd, J = 6.8, 2.5 Hz, 1H), 4.84 (m, 1H), 4.36 (dd, J = 6.7, 4.8 Hz, 1H), 3.76 (s, 3H), 3.21 (d, J = 3.7, 1H), 2.62 (q, J = 7.4 Hz, 2H), 1.27–1.21 (m, 3H), 1.24 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.2, 172.2, 136.9, 128.5, 128.1, 127.7, 86.1, 81.4, 78.0, 77.8, 72.8, 70.1, 52.7, 38.8, 27.2, 25.3, 15.2 ppm; IR (thin film on NaCl): $\tilde{\nu}$ = 3537, 2978, 2933, 1736, 1479, 1456, 1398, 1367, 1144, 1041 cm^{-1}; MALDI-HRMS: m/z: calcd for $C_{21}H_{30}O_7SNa$: 449.1604, found: 449.1602 $[M+Na]^+$.

Methyl (ethyl 2-*O*-pivaloyl-3-*O*-benzyl-5-*O*-levulinoyl-1-thio-β-L-idofuranosyl)uronate (21): Furanose **20** (96 mg, 225 μmol) in CH_2Cl_2 (2 mL) was added dropwise to a solution of levulinic acid (30 μL, 293 μmol), DMAP (36 mg, 293 μmol) and DIPC (42 μL, 270 μmol) in CH_2Cl_2 (2.5 mL) at 0 °C. The mixture was stirred for 4 h at room temperature, diluted with CH_2Cl_2 (50 mL), washed with sat. aq. NH_4Cl, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (cyclohexane/ethyl acetate 3:2) to afford **21** (104 mg, 88%) as a pale yellow oil. R_f = 0.4 (cyclohexane/ethyl acetate 3:2); $[\alpha]_D^{RT} = 58.6$ (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.21 (m, 5H), 5.67 (d, J = 5.5 Hz, 1H), 5.48 (d, J = 4.4 Hz, 1H), 5.29 (t, J = 5.1 Hz, 1H), 4.71 (dd, J = 6.0, 3.6 Hz, 1H), 4.67 (d, J = 11.6 Hz, 1H), 4.50 (d, J = 11.7 Hz, 1H), 4.33 (dd, J = 6.7, 4.6 Hz, 1H), 3.69 (s, 3H), 2.75–2.56 (m, 6H), 2.14 (s, 3H), 1.29–1.20 ppm (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.7, 177.2, 171.3, 168.2, 136.9, 128.3, 127.8, 127.6, 85.7, 80.9, 76.6, 76.6, 72.8, 70.4, 52.6, 38.8, 37.9, 29.8, 28.0, 27.1, 25.4, 15.2 ppm; IR (thin film on NaCl): $\tilde{\nu}$ = 3008, 2978, 2932, 1740, 1478, 1436, 1364, 1281, 1152, 1044 cm^{-1}; MALDI-HRMS: m/z: calcd for $C_{26}H_{36}O_9SNa$: 547.1972, found: 547.1977 $[M+Na]^+$.

Methyl (ethyl 2-*O*-pivaloyl-3-*O*-benzyl-4-*O*-levulinoyl-1-thio-α/β-L-idopyranosyl)uronate (22): Levulinic acid (36 mg, 0.31 mmol) was dissolved in CH_2Cl_2 (3 mL), followed by the addition of DMAP (38 mg, 0.31 mmol). The mixture was cooled to 0 °C and DIPC (49 μL, 0.31 mmol) was added. After 10 min, diol **19** (133 mg, 0.26 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The mixture was stirred at 0 °C for 2.5 h, then diluted with CH_2Cl_2 (50 mL), washed with sat. aq. NH_4Cl and dried over $MgSO_4$. The solvent was removed in vacuo and the crude product was coevaporated with toluene and again dissolved in CH_2Cl_2 (3 mL). NIS (65 mg, 0.29 mmol) was added and stirred for 15 min. Then

