Regio- and Stereoselective Synthesis of β-D-Gluco-, α-L-Ido-, and α-L-Altropyranosiduronic Acids from Δ⁴-Uronates

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The stereoselective synthesis of β-D-glucopyranosiduronic, α-L-idopyranosiduronic, and α-L-altropyranosiduronic acids has been performed from different Δ⁴-uronate monosaccharides. Bromination of the C-4,5 double bond provided the *trans*-diaxial bromohydrin derivatives, which were converted to the corresponding epoxides in high yields. Direct reduction of the epoxides using borane−tetrahydrofuran complex led to the corresponding glucuronic acids in low to good yields. Glucuronic acids were also obtained in satisfactory yields through a two-steps procedure involving bromination of the epoxide with titanium(IV) bromide followed by reduction using tributyltin hydride. Lewis acid-catalyzed rearrangement of these epoxides led to the corresponding α-L C-4 ketopyranosides adopting the $^1C_4$ chair conformation. Hydride reduction afforded the α-L-idopyranosiduronic or the α-L-altropyranosiduronic acids, the stereoselectivity of the reduction being controlled by the appropriate substitution pattern.

Glycosaminoglycans are a family of linear, highly sulfated polysaccharides, consisting of repeating disaccharide units composed of either β-D-glucopyranosiduronic acid (β-D-GlcAp) or α-L-idopyranosiduronic acid (α-L-IdoAp) and hexosamine residues to form linear chains containing *O*-sulfo, *N*-sulfo, and *N*-acetyl groups. Commercial glycosaminoglycans are a polydisperse mixture of polysaccharide chains with an average molecular weight of 10^4-10^6.[1] Glycosaminoglycans bind to hundreds of proteins,[2] primarily through the interaction of their sulfate and carboxylate groups with basic amino acid residues present in shallow pockets or on the surface of glycosaminoglycan-binding proteins.[3] In the past decade, glycosaminoglycans have been shown to play a role in the regulation of a large number of important cellular processes including cell growth and cell−cell interactions.[2,4] The exploitation of protein interactions with specific glycosaminoglycan oligosaccharide sequences might lead to important new therapeutic advances and might be applied, for example, to wound healing/tissue growth[5] or to inhibition of angiogenesis in the eradication of tumors.[4] However, the variability in the substitution pattern of glycosaminoglycans makes it difficult to elucidate their specific protein binding site sequences. Thus, synthetic oligosaccharide sequences of glycosaminoglycans corresponding to protein binding sites are the targets of our synthetic program. These sequences are ideally suited for gaining insight into the structure−activity relationships glycosaminoglycan−protein interactions.

Total chemical synthesis of glycosaminoglycans and glycosaminoglycan oligosaccharides and their derivatives using current, state of the art techniques has severe limitations. The number of synthetic steps required to construct an intricately substituted carbohydrate, while displaying elegant chemistry,[6−10] results in a product that will simply cost too much. Enzyme-based synthesis has made some impressive breakthroughs in the preparation of small neutral or ulosonic acid-containing oligosaccharides such as SLex.[11] Unfortunately, the *N*-deacetylase, *N*- and *O*-sulfotransferases, and C5 epimerase, required for the intricate modification of glycosaminoglycans, have not yet been fully purified and cloned.[12] Cell culturing and recombinant genetic technologies are not sufficiently developed to prepare structurally defined glycosaminoglycans.[2,12]

Polysaccharide lyases have been prepared from microorganisms including *Flavobacterium heparinum*[13] and *Bacteroides stearcoris*.[14] These enzymes have been used to produce Δ⁴-uronic acid disaccharides and higher oligosaccharides from glycosaminoglycans.[15] Our laboratory is exploring the use of these enzymatically prepared oligosaccharides as building blocks for the synthesis of larger glycosaminoglycan oligosaccharides. This approach requires the stereochemically controlled conversion of the

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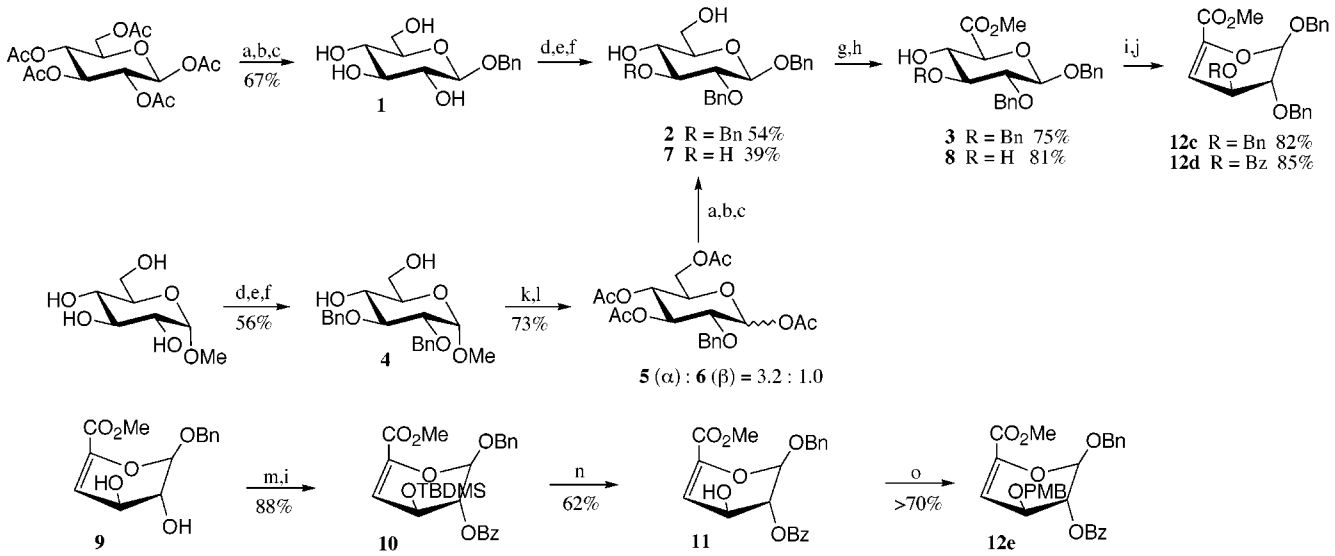
Scheme 1[a]



[a] (a) 30% HBr in AcOH, 0 °C, 2 h; (b) BnOH, Ag_2CO_3, MS 4 Å, CH_2Cl_2, rt, 24 h; (c) MeONa cat. MeOH, rt, 6 h; (d) DMP, *p*-TsOH ca., DMF, rt, 3 h; (e) NaH, 0 °C, 15 min; BnCl, rt, 15 h; (f) 60% AcOH, 80 °C, 15 min; (g) $NaHCO_3$, KBr, TEMPO cat., NaOCl, THF, 0 °C, 20 min; (h) MeOH, IR-120 (H^+), rt, 12 h; (i) BzCl or Ac_2O, Pyr, rt, 10 h; (j) DBU, CH_2Cl_2, rt, 12 h; (k) Ac_2O, Pyr, rt, 5 h; (l) Ac_2O, H_2SO_4 cat., 0 °C, 5 h; (m) TBDMSCl, Pyr, rt, 3 × 24 h; (n) *n*-Bu_4NF, THF, rt, 2 h; (o) PMBTCA, *p*-TsOH cat., CH_2Cl_2, rt, 5 × 24 h.

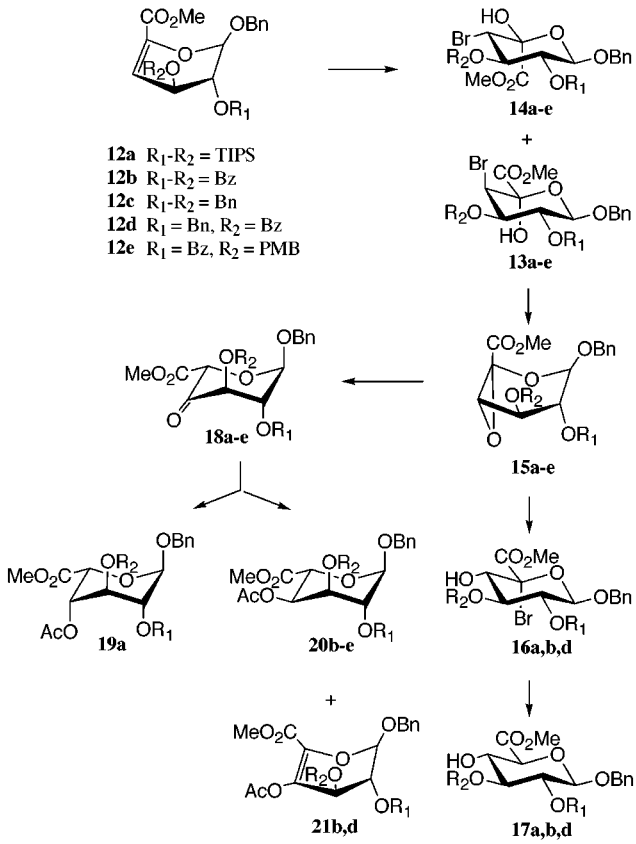
terminal Δ⁴-uronic acid residues to either D-GlcAp or L-IdoAp. We now report the regio- and stereoselective synthesis of β-D-gluco-, α-L-ido-, and α-L-altropyranosiduronic acids from Δ⁴-uronate monosaccharides.

