Stereocontrolled Total Syntheses of Shark Cartilage Chondroitin Sulfate D-Related Tetra- and Hexasaccharide Methyl Glycosides

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Expeditious and stereocontrolled syntheses of β-D-Glc*p*A(2-SO_4)-(1→3)-[β-D-Gal*p*NAc(6-SO_4)-(1→4)-β-D-Glc*p*A(2-SO_4)-(1→3)]$_n$-β-D-Gal*p*NAc(6-SO_4)-(1→OMe) (where n = 1 and 2), which represent structural elements of shark cartilage chondroitin sulfate D, are reported for the first time. The compounds were obtained from a common key disaccharide donor **15**, which was used in an iterative way, and in which the 2-deoxy-2-trichloroacetamido group was used as an efficient stereocontrolling auxiliary. The D-glucuronyl donor **7** was easily prepared from D-glucose, whereas the D-galactosaminyl acceptor **11** was synthesized starting from D-glucosamine precursors.

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Introduction

Chondroitin sulfates (CS) belong to a family of structurally complex, polyanionic, microheterogeneous, linear polysaccharides called glycosaminoglycans (GAGs). They are ubiquitous components of extracellular matrices of all connective tissues, but are also found on mammalian cell surfaces[1] and in neural tissues,[2] and also in invertebrates.[3] They are copolymers made up of dimeric units composed of D-glucuronic acid (GlcA) and 2-acetamido-2-deoxy-D-galactose (GalNAc), namely [→4)-β-D-Glc*p*A-(1→3)-β-D-Gal*p*NAc-(1→]$_n$, and contain, on average, one sulfate group per disaccharide unit. However, several types with sulfate(s) at various positions are known. Ordinary CS chains contain monosulfated disaccharide units, designated as CS-A (4-sulfate) and CS-C (6-sulfate), or hybrid structures, depending on the ratio of A and C units. Oversulfated CS chains are characterized by particular disulfated disaccharide units such as CS-D (6,2′-disulfated), CS-E (4,6-disulfated), and CS-K (4,3′-disulfated). These sulfation patterns within CS vary with the source of the polymer, and give rise to biologically important functions intimately related to the position and the number of sulfate groups. Whereas CS-A and CS-C, the most abundant types, have been extensively studied, the other variants, especially CS-D, have drawn less attention until recently.

Shark cartilage is the main natural source of CS-D, and commercial extracts, mainly used as dietary supplements, are now available. Shark cartilage CS-D chains possess a high proportion (more than 20%)[4] of a unique disulfated disaccharide unit composed of 2-*O*-sulfonated GlcA and 6-*O*-sulfonated GalNAc residues. Recently, several sulfated oligosaccharide fragments were isolated from shark cartilage and their structures were established by highfield NMR spectroscopy.[5,6] No D-D sequence was observed[4] in these fragments, in contrast with the cases of A-A or C-C, but this does not mean that such a pattern is not present in the polymer. The interest in shark cartilage arose when it was claimed[7] that it contained an antiangiogenic substance. Although the structure of this molecule was not firmly established, this postulate resulted in the development of several drugs[8,9] based on shark cartilage extracts. However, clinical trials supporting their beneficial effects are still the subject of severe controversy.[10] More relevant was the finding that CS-D plays an important role in brain development,[11] and exhibits a neurite outgrowth-promoting activity toward embryonic rat mesencephalic and hippocampal neurons.[12]

It is now well established that most of the observed biological functions of GAGs depend on binding with proteins. These associations vary from simple charge interactions of low affinity to highly specific bindings involving a particular oligosaccharide region of definite structure. This has been demonstrated in the case of heparin, in which a specific pentasaccharide sequence is responsible for binding to antithrombin-III.[13] Determination of the precise structures and sizes of such sequences is of prime importance, but severely complicated by the microheterogeneity of the GAG polymer. Thus, detailed structural and functional analyses of CS-D fragments have been hampered by the lack of analytical tools. Although several oligosaccharide fragments have been isolated from shark cartilage CS-D by use of bacterial enzymes,[5,6] these contain $\Delta^{4,5}$-unsaturated nonreducing uronic acid residues (ΔHexA) formed by the action of the eliminases. Their structures are obviously significantly modified, and they cannot be used for binding assays or as

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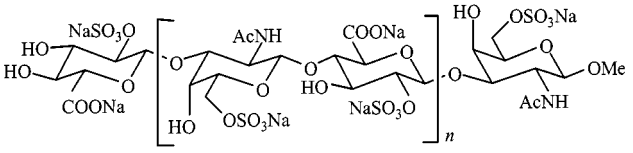
acceptor substrates for biosynthetic enzymes. Until now, the only efficient way to address these problems has been the preparation of molecules of definite size and structure by chemical synthesis.

As a general rule, tetra- to hexasaccharide sequences are required for high-affinity binding to proteins, and smaller molecules such as disaccharides rarely show any significant activity. For these reasons, several syntheses of CS-A and CS-C fragments such as tetra-,[14] penta-,[15] or hexasaccharides[16] have recently been reported. For CS-D, however, with the exception of the chemical synthesis of the basic disaccharide repeating unit[17] and a combinatorial approach that afforded a CS disaccharide library containing the CS-D disaccharide,[18] no preparation of larger molecules has been reported.

We now report for the first time on stereocontrolled total syntheses of shark cartilage CS-D-related tetra- and hexasaccharide methyl glycosides **1** and **2** (Figure 1), in which the methyl group is suitable as a marker for NMR studies.



1: $n = 1$

2: $n = 2$

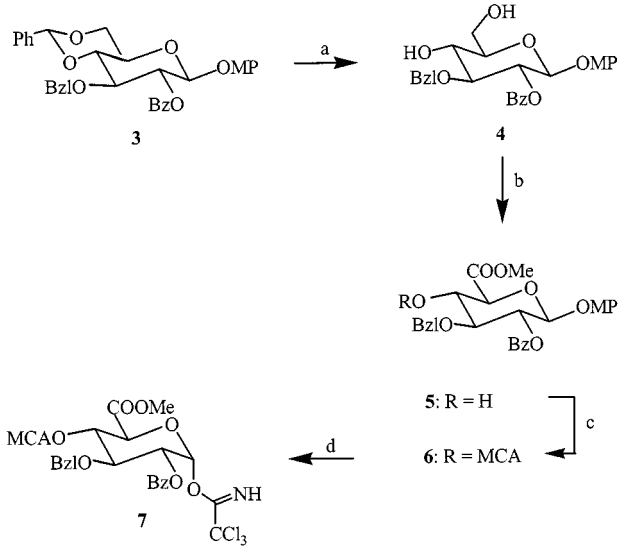
Figure 1. Synthetic chondroitin sulfate D oligosaccharides **1** and **2**

Results and Discussion

For the syntheses of the target oligosaccharides **1** and **2**, a key disaccharide glycosyl donor (**15**) was designed, capable both of being condensed with methanol to afford the reducing disaccharide acceptor **17**, and of being used in an iterative way for the construction of tetra- and hexasaccharide derivatives. Benzyl ethers were selected as permanent protection for those hydroxy groups that should be free in the final product, and benzoate esters as temporary protection for those that would ultimately carry the sulfate esters. This also provided a stereocontrolling auxiliary at C-2 of the D-GlcA moiety, which should induce 1,2-*trans* linkage formation. We had previously demonstrated[19,20] that 2-deoxy-2-trichloroacetamido-D-glucopyranose derivatives activated at C-1 are powerful glycosyl donors for the synthesis of 1,2-*trans*-2-amino-2-deoxy-D-glucosides, and react readily with the poorly reactive 4-hydroxy groups of uronic acid derivatives.[21] In addition, the *N*-trichloroacetyl group, which provides good solubility in conventional organic solvents, can easily be transformed into the *N*-acetyl moiety under neutral conditions (compatible with sensitive uronic acid esters) by use of tributylstannane. Because of the high cost of D-galactosamine, we developed a synthetic route to this amino sugar from readily available D-glucosamine precursors. All glycosylation reactions were achieved by using trichloroacetimidates.[22]

Preparation of Monosaccharide Derivatives

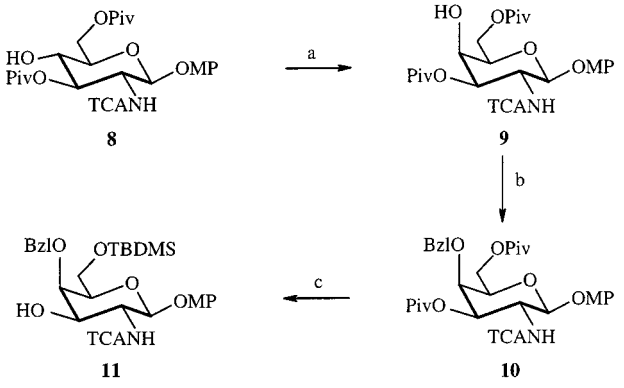
Synthesis of the glycosyl donor **7** was achieved in a straightforward manner as follows (Scheme 1). The known benzylidene derivative **3**,[17] easily prepared from commercial 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, was treated with 60% acetic acid at 100 °C to give the crystalline diol **4** in 85% yield. Transformation of **4** into **5** was achieved by selective oxidation at C-6 with nitroxyl radical.[23] Thus, treatment of the diol **4** with 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) in the presence of calcium hypochlorite[24] as a co-oxidant, under basic phase-transfer conditions, gave the intermediate hydroxy acid sodium salt, which was directly esterified by treatment with methyl iodide in *N,N*-dimethylformamide (DMF) at 50 °C to afford the crystalline methyl uronate **5** in 74% overall yield. Temporary protection at O-4 with chloroacetic anhydride and pyridine in dichloromethane gave the crystalline ester **6** in 84% yield. Introduction of the trichloroacetimidoyl group at C-1 was then achieved through oxidative removal of the 4-methoxyphenyl glycoside with cerium(IV) ammonium nitrate (CAN), followed by imidoylation of the intermediate free hemiacetal with trichloroacetonitrile and 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) at 0 °C to give the crystalline α-imidate **7** in 70% overall yield. Since nearly all compounds in this sequence could be isolated by simple crystallization, this route allowed an easy multigram-scale preparation of the glycosyl donor **7**.



Scheme 1. Synthesis of donor **7** (MCA = monochloroacetyl); reagents and conditions: a, AcOH 60%, 100 °C (85%); b, TEMPO, Aliquat 336, aq. KBr, $NaHCO_3$, $Ca(ClO)_2$, CH_2Cl_2, 0 °C; then MeI, DMF, 50 °C (74%); c, chloroacetic anhydride, pyridine/CH_2Cl_2, 0 °C (84%); d, CAN, toluene/MeCN/water; then CCl_3CN, DBU, CH_2Cl_2, 0 °C (70%)

Preparation of the galactosaminyl acceptor **11** was then achieved (Scheme 2) by a route similar to those described for the synthesis of the CS-D disaccharide repeating unit.[17]

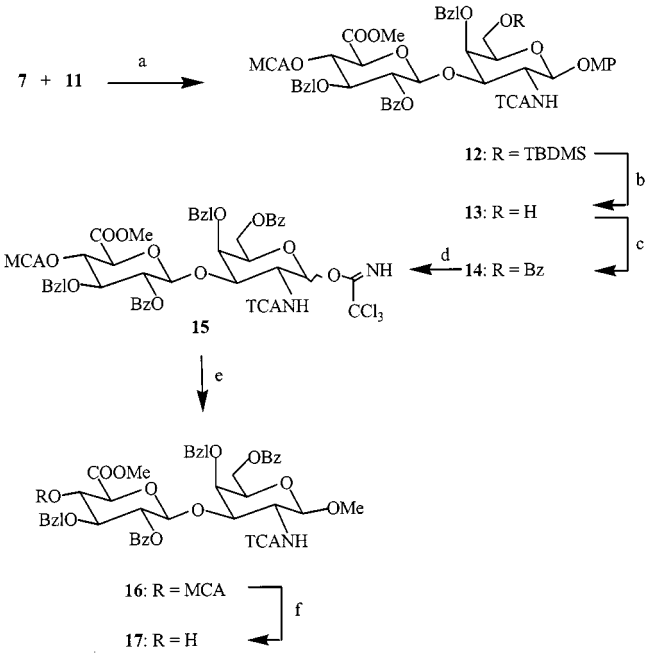
Inversion of the configuration at C-4 in the known alcohol **8**[25] was achieved by treatment with triflic anhydride and pyridine in dichloromethane at low temperature, followed by nucleophilic displacement of the intermediate 4-triflate with sodium nitrite[26] in DMF to afford the crystalline D-*galacto* derivative **9** in 60% overall yield. ^{1}H NMR spectra of **9** showed a signal with small coupling constants for 4-H ($J_{3,4}$ = 3.1, $J_{4,5}$ = 0.8 Hz), in full accord with the expected D-*galacto* structure. Treatment of the alcohol **9** with benzyl bromide, tetrabutylammonium iodide, and sodium hydride in tetrahydrofuran (THF) gave the 4-*O*-benzyl derivative **10** in 68% yield. The ^{1}H NMR spectrum of **10** was in agreement with the expected structure, and showed that no acyl migration had occurred under these basic conditions (3-H: δ = 5.35; 4-H: δ = 3.95). We have previously reported[17] that selective acylation reactions at C-6 could not be achieved with significant selectivity in 4-*O*-benzyl-D-*galacto* structures with free hydroxy groups at C-3 and C-6. Thus, Zemplèn transesterification of the ester **10** gave the corresponding diol derivative, which was treated with *tert*-butyldimethylsilyl chloride and imidazole in DMF at 0 °C to afford the crystalline monosilylated derivative **11**, the D-galactosaminyl acceptor, in 85% overall yield.