sat. aq. sodium thiosulfate (3 mL) was added and the mixture stirred for 10 min. The mixture was diluted with CH_2Cl_2 (100 mL) and the phases were separated. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by silica gel chromatography (hexanes/ethyl acetate 20:1 → 8:1) to give **21** as 1:1 α/β mixture (114 mg, 80%, colorless oil). R_f = 0.3 (hexanes/ethyl acetate 3:2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.25 (m, 10H), 5.40 (s, 1H), 5.27 (d, J=2.3 Hz, 1H), 5.24–5.19 (m, 2H), 5.01 (d, J= 2.0 Hz, 1H), 5.00–4.97 (m, 1H), 4.97–4.94 (m, 1H), 4.81–4.75 (m, 2H), 4.72–4.65 (m, 2H), 4.55 (d, J=1.8 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.73–3.71 (m, 2H), 2.84–2.47 (m, 16H), 2.18 (s, 3H), 2.17 (s, 3H), 1.34–1.19 ppm (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.8, 177.6, 177.2, 171.8, 171.6, 168.9, 167.8, 137.1, 136.9, 128.4, 128.3, 128.0, 127.7, 127.6, 127.4, 82.7, 82.1, 74.3, 73.5, 72.9, 72.7, 72.5, 68.3, 68.0, 66.9, 66.4, 52.3, 52.2, 38.6, 37.6, 29.6, 27.8, 27.7, 27.1, 27.0, 26.9, 26.5, 25.8, 14.8 ppm; IR (thin film on NaCl): $\tilde{\nu}$=3586, 3032, 1740, 1602, 1364, 1150, 1071 cm^{-1}; MALDI-HRMS: m/z: calcd for $C_{26}H_{36}O_9SNa$: 547.1972, found: 547.1965 $[M+Na]^+$.

Methyl 2-*O*-pivaloyl-3-*O*-benzyl-4-*O*-levulinoyl-α/β-L-idopyranosyluronate trichloroacetimidate (23): Levulinic acid (124 mg, 1.07 mmol) was dissolved in CH_2Cl_2 (10 mL), followed by the addition of DMAP (132 mg, 1.07 mmol). The mixture was cooled to 0°C and DIPC (169 μL, 1.07 mmol) was added. After 10 min diol **19** (474 mg, 0.97 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The mixture was stirred at 0°C for 2.5 h, then diluted with CH_2Cl_2 (100 mL), washed with sat. aq. NH_4Cl and dried over $MgSO_4$. The solvent was removed in vacuo and the crude product was dissolved in CH_3CN (20 mL). Water was added (5 mL), followed by addition of bis(trifluoroacetoxy)iodobenzene (1.43 g, 3.3 mmol). After 5 min, $NaHCO_3$ was added (700 mg) and stirred for another 30 min at room temperature. The solvent was removed and water was added (30 mL), followed by dropwise addition of TFA (30 mL). The mixture was stirred for 30 min at 50°C and the solvent was removed again. The resulting colorless oil was coevaporated with toluene, dissolved in CH_2Cl_2/trichloroacetonitrile 2:1 (18 mL) and cooled to 0°C. DBU (14 μL) was added, and the reaction was allowed to warm to room temperature over 30 min. The solvent was removed in vacuo, and the residue was purified by silica gel chromatography (hexanes/ethyl acetate 2:1) to give **23** as α/β mixture (461 mg, 77%) as a colorless oil. The analytical data were in agreement with those reported in the literature.[33]