Results and Discussion

The conversion of Δ⁴-uronate monosaccharides into D-GlcAp or L-IdoAp was first investigated with the methyl [benzyl 4-deoxy-2,3-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-α-L-*threo*-hex-4-enopyranosid]uronate (**12a**)[16] and the benzyl (benzyl 2,3-di-*O*-benzyl-4-deoxy-α-L-*threo*-hex-4-enopyranosid)uronate.[16,17] Both Δ⁴-uronates were successfully converted into the corresponding D-GlcAp[16,17] and **12a** into L-IdoAp.[16] To extend this strategy to other protecting groups, the Δ⁴-uronates **12a**−**c** (Schemes1 and 2) were synthesized. Because uronic acid residues in glycosaminoglycans are often substituted with 2-*O*-sulfo groups, it was necessary to introduce differential protection at the 2- and 3-hydroxyl groups. This was done by synthesizing the Δ⁴-uronates **12d**−**e** as model compounds.

Synthesis of Δ⁴-Uronate Monosaccharides. We already described the synthesis of **12a**[16] and **12b**.[18] The synthesis of **12c** was first attempted by direct benzylation of the Δ⁴-uronate diol **9** (Scheme 1) using standard conditions (sodium hydride, benzyl chloride).[17] However, very low yields of **12c** were obtained, a result of partial transesterification and probably low reactivity of this unsaturated system. Benzylation under acidic conditions[19] using benzyl trichloroacetamidate[19,20] failed. Another approach to **12c** relied on the benzylation of methyl (benzyl β-D-glucopyranosid)uronate, followed by subsequent β-elimination. However, the benzylation reaction led to a complex mixture of saturated and unsaturated methyl/benzyl esters.[17] Finally, **12c** was synthesized starting from β-D-glucose pentaacetate, as described in Scheme 1. Anomeric bromination of the β-D-glucose pentaacetate using a 30% solution of hydrogen bromide in acetic acid, followed by benzylation with benzyl chloride and silver carbonate, and deacetylation, afforded the benzyl β-D-glucopyranoside (**1**) in 67% yield. Isopro-

Scheme 2



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pylidenation of **1** using 2,2-dimethoxypropane-*p*-toluenesulfonic acid, followed by benzylation with sodium hydride−benzyl chloride, and deacetalation in 60% aqueous acetic acid afforded the benzyl 2,3-di-*O*-benzyl-*β*-D-glucopyranoside (**2**) in 54% yield. Regioselective oxidation of the primary 6-hydroxyl group with sodium hypochlorite in the presence of a catalytic amount of TEMPO (2,2,6,6-tetramethyl-1-pyperidinyloxy) afforded the corresponding carboxylate, which was esterified in acidic methanol giving the methyl ester **3** in 75% yield. Acetylation of **3**, using pyridine−acetic anhydride, followed by *β*-elimination with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), gave the corresponding Δ^4-uronate **12c** in 82% yield. The 2-*O*-benzyl-3-*O*-benzoyl Δ^4-uronate **12d** was synthesized from methyl α-D-glucopyranoside using a similar strategy (Scheme 1). After acetylation of the methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside (**4**), the anomeric methyl was acetolyzed by acetic anhydride, in the presence of a catalytic amount of concentrated sulfuric acid at 0 °C until all the starting material had disappeared. The acetolysis took place, as expected, at the anomeric center and also unexpectedly at the 3-position. The substitution of the 3-*O*-benzyl group by an acetate was clearly demonstrated by ^{1}H NMR spectroscopy through the presence of one benzyl and four acetates and the large deshielding of H-3, from 3.79 ppm (**4**) to 5.40 ppm (**5**) or 5.23 ppm (**6**). The two anomeric acetates **5** (α) and **6** (*β*) were obtained in 73% yield from **4** and in a ratio α (**5**):*β* (**6**) 3.2:1.0, as determined by ^{1}H NMR spectroscopy. During anomeric bromination of the anomeric mixture **5**−**6**, partial hydrolysis of the 2-*O*-benzyl group was observed, leading to the peracetylated α-bromide side product in less than 10% yield if the reaction was conducted for 2 h and in 75% yield for a 10 h reaction. Anomeric benzylation, followed by deacetylation, oxidation, methyl esterification, benzoylation and *β*-elimination, afforded the corresponding Δ^4-uronate **12d** in good yield. The Δ^4-uronate diol **9** was used to prepare **12e** in four steps as described in Scheme 1. Regioselective silylation of **9** using the bulky *tert*-butyldimethylsilyl (TBDMS) group, followed by benzoylation, afforded **10** in 88% yield. Desilylation of **10** using tetrabutylammonium fluoride gave **11** in 62% yield. Acid-catalyzed benzylation of **11** using *p*-methoxybenzyl trichloroacetamidate[19,20] afforded **12e** that was isolated, after purification by chromatography on silica gel, together with a contaminant, not removable at this stage. The structure of **12e** was confirmed by ^{1}H NMR spectroscopy, and the impurity could be removed two steps later, without affecting any of the subsequent reactions. It should be noted that the acidic benzylation using *p*-methoxybenzyl trichloroacetamidate was successfully performed, while the benzylation using benzyl trichloroacetamidate failed. Such a difference in reactivity for the acidic benzylation of uronic acid residues has been reported.[21,22]

Conversion to the Epoxide. Direct methods for the conversion of the C-4,5 unsaturated bond to a C-4 hydroxyl group, such as hydroboration or direct epoxidation using *m*-chloroperoxybenzoic acid or Camp's reagent (*m*-CPBA−KF)[23] failed.[16,17] In the latter case, a 5-fluoro derivative was isolated after extended reaction times (up to 2 weeks), together with a significant amount of unreacted glycal. The procedure developed by Goto in his studies of the synthesis of sialic acid glycosides[24] can be used to generate the epoxides **15a**−**e** in two steps through an intermediate bromohydrin, as described in Scheme 2. Thus, treatment of Δ^4-uronates **12a**−**e** with *N*-bromosuccinimide in aqueous tetrahydrofuran (THF: H_2O, v/v, 2/1) led to the corresponding *trans*-diaxial bromohydrins **13a**−**e** in good to excellent yields, together with a smaller amount of *trans*-diequatorial bromohydrins **14a**−**e** (Table 1). The configuration at C-4 was deduced from the coupling constants of the vicinal protons obtained by ^{1}H NMR spectroscopy (Table 2). The high $J_{1,2}$ and $J_{2,3}$ values of bromohydrins **13a**−**e** indicate the axial disposition of H-1, H-2, and H-3, and the smaller $J_{3,4}$ value (<4.0 Hz) indicates a dihedral angle H-3−C-3−C-4−H-4 between 45° and 135°, while the high $J_{1,2}$, $J_{2,3}$, and $J_{3,4}$ values of bromohydrins **14a**−**e** indicate the axial disposition of H-1, H-2, H-3, and H-4. Treatment of the *trans*-diaxial bromohydrins **13a**−**e** with silver oxide led to the corresponding epoxides **15a**−**e** in high yield (Scheme 2 and Table 1). The configuration of these epoxides was determined on the basis of their method of preparation. Base-catalyzed nucleophilic substitution of the C-4 bromide by the axial C-5 hydroxyl group led to the corresponding epoxides with the epoxide oxygen on the α-side of the pyranosiduronic ring.

Table 1. Yields (%) for Compounds 13−17, 19, and 20

compounds		a	b	c	d	e
bromohydrins	**13**	87	56	67	64	70[a]
	14	9	21	22	14	10[a]
epoxides	**15**	92	81	92	85	90
C-5 bromides	**16**	41	26		54	
glucuronic acids	**17**	54	26		78	
iduronic acids	**19**	60				
altruronic acids	**20**		60	82	45	49

[a] Estimated by TLC.

