ELSEVIER

Carbohydrate Research 337 (2002) 673–689

CARBOHYDRATE RESEARCH

www.elsevier.com/locate/carres

An access to various sulfation patterns in dermatan sulfate: chemical syntheses of sulfoforms of trisaccharide methyl glycosides

Nadine Barroca, Jean-Claude Jacquinet*

Institut de Chimie Organique et Analytique, UFR Faculté des Sciences, UMR CNRS 6005, Université d'Orléans, BP 6759, F-45067 Orléans, France

Received 10 January 2002; accepted 15 February 2002

Abstract

The syntheses are reported for the first time of α-L-Ido*p*A2SO$_3$-(1→3)-β-D-Gal*p*NAc4SO$_3$-(1→4)-α-L-Ido*p*A2SO$_3$-(1→OMe), its disulfated analogue α-L-Ido*p*A2SO$_3$-(1→3)-β-D-Gal*p*NAc-(1→4)-α-L-Ido*p*A2SO$_3$-(1→OMe), and of β-D-Gal*p*NAc4SO$_3$-(1→4)-α-L-Ido*p*A2SO$_3$-(1→3)-β-D-Gal*p*NAc4SO$_3$-(1→OMe), which represent structural fragments of dermatan sulfate, unavailable directly by chemical or enzymatic degradation of the glycosaminoglycan polymer. These molecules were readily obtained from a pair of key disaccharide intermediates, in which the relative difference of stability of the D-GalNAc 4-hydroxy protecting groups (acetate or pivalate) toward saponification conditions allowed access to various sulfoforms from a common precursor. For the preparation of these blocks, the 4-*O*-pivaloyl-D-*galacto* moiety was readily obtained through a one-pot stereospecific intramolecular nucleophilic displacement on an easily available 3-*O*-pivaloyl-D-*gluco* precursor, and the L-IdoA moiety through selective radical oxidation at C-6 of a L-ido 4,6-diol derivative with oxoammonium salts.

Keywords: Dermatan sulfate trisaccharides; Sulfoforms; Glycosylation reactions; 2-Deoxy-2-trichloroacetamido-D-*galacto* derivatives

1. Introduction

Dermatan sulfate (DS) belongs to the proteoglycan family, and is found in a wide variety of animal tissues. It is a microheterogeneous, polydisperse, linear copolymer composed of disaccharide repeating units of 2-acetamido-2-deoxy-D-galactose (D-Gal*p*NAc) and of L-iduronic acid (L-Ido*p*A) or D-glucuronic acid (D-Glc*p*A), with sulfate groups most commonly present at C-4 of D-GalNAc and occasionally at C-2 of L-IdoA residues, but other sulfation patterns depending on its origin are known. The most studied biological activities of DS are its anticoagulant[1] and antithrombotic[2] properties, where it displays less hemorragic effects than heparin.[3] But many other implications of DS in important biological processes, even if still poorly understood at the molecular level, are known, such as its potent mediator effect of fibroblast growth factor-2 (FGF-2) responsiveness,[4] its possible anti-oncogenic role,[5] or its interaction of high specificity to hepatocyte growth factor.[6]

Homogeneous, structurally characterized DS fragments might be useful for a better understanding of these biological properties and of the specificity of enzymes acting on DS. Such compounds are not easily accessible by enzymatic or chemical degradation of the polymer, and have generally to be chemically synthesized. To date, several syntheses of DS fragments having an even number of saccharide residues have been reported, such as those of disaccharide derivatives having D-GalNAc[7–9] or L-IdoA[10] residues at the reducing end, or of an hexasaccharide,[11,12] the postulated minimal sequence[1] binding to heparin co-factor II (HCII). Recently, tri- and pentasaccharide fragments exclusively sulfated at C-4 of the D-GalNAc residues were obtained by controlled depolymerization of porcine intestinal mucosal DS using chondroitinase ABC, and removal of the Δ4,5-unsaturated nonreducing L-IdoA residue with mercuric acetate.[13]

The current study describes, for the first time, a versatile approach to various sulfoforms of DS trisac-

* Corresponding author. Tel.: +33-238-417072; fax: +33-238-417281.

E-mail address: jean-claude.jacquinet@univ-orleans.fr (J.-C. Jacquinet).

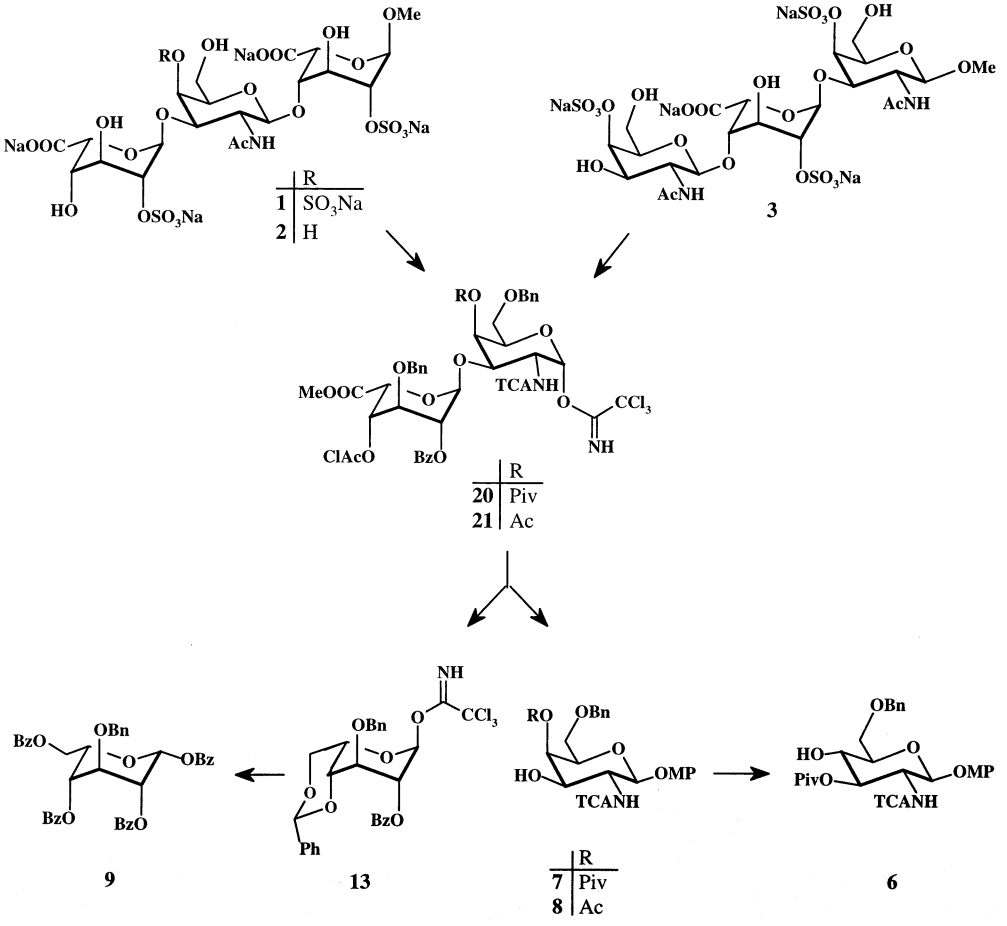
0008-6215/02/$ - see front matter
PII: S0008-6215(02)00060-5

charide derivatives having either L-IdoA (**1**, **2**) or D-GalNAc (**3**) residues at the reducing end (Scheme 1). All compounds were prepared as their methyl glycosides, with the same anomeric configuration as in the natural polymer, in which the methyl group was introduced as a marker for NMR studies. Such molecules are not only useful for the studies of interactions with biologically important proteins, but also for a better understanding of DS biosynthesis, and particularly for the characterization of the specific GalNAc 4-*O*-sulfotransferase.[14]

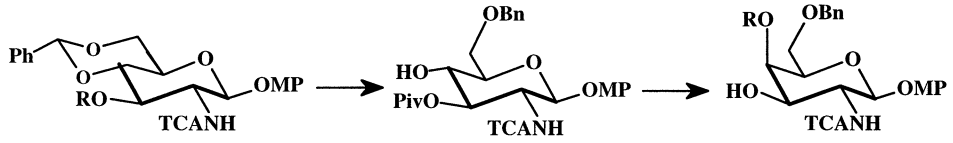
2. Results and discussion

As far as DS fragments contain sulfate esters, the usual strategy[8–12] for their chemical synthesis is to temporarily protect the hydroxy groups which would carry these substituents with ester groups, and those which should remain free with permanent benzyl ethers. Generally, all ester groups, regardless of their nature, are removed at the same time, without seeking for a possible selective removal. Pivaloyl ester is known to be much more resistant to basic conditions[15,16] than are other ester groups (i.e., acetate or benzoate). It is also an excellent candidate for intramolecular nucleophilic displacement reactions leading to inversion of configuration on sugar carbons such as in D-gluco → D-galacto transformations.[17] Thus, its use as a temporary protection at O-4 of D-GalNAc residues might allow to prepare the corresponding 4-sulfate or 4-OH species from a common precursor. But care has to be taken in order to ensure complete removal of this group at the final deprotection step.[16] Consequently, for the syntheses of the target trisaccharide derivatives **1**–**3**, a couple of key disaccharide intermediates (**20**, **21**) were designed, which may, in turn, be bond-disconnected into a glycosyl donor (**13**), and a pair of D-galacto glycosyl acceptors (**7**, **8**) readily obtained from a common precursor (**6**) having the D-gluco configuration (Scheme 1).

Preparation of acceptors **7** and **8** was achieved in a straightforward manner as follows (Scheme 2). Pivaloylation of easily available 4-methoxyphenyl 4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (**4**)[10] gave the crystalline ester **5** in 82% yield. Regioselective reductive cleavage of the benzylidene acetal in **5** with triethylsilane and trifluoroacetic acid[18] afforded the alcohol **6** in 91% yield. It is worth noting



Scheme 1.



	R
4	H
5	Piv

6

	R
7	Piv
8	Ac

Scheme 2.

that direct reductive cleavage on alcohol **4**, followed by regioselective pivaloylation at O-3 of the intermediate proceeded with lower stereospecificity and overall yield. One-pot inversion of configuration with concomitant protection at C-4 was readily achieved by treatment of **6** with triflic anhydride and pyridine in 1,2-dichloroethane at −15 °C, followed by in situ addition of water,[17] and heating at 80 °C to give, via the corresponding 3,4-hemiorthoester intermediate, the 4-*O*-pivaloyl-D-*galacto* acceptor **7** in 82% overall yield, the structure of which was easily deduced from its ^{1}H NMR spectrum (Table 1). With the aim of avoiding deprotection problems with the pivaloyl groups at the end of the syntheses, the 4-*O*-acetyl analogue **8** was prepared, at least as a spare derivative. Thus, Zemplèn transesterification of **7** gave the corresponding diol, which was directly treated with trimethyl orthoacetate and 10-D,L-camphorsulfonic acid in toluene to give the 3,4-orthoester intermediate, which was, in turn, regioselectively opened[19] in acidic medium to give the crystalline acceptor **8** in 86% yield.

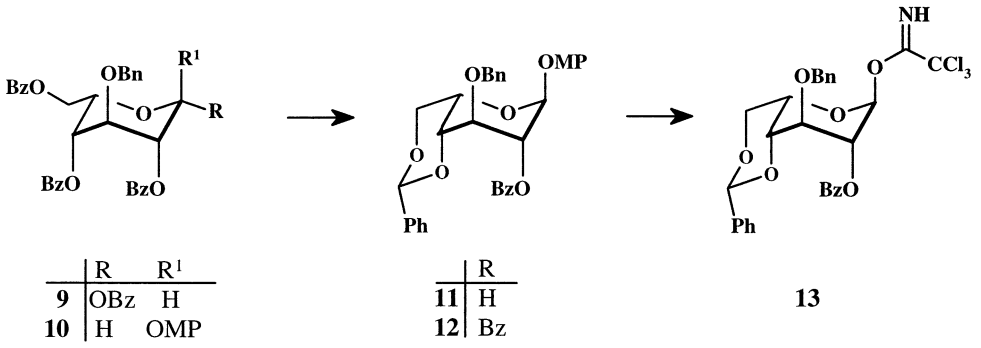
The L-ido donor **13** was then prepared as follows (Scheme 3). Treatment of known[10] 1,2,4,6-tetra-*O*-benzoyl-3-*O*-benzyl-β-L-idopyranose (**9**) with 4-methoxyphenol in dichloromethane, and in the presence of trimethylsilyl triflate (1 equiv), afforded glycoside **10** in nearly quantitative yield, the anomeric configuration of which was deduced from its ^{1}H NMR spectrum (Table 2). Transesterification of **10**, followed by treatment with benzaldehyde and trifluoroacetic acid gave the crystalline 4,6-*O*-benzylidene derivative **11** in 84% yield, which was readily benzoylated to give the crystalline ester **12** in 94% yield. Oxidative removal of the 4-methoxyphenyl anomeric group in **12** with ceric ammonium nitrate, followed by trichloroacetimidoylation with trichloroacetonitrile and 1,8-diazabicyclo[5,4,0]-undec-7-ene (DBU) gave the crystalline α-imidate **13** in 54% overall yield, the structure of which was evident from its ^{1}H NMR spectrum (Table 2).