***N*-(Benzyl)-benzyloxycarbonyl-5-aminopentyl (methyl 2-*O*-pivaloyl-3-*O*-benzyl-α-L-idopyranosyluronate (25)**: Trichloroacetimidate **23** (280 mg, 0.45 mmol) and *N*-(benzyl)-benzyloxycarbonyl-5-aminopentan-1-ol (730 mg, 2.2 mmol) coevaporated five times with toluene and dried under high vacuum. The starting materials were dissolved in CH_2Cl_2 and cooled to −20°C, then TMSOTf (16 μL, 0.09 mmol) was added and the reaction was allowed to warm to −10°C over 30 min. Quenching with triethylamine at −25°C and removal of the solvent followed by purification by column chromatography (hexanes/ethyl acetate 9:1) yielded the product **24** (266 mg, 76% as 95:5 α/β mixture) as a colorless oil. *N*-Benzyloxycarbonyl-5-aminopentyl (methyl 2-*O*-pivaloyl-3-*O*-benzyl-4-*O*-levulinoyl-α-L-idopyranosyluronate **24** (160 mg, 0.2 mmol) was dissolved in CH_2Cl_2 (1.5 mL). Pyridine (0.49 mL) and acetic acid (0.32 mL) were added, followed by the addition of hydrazine monohydrate (20 μL, 0.41 mmol). The reaction mixture was stirred for 90 min at room temperature, quenched with acetone and evaporated to dryness. Glycoside **25** (135 mg, 96%) was isolated after purification by column chromatography (hexanes/ethyl acetate 4:1) as a colorless oil. The analytical data of the α anomer were in agreement with those reported in the literature.[35b] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.15 (m, 15H), 5.16 (d, J=4.8 Hz, 2H), 4.96 (s, 1H), 4.89 (s, 1H), 4.82 (s, 1H), 4.78 (dd, J=11.7, 57.6 Hz, 1H), 4.59 (dd, J=11.7, 57.6 Hz, 1H), 4.45 (brs, 2H), 4.05–4.01 (m, 1H), 3.79–3.65 (m, 5H), 3.43–3.38 (m, 1H), 3.21–3.13 (m, 2H), 2.67 (d, J= 12.1 Hz, 1H), 1.63–1.19 ppm (m, 15H).

***N*-(Benzyl)-benzyloxycarbonyl-5-aminopentyl (6-*O*-acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-methyl (3-*O*-benzyl-2-*O*-pivaloyl-α-L-idopyranosid)uronate (27)**: TMSOTf (1M solution in CH_2Cl_2, 40 μL) was added at −25°C, to a solution of acceptor **25** (135 mg, 0.24 mmol) and imidate **26** (82 mg, 0.12 mmol) in CH_2Cl_2 (2.6 mL). After 30 min, the reaction mixture was quenched with triethylamine, concentrated and the residue was purified by column chromatography (hexanes/ethyl acetate 9:1) to yield disaccharide **27** (106 mg, 81%) as a colorless oil. $[\alpha]_D^{RT}$=10.2 (c=1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.25 (m, 25H), 5.20–5.17 (brd, 2H), 5.07–5.05 (m, 2H), 4.98–4.97 (t, J= 4.4 Hz, 2H), 4.88–4.72 (m, 6H), 4.62–6.60 (d, J=11.1 Hz, 1H), 4.51–4.49 (brd, 2H), 4.37–4.34 (dd, J=2.2, 10.1 Hz, 1H), 4.22–4.19 (dd, J=4.1, 12.2 Hz, 1H), 4.16–4.13 (m, 1H), 3.99–3.96 (m, 2H), 3.92–3.88 (dd, J= 8.8, 10.2 Hz, 1H), 3.80 (s, 3H), 3.75–3.70 (brm, 1H), 3.56–3.53 (dd, J= 8.9, 9.9 Hz, 1H), 3.51–3.41 (brm, 1H), 3.31–3.29 (dd, J=3.6, 10.2 Hz, 1H), 3.29–3.16 (brm, 2H), 2.03 (s, 3H), 1.61–1.31 (m, 6H), 1.24 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$); mixture of rotamers: δ = 177.6, 170.7, 170.0, 156.6/156.3, 138.2, 137.9, 137.8, 137.7, 137.1/137.0, 128.8–127.4, 99.1, 98.5, 80.2, 77.9, 76.0, 75.6, 75.3, 75.0, 74.2, 73.2, 70.2, 70.1, 69.8. 69.2/69.1, 67.4, 63.6, 62.7, 52.5, 50.7/50.4, 47.3/46.4, 39.0, 28.2/27.7, 27.4, 23.5, 21.1 ppm; IR (thin film on NaCl): $\tilde{\nu}$=3007, 2937, 2871, 2109, 1733, 1687, 1492, 1451, 1364, 1143 cm^{-1}; MALDI-HRMS: m/z: calcd for $C_{61}H_{72}O_{15}N_4Na$: 1123.489, found: 1123.486 $[M+Na]^+$.