Direct Reduction of Epoxides 15a−**e**. The most common reducing agent for the conversion of epoxide to alcohol is lithium aluminum hydride, the cleavage usually occurring so that the more substituted alcohol is formed. However, the regioselectivity of the ring epoxide cleavage can be reversed by using borane in tetrahydrofuran.[25] Indeed, we already reported that direct reduction of the benzyl (benzyl 4-deoxy-2,3-di-*O*-benzyl-α-L-*threo*-hex-4-enopyranosid)uronate by BH_3·HF led to the corresponding D-glucopyranosiduronic acid in 84% yield.[16,17] Direct reduction of epoxides **15a** and **15b** with 1 or 2 equiv of BH_3·THF gave no products, even after 24 h at room temperature. When a large excess of reducing agent (10 equiv) was added, **15a** was slowly converted to a more polar product while **15b** did not react at all. Borane (10 equiv) was added every 8 h until disappearance of the epoxide. After purification by chromatography on silica gel, the *β*-D-glucopyranosiduronic acid **17a** was isolated in 38% yield. The stereoselectivity observed during this reduction suggests an initial complexation between the epoxide oxygen and the borane and attack of the hydride anion from the α-face.[17]

Sodium hydrogentelluride (NaTeH) has also been reported for the chemo- and regioselective conversion of

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Table 2. ^{1}H NMR Data of Compounds 13, 14, 16, 17, 19, and 20

	chemical shifts (ppm)					coupling constants (Hz)			
compounds	H-1	H-2	H-3	H-4	H-5	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
trans-diaxial bromohydrins									
13a	4.95 (d)	4.03 (dd)	4.20 (dd)	4.40 (d)		7.2	8.1	3.7	
13b	5.33 (d)	5.97 (dd)	5.70 (dd)	4.82 (d)		8.1	9.9	3.7	
13c	5.08 (d)	3.90 (ovl)	4.06 (dd)	4.45 (d)		7.9	9.3	3.8	
13d	5.27 (d)	4.09 (dd)	5.60 (dd)	4.74 (d)		7.8	8.8	3.5	
13e	5.11 (d)	5.70 (t)	4.10 (dd)	4.51 (d)		8.1	8.1	3.7	
trans-diequatorial bromohydrins									
14a	4.98 (d)	3.68 (dd)	4.08 (dd)	4.22 (d)		7.7	7.9	10.2	
14b	5.31 (d)	5.55 (dd)	5.95 (t)	4.60 (d)		8.1	9.5	11.0	
14c	5.15 (d)	3.58 (dd)	3.96 (dd)	4.32 (d)		8.1	8.5	11.0	
14d	5.27 (d)	3.65 (dd)	5.80 (dd)	4.42 (d)		7.9	8.5	8.8	
C-5 bromides									
16a	4.95 (d)	3.72 (dd)	3.93 (t)	3.65 (dd)		7.9	8.1	8.7	
16b	5.26 (d)	5.60 (dd)	5.77 (t)	4.09 (d)		8.3	9.8	9.6	
16d	5.24 (d)	3.65 (dd)	5.62 (t)	3.90 (t)		8.1	9.6	9.6	
glucuronic acids									
17a	4.43 (d)	3.65 (m)	3.65 (m)	3.91 (bt)	3.85 (d)	7.3	nd	8.7	9.9
17b	4.76 (d)	5.15 (t)	5.46 (t)	4.09 (bt)	4.05 (d)	7.4	7.5	9.6	9.5
17d	4.71 (d)	3.65 (dd)	5.47 (t)	5.30 (bt)	4.07 (d)	7.5	9.5	10.0	10.0
iduronic acids									
19a	4.98 (d)	4.52 (m)	4.53 (m)	4.94 (m)	5.66 (d)	3.8	<6.3	<6.0	2.8
altruronic acids									
20b	5.34 (s)	5.58 (bd)	5.95 (dd)	4.98 (dd)	5.34 (d)	< 1.5	1.8	5.9	8.5
20c	5.07 (s)	4.24 (m)	4.25 (t)	4.82 (t)	5.54 (d)	2.4	5.0	6.4	5.6
20d	5.21 (s)	4.21 (bs)	5.75 (dd)	4.90 (dd)	5.33 (d)	< 1.5	1.8	5.8	8.5
20e	5.21 (s)	5.58 (bs)	4.22 (dd)	4.69 (dd)	5.42 (d)	< 1.5	2.3	5.9	8.0

α,β-epoxy esters to β-hydroxy esters.[26] NaTeH was readily prepared in situ from tellurium and sodium borohydride in ethanol[27] and reacted at 0 °C with **15b**. After 30 min, **15b** was totally converted to a single, less polar compound. ^{1}H NMR spectroscopy of this new compound revealed that transesterification of the methyl ester to the ethyl ester has occurred. No epoxide reduction was observed, even after extended reaction time.

Bromination−Reduction of Epoxides. The 1,2,3,4-tetra-*O*-acetyl β-D-glucopyranosiduronic acid can be reportedly isomerized to the corresponding α-L-idopyranosiduronic acid, in 27%[28] to 67%[29] yield through C-5 bromination of the glucuronic acid, followed by reduction with tributyltin hydride. Bromination of epoxides **15a**, **15b**, and **15d** was performed using titanium(IV) bromide at −78 °C for 30 min and afforded the corresponding C-5 bromides **16a**, **16b**, and **16d** (Scheme 2). The ^{1}H NMR spectra of **16a**, **16b**, and **16d** showed four pyranose ring protons with high vicinal coupling constants and a C-4 hydroxyl indicating the presence of a C-5 bromide (Table 2). While the configuration at C-5 was not determined, the $^4C_1$ chair conformation of the resulting pyranosiduronic acids suggests an axial bromide. Bromination of the siloxane epoxide **15a** afforded **16a** in 46% yield, as well as a second derivative, isolated in 22% yield. ^{1}H NMR spectroscopy of this second compound showed four protons coupled together with smaller coupling constants, consistent with a furanoside derivative. Although bromination of epoxides **15b** and **15d** occurred in 80−90% yield as estimated by TLC, the corresponding bromo derivatives were isolated in lower yield, 26% for **16b** and 54% for **16d**, a result of partial decomposition on silica gel. No furanoside derivatives were detected in the bromination of **15b** and **15d**. The hydride reduction was next performed on the crude bromides with tributyltin hydride in refluxing toluene for 30 min. Reduction of the siloxane-protected bromide **16a** and purification on silica gel gave the corresponding β-D-glucopyranosiduronic acid **17a** in 54% yield. Reduction of **16b** and **16d** afforded **17b** and **17d** in 26% and 78% yields, respectively. The configuration of the β-D-glucopyranosiduronic acids **17a**, **17b**, and **17d** was established by ^{1}H NMR spectroscopy from the large vicinal coupling constants $J_{1,2}$, $J_{2,3}$, and $J_{3,4}$ (Table 2). The ^{1}H NMR spectra of **17a, 17b**, and **17d** showed very well resolved doublets or triplets for H-1, H-2, H-3, and H-5; however, H-4 appeared as a broad triplet, probably the result of a ^{1}H/^{2}H exchange, suggesting the lability of H-4. The acetates of **17b** and **17d** could be isolated in almost quantitative yield following a 1 h acetylation, while after a 3 h acetylation, the formation of a less polar compound (**21b** or **21d**) was observed by TLC. The ^{1}H NMR spectrum of **21b** showed, as expected, the presence of one benzyl, two benzoyl, and one acetyl groups as well as a methyl ester function. However, only three protons corresponding to H-1, H-2, and H-3 were observed, and H-3 was deshielded. The mass spectrum of **21b** indicated a molecular ion of *m*/*e* 546, consistent with the presence of only three ring protons. On the basis of these spectral data and from the partial lability of H-4 observed in **17b**, the enolate structure **21b** shown in Scheme 2 was established. The structure of **21d** was similarly assigned. The partial β-elimination observed on extended acetylation time is similar to the reported β-elimination of similar derivatives observed under desilylation conditions using *n*-Bu_4NF.[30] The glucuronic acids **17a**, **17b**, and **17d** were fully characterized following their peracetylation. Unexpectedly, the reported α-L-

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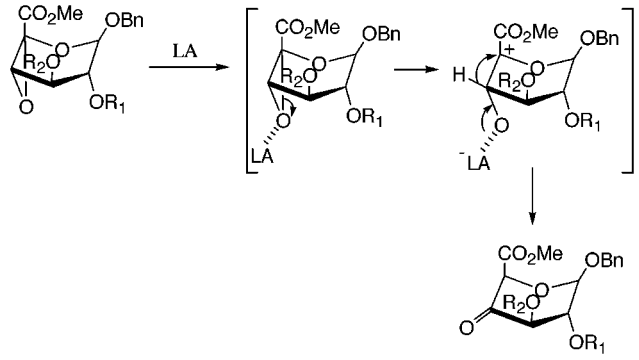

Figure 1. Lewis acid-promoted rearrangement of epoxide to ketone.

idopyranosiduronic acid formation was not observed in the reduction of bromo derivatives **16a**, **16b**, and **16d**.