Preparation of the key intermediates **20** and **21** was next studied (Scheme 4). Condensation of **7** and **8** with a moderate excess (1.1 equiv) of **13**, in dichloromethane at 0 °C, in the presence of trimethylsilyl triflate, afforded readily the α-linked disaccharide derivatives **14** and **15** in 78 and 79% yields, respectively. The ^{1}H NMR spectra for **14** and **15** (Table 3) are in agreement with the expected structures, and show, for the L-ido moieties, a significant staggering from the $^1C_4$ conformation observed for monomers **9**–**13**. Treatment of **14** and **15** with aqueous acetic acid at 100 °C afforded the corresponding $4^{II},6^{II}$-diols, on which regioselective oxidation at C-6 without protection at C-4 was attempted. Selective oxidation of primary alcohol in sugar 4,6-diol by using the oxyammonium ion-catalyzed procedure under phase-transfer conditions has been reported,[20,21] and was successfully applied in our group for the preparation of D-glucuronic acid derivatives in the synthesis of chondroitin sulfate D oligosaccharides.[22] However, frustrating results were obtained starting from L-ido derivatives,[20] as was the case with the diols derived from **14** and **15**. Nevertheless, when these diols were treated at 0 °C with a catalytic amount of 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical (TEMPO), in the presence of stable calcium hypochlorite[21] as a co-

Table 1
^{1}H NMR data: carbohydrate ring protons for monosaccharide derivatives **5**–**8** [a]

Proton	**5**	**6**	**7**	**8**
H-1	4.90	5.00	5.20	5.17
$J_{1,2}$	8.4	8.2	8.5	8.4
H-2	4.50	4.28	3.91	3.98
$J_{2,3}$	10.3	10.7	11.2	10.9
H-3	5.61	5.43	4.36	4.36
$J_{3,4}$	9.8	8.8	3.5	3.5
H-4	3.63	3.82	5.40	5.42
$J_{4,5}$	9.8	9.7	0.9	0.9
H-5	3.50	3.79	3.97	3.93
$J_{5,6a}$	5.0		6.3	6.3
$J_{5,6b}$	9.3		6.3	6.3
H-6a	3.77	3.79	3.64	3.62
$J_{6a,6b}$			−10.2	
H-6b	3.77	3.79	3.59	3.62
NH	7.05	7.25	6.94	7.00
$J_{2,NH}$	9.2	9.4	7.3	7.4

[a] Chemical shifts (δ, ppm) and coupling constants (J, in Hz) for solutions in $CDCl_3$.



	R	R1
9	OBz	H
10	H	OMP

	R
11	H
12	Bz

Scheme 3.

oxidant and sodium hydrogencarbonate, in homogenous[23] medium (acetonitrile–water), the corresponding hydroxy-acid, sodium salts, thus obtained were directly esterified with methyl iodide in *N*,*N*-dimethylformamide at 50 °C to afford the methyl esters **16** and **18** in 63 and 66% overall yields, respectively. The ^{1}H NMR spectra for **16** and **18** (Table 3) are in agreement with the expected structures, and show, for the L-IdoA residues, long-range coupling constants ($J_{1,3}$ and $J_{2,4} \sim 1.0$ Hz), indicating a high proportion of $^1C_4$ conformation in solution. It is to be noted that such a reaction works well on disaccharide units, and should be applied for the synthesis of glycosaminoglycan disaccharide derivatives. Conventional chloroacetylation at O-4^{II} on **16** and **18** gave the esters **17** and **19** in 85 and 91% yields, respectively, which were submitted to oxidative cleavage of the 4-methoxyphenyl glycoside followed by trichloroacetimidoylation, as reported above for the preparation of **13**, to give the key α-trichloroacetimidates **20** and **21** in 55 and 58% overall yields, respectively, the anomeries of which were deduced from their ^{1}H NMR spectra (Table 3).

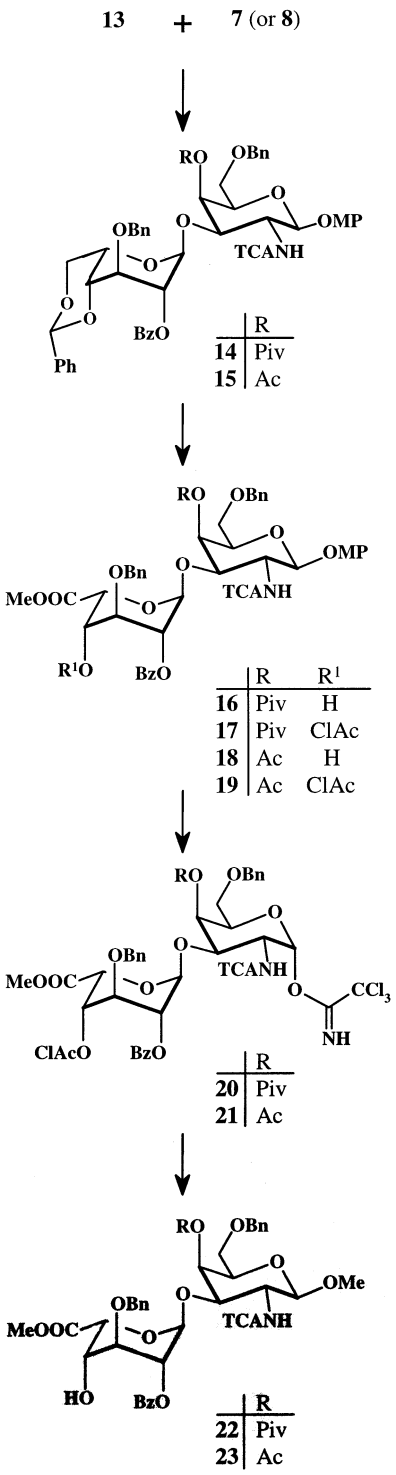
These versatile intermediates, ready to be used for chain-extension at their reducing end, could be easily transformed into a pair of glycosyl acceptors, ready for further coupling at their nonreducing end. Methyl glycosylation of **20** and **21** with methanol, in dichloromethane at room temperature, and in the presence of trimethylsilyl triflate, provided the corresponding methyl β-D-glycoside derivatives, which were submitted to selective *O*-dechloroacetylation by treatment with thiourea in pyridine and ethanol to give the alcohols **22** and **23** in 77 and 79% overall yields, respectively. In these glycosylation reactions, no methyl α-D-glycoside species were isolated, thus showing the excellent stereocontrolling ability of the 2-deoxy-2-trichloroacetamido group[24] which is able to lead stereoselectively to 1,2-trans glycosides with highly reactive alcohol (i.e., methanol) as well as with low-reactive hydroxy groups in sugar derivatives.[17]

Syntheses of the sulfated trisaccharide derivatives **1** and **2**, having an L-IdoA residue at the reducing end, were then achieved as follows (Scheme 5). Condensation of imidate **20** with the known[10] methyl (methyl 2-*O*-benzoyl-3-*O*-benzyl-α-L-idopyranosid)uronate (**24**) (1.5 equiv), in dichloromethane at −15 °C, and in the presence of trimethylsilyl triflate, gave the β-linked trisaccharide derivative **25** in 61% yield. The ^{1}H NMR spectrum for **25** (Table 4) shows a signal at δ 4.86 ppm with a large coupling constant ($J_{1,2}$ 8.4 Hz), in agreement with a newly established 1,2-trans interglycosidic linkage. According to the initial strategy, protection at O-4 of the nonreducing L-IdoA residue by an orthogonal (hydrogenolizable) protecting group was required. To this end, ester **25** was *O*-dechloroacetylated to give the corresponding alcohol, which is available for further chain-extension at its nonreducing end. This intermediate was treated with 4-methoxyphenyl trichloroacetimidate[25] in dichloromethane, in the presence of trimethylsilyl triflate, to give the fully protected

Table 2
^{1}H NMR data: carbohydrate ring protons for monosaccharide derivatives **10**–**13** [a]

Proton	10	11	12	13
H-1	5.71	5.64	5.76	6.54
$J_{1,2}$	1.1	1.0	1.1	1.0
$J_{1,3}$	1.1	0.9	1.0	1.0
H-2	5.47	4.10	5.49	5.43
$J_{2,3}$	2.2	2.6	2.3	2.6
$J_{2,4}$	1.1	1.0	0.9	0.9
H-3	4.18	3.91	3.94	3.94
$J_{3,4}$	3.5	3.4	3.4	3.8
H-4	5.31	4.10	4.27	4.18
$J_{4,5}$	1.6			2.0
H-5	5.01	4.10	4.27	4.27
$J_{5,6a}$	3.7			
$J_{5,6b}$	8.6			
H-6a	4.64	4.27	4.27	4.27
$J_{6a,6b}$	−11.7	−12.6		
H-6b	4.44	4.10	4.27	4.27

[a] Chemical shifts (δ, ppm) and coupling constants (J, in Hz) for solutions in $CDCl_3$.



Scheme 4.

trisaccharide derivative **26** in 68% overall yield. The *N*-trichloroacetyl group in **26** was readily transformed into *N*-acetyl by radical reduction[24] with tributyltin hydride and azobisisobutyronitrile (AIBN) to give the crystalline acetamide **27** in 92% yield.

Selective removal of the ester groups in **27** by controlled saponification was next examined. Firstly, the methyl ester groups in **27** were removed by treatment with lithium hydroperoxide[26] in aqueous tetrahydrofuran to give the corresponding diacid derivative without β-elimination side-reaction. Further in situ saponification with methanolic sodium hydroxide for 5 h, followed by deionization with resin [H^+ form] afforded the pivaloylated hydroxy-acid **28** in 76% yield, whereas the same treatment for 96 h gave the fully saponified derivative **29** in 66% yield. The ^{1}H NMR spectra for **28** and **29** (Table 4) show, apart from the presence in **28** and the absence in **29** of the pivalate ester (δ 1.10 ppm, s, 9 H), signals for H-4^{II} at δ 5.42 and 3.98 ppm, respectively, in full agreement with the postulated structures. The intermediates **28** and **29** were then *O*-sulfonated by treatment with the sulfur trioxide–trimethylamine complex in *N*,*N*-dimethylformamide at 50 °C, followed by ion-exchange chromatography [Na^+ resin] to give the sodium salts **30** and **31** in 63 and 70% yields, respectively. The ^{1}H NMR spectra for **30** and **31** (Table 4) were compared with those of their non-sulfated precursors **28** and **29**, respectively, all being recorded in deuterated methanol under the same conditions. Particularly relevant are the downfield shifts ($\Delta\delta \sim 0.5$–0.6 ppm) of the signals for both IdoA H-2 in **30** and **31**, and those ($\Delta\delta \sim 0.8$ ppm) of the signal for GalNAc H-4 in **31**. These chemical shift differences indicate that sulfation occurred at O-2^{I} and O-2^{III} in both derivatives, and at O-4^{II} in **31**, and are in complete agreement with those reported for synthetic 2-*O*-sulfonated L-IdoA derivatives,[9,10] as well as those for 4-*O*-sulfonated D-GalNAc residues in synthetic oligosaccharides.[17,27] Removal of the pivaloyl group in sulfated **30** was achieved by treatment with methanolic sodium hydroxide for 96 h to afford the disulfated derivative **32** in 72% yield. The ^{1}H NMR spectrum for **32** (Table 4), compared with those of its precursor **30**, shows a significant upfield shift ($\Delta\delta \sim 1.6$ ppm) for the signal for GalNAc H-4 in **32** and no notable changes for the other protons, in good agreement with the expected structure. Final hydrogenation of **31** and **32** with Pd–C in aqueous methanol gave the target molecule **1** and **2** in 93 and 96% yields, respectively. The ^{1}H (Table 4) and ^{13}C NMR spectra for **1** and **2** are in full agreement with the postulated structures, and in accord with those reported[28] for DS polymer isolated from ascidians. The coupling constants observed for the L-IdoA residues indicate once more a predominance of $^1C_4$ conformation in solution for both reducing and nonreducing units.

Synthesis of the sulfated trisaccharide derivative **3** having a D-GalNAc residue at the reducing end was then achieved as follows (Scheme 6). Condensation of acceptors **22** and **23** with the known[10] 4-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-2-trichloroacetamido-1-*O*-trichloroacetimidoyl-α-D-galactopyranose (**33**) (1.5 equiv), in dichloromethane at −15 °C, and in the presence of

trimethylsilyl triflate, afforded the trisaccharide derivatives **34** and **35** in 80 and 75% yields, respectively, the structures of which could be once more determined on the basis of their ^{1}H NMR data (Table 5). Radical reduction on **34** and **35**, as described above for the preparation of **27**, gave the acetamides **36** and **37** in 84 and 88% yields, respectively. Both compounds **36** and **37** were treated with lithium hydroperoxide in aqueous tetrahydrofuran followed by methanolic sodium hydroxide for 5 h to give the pivaloylated derivative **38** and the fully saponified derivative **39**, both in 95% yields. The ^{1}H NMR spectra for **38** and **39** (Table 5) accord with the expected structures and with previous observations reported above for **28** and **29**. The monoester **38** might be used for the preparation of the corresponding disulfated species, showing that it should be possible to differentiate two D-GalNAc residues in such a structure. It is to be noted that treatment of ester **38** with methanolic sodium hydroxide for 96 h gave the hydroxy-acid **39** in 61% yield. *O*-Sulfonation of fully saponified **39**, as described above for the preparation of sulfates **30** or **31**, afforded the sodium salt **40** in 65% yield. Comparison of the ^{1}H NMR spectra of **40** and **39**, both recorded in deuterated methanol (Table 5), showed the expected downfield shifts ($\Delta\delta \sim 0.9$ and 0.5 ppm) of the signals for GalNAc H-4 and IdoA H-2, respectively. Final hydrogenation of **40** with Pd–C in aqueous methanol gave the target molecule **3** in 88% yield. The ^{1}H (Table 5) and ^{13}C NMR data for **3** are in complete agreement with the expected structure, and fit well with those reported for **1** and **2**, as well as with those reported[28] for DS of natural origin.

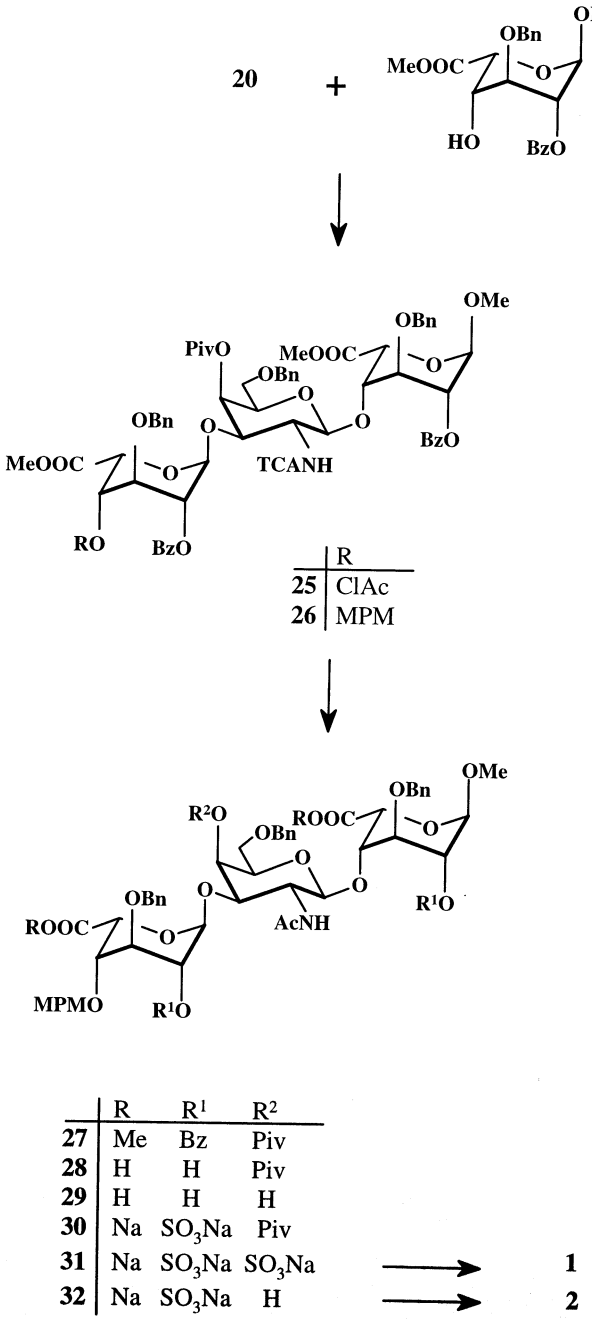
To further test the efficiency of our synthetic route[29] (not described in Section 3), the pivaloylated donor **20** (1.1 equiv) was condensed with the acetylated acceptor **23** (1 equiv) in dichloromethane at −15 °C, and in the presence of trimethylsilyl triflate, to give the corresponding tetrasaccharide derivative in 63% yield (δ 4.85 ppm, d, 1 H, $J_{1,2}$ 8.4 Hz, H-1^{III}). In this derivative, the two D-GalNAc residues might be once more differentiated, starting from a common precursor.