Scheme 2. Synthesis of acceptor **11** (TCA = trichloroacetyl); reagents and conditions: a, Tf_2O, pyridine/CH_2Cl_2, −15 °C to room temp.; then $NaNO_2$, DMF (60%); b, $PhCH_2Br$, Bu_4NI, NaH, THF, 0 °C to room temp. (68%); c, NaOMe, MeOH; then TBDMSCl, imidazole, DMF, 0 °C (85%)

Preparation of the Key Intermediate

Condensation of the imidate **7** (1.1 equiv.) with the alcohol **11** in the presence of TMSOTf (15% based on **7**), in dichloromethane at room temperature, readily afforded the crystalline disaccharide derivative **12**, in 71% yield (Scheme 3). Its structure was assigned by ^{1}H NMR spectroscopic data (GlcA 1-H, $J_{1,2}$ = 7.9 Hz). According to our synthetic plan, and in order to avoid further tricky protective group manipulations on tetra- and hexasaccharide derivatives, the 6-silyl ether on the GalNAc moiety was exchanged for an orthogonal benzoate ester. To this end, the silyl ether **12** was treated with 85% formic acid in THF at room temperature to afford the crystalline alcohol **13** (91% yield), which was conventionally benzoylated to give the crystalline ester **14** in 89% yield. Activation at C-1 of the glycoside **14** was achieved as described for the preparation of the donor **7** to give the disaccharide imidate **15**, the key intermediate, as an α,β-mixture in 64% overall yield. The structural assignment of **15α** and **15β** could again be unambiguously determined on the basis of their ^{1}H NMR spectroscopic data (GalN 1-H: **15α**, $J_{1,2}$ = 3.7 Hz; **15β**, $J_{1,2}$ = 8.7 Hz).

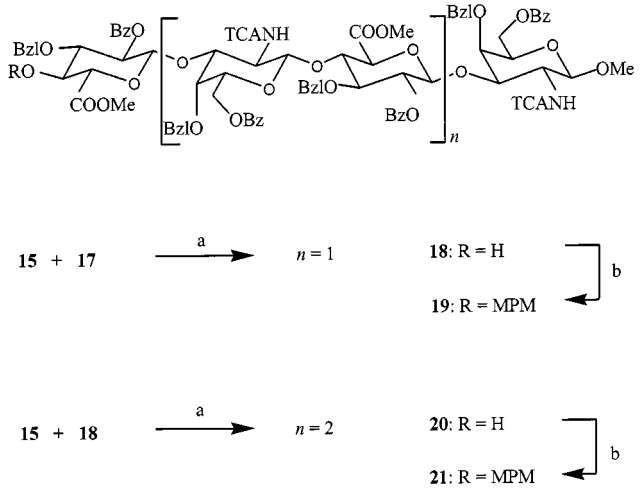


Scheme 3. Synthesis and methyl glycosylation of the key intermediate **15**; reagents and conditions: a, TMSOTf, CH_2Cl_2 (71%); b, 85% HCOOH, THF (91%); c, BzCl, pyridine/CH_2Cl_2, 0 °C (89%); d, CAN, toluene/MeCN/water; then CCl_3CN, DBU, CH_2Cl_2, 0 °C (64%); e, MeOH, TMSOTf, CH_2Cl_2 (86%); f, thiourea, pyridine/EtOH, 80 °C (91%)

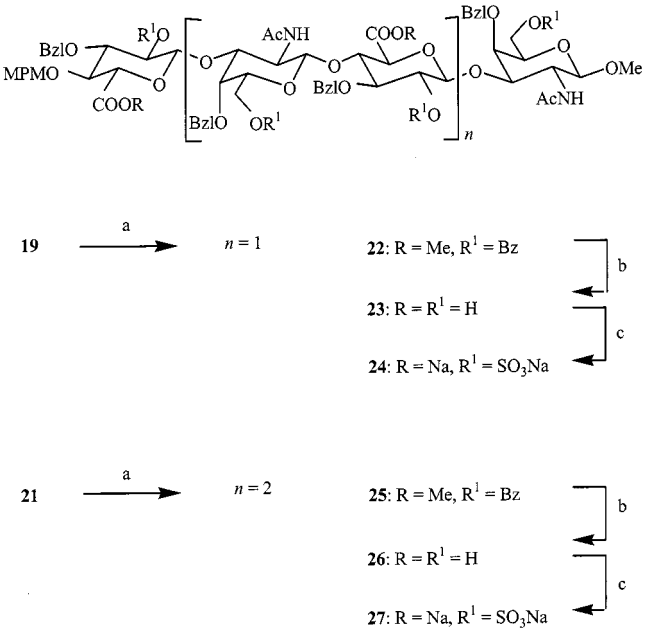
This versatile building block was first transformed into the corresponding disaccharide acceptor. Coupling of the imidate **15** with methanol (5 equiv.) in the presence of TMSOTf (15% based on **15**), in dichloromethane at room temperature, readily afforded the crystalline methyl glycoside **16** (86% yield), the anomeric configuration of which was deduced from its ^{1}H NMR spectrum (GalN 1-H, $J_{1,2}$ = 8.2 Hz). Treatment of the ester **16** with thiourea in pyridine and ethanol at 80 °C gave the crystalline disaccharide acceptor **17** in 91% yield.

Iterative Procedure for the Construction of Oligosaccharides

With both donor **15** and acceptor **17** in hand, an iterative procedure for the preparation of oligosaccharides was investigated (Scheme 4). Condensation of the imidate **15** (1.2 equiv.) with the acceptor **17**, as described for the preparation of **12**, followed by selective *O*-dechloroacetylation as described for the preparation of **17**, afforded the crystalline tetrasaccharide acceptor **18** in 44% overall yield. The anomeric configuration of the newly established interglycosidic linkage was deduced from its ^{1}H NMR spectrum, in which the four anomeric protons showed large coupling constants ($J_{1,2}$ = 7.8−8.4 Hz), in agreement with all 1,2-*trans* link-



Scheme 4. Syntheses of oligosaccharides **18**−**21**; reagents and conditions: a, TMSOTf, CH_2Cl_2; then thiourea, pyridine/EtOH, 80 °C (**18**: 44%; **20**: 46%); b, 4-methoxybenzyl trichloroacetimidate, TMSOTf, CH_2Cl_2, 0 °C (**19**: 60%; **21**: 70%)



Scheme 5. Preparation of protected *O*-sulfonated oligosaccharides **24** and **27**; reagents and conditions: a, Bu_3SnH, AIBN, NN-dimethylacetamide, 95 °C (**22**: 68%; **25**: 81%);b, $LiOH/H_2O_2$, THF, 0 °C to room temp.; then 4 M NaOH, MeOH (**23**: 68%. **26**: 80%); c, $Me_3N.SO_3$, DMF,50 °C; then ion-exchange resin [Na+] (**24**: 67%. **27**: 54%)

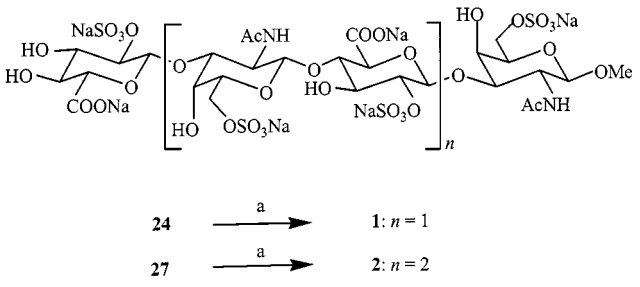
ages. A second condensation of the imidate **15** (1.5 equiv.) with the tetrasaccharide acceptor **18**, followed by selective *O*-dechloroacetylation as described above, afforded the hexasaccharide derivative **20** in 46% overall yield. The structural assignment of this compound could again be achieved on the basis of its ^{1}H NMR spectrum (all $J_{1,2}$ = 7.5−8.5 Hz). To test the efficiency of our synthetic route further (not described in the Exp. Sect.), the imidate **15** (1.7 equiv.) was condensed with the hexasaccharide acceptor **20** as described above to afford, after *O*-dechloroacetylation, the corresponding octasaccharide derivative in 30% yield.[27]

According to our synthetic plan for the preparation of the target molecules **1** and **2**, protection of the nonreducing D-glucuronic acid residue at O-4 by a hydrogenolyzable permanent group was required. To this end, the two alcohols **18** and **20** were treated with 4-methoxybenzyl trichloroacetimidate[28] in the presence of a catalytic amount of TMSOTf, in dichloromethane at 0 °C, to give the fully protected oligosaccharide derivatives **19** and **21** in 60 and 70% yields, respectively. These were now ready for further transformation into the target molecules **1** and **2**.

Access to the Target Molecules 1 and 2

Before the introduction of the sulfate esters onto the two oligosaccharide derivatives, several modifications had to be achieved (Scheme 5). First of all, the *N*-trichloroacetyl groups in **19** and **21** were readily transformed into *N*-acetyl moieties through treatment[19] with tributylstannane and azoisobutyronitrile (AIBN) in *N,N*-dimethylacetamide at 95 °C to afford the acetamides **22** and **25** in 68 and 81% yields, respectively. Saponification of the benzoate and methyl ester groups in **22** and **25** was then achieved through treatment with lithium hydroperoxide[29] in THF, followed by methanolic sodium hydroxide and acidification to give the hydroxy acids **23** and **26** in 68 and 80% yields, respectively. These intermediates were *O*-sulfonated by treatment with the sulfur trioxide-trimethylamine complex in DMF at 50 °C, followed by ion-exchange chromatography (Na^+ resin) to give the sodium salts **24** and **27** in 67 and 54% yields, respectively. As previously reported,[17] while GalNAc 6-*O*-sulfonation proceeded rapidly, GlcA 2-*O*-sulfonation was much more sluggish, and required a large excess of reagent to go to completion. The ^{1}H NMR spectra of **24** and **27**, though highly crowded in the regions of the carbohydrate ring protons, were compared with those of their nonsulfated precursors **23** and **26**, respectively, all recorded in deuterated methanol under the same conditions. Particularly relevant were the downfield shifts ($\Delta\delta \approx 0.5-0.6$ ppm) of the signals for 6a-H and 6b-H in GalNAc, and those ($\Delta\delta \approx$ 1 ppm) of the signals for GlcA 2-H in sulfates **24** and **27**. Comparison of the ^{13}C NMR spectra of these four compounds, although less discriminating as far as GlcA C-2 was concerned, clearly showed the expected[30] downfield shifts ($\Delta\delta \approx 5$ ppm) of the signals for GalNAc C-6 in sulfates **24** and **27**. These chemical shift differences firmly indicated that sulfation had occurred at GalNAc C-6 and GlcA C-2, and were in complete agreement with those observed in synthetic CS-D disaccharide derivatives.[17]

Final deprotection of **24** and **27** was then achieved (Scheme 6) through catalytic hydrogenation with 10% palladium on carbon in aqueous methanol to afford the target molecules **1** and **2** in 93 and 68% yields, respectively. The ^{1}H and ^{13}C NMR spectra of oligosaccharides **1** and **2** were in full agreement with the expected structures, and also in agreement with those reported[5,6,31] for oligosaccharide fragments isolated from shark cartilage and containing unmodified CS-D disaccharide units.



Scheme 6. Catalytic hydrogenation afforded target compounds **1** and **2**; reagents and conditions: a, H_2, 10% Pd/C, MeOH/water (**1**: 93%; **2**: 68%)

Conclusion

We have reported a stereocontrolled approach for the preparation of shark cartilage CS-D oligosaccharides. This route, based on the efficient stereocontrolling effect of the 2-deoxy-2-trichloroacetamido group associated with trichloroacetimidate activation, has been successfully applied for the syntheses of tetra- and hexasaccharide derivatives **1** and **2**, and can be extended to the preparation of larger oligosaccharides. That all the coupling reactions were achieved in good yields with moderate excesses (1.1 to 1.5 equiv.) of the donors renders this route attractive for the syntheses of galactosaminoglycan oligosaccharides. The sulfated molecules **1** and **2** are currently being evaluated in biological assays, and the results of these studies will be reported elsewhere in due course.

Experimental Section

General Remarks: Melting points were determined with a Büchi apparatus and are uncorrected. Optical rotations were measured at room temperature (22 °C) on a Perkin−Elmer 241 polarimeter. ^1H and ^{13}C NMR spectra were recorded with Bruker DPX 250 Advance and Varian Unity 500 spectrometers, with TMS as internal reference, unless otherwise stated. Assignments were based on homo- and heteronuclear correlations with the suppliers' software. Mass spectra were recorded with a Perkin−Elmer SCIEX API 3000 spectrometer in the ion-spray (IS) mode. TLC was carried out on Merck 60 F_{254} precoated plates, and compounds were detected by spraying the plates with 5% H_2SO_4 in ethanol, and heating. Flash column chromatography was performed using Merck C60 silica gel (0.040−0.063 mm). Elemental analyses were carried out at the Service Central de Microanalyse du Centre National de la Recherche Scientifique (Vernaison, France).