Acid-Catalyzed Rearrangement of Epoxides to Ketones and Hydride Reduction. The acid-catalyzed rearrangement of epoxides to carbonyl compounds is a well-known synthetic method and has been used for the synthesis of aldehydes and ketones.[31] This transformation involves the complexation of epoxide ring with a Lewis acid and its cleavage leading to a rearrangement involving a hydrogen shift, affording the corresponding C-4 keto derivative (Figure 1). The acid-catalyzed rearrangement of epoxides **15a**−**e** was performed with scandium(III) triflate, for 30 min at room temperature, in C^2HCl_3. ^{1}H NMR spectroscopy showed only a single rearrangement product of **15c**, having the four protons appearing as two doublets and two singlets as expected for a C-4 ketopyranoside. ^{1}H NMR spectroscopy of the Lewis acid-rearrangement products of **15b** and **15d** showed the presence of a major C-4 ketopyranoside and also revealed the presence of a minor compound (<20%) assigned as a furanoside, formed through a ring contraction reaction competing with hydrogen migration.[16,17] Assignment of the four protons of the C-4 ketopyranosides relied on the comparison of the ^{1}H NMR spectra of **18b**−**d** and 2D COSY NMR spectroscopy. When the spectrum of the 2-*O*-benzoylated **18b** was compared to that of 2-*O*-benzylated **18d**, a large shift to low field was observed for H-2 in **18b**. Similarly, comparison of the 3-*O*-benzoylated **18d** spectrum with that of 3-*O*-benzylated **18c** showed a large downfield shift for H-3 in **18d**. On the basis of these observations, the H-1 and H-2 protons were assigned as singlets and H-3 and H-5 as doublets. Decoupling experiments showed that H-3 and H-5 were coupled together with a large $^4J_{3,5}$ coupling constant of 6.5−6.9 Hz, which is surprising for a C-4 ketopyranoside structure, where H-5 is isolated and expected to be a singlet. This unexpected coupling led us to perform additional spectroscopic measurements to confirm the presence of the ketone functionality. The IR spectrum of **18c** displayed two carbonyl stretches at 1763 and 1757 cm^{-1}, indicating an additional carbonyl to that of the methyl ester. ^{13}C NMR spectroscopy of **18b** showed four carbonyl signals corresponding to the methyl ester at 159.99 ppm, the two benzoyl esters at 164.30 and 164.67 ppm, and a ketone at 187.28 ppm. Mass spectrometry showed identical molecular ions for **15b** and **18b**. Together, these spectroscopic data confirmed the structure

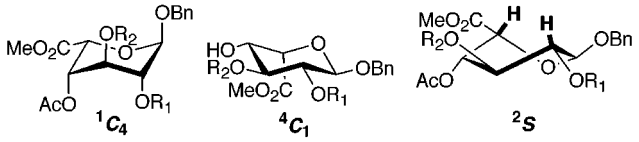

Figure 2. $^1C_4$, $^4C_1$, and $^2S_0$ conformations of iduronic acid.

of the C-4 ketopyranosides **18b**−**e**. All the vicinal coupling constants $J_{1,2}$ and $J_{2,3}$ for **18b**−**e** were <1.0 Hz, suggesting they have the α-L configuration and adopt a $^1C_4$ chair conformation. Smaller (1.1 Hz) $^4J_{3,5}$ coupling constants, between H-3 and H-5 across a carbonyl, have been reported for similar C-4 ulosides.[32] On rearrangement of epoxide **15a** with scandium(III) triflate at room temperature, a mixture of two compounds was obtained in a ratio of 2.5:1.0 (as determined by ^{1}H NMR spectroscopy), which could not be improved by altering the reaction conditions. Both compounds had similar chemical shifts and vicinal coupling constants, and at this stage, it was not possible to differentiate the ketopyranoside from the undesired furanoside. The C-4 ketopyranosides **18a**−**e** were reduced without any further characterization.

The reaction mixture obtained on acid-catalyzed rearrangement of **15a** was reduced using sodium borohydride in methanol at 0 °C. After acetylation, ^{1}H NMR spectroscopy showed the presence of two products in a ratio of 2.3:1.0. Separation by chromatography on silica gel afforded the α-L-idopyranosiduronic acid **19a** as the major compound isolated in 53% yield. Characterization of **19a** by ^{1}H NMR spectroscopy showed the H-1 signal downfield (4.98 ppm) compared to the H-1 of the corresponding glucuronic acid **17a** (4.43 ppm). Although overlapping of the signals of H-2 and H-3 and long-range coupling in H-4 did not allow the accurate determination of $J_{2,3}$ and $J_{3,4}$, these coupling constants were estimated to be <6.3 Hz and <6.0 Hz, respectively. These values, together with the very small $J_{1,2}$ (3.5 Hz) and $J_{4,5}$ (2.8 Hz) coupling constants, were consistent with the α-L-idopyranosiduronic configuration. The conformation of iduronic acid residues is highly dependent on the substitution pattern.[33] Force field studies[34] indicated that the skew boat form $^2S_0$ is equienergetic with the $^1C_4$ and $^4C_1$ forms (Figure 2) and showed that the energy barrier between the three forms is quite high (as large as 9 kcal/mol). These studies strongly indicated that iduronic acid residues exist as an equilibrium between the two or three low-energy conformers. The larger $J_{2,3}$ value observed for **19a** together with the long-range couplings observed for H-1 and H-4, usually related to a "W" planar arrangement of the protons, indicate that **19a** exists as an equilibrium between the two conformers, $^1C_4$ and $^2S_0$.[32] Moreover, 2D ROESY NMR spectroscopy of **19a** showed a substantial nuclear Overhauser enhancement (NOE) effect between H-2 and H-5, confirming their close proximity.[33] This close spatial relationship can only be observed in the unusual $^2S_0$ conformation. Reduction of the reaction mixtures obtained on rearrangement of epoxides **15b**, **15d**, and **15e** with $NaBH_4$ in methanol at 0 °C, followed by acetylation, led to the corresponding

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Table 3. Influence of the Reaction Conditions on the Reduction of Ketones 18b, 18d, and 18e[a]

entry	solvent	temp (°C)	reducing agent	20b	21b	fur.
			Reduction of **18b**			
1	MeOH	0	$NaBH_4$	5.8	1.0	2.5
2	EtOH	0	$NaBH_4$	12.7	1.0	1.2
3	MeOH	−40	$NaBH_4$	10.0	1.0	1.3
4	MeOH	−40	Luche's	1.0	2.5	0.5
5	EtOH	−40	$NaBH_4$	1.0	1.7	0.4
6	EtOH	−40	Luche's	1.0	2.8	0.6
7	MeOH	−78	Luche's	1.0	3.5	1.7
8	$MeOH_d$	−78	Luche's	1.0	1.4	0.3
9	EtOH	−78	Luche's	1.0	5.8	1.3
10	*i*-PrOH	−78	Luche's	1.0	7.8	1.2
11	THF	−40	$NaBH_4$	5.8		1.0
12	THF	−40	Luche's	6.2		1.0
13	EtOH	0	$LiAlHR_3$	traces	1.0	traces
14	THF	0	$LiAlHR_3$	1.3	1.0	0.3
			Reduction of **18d**			
15	MeOH	0	$NaBH_4$	5.8		1.0
16	MeOH	−78	Luche's	1.0	1.6	0.4
			Reduction of **18e**			
17	MeOH	0	$NaBH_4$	2.2		1.0
18	MeOH	−78	Luche's	1.0		
19	*i*-PrOH	−78	Luche's	2.1		1.0

[a] $MeOH_d$ = dilute methanolic solution. R = *O*-*t*-Bu. fur. = furanoside.

α-L-altropyranosiduronic acids **20b**, **20d**, and **20e** in 60%, 45%, and 49% yields, respectively. The corresponding furanosides were also present in the following ratios: **20b**:furanoside 3.9:1.0, **20d**:furanoside 5.8:1.0, and **20e**: furanoside 2.2:1.0. During the reduction of the dibenzoyl derivative **18b**, the enolate **21b** was also detected by ^{1}H NMR spectroscopy as a minor byproduct (Table 3, entry 1). The configurations of **20b**, **20d**, and **20e** were determined by ^{1}H and 2D COSY NMR spectroscopy. The chemical shifts of H-1, 5.21−5.34 ppm, with very small vicinal coupling constants $J_{1,2} < 1.0$ Hz, the $J_{2,3}$ values varying from 0 to 2.2 Hz and large $J_{4,5}$ coupling constants of 8.0−8.5 Hz, are characteristic of the α-L-altropyranosiduronic acid in the $^1C_4$ chair conformation. Reduction of the methyl ester to the corresponding primary alcohol was observed when **18b** was reacted at room temperature. Previously, we reported[16,17] that $Sc(OTf)_3$-promoted rearrangement of the benzyl (benzyl 4,5-anhydro-2,3-di-*O*-benzyl-β-D-glucopyranosid)uronate, followed by reduction with $NaBH_4$, afforded the corresponding α-L-idopyranosiduronic acid. This conclusion was based on the small vicinal coupling constants (<6.0 Hz) observed by ^{1}H NMR spectroscopy, which were similar to those of **20c**. However, the $J_{4,5}$ coupling constant in **20c** of 5.6 Hz, higher than the $J_{4,5}$ (2.8 Hz) in the iduronic acid **19a** and smaller than the $J_{4,5}$ (8.0−8.5 Hz) in the altruronic acids **20b**, **20d**, and **20e**, led us to conduct a more detailed NMR study and revise our previous conclusion. 2D ROESY NMR spectroscopy of **20c** showed a very strong NOE effect between the protons H-1 and H-4, indicating that these protons are spatially close. From this observation, **20c** was assigned as an altruronic acid adopting a $B_{1,4}$ boat conformation (Figure 3).