In conclusion, an expeditious preparation of a pair of key activated disaccharide intermediates bearing a variety of ester groups is reported. Stereocontrolled and

Table 3
^{1}H NMR data: carbohydrate ring protons for disaccharide derivatives **14**–**23** [a]

Proton	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**
H-1^I	5.38	5.41	5.27	5.29	5.29	5.37	6.46	6.42	4.78	4.80
$J_{1,2}$	8.4	8.5	8.4	8.4	8.5	8.4	3.7	3.8	8.5	8.4
H-2^I	3.95	3.90	4.05	4.03	4.13	3.90	4.83	4.80	3.74	3.76
$J_{2,3}$	11.0	11.0	11.5	10.9	10.8	10.9	10.8	10.8	11.1	10.9
H-3^I	4.58	4.61	4.51	4.51	4.56	4.65	4.22	4.22	4.49	4.56
$J_{3,4}$	3.2	3.4	2.9	3.1	3.1	3.2	3.3	3.0	3.0	3.2
H-4^I	5.58	5.57	5.54	5.53	5.55	5.52	5.65	5.60	5.53	5.55
$J_{4,5}$	0.5	0.5	0.5	0.5	0.5	0.5	0.7	0.9	0.5	0.5
H-5^I	3.95	3.96	4.05	3.93	4.01	3.96	4.31	4.28	3.88	3.92
$J_{5,6a}$	6.2	6.1	4.7	4.7	6.0	6.2	6.2	5.8	6.0	5.6
$J_{5,6b}$	6.2	6.1	6.9	6.2	6.0	6.2	6.2	5.8	6.0	6.6
H-6a^I	3.54	3.58	3.54	3.52	3.54	3.56	3.51	3.52	3.47	3.54
$J_{6a,6b}$			−10.1	−10.4			−10.2	−10.0		−10.4
H-6b^I	3.54	3.58	3.48	3.46	3.54	3.56	3.43	3.43	3.47	3.49
NH	6.90	6.88	7.07	7.02	6.95	6.95	6.82	6.72	6.03	6.96
$J_{2,NH}$	7.6	7.3	7.8	7.8	7.8	7.8	9.8	9.6	7.6	7.8
H-1^{II}	5.19	5.19	5.21	5.24	5.23	5.22	5.31	5.35	5.18	5.18
$J_{1,2}$	2.8	2.3	1.0	1.0	1.1	1.1	1.1	1.1	1.2	1.2
$J_{1,3}$			1.0	1.0	0.9	0.9	1.0	0.9	1.0	1.0
H-2^{II}	5.27	5.30	5.15	5.12	5.16	5.15	5.12	5.14	5.12	5.17
$J_{2,3}$	5.0	4.3	2.7	2.6	2.5	2.4	2.3	2.3	2.9	2.7
$J_{2,4}$			1.0	1.0	0.9	1.0	1.0	1.1	1.2	1.2
H-3^{II}	3.80	3.82	3.75	3.82	3.81	3.88	3.84	3.91	3.82	3.79
$J_{3,4}$	2.8	2.6	2.6	2.6	2.5	2.6	2.7	2.1	2.5	2.6
H-4^{II}	4.05	4.18	4.05	5.27	4.13	4.34	5.28	5.32	4.04	4.11
$J_{4,5}$			1.8	2.1	1.9	2.0	1.8	1.5	1.8	1.8
H″5^{II}	4.05	4.18	4.81	4.93	5.07	5.12	4.98	5.19	4.81	5.02
H-6a^{II}	4.45	4.45								
H-6b^{II}	4.15	4.18								

[a] Chemical shifts (δ, ppm) and coupling constants (J, in Hz) for solutions in $CDCl_3$.



Scheme 5.

high-yielding coupling reactions with moderate excess of donors were achieved by using activated 2-deoxy-2-trichloroacetamido-1-*O*-trichloroacetimidoyl-D-*galacto* derivatives. Controlled saponification of ester groups open the way for the preparation of various sulfoforms starting from a common precursor. This strategy can be applied not only for the synthesis of DS fragments, as depicted herein, but also for the preparation of sulfoforms in chondroitin sulfates. In that case, which is currently being investigated, no influence of the nature of the adjacent sugar residue (D-GlcA instead of L-IdoA) could be observed. Finally, the disaccharide building block strategy used herein might be extended for the construction of larger molecules. The sulfated molecules **1**–**3** are currently being evaluated in biological assays, and the results of these studies will be reported elsewhere in due course.

3. Experimental

General methods.—Melting points were determined in capillary tubes with a Büchi apparatus and are uncorrected. Optical rotations were measured at 20–25 °C with a Perkin–Elmer 241 polarimeter. ^{1}H NMR spectra were recorded at 25 °C with Bruker DPX 250 and Varian Unity 500 spectrometers operating at 250 and 500 MHz, respectively, with Me_4Si as internal standard, unless otherwise stated. ^{13}C NMR spectra were recorded with a Bruker Advance DPX 250 operating at 62.8 MHz. Assignments were based on homo- and heteronuclear correlations using the supplier's software. Low-resolution mass spectra were obtained on a Perkin–Elmer SCIEX API 300 spectrometer operating in the ion-spray (IS) mode. Flash-column chromatography was performed on Silica Gel (E. Merck, 40–63 μm). Elemental analyses were performed by the Service Central de Microanalyse du CNRS (Vernaison, France).

*4-Methoxyphenyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-pivaloyl-2-trichloroacetamido-β-*D*-glucopyranoside* (**5**).—Pivaloyl chloride (7 mL, 57 mmol) was added dropwise at 0 °C to a solution of 4-methoxyphenyl 4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (**4**)[10] (9.9 g, 19 mmol) and DMAP (244 mg, 1.9 mmol) in pyridine (30 mL) and CH_2Cl_2 (70 mL), and the mixture was stirred overnight at rt. Methanol (20 mL) was 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 **5** (9.4 g, 82%); mp 205–206 °C; $[\alpha]_D$ −65° (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): carbohydrate ring protons (see Table 1); δ 7.50–6.70 (m, 9 H, aromatic H), 5.52 (s, 1 H, PhC*H*), 3.77 (s, 3 H, OCH_3); ISMS: *m*/*z* 621, $[M + NH_4]^+$ for ^{35}Cl. Anal. Calcd for $C_{27}H_{30}Cl_3NO_8$: C, 53.79; H, 5.01; N, 2.33. Found: C, 53.64; H, 5.00; N, 2.28.

*4-Methoxyphenyl 6-*O*-benzyl-2-deoxy-3-*O*-pivaloyl-2-trichloroacetamido-β-*D*-glucopyranoside* (**6**).—Trifluoroacetic acid (6 mL, 80 mmol) was added at 0 °C under dry Ar to a solution of **5** (9.4 g, 15.5 mmol) and triethylsilane (12.5 mL, 78 mmol) in anhyd CH_2Cl_2 (50 mL), and the mixture was stirred for 1 h at 0 °C and 2 h at rt. Triethylamine (30 mL) was added, and the mixture was diluted with CH_2Cl_2 (100 mL), washed with water, satd aq $NaHCO_3$ and water, dried ($MgSO_4$)

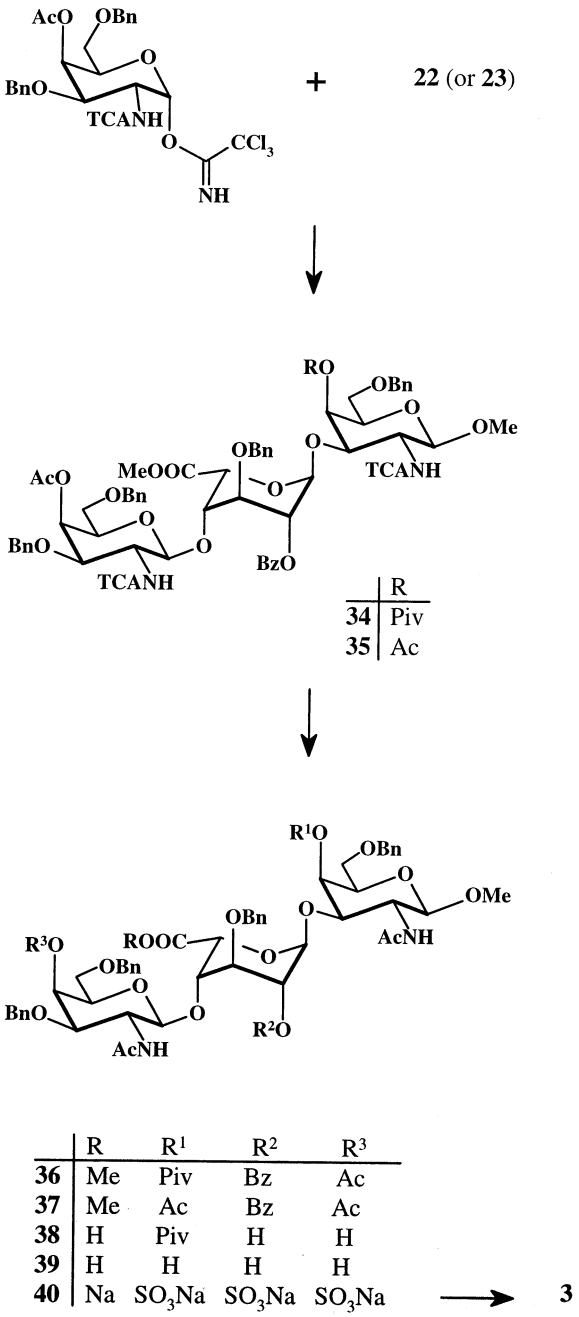
and concentrated. The residue was eluted from a column (100 g) of silica gel with 20:1 CH_2Cl_2–EtOAc to afford **6** as a white foam (8.6 g, 91%); $[\alpha]_D$ −32° (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): carbohydrate ring protons (see Table 1); δ 7.36–6.80 (m, 9 H, aromatic H), 4.57 (ABq, 2 H, CH_2Ph), 3.75 (s, 3 H, OCH_3), 3.00 (d, 1 H, *J* 4.7 Hz, *HO*-4), 1.20 (s, 9 H, $((CH_3)_3C)$; ISMS: *m*/*z* 628, $[M+Na]^+$ for ^{35}Cl. Anal. Calcd for $C_{27}H_{32}Cl_3NO_8$: C, 53.61; H, 5.33; N, 2.33. Found: C, 53.69; H, 5.13; N, 2.41.

4-Methoxyphenyl 6-O-benzyl-2-deoxy-4-O-pivaloyl-2-trichloroacetamido-β-D-galactopyranoside (**7**).—Triflic anhydride (2.8 mL, 17 mmol) was added dropwise at −15 °C under dry Ar to a solution of **6** (8.6 g, 14.2 mmol) in anhyd pyridine (5.8 mL) and anhyd 1,2-dichloroethane (50 mL), and the mixture was stirred for 90 min at this temperature. Water (6.4 mL) was added, and the mixture was stirred for 30 min at 80 °C, then was cooled, diluted with CH_2Cl_2 (50 mL), washed with water, satd aq $NaHCO_3$ and water, dried ($MgSO_4$) and concentrated. The residue was eluted from a column (100 g) of silica gel with 3:2 petroleum ether–EtOAc to give **7** as a white foam (7.0 g, 82%); $[\alpha]_D$ −34° (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): carbohydrate ring protons (see Table 1); δ 7.40–6.90 (m, 9 H, aromatic H), 4.51 (ABq, 2 H, CH_2Ph), 3.76 (s,

Table 4
^{1}H NMR data: carbohydrate ring protons for trisaccharide derivatives **25**–**32**, **1** and **2** [a]