4-Methoxyphenyl 2-*O*-Benzoyl-3-*O*-benzyl-β-D-glucopyranoside (4): A solution of 4-methoxyphenyl 2-*O*-benzoyl-3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside[17] (**3**, 9 g, 15.9 mmol) in AcOH (90 mL) was stirred at 100 °C. Water (60 mL) was then added dropwise, and the mixture was stirred for 45 min at 100 °C, and then cooled, and concentrated. Residual solvent was then removed by coevaporation with water and toluene. The residue was crystallized from EtOAc to give diol **4** (6.5 g, 85%). M.p. 143 °C. $[\alpha]_D^{22} = +60$ (c = 1, chloroform). ^1H NMR (250 MHz, $CDCl_3$): δ = 8.05−6.80 (m, 14 H, Ar_H), 5.48 (dd, $J_{1,2}$ = 7.9, $J_{2,3}$ = 9.3 Hz, 1 H, 2-H), 5.05 (d, 1 H, 1-H), 4.70 (ABq, 2 H, C*H*$_2$Ph), 3.96 (m, $J_{5,6a}$ = 3.4, $J_{6a,6b}$ = 12.0, $J_{6a,OH}$ = 6.0 Hz, 1 H, 6a-H), 3.85 (dd, $J_{3,4}$ = 9.3, $J_{4,5}$ = 9.1 Hz, 1 H, 4-H), 3.84 (m, $J_{5,6b}$ = 4.7, $J_{6b,OH}$ = 6.0 Hz, 1 H, 6b-H), 3.76 (t, 1 H, 3-H), 3.73 (s, 3 H, OC*H*$_3$), 3.55 (m, 1 H, 5-H), 2.50 (br. s, 1 H, 4-O*H*), 2.05 (t, 1 H, 6-O*H*). MS (IS): m/z = 499 [$M^+ + NH_4$], 357 [$M^+ - OC_6H_4OCH_3$]. $C_{27}H_{28}O_8$ (480.50): calcd. C 67.49, H 5.87; found C 67.20, H 5.96.

Methyl (4-Methoxyphenyl 2-*O*-Benzoyl-3-*O*-benzyl-β-D-glucopyranoside)uronate (5): A solution of calcium hypochlorite (1 g, 6.8 mmol) and $NaHCO_3$ (0.6 g, 6.8 mmol) in water (21 mL) was added dropwise at 0 °C to a solution of diol **4** (1.5 g, 3.12 mmol), TEMPO (1.6 10^{-2} M) in CH_2Cl_2 (2 mL), Aliquat 336 (8 10^{-2} M) in CH_2Cl_2 (2 mL), and aq. KBr (0.5 M, 0.65 mL) in CH_2Cl_2 (22 mL), and the mixture was stirred for 15 min at 0 °C, and then concentrated, and dried over P_2O_5 under reduced pressure. Methyl iodide (0.9 mL, 14 mmol) was added to a solution of the residue in DMF (30 mL), and the mixture was stirred for 2 h at 50 °C, cooled, poured into 5% aq. HCl (100 mL), and extracted with EtOAc (3 × 50 mL). The organic extracts were washed with brine and water, dried ($MgSO_4$), and concentrated. Flash chromatography (petroleum ether/EtOAc, 3:2) gave a solid, which was recrystallized from EtOAc/petroleum ether to afford methyl ester **5** (1.2 g, 74%). M.p. 157−158 °C. $[\alpha]_D^{22} = +6$ (c = 1, chloroform). ^1H NMR (250 MHz, $CDCl_3$): δ = 8.00−6.80 (m, 14 H, Ar_H), 5.48 (dd, $J_{1,2}$ = 7.7, $J_{2,3}$ = 9.3 Hz, 1 H, 2-H), 5.02 (d, 1 H, 1-H), 4.79 (ABq, 2 H, C*H*$_2$Ph), 4.17 (m, $J_{3,4}$ = 9.3, $J_{4,5}$ = 9.1, $J_{4,OH}$ = 2.6 Hz, 1 H, 4-H), 4.01 (d, 1 H, 5-H), 3.84 (s, 3 H, COOC*H*$_3$), 3.79 (t, 1 H, 3-H), 3.73 (s, 3 H, OC*H*$_3$), 3.10 (d, 1 H, 4-O*H*). MS (IS): m/z = 527 [$M^+ + NH_4$], 386 [$M^+ - OC_6H_4OCH_3$]. $C_{28}H_{28}O_9$ (508.51): calcd. C 66.13, H 5.55; found C 65.92, H 5.36.

Methyl (4-Methoxyphenyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-chloroacetyl-β-D-glucopyranoside)uronate (6): Chloroacetic anhydride (3.4 g, 19.2 mmol) was added at 0 °C to a solution of alcohol **5** (4.9 g, 9.6 mmol) in CH_2Cl_2 (50 mL) and pyridine (6.5 mL), and the mixture was stirred for 1 h at 0 °C. Crushed ice was then added, and the mixture was diluted with CH_2Cl_2 (100 mL), washed with water, satd. aq. $NaHCO_3$, and water, dried ($MgSO_4$), and concentrated. The residue was crystallized from EtOAc/petroleum ether to give **6** (4.8 g, 84%). M.p. 146−147 °C. $[\alpha]_D^{22} = -8$ (c = 1, chloroform). ^1H NMR (250 MHz, $CDCl_3$): δ = 8.05−6.85 (m, 14 H, Ar_H), 5.58 (dd, $J_{1,2}$ = 7.4, $J_{2,3}$ = 9.0 Hz, 1 H, 2-H), 5.45 (dd, $J_{3,4}$ = 9.0, $J_{4,5}$ = 9.5 Hz, 1 H, 4-H), 5.08 (d, 1 H, 1-H), 4.65 (ABq, 2 H, C*H*$_2$Ph), 4.14 (d, 1 H, 5-H), 4.00 (t, 1 H, 3-H), 3.89 (ABq, 2 H, COC*H*$_2$Cl), 3.73 (s, 6 H, COOC*H*$_3$, OC*H*$_3$). MS (IS): m/z = 602 [$M^+ + NH_4$], 461 [$M^+ - OC_6H_4OCH_3$] for ^{35}Cl. $C_{30}H_{29}ClO_{10}$ (585.00): calcd. C 61.59, H 5.00; found C 61.33, H 4.95.

Methyl 2-*O*-Benzoyl-3-*O*-benzyl-4-*O*-chloroacetyl-1-*O*-trichloroacetimidoyl-α-D-glucopyranuronate (7): A mixture of glycoside **6** (4.4 g, 7.5 mmol) and CAN (21.2 g, 37.5 mmol) in 1:1.5:1 toluene/MeCN/water (140 mL) was vigorously stirred for 30 min at room temperature, and was then diluted with EtOAc (300 mL), washed with water, satd. aq. $NaHCO_3$, and water, dried ($MgSO_4$), and concentrated. Flash chromatography (CH_2Cl_2/MeOH, 99:1→97:3) afforded the corresponding hemiacetal (3.4 g) as a yellow solid.

A mixture of the above isolated hemiacetal, CCl_3CN (7 mL, 70 mmol), and DBU (0.27 mL, 1.8 mmol) in CH_2Cl_2 (60 mL) was stirred for 10 min at 0 °C, and then concentrated to half volume. Flash chromatography (petroleum ether/EtOAc, 4:1, containing 0.2% of Et_3N) and crystallization from diethyl ether/petroleum ether gave imidate **7** (3.3 g, 70% from **6**). M.p. 103−104 °C. $[\alpha]_D^{22} = +79$ (c = 1, chloroform). ^1H NMR (250 MHz, $CDCl_3$): δ = 8.62 (s, 1 H, C=N*H*), 7.98−7.10 (m, 10 H, Ar_H), 6.74 (d, $J_{1,2}$ = 3.4 Hz, 1 H, 1-H), 5.44 (dd, $J_{2,3}$ = 9.7 Hz, 1 H, 2-H), 5.36 (dd, $J_{3,4}$ = 9.7,

$J_{4,5}$ = 10.2 Hz, 1 H, 4-H), 4.71 (ABq, 2 H, CH_2Ph), 4.48 (d, 1 H, 5-H), 4.31 (t, 1 H, 3-H), 3.89 (ABq, 2 H, COCH_2Cl), 3.75 (s, 3 H, COOCH_3). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 167.37, 166.17, 165.22 (C=O), 160.13 (C=NH), 137.40−128.17 (Ar_C), 93.13 (C-1), 90.71 (*C*Cl_3), 75.77 (C-3), 75.30 (*C*H_2Ph), 72.04 (C-4), 71.76 (C-2), 70.75 (C-5), 53.27 (COO*C*H_3), 40.44 (*C*H_2Cl). MS (IS): *m*/*z* = 641 [M^+ + NH_4], 461 [M^+ − OC(NH)CCl_3] for ^{35}Cl. $C_{25}H_{23}Cl_4NO_9$ (623.26): calcd. C 48.18, H 3.72, N 2.25; found C 48.08, H 4.06, N 2.10.

4-Methoxyphenyl 2-Deoxy-3,6-di-*O*-pivaloyl-2-trichloroacetamido-β-D-galactopyranoside (9): Triflic anhydride (8.5 mL, 51.8 mmol) was added dropwise at −15 °C under dry argon to a solution of 4-methoxyphenyl 2-deoxy-3,6-di-*O*-pivaloyl-2-trichloroacetamido-β-D-glucopyranoside[25] (**8**, 22.2 g, 37 mmol) in anhydrous CH_2Cl_2 (150 mL) and anhydrous pyridine (21.5 mL), and the mixture was allowed to come to room temperature over 1 h 30 min. Crushed ice was then added, and the mixture was diluted with CH_2Cl_2 (150 mL), washed with water, brine, and water, dried ($MgSO_4$), and concentrated to give the corresponding 4-triflate as a yellow foam, which was immediately used in the next step.

A mixture of the above isolated triflate and dried $NaNO_2$ (12.8 g, 185 mmol) in DMF (70 mL) was stirred for 2 h at room temperature, and then poured into ice-cold aq. 5% HCl, and extracted with EtOAc (3 × 100 mL). The organic layers were washed with water, dried ($MgSO_4$), and concentrated. Flash chromatography (CH_2Cl_2/EtOAc, 15:1) and crystallization from EtOAc/petroleum ether gave alcohol **9** (13.2 g, 60%). M.p. 212−213 °C. $[\alpha]_D^{22}$ = +12 (*c* = 1, chloroform). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.8 Hz, 1 H, NH), 6.84 (m, 4 H, Ar_H), 5.31 (dd, $J_{2,3}$ = 11.3, $J_{3,4}$ = 3.1 Hz, 1 H, 3-H), 5.02 (d, $J_{1,2}$ = 8.5 Hz, 1 H, 1-H), 4.52 (m, 1 H, 2-H), 4.33 (dd, $J_{5,6a}$ = 4.4, $J_{6a,6b}$ = 11.5 Hz, 1 H, 6a-H), 4.25 (dd, $J_{5,6b}$ = 7.0 Hz, 1 H, 6b-H), 4.04 (m, $J_{4,5}$ = 0.8, $J_{4,OH}$ = 6.0 Hz, 1 H, 4-H), 3.87 (m, 1 H, 5-H), 3.73 (s, 3 H, OCH_3), 2.85 (d, 1 H, 4-O*H*), 1.26, 1.22 [2 s, 18 H, (CH_3)$_3$C]. MS (IS): *m*/*z* = 617 [M^+ + NH_4], 460 [M^+ − $OC_6H_4OCH_3$] for ^{35}Cl. $C_{25}H_{34}Cl_3NO_9$ (598.90): calcd. C 50.14, H 5.72, N 2.34; found C 50.00, H 5.99, N 2.40.

4-Methoxyphenyl 4-*O*-Benzyl-2-deoxy-3,6-di-*O*-pivaloyl-2-trichloroacetamido-β-D-galactopyranoside (10): Sodium hydride (2.1 g, 60% in mineral oil, 48.8 mmol) was added portionwise at 0 °C to a solution of alcohol **9** (11.7 g, 19.5 mmol) in anhydrous THF (70 mL), and the mixture was stirred for 30 min at 0 °C. Tetrabutylammonium iodide (1.4 g, 3.9 mmol) and benzyl bromide (4.6 mL, 39 mmol) were then added, and the mixture was stirred for 1 h at 0 °C, and then for 4 h at room temperature. Acetic acid (5 mL) was carefully added at 0 °C, and the mixture was diluted with EtOAc (300 mL), washed with water, satd. aq. $NaHCO_3$, and water, dried ($MgSO_4$), and concentrated. The residue was crystallized from EtOAc/petroleum ether to afford benzyl ether **10** (9.4 g, 68%). M.p. 194−195 °C. $[\alpha]_D^{22}$ = −2 (*c* = 1, chloroform). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.45−6.89 (m, 9 H, Ar_H), 6.77 (d, *J* = 8.7 Hz, 1 H, NH), 5.35 (dd, $J_{2,3}$ = 11.2, $J_{3,4}$ = 2.9 Hz, 1 H, 3-H), 5.03 (d, $J_{1,2}$ = 8.2 Hz, 1 H, 1-H), 4.73 (ABq, 2 H, CH_2Ph), 4.57 (m, 1 H, 2-H), 4.32 (dd, $J_{5,6a}$ = 5.2, $J_{6a,6b}$ = 11.2 Hz, 1 H, 6a-H), 4.15 (dd, $J_{5,6b}$ = 7.3 Hz, 1 H, 6b-H), 3.95 (dd, $J_{4,5}$ = 0.8 Hz, 1 H, 4-H), 3.88 (m, 1 H, 5-H), 3.75 (s, 3 H, OCH_3), 1.24, 1.20 [2 s, 18 H, (CH_3)$_3$C]. MS (IS): *m*/*z* = 707 [M^+ + NH_4], 564 [M^+ − $OC_6H_4OCH_3$] for ^{35}Cl. $C_{32}H_{40}Cl_3NO_9$ (689.02): calcd. C 55.78, H 5.85, N 2.03; found C 55.96, H 5.90, N 2.21.