The complete stereocontrol obtained in the reduction of **18a** to the α-L-idopyranosiduronic acid and **18b**−**e** to the α-L-altropyranosiduronic acid derivatives is probably the result of steric effects. Reducing agents such as $NaBH_4$ react predominantly on the less hindered face. In compounds **18b**−**e**, the α-L face is extremely crowded by the presence of three axial substituents. The hydride

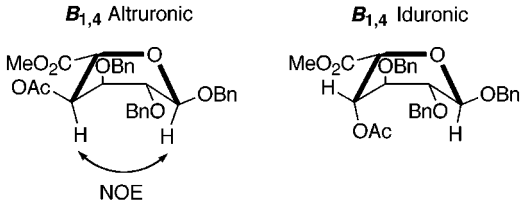

Figure 3. $B_{1,4}$ boat conformation of altruronic and iduronic acid.

anion can only approach the C-4 carbon from the β-L face, leading to the formation of an equatorial C-4 hydroxy product. In the case of **18a**, the presence of the bulky 1,1,3,3-tetraisopropylsiloxane substituent hinders the β-L face, which now becomes more crowded than the α-L face, forcing the hydride anion to approach from the upper face and affording an axial C-4 hydroxy product.

Luche's reagent (sodium borohydride−cerium(III) chloride)[35] has been successfully used for the selective reduction of ketones from the most hindered face of the molecule.[36,37] The use of this reagent was first investigated with the 4-keto derivative **18b**. Reaction of **18b** with $NaBH_4$ in methanol at −40 °C led, after acetylation, to a mixture of altropyranosiduronic acid **20b** and enolate **21b** in a ratio of 10.0:1.0 (Table 3, entry 3), as determined by ^{1}H NMR spectroscopy. When **18b** was reacted with Luche's reagent under the same conditions, a mixture of **20b** and **21b** was again obtained, in a ratio of 1.0:2.5 (Table 3, entry 4). No idopyranosiduronic acid was detected in the reaction mixture. Investigation of this reaction with different solvents and temperatures (Table 3, entries 5−12) always led to a mixture of altropyranosiduronic acid and enolate, albeit in different ratios. The formation of the enolate **21b** was favored by low temperatures, alcohol solvents, and $CeCl_3$. Stabilization of the enolate by chelation with cerium(III) and hydrogen bonding with the alcohol solvents could be responsible for the major formation and isolation of **21b**. The use of dilute methanolic solution (Table 3, entry 8) or THF (Table 3, entries 11−12) for the reaction of **18b** with Luche's reagent minimized or suppressed the formation of the enolate. Reduction of **18d** and **18e** with Luche's reagent led to the same observations (Table 3, entries 15−19), although no enolate was formed during the reduction of **18e** (Table 3, entries 17−19).

The use of a sterically hindered hydride can also reverse the stereoselectivity of the carbonyl reduction by forcing the hydride to attack from the most crowded face. However, when **18b** was reacted with the bulky *tert*-butoxy lithium aluminum hydride $LiAl(O\text{-}t\text{-}Bu)_3H$ at 0 °C and in ethanol, the enolate **21b** was the only product formed, while in THF, a mixture of **20b** and **21b** was observed (Table 3, entries 13 and 14).

Conclusions

A series of glycal monosaccharides **12a**−**e** were prepared as model compounds for Δ⁴-uronic acid oligosaccharides obtained enzymatically from glycosaminoglycans. The regio- and stereoselective synthesis of β-D-gluco- and α-L-idopyranosiduronic acids from Δ⁴-uronate monosaccharides was successfully demonstrated and accomplished in four steps. Moreover, a convenient

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synthesis of α-L-altropyranosiduronic acid has also been developed. The Δ^4-uronates were converted, through the intermediate *trans*-diaxial bromohydrins, to the corresponding epoxides in high yields. The *β*-D-glucopyranosiduronic acids were obtained in moderate to good yields through a two-step procedure involving C-5 bromination of the epoxides, followed by hydride reduction of the bromo derivatives. These glucopyranosiduronic acids underwent a partial *β*-elimination under acetylation conditions. Lewis acid-catalyzed rearrangement of the epoxides led to the corresponding α-L C-4 ketopyranosides adopting the $^1C_4$ chair conformation. This rearrangement was accompanied by the minor formation of furanosides, except for the benzyl-protected epoxide. Reduction of the siloxane ketose led to the corresponding α-L-idopyranosiduronic acid in good yield, while reduction of the ester, ester−ether, or ether-protected 4-keto derivatives led to the α-L-altropyranosiduronic acids. The use of Luche's reagent or a bulky hydride did not reverse the stereoselectivity of this reduction. The siloxane group was shown to be the protection of choice for the conversion of the Δ^4-uronate into either *β*-D-gluco- or α-L-idopyranosiduronic acids. This strategy is currently being applied to the conversion of the terminal Δ^4-uronic acid residue of larger oligosaccharides obtained by treatment of glycosaminoglycans with lyases.

Experimental Section

General Methods. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 25 °C, in deuterated chloroform or methanol. Chemical shifts were recorded in ppm (*δ*) and coupling constants in hertz, relative to tetramethylsilane as internal standard. The ^{1}H NMR spectra were fully assigned using single frequency decoupling. Melting points are uncorrected. Thin-layer chromatography (TLC) was performed using E. Merck plates of silica gel 60 with fluorescent indicator. Visualization was effected by spraying plates with Von's reagent[18] followed by heating at 140 °C. Flash chromatography was conducted with silica gel (230−430 mesh, E. Merck).

Conversion of Δ^4-Uronates to Bromohydrins. A solution of Δ^4-uronate in a mixture THF−H_2O (v/v 2:1) was reacted overnight with *N*-bromosuccinimide (NBS, 1.2 equiv) at room temperature. The reaction mixture was extracted with chloroform. The combined organic extracts were washed with water, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo.

Conversion of Bromohydrins to Epoxides. Silver oxide (3 equiv) was added to a solution of the *trans*-diaxial bromohydrin in a mixture of DMF−THF (v/v 2:1) under nitrogen. After 15 h at room temperature, the reaction mixture was filtered through a pad of Celite and the solvents were evaporated.

Direct Reduction of Epoxides Using Borane−Tetrahydrofuran Complex. Borane−tetrahydrofuran complex (1 M in THF, 10 equiv) was added to a solution of epoxide in anhydrous THF, under nitrogen and at room temperature. BH_3·THF (10 equiv) was added every 8 h until the starting material had disappeared, and the reaction mixture was concentrated under vacuum.

Bromination of Epoxides Using Titanium(IV) Bromide. Titanium(IV) bromide (1.5 equiv) was added to a solution of epoxide in anhydrous CH_2Cl_2, cooled at −78 °C and under nitrogen. After 30 min at −78 °C, the reaction mixture was quenched by addition of saturated aqueous Na_2SO_4, stirred 15 min at room temperature, and extracted with chloroform. The combined organic layers were washed with saturated aqueous Na_2SO_4 and water, dried over anhydrous Na_2SO_4, filtered ,and concentrated under vacuum.

Reduction of the C-5 Bromides Using Tributyltin Hydride. Tributyltin hydride (1.05 equiv) was added to a solution of the C-5 bromo derivative in anhydrous toluene and under nitrogen. After 30 min at reflux, the reaction mixture was concentrated under vacuum.

Lewis Acid-Catalyzed Rearrangement of Epoxides. A catalytic amount of scandium(III) triflate was added to a solution of epoxide in anhydrous CH_2Cl_2 and under nitrogen. After 30 min at room temperature, the reaction mixture was filtered through a pad of Celite, and the solvent was evaporated.

Reduction of the C-4 Ketopyranosides Using Sodium Borohydride. $NaBH_4$ (1 equiv) was added to a solution of ketopyranoside in anhydrous alcohol and under nitrogen. After 30 min at a given temperature, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl, stirred for 30 min at room temperature, and extracted with chloroform. The combined organic extracts were washed with water, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure.

Reduction of the C-4 Ketopyranosides Using Luche's Reagent. $CeCl_3$ (1 equiv) was added to a solution of ketopyranoside in anhydrous alcohol and under nitrogen. After 15 min at room temperature, the reaction mixture was cooled at the desired temperature and $NaBH_4$ (1 equiv) was added. The reaction mixture was treated as described above.