Proton	**25**	**26**	**27**	**28** [b]	**29** [b]	**30** [b]	**31** [b]	**32** [b]	**1** [c]	**2** [c]
H-1^I	4.91	4.90	4.95	4.85	4.78	5.15	5.03	5.12	4.83	4.94
$J_{1,2}$	1.2	1.1	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
$J_{1,3}$	0.9	1.0		1.0	1.0				0.9	1.0
H-2^I	5.07	5.13	5.10	4.09	4.05	4.66	4.62	4.62	**4.06** [d]	**4.07**
$J_{2,3}$	2.4	2.3	2.0	2.0	2.1	2.0			2.5	2.2
$J_{2,4}$	1.2	1.0								
H-3^I	4.09	4.10	4.20	3.95	4.05	4.13	4.12	4.10	4.31	4.19
$J_{3,4}$	2.5	2.6	2.2						2.2	2.0
H-4^I	4.14	4.15	4.15	3.96	4.05	4.24	4.15	4.10	4.07	3.98
$J_{4,5}$	2.0	2.6	1.5	2.0	1.5	1.6	1.5		1.5	1.5
H-5^I	4.83	4.68	4.63	4.56	4.48	4.53	4.44	4.42	4.68	4.54
H-1^{II}	4.86	4.88	4.88	4.62	4.56	4.68	4.62	4.64	4.68	4.64
$J_{1,2}$	8.4	8.4	8.2	8.4	8.4	8.2	8.4	8.4	8.4	8.4
H-2^{II}	3.76	3.80	3.20	3.90	3.80	3.90	3.95	3.80	3.70	3.80
$J_{2,3}$	10.8	11.0	9.9	10.0	10.0	10.0	10.0		10.0	10.0
H-3^{II}	4.19	4.20	4.38	3.68	3.65	3.58	3.82	3.80	3.94	3.85
$J_{3,4}$	2.8	3.0	2.9	3.1	3.0	3.0	3.0	3.0	3.0	3.0
H-4^{II}	5.38	5.37	5.33	5.42	3.98	5.58	4.84	3.98	**4.74**	3.96
$J_{4,5}$	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
H-5^{II}	3.80	3.70	3.70	3.65	3.93	3.90	3.82	3.80	3.88	3.82
H-6a^{II}	3.23	3.28	3.21	3.55	3.65	3.55	3.75	3.70	3.70	3.68
H-6b^{II}	3.23	3.24	3.21	3.55	3.65	3.55	3.75	3.70	3.70	3.68
NH	6.79	6.84	5.62							
$J_{2,NH}$	7.9	7.9	7.0							
H-1^{III}	5.20	5.22	5.03	5.01	5.05	5.34	5.27	5.42	5.11	5.16
$J_{1,2}$	1.0	1.9	1.2	3.0	3.2	1.2	1.2	1.2	1.0	1.0
$J_{1,3}$	0.8					1.0	1.0		1.0	1.0
H-2^{III}	5.14	5.05	5.15	4.08	4.05	4.64	4.58	4.62	**4.18**	**4.18**
$J_{2,3}$	2.0	3.4	2.9	2.5		2.0			2.5	2.3
$J_{2,4}$	1.0	1.2								
H-3^{III}	3.76	3.76	3.75	3.95	4.05	3.98	4.12	4.10	4.32	4.35
$J_{3,4}$	2.2	2.9							2.6	2.5
H-4^{III}	5.23	3.80	3.80	3.65	3.75	3.60	3.72	3.70	3.96	3.94
$J_{4,5}$	1.2	1.8	2.3	2.5		1.7	1.8		1.5	1.5
H-5^{III}	4.80	4.81	4.80	4.66	4.84	4.57	4.34	4.38	4.74	4.44

[a] For solutions in $CDCl_3$, unless otherwise stated.
[b] CD_3OD.
[c] D_2O.
[d] Values in bold type reflect the locations of the sulfate groups.



Scheme 6.

3 H, OCH_3), 2.76 (d, 1 H, *J* 4.6 Hz, *H*O-3), 1.20 (s, 9 H, $(CH_3)_3C$); ^{13}C NMR ($CDCl_3$): selected data; δ 99.67 (C-1), 92.48 (CCl_3), 73.82 (CH_2Ph), 73.12 (C-5), 69.68 (C-3), 69.43 (C-4), 68.34 (C-6), 56.67 (C-2), 55.75 (OCH_3), 39.45 ($(CH_3)_3C$), 27.35 ($(CH_3)_3C$); ISMS: *m*/*z* 628, $[M + Na]^+$ for ^{35}Cl. Anal. Calcd for $C_{27}H_{32}Cl_3NO_8$: C, 53.61; H, 5.33; N, 2.33. Found: C, 53.71; H, 5.37; N, 2.33.

*4-Methoxyphenyl 4-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-trichloroacetamido-β-*D*-galactopyranoside* (**8**).—A solution of **7** (7.1 g, 11.8 mmol) in MeOH (100 mL) was treated for 3 h at rt with methanolic MeONa (1 M, 3 mL), then was deionized with Amberlite IR–120 $[H^+]$ resin, filtered and concentrated to afford the corresponding diol (6.2 g, quantitative), mp 172–173 °C (from EtOAc–petroleum ether).

A mixture of the above isolated diol (6.2 g, 11.8 mmol), trimethyl orthoacetate (17.5 mL, 140 mmol) and 10-D,L-camphorsulfonic acid (0.46 g) in anhyd toluene (30 mL) was stirred for 1 h at rt. Triethylamine (0.83 mL) was added, and the mixture was diluted with toluene (30 mL), washed with water, dried ($MgSO_4$) and concentrated. A solution of the residue in 80% AcOH (100 mL) was stirred for 10 min at rt, then concentrated, evaporated with water and toluene. The residue was crystallized from EtOAc–petroleum ether to give **8** (5.7 g, 86% from **7**); mp 146–147 °C; $[\alpha]_D$ −34° (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): carbohydrate ring protons (see Table 1); δ 7.40–6.80 (m, 9 H, aromatic H), 4.48 (ABq, 2 H, CH_2Ph), 3.76 (s, 3 H, OCH_3), 2.89 (d, 1 H, *J* 5.2 Hz, *H*O-3), 2.12 (s, 3 H, Ac); ^{13}C NMR ($CDCl_3$): selected data; δ 99.92 (C-1), 92.46 (CCl_3), 73.79 (CH_2Ph), 72.95 (C-5), 69.82 (C-4), 69.32 (C-3), 68.21 (C-6), 56.65 (C-2), 55.74 (OCH_3), 20.95 ($COCH_3$); ISMS: *m*/*z* 581, $[M + NH_4]^+$ for ^{35}Cl. Anal. Calcd for $C_{24}H_{26}Cl_3NO_8$: C, 51.21; H, 4.66; N, 2.50. Found: C, 51.19; H, 4.67; N, 2.50.

*4-Methoxyphenyl 2,4,6-tri-*O*-benzoyl-3-*O*-benzyl-α-L-idopyranoside* (**10**).—A mixture of 1,2,4,6-tetra-*O*-benzoyl-3-*O*-benzyl-β-L-idopyranose (**9**)[10] (7.70 g, 11.2 mmol), 4-methoxyphenol (2.80 g, 22.6 mmol), and 4 Å powdered molecular sieves (5 g) in anhyd CH_2Cl_2 (40 mL) was stirred for 1 h at rt under dry Ar. Trimethylsilyl triflate (2.0 mL, 11.2 mmol) was added, and the mixture was stirred for 30 min at rt. Triethylamine (4.6 mL) was then added, and the mixture was diluted with CH_2Cl_2 (30 mL), filtered through a pad of Celite, washed with water, 1 M NaOH and water, dried ($MgSO_4$) and concentrated. The residue was eluted from a column (80 g) of silica gel with 4:1 petroleum ether–EtOAc to give **10** as a light yellow oil (7.70 g, 98%); $[\alpha]_D$ −42° (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): carbohydrate ring protons (see Table 2); δ 8.20–6.80 (m, 24 H, aromatic H), 4.94 (ABq, 2 H, CH_2Ph), 3.70 (s, 3 H, OCH_3); ISMS: *m*/*z* 706, $[M + NH_4]^+$, 565, $[M - OC_6H_4OCH_3]^+$. Anal. Calcd for $C_{41}H_{36}O_{10}$: C, 71.50; H, 5.27. Found: C, 71.62; H, 5.13.

*4-Methoxyphenyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-L-idopyranoside* (**11**).—A solution of **10** (7.70 g, 11.2 mmol) in MeOH (100 mL) was transesterified as described for the preparation of **8**. A mixture of the residue, benzaldehyde (20 mL) and TFA (1 mL) was stirred for 3 h at rt. Triethylamine (6.5 mL) and CH_2Cl_2 (100 mL) were then added, and the mixture was washed with brine and water, dried ($MgSO_4$) and concentrated. The residue was eluted from a column (100 g) of silica gel with 10:1 → 4:1 petroleum ether–EtOAc, and crystallized from EtOAc–petroleum ether to give **11** (4.37

g, 84% from **10**); mp 121–122 °C; $[\alpha]_D$ −70° (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): carbohydrate ring protons (see Table 2); δ 7.50–7.0 (m, 14 H, aromatic H), 5.55 (s, 1 H, PhC*H*), 4.76 (ABq, 2 H, CH_2Ph), 3.80 (s, 3 H, OCH_3), 3.46 (d, 1 H, *J* 11.5 Hz, *H*O-2); ISMS: *m*/*z* 591, $[M + Na]^+$. Anal. Calcd for $C_{34}H_{32}O_8$: C, 71.82; H, 5.67. Found: C, 71.78; H, 5.53.

*4-Methoxyphenyl 2-*O*-benzoyl-3-*O*-benzyl-4,6-*O*-benzylidene-α-*L*-idopyranoside* (**12**).—Benzoyl chloride (5.4 mL, 46.5 mmol) was added at 0 °C to a solution of **11** (10.70 g, 23 mmol) in pyridine (19 mL) and CH_2Cl_2 (100 mL), and the mixture was stirred for 1 h at this temperature. Methanol (10 mL) was 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 **12** (12.30 g, 94%); mp 127–128 °C; $[\alpha]_D$ −54° (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): carbohydrate ring protons (see Table 2); δ 8.0–6.90 (m, 19 H, aromatic H), 5.60 (s, 1 H, PhC*H*), 4.87 (ABq, 2 H, CH_2Ph), 3.70 (s, 3 H, OCH_3); ISMS: *m*/*z* 591, $[M + Na]^+$, 445, $[M - OC_6H_4OCH_3]^+$. Anal.

Table 5
^1H NMR data: carbohydrate ring protons for trisaccharide derivatives **34**–**40**, and **3** [a]

Proton	**34**	**35**	**36**	**37**	**38** [b]	**39** [b]	**40** [b]	**3** [c]
H-1^I	4.77	4.81	4.81	4.94	4.52	4.44	4.55	4.55
$J_{1,2}$	8.2	8.4	8.5	8.4	8.2	8.4	8.2	8.0
H-2^I	3.74	3.76	3.55	3.54	3.93	3.92	3.90	3.92
$J_{2,3}$	10.8	11.3	11.2	11.0	11.0	11.0	11.0	10.5
H-3^I	4.46	4.30	4.41	4.40	4.17	4.24	4.12	3.75
$J_{3,4}$	2.9	3.1	2.9	2.9	2.9	3.0	3.0	3.0
H-4^I	5.51	5.50	5.50	5.52	5.43	4.05	4.96	**4.73** [d]
$J_{4,5}$	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
H-5^I	3.86	3.85	3.87	3.84	3.65	3.65	3.65	3.70
H-6a^I	3.50	3.52	3.45	3.46	3.50	3.65	3.65	3.70
H-6b^I	3.50	3.52	3.45	3.46	3.50	3.65	3.65	3.70
NH	6.88	6.98	5.81	5.72				
$J_{2,NH}$	7.6	7.6	7.9	7.9				
H-1^{II}	5.12	5.14	5.09	5.10	5.03	5.28	5.36	5.07
$J_{1,2}$	1.0	1.0	1.0	1.0	1.0	1.0	1.8	1.0
$J_{1,3}$	1.0	1.0	1.0	1.0	1.0	0.9	0.9	1.0
H-2^{II}	4.99	5.07	4.97	5.03	4.10	4.12	4.58	**4.06**
$J_{2,3}$	2.1	2.2	2.3	2.2			2.5	2.5
$J_{2,4}$	0.9	0.9	0.9	0.8				1.0
H-3^{II}	4.01	4.08	4.01	4.09	3.92	4.05	4.28	3.97
$J_{3,4}$	2.5	2.3	2.5	2.4			2.5	2.2
H-4^{II}	4.13	4.20	4.05	4.09	4.06	4.18	4.38	4.12
$J_{4,5}$	1.8	1.5	1.6	2.0	2.4	1.6	1.6	1.5
H-5^{II}	4.76	4.94	4.74	4.92	4.87	4.92	4.95	4.66
H-1^{III}	4.80	4.85	4.91	4.98	4.48	4.42	4.52	4.53
$J_{1,2}$	8.4	8.4	8.2	8.4	8.4	8.2	8.3	8.2
H-2^{III}	3.50	3.52	3.16	3.46	3.95	3.92	3.90	3.92
$J_{2,3}$	11.1	10.7	11.3	11.0	11.0	11.0	11.0	10.5
H-3^{III}	3.97	3.93	4.36	4.33	3.65	3.65	3.65	3.75
$J_{3,4}$	3.3	3.1	2.8	3.0	3.5	3.5	3.0	3.0
H-4^{III}	5.46	5.47	5.42	5.40	4.02	4.05	4.94	**4.56**
$J_{4,5}$	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
H-5^{III}	3.55	3.62	3.65	3.73	3.65	3.65	3.65	3.70
H-6a^{III}	3.00	3.14	3.15	3.27	3.45	3.50	3.50	3.66
H-6b^{III}	3.00	3.14	3.15	3.27	3.45	3.50	3.50	3.66
NH	6.74	6.75	5.65	5.58				
$J_{2,NH}$	7.6	7.8	7.2	6.6				

[a] For solutions in $CDCl_3$, unless otherwise stated.
[b] CD_3OD.
[c] D_2O.
[d] Values in bold type reflect the locations of the sulfate groups.

Calcd for $C_{34}H_{32}O_8$: C, 71.82; H, 5.67. Found: C, 71.78; H, 5.53.

2-O-Benzoyl-3-O-benzyl-4,6-O-benzylidene-1-O-trichloroacetimidoyl-α-L-idopyranose (**13**).—A mixture of **12** (6.10 g, 10.8 mmol) and ceric ammonium nitrate (29.7 g, 54.1 mmol) in 1:1.5:1 toluene–MeCN–water (210 mL) was stirred vigorously for 5 min at rt, then was diluted with EtOAc (300 mL), washed with water, satd aq $NaHCO_3$ and water, dried ($MgSO_4$) and concentrated. The residue was eluted from a column (200 g) of silica gel with 5:2 petroleum ether–EtOAc to give the corresponding hemiacetal (4.30 g).