4-Methoxyphenyl 4-*O*-Benzyl-6-*O*-*tert*-butyldimethylsilyl-2-deoxy-2-trichloroacetamido-β-D-galactopyranoside (11): Methanolic NaOMe (1 M, 1 mL) was added to a solution of ester **10** (11.8 g, 17.1 mmol) in MeOH (115 mL), and the mixture was stirred for 2 days at room temperature, and was then neutralized with Amberlite IR-120 (H^+) resin, filtered, and concentrated. The residue was crystallized from MeOH to give the corresponding diol (7.6 g, 70%). M.p. 162−163 °C.

A mixture of the above isolated diol (5.6 g, 10.8 mmol), imidazole (2.64 g, 39 mmol), and *tert*-butyldimethylsilyl chloride (2.9 g, 19.4 mmol) in anhydrous DMF (56 mL) was stirred for 30 min at 0 °C. Methanol (2 mL) was then added, and the mixture was diluted with EtOAc (500 mL), washed with satd. aq. $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated. Flash chromatography (toluene/EtOAc, 7:1) and crystallization from diethyl ether/petroleum ether afforded alcohol **11** (5.8 g, 85%). M.p. 155−157 °C. $[\alpha]_D^{22}$ = +0.5 (*c* = 1, chloroform). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.43−6.67 (m, 9 H, Ar_H), 6.88 (d, *J* = 7.3 Hz, 1 H, NH), 7.09 (d, $J_{1,2}$ = 8.1 Hz, 1 H, 1-H), 4.79 (ABq, 2 H, CH_2Ph), 4.10 (m, $J_{2,3}$ = 10.8, $J_{3,4}$ = 3.4, $J_{3,OH}$ = 9.4 Hz, 1 H, 3-H), 3.98 (dd, $J_{4,5}$ = 0.8 Hz, 1 H, 4-H), 3.96 (m, 1 H, 2-H), 3.81 (m, 2 H, 6a-H, 6b-H), 3.75 (s, 3 H, OCH_3), 2.45 (d, 1 H, 3-O*H*), 0.92 [s, 9 H, (CH_3)$_3$Si], 0.08, 0.07 (2 s, 6 H, 2 CH_3Si). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 162.75 (C=O), 155.70−114.62 (Ar_C), 99.94 (C-1), 92.61 (*C*Cl_3), 75.70, 75.63, 75.61.70.71 (C-3, C-4, C-5, *C*H_2Ph), 61.30 (C-6), 57.50 (C-2), 55.74 (O*C*H_3), 25.98 [(*C*H_3)$_3$CSi], 18.27 [(CH_3)$_3$*C*Si], − 5.21, − 5.23 [(CH_3)$_2$Si]. MS (IS): *m*/*z* = 653 [M^+ + NH_4] for ^{35}Cl. $C_{28}H_{38}Cl_3NO_7Si$ (635.05): calcd. C 52.96, H 6.03, N 2.21; found C 53.04, H 6.08, N 2.29.

4-Methoxyphenyl (Methyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-chloroacetyl-β-D-glucopyranosyluronate)-(1→3)-4-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-2-deoxy-2-trichloroacetamido-β-D-galactopyranoside (12): A mixture of donor **7** (2.3 g, 3.8 mmol), acceptor **11** (2.2 g, 3.5 mmol), and powdered 4-Å molecular sieves (2 g) in anhydrous CH_2Cl_2 (35 mL) was stirred for 1 h at room temperature under dry argon. A solution of TMSOTf in toluene (1 M, 0.58 mL) was added, and the mixture was stirred for 30 min at room temperature. Triethylamine (0.3 mL) was added, and the mixture was filtered, and concentrated. Flash chromatography (toluene/EtOAc, 13:1, containing 0.1% of Et_3N) and crystallization from EtOAc/petroleum ether gave disaccharide **12** (2.7 g, 71%). M.p. 209−210 °C. $[\alpha]_D^{22}$ = −17 (*c* = 1, chloroform). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.03−6.82 (m, 19 H, Ar_H), 6.77 (d, *J* = 6.9 Hz, 1 H, NH), 5.42 (dd, $J_{1,2}$ = 7.9, $J_{2,3}$ = 9.0 Hz, 1 H, GlcA 2-H), 5.32 (dd, $J_{3,4}$ = 9.3, $J_{4,5}$ = 9.7 Hz, 1 H, GlcA 4-H), 5.31 (d, $J_{1,2}$ = 8.1 Hz, 1 H, GalN 1-H), 4.86, 4.60 (2 ABq, 4 H, 2 CH_2Ph), 4.83 (d, 1 H, GlcA 1-H), 4.78 (dd, $J_{2,3}$ = 11.0, $J_{3,4}$ = 2.9 Hz, 1 H, GalN 3-H), 4.06 (d, 1 H, GlcA 5-H), 3.88 (dd, 1 H, GlcA 3-H), 3.86 (ABq, 2 H, COCH_2Cl), 3.84 (dd, $J_{4,5}$ = 0.8 Hz, 1 H, GalN 4-H), 3.79 (m, 1 H, GalN 2-H), 3.77 (s, 3 H, COOCH_3), 3.72 (s, 3 H, OCH_3), 3.65 (m, 3 H, GalN 5-H, 6a-H, 6b-H), 0.90 [s, 9 H, (CH_3)$_3$Si], 0.07, 0.05 (2 s, 6 H, 2 CH_3Si). MS (IS): *m*/*z* = 1114 [M^+ + NH_4] for ^{35}Cl. $C_{51}H_{59}Cl_4NO_{15}Si$ (1085.91): calcd. C 55.89, H 5.43, N 1.28; found C 56.13, H 5.50, N 1.32.

4-Methoxyphenyl (Methyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-chloroacetyl-β-D-glucopyranosyluronate)-(1→3)-4-*O*-benzyl-2-deoxy-2-trichloroacetamido-β-D-galactopyranoside (13): A solution of silyl ether **12** (3.1 g, 2.8 mmol) in THF (16 mL) and 85% formic acid (8 mL) was stirred for 15 h at room temperature, and then poured into ice-cold water, and extracted with EtOAc (3 × 100 mL). The organic extracts were washed with satd. aq. $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated. Flash chromatography (CH_2Cl_2/EtOAc, 8:1) and crystallization from MeOH provided diol **13** (2.48 g, 91%). M.p. 210−212 °C. $[\alpha]_D^{22}$ = −25 (*c* = 1, chloroform).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.05−6.82 (m, 19 H, Ar_H), 6.94 (d, *J* = 6.6 Hz, 1 H, NH), 5.45 (dd, $J_{1,2}$ = 7.8, $J_{2,3}$ = 9.3 Hz, 1 H, GlcA 2-H), 5.35 (d, $J_{1,2}$ = 8.4 Hz, 1 H, GalN 1-H), 5.33 (dd, $J_{3,4}$ = 9.0, $J_{4,5}$ = 9.9 Hz, 1 H, GlcA 4-H), 4.92, 4.61 (2 ABq, 4 H, 2 CH_2Ph), 4.82 (d, 1 H, GlcA 1-H), 4.80 (dd, $J_{2,3}$ = 10.1, $J_{3,4}$ = 3.0 Hz, 1 H, GalN 3-H), 4.11 (dd, $J_{4,5}$ = 0.8 Hz, 1 H, GalN 4-H), 4.09 (d, 1 H, GlcA 5-H), 3.90 (dd, 1 H, GlcA 3-H), 3.87 (ABq, 2 H, COCH_2Cl), 3.77 (s, 3 H, COOCH_3), 3.75 (m, 2 H, GalN 2-H, 6a-H), 3.72 (s, 3 H, OCH_3), 3.58 (dd, $J_{5,6a}$ = 5.4, $J_{5,6b}$ = 6.4 Hz, 1 H, GalN 5-H), 3.47 (m, $J_{6a,6b}$ = 12.0, $J_{6b,OH}$ = 4.1 Hz, 1 H, GalN 6b-H), 2.40 (dd, $J_{6a,OH}$ = 8.2 Hz, 1 H, GalN 6-O*H*). MS (IS): *m*/*z* = 999 [M^+ + NH_4] for ^{35}Cl. $C_{45}H_{45}Cl_4NO_{15}\cdot H_2O$ (999.66): calcd. C 54.07, H 4.74, N 1.40; found C 54.18, H 4.64, N 1.50.

4-Methoxyphenyl (Methyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-chloroacetyl-β-D-glucopyranosyluronate)-(1→3)-6-*O*-benzoyl-4-*O*-benzyl-2-deoxy-2-trichloroacetamido-β-D-galactopyranoside (14): Benzoyl chloride (0.6 mL, 5 mmol) was added at 0 °C to a solution of alcohol **13** (2.4 g, 2.5 mmol) in CH_2Cl_2 (50 mL) and pyridine (1 mL), and the mixture was stirred for 30 min at this temperature. Methanol (0.5 mL) was then added, and the mixture was diluted with CH_2Cl_2 (100 mL), washed with water, satd. aq. $NaHCO_3$, and water, dried ($MgSO_4$), and concentrated. The residue was crystallized from EtOAc to give ester **14** (2.4 g, 89%). M.p. 242−244 °C. $[\alpha]_D^{22}$ = −18 (*c* = 1, chloroform). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.10−6.80 (m, 24 H, Ar_H), 6.95 (d, *J* = 6.4 Hz, 1 H, NH), 5.45 (dd, $J_{1,2}$ = 7.8, $J_{2,3}$ = 9.3 Hz, 1 H, GlcA 2-H), 5.32 (dd, $J_{3,4}$ = 9.2, $J_{4,5}$ = 10.0 Hz, 1 H, GlcA 4-H), 5.31 (d, $J_{1,2}$ = 8.2 Hz, 1 H, GalN 1-H), 4.94, 4.61 (2 ABq, 4 H, 2 CH_2Ph), 4.84 (d, 1 H, GlcA 1-H), 4.83 (dd, $J_{2,3}$ = 10.9, $J_{3,4}$ = 0.8 Hz, 1 H, GalN 4-H), 4.50 (dd, $J_{5,6a}$ = 5.6, $J_{6a,6b}$ = 11.1 Hz, 1 H, GalN 6a-H), 4.30 (dd, $J_{5,6b}$ = 7.3 Hz, 1 H, GalN 6b-H), 4.24 (dd, $J_{4,5}$ = 0.8 Hz, 1 H, GalN 4-H), 4.08 (d, 1 H, GlcA 5-H), 3.90 (t, 1 H, GlcA 3-H), 3.85 (m, 2 H, GalN 2-H, 5-H), 3.84 (ABq, 2 H, COCH_2Cl), 3.69 (s, 3 H, COOCH_3), 3.67 (s, 3 H, OCH_3). MS (IS): *m*/*z* = 1103 [M^+ + NH_4], 962 [M^+ −$OC_6H_4OCH_3$] for ^{35}Cl.− $C_{52}H_{49}Cl_4NO_{16}$ (1085.75): calcd. C 57.52, H 4.55, N 1.29; found C 57.49, H 4.55, N 1.34.

(Methyl 2-*O*-Benzoyl-3-*O*-benzyl-4-*O*-chloroacetyl-β-D-glucopyranosyluronate)-(1→3)-6-*O*-benzoyl-4-*O*-benzyl-2-deoxy-2-trichloroacetamido-1-*O*-trichloroacetimidoyl-α,β-D-galactopyranose (15): Glycoside **14** (4.6 g, 4.2 mmol) was submitted to the same procedure as described for the preparation of imidate **7**. Flash chromatography (petroleum ether/EtOAc, 3:1, containing 0.1% of Et_3N) afforded an α,β-mixture of **15** (3.02 g, 64% from **14**) as a white foam. MS (IS): *m*/*z* = 1140 [M^+ + NH_4], 962 [M^+ − OC(NH)CCl_3] for ^{35}Cl. $C_{47}H_{43}Cl_7N_2O_{15}$ (1124.02): calcd. C 50.22, H 3.85, N 2.49; found C 49.96, H 3.88, N 2.54.