***N*-(Benzyl)-benzyloxycarbonyl-5-aminopentyl (2-azido-3,4-di-*O*-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-3-*O*-benzyl-α-L-idopyranosyluronic acid (28)**: H_2O_2 (30%, 0.9 mL) and 1N solution of LiOH (1.5 mL) were added at 0°C to a solution of disaccharide **27** (85 mg, 77 μmol) in THF (2.6 mL). After stirring for 16 h at room temperature, the mixture was cooled to 0°C and MeOH (4.5 mL) and 3M aq. solution of KOH (2.7 mL) were added. After stirring for additional 16 h at room temperature, the reaction mixture was neutralized with IR-120-H$^+$ amberlite resin, filtered and concentrated. The residue was purified by Sephadex LH-20 chromatography (MeOH/CH_2Cl_2 1:1) to afford **28** (63 mg, 85%) as a colorless oil. $[\alpha]_D^{RT}$=−13.2 (c=1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.25 (m, 25H), 5.17 (brs, 2H), 5.02 (s, 1H), 4.92–4.78 (m, 5H), 4.72–4.45 (m, 6H), 4.21 (s, 1H), 3.86–3.44 (m, 9H), 3.21–3.09 (brd, 2H), 1.51–1.27 ppm (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$); mixture of rotamers: δ = 171.2, 156.8/156.3, 137.9, 137.6, 137.5, 137.4, 137.8/137.6, 128.6–127.2, 101.9, 95.8, 77.8, 75.8, 74.9, 73.1, 72.4, 71.9, 71.7, 68.4, 67.3, 66.5, 65.8, 63.9, 61.6, 50.6/50.3, 47.1/46.2, 29.7, 29.1, 27.9/27.5, 23.4 ppm; IR (thin film on NaCl): $\tilde{\nu}$=3513, 3005, 2923, 2102, 1687, 1497, 1451, 1364, 1128 cm^{-1};MALDI-HRMS: m/z: calcd for $C_{53}H_{60}O_4N_4Na$: 983.4055, found: 983.4053 $[M+Na]^+$.

5-Aminopentyl (2-acetamido-2-deoxy-6-*O*-sulfo-α-D-glucopyranosyl)-(1→4)-2-*O*-sulfo-α-L-idopyranosyluronate (32): SO_3·Et_3N complex (44 mg, 0.24 mmol) was added to a solution of disaccharide **28** (23 mg, 24 μmol) in anhydrous pyridine (2.7 mL). After stirring for 4 h at room temperature, the reaction was quenched with triethylamine (0.3 mL) and diluted with MeOH (1 mL) and CH_2Cl_2 (1 mL). The solution was purified by Sephadex LH-20 chromatography (MeOH/CH_2Cl_2 1:1). The fractions that contained the sulfated disaccharide were pooled and evaporated to dryness to give **29** (24 mg, 82%) as a colorless oil. ^{1}H NMR (300 MHz, CD_3OD): δ = 7.37–7.19 (m, 25H), 5.47–5.07 (m, 4H), 4.85–4.72 (m, 7H), 4.63–4.59 (d, J=11.8 Hz, 1H), 4.49–4.45 (m, 3H), 4.36–4.32 (dd, J= 2.8, 8.1 Hz, 1H), 4.25 (brs, 1H), 4.21–4.17 (m, 1H), 4.11 (brs, 1H), 3.97–3.89 (m, 2H), 3.69–3.63 (m, 2H), 3.40–3.36 (m, 1H), 3.21–3.17 (m, 2H), 1.55–1.23 ppm (m, 6H); ESI-MS: m/z: calcd for $C_{53}H_{57}O_{19}N_4S_2$: 1117.3, found: 1119.3 $[M+2H]^{2-}$.