A mixture of the above isolated hemiacetal, CCl_3CN (7.4 mL, 93 mmol), and DBU (0.6 mL, 4.7 mmol) in anhyd CH_2Cl_2 (60 mL) was stirred for 1 h from 0 °C to rt, then was concentrated. The residue was eluted from a column (200 g) of silica gel with 4:1 petroleum ether–EtOAc containing 0.2% of Et_3N, and crystallized from Et_2O–petroleum ether to give **13** (3.50 g, 54% from **12**); mp 151–152 °C; $[\alpha]_D$ −59° (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): carbohydrate ring protons (see Table 2); δ 8.70 (s, 1 H, C=N*H*), 8.0–7.20 (m, 15 H, Ph), 5.58 (s, 1 H, PhC*H*), 4.85 (ABq, 2 H, CH_2Ph); ^{13}C NMR ($CDCl_3$): selected data; δ 165.62 (C=O), 160.40 (C=NH), 137.91–125.51 (aromatic C), 101.17 (Ph*C*H), 95.82 (C-1), 91.26 (CCl_3), 73.23 (C-3), 72.77 (C-5), 72.14 (*C*H_2Ph), 69.50 (C-6), 64.30 (C-2), 61.86 (C-4); ISMS: *m*/*z* 445, $[M-OC(NH)CCl_3]^+$ for ^{35}Cl. Anal. Calcd for $C_{29}H_{26}Cl_3NO_7$: C, 57.39; H, 4.32; N, 2.32. Found: C, 57.43; H, 4.26; N, 2.35.

4-Methoxyphenyl O-(2-O-benzoyl-3-O-benzyl-4,6-O-benzylidene-α-L-idopyranosyl)-(1→3)-6-O-benzyl-2-deoxy-4-O-pivaloyl-2-trichloroacetamido-β-D-galactopyranoside (**14**).—A mixture of alcohol **7** (3.20 g, 7.3 mmol), imidate **13** (3.40 g, 5.7 mmol), and 4 Å powdered molecular sieves (5 g) in anhyd CH_2Cl_2 (50 mL) was stirred for 1 h at rt under dry Ar, then cooled to 0 °C. A solution of Me_3SiOTf in toluene (1 M, 0.86 mL) was added, and the mixture was stirred for 30 min at 0 °C. Triethylamine (0.36 mL) was added, and the mixture was filtered and concentrated. The residue was eluted from a column (200 g) of silica gel with 4:1 petroleum ether–EtOAc containing 0.2% of Et_3N to give **14** as a white foam (4.30 g, 78%); $[\alpha]_D$ −10° (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): carbohydrate ring protons (see Table 3); δ 8.0–6.80 (m, 24 H, aromatic H), 5.56 (s, 1 H, PhC*H*), 4.70 (ABq, 2 H, CH_2Ph), 4.50 (s, 2 H, CH_2Ph), 3.74 (s, 3 H, OCH_3), 1.20 (s, 9 H, $(CH_3)_3C$); ^{13}C NMR ($CDCl_3$): selected data; δ 101.83 (C-1^{II}), 100.80 (Ph*C*H), 99.06 (C-1^{I}), 92.17 (CCl_3), 75.97 (C-3^{I}), 75.28 (C-5^{II}), 75.21 (C-3^{II}), 73.73, 72.11 (*C*H_2Ph), 73.41 (C-5^{I}), 69.66 (C-6^{II}), 69.33 (C-4^{I}), 68.52 (C-6^{I}), 67.95 (C-2^{II}), 61.16 (C-4^{II}), 55.89 (C-2^{I}), 55.71 (OCH_3), 39.29 ($(CH_3)_3C$), 27.34 ($(CH_3)_3C$); ISMS: *m*/*z* 1071, $[M+Na]^+$, 925, $[M-OC_6H_4OCH_3]^+$ for ^{35}Cl. Anal. Calcd for $C_{54}H_{56}Cl_3NO_{14}$: C, 61.80; H, 5.38; N, 1.33. Found: C, 61.76; H, 5.28; N, 1.51.

4-Methoxyphenyl O-(2-O-benzoyl-3-O-benzyl-4,6-O-benzylidene-α-L-idopyranosyl)-(1→3)-4-O-acetyl-6-O-benzyl-2-deoxy-2-trichloroacetamido-β-D-galactopyranoside (**15**).—A mixture of alcohol **8** (5.80 g, 10.4 mmol) and imidate **13** (6.90 g, 11.4 mmol) was treated as described for the preparation of **14** to give **15** as a white foam (8.20 g, 79%); $[\alpha]_D$ −0.5° (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): carbohydrate ring protons (see Table 3); δ 8.0–6.90 (m, 24 H, aromatic H), 5.58 (s, 1 H, PhC*H*), 4.73 (ABq, 2 H, CH_2Ph), 4.51 (s, 2 H, CH_2Ph), 3.74 (s, 3 H, OCH_3), 1.90 (s, 3 H, Ac); ^{13}C NMR ($CDCl_3$): selected data; δ 101.25 (C-1^{II}), 100.75 (Ph*C*H), 99.24 (C-1^{I}), 92.19 (CCl_3), 75.05 (C-3^{I}), 74.87 (C-3^{II}), 74.33 (C-5^{II}), 73.69, 72.16 (*C*H_2Ph), 73.09 (C-5^{I}), 69.61 (C-6^{II}), 69.55 (C-4^{I}), 68.48 (C-6^{I}), 67.27 (C-2^{II}), 60.78 (C-4^{II}), 55.86 (C-2^{I}), 55.64 (OCH_3), 20.60 ($CO\mathit{C}H_3$); ISMS: *m*/*z* 1024, $[M+NH_4]^+$ for ^{35}Cl. Anal. Calcd for $C_{51}H_{50}Cl_3NO_{14}$: C, 60.81; H, 5.00; N, 1.40. Found: C, 61.01; H, 5.15; N, 1.53.

4-Methoxyphenyl O-(methyl 2-O-benzoyl-3-O-benzyl-α-L-idopyranosyluronate)-(1→3)-6-O-benzyl-2-deoxy-4-O-pivaloyl-2-trichloroacetamido-β-D-galactopyranoside (**16**).—A mixture of **14** (3.57 g, 3.4 mmol) and AcOH (25 mL) was stirred at 100 °C. Water (15 mL) was added dropwise, and the mixture was stirred for 30 min at 100 °C, then was cooled, concentrated, evaporated with water and toluene to give the corresponding diol (3.20 g).

A solution of calcium hypochlorite (1.50 g, 10.4 mmol) and $NaHCO_3$ (0.87 g, 10.4 mmol) in water (45 mL) was added dropwise at 0 °C to a solution of the above isolated diol, 1.6×10^{-2} M TEMPO in CH_2Cl_2 (10.8 mL, 0.17 mmol) and 0.5 M aq KBr (0.69 mL) in MeCN (45 mL), and the mixture was stirred for 45 min at 0 °C, then was concentrated and evaporated with toluene.

Methyl iodide (0.96 mL, 15.5 mmol) was added to a solution of the residue in DMF (50 mL), and the mixture was stirred for 1 h at 50 °C, then was cooled, poured into ice-cold 5% aq HCl and extracted with EtOAc (3 × 100 mL). The organic extracts were washed with 5% aq $Na_2S_2O_3$, brine and water, dried ($MgSO_4$) and concentrated. The residue was eluted from a column (150 g) of silica gel with 5:1 CH_2Cl_2–EtOAc to give **16** as a white foam (2.20 g, 63% from **14**); $[\alpha]_D$ −8° (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): carbohydrate ring protons (see Table 3); δ 8.0–6.86 (m, 19 H, aromatic H), 4.69 (ABq, 2 H, CH_2Ph), 4.47 (s, 2 H, CH_2Ph), 3.80 (s, 3 H, $COOCH_3$), 3.69 (s, 3 H, OCH_3), 2.89 (d, 1 H, *J* 10.8 Hz, *H*O-4^{II}), 1.19 (s, 9 H, $(CH_3)_3C$); ISMS: *m*/*z* 1007, $[M+NH_4]^+$ for ^{35}Cl. Anal. Calcd for $C_{48}H_{52}Cl_3NO_{15}$: C, 58.27; H, 5.30; N, 1.41. Found: C, 58.07; H, 5.38; N, 1.55.

4-Methoxyphenyl O-(methyl 2-O-benzoyl-3-O-benzyl-4-O-chloroacetyl-α-L-idopyranosyluronate)-(1→3)-6-O-

benzyl-2-deoxy-4-O-*pivaloyl-2-trichloroacetamido-β*-D-*galactopyranoside* (**17**).—Chloroacetic anhydride (0.75 g, 4.4 mmol) was added at 0 °C to a solution of **16** (2.20 g, 2.2 mmol) in anhyd pyridine (1.2 mL) and anhyd CH_2Cl_2 (30 mL), and the mixture was stirred for 1 h at 0 °C. Crushed ice was added, and the mixture was diluted with CH_2Cl_2 (50 mL), washed with water, satd aq $NaHCO_3$ and water, dried ($MgSO_4$) and concentrated. The residue was eluted from a column (80 g) of silica gel with 10:1 CH_2Cl_2–EtOAc to afford **17** as a white foam (2.0 g, 85%); $[\alpha]_D$ +6° (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): carbohydrate ring protons (see Table 3); δ 8.0–6.80 (m, 19 H, aromatic H), 4.74, 4.47 (2 ABq, 4 H, CH_2Ph), 3.83 (ABq, 2 H, CH_2Cl), 3.77 (s, 3 H, $COOCH_3$), 3.72 (s, 3 H, OCH_3), 1.15 (s, 9 H, $(CH_3)_3C$); ISMS: *m*/*z* 1083, $[M+NH_4]^+$ for ^{35}Cl. Anal. Calcd for $C_{50}H_{53}Cl_4NO_{16}$: C, 56.35; H, 5.01; N, 1.32. Found: C, 56.49; H, 5.09; N, 1.42.

4-Methoxyphenyl O-*(methyl 2*-O-*benzoyl-3*-O-*benzyl-α*-L-*idopyranosyluronate)-(1→3)-4*-O-*acetyl-6*-O-*benzyl-2-deoxy-2-trichloroacetamido-β*-D-*galactopyranoside* (**18**).—Compound **15** (6.12 g, 6.1 mmol) was submitted to acid hydrolysis, TEMPO oxidation, and methyl esterification as described for the preparation of **16** to give **18** as a white foam (3.80 g, 66% from **15**); $[\alpha]_D$ −7° (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): carbohydrate ring protons (see Table 3); δ 8.0–6.80 (m, 19 H aromatic H), 4.71, 4.46 (2 ABq, 4 H, CH_2Ph), 3.79 (s, 3 H, $COOCH_3$), 3.68 (s, 3 H, OCH_3), 2.89 (d, 1 H, *J* 10.0 Hz, *H*O-4^{II}), 1.82 (s, 3 H, Ac); ISMS: *m*/*z* 969, $[M+Na]^+$ for ^{35}Cl. Anal. Calcd for $C_{45}H_{46}Cl_3NO_{15}$: C, 57.06; H, 4.89; N, 1.48. Found: C, 56.94; H, 4.94; N, 1.56.

4-Methoxyphenyl O-*(methyl 2*-O-*benzoyl-3*-O-*benzyl-4*-O-*chloroacetyl-α*-L-*idopyranosyluronate)-(1→3)-4*-O-*acetyl-6*-O-*benzyl-2-deoxy-2-trichloroacetamido-β*-D-*galactopyranoside* (**19**).—Compound **18** (3.80 g, 4 mmol) was treated as described for the preparation of **17** to give **19** as a white foam (3.80 g, 91%); $[\alpha]_D$ +6° (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): carbohydrate ring protons (see Table 3); δ 8.0–6.80 (m, 19 H aromatic H), 4.77, 4.49 (2 ABq, 4 H, CH_2Ph), 3.87 (ABq, 2 H, CH_2Cl), 3.80 (s, 3 H, $COOCH_3$), 3.74 (s, 3 H, OCH_3), 1.82 (s, 3 H, Ac); ISMS: *m*/*z* 1039, $[M+NH_4]^+$ for ^{35}Cl. Anal. Calcd for $C_{47}H_{47}Cl_4NO_{16}$: C, 55.14; H, 4.63; N, 1.37. Found: C, 55.01; H, 4.74; N, 1.42.

(Methyl 2-O-*benzoyl-3*-O-*benzyl-4*-O-*chloroacetyl-α*-L-*idopyranosyluronate)-(1→3)-6*-O-*benzyl-2-deoxy-4*-O-*pivaloyl-2-trichloroacetamido-1*-O-*trichloroacetimidoyl-α*-D-*galactopyranose* (**20**).—A mixture of **17** (2.10 g, 2 mmol) and ceric ammonium nitrate (8.30 g, 15 mmol) in 1:1.5:1 toluene–MeCN–water (52.5 mL) was stirred vigorously for 15 min at rt, then was diluted with EtOAc (100 mL), washed with water, satd aq $NaHCO_3$ and water, dried ($MgSO_4$) and concentrated. The residue was eluted from a column (100 g) of silica gel with 6:1 petroleum ether–EtOAc to give the corresponding free hemiacetal (1.41 g).

A mixture of the above isolated hemiacetal, CCl_3CN (1.3 mL, 13 mmol) and DBU (50 μL, 0.33 mmol) in anhyd CH_2Cl_2 (30 mL) was stirred for 30 min at 0 °C, then was concentrated. The residue was eluted from a column (100 g) of silica gel with 5:2 petroleum ether–EtOAc containing 0.2% of Et_3N to give **20** as a white foam (1.22 g, 55% from **17**); $[\alpha]_D$ +47° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): carbohydrate ring protons (see Table 3); δ 8.80 (s, 1 H, C=N*H*), 8.0–7.20 (m, 15 H, Ph), 4.74, 4.45 (2 ABq, 4 H, CH_2Ph), 3.84 (ABq, 2 H, CH_2Cl), 3.80 (s, 3 H, $COOCH_3$), 1.15 (s, 9 H, $(CH_3)_3C$); ^{13}C NMR ($CDCl_3$): selected data; δ 101.85 (C-1^{II}), 95.38 (C-1^I), 92.31, 90.79 (CCl_3), 77.59 (C-3^I), 73.54, 72.48 (CH_2Ph), 71.76 (C-5^I), 71.37 (C-3^{II}), 69.54 (C-4^{II}), 68.61 (C-4^I), 67.99 (C-6^I), 66.82 (C-2^{II}), 66.46 (C-5^{II}), 52.75 ($COOCH_3$), 50.63 (C-2^I), 40.38 (CH_2Cl), 39.18 ($(CH_3)_3C$), 27.06 ($(CH_3)_3C$); ISMS: *m*/*z* 942, $[M-OC(NH)CCl_3]^+$ for ^{35}Cl. Anal. Calcd for $C_{45}H_{47}Cl_7N_2O_{15}$: C, 48.95; H, 4.29; N, 2.53. Found: C, 48.75; H, 4.12; N, 2.39.