α-Anomer: Crystallized from diethyl ether/petroleum ether (2.3 g, 50% from **14**). M.p. 110−111 °C. $[\alpha]_D^{22}$ = +38 (*c* = 1, chloroform). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.70 (s, 1 H, C=N*H*), 8.10−7.10 (m, 20 H, 4 Ph), 6.78 (d, *J* = 8.3 Hz, 1 H, NH), 6.50 (d, $J_{1,2}$ = 3.7 Hz, 1 H, GalN 1-H), 5.47 (dd, $J_{1,2}$ = 7.6, $J_{2,3}$ = 8.5 Hz, 1 H, GlcA 2-H), 5.35 (dd, $J_{3,4}$ = 8.9, $J_{4,5}$ = 9.8 Hz, 1 H, GlcA 4-H), 5.07 (d, 1 H, GlcA 1-H), 4.82 (m, $J_{2,3}$ = 10.7 Hz, 1 H, GalN 2-H), 4.70, 4.60 (2 ABq, 4 H, 2 CH_2Ph), 4.42−4.34 (m, 5 H, GalN 3-H, 4-H, 5-H, 6a-H, 6b-H), 4.13 (d, 1 H, GlcA 5-H), 3.93 (dd, 1 H, GlcA 3-H), 3.85 (ABq, 2 H, COCH_2Cl), 3.68 (s, 3 H, COOCH_3). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 167.03, 166.12, 166.09, 165.13, 161.73, 160.38 (C=O, C=N), 138.0−127.69 (Ar_C), 99.80 (GlcA C-1), 95.07 (GalN C-1), 92.38, 90.94 (*C*Cl_3), 79.13, 75.29, 75.17, 74.80, 74.18, 72.54, 72.49, 72.41 (GlcA C-2, C-3, C-4, C-5; GalN C-3, C-4, C-5; 2 *C*H_2Ph), 62.83 (GalN C-6), 53.22 (COO*C*H_3), 50.87 (GalN C-2), 40.34 (*C*H_2Cl).

β-Anomer: This was obtained from the mother liquors of crystallization of the α-anomer, still containing ≈ 20% of α-anomer (0.7 g, 14%). ^{1}H NMR (250 MHz, $CDCl_3$), selected data: δ = 8.62 (s, 1 H, C=N*H*), 8.10−7.10 (m, 20 H, 4 Ph), 6.89 (d, *J* = 7.0 Hz, 1 H, NH), 6.28 (d, $J_{1,2}$ = 7.8 Hz, 1 H, GalN 1-H), 5.46 (dd, $J_{1,2}$ = 7.8, $J_{2,3}$ = 9.1 Hz, 1 H, GlcA 2-H), 5.32 (dd, $J_{3,4}$ = 9.0, $J_{4,5}$ = 9.9 Hz, 1 H, GlcA 4-H), 4.91, 4.60 (2 ABq, 4 H, 2 CH_2Ph), 4.87 (dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 2.8 Hz, 1 H, GalN 3-H), 4.86 (d, 1 H, GlcA 1-H), 4.51 (dd, $J_{5,6a}$ = 6.1, $J_{6a,6b}$ = 11.0 Hz, 1 H, GalN 6a-H), 4.35 (dd, $J_{5,6b}$ = 7.5 Hz, 1 H, GalN 6b-H), 4.29 (dd, $J_{4,5}$ = 0.8 Hz, 1 H, GalN 4-H), 4.09 (d, 1 H, GlcA 5-H), 4.05 (m, 1 H, GalN 5-H), 3.89 (t, 1 H, GlcA 3-H), 3.84 (ABq, 2 H, COCH_2Cl), 3.64 (s, 3 H, COOCH_3).

Methyl (Methyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-chloroacetyl-β-D-glucopyranosyluronate)-(1→3)-6-*O*-benzoyl-4-*O*-benzyl-2-deoxy-2-trichloroacetamido-β-D-galactopyranoside (16): A mixture of imidates **15α,β** (3 g, 2.7 mmol), anhydrous MeOH (0.54 mL, 13.5 mmol), and powdered 3-Å molecular sieves (2 g) in anhydrous CH_2Cl_2 (20 mL) was stirred for 1 h at room temperature under dry argon. A solution of TMSOTf in toluene (1 M, 0.4 mL) was then added, and the mixture was stirred for 30 min at this temperature. Triethylamine (0.3 mL) was added, and the mixture was diluted with CH_2Cl_2 (100 mL), filtered, washed with satd. aq. $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated. Crystallization of the residue from EtOAc/petroleum ether gave methyl glycoside **16** (2.3 g, 86%). M.p. 204−205 °C. $[\alpha]_D^{22}$ = −10 (*c* = 1, chloroform). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.18−7.10 (m, 20 H, 4 Ph), 6.79 (d, *J* = 6.6 Hz, 1 H, NH), 5.42 (dd, $J_{1,2}$ = 7.9, $J_{2,3}$ = 9.4 Hz, 1 H, GlcA 2-H), 5.31 (dd, $J_{3,4}$ = 9.0, $J_{4,5}$ = 10.0 Hz, 1 H, GlcA 4-H), 4.90, 4.60 (2 ABq, 4 H, 2 CH_2Ph), 4.82 (d, 1 H, GlcA 1-H), 4.81 (d, $J_{1,2}$ = 8.2 Hz, 1 H, GalN 1-H), 4.78 (dd, $J_{2,3}$ = 11.3, $J_{3,4}$ = 2.9 Hz, 1 H, GalN 3-H), 4.49 (dd, $J_{5,6a}$ = 6.3, $J_{6a,6b}$ = 11.1 Hz, 1 H, GalN 6a-H), 4.27 (dd, $J_{5,6b}$ = 6.8 Hz, 1 H, GalN 6b-H), 4.20 (dd, $J_{4,5}$ = 0.8 Hz, 1 H, GalN 4-H), 4.06 (d, 1 H, GlcA 5-H), 3.89 (dd, 1 H, GlcA 3-H), 3.86 (ABq, 2 H, COCH_2Cl), 3.85 (m, 1 H, GalN 5-H), 3.63 (s, 3 H, COOCH_3), 3.57 (m, 1 H, GalN 2-H), 3.44 (s, 3 H, OCH_3). MS (IS): *m*/*z* = 1011 [M^+ + NH_4], 960 [M^+ − OCH_3] for ^{35}Cl. $C_{46}H_{45}Cl_4NO_{15}$ (993.66): calcd. C 55.60, H 4.56, N 1.41; found C 55.50, H 4.60, N 1.52.

Methyl (Methyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate)-(1→3)-6-*O*-benzoyl-4-*O*-benzyl-2-deoxy-2-trichloroacetamido-β-D-galactopyranoside (17): A mixture of ester **16** (2.3 g, 2.3 mmol) and thiourea (0.7 g, 9.2 mmol) in pyridine (11 mL) and abs. EtOH (11 mL) was stirred for 40 min at 80 °C, and was then cooled, diluted with CH_2Cl_2 (100 mL), washed with water, brine, and water, dried ($MgSO_4$), and concentrated. Flash chromatography (petroleum ether/EtOAc, 3:2) and crystallization from EtOAc/petroleum ether gave alcohol **17** (1.9 g, 91%). M.p. 176−178 °C. $[\alpha]_D^{22}$ = −5 (*c* = 1, chloroform). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.10−7.10 (m, 20 H, 4 Ph), 6.77 (d, *J* = 6.1 Hz, 1 H, NH), 5.34 (dd, $J_{1,2}$ = 7.9, $J_{2,3}$ = 9.3 Hz, 1 H, GlcA 2-H), 4.85 (d, $J_{1,2}$ = 8.2 Hz, 1 H, GalN 1-H), 4.84, 4.76 (2 ABq, 4 H, 2 CH_2Ph), 4.76 (dd, $J_{2,3}$ = 11.1, $J_{3,4}$ = 2.6 Hz, 1 H, GalN 3-H), 4.74 (d, 1 H, GlcA 1-H), 4.48 (dd, $J_{5,6a}$ = 6.4, $J_{6a,6b}$ = 11.1 Hz, 1 H, GalN 6a-H), 4.30 (dd, $J_{5,6b}$ = 6.5 Hz, 1 H, GalN 6b-H), 4.14 (dd, $J_{4,5}$ = 0.8 Hz, GalN 4-H), 4.05 (m, $J_{4,OH}$ = 2.4 Hz, 1 H, GlcA 4-H), 3.94 (d, 1 H, GlcA 5-H), 3.85 (m, 1 H, GalN 5-H), 3.68 (dd, 1 H, GlcA 3-H), 3.66 (s, 3 H, COOCH_3), 3.53 (m, 1 H, GalN 2-H), 3.44 (s, 3 H, OCH_3), 3.08 (d, 1 H, GlcA 4-O*H*). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 169.59, 166.23, 165.10, 162.49 (C=O), 138.23−127.68 (Ar_C),

101.77 (GlcA C-1), 99.29 (GalN C-1), 92.18 (CCl_3), 80.82, 76.40, 74.90, 74.03, 72.90, 72.62, 72.19 (GlcA C-2, C-3, C-4, C-5; GalN C-3, C-4, C-5; 2 CH_2Ph), 63.21 (GalN C-6), 57.33 (OCH_3), 56.62 (GalN C-2), 52.83 ($COOCH_3$). MS (IS): m/z = 935 [$M^+ + NH_4$], 886 [$M^+ - OCH_3$] for ^{35}Cl. $C_{44}H_{44}Cl_3NO_{14}$ (917.17): calcd. C 57.62, H 4.84, N 1.53; found C 57.35, H 4.77, N 1.57.

Methyl (Methyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate)-(1→3)-(6-*O*-benzoyl-4-*O*-benzyl-2-deoxy-2-trichloroacetamido-β-D-galactopyranosyl)-(1→4)-(methyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate)-(1→3)-6-*O*-benzoyl-4-*O*-benzyl-2-deoxy-2-trichloroacetamido-β-D-galactopyranoside (18): A mixture of donor **15** (2.8 g, 2.5 mmol) and acceptor **17** (1.9 g, 2.1 mmol) was submitted to the same procedure as described for the preparation of compound **12**. Flash chromatography (toluene/EtOAc, 8:1, containing 0.2% of Et_3N) gave a fraction that was *O*-dechloroacetylated as described for the preparation of alcohol **17**. Flash chromatography (petroleum ether/EtOAc, 3:2) and crystallization from EtOAc/petroleum ether afforded alcohol **18** (1.6 g, 44% from **17**). M.p. 171−173 °C. $[\alpha]_D^{22}$ = −15 (c = 1, chloroform). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.05−7.02 (m, 40 H, 8 Ph), 6.87 (d, J = 7.3 Hz, 1 H, NH), 6.78 (d, J = 6.2 Hz, 1 H, NH), 5.34 (dd, $J_{1,2}$ = 7.9, $J_{2,3}$ = 9.6 Hz, 1 H, GlcA 2-H), 5.29 (dd, $J_{1,2}$ = 7.8, $J_{2,3}$ = 7.7 Hz, 1 H, GlcA 2-H), 5.08−4.47 (4 ABq, 8 H, 4 CH_2Ph), 5.05 (d, $J_{1,2}$ = 8.2 Hz, 1 H, GalN 1-H), 4.85 (d, 1 H, GlcA 1-H), 4.79 (d, $J_{1,2}$ = 8.4 Hz, 1 H, GalN 1-H), 4.78 (d, 1 H, GlcA 1-H), 4.67 (dd, $J_{2,3}$ = 11.0, $J_{3,4}$ = 2.9 Hz, 1 H, GalN 3-H), 4.58 (dd, $J_{2,3}$ = 10.8, $J_{3,4}$ = 2.8 Hz, 1 H, GalN 3-H), 4.43 (dd, $J_{5,6a}$ 6.0, $J_{6a,6b}$ = 11.3 Hz, 1 H, GalN 6a-H), 4.32 (t, $J_{3,4}$ = $J_{4,5}$ = 7.5 Hz, 1 H, GlcA 4-H), 4.16 (m, 3 H, GalN 2-H, 6a-H, 6b-H), 4.08 (dd, $J_{4,5}$ = 0.8 Hz, GalN 4-H), 4.04 (dd, $J_{4,5}$ = 0.8 Hz, 1 H, GalN 4-H), 4.03 (m, $J_{3,4}$ = 8.2, $J_{4,5}$ = 9.9, $J_{4,OH}$ = 2.6 Hz, 1 H, GlcA 4-H), 4.01 (d, 1 H, GlcA 5-H), 3.97 (d, 1 H, GlcA 5-H), 3.75 (m, 5 H, GalN 2-H, 2 5-H; GlcA 2 3-H), 3.68, 3.56 (2 s, 6 H, 2 $COOCH_3$), 3.54 (m, 1 H, GalN 2-H), 3.43 (s, 3 H, OCH_3), 3.08 (d, 1 H, GlcA 4-O*H*). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 169.58, 168.78, 166.20, 165.24, 162.51, 162.03 (C=O), 138.39−127.43 (Ar_C), 101.40 (GlcA 2 C-1), 99.38, 98.19 (GalN C-1), 92.43, 92.10 (CCl_3), 80.86, 79.83, 76.62, 76.10, 75.34, 75.23, 74.92, 74.68, 74.30, 74.11, 73.01, 72.91, 72.43, 72.13 (GlcA 2 C-2, 2 C-3, 2 C-4, 2 C-5; GalN 2 C-3, 2 C-4, 2 C-5; 4 CH_2Ph), 63.17, 62.79 (GalN C-6), 57.29 (OCH_3), 56.35, 55.94 (GalN C-2), 52.29 (2 $COOCH_3$). $C_{87}H_{84}Cl_6N_2O_{27}$ (1802.31): calcd. C 57.96, H 4.70, N 1.56; found C 57.75, H 4.77, N 1.52.