Acetylation. Acetic anhydride (1.5 equiv) was added to a solution of sugar in anhydrous pyridine cooled at 0 °C and under nitrogen. After 1 h at room temperature, the reaction mixture was quenched by addition of methanol, the solvents were evaporated under vacuum, and the residue was dried by coevaporation with toluene.

Methyl (Benzyl 2-*O*-benzoyl-3-*O*-*tert*-butyldimethylsilyl-4-deoxy-α-L-*threo*-hex-4-enopyranosid)uronate (10). To a solution of **9** (2.08 g, 7.44 mmol) in anhydrous pyridine (20 mL) and under nitrogen was added TBDMSCl (7.44 mmol, 1.12 g) every 15 h until the starting materiel completely disappeared. This reaction mixture was directly benzoylated by addition of benzoyl chloride (14.9 mmol, 1.7 mL). After 5 h at room temperature, the reaction mixture was quenched by addition of methanol (20 mL) and concentrated under reduced pressure to dryness by coevaporation with toluene. Purification by chromatography on silica gel (ethyl acetate−petroleum ether, v/v 1:3) afforded **10** as a colorless oil in 88% yield (3.18 g). $[\alpha_D]^{23} = -74°$ (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 0.72 and 074 (2 s, 3 H each, $SiMe_2$), 0.84 (s, 9 H, *t*-BuSi), 3.84 (s, 3 H, CO_2Me), 4.36 (t, 1 H, $J_{2,3} = 3.7$ Hz, $J_{3,4} = 3.9$ Hz, H-3), 4.69 and 4.92 (2 d, 1 H each, $J_{A,B} = 12.3$ Hz, CH_2Ph), 5.31 (d, 1 H, $J_{1,2} = 4.2$ Hz, H-1), 5.36 (t, 1 H, H-2), 6.13 (dd, 1 H, H-4), 7.20−7.28, 7.41, 7.60 and 8.00 (m, 10 H, 2 C_6H_5). Anal. Calcd for $C_{26}H_{34}O_7Si$ (486.6) C 64.17, H 7.04; found C 64.44, H 6.94.

Methyl (Benzyl 2-*O*-benzoyl-4-deoxy-α-L-*threo*-hex-4-enopyranosid)uronate (11). Compound **10** (2.08 g, 4.28 mmol) was reacted in anhydrous THF (20 mL) and under nitrogen with 1 M *n*-Bu_4NF (5.20 mmol, 5.2 mL). After 1 h at room temperature, the reaction mixture was concentrated under reduced pressure, and the crude mixture was purified by chromatography on silica gel (ethyl acetate−petroleum ether, v/v 1:3) to afford **11** as a colorless oil in 61% yield (1.01 g), and the methyl (benzyl 2-*O*-benzoyl-4-deoxy-α-L-*threo*-hex-4-enopyranosid)uronate[18] in 30% yield (0.50 g). **11**: $[\alpha_D]^{23} = -114°$ (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 2.87 (d, 1 H, 3-OH), 3.86 (s, 3 H, CO_2Me), 4.10 (dd, 1 H, $J_{2,3} < 1.0$ Hz, $J_{3,4} = 5.0$ Hz, H-3), 4.70 and 4.84 (2 d, 1 H each, $J_{A,B} = 11.8$ Hz, 1 CH_2Ph), 5.38 (d, 1 H, $J_{1,2} < 1.0$ Hz, H-1), 5.59 (t, 1 H, H-2), 6.42 (dd, 1 H, H-4), 7.25−7.32, 7.58, 7.98 (m, 10 H, 2 C_6H_5). Anal. Calcd for $C_{21}H_{20}O_7$ (384.4) C 65.62, H 5.24; found C 65.38, H 5.32.

Methyl (Benzyl 2,3-di-*O*-benzyl-4-deoxy-α-L-*threo*-hex-4-enopyranosid)uronate (12c). Acetic anhydride (1.53 mmol, 0.15 mL) was added to a solution of **3** (367 mg, 0.77 mmol) in anhydrous pyridine (10 mL) and under nitrogen. After 3 h at room temperature, the reaction mixture was quenched by addition of methanol (5 mL) and concentrated under reduced pressure. The residue was dissolved in anhydrous CH_2Cl_2 (10 mL) and reacted, under nitrogen, with DBU (0.77 mmol, 0.12 mL). After 15 h at room temperature, the reaction mixture

was quenched by addition of saturated aqueous NH_4Cl (10 mL) and extracted with $CHCl_3$ (20 mL × 3). The combined organic extracts were washed with water (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel (ethyl acetate−petroleum ether, v/v 1:10 → 1:5) to afford **12c** as a white solid in 82% yield (327 mg); mp 96−98 °C; lit. $[\alpha_D]^{22} = -28°$ (*c* 1, $CHCl_3$).[17] $[\alpha_D]^{25} = -25°$ (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.80 (m, 4 H, H-2 and CO_2Me), 4.13 (dd, 1 H, $J_{2,3} = 4.1$ Hz, $J_{3,4} = 3.6$ Hz, H-3), 4.62, 4.63, 4.64, 4.70, 4.75 and 4.97 (6 d, 1 H each, $J_{A,B} = 12.3$ Hz, 3 CH_2Ph), 5.14 (d, 1 H, $J_{1,2} = 5.4$ Hz, H-1), 6.18 (d, 1 H, H-4), 7.20−7.40 (m, 15 H, 3 C_6H_5).

Methyl (Benzyl 3-*O*-benzoyl-2-*O*-benzyl-4-deoxy-α-L-*threo*-hex-4-enopyranosid)uronate (12d). Compound **8** (850 mg, 2.36 mmol) in anhydrous pyridine (15 mL) and under nitrogen was benzoylated by addition of benzoyl chloride (7.1 mmol, 0.82 mL). After 5 h at room temperature, the reaction mixture was quenched by addition of methanol (15 mL) and concentrated under reduced pressure. The residue was dissolved in anhydrous CH_2Cl_2 (10 mL) and reacted, under nitrogen, with DBU (2.83 mmol, 0.5 mL). After 15 h at room temperature, the reaction mixture was treated as described for **12c**. The crude residue was purified by chromatography on silica gel (ethyl acetate−petroleum ether, v/v 1:10 → 1:5) to afford **12d** as an amorphous white solid in 85% yield (951 mg). $[\alpha_D]^{25} = -5°$ (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.82 (s, 3 H, CO_2Me), 3.29 (dd, 1 H, $J_{1,2} = 2.9$ Hz, $J_{2,3} = 3.8$, H-2), 4.64, 4.76, 4.82 and 4.94 (4 d, 1H each, $J_{A,B} = 11.8$ Hz, 2 CH_2Ph), 5.36 (d, 1 H, H-1), 6.00 (dd, 1 H, $J_{3,4} = 4.8$ Hz, H-3), 6.28 (d, 1 H, H-4), 7.30−7.40, 7.60 and 7.96 (m, 15 H, 3 C_6H_5). Anal. Calcd for $C_{28}H_{26}O_7$ (474.5) C 70.87, H 5.52; found C 70.54, H 5.58.

Methyl [Benzyl 4-bromo-5-dehydro-4-deoxy-5-hydroxy-2,3-*O*-(1,1,3,3-tetraisopropylsiloxane-1,3-diyl)-β-D-galactopyranosid]uronate (13a) and Methyl [Benzyl 4-bromo--5-dehydro-4-deoxy-5-hydroxy-2,3-*O*-(1,1,3,3-tetraisopropylsiloxane-1,3-diyl)-α-L-idopyranosid]uronate (14a). Reaction of **12a** (1.19 g, 2.27 mmol) with NBS (2.73 mmol, 485 mg) in THF:H_2O (20 mL:10 mL) and purification by chromatography on silica gel (ethyl acetate−petroleum ether, v/v 1:30 → 1:6) afforded the *trans*-diequatorial isomer **14a** in 9% (127 mg) yield ($[\alpha_D]^{24} = -4.4°$ (*c* 0.1, $CHCl_3$). Anal. Calcd for $C_{26}H_{43}BrO_8$ (619.7) C 50.40, H 6.99; found C 50.00, H 7.09) and the *trans*-diaxial isomer **13a** as a crystalline solid in 87% (1.23 g) yield: mp 124−126 °C; $[\alpha_D]^{24} = -0.5°$ (*c* 0.1, $CHCl_3$). Anal. Calcd for $C_{26}H_{43}BrO_8$ (619.7) C 50.40, H 6.99; found C 50.73, H 7.11.