(Methyl 2-O-*benzoyl-3*-O-*benzyl-4*-O-*chloroacetyl-α*-L-*idopyranosyluronate)-(1→3)-4*-O-*acetyl-6*-O-*benzyl-2-deoxy-2-trichloroacetamido-1*-O-*trichloroacetimidoyl-α*-D-*galactopyranose* (**21**).—Compound **19** (3.80 g, 3.7 mmol) was treated as described for the preparation of **20** to give **21** as a white foam (2.29 g, 58% from **19**); $[\alpha]_D$ +51° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): carbohydrate ring protons (see Table 3); δ 8.83 (s, 1 H, C=N*H*), 8.0–7.20 (m, 15 H, Ph), 4.76, 4.44 (2 ABq, 4 H, CH_2Ph), 3.80 (ABq, 2 H, CH_2Cl), 3.78 (s, 3 H, $COOCH_3$), 1.65 (s, 3 H, Ac); ^{13}C NMR ($CDCl_3$): selected data; δ 101.08 (C-1^{II}), 95.20 (C-1^I), 92.24, 90.69 (CCl_3), 75.57 (C-3^I), 73.57, 72.64 (CH_2Ph), 71.41 (C-3^{II}), 71.19 (C-5^I), 69.39 (C-4^{II}), 68.54 (C-4^I), 67.75 (C-6^I), 66.40 (C-5^{II}), 66.28 (C-2^{II}), 52.79 ($COOCH_3$), 50.87 (C-2^I), 40.20 (CH_2Cl), 19.99 ($COCH_3$); ISMS: *m*/*z* 900, $[M-OC(NH)CCl_3]^+$ for ^{35}Cl. Anal. Calcd for $C_{42}H_{41}Cl_7NO_{15}$: C, 47.50; H, 3.89; N, 2.64. Found: C, 47.25; H, 3.93; N, 2.82.

Methyl O-*(methyl 2*-O-*benzoyl-3*-O-*benzyl-α*-L-*idopyranosyluronate)-(1→3)-6*-O-*benzyl-2-deoxy-4*-O-*pivaloyl-2-trichloroacetamido-β*-D-*galactopyranoside* (**22**).—A mixture of imidate **20** (1.10 g, 0.98 mmol), anhyd MeOH (0.2 mL, 4.9 mmol) and 3 Å powdered molecular sieves (1 g) in anhyd CH_2Cl_2 (20 mL) was stirred for 1 h at rt under dry Ar. A solution of Me_3SiOTf in toluene (1 M, 0.15 mL) was added, and the mixture was stirred for 30 min. Triethylamine (0.1 mL) was added, and the mixture was filtered and concentrated. The residue was eluted from a column (75 g) of silica gel with 2:1 petroleum ether–EtOAc containing 0.2% of Et_3N to give the corresponding methyl glycoside (772 mg, 81%).

A mixture of the methyl glycoside and thiourea (0.25 g, 3.2 mmol) in pyridine (3.5 mL) and abs EtOH (7 mL) was stirred for 30 min at 80 °C, then was cooled and concentrated. A solution of the residue in CH_2Cl_2 (30 mL) was washed with water, satd aq $NaHCO_3$ and water, dried ($MgSO_4$) and concentrated. The residue was eluted from a column (75 g) of silica gel with 1:1 EtOAc–petroleum ether to give **22** as a white foam (677 mg, 77% from **20**); $[\alpha]_D$ +11° (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): carbohydrate ring protons (see Table 3); δ 8.0–7.20 (m, 15 H, Ph), 4.68, 4.48 (2 ABq, 4 H, CH_2Ph), 3.83 (s, 3 H, $COOCH_3$), 3.51 (s, 3 H, OCH_3), 2.74 (d, 1 H, *J* 10.5 Hz, *H*O-4^{II}), 1.15 (s, 9 H, $(CH_3)_3C$); ^{13}C NMR ($CDCl_3$): selected data; δ 101.61 (C-1^{II}), 100.39 (C-1^{I}), 92.34 (CCl_3), 77.45 (C-3^{I}), 74.38 (C-3^{II}), 73.68, 72.15 (*C*H_2Ph), 73.26 (C-5^{I}), 69.10 (C-4^{I}), 68.74 (C-6^{I}), 68.60 (C-4^{II}), 68.43 (C-5^{II}), 68.06 (C-2^{II}), 57.25 (OCH_3), 55.68 (C-2^{II}), 52.52 (COO*C*H_3), 39.13 ($(CH_3)_3C$), 27.14 ($(CH_3)_3$C); ISMS: *m*/*z* 915, $[M + NH_4]^+$ for ^{35}Cl. Anal. Calcd for $C_{42}H_{48}Cl_3NO_{14}$: C, 56.22; H, 5.39; N, 1.57. Found: C, 56.07; H, 5.53; N, 1.60.

Methyl O-*(methyl 2*-O-*benzoyl-3*-O-*benzyl-α*-L-*idopyranosyluronate)-(1→3)-4*-O-*acetyl-6*-O-*benzyl-2-deoxy-2-trichloroacetamido-β*-D-*galactopyranoside* (**23**).—Imidate **21** (1.90 g, 1.76 mmol) was treated as described for the preparation of **22** to give **23** as a white foam (1.11 g, 79% from **21**); $[\alpha]_D$ +12° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): carbohydrate ring protons (see Table 3); δ 8.0–7.20 (m, 15 H, Ph), 4.71, 4.48 (2 ABq, 4 H, CH_2Ph), 3.82 (s, 3 H, $COOCH_3$), 3.46 (s, 3 H, OCH_3), 2.75 (d, 1 H, *J* 11.3 Hz, *H*O-4^{II}), 1.78 (s, 3 H, Ac); ^{13}C NMR ($CDCl_3$): selected data; δ 100.93 (C-1^{II}), 100.20 (C-1^{I}), 92.28 (CCl_3), 75.60 (C-3^{I}), 74.64 (C-3^{II}), 73.70, 72.41 (*C*H_2Ph), 72.96 (C-5^{I}), 69.44 (C-4^{I}), 68.69 (C-6^{I}), 68.37 (C-5^{II}), 68.11 (C-4^{II}), 67.69 (C-2^{II}), 57.42 (OCH_3), 56.23 (C-2^{I}), 52.54 (COO*C*H_3), 20.39 (CO*C*H_3); ISMS: *m*/*z* 942, $[M + NH_4]^+$ for ^{35}Cl. Anal. Calcd for $C_{39}H_{42}Cl_3NO_{14}$: C, 54.78; H, 4.95; N, 1.64. Found: C, 54.84; H, 4.98; N, 1.70.

Methyl O-*(methyl 2*-O-*benzoyl-3*-O-*benzyl-4*-O-*chloroacetyl-α*-L-*idopyranosyluronate)-(1→3)-(6*-O-*benzyl-2-deoxy-4*-O-*pivaloyl-2-trichloroacetamido-β*-D-*galactopyranosyl)-(1→4)-(methyl 2*-O-*benzoyl-3*-O-*benzyl-α*-L-*idopyranosid)uronate* (**25**).—A mixture of imidate **20** (1.10 g, 1 mmol), methyl (methyl 2-*O*-benzoyl-3-*O*-benzyl-α-L-idopyranosid)uronate **24**[10] (609 mg, 1.5 mmol) and 4 Å powdered molecular sieves (1 g) in anhyd CH_2Cl_2 (15 mL) was stirred for 1 h at rt under dry Ar, then cooled to −15 °C. A solution of Me_3SiOTf in toluene (1 M, 0.15 mL) was added, and the mixture was stirred for 30 min at −15 °C. Triethylamine (65 μL) was added, and the mixture was filtered and concentrated. The residue was eluted from a column (60 g) of silica gel with 3:2 petroleum ether–EtOAc containing 0.1% of Et_3N to give **25** as a white foam (818 mg, 61%); $[\alpha]_D$ −9.5° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): carbohydrate ring protons (see Table 4); δ 8.10–7.20 (m, 25 H, Ph), 4.74, 4.70, 4.37 (3 ABq, 6 H, CH_2Ph), 3.82, 3.75 (2 s, 6 H, $COOCH_3$), 3.78 (ABq, 2 H, CH_2Cl), 3.46 (s, 3 H, OCH_3), 0.82 (s, 9 H, $(CH_3)_3C$); ^{13}C NMR ($CDCl_3$): selected data; δ 101.60 (C-1^{III}), 101.33 (C-1^{II}), 100.13 (C-1^{I}), 92.47 (CCl_3), 78.36 (C-3^{II}), 77.36 (C-3^{III}), 74.70 (C-5^{II}), 73.69, 72.48, 72.34 (*C*H_2Ph), 73.50 (C-3^{I}), 73.21 (C-4^{I}), 71.89 (C-4^{II}), 69.66, 68.79 (C-2^{I}, C-2^{III}), 68.58 (C-6^{II}), 67.12, 66.34 (C-5^{I}, C-5^{III}), 67.02 (C-4^{II}), 56.23 (OCH_3), 55.38 (C-2^{II}), 52.76, 52.58 (COO*C*H_3), 40.41 (CH_2Cl), 38.81 ($(CH_3)_3C$), 26.88 ($(CH_3)_3$C); ISMS: *m*/*z* 1376, $[M + NH_4]^+$ for ^{35}Cl. Anal. Calcd for $C_{65}H_{69}Cl_4NO_{22}$: C, 57.48; H, 5.12; N, 1.04. Found: C, 57.35; H, 5.21; N, 1.08.

Methyl O-*[methyl 2*-O-*benzoyl-3*-O-*benzyl-4*-O-*(4-methoxybenzyl)-α*-L-*idopyranosyluronate]-(1→3)-(6*-O-*benzyl-2-deoxy-4*-O-*pivaloyl-2-trichloroacetamido-β*-D-*galactopyranosyl)-(1→4)-(methyl 2*-O-*benzoyl-3*-O-*benzyl-α*-L-*idopyranosid)uronate* (**26**).—Compound **25** (950 mg, 0.7 mmol) was *O*-dechloroacetylated as described for the preparation of **22**. A solution of the resulting alcohol and 4 Å powdered molecular sieves (0.5 g) in anhyd CH_2Cl_2 (7 mL) was stirred for 1 h at rt under dry Ar. Solutions of Me_3SiOTf (1 M in toluene, 115 μL) and 4-methoxybenzyl trichloroacetimidate (1 M in toluene, 2 mL) were successively added dropwise, and the mixture was stirred for 1 h at rt, then was neutralized with Et_3N (33 μL), filtered and concentrated. The residue was eluted from a column (40 g) of silica gel with 1:1 EtOAc–petroleum ether containing 0.2% of Et_3N to provide **26** as a white foam (667 mg, 68% from **25**); $[\alpha]_D$ −25° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): carbohydrate ring protons (see Table 4); δ 8.10–7.20 (m, 29 H, aromatic H), 4.67, 4.64, 4.38, 4.24 (4 ABq, 8 H, CH_2Ph), 3.81 (s, 3 H, OCH_3), 3.75, 3.71 (2 s, 6 H, $COOCH_3$), 3.45 (s, 3 H, OCH_3), 0.84 (s, 9 H, $(CH_3)_3C$); ISMS: *m*/*z* 1419, $[M + NH_4]^+$, 1370, $[M - OCH_3]^+$ for ^{35}Cl. Anal. Calcd for $C_{71}H_{76}Cl_3NO_{22}$: C, 60.83; H, 5.29; N, 1.00. Found: C, 60.63; H, 5.39; N, 1.08.

Methyl O-*[methyl 2*-O-*benzoyl-3*-O-*benzyl-4*-O-*(4-methoxybenzyl)-α*-L-*idopyranosyluronate]-(1→3)-(2-acetamido-6*-O-*benzyl-2-deoxy-4*-O-*pivaloyl-β*-D-*galactopyranosyl)-(1→4)-(methyl 2*-O-*benzoyl-3*-O-*benzyl-α*-L-*idopyranosid)uronate* (**27**).—A mixture of **26** (0.79 g, 0.6 mmol), Bu_3SnH (0.91 mL, 3.4 mmol), and AIBN (100 mg) in dry benzene (12 mL) was stirred for 30 min at rt under a stream of dry Ar, then was heated for 2 h at 80 °C, cooled and concentrated. The residue was stirred with petroleum ether (3 × 20 mL), and the crystalline residue was filtered off and washed with petroleum ether to give **27** (676 mg, 92%); mp 172–173 °C (from EtOAc–petroleum ether); $[\alpha]_D$ −19° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): carbohydrate

ring protons (see Table 4); δ 8.10–7.20 (m, 29 H, aromatic H), 4.78, 4.72, 4.64, 4.12 (4 ABq, 8 H, CH_2Ph), 3.79 (s, 3 H, OCH_3), 3.78, 3.73 (2 s, 6 H, $COOCH_3$), 3.45 (s, 3 H, OCH_3), 1.82 (s, 3 H, NAc), 0.84 (s, 9 H, $(CH_3)_3C$); ISMS: *m/z* 1316, $[M + NH_4]^+$, 1299, $[M + H]^+$. Anal. Calcd for $C_{71}H_{79}NO_{22}$: C, 65.68; H, 6.13; N, 1.08. Found: C, 65.38; H, 6.10; N, 1.22.

[3-O-Benzyl-4-O-(4-methoxybenzyl)-α-L-idopyranosyluronic acid]-(1→3)-(2-acetamido-6-O-benzyl-2-deoxy-4-O-pivaloyl-β-D-galactopyranosyl)-(1→4)-methyl 3-O-benzyl-α-L-idopyranosiduronic acid (**28**).—A solution of **27** (658 mg, 0.5 mmol) in THF (15 mL) was treated at 0 °C with 30% H_2O_2 (2.6 mL) and LiOH (1 M, 5.2 mL), and the mixture was stirred for 1 h at 0 °C and for 15 h at rt, then was cooled to 0 °C. Methanol (5 mL) and NaOH (4 M, 1.2 mL) were added, and the mixture was stirred for 5 h at rt, then was diluted with MeOH (15 mL) and treated with Amberlite IR–120 $[H^+]$ resin to pH 3.5 (pH meter control), filtered and concentrated. The residue was eluted from a column (40 g) of silica gel with 12:1→9:1→4:1 CH_2Cl_2–MeOH to give **28** as a white foam (412 mg, 76%); $[\alpha]_D$ −35° (*c* 1, $CHCl_3$); ^1H NMR (500 MHz, CD_3OD): carbohydrate ring protons (see Table 4); δ 7.40–6.90 (m, 19 H, aromatic H), 4.63–4.45 (m, 8 H, CH_2Ph), 3.80, 3.45 (2 s 6 H, OCH_3), 2.08 (s, 3 H, NAc), 1.10 (s, 9 H, $(CH_3)_3C$); ISMS: *m/z* 1080, $[M + NH_4]^+$. Anal. Calcd for $C_{55}H_{67}NO_{20}$: C, 62.19; H, 6.36; N, 1.32. Found: C, 61.91; H, 6.52; N, 1.18.