Methyl [Methyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-(4-methoxybenzyl)-β-D-glucopyranosyluronate]-(1→3)-(6-*O*-benzoyl-4-*O*-benzyl-2-deoxy-2-trichloroacetamido-β-D-galactopyranosyl)-(1→4)-(methyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate)-(1→3)-6-*O*-benzoyl-4-*O*-benzyl-2-deoxy-2-trichloroacetamido-β-D-galactopyranoside (19): A mixture of alcohol **18** (700 mg, 0.4 mmol) and powdered 4-Å molecular sieves (0.5 g) in anhydrous CH_2Cl_2 (3.5 mL) was stirred for 1 h at 0 °C under dry argon. Toluene solutions of TMSOTf (1 M, 20 μL) and of freshly prepared 4-methoxybenzyl trichloroacetimidate (1 M, 0.4 mL) were successively added, and the mixture was stirred at 0 °C. Additional reagents (same quantities) were added after 15, 30, and 45 min. After 1 h, Et_3N (50 μL) was added, and the mixture was filtered and concentrated. Flash chromatography (petroleum ether/EtOAc, 2:1, containing 0.1% of Et_3N) and crystallization from EtOAc/petroleum ether gave tetrasaccharide **19** (500 mg, 60%). M.p. 164−165 °C. $[\alpha]_D^{22}$ = −13 (c = 1, chloroform). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.05−6.75 (m, 44 H, Ar_H), 6.84 (d, J = 7.3 Hz, 1 H, NH), 6.79 (d, J = 6.3 Hz, 1 H, NH), 5.39 (dd, $J_{1,2}$ = 7.6, $J_{2,3}$ = 8.2 Hz, 1 H, GlcA 2-H), 5.29 (t, $J_{1,2}$ = $J_{2,3}$ = 7.9 Hz, 1 H, GlcA 2-H), 5.06−4.47 (m, 10 H, 5 CH_2Ph), 5.00 (d, $J_{1,2}$ = 8.5 Hz, 1 H, GalN 1-H), 4.82 (d, 1 H, GlcA 1-H), 4.81 (d, 1 H, GlcA 1-H), 4.78 (d, $J_{1,2}$ = 8.5 Hz, 1 H, GalN 1-H), 4.73, 4.68 (2 dd, $J_{2,3}$ = 11.3, $J_{3,4}$ = 2.8 Hz, 2 H, GalN 2 3-H), 4.44 (dd, $J_{5,6a}$ = 6.0, $J_{6a,6b}$ = 11.3 Hz, 1 H, GalN 6a-H), 4.29 (t, $J_{3,4}$ = $J_{4,5}$ = 7.5 Hz, 1 H, GlcA 4-H), 4.20 (m, 3 H, GalN 6a-H, 2 6b-H), 4.0 (m, 5 H, GalN 2 4-H; GlcA 4-H, 2 5-H), 3.79 (s, 3 H, OCH_3), 3.79−375 (m, 6 H, GalN 2 2-H, 2 5-H; GlcA 2 3-H), 3.68, 3.66 (2 s, 6 H, 2 $COOCH_3$), 3.43 (s, 3 H, OCH_3). $C_{95}H_{92}Cl_6N_2O_{28}$ (1922.48): calcd. C 59.35, H 4.82, N 1.42; found C 59.05, H 4.86, N 1.53.

Methyl (Methyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate)-(1→3)-(6-*O*-benzoyl-4-*O*-benzyl-2-deoxy-2-trichloroacetamido-β-D-galactopyranosyl)-(1→4)-(methyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate)-(1→3)-(6-*O*-benzoyl-4-*O*-benzyl-2-deoxy-2-trichloroacetamido-β-D-galactopyranosyl)-(1→4)-(methyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate)-(1→3)-6-*O*-benzoyl-4-*O*-benzyl-2-deoxy-2-trichloroacetamido-β-D-galactopyranoside (20): A mixture of donor **15** (450 mg, 0.41 mmol) and acceptor **18** (480 mg, 0.27 mmol) was submitted to the same procedures as described for the preparation of tetrasaccharide alcohol **18**. Flash chromatography (petroleum ether/EtOAc, 4:1) afforded hexasaccharide alcohol **20** (334 mg, 46% from **18**) as a white foam. $[\alpha]_D^{22}$ = −16 (c = 1, chloroform). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.10−6.90 (m, 60 H, 12 Ph), 6.88 (d, J = 7.3 Hz, 1 H, NH), 6.82 (d, J = 7.3 Hz, 1 H, NH), 6.78 (d, J = 6.4 Hz, 1 H, NH), 5.34 (dd, $J_{1,2}$ = 7.8, $J_{2,3}$ = 9.4 Hz, 1 H, GlcA 2-H), 5.30 (dd, $J_{1,2}$ = 7.9, $J_{2,3}$ = 8.0 Hz, 1 H, GlcA 2-H), 5.29 (t, $J_{1,2}$ = $J_{2,3}$ = 7.5 Hz, 1 H, GlcA 2-H), 5.05−4.45 (m, 12 H, 6 CH_2Ph), 5.02 (d, $J_{1,2}$ = 8.5 Hz, 1 H, GalN 1-H), 5.01 (d, $J_{1,2}$ = 8.1 Hz, 1 H, GalN 1-H), 4.85 (d, 1 H, GlcA 1-H), 4.84 (d, 1 H, GlcA 1-H), 4.79 (d, 1 H, GlcA 1-H), 4.78 (d, $J_{1,2}$ = 8.5 Hz, 1 H, GalN 1-H), 4.65 (m, 3 H, GalN 3 3-H), 4.44 (dd, $J_{5,6a}$ = 6.0, $J_{6a,6b}$ = 11.5 Hz, 1 H, GalN 6a-H), 4.32 (m, 2 H, GlcA 2 4-H), 4.10 (m, 5 H, GalN 2 6a-H, 3 6b-H), 4.04−3.92 (m, 7 H, GalN 3 4-H, GlcA 3 4-H, 5-H), 3.77−3.70 (m, 7 H, GalN 2-H, 3 5-H; GlcA 3 3-H), 3.66 (s, 3 H, $COOCH_3$), 3.62 (m, 2 H, GalN 2 2-H), 3.56, 3.54 (2 s, 6 H, 2 $COOCH_3$), 3.42 (s, 3 H, OCH_3), 3.16 (d, J = 2.2 Hz, 1 H, GlcA 4-O*H*). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 169.46, 168.72, 166.13, 165.19, 165.15, 162.49, 162.08, 161.97 (C=O), 138.35−125.39 (Ar_C), 101.40, 101.31, 101.16 (GlcA C-1), 99.41, 98.39, 98.30 (GalN C-1), 92.45, 92.39, 92.12 (CCl_3), 80.87, 79.87, 79.76, 76.19, 75.19, 75.04, 74.87, 74.60, 74.48, 74.37, 74.15, 72.94, 72.83, 72.51, 72.39, 72.31, 72.11 (GlcA 3 C-2, 3 C-3, 3 C-4, 3 C-5; GalN 3 C-3, 3 C-4, 3 C-5, 6 CH_2Ph), 63.12, 62.86, 62.66 (GalN C-6), 57.24 (OCH_3), 56.38, 55.94, 55.84 (GalN C-2), 52.86, 52.83, 52.80 ($COOCH_3$). $C_{132}H_{125}Cl_9N_3O_{41}$ (2687.51): calcd. C 58.10, H 4.65, N 1.56; found C 57.93, H 4.79, N 1.59.

Methyl [Methyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-(4-methoxybenzyl)-β-D-glucopyranosyluronate]-(1→3)-(6-*O*-benzoyl-4-*O*-benzyl-2-deoxy-2-trichloroacetamido-β-D-galactopyranosyl)-(1→4)-(methyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate)-(1→3)-(6-*O*-benzoyl-4-*O*-benzyl-2-deoxy-2-trichloroacetamido-β-D-galactopyranosyl)-(1→4)-(methyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate)-(1→3)-6-*O*-benzoyl-4-*O*-benzyl-2-deoxy-2-trichloroacetamido-β-D-galactopyranoside (21): Alcohol **20** (825 mg, 0.31 mmol) was submitted to the same procedure as described for the preparation of compound **19**. Flash chromatography (toluene/EtOAc, 6:1, containing 0.1% of Et_3N) afforded hexasaccharide **21** (610 mg, 70%) as a white foam. $[\alpha]_D^{22}$ = −15 (c = 1, chloroform). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.10−6.80 (m, 64 H, Ar_H), 6.86, 6.84 (2 d, J = 7.0 Hz, 2 H, NH), 6.76 (d, J = 6.3 Hz, 1 H, NH), 5.39 (dd,

$J_{1,2}$ = 7.5, $J_{2,3}$ = 8.8 Hz, 1 H, GlcA 2-H), 5.29 (dd, $J_{1,2}$ = 7.5, $J_{2,3}$ = 7.9 Hz, 1 H, GlcA 2-H), 5.28 (t, $J_{1,2}$ = $J_{2,3}$ = 7.5 Hz, 1 H, GlcA 2-H), 5.05−4.39 (m, 14 H, 7 CH_2Ph), 5.05 (d, $J_{1,2}$ = 8.5 Hz, 2 H, GalN 2 1-H), 4.84, 4.83, 4.82 (3 d, 3 H, GlcA 3 1-H), 4.76 (d, $J_{1,2}$ = 8.0 Hz, GalN 1-H), 4.65 (m, 3 H, GalN 3 3-H), 4.32−4.25 (m, 8 H, GalN 3 6a-H, 3 6b-H; GlcA 2 4-H), 4.00−3.93 (m, 7 H, GalN 3 4-H; GlcA 4-H, 3 5-H), 3.83 (m, 2 H, GalN 2 5-H), 3.78 (s, 3 H, OCH_3), 3.75−3.70 (m, 5 H, GalN 2-H, 5-H; GlcA 3 3-H), 3.67, 3.65 (2 s, 6 H, 2 COOCH_3), 3.60 (m, 2 H, GalN 2 2-H), 3.54 (s, 3 H, COOCH_3), 3.42 (s, 3 H, OCH_3). $C_{138}H_{132}Cl_9N_3O_{41}$ (2807.66): calcd. C 59.04, H 4.74, N 1.50; found C 58.85, H 4.81, N 1.54.

Methyl [Methyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-(4-methoxybenzyl)-β-D-glucopyranosyluronate]-(1→3)-(2-acetamido-6-*O*-benzoyl-4-*O*-benzyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-(methyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate)-(1→3)-2-acetamido-6-*O*-benzoyl-4-*O*-benzyl-2-deoxy-β-D-galactopyranoside (22): A mixture of trichloroacetamide **19** (577 mg, 0.3 mmol), tributylstannane (0.9 mL, 3.6 mmol), and AIBN (20 mg) in benzene (10 mL) and *N,N*-dimethylacetamide (2.5 mL) was stirred for 30 min at room temperature under a flow of dry argon, and then heated for 2 h at 80 °C, cooled, and concentrated. The residue was stirred at 0 °C with petroleum ether (30 mL), and the resulting solids were filtered off. Flash chromatography (CH_2Cl_2/EtOAc, 2:1→3:2) and crystallization from EtOAc/petroleum ether gave acetamide **22** (350 mg, 68%). M.p. 164−165 °C. $[\alpha]_D^{22}$ = −21 (*c* = 1, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.05−6.80 (m, 44 H, Ar_H), 6.00 (d, *J* = 6.2 Hz, 1 H, NH), 5.38 (d, *J* = 6.0 Hz, 1 H, NH), 5.35 (dd, $J_{1,2}$ = 8.0, $J_{2,3}$ = 8.4 Hz, 1 H, GlcA 2-H), 5.29 (t, $J_{1,2}$ = $J_{2,3}$ = 7.8 Hz, 1 H, GlcA 2-H), 5.05−4.52 (m, 10 H, 5 CH_2Ph), 5.00 (d, $J_{1,2}$ = 8.2 Hz, 1 H, GalN 1-H), 4.80, 4.78 (2 d, 2 H, GlcA 2 1-H), 4.77 (d, $J_{1,2}$ = 8.3 Hz, 1 H, GalN 1-H), 4.70, 4.68 (2 dd, $J_{2,3}$ = 11.0, $J_{3,4}$ = 2.8 Hz, 2 H, GalN 2 3-H), 4.38 (dd, $J_{5,6a}$ = 6.0, $J_{6a,6b}$ = 11.3 Hz, 1 H, GalN 6a-H), 4.26 (dd, $J_{3,4}$ = 7.5, $J_{4,5}$ = 7.0 Hz, 1 H, GlcA 4-H), 4.15 (m, 3 H, GalN 6a-H, 2 6b-H), 4.02 (d, $J_{4,5}$ = 9.0 Hz, 1 H, GlcA 5-H), 4.00 (d, 1 H, GlcA 4-H), 3.99 (dd, $J_{3,4}$ = 0.8 Hz, 1 H, GalN 4-H), 3.94 (m, 2 H, GalN 4-H; GlcA 4-H), 3.82 (dd, $J_{3,4}$ = 8.8 Hz, 1 H, GlcA 3-H), 3.80 (s, 3 H, OCH_3), 3.75 (m, 3 H, GalN 2 5-H; GlcA 3-H), 3.62, 3.57 (2 s, 6 H, 2 COOCH_3), 3.41 (s, 3 H, OCH_3), 3.28, 3.16 (2 m, 2 H, GalN 2 2-H), 1.54, 1.48 (2 s, 6 H, 2 NHCOCH_3). ^{13}C NMR (67.8 MHz, $CDCl_3$), selected data: δ = 102.33, 101.45 (GlcA C-1), 99.68, 98.32 (GalN C-1), 63.25, 62.75 (GalN C-6), 56.85, 55.72 (OCH_3), 55.60, 55.40 (GalN C-2), 52.71, 52.52 (COOCH_3), 23.54, 23.27 (NHCOCH_3). MS (IS): *m/z* = 1732 [M^+ + NH_4]. $C_{95}H_{98}N_2O_{28}$ (1715.79): calcd. C 66.50, H 5.76, N 1.63; found C 66.30, H 5.75, N 1.68.