Compound **29** (23 mg, 21 μmol) was dissolved in THF (3.5 mL) and treated with a 0.1M aqueous solution of NaOH (0.4 mL). Then, 1M solution of PMe_3 in THF (42 μL) was added and the reaction was allowed to stir for 4 h. The reaction mixture was neutralized with 0.1M aq. HCl, concentrated and the residue was eluted from a Sephadex LH-20 chromatography column with MeOH/CH_2Cl_2 1:1 to afford **30** (21 mg, 87%) as a colorless oil. ESI-MS: m/z: calcd for $C_{53}H_{59}O_{19}N_2S_2$: 1091.3, found: 1093.3 $[M+2H]^{2-}$.

To a solution of **30** (20 mg, 18 μmol) in MeOH (1 mL), triethylamine (10 μL) and acetic anhydride (5 μL) were added. After stirring for 1 h at room temperature, the reaction mixture was purified by Sephadex LH-20 chromatography (MeOH/CH_2Cl_2 1:1). The fractions containing the disaccharide were pooled and evaporated to dryness. The residue was converted into the sodium salt by elution from a column of Dowex 50WX4-Na$^+$ with MeOH/H_2O 9:1 to give **31** (21 mg, quant.) as a white solid. ^{1}H NMR

(300 MHz, CD_3OD): δ = 7.34–7.16 (m, 25H), 5.18–5.11 (m, 3H), 4.84–4.68 (m, 8H), 4.61–4.29 (m, 7H), 4.18–4.09 (m, 3H), 3.86–3.79 (m, 2H), 3.68–3.57 (m, 2H), 3.22–3.11 (m, 2H), 2.02 (s, 3H), 1.74–1.28 ppm (m, 6H); ESI-MS: *m*/*z*: calcd for $C_{55}H_{61}O_{20}N_2S_2$: 1133.3, found: 1135.2 $[M+2H]^{2-}$.

A solution of **31** (21 mg, 18 μmol) in MeOH/H_2O (2 mL + 1 mL) was stirred under H_2-atmosphere in the presence of 10% Pd/C. After 24 h, the suspension was filtered and concentrated to give **32** (11 mg, quant.) as a white solid. ^{1}H NMR (300 MHz, D_2O): δ = 5.11–5.09 (m, 2H), 4.55–4.54 (m, 1H), 4.33–4.21 (m, 4H), 4.03–3.95 (m, 3H), 3.75–3.61 (m, 3H), 3.56–3.52 (m, 1H), 3.07–2.97 (m, 2H), 2.05 (s, 3H), 1.74–1.61 (m, 4H), 1.47–1.41 ppm (m, 2H); ESI-MS: *m*/*z*: calcd for $C_{19}H_{31}O_{18}N_2S_2$: 639.1, found: 641.5 $[M+2H]^{2-}$.

Acknowledgements

This research was supported by ETH Zürich, a Kekulé Fellowship from the Fonds der Chemischen Industrie (to A.A.) and a Niels-Stensen Postdoctoral Fellowship (to M.T.). We thank Professor Dieter Seebach for helpful discussions and Dr. W. Bernd Schweizer for X-ray analysis.

[1] a) T. Ogawa, *Chem. Soc. Rev.* **1994**, *23*, 397–407; b) S. J. Danishefsky, M. T. Bilodeau, *Angew. Chem.* **1996**, *108*, 1482–1522; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1380–1419; c) T. Hudlicky, D. A. Entwistle, K. K. Pitzer, A. J. Thorpe, *Chem. Rev.* **1996**, *96*, 1195–1220.