[3-O-Benzyl-4-O-(4-methoxybenzyl)-α-L-idopyranosyluronic acid]-(1→3)-(2-acetamido-6-O-benzyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-methyl 3-O-benzyl-α-L-idopyranosiduronic acid (**29**).—Compound **27** (389 mg, 0.3 mmol) was treated as described for the preparation of **28**, but the mixture was stirred for 96 h at rt with 4 M NaOH. After deionization, the residue was eluted from a column (20 g) of silica gel with 10:2:1→7:2:1 EtOAc–MeOH–water to give **29** as a white foam (192 mg, 66%); $[\alpha]_D$ −62° (*c* 1, MeOH); ^1H NMR (500 MHz, CD_3OD): carbohydrate ring protons (see Table 4); δ 7.40–6.80 (m, 19 H, aromatic H), 4.75–4.41 (m, 8 H, CH_2Ph), 3.75, 3.38 (2 s, 6 H, OCH_3), 2.02 (s, 3 H, NAc); ISMS: *m/z* 996, $[M + NH_4]^+$, 979, $[M + H]^+$. Anal. Calcd for $C_{50}H_{59}NO_{19}$: C, 61.40; H, 6.08; N, 1.43. Found: C, 61.12; H, 6.32; N, 1.24.

Sodium O-[sodium 3-O-benzyl-4-O-(4-methoxybenzyl)-2-O-sodium sulfonato-α-L-idopyranosyluronate]-(1→3)-(2-acetamido-6-O-benzyl-2-deoxy-4-O-pivaloyl-β-D-galactopyranosyl)-(1→4)-(methyl 3-O-benzyl-2-O-sodium sulfonato-α-L-idopyranosid)uronate (**30**).—A mixture of **28** (185 mg, 0.17 mmol) and sulfur trioxide–trimethylamine complex (526 mg, 3.8 mmol) in anhyd DMF (5 mL) was stirred for 72 h at 50 °C, then was cooled. Methanol (4 mL) was added, and the mixture was concentrated. The residue was eluted from a column (2 × 50 cm) of Sephadex LH–20 with 1:1 CH_2Cl_2–MeOH, then from a column (20 g) of silica gel with 6:2:1 EtOAc–MeOH–water, and finally from a column (1 × 20 cm) of Sephadex SP C25 $[Na^+]$ with 5:5:1 CH_2Cl_2–MeOH–water to afford **30** as a white powder (144 mg, 63%); $[\alpha]_D$ −38° (*c* 1, MeOH); ^1H NMR (500 MHz, CD_3OD): carbohydrate ring protons (see Table 4); δ 7.20–6.80 (m, 19 H, aromatic H), 4.85–4.45 (m, 8 H, CH_2Ph), 3.83, 3.56 (2 s, 6 H, OCH_3), 2.16 (s, 3 H, NAc), 1.23 (s, 9 H, $(CH_3)_3C$). Anal. Calcd for $C_{55}H_{63}NNa_4O_{26}S_2$: C, 50.42; H, 4.85; N, 1.07. Found: C, 50.17; H, 5.05; N, 1.11.

Sodium O-[sodium 3-O-benzyl-4-O-(4-methoxybenzyl)-2-O-sodium sulfonato-α-L-idopyranosyluronate]-(1→3)-(2-acetamido-6-O-benzyl-2-deoxy-4-O-sodium sulfonato-β-D-galactopyranosyl)-(1→4)-(methyl 3-O-benzyl-2-O-sodium sulfonato-α-L-idopyranosid)uronate (**31**).—A mixture of **29** and sulfur trioxide–trimethylamine complex (0.68 g, 4.9 mmol) in anhyd DMF (6 mL) was treated as described for the preparation of **30** to give **31** as a white foam (150 mg, 70%); $[\alpha]_D$ −28° (*c* 1, MeOH); ^1H NMR (500 MHz, CD_3OD): carbohydrate ring protons (see Table 4); δ 7.50–6.90 (m, 19 H, aromatic H), 4.78–4.30 (m, 8 H, CH_2Ph), 3.75, 3.37 (2 s, 6 H, OCH_3), 2.07 (s, 3 H, NAc). Anal. Calcd for $C_{50}H_{54}NNa_5O_{28}S_3$: C, 45.22; H, 4.10; N, 1.05. Found: C, 44.96; H, 4.25; N, 1.01.

Sodium O-[sodium 3-O-benzyl-4-O-(4-methoxybenzyl)-2-O-sodium sulfonato-α-L-idopyranosyluronate]-(1→3)-(2-acetamido-6-O-benzyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-(methyl 3-O-benzyl-2-O-sodium sulfonato-α-L-idopyranosid)uronate (**32**).—A mixture of **30** (144 mg, 0.11 mmol) and NaOH (4 M, 5 mL) in MeOH (8 mL) was stirred for 96 h at rt, then was treated with Amberlite IR–120 $[H^+]$ resin to pH 7.0 (pH meter control), filtered and concentrated. The residue was eluted from a column (10 g) of silica gel with 6:2:1 EtOAc–MeOH–water to give **32** as a white foam (92 mg, 72%); $[\alpha]_D$ −45° (*c* 1, MeOH); ^1H NMR (500 MHz, CD_3OD): carbohydrate ring protons (see Table 4); δ 7.50–6.80 (m, 19 H, aromatic H), 4.85–4.30 (m, 8 H, CH_2Ph), 3.76, 3.34 (2 s, 6 H, OCH_3), 2.15 (s, 3 H, NAc). Anal. Calcd for $C_{50}H_{55}NNa_4O_{25}S_2$: C, 48.98; H, 4.52; N, 1.14. Found: C, 48.61; H, 4.75; N, 1.18.

Sodium O-[sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate]-(1→3)-(2-acetamido-2-deoxy-4-O-sodium sulfonato-β-D-galactopyranosyl)-(1→4)-(methyl 2-O-sodium sulfonato-α-L-idopyranosid)uronate (**1**).—A solution of **31** (150 mg, 0.11 mmol) in 2:1 MeOH–water (6 mL) was hydrogenated in the presence of 10% Pd–C (100 mg) for 96 h at rt. The mixture was filtered and concentrated, then was eluted from a column (1.5 × 30 cm) of Sephadex LH–20 with water and freeze-dried to afford amorphous hygroscopic **1** (98 mg, 93%); $[\alpha]_D$ −21° (*c* 1, water); ^1H NMR (500 MHz, D_2O, internal water, δ_H 4.754): carbohydrate ring protons (see Table 4); δ 3.36 (s, 3 H, OCH_3), 2.02 (s, 3 H,

NAc); ^{13}C NMR (D_2O, internal acetone, δ_C 30.45): δ 176.46, 175.80, 175.15 (C=O), 103.13 (C-1^{II}), 100.99 (C-1^{III}), 100.32 (C-1^{I}), 79.03 (C-4^{I}), 76.97 (C-3^{II}), 76.54 (C-4^{II}), 76.15 (C-5^{II}), 75.21, 74.30 (C-2^{I}, C-2^{III}), 73.24 (C-4^{I}), 69.18, 69.08, 68.55, 67.59 (C-5^{I}, C-5^{III}, C-3^{I}, C-3^{III}), 61.72 (C-6^{II}), 55.92 (OCH_3), 52.55 (C-2^{II}), 23.52 ($COCH_3$). Anal. Calcd for $C_{21}H_{28}NNa_5O_{27}S_3 \cdot H_2O$: C, 26.39; H, 3.16; N, 1.46. Found: C, 26.15; H, 3.27; N, 1.32.

Sodium O-*[sodium 2*-O-*sodium sulfonato*-α-L-*idopyranosyluronate]*-*(1→3)*-*(2-acetamido-2-deoxy*-β-D-*galactopyranosyl)*-*(1→4)*-*(methyl 2*-O-*sodium sulfonato*-α-L-*idopyranosid)uronate* (**2**).—Compound **32** (87 mg, 70 μmol) was treated as described for the preparation of **1** to give amorphous hygroscopic **2** (57 mg, 96%); $[\alpha]_D$ −9° (*c* 1, water); ^{1}H NMR (500 MHz, D_2O, internal water, δ_H 4.754): carbohydrate ring protons (see Table 4); δ 3.30 (s, 3 H, OCH_3), 2.0 (s, 3 H, NAc); ^{13}C NMR (D_2O, internal acetone, δ_C 30.45): δ 176.69, 175.92, 175.25 (C=O), 103.64 (C-1^{II}), 101.75 (C-1^{III}), 100.41 (C-1^{I}), 80.59 (C-4^{I}), 79.01 (C-3^{II}), 75.77 (C-5^{II}), 74.36, 74.22 (C-2^{I}, C-2^{III}), 69.31, 69.22, 68.73, 68.57, 68.46, 67.65 (C-4^{II}, C-4^{I}, C-5^{I}, C-5^{III}, C-3^{I}, C-3^{III}), 61.88 (C-6^{II}), 55.96 (OCH_3), 51.99 (C-2^{II}), 23.43 ($COCH_3$). Anal. Calcd for $C_{21}H_{29}NNa_4O_{24}S_2 \cdot H_2O$: C, 29.55; H, 3.66; N, 1.64. Found: C, 29.27; H, 3.75; N, 1.51.

Methyl O-*(4*-O-*acetyl-3,6-di*-O-*benzyl-2-deoxy-2-trichloroacetamido*-β-D-*galactopyranosyl)*-*(1→4)*-*(methyl 2*-O-*benzoyl-3*-O-*benzyl*-α-L-*idopyranosyluronate)*-*(1→3)-6*-O-*benzyl-2-deoxy-4*-O-*pivaloyl-2-trichloroacetamido*-β-D-*galactopyranoside* (**34**).—A mixture of alcohol **22** (677 mg 0.75 mmol) and 4-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-2-trichloroacetamido-1-*O*-trichloroacetimidoyl-α-D-galactopyranose **33**[10] (756 mg, 1.12 mmol) was treated as described for the preparation of **24**. The residue was eluted from a column (60 g) of silica gel with 2:1 petroleum ether–EtOAc containing 0.2% of Et_3N to give **34** as a white foam (855 mg, 80%); $[\alpha]_D$ +2° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): carbohydrate ring protons (see Table 5); δ 8.0–7.20 (m, 25 H, Ph), 4.66, 4.63, 4.47, 4.35 (4 ABq, 8 H, CH_2Ph), 3.76 (s, 3 H, $COOCH_3$), 3.52 (s, 3 H, OCH_3), 1.82 (s, 3 H, Ac), 1.15 (s, 9 H, $(CH_3)_3C$); ^{13}C NMR ($CDCl_3$): selected data; δ 101.74 (C-1^{II}), 101.30 (C-1^{III}), 100.34 (C-1^{I}), 92.53, 92.30 (CCl_3), 76.73 (C-3^{I}), 75.17 (C-3^{II}), 74.34 (C-3^{III}), 73.69, 73.60, 72.25, 71.65 (CH_2Ph), 73.26 (C-5^{I}), 73.08 (C-4^{I}) 71.90, 79.17, 68.66, 67.84, 67.19, 67.15, 65.12 (C-4^{I}, C-4^{III}, C-5^{III}, C-6^{I}, C-6^{III}, C-2^{II}, C-5^{II}), 57.32 (OCH_3), 56.01, 55.44 (C-2^{I}, C-2^{III}), 52.64 ($COOCH_3$), 39.11 ($(CH_3)_3C$), 27.17 ($(CH_3)_3C$), 20.44 ($COCH_3$); ISMS: *m*/*z* 1444, $[M + NH_4]^+$ for ^{35}Cl. Anal. Calcd for $C_{66}H_{72}Cl_6N_2O_{20}$: C, 55.59; H, 5.09; N, 1.97. Found: C, 55.48; H, 5.10; N, 1.92.

Methyl O-*(4*-O-*acetyl-3,6-di*-O-*benzyl-2-deoxy-2-trichloroacetamido*-β-D-*galactopyranosyl)*-*(1→4)*-*(methyl 2*-O-*benzoyl-3*-O-*benzyl*-α-L-*idopyranosyluronate)*-*(1→3)-4*-O-*acetyl-6*-O-*benzyl-2-deoxy-2-trichloroacetamido*-β-D-*galactopyranoside* (**35**).—A mixture of alcohol **23** (747 mg, 0.87 mmol) and imidate **33** (877 mg, 1.3 mmol) was treated as described for the preparation of **24**. The residue was eluted from a column (80 g) of silica gel with 3:2 petroleum ether–EtOAc containing 0.2% of Et_3N to give **35** as a white foam (910 mg, 75%); $[\alpha]_D$ +5° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): carbohydrate ring protons (see Table 5); δ 8.05–7.20 (m, 25 H, Ph), 4.66, 4.55, 4.48, 4.35 (4 ABq, 8 H, CH_2Ph), 3.73 (s, 3 H, $COOCH_3$), 3.50 (s, 3 H, OCH_3), 1.72, 1.65 (2 s, 6 H, Ac); ISMS: *m*/*z* 1402, $[M + NH_4]^+$ for ^{35}Cl. Anal. Calcd for $C_{63}H_{66}Cl_6N_2O_{20}$: C, 54.67; H, 4.81; N, 2.02. Found: C, 54.51; H, 4.87; N, 2.04.

Methyl O-*(2-acetamido-4*-O-*acetyl-3,6-di*-O-*benzyl-2-deoxy*-β-D-*galactopyranosyl)*-*(1→4)*-*(methyl 2*-O-*benzoyl-3*-O-*benzyl*-α-L-*idopyranosyluronate)*-*(1→3)-2-acetamido-6*-O-*benzyl-2-deoxy-4*-O-*pivaloyl*-β-D-*galactopyranoside* (**36**).—A mixture of **34** (885 mg, 0.62 mmol) and Bu_3SnH (2 mL, 7.4 mmol) was treated as described for the preparation of **27**. The residue was eluted from a column (25 g) of silica gel with 7:2 CH_2Cl_2–EtOAc to give **36** as a white foam (672 mg, 84%); $[\alpha]_D$ +14° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): carbohydrate ring protons (see Table 5); δ 8.0–7.20 (m, 25 H, Ph), 4.62, 4.59, 4.47, 4.37 (4 ABq, 8 H, CH_2Ph), 3.85 (s, 3 H, $COOCH_3$), 3.49 (s, 3 H, OCH_3), 1.95, 1.92, 1.75 (3 s, 9 H, Ac), 1.14 (s, 9 H, $(CH_3)_3C$); ISMS: *m*/*z* 1237, $[M + NH_4]^+$, 1188, $[M - OCH_3]^+$. Anal. Calcd for $C_{66}H_{78}N_2O_{20}$: C, 65.00; H, 6.44; N, 2.30. Found: C, 64.81; H, 6.41; N, 2.29.