Methyl [3-*O*-Benzyl-4-*O*-(4-methoxybenzyl)-β-D-glucopyranosyluronic acid]-(1→3)-(2-acetamido-4-*O*-benzyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-(3-*O*-benzyl-β-D-glucopyranosyluronic acid)-(1→3)-2-acetamido-4-*O*-benzyl-2-deoxy-β-D-galactopyranoside (23): A solution of ester **22** (330 mg, 0.19 mmol) in THF (8 mL) was treated at 0 °C with hydrogen peroxide (30 wt% in water, 1 mL) and lithium hydroxide (1 M, 2 mL), and the mixture was stirred for 30 min at 0 °C and for 15 h at room temperature, and was then cooled to 0 °C. Methanol (8 mL) and sodium hydroxide (4 M, 1.5 mL) were then added, and the mixture was stirred for 15 h at room temperature, and was then adjusted to pH 3 (pH meter monitoring) with Amberlite IR-120 (H^+) resin, filtered, and concentrated. Flash chromatography (EtOAc/MeOH, 2:1) gave hydroxy acid **23** (186 mg, 76%) as a white powder. $[\alpha]_D^{22}$ = −12 (*c* = 1, methanol). ^{1}H NMR (500 MHz, CD_3OD): δ = 7.50−6.80 (m, 24 H, Ar_H), 5.10−4.55 (m, 10 H, 5 CH_2Ph), 4.75 (d, $J_{1,2}$ = 8.0 Hz, 1 H, GalN 1-H), 4.46 (d, $J_{1,2}$ = 7.0 Hz, 1 H, GlcA 1-H), 4.42 (d, $J_{1,2}$ = 7.3 Hz, 1 H, GlcA 1-H), 4.38 (d, $J_{1,2}$ = 8.3 Hz, 1 H, GalN 1-H), 4.15 (dd, $J_{2,3}$ = 11.0 Hz, 1 H, GalN 2-H), 4.08 (dd, $J_{3,4}$ = 2.9 Hz, 1 H, GalN 3-H), 4.06 (dd, $J_{4,5}$ = 0.8 Hz, 1 H, GalN 4-H), 4.05 (dd, $J_{2,3}$ = 11.0 Hz, 1 H, GalN 2-H), 4.04 (dd, $J_{3,4}$ = 2.8 Hz, 1 H, GalN 3-H), 4.02 (dd, $J_{4,5}$ = 0.8 Hz, 1 H, GalN 4-H), 3.89−3.83 (m, 4 H, GlcA 2 4-H, 2 5-H), 3.70 (m, 3 H, GalN 6a-H; GlcA 2 3-H), 3.69 (s, 3 H, OCH_3), 3.55 (m, 5 H, GalN 2 5-H, 6a-H, 2 6b-H), 3.46 (dd, $J_{2,3}$ = 8.5 Hz, 1 H, GlcA 2-H), 3.44 (dd, $J_{2,3}$ = 8.6 Hz, 1 H, GlcA 2-H), 3.44 (s, 3 H, OCH_3), 2.08, 2.05 (2 s, 6 H, 2 NHCOCH_3). ^{13}C NMR (67.8 MHz, CD_3OD): selected data, δ = 108.00 (GlcA 2 C-1), 104.58, 101.13 (GalNAc C-1), 63.78, 63.20 (GalNAc C-6), 57.80, 56.45 (OCH_3), 54.17 (GalNAc 2 C-2), 24.64, 24.08 (NHCOCH_3). MS (IS): *m/z* = 1289 [M^+ + NH_4], 1273 [M^+ + H].

Sodium Methyl [Disodium 3-*O*-benzyl-4-*O*-(4-methoxybenzyl)-2-*O*-sulfonato-β-D-glucopyranosyluronate]-(1→3)-(sodium 2-acetamido-4-*O*-benzyl-2-deoxy-6-*O*-sulfonato-β-D-galactopyranosyl)-(1→4)-(disodium 3-*O*-benzyl-2-*O*-sulfonato-β-D-glucopyranosyluronate)-(1→3)-2-acetamido-4-*O*-benzyl-6-*O*-sulfonato-2-deoxy-β-D-galactopyranoside (24): A solution of hydroxy acid **23** (118 mg, 93 μmol) and the sulfur trioxide−trimethylamine complex (258 mg, 1.8 mmol) in anhydrous DMF (1.5 mL) was stirred under dry argon for 60 h at 50 °C, and then allowed to cool. Methanol (1 mL) was then added, and the mixture was concentrated. The residue was eluted from a column of Sephadex LH−20 (CH_2Cl_2/MeOH, 1:1), and then flash chromatographed (EtOAc/MeOH/water, 6:2:1 → 5:2:1) to give the corresponding trimethylammonium salt, which was eluted from a column of Sephadex SP C25 (Na^+) (CH_2Cl_2/MeOH/water, 5:5:1) to afford sodium salt **24** (107 mg, 67%) as a white powder. $[\alpha]_D^{22}$ −14 (*c* = 1, methanol). ^{1}H NMR (500 MHz, CD_3OD): δ = 7.55−6.78 (m, 24 H, Ar_H), 5.16−4.45 (m, 10 H, 5 CH_2Ph), 4.65 (d, $J_{1,2}$ = 8.0 Hz, 1 H, GalN 1-H), 4.64 (d, $J_{1,2}$ = 8.4 Hz, 1 H, GalN 1-H), 4.62 (d, $J_{1,2}$ = 6.8 Hz, 1 H, GlcA 1-H), 4.58 (dd, $J_{2,3}$ = 8.6 Hz, 1 H, GlcA 2-H), 4.50 (d, $J_{1,2}$ = 7.6 Hz, 1 H, GlcA 1-H), 4.48 (dd, $J_{2,3}$ = 8.5 Hz, 1 H, GlcA 2-H), 4.25−4.20 (m, 3 H, GalN 2 6a-H, 6b-H), 4.18 (dd, $J_{3,4}$ = 3.0, $J_{4,5}$ = 0.8 Hz, 1 H, GalN 4-H), 4.16 (m, 3 H, GalN 4-H, 6b-H; GlcA 5-H), 4.09 (m, 3 H, GalN 2 3-H; GlcA 5-H), 3.96−3.92 (m, 3 H, GlcA 3-H, 2 4-H), 3.91−3.86 (m, 4 H, GalN 2 2-H, 5-H; GlcA 3-H), 3.75 (m, 1 H, GalN 5-H), 3.75, 3.47 (2 s, 6 H, 2 OCH_3), 2.10, 2.06 (2 s, 6 H, 2 NHCOCH_3). ^{13}C NMR (67.8 MHz, CD_3OD), selected data: δ = 104.58, 104.36 (GlcA C-1), 103.21, 102.73 (GalNAc C-1), 68.59, 67.81 (GalNAc C-6), 58.06, 56.45 (OCH_3), 54.81, 54.60 (GalNAc C-2), 24.68, 24.32 (NHCOCH_3). $C_{65}H_{74}N_2Na_6O_{26}S_4$ (1725.47): calcd. C 45.25, H 4.32, N 1.62; found C 44.95, H 4.51, N 1.52.

Methyl [Methyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-(4-methoxybenzyl)-β-D-glucopyranosyluronate]-(1→3)-(2-acetamido-6-*O*-benzoyl-4-*O*-benzyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-(methyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate)-(1→3)-(2-acetamido-6-*O*-benzoyl-4-*O*-benzyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-(methyl 2-*O*-benzoyl-3-*O*-benzyl-β-D-glucopyranosyluronate)-(1→3)-2-acetamido-6-*O*-benzoyl-4-*O*-benzyl-2-deoxy-β-D-galactopyranoside (25): A mixture of trichloroacetamide **21** (184 mg, 66 μmol), tributylstannane (0.32 mL, 0.84 mmol), and AIBN (40 mg) in *N,N*-dimethylacetamide (3 mL) was submitted to the same procedure as described for the preparation of acetamide **22**. Flash chromatography (CH_2Cl_2/MeOH, 30:1) afforded acetamide **25** (132 mg, 81%) as a white foam. $[\alpha]_D^{22}$ = −19 (*c* = 1, chloroform). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.10−6.80 (m, 64 H, Ar_H), 5.96, 5.64 (2 d, *J* = 6.8 Hz, 2 H, NH), 5.39 (d, *J* = 6.7 Hz, 1 H, NH), 5.36 (dd, $J_{1,2}$ = 7.5, $J_{2,3}$ = 9.0 Hz, 1 H, GlcA 2-H), 5.34 (dd, $J_{1,2}$ = 7.5,

$J_{2,3}$ = 8.0 Hz, 1 H, GlcA 2-H), 5.30 (t, $J_{1,2}$ = $J_{2,3}$ = 7.5 Hz, 1 H, GlcA 2-H), 5.05−4.50 (m, 14 H, 7 CH_2Ph), 5.00, 4.98 (2 d, $J_{1,2}$ = 8.0 Hz, 2 H, GalN 2 1-H), 4.84, 4.80, 4.78 (3 d, 3 H, GlcA 3 1-H), 4.75 (d, $J_{1,2}$ = 8.0 Hz, 1 H, GalN 1-H), 4.65 (m, 3 H, GalN 3 3-H), 4.37 (dd, $J_{5,6a}$ = 6.0, $J_{6a,6b}$ = 11.5 Hz, 1 H, GalN 6a-H), 4.20 (m, 5 H, GalN 2 6a-H, 3 6b-H), 4.15 (m, 2 H, GlcA 2 4-H), 4.07 (m, 2 H, GlcA 4-H, 5-H), 4.02 (m, 2 H, GalN 2 4-H), 3.98−3.94 (m, 3 H, GalN 4-H; GlcA 2 5-H), 3.78 (s, 3 H, OCH_3), 3.75 (m, 3 H, GalN 3 5-H), 3.70 (m, 3 H, GalN 3 3-H), 3.60, 3.55, 3.54 (3 s, 9 H, 3 COOCH_3), 3.40 (s, 3 H, OCH_3), 3.30, 3.26, 3.16 (3 m, $J_{2,3}$ = 11.0 Hz, 3 H, GalN 3 2-H), 1.54, 1.50, 1.48 (3 s, 9 H, 3 NHCOCH_3). ^{13}C NMR (67.8 MHz, $CDCl_3$), selected data: δ = 102.20, 101.61, 101.41 (GlcA C-1), 99.75, 98.47, 98.33 (GalN C-1), 63.12, 62.72, 62.57 (GalN C-6), 56.75 (OCH_3), 55.39, 55.28, 55.13 (GalN C-2, OCH_3), 52.59, 52.41 (COOCH_3), 23.26, 23.17 (NHCOCH_3). MS (IS): *m/z* = 2515 [M^+ + NH_4]. $C_{138}H_{141}N_3O_{41}$ (2497.62): calcd. C 66.36, H 5.69, N 1.68; found C 66.08, H 5.67, N 1.76.

Methyl [3-*O*-Benzyl-4-*O*-(4-methoxybenzyl)-β-D-glucopyranosyluronic acid]-(1→3)-(2-acetamido-4-*O*-benzyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-(3-*O*-benzyl-β-D-glucopyranosyluronic acid)-(1→3)-(2-acetamido-4-*O*-benzyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-(3-*O*-benzyl-β-D-glucopyranosyluronic acid)-(1→3)-2-acetamido-4-*O*-benzyl-2-deoxy-β-D-galactopyranoside (26): Ester **25** (230 mg, 92 μmol) was submitted to the same procedure as described for the preparation of hydroxy acid **23**. Flash chromatography (EtOAc/MeOH, 3:2→1:1) afforded hydroxy acid **26** (140 mg, 80%) as a white powder. $[\alpha]_D^{22}$ = −12 (*c* = 1, methanol). ^{1}H NMR (500 MHz, CD_3OD): δ = 7.50−6.70 (m, 34 H, Ar_H), 5.12−4.50 (m, 14 H, 7 CH_2Ph), 4.78, 4.52 (2 d, $J_{1,2}$ = 8.0 Hz, 2 H, GalN 2 1-H), 4.48, 4.45, 4.44 (3 d, $J_{1,2}$ = 7.5 Hz, 3 H, GlcA 3 1-H), 4.38 (d, $J_{1,2}$ = 8.0 Hz, 1 H, GalN 1-H), 4.15 (m, 3 H, GalN 3 2-H), 4.10−4.00 (m, 6 H, GalN 3 3-H, 3 4-H), 3.90−3.80 (m, 6 H, GlcA 3 4-H, 3 5-H), 3.78−3.65 (m, 6 H, GalN 3 6a-H, 3 6b-H), 3.74 (s, 3 H, OCH_3), 3.55 (m, 6 H, GalN 3 5-H; GlcA 3 3-H), 3.46 (s, 3 H, OCH_3), 3.40−3.35 (m, 3 H, GlcA 3 2-H), 2.08, 2.07, 1.99 (3 s, 9 H, 3 NHCOCH_3). ^{13}C NMR (67.8 MHz, CD_3OD): selected data, δ = 107.71, 107.28, 107.10 (GlcA C-1), 106.33, 104.54, 104.43 (GalNAc C-1), 63.70, 63.49, 63.29 (GalNAc C-6), 57.84, 56.48 (OCH_3), 54.12 (GalNAc 3 C-2), 24.76, 24.63, 24.11 (NHCOCH_3). MS (IS): *m/z* = 1848 [M^+ + NH_4].