[2] For reviews on de novo synthesis of carbohydrates, see: a) R. R. Schmidt, *Pure Appl. Chem.* **1987**, *59*, 415–424; b) A. Kirschning, M. Jesberger, K.-U. Schöning, *Synthesis* **2001**, 507–540.

[3] S. Y. Ko, A. W. M. Lee, S. Masamune, L. A. Reed, K. B. Sharpless, F. J. Walker, *Science* **1983**, *220*, 949–951.

[4] a) A. B. Northrup, D. W. C. MacMillan, *Science* **2004**, *305*, 1752–1755; b) D. Enders, C. Grondal, *Angew. Chem.* **2005**, *117*, 1235–1238; *Angew. Chem. Int. Ed.* **2005**, *44*, 1210–1212; c) J. Casas, M. Engqvist, I. Ibrahem, B. Kaynak, A. Córdova, *Angew. Chem.* **2005**, *117*, 1367–1369; *Angew. Chem. Int. Ed.* **2005**, *44*, 1343–1345; d) D. Enders, C. Grondal, M. Vrettou, G. Raabe, *Angew. Chem.* **2005**, *117*, 4147–4151; *Angew. Chem. Int. Ed.* **2005**, *44*, 4079–4083.

[5] a) B. Casu, U. Lindahl, *Adv. Carbohydr. Chem. Biochem.* **2001**, *57*, 159–206.

[6] a) H. E. Conrad, *Heparin-Binding Proteins*, Academic Press, San Diego, CA, **1998**; b) I. Capila, R. J. Linhardt, *Angew. Chem.* **2002**, *114*, 426–450; *Angew. Chem. Int. Ed.* **2002**, *41*, 390–412; c) R. Raman, V. Sasisekharan, R. Sasisekharan, *Chem. Biol.* **2005**, *12*, 267–277; d) C. Noti, P. H. Seeberger, *Chem. Biol.* **2005**, *12*, 731–756.

[7] For a comprehensive review on the synthesis of heparins, see: B. K. S. Yeung, P. Y. C. Chong, P. A. Petillo, *J. Carbohydr. Chem.* **2002**, *21*, 799–865.

[8] For the synthesis of D-glucosamine building blocks and their application to synthesis of heparin see: a) J.-L. de Paz, J. Angulo, J.-M. Lassaletta, P. M. Nieto, M. Redondo-Horcajo, R. M. Lozano, G. Giménez-Gallego, M. Martín-Lomas, *ChemBioChem* **2001**, *2*, 673–685; b) C. Tabeur, J.-M. Mallet, F. Bono, J.-M. Herbert, M. Petitou, P. Sinaÿ, *Bioorg. Med. Chem.* **1999**, *7*, 2003–2012; c) L. Poletti, M. Fleischer, C. Vogel, M. Guerrini, G. Torri, L. Lay, *Eur. J. Org. Chem.* **2001**, 2727–2734; d) H. A. Orgueira, A. Bartolozzi, P. Schell, R. E. J. N. Litjens, E. R. Palmacci, P. H. Seeberger, *Chem. Eur. J.* **2003**, *9*, 140–169; e) J.-C. Lee, X.-A. Lu, S. S. Kulkarni, Y.-S. Wen, S.-C. Hung, *J. Am. Chem. Soc.* **2004**, *126*, 476–477; f) J. D. C. Codée, B. Stubba, M. Schiattarella, H. S. Overkleeft, C. A. A. van Boeckel, J. H. van Boom, G. A. van der Marel, *J. Am. Chem. Soc.* **2005**, *127*, 3767–3773.

[9] C. Tabeur, F. Machetto, J.-M. Mallet, P. Duchaussoy, M. Petitou, P. Sinaÿ, *Carbohydr. Res.* **1996**, *281*, 253–276.

[10] L. Rochepeau-Jobron, J.-C. Jacquinet, *Carbohydr. Res.* **1997**, *303*, 395–406.

[11] P. Schell, H. A. Orgueira, S. Roehrig, P. H. Seeberger, *Tetrahedron Lett.* **2001**, *42*, 3811–3814.