Methyl O-*(2-acetamido-4*-O-*acetyl-3,6-di*-O-*benzyl-2-deoxy*-β-D-*galactopyranosyl)*-*(1→4)*-*(methyl 2*-O-*benzoyl-3*-O-*benzyl*-α-L-*idopyranosyluronate)*-*(1→3)-2-acetamido-4*-O-*acetyl-6*-O-*benzyl-2-deoxy*-β-D-*galactopyranoside* (**37**).—Compound **35** was treated as described for the preparation of **36**. The residue was eluted from a column (40 g) of silica gel with 10:1 CH_2Cl_2–MeOH to give **37** as a white foam (483 mg, 88%); $[\alpha]_D$ +18° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): carbohydrate ring protons (see Table 5); δ 8.05–7.20 (m, 25 H, Ph), 4.70–4.35 (m, 8 H, CH_2Ph), 3.74 (s, 3 H, $COOCH_3$), 3.52 (s, 3 H, OCH_3), 2.05, 1.98, 1.82, 1.71 (4 s, 12 H, Ac); ISMS: *m*/*z* 1200, $[M + Na]^+$, 1146, $[M - OCH_3]^+$. Anal. Calcd for $C_{63}H_{72}N_2O_{20}$: C, 64.27; H, 6.16; N, 2.38. Found: C, 64.18; H, 6.14; N, 2.41.

Methyl O-*(2-acetamido-3,6-di*-O-*benzyl-2-deoxy*-β-D-*galactopyranosyl)*-*(1→4)*-*(3*-O-*benzyl*-α-L-*idopyranosyluronic acid)*-*(1→3)-2-acetamido-6*-O-*benzyl-2-deoxy-4*-O-*pivaloyl*-β-D-*galactopyranoside* (**38**).—Compound **36** (632 mg, 0.52 mmol) was treated as described for the preparation of **28**. The residue was eluted from a column (40 g) of silica gel with 10:1→6:1 CH_2Cl_2–MeOH to give **38** as a white foam (513 mg, 95%); $[\alpha]_D$ −5° (*c* 1, MeOH); ^{1}H NMR (500 MHz, CD_3OD):

carbohydrate ring protons (see Table 5); δ 7.60–7.20 (m, 20 H, Ph), 4.85–4.40 (m, 8 H, CH_2Ph), 3.49 (s, 3 H, OCH_3), 2.05, 1.97 (2 s, 6 H, NAc), 1.14 (s, 9 H, $(CH_3)_3C$); ISMS: m/z 1082, $[M + Na]^+$, 1077, $[M + NH_4]^+$, 1060, $[M + H]^+$. Anal. Calcd for $C_{56}H_{70}N_2O_{18}$: C, 63.50; H, 6.66; N, 2.64. Found: C, 63.32; H, 6.71; N, 2.51.

Methyl O-*(2-acetamido-3,6-di-*O-*benzyl-2-deoxy-β-*D-*galactopyranosyl)-(1→4)-(3-*O-*benzyl-α-*L-*idopyranosyluronic acid)-(1→3)-2-acetamido-6-*O-*benzyl-2-deoxy-β-*D-*galactopyranoside* (**39**).—(a) Compound **37** (470 mg, 0.4 mmol) was treated as described for the preparation of **28**. The residue was eluted from a column (40 g) of silica gel with 10:1→6:1 CH_2Cl_2–MeOH to give **39** as a white foam (373 mg, 95%); $[\alpha]_D$ −27° (*c* 1, MeOH); ^{1}H NMR (500 MHz, CD_3OD): carbohydrate ring protons (see Table 5); δ 7.50–7.10 (m, 20 H, Ph), 4.76–4.50 (m, 8 H, CH_2Ph), 3.44 (s, 3 H, OCH_3), 2.12, 1.96 (2 s, 6 H, NAc); ^{13}C NMR (CD_3OD): selected data; δ 176.95, 176.55, 174.47 (C=O), 106.29 (C-1^{III}), 104.90 (C-1^{I}), 104.09 (C-1^{II}), 81.98 (C-3^{I}), 80.30 (C-3^{III}), 79.47 (C-4^{II}), 77.33 (C-3^{II}), 75.66, 75.37 (C-5^{I}, C-5^{III}), 75.10, 73.84, 72.89, 71.26 (CH_2Ph), 71.03, 70.27, 68.73, 66.48 (C-2^{II}, C-5^{II}, C-4^{I}, C-4^{III}), 62.99, 62.97 (C-6^{I}, C-6^{III}), 57.71 (OCH_3), 53.44, 53.40 (C-2^{I}, C-2^{III}), 24.69, 24.02 ($COCH_3$); ISMS: m/z 993, $[M + NH_4]^+$, 944, $[M - OCH_3]^+$. Anal. Calcd for $C_{51}H_{62}N_2O_{17}$: C, 62.81; H, 6.41; N, 2.87. Found: C, 62.66; H, 6.61; N, 2.77.

(b) A mixture of **38** (467 mg, 0.45 mmol) and NaOH (4 M, 10 mL) in MeOH (10 mL) was stirred for 96 h at rt, then was worked-up as described for the preparation of **28** to give **39** (268 mg, 61%); $[\alpha]_D$ −27°(*c* 1, MeOH); ISMS: m/z 993, $[M + NH_4]^+$.

Methyl O-*(2-acetamido-3,6-di-*O-*benzyl-2-deoxy-4-*O-*sodium sulfonato-β-*D-*galactopyranosyl)-(1→4)-(sodium 3-*O-*benzyl-2-*O-*sodium sulfonato-α-*L-*idopyranosyluronate)-(1→3)-2-acetamido-6-*O-*benzyl-2-deoxy-4-*O-*sodium sulfonato-β-*D-*galactopyranoside* (**40**).—A mixture of **39** (389 mg, 0.4 mmol) and sulfur trioxide–trimethylamine complex (2.20 g, 15.8 mmol) in anhyd DMF (8 mL) was treated and purified as described for the preparation of **30** to give **40** as a white powder (340 mg, 65%); $[\alpha]_D$ +2° (*c* 1, MeOH); ^{1}H NMR (500 MHz, CD_3OD): carbohydrate ring protons (see Table 5); δ 7.65–7.30 (m, 20 H, Ph), 4.80–4.56 (m, 8 H, CH_2Ph), 3.46 (s, 3 H, OCH_3), 2.18, 2.04 (2 s, 6 H, NAc); ^{13}C NMR (CD_3OD): selected data; δ 175.97, 175.64, 175.02 (C=O), 105.76 (C-1^{III}), 104.10 (C-1^{I}), 102.35 (C-1^{II}), 80.63 (C-3^{I}), 79.56 (C-3^{III}), 79.37 (C-4^{II}), 77.88 (C-3^{II}), 77.24, 75.48 (C-5^{I}, C-5^{III}), 75.09, 74.98, 74.02, 73.85 (CH_2Ph), 73.59 (C-4^{I}), 72.97 (C-2^{II}), 72.58 (C-4^{III}), 71.14 (C-5^{II}), 63.05, 62.85 (C-6^{I}, C-6^{III}), 57.94 (OCH_3), 53.40, 53.35 (C-2^{I}, C-2^{III}), 24.61, 24.26 ($COCH_3$). Anal. Calcd for $C_{51}H_{58}N_2Na_4O_{26}S_3$: C, 47.00; H, 4.48; N, 2.15. Found: C, 46.70; H, 4.59; N, 2.07.

Methyl O-*(2-acetamido-2-deoxy-4-*O-*sodium sulfonato-β-*D-*galactopyranosyl)-(1→4)-(sodium 2-*O-*sodium sulfonato-α-*L-*idopyranosyluronate)-(1→3)-2-acetamido-2-deoxy-4-*O-*sodium sulfonato-β-*D-*galactopyranoside* (**3**).—Compound **40** (340 mg, 0.26 mmol) was treated as described for the preparation of **1** and freeze-dried to give amorphous hygroscopic **3** (215 mg, 88%); $[\alpha]_D$ −20° (*c* 1, water); ^{1}H NMR (500 MHz, D_2O, internal water, δ_H 4.754): carbohydrate ring protons (see Table 5); δ 3.42 (s, 3 H, OCH_3), 2.15, 2.13 (2 s, 6 H, NAc); ^{13}C NMR (D_2O, internal acetone, δ_C 30.45): δ 175.81, 175.78, 174.85 (C=O), 103.95 (C-1^{III}), 102.51 (C-1^{I}), 101.18 (C-1^{II}), 77.87 (C-3^{I}), 77.45 (C-3^{III}), 76.54 (C-4^{II}), 76.41 (C-4^{III}), 75.16 (C-4^{I}), 75.05 (C-2^{II}), 73.39 (C-5^{III}), 70.95 (C-5^{I}), 68.76 (C-5^{II}), 67.78 (C-3^{II}), 61.71, 61.57 (C-2^{I}, C-2^{III}), 57.80 (OCH_3), 22.29, 22.05 ($COCH_3$). Anal. Calcd for $C_{23}H_{34}N_2Na_4O_{26}S_3 \cdot H_2O$: C, 28.75; H, 3.57; N, 2.91. Found: C, 28.47; H, 3.71; N, 2.52.

References

1. Maimone, M. M.; Tollefsen, D. M. *J. Biol. Chem.* **1990**, *265*, 18263–18271.
2. Linhardt, R. J.; Desai, U. R.; Liu, J.; Pervin, A.; Hoppenstaedt, D.; Fareed, J. *Biochem. Pharmacol.* **1994**, *47*, 1241–1252.
3. Di Carlo, V.; Agnelli, G.; Prandoni, P.; Coccheri, S.; Gensini, G. F.; Gianesi, F.; Manucci, P. M. *Thromb. Haemost.* **1999**, *82*, 30–34.
4. Penc, S. F.; Pomahac, B.; Winkler, T.; Dorschner, R. A.; Eriksson, E.; Herndon, M.; Gallo, R. L. *J. Biol. Chem.* **1998**, *273*, 28116–28121.
5. Santra, M.; Eichstetter, I.; Iozzo, R. V. *J. Biol. Chem.* **2000**, *275*, 35153–35161.
6. Lyon, M.; Daekin, J.; Rahmoune, H.; Fernig, D.; Nakamura, T.; Gallagher, J. *J. Biol. Chem.* **1998**, *273*, 271–278.
7. Jacquinet, J.-C.; Sinaÿ, P. *Carbohydr. Res.* **1987**, *159*, 229–253.
8. Marra, A.; Dong, X.; Petitou, M.; Sinaÿ, P. *Carbohydr. Res.* **1989**, *195*, 39–50.
9. Rochepeau-Jobron, L.; Jacquinet, J.-C. *Carbohydr. Res.* **1997**, *305*, 181–191.
10. Barroca, N.; Jacquinet, J.-C. *Carbohydr. Res.* **2000**, *329*, 667–679.
11. Goto, F.; Ogawa, T. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 619–624.
12. Bourhis, P.; Machetto, F.; Duchaussoy, P.; Hérault, J.-P.; Mallet, J.-M.; Herbert, J.-M.; Petitou, M.; Sinaÿ, P. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2843–2846.
13. Yang, H. O.; Gunay, N. S.; Toida, T.; Kuberan, B.; Yu, G.; Kim, Y. S.; Linhardt, R. J. *Glycobiology* **2000**, *10*, 1033–1040.
14. Evers, M. R.; Xia, G.; Kang, H.-G.; Schachner, M.; Baenziger, J. *J. Biol. Chem.* **2001**, *276*, 36344–36353.
15. Tailler, D.; Jacquinet, J.-C.; Beau, J.-M. *J. Chem. Soc., Chem. Commun.* **1994**, 827–1828.
16. Neumann, K. W.; Tamura, J.-I.; Ogawa, T. *Bioorg. Med. Chem.* **1995**, *3*, 1637–1650.

17. Bélot, F.; Jacquinet, J.-C. *Carbohydr. Res.* **2000**, *325*, 93–106.
18. De Ninno, M. P.; Etienne, J. B.; Duplantier, K. C. *Tetrahedron Lett.* **1995**, *36*, 669–672.
19. Lemieux, R. U.; Driguez, H. *J. Am. Chem. Soc.* **1975**, *97*, 4069–4075.
20. Davis, N. J.; Flitsch, S. L. *J. Chem. Soc., Perkin Trans. 1* **1994**, 359–369.
21. Magaud, D.; Grandjean, C.; Doutheau, A.; Anker, D.; Schevchik, V.; Cotte-Pattat, N.; Robert-Baudouy, J. *Carbohydr. Res.* **1998**, *314*, 189–199.
22. Karst, N.; Jacquinet, J.-C. *Eur. J. Org. Chem.* **2002**, 815–825.
23. Inokuchi, T.; Matsumoto, S.; Nishiyama, T.; Torii, S. *J. Org. Chem.* **1990**, *55*, 462–466.
24. Blatter, G.; Beau, J.-M.; Jacquinet, J.-C. *Carbohydr. Res.* **1994**, *260*, 189–202.
25. Patil, V. J. *Tetrahedron Lett.* **1996**, *37*, 1481–1484.
26. Lucas, H.; Basten, J. E. M.; van Dinther, T. G.; Meuleman, D. G.; van Aelst, S. F.; van Boeckel, C. A. A. *Tetrahedron* **1990**, *46*, 8207–8228.
27. Jacquinet, J.-C. *Carbohydr. Res.* **1990**, *199*, 153–181.
28. Pavão, M.; Aiello, K.; Werneck, C.; Silva, L.; Valente, A.-P.; Mulloy, B.; Colwell, N.; Tollefsen, D. M.; Mourão, P. *J. Biol. Chem.* **1998**, *273*, 27848–27857.
29. Barroca, N. Ph.D. Thesis, University of Orléans, 2001.