Methyl (Benzyl 2,3-di-*O*-benzoyl-4-bromo-5-dehydro-4-deoxy-5-hydroxy-β-D-galactoyranosid)uronate (13b) and Methyl (Benzyl 2,3-di-*O*-benzoyl-4-bromo-5-dehydro-4-deoxy-5-hydroxy-α-L-idopyranosid)uronate (14b). Reaction of **12b** (3.46 g, 7.09 mmol) with NBS (8.50 mmol, 1.52 g) in THF:H_2O (30 mL:15 mL) and flash chromatography on silica gel (ethyl acetate−petroleum ether, v/v 1:5 → 1:3) afforded the *trans*-diequatorial isomer **14b** as a colorless glass in 21% (0.87 g) yield ($[\alpha_D]^{25} = -14°$ (*c* 1, $CHCl_3$). Anal. Calcd for $C_{28}H_{25}BrO_9$ (585.4) C 57.45, H 4.30; found C 57.80, H 4.47) and the *trans*-diaxial isomer **13b** in 56% (2.32 g) yield, isolated as a colorless glass: $[\alpha_D]^{25} = +35°$ (*c* 1, $CHCl_3$). Anal. Calcd for $C_{28}H_{25}BrO_9$ (585.4) C 57.45, H 4.30; found C 57.23, H 4.63.

Methyl (Benzyl 2,3-di-*O*-benzyl-4-bromo-5-dehydro-4-deoxy-5-hydroxy-β-D-galactopyranosid)uronate (13c) and Methyl (Benzyl 2,3-di-*O*-benzyl-4-bromo-5-dehydro-4-deoxy-5-hydroxy-α-L-idopyranosid)uronate (14c). Reaction of **12c** (180 mg, 0.39 mmol) with NBS (0.47 mmol, 84 mg) in THF:H_2O (4 mL:2 mL) and flash chromatography on silica gel (ethyl acetate−petroleum ether, v/v 1:5 → 1:3) afforded the *trans*-diequatorial isomer **14c** as a colorless glass in 22% (48 mg) yield (lit.[17] $[\alpha_D]^{22} = -73°$ (*c* 1, $CHCl_3$); $[\alpha_D]^{25} = -76°$ (*c* 1, $CHCl_3$)) and the *trans*-diaxial isomer **13c** in 67% (146 mg) yield, isolated as a colorless glass: $[\alpha_D]^{26} = -18°$ (*c* 0.5, $CHCl_3$). HRFABMAS (positive): calcd for $C_{28}H_{29}O_7Br_1$ $[M + Li]^+$ 563.1257; found 563.1255.[17]

Methyl [Benzyl 4,5-anhydro-2,3-*O*-(1,1,3,3-tetraisopropylsiloxane-1,3-diyl)-β-D-glucopyranosid]uronate (15a). *trans*-Diaxial bromohydrin **13a** (1.03 g, 1.67 mmol) in solution in DMF:THF (20 mL:10 mL) was reacted with Ag_2O (5.01 mmol, 1.16 g). Flash chromatography on silica gel (ethyl acetate−petroleum ether, v/v 1:40 → 1:9) afforded the corresponding epoxide **15a** as a colorless oil in 92% (735 mg) yield. $[\alpha_D]^{25} = -2.5°$ (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.97−1.17 (m, 28 H, 4 *i*-Pr), 3.51 (s, 1 H, $J_{3,4} < 1.0$ Hz, H-4), 3.67 (dd, 1 H, $J_{1,2} = 7.8$ Hz, $J_{2,3} = 7.5$ Hz, H-2), 3.86 (s, 3 H, CO_2Me), 4.11 (dd, 1 H, H-3), 4.71 and 4.97 (2 d, 1 H each, $J_{A,B} = 12.6$ Hz, CH_2Ph), 4.77 (d, 1 H, H-1), 7.20−7.40 (m, 5 H, C_6H_5). Anal. Calcd for $C_{26}H_{42}O_8Si_2$ (538.8) C 57.96, H 7.86; found C 57.74, H 8.00.

Methyl (Benzyl 4,5-anhydro-2,3-di-*O*-benzoyl-β-D-glucopyranosid)uronate (15b). *trans*-Diaxial bromohydrin **13b** (2.11 g, 3.61 mmol) in solution in DMF:THF (30 mL:15 mL) was reacted with Ag_2O (10.83 mmol, 2.51 g). Flash chromatography on silica gel (ethyl acetate−petroleum ether, v/v 1:9) afforded the corresponding epoxide **15b** as a colorless oil in 81% (1.48 g) yield. $[\alpha_D]^{25} = -14°$ (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.51 (s, 1 H, $J_{3,4} < 1.0$ Hz, H-4), 3.85 (s, 3 H, CO_2Me), 4.71 and 5.19 (2 d, 1 H each, $J_{A,B} = 12.0$ Hz, CH_2Ph), 5.21 (d, 1 H, $J_{1,2} < 1.0$ Hz, H-1), 5.30 (dd, 1 H, $J_{2,3} = 1.5$ Hz, H-2), 5.68 (dd, 1 H, H-3), 7.36−8.08 (m, 15 H, 3 C_6H_5). Anal. Calcd for $C_{28}H_{24}O_9$ (504.5) C 66.66, H 4.80; found C 66.12, H 4.91.

Methyl (Benzyl 4,5-anhydro-2,3-di-*O*-benzyl-β-D-glucopyranosid)uronate (15c). *trans*-Diaxial bromohydrin **13c** (121 mg, 0.217 mmol) in solution in DMF:THF (8 mL:4 mL) was reacted with Ag_2O (0.652 mmol, 151 mg). Purification by chromatography on silica gel (ethyl acetate−petroleum ether, v/v 1:20 → 1:5) afforded **15c** as a colorless oil in 92% (95 mg) yield. $[\alpha_D]^{25} = -64°$ (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.55 (t, 1 H, $J_{1,2} = 5.7$ Hz, $J_{2,3} = 5.8$ Hz, H-2), 3.62 (s, 1 H, $J_{3,4} < 1.0$ Hz, H-4), 3.82 (s, 3 H, CO_2Me), 5.94 (d, 1 H, H-3), 4.59, 4.65, 4.67, 4.70, 4.72 and 5.03 (6 d, 1 H each, $J_{A,B} = 12.1$ Hz, 3 CH_2Ph), 4.90 (s, 1 H, H-1), 7.22−7.37 (m, 15 H, 3 C_6H_5). Anal. Calcd for $C_{28}H_{28}O_7$ (476.5) C 70.58, H 5.92; found C 70.18, H 5.87.

Methyl [Benzyl 5-bromo-5-dehydro-2,3-*O*-(1,1,3,3-tetraisopropylsiloxane)-β-D-glucopyranosid]uronate (16a). Epoxide **15a** (33 mg, 0.061 mmol) in CH_2Cl_2 (3 mL) was reacted with $TiBr_4$ (0.092 mmol, 34 mg). Flash chromatography on silica gel (ethyl acetate−petroleum ether, v/v 1:40 → 1:15) afforded **16a** as a colorless oil in 41% (16 mg) yield. $[\alpha_D]^{25} = -138°$ (*c* 0.5, $CHCl_3$). Anal. Calcd for $C_{26}H_{43}BrO_8Si_2$ (619.7) C 50.39, H 6.99; found C 50.86, H 7.06.

Methyl (Benzyl 2,3-di-*O*-benzoyl-5-bromo-5-dehydro-β-D-glucopyranosid) uronate (16b). Epoxide **15b** (30 mg, 0.060 mmol) in CH_2Cl_2 (3 mL) was reacted with $TiBr_4$ (0.090 mmol, 33 mg). Flash chromatography on silica gel (ethyl acetate−petroleum ether, v/v 1:8 → 1:3) afforded **16b** as a colorless oil in 26% (9 mg) yield. $[\alpha_D]^{24} = -39°$ (*c* 1, $CHCl_3$). Anal. Calcd for $C_{28}H_{25}BrO_9$ (585.4) C 57.45, H 4.30; found C 56.98, H 4.73.

Methyl [Benzyl 2,3-*O*-(1,1,3,3-tetraisopropylsiloxane)-β-D-glucopyranosid]uronate (17a). Reduction of 15a with BH_3·THF. Compound **15a** (26 mg, 0.048 mmol) in solution in THF (2.5 mL) was reduced with BH_3·THF (1 M in THF, 4 × 0.48 mL). Flash chromatography on silica gel (ethyl acetate−petroleum ether, v/v 1:20) afforded **17a** in 38% (10 mg) yield.