Sodium Methyl [Disodium 3-*O*-benzyl-4-*O*-(4-methoxybenzyl)-2-*O*-sulfonato-β-D-glucopyranosyluronate]-(1→3)-(sodium 2-acetamido-4-*O*-benzyl-2-deoxy-6-*O*-sulfonato-β-D-galactopyranosyl)-(1→4)-(disodium 3-*O*-benzyl-2-*O*-sulfonato-β-D-glucopyranosyluronate)-(1→3)-(sodium 2-acetamido-4-*O*-benzyl-2-deoxy-6-*O*-sulfonato-β-D-galactopyranosyl)-(1→4)-(disodium 3-*O*-benzyl-2-*O*-sulfonato-β-D-glucopyranosyluronate)-(1→3)-2-acetamido-4-*O*-benzyl-6-*O*-sulfonato-2-deoxy-β-D-galactopyranoside (27): Hydroxy acid **26** was submitted to the same procedure as described for the preparation of sulfated compound **24** to afford sodium salt **27** (104 mg, 54%) as a white powder. $[\alpha]_D^{22}$ = −14 (*c* = 1, methanol). ^{1}H NMR (500 MHz, CD_3OD): δ = 7.50−6.70 (m, 34 H, Ar_H), 5.15−4.40 (m, 14 H, 7 CH_2Ph), 4.55, 4.53, 4.50 (3 d, $J_{1,2}$ = 8.0 Hz, 3 H, GalN 3 1-H), 4.46 (m, 2 H, GlcA 1-H, 2-H), 4.35 (m, 4 H, GlcA 2 1-H, 2 2-H), 4.25−4.15 (m, 6 H, GalN 3 6a-H, 3 6b-H), 4.12−4.05 (m, 9 H, GalN 3 3-H, 3 4-H; GlcA 3 5-H), 3.90 (m, 3 H, GlcA 3 4-H), 3.85−3.75 (m, 9 H, GalN 3 2-H, 3 5-H; GlcA 3 3-H), 3.74, 3.46 (2 s, 6 H, 2 OCH_3), 2.08, 2.07, 2.04 (3 s, 9 H, 3 NHCOCH_3). ^{13}C NMR (67.8 MHz, CD_3OD): selected data, δ = 104.52, 104.29, 103.76, 103.22, 103.11 (GlcA C-1, GalNAc C-1), 68.57, 67.80, 67.71 (GalNAc C-6), 58.02, 56.45 (OCH_3), 54.69, 54.62, 54.55 (GalNAc C-2), 24.75, 24.68, 24.33 (NHCOCH_3). $C_{93}H_{102}N_3Na_9O_{53}S_6$ (2509.10): calcd. C 44.52, H 4.10, N 1.67; found C 44.23, H 4.28, N 1.57.

Sodium Methyl (Disodium 2-*O*-sulfonato-β-D-glucopyranosyluronate)-(1→3)-(sodium 2-acetamido-2-deoxy-6-*O*-sulfonato-β-D-galactopyranosyl)-(1→4)-(disodium 2-*O*-sulfonato-β-D-glucopyranosyluronate)-(1→3)-2-acetamido-2-deoxy-6-*O*-sulfonato-β-D-galactopyranoside (1): A solution of benzyl ether **24** (80 mg, 46 μmol) in MeOH/water (5:1, 3 mL) was hydrogenolyzed in the presence of 10% Pd−C catalyst (50 mg) for 24 h at room temperature. More water (2 mL) was then added, and the mixture was hydrogenated for further 24 h. The catalyst was removed by filtration through a Celite pad, and the filtrate was concentrated. The residue was eluted from a column of Sephadex LH-20 with water and lyophilized to give target compound **1** (54 mg, 93%) as a hygroscopic, white foam. $[\alpha]_D^{22}$ = −5 (*c* = 1, water). ^{1}H NMR (500 MHz, D_2O, intern. H_2O): δ = 4.74 (d, $J_{1,2}$ = 7.3 Hz, 1 H, GlcA 1-H), 4.73 (d, $J_{1,2}$ = 7.0 Hz, 1 H, GlcA 1-H), 4.58 (d, $J_{1,2}$ = 8.0 Hz, 1 H, GalN 1-H), 4.48 (d, $J_{1,2}$ = 8.1 Hz, 1 H, GalN 1-H), 4.26−4.17 (m, 6 H, GalN 2 4-H, 2 6a-H, 2 6b-H), 4.13 (dd, $J_{2,3}$ = 8.2 Hz, 1 H, GlcA 2-H), 4.08 (dd, $J_{2,3}$ = 8.0 Hz, 1 H, GlcA 2-H), 3.96−3.87 (m, 8 H, GalN 2 2-H, 2 3-H, 2 5-H; GlcA 2 5-H), 3.81 (m, 2 H, GlcA 2 4-H), 3.72 (dd, $J_{3,4}$ = 9.0 Hz, 1 H, GlcA 3-H), 3.58 (dd, $J_{3,4}$ = 8.0 Hz, 1 H, GlcA 3-H), 3.48 (s, 3 H, OCH_3), 2.03 (s, 6 H, NHCOCH_3). ^{13}C NMR (67.8 MHz, D_2O, intern. acetone): δ = 103.03, 101.72 (GalNAc C-1), 102.26, 102.81 (GlcA C-1), 80.44, 80.24, 80.06 (GalNAc 2 C-3, 2 GlcA 2 C-2), 75.23 (GlcA 2 C-3), 73.40 (GlcA C-4), 73.14, 72.97 (GalNAc C-5), 72.11 (GlcA *C*-4), 68.30, 67.87 (GalNAc C-6), 57.78 (OCH_3), 51.61, 51.35 (GalNAc C-2), 23.08, 22.87 (NHCOCH_3). $C_{29}H_{42}N_2Na_6O_{35}S_4$ (1244.84): calcd. C 27.98, H 3.40, N 2.25; found C 27.65, H 3.58, N 2.10.

Sodium Methyl (Disodium 2-*O*-sulfonato-β-D-glucopyranosyluronate)-(1→3)-(sodium 2-acetamido-2-deoxy-6-*O*-sulfonato-β-D-galactopyranosyl)-(1→4)-(disodium 2-*O*-sulfonato-β-D-glucopyranosyluronate)-(1→3)-(sodium 2-acetamido-2-deoxy-6-*O*-sulfonato-β-D-galactopyranosyl)-(1→4)-(disodium 2-*O*-sulfonato-β-D-glucopyranosyluronate)-(1→3)-2-acetamido-2-deoxy-6-*O*-sulfonato-β-D-galactopyranoside (2): Benzyl ether **27** (100 mg, 40 μmol) was submitted to the same procedure as described for the preparation of compound **1,** to afford the target hexasaccharide **2** (50 mg, 68%) as a hygroscopic, white foam. $[\alpha]_D^{22}$ = −8 (*c* = 1, water). ^{1}H NMR (500 MHz, D_2O, intern. H_2O): δ = 4.77 (d, $J_{1,2}$ = 7.5 Hz, 1 H, GlcA 1-H), 4.75 (d, $J_{1,2}$ = 8.0 Hz, 1 H, GalN 1-H), 4.74 (d, $J_{1,2}$ = 7.5 Hz, 1 H, GlcA 1-H), 4.72 (d, $J_{1,2}$ = 7.5 Hz, 1 H, GlcA 1-H), 4.60 (d, $J_{1,2}$ = 8.0 Hz, 1 H, GalN 1-H), 4.48 (d, $J_{1,2}$ = 8.1 Hz, 1 H, GalN 1-H), 4.25−4.17 (m, 9 H, GalN 3 4-H, 3 6a-H, 3 6b-H), 4.12−4.05 (m, 3 H, GlcA 3 2-H), 3.97−3.78 (m, 16 H, GalN 3 2-H, 3 3-H, 3 5-H; GlcA 3 3-H, 4-H, 3 5-H), 3.75, 3.64 (2 t, $J_{3,4}$ = $J_{4,5}$ = 9.0 Hz, 2 H, GlcA 2 4-H), 3.48 (s, 3 H, OCH_3), 2.03 (br. s, 9 H, 3 NHCOCH_3). ^{13}C NMR (67.8 MHz, D_2O, intern. acetone): δ = 103.04, 102.30, 101.83 (GlcA 3 C-1, GalNAc 3 C-1), 80.24, 80.04, 79.92 (GalNAc 3 C-3, GlcA 3 C-2), 75.25 (GlcA 3 C-3), 73.50, 73.43, 73.15, 72.98 (GlcA 2 C-4, GalNAc 3 C-5), 72.10 (GlcA C-4), 67.94, 67.84, 67.65 (GalNAc C-6), 57.77 (OCH_3), 51.65, 51.39 (GalNAc 3 C-2), 23.41, 23.12 (3 NHCOCH_3). $C_{43}H_{58}N_3Na_9O_{52}S_6$ (1848.21): calcd. C 27.94, H 3.16, N 2.27; found C 27.61, H 3.28, N 2.08.

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[1] L. Å. Fransson, *Trends Biochem. Sci.* **1987**, *12*, 406−411.
[2] R. U. Margolis, R. K. Margolis, *Cell Tissues Rev.* **1997**, *290*, 343−348.
[3] H. B. Nader, T. M. Ferreira, J. F. Paiva, M. G. Medeiros, S. M. Jeronimo, V. M. Paiva, C. P. Dietrich, *J. Biol. Chem.* **1984**, *259*, 1431−1435.
[4] K. Sugahara, S. Yamada, *Trends Glycosci. Glycotechnol.* **2000**, *12*, 321−349.
[5] K. Sugahara, Y. Tanaka, S. Yamada, *Glycoconjugate J.* **1996**, *13*, 609−619.
[6] K. Sugahara, S. Nadanaka, K. Takeda, T. Kojima, *Eur. J. Biochem.* **1996**, *239*, 871−880.
[7] A. Lee, R. Sanger, *Science* **1983**, *221*, 1185−1187.
[8] J. R. Shen, C. C. Fu, M. L. Tsai, W. J. Chung, *Anticancer Res.* **1998**, *18*, 4435−4441.
[9] P. Berbari, A. Thibodeau, L. Germain, M. Saint-Cyr, P. Gaudreau, S. El-Khouri, E. Dupont, D. R. Garrel, *J. Surg. Res.* **1999**, *87*, 108−113.
[10] D. Gingras, A. Renaud, N. Mousseau, R. Beliveau, *Cancer Metastasis Rev.* **2000**, *19*, 83−86.
[11] A. D. Lander, *Current Opin. Neurobiol.* **1993**, *3*, 716−723.
[12] S. Nadanaka, A. Clement, K. Masayama, A. Faissner, K. Sugahara, *J. Biol. Chem.* **1998**, *273*, 3296−3307.
[13] C. A. A. van Boeckel, M. Petitou, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1671−1690.
[14] J. Tamura, K. W. Neumann, S. Kuruno, T. Ogawa, *Carbohydr. Res.* **1998**, *305*, 43−63.
[15] F. Bélot, J.-C. Jacquinet, *Carbohydr. Res.* **2000**, *326*, 88−97.
[16] J.-C. Jacquinet, *Abstracts of Papers*, XXth Intern. Carbohydr. Symp., Hamburg, August **2000**, *B−118*, p. 117.
[17] N. Karst, J.-C. Jacquinet, *J. Chem. Soc., Perkin Trans. 1* **2000**, 2709−2717.
[18] A. Lubineau, D. Bonnaffé, *Eur. J. Org. Chem.* **1999**, 2523−2532.
[19] G. Blatter, J.-M. Beau, J.-C. Jacquinet, *Carbohydr. Res.* **1994**, *260*, 189−202.
[20] G. Blatter, J.-C. Jacquinet, *Carbohydr. Res.* **1996**, *288*, 109−125.
[21] C. Coutant, J.-C. Jacquinet, *J. Chem. Soc., Perkin Trans. 1* **1995**, 1573−1581.
[22] R. R. Schmidt, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 212−235.
[23] N. J. Davis, S. L. Flitsch, *J. Chem. Soc., Perkin Trans. 1* **1994**, 359−368.
[24] D. Magaud, C. Grandjean, A. Doutheau, D. Anker, V. Schevchik, N. Cotte-Pattat, J. Robert-Baudouy, *Carbohydr. Res.* **1998**, *314*, 189−199.
[25] F. Bélot, J.-C. Jacquinet, *Carbohydr. Res.* **2000**, *325*, 93−106.
[26] R. Albert, K. Dax, R. W. Link, A. E. Stutz, *Carbohydr. Res.* **1983**, *118*, c5−c6.
[27] N. Karst, Ph.D. Dissertation, Univ. of Orléans, **2001**.
[28] V. J. Patil, *Tetrahedron Lett.* **1996**, *37*, 1481−1484.
[29] H. Lucas, J. E. M. Basten, T. G. Van Dinther, J. G. Meuleman, S. F. Van Aelst, C. A. A. Van Boeckel, *Tetrahedron* **1990**, *46*, 8207−8228.
[30] J.-C. Jacquinet, *Carbohydr. Res.* **1990**, *199*, 153−181.
[31] A. Mucci, L. Schenetti, N. Volpi, *Carbohydr. Polym.* **2000**, *41*, 37−45.

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