[12] a) W. Ke, D. M. Whitfield, M. Gill, S. Larocque, S.-H. Yu, *Tetrahedron Lett.* **2003**, *44*, 7767–7770; b) O. Gavard, Y. Hersant, J. Alais, V. Duverger, A. Dilhas, A. Bascou, D. Bonnaffé, *Eur. J. Org. Chem.* **2003**, 3603–3620; c) A. Lubineau, O. Gavard, J. Alais, D. Bonnaffé, *Tetrahedron Lett.* **2000**, *41*, 307–311; d) A. Dilhas, D. Bonnaffé, *Carbohydr. Res.* **2003**, *338*, 681–686; e) R. Ojeda, J. L. de Paz, M. Martín-Lomas, J. M. Lassaletta, *Synlett* **1999**, 1316–1318; f) S.-C. Hung, S. R. Thopate, F.-C. Chi, S.-W. Chang, J.-C. Lee, C.-C. Wang, Y.-S. Wen, *J. Am. Chem. Soc.* **2001**, *123*, 3153–3154.

[13] M. S. M. Timmer, A. Adibekian, P. H. Seeberger, *Angew. Chem.* **2005**, *117*, 7777–7780; *Angew. Chem. Int. Ed.* **2005**, *44*, 7605–7607.

[14] a) T. Mukaiyama, K. Banno, K. Narasaka, *J. Am. Chem. Soc.* **1974**, *96*, 7503–7509; b) T. Mukaiyama, *Org. React.* **1982**, *28*, 203–331.

[15] For use of pivaloate esters in heparin synthesis, see: a) R. Ojeda, J.-L. de Paz, M. Martín-Lomas, *Chem. Commun.* **2003**, 2486–2487; b) J. L. de Paz, M. Martín-Lomas, *Eur. J. Org. Chem.* **2005**, 1849–1858.

[16] J. H. van Boom, P. M. J. Burgers, *Tetrahedron Lett.* **1976**, *17*, 4875–4878.

[17] For 2,3-*anti*-selective aldol reactions, see: a) H. Danda, M. M. Hansen, C. H. Heathcock, *J. Org. Chem.* **1990**, *55*, 173–181; b) C. Gennari, A. Bernardi, L. Colombo, C. Scolastico, *J. Am. Chem. Soc.* **1985**, *107*, 5812–5813; c) I. Paterson, J. G. Cumming, J. D. Smith, R. A. Ward, *Tetrahedron Lett.* **1994**, *35*, 441–444; d) C. J. Cowden, I. Paterson, *Org. React.* **1997**, *51*, 1–200; e) D. A. Evans, M. G. Yang, M. J. Dart, J. L. Duffy, A. S. Kim, *J. Am. Chem. Soc.* **1995**, *117*, 9598–9599; f) E. J. Corey, W. Li, G. A. Reichard, *J. Am. Chem. Soc.* **1998**, *120*, 2330–2336.

[18] É. Bozó, S. Boros, J. Kuszmann, E. Gács-Baitz, L. Párkányi, *Carbohydr. Res.* **1998**, *308*, 297–310.

[19] Unlike monosaccharides containing the C5 substituent, the two OH groups at C3 and C4 of xylopyranose are nearly equivalent in reactivity. The necessary differentiation of the OH groups in the reported syntheses[20] proved difficult and required tin ether chemistry.

[20] a) H. B. Mereyala, V. R. Kulkarni, *Carbohydr. Res.* **1989**, *187*, 154–158; b) S. David, S. Hanessian, *Tetrahedron* **1985**, *41*, 643–663; c) E. R. Palmacci, O. J. Plante, M. C. Hewitt, P. H. Seeberger, *Helv. Chim. Acta* **2003**, *86*, 3975–3990.

[21] a) J. Tamura, Y. Miura, H. H. Freeze, *J. Carbohydr. Chem.* **1999**, *18*, 1–14; b) J. G. Allen, B. Fraser-Reid, *J. Am. Chem. Soc.* **1999**, *121*, 468–469.