Bromination−Reduction of 15a. Compound **15a** (38 mg, 0.071 mmol) in CH_2Cl_2 (3.5 mL) was reacted with $TiBr_4$ (0.107 mmol, 39 mg). The crude bromide **16a** was reduced with Bu_3SnH (0.075 mmol, 20 μL) in toluene (3 mL). Purification by chromatography on silica gel (ethyl acetate−petroleum ether, v/v 1:20) afforded **17a** in 54% (21 mg) yield. Acetylated **17a**: $[\alpha_D]^{25} = -64°$ (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.98−1.20 (m, 28 H, 4 *i*-Pr), 2.03 (s, 3H, OAc), 3.71 (dd, 1 H, $J_{1,2} = 7.4$ Hz, $J_{2,3} = 8.4$ Hz, H-2), 3.77 (t, 1 H, $J_{3,4} = 8.9$ Hz, H-3), 3.76 (s, 3 H, CO_2Me), 3.89 (d, 1 H, $J_{4,5} = 10.1$ Hz, H-5), 4.42 (d, 1 H, H-1), 4.68 and 4.94 (2 d, 1 H each, $J_{A,B} = 12.5$ Hz, CH_2Ph), 5.10 (t, 1 H, H-4), 7.24−7.40 (m, 5 H, C_6H_5). Anal. Calcd for $C_{28}H_{46}O_9Si_2$ (582.5) C 57.70, H 7.96; found C 57.82, H 8.16.

Methyl (Benzyl 2,3-di-*O*-benzoyl-*β*-D-glucopyranosid)-uronate (17b). Epoxide **15b** (38 mg, 0.075 mmol) in CH_2Cl_2 (3.5 mL) was reacted with $TiBr_4$ (0.112 mmol, 41 mg) and the crude bromide reduced with Bu_3SnH (0.078 mmol, 21 μL) in toluene (3 mL). Flash chromatography on silica gel (ethyl acetate−petroleum ether, v/v 1:10 → 1:3) afforded **17b** in 26% (10 mg) yield. Acetylated **17b**: $[\alpha_D]^{25} = +19°$ (*c* 1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 1.94 (s, 3 H, OAc), 3.79 (s, 3 H, CO_2Me), 4.18 (d, 1 H, $J_{4,5} = 9.7$ Hz, H-5), 4.68 and 4.94 (2 d, 2 H, $J_{A,B} = 12.5$ Hz, CH_2Ph), 4.78 (d, 1 H, $J_{1,2} = 7.4$ Hz, H-1), 5.50 (t, 1 H, $J_{3,4} = 9.4$ Hz, H-4), 5.52 (t, 1 H, $J_{2,3} = 9.3$ Hz, H-2), 5.64 (t, 1 H, H-3), 7.18−7.60, 7.80 and 8.05 (m, 15 H, 3 C_6H_5). Anal. Calcd for $C_{30}H_{28}O_{10}$ (548.5) C 65.69, H 5.15; found C 65.00, H 5.23.

Methyl [Benzyl 2,3-*O*-(1,1,3,3-tetraisopropylsiloxane)-α-L-*threo*-hexopyranosid-4-ulose]uronate (18a). ^1H NMR (500 MHz, $CDCl_3$): δ 0.96−1.16 (m, 28 H, 4 *i*-Pr), 3.83 (s, 3 H, CO_2Me), 4.24 (dd, 1 H, $J_{1,2} = 4.3$ Hz, $J_{2,3} = 7.2$ Hz, H-2), 4.65 and 4.82 (2 d, 1 H each, $J_{A,B} = 12.9$ Hz, CH_2Ph), 5.01 (t, 1 H, $J_{3,5} = 8.7$ Hz, H-3), 5.18 (d, 1 H, H-1), 5.67 (d, 1 H, H-5), 7.28−7.40 (m, 5H, C_6H_5).

Methyl (Benzyl 2,3-di-*O*-benzoyl-α-L-*threo*-hexopyranosid-4-ulose)uronate (18b). FABMS (positive): $[M + Na]^+$ 527. ^1H NMR (500 MHz, $CDCl_3$): δ 3.89 (s, 3 H, CO_2Me), 4.65 and 5.23 (2 d, 2 H, $J_{A,B} = 11.0$ Hz, CH_2Ph), 5.45 and 5.46 (2 s, 1H each, H-1 and H-2), 5.85 (d, 1 H, $J_{3,5} = 6.5$ Hz, H-5), 6.21 (d, 1 H, H-3), 7.18−7.62, 7.80 and 8.10 (m, 15 H, 3 C_6H_5). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 52.89 (CO_2*Me*), 69.29, 75.97, 79.74 and 84.12 (C-2, C-3, C-5 and *C*H_2Ph), 105.17 (C-1), 127.61−136.98 (*C*$_6H_5$), 159.99 (*C*O_2Me), 164.30 and 164.67 (2 *C*OPh), 187.28 (C-4).

Methyl (Benzyl 2,3-di-*O*-benzyl-α-L-*threo*-hexopyranosid-4-ulose)uronate (18c). ^1H NMR (500 MHz, $CDCl_3$): δ 3.65 (s, 3 H, CO_2Me), 4.04 (s, 1 H, $J_{1,2}$, $J_{2,3} < 1.0$ Hz, H-2), 4.34, 4.47, 4.50, 4.52, 4.57 and 5.13 (6 d, 1 H each, $J_{A,B} = 11.3$ Hz, 3 CH_2Ph), 4.65 (d, 1 H, $J_{3,5} = 6.9$ Hz, H-3), 5.29 (s, 1 H, H-1), 5.66 (d, 1 H, H-5), 7.22−7.38 (m, 15 H, 3 C_6H_5).

Methyl [Benzyl 4-*O*-acetyl-2,3-*O*-(1,1,3,3-tetraisopropylsiloxane-1,3-diyl)-α-L-idopyranosid]uronate (19a). Rearrangement of **15a** (90 mg, 0.17 mmol) followed by reduction with $NaBH_4$ (0.17 mmol, 6.3 mg) in MeOH (3 mL) at 0 °C afforded, after acetylation and purification by chromatography on silica gel (ethyl acetate−petroleum ether, v/v 1:40 → 1:15), **19a** as a colorless oil in 53% (52 mg) yield. $[\alpha_D]^{24} = -32°$ (*c* 1, $CHCl_3$). Anal. Calcd for $C_{28}H_{46}O_9Si_2$ (582.5): C 57.70, H 7.96; found C 57.72, H 8.27.

Methyl (Benzyl 4-*O*-acetyl-2,3-di-*O*-benzoyl-α-L-altropyranosid)uronate (20b). Rearrangement of **15b** (60 mg, 0.119 mmol) followed by reduction with $NaBH_4$ (0.119 mmol, 4.5 mg) in MeOH (3 mL) and at 0 °C afforded, after acetylation and purification by chromatography on silica gel (ethyl acetate−petroleum ether, v/v 1:20), **20b** as a white solid, in 60% (39 mg) yield: mp 100−102 °C. $[\alpha_D]^{25} = +28°$ (*c* 1, $CHCl_3$). FABMS (positive): $[M + H - H_2]^-$ 547.6. Anal. Calcd for $C_{30}H_{28}O_{10}$ (548.5) C 65.69, H 5.14; found C 65.27, H 5.16.

Methyl (Benzyl 4-*O*-acetyl-2,3-di-*O*-benzyl-α-L-altropyranosid)uronate (20c). Rearrangement of **15c** (24 mg, 0.05 mmol) followed by reduction with $NaBH_4$ (0.05 mmol, 1.9 mg) in MeOH (2.5 mL) and at 0 °C afforded, after acetylation and purification by chromatography on silica gel (ethyl acetate−petroleum ether, v/v 1:20), **20c** as a colorless oil in 82% (21 mg) yield. $[\alpha_D]^{25} = -59°$ (*c* 0.5, $CHCl_3$). Anal. Calcd for $C_{30}H_{32}O_8$ (520.6) C 69.22, H 6.20; found C 69.20, H 6.24.

Methyl (Benzyl 4-*O*-acetyl-2,3-di-*O*-benzoyl-α-L-*threo*-hex-4-enopyranosid)uronate (21b). $[\alpha_D]^{24} = +57°$ (*c* 1, $CHCl_3$). FABMS (positive): $[M + Na]^+$ 569.3, $[M + H]^+$ 547.3. ^1H NMR (500 MHz, $CDCl_3$): δ 2.31 (s, 3 H, OAc), 3.66 (s, 3 H, CO_2Me), 4.69 and 4.94 (2 d, 1 H each, $J_{A,B} = 11.5$ Hz, CH_2Ph), 5.44 (s, 1 H, H-1), 5.65 (s, 1 H, H-2), 6.64 (s, 1 H, H-3), 7.32−7.49, 7.54−7.62, 8.00 and 8.18 (m, 15 H, 3 C_6H_5). Anal. Calcd for $C_{30}H_{26}O_{10}$ (546.5) C 65.93, H 4.79; found C 65.37, H 4.96.

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Supporting Information Available: Experimental procedures for the synthesis of **1**−**8**, **12e**, **13d**−**e**, **14d**, **15d**−**e**, **16d**, **17d**, **18d**−**e**, **20d**−**e**, and **21d** and supporting analytical data (10 pages). See any current masthead page for ordering information and Internet access instructions.

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