[22] K. Prydz, K. T. Dalen, *J. Cell Sci.* **2000**, *113*, 193–205.

[23] K. Hattori, H. Yamamoto, *J. Org. Chem.* **1993**, *58*, 5301–5303.

[24] D. A. Evans, V. J. Cee, S. J. Siska, *J. Am. Chem. Soc.* **2006**, *128*, 9433–9441.

[25] Some Lewis acids such as $TiCl_4$ and Bu_2BOTf are known to form the corresponding metal enolates by metal exchange with silyl enolates: a) I. Kuwajima, E. Nakamura, *Acc. Chem. Res.* **1985**, *18*, 181–187; b) M. Sodeoka, K. Ohrai, M. Shibasaki, *J. Org. Chem.* **1995**, *60*, 2648–2649.

[26] For magnesium halide mediated aldol reactions, see: a) K. Takai, C. H. Heathcock, *J. Org. Chem.* **1985**, *50*, 3247–3251; b) J. Uenishi, H. Tomozane, M. Yamato, *Tetrahedron Lett.* **1985**, *26*, 3467–3470; c) A. Bernardi, S. Cardani, L. Colombo, G. Poli, G. Schimperna, C. Scolastico, *J. Org. Chem.* **1987**, *52*, 888–891.

[27] C. H. Heathcock, S. K. Davidsen, K. T. Hug, L. A. Flippin, *J. Org. Chem.* **1986**, *51*, 3027–3037.

[28] D. Seebach, J. Golinski, *Helv. Chim. Acta* **1981**, *64*, 1413–1423.

[29] a) J. R. Parikh, W. v. E. Doering, *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507; b) D. A. Evans, D. H. B. Ripin, D. P. Halstead, K. R. Campos, *J. Am. Chem. Soc.* **1999**, *121*, 6816–6826.

[30] M. T. Reetz, K. Kesseler, A. Jung, *Angew. Chem.* **1985**, *97*, 989–990; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 989–991.

[31] D. E. Ward, M. J. Hrapchak, M. Sales, *Org. Lett.* **2000**, *2*, 57–60.

[32] M. T. Reetz, *Angew. Chem.* **1984**, *96*, 542–555; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556–569.

[33] J.-F. Berrien, J. Royer, H.-P. Husson, *J. Org. Chem.* **1994**, *59*, 3769–3774.
[34] G. J. S. Lohman, D. K. Hunt, J. A. Högermeier, P. H. Seeberger, *J. Org. Chem.* **2003**, *68*, 7559–7561.
[35] G. Stork, K. Zhao, *Tetrahedron Lett.* **1989**, *30*, 287–290.
[36] a) J. L. de Paz, C. Noti, P. H. Seeberger, *J. Am. Chem. Soc.* **2006**, *128*, 2766–2767; b) C. Noti, J. L. de Paz, L. Polito, P. H. Seeberger, *Chem. Eur. J.* **2006**, *12*, 8664–8686.
[37] a) T. K.-K. Mong, H.-K. Lee, S. G. Durón, C.-H. Wong, *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 797–802; b) Y. Wang, X. Huang, L.-H. Zhang, X.-S. Ye, *Org. Lett.* **2004**, *6*, 4415–4417.
[38] When partial N-sulfation of the carbamate moiety was detected during O-sulfation, the N-sulfate group was selectively removed under mild acidic conditions as described in P. Westerduin, J. E. M. Basten, M. A. Broekhoven, V. de Kimpe, W. H. A. Kuijpers, C. A. A. van Boeckel, *Angew. Chem.* **1996**, *108*, 339–342; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 331–333.
[39] P. B. Alper, M. Hendrix, P. Sears, C.-H. Wong, *J. Am. Chem. Soc.* **1998**, *120*, 1965–1978.
[40] CCDC-633131 (**4**), -633132 (**7**), and -633133 (**18a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: January 26, 2007
Published online: April 20, 2007

